Identifying separated time-scales in stochastic models of reaction networks

with Hye-Won Kang

Poisson processes

Suppose Y is a unit Poisson process. Then

$$P\{Y(t+\Delta t)-Y(t)>0|\mathcal{F}_t^Y\}\approx \Delta t\ .$$

Let $Y_\lambda(t)=Y(\lambda t)$. The Y_λ is a Poisson process with parameter λ. If $\mathcal{F}_t^{Y_\lambda}$ represents the information obtained by observing $Y_\lambda(s)$, for $s\leq t$,

$$P\{Y_\lambda(t+\Delta t)-Y_\lambda(t)>0|\mathcal{F}_t^{Y_\lambda}\}=P\{Y_\lambda(t+\Delta t)-Y_\lambda(t)>0\}=1-e^{-\lambda\Delta t}\approx\lambda\Delta t$$

More generally

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

Law of large numbers

$$\lim_{N\to\infty}\sup_{u\leq u_0}\left|\frac{Y(Nu)}{N}-u\right|=0$$

Time-change representation for a Markov chain

Let $Y_1, \ldots, Y_m$ be independent unit Poisson processes.

$$X(t) = X(0) + \sum_{k=1}^{m} Y_k\left(\int_0^t \lambda_k(X(s))ds\right)\zeta_k$$

(Solve from one jump until the next.)

$$P\{X(t+\Delta t) - X(t) = \zeta_k | \mathcal{F}_t^X\} \approx \lambda_k(X(t))\Delta t$$

$p_t(x) = P\{X(t) = x\}$ satisfies master (forward) equation

$$\frac{d}{dt}p_t(x) = \sum_{k=1}^{m} \lambda_k(x-\zeta_k)p_t(x-\zeta_k) - \sum_{k=1}^{m} \lambda_k(x)p_t(x)$$

Reaction networks

We consider a *network* of reactions involving s_0 chemical species, $S_1, \ldots, S_{s_0}$.

$$\sum_{i=1}^{s_0} \nu_{ik} S_i \rightharpoonup \sum_{i=1}^{s_0} \nu'_{ik} S_i$$

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

ν_k the vector whose ith element is ν_{ik}.

ν'_k the vector whose ith element is ν'_{ik}.

$\zeta_k = \nu'_k - \nu_k$.

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

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

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

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

For a binary reaction $S_1 + S_2 \rightharpoonup S_3$ or $S_1 + S_2 \rightharpoonup S_3 + S_4$

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

For $S_1 \rightharpoonup S_2$ or $S_1 \rightharpoonup S_2 + S_3$,

$$\lambda_k(x) = \kappa_k' x_1.$$

For $2S_1 \rightharpoonup S_2$,

$$\lambda_k(x) = \kappa_k' x_1(x_1 - 1).$$

Multiple scales

Fix $N_0 >> 1$. 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 so scale the rate constants $\kappa'_k = \kappa_k N_0^{\beta_k}$.

Then

$$\kappa'_k x_i x_j = N_0^{\beta_k+\alpha_i+\alpha_j} \kappa_k z_i z_j \qquad \kappa'_k x_i(x_i - 1) = N_0^{\beta_k+2\alpha_i} \kappa_k z_i (z_i - N_0^{-\alpha_i})$$

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

Note that the exponent on N_0 is $\rho_k = \beta_k + \alpha \cdot \nu_k$.

A parameterized family of models

Then, noting that $\nu_k \cdot \alpha = \sum_i \nu_{ik}\alpha_i$,

$$Z_i(t) = Z_i(0) + \sum_k N_0^{-\alpha_i} Y_k\left(\int_0^t N_0^{\beta_k + \nu_k \cdot \alpha} \lambda_k(Z(s))ds\right)(\nu'_{ik} - \nu_{ik}).$$

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 $Z = Z^{N_0}$.

Time-scale parameter

Let

$$\begin{aligned} Z_i^{N,\gamma}(t) &\equiv Z_i^N(tN^\gamma) \\ &= Z_i(0) + \sum_k N^{-\alpha_i} Y_k\Big(\int_0^t N^{\gamma+\beta_k+\nu_k\cdot\alpha}\lambda_k(Z^{N,\gamma}(s))ds\Big)\zeta_{ik}. \end{aligned}$$

Equation is "balanced" if

$$\max\{\beta_k + \nu_k\cdot\alpha : \zeta_{ik} > 0\} = \max\{\beta_k + \nu_k\cdot\alpha : \zeta_{ik} < 0\}$$

If the equation is not balanced then we need

$$\gamma + \beta_k + \nu_k\cdot\alpha \le \alpha_i \tag{1}$$

for all i such that $\zeta_{ik} \neq 0$.

The time-scale of species i: $\gamma_i = \alpha_i - \max\{\beta_k + \nu_k\cdot\alpha : \zeta_{ik} \neq 0\}$

Example: Model of a viral infection

Srivastava, You, Summers, and Yin (2002), Haseltine and Rawlings (2002), Ball, Kurtz, Popovic, and Rempala (2006)

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,

$$\begin{aligned} S_1 + \text{stuff} &\stackrel{\kappa_1'}{\rightharpoonup} S_1 + S_2 \\ S_2 &\stackrel{\kappa_2'}{\rightharpoonup} S_1 \\ S_1 + \text{stuff} &\stackrel{\kappa_3'}{\rightharpoonup} S_1 + S_3 \\ S_1 &\stackrel{\kappa_4'}{\rightharpoonup} \emptyset \\ S_3 &\stackrel{\kappa_5'}{\rightharpoonup} \emptyset \\ S_2 + S_3 &\stackrel{\kappa_6'}{\rightharpoonup} S_4 \end{aligned}$$

Stochastic system

$$
\begin{aligned}
X_1(t) &= X_1(0) + Y_2\left(\int_0^t \kappa_2' X_2(s)ds\right) - Y_4\left(\int_0^t \kappa_4' X_1(s)ds\right) \\
X_2(t) &= X_2(0) + Y_1\left(\int_0^t \kappa_1' X_1(s)ds\right) - Y_2\left(\int_0^t \kappa_2' X_2(s)ds\right) \\
&\quad - Y_6\left(\int_0^t \kappa_6' X_2(s)X_3(s)ds\right) \\
X_3(t) &= X_3(0) + Y_3\left(\int_0^t \kappa_3' X_1(s)ds\right) - Y_5\left(\int_0^t \kappa_5' X_3(s)ds\right) \\
&\quad - Y_6\left(\int_0^t \kappa_6' X_2(s)X_3(s)ds\right)
\end{aligned}
$$

κ_1'	1	κ_4'	0.25
κ_2'	0.025	κ_5'	2
κ_3'	1000	κ_6'	7.5×10^{-6}

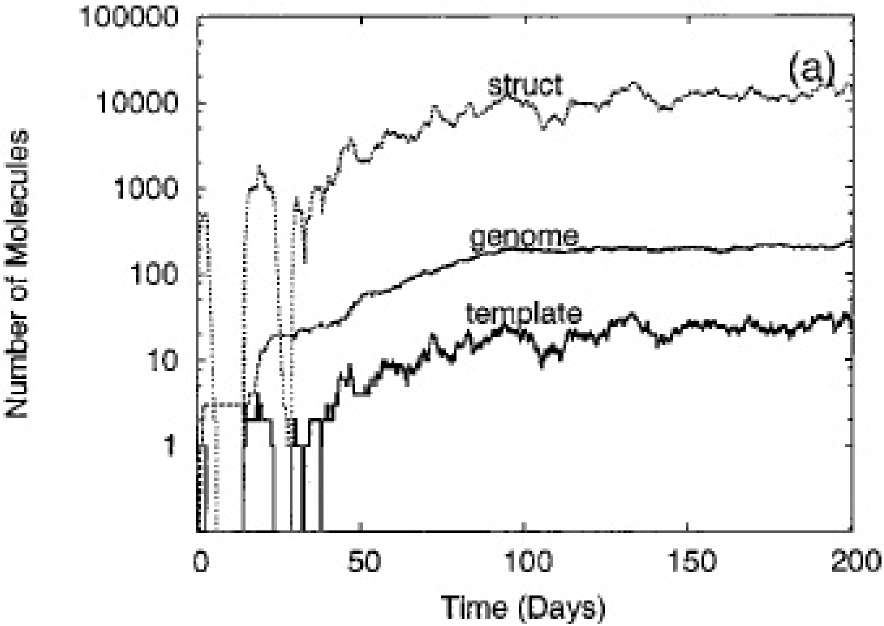


Figure 1: Simulation (Haseltine and Rawlings 2002)

Balance equations for the viral model

$$
\begin{aligned}
Z_1^N(t) &= Z_1(0) + N^{-\alpha_1}Y_2\Big(\int_0^t \kappa_2 N^{\beta_2+\alpha_2} Z_2^N(s)ds\Big) - N^{-\alpha_1}Y_4\Big(\int_0^t \kappa_4 N^{\beta_4+\alpha_1} Z_1^N(s)ds\Big) \\
Z_2^N(t) &= Z_2(0) + N^{-\alpha_2}Y_1\Big(\int_0^t \kappa_1 N^{\beta_1+\alpha_1} Z_1^N(s)ds\Big) - N^{-\alpha_2}Y_2\Big(\int_0^t \kappa_2 N^{\beta_2+\alpha_2} Z_2^N(s)ds\Big) \\
&\quad - N^{-\alpha_2}Y_6\Big(\int_0^t \kappa_6 N^{\beta_6+\alpha_2+\alpha_3} Z_2^N(s)Z_3^N(s)ds\Big) \\
Z_3^N(t) &= Z_3(0) + N^{-\alpha_3}Y_3\Big(\int_0^t \kappa_3 N^{\beta_3+\alpha_1} Z_1^N(s)ds\Big) - N^{-\alpha_3}Y_5\Big(\int_0^t \kappa_5 N^{\beta_5+\alpha_3} Z_3^N(s)ds\Big) \\
&\quad - N^{-\alpha_3}Y_6\Big(\int_0^t \kappa_6 N^{\beta_6+\alpha_2+\alpha_3} Z_2^N(s)Z_3^N(s)ds\Big)
\end{aligned}
$$

$$
\begin{aligned}
\beta_2 + \alpha_2 &= \beta_4 + \alpha_1 \\
\beta_1 + \alpha_1 &= (\beta_2 + \alpha_2) \vee (\beta_6 + \alpha_2 + \alpha_3) \\
\beta_3 + \alpha_1 &= (\beta_5 + \alpha_3) \vee (\beta_6 + \alpha_2 + \alpha_3)
\end{aligned}
$$

$$\beta_3 \geq \beta_5 \geq \beta_1 \geq \beta_4 \geq \beta_2 \geq \beta_6$$

An example

$$\begin{aligned}\beta_2 + \alpha_2 &= \beta_4 + \alpha_1\\ \beta_1 + \alpha_1 &= (\beta_2 + \alpha_2) \vee (\beta_6 + \alpha_2 + \alpha_3)\\ \beta_3 + \alpha_1 &= (\beta_5 + \alpha_3) \vee (\beta_6 + \alpha_2 + \alpha_3)\end{aligned}$$

$$\beta_3 \geq \beta_5 \geq \beta_1 \geq \beta_4 \geq \beta_2 \geq \beta_6$$

β_1	0	α_1	0
β_2	$-\frac{2}{3}$	α_2	$\frac{2}{3}$
β_3	1	α_3	1
β_4	0	γ_1	0
β_5	0	γ_2	$\frac{2}{3}$
β_6	$-\frac{5}{3}$	γ_3	0

Scaling parameters Ball et al. (2006)

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

Normalized system

With the scaled rate constants and abundances, we have

$$\begin{aligned}
Z_1^N(t) &= Z_1^N(0) + Y_2\left(\int_0^t 2.5 Z_2^N(s)ds\right) - Y_4\left(\int_0^t .25 Z_1^N(s)ds\right) \\
Z_2^N(t) &= Z_2^N(0) + N^{-2/3} Y_1\left(\int_0^t Z_1^N(s)ds\right) - N^{-2/3} Y_2\left(\int_0^t 2.5 Z_2^N(s)ds\right) \\
&\quad - N^{-2/3} Y_6\left(\int_0^t .75 Z_2^N(s) Z_3^N(s)ds\right) \\
Z_3^N(t) &= Z_3^N(0) + N^{-1} Y_3\left(\int_0^t N Z_1^N(s)ds\right) - N^{-1} Y_5\left(\int_0^t 2N Z_3^N(s)ds\right) \\
&\quad - N^{-1} Y_6\left(\int_0^t .75 Z_2^N(s) Z_3^N(s)ds\right),
\end{aligned}$$

Limiting system

Passing to the limit, we have

$$
\begin{aligned}
Z_1(t) &= Z_1(0) + Y_2(\int_0^t 2.5 Z_2(s)ds) - Y_4(\int_0^t .25 Z_1(s)ds) \\
Z_2(t) &= Z_2(0) \\
Z_3(t) &= Z_3(0) + \int_0^t Z_1(s)ds - \int_0^t 2 Z_3(s)ds
\end{aligned}
$$

Fast time-scale

Define $Z_i^{N,\gamma}(t) = Z_i^N(N^\gamma t)$. For $\gamma = \frac{2}{3}$,

$$
\begin{aligned}
Z_1^{N,\gamma}(t) &= Z_1(0) + Y_2\Big(\int_0^t 2.5N^{2/3} Z_2^{N,\gamma}(s)ds\Big) - Y_4\Big(\int_0^t .25N^{2/3} Z_1^{N,\gamma}(s)ds\Big) \\
Z_2^{N,\gamma}(t) &= Z_2(0) + N^{-2/3} Y_1\Big(\int_0^t N^{2/3} Z_1^{N,\gamma}(s)ds\Big) \\
&\quad - N^{-2/3} Y_2\Big(\int_0^t 2.5N^{2/3} Z_2^{N,\gamma}(s)ds\Big) \\
&\quad - N^{-2/3} Y_6\Big(N^{2/3} \int_0^t .75 Z_2^{N,\gamma}(s) Z_3^{N,\gamma}(s)ds\Big) \\
Z_3^{N,\gamma}(t) &= Z_3(0) + N^{-1} Y_3\Big(\int_0^t N^{5/3} Z_1^{N,\gamma}(s)ds\Big) - N^{-1} Y_5\Big(\int_0^t 2N^{5/3} Z_3^{N,\gamma}(s)ds\Big) \\
&\quad - N^{-1} Y_6\Big(\int_0^t .75N^{2/3} Z_2^{N,\gamma}(s) Z_3^{N,\gamma}(s)ds\Big)
\end{aligned}
$$

Averaging

As $N \to \infty$, dividing the equations for $Z_1^{N,\gamma}$ and $Z_3^{N,\gamma}$ by $N^{2/3}$ shows that

$$\int_0^t Z_1^{N,\gamma}(s)ds - 10\int_0^t Z_2^{N,\gamma}(s)ds \to 0$$
$$\int_0^t Z_3^{N,\gamma}(s)ds - 5\int_0^t Z_2^{N,\gamma}(s)ds \to 0.$$

The assertion for $Z_3^{N,\gamma}$ and the fact that $Z_2^{N,\gamma}$ is asymptotically regular imply

$$\int_0^t Z_2^{N,\gamma}(s)Z_3^{N,\gamma}(s)ds - 5\int_0^t Z_2^{N,\gamma}(s)^2 ds \to 0.$$

It follows that $Z_2^{N,\gamma}$ converges to the solution of (2).

Law of large numbers

Theorem 1 *Let* $\gamma = \frac{2}{3}$. *For each* $\delta > 0$ *and* $t > 0$,

$$\lim_{N\to\infty} P\{\sup_{0\le s\le t} |Z_2^{N,\gamma}(s) - Z_2^{\infty,\gamma}(s)| \ge \delta\} = 0,$$

where $Z_2^{\infty,\gamma}$ *is the solution of*

$$Z_2^{\infty,\gamma}(t) = Z_2(0) + \int_0^t 7.5 Z_2^{\infty,\gamma}(s)ds) - \int_0^t 3.75 Z_2^{\infty,\gamma}(s)^2 ds. \qquad (2)$$

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 $\lim_{N\to\infty} Z_i^N(\cdot N^\gamma) = Z_i^{\infty,\gamma}$, 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

$$X_2(t) \approx (1000)^{2/3} Z_2^{\infty,\gamma}(t(1000)^{-2/3})$$

Things I haven't told you

In general, additional balance conditions are needed.

A systematic approach to averaging fast components.

How to derive appropriate diffusion/Langevin approximations.

Things I don't know but wish I did

How to automate the analysis.

Criteria for "optimal" selection of the scaling exponents.

How to systematically incorporate biological constraints.

Scaled model

Define

$$\zeta_k = \nu_k' - \nu_k \qquad \rho_k = \beta_k + \nu_k \cdot \alpha,$$

and let γ be the exponent associated with a change of time scale, $Z^{N,\gamma}(t) = Z^N(tN^\gamma)$. The scaled model satisfies

$$\begin{aligned} Z^{N,\gamma}(t) &= Z^{N,\gamma}(0) + \Lambda_N \sum_k Y_k(N^{\beta_k+\nu_k\cdot\alpha+\gamma} \int_0^t \lambda_k(Z^{N,\gamma}(s))ds)(\nu_k' - \nu_k) \\ &= Z^{N,\gamma}(0) + \Lambda_N \sum_k Y_k(N^{\rho_k+\gamma} \int_0^t \lambda_k(Z^{N,\gamma}(s))ds)\zeta_k, \end{aligned}$$

where Λ_N is the diagonal matrix with entries $N^{-\alpha_i}$.

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

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

Conditions for linear combinations

Definition 2 *For $\theta \in [0,\infty)^{s_0}$, define*

$$\Gamma_\theta^+ = \{k : \theta\cdot\zeta_k > 0\} \qquad \Gamma_\theta^- = \{k : \theta\cdot\zeta_k < 0\}$$

Then, noting that

$$\theta^T\Lambda_N^{-1}Z^{N,\gamma}(t) = \sum_{i=1}^{s_0}\theta_i N^{\alpha_i}Z_i^{N,\gamma}(t) = \sum_{i=1}^{s_0}\theta_i X_i^N(N^\gamma t),$$

$$\begin{aligned}
\theta^T\Lambda_N^{-1}Z^{N,\gamma}(t) &= \theta^T\Lambda_N^{-1}Z^{N,\gamma}(0) + \sum_k(\theta\cdot\zeta_k)Y_k(N^{\rho_k+\gamma}\int_0^t\lambda_k(Z^{N,\gamma}(s))ds) \\
&= \theta^T\Lambda_N^{-1}Z^{N,\gamma}(0) + \sum_{k\in\Gamma_\theta^+}(\theta\cdot\zeta_k)Y_k(N^{\rho_k+\gamma}\int_0^t\lambda_k(Z^{N,\gamma}(s))ds) \\
&\qquad - \sum_{k\in\Gamma_\theta^-}|(\theta\cdot\zeta_k)|Y_k(N^{\rho_k+\gamma}\int_0^t\lambda_k(Z^{N,\gamma}(s))ds).
\end{aligned}$$

Collective balance condition

To avoid some kind of degeneracy in the limit, either the positive and negative sums must cancel, or they must grow no faster than N^{α_i} for some i with $\theta_i > 0$. For each $\theta \in [0, \infty)^{s_0}$, the following condition must hold.

Condition 3

$$\max_{k \in \Gamma_\theta^-}(\beta_k + \nu_k \cdot \alpha) = \max_{k \in \Gamma_\theta^+}(\beta_k + \nu_k \cdot \alpha) \tag{3}$$

or $\max_{k \in \Gamma_\theta^+ \cup \Gamma_\theta^-}(\beta_k + \nu_k \cdot \alpha + \gamma) \leq \max_{i:\theta_i > 0} \alpha_i$, *that is*

$$\gamma \leq \gamma_\theta \equiv \max_{i:\theta_i > 0} \alpha_i - \max_{k \in \Gamma_\theta^+ \cup \Gamma_\theta^-}(\beta_k + \nu_k \cdot \alpha). \tag{4}$$

We will refer to (3) as the *balance equation* for the linear combination $\theta \cdot X = \sum_i \theta_i X_i$.

Simplified conditions

For $k \in \{1, \ldots, r_0\}$, define

$$\Lambda_k^{+\,(-,0)} = \{\theta \in [0,\infty)^{s_0} : \theta \cdot \zeta_k > 0 \quad (< 0, = 0)\},$$

and for disjoint Γ_-, Γ_+, Γ_0 satisfying $\Gamma_- \cup \Gamma_+ \cup \Gamma_0 = \{1, \cdots, r_0\}$, define

$$\Lambda_{\Gamma_-,\Gamma_+,\Gamma_0} = (\cap_{k\in\Gamma_-}\Lambda_k^-) \cap (\cap_{k\in\Gamma_+}\Lambda_k^+) \cap (\cap_{k\in\Gamma_0}\Lambda_k^0).$$

Lemma 4 *Fix γ. Condition 3 holds for all $\theta \in [0,\infty)^{s_0}$ provided*

$$\max_{k\in\Gamma_-}(\beta_k + \nu_k \cdot \alpha) = \max_{k\in\Gamma_+}(\beta_k + \nu_k \cdot \alpha)$$

or

$$\gamma \le \min_{\theta\in\Lambda_{\Gamma_-,\Gamma_+,\Gamma_0}} \max_{i:\theta_i>0} \alpha_i - \max_{k\in\Gamma_+\cup\Gamma_-}(\beta_k + \nu_k \cdot \alpha)$$

for all partitions $\{\Gamma_-, \Gamma_+, \Gamma_0\}$ for which $\Lambda_{\Gamma_-,\Gamma_+,\Gamma_0} \neq \emptyset$.

Example

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

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

Balance equations:

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

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

The balance equation is not satisfied for $\{S_1 + S_2\}$, so 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 Bentley (2001). The analysis is from Kang (2009).

Reaction	Intensity	Reaction	Intensity
$\emptyset \to S_8$	4.00×10^0	$S_6 + S_8 \to S_9$	$3.62 \times 10^{-4} X_{S_6} X_{S_8}$
$S_2 \to S_3$	$7.00 \times 10^{-1} X_{S_2}$	$S_8 \to \emptyset$	$9.99 \times 10^{-5} X_{S_8}$
$S_3 \to S_2$	$1.30 \times 10^{-1} X_{S_3}$	$S_9 \to S_6 + S_8$	$4.40 \times 10^{-5} X_{S_9}$
$\emptyset \to S_2$	$7.00 \times 10^{-3} X_{S_1}$	$\emptyset \to S_1$	1.40×10^{-5}
$\text{stuff} + S_3 \to S_5 + S_2$	$6.30 \times 10^{-3} X_{S_3}$	$S_1 \to \emptyset$	$1.40 \times 10^{-6} X_{S_1}$
$\text{stuff} + S_3 \to S_4 + S_2$	$4.88 \times 10^{-3} X_{S_3}$	$S_7 \to S_6$	$1.42 \times 10^{-6} X_{S_4} X_{S_7}$
$\text{stuff} + S_3 \to S_6 + S_2$	$4.88 \times 10^{-3} X_{S_3}$	$S_5 \to \emptyset$	$1.80 \times 10^{-8} X_{S_5}$
$S_7 \to S_2 + S_6$	$4.40 \times 10^{-4} X_{S_7}$	$S_6 \to \emptyset$	$6.40 \times 10^{-10} X_{S_6}$
$S_2 + S_6 \to S_7$	$3.62 \times 10^{-4} X_{S_2} X_{S_6}$	$S_4 \to \emptyset$	$7.40 \times 10^{-11} X_{S_4}$

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 equations

$$
\begin{array}{llcl}
\{Z_1\} & \rho_{13} & = & \rho_{14} \\
\{Z_2\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7, \rho_8\} & = & \rho_2 \vee \rho_9 \\
\{Z_3\} & \rho_2 & = & \max\{\rho_3, \rho_5, \rho_6, \rho_7\} \\
\{Z_4\} & \rho_6 & = & \rho_{18} \\
\{Z_5\} & \rho_5 & = & \rho_{16} \\
\{Z_6\} & \max\{\rho_7, \rho_8, \rho_{12}, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{Z_7\} & \rho_9 & = & \rho_8 \vee \rho_{15} \\
\{Z_8\} & \rho_1 \vee \rho_{12} & = & \rho_{10} \vee \rho_{11} \\
\{Z_9\} & \rho_{10} & = & \rho_{12} \\
\{Z_2 + Z_3 + Z_7\} & \rho_4 & = & \rho_{15} \\
\{Z_2 + Z_3\} & \rho_4 \vee \rho_8 & = & \rho_9 \\
\{Z_2 + Z_7\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7\} & = & \rho_2 \vee \rho_{15} \\
\{Z_6 + Z_7 + Z_9\} & \rho_7 & = & \rho_{17} \\
\{Z_6 + Z_9\} & \max\{\rho_7, \rho_8, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{Z_6 + Z_7\} & \rho_7 \vee \rho_{12} & = & \rho_{17} \vee \rho_{10} \\
\{Z_8 + Z_9\} & \rho_1 & = & \rho_{17}
\end{array}
$$

$\theta \cdot Z$	First scale	Second scale	Third scale
$\{Z_1\}$	$\gamma \leq 2$	balanced	balanced
$\{Z_2\}$	balanced	balanced	balanced
$\{Z_3\}$	balanced	balanced	balanced
$\{Z_4\}$	$\gamma \leq 2$	$\gamma \leq 2$	balanced
$\{Z_5\}$	$\gamma \leq 2$	$\gamma \leq 2$	balanced
$\{Z_6\}$	$\gamma \leq 1$	balanced	balanced
$\{Z_7\}$	$\gamma \leq 1$	$\gamma \leq 1$	balanced
$\{Z_8\}$	$\gamma \leq 0$	$\gamma \leq 1$	balanced
$\{Z_9\}$	balanced	balanced	balanced
$\{Z_2 + Z_3 + Z_7\}$	$\gamma \leq 0$	balanced	balanced
$\{Z_2 + Z_3\}$	$\gamma \leq 0$	$\gamma \leq 1$	balanced
$\{Z_2 + Z_7\}$	balanced	balanced	balanced
$\{Z_6 + Z_7 + Z_9\}$	$\gamma \leq 1$	$\gamma \leq 2$	$\gamma \leq 2$
$\{Z_6 + Z_9\}$	$\gamma \leq 1$	$\gamma \leq 2$	$\gamma \leq 2$
$\{Z_6 + Z_7\}$	$\gamma \leq 1$	balanced	balanced
$\{Z_8 + Z_9\}$	$\gamma \leq 0$	$\gamma \leq 1$	balanced

$$
\begin{aligned}
Z_1^{N,\gamma}(t) &= Z_1^{N,\gamma}(0) + N^{-\alpha_{1,\gamma}} Y_{13}\Big(\int_0^t \kappa_{13} N^{\gamma-2}\,ds\Big) - N^{-\alpha_{1,\gamma}} Y_{14}\Big(\int_0^t \kappa_{14} N^{\gamma-2+\alpha_{1,\gamma}} Z_1^{N,\gamma}(s)\,ds\Big) \\
Z_2^{N,\gamma}(t) &= Z_2^{N,\gamma}(0) + N^{-\alpha_{2,\gamma}} Y_3\Big(\int_0^t \kappa_3 N^{\gamma} Z_3^{N,\gamma}(s)\,ds\Big) + N^{-\alpha_{2,\gamma}} Y_4\Big(\int_0^t \kappa_4 N^{\gamma-1} Z_1^{N,\gamma}(s)\,ds\Big) \\
&\quad + N^{-\alpha_{2,\gamma}} Y_5\Big(\int_0^t \kappa_5 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) + N^{-\alpha_{2,\gamma}} Y_6\Big(\int_0^t \kappa_6 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) \\
&\quad + N^{-\alpha_{2,\gamma}} Y_7\Big(\int_0^t \kappa_7 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) + N^{-\alpha_{2,\gamma}} Y_8\Big(\int_0^t \kappa_8 N^{\gamma-2} Z_7^{N,\gamma}(s)\,ds\Big) \\
&\quad - N^{-\alpha_{2,\gamma}} Y_2\Big(\int_0^t \kappa_2 N^{\gamma+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s)\,ds\Big) - N^{-\alpha_{2,\gamma}} Y_9\Big(\int_0^t \kappa_9 N^{\gamma-2+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s) Z_6^{N,\gamma}(s) \\
Z_3^{N,\gamma}(t) &= Z_3^{N,\gamma}(0) + N^{-\alpha_{2,\gamma}} Y_2\Big(\int_0^t \kappa_2 N^{\gamma+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s)\,ds\Big) \\
&\quad - N^{-\alpha_{2,\gamma}} Y_3\Big(\int_0^t \kappa_3 N^{\gamma+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) - N^{-\alpha_{2,\gamma}} Y_5\Big(\int_0^t \kappa_5 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) \\
&\quad - N^{-\alpha_{2,\gamma}} Y_6\Big(\int_0^t \kappa_6 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) - N^{-\alpha_{2,\gamma}} Y_7\Big(\int_0^t \kappa_7 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big)
\end{aligned}
$$

$$
\begin{aligned}
Z_4^{N,\gamma}(t) &= Z_4^{N,\gamma}(0) + N^{-2}Y_6\Big(\int_0^t \kappa_6 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) - N^{-2}Y_{18}\Big(\int_0^t \kappa_{18} N^{\gamma} Z_4^{N,\gamma}(s)\,ds\Big) \\
Z_5^{N,\gamma}(t) &= Z_5^{N,\gamma}(0) + N^{-2}Y_5\Big(\int_0^t \kappa_5 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) - N^{-2}Y_{16}\Big(\int_0^t \kappa_{16} N^{\gamma} Z_5^{N,\gamma}(s)\,ds\Big) \\
Z_6^{N,\gamma}(t) &= Z_6^{N,\gamma}(0) + Y_7\Big(\int_0^t \kappa_7 N^{\gamma-1+\alpha_{2,\gamma}} Z_3^{N,\gamma}(s)\,ds\Big) + Y_8\Big(\int_0^t \kappa_8 N^{\gamma-2} Z_7^{N,\gamma}(s)\,ds\Big) \\
&\quad + Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma-2+\alpha_{8,\gamma}} Z_9^{N,\gamma}(s)\,ds\Big) + Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma-1} Z_4^{N,\gamma}(s) Z_7^{N,\gamma}(s)\,ds\Big) \\
&\quad - Y_9\Big(\int_0^t \kappa_9 N^{\gamma-2+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s) Z_6^{N,\gamma}(s)\,ds\Big) \\
&\quad - Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma-2+\alpha_{8,\gamma}} Z_6^{N,\gamma}(s) Z_8^{N,\gamma}(s)\,ds\Big) - Y_{17}\Big(\int_0^t \kappa_{17} N^{\gamma-2} Z_6^{N,\gamma}(s)\,ds\Big) \\
Z_7^{N,\gamma}(t) &= Z_7^{N,\gamma}(0) + Y_9\Big(\int_0^t \kappa_9 N^{\gamma-2+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s) Z_6^{N,\gamma}(s)\,ds\Big) \\
&\quad - Y_8\Big(\int_0^t \kappa_8 N^{\gamma-2} Z_7^{N,\gamma}(s)\,ds\Big) \\
&\quad - Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma-1} Z_4^{N,\gamma}(s) Z_7^{N,\gamma}(s)\,ds\Big)
\end{aligned}
$$

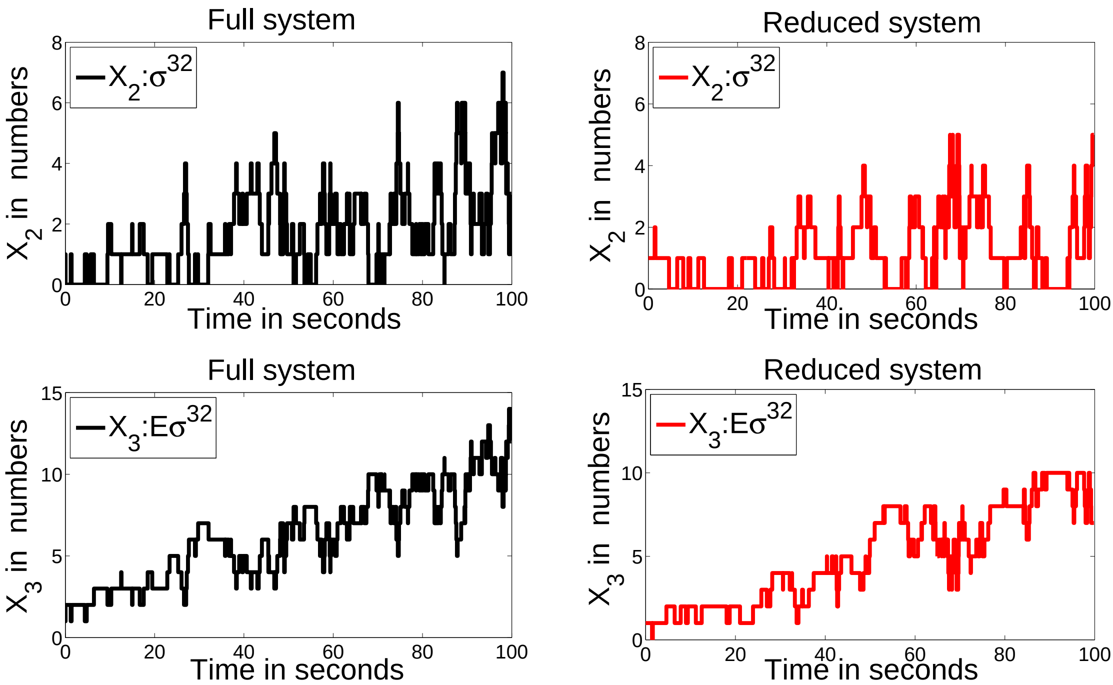
$$
\begin{aligned}
Z_8^{N,\gamma}(t) &= Z_8^{N,\gamma}(0) + N^{-\alpha_{8,\gamma}} Y_1\Big(\int_0^t \kappa_1 N^{\gamma}\, ds\Big) + N^{-\alpha_{8,\gamma}} Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma-2+\alpha_{8,\gamma}} Z_9^{N,\gamma}(s)\, ds\Big) \\
&\quad - N^{-\alpha_{8,\gamma}} Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma-2+\alpha_{8,\gamma}} Z_6^{N,\gamma}(s) Z_8^{N,\gamma}(s)\, ds\Big) \\
&\quad - N^{-\alpha_{8,\gamma}} Y_{11}\Big(\int_0^t \kappa_{11} N^{\gamma-2+\alpha_{8,\gamma}} Z_8^{N,\gamma}(s)\, ds\Big) \\
Z_9^{N,\gamma}(t) &= Z_9^{N,\gamma}(0) + N^{-\alpha_{8,\gamma}} Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma-2+\alpha_{8,\gamma}} Z_6^{N,\gamma}(s) Z_8^{N,\gamma}(s)\, ds\Big) \\
&\qquad - N^{-\alpha_{8,\gamma}} Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma-2+\alpha_{8,\gamma}} Z_9^{N,\gamma}(s)\, ds\Big) \\
Z_{2,3}^{N,\gamma} &= Z_{2,3}^{N,\gamma}(0) + N^{-\alpha_{2,\gamma}} Y_4\Big(\int_0^t \kappa_4 N^{\gamma-1+\alpha_{1,\gamma}} Z_1^{N,\gamma}(s)\, ds\Big) \\
&\quad + N^{-\alpha_{2,\gamma}} Y_8\Big(\int_0^t \kappa_8 N^{\gamma-2} Z_7^{N,\gamma}(s)\, ds\Big) \\
&\quad - N^{-\alpha_{2,\gamma}} Y_9\Big(\int_0^t \kappa_9 N^{\gamma-2+\alpha_{2,\gamma}} Z_2^{N,\gamma}(s) Z_6^{N,\gamma}(s)\, ds\Big)
\end{aligned}
$$

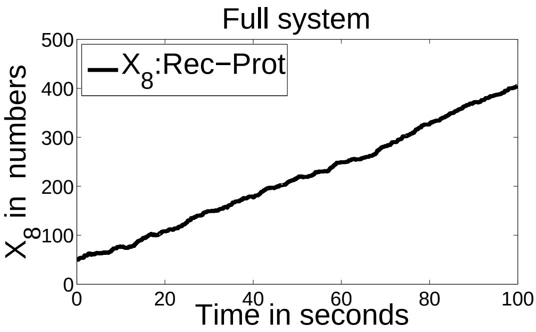
$\gamma = 0$

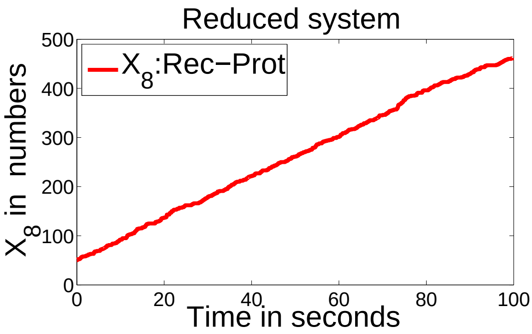
α_1	α_2	α_3	α_4	α_5	α_6	α_7	α_8	α_9
1	0	0	2	2	0	0	0	0

For $\gamma = 0$, $\{Z_2^{N,0}, Z_3^{N,0}, Z_8^{N,0}\}$ converge to the solution of

$$\begin{aligned}
Z_2^0(t) &= Z_2^0(0) + Y_3\left(\int_0^t \kappa_3 Z_3^0(s)\,ds\right) + Y_4\left(\int_0^t \kappa_4 Z_1^0(0)\,ds\right) \\
&\quad - Y_2\left(\int_0^t \kappa_2 Z_2^0(s)\,ds\right) \\
Z_3^0(t) &= Z_3^0(0) + Y_2\left(\int_0^t \kappa_2 Z_2^0(s)\,ds\right) - Y_3\left(\int_0^t \kappa_3 Z_3^0(s)\,ds\right) \\
Z_8^0(t) &= Z_8^0(0) + Y_1\left(\int_0^t \kappa_1\,ds\right)
\end{aligned}$$


Full system
Reduced system
$X_2:\sigma^{32}$
X_2 in numbers
Time in seconds
Full system
Reduced system
$X_3:E\sigma^{32}$
X_3 in numbers
Time in seconds


Full system
X8:Rec−Prot
X8 in numbers
0
100
200
300
400
500
0
20
40
60
80
100
Time in seconds

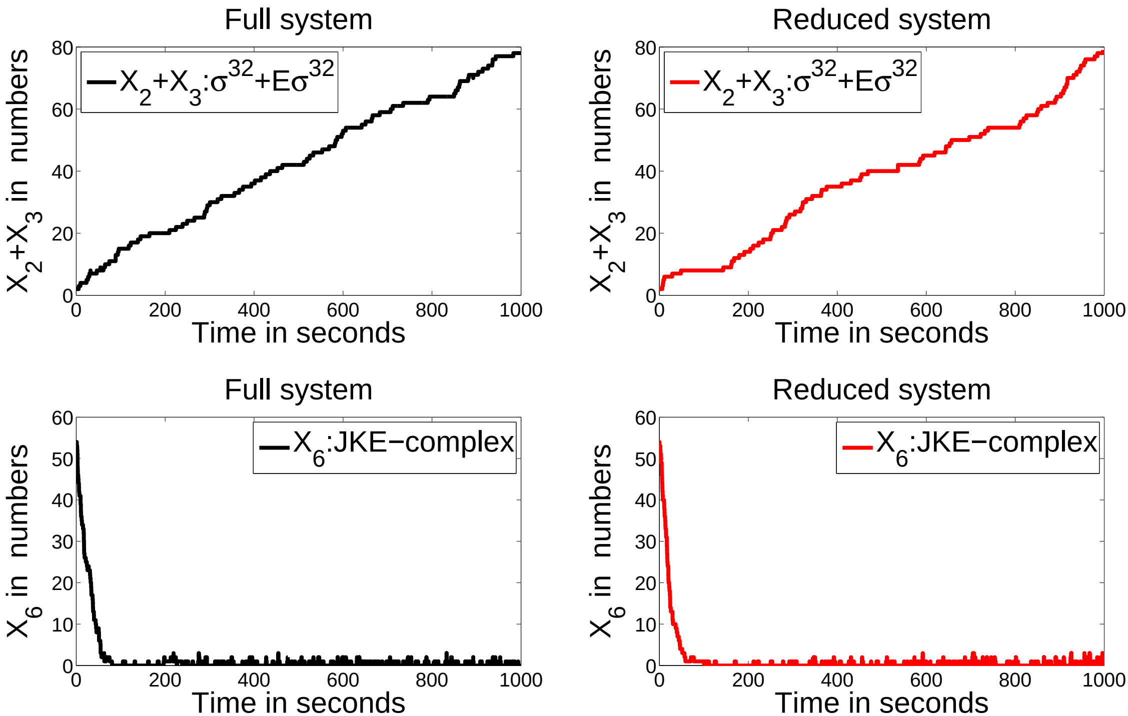

Reduced system
X8:Rec−Prot
X8 in numbers
0
100
200
300
400
500
0
20
40
60
80
100
Time in seconds

$\gamma = 1$

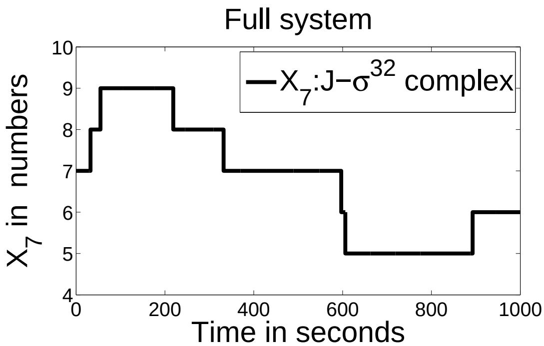
α_1	α_2	α_3	α_4	α_5	α_6	α_7	α_8	α_9
0	0	0	2	2	0	0	1	1

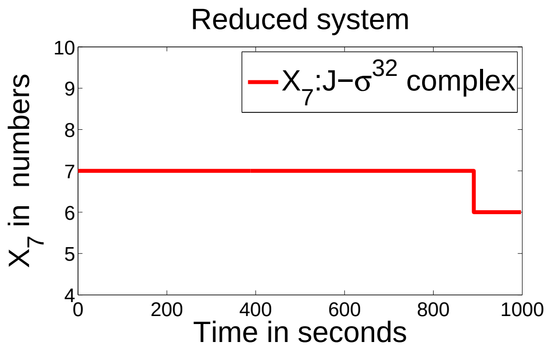
For $\gamma = 1$, $\{Z_{2,3}^{N,1}, Z_6^{N,1}, Z_7^{N,1}, Z_8^{N,1}\}$ converges to the solution of

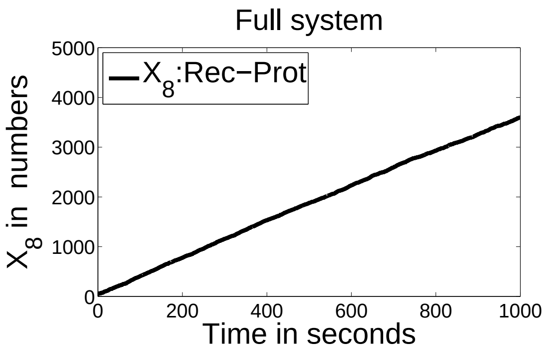
$$\begin{aligned}
Z_{2,3}^1(t) &= Z_{2,3}^1(0) + Y_4\Big(\int_0^t \kappa_4 Z_1^1(0)\, ds\Big) \\
Z_6^1(t) &= Z_6^1(0) + Y_7\Big(\int_0^t \kappa_7 \overline{Z}_3^1(s)\, ds\Big) + Y_{12}\Big(\int_0^t \kappa_{12} Z_9^1(0)\, ds\Big) \\
&\quad + Y_{15}\Big(\int_0^t \kappa_{15} Z_4^1(0) Z_7^1(s)\, ds\Big) - Y_{10}\Big(\int_0^t \kappa_{10} Z_6^1(s) Z_8^1(s)\, ds\Big) \\
Z_7^1(t) &= Z_7^1(0) - Y_{15}\Big(\int_0^t \kappa_{15} Z_4^1(0) Z_7^1(s)\, ds\Big) \\
Z_8^1(t) &= Z_8^1(0) + \int_0^t \kappa_1\, ds \\
\overline{Z}_3^1(t) &= \frac{\kappa_2 Z_{2,3}^1(s)}{\kappa_2 + \kappa_3}
\end{aligned}$$

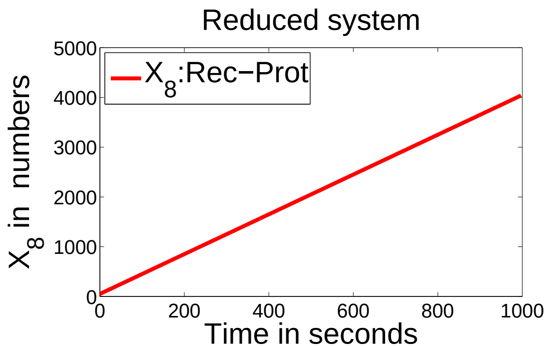


Full system
Reduced system
X_2+X_3 in numbers
Time in seconds
X_2+X_3:σ^32+Eσ^32
Full system
Reduced system
X_6 in numbers
Time in seconds
X_6:JKE−complex


Full system
X_7:J−σ^32 complex
X_7 in numbers
Time in seconds
10
9
8
7
6
5
4
0
200
400
600
800
1000


Reduced system
X_7:J−σ^32 complex
X_7 in numbers
Time in seconds
10
9
8
7
6
5
4
0
200
400
600
800
1000


Full system
X_8:Rec−Prot
X_8 in numbers
Time in seconds
5000
4000
3000
2000
1000
0
0
200
400
600
800
1000


Reduced system
X_8:Rec−Prot
X_8 in numbers
Time in seconds
5000
4000
3000
2000
1000
0
0
200
400
600
800
1000

$\gamma = 2$

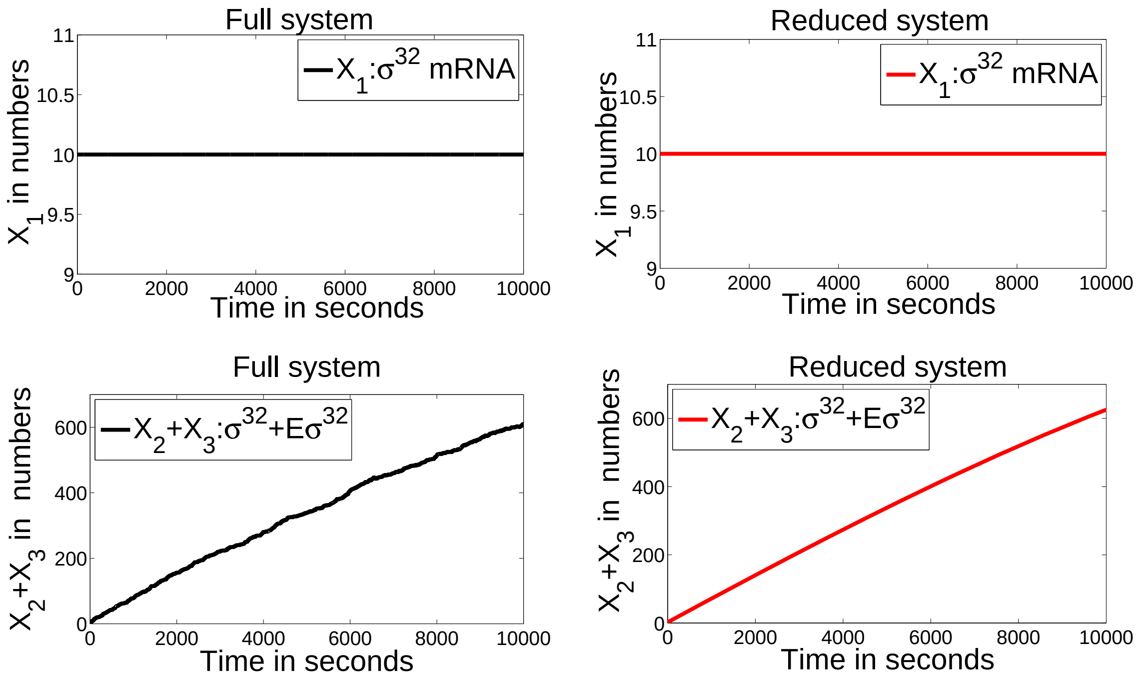
α_1	α_2	α_3	α_4	α_5	α_6	α_7	α_8	α_9
0	1	1	2	2	0	0	2	2

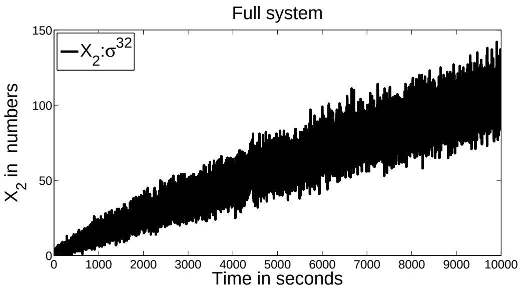
For $\gamma = 2$, $\{Z_1^{N,2}, Z_{2,3}^{N,2}, Z_4^{N,2}, Z_5^{N,2}, Z_8^{N,2}, Z_9^{N,2}\}$ converges to the solution of

$$
\begin{aligned}
Z_1^2(t) &= Z_1^2(0) + Y_{13}\left(\int_0^t \kappa_{13}\, ds\right) - Y_{14}\left(\int_0^t \kappa_{14} Z_1^2(s)\, ds\right) \\
Z_{2,3}^2(t) &= Z_{2,3}^2(0) + \int_0^t \left[\kappa_4 Z_1^2(s) - \kappa_9 \widehat{Z}_2^2(s)\overline{Z}_6^2(s)\Big)\right] ds \\
Z_4^2(t) &= Z_4^2(0) + \int_0^t (\kappa_6 \widehat{Z}_3^2(s) - \kappa_{18} Z_4^2(s))\, ds \\
Z_5^2(t) &= Z_5^2(0) + \int_0^t (\kappa_5 \widehat{Z}_3^2(s) - \kappa_{16} Z_5^2(s))\, ds \\
Z_8^2(t) &= Z_8^2(0) + \int_0^t (\kappa_1 - \kappa_7 \widehat{Z}_3^2(s) - \kappa_{11} Z_8^2(s))\, ds \\
Z_9^2(t) &= Z_9^2(0) + \int_0^t \kappa_7 \widehat{Z}_3^2(s)\, ds
\end{aligned}
$$

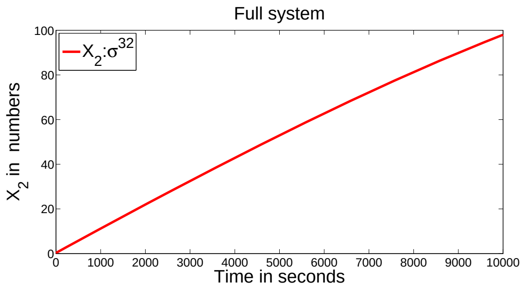
$$\widehat{Z}_3^1(t) = \frac{\kappa_3 Z_{2,3}^1(s)}{\kappa_2 + \kappa_3} \qquad \widehat{Z}_3^1(t) = \frac{\kappa_2 Z_{2,3}^1(s)}{\kappa_2 + \kappa_3}$$

$$\overline{Z}_6^2(s) = \frac{\kappa_7 \widehat{Z}_3^2(s) + \kappa_{12} Z_9^2(s)}{\kappa_{10} Z_8^2(s)} \qquad \overline{Z}_7^2(t) = \frac{\kappa_9 \widehat{Z}_2^2(t) \overline{Z}_6(t)}{\kappa_{15} Z_4^2(t)}$$

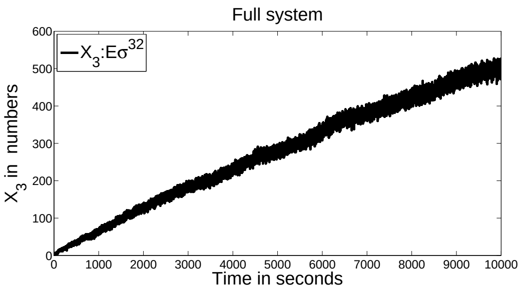

Full system
X1:σ32 mRNA
X1 in numbers
Time in seconds
Reduced system
X1:σ32 mRNA
X1 in numbers
Time in seconds
Full system
X2+X3:σ32+Eσ32
X2+X3 in numbers
Time in seconds
Reduced system
X2+X3:σ32+Eσ32
X2+X3 in numbers
Time in seconds



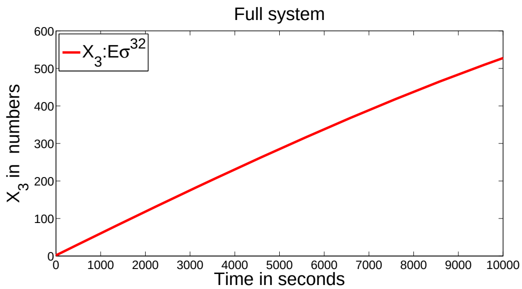
Full system
150
100
50
0
X2 : σ32
X2 in numbers
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Time in seconds



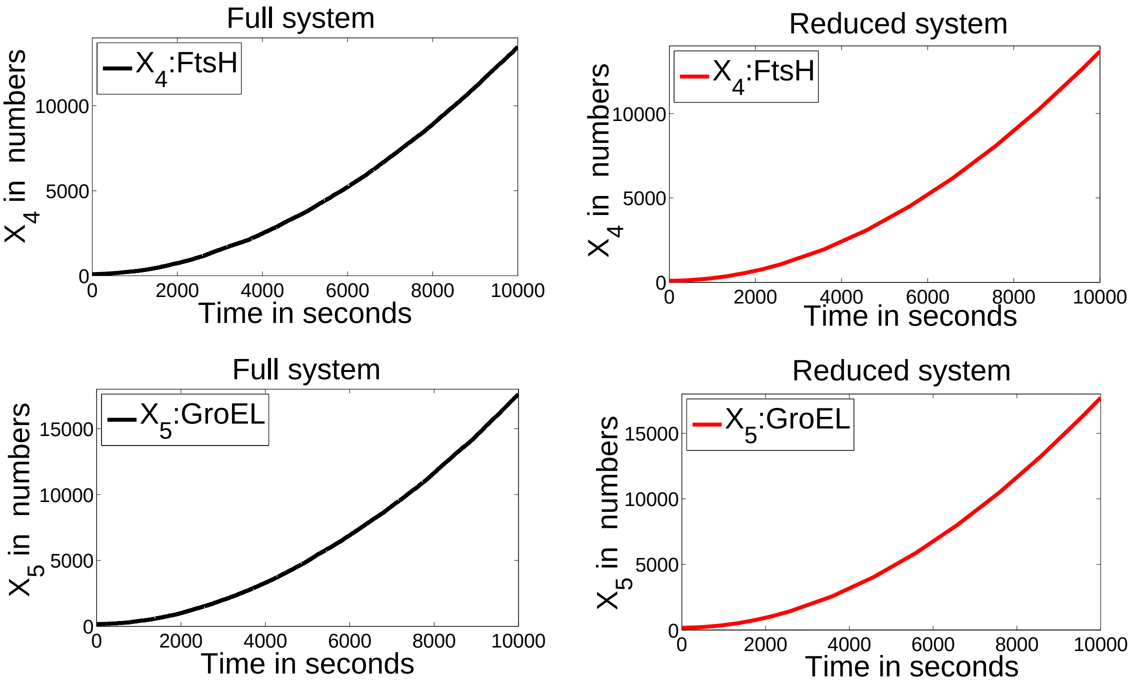
Full system
100
80
60
40
20
0
X2 : σ32
X2 in numbers
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Time in seconds



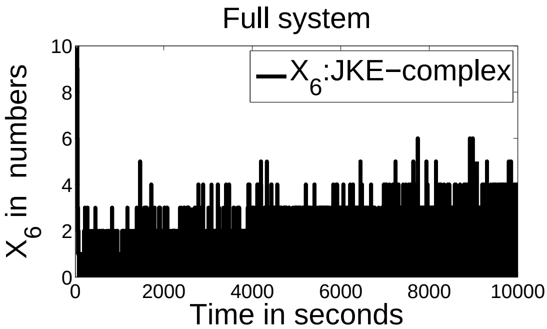
Full system
600
500
400
300
200
100
0
X3 : Eσ32
X3 in numbers
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Time in seconds

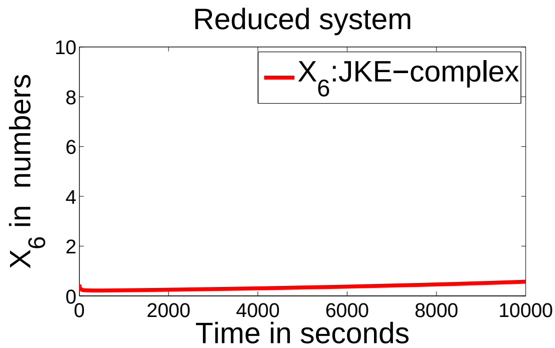


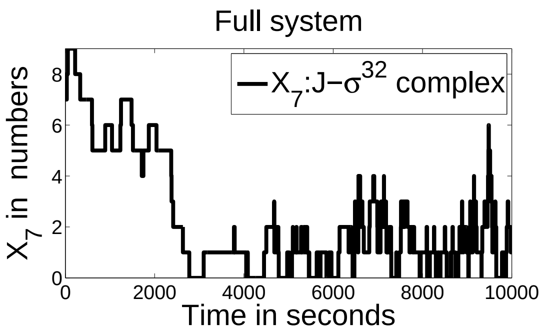
Full system
600
500
400
300
200
100
0
X3 : Eσ32
X3 in numbers
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Time in seconds

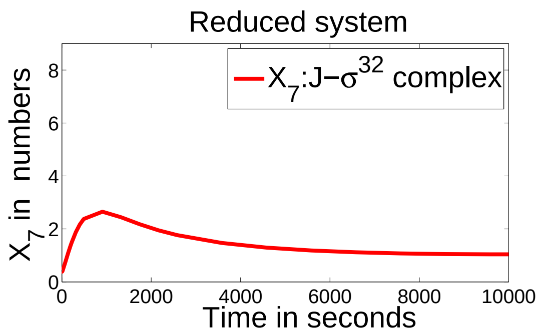


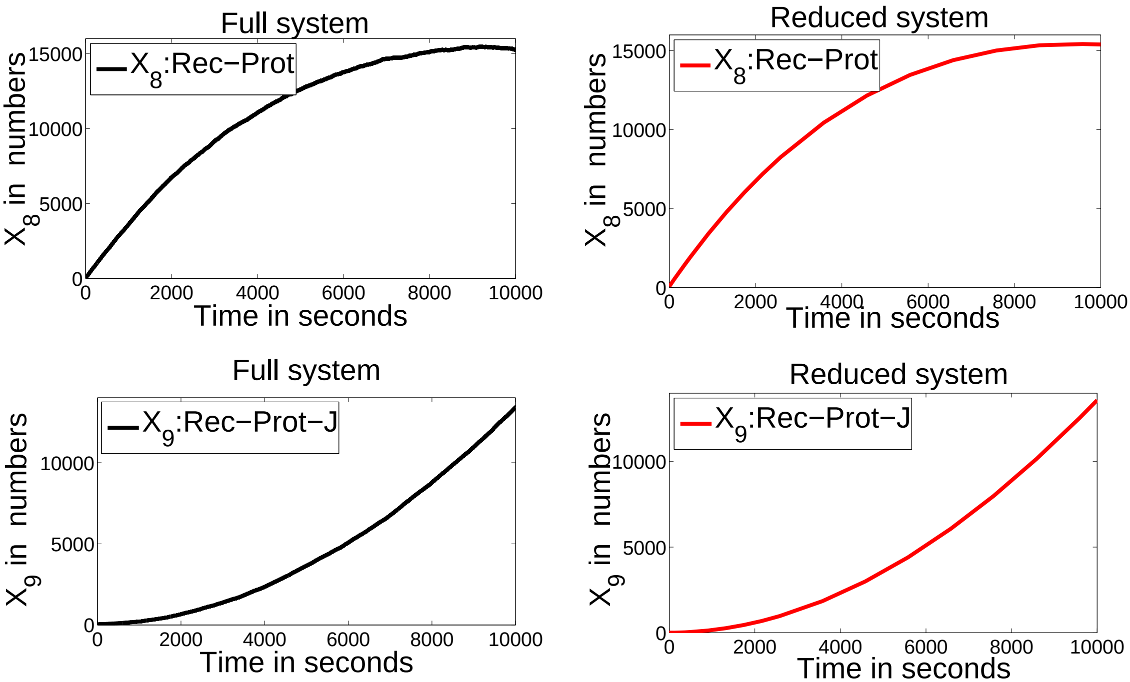
Full system
X4:FtsH
X4 in numbers
10000
5000
0
0
2000
4000
6000
8000
10000
Time in seconds
Reduced system
X4:FtsH
X4 in numbers
10000
5000
0
0
2000
4000
6000
8000
10000
Time in seconds
Full system
X5:GroEL
X5 in numbers
15000
10000
5000
0
0
2000
4000
6000
8000
10000
Time in seconds
Reduced system
X5:GroEL
X5 in numbers
15000
10000
5000
0
0
2000
4000
6000
8000
10000
Time in seconds


Full system
X6:JKE−complex
X6 in numbers
Time in seconds
0
2
4
6
8
10
0
2000
4000
6000
8000
10000


Reduced system
X6:JKE−complex
X6 in numbers
Time in seconds
0
2
4
6
8
10
0
2000
4000
6000
8000
10000


Full system
X7:J−σ32 complex
X7 in numbers
Time in seconds
0
2
4
6
8
0
2000
4000
6000
8000
10000


Reduced system
X7:J−σ32 complex
X7 in numbers
Time in seconds
0
2
4
6
8
0
2000
4000
6000
8000
10000


Full system
Reduced system
X_8:Rec−Prot
X_8 in numbers
X_9:Rec−Prot−J
X_9 in numbers
Time in seconds
0
2000
4000
6000
8000
10000
5000
15000

Strong approximation

Theorem 5 *A unit Poisson process* Y *and a standard Brownian motion* W *can be constructed so that*

$$|Y(u) - u - W(u)| \leq \Gamma \log(2+u)$$

where there exist C *and* λ *such that*

$$P\{\Gamma > x\} \leq Ce^{-\lambda x}.$$

Note that

$$\left|\frac{Y(Ku)}{K} - u - \frac{W(Ku)}{K}\right| \leq \frac{\Gamma}{K} \log(2+Ku)$$

Central limit theorem/Van Kampen Approximation

$$
\begin{aligned}
V_N(t) &\equiv \sqrt{N}(C_N(t) - C(t)) \\
&\approx V_N(0) + \sqrt{N}(\sum_k \frac{1}{N} Y_k(N \int_0^t \widetilde{\lambda}_k^N(C_N(s))ds)(\nu_k' - \nu_k) \\
&\qquad - \int_0^t F(C(s))ds) \\
&= V_N(0) + \sum_k \frac{1}{\sqrt{N}} \widetilde{Y}_k(N \int_0^t \widetilde{\lambda}_k^N(C_N(s))ds)(\nu_k' - \nu_k) \\
&\qquad + \int_0^t \sqrt{N}(F^N(C_N(s)) - F(C(s)))ds \\
&\approx V_N(0) + \sum_k W_k(\int_0^t \widetilde{\lambda}_k(C(s))ds)(\nu_k' - \nu_k) \\
&\qquad + \int_0^t \nabla F(C(s))) V_N(s)ds
\end{aligned}
$$

Gaussian limit

V_N converges to the solution of

$$V(t) = V(0) + \sum_k W_k(\int_0^t \widetilde{\lambda}_k(C(s))ds)(\nu_k' - \nu_k) + \int_0^t \nabla F(C(s))V(s)ds$$

$$C_N(t) \approx C(t) + \frac{1}{\sqrt{N}} V(t)$$

Diffusion approximation

$$\begin{aligned} C^N(t) &= C^N(0) + \sum_k N^{-1} Y_k(\int_0^t \lambda_k(X^N(s))ds)(\nu_k' - \nu_k) \\ &\approx C^N(0) + \sum_k N^{-1}\widetilde{Y}_k(N\int_0^t \widetilde{\lambda}_k(C^N(s))ds)(\nu_k' - \nu_k) \\ &\qquad + \int_0^t F(C^N(s))ds \\ &\approx C^N(0) + \sum_k N^{-1/2} W_k(\int_0^t \widetilde{\lambda}_k(C^N(s))ds)(\nu_k' - \nu_k) \\ &\qquad + \int_0^t F(C^N(s))ds, \end{aligned}$$

where

$$F(c) = \sum_k \widetilde{\lambda}_k(c)(\nu_k' - \nu_k).$$

The diffusion approximation is given by the equation

$$\widetilde{C}^N(t) = \widetilde{C}^N(0) + \sum_k N^{-1/2} W_k\left(\int_0^t \widetilde{\lambda}_k(\widetilde{C}^N(s))ds\right)(\nu_k' - \nu_k) + \int_0^t F(\widetilde{C}^N(s))ds.$$

Itô formulation

The time-change formulation is equivalent to the Itô equation

$$\begin{aligned}\widetilde{C}^N(t) &= \widetilde{C}^N(0) + \sum_k N^{-1/2}\int_0^t \sqrt{\widetilde{\lambda}_k(\widetilde{C}^N(s))}d\widetilde{W}_k(s)(\nu_k' - \nu_k) \\ &\quad + \int_0^t F(\widetilde{C}^N(s))ds \\ &= \widetilde{C}^N(0) + \sum_k N^{-1/2}\int_0^t \sigma(\widetilde{C}^N(s))d\widetilde{W}(s) + \int_0^t F(\widetilde{C}^N(s))ds,\end{aligned}$$

where $\sigma(c)$ is the matrix with columns $\sqrt{\widetilde{\lambda}_k(c)}(\nu_k' - \nu_k)$.

See Kurtz (1971, 1977/78), Ethier and Kurtz (1986), Chapter 10, Gardiner (2004), Chapter 7, and van Kampen (1981).

References

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. ISSN 1050-5164.

Stewart N. Ethier and Thomas G. Kurtz. *Markov processes*. Wiley Series in Probability and Mathematical Statistics: Probability and Mathematical Statistics. John Wiley & Sons Inc., New York, 1986. ISBN 0-471-08186-8. Characterization and convergence.

C. W. Gardiner. *Handbook of stochastic methods for physics, chemistry and the natural sciences*, volume 13 of *Springer Series in Synergetics*. Springer-Verlag, Berlin, third edition, 2004. ISBN 3-540-20882-8.

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.

Hye-Won Kang. The multiple scaling approximation in the heat shock model of e. coli. In Preparation, 2009.

T. G. Kurtz. Limit theorems for sequences of jump Markov processes approximating ordinary differential processes. *J. Appl. Probability*, 8:344–356, 1971. ISSN 0021-9002.

Thomas G. Kurtz. Strong approximation theorems for density dependent Markov chains. *Stochastic Processes Appl.*, 6(3):223–240, 1977/78.

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.

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. ISSN 0022-5193.

N. G. van Kampen. *Stochastic processes in physics and chemistry*. North-Holland Publishing Co., Amsterdam, 1981. ISBN 0-444-86200-5. Lecture Notes in Mathematics, 888.

Abstract

Identifying separated time-scales in stochastic models of reaction networks

For chemical reaction networks in biological cells, 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 one or more complex reaction network models.

An outrageous claim

I taught Søren everything he needed to know. . .

about paddling a canoe in a straight line.