Multiscale approximations for stochastic reaction networks

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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.

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

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

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

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

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.

Basic assumption: The system is uniformly mixed.

First scaling limit

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

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

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

$$C(t) = N^{-1}X(t) \approx C(0) + \sum_k \int_0^t \kappa_k \prod_i C_i(s)^{\nu_{ik}}(\nu_k' - \nu_k)ds,$$

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

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

Diffusion approximation

An appropriately renormalized Poisson process can be approximated by a standard Brownian motion

$$\frac{Y(Nu) - Nu}{\sqrt{N}} \approx W(u),$$

replacing $Y_k(Nu)$ by $\sqrt{N}W_k(u) + Nu$

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

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

Equivalent form

The diffusion approximation is given by the equation

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

which is distributionally equivalent to the Itô equation

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

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

Chemical reactions in cells

- For reactions in cells, the number of molecules involved, at least for some of the species, may be sufficiently small that the deterministic model does not provide a good representation of the behavior of the system.
- Some species may be present in much greater abundance than others.
- The rate constants κ_k may vary over several orders of magnitude.

A multiscale model

Take N to be of the order of magnitude of the abundance of the most abundant species in the system.

For each species i, $0 \leq \alpha_i \leq 1$ and

$$Z_i(t) = N^{-\alpha_i} X_i(t).$$

α_i should be selected so that $Z_i = O(1)$.

Express the reaction rates in terms of Z rather than X and also take into account large variation in the reaction rates.

Select β_k so that the reaction rates can be written as $N^{\beta_k}\lambda_k(z)$, where $\lambda_k(z) = O(1)$ for all relevant values of z. The model becomes

$$Z_i(t) = Z_i(0) + \sum_k N^{-\alpha_i} Y_k\Big(\int_0^t N^{\beta_k}\lambda_k(Z(s))ds\Big)(\nu'_{ik} - \nu_{ik}).$$

A model of intracellular viral infection

Srivastava, You, Summers, and Yin 2002

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,

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

Scaling parameters

N measures the size of the system and 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}	$.75N^{-5/3}$

The normalized system

$$
\begin{aligned}
Z_1(t) &= Z_1(0) + Y_b\Big(\int_0^t k_2 N^{2/3} Z_2(s)ds\Big) - Y_d\Big(\int_0^t k_4 Z_1(s)ds\Big) \\
Z_2(t) &= Z_2(0) + N^{-2/3} Y_a\Big(\int_0^t k_1 Z_1(s)ds\Big) - N^{-2/3} Y_b\Big(\int_0^t k_2 N^{2/3} Z_2(s)ds\Big) \\
&\qquad - N^{-2/3} Y_f\Big(\int_0^t k_6 N^{5/3} Z_2(s) Z_3(s)ds\Big) \\
Z_3(t) &= Z_3(0) + N^{-1} Y_c\Big(\int_0^t k_3 Z_1(s)ds\Big) - N^{-1} Y_e\Big(\int_0^t k_5 N Z_3(s)ds\Big) \\
&\qquad - N^{-1} Y_f\Big(\int_0^t k_6 N^{5/3} Z_2(s) Z_3(s)ds\Big),
\end{aligned}
$$

Normalized system

With the scaled rate constants, we have

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

Probability of a successful infection

We assume that $X_1^N(0) = 1$ and $X_2^N(0) = X_3^N(0) = 0$.

$$
\begin{aligned}
X_1^N(t) &= 1 + Y_b\left(\int_0^t 2.5N^{-2/3}X_2^N(s)ds\right) - Y_d\left(\int_0^t .25X_1^N(s)ds\right) \\
X_2^N(t) &= Y_a\left(\int_0^t X_1^N(s)ds\right) - Y_b\left(\int_0^t N^{-2/3}2.5X_2^N(s)ds\right) \\
&\qquad - Y_f\left(\int_0^t .75N^{-2/3}X_2^N(s)Z_3^N(s)ds\right) \\
Z_3^N(t) &= N^{-1}Y_c\left(\int_0^t NX_1^N(s)ds\right) - N^{-1}Y_e\left(\int_0^t 2NZ_3^N(s)ds\right) \\
&\qquad - N^{-1}Y_f\left(\int_0^t .75N^{-2/3}X_2^N(s)Z_3^N(s)ds\right),
\end{aligned}
$$

$P\{\text{successful infection}\} \approx .75.$

Law of large numbers

Let $0 < \epsilon < 2$ and define $\tau_\epsilon^N = \inf\{t : Z_2^N(t) \geq \epsilon\} = \inf\{t : X_2^N(t) \geq N^{2/3}\epsilon\}$. When $\tau_\epsilon^N < \infty$, define $V_i^N(t) = Z_i(\tau_\epsilon^N + N^{2/3}t)$.

Theorem 1 *a) For* $0 < \epsilon < 2$, $\lim_{N\to\infty} P\{\tau_\epsilon^N < \infty\} = .75$.

b)

$$\lim_{N\to\infty} \frac{\tau_\epsilon^N}{N^{2/3}\log N} = \text{constant}.$$

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

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

where V_2 *is the solution of*

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

Fast time scale

On the event $\tau_\epsilon^N < \infty$,

$$
\begin{aligned}
V_1^N(t) &= Z_1(\tau_\epsilon^N) + Y_b^*\Big(\int_0^t 2.5N^{2/3}V_2^N(s)ds\Big) - Y_d^*\Big(\int_0^t .25N^{2/3}V_1^N(s)ds\Big) \\
V_2^N(t) &= \frac{\lceil \epsilon N^{2/3} \rceil}{N^{2/3}} + N^{-2/3}Y_a^*\Big(\int_0^t N^{2/3}V_1^N(s)ds\Big) \\
&\qquad -N^{-2/3}Y_b^*\Big(\int_0^t 2.5N^{2/3}V_2^N(s)ds\Big) \\
&\qquad -N^{-2/3}Y_f^*\Big(\int_0^t .75N^{2/3}V_2^N(s)V_3^N(s)ds\Big) \\
V_3^N(t) &= Z_3(\tau_\epsilon^N) + N^{-1}Y_c^*\Big(\int_0^t N^{5/3}V_1^N(s)ds\Big) - N^{-1}Y_e^*\Big(\int_0^t 2N^{5/3}V_3^N(s)ds\Big) \\
&\qquad -N^{-1}Y_f^*\Big(\int_0^t .75N^{2/3}V_2^N(s)V_3^N(s)ds\Big),
\end{aligned}
$$

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

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

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

Behavior of V_1^N and V_3^N

V_1^N and V_3^N fluctuate rapidly and locally in time. V_1^N behaves like a simple birth and death process with V_2^N entering as a parameter, and V_3^N tries to follow V_1^N via an ordinary differential equation, on the intervals of constancy of $V_1^N(t)$, that is,

$$V_3^N(a+N^{-2/3}r) \approx V_3^N(a) + \int_0^r (V_1^N(a+N^{-2/3}s) - 2V_3^N(a+N^{-2/3}s))ds,$$

and except for a short interval of time after each jump of V_1^N, $V_3^N(t) \approx \frac{1}{2}V_1^N(t)$.

Computation of generator

$$
\begin{aligned}
&g(V_1^N(t), V_3^N(t)) \\
&= g(Z_1(\tau_\epsilon^N), Z_3(\tau_\epsilon^N)) + \text{martingale} \\
&\quad + N^{2/3}\int_0^t 2.5V_2^N(s)[g(V_1^N(s)+1, V_3^N(s)) - g(V_1^N(s), V_3^N(s))]ds \\
&\quad + N^{2/3}\int_0^t V_1^N(s)N[g(V_1^N(s), V_3^N(s)+1/N) - g(V_1^N(s), V_3^N(s))]ds \\
&\quad + N^{2/3}\int_0^t .25V_1^N(s)[g(V_1^N(s)-1, V_3^N(s)) - g(V_1^N(s), V_3^N(s))]ds \\
&\quad + N^{2/3}\int_0^t 2V_3^N(s)N[g(V_1^N(s), V_3^N(s)-1/N) - g(V_1^N(s), V_3^N(s))]ds
\end{aligned}
$$

Identification of quasistationary distribution

Define $\Gamma^N(C \times D \times [0,t]) = \int_0^t \mathbf{1}_C(V_1^N(s))\mathbf{1}_D(V_3^N(s))ds$ and note that

$$\begin{aligned} & g(V_1^N(t), V_3^N(t) \\ & = g(Z_1(\tau_\epsilon^N), Z_3(\tau_\epsilon^N)) \\ & \qquad + M^N(t) + N^{2/3} \int_{\mathbb{Z}_+ \times \mathbb{R}_+ \times [0,t]} B_s^N g(z,y) \Gamma^N(dz \times dy \times ds), \end{aligned}$$

where M^N is a martingale and

$$\begin{aligned} \lim_{N\to\infty} B_s^N g(z,y) - [2.5V_2^N(s)(g(z+1,y) - g(z,y)) \\ + .25z(g(z-1,y) - g(z,y)) + (z-2y)\frac{\partial g}{\partial y}(z,y)] = 0. \end{aligned}$$

Relative compactness, in an appropriate sense, is easy to verify for (V_2^N, Γ^N) and any limit point (V_2, Γ) will satisfy

$$\Gamma([0,t] \times C \times D) = \int_0^t \mu_s^{13}(C \times D)ds.$$

Dividing by $N^{2/3}$ and letting $N \to \infty$, we have

$$\int_{\mathbb{Z}_+ \times \mathbb{R}_+ \times [0,t]} B_{V_2(s)} g(z,y) \Gamma(dz \times dy \times ds) = 0,$$

where

$$B_v g(z,y) = [2.5v(g(z+1,y) - g(z,y)) + .25z(g(z-1,y) - g(z,y)) + (z-2y)\frac{\partial g}{\partial y}(z,y)].$$

(2) determines all the moments

Let (Z_s, Y_s) be a random vector with the law μ_s^{13}.

Z_s is just a Poisson variable with expectation $10V_2(s)$.

With $g(z,y) = y$ in (2), we get

$$\sum_z \int_y [z-2y]\mu_s^{13}(dz,dy) = 0 \Rightarrow \quad EY_s = \frac{1}{2}EZ_s = 5V_2(s).$$

With $g(z,y) = zy$, we get

$$\sum_z \int_y [z(z-2y) + \frac{5}{2} y V_2(s) - \frac{1}{4} yz] \mu_s^{13}(dz, dy) = 0 \Rightarrow \quad EZ_sY_s = \frac{4}{9} EZ_s^2 + \frac{10}{9} V_2(s$$

and

$$E[Z_sY_s] = \frac{40}{9} V_2(s) + 50 V_2(s)^2.$$

With $g(z,y) = y^2$,

$$\sum_z \int_y [2y(z-2y)] \mu_s^{13}(dz, dy) = 0$$

implies

$$EY_s^2 = \frac{1}{2} EZ_sY_s, \quad \text{etc.}$$

Quasistationarity of fast components

Theorem 2 *Conditioning on* $\tau_\epsilon^N < \infty$, *for each* $t \geq 0$, $(V_1^N(t), V_3^N(t))$ *converges in distribution to a pair* $(V_1(t), V_3(t))$ *with joint distribution* μ_t^{13} *satisfying*

$$\int [2.5V_2(t)(g(z+1,y) - g(z,y)) + .25z(g(z-1,y) - g(z,y)) + (z-2y)\frac{\partial g}{\partial y}(z,y)]\mu_t^{13}(dz,dy) = 0. \tag{2}$$

In particular, $V_1(t)$ *has a Poisson distribution with parameter* $10V_2(t)$, *so*

$$E[V_1(t)] = Var(V_1(t)) = 10V_2(t);$$

$$E[V_3(t)] = 5V_2(t), \quad Var(V_3(t)) = \frac{20}{9}V_2(t);$$

and

$$Cov(V_1(t), V_3(t)) = \frac{40}{9}V_2(t).$$

Branching approximation

Change time variable: $\int_0^{\gamma^N(t)}(\mathbf{1}_{\{X_1^N(s)\geq 1\}} + N^{-2/3}\mathbf{1}_{\{X_1^N(s)=0\}})ds = t$

Define $\hat{X}_i^N(t) = X_i^N \circ \gamma^N(t)$ and $\hat{Z}_3^N(t) = Z_3^N \circ \gamma^N(t)$.

$$\begin{aligned}\hat{X}_1^N(t) &= 1 + Y_b(\int_0^t 2.5(N^{-2/3}\mathbf{1}_{\{\hat{X}_1^N(s)\geq 1\}} + \mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{X}_2^N(s)ds) \\ &\qquad -Y_d(\int_0^t .25\hat{X}_1^N(s)ds)\end{aligned}$$

$$\begin{aligned}\hat{X}_2^N(t) &= Y_a(\int_0^t \hat{X}_1^N(s)ds) \\ &\qquad -Y_b(\int_0^t 2.5(N^{-2/3}\mathbf{1}_{\{\hat{X}_1^N(s)\geq 1\}} + \mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{X}_2^N(s)ds) \\ &\qquad -Y_f(\int_0^t .75(N^{-2/3}\mathbf{1}_{\{\hat{X}_1^N(s)\geq 1\}} + \mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{X}_2^N(s)\hat{Z}_3^N(s)ds)\end{aligned}$$

$$
\begin{aligned}
\hat{Z}_3^N(t) &= N^{-1}Y_c(\int_0^t N\hat{X}_1^N(s)ds) \\
&\quad -N^{-1}Y_e(\int_0^t 2N(\mathbf{1}_{\{\hat{X}_1^N(s)\geq 1\}} + N^{2/3}\mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{Z}_3^N(s)ds) \\
&\quad -N^{-1}Y_f(\int_0^t .75(N^{-2/3}\mathbf{1}_{\{\hat{X}_1^N(s)\geq 1\}} + \mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{X}_2^N(s)\hat{Z}_3^N(s)ds).
\end{aligned}
$$

Since $\hat{Z}_3^N$ decays at rate $N^{2/3}$ when $\hat{X}_1^N = 0$, it follows that

$$
\mathbf{1}_{\{\hat{X}_1^N(s)=0\}})\hat{Z}_3^N(s) \to 0
$$

as $N \to \infty$ for almost every s.

Limiting branching process

Consequently, $(\hat{X}_1^N, \hat{X}_2^N)$ converges to the solution of

$$\begin{aligned}\hat{X}_1(t) &= 1 + Y_b\left(\int_0^t 2.5\mathbf{1}_{\{\hat{X}_1(s)=0\}}\hat{X}_2(s)ds\right) - Y_d\left(\int_0^t .25\hat{X}_1(s)ds\right)\\ \hat{X}_2(t) &= Y_a\left(\int_0^t \hat{X}_1(s)ds\right) - Y_b\left(\int_0^t 2.5\mathbf{1}_{\{\hat{X}_1(s)=0\}}\hat{X}_2(s)ds\right).\end{aligned}$$

The solution of this system has the property that $\hat{X}_1$ only takes on values 0 and 1. Note that the ith interval during which $\hat{X}_1 = 1$ is exponentially distributed with parameter .25 and the number ξ_i of Type 2 molecules created during that interval has distribution

$$P\{\xi = k\} = \int_0^\infty .25e^{-.25t}e^{-t}\frac{t^k}{k!}dt = \frac{1}{5}\left(\frac{4}{5}\right)^k, \quad k = 0, 1, \ldots.$$

Let

$$\sigma_n = \inf\{t : Y_d(\int_0^t .25\hat{X}_1(s)ds) = n\}.$$

If $\sigma_n < \infty$, then

$$\hat{X}_2(\sigma_n) = \sum_{i=1}^{n} \xi_i - (n-1),$$

and for $n > 1$, $\sigma_n < \infty$ if and only if $\hat{X}_2(\sigma_k) > 0$, $k = 1, \ldots, n-1$. In particular, $\sigma_n < \infty$ for all n if and only if the random walk

$$S_n = \sum_{i=1}^{n} \xi_i - (n-1)$$

never hits 0 for $n > 0$, an event of probability .75. In particular, this is essentially the probability that a single virus successfully infects the cell.