Chemical reaction engineering at the small scale — still plenty of room at the bottom

Multiple-time-scale order reduction for stochastic kinetics

James B. Rawlings

Department of Chemical and Biological Engineering

THE UNIVERSITY of WISCONSIN MADISON

March 25, 2009
Sandia National Laboratories
Livermore, CA

Outline

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

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

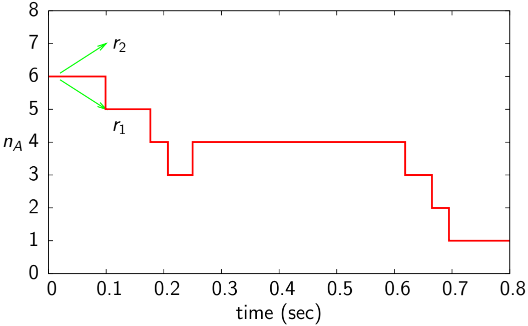
Develop reduced models from stochastic chemical reactions. These models must meet the following requirements:

- Simpler than the full model (fewer reactions, fewer parameters, or faster simulation times)
- Converges to the full model as a specified parameter goes to zero

Stochastic simulation method — kinetic Monte Carlo

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \qquad \begin{array}{ll} k_1 = 2 & k_2 = 1 \\ n_{A0} = 6 & n_{B0} = 3 \end{array}$$

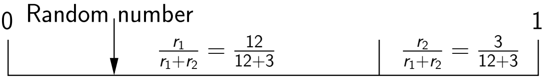
$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \qquad \begin{array}{ll} k_1 = 2 & k_2 = 1 \\ n_{A0} = 6 & n_{B0} = 3 \end{array}$$



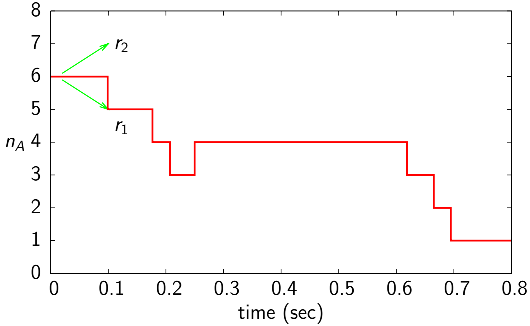
KMC Algorithm

1. Choose which reaction

- Which reaction:



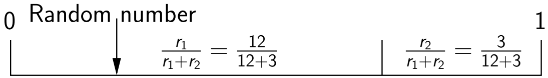
$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \qquad \begin{array}{ll} k_1 = 2 & k_2 = 1 \\ n_{A0} = 6 & n_{B0} = 3 \end{array}$$



KMC Algorithm

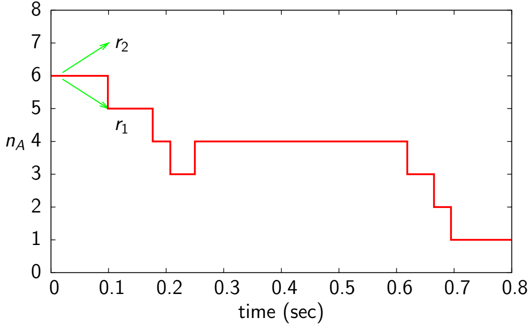
1. Choose which reaction
2. Choose time step

- Which reaction:



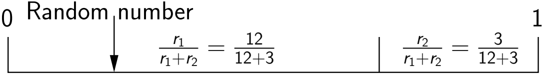
- Time step: Sample from an exponential distribution where the distribution mean is the sum of reaction rates.

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \qquad k_1 = 2 \quad k_2 = 1 \qquad n_{A0} = 6 \quad n_{B0} = 3$$



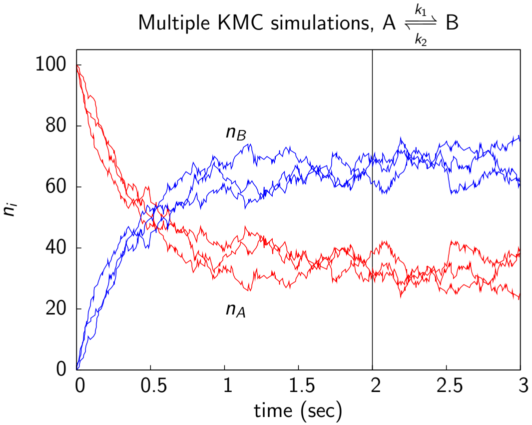
KMC Algorithm

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

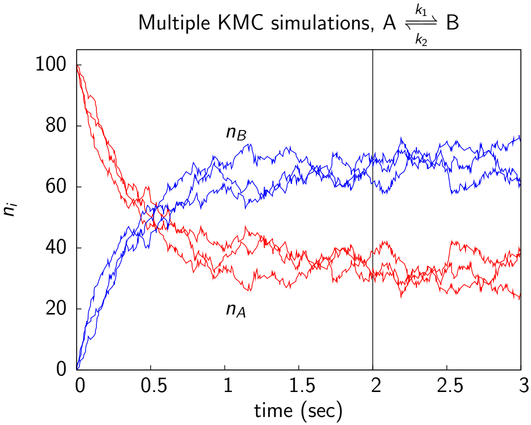
- Which reaction: 

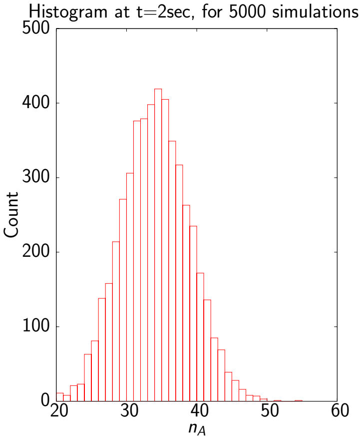
- Time step: Sample from an exponential distribution where the distribution mean is the sum of reaction rates.

KMC simulations and probability



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

$$
\begin{aligned}
\frac{dP(x)}{dt} &= \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x-\nu_j)P(x-\nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x} \\
\frac{dP}{dt} &= AP
\end{aligned}
$$

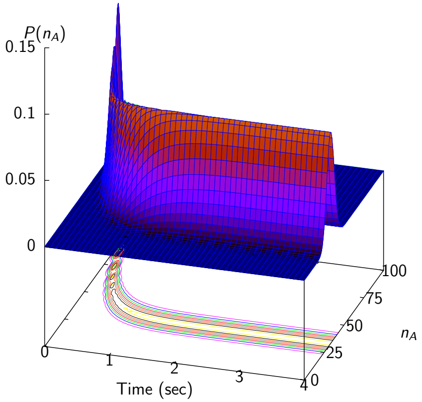
Chemical master equation

$$\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x-\nu_j)P(x-\nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x}$$

$$\frac{dP}{dt} = AP$$

Master equation example

- $\mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{B}$
- $n_{A0} = 100, n_{B0} = 0$
- $k_1 = 2, k_2 = 1$
- 101 possible states
- 101 Coupled ODEs



Master equation — Important points

Chemical master equation

$$\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x-\nu_j)P(x-\nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x}$$

$$\frac{dP}{dt} = AP$$

- Often the dimensionality of the master equation makes direct solution infeasible

Master equation — Important points

Chemical master equation

$$\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x-\nu_j)P(x-\nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x}$$

$$\frac{dP}{dt} = AP$$

- Often the dimensionality of the master equation makes direct solution infeasible
- The master equation shows what probability distribution is sampled in a KMC simulation

Master equation — Important points

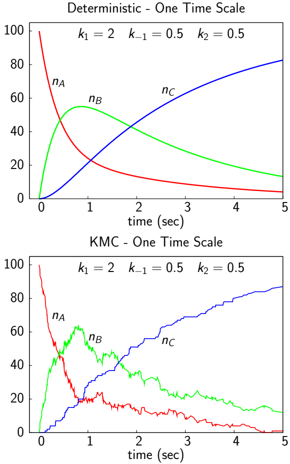
Chemical master equation

$$\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x-\nu_j)P(x-\nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x}$$

$$\frac{dP}{dt} = AP$$

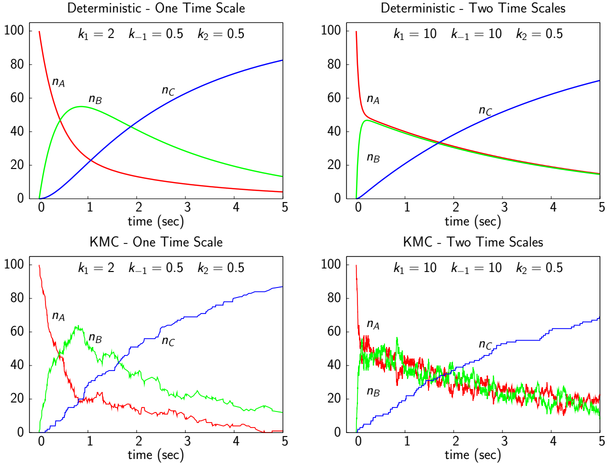
- Often the dimensionality of the master equation makes direct solution infeasible
- The master equation shows what probability distribution is sampled in a KMC simulation
- A reduced master equation can lead to a new/faster simulation schemes

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2} C$$



One time scale

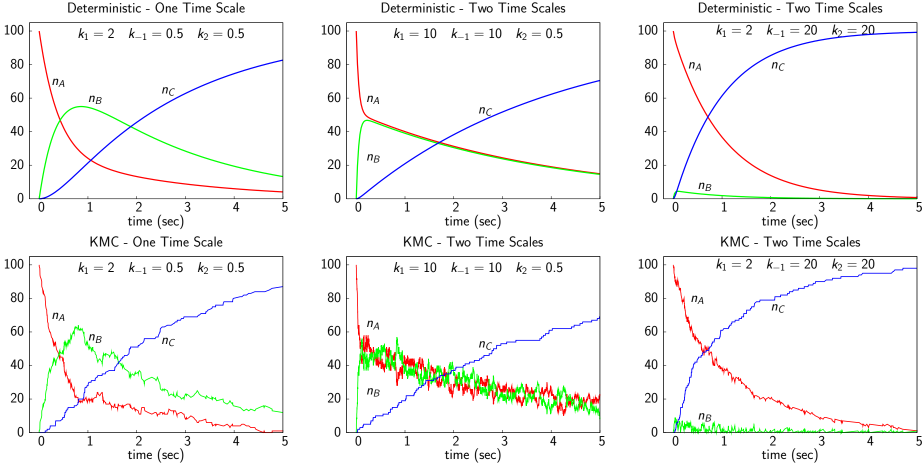
$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2} C$$



One time scale | Reaction equilibrium

Kinetics of multiple time scales

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$



One time scale | Reaction equilibrium | Reactive intermediate

Deterministic model reductions

x non-QSSA species, y QSSA species

$$\frac{dx}{dt} = f(x, y) \qquad \epsilon \frac{dy}{dt} = g(x, y)$$

Deterministic model reductions

x non-QSSA species, y QSSA species

$$\frac{dx}{dt} = f(x,y) \qquad \epsilon\frac{dy}{dt} = g(x,y)$$

Classical QSSA

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ 0 &= g(x,y) \end{aligned}$$

- DAE reduced model

Deterministic model reductions

x non-QSSA species, y QSSA species

$$\frac{dx}{dt} = f(x,y) \qquad \epsilon\frac{dy}{dt} = g(x,y)$$

Classical QSSA

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ 0 &= g(x,y) \end{aligned}$$

- DAE reduced model

Singular Perturbation QSSA

$$\begin{aligned} x &= X_0 + \epsilon X_1 + \epsilon^2 X_2 + \mathcal{O}(\epsilon^3) \\ y &= Y_0 + \epsilon Y_1 + \epsilon^2 Y_2 + \mathcal{O}(\epsilon^3) \end{aligned}$$

- Collect like powers of ϵ
- Equations for $\frac{dX_0}{dt}$ is the reduced model
- Separate models for fast and slow time scale

SPA on the master equation

Our objective

Apply singular perturbation analysis to develop a reduced master equation.

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

$$\begin{aligned}\frac{dP(a,b,c)}{dt} &= k_1(a+1)P(a+1,b-1,c) + k_{-1}(b+1)P(a-1,b+1,c) \\ &\quad + k_2(b+1)P(a,b+1,c-1) - (k_1 a + k_{-1} b + k_2 b)P(a,b,c)\end{aligned}$$

Our objective

Apply singular perturbation analysis to develop a reduced master equation.

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

$$\begin{aligned}
\frac{dP(a,b,c)}{dt} &= k_1(a+1)P(a+1,b-1,c) + k_{-1}(b+1)P(a-1,b+1,c) \\
&\quad + k_2(b+1)P(a,b+1,c-1) - (k_1 a + k_{-1} b + k_2 b)P(a,b,c) \\
P(a,b,c) &= W_0(a,b,c) + \epsilon W_1(a,b,c) + \cdots
\end{aligned}$$

SPA on the master equation

Our objective

Apply singular perturbation analysis to develop a reduced master equation.

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

$$\begin{aligned}\frac{dP(a,b,c)}{dt} &= k_1(a+1)P(a+1,b-1,c) + k_{-1}(b+1)P(a-1,b+1,c) \\ &\quad + k_2(b+1)P(a,b+1,c-1) - (k_1 a + k_{-1} b + k_2 b)P(a,b,c) \\ P(a,b,c) &= W_0(a,b,c) + \epsilon W_1(a,b,c) + \cdots\end{aligned}$$

ϵ^0 terms:

- $W_0(a,b,c) = 0$ if $b > 0$
- In this limit b is always zero

SPA on the master equation

ϵ^1 terms: Reduced master equation

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

ϵ^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

$$\mathrm{A} \longrightarrow \mathrm{C} \qquad r = \tfrac{k_1 k_2}{k_{-1}+k_2} a$$

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

SPA on the master equation

ϵ^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

$$\mathrm{A} \longrightarrow \mathrm{C} \qquad r = \frac{k_1 k_2}{k_{-1}+k_2} a$$

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

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

$\langle b \rangle = f(W_0(a,0,c)) + \mathcal{O}(\epsilon^2)$
$\langle b \rangle = \frac{k_1}{k_{-1}+k_2} \langle a \rangle$

Comparison of mechanisms

$$\begin{array}{lcllll} \mathrm{A} & \rightleftharpoons & 2\mathrm{B} & r_1 = k_1 a & r_{-1} = \frac{k_{-1}}{2} b(b-1) \\ \mathrm{B} & \longrightarrow & \mathrm{C} & r_2 = k_2 b & \end{array}$$

Comparison of mechanisms

$$\begin{array}{lcl} \mathrm{A} & \rightleftharpoons & 2\mathrm{B} \\ \mathrm{B} & \longrightarrow & \mathrm{C} \end{array} \qquad \begin{array}{ll} r_1 = k_1 a & r_{-1} = \frac{k_{-1}}{2} b(b-1) \\ r_2 = k_2 b & \end{array}$$

Stoch SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = \left(\frac{k_1 k_2}{\frac{k_{-1}}{2} + k_2} \right) a$$

Comparison of mechanisms

$$\begin{array}{lcl} \mathrm{A} & \rightleftharpoons & 2\mathrm{B} \\ \mathrm{B} & \longrightarrow & \mathrm{C} \end{array} \qquad \begin{array}{l} r_1 = k_1 a \qquad r_{-1} = \frac{k_{-1}}{2} b(b-1) \\ r_2 = k_2 b \end{array}$$

Stoch SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = \left(\frac{k_1 k_2}{\frac{k_{-1}}{2} + k_2} \right) a$$

Det SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = k_1 a$$

Comparison of mechanisms

$$\mathrm{A} \rightleftharpoons 2\mathrm{B} \qquad r_1 = k_1 a \qquad r_{-1} = \frac{k_{-1}}{2} b(b-1)$$

$$\mathrm{B} \longrightarrow \mathrm{C} \qquad r_2 = k_2 b$$

Stoch SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = \left(\frac{k_1 k_2}{\frac{k_{-1}}{2} + k_2} \right) a$$

Det SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = k_1 a$$

Det QSSA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = k_2 \left[\frac{-k_2 + \sqrt{k_2^2 + 8 k_1 k_{-1} a}}{4 k_{-1}} \right]$$

Comparison of mechanisms

$$\begin{array}{lcl} \mathrm{A} & \rightleftharpoons & 2\mathrm{B} \\ \mathrm{B} & \longrightarrow & \mathrm{C} \end{array} \qquad \begin{array}{l} r_1 = k_1 a \\ r_2 = k_2 b \end{array} \qquad r_{-1} = \frac{k_{-1}}{2} b(b-1)$$

Stoch SPA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = \left(\frac{k_1 k_2}{\frac{k_{-1}}{2} + k_2} \right) a$$

Det SPA

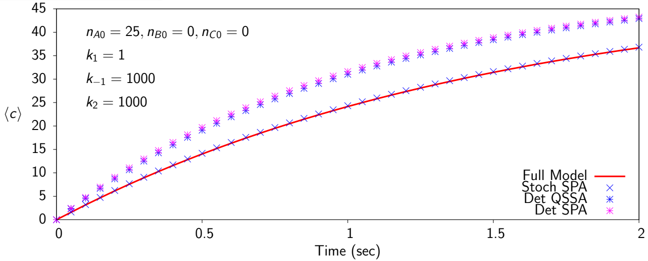
$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = k_1 a$$

Det QSSA

$$\mathrm{A} \longrightarrow 2\mathrm{C}$$

$$r = k_2 \left[\frac{-k_2 + \sqrt{k_2^2 + 8 k_1 k_{-1} a}}{4 k_{-1}} \right]$$

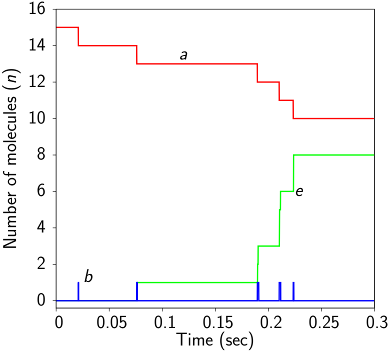


Catalyst Example

$$A \xrightarrow{k_1} \quad B \xrightarrow{k_2} C$$

$$B + D \xrightarrow{k_3} B + E$$

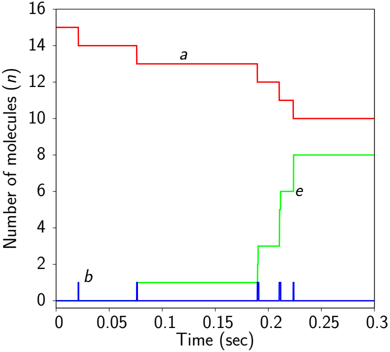
$$k_2, k_3 \gg k_1$$



$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

$$B + D \xrightarrow{k_3} B + E$$

$$k_2, k_3 \gg k_1$$



Stoch SPA mechanism

$$\begin{aligned} A &\longrightarrow C \\ D + A &\longrightarrow E + C \\ 2D + A &\longrightarrow 2E + C \\ &\cdots \\ nD + A &\longrightarrow nE + C \end{aligned}$$

$$r_0 = \frac{k_1 a}{1 + K_3 d} \qquad K_3 = \frac{k_3}{k_2}$$

$$r_1 = r_0 \frac{K_3 d}{1 + K_3(d-1)}$$

$$r_2 = r_1 \frac{K_3(d-1)}{1 + K_3(d-2)}$$

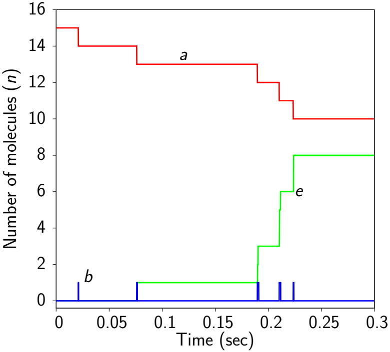
$$r_n = r_{n-1} \frac{K_3(d+1-n)}{1 + K_3(d-n)}$$

Catalyst Example

$$\mathrm{A} \xrightarrow{k_1} \qquad \mathrm{B} \xrightarrow{k_2} \mathrm{C}$$

$$\mathrm{B} + \mathrm{D} \xrightarrow{k_3} \mathrm{B} + \mathrm{E}$$

$$k_2, k_3 \gg k_1$$



Stoch SPA mechanism

$$\begin{aligned} \mathrm{A} &\longrightarrow \mathrm{C} \\ \mathrm{D} + \mathrm{A} &\longrightarrow \mathrm{E} + \mathrm{C} \\ 2\mathrm{D} + \mathrm{A} &\longrightarrow 2\mathrm{E} + \mathrm{C} \\ &\cdots \\ n\mathrm{D} + \mathrm{A} &\longrightarrow n\mathrm{E} + \mathrm{C} \end{aligned}$$

$$r_0 = \frac{k_1 a}{1 + K_3 d} \qquad K_3 = \frac{k_3}{k_2}$$

$$r_1 = r_0 \frac{K_3 d}{1 + K_3(d-1)}$$

$$r_2 = r_1 \frac{K_3(d-1)}{1 + K_3(d-2)}$$

$$r_n = r_{n-1} \frac{K_3(d+1-n)}{1 + K_3(d-n)}$$

Deterministic SPA mechanism

$$\begin{aligned} \mathrm{A} &\longrightarrow \mathrm{C} \\ \mathrm{D} + \mathrm{A} &\longrightarrow \mathrm{E} + \mathrm{A} \end{aligned}$$

$$r_0 = k_1 a$$

$$r_1 = \frac{k_3 k_1}{k_2} ad$$

Conclusions — Stochastic quasi-steady-state approximation

- QSSA species are removed from stochastic models with SPA

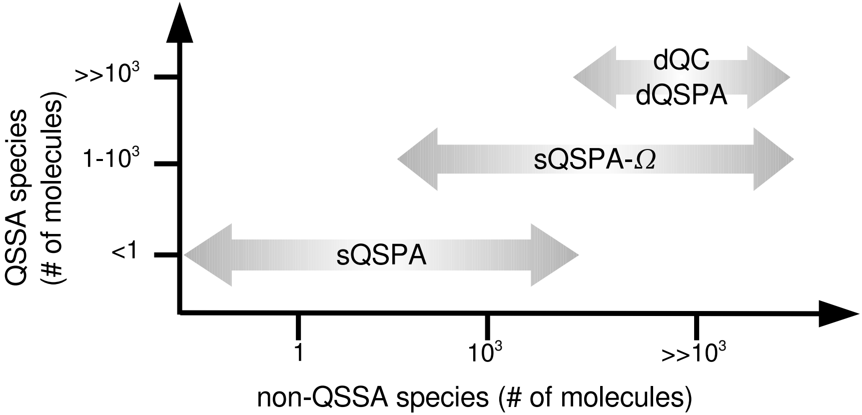
Conclusions — Stochastic quasi-steady-state approximation

- QSSA species are removed from stochastic models with SPA
- Stochastic QSSA mechanisms different than deterministic QSSA mechanisms

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

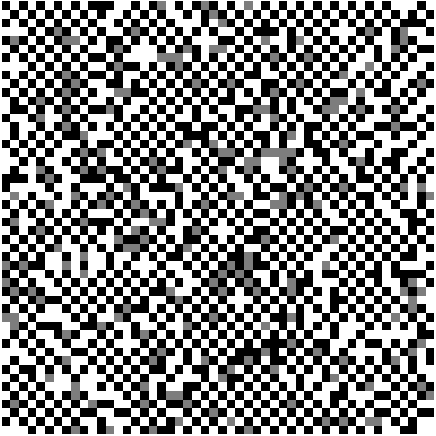


Catalytic surface reaction modeling

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

$$CO + \frac{1}{2}O_2 \longrightarrow CO_2$$



CO-black, O-gray, Empty-white.

Model mechanism and time scales

$$
\begin{array}{lrcl}
\text{Adsorption} & CO(g) + *_i & \xrightarrow{\alpha} & CO_i \\
 & O_2(g) + *_i + *_j & \xrightarrow{\beta} & O_i + O_j \\
\text{Desorption} & CO_i & \xrightarrow{\gamma} & CO(g) + *_i \\
 & O_i + O_j & \xrightarrow{\rho} & O_2(g) + *_i + *_j \\
\text{Reaction} & CO_i + O_j & \xrightarrow{k_r} & CO_2(g) + *_i + *_j \\
\text{Diffusion} & CO_i + *_j & \xrightarrow{d_1} & *_i + CO_j \\
 & O_i + *_j & \xrightarrow{d_2} & *_i + O_j
\end{array}
$$

Model mechanism and time scales

$$
\begin{array}{lrl}
\text{Adsorption} & \mathrm{CO(g)} + *_\mathrm{i} & \xrightarrow{\alpha} \mathrm{CO_i} \\
 & \mathrm{O_2(g)} + *_\mathrm{i} + *_\mathrm{j} & \xrightarrow{\beta} \mathrm{O_i} + \mathrm{O_j} \\
\text{Desorption} & \mathrm{CO_i} & \xrightarrow{\gamma} \mathrm{CO(g)} + *_\mathrm{i} \\
 & \mathrm{O_i} + \mathrm{O_j} & \xrightarrow{\rho} \mathrm{O_2(g)} + *_\mathrm{i} + *_\mathrm{j} \\
\text{Reaction} & \mathrm{CO_i} + \mathrm{O_j} & \xrightarrow{k_r} \mathrm{CO_2(g)} + *_\mathrm{i} + *_\mathrm{j} \\
\text{Diffusion} & \mathrm{CO_i} + *_\mathrm{j} & \xrightarrow{d_1} *_\mathrm{i} + \mathrm{CO_j} \\
 & \mathrm{O_i} + *_\mathrm{j} & \xrightarrow{d_2} *_\mathrm{i} + \mathrm{O_j}
\end{array}
$$

1/sec
$\alpha = 1.6$
$\beta = 0.8$
$\gamma = 0.8$
$\rho = 0.001$
$k_r = 1$
$d_1 \approx 10^{10}$
$d_2 \approx 10^8$

Singular perturbation on the master equation

Surface reaction master equation

x - microscopic configuration $\qquad$ n - number of each species

$$\frac{dP(n,x)}{dt} = \sum_{j=1}^{X_{rxn}} k_j a_j(n-\nu_j, x-\nu_{x,j})P(n-\nu_j, x-\nu_{x,j}) - k_j a_j(n,x)P(n,x)$$
$$+ \sum_{j=1}^{X_{diff}} d_j a_j(n, x-\nu_{x,j})P(n, x-\nu_{x,j}) - d_j a_j(n,x)P(n,x)$$

Singular perturbation on the master equation

Surface reaction master equation

x - microscopic configuration $\qquad$ n - number of each species

$$\frac{dP(n,x)}{dt} = \sum_{j=1}^{X_{rxn}} k_j a_j(n-\nu_j, x-\nu_{x,j}) P(n-\nu_j, x-\nu_{x,j}) - k_j a_j(n,x) P(n,x)$$
$$+ \sum_{j=1}^{X_{diff}} d_j a_j(n, x-\nu_{x,j}) P(n, x-\nu_{x,j}) - d_j a_j(n,x) P(n,x)$$

Singular perturbation

$$\begin{aligned} P(n,x) &= W_0(n,x) + \epsilon W_1(n,x) + \epsilon^2 W_2(n,x) + \cdots \\ \epsilon &= 1/d \end{aligned}$$

ϵ^0 terms: Diffusion equilibration equations for $W_0(x|n)$

Slow time-scale evolution equation

ϵ^1 *terms* : Reduced master equation

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

What have we gained?

- Removed micro-states from the master equation

Slow time-scale evolution equation

ϵ^1 *terms* : Reduced master equation

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

What have we gained?

- Removed micro-states from the master equation

Lattice Size	Species	Micro-states	Coverage states
$N_s = 4$	1	16	5
$N_s = 25$	2	10^{12}	325
$N_s = 100$	2	10^{48}	5050

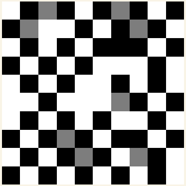
- Tractable number of states, master equation can be solved

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



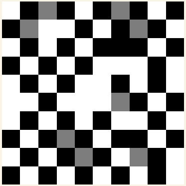
$s_{\mathrm{CO-O}}$=26

Slow time-scale evolution equation

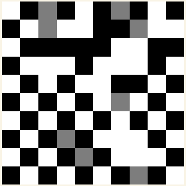
$$\frac{dW_0(n)}{dt} = \sum_{i=1}^{N_{rxn}} k_i \langle s_i(n-\nu_i)\rangle W_0(n-\nu_i) - k_i\langle s_i(n)\rangle W_0(n)$$

Reaction propensities

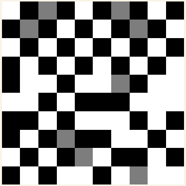
- $s_i(x)$ number of reaction i on configuration x: n_{CO}=45 black, n_{O}=8 gray



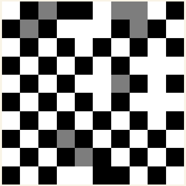
$s_{\mathrm{CO-O}}$=26



$s_{\mathrm{CO-O}}$=22



$s_{\mathrm{CO-O}}$=26



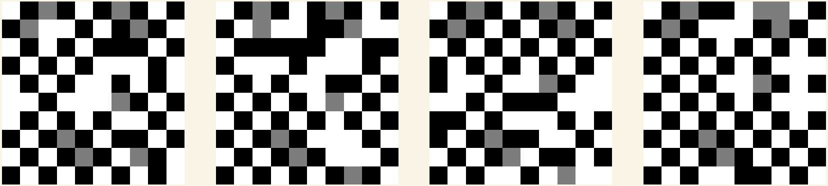
$s_{\mathrm{CO-O}}$=23

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

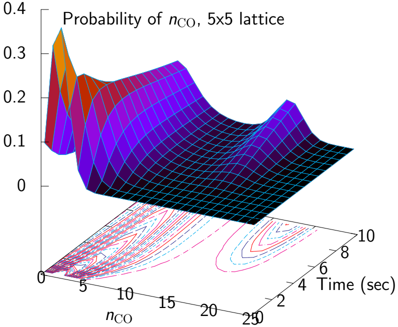


$s_{\mathrm{CO-O}}$=26 $s_{\mathrm{CO-O}}$=22 $s_{\mathrm{CO-O}}$=26 $s_{\mathrm{CO-O}}$=23

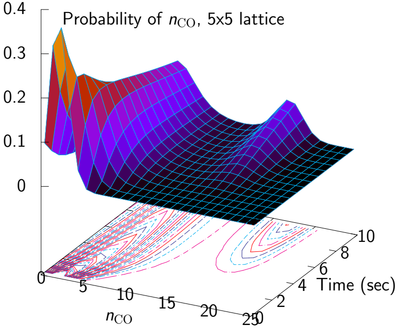
$\langle s_{\mathrm{CO-O}} \rangle = 24.9$

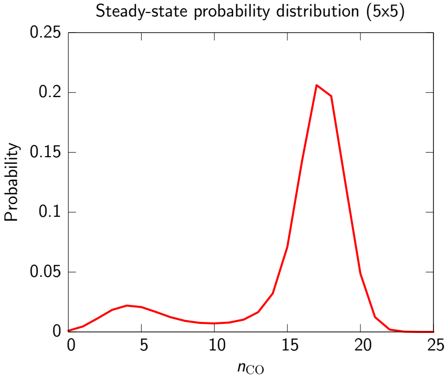
- $\langle s_i(n)\rangle = \sum_x s_i(x) W_0(x|n)$ – Calculate with diffusion only KMC

Reduced master equation solution (5x5 lattice)



Reduced master equation solution (5x5 lattice)





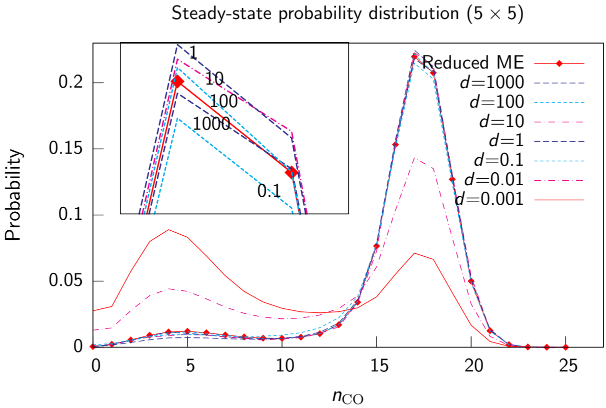
Verification of perturbation method

$$\begin{aligned} \sum_x P(n,x) &= W_0(n) + \epsilon W_1(n) + \mathcal{O}(\epsilon^2) \\ \epsilon &= 1/d \end{aligned}$$

As the diffusion rate increases $P(n)$ approaches $W_0(n)$

$$\sum_x P(n,x) = W_0(n) + \epsilon W_1(n) + \mathcal{O}(\epsilon^2)$$
$$\epsilon = 1/d$$

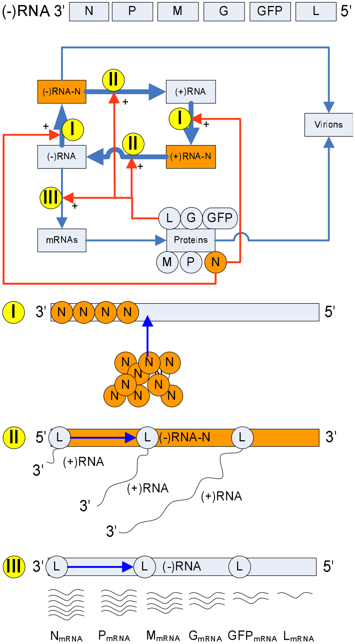
As the diffusion rate increases $P(n)$ approaches $W_0(n)$



Conclusions — Surface reactions in the infinite diffusion limit

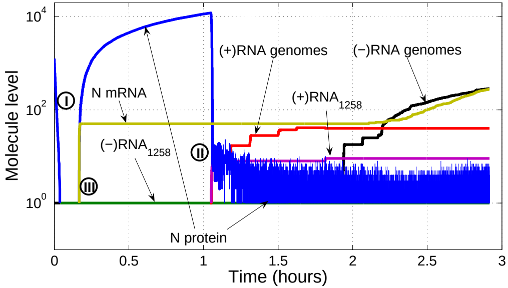
- SPA can be used to eliminate spatial configuration states in a reduced master equation.
- The reduced master equation has sufficiently few states to be simulated on small lattices.
- Reduced master equations of surface reactions can be used to motivate reduced KMC and reduced ODE models.

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

Fast fluctuation and rapid rise in VSV biology

$$
\begin{aligned}
(-)\mathrm{RNA} + \mathrm{L}_1 &\xrightarrow{k_1} (-)\mathrm{RNA} + \mathrm{L}_2 \\
(-)\mathrm{RNA} + \mathrm{L}_2 &\xrightarrow{k_2} 2(-)\mathrm{RNA} + \mathrm{L}_1 \\
2(-)\mathrm{RNA} &\xrightarrow{k_3} (-)\mathrm{RNA}
\end{aligned}
$$

- The formulation considers the amplification of viral genome
- But it does not consider the amplification of viral proteins and messages
- Values of parameters k_1, k_2 and k_3 may cause fast fluctuation in polymerases along with rapid amplification of viral genome

Fast fluctuation and rapid rise — Idealized problem

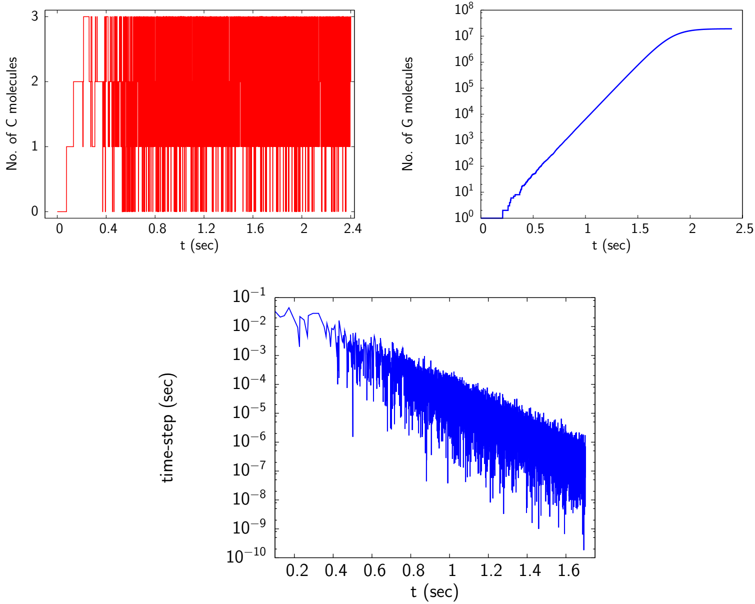
$$\mathrm{A + G} \xrightarrow{k_1} \mathrm{C + G} \qquad r_1 = \frac{1}{\Omega} k_1 a g$$

$$\mathrm{C + G} \xrightarrow{k_2} \mathrm{2G + A} \qquad r_2 = \frac{1}{\Omega} k_2 c g$$

$$\mathrm{2G} \xrightarrow{k_3} \mathrm{G} \qquad r_3 = \frac{1}{\Omega} k_3 \frac{g(g-1)}{2}$$

Species	Initial number	Rate constant $\left(\mathrm{m^3/mol{\cdot}s}\right)$
A	3	$k_1 = 9 \times 10^5$
C	0	$k_2 = 5 \times 10^5$
G	1	$k_3 = 5 \times 10^{-2}$

The full SSA on the system



The hybrid SSA - Ω technique

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

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

- ϕ_G is the deterministic evolution term and ξ is the continuous noise in the evolution of G
- We can obtain approximation for the evolution of system using hybrid SSA - Ω technique

Approximation of pdf of A

$$W_0^1(a) = (1+q)^{-N_0} \binom{N_0}{a} q^a$$

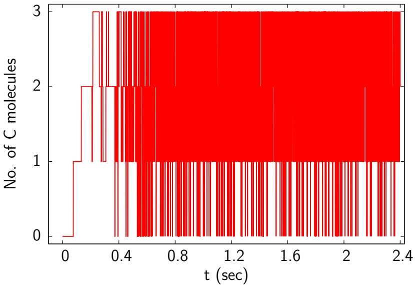
Deterministic evolution of G

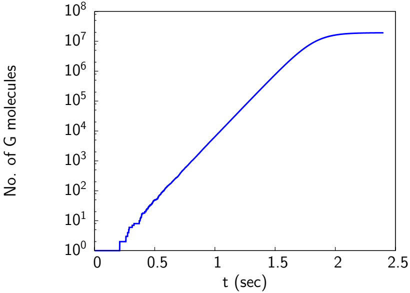
$$\frac{d\phi_G}{dt} = \gamma^{-1} < c > \phi_G - \frac{k_3}{2}\phi_G^2$$

N_0	Initial number of polymerases
$q = \frac{k_2}{k_1}$	Ratio of rate constants

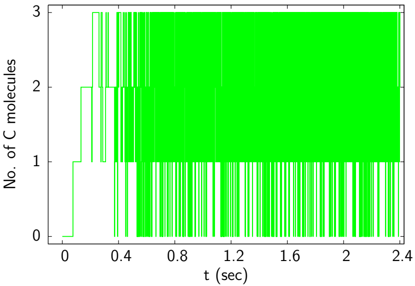
Comparison of full SSA with hybrid SSA - Ω

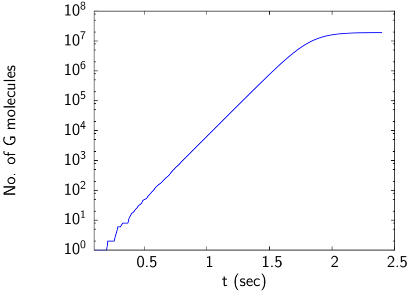
Full SSA



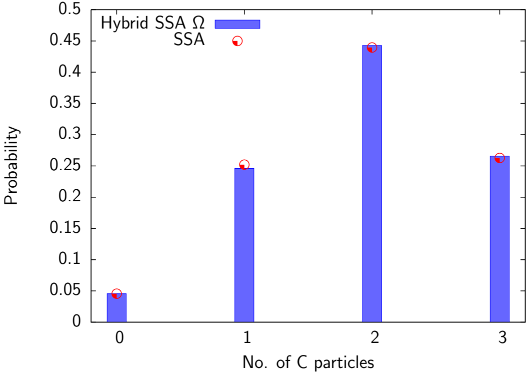


Hybrid SSA - Ω





Probability densities of C from SSA and from hybrid SSA - Ω



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
- Dr. Eric L. Haseltine, Vertex Pharmaceuticals
- Rishi Srivastava, UW
- NSF #CNS–0540147

Further Reading — Stochastic Reaction Equilibrium

Haseltine, E. L. and J. B. Rawlings.
Approximate simulation of coupled fast and slow reactions for stochastic chemical kinetics.
J. Chem. Phys., 117(15):6959–6969, October 2002.

Haseltine, E. L. and J. B. Rawlings.
On the origins of approximations for stochastic chemical kinetics.
J. Chem. Phys., 123:164115, October 2005.

Cao, Y., D. T. Gillespie, and L. R. Petzold.
The slow-scale stochastic simulation algorithm.
J. Chem. Phys., 122(1):014116, January 2005.

Samant, A. and D. G. Vlachos.
Overcoming stiffness in stochastic simulation stemming from partial equilibrium: A multiscale Monte Carlo algorithm.
J. Chem. Phys., 123:144114, 2005.

Salis, H. and Y. Kaznessis.
Accurate hybrid stochastic simulation of a system of coupled chemical or biochemical reactions.
J. Chem. Phys., 122(5):054103, February 2005.

Mastny, E. A., E. L. Haseltine, and J. B. Rawlings.
Stochastic simulation of catalytic surface reactions in the fast diffusion limit.
J. Chem. Phys., 125(19):194715, November 2006.

Further Reading — Stochastic QSSA

Rao, C. V. and A. P. Arkin.
Stochastic chemical kinetics and the quasi-steady-state assumption: Application to the Gillespie algorithm.
J. Chem. Phys., 118(11):4999–5010, March 2003.

van Kampen, N. G.
Stochastic Processes in Physics and Chemistry.
Elsevier Science Publishers, Amsterdam, The Netherlands, 2nd edition, 1992.

Mastny, E. A., E. L. Haseltine, and J. B. Rawlings.
Two classes of quasi-steady-state model reductions for stochastic kinetics.
J. Chem. Phys., 127(9):094106, September 2007.

Hensel, S., J. B. Rawlings, and J. Yin.
Stochastic kinetic modeling of vesicular stomatitis virus intracellular growth.
Submitted for publication in *Bulletin of Math. Bio.*, May 2008.