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Bridging intracellular scales by mechanistic computational models

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The impact of intracellular spatial organization beyond classical compartments on processes such as cell signaling is increasingly recognized. A quantitative, mechanistic understanding of cellular systems therefore needs to account for different scales in at least three coordinates: time, molecular abundances, and space. Mechanistic mathematical models may span all these scales, but corresponding multi-scale models need to resolve mechanistic details on small scales while maintaining computational tractability for larger ones. This typically results in models that combine different levels of description: from a microscopic representation of chemical reactions up to continuum dynamics in space and time. We highlight recent progress in bridging these model classes and outline current challenges in multi-scale models such as active transport and dynamic geometries.

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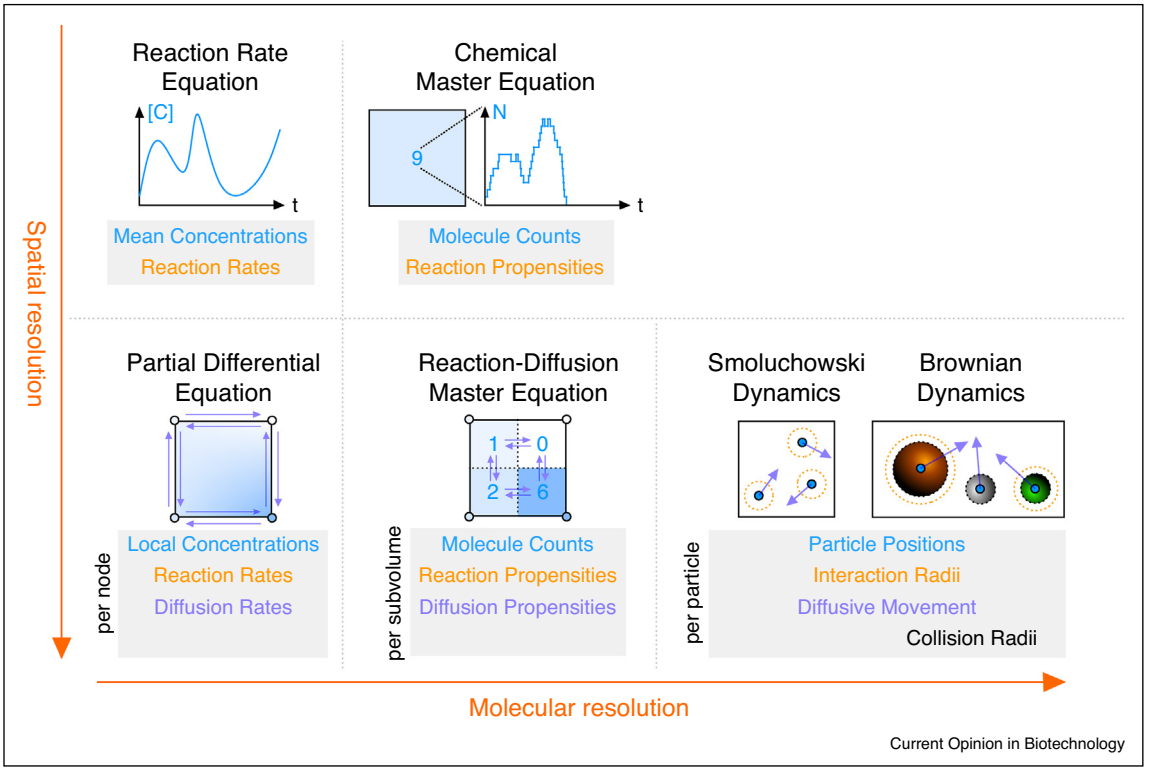
Introduction

Rapid developments of primarily imaging-based technologies have revealed the structural and dynamic richness of life at the single-cell level. Structural organization inside cells reaches substantially beyond classical membrane-delimited compartments and stochastic dynamics resulting from low copy numbers of molecules are increasingly recognized as an important contributor to cellular functions such as information processing [1]. Correspondingly, current cell biology seeks to answer a variety of questions considering drastically different scales, and covering a variety of levels of detail: from the atomistic up to entire cells in space, from picoseconds of enzyme structure fluctuations up to years of population dynamics in time, and from single molecules to crowded macromolecular environments in terms of molecular abundances. While experimental methods such as multi-scale imaging [2] may eventually bridge some of these scales, we argue that computational or mathematical modeling is in a unique position to integrate knowledge of varying levels of detail and a variety of heterogeneous experimental data.

Using cell signaling as an example, systems biology models have been very successful in achieving a holistic and quantitative understanding of the 'signaling ballet in space and time' [3]. Typical systems biology models in this domain, however, use classical systems of ordinary differential equations (ODEs) that ignore spatial distributions of molecules and assume that all chemical species are abundant enough to warrant treatment as a concentration field (Figure 1) [4,5]. To increase spatial resolution, classical partial differential equation (PDE) modeling can describe the evolution of concentrations in time and space; it leads to a purely deterministic model on a spatial domain that is discretized by a mesh for which the temporal evolution of the solution is computed (Figure 1) [6]. To increase molecular resolution, stochastic models based on solving the well-mixed chemical master equation (CME) usually employ simulation algorithms to infer noise statistics from sampled trajectories [7]. Importantly, efficient simulation algorithms exist for all three model classes, for instance a stochastic simulation algorithm with a runtime that is independent of the number of possible reactions [8].

However, while the most prevalent type of model is single-class (using only one of the modeling approaches above) and single-scale (covering only a single spatial, temporal, and abundance scale) [9], biological complexity often requires analyzing phenomena on different temporal and spatial scales as discussed above [5]. The main challenge of multi-scale models is to resolve the necessary mechanistic details on short time-scales, length-scales, and low abundance-scales while maintaining computational tractability for longer and higher ones. This typically results in multi-class models that combine different levels of description. For example, low-abundance species may co-exist with high-abundance species in the same model, making purely stochastic simulation computationally expensive and inefficient. Fully deterministic treatment, in contrast, can lead to inaccurate results due to the low abundance species. High spatial resolution — which leads to low molecule counts per compartment

Figure 1



Spatio-temporal modeling approaches. Reaction rate equation (RRE) models (top left), the most common model class in systems biology that relies on ordinary differential equations (ODEs), disregards space and tracks only the mean of the concentrations (blue) over time. To introduce space in deterministic approaches, partial differential equation (PDE) models track continuous concentrations on mesh nodes and use basis functions to interpolate in the interior, coarse-graining the discrete nature of reacting and diffusing molecules. To increase molecular resolution compared to RRE models requires a stochastic approach; in a system that is assumed to be well-mixed, the chemical master equation (CME) captures how molecules react with reaction propensities depending on molecule counts. Combining increased molecular and spatial resolution is achieved by discretized-geometry, subvolume-based stochastic approaches. The reaction-diffusion master equation (RDME) partitions space into discrete subvolumes in which molecule counts (blue) are tracked. In these subvolumes, molecules react stochastically, and they diffuse with corresponding diffusion propensities for jumps of molecules from one subvolume to an adjacent one (violet). Continuous-geometry, particle-based stochastic approaches yield the highest resolution. In Brownian dynamics (BD), each chemical species is represented as a hard-shell sphere with an explicit position (blue), an interaction radius (orange dotted) at which a molecule reacts (reacting particles in color), and a collision radius (black dotted) at which molecules collide when moving by diffusion (violet). When the simulation advances in time, the particles diffuse, collide and react accordingly. Smoluchowski dynamics considers only the reacting particles (orange reaction radii) and it idealizes particles as points (blue), leading to much faster simulations because collisions of non-reacting particles are neglected.

and therefore increases stochasticity — further increases demand for hybrid methods, that is, multi-class approaches that combine stochastic and deterministic representations of cell states.

Over the past years, substantial effort was put into bridging modeling approaches with the purpose of both elucidating the mechanistic basis of more coarse-grained modeling approaches, and enabling multi-scale models that use the most adequate and computationally efficient approach for each scale considered. For example, efficient hybrid methods that maintain the accuracy of the solution have recently been developed both for simulating spatiotemporally resolved [10] and well-mixed [11,12] models. Here, we summarize recent developments of dynamic models based on the underlying physics and chemistry of the biological process considered, which will eventually enable the simulation of large-scale models that accurately account for microscopic phenomena. While statistical and machine learning models [13] are undoubtedly useful and rising in popularity, they fall outside our scope. We will restrict ourselves to recent applications and methodological progress covering the scales from molecular detail, via protein complexes and sub-cellular compartments, up to the cellular scale. Such models have shed light on a variety of phenomena such as cytoplasmic crowding, intracellular transport, intracellular signaling, and control of cell polarization and movement.

Reaction, diffusion, and crowding

A widespread issue in *in vivo* modeling is accounting for the effects of macromolecular crowding agents [14•] on