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Review

Simulating cancer growth with multiscale agent-based modeling

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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.

1. Introduction

Increasingly, cancer is understood as a large family of diseases characterized by invasive, uncontrolled cell growth. Genetic mutations are considered to be the initial cause of the abnormal growth of cells, hence the main area of focus has been in investigating the genes involved and the intrinsic cellular processes they affect and regulate throughout tumorigenesis [1]. However, recent research has shown that cancer cells not only influence the microenvironment around them for their benefit, but also engage the stroma and other non-cancer cells to allow for tumor metastasis [2]. This is a complex, bidirectional interactive process, which cannot be easily understood by using conventional wet-lab experiments alone, whether *in vitro* or *in vivo* or both. Mathematical models and computation simulations can help overcome these limitations by offering the ability to monitor in real-time, albeit *in silico*, tumor growth, cellular distribution and movement, and to observe the genetic mutations that lead to aggressive growth and metastasis [3].

Current computational cancer modeling approaches can be divided into three categories: discrete, continuum, and hybrid, i.e., the combination of both (interested readers should refer to [4–9] for in depth discussions on this topic). Briefly, discrete models employ experimentally derived, computationally coded rules to define the step-wise or discrete interactions between individual cells and provide insight on tumor microstructure, cell proliferation and death rates, and cell densities. Continuum models represent the tumor as a continuum and give information about the overall tumor morphology and nutrient distribution while neglecting the influences of individual cells in the environment. Hybrid modeling combines aspects of both discrete and continuum modeling to provide a more complete description of the tumor environment. Because discrete and continuum domains are often inescapably linked, directly influencing one another from the viewpoint of an *in vivo* system, the hybrid modeling approach has become the more desirable choice for many computational cancer researchers [4].

Agent-based modeling (ABM) is a discrete-based hybrid modeling approach, offering many advantages over other methods of studying cancer development [10]. For example, ABM enables

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the modeler to control the likelihood of genetic mutations and to know which mutations are occurring; this, in turn, allows for simple determination of which cellular phenotypic changes have the largest influence on tumor behavior. There are several types of ABM techniques that have been widely used in cancer research, including lattice-based, lattice-free, Cellular Potts, lattice-gas, and subcellular element modeling methods (detailed discussion of each ABM technique is beyond the scope of this review; see [11] for a thorough review). Each technique has its advantages and disadvantages, and a particular technique may be favored over another depending on the specific cancer problem(s) being tackled. This implies that researchers should choose an ABM technique solely dependent on their research needs. It is also worth noting that, in the past ten years, a number of ABM simulation packages have been developed and applied to cancer research. Major open source package examples include CompuCell3D (http://www.compucell3d.org/), Chaste (http://www.cs.ox.ac.uk/chaste/), Repast (http://repast.sourceforge.net/), and NetLogo (http://ccl.northwestern.edu/netlogo/), among others (see Refs. [12,13] for excellent reviews). These packages have facilitated the overall process of developing an agent-based cancer model and also enabled computational oncologists to focus their time and energy more on the specific cancer problems of interest.

In an agent-based model, each cell is often represented as an agent. The agents have rules that they must follow in the course of a simulation, both for their independent behavior and for interactions between other agents. A description of a simple ABM with minimal rules is described as follows: Agents may receive signals and input from the environment and their neighboring agents, provide output to the environment and their neighbors, and make 'decisions' based on the input from around them and their internal, sub-cellular decision making rules. An agent may grow, proliferate, enter a quiescent state, or undergo apoptosis or necrosis in response to surrounding environmental conditions. Cellular proliferation often requires enough room to grow or divide into (a typical assumption for simplifying the development of an ABM), and sufficient nutrients available to maintain cell viability. If nutrients are sufficient to sustain the cell but there is not enough room to divide into, the cell enters into a quiescent state. In conditions where nutrient or oxygen levels are not high enough to maintain cellular viability, cells enter into a hypoxic state. If sufficient oxygen supply is restored, the cell will return to a healthy state; if not, it will undergo apoptosis after a defined length of time. Fig. 1 illustrates a flowchart of this simple oxygen-dependent cellular phenotype decision process. More accurate descriptions of the tumor environment and behaviors can be achieved through the additional modeling of more phenotypic factors.

Recent ABM work has seen the introduction of more complex descriptions of cellular agents, pushing the technical frontier of modeling and mathematical descriptions of cancer behavior towards a more complete understanding [14]. Most agent-based models are computationally intensive because of the (temporal–spatial) fine-resolution they operate on. Currently in the quantitative cancer research field, agent-based models often include components and/or simulate processes that occur at two or more spatial or temporal scales, thus rendering them multiscale models. A multiscale ABM is particularly suitable for exploring the diversity of cellular and molecular dynamic features exhibited at the single cell level, and for quantifying the relationship between the molecular properties of individual cancer cells, microenvironmental conditions, and the overall tumor morphology. In fact, in many cases, cancer simulations should not be limited to a specific biological scale, because cancer is an emergent collective phenomenon [15], dependent on the dynamic interactions of cancer cells and the changing heterogeneous microenvironment [16,17]. More importantly, cancer development, invasion, and metastasis processes indeed occur across a large scale range, from the molecular and micro-scale with factors such as signaling molecules and cellular competition, to the macro-scale with environmental factors including tissue oxygen concentration and mechanical stresses on the growing tumor, i.e., spanning multiple spatial and temporal scales biologically [4]. In this review, we focus our discussion on multiscale ABM, especially on how this approach has been used to help advance different areas of cancer research towards new experimentally testable hypotheses. Some agent-based models are not specifically labeled with the 'multiscale' term; however, since they simulate or predict cancer behavior across different spatial and/or temporal scales, we still introduce them here, but our discussion is limited to the introduction of the most recent, representative multiscale ABM works in the literature. Interested readers can refer to other in depth reviews to have a more comprehensive understanding of ABM and its potential in cancer research [4,5,11,18].

2. Overview of multiscale ABM methods

2.1. Scale ranges

A multiscale cancer ABM attempts to integrate across many spatiotemporal scales (from atomic to molecular, cellular, multicellular, organ, up to multi-organ systems) to provide a more complete and accurate representation of a variety of phenomena including cancer initiation, growth, invasion, and metastasis [4]. We only briefly describe the general methods for modeling cancer behavior on the molecular, microscopic (cellular/multicellular), and macroscopic (organ) scales.

Molecular scale modeling involves modeling the bulk average values of molecular interactions. This can include averaged receptor–ligand interactions, oxygen and nutrient concentration effects on cells, and cell–cell signaling molecule concentrations. Signaling molecules trigger cascades that cause changes in cell behavior, and oxygen and nutrient concentrations can allow cells to remain healthy or become hypoxic when they are reduced. These molecular interactions are commonly the smallest scale modeled in agent-based cancer models, and are usually represented using ordinary differential equations (ODEs) to describe the rate at which they are consumed or produced.

Microscopic scale interactions occur between cells. Cells must coexist in their environment, and both their movement and proliferative expansion is limited by their proximity to neighbors. It is at the micro-scale where cancer modeling allows for a mutation of healthy cells into cancerous phenotypes. Micro-scale modeling can be done using ABM (where each cell is modeled individually) or by describing local conditions using partial differential equations (PDEs) to calculate local environmental changes. Agents have rules that define interactions with their environment and other agents, depending on the availability of resources necessary for their survival, such as oxygen and glucose. Agents can interact with each other, influence their microenvironment, undergo taxis and mitosis, enter quiescence or die from hypoxia or apoptosis. Determination of agent behavior is based on the local environmental conditions and molecular signaling, and the biological rules posed on the agents by the modelers.

Macroscopic scale modeling involves factors that encompass the entire tumor tissue, hence spanning across the scale of many agents. Diffusion of nutrient, oxygen, and signaling molecules such as hormones, tumor tissue pH, and chemotherapy drug distribution over the entire tumor can be computed and provided as feedback to the microenvironment. Tumor morphology and vascularization are also sometimes modeled on the macro-scale, providing information on the extent of metastasis and nutrient

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