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Multi-class and multi-scale models of complex biological phenomena

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Computational modeling has significantly impacted our ability to analyze vast (and exponentially increasing) quantities of experimental data for a variety of applications, such as drug discovery and disease forecasting. Single-scale, single-class models persist as the most common group of models, but biological complexity often demands more sophisticated approaches. This review surveys modeling approaches that are *multi-class* (incorporating multiple model types) and/or *multi-scale* (accounting for multiple spatial or temporal scales) and describes how these models, and combinations thereof, should be used within the context of the problem statement. We end by highlighting agent-based models as an intuitive, modular, and flexible framework within which multi-scale and multi-class models can be implemented.

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Introduction

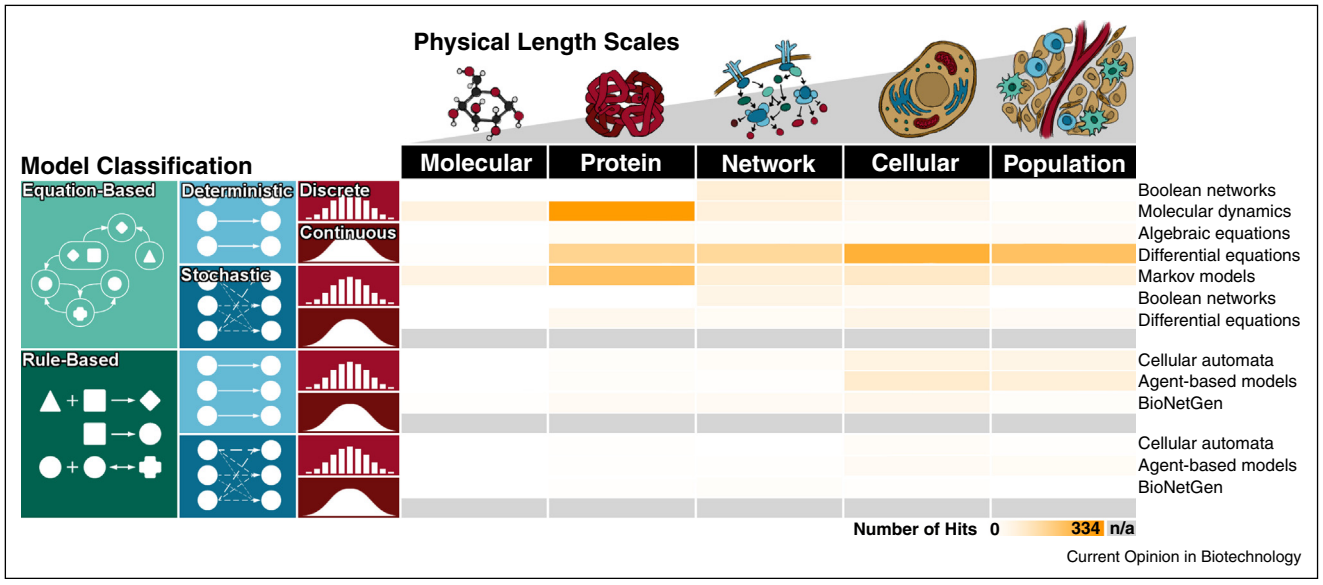
Computational modeling is a powerful tool that impacts science and society in remarkable ways. Major applications include accelerated design and development of drug therapeutics, as well as integration of theory and experiments to advance basic science. In drug therapeutics and in view of a rapidly approaching patent cliff for several major drugs, pharmaceutical companies have embraced computer-aided drug design through techniques such as binding pocket modeling, molecular dynamics simulations, and pharmacokinetic modeling [1–3]. Models of disease and organ level physiology help researchers predict system response to therapeutic perturbations and design clinical trials [4]. On a larger scale, computational models have also been used to investigate incidence, spread, and intervention for diseases such as Ebola and West Nile virus [5–8].

In basic science, computational models predict complex behavior, elucidate regulatory mechanisms, and inform experimental design [9,10]. For instance, a quorum sensing model in *Agrobacterium* described complex, experimentally observed behavior of the organism and provided experimentally-testable hypotheses for the evolutionary significance of the sensing phenomenon [11]. A previously longstanding question in biology involving the regulatory mechanism driving *E. coli* chemotaxis was also resolved by iteration between a computational model of chemotaxis signal transduction and experimental validation with mutant strains [12]. Simulations of the *Drosophila* segment polarity network by von Dassow *et al.* revealed that no parameter sets produced the observed behavior, leading the authors to amend their understanding of the network and propose new candidate mechanisms for further experimentation [13].

With the rapid expansion and improvement of experimental techniques, scientists are generating unprecedented amounts of high-throughput, high-quality biological data [14]. This exponential growth of multi-dimensional biological data requires a parallel growth in quantitative modeling methods of such data to explain non-intuitive observations [14,15]. The appropriate model group and framework necessary for attaining biologically relevant insight depends on context and data. Commonly, these models are single-scale and single-class; Figure 1 outlines a high-level summary of these frameworks used at different biological length scales of interest. At one extreme, models considering the interactions of molecules and protein structure tend to be discrete and based on first principles. At the other extreme, models describing single cells and cell populations tend to be more continuous. Across these scales, rule-based models are less common than equations-based models.

While we acknowledge the existence of countless additional length-scales — including organs, organ systems, individuals, and populations — as well as countless time-scales, these layers of resolution are outside the scope of this review. Statistical learning theory also falls outside the scope of this review. In the following section, we describe fundamental attributes of computational models to establish a common vocabulary. Next, we highlight attributes of multi-scale and/or multi-class models (as well as combinations thereof) and their unique advantages for describing complex biological phenomena.

Figure 1



Number of PubMed 'hits' highlight trends in modeling framework selection across different scales. Representative model frameworks for each of the different model classes are used. The color bar highlights molecular dynamics models of proteins as one of the most published frameworks and rule-based approaches as one of the least explored. Search strings used to generate these numbers are provided on our website.

Classes and scales of computational models

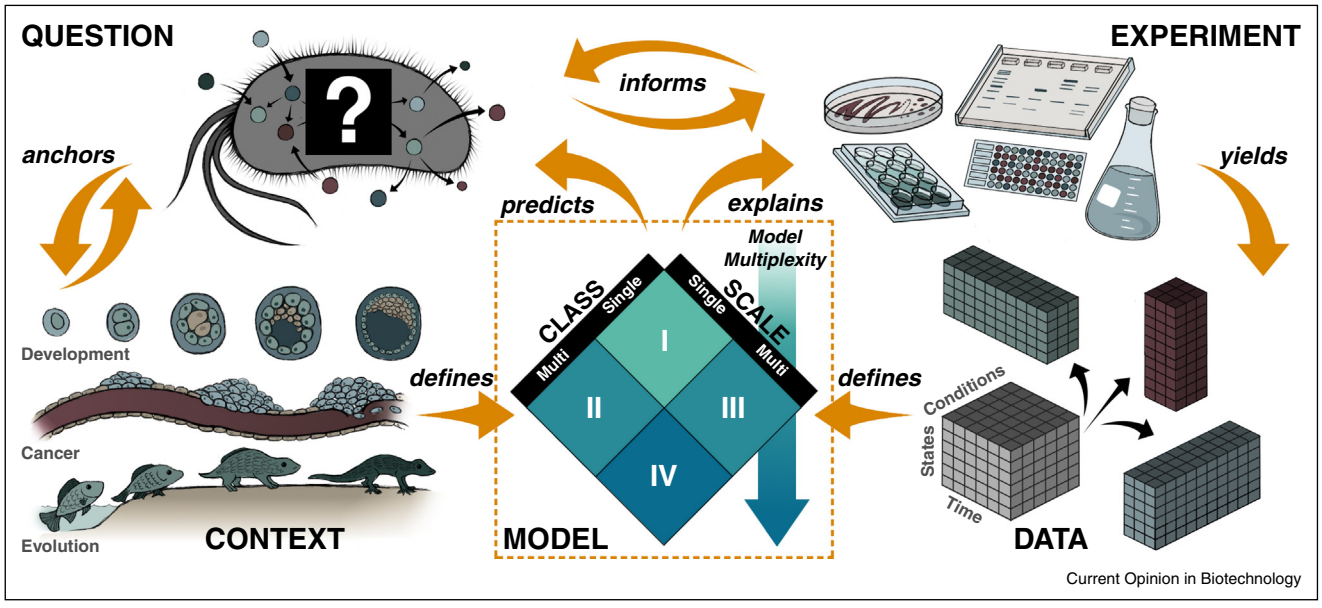
A *model* represents a real-life system or phenomenon of interest [16,17]. Unlike physical models, composed of tangible parts, computational models are mathematical abstractions of a system [16]. *State variables* describe the model at an instance of a computational simulation and *parameter variables* characterize the model itself [16]. Consider a model of a single cell undergoing mitosis: a state variable could denote the phase of the cell cycle at a given time point, whereas the duration of the phase would depend on the value of a parameter variable.

Models can be classified according to two characteristics: (i) the evolution of state variables and (ii) the computational repeatability of the output, or response, trajectory. *Evolution* describes how state variables change: *continuous* variables take on any value, *discrete* variables take on integer values. *Repeatability* characterizes the expected output trajectories from a given set of inputs. *Deterministic* models produce identical output response profiles provided identical initial state and parameter conditions, whereas *stochastic* models allow random or probabilistic events such that a single simulation given identical initial state and parameter conditions can produce a family of response profiles [16]. We include a third characteristic of classification, *specification*, which identifies how the interactions among state variables are defined. *Rule-based* models use qualitative rules to describe interactions, while e*quation-based* models use mathematically formulated ones [18,19]. Thus, a model class is given by its evolution, reproducibility, and specification characteristics. We define models that incorporate multiple model classes in a single framework as *multi-class*; otherwise, the model is *single-class*.

In parallel, we define the *scale*, temporal or spatial, of the model. By definition, *multi-scale* models explicitly incorporate two or more levels of resolution [20,21]. Biological systems are inherently multi-scale: cell population dynamics rely on intercellular protein signaling, which relies on fluctuations of intracellular protein concentrations, and so on [21]. Existing reviews offer detailed discussion of multi-scale models for biological systems [20,22,23]. At the center of Figure 2, the four different groups of models are organized based on increasing *multiplexity* of class and scale.

When modeling complex biological systems, and regardless of approach, the multiplexity of a computational model should be defined by the context of the problem statement, the type of answer sought (i.e., qualitative vs. quantitative) and the experimental data. Disparities between the modeling framework and problem statement can limit predictive capacity and biological insight. A model is too detailed if the training data cannot fully support the model structure or parameter estimation, which can result in over fitting and unnecessary computational expense and be revealed through parameter identifiability or uncertainty analysis. A model is too simple if it is unable to capture the possible depth or breadth of understanding that a qualitative and/or quantitative data set provides. Different aspects of cancer, for

Figure 2



Guiding principles for model development. (Center panel) Class refers to the specific combinations of characteristics of a model (i.e. discrete vs. continuous, stochastic vs. deterministic, and rule-based vs. equation-based). Scale refers to the levels of resolution that are explicitly accounted for in the model (e.g. proteins, single cell, cell population). Multiplexity, the degree to which a model incorporates multiples of either class or scale, increases from Group I (single-class, single-scale), to Group II (single-scale, multi-class) and Group III (multi-scale, single-class), to Group IV (multi-scale, multi-class). These different model groups comprise modeling framework selection for a biological system. (Outer panels) Selection of a modeling framework should be defined by the context of the problem statement, which is anchored to the research question. Modeling framework selection should also be defined by the training data derived from experiments designed to inform the scientific question. Simulations from an accurate model should predict the behavior of the system and explain non-intuitive experimental observations. Throughout the model development process, both successful and unsuccessful predictions should offer insight on, and guide the identification of, key components underlying complex biological phenomena.

example, have been studied using techniques ranging from network graphs [24–26] to differential equations [27•,28,29] to multi-agent systems [30,31,32••]. It is critical to account for how context and data influence model development (Figure 2); failure to do so risks poor modeling framework selection, inaccurate parameter estimation or model training, and misleading conclusions.

Single-scale, multi-class models

Multi-class models represent compound systems incorporating two or more model classes within a single framework. *Hybrid* models specifically incorporate discrete and continuous characteristics. A classic example describes a discrete boundary condition that defines how the state representation of a bouncing ball jumps from one continuous model to another [33]. In biology, a similar phenomenon can be observed when normal, continuous operation is perturbed in a discontinuous or pulse-like manner, such as synchronization of firefly flashing in response to its neighbors [33] or circadian phase in response to a light pulse [34]. An alternative application of hybrid models involves coupling continuous and discrete state dynamics in parallel. Certain pattern formation behavior involves a small number of specialized cells guiding large aggregates of non-specialized cells, such as in angiogenesis and skin repair [35•]. Depending on the context, the relatively small population size of the specialized cells may require a discrete representation, while the larger, non-specialized population can be represented continuously [35•].

Multi-class models are not limited to the integration of continuous and discrete state dynamics; they can involve the integration of other model types, such as rule-based with differential equation systems. Rule-based, discrete particle simulation models have been coupled with species-specific continuous models [36] and reaction-diffusion kinetics have been implemented using colored petri nets [37]. The former approach has been demonstrated in four biological systems, including EGFR, to produce statistically equivalent results at reduced computational cost [36].

Another strategy for multiple model classes involves using one class to identify parameters that define a subsequent model of a different class. For example, budding yeast cell cycle dynamics have been characterized using a stochastic model parameterized by fitting deterministic simulations to experimental data [38•]. In

contrast, a deterministic model demonstrated that a bistable switch exists in the molecular pathway between inflammation and cell transformation and stochastic simulations were then used to examine the effects of noise on the dynamics of that switch [39].

Multi-scale, single-class models

Certain biological phenomena can only be studied by integrating responses at multiple levels of spatial or temporal resolution, such as fluctuations in gene expression at fast time scales driving spontaneous cell phenotype switches at much longer time scales [40,41]. While corresponding models explicitly account for multiple scales, they employ the same class of models to describe each scale. This framework has been used to study hemodynamics, where fluid dynamic equations of blood flow used to describe the tissue-level behavior are coupled to differential equations describing cellular- or subcellular-level interactions [42–44]. Liang *et al.* demonstrated that a multi-scale model of hemodynamics following carotid artery operation predicted results comparable to measured patient data, whereas a single-scale 3D model could not [42]. Coupled systems of equations have also been used for viral infection [45•], tumor growth [46], immune response [47], and bone remodeling [48].

Stochasticity or discretization can also be introduced to the model class, as demonstrated by a multi-scale model of cross-sectional distribution of axonal components [49] and cytochrome P450 drug metabolism [50]. Bannish *et al.* characterized fibrinolysis using two stochastic/discrete models, with the biochemical reactions in the single fiber scale model providing data for the full clot scale model in a decoupled manner [51]. Although instrumental in these contexts, multi-scale single-class models are arguably less common since the appropriate model class often varies across scales.

Multi-scale, multi-class models

Multi-scale, multi-class models incorporate multiple scales using different model classes. By coupling various model classes and scales, we can better characterize and explain the complex interactions underlying emergent behavior, analysis that cannot be achieved by examining individual system components or scales in isolation.

Coupling discrete cells with continuous diffusion

A common implementation of a multi-scale, multi-class model couples discrete cell representations, motivated by the behavior of interest, with continuous equations that describe intracellular, intercellular, and/or extracellular (environmental) responses. For instance, studies have employed spherical representation of cells as autonomous, visco-elastic objects to characterize interactions and motions defined by mechanisms such as adhesion-repulsion or Brownian movement. This representation is useful for systems where cellular movement, especially chemotaxis, is of interest. Developmental cell migration [52,53•], erythropoiesis [54], and palisade formation in glioblastoma [55] have used similar modeling strategies. An alternative representation defines cells as geometric regions to allow behaviors such as changes in cell shape, tissue spreading, and intercalation [56•]. This representation is useful for systems where the spatial distribution and physical interactions of cells is of interest. A third discrete state representation method is termed *cellular automata*, where the cell is represented by a location on a static grid. This framework is commonly used for modeling tumor growth coupled to nutrient or oxygen diffusion because grid locations can be assigned cell states [57–60], which is useful for systems in which cellular phenotype is an important consideration.

Molecular dynamics and Monte Carlo methods

Another implementation of multi-scale, multi-class modeling couples deterministic and stochastic simulations of discrete entities, using techniques such as molecular dynamics (MD) and Monte Carlo (MC). This approach is suitable for systems involving larger numbers of relatively simple interacting particles at two scales, such as platelets and blood flow [61], or histones and chromatin [62]. Note the tradeoff between complexity and quantity; a large number of complex particles can quickly become computationally infeasible.

Agent-based models

Agent-based models (ABMs) utilize autonomous agents that follow a set of rules for interacting with their neighbors and environment. Their intuitive, modular, and flexible framework present a promising strategy for characterizing biological systems [63,64••]. Similar to cellular automata, agents are an *intuitive* abstraction for describing cells, meaning that parameters often have a clear, biological implication (though their values might not reflect a specific mechanism). The agent representation incorporates both the cell-phenotype emphasis of cellular automata and the cell-movement emphasis of a spherical or geometric representation. Agent rule sets are *modular*; different agent can have a different rule sets and relevant protein/genetic level circuits can be substituted in as needed. This capability, in particular, distinguishes ABMs from the general strategy of coupling discrete cells to continuous diffusion as it allows representation of a wider range of behavior. Overall, the modeling framework is *flexible* for incorporating changes environmental conditions or perturbations, which can be difficult in a discrete cell-continuous diffusion system. The ABM framework is therefore well suited, but not limited, to implementing multi-scale and multi-class models. This strategy has been used to study angiogenesis [65,66], immune response [67,68,69••], and liver fibrosis [70]. With increasing interest in resolving and manipulating the cellular microenvironment, we believe ABMs — originally established in the fields of social science and economics — will

be an invaluable tool to elucidate heterogeneous, emergent dynamics by integrating diverse data in a single multi-scale framework [71••,72].

Conclusion

Single-class, single-scale models are the most common group of computational models, providing significant leaps in our understanding of biological systems. Countless well-established strategies exist for model selection, parameter estimation, uncertainty analysis, etc. for single-class, single-scale models. However, the complexity of biology necessitates, and increasingly powerful computers and experimental protocols permit, development of more sophisticated and multiplexed models. Biological complexity arises from the non-additive nature of biological systems; the behavior of a scale cannot necessarily be predicted by the properties of its underlying components. This emergent behavior suggests that modeling a biological system at a single scale and class is not necessarily sufficient.

For single-scale, multi-class models, an important consideration is the tradeoff between simulation efficiency and model multiplexity. Continuous or deterministic models are often more computationally efficient than discrete or stochastic models [36,73]. However, discrete and/or stochastic models are sometimes more suitable to capture the inherent noise and heterogeneity of biological systems. A combination of continuous/discrete or deterministic/stochastic aspects can be implemented by (i) incorporating both aspects into a single framework or (ii) using a single-class model to define parameters that inform the dynamics of a different single-class model.

For multi-scale, single-class models, a key consideration is the relevance of a single model class for describing multiple scales. Deterministic/continuous models, in particular, are appropriate when approximating the mean of a well-mixed, large numbered system. This approach is useful for population-level interactions with larger scale constructs, such as fluid flow or mechanical forces.

Agent-based models are particularly well suited to characterize biological phenomena in a multi-scale, multi-class manner. While promising, ABMs have suffered from three notable limitations. First, implementing an ABM has a higher barrier to entry and requires more programming expertise than a traditional, equation-based approach. In this regard, software tools, most recently Morpheus and Smoldyn with on-lattice functionality, have been developed to allow a broader audience to access this framework [74,75]. A second limitation is computational expense due to the need to simulate large numbers of agents. Third, because ABMs are relatively new and attempt to synthesize different spatiotemporal scales, strategies for improved experimental measurements and associated parameter estimation are underdeveloped. Carbo et al. approached this limitation in the context of immune response by first developing an ODE-based model to provide a starting set of parameter values for their ABM [76]. Alternatively, Wells *et al.* performed a comprehensive parameter sensitivity analysis on their ABM to guide parameter estimation [71••]. Although advances in technology and computing power mitigate the former limitations, expertise in systems theory remains critical to address the latter.

In summary, we stress that models with higher multiplexity do not necessarily offer more accurate predictions or biological insight. Even though we provide a simple illustration of the guiding principles for model development (Figure 2), we acknowledge that the individual components cannot always be decoupled; a simple formula for selecting a modeling framework given a data type does not exist and the modeling process is necessarily iterative and non-trivial. We encourage researchers to consider how modeling fits into the larger framework of the problem statement, the type of answer sought, and the experimental data before selecting a modeling framework to investigate complex biological phenomena.

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