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Agent-Based Modeling in Molecular Systems Biology

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Molecular systems orchestrating the biology of the cell typically involve a complex web of interactions among various components and span a vast range of spatial and temporal scales. Computational methods have advanced our understanding of the behavior of molecular systems by enabling us to test assumptions and hypotheses, explore the effect of different parameters on the outcome, and eventually guide experiments. While several different mathematical and computational methods are developed to study molecular systems at different spatiotemporal scales, there is still a need for methods that bridge the gap between spatially-detailed and computationally-efficient approaches. In this review, we summarize the capabilities of agent-based modeling (ABM) as an emerging molecular systems biology technique that provides researchers with a new tool in exploring the dynamics of molecular systems/pathways in health and disease.

1. Introduction: The Computational Trade-Off of Modeling Molecular Systems: "Spatial Resolution" Versus "Time Scale"

The main challenge in molecular modeling is the complex relationship between spatial resolution and time scale, where increasing one would limit the other. The ideal scenario is to be able to model molecular systems with high spatial resolutions, that is nanometer, and for long time scales, that is seconds to minutes. This is currently not feasible due to the high computational expense. As a result, two categories of modeling techniques are employed, that is macroscopic and microscopic, each focusing on one of the two desired goals: high spatial resolution or extended time scales.

A well-established macroscopic method for modeling cellular pathways is bulk property models such as ordinary differential equations (ODE) of reaction rates that quantify concentration changes over time.[1,2] ODE representation of molecular reaction networks makes the assumption that i) concentrations are high and ii) the system is well mixed.[3] In some systems, the correlation length, or the length at which spatial homogeneity of reactants can be assumed, may be small – for example, reactions occur faster than the product species can diffuse to satisfy the well-mixed assumption. In such cases, spatial details should be considered through the use of partial differential equation (PDE) models. Both ODE and PDE models are well suited for systems with high concentrations that uphold the continuum hypothesis. However, the molecular systems often contain a discrete number of particles, which, in the time scales involved, fluctuates widely with respect to the characteristic length scale and the continuum hypothesis is not valid.[3,4] As a result, deterministic models such as ODEs and PDEs are not well suited for such systems.

Different models are developed to address problems involving a discrete number of particles such as the chemical master equation (CME), and the reaction diffusion master equation (RDME) (also see the Gillespie algorithm or the stochastic simulation algorithm (SSA),[5] next reaction method,[6] and reaction-diffusion SSA).[7] CME and RDME are sets of deterministic ODEs describing the time evolution of a molecular system that is well-mixed or locally well-mixed (dividing the domain into sub-volumes and assuming each to be well-mixed). Although these models capture the stochastic nature of such systems, they apply the stochasticity to the population, not individuals.[8] Therefore, they cannot provide detailed spatial information about individual particles or individual particle tracking which is typically performed with much more computationally expensive Brownian dynamics (BD) or molecular dynamics (MD) techniques. On the other hand, BD and MD are not computationally able to handle large number of molecules involved in molecular pathways (**Figure 1**).[9]

While macroscopic methods make simplifying assumptions to facilitate modeling of the target molecular system, microscopic methods, which are much finer in spatial resolution, are highly computationally expensive and cannot reach high temporal scales. This gap between the capabilities of computationally efficient macroscopic models such as ODE, PDE, CME, and RDME and more detailed models such as BD and MD creates a need for mesoscopic modeling techniques, which can be satisfied using agent based models.

2. Agent-Based Modeling (ABM): Bridging the Gap Between High Resolution and Long Time Scale

Agent-based modeling (ABM) is a computational modeling paradigm that has been employed in a wide range of areas of research such as economics,[11,12] social sciences,[13,14] environmental engineering,[15,16] as well as biological studies including microbiome,[17–19] cancer,[20,21] and systems biology.[22–24] ABM

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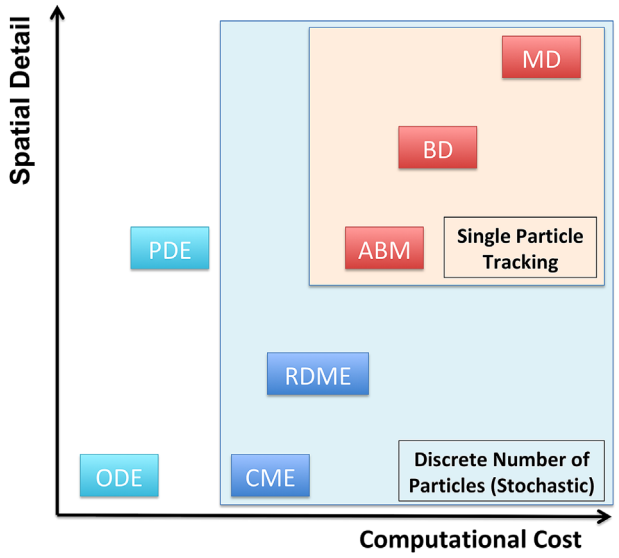

Figure 1. Spatial detail and associated relative computational cost for different computational modeling techniques for molecular systems. ODE: Ordinary Differential Equation; PDE: Partial Differential Equation; CME: Chemical Master Equation; RDME: Reaction Diffusion Master Equation; ABM: Agent-Based Model; BD: Brownian Dynamics; MD: Molecular Dynamics. Taken from ref. [10].

is a complex systems approach for simulating the interactions between multiple independent entities, termed 'agents', with the objective of assessing their individual effect on the overall system and predicting subsequent emergent phenomena.[25] Therefore, ABM is a bottom-up approach that models a complex system from the perspective of its constituent components.[25] Governing rules define how each individual agent moves and interacts, leading to reproduction of a complex phenomenon (**Figure 2**). ABM bridges the gap by observing the dynamics of the molecular system with a finer spatial resolution compared to macroscopic methods, for example ODEs, while with a coarser temporal resolution compared to microscopic methods, for example MD (**Figure 3**).

Besides the discussed advantages of ABM over other computational techniques, several characteristics of ABM make it a perfect candidate for stochastic modeling of molecular systems. Agent-based simulations of molecular systems can achieve extended time scales. Many of the molecular pathways cannot be explored by high-resolution techniques such as BD because it is virtually impossible to reach meaningful time scales. For instance, export of mRNA transcripts through the nuclear pore complex (NPC) requires a millisecond time scale, which is beyond capabilities of MD or BD (Figure 3), but was recently explored through ABM.[40]

ABM also easily accounts for spatial details and constrained environments. Cells are composed of different compartments and most of the molecules are constrained to their associated environment. For example, while the linker of nucleoskeleton and cytoskeleton (LINC) is associated with the nuclear envelope,[41] RNA-binding proteins could travel between the nucleus and the cytoplasm, depending on their binding partners.[42] Representation of structural geometry and the local and non-homogeneous distribution of molecules, which is essential for many cellular processes, can be easily incorporated in ABMs.

Individual particles can be tracked in ABMs, which is also referred to as memory of past events.[8] Study of molecular systems in the cell often requires a high resolution tracking of particles over the time of experiments or simulations. Accordingly, several efforts have been made to increase the spatiotemporal resolution of experimental approaches. For instance, in the case of mRNA export, while experimental approaches such as oligo(dT) in situ hybridization assay or single molecule fluorescence in situ hybridization (smFISH) can primarily perform bulk measurements to determine the intracellular distribution of RNA, they cannot capture high-resolution in vivo dynamics.[43] Recent advancements in RNA labeling as well as imaging methods, however, have provided a platform to capture spatial and temporal dynamics of individual mRNAs in vivo.[44–47] Similarly, in contrary to ODEs or even stochastic methods like Gillespie, individual particles could be tracked in ABMs over the course of simulation.

Moreover, ABM simulations can predict the emergent behavior of a complex system of molecules using the rules governing the behavior of individual molecules. The main objective in molecular systems biology is to understand the overall functionality of a molecular system and how different parameters affect this overall outcome. ABM, as a complex systems approach, has the ability to predict how a molecular system behaves given the rules that govern the behavior of individual molecules. Soheilypour and Mofrad,[35] for example,

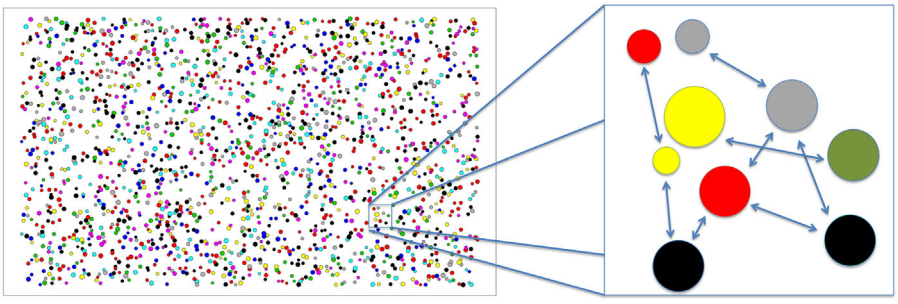

Figure 2. A schematic of agent-based modeling (ABM) of a complex system. The entities in the system, for example people, cells, or molecules, are simulated as "agents" (shown in different sizes and colors) that move and interact with each other. Each agent type has its own characteristics associated with their real-world properties. The complex web of interactions between the agents and the environment results in reproduction of a complex phenomenon.

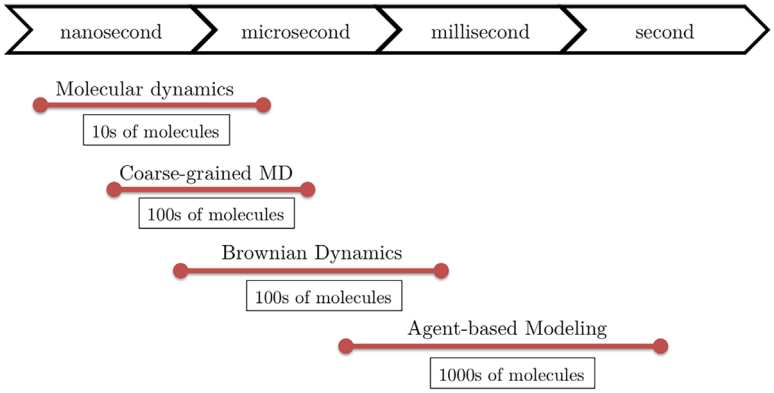

Figure 3. A comparison between the size of the system of interest and the timescales achievable by different molecular computational modeling techniques including molecular dynamics (MD),[26–28] coarse-grained MD,[29–31] Brownian dynamics,[32–34] agent-based modeling.[35–39] Examples of studies employing these approaches are provided as references. ABM can easily achieve extended time scales for a relatively crowded system of molecules.

demonstrated how modulating the affinities between the components involved in mRNA quality control could substantially alter the outcome of the system, that is export versus retention of mRNAs.

ABM is able to efficiently capture the intrinsic complexity of biological pathways and unveil the influence of noise or disruptions of a single factor on the behavior of the system, which could be employed to explore the dynamics of disrupted molecular pathways in diseases. Considering these characteristics as well as incorporation of stochasticity to individual elements in the system,[8,24] which is an essential component in a molecular system, ABMs can be employed in a wide range of applications in molecular systems biology (**Figure 4**).

3. Agent-Based Modeling Tools

To date, several agent-based modeling and simulation tools are developed for different purposes. **Table 1** summarizes some of the more popular general-purpose ABM tools (for a comprehensive review see Abar et al.).[48] Since ABM is a generic complex systems modeling approach, these ABM toolkits are designed to be applicable to a range of systems and problems in various fields of research, yet mostly tailored toward traditional ABM applications such as social behavior and macroscopic natural phenomena. However, they are not always considered the sole resource for ABM in some fields of research. For example, although the available ABM tools are employed for complex biological systems at the cellular level such as epithelial renewal in skin (FLAME),[49] retinal angiogenesis (NetLogo),[50] tumor growth (MASON),[51] bone remodeling[52] and *Escherichia coli* colony dynamics (RePast),[53] and pressure ulcer formation (SPARK),[54] several ABM toolkits are developed specifically for cellular-scale studies including iDynoMics,[55] BSim,[56,57] BNSim,[58] and CellModeller[59] and many other studies have developed their own *in-house* models.[60–63] The main reason, obviously, is that general-purpose ABMs are designed to fit a wide range of needs from significantly different fields of research. As a result, they lack specific features that one expects for a multicellular system. For instance, movement of microorganisms in aqueous environments is governed by Brownian dynamics and flagellar forces.[56] In addition, most of the cellular-scale ABMs use ordinary differential equations (ODEs) or partial differential equations (PDEs) to update molecular concentrations.[64] These features are lacking in general-purpose ABMs.

Similarly, molecular systems have specific features that differ from complex systems usually modeled via general-purpose ABM tools. While molecules have a mere reaction-diffusion behavior, agents in social sciences, for example humans, or microbial populations, that is microorganisms, are considered as intelligent and decision-making entities that demonstrate feedback or stimuli-based behavior. In addition, some molecules, such as DNA and RNA, are polymers, that is chain of monomeric agents, while there is no similar concept in larger-scale ABMs. Furthermore, diffusion and interactions of molecules are governed by well-established biophysical and biochemical rules instead of empirical observations. However, it

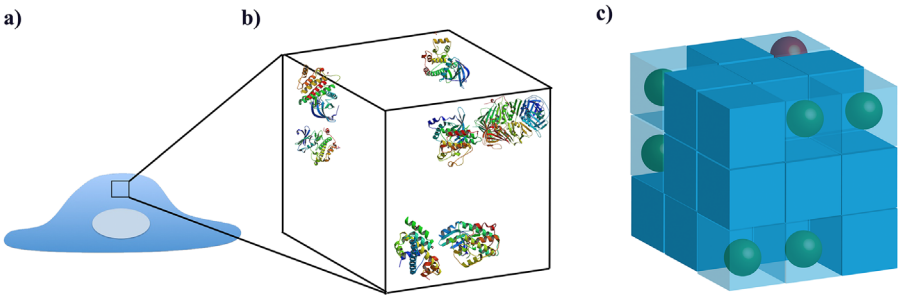

Figure 4. a) Function of a cell is substantially dependent on various complex molecular pathways inside the nucleus as well as the cytoplasm. Each pathway takes place in a particular environment and involves several different factors, that is molecules. The cross-interactions between these molecules lead to the complex behavior of the system. b) A zoomed-in view of seven proteins interacting in an imaginary molecular system in the cytoplasm. c) Agent-based modeling (ABM) representation of the imaginary pathway shown in (b). Information about the environment is projected onto discrete cells. Agents representing biological factors move and interact with other agents and the environment based on the predefined governing rules. Agents interact with other agents only when they are in proximity of each other (green agents as oppose to the red agent).

Table 1. Comparison of some of the general-purpose agent-based modeling tools. Most of these ABM tools are designed to fit a wide range of applications.

ABM Tool	License	Application Area(s)	Modeling Language	3D
FLAME[65]	Academic license	General	XML + C	Yes
Mason[66]	Open Source	General (e.g., social complexity, swarm robotics, machine learning)	Java	Yes
NetLogo[67]	Free	Social and natural sciences	NetLogo	Yes
Repast[68,69]	Open Source	Social sciences	Java	Yes
SeSAm[70]	Open Source	General	Visual	Plug-in
Spark[71]	Open Source	Biomedical	Java	Yes
Swarm[72]	Open Source	General	Java	Yes

is not technically impossible to implement such rules in general-purpose ABMs, as was done by Walpole et al.[50] via NetLogo.[67] In addition, most of the available ABM tools require a strong programming background for developing the models. This restriction limits the use of ABM to a relatively small group of users who are familiar with programming. As a result, most of the molecular systems biology studies have used *in-house* ABMs (**Table 2**).

4. Bringing Physical Accuracy to Computationally Efficient ABMs

Agent-based models rely heavily on the rules governing the movement and interaction of agents. In a molecular system/pathway, the dynamics of molecules, movement and intermolecular interactions, are governed by biophysical and biochemical rules. Therefore, one of the main challenges in using ABM for molecular systems is to directly relate the molecular properties, that is diffusion and interactions, to ABM parameters to ensure that the molecular ABM accurately represents the target molecular system/pathway. In an on-lattice ABM, where the modeling environment is discretized to a cubic lattice, it could be shown that according to the Fick's second law,[77] the molecular diffusion could be related to the probability of movement as follows[38,75]:

$$D = P_{\text{move}} \frac{(\Delta L)^2}{\Delta t}$$
$$\Delta t \to 0, \Delta L \to 0 \quad (1)$$

where D is diffusion coefficient, P_{move} is the movement probability, ΔL is the discretization length and Δt is the time step. Azimi et al. explored two potential diffusion mechanisms using this movement probability.[38] An all-neighbor method, in which the agent searches for neighboring vacant grid cells results in an unnaturally higher effective diffusion coefficients. A single-neighbor method, however, was in agreement with Langevin Dynamics results as well as the analytical relationship. In a single-neighbor approach, the agent randomly picks a neighboring grid cell and if the cell is not vacant, the agent does not move at that time step.

First-order unimolecular reaction, that is molecular unbinding, and second-order molecular binding of two molecules could also be modeled using binding and unbinding probabilities. The reversible binding of two molecules A and B is given in Equation (2).

$$A + B \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftharpoons}} AB \quad (2)$$

It could be demonstrated that the following formula directly relate the binding and unbinding coefficients to ABM probabilities[37,75]:

$$P_{\text{off}} = k_{\text{off}} \Delta \text{t} \quad (3)$$

$$P_{\text{on}} = \frac{k_{\text{on}} \Delta t}{V / N_{\text{Cells}} \cdot N_{\text{neighbors}} \cdot N_{\text{Avogadro}}} \quad (4)$$

where P_{off} is the unbinding probability, k_{off} is the unbinding coefficient, Δt is the time step, P_{on} is the probability of a binding between two neighboring molecules, k_{on} is the binding coefficient, V is the volume of the system, N_{Cells} is the number of grid cells, $N_{\text{Neighbors}}$ is the number of von Neumann neighboring cells, for example 6 in a 3D lattice, and N_{Avogadro} is the Avogadro's number. Using Equation (4), Azimi and Mofrad[37]

Table 2. Examples of agent-based modeling studies of molecular systems. Because of the limitations associated with general-purpose ABMs, they are rarely employed in molecular systems biology.

Molecular System	ABM Tool	Spatial resolution/Size of the system	Time-step/Simulation Time	Number of Agents	Ref(s)
ErbB signaling	*in-house*	–	1 min/100 min	Up to 1.5 million	[73]
mRNA export and quality control	*in-house*	5 nm/5.3 × 10^{-4} μm^3	2.5 μs/20 s	1500–2000	[35,40]
Integrin Clustering	*in-house*	0.01 μm/1 μm^2	–/4 min	5000–10 000	[39]
Toll-like receptor (TLR) 4 signaling	NetLogo	–	4 s/1 min	A few thousands	[74]
Intracellular signaling in prokaryotic cytoplasm	*in-house*	0.5 nm/1000 nm^3	0.1 ns/up to 245 μs	Up to 1.7 million	[75]
NF-κB signalling pathway	*in-house*	27 μm^3	–/ up to 3500 s	<1000	[76]

compared time-course data of a irreversible binding using a deterministic ordinary differential equation (ODE) versus the ABM probabilities, and demonstrated that ABM reproduces the average behavior of the ODE solution without the unnatural smoothness from a deterministic model.

Traditional ABMs mostly employ empirical sets of rules governing the behavior of agents in their environment. At the molecular scale, however, these algorithms do not necessarily represent the molecular species and their dynamics with enough accuracy. Therefore, the above mentioned direct transformations of biophysical and biochemical characteristics of molecules into ABM parameters, which are validated in several different studies,[35–38,75] provide a solid platform to more accurately model molecular systems and pave the path for wide utility of ABM in molecular systems biology.

5. Examples of Molecular Agent-Based Modeling

In order to demonstrate the wide utility and the potential of ABM in molecular systems biology, we summarize some of the studies that have taken advantage of ABM to explore the dynamics of molecular systems.

Diffusion behavior of molecules in the cell and subcellular compartments is critical in molecular pathways, specifically where molecular crowding and constrained environments limit the molecular interactions. Ridgway et al. created a virtual cytoplasm using an experimentally derived proteome of *Escherichia Coli* K12[75] and explored the effect of molecular crowding on in vivo cytoplasmic diffusion and diffusion-limited reactions. Similarly, Azimi et al. explored the effect of structural geometry on diffusion directionality in the cell cytoplasm using an *in-house* ABM.[38] More specifically, they explored how the structural geometry and orientation of actin filaments in the form of lamelliopodia versus filopodia affect the directionality of diffusion of actin monomers. They demonstrated that the parallel orientation of filopodia and the quasi-random structure of lamellipodia give directionality to diffusion of monomers (toward the filopodia) at the filopodia-lamellipodia interface. In addition, it was shown that the angle between the filaments in the lamelliopodia is not directly related to the diffusion directionality and, instead, the web-like structure of the lamelliopodia hinders the diffusion of free actin monomers and results in the biased diffusion toward filopodia.

Different aspects of export of mRNA transcripts from the nucleus into the cytoplasm in eukaryotic cells are also explored via ABMs. Azimi et al. developed an agent-based model of mRNA export and explored a set of unanswered questions about this essential step in gene regulation processes.[36] In order to be exported into the cytoplasm, mRNAs require a category of proteins called nuclear transport receptors (NTRs) that bind to mRNA and enable it to pass through the nuclear pore complex (NPC), that is the only gateway for transport of cargos between the nucleus and the cytoplasm.[78] The authors demonstrated that rate of mRNA export is dependent on the density and distribution of NTRs bound to the mRNA. In addition, previous experimental studies have reported contradictive results in terms of the rate-limiting step in mRNA export. While some studies identified that the rate-limiting step occurs at the nuclear basket of the NPC,[44,46] others have reported it to be at the central channel of the NPC.[79] The mRNA ABM was in agreement with the former observations, showing that the rate-limiting step was associated with reconfiguration of mRNA to thread itself into the central channel of the NPC. Furthermore, we recently explored the mRNA quality control mechanism.[35] Prior to export, mRNAs are quality controlled to ensure the production of appropriately functioning proteins in the cytoplasm.[80] Yet, how normal and aberrant mRNAs are distinguished and how the aberrant ones are retained inside the nucleus are still unknown.[81] Using ABM, we explored this process and demonstrated that regulation of the affinities between the involved components, that is RNA-binding proteins and NTRs, enables the nuclear basket proteins to distinguish normal and aberrant mRNAs, subsequently retaining aberrant mRNAs while allowing normal mRNAs to get exported (**Figure 5**). In addition, we examined how the length of mRNA affects the quality control process and predicted that retention of short mRNAs is more challenging. Since longer aberrant mRNAs spend more time in the nuclear basket to obtain a compact conformation for export, nuclear basket proteins have more time to capture and retain them inside the nucleus.

Different intracellular signaling pathways are also explored using agent-based models. An explored Toll-like receptor-4 (TLR-4) signal transduction pathway and the inflammatory response.[74] Toll-like receptors, primarily located on inflammatory cells, are responsible for recognizing the bacterial cell wall

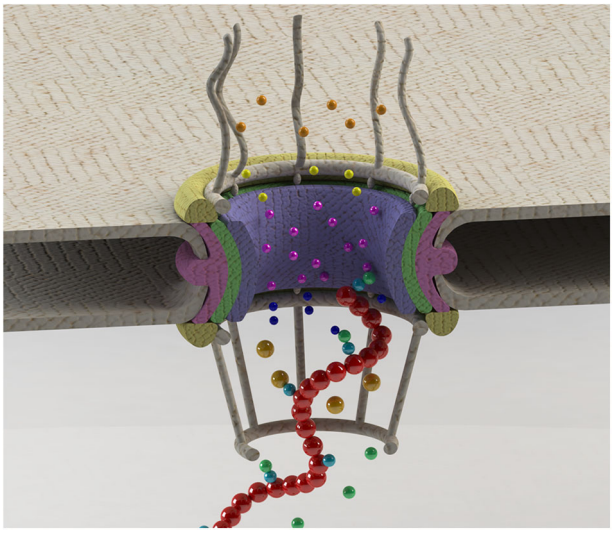

Figure 5. ABM representation of the mRNA export process. ABM can account for spatial details, which is the nuclear membrane as well as the specific donut-like shape of the nuclear pore complex (NPC). While proteins are modeled as single particle agents in corresponding regions of the environment, the mRNA sequence is modeled as a chain of monomeric agents, which can travel into different regions of the system. The interactions between the different components, for example mRNA and RNA-binding proteins, are governed by pre-defined rules. For the sake of visual clarity, a small fraction of actual concentrations is shown. Not drawn to scale Reproduced under the terms and conditions of the Creative Commons Attribution license 4.0.[35] Copyright 2016, the authors, published by Springer Nature.

products to initialize the body's response to infection.[82,83] They demonstrated that agent-based representation of the TLR-4 signal transduction pathway could capture the stochastic signal behavior, dose dependent response, negative feedback control, and preconditioning effect. Pogson et al. also explored the NF-κB signaling pathway via ABM and showed that they could capture the dynamics observed by real-time single cell analysis.[76] More recently, Das et al. studied the ErbB signaling pathway.[73] ErbB receptors are responsible for propagation of signals throughout the cell to regulate cell proliferation, differentiation, migration, adhesion, apoptosis, and embryogenesis. As a result, over-expression of two receptors from the ErbB family, namely EGFR and HER2, has been attributed to different types of cancers.[84,85] The authors demonstrated that one could employ ABM to explore the different scenarios to re-engineer a signaling pathway in virtual experiments.

These examples demonstrate how ABM with its capabilities including particle tracking, accounting for stochasticity and spatial constraints, and the ability to predict the emergent behavior and reaching long time scales provides a platform to study complex molecular systems. It should be noted, however, that besides the advantages of ABM over other computational methods presented here, ABM has its own set of limitations as well. For instance, although an ABM allows modeling a molecular system with a higher spatial resolution over a longer time period, it also requires more details provided about the system of interest.[76] For example, while ODEs only require the dissociation constant (K_d), ABM requires binding and unbinding coefficients (K_{on} and K_{off}) (please refer to Equations (3) and (4)), which are not always reported in experiments. Moreover, ABMs are significantly more computationally expensive compared to ODEs and PDEs. Nevertheless, most ABM simulations could be performed in a few hours and up to a few days on desktop workstations, depending on the size of the system.[38,59,86] However, computational efficiency of ABM simulations heavily depends on their implementation. Efficient implementation of ABM simulations could result in linear (or close to linear) performance scalability.[59,86] In addition, for significantly large systems, ABMs could be easily parallelized with each computing node handling the calculations associated with a subset of agents. Accordingly, several efforts have been made to employ high performance computing (HPC) resources for large scale ABMs.[59,87,88] ABM is also integrated with other methods, for example discrete-event simulation, to improve computational efficiency.[89] It is also important to recognize that ABM, just like any other computational method, is only useful if employed in the right problem. For instance, in a well-mixed molecular system with high concentrations of the involved molecules, if the desired output is changes in concentrations over time, ABM and ODE would provide almost similar results,[8] while ABM simulations would be more computationally expensive.

6. Conclusions and Outlook

Agent-based modeling (ABM) has the potential to become a widely accepted method for efficiently simulating the evolution of stochastic and heterogeneous molecular systems. By offering high spatial resolution combined with long time scales as well as the unique set of capabilities, for example particle tracking and stochasticity, ABM provides a platform for molecular systems biology that could not be achieved through any other single computational method. In addition, integration of ABM with data-driven methods, for example topological data analysis (TDA), provides further capabilities in analysis of complex molecular systems.[90] While several studies have already demonstrated the utility of ABM in molecular systems biology, ABM is not yet commonly employed in biological simulations. Specifically, some barriers have hindered ABM to become a widely used method in the biology community. Lack of ABM frameworks to reduce the complexity of model set-up has kept the community away from this powerful modeling approach. Tools such as COPASI (COmplex PAthway SImulator) have significantly simplified this process for study of biological pathways using ODEs, PDEs, or Gillespie algorithm.[91] Regarding ABM, however, the approach for modeling these systems has been to develop the software framework from the ground up to suit the needs of the specific system being modeled. This poses a major disadvantage in that researchers spend more time on code development, validation, and optimization rather than focusing on the biological problem of interest. Therefore, development of ABM frameworks specifically optimized and validated for molecular systems (similar to PhysiCell[86] as a recent open-source ABM framework for multicellular systems) would substantially enhance the applicability of this powerful technique and enable a wider range of researchers to take advantage of ABM in their research.

Abbreviations

ABM, agent-based modeling; BD, Brownian dynamics; CME, chemical master equation; MD, molecular dynamics; NPC, nuclear pore complex; ODE, ordinary differential equation; PDE, partial differential equation; RDME, reaction diffusion master equation.

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Conflict of Interest

The authors declare no conflict of interest.

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