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Review

Cancer modeling: The holonic agent-based approach

Ali Masoudi-Nejad*, Alireza Meshkin

Laboratory of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran

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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. Holonical 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.

1. Introduction

Global cancer incidence is estimated 14.1 million cases in 2014 and cancer cases worldwide are forecast to rise by 75% and reach close to 25 million over the next two decades. These new figures and projections send a strong signal that immediate action is needed to confront this human disaster [1].

Computational models have been suggested as a method for gaining a more fundamental understanding of cancer. In general terms, computational modeling in cancer research can be classified in three categories: continuum, discrete and hybrids approaches, which combine continuum and discrete techniques in one form or another. Due to the inherent complexity of the cancer environment, arguably neither a true continuum nor a mere discrete model can describe all processes sufficiently [2]. So hybrid models like agent-based modeling (ABM) are becoming more and more popular due to their ability to allow for multiscale cancer modeling [3–6]. ABM is a computational technique that is being used in a variety of research areas such as in social sciences, economics and biomedicine as an interdisciplinary tool to study the dynamics of complex systems. This review focuses on recent advances in agent-based modeling technique that is being used to study the mechanisms involved in cancer formation and progression.

The organization of this paper is as follows. In the first section, an overview to ABM and the key features of an agent will be presented. The second part deals with presenting representative agent-based works in cancer progression, invasion, angiogenesis and metastasis. Comparing ABM technique over other commonly used computational techniques is also provided. Finally, this review is ended by recommending the use of holonic agent-based modeling in cancer research by describing Holon concept and merits of holonic agent-based modeling. A holonic agent-based modeling has not been used in cancer research so far. With regards to the capabilities of agents and Holon systems in complex environments, it seems to be important to create a holonic agent-based model for cancer in future investigations.

2. Agent-based modeling

Agent-based computing [7,8], is a large and widely spread scientific domain. An agent can range from a “software agent” or “service/daemon”, which might not behave very intelligently to an intelligent agent, which is based on models of artificially intelligent behavior [9,10]. An agent-based model is a computational model that represents individual agents and their collective behavior. Agent-based modeling is being used in a variety of research areas such as in social sciences [11], economics [12], healthcare operations management [13], stock market [14], supply chains [15], the spread of epidemics [16], the threat of bio-warfare [17], the

* Corresponding author. Tel.: +98 21 6695 9256; fax: +98 21 6640 4680.
E-mail addresses: amasoudin@ibb.ut.ac.ir, amasoudin@hotmail.com (A. Masoudi-Nejad).
URL: http://www.LBB.ut.ac.ir (A. Masoudi-Nejad).

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growth and decline of ancient civilizations [18] and the deregulation of electric power markets [19], just to name a few.

2.1. Agent definition

From a practical modeling standpoint, we consider agents to have certain characteristics [20]:

- An agent is identifiable, a discrete individual with a set of characteristics and rules governing its behaviors and decision-making capability. Agents are self-contained. The discreteness requirement implies that an agent has a boundary and one can easily determine whether something is part of an agent, is not part of an agent, or is a shared characteristic.
- An agent is autonomous and self-directed. An agent can function independently in its environment and in its dealings with other agents, at least over a limited range of situations that are of interest.
- An agent is situated, living in an environment with which it interacts with other agents. Agents have protocols for interaction with other agents, such as for communication, and the capability to respond to the environment. Agents have the ability to recognize and distinguish the traits of other agents.
- An agent may be goal-directed, having goals to achieve (not necessarily objectives to maximize) with respect to its behaviors. This allows an agent to compare the outcome of its behavior relative to its goals.
- An agent is flexible, having the ability to learn and adapt its behaviors based on experience. This requires some form of memory. An agent may have rules that modify its rules of behavior.

3. Approaches in cancer modeling

Cancer models encompass many different spatial and temporal scales, ranging from nanometers to meters and nanoseconds to days. Fig. 1 presents scaling issues in modeling cancer and indicates which approaches are particularly well-suited to dealing with each area. The techniques that are being developed to permit both temporal and spatio-temporal modeling over this wide range of scales, including: (1) ordinary differential equations (ODEs), partial differential equations (PDEs) and related techniques, (2) Petri nets, (3) cellular automata (CA), dynamic cellular automata (DCA) and agent-based models (ABMs) and (4) hybrid approaches.

A fundamental challenge to computational systems biology is to develop models that can deal with this wide range of granularity, so agent-based models (ABMs) are becoming more and more popular due to their ability to allow for multiscale cancer modeling [3–6].

4. Agent-based approach in cancer research

Several useful agent-based models of the origin, growth and spread of cancers have been developed in an effort to better understand the disease and potential therapeutic approaches. In this section representative agent-based works in cancer research are presented. Though it is impossible in a few lines to review the already vast literature of ABM in cancer research, in what follows a brief sketch is provided. Cancer is a complex specialized multi-scale process that can be studied from the intracellular, cellular or tissue perspectives. Therefore, agent-based modeling is a promising paradigm to model cancer development [21]. Zhang et al. developed an agent-based modeling of a brain tumor named Glioblastoma Multiforme (GBM) [2,22–24]. The different modeling approaches are used in this model: ordinary differential equations (ODE) at the intracellular level, discrete rules typically found in ABM at the cellular level and partial differential equations (PDE) at the tissue level (Fig. 2). Moreover, this model also relies on a multi-resolution approach: heterogeneous clusters, i.e. composed of migrating and proliferating cells are simulated at a high resolution while homogenous clusters of dead cells are simulated at a lower resolution. More computational resource is allocated to heterogenous regions of the cancer and less to homogenous regions [23]. This model incorporates a graphics processing unit (GPU)-based parallel computing algorithm [25], to speed up the previous agent-based models [22,24].

Lepagnot and Hutzler, developed an agent-based system for modeling the growth of avascular tumors to study the impact of PAI-1 molecules on metastasis [26]. To deal with the problem of complexity (a tumor may be composed of millions of cells) two levels are introduced: the cell and the tumor's core levels. Indeed, such cancers are generally structured as a kernel of necrosed or quiescent cells surrounded by living tumor cells. As necrosed and quiescent cells are mostly inactive, tumor's core is reified as a single upper-level agent, interacting with cells and PAI-1 molecules at its boundary. A more comprehensive analysis of this model can be found in [27].

Athale et al. developed a multiscale agent-based model in combination with a gene-protein interaction network for the description of the growth of glioblastoma [28]. In this model, the ABM describes the tumor on the cellular. On the molecular scale, for each cell a system of ordinary differential equations represents a gene–protein interaction network that defines the action rules for the agents. This model integrates sub-cellular network model of EGFR signaling with the prior tumor ABM [29]. It is able to model proliferation versus migration decision based solely on intracellular gene network. Coupling model with experiments will allow hypothesis generation and testing. They also developed an agent-based model [30], Expanded multi-scale ABM from [28]. This model simulates different expression levels of EGFR. It examines the influence of experimentally measured EGFR expression values on protein expression, cell interactions and emergent whole tumor dynamics. The Model suggests that both proliferative and migratory phenotypes are necessary for rapid tumor expansion, and underscores the importance of post-translational regulation of protein expression.

The multiscale 3D agent-based non-small cell lung cancer model [31], encompasses both molecular (signaling pathway) and microscopic (multicellular) scales. At the molecular level, two stimuli, epidermal growth factor (EGF) and transforming growth factor β (TGFβ), trigger downstream signaling through different routes but converge at the activation of the Raf signal. The model found that increasing EGF results in a more invasive phenotype, while increasing EGF concentration together with TGFβ concentration further increased the agents' sensitivity to changes in the environment that could trigger invasiveness.

Mansury et al. added the evolutionary game theory to a previously developed brain tumor ABM [29], to examine feedback effects between tumors and environment. Highly malignant phenotypes can exist without detectable structure changes. Based on this tumor heterogeneity, the authors recommend multiple biopsies to characterize a tumor's true state.

Zhang et al. developed a three-dimensional agent-based tumor model [22]. This model utilized basic gene-protein interactions and multi-cellular patterns specific to brain cancer. This model represented internal cellular processes via differential equations, and the location of cells spatially. Each tumor cell is equipped with an EGFR gene-protein interaction network module that also connects to a simplified cell cycle description.

Mansury and Deisboeck, proposed a two-dimensional agent-based model in which the spatio-temporal expansion of malignant brain tumor cells is guided by environment heterogeneities in mechanical confinement, toxic metabolites and nutrient sources to

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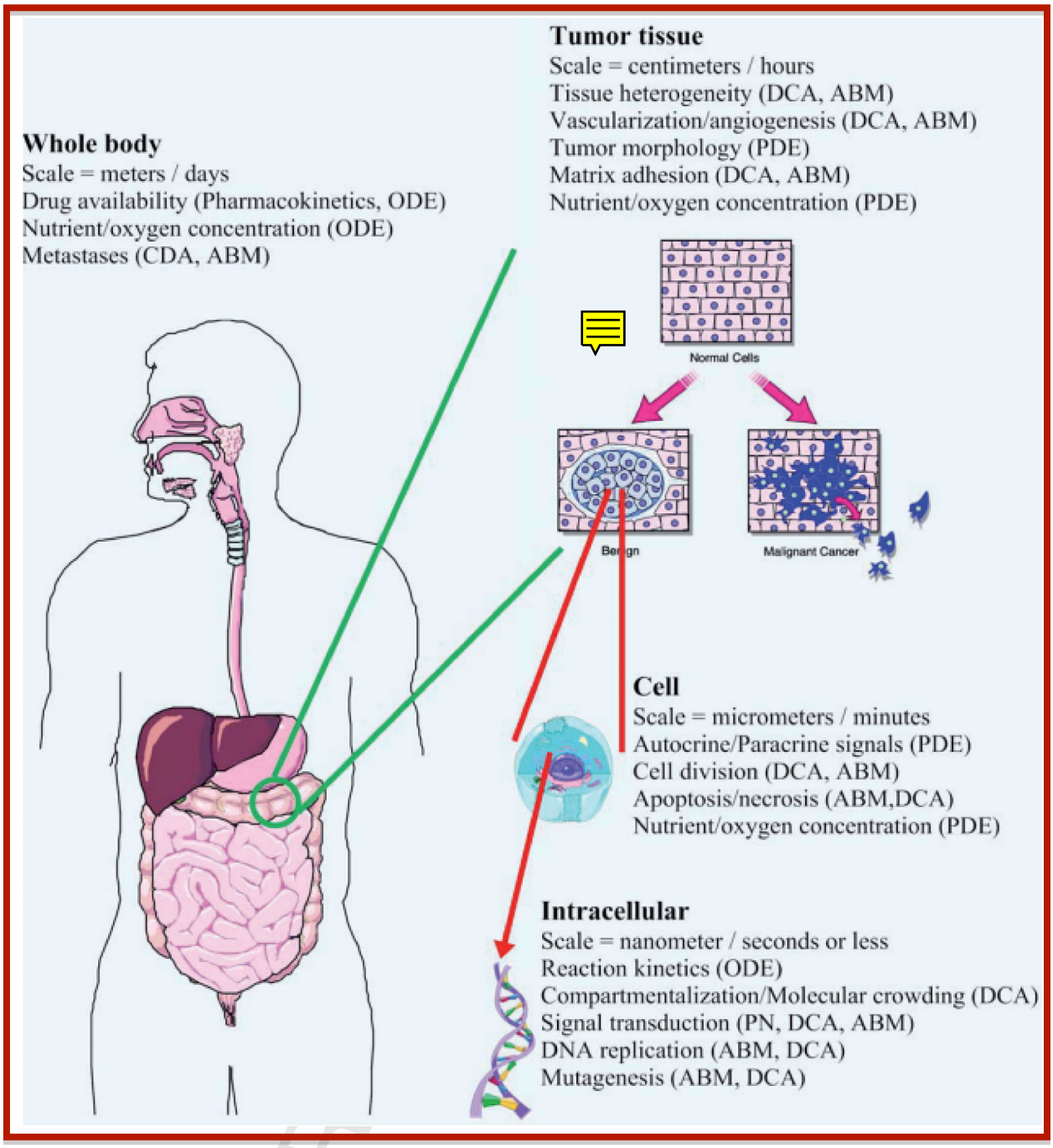

Fig. 1. Issues of modeling cancer. From whole organism to tumor tissue to individual cells to the molecules of replication and metabolism, modeling tumors spans about nine orders of spatio-temporal magnitude. Shown above are some of the modeling issues which need to be addressed at each level of simulation. Each text box includes the relevant spatio-temporal scale and modeling issues encountered at that level. Appropriate modeling approaches to address each issue are shown in brackets. Building hierarchical systems of inter-related models is still a primary challenge to modern researchers. ODE – ordinary differential equation system, PDE – partial differential equation system, DCA – dynamic cellular automaton, PN – Petri net system, ABM – agent based model [71].

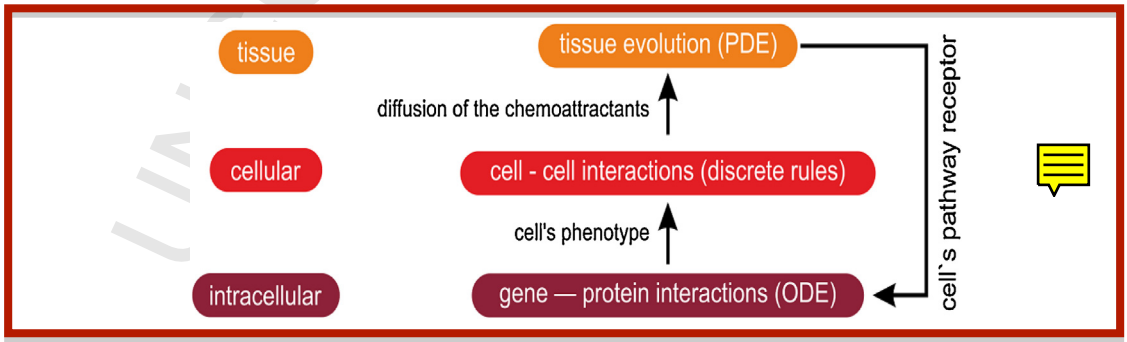

Fig. 2. Agent-based approach in brain tumor modeling [2,22–24].

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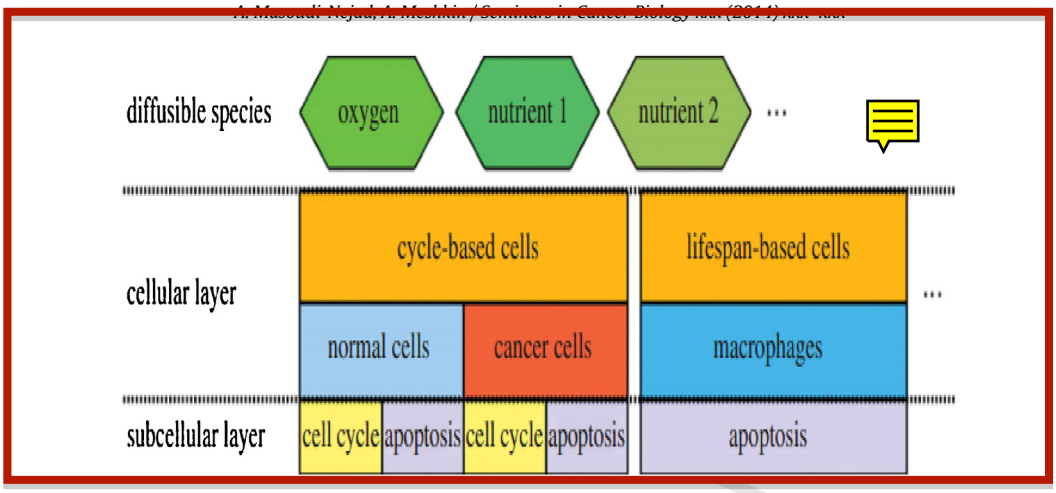

Fig. 3. The conceptual model of the multi-scale environment. There are three layers in the model: the diffusible, the cells and the intracellular phenomena (such as the cell cycles and apoptosis) [35].

gain more insight into the systemic effect of such cellular chemotactic search precision modulations [32]. Moreover, by calibrating the expression of Tenascin C and PCNA using experimental brain tumor data for the migratory phenotype while generating the gene expression for proliferating cells as the output, numerical result from the model [33], confirmed that among the migratory phenotype the expression of Tenascin C is indeed consistently higher, while they reveal the reverse for the proliferating tumor cells, which exhibit consistently higher expression of the proliferating cell nuclear antigen (PCNA) gene.

Brown et al. developed 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 [34]. This model consists of an environment and two teams of agents. The environment is a 3-D lattice structure which represents a discretized section of tissue. Each location within the lattice has a nutrient level which remains static over time. This level combines the availability of various nutrients that cells need to be prosperous (oxygen, glucose, etc.) into a single integer value. Represented as an agent, each cell has an age, a team affiliation, and a location within the environment. The age of a cell indicates the number of time steps a cell has existed in the simulation. The team affiliation of a cell indicates whether a cell is a member of the team of healthy cells or the team of cancerous cells and what policy to execute. The hypothesis of this model is that by modeling healthy cells and cancerous cells as opposing teams, and having policies generated automatically rather than generated by hand, the model may gain a more fundamental understanding of cell behavior.

Figueredo et al. developed an open-source, extensible, agent-based environment for simulation of the dynamics of cell populations and their responses to nutrient shortage [35]. Different elements from distinct time and length scales are coupled together in this model. The model features include competition between cell-cycle-based cells (for example, cancer and normal cells, which can divide) and lifespan-based cells (e.g. macrophages, which can only die after a certain lifespan), cellular random walks and coupling to diffusible substances such as nutrients (e.g. via consumption and/or production by cells). Cell-cycle models and cell death (apoptosis) can be dependent on the diffusible substances (e.g. nutrients such as oxygen). The general structure of the model was therefore divided into three layers, corresponding to the diffusible nutrients, the cellular and the intracellular phenomena, as shown in the conceptual model of Fig. 3. This model was implemented using a multi-method approach comprising (i) two- and three-dimensional lattices containing the cells and molecules from the system; (ii) agents, representing the biological cells that lie in the lattice; (iii) diffusion rules for the agents' motility; (iv) ODEs for subcellular networks that regulate the cell cycle; and (v) PDEs for the transport, release and uptake of nutrients. This environment was developed within Chaste [36], as part of the VPH Toolkit. This tool can be used to test potential new treatments for various pathologies, such as early-stage cancer.

Sun et al. developed a novel multi-scale agent-based brain tumor model [6]. The model incorporates four relevant biological scales: the molecular scale, the cellular scale, the microenvironment scale and the tissue scale. At the molecular scale, a system of ordinary differential equations simulates the dynamics of the EGFR signaling pathway and the cell cycle to determine the cells' phenotypic switch at the cellular scale. The model employed a set of partial differential equations to simulate the concentration changes of five extracellular chemical cues (glucose, oxygen, TGFα, VEGF and fibronectin) in the tumor micro environmental scale. Angiogenesis were coupled into tumor growth through VEGF secreted by the tumor cells and through the glucose and oxygen permeated from the neo-vasculature at the tissue scale. Moreover, in this model, TKI treatment is integrated into an EGFR signaling pathway to block the activation of EGFR. The simulations demonstrate that the entire tumor growth profile is a collective behavior of its cells regulated by the EGFR signaling pathway and the cell cycle.

The Ductal Epithelium Agent-Based Model (DEABM) is composed of computational agents that behave according to rules established from published cellular and molecular mechanisms concerning breast duct epithelial dynamics and oncogenesis [37]. The DEABM implements DNA damage and repair, cell division, genetic inheritance and simulates the local tissue environment with hormone excretion and receptor signaling.

The DEABM was developed such that the baseline dynamic state of the model, representing "health" could give rise to aberrant conditions (i.e. cancer) by introducing recognized functional abnormalities into the cellular agent rule sets (e.g. a mutation inactivating a tumor suppressor). The DEABM was implemented using NetLogo 5.0, [38]. The complete code of the DEABM can be downloaded from http://bionetgen.org/SCAI-wiki/index.php/Main_Page.

Wang et al. [3], developed a 3D multi-scale agent-based model to investigate the role of the tumor angiogenesis interactions in melanoma tumor progression by extending well-developed 2D agent-based tumor growth models [2,22,24]. The model integrates the angiogenesis into tumor growth to study the response of melanoma cancer under combined drug treatment. As a rule based model, this study developed a set of rules to determine the melanoma cell's phenotypic switch. These rules not only underline the migration of endothelial cells and the branching of vessel sprouts, but can also be more easily integrated into the agent-based tumor growth model than previous Hybrid Discrete-Continuum

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(HDC) rules [39]. This model is implemented in the VC++ programming environment.

Schuetz et al. developed an agent-based model of malignant brain tumor growth [4]. The growth of glioblastoma is investigated on the intra-cellular and inter-cellular scale. Go or Grow principle of tumor cells states that tumor cells either migrate or proliferate [4]. For glioblastoma, microRNA-451 has been shown to be an energy dependent key regulator of the LKB1 (liver kinase B1) and AMPK (AMP-activated protein kinase) pathway that influences the signaling for migration or cell division. These biological processes are reproduced in this model. The intracellular molecular interaction network is represented by a system of nine ordinary differential equations. Each cell is equipped with this interaction network and additional rules to determine its new phenotype as either migrating, proliferating or quiescent. The model is implemented in C++.

Olsen et al. developed a three-dimensional multiscale agent-based model of tumor growth with angiogenesis [5]. The model is designed to easily adapt to various cancer types, although it focuses on breast cancer. It includes cellular (genetic control), tissue (cells, blood vessels, angiogenesis), and molecular (VEGF, diffusion) levels of representation. 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. Agent-based models allow each cell to be modeled separately, following some series of rules on its behavior. The definition of the functioning of a cancer cell is based on the hallmarks of cancer [40].

5. Comparison of ABMs with other models in cancer research

It has been evidenced that agent-based models present advantages with respect to other models, like differential equation [41], cellular automata [42], network analysis [43], and Boolean networks [44]. In this section, ABMs are compared with other models very briefly.

5.1. Comparison of ABMs with network analysis and Boolean network models

Network analysis seeks to understand the relationships within biological networks such as metabolic, protein-protein interaction and cancer related networks [45]. Network analysis of cellular subsystems such as the networks of metabolites and enzymes are applied to both analyze and visualize the complex connections of these cellular processes in the field of cancer research. Although biological networks can be constructed from a single type of molecule or entity (such as genes), network biology often attempts to integrate many different data types, such as proteins, small molecules, gene expression data, and others, which are all connected physically and/or functionally [46]. Network analysis is very easy to implement. Some limitations are imposed by its static nature that prevents one from obtaining insights into the causes of a given structure, and from making predictions about its future behavior. Moreover, it cannot take into account complex or multiple relationships or node attributes. Thus, though it is a valid method of research in biology and medicine, which is receiving further interest in the field of cancer research [47–50], it appears severely limited when compared with ABMs. In respect to ABMs, however, network analysis main appeal resides in the ease of use. The approach based on (random or probabilistic) Boolean networks overcomes the problem of being static [51]. In respect of network analysis the gain in making the process dynamic is traded against the complexity of the system description. In this respect, ABMs have, at least in principle, no limitation in dealing with the complexity of the components (agents) and their interactions [52].

5.2. Comparison between ABMs and system dynamic models in cancer research

Basically system dynamic models can be grouped into the ordinary differential equation-based (ODE) models and partial differential equation-based (PDE) models [53]. In mathematics, a PDE is a differential equation that contains unknown multivariable functions and their partial derivatives. PDEs are used to formulate problems involving functions of several variables, and are either solved by hand, or used to create a relevant computer model. An ODE is an equation containing a function of one independent variable and its derivatives. The term “ordinary” is used in contrast with the term partial differential equation which may be with respect to more than one independent variable. One of the major reasons for using ABMs is that they allow for tracking of individual cells and cell properties. This is tedious or impossible to do with PDE models. Another benefit of ABM is that some ABM modeling packages require less coding experience than PDE models, and code can be much more intuitive for a non-modeler to understand. Even with the simplest types of descriptive code, however, all agents and subroutines must be thoroughly tested to ensure that emergent properties do not result from coding artifacts. The heterogeneous properties of tissue are also more easily represented in an ABM. In both ABMs and PDE models, a large number of simulations are required for adequate exploration of the parameter space. In PDE models, there are well-developed mathematical methods for this exploration, while these techniques are just beginning to be applied to ABMs. The speed of execution of ABMs may be more dependent on the skill of the programmer than for PDE models. That said, larger ABMs can monopolize computational resources, and few ABM suites allow for parallel processing to reduce the computational time. Finally, ABMs require the assumption that all properties can be modeled discretely, while PDE models require a continuum approximation. The reality for cancer modeling may lie somewhere in the middle of these approaches-some cell variables may be continuous, while others may have discrete states.

For cancer modelings, ABM can provide more information about the mechanisms of a process than other modeling techniques. Abbott et al. [54] built an ABM, CancerSim, of the interaction of cells exhibiting previously published ‘hallmarks of cancer’ [40] to investigate the mechanisms behind tumorgenesis and compared it to a previously published ordinary differential equation model of the same cell behaviors [55]. The ABM and ODE models both identified a similar combination of phenotypes that would present the shortest path to cancer, but the ABM provided improved cell spreading resolution, was able to follow the fates of single cells, and could examine the interactions between cells within a heterogeneous population [54].

New approaches are being developed to bridge ABM and PDE modeling techniques [38], in order to capitalize on beneficial attributes of these approaches and to compensate for their respective drawbacks. Nova [56], is a new Java-based modeling platform that naturally supports the creation of models in the system dynamics, spatial and agent-based modeling paradigms.

5.3. Comparison of ABMs with cellular automata

A cellular automata is a discrete dynamic system, and the behavior of CA is specified in terms of local relations. The space in a CA system is divided into a lattice or grid of regularly-space cells of the same size and shape, usually square [56]. Each cell has a value either 0 or 1 or on a scale from 0 to 1. The state of a cell and its behavior is determined by the state of other cells in close

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proximity at a previous time step, by a set of local rules and by the cell itself.

An important feature of a CA is that the automata's location does not move; they can only change their state. The position of the cells and their neighborhood relations remain fixed over time. In contrast, agents can be either fixed in location or free to 'roam' around their environment. Unlike agents, CAs cannot have more than one attribute.

Both CA and agent-based models, model the complexity of social systems with similar individual level representations. However, they differ in their emphasis; CA model social dynamics with a focus on the emergence of properties from local interactions while agent-based models simulate more complex situations where agents control their own actions based on their knowledge of the environment [57].

6. Limitations of agent-based modeling

The computational efficiency of ABMs declines as the number of agents (cells) increases and as the length of the rule set increases, making large and complex ABMs time consuming to compute. Because stochastic rules are often incorporated, simulations must be run repeatedly to obtain statistical significance, thereby increasing the run-time needed to complete an analysis.

There are some of the limitations in using agent-based modeling. For example, these methods require a lot of interaction among each agent and it need frequent communication so that the decision and activities was made at the right position. This method might not be selected because it involves large amount to be spend for communication. Beside that this method requires the modeler to be more careful about implementing it in a big systems as it may require a high skill computation and consume a lot of time because large system usually consist of many types of units [58].

The parallel implementations of the agent-based models on GPUs have been a recent trend with significant performance improvement reported from the serial counterpart for extra-large scale simulations. For example, in the work [59], an optimization to the GPGPU implementation of the agent-based model is proposed. This model accelerate simulation of agent-based models on heterogeneous architectures that the generality of the methodology can be used for accelerating agent-based cancer modeling applications in further researches.

7. Holon-based modeling

Cells can be described as open systems which contain collections of autonomous computational agents interacting with each other. These open systems exhibit parallel distributed processing in that different parts of the cell do different things and the adaptive capabilities of the system are reflected in its data driven capacities, considerable degree of fault tolerance, lack of global control, high degree of communication and the ability of multiple parts to carry out partial computations, But none of the existing mathematical models pay attention to autonomous characteristics of cells or can distinguish any local specification of reactions. Hence it is impossible to model the specific interactions of a molecule or the other above mentioned characteristics of cells. Since the structure of a biological system is really compatible with holonic systems structure, we believe that using holonic multi agent systems can help us reach this aim.

In a multi-scale agent-based cancer modeling, there are many agents interacting with each other and hence it is a complex system. An approach to reduce the complexity of such systems is using holonic multi-agent system (HMAS). The holons are hierarchically arranged in multi levels. A holonic organization is a hybrid, recursive and hierarchical structure which is able to generate dynamic linkages to control the structure. The modeling of cancer can be divided into sub-problems each assigned to a Holon in order to improve the efficiency.

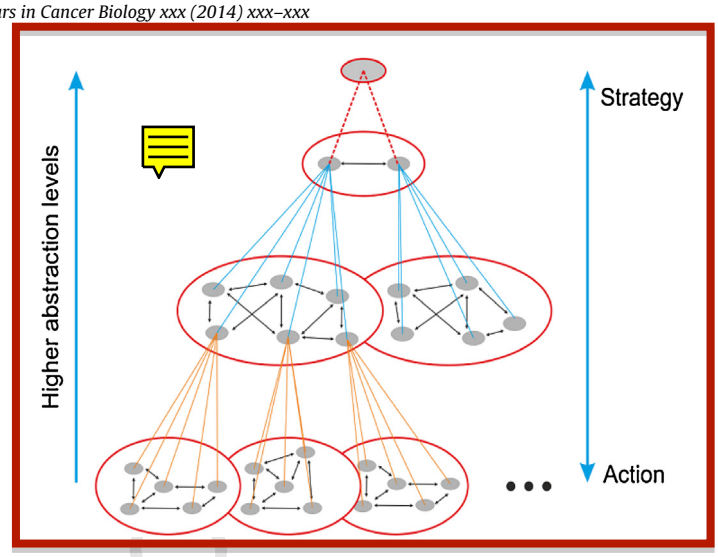

Fig. 4. A holarchy composed of four holarchical levels [72].

It has been proved that HMAS is an effective solution for several problems associated with hierarchical and self-organizing structures [60]. It has been successfully applied in a wide range of complex systems. For instance, we can mention the works done in transportation [61], distributed sensor management [62], adaptive mesh problem [63], supply chain management [64], health organizations [65], biological network simulation [66] and complex software systems [67].

7.1. Holon principles

The Holon which was first proposed by Koestler [68], is a kind of agent with extra ability. It is a self-similar building block that is stable, coherent and has recursive structure. Koestler observed that in living organisms there is no non-interactive entity and each unit comprises several basic units. For instance, a human being consists of organs which consist of cells that can further be decomposed to nucleus and plasma and so on. According to Koestler, a Holon that can be natural or artificial, is a fractal structure which is stable, coherent and which consists of several Holons as sub-structures. Each Holon lives in a hierarchical structure named Holarchy. In other words, Holon has a recursive structure that cannot be understood completely without its sub-components or without the super component that it is part of. Fig. 4 shows a holonic system arranged in four holarchical levels.

Holons and agents share some traits such as action, autonomy, belief, communication and goal-directed behavior, but they differ in some ways. Generally some salient characteristics of Holons and Holarchy, proposed in deferent references, are as follows [66]:

- Each Holon is an autonomous actor which has its own principles and goals but, simultaneously, is able to accept the principles and goals of a super-Holon. Thus the goals and strategies of each Holon are restricted by its super-Holon.
- Sometimes a super-Holon can fulfill its goals from the common goals of its sub-Holons. Notice that it is not necessarily required for sub-Holons to have the same goal as their super-Holon but these two must not contradict each other.
- Communication must obey the Holarchy. Each Holon can only communicate with its super-Holon, sub-Holons and the Holons on its own level. The messages are detailed when they are sent

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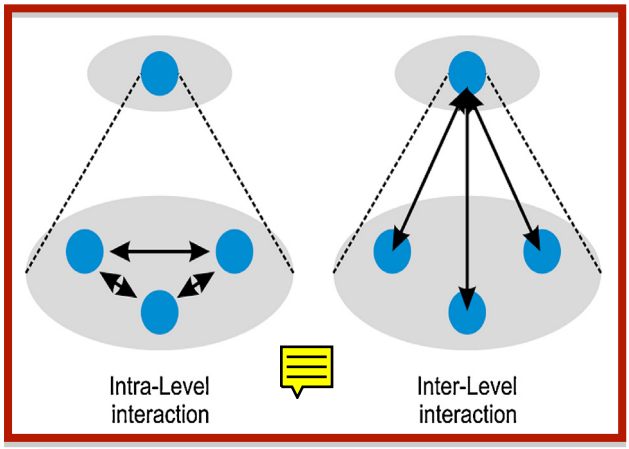

Fig. 5. Two types of interactions between holons in a holarchy [69].

from top to bottom and are synthesized when they are transmitted from bottom to top.
- The communications from the outside of the system (interface) go through the base Holons in the first or lowest level.
- An atomic Holon can autonomously divide into several sub-Holons.
- A sub-Holon can autonomously leave its super-Holon and join the other one.
- A sub-Holon can be the member of several Holons or participate in multiple hierarchies at the same time.
- The complex activity and behavior are situated at the top of the Holarchy, the simple and reactive acts take place at the base of the Holarchy. In other words, upper level Holons are more pro-active and lower levels are more reactive. Hence the upper level is the decision center and the lower level is the interface of the system.

7.2. Interaction between holons

Holonic organization includes a set of holons arranged in different levels. Distributed holons try to achieve a common goal through cooperation and coordination. Two types of interactions can be seen in a holonic organization as shown in Fig. 5. Intra-level interaction has been investigated in multi-agent system research. A holonic or any other intelligent agent-based framework which is entirely based on intra-level negotiation or interaction is likely to be inadequate [69]. In practice, in addition to the intra-level interaction among the agents, there are vital interactions that take place between agents in different levels. For example, in any multi-level hierarchical multi-agent system, inter-level interactions play an important role.

7.3. Criteria for a holonic approach

The strength of the holonic paradigm is its recursive definition of holons. Thus it is well adapted for large complex systems where different granularities are required. Using holons as modeling approach for a small close system may not always be recommended. If the system does not require multiple levels of granularity, holons will probably introduce an unnecessary overhead. Cancer modeling meets the characteristics of a holonic approach [70]. The suitability of the holonic scheme for cancer modeling can be assessed in the following way.

7.3.1. Operator abstraction

Holonic systems are well suited for cancer modeling because of actions of different granularity. Macro-level actions of the model are carried out by the Holon's head and decomposed onto the sub-holons. This could be realized in a traditional multi agent system also; however, the relationship between the individual agents and the group would have to be represented additionally; a holonic system provides all the relevant features a priori. Holonic systems are well suited for analyzing and modeling of large systems where multiple levels of abstraction exist. Another type of systems are those that can be decomposed recursively into smaller sub-components [69].

7.3.2. Hierarchical structure

Cancer modeling exhibits a hierarchical structure so, it is an excellent candidate for a holonic system, since hierarchies of sub-holons can be modeled canonically. The structure of the cancer modeling induces abstraction levels, which can be modeled naturally in a holonic system. Schematic illustration of the biological scales of significant relevance for cancer modeling including atomic, molecular, microscopic (tissue/multicellular), and macroscopic (organ) scales are shown in Fig. 6.

7.3.3. Decomposability

One of the main pre-requisites for a traditional agent-based system is a decentralized or decomposable problem setting, where each agent is assigned to one of the sub-problems. Pro-activeness and autonomy of the agents are the main features.

However, often, problems are neither completely decomposable nor completely non-decomposable; in many *hybrid* cases, some aspects of the problem can be decomposed, while others cannot. Holonic agents are structured hierarchically, they can easily realize actions of different granularity, they are autonomous to a certain degree and they are pro-active; hence holonic agent systems can naturally deal with problems of that type.

7.3.4. Communication

The cancer modeling problem can be decomposed into sub-problems that are not partitioning of the original one, but there is some overlap in the sense that logical interdependencies occur, communication among the problem solvers is needed. Sub-agents of a Holon are communicative and hence, holonic agents are useful in domains of this type. Furthermore, a domain often induces an asymmetric communication behavior between problem solvers in the sense that each unit does not communicate to all other units equally often, i.e. patterns in the communication behavior can be observed. These patterns indicate possible structures for holonic agents: holons provide facilities for efficient *intra-holonic* communication, supporting higher frequent communication inside the Holon than among different holons *(inter-holonic).*

Nearly everything in the biological world, at all scales of magnification, is inter-action: be it the interactions between proteins at a molecular level, inter-cell communications at a cellular level, the web of interactions between organism

7.3.5. Social elements

If there is no cooperation among agents in the domain, the use of holonic agents is not very reasonable. If there are cooperative elements in the domain, holonic agents can be used to model the cooperative sub-domain.

7.3.6. Conclusion

The most important requirements for a holonic agent are structure and cooperation: cancer modeling problems have a holonic structure, i.e. it is recursively decomposable. This structure can map canonically onto the holonic system. Furthermore, there are sufficient cooperative elements between the distinguished problem solvers. One important difference to a traditional multi-agent domain is the possibility to model centralistic aspects of a domain as well.

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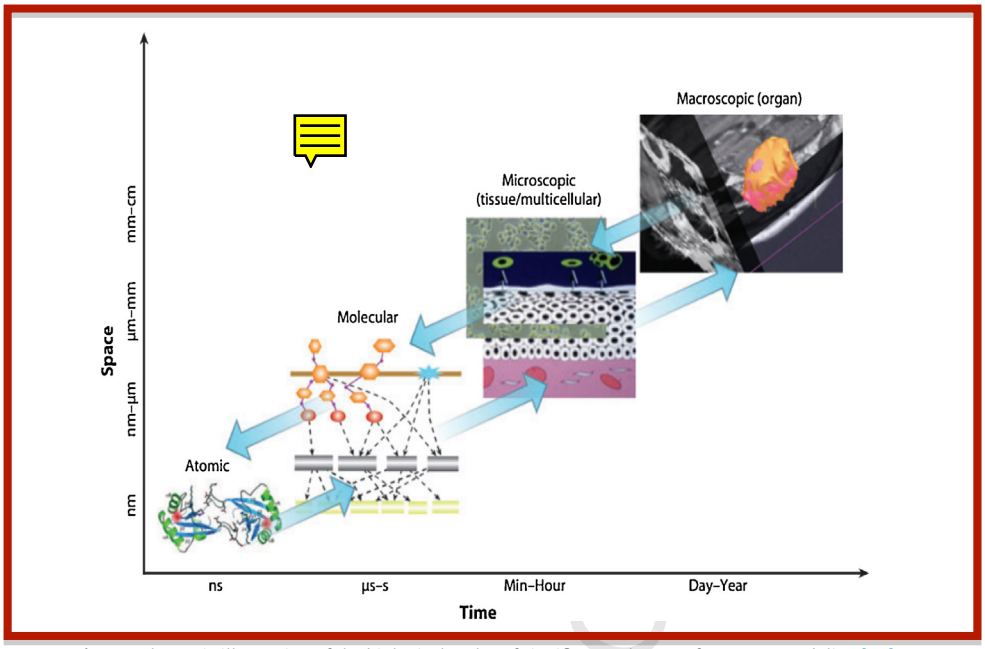

Fig. 6. Schematic illustration of the biological scales of significant relevance for cancer modeling [73].

8. Outline

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.

In this review, an overview to ABM and the key features of an agent is presented. Then ABM technique is compared over other commonly used computational techniques. Holon concept and merits of holonic agent-based modeling are also described. This review is focused on recent advances in agent-based modeling technique that is being used to study the mechanisms involved in cancer formation and progression.

Cancer modeling meets the characteristics of a holonic approach. The suitability of the holonic scheme for cancer modeling is discussed. Since the structure of a cancer system is really compatible with holonic systems structure, it seems to be important to create a holonic agent-based model for cancer in future investigations. It can be concluded that holonic agent-based modeling is an approach that will enable cancer modeling research to meet the challenges.

Conflict of interest

The authors declare that there are no conflicts of interest.

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