Tutorial: stochastic models of biochemical reaction systems

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Goals of this tutorial

Introduce mathematical models from molecular biology – reaction networks:

- Stochastic models – continuous time Markov chains with stochastic mass action kinetics.
- Deterministic models – ODEs with deterministic mass action kinetics.

Introduce the field of chemical reaction network theory – 50%

Focus on deficiency of networks and **deficiency zero** results – 50%

Tomorrow will focus on results related to deficiency one models.

Reaction networks

Models usually begin with something called a reaction network.

$$A + B \to 2B$$
$$B \to A$$

or

$$E + S \rightleftarrows ES \rightleftarrows E + P$$
$$E \rightleftarrows \emptyset$$

The network is a static object. We are not yet choosing a dynamics.

Reaction networks

- Biochemical/population networks can range from simple to very complex.

  Example 1: $\emptyset \rightleftarrows A$.

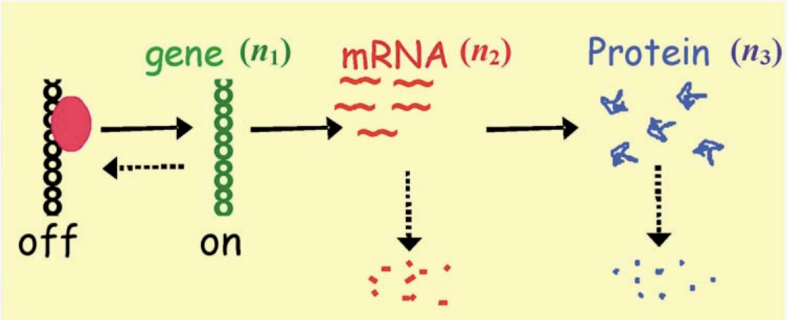
Example 2: $A + B \to 2B$

$B \to A$

Example 3: Gene transcription & translation:

$$G \to G + M \quad \textit{transcription}$$
$$M \to M + P \quad \textit{translation}$$
$$M \to \emptyset \quad \textit{degradation}$$
$$P \to \emptyset \quad \textit{degradation}$$
$$G + P \rightleftarrows B \quad \text{Binding/unbinding}$$

Cartoon representation:



[1]

[1] J. Paulsson, Physics of Life Reviews, **2**, 2005 157 – 175.

Reaction networks

Example 4: EnvZ/OmpR signaling system

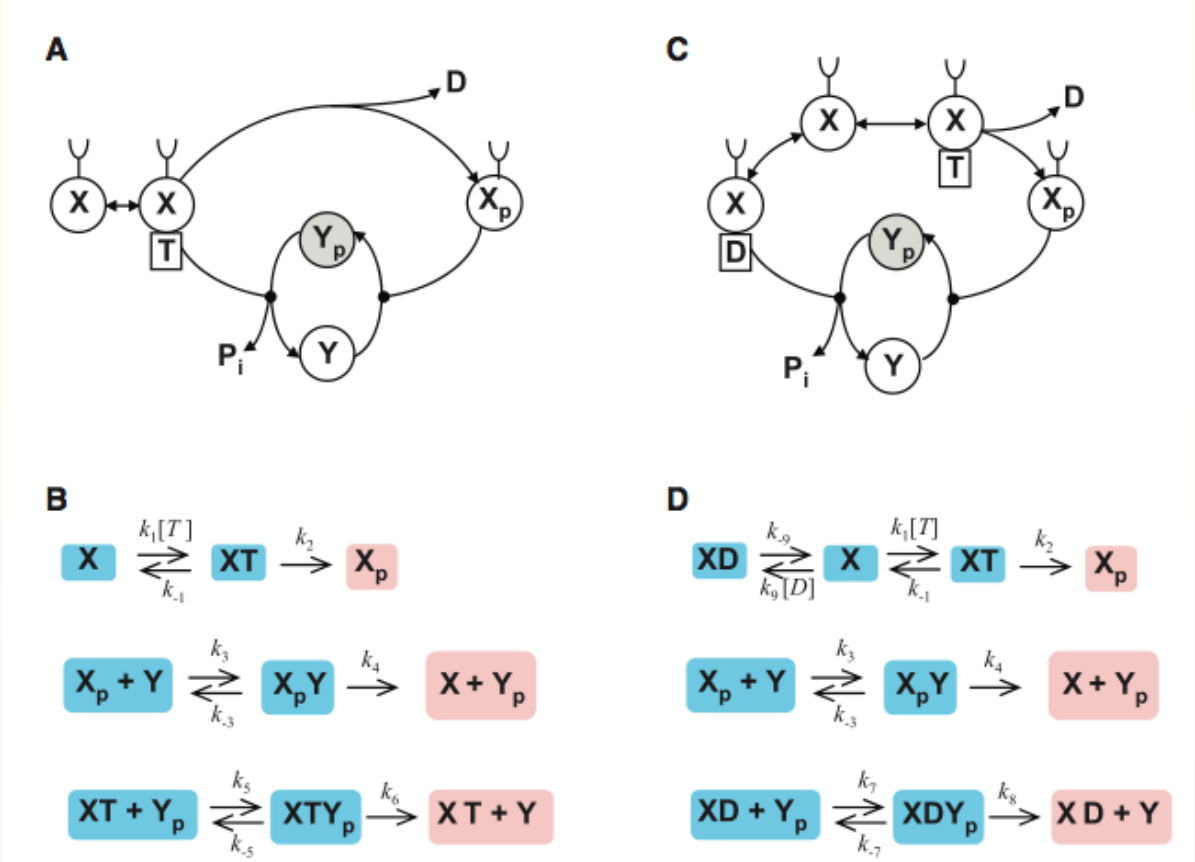


Fig. 2. The EnvZ-OmpR system. **(A)** A schematic diagram of an EnvZ-OmpR model in which ATP is the cofactor in phospho-OmpR dephosphorylation. P_i denotes phosphate ion. **(B)** The mass-action model underlying (A). $[T]$ denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink, and nonterminal nodes are colored blue. **(C)** A schematic diagram of an EnvZ-OmpR model in which ADP is the cofactor in phospho-OmpR dephosphorylation. **(D)** The mass-action model underlying (C). $[D]$ denotes the ADP concentration, assumed fixed.

[2]

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[2] Guy Shinar and Martin Feinberg, *Structural Sources of Robustness in Biochemical Reaction Networks*, Science, 2010

Big picture

Goal of chemical reaction network theory:
discover how the dynamics of the mathematical model depend upon properties of the reaction network.

Key point of research:
want results that are applicable to whole classes of reaction networks, not studying a single model.

Short (incomplete) history of chemical reaction network theory

Dates back to at least work of Horn, Jackson, Feinberg in 1972:

- Detailed balancing is not necessary for many nice results.
- Developed idea of complex balancing.

1970s: development of deficiency theory to predict dynamics of deterministic models based solely on easily checked network conditions (deficiency $= 0$ and weak reversibility).

2000s: many more people started to join this research area

1. Large focus on global attractor conjecture.
2. Focus on possibility of multiple equilibria or oscillations.
3. Beginning to be a focus on stochastic models (green fluorescent proteins, laser traps, etc.)

Reaction Networks: $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$

Example:

$$\emptyset \rightleftarrows A$$

- $\mathcal{S} = \{A\}$.
- $\mathcal{C} = \{\emptyset, A\}$.
- $\mathcal{R} = \{\emptyset \to A,\ A \to \emptyset\}$.

Reaction Networks: $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$

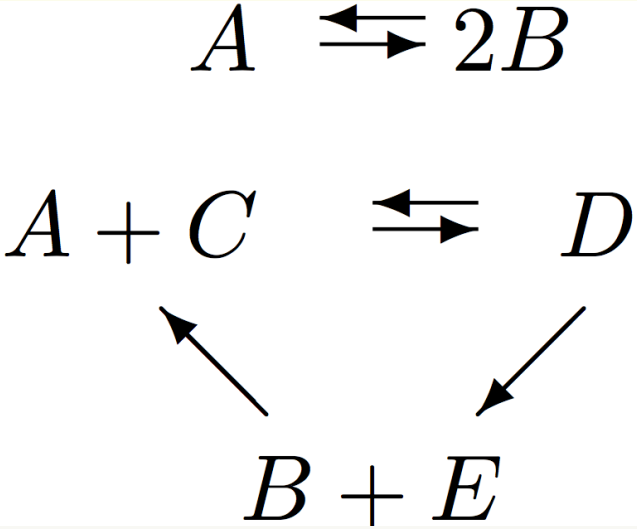
Example:

$$A + B \to 2B$$
$$B \to A$$

- $\mathcal{S} = \{A, B\}$.
- $\mathcal{C} = \{A + B,\ 2B,\ B,\ A\}$.
- $\mathcal{R} = \{A + B \to 2B,\ B \to A\}$.

Reaction Networks: $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$

Example:



Species: $\mathcal{S} = \{A, B, C, D, E\}$.

Complexes: $\mathcal{C} = \{A,\ 2B,\ A + C,\ D,\ B + E\}$.

Reactions:
$\mathcal{R} = \{A \to 2B,\ 2B \to A,\ A+C \to D,\ D \to A+C,\ D \to B+E,\ B+E \to A+C\}$.

Reaction Networks: $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$

Definition

A chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, consists of:

1. Species, $\mathcal{S} := \{S_1, \ldots, S_d\}$: constituent molecules undergoing a series of chemical reactions.

2. Complexes, $\mathcal{C}$: linear combinations of the species representing those used, and produced, in each reaction.

3. A set of reactions, $\mathcal{R} := \{y_k \to y_k'\}$.

Denote reaction vectors

$$\zeta_k = y_k' - y_k.$$

Dynamics – deterministic

Example:

$$A + B \xrightarrow{\kappa_1} 2B \tag{R1}$$

$$B \xrightarrow{\kappa_2} A \tag{R2}$$

Let $x(t) \in \mathbb{R}^2_{\geq 0}$ give concentrations of molecules of A and B:

$$x'(t) = r_1(x(t)) \begin{bmatrix} -1 \\ 1 \end{bmatrix} + r_2(x(t)) \begin{bmatrix} 1 \\ -1 \end{bmatrix}.$$

Deterministic mass-action kinetics says:

$$r_1(x(t)) = \kappa_1 x_A(t) x_B(t), \quad \text{and} \quad r_2(x(t)) = \kappa_2 x_B(t).$$

so

$$\begin{aligned} x'_A(t) &= -\kappa_1 x_A(t) x_B(t) + \kappa_2 x_B(t) \\ x'_B(t) &= \kappa_1 x_A(t) x_B(t) - \kappa_2 x_B(t). \end{aligned}$$

Dynamics – deterministic

Consider a general system with $\mathcal{S} = \{X_1, \ldots, X_d\}$, and kth reaction

$$y_k \to y_k'$$

- The rate of kth reaction is $r_k : \mathbb{R}^d_{\geq 0} \to \mathbb{R}$.
- As before:

$$x'(t) = \sum_k r_k(x(t))(y_k' - y_k),$$

or

$$x(t) = x(0) + \sum_k \left(\int_0^t r_k(x(s))ds \right) (y_k' - y_k).$$

Deterministic mass-action kinetics

Consider reaction

$$y_k \to y_k'$$

Then rate is

$$r_k(x) = \kappa_k x^{y_k} = \kappa_k \prod_{i=1}^{d} x_i^{y_{ki}}.$$

Example: If $S_1 \to$ anything, then $r_k(x) = \kappa_k x_1$.

Example: If $S_1 + S_2 \to$ anything, then $r_k(x) = \kappa_k x_1 x_2$.

Example: If $2S_2 \to$ anything, then $r_k(x) = \kappa_k x_2^2$.

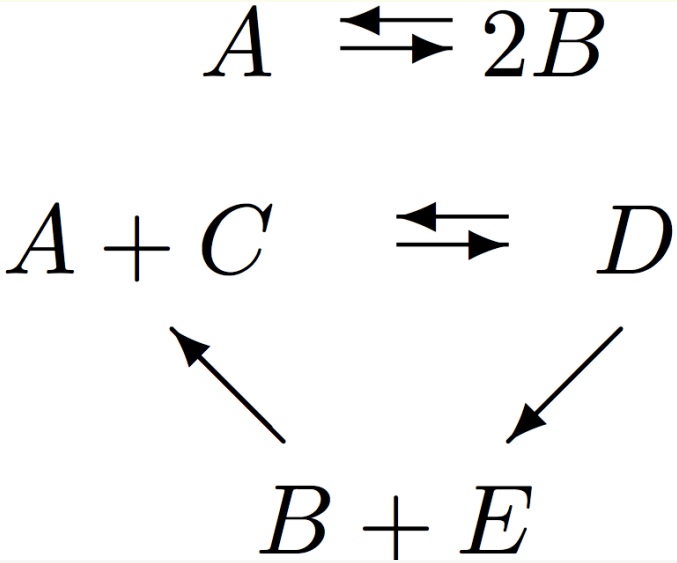
Example: If $3S_1 + 2S_2 + S_3 \to$ anything, then $r_k(x) = \kappa_k x_1^3 x_2^2 x_3$.

Yields:

$$\dot{x} = \sum_k \kappa_k x^{y_k} (y_k' - y_k)$$

Dynamics – deterministic

Example:



$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}
$$

Dynamics: discrete – stochastic

Example:

$$\emptyset \underset{\beta}{\overset{\alpha}{\rightleftarrows}} A \qquad \text{(R1/R2)}$$

Let $X(t)$ represent # molecules of A at time $t \geq 0$.

Suppose rate of reactions are:

$$\lambda_1(X(t)) = \alpha$$
$$\lambda_2(X(t)) = \beta X(t).$$

This means

$$P(\text{reaction } \emptyset \to A \text{ happens in next } \Delta t) = \alpha \Delta t + o(\Delta t)$$
$$P(\text{reaction } A \to \emptyset \text{ happens in next } \Delta t) = \beta X(t) \Delta t + o(\Delta t).$$

This describes a model with exponential holding times.

There are multiple ways to specify this model.

Dynamics: discrete – stochastic

Example:

$$\emptyset \underset{\beta}{\overset{\alpha}{\rightleftarrows}} A \qquad \text{(R1/R2)}$$

Let $X(t)$ represent # molecules of A at time $t \geq 0$.

$$X(t) = X(0) + R_1(t) - R_2(t).$$

For stochastic (Markov) models can take

$$R_1(t) = Y_1(\alpha t)$$
$$R_2(t) = Y_2\left(\beta \int_0^t X_A(s)ds\right)$$

where Y_1, Y_2 are independent unit-rate Poisson processes.

$$X(t) = X(0) + Y_1(\alpha t) - Y_2\left(\beta \int_0^t X_A(s)ds\right).$$

Dynamics: discrete – stochastic

Example:

$$A + B \xrightarrow{\kappa_1} 2B \tag{R1}$$

$$B \xrightarrow{\kappa_2} A \tag{R2}$$

Let $X(t) \in \mathbb{Z}^2_{\geq 0}$ give counts of # molecules of A and B:

$$\begin{aligned} X(t) &= X(0) + R_1(t)\left(\begin{bmatrix} 0 \\ 2 \end{bmatrix} - \begin{bmatrix} 1 \\ 1 \end{bmatrix}\right) + R_2(t)\left(\begin{bmatrix} 1 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 1 \end{bmatrix}\right) \\ &= X(0) + R_1(t)\begin{bmatrix} -1 \\ 1 \end{bmatrix} + R_2(t)\begin{bmatrix} 1 \\ -1 \end{bmatrix}. \end{aligned}$$

For Markov models can take

$$R_1(t) = Y_1\left(\kappa_1 \int_0^t X_A(s)X_B(s)ds\right)$$

$$R_2(t) = Y_2\left(\kappa_2 \int_0^t X_B(s)ds\right)$$

where Y_1, Y_2 are independent unit-rate Poisson processes

$$X(t) = X(0) + Y_1\left(\kappa_1 \int_0^t X_A(s)X_B(s)ds\right)\begin{bmatrix} -1 \\ 1 \end{bmatrix} + Y_2\left(\kappa_2 \int_0^t X_B(s)ds\right)\begin{bmatrix} 1 \\ -1 \end{bmatrix}$$

Dynamics: discrete – stochastic

Consider a general system with $\mathcal{S} = \{X_1, \ldots, X_d\}$, and kth reaction

$$y_k \to y_k'$$

- The rate (or intensity or propensity) of kth reaction is $\lambda_k : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}$.
- As before:

$$X(t) = X(0) + \sum_k R_k(t)(y_k' - y_k),$$

with

$$X(t) = X(0) + \sum_k Y_k \left(\int_0^t \lambda_k(X(s))ds \right) (y_k' - y_k),$$

Y_k are independent, unit-rate Poisson processes.

Stochastic mass-action kinetics

The standard intensity function chosen is stochastic mass-action kinetics:

$$\lambda_k(x) = \kappa_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - y_{ik})!} 1_{\{x_i \geq y_{ik}\}}.$$

Example: If $S_1 \to$ anything, then $\lambda_k(x) = \kappa_k x_1$.

Example: If $S_1 + S_2 \to$ anything, then $\lambda_k(x) = \kappa_k x_1 x_2$.

Example: If $2S_2 \to$ anything, then $\lambda_k(x) = \kappa_k x_2(x_2 - 1) \approx \kappa_2 x_2^2$ if $x_2 \gg 1$.

- Idea: rate is proportional to number of distinct subsets of the molecules present that can form the inputs for the reaction.

Dynamics: discrete – stochastic

Could just say that for $x \in \mathbb{Z}^d_{\geq 0}$,

$$x \to \begin{cases} x + y_1' - y_1, & \text{with rate } \lambda_1(x) \\ x + y_2' - y_2, & \text{with rate } \lambda_2(x) \\ \vdots & \\ x + y_K' - y_K, & \text{with rate } \lambda_K(x) \end{cases}$$

where $y_k' - y_k \in \mathbb{Z}^d$.

Example

$$A \underset{2}{\overset{1}{\rightleftarrows}} B$$

$$A + B \xrightarrow{3} C.$$

If $X(t) = [10, 8, 4]^T$, then rates are

$$\lambda_{A \to B}(X(t)) = 10, \quad \lambda_{B \to A}(X(t)) = 16, \quad \lambda_{A+B \to C}(X(t)) = 240.$$

Dynamics: discrete – stochastic

Model is a continuous time Markov chain with infinitesimal generator

$$\mathcal{A}f(x) = \sum_k \lambda_k(x)(f(x+\zeta_k) - f(x)).$$

where $\zeta_k = y'_k - y_k$.

Kolmogorov's forward equation (chemical master equation)

$$p'_t(x) = \sum_k \lambda_k(x-\zeta_k)p_t(x-\zeta_k)1_{\{x-\zeta_k \in \mathbb{Z}^d_{\geq 0}\}} - p_t(x)\sum_k \lambda_k(x), \quad \forall x \in \mathbb{Z}^d_{\geq 0}$$

Stationary distribution π satisfies

$$0 = \sum_k \lambda_k(x-\zeta_k)\pi(x-\zeta_k) - \pi(x)\sum_k \lambda_k(x), \quad \forall x \in \mathbb{Z}^d_{\geq 0}$$

Example: population growth

Example

$$B \xrightarrow{1/3} 2B$$

with $X(0) = 10$.
Stochastic equation:

$$X(t) = 10 + Y\left(\int_0^t \frac{1}{3} X(s) ds\right).$$

Forward equation (master equation): For $x \in \{10, 11, \dots\}$

$$\frac{d}{dt} p_t(x) = \frac{1}{3}(x-1) p_t(x-1) 1_{\{x-1 \geq 10\}} - \frac{1}{3} x \cdot p_t(x)$$

i.e.

$$\frac{d}{dt} p_t(10) = -\frac{1}{3} \cdot 10 \cdot p_t(10)$$

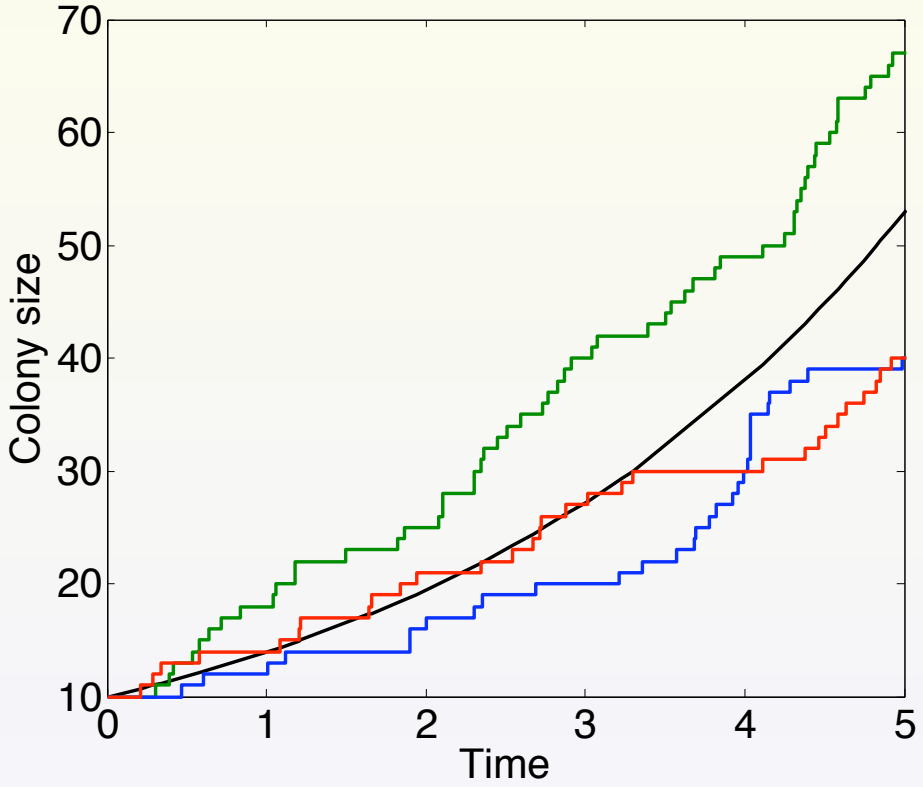
$$\frac{d}{dt} p_t(11) = \frac{1}{3} \cdot 10 \cdot p_t(10) - \frac{1}{3} \cdot 11 \cdot p_t(11)$$

$$\frac{d}{dt} p_t(12) = \frac{1}{3} \cdot 11 \cdot p_t(11) - \frac{1}{3} \cdot 12 \cdot p_t(12)$$

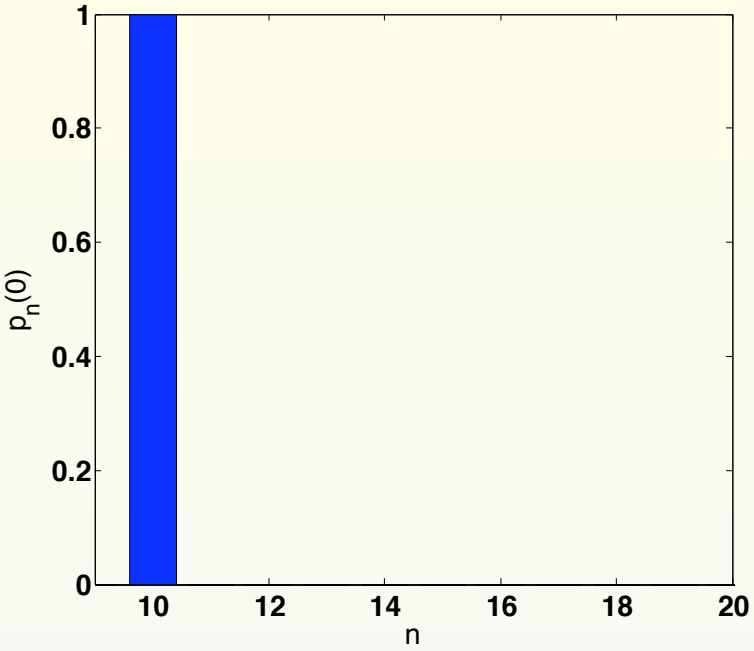
$$\vdots$$

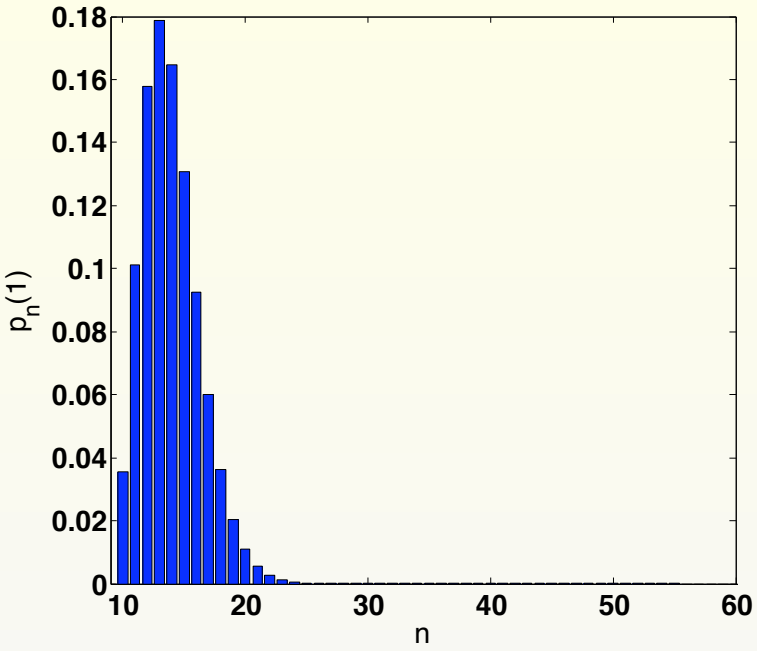
Example: population growth

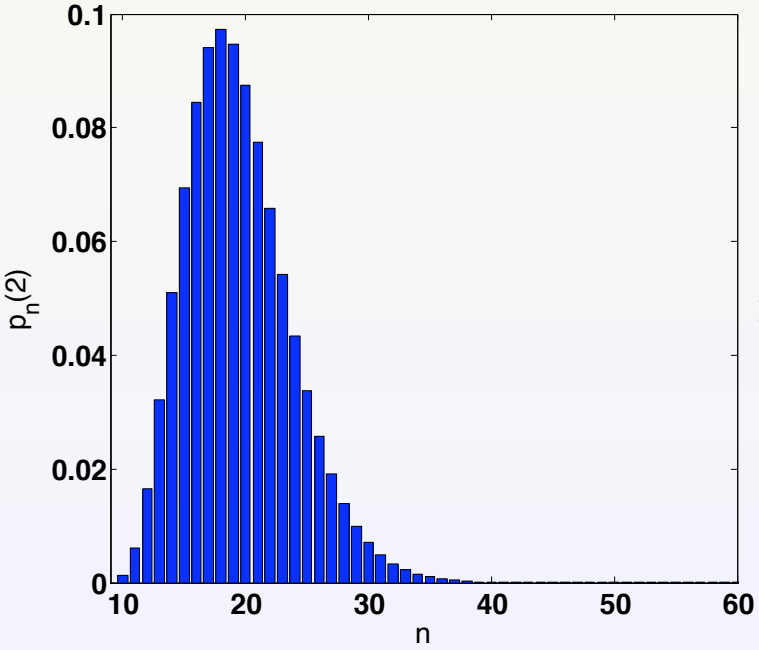
- Below is a plot of the solution of the deterministic system versus three different realizations of the stochastic system.

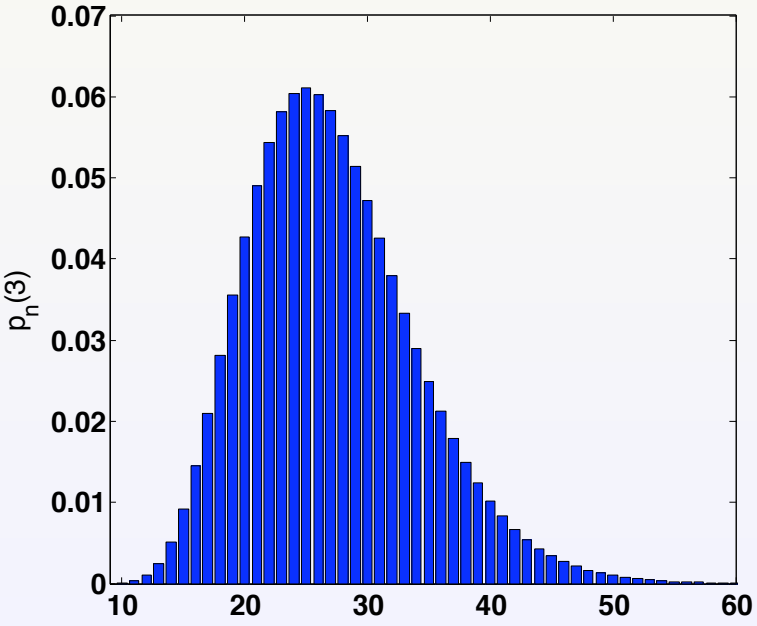


Example: population growth - evolution of distribution









Connection

Suppose V is a (large) scaling parameter and

- $X_i = O(V)$, and $X^V(t) \stackrel{\text{def}}{=} V^{-1} \cdot X(t)$,
- $\lambda_k(X(t)) = O(V)$

Then,

$$X^V(t) \approx \frac{1}{V} X_0 + \sum_k \frac{1}{V} Y_k \left(V \int_0^t \kappa_k X^V(s)^{y_k} ds \right) (y'_k - y_k)$$

LLN for Y_k says

$$\frac{1}{V} Y_k(Vu) \approx u \qquad \left(\lim_{V \to \infty} \sup_{u \leq U} \left| V^{-1} Y_k(Vu) - u \right| = 0, \quad a.s. \right)$$

so a good approximation is solution to

$$x(t) = x(0) + \sum_k \int_0^t \kappa_k x(s)^{y_k} ds \cdot (y'_k - y_k),$$

where

$$u^v = u_1^{v_1} \cdots u_d^{v_d},$$

is standard mass-action kinetics. See Tom Kurtz's works....

LLN: Example

- Stochastic models:

$$A + B \xrightarrow{2/V} 2B \tag{R1}$$

$$B \xrightarrow{1} A \tag{R2}$$

with $X(0) = [3V, V]$ so that $[A^V, B^V] = X/V$ satisfies

$$A^V(0) = 3, \quad B^V(0) = 1.$$

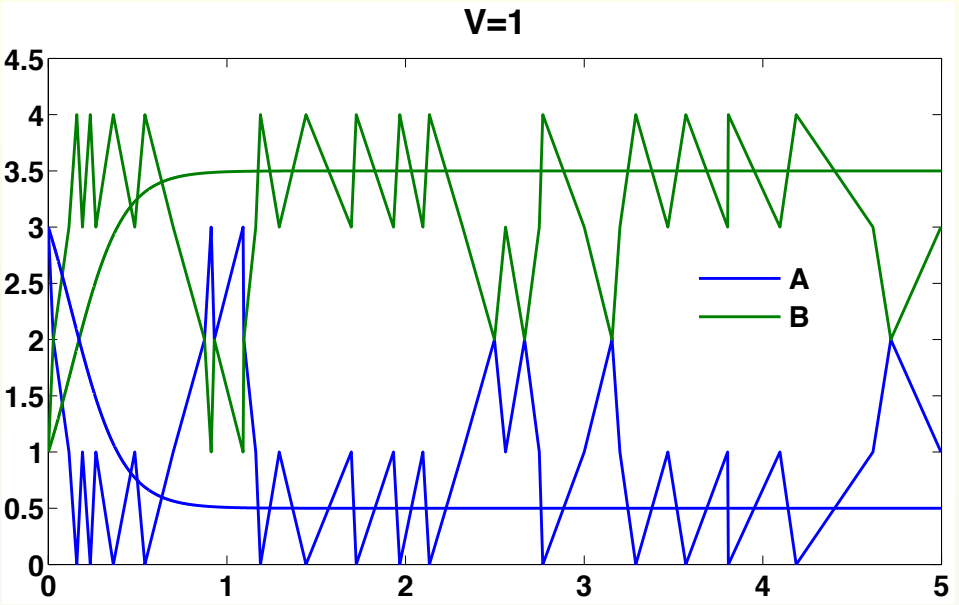
- ODE model of

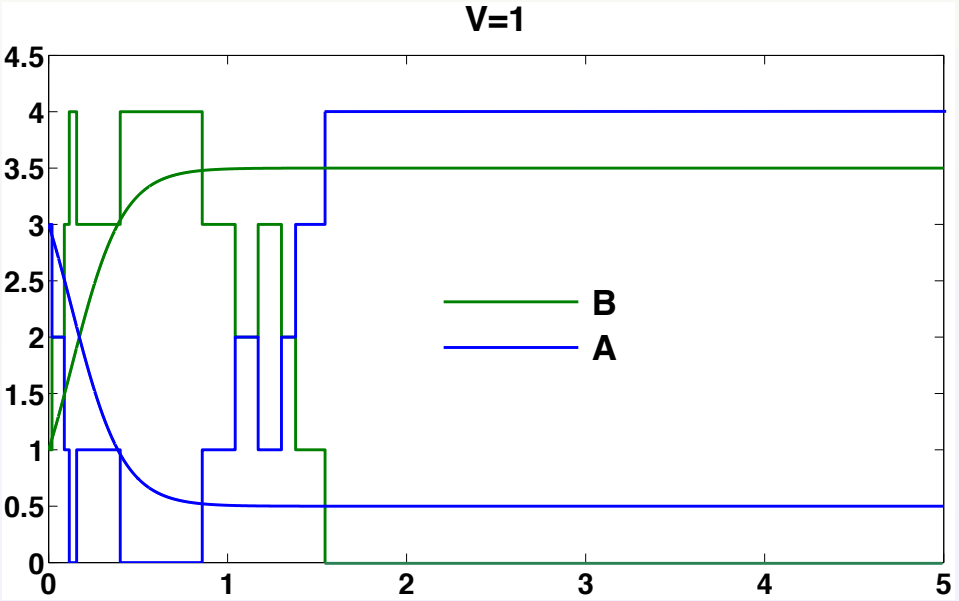
$$A + B \xrightarrow{2} 2B$$

$$B \xrightarrow{1} A,$$

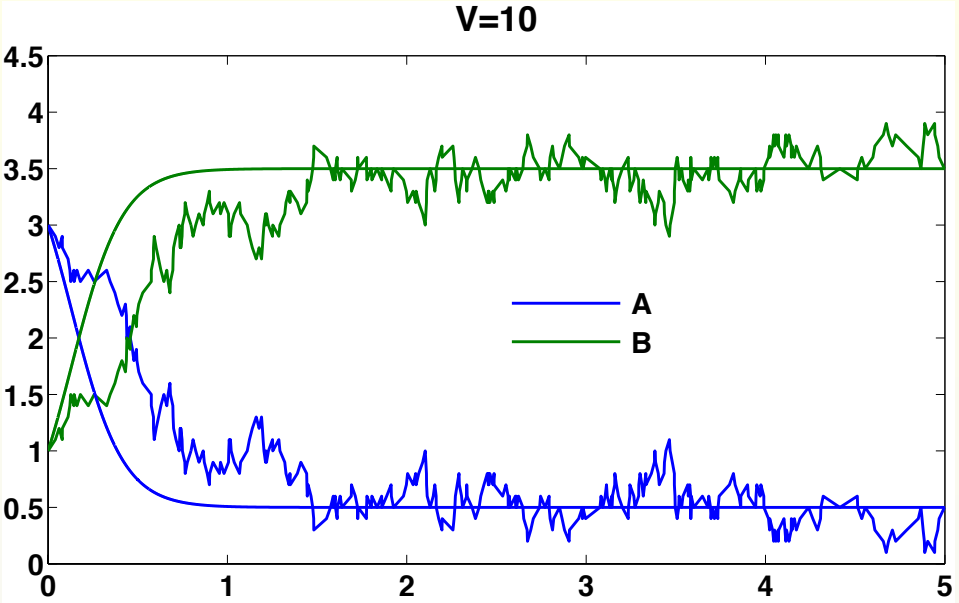
with $x(0) = [3, 1]$.

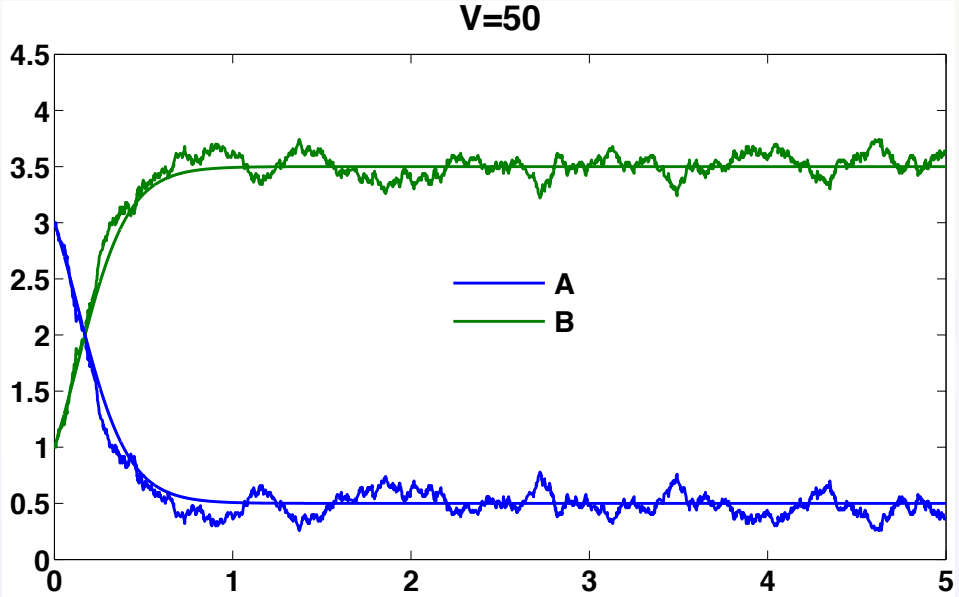
LLN: Example, $A + B \rightarrow 2B \quad B \rightarrow A$



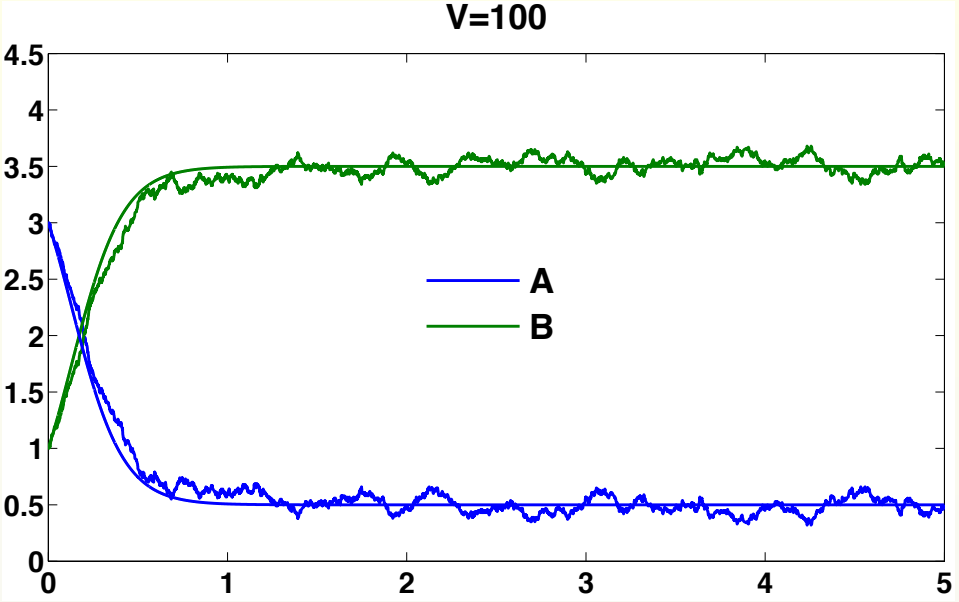


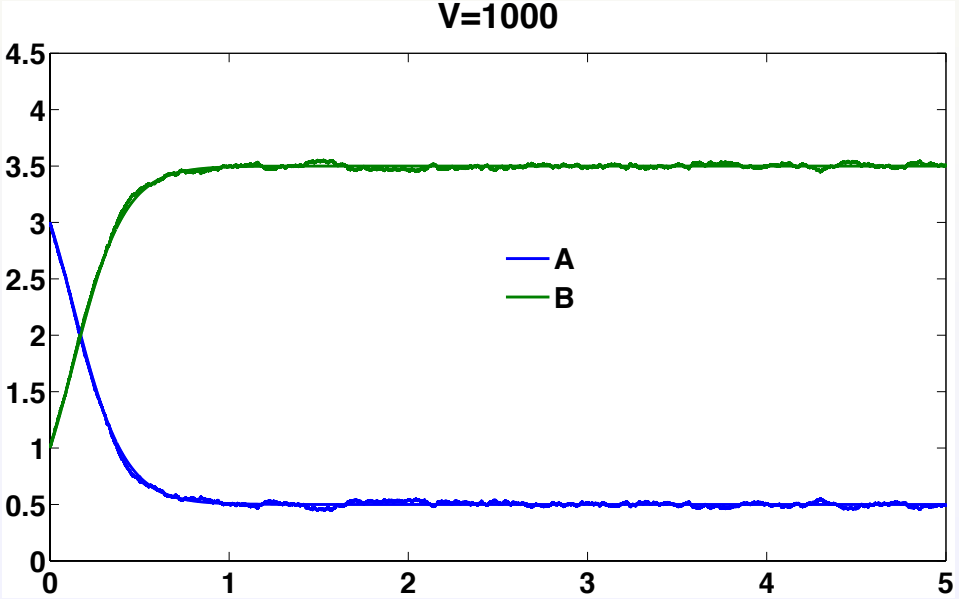
LLN: Example, $A + B \rightarrow 2B \quad B \rightarrow A$





LLN: Example, $A + B \rightarrow 2B \quad B \rightarrow A$





What now?

So now you know what these models are.

Big question: Can we relate network structure to dynamics?

Deficiency zero theorem of Horn, Jackson, Feinberg

Theorem (Series of papers from 1972-1995)

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with deterministic mass-action kinetics. Suppose:

1. *the network is weakly reversible, and*
2. *has a deficiency of zero.*

Then, for any choice of rate constants κ_k, within each positive stoichiometric compatibility class there is precisely one equilibrium value c to the associated ODE system:

$$\sum_k \kappa_k c^{y_k} (y'_k - y_k) = 0,$$

and that equilibrium value is locally (globally?) asymptotically stable relative to its compatibility class.

Actually have stronger result: for each $\eta \in \mathcal{C}$,

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

c is said to be a complex balanced equilibrium

Deficiency Zero Theorem - stochastic

Theorem (A., Craciun, Kurtz, 2010)

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a stochastically modeled reaction network with rate constants κ_k. Suppose:

1. *the network is weakly reversible, and*
2. *has a deficiency of zero.*

Then, for any irreducible communicating equivalence class, Γ, the stochastic system has a product form stationary distribution

$$\pi(x) = \frac{1}{Z_\Gamma} \prod_{i=1}^{d} e^{-c_i} \frac{c_i^{x_i}}{x_i!}, \quad x \in \Gamma, \tag{2}$$

where Z_Γ is a normalizing constant and c is a complexed-balanced equilibrium of the corresponding ODE.

David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz, *Product-form stationary distributions for deficiency zero chemical reaction networks*, Bulletin of Mathematical Biology, Vol. 72, No. 8, 1947 - 1970, 2010.

Stoichiometric compatibility classes

1. Note that for either model:

$$x(t) - x(0) = \sum_k \left(\int_0^t r_k(x(s))\, ds \right) (y'_k - y_k) \in \text{span}_k\{y'_k - y_k\}$$

$$X(t) - X(0) = \sum_k Y_k \left(\int_0^t \lambda_k(X(s)) ds \right) (y'_k - y_k) \in \text{span}_k\{y'_k - y_k\}.$$

Definition.

$$S = \text{span}\{y'_k - y_k\}_k$$

is the stoichiometric subspace of the network. Let $\dim(S) = s$.

We see that solutions are bound to translations:

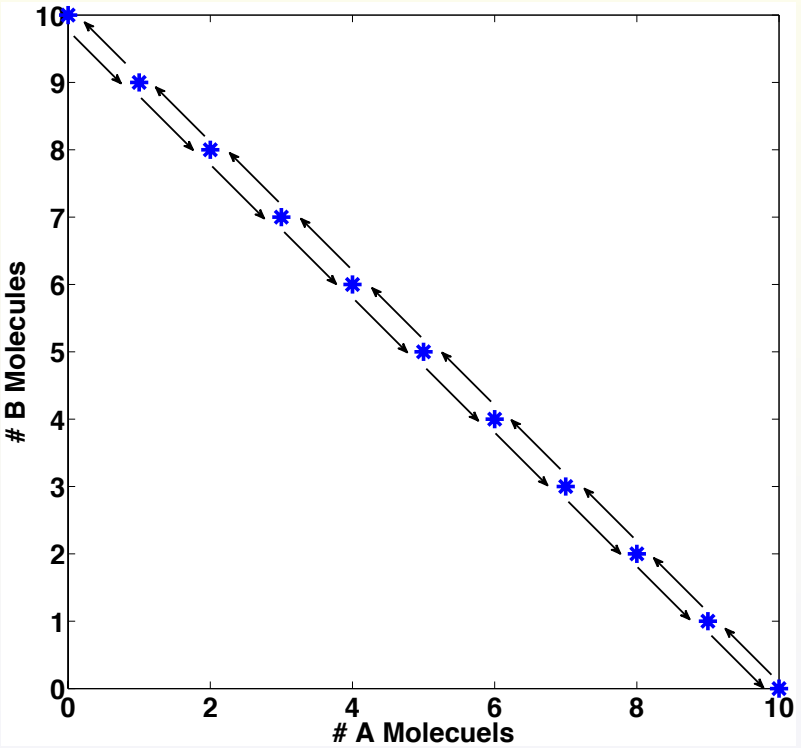
$$x(0) + S,$$

which are the stoichiometric compatibility classes.

Compatibility classes

Example: Reaction network

$$A + B \rightleftarrows 2B$$
$$B \rightleftarrows A$$

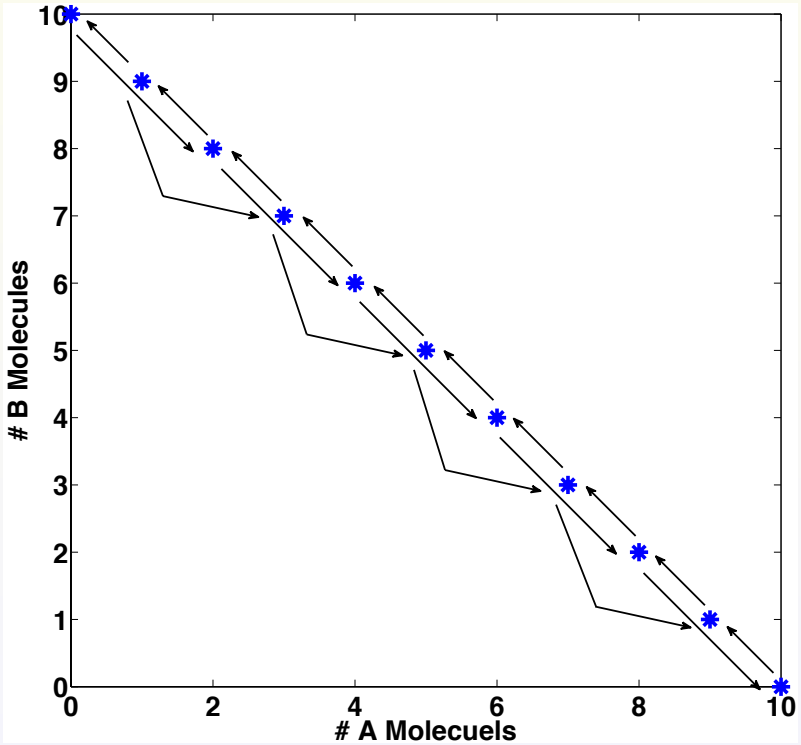


Compatibility classes

Reaction network

$$A \rightarrow B$$

$$2B \rightarrow 2A$$



Compatibility classes

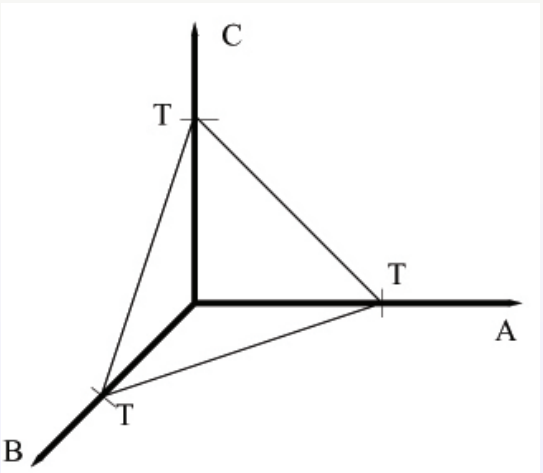
Reaction network

$$2A \rightleftarrows A + B \quad , \quad B \rightleftarrows C,$$

- $S \subset \mathbb{R}^3$ is the plane spanned by $(-1, 1, 0)^T$ and $(0, -1, 1)^T$.

For $T > 0$, the non-negative stoichiometric compatibility classes are two-dimensional triangles

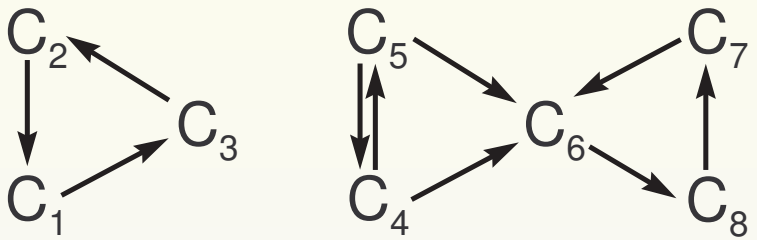
$$\left\{ (x_a, x_b, x_c) \in \mathbb{R}^3_{\geq 0} \mid x_a + x_b + x_c = T \right\}$$



Connectivity

Definition

The connected components of the reaction network are called the *linkage classes*.



Example

$$A + B \xrightarrow{\alpha} 2B \qquad \text{(Linkage Class 1)}$$

$$B \xrightarrow{\beta} A \qquad \text{(Linkage Class 2)}$$

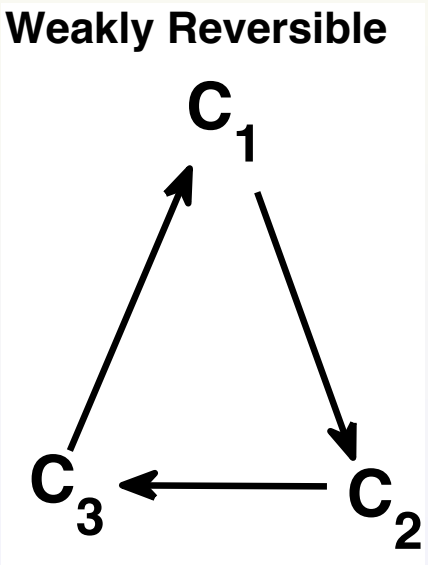
Has two linkage classes.

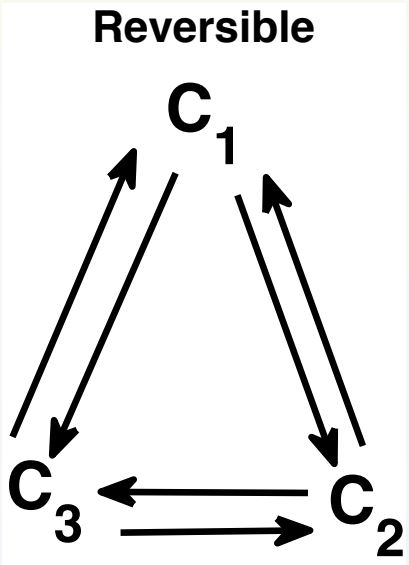
Connectivity

Definition

A chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is said to be *weakly reversible* if each linkage class is strongly connected.

A network is called *reversible* if $y_k \to y_k' \in \mathcal{R} \implies y_k' \to y_k \in \mathcal{R}$.





Connectivity

The following is not weakly reversible:

$$A + B \xrightarrow{\alpha} 2B \qquad \text{(Linkage Class 1)}$$

$$B \xrightarrow{\beta} A \qquad \text{(Linkage Class 2)}$$

Deficiency: in multiple ways!

Attempt 1:

$$\text{deficiency of } \{\mathcal{S}, \mathcal{C}, \mathcal{R}\} = \delta = n - \ell - s,$$

where

1. n = # of complexes.
2. ℓ = # of linkage classes.
3. s = dimension of span of reaction vectors.

So it is easy to check!

Example

$$A + B \rightleftarrows 2B \quad \text{(R1)}$$
$$B \rightleftarrows A \quad \text{(R2)}$$

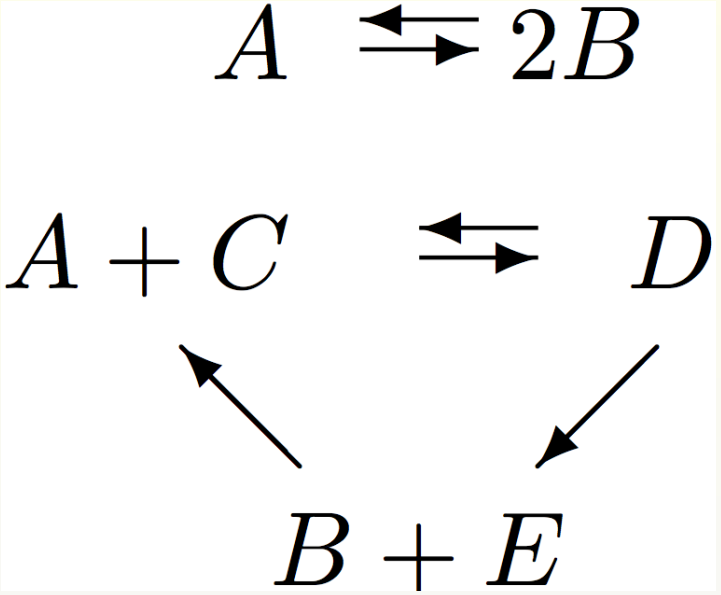
$n = 4, \ell = 2, s = 1 \implies \delta = 1$. But,

$$A + B \rightleftarrows C \quad \text{(R1)}$$
$$B \rightleftarrows A \quad \text{(R2)}$$

$n = 4, \ell = 2, s = 2 \implies \delta = 0$.

Deficiency

Example:



$$
\begin{aligned}
n &= 5 \\
\ell &= 2 \\
s &= 3
\end{aligned}
$$

$$
\Longrightarrow \quad \delta = 5 - 2 - 3 = 0.
$$

Deficiency: in multiple ways!

$$\text{deficiency of } \{\mathcal{S}, \mathcal{C}, \mathcal{R}\} = \delta = n - \ell - s,$$

Now you are probably thinking: Fiiiiine, but that was utterly useless to me. I have no idea what it means!

Attempt 2: a measure of nonlinearity (Technical but *very* useful)

We define

$$f(x) \stackrel{\text{def}}{=} \sum_k \kappa_k x^{y_k} (y'_k - y_k),$$

and will now find other functions, Y, A_κ, and Ψ for which

$$f(x) = Y \circ A_\kappa \circ \Psi(x).$$

Key point: Y and A_κ are matrices!

The hunt for linearity: $f = Y \circ A_\kappa \circ \Psi$

Example

$$A + B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} 2B \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} 2A,$$

then

$$A_\kappa = \begin{bmatrix} -\kappa_1 & \kappa_2 & 0 \\ \kappa_1 & -(\kappa_2 + \kappa_3) & \kappa_4 \\ 0 & \kappa_3 & -\kappa_4 \end{bmatrix},$$

Note: Simply consider linear model:

$$C_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} C_2 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} C_3,$$

then

$$\frac{d}{dt} C(t) = A_\kappa C(t).$$

The hunt for linearity: $f = Y \circ A_\kappa \circ \Psi$

Example

$$A + B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} 2B \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} 2A$$

then

$$Y = \begin{bmatrix} 1 & 0 & 2 \\ 1 & 2 & 0 \end{bmatrix}$$

The hunt for linearity: $f = Y \circ A_\kappa \circ \Psi$

Example

$$A + B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} 2B \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} 2A \qquad \text{gives} \qquad \Psi(x) = \begin{bmatrix} x_A x_B \\ x_B^2 \\ x_A^2 \end{bmatrix}$$

Thus,

$$\dot{x}(t) = \begin{bmatrix} 1 & 0 & 2 \\ 1 & 2 & 0 \end{bmatrix} \begin{bmatrix} -\kappa_1 & \kappa_2 & 0 \\ \kappa_1 & -(\kappa_2 + \kappa_3) & \kappa_4 \\ 0 & \kappa_3 & -\kappa_4 \end{bmatrix} \begin{bmatrix} x_A x_B \\ x_B^2 \\ x_A^2 \end{bmatrix}$$

Deficiency: attempt 2

$$f(x) = Y \circ A_\kappa \circ \Psi(x).$$

The deficiency of the model is

$$\delta = \dim(\ker Y \cap \text{image} A_\kappa).$$

You are probably thinking: Oh my, that did not help at all..... in fact, I think it made things significantly worse.

My response: think about fixed points to ODE model:

$$f(\bar{x}) = Y \circ A_\kappa \circ \Psi(\bar{x}) = 0$$

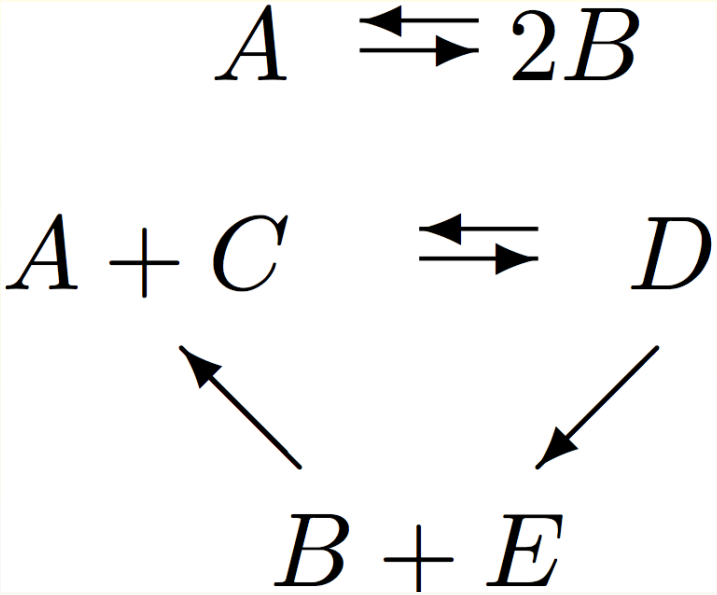
with $\bar{x} \in \mathbb{R}^d_{>0}$. This can happen in one of two ways:

$$(i) \;\; A_\kappa(\Psi(\bar{x})) \in \ker Y \quad \text{or} \quad (ii) \;\; \Psi(\bar{x}) \in \ker A_\kappa.$$

The second is a very nice condition: complexed balanced equilibrium

Deficiency

Example:



We know there is a $\bar{c}$ satisfying,

$$\begin{aligned}
\kappa_{A\to 2B}\bar{c}_A &= \kappa_{2B\to A}\bar{c}_B^2 \\
\kappa_{A+C\to D}\bar{c}_A\bar{c}_C &= \kappa_{D\to A+C}\bar{c}_D + \kappa_{B+E\to A+C}\bar{c}_B\bar{c}_E \\
\kappa_{D\to A+C}\bar{c}_D + \kappa_{D\to B+E}\bar{c}_D &= \kappa_{A+C\to D}\bar{c}_A\bar{c}_C \\
\kappa_{B+E\to A+C}\bar{c}_B\bar{c}_E &= \kappa_{D\to B+E}\bar{c}_D
\end{aligned}$$

Generalizes detailed balancing.

Deficiency zero theorem of Horn, Jackson, Feinberg

Theorem (The Deficiency Zero Theorem - Deterministic)

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be

1. *weakly reversible, and*
2. *have a deficiency zero*

Then, for any choice of rate constants κ_k, within the interior of each positive stoichiometric compatibility class there is precisely one equilibrium value c to the associated ODE system:

$$\sum_k \kappa_k c^{y_k} (y'_k - y_k) = 0,$$

and that equilibrium value is locally (globally?) asymptotically stable relative to its compatibility class.

Actually have stronger result: for each $\eta \in \mathcal{C}$,

$$\sum_{k:y_k=\eta} \kappa_k c^{y_k} = \sum_{k:y'_k=\eta} \kappa_k c^{y_k}. \tag{3}$$

c is said to be a complex balanced equilibrium

Deficiency Zero Theorem - stochastic

Theorem (A., Craciun, Kurtz, 2010)

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with rate constants κ_k. Suppose the associated ODE has a complexed balanced equilibrium c (or

1. *the network is weakly reversible, and*
2. *has a deficiency of zero.*

)

Then, for any irreducible communicating equivalence class, Γ, the stochastic system has a product form stationary distribution

$$\pi(x) = \frac{1}{Z_\Gamma} \prod_{i=1}^{d} e^{-c_i} \frac{c_i^{x_i}}{x_i!}, \quad x \in \Gamma, \tag{4}$$

where Z_Γ is a normalizing constant.

David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz, *Product-form stationary distributions for deficiency zero chemical reaction networks*, Bulletin of Mathematical Biology, Vol. 72, No. 8, 1947 - 1970, 2010.

Proof of stochastic version

Let c be a complexed balanced equilibrium for the deterministically modeled system and for $x \in \mathbb{Z}^d_{\geq 0}$ let

$$\pi(x) = \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i} \quad \text{and} \quad \lambda_k(x) = \kappa_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - y_{ki})!} 1_{\{x_i \geq y_{ki}\}}.$$

Plug $\pi(x)$ and $\lambda_k(x)$ into

$$\sum_k \pi(x - y'_k + y_k)\lambda_k(x - y'_k + y_k) \;=\; \pi(x) \sum_k \lambda_k(x).$$

Simplify (with some tricks) – ask offline if you want to see tricks.

Examples – (M/M/∞ queue)

$$\emptyset \underset{\beta}{\overset{\alpha}{\rightleftarrows}} A$$

Ode model:

$$\dot{x} = \alpha - \beta x \implies c = \frac{\alpha}{\beta}.$$

State space of stochastic model is

$$\{0, 1, 2, \dots\}$$

so

$$\pi(x) = e^{-\frac{\alpha}{\beta}} \cdot \frac{(\frac{\alpha}{\beta})^x}{x!}.$$

Examples

$$A \underset{\beta}{\overset{\alpha}{\rightleftarrows}} 2A$$

ODE model:

$$\dot{x} = \alpha x - \beta x^2 \implies c = \frac{\alpha}{\beta}.$$

State space of stochastic model is

$$\{1, 2, \dots\}$$

So, for $x \in \{1, 2, \dots\}$

$$\pi(x) = \frac{1}{e^{\frac{\alpha}{\beta}} - 1} \cdot \frac{(\frac{\alpha}{\beta})^x}{x!}$$

Enzyme kinetics

Consider the possible enzyme kinetics given by

$$E + S \rightleftarrows ES \rightleftarrows E + P \quad , \quad E \rightleftarrows \emptyset \rightleftarrows S$$

Easy to check that state space is

$$\Gamma = \mathbb{Z}^4_{\geq 0}$$

so in distributional equilibrium

- the specie numbers are independent and
- have Poisson distributions.

Enzyme kinetics

Consider the slightly different enzyme kinetics given by

$$E + S \rightleftarrows ES \rightleftarrows E + P \quad , \quad E \rightleftarrows \emptyset$$

- We see $S + ES + P = N$.
- In distributional equilibrium:
  - E has Poisson distribution,
  - $S,\ ES,\ P$ have a multinomial distribution, and
  - E is independent from $S,\ ES$, and P.

Higher deficiency

What about the situation of $\delta \geq 1$? Tomorrow.

That is the story so far. Thanks!

Collaborators: Gheorghe Craciun and Tom Kurtz

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