Tutorial: chemical reaction network theory for both deterministic and stochastic models

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Programming with Chemical Reaction Networks: Mathematical Foundations

June 9th, 2014

Outline

1. Introduce classical chemical reaction network theory of Horn, Jackson, Feinberg for ODE models:
   - Deficiency.
   - Complex balanced equilibria.
   - Deficiency Zero Theorem and the Global Attractor Conjecture.
2. Discuss continuous time Markov chain (master equation).
   - Connection with ODE models via LLN.
   - Complex balancing and deficiency zero theorem.
3. Leave deficiency zero situation. What changes for models?
4. Leaving lots out, of course.

Main references: classical work for deterministic systems

Jeremy Gunawardena,
Chemical reaction network theory for in-silico biologists,
`http://vcp.med.harvard.edu/papers/crnt.pdf`

Martin Feinberg,
Lectures on Chemical Reaction Networks,
(Delivered at the Mathematics Research Center, U. of Wisconsin, 1979)
`http://crnt.engineering.osu.edu/LecturesOnReactionNetworks`

Chemical Reaction Network Theory for Deterministic Models: overview

1. Ordinary differential equations (ODE) models of chemical and biochemical models of can exhibit a myriad of behaviors:
   - Oscillations,
   - fixed points: $\dot{x}(t) = f(x(t)), \quad f(\bar{x}) = 0.$
     - unique,
     - multiple fixed points (phosphorylation),
     - unstable,
     - locally stable,
     - globally stable,
   - decay of specie counts to zero (extinctions),
   - unbounded growth,
   - explosion in finite time.
   - Single model exhibiting more than one of these behaviors.
2. Big question: can we devise mathematical theorems that provide easy to check conditions that characterize possible system behavior?

   Ideally the results will be easy to check from network, and be independent of specific choice of rate constants.

Can not cover whole field. Focus on fixed points

Question: Are there general theorems that categorize when fixed points exist? What about stability?

Many mathematicians would look at you funny and tell you to find another problem:

- "These are highly nonlinear polynomial systems"
- "Hopeless"

CRNT:

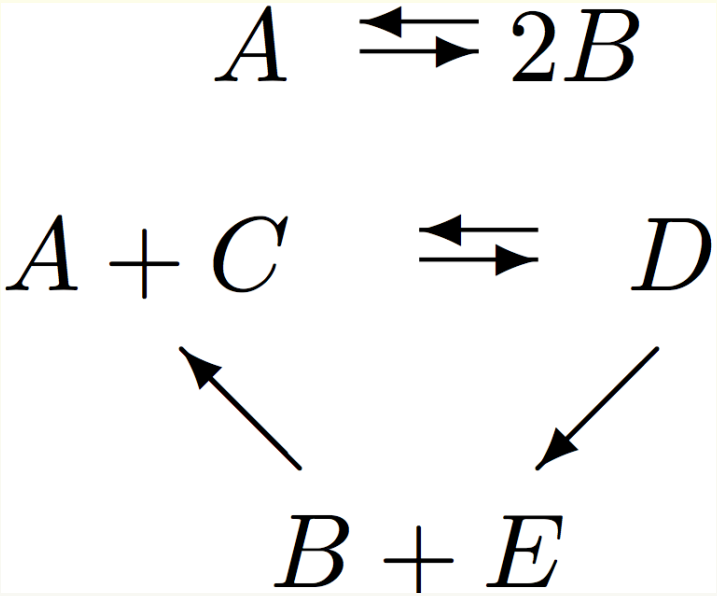
- Provides several theorems about systems of nonlinear, polynomial ODEs.
- I will focus on the results related to fixed points, deficiency theory, and the global attractor conjecture.
- I will also branch out to stochastically modeled systems.

Key insight

The key insight of CRNT is that

- The apparent nonlinearity of the ODEs arising from mass-action kinetics conceals a great amount of linearity.
- This comes from the interplay of nonlinear, polynomial rates, and the linear structure underlying the reaction graph.
  - similar to how linearity shows up in the study of Markov chains....
- Fixed points can arise in two ways:
  1. Due to the linear structure,
  2. Due to an artifact of the nonlinearity.
- The deficiency measures the degree to which the second can arise.
- Deficiency of zero implies only the first kind (and lots of other things!)

A reaction network



There are:

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

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

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

First danger point: Complexes mean something different to me than to many of you!

Reaction graph

David's model: Question: $X_1 = X_2$?

$$
\begin{aligned}
X_1 + X_2 &\to Y \\
Y + N &\to Y \\
X_1 + Y &\to X_1 + N \\
X_2 + Y &\to X_2 + N
\end{aligned}
$$

I will write

$$
\begin{aligned}
X_1 + X_2 &\searrow \\
&\qquad Y \\
Y + N &\nearrow \\
X_1 + Y &\to X_1 + N \\
X_2 + Y &\to X_2 + N
\end{aligned}
$$

Reaction vectors

- Consider

$$A + C \to D$$

- We make the association:

$$A + C \text{ “=” } y = \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \quad D \text{ “=” } y' = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}.$$

- Note: each instance of the reaction

$$A + C \to D \quad \text{or} \quad y \to y'$$

changes the state of the system by the vector:

$$y' - y = \begin{bmatrix} -1 \\ 0 \\ -1 \\ 1 \\ 0 \end{bmatrix}.$$

Chemical Reaction Networks: Species, Complexes, and Reactions

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.

   Can represent as vectors, $y_k, y'_k \in \mathbb{Z}^d_{\geq 0}$, representing the numbers of molecules of each species *consumed* and *created* in the kth reaction, respectively.

3. A set of reactions, $\mathcal{R} := \{y_k \to y'_k\}$, with reaction vectors $y'_k - y_k \in \mathbb{Z}^d$.

Dynamics: development of ordinary differential equation (ODE) model

Let $x(0) \in \mathbb{R}^d_{\geq 0}$ be some initial concentration level, let $x(t)$ be concentration at time t.

Question: How is $x(t)$ changing in time?

Let $r_k(t)$ be rate at which reaction $y_k \to y_k'$ is proceeding at time t. Then,

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

Usually take $r_k(x(t), t)$ to be mass-action kinetics.

Mass-action kinetics

The standard (but not only!) rate function chosen is mass-action kinetics:

Reaction	rate function
$\emptyset \xrightarrow{\kappa_1} S_1$	$r_1(x) = \kappa_1$
$S_1 \xrightarrow{\kappa_2} S_2$	$r_2(x) = \kappa_2 x_1$
$S_1 + S_2 \xrightarrow{\kappa_3} S_3$	$r_3(x) = \kappa_3 x_1 x_2$
$2S_1 \xrightarrow{\kappa_4} S_2$	$r_4(x) = \kappa_4 x_1^2$
$4S_2 + 3S_4 \to$ anything	$r_5(t) = \kappa_5 x_2^4 x_4^3$

Note that for the reaction $y_k \to y'_k$,

$$r_k(x) = \kappa_k \cdot x_1^{y_{k1}} \cdot x_2^{y_{k2}} \cdots x_d^{y_{kd}} = \kappa_k \prod_{i=1}^{d} x_i^{y_{ki}}$$

We define:

$$x^{y_k} \stackrel{\text{def}}{=} \prod_{i=1}^{d} x_i^{y_{ki}}$$

(with $0^0 \stackrel{\text{def}}{=} 1$)

Chemical Reaction Systems

Definition

A mass-action chemical reaction system is a quadruple, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$:

1. Species, $\mathcal{S} := \{S_1, \ldots, S_d\}$.
2. Complexes, $\mathcal{C}$: linear combinations of the species.
3. reactions, $\mathcal{R} := \{y_k \to y_k'\}$.
4. rate constants, $\kappa : \mathcal{R} \to \mathbb{R}_{>0}$

The time evolution of a chemical reaction system is given by:

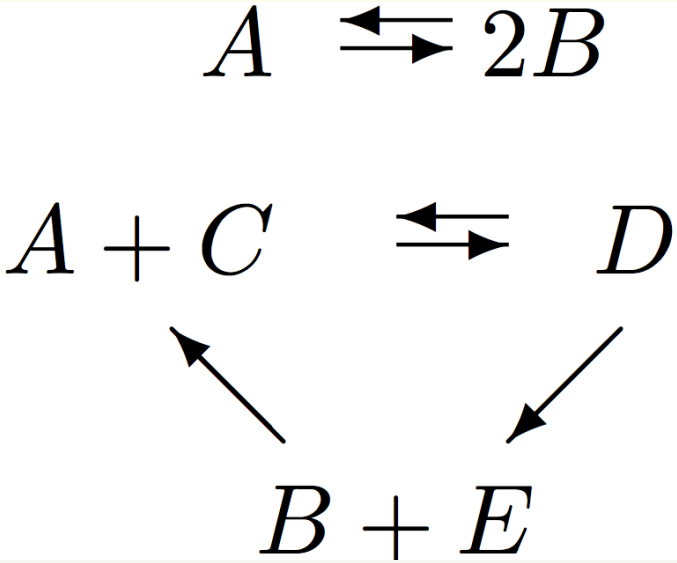
$$\frac{dx}{dt} = \sum_k \kappa_k x^{y_k} (y_k' - y_k)$$

or

$$\frac{dx}{dt} = \sum_{y \to y'} \kappa_{y \to y'} x^y (y' - y)$$

Dynamics: deterministic model

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: deterministic model

Example:

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

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

$$x'(t) = \kappa_1 \cdot x_A(t)x_B(t) \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \kappa_2 \cdot x_B(t) \begin{bmatrix} 1 \\ -1 \end{bmatrix}.$$

or

$$x_A'(t) = -\kappa_1 \cdot x_A(t)x_B(t) + \kappa_2 \cdot x_B(t)$$

$$x_B'(t) = \quad \kappa_1 \cdot x_A(t)x_B(t) - \kappa_2 \cdot x_B(t)$$

Examples

Examples: (You should be thinking: how does he know so much?)

Board 1.

Answer

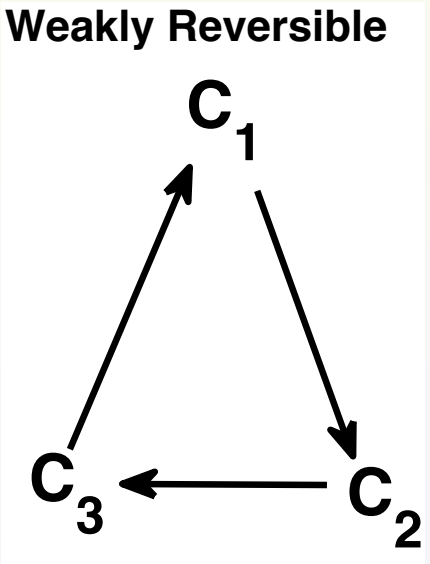
These models are weakly reversible and have a deficiency of zero.

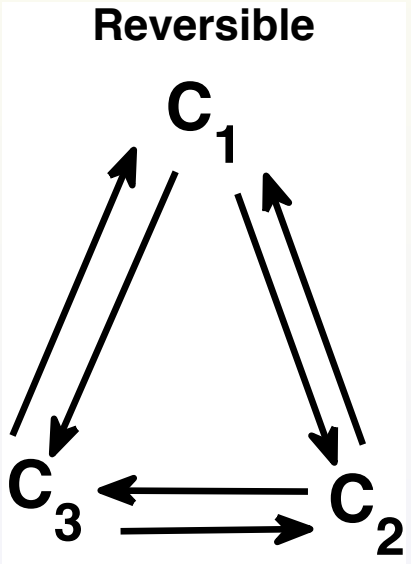
Network reversibility conditions

Definition

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

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





Deficiency

Need: linkage class and span of reaction vectors. Then, Attempt 1:

$$\delta = n - \ell - s,$$

where

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

Now you are probably thinking: Fiiiiine, but what does it mean? Attempt 2:

A measure of how independent reactions are.

Board 2.

But what is really going on here? Attempt 3. (Technical)

The hunt for linearity

We define

$$f(x) \stackrel{\text{def}}{=} \sum_{y \to y'} \kappa_{y \to y'} x^y (y' - y),$$

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

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

The hunt for linearity

Define the linear mapping $A_\kappa : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ by

$$(A_\kappa)_{ij} = \begin{cases} \kappa_{j\to i} & \text{for } j \neq i \\ -\sum_{\ell \neq j} \kappa_{j\to \ell} & \text{for } i = j \end{cases}$$

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: same for $C_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} C_2 \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} C_3$,: $\dot{x} = A_\kappa x$.)

The hunt for linearity

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

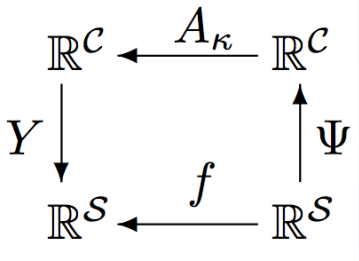
Example

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

Now

$$Y(A_k(\Psi(x))) = \sum_{y \to y'} \kappa_{y \to y'} x^y \cdot (y' - y) =: f(x),$$

the original rate equation!



Example

General Case:

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

$$\Psi : \mathbb{R}^d \to \mathbb{R}^{\mathcal{C}}$$

$$\Psi(x)_y = x^y$$

$$A_\kappa : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$$

$$A_\kappa^{ij} = \begin{cases} \kappa_{j\to i} & \text{for } j \neq i \\ -\sum_{\ell \neq j} \kappa_{j\to \ell} & \text{for } i = j \end{cases}$$

$Y : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^d$ is linear:

$$Y(\omega_y) = y$$

Example: $A + B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} 2B \overset{\kappa_3}{\leftarrow} 2A$

$$\dot{x} = \kappa_1 x_A x_B \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \kappa_2 x_B^2 \begin{bmatrix} 1 \\ -1 \end{bmatrix} + \kappa_3 x_A^2 \begin{bmatrix} -2 \\ 2 \end{bmatrix}$$

$$\Psi(x) = \begin{bmatrix} x_A x_B \\ x_B^2 \\ x_A^2 \end{bmatrix}$$

$$A_\kappa = \begin{bmatrix} -\kappa_1 & \kappa_2 & 0 \\ \kappa_1 & -\kappa_2 & \kappa_3 \\ 0 & 0 & -\kappa_3 \end{bmatrix}$$

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

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

Deficiency: attempt 3

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

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: remember, we are thinking about fixed points:

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

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 the very nice condition I knew we had: all equilibria are nice or Complexed Balanced

Properties of $\bar{x}$ with $\Psi(\bar{x}) \in \ker A_\kappa$

Theorem (Horn and Jackson)

Suppose that there is an $\bar{x} \in \mathbb{R}^d_{>0}$ for which $f(\bar{x}) = 0$ with $A_\kappa(\Psi(\bar{x})) = 0$. Then,

1. *There does not exist a $\bar{c} \in \mathbb{R}^d_{>0}$ for which $f(\bar{c}) = 0$ with $A_\kappa(\Psi(\bar{c})) \neq 0$.*
2. *The network is weakly reversible.*
3. *Every stoichiometric compatibility class (invariant manifold) contains precisely one $\bar{c}$ for which $A_\kappa(\Psi(\bar{c})) = 0$.*
4. *Each such $\bar{c}$ is locally asymptotically stable.*

Conjecture. (Global attractor conjecture)
Each such $\bar{c}$ is globally asymptotically stable relative to its compatibility class.

Theorem (Deficiency Zero Theorem - Feinberg)

If a chemical reaction network has a deficiency of 0 then it has a fixed point $\bar{c}$ for which $A_\kappa(\Psi(\bar{c})) = 0$ if and only if it is weakly reversible.

Local stability: decreasing entropy

Assume that for each $\eta \in \mathcal{C}$,

$$\sum_{k:\eta=y_k} \kappa_k(\overline{c})^{y_k} = \sum_{k:\eta=y'_k} \kappa_k(\overline{c})^{y_k}, \tag{1}$$

Define the function V by

$$V(x) = \sum_{i=1}^{d} x_i(\ln(x_i) - \ln \overline{c}_i - 1) + \overline{c}_i.$$

Theorem

Suppose that $x \in \mathbb{R}^d_{>0}$ and $\bar{c}$ satisfies $A_\kappa(\Psi(\bar{c})) = 0$. Then

$$\nabla V(x) \cdot \sum_k \kappa_k x^{y_k}(y'_k - y_k) = \sum_k \kappa_k x^{y_k}(y'_k - y_k) \cdot (\ln(x) - \ln(\overline{c})) \leq 0,$$

with equality if and only if $x = \overline{c}$.

Proof of local stability: decreasing entropy

Proof.

First rewrite in clever way:

$$\sum_k \kappa_k x^{y_k}(y'_k - y_k)\cdot(\ln x - \ln \overline{c}) = \sum_k \kappa_k (\overline{c})^{y_k} \left(\frac{x}{\overline{c}}\right)^{y_k} \left(\ln\left\{\left(\frac{x}{\overline{c}}\right)^{y'_k}\right\} - \ln\left\{\left(\frac{x}{\overline{c}}\right)^{y_k}\right\}\right).$$

Use $e^a(b-a) \leq e^b - e^a$ with equality if and only if $a = b$

$$\begin{aligned}
&\sum_k \kappa_k (\overline{c})^{y_k} \left(\frac{x}{\overline{c}}\right)^{y_k} \left(\ln\left\{\left(\frac{x}{\overline{c}}\right)^{y'_k}\right\} - \ln\left\{\left(\frac{x}{\overline{c}}\right)^{y_k}\right\}\right) \\
&\qquad \leq \sum_k \kappa_k (\overline{c})^{y_k} \left(\left(\frac{x}{\overline{c}}\right)^{y'_k} - \left(\frac{x}{\overline{c}}\right)^{y_k}\right) \\
&\qquad = \sum_{\eta\in\mathcal{C}} \left(\frac{x}{\overline{c}}\right)^{\eta} \left[\sum_{k:\eta=y'_k} \kappa_k (\overline{c})^{y_k} - \sum_{k:\eta=y_k} \kappa_k (\overline{c})^{y_k}\right] \\
&\qquad = 0
\end{aligned}$$

□

A conjecture

Global Attractor Conjecture.
For a complex-balanced system, each of the equilibria $\bar{c} \in \mathbb{R}^d_{>0}$ is globally asymptotically stable relative to the interior of its compatibility class P.

Why doesn't previous proof work? Because

$$V(x) \not\to \infty \quad \text{as } x \to \partial\mathbb{R}^d_{>0}.$$

We know:

1. Holds if $s \leq 3$ (Craciun, Pantea, Nazarov)
2. Holds if there is a single linkage class (Anderson).
3. Holds if network is *strongly endotactic* (Gopalkrishnan, Miller, Shiu).

Implied by

Persistence Conjecture. If $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is weakly reversible, then for any κ, solution trajectories are persistent:

$$\liminf_{t\to\infty} x_i(t) > 0,$$

for all i.

Transition

Questions? Break? Moving on to Stochastic models:

Aim:

1. Give a representation most of you will not have seen.
   - Useful for analytical methods.
   - Useful for computational methods.
2. Use rep. to show LLN. Diffusion (Langevin) Approximation?
3. Come back to deficiency zero/weakly reversible situation.
4. Move to deficiency of 1 for both deterministic and stochastic models.

Specifying infinitesimal behavior: Random Time Changes and going beyond the Gillespie algorithm

Q: How do we specify model when there are low molecular counts and dynamics appears more random.

Should be

1. discrete space, since counting molecules, and
2. stochastic dynamics.

Let's return to development of ODEs.

An ordinary differential equation is specified by describing how a function should vary over a small period of time

$$X(t + \Delta t) - X(t) \approx F(X(t))\Delta t$$

A more precise description (consider a telescoping sum)

$$X(t) = X(0) + \int_0^t F(X(s))ds$$

Infinitesimal behavior for jump processes

We are interested in functions that are piecewise constant and random.

Changes, when they occur, won't be small. If "reaction k" occurs at time t,

$$X(t) - X(t-) = \zeta_k := y'_k - y_k \in \mathbb{Z}^d$$

What is small? The probability of seeing a jump of a particular size.

$$P\{X(t + \Delta t) - X(t) = \zeta_k \mid \mathcal{F}_t\} \approx \lambda_{\zeta_k}(t)\Delta t$$

Question: Can we specify the λ_{ζ_k} in some way that determines X?

- For the ODE, F depended on X.
- Maybe λ_{ζ_k} should depend on X?

Simple model

For example, consider the simple system

$$A + B \to C$$

where one molecule each of A and B is being converted to one of C.

Intuition for standard stochastic model:

$$P\{\text{reaction occurs in } (t, t+\Delta t] \mid \mathcal{F}_t\} \approx \kappa X_A(t) X_B(t) \Delta t$$

where

- κ is a positive constant, the reaction rate constant.
- $\mathcal{F}_t$ is all the information pertaining to the process up through time t.

Can we specify a reasonable model satisfying this assumption?

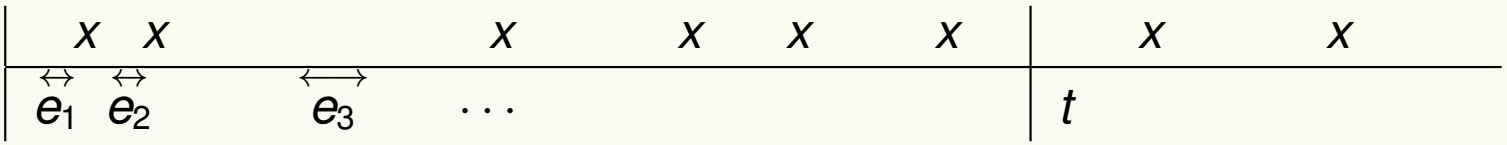
Answer: yes, but we need Poisson processes.

Background information: The Poisson process

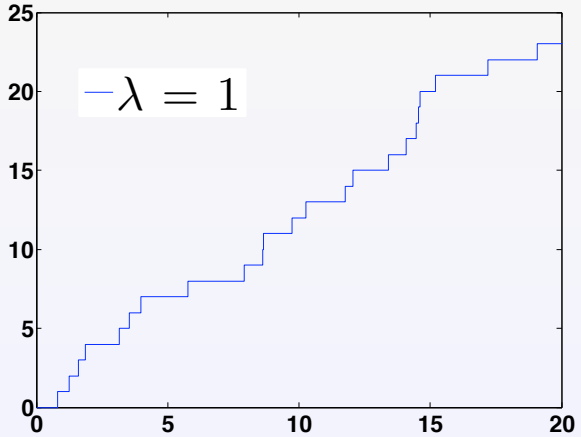
Will view a Poisson process, $Y(\cdot)$, through the lens of an underlying point process.

(a) Let $\{e_i\}$ be i.i.d. exponential random variables with parameter one.

(b) Now, put points down on a line with spacing equal to the e_i:



- Let $Y_1(t)$ denote the number of points hit by time t.
- In the figure above, $Y_1(t) = 6$.

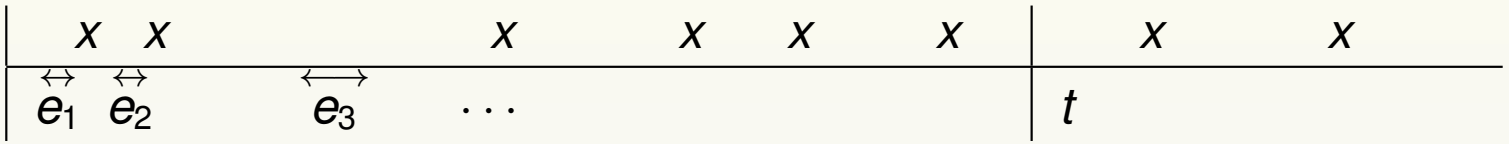


The Poisson process

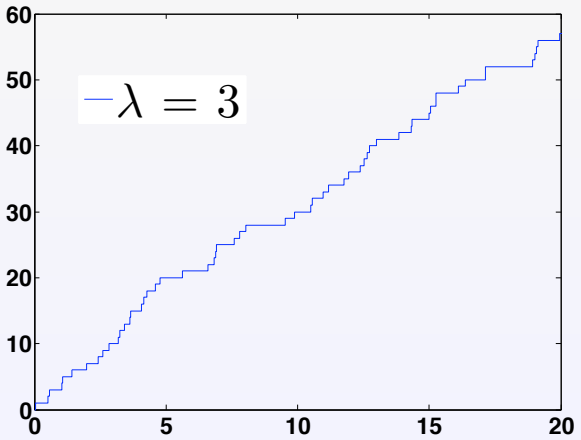
Let

- Y_1 be a unit rate Poisson process.
- Define $Y_\lambda(t) \equiv Y_1(\lambda t)$,

Then Y_λ is a Poisson process with parameter λ.



Intuition: The Poisson process with rate λ is simply the number of points hit (of the unit-rate point process) when we run along the time frame at rate λ.



The Poisson process

There is no reason λ needs to be constant in time, in which case

$$Y_\lambda(t) \equiv Y\left(\int_0^t \lambda(s)ds\right)$$

is a non-homogeneous Poisson process with propensity/intensity $\lambda(t) \geq 0$.

Thus

$$\begin{aligned} P\{Y_\lambda(t+\Delta t) - Y_\lambda(t) > 0|\mathcal{F}_t\} &= 1 - P\{Y_\lambda(t+\Delta t) - Y_\lambda(t) = 0|\mathcal{F}_t\} \\ &= 1 - \exp\left\{-\int_t^{t+\Delta t} \lambda(s)ds\right\} \\ &\approx \lambda(t)\Delta t. \end{aligned}$$

Note:

- We have "changed time" to convert a unit-rate Poisson process to one which has rate or intensity or propensity $\lambda(t)$.

Return to models of interest

Consider the simple system

$$A + B \to C$$

where one molecule each of A and B is being converted to one of C.

Intuition for standard stochastic model:

$$P\{\text{reaction occurs in } (t, t+\Delta t] \,\big|\, \mathcal{F}_t\} \approx \kappa X_A(t) X_B(t) \Delta t$$

where

- κ is a positive constant, the reaction rate constant.
- $\mathcal{F}_t$ is all the information pertaining to the process up through time t.

Models of interest

$$A + B \to C$$

Simple book-keeping says: if

$$X(t) = \begin{bmatrix} X_A(t) \\ X_B(t) \\ X_C(t) \end{bmatrix}$$

gives the state at time t, then

$$X(t) = X(0) + R(t) \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix},$$

where

- $R(t)$ is the # of times the reaction has occurred by time t and
- $X(0)$ is the initial condition.

Goal: represent $R(t)$ in terms of Poisson process.

Models of interest

Recall that for $A + B \to C$ our intuition was to specify infinitesimal behavior

$$P\{\text{reaction occurs in } (t, t+\Delta t] \big| \mathcal{F}_t\} \approx \kappa X_A(t) X_B(t) \Delta t,$$

and that for a counting process with specified intensity $\lambda(t)$ we have

$$P\{Y_\lambda(t+\Delta t) - Y_\lambda(t) = 1 | \mathcal{F}_t\} \approx \lambda(t) \Delta t.$$

This suggests we can model

$$R(t) = Y\left(\int_0^t \kappa X_A(s) X_B(s) ds\right)$$

where Y is a unit-rate Poisson process.
Hence

$$\begin{pmatrix} X_A(t) \\ X_B(t) \\ X_C(t) \end{pmatrix} \equiv X(t) = X(0) + \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} Y\left(\int_0^t \kappa X_A(s) X_B(s) ds\right).$$

This equation uniquely determines X for all $t \geq 0$.

Build up model: Random time change representation of Kurtz

- Now consider a network of reactions involving d chemical species, $S_1, \ldots, S_d$:

$$\sum_{i=1}^{d} y_{ki} S_i \longrightarrow \sum_{i=1}^{d} y'_{ki} S_i$$

Denote reaction vector as

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

so that if reaction k occurs at time t

$$X(t) = X(t-) + \zeta_k.$$

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

$$X(t) = X(0) + \sum_k R_k(t)\zeta_k,$$

with

$$X(t) = X(0) + \sum_k Y_k \left(\int_0^t \lambda_k(X(s))ds \right) \zeta_k,$$

Y_k are independent, unit-rate Poisson processes.

Dynamics: stochastic

Example:

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

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

$$X(t) = X(0) + R_1(t) \begin{bmatrix} -1 \\ 1 \end{bmatrix} + R_2(t) \begin{bmatrix} 1 \\ -1 \end{bmatrix}.$$

For Markov models can take

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

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

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

Mass-action kinetics

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

Reaction	Intensity Function
$\emptyset \xrightarrow{\kappa_1} S_1$	$\lambda_1(x) = \kappa_1$
$S_1 \xrightarrow{\kappa_2} S_2$	$\lambda_2(x) = \kappa_2 x_1$
$S_1 + S_2 \xrightarrow{\kappa_3} S_3$	$\lambda_3(x) = \kappa_3 x_1 x_2$
$2S_1 \xrightarrow{\kappa_4} S_2$	$\lambda_4(x) = \kappa_4 x_1(x_1 - 1)$

Other ways to understand model

We can also describe the model as a continuous time Markov chain with infinitesimal generator

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

where $\zeta_k = y_k' - y_k$.

Dynkin's formula (See Ethier and Kurtz, 1986, Ch. 1) yields

$$\mathbb{E}f(X(t)) - f(X_0) = \mathbb{E}\int_0^t (\mathcal{A}f)(X(s))ds,$$

Letting $f(y) = 1_x(y)$ above so that

$$\mathbb{E}[f(X(t))] = P\{X(t) = x\} = p_x(t),$$

gives Kolmogorov's forward equation (chemical master equation)

$$p_t'(x) = \sum_k \lambda(x-\zeta_k)p_t(x-\zeta_k) - p_t(x)\sum_k \lambda_k(x)$$

Example: population growth

Example

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

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

$$X(t) = X(0) + Y\left(\int_0^t \frac{1}{3} X(s) ds\right).$$

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

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

i.e.

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

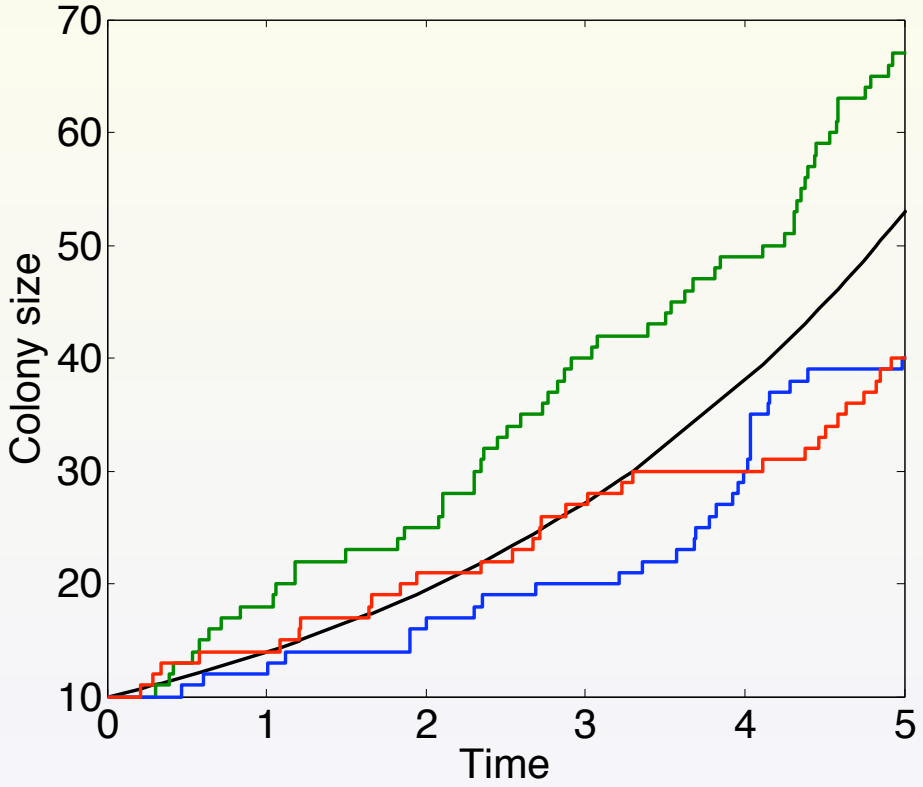
$$\frac{d}{dt} p_t(11) = \frac{1}{3} \cdot 10 \cdot p_t(10) - \frac{1}{3} \cdot 11 \cdot p_t(11)$$

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

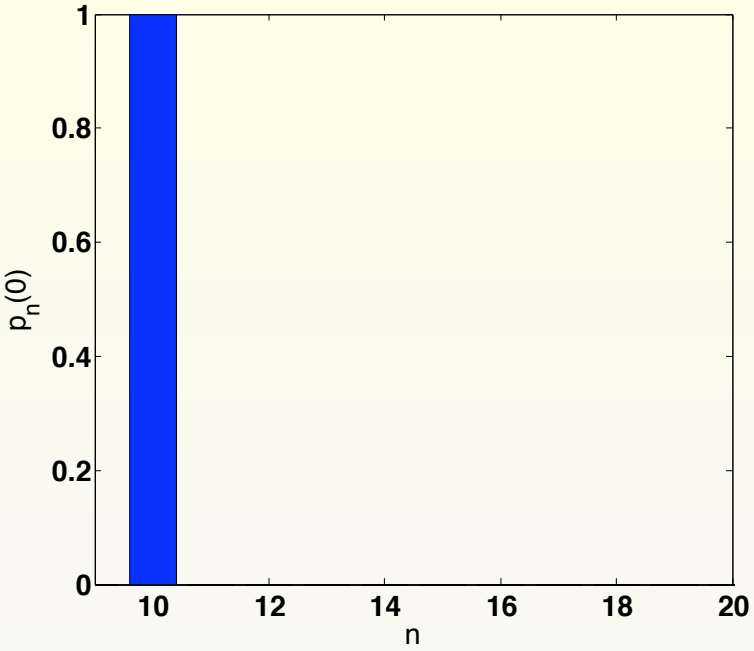
$$\vdots$$

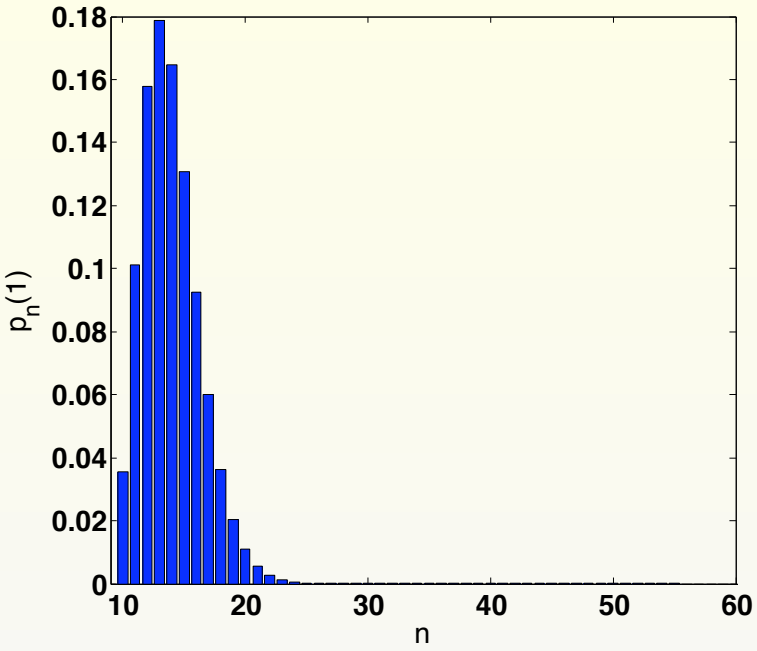
Example: Bacterial Growth - evolution of sample paths

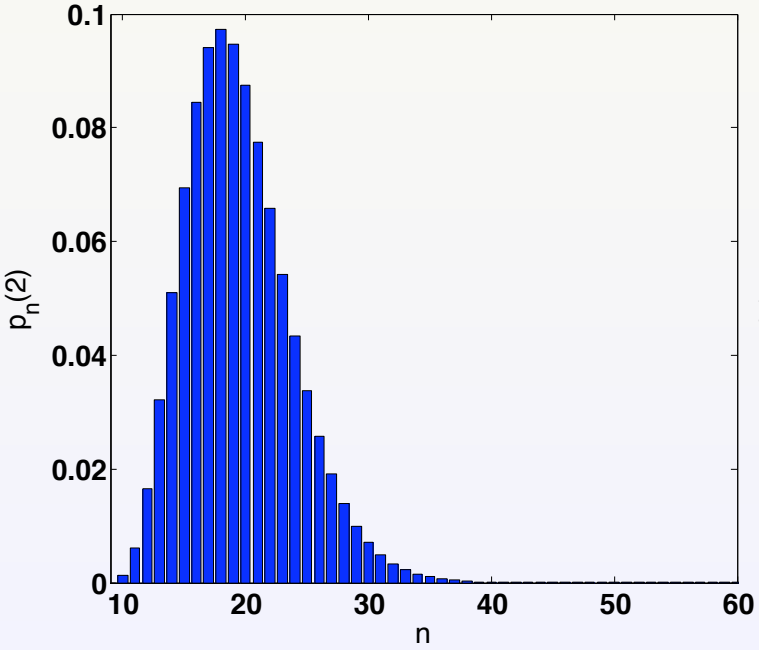
- Below is a plot of the solution of the deterministic system versus three different realizations of the stochastic system.

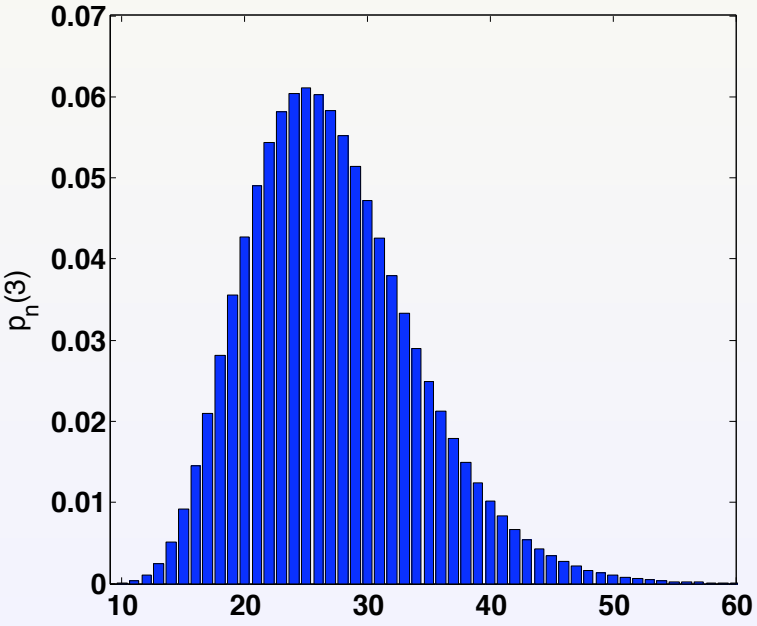


Example: population growth - evolution of distribution









Dynamics: Stochastic Versus Deterministic

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

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

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

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

or

$$\dot{x}(t) = \alpha x_a x_b \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \beta x_B \begin{bmatrix} 1 \\ -1 \end{bmatrix}$$

or

$$\begin{aligned} \dot{x}_A(t) &= -\alpha x_A x_B + \beta x_B \\ \dot{x}_B(t) &= \quad \alpha x_a x_B - \beta x_B. \end{aligned}$$

Dynamics: deterministic model

Assuming:

- V is a scaling parameter (volume times Avogadro's number),
- $X_i = O(V)$, and $X^V(t) \stackrel{\text{def}}{=} X(t)/V$,
- $\lambda_k(X(t)) \approx V\left(\kappa_k X^V(t)^{y_k}\right)$,

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

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

so a good approximation (Gronwall, $V \to \infty$) 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

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

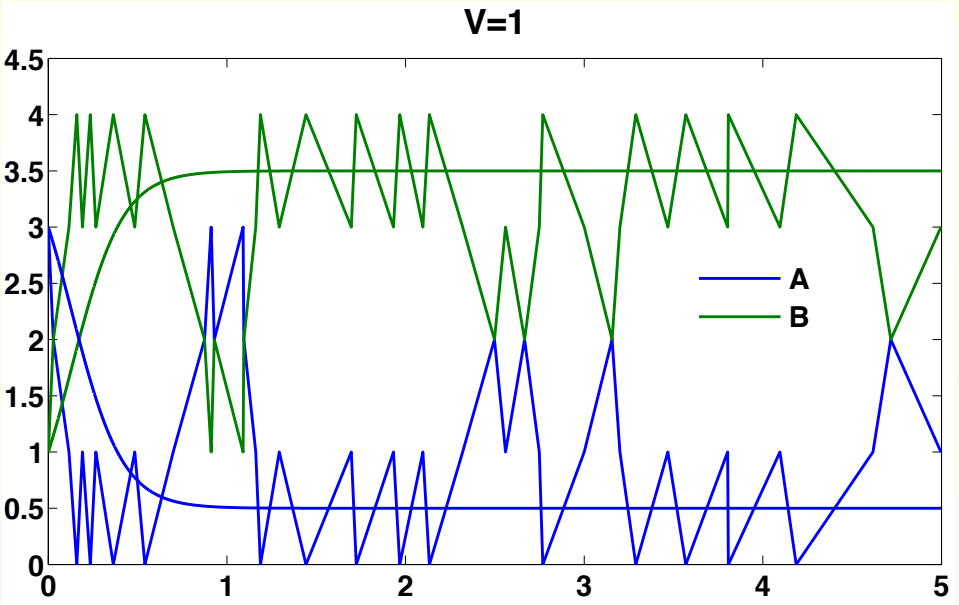
- ODE model of

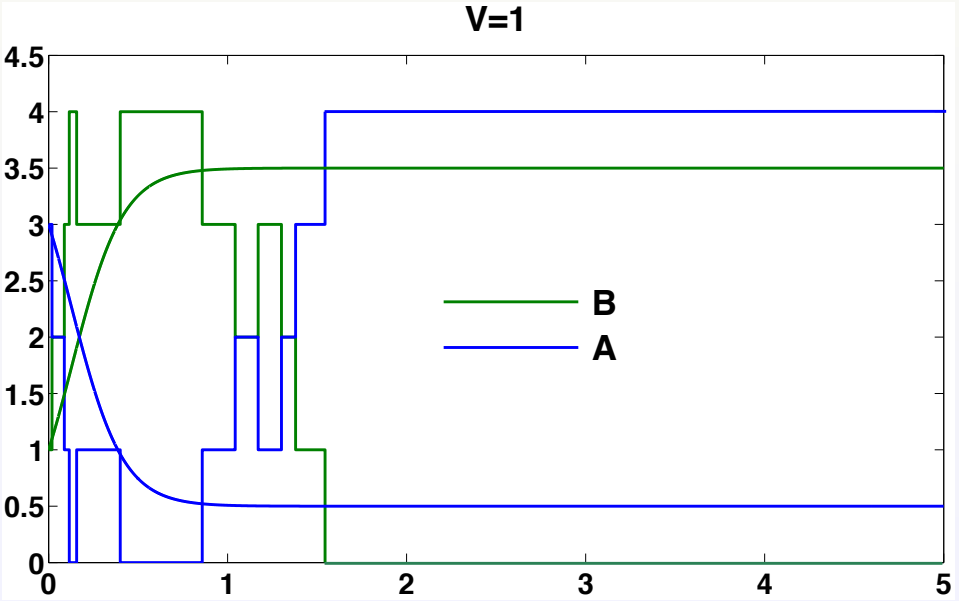
$$A + B \xrightarrow{2} 2B$$

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

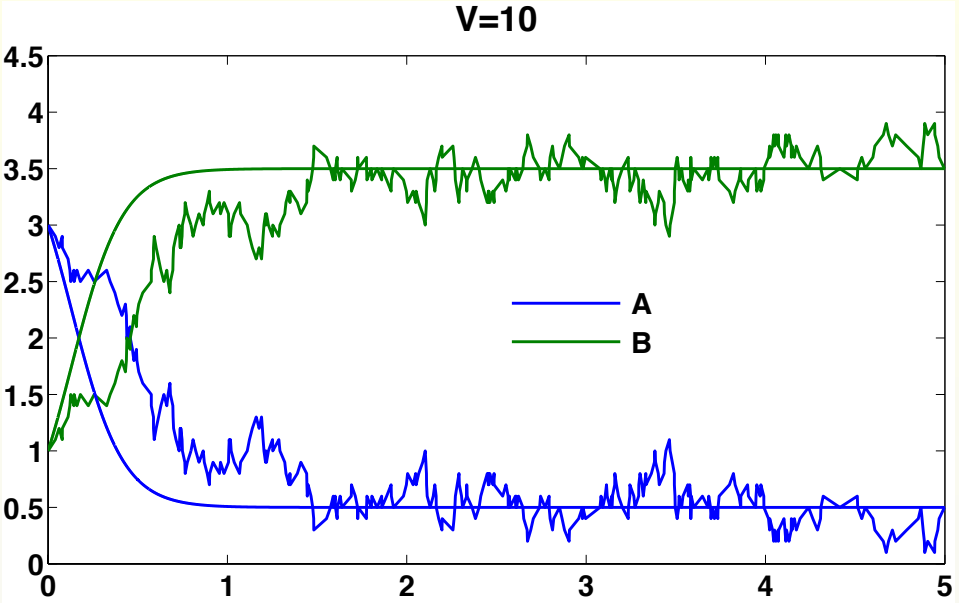
with $x(0) = [3, 1]$.

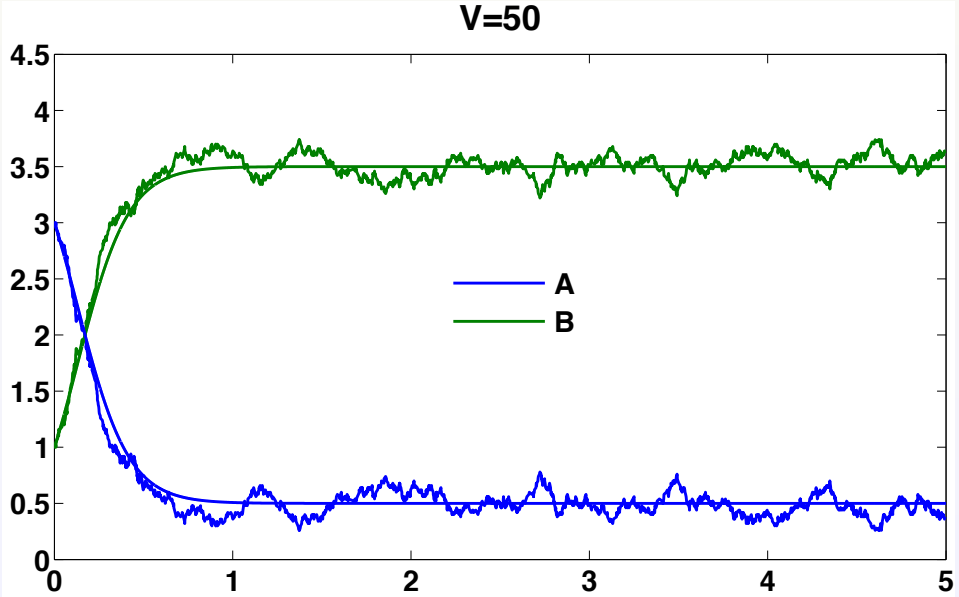
LLN: Example, $A + B \rightarrow 2B \quad B \rightarrow A$



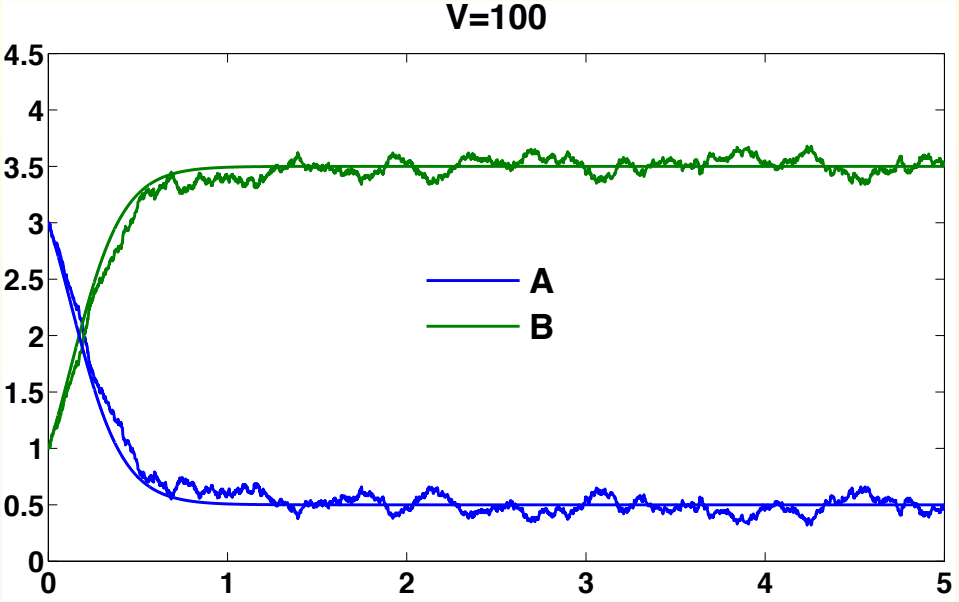


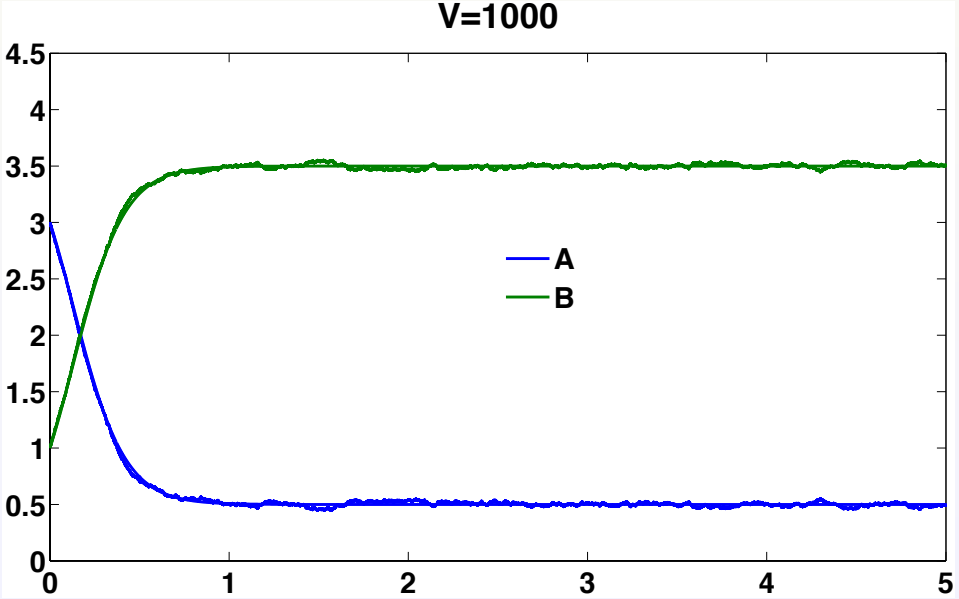
LLN: Example, $A + B \rightarrow 2B \quad B \rightarrow A$





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





CRNT: Stochastic

1. We want to answer the same types of questions in stochastic setting: long term behavior from network structure.

2. No longer can search for fixed points.

3. Can look for fixed points to forward equations (master equation): stationary distribution:

Deficiency Zero Theorem - stochastic

Theorem (Anderson, Craciun, Kurtz, 2010)

Suppose we have a biochemical reaction system for which the ODE model has a complex balanced equilibrium $\bar{c}$ (for example, the network satisfies the following two conditions,

- *Deficiency of zero,*
- *weakly reversible.*

)

Then, the associated stochastic model satisfies:

- *There is a stationary distribution which is the product of Poisson distributions:*

$$\pi(x) = M \prod_{i=1}^{d} \frac{\bar{c}_i^{x_i}}{x_i!}, \quad x \in \Gamma, \tag{2}$$

where M 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.

Example: Open, first-order system

If the network is an open, first-order reaction network, then $\Gamma = \mathbb{Z}^d_{\geq 0}$

$$\pi(x) = e^{-\sum_{i=1}^d c_i} \prod_{i=1}^d \frac{c_i^{x_i}}{x_i!} = \prod_{i=1}^d e^{-c_i} \frac{c_i^{x_i}}{x_i!}, \qquad x \in \mathbb{Z}^d_{\geq 0}.$$

where $c \in \mathbb{R}^N_{>0}$ is the equilibrium of the associated (linear) deterministic system.

- Thus, when in distributional equilibrium, the species numbers are independent and have Poisson distributions. This is well known.

- **However:**

1. Neither the independence nor the Poisson distribution resulted from the fact that the system under consideration was a first order system.

2. Instead, both facts followed from $\Gamma = \mathbb{Z}^d_{\geq 0}$.

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.

Another example

Consider

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

- State space, assuming $X_0 > 0$, is

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

- ODE model satisfies

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

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

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

Another example

Example

$$2A \rightleftarrows 2B.$$

Higher deficiency

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

What about higher deficiency?

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

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

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

$$\begin{aligned}
\dot{x}_A(t) &= -\alpha x_A(t) x_B(t) + \beta x_B(t) \\
\dot{x}_B(t) &= \quad \alpha x_A(t) x_B(t) - \beta x_B(t) \\
M &\stackrel{\text{def}}{=} x_A(0) + x_B(0),
\end{aligned}$$

Solving for equilibria:

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

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

Network has absolute concentration robustness in species A.

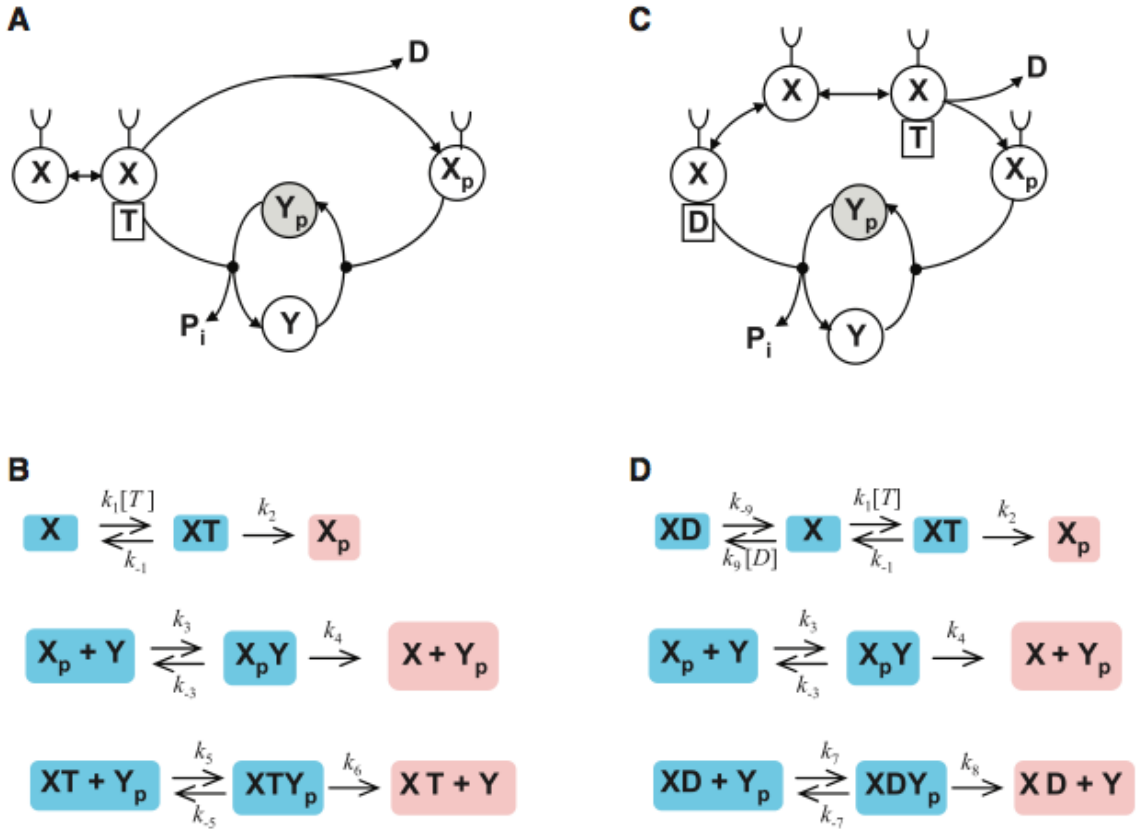


Fig. 2. The EnvZ-OmpR system. (**A**) A schematic diagram of an EnvZ-OmpR model in which ATP is the cofactor in phospho-OmpR dephosphorylation. P_i denotes phosphate ion. (**B**) The mass-action model underlying (A). [*T*] denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink,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

Differing in one species

Examples:

1. $A, \quad A + B$

   differ in species B.

---

2. $XT, \quad XT + Y_p$

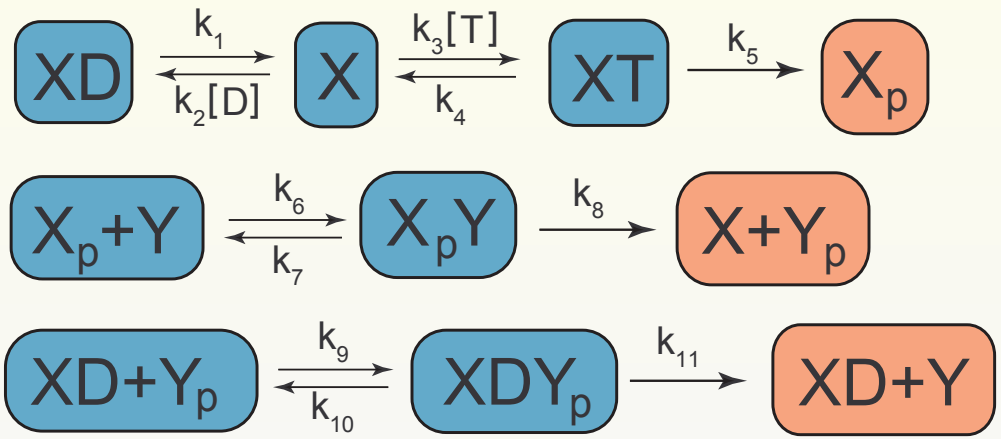
   differ in species Y_p.

---

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 (Marty Feinberg and Guy 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 (Anderson, 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.

---

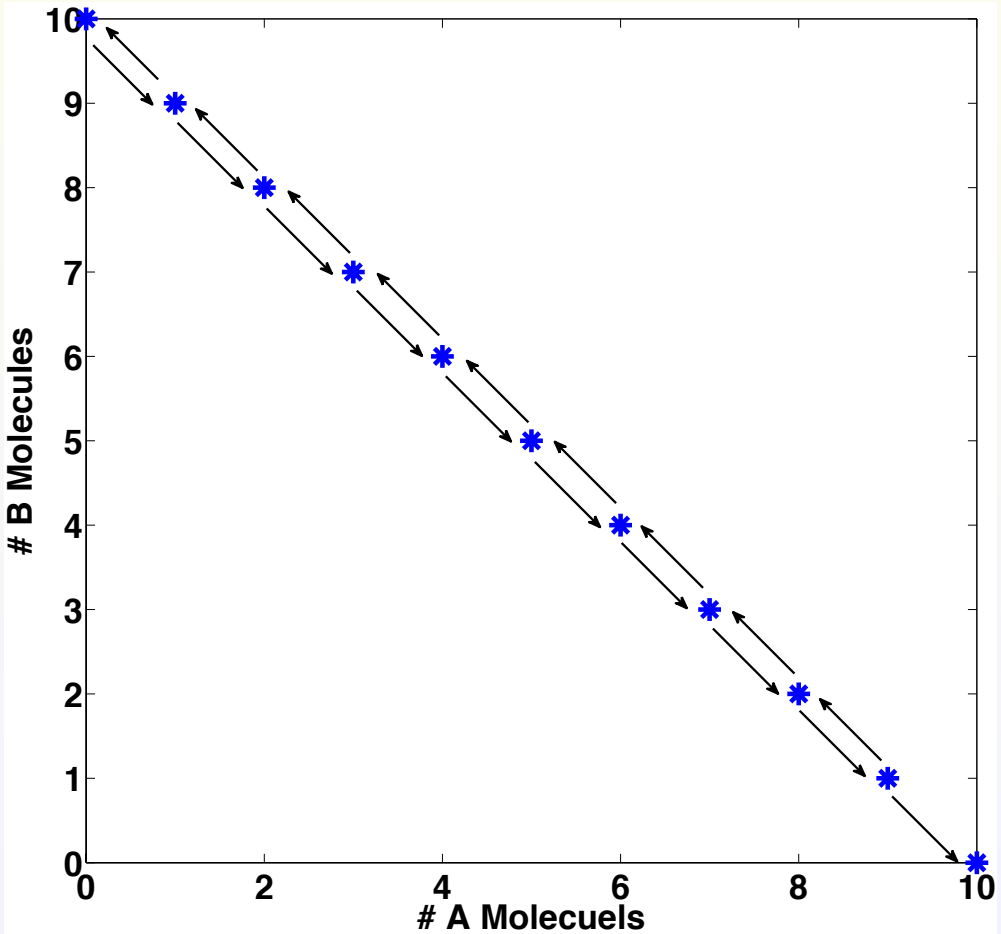
[0] David F. Anderson, Germán Enciso, and Matthew Johnston, *Stochastic analysis of biochemical reaction networks with absolute concentration robustness*, J. Royal Society Interface, Vol. 11, 20130943, February 12, 2014.

Example

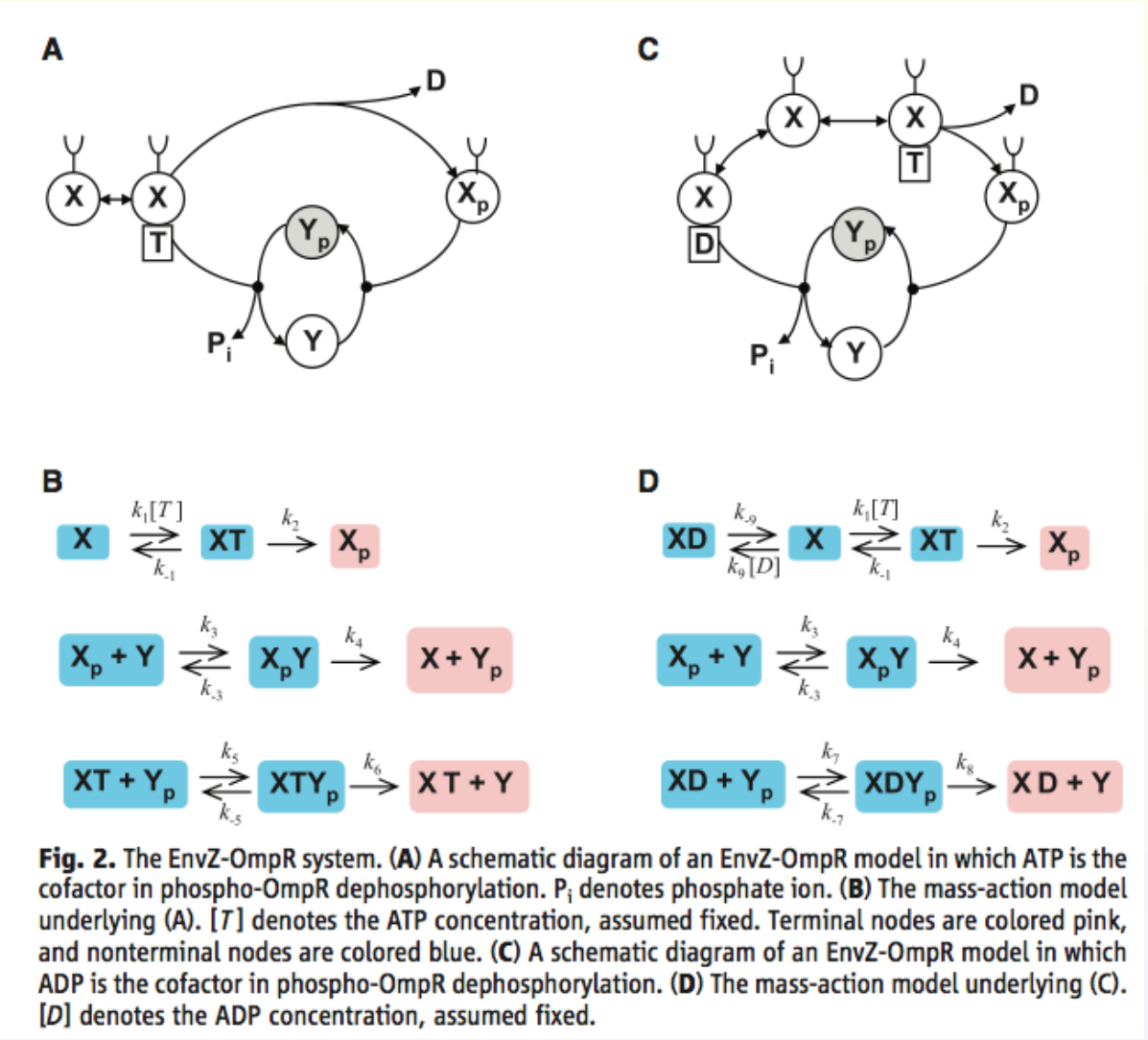
Reaction network

$$A + B \rightarrow 2B$$
$$B \rightarrow A$$

has state space



Example



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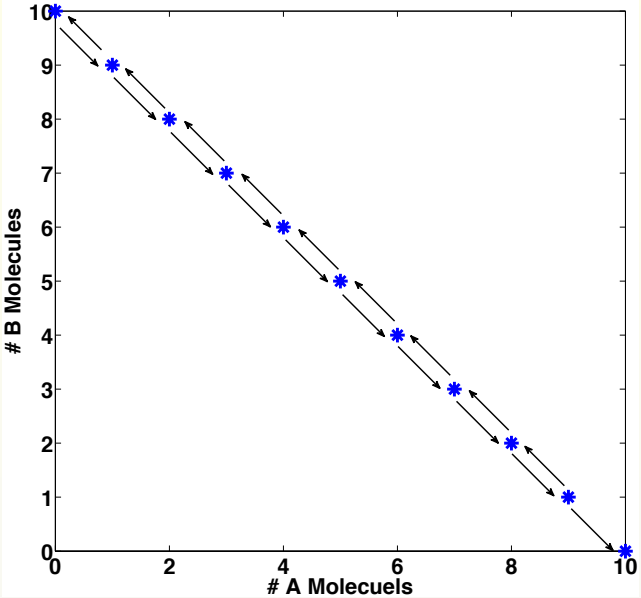
Extinction can be rare event: quasi-stationary distribution

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

$$B \xrightarrow{\beta} A$$

$$X_A(0) + X_B(0) = M,$$



Find π_M^Q so that for τ absorption time and $x \in$ transient states,

$$\lim_{t\to\infty} P_\nu(X(t) = x \mid \tau > t) = \pi_M^Q(x).$$

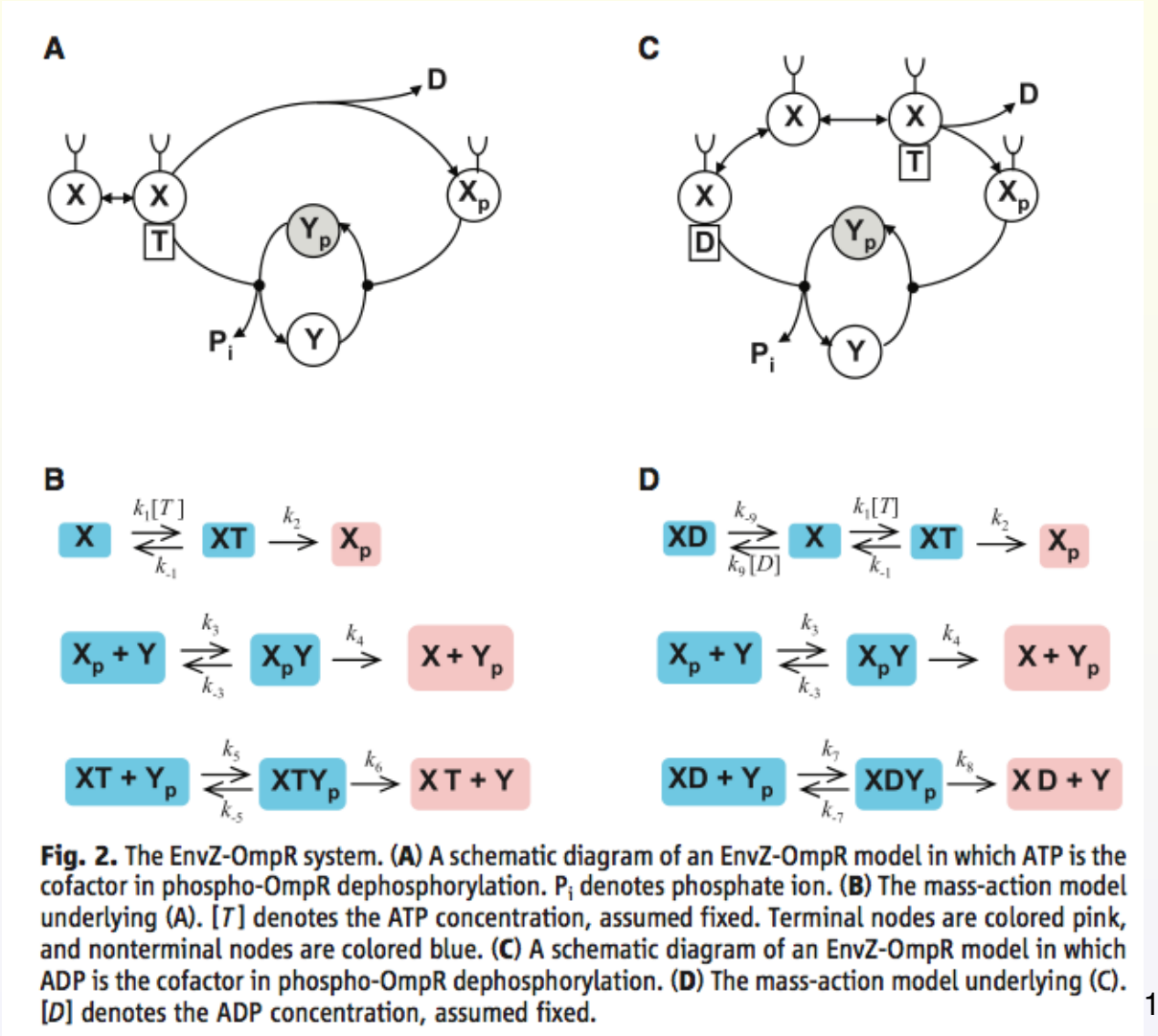
Satisfies

$$\pi_M^Q(x) = P_{\pi_M^Q}(X(t) = x \mid \tau > t).$$

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

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

Quasi-stationary distribution: EnvZ-OmpR signaling system



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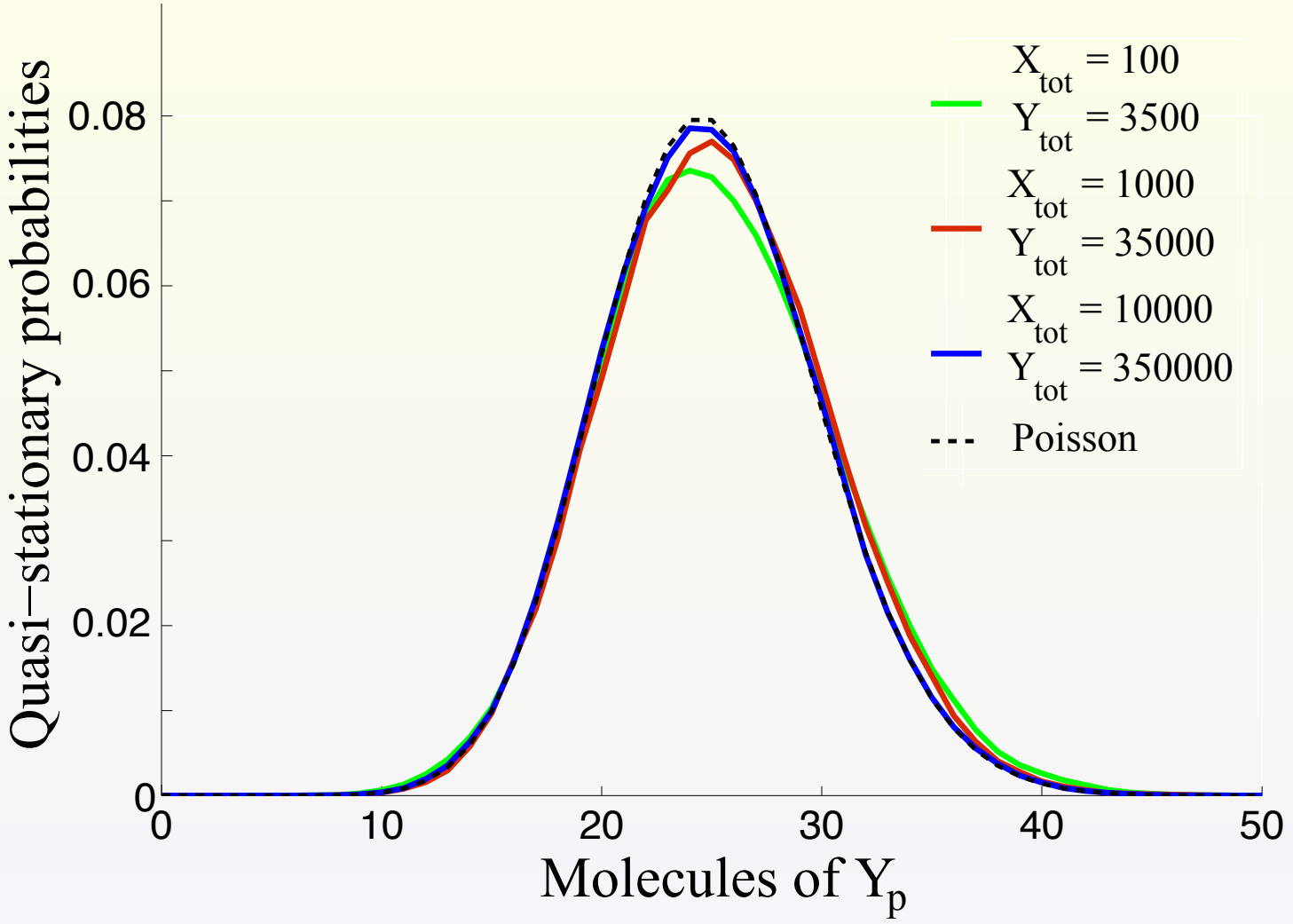
[1] Guy Shinar and Martin Feinberg, *Structural Sources of Robustness in Biochemical Reaction Networks*, Science, 2010

Quasi-stationary distribution



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

Precise statement

Need a more precise statement:

There is an extinction event $\Longleftrightarrow$ there will be a last time the non-terminal complexes "fire".

$$A + B \xrightarrow{\alpha} 2B \qquad \text{(R1)}$$

$$B \xrightarrow{\beta} A \qquad \text{(R2)}$$

How to prove: an example

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

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

$$2A \leftrightarrows B + C. \tag{R3}$$

- Note $|\mathcal{C}| = 6, \quad \ell = 3, \quad s = 2 \implies \delta = 1.$
- $w = (1, 1, 1)$ is conservation relation.

Flavor of proof

Ideas:

- Decompose $\dot{x} = f(x) = Y \circ A_\kappa \circ \Psi(x)$ into linear/nonlinear portions.
- Use deficiency assumption to understand the basis of ker(YA_κ).
- Consider "reduced network" and prove result holds on that model.
- How?
  - Assume result does not hold, and that there is a recurrent state where there should not be.
  - Use stochastic equation

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

with a useful set of stopping times + limit theorem to construct an element in ker(YA_κ) which is impossible.

Flavor of proof

- Can use that the deficiency of model is one to characterize basis of kernel of $YA_\kappa : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$.
- $$\ker(YA_\kappa) = \text{span}\{\overline{\mathbf{c}}, b_1, \ldots, b_T\},$$
- The terms $\{b_1, \ldots, b_T\}$ have support on terminal complexes. Recall: A_κ^T is the infinitesimal generator for the CTMC on network of complexes.
- The term $\overline{\mathbf{c}}$ has support on *all* complexes.
- Now consider reduced model. I.e.

$$A + B \overset{\kappa_1}{\to} 2B$$

$$B \overset{\kappa_2}{\to} A$$

$$2A \underset{\kappa_4}{\overset{\kappa_3}{\leftrightarrows}} B + C.$$

becomes

$$B \overset{\kappa_2}{\to} A$$

$$2A \underset{\kappa_4}{\overset{\kappa_3}{\leftrightarrows}} B + C.$$

flavor of proof

Only work with $A+B$ – reduced network. Call it $\{S, \mathcal{C}, \mathcal{R}^*\}$. Call process X^*.

- Suppose there is a positive recurrent state X_0 which charges a non-terminal complex.
- We want to reach a contradiction (with kernel condition).
- We denote the Nth return time to $\mathbf{X}_0$ as t_N. It follows that we have

$$\mathbf{X}^*(t_N) = \mathbf{X}^*(0)$$

for all N so that

$$\mathbf{X}^*(t_N) = \mathbf{X}^*(0) + \sum_k Y_k \left(\kappa_i \int_0^{t_N} (X^*(s))^{y_k} ds \right) (y_k' - y_k) = \mathbf{X}^*(0), \quad (3)$$

and so

$$\sum_k Y_k \left(\kappa_i \int_0^{t_N} (X^*(s))^{y_k} ds \right) (y_k' - y_k) = 0, \quad (4)$$

- Relatively easy to show that for each y_k

$$\int_0^{t_N} (X^*(s))^{y_k} ds \to \infty, \text{ as } N \to \infty,$$

flavor of proof

$$\sum_k Y_k \left(\kappa_i \int_0^{t_N} (X^*(s))^{y_k} \, ds \right) (y_k' - y_k) = 0,$$

and

$$\int_0^{t_N} (X^*(s))^{y_k} \, ds \to \infty, \text{ as } N \to \infty,$$

- multiplying and dividing by appropriate terms,

$$0 = \sum_k \kappa_k \left[\frac{1}{\kappa_k \int_0^{t_N} (X^*(s))^{y_k} \, ds} Y_k \left(\kappa_k \int_0^{t_N} (X^*(s))^{y_k} \, ds \right) \times \frac{1}{t_N} \int_0^{t_N} (X^*(s))^{y_k} \, ds \right] (y_k' - y_k).$$

- We have

$$\lim_{N \to \infty} \frac{1}{t_N} \int_0^{t_N} (X^*(s))^{y_k} \, ds = \sum_{\mathbf{x} \in \mathcal{I}} \pi_{\mathcal{I}}(\mathbf{X}) \mathbf{X}^{y_k}, \tag{5}$$

- Define the vector $G_\pi \in \mathbf{R}^{\mathcal{C}}$ via

$$[G_\pi]_y := \sum_{\mathbf{x} \in \mathcal{I}} \pi_{\mathcal{I}}(\mathbf{X}) \mathbf{X}^y, \tag{6}$$

  for $y \in \mathcal{C}$, and note that $[G_\pi]_y > 0$ for all remaining y.
- Can then argue that $[G_\pi]$ is in the kernel of $Y \circ A_\kappa$, which it can not be (contradiction). □

May be useful to this community

Can characterize how will go to the boundary. Board 2.5.5.

Open question: how does deficiency relate to computation?

That is the story. Thanks!

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