Identifying separated time scales in stochastic models of reaction networks

Collaboration with David Anderson, Karen Ball, George Craciun, Hye-Won Kang, Lea Popovic, Greg Rempala

Conditional intensities for counting processes

N is a *counting process* if $N(0) = 0$ and N is constant except for jumps of $+1$.

Assume N is adapted to $\{\mathcal{F}_t\}$.

$\lambda \geq 0$ is the $\{\mathcal{F}_t\}$-conditional intensity if (intuitively)

$$P\{N(t + \Delta t) > N(t) | \mathcal{F}_t\} \approx \lambda(t)\Delta t$$

or (precisely)

$$M(t) \equiv N(t) - \int_0^t \lambda(s) ds$$

is an $\{\mathcal{F}_t\}$-local martingale, that is, if τ_k is the kth jump time of N,

$$E[M((t + s) \wedge \tau_k) | \mathcal{F}_t] = M(t \wedge \tau_k)$$

for all $t \geq 0$ and all k.

Lemma 1 *If N has $\{\mathcal{F}_t\}$-intensity λ, then there exists a unit Poisson process (may need to enlarge the sample space) such that*

$$N(t) = Y(\int_0^t \lambda(s)ds)$$

Modeling with counting processes

Specify $\lambda(t) = \gamma(t, N)$, where γ is nonanticipating in the sense that $\gamma(t, N) = \gamma(t, N(\cdot \wedge t))$.

Martingale problem. Require

$$N(t) - \int_0^t \gamma(s, N)ds$$

to be a local martingale.

Time change equation. Require

$$N(t) = Y(\int_0^t \gamma(s, N)ds).$$

These formulations are equivalent in the sense that the solutions have the same distribution.

Systems of counting processes

Lemma 2 *(Meyer [4], Kurtz [3]) Assume* $N = (N_1, \ldots, N_m)$ *is a vector of counting processes with no common jumps and* λ_k *is the* $\{\mathcal{F}_t\}$*-intensity for* N_k*. Then there exist independent unit Poisson processes* $Y_1, \ldots,$ *(may need to enlarge the sample space) such that*

$$N_k(t) = Y_k(\int_0^t \lambda_k(s)ds)$$

Specifying nonanticipating intensities $\lambda_k(t) = \gamma_k(t, N)$:

$$N_k(t) = Y_k(\int_0^t \gamma_k(s, N)ds)$$

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 $2A_1 \rightharpoonup A_2$,

$$\lambda_k(x) = \kappa'_k x_1(x_1 - 1)$$

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 [5]

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}
$\text{stuff} + A_3 \to A_5 + A_2$	$6.30 \times 10^{-3} X_{A_3}$	$A_1 \to \emptyset$	$1.40 \times 10^{-6} X_{A_1}$
$\text{stuff} + A_3 \to A_4 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_7 \to A_6$	$1.42 \times 10^{-6} X_{A_4} X_{A_7}$
$\text{stuff} + A_3 \to A_6 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_5 \to \emptyset$	$1.80 \times 10^{-8} X_{A_5}$
$A_7 \to A_2 + A_6$	$4.40 \times 10^{-4} X_{A_7}$	$A_6 \to \emptyset$	$6.40 \times 10^{-10} X_{A_6}$
$A_2 + A_6 \to A_7$	$3.62 \times 10^{-4} X_{A_2} X_{A_6}$	$A_4 \to \emptyset$	$7.40 \times 10^{-11} X_{A_4}$

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 $Z = Z^{N_0}$.

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

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

Example: Model of a viral infection

Srivastava, You, Summers, and Yin [6], 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

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

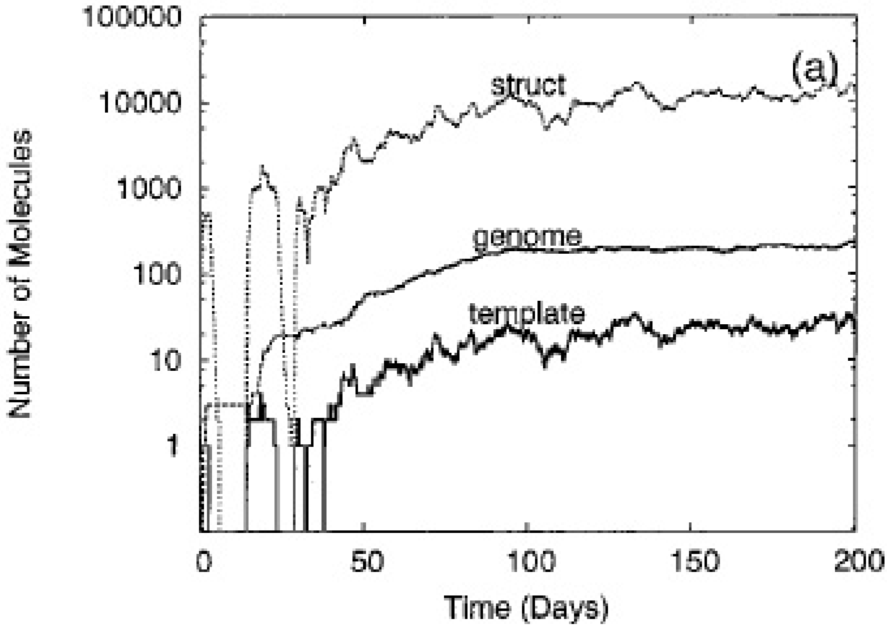


Figure 1: Simulation (Haseltine and Rawlings 2002)

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

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

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

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

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

Law of large numbers

Theorem 3 *For each $\delta > 0$ and $t > 0$,*

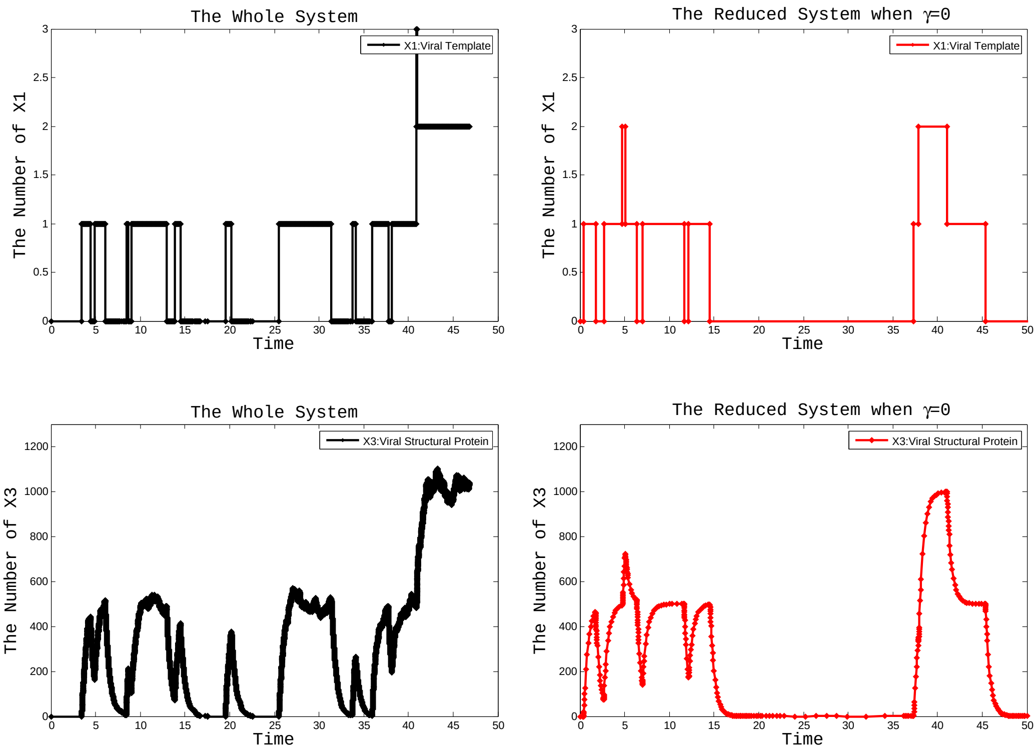
$$\lim_{N\to\infty} P\{\sup_{0\le s\le t} |V_2^N(s) - V_2(s)| \ge \delta\} = 0,$$

where V_2 is the solution of

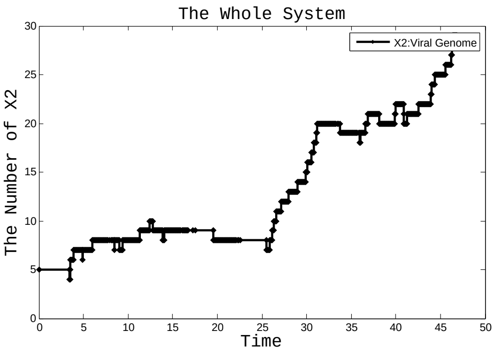
$$V_2(t) = V_2(0) + \int_0^t 7.5V_2(s)ds) - \int_0^t 3.75V_2(s)^2 ds. \tag{1}$$

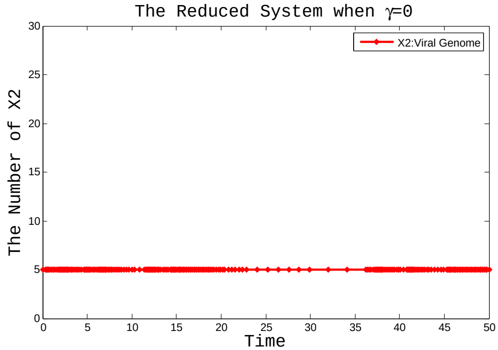
The original X_2 should satisfy

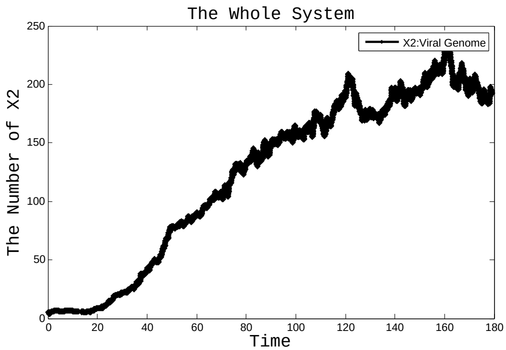
$$X_2(t) \approx (1000)^{2/3} V_2(t(1000)^{-2/3})$$

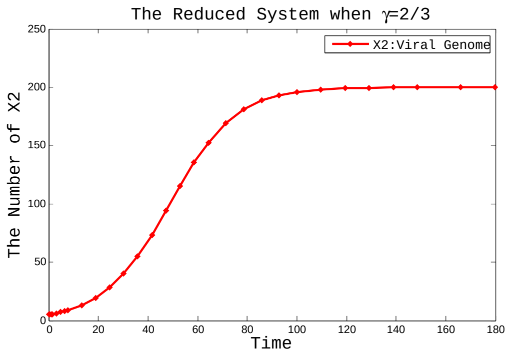


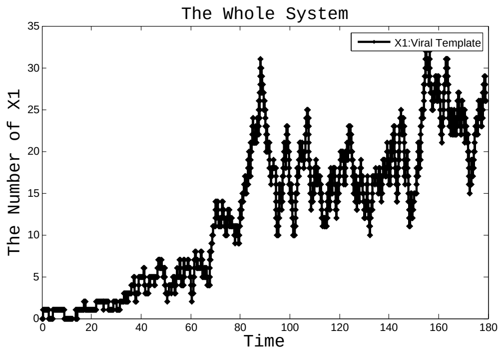
The Whole System
X1:Viral Template
The Number of X1
Time
0 0.5 1 1.5 2 2.5 3
0 5 10 15 20 25 30 35 40 45 50
The Reduced System when γ=0
X1:Viral Template
The Number of X1
Time
0 0.5 1 1.5 2 2.5 3
0 5 10 15 20 25 30 35 40 45 50
The Whole System
X3:Viral Structural Protein
The Number of X3
Time
0 200 400 600 800 1000 1200
0 5 10 15 20 25 30 35 40 45 50
The Reduced System when γ=0
X3:Viral Structural Protein
The Number of X3
Time
0 200 400 600 800 1000 1200
0 5 10 15 20 25 30 35 40 45 50

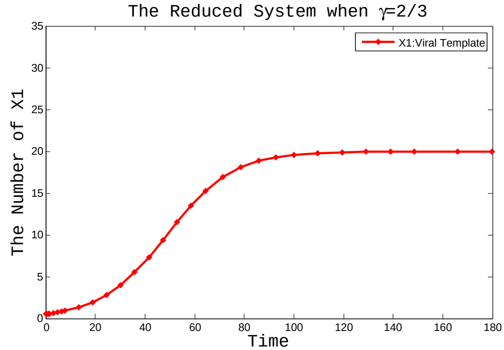

The Whole System
X2:Viral Genome
The Number of X2
Time

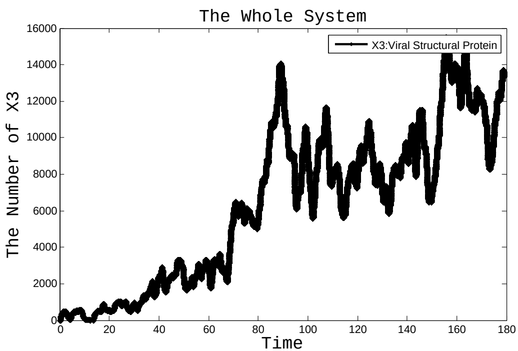

The Reduced System when γ=0
X2:Viral Genome
The Number of X2
Time

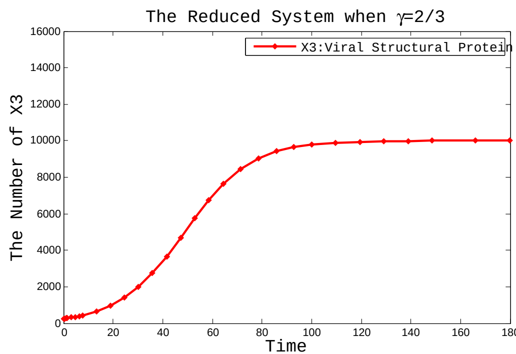

The Whole System
X2:Viral Genome
The Number of X2
Time
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180


The Reduced System when γ=2/3
X2:Viral Genome
The Number of X2
Time
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180


The Whole System
X1:Viral Template
The Number of X1
Time


The Reduced System when γ=2/3
X1:Viral Template
The Number of X1
Time


The Whole System
X3:Viral Structural Protein
The Number of X3
Time


The Reduced System when γ=2/3
X3:Viral Structural Protein
The Number of X3
Time

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 $\quad A_1 + A_2 \rightharpoonup A_3 + A_4 \qquad A_3 + A_5 \rightharpoonup A_6$

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

or scaling time

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

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,

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

or

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

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

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

Then (5) implies

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

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 [5]

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}
$\text{stuff} + A_3 \to A_5 + A_2$	$6.30 \times 10^{-3} X_{A_3}$	$A_1 \to \emptyset$	$1.40 \times 10^{-6} X_{A_1}$
$\text{stuff} + A_3 \to A_4 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_7 \to A_6$	$1.42 \times 10^{-6} X_{A_4} X_{A_7}$
$\text{stuff} + A_3 \to A_6 + A_2$	$4.88 \times 10^{-3} X_{A_3}$	$A_5 \to \emptyset$	$1.80 \times 10^{-8} X_{A_5}$
$A_7 \to A_2 + A_6$	$4.40 \times 10^{-4} X_{A_7}$	$A_6 \to \emptyset$	$6.40 \times 10^{-10} X_{A_6}$
$A_2 + A_6 \to A_7$	$3.62 \times 10^{-4} X_{A_2} X_{A_6}$	$A_4 \to \emptyset$	$7.40 \times 10^{-11} X_{A_4}$

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

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

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

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

$\gamma = 0$

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	$\frac{5}{3}$

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

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

$\gamma = 1$

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

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

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

$\gamma = 5/3$

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

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

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

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

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

$$\lambda_3 \bar{V}_3(s) + \lambda_4 V_1(s) + \lambda_8 V_7(s) - \lambda_2 \bar{V}_2(s) - \lambda_9 \bar{V}_2(s) V_6(s) = 0$$
$$\lambda_2 \bar{V}_2(s) - \lambda_3 \bar{V}_3(s) = 0$$
$$\lambda_1 + \lambda_{12} V_9(s) - \lambda_{10} V_6(s) \bar{V}_8(s) = 0$$
$$\lambda_9 \bar{V}_2(s) V_6(s) - \lambda_8 V_7(s) - \lambda_{15} V_4(s) V_7(s) = 0$$

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

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

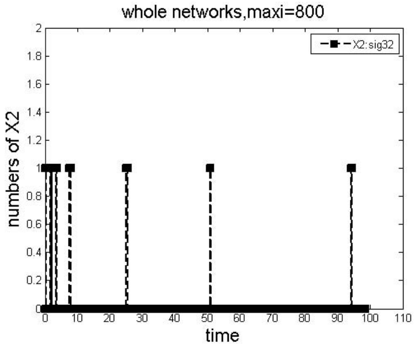
$$V_5(t) = V_5(0) + \int_0^t [\lambda_5 \bar{V}_3(s) - \lambda_{16} V_5(s)]\, ds$$

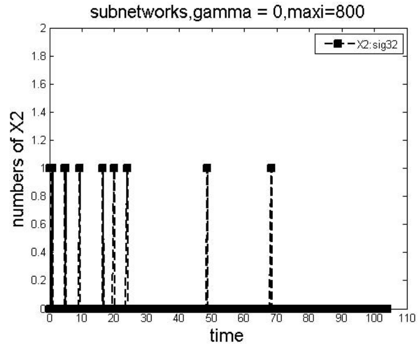
$$V_6(t) = V_6(0) - \int_0^t [\lambda_{17} V_6(s) + \lambda_1]\, ds$$

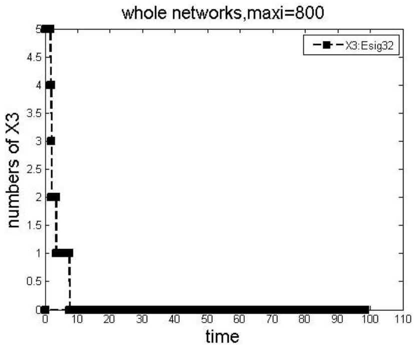
$$V_9(t) = V_9(0) + \lambda_1 t$$

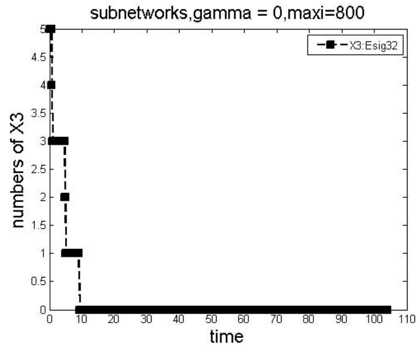
$$\bar{V}_3(s) = \frac{\lambda_2}{\lambda_3} \bar{V}_2(s) = \frac{\lambda_2}{\lambda_3} \frac{\lambda_4 V_1(s) + \lambda_8 V_7(s)}{\lambda_9 V_6(s)}$$

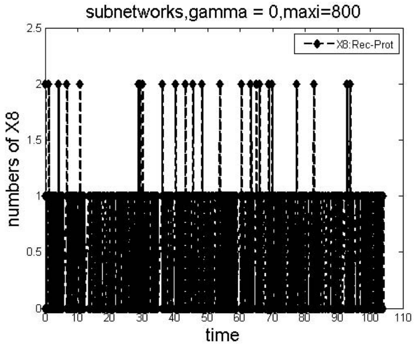
$$V_7(s) = \frac{\lambda_4 V_1(s)}{\lambda_{15} V_4(s)}$$

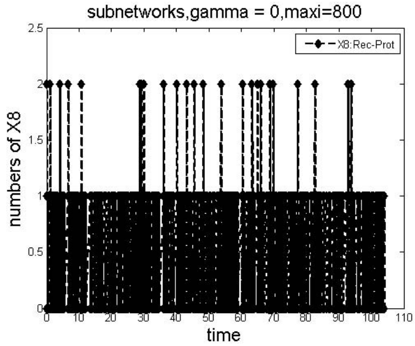

whole networks,maxi=800
X2:sig32
numbers of X2
time

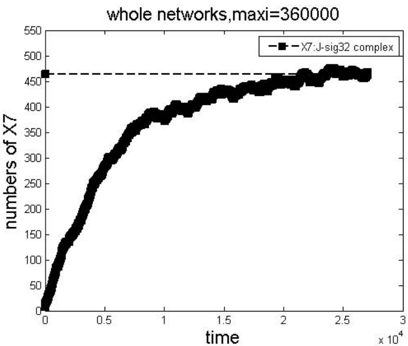

subnetworks,gamma = 0,maxi=800
X2:sig32
numbers of X2
time

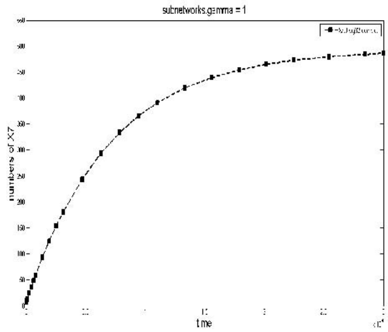

whole networks,maxi=800
X3:Esig32
numbers of X3
time

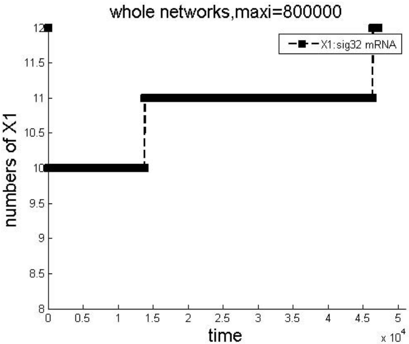

subnetworks,gamma = 0,maxi=800
X3:Esig32
numbers of X3
time

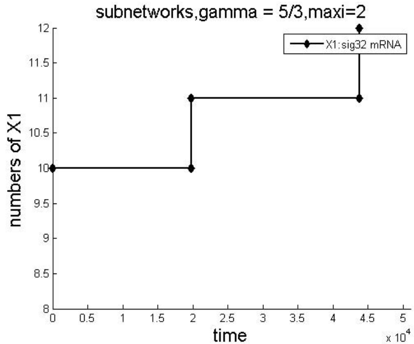

subnetworks,gamma = 0,maxi=800
X8:Rec-Prot
numbers of X8
time

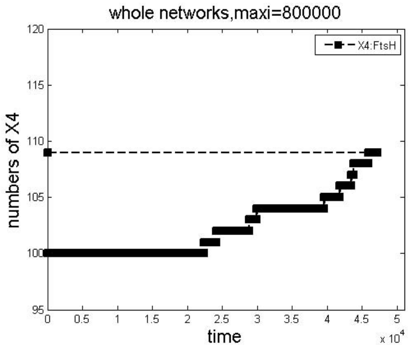

subnetworks,gamma = 0,maxi=800
X8:Rec-Prot
numbers of X8
time

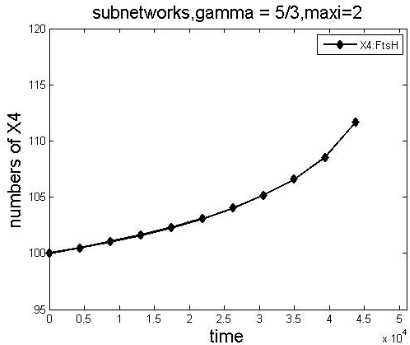

whole networks,maxi=360000
X7:J-sig32 complex
numbers of X7
time
x 10^4

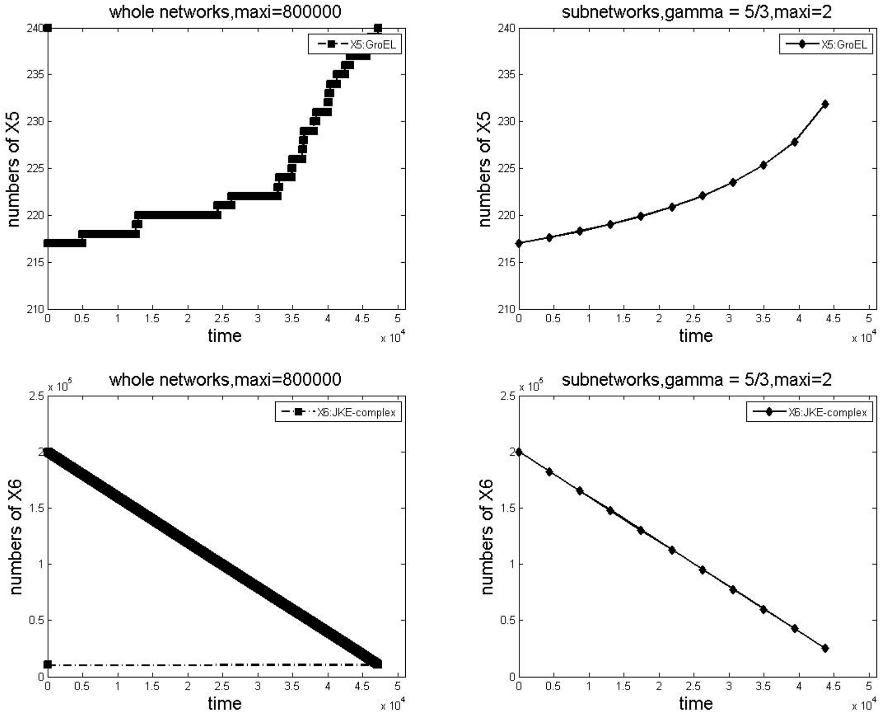

subnetworks,gamma = 1
numbers of X7
time

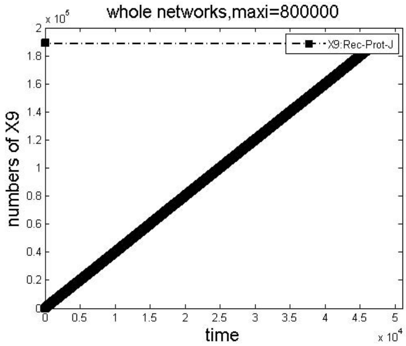

whole networks,maxi=800000
X1:sig32 mRNA
numbers of X1
time
x 10^4

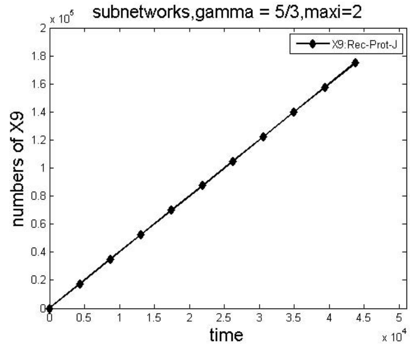

subnetworks,gamma = 5/3,maxi=2
X1:sig32 mRNA
numbers of X1
time
x 10^4


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
subnetworks,gamma = 5/3,maxi=2
X5:GroEL
numbers of X5
time
whole networks,maxi=800000
X6:JKE-complex
numbers of X6
time
subnetworks,gamma = 5/3,maxi=2
X6:JKE-complex
numbers of X6
time


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


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

References

[1] Karen Ball, Thomas G. Kurtz, Lea Popovic, and Greg Rempala. Asymptotic analysis of multiscale approximations to reaction networks. *Ann. Appl. Probab.*, 16(4):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] Thomas G. Kurtz. Representations of Markov processes as multiparameter time changes. *Ann. Probab.*, 8(4):682–715, 1980.

[4] P. A. Meyer. Démonstration simplifiée d'un théorème de Knight. In *Séminaire de Probabilités, V (Univ. Strasbourg, année universitaire 1969–1970)*, pages 191–195. Lecture Notes in Math., Vol. 191. Springer, Berlin, 1971.

[5] 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.

[6] 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

Identifying separated time scales in stochastic models of reaction networks

Reaction rates and chemical species numbers may vary over several orders of magnitude. Combined these large variations can lead to subnetworks operating on very different time scales. Separation of time scales has been exploited in many contexts as a basis for reducing the complexity of dynamic models, but the interaction of the rate constants and the species numbers makes identifying the appropriate time scales tricky at best. Some systematic approaches to this identification will be discussed and illustrated by application to a model of the heat shock response in E. Coli.