

Bibliographic database on multi-level and multi-scale agent-based modeling

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[Abouaïssa:2014] H. Abouaïssa, Y. Kubera, and G. Morvan. Dynamic hybrid traffic flow modeling. *CoRR*, abs/1401.6773, 2014.

Abstract: A flow of moving agents can be observed at different scales. Thus, in traffic modeling, three levels are generally considered: the micro, meso and macro levels, representing respectively the interactions between vehicles, groups of vehicles sharing common properties (such as a common destination or a common localization) and flows of vehicles. Each approach is useful in a given context: micro and meso models allow to simulate road networks with complex topologies such as urban area, while macro models allow to develop control strategies to prevent congestion in highways. However, to simulate large-scale road networks, it can be interesting to integrate different representations, e.g., micro and macro, in a single model. Existing models share the same limitation: connections between levels are fixed a priori and cannot be changed at runtime. Therefore, to be able to observe some emerging phenomena such as congestion formation or to find the exact location of a jam in a large macro section, a dynamic hybrid modeling approach is needed. In 2013 we started the development of a multi-level agent-based simulator called JAM-FREE within the ISART project. It allows to simulate large road networks efficiently using a dynamic level of detail. This simulator relies on a multi-level agent-based modeling framework called SIMILAR.

Keywords: multi-agent based simulation, multi-level, traffic, french team

[Abouaïssa:2014a] H. Abouaïssa, Y. Kubera, and G. Morvan. Modélisation hybride dynamique de flux de trafic. Technical report, LGI2A, 2014.

Abstract: La simulation du trafic routier sur des réseaux de grande échelle est un problème compliqué car il suppose d'intégrer dans un même modèle différentes approches. Ainsi, les sections autoroutières sont généralement représentées à l'aide de modèles macroscopiques alors que pour les sections urbaines, des modèles microscopiques sont utilisés. De manière générale, les modèles microscopiques sont intéressants lorsque les interactions entre véhicules, ainsi que la topologie du réseau deviennent complexes. Les modèles intégrant ces différents niveaux de représentation sont généralement qualifiés d'hybrides. Par ailleurs, ils sont généralement "statiques" : à chaque portion du réseau est associée une représentation unique qui ne changera pas au cours de la simulation. Afin de palier cette limitation, nous avons débuté en 2013 dans le cadre du projet ISART le développement d'un simulateur multi-agent multi-niveaux de flux de trafic routier nommé JAM-FREE permettant : - de simuler des réseaux routier de grande taille efficacement en adaptant dynamiquement le niveau de détail, - de tester de nouveaux algorithmes de régulation, d'observation et routage. Ce simulateur repose sur un framework de modélisation et de simulation multi-agents multi-niveaux nommé SIMILAR (SIMulations with Multi-Level Agents and Reactions), implémenté en Java et distribué prochainement sous licence libre. Dans ce rapport, nous présentons ces résultats scientifiques ainsi que les publications associées.

Keywords: multi-agent based simulation, multi-level, traffic, in french, french team

[Adnan:2016] M. Adnan, F.C. Pereira, Carlos M. Lima A., K. Basak, M. Lovric, S. Raveau, Y. Zhu, J. Ferreira, C. Zegras, and M.E. Ben-Akiva. Simmobility: A multi-scale integrated agent-based simulation platform. In *Transportation Research Board 95th Annual Meeting*, 2016.

Abstract: Developments in integrated agent-based platform has shown progress, however, most of efforts are based on integrating activity-based demand models with dynamic traffic assignment model. Integration beyond this level is limited and mostly based on loosely coupled mechanism (i.e. manual exchange of data). SimMobility is a simulation platform that integrates various mobility-sensitive behavioral models within a multi-scale simulation platform that considers land-use, transportation and communication interactions. It particularly focuses on impacts on transportation networks, intelligent transportation services and vehicular emissions, thereby enabling the simulation of a portfolio of technology, policy and investment options under alternative future scenarios. In short, SimMobility encompasses the modeling of millions of agents, from pedestrians to drivers, from phones, traffic lights to GPS probes, from cars to buses and trains, from second-by-second to year-by-year simulations. Simmobility is designed to support the activity-based modeling paradigm. All choices are ultimately tied to the agent's goal of performing activities on a time scale that can vary from seconds to years. Agents can be grouped in broad ways, from households to firms, and can have varying roles including operators, bus drivers or real-estate agents. Thus, the range of possible decisions is also broad, from travel (e.g. Mode or route choice, driving behaviour) to land-use (e.g. household or firm location choice). This paper describes the SimMobility framework, its key features such as event-based implementation, parallel and distributed architecture and flow of data across three integrated levels. Additionally, application of the whole platform in Singapore context with some details on application of autonomous mobility on demand study is also presented.

Keywords: multi-agent based simulation, multi-level, traffic

[Adra:2010]

S. Adra, T. Sun, S. MacNeil, M. Holcombe, and R. Smallwood. Development of a three dimensional multi-scale computational model of the human epidermis. *PLoS one*, 5(1):e8511, 2010.

Abstract: Transforming Growth Factor (TGF- β 1) is a member of the TGF-beta superfamily ligand-receptor network. and plays a crucial role in tissue regeneration. The extensive in vitro and in vivo experimental literature describing its actions nevertheless describe an apparent paradox in that during re-epithelialisation it acts as proliferation inhibitor for keratinocytes. The majority of biological models focus on certain aspects of TGF- β 1 behaviour and no one model provides a comprehensive story of this regulatory factor's action. Accordingly our aim was to develop a computational model to act as a complementary approach to improve our understanding of TGF- β 1. In our previous study, an agent-based model of keratinocyte colony formation in 2D culture was developed. In this study this model was extensively developed into a three dimensional multiscale model of the human epidermis which is comprised of three interacting and integrated layers: (1) an agent-based model which captures the biological rules governing the cells in the human epidermis at the cellular level and includes the rules for injury induced emergent behaviours, (2) a COmplex PAthway SIMulator (COPASI) model which simulates the expression and signalling of TGF- β 1 at the sub-cellular level and (3) a mechanical layer embodied by a numerical physical solver responsible for resolving the forces exerted between cells at the multi-cellular level. The integrated model was initially validated by using it to grow a piece of virtual epidermis in 3D and comparing the in vitro simulations of keratinocyte behaviour and of TGF- β 1 signalling with the extensive research literature describing this key regulatory protein. This research reinforces the idea that computational modelling can be an effective additional tool to aid our understanding of complex systems. In the accompanying paper the model is used to explore hypotheses of the functions of TGF- β 1 at the cellular and subcellular level on different keratinocyte populations during epidermal wound healing.

Keywords: multi-agent based simulation, multi-level, biology

[Al-Mamun:2017]

M.A. Al-Mamun and Y.T. Grohn. Mabsdairy: a multiscale agent based simulation of a dairy herd. In *Proc. of the 50th Annual Simulation Symposium*, page 8, 2017.

Abstract: Agent based simulation models (ABSM) provide individual information about an agent in a multiscale system problem. Here, we developed a multiscale agent based simulation model of a dairy herd (MABSDairy) by considering several layers of detailed information (i.e., individual animal, overall population and farmer's decision) to make optimal decisions. Previously, dynamic programming (DP) has been widely studied to find the optimal cow replacement policies, but DP models are computationally intensive and might not be practical for daily decision making for a farmer. Hence, we developed new ABSM for individual animals on a previously run DP model to provide fast and accurate predictions of nonlinear and inter correlated parameters. The results show that the model can be applied to estimate critical parameters for management decisions. Overall, the MABSDairy presents an adaptive simulation tool where different diseases and different management policies may be included in the future.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Al-Mamun:2018]

M.A. Al-Mamun, R.L. Smith, A. Nigsch, Y.H. Schukken, and Y.T. Gröhn. A data-driven individual-based model of infectious disease in livestock operation: A validation study for paratuberculosis. *PLOS ONE*, 13(12):1–18, 2018.

Abstract: Chronic livestock diseases cause large financial loss and affect animal health and welfare. Controlling these diseases mostly requires precise information on both individual animal and population dynamics to inform the farmer’s decisions, but even successful control programmes do by no means assure elimination. Mathematical models provide opportunities to test different control and elimination options rather than implementing them in real herds, but these models require robust parameter estimation and validation. Fitting these models to data is a difficult task due to heterogeneities in livestock processes. In this paper, we develop an infectious disease modeling framework for a livestock disease (paratuberculosis) that is caused by *Mycobacterium avium* subsp. paratuberculosis (MAP). Infection with MAP leads to reduced milk production, pregnancy rates, and slaughter value and increased culling rates in cattle and causes significant economic losses to the dairy industry. These economic effects are particularly important motivations in the control and elimination of MAP. In this framework, an individual-based model (IBM) of a dairy herd was built and MAP infection dynamics was integrated. Once the model produced realistic dynamics of MAP infection, we implemented an evaluation method by fitting it to data from three dairy herds from the Northeast region of the US. The model fitting exercises used least-squares and parameter space searching methods to obtain the best-fitted values of selected parameters. The best set of parameters were used to model the effect of interventions. The results show that the presented model can complement real herd statistics where the intervention strategies suggest a reduction in MAP prevalence without elimination. Overall, this research not only provides a complete model for MAP infection dynamics in a dairy herd but also offers a method for estimating parameters by fitting IBM models.

Keywords: multi-agent based simulation, multi-level, multi-scale, epidemiology

[Alfonso:2016]

J. C. L. Alfonso, N. S. Schaadt, R. Schönmeier, N. Brieu, G. Forestier, C. Wemmert, F. Feuerhake, and H. Hatzikirou. In-silico insights on the prognostic potential of immune cell infiltration patterns in the breast lobular epithelium. *Scientific Reports*, 6:33322, 2016.

Abstract: Scattered inflammatory cells are commonly observed in mammary gland tissue, most likely in response to normal cell turnover by proliferation and apoptosis, or as part of immunosurveillance. In contrast, lymphocytic lobulitis (LLO) is a recurrent inflammation pattern, characterized by lymphoid cells infiltrating lobular structures, that has been associated with increased familial breast cancer risk and immune responses to clinically manifest cancer. The mechanisms and pathogenic implications related to the inflammatory microenvironment in breast tissue are still poorly understood. Currently, the definition of inflammation is mainly descriptive, not allowing a clear distinction of LLO from physiological immunological responses and its role in oncogenesis remains unclear. To gain insights into the prognostic potential of inflammation, we developed an agent-based model of immune and epithelial cell interactions in breast lobular epithelium. Physiological parameters were calibrated from breast tissue samples of women who underwent reduction mammoplasty due to orthopedic or cosmetic reasons. The model allowed to investigate the impact of menstrual cycle length and hormone status on inflammatory responses to cell turnover in the breast tissue. Our findings suggested that the immunological context, defined by the immune cell density, functional orientation and spatial distribution, contains prognostic information previously not captured by conventional diagnostic approaches.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Alho:2017]

A. Alho, B.K. Bhavathrathan, M. Stinson, R. Gopalakrishnan, D-T. Le, and M. Ben-Akiva. A multi-scale agent-based modelling framework for urban freight distribution. *Transportation Research Procedia*, 27:188–196, 2017.

Abstract: Comprehensive modelling of urban freight operations remains a challenge in transportation research. This is partly due to the diversity of commodities transported, shipment units, vehicle types used, stakeholders’ objectives (e.g. suppliers, carriers, receivers), and to the limited availability of data. Thus, existing modelling efforts require several assumptions yet have limited behavioral foundations and minimal interaction between agents. This paper proposes a new agent-based modelling framework, which considers the heterogeneity of urban freight agents and their interactions. Agents include establishments (suppliers, carriers, and receivers) and freight vehicle drivers. Agents’ decisions are structured in three temporal resolutions: strategic, tactical,

and operational. A single set of agents is represented throughout all modelling levels ensuring a consistent and sequential flow of information. At the strategic level, establishments' characteristics and strategic decisions are modelled. These include location choices, fleet constitution, annual production/consumption of commodities, and establishment-to-establishment commodity flows. At the tactical level, shipments are assigned to carriers, who in turn plan their operations in terms of vehicle-driver-route assignments. Finally, at the operational level, the interactions between daily operational demands and transportation network supply are simulated. The supply representation has two different resolution levels (micro or meso) allowing for either detailed or computational efficient simulation. The simulation platform is distinct from previous works, as it explicitly considers planning horizons, replicates agent decision makings/interactions and involves a structure that allows for the propagation of influences bottom-up (e.g., prior simulation travel times on future route choice). The paper describes the simulation platform, constituent models, and illustrates its capabilities using an application of the modelling framework to the city of Singapore.

Keywords: multi-agent based simulation, multi-level, multi-scale, traffic

[Alqurashi:2019]

R. Alqurashi. *Hybrid Multi-Level Agent-Based Decision Support System for Modeling and Simulation of Crowd and Traffic Dynamics*. PhD thesis, University of Colorado at Denver, 2019.

Keywords: multi-agent based simulation, multi-level, hybrid model, pedestrian flow modeling, traffic

[Amigoni:1998]

F. Amigoni, V. Schiaffonati, and M. Somalvico. A multilevel architecture of creative dynamic agency. In *Proceedings of the International Conference on Model-Based in Scientific Discovery*, pages 1–19, Décembre 1998.

Abstract: There are two classical and opposite positions about scientific discovery: the one that conceives scientific discovery activity as fully rational and the one that conceives scientific discovery activity as fully irrational. In the first case, machines are regarded as able to perform the scientific discovery process whereas, in the second case, machines are considered unable to perform any part of the scientific discovery process. We adopt a third intermediate approach that envisages a new role for machines, which are conceived as descriptions of the results of scientific discovery activity. More precisely, the purpose of the paper is to illustrate the multilevel structure of a machine, called creative dynamic agency, that represents the articulated and incremental description of the product of scientific discovery process. The multilevel architecture reflects the composition relation that holds among phenomena described by creative agents that compose creative dynamic agency.

Keywords: multi-agent based simulation, multi-level, social simulation

[Amigoni:2000]

F. Amigoni, V. Schiaffonati, and M. Somalvico. A multilevel architecture of creative dynamic agency. *Foundations of Science*, 5:157–184, 2000.

Keywords: social simulation, multi-agent based simulation, multi-level

[An:2008]

G. An. Introduction of an agent-based multi-scale modular architecture for dynamic knowledge representation of acute inflammation. *Theoretical Biology and Medical Modelling*, 5(11), 2008.

Abstract: BACKGROUND: One of the greatest challenges facing biomedical research is the integration and sharing of vast amounts of information, not only for individual researchers, but also for the community at large. Agent Based Modeling (ABM) can provide a means of addressing this challenge via a unifying translational architecture for dynamic knowledge representation. This paper presents a series of linked ABMs representing multiple levels of biological organization. They are intended to translate the knowledge derived from in vitro models of acute inflammation to clinically relevant phenomenon such as multiple organ failure. RESULTS AND DISCUSSION: ABM development followed a sequence starting with relatively direct translation from in-vitro derived rules into a cell-as-agent level ABM, leading on to concatenated ABMs into multi-tissue models, eventually resulting in topologically linked aggregate multi-tissue ABMs modeling organ-organ crosstalk. As an underlying design principle organs were considered to be functionally composed of an epithelial surface, which determined organ integrity, and an endothelial/blood interface, representing the reaction surface for the initiation and propagation of inflammation. The development of the epithelial ABM derived from an in-vitro model of gut epithelial permeability is described. Next, the epithelial ABM was concatenated with the endothelial/inflammatory cell ABM to produce an organ model of the gut. This model was validated against in-vivo models of the inflammatory response of the gut to ischemia. Finally, the gut ABM was linked to a similarly constructed pulmonary ABM to simulate the gut-pulmonary axis in the pathogenesis of multiple

organ failure. The behavior of this model was validated against in-vivo and clinical observations on the cross-talk between these two organ systems. **CONCLUSION:** A series of ABMs are presented extending from the level of intracellular mechanism to clinically observed behavior in the intensive care setting. The ABMs all utilize cell-level agents that encapsulate specific mechanistic knowledge extracted from in vitro experiments. The execution of the ABMs results in a dynamic representation of the multi-scale conceptual models derived from those experiments. These models represent a qualitative means of integrating basic scientific information on acute inflammation in a multi-scale, modular architecture as a means of conceptual model verification that can potentially be used to concatenate, communicate and advance community-wide knowledge.

Keywords: multi-agent based simulation, multi-level, biology

[An:2009]

G. An and U. Wilensky. Artificial life models in software. In *From Artificial Life to In Silico Medicine: NetLogo as a Means of Translational Knowledge Representation in Biomedical Research*, pages 183–212. Springer, 2009.

Abstract: Biomedical research today stands at a crossroads. There is a widening gulf between the extent of knowledge regarding basic mechanistic processes and the ability to integrate that information into explanatory hypotheses of system-level behavior. Techniques from the Artificial Life community can aid in bridging this gulf by providing means for visualizing and instantiating mechanistic hypotheses. This will allow the development of in silico laboratories where conceptual models can be examined, checked, and modified. NetLogo is a “low threshold, high ceiling” software toolkit that has been used to develop agent-based models (ABMs) in a multiplicity of domains and provides a good platform for the computational instantiation of biomedical knowledge. This chapter presents a brief overview of NetLogo and describes a series of ABMs of acute inflammation at multiple levels of biological organization.

Keywords: multi-agent based simulation, multi-level, biology

[An:2012]

G. An, G. Nieman, and Y. Vodovotz. Toward computational identification of multiscale "tipping points" in acute inflammation and multiple organ failure. *Annals of biomedical engineering*, 40(11):2414–2424, 2012.

Abstract: Sepsis accounts annually for nearly 10% of total U.S. deaths, costing nearly \$17 billion/year. Sepsis is a manifestation of disordered systemic inflammation. Properly regulated inflammation allows for timely recognition and effective reaction to injury or infection, but inadequate or overly robust inflammation can lead to Multiple Organ Dysfunction Syndrome (MODS). There is an incongruity between the systemic nature of disordered inflammation (as the target of inflammation-modulating therapies), and the regional manifestation of organ-specific failure (as the subject of organ support), that presents a therapeutic dilemma: systemic interventions can interfere with an individual organ system’s appropriate response, yet organ-specific interventions may not help the overall system reorient itself. Based on a decade of systems and computational approaches to deciphering acute inflammation, along with translationally-motivated experimental studies in both small and large animals, we propose that MODS evolves due to the feed-forward cycle of inflammation → damage → inflammation. We hypothesize that inflammation proceeds at a given, "nested" level or scale until positive feedback exceeds a "tipping point." Below this tipping point, inflammation is contained and manageable; when this threshold is crossed, inflammation becomes disordered, and dysfunction propagates to a higher biological scale (e.g., progressing from cellular, to tissue/organ, to multiple organs, to the organism). Finally, we suggest that a combination of computational biology approaches involving data-driven and mechanistic mathematical modeling, in close association with studies in clinically relevant paradigms of sepsis/MODS, are necessary in order to define scale-specific "tipping points" and to suggest novel therapies for sepsis.

Keywords: multi-agent based simulation, multi-level, biology

[An:2013]

G. An, M. Wandling, and S. Christley. Agent-based modeling approaches to multi-scale systems biology: An example agent-based model of acute pulmonary inflammation. In *Systems Biology - Integrative Biology and Simulation Tools*, pages 429–461. Springer, 2013.

Abstract: Implicit in systems biology is the concept that the whole is greater than the sum of its parts. Agent-based modeling, an object-oriented, discrete event, population-based computational modeling method, is well suited to meeting this goal. By viewing systems as aggregates of populations of interacting components, agent-based models (ABMs) map well to biological conceptual models and present an intuitive means by which biomedical researchers can represent their knowledge in a dynamic computational form. ABMs are particularly suited for representing the behaviour of populations of cells (i.e. “cell-as-agents”), but ABMs have also been used to

model molecular interactions, particularly when spatial and structural properties are involved. Presented herein are a series of ABMs of biomedical systems that cross multiple scales of biological organization, as well as a detailed description of an example ABM of acute pulmonary inflammation. Because of these characteristics agent-based modeling is a useful addition to the suite of equation-based mathematical modeling methods found in systems biology, and can serve as an integrating framework for dynamic knowledge representation of biological systems.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Andasari:2012]

V. Andasari, R.T. Roper, and M.H. Swat and M.A.J. Chaplain. Integrating intracellular dynamics using *compuCell3d* and *bionetsolver*: Applications to multiscale modelling of cancer cell growth and invasion. *PLoS ONE*, 7(3):e33726, 2012.

Abstract: In this paper we present a multiscale, individual-based simulation environment that integrates *CompuCell3D* for lattice-based modelling on the cellular level and *Bionetsolver* for intracellular modelling. *CompuCell3D* or *CC3D* provides an implementation of the lattice-based Cellular Potts Model or CPM (also known as the Glazier-Graner-Hogeweg or GGH model) and a Monte Carlo method based on the metropolis algorithm for system evolution. The integration of *CC3D* for cellular systems with *Bionetsolver* for subcellular systems enables us to develop a multiscale mathematical model and to study the evolution of cell behaviour due to the dynamics inside of the cells, capturing aspects of cell behaviour and interaction that is not possible using continuum approaches. We then apply this multiscale modelling technique to a model of cancer growth and invasion, based on a previously published model of Ramis-Conde et al. (2008) where individual cell behaviour is driven by a molecular network describing the dynamics of E-cadherin and -catenin. In this model, which we refer to as the centre-based model, an alternative individual-based modelling technique was used, namely, a lattice-free approach. In many respects, the GGH or CPM methodology and the approach of the centre-based model have the same overall goal, that is to mimic behaviours and interactions of biological cells. Although the mathematical foundations and computational implementations of the two approaches are very different, the results of the presented simulations are compatible with each other, suggesting that by using individual-based approaches we can formulate a natural way of describing complex multi-cell, multiscale models. The ability to easily reproduce results of one modelling approach using an alternative approach is also essential from a model cross-validation standpoint and also helps to identify any modelling artefacts specific to a given computational approach.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Antonitsch:2019]

A. Da Silva Antonitsch, D. Schaffer, G. Rockenbach, P. Knob, and S. Raupp Musse. Bioclouds: A multi-level model to simulate and visualize large crowds. In *Advances in Computer Graphics*, volume 11542 of *LNCS*, pages 15–27. Springer, 2019.

Abstract: This paper presents a multi-level approach to simulate large crowds [18] called BioClouds. The goal of this work is to model larger groups of agents by simulating aggregation of agents as singular units. This approach combines microscopic and macroscopic simulation strategies, where each group of agents (called cloud) keeps the global characteristics of the crowd unity without simulating individuals. In addition to macroscopic strategy, BioClouds allows to alter from global to local behavior (individuals), providing more accurate simulation in terms of agents velocities and densities. We also propose a new model of visualization focused on larger simulated crowds but keeping the possibility of “zooming” individuals and see their behaviors. Results indicate that BioClouds presents coherent behaviors when compared to what is expected in global and individual levels. In addition, BioClouds provides an important speed up in processing time when compared to microscopic crowd simulators present in literature, being able to achieve until one million agents, organized in 2000 clouds and simulated at 86.85 ms per frame.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling

[Athale:2006]

C.A. Athale and T.S. Deisboeck. The effects of egf-receptor density on multiscale tumor growth patterns. *Journal of theoretical biology*, 238(4):771–779, 2006.

Abstract: We studied the effects of epidermal growth factor receptor (EGFR) density on tumor growth dynamics, both on the sub- and the multi-cellular level using our previously developed model. This algorithm simulates the growth of a brain tumor using a multi-scale two-dimensional agent-based approach with an integrated transforming growth factor alpha (TGFalpha) induced EGFR-gene-protein interaction network. The results confirm that increasing cell receptor density correlates with an acceleration of the tumor system’s spatio-temporal expansion dynamics.

This multicellular behavior cannot be explained solely on the basis of spatial sub-cellular dynamics, which remain qualitatively similar amongst the three glioma cell lines investigated here in silico. Rather, we find that cells with higher EGFR density show an early increase in the phenotypic switching activity between proliferative and migratory traits, linked to a higher level of initial auto-stimulation by the PLCgamma-mediated TGFalpha-EGFR autocrine network. This indicates a more active protein level interaction in these chemotactically acting tumor systems and supports the role of post-translational regulation for the implemented EGFR pathway. Implications of these results for experimental cancer research are discussed.

Keywords: multi-agent based simulation, multi-level, cancer modeling

[Bae:2016]

J.W. Bae, E. Paik, K. Kim, K. Singh, and M. Sajjad. Combining microsimulation and agent-based model for micro-level population dynamics. *Procedia Computer Science*, 80:507–517, 2016.

Abstract: Population dynamics illustrates the changes of the size and age composition of populations. Modeling and simulation techniques have been used to model the population dynamics, and the developed models are utilized to design and analyze public policies. One classic modeling method is microsimulation. The microsimulation describes the population dynamics at the individual level, and actions conducted by the individuals are generated by stochastic process. An emerging method is agent-based model, which rather focuses on the interactions among individuals and expects to see unexpected situations created from the interactions. Their similar but different approaches can make them to complement weak points of the opponent in population dynamics analysis. From this perspective, This paper proposes a hybrid model structure combining microsimulation and agent-based model for modeling population dynamics. In the proposed model, the microsimulation model takes a role to depict how an individual chooses its behavior based on stochastic process parameterized by real data; the agent-based model incorporates interactions among individuals considering their own states and rules. The case study introduces Korean population dynamics model developed by the proposed approach, and its simulation results show the population changes triggered by a variance of behavior and interaction factors.

Keywords: multi-agent based simulation, multi-level, hybrid model, social simulation

[Banos:2015]

A. Banos, N. Corson, B. Gaudou, V. Laperrière, and S. Rey-Coyrehourcq. The importance of being hybrid for spatial epidemic models: A multi-scale approach. *Systems*, 3(4):309–329, 2015.

Abstract: This work addresses the spread of a disease within an urban system, defined as a network of interconnected cities. The first step consists of comparing two different approaches: a macroscopic one, based on a system of coupled Ordinary Differential Equations (ODE) Susceptible-Infected-Recovered (SIR) systems exploiting populations on nodes and flows on edges (so-called metapopulation model), and a hybrid one, coupling ODE SIR systems on nodes and agents traveling on edges. Under homogeneous conditions (mean field approximation), this comparison leads to similar results on the outputs on which we focus (the maximum intensity of the epidemic, its duration and the time of the epidemic peak). However, when it comes to setting up epidemic control strategies, results rapidly diverge between the two approaches, and it appears that the full macroscopic model is not completely adapted to these questions. In this paper, we focus on some control strategies, which are quarantine, avoidance and risk culture, to explore the differences, advantages and disadvantages of the two models and discuss the importance of being hybrid when modeling and simulating epidemic spread at the level of a whole urban system.

Keywords: multi-agent based simulation, multi-level, hybrid model, epidemiology, french team

[Banos:2016]

A. Banos, N. Corson, B. Gaudou, V. Laperrière, and S. Rey-Coyrehourcq. Coupling micro and macro dynamics models on networks: Application to disease spread. In *Multi-Agent Based Simulation XVI*, volume 9568 of *LNCS*, pages 19–33. Springer, 2016.

Abstract: A hybrid model coupling an aggregated equation-based model and an agent-based model is presented in this article. It is applied to the simulation of a disease spread in a city network. We focus here on the evaluation of our hybrid model by comparing it with a simple aggregated model. We progressively introduce heterogeneities in the model and measure their impact on three indicators: the maximum intensity of the epidemic, its duration and the time of the epidemic peak. Finally we present how to integrate mitigation strategies in the model and the benefits we can get from our hybrid approach over single paradigm models.

Keywords: multi-agent based simulation, multi-level, hybrid model, epidemiology, french team

[Banos:2017]

A. Banos, C. Lang, and N. Marilleau. *Agent-based Spatial Simulation with Netlogo, Volume 2: Advanced Concepts*. Elsevier, 2017.

Abstract: Whereas Volume 1 introduced the NetLogo platform as a means of prototyping simple models, this second volume focuses on the advanced use of NetLogo to connect both data and theories, making it ideal for the majority of scientific communities. The authors focus on agent-based modeling of spatialized phenomena with a methodological and practical orientation, demonstrating how advanced agent-based spatial simulation methods and techniques can be implemented. This book provides theoretical and conceptual backgrounds, as well as algorithmic and technical insights, including code and applets, so that readers can test and re-use most of its content.

Keywords: multi-agent based simulation, multi-level, french team

[Bardini:2017]

R. Bardini, G. Politano, A. Benso, and S. Di Carlo. Multi-level and hybrid modelling approaches for systems biology. *Computational and Structural Biotechnology Journal*, 2017.

Abstract: During the last decades, high-throughput techniques allowed for the extraction of a huge amount of data from biological systems, unveiling more of their underlying complexity. Biological systems encompass a wide range of space and time scales, functioning according to flexible hierarchies of mechanisms making an intertwined and dynamic interplay of regulations. This becomes particularly evident in processes such as ontogenesis, where regulative assets change according to process context and timing, making structural phenotype and architectural complexities emerge from a single cell, through local interactions. The information collected from biological systems are naturally organized according to the functional levels composing the system itself. In systems biology, biological information often comes from overlapping but different scientific domains, each one having its own way of representing phenomena under study. That is, the different parts of the system to be modelled may be described with different formalisms. For a model to have improved accuracy and capability for making a good knowledge base, it is good to comprise different system levels, suitably handling the relative formalisms. Models which are both multi-level and hybrid satisfy both these requirements, making a very useful tool in computational systems biology. This paper reviews some of the main contributions in this field.

Keywords: multi-agent based simulation, multi-level, hybrid model, review

[Basu:2018]

R. Basu, A. Araldo, A.P. Akkinapally, Bat H. Nahmias B., K. Basak, R. Seshadri, N. Deshmukh, N. Kumar, C.L. Azevedo, and M. Ben-Akiva. Automated mobility-on-demand vs. mass transit: A multi-modal activity-driven agent-based simulation approach. *Transportation Research Record*, 2018.

Abstract: Among the new transportation services made possible by the introduction of automated vehicles, automated mobility-on-demand (AMoD) has attracted a lot of attention from both industry and researchers. AMoD provides a service similar to taxi or ride-sharing services, while being driverless. It is expected to attract a huge fraction of travelers currently using mass transit or private vehicles and will have a disruptive effect on urban transportation. While most studies have focused on the operational efficiency of the technology itself, our work aims to investigate its impact on urban mobility. Our contribution is two-fold. First, we present a flexible AMoD modeling and simulation framework developed within a multi-modal agent-based urban simulation platform (SimMobility). The framework allows the detailed simulation and assessment of different AMoD operations together with an activity-based framework that accounts for changes in demand, such as activity participation, trip making, mode, destination, or route choice decisions. Second, we focus our attention on the role of mass transit in a futuristic urban system where AMoD is widely available. Mass transit is already challenged by current ride-sharing services, for example, Uber and Lyft, which provide comparatively better and cheaper services. This trend will plausibly be exacerbated with the introduction of AMoD, which may indirectly act as a replacement to mass transit. Our simulation results show that mass transit is irreplaceable, despite the high efficiency of AMoD, in order to avoid congestion and maintain a sustainable urban transportation system with acceptable levels of service.

Keywords: multi-agent based simulation, multi-level, multi-scale, traffic

[Bauer:2020]

R. Bauer, G. Clowry, and M. Kaiser. Creative destruction: a basic computational model of cortical layer formation. *bioRxiv*, 2020.

Abstract: One of the most characteristic properties of many vertebrate neural systems is the layered organization of different cell types. This cytoarchitecture exists in the cortex, the retina,

the hippocampus and many other parts of the central nervous system. The developmental mechanisms of neural layer formation have been subject to substantial experimental efforts. Here, we provide a general computational model for cortical layer formation in 3D physical space. We show that this multi-scale, agent-based model comprising two distinct stages of apoptosis, can account for the wide range of neuronal numbers encountered in different cortical areas and species. Our results demonstrate the phenotypic richness of a basic state diagram structure, and suggest a novel function for apoptosis. Moreover, slightly changed gene regulatory dynamics recapitulate characteristic properties observed in neurodevelopmental diseases. Overall, we propose a novel computational model using gene-type rules, exhibiting many characteristics of normal and pathological cortical development.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Bayrak:2015]

E.S. Bayrak, T. Wang, A. Cinar, and C. Undey. Computational modeling of fed-batch cell culture bioreactor: Hybrid agent-based approach. *IFAC-PapersOnLine*, 48(8):1252–1257, 2015.

Abstract: A hybrid simulation framework was proposed to predict the dynamics in cell culture bioreactors. The model is based on a multi-agent approach where CHO cells are considered as individuals (agents) following a rule base governing their behavior, while a flux balance model is embedded in agents to predict quantitative changes in nutrient and metabolite concentrations. The model takes the measured dissolved oxygen, and sodium data as input along with initial cell culture conditions and predicts the dynamics of viable cell density, viability, concentrations of glucose and lactate. The model showed good agreement with the experimental findings from our laboratory for two sets of cell culture experiments.

Keywords: multi-agent based simulation, multi-level, biology

[Beecham:2002]

J.A. Beecham, S.P. Oom, and C. Birch. Hoofs - a multiscale, agent-based simulation framework for studying the impact of grazing animals on the environment. *IEMS 2002: Integrated Assessment and Decision Support*, 2002.

Abstract: An agent based system (HOOFS) has been developed in order to examine the interactions between foraging animals and a spatially explicit description of the environment, including vegetation growth processes. HOOFS makes use of the agent-based approach to develop a model of foraging in which animal decision making processes are explicitly modelled. The model has evolved from one where foraging decisions are based on a simple biased random walk model with an information weighting parameter, through one in which animals decide between direct walking towards an object as against continuous foraging, ending with a model where memory is used. The model was used to study utilisation of heather around grass patches in a heather-grass mosaic. Model refinement using remote imaging and animal GPS data together with appropriate statistical methods shows the way forward in making a model formulation suitable for predictive modelling.

Keywords: multi-agent based simulation, multi-level, multi-scale, ecology

[Belem:2009]

M. Belem and J-P. Müller. Toward a conceptual framework for multi-points of view analysis in complex system modeling: Orea model. In *7th International Conference on Practical Applications of Agents and Multi-Agent Systems (PAAMS 2009)*, volume 55 of *Advances in Intelligent and Soft Computing*, pages 548–556. Springer, 2009.

Abstract: Complex system design requires a multi-disciplinarily approach deploying a multiplicity of point of views. The OREA (Organization-Role-Entity-Aspect) model presented in this paper proposes a conceptual framework allowing to represent a complex system in different points of view and to integrate them in order to form a coherent system. Using an Agent-Group-Role (AGR) extension, OREA allows not only to represent a system from various points of view through the roles played by entities within organizations, but also to allow various entities to play a same role in various ways through the notion of aspects. Unlike most roles based models, OREA provides a clear distinction between (1) the external properties of an entity described by the roles and (2) the internal properties described by the aspects. The OREA model increases organization reuse and the adaptability of a system. OREA model have been implemented in Mimoso and used to implement a simulator for carbon dynamics analysis at village territory level.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Belem:2009a]

M. Belem. *A conceptual model for multipoints of view analysis of complex systems. Application to the analysis of the carbon dynamics of village territories of the West African savannas*. PhD thesis, AgroParisTech, 2009.

Abstract: Modelling complex systems that cover multiple domains, for their better understanding, increasingly demands collaboration between different disciplines. However, these disciplines do not necessarily share the same points of view on the real objects of the system, and these can be complementary. In addition, the representation of such systems requires multi-scale description implying at least the local (individual), global and underlying environment. This PhD work proposes (1) a conceptual framework for complex systems analysis and representation from different points of view at the global and the local levels while taking into account the environment and (2) its application to the representation and analysis of the carbon dynamics from plot to village levels in the West African savannas (WAS). Using multi-agent system (MAS) organizations-centered approach, the Organization-Role-Entity-Aspect (OREA) meta-model has been proposed to represent a complex system from different points of view. At the global level a point of view is reified as an organization made of the roles the entities can play in the organization; at the local level the points of view decompose an entity internal structure in a set of aspects. Through the concept of role, an entity can play different roles in different organizations. Through the concept of aspects, an entity can play a role in different ways. OREA is an extension of the AgentGroup-Role meta-model where: (1) roles are not limited to agents but can be assigned to any kind of object (including the environment), (2) the decomposition does not only apply to the organizations only, but also to the entities themselves, (3) the use of the framework for knowledge representation rather than a pure software engineering paradigm is emphasized. OREA provides a framework to specify explicitly and separately the macro and the micro levels. The macro-level in OREA is specified without any assumption on the micro-level. The macro-level is relevant to the "what" while the micro-level is concerned by the "how". The environmental objects are explicitly defined in the organization structure allowing defining the perception of the environment by the entities through their roles. The OREA methodology allows specification of the structure of a system based on the identification of the scales of description and their underlying processes. The OREA model has been tested and validated through the analysis, the design and the implementation of a simulation tool: the Carbon Territory Multi-Agents Simulation (CaTMAS) model. CaTMAS assumes that a better analysis of C dynamics at the village level requires consideration of (1) social, economic, physical and biological factors, (2) the individual's actions and the multiplicity of interleaved dynamics. CaTMAS is based on the OREA model, the MAS approach, and coupling with the Century model and a Geographic Information System. The model allows a multiple-point-of-view analysis of C dynamics as organisations made of roles played by entities through various aspects. CaTMAS not only provides a framework for an explicit and realistic description of a farming system but also allows assessment of the viability of farming systems under various socioeconomic and bio-physical scenarios. The model integrates the interactions between the human's activities and the environment and some environmental feedbacks. The model has been used to analyze the impacts of climate and economic change on the one hand, and of two cropping systems on the other hand, on the C dynamics of the village territory. Future efforts on the OREA model should focus on improving the methodology and the verification and on taking into account the holonic representation. Developments on CaTMAS could include enlargement of simulations to the country scale and integration of the economic potential of the C market at the national, regional and the local levels.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Belem:2013]

M. Belem and J-P. Müller. An organizational model for multi-scale and multi-formalism simulation: Application in carbon dynamics simulation in west-african savanna. *Simulation Modelling Practice and Theory*, 32:83–98, 2013.

Abstract: This paper presents Organization-Role-Entity-Aspect (OREA) model, an organizational model for multi-scale and multi-formalism description of complex systems. OREA is based on the assumption that one issue in complex system simulation is to integrate multi-scale and multi-formalism representation. To achieve this issue, we use an approach based on organization-centered multi-agents systems and Discrete Event System Specification (DEVS) formalism. While the organizational approach allows to deal with an explicit representation of global and local levels, DEVS formalism allows integration of models of different types to describe a system perceived at different scales. Integration of OREA formalism within DEVS allows multi-formalism specification of a model both at global and local levels. In addition, this allows specification of the social structure of a complex system following DEVS formalism. In OREA, the organizational structure is specified without any assumption on entities structure. The roles description in OREA concerns only the detailed description of interactions within organization. The way that individuals conceive their system and make decision is defined through the concepts of aspect. OREA is applied in implementation of a generic model for carbon dynamics simulation in West-African

Savanna. Future works would concern the integration of organizational dynamics and holonic representation in OREA.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Bergman:2020]

D.R. Bergman, M.K. Karikomi, M. Yu, Q. Nie, and A.L. MacLean. Modeling the effects of emt-immune dynamics on epithelial cancer progression. *bioRxiv*, page 615971, 2020.

Abstract: During progression from carcinoma in situ to an invasive tumor, the immune system is engaged in complex sets of interactions with various tumor cells. Tumor cell plasticity also alters disease trajectories via epithelial-to-mesenchymal transition (EMT). Several of the same pathways that regulate EMT are involved in tumor-immune interactions, yet little is known about the mechanisms and consequences of crosstalk between these regulatory processes. Here we introduce a multiscale evolutionary model to describe tumor-immune-EMT interactions and their impact on epithelial cancer progression from in situ to invasive disease. Through in silico analyses of large patient cohorts, we find controllable regions that maximize invasion-free survival. We identify that delaying tumor progression depends crucially on properties of the mesenchymal tumor cell phenotype: its growth rate and its immune-evasiveness. Through analysis of EMT-inflammation-associated data from The Cancer Genome Atlas, we find that association with EMT significantly worsens invasion-free survival probabilities in support of our model, and we predict new genes influencing outcomes in bladder and uterine cancer, including FGF pathway members. These results offer novel means to delay disease progression by regulating properties of EMT through specific gene interactions, and demonstrate the importance of studying cancer-immune interactions in light of EMT.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Bertelle:2002]

C. Bertelle, V. Jay, S. Lerebourg, D. Olivier, and P. Tranouez. Dynamic clustering for auto-organized structures in complex fluid flows. In *ESS 2002 Conference*, 2002.

Abstract: This paper presents an original approach for the detection of auto-organized coherent structures in a fluid flow simulation. This method is based on vortex methods and multiagent systems. We then use automata to simulate the interactions between these structures and the induced evolution of their stability.

Keywords: multi-agent based simulation, multi-level, emergence detection, flow model, french team

[Beurier:2002]

G. Beurier, O. Simonin, and J. Ferber. Model and simulation of multi-level emergence. In *Proc. of 2nd IEEE International Symposium on Signal Processing and Information Technology (ISSPIT)*, pages 231–236, 2002.

Abstract: This work propose a model of multiple emergence phenomenon, which is based on a reactive multi-agent system. Each agent is defined as a minimal living-like entitie exchanging information for aggregation with others. This model is evaluated from several simulations implemented on the MadKit platform. Thus we can show and analyze different interesting properties of emergent structures such as robustness and adaptability. Finally, this study is positioned in a larger objective of understanding and designing artificial and natural complex systems.

Keywords: multi-agent based simulation, multi-level, multi-level emergence, artificial life, french team

[Beurier:2002a]

G. Beurier. Modèle de sma réactif et récursif pour l'émergence multi-niveaux. Master's thesis, Université de Montpellier II, 2002.

Keywords: multi-agent based simulation, multi-level, multi-level emergence, artificial life, in french, french team

[Beurier:2003]

G. Beurier, O. Simonin, and J. Ferber. Un modèle de système multi-agents pour l'émergence multi-niveaux. In *Actes des 11èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, volume 22 of *Technique et Science Informatiques*, pages 235–247. Hermès, 2003.

Abstract: This paper deals with the problem of multi-level emergence. For this purpose, a multi-agent system model is developped as a framework to produce multi-level emergence of structures. This model is based on reactive agents with a recursive behavior. Several simulations are then presented. To conclude, we discuss the potential of such a work for the study of multi-level emergence and the applicative possibilities for complex systems modelization.

Keywords: multi-agent based simulation, multi-level, multi-level emergence, artificial life, in french, french team

[Beurier:2007]

G. Beurier. *Codage indirect de la forme dans les systèmes multi-agents: Emergence multi-niveaux, Morphogénèse et Evolution*. PhD thesis, Université de Montpellier II, 2007.

Abstract: Since the end of the XXth century, the man-made systems increased dramatically their internal complexity. This new class of systems comes with a lot of comprehension and implementation problems. In this thesis, we aim to contribute to the design problem of artificial complex systems from the perspective of the form. The form is indeed the support and the adaptation mechanism of the global function of systems. It is thus interesting to control this parameter in order to develop artificial complex systems. We present in this thesis a constructive work on forms. Our goal is to provide behavioral models able to imprint a given form in systems composed by a huge number of autonomous interacting entities. We first justify the use of multiagent systems (MAS) as a paradigm of modeling and simulation and then we present two MAS models able to organize thanks to a given pattern. The first model implements a multi-pheromonal model to produce multi-level emergent forms. The agents react to behavioral and recursive rules and move thanks to tropisms on perceived pheromones. The second model uses morphogenetic rules to make a genetic set of parameters evolve to encode a form. Thanks to the use of tools from evolutionary computing and inspirations taken in the functioning of animal genes (segmentations and selectors) we develop MAS systems able to mutate and to evolve in order to learn specific and complex forms. Then we add some tropism functionalities to the model in order to reproduce the evolution of the form by the mean of aggregation. We finally present the TurtleKit 2 simulation platform and the modifications that we made on it and we conclude by giving some perspectives of such a work

Keywords: multi-agent based simulation, multi-level, multi-level emergence, artificial life, french team, in french

[Biedermann:2014]

D.H. Biedermann, P.M. Kielar, O. Handel, and A. Borrmann. Towards transitum: A generic framework for multiscale coupling of pedestrian simulation models based on transition zones. *Transportation Research Procedia*, 2:495–500, 2014.

Abstract: Existing pedestrian dynamics models differ in computational effort and their ability to authentically describe human movement behaviour. Hybrid approaches combine different models to speed up simulation time and to improve the results of the simulation. Current hybrid approaches can only combine a specific set of models. It is not possible to independently change the coupled models from the hybrid approach. Furthermore, transition of pedestrians between the different models is only possible at specific entry points. TransiTUM overcomes these issues and can combine any model if provided a certain set of parameters, which are common in pedestrian dynamics (e.g., pedestrians' positions, velocities). In this paper, the coupling of mesoscopic and microscopic scales is presented.

Keywords: multi-agent based simulation, multi-level, hybrid model, pedestrian flow modeling, flow model

[Biggs:2013]

M.B. Biggs and J.A. Papin. Novel multiscale modeling tool applied to pseudomonas aeruginosa biofilm formation. *PloS one*, 8(10):e78011, 2013.

Abstract: Multiscale modeling is used to represent biological systems with increasing frequency and success. Multiscale models are often hybrids of different modeling frameworks and programming languages. We present the MATLAB-NetLogo extension (MatNet) as a novel tool for multiscale modeling. We demonstrate the utility of the tool with a multiscale model of Pseudomonas aeruginosa biofilm formation that incorporates both an agent-based model (ABM) and constraint-based metabolic modeling. The hybrid model correctly recapitulates oxygen-limited biofilm metabolic activity and predicts increased growth rate via anaerobic respiration with the addition of nitrate to the growth media. In addition, a genome-wide survey of metabolic mutants and biofilm formation exemplifies the powerful analyses that are enabled by this computational modeling tool.

Keywords: multi-agent based simulation, multi-level, biology

[Bijak:2013]

J. Bijak, J. Hilton, E. Silverman, and V.D. Cao. Reforging the wedding ring: Exploring a semi-artificial model of population for the united kingdom with gaussian process emulators. *Demographic Research*, 29:729–766, 2013.

Abstract: Background: We extend the "Wedding Ring" agent-based model of marriage formation to include some empirical information on the natural population change for the United Kingdom together with behavioural explanations that drive the observed nuptiality trends. Objective: We propose a method to explore statistical properties of agent-based demographic models. By coupling rule-based explanations driving the agent-based model with observed data we wish to bring agent-based modelling and demographic analysis closer together. Methods: We present a Semi-Artificial Model of Population, which aims to bridge demographic micro-simulation and agent-based traditions. We then utilise a Gaussian process emulator - a statistical model of the base model - to analyse the impact of selected model parameters on two key model outputs: population size and share of married agents. A sensitivity analysis is attempted, aiming to assess the relative importance of different inputs. Results: The resulting multi-state model of population dynamics has enhanced predictive capacity as compared to the original specification of the Wedding Ring, but there are some trade-offs between the outputs considered. The sensitivity analysis allows identification of the most important parameters in the modelled marriage formation process. Conclusions: The proposed methods allow for generating coherent, multi-level agent-based scenarios aligned with some aspects of empirical demographic reality. Emulators permit a statistical analysis of their properties and help select plausible parameter values. Comments: Given non-linearities in agent-based models such as the Wedding Ring, and the presence of feedback loops, the uncertainty in the model may not be directly computable by using traditional statistical methods. The use of statistical emulators offers a way forward.

Keywords: multi-agent based simulation, multi-level, social simulation

[Binder:2012]

B. Binder, J. Ross, and M. Simpson. A hybrid model for studying spatial aspects of infectious diseases. *The ANZIAM Journal*, 54(1-2):37-49, 2012.

Abstract: We consider a hybrid model, created by coupling a continuum and an agent-based model of infectious disease. The framework of the hybrid model provides a mechanism to study the spread of infection at both the individual and population levels. This approach captures the stochastic spatial heterogeneity at the individual level, which is directly related to deterministic population level properties. This facilitates the study of spatial aspects of the epidemic process. A spatial analysis, involving counting the number of infectious agents in equally sized bins, reveals when the spatial domain is nonhomogeneous.

Keywords: multi-agent based simulation, multi-level, epidemiology

[Bittig:2010]

A.T. Bittig and A.M. Uhrmacher. Spatial modeling in cell biology at multiple levels. In *Winter Simulation Conference (WSC), Proceedings of the 2010*, pages 608-619. IEEE, 2010.

Abstract: Most modeling and simulation approaches applied in cell biology assume a homogeneous distribution of particles in space, although experimental studies reveal the importance of space to understand the dynamics of cells. There are already numerous spatial approaches focusing on the simulation of cells. Recently, they have been complemented by a set of spatial modeling languages whose operational semantics are tied partly to existing simulation algorithms. These modeling languages allow an explicit description of spatial phenomena, and facilitate analysis of the temporal spatial dynamics of cells by a clear separation between model, semantics, and simulator. With the supported level of abstraction, each of those offers a different perception of the spatial phenomena under study. In this paper, we give an overview of existing modeling formalisms and discuss some ways of combining approaches to tackle the problem the computational costs induced by spatial dynamics.

Keywords: multi-agent based simulation, multi-level, biology

[Blanchart:2009]

E. Blanchart, N. Marilleau, J.L. Chotte, A. Drogoul, E. Perrier, and C. Cambier. SWORM: an agent-based model to simulate the effect of earthworms on soil structure. *European Journal of Soil Science*, 60(1):13-21, 2009.

Abstract: Soil structure can be defined as the spatial organization of solid mineral and organic particles, and pore space. It is of great importance for soil functioning as it drives ecosystem functions (carbon sequestration, emission of greenhouse gases, nutrient cycling, primary productivity, etc.). Soil structure results from biotic and abiotic factors. Among biotic factors, numerous studies have shown the importance of organic matter, microorganisms, roots and invertebrates. Earthworms are known to play a key role in soil structure formation and maintenance through a continuous production of biogenic structures (casts and burrows). As far as we know, no models describe or quantify the effect of soil invertebrates on soil aggregation and porosity. It is a

challenge to describe the physical soil environment for purposes of modelling because a soil is a multi-scale heterogeneous, three-dimensional and dynamic environment. An approach based on fractal theory (often used in soil sciences) was chosen to model such a real complex environment; it was integrated into a multi-agent system (MAS), which allows us to simulate agents (e.g. earthworms) situated in a virtual world (e.g. soil). It is a bottom-up approach that allows us to describe a system at a micro level (e.g. earthworms and their local soil environment) in order to observe, during simulations, macroscopic changes (e.g. soil structure evolution, organic matter dynamics, and microbial functions). In this paper we describe the SWORM (for ‘Simulated Worms’) model and the simulator, and present the results of the simulation applied to a case study. The effect of compacting and decompacting earthworm species on the structure of humid savanna soil at Lamto in Côte d’Ivoire has been widely studied. Quantitative and graphical outputs (e.g. thin sections of the virtual soil) indicate that the simulator was able to reproduce the effects of both compacting and decompacting species. Different ways to improve the model are discussed.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Bouchnita:2017]

A. Bouchnita, G. Bocharov, A. Meyerhans, and V. Volpert. Towards a multiscale model of acute hiv infection. *Computation*, 5(1):6, 2017.

Abstract: Human Immunodeficiency Virus (HIV) infection of humans represents a complex biological system and a great challenge to public health. Novel approaches for the analysis and prediction of the infection dynamics based on a multi-scale integration of virus ontogeny and immune reactions are needed to deal with the systems’ complexity. The aim of our study is: (1) to formulate a multi-scale mathematical model of HIV infection; (2) to implement the model computationally following a hybrid approach; and (3) to calibrate the model by estimating the parameter values enabling one to reproduce the “standard” observed dynamics of HIV infection in blood during the acute phase of primary infection. The modeling approach integrates the processes of infection spread and immune responses in Lymph Nodes (LN) to that observed in blood. The spatio-temporal population dynamics of T lymphocytes in LN in response to HIV infection is governed by equations linking an intracellular regulation of the lymphocyte fate by intercellular cytokine fields. We describe the balance of proliferation, differentiation and death at a single cell level as a consequence of gene activation via multiple signaling pathways activated by IL-2, IFN α and FasL. Distinct activation thresholds are used in the model to relate different modes of cellular responses to the hierarchy of the relative levels of the cytokines. We specify a reference set of model parameter values for the fundamental processes in lymph nodes that ensures a reasonable agreement with viral load and CD4+ T cell dynamics in blood.

Keywords: multi-agent based simulation, multi-level, epidemiology

[Bouchnita:2019]

A. Bouchnita, A. Hellander, and A. Hellander. A 3d multiscale model to explore the role of egfr overexpression in tumourigenesis. *Bulletin of Mathematical Biology*, 2019.

Abstract: The epidermal growth factor receptor (EGFR) signalling cascade is one of the main pathways that regulate the survival and division of mammalian cells. It is also one of the most altered transduction pathways in cancer. Acquired mutations in the EGFR/ERK pathway can cause the overexpression of EGFR on the surface of the cell, while others downregulate the inactivation of switched on intracellular proteins such as Ras and Raf. This upregulates the activity of ERK and promotes cell division. We develop a 3D multiscale model to explore the role of EGFR overexpression on tumour initiation. In this model, cells are described as individual objects that move, interact, divide, proliferate, and die by apoptosis. We use Brownian Dynamics to describe the extracellular and intracellular regulations of cells as well as the spatial and stochastic effects influencing them. The fate of each cell depends on the number of active transcription factors in the nucleus. We use numerical simulations to investigate the individual and combined effects of mutations on the intracellular regulation of individual cells. Next, we show that the distance between active receptors increase the level of EGFR/ERK signalling. We demonstrate the usefulness of the model by quantifying the impact of mutational alterations in the EGFR/ERK pathway on the growth rate of in silico tumours.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Bouha:2015]

N. Bouha, G. Morvan, H. Abouaïssa, and Y. Kubera. A first step towards dynamic hybrid traffic modeling. In *Proc. of 29th European Conf. on modelling and simulation (ECMS)*, pages 64–70, 2015.

Abstract: Hybrid traffic modeling and simulation provide an important way to represent and evaluate large-scale traffic networks at different levels of details. The first level, called "microscopic" allows the description of individual vehicles and their interactions as well as the study

of driver's individual behavior. The second, based on the analogy with fluidic dynamic, is the "macroscopic" one and provides an efficient way to represent traffic flow behavior in large traffic infrastructures, using three aggregated variables: traffic density, mean speed and traffic volume. An intermediate level called "mesoscopic" considers a group of vehicles sharing common properties such as a same origin and destination. The work conducted in this paper presents a first step allowing simulation of wide area traffic network on the basis of dynamic hybrid modeling, where the representation associated to a network section can change at runtime. The proposed approach is implemented in a simulation platform, called Jam-free.

Keywords: multi-agent based simulation, multi-level, traffic, french team

[Boulet:2020]

X. Boulet, M. Zargayouna, G. Scemama, and F. Leurent. Coupling multi-agent and macroscopic simulators of traffic. In *Agents and Multi-agent Systems: Technologies and Applications 2019*, volume 148 of *SIST*, pages 323–332. Springer, 2020.

Abstract: Traffic simulations exist in multiple scales and each of these scales presents some advantages and is useful in certain contexts. Usually, multi-agent simulations use more detailed models and give more precise results than macroscopic models but their high calculation cost does not allow them to simulate very big areas such as an entire region. To overcome these limitations, multiscale simulations emerged with the coupling of two or more simulations of different scales. This paper presents a generic solution to combine a macroscopic simulator working on a large area, which contains a smaller area simulated by a multi-agent simulator. The main challenge is to assure the coherence between both simulators on the smallest area since it is simulated by both simulators at the same time. We first highlight the issues to tackle and the problems to solve when coupling two existing simulators, then we propose solutions for the coupling, and finally evaluate them on an example scenario.

Keywords: multi-agent based simulation, multi-level, hybrid model, traffic

[Bourrel:2002]

E. Bourrel and V. Henn. Mixing micro and macro representations of traffic flow: a first theoretical step. In *Proceedings of the 9th Meeting of the Euro Working Group on Transportation*, 2002.

Keywords: hybrid model, traffic, multi-agent based simulation, multi-level, french team

[Bourrel:2003]

E. Bourrel and J.P. Lesort. Mixing micro and macro representations of traffic flow: a hybrid model based on the LWR theory. *82th Annual Meeting of the Transportation Research Board*, 2003.

Abstract: Hybrid traffic flow models, coupling a microscopic (vehicle based) and a macroscopic (flow based) representations of traffic flow may be a useful tool to better understand the relationships between the various types of representation. They can also be a basis for implementing various model extensions, which may be easier using one type of representation or the other. The hybrid model presented here combines a flow and a vehicular representations of the same model, which is the classical Lighthill-Witham-Richards model. The use of a simple and unique model makes it possible to focus on the specific problems raised by translating boundary conditions from vehicular to flow formulation and conversely. This translation is made in order to ensure the conservation of flow, a proper transmission of the information both downstream and upstream, and to minimize the perturbations induced by the transitions between a continuous and a discrete representations of flow. The resulting model is shown to have good properties, particularly concerning congestion propagation and flow smoothing at the interfaces between the two models.

Keywords: hybrid model, traffic, multi-level, multi-agent based simulation, french team

[Bourrel:2003a]

E. Bourrel. *Modélisation dynamique de l'écoulement du trafic routier : du macroscopique au microscopique*. PhD thesis, Institut National des Sciences Appliquées de Lyon, 2003.

Abstract: Pour répondre aux attentes des exploitants de réseaux routiers, de nombreux modèles d'écoulement dynamique du trafic ont été développés. Ces modèles sont généralement classés en deux grandes catégories : les modèles microscopiques et les modèles macroscopiques. L'objet de cette thèse est d'approfondir ces problèmes d'échelles liés à ces modèles à travers le développement d'un modèle hybride d'écoulement, couplage entre un modèle microscopique et un modèle macroscopique. L'intérêt d'un tel modèle est de permettre d'adapter le modèle d'écoulement aux besoins de modélisation des différents éléments du réseau. Nous proposons dans cette thèse un cadre théorique général de la modélisation hybride, puis nous construisons un modèle hybride fondé sur un modèle macroscopique du premier ordre. La particularité du modèle proposé est qu'il permet de prendre en compte la diversité de comportement des véhicules dans la partie microscopique en introduisant des distributions sur certains paramètres.

Keywords: hybrid model, traffic, multi-agent based simulation, multi-level, in french, french team

[Bravo:2020]

R.R. Bravo, E. Baratchart, J. West, R.O. Schenck, A.K. Miller, J. Gallaher, C.D. Gatenbee, D. Basanta, M. Robertson-Tessi, and A.R.A. Anderson. Hybrid automata library: A flexible platform for hybrid modeling with real-time visualization. *PLOS Computational Biology*, 16(3):e1007635, 2020.

Abstract: The Hybrid Automata Library (HAL) is a Java Library developed for use in mathematical oncology modeling. It is made of simple, efficient, generic components that can be used to model complex spatial systems. HAL's components can broadly be classified into: on- and off-lattice agent containers, finite difference diffusion fields, a GUI building system, and additional tools and utilities for computation and data collection. These components are designed to operate independently and are standardized to make them easy to interface with one another. As a demonstration of how modeling can be simplified using our approach, we have included a complete example of a hybrid model (a spatial model with interacting agent-based and PDE components). HAL is a useful asset for researchers who wish to build performant 1D, 2D and 3D hybrid models in Java, while not starting entirely from scratch. It is available on GitHub at <https://github.com/MathOnco/HAL> under the MIT License. HAL requires the Java JDK version 1.8 or later to compile and run the source code.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology, cancer modeling

[Brown:2011]

M. Brown, E. Bowring, S. Epstein, M. Jhaveri, R. Maheswaran, P. Mallick, S. Mumenthaler, M. Povinelli, and M. Tambe. Applying multi-agent techniques to cancer modeling. In *Sixth Annual Workshop on Multiagent Sequential Decision Making in Uncertain Domains (MSDM-2011)*, 2011.

Abstract: Each year, cancer is responsible for 13% of all deaths worldwide. In the United States, that percentage increases to 25%, translating to an estimated 569,490 deaths in 2010 [1]. Despite significant advances in the fight against cancer, these statistics make clear the need for additional research into new treatments. As such, there has been growing interest in the use of computer simulations as a tool to aid cancer researchers. We propose an innovative multi-agent approach in which healthy cells and cancerous cells are modeled as opposing teams of agents using a decentralized Markov decision process (DEC-MDP). We then describe changes made to traditional DEC-MDP algorithms in order to better handle the complexity and scale of our domain. We conclude by presenting and analyzing preliminary simulation results. This paper is intended to introduce the cancer modeling domain to the multi-agent community with the hope of fostering a discussion about the opportunities and challenges it presents. Given the complexity of the domain, we do not claim our approach to be a definitive solution but rather a first step toward the larger goal of creating realistic simulations of cancer.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Budde:2017]

K. Budde, T. Warnke, A.M. Uhrmacher, E. Schätz, J. Starke, and F. Haack. Exploiting equation-free analysis for multi-level, agent-based models in cell biology. In *Winter Simulation Conference (WSC)*, pages 4564–4565, 2017.

Abstract: Multi-level modeling approaches have been successfully applied in systems biology to model complex systems with different levels of organization. They allow for straightforwardly integrating upward and downward causation as well as compartmental dynamics. This makes multi-level models powerful, but also expensive to simulate. Consequently, the effort required for comprehensive simulation studies with complex multi-level models is often prohibitive. One way to decrease the demand for simulations is to apply analysis methods. However, most approaches focus on differential equations models and cannot handle models with stochasticity or dynamical nesting. Among the new approaches that allow for analysis of complex systems is equation-free analysis, which has been applied to perform coarse level bifurcation analysis in various areas. We present the integration of an equation-free method into the simulation language Simulation Experiment Specification on a Scala Layer (SESSL) to analyze bi-or multistability of biochemical models, defined in the multi-level modeling language ML-Rules, and its role in cell fate selection.

Keywords: multi-agent based simulation, multi-level, biology

[Burghout:2005]

W. Burghout, H.N. Koutsopoulos, and I. Andreasson. Hybrid mesoscopic-microscopic traffic simulation. *Transportation Research Record: Journal of the Transportation Research Board*, 1934(1):218–255, 2005.

Abstract: Traffic simulation is an important tool for modeling the operations of dynamic traffic systems. Although microscopic simulation models provide a detailed representation of the traffic process, macroscopic and mesoscopic models capture the traffic dynamics of large networks in less detail but without the problems of application and calibration of microscopic models. This paper presents a hybrid mesoscopic-microscopic model that applies microscopic simulation to areas of specific interest while simulating a large surrounding network in less detail with a mesoscopic model. The requirements that are important for a hybrid model to be consistent across the models at different levels of detail are identified. These requirements vary from the network and route choice consistency to the consistency of the traffic dynamics at the boundaries of the microscopic and mesoscopic submodels. An integration framework that satisfies these requirements is proposed. A prototype hybrid model is used to demonstrate the application of the integration framework and the solution of the various integration issues. The hybrid model integrates MITSIMLab, a microscopic traffic simulation model, and Mezzo, a newly developed mesoscopic model. The hybrid model is applied in two case studies. The results are promising and support both the proposed architecture and the importance of integrating microscopic and mesoscopic models

Keywords: multi-level, hybrid model, multi-agent based simulation, traffic, flow model

[Butner:2016]

J.D. Butner, Y-L. Chuang, E. Simbawa, A.S. Al-Fhaid, S.R. Mahmoud, V. Cristini, and Z. Wang. A hybrid agent-based model of the developing mammary terminal end bud. *Journal of Theoretical Biology*, 407:259–270, 2016.

Abstract: Mammary gland ductal elongation is spearheaded by terminal end buds (TEBs), where populations of highly proliferative cells are maintained throughout post-pubertal organogenesis in virgin mice until the mammary fat pad is filled by a mature ductal tree. We have developed a hybrid multiscale agent-based model to study how cellular differentiation pathways, cellular proliferation capacity, and endocrine and paracrine signaling play a role during development of the mammary gland. A simplified cellular phenotypic hierarchy that includes stem, progenitor, and fully differentiated cells within the TEB was implemented. Model analysis finds that mammary gland development was highly sensitive to proliferation events within the TEB, with progenitors likely undergoing 2-3 proliferation cycles before transitioning to a non-proliferative phenotype, and this result is in agreement with our previous experimental work. Endocrine and paracrine signaling were found to provide reliable ductal elongation rate regulation, while variations in the probability a new daughter cell will be of a proliferative phenotype were seen to have minimal effects on ductal elongation rates. Moreover, the distribution of cellular phenotypes within the TEB was highly heterogeneous, demonstrating significant allowable plasticity in possible phenotypic distributions while maintaining biologically relevant growth behavior. Finally, simulation results indicate ductal elongation rates due to cellular proliferation within the TEB may have a greater sensitivity to upstream endocrine signaling than endothelial to stromal paracrine signaling within the TEB. This model provides a useful tool to gain quantitative insights into cellular population dynamics and the effects of endocrine and paracrine signaling within the pubertal terminal end bud.

Keywords: multi-agent based simulation, multi-level, biology

[Butner:2016a]

J.D. Butner, V. Cristini, and Z. Wang. Development of a three dimensional, lattice-free multiscale model of the mammary terminal end bud. In *Proc. of 38th Annual Int. Conf. of the Engineering in Medicine and Biology Society (EMBC)*, pages 6134–6137, 2016.

Abstract: The terminal end bud (TEB) is a bulbous structure composed of highly proliferative cells that is responsible for mammary gland development during the pubertal stage. This is a highly organized process, involving cellular differentiation hierarchies regulated by endocrine and paracrine signaling. Here, we present development of a lattice-free, three dimensional multiscale agent based model of the TEB to study the effects of cellular phenotypic hierarchies, endocrine and paracrine signaling, and proliferation demographics on pubertal mammary gland development. Cells in the TEB experience complex physical interaction during the active growth involved in pubertal ductal elongation, which we represent mathematically based on the physical forces involved in cell-cell and cell-microenvironment interactions. We observe that maximum ductal elongation rates are achievable due to each progenitive phenotype cell only undergoing a couple proliferation cycles before losing the progenitive capability, and that molecular signaling is necessary to restrict ductal elongation to biologically relevant rates. Cellular proliferation and growth is sufficient to achieve these elongation rates in the absence of other cellular behaviors such as migration or conformational changes. This model serves as a valuable tool to gain insights into the cell population dynamics of mammary gland development, and can serve as a foundation

to study the early stages of breast cancer development based on endocrine-mediated phenotypic population shifts.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Butner:2017]

J.D. Butner, V. Cristini, and Z. Wang. Development of a three dimensional, multiscale agent-based model of ductal carcinoma in situ. In *Proc. of Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual Int. Conf. of the IEEE*, pages 86–89, 2017.

Abstract: Ductal carcinoma in situ (DCIS) is the most commonly diagnosed form of non-invasive breast cancer, constituting 20% of all new breast cancer cases in the United States. Although non-invasive, DCIS is usually treated surgically through resection. Interestingly, long-term survival studies have shown that patient survival rates are not significantly impacted by the type or resection, indicating that increased breast conservation through minimized surgical resection may indeed be possible. This requires a greater understanding of disease development, so that clinicians may more accurately determine surgical margins which minimize patient impact while maintaining survival rates. To this end, we have developed a three-dimensional, lattice-free multiscale agent based model of DCIS designed to help quantify ductal invasion rates, in order to allow clinicians to better estimate disease age and extent of invasion, and to predict surgical margins based on parameters obtainable from non-invasive testing (i.e., mammography). Here, we present the model development to date, and discuss some preliminary results.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Butner:2017a]

J.D. Butner. *A multiscale modeling study of the mammary gland*. PhD thesis, University of New Mexico, 2017.

Abstract: Multiscale, hybrid computer modeling has emerged as a valuable tool in the fields of computational systems biology and mathematical oncology. In this work, we present an overview of the motivations for, and development and implementation of, three hybrid multiscale models of the mammary gland system and early stage ductal carcinoma in situ (DCIS) in the gland. Pubertal mammary gland development was described first using a two-dimensional, lattice-based hybrid agent-based model description of the mammary terminal end bud (TEB), and then with a three-dimensional lattice-free TEB model. Both models implement a discrete, agent-based description of the cell scale, and a continuum, finite element method description of tissue scale spatiotemporal molecular profiles, which are explicitly linked into a hybrid model. This lattice-free pubertal development TEB model was then transitioned into a post-menopausal early stage DCIS model, used for study of the phenotypic dynamics and molecular signaling disruptions involved in development of the DCIS tumor mass. Both TEB and DCIS models implemented simplified, literature-based cellular phenotypic developmental hierarchies and endocrine and paracrine signaling pathways. All models provided valuable insights into the effects of these aspects on the development of both the healthy gland and the pre-invasive DCIS cancer state, and results from model outputs were found to be within literature supported ranges. Cells of both healthy and cancerous phenotypes were found to be sensitive to changes in molecular signaling intensities and phenotypic hierarchies, which played an important part in overall development in both cases, with all cases demonstrating a greater effect of upstream estrogen paracrine signaling relative to the downstream AREG-FGF epithelial to stromal pathway also tested. Here, we provide detailed descriptions of these studies and results, as well as other useful discoveries, and also an overview of the modeling approaches, techniques, and rationale for their specific designs and implementations.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Butner:2018]

J-D. Butner, V. Cristiani, and Z. Wang. Understanding ductal carcinoma in situ invasion using a multiscale agent-based model. In *40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2018.

Abstract: Ductal carcinoma in situ (DCIS) is commonly treated clinically through surgical resection. Although surgical options exist for resection, it is unclear which is optimal to reduce the likelihood of future invasive disease. This is further complicated by challenges in determining correct surgical margins from disease diagnostics, with mammographic imaging misidentifying surgical margins by as much as 2 cm vs. histological examination. We have implemented a three-dimensional, hybrid multiscale model of DCIS to study disease initiation and progression. In order to shed new light on current biological questions and clinical challenges surrounding the disease, we present here an improved version of this model, with more biologically relevant molecular signaling pathways, cell phenotype hierarchies, and duct architecture variation. In particular,

a cell necrosis, lysis and calcification pathway has been incorporated into the model to help better understand the relationship between diagnostic imaging and the true extent of disease invasion. We observe that deficiencies in availability of molecular signaling molecules that upregulate cell proliferation may be overcome by dynamic shifts in phenotypic distributions within the disease mass. Hypoxia, necrosis, and calcification together functioned as a hypoxia relief mechanism, and were observed to maintain a consistent distance between the DCIS leading edge and the site of necrosis onset, providing insights for improving surgical margins.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Cacciagrano:2010]

D. Cacciagrano, F. Corradini, and E. Merelli. Bone remodelling: A complex automata-based model running in bioshape. *Cellular Automata*, pages 116–127, 2010.

Abstract: Bone remodelling, as many biological phenomena, is inherently multi-scale, i.e. it is characterised by interactions involving different scales at the same time. At this aim, we exploit the Complex Automata paradigm and the BioShape 3D spatial simulator respectively (i) for describing the bone remodelling process in terms of a 2-scale aggregation of uniform Cellular Automata coupled by a well-established composition pattern, and (ii) for executing them in a uniform and integrated way in terms of shapes equipped with perception and movement capabilities. On the one hand, the proposed model confirms the high expressiveness degree of Complex Automata to describe multi-scale phenomena. On the other hand, the possibility of executing such a model in BioShape highlights the existence of a general mapping - from Complex Automata into the BioShape native modelling paradigm - also enforced by the fact that both approaches result to be suitable for handling different scales in a uniform way, for including spatial information and for bypassing inter-scale homogenization problems.

Keywords: cellular automata, multi-agent based simulation, multi-level, biology

[Caillou:2012]

P. Caillou and J. Gil-Quijano. Simanalyzer : Automated description of groups dynamics in agent-based simulations. In *Proc. of 11th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS 2012)*, pages 1353–1354, 2012.

Abstract: Multi agent based simulations (MABS) have been successfully exploited to model complex systems in different areas. Nevertheless a pitfall of MABS is that their complexity increases with the number of agents and the number of different types of behaviours considered in the model. For average and large systems it is impossible to validate the trajectories of single agents in a simulation. The classical validation approaches, where only global indicators are evaluated, are too simplistic to give enough confidence on the simulation's model. It is then necessary to introduce intermediate levels of validation. In this paper we propose the use of data clustering and automated characterization of clusters in order to build, describe and follow the evolution of groups of agents in simulations. The description of clusters is used to generate profiles of agents that are reintroduced in simulations in order to study the stability of the descriptions and structures of clusters over several simulations and decide their capability to describe the modelled phenomena. These tools provides the modeller with an intermediate point of view on the evolution of the model. They are flexible enough to be applied both offline and online, and we illustrate it with both a NetLogo and a CSV-simulation log example.

Keywords: multi-agent based simulation, multi-level, emergence detection, french team

[Caillou:2012a]

P. Caillou and J. Gil-Quijano. Description automatique de dynamiques de groupes dans des simulations à base d'agents. In *Actes des 20èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, Honfleur, France, October 17–19 2012.

Abstract: Les simulations à base d'agents (MABS) ont été utilisées avec succès pour modéliser des systèmes complexes dans de nombreux domaines. Néanmoins, un problème des MABS est que leur complexité augmente avec le nombre d'agents et de types de comportements différents considérés dans les modèles. Pour des systèmes de taille moyenne à grande, il est impossible de valider, voire même d'observer simplement les trajectoires des agents individuels lors d'une simulation. Les approches de validation classiques, où seuls des indicateurs globaux sont calculés, sont trop simplistes pour permettre d'évaluer le modèle de simulation avec un degré de confiance suffisant. Il est alors nécessaire d'introduire des niveaux intermédiaires de validation et d'observation. Dans cet article, nous proposons l'utilisation de la classification automatique de données (clustering) combinée à la caractérisation automatisée de clusters pour construire, décrire et suivre l'évolution de groupes d'agents en simulation. La description de clusters est utilisée pour générer des profils d'agents qui sont réintroduits dans les simulations avec l'objectif d'étudier la stabilité des descriptions et des structures des clusters sur plusieurs simulations et de décider de leur capacité à décrire

les phénomènes modélisés. Ces outils permettent au modélisateur d'avoir un point de vue intermédiaire sur l'évolution du modèle. Ils sont suffisamment flexibles pour être appliqués à la fois hors ligne et en ligne comme le montrent les analyses réalisées à la fois sur des simulations Netlogo et sur des logs de simulations.

Keywords: multi-agent based simulation, multi-level, emergence detection, in french, french team

[Caillou:2012b]

P. Caillou, J. Gil-Quijano, and X. Zhou. Automated observation of multi-agent based simulations: a statistical analysis approach. *Studia Informatica Universalis*, 10(3):62–86, 2012.

Abstract: Multi-agent based simulations (MABS) have been successfully used to model complex systems in different areas. Nevertheless a pitfall of MABS is that their complexity increases with the number of agents and the number of different types of behavior considered in the model. For average and large systems, it is impossible to validate the trajectories of single agents in a simulation. The classical validation approaches, where only global indicators are evaluated, are too simplistic to give enough confidence in the simulation. It is then necessary to introduce intermediate levels of validation. In this paper we propose the use of data clustering and automated characterization of clusters in order to build, describe and follow the evolution of groups of agents in simulations. These tools provides the modeler with an intermediate point of view on the evolution of the model. Those tools are flexible enough to allow the modeler to define the groups level of abstraction (i.e. the distance between the groups level and the agents level) and the underlying hypotheses of groups formation. We give an online application on a simple NetLogo library model (Bank Reserves) and an offline log application on a more complex Economic Market Simulation.

Keywords: multi-agent based simulation, multi-level, emergence detection, french team

[Caillou:2014]

P. Caillou and J. Gil-Quijano. Description automatique de dynamiques de groupes dans des simulations à base d'agents. *RIA*, 27(6):739–764, 2014.

Abstract: Les simulations à base d'agents (MABS) ont été utilisées avec succès pour modéliser des systèmes complexes dans de nombreux domaines. Néanmoins, un problème des MABS est que leur complexité augmente avec le nombre d'agents et de types de comportements différents considérés dans les modèles. Pour des systèmes de taille moyenne à grande, il est impossible de valider, voire même d'observer simplement les trajectoires des agents individuels lors d'une simulation. Les approches de validation classiques, où seuls des indicateurs globaux sont calculés, sont trop simplistes pour permettre d'évaluer le modèle de simulation avec un degré de confiance suffisant. Il est alors nécessaire d'introduire des niveaux intermédiaires de validation et d'observation. Dans cet article, nous proposons l'utilisation de la classification automatique de données (clustering) combinée à la caractérisation automatisée de clusters pour construire, décrire et suivre l'évolution de groupes d'agents en simulation. La description de clusters est utilisée pour générer des profils d'agents qui sont réintroduits dans les simulations avec l'objectif d'étudier la stabilité des descriptions et des structures des clusters sur plusieurs simulations et de décider de leur capacité à décrire les phénomènes modélisés. Ces outils permettent au modélisateur d'avoir un point de vue intermédiaire sur l'évolution du modèle. Ils sont suffisamment flexibles pour être appliqués à la fois hors ligne et en ligne comme le montrent les analyses réalisées à la fois sur des simulations Netlogo et sur des logs de simulations.

Keywords: multi-agent based simulation, multi-level, emergence detection, in french, french team

[Camargo:2020]

C.Q. Camargo. New methods for the steady-state analysis of complex agent-based models. *Frontiers in Physics*, 8:103, 2020.

Abstract: Among all tools used to understand collective human behavior, few tools have been as successful as agent-based models (ABMs). These models have been particularly effective at describing emergent social behavior, such as spatial segregation in neighborhoods or opinion polarization on social networks. ABMs are particularly common in the study of opinion and belief dynamics, being used by fields ranging from anthropology to statistical physics. These models, much like the social systems they describe, often do not have unique output variables, scales, or clear order parameters. This lack of clearly measurable emergent behavior makes such complex ABMs difficult to study, ultimately limiting their application to cases of empirical interest. In this paper, we introduce a series of approaches to analyze complex multidimensional ABMs, drawing from information theory and cluster analysis. We use these approaches to explore a multi-level agent-based model of ideological alignment introduced by Banisch and Olbrisch to extend Mäs and Flache's argument communication theory of bi-polarization. We use the tools introduced

here to perform a thorough analysis of the model for small system sizes, identifying the convergence toward steady-state behavior, and describing the full spectrum of steady-state distributions produced by this model. Finally, we show how the approach we introduced can be easily adapted for larger implementations, as well as for other complex agent-based models of social behavior.

Keywords: multi-agent based simulation, multi-level, social simulation

[Camus:2012]

B. Camus, J. Siebert, C. Bourjot, and V. Chevrier. Modélisation multi-niveaux dans AA4MM. In *Actes des 20èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 43–52. Cépaduès, 2012.

Abstract: In this article, we propose to represent a multi-level phenomenon as a set of interacting models. This perspective makes the levels of representation and their relationships explicit. To deal with coherence, causality and coordination issues between models, we rely on AA4MM, a metamodel dedicated to such a representation. We illustrate our proposal and we show the interest of our approach on a flocking phenomenon.

Keywords: multi-agent based simulation, multi-level, meta-model, in french, french team

[Camus:2013]

B. Camus, C. Bourjot, and V. Chevrier. Multi-level modeling as a society of interacting models. In *Spring Simulation Multi-Conf., Agent-Directed Simulation Symp.*, volume 1, pages 15–22, 2013.

Abstract: We propose to consider a multi-level representation from a multi-modeling point of view. We define a framework to better specify the concepts used in multi-level modeling and their relationships. This framework is implemented through the AA4MM meta-model, which benefits from a middleware layer. This meta-model uses the multi-agent paradigm to consider a multi-model as a society of interacting models. We extend this meta-model to consider multi-level modeling and present a proof of concept of a collective motion example where we show the ability of this approach to rapidly change from one pattern of interaction to another one by reusing some of the meta-model's components.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Camus:2015]

B. Camus, C. Bourjot, and V. Chevrier. Combining devs with multi-agent concepts to design and simulate multi-models of complex systems. In *Proc. of the Symp. on Theory of Modeling & Simulation – DEVS Integrative M&S Symp.*, 2015.

Abstract: We are interested in the multi-modeling and simulation of complex systems, that is representing a complex system as a set of interacting models and simulating it with a co-simulation approach. Representing and simulating a complex system multi-model requires to integrate heterogeneity at several levels (representations, formalisms, simulation software, models' interactions. . .). In this article, we present our approach that consists of combining the Discrete Event System Specification (DEVS) formalism and multi-agent concepts in order to achieve these requirements. The use of the DEVS formalism enables a rigorous integration of models described with heterogeneous formalisms and a rigorous simulation protocol. Multi-agent concepts ease the description of multi-perspective integration and the reuse of existing heterogeneous simulators. We detail the combination of both in the Agent & Artifact for Multi-Modeling (AA4MM) approach and illustrate its use in a proof of concept.

Keywords: multi-agent based simulation, DEVS, multi-level, french team

[Camus:2015a]

B. Camus, C. Bourjot, and V. Chevrier. Considering a multi-level model as a society of interacting models: Application to a collective motion example. *Journal of Artificial Societies & Social Simulation*, 18(3), 2015.

Abstract: As they involve relationships between interacting individuals and groups, social systems can be described at different levels of resolution. In a number of modeling cases, only one of these levels is explicitly represented. In order to study phenomena where both individual and collective representations are needed, multi-level modeling is a good approach as it explicitly represents these different levels. We propose to consider a multi-level representation from a multi-modeling point of view. This perspective allows explicitly specifying the level's relationships and, therefore, to test hypothesis about interaction between individuals and groups in social systems. We define a framework to better specify the concepts used in multi-level modeling and their relationships. This framework is implemented through the AA4MM meta-model, which benefits from a middleware layer. This meta-model uses the multi-agent paradigm to consider a multi-model as a society of interacting models. We extend this meta-model to consider multi-level modeling, and present a proof of concept of a collective motion example, where we show the advantages of this approach for the study of social phenomena.

Keywords: multi-agent based simulation, multi-level, french team

[Camus:2016]

B. Camus, T. Paris, J. Vaubourg, Y. Presse, C. Bourjot, L. Ciarletta, and V. Chevrier. MECSYCO: a multi-agent DEVS wrapping platform for the co-simulation of complex systems. Technical report, LORIA, UMR 7503, Université de Lorraine, CNRS, Inria Nancy-Grand Est, France, 2016.

Abstract: Most modeling and simulation (M&S) questions about complex systems require to take simultaneously account of several points of view. Phenomena evolving at different scales and at different levels of resolution have to be considered. Moreover, expert skills belonging to different scientific fields are needed. The challenges are then to reconcile these heterogeneous points of view, and to integrate each domain tools (formalisms and simulation software) within the rigorous framework of the M&S process. To answer to this issue, we propose here the specifications of the MECSYCO co-simulation middleware. MECSYCO relies on the universality of the DEVS formalism in order to integrate models written in different formalism. This integration is based on a wrapping strategy in order to make models implemented in different simulation software interoperable. The middleware performs the co-simulation in a parallel, decentralized and distributable fashion thanks to its modular multi-agent architecture. We detail how MECSYCO perform hybrid co-simulations by integrating in a generic way already implemented continuous models thanks to the FMI standard, the DEV&DESS formalism and the QSS method. The DEVS wrapping of FMI that we propose is not restricted to MECSYCO but can be performed in any DEVS-based platform. We show the modularity and the genericity of our approach through an iterative smart heating system M&S. Compared to other works in the literature, our proposition is generic thanks to the strong foundation of DEVS and the unifying features of the FMI standard, while being fully specified from the concepts to their implementations .

Keywords: multi-agent based simulation, multi-level, DEVS, french team

[Carley:2012]

K. M. Carley, G. Morgan, M. Lanham, and J. Pfeffer. *Advances in Design for Cross-Cultural Activities Part II*, chapter Multi-Modeling and Socio-cultural complexity: Reuse and Validation, pages 128–137. CRC Press, 2012.

Abstract: Socio-cultural complexity is often best approached through the use of hybrid models that blend the effects of atomic models built from different social and mathematical theoretical bases. Such approaches are often referred to as multi-modeling. This paper discusses the types of multi-modeling, with attention to the factors that support reuse and validation. Illustrations of multi-modeling are shown using examples from multiple multi-modeling exercises. Multi-modeling supports in-depth analysis by enabling cross-validation of results through triangulation, insight into implications at multiple levels of granularity through cross-model consistency, and model advancement through re-use across multiple domains.

Keywords: multi-agent based simulation, multi-level, multi-model, social simulation

[Carley:2017]

K. M Carley, G.P. Morgan, and M.J. Lanham. Detering the development and use of nuclear weapons: A multi-level modeling approach. *The Journal of Defense Modeling and Simulation*, 14(1):95–105, 2017.

Abstract: We describe a multi-country, multi-stakeholder model for the accrual and use of nuclear weapons and illustrate the model’s value for addressing nuclear weapon proliferation issues using an historic Pacific Rim scenario. We instantiate the agent-based dynamic-network model for information and belief diffusion using data from subject matter experts and data mined from open source news documents. We present the techniques that supported model instantiation. A key feature of this model and these techniques is enabling rapid model reuse through the ability to instantiate at two levels: generically and for specific cases. We demonstrate these generic and specific cases using a scenario regarding North Korea’s interest in nuclear weapons and the resulting impact on the Pacific Rim circa 2014-that is, prior to the fourth and fifth nuclear weapons test by the Democratic People’s Republic of Korea. A key feature of this model is that it uses two levels of network interaction-country level and stakeholder level-thus supporting the inclusion of non-state actors and the assessment of complex scenarios. Using this model, we conducted virtual experiments in which we assessed the impact of alternative courses of action on the overall force posture and desire to develop and use nuclear weapons.

Keywords: multi-agent based simulation, multi-level, military simulation

[Carneiro:2006]

T. Carneiro. *Nested-CA: A Foundation for multiscale modelling of land use and land cover change*. PhD thesis, Instituto Nacional de Pesquisas Espaciais, São José dos Campos, 2006.

Abstract: This work presents the mathematical foundations of the Nested Cellular Automata (nested-CA) model, a model of computation for multiple scale Land Use and Land Cover Change studies. The main properties of nested-CA model are described and compared to the agent-based and cellular automata models of computation. The nested- CA model has been implemented in a software environment, called TerraME (Terra Modeling Environment), which provides a high-level modeling language for model description, a set of spatiotemporal data structures for model representation and simulation, a module for spatiotemporal data management and analysis integrated to a geographic information system, and a set of functions for model calibration and validation. We describe the main design choices involved in the development of the TerraME modeling environment. Its architecture is detailed and the main properties are compared with other modeling tools: Swarm, STELLA, and GEONAMICA. Finally, the concept of nested-CA and the TerraME architecture are demonstrated in two applications of land cover change in the Brazilian Amazon.

Keywords: multi-agent based simulation, cellular automata, multi-level, ecology

[Carneiro:2013]

T. Carneiro, P.R. de Andrade, G. Câmara, A. Monteiro, and R. Pereira. An extensible toolbox for modeling nature–society interactions. *Environmental Modelling & Software*, 46:104 – 117, 2013.

Abstract: Modeling interactions between social and natural systems is a hard task. It involves collecting data, building up a conceptual approach, implementing, calibrating, simulating, validating, and possibly repeating these steps again and again. There are different conceptual approaches proposed in the literature to tackle this problem. However, for complex problems it is better to combine different approaches, giving rise to a need for flexible and extensible frameworks for modeling nature–society interactions. In this paper we present TerraME, an open source toolbox that supports multi-paradigm and multi-scale modeling of coupled human–environmental systems. It enables models that combine agent-based, cellular automata, system dynamics, and discrete event simulation paradigms. TerraME has a GIS interface for managing real-world geospatial data and uses Lua, an expressive scripting language.

Keywords: multi-agent based simulation, multi-level, ecology

[Carroll:2016]

J. Carroll. Experimenting with multilevel agent based archaeological modeling in netlogo. In *81st Annual Meeting of the Society for American Archaeology*, 2016.

Abstract: Agent Based Modeling (ABM) has become increasingly popular because of its relatively shallow learning curve and robust capacity for simulating social and environmental phenomena. This paper discusses new developments in ongoing work simulating social interaction in Pre-contact small-scale societies using NetLogo, a freely available software package. Model design, assessment and experimentation of a multilevel ABM are discussed, as well as how the simulation results compare to real world, geospatially referenced archaeological datasets drawn from the Great Lakes region of North America.

Keywords: multi-agent based simulation, multi-level, social simulation, archaeology

[Ceresa:2017]

M. Ceresa, A.L. Olivares, S.F. Suelves, J. Noailly, and M.A.G. Ballester. Multi-scale immunological and biomechanical model of emphysema progression. In *Proc. of Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual Int. Conf. of the IEEE*, pages 2712–2715, 2017.

Abstract: This work presents a multi-scale agent-based model of emphysema progression that includes both the slow action of the immune system and the fast action of force redistribution and fracture propagation of the biological tissue. The two scales are coupled because the immune response causes inflammation and adaptation, which affects the biomechanical parameters of the tissue such as his elasticity. During repeated inflammation and breathing cycles, the tissue weakens and breaks down. We found that macrophages lifespan and cytokynes diffusion ratio are the parameters that influence the outcome of the model the most.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Ceresa:2018]

M. Ceresa, A.L. Olivares, J. Noailly, and M.A.G. Ballester. Coupled immunological and biomechanical model of emphysema progression. *Frontiers in physiology*, 9, 2018.

Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a disabling respiratory pathology, with a high prevalence and a significant economic and social cost. It is characterized by different clinical phenotypes with different risk profiles. Detecting the correct phenotype, especially for the emphysema subtype, and predicting the risk of major exacerbations are key elements in order

to deliver more effective treatments. However, emphysema onset and progression are influenced by a complex interaction between the immune system and the mechanical properties of biological tissue. The former causes chronic inflammation and tissue remodeling. The latter influences the effective resistance or appropriate mechanical response of the lung tissue to repeated breathing cycles. In this work we present a multi-scale model of both aspects, coupling Finite Element (FE) and Agent Based (AB) techniques that we would like to use to predict the onset and progression of emphysema in patients. The AB part is based on existing biological models of inflammation and immunological response as a set of coupled non-linear differential equations. The FE part simulates the biomechanical effects of repeated strain on the biological tissue. We devise a strategy to couple the discrete biological model at the molecular /cellular level and the biomechanical finite element simulations at the tissue level. We tested our implementation on a public emphysema image database and found that it can indeed simulate the evolution of clinical image biomarkers during disease progression.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Chakrabarti:2012]

A. Chakrabarti, S. Verbridge, A.D. Stroock, C. Fischbach, and J.D. Varner. Multiscale models of breast cancer progression. *Annals of biomedical engineering*, 40(11):2488–2500, 2012.

Abstract: Breast cancer initiation, invasion and metastasis span multiple length and time scales. Molecular events at short length scales lead to an initial tumorigenic population, which left unchecked by immune action, acts at increasingly longer length scales until eventually the cancer cells escape from the primary tumor site. This series of events is highly complex, involving multiple cell types interacting with (and shaping) the microenvironment. Multiscale mathematical models have emerged as a powerful tool to quantitatively integrate the convective-diffusion-reaction processes occurring on the systemic scale, with the molecular signaling processes occurring on the cellular and subcellular scales. In this study, we reviewed the current state of the art in cancer modeling across multiple length scales, with an emphasis on the integration of intracellular signal transduction models with pro-tumorigenic chemical and mechanical microenvironmental cues. First, we reviewed the underlying biomolecular origin of breast cancer, with a special emphasis on angiogenesis. Then, we summarized the development of tissue engineering platforms which could provide highfidelity ex vivo experimental models to identify and validate multiscale simulations. Lastly, we reviewed top-down and bottom-up multiscale strategies that integrate subcellular networks with the microenvironment. We present models of a variety of cancers, in addition to breast cancer specific models. Taken together, we expect as the sophistication of the simulations increase, that multiscale modeling and bottom-up agent-based models in particular will become an increasingly important platform technology for basic scientific discovery, as well as the identification and validation of potentially novel therapeutic targets.

Keywords: multi-agent based simulation, multi-level, cancer modeling

[Checa:2018]

S. Checa. Multiscale agent-based computer models in skeletal tissue regeneration. In *Numerical Methods and Advanced Simulation in Biomechanics and Biological Processes*, chapter 13, pages 239 – 244. Academic Press, 2018.

Abstract: Bone regeneration is a fascinating process in which, after injury, bone is able to regain full functionality without scar formation. Although the process is successful in most cases, there are conditions in which the bone fails to heal leading to delayed or nonunions (e.g., large segmental defects due to trauma or cancer). The treatment of those conditions remains a clinical challenge; therefore, a full understanding of the regeneration process is needed to develop new treatment strategies. Bone regeneration involves many different processes at multiple length and time scales (intracellular, cellular, tissue, organ). Understanding the process as a whole requires assessing how individual events interact within and across the different scales. Experimental approaches are usually focused on understanding specific processes occurring at a single scale, making it difficult to assess their relevance to the overall process. Computer modeling techniques are a powerful tool to investigate across scales processes. In particular, agent-based modeling approaches are especially well suited to study the bone regeneration response. In this chapter, we describe the main components of agent-based models, how they can be used to investigate bone regeneration at the different time and length scales, and provide simple examples of the integration between the different scales.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Chen:2008]

C.C. Chen, S. Nagl, and C. Clack. A method for validating and discovering associations between multi-level emergent behaviours in agent-based simulations. In R.J. Howlett N.T. Nguyen, G.S. Jo and L.C. Jain, editors, *Agent and Multi-Agent Systems: Technologies and Applications*, volume 4953 of LNCS, pages 1–10. Springer, 2008.

Abstract: Agent-based models (ABM) and their simulations have been used to study complex systems with interacting entities and to model multi-agent systems. Simulations are used to explore the dynamic consequences of these models. In many cases, the behaviours that are of interest are emergent ones that arise as a result of interactions between agents rather than the actions of any individual agent. In this paper, we propose a formalism for describing emergent behaviours at any level of abstraction based on the idea that event types can be defined that characterise sets of behavioural ‘motifs’. This provides the basis for a method for studying the associations between multi-level behaviours in simulations. There are two categories of hypotheses that we seek to address with respect to an ABM and its simulations: - Hypotheses concerned with associations between emergent behaviours defined at various levels of abstraction. - Hypotheses concerned with the links between parameter sensitivity / initial conditions and emergent behaviours e.g. the ABM is sensitive to a parameter x because x predisposes the system or part of the system to exhibit a particular (emergent) behaviour.

Keywords: multi-agent based simulation, multi-level, emergence detection

[Chen:2009]

C.C. Chen, S. Nagl, and C. Clack. A formalism for multi-level emergent behaviours in designed component-based systems and agent-based simulations. In *From System Complexity to Emergent Properties*, volume 12 of *Understanding Complex Systems*, pages 101–114. Springer, 2009.

Abstract: There currently exists no means of specifying or analysing specific emergent behaviours in designed multi-component systems. For this reason, important questions about the lower level mechanisms giving rise to emergent behaviours cannot be resolved. We provide a compositional definition of behaviours in terms of complex events, which can be defined at multiple levels of abstraction and related hierarchically. Based on existing theories of emergence, we also distinguish complex events that constitute emergent behaviours and those that do not. We describe how such emergent behaviours can be analysed by decomposition in terms of their underlying mechanisms.

Keywords: multi-agent based simulation, multi-level, emergence detection

[Chen:2009a]

C.C. Chen. *Complex Event Types for Agent-Based Simulation*. PhD thesis, University College London, 2009.

Abstract: This thesis presents a novel formal modelling language, complex event types (CET s), to describe behaviours in agent-based simulations. CET s are able to describe behaviours at any computationally represented level of abstraction. Behaviours can be specified both in terms of the state transition rules of the agent-based model that generate them and in terms of the state transition structures themselves. Based on CET s, novel computational statistical methods are introduced which allow statistical dependencies between behaviours at different levels to be established. Different dependencies formalise different probabilistic causal relations and Complex Systems constructs such as ‘emergence’ and ‘autopoiesis’. Explicit links are also made between the different types of CET inter-dependency and the theoretical assumptions they represent. With the novel computational statistical methods, three categories of model can be validated and discovered: (i) inter-level models, which define probabilistic dependencies between behaviours at different levels; (ii) multi-level models, which define the set of simulations for which an inter-level model holds; (iii) inferred predictive models, which define latent relationships between behaviours at different levels. The CET modelling language and computational statistical methods are then applied to a novel agent-based model of Colonic Cancer to demonstrate their applicability to Complex Systems sciences such as Systems Biology. This proof of principle model provides a framework for further development of a detailed integrative model of the system, which can progressively incorporate biological data from different levels and scales as these become available.

Keywords: multi-agent based simulation, multi-level, emergence detection

[Chen:2010]

C.C. Chen, C.D. Clack, and S.B. Nagl. Identifying multi-level emergent behaviors in agent-directed simulations using complex event type specifications. *Simulation*, 86(1):41–51, 2010.

Abstract: Agent-directed simulations (ADS) are used in many domains to study complex systems. These are systems where non-linear effects can result from these emergent behaviors, making them difficult to analyze and predict. Correspondingly, in ADS, as well as explicitly specified behaviors of individual agents, higher level behaviors can emerge spontaneously from agent action sequences and agent–agent interactions. We have previously introduced the complex event formalism for specifying emergent behaviors in dynamically executing ADS [1, 2]. Based on the formalism, we also described a method for detecting and analyzing emergent behaviors in multi-agent simulations, giving us an effective means of studying, and a more reliably way of predicting, these systems. Complex event types define sets of multi-dimensional structures of interrelated

events arising from the actions of one or more agents. They are therefore directly related to the agent specifications, which determine the behavior of individual agents. Although the abstract constructs of the formalism have already been introduced in [1] and [2], they have not yet been related to a specific agent-based specification language. Here, we define the constructs in terms of the X-machine formalism, which is widely used to specify multi-agent systems. This extends the existing X-machine framework to model higher level emergent behaviors as well as agent-level state transitions. Thus, emergent behaviors at any level of abstraction can be specified for detection and analysis in a dynamically executing ADS.

Keywords: multi-agent based simulation, multi-level, emergence detection

[Chen:2010a]

C.C. Chen and DR Hardoon. Learning from multi-level behaviours in agent-based simulations: a systems biology application. *Journal of Simulation*, 4(3):196–203, 2010.

Abstract: This paper presents a novel approach towards showing how specific emergent multi-level behaviours in agent-based simulations (ABSs) can be quantified and used as the basis for inferring predictive models. First, we first show how behaviours at different levels can be specified and detected in a simulation using the complex event formalism. We then apply partial least squares regression to frequencies of these behaviours to infer models predicting the global behaviour of the system from lower-level behaviours. By comparing the mean predictive errors of models learned from different subsets of behavioural frequencies, we are also able to determine the relative importance of different types of behaviour and different resolutions. These methods are applied to ABSs of a novel agent-based model of cancer in the colonic crypt, with tumorigenesis as the global behaviour we wish to predict.

Keywords: multi-agent based simulation, multi-level, emergence detection, biology

[Chen:2012]

C.C. Chen, S. Nagl, and C. Clack. Multi-level behaviours in agent-based simulation: colonic crypt cell populations. In *Unifying Themes in Complex Systems VII – Proceedings of the Seventh International Conference on Complex Systems*, pages 14–26. Springer, 2012.

Abstract: Agent-based modelling and simulation is now beginning to establish itself as a suitable technique for studying biological systems. However, a major issue in using agent-based simulations to study complex systems such as those in Systems Biology is the fact that simulations are ‘opaque’. While we have knowledge of individuals’ behaviour through agent rules and have techniques for evaluating global behaviour by aggregating the states of individuals, methods for identifying the interactive mechanisms giving rise to this global behaviour are lacking. Formulating precise hypotheses about these multi-level behaviours is also difficult without an established formalism for describing them. The complex event formalism allows relationships between agent-rule-generated events to be defined so that behaviours at different levels of abstraction to be described. Complex event types define categories of these behaviours, which can then be detected in simulation, giving us computational method for distinguishing between alternative interactive mechanisms underlying a higher level behaviour. We apply the complex event formalism to an agent-based model of cell populations in the colonic crypt and demonstrate how competition and selection events can be identified in simulation at both the individual and clonal level, allowing us to computationally test hypotheses about the interactive mechanisms underlying a clone’s success.

Keywords: multi-agent based simulation, multi-level, emergence detection

[Chen:2013]

C.C. Chen. A theoretical framework for conducting multi-level studies of complex social systems with agent-based models and empirical data. *CoRR*, abs/1302.4774, 2013.

Abstract: A formal but intuitive framework is introduced to bridge the gap between data obtained from empirical studies and that generated by agent-based models. This is based on three key tenets. Firstly, a simulation can be given multiple formal descriptions corresponding to static and dynamic properties at different levels of observation. These can be easily mapped to empirically observed phenomena and data obtained from them. Secondly, an agent-based model generates a set of closed systems, and computational simulation is the means by which we sample from this set. Thirdly, properties at different levels and statistical relationships between them can be used to classify simulations as those that instantiate a more sophisticated set of constraints. These can be validated with models obtained from statistical models of empirical data (for example, structural equation or multi-level models) and hence provide more stringent criteria for validating the agent-based model itself.

Keywords: multi-agent based simulation, multi-level, social simulation

[Chen:2015]

J.-J. Chen, Lei L. Tan, and B. Zheng. Agent-based model with multi-level herding for complex financial systems. *Scientific reports*, 5(8399), 2015.

Abstract: In complex financial systems, the sector structure and volatility clustering are respectively important features of the spatial and temporal correlations. However, the microscopic generation mechanism of the sector structure is not yet understood. Especially, how to produce these two features in one model remains challenging. We introduce a novel interaction mechanism, i.e., the multi-level herding, in constructing an agent-based model to investigate the sector structure combined with volatility clustering. According to the previous market performance, agents trade in groups, and their herding behavior comprises the herding at stock, sector and market levels. Further, we propose methods to determine the key model parameters from historical market data, rather than from statistical fitting of the results. From the simulation, we obtain the sector structure and volatility clustering, as well as the eigenvalue distribution of the cross-correlation matrix, for the New York and Hong Kong stock exchanges. These properties are in agreement with the empirical ones. Our results quantitatively reveal that the multi-level herding is the microscopic generation mechanism of the sector structure, and provide new insight into the spatio-temporal interactions in financial systems at the microscopic level.

Keywords: multi-agent based simulation, multi-level, finance

[Cheong:2012]

S.M. Cheong, D.G. Brown, K. Kok, and D. Lopez-Carr. Mixed methods in land change research: towards integration. *Transactions of the Institute of British Geographers*, 37(1):8–12, 2012.

Keywords: multi-agent based simulation, multi-level, ecology

[Christley:2007]

S. Christley, X. Zhu, S.A. Newman, and M.S. Alber. Multiscale agent-based simulation for chondrogenic pattern formation in vitro. *Cybernetics and Systems: An International Journal*, 38(7):707–727, 2007.

Abstract: Mathematical and computational multiscale models are becoming increasingly important investigative tools in developmental biological research. During certain developmental processes cells that start out as independent entities interact to form multicellular structures. Cells of the embryonic vertebrate limb in high-density culture undergo chondrogenic pattern formation, which results in the formation of regularly-spaced “islands” of cartilage analogous to the cartilage primordia of the developing limb skeleton. In this article we describe a discrete, agent-based stochastic model for studying the behavior of limb bud precartilaginous mesenchymal cells in vitro. This model, like an earlier one, employs a biologically motivated reaction-diffusion process and cell-matrix adhesion as the basis of self-organizing pattern formation, but constitutes an improvement in biological fidelity over previous descriptions in that it is multiscale (i.e., cell and molecular dynamics occur on distinct scales), and the cells are represented as spatially extended objects. The improved model reproduces a broader set of results of the micromass culture system than the previous one and discloses multiple dynamical regimes that suggest new biological experiments.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Cilfone:2014]

N.A. Cilfone, D.E. Kirschner, and J.J. Linderman. Strategies for efficient numerical implementation of hybrid multi-scale agent-based models to describe biological systems. *Cellular and Molecular Bioengineering*, pages 1–18, 2014.

Abstract: Biologically related processes operate across multiple spatiotemporal scales. For computational modeling methodologies to mimic this biological complexity, individual scale models must be linked in ways that allow for dynamic exchange of information across scales. A powerful methodology is to combine a discrete modeling approach, agent-based models (ABMs), with continuum models to form hybrid models. Hybrid multi-scale ABMs have been used to simulate emergent responses of biological systems. Here, we review two aspects of hybrid multi-scale ABMs: linking individual scale models and efficiently solving the resulting model. We discuss the computational choices associated with aspects of linking individual scale models while simultaneously maintaining model tractability. We demonstrate implementations of existing numerical methods in the context of hybrid multi-scale ABMs. Using an example model describing Mycobacterium tuberculosis infection, we show relative computational speeds of various combinations of numerical methods. Efficient linking and solution of hybrid multi-scale ABMs is key to model portability, modularity, and their use in understanding biological phenomena at a systems level.

Keywords: multi-agent based simulation, multi-level, biology

[Cilfone:2015]

N.A. Cilfone, C.B. Ford, S. Marino, J.T. Mattila, H.P. Gideon, J.L. Flynn, D.E. Kirschner, and J.J. Linderman. Computational modeling predicts il-10 control of lesion sterilization by balancing early host immunity-mediated antimicrobial responses with caseation during mycobacterium tuberculosis infection. *The Journal of Immunology*, 194(2):664–677, 2015.

Abstract: Although almost a third of the world’s population is infected with the bacterial pathogen *Mycobacterium tuberculosis*, our understanding of the functions of many immune factors involved in fighting infection is limited. Determining the role of the immunosuppressive cytokine IL-10 at the level of the granuloma has proven difficult because of lesional heterogeneity and the limitations of animal models. In this study, we take an in silico approach and, through a series of virtual experiments, we predict several novel roles for IL-10 in tuberculosis granulomas: 1) decreased levels of IL-10 lead to increased numbers of sterile lesions, but at the cost of early increased caseation; 2) small increases in early antimicrobial activity cause this increased lesion sterility; 3) IL-10 produced by activated macrophages is a major mediator of early antimicrobial activity and early host-induced caseation; and 4) increasing levels of infected macrophage derived IL-10 promotes bacterial persistence by limiting the early antimicrobial response and preventing lesion sterilization. Our findings, currently only accessible using an in silico approach, suggest that IL-10 at the individual granuloma scale is a critical regulator of lesion outcome. These predictions suggest IL-10-related mechanisms that could be used as adjunctive therapies during tuberculosis.

Keywords: multi-agent based simulation, multi-level, biology

[Cleri:2018]

F. Cleri. Agent-based model of multicellular tumor spheroid evolution including cell metabolism. *bioRxiv*, page 431163, 2018.

Abstract: Computational models aiming at the spatio-temporal description of cancer evolution are a suitable framework for testing biological hypotheses from experimental data, and generating new ones. Building on our recent work [J Theor Biol 389, 146-158 (2016)] we develop a 3D agent-based model, capable of tracking hundreds of thousands of interacting cells, over time scales ranging from seconds to years. Cell dynamics is driven by a Monte Carlo solver, incorporating partial differential equations to describe chemical pathways and the activation/repression of “genes”, leading to the up- or down-regulation of specific cell markers. Each cell-agent of different kind (stem, cancer, stromal etc.) runs through its cycle, undergoes division, can exit to a dormant, senescent, necrotic state, or apoptosis, according to the inputs from their systemic network. The basic network at this stage describes glucose/oxygen/ATP cycling, and can be readily extended to cancer-cell specific markers. Accumulation of chemical/radiation damage to each cell’s DNA is described by a Markov chain of internal states, and by a damage-repair network, whose evolution is linked to the cell systemic network. By direct comparison with experiments of tumorsphere growth from stem cells, the present model allows to quantitatively study the role of transcription factors involved in the reprogramming and variable radio-resistance of simulated cancer-stem cells, evolving in a realistic computer simulation of a growing multicellular tumorsphere.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling, french team

[Conte:1996]

R. Conte and C. Castelfranchi. Simulating multi-agent interdependencies. a two-way approach to the micro-macro link. In *Social Science Microsimulation*, pages 394–415. Springer, 1996.

Keywords: multi-agent based simulation, multi-level, social simulation

[Conte:2007]

R. Conte, G. Andrighetto, M. Campenni, and M. Paolucci. Emergent and immergent effects in complex social systems. In *Proceedings of AAAI Symposium, Social and Organizational Aspects of Intelligence, Washington DC.*, 2007.

Abstract: In this paper the notion of emergence in complex social systems is rediscussed as a necessary instrument for a theory of the macro-micro link. Referring to Schelling’s model of segregation, emergent effects are defined as effects generated by (inter)acting micro-social entities, and implemented upon, but not incorporated into, their rules. In the successive section, the way back from macro to micro, i.e. downward causation, is examined. Simple and complex loops are distinguished, with reference to concrete examples drawn from the social scientific and the computational literature. Next, how a given macro-effect is implemented on the lower levels is shown, and two specific mechanisms of implementation, 2nd order emergence and immergence, are discussed.

Keywords: multi-agent based simulation, multi-level, social simulation

- [Cristiani:2011] E. Cristiani, B. Piccoli, and A. Tosin. Multiscale modeling of granular flows with application to crowd dynamics. *Multiscale Modeling & Simulation*, 9(1):155–182, 2011.
- Keywords:** multi-agent based simulation, multi-level, multi-scale, hybrid model, pedestrian flow modeling
- [Cristiani:2014] E. Cristiani, B. Piccoli, and A. Tosin. *Multiscale modeling of pedestrian dynamics*, volume 12. Springer, 2014.
- Abstract:** This book presents mathematical models and numerical simulations of crowd dynamics. The core topic is the development of a new multiscale paradigm, which bridges the microscopic and macroscopic scales taking the most from each of them for capturing the relevant clues of complexity of crowds. The background idea is indeed that most of the complex trends exhibited by crowds are due to an intrinsic interplay between individual and collective behaviors. The modeling approach promoted in this book pursues actively this intuition and profits from it for designing general mathematical structures susceptible of application also in fields different from the inspiring original one. The book considers also the two most traditional points of view: the microscopic one, in which pedestrians are tracked individually, and the macroscopic one, in which pedestrians are assimilated to a continuum. Selected existing models are critically analyzed. The work is addressed to researchers and graduate students.
- Keywords:** multi-agent based simulation, multi-level, multi-scale, hybrid model, pedestrian flow modeling
- [Cristiani:2016] E. Cristiani and S. Sahu. On the micro-to-macro limit for first-order traffic flow models on networks. *Networks & Heterogeneous Media*, 11(3):395–413, 2016.
- Abstract:** Connections between microscopic follow-the-leader and macroscopic fluid-dynamics traffic flow models are already well understood in the case of vehicles moving on a single road. Analogous connections in the case of road networks are instead lacking. This is probably due to the fact that macroscopic traffic models on networks are in general ill-posed, since the conservation of the mass is not sufficient alone to characterize a unique solution at junctions. This ambiguity makes more difficult to find the right limit of the microscopic model, which, in turn, can be defined in different ways near the junctions. In this paper we show that a natural extension of the first-order follow-the-leader model on networks corresponds, as the number of vehicles tends to infinity, to the LWR-based multi-path model introduced in [4,5].
- Keywords:** multi-agent based simulation, multi-level, multi-scale, hybrid model, traffic
- [Cristiani:2017] E. Cristiani. A multiscale method for reducing the complexity of (controlled) large multi-agent systems. In *Numerical methods for optimal control problems: algorithms, analysis and applications Workshop INdAM*, 2017.
- Keywords:** multi-agent based simulation, multi-level, multi-scale, hybrid model, pedestrian flow modeling
- [Cristiani:2018] E. Cristiani and E. Iacomini. An interface-free multi-scale multi-order model for traffic flow. *arXiv preprint arXiv:1805.08668*, 2018.
- Abstract:** In this paper we present a new kind of model for traffic flow which couples a first-order macroscopic approach with a second-order microscopic approach, avoiding any interface or boundary conditions between them. The Euler-Godunov scheme associated to the model is conservative and it is able to reproduce typical traffic phenomena like stop & go waves.
- Keywords:** multi-agent based simulation, multi-level, hybrid model, multi-scale, traffic
- [Cristiani:2018a] E. Cristiani and M.C. Saladino. Comparing comparisons between vehicular traffic states in microscopic and macroscopic models. *arXiv preprint arXiv:1803.05735*, 2018.
- Abstract:** In this paper we deal with the analysis of the solutions of traffic flow models at multiple scales, both in the case of a single road and of road networks. We are especially interested in measuring the distance between traffic states (as they result from the mathematical modeling) and investigating whether these distances are somehow preserved passing from the microscopic to the macroscopic scale. By means of both theoretical and numerical investigations, we show that, on a single road, the notion of Wasserstein distance fully catches the human perception of distance independently of the scale, while in the case of networks it partially loses its nice properties.
- Keywords:** multi-agent based simulation, multi-level, hybrid model, traffic

[Crociani:2016]

L. Crociani, G. Lämmel, and G. Vizzari. Multi-scale simulation for crowd management: a case study in an urban scenario. In *AAMAS 2016 Workshops, Best Papers*, volume 10002 of *LNCS*, pages 147–162. Springer, 2016.

Abstract: Safety, security, and comfort of pedestrian crowds during large gatherings are heavily influenced by the layout of the underlying environment. This work presents a systematic agent-based simulation approach to appraise and optimize the layout of a pedestrian environment in order to maximize safety, security, and comfort. The performance of the approach is demonstrated based on annual “Salone del mobile” (Design Week) exhibition in Milan, Italy. Given the large size of the scenario, and the proportionally high number of simultaneously present pedestrians, the computational costs of a pure microscopic simulation approach would make this hardly applicable, whereas a multi-scale approach, combining simulation models of different granularity, provides a reasonable trade off between a detailed management of individual pedestrians and possibility to effectively carry out what-if analyses with different environmental configurations. The paper will introduce the scenario, the base model and the alternatives discussing the achieved results.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling

[Crociani:2017]

L. Crociani, G. Lämmel, and G. Vizzari. Simulation-aided crowd management: A multi-scale model for an urban case study. In *Agent Based Modelling of Urban Systems: First International Workshop, ABMUS 2016, Held in Conjunction with AAMAS, Singapore, Singapore, May 10, 2016, Revised, Selected, and Invited Papers*, volume 10051 of *LNCS*, pages 151–171. Springer, 2017.

Abstract: Safety, security, and comfort of pedestrian crowds during large gatherings are heavily influenced by the layout of the underlying environment. This work presents a systematic agent-based simulation approach to appraise and optimize the layout of a pedestrian environment in order to maximize safety, security, and comfort. The performance of the approach is demonstrated based on annual “Salone del mobile” (Design Week) exhibition in Milan, Italy. Given the large size of the scenario and the proportionally high number of simultaneously present pedestrians, the computational costs of a pure microscopic simulation approach would make this hardly applicable, whereas a multi-scale approach, combining simulation models of different granularity, provides a reasonable trade off between a detailed management of individual pedestrians and possibility to effectively carry out what-if analyses with different environmental configurations. The paper will introduce the scenario, the base model and the alternatives, discussing the achieved results.

Keywords: multi-agent based simulation, multi-level, multi-scale, pedestrian flow modeling

[Dada:2012]

J. O. Dada and P. Mendes. ManyCell: a multiscale simulator for cellular systems. In *Computational Methods in Systems Biology*, pages 366–369. Springer, 2012.

Abstract: The emergent properties of multiscale biological systems are driven by the complex interactions of their internal compositions usually organized in hierarchical scales. A common representation takes cells as the basic units which are organized in larger structures: cultures, tissues and organs. Within cells there is also a great deal of organization, both structural (organelles) and biochemical (pathways). A software environment capable of minimizing the computational cost of simulating large-scale multiscale models is required to help understand the functional behaviours of these systems. Here we present ManyCell, a multiscale simulation software environment for efficient simulation of such cellular systems. ManyCell does not only allow the integration and simulation of models from different biological scales, but also combines innovative multiscale methods with distributed computing approaches to accelerate the process of simulating large-scale multiscale agent-based models. Thereby opening up the possibilities of understanding the functional behaviour of cellular systems in an efficient way.

Keywords: multi-agent based simulation, multi-level, biology

[Dangelo:2017]

G. D’Angelo, S. Ferretti, and V. Ghini. Multi-level simulation of internet of things on smart territories. *Simulation Modelling Practice and Theory*, 73:3–21, 2017.

Abstract: In this paper, a methodology is presented and employed for simulating the Internet of Things (IoT). The requirement for scalability, due to the possibly huge amount of involved sensors and devices, and the heterogeneous scenarios that might occur, impose resorting to sophisticated modeling and simulation techniques. In particular, multi-level simulation is regarded as a main framework that allows simulating large-scale IoT environments while keeping high levels of detail,

when it is needed. We consider a use case based on the deployment of smart services in decentralized territories. A two level simulator is employed, which is based on a coarse agent-based, adaptive parallel and distributed simulation approach to model the general life of simulated entities. However, when needed a finer grained simulator (based on OMNeT++) is triggered on a restricted portion of the simulated area, which allows considering all issues concerned with wireless communications. Based on this use case, it is confirmed that the ad-hoc wireless networking technologies do represent a principle tool to deploy smart services over decentralized countrysides. Moreover, the performance evaluation confirms the viability of utilizing multi-level simulation for simulating large scale IoT environments.

Keywords: multi-agent based simulation, multi-level, iot

[Dascalu:2009]

M. Dascalu, S. Gheorghe, and A. Zafiu. Multi-level simulator for artificial societies. *Romanian Journal of Information Science and Technology*, 12(4):466–484, 2009.

Abstract: The simulator presented in this paper is used for human society modelling in order to understand its specific phenomena and to predict the future evolution of large human collectivities. The present paper presents also some new and original artificial society experiments, highlighting how the artificial societies model allows collective significant behaviors to appear through simple individual rules. The artificial society concept basically consists of a “cellular” landscape that contains different resources and a population of agents grouped in social categories which have economical and political activities. The experiments were related to the real conditions of our country. This simulator create a proper environment in order to identify the causes and mechanism which influence the economical, social and political phenomena evolution from the human society: production of goods, trade, diseases’ spreading / the efficiency of the immunizing methods, the impact of information in different welfare and cultural conditions of population, voting mechanisms.

Keywords: multi-agent based simulation, multi-level, social simulation

[Dascalu:2011]

M. Dascalu, G. Stefan, A. Zafiu, and A. Plavitu. Applications of multilevel cellular automata in epidemiology. In *Proceedings of the 13th WSEAS international conference on Automatic control, modelling & simulation*, pages 439–444. World Scientific and Engineering Academy and Society (WSEAS), 2011.

Abstract: This paper presents a multilevel simulator for a hierarchical cellular automata with applications in epidemiology, describing some particular experiments and general capacities of the model. In the particular example of the spreading of an infectious disease between children, various realistic features can be modeled with this tool. Taking into account the recent outspreading of various dangerous epidemics, the tool proposed here can be very useful for development of health strategies in fighting these epidemics, mainly because it can be easily configured for different landscapes and for the configuration of a particular city.

Keywords: multi-agent based simulation, multi-level, social simulation

[Daude:2010]

E. Daudé, P. Langlois, B. Blanpain, and E. Sapin. Aoc, une ontologie formelle pour la modélisation de systèmes complexes en géographie. In *Conf. Int. de Géomatique et Analyse Spatiale*, 2010.

Abstract: This paper presents a meta-model named AOC (Agents-Organisation-Behaviour) that is described by a formal ontology. This meta-model is the theoretical concept of a simulation platform of spatial complex systems that are compatible with the largest dynamic geographic problems. The geographer should be able to conceive his model and to formalise it in a coherent language according to his way of thinking. Thanks to the concept of ‘organisation’, AOC offers the possibilities to structure the relationships between agents and to create multi-level models. Moreover, a general formalisation of the notion of behaviour is used to simulate the dynamic of very large types of systems.

Keywords: multi-agent based simulation, multi-level, geography, in french, french team

[David:2008]

D. David and R. Courtier. Emergence as metaknowledge: refining simulation models through emergence reification. In *Proceedings of ESM’2008, Le Havre, France*, pages 25–27, 2008.

Abstract: This paper deals with the important concept of emergence in complex systems and in multiagent simulation. Research in this area yield to several definitions and classifications of emergent phenomena, but only a few of them offer a solution for emergence reification. As we know, this kind of notion does not have yet, formal definition, if any could be expressed, and we need to progress on the conceptual meaning, leading to more global definitions but allowing

to give a general conceptual framework for emergence manipulation. We define emergence as a metaknowledge controlled by emergence laws, and we present such a framework in which emergence is reified through emergent structures. Within this framework, emergent phenomena can be detected and injected in simulation systems to be manipulated like any other entity.

Keywords: multi-agent based simulation, multi-level, meta-model, emergence detection, french team

[David:2009]

D. David and R. Courdier. See emergence as a metaknowledge. a way to reify emergent phenomena in multiagent simulations? In *Proceedings of ICAART'09*, pages 564–569, Porto, Portugal, 2009.

Abstract: Emergence is a fascinating concept for most scientists, and multiagent simulations are known to allow and facilitate its representation. Research in this area yield to several definitions and classifications of emergent phenomena, but only a few of them offers a solution for a concrete reification of emergence in simulation. This paper deals with this important notion of emergence reification that, as we know, does not have yet formal mathematic definition, if any could be expressed. We need to progress on the conceptual meaning, leading to more global definitions but allowing to give a general conceptual framework that makes possible the reification of emergent phenomena in multiagent simulations. We define emergence as being a metaknowledge and we present a conceptual framework in which emergent phenomena can be detected and injected into simulation systems and be handled like other entities.

Keywords: multi-agent based simulation, multi-level, meta-model, methodology, emergence detection, french team

[David:2010]

D. David. *Prospective Territoriale par Simulation Orientée Agent*. PhD thesis, Université de La Réunion, 2010.

Abstract: L'île de La Réunion, inscrite au patrimoine mondial de l'UNESCO pour la beauté de ses paysages et pour sa biodiversité exceptionnelle, va accueillir dans les prochaines années une population de plus en plus importante. Les documents de planification réglementant l'évolution de l'urbanisation dans l'île doivent donc en tenir compte afin de gérer au mieux l'évolution et la structuration du foncier local. Dans un contexte de recherche pluridisciplinaire, l'enjeu de nos travaux est donc de proposer des méthodes et outils facilitant les interactions entre les informaticiens et les thématiciens qui apportent leur expertise à la construction de modèles de simulation dédiés à la prospective territoriale et de faire en sorte que ces modèles puissent fournir des pistes de réflexions aux décideurs confrontés aux choix de demain afin d'aider à mettre en place une organisation des territoires qui soit la plus cohérente possible. Après avoir participé à la réalisation de DS, un modèle qui permet de simuler conjointement l'évolution de la population et celle du Mode d'Occupation des Sols à La Réunion, nous nous sommes focalisés sur l'étude de l'émergence, une notion qui apparaît dans nos simulations en environnement spatialisé, mais pour laquelle il n'existe pas d'outils génériques permettant de la manipuler. Nous l'avons définie comme étant une méta-connaissance, ce qui nous a permis de proposer une méthodologie de conception de simulations et un cadre formel qui ont abouti à la mise en place de structures émergentes dans la plateforme de simulation GEAMAS-NG. Celle-ci, ou les entités de la SOA elles-mêmes, peuvent ainsi prendre conscience de l'émergence de phénomènes et les matérialiser en ayant recours à la connaissance des thématiciens. Nous avons alors montré l'intérêt de ces propositions en expérimentant la réification de phénomènes émergents observés dans DS.

Keywords: multi-agent based simulation, multi-level, social simulation, emergence detection, in french, french team

[David:2011]

D. David, D. Payet, and R. Courdier. Réification de zones urbaines émergentes dans un modèle simulant l'évolution de la population à la réunion. In *Actes des 19èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 63–72. Cepaduès, 2011.

Abstract: La prise en compte des phénomènes émergents présente un intérêt manifeste pour les utilisateurs et les concepteurs de Simulations Orientées Agent. Mais la réification éventuelle de ces phénomènes soulève de nombreuses questions, que ce soit sur le plan conceptuel (doit-elle se faire ?) ou sur le plan technique (comment la faire ?). Dans cet article, nous montrons qu'une telle réification peut être considérée comme étant un moyen efficace pour affiner ponctuellement des modèles de simulation existants dans lesquels des modifications directes, rendues laborieuses de par la multiplicité des entités et des comportements, se font souvent habituellement au risque de déstabiliser le système. Nous proposons donc une technique de réification des phénomènes qui émergent dans une Simulation Orientée Agent et nous illustrons cette proposition à travers

la réification de nouvelles zones urbaines, un phénomène émergent observé dans un modèle permettant de simuler l'évolution de la population à La Réunion.

Keywords: multi-agent based simulation, multi-level, emergence detection, social simulation, in french, french team

[David:2012]

D. David, Y. Gangat, D. Payet, and R. Courdier. Reification of emergent urban areas in a land-use simulation model in reunion island. In *ECAI workshop on Intelligent Agents in Urban Simulations and Smart Cities (IAUSSC2012)*, pp. 28-32, Montpellier, pages 28–32, Montpellier, France, august 27–31 2012.

Abstract: Emergent phenomena are often relevant for users and developers of simulation models. But the potential reification of these phenomena raises many questions, conceptually (should they be reified?) and technically (how to do it?). In this paper, we show that such a reification can be considered as an effective way to refine simulation models in which direct modifications, that are made laborious by the multiplicity of the entities and behaviors, often leads to the destabilization of the entire system. We propose a reification technique of the emergent phenomena that do emerge in an agent-based simulation. We illustrate this proposition through the reification of new urban areas, an emergent phenomenon observed in a model that we created to simulate land-use evolutions in Reunion Island.

Keywords: multi-agent based simulation, multi-level, emergence detection, french team

[Deisboeck:2010]

T.S. Deisboeck and G.S. Stamatakos. *Multiscale cancer modeling*, volume 34. CRC Press, 2010.

Abstract: Simulating cancer behavior across multiple biological scales in space and time, i.e., multiscale cancer modeling, is increasingly being recognized as a powerful tool to refine hypotheses, focus experiments, and enable more accurate predictions. A growing number of examples illustrate the value of this approach in providing quantitative insights in the initiation, progression, and treatment of cancer. In this review, we introduce the most recent and important multiscale cancer modeling works that have successfully established a mechanistic link between different biological scales. Biophysical, biochemical, and biomechanical factors are considered in these models. We also discuss innovative, cutting-edge modeling methods that are moving predictive multiscale cancer modeling toward clinical application. Furthermore, because the development of multiscale cancer models requires a new level of collaboration among scientists from a variety of fields such as biology, medicine, physics, mathematics, engineering, and computer science, an innovative Web-based infrastructure is needed to support this growing community.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Demange:2012]

J. Demange. *Un modèle d'environnement pour la simulation multiniveau - Application à la simulation de foules*. PhD thesis, UTBM, 2012.

Abstract: Cette thèse propose un modèle organisationnel et holonique de l'environnement pour la simulation des déplacements de piétons dans des bâtiments. Une foule de piétons peut être considérée comme un système composé d'un grand nombre d'entités en interaction, dont la dynamique globale ne peut se réduire à la somme des comportements de ses composants. La simulation multiniveau fondée sur les modèles multiagents holoniques constitue une approche permettant d'analyser la dynamique de tels systèmes. Elle autorise leur analyse en considérant plusieurs niveaux d'observation (microscopique, mésoscopique et macroscopique) et prend en compte les ressources de calcul disponibles. Dans ces systèmes, l'environnement est considéré comme l'une des parties essentielles. La dynamique des piétons composant la foule est alors clairement distinguée de celle de l'environnement dans lequel ils se déplacent. Un modèle organisationnel décrivant la structure et la dynamique de l'environnement est proposé. L'environnement est structurellement décomposé en zones, sous-zones, etc. Les organisations et les rôles de cet environnement sont projetés dans une société d'agents ayant en charge de simuler la dynamique de l'environnement et les différentes missions qui lui sont classiquement assignées dans les systèmes multiagents. Ce modèle précise également les règles de passage entre deux niveaux d'observation. Ainsi, chaque agent appartenant au modèle de l'environnement tente d'utiliser une approximation des comportements de ses sous-zones afin de limiter la consommation de ressources durant la simulation. La qualité de l'approximation entre ces deux niveaux d'observation est évaluée avec des indicateurs énergétiques. Ils permettent de déterminer si l'agent approxime correctement les comportements des agents associés aux sous-zones. En sus du modèle organisationnel et holonique proposé, nous présentons un modèle concret de la simulation de voyageurs dans un terminal d'aéroport. Ce modèle concret est implanté sur les plateformes JaSIM et Janus.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling, in french, french team

[Desmeulles:2009]

G. Desmeulles, S. Bonneaud, P. Redou, V. Rodin, and J. Tisseau. In virtuo experiments based on the multi-interaction system framework: the RÉISCOP meta-model. *Computer Modeling in Engineering and Sciences*, 47(3):299–329, 2009.

Abstract: Virtual reality can enable computer scientists and domain experts to perform in virtuo experiments of numerical models of complex systems. Such dynamical and interactive experiments are indeed needed when it comes to complex systems with complex dynamics and structures. In this context, the question of the modeling tool to study such models is crucial. Such tool, called a virtuoscope, must enable the virtual experimentation of models inside a conceptual and experimental framework for imagining, modeling and experimenting the complexity of the studied systems. This article describes a conceptual framework and a meta model, called RÉISCOP, that enable the construction and simulation of models of biological, chemical or physical systems. The multi-interaction conceptual framework, based on the reification of interactions, is built upon the concepts of autonomy, structural coupling and asynchronous scheduling of those reified interactions. Applications and virtual reality experiments described in the last section show the expressiveness of this approach and its capacity to actually formulate heterogeneous models in heterogeneous time and space scales, which is required for studying biological complex systems.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Drogoul:2013]

A. Drogoul, E. Amouroux, P. Caillou, B. Gaudou, A. Grignard, N. Marilleau, P. Taillandier, M. Vavasseur, D-A. Vo, and J-D. Zucker. GAMA: A spatially explicit, multi-level, agent-based modeling and simulation platform. In *Advances on Practical Applications of Agents and Multi-Agent Systems*, pages 271–274. Springer, 2013.

Abstract: Agent-based modeling is now widely used to investigate complex systems but still lacks integrated and generic tools to support the representation of features usually associated with real complex systems, namely rich, dynamic and realistic environments or multiple levels of agency. The GAMA platform has been developed to address such issues and allow modelers, thanks to the use of a high-level modeling language, to build, couple and reuse complex models combining various agent architectures, environment representations and levels of abstraction.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Drogoul:2013a]

A. Drogoul, E. Amouroux, P. Caillou, B. Gaudou, A. Grignard, N. Marilleau, P. Taillandier, M. Vavasseur, D-A. Vo, and J-D. Zucker. GAMA: multi-level and complex environment for agent-based models and simulations. In *Proc. of 12th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)*, pages 1361–1362, 2013.

Abstract: Agent-based models are now used in numerous application domains (ecology, social sciences, etc.) but their use is still impeded by the lack of generic yet ready-to-use tools supporting the design and the simulation of complex models integrating multiple level of agency and realistic environments. The GAMA modeling and simulation platform is proposed to address such issues. It allows modelers to build complex models thanks to high-level modeling language, various agent architectures and advanced environment representations and built-in multi-level support.

Keywords: multi-agent based simulation, multi-level, french team

[Dubovi:2017]

I. Dubovi, E. Dagan, L. Nasar, O.S. Mazbar, and S.T. Levy. Follow the glucose molecule: Learning pharmacology by exploring multi-scale agent-based computer models of cellular biochemical processes and their interactions between organs. In *Proc. of the 12th Chais Conf. for the Study of Innovation and Learning Technologies: Learning in the Technological Era*, pages 21–30, 2017.

Abstract: This paper presents the Pharmacology Inter-Leaved Learning-Cells (PILLCells) environment. This is a suite of multi-scale agent-based computer models that enable nursing students to investigate the biochemical processes of diabetes and its related medications. These range from the molecular to the cellular to the interactions between organs within a sick or healthy cell-organ. The participants were nursing students who learned about the pharmacology related to diabetes either with computer models (experimental group; $n = 94$) or via a lecture-based curriculum (comparison group; $n = 54$). The results revealed significantly higher conceptual learning gains following learning with the PILL-Cells environment compared to studying via the lecture-based curriculum ($U = 940, p < 0.001$). It was found that the highest conceptual learning gains were for the medication treatment subscale and the highest complex systems learning gains were at

the micro-level. These results suggest that learning with the PILL-Cells is highly effective and enhances a micro-level molecular view of the biochemical phenomena, and that this understanding is then related to macro-level phenomena such as medication actions. Additionally, the scores of the course final exam were higher in the experimental group (unpaired $t = -2.9, p < 0.05$), which suggest that the environment continues to provide a more general reasoning scheme for biochemical processes, and thus enhances the pharmacology curriculum.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Dubovi:2018]

I. Dubovi, E. Dagan, O.S. Mazbar, L. Nassar, and S.T. Levy. Nursing students learning the pharmacology of diabetes mellitus with complexity-based computerized models: A quasi-experimental study. *Nurse education today*, 61:175–181, 2018.

Abstract: Background: Pharmacology is a crucial component of medications administration in nursing, yet nursing students generally find it difficult and self-rate their pharmacology skills as low. Objectives: To evaluate nursing students learning pharmacology with the Pharmacology Inter-Leaved Learning-Cells environment, a novel approach to modeling biochemical interactions using a multiscale, computer-based model with a complexity perspective based on a small set of entities and simple rules. This environment represents molecules, organelles and cells to enhance the understanding of cellular processes, and combines these cells at a higher scale to obtain whole-body interactions. Participants: Sophomore nursing students who learned the pharmacology of diabetes mellitus with the Pharmacology Inter-Leaved Learning-Cells environment (experimental group; $n = 94$) or via a lecture-based curriculum (comparison group; $n = 54$). Methods: A quasi-experimental pre- and post-test design was conducted. The Pharmacology-Diabetes-Mellitus questionnaire and the course's final exam were used to evaluate students' knowledge of the pharmacology of diabetes mellitus. Results: Conceptual learning was significantly higher for the experimental than for the comparison group for the course final exam scores (unpaired $t = -3.8, p < 0.001$) and for the Pharmacology-Diabetes-Mellitus questionnaire ($U = 942, p < 0.001$). The largest effect size for the Pharmacology-Diabetes-Mellitus questionnaire was for the medication action subscale. Analysis of complex-systems component reasoning revealed a significant difference for micro-macro transitions between the levels ($F(1, 82) = 6.9, p < 0.05$). Conclusions: Learning with complexity-based computerized models is highly effective and enhances the understanding of moving between micro and macro levels of the biochemical phenomena, this is then related to better understanding of medication actions. Moreover, the Pharmacology Inter-Leaved Learning-Cells approach provides a more general reasoning scheme for biochemical processes, which enhances pharmacology learning beyond the specific topic learned. The present study implies that deeper understanding of pharmacology will support nursing students' clinical decisions and empower their proficiency in medications administration.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Duboz:2003]

R. Duboz, É. Ramat, and P. Preux. Scale transfer modeling: using emergent computation for coupling an ordinary differential equation system with a reactive agent model. *Systems Analysis Modelling Simulation*, 43(6):793–814, 2003.

Abstract: This article deals with the coupling of analytical models with individual based models design with the reactive agents paradigm. Such a coupling of models of different natures is motivated by the need to find a way to model scale transfer in large complex systems, i.e. to model how low level of organization can be made to influence upper level and vice versa. This is a fundamental issue, and more particularly in ecological modeling where models are a real scientific tool of investigation. Individuals and populations are not described at the same scale of time and space but it is known that they act on each others. Based on this example, we model individuals in their environment and the population dynamics. While behavior is best modeled using an algorithmic framework (the reactive agent paradigm), population dynamics (because of the number of interacting entities) is best modeled using numerical models. We propose the use of the concept of emergent computation as a framework for coupling heterogeneous formalisms. In the same time, it is crucial to be aware of the consequences of the simplifications and of the choices that are made in the reactive agent model, such as the topology of space and various parameters. In this article, we discuss these issues and our approach on a case study drawn from marine ecology and we show that it is possible to find classical mathematical functional responses with a reactive agent system. Then, we propose a methodology to deal with the coupling of heterogeneous formalism useful in any kind of system modeling.

Keywords: multi-agent based simulation, multi-level, multi-scale, ecology, multi-model, french team

[Duboz:2004]

R. Duboz. *Intégration de modèles hétérogènes pour la modélisation et la simulation de systèmes complexes*. PhD thesis, Université du Littoral, 2004.

Abstract: Complex systems studies are becoming a science. Computer science is one of the theoretical and operational basis towards this evolution. Modelling and simulation (M&S) of dynamical systems is currently a central activity in a lot of sciences. M&S brings numerous paradigms and methods for the specification and the simulation of complex artificial or natural systems. This work aims at tackling the issue of interoperability between heterogeneous models following three directions: formal integration, operationnal integration, multi-scales integration. Considering a marine prey-predator systems (copepods grazing on phytoplankton). First, we bring together the reactive agent paradigm with the DEVS formal specification langage. DEVS enables the complete formal description of a Multi-Agents System (MAS), well suited for individual modelling, coupled with a differential equations system (well suited for population modelling). Secondly, we propose a framework for the integration of heterogeneous models. Our framework is mainly based on the concept of "wrapper". It provides us a way to interoperate different models based on DEVS abstract simulators. In this context, we develop a particular XML application for the description of models and models coupling. The last point of our work concerns scale transfers modelling in natural systems. We develop a method to achieve it and illustrate this method with our prey-predator model. The construction of a mathematical model based on simulations from our MAS leads to the coupling of our MAS with a differential equations systems. Then, we show that micro-level activity (individuals) has a potentially strong effect on macro-level dynamics (populations).

Keywords: multi-agent based simulation, multi-level, multi-model, multi-scale, ecology, in french, french team

[Ducrot:2010]

R. Ducrot, A. Botta, P. D'Aquino, M. Antona, G. Abrami, S. Farolfi, J-P. Müller, E. Lagabriele, and C. Le Page. *Modélisation d'accompagnement*, chapter Changement d'échelle et niveaux d'organisation multiples, pages 251–275. Editions Quæ, 2010.

Keywords: multi-agent based simulation, multi-level, ecology, in french, french team

[Ducrot:2014]

R. Ducrot, A. Botta, P. D'Aquino, M. Antona, G. Abrami, S. Farolfi, J-P. Müller, E. Lagabriele, and C. Le Page. *Companion Modelling*, chapter The Companion Modelling Approach: Dealing with Multiple Scales and Multiple Levels of Organization, pages 263–290. Editions Quæ, 2014.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Duhail:2013]

N. Duhail. DEVS et ses extensions pour des simulations multi-modèles en interaction multi-échelles. Master's thesis, Université de Rennes 1 — Telecom Bretagne, 2013.

Keywords: multi-agent based simulation, multi-level, DEVS, review, in french, french team

[Dutta:2014]

J. Dutta-Moscato, A. Solovyev, Q. Mi, T. Nishikawa, A. Soto-Gutierrez, I. J. Fox, and Y. Vodovotz. A multiscale agent-based in silico model of liver fibrosis progression. *Frontiers in Bioengineering and Biotechnology*, 2(18), 2014.

Abstract: Chronic hepatic inflammation involves a complex interplay of inflammatory and mechanical influences, ultimately manifesting in a characteristic histopathology of liver fibrosis. We created an agent-based model (ABM) of liver tissue in order to computationally examine the consequence of liver inflammation. Our liver fibrosis ABM (LFABM) is comprised of literature-derived rules describing molecular and histopathological aspects of inflammation and fibrosis in a section of chemically injured liver. Hepatocytes are modeled as agents within hexagonal lobules. Injury triggers an inflammatory reaction, which leads to activation of local Kupffer cells and recruitment of monocytes from circulation. Portal fibroblasts and hepatic stellate cells are activated locally by the products of inflammation. The various agents in the simulation are regulated by above-threshold concentrations of pro- and anti-inflammatory cytokines and damage-associated molecular pattern molecules. The simulation progresses from chronic inflammation to collagen deposition, exhibiting periportal fibrosis followed by bridging fibrosis, and culminating in disruption of the regular lobular structure. The ABM exhibited key histopathological features observed in liver sections from rats treated with carbon tetrachloride (CCl₄). An in silico "tension test" for the hepatic lobules predicted an overall increase in tissue stiffness, in line with clinical elastography literature and published studies in CCl₄-treated rats. Therapy simulations suggested differential anti-fibrotic effects of neutralizing tumor necrosis factor alpha vs. enhancing M2 Kupffer cells. We conclude that a computational model of liver inflammation on a structural skeleton of physical forces can recapitulate key histopathological and macroscopic properties of CCl₄-injured liver. This multiscale approach linking molecular and chemomechanical stimuli enables a model that could be used to gain translationally relevant insights into liver fibrosis.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Edgington:2015]

M.P. Edgington and M.J. Tindall. Understanding the link between single cell and population scale responses of escherichia coli in differing ligand gradients. *Computational and Structural Biotechnology Journal*, 2015.

Abstract: We formulate an agent-based population model of Escherichia coli cells which incorporates a description of the chemotaxis signalling cascade at the single cell scale. The model is used to gain insight into the link between the signalling cascade dynamics and the overall population response to differing chemoattractant gradients. Firstly, we consider how the observed variation in total (phosphorylated and unphosphorylated) signalling protein concentration affects the ability of cells to accumulate in differing chemoattractant gradients. Results reveal that a variation in total cell protein concentration between cells may be a mechanism for the survival of cell colonies across a wide range of differing environments. We then study the response of cells in the presence of two different chemoattractants. In doing so we demonstrate that the population scale response depends not on the absolute concentration of each chemoattractant but on the sensitivity of the chemoreceptors to their respective concentrations. Our results show the clear link between single cell features and the overall environment in which cells reside.

Keywords: multi-agent based simulation, multi-level, biology

[El-Hmam:2006b]

M.S. El hмам, D. Jolly, H. Abouaïssa, and A. Benasser. Modélisation hybride du flux de trafic. *Revue électronique Sciences et Technologies de l'Automatique*, 2006.

Abstract: Cet article présente une approche de modélisation de flux de trafic dite hybride. Cette démarche récemment adoptée par les chercheurs en transport utilise conjointement les deux représentations de flux de trafic : microscopique et macroscopique. L'intérêt de ce couplage est de bénéficier des atouts des deux modèles tout en évitant leurs inconvénients. En effet, il s'agit d'adapter le modèle au niveau de détails et à la taille des phénomènes à traiter.

Keywords: multi-agent based simulation, multi-level, hybrid model, flow model, traffic, in french, french team

[El-hmam:2006]

M.S. El hмам, H. Abouaïssa, D. Jolly, and A. Benasser. Macro-micro simulation of traffic flow. In *Proceedings of the 12th IFAC Symposium on Information Control Problems in Manufacturing (INCOM06)*, pages 351–356, 2006.

Abstract: This paper presents the recent progress in the development of the hybrid concept for the traffic simulation. The main objective is to couple two traffic representation models with different scale levels. The first allows a global traffic representation providing the possibility to simulate a large network. The second model focuses on the individual interactions of vehicles and allows then to understand the phenomena of the microscopic point of view. The paper shows that the proposed approach is generic allowing the cohabitation of various macroscopic models with the microscopic model developed using the agent paradigm. It presents also some simulation results that illustrate the relevance of the elaborated approach.

Keywords: multi-agent based simulation, multi-level, hybrid model, flow model, traffic, french team

[El-hmam:2006a]

M.S. El hмам, H. Abouaïssa, D. Jolly, and A. Benasser. Simulation hybride de flux de trafic basée sur les systèmes multi-agents. In *6e Conférence Francophone de Modélisation et Simulation-MOSIM*, 2006.

Keywords: multi-agent based simulation, multi-level, hybrid model, flow model, traffic, in french, french team

[El-hmam:2008]

M.S. El hмам, H. Abouaïssa, and D. Jolly. Contribution à la modélisation et la simulation du flux de trafic: approche hybride basée sur les systèmes multi-agents. *Actes INRETS*, pages 93–111, 2008.

Keywords: multi-agent based simulation, multi-level, hybrid model, flow model, traffic, in french, french team

[Espie:2006]

S. Espié, D. Gattuso, and F. Galante. Hybrid traffic model coupling macro- and behavioral microsimulation. In *85th Annual Meeting of Transportation Research Board*, 2006.

Abstract: The dynamics of traffic flow are affected by phenomena occurring and interacting on a wide range of spatial dimensions. The scales involved range from individual vehicles through collective effects and up to the network level. A promising approach to this problem is the coupling of two different traffic models able to handle a wide range of phenomena. The result of this approach is a “hybrid” model. After the introduction of the general description and the fundamental

properties of hybrid models, a hybrid model is presented, mixing ARCHISIM, a microscopic behavioural model, and SSMT, a shock-wave based macroscopic model. After a short description of the two models the coupling scheme is illustrated; it has been developed in order to allow a proper transmission and translation of the information between the presented models. Finally, a validation of the resulting model is proposed for three different traffic conditions and some possible future extensions to this model are shown.

Keywords: multi-agent based simulation, multi-level, traffic, french team

[Ezanno:2018]

P. Ezanno, G. Beaunée, S. Picault, S. Arnoux, V. Sicard, F. Beaudou, A. Rault, and E. Vergu. Gestion des maladies endémiques du troupeau aux territoires : contribution de la modélisation épidémiologique pour soutenir la prise de décision (projet mihmes, 2012-2017). *Innovations Agronomiques*, 66:53–65, 2018.

Abstract: Une bonne maîtrise des maladies endémiques contribue à la durabilité et la compétitivité de l'élevage, à la santé publique vétérinaire, et au bien-être animal. L'enjeu est de mieux comprendre les interactions entre processus d'infection, processus de gestion, et allocation des ressources à la maîtrise, ainsi que d'évaluer et hiérarchiser le panel de stratégies de maîtrise disponibles en tenant compte des spécificités du système. Face à ces enjeux de compréhension et de prédiction, la modélisation mécaniste est une approche pertinente. De plus, il est possible de développer des outils logiciels reposant sur ces modèles, valorisant connaissances et méthodes acquises lors de travaux de recherche et fournissant aux gestionnaires de la santé des outils innovants pour soutenir les décisions individuelles et collectives. Au travers de résultats marquants du projet investissements d'avenir MIHMES (2012-2017), notre objectif est d'illustrer la contribution d'une approche de modélisation mécaniste pour répondre aux enjeux sanitaires actuels en contexte de ressources contraintes et de discuter des enjeux nouveaux identifiés et des perspectives de recherche et développement associées

Keywords: multi-agent based simulation, multi-level, multi-scale, epidemiology

[Foni:2018]

S. Foni and L. Ronchini. A cyber security strategy to mitigate risks in complex and critical environments: the case of airports. *Cybersecurity Trends*, (2):12–15, 2018.

Abstract: Airports are critical and complex systems that represent an excellent case study for establishing a flexible and reusable cyber security framework for risk mitigation. A complex system is made up of interacting components (agents) that adapt their behavior overtime in reaction to changes with respect to their environment and to each other [3]. Within such infrastructures, absolute security does not exist, because it is unfeasible to protect the whole system against every possible threat that might occur, especially those due to human errors and IT cyber degradation events. However the right use of cyber security best practices, the adoption of a cyclic and stratified Topdown investigative approach, the non-stop review of operating processes, the exertion of an appropriate cyber resilience plan, and the admission of staff training courses in order to raise employee awareness on security issues, can limit the likelihood of triggering events that could cause damage to people, structures, and assets, preventing them from experiencing economic losses or reputation damages. The only viable solution is to establish a never ending procedure of cyber security improvement, providing a suitable trade off in terms of protection and usability, with the aim of merging it with common everyday practices, avoiding any kind of impact on the company mission. In this investigation we will assess airport security using an emergent vision, inspired by the paradigms of stigmergy and swarm intelligence, in order to establish a capillary control of complex systems endowed with a chaotic, interconnected, sociotechnical and strongly dynamic-dependent nature, both from a physical and operational point of view. This research has the aim to minimize the risk related to airport weaknesses taking advantage of an analytical complex systems approach and of a continuous improvement in cyber resilience.

Keywords: multi-agent based simulation, multi-level, security

[Franceschini:2019]

R. Franceschini, S. Van Mierlo, and H. Vangheluwe. Towards adaptive abstraction in agent based simulation. In *2019 Winter Simulation Conference (WSC)*, pages 2725–2736, 2019.

Abstract: Humans often switch between different levels of abstraction when reasoning about salient properties of systems with complex dynamics. In this paper, we study and compare multiple modelling and simulation techniques for switching between abstractions. This improves insight and explainability as well as simulation performance, while still producing identical answers to questions about properties. Traffic flow modelled using an Agent Based Simulation formalism is used to demonstrate the introduced concepts. The technique requires explicit models (1) of the dynamics of both individual cars and of emergent “jams”, (2) of the conditions –often involving

complex temporal patterns– under which switching between the levels of abstraction becomes possible/necessary and (3) of the state initialization after a switch. While aggregation is natural when going from detailed to abstract, the opposite direction requires additional state variables in the abstract model.

Keywords: multi-agent based simulation, multi-level, traffic

- [Franceschini:2019a] R. Franceschini, M. Challenger, A. Cicchetti, J. Denil, and H. Vangheluwe. Challenges for automation in adaptive abstraction. In *Proc of 22nd Int. Conf. on Model Driven Engineering Languages and Systems Companion (MODELS-C)*, pages 443–448, 2019.

Abstract: Models are well-defined abstractions that provide cost-effective representations of the real-world for a precise purpose. When dealing with complex problems, there usually exist multiple abstractions, typically describing partially overlapping details of the system under study, and resulting in a hierarchy of abstractions. Adaptive abstraction leverages these levels with the aim of dynamically adapting the abstractions used during system execution. In this paper, we describe such process in terms of a MAPE-K (Monitor-Analyze-Plan-Execute over a shared Knowledge) control loop to discuss the challenges towards adaptive abstraction automation. In particular, we elaborate on adaptively selecting a candidate over multiple abstractions, an unaddressed issue in the literature. The discussion is supported by a running example in an agent-based simulation scenario.

Keywords: multi-agent based simulation, multi-level

- [Fuchs:2005] C. Fuchs and W. Hofkirchner. The dialectic of bottom-up and top-down emergence in social systems. *Cognition, Communication, Co-operation*, 3(2), 2005.

Abstract: In this paper we will present a theoretical explanation of the relationship between so-called individual emergence and the emergence of social systems. We want to take as our point of departure the assumption that from the perspective of hierarchical systems theory self-organization on the level of social systems includes a bottom-up process as well as a top-down process. The bottom-up process refers to what in sociology is called agency, the top-down process refers to what is called structure. We will show that it is convenient to suggest that these processes be linked in a dialectical manner. In this respect we will discuss problems of determinism and indeterminism. This is the background against which we will try to clarify the notion of individual emergence. Our rather general considerations will be illustrated by how ideology, that is consciousness in a collective as well as an individual sense, is conceived of by a number of theories and how it should be conceived of when aspects of self-organization are included. We will conclude with a statement that makes clear why consciousness is a property of individuals that emerges only when individuals participate in society and why society emerges only when individuals are endowed with consciousness.

Keywords: multi-agent based simulation, social simulation, multi-level

- [Gao:2017] H. Gao, Z. Yin, Z. Cao, and L. Zhang. Developing an agent-based drug model to investigate the synergistic effects of drug combinations. *Molecules*, 22(12):2209, 2017.

Abstract: The growth and survival of cancer cells are greatly related to their surrounding microenvironment. To understand the regulation under the impact of anti-cancer drugs and their synergistic effects, we have developed a multiscale agent-based model that can investigate the synergistic effects of drug combinations with three innovations. First, it explores the synergistic effects of drug combinations in a huge dose combinational space at the cell line level. Second, it can simulate the interaction between cells and their microenvironment. Third, it employs both local and global optimization algorithms to train the key parameters and validate the predictive power of the model by using experimental data. The research results indicate that our multicellular system can not only describe the interactions between the microenvironment and cells in detail, but also predict the synergistic effects of drug combinations.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

- [Garbey:2017] M. Garbey, G. Joerger, J. Rambourg, B. Dunkin, and B. Bass. Multiscale modeling of surgical flow in a large operating room suite: Understanding the mechanism of accumulation of delays in clinical practice. *Procedia Computer Science*, 108:1863–1872, 2017.

Abstract: Improving operating room (OR) management in large hospitals has been a challenging problem that remains largely unresolved [7]. Fifty percent of hospital income depends on OR activities and among the main concerns in most institutions is to improve efficiency of a large OR suite that. We advocate that optimizing surgical flow in large OR suites is a complex multi-factorial problem with an underlying multiscale structure. Numerous components of the system can combine nonlinearly result in the large accumulated delays observed in daily clinical practice. We propose a multiscale agent-based model (ABM) of surgical flow. We developed a smartOR system that utilizes a dedicated network of non-invasive, wireless sensors to automatically track the state of the OR and accurately computes major indicators of performances such as turnover time between procedures. We show that our model can fit these time measurements and that a multiscale description of the system is possible. We will discuss how this model can be used to quantify and target the main limiting factors in optimizing OR suite efficiency.

Keywords: multi-agent based simulation, multi-level, multi-scale

[Gaud:2007]

N. Gaud. *Systèmes multi-agent holoniques : De l'analyse à l'implantation. Méta-modèle, méthodologie, et simulation multi-niveaux*. PhD thesis, UTBM, 2007.

Abstract: The work, presented in this PhD thesis, is concerned with the study of complex systems and aims at providing a full set of abstractions and the associated methodological guidelines for the analysis, design, implementation and simulation of Holonic MultiAgent Systems (HMAS). HMAS offers a promising software engineering approach for developing complex open software systems. This kind of systems consists in self-similar structures called holons. A set of holons maybe seen, depending on the level of observation, as a unique entity or as a group of holons in interaction. A complex system is made up of a large number of parts that have many interactions. In such systems, the behavior of the whole cannot be directly understood only by knowing the behavior of the parts and their interactions. Complex systems often exhibit a hierarchical structure. The foundation of this thesis consist in exploiting the intrinsic hierarchical structure of complex systems to analyse and decompose them. In order to conceive modular and reusable models, an organizational approach is adopted. The principle of the analysis is based on the identification of a hierarchy of organizations, which the global behavior may represent the system under the chosen perspective. The behaviors of the system are recursively decomposed into a set of interacting sub-behaviors, each of these latter being in turn decomposed until we reach some lowest level of elementary sub-behaviors. At a given level, the composed behavior is modeled using an organization, and the associated sub-behaviors using roles. The hierarchical organization structure is then mapped to holarchy (hierarchy of holons) in charge of its execution. The concepts presented are then used to study the issues related to the multilevel multiagent simulation. The resulting model is finally applied to the pedestrians simulation in virtual environment.

Keywords: multi-agent based simulation, multi-level, holonic systems, in french, french team

[Gaud:2008]

N. Gaud, S. Galland, F. Gechter, V. Hilaire, and A. Koukam. Holonic multilevel simulation of complex systems : Application to real-time pedestrians simulation in virtual urban environment. *Simulation Modelling Practice and Theory*, 16:1659–1676, 2008.

Abstract: Simulation, which creates abstractions of the system is an appropriate approach for studying complex systems that are inaccessible through direct observation and measurement. The problem with simulation of great numbers of interacting entities is that it is difficult to create a reliable and tractable abstraction of the real system. Indeed, simulating large numbers of entities requires great computing resources. A solution to avoid this problem is to use macroscopic models. However, this type of model may be unavailable or not reliable for the problem at hand and it does not allow the observation of individual behaviours. In this paper, a multilevel simulation model is proposed to allow the use of both microscopic and macroscopic techniques. This model is based upon Holonic Multi-Agent Systems which offer a promising approach for developing applications in complex domains characterised by a hierarchical structure. The proposed approach provides a generic scheduling model for multilevel simulations: dynamically adapting the level of simulated behaviours while being as faithful as possible to the simulated model. It does not only manage the level of entities' behaviour but also of behaviours classically assigned to the environmental part of a simulation. A set of physics-based indicators is also introduced to dynamically determine the most suitable level for each entity and to maintain the best trade-off between simulation accuracy and constraints (dependent on the model or the experimental context).

Keywords: multi-agent based simulation, multi-level, holonic systems, french team

[Gaud:2008a]

N. Gaud, S. Galland, and A. Koukam. Towards a multilevel simulation approach based on holonic multi-agent systems. In *UKSIM*, pages 180–185, Cambridge, UK, april 2008.

Abstract: Simulation is an appropriate approach for studying complex systems that are inaccessible through direct observations and measurements. In a simulation involving a great number of interacting entities, it is difficult to create a reliable and tractable abstraction of the real reference system. One of the involved problems is amount of computational resources required to handle microscopic simulation of large number of entities. One solution is to use macroscopic models. However, this type of models may be at hand unavailable or not reliable, or it doesn't allow observations of individual behaviours. In this paper a multilevel simulation model is proposed to dynamically adapt the level of simulated behaviours while being as faithful as possible to the reference model. Our approach is based on Holonic Multi-Agent Systems and provides a generic scheduling model for multilevel simulations.

Keywords: multi-agent based simulation, multi-level, holonic systems, meta-model, french team

[Gauthier:2019]

N. Gauthier. Multilevel simulation of demography and food production in ancient agrarian societies: A case study from roman north africa. *SocArXiv*, 2019.

Abstract: Feedbacks between population growth, food production, and the environment were central to the growth and decay of ancient agrarian societies. Population growth increases both the number of mouths a society must feed and the number of people working to feed them. The balance between these two forces depends on the population's age structure. Although age structure ultimately reflects individual fertility and mortality, it is households that make decisions about the production and consumption of food, and their decisions depend on interactions with all other households in a settlement. How do these organizational levels interact to influence population growth and regulation? Here, I present a multi-level agent-based model of demography, food production, and social interaction in agricultural societies. I use the model to simulate the interactions of individuals, households, and settlements in a food-limited environment, and investigate the resulting patterns of population growth. Using Roman North Africa as a motivating example, I illustrate how abstract properties like "carrying capacity" emerge from the concrete actions and interactions of millions of individual people. Looking forward, bottom-up simulations rooted in first principles of human behavior will be crucial for understanding the coevolution of preindustrial societies and their natural environments.

Keywords: multi-agent based simulation, multi-level, social simulation

[Gauthier:2019a]

N. Gauthier. *Archaeological Approaches to Population Growth and Social Interaction in Semiarid Environments: Pattern, Process, and Feedbacks*. PhD thesis, Arizona State University, 2019.

Abstract: Population growth, social interaction, and environmental variability are interrelated facets of the same complex system. Tracing the flow of food, water, information, and energy within these social-ecological systems is essential for understanding their long-term behavior. Leveraging an archaeological perspective of how past societies coevolved with their natural environments will be critical to anticipating the impact of impending climate change on farming communities in the developing world. However, there is currently a lack of formal, quantitative theory rooted in first principles of human behavior that can predict the empirical regularities of the archaeological record in semiarid regions. Through a series of models – statistical, computational, and mathematical – and empirical data from two long-term archaeological case studies in the pre-Hispanic American Southwest and Roman North Africa, I explore the feedbacks between population growth and social interaction in water-limited agrarian societies. First, I use a statistical model to analyze a database of 7.5 million artifacts collected from nearly 500 archaeological sites in the Southwest and found that sites located in different climatic zones were more likely to interact with one another than a sites occupying the same zone. Next, I develop a computational model of demography and food production in ancient agrarian societies and, using North Africa as a motivating example, show how the concrete actions and interactions of millions of individual people lead to emergent patterns of population growth and stability. Finally, I build a simple mathematical model of trade and migration among agricultural settlements to determine how the relative costs and benefits of social interaction drive population growth and shape long-term settlement patterns. Together, these studies form the foundation for a unified quantitative approach to regional social-ecological systems. By combining theory and methods from ecology, geography, and climate science, archaeologists can better leverage insights from diverse times and places to fill critical knowledge gaps in the study of food security and sustainability in the drylands of today.

Keywords: multi-agent based simulation, multi-level, social simulation

[Gerst:2013]

M.D. Gerst, P. Wang, A. Roventini, G. Fagiolo, G. Dosi, R.B. Howarth, and M.E. Borsuk. Agent-based modeling of climate policy: An introduction to the ENGAGE multi-level model framework. *Environmental Modelling & Software*, 44:62–75, 2013.

Abstract: Model-based support of climate policy is scientifically challenging because climate change involves linked physical and social systems that operate on multiple levels: local, national, and international. As a result, models must employ some strongly simplifying assumptions. The most frequently used models typically assume hyper-rational and homogenous human behavior. These ensure tractability but, as a trade-off, abstract away the effects of less-than-rational decision-making and actor heterogeneity on domestic policy effectiveness and the influence of domestic constituents on international policy agreement. In this paper, we introduce a multi-level model framework, called ENGAGE, that relaxes some common modeling assumptions by adopting an agent-based approach. ENGAGE is styled after the Putnam two-level game, in which negotiators at the international level are constrained by the heterogeneous policy preferences and power of constituents at the domestic level. We proceed to provide a detailed description and demonstration of the prototype domestic-level module. Domestic actors include firms and households who function as agents within an evolutionary representation of economic growth, energy technology, and climate change. This allows an evaluation of policies that accounts for agent decision-making and social and technological change. Ultimately, we plan to use the ENGAGE model to simulate the two-way dynamic feedback between international agreements and domestic policy outcomes.

Keywords: multi-agent based simulation, multi-level, ecology

[Ghadiri:2017]

M. Ghadiri, M. Heidari, S-A. Marashi, and S.A. Mousavi. A multiscale agent-based framework integrated with a constraint-based metabolic network model of cancer for simulating avascular tumor growth. *Molecular BioSystems*, 2017.

Abstract: In recent years, many efforts have been made in the field of computational modeling of cancerous tumors, in order to obtain a better understanding and predictions of their growth patterns. Furthermore, constraint-based modeling of metabolic networks has become increasingly popular, which is appropriate for the systems-level reconstruction of cell physiology. The goal of the current study is to integrate a multiscale agent-based modeling framework with a constraint-based metabolic network model of cancer cells in order to simulate the three dimensional early growth of avascular tumors. In order to develop the integrated model, a previously published generic metabolic network model of cancer cells was introduced into a multiscale agent-based framework. This model is initiated with a single tumor cell. Nutrients can diffuse through the simulation space and the cells uptake or excrete metabolites, grow, proliferate or become necrotic based on certain defined criteria and flux values of particular reactions. The simulation was run for a period of 20 days and the plots corresponding to various features such as the growth profile and necrotic core evolution were obtained. These features were compared with the ones observed in other (experimental) studies. One interesting characteristic of our modeling is that it provides us with the ability to predict gene expression patterns through different layers of a tumor, which can have important implications, especially in drug target selection in the field of cancer therapy.

Keywords: multi-agent based simulation, multi-level, multi-scale, cancer modeling

[Gil-Quijano:2007]

J. Gil-Quijano. *Modèles d'auto-organisation pour l'émergence de formes urbaines à partir de comportements individuels à Bogota*. PhD thesis, Université Paris VI, 2007.

Abstract: L'objectif principal de notre travail est de reproduire l'évolution de la distribution de la population d'une ville. Le parti pris est de privilégier une vision synthétique de la ville. Notre approche se fonde sur une modélisation de l'interaction entre un niveau intermédiaire (constitué par des groupes sociaux et des types d'habitat) et un niveau individuel (constitué par des ménages et des logements). Pour représenter l'évolution de la population de la ville et du parc du logement à la différence des approches classiques de microsimulation, nous privilégions une approche globale : nous considérons des règles générales d'évolution basées sur des quotas de ménages et de logements. À partir de ces principes, nous avons développé un modèle de simulation multi-agent basé sur la concurrence entre groupes sociaux pour des groupes de logements libres, dans un marché du logement. Nous avons utilisé ce modèle pour reproduire l'évolution de la distribution de la ville de Bogota entre 1973 et 1993.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Gil-Quijano:2007a]

J. Gil-Quijano and M. Piron. Formation automatique de groupes d'agents sociaux par techniques d'apprentissage non supervisé. In *Actes de EGC'07 Atelier Fouille de Données et Algorithmes Biomimétiques*, january 23 2007.

Keywords: multi-agent based simulation, multi-level, social simulation, emergence detection, in french, french team

- [Gil-Quijano:2007b] J. Gil-Quijano, M. Piron, and A. Drogoul. Vers une simulation multi-agent de groupes d'individus pour modéliser les mobilités résidentielles intra-urbaines. *Revue internationale de géomatique*, 17(2):161–181, 2007.

Abstract: Within the framework of a research program on spatial mobility and the territorial transformations of the town of Bogotá, we propose a multi-agent simulation system to model intra-urban residential mobility. For that model we have chosen to locate the decisionmaking at the mesoscopic level of relevant groups of individuals, built in an emergent way from the individual level. The system consists of two intertwined models. The first one models the formation of groups of individuals (based on similarity calculations based on their socioeconomical characteristics) and their evolution thanks to the definition of general rules; the motivation to move is implemented at the individual level. The second model is economical: it locates the decision to move at the aggregate level and models residential mobility using a mechanism of housings auctions.

Keywords: multi-agent based simulation, multi-level, in french, french team

- [Gil-Quijano:2008] J. Gil-Quijano, M. Piron, and A. Drogoul. *Social Simulation: Technologies, Advances and New Discoveries*, chapter Mechanisms of Automated Formation and Evolution of Social-Groups: A Multi-Agent System to Model the Intra-Urban Mobilities of Bogota City, pages 151–168. IGI Global, 2008.

Abstract: In this chapter, we present a multi-agent system that models and simulates the dynamics of intra-urban mobility through the automated formation and evolution of both groups of households and groups of housing-units. We consider global rules of evolution instead of individual events to represent the evolution of both the population and the housing-stock. The moving mechanism is modelled by interactions between groups and urban-sectors agents in a simulated housing market. We have tested this system on the basis of several censuses datasets of Bogotá city. The evolution of groups has been simulated over 20 years and compared to real data. The results of group formation and evolution mechanisms have been compared to classes produced by classical classification methods. Very good correlations have been found. The simulated population has been compared to real distributions of several Bogotá districts and appears to be close for an important number of them.

Keywords: multi-agent based simulation, multi-level, social simulation, emergence detection, french team

- [Gil-Quijano:2009] J. Gil-Quijano, G. Hutzler, and T. Louail. De la cellule biologique à la cellule urbaine : retour sur trois expériences de modélisation multi-échelles à base d'agents. In *Actes des 17èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA'09)*, 2009.

Abstract: Lorsque l'on simule des systèmes complexes, il est souvent nécessaire de considérer des entités à différentes échelles d'organisation, et prendre en compte la façon dont celles-ci s'influencent. Le choix des échelles est conditionné par des contraintes méthodologiques qui incluent les objets manipulés par les thématiciens, la disponibilité des données, la question d'intérêt et également des contraintes algorithmiques. Différentes manières d'aborder les structures multi-échelles et les influences entre niveaux peuvent être identifiées. Dans un premier temps, nous présentons trois modèles multi-agents de dynamiques multi-échelles existants, centrés sur la croissance d'une tumeur cancéreuse, l'évolution de la distribution spatiale d'une population urbaine et l'évolution d'un réseau de villes. Nous proposons ensuite une grille de lecture de manière à comparer les différentes formes prises potentiellement par la notion de multi-échelles.

Keywords: multi-agent based simulation, multi-level, review, in french, french team

- [Gil-Quijano:2010] J. Gil-Quijano, G. Hutzler, and T. Louail. Accroche-toi au niveau, j'enlève l'échelle. éléments d'analyse des aspects multiniveaux dans la simulation à base d'agents. *RIA*, 24(5):625–648, 2010.

Abstract: Lorsque l'on modélise des systèmes complexes, il est souvent nécessaire de considérer des entités à plusieurs niveaux d'organisation et niveaux d'échelles. La prise en compte de ces niveaux, de leurs influences réciproques, et des dynamiques d'organisation aux interfaces entre eux, est un problème ardu pour lequel les solutions proposées sont souvent liées à une discipline ou à un cas d'étude particulier. Pour essayer d'aller vers une méthodologie plus générale de conception de modèles multiniveaux, nous proposons une grille d'analyse des approches utilisées, élaborée notamment à partir de l'étude de trois exemples en biologie et en géographie. Nous montrons ensuite, dans le cadre d'un exemple unificateur, comment différentes approches peuvent être combinées.

Keywords: multi-agent based simulation, multi-level, review, in french, french team

[Gil-Quijano:2010a] J. Gil-Quijano. Learning tools to assist modeling of multilevel complex systems. In *Technical Forum Group on Agent and Multi-agent-based Simulation*, 2010.

Keywords: multi-agent based simulation, multi-level, emergence detection, french team

[Gil-Quijano:2012] J. Gil-Quijano, T. Louail, and G. Hutzler. From biological to urban cells: Lessons from three multilevel agent-based models. In *Principles and Practice of Multi-Agent Systems*, volume 7057 of *LNCS*, pages 620–635. Springer, 2012.

Abstract: Modeling complex systems often implies to consider entities at several levels of organization and levels of scales. Taking into account these levels, their mutual interactions, and the organizational dynamics at the interface between levels, is a difficult problem, for which the proposed solutions are often related to a specific disciplinary field or a particular case study. In order to develop a broader methodology for designing multilevel models, we propose an analytical framework of existing approaches, drawn in particular from the study of three examples in biology and geography.

Keywords: multi-agent based simulation, multi-level, review, french team

[Girel:2018] S. Girel, C. Arpin, J. Marvel, O. Gandrillon, and F. Crauste. Model-based assessment of the role of uneven partitioning of molecular content on heterogeneity and regulation of differentiation in cd8 t-cell immune responses. *bioRxiv*, page 345165, 2018.

Abstract: Activation of naive CD8 T-cells can lead to the generation of multiple effector and memory subsets. Multiple parameters associated with activation conditions are involved in generating this diversity that is associated with heterogeneous molecular contents of activated cells. Naive cell polarisation upon antigenic stimulation and the asymmetric division that results are known to be a major source of heterogeneity and cell fate regulation. The consequences of stochastic uneven partitioning of molecular content upon subsequent divisions remain unclear. Here we aim at studying the impact of uneven partitioning on molecular-content heterogeneity and then on the immune response dynamics at the cellular level. To do so, we introduce a multiscale mathematical model of the CD8 T-cell immune response in the lymph node. In the model, cells are described as agents evolving and interacting in a 2D environment while a set of differential equations, embedded in each cell, models the regulation of intra and extracellular proteins involved in cell differentiation. Based on the analysis of *in silico* data at the single cell level, we show that immune response dynamics can be explained by the molecular-content heterogeneity generated by uneven partitioning at cell division. In particular, uneven partitioning acts as a regulator of cell differentiation and induces the emergence of two coexisting sub-populations of cells exhibiting antagonistic fates. We show that the degree of unevenness of molecular partitioning, along all cell divisions, affects the outcome of the immune response and can promote the generation of memory cells.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology, french team

[Gong:2017] C. Gong, O. Milberg, B. Wang, P. Vicini, R. Narwal, and A.S. Popel L. Roskos. A multiscale computational model for spatio-temporal tumor immune response. *ACCR Cancer Research, Proc. of the American Association for Cancer Research Annual Meeting*, 77(13 Suppl):Abstract nr 975, 2017.

Abstract: When the immune system responds to tumor development, patterns of immune infiltrates emerge, highlighted by expression of immune checkpoint-related molecules such as PD-L1 on cancer cells and its receptor PD-1 on cytotoxic T cells. Pre-treatment tumor spatial heterogeneity could bear information on intrinsic characteristics of the tumor lesion for individual patient, and thus has the potential to comprise biomarkers for anti-tumor therapeutics. We developed a systems biology computational multiscale agent-based model to capture the interactions between immune cells and cancer cells during tumor progression. Cytotoxic T cells and cancer cells are modeled as free-moving agents in a 3-dimensional grid, where each cell acts in response to its local microenvironment and carries out functions such as division, apoptosis, cytotoxic killing and switching between states with different PD-1 or PD-L1 expression levels. Subsequently, we analyzed the emergent behavior of tumor progression by looking at all these local interactions as a whole. Using this model, we are able to reproduce temporal dynamics of cytotoxic T cells and cancer cells during general tumor progression, as well as 3-dimensional spatial distributions of these cells over the time course of the simulation. By varying the characteristics of the neoantigen profile of individual patients, such as mutational burden and immunogenicity, a spectrum

of pre-treatment spatial patterns of PD-1/PD-L1 expression is generated in our simulations, resembling immune-architectures obtained via immunohistochemistry from patient biopsies. We evaluate potential prognostic biomarkers by correlating these spatial characteristics with *in silico* treatment results with immune checkpoint inhibitors. Simulation results demonstrate that the percentage of PD-L1 positive cancer cells which are not in close proximity of the tumor boundary or vasculature is more indicative of successful anti-PD1/anti-PD-L1 treatment. Our findings suggest that tumor spatial heterogeneity, especially its immune-architecture, reflects the course of tumor progression as well as patient-specific properties, and is thus likely to carry important information about tumor susceptibility to treatment such as with immune checkpoint inhibitors. We demonstrated how prognostic biomarkers could be realistically simulated in a general cancer scenario. The model is further refined for use to predict treatment/biomarker combinations in specific cancer types.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Gong:2017a]

C. Gong, O. Milberg, B. Wang, P. Vicini, R. Narwal, L. Roskos, and A.S. Popel. A computational multiscale agent-based model for simulating spatio-temporal tumour immune response to pd1 and pdl1 inhibition. *Journal of The Royal Society Interface*, 14(134):20170320, 2017.

Abstract: When the immune system responds to tumour development, patterns of immune infiltrates emerge, highlighted by the expression of immune checkpoint-related molecules such as PDL1 on the surface of cancer cells. Such spatial heterogeneity carries information on intrinsic characteristics of the tumour lesion for individual patients, and thus is a potential source for biomarkers for anti-tumour therapeutics. We developed a systems biology multiscale agent-based model to capture the interactions between immune cells and cancer cells, and analysed the emergent global behaviour during tumour development and immunotherapy. Using this model, we are able to reproduce temporal dynamics of cytotoxic T cells and cancer cells during tumour progression, as well as three-dimensional spatial distributions of these cells. By varying the characteristics of the neoantigen profile of individual patients, such as mutational burden and antigen strength, a spectrum of pretreatment spatial patterns of PDL1 expression is generated in our simulations, resembling immuno-architectures obtained via immunohistochemistry from patient biopsies. By correlating these spatial characteristics with *in silico* treatment results using immune checkpoint inhibitors, the model provides a framework for use to predict treatment/biomarker combinations in different cancer types based on cancer-specific experimental data.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Grebennikov:2019emational] D.S. Grebennikov, D.O. Donets, O.G. Orlova, J. Argilaguet, A. Meyerhans, and G.A. Bocharov. Mathematical modeling of the intracellular regulation of immune processes. *Molecular Biology*, 53(5):718–731, 2019.

Abstract: The modern era of research in immunology is characterized by an unprecedented level of detail about structural characteristics of the immune system and the regulation of activities of its numerous components, which function together as a whole distributed-parameter system. Mathematical modeling provides an analytical tool to describe, analyze, and predict the dynamics of immune responses by applying a reductionist approach. In modern systems immunology and mathematical immunology as a new interdisciplinary field, a great challenge is to formulate the mathematical models of the human immune system that reflect the level achieved in understanding its structure and describe the processes that sustain its function. To this end, a systematic development of multiscale mathematical models has to be advanced. An appropriate methodology should consider (1) the intracellular processes of immune cell fate regulation, (2) the population dynamics of immune cells in various organs, and (3) systemic immunophysiological processes in the whole host organism. Main studies aimed at modeling the intracellular regulatory networks are reviewed in the context of multiscale mathematical modelling. The processes considered determine the regulation of the immune cell fate, including activation, division, differentiation, apoptosis, and migration. Because of the complexity and high dimensionality of the regulatory networks, identifying the parsimonious descriptions of signaling pathways and regulatory loops is a pressing problem of modern mathematical immunology.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Grignard:2013]

A. Grignard, P. Taillandier, B. Gaudou, D. A. Vo, N. Q. Huynh, and A. Drogoul. GAMA 1.6: Advancing the art of complex agent-based modeling and simulation. In *PRIMA 2013: Principles and Practice of Multi-Agent Systems*, volume 8291 of *LNCS*, pages 117–131. Springer, 2013.

Abstract: Agent-based models tend to be more and more complex. In order to cope with this increase of complexity, powerful modeling and simulation tools are required. These last years have seen the development of several platforms dedicated to the development of agent-based models. While some of them are still limited to the development of simple models, others allow to develop rich and complex models. Among them, the GAMA modeling and simulation platform is aimed at supporting the design of spatialized, multiple-paradigms and multiple-scales models. Several papers have already introduced GAMA, notably in earlier PRIMA conferences, and we would like, in this paper, to introduce the new features provided by GAMA 1.6, the latest revision to date of the platform. In particular, we present its capabilities concerning the tight combination of 3D visualization, GIS data management, and multi-level modeling. In addition, we present some examples of real projects that rely on GAMA to develop complex models.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Gurkan:2019]

C. Gurkan, L. Rasmussen, and U. Wilensky. Effects of visual sensory range on the emergence of cognition in early terrestrial vertebrates: An agent-based modeling approach. In *The 2018 Conference on Artificial Life: A Hybrid of the European Conference on Artificial Life (ECAL) and the International Conference on the Synthesis and Simulation of Living Systems (ALIFE)*, pages 475–476. MIT Press, 2019.

Abstract: As water dwelling vertebrates began to progressively evolve features that enabled them to survive on land, they also developed larger eyes, which would have considerably increased their range of vision above water. This increase in visual range may have facilitated their exploitation of new food sources on land and promoted increased cognitive capacity in the form of planning (MacIver et al., 2017). In this study, we use a multi-level agent-based model to attempt to replicate the dynamics of the hypothetical evolutionary scenario described above. To do so, we use a novel method called agent-centric Monte Carlo cognition (ACMCC) (Head and Wilensky, 2018), which allows us to represent the agents' cognition in a quantifiable manner by performing micro-simulations in a separate agent-based model. In our simulations, we observe that as a population that is adapted to live on land emerges, their mean eye size and cognitive capacity increase.

Keywords: multi-agent based simulation, multi-level, biology, evolution

[Gutlein:2018]

M. Gutlein, R. German, and A. Djanatliev. Towards a hybrid co-simulation framework: Hla-based coupling of matsim and sumo. In *2018 IEEE/ACM 22nd Int. Symp. on Distributed Simulation and Real Time Applications (DS-RT)*, pages 1–9. IEEE, 2018.

Abstract: Recent topics of interest such as smart cities and autonomous driving are currently in focus of many research activities. In this context, simulations are used to evaluate new algorithms, performance of current technologies, or the impact of upcoming products. In particular, they allow finding errors and optimizing parameter sets prospectively, prior to a real-world implementation. Simulation models of many traffic problems need to handle large-scale scenarios, connect entities from different domains, and run in feasible time. In order to meet these challenges, an extendable multi-level traffic simulation approach is proposed in this paper. We briefly introduce existing traffic simulation techniques, name upcoming problems, available solution approaches, and topics regarding the development of our framework. As a first step, we coupled two different resolution levels of traffic simulation by using High Level Architecture (HLA) and evaluated this approach in light of simulation results and simulation performance.

Keywords: multi-agent based simulation, multi-level, hybrid model, co-simulation, traffic

[Hamis:2019]

S. Hamis, J. Yates, M.A.J. Chaplain, and G.G Powathil. Targeting cellular dna damage responses: Predicting in vivo treatment responses using an in vitro-calibrated agent-based mathematical model. *bioRxiv*, 2019.

Abstract: The ATR (ataxia telangiectasia mutated and rad3-related kinase) inhibitor AZD6738 is an anti-cancer drug that potentially hinders tumour proliferation by targeting cellular DNA damage responses. In this study, we combine a systems pharmacology approach with an agent-based modelling approach to simulate AZD6738 treatment responses in silico. The mathematical model is governed by a set of empirically observable rules. By adjusting only the rules, whilst keeping the fundamental mathematical framework and model parameters intact, the mathematical model can first be calibrated by in vitro data and thereafter be used to successfully predict treatment responses in human tumour xenografts in vivo qualitatively, and quantitatively up to approximately 10 days post tumour injection.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology

[Hassoumi:2012]

I. Hassoumi, C. Lang, N. Marilleau, M. Temani, and J-D. Zucker. Toward a spatially-centered approach to integrate heterogeneous and multi-scales urban component models. In *Advances on Practical Applications of Agents and Multi-Agent Systems*, volume 155 of *Advances in Intelligent and Soft Computing*, pages 81–86. Springer, 2012.

Abstract: This article addresses a model coupling based approach (i.e reusing and combining spatial models) for modeling and simulating complex systems. Our research is conducted by a land use program of Métouia city (Tunisia) for which administration would study (by simulations) different planning scenarios to identify strategies of industrial development. These simulations should take into account demographic, socio-economic and environmental factors. Many urban models are available but they do not integrate these three aspects. This limitation could be solved by a model coupling based approach. In this paper, from an analysis of models and approaches presented in the literature, we identify key points, needs and the basis of an approach to couple models. Then, we introduce an original approach, based on agent paradigm, in which space is the coupling factor to interconnect heterogeneous models (mathematical models, stochastic models, individual based models, and so on). The pertinence of this coupling approach is also raised by the correlation to observe the impact of models on each other.

Keywords: multi-agent based simulation, multi-level, social simulation, urban systems, french team

[Hayenga:2011]

H.N. Hayenga, B.C. Thorne, S.M. Peirce, and J.D. Humphrey. Ensuring congruency in multiscale modeling: towards linking agent based and continuum biomechanical models of arterial adaptation. *Annals of biomedical engineering*, pages 1–14, 2011.

Abstract: There is a need to develop multiscale models of vascular adaptations to understand tissue-level manifestations of cellular level mechanisms. Continuum-based biomechanical models are well suited for relating blood pressures and flows to stress-mediated changes in geometry and properties, but less so for describing underlying mechanobiological processes. Discrete stochastic agent-based models are well suited for representing biological processes at a cellular level, but not for describing tissue-level mechanical changes. We present here a conceptually new approach to facilitate the coupling of continuum and agent-based models. Because of ubiquitous limitations in both the tissue- and cell-level data from which one derives constitutive relations for continuum models and rule-sets for agent-based models, we suggest that model verification should enforce congruency across scales. That is, multiscale model parameters initially determined from data sets representing different scales should be refined, when possible, to ensure that common outputs are consistent. Potential advantages of this approach are illustrated by comparing simulated aortic responses to a sustained increase in blood pressure predicted by continuum and agent-based models both before and after instituting a genetic algorithm to refine 16 objectively bounded model parameters. We show that congruency-based parameter refinement not only yielded increased consistency across scales, it also yielded predictions that are closer to in vivo observations.

Keywords: multi-agent based simulation, multi-level, biology

[Head:2016]

B. Head, A. Hjorth, C. Brady, and U. Wilensky. Evolving agent cognition with netlogo levelspace. In *Proc. of the Winter Simulation Conf.*, 2016.

Abstract: Any agent-based model (ABM) involving agents that think or make decisions must inevitably have some model of agent cognition. Often, this cognitive model is incredibly simple, such as choosing actions at random or based on simple conditionals. In reality, agent cognition can be complex and dynamic, and for some models, this process can be worthy of its own dedicated ABM. The LevelSpace extension (Hjorth, Head and Wilensky, 2015) for NetLogo (Wilensky 1999) allows NetLogo models to open instances of other NetLogo models and interact with them. We demonstrate a method for using LevelSpace to simulate agents with complex, evolving cognitive models. We give the agents in a NetLogo predator-prey model "brains," themselves represented as independent instances of a NetLogo neural network model.

Keywords: multi-agent based simulation, multi-level

[Head:2018]

B. Head and U. Wilensky. Agent cognition through micro-simulations: Adaptive and tunable intelligence with netlogo levelspace. In *Unifying Themes in Complex Systems IX. ICCS 2018*, Springer Proceedings in Complexity, pages 71–81. Springer, 2018.

Abstract: We present a method of endowing agents in an agent-based model (ABM) with sophisticated cognitive capabilities and a naturally tunable level of intelligence. Often, ABMs use random behavior or greedy algorithms for maximizing objectives (such as a predator always chasing after

the closest prey). However, random behavior is too simplistic in many circumstances and greedy algorithms, as well as classic AI planning techniques, can be brittle in the context of the unpredictable and emergent situations in which agents may find themselves. Our method, called agent-centric Monte Carlo cognition (ACMCC), centers around using a separate agent-based model to represent the agents' cognition. This model is then used by the agents in the primary model to predict the outcomes of their actions, and thus guide their behavior. To that end, we have implemented our method in the NetLogo agent-based modeling platform, using the recently released LevelSpace extension, which we developed to allow NetLogo models to interact with other NetLogo models. As an illustrative example, we extend the Wolf Sheep Predation model (included with NetLogo) by using ACMCC to guide animal behavior, and analyze the impact on agent performance and model dynamics. We find that ACMCC provides a reliable and understandable method of controlling agent intelligence, and has a large impact on agent performance and model dynamics even at low settings.

Keywords: multi-agent based simulation, multi-level

[Helms:2014]

T. Helms, C. Maus, F. Haack, and A. M. Uhrmacher. Multi-level modeling and simulation of cell biological systems with ml-rules: a tutorial. In *Proc. of the Winter Simulation Conf.*, pages 177–191, 2014.

Abstract: Multi-level modeling is concerned with describing a system at different levels of organization and relating their dynamics. ML-Rules is a rule-based language developed for supporting the modeling of cell biological systems. It supports nested rule schemata, the hierarchical dynamic nesting of species, the assignment of attributes and solutions to species at each level, and a flexible definition of reaction rate kinetics. As ML-Rules allows the compact description of rather complex models, means for an efficient execution were developed, e.g., approximate and adaptive algorithms. Experimentation with ML-Rules models is further supported by domain-specific languages for instrumentation and experimentation which have been developed in the context of the modeling and simulation framework JAMES II. A signaling pathway example will illustrate modeling and simulation with ML-Rules.

Keywords: multi-agent based simulation, multi-level, biology

[Henane:2012]

I. Henane, S. El Hadouaj, and K. Ghédira. Multi-agent based modeling of the tunisian pastoral dynamic - multi-level organization. In *Proc. of 4th Int. Conf. on Agents and Artificial Intelligence (ICAART)*, pages 254–258, 2012.

Abstract: Pastoral systems in arid and semi arid areas are characterized by a continued deterioration. This degradation is the result of the mismanagement of resources in response to natural, economic and social mutations. These systems are considered as complex systems, given the large number of stakeholders in interaction and levels of granularity. To address this situation, analytical and systemic approaches are no longer adequate. In this paper, we propose a multi-agent based model of Tunisian pastoral dynamics taking into account the interaction dynamics of the different stakeholders and the different levels of granularity. The completion of this work is within the scope of the development of the Intelligent Decision Support System PASDES (Pastoral Strategies Definition System). PASDES aims to support pastoral strategic decision making in short and long terms.

Keywords: multi-agent based simulation, multi-level, ecology

[Henane:2014]

I. Henane, S. El Hadouaj, K. Ghédira, and A. Ferchichi. Towards a generic approach for multi-level modeling of renewable resources management systems. In *Proc. of 13th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)*, pages 1471–1472, 2014.

Abstract: Multi-agent systems are widely used in renewable and natural resources management. Multi-agent systems are able to manage the complexity of such systems characterized by a large number of interacting entities with different levels of granularity and including dynamics of different contexts (ecological, economic, social). In this work, we propose a generic multi-level architecture for renewable and natural resources management.

Keywords: multi-agent based simulation, multi-level, ecology

[Henane:2016]

I. Hènane, S. Hadouaj, K. Ghédira, and A. Ferchichi. Modeling organizational and institutional aspects in renewable and natural resources management context. In *International Conference on Principles and Practice of Multi-Agent Systems*, volume 9862 of *LNCS*, pages 333–343. Springer, 2016.

Abstract: Since 1990, there has been a striking increase in using multi-agent systems to study renewable resources management systems. The ultimate objective is to contribute to decisions support on resources management. The adopted strategic decisions are always joined with access to resources norms. However, the defined norms are statics and suppose that all agents are not autonomous and always obey to the underlying norms which do not reflect reality. In previous work, we proposed ML-MA [1], a multi-level multi-agent architecture to support renewable resources management systems modeling. In this work, we focus on the integration of normative aspects in our architecture. Our approach is illustrated using “Ouled Chehida” case study from Tunisian pastoral context.

Keywords: multi-agent based simulation, multi-level, ecology

[Hjorth:2015]

A. Hjorth, C. Brady, B. Head, and U. Wilensky. Thinking within and between levels: Exploring reasoning with multi-level linked models. In *Proc. of 11th Int. Conf. on Computer Supported Collaborative Learning (CSCL)*, 2015.

Abstract: This poster presents a pilot study with a prototype technology that allows learners to link agent-based models written in NetLogo models and run them simultaneously as a coupled system. We describe ongoing design work using this prototype to investigate how learners conceptualize multi-level modeling of complex systems in ecology.

Keywords: multi-agent based simulation, multi-level, biology

[Hjorth:2015a]

A. Hjorth, C. Brady, B. Head, and U. Wilensky. Levelspacegui - scaffolding novice modelers' inter-model explorations. In *Proc. for Interaction Design & Children*, 2015.

Abstract: We present an interface for programming relationships between two or more NetLogo [18] models running concurrently. The interface is designed specifically to help high school aged novices explore and define computational relationships between agent-based models, and to investigate how prompting learners to reason about the relationships between complex systems may change how they reason about the systems individually.

Keywords: multi-agent based simulation, multi-level

[Hjorth:2015b]

A. Hjorth, B. Head, and U. Wilensky. Levelspace netlogo extension. <http://ccl.northwestern.edu/rp/levelspace/index.shtml>, 2015.

Abstract: In Borges' fable On the Exactitude of Science, cartographers had invented a map with a one mile to one mile relationship. While initially hailed for its preciseness and level of detail, the map was quickly abandoned as too impractical to be of any use. Lest we end like the cartographers in Borges' fable, we have to simplify and abstract our computational models to represent only the particular and clearly delimited aspects of reality that address our specific curiosities. Unlike the cartographers, whose map was too physically unwieldy, our models may end up too conceptually and computationally unwieldy: conceptually, because we want models that are simple enough that we can think in-depth with them by reflecting on the specificities of individual phenomena, and computationally because the more moving parts, the longer the runtime. Alas, this comes at a cost of excluding everything that lies "outside" of the model: We have climate change models, and ecosystem models, and urban development models, and these models simultaneously help us think about these phenomena and constrain us from connecting them. But if modeling the whole world, a mile to a mile, is not the solution, how do we bridge this inherent tension in modeling? We believe the answer is breaking up large, interrelated, complex systems into smaller, manageable models. For this purpose, we have designed LevelSpace, a NetLogo extension that allows modelers to build multi-level agent-based model systems with hundreds or thousands of concurrent models. The purpose of this grant is three-fold: 1. develop software that allows for the construction of multi-level agent-based model systems, 2. develop curriculum that investigates the cognitive affordances of ML-ABM systems as 'tools to think with' 3. implement these curricular activities, and study thinking with these new kinds of models

Keywords: multi-agent based simulation, multi-level

[Hjorth:2016]

A. Hjorth, D. Weintrop, Brady C., and U. Wilensky. Levelspace: Constructing models and explanations across levels. In *Constructionism*, 2016.

Abstract: In this hands-on workshop, we will introduce participants to the recently released LevelSpace NetLogo extension. By using LevelSpace, it is possible to programmatically open NetLogo

models from inside NetLogo, essentially treating models like agents. This has a wide and interesting applications for modellers, curriculum developers, and researchers interested in eliciting and studying complex systems and how people reason about them. We will introduce the LevelSpace extension's programming primitives and how to use them by building connected model ecologies. We will talk about the different kinds of ways that phenomena might be connected, and how to model that using LevelSpace. We will also discuss our experience with using LevelSpace in classrooms, and discuss best practices for using it as a tool for studying student reasoning within and between complex phenomena.

Keywords: multi-agent based simulation, multi-level

[Hjorth:2016a]

A. Hjorth, C. Brady, B. Head, and U. Wilensky. Turtles all the way down: Presenting levelspace, a netlogo extension for reasoning about complex connectedness. In *Constructionism*, 2016.

Keywords: multi-agent based simulation, multi-level

[Hjorth:2018]

A. Hjorth and B. Head. Building multi-level agent-based models with netlogo and levelspace. In *4th Proc. of 4th Annual Int. Conf. on Computational Social Science*, 2018.

Abstract: In this hands-on workshop, participants will learn to build multi-level agent-based models in NetLogo with the recently developed LevelSpace Extension. The workshop is led by members of the Center for Connected Learning and Computer-Based Modeling, and directed by Prof. Uri Wilensky, the inventor of NetLogo. We will run the workshop to accommodate a wide range of experience levels. No programming or modeling experience is required. Multi-level Agent-Based Modeling (ML-ABM) enables modelers to easily expand on models by connecting them to other models. Typical use cases for ML-ABM include modeling interactions between levels by delegating each representational level to each own model, e.g. representing an organization as a collection of individual departments, each represented by a model; zooming in on particular event by designing higher spatial or temporal granularity event-specific models, e.g. a model for simulating a shipping accident embedded inside a larger time-scale logistics model; or connecting different types of models like agent based models and systems dynamics models. LevelSpace is a recently developed ML-ABM extension to NetLogo, one of the most widely used ABM environments. In this workshop, participants will learn about ML-ABM, and use NetLogo and LevelSpace to build and/or expand on models. Participants are encouraged to bring their own models if they have them, but we will provide interesting models for participants as well.

Keywords: multi-agent based simulation, multi-level

[Hjorth:2020]

A. Hjorth, B. Head, C. Brady, and U. Wilensky. Levelsace: A netlogo extension for multi-level agent-based modeling. *Journal of Artificial Societies and Social Simulation*, 23(1):1–4, 2020.

Abstract: Multi-Level Agent-Based Modeling (ML-ABM) has been receiving increasing attention in recent years. In this paper we present LevelSpace, an extension that allows modelers to easily build ML-ABMs in the popular and widely used NetLogo language. We present the LevelSpace framework and its associated programming primitives. Based on three common use-cases of ML-ABM — coupling of heterogenous models, dynamic adaptation of detail, and cross-level interaction - we show how easy it is to build ML-ABMs with LevelSpace. We argue that it is important to have a unified conceptual language for describing LevelSpace models, and present six dimensions along which models can differ, and discuss how these can be combined into a variety of ML-ABM types in LevelSpace. Finally, we argue that future work should explore the relationships between these six dimensions, and how different configurations of them might be more or less appropriate for particular modeling tasks.

Keywords: multi-agent based simulation, multi-level, simulation platform

[Hjorth:2020a]

A. Hjorth and U. Wilensky. Thinking in levels across multiple levels. In *Constructionism 2020*, 2020.

Abstract: In this paper, we present a study of our first implementation of a classroom learning activity in which a Multi-Level Agent-Based Model (ML-ABM) is used to support learners in developing Complex Systems Thinking about issues of sustainability and food production. Using Agent-Based models in complex systems education is a well-established approach. Agent-Based Models (ABMs) have been used as learning tools for teaching complexity and complex systems for decades. ABMs are particularly well suited for this task because they allow learners to break down phenomena into their constituent parts, and then to piece together the interactions between these individual parts at the micro-level into causal explanations of the phenomenon at the macro-level. ABMs restrict the representational scope of phenomena because they always exist

at one temporal and spatial scale. Recently, Multi-Level Agent-Based Modelling (ML-ABM), in which many concurrent and interdependent ABMs interact to create a larger system-of-systems model has started to gain attention in modelling research. However, to our knowledge, using a multi-level model for educational purposes has not been done before. We therefore first discuss the potential educational benefits of using ML-ABMs, and present an exemplar ML-ABM learning activity.

Keywords: multi-agent based simulation, multi-level, simulation platform

[Hoekstra:2017]

A. Hoekstra and P. Hogeveen. Agent-based model for the adoption and impact of electric vehicles in real neighbourhoods. In *EVS30 Symposium*, 2017.

Abstract: This paper describes the methodology and first results of an agent-based model for the buying, charging and driving of electric vehicles (ABCD model). The model can be used to predict the adoption, use and impact (e.g. on CO₂ output and the electricity grid) of the transition to electric vehicles. It uses an integral, multi-level agent-based approach grounded in transition management theory with representative Dutch neighbourhoods and brings together domain experts from a wide range of fields. We present a variety of results that illustrate the capabilities of such a model and highlights a number of causalities. It should however be noted that these results are not yet generalized to the national level, that parameterization with domain experts is ongoing and that vehicle and battery supply are not yet included as a constraint. As such the results are preliminary and have limited generalization potential.

Keywords: multi-agent based simulation, multi-level, social simulation

[Hu:2016]

Z. Hu, M. Sha, M. Jarrah, J. Zhang, and H. Xi. Efficient computation of emergent equilibrium in agent-based simulation. In *Proc. of 30th AAAI Conf. on Artificial Intelligence (AAAI)*, pages 2501–2508, 2016.

Abstract: In agent-based simulation, emergent equilibrium describes the macroscopic steady states of agents' interactions. While the state of individual agents might be changing, the collective behavior pattern remains the same in macroscopic equilibrium states. Traditionally, these emergent equilibriums are calculated using Monte Carlo methods. However, these methods require thousands of repeated simulation runs, which are extremely time-consuming. In this paper, we propose a novel three-layer framework to efficiently compute emergent equilibriums. The framework consists of a macro-level pseudo-arclength equilibrium solver (PAES), a micro-level simulator (MLS) and a macro-micro bridge (MMB). It can adaptively explore parameter space and recursively compute equilibrium states using the predictor-corrector scheme. We apply the framework to the popular opinion dynamics and labour market models. The experimental results show that our framework outperformed Monte Carlo experiments in terms of computation efficiency while maintaining the accuracy.

Keywords: multi-agent based simulation, multi-level

[Huraux:2014]

T. Huraux, N. Sabouret, and Y. Haradji. A multi-level model for multi-agent based simulation. In *Proc. of 6th Int. Conf. on Agents and Artificial Intelligence (ICAART)*, 2014.

Abstract: In this paper, we consider the problem of modeling complex systems at several levels of abstraction. We design SIMLAB, a multi-level model for multi-agent based simulation. Our approach is based on the coexistence of different levels during simulation to enhance the model with complementary experts' opinion. We present how a same concept can be defined independently of its granularity using the notion of modeling axis. We consider recursive agents with interactions and influences which captures the inter-level dynamics. We also propose observations to detect and to reify macroscopic entities.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Huraux:2014a]

T. Huraux, N. Sabouret, and Y. Haradji. Un modèle multi-niveau pour simuler l'activité humaine dans le contexte de la consommation énergétique résidentielle. In *Proc. of 12e Rencontres des Jeunes Chercheurs en Intelligence Artificielle (RJCIA)*, 2014.

Abstract: In this paper, we present a model for multi-level simulation with levels on several axes, and use it to extend the SMACH simulator that helps energy experts to analyze household activities in relation to energy consumption. We first present the model. We then introduce three modeling axes : populations, activities and the environment. We then present a preliminary evaluation of the inter-level influences mechanism and the dynamic reification model.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Huraux:2015]

T. Huraux, N. Sabouret, and Y. Haradji. Study of human activity related to residential energy consumption using multi-level simulations. In *Proc. of 7th Int. Conf. on Agents and Artificial Intelligence (ICAART)*, 2015.

Abstract: In this paper, we illustrate how multi-agent multi-level modeling can help energy experts to better understand and anticipate residential energy consumption. The problem we study is the anticipation of electricity consumption peaks. We explain in this context the benefit of the coexistence of microscopic (human activity) and macroscopic (social characteristics, overall consumption) levels of representation. We present briefly the SIMLAB model (Huraux et al., 2014) that extends the SMACH simulator (Amouroux et al., 2013) with coexisting levels on different modeling axes. We then present a model of the households activity and its electrical consumption consistent with energy experts' observations in the residential sector. We show the impact of different social factors, such as individual sensitivity to price or to personal comfort, on the apparition of peaks on the consumption. We illustrate the contribution of multi-level modeling in the understanding of macroscopic phenomena.

Keywords: multi-agent based simulation, multi-level, social simulation, french team

[Huraux:2015a]

T. Huraux, N. Sabouret, and Y. Haradji. Combiner les expertises au sein d'une simulation multi-agent multi-niveau. In *23es Journées Francophones sur les Systèmes Multi-Agents (JFSMA'15)*, pages 29–38. Cepaduès, 2015.

Abstract: This paper tackles the question of multi-agent simulation for multiple domain experts. We show that this requires to combine multi-domain simulation with multi-level modeling. To this purpose, we propose the SIMLAB agent model which is based on an unified representation of concepts as agents that can influence each other within different axes and different levels of abstraction. We illustrate this approach on a typical example of multi-expert complex system: reduction of household consumption, which requires to combine expertise on human activity, energy efficiency, thermodynamics, etc.

Keywords: multi-agent based simulation, multi-level, in french, french team

[Huraux:2015b]

T. Huraux. *Simulation multi-agent d'un système complexe : combiner des domaines d'expertise par une approche multi-niveau – Le cas de la consommation électrique résidentielle*. PhD thesis, Université Paris VI, 2015.

Abstract: Nous abordons dans cette thèse un problème important en simulation multi-agent pour l'étude des systèmes complexes: celui d'assembler de multiples expertises par une approche multi-niveau. Alors que les approches existantes considèrent habituellement la vue d'un seul expert principal sur le système, nous proposons d'utiliser une approche multi-niveau pour intégrer plusieurs expertises sous la forme d'agents de différents niveaux d'abstraction. Nous montrons qu'il est ainsi possible de rester proche des concepts manipulés par les différents experts (ce qui permet de faciliter le processus de validation dans leurs domaines respectifs) et de combiner les différents niveaux de ces concepts, de manière à ce que chaque expert puisse comprendre les dynamiques des éléments liés à son domaine. Nous proposons le méta-modèle SIMLAB basé sur une représentation unifiée des concepts par des agents pouvant s'influencer les uns les autres dans différents axes et différents niveaux. Ce travail est concrétisé dans le cadre de l'étude de l'activité humaine en relation avec la consommation électrique. Il s'agit là d'un exemple typique de système complexe nécessitant de multiples expertises issues de différents domaines tels que l'ergonomie, l'énergétique, la sociologie, la thermique, ... Dans ce contexte, nous présentons ensuite la mise en oeuvre de notre approche dans la plate-forme SMACH de simulation des comportements humains et nous décrivons un ensemble d'expérimentations illustrant les différentes caractéristiques de notre approche. Nous montrons enfin la capacité de SIMLAB à reproduire et à étendre en simulation une étude réalisée sur le terrain de gestion de la demande énergétique.

Keywords: multi-agent based simulation, multi-level, social simulation, french team

[Hutzler:2011]

G. Hutzler. *Le Has (Art) et la néce (Cité)-Une approche (auto-) poétique des systèmes complexes*. Habilitation à diriger des recherches, Université d'Evry-Val d'Essonne, 2011.

Abstract: Les systèmes complexes, naturels et artificiels, ont reçu récemment une attention renouvelée : les systèmes naturels, notamment biologiques, du fait de la nécessité de les appréhender dans une démarche systémique ; les systèmes artificiels, du fait de la dématérialisation de l'ordinateur amorcée avec l'informatique ubiquitaire. L'art, de son côté, explore depuis toujours le détournement des dernières avancées scientifiques et technologiques pour la création d'oeuvres singulières. Le travail mené depuis dix ans se situe à la croisée de ces chemins, dans le cadre unificateur des systèmes multi-agents. Je me suis intéressé plus particulièrement à l'interaction homme-machine dans le contexte de l'informatique ambiante, dans l'idée d'une construction automatique et d'une

régulation dynamique de systèmes d'interaction. Ce travail est alimenté par la recherche menée dans le cadre de la simulation à base d'agents, aussi bien du point de vue des concepts et outils développés, que du point de vue de l'inspiration tirée des mécanismes d'auto-organisation et de régulation des systèmes étudiés. L'art fournit quant à lui un cadre expérimental original par la mise en scène métaphorique, dans des performances numériques interactives, des situations étudiées.

Keywords: multi-agent based simulation, multi-level, in french, french team

[Ingham:2018]

T. Ingham-Dempster. *A Multi-Scale Agent Based Model of Colon Carcinogenesis*. PhD thesis, University of Sheffield, 2018.

Abstract: Colorectal cancer (CRC) is a major cause of cancer mortality and there remain aspects of its formation which are not understood. The colon contains an epithelium punctuated by flask shaped invaginations called the crypts of Lieberkühn. These crypts are monoclonal in nature while adenomas are thought to be polyclonal, suggesting that multiple crypts are involved in carcinogenesis. It has been reported that fields of mutated tissue surround adenomas but the causes and growth of these fields are not well understood. There are two competing hypotheses regarding growth, the first being that mutated cells from one crypt invade neighbouring crypts, and the second that mutated crypts replicate themselves more often than wild-type crypts. To investigate these processes two agent based models were developed. The first model represents cells as agents and is similar to previous models in the field, but is novel in including the geometry of the crypt mouth. This is necessary to model multiple interacting crypts. This model is the first in the literature to be used to represent multiple crypts and is used to investigate invasion of neighbour crypts by mutated cells. The second model represents whole crypts as agents, which allows the entire colon to be simulated for multiple decades of biological time, as far as we are aware this is the first such model. The cell scale model predicts that crypt invasion does not occur, but that mutated cells can invade the flat mucosa above neighbouring crypts. Analysis of in-vivo data is consistent with this prediction. The crypt as agent model predicts fields of 41,000 crypts, in agreement with data in the literature, this corresponds to a field 23mm in diameter. This project models pre-cancerous fields for the first time over a variety of scales, making specific novel predictions which are in agreement with in-vivo data where such data exist. Two agent based models were created to study the development of precancerous fields, one a model with cells as agents to study cell scale phenomena and the other with crypts as agents to allow processes to be studied on larger spatial and temporal scales. These models could potentially be used to refine clinic practice by predicting the required frequency of post-intervention monitoring of patients or the necessity of further intervention.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Jacob:2012]

C. Jacob, S. von Mammen, T. Davison, A. Sarraf-Shirazi, V. Sarpe, A. Esmaeili, D. Phillips, I. Yazdanbod, S. Novakowski, and S. Steil. Lindsay virtual human: Multi-scale, agent-based, and interactive. In *Advances in Intelligent Modelling and Simulation*, pages 327–349. Springer, 2012.

Abstract: We are developing LINDSAY Virtual Human, a 3-dimensional, interactive computer model of male and female anatomy and physiology. LINDSAY is designed to be used for medical education. One key characteristic of LINDSAY is the integration of computational models across a range of spatial and temporal scales. We simulate physiological processes in an integrative fashion: from the body level to the level of organs, tissues, cells, and sub-cellular structures. For use in the classroom, we have built LINDSAY Presenter, a 3D slide-based visualization and exploration environment that presents different scenarios within the simulated human body. We are developing LINDSAY Composer to create complex scenes for demonstration, exploration and investigation of physiological scenarios. At LINDSAY Composer's core is a graphical programming environment, which facilitates the composition of complex, interactive educational modules around the human body.

Keywords: multi-agent based simulation, multi-level, biology

[Jeschke:2008]

M. Jeschke and A.M. Uhrmacher. Multi-resolution spatial simulation for molecular crowding. In *Proc. of the Winter Simulation Conference*, pages 1384–1392. IEEE, 2008.

Abstract: Spatial phenomena attract increasingly interest in computational biology. Molecular crowding, i.e. a dense population of macromolecules, is known to have a significant impact on the kinetics of molecules. However, an in-detail inspection of cell behavior in time and space is extremely costly. To balance between cost and accuracy, multi-resolution approaches offer one solution. Particularly, a combination of individual and lattice-population based algorithms promise an

adequate treatment of phenomena like macromolecular crowding. In realizing such an approach, central questions are how to specify and synchronize the interaction between population and individual spatial level, and to decide what is best treated at a specific level, respectively. Based on an algorithm which combines the Next Subvolume Method and a simple, individual-based spatial approach, we will present possible answers to these questions, and will discuss first experimental results.

Keywords: multi-agent based simulation, multi-level, biology

[Ji:2016]

Z. Ji, J. Su, D. Wu, H. Peng, W. Zhao, Brian N. Zhao, and X. Zhou. Predicting the impact of combined therapies on myeloma cell growth using a hybrid multi-scale agent-based model. *Oncotarget*, 5, 2016.

Abstract: Multiple myeloma is a malignant still incurable plasma cell disorder. This is due to refractory disease relapse, immune impairment, and development of multi-drug resistance. The growth of malignant plasma cells is dependent on the bone marrow (BM) microenvironment and evasion of the host's anti-tumor immune response. Hence, we hypothesized that targeting tumor-stromal cell interaction and endogenous immune system in BM will potentially improve the response of multiple myeloma (MM). Therefore, we proposed a computational simulation of the myeloma development in the complicated microenvironment which includes immune cell components and bone marrow stromal cells and predicted the effects of combined treatment with multi-drugs on myeloma cell growth. We constructed a hybrid multi-scale agent-based model (HABM) that combines an ODE system and Agent-based model (ABM). The ODEs was used for modeling the dynamic changes of intracellular signal transductions and ABM for modeling the cell-cell interactions between stromal cells, tumor, and immune components in the BM. This model simulated myeloma growth in the bone marrow microenvironment and revealed the important role of immune system in this process. The predicted outcomes were consistent with the experimental observations from previous studies. Moreover, we applied this model to predict the treatment effects of three key therapeutic drugs used for MM, and found that the combination of these three drugs potentially suppress the growth of myeloma cells and reactivate the immune response. In summary, the proposed model may serve as a novel computational platform for simulating the formation of MM and evaluating the treatment response of MM to multiple drugs.

Keywords: multi-agent based simulation, multi-level, biology

[Ji:2019]

Z. Ji, C. Liu, W. Zhao, C. Soto, and X. Zhou. Systematically understanding the key roles of microglia in ad development. *bioRxiv*, 2019.

Abstract: Alzheimer's disease (AD) is the leading cause of age-related dementia, affecting over 5 million people in the United States. Unfortunately, current therapies are largely palliative and several potential drug candidates have failed in late-stage clinical trials. Studies suggest that microglia-mediated neuroinflammation might be responsible for the failures of various therapies. Microglia contribute to $A\beta$ clearance in the early stage of neurodegeneration and may contribute to AD development at the late stage by releasing pro-inflammatory cytokines. However, the activation profile and phenotypic changes of microglia during the development of AD are poorly understood. To systematically understand the key role of microglia in AD progression and predict the optimal therapeutic strategy in silico, we developed a 3D multi-scale model of AD (MSMAD) by integrating multi-level experimental data, to manipulate the neurodegeneration in a simulated system. Based on our analysis, we revealed how TREM2-related signal transduction leads to an imbalance in the activation of different microglia phenotypes, thereby promoting AD development. Our MSMAD model also provides an optimal treatment strategy for improving the outcome of AD treatment.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Joueiai:2013]

M. Joueiai, H. van Lint, and S. Hoogendoorn. Generic solutions for consistency problems in multi-scale traffic flow models - analysis and preliminary results. In *16th Int. IEEE Conf. on Intelligent Transportation Systems (ITSC)*, pages 310–315, 2013.

Abstract: Multi-scale traffic models aim to describe traffic operations in transportation networks by combining and connecting different representations of traffic flows (microscopic, macroscopic) along with the corresponding spatial representations (links, nodes at different levels of aggregation) and temporal scales (discrete time steps) in a single framework. Multi-scale modelling is an increasingly important research subject, particularly in the design and evaluation of large scale ITS, since these may affect travel and driving behaviour at different scales, ranging from route choice behaviour to (ontrip) path planning and actual driving behaviour. In such applications, the

consistency of travel and traffic operations between the different models in a multi-scale framework is critically important. In this paper we provide a new taxonomy that enables the identification of the sources of inconsistency between traffic flow models of different scales. We show that these inconsistencies can be categorised into two main categories, which we term global and local inconsistency respectively. Since these two classes relate to the endogeneity or exogeneity of the variables and parameters of interest, two models connected in a multi-scale framework can be both locally and/or globally inconsistent. On the basis thereof we sketch two main solution directions targeted at resolving both classes of inconsistencies. In this paper we demonstrate the applicability of both solution directions with an example case. We close with a discussion on the further development of a multi-scale modelling framework based on these results.

Keywords: multi-agent based simulation, multi-level, hybrid model, traffic, multi-scale

[Kameni:2017]

E. Kameni, T. Van Der Weide, and W.T. De Groot. From conceptual model to implementation model piloting a multi-level case study in cameroon. *HAL*, page 01570397, 2017.

Abstract: This paper presents the application of a Multi-Level Agent Based Model technology to describe a class of environmental problems. It is based on the Problem-in-Context (PiC) and AiC (Action-in-Context) framework to describe and explain agent motivations and cooperation. We show how the associated TiC (Tool-in-Context) develop can help the domain expert to describe in seminatural language the problem of domain. This description not only provides a corresponding Domain Specific Language. It is also the basis for TiC to generate a simulation tool. On the base of this, we transform the Specific Language to NetLogo code, thereby facilitating an early prototype application to be used by the domain expert. To validate and showcase our approach, we have used this approach to explain and analyze the process of deforestation around the Laf-Madiam forest reserve. We discuss the prototype resulting from our approach and show how it allows the domain expert to focus on the social causes of environmental problems.

Keywords: multi-agent based simulation, multi-level, social simulation

[Karbovskii:2015]

V. Karbovskii, D. Voloshin, A. Karsakov, A. Bezgodov, and A. Zagarskikh. Multiscale agent-based simulation in large city areas: Emergency evacuation use case. *Procedia Computer Science*, 51:2367–2376, 2015.

Abstract: Complex phenomena are increasingly attracting the interest of researchers from various branches of computational science. So far, this interest has conditioned the demand not only for more sophisticated autonomous models, but also for mechanisms that would bring them together. This paper presents a multiscale agent-based modeling and simulation technique based on the incorporation of multiple modules. Two key principles are presented as guiding such an integration: common abstract space as a space, where entities of different models interact, and commonly controlled agents – abstract actors operating in a common space, which can be handled by different agent-based models. The proposed approach is evaluated through a series of experiments simulating the emergency evacuation from cinema building to the city streets, where building and street levels are reproduced in heterogeneous models.

Keywords: multi-agent based simulation, multi-level, emergency evacuation

[Kim:2012]

M. Kim, S. Christley, J. Alverdy, D. Liu, and G. An. A multi-scale agent-based model of necrotizing enterocolitis integrating oxidative stress, inflammation, and microvascular thrombosis. *Journal of Surgical Research*, 172(2):196, 2012.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Kirschner:2014]

D.E. Kirschner, C.A. Hunt, S. Marino, M. Fallahi-Sichani, and J.J. Linderman. Tuneable resolution as a systems biology approach for multi-scale, multi-compartment computational models. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 2014.

Abstract: The use of multi-scale mathematical and computational models to study complex biological processes is becoming increasingly productive. Multi-scale models span a range of spatial and/or temporal scales and can encompass multi-compartment (e.g., multi-organ) models. Modeling advances are enabling virtual experiments to explore and answer questions that are problematic to address in the wet-lab. Wet-lab experimental technologies now allow scientists to observe, measure, record, and analyze experiments focusing on different system aspects at a variety of biological scales. We need the technical ability to mirror that same flexibility in virtual experiments using multi-scale models. Here we present a new approach, tuneable resolution, which can begin providing that flexibility. Tuneable resolution involves fine- or coarse-graining existing multi-scale

models at the user's discretion, allowing adjustment of the level of resolution specific to a question, an experiment, or a scale of interest. Tuneable resolution expands options for revising and validating mechanistic multi-scale models, can extend the longevity of multi-scale models, and may increase computational efficiency. The tuneable resolution approach can be applied to many model types, including differential equation, agent-based, and hybrid models. We demonstrate our tuneable resolution ideas with examples relevant to infectious disease modeling, illustrating key principles at work.

Keywords: multi-agent based simulation, multi-level, multi-scale, cancer modeling

[Kiselev:2016]

A.V. Kiselev, V.A. Karbovskii, and S.V. Kovalchuk. Agent-based modelling using ensemble approach with spatial and temporal composition. *Procedia Computer Science*, 80:530–541, 2016.

Abstract: Crowd behavior and its movement has been an actively studied domain during last three decades. There are microscopic models used for realistic simulation of crowds in different conditions. Such models reproduce pedestrian movement quite well, however, their efficiency can vary depending on the conditions of simulation. For instance, some models show realistic results in high density of pedestrians and vice versa in low density. This work describes an early study aimed at developing an approach to combine several microscopic models using an ensemble approach to overcome individual weaknesses of the models. Possible ways to build hybrid models, as well as the main classes of ensembles are described. A prior calibration procedure was implemented using the evolutionary approach to create an ensemble of the most suitable models using dynamical macro-parameters such as density and speed as the optimization objectives. Several trial experiments and comparisons with single models were carried out for selected types of hybridization.

Keywords: multi-agent based simulation, multi-level, hybrid model, pedestrian flow modeling

[Koleva:2014]

K. Z. Koleva and F. L. Hellweger. From protein damage to cell aging to population fitness in e. coli: Insights from a multi-level agent-based model. In *114th general meeting of the American Society for Microbiology (ASM)*, 2014.

Abstract: Aging is an important process affecting many organisms, including bacteria that appear to divide symmetrically. Recent research has established much of the mechanisms underlying aging in *Escherichia coli*, including the role of damaged protein aggregates (DPAs) that are transported by diffusion within the nucleoid-free intracellular space, which leads to their polar localization and asymmetric inheritance (i.e. aging). This provides an opportunity to develop a mechanistic model of *E. coli* and use it to assess the role of this process at the population level. Is there a fitness benefit to asymmetric inheritance of DPAs? Here we explore this question using a multi-level agent-based model, which simulates a population of individual cells, each with a population of individual DPAs. The model is compared to relevant data compiled from four published studies, which shows it reproduces the main patterns observed, including intracellular localization and inheritance of DPAs, their effect on growth rate, differences in growth rate between sibling pairs, under unstressed and heat shock conditions, for wild type and a mutant that partitions DPAs symmetrically. The model is used to estimate population growth rates of the wildtype and mutant, which shows a statistically significant benefit of aging by asymmetric DPA segregation. However, the benefit is very small and probably not relevant in the context of the ecology of the bacteria's primary habitat (the intestinal tract of warm-blooded animals). But, at an evolutionary time scale even this small benefit may be relevant for bacteria with large population sizes and short generation times.

Keywords: multi-agent based simulation, multi-level, biology

[Koleva:2015]

K.Z. Koleva and F.L. Hellweger. From protein damage to cell aging to population fitness in e. coli: Insights from a multi-level agent-based model. *Ecological Modelling*, 301:62–71, 2015.

Abstract: Aging is an important process affecting many organisms, including bacteria that appear to divide symmetrically. Recent research has established much of the mechanisms underlying aging in *Escherichia coli*, including the role of damaged protein aggregates (DPAs) that are transported by diffusion within the nucleoid-free intracellular space, which leads to their polar localization and asymmetric inheritance (i.e. aging). This provides an opportunity to develop a mechanistic model of *E. coli* and use it to assess the role of this process at the population level. Is there a fitness benefit to asymmetric inheritance of DPAs? Here we explore this question using a multi-level agent-based model, which simulates a population of individual cells, each with a population of individual DPAs. The model is compared to relevant data compiled from four

published studies, which shows it reproduces the main patterns observed, including intracellular localization and inheritance of DPAs, their effect on growth rate, differences in growth rate between sibling pairs, under unstressed and heat shock conditions, for wild type and a mutant that partitions DPAs symmetrically. The model is used to estimate population growth rates of the wildtype and mutant, which shows a statistically significant benefit of aging by asymmetric DPA segregation. However, the benefit is very small and probably not relevant in the context of the ecology of the bacteria's primary habitat (the intestinal tract of warm-blooded animals). But, at an evolutionary time scale even this small benefit may be relevant for bacteria with large population sizes and short generation times.

Keywords: multi-agent based simulation, multi-level, ecology

[Labba:2017]

C. Labba, N.B. Salah, and N.B. Saoud. An agent-based meta-model for response organization structures. In *International Conference on Information Systems for Crisis Response and Management in Mediterranean Countries*, volume 301 of *LNBIP*, pages 154–167. Springer, 2017.

Abstract: An effective crisis response requires pre-established response structures as well as a predefined reliable command chain. In the literature, multiple meta-models have been elaborated to describe the disaster management domain. However, in regards to the hierarchical response organizations, we did not find any generic model that can be used to identify the involved multidisciplinary agencies scattered on different decision levels. In this paper, we firstly studied the standardized emergency management command chains and organization structures defined in the emergency plans of France, UK and USA. Then, we elaborate a hierarchical and multi-level agent-based meta-model that defines a generic response command chain structure dependent on the type and severity of a disaster. As proof of concept, we instantiate the proposed meta-model for a given disaster within a given country and then implement it as an agent-based simulator.

Keywords: multi-agent based simulation, multi-level, social simulation

[Lamarache:2013]

R. Lamarache-Perrin. *Analyse macroscopique des grands systèmes: émergence épistémique et agrégation spatio-temporelle*. PhD thesis, Université de Grenoble, 2013.

Abstract: L'analyse des systèmes de grande taille est confrontée à des difficultés d'ordre syntaxique et sémantique : comment observer un million d'entités distribuées et asynchrones ? Comment interpréter le désordre résultant de l'observation microscopique de ces entités ? Comment produire et manipuler des abstractions pertinentes pour l'analyse macroscopique des systèmes ? Face à l'échec de l'approche analytique, le concept d'émergence épistémique - relatif à la nature de la connaissance - nous permet de définir une stratégie d'analyse alternative, motivée par le constat suivant : l'activité scientifique repose sur des processus d'abstraction fournissant des éléments de description macroscopique pour aborder la complexité des systèmes. Cette thèse s'intéresse plus particulièrement à la production d'abstractions spatiales et temporelles par agrégation de données. Afin d'engendrer des représentations exploitables lors du passage à l'échelle, il apparaît nécessaire de contrôler deux aspects essentiels du processus d'abstraction. Premièrement, la complexité et le contenu informationnel des représentations macroscopiques doivent être conjointement optimisés afin de préserver les détails pertinents pour l'observateur, tout en minimisant le coût de l'analyse. Nous proposons des mesures de qualité (critères internes) permettant d'évaluer, de comparer et de sélectionner les représentations en fonction du contexte et des objectifs de l'analyse. Deuxièmement, afin de conserver leur pouvoir explicatif, les abstractions engendrées doivent être cohérentes avec les connaissances mobilisées par l'observateur lors de l'analyse. Nous proposons d'utiliser les propriétés organisationnelles, structurelles et topologiques du système (critères externes) pour contraindre le processus d'agrégation et pour engendrer des représentations viables sur les plans syntaxique et sémantique. Par conséquent, l'automatisation du processus d'agrégation nécessite de résoudre un problème d'optimisation sous contraintes. Nous proposons dans cette thèse un algorithme de résolution générique, s'adaptant aux critères formulés par l'observateur. De plus, nous montrons que la complexité de ce problème d'optimisation dépend directement de ces critères. L'approche macroscopique défendue dans cette thèse est évaluée sur deux classes de systèmes. Premièrement, le processus d'agrégation est appliqué à la visualisation d'applications parallèles de grande taille pour l'analyse de performance. Il permet de détecter les anomalies présentes à plusieurs niveaux de granularité dans les traces d'exécution et d'expliquer ces anomalies à partir des propriétés syntaxiques du système. Deuxièmement, le processus est appliqué à l'agrégation de données médiatiques pour l'analyse des relations internationales. L'agrégation géographique et temporelle de l'attention médiatique permet de définir des événements macroscopiques pertinents sur le plan sémantique pour l'analyse du système international. Pour autant, nous pensons que l'approche et les outils présentés dans cette thèse peuvent être généralisés à de nombreux autres domaines d'application.

Keywords: multi-agent based simulation, multi-level, observation, macroscopic representation, in french, french team

[Lamarche:2016]

R. Lamarche-Perrin, S. Banisch, and E. Olbrich. The information bottleneck method for optimal prediction of multilevel agent-based systems. *Advances in Complex Systems*, 19(1,2):1650002, 2016.

Abstract: Because the dynamics of complex systems is the result of both decisive local events and reinforced global effects, the prediction of such systems could not do without a genuine multilevel approach. This paper proposes to found such an approach on information theory. Starting from a complete microscopic description of the system dynamics, we are looking for observables of the current state that allows to efficiently predict future observables. Using the framework of the Information Bottleneck method, we relate optimality to two aspects: the complexity and the predictive capacity of the retained measurement. Then, with a focus on Agent-based Models, we analyse the solution space of the resulting optimisation problem in a generic fashion. We show that, when dealing with a class of feasible measurements that are consistent with the agent structure, this solution space has interesting algebraic properties that can be exploited to efficiently solve the problem. We then present results of this general framework for the Voter Model with several topologies and show that, especially when predicting the state of some sub-part of the system, multilevel measurements turn out to be the optimal predictors.

Keywords: multi-agent based simulation, multi-level, observation

[Langlois:2009]

P. Langlois. Une ontologie formelle pour la modélisation de systèmes complexes en géographie: Le modèle aoc. In *Actes des 16èmes journées de Rochebrune*, 2009.

Abstract: Cet article présente un méta-modèle nommé AOC (Agents-Organisations-Comportements), qui s'exprime par une ontologie formelle et sert de cadre conceptuel à une plateforme de simulation de systèmes complexes spatialisés, compatible avec les problématiques de dynamiques géographiques les plus larges. Le modélisateur géographe doit pouvoir concevoir son modèle et le formaliser dans un langage cohérent relativement à son cadre de pensée. AOC offre ainsi la possibilité de structurer les relations entre agents via le concept d'organisation, qui permet de créer des modèles multi-niveaux. De plus, une formalisation générale de la notion de comportement permet de modéliser la dynamique d'une classe très large de systèmes.

Keywords: multi-agent based simulation, multi-level, geography, in french, french team

[Latif:2018]

M. Latif and E.E. May. A multiscale agent-based model for the investigation of e. coli k12 metabolic response during biofilm formation. *Bulletin of mathematical biology*, 80(11):2917–2956, 2018.

Abstract: Bacterial biofilm formation is an organized collective response to biochemical cues that enables bacterial colonies to persist and withstand environmental insults. We developed a multiscale agent-based model that characterizes the intracellular, extracellular, and cellular scale interactions that modulate *Escherichia coli* MG1655 biofilm formation. Each bacterium's intracellular response and cellular state were represented as an outcome of interactions with the environment and neighboring bacteria. In the intracellular model, environment-driven gene expression and metabolism were captured using statistical regression and Michaelis–Menten kinetics, respectively. In the cellular model, growth, death, and type IV pili- and flagella-dependent movement were based on the bacteria's intracellular state. We implemented the extracellular model as a three-dimensional diffusion model used to describe glucose, oxygen, and autoinducer 2 gradients within the biofilm and bulk fluid. We validated the model by comparing simulation results to empirical quantitative biofilm profiles, gene expression, and metabolic concentrations. Using the model, we characterized and compared the temporal metabolic and gene expression profiles of sessile versus planktonic bacterial populations during biofilm formation and investigated correlations between gene expression and biofilm-associated metabolites and cellular scale phenotypes. Based on our *in silico* studies, planktonic bacteria had higher metabolite concentrations in the glycolysis and citric acid cycle pathways, with higher gene expression levels in flagella and lipopolysaccharide-associated genes. Conversely, sessile bacteria had higher metabolite concentrations in the autoinducer 2 pathway, with type IV pili, autoinducer 2 export, and cellular respiration genes upregulated in comparison with planktonic bacteria. Having demonstrated results consistent with *in vitro* static culture biofilm systems, our model enables examination of molecular phenomena within biofilms that are experimentally inaccessible and provides a framework for future exploration of how hypothesized molecular mechanisms impact bulk community behavior.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Laville:2012]

G. Laville, K. Mazouzi, C. Lang, N. Marilleau, and L. Philippe. Using GPU for multi-agent multi-scale simulations. In *Distributed Computing and Artificial Intelligence*, volume 151 of *Advances in Intelligent and Soft Computing*, pages 197–204. Springer, 2012.

Abstract: Multi-Agent System (MAS) is an interesting way to create models and simulators and is widely used to model complex systems. As the complex system community tends to build up larger models to fully represent real systems, the need for computing power raise significantly. Thus MAS often lead to long computing intensive simulations. Parallelizing such a simulation is complex and its execution requires the access to large computing resources. In this paper, we present the adaptation of a MAS system, Sworm, to a Graphical Processing Unit. We show that such an adaptation can improve the performance of the simulator and advocate for a more wider use of the GPU in Agent Based Models in particular for simple agents.

Keywords: multi-agent based simulation, multi-level, ecology, french team

[Le-Yaouanq:2011]

S. Le Yaouanq, P. Redou, C. Le Gal, J-F. Abgrall, and J. Tisseau. Multi-agent systems and heterogeneous scales interactions. application to pharmacokinetics of vitamin k antagonists. In *Advances in Artificial Life, ECAL*, pages 447–454. MIT Press, 2011.

Abstract: The study of complex systems consists in considering entities submitted to interactions which define the dynamics of the system. Virtual reality opens the way to interactive simulation of complex systems, so called the in virtuo experimentation. For that purpose we use multi-interactions systems, based on the reification of interactions and multi-agent systems, in a phenomenological approach. Interaction agents represent the modeler understanding of the relations between the constituents of the system. Such descriptive models lead us to define parameters a priori. Moreover these parameters can be fluctuant, or even unknown, during a simulation in relation to the system dynamics or user interventions. To respond to this problem, we expose in this paper a redundant multiscale architecture which rests upon the fact that we can establish models of a same phenomenon at heterogeneous time and space scales. Heterogenous Multiscale Methods provide a general framework to mix levels of description of a system. Our intention is to implement this framework in multi-interactions systems by means of a Scale-Interaction agent. Then we illustrate our architecture through a pharmacokinetics application. Indeed biochemical kinetics abounds of parametric phenomena. Finally we discuss about some questions raised by this methodology, such as synchronicity, organization detection and genericity.

Keywords: multi-agent based simulation, multi-level, biology, french team

[Le:2011]

Q.B. Le, R. Seidl, and R.W. Scholz. Feedback loops and types of adaptation in the modelling of land-use decisions in an agent-based simulation. *Environmental Modelling & Software*, 2011.

Abstract: A key challenge of land-use modelling for supporting sustainable land management is to understand how environmental feedback that emerges from land-use actions can reshape land-use decisions in the long term. To investigate this issue, we apply the Human-Environment System framework formulated by Scholz (2011) as a conceptual guide to read typical feedback loops in land-use systems. We use an agent-based land-use change model (LUDAS) developed by Le et al. (2008, 2010) to test the sensitivity of long-term land-use dynamics to the inclusion of secondary feedback loop learning with respect to different system performance indicators at different levels of aggregation. Simulation experiments were based on a case study that was carried out in the Hong Ha watershed (Vietnam). We specified two model versions that represent two mechanisms of human adaptation in land-use decisions to environmental changes that emerged from land-use actions. The first mechanism includes only primary feedback loop learning, i.e. households adapt to the annual change in socio-ecological conditions and direct environmental response to land-use activities. The second mechanism includes the first one and secondary feedback loop learning, in which households can change their behavioural model in response to changes in socio-ecological conditions at the landscape-community level in the longer term. Spatial-temporal patterns of land-use and interrelated community income changes driven from the two feedback mechanisms are compared in order to evaluate the added value of the inclusion of secondary feedback loop learning. The results demonstrate that the effect of the added secondary feedback loop learning on land-use dynamics depends on domain type, time scale, and aggregation level of the impact indicators.

Keywords: multi-agent based simulation, multi-level, social simulation, ecology

[Le:2016]

T. Le-Kim, A. Nguyen-Thi-Ngoc, D. Nguyen-Ngoc, N.H. Quang, and E. Amouroux. A multi-scale model for spreading of infectious disease in an office building. In *Computing & Communication Technologies, Research, Innovation, and Vision for the Future (RIVF)*, 2016 *IEEE RIVF International Conference on*, pages 199–204, 2016.

Abstract: We presented a multi-scale model, by coupling of three different component models: individual based model (IBM), spatial moment-based model (SMBM) and equation-based model (EBM), for studying of spreading of infectious disease in a 3D office building. We proposed an up-scaling methodology to derive a SMBM from a given IBM, and to generate an EBM from the SMBM. Our results showed that the multi-scale model, by taking advantages of the three component models, is able to support different and complementary views of the spreading of infectious disease system. It is, therefore, can be seen as an effective model to describe disease spreading in a heterogeneous environment.

Keywords: multi-agent based simulation, multi-level, multi-scale, epidemiology

[LePage:2000]

C. Le Page, F. Bousquet, I. Bakam, A. Bah, and C. Baron. CORMAS: A multiagent simulation toolkit to model natural and social dynamics at multiple scales. In *Proceedings of Workshop "The ecology of scales"*, Wageningen, The Netherlands, 2000.

Abstract: Dealing with multiple scales is often a key question in renewable resources management. In some cases, the decision to incorporate a spatial entity is influenced by the fact that information is available at this level. In other cases, the system dynamics is intrinsically linked to a specific spatial entity, which should obviously be taken into account in the model. Nevertheless, it is important to have the possibility to manipulate and to incorporate into the same model spatial entities defined at different hierarchical levels. Originated from the field of Distributed Artificial Intelligence, Multi-Agent Systems (MAS) are potentially suitable for linking several hierarchical levels. In a MAS, an agent is a computerized autonomous entity that is able to act locally in response to stimuli from the environment or to communication with other agents. Cormas (Common-pool Resources and Multi-Agent Systems) is a multi-agent simulation platform specially designed for renewable resource management. It provides the framework for building models of interactions between individuals and groups sharing natural resources. With Cormas, the design of the spatial support rests on spatial entities, which are themselves a category of agents. When these entities yield resources, they are competent to arbitrate their allocation, according to pre-defined protocols, between concurrent demands formulated by other agents exploiting these resources. The way agents are exploiting resources may depend on their own partial representation of the environment, which are based on these same spatial entities. Following a general overview of the Cormas simulation platform, examples of models built by using this toolkit are presented, by emphasizing the overlapping of their multiple hierarchical scales. Finally, the use of multi-agent systems to represent knowledge on processes at various levels of complexity and to simulate their interactions according to a bottom-up approach for understanding landscape dynamics are discussed.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Lejon:2017]

A. Lejon, B. Mortier, and G. Samaey. Variance-reduced simulation of stochastic agent-based models for tumor growth. *Multiscale Model. Simul.*, 15(1):388–409, 2017.

Abstract: We are interested in the mean-field evolution of a growing tumor as it emerges from a stochastic agent-based multiscale model. To this end, we introduce a hybrid PDE/Monte Carlo variance reduction technique. The variance reduction on the cell densities is achieved by combining a simulation of the stochastic agent-based model on the microscopic scale with a deterministic solution of a simplified (coarse) PDE on the macroscopic scale as a control variable. We show that this technique is able to significantly reduce the variance with only the (limited) additional computational cost associated with the deterministic solution of the coarse PDE. We illustrate the performance with numerical experiments in different biological scenarios.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Lepagnot:2009]

J. Lepagnot and G. Hutzler. A multiscale agent-based model for the simulation of avascular tumour growth. *J. Biol. Phys. Chem.*, 9(1):17–25, 2009.

Abstract: An agent-based paradigm for the simulation of complex systems is based on the modelling of the individual entities of the system. Given a chosen level of description, this implies modelling each and every entity of the system. When modelling biological systems at the cellular and/or molecular level, this results in the simulation of multitudes of agents, which raises performance issues. However, it is generally not necessary to have the same level of detail in every part of the system. In this paper, we propose to introduce dynamically an aggregated level in the simulation of avascular tumour growth. This model handles cells and PAI-1 molecules that are believed to play a key rôle in the amoeboid migration of cancerous cells. However, migratory events

can only be triggered on the periphery of the tumour. The interior can therefore be modelled in an aggregated way by replacing the individual cells and molecules by a global agent. We show that this can be done without changing the global dynamics of the system, and gaining a linear increase of computing time while the number of cells and molecules increases exponentially.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling, dynamic level of detail, french team

[Letort:2018]

G. Letort, A. Montagud, G. Stoll, R. Heiland, E. Barillot, P. Macklin, A. Zinovyev, and L. Calzone. PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling. *bioRxiv*, 2018.

Abstract: Due to the complexity of biological systems, their heterogeneity, and the internal regulation of each cell and its surrounding, mathematical models that take into account cell signalling, cell population behaviour and the extracellular environment are particularly helpful to understand such complex systems. However, very few of these tools, freely available and computationally efficient, are currently available. To fill this gap, we present here our open-source software, PhysiBoSS, which is built on two available software packages that focus on different scales: intracellular signalling using continuous-time markovian Boolean modelling (MaBoSS) and multicellular behaviour using agent-based modelling (PhysiCell). The multi-scale feature of PhysiBoSS — its agent-based structure and the possibility to integrate any Boolean network to it — provide a flexible and computationally efficient framework to study heterogeneous cell population growth in diverse experimental set-ups. This tool allows one to explore the effect of environmental and genetic alterations of individual cells at the population level, bridging the critical gap from genotype to phenotype. PhysiBoSS thus becomes very useful when studying population response to treatment, mutations effects, cell modes of invasion or isomorphic morphogenesis events. To illustrate potential use of PhysiBoSS, we studied heterogeneous cell fate decisions in response to TNF treatment in a 2-D cell population and in a tumour cell 3-D spheroid. We explored the effect of different treatment regimes and the behaviour and selection of several resistant mutants. We highlighted the importance of spatial information on the population dynamics by considering the effect of competition for resources like oxygen. PhysiBoSS is freely available on GitHub (<https://github.com/gletort/PhysiBoSS>), and is distributed open source under the BSD 3-clause license. It is compatible with most Unix systems, and a Docker package (<https://hub.docker.com/r/gletort/physiboss/>) is provided to ease its deployment in other systems.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Li:2015]

X.L. Li, W.O. Oduola, L. Qian, and E.R. Dougherty. Integrating multiscale modeling with drug effects for cancer treatment. *Cancer Informatics*, 14(S5):21–31, 2015.

Abstract: In this paper, we review multiscale modeling for cancer treatment with the incorporation of drug effects from an applied system's pharmacology perspective. Both the classical pharmacology and systems biology are inherently quantitative; however, systems biology focuses more on networks and multi factorial controls over biological processes rather than on drugs and targets in isolation, whereas systems pharmacology has a strong focus on studying drugs with regard to the pharmacokinetic (PK) and pharmacodynamic (PD) relations accompanying drug interactions with multiscale physiology as well as the prediction of dosage-exposure responses and economic potentials of drugs. Thus, it requires multiscale methods to address the need for integrating models from the molecular levels to the cellular, tissue, and organism levels. It is a common belief that tumorigenesis and tumor growth can be best understood and tackled by employing and integrating a multifaceted approach that includes in vivo and in vitro experiments, in silico models, multiscale tumor modeling, continuous/discrete modeling, agent-based modeling, and multiscale modeling with PK/PD drug effect inputs. We provide an example application of multiscale modeling employing stochastic hybrid system for a colon cancer cell line HCT-116 with the application of Lapatinib drug. It is observed that the simulation results are similar to those observed from the setup of the wet-lab experiments at the Translational Genomics Research Institute.

Keywords: multi-agent based simulation, multi-level, cancer modeling, biology

[Liang:2018]

W. Liang, J. Zhang, and X. Sun. Multi-scale modeling reveals angiogenesis-induced drug resistance in brain tumor and predicts a synergistic drug combination targeting egfr and vegfr pathways. *bioRxiv*, page 394668, 2018.

Abstract: Experimental studies have demonstrated that both the extracellular vasculature, microenvironment and intracellular molecular network (e.g. epidermal growth factor receptor (EGFR) signaling pathways) are essentially important for brain tumor growth. Some drugs have been developed to inhibit the EGFR signaling pathways. However, how does angiogenesis affect the response of tumor cells to the drug treatment has rarely been mechanistically studied. Therefore, a multiscale model is required to investigate such complex biological systems that contain interactions and feedbacks among multi-levels. In this study, we developed a single cell-based multi-scale spatio-temporal model to simulate more realistic vascular tumor growth and drug response, based on VEGFR signaling pathways, EGFR signaling pathway and cell cycle as well as several microenvironmental factors that determine cell fate switches in a temporal and spatial context. The simulation reconstructed an evolving profile of vascular tumor growth, demonstrating the dynamic interplay between angiogenesis and various types of tumor cells (e.g., migrating, proliferating, apoptosis and quiescent cells). Moreover, we revealed the critical role of angiogenesis in the acquired drug resistance. We further investigated the optimal timing of combining VEGFR inhibition with EGFR inhibition and predicted that the drug combination targeting both EGFR pathway and VEGFR pathway has a synergistic effect. The experimental data validated the prediction of drug synergy, confirming the effectiveness of our model. The developed multiscale model explored mechanistic and functional mechanisms of angiogenesis underlying tumor growth and drug resistance, which advances our understanding of novel mechanisms of drug resistance and provides implications for designing more effective cancer therapies.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Lopez-Ridaura:2012] S. Lopez Ridaura, S. Delmotte, and J.-C. Mouret. Regional conversion to organic farming in camargue, south france: a multiscale integrated assessment of scenarios. In *10th European IFSA Symposium*, 2012.

Abstract: The rapid growth of organic agriculture in the last decade suggests that this form of farming might become more common and its extension may cover large parts of certain regions. The regional conversion to Organic Farming (OF) might represent great advantages in terms of ecosystems integrity and local natural resources conservation. However, is this regional conversion plausible? What could be the impact of such conversion for agri-cultural production and nature conservation? Taking into account the heterogeneity of farms and farming systems in a region, are there farming systems more easily convertible than others? The objective of this paper is to show the results of different scenario analyses about the extension of OF in Camargue, South of France. The application of different modeling approaches with great potential for the multi-scale and multi-criteria evaluation scenarios is presented. These models include Bio-economic models, Agent-based models and Land use/cover change models. According to our results, in the Camargue, the most probable conversion in the near future would take place in fields with low salt pressure belonging to livestock breeders and diversified cereal producers. However, the regional conversion to OF is plausible as the region could maintain its economic productivity while decreasing the potential harmful effect to the environment. Finally, the possible trajectories of conversion suggest that certain farmers (specialized in rice production) might need greater help to assure such conversion to OF as their economic performance is hampered during that period. The application of these three modeling approaches to assess the same scenario in one region revealed their complementarity for exploring the issue of regional conversion to OF from different angles and at different scales.

Keywords: multi-agent based simulation, multi-level

[Louail:2010] T. Louail. *Comparer les morphogénèses urbaines en Europe et aux États-Unis par la simulation à base d'agents - Approches multi-niveaux et environnements de simulation spatiale*. PhD thesis, Université d'Evry-Val d'Essonne, 2010.

Abstract: La comparaison, à différents niveaux (systèmes de villes, villes, quartiers), de l'organisation spatiale et hiérarchique des systèmes urbains dans le monde fait apparaître des propriétés universelles (loi rang-taille, structure centre-périphérie des villes, etc.) mais également une grande variété de formes (notamment en termes de répartition des populations, densités, prix, activités). Si la théorie évolutionnaire urbaine et celles d'économie spatiale offrent des schémas explicatifs de cette émergence de formes, les modèles qui en sont issus se sont jusqu'à présent focalisés sur un seul niveau d'organisation spatiale, qu'il soit intra- ou inter-urbain. Dans une optique d'aménagement durable, il est important de disposer de modèles permettant de raisonner sur les inter-dépendances qu'entretiennent ces niveaux d'organisation du peuplement. Cette thèse présente une famille de modèles entités-centrés et d'outils dédiés à l'étude de cette problématique par la simulation à base d'agents. Ils s'inscrivent dans le projet Simpop et sont mis en oeuvre sur la comparaison des morphogénèses urbaines en Europe et aux États-Unis, sur la période 1800-2000.

Ils incluent notamment le simulateur simpopNano, accompagné d'un environnement modulaire construit autour d'un SIG pour une exploitation systématique, intelligente et collective de modèles spatiaux. Ensemble, ils confortent l'idée que la seule différence des maillages des réseaux viaires des villes suffit à exprimer des répartitions spatiales plus diffuses sur les grilles américaines que sur les plans radioconcentriques européens. Ce modèle intra-urbain est ensuite articulé avec le modèle de systèmes de villes Simpop2 dans un modèle multi-niveaux, inter et intra-urbain. Il est le point d'ancrage d'une comparaison d'approches dédiées à l'intégration de modèles dynamiques associés à différents niveaux d'abstraction.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Lukens:2014]

S. Lukens, J. DePasse, R. Rosenfeld, E. Ghedin, E. Mochan, S. T. Brown, J. Grefenstette, D. S. Burke, D. Swigon, and G. Clermont. A large-scale immuno-epidemiological simulation of influenza a epidemics. *BMC Public Health*, 14:1019, 2014.

Abstract: Background Agent based models (ABM) are useful to explore population-level scenarios of disease spread and containment, but typically characterize infected individuals using simplified models of infection and symptoms dynamics. Adding more realistic models of individual infections and symptoms may help to create more realistic population level epidemic dynamics. Methods Using an equation-based, host-level mathematical model of influenza A virus infection, we develop a function that expresses the dependence of infectivity and symptoms of an infected individual on initial viral load, age, and viral strain phenotype. We incorporate this response function in a population-scale agent-based model of influenza A epidemic to create a hybrid multiscale modeling framework that reflects both population dynamics and individualized host response to infection. Results At the host level, we estimate parameter ranges using experimental data of H1N1 viral titers and symptoms measured in humans. By linearization of symptoms responses of the host-level model we obtain a map of the parameters of the model that characterizes clinical phenotypes of influenza infection and immune response variability over the population. At the population-level model, we analyze the effect of individualizing viral response in agent-based model by simulating epidemics across Allegheny County, Pennsylvania under both age-specific and age-independent severity assumptions. Conclusions We present a framework for multi-scale simulations of influenza epidemics that enables the study of population-level effects of individual differences in infections and symptoms, with minimal additional computational cost compared to the existing population-level simulations.

Keywords: multi-agent based simulation, multi-level, epidemiology

[Magliocca:2013]

N.R. Magliocca and E.C. Ellis. Using pattern-oriented modeling (pom) to cope with uncertainty in multi-scale agent-based models of land change. *Transactions in GIS*, 17(6):883–900, 2013.

Abstract: Local land-use and -cover changes (LUCCs) are the result of both the decisions and actions of individual land-users, and the larger global and regional economic, political, cultural, and environmental contexts in which land-use systems are embedded. However, the dearth of detailed empirical data and knowledge of the influences of global/regional forces on local land-use decisions is a substantial challenge to formulating multi-scale agent-based models (ABMs) of land change. Pattern-oriented modeling (POM) is a means to cope with such process and parameter uncertainty, and to design process-based land change models despite a lack of detailed process knowledge or empirical data. POM was applied to a simplified agent-based model of LUCC to design and test model relationships linking global market influence to agents' land-use decisions within an example test site. Results demonstrated that evaluating alternative model parameterizations based on their ability to simultaneously reproduce target patterns led to more realistic land-use outcomes. This framework is promising as an agent-based virtual laboratory to test hypotheses of how and under what conditions driving forces of land change differ from a generalized model representation depending on the particular land-use system and location.

Keywords: multi-agent based simulation, multi-level, multi-scale, social simulation

[Magne:2000]

L. Magne, S. Rabut, and J.F. Gabard. Towards an hybrid macro-micro traffic flow simulation model. In *Proc. of the INFORMS Conf.*, 2000.

Abstract: This paper presents recent advances in the development of a new traffic flow simulation concept, which consists in using jointly a macroscopic and a microscopic model. This approach enables modelling a large network at the macroscopic level while selected parts can be detailed at the microscopic level. The paper focuses on the compatibility problems induced by the juxtaposition of two different modelling levels (macro-micro interfaces, macroscopic traffic stream

models and microscopic car-following models compatibility), which led us to propose a new car following model for SITRA-B+. First results obtained on a simplified network are presented.

Keywords: multi-agent based simulation, multi-level, multi-scale, flow model, traffic, french team

[Mammar:2006]

J.P. Mammar, S. Lebacque and H. Haj-Salem. Hybrid model based on second-order traffic model. In *85th Annual Meeting of the Transportation Research Board*, 2006.

Abstract: The behaviour of traffic phenomena is described through three types of approaches. The first approach is macroscopic, based on the analogy with fluid mechanics through three basic variables: the flow rate q , the density p and the speed v . The second approach is microscopic, enabling one to point out the interaction phenomena between vehicles, through the vehicle speed v , the position x and the acceleration y . The third approach, which is the hybrid approach, is less known in the traffic domain. It makes it possible to combine the macroscopic and microscopic approaches. This paper proposes a hybrid model, based on a second order macroscopic modelling principle. As a first step, the models to be coupled will be chosen, and the analytical solution of the second order macroscopic model will be carried out. This model will be reformulated under the form of a supply and demand function, similar to the model by Lighthill-Witham-Richards. More precisely, two scenarios will be studied: first a hybrid model in the case of traffic at equilibrium, which will enable us to do a comparative study with an existing hybrid model in the literature. As a second step, the transition from a macroscopic representation of traffic to a microscopic representation in the conditions of an out of equilibrium traffic will be studied. The validation of the proper transmission of information from one traffic vision to another will be done, studying the propagation of congestion from upstream to downstream.

Keywords: multi-agent based simulation, multi-level, traffic, hybrid model, french team

[Mao:2018]

X. Mao, S. McManaway, J.K. Jaiswal, P.B. Patel, W.R. Wilson, K.O. Hicks, and G. Bogle. An agent-based model for drug-radiation interactions in the tumour microenvironment: Hypoxia-activated prodrug sn30000 in multicellular tumour spheroids. *PLOS Computational Biology*, 14(10):1–30, 2018.

Abstract: Studies in 3D cultures, notably multicellular tumour spheroids that mimic many features of solid tumours, have great potential for speeding up anticancer drug development. However the increased complexity of 3D cultures makes interpretation of experiments more difficult. We have developed a hybrid continuum/agent-based mathematical model, validated by experiments, to aid interpretation of spheroid experiments in developing drugs designed to eliminate radiation-resistant hypoxic cells. This model includes key features of the tumour microenvironment including oxygen and glucose transport and regions of hypoxia where the cells are resistant to radiation, but sensitive to hypoxia-activated prodrugs such as SN30000. This enables us to predict the growth and cell response in untreated spheroids and compare the results to spheroids treated with radiation and SN30000. We demonstrate good prediction of cellular responses in spheroids treated with radiation and SN30000 and good agreement with spheroid regrowth after treatment when additional effects of cellular growth delay are added. This demonstrates that the modelling approach has potential to improve interpretation of experimental investigations of drug and radiation combinations.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology, cancer modeling

[Marcenac:1998]

P. Marcenac, R. Courdier, S. Calderoni, and J. Soulie. Towards an emergence machine for complex systems simulations. In *Tasks and Methods in Applied Artificial Intelligence*, volume 416, pages 785–794. Springer, 1998.

Abstract: This paper presents a simulation platform that has been realised in Java 1.1 for the study of behaviour and evolutionary processes in non-linear systems. To support the modelling of such systems, we propose the use of agent technology as high level tool to design applications. The framework enables to study emergence by exploiting distributed computing as key issues of the system behaviour. Applications developed with the platform are then simulated to adequately capture any behaviour likely to be observed, to exhibit self organised structures, and to emphasise complex processes, which are brought in action. This approach then allows the study of macroscopic collections endowed with the potential to evolve during time.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Marcenac:1998a]

P. Marcenac and S. Giroux. GEAMAS: A generic architecture for agent-oriented simulations of complex processes. *Applied Intelligence*, 8(3):247–267, 1998.

Abstract: This paper's object is to present the results of the GEAMAS project which aims at modeling and simulating natural complex systems. GEAMAS is a generic architecture of agents used to study the behavior emergence in such systems. It is a multiagent program meant to develop simulation applications. Modeling complex systems requires to reduce, to organize the system complexity and to describe suitable components. Complexity of the system can then be tackled with an agent-oriented approach, where interactions lead to a global behavior. This approach helps in understanding how non-determinist behavior can emerge from interactions between agents, which is near of self-organized criticality used to explain natural phenomena. In the Applied Artificial Intelligence context, this paper presents an agent software architecture using a model of agent. This architecture is composed of three abstract levels over which the complexity is distributed and reduced. The architecture is implemented in ReActalk, an open agent-oriented development tool, which was developed on top of Smalltalk-80. To illustrate our purpose and to validate the architecture, a simulation program to help in predicting volcanic eruptions was investigated. This program was run over a period of one year and has given many satisfying results unattainable up to there with more classical approaches.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Marcenac:1998b]

P. Marcenac, R. Courdier, and S. Calderoni. Towards a toolkit to study emergence in complex systems simulations. http://personnel.univ-reunion.fr/courdier/pdfs/int_ia1998_MC98.pdf, 1998.

Abstract: This paper presents a simulation platform which has been realized in Java 1.1 for the study of chaotic behavior and evolutionary processes in non-linear systems. To support the modeling of such complex systems, we propose the use of agent technology as high level tool to design simulation applications. The framework enables to study emergence by exploiting distributing computing as key issues of the system behavior. Applications developed with the platform are then simulated to adequately capture any behavior likely to be observed, to exhibit self-organized structures, and to emphasize complex processes which are brought in action. This approach then allows the study of macroscopic collections endowed with the potential to evolve during time.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Marilleau:2008]

N. Marilleau, C. Cambier, A. Drogoul, J.L. Chotte, E. Perrier, and E. Blanchart. Multiscale MAS modelling to simulate the soil environment: Application to soil ecology. *Simulation Modelling Practice and Theory*, 16(7):736–745, 2008.

Abstract: Soils are important components of ecosystem and their functioning is of great importance for human well-being. Describing, understanding, foreseeing, and controlling biological activities and functions in soil in the context of global change are major objectives for scientists. Modelling soil bioturbation by soil engineers is of great importance although it is faced with the difficulty to describe the soil physical environment. Creating a model of a soil leads to complexity problems: a soil is a multi-scale heterogeneous, three-dimensional and dynamic environment that cannot be modelled and simulated without defining a suitable and optimized representation and taking assumptions about the studied system. An approach based on fractal theory (often used in soil sciences) was chosen to model such a real complex environment; it was integrated into a multi-agent system (MAS). MAS allows to simulate situated agents (earthworms) in a virtual world. The originality of this present MAS is that it is based on a dynamic environment which builds itself, on demand, according to an abstract canvas tree and agent movements. The aim of this paper is to present this approach and its originality, and to describe the model and the simulator. A theoretical view of the approach is given and applied to a case study: the impact of earthworms on soil structure and organic matter dynamics.

Keywords: multi-agent based simulation, multi-level, ecology

[Marilleau:2008a]

N. Marilleau, C. Cambier, A. Drogoul, J-L. Chotte, E. Perrier, and E. Blanchart. Environnement multi-échelles à base de fractales pour la modélisation agent d'écosystèmes. In *Actes des 16èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 23–32. Cépadués, 2008.

Keywords: multi-agent based simulation, multi-level, ecology, in french, french team

[Marino:2011]

S. Marino, M. El-Kebir, and D.E. Kirschner. A hybrid multi-compartment model of granuloma formation and T cell priming in tuberculosis. *Journal of Theoretical Biology*, 280(1):50–62, 2011.

Abstract: Tuberculosis is a worldwide health problem with 2 billion people infected with *Mycobacterium tuberculosis* (Mtb, the bacteria causing TB). The hallmark of infection is the emergence of organized structures of immune cells forming primarily in the lung in response to infection. Granulomas physically contain and immunologically restrain bacteria that cannot be

cleared. We have developed several models that spatially characterize the dynamics of the host-mycobacterial interaction, and identified mechanisms that control granuloma formation and development. In particular, we published several agent-based models (ABMs) of granuloma formation in TB that include many subtypes of T cell populations, macrophages as well as key cytokine and chemokine effector molecules. These ABM studies emphasize the important role of T-cell related mechanisms in infection progression, such as magnitude and timing of T cell recruitment, and macrophage activation. In these models, the priming and recruitment of T cells from the lung draining lymph node (LN) was captured phenomenologically. In addition to these ABM studies, we have also developed several multi-organ models using ODEs to examine trafficking of cells between, for example, the lung and LN. While we can predict temporal dynamic behaviors, those models are not coupled to the spatial aspects of granuloma. To this end, we have developed a multi-organ model that is hybrid: an ABM for the lung compartment and a non-linear system of ODE representing the lymph node compartment. This hybrid multi-organ approach to study TB granuloma formation in the lung and immune priming in the LN allows us to dissect protective mechanisms that cannot be achieved using the single compartment or multi-compartment ODE system. The main finding of this work is that trafficking of important cells known as antigen presenting cells from the lung to the lymph node is a key control mechanism for protective immunity: the entire spectrum of infection outcomes can be regulated by key immune cell migration rates. Our hybrid multi-organ implementation suggests that effector CD4+ T cells can rescue the system from a persistent infection and lead to clearance once a granuloma is fully formed. This could be effective as an immunotherapy strategy for latently infected individuals.

Keywords: multi-agent based simulation, multi-level, hybrid model, biology

[Martinez:2016]

I.J. Martinez-Moyano and C.M. Macal. A primer for hybrid modeling and simulation. In *Proc. of the Winter Simulation Conf. (WSC)*, pages 133–147, 2016.

Abstract: In dealing with complex systems, there is no single “best” possible modeling approach, as each specific system and modeling purpose has subtleties and specific needs. Consequently, in developing models that capture the complexity of real systems, it is useful to combine modeling approaches yielding what is referred to as a hybrid modeling approach. By combining different modeling paradigms, hybrid modeling and simulation provide a more comprehensive and holistic view of the system under investigation and a very powerful approach to understanding complexity. This paper discusses the uses and applications of hybrid modeling, general lessons related to how and when to use such an approach, and relevant tools.

Keywords: multi-agent based simulation, multi-level, hybrid model

[Masoudi:2014]

A. Masoudi-Nejad and A. Meshkin. Withdrawn: Cancer modeling: the holonic agent-based approach. *Seminars in Cancer Biology*, 2014.

Abstract: Cancer behaves as a complex, dynamic, adaptive and self-organizing system, and agent-based models are capable of describing such a system as a collection of autonomous decision-making entities called agents. This review provides an overview of how an agent-based approach can be established, and is being used to model a variety of cancer-related processes including tumor genesis, tumor growth, apoptosis, angiogenesis, vascularization and anti-cancer therapy and discuss both challenges and future directions for agent-based modeling in the field of cancer research. We provide rationales for using holonic agent-based modeling toward the goal of creating realistic simulations of cancer in future research directions. Holonic systems guarantee to provide a recursive and hierarchical modeling for complex systems with dynamic and runtime reorganization. They are adopted for cancer modeling since living organisms have a hierarchical structure and can be decomposed into individual cooperating entities.

Keywords: multi-agent based simulation, multi-level, cancer modeling, plagiarism, withdrawn

[Mathieu:2007]

J. Mathieu, J. Melhuish, J. James, P. Mahoney, L. Boiney, and B. White. Multi-scale modeling of the air operations center. http://www.mitre.org/work/tech_papers/tech_papers_07/06_1497/06_1497.pdf, February 2007.

Abstract: The goal of this effort is to use multi-scale modeling to understand the effect of operator environment interaction and the global environment on Air and Space Operations Center (AOC) processes. Models were developed at 3 scales, including: 1) Operator interaction with computer interface (Agent-Based model); 2) Processing of Time Sensitive Targets (TST, Petri net model); and 3) Mission-scale objectives, strategy, and processes, including adversary response and global and US public perception (System Dynamics model). An existing Petri net model of the

operational architecture of the AOC was updated for this study; all models were developed with subject matter experts.

Keywords: multi-agent based simulation, multi-level, military simulation

[Mathieu:2007a]

J. Mathieu, J. James, P. Mahoney, L. Boiney, R. Hubbard, and B. White. Hybrid systems dynamic, petri net, and agent-based modeling of the air and space operations center. http://www.mitre.org/work/tech_papers/tech_papers_07/07_0455/07_0455.pdf, October 2007.

Abstract: It has been observed that many Air and Space Operations Center operators can become distracted by a pilot down critical event, even if the operator is not able to directly assist in the rescue. The focus of this paper is the development of an operator environment model (i.e., Agent-Based Model).

Keywords: multi-agent based simulation, multi-level, hybrid model, military simulation

[Mathieu:2016]

P. Mathieu, S. Picault, and G. Morvan. Simulations multi-agents multi-niveaux : quatre patterns de conception. In *Actes des 24èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 117–126, 2016.

Abstract: Cet article introduit quatre patterns de conception, définis à partir de l'identification de "situation-types" minimales rencontrées dans la littérature et destinés à systématiser et simplifier la conception de simulations multi-agents multi-niveaux. Ces simulations ont pour but de gérer des entités appartenant à des niveaux d'abstraction ou d'organisation différents mais couplés. Pour chaque pattern, nous présentons des cas d'utilisation ainsi que les structures de données et algorithmes associés. À des fins de généralité, ces patterns font appel à une description unifiée des capacités d'action et d'évolution des agents. Nous proposons ainsi un cadre conceptuel et opérationnel précis pour les concepteurs de simulations multi-niveaux.

Keywords: multi-agent based simulation, multi-level, design patterns, in french, french team

[Mathieu:2018]

P. Mathieu, S. Picault, and G. Morvan. Multi-level agent-based simulations: Four design patterns. *Simulation Modelling Practice and Theory*, 83:51–64, 2018.

Abstract: This paper describes four design patterns that aim at systematizing and simplifying the modelling and the implementation of multi-level agent-based simulations. Such simulations are meant to handle entities belonging to different, yet coupled, abstractions or organization levels. The patterns we propose are based on minimal typical situations drawn from the literature. For each pattern, we present use cases, associated data structures and algorithms. For genericity purposes, these patterns rely on a unified description of the capabilities for action and change of the agents. Thus, we propose a precise conceptual and operational framework for the designers of multi-level simulations.

Keywords: multi-agent based simulation, multi-level, design patterns, french team

[Maudet:2013]

A. Maudet. Interactions between levels in an agent oriented model for generalisation. In *Proceedings of the 2nd AGILE PhD School*, 2013.

Abstract: Generalisation is a complex operation of the mapping process seeking to simplify geographic data. In order to carry out this process, algorithms are used. Multi-agent systems are an approach to orchestrate the application of these algorithms. Models were proposed in the literature, but some situation are not automatically generalised in a satisfying way. Our hypothesis is that, if the behaviour of the agents is described in a way that takes into account the organisation of geographic objects in levels, we may solve these issues. Methods to explore this hypothesis are introduced in this paper.

Keywords: multi-agent based simulation, multi-level, geography, french team

[Maudet:2013a]

A. Maudet, G. Touya, C. Duchêne, , and S. Picault. Improving multi-level interactions modelling in a multi-agent generalisation model: first thoughts. In *16th ICA Workshop on Generalisation and Multiple Representation*, 2013.

Keywords: multi-agent based simulation, multi-level, geography, french team

[Maudet:2014]

A. Maudet, G. Touya, C. Duchêne, and S. Picault. Representation of interactions in a multi-level multi-agent model for cartography constraint solving. In *Advances in Practical Applications of Heterogeneous Multi-Agent Systems. The PAAMS Collection*, volume 8473 of LNCS, pages 183–194. Springer, 2014.

Abstract: The objective of cartographic generalisation is to simplify geographic data in order to create legible maps when scale decreases. It often requires to reason at different levels of abstraction (e.g. a building, a city). To automate this process, Multi-Agent approaches have been used for several years. Map objects (e.g. buildings) are modelled as autonomous entities that try to solve constraints through appropriate transformations. Yet, those approaches are not able to deal with all situations that appear between cartographic objects in a map. Indeed, though a map intrinsically involves objects that belong to several description, scale or organisation levels, there is no explicit multi-level representation in agent-based cartographic models. Thus we assume that the use of a multi-level multi-agent model would improve the automated generalisation process. Especially, the PADAWAN model is a multi-agent model offering multi-level capabilities which meet quite well the requirements for the multi-level organisation of cartographic objects. In this paper, we expose how we use this model on the one hand, to reify multi-level relations between cartographic agents, and on the other hand, to represent the constraints and the actions proposed to solve them, as interactions between the agents.

Keywords: multi-agent based simulation, multi-level, geography, french team

[Maudet:2014a]

A. Maudet, G. Touya, C. Duchêne, and S. Picault. Multi-agent multi-level cartographic generalisation in cartagen. In *Advances in Practical Applications of Heterogeneous Multi-Agent Systems. The PAAMS Collection*, volume 8473 of *LNCS*, pages 355–358. Springer, 2014.

Abstract: The objective of cartographic generalisation is to simplify geographic data in order to create legible maps when scale decreases. This demonstration presents the implementation of a work in progress, aiming at defining a multi-agent, multi-level solution for generalisation. The demonstration introduces the basics of cartographic generalisation and shows some aspects of the model currently being developed, including parameterisation and detailed execution of some interactions, as well as results.

Keywords: multi-agent based simulation, multi-level, geography, french team

[Maudet:2015]

A. Maudet, G. Touya, C. Duchêne, and S. Picault. Patterns multi-niveaux pour les sma. In *23es Journées Francophones sur les Systèmes Multi-Agents*, pages 19–28. Cépaduès, 2015.

Abstract: Depuis quelques années, les travaux sur les SMA multi-niveaux ont pris une importance croissante. Devant la diversité des modèles proposés, nous pensons qu’il est utile d’identifier des situations récurrentes et de les caractériser d’une manière suffisamment abstraite pour pouvoir comparer de manière formelle les modèles existants et faciliter la conception de nouveaux modèles. Dans ce but, nous proposons une première liste de patterns SMA multi-niveaux. Ces patterns sont issus d’un travail d’unification de modèles SMA multi-niveaux dédiés à la résolution d’un problème spatialisé (la généralisation cartographique). La structure et la dynamique de chaque pattern sont décrites formellement et accompagnées d’exemples issus d’une part du contexte de la généralisation cartographique, d’autre part d’autres contextes applicatifs multi-agents, en simulation notamment. Nous discutons également la possibilité de réutiliser et composer ces patterns.

Keywords: multi-agent based simulation, multi-level, geography, in french, french team

[Maudet:2017]

A. Maudet, G. Touya, C. Duchêne, and S. Picault. DIOGEN, a multi-level oriented model for cartographic generalization. *International Journal of Cartography*, pages 1–13, 2017.

Abstract: Among approaches for automated generalization of vector data, we focus on the multi-agent paradigm: cartographic objects are modeled as agents (autonomous objects) that apply generalization algorithms to themselves to satisfy cartographic constraints. Several agent levels are considered, for example, individual agents, such as a building, and agents representing a group of agents, such as an urban block composed of the surrounding roads and contained buildings. Several multi-agent models were proposed to automate the orchestration of map generalization processes. Existing multi-agent generalization models have different approaches to manage the relations between agent levels. In this paper, we unify existing models, adapting a multi-level simulation model, to simplify interactions between agents in different levels. We propose the DIOGEN model, in which the principle of interactions between agents of different levels is adapted to constraint-driven cartographic generalization. DIOGEN unifies three existing multi-agent generalization models (AGENT, CartACom and GAEL), combine their behaviors and take advantage of their skills. Our proposal is evaluated on different use cases: instances of topographic mapping, and mapping of hiking routes over topographic data as an example of thematic mapping.

Keywords: multi-agent based simulation, multi-level, geography, french team

[Maus:2011]

C. Maus, S. Rybacki, and A.M. Uhrmacher. Rule-based multi-level modeling of cell biological systems. *BMC systems biology*, 5(1):166–186, 2011.

Abstract: Background Proteins, individual cells, and cell populations denote different levels of an organizational hierarchy, each of which with its own dynamics. Multi-level modeling is concerned with describing a system at these different levels and relating their dynamics. Rule-based modeling has increasingly attracted attention due to enabling a concise and compact description of biochemical systems. In addition, it allows different methods for model analysis, since more than one semantics can be defined for the same syntax. Results Multi-level modeling implies the hierarchical nesting of model entities and explicit support for downward and upward causation between different levels. Concepts to support multi-level modeling in a rule-based language are identified. To those belong rule schemata, hierarchical nesting of species, assigning attributes and solutions to species at each level and preserving content of nested species while applying rules. Further necessities are the ability to apply rules and flexibly define reaction rate kinetics and constraints on nested species as well as species that are nested within others. An example model is presented that analyses the interplay of an intracellular control circuit with states at cell level, its relation to cell division, and connections to intercellular communication within a population of cells. The example is described in ML-Rules - a rule-based multi-level approach that has been realized within the plug-in-based modeling and simulation framework JAMES II. Conclusions Rule-based languages are a suitable starting point for developing a concise and compact language for multi-level modeling of cell biological systems. The combination of nesting species, assigning attributes, and constraining reactions according to these attributes is crucial in achieving the desired expressiveness. Rule schemata allow a concise and compact description of complex models. As a result, the presented approach facilitates developing and maintaining multi-level models that, for instance, interrelate intracellular and intercellular dynamics.

Keywords: multi-agent based simulation, multi-level, biology, meta-model

[Maus:2013]

C. Maus. *Toward Accessible Multilevel Modeling in Systems Biology: A Rule-based Language Concept*. PhD thesis, University of Rostock, Germany, 2013.

Abstract: Promoted by advanced experimental techniques for obtaining high-quality data and the steadily accumulating knowledge about the complexity of life, modeling biological systems at multiple interrelated levels of organization attracts more and more attention recently. Current approaches for modeling multilevel systems typically lack an accessible formal modeling language or have major limitations with respect to expressiveness. The aim of this thesis is to provide a comprehensive discussion on associated problems and needs and to propose a concrete solution addressing them. At first, several formal modeling approaches are examined regarding their suitability for describing biological models at multiple organizational levels. Thereby, diverse aspects are taken into account, such as the ability to describe dynamically changing hierarchical model structures and how upward and downward causation between different levels can be expressed. Based on the results of this study, a domain-specific language concept is developed to facilitate multilevel modeling in systems biology. The presented approach combines a rule-based modeling paradigm with dynamically nested model structures, attributed entities, and flexibly constrained reaction rates. Its expressive power, accessibility, and general usefulness for describing biological multilevel models are illustrated with the help of two exemplary case studies.

Keywords: multi-agent based simulation, multi-level, meta-model, biology

[Mboup:2017]

P.A. Mboup, K. Konaté, and J. Le Fur. A multi-world agent-based model working at several spatial and temporal scales for simulating complex geographic systems. *Procedia Computer Science*, 108:968–977, 2017.

Abstract: Interest in the modelling and simulation of complex systems with processes occurring at several spatial and temporal scales is increasing, particularly in biological, historical and geographic studies. In this multi-scale modelling study, we propose a generic model to account for processes operating at several scales. In this approach, a ‘world’ corresponds to a complete and self-sufficient submodel with its own places, agents, spatial resolution and temporal scale. Represented worlds can be nested: a world (with new scales) may have a greater level of detail than the model at the next level up, making it possible to study phenomena with greater precision. This process can be reiterated, to create additional scales, with no formal limit. Worlds’ simulations can be triggered simultaneously or in cascade. Within a world, agents can choose destinations in other worlds, to which they can travel using routes and inter-world ‘gates’. Once they arrive in a destination world, the agents ‘fit’ the new scale. An agent in a given world can also perceive and interact with other agents, regardless of the world to which they belong, provided they are encompassed by its perception disc. We present and discuss an application of this model to the issue of the spread of black rats by means of commercial transportation in Senegal (West Africa).

Keywords: multi-agent based simulation, multi-level, geography, french team

[Mboup:2017a]

P.A. Mboup. *Un meta-modèle multi-monde et multi-échelle pour la simulation à base d'agents de systèmes complexes présentant des phénomènes historiques et géographiques : Application à l'étude de la diffusion du rat noir au Sénégal*. PhD thesis, Université Cheikh Anta Diop de Dakar, 2017.

Abstract: The general problematic of this thesis concerns the modeling and simulation of complex systems with historical and geographical phenomena in several space and time scales. The model particularly aimed to simulate the history (over a century) of the diffusion (through human transport) of the black rat (*Rattus Rattus*) in Senegal, from colonial trading posts (extreme west) to the city of Kedougou (extreme east). It leads to a diffusion simultaneously represented in three different levels of spatial and temporal scales and environments that are built over time from multidisciplinary data. This thesis is part of the wider problematic of multi-scale modeling in agent-based model. It meets the need of tools in this field by proposing an agent-based meta-model, multi-worlds and multiscale, coupled with knowledge and event oriented approach as well as the algorithms associated with it. This approach allows a good representation of multiscale phenomena involving several types of disciplines such as history, geography, biology or ecology. Worlds represent complete and autonomous sub-models. They each have their own spatial and temporal scales and an environment that can be built and updated over time using data accounted for as historical events. Represented worlds are nested: a world can be a sub-model representing a part of another world in which we want to enter in more detail taking into account the fact that the worlds feed each other. Nesting is performed in cascade: the simulation of a first world can start before the others and then, after a certain time of simulation, a second one for a second world concerning a smaller area of the first world starts with a finer spatial and temporal scales. The process can be repeated for finer scales without formal limiting number. This meta-model takes into account the interaction between worlds on two ways: (1) agents (carriers, which can transport other types of agents) in a world can choose destinations in other one and travel there via itineraries and inter-worlds doors. Upon arrival in a destination world, agents adapt themselves to the new environment and the new spatial and temporal scales; (2) an agent in a world is able to perceive and act on agents that are located in its perception disk (on the continuous space), even if they are in different worlds.

Keywords: multi-agent based simulation, multi-level, social simulation

[Mei:2015]

Y. Mei, V. Abedi, A. Carbo, X. Zhang, P. Lu, C. Philipson, R. Hontecillas, S. Hoops, N. Liles, and J. Bassaganya-Riera. Multiscale modeling of mucosal immune responses. *BMC bioinformatics*, 16(Suppl 12), 2015.

Abstract: **BACKGROUND:** Computational techniques are becoming increasingly powerful and modeling tools for biological systems are of greater needs. Biological systems are inherently multiscale, from molecules to tissues and from nano-seconds to a lifespan of several years or decades. ENISI MSM integrates multiple modeling technologies to understand immunological processes from signaling pathways within cells to lesion formation at the tissue level. This paper examines and summarizes the technical details of ENISI, from its initial version to its latest cutting-edge implementation. **IMPLEMENTATION:** Object-oriented programming approach is adopted to develop a suite of tools based on ENISI. Multiple modeling technologies are integrated to visualize tissues, cells as well as proteins; furthermore, performance matching between the scales is addressed. **CONCLUSION:** We used ENISI MSM for developing predictive multiscale models of the mucosal immune system during gut inflammation. Our modeling predictions dissect the mechanisms by which effector CD4+ T cell responses contribute to tissue damage in the gut mucosa following immune dysregulation. Computational modeling techniques are playing increasingly important roles in advancing a systems-level mechanistic understanding of biological processes. Computer simulations guide and underpin experimental and clinical efforts. This study presents ENteric Immune Simulator (ENISI), a multiscale modeling tool for modeling the mucosal immune responses. ENISI's modeling environment can simulate in silico experiments from molecular signaling pathways to tissue level events such as tissue lesion formation. ENISI's architecture integrates multiple modeling technologies including ABM (agent-based modeling), ODE (ordinary differential equations), SDE (stochastic modeling equations), and PDE (partial differential equations). This paper focuses on the implementation and developmental challenges of ENISI. A multiscale model of mucosal immune responses during colonic inflammation, including CD4+ T cell differentiation and tissue level cell-cell interactions was developed to illustrate the capabilities, power and scope of ENISI MSM.

Keywords: multi-agent based simulation, multi-level, biology

[Merelli:2011]

P. Liò E. Merelli, N. Paoletti. Methodological bridges for multi-level systems. In *Proc. of the 2nd European Future Technologies Conf. and Exhibition (FET)*, volume 7 of *Procedia Computer Science*, pages 180–182. Elsevier, 2011.

Abstract: We are certainly flooded with data (socio-economical, biomedical, astro-nuclear physics, weather conditions, communication network, land, air, naval traffic etc) and we want to use them. There is a growing tendency to use computers to make predictions which would require constructing models. Following George Box we also know that models are wrong but some are useful. This is particularly true when we would like to model multiscale phenomena, for example diseases in which we investigate effects that originate across molecular, tissue, organ and organismal scale, or an epidemic in which the dynamics of an antibiotic at cellular level affects (and is affected by) the health and psychology at individual level (which in turn decide on vaccination) and the dynamics at population levels. In social sciences we often deal with matrioska of communities (it could be linguistic, economic, political, geographic, age related) embedded in larger communities (again linguistic, economy, geographic, age related) and so on. Here we are considering a framework based on a theoretical computer science approach, called Shape Calculus [1] which belongs to a class of methodologies defined Formal Methods. We found these to help in expressing a large class of biomedical and social networks models in a computational well posed and general manner, but we find the first difficulty because beyond the multiscale framework we need to build a multi field interface framework: physicists and mathematicians know very well about the math of modeling but they have not been trained in using formal methods which have been developed by computer scientists firstly to address specific issues in software engineering. So we are facing a “language” barrier that make harder solving the multiscale modeling problem. In formal methods we address issues related to the specification, development and verification of software with particularly attention to the properties related to high-integrity of the software, namely safety (robustness from errors, failures) and/or security. How does this relate to modeling?

Keywords: multi-agent based simulation, multi-level

[Michel:2003a]

F. Michel, G. Beurier, and J. Ferber. The turtlekit simulation platform: Application to multi-level emergence. In *Agent Based Simulation 4*, 2003.

Abstract: This paper presents the TurtleKit simulation platform. This platform relies on the combination of a Logo simulation model with high level programming languages.

Keywords: multi-agent based simulation, multi-level, multi-level emergence, artificial life, french team

[Minelli:2015]

A. Minelli, C. Tissot, M. Rouan, and M. Le Tixerant. Multi-scale modelling for simulating marine activities under heterogeneous environmental constraints. In *Proc. of Spatial Analysis and GEomatics (SAGEO)*, 2015.

Abstract: This paper describes the concepts behind the implementation of a multi-agent model aiming to explore how marine activities respond to various environmental constraints. The method benefits from a responsive agent-based structure, and treats the environment as a set of forcing variables (biophysical, socio-economic and regulatory data). A first experiment in the Iroise Sea area, France, shows this approach has great potential for assessing the intensity and the variability of marine activities at different scales. The complete method is presented in this paper in order to comprehensively analyse the contributions and limitations of the SIMARIS prototype.

Keywords: multi-agent based simulation, multi-level, ecology

[Minelli:2016]

A. Minelli and M. Tonini. A multi-level agent-based model to assess the forest fire management in the southern swiss alpine region. *PeerJ Preprints*, 4:e2152v3, 2016.

Abstract: Alpine fires are mainly slope-driven, spreading along the forested steep slopes. Fire ignitions are here highly clustered near anthropogenic infrastructures and this characteristic behavior also affects the definition of the wildland urban interface (WUI). This last is known as the area where houses and other human infrastructures meet or intermingle with wildland vegetation, rural zone or forest. The main objective of the present study is to create a simulation model to assess the forest fire dynamic in pilot area located in the in the southern Swiss alpine region. This allows to investigate, for example, the influence of the mobility of people on the fires occurrences by simulating the daily movement of each single active person; or to simulate the displacement of the firefighters over the territory in order to evaluate the efficiency of different fires fight strategies in time. In this preliminary study the core simulation model has been implemented in GAMA, an open source agent based simulation platform. A long term objective is to conduct a study at

global scale, over a wider area (e.g. the entire Canton Ticino), to understand the evolution of the WUI in time, analysing the affecting factors like the population growth or of the urbanisation and land use management.

Keywords: multi-agent based simulation, multi-level, ecology

[Moncion:2008]

T. Moncion. *Modélisation de la complexité et de la dynamique des simulations multi-agents: application pour l'analyse des phénomènes émergents*. PhD thesis, Université d'Evry-Val d'Essonne, 2008.

Abstract: Multi-agent systems are characterized by the cooperative work of a set of autonomous agents, operating in a decentralized manner with a view to achieving a goal. Within these systems produce phenomena known as emergence, or self-organization, in which structures or organizations may appear on a collective level that were not explicitly described at the individual level. Thus ants that are organized into files of individuals without having representation corresponding to the "file". Through their interactions at the local level, the agents produce and maintain structural dynamics at the global level which in turn constrain the activities of each individual. These phenomena are fundamental in the study of complex biological systems but are very difficult to formalize because usually related to a subjective interpretation of an observer outside the system. The subject is intended to address the problem of transition from one level of abstraction to another, and the interaction, within a system between officers of different levels, combining several complementary approaches: a first approach concerns study formalisms adapted to the representation of emergent phenomena. This includes taking account of relationships between entities of different levels of abstraction, and by taking behaviors that are expressed differently depending on the level of abstraction to which the entity is considered. a second approach which builds on the previous concerns the automatic detection of emergent phenomena. To do this, it will be necessary to develop mechanisms that allow entities that participate in the system to detect the emergence of structures (spatial and / or temporal, static or dynamic) and characterize the passage of a given level of abstraction to the next level. because of the great difficulty of dealing with the previous problem in all its generality, we plan to develop a semi-interactive approach in which a human observer may have a role to guide the system to detect structures and their characterization of a particular way. In addition to assisting the system, it is the guide to take into account a priori abstractions useful and interesting. This includes the design of procedures for display and interaction adapted to this problem. these issues will be explored in several issues of multi-agent simulation in biology.

Keywords: multi-agent based simulation, multi-level, emergence detection, in french, french team

[Moncion:2010]

T. Moncion, P. Amar, and G. Hutzler. Automatic characterization of emergent phenomena in complex systems. *J. Biol. Phys. Chem.*, 10:16–23, 2010.

Abstract: One of the main characteristics of complex systems is that the interrelations between the entities composing the system are not permanently established but evolve along time. As opposed to complicated systems, the structure of complex systems also evolve in a dynamic organizational process. When studying complex systems, self-organization and emergent phenomena must therefore be taken into account and studied carefully. In this paper, we propose to provide tools in order to automatically detect and characterize the emergent phenomena occurring in agent-based simulations. To this end, we consider the interactions between the entities at the lower level as the main organizational forces that shape the structure of the system at a higher level. These interactions are detected during the simulation and represented as dynamic graphs. Measures can then be made on various properties of the graph so as to detect the occurrence of structuring processes. Groups detection and tracking techniques are then introduced so as to characterize more precisely the exact nature of these processes.

Keywords: multi-agent based simulation, multi-level, emergence detection, french team

[Montagna:2010]

S. Montagna, N. Donati, and A. Omicini. An agent-based model for the pattern formation in drosophila melanogaster. *Artificial Life XII*, pages 110–117, 2010.

Abstract: The hierarchical organisation of biological systems plays a crucial role in the pattern formation of gene expression resulting from the morphogenetic processes. Being able to reproduce the systems dynamics at different levels of such a hierarchy might be very useful for studying such a complex phenomenon of self-organisation. In this paper we propose the adoption of the agent-based model as an approach capable of capture multi-level dynamics. We then realise an agent-based model of Drosophila Melanogaster morphogenesis demonstrating its capability of reproducing the expression pattern of the embryo.

Keywords: multi-agent based simulation, multi-level, biology

[Montagna:2010a]

S. Montagna, A. Omicini, and A. Ricci. A multiscale agent-based model of morphogenesis in biological systems. In A. Omicini and M. Viroli, editors, *Proceedings of 11° Workshop nazionale "Dagli Oggetti agli Agenti" WOA 2010*, Rimini, Italy, September 5–7 2010.

Abstract: Studying the complex phenomenon of pattern formation created by the gene expression is a big challenge in the field of developmental biology. This spatial self-organisation autonomously emerges from the morphogenetic processes and the hierarchical organisation of biological systems seems to play a crucial role. Being able to reproduce the systems dynamics at different levels of such a hierarchy might be very useful. In this paper we propose the adoption of the agent-based model as an approach capable of capture multi-level dynamics. Each cell is modelled as an agent that absorbs and releases substances, divides, moves and autonomously regulates its gene expression. As a case study we present an agent-based model of *Drosophila melanogaster* morphogenesis. We then propose a formalisation of the model which clearly describe its main components. We finally show simulation results demonstrating the capability of the model of reproducing the expression pattern of the embryo.

Keywords: multi-agent based simulation, multi-level, biology

[Moreira:2009]

E. Moreira, S. Costa, Ana P. A., G. Câmara, and T. Carneiro. Dynamical coupling of multiscale land change models. *Landscape Ecology*, 24(9):1183–1194, 2009.

Abstract: No single model or scale can fully capture the causes of land change. For a given region, land changes may have different impacts at different places. Limits and opportunities imposed by biophysical and socio-economic conditions, such as local policies and accessibility, may induce distinct land change trajectories. These local land change trajectories may, in turn, indirectly affect other places, as local actions interact with higher-level driving forces. Such intraregional interdependencies cannot be captured by studies at a single scale, calling for multiscale and multilocality studies. This paper proposes a software organization for building computational models that support dynamical linking of multiple scales. This structure couples different types of models, such as cell-space models with agent-based models. We show how results in multiscale models can flow both in bottom-up and top-down directions, thus allowing feedback from local actors to regional scales. The proposal is general and independent of specific software, and it is effective to model intraregional, bottom-up and top-down interactions in land change models. To show the model's potential, we develop a case study that shows how a multiscale model for the Brazilian Amazonia can include feedbacks between local to regional scales.

Keywords: multi-agent based simulation, multi-level, ecology

[Morvan:2008]

G. Morvan, D. Jolly, A. Veremme, D. Dupont, and D. Charabidze. Vers une méthode de modélisation multi-niveaux. In *Actes de la 7ème Conférence de Modélisation et Simulation MOSIM, Paris, France*, volume 1, pages 167–174, 2008.

Abstract: Cet article présente les fondements d'une méthode de modélisation basée sur le paradigme agent et permettant d'intégrer dans un même modèle des connaissances issues de différents niveaux d'observation d'un système. La problématique à laquelle répond cette méthode est essentiellement d'ordre pratique, à savoir la difficulté à spécifier intégralement un système à un niveau d'observation donné. Nous présenterons également le contexte de ce travail : la modélisation du comportement des Diptères nécrophages dans un environnement complexe. Nous aborderons enfin quelques problèmes liés à l'implémentation de cette méthode et proposerons des pistes de réflexion basées sur des travaux antérieurs.

Keywords: multi-agent based simulation, multi-level, meta-model, ecology, emergence detection, in french, french team

[Morvan:2009a]

G. Morvan, A. Veremme, D. Dupont, and D. Jolly. Modélisation et conception multiniveau de systèmes complexes : stratégie d'agentification des organisations. *Journal Européen des Systèmes Automatisés*, 43(4-5):381–406, 2009.

Keywords: multi-agent based simulation, multi-level, flow model, emergence detection, in french, french team

[Morvan:2011]

G. Morvan, A. Veremme, and D. Dupont. IRM4MLS: the influence reaction model for multi-level simulation. In *Multi-Agent-Based Simulation XI*, volume 6532 of *LNCS*, pages 16–27. Springer, 2011.

Abstract: In this paper, a meta-model called IRM4MLS, that aims to be a generic ground to specify and execute multi-level agent-based models is presented. It relies on the influence/reaction principle and more specifically on IRM4S [13,14]. Simulation models for IRM4MLS are defined. The capabilities and possible extensions of the meta-model are discussed.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Morvan:2012a]

G. Morvan, D. Dupont, J-B. Soyeux, and R. Merzouki. Engineering hierarchical complex systems: an agent-based approach – the case of flexible manufacturing systems. In *Service Orientation in Holonic and Multi Agent Manufacturing Control*, volume 402 of *Studies in Computational Intelligence*. Springer, 2012.

Abstract: This chapter introduces a formal model to specify, model and validate hierarchical complex systems described at different levels of analysis. It relies on concepts that have been developed in the multi-agent-based simulation (MABS) literature: level, influence and reaction. One application of such model is the specification of hierarchical complex systems, in which decisional capacities are dynamically adapted at each level with respect to the emergences/constraints paradigm. In the conclusion, we discuss the main perspective of this work: the definition of a generic meta-model for holonic multi-agent systems (HMAS).

Keywords: multi-agent based simulation, multi-level, flow model, french team

[Morvan:2012b]

G. Morvan and D. Jolly. Multi-level agent-based modeling with the Influence Reaction principle. *CoRR*, abs/1204.0634, 2012.

Abstract: This paper deals with the specification and the implementation of multi-level agent-based models, using a formal model, IRM4MLS (an Influence Reaction Model for Multi-Level Simulation), based on the Influence Reaction principle. Proposed examples illustrate forms of top-down control in (multi-level) multi-agent based-simulations.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Morvan:2013]

G. Morvan. Multi-level agent-based modeling - a literature survey. *CoRR*, abs/1205.0561, 2013.

Abstract: During last decade, multi-level agent-based modeling has received significant and dramatically increasing interest. In this article we present a comprehensive and structured review of literature on the subject. We present the main theoretical contributions and application domains of this concept, with an emphasis on social, flow, biological and biomedical models.

Keywords: multi-agent based simulation, multi-level, review, french team

[Morvan:2013a]

G. Morvan and D. Jolly. Multi-level agent-based modeling with the Influence Reaction principle. In *MASyCo'2013 : Modélisation Agents pour les Systèmes Complexes*, 2013.

Abstract: This paper deals with the specification and the implementation of multi-level agent-based models, using a formal model, IRM4MLS (an Influence Reaction Model for Multi-Level Simulation), based on the Influence Reaction principle. Proposed examples illustrate forms of top-down control in (multi-level) multi-agent based-simulations.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Morvan:2017]

G. Morvan and Y. Kubera. On time and consistency in multi-agent-based simulations. *CoRR*, arXiv:1703.02399, 2017.

Abstract: The integration of multiple viewpoints became an increasingly popular approach to deal with agent-based simulations. Despite their disparities, recent approaches successfully manage to run such multi-level simulations. Yet, are they doing it appropriately? This paper tries to answer that question, with an analysis based on a generic model of the temporal dynamics of multi-level simulations. This generic model is then used to build an orthogonal approach to multi-level simulation called SIMILAR. In this approach, most time-related issues are explicitly modeled, owing to an implementation-oriented approach based on the influence/reaction principle.

Keywords: multi-agent based simulation, multi-level, french team

[Mudera:2018]

C. Mudera, R. Torii, D. Hodgson, and R. Velliou. Modelling multi-scale cell-tissue interaction of tissue-engineered muscle constructs. *Journal of Tissue Engineering*, 2018.

Abstract: Expectation on engineered tissue substitute continues to grow and for an effective development of a functional tissue and to control its quality, cellular mechnoresponse plays a key role. Although the mechanoresponse – in terms of cell-tissue interaction across scales – has been understood better in recent years, there are still technical limitations to quantitatively monitor the processes involved in the development of both native and engineered tissues. Computational (in silico) studies have been utilised to complement the experimental limitations and successfully applied to prediction of tissue growth. We here review recent activities in the area of combined experimental and computational analyses of tissue growth, especially in tissue-engineering context, and highlight the advantages of such an approach for the future of the tissue engineering, using our own case study of predicting musculoskeletal tissue-engineering construct development.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology

[Muller:2005]

J-P. Müller, C. Ratzé, F. Gillet, and K. Stoffel. Modeling and simulating hierarchies using an agent-based approach. In *Proceedings of the MODSIM 2005 International Congress on Modelling and Simulation*, pages 1631–1638, 2005.

Abstract: The notion of complex system covers many different meanings. Socio-economical and ecological systems are typically kind of 'organized complex systems', defined as a middle number of heterogeneous components interacting in an intricate manner and producing emergent properties and dynamics. The only possibility to understand and to model such complex systems is to exhibit some organizational principles behind the apparent inextricability. The hierarchy theory in ecology allows a decomposition of this kind of systems that could improve our understanding of the underlying dynamic processes. Formally, it is a view of ecological systems, which takes the scales of observation explicitly into account and which tries to conceptualize the phenomena at their proper scale. This conceptualization mostly exhibits nested hierarchical systems in the sense that a system at a given scale contains its component subsystems at the underlying scale. Socio-economical systems additionally exhibit nonnested hierarchies in which representatives of social groups (and not the groups themselves) form higher level groups or organizations. The aim of this paper is to propose a set of concepts to formalize both nested and non-nested hierarchical systems. For the first kind of systems, we will review the hierarchy theory in ecology to extract the main concepts, mainly the concept of holon. Independently, we will review the concepts of agents, groups and roles (AGR) to represent ecosociological systems as proposed in Ferber et Gutknecht (1998). Finally, we will propose a modeling and simulation formalism able to represent these concepts in a unified framework and discuss some of its advantages and disadvantages.

Keywords: multi-agent based simulation, multi-level, methodology, french team

[Muller:2011]

J-P. Müller and S. Aubert. L'ontologie pour construire une représentation multi-niveau de et par les systèmes sociaux. In *Actes des 18èmes journées de Rochebrune*, 2011.

Keywords: multi-agent based simulation, multi-level, meta-model, social simulation, methodology, in french, french team

[Muller:2011a]

J-P. Müller, A. Diallo, J-C. François, L. Sanders, R. Waldeck, and H. Mathian. Building ontologies from a variety of points of view. In *Proceedings of the 7th European Social Simulation Association Conference*, 2011.

Abstract: Methodologically, we suggest that modelling must start by an enumeration of the actors and institutions implied in the exercise of modelling, both the actors and institutions to be modelled (internal), and the modelling scientists, and possibly the interested decision makers and/or stakeholders (external). The aim of this paper is to illustrate this methodology by making a medium sized model. This proposed model objective is to understand the relationships between residential segregation and school segregation, resulting from the interaction between school supply and students' choices. We will first identify the various so-called actors, their objectives and their resulting point of view on the targeted system. Then we provide a synthesis of these points of view. Finally we will discuss the pros and cons of the proposed methodology with respect to knowledge elicitation potentials.

Keywords: multi-agent based simulation, multi-level, meta-model, social simulation, methodology, french team

[Muller:2012]

J-P. Müller and A. Diallo. Vers une méthode multi-point de vue de modélisation multi-agent. In *Actes des 20èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 33–42. Cépaduès, 2012.

Abstract: La modélisation multi-agent est de plus en plus utilisée pour comprendre les dynamiques des socio-écosystèmes, faisant intervenir de ce fait de nombreuses disciplines autour d'une ou plusieurs questions. Dans ce papier, nous proposons une méthode de production d'un modèle conceptuel à partir de l'ensemble des modèles conceptuels issus des différents points de vue à la fois des thématiciens et des agents modélisés. Nous proposons également un ensemble de notations pour exprimer ces modèles conceptuels fondés sur les logiques de description et certaines possibilités d'UML. Nous illustrons son fonctionnement et son utilité sur un exemple de ségrégation scolaire.

Keywords: multi-agent based simulation, multi-level, meta-model, methodology, in french, french team

[Murphy:2014]

S.Ó. Murphy. *Integration of micro-and macroscopic models for pedestrian evacuation simulation*. PhD thesis, University College Cork, 2014.

Abstract: Simulation of pedestrian evacuations of smart buildings in emergency is a powerful tool for building analysis, dynamic evacuation planning and real-time response to the evolving state of evacuations. Macroscopic pedestrian models are low-complexity models that are and well suited to algorithmic analysis and planning, but are quite abstract. Microscopic simulation models allow for a high level of simulation detail but can be computationally intensive. By combining micro- and macro- models we can use each to overcome the shortcomings of the other and enable new capability and applications for pedestrian evacuation simulation that would not be possible with either alone. We develop the EvacSim multi-agent pedestrian simulator and procedurally generate macroscopic flow graph models of building space, integrating micro- and macroscopic approaches to simulation of the same emergency space. By “coupling” flow graph parameters to microscopic simulation results, the graph model captures some of the higher detail and fidelity of the complex microscopic simulation model. The coupled flow graph is used for analysis and prediction of the movement of pedestrians in the microscopic simulation, and investigate the performance of dynamic evacuation planning in simulated emergencies using a variety of strategies for allocation of macroscopic evacuation routes to microscopic pedestrian agents. The predictive capability of the coupled flow graph is exploited for the decomposition of microscopic simulation space into multiple future states in a scalable manner. By simulating multiple future states of the emergency in short time frames, this enables sensing strategy based on simulation scenario pattern matching which we show to achieve fast scenario matching, enabling rich, real-time feedback in emergencies in buildings with meagre sensing capabilities.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling, traffic

[Nähring:2013]

S. Nähring, R. Ewald, A.M. Uhrmacher, and C. Maus. From standardized modeling formats to modeling languages and back: an exploration based on sbml and ml-rules. In *Proceedings of the 2013 Winter Simulation Conference: Simulation: Making Decisions in a Complex World*, pages 1359–1370. IEEE Press, 2013.

Abstract: Standardized model exchange formats give practitioners the freedom to choose the most suitable tool and facilitate both cross-validation and reproduction of simulation results. On the other hand, standardization necessarily implies a compromise between the capabilities of individual modeling languages and a common ground of concepts and underlying assumptions of the given application domain. This compromise often leads to a mismatch of expressiveness between modeling language and exchange format, which should be resolved automatically, e.g., by offering a transformation. We explore the challenges of such an approach for the Systems Biology Markup Language (SBML), a well-established model format in systems biology, and ML-Rules, a rule-based modeling language for describing cell biological systems at multiple interrelated levels. Our transformation approach can be extended both in terms of the heuristics it employs and in terms of the modeling formalisms it supports.

Keywords: multi-agent based simulation, multi-level, biology

[Nähring:2014]

S. Nähring, T. Helms, S. Rybacki, and A.M. Uhrmacher. Functions on solutions-language extensions for ml-rules. In *Proc. of 12th Conf. on Computational Methods in Systems Biology (CMSB)*, LNCS. Springer, 2014.

Keywords: multi-agent based simulation, multi-level, biology

[Navarro:2011]

L. Navarro, F. Flacher, and V. Corruble. Dynamic level of detail for large scale agent-based urban simulations. In *Proc. of 10th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)*, pages 701–708, 2011.

Abstract: Large scale agent-based simulations typically face a trade-off between the level of detail in the representation of each agent and the scalability seen as the number of agents that can be simulated with the computing resources available. In this paper, we aim at bypassing this trade-off by considering that the level of detail is itself a parameter that can be adapted automatically and dynamically during the simulation, taking into account elements such as user focus, or specific events. We introduce a framework for such a methodology, and detail its deployment within an existing simulator dedicated to the simulation of urban infrastructures. We evaluate the approach experimentally along two criteria: (1) the impact of our methodology on the resources (CPU use), and (2) an estimate of the dissimilarity between the two modes of simulation, i.e. with and without applying our methodology. Initial experiments show that a major gain in CPU time can be obtained for a very limited loss of consistency.

Keywords: multi-agent based simulation, multi-level, dynamic level of detail, french team

[Navarro:2012]

L. Navarro, V. Corruble, F. Flacher, and J-D. Zucker. Mesoscopic level: A new representation level for large scale agent-based simulations. In *Proc. of 4th Int. Conf. on Advances in System Simulation (SIMUL)*, pages 68–73, 2012.

Keywords: multi-agent based simulation, multi-level, emergence detection, generic representation of aggregated agents, french team

[Navarro:2013]

L. Navarro, V. Corruble, and J-D. Zucker. A flexible approach to multi-level agent-based simulation with the mesoscopic representation. In *Proc. of 12th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)*, pages 159–166, 2013.

Abstract: Large-scale simulations often use multiple agent representations to permit the study of specific multi-agent phenomena, and to find a balance between run-time performance and level of detail of the simulation. Although these approaches are effective, they do not always offer the desired level of analysis, especially when this level is between the resolutions of the models available. In this paper, we aim at offering a finer method in exploring this tradeoff by introducing an intermediate level between two given resolutions, which can apply to all agent models and allows a more progressive transition to offer the desired level of analysis. We introduce a framework for such a methodology and evaluate it through the extension of an existing approach, along two criteria: its impact on computational resources, and an estimate of the dissimilarity between a simulation using our methodology and one without. Initial experiments show that consistency is almost maintained while CPU gain varies from low to significant depending on the context.

Keywords: multi-agent based simulation, multi-level, dynamic level of detail, generic representation of aggregated agents, french team

[Navarro:2013a]

L. Navarro. *Niveau de Détail Dynamique et Progressif de l'Intelligence Artificielle pour le passage à l'Echelle dans la Simulation de Comportements Humains à Base d'Agents*. PhD thesis, Université Paris VI, 2013.

Abstract: Les approches d'agrégation dynamique et mésoscopique ont donné naissance à une méthodologie unifiée et puissante pour la simulation d'un grand nombre d'agents, avec des comportements complexes au sein d'un environnement de grande taille. Sa structure peut être adaptée à un large spectre de modèles agent, pour un coût de conception modéré, principalement employé en expertise et en configuration. L'étude de son impact sur la cohérence de la simulation permet d'exhiber un petit ensemble de paramètres contrôlant la globalité du processus, et offrant potentiellement le compromis souhaité entre gain en ressources computationnelles et maintien de la cohérence de la simulation. Tout ceci met en évidence l'unicité et l'adaptabilité de cette méthodologie, qui peut être facilement reproduite grâce à son formalisme simple. Les résultats expérimentaux des approches d'agrégation dynamique et mésoscopique sont extrêmement encourageants, et ont permis à un simulateur de comportement humain à l'état de l'art de multiplier le nombre d'acteurs virtuels simulés pour une faible perte en cohérence de simulation. De plus, elles ont fourni des capacités d'analyse multi-niveaux tout en demeurant relativement imperceptibles aux utilisateurs. Leur intégration validée au sein d'un simulateur de comportement humain industriel est l'une des réalisations majeures de cette thèse. Enfin, ces approches n'en sont qu'à leurs balbutiements. Elles permettent d'ouvrir la voie à d'autres plus complexes, qui pourraient inclure des méthodes d'apprentissage automatique, facilitant la recherche des fonctions de mappage les plus appropriées entre représentations à différents niveaux de résolution, et la gestion native des interactions inter-résolutions. Le spectre applicatif extrêmement large, qui s'étend au-delà de la simulation de comportement humain, facilite l'exploration de ces sujets de recherche.

Keywords: multi-agent based simulation, multi-level, in french, french team

- [Navarro:2015] L. Navarro, F. Flacher, and C. Meyer. Se-star: A large-scale human behavior simulation for planning, decision-making and training. In *Proc. of the 14th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS)*, pages 1939–1940, 2015.
- Abstract:** The purpose of this extended abstract is to present SE-Star, a Thales proprietary large-scale multi-agent simulator, together with the content of two scenarios, designed with the Paris Police Department, demonstrating its capabilities at offering powerful features for planning, decision-making and training in real-life scenarios.
- Keywords:** multi-agent based simulation, multi-level, pedestrian flow modeling, traffic, french team
- [Nazari:2020] F. Nazari, A. E Oklejas, J.E. Nör, A.T. Pearson, and T.L. Jackson. In silico models accurately predict in vivo response for il-6 blockade in head and neck cancer. *Cancer Research*, 2020.
- Abstract:** Malignant features of head and neck squamous cell carcinoma (HNSCC) may be derived from the presence of stem-like cells that are characterized by uniquely high tumorigenic potential. These cancer stem cells (CSCs) function as putative drivers of tumor initiation, therapeutic evasion, metastasis, and recurrence. Though they are an appealing conceptual target, CSC-directed cancer therapies remain scarce. One promising CSC target is the interleukin-6 (IL-6) pathway, which is strongly correlated with poor patient survival. In this study we created and validated a multiscale mathematical model to investigate the impact of crosstalk between tumor cell (TC)- and endothelial cell (EC)- secreted IL-6 on HNSCC growth and the CSC fraction. We then predicted and analyzed the responses of HNSCC to tocilizumab (TCZ) and cisplatin combination therapy. The model was validated with in vivo experiments involving human ECs co-implanted with HNSCC cell line xenografts. Without artificial tuning to the laboratory data, the model showed excellent predictive agreement with the decrease in tumor volumes observed in TCZ treated mice, as well as a decrease in the CSC fraction. This computational platform provides a framework for preclinical cisplatin and tocilizumab dose and frequency evaluation to be tested in future clinical studies.
- Keywords:** multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling
- [Nguyen:2011] T. Nguyen, J-D. Zucker, D. Nguyen, A. Drogoul, and A. Vo. Hybrid equation-based and agent-based modeling of crowd evacuation on road network. In *Eighth International Conference on Complex Systems (ICSS)*, pages 558–570, 2011.
- Abstract:** The major methodologies of crowd simulation in dynamic environment are either based on micro and macro models. Each of the two types of model represent choices in the trade-off between level of details and efficiency. The domain of pedestrian flow simulation in road networks is no exception and theories rely either on equation based model (LWR) or agent based models. There is a growing interest for hybrid modeling that combines both models together. This paper addresses the problem of combining both micro and macro models of pedestrians to speedup identification of optimal evacuation plan. The goal is therefor to use efficient macro modeling in part of the road networks that do not require fine grained model and less efficient but more detailed micro modeling elsewhere. The key issue raised by such an approach is to demonstrate the consistency of the resulting hybrid model. Preliminary results presented in this article are a proof of concept of how important speed up may be obtained using hybrid model to simulate evacuation plan in road networks.
- Keywords:** multi-agent based simulation, multi-level, flow model, pedestrian flow modeling, french team
- [Nguyen:2012] T. Nguyen, J-D. Zucker, D. Nguyen, A. Drogoul, and A. Vo. A hybrid macro-micro pedestrians evacuation model to speed up simulation in road networks. In *Advanced Agent Technology*, volume 7068 of *LNCS*, pages 371–383. Springer, 2012.
- Abstract:** The major methodologies of crowd simulation in a dynamic environments are either based on micro or macro models. These two types of models represent the trade-off between the level of detail and efficiency. The domain of pedestrian flow simulation on road networks is no exception and theories rely either on equation based model or agent based models. There is a growing interest in hybrid modeling that combines both of these types. This paper addresses the problem of combining both micro and macro models of pedestrians movement to speedup simulations. Hybrid model uses efficient macro modeling in part of the road networks that do not require a fine grained model and more detailed but less efficient micro modeling in critical locations. One key issue raised by such an approach and discussed is the consistency of the resulting

hybrid model. Preliminary results presented in this article is a proof of concept that the use of hybrid model to simulate evacuation plan in road networks may be more efficient than the use of micro model alone.

Keywords: multi-agent based simulation, multi-level, hybrid model, flow model, pedestrian flow modeling, french team

[Nguyen:2012a]

N. Nguyen, P. Taillandier, A. Drogoul, and P. Auger. Inferring equation-based models from agent-based models: a case study in competition dynamics. In *Principles and Practice of Multi-Agent Systems*, volume 7455 of *LNC3*, pages 413–427. Springer, 2012.

Abstract: Two types of model, equation-based models (EBMs) and agent-based models (ABMs) are now widely used in modeling ecological complex systems and seem not to be reconciled. While ABMs can help in exploring and explaining the local causes of global phenomena, EBMs are useful for predicting their long-term evolution without having to explore them through simulated experiments. In this paper, we show that it is possible to use an ABM to infer an EBM. Base on the case study, a dynamics of two competing species, we illustrate our methodology through the presentation of two models: an ABM and an EBM. We also show that the two models give the same results on coexistence of the two competing species.

Keywords: multi-agent based simulation, multi-level, multi-model, methodology, french team

[Nguyen:2012b]

V.G.N. Nguyen, A. Drogoul, and H.X. Huynh. Toward an agent-based multi-scale recommendation system for brown plant hopper control. In *Proc. of Computer Modeling and Simulation (EMS)*, pages 9–14. IEEE, 2012.

Abstract: Rice pest control problem is multi-disciplinary in scope and includes multi-scale processes. Brown plant hopper is one of the most destructive pests of rice, there are potential risks for rice production if population of this insect is high. In this paper, an agent-based multi-scale model is made of agent-based sub-models in different studies, this model works as a Brown plant hopper recommendation system and supports experts to simulate Brown plant hopper control strategies. This recommendation system includes sub-models that have different functions: growth and invasion models of Brown plant hopper, upscaling and downscaling information models. Simulation results of Brown plant hopper management strategies help stakeholders assess Brown plant hopper infestation status of rice areas and make recommendation messages to farmers.

Keywords: multi-level, multi-agent based simulation, ecology

[Nguyen:2014]

T.N.A. Nguyen. *Dynamic Multilevel Modeling in the design of Decision Support Systems for rescue simulation : combining Agent-based and Mathematical approaches*. PhD thesis, Université Paris VI, 2014.

Abstract: Tsunami est une des pires catastrophes naturelles de la planète, particulièrement pour les villes côtières et bondées. Une question importante dans le domaine est comment trouver une meilleure procédure d'évacuation qui permet de minimiser le nombre de victimes. Dans le cadre de cette thèse, nous nous intéressons au problème des simulations grande échelle pour évacuer des piétons sur un réseau routier d'une ville. Tout d'abord, les modèles base d'équations (EBM) ont l'avantage de résoudre les grands problèmes dans un délai de temps acceptable. Par conséquent, nous choisissons EBM pour optimiser le système de signe de placement. Nous avons appelé Minimisation du Temps Moyen d'Evacuation (MAET). En outre, nous utilisons le modèle Lighthill, Whitham et Richards des flux de piétons sur un réseau routier. Cependant, il est difficile de considérer le problème en détail avec différents facteurs réalistes. Pour examiner le problème en détail, les modèles multi-agents sont l'approche. Les modèles multi-agents (ABM) prennent en compte l'hétérogénéité des comportements des piétons. Cependant, le coût de calcul était énorme lorsqu'il est appliqué avec un grand nombre de personnes évacuées et un milieu dynamique, large. Le résultat de la simulation nécessite d'énormes expérimentations, donc la vitesse de la simulation est un problème que nous voulons Étudier. Nous considérons un modèle hybride qui combine les avantages des deux ABM et EBM. Troisièmement, le problème d'accélération d'un très grand environnement dans les ABMs, tels que ceux utilisés dans la simulation de foule est la clé pour soutenir les systèmes d'aide à la décision réalistes. L'idée principale est d'exploiter les avantages à la fois de la macro et de la micro modélisation. Les résultats que nous obtenons dans la thèse sont : a) Formulation du problème de l'Évacuation ; b) Formulation optimal du système de signes d'alerte ; c) Description de la répartition de la population initiale; d) Simulation de l'évacuation de Tsunami sur le réseau de routier de Nha Trang; e) Construction du modèle hybride pour accélérer la simulation; f) Intégration de ABM et MAET pour un meilleur résultat pour le système alerte de signe optimal.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling, french team

[Nguyen:2017]

K. Nguyen-Trong, A. Nguyen-Thi-Ngoc, D. Nguyen-Ngoc, and V. Dinh-Thi-Hai. Optimization of municipal solid waste transportation by integrating gis analysis, equation-based, and agent-based model. *Waste management*, 59:14–22, 2017.

Abstract: The amount of municipal solid waste (MSW) has been increasing steadily over the last decade by reason of population rising and waste generation rate. In most of the urban areas, disposal sites are usually located outside of the urban areas due to the scarcity of land. There is no fixed route map for transportation. The current waste collection and transportation are already overloaded arising from the lack of facilities and insufficient resources. In this paper, a model for optimizing municipal solid waste collection will be proposed. Firstly, the optimized plan is developed in a static context, and then it is integrated into a dynamic context using multi-agent based modelling and simulation. A case study related to Hagiang City, Vietnam, is presented to show the efficiency of the proposed model. From the optimized results, it has been found that the cost of the MSW collection is reduced by 11.3%.

Keywords: multi-agent based simulation, multi-level, waste management, traffic

[Nongaillard:2016]

A. Nongaillard and S. Picault. Modélisation multi-niveaux des problèmes d’affectation et d’appariement. In *Actes des 24èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 75–84, 2016.

Abstract: Les problèmes d’appariement ou d’affectation ont depuis quelques années fait l’objet de modélisation multi-agents variées. Celles-ci visent notamment à renforcer le caractère privé des préférences ou des contraintes de chaque individu, et facilitant la distribution des méthodes de résolution. Néanmoins, cette agentification des problèmes ainsi abordés nous semble rester en deçà des possibilités offertes par une modélisation multi-agents, en s’appuyant peu sur la structure organisationnelle dont on peut doter un SMA. Dans cet article, nous proposons au contraire de partir de la capacité des SMA multi-niveaux à représenter des points de vue intermédiaires entre l’individu et le collectif, pour exprimer dans un formalisme homogène des problèmes d’appariement ou d’affectation variés. Nous montrons comment cette modélisation permet de choisir des métriques pertinentes pour évaluer le bien-être de groupes d’agents et leur permettre de construire des solutions qui améliorent le bien-être global sans divulguer toutes leurs informations individuelles. Enfin, nous esquissons des principes généraux pour la construction de solveurs distribués pour ce type de modélisation.

Keywords: multi-agent based simulation, multi-level, assignment problem, matching problem, in french, french team

[Nongaillard:2017]

A. Nongaillard and S. Picault. An agent-based, multilevel welfare assessment model for encompassing assignment and matching problems. In *International Conference on Practical Applications of Agents and Multi-Agent Systems*, volume 10349 of *LNCS*, pages 196–208. Springer, 2017.

Abstract: Multi-Agent Systems (MAS) have been applied in recent years to assignment or matching problems in order to enhance privacy in preferences and constraints for individuals, and to facilitate the distribution of solving. A further step in this direction consists in using the organisational structures provided by MAS. Thus, in this paper, we rely upon the capability of Multilevel MAS to reify intermediate viewpoints between the individual and the collective levels, in order to encompass matching or assignment problems. Therefore we define a meta-model for assessing the welfare of agent groups with respect to relevant metrics, so that these groups are able to elaborate solutions that improve the collective well-being without forcing them to disclose all their private information. Finally, we outline the general principles for distributed solvers designed for this type of modelling.

Keywords: multi-agent based simulation, multi-level, assignment problem, matching problem, french team

[North:2010]

M.J. North, C.M. Macal, J.S. Aubin, P. Thimmapuram, M. Bragen, J. Hahn, J. Karr, N. Brigham, M.E. Lacy, and D. Hampton. Multiscale agent-based consumer market modeling. *Complexity*, 15(5):37–47, 2010.

Abstract: Consumer markets have been studied in great depth, and many techniques have been used to represent them. These have included regression-based models, logit models, and theoretical market-level models, such as the NBD-Dirichlet approach. Although many important contributions and insights have resulted from studies that relied on these models, there is still a need for a model that could more holistically represent the interdependencies of the decisions made by consumers, retailers, and manufacturers. When the need is for a model that could be used repeatedly

over time to support decisions in an industrial setting, it is particularly critical. Although some existing methods can, in principle, represent such complex interdependencies, their capabilities might be outstripped if they had to be used for industrial applications, because of the details this type of modeling requires. However, a complementary method—agent-based modeling—shows promise for addressing these issues. Agent-based models use business-driven rules for individuals (e.g., individual consumer rules for buying items, individual retailer rules for stocking items, or individual firm rules for advertizing items) to determine holistic, system-level outcomes (e.g., to determine if brand X's market share is increasing). We applied agent-based modeling to develop a multi-scale consumer market model. We then conducted calibration, verification, and validation tests of this model. The model was successfully applied by Procter & Gamble to several challenging business problems. In these situations, it directly influenced managerial decision making and produced substantial cost savings.

Keywords: multi-agent based simulation, multi-level, social simulation

[Northridge:2018]

M.E. Northridge, S.S. Metcalf, S. Yi, Q. Zhang, X. Gu, and C. Trinh-Shevrin. A protocol for a feasibility and acceptability study of a participatory, multi-level, dynamic intervention in urban outreach centers to improve the oral health of low-income chinese americans. *Frontiers in Public Health*, 6:29, 2018.

Abstract: Introduction: While the US health care system has the capability to provide amazing treatment of a wide array of conditions, this care is not uniformly available to all population groups. Oral health care is one of the dimensions of the US health care delivery system in which striking disparities exist. More than half of the population does not visit a dentist each year. Improving access to oral health care is a critical and necessary first step to improving oral health outcomes and reducing disparities. Fluoride has contributed profoundly to the improved dental health of populations worldwide and is needed regularly throughout the life course to protect teeth against dental caries. To ensure additional gains in oral health, fluoride toothpaste should be used routinely at all ages. Evidence-based guidelines for annual dental visits and brushing teeth with fluoride toothpaste form the basis of this implementation science project that is intended to bridge the care gap for underserved Asian American populations by improving access to quality oral health care and enhancing effective oral health promotion strategies. The ultimate goal of this study is to provide information for the design and implementation of a randomized controlled trial of a participatory, multi-level, partnered (i.e., with community stakeholders) intervention to improve the oral and general health of low-income Chinese American adults. Methods: This study will evaluate the feasibility and acceptability of implementing a partnered intervention using remote data entry into an electronic health record (EHR) to improve access to oral health care and promote oral health. The research staff will survey a sample of Chinese American patients (planned n = 90) screened at 3 outreach centers about their satisfaction with the partnered intervention. Providers (dentists and community health workers), research staff, administrators, site directors, and community advisory board members will participate in structured interviews about the partnered intervention. The remote EHR evaluation will include group adaptation sessions and workflow analyses via multiple recorded sessions with research staff, administrators, outreach site directors, and providers. The study will also model knowledge held by non-patient participants to evaluate and enhance the partnered intervention for use in future implementations.

Keywords: multi-agent based simulation, multi-level, biology

[Norton:2015]

K-A. Norton, M. Pryor, and A. Popel. Multiscale modeling of cancer. *bioRxiv*, page 033977, 2015.

Abstract: Breast cancer remains the second leading cause of cancer death in women, exceeded only by lung cancer. Specifically, triple-negative breast cancer (TNBC) has the worst prognosis, as it is more invasive and lacks estrogen, progesterone, and HER2 receptors that can be targeted with therapies. Due to the need for effective therapies for this type of breast cancer, it is critical to develop methods to (1) understand how TNBC progresses and (2) facilitate development of effective therapies. Here, we describe a multiscale model focusing on tumor formation. Our approach uses multiple scales to investigate the progression and possible treatments of tumors.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Norton:2019]

K-A. Norton, C. Gong, S. Jamalian, and A.S. Popel. Multiscale agent-based and hybrid modeling of the tumor immune microenvironment. *Processes*, 7(1):37, 2019.

Abstract: Multiscale systems biology and systems pharmacology are powerful methodologies that are playing increasingly important roles in understanding the fundamental mechanisms of biological phenomena and in clinical applications. In this review, we summarize the state of the

art in the applications of agent-based models (ABM) and hybrid modeling to the tumor immune microenvironment and cancer immune response, including immunotherapy. Heterogeneity is a hallmark of cancer; tumor heterogeneity at the molecular, cellular, and tissue scales is a major determinant of metastasis, drug resistance, and low response rate to molecular targeted therapies and immunotherapies. Agent-based modeling is an effective methodology to obtain and understand quantitative characteristics of these processes and to propose clinical solutions aimed at overcoming the current obstacles in cancer treatment. We review models focusing on intra-tumor heterogeneity, particularly on interactions between cancer cells and stromal cells, including immune cells, the role of tumor-associated vasculature in the immune response, immune-related tumor mechanobiology, and cancer immunotherapy. We discuss the role of digital pathology in parameterizing and validating spatial computational models and potential applications to therapeutics.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Occello:2019]

Michel Occello, Jean-Paul Jamont, Choukri-Bey Ben-Yelles, and Thi Thanh Ha Hoang. A multi-level generic multi-agent architecture for supervision of collective cyber-physical systems. *International Journal of Autonomous and Adaptive Communications Systems*, 12(2):109–128, 2019.

Abstract: Cyber-physical systems like networked embedded systems or ambient sensors networks are called large-scale artificial complex systems. They are difficult to supervise because of their numerous components in interaction relying upon physical devices, their extension and their openness. A multi-scale organisation can be a solution to make them more accessible. Multi-agent systems (MAS) are well suited for modeling large complex systems, as multi-agent organisational capabilities allow introducing multi-level observation. This paper proposes a multi-level multi-agent mechanism based on recursion for supervision and observation of large-scale artificial complex systems. It is developed as a free framework that is a decentralised application allowing truly physically decentralised MAS to communicate with abstract multi-agent layers. As an illustration, the framework is applied to a wireless sensor network supervision system.

Keywords: multi-agent based simulation, multi-agent system, multi-level, cyber-physical systems

[Olsen:2013]

M.M. Olsen and H.T. Siegelmann. Multiscale agent-based model of tumor angiogenesis. In *International Conference on Computational Science, ICCS 2013*, volume 18 of *Procedia Computer Science*, pages 1026–1035. Elsevier, 2013.

Abstract: Computational models of cancer complement the biological study of tumor growth. However, existing modeling approaches can be both inefficient and inaccurate due to the difficulties of representing the complex interactions between cells and tissues. We present a three-dimensional multiscale agent-based model of tumor growth with angiogenesis. The model is designed to easily adapt to various cancer types, although we focus on breast cancer. It includes cellular (genetic control), tissue (cells, blood vessels, angiogenesis), and molecular (VEGF, diffusion) levels of representation. Unlike in most cancer models, both normally functioning tissue cells and tumor cells are included in the model. Tumors grow following the expected spheroid cluster pattern, with growth limited by available oxygen. Angiogenesis, the process by which tumors may encourage new vessel growth for nutrient diffusion, is modeled with a new discrete approach that we propose will decrease computational cost. Our results show that despite proposing these new abstractions, we see similar results to previously accepted angiogenesis models. This may indicate that a more discrete approach should be considered by modelers in the future.

Keywords: multi-agent based simulation, multi-scale, multi-level, cancer modeling

[Olsen:2019]

M. Olsen. Stigmergy for biological spatial modeling. In *Complex Adaptive Systems, Understanding Complex Systems*, pages 169–197. Springer, 2019.

Abstract: Complex adaptive systems can be characterized as systems that are comprised of groups of agents following simple rules that, collectively, produce emergent, complex behavior. The key to these emergent properties are the interactions—the exchanges of information—between the agents. Many biological systems can be studied using a complex adaptive systems approach, such as colonies of bees or ants. In some of these biological systems, the communication between individual agents is indirect. This type of communication is termed stigmergy: a relatively small amount of information being shared through the environment, rather than directly from agent to agent. This information is nonetheless crucial to the self-organizing properties of the system, and is used by the agents to inform decision making, such as when ants follow a trail of pheromones left by other ants. In this chapter we describe computer simulations of two such systems, created and used to conduct experiments on various types of stigmergy: collaboration within a predator-prey system, and angiogenesis in cancer growth. The first utilizes a cellular automata model,

and the second a multiscale agent-based model. Further, this paper defines various options of communications for these simulations, and examines the use of similar communication paradigms in these two different types of models. Results support that stigmergy can be adapted to a variety of situations. Also, that awareness of the speed of algorithmic decisions can increase its usefulness in biological modeling. These ideas can be adapted to many other modeling situations other than the classic examples of self-organization like bees or ants.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Osorio:2017]

C. Osorio and K.K. Selvam. Simulation-based optimization: Achieving computational efficiency through the use of multiple simulators. *Transportation Science*, 51(2):395–411, 2017.

Abstract: Transportation agencies often resort to the use of traffic simulation models to evaluate the impacts of changes in network design or network operations. They often have multiple traffic simulation tools that cover the network area where changes are to be made. These multiple simulators may differ in their modeling assumptions (e.g., macroscopic versus microscopic), in their reliability (e.g., quality of their calibration), as well as in their modeling scale (e.g., city-scale versus regional-scale). The choice of which simulation model to rely on, let alone of how to combine their use, is intricate. A larger-scale model may, for instance, capture more accurately the local-global interactions; yet may do so at a greater computational cost. This paper proposes an optimization framework that enables multiple simulation models to be jointly and efficiently used to address continuous urban transportation optimization problems. We propose a simulation-based optimization algorithm that embeds information from both a high-accuracy low-efficiency simulator and a low-accuracy high-efficiency simulator. At every iteration, the algorithm decides which simulator to evaluate. This decision is based on an analytical approximation of the accuracy loss as a result of running the lower-accuracy model. We formulate an analytical expression that is based on a differentiable and computationally efficient to evaluate traffic assignment model. We evaluate the performance of the algorithm with a traffic signal control problem on both a small network and a city network. We show that the proposed algorithm identifies signal plans with excellent performance, and can do so at a significantly lower computational cost than when systematically running the high-accuracy simulator. The proposed methodology contributes to enable large-scale high-resolution traffic simulation models to be used efficiently for simulation-based optimization. More broadly, it enables the use of multiple simulation models that may differ, for instance, in their scale, their resolution, or their computational costs, to be used jointly for optimization.

Keywords: hybrid model, traffic, multi-agent based simulation, multi-level

[Ozik:2008]

J. Ozik, D.L. Sallach, and C.M. Macal. Modeling dynamic multiscale social processes in agent-based models. *IEEE Intelligent Systems*, 23(4):36–42, 2008.

Abstract: Identity-related issues play central roles in many current events, including those involving factional politics, sectarianism, and tribal conflicts. Two popular models from the computational-social-science (CSS) literature - the threat anticipation program and SharedID models - incorporate notions of identity (individual and collective) and processes of identity formation. A multiscale conceptual framework that extends some ideas presented in these models and draws other capabilities from the broader CSS literature is useful in modeling the formation of political identities. The dynamic, multiscale processes that constitute and transform social identities can be mapped to expressive structures of the framework.

Keywords: multi-agent based simulation, multi-level, social simulation

[Ozik:2018]

J. Ozik, N. Collier, J. Wozniak, C. Macal, C. Cockrell, S. Friedman, S. Ghaffarizadeh, R. Heiland, G. An, and P. Macklin. High-throughput cancer hypothesis testing with an integrated physicell-emews workflow. *bioRxiv*, 2018.

Abstract: Cancer is a complex, multiscale dynamical system, with interactions between tumor cells and non-cancerous systems. Therapies act on this cancer-host system, sometimes with unexpected results. Systematic investigation of mechanistic models could help identify the factors driving a treatment's success or failure, but exploring mechanistic models over high-dimensional parameter spaces is computationally challenging. In this paper, we introduce a high throughput computing (HTC) framework that integrates a mechanistic 3-D multicellular simulator (PhysiCell) with an extreme-scale model exploration platform (EMEWS) to investigate high-dimensional parameter spaces. We show early results in adapting PhysiCell-EMEWS to 3-D cancer immunotherapy and show insights on therapeutic failure. We describe a PhysiCell-EMEWS workflow for high-throughput cancer hypothesis testing, where thousands of mechanistic simulations are compared

against data-driven error metrics to perform hypothesis optimization. We close by discussing novel applications to synthetic multicellular systems for cancer therapy.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Padmanabha:2017]

A. Padmanabha. Smart mobility: behavioral data collection and simulation. Master's thesis, Massachusetts Institute of Technology, 2017.

Abstract: On-demand ridesharing services, such as Uber and Lyft, and autonomous vehicles are significantly changing the landscape of transportation and mobility. In light of these disruptions, we aim to determine consumer preferences with regards to transportation and use this data to simulate and analyze the urban effects of smart mobility solutions. We collect behavioral data using Future Mobility Sensing (FMS), a smartphone and prompted-recall-based integrated activity-travel survey, and create simulations using the data with SimMobility, a simulation platform that integrates various mobility-sensitive behavioral models with state-of-the-art scalable simulators to predict the impact of mobility demands on transportation networks, intelligent transportation services, and vehicular emissions. Enhancing these projects with on-demand preferences, individual patterns, and incentives as inputs, we aim to simulate and analyze a wide range of viable smart mobility solutions.

Keywords: multi-agent based simulation, multi-level, multi-scale, traffic

[Pageaud:2019]

S. Pageaud. *SmartGov: architecture générique pour la co-construction de politiques urbaines basée sur l'apprentissage par renforcement multi-agent*. PhD thesis, Université de Lyon, 2019.

Abstract: Dans cette thèse, nous proposons un outil SmartGov, mixant simulation multi-agents et apprentissage multi-agents par renforcement profond, pour permettre la co-construction de politiques urbaines et inscrire les acteurs de la ville dans la boucle de conception. La Smart City permet à l'outil d'intégrer les données collectées par les capteurs présents dans la ville pour la modéliser de façon réaliste. Notre première contribution est une architecture générique pour construire une simulation multi-agents représentant la ville, et étudier l'émergence de comportement globaux avec des agents réalistes capables de réagir aux décisions politiques. Grâce à une modélisation multi-niveaux, et le couplage de différentes dynamiques, le système apprend les spécificités de l'environnement pour proposer des politiques pertinentes. Notre seconde contribution concerne l'autonomie et l'adaptation de la couche décisionnelle avec un apprentissage par renforcement multi-agents et multi-niveaux. Un ensemble d'agents, regroupés en clusters, est distribué dans le périmètre étudié pour apprendre des spécificités locales sans connaissance a priori de son environnement. L'attribution d'un score de confiance et de récompenses individuelles permettent d'atténuer l'impact de la non-stationnarité sur la réutilisation d'expériences nécessaire à l'apprentissage profond. Ces contributions conduisent à un système complet de co-construction de politiques urbaines dans le contexte de la Smart City. Nous comparons notre modèle avec d'autres approches de la littérature sur une politique de tarification du stationnement urbain, afin de mettre en évidence les apports et les limites de nos contributions.

Keywords: multi-agent based simulation, multi-level, social simulation, urban systems, french team

[Pageaud:2019a]

S. Pageaud, V. Deslandres, V. Lehoux, and S. Hassas. Application du clustered deep q-network aux politiques tarifaires. In *Conférence Nationale d'Intelligence Artificielle Année 2019*, page 113, 2019.

Abstract: Ce travail présente une nouvelle approche multi-agent et multi-niveaux, nommée Clustered Deep Q-Network (CDQN), avec pour objectif de répondre aux problèmes de passage à l'échelle et de non-stationnarité dans des contextes d'apprentissages décentralisés. Notre approche repose sur : 1) une gestion de chaque agent dans des clusters dynamiques avec une action jointe contrainte pour réduire la non-stationnarité ; 2) l'attribution d'un score de confiance joint pour évaluer la contribution individuelle de chaque agent. Les expérimentations et les résultats sur une politique urbaine montrent que notre modèle permet une coordination efficace d'agents indépendants en utilisant l'apprentissage par renforcement profond multi-agent et la réutilisation d'expériences pour augmenter à la fois le gain individuel et global.

Keywords: multi-agent based simulation, multi-level, social simulation, french team

[Paiva:2009]

L.R. Paiva, C. Binny, S.C. Ferreira Jr., and M.L. Martins. A multiscale mathematical model for oncolytic virotherapy. *Cancer Research*, 69:1205–1211, 2009.

Abstract: One of the most promising strategies to treat cancer is attacking it with viruses. Oncolytic viruses can kill tumor cells specifically or induce anticancer immune response. A multiscale model for virotherapy of cancer is investigated through simulations. It was found that, for intratumoral virus administration, a solid tumor can be completely eradicated or keep growing after a transient remission. Furthermore, the model reveals undamped oscillatory dynamics of tumor cells and virus populations, which demands new in vivo and in vitro quantitative experiments aiming to detect this oscillatory response. The conditions for which each one of the different tumor responses dominates, as well as the occurrence probabilities for the other non-dominant therapeutic outcomes, were determined. From a clinical point of view, our findings indicate that a successful, single agent virotherapy requires a strong inhibition of the host immune response and the use of potent virus species with a high intratumoral mobility. Moreover, due to the discrete and stochastic nature of cells and their responses, an optimal range for viral cytotoxicity is predicted because the virotherapy fails if the oncolytic virus demands either a too short or a very large time to kill the tumor cell. This result suggests that the search for viruses able to destroy tumor cells very fast does not necessarily lead to a more effective control of tumor growth.

Keywords: multi-agent based simulation, multi-level, biology

[Paiva:2013]

L.R. Paiva, H.S. Silva, S.C. Ferreira, and M.L. Martins. Multiscale model for the effects of adaptive immunity suppression on the viral therapy of cancer. *Physical biology*, 10(2):025005, 2013.

Abstract: Oncolytic virotherapy—the use of viruses that specifically kill tumor cells—is an innovative and highly promising route for treating cancer. However, its therapeutic outcomes are mainly impaired by the host immune response to the viral infection. In this paper, we propose a multi-scale mathematical model to study how the immune response interferes with the viral oncolytic activity. The model assumes that cytotoxic T cells can induce apoptosis in infected cancer cells and that free viruses can be inactivated by neutralizing antibodies or cleared at a constant rate by the innate immune response. Our simulations suggest that reprogramming the immune microenvironment in tumors could substantially enhance the oncolytic virotherapy in immune-competent hosts. Viable routes to such reprogramming are either in situ virus-mediated impairing of CD8(+) T cells motility or blockade of B and T lymphocytes recruitment. Our theoretical results can shed light on the design of viral vectors or new protocols with neat potential impacts on the clinical practice.

Keywords: multi-agent based simulation, multi-level, multi-scale, cancer modeling

[Pantziarka:2019]

P. Pantziarka, L. Ghibelli, and A. Reichle. A computational model of tumor growth and anakinosis. *Frontiers in Pharmacology*, 10:287, 2019.

Abstract: Anakinosis is a new cancer treatment paradigm that posits a key role for communicative reprogramming within tumour systems. To date no mathematical or computational models of anakinosis have been developed. Here we outline the NEATG_A system, a first computational model of communicative reprogramming. The model recapitulates key features of real tumour systems and responses to both traditional cytotoxic treatments and biomodulatory/anakinotic treatments. Results are presented and discussed, particularly with respect to the implications for future cancer treatment protocols.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Parry:2012]

H.R. Parry and M. Bithell. *Agent-based models of geographical systems*, chapter Large scale agent-based modelling: A review and guidelines for model scaling, pages 271–308. Springer, 2012.

Abstract: This chapter provides a review and examples of approaches to model scaling when constructing large agent-based models. A comparison is made between an aggregate ‘super-individual’ approach, as run on a single processor machine, and two different approaches to parallelisation of agent models run on multi-core hardware. Super-individuals provide a straightforward solution without much alteration of the model formulation and result in large improvements in model efficiency (speed and memory use). However, there are significant challenges to using a super-individual approach when relating super-individuals to individuals in time and space. Parallel computing approaches accept the requirement for large amounts of memory or CPU and attempt to solve the problem by distributing the calculation over many computational units. This requires some modification of the model software and algorithms to distribute the model components across multiple computational cores. This can be achieved in a number of different ways, two of which we illustrate further for the case of spatial models, an ‘agent-parallel’ and an

‘environment-parallel’ approach. However, the success of such approaches may also be affected by the complexity of the model (such as multiple agent types and agent interactions), as we illustrate by adding a predator to our example simulation. Between these two parallelisation approaches to the case study, the environment-parallel version of the model, written in C++ instead of Java, proved more efficient and successful at handling parallel processing of complex agent interactions. In conclusion, we use our experiences of creating large agent-based simulations to provide some general guidelines for best practice in agent-based model scaling.

Keywords: multi-agent based simulation, multi-level, dynamic level of detail, social simulation

[Parunak:2009]

H.V.D. Parunak, J. Sauter, and J. Crossman. Multi-layer simulation for analyzing IED threats. In *Technologies for Homeland Security, 2009. HST'09. IEEE Conference on*, pages 323–330. IEEE, 2009.

Abstract: IEDs, made infamous in Iraq and Afghanistan, are a potential terrorist weapon anywhere in the world. Most counter-IED technologies are targeted at the point of the blast. DEFUSE can interdict and disrupt OPFOR activities left of the blast, well before planting and detonating the IED. The system integrates three layers of simulation: social, process, and environmental.

Keywords: multi-agent based simulation, multi-level, military simulation

[Parunak:2010]

H.V.D. Parunak and S.A. Brueckner. Multi-perspective, multi-future modeling and model analysis. In *Proceedings of ICCDM*, Miami, FL, July 2010.

Keywords: multi-agent based simulation, multi-level

[Parunak:2010a]

H.V.D. Parunak, R. Bisson, and S.A. Brueckner. Agent interaction, multiple perspectives, and swarming simulation. In *Proc. of 9th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS 2010)*, pages 549–556, 2010.

Abstract: Agents in a multi-agent system do not act in a vacuum. The outcome of their efforts depends on the environment in which they seek to act, and in particular on the efforts of other agents with whom they share the environment. We review previous efforts to address this problem, including active environments, concurrency modeling, recursive reasoning, and stochastic processes. Then we propose an approach that combines active environments and stochastic processes while addressing their limitations: a swarming agent simulation (which maintains transition probabilities dynamically, avoiding the static assumptions most convenient with traditional Markov models), applied concurrently to multiple perspectives (thus partitioning the active environment and addressing its scalability challenges). We demonstrate this method on a simple example.

Keywords: multi-agent based simulation, multi-level

[Parunak:2012]

H.V.D. Parunak. Between agents and mean fields. In *Multi-Agent-Based Simulation XII*, volume 7124 of *LNCS*, pages 113–126. Springer, 2012.

Keywords: multi-agent based simulation, multi-level, generic representation of aggregated agents

[Parvu:2016]

O. Pârveu and D. Gilbert. A novel method to verify multilevel computational models of biological systems using multiscale spatio-temporal meta model checking. *PLoS one*, 11(5):e0154847, 2016.

Abstract: Insights gained from multilevel computational models of biological systems can be translated into real-life applications only if the model correctness has been verified first. One of the most frequently employed in silico techniques for computational model verification is model checking. Traditional model checking approaches only consider the evolution of numeric values, such as concentrations, over time and are appropriate for computational models of small scale systems (e.g. intracellular networks). However for gaining a systems level understanding of how biological organisms function it is essential to consider more complex large scale biological systems (e.g. organs). Verifying computational models of such systems requires capturing both how numeric values and properties of (emergent) spatial structures (e.g. area of multicellular population) change over time and across multiple levels of organization, which are not considered by existing model checking approaches. To address this limitation we have developed a novel approximate probabilistic multiscale spatio-temporal meta model checking methodology for verifying multilevel computational models relative to specifications describing the desired/expected system behaviour. The methodology is generic and supports computational models encoded using various high-level modelling formalisms because it is defined relative to time series data and not the models used to generate it. In addition, the methodology can be automatically adapted to case study specific types of spatial structures and properties using the spatio-temporal meta model checking

concept. To automate the computational model verification process we have implemented the model checking approach in the software tool Mule (<http://mule.modelchecking.org>). Its applicability is illustrated against four systems biology computational models previously published in the literature encoding the rat cardiovascular system dynamics, the uterine contractions of labour, the *Xenopus laevis* cell cycle and the acute inflammation of the gut and lung. Our methodology and software will enable computational biologists to efficiently develop reliable multilevel computational models of biological systems.

Keywords: multi-agent based simulation, multi-level, model checking

[Pasquale:2018]

C. Pasquale, S. Sacone, S. Siri, and A. Ferrara. A new micro-macro metanet model for platoon control in freeway traffic networks. In *2018 21st International Conference on Intelligent Transportation Systems (ITSC)*, pages 1481–1486, 2018.

Keywords: multi-agent based simulation, multi-level, hybrid model, traffic

[Peng:2013]

D. Peng, A. Steiniger, T. Helms, and A.M. Uhrmacher. Towards composing ml-rules models. In *Proc. of the Winter Simulation Conf. (WSC)*, pages 4010–4011. IEEE Press, 2013.

Abstract: In cell biology, particularly to describe intra-cellular dynamics, network centered models prevail. Reusing those models requires additional effort as it often prevents a traditional black box based composition, i.e., aggregation, but asks for a fusion of models, where the internals of the models to be composed (not only their interfaces) are accessible as well. This is particularly the case if multi-level models, as those defined in ML-Rules, shall be composed. Still declarative interfaces that are separated from the concrete models help in retrieving suitable models for composition, whether those are aggregated or fused at the end. Here, we present a concept for composing multi-level network centered models.

Keywords: multi-agent based simulation, multi-level, biology

[Phillips:2020]

C.M. Phillips, E.A.B.F. Lima, R.T. Woodall, A. Brock, and T.E. Yankeelov. A hybrid model of tumor growth and angiogenesis: In silico experiments. *Plos one*, 15(4):e0231137, 2020.

Abstract: Tumor associated angiogenesis is the development of new blood vessels in response to proteins secreted by tumor cells. These new blood vessels allow tumors to continue to grow beyond what the pre-existing vasculature could support. Here, we construct a mathematical model to simulate tumor angiogenesis by considering each endothelial cell as an agent, and allowing the vascular endothelial growth factor (VEGF) and nutrient fields to impact the dynamics and phenotypic transitions of each tumor and endothelial cell. The phenotypes of the endothelial cells (i.e., tip, stalk, and phalanx cells) are selected by the local VEGF field, and govern the migration and growth of vessel sprouts at the cellular level. Over time, these vessels grow and migrate to the tumor, forming anastomotic loops to supply nutrients, while interacting with the tumor through mechanical forces and the consumption of VEGF. The model is able to capture collapsing and breaking of vessels caused by tumor-endothelial cell interactions. This is accomplished through modeling the physical interaction between the vasculature and the tumor, resulting in vessel occlusion and tumor heterogeneity over time due to the stages of response in angiogenesis. Key parameters are identified through a sensitivity analysis based on the Sobol method, establishing which parameters should be the focus of subsequent experimental efforts. During the avascular phase (i.e., before angiogenesis is triggered), the nutrient consumption rate, followed by the rate of nutrient diffusion, yield the greatest influence on the number and distribution of tumor cells. Similarly, the consumption and diffusion of VEGF yield the greatest influence on the endothelial and tumor cell numbers during angiogenesis. In summary, we present a hybrid mathematical approach that characterizes vascular changes via an agent-based model, while treating nutrient and VEGF changes through a continuum model. The model describes the physical interaction between a tumor and the surrounding blood vessels, explicitly allowing the forces of the growing tumor to influence the nutrient delivery of the vasculature.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Picault:2010]

S. Picault, P. Mathieu, and Y. Kubera. PADAWAN, un modèle multi-échelles pour la simulation orientée interactions. In *Actes des 18èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 195–204. Cépaduès, 2010.

Abstract: La conception de simulations multi-agents appliquées aux systèmes complexes pose entre autres le problème de la modélisation de comportements intervenant à des échelles spatiales, temporelles, comportementales différentes, chacune pertinente pour représenter un des aspects

du phénomène étudié. Nous proposons ici un formalisme générique destiné à la représentation d'environnements multiples, disposant d'échelles spatio-temporelles propres, et auxquels on peut associer un ensemble de règles comportementales auxquelles se soumettent les agents présents dans ces environnements. Par ailleurs chaque environnement peut être encapsulé au sein d'un agent, lui-même situé dans un autre environnement. Cette uniformité de représentation est rendue possible grâce à l'approche orientée interaction pour la conception de simulation (IODA), qui établit une séparation entre agents et interactions, et ce de la modélisation jusqu'au code. Nous expliquons également comment ce modèle est implémenté et donnons quelques exemples d'utilisation.

Keywords: multi-agent based simulation, multi-level, multi-scale, in french, french team

[Picault:2011]

S. Picault and P. Mathieu. An interaction-oriented model for multi-scale simulation. In *Proc of the 22nd Int. Joint Conf. on Artificial Intelligence*, pages 332–337. AAAI Press, 2011.

Abstract: The design of multiagent simulations devoted to complex systems, addresses the issue of modeling behaviors that are involved at different space, time, behavior scales, each one being relevant so as to represent a feature of the phenomenon. We propose here a generic formalism intended to represent multiple environments, endowed with their own spatiotemporal scales and with behavioral rules for the agents they contain. An environment can be nested inside any agent, which itself is situated in one or more environments. This leads to a lattice decomposition of the global system, which appears to be necessary for an accurate design of multi-scale systems. This uniform representation of entities and behaviors at each abstraction level relies upon an interaction-oriented approach for the design of agent simulations, which clearly separates agents from interactions, from the modeling to the code. We also explain the implementation of our formalism within an existing interaction-based platform.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Picault:2013]

S. Picault. *De la simulation multi-agents à la simulation multi-niveaux. Pour une réification des interactions*. Habilitation à diriger des recherches, Université de Lille 1, 2013.

Abstract: Dans ce mémoire de synthèse d'habilitation à diriger des recherches, je présente les travaux en simulation multi-agents que j'ai menés au sein de l'équipe SMAC (LIFL, Université Lille 1) depuis le début de ma carrière d'enseignant-chercheur en 2002. Ceux-ci portent sur la conception et la mise en application de méthodes et d'outils de simulation destinés à faciliter la modélisation de systèmes complexes à large échelle. Dans ce but, j'ai développé avec mes collègues une approche " orientée interactions " caractérisée par une unification des concepts utilisés dans le domaine des SMA. Elle a donné lieu à une importante élaboration méthodologique et algorithmique (la méthode IODA) dans laquelle toute entité du modèle est représentée par un agent, et tout comportement par une règle appelée interaction. Cette méthode s'appuie sur une séparation entre déclaratif et procédural qui facilite l'acquisition de l'expertise auprès des thématiciens. Par ailleurs de nombreux outils logiciels sont nés de ces recherches (dont la plateforme JEDI et une extension IODA pour la plateforme NetLogo), ainsi que diverses applications dans des domaines variés (biologie cellulaire, serious games, marketing, cartographie). Pour conclure, je présente mon projet de recherche pour les prochaines années qui se propose d'articuler des problématiques issues de travaux récents, d'une part sur la simulation multi-niveaux (qui vise à définir un cadre opérationnel permettant le changement d'échelle d'observation ou de point de vue sur les sous-systèmes d'un système complexe), et d'autre part sur la recherche automatique d'informations dans des données réelles pour augmenter le réalisme comportemental des populations d'agents. Par ailleurs une collaboration avec l'IGN sur l'utilisation de ces techniques pour la généralisation cartographique permet également d'envisager la transposition de ces méthodes de simulation à la résolution de problèmes.

Keywords: multi-agent based simulation, multi-level, in french, french team

[Picault:2017]

S. Picault, Y-L. Huang, V. Sicard, F. Beaudou, and P. Ezanno. A multi-level multi-agent simulation framework in animal epidemiology. In *International Conference on Practical Applications of Agents and Multi-Agent Systems*, volume 10349 of *LNCS*, pages 209–221. Springer, 2017.

Abstract: In order to recommend better control measures in public or animal health, epidemiologists incorporate ever-finer details in their models, from individual diversity to public policies, which often involve several observation scales. Due to the variety of modelling paradigms, it becomes more and more difficult to compare hypotheses and outcomes, all the more that the increased complexity of simulation programs is not yet counterbalanced by design principles nor by software engineering methods. We propose in this paper to use the multi-level agent-based

paradigm to integrate existing methods within a common interface, provide a separation between concerns and reduce the part of code devoted to model designers. We illustrate our approach with an application to the Q fever disease in cattle.

Keywords: multi-agent based simulation, multi-level, epidemiology, french team

[Picault:2017a]

S. Picault, Y-L. Huang, V. Sicard, and P. Ezanno. Enhancing sustainability of complex epidemiological models through a generic multilevel agent-based approach. In *Proc. of 26th Int. Joint Conf. on Artificial Intelligence*, 2017.

Abstract: The development of computational sciences has fostered major advances in life sciences, but also led to reproducibility and reliability issues, which become a crucial stake when simulations are aimed at assessing control measures, as in epidemiology. A broad use of software development methods is a useful remediation to reduce those problems, but preventive approaches, targeting not only implementation but also model design, are essential to sustainable enhancements. Among them, AI techniques, based on the separation between declarative and procedural concerns, and on knowledge engineering, offer promising solutions. Especially, multilevel multi-agent systems, deeply rooted in that culture, provide a generic way to integrate several epidemiological modeling paradigms within a homogeneous interface. We explain in this paper how this approach is used for building more generic, reliable and sustainable simulations, illustrated by real-case applications in cattle epidemiology.

Keywords: multi-agent based simulation, multi-level, epidemiology, french team

[Picault:2017b]

S. Picault, Y-L. Huang, V. Sicard, F. Beaudeau, and P. Ezanno. EMuLSion, a generic simulation framework in animal epidemiology based on multi-level multi-agent modelling. In *Modelling in Animal Health conference (ModAH)*, 2017.

Abstract: To recommend better control measures in public or animal health, epidemiologists incorporate ever-finer details in their models, from individual diversity to public policies, which often involve several observation scales. Due to the variety of modelling paradigms, it becomes more and more difficult to compare hypotheses and outcomes, or explore new assumptions or scenarios, especially since the increased complexity of simulation programs is not yet counterbalanced by design principles nor by software engineering methods. Thus, any change in the model often induces a substantial coding effort. The EMuLSion framework, developed within the MIHMES project, rely upon the multi-level agent-based paradigm to integrate existing methods within a common interface, provide a separation between concerns and reduce the part of code devoted to model designers. Multi-agent systems are composed of interacting autonomous entities (agents) endowed with behaviors, and are quite flexible since an agent can be used to model any kind of entity. Especially, in multi-level agent-based systems [1], agents can represent several organization or observation levels, from individuals to metapopulations. Thus, multi-level agent-based systems are a convenient way to encompass classical modelling paradigms used in epidemiology (e.g. compartments, IBM, metapopulations). We also advocate for a strong separation of concerns, i.e. a clear separation between a generic simulation engine (code) on the one hand, and an explicit, human-readable and highly modular description of the model structure, parameters and assumptions on the other hand. Thanks to this approach, the EMuLSion framework is able to process epidemiological models with very little specific code development, allowing for quick model refactoring, alternative hypotheses assessment, and objective model comparison. Models can involve several modelling paradigms at the same time, and the framework also provides efficient individual grouping methods to benefit from the detail level of IBM without excessive performance degradation. We illustrate our approach with an application to the Q fever disease in cattle, first to reproduce a within-herd model developed previously [2], study possible simplifications of assumptions, and extend it to the between-herd level.

Keywords: multi-agent based simulation, multi-level, epidemiology, french team

[Picault:2018]

S. Picault, Y-L. Huang, V. Sicard, T. Hoch, E. Vergu, F. Beaudeau, and P. Ezanno. A generic multi-level stochastic modelling framework in computational epidemiology. *bioRxiv*, 2018.

Abstract: There is currently an overwhelming increased interest in predictive biology and computational modelling. The development of reliable, reproducible and revisable simulation models in computational life sciences is often pointed out as a challenging issue. Population dynamics, including epidemiology, has not yet developed a language to formalize complex models in a univocal and automatable way, hence hindering the capability to implement in short time reliable, revisable and expert-friendly models intended for realistic mechanistic simulations. In epidemiology specifically, models aim not only at understanding pathogen spread but also at assessing

control measures at several scales. To achieve this goal efficiently, best software practices should be supported by Artificial Intelligence methods to handle experts' knowledge. The framework EMULSION presented here intends to both tackle multiple modelling paradigms in epidemiology and facilitate the automation of model design. We therefore built both a domain-specific language (DSL) for the modular description of complex epidemiological models, and a generic simulation engine designed to embed existing modelling paradigms within a homogeneous architecture based on adaptive software agents. The diversity of concerns (biology, economics, human activities) involved in real pathosystems requires an explicit, comprehensive and intelligible way to describe epidemiological models, to involve experts without computer science skills throughout the modelling, simulation and output analysis steps. This approach was applied to compare hypotheses in modelling a zoonosis (Q fever), to study its transmission dynamics within and between cattle herds at a regional scale, and to assess the contribution of transmission pathways. Separating model description from the simulation engine allowed epidemiologists to be involved in assumption revision, while guaranteeing very few code modifications. We assessed the added value of EMULSION by applying the DSL and the simulation engine to a concrete disease. Future extensions of EMULSION towards a broader range of epidemiological concerns will reduce significantly the time required to design and assess models and control measures against endemic and epidemic diseases. Ultimately, we believe this effort is a major lever to increase scientists' preparedness to face emerging threats for public health and provide rapid, reliable, and reasoned assessments of control measures.

Keywords: multi-agent based simulation, multi-level, epidemiology

[Picault:2019]

S. Picault, Y-L. Huang, V. Sicard, S. Arnoux, G. Beaunée, and P. Ezanno. Emulsion: transparent and flexible multiscale stochastic models in epidemiology. *PLOS Computational Biology*, 15(9):e1007342, 2019.

Abstract: Stochastic mechanistic models are essential to predictive epidemiology, to better explore biological assumptions and anticipate effects of control measures on pathogen spread. Their development is usually long and iterative, involving multi-disciplinary knowledge integration. However, knowledge often becomes lost in model code, hindering late changes in assumptions and often making models appearing as black boxes to end-users. We introduce here EMULSION, an artificial intelligence-based software intended to help modellers focus on model design rather than programming. EMULSION defines a domain-specific language to make all components of an epidemiological model (structure, processes, parameters...) explicit as a structured text file. This file is readable by scientists from other fields (epidemiologists, biologists, economists), who can contribute to validate or revise assumptions at any stage of model development. It is then automatically processed by EMULSION generic simulation engine, preventing any discrepancy between model description and implementation. The modelling language and simulation architecture both rely on the combination of advanced artificial intelligence methods (knowledge representation and multi-level agent-based simulation), allowing several modelling paradigms (from compartment- to individual-based models) at several scales (up to metapopulations). The flexibility of EMULSION and its capability to support iterative modelling are illustrated here through examples of progressive complexity, including late revisions of core model assumptions. EMULSION is also currently used to model the spread of several diseases in real pathosystems (zoonoses such as Q fever or the vector-borne Rift Valley fever; or bovine respiratory diseases, with a focus on detection and treatment protocols). EMULSION provides a command-line tool for checking models, producing model diagrams, running simulations, and plotting outputs. Implemented in Python 3, EMULSION runs on Linux, MacOS, and soon Windows. It is released under Apache-2.0 license. A comprehensive documentation with installation instructions, tutorial and examples is available from: <https://sourcesup.renater.fr/emulsion-public>.

Keywords: multi-agent based simulation, multi-level, epidemiology, french team

[Pike:2019]

T. Pike. Multi-level mesa. *arXiv preprint arXiv:1904.08315*, 2019.

Abstract: Multi-level Mesa is an extension to support the Python based Agents Based Model (ABM) library Mesa. Multi-level Mesa provides ABM infrastructure to allow for the inclusion of complex networks, which have modules (groups) and hierarchies (layers) of agents. This approach allows for users to define and simulate multi-layered adaptations of complex networks. This study reviews other multi-level libraries currently in the field, describes the main functions and classes of the Multi-level Mesa, and describes its implementation and impact in numerous varieties using the seminal ABM - Sugarscape. Multi-level Mesa and Sugarscape examples are available on GitHub at this [https](https://github.com/tpike/mesa) URL and this [https](https://github.com/tpike/mesa) URL.

Keywords: multi-agent based simulation, multi-level, simulation platform

[Pike:2019a]

T. Pike. *Standardizing Complexity: Doctrine and Computation for Integrated Campaigning*. PhD thesis, George Mason University, 2019.

Abstract: This dissertation examines the integration of complexity theory and computational tools into U.S. foreign policy. It identifies ways to improve the Department of Defense's main analytic framework to ensure a more accurate reflection of complex systems and it provides a holistic assessment of the integration of computational tools into Joint campaigns. Based on this analysis, this dissertation advocates the incorporation of Agent Based Models (ABMs) as simulations to support both analysis and foreign policy development at all levels of the foreign policy enterprise. To aid this integration, two Mesa based ABM libraries are created. (1) Multi-level Mesa, the first Python based multi-level library to facilitate the integration and evolution of layered adaptive networks. This library goes beyond existing multi-level libraries by providing greater user flexibility and allowing for the integration and adaptation of more complex networks. (2) Distributed Space Mesa, a first attempt at starting a Distributed Mesa metalibrary. This library provides modest time improvements to spatial Mesa ABMs and critical lessons for the continued development of a suite of distributed Mesa libraries.

Keywords: multi-agent based simulation, multi-level, simulation platform

[Poleszczuk:2015]

J. Poleszczuk and H. Enderling. Vectorization techniques for efficient agent-based model simulations of tumor growth. *bioRxiv*, page 032086, 2015.

Abstract: Multi-scale agent-based models are increasingly used to simulate tumor growth dynamics. Simulating such complex systems is often a great challenge despite large computational power of modern computers and, thus, implementation techniques are becoming as important as the models themselves. Here we show, using a simple agent-based model of tumor growth, how the computational time required for simulation can be decreased by using vectorization techniques. In numerical examples we observed up to 30-fold increases in computation performance when standard approaches were, at least in part, replaced with vectorized routines in MATLAB.

Keywords: multi-agent based simulation, multi-level, cancer modeling, biology

[Poschinger:2002]

A. Poschinger, R. Kates, and H. Keller. Coupling of concurrent macroscopic and microscopic traffic flow models using hybrid stochastic and deterministic disaggregation. *Transportation and Traffic Theory for the 21st century*, 2002.

Abstract: The paper addresses the general problem of coupling macroscopic traffic data to microscopic traffic flow models, regardless of their source. The approach presented in this paper provides key structures and all mathematical solutions including a new hybrid disaggregator required for carrying out coupling of concurrent microscopic and macroscopic models. The results of the coupling of models are provided. The results show that the hybrid disaggregator can be used to couple microscopic models to aggregated traffic data from a wide range of non concurrent sources. Another possible application is the hybrid microscopic and macroscopic simulation of road networks.

Keywords: multi-agent based simulation, multi-level, traffic, hybrid model

[Prevost:2004]

G. Prévost, P. Tranouez, S. Lerebourg, C. Bertelle, and D. Olivier. Ecosystem complexity described with ontological tool for a multi-scale, multi-model approaches in distributed environment. In *Jordan Int. Conf. on Computer Sciences and Engineering*, Al-Salt, Jordan, 2004.

Abstract: Aquatic ecosystems are natural complex systems. They are the site of a great number of phenomena. Thus, many studies model each of these phenomena, using law-based approach (most of the time differential equations) or rulebased approach (individual-based models in particular). Owing to their complex nature, aquatic ecosystems are hard to study and resist a reductionist approach. We based our model on the holarchic (non directional hierarchic) nature of the ecosystems. First, aquatic ecosystems are crossed by structuring fluxes (light radiation, mass transport, etc.) which are mainly conveyed by fluid flow. So, we propose to model these fluid flows with a multi-scale simulation detecting emergent formation and managing them on different scales. Second, a part of aquatic ecosystems are species organizations called food chain. These ones are themselves interacting complex subsystems with multi non-directional retroactions between them and their environment. These retroactions can be modeled at different levels. Thus, we propose an hybrid holarchic compartmental model. This one aims at easing the gathering of phenomenon in a multi-model, multilevel simulation for studying food chain. We finally present a fluid-flow simulation and a food chain simulation using the proposed models.

Keywords: multi-agent based simulation, multi-level, multi-model, french team

[Prevost:2009]

G. Prévost and C. Bertelle. Detection and reification of emerging dynamical ecosystems from interaction networks. In *Complex Systems and Self-organization Modelling*, volume 39 of *Understanding Complex Systems*, pages 139–161. Springer, 2009.

Abstract: In this paper, we present an hybrid ecosystem modeling based on emerging computation from interaction networks. Initially based on an individualbased modeling (IBM) simulation, we propose an automatic computation to detect predator-preys systems. After their detection, these systems are replaced by a differential system during the simulation. In this way, we can change the description level and improve both the computation time and the whole system analysis by detecting some emergent organizations. The description modification between IBM representation to differential one needs to identify the global coefficients of these differential equations. Due to the complexity of relations between these two kinds of representations, a genetic algorithm is proposed to solve this identification.

Keywords: multi-agent based simulation, multi-level, ecology, emergence detection, french team

[Pumain:2009a]

D. Pumain and T. Louail. Interaction des ontologies informatique et géographique pour simuler les dynamiques multiscalaires. In *Actes des 16èmes journées de Rochebrune*, 2009.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Qiao:2015]

M. Qiao, D. Wu, M. Carey, X. Zhou, and L. Zhang. Multi-scale agent-based multiple myeloma cancer modeling and the related study of the balance between osteoclasts and osteoblasts. *PLoS one*, 10(12), 2015.

Abstract: Research Background Currently, multiple myeloma is the second most common hematological malignancy in the U.S., constituting 1% of all cancers. With conventional treatment, the median survival time is typically 3–4 years, although it can be extended to 5–7 years or longer with advanced treatments. Recent research indicated that an increase in osteoclast (OC) activity is often associated with multiple myeloma (MM) and that a decrease in osteoblast (OB) activity contributes to the osteolytic lesions in MM. Normally, the populations of OCs and OBs are in equilibrium, and an imbalance in this state contributes to the development of lesions. Research procedures A multi-scale agent-based multiple myeloma model was developed to simulate the proliferation, migration and death of OBs and OCs. Subsequently, this model was employed to investigate the efficacy of the three most commonly used drugs for MM treatment under the following two premises: the reduction in the progression of MM and the re-establishment of the equilibrium between OCs and OBs. Research purposes The simulated results not only demonstrated the capacity of the model to choose optimal combinations of the drugs but also showed that the optimal use of the three drugs can restore the balance between OCs and OBs as well as kill MMs. Furthermore, the drug synergism analysis function of the model revealed that restoring the balance between OBs and OCs can significantly increase the efficacy of drugs against tumor cells.

Keywords: multi-agent based simulation, multi-level, cancer modeling, biology

[Radzvilavicius:2016]

A.L. Radzvilavicius, Z. Hadjivasiliou, A. Pomiankowski, and N. Lane. Selection for mitochondrial quality drives evolution of the germline. *PLoS Biology*, 14(12):e2000410, 2016.

Abstract: The origin of the germline–soma distinction is a fundamental unsolved question. Plants and basal metazoans do not have a germline but generate gametes from pluripotent stem cells in somatic tissues (somatic gametogenesis). In contrast, most bilaterians sequester a dedicated germline early in development. We develop an evolutionary model which shows that selection for mitochondrial quality drives germline evolution. In organisms with low mitochondrial replication error rates, segregation of mutations over multiple cell divisions generates variation, allowing selection to optimize gamete quality through somatic gametogenesis. Higher mutation rates promote early germline sequestration. We also consider how oogamy (a large female gamete packed with mitochondria) alters selection on the germline. Oogamy is beneficial as it reduces mitochondrial segregation in early development, improving adult fitness by restricting variation between tissues. But it also limits variation between early-sequestered oocytes, undermining gamete quality. Oocyte variation is restored through proliferation of germline cells, producing more germ cells than strictly needed, explaining the random culling (atresia) of precursor cells in bilaterians. Unlike other models of germline evolution, selection for mitochondrial quality can explain the stability of somatic gametogenesis in plants and basal metazoans, the evolution of oogamy in all plants and animals with tissue differentiation, and the mutational forces driving early germline sequestration in active bilaterians. The origins of predation in motile bilaterians in the Cambrian

explosion is likely to have increased rates of tissue turnover and mitochondrial replication errors, in turn driving germline evolution and the emergence of complex developmental processes.

Keywords: multi-agent based simulation, multi-level, biology

[Raimbault:2019]

J. Raimbault. A multi-scalar model for system of cities. In *Conference on Complex Systems (CCS)*, 2019.

Abstract: The modeling of urban growth is a crucial issue for the design of sustainable territorial policies, through the understanding of past urbanization processes and the forecasting of future urban trajectories. Several models have been proposed at different scales and integrating different dimensions of urban systems, such as land-use transport interaction models (Wegener and Furst, 2004) or systems of cities models (Pumain and Reuillon, 2017). While multi-scalar models are recognized as crucial for the study of such systems (Rozenblat and Pumain, 2018), they remain in practice unexplored. This contribution introduces a parsimonious multi-scalar model for systems of cities, based on simple dimensions (mainly populations) with stylized processes, but yielding an effective strong coupling between the metropolitan mesoscopic scale and the macroscopic scale of the system of cities. The model couples the spatial interaction model of (Raimbault, 2018a) for the macro scale with the reaction-diffusion model for urban form studied by (Raimbault, 2018b). More precisely, urban areas viewed as a population grid are embedded into the macroscopic interaction model. To evolve populations and local urban forms, one time step consists of (i) population differences are computed by the interaction model; (ii) top-down feedback modifies parameters of mesoscopic models, given control parameters to capture typical scenarios (transit-oriented development or sprawl for diffusion, metropolization or uniformization for aggregation); (iii) local urban form are evolved with the reaction-diffusion models at a given speed conditionally to the population variations; (iv) changes in urban form influence macroscopic interaction ranges (capturing the impact of local activity on global insertion), by integrating gravity flows in the area with a squared cost function making a compromise between congestion and flows. The model is applied on synthetic systems of cities typical of a continental range (500km, hierarchy around 1, 20 cities), with initial local population grid configurations as monocentric. Parameter space is explored with the OpenMOLE model exploration software (Reuillon et al., 2013), eased by the implementation of the model in scala. First results show a strong impact of the strong meso-macro coupling, such as for example a qualitative inversion of the behavior as a function of interaction range of macroscopic indicators trajectories when switching from a "transit-oriented development" scenario (negative feedback of population growth on diffusion) to a "sprawl" scenario (positive feedback). Similarly, mesoscopic urban form indicators are significantly influenced by the coupling process. Further work will consist in more targeted simulation experiments, including specific exploration algorithms such as diversity search for model regimes, to test the model as a proof-of-concept of models for policies. Such a model can also be calibrated on real city systems and urban form trajectories, to extrapolate coupling parameters that would be difficult to obtain otherwise. Our contribution is thus a first step towards multi-scalar simulation models for systems of cities.

Keywords: multi-agent based simulation, multi-level, social simulation, french team

[Ratze:2007]

C. Ratze, F. Gillet, J-P. Müller, and K. Stoffel. Simulation modelling of ecological hierarchies in constructive dynamical systems. *Ecological Complexity*, 4(1-2):13-25, 2007.

Abstract: Organized complexity is a characteristic feature of ecological systems with heterogeneous components interacting at several spatio-temporal scales. The hierarchy theory is a powerful epistemological framework to describe such systems by decomposing them vertically into levels and horizontally into holons. It was at first developed in a temporal and functional perspective and then, in the context of landscape ecology, extended to a spatial and structural approach. So far, most ecological applications of this theory were restricted to observational purposes, using multi-scale analysis to describe hierarchies. In spite of an increasing attention to dynamics of hierarchically structured ecological systems, current simulation models are still very limited in their representation of self-organization in complex adaptive systems. An ontological conceptualization of the hierarchy theory is outlined, focusing on key concepts, such as levels of organization and the compound and component faces of the holons. Various existing formalisms are currently used in simulation modelling, such as system dynamics, discrete event and agent based paradigms. Their ability to express the hierarchical organization of dynamical ecological systems is discussed. It turns out that a multi-modelling approach linking all these formalisms and oriented toward the specification of a constructive dynamical system would be able to express the dynamical structure of the hierarchy (creation, destruction and change of holons) and the functional and structural links between levels of organization.

Keywords: multi-agent based simulation, multi-level, ecology

[Raub:2011]

W. Raub, V. Buskens, and M. van Assen. Micro-macro links and microfoundations in sociology. *The Journal of Mathematical Sociology*, 35(1-3):1–25, 2011.

Abstract: Using Coleman’s well-known scheme as an anchor, we review key features of explanations of social phenomena that employ micro-macro models. Some antecedents of micro-macro models and of Coleman’s scheme as well as some paradigmatic examples of micro-macro links are sketched. We then discuss micro-level assumptions in micro-macro explanations and the robustness of macro-level implications to variations in micro-level assumptions. We conclude with an overview of some recent developments in micro-macro modeling and of the contributions to the special issue.

Keywords: multi-agent based simulation, multi-level, social simulation

[Razavi:2012]

S.N. Razavi, N. Gaud, A. Koukam, and N. Mozayani. Automatic dynamics simplification in fast multipole method: application to large flocking systems. *The Journal of Supercomputing*, 2012.

Abstract: This paper introduces a novel framework with the ability to adjust simulation’s accuracy level dynamically for simplifying the dynamics computation of large particle systems to improve simulation speed. Our new approach follows the overall structure of the well-known Fast Multipole Method (FMM) coming from computational physics. The main difference is that another level of simplification has been introduced by combining the concept of motion levels of detail from computer graphics with the FMM. This enables us to have more control on the FMM execution time and thus to trade accuracy for efficiency whenever possible. At each simulation cycle, the motion levels of detail are updated and the appropriate ones are chosen adaptively to reduce computational costs. The proposed framework has been tested on the simulation of a large dynamical flocking system. The preliminary results show a significant complexity reduction without any remarkable loss in the visual appearance of the simulation, indicating the potential use of the proposed model in more realistic situations such as crowd simulation.

Keywords: multi-agent based simulation, multi-level, dynamic level of detail

[Rejniak:2011]

K.A. Rejniak and A.R.A. Anderson. Hybrid models of tumor growth. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 3(1):115–125, 2011.

Abstract: Cancer is a complex, multiscale process, in which genetic mutations occurring at a subcellular level manifest themselves as functional changes at the cellular and tissue scale. The multiscale nature of cancer requires mathematical modeling approaches that can handle multiple intra- and extracellular factors acting on different time and space scales. Hybrid models provide a way to integrate both discrete and continuous variables that are used to represent individual cells and concentration or density fields, respectively. Each discrete cell can also be equipped with sub-models that drive cell behavior in response to microenvironmental cues. Moreover, the individual cells can interact with one another to form and act as an integrated tissue. Hybrid models form part of a larger class of individual-based-models that can naturally connect with tumor cell biology and allow for the integration of multiple interacting variables both intrinsically and extrinsically and are therefore perfectly suited to a systems biology approach to tumor growth.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Rocha:2018]

H.L. Rocha, R.C. Almeida, E.A.B.F. Lima, A.C.M. Resende, J.T. Oden, and T.E. Yankeelov. A hybrid three-scale model of tumor growth. *Mathematical Models and Methods in Applied Sciences*, 28(01):61–93, 2018.

Abstract: Cancer results from a complex interplay of different biological, chemical, and physical phenomena that span a wide range of time and length scales. Computational modeling may help to unfold the role of multiple evolving factors that exist and interact in the tumor microenvironment. Understanding these complex multiscale interactions is a crucial step toward predicting cancer growth and in developing effective therapies. We integrate different modeling approaches in a multiscale, avascular, hybrid tumor growth model encompassing tissue, cell, and sub-cell scales. At the tissue level, we consider the dispersion of nutrients and growth factors in the tumor microenvironment, which are modeled through reaction–diffusion equations. At the cell level, we use an agent-based model (ABM) to describe normal and tumor cell dynamics, with normal cells kept in homeostasis and cancer cells differentiated into quiescent, proliferative, migratory, apoptotic, hypoxic, and necrotic states. Cell movement is driven by the balance of a variety of forces according to Newton’s second law, including those related to growth-induced stresses. Phenotypic

transitions are defined by specific rule of behaviors that depend on microenvironment stimuli. We integrate in each cell/agent a branch of the epidermal growth factor receptor (EGFR) pathway. This pathway is modeled by a system of coupled nonlinear differential equations involving the mass laws of 20 molecules. The rates of change in the concentration of some key molecules trigger proliferation or migration advantage response. The bridge between cell and tissue scales is built through the reaction and source terms of the partial differential equations. Our hybrid model is built in a modular way, enabling the investigation of the role of different mechanisms at multiple scales on tumor progression. This strategy allows representing both the collective behavior due to cell assembly as well as microscopic intracellular phenomena described by signal transduction pathways. Here, we investigate the impact of some mechanisms associated with sustained proliferation on cancer progression. Specifically, we focus on the intracellular proliferation/migration-advantage-response driven by the EGFR pathway and on proliferation inhibition due to accumulation of growth-induced stresses. Simulations demonstrate that the model can adequately describe some complex mechanisms of tumor dynamics, including growth arrest in avascular tumors. Both the sub-cell model and growth-induced stresses give rise to heterogeneity in the tumor expansion and a rich variety of tumor behaviors.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology

[Rounsevell:2012]

M.D.A. Rounsevell, B. Pedroli, K.H. Erb, M. Gramberger, A.G. Busck, H. Haberl, S. Kristensen, T. Kuemmerle, S. Lavorel, M. Lindner, et al. Challenges for land system science. *Land Use Policy*, 2012.

Abstract: While considerable progress has been made in understanding land use change, land system science continues to face a number of grand challenges. This paper discusses these challenges with a focus on empirical land system studies, land system modelling and the analysis of future visions of land system change. Contemporary landscapes are contingent outcomes of past and present patterns, processes and decisions. Thus, empirical analysis of past and present land use change has an important role in providing insights into the socio-economic and ecological processes that shape land use transitions. This is especially important with respect to gradual versus rapid land system dynamics and in understanding changes in land use intensity. Combining the strengths of empirical analysis with multi-scale modelling will lead to new insights into the processes driving land system change. New modelling methods that combine complex systems thinking at a local level with macro-level economic analysis of the land system would reconcile the multi-scale dynamics currently encapsulated in bottom-up and top-down modelling approaches. Developments in land use futures analysis could focus on integrating explorative scenarios that reflect possible outcomes with normative visions that identify desired outcomes. Such an approach would benefit from the broad and in-depth involvement of stakeholders in order to link scientific findings to political and societal decision-making culminating in a set of key choices and consequences. Land system models have an important role in supporting future land use policy, but model outputs require scientific interpretation rather than being presented as predictions. The future of land system science is strongly dependent on the research community's capacity to bring together the elements of research discussed in the paper, via empirical data collection and analysis of observed processes, computer simulation across scale levels and futures analysis of alternative, normative visions through stakeholder engagement.

Keywords: multi-agent based simulation, multi-level, ecology

[Salavati:2018]

H. Salavati, M. Soltani, and S. Amanpour. The pivotal role of angiogenesis in a multi-scale modeling of tumor growth exhibiting the avascular and vascular phases. *Microvascular research*, 119:105–116, 2018.

Abstract: The mechanisms involved in tumor growth mainly occur at the microenvironment, where the interactions between the intracellular, intercellular and extracellular scales mediate the dynamics of tumor. In this work, we present a multi-scale model of solid tumor dynamics to simulate the avascular and vascular growth as well as tumor-induced angiogenesis. The extracellular and intercellular scales are modeled using partial differential equations and cellular Potts model, respectively. Also, few biochemical and biophysical rules control the dynamics of intracellular level. On the other hand, the growth of melanoma tumors is modeled in an animal in-vivo study to evaluate the simulation. The simulation shows that the model successfully reproduces a completed image of processes involved in tumor growth such as avascular and vascular growth as well as angiogenesis. The model incorporates the phenotypes of cancerous cells including proliferating, quiescent and necrotic cells, as well as endothelial cells during angiogenesis. The results clearly demonstrate the pivotal effect of angiogenesis on the progression of cancerous cells. Also, the model exhibits important events in tumor-induced angiogenesis like anastomosis. Moreover, the computational trend of tumor growth closely follows the observations in the experimental study.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling, hybrid model

[Sawyer:2001]

R.K. Sawyer. Simulating emergence and downward causation in small groups. In *Multi-agent-based simulation*, LNCS, pages 49–67. Springer, 2001.

Abstract: Emergence has been a central issue not only in computational models of social systems, but also throughout 20th century sociological theory. In this paper, I first define the key concepts of emergence, downward causation, and bi-directional causation, and I identify these processes in an example of improvised dialog. I then draw on emergentist trends in sociological theory to propose a computational model of collaborative emergence among small groups of improvising agents.

Keywords: multi-agent based simulation, social simulation, multi-level

[Sawyer:2003]

R.K. Sawyer. Artificial societies, multiagent systems and the micro-macro link in sociological theory. *Sociological Methods & Research*, 31(3):325–363, 2003.

Abstract: This article introduces a general sociological readership to multiagent systems (MAS), a new computer simulation technology that has increasingly been used to describe and explain sociological phenomena. The author uses the term artificial societies to refer to social simulations using MAS and he describes MAS technology and contrasts it with other social simulation technologies. The author argues that MAS have attained a level of maturity where they can be useful tools for sociologists, and he shows how MAS provide new perspectives on contemporary discussions of the micro-macro link in sociological theory by focusing on three aspects of the micro-macro link: micro-to-macro emergence, macro-to-micro social causation, and the dialectic between emergence and social causation.

Keywords: social simulation, multi-level, multi-agent based simulation

[Scerri:2010]

D. Scerri, A. Drogoul, S. Hickmott, and L. Padgham. An architecture for modular distributed simulation with agent-based models. In *Proc. of 9th Int. Conf. on Autonomous Agents and Multiagent Systems (AAMAS 2010)*, pages 541–548. International Foundation for Autonomous Agents and Multiagent Systems, 2010.

Abstract: Agent-based simulations are an increasingly popular means of exploring and understanding complex social systems. In order to be useful, these simulations must capture a range of aspects of the modeled situation, each possibly requiring distinct expertise. Moreover, different paradigms may be useful in modelling, ranging from those that use many lightweight reactive agents, to those that use cognitive agents, to those that focus on agent teams and organisational structures. There is need for an architecture which supports the development of a large simulation, through the integration of separately developed modules. This paper describes a framework and architecture which facilitates the integration of multiple agent-based simulations into a single global simulation. This architecture naturally supports distributed simulation and incremental development, which are ways of addressing the computational and conceptual complexity of such systems. In this paper we focus particularly on how to ensure proper management of simulation data that is affected by agents in different modules, at the same logical time. We also provide some preliminary performance evaluation addressing scalability, as well as a comparison of how other available systems handle the issue of shared data.

Keywords: meta-model, multi-agent based simulation, multi-level

[Schaller:2012]

N. Schaller, E.G. Lazrak, P. Martin, J.F. Mari, C. Aubry, and M. Benoît. Combining farmers' decision rules and landscape stochastic regularities for landscape modelling. *Landscape Ecology*, 27(3):1–14, 2012.

Abstract: Landscape spatial organization (LSO) strongly impacts many environmental issues. Modelling agricultural landscapes and describing meaningful landscape patterns are thus regarded as key-issues for designing sustainable landscapes. Agricultural landscapes are mostly designed by farmers. Their decisions dealing with crop choices and crop allocation to land can be generic and result in landscape regularities, which determine LSO. This paper comes within the emerging discipline called “landscape agronomy”, aiming at studying the organization of farming practices at the landscape scale. We here aim at articulating the farm and the landscape scales for landscape modelling. To do so, we develop an original approach consisting in the combination of two methods used separately so far: the identification of explicit farmer decision rules through on-farm surveys methods and the identification of landscape stochastic regularities through data-mining. We applied this approach to the Niort plain landscape in France. Results show that generic farmer decision rules dealing with sunflower or maize area and location within landscapes are consistent

with spatiotemporal regularities identified at the landscape scale. It results in a segmentation of the landscape, based on both its spatial and temporal organization and partly explained by generic farmer decision rules. This consistency between results points out that the two modelling methods aid one another for land-use modelling at landscape scale and for understanding the driving forces of its spatial organization. Despite some remaining challenges, our study in landscape agronomy accounts for both spatial and temporal dimensions of crop allocation: it allows the drawing of new spatial patterns coherent with land-use dynamics at the landscape scale, which improves the links to the scale of ecological processes and therefore contributes to landscape ecology.

Keywords: multi-agent based simulation, multi-level, social simulation

[Scheff:2012]

J.D. Scheff, P.D. Mavroudis, P.T. Foteinou, G. An, S.E. Calvano, J. Doyle, T.E. Dick, S.F. Lowry, Y. Vodovotz, and I.P. Androulakis. A multiscale modeling approach to inflammation: A case study in human endotoxemia. *Journal of Computational Physics*, 2012.

Abstract: Inflammation is a critical component in the body’s response to injury. A dysregulated inflammatory response, in which either the injury is not repaired or the inflammatory response does not appropriately self-regulate and end, is associated with a wide range of inflammatory diseases such as sepsis. Clinical management of sepsis is a significant problem, but progress in this area has been slow. This may be due to the inherent nonlinearities and complexities in the interacting multiscale pathways that are activated in response to systemic inflammation, motivating the application of systems biology techniques to better understand the inflammatory response. Here, we review our past work on a multiscale modeling approach applied to human endotoxemia, a model of systemic inflammation, consisting of a system of compartmentalized differential equations operating at different time scales and through a discrete model linking inflammatory mediators with changing patterns in the beating of the heart, which has been correlated with outcome and severity of inflammatory disease despite unclear mechanistic underpinnings. Working towards unraveling the relationship between inflammation and heart rate variability (HRV) may enable greater understanding of clinical observations as well as novel therapeutic targets.

Keywords: multi-agent based simulation, multi-level, biology

[Scheutz:2005]

M. Scheutz, G. Madey, and S. Boyd. tMANS - the multi-scale agent-based networked simulation for the study of multi-scale, multi-level biological and social phenomena. In *Spring Simulation Multiconference*, 2005.

Abstract: We propose a multi-scale agent-based framework towards understanding and modeling multi-scale interdependent behavioral phenomena. This framework combines the ideas of agent-based modeling with that of hierarchies or levels of organization found in nature and allows for multiple levels in the model to interact at various time scales. We first summarize our rationale for pursuing agent-based models (rather than equation-based models) and then describe the proposed multi-level, multi-scale agent-based modeling framework formally, followed briefly by a discussion of how biological phenomena at different levels could be modeled in the framework. We list some of the requirements and desirable properties for a software simulation tool that can implement such multi-scale, multi-level models, briefly pointing to work in progress on the development of our “tMANS” tool (“the Multi-scale Agent-based Network System”).

Keywords: multi-agent based simulation, multi-level, meta-model

[Schiller:2015]

M. Schiller, M. Dupuis, D. Krajzewicz, A. Kern, and A. Knoll. Multi-resolution traffic simulation for large scale high fidelity evaluation of vanet applications. In *Proc. of SUMO User Conf.*, 2015.

Abstract: This paper presents an approach for coupling traffic simulators of different resolutions in order to conduct both large scale and high fidelity virtual evaluations of Advanced Driver Assistance Systems based on Vehicular Adhoc Networks. The emphasis is put on the need for such an attempt to satisfy the constraint of performing simulations in real time. Both, the methods to accomplish this as well as the resulting performance are described.

Keywords: multi-agent based simulation, multi-level, multiresolution, traffic

[Schillo:2001]

M. Schillo, K. Fischer, and C.T. Klein. The micro-macro link in DAI and sociology. In *Multi-Agent Based Simulation*, volume 1979 of *LNCS*, pages 133–148. Springer, 2001.

Abstract: No matter if a population is human or artificial, we can surely identify phenomena that can be described as micro or macro phenomena. In this paper, we discuss micro and macro aspects of a population from a DAI and a sociological point of view. We analyse similarities and differences in these viewpoints, and identify misperceptions in the DAI community about the micro-macro

terminology. We explain these misperceptions and argue for the transfer of sociologically founded concepts to agent-based social simulation. Our research is done in the DFG focus programme socionics. We cooperate with sociologists from University Hamburg-Harburg with the intention to transfer knowledge from sociology to DAI as well as from DAI to sociology. In cooperation with DFKI Saarbrücken we work on improving agent theories to be applied in large sized multi-agent systems in the freight logistics domain.

Keywords: social simulation, multi-agent based simulation, multi-level

[Schmidt:2011]

S.I. Schmidt, C. Picioreanu, B. Craenen, R. Mackay, J.U. Kreft, and G. Theodoropoulos. A multi-scale agent-based distributed simulation framework for groundwater pollution management. In *15th International Symposium on Distributed Simulation and Real Time Applications (DS-RT)*, pages 18–27. IEEE, 2011.

Abstract: Groundwater is like dark matter - we know very little apart from the fact that it is hugely important. Given the scarcity of data, mathematical modelling can come to the rescue but existing groundwater models are mainly restricted to simulate the transport and degradation of contaminants on the scale of whole contaminated field sites by averaging out the effect of spatial heterogeneity on the availability of the pollutant to the degrading organisms. These coarse-scale mean-field models therefore tend to rely on fitting to data rather than being predictive. Also, they are less suited to incorporate spatial variability and non-linear kinetics and feedbacks. We propose to solve the two mutually exacerbating problems of environmental patchiness and data scarcity by developing a flexible and robust distributed simulation framework that uses an ensemble of small scale simulations running on different processors/computers to scale-up, i.e. to feed the effect of small-scale patchiness into a concurrent site-scale simulation of the dynamics of groundwater pollutant degradation. Our scaling approach solves problem 1) by simulating dynamics also on the small scale where some of the patchiness resides, and problem 2) by enabling rigorous validation of our small-scale model and scaling approach with laboratory data, which are high quality at low cost.

Keywords: multi-level, multi-agent based simulation, ecology

[Schmidtchen:2016]

M. Schmidtchen, O. Tse, and S. Wackerle. A multiscale approach for spatially inhomogeneous disease dynamics. *arXiv:1602.05927 [math.DS]*, 2016.

Abstract: In this paper we introduce an agent-based epidemiological model that generalizes the classical SIR model by Kermack and McKendrick. We further provide a multiscale approach to the derivation of a macroscopic counterpart via the mean-field limit. The chain of equations acquired via the multiscale approach are investigated, analytically as well as numerically. The outcome of these results provide strong evidence of the models' robustness and justifies their applicability in describing disease dynamics, in particularly when mobility is involved.

Keywords: multi-agent based simulation, multi-level, macroscopic representation

[Seal:2011]

J.B. Seal, J.C. Alverdy, O. Zaborina, G. An, et al. Agent-based dynamic knowledge representation of *Pseudomonas aeruginosa* virulence activation in the stressed gut: Towards characterizing host-pathogen interactions in gut-derived sepsis. *Theoretical Biology and Medical Modelling*, 8(1):33, 2011.

Abstract: Background There is a growing realization that alterations in host-pathogen interactions (HPI) can generate disease phenotypes without pathogen invasion. The gut represents a prime region where such HPI can arise and manifest. Under normal conditions intestinal microbial communities maintain a stable, mutually beneficial ecosystem. However, host stress can lead to changes in environmental conditions that shift the nature of the host-microbe dialogue, resulting in escalation of virulence expression, immune activation and ultimately systemic disease. Effective modulation of these dynamics requires the ability to characterize the complexity of the HPI, and dynamic computational modeling can aid in this task. Agent-based modeling is a computational method that is suited to representing spatially diverse, dynamical systems. We propose that dynamic knowledge representation of gut HPI with agent-based modeling will aid in the investigation of the pathogenesis of gut-derived sepsis. Methodology/Principal Findings An agent-based model (ABM) of virulence regulation in *Pseudomonas aeruginosa* was developed by translating bacterial and host cell sense-and-response mechanisms into behavioral rules for computational agents and integrated into a virtual environment representing the host-microbe interface in the gut. The resulting gut milieu ABM (GMABM) was used to: 1) investigate a potential clinically relevant laboratory experimental condition not yet developed - i.e. non-lethal transient segmental intestinal ischemia, 2) examine the sufficiency of existing hypotheses to explain experimental data - i.e. lethality in a model of major surgical insult and stress, and 3) produce behavior to potentially

guide future experimental design - i.e. suggested sample points for a potential laboratory model of non-lethal transient intestinal ischemia. Furthermore, hypotheses were generated to explain certain discrepancies between the behaviors of the GMABM and biological experiments, and new investigatory avenues proposed to test those hypotheses. Conclusions/Significance Agent-based modeling can account for the spatio-temporal dynamics of an HPI, and, even when carried out with a relatively high degree of abstraction, can be useful in the investigation of system-level consequences of putative mechanisms operating at the individual agent level. We suggest that an integrated and iterative heuristic relationship between computational modeling and more traditional laboratory and clinical investigations, with a focus on identifying useful and sufficient degrees of abstraction, will enhance the efficiency and translational productivity of biomedical research.

Keywords: multi-agent based simulation, multi-level, biology

[Seck:2009]

M.D. Seck. Towards multi-perspective modeling and simulation for complex systems. In *Proc. of Summer Computer Simulation Conf. (SCSC)*, 2010.

Abstract: This conceptual paper discusses the role of hierarchy in complex systems modeling and simulation and discusses the difficulty of subsuming a complex system into a model having a unique hierarchical decomposition. After elaborating on the potential of multiperspective modeling and simulation, a first formalization of multi-perspective models is proposed.

Keywords: multi-agent based simulation, multi-level, social simulation

[Seck:2012]

M.D. Seck and H.J. Honig. Multi-perspective modelling of complex phenomena. *Computational & Mathematical Organization Theory*, 18(1):128-144, 2012.

Abstract: This conceptual paper discusses the limitations of a single-perspective hierarchical approach to modelling and proposes multi-perspective modelling as a way to overcome them. As it turns out, multi-perspective modelling is primarily a new methodology, using existing modelling techniques but extending the modelling hierarchy with a new epistemological level which integrates the different perspectives. The methodology will be presented in some detail, and its use will be demonstrated by analyzing an example taken from a socio-political context.

Keywords: multi-agent based simulation, multi-level, meta-model

[Seekhao:2018]

N. Seekhao, C. Shung, J. JaJa, L. Mongeau, and N.Y.K. Li-Jessen. High-performance agent-based modeling applied to vocal fold inflammation and repair. *Frontiers in Physiology*, 9:304, 2018.

Abstract: Fast and accurate computational biology models offer the prospect of accelerating the development of personalized medicine. A tool capable of estimating treatment success can help prevent unnecessary and costly treatments and potential harmful side effects. A novel high-performance Agent-Based Model (ABM) was adopted to simulate and visualize multi-scale complex biological processes arising in vocal fold inflammation and repair. The computational scheme was designed to organize the 3D ABM sub-tasks to fully utilize the resources available on current heterogeneous platforms consisting of multi-core CPUs and many-core GPUs. Subtasks are further parallelized and convolution-based diffusion is used to enhance the performance of the ABM simulation. The scheme was implemented using a client-server protocol allowing the results of each iteration to be analyzed and visualized on the server (i.e., in-situ) while the simulation is running on the same server. The resulting simulation and visualization software enables users to interact with and steer the course of the simulation in real-time as needed. This high-resolution 3D ABM framework was used for a case study of surgical vocal fold injury and repair. The new framework is capable of completing the simulation, visualization and remote result delivery in under 7 s per iteration, where each iteration of the simulation represents 30 min in the real world. The case study model was simulated at the physiological scale of a human vocal fold. This simulation tracks 17 million biological cells as well as a total of 1.7 billion signaling chemical and structural protein data points. The visualization component processes and renders all simulated biological cells and 154 million signaling chemical data points. The proposed high-performance 3D ABM was verified through comparisons with empirical vocal fold data. Representative trends of biomarker predictions in surgically injured vocal folds were observed.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Seidl:2010]

R. Seidl, W. Rammer, R.M. Scheller, T.A. Spies, and M.J. Lexer. A mechanistic, individual-based approach to modeling complexity and dynamics of forest ecosystems across scales. *The 95th ESA Annual Meeting*, 2010.

Abstract: Forest ecosystem dynamics emerges from nonlinear interactions between adaptive biotic agents (i.e., individual trees) and their relationship with a spatially and temporally heterogeneous abiotic environment. Understanding and predicting the dynamics resulting from these complex interactions is crucial for the sustainable stewardship of ecosystems, particularly in the context of rapidly changing environmental conditions. Here we present iLand (the individual-based forest landscape and disturbance model), a novel approach to simulating forest dynamics as an emergent property of environmental drivers, ecosystem processes and dynamic interactions across scales. Our specific objectives were (i) to describe the model, in particular its novel approach to simulate spatially explicit individual-tree competition for resources over large scales within a process-based framework of physiological resource use, and (ii) to present a suite of evaluation experiments assessing iLands ability to simulate tree growth and mortality for a wide range of forest ecosystems. Adopting an approach rooted in ecological field theory, iLand calculates a continuous field of light availability over the landscape, with every tree represented by a mechanistically derived, size- and species-dependent pattern of light interference. Within a hierarchical multi-scale framework productivity is derived at stand-level by means of a light-use efficiency approach, and downscaled to individuals via local light availability. Allocation (based on allometric ratios) and mortality (resulting from carbon starvation) are modeled at the individual-tree level, accounting for adaptive behavior of trees in response to their environment. To evaluate the model we conducted simulations over the extended environmental gradient of a longitudinal transect in Oregon, USA, and successfully compared results against independently observed productivity estimates (63.4% of variation explained) and mortality patterns in even-aged stands. This transect experiment was furthermore replicated for a different set of species and ecosystems in the Austrian Alps, documenting the robustness and generality of our approach. Model performance was also successfully evaluated for structurally and compositionally complex old-growth forests in the western Cascades of Oregon. Finally, the ability of our approach to address forest ecosystem dynamics at landscape scales was demonstrated by a computational scaling experiment. In simulating the emergence of ecosystem patterns and dynamics as a result of complex process interactions across scales our approach has the potential to contribute crucial capacities to understanding and fostering forest ecosystem resilience under changing climatic conditions.

Keywords: multi-agent based simulation, multi-level, ecology

[Seidl:2012]

R. Seidl, W. Rammer, R.M. Scheller, and T.A. Spies. An individual-based process model to simulate landscape-scale forest ecosystem dynamics. *Ecological Modelling*, 231:87–100, 2012.

Abstract: Forest ecosystem dynamics emerges from nonlinear interactions between adaptive biotic agents (i.e., individual trees) and their relationship with a spatially and temporally heterogeneous abiotic environment. Understanding and predicting the dynamics resulting from these complex interactions is crucial for the sustainable stewardship of ecosystems, particularly in the context of rapidly changing environmental conditions. Here we present iLand (the individual-based forest landscape and disturbance model), a novel approach to simulating forest dynamics as an emergent property of environmental drivers, ecosystem processes and dynamic interactions across scales. Our specific objectives were (i) to describe the model, in particular its novel approach to simulate spatially explicit individual-tree competition for resources over large scales within a process-based framework of physiological resource use, and (ii) to present a suite of evaluation experiments assessing iLands ability to simulate tree growth and mortality for a wide range of forest ecosystems. Adopting an approach rooted in ecological field theory, iLand calculates a continuous field of light availability over the landscape, with every tree represented by a mechanistically derived, size- and species-dependent pattern of light interference. Within a hierarchical multi-scale framework productivity is derived at stand-level by means of a light-use efficiency approach, and downscaled to individuals via local light availability. Allocation (based on allometric ratios) and mortality (resulting from carbon starvation) are modeled at the individual-tree level, accounting for adaptive behavior of trees in response to their environment. To evaluate the model we conducted simulations over the extended environmental gradient of a longitudinal transect in Oregon, USA, and successfully compared results against independently observed productivity estimates (63.4% of variation explained) and mortality patterns in even-aged stands. This transect experiment was furthermore replicated for a different set of species and ecosystems in the Austrian Alps, documenting the robustness and generality of our approach. Model performance was also successfully evaluated for structurally and compositionally complex old-growth forests in the western Cascades of Oregon. Finally, the ability of our approach to address forest ecosystem dynamics at landscape scales was demonstrated by a computational scaling experiment. In simulating the emergence of ecosystem patterns and dynamics as a result of complex process interactions across scales our approach has the potential to contribute crucial capacities to understanding and fostering forest ecosystem resilience under changing climatic conditions.

Keywords: multi-agent based simulation, multi-level, ecology

[Semenchenko:2016] A. Semenchenko, G. Oliveira, and A.P.F. Atman. Hybrid agent-based model for quantitative in-silico cell-free protein synthesis. *Biosystems*, 150:22–34, 2016.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology

[Semeniuk:2011] C.A.D. Semeniuk, M. Musiani, and D.J. Marceau. *Biodiversity*, chapter Integrating Spatial Behavioral Ecology in Agent-Based Models for Species Conservation, pages 3–26. InTech, 2011.

Keywords: multi-agent based simulation, multi-level, ecology

[Senge:2012] S. Senge and H.F. Wedde. 2-way evaluation of the distributed BeeJamA vehicle routing approach. In *Proceedings of the IEEE Intelligent Vehicles Symposium*, pages 205–210, 2012.

Abstract: We present and evaluate our adaptive and distributed vehicle routing approach, termed BeeJamA, which provides drivers safely with routing directions well before each intersection. Our approach is based on a multi-agent system which is inspired by the honey bee behavior and relies on a V2I architecture. We report on our extensive simulation experiments verifying for very large systems that BeeJamA substantially outperforms all A*-based algorithms relying on global information systems, in particular under all degrees of penetration rates as well as considering reactive flexibility and easy scalability.

Keywords: multi-agent based simulation, multi-level, flow model

[Serban:2015] A. Serban, F.J. Yammarino, S.D. Dionne, S.S. Kahai, C. Hao, K.A. McHugh, K.L. Sotak, A.B.R. Mushore, T.L. Friedrich, and D.R. Peterson. Leadership emergence in face-to-face and virtual teams: A multi-level model with agent-based simulations, quasi-experimental and experimental tests. *The Leadership Quarterly*, 26(3):402–418, 2015.

Abstract: With leadership as a major predictor of team performance in both face-to-face and virtual teams, research on differences in leadership emergence in these contexts seems warranted. We offer a multi-level model analyzing the roles of degree of team virtuality and density of social network ties as boundary conditions on leadership emergence, viewed as a fundamentally social-cognitive process. Using agent-based modeling and simulations, our results suggest that virtuality moderates the relationships between cognitive ability, extraversion, and self-efficacy (as independent variables) and leadership emergence (as dependent variable); and density of network ties serves as a moderator for the associations of cognitive ability and self-efficacy with leadership emergence. Subsequent quasi-experimental and experimental tests support the role of density of network ties as a moderator for the association of extraversion with leadership emergence. Implications of these findings and future paths for research bridging the fields of leadership, team virtuality and social networks are discussed.

Keywords: multi-agent based simulation, multi-level, social simulation

[Servat:1998] D. Servat, E. Perrier, J-P. Treuil, and A. Drogoul. When agents emerge from agents: Introducing multi-scale viewpoints in multi-agent simulations. In *Multi-Agent Systems and Agent-Based Simulation*, volume 1534 of *LNCS*, pages 183–198. Springer, 1998.

Abstract: Current multi-agent simulations, which have many individual entities evolve and interact, often lead to the emergence of local groups of entities, but provide no means of manipulating them. To our mind, giving full a sense to multi-agent simulations would consist though in making use of such dynamically created potential groups, by granting them an existence of their own, and specific behaviours. Brought into operation, they would provide effective and new tools for modelling purposes : for instance, encapsulating physical laws which depend on scaling, thus giving means of apprehending micro-macro links in multi-agent simulations, or introducing the experimenter's viewpoints on the specific behaviours of such groups. We thus have to imagine how to give any set of agents means of becoming aware of their mutual interaction, and giving birth to new types of agents out of their collective activity. In other words we look for a computer equivalent to our own emergence recognition ability. We present here a conceptual reflexion on such matters in the light of our own experience in the development of the RIVAGE project at Orstom, which aims at simulating runoff and infiltration processes. Conversely, we believe that the development of our methods in such a novel and original field of research as the multi-agent simulation of pure physical processes will provide new ideas and tools useful for many multi-agent architectures and modelling purposes.

Keywords: multi-level, hydrology, multi-agent based simulation, flow model, emergence detection, dynamic level of detail, french team

[Servat:1998a]

D. Servat, E. Pierrer, JP. Treuil, and A. Drogoul. Towards virtual experiment laboratories : How multi-agent simulations can cope with multiple scales of analysis and viewpoints. In *Virtual Worlds*, volume 1434 of *LNCS*, pages 205–217. Springer, 1998.

Abstract: When studying complex phenomena, we face huge difficulties to conceive, understand, not to say handle the synthesis process which, from many interacting events, produces an emerging, recognizable, persistent and structurally stable, macroscopic event. Such a topical issue calls for specific tools, among which the development of multi-agent simulations has proved a promising approach. However, current multi-agent simulations provide no means of manipulating as a whole dynamically created groups of entities which emerge at different granularity levels. To our mind, giving full a sense to multi-agent simulations would consist though in making use of such potential groups, by granting them an existence of their own and specific behaviours, thus providing means of apprehending micro-macro links within simulations. We present here a conceptual reflexion on such an organization, in the light of our own experience in the development of the RIVAGE project at Orstom, which aims at simulating runoff and infiltration processes. We believe that the development of our methods in the field of physical processes will provide new ideas and tools useful for many multi-agent architectures and modelling purposes, so as to give shape to the concept of virtual experiment laboratories.

Keywords: multi-agent based simulation, multi-level, emergence detection, methodology, hydrology, french team

[Servat:1999]

D. Servat, J. Leonard, E. Perrier, and J-P. Treuil. The rivage-project: a new approach for simulating runoff dynamics. In *Workshop of EurAgEng's Field of Interest on Soil and Water*, pages 592–601, 1999.

Abstract: The RIVAGE project is an ongoing methodological research whose long term objective aims at coupling runoff dynamics, infiltration and erosion, so as to integrate heterogeneous events occurring at different time and space scales. Our work involves a distributed particle-based hydrological modelling which lies in between deterministic laws of surface water routing and more complex physically-based hydrodynamics models. In this paper we present a thorough description of the overland flow model, followed by some early results of test-case simulations: preliminary tests involving runoff on an inclined plane and an application to a small topographic plot. In this latter case, we give elements of comparison with an available two-dimensional shallow water equation model.

Keywords: multi-level, multi-agent based simulation, hydrology, french team

[Servat:2000]

D. Servat. *Modélisation de dynamiques de flux par agents. Application aux processus de ruissellement, infiltration et érosion*. PhD thesis, Université Paris VI, November 2000.

Abstract: L'étude de dynamiques de flux est une question centrale dans la modélisation des milieux naturels, physiques et sociaux. Ce travail de these expose une recherche methodologique et pratique sur la modélisation informatique de telles dynamiques a l'aide de systemes multi-agents. L'idée centrale consiste a decrir de tels processus en termes d'agents heterogenes interagissant dans un espace continu, l'introduction de couplages entre differents processus s'interpretant comme l'identification de regles d'interaction entre ces agents. En dotant les agents de moyens de reconnaissance de situations d'interaction remarquables, des mecanismes generiques ont ete mis au point d'agentification des modes d'organisation qui emergent en cours de simulation. Ces idees se sont concretisees dans une thematique particuliere d'etude de dynamiques de flux : les processus de ruissellement, d'infiltration et d'erosion en hydrologie, a travers la construction du simulateur rivage. Ce travail dans le domaine de l'hydrologie montre que le choix d'une description particuliere pour la dynamique de circulation de l'eau, sous la forme d'entites en mouvement dans un espace continu, presente certaines qualites : possibilite de conduire des analyses de trajectoires individuelles, souplesse de gestion de conditions aux limites complexes, ouverture a la prise en compte de differents situations de couplages entre processus, prise en compte de differents niveaux d'agregation de ces dynamiques. Des pistes de transposition a d'autres thematiques ont pu etre identifiees, notamment la modélisation de dynamiques de foules et la representation spatiale et hierarchique de flux d'information. Enfin, ce travail a montre que les systemes multi-agents, en federant approches particulieres et individus-centrees, constituent dans ce cadre un outil de fond tout a fait interessant. En mettant en avant un certain nombre de concepts cles, comme interaction, groupe et organisation, les systemes multi-agents proposent un cadre de conception sur lequel peut s'appuyer la construction de modeles informatiques qui deviennent des outils d'analyse et d'interpretation de systemes complexes.

Keywords: multi-agent based simulation, multi-level, flow model, emergence detection, hydrology, in french, french team

[Sewall:2011]

J. Sewall, D. Wilkie, and M.C. Lin. Interactive hybrid simulation of large-scale traffic. *ACM Transaction on Graphics (Proc. of SIGGRAPH Asia)*, 30(6), 2011.

Abstract: We present a novel, real-time algorithm for modeling large-scale, realistic traffic using a hybrid model of both continuum and agent-based methods for traffic simulation. We simulate individual vehicles in regions of interest using state-of-the-art agent-based models of driver behavior, and use a faster continuum model of traffic flow in the remainder of the road network. Our key contributions are efficient techniques for the dynamic coupling of discrete vehicle simulation with the aggregated behavior of continuum techniques for traffic simulation. We demonstrate the flexibility and scalability of our interactive visual simulation technique on extensive road networks using both real-world traffic data and synthetic scenarios. These techniques demonstrate the applicability of hybrid techniques to the efficient simulation of large-scale flows with complex dynamics.

Keywords: multi-agent based simulation, traffic, hybrid model, multi-level

[Sharpanskykh:2011]

A. Sharpanskykh and J. Treur. Group abstraction for large-scale agent-based social diffusion models. In *International conference on Privacy, security, risk and trust and international conference on social computing*, pages 830–837. IEEE, 2011.

Abstract: In this paper an approach is proposed to handle complex dynamics of large-scale multi-agents systems modelling social diffusion processes. Based on local properties of the individual agents and their connections, groups and dynamic properties of these groups are identified. To determine such dynamic group properties two abstraction methods are proposed: determining a group invariant and approximation of group processes by weighted averaging of interactions. This enables simulation of the multi-agent system at a more abstract level by considering groups as single entities substituting a large number of interacting agents. In this way the scalability of large-scale simulation can be improved significantly. Computational properties of the developed approach are addressed in the paper. The approach is illustrated for a collective decision making model.

Keywords: multi-agent based simulation, multi-level

[Shimoni:2011]

Y. Shimoni, G. Nudelman, F. Hayot, and S.C. Sealfon. Multi-scale stochastic simulation of diffusion-coupled agents and its application to cell culture simulation. *PLoS one*, 6(12):e29298, 2011.

Abstract: Many biological systems consist of multiple cells that interact by secretion and binding of diffusing molecules, thus coordinating responses across cells. Techniques for simulating systems coupling extracellular and intracellular processes are very limited. Here we present an efficient method to stochastically simulate diffusion processes, which at the same time allows synchronization between internal and external cellular conditions through a modification of Gillespie's chemical reaction algorithm. Individual cells are simulated as independent agents, and each cell accurately reacts to changes in its local environment affected by diffusing molecules. Such a simulation provides time-scale separation between the intra-cellular and extra-cellular processes. We use our methodology to study how human monocyte-derived dendritic cells alert neighboring cells about viral infection using diffusing interferon molecules. A subpopulation of the infected cells reacts early to the infection and secretes interferon into the extra-cellular medium, which helps activate other cells. Findings predicted by our simulation and confirmed by experimental results suggest that the early activation is largely independent of the fraction of infected cells and is thus both sensitive and robust. The concordance with the experimental results supports the value of our method for overcoming the challenges of accurately simulating multiscale biological signaling systems.

Keywords: multi-agent based simulation, multi-level, biology

[Shirazi:2013]

A.S. Shirazi. *Abstraction Mechanisms Towards Large-Scale Agent-Based Simulations*. PhD thesis, University of Calgary, 2013.

Abstract: The typically large degrees of interaction in agent-based simulations come at considerable computational costs. In this thesis, we propose an abstraction framework to reduce the run-time of the simulations by learning recurring patterns. We employ machine learning techniques to abstract groups of agents or their behaviours to cut down computational complexity, while preserving the inherent flexibility of agent-based models. The learned abstractions, which

subsume the underlying model agents' interactions, are constantly tested for their validity—after all, the dynamics of a system may change over time to such an extent that previously learned patterns would not reoccur. An invalid abstraction is, therefore, removed from the simulation. The creation and removal of abstractions continues throughout the course of a simulation in order to ensure an adequate adaptation to the system dynamics. Experimental results on biological agent-based simulations show that our proposed framework can successfully boost the simulation speed while maintaining the freedom of arbitrary interactions.

Keywords: multi-agent based simulation, multi-level, biology

[Shirazi:2013a]

A.S. Shirazi, S. Von Mammen, and C. Jacob. Abstraction of agent interaction processes: Towards large-scale multi-agent models. *Simulation*, 89(4):524–538, 2013.

Abstract: The typically large numbers of interactions in agent-based simulations come at considerable computational costs. In this article, we present an approach to reduce the number of interactions based on behavioural patterns that recur during runtime. We employ machine learning techniques to abstract the behaviour of groups of agents to cut down computational complexity while preserving the inherent flexibility of agent-based models. The learned abstractions, which subsume the underlying model agents' interactions, are constantly tested for their validity: after all, the dynamics of a system may change over time to such an extent that previously learned patterns would not reoccur. An invalid abstraction is, therefore, removed again from the system. The creation and removal of abstractions continues throughout the course of a simulation in order to ensure an adequate adaptation to the system dynamics. Experimental results on biological agent-based simulations show that our proposed approach can successfully reduce the computational complexity during the simulation while maintaining the freedom of arbitrary interactions.

Keywords: multi-agent based simulation, multi-level, biology

[Shirazi:2014]

A.S. Shirazi, T. Davison, S. Von Mammen, J. Denzinger, and C. Jacob. Adaptive agent abstractions to speed up spatial agent-based simulations. *Simulation Modelling Practice and Theory*, 40:144–160, 2014.

Abstract: Simulating fine-grained agent-based models requires extensive computational resources. In this article, we present an approach that reduces the number of agents by adaptively abstracting groups of spatial agents into meta-agents that subsume individual behaviours and physical forms. Particularly, groups of agents that have been clustering together for a sufficiently long period of time are detected by observer agents and then abstracted into a single meta-agent. Observers periodically test meta-agents to ensure their validity, as the dynamics of the simulation may change to a point where the individual agents do not form a cluster any more. An invalid meta-agent is removed from the simulation and subsequently, its subsumed individual agents will be put back in the simulation. The same mechanism can be applied on meta-agents thus creating adaptive abstraction hierarchies during the course of a simulation. Experimental results on the simulation of the blood coagulation process show that the proposed abstraction mechanism results in the same system behaviour while speeding up the simulation.

Keywords: multi-agent based simulation, multi-level, biology

[Shokhirev:2015]

M.N. Shokhirev, J. Almaden, J. Davis-Turak, H.A. Birnbaum, T.M. Russell, J.A.D. Vargas, and A. Hoffmann. A multi-scale approach reveals that $\text{nf-}\kappa\text{b}$ crel enforces a b-cell decision to divide. *Molecular systems biology*, 11(2):783, 2015.

Abstract: Understanding the functions of multi-cellular organs in terms of the molecular networks within each cell is an important step in the quest to predict phenotype from genotype. B-lymphocyte population dynamics, which are predictive of immune response and vaccine effectiveness, are determined by individual cells undergoing division or death seemingly stochastically. Based on tracking single-cell time-lapse trajectories of hundreds of B cells, single-cell transcriptome, and immunofluorescence analyses, we constructed an agent-based multi-modular computational model to simulate lymphocyte population dynamics in terms of the molecular networks that control $\text{NF-}\kappa\text{B}$ signaling, the cell cycle, and apoptosis. Combining modeling and experimentation, we found that $\text{NF-}\kappa\text{B}$ cRel enforces the execution of a cellular decision between mutually exclusive fates by promoting survival in growing cells. But as cRel deficiency causes growing B cells to die at similar rates to non-growing cells, our analysis reveals that the phenomenological decision model of wild-type cells is rooted in a biased race of cell fates. We show that a multi-scale modeling approach allows for the prediction of dynamic organ-level physiology in terms of intra-cellular molecular networks.

Keywords: multi-agent based simulation, multi-level, biology

[Siettos:2016]

C.I. Siettos, C. Anastassopoulou, L. Russo, Christos Grigoras, E. Mylonakis, T. Simos, and C. Tsitouras. Estimation of the age-specific per-contact probability of ebola virus transmission in liberia using agent-based simulations. In *AIP Conference Proceedings*, volume 1738, page 150004, 2016.

Abstract: Based on multiscale agent-based computations we estimated the per-contact probability of transmission by age of the Ebola virus disease (EVD) that swept through Liberia from May 2014 to March 2015. For the approximation of the epidemic dynamics we have developed a detailed agent-based model with small-world interactions between individuals categorized by age. For the estimation of the structure of the evolving contact network as well as the per-contact transmission probabilities by age group we exploited the so called Equation-Free framework. Model parameters were fitted to official case counts reported by the World Health Organization (WHO) as well as to recently published data of key epidemiological variables, such as the mean time to death, recovery and the case fatality rate.

Keywords: multi-agent based simulation, multi-level, multi-scale, epidemiology

[Silva:2010]

V. Silva. *Conception et évaluation d'un prototype de simulation de la morphogenèse urbaine par agents vecteurs multi-échelles*. PhD thesis, EPFL, 2010.

Abstract: The research work of this PhD thesis was carried out in the context of an interdisciplinary project related to the study of urban morphogenesis. A team composed of architects and engineers specialized in GIS technologies have worked together in this project during three years, sharing their knowledge in order to understand and simulate the evolution of the urban environment of cities. The fundamental hypothesis that conducted this research is that the city can be seen as a self-organizing system governed by a set of morphogenesis rules, which can for example, determine the location of new architectural programs and induce the city's organization, from local to global scales. Architectural programs themselves are supposed to determine city's development. In this PhD thesis a simulation prototype of the urban growth based on the use of multi-agents systems was carried out. This prototype is a computer tool that allows the analysis and representation of the growth of the built environment. Nowadays, the ability to understand and simulate urban evolution proves to be essential in order to control the evolution of a city in a sustainable development view. Furthermore, this tool should facilitate the understanding and decision-making of those concerned with problems related to urban development. The urban system has been modeled as a set of space objects, such as buildings and networks, which interact between themselves. These interactions are carried out at different levels, from local to global scales, being controlled by behavioral rules or laws of growth. The result of their interaction can be figures or emergent phenomena represented at several scales. The approach using multi-agents vector systems was chosen in order to model a geographical complex system like a city, which integrates a vectorial modeling of space. Hence, each spatial agent does not possess a limit of form and size. The interest of using multi-agents vector systems also lies in their ability to manage various models of individuals, from simple entities to more complex ones. Thus, various levels of representation, such as individuals and groups of individuals, can be managed, which is not easily feasible, for example, with cellular agents. The development platform used is GeOxygene (Java computer programming language), which is an open-source platform developed at IGN (Institut Géographique National, France), by COGIT laboratory. This platform provides several GIS functions, allowing the development and implementation of the prototype here presented. An interaction model between agents was defined and the type of scenarios of each of these interactions was detailed. A set of methods and associated classes was developed. Agent's architecture was conceived in order to allow manipulation (sending, receiving and treatment) of exchanged messages. In order to show the relevance of the multi-agent multi-scale methodology, examples of buildings creation in a case study zone were carried out. Using the multi-scale vector simulation prototype here presented, the development of cities can be computed in a very innovative way. However, the developed prototype still lacks some accuracy, mostly due to the fact that the specified laws adopted for simulation do not reflect the whole reality, which is obviously much more complex to traduce. We have not yet validated the model for other cities – nevertheless, the model could already be used as a decision support tool, particularly as a planning support instrument for architects and urban planners. With regards to future work this prototype shall be integrated in a global approach of urban simulation, allowing the analysis of environmental risks, demographic and economic growth and transports simulation at different scales of analysis and 2D/3D visualization output, such as district and city.

Keywords: multi-agent based simulation, multi-level, multi-scale, social simulation

[Smallwood:2006] R. Smallwood and M. Holcombe. The epitheliome project: multiscale agent-based modeling of epithelial cells. In *Biomedical Imaging: Nano to Macro, 2006. 3rd IEEE International Symposium on*, pages 816–819. IEEE, 2006.

Abstract: The aim of the Epitheliome Project is to develop a computational model of cell behaviour within the context of tissue architecture, differentiation, wound repair and malignancy. Integration is central to tissue development for skin, integration between mesenchymal and epithelial tissue; at the physical level from focal adhesions and adherens junctions to cytoskeleton to whole tissue; at the signaling level from control of gene expression through to development of gradients controlling histodifferentiation; and integration in the sense of the development of tissues as an emergent property of cell behaviour. An individual-based model of the cell is used, and tissue development is thus a result of the interaction of individual cells. The limit of a large number of individual cells is a continuum model of tissue, and individual cells can contain continuum or differential equation models of cellular mechanisms. The hierarchical modeling paradigm is described

Keywords: multi-agent based simulation, multi-level, biology

[Smallwood:2010] R. Smallwood, S. Adra, and G. Khodabakshi. Multiscale, multi-paradigm modelling of tissues: embedding development in tissue behaviour. http://www.dcs.shef.ac.uk/~rod/integrative_biology/Smallwood_Cellular_dynamics_and_tissue_behaviour.pdf, 2010.

Abstract: The term 'Development', as usually used in biology, relates to the embryonic changes from the fertilisation of the egg up to the fully formed embryo. However, development continues throughout the life of the organism, as a result of growth from birth to the adult state, cell turnover, the response to insult and injury, and the effects of neurodegeneration, diabetes, cancer and ageing. We are concerned here with development in this broader sense. Computational modelling of physiology, as exemplified in the Physiome and Virtual Physiological Human Projects, currently provides a snapshot of a particular (usually adult) stage in the organism's development, and developmental changes are excluded. Current models are therefore unable to provide any information on how the organism reached its current (normal or aberrant) state, and how the current state will change during the life of the organism. Development is a cellular-level function, an emergent property of cellular interaction, and the majority of computational models of physiology do not explicitly include either individual cells, or the cellular processes of growth, division, differentiation and death. We initially discuss what is required of an individual cell model for it to be useful in studying development; provide examples of its use in the exploration of the growth and wound response of epithelial tissues; and then consider how individual cell models could be incorporated into existing continuum models, and themselves include molecular level models, in order to produce multiscale, multi-paradigm models of organismal development.

2 Introduction The Physiome Project is 'a worldwide public domain effort to provide a computational framework for understanding human and other eukaryotic physiology. 1 It aims to develop integrative models at all levels of biological organisation, from genes to the whole organism via gene regulatory networks, protein pathways, integrative cell function, and tissue and whole organ structure/function relations' (<http://www.physiome.org.nz/>). The challenges, which include the range of length and timescales, are eloquently described by Bassingthwaite [3]. What might be termed vertical integration – from molecular length scale to the organ or organism level – has been extensively discussed (e.g. see Hunter et al [21] for a cardiac modelling example), but horizontal integration – the change in the organism as the result of the passage of time – is almost unexplored territory. We will discuss here an approach to the modelling of developmental changes in the progression from birth to death, based on the assertion that cellular behaviour is central to an understanding of development. We will make use of the modelling paradigm in the Epitheliome Project, and the application of the modelling paradigm to epithelial tissues [37, 41, 42, 40, 47, 48, 46, 45]. This paper will concentrate on three particular aspects of the problem: developing an individual-based model of the cell; linking the individual-based cell model to sub-cellular models developed using other modelling paradigms (the incorporation of CellML and SBML models as function calls); and linking cell-level and tissue level physical models; and will discuss how these can introduce the concept of development into Physiome modelling. We will not discuss the next (essential) stage – the integration of the regulation of gene expression, which in itself is a multiscale problem [31, 32].

Keywords: multi-agent based simulation, multi-level, biology

[Smith:2014] A.K. Smith, G.E.P. Ropella, N. Kaplowitz, M. Ookhtens, and C.A. Hunt. Mechanistic agent-based damage and repair models as hypotheses for patterns of necrosis caused by drug induced liver injury. In *Proc. of the 2014 Summer Simulation Conf. (SummerSim)*, 2014.

Abstract: Increasing model reuse and facilitating repurposing is expected to expand simulation use for better understanding biological phenomena. We demonstrate doing so in the context of liver diseases caused by toxic exposure to xenobiotics. A clinical goal is improved mechanistic explanations of how damage is generated, which can lead to new strategies to block and/or reverse injury. A goal for this work is to provide concrete, plausible explanations for acetaminophen induced liver injury (AILI) in mice. We instantiate mechanistic hypotheses that map to cellular damage and repair pathways and begin identifying plausible simulated causal cascades capable of generating the characteristic AILI spatial and temporal patterns. We use discrete event simulation of agent-based, multiscale, biomimetic models and Monte Carlo sampling. We use an Iterative Refinement protocol for implementing and validating/falsifying mechanistic hypotheses on a previously validated In Silico Liver. We simulated an observed necrosis pattern. Further approach improvement will yield new methods that combine iterations of in-silico and wet-lab experiments.

Keywords: multi-agent based simulation, multi-level, biology

[Solovyev:2010]

A. Solovyev, M. Mikheev, L. Zhou, J. Dutta-Moscato, C. Ziraldo, G. An, Y. Vodovotz, and Q. Mi. SPARK: A framework for multi-scale agent-based biomedical modeling. *International Journal of Agent Technologies and Systems*, 2(3):18–30, 2010.

Abstract: Multi-scale modeling of complex biological systems remains a central challenge in the systems biology community. A method of dynamic knowledge representation known as agent-based modeling enables the study of higher level behavior emerging from discrete events performed by individual components. With the advancement of computer technology, agent-based modeling has emerged as an innovative technique to model the complexities of systems biology. In this work, the authors describe SPARK (Simple Platform for Agent-based Representation of Knowledge), a framework for agent-based modeling specifically designed for systems-level biomedical model development. SPARK is a stand-alone application written in Java. It provides a user-friendly interface, and a simple programming language for developing Agent-Based Models (ABMs). SPARK has the following features specialized for modeling biomedical systems: 1) continuous space that can simulate real physical space; 2) flexible agent size and shape that can represent the relative proportions of various cell types; 3) multiple spaces that can concurrently simulate and visualize multiple scales in biomedical models; 4) a convenient graphical user interface. Existing ABMs of diabetic foot ulcers and acute inflammation were implemented in SPARK. Models of identical complexity were run in both NetLogo and SPARK; the SPARK-based models ran two to three times faster.

Keywords: multi-level, multi-agent based simulation, biology, meta-model

[Solovyev:2013]

A. Solovyev, Q. Mi, Y-T. Tzen, D. Brienza, and Y. Vodovotz. Hybrid equation/agent-based model of ischemia-induced hyperemia and pressure ulcer formation predicts greater propensity to ulcerate in subjects with spinal cord injury. *PLoS computational biology*, 9(5):e1003070, 2013.

Abstract: Pressure ulcers are costly and life-threatening complications for people with spinal cord injury (SCI). People with SCI also exhibit differential blood flow properties in non-ulcerated skin. We hypothesized that a computer simulation of the pressure ulcer formation process, informed by data regarding skin blood flow and reactive hyperemia in response to pressure, could provide insights into the pathogenesis and effective treatment of post-SCI pressure ulcers. Agent-Based Models (ABM) are useful in settings such as pressure ulcers, in which spatial realism is important. Ordinary Differential Equation-based (ODE) models are useful when modeling physiological phenomena such as reactive hyperemia. Accordingly, we constructed a hybrid model that combines ODEs related to blood flow along with an ABM of skin injury, inflammation, and ulcer formation. The relationship between pressure and the course of ulcer formation, as well as several other important characteristic patterns of pressure ulcer formation, was demonstrated in this model. The ODE portion of this model was calibrated to data related to blood flow following experimental pressure responses in non-injured human subjects or to data from people with SCI. This model predicted a higher propensity to form ulcers in response to pressure in people with SCI vs. non-injured control subjects, and thus may serve as novel diagnostic platform for post-SCI ulcer formation.

Keywords: multi-agent based simulation, multi-level, hybrid model, biology

[Somogyi:2016]

E. Somogyi and J.A. Glazier J.P. Sluka. Formalizing knowledge in multi-scale agent-based simulations. In *Proc. of ACM/IEEE 19th Int. Conf. on Model Driven Engineering Languages and Systems*, 2016.

Abstract: Multi-scale, agent-based simulations of cellular and tissue biology are increasingly common. These simulations combine and integrate a range of components from different domains. Simulations continuously create, destroy and reorganize constituent elements causing their interactions to dynamically change. For example, the multi-cellular tissue development process coordinates molecular, cellular and tissue scale objects with biochemical, biomechanical, spatial and behavioral processes to form a dynamic network. Different domain specific languages can describe these components in isolation, but cannot describe their interactions. No current programming language is designed to represent in human readable and reusable form the domain specific knowledge contained in these components and interactions. We present a new hybrid programming language paradigm that naturally expresses the complex multi-scale objects and dynamic interactions in a unified way and allows domain knowledge to be captured, searched, formalized, extracted and reused.

Keywords: multi-agent based simulation, multi-level, biology

[Somogyi:2016a]

E. Somogyi, A. Hagar, and J.A. Glazier. Towards a multi-scale agent-based programming language methodology. In *Proc. of the Winter Simulation Conf. (WSC)*, pages 1230–1240, 2016.

Abstract: Living tissues are dynamic, heterogeneous compositions of objects, including molecules, cells and extra-cellular materials, which interact via chemical, mechanical and electrical process and reorganize via transformation, birth, death and migration processes. Current programming language have difficulty describing the dynamics of tissues because: 1: Dynamic sets of objects participate simultaneously in multiple processes, 2: Processes may be either continuous or discrete, and their activity may be conditional, 3: Objects and processes form complex, heterogeneous relationships and structures, 4: Objects and processes may be hierarchically composed, 5: Processes may create, destroy and transform objects and processes. Some modeling languages support these concepts, but most cannot translate models into executable simulations. We present a new hybrid executable modeling language paradigm, the Continuous Concurrent Object Process Methodology (CCOPM) which naturally expresses tissue models, enabling users to visually create agent-based models of tissues, and also allows computer simulation of these models.

Keywords: multi-agent based simulation, multi-level, biology

[Soyez:2011]

J-B. Soyez, G. Morvan, R. Merzouki, D. Dupont, and P. Kubiak. Multi-agent multi-level modeling – a methodology to simulate complex systems. In *Proceedings of the 23rd European Modeling & Simulation Symposium*, 2011.

Abstract: This article deals with the conception, modeling and simulation of complex systems, represented at different levels of analysis with respect to the agent-based modeling (ABM) paradigm and more precisely on the generic meta-model IRM4MLS. A methodology, using IRM4MLS, is proposed to save computational resources in multi-level agent-based simulations, representing only the relevant elements. It means that the structure of agents can be modified during simulation, by temporarily aggregating, removing or approximating their characteristics to maximize their life-cycles.

Keywords: multi-level, multi-agent based simulation, meta-model, dynamic level of detail, french team

[Soyez:2011a]

J-B. Soyez, G. Morvan, R. Merzouki, and D. Dupont. Modélisation multi-agents multi-niveaux de systèmes complexes. In *4ème Workshop du Groupement d'Intérêt Scientifique Surveillance, Sécurité, Sécurité des Grands Systèmes*, Valenciennes, 12-13 octobre 2011.

Keywords: multi-agent based simulation, multi-level, meta-model, dynamic level of detail, in french, french team

[Soyez:2013]

J-B. Soyez, G. Morvan, D. Dupont, and R. Merzouki. A methodology to engineer and validate dynamic multi-level multi-agent based simulations. In *Multi-Agent-Based Simulation XIII*, volume 7838 of *LNCS*, pages 130–142. Springer, 2013.

Abstract: This article proposes a methodology to model and simulate complex systems, based on IRM4MLS, a generic agent-based meta-model able to deal with multi-level systems. This methodology permits the engineering of dynamic multi-level agent-based models, to represent complex systems over several scales and domains of interest. Its goal is to simulate a phenomenon using dynamically the lightest representation to save computer resources without loss of information. This methodology is based on two mechanisms: (1) the activation or deactivation of agents representing different domain parts of the same phenomenon and (2) the aggregation or disaggregation of agents representing the same phenomenon at different scales.

Keywords: multi-level, multi-agent based simulation, methodology

[Soyez:2013a]

J-B. Soyez, G. Morvan, D. Dupont, and R. Merzouki. General formalism and algorithms to insure SoS feasibility. In *MASyCo'2013 : Modélisation Agents pour les Systèmes Complexes*, 2013.

Keywords: multi-agent based simulation, multi-level, SoS, meta-model, french team

[Soyez:2013b]

J-B. Soyez. *Conception et modélisation de systèmes de systèmes : une approche multi-agents multi-niveaux*. PhD thesis, Université de Lille 1, 2013.

Abstract: La problématique générale de cette thèse, qui s'inscrit dans le contexte du projet européen InTraDE (Intelligent Transportation for Dynamic Environment), concerne la modélisation de systèmes de systèmes (SdS). Un SdS est un système composé d'une hiérarchie de systèmes autonomes présents à différents niveaux de représentation. Cette thèse répond au besoin d'outils de modélisation généralistes respectant les caractéristiques fondamentales des SdS, en proposant un formalisme multi-agents multi-niveaux et les algorithmes qui assurent le respect de ces caractéristiques. L'utilisation d'un modèle multi-agents permet de profiter de l'autonomie naturelle des agents et l'aspect multi-niveaux de notre modèle permet aux entités modélisées de raisonner à propos de l'organisation hiérarchique du système en leur offrant la notion explicite de niveau. En plus de la modélisation des systèmes complexes, cette thèse aborde les problématique liées à leur simulation, en particulier, le fait que les ressources informatiques (mémoire et microprocesseur utilisés) nécessaires pour simuler avec précision de tels systèmes sont particulièrement importantes. Nous proposons ainsi une méthodologie pour tirer partie de la capacité des simulations multi-niveaux à produire un compromis entre la précision de la simulation et les ressources informatiques utilisées.

Keywords: multi-agent based simulation, multi-level, in french, french team

[Soyez:2017]

J-B. Soyez, G. Morvan, R. Merzouki, and D. Dupont. Multilevel agent-based modeling of system of systems. *IEEE Systems Journal*, 11(4):2084–2095, 2017.

Abstract: This paper deals with the generic modeling of systems of systems (SoSs) using agent-based modeling. SoSs are large-scale systems, including numerous-possibly heterogeneous-interacting component systems evolving in a dynamic environment. The aim of this paper is to provide generic formalism allowing to represent and control the whole complexity of a SoS using agent-based simulations. In particular, organizational aspects of SoSs are managed with the Agent-Group-Role model. Functional aspects, guiding SoSs to accomplish their global goals, are handled via a functional specification. Multilevel aspects are modeled with the Influence Reaction Model for Multilevel Simulation (IRM4MLS) agent-based meta-model. Models generated using this formalism encompass static and dynamic aspects of SoSs. They consider reorganization of SoSs caused by changes of goals or subsystem capacity. All these elements are illustrated in this paper using a SoS case study of Intelligent Autonomous Vehicles initiated by the Intelligent Transportation for Dynamic Environment (InTraDE) European project to automate the port container logistic.

Keywords: multi-agent based simulation, multi-level, SoS, port logistics

[Steiniger:2012]

A. Steiniger, F. Kruger, and A.M. Uhrmacher. Modeling agents and their environment in multi-level-DEVS. In *Proc. of the Winter Simulation Conference*, pages 1–12. IEEE, 2012.

Abstract: Environments play an important role in multi-agent systems. They present the context agents operate in. When testing multi-agent systems by simulation, the environment and partly agents have to be modeled. We explore the potential of Multi-Level-DEVS to serve as a modeling formalism for agents, their environment, and the interaction between them. Multi-Level-DEVS combines a modular, hierarchical modeling with variable structures, dynamic interfaces, and explicit means for describing up- and downward causation between different levels of the compositional hierarchy. The modeling in Multi-Level-DEVS emphasizes the role of the environment to provide information for and enforce constraints on the situated agents. A smart meeting room scenario is modeled, and an approach aimed at recognizing user activities in smart environments is tested and evaluated in a simulation study.

Keywords: multi-agent based simulation, multi-level, meta-model

[Stieglmeyer:2013]

S.M. Stieglmeyer and M.C. Giddings. Agent-based modeling of competence phenotype switching in *Bacillus subtilis*. *Theoretical Biology and Medical Modelling*, 10(1):23, 2013.

Abstract: Background It is a fascinating phenomenon that in genetically identical bacteria populations of *Bacillus subtilis*, a distinct DNA uptake phenotype called the competence phenotype may emerge in 10–20% of the population. Many aspects of the phenomenon are believed to be due to the variable expression of critical genes: a stochastic occurrence termed “noise” which has made the phenomenon difficult to examine directly by lab experimentation. Methods To capture and model noise in this system and further understand the emergence of competence both at the intracellular and culture levels in *B. subtilis*, we developed a novel multi-scale, agent-based model. At the intracellular level, our model recreates the regulatory network involved in the competence phenotype. At the culture level, we simulated growth conditions, with our multi-scale model providing feedback between the two levels. Results Our model predicted three potential sources of genetic “noise”. First, the random spatial arrangement of molecules may influence the manifestation of the competence phenotype. In addition, the evidence suggests that there may be a type of epigenetic heritability to the emergence of competence, influenced by the molecular concentrations of key competence molecules inherited through cell division. Finally, the emergence of competence during the stationary phase may in part be due to the dilution effect of cell division upon protein concentrations. Conclusions The competence phenotype was easily translated into an agent-based model – one with the ability to illuminate complex cell behavior. Models such as the one described in this paper can simulate cell behavior that is otherwise unobservable in vivo, highlighting their potential usefulness as research tools.

Keywords: multi-agent based simulation, multi-level, biology

[Su:2014]

J. Su, L. Zhang, W. Zhang, D.S. Choi, J. Wen, B. Jiang, C-C. Chang, and X. Zhou. Targeting the biophysical properties of the myeloma initiating cell niches: A pharmaceutical synergism analysis using multi-scale agent-based modeling. *PLoS one*, 9(1):e85059, 2014.

Abstract: Multiple myeloma, the second most common hematological cancer, is currently incurable due to refractory disease relapse and development of multiple drug resistance. We and others recently established the biophysical model that myeloma initiating (stem) cells (MICs) trigger the stiffening of their niches via SDF-1/CXCR4 paracrine; The stiffened niches then promote the colonogenesis of MICs and protect them from drug treatment. In this work we examined in silico the pharmaceutical potential of targeting MIC niche stiffness to facilitate cytotoxic chemotherapies. We first established a multi-scale agent-based model using the Markov Chain Monte Carlo approach to recapitulate the niche stiffness centric, pro-oncogenic positive feedback loop between MICs and myeloma-associated bone marrow stromal cells (MBMSCs), and investigated the effects of such intercellular chemo-physical communications on myeloma development. Then we used AMD3100 (to interrupt the interactions between MICs and their stroma) and Bortezomib (a recently developed novel therapeutic agent) as representative drugs to examine if the biophysical properties of myeloma niches are drugable. Results showed that our model recaptured the key experimental observation that the MBMSCs were more sensitive to SDF-1 secreted by MICs, and provided stiffer niches for these initiating cells and promoted their proliferation and drug resistance. Drug synergism analysis suggested that AMD3100 treatment undermined the capability of MICs to modulate the bone marrow microenvironment, and thus re-sensitized myeloma to Bortezomib treatments. This work is also the first attempt to virtually visualize in 3D the dynamics of the bone marrow stiffness during myeloma development. In summary, we established a multi-scale model to facilitate the translation of the niche-stiffness centric myeloma model as well as experimental observations to possible clinical applications. We concluded that targeting the biophysical properties of stem cell niches is of high clinical potential since it may re-sensitize tumor initiating cells to chemotherapies and reduce risks of cancer relapse.

Keywords: multi-agent based simulation, multi-level, multi-scale, cancer modeling

[Sun:2009]

T. Sun, S. Adra, R. Smallwood, M. Holcombe, and S. MacNeil. Exploring hypotheses of the actions of $\text{tgf-}\beta 1$ in epidermal wound healing using a 3d computational multiscale model of the human epidermis. *PLoS one*, 4(12):e8515, 2009.

Abstract: In vivo and in vitro studies give a paradoxical picture of the actions of the key regulatory factor $\text{TGF-}\beta 1$ in epidermal wound healing with it stimulating migration of keratinocytes but also inhibiting their proliferation. To try to reconcile these into an easily visualized 3D model of wound healing amenable for experimentation by cell biologists, a multiscale model of the formation of a 3D skin epithelium was established with $\text{TGF-}\beta 1$ literature-derived rule sets and equations embedded within it. At the cellular level, an agent-based bottom-up model that focuses on individual interacting units (keratinocytes) was used. This was based on literature-derived rules governing keratinocyte behavior and keratinocyte/ECM interactions. The selection of these rule

sets is described in detail in this paper. The agent-based model was then linked with a subcellular model of TGF- β 1 production and its action on keratinocytes simulated with a complex pathway simulator. This multiscale model can be run at a cellular level only or at a combined cellular/subcellular level. It was then initially challenged (by wounding) to investigate the behavior of keratinocytes in wound healing at the cellular level. To investigate the possible actions of TGF- β 1, several hypotheses were then explored by deliberately manipulating some of these rule sets at subcellular levels. This exercise readily eliminated some hypotheses and identified a sequence of spatial-temporal actions of TGF- β 1 for normal successful wound healing in an easy-to-follow 3D model. We suggest this multiscale model offers a valuable, easy-to-visualize aid to our understanding of the actions of this key regulator in wound healing, and provides a model that can now be used to explore pathologies of wound healing.

Keywords: multi-agent based simulation, multi-level, biology

[Sun:2012]

X. Sun, L. Zhang, H. Tan, J. Bao, C. Strouthos, and X. Zhou. Multi-scale agent-based brain cancer modeling and prediction of TKI treatment response: Incorporating egfr signaling pathway and angiogenesis. *BMC bioinformatics*, 13(1):218, 2012.

Abstract: Background The epidermal growth factor receptor (EGFR) signaling pathway and angiogenesis in brain cancer act as an engine for tumor initiation, expansion and response to therapy. Since the existing literature does not have any models that investigate the impact of both angiogenesis and molecular signaling pathways on treatment, we propose a novel multi-scale, agent-based computational model that includes both angiogenesis and EGFR modules to study the response of brain cancer under tyrosine kinase inhibitors (TKIs) treatment. Results The novel angiogenesis module integrated into the agent-based tumor model is based on a set of reaction-diffusion equations that describe the spatio-temporal evolution of the distributions of micro-environmental factors such as glucose, oxygen, TGF α , VEGF and fibronectin. These molecular species regulate tumor growth during angiogenesis. Each tumor cell is equipped with an EGFR signaling pathway linked to a cell-cycle pathway to determine its phenotype. EGFR TKIs are delivered through the blood vessels of tumor microvasculature and the response to treatment is studied. Conclusions Our simulations demonstrated that entire tumor growth profile is a collective behaviour of cells regulated by the EGFR signaling pathway and the cell cycle. We also found that angiogenesis has a dual effect under TKI treatment: on one hand, through neo-vasculature TKIs are delivered to decrease tumor invasion; on the other hand, the neo-vasculature can transport glucose and oxygen to tumor cells to maintain their metabolism, which results in an increase of cell survival rate in the late simulation stages.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Sun:2018]

X. Sun and B. Hu. Mathematical modeling and computational prediction of cancer drug resistance. *Briefings in Bioinformatics*, 19(6):1382-1399, 2018.

Abstract: Diverse forms of resistance to anticancer drugs can lead to the failure of chemotherapy. Drug resistance is one of the most intractable issues for successfully treating cancer in current clinical practice. Effective clinical approaches that could counter drug resistance by restoring the sensitivity of tumors to the targeted agents are urgently needed. As numerous experimental results on resistance mechanisms have been obtained and a mass of high-throughput data has been accumulated, mathematical modeling and computational predictions using systematic and quantitative approaches have become increasingly important, as they can potentially provide deeper insights into resistance mechanisms, generate novel hypotheses or suggest promising treatment strategies for future testing. In this review, we first briefly summarize the current progress of experimentally revealed resistance mechanisms of targeted therapy, including genetic mechanisms, epigenetic mechanisms, posttranslational mechanisms, cellular mechanisms, microenvironmental mechanisms and pharmacokinetic mechanisms. Subsequently, we list several currently available databases and Web-based tools related to drug sensitivity and resistance. Then, we focus primarily on introducing some state-of-the-art computational methods used in drug resistance studies, including mechanism-based mathematical modeling approaches (e.g. molecular dynamics simulation, kinetic model of molecular networks, ordinary differential equation model of cellular dynamics, stochastic model, partial differential equation model, agent-based model, pharmacokinetic-pharmacodynamic model, etc.) and data-driven prediction methods (e.g. omics data-based conventional screening approach for node biomarkers, static network approach for edge biomarkers and module biomarkers, dynamic network approach for dynamic network biomarkers and dynamic module network biomarkers, etc.). Finally, we discuss several further questions and future directions for the use of computational methods for studying drug resistance,

including inferring drug-induced signaling networks, multiscale modeling, drug combinations and precision medicine.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Tahir:2011]

H. Tahir, A.G. Hoekstra, E. Lorenz, P.V. Lawford, D.R. Hose, J. Gunn, and D.J.W. Evans. Multi-scale simulations of the dynamics of in-stent restenosis: impact of stent deployment and design. *Interface Focus*, 1(3):365–373, 2011.

Abstract: Neointimal hyperplasia, a process of smooth muscle cell re-growth, is the result of a natural wound healing response of the injured artery after stent deployment. Excessive neointimal hyperplasia following coronary artery stenting results in in-stent restenosis (ISR). Regardless of recent developments in the field of coronary stent design, ISR remains a significant complication of this interventional therapy. The influence of stent design parameters such as strut thickness, shape and the depth of strut deployment within the vessel wall on the severity of restenosis has already been highlighted but the detail of this influence is unclear. These factors impact on local haemodynamics and vessel structure and affect the rate of neointima formation. This paper presents the first results of a multi-scale model of ISR. The development of the simulated restenosis as a function of stent deployment depth is compared with an in vivo porcine dataset. Moreover, the influence of strut size and shape is investigated, and the effect of a drug released at the site of injury, by means of a drug-eluting stent, is also examined. A strong correlation between strut thickness and the rate of smooth muscle cell proliferation has been observed. Simulation results also suggest that the growth of the restenotic lesion is strongly dependent on the stent strut cross-sectional profile.

Keywords: multi-agent based simulation, multi-level, biology

[Taillandier:2010]

P. Taillandier, D-A. Vo, E. Amouroux, and A. Drogoul. GAMA: bringing GIS and multi-level capabilities to multi-agent simulation. In *European Workshop on Multi-Agent Systems*, 2010.

Abstract: The agent-based modeling is now widely used to study complex systems. Its ability to represent several levels of interaction along a detailed (complex) environment representation favored such a development. However, in many models, these capabilities are not fully used. Indeed, only simple, usually discrete, environment representation and one level of interaction (rarely two or three) are considered in most of the agent-based models. The major reason behind this fact is the lack of simulation platforms assisting the work of modelers in these domains. To tackle this problem, we developed a new simulation platform, GAMA. This platform allows modelers to define spatially explicit and multi-level models. In particular, it integrates powerful tools coming from Geographic Information Systems (GIS) and Data Mining easing the modeling and analysis efforts. In this paper, we present how this platform addresses these issues and how such tools are available right out of the box to modelers.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Taillandier:2012]

P. Taillandier, D-A. Vo, E. Amouroux, and A. Drogoul. GAMA: A simulation platform that integrates geographical information data, agent-based modeling and multi-scale control. In Nirmal Desai, Alan Liu, and Michael Winikoff, editors, *Principles and Practice of Multi-Agent Systems*, volume 7057 of *LNCS*, pages 242–258. Springer, 2012.

Abstract: The agent-based modeling is now widely used to study complex systems. Its ability to represent several levels of interaction along a detailed (complex) environment representation favored such a development. However, in many models, these capabilities are not fully used. Indeed, only simple, usually discrete, environment representation and one level of interaction (rarely two or three) are considered in most of the agent-based models. The major reason behind this fact is the lack of simulation platforms assisting the work of modelers in these domains. To tackle this problem, we developed a new simulation platform, GAMA. This platform allows modelers to define spatially explicit and multi-levels models. In particular, it integrates powerful tools coming from Geographic Information Systems (GIS) and Data Mining easing the modeling and analysis efforts. In this paper, we present how this platform addresses these issues and how such tools are available right out of the box to modelers.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Tchappi:2017]

I.H. Tchappi, V.C. Kamla, S. Galland, and J.C. Kamgang. Towards an multilevel agent-based model for traffic simulation. *Procedia Computer Science*, 109:887–892, 2017.

Abstract: Large scale road traffic is a complex system that could be modelled with a multilevel approach. Most of the multilevel models from the literature have fixed a priori the two levels of detail (micro-meso, micro-macro, meso-macro). This paper has two goals: it presents the state of the art related to large scale traffic models, and it gives the main research direction to create a novel multilevel model that support dynamic selection of the level during the simulation. Our proposal is based on an organizational modelling approach and the use of the concept of holon (agent composed of agents).

Keywords: multi-agent based simulation, multi-level, traffic, holonic systems, french team

[Tchappi:2018]

I.H. Tchappi, S. Galland, V.C. Kamla, and J-C. Kamgang. Holonification of road traffic based on graph theory. In *International Conference on Cellular Automata (ICRA)*, volume 11115 of *LNCS*, pages 513–525. Springer, 2018.

Abstract: Organizational models and holonic multiagent systems are growing as a powerful tool for modeling and developing large-scale complex system. The main issue in deploying holonic multiagent systems is the building of the holonic model called holarchy. This paper presents a novel top down approach based on graph theory in order to build recursively the initial holarchy of road traffic. Moreover, multilevel indicators based on standard deviation is proposed to evaluate the consistency of the holonification process.

Keywords: multi-agent based simulation, multi-level, hybrid model, traffic, french team

[Tchappi:2018a]

I.H. Tchappi, S. Galland, V.C. Kamla, and J-C. Kamgang. A brief review of holonic multi-agent models for traffic and transportation systems. *Procedia computer science*, 134:137–144, 2018.

Abstract: The paper presents a state of the art of multilevel models for traffic and transportation modeling and simulation using holonic multi-agent approach. After an introduction and presentation of holonic principles, concepts and framework, the paper summarizes research works on traffic models using holonic multi-agent systems. Then a discussion is given, in particular, a rationale of holonic systems in modeling and simulation of traffic and transportation and open issues are given.

Keywords: multi-agent based simulation, multi-level, holonic systems, traffic, review, french team

[Tchappi:2018b]

I.H. Tchappi, S. Galland, V.C. Kamla, J-C. Kamgang, C.M.S. Nono, and H. Zhao. Holonification model for a multilevel agent-based system. *Personal and Ubiquitous Computing*, pages 1–19, 2018.

Abstract: Organizational models and holonic multiagent systems are growing as a powerful tool for modeling and developing a large-scale complex system. The main issue in deploying holonic multiagent systems is the building of the holonic model called holarchy. This paper presents a novel density approach to cluster and hierarchize population in order to build the initial holarchy. The proposal extends Density-Based Spatial Clustering of Applications with Noise (DBSCAN) algorithm. Moreover, multilevel indicators based on standard deviation are proposed in order to evaluate the consistency of the holonification process. The proposed model is tested in a road traffic modeling in order to build the initial holarchy. The paper presents also the main research direction towards the control of internal and external stimuli of traffic over time.

Keywords: multi-agent based simulation, multi-level, holonic systems, traffic

[Thorne:2011]

B.C. Thorne, H.N. Hayenga, J.D. Humphrey, and S.M. Peirce. Toward a multi-scale computational model of arterial adaptation in hypertension: verification of a multi-cell agent based model. *Frontiers in Physiology*, 2, 2011.

Abstract: Agent-based models (ABMs) represent a novel approach to study and simulate complex mechano chemo-biological responses at the cellular level. Such models have been used to simulate a variety of emergent responses in the vasculature, including angiogenesis and vasculogenesis. Although not used previously to study large vessel adaptations, we submit that ABMs will prove equally useful in such studies when combined with well-established continuum models to form multi-scale models of tissue-level phenomena. In order to couple agent-based and continuum models, however, there is a need to ensure that each model faithfully represents the best data available at the relevant scale and that there is consistency between models under baseline conditions. Toward this end, we describe the development and verification of an ABM of endothelial and smooth muscle cell responses to mechanical stimuli in a large artery. A refined rule-set is proposed based on a broad literature search, a new scoring system for assigning confidence in the rules, and a parameter sensitivity study. To illustrate the utility of these new methods for

rule selection, as well as the consistency achieved with continuum-level models, we simulate the behavior of a mouse aorta during homeostasis and in response to both transient and sustained increases in pressure. The simulated responses depend on the altered cellular production of seven key mitogenic, synthetic, and proteolytic biomolecules, which in turn control the turnover of intramural cells and extracellular matrix. These events are responsible for gross changes in vessel wall morphology. This new ABM is shown to be appropriately stable under homeostatic conditions, insensitive to transient elevations in blood pressure, and responsive to increased intramural wall stress in hypertension.

Keywords: multi-agent based simulation, multi-level, biology

[Timm:2016]

I.J. Timm, F. Lorig, E. Hölzchen, and C. Hertler. Multi-scale agent-based simulation of long-term dispersal processes: Towards a sophisticated simulation model of hominin dispersal. In *Simulating Prehistoric and Ancient Worlds*, pages 141–157. Springer, 2016.

Abstract: According to the Out-of-Africa-Hypothesis, the geographic origin of hominins known to be ancestors of anatomically modern humans, such as homo sapiens, is located in Africa. Due to the discovery of numerous fossils there is archaeological evidence on the existence of waves of early dispersal from Africa to Eurasia. Yet, the reason as well as the actual route of migration are being discussed controversially among experts. However, there is a scientific consensus that a conjunction of several local factors, such as climatic changes or carnivore competition, caused the global effect of hominids migrating to Eurasia to occur. In order to understand these emergent phenomena and to validate different scientific hypotheses, the dispersal processes need to be reproduced. In this article we propose the use of agent-based modeling for developing a simulation platform which enables researchers to evaluate assumptions and hypotheses using artificial and customizable scenarios. Furthermore, potential fields are proposed as a first step approach for modeling and simulating environmental factors influencing migration processes.

Keywords: multi-agent based simulation, multi-level, history, social simulation

[Tong:2015]

X. Tong, J. Chen, H. Miao, T. Li, and L. Zhang. Development of an agent-based model (abm) to simulate the immune system and integration of a regression method to estimate the key abm parameters by fitting the experimental data. *PLoS one*, 10(11):e0141295, 2015.

Abstract: Agent-based models (ABM) and differential equations (DE) are two commonly used methods for immune system simulation. However, it is difficult for ABM to estimate key parameters of the model by incorporating experimental data, whereas the differential equation model is incapable of describing the complicated immune system in detail. To overcome these problems, we developed an integrated ABM regression model (IABMR). It can combine the advantages of ABM and DE by employing ABM to mimic the multi-scale immune system with various phenotypes and types of cells as well as using the input and output of ABM to build up the Loess regression for key parameter estimation. Next, we employed the greedy algorithm to estimate the key parameters of the ABM with respect to the same experimental data set and used ABM to describe a 3D immune system similar to previous studies that employed the DE model. These results indicate that IABMR not only has the potential to simulate the immune system at various scales, phenotypes and cell types, but can also accurately infer the key parameters like DE model. Therefore, this study innovatively developed a complex system development mechanism that could simulate the complicated immune system in detail like ABM and validate the reliability and efficiency of model like DE by fitting the experimental data.

Keywords: multi-agent based simulation, multi-level, biology

[Torii:2005]

D. Torii, T. Ishida, S. Bonneaud, and A. Drogoul. Layering social interaction scenarios on environmental simulation. In *Multi-Agent and Multi-Agent-Based Simulation*, volume 3415 of *LNCS*, pages 78–88. Springer, 2005.

Abstract: For an integrated simulation such as the natural environment affected by human society, it is indispensable to provide an integrated simulator that incorporates multiple computational models. We proposed a multi-layer socio-environmental simulation by layering the social interaction scenario on environmental simulation. For this simulation, we connect two different systems. One is a scenario description language Q, which is suitable for describing social interactions. Another is CORMAS, which models interactions between a natural environment and humans. The key idea is to realize a mapping between agents in different systems. This integration becomes possible by the salient feature of Q: users can write scenarios for controlling legacy agents in other systems. Moreover, we find that controlling the flow of information between the

two systems can create various types of simulations. We also confirm the capability of COR-MAS/Q, in the well-known Fire-Fighter domain.

Keywords: multi-agent based simulation, multi-level, social simulation

[Torrel:2006]

J-C. Torrel, C. Lattaud, and J-C. Heudin. Complex stellar dynamics using a hierarchical multi-agent model. In *NECSI International Conference on Complex Systems*, 2006.

Abstract: This paper defines a new approach for cosmological simulation based on complex systems theory : a hierarchical multi-agent system is used to study stellar dynamics. At each level of the model, global behavior emerges from agent interactions. The presented model uses physically-based laws and agent-interactions to present stellar structures has the result of self-organisation. Nevertheless a strong bond with cosmology is kept by showing the capacity of the model to exhibit structures close to thoses of the observable universe.

Keywords: multi-agent based simulation, multi-level, cosmology, french team

[Torrel:2007]

J-C. Torrel. *Modélisation et Simulation de phénomènes complexes par systèmes multi-agents hiérarchiques: application en cosmologie*. PhD thesis, Paris 5, 2007.

Abstract: Numerical simulation has been, for a few years, used like a essential complement to the observational and theoretical approaches in cosmology. If the methods usually employed allowed a great number of success they present some limitations: - they require a high computing power ; - the results obtained vary according to the computing power used ; - the existing models are not very adaptable, mainly dedicated to the study of a phenomenon or a class of phenomena in particular. Simultaneously with these methods developed in cosmology, it appeared, in the sciences of complexity, other models of simulation, in particular based on cellular automata or multi-agents systems. However, if these models can be used to predict the general tendencies of a system, they are inadequate for the prediction and quantitative analysies. In this work, we propose an hybrid approach, inspired of the models used in cosmology and sciences of complexity, in order to study the dynamics of the stellar structures. We use a hierarchical multi-agents system based on physical laws to leave room to self-organization of the system while preserving a strong bond with physics.

Keywords: multi-agent based simulation, multi-level, cosmology, french team

[Torrel:2007a]

J-C. Torrel, C. Lattaud, and J-C. Heudin. Studying complex stellar dynamics using a hierarchical multi-agent model. In *Modelling and Simulation in Science*, pages 307–312. World Scientific, 2007.

Abstract: This paper defines a new approach for cosmological simulation based on complex systems theory: a hierarchical multi-agent system is used to study stellar dynamics. At each level of the model, global behavior emerges from agent interactions. The presented model uses physically-based laws and agent-interactions to present stellar structures has the result of self-organization. Nevertheless a strong bond with cosmology is kept by showing the capacity of the model to exhibit structures close to those of the observable universe.

Keywords: multi-agent based simulation, multi-level, cosmology

[Torrel:2009]

J-C. Torrel, C. Lattaud, and J-C. Heudin. Complex systems in cosmology: "the antennae" case study. In *Complex Sciences*, volume 5 of *LNICST*, pages 1887–1897. Springer, 2009.

Abstract: Due to its particular shape, "The Antennae" is a well-known complex cosmological dynamical structure. Classical simulations of this phenomenon are based on "top-down" models that required thousands of point-mass particles. We describe an approach for cosmological simulation, based on a hierarchical multi-agent system, and evidence is shown that this approach significantly reduces the number of elements needed to simulate "The Antennae" structure.

Keywords: multi-agent based simulation, multi-level, cosmology, french team

[Tranouez:2001]

P. Tranouez, C. Bertelle, and D. Olivier. Changing the level of description of a fluid flow in agent-based simulation. In *ESS Conference*, 2001.

Keywords: multi-agent based simulation, multi-level, flow model, emergence detection, french team

[Tranouez:2003]

P. Tranouez, S. Lerebourg, C. Bertelle, and D. Olivier. Contribution à la représentation multi-échelle des écosystèmes aquatiques. In *Actes des 11èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, volume 22 of *Technique et Science Informatiques*, pages 255–259. Hermès, 2003.

Abstract: Aquatic ecosystems are naturally open hierarchical systems. They are crossed by energetic fluxes that structure them. One of these fluxes is mass transport that is carried by fluid flow. This flow is the essential vector for interaction inside the system and thus one of the main contributor to emergent formations structuring these ecosystems. Furthermore, to follow ecosystem evolution, we have to observe and represent organizations that span over different scales. We present a fluid flow simulation which dynamically detect emergent formations, then manage them on different scales.

Keywords: multi-agent based simulation, multi-level, emergence detection, ecology, in french, french team

[Tranouez:2005]

P. Tranouez. *Contribution à la modélisation et à la prise en compte informatique de niveaux de descriptions multiples. Application aux écosystèmes aquatiques*. PhD thesis, Université du Havre, 2005.

Abstract: Most sciences use simulation in their usual cycle of self-construction. The focus of our work is improving the handling of multiple scales in computer simulations. We have therefore to understand how different sciences build themselves, and how this epistemology relates to simulation. The present work therefore starts with a chapter summing up various epistemological tendencies and endeavors to link them to our present goal. The second chapter more specifically presents what is meant by multiple scales or level of description in different scientific work, with an emphasis on what is closer to our future main application, hydrodynamics in ecosystems model. Chapter 3 presents the early application that in fact prompted the present work, a system meant to improve intelligibility in a written communication system during emergency situations, by using the shape and the dynamics of the discourse itself to help summing up the semantics. Follows afterwards a summing up of what ecology delves into, the importance of fluxes in modern ecosystems model, and the main approaches of fluid flow modeling in current hydrodynamics. This leads to the relative novelty of our work, which is an application to handling different scales in a fluid flow simulation, with a view to integration in a more complex ecosystems simulation. We use a standard model called vortex based upon which we apply two different schemes to detect structures or organizations in the midst of the simulation. One of these leads to the replacement of the basic particles that self-organized to a new simulation entity that represents this organization or structure. The metaphorical social life of these entities can lead to the creation of still new scales of description, in a iterative theoretical upper open-ended way. We conclude with the integration of an article (in English) that emphasizes how this work will lead to a more developed ecosystems simulation, and what the ties are.

Keywords: multi-agent based simulation, multi-level, ecology, in french, french team

[Tranouez:2006]

P. Tranouez, C. Bertelle, and D. Olivier. *Emergent properties in natural and artificial dynamical systems*, chapter Changing levels of description in a fluid flow simulation, pages 87–99. Springer, 2006.

Abstract: We described here our perception of complex systems, of how we feel the different layers of description are an important part of a correct complex system simulation. We described a rough models categorization between rules based and law based, of how these categories handled the levels of descriptions or scales. We then described our fluid flow simulation, which combines different fineness of grain in a mixed approach of these categories. This simulation is built keeping in mind an ulterior use inside a more general aquatic ecosystem.

Keywords: multi-agent based simulation, multi-level, flow model, emergence detection, french team

[Tranouez:2009]

P. Tranouez and A. Dutot. Different goals in multiscale simulations and how to reach them. In *Complex Systems and Self-organization Modelling*, Understanding Complex Systems, pages 29–39. Springer, 2009.

Keywords: multi-agent based simulation, multi-level, flow model, emergence detection, french team

[Unsal:2019]

S. Unsal, A. Acar, M. Itik, A. Kabatas, O. Gedikli, F. Ozdemir, and K. Turhan. Personalized tumor growth prediction with multiscale tumor modeling. *bioRxiv*, 2019.

Abstract: Background: Cancer is one of the most complex phenomena in biology and medicine. Extensive attempts have been made to work around this complexity. In this study, we try to take a selective approach; not modeling each particular facet in detail but rather only the pertinent and essential parts of the tumor system are simulated and followed by optimization, revealing specific traits. This leads us to a pellucid personalized model which is noteworthy as it closely approximates existing experimental results. Method: For years, research has focused on modeling tumor

growth but not many studies have put forward a framework for the personalization of models. In the present study, a hybrid modeling approach which consists of cellular automata for discrete cell state representation and diffusion equations to calculate distribution of relevant substances in the tumor micro-environment is favored. Moreover, naive Bayesian decision making with weighted stochastic equations and a Bayesian network to model the temporal order of mutations is presented. The model is personalized according to the evidence using Markov Chain Monte Carlo. Ultimately, this way of thinking about tumor modeling leads us to a vascular multi-scale model of tumor growth. Results: To validate the tumor model, a data set belonging to the A549 cell line is used. The data represents the growth of a tumor for 30 days. We optimize the coefficients of the stochastic decision making equations using first half of the timeline. Then we predict next 15 days of growth without any other supervision. Results are promising with their low error margin and simulated growth data is in line with laboratory results. Conclusion: There are many subsystems which have an effect in the growth of a tumor. A detailed model which includes all of them is currently virtually impossible to implement. We have therefore focused on a system that only includes fundamental components in this study, and have evaluated its predictions. We propose novel probability functions to obtain a personalized model and estimate the individual importance (weights) of each with parameter optimization. Our approach of using simulated annealing for parameter estimation and the subsequent validation of the prediction with in-vitro tumor growth data are, to our knowledge, unique in the literature.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Vanbergue:2002]

D. Vanbergue and A. Drogoul. Approche multi-agent pour la simulation urbaine. In *Actes des 6èmes Journées CASSINI*, pages 95–112, 2002.

Abstract: Le but de cet article est de montrer quelles sont les potentialités qu’offrent les outils de simulation multi-agent en géographie. En effet, la simulation multi-agent ajoute aux techniques dont elle est l’héritière (en particulier, la microsimulation, les approches orientées-objet, les automates cellulaires), des propriétés encore peu exploitées et particulièrement utiles à la géographie. Nous présenterons les plus intéressantes : la gestion d’entités hétérogènes, l’intégration de différents modèles et la prise en compte de plusieurs niveaux d’analyse. Notre propos sera illustré par la présentation de MMINUS, outil de simulation dédié aux migrations intra-urbaines, qui permet d’appréhender la complexité urbaine selon les 3 axes de compréhension espace-temps-social en intégrant différents modèles issus de domaines liés à la recherche urbaine (économie, démographie, sociologie, géographie). Dans MMINUS, nous avons choisi une approche hiérarchique mixte, les entités "sociales" (individus et ménages) évoluant sur, et pouvant interagir avec des entités "spatiales" (logements et secteurs). Dans cette perspective, un "modèle" est vu comme un ensemble de comportements applicables à certaines des entités mises en jeu. Nous détaillerons par l’étude des interactions (entre entités d’un même niveau, entités de différents niveaux mais aussi entre modèles) l’intérêt d’une telle approche dans une perspective d’application à la géographie.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Vanbergue:2003]

D. Vanbergue. *Conception de simulation multi-agents: application à la simulation des migrations intra-urbaines de la ville de Bogota*. PhD thesis, Université Paris VI, 2003.

Abstract: Au cours des dernières années, la simulation orientée agent a démontré l’efficacité de son paradigme auprès des autres sciences. Aujourd’hui, elle apparaît comme une science à part entière et non plus comme un simple outil. Le travail présenté propose une réflexion méthodologique qui se base sur une approche de méthodologie appliquée, c’est-à-dire utiliser un domaine d’applications complexe, ici la ville, et en particulier les migrations intra-urbaines de Bogota pour proposer une réflexion plus globale. Un cadre méthodologique de conception de simulation orientée agent est proposée avant d’être appliqué à un outil de simulation dédié à la ville, basé sur un formalisme orienté activité. Les différentes implémentations qui ont été effectuées montrent que l’utilisation de cette méthodologie et d’un tel formalisme permet non seulement de ré-implémenter des modèles mais aussi de les faire fonctionner dans la même simulation, permettant une approche multi-modèles, nécessaire à l’étude des phénomènes complexes.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Vanbergue:2006]

D. Vanbergue. *Quatre ans de recherche urbaine 2001-2004. Volume I: Action concertée incitative Ville. Ministère de la Recherche*, chapter Conception de simulation multi-agents : application à la simulation des migrations intra-urbaines de la ville de Bogota, pages 184–190. Presses universitaires François-Rabelais, 2006.

Abstract: Mon travail se situe dans un axe de recherche méthodologique de la recherche en simulation multi-agents. Elle relève d'une démarche que je qualifierais de méthodologie appliquée : le travail proposé n'est pas purement théorique puisqu'il s'appuie sur un domaine d'application particulier mais il s'en démarque fortement pour proposer une réflexion globale. Depuis une quinzaine d'années, la simulation multi-agents a démontré, grâce aux différents travaux en la matière, l'efficacité de son paradigme auprès des autres sciences. Cependant, elle n'est pas qu'un simple outil offert aux autres sciences, ni même qu'une simple application des systèmes multi-agents. En effet, aujourd'hui, on peut considérer qu'elle constitue un domaine de recherche à part entière au vu, d'une part, du nombre de conférences qui lui sont consacrées, et d'autre part, aux questions méthodologiques et épistémologiques qu'elle soulève. Consacrées à l'étude de phénomènes complexes, les solutions informatiques proposées sont le fruit d'un processus de conception lui-même complexe. Une réflexion générale est nécessaire pour rationaliser ce processus, ce qui permettrait, d'une part, une meilleure compréhension de ce processus par tous les acteurs de la conception, et, d'autre part, à long terme, une plus grande ré-utilisabilité des travaux antérieurs. Mon travail consiste à proposer une méthodologie de conception, de répondre à la question « Comment concevoir un outil de simulation orienté agent ? », puis de fournir un formalisme et une solution informatique. Le domaine d'application permet alors de définir les propriétés exigibles pour ce type d'outil et de fournir une validation par rapport aux solutions proposées. Le domaine d'application est les migrations intra-urbaines de la ville de Bogota, choix qui a été fait au vu de la richesse des données et des travaux existants. L'intérêt d'un tel objet d'étude dans une optique méthodologique, est sa complexité due à l'interaction de différents processus, analysables à travers trois axes de compréhension (social, espace, temps) qui fait appel à différentes expertises émanant de domaines de recherche différents qui utilisent des approches diversifiées. En d'autres termes, mon travail propose de réfléchir à la conception d'un outil de simulation, permettant à des utilisateurs non-informaticiens de mieux appréhender la ville, et particulièrement les migrations intra-urbaines. L'idée est d'intégrer des connaissances de différents champs de recherche urbaine (géographie, démographie, urbanisme, sociologie, économie, etc.) pour avoir une meilleure appréhension du sujet d'étude la ville.

Keywords: multi-agent based simulation, multi-level, social simulation, in french, french team

[Vaubourg:2015]

J. Vaubourg, Y. Presse, B. Camus, L. Ciarletta, V. Chevrier, J-P. Tavella, B. Deneuille, and O. Chilard. Simulation de smart grids avec mecsyco. In *Actes des 23èmes Journées Francophones sur les Systèmes Multi-Agents (JFSMA)*, pages 217–218. Cépaduès, 2015.

Abstract: Cette démonstration présente l'application de la plateforme de simulation MECSYCO (Multiagent Environment for Complex SYstems COsimulation), antérieurement appelée AA4MM, dans le contexte des smart grids. Nous montrons, notamment à partir d'un cas d'usage tiré d'un scénario réel, comment cette plateforme permet d'intégrer des simulateurs hétérogènes existants et de simuler l'ensemble de manière cohérente et complètement décentralisée.

Keywords: multi-agent based simulation, multi-level, french team

[Vaubourg:2015a]

J. Vaubourg, Y. Presse, B. Camus, C. Bourjot, L. Ciarletta, V. Chevrier, J-P. Tavella, H. Morais, B. Deneuille, and O. Chilard. Smart grids simulation with mecsyco. In *Advances in Practical Applications of Agents, Multi-Agent Systems, and Sustainability*, volume 9086 of *LNCS*, pages 320–323. Springer, 2015.

Abstract: These demonstrations are part of the MS4SG project and show the current results of the DEVS-based platform called MECSYCO (Multi-agent Environment for Complex SYstems COsimulation), formerly named AA4MM (Agents & Artifacts for Multi-Modeling), in the context of smart grids simulation with different use cases based on real scenarios.

Keywords: multi-agent based simulation, multi-level, french team

[Vaubourg:2015b]

J. Vaubourg, Y. Presse, B. Camus, C. Bourjot, L. Ciarletta, V. Chevrier, and H. Morais. Multi-agent multi-model simulation of smart grids in the ms4sg project. In *Advances in Practical Applications of Agents, Multi-Agent Systems, and Sustainability*, volume 9086 of *LNCS*, pages 240–251. Springer, 2015.

Abstract: This paper illustrates how the multi-agent approach, or paradigm, can help in the modeling and the simulation of smart grids in the context of MS4SG (a joint project between LORIA-INRIA and EDF R&D). Smart grids simulations need to integrate together pre-existing and heterogeneous models and their simulation software; for example modeling tools of the power grids, of telecommunication networks, and of the information and decision systems. This paper describes the use of MECSYCO as a valid approach to integrate these heterogeneous models in a multi-agent smart grid simulation platform. Several use cases show the ability of MECSYCO to effectively take into account the requirements of smart grids simulation in MS4SG.

Keywords: multi-agent based simulation, multi-level, smart grids, french team

[Vermeer:2016]

W. Vermeer, B. Head, and U. Wilensky. The effects of local network structure on disease spread in coupled networks. In *Proc. of 5th Int. Workshop on Complex Networks and their Applications*, volume 693 of *Studies in Computational Intelligence*, pages 487–498. Springer, 2016.

Abstract: Epidemiology has long used human interaction patterns to understand spreading dynamics. Recently network scientists have embraced the notion that these patterns are best described using a complex multi-layered system, a network of networks, yielding a stream of literature focused on understanding spreading in such coupled systems. Adding this macro level perspective to disease spreading, focusing on the interaction among systems, has shifted focus away from the role of local (within-system) structure. In this paper, using a multi-level Agent-based model, we highlight the importance of the local structure in determining spreading dynamics in coupled settings. We show that the local dynamics in both the focal and neighboring networks, play a significant role in determining focal dynamics. As both are driven by the local structure this highlights a need for incorporating structural details across all levels for accurate modeling of disease spreading dynamics.

Keywords: multi-agent based simulation, multi-level, epidemiology

[Vincenot:2011]

C.E. Vincenot, F. Giannino, M. Rietkerk, K. Moriya, and S. Mazzoleni. Theoretical considerations on the combined use of system dynamics and individual-based modeling in ecology. *Ecological Modelling*, 222(1):210–218, 2011.

Abstract: Modeling could be summed up as the task of reproducing the structure and imitating the behavior of complex real-life systems with components interacting with one another at different scales. In many disciplines of ecology, System Dynamics and more recently Individual-Based modeling have emerged as the major tools to support this task. These techniques have usually been considered until now as exclusive alternatives instead of synergistic tools. The present paper starts by presenting the two approaches, and compares them to identify their strong and weak points depending on the type of components constituting the system under consideration. Then we isolate a class of systems difficult or in some cases impossible to model dynamically using any of these approaches alone, because of conceptual limitations. We further point out the usefulness of merging the two paradigms inside of a hybrid modeling framework to handle this class of systems, and present what we consider as the elementary combination patterns of System Dynamics and Individual-Based modeling. Since the power of this promising approach has been unexplored in most fields of ecology, we suggest some possible applications illustrating its usefulness.

Keywords: multi-agent based simulation, multi-level, ecology

[Vo:2012]

D-A. Vo, A. Drogoul, J-D. Zucker, and T-V. Ho. A modelling language to represent and specify emerging structures in agent-based model. In *Principles and Practice of Multi-Agent Systems*, volume 7057 of *LNCS*, pages 212–227. Springer, 2012.

Abstract: All modellers have come across, one day, one of these popular toy agent-based models (ABMs), like "Ants", for instance, which depicts the appearance of pheromone trails built by simulated ants. They are simple, but representative of the way "real", more complex, ABMs are designed: in addition to explicitly describe the individual entities used to represent the system, modellers make implicit references to abstractions corresponding to the emerging structures they are tracking in the simulations. Yet, these abstractions are not represented in the models themselves as first-class entities: they are either hidden in ex-post computations or only part of visualization tasks, as if an explicit representation could somehow damage the processes at work in their emergence. This clearly constitutes an obstacle to the development of multi-level models, where emergence is likely to occur at different levels of abstraction of the system: if some of these levels are not represented in the models, the emergence of higher-level structures is not likely to be observed. This paper describes a modelling language that allows a modeller to represent and specify emerging structures in agent-based models. Firstly, to ease the description, we present these structures and their properties in four toy ABMs: Schelling, Boids, Collective Sort and Ants. Then we define the operations that are needed to represent and specify them without sacrificing the properties of the original model. An implementation of these operations in the GAML modelling language (part of the GAMA agent-based platform) is then presented. Finally, two simulations of the Boids model are used to illustrate the expressivity of this language and the multiple advantages it brings in terms of analysis, visualization and modeling of multi-level ABMs.

Keywords: multi-agent based simulation, multi-level, meta-model, emergence detection, french team

[Vo:2012a]

D-A. Vo, A. Drogoul, and J-D. Zucker. An operational meta-model for handling multiple scales in agent-based simulations. In *International Conference on Computing and Communication Technologies, Research, Innovation, and Vision for the Future (RIVF)*, pages 1–6, Ho Chi Minh City, 2012. IEEE.

Abstract: There is a growing interest for multi-scale agent-based modeling. The research community has made several efforts in proposing agent-based simulators or meta-models, which accommodate for multi-scale agent-based modeling. Unfortunately, the proposed simulators are often tight to a specific model. And the proposed meta-models exist only as formal proposals without a concrete implementation supported by an operational modeling language. The lack of a common operational meta-model and an associated operational modeling language raises the question of reusability and increase the danger of "re-inventing the wheel" when one develops new models. Moreover, the operational semantics of such multi-scale models may differ without having defined a solid theoretical ground. Our research aims at proposing a generic meta-model for multi-scale agent-based modeling. In our approach, we revisit the fundamental notions of agent modeling (agent/environment/scheduler) in order to support a recursive representation of these notions in an agent-based model. To test the operational semantic of the proposed model, we implement this meta-model as an agent-based modeling language in the GAMA simulation platform. This paper presents such a meta-model and how its concepts can be used to formalize multi-scale agent-based models.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Vo:2012b]

D-A. Vo. *An operational architecture to handle multiple levels of representation in agent-based models*. PhD thesis, Université Paris VI, 2012.

Abstract: Agent-based modeling (ABM) is a modeling approach that can be viewed as a successful crossbreeding of Individual-Based Modeling (IBM), originated in Ecology, and Object-Oriented Programming (OOP), originated in Computer Science. Like the former, it aims at building generative models where the general behavior of the model is the result of the interactions between its components; like the latter, it allows building these models in a modular and incremental way, promising reusability and flexibility to the modelers. However, it also inherits some of the limits of its two ancestors, in particular the absence of dedicated abstractions for handling more than one level of representation at once in a same model. I describe in my thesis a conceptual and fully operational proposal to support multiple levels of representation within a pure agent-based modeling approach. This proposal consists in an evolution of the meta-model usually associated with ABM and an implementation of this meta-model in the kernel of the GAMA platform (along an enrichment of the GAML language). Contrary to similar contributions found in the literature, which are either purely conceptual or specific to one application domain, the one I propose is generic, completely implemented and immediately reusable by modelers. As a matter of fact, it is already in use in several large-scale models. My contribution has been formalized after a careful analysis of the requirements of modelers working on multi-level agent-based models and a specific attention to providing them with reusable and generic abstractions. Given that most of the existing ABM meta-models follow the principles of OOP (i. E. A model being a set of "classes" allowing building "instances" of agents, providing them with attributes and operations, and allowing specialization through inheritance between "classes"), I have proposed an extension of this meta-model that integrates and generalizes the following notions: description of a "host" relationship between "classes" in addition to inheritance, explicit description of the "populations" of agents (instances of the same "class" that belong to the same host), possibility to attach a temporal and spatial scale to each "class", and addition of a primary operator of "migration" between "populations" to complement "instantiation". This meta-model has been implemented in an open-source agent-based modeling platform, GAMA, initially developed in 2006 as an extension of the Repast platform with explicit support for geographical information. I completely re-factored the meta-model of GAMA and enriched its modeling language in order to make it capable of supporting the development of multi-level agent-based models. This evolution (1) allows modelers to represent multi-level organizations and their dynamics as first-class citizens in their model; (2) allows them to proceed methodologically in a bottom-up fashion, adding multi-level capabilities to existing "single-level" models without breaking or even changing the initial model; (3) does not break the core concepts of ABM, as the "classic" ABM meta-model is still a subset of my proposal. This new architecture has been extensively and successfully validated during the course of the development, by independent modelers, of two multi-level agent-based models on the GAMA platform: the first one concerning the organization of evacuations in response to a tsunami warning in a

Vietnamese coastal city, the second one dealing with the assessment of policies against the invasions of rice pests in the Mekong delta region. The development of several new models, as well as a porting of the meta-model to other environments, is under consideration at the time of this writing.

Keywords: multi-agent based simulation, multi-level, meta-model, french team

[Vo:2013]

D-A. Vo, A. Drogoul, and J-D. Zucker. *Advanced Methods and Technologies for Agent and Multi-Agent Systems*, volume 252, chapter Multi-Level Agent-Based Modeling: a Generic Approach and an Implementation, pages 91–101. IOS press, 2013.

Abstract: Multi-level agent-based modeling (ML-ABM) requires representing agents at different levels of representation in the same model w.r.t. to time, space and behavior. This paper describes a generic and operational proposal for ML-ABM. First, a generic meta-model for ML-ABM and an associated "morphogenesis" operation are introduced. The generic meta-model allows a modeler to describe multiple levels of representation in the same model, while the "morphogenesis" operation supports agent change of representation level dynamically during the course of the simulation. Second, in order to demonstrate how to operationalize the proposal, we present an implementation of the generic meta-model and the "morphogenesis" operation in the GAMA ABM platform. Finally, we illustrate how our proposal, implemented in the GAMA platform, allows modeler in practice to develop a multi-level agent-based model. To do so, we rely on the famous "Boids" model of Craig Reynolds and show how the modeler can easily introduce a new level of representation of an entity to transform the model into a two-levels agent-based model without having to modify the existing model.

Keywords: multi-agent based simulation, multi-level, french team

[Vodovotz:2008]

Y. Vodovotz, M. Csete, J. Bartels, S. Chang, and G. An. Translational systems biology of inflammation. *PLoS Comput Biol*, 4(4):e1000014, 04 2008.

Abstract: <p>Inflammation is a complex, multi-scale biologic response to stress that is also required for repair and regeneration after injury. Despite the repository of detailed data about the cellular and molecular processes involved in inflammation, including some understanding of its pathophysiology, little progress has been made in treating the severe inflammatory syndrome of sepsis. To address the gap between basic science knowledge and therapy for sepsis, a community of biologists and physicians is using systems biology approaches in hopes of yielding basic insights into the biology of inflammation. "Systems biology" is a discipline that combines experimental discovery with mathematical modeling to aid in the understanding of the dynamic global organization and function of a biologic system (cell to organ to organism). We propose the term <italic>translational systems biology</italic> for the application of similar tools and engineering principles to biologic systems with the primary goal of optimizing clinical practice. We describe the efforts to use translational systems biology to develop an integrated framework to gain insight into the problem of acute inflammation. Progress in understanding inflammation using translational systems biology tools highlights the promise of this multidisciplinary field. Future advances in understanding complex medical problems are highly dependent on methodological advances and integration of the computational systems biology community with biologists and clinicians.</p>

Keywords: multi-agent based simulation, multi-level, biology

[Wakeland:2007]

W. Wakeland, L. Macovsky, and G. An. A hybrid simulation model for studying acute inflammatory response. In *Proceedings of the 2007 spring simulation multiconference*, volume 2 of *SpringSim '07*, pages 39–46. Society for Computer Simulation International, 2007.

Abstract: The modeling of complex biological systems presents a significant challenge. Central to this challenge is striking a balance between the degree of abstraction required to facilitate analysis and understanding, and the degree of comprehensiveness required for fidelity of the model to its reference-system. It is likely necessary to utilize multiple modeling methods in order to achieve this balance. Our research created a hybrid simulation model by melding an agent-based model of acute local infection with a system dynamics model that reflects key systemic properties. The agent based model was originally developed to simulate global inflammation in response to injury or infection, and has been used to simulate clinical drug trials. The long term objective is to develop models than can be scaled up to represent organ and system level phenomena such as multiple organ failure associated with severe sepsis. The work described in this paper is an initial proof of concept of the ability to combine these two modeling methods into a hybrid

model, the type of which will almost certainly be needed to accomplish the ultimate objective of comprehensive in silico research platforms.

Keywords: multi-agent based simulation, multi-level, hybrid model, biology

[Wang:2007]

Z. Wang, L. Zhang, J. Sagotsky, and T.S. Deisboeck. Simulating non-small cell lung cancer with a multiscale agent-based model. *Theoretical Biology and Medical Modelling*, 4, 2007.

Abstract: Background The epidermal growth factor receptor (EGFR) is frequently overexpressed in many cancers, including non-small cell lung cancer (NSCLC). In silico modeling is considered to be an increasingly promising tool to add useful insights into the dynamics of the EGFR signal transduction pathway. However, most of the previous modeling work focused on the molecular or the cellular level only, neglecting the crucial feedback between these scales as well as the interaction with the heterogeneous biochemical microenvironment. Results We developed a multiscale model for investigating expansion dynamics of NSCLC within a two-dimensional in silico microenvironment. At the molecular level, a specific EGFR-ERK intracellular signal transduction pathway was implemented. Dynamical alterations of these molecules were used to trigger phenotypic changes at the cellular level. Examining the relationship between extrinsic ligand concentrations, intrinsic molecular profiles and microscopic patterns, the results confirmed that increasing the amount of available growth factor leads to a spatially more aggressive cancer system. Moreover, for the cell closest to nutrient abundance, a phase-transition emerges where a minimal increase in extrinsic ligand abolishes the proliferative phenotype altogether. Conclusion Our in silico results indicate that in NSCLC, in the presence of a strong extrinsic chemotactic stimulus (and depending on the cell's location) downstream EGFR-ERK signaling may be processed more efficiently, thereby yielding a migration-dominant cell phenotype and overall, an accelerated spatio-temporal expansion rate.

Keywords: multi-agent based simulation, multi-level, biology

[Wang:2008]

Z. Wang and T.S. Deisboeck. Computational modeling of brain tumors: discrete, continuum or hybrid? *Scientific Modeling and Simulation*, 15(1):381–393, 2008.

Abstract: In spite of all efforts, patients diagnosed with highly malignant brain tumors (gliomas), continue to face a grim prognosis. Achieving significant therapeutic advances will also require a more detailed quantitative understanding of the dynamic interactions among tumor cells, and between these cells and their biological microenvironment. Data-driven computational brain tumor models have the potential to provide experimental tumor biologists with such quantitative and cost-efficient tools to generate and test hypotheses on tumor progression, and to infer fundamental operating principles governing bidirectional signal propagation in multicellular cancer systems. This review highlights the modeling objectives of and challenges with developing such in silicobrain tumor models by outlining two distinct computational approaches: discrete and continuum, each with representative examples. Future directions of this integrative computational neuro-oncology field, such as hybrid multiscale multiresolution modeling are discussed.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Wang:2009]

Z. Wang, C.M. Birch, J. Sagotsky, and T.S. Deisboeck. Cross-scale, cross-pathway evaluation using an agent-based non-small cell lung cancer model. *Bioinformatics*, 25(18):2389–2396, 2009.

Abstract: We present a multiscale agent-based non-small cell lung cancer model that consists of a 3D environment with which cancer cells interact while processing phenotypic changes. At the molecular level, transforming growth factor beta (TGFbeta) has been integrated into our previously developed in silico model as a second extrinsic input in addition to epidermal growth factor (EGF). The main aim of this study is to investigate how the effects of individual and combinatorial change in EGF and TGFbeta concentrations at the molecular level alter tumor growth dynamics on the multi-cellular level, specifically tumor volume and expansion rate. Our simulation results show that separate EGF and TGFbeta fluctuations trigger competing multi-cellular phenotypes, yet synchronous EGF and TGFbeta signaling yields a spatially more aggressive tumor that overall exhibits an EGF-driven phenotype. By altering EGF and TGFbeta concentration levels simultaneously and asynchronously, we discovered a particular region of EGF-TGFbeta profiles that ensures phenotypic stability of the tumor system. Within this region, concentration changes in EGF and TGFbeta do not impact the resulting multi-cellular response substantially, while outside these concentration ranges, a change at the molecular level will substantially alter either tumor volume or tumor expansion rate, or both. By evaluating tumor growth dynamics across different scales, we show that, under certain conditions, therapeutic targeting of only one signaling pathway may

be insufficient. Potential implications of these in silico results for future clinico-pharmacological applications are discussed.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Wang:2012]

Z. Wang, V. Bordas, J. Sagotsky, and T.S. Deisboeck. Identifying therapeutic targets in a combined egfr-tgf β r signalling cascade using a multiscale agent-based cancer model. *Mathematical Medicine and Biology*, 29(1):95–108, 2012.

Abstract: Applying a previously developed non-small cell lung cancer model, we assess ‘cross-scale’ the therapeutic efficacy of targeting a variety of molecular components of the epidermal growth factor receptor (EGFR) signalling pathway. Simulation of therapeutic inhibition and amplification allows for the ranking of the implemented downstream EGFR signalling molecules according to their therapeutic values or indices. Analysis identifies mitogen-activated protein kinase and extracellular signal-regulated kinase as top therapeutic targets for both inhibition and amplification-based treatment regimen but indicates that combined parameter perturbations do not necessarily improve the therapeutic effect of the separate parameter treatments as much as might be expected. Potential future strategies using this in silico model to tailor molecular treatment regimen are discussed.

Keywords: multi-agent based simulation, multi-scale, multi-level, cancer modeling

[Wang:2013]

J. Wang, L. Zhang, C. Jing, G. Ye, H. Wu, H. Miao, Y. Wu, and X. Zhou. Multi-scale agent-based modeling on melanoma and its related angiogenesis analysis. *Theoretical Biology and Medical Modelling*, 10(1):41, 2013.

Abstract: Background Recently, melanoma has become the most malignant and commonly occurring skin cancer. Melanoma is not only the major source (75%) of deaths related to skin cancer, but also it is hard to be treated by the conventional drugs. Recent research indicated that angiogenesis is an important factor for tumor initiation, expansion, and response to therapy. Thus, we proposed a novel multi-scale agent-based computational model that integrates the angiogenesis into tumor growth to study the response of melanoma cancer under combined drug treatment. Results Our multi-scale agent-based model can simulate the melanoma tumor growth with angiogenesis under combined drug treatment. The significant synergistic effects between drug Dox and drug Sunitinib demonstrated the clinical potential to interrupt the communication between melanoma cells and its related vasculatures. Also, the sensitivity analysis of the model revealed that diffusivity related to the micro-vasculatures around tumor tissues closely correlated with the spread, oscillation and destruction of the tumor. Conclusions Simulation results showed that the 3D model can represent key features of melanoma growth, angiogenesis, and its related micro-environment. The model can help cancer researchers understand the melanoma developmental mechanism. Drug synergism analysis suggested that interrupting the communications between melanoma cells and the related vasculatures can significantly increase the drug efficacy against tumor cells.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Wang:2013a]

Z. Wang and T.S. Deisboeck. Mathematical modeling in cancer drug discovery. *Drug discovery today*, 2013.

Abstract: Mathematical models have the potential to help discover new therapeutic targets and treatment strategies. In this review, we discuss how the latest developments in mathematical modeling can provide useful context for the rational design, validation and prioritization of novel cancer drug targets and their combinations. We give special attention to two modeling approaches: network-based modeling and multiscale modeling, because they have begun to show promise in facilitating the process of effective cancer drug discovery. Both modeling approaches are integrated with a variety of experimental methods to ensure proper parameterization and to maximize their predictive value. We also discuss several challenges faced in modeling-based drug discovery.

Keywords: multi-agent based simulation, multi-level, multi-scale

[Wang:2015]

Z. Wang, J-D. Butner, R. Kerketta, V. Cristini, and T.S. Deisboeck. Simulating cancer growth with multiscale agent-based modeling. *Seminars in cancer biology*, 30:70–78, 2015.

Abstract: There have been many techniques developed in recent years to in silico model a variety of cancer behaviors. Agent-based modeling is a specific discrete-based hybrid modeling approach that allows simulating the role of diversity in cell populations as well as within each individual cell; it has therefore become a powerful modeling method widely used by computational cancer researchers. Many aspects of tumor morphology including phenotype-changing mutations,

the adaptation to microenvironment, the process of angiogenesis, the influence of extracellular matrix, reactions to chemotherapy or surgical intervention, the effects of oxygen and nutrient availability, and metastasis and invasion of healthy tissues have been incorporated and investigated in agent-based models. In this review, we introduce some of the most recent agent-based models that have provided insight into the understanding of cancer growth and invasion, spanning multiple biological scales in time and space, and we further describe several experimentally testable hypotheses generated by those models. We also discuss some of the current challenges of multiscale agent-based cancer models.

Keywords: multi-agent based simulation, multi-level, multi-scale, cancer modeling

[Wang:2017]

Z. Wang and P.K. Maini. Editorial special section on multiscale cancer modeling. *IEEE Transactions on Biomedical Engineering*, 64(3):501–503, 2017.

Abstract: The papers in this special section focus on the use of multiscale modeling in the field of cancer research. Cancer is a complex, heterogeneous disease, characterized by many interaction processes on, and across, multiple scales in time and space that act in concert to drive cancer formation, progression, invasion, and metastasis. These processes range from molecular reactions to cell-cell interactions, to tumor growth and invasion on the tissue-scale, and even to larger scales, such as the physiology, pathophysiology, and population scales. In addition, many cancer properties (including, e.g., size, cell density, extracellular ligands, cellular receptors, mutation type(s), phenotypic distribution, vasculature status, blood vessel permeability, and treatment prognosis) are dynamic and patient-dependent, changing and evolving with both time and treatments. For example, cell death rate may change over time due to chemotherapy. All these dynamically changing cancer properties make development of effective cancer therapies extremely difficult. Computational modeling has the potential to predict complex behaviors of cancer, elucidate regulatory mechanisms, and help inform experimental design. Everyone would agree that computer simulations are usually more cost-effective, efficient, and tractable, relative to laboratory experiments.

Keywords: multi-agent based simulation, multi-level, cancer modeling, biology

[Wang:2020]

Y. Wang, R. Heiland, M. Craig, C.L. Davis, A.N.F. Versypt, A. Jenner, J. Ozik, N. Collier, C. Cockrell, and A. Becker. Rapid community-driven development of a sars-cov-2 tissue simulator. *bioRxiv*, 2020.

Abstract: The 2019 novel coronavirus, SARS-CoV-2, is an emerging pathogen of critical significance to international public health. Knowledge of the interplay between molecular-scale virus-receptor interactions, single-cell viral replication, intracellular-scale viral transport, and emergent tissue-scale viral propagation is limited. Moreover, little is known about immune system-virus-tissue interactions and how these can result in low-level (asymptomatic) infections in some cases and acute respiratory distress syndrome (ARDS) in others, particularly with respect to presentation in different age groups or pre-existing inflammatory risk factors like diabetes. A critical question for treatment and protection is why it appears that the severity of infection may correlate with the initial level of virus exposure. Given the nonlinear interactions within and among each of these processes, multiscale simulation models can shed light on the emergent dynamics that lead to divergent outcomes, identify actionable "choke points" for pharmacologic interactions, screen potential therapies, and identify potential biomarkers that differentiate response dynamics. Given the complexity of the problem and the acute need for an actionable model to guide therapy discovery and optimization, we introduce a prototype of a multiscale model of SARS-CoV-2 dynamics in lung and intestinal tissue that will be iteratively refined. The first prototype model was built and shared internationally as open source code and interactive, cloud-hosted executables in under 12 hours. In a sustained community effort, this model will integrate data and expertise across virology, immunology, mathematical biology, quantitative systems physiology, cloud and high performance computing, and other domains to accelerate our response to this critical threat to international health.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Ward:2019]

D. Ward. *Multiscale modelling of stem cell population dynamics*. PhD thesis, University of Bristol, 2019.

Abstract: Stem cells, with their propensity for pluripotency and self-regulation, have been the focus of intense research over the past decades. Understanding how the pluripotent phenotype is governed, across scales ranging from the cells' underlying genetic components to population-level interactions, is key to progressing from cultures of thousands of stem cells to maximal cell cultures, or entire tissues, from a small starting population. Stem cells are the precursors to all living cell types, existing during the embryonic development stage, but they can also be found

throughout the bodies of all developed living creatures, for example within the bone marrow or residing at the base of an intestinal crypt. The differential behaviours of embryonic and adult stem cells, combined with complex underlying genetic regulation and environment specific dynamics, present a number of open and pressing questions. In this thesis, we present mathematical and computational modelling approaches which allow us to elucidate the key dynamics of three different stem cell populations, to shine a light on the differential effects of culture conditions on each cell type, as well as to highlight the usefulness of modelling for driving experimental research and development of culture protocols. In the first part of the thesis, we develop a delay differential equation model to capture the culture-dependent dynamics of a homogeneous population of human haematopoietic stem cells, and show that a key culture protocol component, epo, has two response phases in which it differentially affects cell proliferation and differentiation. In the second part, we introduce agent-based modelling as a method for capturing the population dynamics of mouse embryonic stem cells (mESCs) in different culture conditions. We showed that linking the MycN component of the mESC gene regulatory network to the cell cycle captures both the subcellular distributions of key proteins and growth dynamics in vitro. Finally, we develop a multiscale agent-based model of intestinal crypts, that couples ordinary differential equation modelling of subcellular kinetics to a cell-based description of cell movement, proliferation, and contact inhibition (CI). This enables us to recapitulate tissue level dynamics of intestinal crypts, as well as to present an alternative approach to describing the formation of the Wnt expression gradient. We showed that cross-talk between the Hippo and Wnt signalling pathways is able to affect CI and that CI is likely significantly reduced in intestinal crypt mutations. Together, this research shows the effectiveness of modelling, across physical and temporal scales, to recapitulate in vitro and in vivo stem cell dynamics, as well as to capture the contributions of key behaviours such as proliferation and differentiation to healthy and dysplastic population growth.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Warsinske:2016]

H.C. Warsinske, A. Wheaton, K.K. Kim, J. Linderman, B.B. Moore, and D. Kirschner. Computational modeling predicts simultaneous targeting of fibroblasts and epithelial cells is necessary for treatment of pulmonary fibrosis. *Frontiers in Pharmacology*, 7(183), 2016.

Abstract: Pulmonary fibrosis is pathologic remodeling of lung tissue that can result in difficulty breathing, reduced quality of life, and a poor prognosis for patients. Fibrosis occurs as a result of insult to lung tissue, though mechanisms of this response are not well-characterized. The disease is driven in part by dysregulation of fibroblast proliferation and differentiation into myofibroblast cells, as well as pro-fibrotic mediator-driven epithelial cell apoptosis. The most well-characterized pro-fibrotic mediator associated with pulmonary fibrosis is TGF- β 1. Excessive synthesis of, and sensitivity to, pro-fibrotic mediators as well as insufficient production of and sensitivity to anti-fibrotic mediators has been credited with enabling fibroblast accumulation. Available treatments neither halt nor reverse lung damage. In this study we have two aims: to identify molecular and cellular scale mechanisms driving fibroblast proliferation and differentiation as well as epithelial cell survival in the context of fibrosis, and to predict therapeutic targets and strategies. We combine in vitro studies with a multi-scale hybrid agent-based computational model that describes fibroblasts and epithelial cells in co-culture. Within this model TGF- β 1 represents a pro-fibrotic mediator and we include detailed dynamics of TGF- β 1 receptor ligand signaling in fibroblasts. PGE2 represents an anti-fibrotic mediator. Using uncertainty and sensitivity analysis we identify TGF- β 1 synthesis, TGF- β 1 activation, and PGE2 synthesis among the key mechanisms contributing to fibrotic outcomes. We further demonstrate that intervention strategies combining potential therapeutics targeting both fibroblast regulation and epithelial cell survival can promote healthy tissue repair better than individual strategies. Combinations of existing drugs and compounds may provide significant improvements to the current standard of care for pulmonary fibrosis. Thus, a two-hit therapeutic intervention strategy may prove necessary to halt and reverse disease dynamics.

Keywords: multi-agent based simulation, multi-level, biology

[Wegener:2011]

M. Wegener. From macro to micro – how much micro is too much? *Transport Reviews*, 31(2):161–177, 2011.

Abstract: This paper discusses the usefulness of the trend towards microsimulation in urban transport and land-use modelling for the planning practice. It starts with a history of urban transport and land-use models and observes a trend towards increasing conceptual, spatial and temporal resolution stimulated by improved data availability, higher computer speed and better theories about mobility and location of individual behaviour. While recognizing these advances, the paper calls attention to the problems of disaggregate models in terms of data requirements, computing time

and stochastic variation and shows that in the light of new challenges cities are facing environmental problems, such as energy scarcity and climate change, not further refinement but more focus on basic needs and constraints is needed to make the models useful for the planning practice. As a possible solution to the macro–micro debate, it calls for a theory of multi-level models according to which for each planning task there is an appropriate level of conceptual, spatial and temporal resolution. The paper closes with an example of a multi-level land use, transport and environment model ranging from the European to the grid cell level.

Keywords: multi-agent based simulation, multi-level, traffic

[Wessler:2019]

T. Wessler, L.R. Joslyn, H.J. Borish, H.P. Gideon, J.L. Flynn, D.E. Kirschner, and J.J. Linderman. A computational model tracks whole-lung mycobacterium tuberculosis infection and predicts factors that inhibit dissemination. *BioRxiv*, page 713701, 2019.

Abstract: Mycobacterium tuberculosis (Mtb), the causative infectious agent of tuberculosis (TB), kills more individuals per year than any other infectious agent. Granulomas, the hallmark of Mtb infection, are complex structures that form in lungs, composed of immune cells surrounding bacteria, infected cells, and a caseous necrotic core. While granulomas serve to physically contain and immunologically restrain bacteria growth, some granulomas are unable to control Mtb growth, leading to bacteria and infected cells leaving the granuloma and disseminating, either resulting in additional granuloma formation (local or non-local) or spread to airways or lymph nodes. Dissemination is associated with development of active TB. It is challenging to experimentally address specific mechanisms driving dissemination from TB lung granulomas. Herein, we develop a novel hybrid multi-scale computational model, MultiGran, that tracks Mtb infection within multiple granulomas in an entire lung. MultiGran follows cells, cytokines, and bacterial populations within each lung granuloma throughout the course of infection and is calibrated to multiple non-human primate (NHP) cellular, granuloma, and whole-lung datasets. We show that MultiGran can recapitulate patterns of in vivo local and non-local dissemination, predict likelihood of dissemination, and predict a crucial role for multifunctional CD8+ T cells and macrophage dynamics for preventing dissemination.

Keywords: multi-agent based simulation, multi-level, multi-scale, hybrid model, biology

[Wijermans:2013]

N. Wijermans, R. Jorna, W. Jager, T. van Vliet, and O. Adang. Cross: modelling crowd behaviour with social-cognitive agents. *Journal of Artificial Societies and Social Simulation*, 16(4):1, 2013.

Abstract: The use of computer simulations in crowd research is a powerful tool to describe and analyse complex social systems. This paper presents CROSS, a generic framework to model crowd simulations as a social scientific tool for understanding crowd behaviour. In CROSS, individuals are represented by social-cognitive agents that are affected by their social and physical surroundings and produce cognition-based behaviour and behaviour patterns. Understanding is sought by relating intra- and inter-individual levels of behaviour generation with behaviour pattern emergence at group level. By specifying the CROSS framework for a festival context we demonstrate how CROSS meets the need for a theory that reflects the dynamic interplay between individuals and their environment as well as the need for a method that allows for testing.

Keywords: multi-agent based simulation, multi-level, pedestrian flow modeling

[Xi:2012]

H. Xi and Y-J. Son. Two-level modeling framework for pedestrian route choice and walking behaviors. *Simulation Modelling Practice and Theory*, 22:28–46, 2012.

Abstract: A microscopic two-level simulation modeling framework is proposed to analyze both decision-making processes at a crosswalk as well as physical interactions among pedestrians when they cross a street. The model at the higher level is based on Decision Field Theory to represent the psychological preferences of pedestrians with respect to different route choice options during their deliberation process after evaluating current surroundings. At the lower level, physical interactions among pedestrians and consequent congestions are represented using a Cellular Automata model, in which pedestrians are allowed biased random-walking without back step towards their destination that has been given by the higher level model. A typical crosswalk with split sidewalks in the Chicago Loop area is employed as a case study, which has been implemented in AnyLogic® software. Weekday pedestrian counts on the 15-min basis near the studied crosswalk have been collected and used to construct and validate the simulation models. Experiments have been conducted to investigate the impact of corresponding environment parameters, such as pedestrian types and green/red phase length, as well as social parameters such as leadership in group decision making, on the average pedestrian waiting time at the crosswalk. Initial results look quite

interesting. An extension on coupling the proposed pedestrian model with a transportation simulation model is also briefly discussed.

Keywords: multi-agent based simulation, multi-level, flow model

[Xing:2015]

F. Xing. *Towards Agent-based Multi-scale Tumor Growth Modeling: Software Environment and Computational Complexity*. PhD thesis, University of Heidelberg, 2015.

Abstract: Understanding tumor development crossing multiple spatial-temporal scales is of great practical importance to better fighting against cancers. It is hard to attack this problem with pure biological means. In recent decades, computer-based modeling and simulation techniques have been playing an increasingly important role in addressing it. After reviewing the literature, however, we notice that existing tumor models are either highly simplified or too complicated to be scaled to large tumor systems. In light of these problems, we have developed a software environment TUGME to facilitate the multi-scale modeling and simulation of tumor development based on the agent-based method. The most important feature of this software environment is its flexibility which enables straight-forward model reuse and extension. Tumor models of TUGME are hybrid as discrete and continuous approaches are coupled to model the discrete and continuous nature of the tumor system. TUGME is highly modularized, thus changing one module only requires few or no modifications to the others. Using TUGME, we have simulated the avascular growth of a multicellular tumor spheroid system of the tumor cell line, EMT6/Ro. Our tumor models treat individual tumor cells as single agents. The cell morphology and topology are represented by a 3D Voronoi tessellation. Cell motion, which is driven by mechanical interactions between a cell and its surroundings, is modeled using Newton's second law. Oxygen and glucose are treated as nutrients for cell energy production. Their transport and metabolism by cells are described by reaction-diffusion equations. Cell proliferation is defined considering the availability of both oxygen and glucose as well as the availability of space as its controllers. Based on these models, a series of simulations have been carried out. Good agreements between our simulations and experiments indicate the applicability of TUGME and the validity of our tumor models. In addition, the investigation of the invasive tumor morphology under different nutrient conditions shows that a lower nutrient concentration gives rise to a rougher tumor surface. One of the key challenges of agent-based multi-scale cancer modeling and simulation is the sharp increase of the computational cost of model solving with increasing system size (the number of tumor cells). According to our tests, the main computational bottleneck of our tumor models consists in solving the linear system of cell motion. To better understand this problem, we look into the properties of the matrix of the linear system. Our conclusion is that its matrix is extremely sparse, symmetric and positive-definite. These properties can help find a more efficient solver for the linear system. This work can be important reference for people who intend to work on individual-cell-oriented cancer modeling.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Xing:2015a]

F. Xing, J. Eisele, P. Bastian, and D.W. Heermann. Computational complexity of agent-based multi-scale cancer modeling. In *Proc. of the Conf. on Summer Computer Simulation*, pages 1–8, 2015.

Abstract: The computational cost of agent-based multi-scale tumor growth simulations usually grows explosively with increasing the system size. Current models have to comprise a lot between model complexity and model fidelity. In this paper, this problem is investigated using a tumor model developed by us. Our model takes into account the discrete and the continuous nature involved in tumor development by integrating the discrete and the continuum approaches. Each individual tumor cell is modeled as a single agent that interacts with its surroundings biochemically and biomechanically. Cells move in an over-damped manner, producing a system of linear equations. The transport and metabolism of nutrients are described by reaction-diffusion equations. Cell proliferation is performed according to the biochemical and biomechanical conditions of the environment. Several methods for numerically solving the linear system of cell motion are compared in terms of performance and stability. After that, our model is analyzed referring to its computational bottlenecks. In general, this work can provide important instructing information for people who intend to work on multi-scale cancer modeling using the agent-based method.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Xiong:2010]

M. Xiong, M. Lees, W. Cai, W. Zhou, and M.Y.H. Low. Hybrid modelling of crowd simulation. *Procedia Computer Science*, 1(1):57–65, 2010.

Abstract: Macroscopic and microscopic modeling have become mainstream methodologies for crowd simulation in dynamic environments. The two models make a trade-off between efficiency and accuracy, but neither of them is able to achieve both goals at the same time. With the aim of achieving both efficiency and accuracy, a hybrid modelling method is proposed in this paper for crowd simulation. This paper illustrates how the two types of models co-exist in a single simulation and work collaboratively. A case study for this method is also conducted, the simulation result of which shows that the proposed method can not only benefit from the macroscopic model by improving the simulation efficiency, but also obtain a fine-grained simulation result by adopting the microscopic model.

Keywords: multi-agent based simulation, multi-level, hybrid model, pedestrian flow modeling, flow model

[Yahyaoui:2017]

F. Yahyaoui and M. Tkiouat. A multi-level agent-based model of reinsurance. *Journal of Applied Economic Sciences*, 3(49):746–752, 2017.

Abstract: Advances in agent-based modeling continue to offer new tools and concepts to model and study phenomena involving more complexity. In particular, economic and social issues with different levels of interactions and representations can benefit from frameworks of multi-level agent-based modeling that have successfully simulated other problems sharing similar properties. We show through our work how reinsurance fits into this category of complex multi-level problems, how we adapted recent concepts with recent tools to go through the modeling obstacles of this issue to come up with a model that confirms the results of other renowned works and surpasses them in terms of analysis depth and assumptions flexibility.

Keywords: multi-agent based simulation, multi-level, economy

[Yahyaoui:2018]

F. Yahyaoui and M. Tkiouat. Agent-based co-modeling of information society and wealth distribution. *International Journal of Advanced Computer Science and Applications*, 9(11), 2018.

Abstract: With empirical studies suggesting that information technology influence wealth distribution in different ways, and with economic interactions and information technology adoption being two complex phenomena, there is a need for simulation approach that addresses the whole complexity of the issue without being too costly in terms of computations and without ignoring relevant empirical facts in defining the behavior of different agents.. While this problem seems to require a bottom-up approach using agent-based modeling, further complexity levels in managing the heterogeneous agents in space and time and an appropriate separation in domain areas show its limitations in practice. In this paper we illustrate the use of novel multi-level agent based concepts on this socio-economic issue, by considering our studied phenomenon as an interference of multiple simple other phenomena, namely a basic producer/consumer economy and a diffusion of information model. Such an approach involves writing models following a formalism allowing compatibility and exchange of variables, in addition to implementing appropriate synchronization algorithms. Our simulation used Levelspace, a recent extension project of Netlogo simulation tool combined with data exploration tools but the patterns described are generic and can be implemented in other simulation tools. Indeed, our case study offers a building block for a framework that can investigate wealth dynamics and other analogue cases with influence between models. Our approach successfully validates against empirical macro-trends in the distribution of wealth and other social patterns. Thanks to its flexibility in conducting experiments, we could reduce the hypotheses that restricted previous models from conducting a multi-dimensional analysis for the Gini index and enabled solving conflicting research issues.

Keywords: multi-agent based simulation, multi-level, co-simulation, social simulation, economy

[Yin:2018]

Z. Yin, Z. Deng, W. Zhao, and Z. Cao. Searching synergistic dose combinations for anticancer drugs. *Frontiers in Pharmacology*, 9:535, 2018.

Abstract: Recent development has enabled synergistic drugs in treating a wide range of cancers. Being highly context-dependent, however, identification of successful ones often requires screening of combinational dose on different testing platforms in order to gain the best anticancer effects. To facilitate the development of effective computational models, we reviewed the latest strategy in searching optimal dose combination from three perspectives: (1) mainly experimental-based approach; (2) Computational-guided experimental approach; and (3) mainly computational-based approach. In addition to the introduction of each strategy, critical discussion of their advantages and disadvantages were also included, with a strong focus on the current applications and future improvements.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling, review

[Yu:2016] J.S. Yu and N. Bagheri. Multi-class and multi-scale models of complex biological phenomena. *Current Opinion in Biotechnology*, 39:167 – 173, 2016.

Abstract: Computational modeling has significantly impacted our ability to analyze vast (and exponentially increasing) quantities of experimental data for a variety of applications, such as drug discovery and disease forecasting. Single-scale, single-class models persist as the most common group of models, but biological complexity often demands more sophisticated approaches. This review surveys modeling approaches that are multi-class (incorporating multiple model types) and/or multi-scale (accounting for multiple spatial or temporal scales) and describes how these models, and combinations thereof, should be used within the context of the problem statement. We end by highlighting agent-based models as an intuitive, modular, and flexible framework within which multi-scale and multi-class models can be implemented.

Keywords: multi-agent based simulation, hybrid model, multi-level

[Yu:2020] J.S. Yu and N. Bagheri. Agent-based models predict emergent behavior of heterogeneous cell populations in dynamic microenvironments. *Frontiers in Bioengineering and Biotechnology*, 8:249, 2020.

Abstract: Computational models are most impactful when they explain and characterize biological phenomena that are non-intuitive, unexpected, or difficult to study experimentally. Countless equation-based models have been built for these purposes, but we have yet to realize the extent to which rules-based models offer an intuitive framework that encourages computational and experimental collaboration. We develop ARCADE, a multi-scale agent-based model to interrogate emergent behavior of heterogeneous cell agents within dynamic microenvironments and demonstrate how complexity of intracellular metabolism and signaling modules impacts emergent dynamics. We perform *in silico* case studies on context, competition, and heterogeneity to demonstrate the utility of our model for gaining computational and experimental insight. Notably, there exist (i) differences in emergent behavior between colony and tissue contexts, (ii) linear, non-linear, and multimodal consequences of parameter variation on competition in simulated co-cultures, and (iii) variable impact of cell and population heterogeneity on emergent outcomes. Our extensible framework is easily modified to explore numerous biological systems, from tumor microenvironments to microbiomes.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology

[Zahedmanesh:2012] H. Zahedmanesh and C. Lally. A multiscale mechanobiological modelling framework using agent-based models and finite element analysis: application to vascular tissue engineering. *Biomechanics and Modeling in Mechanobiology*, 11(3):363–377, 2012.

Abstract: Computational models of mechanobiological systems have been widely used to provide insight into these systems and also to predict their behaviour. In this context, vascular tissue engineering benefits from further attention given the challenges involved in developing functional low calibre vascular grafts with long-term patency. In this study, a novel multiscale mechanobiological modelling framework is presented, which takes advantage of lattice-free agent-based models coupled with the finite element method to investigate the dynamics of VSMC growth in vascular tissue engineering scaffolds. The results illustrate the ability of the mechanobiological modelling approach to capture complex multiscale mechanobiological phenomena. Specifically, the framework enabled the study of the influence of scaffold compliance and loading regime in regulating the growth of VSMCs in vascular scaffolds and their role in development of intimal hyperplasia (IH). The model demonstrates that low scaffold compliance compared to host arteries leads to increased luminal ingrowth and IH development. In addition, culture of a tissue-engineered blood vessel under a pulsatile luminal pressure reduced luminal ingrowth and enhanced collagen synthesis within the scaffold compared to non-pulsatile culture. The mechanobiological framework presented provides a robust platform for testing hypotheses in vascular tissue engineering and lends itself to use as an optimisation design tool.

Keywords: multi-agent based simulation, multi-level, biology

[Zangoeei:2017] M.H. Zangoeei and J. Habibi. Hybrid multiscale modeling and prediction of cancer cell behavior. *PloS one*, 12(8):e0183810, 2017.

Abstract: BACKGROUND: Understanding cancer development crossing several spatial-temporal scales is of great practical significance to better understand and treat cancers. It is difficult to tackle this challenge with pure biological means. Moreover, hybrid modeling techniques have been proposed that combine the advantages of the continuum and the discrete methods to model multiscale problems. METHODS: In light of these problems, we have proposed a new hybrid vascular model to facilitate the multiscale modeling and simulation of cancer development with respect to the agent-based, cellular automata and machine learning methods. The purpose of this simulation is to create a dataset that can be used for prediction of cell phenotypes. By using a proposed Q-learning based on SVR-NSGA-II method, the cells have the capability to predict their phenotypes autonomously that is, to act on its own without external direction in response to situations it encounters. RESULTS: Computational simulations of the model were performed in order to analyze its performance. The most striking feature of our results is that each cell can select its phenotype at each time step according to its condition. We provide evidence that the prediction of cell phenotypes is reliable. CONCLUSION: Our proposed model, which we term a hybrid multiscale modeling of cancer cell behavior, has the potential to combine the best features of both continuum and discrete models. The in silico results indicate that the 3D model can represent key features of cancer growth, angiogenesis, and its related micro-environment and show that the findings are in good agreement with biological tumor behavior. To the best of our knowledge, this paper is the first hybrid vascular multiscale modeling of cancer cell behavior that has the capability to predict cell phenotypes individually by a self-generated dataset.

Keywords: multi-agent based simulation, multi-level, multi-scale, biology, cancer modeling

[Zehe:2015]

D. Zehe, D. Grotzky, H. Aydin, W. Cai, and A. Knoll. Traffic simulation performance optimization through multi-resolution modeling of road segments. In *Proc. of the 3rd ACM SIGSIM Conf. on Principles of Advanced Discrete Simulation (PADS)*, pages 281–288, 2015.

Abstract: In an agent-based traffic simulation the level of detail is crucial to the system's runtime performance as well as the fidelity of the results. Therefore, different model abstractions have been used throughout literature. Macroscopic, mesoscopic and microscopic models have their use-cases and benefits. Microscopic traffic simulations have a high level of detail but at the same time require a large amount of computational resources. In a large traffic network of a mega-city or an entire country, the use of a complete microscopic simulation is just not feasible. The resource required to do so are for most use-cases in no relation to the actual outcome. We propose a hybrid traffic simulation model that uses both, a high-resolution agent based microscopic simulation alongside a lower resolution flow-based macroscopic simulation for specific road segments. The problem with using different simulation models is the fidelity at the boundary between such simulation models. This fidelity discrepancy is caused by the difficulties with aggregation and disaggregation passing through the boundary. We show, in this paper, that the computational performance (simulation time) can be improved by 20% while maintaining a relative high accuracy of below 5% deviation from a pure microscopic simulation.

Keywords: multi-agent based simulation, multi-level, traffic

[Zhang:2007]

L. Zhang, C.A. Athale, and T.S. Deisboeck. Development of a three-dimensional multiscale agent-based tumor model: Simulating gene-protein interaction profiles, cell phenotypes and multicellular patterns in brain cancer. *Journal of Theoretical Biology*, 244(1):96–107, 2007.

Abstract: Experimental evidence suggests that epidermal growth factor receptor (EGFR)-mediated activation of the signaling protein phospholipase Cgamma plays a critical role in a cancer cell's phenotypic decision to either proliferate or to migrate at a given point in time. Here, we present a novel three-dimensional multiscale agent-based model to simulate this cellular decision process in the context of a virtual brain tumor. Each tumor cell is equipped with an EGFR gene-protein interaction network module that also connects to a simplified cell cycle description. The simulation results show that over time proliferative and migratory cell populations not only oscillate but also directly impact the spatio-temporal expansion patterns of the entire cancer system. The percentage change in the concentration of the sub-cellular interaction network's molecular components fluctuates, and, for the 'proliferation-to-migration' switch we find that the phenotype triggering molecular profile to some degree varies as the tumor system grows and the microenvironment changes. We discuss potential implications of these findings for experimental and clinical cancer research.

Keywords: multi-agent based simulation, multi-level, biology

[Zhang:2009]

L. Zhang, Z. Wang, J.A. Sagotsky, and T.S. Deisboeck. Multiscale agent-based cancer modeling. *Journal of Mathematical Biology*, 48(4–5):545–559, 2009.

Abstract: Agent-based modeling (ABM) is an in silico technique that is being used in a variety of research areas such as in social sciences, economics and increasingly in biomedicine as an interdisciplinary tool to study the dynamics of complex systems. Here, we describe its applicability to integrative tumor biology research by introducing a multi-scale tumor modeling platform that understands brain cancer as a complex dynamic biosystem. We summarize significant findings of this work, and discuss both challenges and future directions for ABM in the field of cancer research.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Zhang:2009a]

L. Zhang, L.L. Chen, and T.S. Deisboeck. Multi-scale, multi-resolution brain cancer modeling. *Mathematics and computers in simulation*, 79(7):2021–2035, 2009.

Abstract: In advancing discrete-based computational cancer models towards clinical applications, one faces the dilemma of how to deal with an ever growing amount of biomedical data that ought to be incorporated eventually in one form or another. Model scalability becomes of paramount interest. In an effort to start addressing this critical issue, here, we present a novel multi-scale and multi-resolution agent-based in silico glioma model. While ‘multi-scale’ refers to employing an epidermal growth factor receptor (EGFR)-driven molecular network to process cellular phenotypic decisions within the micro-macroscopic environment, ‘multi-resolution’ is achieved through algorithms that classify cells to either active or inactive spatial clusters, which determine the resolution they are simulated at. The aim is to assign computational resources where and when they matter most for maintaining or improving the predictive power of the algorithm, onto specific tumor areas and at particular times. Using a previously described 2D brain tumor model, we have developed four different computational methods for achieving the multi-resolution scheme, three of which are designed to dynamically train on the high-resolution simulation that serves as control. To quantify the algorithms’ performance, we rank them by weighing the distinct computational time savings of the simulation runs versus the methods’ ability to accurately reproduce the high-resolution results of the control. Finally, to demonstrate the flexibility of the underlying concept, we show the added value of combining the two highest-ranked methods. The main finding of this work is that by pursuing a multi-resolution approach, one can reduce the computation time of a discrete-based model substantially while still maintaining a comparably high predictive power. This hints at even more computational savings in the more realistic 3D setting over time, and thus appears to outline a possible path to achieve scalability for the all-important clinical translation.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Zhang:2011]

L. Zhang, B. Jiang, Y. Wu, C. Strouthos, P.Z.H.E. Sun, J. Su, and X. Zhou. Developing a multiscale, multi-resolution agent-based brain tumor model by graphics processing units. *Theoretical Biology and Medical Modelling*, 8(1):46, 2011.

Abstract: Multiscale agent-based modeling (MABM) has been widely used to simulate Glioblastoma Multiforme (GBM) and its progression. At the intracellular level, the MABM approach employs a system of ordinary differential equations to describe quantitatively specific intracellular molecular pathways that determine phenotypic switches among cells (e.g. from migration to proliferation and vice versa). At the intercellular level, MABM describes cell-cell interactions by a discrete module. At the tissue level, partial differential equations are employed to model the diffusion of chemoattractants, which are the input factors of the intracellular molecular pathway. Moreover, multiscale analysis makes it possible to explore the molecules that play important roles in determining the cellular phenotypic switches that in turn drive the whole GBM expansion. However, owing to limited computational resources, MABM is currently a theoretical biological model that uses relatively coarse grids to simulate a few cancer cells in a small slice of brain cancer tissue. In order to improve this theoretical model to simulate and predict actual GBM cancer progression in real time, a graphics processing unit (GPU)-based parallel computing algorithm was developed and combined with the multi-resolution design to speed up the MABM. The simulated results demonstrated that the GPU-based, multi-resolution and multiscale approach can accelerate the previous MABM around 30-fold with relatively fine grids in a large extracellular matrix. Therefore, the new model has great potential for simulating and predicting real-time GBM progression, if real experimental data are incorporated.

Keywords: multi-agent based simulation, multi-level, gpu, biology, cancer modeling

[Zhang:2014]

L. Zhang, Y. Xue, B. Jiang, C. Strouthos, Z. Duan, Y. Wu, J. Su, and X. Zhou. Multiscale agent-based modelling of ovarian cancer progression under the stimulation of the stat 3 pathway. *International journal of data mining and bioinformatics*, 9(3):235–253, 2014.

Abstract: This research is developed to simulate ovarian cancer progression with signal transducers and activators of the transcription 3 (STAT 3) pathway. The main focus is on studying how the STAT 3 pathway affects the cancer cells' biomechanical phenotype under the stimulation of the interleukin-6 (IL-6) cytokine and various well-known microscopic factors. The simulated results agreed with recent experimental evidence that ovarian cancer cells with a stimulated STAT 3 pathway have high survival rates and drug resistance. And we discussed how the IL6 and these well-known microscopic factors impacted the cancer progression.

Keywords: multi-agent based simulation, multi-level, biology, cancer modeling

[Zhang:2016]

L. Zhang, M. Qiao, H. Gao, B. Hu, H. Tan, X. Zhou, and C. Li. Investigation of mechanism of bone regeneration in a porous biodegradable calcium phosphate (cap) scaffold by combination of multi-scale agent based model and experimental optimization/validation. *Nanoscale*, 2016.

Abstract: Herein, we have developed a novel approach to investigate the mechanism of bone regeneration in a porous biodegradable calcium phosphate (CaP) scaffold by a combination of a multi-scale agent-based model, experimental optimization of key parameters and experimental data validation of the predictive power of the model. The advantages of this study are that the impact of mechanical stimulation on bone regeneration in a porous biodegradable CaP scaffold is considered, experimental design is used to investigate the optimal combination of growth factors loaded on the porous biodegradable CaP scaffold to promote bone regeneration and the training, testing and analysis of the model are carried out by using experimental data, a data-mining algorithm and related sensitivity analysis. The results reveal that mechanical stimulation has a great impact on bone regeneration in a porous biodegradable CaP scaffold and the optimal combination of growth factors that are encapsulated in nanospheres and loaded into porous biodegradable CaP scaffolds layer-by-layer can effectively promote bone regeneration. Furthermore, the model is robust and able to predict the development of bone regeneration under specified conditions.

Keywords: multi-agent based simulation, multi-level, biology

[Zitzow:2015]

S. Zitzow, D. Lehrke, and J. Hourdos. Developing a large-scale hybrid simulation model: Lessons learned. *Transportation Research Record*, 2491:107–116, 2015.

Abstract: Long-term, regional travel demand models are essential tools used by planning organizations for resource management, project scheduling, and impact studies. Developed primarily at the macroscopic level, these tools lack sufficient detail to capture the influence of local geometry, dynamic traffic controls, or advanced transportation demand management strategies. To bridge the gap, a hybrid mesoscopic–microscopic model was developed. The core of the model, surrounding two light rail corridors in Minneapolis–Saint Paul, Minnesota (the Twin Cities), was developed at high resolution for microscopic simulation to capture the interaction between traffic signals, transit systems, and the road network. The remainder of the greater Twin Cities area was implemented according to the regional planning model (RPM) maintained by the Metropolitan Council. Interfacing the AIMSUN-based hybrid model with the CUBE-based RPM, the Twin Cities metro hybrid simulation was used to improve mode choice and traffic assignment iteratively to achieve a dynamic user equilibrium state. Significant lessons were learned about the effort needed to develop and to maintain such a model, with implications for future large-scale regional modeling.

Keywords: multi-agent based simulation, multi-level, traffic, hybrid model