Analyzing stochastic models

Bilingual dictionary

Chemistry	Probability
propensity	intensity
master equation	forward equation
Langevin approximation	diffusion approximation
Van Kampen approximation	central limit theorem
quasi steady state/partial equilibrium	averaging

Intensities for continuous-time Markov chains

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

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

A Poisson process is counting process with stationary independent increments

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

If Y is a unit Poisson process (that is, $\lambda = 1$), then $Y(\lambda \cdot)$ is Poisson with intensity λ.

The forward/master equation

Setting $p_k(t) = P\{X(t) = k\}$,

$$\dot{p}_k(t) = \sum_l p_{k-l}(t)\beta_l(k-l) - p_k(t)\sum_l \beta_l(k)$$

gives the forward equation (the *master equation* in the chemical literature).

Time change equation

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

where $N_l(t)$ is the number of jumps of l at or before time t. N_l is a counting process with intensity (*propensity*) $\beta_l(X(t))$. Consequently, we can write

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

where the Y_l are independent, unit Poisson processes, and

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

Random jump equation

Alternatively, setting $\bar{\beta}(k) = \sum_l \beta_l(k)$,

$$N(t) = Y(\int_0^t \bar{\beta}(X(s))ds)$$

and

$$X(t) = X(0) + \int_0^t F(X(s-), \xi_{N(s-)})dN(s)$$

where Y is a unit Poisson process, $\{\xi_i\}$ are iid uniform $[0, 1]$, and

$$P\{F(k, \xi) = l\} = \frac{\beta_l(k)}{\bar{\beta}(k)}.$$

Connections to simulation schemes

Simulating the random-jump equation gives Gillespie's [5, 6] *direct method* (the *stochastic simulation algorithm* SSA).

Simulating the time-change equation gives the *next reaction* (next jump) method as defined by Gibson and Bruck [4].

For $0 = \tau_0 < \tau_1 < \cdots$,

$$\hat{X}(t) = X(0) + \sum_l l Y_l \left(\sum_{k=0}^{m-1} \beta_l(\hat{X}(\tau_k))(\tau_{k+1} - \tau_k) \right), \quad \tau_m \le t < \tau_{m+1}$$

gives Gillespie's [7] τ-leap method

See, for example, Arnab Ganguly's poster for further discussion of τ-leaping. Cipcigan and Rathinam's poster addresses related problems of accelerating simulations.

Application of the LLN and CLT

Theorem 1 *If Y is a unit Poisson process, then for each $u_0 > 0$,*

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

The central limit theorem suggests that for large K

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

where W is *standard Brownian motion.* More precisely, W can be constructed so that

$$\left|\frac{Y(Ku)}{K} - (u + \frac{1}{K} W(Ku))\right| \le \Gamma \frac{\log(Ku+2)}{K}$$

for a random variable Γ independent of u and K.

Reaction networks

Standard notation for chemical reactions

$$A + B \overset{\kappa}{\rightharpoonup} C$$

is interpreted as "a molecule of A combines with a molecule of B to give a molecule of C.

$$A + B \rightleftharpoons C$$

means that the reaction can go in either direction, that is, a molecule of C can dissociate into a molecule of A and a molecule of B

We consider a *network* of reactions involving m chemical species, $S_1, \ldots, S_m$.

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

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

Markov chain models

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

ν_k number of molecules of each chemical species consumed in the kth reaction.

ν'_k number of molecules of each species created by the kth reaction.

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

If the kth reaction occurs at time t, the new state becomes

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

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

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

where the Y_k are independent unit Poisson processes.

Equations for the system state

The state of the system satisfies

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

ν' is the matrix with columns given by the ν'_k.

ν is the matrix with columns given by the ν_k.

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

Rates for the law of mass action

For a binary reaction $S_1 + S_2 \rightharpoonup S_3$ 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 $\kappa_k' = \kappa_k N_0^{\beta_k}$, so for a binary reaction

$$\kappa_k' x_i x_j = N_0^{\beta_k + \alpha_i + \alpha_j} \kappa_k z_i z_j = N_0^{\beta_k + \nu_k \cdot \alpha} \kappa_k z_i z_j$$

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

$$Z_i^N(0) = N_0^{-\alpha_i} X_i(0),$$

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

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

A model of intracellular viral infection

Srivastava, You, Summers, and Yin [10], Haseltine and Rawlings [8], Ball, Kurtz, Popovic, and Rempala [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

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

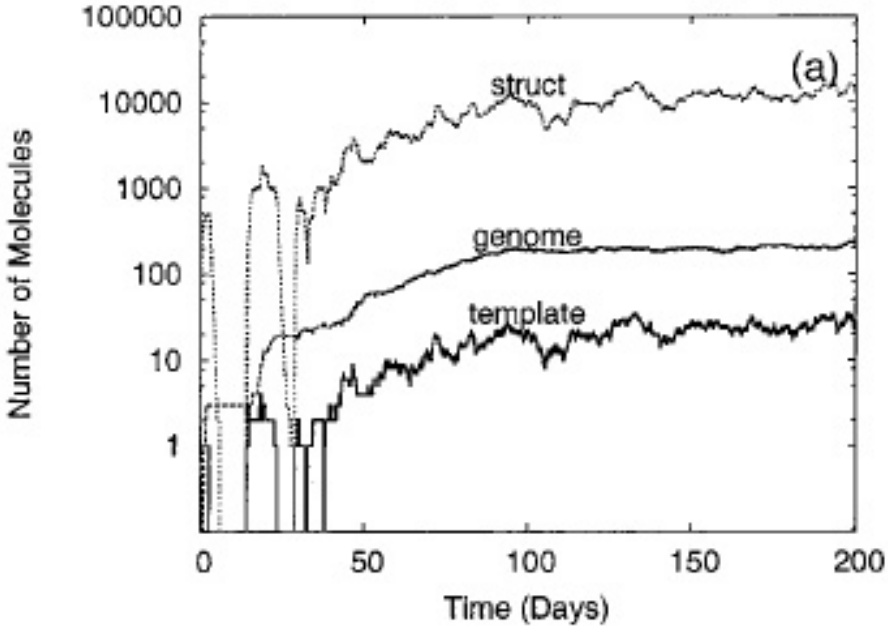


Figure 1: Simulation (Haseltine and Rawlings 2002)

Scaling parameters

For $N_0 = 1000$, $X_1 = O(N_0^0)$, $X_2 = O(N_0^{2/3})$, and $X_3 = O(N_0)$, that is $\alpha_1 = 0$, $\alpha_2 = 2/3$, $\alpha_3 = 1$.

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}	$.75N_0^{-5/3}$

That is, $\beta_1 = \beta_4 = \beta_5 = 0$, $\beta_2 = -2/3$, $\beta_3 = 1$, $\beta_6 = -5/3$.

Normalized system

With the scaled rate constants, we have

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

Limiting system

For $\gamma = 0$, the system converges to

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

Fast time scale

When $\tau_\epsilon^N = \inf\{t : Z_2^N(t) \geq \epsilon\} < \infty$, define $V_i^N(t) = Z_i(\tau_\epsilon^N + N^{2/3}t)$. On the event $\tau_\epsilon^N < \infty$,

$$V_1^N(t) = Z_1(\tau_\epsilon^N) + Y_b^*\left(\int_0^t 2.5N^{2/3}V_2^N(s)ds\right) - Y_d^*\left(\int_0^t .25N^{2/3}V_1^N(s)ds\right)$$

$$\begin{aligned} V_2^N(t) &= \frac{\lceil \epsilon N^{2/3} \rceil}{N^{2/3}} + N^{-2/3}Y_a^*\left(\int_0^t N^{2/3}V_1^N(s)ds\right) \\ &\quad - N^{-2/3}Y_b^*\left(\int_0^t 2.5N^{2/3}V_2^N(s)ds\right) \\ &\quad - N^{-2/3}Y_f^*\left(N^{2/3}\int_0^t .75V_2^N(s)V_3^N(s)ds\right) \end{aligned}$$

$$\begin{aligned} V_3^N(t) &= Z_3(\tau_\epsilon^N) + N^{-1}Y_c^*\left(\int_0^t N^{5/3}V_1^N(s)ds\right) - N^{-1}Y_e^*\left(\int_0^t 2N^{5/3}V_3^N(s)ds\right) \\ &\quad - N^{-1}Y_f^*\left(\int_0^t .75N^{2/3}V_2^N(s)V_3^N(s)ds\right) \end{aligned}$$

Averaging

As $N \to \infty$, dividing the equations for V_1^N and V_3^N by $N^{2/3}$ shows that

$$\int_0^t V_1^N(s)ds - 10\int_0^t V_2^N(s)ds \to 0$$
$$\int_0^t V_3^N(s)ds - 5\int_0^t V_2^N(s)ds \to 0.$$

The assertion for V_3^N and the fact that V_2^N is asymptotically regular imply

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

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

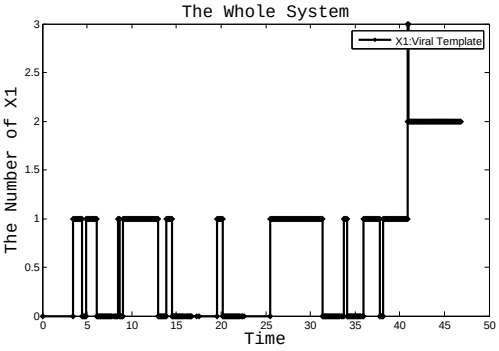
Law of large numbers

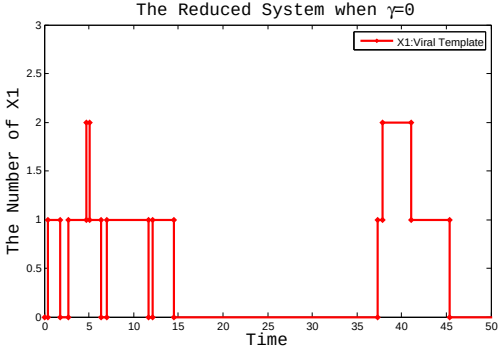
Theorem 2 *Conditioning on* $\tau_\epsilon^N < \infty$, *for each* $\delta > 0$ *and* $t > 0$,

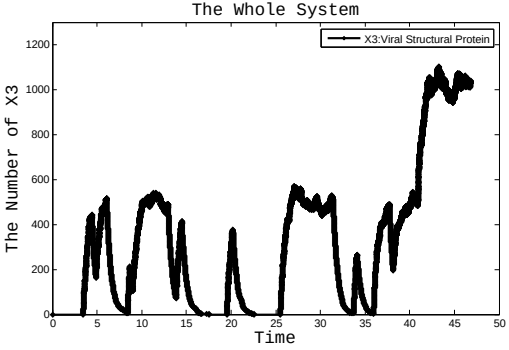
$$\lim_{N\to\infty} P\{\sup_{0\le s\le t} |V_2^N(s) - V_2(s)| \ge \delta\} = 0,$$

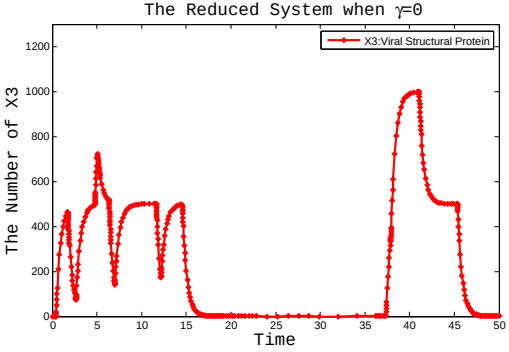
where V_2 *is the solution of*

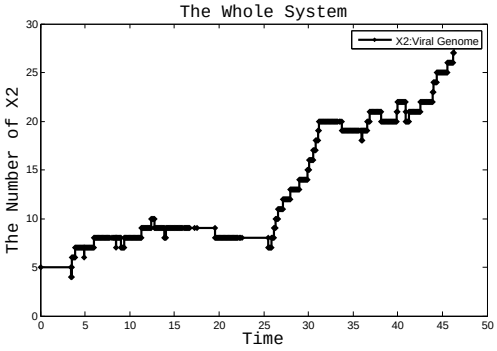
$$V_2(t) = \epsilon + \int_0^t 7.5V_2(s)ds) - \int_0^t 3.75V_2(s)^2 ds. \tag{1}$$

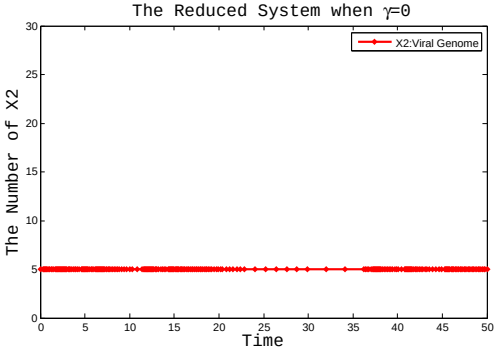

The Whole System
X1:Viral Template
The Number of X1
Time

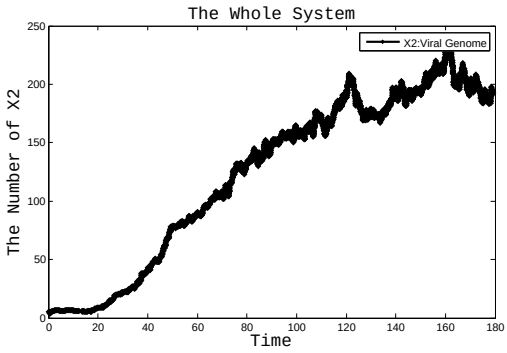

The Reduced System when γ=0
X1:Viral Template
The Number of X1
Time

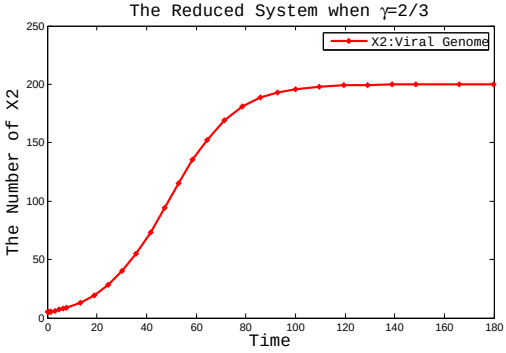

The Whole System
X3:Viral Structural Protein
The Number of X3
Time


The Reduced System when γ=0
X3:Viral Structural Protein
The Number of X3
Time


The Whole System
X2:Viral Genome
The Number of X2
Time
0
5
10
15
20
25
30
35
40
45
50


The Reduced System when γ=0
X2:Viral Genome
The Number of X2
Time
0
5
10
15
20
25
30
35
40
45
50


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

Models with delay

$$
\begin{aligned}
X_1(t) &= X_1(0) + Y_b\Big(\int_0^t \kappa_2' X_2(s-d_1)ds\Big) - Y_d\Big(\int_0^t \kappa_4' X_1(s)ds\Big) \\
X_2(t) &= X_2(0) + Y_a\Big(\int_0^t \kappa_1' X_1(s-d_2)ds\Big) - Y_b\Big(\int_0^t \kappa_2' X_2(s)ds\Big) \\
&\qquad - Y_f\Big(\int_0^t \kappa_6' X_2(s)X_3(s)ds\Big) \\
X_3(t) &= X_3(0) + Y_c\Big(\int_0^t \kappa_3' X_1(s)ds\Big) - Y_e\Big(\int_0^t \kappa_5' X_3(s)ds\Big) \\
&\qquad - Y_f\Big(\int_0^t \kappa_6' X_2(s)X_3(s)ds\Big)
\end{aligned}
$$

cf. posters by Arnab Ganguly and Rishi Srivastava

Determining the scaling exponents

Suppose that the rate constants satisfy

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

Then it seems natural to select

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

and define κ_k so that

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

General principles

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

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

or scaling time

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

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

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

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

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

Species balance condition

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

Condition 3 *For each species A_i,*

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

or

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

General balance condition

Even if the species rates are balanced, 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.

Condition 4 *For each subset G_0 of an atom graph*

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

or

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

Then (5) implies

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

where the minimum is over all G_0 for which (4) is not satisfied.

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 [9]

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 conditions

$$
\begin{array}{lrcl}
\{S_1\} & \rho_{13} & = & \rho_{14} \\
\{S_2\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7, \rho_8\} & = & \rho_2 \vee \rho_9 \\
\{S_3\} & \rho_2 & = & \max\{\rho_3, \rho_5, \rho_6, \rho_7\} \\
\{S_4\} & \rho_6 & = & \rho_{18} \\
\{S_5\} & \rho_5 & = & \rho_{16} \\
\{S_6\} & \max\{\rho_7, \rho_8, \rho_{12}, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{S_7\} & \rho_9 & = & \rho_8 \vee \rho_{15} \\
\{S_8\} & \rho_1 \vee \rho_{12} & = & \rho_{10} \vee \rho_{11} \\
\{S_9\} & \rho_{10} & = & \rho_{12} \\
\{S_2, S_3, S_7\} & \rho_4 & = & \rho_{15} \\
\{S_2, S_3\} & \rho_4 \vee \rho_8 & = & \rho_9 \\
\{S_2, S_7\} & \max\{\rho_3, \rho_4, \rho_5, \rho_6, \rho_7\} & = & \rho_2 \vee \rho_{15} \\
\{S_6, S_7, S_9\} & \rho_7 & = & \rho_{17} \\
\{S_6, S_9\} & \max\{\rho_7, \rho_8, \rho_{15}\} & = & \rho_9 \vee \rho_{17} \\
\{S_6, S_7\} & \rho_7 \vee \rho_{12} & = & \rho_{17} \vee \rho_{10} \\
\{S_8, S_9\} & \rho_1 & = & \rho_{17}
\end{array}
$$

See Hye-Won Kang's poster

An enzyme reaction model

$$A + E \rightleftharpoons AE \rightharpoonup B + E \qquad E \rightleftharpoons F + G \qquad \emptyset \rightharpoonup G \to \emptyset$$

$$\begin{aligned}
Z_A^N(t) &= Z_A^N(0) - N^{-1}Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds + N^{-1}Y_2(N\int_0^t \kappa_2 X_{AE}^N(s)ds) \\
X_E^N(t) &= X_E^N(0) - Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds + Y_2(N\int_0^t \kappa_2 X_{AE}^N(s)ds) \\
&\quad + Y_3(N\int_0^t \kappa_3 X_{AE}^N(s)ds + Y_4(N\int_0^t \kappa_4 X_F^N(s)X_G^N(s))ds - Y_5(N\int_0^t \kappa_5 X_E^N(s)ds) \\
X_F^N(t) &= X_F^N(0) + Y_5(N\int_0^t \kappa_5 X_E^N(s)ds) - Y_4(N\int_0^t \kappa_4 X_F^N(s)X_G^N(s))ds) \\
X_G^N(t) &= X_G^N(0) + Y_6(N\kappa_6 t) + Y_5(N\int_0^t \kappa_5 X_E^N(s)ds) - Y_4(N\int_0^t \kappa_4 X_F^N(s)X_G^N(s))ds) \\
&\quad - Y_7(N\int_0^t \kappa_7 X_G(s)ds)
\end{aligned}$$

$M = X_E^N + X_{AE}^N + X_F^N$ is conserved.

Stationary expectations for fast process

Need the stationary expectations for the fast subsystem

$$\begin{aligned} -(\kappa_1 z + \kappa_5)E[X_E] + (\kappa_2 + \kappa_3)E[X_{AE}] + \kappa_4 E[X_F X_G] &= 0 \\ \kappa_5 E[X_E] - \kappa_4 E[X_F X_G] &= 0 \\ \kappa_6 + \kappa_5 E[X_E] - \kappa_4 E[X_F X_G] - \kappa_7 E[X_G] &= 0 \\ E[X_E] + E[X_{AE}] + E[X_F] &= M \end{aligned}$$

The system is not closed, so we need a better understanding of the stationary distribution of the fast process. One approach, suggested by E, Liu, and Vanden-Eijnden [2, 3], would be to estimate $E[X_F X_G]$ by a small scale simulation.

The fast subnetwork

$$E \rightleftharpoons AE \qquad E \rightleftharpoons F + G \qquad \emptyset \rightharpoonup G \to \emptyset$$

is a *weakly reversible, zero deficiency* network.

See David Anderson's poster

The network has a *product form* stationary distribution and

$$E[X_F X_G] = E[X_F]E[X_G]$$

so

$$E[X_E] = \frac{\kappa_4\kappa_6 M}{\kappa_5\kappa_7 + \kappa_4\kappa_6 + \frac{\kappa_1\kappa_4\kappa_6 z}{\kappa_2+\kappa_3}}.$$

and Z_A^N converges to the solution of

$$Z_A(t) = Z_A(0) - \int_0^t \frac{\kappa_3\kappa_1\kappa_4\kappa_6 M Z_A(s)}{(\kappa_2+\kappa_3)(\kappa_5\kappa_7+\kappa_4\kappa_6) + \kappa_1\kappa_4\kappa_6 Z_A(s)} ds.$$

Focused Research Group on Stochastic Models for Intracelluar Reaction Networks

Faculty

- George Craciun
- Tom Kurtz
- Lea Popovic
- Greg Rempala
- John Yin

Postdoctoral Researchers

- David Anderson
- Anil Devarapu

Graduate Students

- Arnab Ganguly
- Hye-Won Kang
- Casian Pantea
- Ying Zhu

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Abstract

Analyzing stochastic models

Classical stochastic models for chemical reaction networks are given by continuous time Markov chains. Methods for characterizing these models will be reviewed focusing primarily on obtaining the models as solutions of stochastic equations. The relationship between these equations and standard simulation methods will be described. The primary focus of the talk will be on employing stochastic analytic methods for these equations to understand the multiscale nature of complex networks and to exploit the multiscale properties to simplify the network models.