Multiscale methods in a Heat Shock Response Model

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Outline

- Multiscale Methods
- Time Change Equation
- Law of Mass Action
- Species Balance
- Description of Heat Shock Model
- An Example with 3 time scales and Simulation results

Multiscale Methods

- N : a scaling parameter(order of magnitude of the abundance of the most abundant species in the system); N_0 is a real scaling parameter.
- $X_i(t)$: the ith component of $X(t)$ representing the number of molecules of ith species at time t. $X(t)$ is a state vector which is a **continuous-time Markov jump process**.
- Time Change Equation: the state of the system satisfies

$$X(t) = X(0) + \sum_k Y_k\Big(\int_0^t \Lambda_k(X(s))\,ds\Big)(\nu_k' - \nu_k)$$

  where Λ_k is the kth reaction rate and Y_k is a unit Poisson process.
- $V_i(t) = N^{-\alpha_i} X_i(N^{\gamma} t)$: the number of ith species after normalization and time change; α_i is selected so that $V_i = O(1)$ and γ is a time change parameter.
- $\kappa_k = N_0^{\beta_k} \lambda_k$: an original stochastic rate constant of kth reaction. A reaction constant κ_k is scaled by N^{β_k} so that $\lambda_k = O(1)$.

$$X_i(t) \approx N_0^{\alpha_i} V_i(N_0^{-\gamma} t)$$

After normalization and time change

- The system state equation

$$V_i^N(t) = V_i^N(0) + N^{-\alpha_i} \sum_k Y_k\left(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k} \Lambda_k'(V^N(s))\, ds\right)(\nu_{ik}' - \nu_{ik})$$

  where $\nu_k(\nu_k')$ is the number of molecules of each species consumed(created) in the kth reaction.

- **Law of mass action**: For a binary reaction $A_1 + A_2 \to A_3$ or $A_1 + A_2 \to A_3 + A_4$,

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

  For $A_1 \to A_2$ or $A_1 \to A_2 + A_3$, $\Lambda_k(x) = \kappa_k x_1$. For $2A_1 \to A_2$, $\Lambda_k(x) = \kappa_k x_1(x_1 - 1)$.
  For a binary reaction $A_1 + A_2 \to A_3$ the rate should vary inversely with volume, so it would better to write

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

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

$$\Lambda_k^N(x) = \kappa_k x_1 = N\kappa_k z_1$$

- **Goal: To make each species balanced after the normalization. i.e. $V_i^N(t) \approx O(1)$, To divide the system into several subsystems.**
- Rule: **Species Balance**
  "Maximal order of input rate = Maximal order of output rate"

$$\max_{\{k:\nu'_{ik}-\nu_{ik}>0\}} (\gamma + \alpha \cdot \nu_k + \beta_k) = \max_{\{k:\nu'_{ik}-\nu_{ik}<0\}} (\gamma + \alpha \cdot \nu_k + \beta_k)$$

$$\max_{\{k:\nu'_{ik}-\nu_{ik}\neq 0\}} (\gamma + \alpha \cdot \nu_k + \beta_k) \leq \alpha_i$$

Heat Shock Model

- Heat Shock Model: 9 species and 18 reactions.

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

Solution set of species balance by Maple

- Solution sets

Equalities
$\alpha_1 = \beta_{13} - \beta_{14}$
$\alpha_2 - \alpha_4 = -\beta_2 + \beta_3 - \beta_6 + \beta_{18}$
$\alpha_3 - \alpha_4 = -\beta_6 + \beta_{18}$
$\alpha_5 - \alpha_4 = \beta_5 - \beta_6 - \beta_{16} + \beta_{18}$
$\alpha_6 + \alpha_8 = \beta_1 - \beta_{10}$
$\alpha_7 - \alpha_4 + \alpha_8 = \beta_1 - \beta_2 + \beta_3 - \beta_6 - \beta_8 + \beta_9 - \beta_{10} + \beta_{18}$
$\alpha_9 = \beta_1 - \beta_{12}$
Inequalities
$\beta_1 - \beta_2 + \beta_9 - \beta_{10} \leq \alpha_8 \leq \beta_1 - \beta_2 + \beta_3 - \beta_7 + \beta_9 - \beta_{10}$
$-\beta_3 + \beta_4 + \beta_6 + \beta_{13} - \beta_{14} - \beta_{18} \leq \alpha_4 \leq \beta_8 - \beta_{15}$
$\beta_2 - \beta_3 + \beta_6 - \beta_9 + \beta_{10} - \beta_{18} \leq \alpha_4 - \alpha_8 \leq -\beta_1 + \beta_2 + \beta_8 - \beta_9 + \beta_{10} - \beta_{15}$
$\beta_3 \geq \beta_7,\ \beta_3 \geq \beta_6,\ -\beta_3 + \beta_5 - \beta_6 + \beta_{16} \leq 0$

- Initial values

$X_1(0)$	$X_2(0)$	$X_3(0)$	$X_4(0)$	$X_5(0)$	$X_6(0)$	$X_7(0)$	$X_8(0)$	$X_9(0)$
10	1	5	100	217	200000	7	1	0

Example with the species balance

- A real scaling parameter $N_0 = 10^3$
- Specific values of α_i's and β_k's

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	$\frac{5}{3}$

	β_k	Stoch Rate(κ_k)	λ_k		β_k	Stoch Rate(κ_k)	λ_k
β_1	0	4.00×10^{0}	4	β_{10}^*	$-\frac{5}{3}$	3.62×10^{-4}	36.2
β_2	0	7.00×10^{-1}	0.7	β_{11}	$-\frac{5}{3}$	9.99×10^{-5}	9.99
β_3	0	1.30×10^{-1}	0.13	β_{12}	$-\frac{5}{3}$	4.40×10^{-5}	4.4
β_4	0	7.00×10^{-3}	0.007	β_{13}	$-\frac{5}{3}$	1.40×10^{-5}	1.4
β_5^*	$-\frac{2}{3}$	6.30×10^{-3}	0.63	β_{14}	$-\frac{5}{3}$	1.40×10^{-6}	0.14
β_6^*	-1	4.88×10^{-3}	4.88	β_{15}^*	$-\frac{5}{3}$	1.42×10^{-6}	0.142
β_7^*	-1	4.88×10^{-3}	4.88	β_{16}	$-\frac{5}{3}$	1.80×10^{-8}	0.0018
β_8	-1	4.40×10^{-4}	0.44	β_{17}	$-\frac{5}{3}$	6.40×10^{-10}	0.000064
β_9^*	$-\frac{5}{3}$	3.62×10^{-4}	36.2	β_{18}	$-\frac{5}{3}$	7.40×10^{-11}	0.0000074

- Simulation: Using the Gillespie's Stochastic Simulation Algorithm.

When $\gamma = 0$ (Slow time scale)

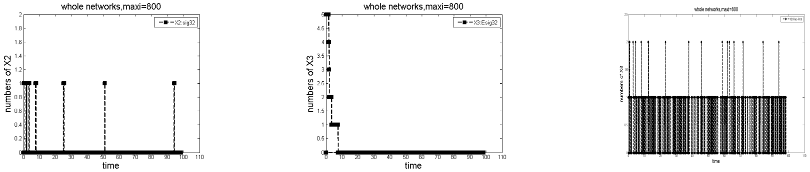
- Identify the fast processes

$$
\begin{aligned}
V_2(t) &= V_2(0) + Y_3\left(\int_0^t \lambda_3 V_3(s)\,ds\right) + Y_4\left(\int_0^t \lambda_4 V_1(s)\,ds\right) + Y_8\left(\int_0^t \lambda_8 V_7(s)\,ds\right) \\
&\quad - Y_2\left(\int_0^t \lambda_2 V_2(s)\,ds\right) - Y_9\left(\int_0^t \lambda_9 V_2(s) V_6(s)\,ds\right) \\
V_3(t) &= V_3(0) + Y_2\left(\int_0^t \lambda_2 V_2(s)\,ds\right) - Y_3\left(\int_0^t \lambda_3 V_3(s)\,ds\right) \\
V_8(t) &= V_8(0) + Y_1\left(\int_0^t \lambda_1\,ds\right) + Y_{12}\left(\int_0^t \lambda_{12} V_9(s)\,ds\right) - Y_{10}\left(\int_0^t \lambda_{10} V_6(s) V_8(s)\,ds\right) \\
V_1(t) &= V_1(0),\ V_4(t) = V_4(0),\ V_5(t) = V_5(0),\ V_6(t) = V_6(0) \\
V_7(t) &= V_7(0),\ V_9(t) = V_9(0)
\end{aligned}
$$

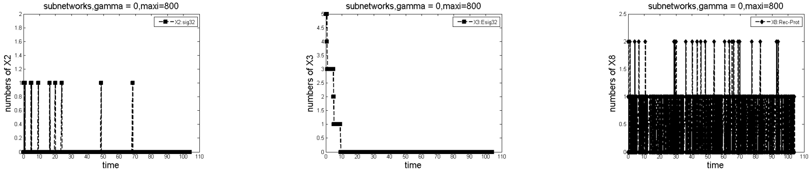
- The system is 3 dimensional stochastic equations. A fixed point gives a stationary distribution for V_2, V_3, and V_8 in terms of V_1, V_6, V_7, and V_9. These 3 equations are linear in V_2, V_3, and V_8, so we get independent Poisson distributions for the stationary distribution.

When $\gamma = 0$ (Slow time scale)

Original X_2 X_3 X_8



Reduced

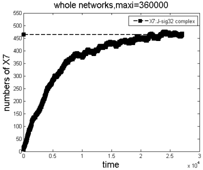


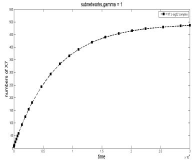
When $\gamma = 1$ (medium time scale)

- V_7 is expressed as an ODE with slow variables. We can get $\bar{V}_2$, $\bar{V}_3$ and $\bar{V}_8$, means for the Poisson processes in the previous time scale, in terms of V_7 and constants.

$$
\begin{aligned}
V_7(t) &= V_7(0) + \int_0^t [\lambda_4 V_1(s) - \lambda_{15} V_4(s) V_7(s)]\, ds \\
\bar{V}_2(s) &= \frac{\lambda_4 V_1(s) + \lambda_8 V_7(s)}{\lambda_9 V_6(s)} \\
\bar{V}_3(s) &= \frac{\lambda_2(\lambda_4 V_1(s) + \lambda_8 V_7(s))}{\lambda_3 \lambda_9 V_6(s)} \\
\bar{V}_8(s) &= \frac{\lambda_1 + \lambda_{12} V_9(s)}{\lambda_{10} V_6(s)} \\
V_1(t) &= V_1(0),\ V_4(t) = V_4(0),\ V_5(t) = V_5(0),\ V_6(t) = V_6(0),\ V_9(t) = V_9(0)
\end{aligned}
$$

X_7 original reduced





When $\gamma = \frac{5}{3}$ (Fast time scale)

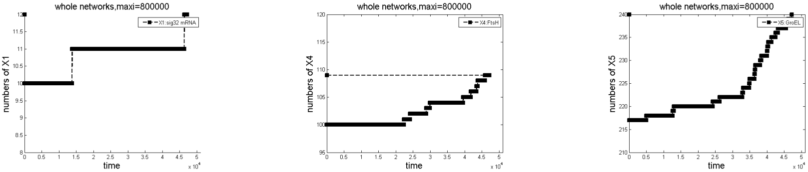
- Identify the slow processes

$$
\begin{aligned}
V_1(t) &= V_1(0) + Y_{13}\Big(\int_0^t \lambda_{13}\, ds\Big) - Y_{14}\Big(\int_0^t \lambda_{14} V_1(s)\, ds\Big) \\
V_4(t) &= V_4(0) + \int_0^t [\lambda_6 \bar{V}_3(s) - \lambda_{18} V_4(s)]\, ds \\
V_5(t) &= V_5(0) + \int_0^t [\lambda_5 \bar{V}_3(s) - \lambda_{16} V_5(s)]\, ds \\
V_6(t) &= V_6(0) + \int_0^t [-\lambda_1 - \lambda_{17} V_6(s)]\, ds \\
V_9(t) &= V_9(0) + \int_0^t \lambda_1\, ds \\
\bar{V}_2(s) &= \frac{\lambda_4 V_1(s)}{\lambda_9 V_6(s)}\Big(1 + \frac{\lambda_8}{\lambda_{15} V_4(s)}\Big), \qquad \bar{V}_3(s) = \frac{\lambda_2 \lambda_4 V_1(s)}{\lambda_3 \lambda_9 V_6(s)}\Big(1 + \frac{\lambda_8}{\lambda_{15} V_4(s)}\Big) \\
V_7(s) &= \frac{\lambda_4 V_1(s)}{\lambda_{15} V_4(s)}, \qquad \bar{V}_8(s) = \frac{\lambda_1 + \lambda_{12} V_9(s)}{\lambda_{10} V_6(s)}
\end{aligned}
$$

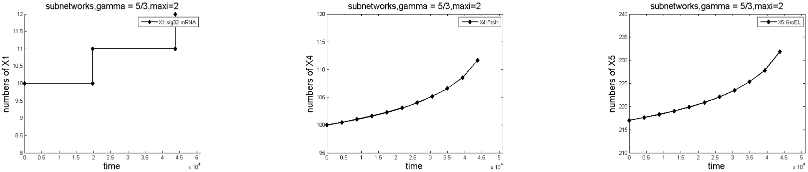
- Since V_1 has constant input and linear output, its stationary distribution is a Poisson distribution. The system of ordinary differential equation include $\bar{V}_3$ term. First, we can get V_7 in terms of V_1 and V_4. Then, we will use this to get $\bar{V}_2$, $\bar{V}_3$ and $\bar{V}_8$.

When $\gamma = \frac{5}{3}$ (Fast time scale)

original X_1 X_4 X_5

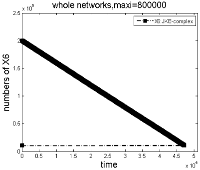


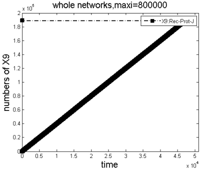
reducued



When $\gamma = \frac{5}{3}$ (Fast time scale)

original X_6 X_9





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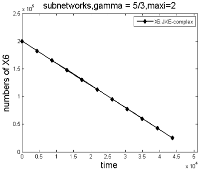

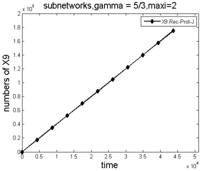

Reference

- Thomas G.Kurtz, *Markov Processes - Characterization and Convergence*
- Thomas G.Kurtz, Karen Ball, Lea Popovic, and Greg Rempala, *Asymptotic analysis of multiscale approximations to reaction networks*, Annal of Applied Probabability 16 (2006), 1925-1961.
- R.Srivastava, M.S.Peterson, and W.E.Bentley, *Stochastic Kinetic Analysis of the Escherichia coli Stress Circuit Using σ^{32}-Targeted Antisense*, Biotechnology and Bioengineering 75(1) (2001), 120-129
- Daniel T. Gillespie, *Exact Stochastic Simulation of Coupled Chemical Reactions*, The Journal of Physical Chemistry, Vol. 81, No. 25, 1977
- Thomas G.Kurtz, *Talk in SIAM Conference on Applications of Dynamical Systems*