Error analysis of approximation methods for stochastically modeled population processes

David F. Anderson*
with Arnab Ganguly and Thomas Kurtz

*anderson@math.wisc.edu
Department of Mathematics
University of Wisconsin - Madison

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Outline

1. Describe the models of interest: stochastically modeled population processes.

2. Discuss possible numerical algorithms: exact and approximate.

3. Discuss error analysis and the importance of proper scalings.
Chemical reactions

- Standard notation for chemical reactions:

\[ A + B \rightarrow C \]

is interpreted as “a molecule of A combines with a molecule of B to give a molecule of C.”

- Each instance of the reaction \( A + B \rightarrow C \) changes the state of the system by the vector:

\[ \nu_k = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}. \]
The model and notation

- Have $d$ chemical species $\{S_1, S_2, \ldots, S_d\}$ undergoing a series of reactions, indexed by $k$.

- If reaction $k$ occurs at time $t$, then the state of the system, $X(t)$, is updated via addition of the reaction vector $\nu_k \in \mathbb{Z}^d$:

$$X(t) = X(t-) + \nu_k.$$ 

- The waiting times for the reactions are exponentially distributed with intensity (propensity) functions $\lambda_k : \mathbb{R}^d \to \mathbb{R}_{\geq 0}$:

$$P( X(t + \Delta t) = X(t) + \nu_k | X(t) ) = \lambda_k(X(t))\Delta t + o(\Delta t).$$

- “Intensities give the rates of the reactions”
The model

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

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

Kolmogorov’s forward equation (“Chemical Master Equation”)

$$\frac{d}{dt} P(x, t) = \sum_k \lambda_k(x - \nu_k) P(x - \nu_k, t) - \sum_k \lambda_k(x) P(x, t).$$

describes how the distribution of the process changes in time.
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describes how the distribution of the process changes in time.

One intuitive representation for path-wise solutions is given by a random time-change

\[X(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X(s))ds \right) \nu_k,\]

where the $Y_k$ are independent, unit-rate Poisson processes.
Examples

Gene transcription & translation:

\[ G_i \rightarrow G_i + M_i \]
\[ M_i \rightarrow M_i + P_i \]
\[ M_i \rightarrow \emptyset \]
\[ P_i \rightarrow \emptyset \]
\[ G_i + P_j \rightarrow \text{Bound}_i \]

Cartoon representation:

Examples

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Cartoon representation:

Heat Shock Response Model. 9 species, 18 reactions.

Mass-action kinetics

The standard intensity function chosen is mass-action kinetics:

\[ \lambda_k(x) = \kappa_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - \nu_{ki}^s)!} . \]

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 \( \lambda_k(x) = \kappa_k x_1 x_2(x_2 - 1) \).
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- This type of model is used ubiquitously for cellular biochemical processes and is filling the pages of Science and PNAS.
- Typically referred to as a “chemical master equation” (Kolmogorov’s forward equation) model in this literature.
- Models can be “simple” (single Gene-mRNA-Protein) or extremely complicated (E. coli heat shock response)
Example: Lotka-Volterra predator-prey model

Think of $A$ 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 $\kappa_1 = 2, \kappa_2 = .002, \kappa_3 = 2$. 
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Deterministic model. Let \( x(t) = [A(t), B(t)]^T \).

\[
x(t) = x(0) + \kappa_1 \int_0^t x_1(s)ds \begin{bmatrix} 1 \\ 0 \end{bmatrix} + \kappa_2 \int_0^t x_1(s)x_2(s)ds \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \kappa_3 \int_0^t x_2(s)ds \begin{bmatrix} 0 \\ -1 \end{bmatrix}
\]
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**Deterministic model.** Let $x(t) = [A(t), B(t)]^T$.

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**Stochastic model.** Let $X(t) = [A(t), B(t)]^T$.

$$X(t) = X(0) + Y_1 \left( \kappa_1 \int_0^t X_1(s)ds \right) \begin{bmatrix} 1 \\ 0 \end{bmatrix} + Y_2 \left( \kappa_2 \int_0^t X_1(s)X_2(s)ds \right) \begin{bmatrix} -1 \\ 1 \end{bmatrix} + Y_3 \left( \kappa_3 \int_0^t X_2(s)ds \right) \begin{bmatrix} 0 \\ -1 \end{bmatrix}$$
**Lotka-Volterra**

Think of $A$ 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 $\kappa_1 = 2$, $\kappa_2 = 0.002$, $\kappa_3 = 2$.

Behavior is qualitatively different:

1. Deterministic always periodic while stochastic oscillates in random way.
2. Predator and/or prey will end up extinct in stochastic model.
Methods of investigation: numerical simulation

\[ X(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X(s)) ds \right) \nu_k, \]

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

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

For each step of these methods one 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: \( \Delta_n \).

(the minimum of exponential RVs)

(ii) which reaction takes place at that time.

(BAD NEWS) If \( \sum_k \lambda_k(X(t)) \gg 0 \), 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.
Tau-leaping

Standard “τ-leaping” 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 $\int_0^t \lambda_k(X(s)) ds$:

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

$$\approx Z(0) + \sum_k Y_k \left( \lambda_k(Z(0)) \, h \right) \nu_k$$

$$= Z(0) + \sum_k \text{Poisson} \left( \lambda_k(Z(0)) \, h \right) \nu_k.$$
One “intuitive” representation for $Z(t)$ generated by $\tau$-leaping is

$$Z(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(Z \circ \eta(s)) ds \right) \nu_k,$$

where

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

is a step function giving left endpoints of time discretization.
Another algorithm: A midpoint method

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

\[
\rho(z) = z + \frac{1}{2} h \sum_k \lambda_k(z) \nu_k,
\]

be a “deterministic” midpoint approximation

and let \(Z(t)\) solve:

\[
Z(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k \circ \rho(Z \circ \eta(s)) ds \right) \nu_k,
\]

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

Under the scaling $h \to 0$:

1. Rathinam, Petzold, Cao, and Gillespie\textsuperscript{4} 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{5} 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:

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

$$|E f(Z(T)) - E f(X(T))| \leq C h,$$

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.


\textsuperscript{5}T. Li, SIAM Multi. Model. Simul., 6, 2007, 417 – 436.
An example that needs explaining
Consider the simple example

\[ X \overset{1}{\rightarrow} 0, \quad X(0) = 10^6. \]

Letting \( h = 1/10^2 \) and simulating 100,000 sample paths with each method yields the following approximate distributions for \( X(1) \):
Another example that needs explaining

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

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

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

So $h \to 0$ does not seem to be an appropriate scaling to describe the accuracy of these methods.
The “classical scaling”

Summary: τ-leaping is only useful if

\[ h \sum_k \lambda_k(X(t)) \gg 1 \quad \text{while} \quad \frac{1}{\sum_k \lambda_k(X(t))} \ll 1. \]

We will make the following natural assumptions on our model:

\( i \) \( X_i(0) = O(V) \) for some \( V \gg 1 \) (think of as the “volume”).

\( ii \) The rate constants of reactions of the form

\[ S_1 \to \ast, \quad S_1 + S_2 \to \ast, \quad S_1 + S_2 + S_3 \to \ast, \]

scale with \( V \) like:

\( \kappa_k = O(1), \quad \kappa_k = O\left(\frac{1}{V}\right), \quad \kappa_k = O\left(\frac{1}{V^2}\right). \)
A key property of this scaling

For each $k$ and $x \in \mathbb{R}^d$

$$\lambda_k(Vx) = VA_k^V(x) = O(V).$$

Example:

- For the reaction $S_1 + S_2 \rightarrow \ast$, 

  $$\lambda_k(Vx) = \frac{d_k}{V}(Vx_1)(Vx_2) = V(d_kx_1x_2).$$
Recall: $\tau$-leaping is only useful if 

\[ h \sum_k \lambda_k(X(t)) \gg 1 \quad \text{while} \quad \frac{1}{\sum_k \lambda_k(X(t))} \ll 1. \]

For $\beta \in (0, 1)$, we let 

\[ h = 1/V^\beta. \]

This scaling satisfies the above requirements: 

\[ h \sum_k \lambda(X(t)) = V^{-\beta} O(V) = O(V^{1-\beta}) \gg 1. \]
Error analysis on scaled processes

We consider the scaled processes

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

which satisfy

\[
X^V(t) = X^V(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t A_k^V (X^V(s)) ds \right) \nu_k
\]

\[
Z^V(t) = X^V(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t A_k^V (Z^V \circ \eta(s)) ds \right) \nu_k
\]

\[
\bar{Z}^V(t) = X^V(0) + \frac{1}{V} \sum_k Y_k \left( V \int_0^t A_k^V \circ \rho^V (\bar{Z}^V \circ \eta(s)) ds \right) \nu_k,
\]

where

\[
\rho^V(z) \overset{\text{def}}{=} z + \frac{1}{2} h \sum_k A_k^V (z) \nu_k,
\]

and prove theorems in this setting.
Theorem (Anderson, Ganguly, Kurtz – 2009)

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

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

To sharpen the result, let

$$X^V(t) = X^V(0) + \frac{1}{\mathbb{V}} \sum_k \left[ Y_{k,1} \left( \mathbb{V} \int_0^t A^V_k(X^V(s)) \wedge A^V_k(Z^V \circ \eta(s)) \, ds \right) 
+ Y_{k,2} \left( \mathbb{V} \int_0^t A^V_k(X^V(s)) - A^V_k(X^V(s)) \wedge A^V_k(Z^V \circ \eta(s)) \, ds \right) \right] \nu_k$$

$$Z^V(t) = X^V(0) + \frac{1}{\mathbb{V}} \sum_k \left[ Y_{k,1} \left( \mathbb{V} \int_0^t A^V_k(X^V(s)) \wedge A^V_k(Z^V \circ \eta(s)) \, ds \right) 
+ Y_{k,3} \left( \mathbb{V} \int_0^t A^V_k(Z^V \circ \eta(s)) - A^V_k(X^V(s)) \wedge A^V_k(Z^V \circ \eta(s)) \, ds \right) \right] \nu_k,$$

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

**Note:** distribution of the “marginal processes” $X^V(t)$ and $Z^V(t)$ are unchanged.
Exact asymptotics for standard tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2009)

Let $X^V(t)$ and $Z^V(t)$ satisfy the new coupling for $t \in [0, T]$. Then as $V \to \infty$

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

where $\mathcal{E}(t)$ is deterministic and satisfies

$$\mathcal{E}(t) = \int_0^t DF(x(s))\mathcal{E}(s)ds + \frac{1}{2} \int_0^t DF(x(s))F(x(s))ds, \quad \mathcal{E}(0) = 0,$$

and where $f^V \to f$ means either

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

and

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

Can show:

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

where \( M^\gamma(t) \) is a martingale and \( V^{(1+\beta)/2}M^\gamma \Rightarrow M \), where \( M \) is a mean-zero Gaussian process.

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

The following is now immediate.

**Theorem (Anderson, Ganguly, Kurtz – 2009)**

Let $X^V(t)$ and $Z^V(t)$ be as before. Then, for any continuous differentiable function $f$

$$
\lim_{V \to \infty} V^\beta \left( \mathbb{E} f(X^V(t)) - \mathbb{E} f(Z^V(t)) \right) = \mathcal{E}(t) \cdot \nabla f(x(t)).
$$
Strong error of midpoint tau-leaping

**Theorem (Anderson, Ganguly, Kurtz – 2009)**

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

$$\sup_{t \leq T} \mathbb{E} |X^V(t) - Z^V(t)| \leq \frac{C}{\sqrt[1]{\kappa(\beta)}},$$

where $\kappa(\beta) = \min \left\{ \frac{2\beta}{\kappa(\beta)}, \frac{1 + \beta}{2} \right\}$. 

A new coupling of $X^V(t)$ and $Z^V(t)$

To sharpen the result, let

$$X^V(t) = X^V(0) + \frac{1}{V} \sum_k \left[ Y_{k,1} \left( V \int_0^t A_k^V(X^V(s)) \wedge A_k^V(\rho^V \circ Z^V \circ \eta(s)) \, ds \right) \right. \nonumber$$

$$\left. + Y_{k,2} \left( V \int_0^t A_k^V(X^V(s)) - A_k^V(X^V(s)) \wedge A_k^V(\rho^V \circ Z^V \circ \eta(s)) \, ds \right) \right] \nu_k \nonumber$$

$$Z^V(t) = X^V(0) + \frac{1}{V} \sum_k \left[ Y_{k,1} \left( V \int_0^t A_k^V(X^V(s)) \wedge A_k^V(\rho^V \circ Z^V \circ \eta(s)) \, ds \right) \right. \nonumber$$

$$\left. + Y_{k,3} \left( V \int_0^t A_k^V(\rho^V \circ Z^V \circ \eta(s)) - A_k^V(X^V(s)) \wedge A_k^V(Z^V \circ \eta(s)) \, ds \right) \right] \nu_k, \nonumber$$

where the $Y_{k,i}$ are mutually independent Poisson processes.
Exact asymptotics for midpoint tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2009)

Let $X^V(t)$ and $Z^V(t)$ satisfy the new coupling for $t \in [0, T]$. 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 $\mathcal{E}_1$ solves

\[
\mathcal{E}_1(t) = \int_0^t DF(x(s))\mathcal{E}_1(s)ds + \mathcal{H}(t),
\]

$\mathcal{E}_2$ solves

\[
\mathcal{E}_2(t) = M(t) + \int_0^t DF(x(s))\mathcal{E}_2(s)ds + \mathcal{H}(t),
\]

$\mathcal{E}_3$ solves

\[
\mathcal{E}_3(t) = M(t) + \int_0^t DF(x(s))\mathcal{E}_3(s)ds.
\]
Idea of proof

Can show:

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

where \( V^{(1+\beta)/2}M^V \Rightarrow M(t) \).

For those who must know:

\[ H(t) = \frac{1}{6} \int_0^t DF(x(s))^2 F(x(s))ds + \frac{1}{24} \int_0^t F(x(s))^T HF(x(s))F(x(s))ds. \]
Weak error of midpoint tau-leaping

Theorem (Anderson, Ganguly, Kurtz – 2009)

Let $X^V(t)$ and $Z^V(t)$ be as before. Then, for any $C^3$ function $f$, there exists a constant $C = C(f, T) > 0$ such that

$$V^{2\beta} \sup_{t \leq T} \left| \mathbb{E} f(X^V(t)) - \mathbb{E} f(Z^V(t)) \right| \leq C.$$
An example that needs explaining: part II
Consider the simple example

\[ X \xrightarrow{1} 0, \quad X(0) = 10^6. \]

\[ V = 10^6. \] Letting \( h = 1/10^2 = 1/V^{1/3} \) (so \( \beta = 1/3 \)) and simulating 100,000 sample paths with each method yields the following approximate distributions
Another example that needs explaining: part II

Again think of \( A \) 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 \( \kappa_1 = 2, \kappa_2 = .002, \kappa_3 = 2. \)

\( V = 10^3 \) and \( h = 1/20 = V^{-.434} \) (so \( \beta = .434 \)). Simulating 30,000 sample paths yields the following approximate distributions for \( B(10) \):

![Graph showing approximate distributions for B(10) using different algorithms.]
Take home messages

1. Scaling to get instructive error estimates is a tricky business and must be handled with care.

2. Can be informative in that it tells you what algorithms do (and which should be used).

3. This field still has *lots* of open problems and ways to make contributions.
Take home messages

1. Scaling to get instructive error estimates is a tricky business and must be handled with care.

2. Can be informative in that it tells you what algorithms do (and which should be used).

3. This field still has lots of open problems and ways to make contributions.

4. Interested in these models? Stochastic Models in Biology being taught next semester!