Averaging fast subsystems in chemical network models

See References, in particular Anderson and Kurtz (2015).

Markov chains

Infinitesimal specification of a Markov chain:

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

Generator:

$$Af(x) = \sum_k \beta_k(x)(f(x+\zeta_k) - f(x))$$

(For simplicity assume only finitely many possible jumps ζ_k.)

$$X(t) = X(0) + \sum_k R_k(t)\zeta_k,$$

R_k a counting process counting the times X takes jump ζ_k.

$$P\{R_k(t+\Delta t) - R_k(t) = 1 | \mathcal{F}_t^X\} \approx \beta_k(X(t))\Delta t.$$

For independent unit Poisson processes Y_k, we should have

$$X(t) = X(0) + \sum_k Y_k(\int_0^t \beta_k(X(s))ds)\zeta_k$$

Chemical networks

Modeling counts of individual chemical species: $X(t)$ will be the vector whose components give the numbers of molecules of each chemical species.

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

$$\lambda_k(x) = \kappa_k' x_1 x_2 \qquad \zeta_k = \nu_k' - \nu_k = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} - \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix} \text{ or } \begin{pmatrix} -1 \\ -1 \\ 1 \\ 1 \end{pmatrix}$$

where ν_k is the vector giving the numbers of molecules consumed and ν_k' gives the numbers produced. For $S_1 \rightharpoonup S_2$ or $S_1 \rightharpoonup S_2 + S_3$,

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

For $2S_1 \rightharpoonup S_2$,

$$\lambda_k(x) = \kappa_k' x_1(x_1 - 1) \qquad \zeta_k = \begin{pmatrix} -2 \\ 1 \end{pmatrix}$$

Enzyme reaction

$$A + E \rightleftharpoons AE \rightharpoonup E + B$$

$$\begin{aligned} X_E(t) &= X_E(0) - Y_1\left(\int_0^t \kappa_1 X_A(s) X_E(s) ds\right) + Y_2\left(\kappa_2 \int_0^t X_{AE}(s) ds\right) \\ &\quad + Y_3\left(\kappa_3 \int_0^t X_{AE}(s) ds\right) \\ X_A(t) &= X_A(0) - Y_1\left(\int_0^t \kappa_1 X_A(s) X_E(s) ds\right) + Y_2\left(\kappa_2 \int_0^t X_{AE}(s) ds\right) \end{aligned}$$

The remainder of the system is determined by

$$X_{AE}(t) = M - X_E(t) \qquad X_B(t) = X_B(0) + X_A(0) + X_{AE}(0) - X_A(t) - X_{AE}(t)$$

Generator: $\zeta_1 = \begin{pmatrix} -1 \\ -1 \end{pmatrix}, \zeta_2 = \begin{pmatrix} 1 \\ 1 \end{pmatrix}, \zeta_3 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$

$$\begin{aligned} Af(x) = \kappa_1 x_A x_E (f(x + \zeta_1) - f(x)) + \kappa_2 (M - x_E)(f(x + \zeta_2) - f(x)) \\ + \kappa_3 (M - x_E)(f(x + \zeta_3) - f(x)) \end{aligned}$$

Multiscale models

Kang and Kurtz (2013)

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 $\kappa_k' = \kappa_k N_0^{\beta_k}$ so that $\kappa_k = O(1)$.

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

Kang and Kurtz (2013)

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 and k 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,

$$\begin{aligned} S_1 + \text{stuff} &\xrightarrow{\kappa'_1} S_1 + S_2 \\ S_2 &\xrightarrow{\kappa'_2} S_1 \\ S_1 + \text{stuff} &\xrightarrow{\kappa'_3} S_1 + S_3 \\ S_1 &\xrightarrow{\kappa'_4} \emptyset \\ S_3 &\xrightarrow{\kappa'_5} \emptyset \\ S_2 + S_3 &\xrightarrow{\kappa'_6} S_4 \end{aligned}$$

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}

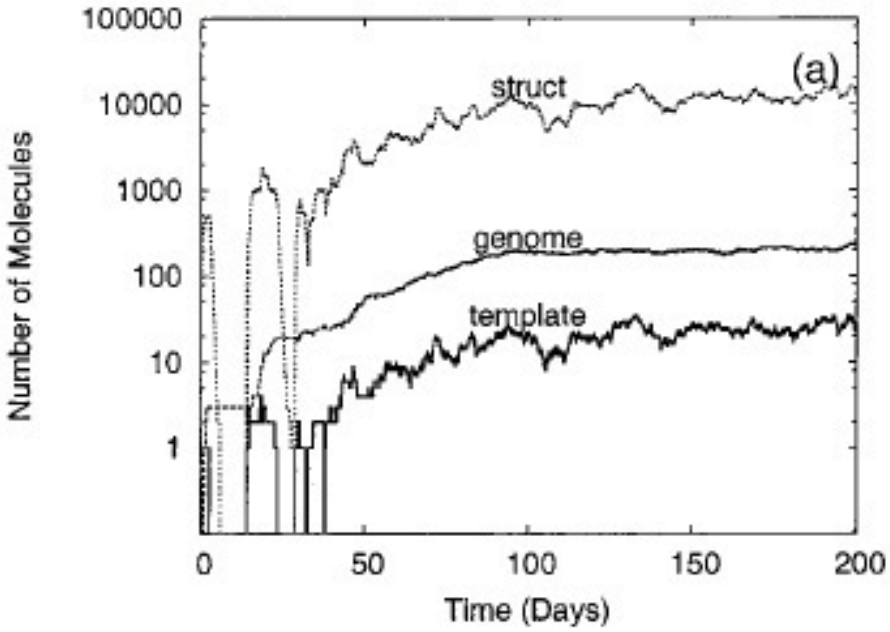

Figure 1: Simulation (Haseltine and Rawlings 2002)

Balance equations for the viral model

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

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

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

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, Kurtz, Popovic, and Rempala (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

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

Limiting system for $\gamma = 0$

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 $\gamma = \frac{2}{3}$,

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

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

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

Martingale approach to averaging

Kurtz (1992)
Kang and Kurtz (2013)

.

Let e_k be the vector in $\mathbb{Z}^3$ with kth component 1 and other components zero. For $\gamma = 2/3$, the generator is

$$\begin{aligned}A^N f(z) &= N^{2/3} z_1 (f(z + N^{-2.3} e_2) - f(z)) \\ &+2.5 N^{2/3} z_2 (f(z + e_1 - N^{-2/3} e_2) - f(z)) + N^{5/3} z_1 (f(z + N^{-1} e_3) - f(z)) \\ &+.25 N^{2/3} z_1 (f(z - e_1) - f(z)) + 2 N^{5/3} z_3 (f(z - N^{-1} e_3) - f(z)) \\ &+.75 N^{2/3} z_2 z_3 (f(z - N^{-1} e_3 - N^{-2/3} e_2) - f(z))\end{aligned}$$

If f depends only on z_2, then

$$\lim_{N \to \infty} A^N f(z) = (z_1 - 2.5 z_2 - .75 z_2 z_3) f'(z_2).$$

If f depends only on z_1 and z_3, then

$$\begin{aligned}\lim_{N \to \infty} N^{-2/3} A^N f(z) \;=\; & 2.5 z_2 (f(z_1 + 1, z_3) - f(z_1, z_3)) \\ & +.25 z_1 (f(z_1 - 1, z_3) - f(z_1, z_3)) \\ & +(z_1 - 2 z_3) \partial_{z_3} f(z_1, z_3)\end{aligned}$$

Limiting martingale

$$\begin{aligned}& f(Z_2^N(t)) - \int_0^t (Z_1^N(s) - 2.5 Z_2^N(s) - .75 Z_2^N(s) Z_3^N(s)) f'(Z_2^N(s)) ds + \epsilon_N(t) \\ &= f(Z_2^N(t)) - \int_{[0,t] \times [0,\infty)^2} (z_1 - 2.5 Z_2^N(s) - .75 Z_2^N(s) z_3) f'(Z_2^N(s)) \Gamma^N(ds, dz_1, dz_3) + \epsilon_N(t) \\ &\Rightarrow f(Z_2(t)) - \int_0^t \int_{[0,\infty)^2} (z_1 - 2.5 Z_2(s) - .75 Z_2(s) z_3) f'(Z_2(s)) \Gamma_s(dz_1, dz_3) ds\end{aligned}$$

Need to check relative compactness of $\{\Gamma^N\}$.

Exercise: Bound the expectations of Z_1^N, Z_2^N, Z_3^N by taking expectations of the stochastic equations and throwing away the nonliner terms.

Need to identify the limit $\Gamma^N \Rightarrow \Gamma$.

Identification of Γ

For a function of z_1, z_2

$$\begin{aligned}
&N^{-2/3} f(Z_1^N(t), Z_3^N(t)) - \int_0^t N^{-2/3} A^N f(Z^N(s)) ds \\
&\approx \int_{[0,t]\times[0,\infty)^2} \Big[2.5 Z_2^N(s)(f(z_1+1, z_3) - f(z_1, z_3)) \\
&\qquad +.25 z_1 (f(z_1 - 1, z_3) - f(z_1, z_3)) \\
&\qquad +(z_1 - 2z_3)\partial_{z_3} f(z_1, z_3) \Big] \Gamma^N(ds, dz_1, dz_3) \\
&\Rightarrow \int_0^t \int_{[0,\infty)^2} \Big[2.5 Z_2(s)(f(z_1+1, z_3) - f(z_1, z_3)) \\
&\qquad +.25 z_1 (f(z_1 - 1, z_3) - f(z_1, z_3)) \\
&\qquad +(z_1 - 2z_3)\partial_{z_3} f(z_1, z_3) \Big] \Gamma_s(dz_1, dz_3) ds
\end{aligned}$$

A martingale that is continuous and finite variation is a constant. Consequently, the last expression is zero.

Γ_s is a "stationary distribution"

Almost surely, for almost every s

$$\begin{aligned}
&\int_{[0,\infty)^2} \Big[2.5 Z_2(s)(f(z_1+1, z_3) - f(z_1, z_3)) \\
&\qquad +.25 z_1 (f(z_1 - 1, z_3) - f(z_1, z_3)) \\
&\qquad +(z_1 - 2z_3)\partial_{z_3} f(z_1, z_3) \Big] \Gamma_s(dz_1, dz_3) = 0
\end{aligned}$$

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 initial 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

$$X_i(t) \approx N_0^{\alpha_i} Z_i^\infty(tN_0^{-\gamma}).$$

For example, in the virus model

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

Enzyme reaction (cf. Darden (1982))

Basic assumption: A small number of enzymes interacts with a large number $O(N)$ of substrate molecules.

$$A + E \rightleftharpoons AE \rightharpoonup E + B$$

$$\begin{aligned} X_E(t) &= X_E(0) - Y_1\Big(\int_0^t \kappa_1 X_A(s) X_E(s) ds\Big) + Y_2\Big(\kappa_2 \int_0^t X_{AE}(s) ds\Big) \\ &\quad + Y_3\Big(\kappa_3 \int_0^t X_{AE}(s) ds\Big) \\ X_A(t) &= X_A(0) - Y_1\Big(\int_0^t \kappa_1 X_A(s) X_E(s) ds\Big) \\ &\quad + Y_2\Big(\kappa_2 \int_0^t X_{AE}(s) ds\Big) \end{aligned}$$

Scaled model

Assume that production and dissociation reactions are fast, and the substrate is present in large numbers. $Z_A^N = N^{-1}X_A^N$.

$$\begin{aligned} X_E^N(t) &= X_E(0) - Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds) + Y_2(N\kappa_2\int_0^t X_{AE}^N(s)ds) \\ &\quad + Y_3(N\kappa_3\int_0^t X_{AE}^N(s)ds) \\ Z_A^N(t) &= Z_A^N(0) - N^{-1}Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds) \\ &\quad + N^{-1}Y_2(N\kappa_2\int_0^t X_{AE}^N(s)ds) \end{aligned}$$

$m \equiv X_E^N(t) + X_{AE}^N(t)$ does not depend on t.

Averaging by the equation

Dividing the first equation by N and taking the limit

$$\begin{aligned} N^{-1}X_E^N(t) &= N^{-1}X_E(0) - N^{-1}Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds) \\ &\quad + N^{-1}Y_2(N\kappa_2\int_0^t X_{AE}^N(s)ds) \\ &\quad + N^{-1}Y_3(N\kappa_3\int_0^t X_{AE}^N(s)ds) \\ 0 &= \lim_{N\to\infty}\int_0^t(-\kappa_1 Z_A^N(s)X_E^N(s) + \kappa_2 X_{AE}^N(s) + \kappa_3 X_{AE}^N(s))ds \end{aligned}$$

and

$$\lim_{N\to\infty}\int_0^t X_E^N(s)ds = \lim_{N\to\infty}\int_0^t (m - X_{AE}^N(s))ds = \int_0^t \frac{m(\kappa_2+\kappa_3)}{\kappa_1 Z_A(s) + \kappa_2 + \kappa_3}ds.$$

Michaelis-Menten equation

$$\begin{aligned} Z_A^N(t) &= Z_A^N(0) - N^{-1}Y_1(N\int_0^t \kappa_1 Z_A^N(s)X_E^N(s)ds) \\ &\quad + N^{-1}Y_2(N\kappa_2\int_0^t X_{AE}^N(s)ds) \end{aligned}$$

which converges to

$$\begin{aligned} Z_A(t) &= Z_A(0) - \int_0^t \kappa_1 Z_A(s)\frac{m(\kappa_2+\kappa_3)}{\kappa_1 Z_A(s)+\kappa_2+\kappa_3}ds \\ &\quad + \kappa_2\int_0^t \frac{m\kappa_1 Z_A(s)}{\kappa_1 Z_A(s)+\kappa_2+\kappa_3}ds \\ &= Z_A(0) - \int_0^t \frac{m\kappa_1\kappa_3 Z_A(s)}{\kappa_1 Z_A(s)+\kappa_2+\kappa_3}ds \end{aligned}$$

Gaussian limit

Kang, Kurtz, and Popovic (2014)

Call the limiting quadratic variation $\int_0^t \sigma^2(Z_A(s))ds$.

$$\begin{aligned} &\int_0^t \sigma^2(Z_A(s))ds \\ &= \int_0^t ((h(Z_A(s))-1)^2(\kappa_2+\kappa_3) + (h(Z_A(s))+1)^2\kappa_2 + h(Z_A(s))^2\kappa_3) \\ &\qquad \times \frac{m\kappa_1 Z_A(s)}{\kappa_1 Z_A(s)+\kappa_2+\kappa_3}ds \end{aligned}$$

Then

$$U^N(t) = \sqrt{N}(Z_A^N(t) - Z(t))$$

converges to the solution of

$$U(t) = U(0) + W(\int_0^t \sigma^2(Z_A(s))ds) - \int_0^t \frac{m\kappa_1\kappa_3(\kappa_2+\kappa_3)}{(\kappa_2+\kappa_3+\kappa_1 Z_A(s))^2}U(s)ds$$

Diffusion approximation

Rationale: Find a sequence of diffusion processes D_A^N such that

$$\sqrt{N}(D_A^N - Z_A) \Rightarrow U.$$

So

$$D_A^N(t) = Z_A^N(0) + \frac{1}{\sqrt{N}} \int_0^t \sigma(D_A^N(s))dW(s) - \int_0^t \frac{m\kappa_1\kappa_3 D_A^N(s)}{\kappa_2 + \kappa_3 + \kappa_1 D_A^N(s)} ds$$

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 (2012).

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}
stuff $+ S_3 \to S_5 + S_2$	$6.30 \times 10^{-3} X_{S_3}$	$S_1 \to \emptyset$	$1.40 \times 10^{-6} X_{S_1}$
stuff $+ S_3 \to S_4 + S_2$	$4.88 \times 10^{-3} X_{S_3}$	$S_7 \to S_6$	$1.42 \times 10^{-6} X_{S_4} X_{S_7}$
stuff $+ S_3 \to S_6 + S_2$	$4.88 \times 10^{-3} X_{S_3}$	$S_5 \to \emptyset$	$1.80 \times 10^{-8} X_{S_5}$
$S_7 \to S_2 + S_6$	$4.40 \times 10^{-4} X_{S_7}$	$S_6 \to \emptyset$	$6.40 \times 10^{-10} X_{S_6}$
$S_2 + S_6 \to S_7$	$3.62 \times 10^{-4} X_{S_2} X_{S_6}$	$S_4 \to \emptyset$	$7.40 \times 10^{-11} X_{S_4}$

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