

# Extending the Tools of Chemical Reaction Engineering to the Molecular Scale

Multiple-time-scale order reduction for stochastic kinetics

James B. Rawlings

Department of Chemical and Biological Engineering



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Model Reduction in Reacting Flows  
University of Notre Dame

- 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

## 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

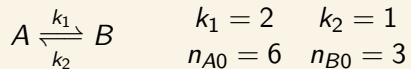
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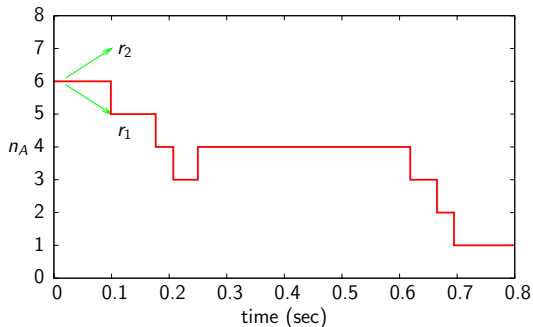
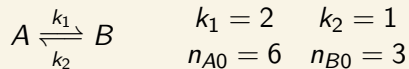
## Model reduction

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



# Stochastic simulation method — kinetic Monte Carlo

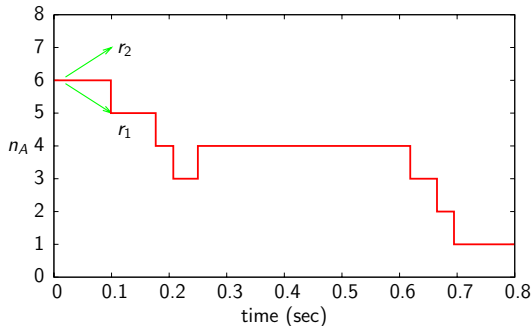
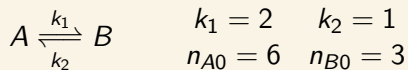


## KMC Algorithm

- 1 Choose which reaction

● Which reaction:  $\left[ \begin{array}{c} 0 \text{ Random number} \\ \downarrow \\ \frac{r_1}{r_1+r_2} = \frac{12}{12+3} \end{array} \right] \left| \frac{r_2}{r_1+r_2} = \frac{3}{12+3} \right| 1$

# Stochastic simulation method — kinetic Monte Carlo



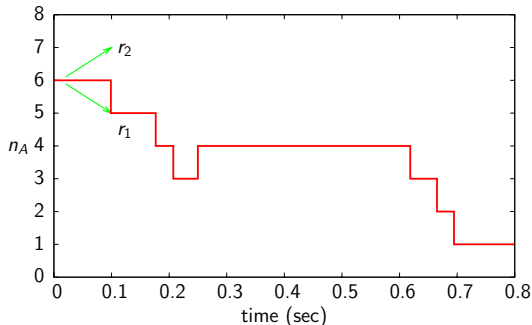
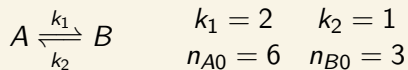
## KMC Algorithm

- 1 Choose which reaction
- 2 Choose time step

- Which reaction: 

0	Random number	1
$\frac{r_1}{r_1+r_2} = \frac{12}{12+3}$		$\frac{r_2}{r_1+r_2} = \frac{3}{12+3}$
- Time step: Sample from an exponential distribution where the distribution mean is the sum of reaction rates.

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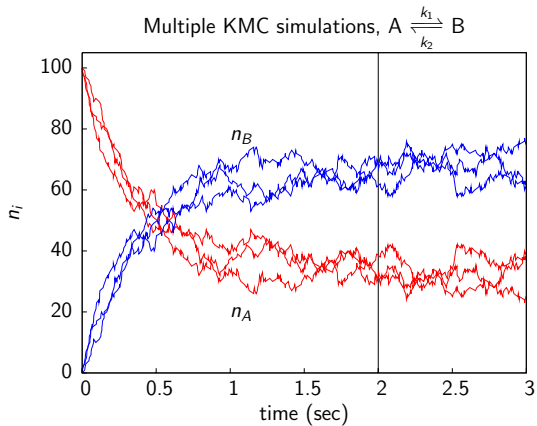


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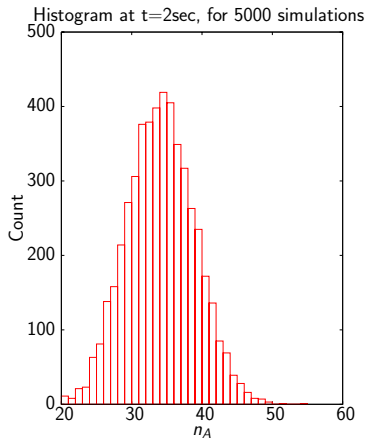
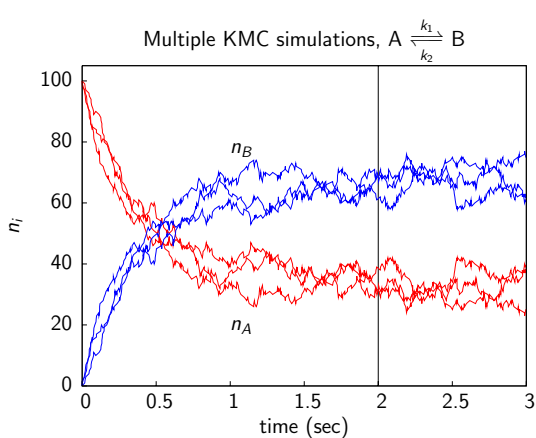
- 1 Choose which reaction
- 2 Choose time step
- 3 Repeat

- Which reaction:  $\left[ \begin{array}{c} 0 \text{ Random number} \\ \downarrow \\ \frac{r_1}{r_1+r_2} = \frac{12}{12+3} \end{array} \right] \left| \frac{r_2}{r_1+r_2} = \frac{3}{12+3} \right| 1$
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# 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

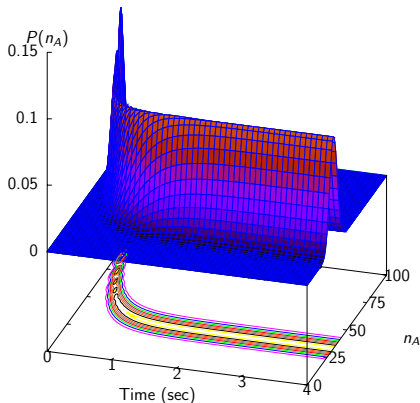
$$\frac{dP(x)}{dt} = \sum_{j=1}^{N_{rxn}} \underbrace{r_j(x - \nu_j)P(x - \nu_j)}_{\text{rate into state } x} - \underbrace{r_j(x)P(x)}_{\text{rate out of state } x}$$
$$\frac{dP}{dt} = AP$$

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## Master equation example

- $A \xrightleftharpoons[k_2]{k_1} B$
- $n_{A0} = 100, n_{B0} = 0$
- $k_1 = 2, k_2 = 1$
- 101 possible states
- 101 Coupled ODEs



## Chemical master equation

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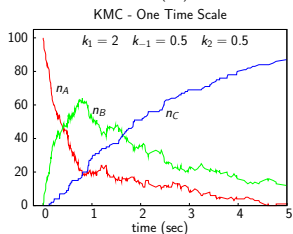
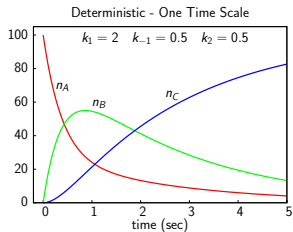
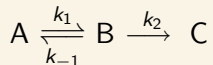
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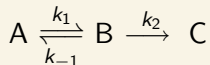
- Often the dimensionality of the master equation makes direct solution infeasible
- The master equation shows what probability distribution is sampled in a KMC simulation
- A reduced master equation can lead to a new/faster simulation schemes

# Kinetics of multiple time scales

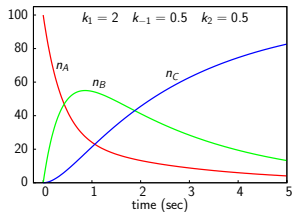


One time scale

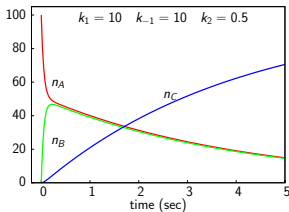
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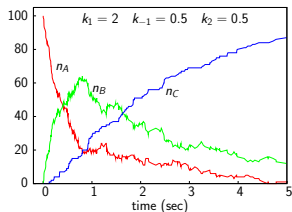
Deterministic - One Time Scale



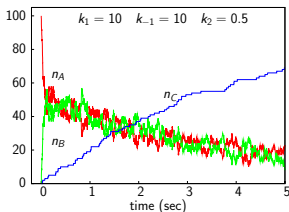
Deterministic - Two Time Scales



KMC - One Time Scale



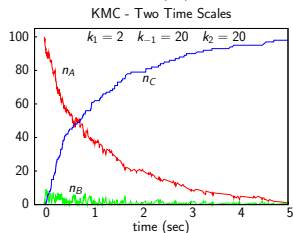
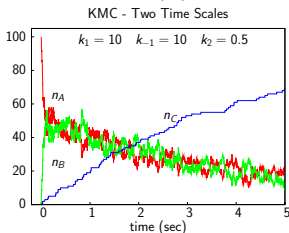
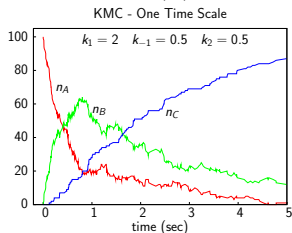
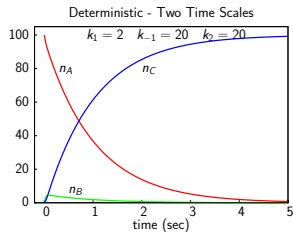
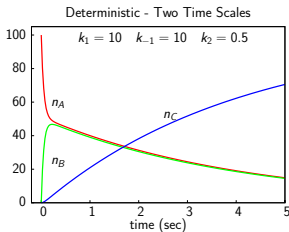
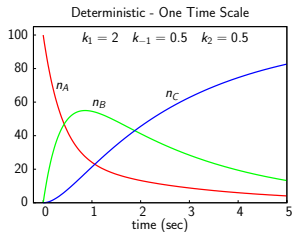
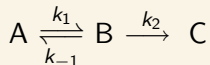
KMC - Two Time Scales



One time scale

Reaction equilibrium

# Kinetics of multiple time scales



One time scale

Reaction equilibrium

Reactive intermediate

# Deterministic model reductions

$x$  non-QSSA species,  $y$  QSSA species

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

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## Classical QSSA

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

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## Singular Perturbation QSSA

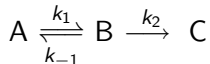
$$\begin{aligned} x &= X_0 + \epsilon X_1 + \epsilon^2 X_2 + \mathcal{O}(\epsilon^3) \\ y &= Y_0 + \epsilon Y_1 + \epsilon^2 Y_2 + \mathcal{O}(\epsilon^3) \end{aligned}$$

- Collect like powers of  $\epsilon$
- 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.

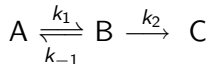


$$\begin{aligned} \frac{dP(a, b, c)}{dt} = & k_1(a+1)P(a+1, b-1, c) + k_{-1}(b+1)P(a-1, b+1, c) \\ & + k_2(b+1)P(a, b+1, c-1) - (k_1a + k_{-1}b + k_2b)P(a, b, c) \end{aligned}$$

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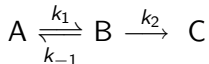


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## $\epsilon^0$ terms:

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

# SPA on the master equation

$\epsilon^1$  terms: Reduced master equation

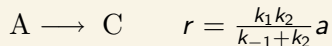
$$\frac{dW_0(a, 0, c)}{dt} = \tilde{k}(a + 1)W_0(a + 1, 0, c - 1) - \tilde{k}aW_0(a, 0, c)$$

# 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



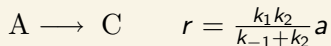
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- Same mechanisms due to linearity

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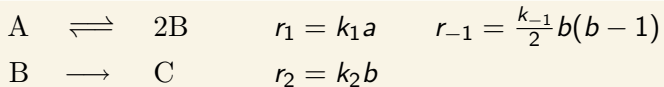
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First-order correction,  $\langle b \rangle$

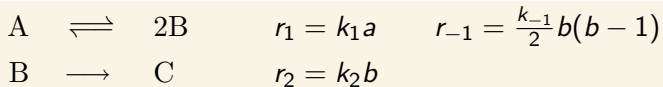
$$\langle b \rangle = f(W_0(a, 0, c)) + \mathcal{O}(\epsilon^2)$$

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

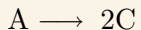
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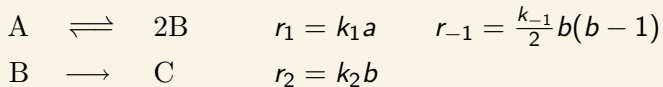


## Stoch SPA

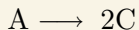


$$r = \left( \frac{k_1 k_2}{\frac{k_{-1}}{2} + k_2} \right) a$$

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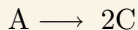


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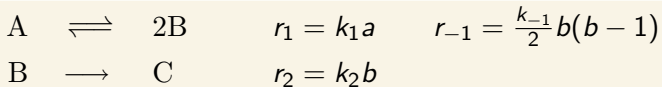
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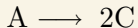


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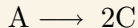


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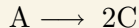
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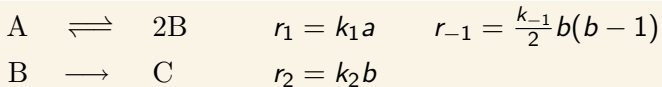
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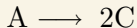


$$r = k_2 \left[ \frac{-k_2 + \sqrt{k_2^2 + 8k_1 k_{-1} a}}{4k_{-1}} \right]$$

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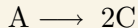


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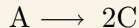
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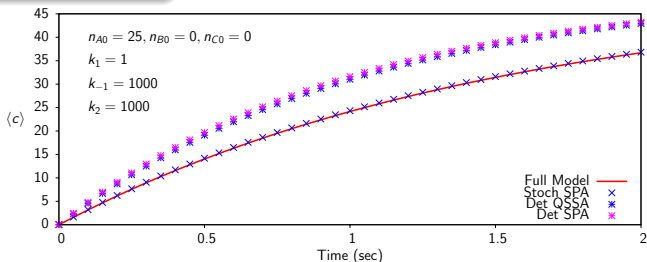


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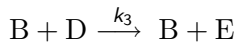
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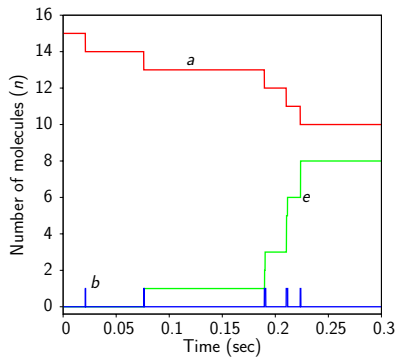
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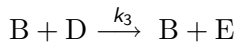
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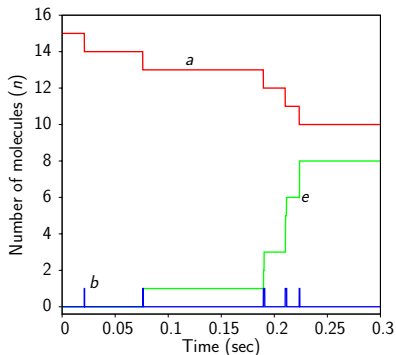
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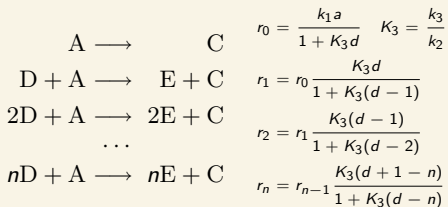
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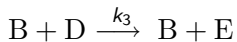
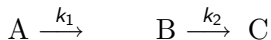
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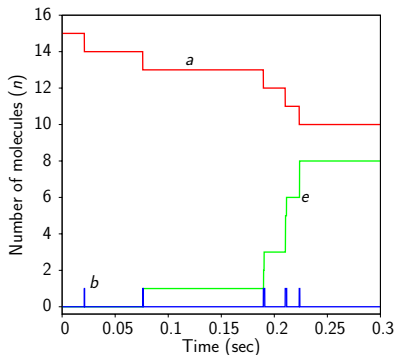
## Stoch SPA mechanism



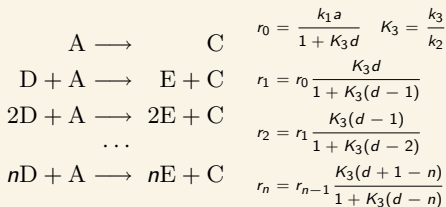
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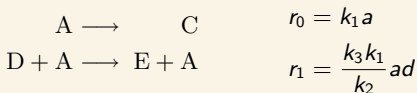
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## Stoch SPA mechanism



## Deterministic SPA mechanism



# Conclusions — Stochastic quasi-steady-state approximation

- QSSA species are removed from stochastic models with SPA

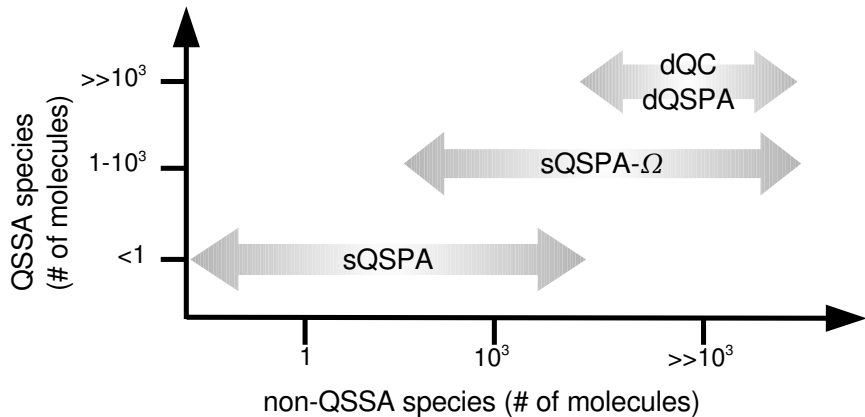
# Conclusions — Stochastic quasi-steady-state approximation

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# Conclusions — Stochastic quasi-steady-state approximation

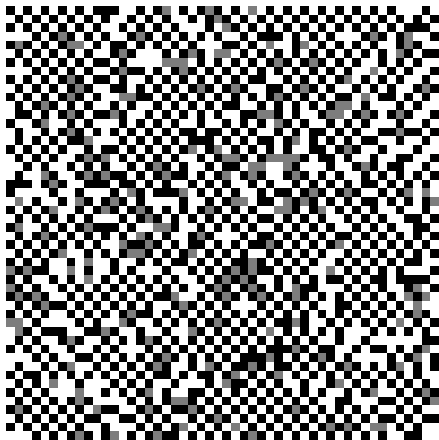
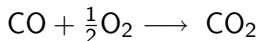
- QSSA species are removed from stochastic models with SPA
- Stochastic QSSA mechanisms different than deterministic QSSA mechanisms
- Application of stochastic QSSA:
  - ▶ Reduces the number of kinetic parameters
  - ▶ Speeds up KMC simulations (fewer events)

# Conclusions — Stochastic quasi-steady-state approximation



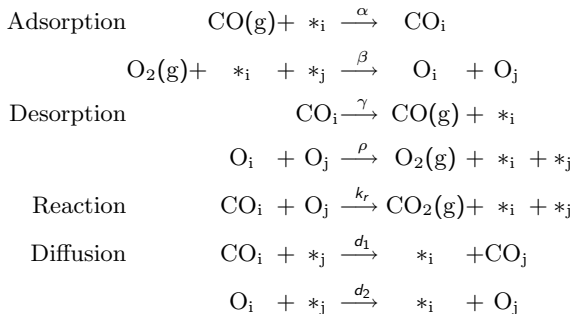
## Assumptions for this talk

- 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

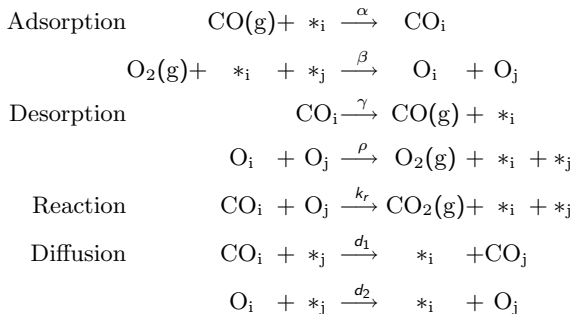


CO-black, O-gray, Empty-white.

# Model mechanism and time scales



# Model mechanism and time scales



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

$n$  - number of each species

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

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## Singular perturbation

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

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

# Slow time-scale evolution equation

$\epsilon^1$  terms : Reduced master equation

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

What have we gained?

- Removed micro-states from the master equation

# Slow time-scale evolution equation

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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  $x$ :  $n_{\text{CO}}=45$  black,  $n_{\text{O}}=8$  gray



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

# Slow time-scale evolution equation

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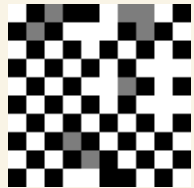
$$s_{CO-O}=26$$



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



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



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

# Slow time-scale evolution equation

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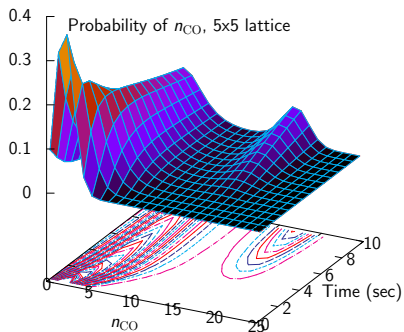


$s_{CO-O}=23$

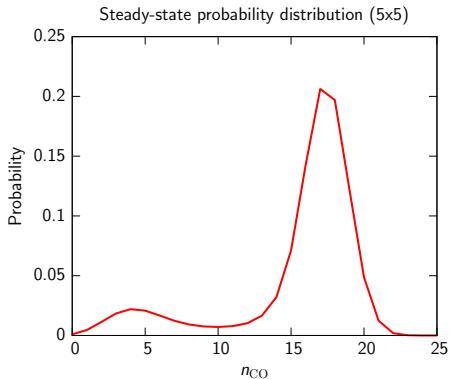
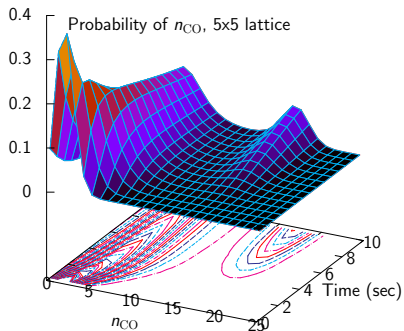
$$\langle s_{CO-O} \rangle = 24.9$$

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

# Reduced master equation solution (5x5 lattice)



# Reduced master equation solution (5x5 lattice)



## Verification of perturbation method

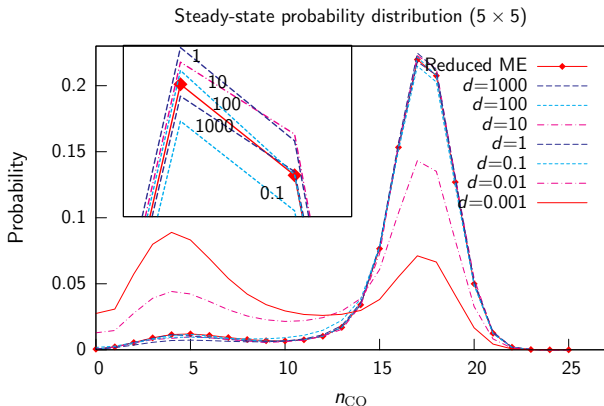
$$\sum_x P(n, x) = W_0(n) + \epsilon W_1(n) + \mathcal{O}(\epsilon^2)$$
$$\epsilon = 1/d$$

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

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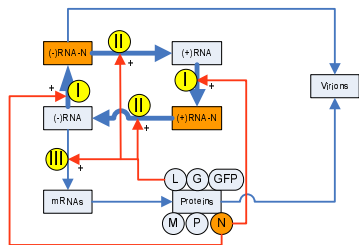


# Conclusions — Surface reactions in the infinite diffusion limit

- 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

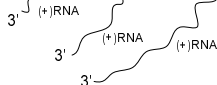
(-)RNA 3' [N] [P] [M] [G] [GFP] [L] 5'



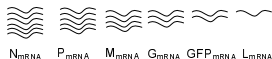
I 3' [N] [N] [N] [N] 5'



II 5' [L] [L] (-)RNA-N [L] 3'

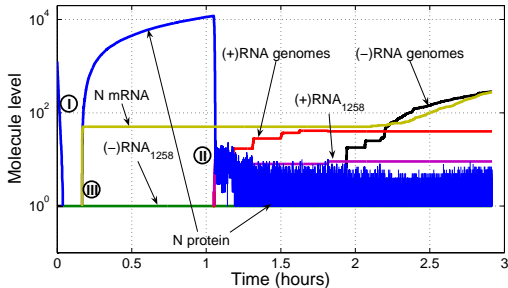


III 3' [L] [L] (-)RNA [L] 5'



- I is *encapsidation* of viral genome
- II is *replication* of encapsidated genome
- III is *transcription* of genome to messenger RNA

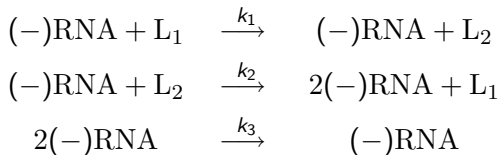
# Onset of fast fluctuations in the N protein



## Features of simulation

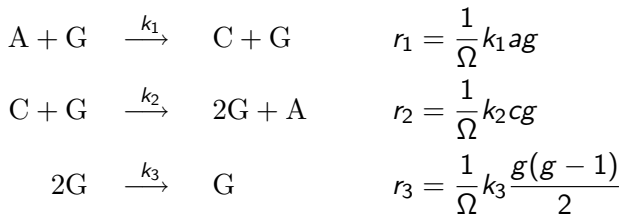
- Presence of **fast fluctuating** and **rapidly rising** species
- Fast fluctuations slow the full KMC simulation
- Motivates the formulation of a simpler example to understand this phenomenon

# Fast fluctuation and rapid rise in VSV biology



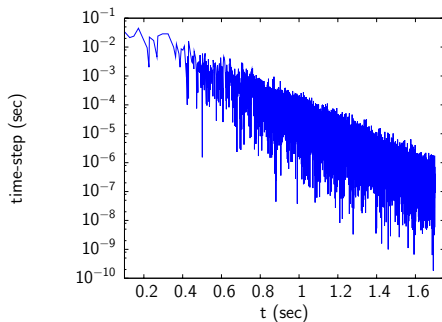
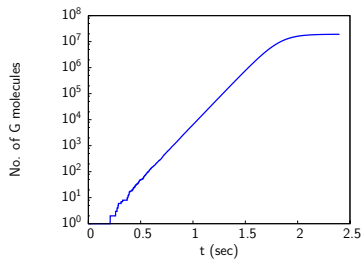
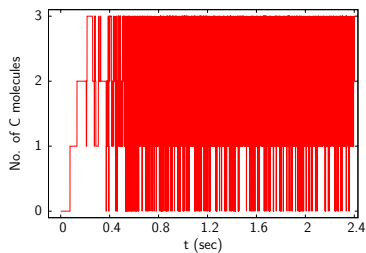
- The viral genome is amplified by first two reactions
- The free viral proteins and messages are not amplified
- Values of parameters  $k_1$ ,  $k_2$  and  $k_3$  may cause fast fluctuation in polymerases along with rapid amplification of viral genome

# Fast fluctuation and rapid rise — Idealized problem



Species	Initial number	Rate constant ( $\text{m}^3/\text{mol}\cdot\text{s}$ )
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 - $\Omega$ 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 $C$

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

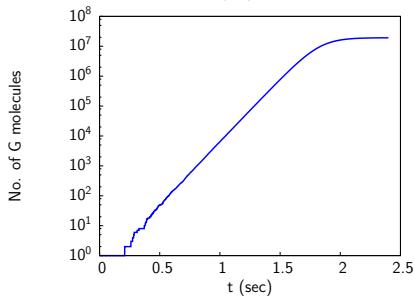
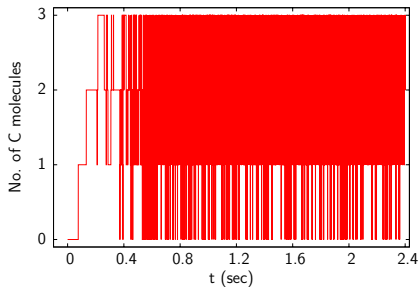
## Deterministic evolution of $G$

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

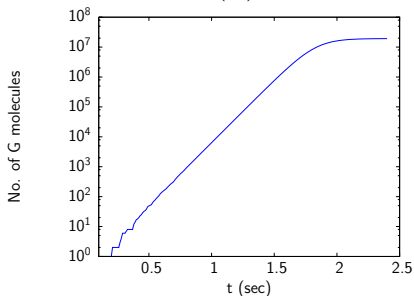
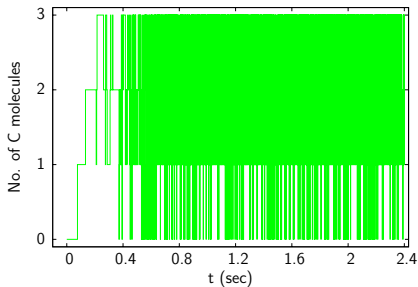
$N_0$	Initial number of polymerases
$q = \frac{k_2}{k_1}$	Ratio of rate constants

# Comparison of full SSA with hybrid SSA - $\Omega$

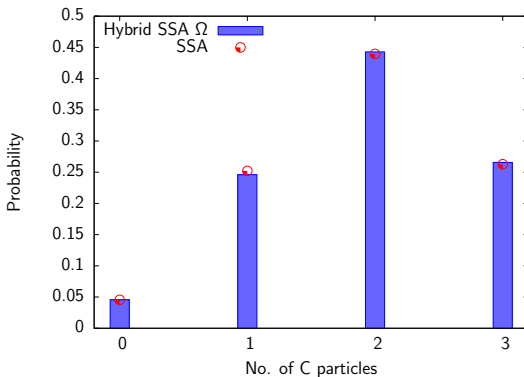
## Full SSA



## Hybrid SSA - $\Omega$



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



- Hybrid SSA –  $\Omega$  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



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