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Spatial Aspects in Biological System Simulations

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Abstract

Mathematical models of the dynamical properties of biological systems aim to improve our understanding of the studied system with the ultimate goal of being able to predict system responses in the absence of experimentation. Despite the enormous advances that have been made in biological modeling and simulation, the inherently multiscale character of biological systems and the stochasticity of biological processes continue to present significant computational and conceptual challenges.

Biological systems often consist of well-organized structural hierarchies, which inevitably lead to multiscale problems. This chapter introduces and discusses the advantages and shortcomings of several simulation methods that are being used by the scientific community to investigate the spatiotemporal properties of model biological systems. We first describe the foundations of the methods and then describe their relevance and possible application areas with illustrative examples from our own research. Possible ways to address the encountered computational difficulties are also discussed.

1. Introduction

A kinetic model is the mathematical description of the interactions that can occur among a set of reactants in a given physical construct (Resat *et al.*, 2009). The mathematical formulation has to define the occurrence properties of the reactions and where they can occur, that is, the model identifies reaction rates, propensities, allowed physical regions, etc. The formalism used for representation (stochastic, deterministic, hybrid, agent-based) as well as the method used to simulate the system properties are the other components that define a computational kinetic study.

Mathematical representations that are typically used to simulate the dynamics of biological systems cover a wide complexity spectrum. Figure 17.1 summarizes which types of mathematical approaches are most suitable as a function of process rates and system size. Nonlinear, ordinary, or partial differential equations (PDEs) have been the most traditional approach to model the time evolution of biological systems (Gillespie, 1992a, 2000; Resat *et al.*, 2009). Arguably the simplest representation involves a set of coupled, first-order ordinary differential equations (ODEs) called the *reaction rate equations* (RREs). The RREs are phenomenological equations derived under the assumption that the system is spatially homogeneous; that is, it is well stirred that no persistent correlations develop among the positions and among the interaction patterns of the molecules. Although it is a crude representation, the RRE has the advantage of being the least computationally expensive approach, and it can accommodate vastly different time scales that the model system may require. The latter aspect (the “dynamical stiffness” condition) arises due to the wide differences in the rates at which the various reactions can proceed. The dynamical stiffness issue has been the subject of many studies in a multitude of scientific disciplines, and there are good ODE solvers which overcome the numerical difficulties (Ascher and Petzold, 1998).

Even though it has been employed successfully in many studies, an ODE-based deterministic approach alone may be inappropriate for certain systems when the underlying problem is inherently stochastic (Bortz *et al.*, 1975; Gillespie, 1976, 1977b). Stochastic effects could be due to the large fluctuations in the concentrations of biomolecules, which becomes particularly important when reacting particles exist at small copy number levels. At this limit, since the assumption of continuous molecular concentrations is no longer valid, differential equation-based models break down. Such limits are often encountered for molecular species involved in the transcriptional regulation of gene expression (McAdams and Arkin, 1999). Under such conditions, special treatment is required to model the studied biological network (Gillespie, 1976, 1977a,b), and a more general approach based on discrete stochastic simulation methods in which natural fluctuations are treated in an explicit manner has been advocated for the quantitative analysis of biological networks (Arkin *et al.*, 1998; McAdams and Arkin, 1997).

At the fundamental level, the stochastic approach involves the solution of the same underlying reaction equations that also define the corresponding deterministic models. However, in addition to the mean solutions that deterministic methods can provide, stochastic simulations also provide information about the intrinsic fluctuations of the system and about the possible roles of limiting reaction species. *Discrete stochastic simulations* were pioneered by Gillespie, who showed the equivalency of deterministic and stochastic formalisms in the limit where the abundances of all constituent chemical species tend to infinity, and discussed the importance of stochastic fluctuations when the abundances are small (Gillespie, 1977a,b). We note the distinction between discrete stochastic solution of the reaction kinetic equations and stochastic differential equations (Resat *et al.*, 2009). The latter has long been used in other physical sciences (Gillespie, 1992b, 2000), and they are usually obtained by starting with an assumed ODE and then adding a “noise” term. Although such approaches have the advantage of being much less expensive computationally, they are basically phenomenological equations designed to capture the intrinsic fluctuations where it is assumed implicitly that a presumed statistical distribution (e.g., Gaussian noise) characterizes the system fluctuations. Hence, their applicability is more appropriate when system sizes are large enough to justify the employed statistical distribution profile. Therefore, the use of discrete stochastic approaches to solve the reaction equations is often more suitable in studying biological systems, particularly when the expression levels of the reacting species are small. However, discrete stochastic simulations are often too slow and computationally expensive, and the exclusive use of this technique is impractical for most realistic systems. Thus, there is a need to develop multiresolution methods which make use of fast deterministic simulations for those parts of the system when justified, and employ discrete stochastic simulations wherever it is necessary. Such hybrid methods can utilize a hierarchy of mathematical schemes that range from the most accurate but most computationally intensive (discrete stochastic) to the most coarse but most computationally efficient (ODE) method.

The major focus areas of this chapter—spatial organization and structural hierarchies—add an additional degree of complexity to biological system simulations. Hierarchical organization is frequently observed in biological systems where biochemical activities and biological functions are restricted to defined niches that respond to the local environment. An obvious example is the cell — cells often survey their immediate surroundings and adjust their metabolic or signaling patterns according to the local extracellular conditions they are exposed to. Similarly, within the cell there are additional levels of organization where the local intracellular conditions become important — cells utilize specialized compartments that create favorable environments for specific biological activities. These subcellular compartments exchange material in a concerted fashion to fulfill their roles in fundamental cellular processes such as synthesis, degradation, and signal transduction. Further, in a

multicellular organism cells reside and function in the context of a tissue. Thus, compartmentalized reactions that occur at many smaller spatial scales simultaneously drive and respond to changes at the tissue level. Capturing this hierarchical organization in dynamic models presents significant additional challenges in multiscale modeling.

Particle transport is central to the information and material transfer that occurs between compartments in biological systems (Berg, 1993; Slepchenko *et al.*, 2003; Stundzia and Lumsden, 1996). We note that material transfer often occurs over spatial distances many orders of magnitude larger than the size of involved transporters, and its mechanisms can include both passive transport through concentration gradient relaxation or active transport through the involvement of transporters, chaperones, or vesicles. This chapter focuses on modeling the dynamics in biological systems when spatial aspects play a role. We advocate a system-of-systems approach and discuss how such approaches can be constructed by the inclusion of spatial aspects either directly or through compartment-based formalisms. As speedy progress in experimental techniques, particularly fluorescent labeling and high-resolution microscopy, has started to make it possible to collect biological information about local dynamical activities (see, e.g., Burke *et al.*, 2001; Judd *et al.*, 2003; McAdams and Shapiro, 2003; Ozcelik *et al.*, 2004; Viollier *et al.*, 2004), development of kinetic models that can capture the effects due to local inhomogeneities is certainly becoming feasible. These efforts will allow researchers to make headway into the last frontier—spatial dynamics—in systems biology efforts (Kholodenko, 2003, 2006; Lemerle *et al.*, 2005).

2. Methods and Frameworks

2.1. Construction of spatial frameworks

Approaches to incorporate spatial aspects into biological models mostly fall into two broad categories which we designate as: (i) multicompartment models and (ii) models that explicitly incorporate spatial dimension. Specifically, spatial models are usually built using the following two approaches, or using a combination thereof:

- i. Multicompartment models involve the phenomenological partitioning of the system into distinct reaction volumes, and they are arguably the simplest to construct and simulate (Chaturvedi *et al.*, 1977). The system is constructed as a collection of *idealized* compartments, which may not be faithful representations of the physical reality, but possess biological relevance. Each compartment constitutes an independent *reactor volume* with compartments being linked at the higher whole-system scale. Mass/information transport is included in these models as exchange reactions between compartments. For example, modeling a eukaryotic cell as a collection of subcellular structures, defining which types of reactions can occur within each subcellular structure, and how these subcompartments exchange material through excretion or uptake of biomolecules would result in a multicompartment model of the cell. This model can be extended out to a higher spatial level of organization, where each cell in a collection of cells forms a compartment of the system. In multicompartment models, the compartment identity is merely used to dictate reaction and mass/information transport rates while the spatial location of the compartment is not modeled. This representation is particularly well suited to study vesicle-mediated processes such as endocytosis/phagocytosis (Birtwistle and Kholodenko, 2009; Resat *et al.*, 2003; Shankaran *et al.*, 2006) while keeping the complexity to a minimum.
- ii. In models that explicitly incorporate space, a grid-like construction is typically used for physical partitioning of the system (Beyenal *et al.*, 2004; Noguera *et al.*, 1999a). The total system volume is subdivided into physical subvolumes that are small enough for each to be considered spatially homogeneous within the desired

level of accuracy and sensitivity. Each grid unit can be thought of as a distinct reactor and, whenever a chemical reaction occurs in the system, where it occurred is known within the resolution of the subdivisions. The spatial resolution comes at a considerable cost in computational complexity. If ODEs are used to represent the reaction kinetics, the model converts to a more demanding PDE where the kinetics are ruled by the local conditions of the subdivision grid points. The PDE model would also require the inclusion of transport/exchange between subvolumes and the definition of spatial boundary conditions. These types of models are well suited when diffusion and/or hydrodynamics play a significant role in system dynamics.

Conceptually speaking, there are equivalencies between the above approaches. Each grid unit in a grid-based explicit spatial simulation can in fact be thought of as a “compartment” when it comes to constructing mathematical models. For both treatments, we need to specify the equations that govern the reaction kinetics within each system partition and the rules for mass/information exchange. In multicompartment models, we need to phenomenologically define the rules that govern mass/information transport between the compartments. In explicit spatial simulations, mass transport between the grid units is taken care of using physical laws such as the diffusion equation or the Navier–Stokes equation. We note that while explicit spatial simulations do not necessarily have to include a grid, we only consider grid-based formalisms in detail here. Scenarios where the problem is simple enough to allow the use of Newtonian dynamics type models where exact locations are tracked in a continuum space are likely to be rare as we construct increasingly realistic 3D models of biological systems.

Obviously, an approach that combines the above two fundamental representations is also possible and often required for realistic models of biological systems. Such mixed representations can help with splitting the investigated system into two parts; components whose spatial dynamics can be defined on the grid structure and components that are directly included as compartments. The latter can also be recorded according to their positions in the underlying grid frame. These mixed representations are particularly well suited when the details included in the model are disparate and emphasizes different aspects. For example, dynamics of small messenger reactants are primarily ruled by their uptake/release and diffusion. So their profiles can be represented using the grid frame. In contrast to such reactant molecules, individual cells can have several attributes (cell states) that dictate their internal kinetics and behavior. Thus, it may be necessary to represent cells as individual compartments with their own dynamics and regulatory rules and possibly containing their own subcompartments if subcellular structures are included in the model. Such mixed representations have been successfully used in individual-based models where cellular motility and migration dynamics or the dynamics of subcellular vesicles are investigated or to study higher order structure formation in research areas such as tissue/tumor modeling (Zhang *et al.*, 2009a), biofilms (Xavier *et al.*, 2005, 2007), and bacterial colonies (Allison, 2005; Picioreanu *et al.*, 2005, 2007).

2.2. Treatment of reaction kinetics

Irrespective of the model formulation, kinetics of the compartments essentially consists of two parts; what happens internally and how a compartment interacts with its surroundings or with other compartments. These can be dealt with in different ways according to the desired accuracy and resolution. This section discusses several of the most commonly used approaches to model these aspects. It should be noted that in principle, apart from practical implementation issues, one is not limited to using a single type of formalism and can mix-and-match different representations in a unified model as desired.

2.2.1. Models for internal kinetics of compartments—As discussed in Section 1, regardless of whether compartments are defined from a biological standpoint or as spatial grid units, an ODE-based deterministic treatment is the easiest approach to model the internal kinetics of system compartments. To develop such a model (Resat *et al.*, 2009), one starts with identifying the input and output variables as well as the reaction intermediates, that is, key species and physical properties to be simulated are determined and tabulated. For example, assume that a receptor (R) system is studied, where R can bind to a ligand L to form ligand-bound receptors (RL). RL can then dimerize to form dimer complex (D) which can bind to an effector/adaptor/scaffold molecule E to form the DE complex and trigger the involved signal transduction cascade. Let us also assume that the level of formed DE complexes regulate the ligand shedding by the cell. In this example, one would need to include the reactants L , R , RL , D , E , and DE . If the reaction occurrences are modeled with mass-action formulas, the mathematical model would consist of the following rate equations:

(17.1)

In these equations, square brackets $[X]$ denote the concentration of species X in cellular volume. The cytoplasmic to extracellular volume ratio V_R accommodates the difference that free ligand L resides in the extracellular media while other reactant species are defined in association with the cell. $f_s(DE)$ is the function defining the ligand synthesis and shedding rate. For example, if the rate is hyperbolically proportional to the DE levels, then $f_s(DE) = k_s [DE]/(K_{DE} + [DE])$.

We note that rate equations tabulated in Eq. (17.1) could equally be written out if they were not occurring as part of the internal kinetics of a cell but instead as a set of reactions in a particular unit of the grid that discretizes the physical system into subcompartments. A grid unit may constitute a part of a subcompartment or of the medium that surrounds the compartment objects. In this case, mathematical equations (e.g., Eq. (17.1)) need to be expanded to include terms that represent the movement of reacting species in between grid units. This will be discussed in the next section.

2.2.2. Coupling the compartments—In most instances, how compartments interact with each other or with the environment in the context of the larger biological system is the defining factor in biological responses. For example, the ligand/messenger molecule in the above model might be brought to the vicinity of the cell through the blood stream flow or messenger agents could be secreted and absorbed as part of intercellular communication. We note that intercellular communication itself can be autocrine, juxtacrine, or endocrine in origin, and these processes couple the system elements over vastly different length scales. Another example relevant to direct intercellular interactions in eukaryotic systems is the signaling through cell–cell junction formation. In this case, dynamics of the receptors could depend on whether they occupy the junction regions. Such details can be included in the models by splitting the receptor pool into “at the junction” and “away from the junction” categories where each category can have different binding and complexation rates. Receptor movement in-and-out of the junctions can be modeled as reactant exchanges in the equations. Similarly, cell–cell contacts can impact the cell polarities, motility, and internal cellular kinetics and cell behavior. Bacterial systems too provide many relevant examples

where interactions between the system elements is critical, a prominent example being the synergy between the organisms in a microbial community where trophic interactions are one of the dominant factors in determining system characteristics.

System (sub)compartments are usually coupled in the models using material transfer reactions or as rules that alter the kinetic parameters. For example, material can be transported in and out of organelles or nucleus to exchange material with the cytoplasm. One way to implement this is to add transfer terms to the rate equations

$$d[X_i]/dt = \text{"internal reactions"} + T_{X,j \rightarrow i} - T_{X,i \rightarrow j} \quad (17.2)$$

where $T_{X,j \rightarrow i}$ is the transfer rate of X from (sub)compartment j to (sub) compartment i . "Internal reactions" are the kinetic terms to characterize the fate of X internally in the compartment, for example, the network model described with Eq. (17.1).

Example 1: Endocytic trafficking of many types of receptors can have profound effects on subsequent signaling events. In an earlier study, we have constructed a multicompartment model to investigate the role of endocytic trafficking in epidermal growth factor receptor (EGFR) signaling (Resat *et al.*, 2003). Our quantitative model combined the trafficking and signaling processes in an integrated model (Fig. 17.2). This model consisted of hundreds of distinct endosome compartments and about 13,000 reactions/events that occur over a broad spatiotemporal range. Dynamic formation and recycling of the endocytic vesicles were built into the model by defining them as probabilistic events with a defined mean occurrence rates λ_f and λ_x , respectively (Resat *et al.*, 2001). When an early endosome is formed, the vesicle encompasses a certain portion of the receptors and other protein complexes, which get internalized through the trafficking vesicle. As the conditions in the vesicles and the transmembrane/cytoplasm boundary may differ (e.g., due to the pH difference, concentration enhancement, colocalization, etc.), this downregulation process allows cells to regulate their signaling patterns spatially.

Use of a realistic multicompartment model allowed us to investigate the distribution of the receptors among cellular compartments as well as their potential signal transduction characteristics (Resat *et al.*, 2003). Our model accurately predicted the differential kinetics and extent of receptor down-regulation induced by different ligands of EGFR, and our results led to the prediction that receptor trafficking controls the compartmental bias of signal transduction, rather than simply modulating signal magnitude.

It should be noted that a similar strategy is applicable when a grid frame is used to define system subvolumes (Example 2). Continuing with the network model example from Eq. (17.1), say that we are dealing with the receptor R level in the grid unit i , R_i . Then the corresponding rate equation would need to be modified to

$$d[R_i]/dt = -k_1[L_i][R_i] + k_2[RL_i] + \sum (T_{R,j \rightarrow i} - T_{R,i \rightarrow j}) \quad (17.3)$$

Here $T_{R,j \rightarrow i}$ denotes the transfer rate of R from the neighboring grid units j to unit i . The sum in Eq. (17.3) is over the grid units to/from which the exchange is allowed. Notice that the mechanisms or causes of the material exchanges can be many fold, ranging from transporter mediated active transport to passive diffusion to advective flows. Depending on the involved mechanism, appropriate mathematical expressions should be used to represent the material transfer in the equations.

We also note that the above discussion is not limited to hypothetical compartments or compartmentalization via gridding; a mixed approach can similarly be used where one utilizes internal kinetic models for the explicitly included objects (e.g., cells, organelles, vesicles) and overlays those objects on the grid. In this hybrid approach, objects are defined in terms of their grid location, which enables the specification of the relative physical separation between objects. Such mixed approaches are discussed in Section 2.3.3.

Example 2: Spatially regulated signaling discussed in Example 1 can also be studied using a grid frame to define system subvolumes (Fig. 17.3) (Pettigrew and Resat, 2005).

In this case, the reactions can be characterized either as biochemical or as mass transfer reaction, and rules can be imposed on the reactions and species locations. For example, unbound effector proteins can reside in the cytoplasm only, but upon forming a complex with receptors they become part of the compartment that the interacting receptor resides in. Similarly, upon dissociation from the receptor complex the effector protein returns to the cytoplasm.

In the above reaction equation, the first index shows the reactant type, second index labels the compartment (Fig. 17.3), and the last index indicates the grid unit that the reacting molecule is residing in before and after the reaction. In the above reaction, effector (E) present in the cytoplasm (C) can complex with the receptor dimers that reside in transmembrane (T) and endosome (E) compartments. Such association/dissociation reactions couple the different compartments through biochemical reactions. Compartment coupling can also occur through mass transfer reactions, which rule the localization and spatial distribution of molecules between system compartments. Material exchange between two grid units that belong to the same compartment; $L_{-X-K_s} \xrightarrow{k_t} L_{-X-K_t}$ results in material redistribution within that major cellular compartment. In contrast, material exchange between two adjacent grid units that belong to different major compartments results in material transport between cellular compartments. We note that modeling the mass transfer reactions as first order reactions can accurately mimic the diffusion equation if the transfer rate constants are adjusted according to the relationship between the average squared displacement $\langle r^2 \rangle$ of a particle and its diffusion coefficient D for random motion (Berg, 1993).

2.2.3. Issues related to internal kinetic models—The development of kinetic models requires the specification of the variables to represent the system internal states and readouts, and the appropriate equations governing the interactions between these variables. In practical terms, a modeler has to carefully choose the biomolecular reactions and processes to include in the model, and decide the level of detail at which these processes are to be modeled. Cells utilize exceedingly complex interconnected networks of biomolecular reactions to carry out their myriad functions. An all encompassing model of the cell that includes all of these reactions at the molecular level of detail would be impractical. Fortunately, in practical terms, cellular processes exhibit a certain level of modularity which makes it possible to model particular portions of the cell in isolation from the rest of the cell. As a simple example, a model of a signaling pathway does not need to include the transcriptional responses triggered by the pathway if these responses have little effect on the species abundances and reaction rates within the pathway during the time scale of interest.

Such notions of modularity have enabled the development of several successful models for particular cellular pathways (e.g., signaling pathways) and processes (e.g., cell cycle). These models are typically developed for well-studied pathways and processes for which the detailed molecular mechanisms are known. While this enables the construction of an initial reaction network, inclusion of all the mechanistic details, as often done in biological modeling, leads to extremely large models even for relatively simple systems and makes parameter estimation, and hence the model unreliable when the supporting experimental information is lacking. An effective model is the one whose size is limited by the scope and limitations of the experimentally measured quantities, while still capturing the fundamental biochemical/biophysical processes of the studied system. We further elaborate on this point below.

First, we address the issue of model scope (breadth) and granularity (depth). Consider the network model presented in Eq. (17.1). This is a model of a receptor system that is restricted to a few key species—a receptor R , a ligand L , and a scaffold molecule E . The implicit assumption here is that there are no other species that have a significant bearing on the rate expressions listed in Eq. (17.1)—that is, this reaction network can be treated as a self-contained module. Although networks such as those in Eq. (17.1) may be embedded as part of larger more complex signaling pathways, modeling such portions of the signaling pathway can often provide sufficient insight into the operation of the pathway as a whole. It is useful to identify such networks where possible, and thereby restrict the scope of the model to make modeling tractable. It should be noted that the scope of the model can also be imposed upon the modeler due to unavailability of detailed mechanistic information about large signaling networks of interest. In this regard, an important aspect of Eq. (17.1) is the use of the phenomenological function $f_s(DE)$ to link the ligand shedding rate to the number of dimer–adaptor complexes—in other words the actual molecular mechanisms that effect this link are considered to be beyond-the-scope of the model because they are either unavailable and/or irrelevant. With regards to granularity—the level of detail in the model—Eq. (17.1) is a much simpler abstraction of the actual molecular mechanisms at work in this core network. For instance, in the receptor system that the model is built for, receptor dimerization is followed by phosphorylation of the receptor cytoplasmic tails at several distinct amino acid sites with particular phosphorylation sites being capable of recruiting specific adaptor molecules (Wolf-Yadlin *et al.*, 2006). Should we then employ distinct variables in our model to explicitly track the various possible phosphorylated receptor types and their associated adaptors? This would vastly increase the number of model parameters due to combinatorial complexity (Blinov *et al.*, 2004) and, as discussed below, would render the model unreliable if we did not have the right kind of experimental data to establish these parameter values.

In order to construct a predictive kinetic model, in addition to the reactants and rate expressions (e.g., Eq. (17.1)) we also need parameter values—rate constants and the reactant abundances that would form the initial conditions for the ODEs. Whereas at first glance, species abundances and rate constants may be available in the literature, these quantities are often cell-type specific, and may not be applicable to the particular cell type under study. Further, due to the specific experimental techniques involved, some of the available parameters may have large uncertainties associated with them. Hence, it is always desirable to establish a consistent set of parameter values by fitting the entire model to experimental data collected in the cell type of interest. Such parameter estimation exercises place additional constraints on model building. Several biochemical reactions occur at second or subsecond time scales and may be unobservable in traditional biological experiments where the sampling times are in the order of 10s of seconds or minutes. Such reactions can hence be treated as pseudo-steady state reactions thereby reducing the number of model variables. Further, once the relevant system observables have been established based on constraints

imposed by experimental techniques, one could then perform structural and practical identifiability analysis (Raue *et al.*, 2009) to further assist in model simplification. Structural identifiability is related to the model structure—potential correlations between the model parameters—and is independent of the experimental data. Practical identifiability is related to the amount and quality of available data. There are other techniques that can specifically be applied for formally reducing kinetic models (Ho, 2008). Any model reduction should be done with care so as to ensure that the resulting lumped parameters, if any, can be properly interpreted. Finally, most parameter estimation exercises culminate with the tabulation of best-fit point estimates for the model parameters that may provide a false sense of security when it comes to understanding system behavior. Proper care should be taken to establish that the obtained solution is unique, and to calculate the confidence intervals in the parameters and the predictions (Shankaran *et al.*, 2008). On a related note, any point estimate for a particular rate constant that is presented in the literature using model-based analysis of experimental data may be completely unrealistic when used outside the context of the presented model and needs to be interpreted with care.

In summary, the development of an effective kinetic model is a nontrivial exercise that contains several pitfalls. A general rule of thumb is that a model should be parsimonious—as simple as possible to address the question at hand—and should take into account the limitations of the available information about the system and of experimentally measured quantities.

Example 3: The human epidermal growth factor receptor (HER) family comprises four homologous receptors (named HER1–4; HER1 is more commonly called EGFR), and particularly HER2 and HER3 are overexpressed in cancer. HER receptors can form homo- and heterodimers, and the pattern of receptor dimerization between HER molecules is a critical determinant of cell signaling and biological outcomes. While dimer abundances are difficult to measure experimentally, we can easily measure the levels of phosphorylated HER molecules using ELISAs. The level of receptor phosphorylation contains information about receptor dimerization affinities, and this information needs to be deconvoluted from the experimental measurements using a mathematical model (Fig. 17.4).

In an ongoing research effort, we measured the phosphorylation patterns of HER receptors in epithelial cells expressing endogenous levels of EGFR and varying levels of HER2 and HER3 receptors that were exposed to various ligand treatments (Zhang *et al.*, 2009b). We then used a parsimonious mathematical model that included the fundamental processes that occur in this system—receptor dimerization, phosphorylation, and endocytic trafficking to analyze the experimental data and to extract the receptor dimerization affinities (Shankaran *et al.*, 2008). Note that while this model shares the basic features presented in Example 1 and in other detailed models from our group (Shankaran *et al.*, 2006), it is vastly simpler—it has a single internal compartment and does not explicitly model receptor–ligand binding. These model simplification choices were made based on the nature of the experimental data being collected; for example, ELISAs measurements sampled at the minute time scales does not provide the sampling coverage needed to determine the kinetic rates for ligand–receptor binding that occurs at much faster time scales. The parsimonious model contained 19 parameters, all of which could be estimated with a good degree of confidence solely based on the experimental data collected in the study.

2.3. Algorithms to model spatial aspects

2.3.1. Multicompartment models—Multicompartment models are not truly spatially resolved approaches. From a computational perspective, they simply are an artificial partitioning of the system into subsystems where system components are built to mimic the

known spatial aspects of the problem. This is in reality nothing more than employing a *system-of-systems* approach where each compartment is its own internal subsystem, and these subsystems also interact with each other at the whole system level, that is, a system-of-systems is formed. Spatial information can be introduced into such models phenomenologically in a way that material transfer rates can be adjusted based on presumed locations and distances. If there are N compartments each with an internal reaction network of size S_{in} , then a system-of-systems modeling approach would result in a network of size $N \cdot S_{in} + S_{tr}$ where S_{tr} is the number of intercompartment reactions. If the compartments interact in a pairwise manner bidirectionally through S_{pair} interactions, then $S_{tr} = N(N-1)/2 \cdot S_{pair}$.

Once the mathematical model equations are constructed, handling of the model is the same as that of a single system case with the exception that the system size is now much larger. So either a deterministic or stochastic method can be used as needed and desired to solve the model equations during simulations.

2.3.1.1. Solution of model equations: Deterministic solution of ODEs is a very well-established area with widely available software (Ascher and Petzold, 1998). Thus, it will not be discussed here. Deterministic methods can provide acceptable solutions to *population-based* representations where spatiotemporal properties are captured using averaging techniques (Fig. 17.1). One computes mean quantities, such as the abundances of organisms or the levels of reactant proteins. This approach may be suitable for well-mixed systems (e.g., lysates of tissue samples, samples taken from a stirred batch reactor) in which the role of spatial variations on the dynamics of constituents can be overlooked because mixing tends to equalize the local conditions.

Discrete stochastic simulation algorithm (SSA) is an alternate way to solve the model equations (Gillespie, 1976, 1977b). SSA provides unbiased stochastic realizations for system dynamics based on the model equations. As the solution space is sampled statistically, in addition to the mean observations, stochastic methods can also provide information about the variability in the system. Therefore, they are more applicable when it is expected that small portions of the system may show noticeable and functionally important differences in their dynamics. Steps of SSA are (Resat *et al.*, 2009):

- i. Initialize the system's state $x = x_0$ at time $t = t_0$;
- ii. Evaluate the reaction propensities $a_j(x)$ and their sum $a_0(x)$;
- iii. Draw two random numbers r_1 and r_2 from a uniform distribution in the unit interval, and compute the time interval between the reactions $\tau = -\ln(r_1)/a_0(x)$ and determine which reaction type R_j occurs next by finding the smallest integer that satisfies $\sum_{j'=1}^j a_{j'}(x) > r_2 a_0(x)$;
- iv. Record and update the changes in the system $t \rightarrow t + \tau$ and $x \rightarrow x + \nu_j$ where the stoichiometry coefficients ν_j indicates how the chosen reaction affect the species; and
- v. Return to step (ii) or end the simulation.

2.3.2. Models that explicitly include spatial aspects—Arguably the simplest way to directly include spatial resolution into kinetic models is through the use of a grid framework. In as much as the grid units in a spatial simulation are analogous to individual system compartments, explicit spatial models can also be thought of system-of-systems formulations. Grid structures can be formed and investigated using either regular static grids

or adaptive meshes that can fold and bend as simulations progress. Finite element methods employing adaptive meshes could be more appropriate when there are considerable gradients in the system but, for simplicity, we will discuss finite difference methods that employ regular grids here. Extension of the presented ideas to adaptive mesh representations is conceptually straightforward.

2.3.2.1. Deterministic solutions: When spatial resolution is included, rate equations get converted to PDEs. If diffusive motion of reactants is incorporated, the resulting reaction–diffusion equations become

$$\frac{\partial S}{\partial t} = \nabla D_s \nabla S + \text{“internal reactions”} \quad (17.4)$$

As in Eq. (17.2), “internal reactions” stand for the kinetic reactions that occur within a particular grid unit that have a bearing on the reactant abundances. With the use of a regular grid and the finite difference method, reaction–diffusion equations reduce to differential algebraic equations (DAEs), the discrete algebraic form of PDEs (Ascher and Petzold, 1998).

Example 4: Spatial grids have long been used to simulate the reaction dynamics in 3D systems. For example, Noguera and coworkers have used such an approach to study the growth patterns of sulfate-reducing microbial communities in anaerobic environments (Noguera *et al.*, 1999b) (Fig. 17.5).

Even though this example employed a simple metabolic network for substrate utilization and biomass growth as well as simple geometries, these aspects are not limiting in such studies. For example, using a conceptually equivalent computational approach, Scheibe and coworkers have studied the dynamics of underground systems where heterogeneous soil structure, hydrodynamic mass transport, and genome-based metabolic network models were combined into a much more realistic and first-principles-based model (Scheibe *et al.*, 2009).

2.3.2.2. Stochastic solutions: With the exception of the diffusion term, stochastic solution of the reaction–diffusion equation parallels Section 2.3.1.1. Diffusion aspects can be incorporated in several ways. In the uniform treatment case, all reactant species are considered stochastically. In this case, diffusive motion can be handled as material transport from one grid unit to next according to the kinetic rate parameters, that is, diffusion is treated as a transfer reaction where reactants *hop* between grid units. This type of *jump Markov* approach has roots in Ising (1925) and Potts models (Potts, 1952; Wu, 1982), and they have been adapted to biological simulations (Chatterjee and Vlachos, 2006; Collins *et al.*, 2008; Fallahi-Sichani and Linderman, 2009; Gillespie, 1978; Pettigrew and Resat, 2005; Stiles and Bartol, 2001; Turner *et al.*, 2004).

Example 2 given above uses fixed boundaries to identify the system subparts. This rigidity can be removed from the layout to allow for temporal geometrical variations. A good example would be the CompCell3D simulation environment (www.compucell3d.org) where the assignment of the grid units are decided based on biomechanical properties to allow for cellular growth, motility, or simply shape changes. It should be noted that varying spatial resolutions can be introduced to different parts of the system using a coarse-graining approach that may employ multiple grids and/or treatment methods. Utilization of multiple grids for different regions of the system is one way of allowing the spatial resolution to differ between system parts. In addition, different regions defined by the grid partitioning can be treated with different methods, for example, spatial Monte Carlo (MC) approaches

that treat the particles/objects individually and stochastic simulation approaches that ignore the local spatial details can be used for different parts of the system. These concepts are further explained in Example 5.

Example 5: In receptor signaling, a model that can track individual receptor molecules would allow the investigation of how receptor distribution in the plasma membrane affects cell-wide signaling patterns. The large difference between the volume fractions of the plasma membrane and the cell interior makes it impractical to use the same resolution to model all of the relevant molecular events in the system. Hence, a multiresolution model where cytoplasm is described with the well-mixed SSA model, and a grid framework is employed to describe the reaction and diffusion processes on the heterogeneous plasma membrane could be appropriate (Costa *et al.*, 2009). In this setup, updates for membrane-localized species were done for each individual molecule on the grid framework, whereas populations of intracellular species were updated via SSA simulations. Molecules were moved from the membrane to the cytosol and vice versa based on the stoichiometry of molecular events. The spatial MC was performed only for those reactions that contain at least one membrane-bound species. Time was updated in a “combined” approach by computing the total propensity. Using this framework, the effects of receptor clustering on downstream signal transduction was investigated. Simulation results indicated that spatial heterogeneity due to receptor dense domains can have pronounced effects on the signaling patterns of downstream proteins, indicating the importance of spatiotemporal modeling (Costa *et al.*, 2009).

The above model can be taken one step further in complexity by extending the spatial grid into the intracellular space (Fig. 17.6) (Costa *et al.*, in preparation). It is desirable to individually track cytoplasmic adaptor proteins near the membrane where location-specific effects are expected to be important. On the other hand, reactions are expected to occur homogeneously further downstream in the cytoplasm, and therefore, do not need to be tracked individually. Thus, the well-mixed SSA representation can be used for cytoplasmic regions away from the membrane. These different requirements can be met by applying coarse-graining along the axis normal to the cell membrane (z -axis in the figure). Figure 17.6 shows a framework that uses three levels of resolution: the top lattice (#1) represents the plasma membrane and the membrane-proximal portion of the cytoplasm. This lattice contains seven layers at a z -lattice spacing of 10 nm. The first and second layers respectively of the top lattice represent the plasma membrane and the part of the cytoplasm adjacent to the membrane. The next three lattices (#2–#4) are coarse grained at the indicated lengths. Layers 2–7 of lattice 1 and the coarse grained lattices 2–4 together represent the cytoplasm in this framework.

Conceptually coarse-graining is equivalent to merging of microscopic grid units into larger entities: A unit C_k in a coarse-grained lattice can consists of q_k microscopic sites, where $q_k = q_k^x q_k^y q_k^z$, and q_k^j is the number of microscopic partitions in C_k along the j axis ($j = x, y$, or z). To adjust for coarse-graining, the reaction rates are redefined according to the mean occupancies of the coarser grid units $\bar{\eta}$. For example, the diffusion transition rate from a coarse-cell C_k to coarse-cell C_l adjacent in the z -direction is $\Gamma_{k \rightarrow l}^d = \frac{\Gamma^d}{q_k(q_k + q_l)} \eta_k (1 - \bar{\eta}_l)$, where Γ^d is the macroscopic diffusion rate. The coarse-grained reaction occurrence rates are adjusted analogously but with defining $\bar{\eta}_l$ as the mean concentration of the reactant l over the neighboring microscopic lattice sites. Detailed derivation of these rate expressions and further details on the implementation of adaptive coarse graining techniques can be found in Chatterjee *et al.* (2004, 2005) and Chatterjee and Vlachos (2006).

2.3.3. Mixed representations and individual-based methods—Realistic modeling of heterogeneous biological systems often demands the incorporation of compartmental aspects in addition to explicit spatial modeling. Such mixed frameworks can provide significant advantages, particularly when the desired resolution requires the use of individual-based modeling (O'Donnell *et al.*, 2007) for certain particles of the system (most commonly for the cells). For heterogeneous systems where local environmental conditions can vary (e.g., soil systems for bacterial and fungal dynamics, depth profiles in tissues or organs for eukaryotic system), treating each cell as a separate entity with its own dynamics and rules about its behavior would make it possible to investigate the properties of multicellular systems more realistically while including the effects of local variations on kinetics.

Individual-based approaches, which are one type of *agent-based modeling*, have their roots in cellular automata. Each object/agent (which can be real physical objects or fictitious objects that play a direct role in defining the dynamics) can be treated as having its own rules that define the dynamics of autonomous agents and how they interact with other objects. Rules can be based on the solution of mathematical equations which incorporate the internal and external conditions of the agents, or they can be logical rules that define the regulatory dynamics. Logical rules too can depend on an agent's environmental/boundary conditions. In most instances, logical rules lead to a hierarchy in the system, where the dynamics of the system takes the form of a branched tree in terms of decision-making mechanisms (Ratze *et al.*, 2007). To give an example, say that receptor signaling in a 3D tissue is being investigated. The tissue can then be thought of as a collection of cell objects/agents that organize to form a 3D structure. The receptor signaling patterns of the system objects (i.e., cells) can then be formulated using equations such as Eq. (17.1) reported above. In this case, the local concentration around every cell provides the input (local ligand concentration) to the network of that particular cell object. Dynamics of the diffusing ligand through the tissue can be modeled using Eq. (17.4), for example. These mathematical equations can be further supplemented with equations that describe the translational motion (i.e., motility) of the cell objects.

Individual-based modeling approaches have been used to model bacterial systems and biofilms for sometime (Kreft *et al.*, 2001; Vlachos *et al.*, 2006). For example, the *BacSim* modeling approach treats the biological system as consisting of two parts: bacterial cells as autonomous agents, and the metabolic substrates and products that diffuse and react in the surrounding environment. PDEs describing the metabolite dynamics are solved on a Cartesian grid, and obtained steady-state values are then used to define the local environmental conditions of the cells. In the next step, cellular dynamics are propagated using the determined metabolite concentrations where cell growth and division decisions are based on the growth pattern and size of the cells. Using BacSim simulation software, Kreft and coworkers were able to simulate the biofilm growth for a composite system consisting of nitrite and ammonia oxidizing organisms (Kreft *et al.*, 2001).

Example 6: The power of mixed modeling frameworks will be illustrated with an example from cellulose degrading microbial communities in soil aggregates (Resat *et al.*, in preparation). Although realistic models are constructed in 3D, here we report the results for 2D simulations to keep illustration simple (Fig. 17.7). The dynamics of microbes was simulated in a cellulose rich system where the polymeric cellulose is seeded at certain locations (a total of 12 grid points in four separate locations labeled in yellow). The initial concentration of deposited cellulose was set to 95 picogram carbon (pgC) per grid unit. Initial configuration is that of 20 randomly placed microbial cells in the aggregate.

Individual diffusive movements of the cells were modeled as random Markov motion while resource distribution is computed on the grid using the reaction–diffusion equation.

The top panels show the time progression of the simpler carbon substrate cellobiose concentrations in the system. Modeled organism had a doubling time of ~2 h when growing actively. It is clear from the time progression that the dynamics is regional in character. Since microbial cells graze around the system to locate and use the cellulose resource for growth, the growth and substrate consumption cycles are different in different regions. Hydrolysis of cellulose precedes the active growth of the cells; cells first create a substrate rich environment by hydrolyzing the cellulose and then use it to grow. As growth in turn increases the demand for carbon, hydrolysis and growth processes create a spatially dependent causal cycle. Tracking of the cells individually made it possible to define the biochemical reactions locally, which implicitly incorporates causality effects between resource consumption and cellular metabolism into the unified biological model.

3. Summary and Future Prospects

Computational biology has gone through rapid progress in recent years. It is now quite common to use computational models to analyze and integrate experimental observations and to make *in silico* predictions that can be validated in wet lab experiments. Smart adaptations of the methods that have been used in other natural science fields to biological problems and the development of modeling and simulation approaches that are particularly well suited to biology research have fueled this progress. This chapter outlined the basics of how mathematical models can be constructed for biological systems and the approaches and algorithms to simulate the dynamical behavior of the constructed models. Examples to illustrate the presented methods were chosen from mostly our own research for practical purposes. Excellent recent reviews summarize the substantial contributions to the computational biology field by many groups, and the readers are referred to those publications for further reading on the state-of-the-art for kinetic simulations.

Even though the progress has been immense, there is still plenty of room for improvement to develop computationally efficient methods to build and simulate biological models. The need is particularly dire for methods that can handle multiple spatiotemporal scales while still providing the necessary resolution for accurate representation. The development of efficient and adaptive multiscale algorithms is critical. Stochastic and deterministic methods are the preferred choices for better resolution and computational requirements, respectively. However, stochastic methods can be extremely expensive computationally and deterministic methods may not provide the needed resolution. Hybrid schemes that split the system into the continuous and discrete regimes to combine the traditional deterministic RRE with the SSA can nicely balance these extremes and show the best promise for progress (Elf *et al.*, 2003; Isaacson and Peskin, 2004; Wagner *et al.*, 2006). However, although they may be able to efficiently address the multiscale issues, there are still unsolved fundamental problems with hybrid methods as well: For example, automatic partitioning of the system into deterministic and stochastic parts needs to be done very carefully, because both accuracy and efficiency depends on a proper partitioning (Resat *et al.*, 2009; Wagner *et al.*, 2006). Similar concerns about automatic step size selection exist as well. Still, continuing improvements in algorithm and software development, in model development and in simulation methods are making kinetic simulations justly occupy a central role in ongoing systems biology research. While there is still plenty of room for improvement, rapid past progress is an indicator of significant future advances.

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Figure 17.1.

Tabulation of mathematical methods that are often employed in kinetic studies: ODE, ordinary differential equation; PDE, partial differential equation; SPDE, stochastic PDE; SDE, stochastic ODE; MC, Monte Carlo; SSA, Gillespie-type stochastic simulation approach; k_{react} , rate of biochemical processes; k_{diff} , rate of diffusion processes.

Figure 17.2.

Multicompartment model for receptor signaling. Early endosome (EE) vesicles can form from the cell membrane. EE vesicles can be of two types, smooth and coated pit, with different receptor complex internalization characteristics. Smooth and coated pit EE vesicles also have different trafficking dynamic rates. These vesicles can either recycle back to the plasma membrane or merge into the sorting endosome, which regulates the eventual protein degradation process through the lysosome pathway. The number of EE vesicles changes in time according to the system dynamics. Each compartment is represented with its own receptor signaling network, which is essentially a more complex version of the example given in Eq. (17.1). Further details can be found in Resat *et al.* (2001, 2003).

Figure 17.3.

Schematic diagram showing how spatial details can be incorporated into grid-based multicompartment models during kinetic model development. In this example, cell and its surroundings are modeled as having four compartments: Extracellular (X), transmembrane (T), endosomes (E), and cytoplasm (C). These subcellular compartments are laid out on a regular rectangular grid where each grid unit is labeled (e.g., E1, X8, etc.) to track location information at the subcompartment level. Note that, if desired, a finer grid may be used for particular regions of the system (e.g., the subdivision of the E1 grid unit).

Figure 17.4.

Parsimonious mathematical model to analyze receptor dimerization (Shankaran *et al.*, 2008). The model contains 10 species: Receptor monomers (R_1 : EGFR and R_2 : HER2) and phosphorylated receptor dimers (R_{11}^* , EGFR homodimers; R_{12}^* , EGFR-HER2 heterodimer; and R_{22}^* , HER2 homodimer) at the cell surface (subscript s) and in the internal (i) compartments. Monomers at the cell surface interact to yield phosphorylated dimers with a forward rate k_{fs} and a dimer-dependent reverse rate k_{rs} . Internalized dimers dissociate with a dimer-dependent rate k_{di} . Monomers are internalized with rate k_t . Dimers are internalized with a dimer-dependent rate k_e . In the absence of ligand, EGFR and HER2 monomers are assumed to have a surface-to-internal receptor ratios of α_1 and α_2 , respectively, and the respective monomer degradation rates k_{d1} and k_{d2} can be expressed as a product of these α values and k_t . Internalized dimers are degraded with a dimer-dependent rate k_d^* . V_{R1} and V_{R2} are the zero-order synthesis rates for EGFR and HER2.

Figure 17.5.

Description of a grid framework in biofilm simulations (adapted from Noguera *et al.*, 1999b). The physical domain is divided into rectangular grid units. First layer forms the surface that microbial species can attach to grow into biofilms. Grid units are labeled as being occupied by the growing biofilm (gray), colony boundary units (yellow). Note that only the units in the first layer are illustrated in the figure for clarity, and the rest are not shown. The diffusing elements can occupy any of the grid units and their dynamics can be modeled using the reaction-diffusion equation, Eq. (17.4). Time evolution of biomass in the grid units is tracked. When a grid unit is filled with biomass, the growing colony occupies the neighboring sites and the interface boundary layer moves accordingly.

Figure 17.6.

Construction of multigrid framework in multiresolution coarse-grained approaches. In this particular cell receptor signaling study, three levels of resolution was used: Top lattice (#1) contains seven layers at a z -lattice spacing of 10 nm. First and second layers respectively represent the plasma membrane and part of cytosol that forms the membrane boundary. Next two lattices (#2 and #3) are coarse grained at a z -spacing of 50 nm, and the last lattice (#4) is coarse-grained to 100 nm. Layers 2–7 of lattice 1 and the bottom coarse grained lattices 2–4 represent the cytoplasm. Layers in the lattices use a 50×50 grid mesh with 10 nm spacing in the x – y directions, and individual receptors are represented by their occupancy on a single grid unit. When bound to a membrane receptor, cytoplasmic species can diffuse as part of a receptor complex at the first layer of the top lattice. Upon dissociation from the receptor complex, adaptor proteins are placed at the second layer. Cytoplasmic species can diffuse in between lattices as they move around in the cytoplasm.

Figure 17.7.

Model for cellulose utilization by a microbial community. Although the actual model is constructed and simulated in 3D, results of a 2D simulation are reported here to keep illustration simple. (A) Metabolic network of the microbial cells. Cells uptake soluble carbon substrate S , and use it for maintenance, protein synthesis, and biomass growth. Cells express (i) regulatory ribosomal proteins EnzP, which controls the growth rates; (ii) transport enzymes EnzT, which facilitates the substrate uptake; and (iii) hydrolases EnzX, which convert polymeric carbon cellulose to simpler carbon forms such as cellobiose, which is consumed by the cells for maintenance and growth. Synthesis rates of these proteins depend on the growth state of the cells. (B) Spatiotemporal profile of cellobiose and biomass in the system. Simulations use a 31×31 grid with a 5 micron grid size; the dark blue areas are soil-covered grid points and the light blue units are the pores for the cells to reside. Panels report and compare the soluble substrate and the biomass in the system at the indicated times. Although the simulations keep track of individual cells, total biomass in the grid units is reported using a color scale.