Error analysis of tau-leap methods

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Overview

1. Notation/terminology: stochastic models of biochemical reaction networks.

2. Discuss class of numerical approximation methods: leaping algorithms.

3. Question: how well do different methods approximate exact process?
Stochastic models of (bio)chemical reactions

- Standard notation for chemical reactions:

  \[ S_1 + S_2 \rightarrow S_3 \]

  is interpreted as “a molecule of \( S_1 \) combines with a molecule of \( S_2 \) to give a molecule of \( S_3 \).”

- We consider a network of reactions involving \( d \) chemical species, \( S_1, \ldots, S_d \):

  \[
  \sum_{i=1}^{d} \nu_{ik} S_i \rightarrow \sum_{i=1}^{d} \nu'_{ik} S_i
  \]
Markov chain models

- The state of the system, $X(t) \in \mathbb{Z}^d_{\geq 0}$, gives the number of molecules of each species in the system at time $t$.

- $\nu_k$: number of molecules of each chemical species consumed in the $k$th reaction.

- $\nu'_k$: number of molecules of each chemical species created in the $k$th reaction.

- If $k$th reaction occurs at time $t$, the new state becomes
  \[ X(t) = X(t-) + \nu'_k - \nu_k. \]

- The waiting times for the reactions are exponentially distributed with rate (intensity/propensity) functions $\lambda_k : \mathbb{R}^d \rightarrow \mathbb{R}_{\geq 0}$.
Markov chain models

This model is a continuous time Markov chain in $\mathbb{Z}^d_{\geq 0}$ with generator

$$(Af)(x) = \sum_k \lambda_k(x)(f(x + \nu'_k - \nu_k) - f(x)).$$

Kolmogorov’s forward equation ("Chemical Master Equation") describes the evolution of the distribution of the state of the system

$$\dot{p}_x(t) = \sum_k \lambda_k(x - \nu'_k + \nu_k)p_{x - \nu'_k + \nu_k}(t) - \left(\sum_k \lambda_k(x)\right)p_x(t),$$

where $p_x(t) = P\{X(t) = x\}$. 
# of times $k$th reaction occurs by time $t$ is a **counting process** with intensity $\lambda_k(X(t))$, and can be written as:

$$R_k(t) = Y_k \left( \int_0^t \lambda_k(X(s)) ds \right),$$

where the $Y_k$ are **independent, unit-rate Poisson process**.
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where the $Y_k$ are independent, unit-rate Poisson process.

Therefore, a path-wise representation is given by random time-changes of Poisson processes

$$X(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X(s)) ds \right) (\nu'_k - \nu_k).$$
Mass-action kinetics

The standard intensity function chosen is **mass-action kinetics**:

\[
\lambda_k(x) = \kappa_k \left( \prod_i \nu_{ik}! \right) \left( \frac{x}{\nu_k} \right) = \kappa_k \prod_i \frac{x_i!}{(x_i - \nu_{ik})!}.
\]

Rate is proportional to the number of distinct subsets of the molecules present that can form inputs for the reaction. (this assumes vessel is “well-stirred”.)

Example: If \( S_1 \rightarrow \text{anything} \), then \( \lambda_k(x) = \kappa_k x_1 \).

Example: If \( S_1 + S_2 \rightarrow \text{anything} \), then \( \lambda_k(x) = \kappa_k x_1 x_2 \).

Example: If \( S_1 + 2S_2 \rightarrow \text{anything} \), then \( \lambda_k(x) = \kappa_k x_1 x_2(x_2 - 1) \).
Methods of investigation: numerical simulation

\[ X(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X(s)) \, ds \right) (\nu'_k - \nu_k), \]

(GOOD NEWS) There are a number of numerical methods that produce statistically exact sample paths (discrete even simulation):

1. Gillespie’s algorithm.
2. The next reaction method.

For each step of these methods must find:

(i) the amount of time that passes until the next reaction takes place: \( \Delta_n \).
   (the minimum of exponential RVs).

(ii) which reaction takes place at that time.
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(i) the amount of time that passes until the next reaction takes place: \( \Delta_n \).
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(BAD NEWS) If \( \sum_k \lambda_k(X(t)) \gg 1 \), then

\[ \Delta_n \approx \frac{1}{\sum_k \lambda_k(X(t))} \ll 1 \]

and the time needed to produce a single exact sample path over an interval \([0, T]\) can be prohibitive.
Standard explicit “$\tau$-leaping”\(^1\) was developed by Dan Gillespie in an effort to overcome the problem that $\Delta n$ may be prohibitively small.

Tau-leaping is essentially an Euler approximation of $\int_0^t \lambda_k(X(s))ds$:

$$Z(\tau) = Z(0) + \sum_k Y_k \left( \int_0^\tau \lambda_k(Z(s)) \, ds \right) (\nu_k' - \nu_k)$$

$$\approx Z(0) + \sum_k Y_k \left( \lambda_k(Z(0)) \tau \right) (\nu_k' - \nu_k)$$

$$\overset{d}{=} Z(0) + \sum_k \text{Poisson} \left( \lambda_k(Z(0)) \tau \right) (\nu_k' - \nu_k).$$

Tau-leaping

Algorithm: For each time-step do the following:

1. For each reaction, calculate $P_{k,n} = \text{Poisson}(\lambda_k(Z(t_n)) \cdot \tau)$.

2. Update, $Z(t_{n+1}) = Z(t_n) + \sum_k P_{k,n} \times (\nu'_k - \nu_k)$.
Algorithm: For each time-step do the following:

1. For each reaction, calculate $P_{k,n} = \text{Poisson}(\lambda_k(Z(t_n)) \tau)$.

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A pathwise representation for $Z(t)$ generated by $\tau$-leaping is

$$Z(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(Z \circ \eta(s)) ds \right) (\nu'_k - \nu_k),$$

where

$$\eta(s) = t_n, \quad \text{if} \quad t_n \leq s < t_{n+1} = t_n + \tau$$

is a step function giving left endpoints of time discretization.
An approximate midpoint method

For a time discretization $0 = t_0 < t_1 < \cdots < t_N = T$, with $\tau = t_n - t_{n-1}$, let

$$\rho(z) = z + \frac{1}{2}\tau \sum_k \lambda_k(z)(\nu'_k - \nu_k),$$

be a “deterministic” midpoint approximation
An approximate midpoint method

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Algorithm: For each time step do the following:

1. Let $y^*_n = \rho(\mathcal{Z}(t_n))$.

2. For each reaction, calculate $P_{k,n} = \text{Poisson}(\lambda_k(y^*_n) \tau)$.

3. Update, $\mathcal{Z}(t_{n+1}) = \mathcal{Z}(t_n) + \sum_k P_{k,n} \times (\nu'_k - \nu_k)$.

Note: still just require one random variable per reaction per step.
An approximate midpoint method

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1. Let $y^*_n = \rho(\mathcal{Z}(t_n))$.

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*Note*: still just require one random variable per reaction per step.

Then $\mathcal{Z}(t)$ solves:

$$
\mathcal{Z}(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k \left( \rho(\mathcal{Z} \circ \eta(s)) \right) ds \right) (\nu'_k - \nu_k),
$$

where $\eta(s) = t_n$, if $t_n \leq s < t_{n+1} = t_n + \tau$. 
Previous error analysis

Under the scaling $\tau \to 0$:

1. Rathinam, Petzold, Cao, and Gillespie\textsuperscript{2} showed, among other things (implicit methods, etc.), that tau-leaping is first order accurate in a weak sense if the intensity functions $\lambda_k$ are linear.

2. Li\textsuperscript{3} extended this result by showing that standard tau-leaping has a strong error (in the $L^2$ norm) of order $1/2$ and a weak error of order one:

$$\sup_{n \leq N} \sqrt{\mathbb{E} |Z(t_n) - X(t_n)|^2} \leq C\tau^{1/2}$$

$$|\mathbb{E}f(Z(T)) - \mathbb{E}f(X(T))| \leq C\tau,$$

where $0 = t_0 < t_1 < \cdots < t_N = T$ is a partition of $[0, T]$.

3. The midpoint method is no more accurate than standard tau-leaping.

Example I
Consider the simple example

\[ A \xrightarrow{1} B, \quad X(0) = 10,000. \]

Letting \( h = 1/20 \) and simulating 200,000 sample paths with each method yields the following approximate distributions for \( X(1) \):
Example
Consider $A$ as a prey and $B$ as a predator.

$$A \xrightarrow{\kappa_1} 2A, \quad A + B \xrightarrow{\kappa_2} 2B, \quad B \xrightarrow{\kappa_3} \emptyset,$$

with $A(0) = B(0) = 1000$ and $\kappa_1 = 2$, $\kappa_2 = .002$, $\kappa_3 = 2$.

Letting $\tau = 1/20$ and simulating 30,000 sample paths with each method yields the following approximate distributions for $B(10)$:
Problem with the $\tau \to 0$ scaling

Recall, tau-leaping methods are only useful if $\tau \gg \Delta_n$, for otherwise an exact method would be performed. Therefore, we should require that

$$\tau \gg \frac{1}{\sum_k \lambda_k(X(t))} \approx \Delta_n \quad \text{while} \quad \sum_k \lambda_k(X(t)) \gg 1.$$

So $\tau \to 0$ does not seem to be an appropriate scaling to describe the accuracy of these methods.
Recall, tau-leaping methods are only useful if $\tau \gg \Delta n$, for otherwise an exact method would be performed. Therefore, we should require that

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So $\tau \to 0$ does not seem to be an appropriate scaling to describe the accuracy of these methods.

Begs the question: how should one perform useful error analyses?
What is an appropriate scaling?

I can not answer in generality. It will depend upon how the system satisfies

$$\sum_k \lambda_k(X(t)) \gg 1$$

Multiple possibilities:

1. Could be that $X_i = \mathcal{O}(V^{\alpha_i})$ for $V \gg 1$ with $\kappa_k = \mathcal{O}(1)$.

2. Could be that $\kappa_k = \mathcal{O}(V^{\beta_k})$ for $V \gg 1$ with $X_i = \mathcal{O}(1)$.

3. Could be multiple scales.

4. Infinite number of possibilities.
The classical scaling

We will assume that:

(i) Numbers of molecules $X_i^V = \mathcal{O}(V)$ for some $V$ large (100’s, 1000’s, ...).

(ii) $\lambda_k(X^V(t)) = \mathcal{O}(V)$ (really a condition on the rate constants).
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These conditions imply that for each $k$ and $x \in \mathbb{R}^d$:

$$\lambda_k(Vx) = V\lambda_k(x),$$

where $\lambda_k$ is deterministic mass action kinetics with rate constants $c_k$. 
The classical scaling

- We had

\[ X^V(t) = X^V(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X^V(s))ds \right) (\nu'_k - \nu_k) \]

Normalizing by

\[ \overline{X}^V \overset{\text{def}}{=} \frac{X^V}{V} \]

now gives us

\[ \overline{X}^V(t) = \overline{X}^V(0) + \sum_k \frac{1}{V} Y_k \left( V \int_0^t \lambda_k(\overline{X}^V(s))ds \right) (\nu'_k - \nu_k) \]
Q: Given a system satisfying our scaling, what size $\tau$ would a user choose?
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Partial answer: something small, $\tau < 1$. 
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Complete answer: something not too small

$$\tau \gg \frac{1}{\sum_k \lambda_k(X(t))} \approx \Delta_n = \mathcal{O}\left(\frac{1}{V}\right).$$
Q: Given a system satisfying our scaling, what size $\tau$ would a user choose?

Partial answer: something small, $\tau < 1$.

Complete answer: something not too small

$$\tau \gg \frac{1}{\sum_k \lambda_k(X(t))} \approx \Delta_n = O\left(\frac{1}{V}\right).$$

That is, for some $\beta \in (0, 1)$,

$$\tau = \frac{1}{V^\beta}.$$
Error analysis on scaled processes

We consider the scaled processes

\[
\overline{X}(t) \overset{\text{def}}{=} \frac{X(t)}{V}, \quad \overline{Z}(t) \overset{\text{def}}{=} \frac{Z(t)}{V}, \quad \overline{\overline{Z}}(t) \overset{\text{def}}{=} \frac{\overline{Z}(t)}{V}.
\]

which satisfy

\[
\overline{X}(t) = \overline{X}(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t \overline{\lambda}_k (\overline{X}(s)) ds \right) (\nu'_k - \nu_k)
\]

\[
\overline{Z}(t) = \overline{X}(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t \overline{\lambda}_k (\overline{Z} \circ \eta(s)) ds \right) (\nu'_k - \nu_k)
\]

\[
\overline{\overline{Z}}(t) = \overline{X}(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t \overline{\lambda}_k \circ \rho (\overline{Z} \circ \eta(s)) ds \right) (\nu'_k - \nu_k),
\]

where \( \rho^V(z) \overset{\text{def}}{=} z + \frac{1}{2} \tau \sum_k \overline{\lambda}_k(z)(\nu'_k - \nu_k), \)

and consider the relationship of the normalized approximate processes, \( \overline{Z}(t) \) and \( \overline{\overline{Z}}(t) \), to the original process \( \overline{X}(t) \), normalized similarly.
Theorem (Anderson, Ganguly, Kurtz – 2010)

Let $X^V(t)$ and $Z^V(t)$ denote the exact and Euler tau-leap processes for $t \in [0, T]$, respectively, with $\tau = V^{-\beta}$. There exists a constant $C = C(T) > 0$ such that

$$\sup_{t \leq T} \mathbb{E}|X^V(t) - Z^V(t)| \leq \frac{C}{V^{\beta}} = C\tau.$$
A new coupling of $\bar{X}^V(t)$ and $\bar{Z}^V(t)$

To sharpen the result, let

$$\bar{X}^V(t) = \bar{X}^V(0) + \frac{1}{V} \sum_k \left[ Y_{k,1} \left( V \int_0^t \bar{\lambda}_k(\bar{X}^V(s)) \land \bar{\lambda}_k(\bar{Z}^V \circ \eta(s)) \, ds \right) 
+ Y_{k,2} \left( V \int_0^t \bar{\lambda}_k(\bar{X}^V(s)) - \bar{\lambda}_k(\bar{X}^V(s)) \land \bar{\lambda}_k(\bar{Z}^V \circ \eta(s)) \, ds \right) \right] (\nu'_k - \nu_k)$$

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+ Y_{k,3} \left( V \int_0^t \bar{\lambda}_k(\bar{Z}^V \circ \eta(s)) - \bar{\lambda}_k(\bar{X}^V(s)) \land \bar{\lambda}_k(\bar{Z}^V \circ \eta(s)) \, ds \right) \right] (\nu'_k - \nu_k),$$

where the $Y_{k,i}$ are mutually independent Poisson processes.

Note: distribution of $\bar{X}^V(t)$ and $\bar{Z}^V(t)$ are unchanged.
Exact asymptotics for Euler tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2010)

1 Let $\bar{X}^V(t)$ and $\bar{Z}^V(t)$ denote the exact and Euler tau-leap solutions for $t \in [0, T]$ under new coupling. Then as $V \to \infty$

$$V^\beta (\bar{X}^V - \bar{Z}^V) \to \mathcal{E},$$

where

- $\mathcal{E}(t)$ is deterministic and independent of $V$ and $\beta$.
- And where $f^V \to f$ means strong path-wise convergence:

$$\lim_{V \to \infty} P\{\sup_{t \leq T} |f^V(t) - f(t)| > \epsilon\} = 0, \quad \text{for all} \quad \epsilon > 0$$

$$\lim_{V \to \infty} \mathbb{E} \sup_{t \leq T} |f^V(t) - f(t)| = 0.$$

Interpret as

$$\bar{Z}^V = \bar{X}^V + \frac{\mathcal{E}}{V^\beta} + \text{H.O.T.}$$

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1 To appear in Annals of Applied Probability
Idea of proof

Can show:

\[
\bar{X}^V(t) - \bar{Z}^V(t) \approx M^V(t) + \int_0^t DF^V(\bar{Z}^V \circ \eta(s))(\bar{X}^V(s) - \bar{Z}^V(s)) \, ds
\]

\[
+ V^{-\beta} \frac{1}{2} \int_0^t DF^V(\bar{Z}^V \circ \eta(s))F^V(\bar{Z}^V \circ \eta(s)) \, ds
\]

where \( M^V(t) \) is a Martingale such that \( M^V \approx \mathcal{O}(V^{-(1+\beta)/2}) \).

- \( (1 + \beta)/2 > \beta \), so done.
Weak error of Euler tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2010)

Let $\overline{X}^V(t)$ and $\overline{Z}^V(t)$ be as before. Then, for any continuously differentiable function $f$

$$\lim_{V \to \infty} V^\beta \left( \mathbb{E} f(\overline{X}^V(t)) - \mathbb{E} f(\overline{Z}^V(t)) \right) = \mathcal{E}(t) \cdot \nabla f(x(t)).$$

Interpret as

$$\mathbb{E} f(\overline{Z}^V(t)) = \mathbb{E} f(\overline{X}^V(t)) + \frac{1}{V^\beta} \mathcal{E}(t) \cdot \nabla f(x(t)) + H.O.T.$$
Strong error of midpoint tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2010)

Let $X^V(t)$ and $Z^V(t)$ denote the exact and midpoint tau-leap processes for $t \in [0, T]$. Then there exists a constant $C = C(T) > 0$ such that

$$\sup_{t \leq T} \mathbb{E}|X^V(t) - Z^V(t)| \leq \frac{C}{V \kappa(\beta)}, \quad \text{where} \quad \kappa(\beta) = \min \left\{ 2\beta, \frac{1 + \beta}{2} \right\}. $$

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$$\sup_{t \leq T} \mathbb{E} |X^V(t) - Z^V(t)| \leq \frac{C}{V^{\kappa(\beta)}}, \quad \text{where} \quad \kappa(\beta) = \min \left\{ 2\beta, \frac{1 + \beta}{2} \right\}.$$
A new coupling of $\bar{X}^V(t)$ and $\bar{Z}^V(t)$

To sharpen the result, let

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\bar{X}^V(t) = \bar{X}^V(0) + \frac{1}{V} \sum_k \left[ Y_{k,1} \left( \int_0^t \bar{\lambda}_k(\bar{X}^V(s)) \wedge \bar{\lambda}_k(\rho^V \circ \bar{Z}^V \circ \eta(s)) \, ds \right)
+ Y_{k,2} \left( \int_0^t \bar{\lambda}_k(\bar{X}^V(s)) - \bar{\lambda}_k(\bar{X}^V(s)) \wedge \bar{\lambda}_k(\rho^V \circ \bar{Z}^V \circ \eta(s)) \, ds \right) \right] (\nu'_k - \nu_k)
$$

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\bar{Z}^V(t) = \bar{X}^V(0) + \frac{1}{V} \sum_k \left[ Y_{k,1} \left( \int_0^t \bar{\lambda}_k(\bar{X}^V(s)) \wedge \bar{\lambda}_k(\rho^V \circ \bar{Z}^V \circ \eta(s)) \, ds \right)
+ Y_{k,3} \left( \int_0^t \bar{\lambda}_k(\rho^V \circ \bar{Z}^V \circ \eta(s)) - \bar{\lambda}_k(\bar{X}^V(s)) \wedge \bar{\lambda}_k(\rho^V \circ \bar{Z}^V \circ \eta(s)) \, ds \right) \right] (\nu'_k - \nu_k),
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where the $Y_{k,i}$ are mutually independent Poisson processes.
Theorem (Anderson, Ganguly, Kurtz – 2010)

Let $X^V(t)$ and $Z^V(t)$ denote the exact and midpoint tau-leap process for $t \in [0, T]$ under the new coupling. Then as $V \to \infty$

$$V^{2\beta}(X^V - Z^V) \to \mathcal{E}_1, \quad \text{if} \quad \beta < 1/3.$$  

$$V^{2\beta}(X^V - Z^V) \Rightarrow \mathcal{E}_2, \quad \text{if} \quad \beta = 1/3.$$  

$$V^{(1+\beta)/2}(X^V - Z^V) \Rightarrow \mathcal{E}_3, \quad \text{if} \quad \beta > 1/3.$$  

Where $\mathcal{E}_1$ is deterministic and $\mathcal{E}_2, \mathcal{E}_3$ are stochastic.
Idea of proof

Can show:

\[ X^V(t) - Z^V(t) \approx M^V(t) + \int_0^t DF^V(Z^V \circ \eta(s))(X^V(s) - Z^V(s))ds + V^{-2\beta}H^V(t) \]

where \( M^V(t) \) is a Martingale such that \( M^V \approx O(V^{-(1+\beta)/2}) \) and \( H^V \to H \).
Weak error of midpoint tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2010)

\[ 1 \text{ Let } \overline{X}^V(t) \text{ and } \overline{Z}^V(t) \text{ be as before. Then, for any } C^3 \text{ function } f, \text{ there exists a constant } C = C(f, T) > 0 \text{ such that} \]

\[ V^{2\beta} \sup_{t \leq T} \left| \mathbb{E}f(\overline{X}^V(t)) - \mathbb{E}f(\overline{Z}^V(t)) \right| \leq C. \]

\[ ^1 \text{To appear in Annals of Applied Probability} \]
Example I

Consider the simple example

\[ A \xrightarrow{1} B, \quad X(0) = 10,000. \]

\[ V = 10,000. \] Letting \( h = 1/20 = 1/V^{.325} \) (so \( \beta = .325 \)) and simulating 200,000 sample paths with each method yields the following approximate distributions for \( X(1) \).
Example

Consider $A$ as a prey and $B$ as a predator.

\[ A \xrightarrow{\kappa_1} 2A, \quad A + B \xrightarrow{\kappa_2} 2B, \quad B \xrightarrow{\kappa_3} \emptyset, \]

with $A(0) = B(0) = 1000$ and $\kappa_1 = 2$, $\kappa_2 = .002$, $\kappa_3 = 2$.

$V = 1,000$ and $\tau = 1/20 = 1/V^{.434}$ (so $\beta = .434$). Simulating 30,000 sample paths yields the following approximate distributions for $B(10)$: