

# Identifying separated time scales in stochastic models of reaction networks

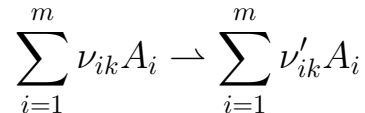
- Reaction networks
- Multiple scales
- Virus model
- Selecting scaling exponents
- General balance condition
- Heat shock model
- References
- Abstract

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



# Reaction networks

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



where the  $\nu_{ik}$  and  $\nu'_{ik}$  are nonnegative integers,  $\nu_{ik}$  is the number of molecules of  $A_i$  that are consumed by the  $k$ th reaction and  $\nu'_{ik}$  the number of molecules of  $A_i$  produced by the  $k$ th reaction.



# Markov chain models

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

$\nu_k$  number of molecules of each chemical species consumed in the  $k$ th reaction.

$\nu'_k$  number of molecules of each species created by the  $k$ th reaction.

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

If the  $k$ th reaction occurs at time  $t$ , the new state becomes

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

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

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

where the  $Y_k$  are independent unit Poisson processes.



# Equations for the system state

The state of the system satisfies

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

$\nu'$  is the matrix with columns given by the  $\nu'_k$ .

$\nu$  is the matrix with columns given by the  $\nu_k$ .

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



## Rates for the law of mass action

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

$$\lambda_k(x) = \kappa'_k x_1 x_2$$

For  $A_1 \rightarrow A_2$  or  $A_1 \rightarrow A_2 + A_3$ ,

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

For  $2A_1 \rightarrow A_2$ ,

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



# Heat shock model

The following reaction network is given as a model for the heat shock response in E. Coli by Srivastava, Peterson and Bently [5]

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



## 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  $N \rightarrow \infty$  (perhaps with a change of time scale) give approximate models. The challenge is to select the  $\alpha_i$ , but once that is done, the initial condition for index  $N$  is given 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  $\lim_{N \rightarrow \infty} Z_i^N(\cdot N^\gamma) = Z_i^\infty$ , then we should have

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



# 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  $\kappa_k$  so that

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



## General principles

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

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

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

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

or if

$$\beta_1 + \alpha_1 + \alpha_2 = \beta_2 + \alpha_3 + \alpha_5 > \alpha_3 \\ (Z_3^N(t) \approx \frac{\kappa_1 Z_1^N(t) Z_2^N(t)}{\kappa_2 Z_5^N(t)} ) .$$



## Species balance condition

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

**Condition 1** For each species  $A_i$ ,

$$\max_{k \in \Gamma_i^-} (\beta_k + \nu_k \cdot \alpha) = \max_{k \in \Gamma_i^+} (\beta_k + \nu_k \cdot \alpha). \quad (1)$$

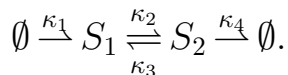
or

$$\max_{k \in \Gamma_i^+ \cup \Gamma_i^-} (\beta_k + \nu_k \cdot \alpha) + \gamma \leq \alpha_i. \quad (2)$$



## 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.



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

$$Z_1^N(t) = Z_1^N(0) + Y_1(\lambda_1 N^{\beta_1} t) + Y_3(\lambda_3 N^{\beta_3} \int_0^t Z_2^N(s) ds) - Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s) ds)$$

$$Z_2^N(t) = Z_2^N(0) + Y_2(\lambda_2 N^{\beta_2} \int_0^t Z_1^N(s) ds) - Y_3(\lambda_3 N^{\beta_3} \int_0^t Z_2^N(s) ds) \\ - Y_4(\lambda_4 N^{\beta_4} \int_0^t Z_2^N(s) ds)$$

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



## 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 2** For each subset  $G_0$  of an atom graph

$$\max_{k \in \Gamma_{G_0}^-} (\beta_k + \nu_k \cdot \alpha) = \max_{k \in \Gamma_{G_0}^+} (\beta_k + \nu_k \cdot \alpha) \quad (3)$$

or

$$\max_{k \in \Gamma_{G_0}^+ \cup \Gamma_{G_0}^-} (\beta_k + \nu_k \cdot \alpha) + \gamma \leq \max_{i \in G_0} \alpha_i. \quad (4)$$

Then (5) implies

$$\gamma \leq \min_G \min_{G_0 \subset G, G_0 \text{ unbalanced}} \left( \max_{i \in G_0} \alpha_i - \max_{k \in \Gamma_{G_0}^+ \cup \Gamma_{G_0}^-} (\beta_k + \nu_k \cdot \alpha) \right), \quad (5)$$

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

$$\emptyset \xrightarrow{\kappa_1} S_1 \xrightleftharpoons[\kappa_3]{\kappa_2} S_2,$$

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

### Balance conditions:

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

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  $\gamma = -\beta_1$ ,

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

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

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

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  $\gamma = -\beta_3$ ,

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

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

$\lambda_2 \int_0^t Z_1^N(sN^\gamma) ds \sim \lambda_1 t + \lambda_3 \int_0^t Z_2^N(sN^\gamma) ds$  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  $Z_2^N(tN^\gamma) \rightarrow \infty$  for each  $t > 0$ .



# Heat shock model

The following reaction network is given as a model for the heat shock response in E. Coli by Srivastava, Peterson and Bently [5]

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



# Exponents

$$\rho_1 = \beta_1$$

$$\rho_2 = \alpha_2 + \beta_2$$

$$\rho_3 = \alpha_3 + \beta_3$$

$$\rho_4 = \alpha_1 + \beta_4$$

$$\rho_5 = \alpha_3 + \beta_5$$

$$\rho_6 = \alpha_3 + \beta_6$$

$$\rho_7 = \alpha_3 + \beta_7$$

$$\rho_8 = \alpha_7 + \beta_8$$

$$\rho_9 = \alpha_2 + \alpha_6 + \beta_9$$

$$\rho_{10} = \alpha_6 + \alpha_8 + \beta_{10}$$

$$\rho_{11} = \alpha_8 + \beta_{11}$$

$$\rho_{12} = \alpha_9 + \beta_{12}$$

$$\rho_{13} = \beta_{13}$$

$$\rho_{14} = \alpha_1 + \beta_{14}$$

$$\rho_{15} = \alpha_4 + \alpha_7 + \beta_{15}$$

$$\rho_{16} = \alpha_5 + \beta_{16}$$

$$\rho_{17} = \alpha_6 + \beta_{17}$$

$$\rho_{18} = \alpha_4 + \beta_{18}$$



# Balance conditions

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



$$V_1^N(t) = V_1^N(0) + Y_{13} \left( \int_0^t \lambda_{13} N^{\gamma - \frac{5}{3}} ds \right) - Y_{14} \left( \int_0^t \lambda_{14} N^{\gamma - \frac{5}{3}} V_1^N(s) ds \right)$$

$$V_2^N(t) = V_2^N(0) + Y_3 \left( \int_0^t \lambda_3 N^\gamma V_3^N(s) ds \right) + Y_4 \left( \int_0^t \lambda_4 N^\gamma V_1^N(s) ds \right)$$

$$+ Y_5 \left( \int_0^t \lambda_5 N^{\gamma - \frac{2}{3}} V_3^N(s) ds \right) + Y_6 \left( \int_0^t \lambda_6 N^{\gamma - 1} V_3^N(s) ds \right)$$

$$+ Y_7 \left( \int_0^t \lambda_7 N^{\gamma - 1} V_3^N(s) ds \right) + Y_8 \left( \int_0^t \lambda_8 N^\gamma V_7^N(s) ds \right)$$

$$- Y_2 \left( \int_0^t \lambda_2 N^\gamma V_2^N(s) ds \right) - Y_9 \left( \int_0^t \lambda_9 N^\gamma V_2^N(s) V_6^N(s) ds \right)$$

$$V_3^N(t) = V_3^N(0) + Y_2 \left( \int_0^t \lambda_2 N^\gamma V_2^N(s) ds \right) - Y_3 \left( \int_0^t \lambda_3 N^\gamma V_3^N(s) ds \right)$$

$$- Y_5 \left( \int_0^t \lambda_5 N^{\gamma - \frac{2}{3}} V_3^N(s) ds \right) - Y_6 \left( \int_0^t \lambda_6 N^{\gamma - 1} V_3^N(s) ds \right) - Y_7 \left( \int_0^t \lambda_7 N^{\gamma - 1} V_3^N(s) ds \right)$$

$$V_4^N(t) = V_4^N(0) + N^{-\frac{2}{3}} Y_6 \left( \int_0^t \lambda_6 N^{\gamma - 1} V_3^N(s) ds \right) - N^{-\frac{2}{3}} Y_{18} \left( \int_0^t \lambda_{18} N^{\gamma - 1} V_4^N(s) ds \right)$$

$$V_5^N(t) = V_5^N(0) + N^{-1} Y_5 \left( \int_0^t \lambda_5 N^{\gamma - \frac{2}{3}} V_3^N(s) ds \right) - N^{-1} Y_{16} \left( \int_0^t \lambda_{16} N^{\gamma - \frac{2}{3}} V_5^N(s) ds \right)$$



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





$$\gamma = 0$$

$\alpha_1$	$\alpha_2$	$\alpha_3$	$\alpha_4$	$\alpha_5$	$\alpha_6$	$\alpha_7$	$\alpha_8$	$\alpha_9$
0	0	0	$\frac{2}{3}$	1	$\frac{5}{3}$	1	0	$\frac{5}{3}$

$$V_2(t) = V_2(0) + Y_3 \left( \int_0^t \lambda_3 V_3(s) ds \right) + Y_4 (\lambda_4 V_1(0) t) + Y_8 (\lambda_8 V_7(0) t) \\ - Y_2 \left( \int_0^t \lambda_2 V_2(s) ds \right) - Y_9 \left( \int_0^t \lambda_9 V_2(s) V_6(0) ds \right)$$

$$V_3(t) = V_3(0) + Y_2 \left( \int_0^t \lambda_2 V_2(s) ds \right) - Y_3 \left( \int_0^t \lambda_3 V_3(s) ds \right)$$

$$V_8(t) = V_8(0) + Y_1 (\lambda_1 t) + Y_{12} (\lambda_{12} V_9(0) t) - Y_{10} \left( \int_0^t \lambda_{10} V_6(0) V_8(s) ds \right)$$

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



$$\gamma = 1$$

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

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

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

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

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



$$\gamma = 5/3$$

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

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

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

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

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

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

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

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

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



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

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

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

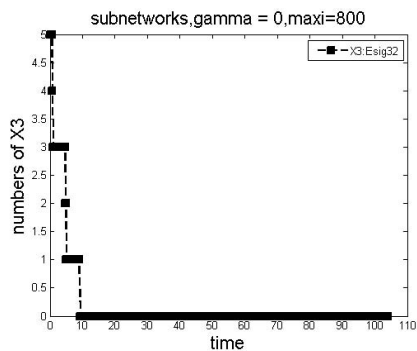
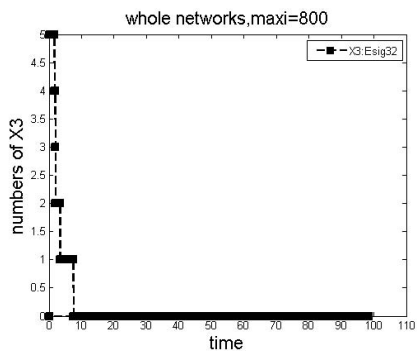
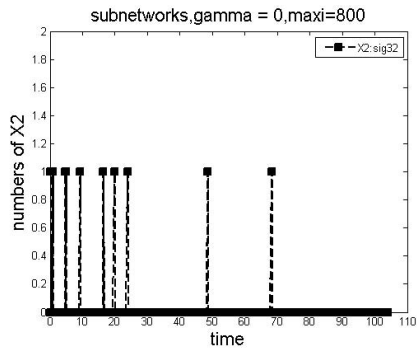
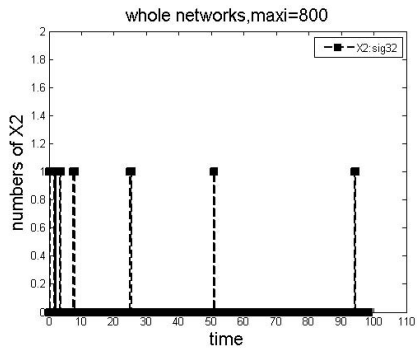
$$V_6(t) = V_6(0) - \int_0^t [\lambda_{17} V_6(s) + \lambda_1] ds$$

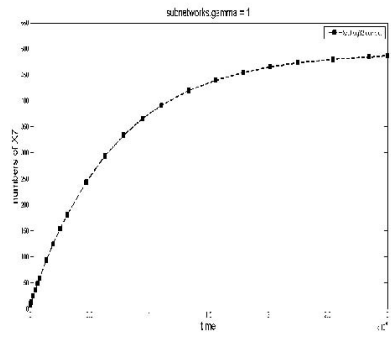
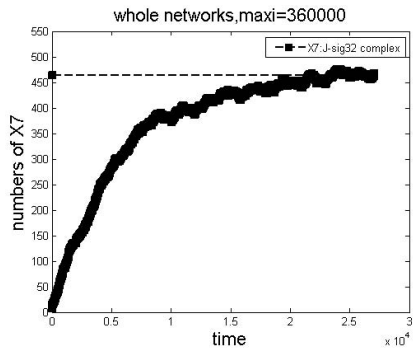
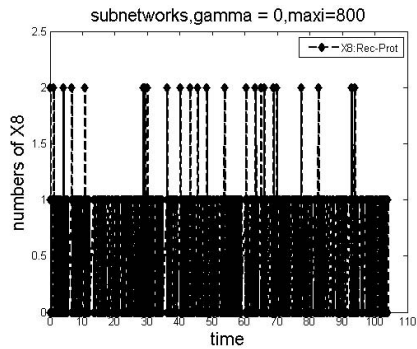
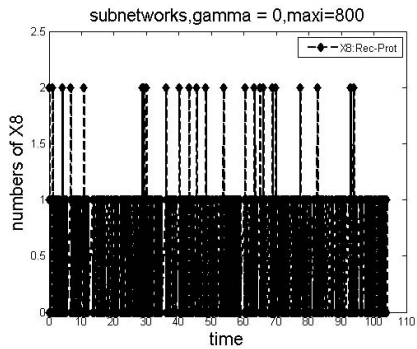
$$V_9(t) = V_9(0) + \lambda_1 t$$

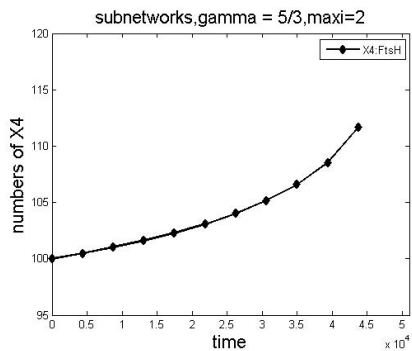
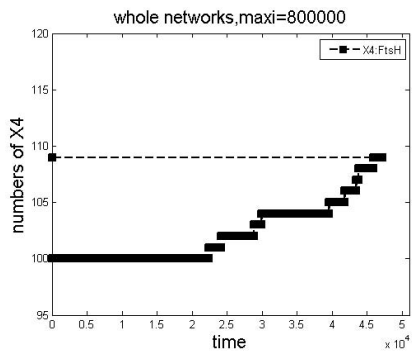
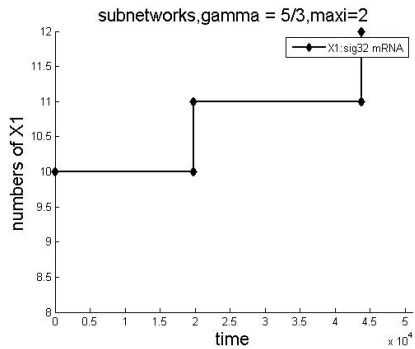
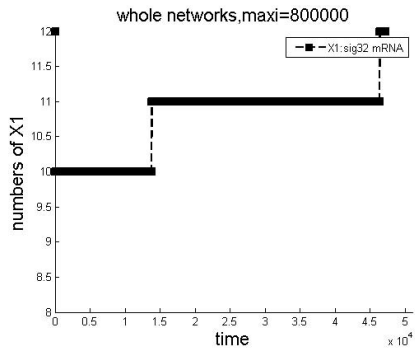
$$\bar{V}_3(s) = \frac{\lambda_2}{\lambda_3} \bar{V}_2(s) = \frac{\lambda_2}{\lambda_3} \frac{\lambda_4 V_1(s) + \lambda_8 V_7(s)}{\lambda_9 V_6(s)}$$

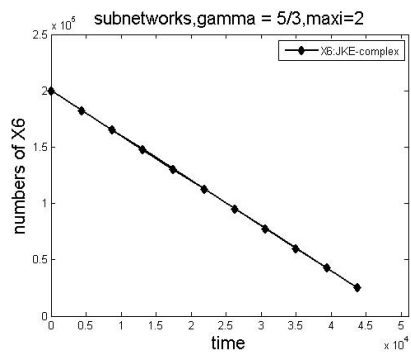
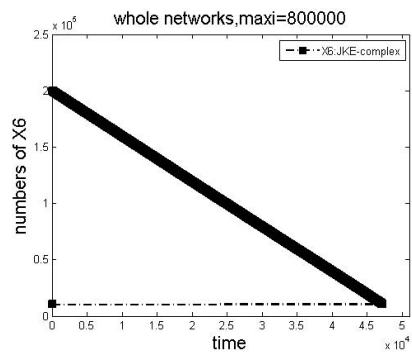
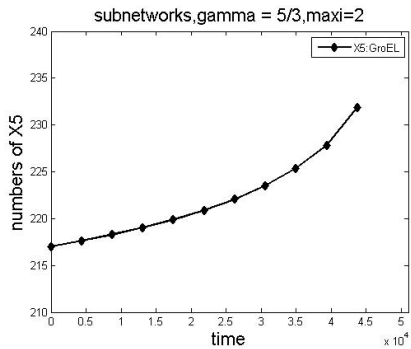
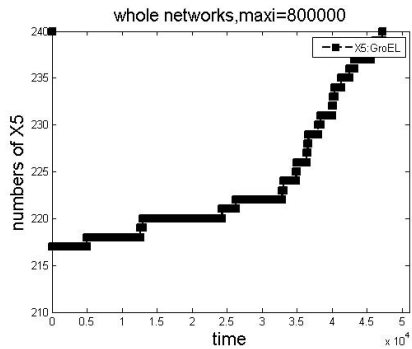
$$V_7(s) = \frac{\lambda_4 V_1(s)}{\lambda_{15} V_4(s)}$$



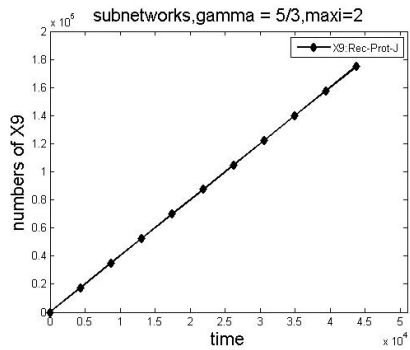
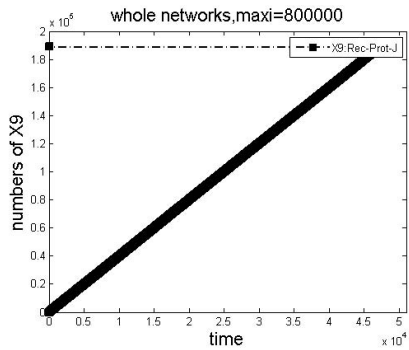












## References

- [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*.

