EPiC Series in Computing

Volume 101, 2024, Pages 103–112

Proceedings of the 16th International Conference on Bioinformatics and Computational Biology (BICOB-2024)

Case-Studies of Parameter Estimation in the Stochastic Reaction-Diffusion Master Equation

Kannon Hossain[1] and Roger B. Sidje[2]

[1] Department of Mathematics, The University of Alabama, Tuscaloosa, AL, USA
khossain@crimson.ua.edu
orcid: 0000-0002-0076-0216

[2] Department of Mathematics, The University of Alabama, Tuscaloosa, AL, USA
roger.b.sidje@ua.edu
orcid: 0000-0001-5353-3642

Abstract

Stochastic approaches to the reaction-diffusion master equation (RDME) are commonly employed in systems biology to model the intrinsic randomness of diffusing molecular species. For accurate modeling and numerical simulation of the reaction-diffusion process, parameter estimation from experimental or synthetic data is a topic of interest. Parameter estimation is a challenging task in stochastic RDME since the reaction rate parameters are always coupled with the diffusion rate parameters, and the state of the system itself is random. We present a fitting scheme based on a maximum likelihood estimation (MLE) to approximate both the reaction and diffusion rate parameters. The quality of the method is evaluated by applying it to two case-studies from systems biology, such as the birth-death process and the annihilation system. The results obtained from our experiments demonstrate a reasonable approximation of the estimated parameters compared to the true parameter values.

1 Introduction

Reaction-diffusion models first developed [1] to provide a microscopic description of morphogenesis, have been extensively employed to describe spatio-temporal dynamics where molecules diffuse, generate, degrade, and engage in chemical reactions when they are close together. Numerous biological phenomena, including gene regulation, metabolic, and signaling processes can be explained by the reaction diffusion process [2]. In order to obtain an accurate representation of the discrete and stochastic models, we employ the Chemical Master Equation (CME) [3] when low copy numbers of molecules are present in the system. The reaction–diffusion master equation (RDME) extends the CME to incorporate diffusion process where species are divided into compartments (voxels) [4]. We assume that all reactions within a given compartment are consistent with the homogeneous case where the compartments are well-mixed so that they can contain at least a few molecules. Additionally, molecular diffusion can occur between neighboring compartments. At any given time, the state of the system is determined by the number

H. Al-Mubaid, T. Aldwairi and O. Eulenstein (eds.), BICOB-2024 (EPiC Series in Computing, vol. 101), pp. 103–112

of molecules of each species in each compartment and is represented as a discrete Markov process [5–9] whose evolution is regulated by chemical and diffusion reaction events. While the RDME model shares similarities with the CME, it experiences higher computational costs due to the significantly larger state space.

Fitting a system of ordinary differential equations to the observed data yields model parameters for deterministic [10–12] systems. These parameters may not be ideal for the CME; hence, we need different estimating techniques. Additionally, spatial models incorporate rapid diffusions and reactions, and they may have unknown parameter values. In this work, we present the maximum likelihood estimation (MLE) method [13, 14] to approximate the reaction and diffusion rate parameters where it maximizes a probability function to fit the observed data into an assumed statistical model, resulting in the highest possible estimate in the parameter space. Parameter estimation for stochastic RDME is an iterative process. Stochastic biological models are highly nonlinear and non-convex, so estimation by implementing the iterative process carries the risk of getting stuck in a local minima by using the local optimization routine. Here, we have employed *Multistart* [15] global optimization routine, a MATLAB toolbox to optimize the objective function, which can tackle the identifiability issues of the unknown parameters and shown to be worked well for our RDME models.

The rest of the paper is organized as follows: In section 2, we summarize the CME, FSP, DME and RDME. Section 3 discusses parameter estimation techniques and optimization algorithms. Lastly, section 4 shows numerical tests and discussions.

2 Methods

2.1 Chemical Master Equation (CME)

Consider a chemical reaction system involving N molecular species that interact through M reactions where we denote $\boldsymbol{x}(t) = (x_1, \ldots, x_N)^T$ as the state of the system at time t. The propensity function $\alpha_k(\boldsymbol{x}(t))$ of reaction R_k at the current state $\boldsymbol{x}(t)$ is defined so that the probability of such a reaction occurring during the infinitesimal time interval $[t, t+dt)$ is $\alpha_k(\boldsymbol{x}(t))dt$. When reaction R_k happens, the state vector is updated with the stoichiometric vector $\boldsymbol{\nu}_k$, representing the change in species numbers.

Denote $P(\boldsymbol{x}, t) = \text{Prob}\{\boldsymbol{x}(t) = \boldsymbol{x}\}$, the probability that the system is at state $\boldsymbol{x}$ at time t. As given in [16], a characterization CME is that

$$\frac{dP(\boldsymbol{x}, t)}{dt} = \sum_{k=1}^{M} \alpha_k \left(\boldsymbol{x} - \boldsymbol{\nu}_k\right) P\left(\boldsymbol{x} - \boldsymbol{\nu}_k, t\right) - \sum_{k=1}^{M} \alpha_k(\boldsymbol{x}) P(\boldsymbol{x}, t) \tag{1}$$

Let $\boldsymbol{X}$ be the set of all possible states, if we order these states as $\boldsymbol{X} = \{\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n\}$, where $\boldsymbol{x}_i = (x_{1i}, \ldots, x_{Ni})^T$ and n is the total number of states, then (1) defines a set of ODEs

$$\dot{\boldsymbol{p}}\left(t\right) = \mathscr{R} \cdot \boldsymbol{p}\left(t\right), \quad t \in [0, t_f] \tag{2}$$

where $\mathscr{R} = [a_{ij}] \in \mathbb{R}^{n \times n}$ the transition rate matrix. From (2) the probability vector at the end point t_f is

$$\boldsymbol{p}\left(t_f\right) = exp\left(t_f \mathscr{R}\right) \boldsymbol{p}(0) \tag{3}$$

Because of the 'curse of the dimensionality', the size of CME can be extremely large or theoretically infinite. Finite state projection (FSP) [17], an advancement in the numerical treatment

of the CME, gives us a reasonable approximation to the solution of the CME, which we will describe shortly in the next subsection.

2.2 Finite State Projection (FSP)

The enormous size of the CME usually makes it too challenging to solve directly. The FSP makes a truncation with an analytical bound on the error of the probability distribution. We define $\boldsymbol{X}_J$ to be a finite subset of states in $\boldsymbol{X}$, where J is the index set of those finite states. For a truncated state transition matrix $\mathscr{R}_J$, the FSP finds $\boldsymbol{p}_J(t)$ with the truncated CME

$$\dot{\boldsymbol{p}}_J(t) = \mathscr{R}_J \cdot \boldsymbol{p}_J(t), \quad t \in [0, t_f] \tag{4}$$

and its solution is given by

$$\boldsymbol{p}_J(t) = exp(t_f \mathscr{R}_J)\boldsymbol{p}_J(0) \tag{5}$$

2.3 Diffusion Master Equation (DME)

Assume the domain Ω is partitioned into compartments (voxels). We label the compartments with $V_k, k = 1, \ldots, K$. Molecules within each compartment can react with one another within that compartment, and they can also diffuse across the boundaries and move to neighboring compartments. Both the reaction and diffusion processes are considered as random processes. Let, $X_{i,k}(t)$ be the number of molecules of species S_i in compartment V_k at time t. Then each species in the domain is given by the sub vector $\boldsymbol{X}_i(t) = [X_{i,1}(t), \ldots, X_{i,K}(t)], i = 1, \ldots, N$. The diffusion propensity function $d_{i,j,k}$ and the state change vector $\boldsymbol{\mu}_{k,j}$ characterize the dynamics of the diffusion of species S_i from compartment V_k to V_j in the next infinitesimal time interval $[t, t + dt]$. The vector $\boldsymbol{\mu}_{k,j}$ has a length of K with -1 in the k th position, 1 in the j th position, and 0 elsewhere. Given, $\boldsymbol{X} = \{\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n\}$, the diffusion master equation (DME) can be written by

$$\frac{dP(\boldsymbol{x}, t)}{dt} = \sum_{i=1}^{N} \sum_{k=1}^{K} \sum_{j=1}^{K} \left[d_{i,j,k}\left(\boldsymbol{x}_i - \boldsymbol{\mu}_{k,j}\right) P\left(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_i - \boldsymbol{\mu}_{k,j}, \ldots, \boldsymbol{x}_N, t\right) - d_{i,j,k}\left(\boldsymbol{x}_i\right) P(\boldsymbol{x}, t) \right] \tag{6}$$

with the diffusion propensity functions $d_{i,j,k}(\boldsymbol{x}_i)$. If $\mathscr{D}$ is the transition matrix describing the diffusion of molecules, the equivalent matrix-vector form can be written by

$$\dot{\boldsymbol{p}}(t) = \mathscr{D} \cdot \boldsymbol{p}(t), \quad t \in [0, t_f] \tag{7}$$

2.4 Reaction-Diffusion Master Equation (RDME)

Accounting for all the reactions in (2) and diffusions in (7) yields the matrix-vector form of the RDME

$$\dot{\boldsymbol{p}}(t) = \mathscr{R} \cdot \boldsymbol{p}\left(t\right) + \mathscr{D} \cdot \boldsymbol{p}(t) \tag{8}$$

Since there are more possible states in (8) than in (2) or in (7), the transition rate matrix that corresponds to it has been significantly expanded so that it may accurately represent species in different compartments. Since RDME accounts for both the reaction and diffusion as a whole, its dimensionality is significantly higher and computationally expensive [18] to solve, hence we often seek the numerical solution rather than the analytical solution.

3 Parameter Estimation Techniques

Several different optimization techniques [19–23] exist for parameter estimation in stochastic biological systems. The selection of methodology typically relies on the nature of the model equations, the number of unknown parameters, and the correlation between the model solution and parameters, such as whether they are linear or nonlinear, continuous or discontinuous. This work utilizes the maximum likelihood estimator (MLE) due to its probabilistic nature [24] to solve an optimization problem for stochastic models.

We first employed the FSP method to approximately solve the RDME that provides the state transition probability vector of each species. There is an implicit dependency on the reaction and diffusion parameters while setting up the RDME in (8). To clarify that the system's behavior relies on some reaction and diffusion rate parameters $\boldsymbol{\theta}$ we write

$$\dot{\boldsymbol{p}}\,(t) = (\mathscr{R} + \mathscr{D})(\boldsymbol{\theta}) \cdot \boldsymbol{p}\,(t)\,, \quad t \in [0, t_f] \tag{9}$$

for which the solution is the probability vector $\boldsymbol{p}(t, \boldsymbol{\theta}) = (p_1(t, \boldsymbol{\theta}), \ldots, p_n(t, \boldsymbol{\theta}))^T$ where $p_\gamma(t, \boldsymbol{\theta}) = P(\boldsymbol{x}_\gamma, t, \boldsymbol{\theta})$ is the probability of finding the system in state $\boldsymbol{x}_\gamma$ at time t, with the $\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n$ being the states retained by the FSP. For the data set $\boldsymbol{\mathcal{H}}$ and at fixed time $t = t_f$, the likelihood function $\mathcal{L}^{\text{FSP}}_{\boldsymbol{\mathcal{H}}}(\boldsymbol{\theta})$ is obtained as the product of the transition probabilities

$$\mathcal{L}^{\text{FSP}}_{\boldsymbol{\mathcal{H}}}(\boldsymbol{\theta}) = \prod_{\gamma} P(\boldsymbol{x}_\gamma, t, \boldsymbol{\theta}) \tag{10}$$

and we restrict the running index γ in (10) to plausible states determined by the data set $\boldsymbol{\mathcal{H}}$. By rephrasing the problem using the log-likelihood function, it is possible to enhance numerical stability with the goal of determining the parameter set $\boldsymbol{\theta}_{\text{Fit}}$ which will maximize (10). Therefore the FSP-based MLE problem is:

$$\boldsymbol{\theta}_{\text{Fit}} = \arg\max_{\boldsymbol{\theta}}(\mathcal{L}^{\text{FSP}}_{\boldsymbol{\mathcal{H}}}(\boldsymbol{\theta})) \tag{11}$$

$$= \arg\max_{\boldsymbol{\theta}}(\log(\mathcal{L}^{\text{FSP}}_{\boldsymbol{\mathcal{H}}}(\boldsymbol{\theta}))) \tag{12}$$

$$= \arg\max_{\boldsymbol{\theta}} \left(\sum_{\gamma} \log(P(\boldsymbol{x}_\gamma, t, \boldsymbol{\theta})) \right) \tag{13}$$

Each evaluation of the objective function with a different $\boldsymbol{\theta}$ implies solving the RDME to retrieve the $P(\boldsymbol{x}_\gamma, t, \boldsymbol{\theta})$, and this is why efficient solution techniques are critical. Either way, maximizing the likelihood, or correspondingly minimizing the negative log-likelihood, yields maximum-likelihood parameter estimates.

3.1 Optimization Algorithms

Parameter estimation in reaction-diffusion models, even in the deterministic case [25] suffers from identifiability issues. Stochastic biological models are known to be non-convex, nonlinear programming problems (NLP), and often optimization of the objection function is confounded by many locally optimal solutions to find the best fit. For RDME, further complications arise when the reaction and diffusion rate parameters are interconnected, which makes the exact statistical inference computationally very intensive. Although optimization-based methods have proven effective for deterministic systems [25, 26], there are currently no equivalent methods

available for stochastic systems that can assure good accuracy. We employed *Multistart* global optimizer to maximize the objective function in (13). Multistart is a heuristic-based method that starts a local solver from multiple starting points to find the global minimum and selects the best result. The total time it takes for our method to run depends on both the initial guess and the intervals that we use for unknown parameters. Different initial points yielded similar results. We choose the initial guess so that it is defined when the local solver iterates. It is important that a range is given for each parameter space in order to ensure that the values are reasonable from a biological standpoint. Exploring large parameter spaces can give wrong estimation if the estimation problems are ill-conditioned and multi-modal [27].

3.2 Data Set

We generate the synthetic data by using a compartment-based stochastic simulation algorithm (SSA) [7], which is a standard approach for Markov jump processes in a discrete state space. As the true values of the parameters are known, they have been employed to generate the data with 10^2 SSA realizations for each test model.

4 Numerical Tests and Discussions

4.1 Annihilation System

The annihilation system [28] consists of two species A and B, which react to annihilate each other. The following reaction takes place in each compartment:

$$R : A + B \xrightarrow{c} \varnothing$$

A compartment-based approach is a good way to show reaction-diffusion spatio-temporal systems. In this approach, space is split into uniformly spaced compartments where species can interact with neighboring compartments. Here we consider two neighboring compartments, named as V_1 and V_2, where the reactions R can take place inside both compartments separately and species A and B can move back and forth between V_1 and V_2. Since there are two species and two compartments in our model, there will be two diffusion rate parameters, say D_A and D_B for species A and B, respectively. For test purposes, we assume all of the reaction and diffusion rate parameter values are the same in each compartment with $\boldsymbol{\theta}_{true} = (c, D_A, D_B)^T = (0.2, 1.0, 1.0)^T$.

Table 1: Results of the global optimization of the annihilation system

Parameter	c	D_A	D_B
True	0.2	1.0	1.0
Estimated	0.1777	0.9329	1.05

The goal of the algorithms employed in global optimization is to identify the maximum value of the objective function throughout the entire range. *Multistart* runs a local solver *fmincon* from each set of starting points to find the global maximum within the range chosen. Within our optimization technique, we have set 10 instances, indicating that the solver attempts to identify multiple local solutions to a problem by starting from 10 distinct points. For the annihilation system, we generate the data by 10^2 SSA realizations with the settings of

$\boldsymbol{\theta}_{true} = (c, D_A, D_B)^T = (0.2, 1.0, 1.0)^T$, initial state vector $(5, 4, 4, 5)^T$, and time $t = 15s$. To run the optimizer, we choose the initial guess from a given set of uniform distributions with $c_0 = 1.2$ and $\boldsymbol{D_0} = (0.5, 0.5)^T$. Table 1 shows the optimization results of the estimated parameters, while Figure 1 shows the graphical representation of the true and estimated parameters of the annihilation system. We have seen that both the reaction rate parameters and the diffusion rate parameters were well estimated. We adjusted *FunctionTolerance*, *XTolerance* as 10^{-6} and lower and upper bounds as $[0, 0, 0]$ and $[0.5, 1.5, 1.5]$, respectively while we performed this test. Sensitivity analysis is crucial in parameter estimation, as minor changes in parameters can significantly impact system performance and vice versa. Thus, we have tested the sensitivity of the marginal probability distribution of each species in different compartments of the annihilation system with the true and estimated parameters shown in Figure 2. Since the approximations of our parameter estimation are good enough, a reasonable fitting of the marginal probability distribution has been obtained.

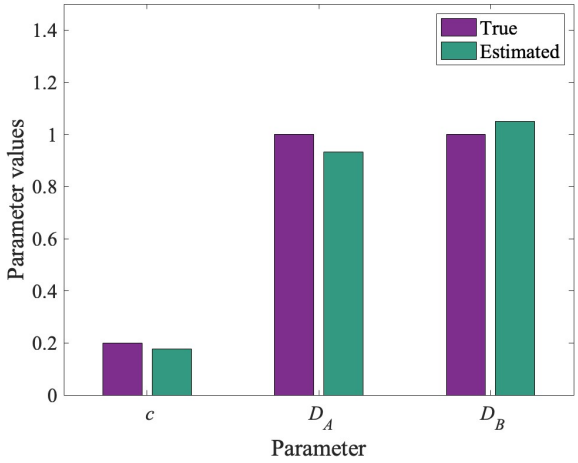


Figure 1: True and estimated parameter values of the annihilation system

4.2 Birth-Death Process

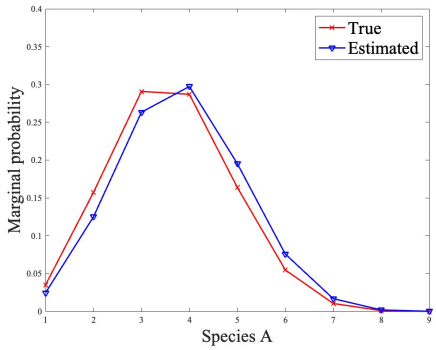
Consider the following model [29] for production and degradation of a species A where in reaction R_1 protein is produced at a constant rate c_1 and in reaction R_2 protein is degraded at a constant rate c_2.

$$R_1: \quad \mathrm{A} \xrightarrow{c_1} 2\mathrm{A}$$

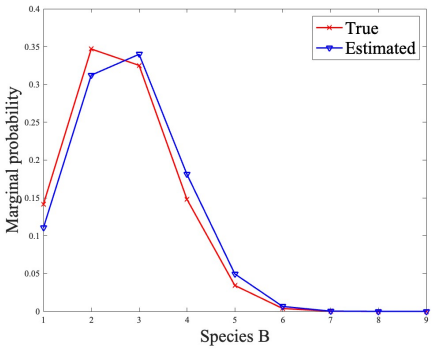
$$R_2: \quad \mathrm{A} \xrightarrow{c_2} \varnothing$$

Here we consider two neighboring compartments, named as V_1 and V_2, where the reactions R_1 and R_2 can take place inside both compartments separately and proteins can move back and forth between V_1 and V_2.

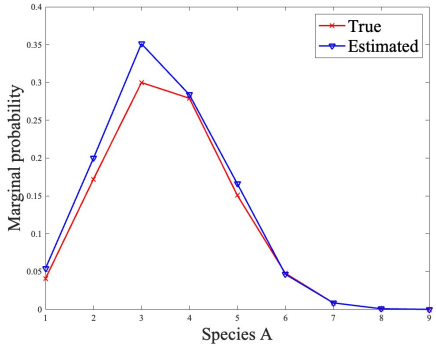
Since there are only one species and we consider two compartments in our system, there will be only one diffusion rate parameter, say D_A.For testing purposes, we consider true parameters $\boldsymbol{\theta}_{true} = (c_1, c_2, D_A) = (0.3, 0.7, 0.01)$.



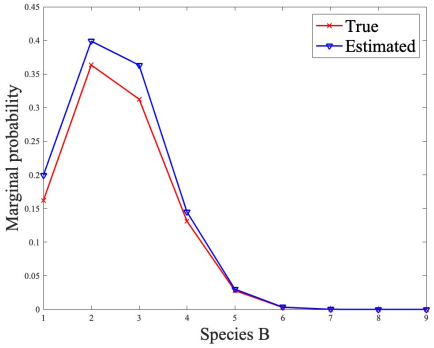
(a) Species A in compartment V_1



(b) Species B in compartment V_1



(c) Species A in compartment V_2



(d) Species B in compartment V_2

Figure 2: A comparison of the marginal probability distribution with the true and estimated parameter values in different compartments of the annihilation system

Table 2: Results of the global optimization of the birth-death process

Parameter	c_1	c_2	D_A
True	0.3	0.7	0.01
Estimated	0.3703	0.6622	0.0102

With the settings of $\boldsymbol{\theta}_{true} = (c_1, c_2, D_A)^T = (0.3, 0.7, 0.01)^T$, initial state vector $(3, 2)^T$, and time $t = 20s$, we generate the data by 10^2 SSA realizations. The optimization routine requires an initial guess of the parameters, and we choose the initial guess from a given set of uniform distributions with $\boldsymbol{c_0} = (0.9, 1.2)^T$ and $D_{A_0} = 0.07$. Table 2 shows the optimization results of the estimated parameters, while Figure 3 shows the graphical representation of the true and estimated parameters of the birth-death process. Again, we have seen that both the reaction rate parameters and the diffusion rate parameters are well inferred. We keep the same convergence properties with the previous model and adjust the lower and upper bounds as $[0, 0, 0]$ and $[0.6, 1.5, 0.05]$, respectively. Figure 4 shows the sensitivity of the marginal probability distribution of each species in different compartments for the birth-death process with a good fit.

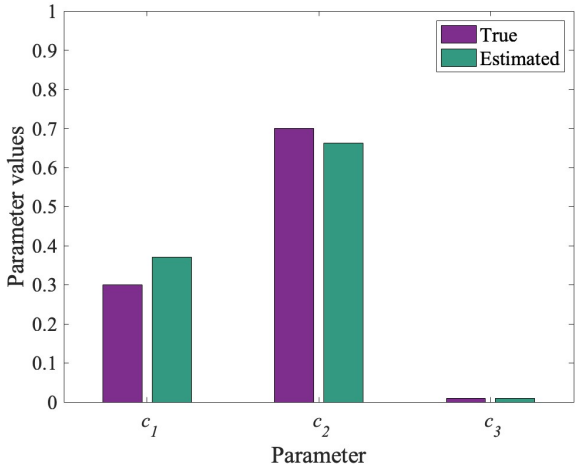
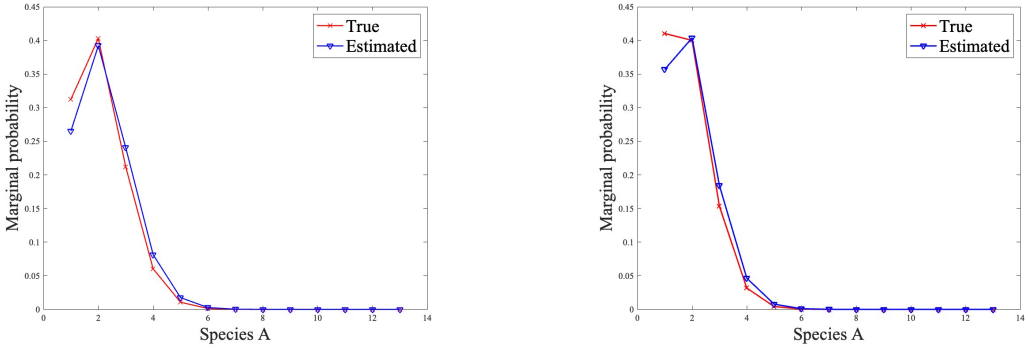


Figure 3: True and estimated parameter values of the birth-death process



(a) Species A in compartment V_1

(b) Species A in compartment V_2

Figure 4: A comparison of the marginal probability distribution with the true and estimated parameter values in different compartments of the birth-death process

5 Conclusion

The process of estimating parameters for stochastic biochemical models necessitates a large computing infrastructure. Occasionally, it is conceivable to identify the unknown parameters by experimentation, but in the majority of instances, this is challenging or even unachievable. For RDME, this is even more difficult since the estimation requires both reaction and diffusion rate parameters. In this work, we have shown that by implementing the compartment-based approach, we can extend the CME to RDME, and later on, the MLE method can be used to estimate both the reaction and diffusion rate parameters. There are prospects for extension and additional study, e.g., we intend to explore more complex systems incorporating biological models with different optimization algorithms.

References

[1] A Turing. The chemical basis of mokphogenesis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 237(641):37–72, 1952.

[2] Radek Erban and S Jonathan Chapman. *Stochastic modelling of reaction–diffusion processes*, volume 60. Cambridge University Press, 2020.

[3] Harley H McAdams and Adam Arkin. Stochastic mechanisms in gene expression. *Proceedings of the National Academy of Sciences*, 94(3):814–819, 1997.

[4] Audrius B Stundzia and Charles J Lumsden. Stochastic simulation of coupled reaction–diffusion processes. *Journal of computational physics*, 127(1):196–207, 1996.

[5] Radek Erban, Jonathan Chapman, and Philip Maini. A practical guide to stochastic simulations of reaction-diffusion processes. *arXiv preprint arXiv:0704.1908*, 2007.

[6] Daniel T Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of computational physics*, 22(4):403–434, 1976.

[7] Daniel T Gillespie. Exact stochastic simulation of coupled chemical reactions. *The journal of physical chemistry*, 81(25):2340–2361, 1977.

[8] Daniel T Gillespie. Approximate accelerated stochastic simulation of chemically reacting systems. *The Journal of chemical physics*, 115(4):1716–1733, 2001.

[9] Daniel T Gillespie. Stochastic simulation of chemical kinetics. *Annu. Rev. Phys. Chem.*, 58:35–55, 2007.

[10] AR Ortiz, HT Banks, Carlos Castillo-Chavez, G Chowell, and X Wang. A deterministic methodology for estimation of parameters in dynamic markov chain models. *Journal of Biological Systems*, 19(01):71–100, 2011.

[11] Anton Miró, Carlos Pozo, Gonzalo Guillén-Gosálbez, Jose A Egea, and Laureano Jiménez. Deterministic global optimization algorithm based on outer approximation for the parameter estimation of nonlinear dynamic biological systems. *BMC bioinformatics*, 13(1):1–12, 2012.

[12] Youdong Lin and Mark A Stadtherr. Deterministic global optimization for parameter estimation of dynamic systems. *Industrial & engineering chemistry research*, 45(25):8438–8448, 2006.

[13] Cari Prodi and Try Out. Maximum likelihood.

[14] Samuel S Wilks. The large-sample distribution of the likelihood ratio for testing composite hypotheses. *The annals of mathematical statistics*, 9(1):60–62, 1938.

[15] Zsolt Ugray, Leon Lasdon, John Plummer, Fred Glover, James Kelly, and Rafael Martí. Scatter search and local nlp solvers: A multistart framework for global optimization. *INFORMS Journal on computing*, 19(3):328–340, 2007.

[16] Daniel T Gillespie. A rigorous derivation of the chemical master equation. *Physica A: Statistical Mechanics and its Applications*, 188(1-3):404–425, 1992.

[17] Brian Munsky and Mustafa Khammash. The finite state projection algorithm for the solution of the chemical master equation. *The Journal of chemical physics*, 124(4), 2006.

[18] Md Mustafijur Rahman and Roger B Sidje. A study of a metapopulation model using the stochastic reaction diffusion master equation. (in press).

[19] Yuanfeng Wang, Scott Christley, Eric Mjolsness, and Xiaohui Xie. Parameter inference for discretely observed stochastic kinetic models using stochastic gradient descent. *BMC systems biology*, 4(1):1–16, 2010.

[20] Bernie J Daigle, Min K Roh, Linda R Petzold, and Jarad Niemi. Accelerated maximum likelihood parameter estimation for stochastic biochemical systems. *BMC bioinformatics*, 13(1):1–18, 2012.

[21] Tianhai Tian, Songlin Xu, Junbin Gao, and Kevin Burrage. Simulated maximum likelihood method for estimating kinetic rates in gene expression. *Bioinformatics*, 23(1):84–91, 2007.

[22] Kannon Hossain and Roger B Sidje. Parameter estimation in biochemical models using marginal probabilities. (in press).

[23] Kannon Hossain and Roger B Sidje. Parameter estimation in biochemical models using moment approximations. (in press).

[24] Darren J Wilkinson. Stochastic modelling for quantitative description of heterogeneous biological systems. *Nature Reviews Genetics*, 10(2):122–133, 2009.

[25] Maksat Ashyraliyev, Johannes Jaeger, and Joke G Blom. Parameter estimation and determinability analysis applied to drosophila gap gene circuits. *BMC Systems Biology*, 2(1):1–19, 2008.

[26] Yves Fomekong-Nanfack, Jaap A Kaandorp, and Joke Blom. Efficient parameter estimation for spatio-temporal models of pattern formation: case study of drosophila melanogaster. *Bioinformatics*, 23(24):3356–3363, 2007.

[27] Pang-Kai Liu and Feng-Sheng Wang. Hybrid differential evolution with geometric mean mutation in parameter estimation of bioreaction systems with large parameter search space. *Computers & Chemical Engineering*, 33(11):1851–1860, 2009.

[28] Robert Strehl and Silvana Ilie. Hybrid stochastic simulation of reaction-diffusion systems with slow and fast dynamics. *The Journal of Chemical Physics*, 143(23), 2015.

[29] Darren J Wilkinson. *Stochastic modelling for systems biology*. CRC press, 2018.