# Numerical Exploration of Stochastic Compartment Models

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## 1 Introduction

Chemical reaction networks have been studied for decades. One potential problem of chemical reaction network theory is the connection between network structure and dynamics properties. The approach in the recent paper is a Markov model for stochastic reaction networks within interacting compartments. There are a number of interesting questions pertaining to this model that remain unanswered and that we hope to resolve with this project.
In this project, we will focus on developing code that generates realizations of a particular model and using the simulations to make (and possibly resolve) conjectures about the behavior of this particular model.

## 2 Chemical Reaction Networks

A Chemical Reaction Network, denoted $I = \{S, C, R\}$, is comprised of species ($S$), complexes ($C$), and reactions ($R$). It is modeled 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 $I_K = S, C, R, K$.

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

## 3 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 $\mu$. 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, $S$.

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

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

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

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

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

## 4 Simulation Result

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 $\kappa_F > 3$.

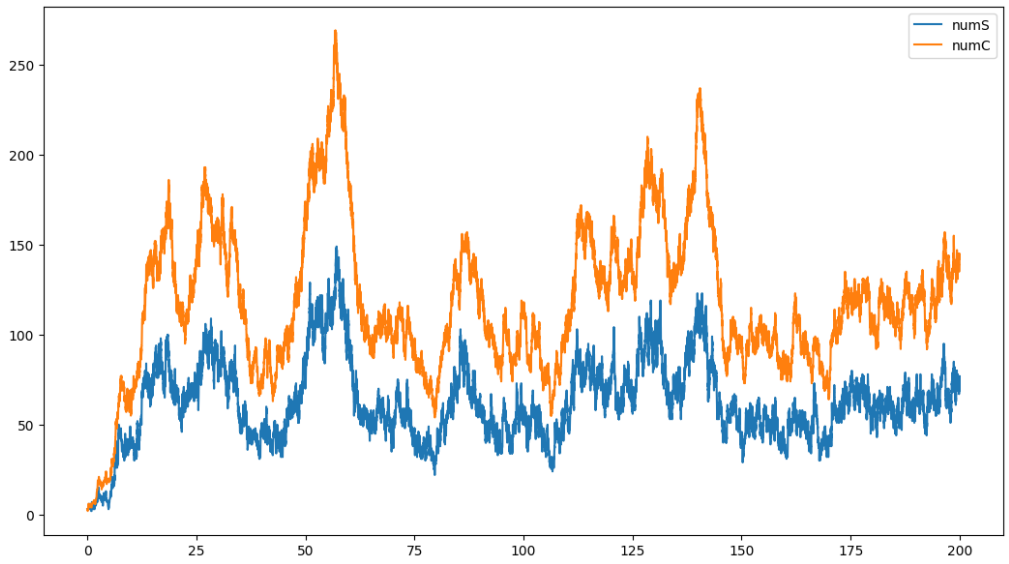


Figure 1: The fragmentation rate $\kappa_F = 1.9$. Number of compartments at time $t = 200$ is about 130.

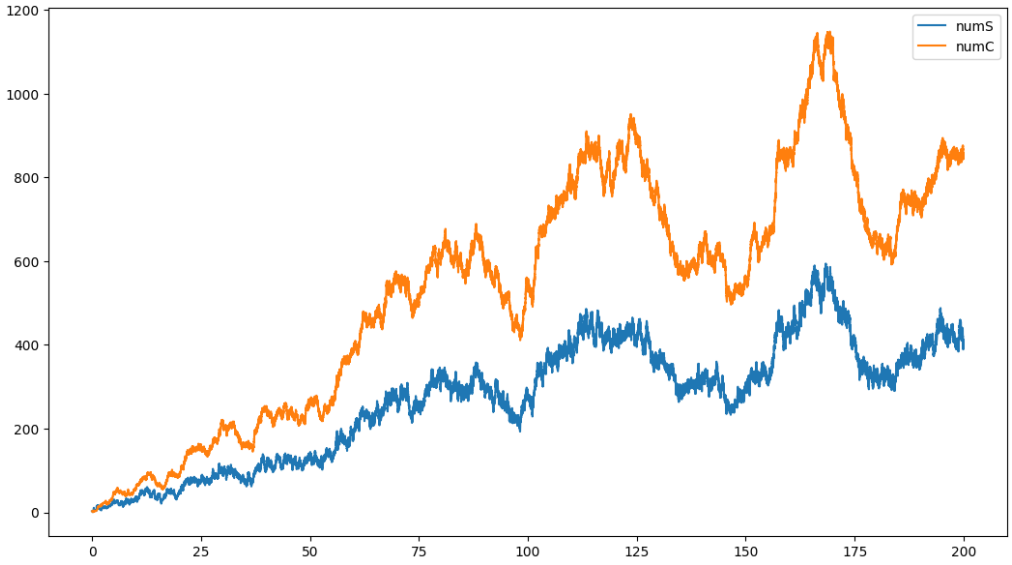


Figure 2: The fragmentation rate $\kappa_F = 2.0$. Number of compartments at time $t = 200$ is about 800.

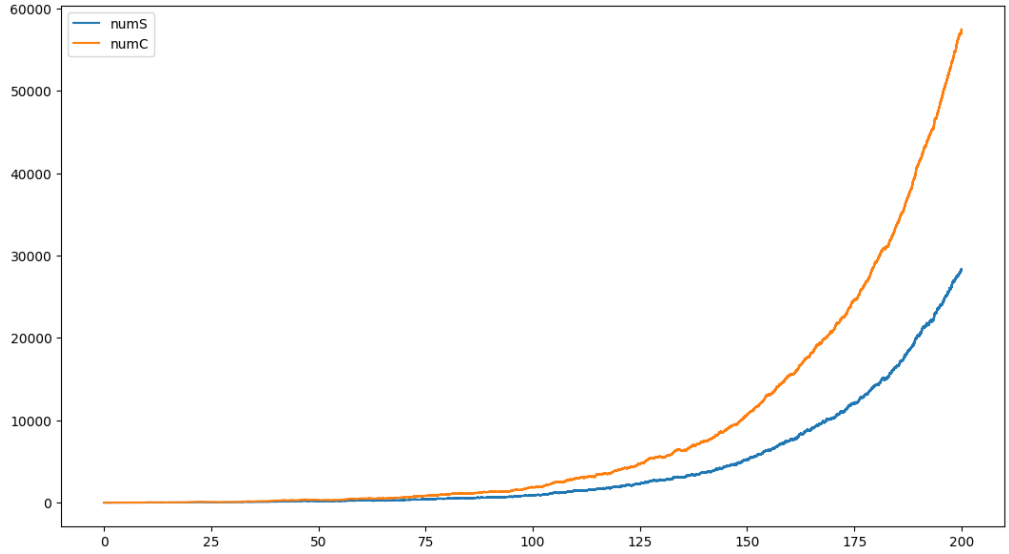


Figure 3: The fragmentation rate $\kappa_F = 2.1$. The number of compartments at time $t = 200$ is about $58,000$.

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.

## 5 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. This particular version of the algorithm seems customized for scenarios like population dynamics or complex chemical reactions with multiple states or compartments. 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 $X(t)$

Initially, the system is defined by compartments $C = [S_0, S_1, \ldots]$, with $S$ representing the total count across these compartments, and time $t$ set to zero. The core of the algorithm is a loop where events are stochastically simulated over time. At each iteration, a propensity vector $p = (\kappa_I, \kappa_E \cdot |C|, \kappa_F \cdot S, \kappa_B \cdot |C|, \kappa_D \cdot S)$ is computed, representing the probabilities of various events, influenced by rate constants $\kappa$ and the system's current state. The algorithm then advances time by an increment drawn from an exponential distribution with a rate determined by the 1-norm of $p$, effectively simulating the waiting time for the next event. An event $A$ is subsequently selected and executed based on the calculated propensities, with the method of compartment selection contingent on the event type (random or proportional to compartment characteristics). Finally, the system's state $X(t)$ is recorded at the updated time, capturing the evolution of the system's dynamics. This modified Gillespie algorithm is particularly adept at simulating systems where traditional deterministic approaches fail to capture the inherent stochasticity, offering a robust tool for understanding complex, discrete-event systems.

## 6 Alternate Simulation Algorithm

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

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

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

## 7 Summary and Future Direction

In this project, we have developed code that generates realizations of the compartment model and utilized the version of Gillespie's algorithm to simulate and make conjectures about the behavior of this particular model. We also attempted to work on the parametric sensitivity analysis. We tried to minimize the variance of state on time $t$ by implementing the coupled processes. However, we got different results on our coupling process and also differed in the variance of $X$.

Our future direction is about estimating derivatives. For some given compartment model, it has an expected number of compartments at some time $t_0 > 0$. We may want to see how increasing the fragmentation rate increases the expected number of compartments. That is, we wish to estimate

$$\frac{d}{d\theta}\mathbb{E}[X^{\theta}(t_0)]\Big|_{\theta=2}$$

where $X$ is described by, for example,

$$0 \underset{\kappa_d}{\overset{\kappa_b}{\rightleftarrows}} S \qquad\qquad 0 \underset{\kappa_E}{\overset{\kappa_I}{\rightleftarrows}} C \underset{\kappa_C}{\overset{\theta}{\rightleftarrows}} 2C \qquad\qquad \mu.$$

## 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.