Extending the Tools of Chemical Reaction Engineering to the Molecular Scale
Multiple-time-scale order reduction for stochastic kinetics

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Model Reduction in Reacting Flows
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Outline

1. Introduction to stochastic kinetics
2. Model reduction — fast reactions and reactive intermediates
3. Catalyst example with fast diffusion
4. Virus example with fast fluctuation
5. Further reading
Introduction to stochastic kinetics

**Stochastic kinetics**
- Small species populations
- Species numbers are integers, reactions cause integer jumps
- Large fluctuations in species numbers and reaction rates
- Biological networks and catalyst particles

**Model reduction**
Develop reduced models from stochastic chemical reactions. These models must meet the following requirements:
- Simpler than the full model (fewer reactions, fewer parameters, or faster simulation times)
- Converge to the full model as a specified parameter goes to zero
The KMC algorithm for the reaction $A \xrightleftharpoons[k_2]{k_1} B$ with $k_1 = 2$, $k_2 = 1$, $n_{A0} = 6$, and $n_{B0} = 3$ is as follows:

1. Choose which reaction
2. Choose time step
3. Repeat

**KMC Algorithm**

- Which reaction: 
  \[ \frac{r_1}{r_1 + r_2} = \frac{12}{12+3} \quad \text{or} \quad \frac{r_2}{r_1 + r_2} = \frac{3}{12+3} \]
- Time step: Sample from an exponential distribution where the distribution mean is the sum of reaction rates.
KMC simulations and probability

KMC simulations are samples of a probability distribution that evolves in time.

We can write the evolution equation for the probability density (master equation).
Chemical master equation

\[
\frac{dP(x)}{dt} = \sum_{j=1}^{N_{\text{rxn}}} r_j(x - \nu_j)P(x - \nu_j) - r_j(x)P(x)
\]

- rate into state \( x \)
- rate out of state \( x \)

\[
\frac{dP}{dt} = AP
\]

Master equation example

- \( A \xrightarrow{k_1} B \xleftarrow{k_2} \)
- \( n_{A0} = 100, n_{B0} = 0 \)
- \( k_1 = 2, k_2 = 1 \)
- 101 possible states
- 101 Coupled ODEs
Master equation — Important points

Chemical master equation

\[
\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} r_j(x - \nu_j)P(x - \nu_j) - r_j(x)P(x)
\]

\[
\frac{dP}{dt} = AP
\]

- Often the dimensionality of the master equation makes direct solution infeasible
- The master equation shows what probability distribution is sampled in a KMC simulation
- A reduced master equation can lead to a new/faster simulation schemes
Kinetics of multiple time scales

\[ A \xrightleftharpoons[k_{-1}]{k_1} B \xrightarrow[k_2]{1} C \]

**Deterministic - One Time Scale**

\[ k_1 = 2, \quad k_{-1} = 0.5, \quad k_2 = 0.5 \]

**KMC - One Time Scale**

\[ k_1 = 2, \quad k_{-1} = 0.5, \quad k_2 = 0.5 \]

**Deterministic - Two Time Scales**

\[ k_1 = 10, \quad k_{-1} = 10, \quad k_2 = 0.5 \]

**KMC - Two Time Scales**

\[ k_1 = 2, \quad k_{-1} = 20, \quad k_2 = 20 \]

**Deterministic - Two Time Scales**

\[ k_1 = 10, \quad k_{-1} = 10, \quad k_2 = 0.5 \]

**KMC - Two Time Scales**

\[ k_1 = 2, \quad k_{-1} = 20, \quad k_2 = 20 \]

One time scale  
Reaction equilibrium  
Reactive intermediate
Deterministic model reductions

\( x \) non-QSSA species, \( y \) QSSA species

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y) \\
\epsilon \frac{dy}{dt} &= g(x, y)
\end{align*}
\]

Classical QSSA

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y) \\
0 &= g(x, y)
\end{align*}
\]

- DAE reduced model

Singular Perturbation QSSA

\[
\begin{align*}
x &= X_0 + \epsilon X_1 + \epsilon^2 X_2 + O(\epsilon^3) \\
y &= Y_0 + \epsilon Y_1 + \epsilon^2 Y_2 + O(\epsilon^3)
\end{align*}
\]

- Collect like powers of \( \epsilon \)
- Equations for \( \frac{dX_0}{dt} \) is the reduced model
- Separate models for fast and slow time scale
Our objective

Apply singular perturbation analysis to develop a reduced master equation.

\[
\begin{align*}
A & \xrightleftharpoons[\kappa_{-1}]{\kappa_1} B \xrightarrow{k_2} C \\
\frac{dP(a, b, c)}{dt} &= k_1(a + 1)P(a + 1, b - 1, c) + k_{-1}(b + 1)P(a - 1, b + 1, c) \\
&\quad + k_2(b + 1)P(a, b + 1, c - 1) - (k_1a + k_{-1}b + k_2b)P(a, b, c) \\
P(a, b, c) &= W_0(a, b, c) + \epsilon W_1(a, b, c) + \cdots
\end{align*}
\]

\(\epsilon^0\) terms:

- \(W_0(a, b, c) = 0\) if \(b > 0\)
- In this limit \(b\) is always zero
SPA on the master equation

$\epsilon^1$ terms: Reduced master equation

$$\frac{dW_0(a, 0, c)}{dt} = \tilde{k}(a + 1)W_0(a + 1, 0, c - 1) - \tilde{k}aW_0(a, 0, c)$$

Reduced mechanism

$$A \rightarrow C \quad r = \frac{k_1k_2}{k_{-1} + k_2} a$$

- Stochastic same as deterministic SPA mechanism
- Same mechanisms due to linearity

First-order correction, $\langle b \rangle$

$$\langle b \rangle = f(W_0(a, 0, c)) + O(\epsilon^2)$$

$$\langle b \rangle = \frac{k_1}{k_{-1} + k_2} \langle a \rangle$$
Comparison of mechanisms

\[
\begin{align*}
A & \iff 2B & r_1 &= k_1a & r_1 = k_1a \\
B & \rightarrow C & r_2 &= k_2b & r_1 = \frac{k_1}{2} b(b - 1)
\end{align*}
\]

Stoch SPA

\[
A \rightarrow 2C \\
r = \left(\frac{k_1 k_2}{k_2 + k_1}\right) a
\]

Det SPA

\[
A \rightarrow 2C \\
r = k_1a
\]

Det QSSA

\[
A \rightarrow 2C \\
r = k_2 \left[\frac{-k_2 + \sqrt{k_2^2 + 8k_1k_{-1}a}}{4k_{-1}}\right]
\]

\[
\langle c \rangle \\
n_A = 25, n_B = 0, n_C = 0 \\
k_1 = 1 \\
k_{-1} = 1000 \\
k_2 = 1000
\]
Catalyst Example

\[
\begin{align*}
A & \xrightarrow{k_1} B \xrightarrow{k_2} C \\
B + D & \xrightarrow{k_3} B + E \\
k_2, k_3 & \gg k_1
\end{align*}
\]

Stoch SPA mechanism

\[
\begin{align*}
A & \rightarrow C \\
D + A & \rightarrow E + C \\
2D + A & \rightarrow 2E + C \\
\cdots \\
nD + A & \rightarrow nE + C
\end{align*}
\]

\[
\begin{align*}
 r_0 &= \frac{k_1 a}{1 + K_3 d} \\
 r_1 &= \frac{k_3 d}{1 + K_3 (d - 1)} \\
 r_2 &= \frac{k_3 (d - 1)}{1 + K_3 (d - 2)} \\
 r_n &= \frac{k_3 (d + 1 - n)}{1 + K_3 (d - n)}
\end{align*}
\]

Deterministic SPA mechanism

\[
\begin{align*}
A & \rightarrow C \\
D + A & \rightarrow E + A \\
\end{align*}
\]

\[
\begin{align*}
 r_0 &= k_1 a \\
 r_1 &= \frac{k_3 k_1}{k_2} ad
\end{align*}
\]
Conclusions — Stochastic quasi-steady-state approximation

- QSSA species are removed from stochastic models with SPA
- Stochastic QSSA mechanisms different than deterministic QSSA mechanisms
- Application of stochastic QSSA:
  - Reduces the number of kinetic parameters
  - Speeds up KMC simulations (fewer events)
Conclusions — Stochastic quasi-steady-state approximation

QSSA species (# of molecules)

non-QSSA species (# of molecules)

<<1

<<1

<<10^3

10^3

10^3

1

10^3

10^3

sQSPA

sQSPA-Ω

dQC

dQSPA
Assumptions for this talk

- Two dimensional surface with a lattice for adsorption, diffusion, reaction, and desorption.
- Square lattice, Z=4
- All sites have identical properties
- Constant temperature
- Adsorbed CO molecules exhibit nearest neighbor repulsions

\[ \text{CO} + \frac{1}{2}\text{O}_2 \longrightarrow \text{CO}_2 \]

CO-black, O-gray, Empty-white.
Model mechanism and time scales

Adsorption
\[ \text{CO(g)} + *_{i} \xrightarrow{\alpha} \text{CO}_{i} \]
\[ \text{O}_2(g) + *_{i} + *_{j} \xrightarrow{\beta} \text{O}_{i} + \text{O}_{j} \]

Desorption
\[ \text{CO}_{i} \xrightarrow{\gamma} \text{CO(g)} + *_{i} \]
\[ \text{O}_{i} + \text{O}_{j} \xrightarrow{\rho} \text{O}_2(g) + *_{i} + *_{j} \]

Reaction
\[ \text{CO}_{i} + \text{O}_{j} \xrightarrow{k_{r}} \text{CO}_2(g) + *_{i} + *_{j} \]

Diffusion
\[ \text{CO}_{i} + *_{j} \xrightarrow{d_1} *_{i} + \text{CO}_{j} \]
\[ \text{O}_{i} + *_{j} \xrightarrow{d_2} *_{i} + \text{O}_{j} \]

\[
\begin{array}{|c|}
\hline
1/\text{sec} \\
\hline
\alpha = 1.6 \ \beta = 0.8 \ \gamma = 0.8 \ \rho = 0.001 \ \ k_{r} = 1 \ \ d_1 \approx 10^{10} \ \ d_2 \approx 10^{8} \\
\hline
\end{array}
\]
Singular perturbation on the master equation

Surface reaction master equation

\[ \frac{dP(n, x)}{dt} = X_{\text{rxn}} \sum_{j=1}^{X_{\text{rxn}}} k_j a_j (n - \nu_j, x - \nu_{x,j}) P(n - \nu_j, x - \nu_{x,j}) - k_j a_j (n, x) P(n, x) \]

\[ + X_{\text{diff}} \sum_{j=1}^{X_{\text{diff}}} d_j a_j (n, x - \nu_{x,j}) P(n, x - \nu_{x,j}) - d_j a_j (n, x) P(n, x) \]

Singular perturbation

\[ P(n, x) = W_0(n, x) + \epsilon W_1(n, x) + \epsilon^2 W_2(n, x) + \cdots \]

\[ \epsilon = 1/d \]

\( \epsilon^0 \) terms: Diffusion equilibration equations for \( W_0(x|n) \)
Slow time-scale evolution equation

$\epsilon^1$ terms : Reduced master equation

\[
\frac{dW_0(n)}{dt} = \sum_{i=1}^{N_{\text{rxn}}} k_i \langle s_i(n - \nu_i) \rangle W_0(n - \nu_i) - k_i \langle s_i(n) \rangle W_0(n)
\]

What have we gained?

- Removed micro-states from the master equation

<table>
<thead>
<tr>
<th>Lattice Size</th>
<th>Species</th>
<th>Micro-states</th>
<th>Coverage states</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_s = 4$</td>
<td>1</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>$N_s = 25$</td>
<td>2</td>
<td>$10^{12}$</td>
<td>325</td>
</tr>
<tr>
<td>$N_s = 100$</td>
<td>2</td>
<td>$10^{48}$</td>
<td>5050</td>
</tr>
</tbody>
</table>

- Tractable number of states, master equation can be solved
Slow time-scale evolution equation

\[ \frac{dW_0(n)}{dt} = \sum_{i=1}^{N_{rxn}} k_i \langle s_i(n - \nu_i) \rangle W_0(n - \nu_i) - k_i \langle s_i(n) \rangle W_0(n) \]

Reaction propensities

- \( s_i(x) \) number of reaction \( i \) on configuration \( x \): \( n_{CO} = 45 \) black, \( n_O = 8 \) gray

- \( s_{CO-O} = 26 \)
- \( s_{CO-O} = 22 \)
- \( s_{CO-O} = 26 \)
- \( s_{CO-O} = 23 \)

- \( \langle s_{CO-O} \rangle = 24.9 \)

- \( \langle s_i(n) \rangle = \sum_x s_i(x) W_0(x|n) \) – Calculate with diffusion only KMC
Reduced master equation solution (5x5 lattice)

Probability of $n_{CO}$, 5x5 lattice

Steady-state probability distribution (5x5)
Verification of perturbation method

\[ \sum_x P(n, x) = W_0(n) + \epsilon W_1(n) + O(\epsilon^2) \]

\[ \epsilon = 1/d \]

As the diffusion rate increases, \( P(n) \) approaches \( W_0(n) \)

Steady-state probability distribution (5 × 5)

![Steady-state probability distribution](image)
Conclusions — Surface reactions in the infinite diffusion limit

- SPA can be used to eliminate spatial configuration states in a reduced master equation.
- The reduced master equation has sufficiently few states to be simulated on small lattices.
- Reduced master equations of surface reactions can be used to motivate reduced KMC and reduced ODE models.
Model for Vesicular Stomatitis Virus (VSV) infection

I is encapsidation of viral genome
II is replication of encapsidated genome
III is transcription of genome to messenger RNA
Onset of fast fluctuations in the N protein

Features of simulation
- Presence of fast fluctuating and rapidly rising species
- Fast fluctuations slow the full KMC simulation
- Motivates the formulation of a simpler example to understand this phenomenon
The viral genome is amplified by first two reactions

- The free viral proteins and messages are not amplified
- Values of parameters $k_1$, $k_2$ and $k_3$ may cause fast fluctuation in polymerases along with rapid amplification of viral genome
\[
\begin{align*}
A + G & \xrightarrow{k_1} C + G & r_1 = \frac{1}{\Omega} k_1 ag \\
C + G & \xrightarrow{k_2} 2G + A & r_2 = \frac{1}{\Omega} k_2 cg \\
2G & \xrightarrow{k_3} G & r_3 = \frac{1}{\Omega} k_3 \frac{g(g-1)}{2}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Species</th>
<th>Initial number</th>
<th>Rate constant ((\text{m}^3/\text{mol} \cdot \text{s}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>(k_1 = 9 \times 10^5)</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>(k_2 = 5 \times 10^5)</td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>(k_3 = 5 \times 10^{-2})</td>
</tr>
</tbody>
</table>
The full SSA on the system

Graph showing the number of C and G molecules over time, with time-step and time axes.

Graph showing the log of the number of molecules over time.

Graph showing the log of the time-step over time.

Graph showing the log of the number of molecules over time.

Graph showing the log of the time-step over time.
The hybrid SSA - $\Omega$ technique

At large population of $G$ we want to switch to a continuous description for it:

$$g = \Omega \phi_G + \Omega^{1/2} \xi$$

- $\phi_G$ is the deterministic evolution term and $\xi$ is the continuous noise in the evolution of $G$
- We can obtain approximation for the evolution of system using hybrid SSA - $\Omega$ technique

**Approximation of pdf of $C$**

$$W_0(c) = (1 + q)^{-N_0} \left(\begin{array}{c} N_0 \\ c \end{array}\right) q^{(N_0 - c)}$$

**Deterministic evolution of $G$**

$$\frac{d\phi_G}{dt} = \gamma^{-1} \langle c \rangle \phi_G - \frac{k_3}{2} \phi_G^2$$

<table>
<thead>
<tr>
<th>$N_0$</th>
<th>Initial number of polymerases</th>
</tr>
</thead>
<tbody>
<tr>
<td>$q = \frac{k_2}{k_1}$</td>
<td>Ratio of rate constants</td>
</tr>
</tbody>
</table>
Comparison of full SSA with hybrid SSA - $\Omega$

**Full SSA**

**Hybrid SSA - $\Omega$**

Rawlings

Molecular reaction engineering
Comparison of full SSA with hybrid SSA - $\Omega$

Probability densities of $C$ from SSA and from hybrid SSA - $\Omega$

![Graph showing probability densities of C particles from SSA and hybrid SSA]
Conclusions — QSSA and fast fluctuations

- Hybrid SSA – Ω expansion matches closely the full SSA
- Computation speed increases by factor of 450
- Application to kinetic virus infection models
Acknowledgments

- Dr. Ethan A. Mastny, BP Alaska
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- Rishi Srivastava, UW
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Further reading — Stochastic reaction equilibrium

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On the origins of approximations for stochastic chemical kinetics. 

The slow-scale stochastic simulation algorithm. 

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Stochastic simulation of catalytic surface reactions in the fast diffusion limit. 
Rao, C. V. and A. P. Arkin.  
Stochastic chemical kinetics and the quasi-steady-state assumption: Application to the Gillespie algorithm.  

van Kampen, N. G.  
*Stochastic Processes in Physics and Chemistry.*  

Two classes of quasi-steady-state model reductions for stochastic kinetics.  

Hensel, S., J. B. Rawlings, and J. Yin.  
Stochastic kinetic modeling of vesicular stomatitis virus intracellular growth.  