Stochastic models for chemical reactions

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Bilingual dictionary

Chemistry	**Probability**
propensity	intensity
master equation	forward equation
nonlinear diffusion approximation	
Langevin approximation	diffusion approximation
Van Kampen approximation	central limit theorem
quasi steady state/partial equilibrium	averaging

Reaction networks

Standard notation for chemical reactions

$$A + B \overset{\kappa}{\rightharpoonup} C$$

is interpreted as "a molecule of A combines with a molecule of B to give a molecule of C."

$$A + B \rightleftharpoons C$$

means that the reaction can go in either direction, that is, a molecule of C can dissociate into a molecule of A and a molecule of B.

We consider a *network* of reactions involving m chemical species, $A_1, \ldots, A_m$.

$$\sum_{i=1}^{m} \nu_{ik} A_i \rightharpoonup \sum_{i=1}^{m} \nu'_{ik} A_i$$

where the ν_{ik} and ν'_{ik} are nonnegative integers.

Markov chain models

$X(t)$ number of molecules of each species in the system at time t.

ν_k number of molecules of each chemical species consumed in the kth reaction.

ν'_k number of molecules of each species created by the kth reaction.

$\lambda_k(x)$ rate at which the kth reaction occurs. (The propensity/intensity.)

If the kth reaction occurs at time t, the new state becomes

$$X(t) = X(t-) + \nu'_k - \nu_k.$$

The number of times that the kth reaction occurs by time t is given by the counting process satisfying

$$R_k(t) = Y_k(\int_0^t \lambda_k(X(s))ds),$$

where the Y_k are independent unit Poisson processes.

Equations for the system state

The state of the system satisfies

$$\begin{aligned} X(t) &= X(0) + \sum_k R_k(t)(\nu_k' - \nu_k) \\ &= X(0) + \sum_k Y_k\left(\int_0^t \lambda_k(X(s))ds\right)(\nu_k' - \nu_k) = (\nu' - \nu)R(t) \end{aligned}$$

ν' is the matrix with columns given by the ν_k'.

ν is the matrix with columns given by the ν_k.

$R(t)$ is the vector with components $R_k(t)$.

Rates for the law of mass action

For a binary reaction $A_1 + A_2 \rightharpoonup A_3$ or $A_1 + A_2 \rightharpoonup A_3 + A_4$

$$\lambda_k(x) = \kappa_k x_1 x_2$$

For $A_1 \rightharpoonup A_2$ or $A_1 \rightharpoonup A_2 + A_3$, $\lambda_k(x) = \kappa_k x_1$. For $2A_1 \rightharpoonup A_2$, $\lambda_k(x) = \kappa_k x_1(x_1 - 1)$.

For a binary reaction $A_1 + A_2 \rightharpoonup A_3$, the rate should vary inversely with volume, so it would be better to write

$$\lambda_k^N(x) = \kappa_k N^{-1} x_1 x_2 = N \kappa_k z_1 z_2,$$

where classically, N is taken to be the volume of the system times Avogadro's number and $z_i = N^{-1} x_i$ is the concentration in moles per unit volume. Note that unary reaction rates also satisfy

$$\lambda_k(x) = \kappa_k x_i = N \kappa_k z_i.$$

General form for classical scaling

All the rates naturally satisfy

$$\lambda_k^N(x) \approx N\kappa_k \prod_i z_i^{\nu_{ik}} \equiv N\widetilde{\lambda}_k(z).$$

For example, for $2A_1 \rightarrow A_2$ and $z_1 = N^{-1}x_1$,

$$\frac{1}{N}\kappa_k x_1(x_1 - 1) = N\kappa_k z_1(z_1 - \frac{1}{N}) \approx N\kappa_k z_1^2.$$

First scaling limit

Setting $C^N(t) = N^{-1}X(t)$

$$\begin{aligned} C^N(t) &= C^N(0) + \sum_k N^{-1} Y_k\Big(\int_0^t \lambda_k^N(X(s))ds\Big)(\nu_k' - \nu_k) \\ &\approx C^N(0) + \sum_k N^{-1} Y_k\Big(N\int_0^t \tilde{\lambda}_k(C^N(s))ds\Big)(\nu_k' - \nu_k) \end{aligned}$$

The law of large numbers for the Poisson process implies $N^{-1}Y(Nu) \approx u$,

$$C^N(t) \approx C^N(0) + \sum_k \int_0^t \kappa_k \prod_i C_i^N(s)^{\nu_{ik}}(\nu_k' - \nu_k)ds,$$

which in the large volume limit gives the classical deterministic law of mass action

$$\dot{C}(t) = \sum_k \kappa_k \prod_i C_i(t)^{\nu_{ik}}(\nu_k' - \nu_k) \equiv F(C(t)).$$

Multiple scales

Let $N_0 >> 1$.

For each species i, define the *normalized abundances* (or simply, the abundances) by

$$Z_i(t) = N_0^{-\alpha_i} X_i(t),$$

where $\alpha_i \geq 0$ should be selected so that $Z_i = O(1)$. Note that the abundance may be the species number ($\alpha_i = 0$) or the species concentration or something else.

The rate constants may also vary over several orders of magnitude $\kappa'_k = \kappa_k N_0^{\beta_k}$, so for a binary reaction

$$\kappa'_k x_i x_j = N_0^{\beta_k + \alpha_i + \alpha_j} \kappa_k z_i z_j$$

A parameterized family of models

Let

$$Z_i^N(t) = Z_i(0) + \sum_k N^{-\alpha_i} Y_k\left(\int_0^t N^{\beta_k+\nu_k\cdot\alpha} \lambda_k(Z^N(s))ds\right)(\nu'_{ik} - \nu_{ik}).$$

Then the “true” model is $Z = Z^{N_0}$.

Example: Michaelis-Menten kinetics

Consider the reaction system $A + E \rightleftharpoons AE \rightharpoonup B + E$

modeled as a continuous time Markov chain satisfying

$$\begin{aligned}
X_A(t) &= X_A(0) - Y_1\Big(\int_0^t \kappa_1' X_A(s)X_E(s)ds\Big) + Y_2\Big(\int_0^t \kappa_2' X_{AE}(s)ds\Big)\\
X_E(t) &= X_E(0) - Y_1\Big(\int_0^t \kappa_1' X_A(s)X_E(s)ds\Big) + Y_2\Big(\int_0^t \kappa_2' X_{AE}(s)ds\Big)\\
&\qquad + Y_3\Big(\int_0^t \kappa_3' X_{AE}(s)ds\Big)\\
X_B(t) &= Y_3\Big(\int_0^t \kappa_3' X_{AE}(s)ds\Big)
\end{aligned}$$

$\kappa_2', \kappa_3' >> \kappa_1'$

Scaling

Note that $M = X_{AE}(t) + X_E(t)$ is constant. Let

$$N_0 = O(X_A) >> M.$$

Setting $\beta_2 = \beta_3 = 1$, $\alpha_A = 1$, $\alpha_E = \alpha_{AE} = 0$,

$$\kappa_1 = \kappa_1', \quad \kappa_2 = \kappa_2' N_0^{-1}, \quad \kappa_3 = \kappa_3' N_0^{-1}$$

$$V_E(t) = \int_0^t M^{-1} X_E(s) ds, \quad Z_A(t) = N^{-1} X_A(t)$$

$$\begin{aligned} Z_A(t) &= Z_A(0) - N^{-1} Y_1(N \int_0^t \kappa_1 M Z_A(s) M^{-1} X_E(s) ds) + N^{-1} Y_2(N\kappa_2 \int_0^t X_{AE}(s) ds) \\ &= Z_A(0) - N^{-1} Y_1(N \int_0^t \kappa_1 M Z_A(s) dV_E(s)) + N^{-1} Y_2(N\kappa_2 M(t - V_E(t))) \end{aligned}$$

Analysis

Similarly,

$$\begin{aligned} X_E(t) &= X_E(0) - Y_1(N\int_0^t \kappa_1 M Z_A(s)dV_E(s)) + Y_2(N\kappa_2 M(t - V_E(t))) \\ &\quad + Y_3(N\kappa_3 M(t - V_E(t))) \end{aligned}$$

and dividing by N and letting $N \to \infty$,

$$\lim_{N\to\infty}\left((\kappa_2+\kappa_3)M(t - V_E(t))) - \int_0^t \kappa_1 M Z_A(s)dV_E(s)\right) = 0.$$

Also

$$\lim_{N\to\infty}\left(Z_A(t) - Z_A(0) + \int_0^t \kappa_1 M Z_A(s)dV_E(s) - \kappa_2 M(t - V_E(t))\right) = 0$$

Derivation of Michaelis-Menten equation

Theorem 1 *(Darden [2, 3]) Assume that* $N \to \infty$ *and* $Z_A^N(0) = X_A(0)/N \to x_A(0)$*. Then* (Z_A^N, V_E^N) *converges to* $(x_A(t), v_E(t))$ *satisfying*

$$\begin{aligned} x_A(t) &= x_A(0) - \int_0^t \kappa_1 M x_A(s) \dot{v}_E(s) ds + \int_0^t \kappa_2 M (1 - \dot{v}_E(s)) ds \\ 0 &= -\int_0^t \kappa_1 x_A(s) \dot{v}_E(s) ds + \int_0^t (\kappa_2 + \kappa_3)(1 - \dot{v}_E(s)) ds, \end{aligned}$$

and hence $\dot{v}_E(s) = \frac{\kappa_2+\kappa_3}{\kappa_2+\kappa_3+\kappa_1 x_A(s)}$ *and*

$$\dot{x}_A(t) = -\frac{M\kappa_1\kappa_3 x_A(t)}{\kappa_2 + \kappa_3 + \kappa_1 x_A(t)}.$$

Example: Model of a viral infection

Srivastava, You, Summers, and Yin [5], Haseltine and Rawlings [4], Ball, Kurtz, Popovic, and Rampala [1]

Three time-varying species, the viral template, the viral genome, and the viral structural protein (indexed, 1, 2, 3 respectively).

The model involves six reactions,

$$
\begin{aligned}
T + \text{stuff} &\xrightarrow{\kappa'_1} T + G \\
G &\xrightarrow{\kappa'_2} T \\
T + \text{stuff} &\xrightarrow{\kappa'_3} T + S \\
T &\xrightarrow{\kappa'_4} \emptyset \\
S &\xrightarrow{\kappa'_5} \emptyset \\
G + S &\xrightarrow{\kappa'_6} V
\end{aligned}
$$

Stochastic system

$$
\begin{aligned}
X_1(t) &= X_1(0) + Y_b\left(\int_0^t \kappa_2' X_2(s)ds\right) - Y_d\left(\int_0^t \kappa_4' X_1(s)ds\right) \\
X_2(t) &= X_2(0) + Y_a\left(\int_0^t \kappa_1' X_1(s)ds\right) - Y_b\left(\int_0^t \kappa_2' X_2(s)ds\right) \\
&\qquad -Y_f\left(\int_0^t \kappa_6' X_2(s)X_3(s)ds\right) \\
X_3(t) &= X_3(0) + Y_c\left(\int_0^t \kappa_3' X_1(s)ds\right) - Y_e\left(\int_0^t \kappa_5' X_3(s)ds\right) \\
&\qquad -Y_f\left(\int_0^t \kappa_6' X_2(s)X_3(s)ds\right)
\end{aligned}
$$

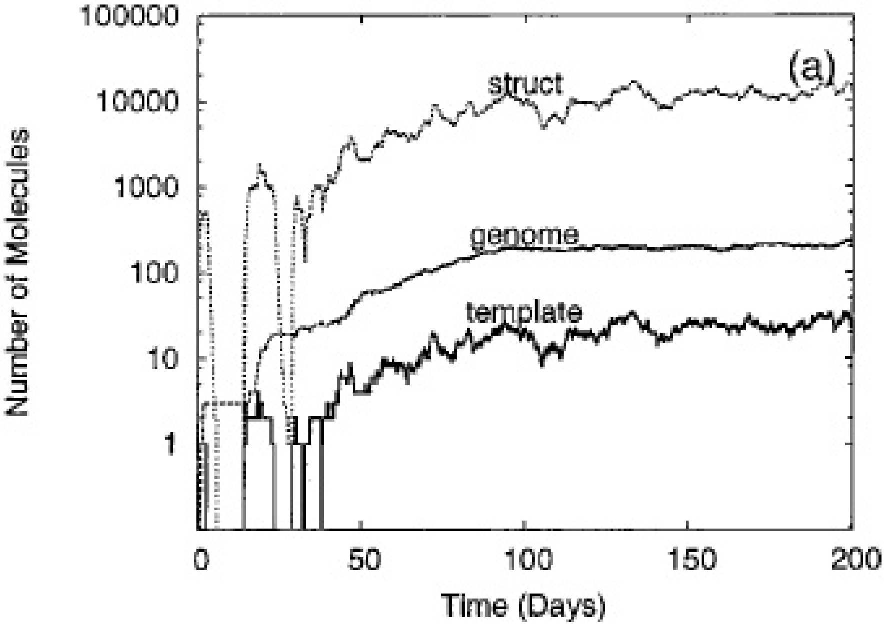


Figure 1: Simulation (Haseltine and Rawlings 2002)

Scaling parameters

Each X_i is scaled according to its abundance in the system.

For $N_0 = 1000$, $X_1 = O(N_0^0)$, $X_2 = O(N_0^{2/3})$, and $X_3 = O(N_0)$ and we take $Z_1 = X_1$, $Z_2 = X_2 N_0^{-2/3}$, and $Z_3 = X_3 N_0^{-1}$.

Expressing the rate constants in terms of $N_0 = 1000$

κ_1'	1	1
κ_2'	0.025	$2.5 N_0^{-2/3}$
κ_3'	1000	N_0
κ_4'	0.25	$.25$
κ_5'	2	2
κ_6'	7.5×10^{-6}	$.75 N_0^{-5/3}$

Normalized system

With the scaled rate constants, we have

$$\begin{aligned}
Z_1^N(t) &= Z_1^N(0) + Y_b\Big(\int_0^t 2.5 Z_2^N(s)ds\Big) - Y_d\Big(\int_0^t .25 Z_1^N(s)ds\Big) \\
Z_2^N(t) &= Z_2^N(0) + N^{-2/3} Y_a\Big(\int_0^t Z_1^N(s)ds\Big) - N^{-2/3} Y_b\Big(\int_0^t 2.5 Z_2^N(s)ds\Big) \\
&\qquad - N^{-2/3} Y_f\Big(\int_0^t .75 Z_2^N(s) Z_3^N(s)ds\Big) \\
Z_3^N(t) &= Z_3^N(0) + N^{-1} Y_c\Big(\int_0^t N Z_1^N(s)ds\Big) - N^{-1} Y_e\Big(\int_0^t 2N Z_3^N(s)ds\Big) \\
&\qquad - N^{-1} Y_f\Big(\int_0^t .75 Z_2^N(s) Z_3^N(s)ds\Big),
\end{aligned}$$

Limiting system

With the scaled rate constants, we have

$$\begin{aligned} Z_1(t) &= Z_1(0) + Y_b\left(\int_0^t 2.5 Z_2(s)ds\right) - Y_d\left(\int_0^t .25 Z_1(s)ds\right) \\ Z_2(t) &= Z_2(0) \\ Z_3(t) &= Z_3(0) + \int_0^t Z_1(s)ds - \int_0^t 2Z_3(s)ds \end{aligned}$$

Fast time scale

Define $V_i^N(t) = Z_i(N^{2/3}t)$.

$$\begin{aligned}
V_1^N(t) &= V_1^N(0) + Y_b\Big(\int_0^t 2.5N^{2/3}V_2^N(s)ds\Big) - Y_d\Big(\int_0^t .25N^{2/3}V_1^N(s)ds\Big) \\
V_2^N(t) &= V_2^N(0) + N^{-2/3}Y_a\Big(\int_0^t N^{2/3}V_1^N(s)ds\Big) \\
&\qquad -N^{-2/3}Y_b\Big(\int_0^t 2.5N^{2/3}V_2^N(s)ds\Big) \\
&\qquad -N^{-2/3}Y_f\Big(N^{2/3}\int_0^t .75V_2^N(s)V_3^N(s)ds\Big) \\
V_3^N(t) &= V_3^N(0) + N^{-1}Y_c\Big(\int_0^t N^{5/3}V_1^N(s)ds\Big) - N^{-1}Y_e\Big(\int_0^t 2N^{5/3}V_3^N(s)ds\Big) \\
&\qquad -N^{-1}Y_f\Big(\int_0^t .75N^{2/3}V_2^N(s)V_3^N(s)ds\Big)
\end{aligned}$$

Averaging

As $N \to \infty$, dividing the equations for V_1^N and V_3^N by $N^{2/3}$ shows that

$$\int_0^t V_1^N(s)ds - 10\int_0^t V_2^N(s)ds \to 0$$
$$\int_0^t V_3^N(s)ds - 5\int_0^t V_2^N(s)ds \to 0.$$

The assertion for V_3^N and the fact that V_2^N is asymptotically regular imply

$$\int_0^t V_2^N(s)V_3^N(s)ds - 5\int_0^t V_2^N(s)^2 ds \to 0.$$

It follows that V_2^N converges to the solution of (1).

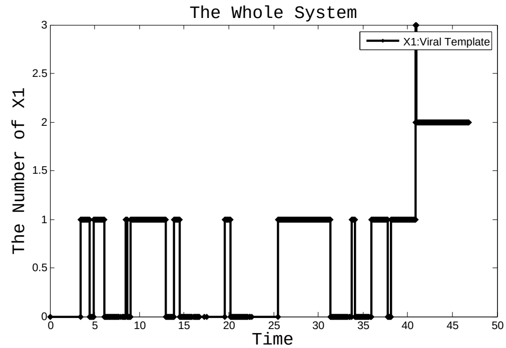
Law of large numbers

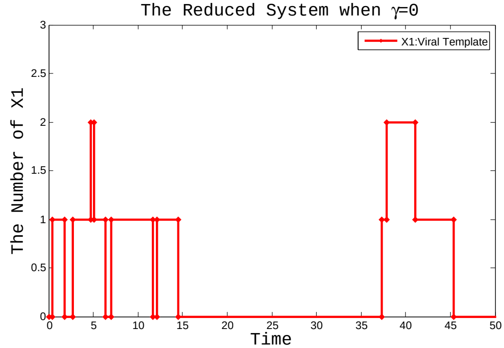
Theorem 2 *For each* $\delta > 0$ *and* $t > 0$,

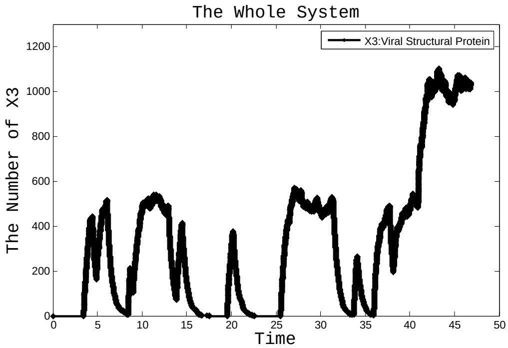
$$\lim_{N\to\infty} P\{\sup_{0\le s\le t} |V_2^N(s) - V_2(s)| \ge \delta\} = 0,$$

where V_2 *is the solution of*

$$V_2(t) = V_2(0) + \int_0^t 7.5V_2(s)ds) - \int_0^t 3.75V_2(s)^2 ds. \tag{1}$$


The Whole System


The Reduced System when γ=0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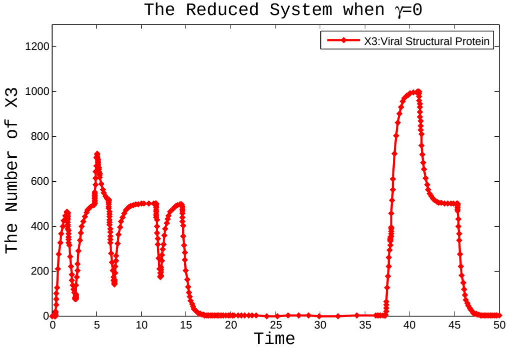
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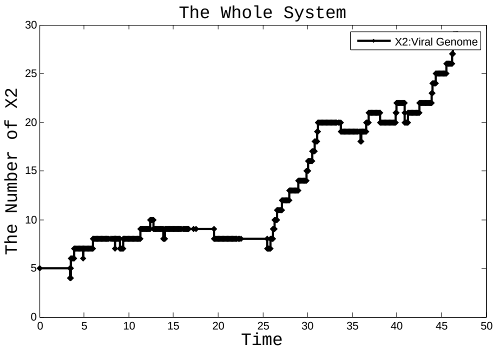
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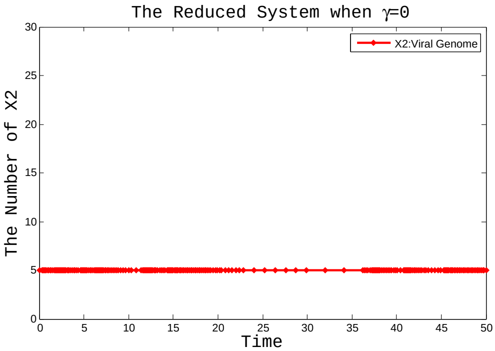
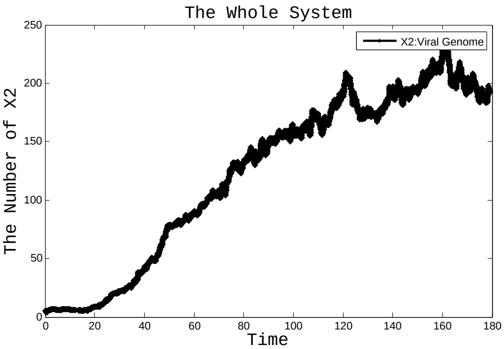

The Reduced System when γ=0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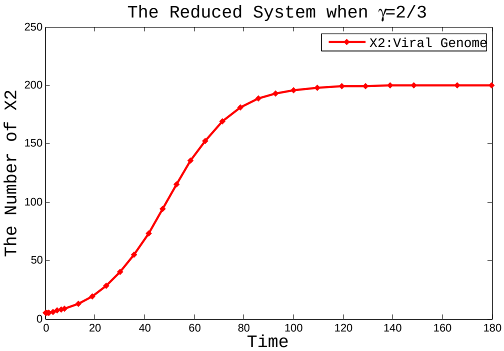
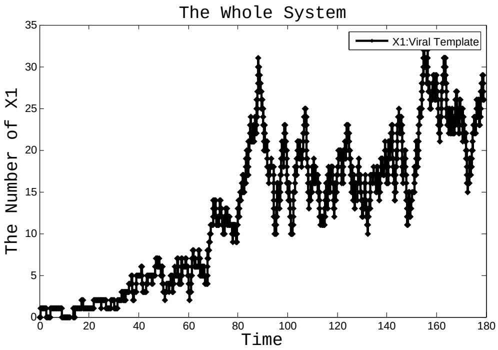

The Reduced System when γ=2/3



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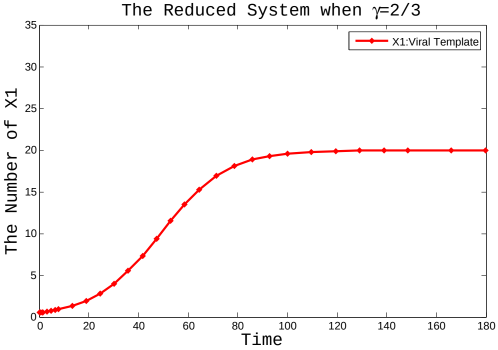
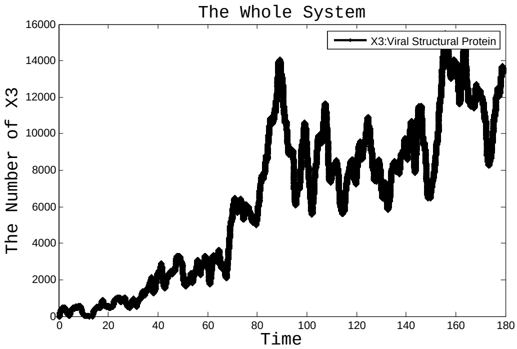
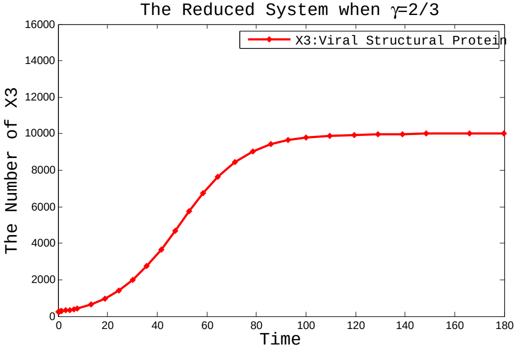


The Reduced System when γ=2/3



The Whole System



The Reduced System when γ=2/3

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Abstract

Stochastic models for chemical reactions

Attempts to model chemical reactions within biological cells have led to renewed interest in stochastic models for these systems. The classical stochastic models for chemical reaction networks will be reviewed, and multiscale methods for model reduction will be described. The methods will be illustrated with derivation of the Michaelis-Menten model for enzyme reactions and a simple model of viral infection of a cell.