A shout-out to IMA

2003-2004 Year on Probability and Statistics in Complex Systems.

$$
\begin{aligned}
Ball + Popovic + Rempala + Kurtz &\overset{\text{IMA}}{\rightharpoonup} FRG \\
FRG &\rightharpoonup FRG^{-} + Ball \\
FRG^{-} + Craciun + Yin &\rightharpoonup FRG \\
FRG + !!!!!!!!!!!Williams(\text{unfunded collaborator})!!!!!!!!!!!! &\rightharpoonup SuperFRG \\
SuperFRG + \text{postdocs} + \text{grad students} &\rightharpoonup SuperDuperFRG
\end{aligned}
$$

Homotopy methods for counting reaction network equilibria Craciun, Helton, and Williams (2008)

At the interface of stochastic networks and systems biology

Enzyme reactions Mather, Cookson, Hasty, Tsimring, and Williams (2010)

$$D_i \xrightarrow{\lambda_i} S_i + D_i$$
$$S_i + E \xrightarrow{\eta} S_i E \xrightarrow{\mu} E + B_i$$

$X_{D_i} = 1$, $|X_S| = \sum_{i=1}^m X_{S_i}$, $|X_{SE}| = \sum_{i=1}^m X_{S_i E}$, $|X_B| = \sum_{i=1}^m X_{B_i}$, $X_E = M - |X_{SE}|$.

$$\begin{aligned} Af(s,c,b) &= \sum_{i=1}^m \lambda_i (f(s+e_i,c,b) - f(s,c,b)) \\ &\quad + \sum_{i=1}^m \eta s_i (M-|c|)(f(s-e_i,c_i+e_i,b) - f(s,c,b)) \\ &\quad + \sum_{i=1}^m \mu c_i (f(s,c_i-e_i,b+e_i) - f(s,c,b)) \end{aligned}$$

Conditional distribution of $X(t) = (X_S(t), X_{SE}(t), X_B(t))$ given $|X| = (|X_S(t)|, |X_{SE}(t)|, |X_B(t)|)$ should be multinomial.

A martingale fact

If X is a solution of the martingale problem for A, that is

$$f(X(t)) - f(X(0)) - \int_0^t Af(X(s))ds$$

is a $\{\mathcal{F}_t\}$-martingale for all $f \in \mathcal{D}(A)$, and $\pi_t(C) = P\{X(t) \in C|\mathcal{G}_t\}$ (e.g. $\mathcal{G}_t = \sigma(|X(s)|, s \leq t)$) then ($\mu f = \int f d\mu$)

$$\pi_t f - \pi_0 f - \int_0^t \pi_s Af ds$$

is a $\{\mathcal{G}_t\}$-martingale. Under mild conditions, the converse holds.

Kurtz and Ocone (1988); Kurtz (1998); Kurtz and Nappo (2011)

Rogers and Pitman (1981)

Reduced model

Setting $\lambda = \sum_{i=1}^m \lambda_i$, $p_i = \lambda^{-1}\lambda_i$, $|s| = \sum_{i=1}^m s_i$, $|c| = \sum_i^m c_i$, $|b| = \sum_{i=1}^m b_i$, define

$$\alpha(|s|,|c|,|b|,ds,dc,db)$$
$$= \binom{|s|}{s_1,\ldots,s_m} p_1^{s_1}\cdots p_m^{s_m} \binom{|c|}{c_1,\ldots,c_m} p_1^{c_1}\cdots p_m^{c_m} \binom{|b|}{b_1,\ldots,b_m} p_1^{b_1}\cdots p_m^{b_m}$$

Let

$$\alpha f(|s|,|c|,|b|) = \int f(s,c,b)\alpha(|s|,|c|,|b|,ds,dc,db)$$

and observe that

$$\alpha A f = C\alpha f$$

$$\begin{aligned} Cg(x,y.z) &= \lambda(g(x+1,y,z) - g(x,y,z) \\ &\quad +\eta x(M-y)(g(x-1,y+1,z) - g(x,y,z)) \\ &\quad +\mu y(g(x,y-1,z+1) - g(x,y,z)) \end{aligned}$$

Check the calculation for

$$f(s,c,b) = \exp\{-\sum_{i=1}^{m} \alpha_i s_i - \sum_{i=1}^{m} \beta_i c_i - \sum_{i=1}^{m} \gamma_i b_i\}$$

Relationship of processes

Let $|X|$ be a solution of the martingale problem for C and set

$$\pi_t(ds, dc, db) = \alpha(|X(t)|, ds, dc, db)$$

A solution of the martingale problem for C, that is, the Markov chain with generator C, with initial distribution $\nu(dx, dy, dz)$ is the projection of the solution of the martingale problem for A with initial distribution

$$\int \alpha(x, y, z, ds, dc, db)\nu(dx, dy, dz).$$

Stationary distributions

In particular, ifX we ignore the B_i, and set

$$\alpha(|s|,|c|,ds,dc) = \binom{|s|}{s_1,\ldots,s_m} p_1^{s_1}\cdots p_m^{s_m} \binom{|c|}{c_1,\ldots,c_m} p_1^{c_1}\cdots p_m^{c_m}$$

the stationary distribution for $(X_{S_1},\ldots,X_{S_m},X_{C_1},\ldots,X_{C_m})$ is

$$\pi(ds,dc) = \int \alpha(x,y,,ds,dc,)\pi^0(dx,dy)$$

where π^0 is the stationary distribution for (X_S,X_C), and for $i \neq j$

$$Cov(X_{S_i},X_{S_j}) = (Var(|X_S|) - E[|X_S|)p_i p_j.$$

Heavy traffic limit

Consider

$$\begin{aligned} D &\overset{\lambda}{\rightarrow} S + D \\ S + E &\overset{\eta}{\rightarrow} SE \overset{\mu}{\rightarrow} E + B. \end{aligned}$$

The Markov chain model can be obtained as the solution of

$$\begin{aligned} X_S(t) &= X_S(0) + Y_1(\lambda t) - Y_2(\int_0^t \eta X_S(s) X_E(s) ds) \\ X_{SE}(t) &= X_{SE}(0) + Y_2(\int_0^t \eta X_S(s) X_E(s) ds) - Y_3(\mu \int_0^t X_{SE}(s) ds) \\ X_E(t) &= X_E(0) - Y_2(\int_0^t \eta X_S(s) X_E(s) ds) + Y_3(\mu \int_0^t (M - X_E(s)) ds), \end{aligned}$$

where $M = X_E + X_{SE}$

Assume that λ varies with N so that $\sqrt{N}(\mu M - \lambda) \to \alpha$.

Rescaled equations

Speed up time by a factor of N, and scale X_S by $\sqrt{N}$.

$$
\begin{aligned}
X_S^N(t) &= X_S^N(0) + \frac{1}{\sqrt{N}} Y_1(N\lambda t) - \frac{1}{\sqrt{N}} Y_2(N^{3/2} \int_0^t \eta X_S^N(s) X_E^N(s) ds) \\
X_E^N(t) &= X_E^N(0) - Y_2(N^{3/2} \int_0^t \eta X_S^N(s) X_E^N(s) ds) \\
&\qquad + Y_3(\mu N \int_0^t (M - X_E^N(s)) ds)
\end{aligned}
$$

$$
\sqrt{N} \int_0^t \eta X_S^N(s) X_E^N(s) ds \to \mu M t
$$

Limiting equations

$$X_S^N(t) \approx X_S^N(0) + \frac{1}{\sqrt{N}} Y_1(N\lambda t) - \frac{1}{\sqrt{N}} Y_3(\mu N \int_0^t (M - X_E^N(s))ds)$$

$$= X_S^N(0) + \frac{1}{\sqrt{N}} \widetilde{Y}_1(N\lambda t) - \frac{1}{\sqrt{N}} \widetilde{Y}_3(\mu N \int (M - X_E^N(s))ds)$$

$$+\sqrt{N}(\lambda t - \int_0^t \mu(M - X_E^N(s))ds)$$

$$= X_S^N(0) + \frac{1}{\sqrt{N}} \widetilde{Y}_1(N\lambda t) - \frac{1}{\sqrt{N}} \widetilde{Y}_3(\mu N \int_0^t (M - X_E^N(s))ds)$$

$$+\sqrt{N}(\lambda - \mu M)t + \sqrt{N} \int_0^t \mu X_E^N(s)ds$$

Limiting equation

$$X_S(t) = X_S(0) + \sqrt{2\mu M}W(t) - \alpha t + \Lambda_+(t) + \Lambda_0(t)$$

$$\int_0^t \frac{\eta}{\mu} X_S(s) d\Lambda_+(s) = \mu M t$$

where Λ_+ and Λ_0 are nondecreasing, Λ_+ increases only when $X_S > 0$ and Λ_0 increases only when $X_S = 0$.

Equivalently,

$$X_S(t) = X_S(0) + \sqrt{2\mu M}W(t) - \alpha t + \int_0^t \frac{\mu^2 M}{\eta X_S(s)} ds + \Lambda_0(t).$$

If $\eta \leq \mu$, X_S does not hit zero.

Chemical network models

$\mathcal{S} = \{A_i : i = 1, \ldots, m\}$ chemical species

$\mathcal{C} = \{\nu_k, \nu'_k : k = 1, \ldots, n\}$ complexes

$\mathcal{R} = \{\nu_k \to \nu'_k : k = 1, \ldots, n\}$ reactions

determine a *chemical reaction network*.

$$\sum \nu_{ki} A_i \rightharpoonup \sum \nu'_{ki} A$$

Deterministic model (law of mass action) $\quad c^\nu = \prod_i c_i^{\nu_i}$

$$\dot{C} = \sum_k \kappa_k C^{\nu_k} (\nu'_k - \nu_k)$$

Stochastic model

$$X(t) = X(0) + \sum_k Y_k(\kappa_k \int_0^t \prod_i \binom{X_i(s)}{\nu_{k_i}} ds)(\nu'_k - \nu_k)$$

Weak reversibility

Definition 1 *A chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is called* weakly reversible *if for any reaction $\nu_k \to \nu_k'$, there is a sequence of directed reactions beginning with ν_k' as a source complex and ending with ν_k as a product complex. That is, there exist complexes $\nu_1, \ldots, \nu_r$ such that $\nu_k' \to \nu_1, \nu_1 \to \nu_2, \ldots, \nu_r \to \nu_k \in \mathcal{R}$. A network is called* reversible *if $\nu_k' \to \nu_k \in \mathcal{R}$ whenever $\nu_k \to \nu_k' \in \mathcal{R}$.*

Linkage classes

Let $\mathcal{G}$ be the directed graph with nodes given by the complexes $\mathcal{C}$ and directed edges given by the reactions $\mathcal{R} = \{\nu_k \to \nu_k'\}$, and let $\mathcal{G}_1, \ldots, \mathcal{G}_\ell$ denote the connected components of $\mathcal{G}$. $\{\mathcal{G}_j\}$ are the *linkage classes* of the reaction network.

Intuition for probabilists: If the network is weakly reversible, then, thinking of the complexes as states of a Markov chain, the linkage classes are the irreducible communicating equivalence classes of classical Markov chain theory. BUT, these equivalence classes do not correspond to the communicating equivalence classes of the Markov chain model of the reaction network.

Stoichiometric subspace

Definition 2 $S = \text{span}_{\{\nu_k \to \nu_k' \in \Re\}}\{\nu_k' - \nu_k\}$ is the *stoichiometric subspace* of the network. For $c \in \mathbb{R}^m$ we say $c + S$ and $(c + S) \cap \mathbb{R}^m_{>0}$ are the *stoichiometric compatibility classes* and *positive stoichiometric compatibility classes* of the network, respectively. Denote $\dim(S) = s$.

Note that $X(t) - X(0) \in S$.

If the network is weakly reversible, then the communicating equivalence classes for the Markov chain model are of the form

$$\{z + \sum_k a_k(\nu_k' - \nu_k) : a = (a_1, \ldots, a_n) \in \mathbb{Z}^n_{\geq 0}\}$$

for some $z \in \mathbb{Z}^m_{\geq 0}$.

Deficiency of a network

Definition 3 The *deficiency* of a a chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is $\delta = |\mathcal{C}| - \ell - s$, where $|\mathcal{C}|$ is the number of complexes, ℓ is the number of linkage classes, and s is the dimension of the stoichiometric subspace.

Lemma 4 (Feinberg (1987)) *The deficiency of a network is nonnegative.*

Proof. Let $\mathcal{C}_i$ be the complexes in the ith linkage class and let S_i be the span of the reaction vectors giving the edges in the ith linkage class. Then $\dim(S_i) \leq |\mathcal{C}_i| - 1$ and

$$\dim(S) \leq \sum_i \dim(S_i) \leq \sum_{i=1}^{\ell} |\mathcal{C}_i| - \ell = |\mathcal{C}| - \ell.$$

□

Deficiency zero theorem

Theorem 5 (The Deficiency Zero Theorem, Feinberg (1987))

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a weakly reversible, deficiency zero chemical reaction network with mass action kinetics. Then, for any choice of rate constants κ_k, within each positive stoichiometric compatibility class there is precisely one equilibrium value c, $\sum_k \kappa_k c^{\nu_k}(\nu'_k - \nu_k) = 0$, and that equilibrium value is locally asymptotically stable relative to its compatibility class. More precisely, for each $\eta \in \mathcal{C}$,

$$\sum_{k:\nu_k=\eta} \kappa_k c^{\nu_k} = \sum_{k:\nu'_k=\eta} \kappa_k c^{\nu_k}. \tag{1}$$

$$c^{\nu_k} = \prod_{i=1}^{m} c_i^{\nu_{ki}}$$

Zero deficiency theorem for stochastic models

For $x \in \mathbb{Z}^m_{\geq 0}$, $c^x = \prod_{i=1}^m c_i^{x_i}$ and $x! = \prod_{i=1}^m x_i!$. If $c \in \mathbb{R}^m_{>0}$ satisfies

$$\sum_{k:\nu_k=\eta} \kappa_k c^{\nu_k} = \sum_{k:\nu'_k=\eta} \kappa_k c^{\nu_k}, \quad \eta \in \mathcal{C}, \tag{2}$$

then the network is *complex balanced.*

Theorem 6 (Kelly (1979),Anderson, Craciun, and Kurtz (2010))

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with rate constants κ_k. Suppose that the system is complex balanced with equilibrium $\overline{c} \in \mathbb{R}^m_{>0}$. Then, for any irreducible communicating equivalence class, Γ, the stochastic system has a product form stationary measure

$$\pi(x) = M\frac{\overline{c}^x}{x!}, \quad x \in \Gamma, \tag{3}$$

where M is a normalizing constant.

Michaelis-Menten (cf. Darden (1982); Kang, Kurtz, and Popovic (2013))

$$S + E \rightleftharpoons SE \rightharpoonup E + B$$

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

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

Averaging

$$M^{N,1}(t) = Z_S^N(t) - Z_S^N(0) - \int_0^t (\kappa_2 X_{SE}^N(s) - \kappa_1 Z_S^N(s) X_E^N(s)) ds \to 0$$

$$\int_0^t \kappa_1 Z_S^N(s) X_E^N(s) ds - \kappa_2 \int_0^t (m - X_E^N(s)) ds - \kappa_3 \int_0^t (m - X_E^N(s)) ds)$$
$$= \int_0^t (\kappa_1 Z_S^N(s) + \kappa_2 + \kappa_3) X_E^N(s) ds - (\kappa_2 + \kappa_3) mt \to 0$$

and

$$\int_0^t X_E^N(s) ds - \int_0^t \frac{m(\kappa_2 + \kappa_3)}{\kappa_1 Z_S^N(s) + \kappa_2 + \kappa_3} ds \to 0$$

Side calculation:

$$[M^{N,1}]_t = N^{-2} Y_1(N \int_0^t \kappa_1 Z_S^N(s) X_E^N(s) ds) + N^{-2} Y_2(N \kappa_2 \int_0^t X_{SE}^N(s) ds)$$

Deterministic limit

$$
\begin{aligned}
Z_S^N(t) &= Z_S^N(0) - N^{-1}Y_1(N\int_0^t \kappa_1 Z_S^N(s)X_E^N(s)ds) \\
&\quad + N^{-1}Y_2(N\kappa_2\int_0^t X_{SE}^N(s)ds) \\
&\approx Z_S^N(0) - \int_0^t \kappa_1 Z_S^N(s)X_E^N(s)ds) + \kappa_2\int_0^t X_{SE}^N(s)ds) \\
&\approx Z_S^N(0) - \kappa_3\int_0^t (m - \frac{m(\kappa_2+\kappa_3)}{\kappa_1 Z_S^N(s) + \kappa_2 + \kappa_3})ds \\
&= Z_S^N(0) - \int_0^t \frac{m\kappa_1\kappa_3 Z_S^N(s)}{\kappa_1 Z_S^N(s) + \kappa_2 + \kappa_3}ds
\end{aligned}
$$

so $Z_S^N \Rightarrow Z_S$ satisfying

$$
Z_S(t) = Z_S(0) - \int_0^t \frac{m\kappa_1\kappa_3 Z_S(s)}{\kappa_1 Z_S(s) + \kappa_2 + \kappa_3}ds
$$

Another enzyme reaction model

$$S + E \rightleftharpoons SE \rightharpoonup B + E \qquad E \rightleftharpoons F + G \qquad \emptyset \rightharpoonup G \to \emptyset$$

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

Stationary expectations for fast process

Need the stationary expectations for the fast subsystem

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

Claim:

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

and hence

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

Fast subnetwork

$$S + E \rightleftharpoons SE \rightharpoonup B + E \qquad E \rightleftharpoons F + G \qquad \emptyset \rightharpoonup G \to \emptyset$$

But we can treat S as constant in abundance, so

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

But B has no further effect on the network, so

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

This network is weakly reversible.

There are four species and possible changes in species numbers are

$$\pm \begin{pmatrix} -1 \\ 1 \\ 0 \\ 0 \end{pmatrix}, \quad \pm \begin{pmatrix} -1 \\ 0 \\ 1 \\ 1 \end{pmatrix}, \quad \pm \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}$$

so $s = 3$. Sine $|\mathcal{C}| = 5$ and $|\ell| = 2$, $\delta = 0$.

References

David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz. Product-form stationary distributions for deficiency zero chemical reaction networks. *Bull. Math. Biol.*, 72(8):1947–1970, 2010.

Gheorghe Craciun, J. William Helton, and Ruth J. Williams. Homotopy methods for counting reaction network equilibria. *Math. Biosci.*, 216(2):140–149, 2008. ISSN 0025-5564. doi: 10.1016/j.mbs.2008.09.001. URL http://dx.doi.org/10.1016/j.mbs.2008.09.001.

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.

Martin Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors i. the deficiency zero and deficiency one theorems. *Chem. Engr. Sci.*, 42(10):2229–2268, 1987.

Hye-Won Kang, Thomas G. Kurtz, and Lea Popovic. Central limit theorems and diffusion approximations for multiscale Markov chain models. *Ann. Appl. Probab.*, 2013. to appear.

Frank P. Kelly. *Reversibility and stochastic networks*. John Wiley & Sons Ltd., Chichester, 1979. ISBN 0-471-27601-4. Wiley Series in Probability and Mathematical Statistics.

Thomas G. Kurtz. Martingale problems for conditional distributions of Markov processes. *Electron. J. Probab.*, 3:no. 9, 29 pp. (electronic), 1998. ISSN 1083-6489.

Thomas G. Kurtz and Giovanna Nappo. The filtered martingale problem. In Dan Crisan and Boris Rozovskii, editors, *Handbook on Nonlinear Filtering*, chapter 5, pages 129–165. Oxford University Press, 2011.

Thomas G. Kurtz and Daniel L. Ocone. Unique characterization of conditional distributions in nonlinear filtering. *Ann. Probab.*, 16(1):80–107, 1988. ISSN 0091-1798.

William H. Mather, Natalie A. Cookson, Jeff Hasty, Lev S. Tsimring, and Ruth J. Williams. Correlation resonance generated by coupled enzymatic processing. *Biophysical J.*, 99:3172–3181, 2010.

L. C. G. Rogers and J. W. Pitman. Markov functions. *Ann. Probab.*, 9(4):573–582, 1981. ISSN 0091-1798. URL http://links.jstor.org/sici?sici=0091-1798(198108)9:4<573:MF>2.0.CO;2-G&origin=MSN.

Abstract

At the interface of stochastic networks and systems biology

Beginning with a model of a system of enzyme reactions used by Ruth and her collaborators, connections between results on queueing network models and chemical reaction network models used in systems biology will be explored, including product form stationary distributions, Burke's theorem, fluid limit approximations, heavy traffic limits, and, perhaps, large deviations.