

Stochastic models of biochemical reaction systems: network structure and qualitative dynamics

David F. Anderson

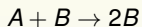
Department of Mathematics
University of Wisconsin - Madison

Duke University – Mathematics Biology colloquium

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Big picture

General focus of research. Many models in molecular biology begin with a reaction network giving high level description of model:



or



We want to discover how the dynamics of the mathematical model depends upon properties of the reaction network.

Big picture

Key point of research: want results that are applicable to many reaction networks, not studying just one model.

This research is part of **chemical reaction network theory**, which is part of **systems biology**.

Outline for talk

Give idea of main results for today.

Introduce reaction networks and some terminology.

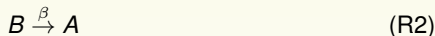
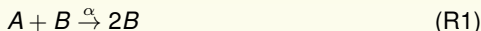
Introduce dynamical models: **deterministic** (ODE) and **stochastic** (CTMC)

Focus on **deficiency**

Present results pertaining to networks with a **deficiency of one**.

Story for today: Absolute Concentration Robustness

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



$$\dot{x}_A(t) = -\alpha x_A(t)x_B(t) + \beta x_B(t)$$

$$\dot{x}_B(t) = \alpha x_A(t)x_B(t) - \beta x_B(t)$$

$$M \stackrel{\text{def}}{=} x_A(0) + x_B(0),$$

Solving for equilibria:

$$\bar{x}_A = \frac{\beta}{\alpha},$$

$$\bar{x}_B = M - \frac{\beta}{\alpha},$$

Network has **absolute concentration robustness** in species A.

Example

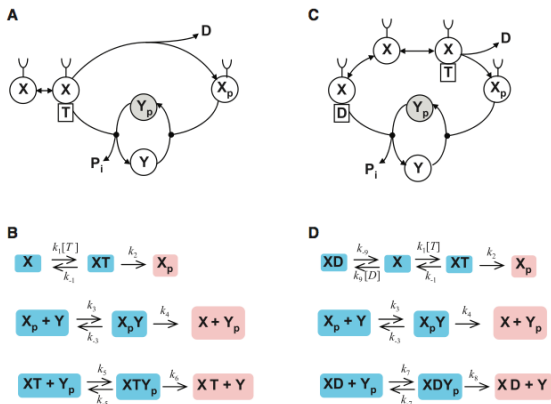
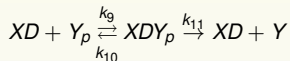
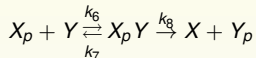
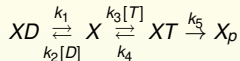


Fig. 2. The EnvZ-OmpR system. **(A)** A schematic diagram of an EnvZ-OmpR model in which ATP is the cofactor in phospho-OmpR dephosphorylation. P_i denotes phosphate ion. **(B)** The mass-action model underlying **(A)**. $[T]$ denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink,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

$$X_{tot} := X + XD + XT + X_p + X_p Y + XDY_p$$

$$Y_{tot} := Y + X_p Y + XDY_p + Y_p.$$

Example



$$\dot{c}_X = k_1 c_{XD} - (k_2[D] + k_3[T])c_X + k_4 c_{XT} + k_8 c_{X_p Y}$$

$$\dot{c}_{XD} = -k_1 c_{XD} + k_2[D]c_X - k_9 c_{XD} c_{Y_p} + (k_{10} + k_{11})c_{XDY_p}$$

$$\dot{c}_{XT} = k_3[T]c_X - (k_4 + k_5)c_{XT}$$

$$\dot{c}_{X_p} = k_5 c_{XT} - k_6 c_{X_p} c_Y + k_7 c_{X_p Y}$$

$$\dot{c}_Y = -k_6 c_{X_p} c_Y + k_7 c_{X_p Y} + k_{11} c_{XDY_p}$$

$$\dot{c}_{X_p Y} = k_6 c_{X_p} c_Y - (k_7 + k_8)c_{X_p Y}$$

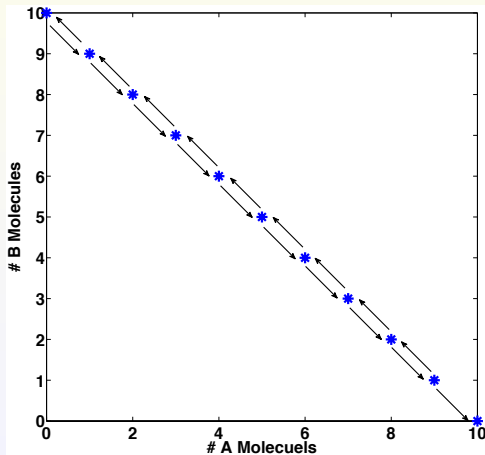
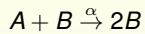
$$\dot{c}_{X_p Y} = k_8 c_{X_p Y} - k_9 c_{XD} c_{Y_p} + k_{10} c_{XDY_p}$$

$$\dot{c}_{XDY_p} = k_9 c_{XD} c_{Y_p} - (k_{10} + k_{11})c_{XDY_p}$$

\bar{c}_{Y_p} is absolutely robust (?!?)

Stochastic model

Reaction network



Example

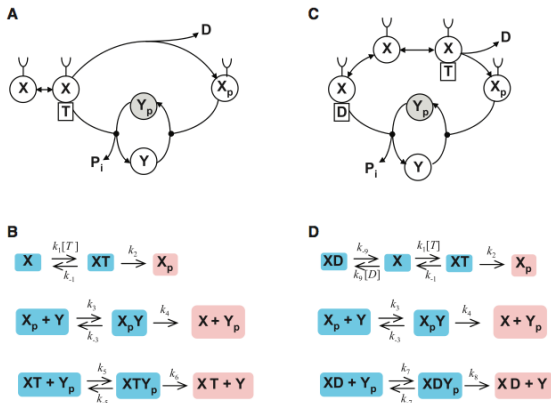


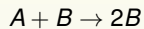
Fig. 2. The EnvZ-OmpR system. **(A)** A schematic diagram of an EnvZ-OmpR model in which ATP is the cofactor in phospho-OmpR dephosphorylation. P_i denotes phosphate ion. **(B)** The mass-action model underlying **(A)**. $[T]$ denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink,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

$$X_{tot} := X + XD + XT + X_p + X_p Y + XDY_p$$

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

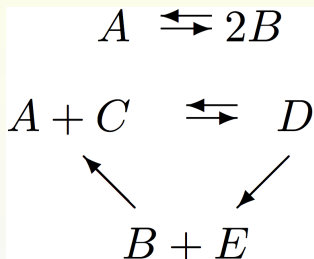
Example:



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

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

Example:



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

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

Reactions:

$R = \{A \rightarrow 2B, 2B \rightarrow A, A + C \rightarrow D, D \rightarrow A + C, D \rightarrow B + E, B + E \rightarrow A + C\}$.

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

Definition

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

1. **Species**, $\mathcal{S} := \{S_1, \dots, S_d\}$: 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**, $\mathcal{R} := \{y_k \rightarrow y'_k\}$.

Denote **reaction vectors**

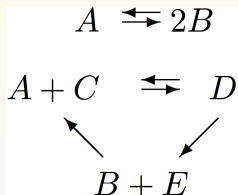
$$\zeta_k = y'_k - y_k.$$

Network properties

Definition

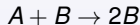
The connected components of the reaction network are called the *linkage classes*.

Example



has two linkage classes

Example



(Linkage Class 1)



(Linkage Class 2)

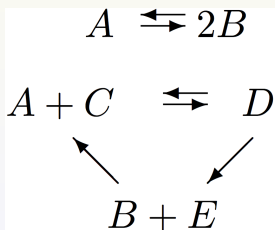
Has two linkage classes.

Connectivity

Definition

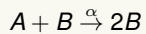
A chemical reaction network, $\{S, C, \mathcal{R}\}$, is said to be *weakly reversible* if each linkage class is strongly connected.

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



Connectivity

The following is **not weakly reversible**:



(Linkage Class 1)



(Linkage Class 2)

Network properties

Definition

$$S = \text{span}_{\{y_k \rightarrow y'_k \in \mathcal{R}\}} \{y'_k - y_k\}$$

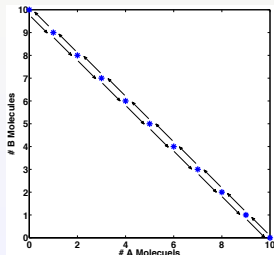
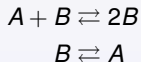
is the *stoichiometric subspace* of the network.

Denote

$$\dim(S) = s.$$

Implication: Solutions bound to translations of S : *stoichiometric compatibility classes*

Example: Reaction network



Deficiency

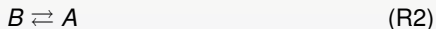
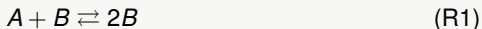
$$\text{deficiency of } \{S, C, \mathcal{R}\} = \delta = n - \ell - s,$$

where

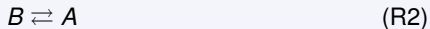
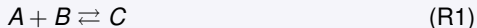
1. n = # of complexes.
2. ℓ = # of linkage classes.
3. s = dimension of span of reaction vectors.

So it is easy to check!

Example



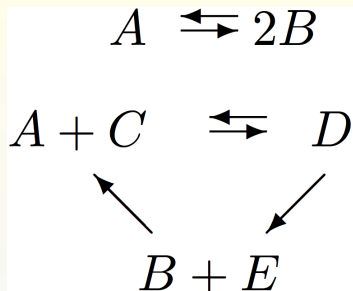
$n = 4, \ell = 2, s = 1 \implies \delta = 1$. But,



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

Deficiency

Example:



$$n = 5$$

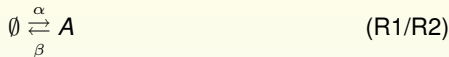
$$l = 2$$

$$s = 3$$

$$\Rightarrow \delta = 5 - 2 - 3 = 0.$$

Dynamics: discrete – stochastic

Example:



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

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

For Markov models can take

$$R_1(t) = Y_1(\alpha t)$$

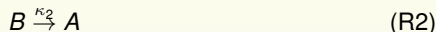
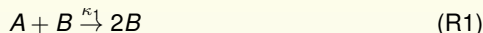
$$R_2(t) = Y_2\left(\beta \int_0^t X_A(s) ds\right)$$

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:



Let $X(t) \in \mathbb{Z}_{\geq 0}^2$ 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.

Dynamics: discrete – stochastic

For general system, we have $\mathcal{S} = \{X_1, \dots, X_d\}$, with k th reaction



- The **rate** (or **intensity** or **propensity**) of k th reaction is $\lambda_k : \mathbb{Z}_{\geq 0}^d \rightarrow \mathbb{R}$.
- 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.

Mass-action kinetics

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

$$\lambda_k(x) = \kappa_k \prod_i \frac{x_i!}{(x_i - y_{ik})!}.$$

Example: If $S_1 \rightarrow \text{anything}$, then $\lambda_k(x) = \kappa_k x_1$.

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

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

Other ways to understand model

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

$$x \rightarrow \begin{cases} x + y'_1 - y_1, & \text{with rate } \lambda_1(x) \\ x + y'_2 - y_2, & \text{with rate } \lambda_2(x) \\ \vdots \\ x + y'_K - y_K, & \text{with rate } \lambda_K(x) \end{cases}$$

where $y'_k - y_k \in \mathbb{Z}^d$. Rate gives parameter of exponential random variable.

So a continuous time Markov chain with infinitesimal generator

$$Af(x) = \sum_k \lambda_k(x)(f(x + \zeta_k) - f(x)).$$

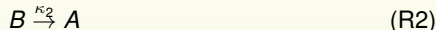
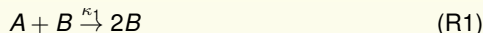
where $\zeta_k = y'_k - y_k$.

Kolmogorov's forward equation (chemical master equation)

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

Dynamics – deterministic

Example:



Let $x(t) \in \mathbb{R}_{\geq 0}^2$ 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 $\mathcal{S} = \{X_1, \dots, X_d\}$, and k th reaction



- The **rate** of k th reaction is $r_k : \mathbb{R}_{\geq 0}^d \rightarrow \mathbb{R}$.
- As before:

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

so

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

Deterministic mass-action kinetics

Consider reaction



Then rate is

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

Example: If $S_1 \rightarrow \text{anything}$, then $r_k(x) = \kappa_k x_1$.

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

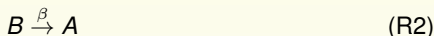
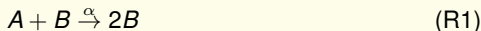
Example: If $2S_2 \rightarrow \text{anything}$, then $r_k(x) = \kappa_k x_2^2$.

Example: If $3S_1 + 2S_2 + S_3 \rightarrow \text{anything}$, 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. Example



Stochastic equations

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

Deterministic equations

$$x(t) = x(0) + \alpha \int_0^t x_A(s) x_B(s) ds \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \beta \int_0^t x_B(s) ds \begin{bmatrix} 1 \\ -1 \end{bmatrix},$$

ODE form:

$$x'(t) = \alpha x_A(t) x_B(t) \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \beta x_B(t) \begin{bmatrix} 1 \\ -1 \end{bmatrix},$$

or

$$x'_A(t) = -\alpha x_A(t) x_B(t) + \beta x_B(t)$$

$$x'_B(t) = \alpha x_A(t) x_B(t) - \beta x_B(t).$$

Yesterday: Deficiency zero theorem – Horn, Jackson, Feinberg

Theorem

Let $\{S, C, \mathcal{R}\}$ 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 $\eta \in C$,

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

c is said to be a *complex balanced* equilibrium

Yesterday: deficiency zero theorem - stochastic

Theorem (A., Craciun, Kurtz, 2010)

Let $\{S, C, R\}$ be a chemical 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

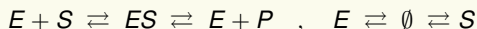
$$\pi(x) = \frac{1}{Z_\Gamma} \prod_{i=1}^d \frac{c_i^{x_i}}{x_i!}, \quad x \in \Gamma, \quad (2)$$

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.

Enzyme kinetics

Consider the possible enzyme kinetics given by



Easy to check that state space is

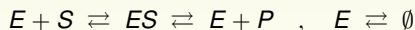
$$\Gamma = \mathbb{Z}_{\geq 0}^4$$

so in distributional equilibrium

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

Enzyme kinetics

Consider the slightly different enzyme kinetics given by



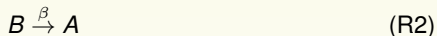
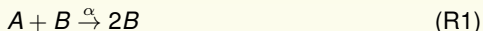
- ▶ We see $S + ES + P = N$.
- ▶ In distributional equilibrium:
 - ▶ E has Poisson distribution,
 - ▶ S, ES, P have a multinomial distribution, and
 - ▶ E is independent from S, ES , and P .

Higher deficiency

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

Story for today: Absolute Concentration Robustness

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



$$\dot{x}_A(t) = -\alpha x_A(t)x_B(t) + \beta x_B(t)$$

$$\dot{x}_B(t) = \alpha x_A(t)x_B(t) - \beta x_B(t)$$

$$M \stackrel{\text{def}}{=} x_A(0) + x_B(0),$$

Solving for equilibria:

$$\bar{x}_A = \frac{\beta}{\alpha},$$

$$\bar{x}_B = M - \frac{\beta}{\alpha},$$

Network has **absolute concentration robustness** in species A.

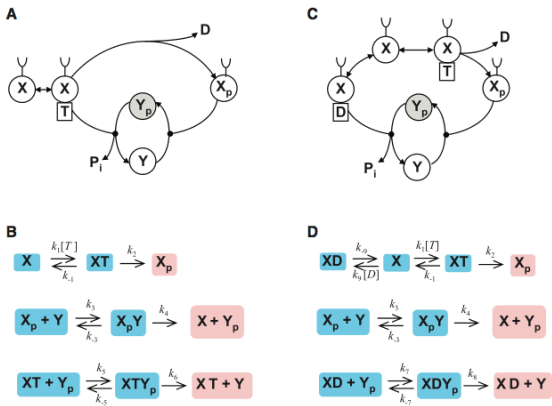


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Theorems: deterministic and stochastic

Theorem (M. Feinberg and G. Shinar, *Science*, 2010 – deterministic)

Consider a deterministic mass-action system that

- ▶ *has a deficiency of one.*
- ▶ *admits a positive steady state and*
- ▶ *has two non-terminal complexes that differ only in species S ,*

then the system has absolute concentration robustness in S .

Theorem (A., Enciso, Johnston – stochastic)

Consider a reaction network satisfying the following:

- ▶ *has a deficiency of one,*
- ▶ *the deterministic model admits a positive steady state,*
- ▶ *has two non-terminal complexes that differ only in species S ,*
- ▶ *(new) is conservative,*

then with probability one there there is a last time a nonterminal reaction fires.

⁰David F. Anderson, Germán Enciso, and Matthew Johnston, *Stochastic analysis of biochemical reaction networks with absolute concentration robustness*, *J. Royal Society Interface*, Vol. 11, 20130943, February 12, 2014.

Differing in one species

Examples:

1.

$$A, \quad A + B$$

differ in species B .

2.

$$XT, \quad XT + Y_p$$

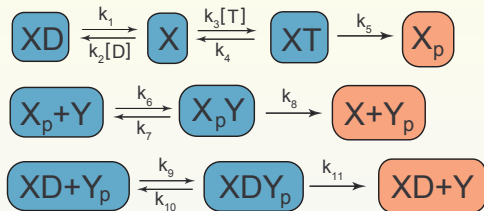
differ in species Y_p .

3.

$$T, \quad T + G$$

differ in species G .

Terminal and non-terminal complexes



- ▶ The orange complexes are called **terminal**.
- ▶ The blue complexes are called **non-terminal**.

Theorems: deterministic and stochastic

Theorem (M. Feinberg and G. Shinar, Science, 2010 – deterministic)

Consider a deterministic mass-action system that

- ▶ has a *deficiency of one*.
- ▶ *admits a positive steady state* and
- ▶ has two non-terminal complexes that *differ only in species S*,

then the system has *absolute concentration robustness in S*.

Theorem (A., Enciso, Johnston – stochastic)

Consider a reaction network satisfying the following:

- ▶ has a *deficiency of one*,
- ▶ the deterministic model *admits a positive steady state*,
- ▶ has two non-terminal complexes that *differ only in species S*,
- ▶ *(new)* is conservative,

then with probability one there there is a last time a nonterminal reaction fires.

⁰David F. Anderson, Germán Enciso, and Matthew Johnston, *Stochastic analysis of biochemical reaction networks with absolute concentration robustness*, J. Royal Society Interface, Vol. 11, 20130943, February 12, 2014.

Deficiency: again

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

This is not useful

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

We define

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

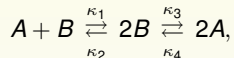
There are functions Y , A_{κ} , and Ψ for which

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

Key point: Y and A_{κ} are matrices!

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

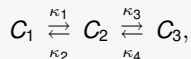
Example



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:



then

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

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

Example

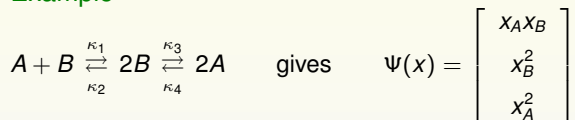
$$A + B \begin{array}{c} \xrightarrow{\kappa_1} \\ \xleftarrow{\kappa_2} \end{array} 2B \begin{array}{c} \xrightarrow{\kappa_3} \\ \xleftarrow{\kappa_4} \end{array} 2A$$

then

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

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

Example



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

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

The deficiency of the model is

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

So what does $\delta = 1$ mean?!?!?!?

$$\ker(YA_{\kappa}) = \ker(A_{\kappa}) \cup [\ker(YA_{\kappa}) \setminus \ker(A_{\kappa})]$$

$\ker(A_{\kappa})$ is very well understood: support only on terminal complexes.

Other term can have support anywhere.

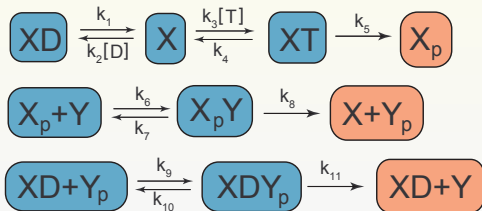
Existence of positive equilibrium tells us it has support on all non-terminal complexes

$$\ker(YA_{\kappa}) = \{z, b_1, \dots, b_T\}.$$

Deficiency of one

$$\ker(YA_{\kappa}) = \{z, b_1, b_2, b_3\}.$$

$$Y \circ A_{\kappa} \circ v = 0$$



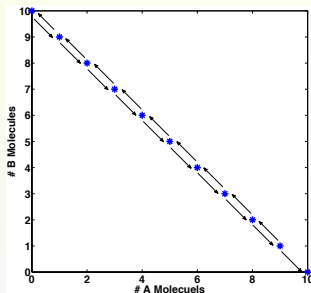
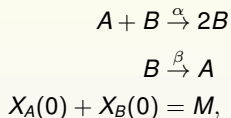
$$\sum_k \kappa_k v_{y_k} (y'_k - y_k) = 0,$$

and $v_{y_k} > 0$ for all $y_k \in \mathcal{C}$.

So how to we use this?

partial proof on board

Extinction can be rare event: want to consider compact time intervals



Can show that quasi-stationary distribution for A converges to Poisson

$$\pi_M^Q(x) \rightarrow e^{-(\beta/\alpha)} \frac{(\beta/\alpha)^x}{x!}, \quad \text{as } M \rightarrow \infty.$$

Quasi-stationary distribution: EnvZ-OmpR signaling system

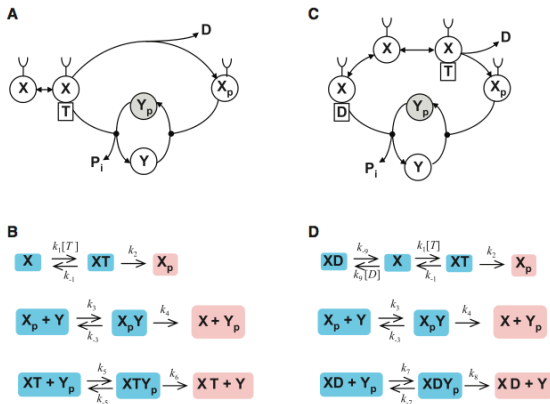
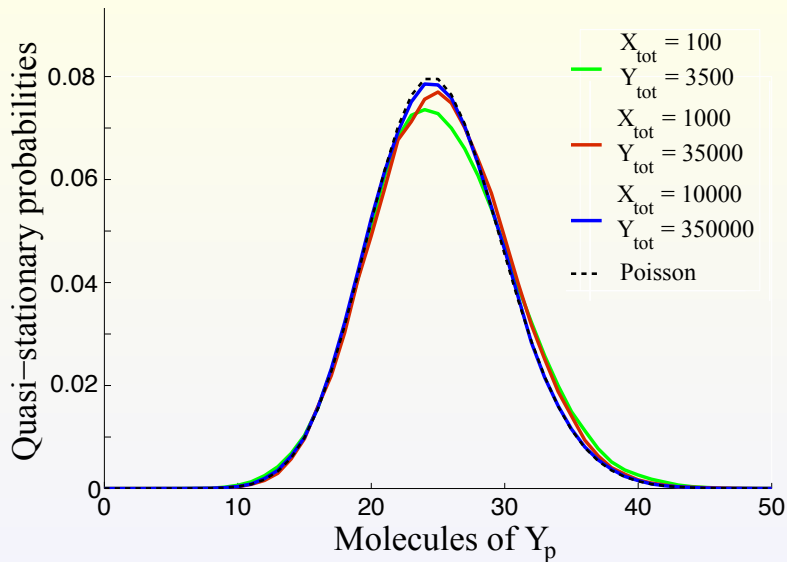


Fig. 2. The EnvZ-OmpR system. **(A)** A schematic diagram of an EnvZ-OmpR model in which ATP is the cofactor in phospho-OmpR dephosphorylation. P_i denotes phosphate ion. **(B)** The mass-action model underlying **(A)**. $[T]$ denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink,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

1

Quasi-stationary distribution



Open question: are all such distributions well approximated by a Poisson?

Partial answer: yes!

Let N be a scaling parameter (total conserved value), and consider $N \gg 1$.

Let q be the value of the ACR equilibrium value and let

$$J \sim \text{Poisson}(q). \quad (3)$$

Theorem (A., Cappelletti, Kurtz, 2015)

Suppose $T > 0$ and that *some technical assumptions hold* on the reaction network and let J be as in (3). Then, for any continuous function

$\hat{g}: \mathbb{R}_{\geq 0}^{|X_{ACR}|} \rightarrow \mathbb{R}$ with at most polynomial growth rate we have

$$\int_0^{\cdot \wedge T} \left(\hat{g}(X_{ACR}^N(s)) - E[\hat{g}(J)] \right) ds \xrightarrow[N \rightarrow \infty]{} 0.$$

or equivalently,

$$P \left(\sup_{\substack{t_1, t_2 \in [0, T] \\ t_1 < t_2}} \left| \int_{t_1}^{t_2} \left(\hat{g}(X_{ACR}^N(s)) - E[\hat{g}(J)] \right) ds \right| > \varepsilon \right) \xrightarrow[N \rightarrow \infty]{} 0$$

That is the story. Thanks!

Collaborators: Gheorghe Craciun, Tom Kurtz, German Enciso, Matthew Johnston,
Daniele Cappelletti.

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6. David F. Anderson, Daniele Cappelletti, and Thomas G. Kurtz, *Finite time behavior of stochastically modeled chemical systems with absolute concentration robustness*, to appear.