

Chapter 2

Stochastic Simulation for Spatial Modelling of Dynamic Processes in a Living Cell

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Abstract One of the fundamental motivations underlying computational cell biology is to gain insight into the complicated dynamical processes taking place, for example, on the plasma membrane or in the cytosol of a cell. These processes are often so complicated that purely temporal mathematical models cannot adequately capture the complex chemical kinetics and transport processes of, for example, proteins or vesicles. On the other hand, spatial models such as Monte Carlo approaches can have very large computational overheads. This chapter gives an overview of the state of the art in the development of stochastic simulation techniques for the spatial modelling of dynamic processes in a living cell.

Keywords Plasma membrane · Chemical kinetics · Gene regulation · Stochastic simulation algorithm · Multiscale stochastic modelling · Diffusion · Delayed reactions · Stochastic simulators

Introduction

Why Do We Need Spatial Models of a Cell?

Recent progress in genetic sequencing, microscopy and other experimental methods has shed light on membrane structures and phenomena, including the discovery that the plasma membrane of a cell may possess significant lateral structure (microdomains). Similar progress has been made in the understanding of transport phenomena on the membrane, of ion channel function and of transport across

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the membrane [20, 58, 63]. Indeed, a number of research groups are now building dynamic maps of all the ultrastructure within a living cell. The Visible Cell [47] is one such project using electron tomography and 3D rendering to build a complete view of the ultrastructure within a pancreatic Beta cell. However, the integration of this information into comprehensive and coherent models of cellular transport and kinetics, for example linking the plasma membrane with transport processes in the cell to complex genetic regulatory processes, has been slow. In order to produce a coherent picture of cellular dynamics, mathematical modelling and simulation provide an indispensable tool.

On the other hand, the modelling of cellular processes poses mathematical challenges of its own. The main modelling challenges are due to the essential multi-scale nature of the processes we are trying to understand. For example, the classical view of the plasma membrane lipid bilayer as a two-dimensional fluid acting as a neutral solvent for membrane proteins in which all particles diffuse freely [65] has been substantially modified in recent years. The plasma membrane is in fact a highly complex structure that is compartmentalized on multiple length and time scales. This compartmentalization is driven by a variety of lipid-lipid, lipid-protein and actin-cytoskeleton interactions [2, 20, 39, 50]. In addition, an important role that has been ascribed to all plasma membrane microdomains is that of selectively concentrating proteins to facilitate the assembly of signalling complexes [64]. However, little quantitative analysis has been attempted to explore the basic mechanics of how microdomains might drive protein-protein interactions as demanded of their role in supporting the assembly of signalling platforms. For example, if microdomains do aggregate proteins, are there any constraints on size and dynamics that need to be imposed for them to achieve this function? If so, are these constraints realistic and how do the predictions compare with recent estimates of microdomain size and dynamics?

Thus, the building of mathematical models and innovative simulation techniques provide a vital component when we attempt to understand the complex feedbacks between dynamic processes on the membrane and, for example, genetic regulation. In building these models we must address two fundamental questions, namely (1) are the processes well-described by assuming homogenization and deterministic principles, or (2) do we need to explicitly model the underlying heterogeneity and stochasticity of these cellular processes?

Why Do We Need Stochastic Models?

There has been a long and successful history in computational cell biology of using rate kinetic ordinary differential equations to model chemical kinetics within a living cell. These techniques have been applied on the plasma membrane, in the cytosol, and in the nucleus of eukaryotic cells to understand gene regulation. Modifications via delay differential equations were first considered as far back as [31], in order to represent the fact that the complex regulatory processes of transcription and translation were not immediate but were in fact examples of delayed processes.

It was the pioneering work of Gillespie [29] and Kurtz [38] who challenged this deterministic view of cellular kinetics. They argued that when the cellular environment contained small to moderate numbers of proteins, that the Law of Mass Action is not an adequate description of the underlying chemical kinetics because it only describes the average behaviour. In this regard, the fundamental principle is that of intrinsic noise. Intrinsic noise is associated with the inherent uncertainty in knowing when a reaction occurs and what that reaction is. The variance associated with this uncertainty increases as the number of proteins in the cellular environment becomes small. Gillespie [29] and Kurtz [38] showed how to model intrinsic noise through the concept of nonlinear discrete Markov processes, and Poisson processes, respectively. These two approaches both model the same processes and are now lumped together under the title the Stochastic Simulation Algorithm (SSA). The essential observation underlying the SSA is that the waiting time between reactions is exponentially distributed and that the most likely reaction to occur in this time interval is based on the relative sizes of the propensity functions. However, the need for a time step small enough to capture one reaction at each step can lead to prohibitive computational costs.

The SSA describes the evolution of a nonlinear discrete Markov process and as such this stochastic process has a probability density function whose solution is described by the Chemical Master Equation (CME). The solution of the CME can be reduced to the computation of the evolution of the exponential of a matrix times an initial probability vector. As there is one equation for each possible configuration of the state space this can be very computationally challenging, although recently developed methods can cope with some of these computational costs [23,35,43,44,55].

There is in fact an intermediate regime that can still capture the inherent stochastic effects but reduce the computational complexity associated with the SSA. This intermediate framework is called the Chemical Langevin Equation. It is described by an Itô stochastic differential equation (SDE) driven by a set of Wiener processes that describes the fluctuations in concentrations of the molecular species. Various numerical methods can then be applied to this equation – the simplest method being the Euler-Maruyama method [37]. These temporal approaches are applied under the principle of homogeneity. It is well known, however, that diffusion on the cell membrane is not only highly anomalous but the diffusion rate of proteins on live cell membranes is between one and two orders of magnitude slower than in reconstituted artificial membranes with the same composition [50]. Furthermore, diffusion is dependent on the dimensions of the medium so that diffusion on the highly disordered cell membrane is not a perfectly mixing process and therefore the assumptions underlying the classical theory of chemical kinetics fail, requiring new approaches to modelling chemistry on a spatially crowded membrane [53].

Simulation Toolkits

Increasingly, scientists are using a mix of experimental, mathematical modelling and simulation to extract deep biological insights at subcellular and tissue levels.

Table 2.1 Spatial stochastic simulators ordered by their underlying simulation method

Simulation method		Software	Spatial mode	Spatial scale	Time	Features
Lattice-based	RDME-based	MesoRD	Lattice	Meso	E	RDS
		SmartCell	Lattice	Meso	E	RDS
		GMP	Lattice	Meso	E+F	RDS
		STEPS	Tetrahedral Mesh	Meso	E	RDS
	Microscopic lattice	GridCell	Lattice	Micro	F	EV
		E-Cell (Spatocyte)	Lattice	Micro + Meso	E+F	RDS, EV
Off-lattice particle		ChemCell	Continuum ^a	Micro	F	RDS
		MCell	Continuum ^a	Micro	A	RDS
		Smoldyn	Continuum ^a	Micro	F	RDS, EV
		Cell++	Continuum + Gradient	Micro + Macro	F	RDS
		CyberCell	Continuum	Micro	F	EV
	GFRD	E-Cell (eGFRD)	Continuum	Micro	E	EV

E event-based, *F* fixed time steps, *A* adaptive, *EV* excluded volume effect is reproducible, *RDS* reaction and diffusion on surfaces and between surfaces and volumes is supported (at different degrees of accuracy)

^aThese programs represent surfaces as lists of primitive objects. Depending on the program this can be triangles, spheres, boxes, or others elements

This not only enriches biology but also enriches computer science and computational and applied mathematics through new methodologies operating at a variety of spatial and temporal scales. Some of these ideas have been incorporated into software toolkits, for example [42]. See Table 2.1 for a list of spatial stochastic simulators. At the same time markup language environments such as CellML [33] and FieldML [17] are being developed which act as both a repository and an environment for simulating a variety of biological models.

Temporal Models of Chemical Kinetics

In a purely temporal homogeneous setting and when there are large numbers of molecules present, chemical reactions are modelled by ordinary differential equations that are based on the laws of Mass Action and that estimate reaction rates on the basis of average values of the reactant density. Any set of *m* chemical reactions can be characterised by two sets of quantities: the stoichiometric vectors (update rules for each reaction) $\nu_1, \dots, \nu_m$ and the propensity functions $a_1(X(t)), \dots, a_m(X(t))$. The propensity functions represent the relative probabilities of each of the *m* reactions occurring. They are formed by multiplying the rate

constant and the product of the reactants on the left-hand-side of each reaction. Here $X(t)$ is the vector of concentrations at time t of the N species involved in the reactions. The ODE that describes this chemical system is given by

$$X'(t) = \sum_{j=1}^m v_j a_j(X(t)).$$

In the case of small numbers of molecules the appropriate formulation is the Stochastic Simulation Algorithm (SSA) [29], as ODEs can only describe a mean behaviour. The SSA is an exact procedure that describes the evolution of a discrete nonlinear Markov process. It accounts for the inherent stochasticity (internal noise) of the m reacting channels and only assigns integer numbers of molecules to the state vector. At each step, the SSA samples two random numbers from the uniform distribution $U[0,1]$ to evaluate an exponential waiting time, τ , for the next reaction to occur and an integer j between 1 and m that indicates which reaction occurs. The state vector is updated at the new time point by the addition of the j th stoichiometric vector to the previous value of the state vector, that is

$$X(t + \tau) = X(t) + v_j.$$

The main limiting feature of SSA is that the time step can become very small, especially if there are large numbers of molecules or widely varying rate constants. τ -leap methods have been suggested in which the sampling of likely reactions is taken from either Poisson [30] or Binomial [72] distributions. In these approaches a much larger time step can be used at the loss of a relatively small amount of accuracy.

A different approach is to compute the probability density function associated with the SSA, which is the solution of the Chemical Master Equation (CME). The CME is a discrete parabolic partial differential equation in which there is one equation for each configuration of the ‘state space’. When the state space is enumerated, the CME becomes a linear ODE and the probability density function takes the form

$$p(t) = e^{At} p(0)$$

where A is the state-space matrix. Even for relatively small systems, the dimension of A can be in the millions, but a variety of techniques have been proposed [23, 35, 43, 44, 55] to make this a very feasible technique.

The regime intermediate to the discrete stochastic regime and the continuous deterministic ODE regime is described by the Chemical Langevin Equation (CLE). The CLE attempts to preserve the correct dynamics for the first two moments of the SSA and takes the form

$$dX = \sum_{j=1}^m v_j a_j(X(t)) + B(X(t))dW(t).$$

Here $W(t) = (W_1(t), \dots, W_N(t))^T$ is a vector of N independent Wiener processes whose increments $\Delta W_j = W_j(t+h) - W_j(t)$ are $N(0, h)$ and where

$$B(x) = \sqrt{C}, \quad C = (v_1, \dots, v_m) \text{Diag}(a_1(X), \dots, a_m(X))(v_1, \dots, v_m)^T.$$

Here h is the time discretisation step. Effective methods designed for the numerical solution of SDEs [11, 13, 37] can be used to simulate the chemical kinetics in this intermediate regime. Mélykúti et al. [48] have shown how to construct the CLE so that it minimizes the number of Wiener processes. Furthermore, adaptive multiscale methods have been developed that attempt to move back and forth between these three regimes as the numbers of molecules change [10].

Sometimes temporal models are not sufficiently rich to capture complicated spatial effects. But rather than abandoning temporality, it is possible to capture important spatial aspects and incorporate them into temporal models. This can be done in a number of ways. For example, compartmental models have been developed that couple together the plasma membrane, cytosol and nucleus – see for example Tian et al. [73], in which an SSA implementation of Ras nanoclusters on the plasma membrane is coupled with an ODE model for the MAPK pathway in the cytosol. Diffusion and translocation can be captured through the use of distributed delays that can then be incorporated into mathematical frameworks through the use of delay differential equations or delay variants of the Stochastic Simulation Algorithm (see [8], for example). Very recently, Marquez-Lago et al. [46] have explored a number of spatial scenarios, run detailed spatial simulations to capture diffusion and translocation processes and then incorporated this information into purely temporal models through distributed delays. Another way in which spatial information can be captured and then incorporated into purely temporal models is the area of anomalous diffusion, where spatial crowding and molecular binding can affect chemical kinetics. In this setting the mean square deviation of a diffusing molecule is no longer linear but sublinear in time t and of the form

$$E[X^2(t)] = 2Dt^\alpha, \quad \alpha \in (0, 1].$$

Here, α is called the anomalous diffusion parameter. If the value of α can be estimated, either experimentally or from detailed Monte Carlo simulations, then the SSA can be modified so that the waiting time between reactions is no longer exponentially distributed but has a heavy tail [53].

Monte-Carlo Approaches

In many cases, the heterogeneous nature of a living cell means that spatial models are mandatory. The fundamental transport process within a cell is either diffusion or the motion of proteins or vesicles along microtubules by molecular motors. To capture these processes, we can use continuum models based on partial differential

equations in which diffusion is represented by a Laplacian operator and directed transport by a convective term. If chemical kinetics are involved, then this leads to the framework of the reaction-diffusion partial differential equation. However as spatial structures become more and more complex, so that the homogenisation process breaks down, Monte Carlo simulations become more appropriate. One such environment is the plasma membrane.

The plasma membrane is an extremely complex and crowded environment that has many roles including signalling, cell-cell communication, cell feeding and excretion and protection of the interior of a cell. It is heterogeneous – the cytoskeletal structure just inside the plasma membrane can corral and compartmentalize membrane proteins. Chemically inert objects can form barriers to protein diffusion on the plasma membrane, and this can lead to anomalous diffusion rather than pure diffusion. Trying to capture such complexity using higher-level mathematical frameworks such as partial differential equations is extremely challenging, so instead a stochastic spatial model using the Monte-Carlo technique becomes appropriate, especially as the domain of interest is essentially two dimensional. In such a simulation the plasma membrane can be mapped to a two dimensional lattice, usually regular but not necessarily so. The size of each computational cell “voxel” depends on what biological questions are being asked, but taking into account volume-exclusion effects, usually the voxel is such that at most one protein per voxel is allowed. Given the dimensions of typical membrane protein anchors, a typical voxel size is thus of the order of 1–3 nm. Assuming that we wish to model the dynamics on the plasma membrane of a typical cell, say $10 \times 10 \mu\text{m}$, then the computational lattice has $5,000 \times 5,000$ voxels. In a spatial Monte Carlo simulation of this type, a random walk is carried out by each protein on the membrane; a protein is selected at random, and a movement direction (north, south, east or west, in the case of a rectangular lattice arrangement) is randomly determined. The distance moved depends on the diffusion rates for each species. Chemical reactions can be simulated by checking the chemical reaction rules and then replacing that protein and/or creating a new protein at that location whenever a collision (volume exclusion event) occurs. In one step, each protein must statistically (but not necessarily deterministically) be selected to move, so if we are interested in the dynamics over large regions or long time scales, then this approach is computationally demanding. In addition, since the approach is stochastic, a number of simulations must be run in order to collect appropriate statistics. Nicolau et al. [51,52] have used this approach to model the effects of compartmentalisation, anomalous diffusion and the motion of lipid rafts on the chemical kinetics taking place on the membrane. However, only relatively small sections of the membrane on short time scales are considered due to the slow computational performance. There are a number of approaches to address this issue, one of which we discuss below. As computational speeds and memory sizes increase, longer times and larger systems will be able to be modelled.

Recently, in [12], a plasma membrane stochastic spatial model was implemented in a parallel setting, so that both long-range diffusion rates could be investigated and an entire cell membrane could be modelled with the simulation running for several real-time seconds. Domain decomposition was applied to allocate portions of the

membrane to different parallel processes; each membrane portion was populated with molecules of various species, inert obstacles, cytoskeletal fences and mobile or immobile lipid rafts. OpenMPI was used for message-passing between processes, and MPI's Cartesian topology management commands ensured the physical proximity of processes with adjacent membrane portions. By allowing each parallel process to have a "ghost" copy of its right-hand neighbour's leftmost column and its left-hand neighbour's rightmost column of membrane data, along with its own membrane portion, communication costs between processes can be minimised while maintaining an accurate view of the current membrane state. Data moving between processes was first moved into these "ghost" columns and these were then merged with the neighbours' membrane portions at every time step of the simulation. Slave to slave implementations gained excellent speed-up [12] so a cross-cluster implementation can allow a simulation on the entire cell membrane to be run for several real-time seconds and hence may provide valuable data and insights for biologists.

In a spatial Monte Carlo simulation of proteins diffusing on a lattice, diffusion can be considered as a unimolecular reaction. Thus if we order the voxel elements within the lattice into a vector, we can consider this approach in the SSA framework and apply the same tools that have been developed in the purely temporal setting. In particular, there is a spatial CME associated with this approach [19]. Finally, we note that although we have emphasised Monte Carlo simulations for heterogeneous models, there is a recent approach where a continuum finite element partial differential equation method has been used to understand the effect of lipid rafts on chemical kinetics on the plasma membrane [62].

Multi-scale Modelling

Lattice Versus Off-Lattice Methods

Spatially resolved simulations are computationally expensive, a fact that becomes more evident when compared with their solely temporal counterparts. Nevertheless, adequate modelling of biological systems often requires spatially resolved simulations. By consequence, one should always keep in mind the trade-off between simulation time and necessary level of resolution.

Of all spatial methods, the option with the lowest computational cost consists of solving reaction-diffusion partial differential equations, each of which represents the concentration of a molecular species in the system. This approach is only valid if and when: (1) all molecular species in the system have large molecular concentrations, and (2) noise is not amplified throughout the system. If at least one of these conditions fails to hold, we must rely on spatial stochastic simulators, which can be of discrete or continuous nature. In turn, the highly resolved end of the discrete spatial stochastic simulators spectrum is represented by lattice and off-lattice particle based methods.

In off-lattice methods, all particles in the system have explicit spatial coordinates, at all times. At each time step, molecules with non-zero diffusion coefficients are able to move, in a random walk fashion, to new positions. In many cases, reaction bins whose size depends on the particular diffusion rates are drawn around each particle. If one or more molecules happen to be inside such a bin, appropriate chemical reactions can take place with a certain probability, and if a reaction is readily performed, the reactant particles are flagged, to avoid repetition of chemical events. Noticeably, in off-lattice methods, the domains and/or compartments can still be discretized, to aid the localization of particles within the simulation domain. Particle methods can provide very detailed simulations of highly complex systems at the cost of exceedingly large amounts of computational time and, possibly, restrictions on the size of the simulation domain. Hence, such detailed simulations can often only yield short simulation time spans that, in many cases, are of no interest to the experimentalists.

For lattice methods, and within the context of Molecular Biology, a computational mesh (generally two dimensional or three dimensional) is used to represent a cellular compartment, such as a membrane or the interior of some part of a cell [49, 51, 75]. The lattice is then “populated” with particles of the different molecular species that comprise the system, either at random or at chosen spatial locations, depending on the theoretical question at hand. All particles with non-zero diffusion coefficient are able to diffuse throughout the simulation domain by jumping to empty neighbouring sites and, depending on user-specified reaction rules, appropriate chemical reactions can take place with a certain probability. It is worth noting the mesh can represent microscopic or mesoscopic domains. In the former, each lattice site is allowed to host at most one molecule. These microscopic lattice-based simulators are often called Kinetic Monte Carlo Methods, which might create some confusion as this name is shared by general stochastic simulation strategies.

A less computationally intensive alternative, albeit still costly in many scenarios, is to consider molecular interactions in the mesoscopic realm. Here, the discretization of the Reaction-Diffusion Master Equation (RDME) results in reactive neighbouring sub-volumes within which several particles can coexist, while well-mixedness is assumed in each subvolume. Following this line of thought, there are a few algorithms in the literature extending discrete stochastic simulators to approximate solutions of the RDME by introducing diffusion steps as first order reactions, with a reaction rate constant proportional to the diffusion coefficient. For instance, in [7, 67] the authors provide the specific outline for extending discrete stochastic simulators to the RDME regime, while the algorithms in [1, 21] provide clever extensions of the ‘next reaction method’ [28], commonly known as the ‘next subvolume method’. Additionally, a review on the construction of such methods can be found in [25]. Figure 2.1 attempts to provide an illustration of the spatio-temporal advancement scheme of lattice and off-lattice algorithms.

A few additional aspects are worth considering. First, in mesoscopic lattice methods, as well as inefficiently posed off-lattice methods, problems may arise due to neglecting the ‘volume exclusion’ effect (for example, whenever a (sub)domain

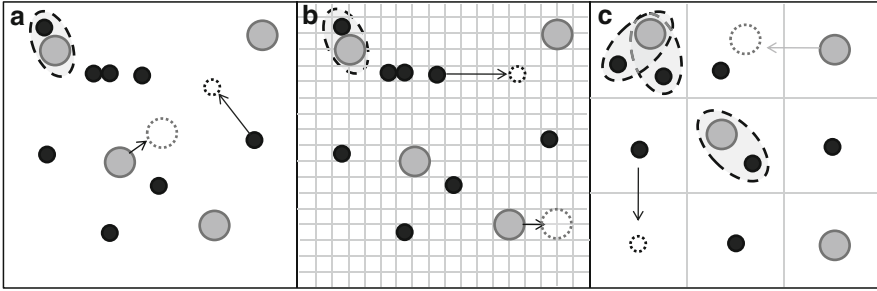


Fig. 2.1 Illustration of the advancement schemes for idealized (a) off-lattice methods, (b) microscopic lattice methods and (c) mesoscopic lattice methods. *Arrows in black* represent diffusion over the same time scale, while *grey arrows* represent diffusion over a considerable larger time step. *Dashed black lines* represent potential reaction partners, over a single time step (before or after diffusion changes, not simultaneously)

Table 2.2 Software and corresponding websites

MesoRD	http://mesord.sourceforge.net/
SmartCell	http://smartcell.crg.es/
GMP	http://www.science.uva.nl/research/scs/CellMath/GMP
STEPS	http://sourceforge.net/projects/steps
GridCell	http://iml.ece.mcgill.ca/GridCell/
ChemCell	http://www.sandia.gov/~sjplimp/chemcell.html
MCell	http://www.mcell.cnl.salk.edu/
Smoldyn	http://www.smoldyn.org/
Cell++	http://www.compsysbio.org/lab/cell_simulations
E-cell	http://www.e-cell.org/

is populated by a large number of molecules that would not physically fit). The same would hold for inefficiently posed microscopic lattice methods, where each molecule is set to occupy a single site, irrespective of its physical size.

Secondly, molecular crowding can prevent reacting molecules from reaching regions of the domain, due to the high concentration of macromolecules impeding their passage [5]. While this effect can be explicitly treated by microscopic lattice methods (as well as some off-lattice methods), mesoscopic lattice methods are in a great disadvantage, their expected accuracy being low when treating these cases. Lastly, the artificial nature of the lattice may not only limit the spatial resolution of the simulation, but also introduce lattice anisotropy [59].

In the following section, we describe the Next Subvolume Method in more detail, as well as a coarse-grained version that accelerates simulations by 2–3 orders of magnitude. We additionally report recent extensions and corrections to these algorithms. Lastly, we refer to Table 2.2 for a list of publicly available lattice and off-lattice simulators.

The Next Subvolume Method and Its Coarse-Grained Version, B τ -SSSA

The Next Subvolume Method (NSM) [1, 21, 22, 32] is a generalization of the SSA [29], where the simulation domain is divided into uniform separate subvolumes that are small enough to be considered homogeneous by diffusion over the time scale of the reaction. At each step, the state of the system is updated by performing an appropriate reaction within a single subvolume, or by allowing a molecule to jump to a randomly selected neighbouring subvolume. Diffusion is then modelled as a unary reaction, with rate proportional to the two-dimensional molecular diffusion coefficient divided by the length of a side of the subvolume. In this way, diffusion inside the algorithm becomes another possible event with a regular propensity function, and follows the same update procedure as any chemical reaction. The expected time for the next event in a subvolume is calculated in a similar way to the SSA algorithm, including the reaction and diffusion propensities of all molecules contained in that subvolume, at that particular time. However, times for subsequent events will only be recalculated for those SVs that were involved in the current time step, and they are subsequently re-ordered in an event queue.

Even though mesoscopic simulations are much faster than their microscopic counterparts, often we will need to coarse-grain the simulation to provide for a spatially resolved model that yields accurate chemical kinetics in meaningful simulation times that are of actual biological interest to the experimentalists. With this in mind, a very natural extension of the NSM comes down to performing τ -leaps (slightly larger time steps) that account for one or more diffusion and reaction events, without significantly compromising spatio-temporal accuracy. This is the idea behind the Binomial τ -leap Spatial Simulation Algorithm, B τ -SSSA [45] where, at each iteration, the subvolume with shortest reaction-diffusion τ -leap is selected. Then, the algorithm performs a number of possible, yet randomly chosen, events inside each subvolume, re-calculates a new τ -leap for all subvolumes that were affected by current reactive or diffusive events, re-orders the time event queue in increasing time, and consequently chooses the subvolume indicated by the top of the time event queue.

A few additional notes and issues are worth considering. First, in order to calculate the expected time for the next event in any subvolume, the sum of diffusion propensities needs to be multiplied by the number of directions in which the molecules can diffuse, that is, the number of neighbours contained in the connectivity matrix for that subvolume. While this is explicitly stated in [22], it is implicitly assumed in [21]. The same holds for the coarse-grained version presented in [45], which implicitly considers the number of neighbouring subvolumes when calculating τ -leaps. We have noticed that, neglecting the number of neighbours for the calculation of the diffusion propensity yields radically low accuracy, whenever the system contains zero-order reactions (namely, when one of the molecular species is constitutively created).

Secondly, and perhaps more importantly, it has been readily noticed that accuracy is lost when considering commonly used implementations of bimolecular reactions. Early on, [7] reported that: “Too large a cell size violates the cell statistical homogeneity assumptions, whereas too small a cell size may compromise the separability of reaction and diffusion viewed as independent elementary processes in significantly small subvolumes”. Furthermore, the authors in [34] reported their concern for the dependence of solutions to the RDME on mesh spacing. In response to these open issues, Erban and Chapman suggested clever corrections for the propensity values in lattice based models, hence homogenizing results with varying degrees of mesh finesse [26]. Extrapolations of these considerations are current work in progress, and include several implications in: (1) two-dimensional domains, (2) coarse-grained scenarios, and (3) unstructured meshes [41].

Hybrid Discrete-Continuous

There are probably many ways to create hybrid reaction-diffusion algorithms. For example, we can group species according to size, treat small molecules deterministically, and treat large particles and their interactions with large and small molecules stochastically. The latter implies molecules exist in high numbers and/or diffuse rapidly.

In another approach, Engblom et al. [24] split the time integration of the RDME into a macroscopic diffusion (for species with large numbers of molecules) and a stochastic mesoscopic reaction/diffusion part (for species with small numbers of molecules) obtaining the mesoscopic diffusion coefficients from proper FEM discretizations. At the same time, as with purely temporal hybrid algorithms, there are a number of options for designing a spatial hybrid algorithm, in particular with respect to the methods being combined and the partitioning criteria.

Software and Other Spatial Approaches

Capturing Spatial Attributes

Despite increasingly available computational resources, simulating highly-resolved spatial models of cellular processes and pathways can still be computationally demanding, if not prohibitively expensive. This motivates the search for alternative, indirect ways to incorporate spatial information in purely temporal models, while aiming at reasonable accuracy when compared to its fully spatial counterparts.

Recently, such an alternative methodology based on reactions with associated distributed time-delay was presented in Marquez-Lago et al. [46]. The method consists of two steps: (1) distribution fitting and (2) stochastic simulation. The delay distributions stem from diffusion profiles and can be directly obtained from *in silico*

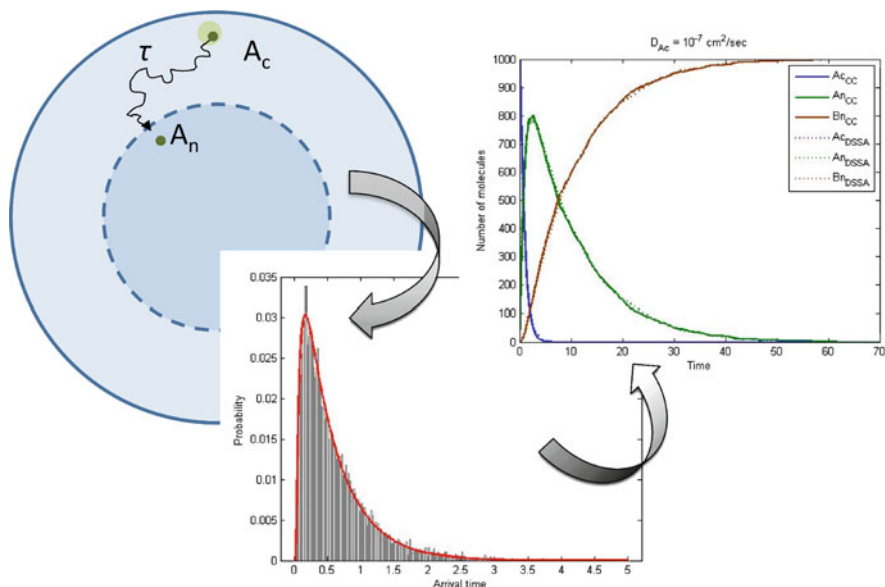


Fig. 2.2 Simplification of the idea behind distributed delays. For a translocation process, we can obtain first arrival (first passage) times either directly from experiments, from analytical or numerical solutions of a corresponding PDE, or from particle simulators such as ChemCell (illustrated in the figure on the *left*). We calculate the delay distribution (*middle*) and draw from it random delays, to be used in the delay stochastic simulation algorithm whenever a translocation reaction is occurring (*right*)

(particle-based) simulations, in vitro experiments, or by solving the corresponding PDEs. Once these tailored distributions are calculated they are used with their associated reactions in a modified version of the delay stochastic simulation algorithm (DSSA) (Fig. 2.2).

The methodology captures some spatial processes with accuracy that is unmatched by any other purely temporal method.

Spatial Simulation Software

In this section, we give a brief and not exhaustive overview of software packages for spatial modelling of chemical reaction networks and cellular processes. Spatial stochastic simulation software can be classified according to its underlying methodology, that is, the choice of spatial representation and the temporal evolution scheme. It is customary to distinguish between lattice and off-lattice (particle) methods. As explained above, the former can be subdivided into spatial SSA implementations, leading to trajectories that are exact or approximate realizations of the reaction-diffusion master equation (RDME), and methods based

on microscopic discretizations of the spatial domain, such as kinetic Monte Carlo methods. Off-lattice methods can be subdivided into particle based methods with fixed time-stepping, and Green's Function Reaction Dynamics (GFRD) methods. GFRD effectively reduce the multi-body reaction-diffusion problem into multiple single-body and two-body problems that are then solved using Green's functions. The simulation advances from the time of one reaction to the time of the next reaction. Table 2.1 summarizes the method and features of each approach. Table 2.2 lists the software packages and the corresponding webpages for additional information and download links. More detailed summaries and recent comparisons between particle-based simulators can be found in [4, 6, 70].

RDME-Based Methods

Stundzia and Lumsden [67] were the first to introduce diffusion reactions between sub-volumes to the SSA framework [29, 30], followed by [7]. Essentially, Stundzia and Lumsden implemented a spatial version of Gillespie's Direct Method (DM) and used it to simulate the propagation of an ionic reaction-diffusion calcium wave through a cell. Later, Ander et al. [1] and Elf et al. [21] independently developed spatial schemes of the Next Reaction Method (NRM) [28] the latter being coined the Next-Subvolume Method (NSM). This method is now included in two software packages, namely in **SmartCell** (version 4.2) and **MesoRD** [32] (version 0.3). A recent extension of MesoRD allows also for a correct description of reaction rates when the subvolume size is close to the reaction radii of the molecules. The MesoRDToolBox is a MatLab toolbox for visualizing MesoRD simulation data. SmartCell provides a Java GUI to process its outputs. Both SmartCell and MesoRD allow the option of choosing other methods for simulating a chemical diffusion-reaction system. MesoRD has been used to study spatial oscillation patterns displayed by the Min system of *Escherichia coli* [27]. To our knowledge, coarse-grained versions of NSM have not been implemented in any publicly available software package.

Other algorithms that have been recently proposed for simulating reaction-diffusion systems include the **Gillespie-Multi-Particle (GMP)** method [60] and the multinomial simulation algorithm (MSA) [40]. In GMP, the reaction and diffusion processes are executed independently of each other (operator splitting scheme). The method uses the multi-particle method (a.k.a. Lattice Gas Automata algorithm) [14, 15] to simulate diffusion: at each diffusion step, molecules from one subvolume are uniformly distributed among its adjacent subvolumes. While diffusion steps occur at predetermined times, reactions are simulated in between those steps using standard SSA. The fixed diffusion time step corresponds to the average time between diffusion events in the RDME. In Dobrzyński et al. [18], GMP has been compared to MesoRD, Smoldyn, GFRD, and (non-spatial) SSA, using a model of regulated gene expression and diffusion of phosphorylated CheY in the *E.coli* chemotaxis pathway as case studies.

Unlike GMP, the MSA does not decouple reaction and diffusion events, instead diffusive steps are taken until time to the next reaction is reached. The probabilities for diffusion events are taken from a multinomial distribution and diffusion is not limited to directly neighbouring subvolumes. However, the coupling of diffusive steps and reactions causes a problem, namely when particles are chosen for diffusion that have been chosen before as reactants in the next reaction event. The MSA deals with this issue by removing reactants immediately once a reaction is chosen (such that they are no longer available for diffusion) and adding the product(s) after the reaction occurs. There is no source code available for MSA.

Finally, **STEPS** [78] (v1.1.1) is a platform for simulating reaction-diffusion processes in 3D, using irregular, tetrahedral meshes for volume discretization. STEPS has the spatial version of the direct reaction method implemented, but also allows non-spatial SSA implementations on individual compartments ignoring the domain discretization. Volumes are bounded by membranes that can contain stationary reaction molecules such as channel proteins. It is intended to extend STEPS allowing diffusion also on membranes.

Methods Based on Microscopic Lattices

GridCell [9] (v1.2) subdivides the 3D domain into microscopic compartments (voxels), each having 26 surrounding neighbours plus itself (a so-called D3Q27 model) for diffusion and reaction. Each voxel may contain at most one molecule. Molecules diffuse by hopping with a species-dependent moving probability to a randomly chosen neighbour and can react with other molecules in neighbouring voxels. Particle moves and reactions are independent events. The simulation evolves in fixed time steps in which each particle may move and/or react only once. As with all other methods based on microscopic lattices, GridCell is able to capture the effects of volume exclusion and molecular crowding by introducing inert particles.

Spatiocyte [5, 6] has been designed to simulate reaction and diffusion in 3D and 2D volumes and between 3D and 2D compartments, and to reproduce implications of molecular crowding. In Spatiocyte, the domain is discretized into a hexagonal close-packed lattice. Each compartment is a voxel with a radius equal to that of the simulated molecules and has 12 adjoining neighbours. Aside from individual molecules that are simulated on the microscopic scale, Spatiocyte also supports the simulation of homogeneously distributed (HD) species on a compartmental scale. Diffusion-influenced reactions are modelled using a discretized version of Collins and Kimball [16] for obtaining a reaction probability. Temporal evolution is based on hybrid time-driven and event-driven methods [69]. Diffusion steps occur at pre-defined time steps while diffusion-independent reactions are performed according to the NRM [28].

The spatiocyte algorithm has been implemented as a plug-in module to **ECell** [5, 6]. ECell [5, 68, 74] (v3.2.0) is a simulation platform for modelling and analyzing chemical reaction networks. Originally, it only supported temporal simulation

algorithms ranging from stochastic simulation algorithms (such as SSA or explicit/implicit tau-leap methods) to ODE and DAE solvers. Recently, it has been extended by two spatial algorithms, one of which is Spatiocyte. This has been recently used to investigate the MinDE system. Simulation results showed a link between transient membrane attachment of *E. coli* MinE and the formation of E-rings [5].

Off-Lattice Particle Methods

ChemCell [56, 57], **MCell** [36, 66], and **Smoldyn** [3, 4] are the most popular and widely used off-lattice stochastic particle-based reaction-diffusion simulators. While ChemCell (last version 10 Sep. 2008) also allows for non-spatial simulations using ODE solvers or standard SSA, MCell (v3.1.846) and Smoldyn (v2.1) offer particle simulations only. Smoldyn is the only simulator that supports reaction and diffusion of particles in 1D, 2D, and 3D. ChemCell and Smoldyn use a fixed time step, whereas MCell uses an adaptive time-stepping, but allows the user to specify an upper limit. These particle-based simulators vary in many more features, such as system boundaries, geometric primitives, support of 0-order reactions, and surface interactions, to name a few. We refer for a more detailed comparison of these methods to the paper by Andrews et al. [4].

Another particle simulator is **Cell++** [61]. This spatial modelling and simulation platform combines a cellular automata engine with Brownian dynamics. Cell++ allows the simulation of large numbers of small molecules (such as calcium ions, pyruvate, ATP), while simultaneously treating larger molecules, such as enzymes, as entities. The continuum domain is superimposed by a 3D lattice. Each cubic subvolume describes the cellular environment (cytosol, nucleus, or membrane) and stores the local concentration of small molecules. The simulation evolves in discrete time steps. At each step, the relative flux of small molecule (metabolite) concentrations between two lattice cells, the diffusion step of all large molecules (enzymes), reactions among large molecules and those between small and large molecules are calculated. Cell++ was designed to study the impact of spatial organization on several biochemical systems including metabolism, signalling pathways, calcium waves and lipid raft mediated signalling.

CyberCell [59] is a particle-based simulator that was built to study the volumetric impact of macromolecular crowding on cellular reaction-diffusion systems. The simulation advances in discrete time steps of fixed size. Particles diffuse by a fixed length in a random direction, uniformly distributed over the surface of a sphere. The moving probability depends on the diffusion constant. After the diffusion step, particles that moved are checked for potential collisions with other particles. If a collision is observed, it is determined if a reaction occurred. If no reaction happened, the move is rejected. This approach is used to enforce volume exclusion.

Greens-Function Reaction Dynamics (GFRD) Methods

The idea of Green's Function Reaction Dynamics (GFRD) [76, 77] is to choose a maximum time step that is still small enough such that only single particles or pairs of particles have to be considered, and no particle can collide with more than one other particle during this step. The corresponding Einstein equation (for propagating single particles) and Smoluchowski equation (for the two-body problem) can be solved analytically, using Green's functions. From these solutions, probabilities for the next unimolecular and bimolecular reactions to happen are derived, and these probabilities can be subsequently used in an event-driven GFRD algorithm. This algorithm iteratively (1) determines the maximum time step, the next reaction to occur and the time when it occurs (within the maximum time step), (2) propagates all particles, and (3) updates particles according to the reaction.

The GFRD algorithm is very accurate and much faster than other particle-based methods for systems that are diffusion-dominated. However, the GFRD algorithm is not exact since the decomposition into one-body and two-body problems involves cut-off distances [71]. Also, the original GFRD can be computationally very intensive due to the synchronized updates of all particles at each step, and the fact that the system evolves according to the smallest tentative reaction time. Recently, Takahashi et al. [71] introduced an asynchronous version of the GFRD, called eGFRD, which was inspired by the work of Oppelstrup et al. [54]. In eGFRD, spherical protective domains are placed around single particles and pairs of particles, making the new scheme exact.

In the upcoming **E-Cell** version 4 a particle-based simulator based on the eGFRD algorithm will be included. In Takahashi et al. [71] eGFRD has been used to demonstrate how spatiotemporal correlations can change the response of the MAPK pathway.

Conclusions

The last few years have seen a rapid development in spatial algorithms and toolkits. The remaining challenges are to make these approaches robust and efficient in multiscale heterogeneous environments and to allow them to be integrated in, for example, whole organ models.

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