Lecture 21 Application in chemical reaction kinetics [*]

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1 Setup for chemical reaction kinetics

Consider a well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M reaction channels $\{R_1, R_2, \ldots, R_M\}$. The following quantities are used to characterize the whole reaction dynamics.

1. State of the system:
$$\boldsymbol{X}_t = (X_t^1, X_t^2, \ldots, X_t^N). \tag{1}$$

2. Each reaction channel R_j is characterized by ites propensity function $a_j(x)$ and its state change vector
$$\boldsymbol{\nu}_j = (\nu_j^1, \nu_j^2, \ldots, \nu_j^N), \tag{2}$$
where $a_j(\boldsymbol{x}) \geq 0$ for physical states. Here $a_j(\boldsymbol{x})dt$ gives the probability that the system will experience an R_j reaction in the next infinitesimal time dt when the current state $\boldsymbol{X}_t = \boldsymbol{x}$. ν_j^i is the change in the number of S_i molecules caused by one R_j reaction.

Usually we define $a_0(\boldsymbol{x}) = \sum_{j=1}^{M} a_j(\boldsymbol{x})$. The chemical master equation for the system is

$$\partial_t P(\boldsymbol{x}, t | \boldsymbol{x}_0, t_0) = \sum_{j=1}^{M} a_j(\boldsymbol{x} - \boldsymbol{\nu}_j) P(\boldsymbol{x} - \boldsymbol{\nu}_j, t | \boldsymbol{x}_0, t_0) - \sum_{j=1}^{M} a_j(\boldsymbol{x}) P(\boldsymbol{x}, t | \boldsymbol{x}_0, t_0). \tag{3}$$

It can be easily obtained through

$$P(\boldsymbol{x}, t + dt | \boldsymbol{x}_0, t_0) = \sum_{j=1}^{M} P(\boldsymbol{x} - \boldsymbol{\nu}_j, t | \boldsymbol{x}_0, t_0) a_j(\boldsymbol{x} - \boldsymbol{\nu}_j) dt + (1 - \sum_{j=1}^{M} a_j(\boldsymbol{x}) dt) P(\boldsymbol{x}, t | \boldsymbol{x}_0, t_0)$$

with suitable manipulation.

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2 Stochastic simulation algorithm (SSA)

The classical simulation algorithm for chemical reaction kinetics is called SSA, which is proposed by Gillespie [2] in 1970's. It is essentially the same as the kinetic Monte Carlo (KMC) algorithm.

- Step 1: Sampling the waiting time τ as an exponentially distributed random variable (R.V.) with rate $a_0(\boldsymbol{X}_t)$;

- Step 2: Sampling an M point R.V. k with probability $\frac{a_j(\boldsymbol{X}_t)}{a_0(\boldsymbol{X}_t)}$ for the j-th reaction;

- Step 3: Update $\boldsymbol{X}_{t+\tau} = \boldsymbol{X}_t + \boldsymbol{\nu}_k$, then return to Step 1.

But there are shortcomings of SSA:

- When population of molecules is very large, the reactions fire very frequently, which is quite time-consuming.

- When the reaction rate is very large for a reversible reaction

$$S_1 \longrightarrow S_2 \quad \text{with rate } C_1 \tag{4}$$

$$S_2 \longrightarrow S_1 \quad \text{with rate } C_2 \tag{5}$$

The simulation will go back and forth, but the net effect is small.

The philosophy is to accelerate at the cost of accuracy.

3 Tau-leaping algorithm

3.1 Tau-leaping algorithm

Gillespie proposed the following condition for accelerating the simulation:

> "*Leap Condition*: Require the leap time τ to be small enough that the change in the state during $[t, t+\tau)$ will be so slight that no propensity function will suffer an appreciable (i.e., macroscopically noninfinitesimal) change in its value."

This means that we set $a_j(\boldsymbol{X}_t)$ fixed, and leap with time stepsize δt. Then the number of j-th reaction will be $\mathcal{P}(a_j(\boldsymbol{X}_t)\delta t$, which is a Poisson random variable with distribution $\lambda^k/k! \exp(-\lambda)$. Here $\lambda = a_j(X_t)\delta t$. So we have the tau-leaping scheme

$$\boldsymbol{X}_{t+\delta t} = \boldsymbol{X}_t + \sum_{j=1}^{M} \boldsymbol{\nu}_j \mathcal{P}(a_j(\boldsymbol{X}_t)\delta t) \tag{6}$$

The procedure for selecting tau (time stepsize) is as follows. Note that the state after τ-leaping is

$$\boldsymbol{X} \to \boldsymbol{X} + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\boldsymbol{X})\tau := \boldsymbol{X} + \tau\boldsymbol{\xi}.$$

Then the leap condition will be

$$|a_j(\boldsymbol{X} + \tau\boldsymbol{\xi}) - a_j(\boldsymbol{X})| \le \epsilon a_0(\boldsymbol{X}),$$

where $0 < \epsilon < 1$ is a specified value. The Taylor expansion of the LHS gives $\tau|\boldsymbol{\xi} \cdot \nabla a_j| \le \epsilon a_0(\boldsymbol{X})$, which gives one stepsize selection strategy

$$\tau \approx \min_{j=1,\dots,M} \left\{ \frac{\epsilon a_0(\boldsymbol{X})}{|\boldsymbol{\xi} \cdot \nabla a_j|} \right\}.$$

Many more robust stepsize selection strategies are also proposed.

Remark 1. *The total propensity is $a_0(\boldsymbol{X})$. So the expected waiting time for one reaction fires is $\mathcal{O}(1/a_0(\boldsymbol{X}))$. If*

$$\tau \le m/a_0(\boldsymbol{X}), \quad m \sim \mathcal{O}(1)$$

One will use SSA instead.

Remark 2. *Compare with the forward Euler step $x_{n+1} = x_n + f(x_n)\delta t$ for ODE*

$$\dot{x} = f(x).$$

We actually fix $f(x)$ as a constant $f(x_n)$ in $[t_n, t_{n+1})$ with a similar idea. One will find more connections along this direction.

3.2   Multi-scale picture

The multi-scale picture from tau-leaping is charming.

- From tau-leaping to Chemical Langevin Equation:

  When $a_j(\boldsymbol{X}_t)\tau \gg 1$, $P(a_j(\boldsymbol{X}_t)\tau) \approx N(a_j(\boldsymbol{X}_t)\tau, a_j(\boldsymbol{X}_t)\tau)$ by Central Limit Theorem

  $$\boldsymbol{X}_{t+\tau} \approx \boldsymbol{X}_t + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\boldsymbol{X}_t)\tau + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\boldsymbol{X}_t)\tau} N(0,1)$$

  which corresponds to CLE

  $$d\boldsymbol{X}_t = \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\boldsymbol{X}_t)dt + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\boldsymbol{X}_t)}d\boldsymbol{W}_t$$

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- From Chemical Langevin Equation to Reaction Rate Equation:

  When $a_j(\boldsymbol{X}_t)\tau \to +\infty$, $N(a_j(\boldsymbol{X}_t)\tau, a_j(\boldsymbol{X}_t)\tau) \approx a_j(\boldsymbol{X}_t)\tau$ by Law of Large Numbers

  $$\boldsymbol{X}_{t+\tau} \approx \boldsymbol{X}_t + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\boldsymbol{X}_t)\tau$$

  which corresponds to RRE

  $$\frac{d\boldsymbol{X}_t}{dt} = \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\boldsymbol{X}_t)$$

  Tau-leaping bridges all of the equations in different scales with a seamless way!

  The comparison with fluid mechanics (upscaling) will be instructive.

$$
\begin{array}{ccc}
\text{SSA} & \longrightarrow & \text{Molecular dynamics} \\
\downarrow & & \downarrow \\
\text{CLE} & \longrightarrow & \text{Kinetic theory} \\
\downarrow & & \downarrow \\
\text{RRE} & \longrightarrow & \text{Continuum mechanics}
\end{array}
$$
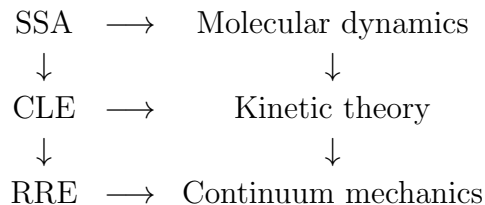
3.3 Avoiding negative populations

Because of unboundedness of Poisson R.V., negative populations may appear. One choice to avoid N.P. is by binomial tau-leaping. Note that Poisson distribution may be viewed as a limit of binomial distribution $B(n,p)$ when $n \to \infty$ with $\lambda = np$ fixed. That is

$$B(k; n, p) = C_n^k p^k (1-p)^{n-k} \to \mathcal{P}(\lambda).$$

Algorithm 1 (Binomial tau-leaping [5]). *Avoiding negative populations.*

- *Step 1: At time t, set $\tilde{\boldsymbol{X}} = \boldsymbol{X}_t$, select τ;*

- *Step 2: Sequentially for $j = 1, 2, \ldots, M$ do:*

  - *Find $k_{\max}^{(j)} \sim$ Maximal admissible number of j-th reactions according to $\tilde{\boldsymbol{X}}$;*
  - *Define $p = a_j\tau/k_{\max}^{(j)}$;*
  - *Sample binomial distribution R.V. $k_j \sim B(k_{\max}^{(j)}, p)$;*
  - *Firing j-th reaction k_j times:*

  $$\tilde{\boldsymbol{X}} + \boldsymbol{\nu}_j k_j \to \tilde{\boldsymbol{X}}$$

- *Step 3: The iteration is repeated until the final time T is achieved.*

A simple analysis of binomial tau-leaping as follows. Note that the number of j-th reactions:

$$\text{Poisson}: \quad a_j\tau \pm \sqrt{a_j\tau}$$

$$\text{Binomial}: \quad a_j\tau \pm \sqrt{a_j\tau}\left(1 - a_j\tau/k_{\max}^{(j)}\right)^{\frac{1}{2}}$$

in the law of rare events limit ($a_j\tau \ll k_{\max}^{(j)}$), they give same result; in the finite size case, the noise is different!

3.4 Stiff system

Chemical reactions are usually stiff.

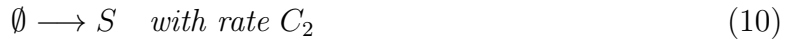**Example 1** (Reversible reaction). *Consider the reversible reaction system*

$$S_1 \longrightarrow S_2 \quad \text{with rate } C_1 \tag{7}$$

$$S_2 \longrightarrow S_1 \quad \text{with rate } C_2 \tag{8}$$

when C_1 and C_2 are both large.

Define $C_1 + C_2 = \lambda$, $X_t^1 + X_t^2 = X^T$ (total number). Here $\lambda \gg 1$. Then we have

$$\mathbb{E}X_t^1 = \frac{C_2 X^T}{\lambda}(1 - e^{-\lambda t}) + e^{-\lambda t}X_0^1$$

$$\mathbb{E}X_t^2 = \frac{C_1 X^T}{\lambda}(1 - e^{-\lambda t}) + e^{-\lambda t}X_0^2$$

The trajectory of $\boldsymbol{X}_t$ is sketched as follows.

Example 2 (Fast decaying). *Consider the following system*

$$S \longrightarrow \emptyset \quad \text{with rate } C_1 \tag{9}$$

$$\emptyset \longrightarrow S \quad \text{with rate } C_2 \tag{10}$$

when $C_1 - C_2$ is large.

Define $\lambda = C_1 - C_2$, we have $\mathbb{E}X_t = e^{-\lambda t}X_0$. The trajectory of X_t is sketched as follows.

Now we perform some analysis for the stiff reversible reaction system. Suppose the explicit tau-leaping is applied.

$$\begin{cases} X_{n+1}^1 = X_n^1 - \mathcal{P}(C_1 X_n^1 \delta t) + \mathcal{P}(C_2 X_n^2 \delta t) \\ X_{n+1}^2 = X_n^2 - \mathcal{P}(C_2 X_n^2 \delta t) + \mathcal{P}(C_1 X_n^1 \delta t) \end{cases}$$

We have $X_n^1 + X_n^2 = X^T = Const.$. So we have

$$X_{n+1}^1 = X_n^1 - \mathcal{P}(C_1 X_n^1 \delta t) + \mathcal{P}(C_2(X^T - X_n^1)\delta t).$$

Taking expectation we obtain

$$\mathbb{E}X_{n+1}^1 = (1 - \lambda\delta t)\mathbb{E}X_n^1 + C_2 X^T \delta t.$$

The stability condition is

$$|1 - \lambda\delta t| \le 1 \Longrightarrow \delta t \le \frac{2}{\lambda}.$$

When $\lambda \gg 1$, we have $\delta t \ll 1$. That is the stiffness! As $n \to \infty$, we have

$$\mathbb{E}X_n^1 \to \frac{C_2}{\lambda}X^T,$$

which is the correct limit state.

Now consider the variance. At first we have

$$\mathrm{Var}(Y) = \mathbb{E}(\mathrm{Var}(Y|X)) + \mathrm{Var}(\mathbb{E}(Y|X)).$$

Then

$$
\begin{aligned}
\mathrm{Var}(X_{n+1}^1) &= C_1\delta t\mathbb{E}X_n^1 + C_2\delta t\mathbb{E}(X^T - X_n^1) + \mathrm{Var}\left(X_n^1 - C_1 X_n^1 \delta t + C_2(X^T - X_n^1)\delta t\right) \\
&= (1 - \lambda\delta t)^2\mathrm{Var}(X_n^1) + (C_1 - C_2)\delta t\mathbb{E}X_n^1 + C_2\delta t X^T.
\end{aligned}
$$

As $n \to \infty$, we have

$$\mathrm{Var}(X_n^1) \to \frac{2}{2 - \lambda\delta t}\frac{C_1 C_2 X^T}{(C_1 + C_2)^2} = \frac{2}{2 - \lambda\delta t}\mathrm{Var}(X_\infty^1) \ge \mathrm{Var}(X_\infty^1).$$

In order to get the right variance, we need $\lambda\delta t \to 0$. Since $\lambda \gg 1$, we need $\delta t \to 0$, which is a strict constraint.

Strategy: Implicit method to overcome stiffness.

The first choice is

$$X_{n+1}^1 = X_n^1 - \mathcal{P}(C_1 X_{n+1}^1 \delta t) + \mathcal{P}(C_2(X^T - X_{n+1}^1)\delta t).$$

But the problem is how to sample $\mathcal{P}(C_1 X_{n+1}^1 \delta t)$. If we apply the iteration

$$X_{n+1}^{1,k+1} = X_n^1 - \mathcal{P}(C_1 X_{n+1}^{1,k}\delta t) + \mathcal{P}(C_2(X^T - X_{n+1}^{1,k})\delta t),$$

there will be no fixed point because of randomness.

The second choice is semi-implicit method as

$$
\begin{aligned}
X_{n+1}^1 &= X_n^1 - C_1 X_{n+1}^1 \delta t + C_2(X^T - X_{n+1}^1)\delta t \\
&\quad - \left[\mathcal{P}(C_1 X_n^1\delta t) - C_1 X_n^1\delta t\right] + \left[\mathcal{P}(C_2(X^T - X_n^1)\delta t) - C_2(X^T - X_n^1)\delta t\right].
\end{aligned}
$$

Similar analysis as before shows the stability condition

$$\left|\frac{1}{1 + \lambda t}\right| \le 1.$$

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So the stiffness is resolved! But the variance

$$\text{Var}(X_n^1) \to \frac{2}{2 + \lambda \delta t} \text{Var}(X_\infty^1) \le \text{Var}(X_\infty^1).$$

because of the damping effect of implicit method. Trapezoidal method is a good choice for linear problem. But the story goes on for nonlinear stiff problem!

3.5 Mathematical analysis

Consider the jump process with state dependent intensity:

$$d\boldsymbol{X}_t = \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(a; \boldsymbol{X}_{t-}) \lambda(dt \times da). \tag{11}$$

Here

$$c_j(a; \boldsymbol{X}_t) = \begin{cases} 1, & \text{if } a \in (h_{j-1}(\boldsymbol{X}_t), h_j(\boldsymbol{X}_t)], \\ 0, & \text{otherwise.} \end{cases} \quad j = 1, 2, \ldots, M, \tag{12}$$

and $A = \max_{\boldsymbol{X}_t} a_0(\boldsymbol{X}_t)$. $\lambda(dt \times da)$ is the reference Poisson random measure associated with a Poisson point process $(q_t, t \ge 0)$ taking values in $(0, A]$. That is,

$$\int_0^t \int_{\mathcal{B}} \lambda(dt \times da) = \#\{0 \le s < t; q_s \in \mathcal{B}\}, \tag{13}$$

where $\mathcal{B}$ is a Borel set in $(0, A]$. And we assume $\lambda(dt \times da)$ has Lebesgue intensity measure $m(dt \times da) = dt \times da$.

Based on this form, we can prove explicit tau-leaping is of strong order $1/2$, weak order 1 under suitable assumptions [6].

3.6 Stationary distribution

The chemical master equation (FPE) is (3) as before. Denote it as $\partial_t P = \mathcal{L}P$. Here $\mathcal{L}$ is the adjoint operator of the infinitesimal generator

$$\begin{aligned} \mathcal{L}^* u &= \sum_{j=1}^{M} a_j(\boldsymbol{x}) u(\boldsymbol{x} + \boldsymbol{\nu}_j, t) - \sum_{j=1}^{M} a_j(\boldsymbol{x}) u(\boldsymbol{x}, t) \\ &= \sum_{j=1}^{M} a_j(\boldsymbol{x}) \Big(u(\boldsymbol{x} + \boldsymbol{\nu}_j, t) - u(\boldsymbol{x}, t) \Big). \end{aligned}$$

For the stationary solution, we ask

$$\mathcal{L}P = 0.$$

For reversible reaction, we only consider the equation for x since $x + y = x^T$ ($\nu_1 = -1, \nu_2 = 1$):

$$\Big(C_1(x+1)p(x+1) - C_1xp(x)\Big) + \Big(C_2(x^T - x + 1)p(x-1) - C_2(x^T - x)p(x)\Big) = 0.$$

Define $a_2(x) = C_2(x^T - x), a_1(x) = C_1x, (0 \le x \le x^T)$, we have

$$\Big(a_1(x+1)p(x+1) - a_2(x)p(x)\Big) - \Big(a_1(x)p(x) - a_2(x-1)p(x-1)\Big) = 0.$$

If $x = 0$, $a_1(x)p(x) - a_2(x-1)p(x-1) = a(0)p(0) = 0$, we have the detailed balance $a_1(x)p(x) = a_2(x-1)p(x-1)$, so

$$\frac{p(x)}{p(x-1)} = \frac{a_2(x-1)}{a_1(x)} \implies \frac{p(x)}{p(0)} = \frac{a_2(x-1)}{a_1(x)} \frac{a_2(x-2)}{a_1(x-1)} \cdots \frac{a_2(0)}{a_1(1)}$$

We obtain the stationary distribution

$$\begin{aligned} p(x) &= p(0)\Big(\frac{C_2}{C_1}\Big)^x \frac{x^T!}{x!(x^T - x)!} \\ &= \frac{x^T!}{x!(x^T - x)!}\Big(\frac{C_2}{C_1 + C_2}\Big)^x \Big(\frac{C_1 + C_2}{C_1}\Big)^x \end{aligned}$$

From the normalization we have

$$p(x) \sim B(x^T, q), \quad q = \frac{C_2}{C_1 + C_2}$$

with mean $x^T C_2/(C_1 + C_2)$, and variance $x^T C_1 C_2/(C_1 + C_2)$.

References

[1] D.T. GILLESPIE, *A general method for numerically simulating the stochastic time evolution of coupled chemical reactions*, J. Comp. Phys. 22 (1976), 403-434.

[2] D.T. GILLESPIE, *Exact stochastic simulation of coupled chemical reactions*, J. Phys. Chem. 81 (1977), 2340-2361.

[3] D.T. GILLESPIE, *Markov processes: an introduction for physical scientists*, Academic Press, Boston, 1992.

[4] D.T. GILLESPIE, *Approximate accelerated stochastic simulation of chemically reacting systems*, J. Chem. Phys. 115 (2001), 1716.

[5] D.G. Vlachos et al, J. Chem. Phys. 122 (2005), 24112.

[6] Tiejun Li, Analysis of explicit tau-leaping schemes for simulating chemically reacting systems, Multi. Model. Simul. 6, 447-466 (2007).