Reflected Diffusions and (Bio)Chemical Reaction Networks

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Joint work with Saul Leite, David Anderson and Des Higham

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Chemistry and Systems Biology: Continuous-time Markov chains describe the stochastic dynamics of networks of reacting chemical species.

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-Diffusion approximation I: **fluctuations around the ODE solution (linear noise approximation).**
Two-step process. Does not respect the constraint that chemical concentrations are never negative.

-Diffusion approximation II: direct Langevin-type approximation. Only valid in general until boundary of the orthant is reached.

SIMPLE EXAMPLE

Simple Example: Two species, two reactions

$$S_1 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} S_2$$

V : volume times Avogadro's number (fixed)
$\bar{X}^V$: vector of concentrations of the chemical species S_1, S_2 in Markov chain model

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ODE approximation: $\bar{X}^V(\cdot) \approx \bar{x}(\cdot)$

$$\frac{d\bar{x}_1}{dt} = \beta\bar{x}_2(t) - \alpha\bar{x}_1(t)$$
$$\frac{d\bar{x}_2}{dt} = \alpha\bar{x}_1(t) - \beta\bar{x}_2(t)$$

Simple Example: Linear noise diffusion approximation

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Linear noise approximation: $\bar{X}^V(\cdot) \approx \bar{x}(\cdot) + \frac{1}{\sqrt{V}}\tilde{Z}(\cdot)$

$$d\tilde{Z}_1(t) = (\beta\tilde{Z}_2(t) - \alpha\tilde{Z}_1(t))dt + \sqrt{\beta\bar{x}_2(t)}dW_2(t) - \sqrt{\alpha\bar{x}_1(t)}dW_1(t)$$
$$d\tilde{Z}_2(t) = (\alpha\tilde{Z}_1(t) - \beta\tilde{Z}_2(t))dt + \sqrt{\alpha\bar{x}_1(t)}dW_1(t) - \sqrt{\beta\bar{x}_2(t)}dW_2(t)$$

Simple Example: Langevin approximation

$$S_1 \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} S_2$$

Langevin approximation: $\bar{X}^V(\cdot) \approx Z(\cdot)$

$$\begin{aligned} dZ_1(t) &= (\beta Z_2(t) - \alpha Z_1(t))\, dt \\ &\quad + \frac{1}{\sqrt{V}} \left(\sqrt{\beta Z_2(t)} dW_2(t) - \sqrt{\alpha Z_1(t)} dW_1(t) \right) \\ dZ_2(t) &= (\alpha Z_1(t) - \beta Z_2(t))\, dt \\ &\quad + \frac{1}{\sqrt{V}} \left(\sqrt{\alpha Z_1(t)} dW_1(t) - \sqrt{\beta Z_2(t)} dW_2(t) \right) \end{aligned}$$

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Only valid until the first time Z_1 or Z_2 is zero.

Kurtz's Theorems

In general, theorems in
T. G. Kurtz, Limit theorems and diffusion approximations for density-dependent Markov chains (1976) and Strong approximations theorems for density-dependent Markov chains (1978)
can be used to justify the linear noise approximation for all time and the Langevin approximation until the concentration of some species is zero, i.e., Z reaches the boundary of the orthant, $\partial\mathbb{R}^d_+$

These theorems require
Linear noise approximation: drift Lipschitz continuous and continuously differentiable
Langevin approximation: drift and dispersion coefficients Lipschitz continuous (implies linear growth bound)

GENERAL REACTION NETWORK SETUP

Chemical Reaction Network Model

Species: $S_1, \ldots, S_d$
Reactions:

$$\sum_{i=1}^{d} v_{ik} S_i \xrightarrow{c_k} \sum_{i=1}^{d} v'_{ik} S_i, \quad k = 1, \ldots, r$$

Change in state of Markov chain for reaction k: $\tilde{v}_k = v'_k - v_k$

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Example:

$$S_2 + S_3 \to S_1 + S_3$$

$$v_1 = \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix} \quad v'_1 = \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \quad \tilde{v}_1 = \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}$$

Assumptions

Assume the set of reactions divides into three sets:
-A set of reactions indexed by $\mathcal{R}_1$ that are mass-dissipating: there exists a vector $u \geq 1$ such that $u \cdot \tilde{v}_k \leq 0$ for all $k \in \mathcal{R}_1$
-A set of reactions indexed by $\mathcal{R}_2$ that involve only external inputs: $v_k = 0$ for all $k \in \mathcal{R}_2$
-A set of reactions indexed by $\mathcal{R}_3$ that involve only external outputs: $v'_k = 0$ for all $k \in \mathcal{R}_3$

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Example

$$\emptyset \underset{c_1}{\overset{c_2}{\rightleftharpoons}} S_1 \underset{c_6}{\overset{c_5}{\rightleftharpoons}} S_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} \emptyset$$

MARKOV CHAIN MODEL AND APPROXIMATIONS

Markov Chain Model for Concentrations

For independent Poisson processes, $N_1, \ldots, N_r$,

$$\bar{X}^V(t) = \bar{X}^V(0) + \frac{1}{V} \sum_{k=1}^{r} \tilde{v}_k N_k \left(V \int_0^t \lambda_k^V(\bar{X}^V(s)) ds \right)$$

$$\lambda_k^V(x) \approx \lambda_k(x) = c_k \prod_{i=1}^{d} x_i^{v_{ik}}$$

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Langevin approximation (up until the boundary is reached)

$$Z(t) = \bar{X}^V(0) + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}}\sum_{k=1}^{r} \tilde{v}_k \int_0^t \sqrt{\lambda_k(Z(s))}d\tilde{W}_k(s)$$

where $\mu(x) = \sum_{k=1}^{r} \tilde{v}_k \lambda_k(x)$.

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where $\mu(x) = \sum_{k=1}^{r} \tilde{v}_k \lambda_k(x)$. Equivalent in law to

$$Z(t) = \bar{X}^V(0) + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}}\int_0^t \sigma(Z(s)) \cdot dW(s)$$

where σ is the positive definite square root of

$$\Gamma(x) = \sum_{k=1}^{r} \tilde{v}_k \tilde{v}_k^T \lambda_k(x)$$

Jump-Diffusion Approximation

$$\hat{Z}(t) = \bar{X}^V(0) + \int_0^t \mu(\hat{Z}(s)) 1_{\{\hat{Z}(s)>0\}} ds$$
$$+ \frac{1}{\sqrt{V}} \left(\int_0^t \sigma(\hat{Z}(s)) 1_{\{\hat{Z}(s)>0\}} \cdot dW(s) \right)$$
$$+ \frac{1}{\sqrt{V}} \left(\frac{1}{\sqrt{V}} \sum_{k=1}^{r} \tilde{\nu}_k N_k \left(V \int_0^t \hat{\lambda}_k(\hat{Z}(s)) 1_{\{\hat{Z}(s) \in \partial \mathbb{R}^d_+\}} ds \right) \right)$$

where

$$\hat{\lambda}_k(x) = \lambda_k(x) 1_{\{x_i \geq \frac{1}{V} \nu_{ik} \text{ for } i=1,\ldots,d\}}$$

Jump-Diffusion Approximation (cont.)

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$$= Z^\delta(t) \text{ with } \delta = \frac{1}{\sqrt{V}} \quad \text{where}$$

$$Z^\delta(t) = \bar{X}^V(0) + \int_0^t \mu(Z^\delta(s)) 1_{\{Z^\delta(s)>0\}} ds$$
$$+ \frac{1}{\sqrt{V}} \left(\int_0^t \sigma(Z^\delta(s)) 1_{\{Z^\delta(s)>0\}} \cdot dW(s) \right)$$
$$+ \frac{1}{\sqrt{V}} \left(\delta \sum_{k=1}^{r} \tilde{\nu}_k N_k \left(\delta^{-2} \int_0^t \hat{\lambda}_k^\delta(Z^\delta(s)) 1_{\{Z^\delta(s)\in\partial\mathbb{R}_+^d\}} ds \right) \right)$$

CONSTRAINED LANGEVIN EQUATION

(REFLECTED DIFFUSION APPROXIMATION)

Constrained Langevin Equation (Reflected Diffusion)

$$Z(t) = \overline{X}^V(0) + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}} \int_0^t \sigma(Z(s))dW(s)$$
$$+ \frac{1}{\sqrt{V}} \int_0^t \gamma(Z(s))dL(s)$$

Reflection Vector Field on $\partial\mathbb{R}^d_+$:

$$\gamma(x) = \frac{\mu(x)}{|\mu(x)|} \qquad \mu(x) = \sum_{k=1}^{r} \tilde{v}_k \lambda_k(x)$$

Boundary process (one-dimensional, cts, non-decreasing):

$$L(t) = \int_0^t 1_{\{Z(s) \in \partial\mathbb{R}^d_+\}} dL(s)$$

Main Theorem (Leite-W)

Weak (and strong) existence and uniqueness holds for the Constrained Langevin Equation (CLE):

$$Z(t) = z + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}} \int_0^t \sigma(Z(s))dW(s) + \frac{1}{\sqrt{V}} \int_0^t \gamma(Z(s))dL(s)$$

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Moreover,

$$Z^{\delta_n} \Longrightarrow Z \text{ as } \delta_n \to 0,$$

where Z solves the CLE.

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where Z solves the CLE.

Proof: C-tightness argument (modified from Kang-W '07) and any limit point solves the CLE. Use weak uniqueness for CLE to prove convergence.

Identifying the Limit

$$
\begin{aligned}
Z^{\delta}(t) = \bar{X}^{V}(0) &+ \int_0^t \mu(Z^{\delta}(s)) 1_{\{Z^{\delta}(s)>0\}}\, ds \\
&+ \frac{1}{\sqrt{V}} \left(\int_0^t \sigma(Z^{\delta}(s)) 1_{\{Z^{\delta}(s)>0\}} \cdot dW(s) \right) \\
&+ \frac{\delta^{-1}}{\sqrt{V}} \int_0^t \sum_{k=1}^{r} \tilde{v}_k \hat{\lambda}_k^{\delta}(Z^{\delta}(s)) 1_{\{Z^{\delta}(s)\in\partial\mathbb{R}_+^d\}}\, ds \\
&+ \frac{\delta}{\sqrt{V}} \sum_{k=1}^{r} \tilde{v}_k \hat{N}_k \left(\delta^{-2} \int_0^t \hat{\lambda}_k^{\delta}(Z^{\delta}(s)) 1_{\{Z^{\delta}(s)\in\partial\mathbb{R}_+^d\}}\, ds \right)
\end{aligned}
$$

EXAMPLES

Example I: Two species, six reactions

$$\emptyset \underset{c_1}{\overset{c_2}{\rightleftharpoons}} S_1 \underset{c_6}{\overset{c_5}{\rightleftharpoons}} S_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} \emptyset$$

$$\lambda_1(x) = c_1 x_1,\ \lambda_2(x) = c_2,\ \lambda_3(x) = c_3 x_2,\ \lambda_4(x) = c_4$$
$$\lambda_5(x) = c_5 x_1,\ \lambda_6(x) = c_6 x_2$$

With $c_1 = 10^{-4}$, $c_2 = 1$, $c_3 = 1$, $c_4 = 10^{-4}$, $c_5 = 100$, $c_6 = 1$, $V = 100$, and starting state $x_0 = (0.02, 1.00)$ (near steady-state for deterministic model)

Our diffusion approximation (CLE)

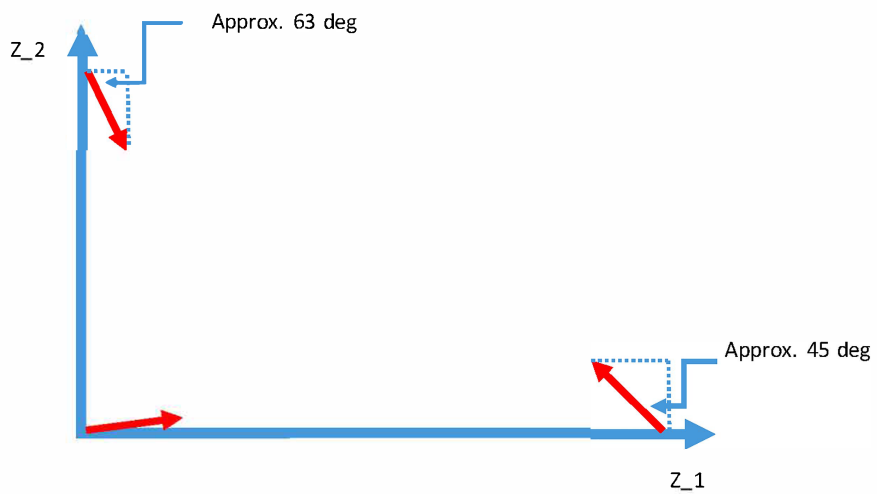
$$\emptyset \underset{c_1}{\overset{c_2}{\rightleftharpoons}} S_1 \underset{c_6}{\overset{c_5}{\rightleftharpoons}} S_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} \emptyset$$

$$Z(t) = z + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}}\left(\int_0^t \sigma(Z(s)) \cdot dW(s) + \int_0^t \gamma(Z(s))dL(s)\right)$$

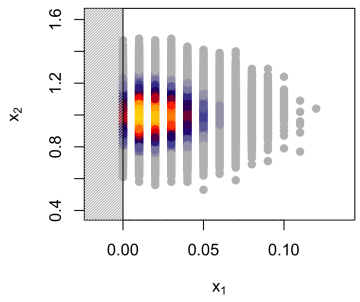
$$\mu_1(x) = c_2 - c_1 x_1 - c_5 x_1 + c_6 x_2, \quad \mu_2(x) = c_4 - c_3 x_2 + c_5 x_1 - c_6 x_2$$

$$(\sigma\sigma^T)(x) = \begin{bmatrix} c_2 + c_1 x_1 + c_5 x_1 + c_6 x_2 & -(c_5 x_1 + c_6 x_2) \\ -(c_5 x_1 + c_6 x_2) & c_4 + c_3 x_2 + c_5 x_1 + c_6 x_2 \end{bmatrix}$$

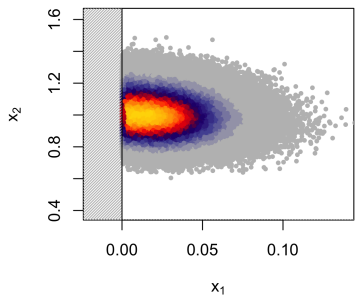
$$\gamma(x) = \mu(x)/|\mu(x)|$$



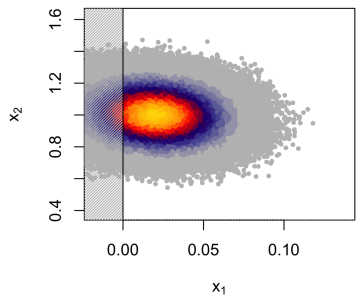
Comparison of different methods



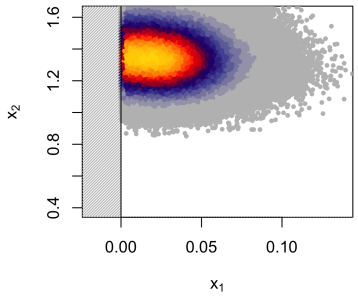
MCM



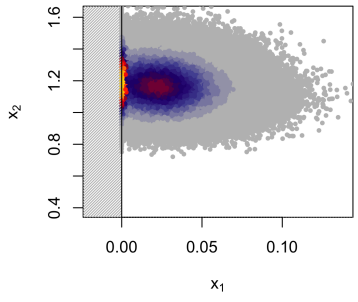
CLE



LNA



LE-NR



LE-Chop

Figure: MCM=Markov Chain Model, CLE=Constrained Langevin Equation, LNA=Linear Noise Approximation, LE-NR=Langevin Equation with Normal Reflection at boundary, LE-Chop=LE with Chopping off of negative excursions. Simulations run until time $\boldsymbol{t = 10^4}$

Comparison of mean running times

Model	Mean Running Time	95%-C.I.
MCM	**310.338 s**	**(309.624, 311.052)**
LNA	**320.178 s**	**(319.645, 320.711)**
CLE	**308.922 s**	**(307.686, 310.159)**
LE-NR	**282.607 s**	**(281.706, 283.509)**
LE-Chop	**251.664 s**	**(251.584, 251.743)**

Table: Mean running time in seconds for the simulations. The mean running time is calculated by averaging the running times over 10 independent runs. The 95%-confidence interval for this average is also calculated.

Example II (Brusselator): Two species, six reactions

$$\emptyset \underset{c_1}{\overset{c_2}{\rightleftharpoons}} S_1 \overset{c_5}{\rightarrow} S_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} \emptyset$$
$$2S_1 + S_2 \overset{c_6}{\rightarrow} 3S_1$$

$$\lambda_1(x) = c_1 x_1,\ \lambda_2(x) = c_2,\ \lambda_3(x) = c_3 x_2,\ \lambda_4(x) = c_4$$
$$\lambda_5(x) = c_5 x_1,\ \lambda_6(x) = c_6 x_1^2 x_2$$

With $c_1 = 1$, $c_2 = 1$, $c_3 = 10^{-4}$, $c_4 = 10^{-4}$, $c_5 = 11$, $c_6 = 10, V = 100$, and starting state $x_0 = (2, 1)$.

The deterministic ODE model for this chemical reaction system exhibits a stable limit cycle (with parameters shown).

Our diffusion approximation (CLE)

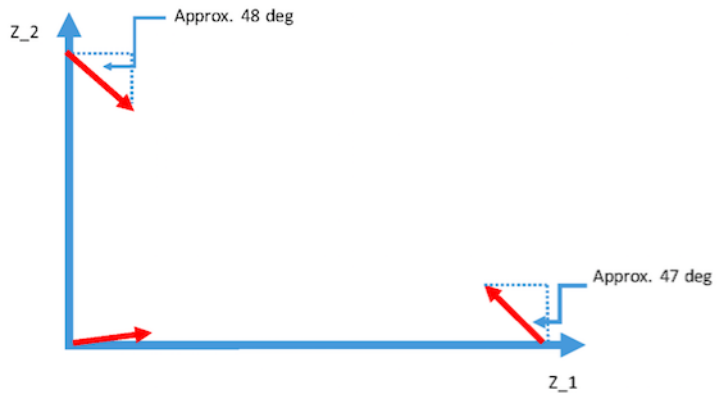
$$Z(t) = z + \int_0^t \mu(Z(s))ds + \frac{1}{\sqrt{V}}\left(\int_0^t \sigma(Z(s)) \cdot dW(s) + \int_0^t \gamma(Z(s))dL(s)\right)$$

$$\mu_1(x) = c_2 - c_1 x_1 - c_5 x_1 + c_6 x_1^2 x_2,$$

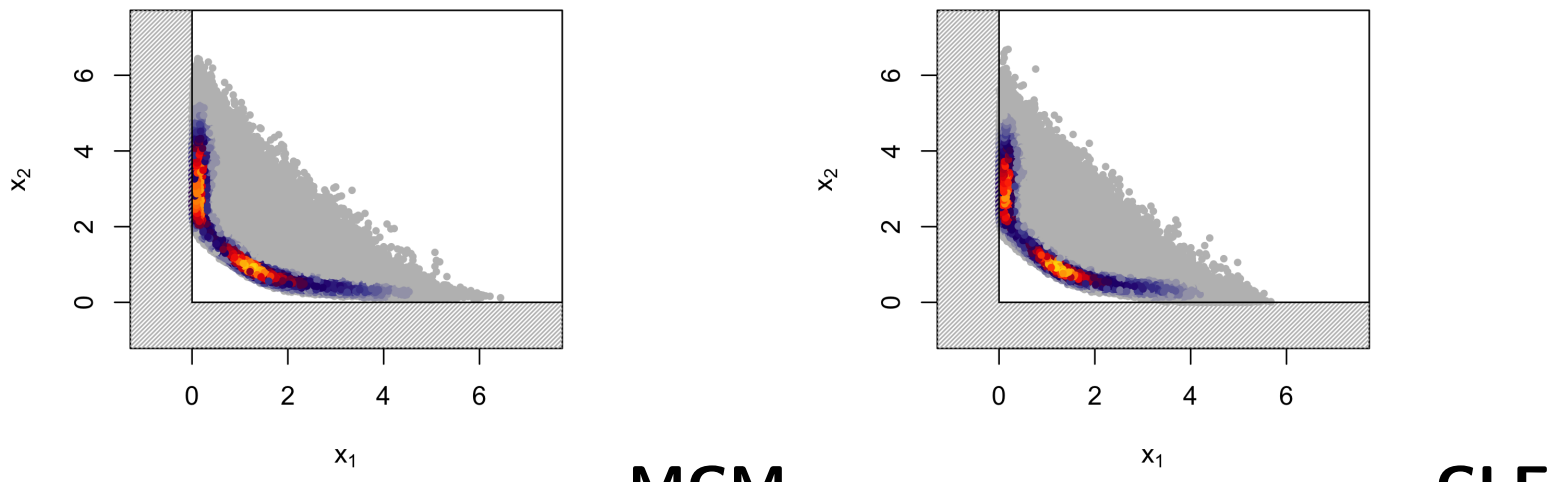
$$\mu_2(x) = c_4 - c_3 x_2 + c_5 x_1 - c_6 x_1^2 x_2$$

$$(\sigma\sigma^T)(x) = \begin{bmatrix} c_2 + c_1 x_1 + c_5 x_1 + c_6 x_1^2 x_2 & -(c_5 x_1 + c_6 x_1^2 x_2) \\ -(c_5 x_1 + c_6 x_1^2 x_2) & c_4 + c_3 x_2 + c_5 x_1 + c_6 x_1^2 x_2 \end{bmatrix}$$

$$\gamma(x) = \mu(x)/|\mu(x)|$$



Comparison of MCM and CLE



MCM **CLE**

Figure: Simulations run until $t = 10^4$. A scatter plot for LNA is not shown since LNA oscillates and diverges during a long simulation.

Comparison of Running Times for MCM and CLE

Model	Mean Running Time	95%-C.I.
MCM	**915.332 s**	**(912.949, 917.715)**
CLE	**255.127 s**	**(254.843, 255.410)**

Table: Mean running time in seconds for the simulation of MCM and CLE. The mean running time is calculated by averaging the running times over the 10 independent runs. The 95%-confidence interval from this average is also calculated.

Simulations of Trajectories in Time

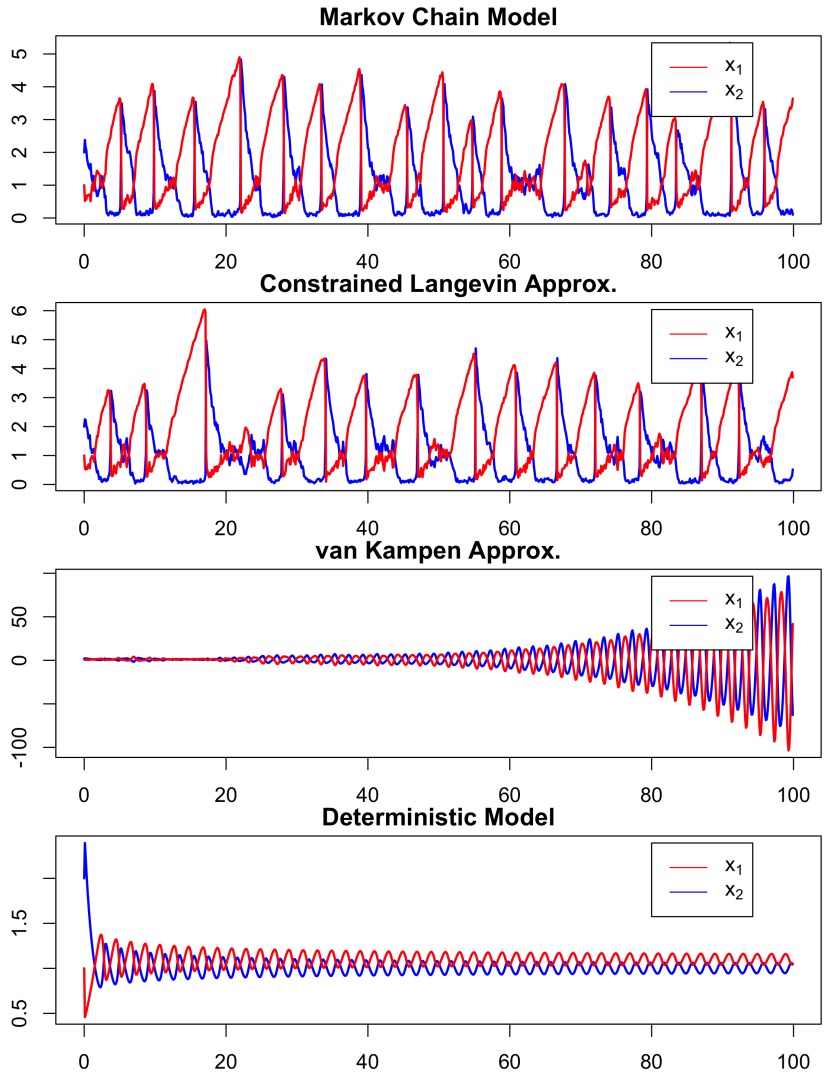


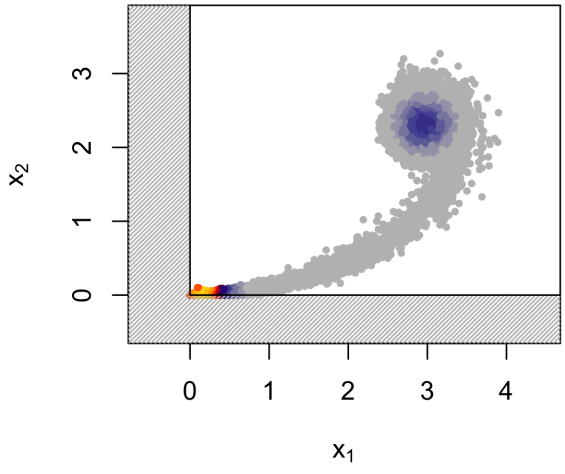
Figure: LNA increases in oscillation and diverges during a long simulation.

Example III (Bistability)

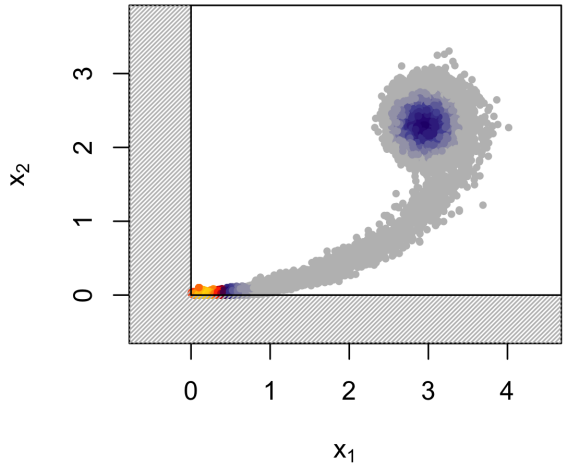
$$S_1 \underset{c_2}{\overset{c_1}{\rightleftharpoons}} \emptyset \qquad S_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} \emptyset \qquad S_3 \underset{c_6}{\overset{c_5}{\rightleftharpoons}} \emptyset$$

$$S_3 + S_2 \xrightarrow{c_7} 2S_1 \qquad 2S_1 \xrightarrow{c_8} S_1 + S_2 \qquad S_1 + S_2 \xrightarrow{c_9} S_2.$$

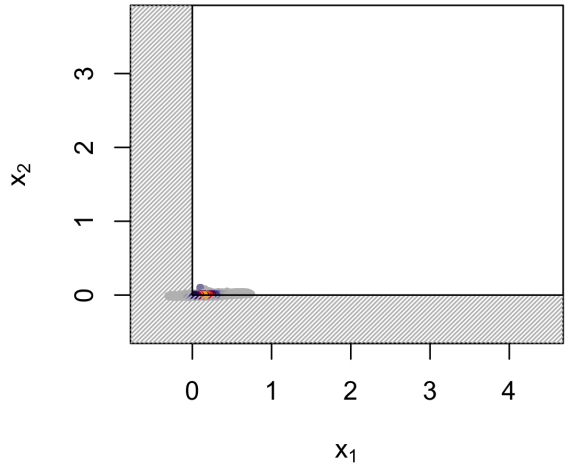
$c_1 = 1/\sqrt{10}$, $c_2 = 0.01$, $c_3 = 1$, $c_4 = 0.01$, $c_5 = 1$, $c_6 = 10$, $c_7 = 8/10$, $c_8 = 1$, $c_9 = 1.5/\sqrt{10}$. ODE model is bistable with two real stable points near $(1.2679 \cdot 10^{-1}, 2.90328 \cdot 10^{-3}, 9.97683)$ and $(2.96686, 2.31681, 3.50454)$.



MCM



CLE



LNA

Future Work

Investigate what happens if some species do not have inflows.

Other applications: population genetics, neuroscience?

Error estimates for approximation of $\bar{X}^V$ by CLE.

Numerical approximation of reflected diffusion.

THANK YOU!

Reflected Diffusions and (Bio)Chemical Reaction Networks
Abstract

Continuous-time Markov chain models are often used to describe the stochastic dynamics of networks of reacting chemical species, especially in the growing field of systems biology. Discrete-event stochastic simulation of these models rapidly becomes computationally intensive. Consequently, more tractable diffusion approximations are commonly used in numerical computation, even for modest-sized networks. However, existing approximations (e.g., linear noise and Langevin), do not respect the constraint that chemical concentrations are never negative.
In this talk, we propose an approximation for such Markov chains, via reflected diffusion processes, that respects the fact that concentrations of chemical species are non-negative. This fixes a difficulty with Langevin approximations that they are frequently only valid until the boundary of the positive orthant is reached. Our approximation has the added advantage that it can be written down immediately from the chemical reactions. This contrasts with the linear noise approximation, which involves a two-stage procedure — first solving a deterministic ordinary differential equation, followed by a stochastic differential equation for fluctuations around those solutions.
An invariance principle for reflected diffusions, due to Kang and Williams, is adapted in justifying our approximation under mild assumptions. Some numerical examples illustrate the advantages of our approximation over direct simulation of the Markov chain or use of the linear noise approximation.

This talk is based on joint work with David Anderson, Des Higham and Saul Leite.