In 2019, Leite and Williams proposed certain reflected diffusion processes as approximations to continuous time Markov chain models frequently used to model biochemical reaction networks. These diffusions live in the positive orthant of a d-dimensional space and are confined there by a smoothly varying oblique reflection field on the boundary. Leite and Williams showed that, under mild conditions, these diffusions can be obtained as weak limits of certain jump-diffusion extensions of the traditional Langevin approximations, and therefore called these constrained Langevin approximations. In this talk, we will review this approximation and describe some progress on proving error estimates for strong versions of this approximation and also describe some remaining open problems. Part of this work is joint with Felipe Campos.
Stochastic Models of Biochemical Reaction Networks and Reflected Diffusions

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Joint work with Saul Leite and Felipe Campos
**Motivation**

**Stochastic (Bio)Chemical Reaction Networks (CRN):** continuous-time Markov chain models used to describe the stochastic dynamics of finitely many species undergoing changes in their quantities due to finitely many reactions.

**Discrete-event stochastic simulation (Gillespie algorithm):** Rapidly becomes computationally intensive.

**Approximations**

- **Reaction Rate Equations:** ODE model, good if all species have large numbers.

- **Linear Noise Approximation:** Diffusion, components can be negative, does not capture nonlinearities well, numerical instability.

- **Langevin Approximation:** Diffusion in positive orthant, good until boundary of orthant is reached.

**How can one continue the Langevin approximation beyond the first time the boundary of the orthant is reached?**
Simple Example: SIS model

\[ S + I \xrightarrow{c_1} 2I, \quad I \xrightarrow{c_2} S \]

\( r \) : volume times Avogadro’s number (fixed)
\( \bar{X}^r \) : vector of concentrations of the species \( I, S \) in Markov chain model

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

\[
\frac{d\bar{x}_1}{dt} = c_1 \bar{x}_1(t) \bar{x}_2(t) - c_2 \bar{x}_1(t) \\
\frac{d\bar{x}_2}{dt} = c_2 \bar{x}_1(t) - c_1 \bar{x}_1(t) \bar{x}_2(t)
\]

Linear noise approximation: \( \bar{X}^r(\cdot) \approx \bar{x}(\cdot) + \frac{1}{\sqrt{r}} D(\cdot) \)

\[
dD_1(t) = -dD_2(t) \\
= ((c_1 \bar{x}_2(t) - c_2) D_1(t) + c_1 \bar{x}_1(t) D_2(t)) dt \\
+ \sqrt{c_1 \bar{x}_1(t) \bar{x}_2(t)} dW_1(t) - \sqrt{c_2 \bar{x}_1(t)} dW_2(t)
\]

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

\[
dZ_1^r(t) = -dZ_2^r(t) \\
= (c_1 Z_1^r(t) Z_2^r(t) - c_2 Z_1(t)) dt \\
+ \frac{1}{\sqrt{r}} \left( \sqrt{c_1 Z_1^r(t) Z_2^r(t)} dW_1(t) - \sqrt{c_2 Z_1^r(t)} dW_2(t) \right)
\]
Simple Example: SIS model

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**ODE approximation:** \( \bar{X}^r(\cdot) \approx \bar{x}(\cdot) \)

\[
\begin{align*}
\frac{d\bar{x}_1}{dt} &= c_1 \bar{x}_1(t) x_2(t) - c_2 \bar{x}_1(t) \\
\frac{d\bar{x}_2}{dt} &= c_2 \bar{x}_1(t) - c_1 \bar{x}_1(t) \bar{x}_2(t)
\end{align*}
\]

**Linear noise approximation:** \( \bar{X}^r(\cdot) \approx \bar{x}(\cdot) + \frac{1}{\sqrt{r}} D(\cdot) \)

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&\quad + \sqrt{c_1 \bar{x}_1(t) \bar{x}_2(t)} dW_1(t) - \sqrt{c_2 \bar{x}_1(t)} dW_2(t)
\end{align*}
\]

**Langevin approximation:** \( \bar{X}^r(\cdot) \approx Z^r(\cdot) \)

\[
\begin{align*}
dZ_1^r(t) &= -dZ_2^r(t) \\
&= (c_1 Z_1^r(t) Z_2^r(t) - c_2 Z_1(t)) dt \\
&\quad + \frac{1}{\sqrt{r}} \left( \sqrt{c_1 Z_1^r(t) Z_2^r(t)} dW_1(t) - \sqrt{c_2 Z_1^r(t)} dW_2(t) \right)
\end{align*}
\]

Only valid until the first time \( Z_2^r \) is zero.
**Stochastic Chemical Reaction Network**

Species: $\mathcal{S} = \{S_1, \ldots, S_d\}$

Reactions: $\mathcal{R} = \{(v_j^-, v_j^+) \in (\mathbb{Z}_+^d \times \mathbb{Z}_+^d) : v_j^- \neq v_j^+, j = 1, \ldots, n\}$

$$
\sum_{i=1}^{d} v_{ij}^- S_i \xrightarrow{c_j} \sum_{i=1}^{d} v_{ij}^+ S_i.
$$

Net change vectors (reaction vectors) $v_j := v_j^+ - v_j^-$, $j = 1, \ldots, n$.

Denote by $[v_j^-] := \sum_{i=1}^{d} v_{ij}^-$ the order of reaction $R_j$.

Concentration Process (Continuous Time Markov Chain): For $N_1, \ldots, N_n$ independent Poisson processes,

$$
\bar{X}^r(t) = \frac{X^r(t)}{r} = \bar{X}^r(0) + \frac{1}{r} \sum_{j=1}^{n} v_j N_j \left( \int_{0}^{t} r \beta_j (\bar{X}^r(s)) \, ds \right).
$$

where $\beta_j (x) = c_j \prod_{i=1}^{d} (x_i)^{v_{ij}^-}$ (mass action kinetics).
Approximations

ODE (Kurtz ’70): under mild assumptions, for every $T \geq 0$,

$$\lim_{r \to \infty} \sup_{0 \leq t \leq T} |\bar{X}^r(t) - \bar{x}(t)| = 0 \quad \text{a.s.,}$$

where for $\mu(x) = \sum_{j=1}^{n} v_j \beta_j(x)$,

$$\frac{d\bar{x}}{dt} = \mu(\bar{x}(t)).$$

Linear Noise Approximation (van Kampen ‘61, Kurtz ‘75): $\bar{X}^r(\cdot) \approx \bar{x}(\cdot) + \frac{1}{\sqrt{r}} D(\cdot)$

$$D(t) = \int_{0}^{t} J \mu(\bar{x}(s)) D(s)ds + \sum_{j=1}^{n} \int_{0}^{t} v_j \sqrt{\beta_j(\bar{x}(s))} dW_j(s)$$

Langevin Approximation (Kurtz ‘76): $\bar{X}^r(\cdot) \approx Z^r(\cdot)$, where until $Z^r$ reaches $\partial \mathbb{R}^d_+$,

$$Z^r(t) = Z^r(0) + \int_{0}^{t} \mu(Z^r(s))ds + \frac{1}{\sqrt{r}} \sum_{j=1}^{n} v_j \int_{0}^{t} \sqrt{\beta_j(Z^r(s))} dW_j(s)$$

$$= Z^r(0) + \int_{0}^{t} \mu(Z^r(s))ds + \frac{1}{\sqrt{r}} \int_{0}^{t} \sigma(Z^r(s))dW^r(s)$$

Here $W = (W_1, \ldots, W_n)$ is an $n$-dimensional standard Brownian motion, $W^r$ is a $d$-dimensional standard Brownian motion and $(\sigma \sigma')(x) = \sum_{j=1}^{n} v_j v'_j \beta_j(x)$. 
Leite & Williams ('19) proposed the **Constrained Langevin Approximation (CLA)** $Z^r$ for $\overline{X^r}$ where $Z^r$ is the solution to the following SDE with reflection:

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

where $(\sigma\sigma')(x) = \sum_{j=1}^n v_j v_j' \beta(x, v_j)$ and $\gamma(x) = \frac{\mu(x)}{|\mu(x)|}$, for $x \in \mathbb{R}^d$.

Assuming production and degradation for each species, LW19 proved $Z^r$ is well defined and can be obtained as a limit of jump-diffusions which behave like the Langevin approximation in the interior of the orthant and as a rescaled version of the Markov chain on the boundary.
\[
\emptyset \xrightarrow{\frac{c_2}{c_1}} S_1 \xrightarrow{\frac{c_5}{c_6}} S_2 \xrightarrow{\frac{c_3}{c_4}} \emptyset
\]

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

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

\[
(\sigma\sigma')(x) = \begin{bmatrix}
  c_2 + c_1 x_1 + c_5 x_1 + c_6 x_2 & -(c_5 x_1 + c_6 x_2) \\
  -(c_5 x_1 + c_6 x_2) & c_4 + c_3 x_2 + c_5 x_1 + c_6 x_2
\end{bmatrix}
\]

\[
\gamma(x) = \mu(x)/|\mu(x)|
\]

Parameters: \(c_1 = 10^{-4}, c_2 = 1, c_3 = 1, c_4 = 10^{-4}, c_5 = 100, c_6 = 1, r = 100\).
Comparison of Approximations

Figure: MCM=Markov Chain Model, CLA=Constrained Langevin Approximation, 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 $t = 10^4$. 
Further Questions

Error estimates for approximation of $\tilde{X}^r$ by CLA $Z^r$

What happens if some species do not have production or degradation? Problems with well posedness.

Numerical approximation of the reflected diffusion (CLA).
One-dimensional Case

Includes

Chemical reaction networks (CRNs) with one species.

Some reduced CRNs because of mass conservation.

Some reduced CRNs because of multiscaling.

Does not need production or degradation of species.

There are two cases, the CLA state space is $\mathcal{I} = [0, a]$, where $a > 0$, or $\mathcal{I} = [0, \infty)$. For $r \geq 1$, define $\mathcal{I}^r := \mathcal{I} \cap (\mathbb{Z}_+/r)$.

Extension to nearly density dependent Markov chains (not displayed here).
**Bounded Interval Case** ($\mathcal{I} = [0, a]$)

**Concentration Process:**

(1) \[ \bar{X}^r(t) = \bar{X}^r(0) + \frac{1}{r} \sum_{j=1}^{n} v_j N_j \left( \int_0^t r \beta_j (\bar{X}^r(s)) \, ds \right) \]

where the functions $\beta_j(\cdot)$ are Lipschitz continuous on $\mathcal{I}$ for $j = 1, \ldots, n$.

**Constrained Langevin Approximation (CLA) $Z^r$:**

\[ Z^r(t) = Z^r(0) + \int_0^t \mu(Z^r(s)) \, ds + \frac{1}{\sqrt{r}} \int_0^t \sigma(Z^r(s)) \, dW^r(s) + \frac{1}{\sqrt{r}} \int_0^t \gamma(Z^r(s)) \, d\bar{L}^r(s) \]

where $\mu, \sigma, \gamma : \mathcal{I} \to \mathbb{R}$ are defined by:

\[ \mu(x) := \sum_{j=1}^{n} v_j \beta_j(x), \quad \sigma(x) := \left( \sum_{j=1}^{n} v_j^2 \beta_j(x) \right)^{1/2} \]

\[ \gamma = \begin{cases} 1_{\{0\}} - 1_{\{a\}} & \text{if } \mathcal{I} = [0, a] \\ 1_{\{0\}} & \text{if } \mathcal{I} = [0, \infty). \end{cases} \]

Strong existence and pathwise uniqueness holds for the CLA. Note that $\sigma$ may be only Hölder continuous of order $1/2$. 
There exists a filtered probability space \((\Omega, \mathcal{F}, \{\mathcal{F}_t\}, \mathbb{P})\) such that for each \(r \geq 8\) and \(\bar{x}_0^r \in \bar{I}^r\), there are processes \(Z^r, W^r, L^r, \bar{X}^r\) defined on \((\Omega, \mathcal{F}, \mathbb{P})\) such that:

(i) \(\bar{X}^r\) satisfies the concentration process equation (1) with \(\bar{X}^r(0) = \bar{x}_0^r\).

(ii) The tuple \((\Omega, \mathcal{F}, \mathbb{P}, \{\mathcal{F}_t\}, Z^r, W^r, L^r)\) is a weak solution to the CLA equation, with \(Z^r(0) = \bar{x}_0^r\), \(\mathbb{P}\)-a.s.

Furthermore,

(iii) there is a family of nonnegative random variables \(\{\Theta_T^r\}_{T \geq 1}\) such that for every \(T \geq 1\)

\[
\sup_{0 \leq t \leq T} |\bar{X}^r(t) - Z^r(t)| \leq \Theta_T^r \frac{\log r}{r} \quad \mathbb{P} - \text{a.s.}
\]

and

\[
\mathbb{P}[\Theta_T^r > C_T + x] \leq \frac{K_T}{r^2} \exp (-\lambda_T x \log r)
\]

for every \(x \geq 0\), where \(\lambda_T, C_T\) and \(K_T\) do not depend on \(r\).
\[ S + I \xrightarrow{c_1} 2I, \quad I \xrightarrow{c_2} S \]

- Define \( \bar{X}^r := \bar{X}_1^r \) fraction of the total population of size \( r \) that are infected
- The CLA \( Z^r \) that approximates \( \bar{X}^r \) satisfies:

\[
Z^r(t) = Z^r(0) + \int_0^t (c_1 Z^r(s)(1 - Z^r(s)) - c_2 Z^r(s)) \, ds \\
+ \frac{1}{\sqrt{r}} \int_0^t \sqrt{c_1 Z^r(s)(1 - Z^r(s)) + c_2 Z^r(s)} \, dW^r(s) \\
+ \frac{1}{\sqrt{r}} \int_0^t (\mathbb{1}_\{0\}(Z^r(s)) - \mathbb{1}_\{1\}(Z^r(s))) \, dL^r(s).
\]
**SIS model**

**Example**

![Simulation](image)

**Figure:** Simulation for one run of the MC $X^r$, CLA $Z^r$ and ODE solution $\bar{x}$ for the SIS model with $x_0^r = 0.82$, $r = 100$, $c_1 = c_2 = 1$.

$X^r$ and $Z^r$ both reach 0 in finite time and absorb there.
Figure: Densities (simulated) for the hitting time to 0 (absorbing time) for the Markov chain $X^r$ and the CLA $Z^r$ with parameters $c_1 = 1$, $c_2 = 0.95$, $r = 100$, $a = 1$ and $\bar{x}_0^r = 0.99$. 
HALFLINE CASE \( (I = [0, \infty)) \)

**Theorem 2** ▶ *Campos-Williams ‘23*

When \( I = [0, \infty) \), under suitable conditions, for \( r \geq 8 \) we can construct a coupling \((X^r, Z^r)\) where for every compact set \( \mathcal{K} \subseteq I \) such that \( x_0^r \in \mathcal{K} \) there is a family of nonnegative random variables \( \{\Theta_{T, \mathcal{K}}^r\}_{T \geq 1} \) such that:

\[
\sup_{0 \leq t \leq T \land \tau_{\mathcal{K}}} |X^r(t) - Z^r(t)| \leq \Theta_{T, \mathcal{K}}^r \frac{\log r}{r} \quad \mathbb{P} \text{ – a.s.}
\]

\[
\mathbb{P}[\Theta_{T, \mathcal{K}}^r > C_T + x] \leq \frac{K_T}{r^2} \exp \left( -\lambda_T x \log r \right)
\]

for every \( x \geq 0 \), where \( \tau_{\mathcal{K}} = \inf\{t \geq 0 \mid X^r(t) \notin \mathcal{K} \text{ or } Z^r(t) \notin \mathcal{K}\} \).
Main Ingredients of the Proof

- Komlós-Major-Tusnády type strong approximation (Komlós, Major & Tusnády '75 & '76 and Ethier & Kurtz '86)

\[ N_j(t) = t + W_j(t) + O(\log t) \]

- Lipschitz continuity of the Skorokhod map
  - For \( \mathcal{I} = [0, \infty) \), there is an explicit formula and it is straightforward to check the Lipschitz property.
  - The case \( \mathcal{I} = [0, a] \) was proved in Kruk, Lehoczky, Ramanan & Shreve '07

Much of what we have done extends to the CLA in higher dimensions

Two challenges:
- Lipschitz continuity of the Skorokhod map for a smoothly varying oblique reflection field on the boundary of the orthant
- Well posedness of the CLA without production/degradation


