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:

$$X_t = (X^1_t, X^2_t, \ldots, X^N_t). \quad (1)$$

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

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

$$\partial_t P(x, t|x_0, t_0) = \sum_{j=1}^{M} a_j(x - \nu_j)P(x - \nu_j, t|x_0, t_0) - \sum_{j=1}^{M} a_j(x)P(x, t|x_0, t_0). \quad (3)$$

It can be easily obtained through

$$P(x, t + dt|x_0, t_0) = \sum_{j=1}^{M} P(x - \nu_j, t|x_0, t_0)a_j(x - \nu_j)dt + (1 - \sum_{j=1}^{M} a_j(x)dt)P(x, t|x_0, t_0)$$

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 $\tau$ as an exponentially distributed random variable (R.V.) with rate $a_0(X_t)$;
- Step 2: Sampling an $M$ point R.V. $k$ with probability $\frac{a_j(X_t)}{a_0(X_t)}$ for the $j$-th reaction;
- Step 3: Update $X_{t+\tau} = X_t + \nu_k$, 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

\[ S_1 \rightarrow S_2 \quad \text{with rate } C_1 \]  \hspace{1cm} (4)

\[ S_2 \rightarrow S_1 \quad \text{with rate } C_2 \]  \hspace{1cm} (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 $\tau$ 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 $a_j(X_t)$ fixed, and leap with time stepsize $\delta t$. Then the number of $j$-th reaction will be $\mathcal{P}(a_j(X_t)\delta t$, 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

\[ X_{t+\delta t} = X_t + \sum_{j=1}^{M} \nu_j \mathcal{P}(a_j(X_t)\delta t) \]  \hspace{1cm} (6)
The procedure for selecting tau (time stepsize) is as follows. Note that the state after \( \tau \)-leaping is

\[
X \to X + \sum_{j=1}^{M} \nu_j a_j(X) \tau := X + \tau \xi.
\]

Then the leap condition will be

\[
|a_j(X + \tau \xi) - a_j(X)| \leq \epsilon a_0(X),
\]

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

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

Many more robust stepsize selection strategies are also proposed.

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

\[
\tau \leq m/a_0(X), \quad m \sim \mathcal{O}(1)
\]

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 \( a_j(X_t) \tau \gg 1 \), \( P(a_j(X_t) \tau) \approx N(a_j(X_t) \tau, a_j(X_t) \tau) \) by Central Limit Theorem

  \[
  X_{t+\tau} \approx X_t + \sum_{j=1}^{M} \nu_j a_j(X_t) \tau + \sum_{j=1}^{M} \nu_j \sqrt{a_j(X_t) \tau} N(0, 1)
  \]

  which corresponds to CLE

  \[
  dX_t = \sum_{j=1}^{M} \nu_j a_j(X_t) dt + \sum_{j=1}^{M} \nu_j \sqrt{a_j(X_t)} dW_t
  \]
From Chemical Langevin Equation to Reaction Rate Equation:

When $a_j(X_t)\tau \to +\infty$, $N(a_j(X_t)\tau, a_j(X_t)\tau) \approx a_j(X_t)\tau$ by Law of Large Numbers

$$X_{t+\tau} \approx X_t + \sum_{j=1}^{M} \nu_j a_j(X_t)\tau$$

which corresponds to RRE

$$\frac{dX_t}{dt} = \sum_{j=1}^{M} \nu_j a_j(X_t)$$

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

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

SSA $\longrightarrow$ Molecular dynamics
↓ ↓
CLE $\longrightarrow$ Kinetic theory
↓ ↓
RRE $\longrightarrow$ Continuum mechanics

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

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

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

- **Step 1:** At time $t$, set $\tilde{X} = X_t$, select $\tau$;
- **Step 2:** Sequentially for $j = 1, 2, \ldots, M$ do:
  - Find $k_{\text{max}}^{(j)} \sim$ Maximal admissible number of $j$-th reactions according to $\tilde{X}$;
  - Define $p = a_j\tau/k_{\text{max}}^{(j)}$;
  - Sample binomial distribution R.V. $k_j \sim B(k_{\text{max}}^{(j)}, p)$;
  - Firing $j$-th reaction $k_j$ times:
    $$\tilde{X} + \nu_j k_j \rightarrow \tilde{X}$$
- **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:

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

in the law of rare events limit ($a_j \tau \ll k_{\text{max}}^{(j)}$), 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

\begin{align*}
S_1 &\rightarrow S_2 \quad \text{with rate } C_1 \quad (7) \\
S_2 &\rightarrow S_1 \quad \text{with rate } C_2 \quad (8)
\end{align*}

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

\begin{align*}
\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
\end{align*}

The trajectory of $X_t$ is sketched as follows.

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

\begin{align*}
S &\rightarrow \emptyset \quad \text{with rate } C_1 \quad (9) \\
\emptyset &\rightarrow S \quad \text{with rate } C_2 \quad (10)
\end{align*}

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 $X_n^1 + X_n^2 = X^T = \text{Const.}$. 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
\[ |1 - \lambda \delta t| \leq 1 \implies \delta t \leq \frac{2}{\lambda}. \]

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
\[ \text{Var}(Y) = \mathbb{E}(\text{Var}(Y|X)) + \text{Var}(\mathbb{E}(Y|X)). \]

Then
\[
\text{Var}(X_{n+1}^1) = C_1 \delta t \mathbb{E}X_n^1 + C_2 \delta t \mathbb{E}(X^T - X_n^1) + \text{Var}\left(X_n^1 - C_1 X_n^1 \delta t + C_2 (X^T - X_n^1) \delta t \right)
\]
\[ = (1 - \lambda \delta t)^2 \text{Var}(X_n^1) + (C_1 - C_2) \delta t \mathbb{E}X_n^1 + C_2 \delta t X^T. \]

As \( n \to \infty \), we have
\[ \text{Var}(X_n^1) \to \frac{2}{2 - \lambda \delta t (C_1 + C_2)^2} \frac{C_1 C_2 X^T}{2 - \lambda \delta t} \text{Var}(X_n^\infty) \geq \text{Var}(X^\infty). \]

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

But the problem is how to sample \( P(C_1 X_{n+1}^1 \delta t) \). If we apply the iteration
\[ X_{n+1}^{1,k+1} = X_n^1 - P(C_1 X_{n+1}^{1,k} \delta t) + P(C_2 (X^T - X_{n+1}^{1,k}) \delta t), \]
there will be no fixed point because of randomness.

The second choice is semi-implicit method as
\[
X_{n+1}^1 = X_n^1 - C_1 X_{n+1}^1 \delta t + C_2 (X^T - X_{n+1}^1) \delta t \\
- \left[ P(C_1 X_n^1 \delta t) - C_1 X_n^1 \delta t \right] + \left[ P(C_2 (X^T - X_n^1) \delta t) - C_2 (X^T - X_n^1) \delta t \right].
\]

Similar analysis as before shows the stability condition
\[ \left| \frac{1}{1 + \lambda \delta t} \right| \leq 1. \]
So the stiffness is resolved! But the variance
\[
\text{Var}(X^1_n) \to \frac{2}{2 + \lambda \delta t} \text{Var}(X^1_\infty) \leq \text{Var}(X^1_\infty),
\]
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:
\[
dX_t = \sum_{j=1}^{M} \int_0^A \nu_j c_j(a; X_t-) \lambda(dt \times da).
\]
(11)

Here
\[
c_j(a; X_t) = \begin{cases} 
1, & \text{if } a \in (h_{j-1}(X_t), h_j(X_t)], \\
0, & \text{otherwise},
\end{cases}
\]
and \( A = \max_{X_t} a_0(X_t) \). \( \lambda(dt \times da) \) is the reference Poisson random measure associated with a Poisson point process \( (q_t, t \geq 0) \) taking values in \( (0, A] \). That is,
\[
\int_0^t \int_B \lambda(dt \times da) = \# \{0 \leq s < t; q_s \in B\},
\]
(13)
where \( B \) 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
\[
\mathcal{L}^* u = \sum_{j=1}^{M} a_j(x) u(x + \nu_j, t) - \sum_{j=1}^{M} a_j(x) u(x, t)
\]
\[
= \sum_{j=1}^{M} a_j(x) \left( u(x + \nu_j, t) - u(x, t) \right).
\]

For the stationary solution, we ask
\[
\mathcal{L} P = 0.
\]
For reversible reaction, we only consider the equation for $x$ since $x + y = x^T$ ($\nu_1 = -1, \nu_2 = 1$):

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

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

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

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

$$
p(x) = p(0) \left( \frac{C_2}{C_1} \right)^x \frac{x^T!}{x!(x^T - x)!}
$$

$$
= \frac{x^T!}{x!(x^T - x)!} \left( \frac{C_2}{C_1 + C_2} \right)^x \left( \frac{C_1 + C_2}{C_1} \right)^x
$$

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


