Analysis of tau-leaping methods for simulating chemical kinetic systems

Tiejun Li

School of Mathematical Sciences,
Peking University,
Beijing 100871
tieli@pku.edu.cn

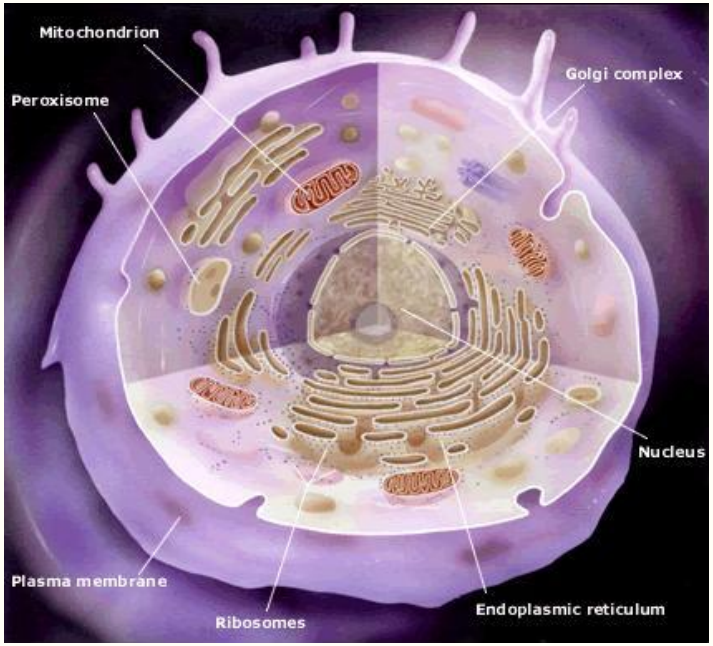
Ecole des Ponts - Peking University joint workshop, Jan. 5-9th 2009

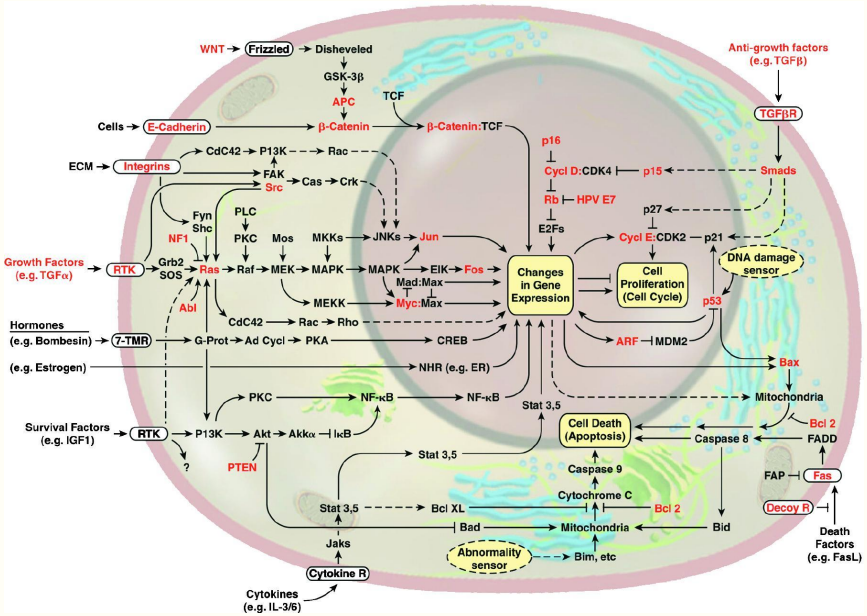
Outline

- Introduction to CKS
- Part I: Convergence analysis of tau-leaping methods
- Part II: RC-tau-leaping algorithm
- Summary

Introduction to CKS

Modeling the biological processes in the cell





Left figure — a schematic picture of cell, Right figure — Bioengineering modeling of cellular processes

Traditional chemical reaction dynamics — ODE

- Decaying-dimerizing reaction

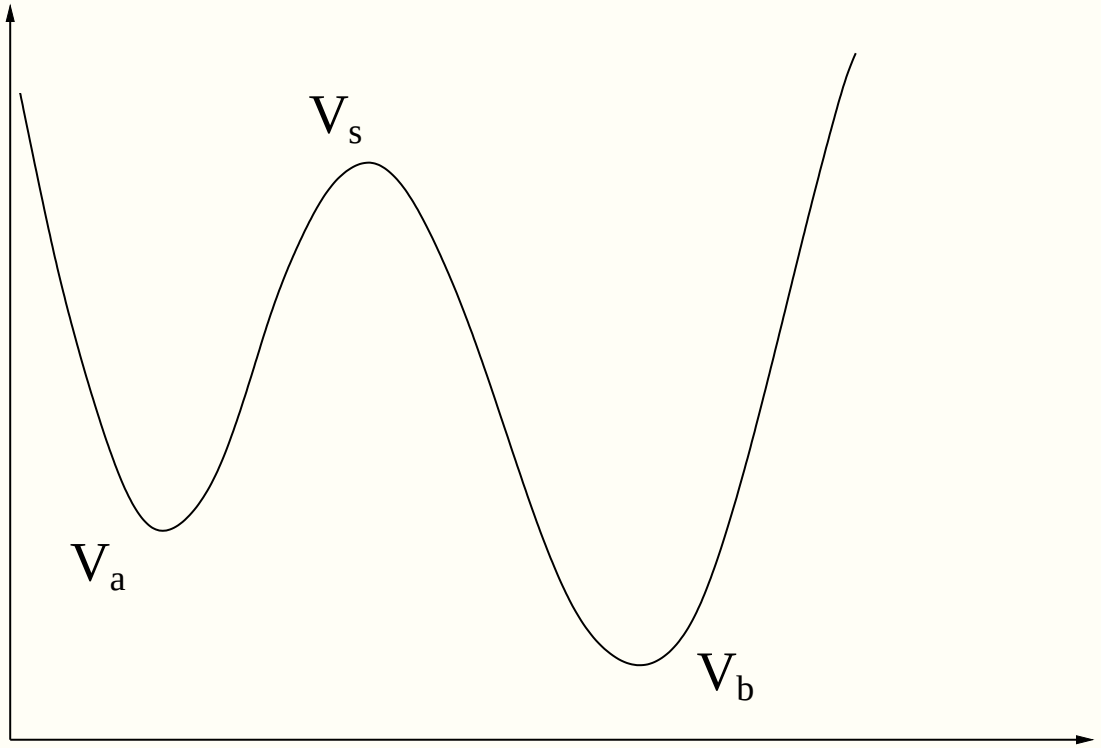
$$
\begin{aligned}
S_1 &\xrightarrow{k_1} \emptyset, \\
2S_1 &\underset{k_3}{\overset{k_2}{\rightleftharpoons}} S_2, \\
S_2 &\xrightarrow{k_4} S_3,
\end{aligned}
$$

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

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

k_1, k_2, k_3, k_4 are reaction rates.

Reaction rate theory



Reaction rate theory for the determination of the rate constant k.

$$k \propto e^{-\frac{\Delta V}{k_B T}}, \quad \Delta V = V_s - V_a.$$

Drawbacks of ODE description

- Deterministic model describes an average behavior and is only 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 (well-mixed) 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 the total propensity $a_0(\boldsymbol{x}) = \sum_{j=1}^{M} a_j(\boldsymbol{x})$.

Chemical master equation (CME)

- Denote $P(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0)$ the proability distribution of CKS. Then

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

  from the Markov property.

- The chemical master equation for the system is

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

An example

- Decaying-dimerizing reaction:

$$\begin{aligned} R_1: &\quad S_1 \longrightarrow \phi \\ R_2: &\quad 2S_1 \longrightarrow S_2 \\ R_3: &\quad 2S_1 \longleftarrow S_2 \\ R_4: &\quad S_2 \longrightarrow S_3 \end{aligned}$$

Suppose $k_1 = 1, k_2 = 10, k_3 = 1000, k_4 = 0.1$, then the propensity functions are given by

$$a_1 = 1 \cdot x_1, \ a_2 = 10 \cdot \frac{x_1(x_1-1)}{2}, \ a_3 = 1000 \cdot x_2, \ a_4 = 0.1 \cdot x_2$$

and state change vector

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

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

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.
- It is an exact simulation which obeys the chemical master equation.
- It is also named 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.

- 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 (e.g. $+100 - 80 = +20$)

$$2S_1 \longleftrightarrow S_2$$

- How to accelerate the simulation process?

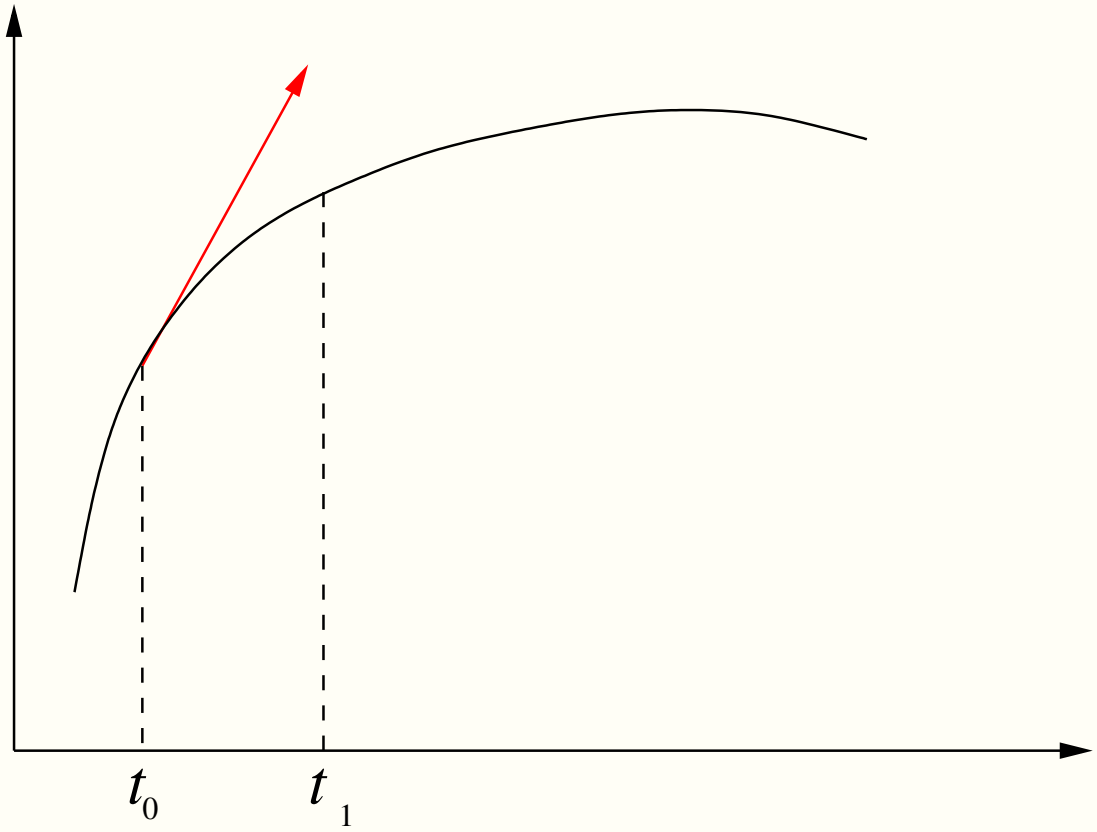
Tau-leaping algorithm

- Proposed by Gillespie, J. Chem. Phys. 115 (2001), 1716.
- 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 non-infinitesimal) change in its value."
- The number of jumps within a fixed time interval for a Poisson process is a Poisson R.V.
- Tau-leaping algorithm

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

where $P(a_j(\boldsymbol{X}_t)\tau)$ is a Poisson R.V. with mean and variance $a_j(\boldsymbol{X}_t)\tau$.

Tau-leaping algorithm — continued



Comparison of the philosophy between tau-leaping and explicit Euler for ODE: freezing the "slope" of a curve if it does not have an appreciable change from t_n to t_{n+1}.

Tau-leaping algorithm — continued

- 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 — continued

- 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!

Tau-leaping algorithm — continued

- 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!

A comprehensive explanation for CKS

- Comparison with fluid mechanics (upscaling)

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

Continued works on tau-leaping and SSA

- More robust stepsize selection for avoiding negative population.
- Overcoming stiffness issue (chemical reaction system is usually stiff).
- Mathematical analysis of tau-leaping algorithm.
- Multiscale system: slow-scale SSA, nested SSA.
- .....

Basic motivation

Project plan: Systematic analysis and mathematical understanding of tau-leaping scheme, constructing more accurate schemes for CKS.

Part I: Convergence analysis of tau-leaping methods

Existed result

- Only weak convergence for linear propensity functions is obtained (Rathinam-Petzold-Cao-Gillespie, MMS 4 (2005), 867).
- Local weak consistency estimates for general nonlinear propensity functions.

Mathematical formulation

- Issue 1: 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

$$c_j(x;\boldsymbol{X}_t) = \begin{cases} 1, & \text{if } x \in (\sum_{i=1}^{j-1} a_i(\boldsymbol{X}_t), \sum_{i=1}^{j} a_i(\boldsymbol{X}_t)], \\ 0, & \text{otherwise.} \end{cases} \qquad j = 1, 2, \ldots, M.$$

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
- 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! This motivates us to construct the higher order methods from another way!

Convergence Theorem: Assumptions

Assumption (Bound on $\boldsymbol{X}_t$)

The number of the elements in $\Omega_{\boldsymbol{X}_0}$ (the set of all available states) is finite, i.e. $\boldsymbol{X}_t$ is in a bounded lattice.

Assumption (Local Lipschitz condition on $a_j(\boldsymbol{x})$)

The function $a_j(\boldsymbol{x})$ is Lipschitz continuous in a bounded domain.

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 $\tau = \max_n \delta t_n$. *(Strong order 1/2)*

- **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 $T = t_{N_T}$, $\tau = \max_n \delta t_n$. *(Weak order 1)*

Part II: RC-tau-leaping algorithm

Basic motivation

- How to construct higher order tau-leaping scheme?

- Some existing attempts:

  Midpoint-tau-leaping scheme (Gillespie);

  Poisson-Runge-Kutta scheme (Burrage-Tian);

  Stochastic Taylor expansion (Platen et al.)

Remark

- Numerical Scheme

$$\mathbb{E}^N X_n := \frac{1}{N} \sum_{i=1}^{N} X_{n,i}$$

- Numerical error

$$|\mathbb{E}X_{t_n} - \mathbb{E}^N X_n| \sim O(\delta t^p) + O\left(\sqrt{\frac{1}{N}\mathsf{Var}(X_n)}\right)$$

  Higher order means in the time (Improve p).

Tau-leaping method: Revisited

- A general form for simulations in CKS

$$\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + \boldsymbol{\nu} \cdot \boldsymbol{r}^*.$$

$\boldsymbol{r}^*$ is a random vector.

Tau-leaping with random corrections (RC-tau-leaping)

- To introduce the correlation, we make decomposition

$$\boldsymbol{r}^* = \boldsymbol{r} + \tilde{\boldsymbol{r}}$$

where $r_j = \mathcal{P}(a_j(\boldsymbol{X}_n)\tau), j = 1, \ldots, M$, but the components of $\tilde{\boldsymbol{r}}$ are dependent, which plays the role of corrections.

- To impove the accuracy, we attack from the analysis of the locally weak truncation error

$$\left\| \mathbb{E}_{\boldsymbol{x}} \left[(\boldsymbol{X}_{n+1} - \boldsymbol{X}_n)^p \right] - \mathbb{E}_{\boldsymbol{x}} \left[(\boldsymbol{X}_{t_n+\tau} - \boldsymbol{X}_{t_n})^p \right] \right\| \leq C\tau^{q+1}.$$

under the condition $\boldsymbol{X}_n = \boldsymbol{X}_{t_n} = x$.

Basic idea

- We search for the statistics of $\boldsymbol{r}^*$ such that it has the higher order local truncation error, not from the Taylor expansion of the SDEs.

- **Proposition**

  Assume $\boldsymbol{r}^* = \boldsymbol{r} + \tilde{\boldsymbol{r}}$. $\boldsymbol{r}$ is a vector with M mutually independent components $r_j = \mathcal{P}(a_j(\boldsymbol{X}_n)\tau), j = 1, \ldots, M$. Given $\boldsymbol{X}_n = \boldsymbol{x}$, if the components of $\tilde{\boldsymbol{r}}$ satisfy

$$\mathbb{E}_{\boldsymbol{x}}\left[\mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_j\right]\right] = \frac{\tau^2}{2}\sum_{k=1}^{M} a_k(\boldsymbol{x})\eta_{jk}(\boldsymbol{x}) + \mathcal{O}(\tau^3), \quad j = 1, \ldots, M,$$

  then the scheme is of second order consistency for the mean. Here $\eta_{jk}(\boldsymbol{x}) = a_j(\boldsymbol{x} + \boldsymbol{\nu}_k) - a_j(\boldsymbol{x})$.

Adding Poisson corrections

If we choose

$$\tilde{r}_j = \mathrm{sgn}(\lambda_j)\mathcal{P}_j\left(|\lambda_j|\right),$$

we have several choices for λ_j

1. $\lambda_j = \dfrac{\tau}{2}\displaystyle\sum_{k=1}^{M} r_k \eta_{jk}.$
2. $\lambda_j = \dfrac{1}{2}\displaystyle\sum_{k=1}^{M} \dfrac{r_k(r_k-1)}{a_k}\eta_{jk}$, assuming $a_k \neq 0$ here.
3. $\lambda_j = \dfrac{\tau^2}{2}\displaystyle\sum_{k=1}^{M} a_k \eta_{jk}.$ (Does not depend on r_k)

Tau-leaping with Poisson corrections (PRC-tau-leaping)

Algorithm

PRC-tau-leaping.

- *Step 1: Given the state* $\boldsymbol{X}_n$ *at time* t_n*, compute the matrix* $\boldsymbol{\eta}(\boldsymbol{X}_n)$*, determine a leap time* τ*;*
- *Step 2: Generate Poisson R.V.s* $r_j^* = \mathcal{P}(\mu_j)$*, where* μ_j *is defined as below*

$$\mu_j = a_j \tau + \frac{\tau^2}{2} \sum_{k=1}^{M} a_k \eta_{jk}.$$

- *Step 3: Update time to* $t_n + \tau$ *and* $\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + \boldsymbol{\nu} \cdot \boldsymbol{r}^*$.

Conditions for second order tau-leaping for mean and covariance

- Proposition

  For a numerical method with the form above, if the R.V.s $\{r_j^*\}$ are mutually independent, then in general it cannot be second order consistent for the covariance of $\boldsymbol{X}$.

  - With the above lemma and similar idea, we can prove that the Midpoint (Gillespie) and PRK (Burrage and Tian) can not be second order for covariance!

Second order tau-leaping for mean and covariance

Proposition

Assume that we have a numerical scheme $\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + \boldsymbol{\nu} \cdot \boldsymbol{r}^*$, *where* $\boldsymbol{r}^* = \boldsymbol{r} + \tilde{\boldsymbol{r}}$. $\boldsymbol{r}$ *is a vector with* M *mutually independent components* $r_j = \mathcal{P}(a_j(\boldsymbol{X}_n)\tau), j = 1, \ldots, M$. *Given* $\boldsymbol{X}_n = \boldsymbol{x}$, *if the components of* $\tilde{\boldsymbol{r}}$ *satisfy*

1. $\mathbb{E}_{\boldsymbol{x}}\left[\mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_j\right]\right] = \dfrac{\tau^2}{2}\sum_{k=1}^{M} a_k \eta_{jk} + \mathcal{O}(\tau^3)$;
2. *for* $j \neq k$, $\mathbb{E}_{\boldsymbol{x}}\left[\mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_j \tilde{r}_k\right]\right] = \mathcal{O}(\tau^3)$;
3. *for* $j \neq k$, $\mathbb{E}_{\boldsymbol{x}}\left[r_j \mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_k\right]\right] = \dfrac{\tau^2}{2} a_j \eta_{kj} + \mathcal{O}(\tau^3)$;
4. $\mathbb{E}_{\boldsymbol{x}}\left[\mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_j^2\right]\right] + 2\mathbb{E}_{\boldsymbol{x}}\left[r_j \mathbb{E}_{\boldsymbol{r}}\left[\tilde{r}_j\right]\right] = \dfrac{\tau^2}{2}\sum_{k=1}^{M} a_k \eta_{jk} + \tau^2 a_j \eta_{jj} + \mathcal{O}(\tau^3)$,

then the scheme is second order consistent for both mean and covariance.

Tau-leaping with Gaussian corrections (GRC-tau-leaping)

- Conditioned on $\boldsymbol{r}$, if random vector $\tilde{\boldsymbol{r}}$ has mutually independent components with mean $\mathbb{E}_{\boldsymbol{r}}[\tilde{r}_j]$ and variance $\mathrm{Var}_{\boldsymbol{r}}[\tilde{r}_j]$

$$\begin{aligned}\mathbb{E}_{\boldsymbol{r}}[\tilde{r}_j] &= \frac{\tau}{2}\sum_{k=1}^{M} r_k \eta_{jk} + \frac{\tau}{2}\sum_{\eta_{jk}<0}\left(\frac{a_k}{a_j} r_j - \tau a_k\right)\eta_{jk}, \\ \mathrm{Var}_{\boldsymbol{r}}[\tilde{r}_j] &= \frac{\tau^2}{2}\sum_{k=1}^{M} a_k |\eta_{jk}| \geq 0,\end{aligned}$$

  then the scheme is weakly second order consistent for both mean and covariance.

- Introducing non-integer number of states and reactions. How to understand? (Similar considerations in quantum mechanics: Schrödinger's cat)

Tau-leaping with Gaussian corrections (GRC-tau-leaping)

Algorithm

GRC-tau-leaping (version 1).

- *Step 1: Given the state $\boldsymbol{X}_n$ at time t_n, compute the matrix $\boldsymbol{\eta}(\boldsymbol{X}_n)$, determine a leap time τ;*
- *Step 2: Generate the random vector $\boldsymbol{r}$ whose components are mutually independent Poisson R.V.s $r_j = \mathcal{P}\left(a_j(\boldsymbol{X}_n)\tau\right)$;*
- *Step 3: Conditioned on $\boldsymbol{r}$, generate random vector $\tilde{\boldsymbol{r}}$, whose components are mutually independent Gaussian R.V.s with mean $\mathbb{E}_{\boldsymbol{r}}[\tilde{r}_j]$ and variance $\mathrm{Var}_{\boldsymbol{r}}[\tilde{r}_j]$ as below*

$$\begin{aligned}\mathbb{E}_{\boldsymbol{r}}[\tilde{r}_j] &= \frac{\tau}{2}\sum_{k=1}^{M} r_k\eta_{jk} + \frac{\tau}{2}\sum_{\eta_{jk}<0}\left(\frac{a_k}{a_j}r_j - \tau a_k\right)\eta_{jk},\\ \mathrm{Var}_{\boldsymbol{r}}[\tilde{r}_j] &= \frac{\tau^2}{2}\sum_{k=1}^{M} a_k|\eta_{jk}| \geq 0,\end{aligned}$$

- *Step 4: Update time to $t_n + \tau$ and $\boldsymbol{X}_{n+1} = \boldsymbol{X}_n + \boldsymbol{\nu}\cdot(\boldsymbol{r} + \tilde{\boldsymbol{r}})$.*

Test examples

- System 1: $S \longrightarrow \emptyset$
- System 2: $S \longrightarrow 2S$
- System 3: Michaelis-Menten system

$$\begin{aligned} S_1 + S_2 &\xrightarrow{k_1} S_3 \\ S_3 &\xrightarrow{k_2} S_1 + S_2 \\ S_3 &\xrightarrow{k_3} S_2 + S_4. \end{aligned}$$

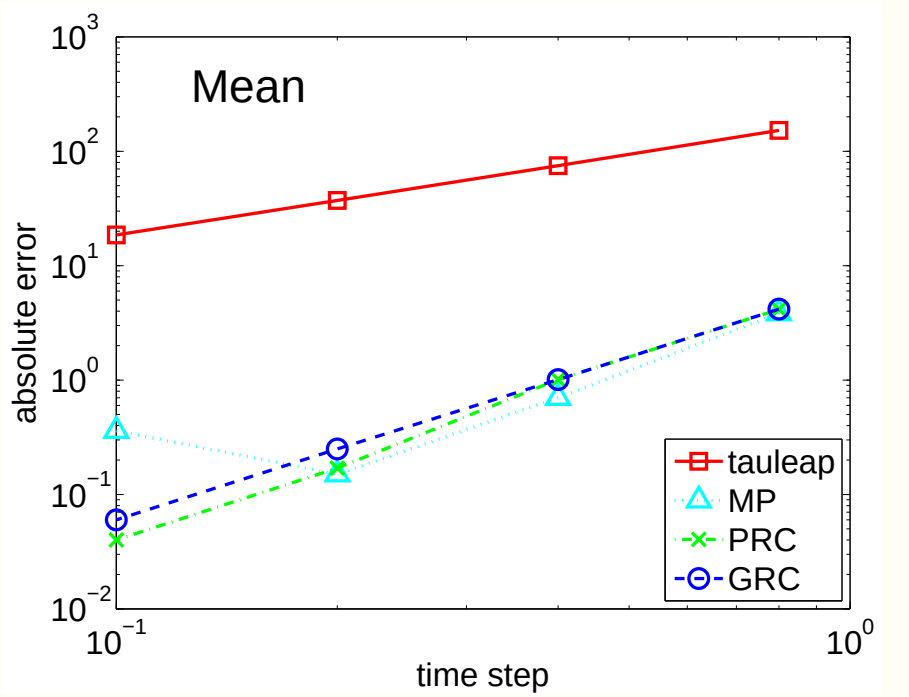
Test examples

System 4: A more complex system

	Reaction	Propensity	Rate constant
1.	$E_A \rightarrow E_A + A$	$a_1 = c_1[E_A]$	$c_1 = 150$
2.	$E_B \rightarrow E_B + B$	$a_2 = c_3[E_B]$	$c_2 = 150$
3.	$E_A + B \rightarrow E_AB$	$a_3 = c_3[E_A][B]$	$c_3 = 0.001$
4.	$E_AB \rightarrow E_A + B$	$a_4 = c_4[E_AB]$	$c_4 = 6$
5.	$E_AB + B \rightarrow E_AB_2$	$a_5 = c_5[E_AB][B]$	$c_5 = 0.001$
6.	$E_AB_2 \rightarrow E_AB + B$	$a_6 = c_6[E_AB_2]$	$c_6 = 6$
7.	$A \rightarrow \emptyset$	$a_7 = c_7[A]$	$c_7 = 5$
8.	$E_B + A \rightarrow E_BA$	$a_8 = c_8[E_B][A]$	$c_8 = 0.001$
9.	$E_BA \rightarrow E_B + A$	$a_9 = c_9[E_BA]$	$c_9 = 6$
10.	$E_BA + A \rightarrow E_BA_2$	$a_{10} = c_{10}[E_BA][A]$	$c_{10} = 0.001$
11.	$E_BA_2 \rightarrow E_BA + A$	$a_{11} = c_{11}[E_BA_2]$	$c_{11} = 6$
12.	$B \rightarrow \emptyset$	$a_{12} = c_{12}[B]$	$c_{12} = 5$

Table: List of reactions and propensity functions for system 4.

Numerical results



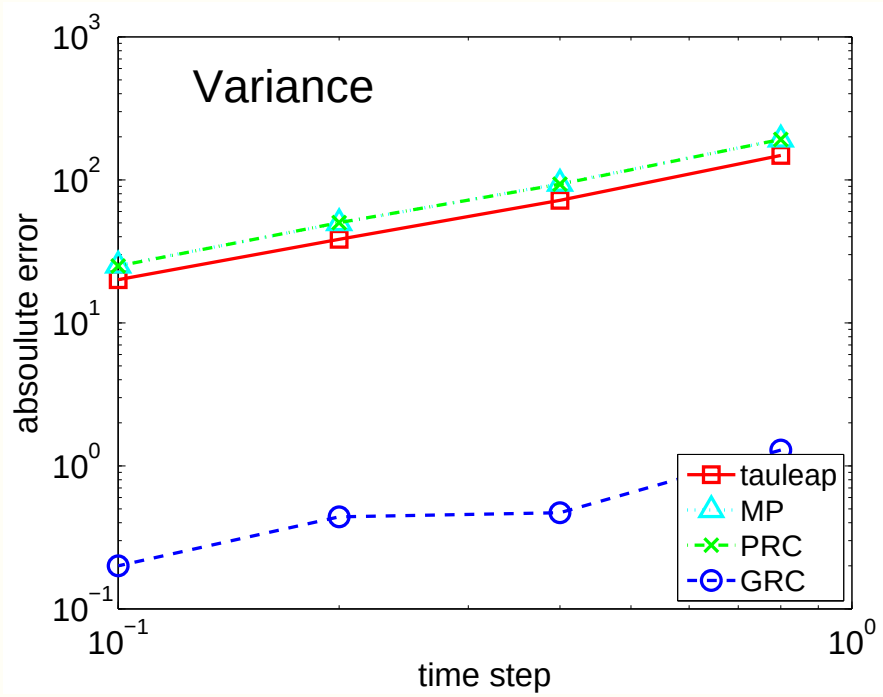
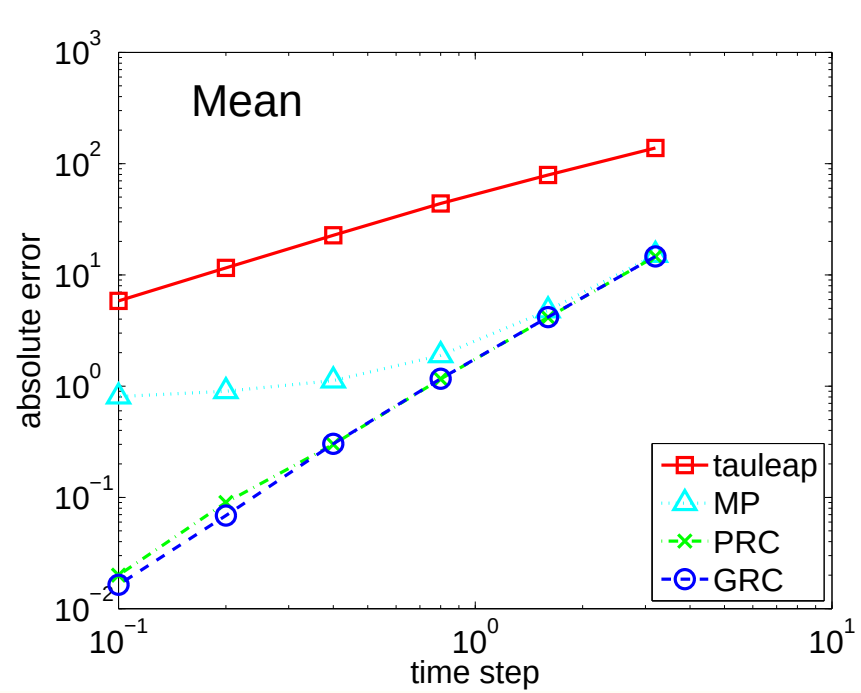


Figure: The estimated mean and variance for the example 1

Numerical results



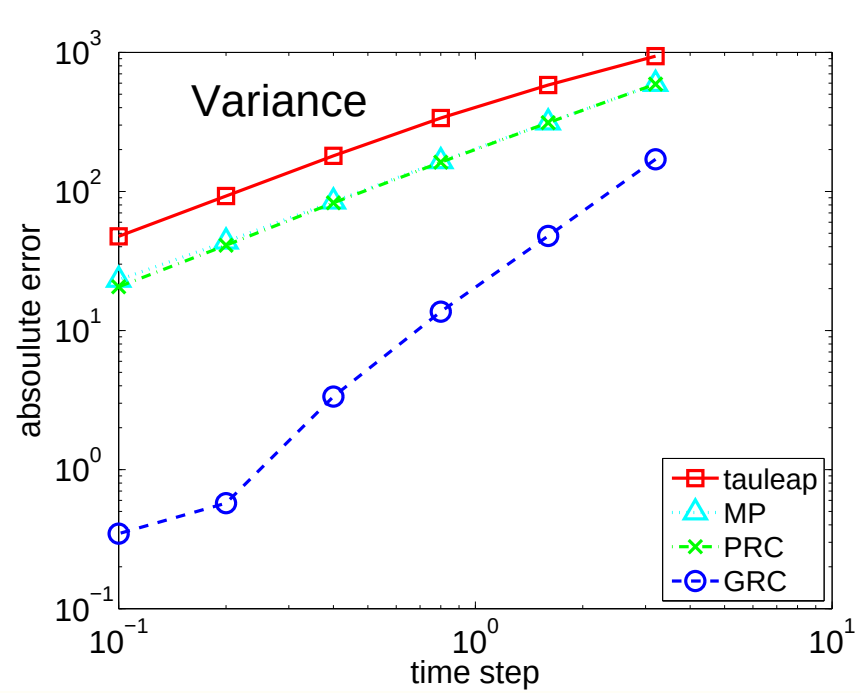
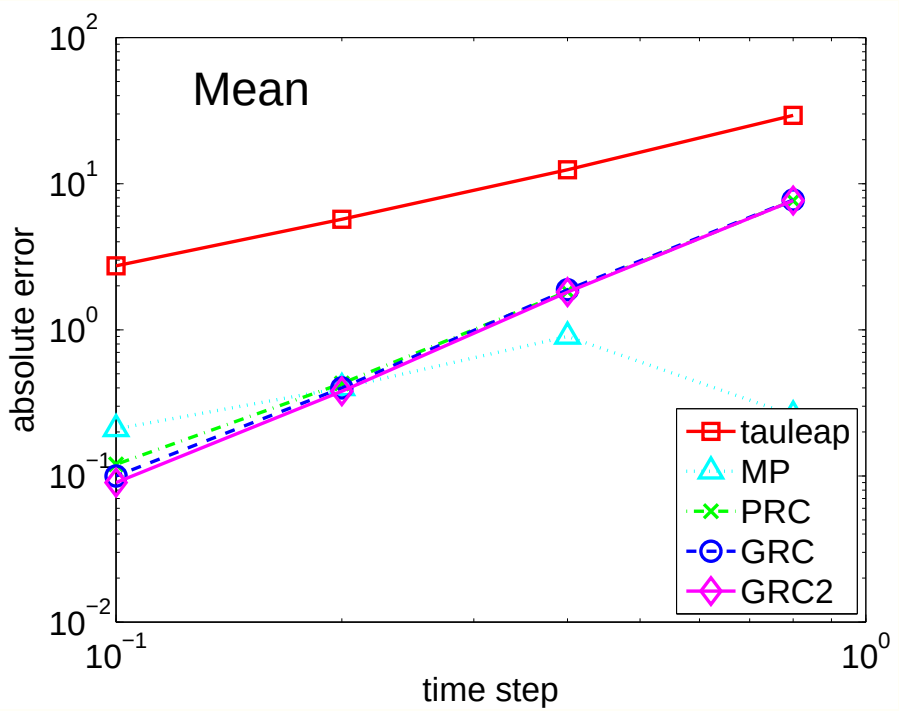


Figure: The estimated mean and variance for the example 2

Numerical results



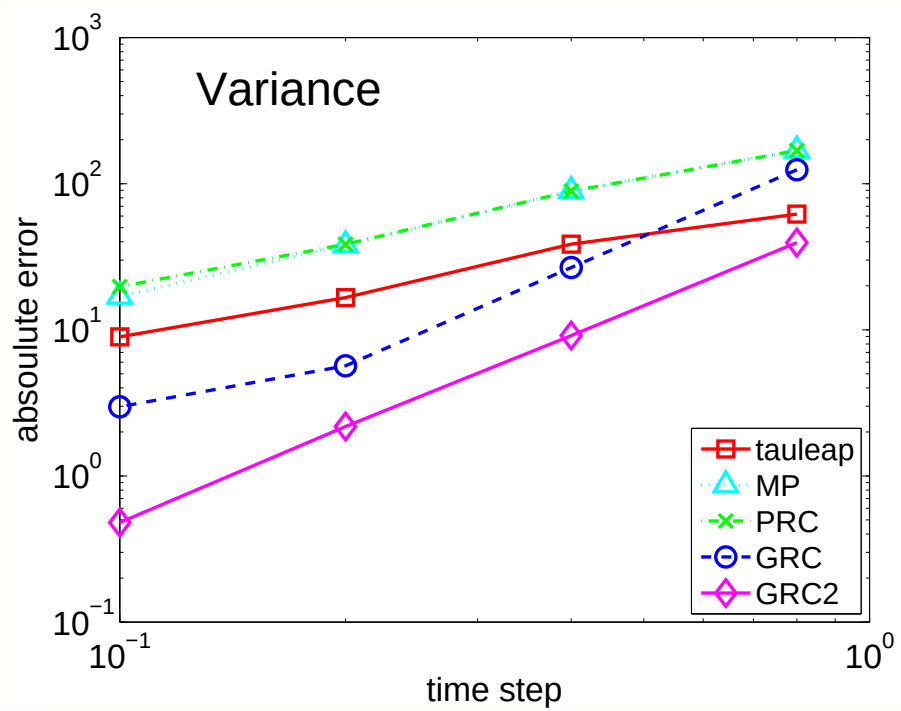


Figure: The estimated mean and variance for the example 3

Numerical results

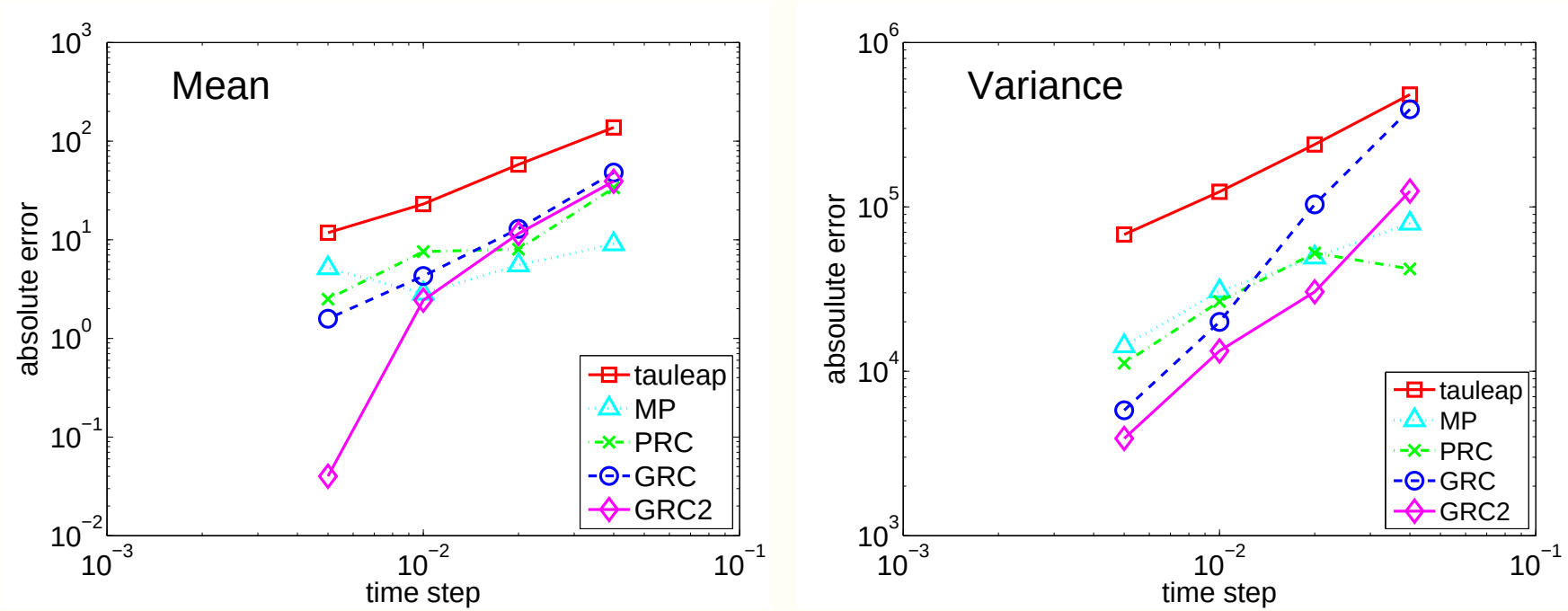


Figure: The estimated mean and variance for the example 4

Summary

Summary

- The convergence analysis of tau-leaping methods based on its SDE form is performed, which will be fruitful for the future research.
- A second order scheme (in time) for both the mean and covariance is constructed. So far it is the most accurate scheme for CKS with sound mathematical background.
- More systematic studies on RC-tau-leaping and the higher order methods are in progressing.....

Thank you!