# Editorial
# Special Section on Multiscale Cancer Modeling

## I. Introduction

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 [1]. 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 [2]. Everyone would agree that computer simulations are usually more cost-effective, efficient, and tractable, relative to laboratory experiments. This is especially true when testing combinations of parameters that can be varied simultaneously in a controlled manner and over a wide range of values – a process which can easily become expensive and time-consuming using traditional wet lab techniques. As our understanding of cancer biology and treatment evolves, multiscale cancer models (i.e., computer models that examine cancer behavior across different spatial, temporal, and/or functional biological scales) are uniquely positioned to capture the space- and time-dependent changes and the heterogeneities that occur in tumor properties, and to provide potentially clinically useful insights. Using these multiscale models, one can quantitatively study how separate or collective changes in parameters related to tumor pathological, chemical, and physical processes on one scale affect parameters or functions on another scale – information that would not be accessible through scale-specific models. For example, perturbations of smaller-scale parameters (e.g., drug-cell binding kinetics) can generate observable and measurable changes in larger-scale outputs (e.g., tumor size and shape), thus allowing for identification of the smaller-scale parameters (and their combinations) that have significant impact on larger-scale outputs.

Multiscale modeling is now being conducted iteratively with experiments and used as a means to investigate cancer phenomena in more experimentally relevant ways. At the same time, new approaches in multiscale modeling are being developed to bridge the relevant scales for a specific problem of interest. From a broader perspective, multiscale models can help biologists and medical scientists test experimental hypotheses, facilitate drug development, reveal new biomarkers and drug targets, predict biological mechanisms and treatment responses, and optimize drug delivery and therapeutic effect [3]–[6].

## II. Multiscale Modeling Methods and Overview of This Special Section

Here, we will briefly discuss continuum, discrete, and hybrid approaches in modeling cancer behavior and treatment, and we encourage the reader to refer to, e.g., [7]–[10] for more in-depth discussions. Continuum modeling describes tumor growth by implementing model variables as continuous fields, mostly by means of ordinary or partial differential equations, but cannot be used to examine discrete cell-cell and cell-environment interaction events. Because the representation of large scale factors by relatively few equations is computationally less demanding (than discrete methods), this approach is more appropriate for studying larger-scale systems, such as tissues, organs, and populations. Discrete modeling is basically a stochastic approach, and can be used to predict emergent properties generated by interactions amongst individual entities (usually cells or cell clusters). However, the computational demand increases rapidly with the number of entities modeled (and their interactions), limiting the spatial and temporal scales that a discrete model can represent. Hybrid models couple continuous and discrete systems in order to best describe and capture biological information across spatial scales. Individual cells are often treated discretely, but interact with overlying chemical and mechanical fields which are modeled as continua. Hybrid modeling presents a promising strategy for characterizing cancer systems; indeed, the complexity of cancer systems and the interactions among their constitutive elements is probably best described by a hybrid continuum and discrete approach.

This Special Section includes five articles, with two based on a continuum approach and three on a discrete-continuum hybrid approach. All papers have gone through a rigorous peer-review procedure, according to the journal's editorial policy. It is interesting and exciting to see that, in addition to presenting models that address important questions in cancer progression, all five papers have demonstrated additional potential by suggesting new approaches for developing more effective and personalized cancer therapies based on their modeling results. This exhibits a clear trend in this field. We also believe this Special Section should inspire opportunities for further research within and beyond the study of cancer.

Brown *et al.* [11] point out that current research in cancer chemoresistance is typically limited to the evolutionary adaptive phenotypic properties of individual cells. They apply the ecological concept of aggregation effects to a continuum mathematical model that accounts for the interactions between populations of phenotypically and environmentally diverse tumor

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cells. In their model, the response of an individual cancer cell to an externally applied therapy may be altered by its interactions with neighboring cells; thus, the outcome of the perturbation(s) may be substantially different than expected based on the phenotypic properties of the cell alone. They studied four different types of aggregation effects, and found that these aggregation effects influence response to chemotherapy independent of the properties of individual cells. While validation of the model with appropriate *in vivo* experiments remains to be done, this model has shown how important it is for the design of evolutionarily-based therapies to take into account the detrimental effects that neighboring cells may have on each other.

Kim *et al.* [12] present a continuum model of reaction-diffusion type to investigate how glioma cells can manipulate, through cell-cell signaling, the microglia so that, instead of mounting an immune response, the latter actually promote tumor invasion. The purpose of this study was to understand and identify important factors in determining the active components of invasive glioma cell movement (haptotaxis and chemotaxis). Model results were found to be in agreement with a series of experimental observations. Furthermore, sensitivity analyses of model parameters show that blocking both transforming growth factor beta (TGF-$\beta$) signaling and matrix metalloproteinase (MMP) activity simultaneously can effectively block the glioma invasion in the system investigated. Hence, this result suggests a new, potentially effective therapeutic approach for preventing glioma cells from invading the surrounding tissues.

Grogan *et al.* [13] develop a hybrid multiscale agent-based model to investigate how the structure and distribution of microvascular networks influences tissue oxygenation and the tumor response to radiotherapy. While it is well-accepted that the maturity of the tumor vascularity affects oxygen delivery – a process known as "vessel normalization" [14], relatively little attention has been paid to the effect of the spatial distribution of the vasculature. Grogan *et al.* analyzed artificial vessel networks and biologically-derived vessel networks (obtained from imaging data from well-vascularized mouse tumors) with their model. Simulation results showed no significant differences in either tissue oxygen levels or tumor burden when 3D simulations were generated from the three different types of vessel networks under consideration; however, in 2D there can be significant differences. Further development of this model may provide insight into how vessel normalization strategies can be administered to maximize the radiotherapy efficacy and how radiotherapy, alone or in combination with other treatment methods, can be personalized for individual patients.

Picco *et al.* [15] propose a 2D spatially-extended hybrid model to examine the role of context-driven cancer stem cell (CSC) plasticity in the early stage of breast cancer. CSC is the name given to a small population of cancer cells that are hypothesized [16] to self-renew and give rise to subpopulations of more differentiated cells with limited capacity for proliferation. In this model, stemness continuously varies across a phenotypic spectrum and is also directly modulated by the local environment (the so-called "stem cell niche"). After introducing mutation to induce carcinogenesis in homeostatic mammary duct cells, the model predicts an invasive phenotype that breaches the duct structure, invading out of the lumen and into surrounding tissue. Their results highlight that the stem cell niche is a dynamic and emergent property of the interactions that occur between cells and environmental factors, motivating a new therapeutic perspective that accounts for, and targets, both the dynamic and emergent nature of the niche.

Yan *et al.* [17] present a 3D hybrid model of glioblastoma (GBM) progression and vasculature growth which accounts for the feedback among various cell types considered in a cell lineage, tumor-induced vascularization, and crosstalk between vascular endothelial cells (VECs) and glioma stem cells (GSCs). The VEC-GSC crosstalk was implemented via vascular endothelial growth factor (VEGF), which promotes vessel formation, and a VEC-secreted factor that promotes GSC self-renewal and proliferation. Model analysis found that partially disrupting the VEC-GSC crosstalk reduces tumor size but does not significantly increase invasiveness. This result is interesting because current anti-angiogenic therapies show a somewhat opposite outcome: while tumor size can be reduced, tumor invasiveness may be increased [18]. Hence, further investigation of the anti-tumor effects of blocking this VEC-GSC crosstalk is both needed and expected, and this crosstalk may serve as a new target for GBM treatment.

## III. Future Directions

It is clear that multiscale modeling can complement current experimental and clinical studies in prevention, diagnosis, and treatment of cancer, and it also has the potential for shaping current research in cancer biology [9]. In particular, the exponential growth of multidimensional biological data requires a parallel growth in quantitative modeling methods to explain non-intuitive observations from such data [19]. Thus, it is foreseeable that multiscale modeling will become ever more important, as more quantitative measurements become available from preclinical models and patient samples.

We emphasize that any computational model, including multiscale models, should be appropriately parameterized, extensively tested, and thoroughly validated, at least within the defined context of use. In particular, as with all modeling efforts, validation is key to achieving acceptance in the cancer biology and clinical oncology communities. Some of the modeling approaches that are being presently developed can be extended to couple with quantitative data from high-throughput experimental methodologies or specific patient data to individualize the models to improve predictive power. Indeed, mechanism-based multiscale models that include patient-specific parameters are an important complement to current statistical approaches in developing more personalized medicine [20]–[24]. It is our hope that the techniques and practices presented and discussed in this Special Section will guide future efforts in this field toward the development of high-quality and more predictive multiscale models.

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