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Multiscale modeling in disease

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Abstract

Multiscale computational modeling aims to connect the complex networks of effects at different length and/or time scales. For example, these networks often include intracellular molecular signaling, crosstalk, and other interactions between neighboring cell populations, and higher levels of emergent phenomena across different regions of tissues and among collections of tissues or organs interacting with each other in the whole body. Recent applications of multiscale modeling across intracellular, cellular, and/or tissue levels are highlighted here. These models incorporated the roles of biochemical and biomechanical modulation in processes that are implicated in the mechanisms of several diseases including fibrosis, joint and bone diseases, respiratory infectious diseases, and cancers.

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Introduction

Chemical, physical, and biological processes interact across multiple scales of organization—molecular, cellular, tissue, organ systems, and whole-body scales. These multiple scales lead to both localized and systemic consequences for physiology, disease progression, and medical therapeutics. Dynamic effects including clinical outcomes emerge from the collective behavior across multiple scales and cannot be explained simply by studying the isolated parts at a single scale. Multiscale computational modeling allows for quantitative descriptions of interconnected processes, which can aid in understanding the mechanisms linking processes that cannot be decoupled easily in experiments. Computational investigations of the mechanisms and conditions that contribute to the progression from healthy to diseased states of increasing severity and the effects of treatments that may restore normal physiological function can greatly benefit clinical medicine and pharmacology. Multiscale modeling (MSM) aims to connect the complex networks of effects at various scales. With MSM, contributing factors can be tested in isolation and in systematic combinations to generate hypotheses for future experiments or to verify proposed mechanisms. Having many interrelated processes presents a challenge for gaining a full understanding of the progression of the disease and the efficacy of new treatments. MSM has the potential to translate reductionist theories, integrate disparate data, and compile the multiple mechanistic processes that contribute to the onset and progression of a disease into a systematic framework. Ideally, the framework is user-friendly and capable of taking the interconnected chemical, physical, and biological factors into account in a coupled fashion and in the appropriate magnitudes and sequences to make testable predictions. In the absence of such a framework, unraveling the network of events in human diseases will continue to be perplexing, and the development of effective treatments will remain a piecemeal and slow process.

In this brief review, first, common MSM methods are overviewed. Then, recent publications are highlighted that feature MSM involving at least two biological length scales to simulate a network of pathophysiological effects of a disease. MSM in systems biology is a vast field, and surveying every disease is beyond the scope of the present review. MSM case studies for a subset of diseases are discussed. These case studies are organized by disease type: fibrosis, joint and bone diseases, respiratory infectious diseases, and cancers. These were selected as representative examples that contribute to the fundamental understanding of pathology related to the synchrony and interconnections between a) biochemical signaling pathways in cells, b) tissue formation or degradation through extracellular matrix (ECM) remodeling often in conjunction with heterogeneous cell populations and secreted factors, and/or c) biomechanical effects on tissues. ECM remodeling, inflammation, mechanical forces, and metabolic growth are all involved to

various extents in diseases of tissue expansion, degradation, and fibrosis [1–4].

Overview of multiscale modeling methods

The purpose of this section is to introduce key terminology of popular MSM methods so that the later discussion of MSM in the context of human diseases is clear. This section is not intended to comprehensively cover the history and scope of MSM methods. Others have previously published overviews of MSM methods and considerations for suitability at various scales for immunology and infectious diseases [5–11], cancer [12,13], tissue growth [14], and more generally for biomedical systems [15–17]. There is also a relevant issue of Current Opinion in Biomedical Engineering themed on "Biomechanics: multiscale modeling" that will likely be of interest to readers of this manuscript [18].

Computational models based on deterministic differential equations are well-suited for studying dynamics and transport in complex systems. Differential equations can track populations, mass, forces, energy, momentum, and other quantities and the interactions between them. Ordinary differential equations (ODEs) are generally used to consider dynamic effects. Partial differential equations (PDEs) consider spatial and temporal effects. ODEs or PDEs can be converted to delay differential equations to account for processes at multiple time scales where the nonprimary time scales occur after a lag time interval relative to the primary time. The main drawbacks to deterministic differential equations are that continuous collective responses are built into the model assumptions and that the equations do not account for the stochasticity inherent in biological systems. To overcome the latter drawback, differential equations may be solved through stochastic simulation algorithms to account for uncertainty in parameter values and biological responses. This technique is still best suited for continuum-based modeling where the concentrations of interacting species or chemicals are sufficiently large. In contrast to equation-based modeling paradigms, agent-based models (ABMs) involve discrete individuals or "agents" with assigned rules to describe interactions with other agents and how each behaves stochastically in different scenarios (note that these behavioral rules can be based on Boolean logic or can use sampling from probability distributions). ABMs can involve spatial variations and can capture behaviors that emerge from many individuals interacting dynamically without predetermined collective properties. ABMs are best suited for relatively small numbers of interacting agents (on the order of a few thousand). The drawback of ABMs is that they take much longer to simulate compared to differential equations representing the same time periods, spatial domains, and populations of species [19]. A "hybrid" computational approach is often adopted in MSM that takes advantage of the benefits of PDEs to describe chemical species that react and interact in large quantities in a background spatial region or field and of ABMs to describe cells and chemical species that interact in small quantities or in logic-based upregulation or downregulation fashions. This approach reduces the limitations of either method alone. Other hybrid approaches may also include using intracellular networks described by systems of ODEs combined with ABMs at the intercellular or tissue level. Both the platforms CompuCell3D [20] and PhysiCell [21] allow for hybrid coupling of ABMs to intracellular ODEs and/or extracellular PDEs. In the following sections, combinations of equation-based models and/or discrete ABMs at various scales will be discussed for applications in human diseases.

Fibrosis

In healthy tissue homeostasis, the ECM regularly undergoes remodeling that usually results in a net balance between production and degradation of collagen and other fibrous components. ECM is degraded by matrix metalloproteinases (MMP) and other matrix degrading enzymes, and this degradation is inhibited by tissue inhibitor of metalloproteinases. Neighboring cells or pathogen infections affect the ECM through secretions of various chemicals that generally either a) promote matrix accumulation and fibrosis or b) enhance matrix degradation and inflammation. Fibrotic diseases characterized by net matrix accumulation are considered in this section. Arthritis and osteoporosis are examples of diseases characterized by inflammation and enhanced matrix degradation and are discussed in the next section. More complex interplay between ECM remodeling and inflammation in various disease conditions are possible in respiratory infectious diseases and cancers, which are discussed subsequently.

Fibrosis affects many tissues, and MSM has been applied to study fibrosis in the heart [22,23], lungs [24], and kidneys [25]. In the heart, cardiac fibroblasts respond to electrophysiological cues in addition to chemical and biomechanical cues. Ref. [22] reviewed computational modeling efforts for all three of these areas as well as some early MSM applications to the heart. MSM was used to study cardiac fibrosis following myocardial infarction [23]. This model coupled a logic-based ODE model for the intracellular signaling network in fibroblasts to an ABM for migratory fibroblast agents and discrete values of cytokines and collagen across a spatial domain that respond dynamically to

outputs from the network model. The discrete values were assigned to individual grid cells and could not diffuse. The network model integrated several biochemical and mechanical inputs across signaling pathways for fibroblast activation and ECM remodeling. The collagen dynamics depended on collagen I and III mRNA from the network model for production and the current value of collagen in the ABM for degradation. MMP was not explicitly represented. Cytokine spatial gradients were used to explore combinations of fibrotic and inflammatory phenotypes.

A recent review [24] focused on MSM and covered models for fibrosis, lung diseases, MSM, and the intersections of these categories. A model was developed for renal interstitial fibrosis [25] that was structurally similar to several of the MSM works reviewed for the lungs in Ref. [24]. In the kidney application, a hybrid approach was used that coupled an ABM at the cellular and tissue scale to a PDE for extracellular chemical fields. Additionally, ODEs were used at the molecular scale for the intracellular response to transforming growth factor beta and ECM through integrin receptor binding. The model explicitly incorporated the roles of macrophages in addition to myofibroblasts, fibroblasts, and epithelial cells. The effects of drugs were also simulated.

Although not explicitly studying fibrotic diseases, two recent MSM efforts accounted for dysregulated growth mechanisms related to growth and remodeling in the heart [26] and arteries [27]. Both [26,27] incorporated intracellular network models comparable to those used in for cardiac fibrosis [23] and renal interstitial fibrosis [25]. In Ref. [26], cell signaling for hypertrophy subject to mechanical inputs determined changes in cellular area, and these changes were coupled to a PDE model for the mechanics of growth of the left ventricle. Similarly, in Ref. [27], a logic-based network model for cell signaling was coupled to a mechanical model for growth and remodeling of an artery. The mechanical model was a constrained mixture model that incorporated the effects on three tissue constituents: elastin, collagen, and smooth muscle. The proportions of these constituents changed due to muscle cell proliferation and collagen remodeling via multiple MMP species from the intracellular model. Stresses resulting from growth and remodeling were input to the signaling network model.

Joint and bone diseases

Computational modeling for joint degradation by arthritis focusing primarily on mechanical signals at various scales was recently reviewed [28]. From a biochemical and cellular perspective, a multiscale model was developed for joints subject to cartilage degradation by rheumatoid arthritis using three compartments representing synovial membrane, synovial fluid, and cartilage [29]. Each compartment was described by a set of continuous reaction-diffusion PDEs for the populations of immune cells, fibroblasts, and chondrocytes and concentrations of cytokines, drugs, MMP, and tissue inhibitor of metalloproteinases. Both chondrocyte cells and ECM were described by nonconstant volume population/mass balance equations. The degradation of ECM resulted in an advection term in the cartilage compartment to account for the velocity of the synovial membrane interface.

For application to osteoporosis, a hybrid model for bone osteoblast cells was developed that coupled an ABM to a mechanical model [30]. The ABM was used to simulate the intracellular molecular network through two compartments (cytoplasm and nucleus) for transduction of mechanical stimuli into cellular responses. The tissue-level mechanical model with an applied load was coupled to the ABM through mechanosensing of the tissue through integrin receptors on the cells and through modulation of the ECM material properties, particularly stiffness, through the expressed ECM proteins. The dynamics of the model have been further analyzed in subsequent studies [31,32].

Respiratory infectious diseases

Several more scales are relevant to modeling of infectious diseases compared to noncommunicable diseases, for example, pathogen, environment, and population scales. Here, the focus is refined to MSM for the immune system that covers at least two of the following scales in the lungs of human hosts: intracellular, intercellular, and tissue.

The SARS-CoV-2-induced COVID-19 pandemic has led to multiple recent MSM efforts to understand the infection and immune response in lung epithelial tissues [33,34]. Both efforts considered that epithelial cells may be killed by viral infection, immune response to control infection, both, or neither depending on the dynamics and magnitudes of and interplay between the infection and immune response. Using the physics-based multicellular simulator PhysiCell [21], a hybrid approach was developed in Ref. [33] to model the lung epithelial cells discretely with internal ODEs for intracellular receptor trafficking, pathogen dynamics, and cell response to viral load along with discrete agents for cells of the immune response and PDEs for diffusing cytokines and virions that spread through the tissue. Tissue damage in the forms of epithelial cell death and fibrotic collagen replenishment were incorporated. In Ref. [34], the multiscale, multicell simulation environment CompuCell3D [20] was used, and three compartments were considered: a simplified epithelial compartment compared to that Ref. [33], an extracellular compartment for an immune response, and a lymph node compartment from which immune cells are recruited. Both of these MSM approaches made many assumptions

in the absence of experimental data on SARS-CoV-2 infection, but both were formulated to easily incorporate future mechanistic refinements in a modular fashion.

In tuberculosis, which results from a bacterial lung infection, the formation and integrity of fibrous tissue structures called granulomas are important for disease outcomes. MSM of the regulation of these formations by pro inflammatory and anti-inflammatory processes was reviewed in Ref. [35]. The integrity of granulomas controlled by ECM remodeling was modeled in Ref. [36]. Note that Ref. [35] reviewed an extensive history of MSM in tuberculosis and other infectious diseases.

Cancers

Here, two areas of cancer research are highlighted where the interactions between cancer cells and the neighboring tissue are important: (1) cancer growth and (2) metastatic invasion and related ECM remodeling.

Cancer growth

One MSM approach for tumor growth shows the influence of the intracellular metabolism on regulating growth [37]. ODEs were used to simulate a kinetic model of intracellular metabolic processes. The kinetic model was coupled to a discrete ABM for cellular processes such as growth, death, mitosis, and transitions between discrete cell states (e.g., quiescent stem cells, proliferating cancer cells, and necrotic). Additionally, the model considered a third scale of influence from extracellular tissue concentrations of nutrients using a system of PDEs. This model used the Systems Biology Markup Language (SBML) [38] standard formalism for the ODE intracellular scale and CompuCell3D for hybrid modeling of the cellular and extracellular scales. The authors explicitly discussed how they handled the disparate time scales in their simulations.

An alternative MSM approach considered heterogeneity in intracellular metabolism and signaling mechanisms on the emerging cellular phenotype within different microenvironments through a custom ABM framework [39], which is generalized beyond just the application to tumor growth. Nutrients were subject to reaction-diffusion equations, metabolism was described by a suite of rules, signaling was modeled via ODEs, and cell dynamics were captured by discrete ABM rules.

Another MSM approach to simulate cancer growth focused on the biomechanics of tumor cell proliferation and invasion [40]. Discrete mechanics were used at the cellular level to simulate cell–cell interactions among tumor and host cells, adhesion to ECM, and cell migration. Proliferation of tumor cells was also considered in a discrete fashion. These processes were averaged over a lattice to connect to the tissue scale where the tumor growth was considered as a moving boundary and continuum mechanics were used to calculate the resulting solid stresses experienced in the tissue. The influences of stiffness for the cellular-level ECM and tumor cells and for the surrounding tissue stiffness were also explored.

Cancer metastasis

In cancer metastasis, remodeling of collagen fibers in the ECM facilitates the migration of cancer cells from the primary tumor to the vasculature and then to distant metastatic sites. Matrix degrading enzymes including MMP are secreted by cells in the tumor microenvironment to prepare the domain to be favorable for cellular dissemination. Tumor invasion and spread due to interactions with and remodeling of the ECM have been frequently studied with mathematical models. MSM is appropriate for addressing cancer metastasis as it involves intercellular tumor cell processes, secreted factors, nonsoluble ECM components, and mobile cells that traverse or even leave a local tissue. Three popular MSM approaches have emerged. In approach 1, reaction-diffusion PDEs are defined for concentrations of one or more matrix degrading enzyme(s) such as MMP, populations of tumor cells, and density of ECM [41–43] (see references cited in Ref. [42] for historical overview). Approach 2 involves continuous modeling at the macroscale and microscale with a moving boundary front representing where ECM remodeling occurs at the microscale at the edge of the macroscopic tumor mass [44–48]. Approach 3 employs hybrid modeling using ABMs at the cellular level and PDEs for ECM and chemical factors [49–51].

Three recent contributions using approach 1 are highlighted. Ref. [41] considered the effects of the enzyme lysyl oxidase on cross-linking collagen fibers of the ECM to influence haptotaxis towards cross-linked and aligned fibers. Ref. [42] compared two mathematical formulations for haptotaxis via local gradient-based and nonlocal adhesion-based terms. Ref. [43] incorporated a function termed “contractivity” to couple microscale biochemical remodeling events to the cell motility. The contractivity function implicitly accounted for variations in cellular adhesion and resulting haptotaxis due to ECM remodeling-induced changes in material properties.

A line of research using approach 2 has continued to develop in the last few years from the same groups of authors. In Ref. [45], careful consideration of cell adhesion and microscopic fiber dynamics was added to a previous model [44]. The fiber and nonfiber constituents of ECM allowed for dynamic biochemical remodeling of the fibers at the microscale. Cell adhesion and cell-scale mechanical fiber redistribution were also included. A cell-scale cross-talk interaction between cell migration and ECM remodeling along the moving boundary was refined in Ref. [46]. Heterogeneous

tumor cell populations were simulated in Ref. [47]. The model was extended to consider the influence of tumor-associated macrophages on ECM remodeling in Ref. [48].

Several papers have used approach 3 via CompuCell3D. Ref. [49] considered both tumor cells and ECM fibers as discrete in the ABM and used PDEs to describe the secretion and diffusion of MMP to degrade ECM fibers. In Ref. [50], the ABM described the tumor cell behaviors, and the fibers of the ECM were modeled as a continuous field subject to microscopic biochemical remodeling by MMP and cross-linking by lysyl oxidase. Haptotaxis in the presence and absence of cross-linked fiber gradients were explored. Another model was developed to study the process of endothelial to mesenchymal transition due to mechanical signals that results in remodeling in a metastatic tumor microenvironment [51]. This model used a 3D spatial domain compared to the 2D domain used in most of the models reviewed here. An ABM tracked quiescent, activated, and metastatic cancer cells; quiescent endothelial cells; and fibroblasts activated via the endothelial to mesenchymal transition. The ECM was considered to be a continuous medium along with another nonmatrix medium representing the extracellular void space. Nutrients, cytokines, ECM proteins, and matrix degrading enzymes were modeled by reaction-diffusion equations. The role of inflammation was included. Substrate ECM stiffness was modulated through the ratio of the ECM and the void space medium.

MSM for the whole-body scope of metastatic cancer spread was formulated in Ref. [52]. ECM and MMP were modeled by PDEs to capture remodeling on spatial domains presenting primary tumor and secondary site tissue scales. PDEs are used to prescribe the diffusion and haptotaxis of two populations of cancer cell phenotypes. To this point, the MSM was consistent with approach 1. However, the cells were modeled with a more elaborate hybrid discrete-continuum approach. A rule-based ABM framework was used at the whole-body scale to move cancer cells and clusters between the primary and secondary tissue domains through the vasculature. The movement and cell proliferation at different scales was determined through rules and probabilities determined from the PDE formulations.

Commentary, conclusions, and future directions

Several of the case studies discussed in the prior sections demonstrated use of ABM for at least one of the modeling scales. The inclusion of biological variability through stochastic simulations is often a compelling motivation to use ABM. While ABM is not required to integrate multiple scales of components, software platforms such as CompuCell3D and PhysiCell have facilitated the adoption of ABM for MSM in biomedical systems by streamlining and modularizing model construction. These tools have lowered the barrier for researchers new to MSM in much the same way that computational fluid dynamics software such as COMSOL and ANSYS Fluent fostered widespread use of multiphysics modeling. It is worth noting that many other valid MSM methods exist that do not incorporate ABM, such as those referred to as approach 1 and approach 2 applied to cancer metastasis.

Many challenges and opportunities still remain for MSM researchers. The first challenge to MSM that most researchers face is training and communicating across disparate biological and/or computational backgrounds. Recent commentaries have highlighted some important challenges to overcome regarding standards for developing interoperable and reusable tools for MSM [53,54] and opportunities to pursue for integrating modern machine learning efforts into MSM [54–56]. Others have previously provided perspectives on efforts at integrating complex and varied data obtained from multiple experiments, models, and/or scales [57]. Prior knowledge of disease mechanisms is being curated into static multiscale network representations through various disease mapping projects [58,59], which could provide rich information for the development of future spatial and temporal MSM modules. Another limitation is a lack of opportunities that incentivize MSM researchers to work collaboratively. While it is very common for MSM projects to involve collaborations between experimental and computational labs, it is much less common for multiple computational labs to work together without large center funding. However, such productive computational collaborations have emerged by combining the modeling expertise at various scales or from different approaches, for example, Refs. [23,33].

As with all modeling approaches, MSM certainly has tradeoffs and limitations. Large integrated models have greater computational expense and generally take longer to develop than models at a single scale. Training, validation, and uncertainty quantification, particularly of stochastic processes, is not as straightforward for MSM as for a single model scale. See Ref. [60] for a clear overview of the similarities and differences between some of these techniques at single and multiple scales. Even with the challenges and complexities, MSM enables insights into the mechanisms that explain how various higher level physiological phenomena are connected and modulated by interventions at lower scales (i.e., genetic or molecular). A long-term vision for the MSM field is to provide a suite of configurable computational biology building blocks that describe the rules of life at various scales and are informed by the entire range of molecular biology data types. The components should be able to be assembled for predictive

simulations much like the computational chemistry and physics first principles modeling approaches that are very powerful in materials science.

Another promising more near-term future direction that is already underway in the cancer-immunology research area [61–66] is to include the interplay of the immune system along with tissue and organ-specific diseases models to better consider both local and systemic impacts of diseases and treatments. For example, modeling the infection dynamics and proliferation sites of SARS-CoV-2 connected to the mechanisms of the damage inflicted to several organs would be helpful for designing treatments for and understanding short-term severity and long-term effects of COVID-19. Deciphering the role of the immune system in mediating gut-induced changes in bone [67] in inflammatory or sex-hormone depletion diseases is another area ripe for such MSM. MSM is also promising for other important problems in diseases such as diabetes where the roles of chronic inflammation on regulation, comorbidities, and local complications in a number of tissues including the kidneys are still being elucidated [68,69]. For these directions, standards for reproducible research computing and for reusability of existing models become critical for enabling feasibility and reliability of such MSM efforts.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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