MATH 466/564: APPLIED RANDOM PROCESSES CLASS REPORT

Stochastic Chemical Reaction Networks

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1 Introduction

Chemical reaction network (CRN) theory is a disciplinary area between mathematics and systems biology. The main goal for this area is to know the properties of dynamical system only from its network structure alone.

Starting from the toy example, let's think about the following chemical reaction

$$2H_2 + O_2 \to 2H_2O$$

Here, $H_2,\ O_2,\ H_2O$ are molecules, which is the basic unit for biochemical interactions. In CRN, we call them **species**. So, the above chemical reaction can be written as

$$2A + B \to 2C$$

And when we think the reaction as a directed edge, what corresponds to the vertex is called a **complex**. So generally speaking, CRN is described with three sets : **species** $\mathscr{S}$, **complexes** $\mathscr{C}$, and **reactions** $\mathscr{R}$ where

- $\mathscr{S}$: Chemical species (i.e. molecules)
- $\mathscr{C}$: Non-negative linear combination of species that reactions interact (reactant and products)
- $\mathscr{R}$: Reactions that one complex is converted to another.

For example, if we think about the following set of reactions,

$$A + B \to 2B \tag{1}$$
$$B \to A \tag{2}$$
$$2B \to A + B \tag{3}$$

Then the sets are

$$\mathscr{S} = \{A,\ B\}$$
$$\mathscr{C} = \{A + B,\ 2B,\ B,\ A\}$$
$$\mathscr{R} = \{A + B \to 2B,\ B \to A,\ 2B \to A + B\}$$

And when we graphically describe this reactions, we do not make one complex to appear several times. i.e., it can be graphically described as

$$A + B \leftrightharpoons 2B$$
$$B \to A$$

2 Formulation of continuous-time Markov chain

There are two ways to model biochemical reaction - one by ODE which describes the concentration, and other one by continuous-time Markov chain which described the number of molecules. In this report, we will focus on continuous-time Markov chain.

When we look at the reaction, there are two things we could ask.

- How does this reaction changes the state?
- How fast does the reaction fires?

For the first question, the state space I becomes

$$I = \mathbb{Z}_{\geqslant 0}^{|\mathscr{S}|}$$

and each reaction has a **stoichiometric vector**, which is

$$c_1X_1 + c_2X_2 + \cdots + c_mX_m \to c_1'X_1 + c_2'X_2 + \cdots + c_m'X_m \quad : \quad (c_1' - c_1,\ \cdots\ , c_m' - c_m)^T$$

For the example (1),

$$\begin{aligned} I &= \mathbb{Z}_{\geqslant 0}^2 \\ A + B \to 2B &\ :\ (-1,\ 1)^T \\ B \to A &\ :\ (1,\ -1)^T \\ 2B \to A + B &\ :\ (1,\ -1)^T \end{aligned}$$

For the second question, the most general (but not the only) choice is the **mass-action kinetics**, which defines the reaction rate as

$$\begin{aligned} c_1X_1 + c_2X_2 + \cdots + c_mX_m \to \cdots \quad : \quad & kn_1(n_1-1)\cdots(n_1-c_1+1)\cdots n_m(n_m-1)\cdots(n_m-c_m+1) \\ & = k\frac{n_1!}{(n_1-c_1)!}\frac{n_2!}{(n_2-c_2)!}\cdots\frac{n_m!}{(n_m-c_m)!} \end{aligned}$$

where n_i denotes the number of X_i. We can notice that if n_i is less than c_i, then the reaction rate becomes zero, which means that the reaction does not fires.

By these description, we can construct a continuous-time Markov chain. For example, when we think the following reaction network

$$0 \xrightarrow{k_1} A \tag{4}$$

$$0 \xrightarrow{k_2} B \tag{5}$$

$$A \xrightarrow{k_3} B \tag{6}$$

$$B \xrightarrow{k_4} 0 \tag{7}$$

$$A + B \xrightarrow{k_5} 2C \tag{8}$$

$$2C \xrightarrow{k_6} A + B \tag{9}$$

then the state space becomes

$$I = \{(a, b, c) \mid a, b, c \in \mathbb{Z}_{\geqslant 0}\} = \mathbb{Z}^3_{\geqslant 0}$$

and the Q-matrix becomes

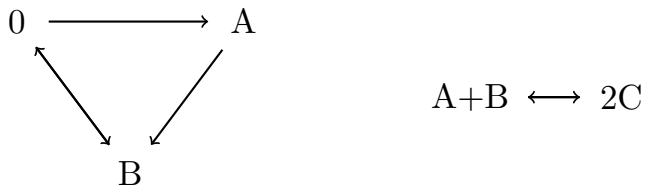
$$Q_{(a_1,b_1,c_1),(a_2,b_2,c_2)} = \begin{cases} k_1 & \text{if } a_2 = a_1 + 1,\ b_2 = b_1,\ c_2 = c_1 \\ k_2 & \text{if } b_2 = b_1 + 1,\ a_2 = a_1,\ c_2 = c_1 \\ k_3 a_1 & \text{if } a_2 = a_1 - 1,\ b_2 = b_1 + 1,\ c_2 = c_1 \\ k_4 b_1 & \text{if } a_2 = a_1,\ b_2 = b_1 - 1,\ c_2 = c_1 \\ k_5 a_1 b_1 & \text{if } a_2 = a_1 - 1,\ b_2 = b_1 - 1,\ c_2 = c_1 + 2 \\ k_6 c_1(c_1 - 1) & \text{if } a_2 = a_1 + 1,\ b_2 = b_1 + 1,\ c_2 = c_1 - 2 \\ -(k_1 + k_2 + k_3 a_1 + k_4 b_1 & \text{if } a_2 = a_1, \\ \quad + k_5 a_1 b_1 + k_6 c_1(c_1 - 1)) & \quad b_2 = b_1,\ c_2 = c_1 \\ 0 & \text{otherwise} \end{cases}$$

In terms of biology, it is important for such continuous-time Markov chain to be positive recurrent and having a convergent stationary distribution. We could easily imagine that if some biochemical reaction networks in our body is either transient or null recurrent, then the number of some chemical species will blow up, which will cause serious problems in our body.

3 Deficiency zero theorem

Definition 1. *Suppose that we represent the CRN by the way that no complexes appear twice. We say the CRN is* ***weakly reversible*** *when we pick any two complex c_1, c_2 such that there exists reaction $c_1 \to c_2$, then there always exists the path from c_2 to c_1 connected by some reactions.*

For example, we can represent the CRN from the previous example (4) as the following



Then, we can check that this CRN is weakly reversible. For example, there is a reaction $0 \to A$, then there is a path of reactions $A \to B \to 0$.

Definition 2. *The* ***stiochiometry space*** *S is the vector space spanned by the stoichiometric vectors.*

Definition 3. *The* ***deficiency*** *δ of the CRN is defined as*

$$\delta = n - \ell - s$$

where n is the number of complexes, ℓ is the number of linkage class, and $s = dim(S)$

For example, when we calculate the deficiency of the previous example (4),

- $n = 5$
- $\ell = 2$
- $s = dim(span\{(1,0,0),(0,1,0),(0,-1,0),(-1,1,0),(-1,-1,2),(1,1,-2)\}) = 3$

therefore $\delta = 0$.

Theorem 1. *[1] Suppose that the CRN has deficiency zero and weakly reversible. Then the corresponding continuous-time Markov chain is positive recurrent and has a stationary distribution consisting of the product of Poisson distributions,*

$$\pi(x) = \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \quad x \in \mathbb{Z}_{\geqslant 0}^m \tag{10}$$

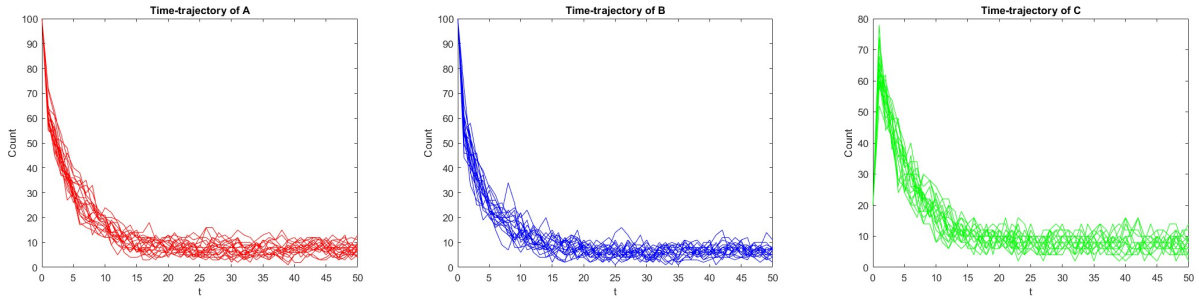
Also, if $\mathbb{Z}_{\geqslant 0}^m$ is irreducible, then this is the unique stationary distribution. If $\mathbb{Z}_{\geqslant 0}^m$ is not irreducible, then the stationary distribution has the form on the state space Γ

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \quad x \in \Gamma \tag{11}$$

where $\pi_\Gamma(x) = 0$ if $x \notin \Gamma$, and M_Γ is the normalizing constant.

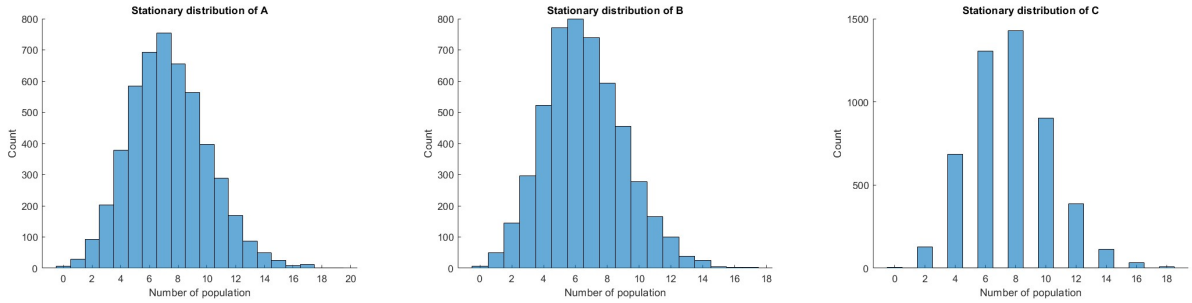
By applying this theorem, we can know that the CRN (4) is positive recurrent and the probability distribution converges to its stationary distribution, which is the product-form of Poisson distributions (Notice that $\mathbb{Z}_{\geqslant 0}^m$ is not irreducible since the number of C always changes by two units, therefore the distribution Fig. 2c is not exactly Poisson distribution). The proof of this theorem needs large amount of background knowledge, so we omit here.

Performing the numerical simulation of the previous example (4) (by the Gillespie's algorithm [2]) shows the following trajectory and stationary distributions, which coincides with the theorem.



(a) Species A (b) Species B (c) Species C

Figure 1: Time-trajectory of 20 simulations of (4)



(a) Species A (b) Species B (c) Species C

Figure 2: Stationary distribution of 5000 simulations of (4)

4 Conclusion

In this report, we have a slight overview about stochastic chemical reaction network, which shows how the continuous-time Markov chain can be applied to systems biology. The importance of stochastic CRN increases as the synthetic biology is developed, so that we could construct any biochemical reaction we want. For instance, one of the previous research suggested the structure of biochemical reactions to obtain some property in continuous-time Markov chains, and showed by experiment that the property can be really satisfied in real biological systems [3, 4]. It would be interesting to explore other properties of CRN and realize it by synthetic biology.

References

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