Multiscale analysis of stochastic reaction networks

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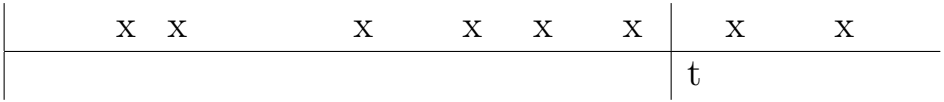
Poisson processes

A Poisson process is a model for a series for random observations occurring in time.



Let $Y(t)$ denote the number of observations by time t. In the figure above, $Y(t) = 6$. Note that for $t < s$, $Y(s) - Y(t)$ is the number of observations in the time interval $(t, s]$. We make the following assumptions about the model.

1) Observations occur one at a time.

2) Numbers of observations in disjoint time intervals are independent random variables, i.e., if $t_0 < t_1 < \cdots < t_m$, then $Z(t_k) - Z(t_{k-1})$, $k = 1, \ldots, m$ are independent random variables.

3) The distribution of $Z(t + a) - Z(t)$ does not depend on t.

Characterization of a Poisson process

Theorem 1 *Under assumptions 1), 2), and 3), there is a constant* $\lambda > 0$ *such that, for* $t < s$, $Z(s) - Z(t)$ *is Poisson distributed with parameter* $\lambda(s-t)$, *that is,*

$$P\{Z(s) - Z(t) = k\} = \frac{(\lambda(s-t))^k}{k!} e^{-\lambda(s-t)}.$$

If $\lambda = 1$, then Z is a *unit* (or rate one) Poisson process. If Y is a unit Poisson process and $Y_\lambda(t) \equiv Y(\lambda t)$, then Y_λ is a Poisson process with parameter λ.

Application of the LLN and CLT to Poisson processes

Theorem 2 *If Y is a unit Poisson process, then for each $u_0 > 0$,*

$$\lim_{K\to\infty} \sup_{u\le u_0} \left|\frac{Y(Ku)}{K} - u\right| = 0 \quad a.s.$$

Proof. For fixed u, by the independent increments assumption, the result is just the ordinary law of large numbers. The uniformity follows by monotonicity. □

The central limit theorem suggests that for large K

$$\frac{Y(Ku) - Ku}{\sqrt{K}} \approx W(u), \quad \frac{Y(Ku)}{K} \approx u + \frac{1}{\sqrt{K}} W(u)$$

where W is *standard Brownian motion.*

Formulating Markov models

Suppose $Y_\lambda(t) = Y(\lambda t)$ and $\mathcal{F}_t$ represents the information obtained by observing $Y_\lambda(s)$, for $s \le t$.

$$P\{Y_\lambda(t+\Delta t) - Y_\lambda(t) = 1 | \mathcal{F}_t\} = P\{Y_\lambda(t+\Delta t) - Y_\lambda(t) = 1\} = 1 - e^{-\lambda \Delta t} \approx \lambda \Delta t$$

A continuous time Markov chain X taking values in $\mathbb{Z}^d$ is specified by giving its transition intensities that determine

$$P\{X(t+\Delta t) - X(t) = l | \mathcal{F}_t^X\} \approx \beta_l(X(t))\Delta t, \quad l \in \mathbb{Z}^d.$$

Counting process representation

If we write

$$X(t) = X(0) + \sum_l l N_l(t)$$

where $N_l(t)$ is the number of jumps of l at or before time t, then

$$P\{N_l(t+\Delta t) - N_l(t) = 1 | \mathcal{F}_t^X\} \approx \beta_l(X(t))\Delta t, \quad l \in \mathbb{Z}^d.$$

N_l is a *counting process* with intensity (*propensity* in the chemical literature) $\beta_l(X(t))$ and we can write

$$N_l(t) = Y_l(\int_0^t \beta_l(X(s))ds),$$

where the Y_l are independent, unit Poisson processes. Consequently,

$$X(t) = X(0) + \sum_l l Y_l(\int_0^t \beta_l(X(s))ds).$$

Reaction networks

Standard notation for chemical reactions

$$A + B \xrightarrow{k} C$$

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

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

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

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

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

Take N_0 to be of the order of magnitude of the abundance of the most abundant species in the system.

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

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

where $0 \leq \alpha_i \leq 1$ 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: Model of a viral infection

Srivastava, You, Summers, and Yin [4], Haseltine and Rawlings [2], 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

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

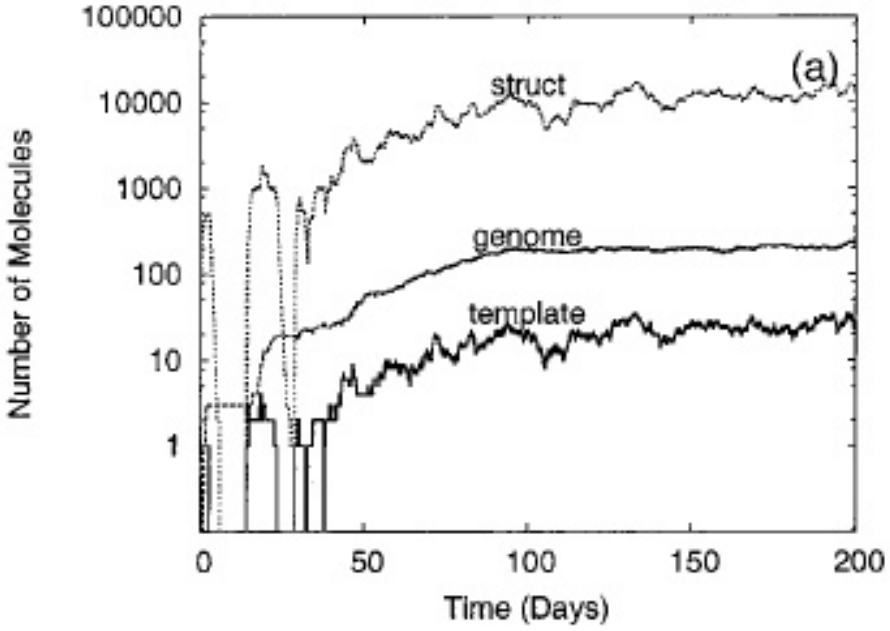


Figure 1: Simulation (Haseltine and Rawlings 2002)

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

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

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

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

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

Law of large numbers

Theorem 3 *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*

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

Approximate models

We have a family of models indexed by N for which $N = N_0$ gives the "correct" model.

Other values of N and any limits as $N \to \infty$ (perhaps with a change of time scale) give approximate models. The challenge is to select the α_i, but once that is done, the intial condition for index N is give by

$$Z_i^N(0) = N_i^{-\alpha_i} X_i(0),$$

where the $X_i(0)$ are the initial species numbers in the correct model.

If $\lim_{N\to\infty} Z_i^N(\cdot N^\gamma) = Z_i^\infty$, then we should have

$$X_i(t) \approx N_0^{\alpha_i} Z_i^\infty(t N_0^{-\gamma}).$$

For example, in the virus model

$$X_2(t) \approx (1000)^{2/3} V_2(t(1000)^{-2/3})$$

Determining the scaling exponents

Suppose that the rate constants satisfy

$$\kappa'_1 \geq \kappa'_2 \geq \cdots \geq \kappa'_{r_0}$$

Then it seems natural to select

$$\beta_1 \geq \cdots \geq \beta_{r_0}$$

and define κ_k so that

$$\kappa'_k = \kappa_k N_0^{\beta_k}.$$

General principles

Consider $A_1 + A_2 \rightharpoonup A_3 + A_4$ $A_3 + A_5 \rightharpoonup A_6$

$$Z_3^N(t) = Z_3^N(0) + N^{-\alpha_3} Y_1(N^{\beta_1+\alpha_1+\alpha_2} \int_0^t \kappa_1 Z_1^N(s) Z_2^N(s) ds)$$
$$- N^{-\alpha_3} Y_2(N^{\beta_2+\alpha_3+\alpha_5} \int_0^t \kappa_2 Z_3^N(s) Z_5^N(s) ds) \ ,$$

or scaling time

$$Z_3^N(tN^\gamma) = Z_3^N(0) + N^{-\alpha_3} Y_1(N^{\beta_1+\alpha_1+\alpha_2+\gamma} \int_0^t \kappa_1 Z_1^N(sN^\gamma) Z_2^N(sN^\gamma) ds)$$
$$- N^{-\alpha_3} Y_2(N^{\beta_2+\alpha_3+\alpha_5+\gamma} \int_0^t \kappa_2 Z_3^N(sN^\gamma) Z_5^N(sN^\gamma) ds) \ .$$

Assuming the other $Z_i^N = O(1)$, $Z_3^N = O(1)$ if

$$\beta_1 + \alpha_1 + \alpha_2 = \beta_2 + \alpha_3 + \alpha_5$$

($Z_3^N(t) \approx \frac{\kappa_1 Z_1^N(t) Z_2^N(t)}{\kappa_2 Z_5^N(t)}$ or $Z_3^N(t) \approx Z_3^N(0)$) or if

$$(\beta_1 + \alpha_1 + \alpha_2 + \gamma) \vee (\beta_2 + \alpha_3 + \alpha_5 + \gamma) \leq \alpha_3.$$

Species balance condition

Let $\Gamma_i^+ = \{k : \nu'_{ik} > \nu_{ik}\}$, that is, Γ_i^+ gives the set of reactions that result in an increase in the ith species, and let $\Gamma_i^- = \{k : \nu'_{ik} < \nu_{ik}\}$.

Condition 4 *For each species A_i,*

$$\max_{k\in\Gamma_i^-}(\beta_k + \nu_k \cdot \alpha) = \max_{k\in\Gamma_i^+}(\beta_k + \nu_k \cdot \alpha). \tag{2}$$

or

$$\max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\beta_k + \nu_k \cdot \alpha) + \gamma \leq \alpha_i. \tag{3}$$

Subnetwork balance

There may be subsets of species such that the collective rate of production is of a different order of magnitude than the collective rate of consumption.

$$\emptyset \xrightarrow{\kappa_1} S_1 \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} S_2 \xrightarrow{\kappa_4} \emptyset.$$

If $0 < \beta_4 < \beta_1 < \beta_2 = \beta_3$ and $\alpha_1 = \alpha_2 = 0$, then

$$\begin{aligned} Z_1^N(t) &= Z_1^N(0) + Y_1(\lambda_1 N^{\beta_1} t) + Y_3(\lambda_3 N^{\beta_3} \int_0^t Z_2^N(s)ds) - Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s)ds) \\ Z_2^N(t) &= Z_2^N(0) + Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s)ds) - Y_3(\lambda_3 N^{\beta_3} \int_0^t Z_2^N(s)ds) \\ &\quad - Y_4(\lambda_4 N^{\beta_4} \int_0^t Z_2^N(s)ds) \end{aligned}$$

The species balance condition is satisfied, but the species numbers will go to infinity as $N \to \infty$.

Atom graphs

Corresponding to each "atom" (molecular subspecies that is left intact by all reactions), define a directed graph in which the nodes are identified with the species that contain the atom and the edges correspond to the reactions that transform one species containing the atom into another species containing the atom.

Let G_0 be any subset of the nodes G of an atom graph. Let $\Gamma^+_{G_0}$ be the collection of edges (reactions) that are entrance edges or that lead from a node in $G - G_0$ to a node in G, and let $\Gamma^-_{G_0}$ be the collection of edges that are exit edges or lead from a node in G_0 to a node in $G - G_0$.

General balance condition

Condition 5 *For each subset G_0 of an atom graph*

$$\max_{k\in\Gamma^-_{G_0}}(\beta_k+\nu_k\cdot\alpha)=\max_{k\in\Gamma^+_{G_0}}(\beta_k+\nu_k\cdot\alpha) \tag{4}$$

or

$$\max_{k\in\Gamma^+_{G_0}\cup\Gamma^-_{G_0}}(\beta_k+\nu_k\cdot\alpha)+\gamma\le\max_{i\in G_0}\alpha_i. \tag{5}$$

Then (5) implies

$$\gamma\le\min_{G}\ \min_{G_0\subset G,G_0\ \text{unbalanced}}(\max_{i\in G_0}\alpha_i-\max_{k\in\Gamma^+_{G_0}\cup\Gamma^-_{G_0}}(\beta_k+\nu_k\cdot\alpha)), \tag{6}$$

where the first minimum is over all atom graphs G and the second minimum is over all subsets $G_0\subset G$ that do not satisfy the balance equality (4).

Heat shock example

Example

$$\emptyset \xrightarrow{\kappa_1} S_1 \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} S_2,$$

Assume $\kappa_i = \lambda_i N_0^{\beta_i}$, where $\beta_1 = \beta_2 > \beta_3$.

Balance conditions:

$$\begin{array}{lrcl} S_2 & \beta_2 + \alpha_1 & = & \beta_3 + \alpha_2 \\ S_1 & \beta_1 \vee (\beta_3 + \alpha_2) & = & \beta_2 + \alpha_1 \\ \{S_1, S_2\} & \beta_1 & = & -\infty \end{array}$$

Let $\alpha_1 = 0$, so balance for S_1 and S_2 is satisfied if $\alpha_2 = \beta_2 - \beta_3$.

we require

$$\gamma \leq \alpha_1 \vee \alpha_2 - \beta_1 = -\beta_3.$$

Time scales

There are two time-scales of interest in this model, $\gamma = -\beta_1$, the time-scale of S_1, and $\gamma = -\beta_3$, the time-scale of S_2. The system of equations is

$$\begin{aligned} Z_1^N(t) &= Z_1^N(0) + Y_1(\lambda_1 N^{\beta_1} t) - Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s)ds) \\ &\quad + Y_3(\lambda_3 N^{\beta_3+\alpha_2} \int_0^t Z_2^N(s)ds) \\ Z_2^N(t) &= Z_2^N(0) + N^{-\alpha_2} Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s)ds) \\ &\quad - N^{-\alpha_2} Y_3(\lambda_3 N^{\beta_3+\alpha_2} \int_0^t Z_2^N(s)ds). \end{aligned}$$

Limiting systems

For $\gamma = -\beta_1$,

$$\begin{aligned} Z_1^N(tN^\gamma) &= Z_1^N(0) + Y_1(\lambda_1 t) - Y_2(\lambda_2 \int_0^t Z_1^N(sN^\gamma)ds) \\ &\quad + Y_3(\lambda_3 \int_0^t Z_2^N(sN^\gamma) \\ Z_2^N(tN^\gamma) &= Z_2^N(0) + N^{-\alpha_2} Y_2(\lambda_2 \int_0^t Z_1^N(sN^\gamma)ds) \\ &\quad - N^{-\alpha_2} Y_3(\lambda_3 \int_0^t Z_2^N(sN^\gamma)ds). \end{aligned}$$

the limit of $Z^N(\cdot N^\gamma)$ satisfies

$$\begin{aligned} Z_1(t) &= Z_1(0) + Y_1(\lambda_1 t) - Y_2(\lambda_2 \int_0^t Z_1(s)ds) + Y_3(\lambda_3 \int_0^t Z_2(s)) \\ Z_2(t) &= Z_2(0). \end{aligned}$$

Note that the stationary distribution for Z_1 is Poisson with $E[Z_1] = \frac{\lambda_1 + \lambda_3 Z_2}{\lambda_2}$.

Second time scale

For $\gamma = -\beta_3$,

$$\begin{aligned} Z_1^N(tN^\gamma) &= Z_1^N(0) + Y_1(\lambda_1 N^{\beta_1-\beta_3}t) - Y_2(\lambda_2 N^{\beta_2-\beta_3}\int_0^t Z_1^N(sN^\gamma)ds) \\ &\quad + Y_3(\lambda_3 N^{\alpha_2}\int_0^t Z_2^N(sN^\gamma)ds) \\ Z_2^N(tN^\gamma) &= Z_2^N(0) + N^{-\alpha_2}Y_2(\lambda_2 N^{\beta_2-\beta_3}\int_0^t Z_1^N(sN^\gamma)ds) \\ &\quad - N^{-\alpha_2}Y_3(\lambda_3 N^{\alpha_2}\int_0^t Z_2^N(sN^\gamma)ds). \end{aligned}$$

$\lambda_2 \int_0^t Z_1^N(sN^\gamma)ds \sim \lambda_1 t + \lambda_3 \int_0^t Z_2^N(sN^\gamma)ds$ and $Z_2^N(\cdot N^\gamma)$ converges to the solution of

$$Z_2(t) = Z_2(0) + \lambda_1 t.$$

Note that if we took $\gamma > -\beta_3$, then $Z_2^N(tN^\gamma) \to \infty$ for each $t > 0$.

Heat shock model

The following reaction network is a given as a model for the heat shock response in E. Coli by Srivastava, Peterson and Bently [3]

Reaction	Intensity	Reaction	Intensity
$\emptyset \to A_8$	4.00×10^{0}	$A_6 + A_8 \to A_9$	$3.62 \times 10^{-4} X_{A_6} X_{A_8}$
$A_2 \to A_3$	$7.00 \times 10^{-1} X_{A_2}$	$A_8 \to \emptyset$	$9.99 \times 10^{-5} X_{A_8}$
$A_3 \to A_2$	$1.30 \times 10^{-1} X_{A_3}$	$A_9 \to A_6 + A_8$	$4.40 \times 10^{-5} X_{A_9}$
$\emptyset \to A_2$	$7.00 \times 10^{-3} X_{A_1}$	$\emptyset \to A_1$	1.40×10^{-5}
stuff $+ A_3 \to A_5 + A_2$	$6.30 \times 10^{-3} X_{A_3}$	$A_1 \to \emptyset$	$1.40 \times 10^{-6} X_{A_1}$
stuff $+ A_3 \to A_4 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_7 \to A_6$	$1.42 \times 10^{-6} X_{A_4} X_{A_7}$
stuff $+ A_3 \to A_6 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_5 \to \emptyset$	$1.80 \times 10^{-8} X_{A_5}$
$A_7 \to A_2 + A_6$	$4.40 \times 10^{-4} X_{A_7}$	$A_6 \to \emptyset$	$6.40 \times 10^{-10} X_{A_6}$
$A_2 + A_6 \to A_7$	$3.62 \times 10^{-4} X_{A_2} X_{A_6}$	$A_4 \to \emptyset$	$7.40 \times 10^{-11} X_{A_4}$

Exponents

$$
\begin{aligned}
\rho_1 &= \beta_1 \\
\rho_2 &= \alpha_2 + \beta_2 \\
\rho_3 &= \alpha_3 + \beta_3 \\
\rho_4 &= \alpha_1 + \beta_4 \\
\rho_5 &= \alpha_3 + \beta_5 \\
\rho_6 &= \alpha_3 + \beta_6 \\
\rho_7 &= \alpha_3 + \beta_7 \\
\rho_8 &= \alpha_7 + \beta_8 \\
\rho_9 &= \alpha_2 + \alpha_6 + \beta_9
\end{aligned}
$$

$$
\begin{aligned}
\rho_{10} &= \alpha_6 + \alpha_8 + \beta_{10} \\
\rho_{11} &= \alpha_8 + \beta_{11} \\
\rho_{12} &= \alpha_9 + \beta_{12} \\
\rho_{13} &= \beta_{13} \\
\rho_{14} &= \alpha_1 + \beta_{14} \\
\rho_{15} &= \alpha_4 + \alpha_7 + \beta_{15} \\
\rho_{16} &= \alpha_5 + \beta_{16} \\
\rho_{17} &= \alpha_6 + \beta_{17} \\
\rho_{18} &= \alpha_4 + \beta_{18}
\end{aligned}
$$

Balance conditions

$$
\begin{array}{lrcl}
\{A_1\} & \rho_{13} & = & \rho_{14} \\
\{A_2\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7, \rho_8\} & = & \rho_2 \vee \rho_9 \\
\{A_3\} & \rho_2 & = & \max\{\rho_3, \rho_5, \rho_6, \rho_7\} \\
\{A_4\} & \rho_6 & = & \rho_{18} \\
\{A_5\} & \rho_5 & = & \rho_{16} \\
\{A_6\} & \max\{\rho_7, \rho_8, \rho_{12}, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{A_7\} & \rho_9 & = & \rho_8 \vee \rho_{15} \\
\{A_8\} & \rho_1 \vee \rho_{12} & = & \rho_{10} \vee \rho_{11} \\
\{A_9\} & \rho_{10} & = & \rho_{12} \\
\{A_2, A_3, A_7\} & \rho_4 & = & \rho_{15} \\
\{A_2, A_3\} & \rho_4 \vee \rho_8 & = & \rho_9 \\
\{A_2, A_7\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7\} & = & \rho_2 \vee \rho_{15} \\
\{A_6, A_7, A_9\} & \rho_7 & = & \rho_{17} \\
\{A_6, A_9\} & \max\{\rho_7, \rho_8, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{A_6, A_7\} & \rho_7 \vee \rho_{12} & = & \rho_{17} \vee \rho_{10} \\
\{A_8, A_9\} & \rho_1 & = & \rho_{17}
\end{array}
$$

See Hye-Won Kang's poster

$$
\begin{aligned}
V_1^N(t) &= V_1^N(0) + Y_{13}\Big(\int_0^t \lambda_{13} N^{\gamma-\frac{5}{3}}\, ds\Big) - Y_{14}\Big(\int_0^t \lambda_{14} N^{\gamma-\frac{5}{3}} V_1^N(s)\, ds\Big) \\
V_2^N(t) &= V_2^N(0) + Y_3\Big(\int_0^t \lambda_3 N^{\gamma} V_3^N(s)\, ds\Big) + Y_4\Big(\int_0^t \lambda_4 N^{\gamma} V_1^N(s)\, ds\Big) \\
&\quad + Y_5\Big(\int_0^t \lambda_5 N^{\gamma-\frac{2}{3}} V_3^N(s)\, ds\Big) + Y_6\Big(\int_0^t \lambda_6 N^{\gamma-1} V_3^N(s)\, ds\Big) \\
&\quad + Y_7\Big(\int_0^t \lambda_7 N^{\gamma-1} V_3^N(s)\, ds\Big) + Y_8\Big(\int_0^t \lambda_8 N^{\gamma} V_7^N(s)\, ds\Big) \\
&\quad - Y_2\Big(\int_0^t \lambda_2 N^{\gamma} V_2^N(s)\, ds\Big) - Y_9\Big(\int_0^t \lambda_9 N^{\gamma} V_2^N(s) V_6^N(s)\, ds\Big) \\
V_3^N(t) &= V_3^N(0) + Y_2\Big(\int_0^t \lambda_2 N^{\gamma} V_2^N(s)\, ds\Big) - Y_3\Big(\int_0^t \lambda_3 N^{\gamma} V_3^N(s)\, ds\Big) \\
&\quad - Y_5\Big(\int_0^t \lambda_5 N^{\gamma-\frac{2}{3}} V_3^N(s)\, ds\Big) - Y_6\Big(\int_0^t \lambda_6 N^{\gamma-1} V_3^N(s)\, ds\Big) - Y_7\Big(\int_0^t \lambda_7 N^{\gamma-1} V_3^N(s)\, ds\Big) \\
V_4^N(t) &= V_4^N(0) + N^{-\frac{2}{3}} Y_6\Big(\int_0^t \lambda_6 N^{\gamma-1} V_3^N(s)\, ds\Big) - N^{-\frac{2}{3}} Y_{18}\Big(\int_0^t \lambda_{18} N^{\gamma-1} V_4^N(s)\, ds\Big) \\
V_5^N(t) &= V_5^N(0) + N^{-1} Y_5\Big(\int_0^t \lambda_5 N^{\gamma-\frac{2}{3}} V_3^N(s)\, ds\Big) - N^{-1} Y_{16}\Big(\int_0^t \lambda_{16} N^{\gamma-\frac{2}{3}} V_5^N(s)\, ds\Big)
\end{aligned}
$$

$$
\begin{aligned}
V_6^N(t) &= V_6^N(0) + N^{-\frac{5}{3}} Y_7 \Big(\int_0^t \lambda_7 N^{\gamma-1} V_3^N(s)\, ds \Big) + N^{-\frac{5}{3}} Y_8 \Big(\int_0^t \lambda_8 N^{\gamma} V_7^N(s)\, ds \Big) \\
&\quad + N^{-\frac{5}{3}} Y_{12} \Big(\int_0^t \lambda_{12} N^{\gamma} V_9^N(s)\, ds \Big) + N^{-\frac{5}{3}} Y_{15} \Big(\int_0^t \lambda_{15} N^{\gamma} V_4^N(s) V_7^N(s)\, ds \Big) \\
&\quad - N^{-\frac{5}{3}} Y_9 \Big(\int_0^t \lambda_9 N^{\gamma} V_2^N(s) V_6^N(s)\, ds \Big) - N^{-\frac{5}{3}} Y_{10} \Big(\int_0^t \lambda_{10} N^{\gamma} V_6^N(s) V_8^N(s)\, ds \Big) \\
&\quad - N^{-\frac{5}{3}} Y_{17} \Big(\int_0^t \lambda_{17} N^{\gamma} V_6^N(s)\, ds \Big) \\
V_7^N(t) &= V_7^N(0) + N^{-1} Y_9 \Big(\int_0^t \lambda_9 N^{\gamma} V_2^N(s) V_6^N(s)\, ds \Big) - N^{-1} Y_8 \Big(\int_0^t \lambda_8 N^{\gamma} V_7^N(s)\, ds \Big) \\
&\quad - N^{-1} Y_{15} \Big(\int_0^t \lambda_{15} N^{\gamma} V_4^N(s) V_7^N(s)\, ds \Big) \\
V_8^N(t) &= V_8^N(0) + Y_1 \Big(\int_0^t \lambda_1 N^{\gamma}\, ds \Big) + Y_{12} \Big(\int_0^t \lambda_{12} N^{\gamma} V_9^N(s)\, ds \Big) \\
&\quad - Y_{10} \Big(\int_0^t \lambda_{10} N^{\gamma} V_6^N(s) V_8^N(s)\, ds \Big) - Y_{11} \Big(\int_0^t \lambda_{11} N^{\gamma-\frac{5}{3}} V_8^N(s)\, ds \Big) \\
V_9^N(t) &= V_9^N(0) + N^{-\frac{5}{3}} Y_{10} \Big(\int_0^t \lambda_{10} N^{\gamma} V_6^N(s) V_8^N(s)\, ds \Big) - N^{-\frac{5}{3}} Y_{12} \Big(\int_0^t \lambda_{12} N^{\gamma} V_9^N(s)\, ds \Big)
\end{aligned}
$$

$\gamma = 0$

α_1	α_2	α_3	α_4	α_5	α_6	α_7	α_8	α_9
0	0	0	$\frac{2}{3}$	1	$\frac{5}{3}$	1	0	$\frac{5}{3}$

$$V_2(t) = V_2(0) + Y_3(\int_0^t \lambda_3 V_3(s)\, ds) + Y_4(\lambda_4 V_1(0)\, t) + Y_8(\lambda_8 V_7(0)\, t)$$
$$-Y_2(\int_0^t \lambda_2 V_2(s)\, ds) - Y_9(\int_0^t \lambda_9 V_2(s) V_6(0)\, ds)$$
$$V_3(t) = V_3(0) + Y_2(\int_0^t \lambda_2 V_2(s)\, ds) - Y_3(\int_0^t \lambda_3 V_3(s)\, ds)$$
$$V_8(t) = V_8(0) + Y_1(\lambda_1\, t) + Y_{12}(\lambda_{12} V_9(0)\, t) - Y_{10}(\int_0^t \lambda_{10} V_6(0) V_8(s)\, ds)$$

$$V_1(t) = V_1(0),\ V_4(t) = V_4(0),\ V_5(t) = V_5(0),\ V_6(t) = V_6(0),\ V_7(t) = V_7(0),\ V_9(t) = V_9(0)$$

$\gamma = 1$

$$V_7(t) = V_7(0) + \int_0^t [\lambda_9 \bar{V}_2(s) V_6(0) - \lambda_8 V_7(s) - \lambda_{15} V_4(0) V_7(s)]\, ds$$
$$= V_7(0) + \int_0^t [\lambda_4 V_1(0) - \lambda_{15} V_4(0) V_7(s)]\, ds$$

$$\lambda_3 \bar{V}_3(s) + \lambda_4 V_1(0) + \lambda_8 V_7(s) - \lambda_2 \bar{V}_2(s) - \lambda_9 \bar{V}_2(s) V_6(0) = 0$$
$$\lambda_2 \bar{V}_2(s) - \lambda_3 \bar{V}_3(s) = 0$$
$$\lambda_1 + \lambda_{12} V_9(0) - \lambda_{10} V_6(0) \bar{V}_8(s) = 0$$

$V_1(t) = V_1(0)$, $V_4(t) = V_4(0)$, $V_5(t) = V_5(0)$, $V_6(t) = V_6(0)$, $V_9(t) = V_9(0)$

$$\gamma = 5/3$$

$$V_1(t) = V_1(0) + Y_{13}(\lambda_{13}\, t) - Y_{14}(\int_0^t \lambda_{14} V_1(s)\, ds)$$

$$V_4(t) = V_4(0) + \int_0^t [\lambda_6 \bar{V}_3(s) - \lambda_{18} V_4(s)]\, ds$$

$$V_5(t) = V_5(0) + \int_0^t [\lambda_5 \bar{V}_3(s) - \lambda_{16} V_5(s)]\, ds$$

$$V_6(t) = V_6(0) + \int_0^t [\lambda_8 V_7(s) + \lambda_{12} V_9(s) + \lambda_{15} V_4(s) V_7(s) - \lambda_9 \bar{V}_2(s) V_6(s) - \lambda_{10} V_6(s) \bar{V}_8(s) -$$

$$V_9(t) = V_9(0) + \int_0^t [\lambda_{10} V_6(s) \bar{V}_8(s) - \lambda_{12} V_9(s)]\, ds$$

$$\lambda_3 \bar{V}_3(s) + \lambda_4 V_1(s) + \lambda_8 V_7(s) - \lambda_2 \bar{V}_2(s) - \lambda_9 \bar{V}_2(s) V_6(s) = 0$$

$$\lambda_2 \bar{V}_2(s) - \lambda_3 \bar{V}_3(s) = 0$$

$$\lambda_1 + \lambda_{12} V_9(s) - \lambda_{10} V_6(s) \bar{V}_8(s) = 0$$

$$\lambda_9 \bar{V}_2(s) V_6(s) - \lambda_8 V_7(s) - \lambda_{15} V_4(s) V_7(s) = 0$$

$$V_1(t) = V_1(0) + Y_{13}(\lambda_{13}\, t) - Y_{14}(\int_0^t \lambda_{14} V_1(s)\, ds)$$

$$V_4(t) = V_4(0) + \int_0^t [\lambda_6 \bar{V}_3(s) - \lambda_{18} V_4(s)]\, ds$$

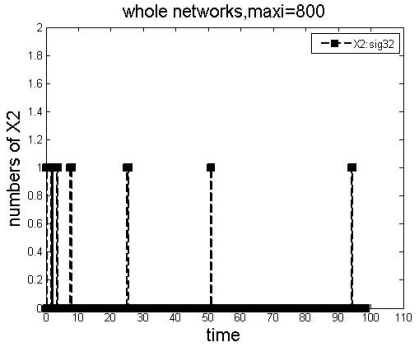
$$V_5(t) = V_5(0) + \int_0^t [\lambda_5 \bar{V}_3(s) - \lambda_{16} V_5(s)]\, ds$$

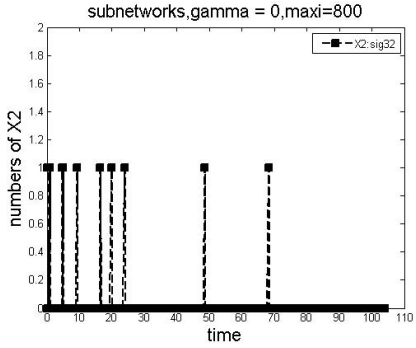
$$V_6(t) = V_6(0) - \int_0^t [\lambda_{17} V_6(s) + \lambda_1]\, ds$$

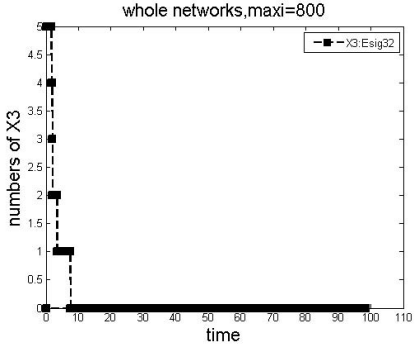
$$V_9(t) = V_9(0) + \lambda_1 t$$

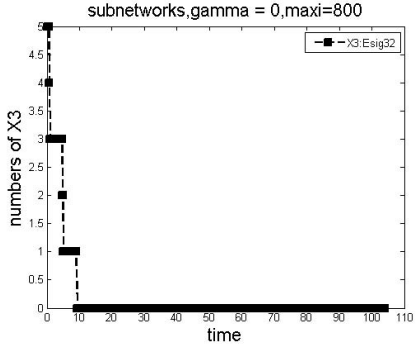
$$\bar{V}_3(s) = \frac{\lambda_2}{\lambda_3}\bar{V}_2(s) = \frac{\lambda_2}{\lambda_3}\frac{\lambda_4 V_1(s) + \lambda_8 V_7(s)}{\lambda_9 V_6(s)}$$

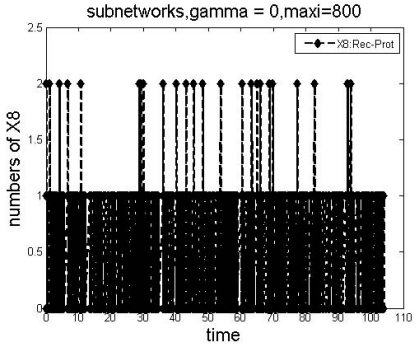
$$V_7(s) = \frac{\lambda_4 V_1(s)}{\lambda_{15} V_4(s)}$$

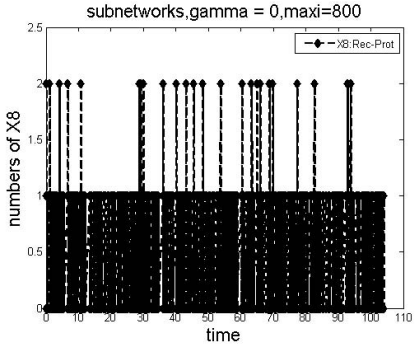

whole networks,maxi=800
X2:sig32
numbers of X2
time

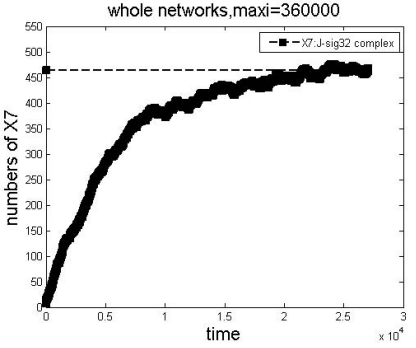

subnetworks,gamma = 0,maxi=800
X2:sig32
numbers of X2
time

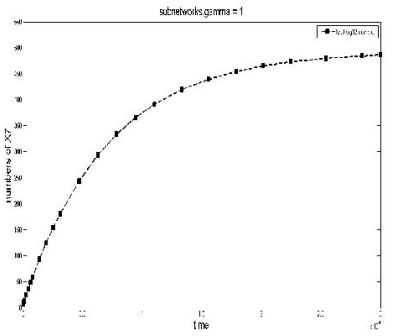

whole networks,maxi=800
X3:Esig32
numbers of X3
time

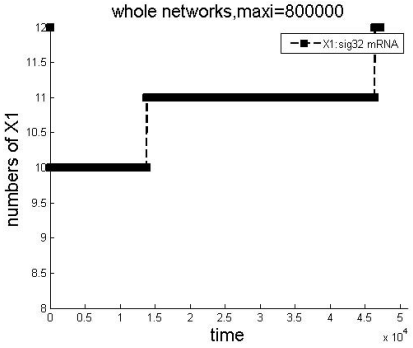

subnetworks,gamma = 0,maxi=800
X3:Esig32
numbers of X3
time

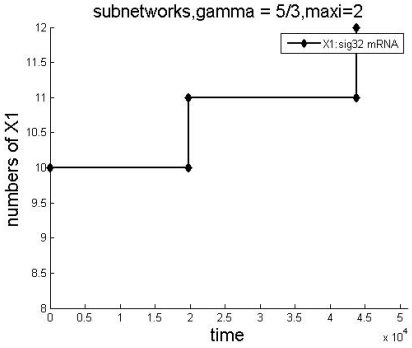

subnetworks,gamma = 0,maxi=800
X8:Rec-Prot
numbers of X8
time

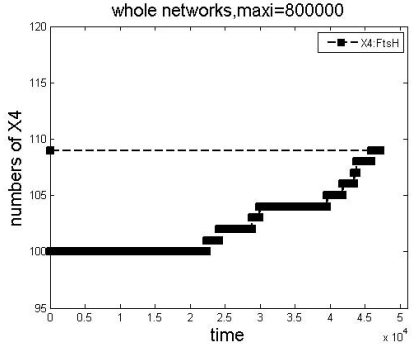

subnetworks,gamma = 0,maxi=800
X8:Rec-Prot
numbers of X8
time

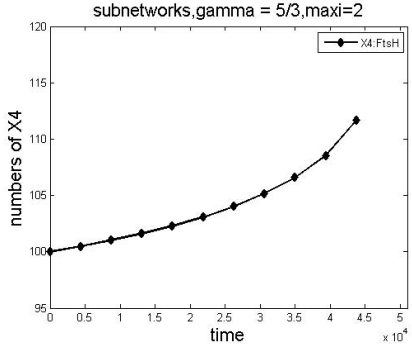

whole networks,maxi=360000
X7:J-sig32 complex
numbers of X7
time
x 10^4

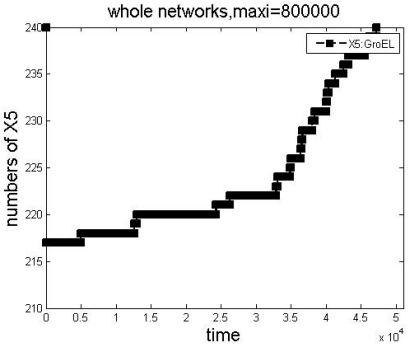

subnetworks,gamma = 1
time

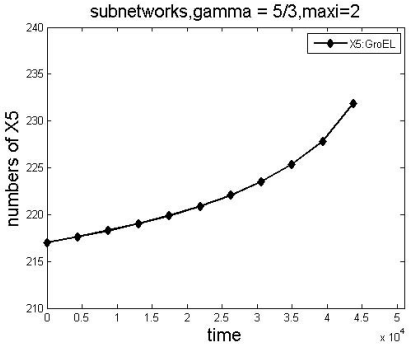

whole networks,maxi=800000
X1:sig32 mRNA
numbers of X1
time
x 10^4

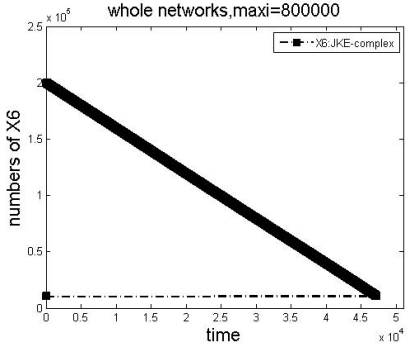

subnetworks,gamma = 5/3,maxi=2
X1:sig32 mRNA
numbers of X1
time
x 10^4

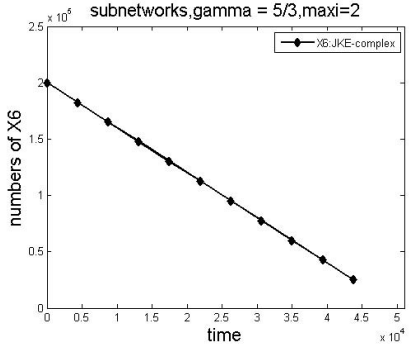

whole networks,maxi=800000
X4:FtsH
numbers of X4
time
x 10^4

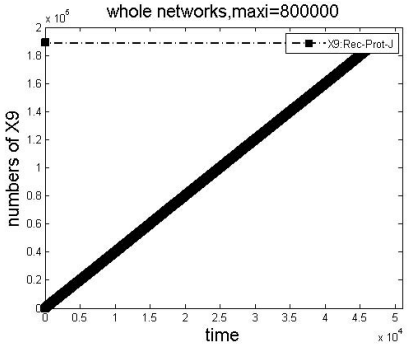

subnetworks,gamma = 5/3,maxi=2
X4:FtsH
numbers of X4
time
x 10^4

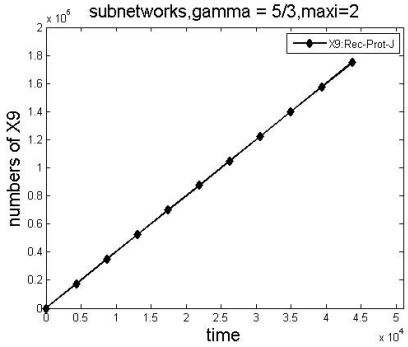

whole networks,maxi=800000
X5:GroEL
numbers of X5
time
x 10^4


subnetworks,gamma = 5/3,maxi=2
X5:GroEL
numbers of X5
time
x 10^4


whole networks,maxi=800000
x 10^5
X6:JKE-complex
numbers of X6
time
x 10^4


subnetworks,gamma = 5/3,maxi=2
x 10^5
X6:JKE-complex
numbers of X6
time
x 10^4


whole networks,maxi=800000
x 10^5
numbers of X9
time
x 10^4
X9:Rec-Prot-J


subnetworks,gamma = 5/3,maxi=2
x 10^5
numbers of X9
time
x 10^4
X9:Rec-Prot-J

References

[1] Karen Ball, Thomas G. Kurtz, Lea Popovic, and Grzegorz A. Rempala. Asymptotic analysis of multiscale approximations to reaction networks. *Ann. Appl. Probab.*, 16:1925–1961, 2006.

[2] Eric L. Haseltine and James B. Rawlings. Approximate simulation of coupled fast and slow reactions for stochastic chemical kinetics. *J. Chem. Phys.*, 117(15):6959–6969, 2002.

[3] R. Srivastava, M. S. Peterson, and W. E. Bentley. Stochastic kinetic analysis of escherichia coli stress circuit using sigma(32)-targeted antisense. *Biotechnol. Bioeng.*, 75:120–129, 2001.

[4] R. Srivastava, L. You, J. Summers, and J. Yin. Stochastic vs. deterministic modeling of intracellular viral kinetics. *J. Theoret. Biol.*, 218(3):309–321, 2002.

Abstract

Multiscale analysis of stochastic reaction networks

Stochastic models of cellular chemical reaction networks typically involve chemical species numbers and reaction rates varying over several orders of magnitude. A number of researchers have proposed exploiting the "multiscale" nature of these models to reduce the complexity of the model to be analyzed or simulated. Using elementary understanding of some basic stochastic processes, systematic approaches to model reduction will be discussed.