Lecture 21. Application in Chemical Reaction Kinetics

Tiejun Li[1,2]

[1]School of Mathematical Sciences (SMS),
&
[2]Center for Machine Learning Research (CMLR),
Peking University,
Beijing 100871,
P.R. China
tieli@pku.edu.cn

Office: No. 1 Science Building, Room 1376E

Table of Contents

Traditional chemical reaction dynamics — ODE

- Decaying-dimerizing reaction

$$\begin{aligned} S_1 &\longrightarrow \emptyset, \\ S_1 + S_1 &\longleftrightarrow S_2, \\ S_2 &\longrightarrow S_3, \end{aligned}$$

Traditional chemical reaction dynamics — ODE

- Decaying-dimerizing reaction

$$\begin{aligned} S_1 &\longrightarrow \emptyset, \\ S_1 + S_1 &\longleftrightarrow S_2, \\ S_2 &\longrightarrow S_3, \end{aligned}$$

- Traditional model — ODEs for the concentration (Law of Mass Action)

$$\begin{aligned} \frac{dx_1}{dt} &= -k_1 x_1 - 2k_2 x_1^2 + 2k_3 x_2 \\ \frac{dx_2}{dt} &= k_2 x_1^2 - k_3 x_2 - k_4 x_2 \\ \frac{dx_3}{dt} &= k_4 x_2 \end{aligned}$$

k_1, k_2, k_3, k_4 are reaction rates.

Drawbacks of ODE description

- Deterministic model describes an average behavior and is valid for large population

Drawbacks of ODE description

- Deterministic model describes an average behavior and is valid for large population
- Species of small population may play important role in biological system

Drawbacks of ODE description

- Deterministic model describes an average behavior and is valid for large population
- Species of small population may play important role in biological system
- Examples of stochasticity
  A. Arkin et al., Genetics 149 (1998), 1633 — Stochastic variations can produce probabilistic pathway selection.
  M. Elowitz et al., Science 297 (2002), 391 — Gene expression is affected by both extrinsic and intrinsic noise.

Chemical kinetic system (CKS)

Taking into account the stochasticity in biological chemical reactions, this opens a new way for modeling and simulation!

Chemical reaction kinetics — stochastic version

- Well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, R_2, \ldots, R_M\}$.

Chemical reaction kinetics — stochastic version

- Well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, R_2, \ldots, R_M\}$.
- State of the system

$$\boldsymbol{X}_t = (X_t^1, X_t^2, \ldots, X_t^N).$$

Chemical reaction kinetics — stochastic version

- Well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, R_2, \ldots, R_M\}$.
- State of the system

$$\boldsymbol{X}_t = (X_t^1, X_t^2, \ldots, X_t^N).$$

- Each reaction channel R_j is characterized by its propensity function $a_j(\boldsymbol{x})$ and its state change vector

$$\boldsymbol{\nu}_j = (\nu_j^1, \nu_j^2, \ldots, \nu_j^N).$$

Chemical reaction kinetics — stochastic version

- Well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, R_2, \ldots, R_M\}$.
- State of the system

$$\boldsymbol{X}_t = (X_t^1, X_t^2, \ldots, X_t^N).$$

- Each reaction channel R_j is characterized by its propensity function $a_j(\boldsymbol{x})$ and its state change vector

$$\boldsymbol{\nu}_j = (\nu_j^1, \nu_j^2, \ldots, \nu_j^N).$$

- 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.

Chemical reaction kinetics — stochastic version

- Well-stirred system of N molecular species $\{S_1, S_2, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, R_2, \ldots, R_M\}$.
- State of the system

$$\boldsymbol{X}_t = (X_t^1, X_t^2, \ldots, X_t^N).$$

- Each reaction channel R_j is characterized by its propensity function $a_j(\boldsymbol{x})$ and its state change vector

$$\boldsymbol{\nu}_j = (\nu_j^1, \nu_j^2, \ldots, \nu_j^N).$$

- 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.
- We will define $a_0(\boldsymbol{x}) = \sum_{j=1}^{M} a_j(\boldsymbol{x})$.

An example

- Decaying-dimerizing reaction:

$$S_1 \xrightarrow{R_1} \phi$$

$$S_1 + S_1 \xrightarrow{R_2} S_2$$

$$S_1 + S_1 \xleftarrow{R_3} S_2$$

$$S_2 \xrightarrow{R_4} S_3$$

The propensity functions are given by

$$a_1 = x_1,\ a_2 = 5x_1(x_1 - 1),\ a_3 = 1000x_2,\ a_4 = 0.1x_2$$

and state change vector

$$\nu_1 = (-1, 0, 0),\ \nu_2 = (-2, 1, 0),\ \nu_3 = (2, -1, 0),\ \nu_4 = (-1, 0, 1).$$

Initial state $\boldsymbol{X}(0) = (400, 798, 0)$.

Chemical Master Equation

- The Chapman-Kolmogorov equation in the time interval $[t, t+dt)$

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

where dt is an infinitesimal time, and we have already omitted the higher order terms in $o(dt)$.

Chemical Master Equation

- The Chapman-Kolmogorov equation in the time interval $[t, t+dt)$

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

  where dt is an infinitesimal time, and we have already omitted the higher order terms in $o(dt)$.

- With some algebra, we get the well-known *chemical master equation*.

$$\partial_t P(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0) = \sum_{j=1}^{M} a_j(\boldsymbol{x}-\boldsymbol{\nu}_j) P(\boldsymbol{x}-\boldsymbol{\nu}_j, t|\boldsymbol{x}_0, t_0) - a_0(\boldsymbol{x}) P(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0)$$

  where $a_0(\boldsymbol{x}) := \sum_{j=1}^{M} a_j(\boldsymbol{x})$ is the total propensity.

Table of Contents

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)
  - Step 1: Sampling the waiting time τ as an exponentially distributed random variable (R.V.) with rate $a_0(\boldsymbol{X}_t)$;

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)
  - 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;

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)
  - 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.

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)
  - 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.
- Understood as an exact simulation since the waiting time of the j-th reaction firing is distributed as $a_j(\boldsymbol{x}) \exp(-a_0(\boldsymbol{x})t)$.

SSA — Gillespie's algorithm

- SSA (Stochastic Simulation Algorithm) (Gillespie, JCP 22 (1976), 403.)
  - 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.
- Understood as an exact simulation since the waiting time of the j-th reaction firing is distributed as $a_j(\boldsymbol{x}) \exp(-a_0(\boldsymbol{x})t)$.
- It is essentially the BKL algorithm (Bortz-Kalos-Lebowitz) or KMC in condensed matter physics.

Shortcomings of SSA

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

Shortcomings of SSA

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

- When the reaction rate is very large for a reversible reaction, the reactions will fire back and forth very frequently, but cause very little change of the state.

$$S_1 + S_1 \longleftrightarrow S_2$$

Shortcomings of SSA

- When the population of molecules is very large, the reaction will fire very frequently, which is quite time consuming.
- When the reaction rate is very large for a reversible reaction, the reactions will fire back and forth very frequently, but cause very little change of the state.

$$S_1 + S_1 \longleftrightarrow S_2$$

- How to accelerate the simulation process?

Table of Contents

Tau-leaping Algorithm

- The philosophy is to accelerate SSA at the cost of accuracy.

Tau-leaping Algorithm

- The philosophy is to accelerate SSA at the cost of accuracy.
- 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."

Tau-leaping Algorithm

- The philosophy is to accelerate SSA at the cost of accuracy.
- 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.

Tau-leaping Algorithm

- The philosophy is to accelerate SSA at the cost of accuracy.
- 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 $\lambda = a_j(X_t)\delta t$.

Tau-leaping Algorithm

- The philosophy is to accelerate SSA at the cost of accuracy.
- 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

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

Tau-leaping Algorithm: Stepsize Selection

- The procedure for selecting tau (time stepsize) is as follows.

Tau-leaping Algorithm: Stepsize Selection

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

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

Tau-leaping Algorithm: Stepsize Selection

- 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

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

where $0 < \epsilon < 1$ is a specified value.

Tau-leaping Algorithm: Stepsize Selection

- 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

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

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

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

Tau-leaping Algorithm: Stepsize Selection

- 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

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

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

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

- Many more robust stepsize selection strategies are also proposed.

Some Remarks

Remark

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

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

One will use SSA instead.

Some Remarks

Remark

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

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

One will use SSA instead.

Remark

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.

Tau-leaping Algorithm: Multiscale Picture

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

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

Tau-leaping Algorithm: Multiscale Picture

- 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!

Multiscale Picture

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

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

Negative Populations

- Because of unboundedness of Poisson R.V., negative populations may appear.

Negative Populations

- Because of unboundedness of Poisson R.V., negative populations may appear.
- One choice to avoid N.P. is by binomial tau-leaping.

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

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

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

Avoiding negative populations.

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

Avoiding negative populations.

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

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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:*

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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* $\tilde{\boldsymbol{X}}$*;*

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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* $p = a_j \tau / k_{\max}^{(j)}$*;*

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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.* $k_j \sim B(k_{\max}^{(j)}, p)$*;*

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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:*

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

Binomial Tau-leaping

Algorithm (Binomial Tau-leaping)

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.*

Simple Analysis of Binomial Tau-leaping

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

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

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

Simple Analysis of Binomial Tau-leaping

- 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!

Stiff System: Model System 1

- Chemical reactions are usually stiff.

Stiff System: Model System 1

- Chemical reactions are usually stiff.

Example (Reversible reaction)

Consider the reversible reaction system

$$S_1 \longrightarrow S_2 \quad \text{with rate } C_1 \tag{1}$$

$$S_2 \longrightarrow S_1 \quad \text{with rate } C_2 \tag{2}$$

when C_1 and C_2 are both large.

Stiff System: Model System 1

- Chemical reactions are usually stiff.

Example (Reversible reaction)

Consider the reversible reaction system

$$S_1 \longrightarrow S_2 \quad \text{with rate } C_1 \tag{1}$$

$$S_2 \longrightarrow S_1 \quad \text{with rate } C_2 \tag{2}$$

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

$$\begin{aligned} \mathbb{E}X_t^1 &= \frac{C_2 X^T}{\lambda}(1 - e^{-\lambda t}) + e^{-\lambda t} X_0^1 \\ \mathbb{E}X_t^2 &= \frac{C_1 X^T}{\lambda}(1 - e^{-\lambda t}) + e^{-\lambda t} X_0^2 \end{aligned}$$

Stiff System: Model System 2

Example (Fast decaying)

Consider the following system

$$S \longrightarrow \emptyset \quad \text{with rate } C_1 \tag{3}$$

$$\emptyset \longrightarrow S \quad \text{with rate } C_2 \tag{4}$$

when $C_1 - C_2$ is large.

Define $\lambda = C_1 - C_2$, we have $\mathbb{E}X_t = e^{-\lambda t} X_0$.

Stability Analysis

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

$$\begin{cases} X^1_{n+1} &= X^1_n - \mathcal{P}(C_1 X^1_n \delta t) + \mathcal{P}(C_2 X^2_n \delta t) \\ X^2_{n+1} &= X^2_n - \mathcal{P}(C_2 X^2_n \delta t) + \mathcal{P}(C_1 X^1_n \delta t) \end{cases}$$

Stability Analysis

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

$$\begin{cases} X^1_{n+1} &= X^1_n - \mathcal{P}(C_1 X^1_n \delta t) + \mathcal{P}(C_2 X^2_n \delta t) \\ X^2_{n+1} &= X^2_n - \mathcal{P}(C_2 X^2_n \delta t) + \mathcal{P}(C_1 X^1_n \delta t) \end{cases}$$

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

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

Stability Analysis for the Mean

- Taking expectation we obtain

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

Stability Analysis for the Mean

- 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

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

Stability Analysis for the Mean

- 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

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

- When $\lambda \gg 1$, we have $\delta t \ll 1$. That is the stiffness!

Stability Analysis for the Mean

- 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

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

- 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.

Stability Analysis for the Variance

- Now consider the variance. At first we have

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

Stability Analysis for the Variance

- Now consider the variance. At first we have

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

- Then

$$\begin{aligned}
\mathrm{Var}(X^1_{n+1}) &= C_1\delta t\mathbb{E}X^1_n + C_2\delta t\mathbb{E}(X^T - X^1_n) \\
&+ \mathrm{Var}\Big(X^1_n - C_1X^1_n\delta t + C_2(X^T - X^1_n)\delta t\Big) \\
&= (1-\lambda\delta t)^2\mathrm{Var}(X^1_n) + (C_1 - C_2)\delta t\mathbb{E}X^1_n + C_2\delta t X^T.
\end{aligned}$$

Stability Analysis for the Variance

- Now consider the variance. At first we have

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

- Then

$$\begin{aligned}
\mathrm{Var}(X_{n+1}^1) &= C_1\delta t\mathbb{E}X_n^1 + C_2\delta t\mathbb{E}(X^T - X_n^1) \\
&+ \mathrm{Var}\Big(X_n^1 - C_1X_n^1\delta t + C_2(X^T - X_n^1)\delta t\Big) \\
&= (1-\lambda\delta t)^2\mathrm{Var}(X_n^1) + (C_1 - C_2)\delta t\mathbb{E}X_n^1 + C_2\delta t X^T.
\end{aligned}$$

- As $n \to \infty$, we have

$$\mathrm{Var}(X_n^1) \to \frac{2}{2-\lambda\delta t}\frac{C_1C_2X^T}{(C_1+C_2)^2} = \frac{2}{2-\lambda\delta t}\mathrm{Var}(X_\infty^1) \geq \mathrm{Var}(X_\infty^1).$$

Stability Analysis for the Variance

- Now consider the variance. At first we have

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

- Then

$$\begin{aligned}
\mathrm{Var}(X^1_{n+1}) &= C_1\delta t\mathbb{E}X^1_n + C_2\delta t\mathbb{E}(X^T - X^1_n) \\
&+ \mathrm{Var}\Big(X^1_n - C_1X^1_n\delta t + C_2(X^T - X^1_n)\delta t\Big) \\
&= (1-\lambda\delta t)^2\mathrm{Var}(X^1_n) + (C_1 - C_2)\delta t\mathbb{E}X^1_n + C_2\delta t X^T.
\end{aligned}$$

- As $n \to \infty$, we have

$$\mathrm{Var}(X^1_n) \to \frac{2}{2-\lambda\delta t}\frac{C_1C_2X^T}{(C_1+C_2)^2} = \frac{2}{2-\lambda\delta t}\mathrm{Var}(X^1_\infty) \geq \mathrm{Var}(X^1_\infty).$$

- 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.

Stiff System

Strategy: Implicit method to overcome stiffness.

- The first choice is

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

Stiff System

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.

Stiff System

Strategy: Implicit method to overcome stiffness.

- The first choice is

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

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

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

  there will be no fixed point because of randomness.

- The second choice is semi-implicit method as

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

Stiff System

- Similar analysis as before shows the stability condition

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

So the stiffness is resolved!

Stiff System

- Similar analysis as before shows the stability condition

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

  So the stiffness is resolved!

- But the variance

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

  because of the damping effect of implicit method.

Stiff System

- Similar analysis as before shows the stability condition

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

  So the stiffness is resolved!

- But the variance

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

  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!

Convergence Analysis

- Issue: the chemical reaction kinetics is a pure jump process with state dependent intensity.

Convergence Analysis

- Issue: the chemical reaction kinetics is a pure jump process with state dependent intensity.
- Construct jump process with state dependent intensity from constant jump intensity process (P. Protter, 1983) — Acceptance rejection method

$$\mu(dt) = \int_0^A 1_{\{0<x\leq a_0(\boldsymbol{X}_t)\}}\lambda(dt \times dx).$$

$\lambda(dt \times dx)$ is the Poisson random measure generated from a constant jump intensity process. $\mu(dt)$ has intensity $a_0(\boldsymbol{X}_t)$.

Convergence Analysis

- Issue: the chemical reaction kinetics is a pure jump process with state dependent intensity.
- Construct jump process with state dependent intensity from constant jump intensity process (P. Protter, 1983) — Acceptance rejection method

$$\mu(dt) = \int_0^A 1_{\{0<x\leq a_0(\boldsymbol{X}_t)\}}\lambda(dt \times dx).$$

$\lambda(dt \times dx)$ is the Poisson random measure generated from a constant jump intensity process. $\mu(dt)$ has intensity $a_0(\boldsymbol{X}_t)$.

- The SDE form for the CME

$$d\boldsymbol{X}_t = \sum_{j=1}^{M}\int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-})\lambda(dt \times dx),$$

where

$$c_j(x; \boldsymbol{X}_t) = \begin{cases} 1, & \text{if } x \in (\sum_{i=1}^{j-1} a_i(\boldsymbol{X}_t), \sum_{i=1}^{j} a_i(\boldsymbol{X}_t)], \\ 0, & \text{otherwise.} \end{cases}$$

Tau-leaping is an explicit Euler scheme

- Decomposition

$$
\begin{aligned}
d\boldsymbol{X}_t &= \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-}) m(dt \times dx) \\
&+ \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-}) (\lambda - m)(dt \times dx) \\
&= \boldsymbol{P}_1 + \boldsymbol{P}_2.
\end{aligned}
$$

Tau-leaping is an explicit Euler scheme

- Decomposition

$$\begin{aligned} d\boldsymbol{X}_t &= \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-}) m(dt \times dx) \\ &+ \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-})(\lambda - m)(dt \times dx) \\ &= \boldsymbol{P}_1 + \boldsymbol{P}_2. \end{aligned}$$

- We call $\boldsymbol{P}_1$ the drift term and $\boldsymbol{P}_2$ is the jump term.

Tau-leaping is an explicit Euler scheme

- Decomposition

$$\begin{aligned} d\boldsymbol{X}_t &= \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-}) m(dt \times dx) \\ &+ \sum_{j=1}^{M} \int_0^A \boldsymbol{\nu}_j c_j(x; \boldsymbol{X}_{t-})(\lambda - m)(dt \times dx) \\ &= \boldsymbol{P}_1 + \boldsymbol{P}_2. \end{aligned}$$

- We call $\boldsymbol{P}_1$ the drift term and $\boldsymbol{P}_2$ is the jump term.
- Explicit Euler scheme — tau-leaping method!

$$\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + \sum_{j=1}^{M} \boldsymbol{\nu}_j \mathcal{P}(a_j(\boldsymbol{X}_n)\delta t_n)$$

Other tau-leaping schemes

- Implicit tau-leaping: semi-implicit Euler of SDEs

Other tau-leaping schemes

- Implicit tau-leaping: semi-implicit Euler of SDEs
- Stochastic theta methods:

$$\begin{aligned} \boldsymbol{X}_{n+1} &= \boldsymbol{X}_n + \sum_{j=1}^{M} \theta \boldsymbol{\nu}_j \Big(a_j(\boldsymbol{X}_{n+1}) - a_j(\boldsymbol{X}_n) \Big) \delta t_n \\ &+ \sum_{j=1}^{M} \boldsymbol{\nu}_j \mathcal{P}(a_j(\boldsymbol{X}_n)\delta t_n). \end{aligned}$$

Other tau-leaping schemes

- Implicit tau-leaping: semi-implicit Euler of SDEs
- Stochastic theta methods:

$$\begin{aligned} \boldsymbol{X}_{n+1} &= \boldsymbol{X}_n + \sum_{j=1}^{M} \theta \boldsymbol{\nu}_j \Big(a_j(\boldsymbol{X}_{n+1}) - a_j(\boldsymbol{X}_n) \Big) \delta t_n \\ &+ \sum_{j=1}^{M} \boldsymbol{\nu}_j \mathcal{P}(a_j(\boldsymbol{X}_n)\delta t_n). \end{aligned}$$

- Milstein scheme: Not directly imply any implementable scheme!

Convergence Theorem

Theorem (Mean square convergence)

With the assumptions before we have

$$\sup_{n \leq N_T} \mathbb{E}|\boldsymbol{X}_n - \boldsymbol{X}_{t_n}|^2 \leq C\tau,$$

where $\tau = \max_n \delta t_n$.

Convergence Theorem

Theorem (Mean square convergence)

With the assumptions before we have

$$\sup_{n \le N_T} \mathbb{E}|\boldsymbol{X}_n - \boldsymbol{X}_{t_n}|^2 \le C\tau,$$

where $\tau = \max_n \delta t_n$.

Theorem (Weak convergence)

Under the assumptions, for any continuous function $g(\boldsymbol{x})$ *satisfying exponential growth condition*

$$|g(\boldsymbol{x})| \le C_g B^{|\boldsymbol{x}|}, \quad \boldsymbol{x} \in \mathbb{R}^N \text{ and } C_g, B > 0.$$

We have

$$\left|\mathbb{E}g(\boldsymbol{X}_{N_T}) - \mathbb{E}g(\boldsymbol{X}_T)\right| \le C\tau,$$

where $T = t_{N_T}$, $\tau = \max_n \delta t_n$.

Stationary Distribution

The chemical master equation (FPE) is 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

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

Stationary Distribution

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

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

Stationary Distribution

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

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

- Define $a_2(x) = C_2(x^T - x), a_1(x) = C_1 x, (0 \le x \le x^T)$, we have

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

Stationary Distribution

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

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

- Define $a_2(x) = C_2(x^T - x), a_1(x) = C_1 x, (0 \le x \le x^T)$, 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

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

Stationary Distribution

- We obtain the stationary distribution

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

Stationary Distribution

- 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 $x^T C_1 C_2/(C_1+C_2)$.