Stochastic models for chemical reactions

Bilingual dictionary

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

Intensities for continuous-time Markov chains

Assume X is a continuous time Markov chain in $E \subset \mathbb{Z}^d$. The Q-matrix, $Q = \{q_{kl}\}$, for the chain gives

$$P\{X(t+\Delta t) = l | X(t) = k\} \approx q_{kl}\Delta t, \quad k \neq l \in E,$$

and hence

$$E[f(X(t+\Delta t)) - f(X(t))|\mathcal{F}_t^X] \approx \sum_l q_{X(t),l}(f(l) - f(X(t))\Delta t \equiv \mathbb{A}f(X(t))\Delta t$$

Alternative notation: Define $\beta_l(k) = q_{k,k+l}$. Then

$$\mathbb{A}f(k) = \sum_l \beta_l(k)(f(k+l) - f(k))$$

Martingale problems

$\approx$ is made precise by the requirement that

$$f(X(t)) - f(X(0)) - \int_0^t \mathbb{A}f(X(s))ds$$

be a $\{\mathcal{F}_t^X\}$-martingale for f in an appropriate domain $\mathcal{D}(\mathbb{A})$.

X is called a solution of the *martingale problem* for $\mathbb{A}$.

Backward and forward equations

Defining $u(x,t) = E[f(X(t))|X(0) = x]$, one can derive the *backward equation*

$$\partial_t u(t,x) = \mathbb{A}u(t,x)$$

and setting $\nu_t(G) = P\{X(t) \in G\}$ and $\nu_t f = \int_E f d\nu_t$, the martingale property gives the *forward equation* (in weak form)

$$\nu_t f = \nu_0 f + \int_0^t \nu_s \mathbb{A} f ds, \quad f \in \mathcal{D}(\mathbb{A}).$$

The forward/master equation

Taking $f = \mathbf{1}_{\{k\}}$ and setting $p_k(t) = \nu_t(\{k\})$,

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

giving the usual form of 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* in the chemical literature) $\beta_l(X(t))$, that is,

$$N_l(t) - \int_0^t \beta_l(X(s))ds$$

is a martingale. 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 equaton

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

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

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 [6, 7] *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 [5].

For $0 = \tau_0(x) < \tau_1(x) < \cdots$, satisfying $\tau_k(x) = \tau_k(x^{\tau_k-})$, where

$$x^{\tau_k-}(s) = \begin{cases} x(s) & s < \tau_k(x) \\ x(\tau_k(x)-) & s \geq \tau_k(x) \end{cases}$$

(typically, $\tau_{k+1}(x) = \tau_k(x) + g_{k+1}(x(\tau_k))$), simulation of

$$\hat{X}(t) = X(0) + \sum_l l Y_l \left(\sum_k \beta_l(\hat{X}(\tau_k))(\tau_{k+1} \wedge t - \tau_k \wedge t) \right)$$

gives Gillespie's [8] τ-leap method

Reaction networks

Standard notation for chemical reactions

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

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, $A_1, \ldots, A_m$.

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

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 $R_k(t)$.

Basic assumption: The system is *well-mixed*.

Rates for the law of mass action

$$\lambda_k^N(x) = \kappa_k \frac{\prod_i \nu_{ik}!}{N^{|\nu_k|-1}} \prod_i \binom{x_i}{\nu_{ik}} = N\kappa_k \frac{\prod_i \nu_{ik}!}{N^{|\nu_k|}} \prod \binom{x_i}{\nu_{ik}},$$

where $|\nu_k| = \sum_i \nu_{ik}$ and N is a scaling parameter usually taken to be the volume of the system times Avogadro's number.

If x gives the number of molecules of each species present, then $c = N^{-1}x$ gives the concentrations in moles per unit volume.

Then

$$\lambda_k^N(x) \approx N\kappa_k \prod_i c_i^{\nu_{ik}} \equiv N\tilde{\lambda}_k(c).$$

First scaling limit

Setting $C^N(t) = N^{-1}X(t)$

$$\begin{aligned} C^N(t) &= C^N(0) + \sum_k N^{-1} Y_k\Big(\int_0^t \lambda_k^N(X(s))ds\Big)(\nu_k' - \nu_k) \\ &\approx C^N(0) + \sum_k N^{-1} Y_k\Big(N\int_0^t \tilde{\lambda}_k(C^N(s))ds\Big)(\nu_k' - \nu_k) \end{aligned}$$

The law of large numbers for the Poisson process implies $N^{-1}Y(Nu) \approx u$,

$$C^N(t) \approx C^N(0) + \sum_k \int_0^t \kappa_k \prod_i C_i^N(s)^{\nu_{ik}}(\nu_k' - \nu_k)ds,$$

which in the large volume limit gives the classical deterministic law of mass action

$$\dot{C}(t) = \sum_k \kappa_k \prod_i C_i(t)^{\nu_{ik}}(\nu_k' - \nu_k) \equiv F(C(t)).$$

skip

Central limit theorem/Van Kampen Approximation

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

Gaussian limit

V_N converges to the solution of

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

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

Diffusion approximation

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

where

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

The diffusion approximation is given by the equation

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

Itô formulation

The time-change formulation is equivalent to the Itô equation

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

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

See Kurtz [11], Ethier and Kurtz [3], Chapter 10, Gardiner [4], Chapter 7, and Van Kampen, [14].

General approaches to averaging

Models with two time scales: (X, Y), Y is "fast"

Occupation measure: $\Gamma^Y(C \times [0,t]) = \int_0^t \mathbf{1}_C(Y(s))ds$

Replace integrals involving Y by integrals against Γ^Y

$$\begin{aligned}\int_0^t f(X(s), Y(s))ds &= \int_{E^Y \times [0,t]} f(X(s), y)\Gamma^Y(dy \times ds) \\ &\approx \int_0^t \int_{E^Y} f(X(s), y)\eta_s(dy)ds\end{aligned}$$

How do we identify η_s?

Generator approach

Suppose $\mathbb{B}_r f(x,y) = r\mathbb{C}f(x,y) + \mathbb{D}f(x,y)$ where $\mathbb{C}$ operates on f as a function of y alone.

$$f(X_r(t), Y_r(t)) - r\int_{E^Y\times[0,t]} \mathbb{C}f(X_r(s), y)\Gamma_r^Y(dy\times ds) \\ - \int_{E^Y\times[0,t]} \mathbb{D}f(X_r(s), y)\Gamma_r^Y(dy\times ds)$$

Assuming $(X_r, \Gamma_r^Y) \Rightarrow (X, \Gamma^Y)$, dividing by r, we should

$$\int_{E^Y\times[0,t]} \mathbb{C}f(X(s), y)\Gamma^Y(dy\times ds) = \int_{E^Y\times[0,t]} \mathbb{C}f(X(s), y)\eta_s(dy)ds = 0$$

Suppose that for each x, the solution of $\int_{E^Y} \mathbb{C}f(x,y)\mu_x(dy) = 0$, $f\in\mathcal{D}$. Then $\eta_s(dy) = \mu_{X(s)}(dy)$

Well-mixed reactions

Consider $A + B \overset{\kappa}{\rightharpoonup} C$. The *generator* for the Markov chain model is

$$\mathbb{A}f(m,n) = \kappa mn(f(m-1,n-1) - f(m,n))$$

Spatial model

U_i state (location and configuration) of ith molecule of A

V_j state of jth molecule of B

$$\begin{aligned}\mathbb{B}f(u,v) &= \sum_{i=1}^{m} r\mathbb{C}^A_{u_i} f(u,v) + \sum_{j=1}^{n} r\mathbb{C}^B_{v_j} f(u,v) \\ &\quad + \sum_{i,j} \rho(u_i, v_j)(f(\theta_i u, \theta_j v) - f(u,v))\end{aligned}$$

where $r\mathbb{C}^A$ is a generator modeling the evolution of a molecule of A and $r\mathbb{C}^B$ models the evolution of a molecule of B.

Independent evolution of molecules

If there was no reaction

$$r\mathbb{C}f(u,v) = \sum_{i=1}^{m} r\mathbb{C}^A_{u_i} f(u,v) + \sum_{j=1}^{n} r\mathbb{C}^B_{v_j} f(u,v)$$

would model the independent evolution of m molecules of A and r molecules of B.

Averaging: Markov chain model

Assume that the state spaces E_A, E_B for molecules of A and B are compact and let $\mathcal{E} = \cup_{m,n} E_A^m \times E_B^n$.

Let Γ^r be the occupation measure

$$\Gamma^r(C \times [0,t]) = \int_0^t \mathbf{1}_C(U^r(s), V^r(s))ds,$$

so

$$f(U^r(t), V^r(t)) - \int_{\mathcal{E}\times[0,t]} (r\mathbb{C}f(u,v) + \mathbb{D}f(u,v))\Gamma^r(du \times dv \times ds)$$

is a martingale. Then $\{(\Gamma^r, X_A^r, X_B^r)\}$ is relatively compact, and assuming all functions are continuous, any limit point (Γ, X_A, X_B) of Γ^r as $r \to \infty$ satisfies

$$\int_{\mathcal{E}\times[0,t]} \mathbb{C}f(u,v)\Gamma(du, dv, ds) = 0.$$

cf. Kurtz [12]

Averaged generator

If f depends only on the numbers of molecules the martingale becomes

$$f(X_A(t), X_B(t)) - \int_{\mathcal{E}\times[0,t]} \sum_{i,j} \rho(u_i, v_j)(f(X_A(s)-1, X_B(s)-1) - f(X_A(s), X_B(s)))\Gamma(du, dv, ds).$$

If $\mathbb{C}^A$ and $\mathbb{C}^B$ have unique stationary distributions μ_A, μ_B, then for $f(u,v) = \prod_{i=1}^m g(u_i) \prod_{j=1}^n h(u_j)$,

$$\int f(u,v)\Gamma(du, dv, t) = \int_0^t \langle g, \mu_A\rangle^{X_A(s)} \langle h, \mu_B\rangle^{X_B(s)} ds$$

and setting $\kappa = \int \rho(u_0, v_0)\mu_A(du_0)\mu_B(dv_0)$,

$$f(X_A(t), X_B(t)) - \int_0^t \kappa X_A(s) X_B(s) f(X_A(s) - 1, X_B(s) - 1) - f(X_A(s), X_B(s)))ds$$

is a martingale.

Averaging: Michaelis-Menten kinetics

Consider the reaction system $A + E \rightleftharpoons AE \rightharpoonup B + E$

modeled as a continuous time Markov chain satisfying

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

Note that $M = X_{AE}(t) + X_E(t)$ is constant, and define

$$V_E(t) = \int_0^t M^{-1} X_E(s) ds.$$

Theorem 1 *(Darden [1, 2]) Assume that* $N \to \infty$, $M/N \to 0$, $M\kappa_1 \to \gamma_1$, $M\kappa_2/N \to \gamma_2$, $M\kappa_3/N \to \gamma_3$, *and* $X_A(0)/N \to x_A(0)$, *and*

Then $(N^{-1}X_A, V_E)$ *converges to* $(x_A(t), v_E(t))$ *satisfying*

$$\begin{aligned} x_A(t) &= x_A(0) - \int_0^t \gamma_1 x_A(s)\dot{v}_E(s)ds + \int_0^t \gamma_2(1-\dot{v}_E(s))ds \qquad (1) \\ 0 &= -\int_0^t \gamma_1 x_A(s)\dot{v}_E(s)ds + \int_0^t (\gamma_2+\gamma_3)(1-\dot{v}_E(s))ds, \end{aligned}$$

and hence $\dot{v}_E(s) = \frac{\gamma_2+\gamma_3}{\gamma_2+\gamma_3+\gamma_1 x_A(s)}$ *and*

$$\dot{x}_A(t) = -\frac{\gamma_1\gamma_3 x_A(t)}{\gamma_2+\gamma_3+\gamma_1 x_A(s)}.$$

Quasi-steady state

Assume M is constant $\gamma_1 = M\kappa_1$, $\kappa_2 = \gamma_2 N/M$, $\kappa_3 = \gamma_3 N/M$. Then

$$f(X_E(t)) - f(X_E(0)) - \int_0^t \kappa_1 X_A(s) X_E(s)(f(X_E(s)-1) - f(X_E(s)))ds$$
$$- \int_0^t N(\gamma_2+\gamma_3)(M - X_E(s))(f(X_E(s)+1) - f(X_E(s)))ds$$

Since $N^{-1}X_A(s) \to x_A(s)$, we must have

$$\sum_{k=0}^{M} \eta_s(k)(\kappa_1 x_A(s)k(f(k-1)-f(k)+(\gamma_2+\gamma_3)(M-k)(f(k+1)-f(k)) = 0$$

so η_s is binomial(M, p_s), where

$$p_s = \frac{\gamma_2+\gamma_3}{\gamma_2+\gamma_3+\kappa_1 x_A(s)}.$$

A model of intracellular viral infection

Srivastava, You, Summers, and Yin [13], Haseltine and Rawlings [9], Ball, Kurtz, Popovic, and Rampala [10]

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,

$$\begin{aligned} T + \text{stuff} &\xrightarrow{k_1} T + G \\ G &\xrightarrow{k_2} T \\ T + \text{stuff} &\xrightarrow{k_3} T + S \\ T &\xrightarrow{k_4} \emptyset \\ S &\xrightarrow{k_5} \emptyset \\ G + S &\xrightarrow{k_6} V \end{aligned}$$

Stochastic system

$$
\begin{aligned}
X_1(t) &= X_1(0) + Y_b\Big(\int_0^t k_2 X_2(s)ds\Big) - Y_d\Big(\int_0^t k_4 X_1(s)ds\Big) \\
X_2(t) &= X_2(0) + Y_a\Big(\int_0^t k_1 X_1(s)ds\Big) - Y_b\Big(\int_0^t k_2 X_2(s)ds\Big) \\
&\qquad - Y_f\Big(\int_0^t k_6 X_2(s)X_3(s)ds\Big) \\
X_3(t) &= X_3(0) + Y_c\Big(\int_0^t k_3 X_1(s)ds\Big) - Y_e\Big(\int_0^t k_5 X_3(s)ds\Big) \\
&\qquad - Y_f\Big(\int_0^t k_6 X_2(s)X_3(s)ds\Big)
\end{aligned}
$$

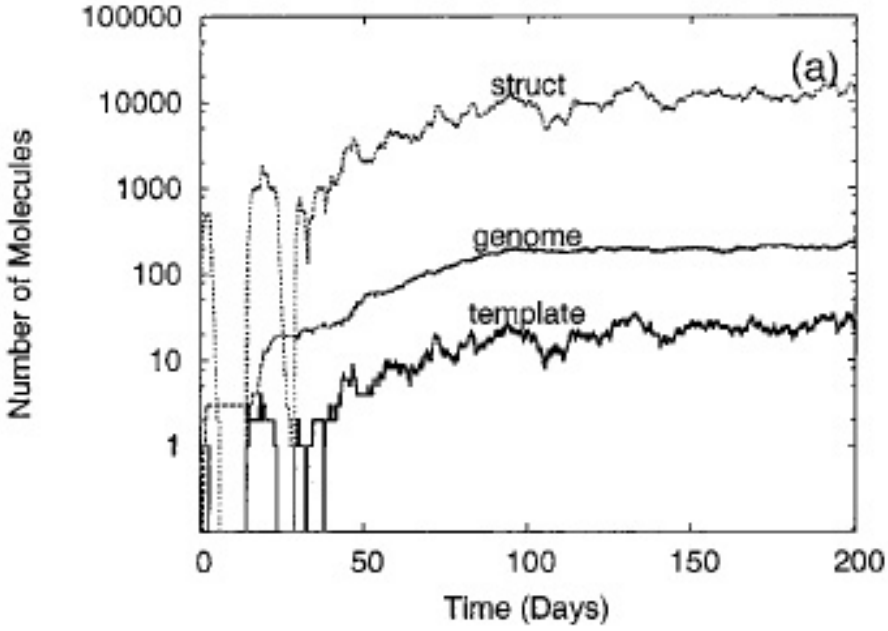

Figure 1: Simulation (Haseltine and Rawlings 2002)

Scaling parameters

N scaling parameter

Each X_i is scaled according to its abundance in the system.

For $N = 1000$, $X_1 = O(N^0)$, $X_2 = O(N^{2/3})$, and $X_3 = O(N)$ and we take $Z_1 = X_1$, $Z_2 = X_2 N^{-2/3}$, and $Z_3 = X_3 N^{-1}$.

Expressing the rate constants in terms of $N = 1000$

k_1	1	1
k_2	0.025	$2.5N^{-2/3}$
k_3	1000	N
k_4	0.25	.25
k_5	2	2
k_6	7.5×10^{-6}	$.75N^{-5/3}$

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

With the scaled rate constants, we have

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

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 (2).

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*

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

Appendix

Proof.(of Theorem 1 By the law of large numbers, $N^{-1}Y_i(Nu) - u \to 0$ uniformly in u on bounded intervals. In fact, by the functional central limit theorem, $\sup_{u \le u_0} \sqrt{N}|N^{-1}Y_i(Nu) - u|$ is stochastically bounded. (For every $\epsilon > 0$, there exists K_ϵ such that $P\{\sup_{u \le u_0} \sqrt{N}|N^{-1}Y_i(Nu) - u| \ge K_\epsilon\} \le \epsilon$.)

Let $\hat{X}_A(t) = N^{-1}X_A(t)$. Dividing both equations by N, it follows that

$$\begin{aligned} \hat{X}_A(t) &= \hat{X}_A(0) - \int_0^t \gamma_1 \hat{X}_A(s) dV_E(s) + \gamma_2(t - V_E(t)) + \epsilon_A(t) \\ 0 &= -\int_0^t \gamma_1 \hat{X}_A(s) dV_E(s) + (\gamma_2 + \gamma_3)(t - V_E(t)) + \epsilon_E(t) \end{aligned}$$

where the error terms ϵ_A and ϵ_E are uniformly small on bounded time intervals. Since V_E is Lipschitz, at least along a subsequence, V_E converges to a Lipschitz function v_E. An application of Gronwall's inequality then gives convergence of $\hat{X}_A$ to x_A satisfying (1). □

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Software

StochKit
Petzold group, UC Santa Barbara
http://www.engineering.ucsb.edu/%7Ecse/

Hy3S Hybrid Stochastic Simulation for Supercomputers
Kaznessis Group, University of Minnesota
http://hysss.sourceforge.net/

StochSim
Computational Cell Biology Group, Cambridge
http://info.anat.cam.ac.uk/groups/comp-cell/StochSim.html

Stochastirator
Molecular Sciences Institute, Berkeley
http://opnsrcbio.molsci.org/stochastirator/stoch-main.html

Abstract

Attempts to model chemical reactions within biological cells has led to renewed interest in stochastic models for these systems. The classical stochastic models for chemical reaction networks will be reviewed, and multiscale methods for model reduction will be described. New models motivated by the particular nature of biochemical processes will also be discussed.