Multiscale analysis of stochastic spatial chemical reaction networks

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1 Overview of the Field

Stochastic modeling of chemical reactions of a set $\mathcal{I}$ of species by a set $\mathcal{K}$ of reactions is usually done by writing

$$\underline{\nu}_{\cdot k} \xrightarrow{\kappa'_k} \underline{\nu}'_{\cdot k} \tag{1}$$

for the kth reaction, $k \in \mathcal{K}$. Here, $\underline{\nu}_{\cdot k}$ is the vector of numbers of reacting molecules and $\underline{\nu}'_{\cdot k}$ is the vector of numbers of output molecules, and κ'_k determines the speed of the reaction. Assuming the law of mass action, this modeling results in a Markov chain $(\underline{X}(t))_{t \geq 0}$, $\underline{X}(t) = (X_i(t))_{i \in \mathcal{I}}$ with transitions by the kth reaction happening at rate proportional to

$$\binom{\underline{X}(t)}{\underline{\nu}_{\cdot k}},$$

which determines the number of possibilities of reacting molecues in the system.

In recent work, [1] and [3] have obtained scaling limits of multiscale-reaction networks, which arise in prominent examples such as Michaelis-Menten kinetics. In the simplest case of a two-scale system, there is a partition $\mathcal{I} = \mathcal{I}_f \uplus \mathcal{I}_s$ of species which evolve *fast* and *slow*ly. In addition, every reaction $k \in \mathcal{K}$ can be rate determining for every species. For example, the fast subsystem of reactions consists of all reactions which change the fast species on their time-scale.

Of high practical (e.g. biochemical) relevance are spatial systems [4, 2], where molecules are allowed to migrate between compartments. Here, when considering a multi-scale system within a compartment, involving slow and fast species, movement of molecules may introduce a new time-scale. Assuming that the system is not limited by movement, we assume that all species counts within compartments are fast variables, but their sum total is conserved by movement. Here, two cases arise: either, movement is even faster than fast reactions or it is slower. In a recent paper, we have given convergence results for spatial chemical reaction networks [5], which result in describing the sum total of the slow chemical species on the slow time-scale, which depends on both, movement and equilibria of fast reactions.

2   Recent Developments and Open Problems

Assume a *S*ubstrate is turned into a *P*roduct via an *E*nzyme and an *E*nzyme-*S*ubstrate complex. In other words, consider Michaelis-Menten kinetics in multiple compartments, as given by

$$E + S \xrightarrow{\kappa'_{1d}} ES, \qquad ES \xrightarrow{\kappa'_{-1d}} E + S, \qquad ES \xrightarrow{\kappa'_{2d}} E + P,$$
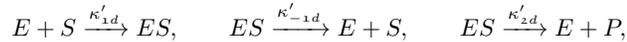
where κ_{kd} is the reaction constant of reaction $k \in \mathcal{K}$ in compartment d. (Classically, E and ES are fast species, and S and P are slow.) Let all reactions be fast for E and ES (which are in low abundance), i.e. the reaction rates are proportional to some scaling factor N. Assuming in addition that substrate, enzymes and the complex move fast between compartments, i.e. at rate N^η for some $\eta > 0$, the question is:

> Is the amount of product obtained within a given time higher for faster (i.e. $\eta > 1$) or for slower (i.e. $\eta < 1$) movement, given the reaction rates?

While this specific example can be computed efficiently, we were interested in general conditions we have to impose on the network in order to be able to determine more efficient turnover rates.

3   Scientific Progress Made

At least in some important special cases, we could give precise conditions when turnover is most efficient. Let κ_{kd} be the reaction rate of reaction $k \in \mathcal{K}$ in compartment d, π_i the equilibrium probability distribution for movement of one molecule of species i and ν_{ik} as in (1).

1. Assume a homogeneous space in the sense that reaction rates satisfy

   $$\kappa_k = \kappa_{kd} \prod_i \pi_i(d)^{\nu_{ik}}$$

   for some κ_k's. Note that the right hand side is proportional to the probability that molecules, distributed randomly according to the equilibrium movement, have the same chance to react in all compartments. Then, if the fast subsystem of chemical reactions is of first order and assuming mass action (i.e. the speed of all reactions on the fast time-scale is linear), the turnover rates are the same, no matter if movement is faster or slower than fast chemcial reactions.

2. Assume that in the one-compartment case the dynamics of the slow species reads

   $$\dot{x}_s = \varphi_0(x_s, \underline{\kappa}) + \varphi_1(x_s, \underline{\kappa}),$$

   for functions φ_0, φ_1, where at most one fast species occurs on either side of reaction equations. (If no fast species reacts, the corresponding reaction enters φ_0, and if a single species reacts, it enters φ_1.) Clearly, this implies that the subsystem of fast reactions is linear. Further, assume that all fast species move according to the same rules with equilibrium distribution π_f and $\kappa_{kd} = \kappa_k \pi_f(d)^{1-\nu_{fk}}$, i.e. the fast subsystem is homogeneous. Then we have:

   (a) If φ_1 is convex, then turnover is more efficient if movement is slower than fast reactions.
   (b) If φ_1 is concave, then turnover is more efficient if movement is faster than fast reactions.

It is most instructive to consider the example of a positive or negative feedback loop. Consider a single slow chemical species S, such that the fast species help in a superlinear increase of S, i.e. a positive feedback loop. (In essence, the more S is produced, the faster it is going to be produced in the future.) This means that the function φ_1 is convex and hence, the spatial system according to 2. is more effective if movement is slower. This is intuitive because slower movement keeps S higher in some compartments, whereas faster movement distributes S uniformly in all islands, partly negating the effect of the positive feedback. Another example arises for Michaelis-Menten kinetics – see above – where the dynamics of the substrate reads

$$\dot{x}_s \sim \frac{a x_s}{b + c x_s}$$

for constants a, b, c, i.e. the right hand side is concave in x_s. Then, according to the above, turnover is highest of movement is faster than fast reactions.

Our new insights will be turned into a manuscript which we will publish for readers in both, biology and mathematics [6].

References

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