

Model reduction for chemical reaction networks

- Formulating Markov models
- Reaction networks
- Scaling limit
- Multiscale models
- General approaches to averaging
- Michaelis-Menten equation
- Forcing onto a lower dimensional manifold
- Appendix
- References
- Abstract



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} .

Note that a change of time scale corresponds to multiplying the generator by the appropriate constant.

$$\begin{aligned} f(X(\rho t)) - f(X(0)) - \int_0^{\rho t} \mathbb{A}f(X(s))ds \\ = f(X(\rho t)) - f(X(0)) - \int_0^t \rho \mathbb{A}f(X(\rho s))ds \end{aligned}$$



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

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

where the Y_l are independent, unit Poisson processes, and

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



Reaction networks

Standard notation for chemical reactions

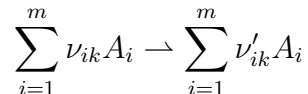


is interpreted as “a molecule of A combines with a molecule of B to give a molecule of C .”



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, \dots, A_m .



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 k th reaction.

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

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

If the k th reaction occurs at time t , the new state becomes

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

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

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

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

For a binary reaction $A_1 + A_2 \rightarrow A_3$ or $A_1 + A_2 \rightarrow A_3 + A_4$

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

For $A_1 \rightarrow A_2$ $A_1 \rightarrow A_2 + A_3$,

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

For $2A_1 \rightarrow A_2$,

$$\lambda_k(x) = \kappa_k x_1 (x_1 - 1)$$

For a binary reaction $A_1 + A_2 \rightarrow A_3$, the rate should vary inversely with volume, so it would be better to write

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

where classically, N is a scaling parameter 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. Note that unary reaction rates also satisfy

$$\lambda_k(x) = \kappa_k x_i = N \kappa_k z_i.$$



Classical scaling limit

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

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

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

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



A multiscale model [1]

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 $Z_i = O(1)$.

The rate constants may also scale $\kappa'_k = \kappa_k N^{\gamma_k}$, so for a binary reaction

$$\kappa'_k x_i x_j = N^{\gamma_k + \alpha_i + \alpha_j} \kappa_k z_i z_j$$

Select β_k so that $\lambda'_k(x) = N^{\beta_k} \lambda_k(z)$, where $\lambda_k(z) = O(1)$ for all (most?) relevant values of z .

The model becomes

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



Identifying the “fast” process

Let $\Lambda_N = \text{diag}(N^{-\alpha_1}, \dots, N^{-\alpha_m})$ and $\zeta_k = \nu'_k - \nu_k$. The generator for Z is

$$\mathbb{B}_N f(z) = \sum_k N^{\beta_k} \lambda_k(z) (f(z + \Lambda_N \zeta_k) - f(z)).$$

Select the smallest r_1 (possibly negative) such that

$$\mathbb{C}_0 f(z) = \lim_{N \rightarrow \infty} N^{-r_1} \mathbb{B}_N f(z)$$

exists for each $f \in C_c^2(\mathbb{R}^m)$, $z \in \mathbb{R}^m$, and let \mathcal{D}_1 be the collection of $f \in C^2(\mathbb{R}^m)$ such that $\mathbb{C}_0 f(z) = 0$.



Identifying r_1

Critical exponents: Let

$$r_{10} = \max\{\beta_k : \exists i, \alpha_i = 0, \zeta_{ik} \neq 0\}$$

$$r_{11} = \max\{\beta_k - \alpha_i : \sum_{\beta_l = \beta_k} \lambda_l(z) \zeta_{il} \neq 0\}$$

$$r_{12} = \max\{\beta_k - 2\alpha_i : \sum_{\beta_k = \beta^i} \lambda_k(z) \zeta_{ik}^2 \neq 0\}.$$

Then $r_1 = \max\{r_{10}, r_{11}, r_{12}\}$.



Second time scale

Select the smallest r_2 such that

$$\mathbb{C}_1 f(z) = \lim_{N \rightarrow \infty} N^{-r_2} \mathbb{B}_N f(z)$$

exists for all $f \in \mathcal{D}_1$, so in some sense, for general f

$$N^{-r_2} \mathbb{B}_N f(z) \approx \mathbb{C}_1 f(z) + N^{r_1 - r_2} \mathbb{C}_0 f(z)$$



General approaches to averaging [7]

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 $\mathbb{B}_r f(x, y) = r\mathbb{C}_0 f(x, y) + \mathbb{C}_1 f(x, y)$ where \mathbb{C} operates on f as a function of y alone.

$$\begin{aligned} f(X_r(t), Y_r(t)) - r \int_{E^Y \times [0, t]} \mathbb{C}_0 f(X_r(s), y) \Gamma_r^Y(dy \times ds) \\ - \int_{E^Y \times [0, t]} \mathbb{C}_1 f(X_r(s), y) \Gamma_r^Y(dy \times ds) \end{aligned}$$

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

$$\int_{E^Y \times [0, t]} \mathbb{C}_0 f(X(s), y) \Gamma^Y(dy \times ds) = \int_{E^Y \times [0, t]} \mathbb{C}_0 f(X(s), y) \eta_s(dy) ds = 0$$

Suppose that for each x , the solution of $\int_{E^Y} \mathbb{C}_0 f(x, y) \mu_x(dy) = 0$, $f \in \mathcal{D}$. Then $\eta_s(dy) = \mu_{X(s)}(dy)$



Michaelis-Menten kinetics

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

modeled as a continuous time Markov chain satisfying

$$X_A(t) = X_A(0) - Y_1\left(\int_0^t \kappa_1 X_A(s) X_E(s) ds\right) + Y_2\left(\int_0^t \kappa_2 X_{AE}(s) ds\right)$$

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

$$X_B(t) = Y_3\left(\int_0^t \kappa_3 X_{AE}(s) ds\right)$$



Scaling

Note that $M = X_{AE}(t) + X_E(t)$ is constant. Let $N = O(X_A)$ define

$$V_E(t) = \int_0^t M^{-1} X_E(s) ds, \quad Z_A(t) = N^{-1} X_A(t)$$

$$\kappa_1 = M^{-1} \gamma_1, \quad \kappa_2 = NM^{-1} \gamma_2, \quad \kappa_3 = NM^{-1} \gamma_3$$

$$Z_A(t) = Z_A(0) - N^{-1} Y_1 \left(N \int_0^t \gamma_1 Z_A(s) dV_E(s) \right) + N^{-1} Y_2 (N \gamma_2 (t - V_E(t)))$$

$$X_E(t) = X_E(0) - Y_1 \left(N \int_0^t \gamma_1 Z_A(s) dV_E(s) \right) + Y_2 (N \gamma_2 (t - V_E(t))) \\ + Y_3 (N \gamma_3 (t - V_E(t)))$$

$$Z_B(t) = N^{-1} Y_3 (N \gamma_3 (t - V_E(t)))$$

Along a subsequence $(Z_A, Z_B, V_E) \Rightarrow (x_A, x_B, v_E)$ and

$$\int_0^t Z_A(s) dV_E(s) \Rightarrow \int_0^t x_A(s) dv_E(s) = \int_0^t x_A(s) \dot{v}_E(s) ds$$



Theorem 1 (Darden [3, 4]) Assume that $N \rightarrow \infty$, $M/N \rightarrow 0$, $M\kappa_1 \rightarrow \gamma_1$, $M\kappa_2/N \rightarrow \gamma_2$, $M\kappa_3/N \rightarrow \gamma_3$, and $X_A(0)/N \rightarrow x_A(0)$, and

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

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

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 $\kappa_2 = \gamma_2 N/M$, $\kappa_3 = \gamma_3 N/M$. Then

$$\begin{aligned} f(X_E(t)) - f(X_E(0)) - \int_0^t N\gamma_1 Z_A(s) M^{-1} X_E(s) (f(X_E(s)) - 1) - f(X_E(s)) ds \\ - \int_0^t N(\gamma_2 + \gamma_3)(1 - M^{-1} X_E(s)) (f(X_E(s)) + 1) - f(X_E(s)) ds \end{aligned}$$

Since $Z_A(s) \rightarrow x_A(s)$, $\int \mathbb{C} f(x_A(s), k) \eta_s(dk) = 0$ becomes

$$\begin{aligned} \sum_{k=0}^M \eta_s(k) \left[(\gamma_1 x_A(s) M^{-1} k (f(k) - 1) - f(k) \right. \\ \left. + (\gamma_2 + \gamma_3)(1 - M^{-1} k)(f(k) + 1) - f(k) \right] = 0 \end{aligned}$$

so η_s is binomial(M, p_s), where $p_s = \frac{\gamma_2 + \gamma_3}{\gamma_2 + \gamma_3 + \gamma_1 x_A(s)}$.



Forcing onto a lower dimensional manifold

Assume

$$F : \mathbb{R}^d \rightarrow \mathbb{R}^d$$

$\Xi \subset \{x \in \mathbb{R}^d : F(x) = \infty\}$ a submanifold of dimension $m < d$

$\partial F(x)$, $x \in \Xi$, has rank $d - m$ and the nonzero eigenvalues have negative real parts

$$\dot{\psi}(t, x) = x + \int_0^t F(\psi(s, x)) ds,$$

$$\Upsilon = \{x : \Phi(x) \equiv \lim_{t \rightarrow \infty} \psi(t, x) \text{ exists}\}$$

Then, under additional regularity conditions, Φ is C^2 and $\partial\Phi(x)F(x) = 0$ in a neighborhood of Ξ (Falconer (1983) [5]).



Convergence theorem

Katzenberger (1991) [6]

Theorem 2 Let $\{V_N\}$ be a sequence of semimartingales satisfying a *uniformity condition* and $V_N \Rightarrow V$, $\{A_N\}$ continuous nondecreasing processes such that

$$\inf_{t \geq 0} A_N(t + \epsilon) - A_N(t) \rightarrow \infty$$

for each $\epsilon > 0$. Suppose

$$Z_N(t) = V_N(t) + \int_0^t F(Z_N(s)) dA_N(s)$$

and $V_N(0) \Rightarrow Z(0) \in \Xi$. Then $Z_N \Rightarrow Z$ satisfying

$$Z(t) = Z(0) + \int_0^t \partial \Phi(Z(s)) dV(s) + \frac{1}{2} \sum_{k,l} \int_0^t \partial_{k,l}^2 \Phi(Z(s)) d[V_k, V_l]_s$$



Slow time scale limit

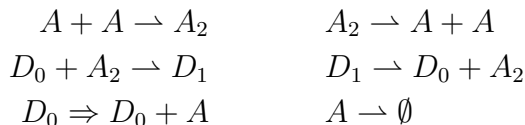
$$\begin{aligned}
 Z(t) &= Z(0) + \sum_k Y_k \left(\int_0^t N^{\beta_k} \lambda_k(Z(s)) ds \right) \Lambda_N \zeta_k \\
 &= Z(0) + \sum_k Y_k \left(\int_0^t N^{\beta_k} \lambda_k(Z(s)) ds \right) (\Lambda_N - \Lambda_N^0) \zeta_k \\
 &\quad + \sum_k \tilde{Y}_k \left(\int_0^t N^{\beta_k} \lambda_k(Z(s)) ds \right) \Lambda_N^0 \zeta_k \\
 &\quad + \int_0^t \sum_k N^{\beta_k} \lambda_k(Z(s)) \Lambda_N^0 \zeta_k ds
 \end{aligned}$$

Define $U^N(t) = Z(N^{-r_2}t)$ and assume $\zeta_{ik} \neq 0$ implies $\beta_k - r_2 \leq 2\alpha_i$ and

$$\begin{aligned}
 U^N(t) &= U^N(0) + \sum_k Y_k \left(\int_0^t N^{\beta_k - r_2} \lambda_k(U^N(s)) ds \right) (\Lambda_N - \Lambda_N^0) \zeta_k \\
 &\quad + \sum_k \tilde{Y}_k \left(\int_0^t N^{\beta_k - r_2} \lambda_k(U^N(s)) ds \right) \Lambda_N^0 \zeta_k \\
 &\quad + \int_0^t G(U^N(s)) ds + N^{r_1 - r_2} \int_0^t F(U^N(s)) ds
 \end{aligned}$$



Negative feedback with dimerization Bratsun, Volfson, Tsimring, and Hasty [2]



The model becomes

$$\begin{aligned} \theta(t) &= \theta(0) + Y_1 \left(\int_0^t \kappa_{-1} (1 - \theta(s)) ds \right) - Y_2 \left(\int_0^t \kappa_1 \theta(s) X_2(s) ds \right) \\ X_1(t) &= X_1(0) + Y_3 \left(\int_{-\tau}^{t-\tau} \kappa_3 \theta(s) ds \right) - Y_4 \left(\int_0^t \kappa_4 X_1(s) ds \right) \\ &\quad - 2Y_5 \left(\int_0^t \kappa_2 X_1(s) (X_1(s) - 1) ds \right) + 2Y_6 \left(\int_0^t \kappa_{-2} X_2(s) ds \right) \\ X_2(t) &= X_2(0) + Y_5 \left(\int_0^t \kappa_2 X_1(s) (X_1(s) - 1) ds \right) - Y_6 \left(\int_0^t \kappa_{-2} X_2(s) ds \right) \\ &\quad + Y_1 \left(\int_0^t \kappa_{-1} (1 - \theta(s)) ds \right) - Y_2 \left(\int_0^t \kappa_1 \theta(s) X_2(s) ds \right). \end{aligned}$$



Scaling

Replace κ_{-1} by $N\kappa_{-1}$, κ_{-2} by $N\kappa_{-2}$, κ_3 by $N\kappa_3$, and $(X_1(0), X_2(0))$ by $(NZ_1(0), NZ_2(0))$, and divide the three equations by N . Define $Z_1^N = N^{-1}X_1^N$, $Z_2^N = N^{-1}X_2^N$

$$\begin{aligned}\theta(t) &= \theta(0) + Y_1(N \int_0^t \kappa_{-1}(1 - \theta(s))ds) - Y_2(\int_0^t \kappa_1\theta(s)X_2(s)ds) \\ X_1(t) &= X_1(0) + Y_3(N \int_{-\tau}^{t-\tau} \kappa_3\theta(s)ds) - Y_4(\int_0^t \kappa_4X_1(s)ds) \\ &\quad - 2Y_5(\int_0^t \kappa_2X_1(s)(X_1(s) - 1)ds) + 2Y_6(N \int_0^t \kappa_{-2}X_2(s)ds) \\ X_2(t) &= X_2(0) + Y_5(\int_0^t \kappa_2X_1(s)(X_1(s) - 1)ds) - Y_6(N \int_0^t \kappa_{-2}X_2(s)ds) \\ &\quad + Y_1(N \int_0^t \kappa_{-1}(1 - \theta(s))ds) - Y_2(\int_0^t \kappa_1\theta(s)X_2(s)ds).\end{aligned}$$



$$\begin{aligned}
0 &\approx \int_0^t \kappa_{-1}(1 - \theta^N(s))ds - \int_0^t \kappa_1 \theta^N(s) Z_2^N(s) ds \\
Z_1^N(t) &= Z_1^N(0) + N^{-1} \tilde{Y}_3(N \int_{-\tau}^{t-\tau} \kappa_3 \theta^N(s) ds) - N^{-1} \tilde{Y}_4(N \int_0^t \kappa_4 Z_1^N(s) ds) \\
&\quad - 2N^{-1} \tilde{Y}_5(N^2 \int_0^t \kappa_2 Z_1^N(s)(Z_1^N(s) - N^{-1}) ds) + 2N^{-1} \tilde{Y}_6(N^2 \int_0^t \kappa_{-2} Z_2^N(s) ds) \\
&\quad + \int_{-\tau}^{t-\tau} \kappa_3 \theta^N(s) ds + \int_0^t (2\kappa_2 - \kappa_4) Z_1^N(s) ds \\
&\quad \quad + N \int_0^t 2(\kappa_{-2} Z_2^N(s) - \kappa_2 Z_1^N(s)^2) ds \\
Z_2^N(t) &= Z_2^N(0) + N^{-1} \tilde{Y}_5(N^2 \int_0^t \kappa_2 Z_1^N(s)(Z_1^N(s) - N^{-1}) ds) - N^{-1} \tilde{Y}_6(N^2 \int_0^t \kappa_{-2} Z_2^N(s) ds) \\
&\quad + N^{-1} Y_1(N \int_0^t \kappa_{-1}(1 - \theta^N(s)) ds) - N^{-1} Y_2(N \int_0^t \kappa_1 \theta^N(s) Z_2^N(s) ds) \\
&\quad - \int_0^t \kappa_2 Z_1^N(s) ds + N \int_0^t (\kappa_2 Z_1^N(s)^2 - \kappa_{-2} Z_2^N(s)) ds,
\end{aligned}$$



Strong drift

$$F(z_1, z_2) = (\kappa_{-2}z_2 - \kappa_2z_1^2) \begin{pmatrix} 2 \\ -1 \end{pmatrix}$$

$$\Xi = \{(z_1, z_2) : z_2 = \frac{\kappa_2}{\kappa_{-2}}z_1^2\}$$

Noting that

$$\begin{aligned} Z_1^N(t) + 2Z_2^N(t) &= Z_1^N(0) + 2Z_2^N(0) \\ &+ N^{-1}\tilde{Y}_3(N \int_{-\tau}^{t-\tau} \kappa_3\theta^N(s)ds) - N^{-1}\tilde{Y}_4(N \int_0^t \kappa_4Z_1^N(s)ds) \\ &+ \int_{-\tau}^{t-\tau} \kappa_3\theta^N(s)ds - \int_0^t \kappa_4Z_1^N(s)ds \\ &+ N^{-1}(\theta(t) - \theta(0)) \end{aligned}$$



Limiting equation

Let $\epsilon = \frac{\kappa_1}{\kappa_{-1}}$ and $\delta = \frac{\kappa_2}{\kappa_{-2}}$. Then

$$\hat{\theta}(t) = \frac{1}{1 + \epsilon Z_2(t)} = \frac{1}{1 + \epsilon \delta Z_1(t)^2}$$

and

$$Z_1(t) + 2\delta Z_1(t)^2 = Z_1(0) + 2\delta Z_1(0)^2 + \int_{-\tau}^{t-\tau} \frac{\kappa_3}{1 + \epsilon \delta Z_1(s)^2} ds - \int_0^t \kappa_4 Z_1(s) ds.$$



Appendix



Uniformity condition

$V_N = M_N + R_N$, a semimartingale adapted to $\{\mathcal{F}_t^N\}$

$T_t(R_N)$, the total variation of R_N on $[0, t]$

$[M_N]_t$, the quadratic variation of M_N on $[0, t]$

Condition 3 a)

$$\{T_t(R_N), N = 1, 2, \dots\}$$

is stochastically bounded.

b) *There exist stopping times $\{\tau_N^c\}$ such that*

$$\limsup_{c \rightarrow \infty} \sup_N P\{\tau_N^c \leq c\} = 0$$

and

$$\sup_N E[[M_N]_{t \wedge \tau_N^c}] < \infty$$



References

- [1] Karen Ball, Thomas G. Kurtz, Lea Popovic, and Grzegorz A. Rempala. Asymptotic analysis of multiscale approximations to reaction networks. *Ann. Appl. Probab.*, 2006. to appear.
- [2] Dmitri Bratsun, Dmitri Volfson, Lev S. Tsimring, and Jeff Hasty. Delay-induced stochastic oscillations in gene regulation. *PNAS*, 102:14593 – 14598, 2005.
- [3] Thomas Darden. A pseudo-steady state approximation for stochastic chemical kinetics. *Rocky Mountain J. Math.*, 9(1):51–71, 1979. Conference on Deterministic Differential Equations and Stochastic Processes Models for Biological Systems (San Cristobal, N.M., 1977).
- [4] Thomas A. Darden. Enzyme kinetics: stochastic vs. deterministic models. In *Instabilities, bifurcations, and fluctuations in chemical systems (Austin, Tex., 1980)*, pages 248–272. Univ. Texas Press, Austin, TX, 1982.
- [5] K. J. Falconer. Differentiation of the limit mapping in a dynamical system. *J. London Math. Soc. (2)*, 27(2):356–372, 1983.
- [6] G. S. Katzenberger. Solutions of a stochastic differential equation forced onto a manifold by a large drift. *Ann. Probab.*, 19(4):1587–1628, 1991.



- [7] Thomas G. Kurtz. Averaging for martingale problems and stochastic approximation. In *Applied stochastic analysis (New Brunswick, NJ, 1991)*, volume 177 of *Lecture Notes in Control and Inform. Sci.*, pages 186–209. Springer, Berlin, 1992.



Abstract

Model reduction for chemical reaction networks

Stochastic models of cellular chemical reaction networks typically involve chemical species numbers and reaction rates varying over several orders of magnitude. A number of researchers have proposed exploiting the multiscale nature of these models to reduce the complexity of the model to be analyzed or simulated. Systematic approaches to model reduction will be discussed.

