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Multiscale computational models of cancer

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Abstract

Cancer is an inherently multiscale process, wherein genetic lesions at the sub-nuclear level propagate to changes in intracellular biochemistry, cell-level behaviors, and ultimately to tissue-scale interactions that are also partially controlled by tumor cell-extrinsic aspects of the microenvironment. As computational modeling methodologies across those scales have improved, so too has our ability to embrace fully the multiscale nature of cancer in developing models to predict key aspects of tumor development, diagnosis, and response to therapy. The explosion of studies to understand the origins and effects of cell-to-cell heterogeneity in tumors has provided impetus for the development of multiscale models capable of predicting dynamics in systems where spatial heterogeneities exist. Here, we summarize recent progress and developments in this field.

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Keywords

Agent-based models, Differential equations, Continuum, Discrete, Heterogeneity.

Abbreviations

CSC, cancer stem cell; CTL, cytotoxic T lymphocyte; EGFR, epidermal growth factor receptor; GBM, glioblastoma; MM, multiple myeloma; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; PDE, Partial differential equation; ODE, Ordinary differential equation; ECM, Extracellular matrix; ABM, Agent-based model.

Introduction

Cancer spans biological scales, from genetic alterations that affect intracellular biochemistry to tissue-level behaviors that regulate tumor growth and metastatic dissemination. These biological scales naturally span physical scales of length and time. For example, intracellular biochemical reactions may occur with characteristic times of seconds or less and may involve gradients over microns. Cell-level and cell–cell phenotypes play out over length scales of tens of microns, often with time scales of tens of seconds to minutes. Relevant scales at the tissue level are even larger. Multiscale computational models offer ways to bridge those scales so that effects of perturbations at one scale can be predicted at others.

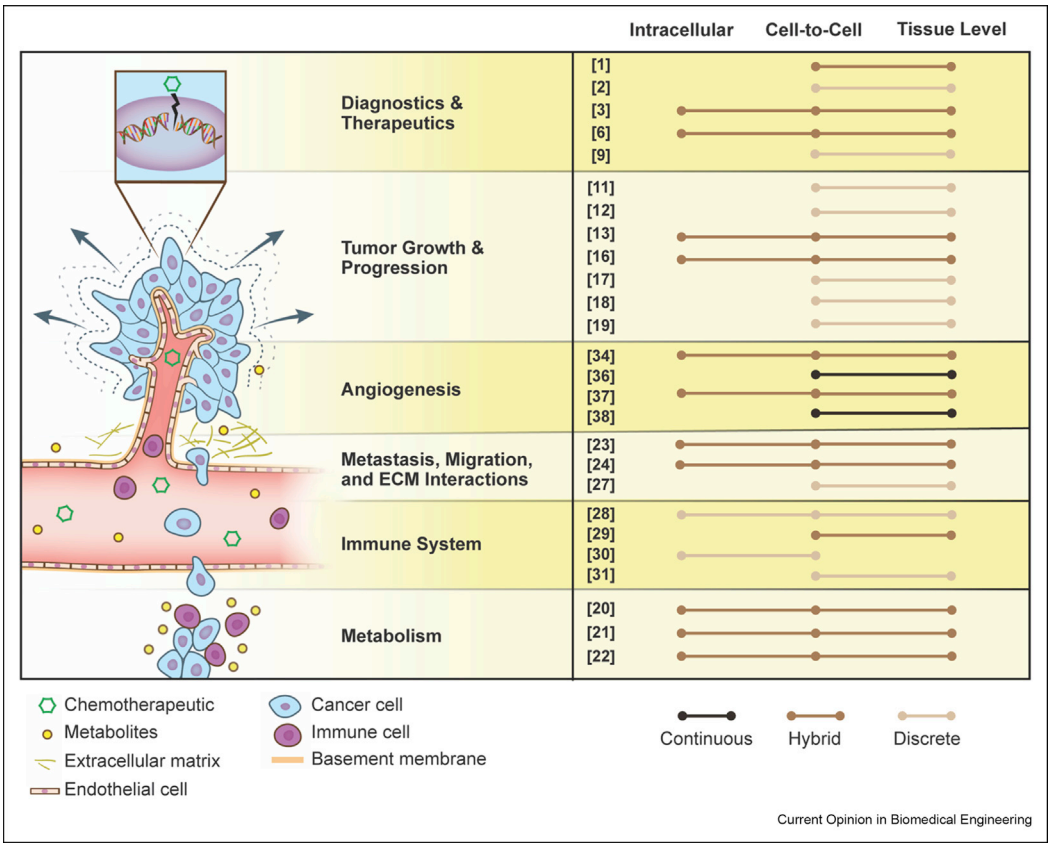
Multiscale models can focus on continuum descriptions of variables (as in differential equation-based models), descriptions of discrete entities or events within cells and tissues (as in agent-based or stochastic models), or a combination of approaches (hybrid models). The need for breadth of approaches is a natural consequence of the multiscale nature of cancer, with critical processes playing out at intracellular, cell-to-cell, and tissue levels (Figure 1). For example, continuum models can be leveraged to compute the spatiotemporal evolution of intracellular signaling pathways so long as proteins are sufficiently abundant and rate expressions can be adequately characterized. Discrete models are more useful for representing processes that depend upon cell–cell interactions that create spatial heterogeneities. In some scenarios, hybrid models are required to model spatially heterogeneous processes that occur under the control of a field (e.g., a chemokine gradient) that can be described using continuum approaches.

The goal of this review is to survey the current state of multiscale modeling of cancer. The discussion is organized based on biological or therapeutic processes, rather than by scales, in hopes that this will be most useful to readers with a primarily biological or clinical background who seek to gain understanding of how modeling can be applied to problems of interest.

Diagnostics & therapies

Early detection leads to the best possible outcomes for cancer patients, and multiscale models are inherently useful for understanding how to improve diagnostics which involve limited tissue sampling. As one example, Curtius et al. [1] developed a 2D hybrid model to predict the likelihood of a biopsy missing esophageal carcinoma in Barrett's esophagus patients due to sampling or biopsy sensitivity issues. The model was based on a cellular expansion model in continuous time, a tissue model based on stochastic simulations, and a probabilistic screening model. The model was used to predict the efficacy of tissue ablative treatments and to propose

Figure 1



For a subset of the references cited in this review, and organized by the biological or treatment related categories that frame the discussion, the biological scales (intracellular, cell-to-cell, and tissue level) and models types (continuous, hybrid, and discrete) addressed by each reference are shown.

how limitations in current biopsy approaches could be overcome by higher-resolution imaging.

Another active area of multiscale cancer modeling has been to predict tumor response to therapy [2–5]. For example, Gallaher et al. [2] employed an off-lattice agent-based model (ABM) to investigate how populations of treatment-sensitive and -resistant cells respond to different therapy schedules. A key finding was that heterogeneous mixtures of sensitive and resistant cells responded best to non-continuous dosing that slowed the Darwinian effect of competitive release. Several recent studies focused on multi-drug resistance in multiple myeloma (MM) [3–5]. For example, Ji et al. [3] developed a hybrid multiscale model to explore the hypothesis that targeting tumor–stroma interactions and the immune system could be leveraged to impede MM cell growth. The hybrid model included ordinary differential equation (ODE) based descriptions of intracellular signaling and ABM-based descriptions of immune, tumor, and stromal interactions. The model was used to predict the potential drug synergies and effects on different cell populations.

Multiscale hybrid computational models have also been used to study tumor growth and spreading in response to therapy [6–8]. Kim et al. [6] developed a multiscale hybrid model of glioblastoma (GBM) based on submodels of intracellular signaling, extracellular distributions of oxygen and chemokines, and cell mechanics, to predict how best to impede diffuse local spreading of GBM cells. They used their model to predict the efficacy of therapeutic approaches including the potential use of chemoattractants to home cells back to resection sites in combination with conventional chemotherapy. Other models have sought to make similar predictions based on considerations including the coupling between tumor microenvironment parameters and conversion of specific prodrugs [7] and pharmacokinetic and pharmacodynamics effects [8].

Multiscale modeling has also been used to investigate how tumor heterogeneity, for example that arising from stem-like traits of a subpopulation of cancer cells, impacts progression and response to therapy [9,10]. This is of interest because cancer stems cells (CSCs) are intrinsically chemoresistant and can reproduce fully

differentiated tumors from a very small number of cells. As one example, an ABM of triple negative breast cancer was developed to account for the effects of heterogeneous expression of chemokine receptor CCR5 which can drive signaling promoting tumor cell stemness [9]. The model predicted that targeting of CSC proliferation was a more effective approach for reducing tumor volumes than antagonizing the migration of CCR5-expressing cells, highlighting the possibilities for multiscale models to make predictions about the benefits of multiple possible therapeutic approaches.

Tumor growth & progression

Cell-to-cell and tissue-level agent-based or hybrid models have been used to study the roles of migration and proliferation in tumor growth and spreading [11–13]. For example, Klank et al. [12] developed an ABM to resolve discrepancies between migration rates of single cells in tumor tissues and apparent migration rates based on conceptualization of tumor spreading as a diffusive process that were one to two orders of magnitude larger. The authors identified a lack of consideration of the excluded volumes of individual tumor cells in the reaction-diffusion model as the primary source of the discrepancy, and resolution of this issue provides an improved path for developing realistic prognostic growth models of highly invasive GBM tumors, which may eventually help guide treatment choices for individual patients. Related ABM [11] or hybrid [13] models of tumor growth have been used to predict the effects of fitness tradeoffs between proliferation and migration due to cell crowding and competition for resources in finite volumes or to integrate specific growth factor receptor pathways in models that bridge the cellular, cell-to-cell and tissue scales. Other recent multiscale hybrid and ABM models of tumor growth have been designed to consider additional types of biological or biophysical complexity, including metabolic constraints impacting the formation of necrotic and non-proliferating tumor regions [14] or mechanics that impact stress distributions in tumor cell spheroids that may help explain observed differences between cells in 2D and 3D cultures [15].

Models are increasingly considering greater degrees of complexity simultaneously. For example, Rahman et al. [16] developed a hybrid model for tumor growth with tissue, cell, and subcellular signaling components. The model included partial differential equations (PDEs) governing tumor volume fractions and nutrient concentrations, an ABM to describe processes in heterogeneous mixtures of tumor and normal cells undergoing hypoxic or necrotic programs, and ODE-based models of critical oncogenic signaling pathways (e.g., epidermal growth factor receptor (EGFR)). The authors used the model to predict tumor growth patterns in response to different doses of rapamycin. You et al. [17] investigated spatial competition among three distinct cell types (relating to their dependence on or ability to produce testosterone) in metastatic prostate cancer tumors, using an ABM to model the process from an evolutionary perspective involving density-dependent (e.g., cell death) and frequency-dependent (e.g., likelihood of proliferating) interactions and decisions. The complexity of this model allowed the authors to demonstrate that the radii over which cells interact with one another, sense spatial constraints to growth, and disperse after cellular division all exert strong control over tumor growth. In addition to modeling cell growth and proliferation [18], the relationship between cell death and tissue shrinkage has similarly been explored using a mechanically-focused multiscale ABM [19]. These models simulate cell interactions using "peridynamics", a theoretical approach developed for studying fracture mechanics that uses a constitutive relationship to model discontinuities and long-range forces between cells based on their pair-wise interactions.

Metabolism

Multiscale modeling has been employed to understand how metabolic changes can influence tumor progression [20–22]. Shan et al. [22] created a hybrid multiscale model to compare how three hypothesized metabolic states affect tumor growth dynamics at the level of multi-cell populations. The authors developed metabolic network models for tumor cells and stromal cells, which included glucose uptake, lactate production and uptake, and glutamine uptake. They performed flux-balance analysis to estimate metabolic fluxes when these pathways were activated to varying degrees to simulate: 1) the Warburg effect (high glycolytic flux and lactate production), 2) the reverse Warburg effect (uptake of lactate), and 3) glutamine addiction (uptake of glutamine as a source of carbon). This analysis provided parameters for a coarse-grained description of cellular growth kinetics, which were incorporated into a multi-cell ABM that predicted tumor growth dynamics and the spatial distribution of cell subpopulations in different metabolic states and under varying resource-limited conditions (e.g., low oxygen). The model made a number of potentially therapeutically relevant predictions by linking single-cell metabolism to population growth. For example, it predicted that the metabolic state defined by the Warburg effect is favorable for tumor growth when resources are limited, while the reverse Warburg effect confers an early growth advantage to tumors located deeper in the tissue when they are surrounded by more layers of "hijacked" glycolytic stromal cells.

Metastasis, migration, and extracellular matrix interactions

Multiscale computational models have been used to study the coupled processes involved in tumor cell

migration and metastasis, including: 1) invasion of cancer cells into surrounding tissue, 2) intravasation of single cancer cells and cell clusters into the circulation, 3) binding of circulating tumor cells to the microvascular endothelium, 4) extravasation of circulating tumor cells at distant secondary sites in the body, and 5) growth and expansion of metastasized cells [23]. Most models used to study these steps are ABMs because they can simulate cell-to-cell heterogeneity within a tumor, such as that resulting from epithelial-to-mesenchymal phenotypic transitions, and interactions between different cell types using discrete, autonomous agents that undergo phenotypic shifts. Multiscale ABMs have been developed to better understand the heterotypic and homotypic cell-to-cell interactions that facilitate metastasis, including: mesenchymal stem cells in the bone marrow aiding in the engraftment of metastatic prostate cancer cells there [24], seeding of a metastatic site with circulating stem cells to accelerate the growth of breast cancer metastases in the lung [25], and mechanically-driven formation of gaps between microvascular endothelial cells that promote circulating tumor cell intravasation and extravasation [26].

Multiscale modeling has also been used to explore the effects of extracellular matrix (ECM) organization and composition on tumor cell invasion. For example, a differential equation-based model was used to simulate interactions between cancer cells and ECM fibers to study the influences of cell migration on ECM fiber degradation and rearrangement, as well as reciprocal effects of the ECM on adhesion-driven cell migration [27]. The model predicted that increased adhesion between tumor cells and ECM fibers accelerated tumor invasion into the surrounding ECM and resulted in spatial realignment of ECM fibers at the boundary perpendicular to those in the peritumoral region.

Immune system role in cancer

Chronic inflammation resulting in DNA damage is recognized as a cancer risk. For example, patients with chronic inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, have an increased risk of colon cancer. An and Kulkarni [28] studied this basis for disease by combining two previous ABMs of onconeogenesis and inflammation. The coupled model, which spans the intracellular, cell-to-cell, and tissue scales, simulates endothelial cell interactions with circulating leukocytes, and includes pro- and anti-inflammatory chemokines that stimulate their adhesion, extravasation into inflamed tissue, and production of reactive oxygen species (ROS). Because ROS accumulation causes DNA damage, the authors performed simulations wherein the parameter linking ROS levels (predicted by the inflammation ABM) to epithelial cell transformation (predicted by the onconeogenesis ABM) was systematically varied. They ran 500 simulations of the stochastic model for each parameter value, simulating the effects of non-resolving inflammation over a 60-year time-course. The model predicted that the percentage of simulations resulting in "microtumors" (containing fewer than ten cancer cells) increased with increasing inflammation but only to a point, beyond which additional inflammation reduced the prevalence of microtumors because larger tumors (more than ten cells) grew more frequently. This model has potential utility for studying early cancer progression and may inform early detection strategies and treatment scheduling.

Other groups have created multiscale models to inform the development of cancer immunotherapies [29–32]. For example, Frascoli et al. [32] developed a three-dimensional hybrid model to simulate dynamic interactions between cytotoxic T lymphocytes (CTLs) and an early-stage tumor. Cancer cell motility, modeled with a random walk, and cell-to-cell adhesive and repulsive interactions with CTLs and other cancer cells were simulated using a probabilistic ABM. Activation of CTLs in lymph nodes by antigen-presenting cells, and their division and migration into the tumor was modeled using differential equations because an ABM formulation was viewed as computationally inefficient, due to the small time scales for immune cell interactions and because their concentrations in the lymph node are orders of magnitude higher than in the periphery. The attack of tumor cells by activated CTLs was modeled as a probabilistic function (Poisson distribution) based on the time required for a CTL to kill a cancer cell. The authors used their model to investigate how cell motility and cell-to-cell adhesion impact the ability of activated CTLs to eradicate a tumor. The model predicted that highly migratory cancer cells can escape CTL attack, whereas tumors containing fewer migratory cells are more easily detected and eliminated by CTLs unless cell-to-cell adhesion strength is high, which can result in more compact tumors that impede CTL penetration. This model suggests that measurable morphometric parameters (e.g., tumor size and compaction) and molecular biomarkers (e.g., cell-to-cell adhesion molecules) may be useful for stratifying patients for immunotherapy.

Angiogenesis

Multiscale models of angiogenesis have been developed to study the role of blood vessel growth in tumor progression. Most of these have used hybrid approaches because they can represent diffusion of oxygen and pro-angiogenic molecules using continuum modeling (e.g., with reaction-diffusion equations) and endothelial cell migration and proliferation using discrete modeling (e.g., cellular Potts models) [33,34]. For example, Zangooei and Habibi [34] developed a three-dimensional hybrid model to simulate morphological changes during tumor growth as a function of

angiogenesis. They modeled concentrations of diffusible substances in the environment, such as ligands for growth factor receptors, oxygen, and glucose using PDEs. Vascular endothelial cells, cancer cells, and healthy stromal cells were simulated as discrete agents that exhibited key behaviors, such as migration, proliferation, quiescence, and apoptosis governed by intracellular signals. The kinetics of intracellular signaling pathways associated with EGFR and tumor necrosis factor receptor (TNFR) were modeled using ordinary differential equations. The model predicted changes in tumor size and shape as a result of blood vessel growth, and the authors found good agreement between model predictions and previously published measurements of cancer cell density and vascularization (e.g., vessel length density and branchpoints). An innovative feature was the use of machine learning to identify optimal agent behaviors constrained by governing rules for specific environmental conditions. One such rule, for example, asserted that the probability of cell survival decreases and the probability of cell death increases with increasing TNFR expression. The bridging of scales enabled by this model is essential for predicting how pharmacological interventions targeting specific ligands and their cell surface receptors will affect tissue-scale changes both in tumors and in the microcirculation that perfuses them.

Motivated by the fact that anti-angiogenic therapies exhibit variable efficacy in the clinic [35], multiscale computational models have also been used to predict biomarkers (e.g., vascular endothelial growth factor (VEGF) receptor expression [36]) for profiling patient responses to anti-angiogenic therapies, to explore combination anti-angiogenic therapies (e.g., anti-VEGF bevacizumab and a thrombospondin-1 mimetic [36–38]), and for optimizing anti-angiogenic treatment schedules [36]. For example, Cai et al. [37] developed a three-layer (intracellular, cell-to-cell, and tissue level) hybrid model employing reaction-diffusion PDEs to describe concentrations of VEGF, oxygen, and matrix degradation enzymes and grid-based methods to model the interactions of tumor cells and the microenvironment in response to anti-angiogenic therapy. The model predicted that administering endostatin (an anti-angiogenic agent) at the beginning of the angiogenic phase of tumor growth, when immature endothelial cells are hypothesized to be more prone to apoptosis, reduced the tumor burden by 50%, while administering before or after the angiogenesis phase only reduced total tumor cells by 30% or 21%, respectively.

Comparing approaches & future perspectives

Multiscale computational models of cancer have evolved significantly from early continuous models in the 1970s, such as a pharmacokinetics model of Adriamycin [39], and discrete models, such as those published in the 1990s focused on tumor angiogenesis [40]. Since then, models have grown in complexity by bridging a broader range of spatial and temporal scales and containing as few as twenty parameters [41] to as many as two hundred parameters [42]. Smaller models (i.e., those defined by fewer equations, rules, or parameters) generally run more efficiently, and often simplifying assumptions are made to decrease model run time. However, even smaller models can require significant computational power, and software for modeling has been developed and extended to leverage high performance computing [43] and high-speed frameworks that use graphics processing units [44].

The prevalence of references cited here utilizing hybrid or discrete modeling approaches is perhaps not surprising, given the ability of discrete models to represent important aspects of tumor biology such as cellular heterogeneity and stochastic events. Even in cases where these aspects of tumor biology need to be captured, there are choices of approaches that may strongly influence model efficiency and the types of predictions that are possible. Some recent papers have addressed these points directly. For example, Figuerdo et al. [45] used three case studies of tumor-immune system interactions to compare outputs of ABM and stochastic ODE models. The authors demonstrated that mean differences between the two approaches (computed over many model runs) existed, and they attributed these differences to the ability of ABMs to capture emergent phenomena through the tracking of individual agents rather than by modeling stochasticity in aggregate. In a similar spirit, Voulgarelis et al. [46] compared ODE and ABM models of tumor progression and demonstrated that in certain parameter ranges of cell density results from the two approaches were reasonably similar. For such parameter ranges therefore, a choice can be made about balancing the relative speed and efficiency of ODE-based descriptions with the more information-rich model outputs provided by ABMs.

The accuracy and utility of mathematical and computational models of biological processes are heavily reliant on the quality of experimental data that is used to construct and parameterize them, and multiscale computational models of cancer are no different in this regard. Determining the specific parameters for multiscale models inherently requires heterogeneous data (i.e., data from different spatial and temporal scales using different methodologies for data collection and analysis). This means that the both the degree and sources of uncertainty in each parameter of a multiscale model will likely vary from one parameter to the next. However, one benefit of multiscale modeling is the ability to cross–validate parameters from different spatial and temporal scales, which reduces the overall uncertainty in the parameter set [47]. While there are

currently no formalized methods for assessing uncertainty in multiscale modeling of cancer, per se, there are some more generalized approaches for addressing this issue that have been developed by the multiscale modeling community at large. For example, performing a global sensitivity analysis on a continuum ODE model can reveal how each parameter contributes variability to the model output [36]. If the model is an ABM, the uncertainty in the parameters can be built directly into the rules (e.g., using probability distributions) and/or one can conduct large−scale parameter sweeps using the model, where the parameters are varied systematically [28] and simultaneously [19]. Of relevance, in the field of cardiovascular disease, recent work has led to an automatic, Bayesian approach for parameter tuning to decrease uncertainty [48]. A handful of other papers have been published over the years with various methods and best practices for dealing with parameter uncertainty [49−51], and this continues to be an area of future growth for multiscale models of cancer.

Our review has focused primarily on conventional predictive applications of multiscale models of cancer based on already known cause-and-effect relationships. However, as the ability to run multiscale models with computational efficiency increases, we anticipate that there will be an increase in their application to generate large datasets that can be used to search for new hypothesized cause-and-effect relationships. A recent study described an initial application of this concept by using large sweeps through parameter space that represented different possible hypothesized mechanisms in order to identify mechanisms that led to model outputs consistent with observed behaviors [52]. Eventually, we anticipate that data-driven statistical modeling and machine learning approaches may find direct application in these kinds of studies to systematically identify combinations of rules for ABM-based models that most accurately produce desirable model outputs. In time, we also anticipate that a variety of other modeling approaches that have been recently applied in cancer biology, including constrained fuzzy logic ensemble modeling [53], statistical physics-based models [54], novel systems-level network analyses [55], will also be integrated with and applied to multiscale descriptions of cancer biology.

Conflict of interest statement

Nothing declared.

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