Numerical Exploration of Stochastic Compartment Models

Carina Guo†, Olivia Guo†, Leo Shen†, Yikai Zhang†

†University of Wisconsin–Madison

Introduction

Chemical reaction networks have been studied for decades. One potential problem of chemical reaction network theory is the connection between network structure and properties of dynamics. The approach in the recent paper is a Markov model for stochastic reaction networks within interacting compartments from [1].

Chemical Reaction Networks

A Chemical Reaction Network, denoted $I = \{S, C, R\}$, is comprised of species (S), complexes (C), and reactions (R). It is modelled as a continuous-time Markov chain, so reactions are Poisson processes. To ensure realistic results, mass-action kinetics are used, which is where rates are proportional to the number of ways chemicals can combine. As an example, consider a model of gene transcription and translation: $S = G, M, P$, with complexes $C = G, G+M, M, M+P, P, \emptyset$, reactions $R = R_1, R_2, R_3, R_4$, and rate constants $K = \kappa_1, \kappa_2, d_M, d_P$. The overall stochastic reaction network is represented by $I_K = S, C, R, K$.

$$
\begin{aligned}
&R1) \quad G \xrightarrow{\kappa_1} G + M && \text{(Transcription)}\\
&R2) \quad M \xrightarrow{\kappa_2} M + P && \text{(Translation)}\\
&R3) \quad M \xrightarrow{d_M} \varnothing && \text{(Degradation of mRNA)}\\
&R4) \quad P \xrightarrow{d_P} \varnothing && \text{(Degradation of protein)}
\end{aligned}
$$

Compartment Models

We studied the models in [1], called Reaction Network Within Interacting Compartments (RNIC). These models are also treated as continuous-time Markov chains and they consist of:

- A network of compartments;
- I.i.d. chemical reaction network inside each compartment.

Compartment dynamics encompass intake, exit, coagulation, and fragmentation. Intake creates a new compartment with an initial state drawn from μ. Exit is a whole compartment disappears, coagulation when two compartments merge, and fragmentation when one compartment fragments into two new ones. The total concentration of species is preserved. This is where the difficulty lies; the dynamics have been chosen where a compartment fragments at a rate proportional to its species content. As such, the chemical reaction is kept simple and only contains one species, S.

$$
0 \underset{\kappa_d}{\overset{\kappa_b}{\rightleftarrows}} S \qquad 0 \underset{\kappa_E}{\overset{\kappa_I}{\rightleftarrows}} C \underset{\kappa_C}{\overset{\kappa_F S_C}{\rightleftarrows}} 2C \qquad \mu,
$$

More precisely, if Y_b, Y_b, Y_I, Y_E, Y_F and Y_C are unit-rate Poisson processes, the number of compartments at time t, $M_C(t)$, is given by

$$
\begin{aligned}
M_C(t) = M_C(0) + Y_I(\kappa_I t) - Y_E\left(\int_0^t \kappa_E M_C(s)\, ds\right) + Y_F\left(\int_0^t \kappa_F S(s)\, ds\right)\\
- Y_C\left(\int_0^t \frac{\kappa_C}{2}[M_C(s)(M_C(s)-1)]\, ds\right),
\end{aligned}
$$

where $S(t)$ is the concentration of species

$$
S(t) = S(0) + Y_b(\kappa_b t) - Y_d\left(\int_0^t \kappa_d S(s)\, ds\right).
$$

Simulation Results

Using a modified version of Gillespie's algorithm [2], we simulate one particular model and obtain the following results. In this case, the exact parameters are $\kappa_i = 1$ for $i \in \{B, D, I, E\}$ and $\kappa_F \in \{1.9, 2.0, 2.1\}, \kappa_C = 0$. These parameters were chosen as they fall in an area where the long term behavior of the Markov chain is unknown. The case of $\kappa_F = 1.9$ is actually known to be positive recurrent, but for $2 \leq \kappa_F \leq 3$ the system may be recurrent or transient, or some combination. The system is known to be transient if $\kappa_F > 3$.

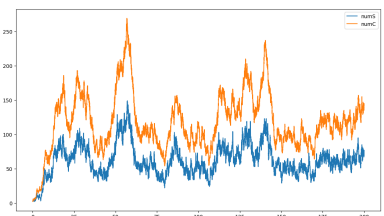

Fig. 1: The fragmentation rate $\kappa_F = 1.9$. Number of compartments at time $t = 200$ is about 130.

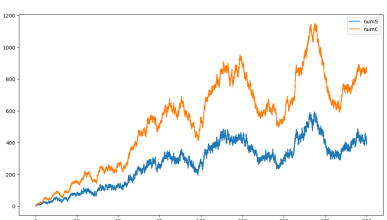

Fig. 2: The fragmentation rate $\kappa_F = 2.0$. Number of compartments at time $t = 200$ is about 800.

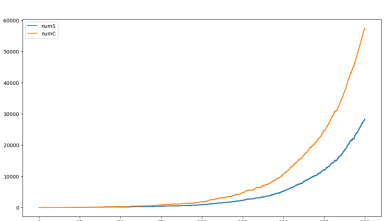

Fig. 3: The fragmentation rate $\kappa_F = 2.1$. Number of compartments at time $t = 200$ is about $58,000$.

The case of $\kappa_F = 2.1$ is highly suggestive that the system is transient. Indeed, the final number of compartments represents an over $4,000\times$ increase, and the growth is very stable. In the case of $\kappa_F = 2.0$, the growth is still substantially higher than the case of 1.9 but it is not nearly as stable as the case of 2.1.

Simulation Algorithm

Gillespie's algorithm, also known as the Gillespie stochastic simulation algorithm (SSA), is a computer simulation method used to simulate the time evolution of a chemical reaction networks. More precisely, it simulates the discrete-time Markov chain embedded in the continuous-time Markov chain. It is quite general, so extending it to compartment models is not too difficult. The algorithm combines all reactions into one single rate, and when that timer goes off, the choice of reaction is selected with probability proportional to its corresponding rate. For the sake of efficiency, compartments have been reduced down to one entry in an integer array.

$$
C = [S_0, S_1, ...], S = \sum_n^{|C|} S_n
$$

$t = 0$

Loop :

$p = (\kappa_I, \kappa_E \cdot |C|, \kappa_F \cdot S, \kappa_B |C|, \kappa_D \cdot S)$

$t = t + \text{Exp}(1/||p||_1)$

$A \leftarrow i$ with probability $\frac{p[i]}{\|p\|_1}, i \in \{0, 1, 2, 3, 4\}$

if A is birth, intake or exit, randomly select a compartment.

if A is fragment or death, select a compartment proportional to $C(S)$.

do A

record $X(t)$

Alternate Simulation Algorithm and Sensitivity

There is another way to simulate this process, and it gives the same results but it enables coupling two processes. It works by preserving the 'reaction timers' resetting them. When one goes off, the elapsed time is subtracted from all of the others.We implement the coupled processes as shown below and try to minimize the variance of difference $(X^{\theta+\epsilon}, X^{\theta})$ via

$$
\begin{aligned}
X^{\theta+\epsilon}(t) = X^{\theta+\epsilon}(0) + \sum_k Y_{k,1}\left(\int_0^t \lambda_k^{\theta+\epsilon}(X^{\theta+\epsilon}(s)) \wedge \lambda_k^{\theta}(X^{\theta}(s))ds\right)\xi_k\\
+ \sum_k Y_{k,2}\left(\int_0^t \left(\lambda_k^{\theta+\epsilon}(X^{\theta+\epsilon}(s)) - \lambda_k^{\theta}(X^{\theta+\epsilon}(s))\right) \wedge \lambda_k^{\theta}(X^{\theta}(s))ds\right)\xi_k,\\
X^{\theta}(t) = X^{\theta}(0) + \sum_k Y_{k,1}\left(\int_0^t \lambda_k^{\theta+\epsilon}(X^{\theta+\epsilon}(s)) \wedge \lambda_k^{\theta}(X^{\theta}(s))ds\right)\xi_k\\
+ \sum_k Y_{k,3}\left(\int_0^t \left(\lambda_k^{\theta}(X^{\theta+\epsilon}(s)) - \lambda_k^{\theta}(X^{\theta}(s))\right) \wedge \lambda_k^{\theta}(X^{\theta}(s))ds\right)\xi_k,
\end{aligned}
$$

where the $Y_{k,i}$ are the unit-rate Poisson processes

References

[1] Lorenzo Duso and Christoph Zechner. "Stochastic reaction networks in dynamic compartment populations". In: *Proceedings of the National Academy of Sciences* 117.37 (2020), pp. 22674–22683. ISSN: 0027-8424. DOI: 10.1073/pnas.2003734117. eprint: https://www.pnas.org/content/117/37/22674.full.pdf. URL: https://www.pnas.org/content/117/37/22674.

[2] Daniel T. Gillespie. "Exact Stochastic Simulation of Coupled Chemical Reactions". In: *J. Phys. Chem.* 81.25 (1977), pp. 2340–2361.