

# Averaging fast subsystems

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# Intensities for continuous-time Markov chains

Assume  $X$  is a continuous time Markov chain in  $\mathbb{Z}^d$ . Then

$$P\{X(t + \Delta t) - X(t) = l | X(t) = k\} \approx \beta_l(k)\Delta t,$$

and hence

$$\begin{aligned} E[f(X(t + \Delta t)) - f(X(t)) | \mathcal{F}_t^X] &\approx \sum_l \beta_l(X(t))(f(X(t) + l) - f(X(t)))\Delta t \\ &\equiv \mathbb{A}f(X(t))\Delta t \end{aligned}$$

Then

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

is the *generator* for the chain



# 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  $\mathbb{A}$ .



# Martingale problem

$E$  state space (a complete, separable metric space)

$\mathbb{A}$  generator (a linear operator with domain and range in  $B(E)$ )

$\mu \in \mathcal{P}(E)$

$X$  is a solution of the martingale problem for  $(\mathbb{A}, \mu)$  if and only if  $\mu = PX(0)^{-1}$  and there exists a filtration  $\{\mathcal{F}_t\}$  such that

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

is an  $\{\mathcal{F}_t\}$ -martingale for each  $f \in \mathcal{D}(\mathbb{A})$



# Examples

Standard Brownian motion ( $E = \mathbb{R}^d$ )

$$\mathbb{A}f = \frac{1}{2}\Delta f, \quad \mathcal{D}(\mathbb{A}) = C_c^2(\mathbb{R}^d)$$

Poisson process ( $E = \{0, 1, 2, \dots\}$ ,  $\mathcal{D}(\mathbb{A}) = B(E)$ )

$$\mathbb{A}f(k) = \lambda(f(k+1) - f(k))$$

Pure jump process ( $E$  arbitrary)

$$\mathbb{A}f(x) = \lambda(x) \int_E (f(y) - f(x))\mu(x, dy)$$

Diffusion ( $E = \mathbb{R}^d$ )

$$\mathbb{A}f(x) = \frac{1}{2} \sum_{i,j} a_{ij}(x) \frac{\partial^2}{\partial x_i \partial x_j} f(x) + \sum_i b_i(x) \frac{\partial}{\partial x_i} f(x), \quad \mathcal{D}(\mathbb{A}) = C_c^2(\mathbb{R}^d)$$



# Uniqueness and the Markov property

**Theorem 1** *If any two solutions of the martingale problem for  $\mathbb{A}$  satisfying  $PX_1(0)^{-1} = PX_2(0)^{-1}$  also satisfy  $PX_1(t)^{-1} = PX_2(t)^{-1}$  for all  $t \geq 0$ , then the f.d.d. of a solution  $X$  are uniquely determined by  $PX(0)^{-1}$*

If  $X$  is a solution of the MGP for  $\mathbb{A}$  and  $X_a(t) = X(a + t)$ , then  $X_a$  is a solution of the MGP for  $\mathbb{A}$ .

**Theorem 2** *If the conclusion of the above theorem holds, then any solution of the martingale problem for  $\mathbb{A}$  is a Markov process.*



# General approaches to averaging

Models with two time scales:  $(X, V)$ ,  $V$  is “fast”

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

Replace integrals involving  $V$  by integrals against  $\Gamma^V$

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

How do we identify  $\eta_s$ ?



# Generator approach

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

$$\begin{aligned} f(X_r(t), V_r(t)) - r \int_{E^V \times [0, t]} \mathbb{C}f(X_r(s), v) \Gamma_r^V(dv \times ds) \\ - \int_{E^V \times [0, t]} \mathbb{D}f(X_r(s), v) \Gamma_r^V(dv \times ds) \end{aligned}$$

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

$$\int_{E^V \times [0, t]} \mathbb{C}f(X(s), v) \Gamma^V(dv \times ds) = \int_{E^V \times [0, t]} \mathbb{C}f(X(s), v) \eta_s(dv) ds = 0 \quad (1)$$

Suppose that for each  $x$ , the solution  $\mu_x \in \mathcal{P}(E^V)$  of  $\int_{E^V} \mathbb{C}f(x, v) \mu_x(dv) = 0$ ,  $f \in \mathcal{D}$ , is unique. Then  $\eta_s(dv) = \mu_{X(s)}(dv)$





## Prohorov metric

The *Prohorov metric* on  $\mathcal{M}_f(S)$ , the space of finite measures on a complete, separable metric space  $S$ , is

$$\rho(\mu, \nu) = \inf\{\epsilon > 0 : \mu(B) \leq \nu(B^\epsilon) + \epsilon, \nu(B) \leq \mu(B^\epsilon) + \epsilon, B \in \mathcal{B}(S)\}, \quad (2)$$

where  $B^\epsilon = \{x \in S : \inf_{y \in B} d(x, y) < \epsilon\}$ .

**Lemma 3**  $(\mathcal{M}_f(S), \rho)$  is a complete, separable metric space.

**Lemma 4** Convergence in the Prohorov metric is equivalent to weak convergence, that is,  $\rho(\mu_n, \mu) \rightarrow 0$  if and only if

$$\int f d\mu_n \rightarrow \int f d\mu, \quad f \in \bar{C}(S).$$



# Convergence of random measures

**Lemma 5** *Let  $\{\Gamma_n\}$  be a sequence of  $\mathcal{M}_f(S)$ -valued random variables. Then  $\Gamma_n$  is relatively compact if and only if  $\{\Gamma_n(S)\}$  is relatively compact as a family of  $\mathbb{R}$ -valued random variables and for each  $\epsilon > 0$ , there exists a compact  $K \subset S$  such that  $\sup_n P\{\Gamma_n(K^c) > \epsilon\} < \epsilon$ .*

**Corollary 6** *Let  $\{\Gamma_n\}$  be a sequence of  $\mathcal{M}_f(S)$ -valued random variables. Suppose that  $\sup_n E[\Gamma_n(S)] < \infty$  and that for each  $\epsilon > 0$ , there exists a compact  $K \subset S$  such that*

$$\limsup_{n \rightarrow \infty} E[\Gamma_n(K^c)] \leq \epsilon.$$

*Then  $\{\Gamma_n\}$  is relatively compact.*



## Space-time measures

Let  $\mathcal{L}(S)$  be the space of measures on  $[0, \infty) \times S$  such that  $\mu([0, t] \times S) < \infty$  for each  $t > 0$ , and let  $\mathcal{L}_m(S) \subset \mathcal{L}(S)$  be the subspace on which  $\mu([0, t] \times S) = t$ . For  $\mu \in \mathcal{L}(S)$ , let  $\mu^t$  denote the restriction of  $\mu$  to  $[0, t] \times S$ . Let  $\rho_t$  denote the Prohorov metric on  $\mathcal{M}([0, t] \times S)$ , and define  $\hat{\rho}$  on  $\mathcal{L}(S)$  by

$$\hat{\rho}(\mu, \nu) = \int_0^\infty e^{-t} 1 \wedge \rho_t(\mu^t, \nu^t) dt,$$

that is,  $\{\mu_n\}$  converges in  $\hat{\rho}$  if and only if  $\{\mu_n^t\}$  converges weakly for almost every  $t$ . In particular, if  $\hat{\rho}(\mu_n, \mu) \rightarrow 0$ , then  $\rho_t(\mu_n^t, \mu^t) \rightarrow 0$  if and only if  $\mu_n([0, t] \times S) \rightarrow \mu([0, t] \times S)$ .



## Relative compactness in $\mathcal{L}_m(S)$

**Lemma 7** *A sequence of  $(\mathcal{L}_m(S), \hat{\rho})$ -valued random variables  $\{\Gamma_n\}$  is relatively compact if and only if for each  $\epsilon > 0$  and each  $t > 0$ , there exists a compact  $K \subset S$  such that  $\inf_n E[\Gamma_n([0, t] \times K)] \geq (1 - \epsilon)t$ .*

**Lemma 8** *If  $V_r$  takes values in a locally compact space  $E^V$ ,  $\psi \geq 1$  and  $\{v \in E^V : \psi(v) \leq c\}$  is compact for each  $c > 1$ , and*

$$\sup_r E\left[\int_0^t \psi(V_r(s)) ds\right] = \sup_r \int_0^t E[\psi(V_r(s))] ds < \infty,$$

*then the family of occupation measures  $\{\Gamma_r\}$  is relatively compact in  $\mathcal{L}_m(E^V)$ .*



# Disintegration of measures

**Lemma 9** *Let  $\Gamma$  be an  $(\mathcal{L}(S), \hat{\rho})$ -valued random variable adapted to a complete filtration  $\{\mathcal{F}_t\}$  in the sense that for each  $t \geq 0$  and  $H \in \mathcal{B}(S)$ ,  $\Gamma([0, t] \times H)$  is  $\mathcal{F}_t$ -measurable. Let  $\lambda(G) = \Gamma(G \times S)$ . Then there exists an  $\{\mathcal{F}_t\}$ -optional,  $\mathcal{P}(S)$ -valued process  $\gamma$  such that*

$$\int_{[0, t] \times S} h(s, y) \Gamma(ds \times dy) = \int_0^t \int_S h(s, y) \gamma_s(dy) \lambda(ds). \quad (3)$$

*for all  $h \in B([0, \infty) \times S)$  with probability one. If  $\lambda([0, t])$  is continuous, then  $\gamma$  can be taken to be  $\{\mathcal{F}_t\}$ -predictable.*



# Convergence of integrals

**Lemma 10** *Let  $\{(x_n, \mu_n)\} \subset D_E[0, \infty) \times \mathcal{L}(S)$ , and  $(x_n, \mu_n) \rightarrow (x, \mu)$ . Let  $h \in \bar{C}(E \times S)$ . Define*

$$u_n(t) = \int_{[0,t] \times S} h(x_n(s), y) \mu_n(ds \times dy), \quad u(t) = \int_{[0,t] \times S} h(x(s), y) \mu(ds \times dy)$$

$$z_n(t) = \mu_n([0, t] \times S), \text{ and } z(t) = \mu([0, t] \times S).$$

- a) *If  $x$  is continuous on  $[0, t]$  and  $\lim_{n \rightarrow \infty} z_n(t) = z(t)$ , then  $\lim_{n \rightarrow \infty} u_n(t) = u(t)$ .*
- b) *If  $(x_n, z_n, \mu_n) \rightarrow (x, z, \mu)$  in  $D_{E \times \mathbb{R}}[0, \infty) \times \mathcal{L}(S)$ , then  $(x_n, z_n, u_n, \mu_n) \rightarrow (x, z, u, \mu)$  in  $D_{E \times \mathbb{R} \times \mathbb{R}}[0, \infty) \times \mathcal{L}(S)$ . In particular,  $\lim_{n \rightarrow \infty} u_n(t) = u(t)$  at all points of continuity of  $z$ .*



- c) *The continuity assumption on  $h$  can be replaced by the assumption that  $h$  is continuous a.e.  $\nu_t$  for each  $t$ , where  $\nu_t \in \mathcal{M}(E \times S)$  is the measure determined by  $\nu_t(A \times B) = \mu\{(s, y) : x(s) \in A, s \leq t, y \in B\}$ .*
- d) *In both (a) and (b), the boundedness assumption on  $h$  can be replaced by the assumption that there exists a nonnegative convex function  $\psi$  on  $[0, \infty)$  satisfying  $\lim_{r \rightarrow \infty} \psi(r)/r = \infty$  such that*

$$\sup_n \int_{[0,t] \times S} \psi(|h(x_n(s), y)|) \mu_n(ds \times dy) < \infty \quad (4)$$

*for each  $t > 0$ .*



# Well-mixed reactions

Consider  $A + B \xrightarrow{\kappa} C$ . 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  $i$ th molecule of  $A$

$V_j$  state of  $j$ th molecule of  $B$

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

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

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

would model the independent evolution of  $m$  molecules of  $A$  and  $n$  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  $\Gamma^r$  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  $(\Gamma, X_A, X_B)$  of  $\Gamma^r$  as  $r \rightarrow \infty$  satisfies

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

cf. Kurtz [4]



## 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  $\mu_A, \mu_B$ , 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  $A + E \rightleftharpoons AE \rightarrow B + E$  modeled as a continuous time Markov chain satisfying

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

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

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

Note that  $M = X_{AE}^N(t) + X_E^N(t)$  is constant.



## Quasi-steady state

Then

$$f(X_E^N(t)) - f(X_E^N(0)) - \int_0^t N\kappa_1 Z_A^N(s) X_E^N(s) (f(X_E^N(s) - 1) - f(X_E^N(s))) ds \\ - \int_0^t N(\kappa_2 + \kappa_3)(M - X_E^N(s)) (f(X_E^N(s) + 1) - f(X_E^N(s))) ds$$

At least along a subsequence  $Z_A^N = N^{-1} X_A^N \rightarrow Z_A$ , and by (1),

$$\sum_{k=0}^M \eta_s(k) (\kappa_1 Z_A(s) k (f(k-1) - f(k)) + (\kappa_2 + \kappa_3)(M - k) (f(k+1) - f(k))) = 0$$

so  $\eta_s$  is binomial( $M, p_s$ ), where

$$p_s = \frac{\kappa_2 + \kappa_3}{\kappa_2 + \kappa_3 + \kappa_1 Z_A(s)}.$$



## Substrate dynamics

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

Noting that  $\sum_{k=0}^M k\eta_s(k) = Mp_s$ , so the averaged generator becomes

$$f(Z_A(t)) - f(Z_A(0)) - \int_0^t (\kappa_2 M(1 - p_s) - \kappa_1 Mp_s Z_A(s)) f'(Z_A(s)) dx$$

is a martingale (actually  $\equiv 0$ ), so

$$\begin{aligned} Z_A(t) &= Z_A(0) + \int_0^t (\kappa_2 M(1 - p_s) - \kappa_1 Mp_s Z_A(s)) ds \\ &= Z_A(0) + \int_0^t \frac{M\kappa_1\kappa_3 Z_A(s)}{\kappa_2 + \kappa_3 + \kappa_1 Z_A(s)} ds \end{aligned}$$



## Another enzyme reaction model



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

$$X_E^N(t) = X_E^N(0) - Y_1(N \int_0^t \kappa_1 Z_A^N(s) X_E^N(s) ds) + Y_2(N \int_0^t \kappa_2 X_{AE}^N(s) ds) \\ + Y_3(N \int_0^t \kappa_3 X_{AE}^N(s) ds) + Y_4(N \int_0^t \kappa_4 X_F^N(s) X_G^N(s) ds) - Y_5(N \int_0^t \kappa_5 X_E^N(s) ds)$$

$$X_F^N(t) = X_F^N(0) + Y_5(N \int_0^t \kappa_5 X_E^N(s) ds) - Y_4(N \int_0^t \kappa_4 X_F^N(s) X_G^N(s) ds)$$

$$X_G^N(t) = X_G^N(0) + Y_6(N \kappa_6 t) + Y_5(N \int_0^t \kappa_5 X_E^N(s) ds) - Y_4(N \int_0^t \kappa_4 X_F^N(s) X_G^N(s) ds) \\ - Y_7(N \int_0^t \kappa_7 X_G(s) ds)$$



# Stationary expectations for fast process

Need the stationary expectations for the fast subsystem

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

Claim:

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

and hence

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





# Network reversibility conditions

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

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

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

determine a *chemical reaction network*.

**Definition 11** A chemical reaction network,  $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ , is called weakly reversible if for any reaction  $\nu_k \rightarrow \nu'_k$ , there is a sequence of directed reactions beginning with  $\nu'_k$  as a source complex and ending with  $\nu_k$  as a product complex. That is, there exist complexes  $\nu_1, \dots, \nu_r$  such that  $\nu'_k \rightarrow \nu_1, \nu_1 \rightarrow \nu_2, \dots, \nu_r \rightarrow \nu_k \in \mathcal{R}$ . A network is called reversible if  $\nu'_k \rightarrow \nu_k \in \mathcal{R}$  whenever  $\nu_k \rightarrow \nu'_k \in \mathcal{R}$ .



# Linkage classes

Let  $\mathcal{G}$  be the directed graph with nodes given by the complexes  $\mathcal{C}$  and directed edges given by the reactions  $\mathcal{R} = \{\nu_k \rightarrow \nu'_k\}$ , and let  $\mathcal{G}_1, \dots, \mathcal{G}_\ell$  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 12**  $S = \text{span}_{\{\nu_k \rightarrow \nu'_k \in \mathfrak{R}\}} \{\nu'_k - \nu_k\}$  is the *stoichiometric subspace* of the network. For  $c \in \mathbb{R}^m$  we say  $c+S$  and  $(c+S) \cap \mathbb{R}_{>0}^m$  are the *stoichiometric compatibility classes* and *positive stoichiometric compatibility classes* of the network, respectively. Denote  $\dim(S) = s$ .

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

$$\left\{ z + \sum_k a_k (\nu'_k - \nu_k) : a = (a_1, \dots, a_n) \in \mathbb{Z}_{\geq 0}^n \right\}$$

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



# Deficiency of a network

**Definition 13** The *deficiency* of a chemical reaction network,  $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ , is  $\delta = |\mathcal{C}| - \ell - s$ , where  $|\mathcal{C}|$  is the number of complexes,  $\ell$  is the number of linkage classes, and  $s$  is the dimension of the stoichiometric subspace.

**Lemma 14 (Feinberg [2])** *The deficiency of a network is nonnegative.*

**Proof.** Let  $\mathcal{C}_i$  be the complexes in the  $i$ th linkage class and let  $S_i$  be the span of the reaction vectors giving the edges in the  $i$ th 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 15 (The Deficiency Zero Theorem, Feinberg [2])** *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  $\kappa_k$ , 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  $\eta \in \mathcal{C}$ ,*

$$\sum_{k:\nu_k=\eta} \kappa_k c^{\nu_k} = \sum_{k:\nu'_k=\eta} \kappa_k c^{\nu_k}. \quad (5)$$



# Zero deficiency theorem for stochastic models

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

$$\sum_{k:\nu_k=\eta} \kappa_k c^{\nu_k} = \sum_{k:\nu'_k=\eta} \kappa_k c^{\nu_k}, \quad \eta \in \mathcal{C}, \quad (6)$$

then the network is *complex balanced*.

**Theorem 16** (Kelly [3], Anderson, Craciun, and Kurtz [1]) *Let  $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$  be a chemical reaction network with rate constants  $\kappa_k$ . Suppose that the system is complex balanced with equilibrium  $\bar{c} \in \mathbb{R}_{>0}^m$ . Then, for any irreducible communicating equivalence class,  $\Gamma$ , the stochastic system has a product form stationary measure*

$$\pi(x) = M \frac{\bar{c}^x}{x!}, \quad x \in \Gamma, \quad (7)$$

where  $M$  is a normalizing constant.



## References

- [1] David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz. Product-form stationary distributions for deficiency zero chemical reaction networks.
- [2] 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.
- [3] Frank P. Kelly. *Reversibility and stochastic networks*. John Wiley & Sons Ltd., Chichester, 1979. Wiley Series in Probability and Mathematical Statistics.
- [4] 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

## Averaging fast subsystems

Reducing the complexity of system models by averaging fast subsystems has a long history in applied mathematics in general and for stochastic models in particular. The previous lectures exploited ad hoc, stochastic analytic relationships to derive the desired averages. This lecture will focus on more systematic methods based on the martingale properties of the underlying Markov processes.

