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COMMENTARY

Embracing Noise in Chemical Reaction Networks

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Abstract
We provide a short review of stochastic modeling in chemical reaction networks for mathematical and quantitative biologists. We use as case studies two publications appearing in this issue of the Bulletin, on the modeling of quasi-steady-state approximations and cell polarity. Reasons for the relevance of stochastic modeling are described along with some common differences between stochastic and deterministic models.

Keywords Stochasticity · Chemical reaction network · Noise · Scaling limit · Systems biology

1 Introduction

Continuous models in biology are often approximations of discrete phenomena. An ecologist keeping track of the number of wolves and rabbits in an island would not claim that the number of rabbits is truly a continuous variable, but he or she might assume that it is in order to simplify the model and its analysis. Similarly, chemical reaction models have traditionally been continuous, the number of atoms inside any reasonably sized pipette or container being staggeringly large. However, a surprisingly small number of molecules (think ten or fewer) often regulate cellular behaviors, as is becoming increasingly clear with recent high-resolution measurements in single cells. Decision-making processes in biology often take place at the cellular level, and cells are usually very small containers. An extreme example of low copy numbers is any given DNA sequence, which is usually present in just one or two copies per cell.

The papers by Kang et al. (2019) and Xu et al. (2019), both appearing in this issue of the Bulletin of Mathematical Biology, reflect a growing effort by our modeling community to take into account the stochastic and discrete nature of chemical reaction networks inside cells. The basic framework for such stochastic models was laid out in

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the early twentieth century by Markov and others, with what is now known as discrete-space, continuous-time Markov processes (Gagniuc 2017). Credit for applying this framework in the context of chemical reactions in the 1970s is usually given to Gillespie (1977), although earlier work appears to have been carried out by Delbrück and others (Bartholomay 1958, 1959; Delbrück 1940; McQuarrie 1967).

Both papers in the present issue compare the behavior of stochastic chemical reaction networks with their deterministic counterparts, in order to obtain insights about phenomena that can arise when relevant sources of noise are taken into account. Kang et al. (2019) carry out different forms of quasi-steady-state analysis (QSSA) in a stochastic enzymatic system, determine sufficient conditions for their validity and compare these conditions with the deterministic case. Xu et al. (2019) introduce noise into an important model of cell polarity controlled by the protein Cdc42 and find both differences and similarities, such as oscillations in the stochastic system that are not found for comparable parameters in the deterministic case.

Other efforts to expand deterministic models by including stochastic effects have already yielded spectacular results. The classical experimental system known as the repressilator (Elowitz and Leibler 2000) was not known for being a very reliable oscillator, and other experimental teams had tried to stabilize the oscillations by including additional feedback loops. The laboratory of Johan Paulsson set out instead to understand the effects that stochasticity caused in the original system. After carrying out this theoretical analysis, they made targeted changes to the original repressilator by stripping it down to its essential elements, and the resulting oscillating colonies stayed synchronized over hundreds of generations without coupling (Potvin-Trottier et al. 2016). This illustrates that even simple genetic circuits are capable of high precision if the effects of noise are properly handled.

Sample solutions of a stochastic system (such as in Figs. 1, 2) are generally calculated using the so-called Gillespie algorithm. Theoretical analysis is usually based on the so-called chemical master equation of the system, an ODE whose individual variables $p_I(t)$ are the probabilities of the system being in state I at time t. Since a proper introduction to these two main tools is out of the scope of this short review, we refer the reader to Section 7.6 of the book by Ingalls (2012) for an accessible primer. See also Hahl and Kremling (2016), Paulsson (2005) and Székely and Burrage (2014) for additional reviews and comments on the stochastic modeling of biochemical networks.

2 Comparing Stochastic and Deterministic Systems

Many stochastic biological systems have similar behavior to their deterministic counterparts, at least in the short term. Going back to the model of wolves and rabbits on an island, the same oscillatory dynamics found in a predator–prey Lotka–Volterra model might be found in the corresponding stochastic system with a finite number of animals. However, if the stochastic system runs for sufficiently long, a time will come where the wolves accidentally eat all the rabbits or the wolves themselves die off, at which point the stochastic system will have a starkly different qualitative behavior from the deterministic system. In this way, it is not difficult to find biologically relevant models that have very different long-term behavior when modeled stochastically.

In the case of chemical reaction networks, classical work by Kurtz (1972) showed a similar correspondence between deterministic and stochastic systems. Kurtz considered an arbitrary stochastic chemical reaction network inside a container of volume V, and he imagined V becoming increasingly larger. This leads to a scaling of both the initial species amounts and the reaction parameters. In the limit, as V converges to infinity, the rescaled system is shown to converge toward the associated deterministic network, but *only over a fixed time interval*. In this way, the short-term behavior of stochastic and deterministic systems coincides (at least under this particular scaling limit), but their long-term behavior may be quite different.

The so-called deficiency theory for chemical reaction networks offers some insights into systems that display an analogous short-term and long-term behavior when modeled deterministically or stochastically. Much of this theory is centered around reaction networks with deficiency zero and weakly reversible reactions. The deterministic ODE in any such network admits a unique and locally stable steady state on each stoichiometric compatibility class (Feinberg 1972; Horn 1972). Similarly, Anderson and colleagues showed that the stochastic counterpart of these systems admits a product form of Poisson stationary distributions centered around the deterministic steady state (Anderson et al. 2010). Intuitively, this means that individual solutions of the nondeterministic system will eventually hover around the corresponding deterministic steady state. But more recently, another family of chemical reaction networks was found to behave rather like the wolves and the rabbits on the island. Networks with so-called absolute concentration robustness in the deterministic setting were found under additional hypotheses to encounter an 'extinction event' when modeled stochastically. That is, in such systems one or more of the species die off entirely in the long term with probability one (Anderson et al. 2014). See Anderson and Cappelletti (2018) for more examples where the two types of model have different dynamical behaviors.

3 Stochastic QSSA Analysis

In this issue of the Bulletin, Kang along with collaborators KhudaBukhsh, Koeppl and Rempala continue the work initiated by Kurtz in the above section and consider the traditional enzyme–substrate network

$$S + E \underset{\kappa_{-1}}{\overset{\kappa_1}{\rightleftharpoons}} C \xrightarrow{\kappa_2} P + E. \tag{1}$$

A new system of equations is defined by scaling variables and parameters using powers of a single scaling parameter N, generalizing the Kurtz approximation. Choosing the scaling powers appropriately leads to interesting and nontrivial limiting systems. Moreover, this framework provides significant flexibility to represent desired ratios of parameters or species quantities, which is particularly appropriate to study different quasi-steady-state approximations.

For instance, choosing E_0 to be $O(1)$ and S_0 to be $O(N)$ is analogous to the standard quasi-steady-state assumption $E_0 \ll S_0$. As was the case in the Kurtz approximation, some of the parameters also need to be rescaled to preserve balance in the equations.

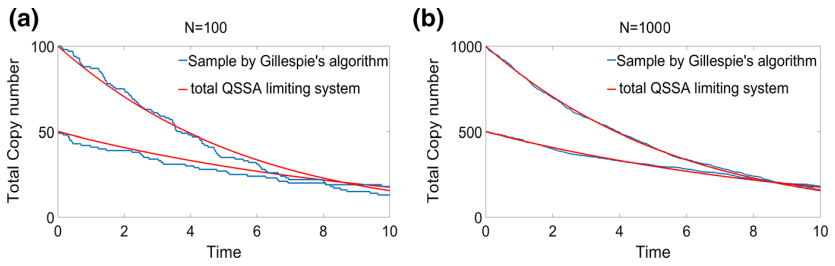

Fig. 1 Sample solutions of the enzyme–substrate stochastic model (1), pictured in blue and obtained using the Gillespie algorithm, compared with solutions of the total QSSA limiting system pictured in red. **a** Simulation with scaling parameter $N = 100$, using two different initial conditions. **b** Scaling parameter $N = 1000$. In both subfigures, the displayed curves correspond to the sum of the substrate S and the complex C (Color figure online)

Using the law of large numbers for the Poisson distribution, the limiting system is shown to be deterministic and to satisfy the standard Michaelis–Menten formula.

While the above analysis was already present in the literature for the standard QSSA, Kang et al. (2019) carry out a similar procedure with two other existing forms of QSSA, known as total QSSA and reverse QSSA, by using different assumptions on ratios between different species or parameters and implementing these ratios with the proper scaling scheme. See Fig. 1 for a comparison of the total QSSA system and its limiting solution. Kang et al. also carry out a form of QSSA with an enzyme–substrate–inhibitor model, to illustrate the same analysis in other chemical reaction systems. In every case, they show that individual runs of the stochastic model agree with the corresponding limiting system.

Notice that the scaling method replaces the standard quasi-steady-state method of setting some of the time derivatives to zero, e.g., $C' \approx 0$ in the classic approximation. Since the two methods are not identical, one might consider the systematic scaling analysis of a *deterministic* system, compared with the same scaling limit applied to the corresponding stochastic system. Indeed, a scaling analysis of the deterministic standard QSSA network was already performed by Lin and Segel (1988) and Segel and Slemrod (1989). For certain systems, the scaling limit of both the stochastic and deterministic models can be the same. Also, there are examples such as Example 4.2 in Kang et al., in which the limit system after scaling the stochastic network is still stochastic and thus necessarily different from any scaling limit of the corresponding deterministic model.

4 Stochastic Cell Polarity Model

Cell polarization is a process that precedes many spatial biological functions such as cell division or the generation of specialized shapes. The protein Cdc42 is one of the main regulators of cell polarization in various organisms, from yeast to humans (Etienne-Manneville 2004), and it has been observed in fission yeast to have periodic oscillations in addition to bistability.

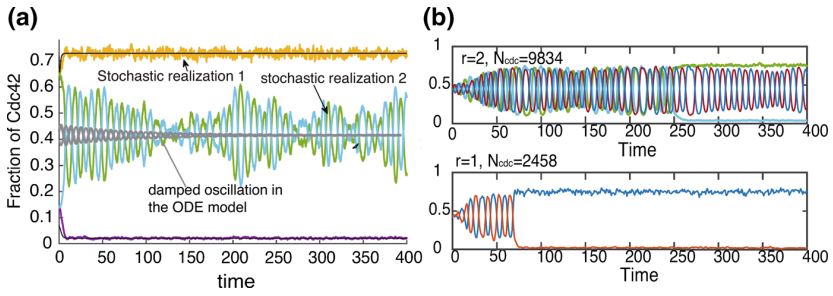

Fig. 2 Dynamics of the stochastic Cdc42 regulatory system, in parameter regimes where the deterministic system contains **a** a damped oscillation and nearby stable steady state, or **b** a limit cycle and multiple steady states. Images from Xu et al. (2019) (Color figure online)

Xu et al. (2019) carry out the computational and quantitative analysis of a stochastic model of Cdc42 under low protein copy numbers. They had previously published a deterministic model of Cdc42 oscillations in fission yeast, which they use as the basis for this analysis (Xu and Jilkine 2018). Similar to Kang et al., they also carry out a scaling process and show that in the limit the stochastic model approaches the deterministic model.

Given this limiting behavior, one would expect that for fixed parameters the stochastic and deterministic systems would present similar dynamics. However, many examples in the literature show a more complicated picture. In certain biology models with nonlinear kinetics, noise can cause bimodality in the stochastic system, even when the deterministic dynamics is monostable (Samoilov et al. 2005), and noise also can add oscillations to the deterministic dynamics by so-called stochastic resonance (Benzi et al. 1999; Gammaitoni et al. 1998) or coherence resonance (Gang et al. 1993; Pikovsky and Kurths 1997). Xu et al. (2019) study the effect of stochasticity in several parameter regimes such as when the deterministic system has (i) multiple steady states with damped oscillations (Fig. 2a), or (ii) multiple steady states and a limit cycle (Fig. 2b).

It is shown that the stochastic system in the first parameter regime is capable of irregular but persistent 'quasi-cycles,' shown in Fig. 2a, which tend to decrease in amplitude but are regularly restarted by the noise in the system. Using power spectrum analysis, they are able to find the frequency of these quasi-cycles and show that the dominant frequency is close to the frequency of oscillation at the Hopf bifurcation point of the deterministic system. The authors also consider the stochastic system in the second parameter regime where the deterministic system has a limit cycle (Fig. 2b), showing that after a transient period stochastic solutions may leave the limit cycle and converge toward a nearby stable steady state.

5 Conclusion

Stochastic systems may or may not behave like their deterministic counterparts, especially after long time periods, and we ignore stochastic effects at our own peril when

modeling cellular processes. Even when a molecule of interest is present in high copy numbers, if this molecule was produced or influenced by molecules in low copy numbers, then its dynamics may still be subject to high variability. Notice that the source of the noise here is different from that in continuous-space processes like Brownian motion or many financial models. It is not sufficient to model 'noise' into the system, but it must also represent the right source of noise.

Some of the most interesting stochastic models are the ones where the overall qualitative behavior is truly different from that of the corresponding deterministic system. Models have been developed that use noise to sharpen tissue boundaries (Wang et al. 2017), increase sensitivity of a dose response (Paulsson et al. 2000) or increase system reliability as we saw above (Potvin-Trottier et al. 2016). A basic understanding of stochastic effects can allow for better design of synthetic circuits and experimental systems. Finally, many of these applications have only recently become available due to the recent development of single-cell experimental assays and microfluidic devices, opening up new avenues for enterprising modelers in the mathematical biology community.

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