Stochastic models of reaction networks

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Outline

1. Introduction to the stochastic models.
2. Large volume limits (on compact time intervals)
3. Convergence to equilibrium for stochastic models, what does it mean and when does it happen?
4. Similarities and discrepancies between the behavior of the stochastic and deterministic models as $t \to \infty$.

We've seen reaction networks: $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$

- $\mathcal{S}$: species.
  For example $\{A, B\}$.
- $\mathcal{C}$: complexes, linear combinations of the species over $\mathbb{Z}$.
  For example, $\{2A, A + B, \dots\}$
- $\mathcal{R}$: reactions. We will denote by

  $$y \to y' \in \mathcal{R}$$

  with usual convention (abuse of notation)

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

  For example, $\{2A \to A + B, \dots\}$

Will assume certain terminology: linkage class, weakly reversible, detailed balanced, complex balanced, stoichiometric compatibility class.

Assumed knowledge: deterministic models

We know that for a given network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ we have a system of autonomous ODEs that govern dynamics of the concentrations

$$\dot{x}(t) = \sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} x(t)^y (y' - y),$$

where for vectors u, v, we have

$$u^v = \prod_{i=1}^{d} u_i^{v_i}.$$

where we take $0^0 = 1$.

- Assuming deterministic mass-action kinetics.
- This model is appropriate when the counts of the molecules are high, which I'll discuss soon.

Example

$$A + B \xrightarrow{\kappa_1} 2B$$
$$B \xrightarrow{\kappa_2} A$$

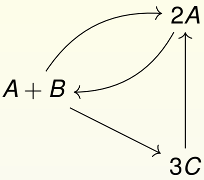
yields

$$\begin{aligned}\dot{x}_A(t) &= -\kappa_1 x_A(t) x_B(t) + \kappa_2 x_B(t)\\ \dot{x}_B(t) &= \quad \kappa_1 x_A(t) x_B(t) - \kappa_2 x_B(t)\end{aligned}$$

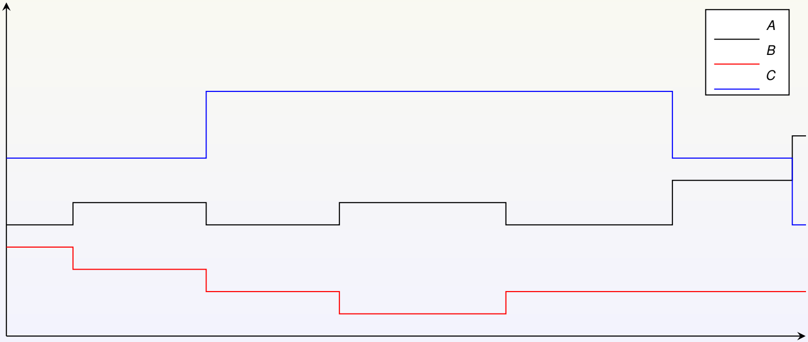
or

$$\dot{x}(t) = \kappa_1 x_A(t) x_B(t) \begin{pmatrix} -1 \\ 1 \end{pmatrix} + \kappa_2 x_B(t) \begin{pmatrix} 1 \\ -1 \end{pmatrix}$$

Stochastic model



and imagine that we want to track the counts of the molecules.



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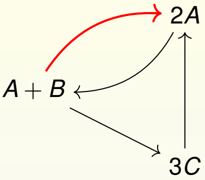

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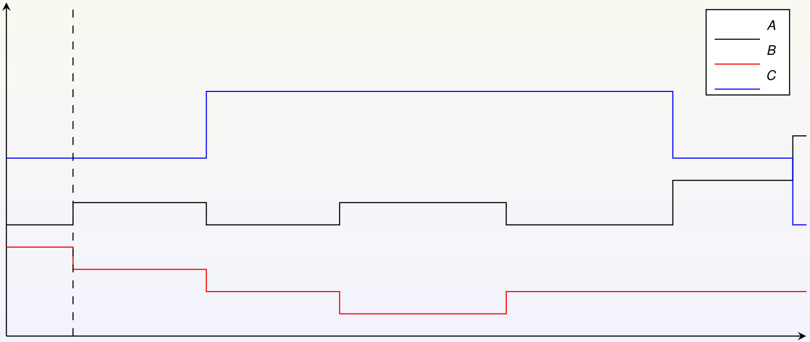

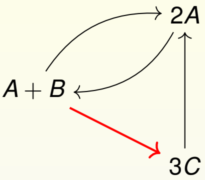

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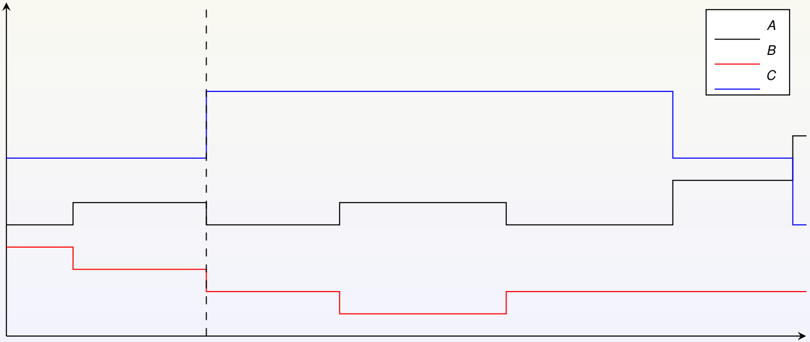

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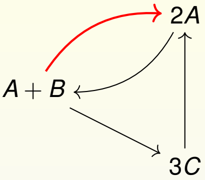

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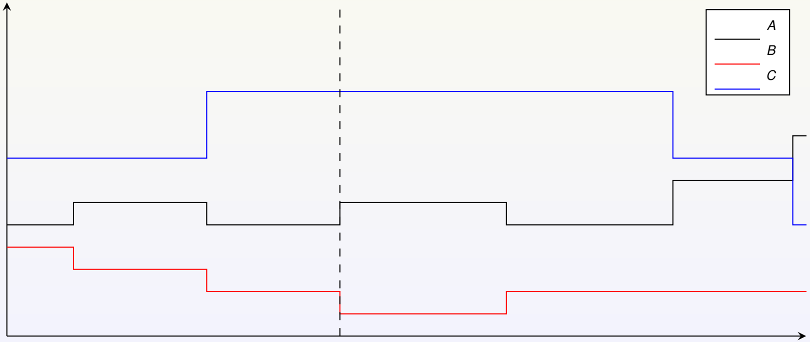

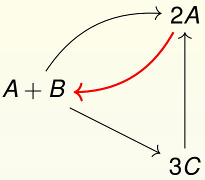

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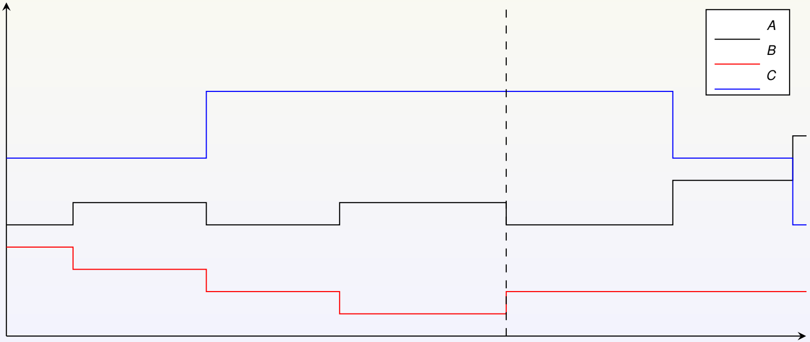

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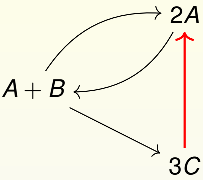

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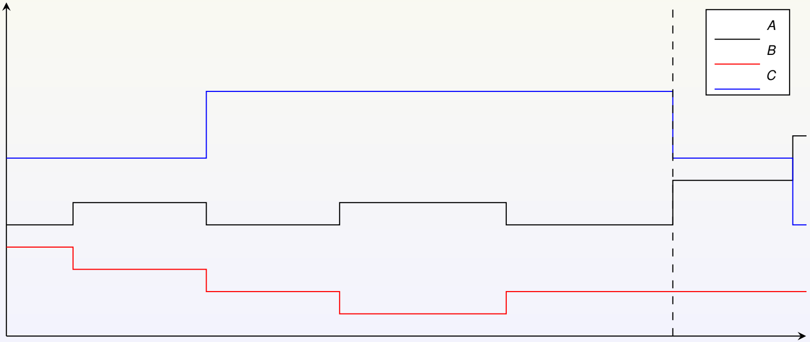

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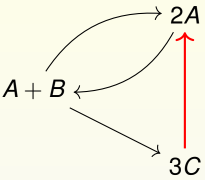

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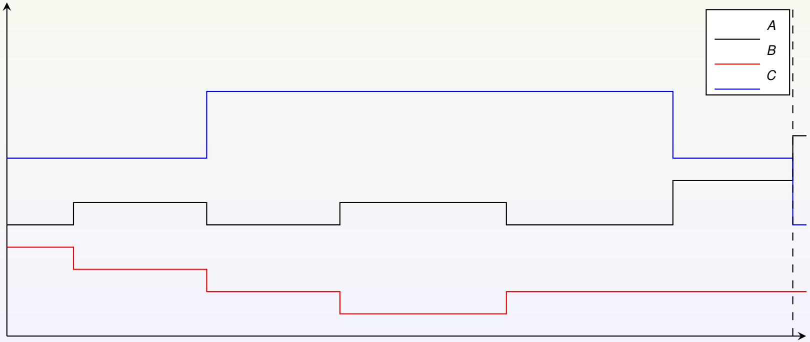

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Modelling assumption:

- at time t, reaction $y \to y' \in \mathcal{R}$ has an associated clock set to go off after an amount of time given by an exponential random variable with a parameter of

$$\lambda_{y \to y'}(X(t)),$$

independently on what happened in the past. The higher the parameter, the lower tends to be the exponential random variable.

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- Throw away all the clocks.
- Now repeat.

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The described process is a continuous-time Markov chain.

By the properties of exponential random variables, an equivalent simulation strategy is given by the Gillespie's algorithm.

- Suppose $X(t) = x$.
- Let
$$\lambda_0(x) = \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(x)$$
and let $\Delta = \text{Exp}(\lambda_0(x))$.
- Independently choose $\bar{y} \to \bar{y}' \in \mathcal{R}$ with probability
$$\frac{\lambda_{\bar{y} \to \bar{y}'}(x)}{\sum_{y \to y'} \lambda_{y \to y'}(x)}.$$
- Update $X(t+s) = X(t)$ for $0 \leq s < \Delta$ and
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This is not efficient if rates are very high, so many reactions take place in a short amount of time and use a lot of computational power.

Mass-action kinetics

A popular choice for intensity functions is stochastic mass-action kinetics:

$$\lambda_{y\to y'}(x) = \kappa_{y\to y'} \prod_i \frac{x_i!}{(x_i - y_i)!}.$$

Example: If $S_1 \to$ anything, then

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Example: If $2S_2 \to$ anything, then

$$\lambda_{y\to y'}(x) = \kappa_{y\to y'} \frac{x_2!}{(x_2-2)!} = \kappa_{y\to y'} x_2(x_2-1).$$

Nonlinear if any reaction requires two or more molecules.

Model of viral infection: Srivistava, You, Summers, and Yin, J. Theor. Biol., **218** (2002)

$$R_1) \quad T \xrightarrow{1} T + G, \qquad R_2) \quad G \xrightarrow{0.025} T, \qquad R_3) \quad T \xrightarrow{1000} T + S,$$

$$R_4) \quad T \xrightarrow{0.25} \emptyset, \qquad R_5) \quad S \xrightarrow{2} \emptyset, \qquad R_6) \quad G + S \xrightarrow{7.5\times 10^{-6}} V,$$

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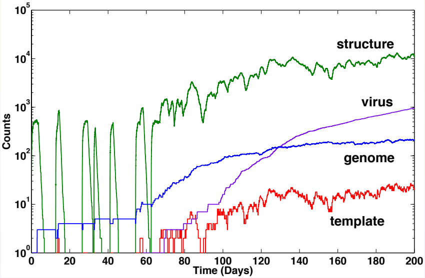
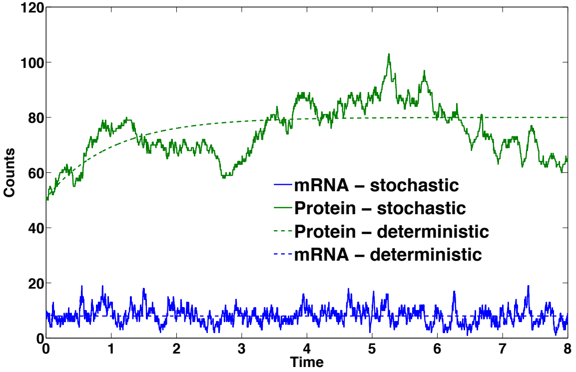


Gene network

$$\begin{array}{llr} R1) & G \xrightarrow{200} G + M & \text{(Transcription)} \\ R2) & M \xrightarrow{10} M + P & \text{(Translation)} \\ R3) & M \xrightarrow{25} \emptyset & \text{(Degradation of mRNA)} \\ R4) & P \xrightarrow{1} \emptyset & \text{(Degradation of protein)} \end{array}$$



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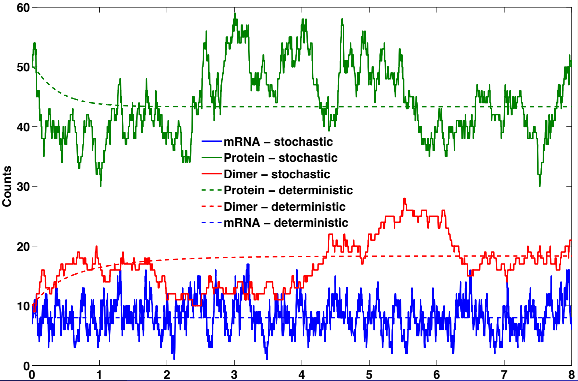

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&R7 \,\&\, R8) && D + G \underset{0.1}{\overset{2}{\rightleftarrows}} B && \text{(Binding)}
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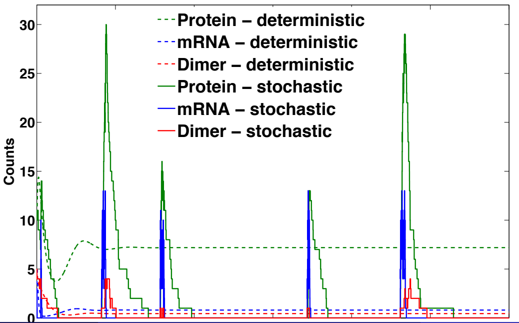

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  - ...
- Use an approximate simulation strategy, such as tau leaping: count the number of reactions that would occur in a time window if the state were constant, then update.

Section 1

Structural differences between deterministic and stochastic reaction networks

Structural differences

If at time t^* the reaction $y \to y'$ takes place, then

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Therefore, the evolution of X_t is confined within the stoichiometric compatibility classes.
What is different from the deterministic case?
The state space for X_t is $\mathbb{N}^{|\mathcal{S}|}$.

Consider

$$2A \xrightarrow{\kappa_1} 2B \qquad A + 3B \xrightarrow{\kappa_2} 3A + B$$

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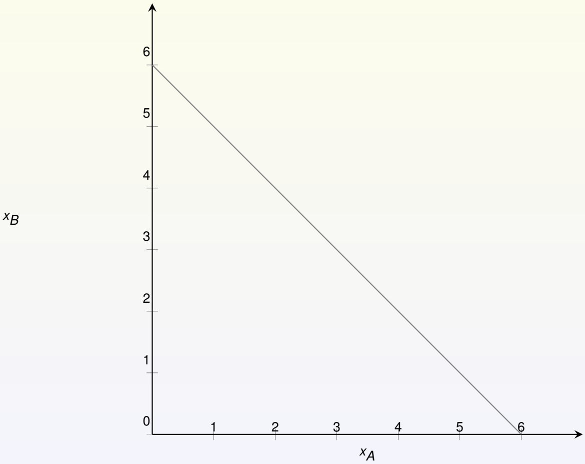

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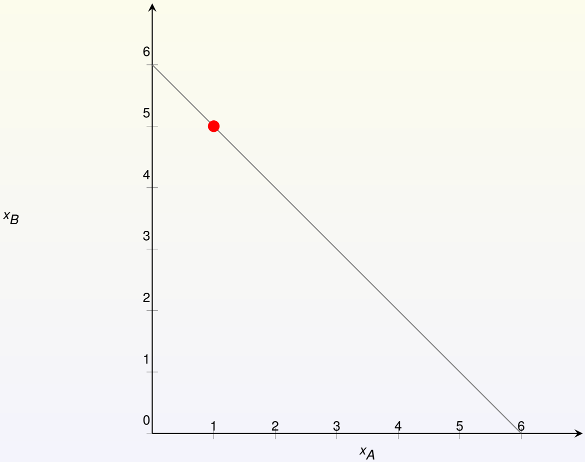

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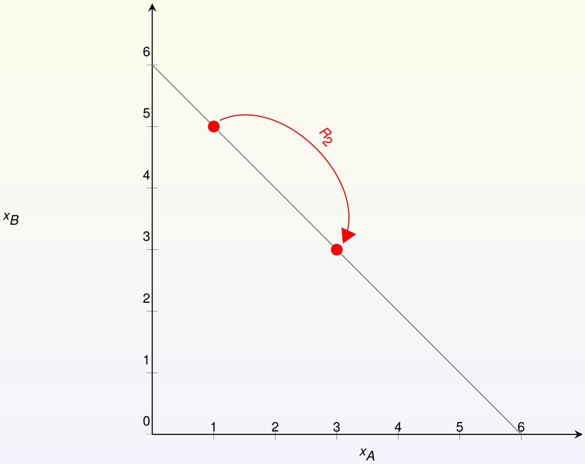

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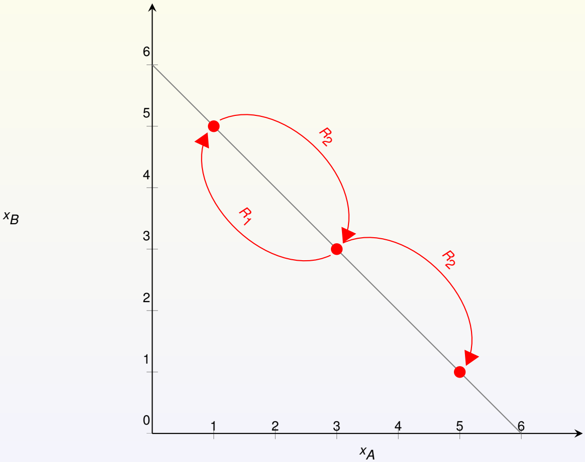

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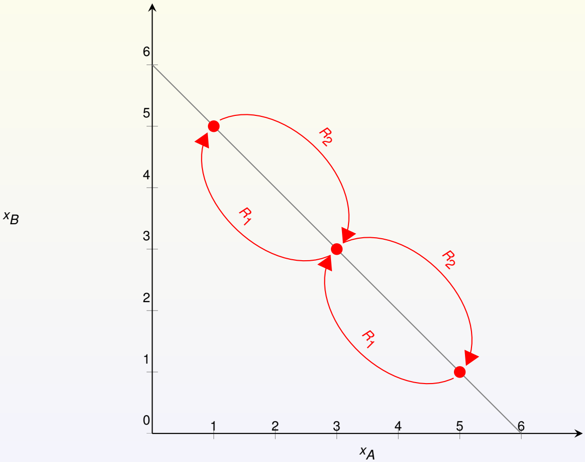

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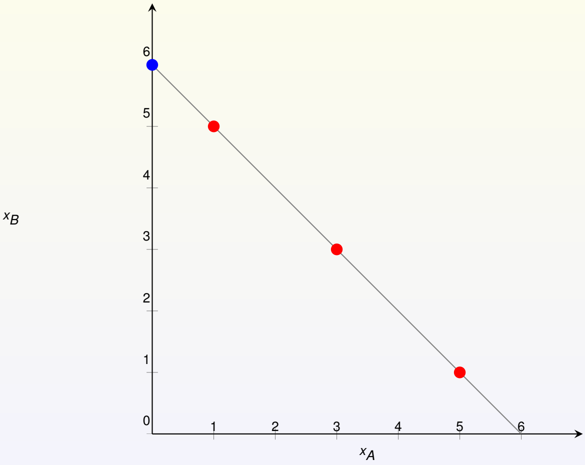

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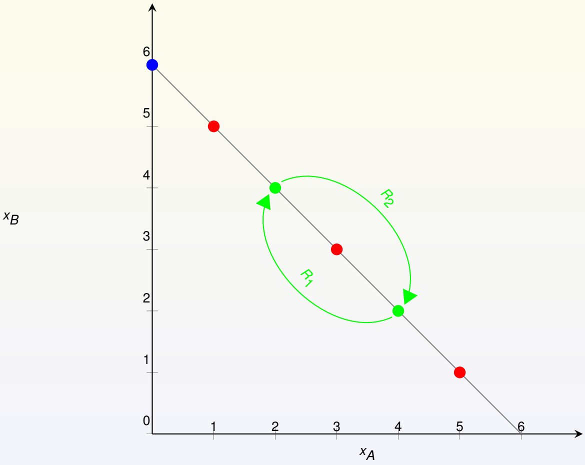

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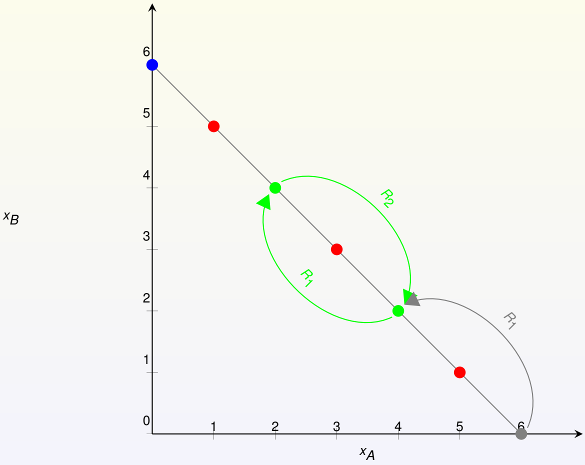

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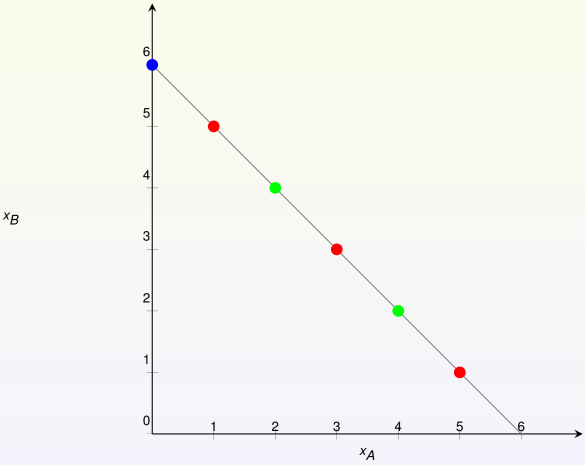

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Definition (Accessible states)

z is accessible from x if $\exists\ (y_i \to y'_i)_{i=1,\ldots,q}$ such that

$$z = x + \sum_{i=1}^{q} \xi_i,$$

and for any $1 \leq j \leq q$, $y_j \to y'_j$ is switched on at $x + \sum_{i=1}^{j-1} \xi_i$. In particular, x is accessible from x.

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Definition (Communicating states)

x and z are communicating if z is accessible from x and vice versa.

Definition (Irreducible components)

An irreducible components of a reaction network is a set $\Gamma \subseteq \mathbb{N}^{|\mathcal{S}|}$ such that, for any $x \in \Gamma$, $z \in \Gamma$ if and only if it is accessible from x.

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- The irreducible components are not necessarily a partition of $\mathbb{N}^{|\mathcal{S}|}$;

Definition (Irreducible components)

An irreducible components of a reaction network is a set $\Gamma \subseteq \mathbb{N}^{|\mathcal{S}|}$ such that, for any $x \in \Gamma$, $z \in \Gamma$ if and only if it is accessible from x.

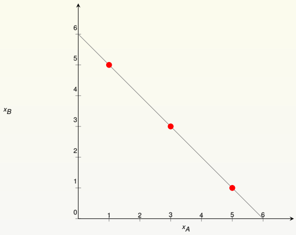
Γ is an irreducible component if and only if all the states of Γ are communicating, and no state outside Γ is accessible from any $x \in \Gamma$.

- Eventually, X_t will enter an irreducible component or drift to infinity;
- The irreducible components are not necessarily a partition of $\mathbb{N}^{|\mathcal{S}|}$;
- If a single state constitutes an irreducible component, it is a absorbing state.

Consider

$$2A \xrightarrow{\kappa_1} 2B \qquad A + 3B \xrightarrow{\kappa_2} 3A + B$$

on



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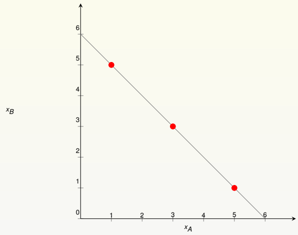

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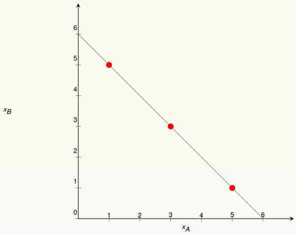

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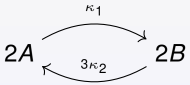

$$7A \xrightarrow{\kappa_3} 0$$

If $R_{y\to y'}(t)$ is the number of times reaction $y \to y'$ fires by time t, then simple booking:

$$X(t) = X(0) + \sum_{y\to y'} (y' - y) \cdot R_{y\to y'}(t).$$

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$R_{y\to y'}(t)$ is a counting process with (think exponential clocks)

$$P(R_{y\to y'}(t+\Delta) - R_{y\to y'}(t) = 1 \mid X(t)) = \lambda_{y\to y'}(X(t))\Delta + o(\Delta).$$

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Note that if Y is a unit-rate Poisson process then

$$P\left(Y\left(\int_0^{t+\Delta} \lambda_{y\to y'}(X(s))ds\right) - Y\left(\int_0^{t} \lambda_{y\to y'}(X(s))ds\right) = 1\right) \approx \lambda_{y\to y'}(X(t))\Delta.$$

- This suggests that the process can be represented as the solution to

$$X(t) = X(0) + \sum_{y\to y'\in\mathcal{R}} \underbrace{Y_{y\to y'}\left(\int_0^t \lambda_{y\to y'}(X(s))ds\right)}_{R_{y\to y'}(t)} \cdot (y' - y),$$

  where the $\{Y_{y\to y'}\}$ are independent unit rate Poisson processes.

- Called the random time change representation and is due to Thomas Kurtz.

- Very useful for purposes of both analysis and simulation.

Example

$$B \stackrel{1/3}{\to} 2B,$$

with $X(0) = 10$.

Example: population growth

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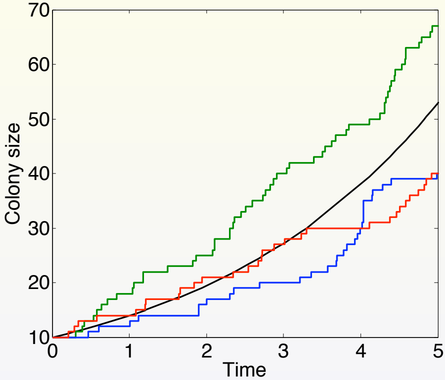
ODE:

$$\dot{x}(t) = \tfrac{1}{3}x(t)$$

Stochastic equation:

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

Example: population growth



Connections between the models: LLN

Consider a parameterized family of models satisfying the following

- $X_i^V(0) = O(V)$, and
- For $y \to y' \in \mathcal{R}$,

$$\kappa^V_{y\to y'} = \frac{1}{V^{\|y\|_1 - 1}} \kappa_{y \to y'},$$

where $\|y\|_1 = y_1 + \cdots + y_d$.

Example:

$$\emptyset \quad \overset{V\kappa_{y\to y'}}{\rightarrow} \quad C_{\text{complex}}$$

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Consider $Vx \in \mathbb{Z}^d_{\geq 0}$ and note that in each case,

$$\lambda_k^V(Vx) = \kappa_{y\to y'}^V \frac{Vx!}{(Vx-y)!} \approx V\kappa_{y\to y'} x^y.$$

Example: $A + B \to \ldots$

$$\kappa_{y\to y'}^V \frac{Vx!}{(Vx-y)!} = V^{-1}\kappa_{y\to y'}(Vx_A)(Vx_B) = V\kappa_{y\to y'} x_A x_B.$$

Now define

$$\overline{X}^V = V^{-1}X^V,$$

to be normalized process and note

$$\overline{X}^V(t) = \frac{1}{V}X_0 + \sum_{y\to y'} \frac{1}{V} Y_{y\to y'}\left(\int_0^t \lambda^V_{y\to y'}(X^V(s))ds\right)(y'-y)$$

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\end{aligned}$$

Apply the Law of Large Numbers:

$$\frac{1}{V}Y_{y\to y'}(Vu) \approx u,$$

to get the usual ODE (integral version).

$$x(t) = x(0) + \sum_{y\to y'} \int_0^t \kappa_{y\to y'} x(s)^y ds \cdot (y'-y).$$

Precise statement

Theorem

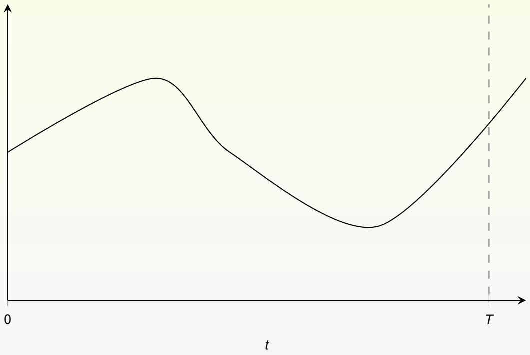
Assume that for a fixed positive state $z_0 \in \mathbb{R}^d_{>0}$ *and for all* $\varepsilon > 0$ *we have*

$$\lim_{V \to \infty} P\left(\left|V^{-1}X^V(0) - z_0\right| > \varepsilon\right) = 0.$$

Moreover, assume that the solution z *of the ODE with* $z(0) = z_0$ *is unique and is defined up to a finite fixed time* $T > 0$*. Then, for any* $\varepsilon > 0$

$$\lim_{V \to \infty} P\left(\sup_{t \in [0,T]} \left|V^{-1}X^V(t) - z(t)\right| > \varepsilon\right) = 0.$$

Precise statement



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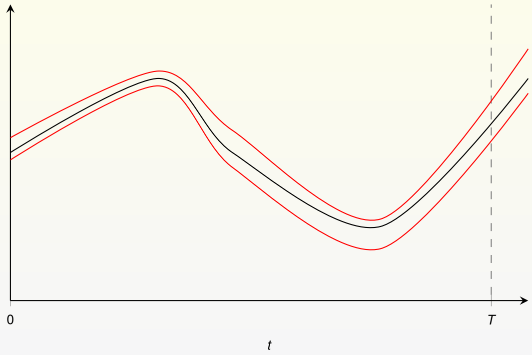

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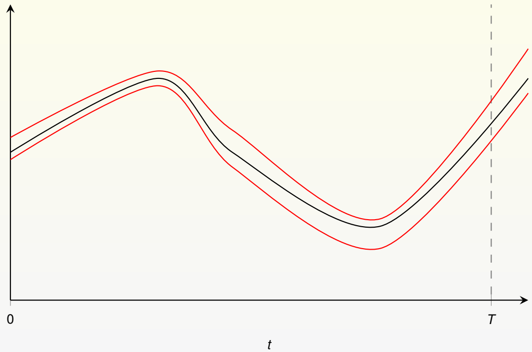

The probability that, up to time T, $V^{-1}X^V(t)$ is between the two red lines tends to one for $V \to \infty$.

Consider a collection of stochastic reaction networks X^V and assume there exist two non-negative vectors α, β such that:

Multiscale Setting (single time scale)

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Theorem (Ball, Kurtz, Popovich and Rempala 2006, Pfaffelhuber and Popovich 2013, Kang and Kurtz 2013)

$$V^{-\alpha} X^V_t \underset{V\to\infty}{\Longrightarrow} Z_0 + \sum_{y\to y' \in \mathbb{R}_1} \widehat{\xi}_{y\to y'} \int_0^t \lambda_{y\to y' \in \mathbb{R}_2}(Z_s) ds + \sum_{y\to y'} \widehat{\xi}_{y\to y'} Y_{r'} \left(\int_0^t \lambda_{r'}(Z_s)\, ds \right)$$

up to a fixed finite time T.

Section 2

Probability measures moving!

Stochastic models

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It turns out, that's just a linear ODE! It is called the Kolmogorov Forward equation, or the chemical master equation in this context:

$$\frac{d}{dt}p(x,t) = \sum_{y \to y'} p(x - y' + y, t)\lambda_{y \to y'}(x - y' + y) - \sum_{y \to y'} p(x,t)\lambda_{y \to y'}(x),$$

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Solving this equation analytically is often difficult (impossible). Of course, if finite state space,

$$\dot{P}_t = P_t Q \implies P_t = e^{tQ}.$$

Example: population growth

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$$B \stackrel{1/3}{\rightarrow} 2B,$$

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

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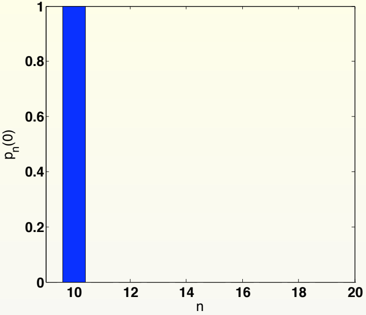
i.e.

$$\begin{aligned}
\frac{d}{dt}p(10,t) &= \frac{1}{3}\cdot 9 \cdot p(9,t) - \frac{1}{3}\cdot 10 \cdot p(10,t) \\
\frac{d}{dt}p(11,t) &= \frac{1}{3}\cdot 10 \cdot p(10,t) - \frac{1}{3}\cdot 11 \cdot p(11,t) \\
\frac{d}{dt}p(12,t) &= \frac{1}{3}\cdot 11 \cdot p(11,t) - \frac{1}{3}\cdot 12 \cdot p(12,t) \\
&\vdots
\end{aligned}$$

Example: population growth - evolution of distribution



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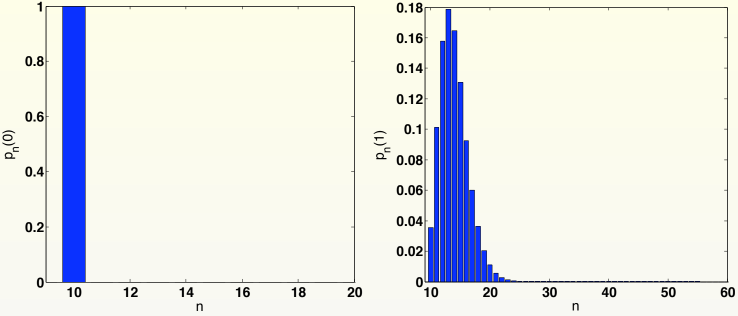

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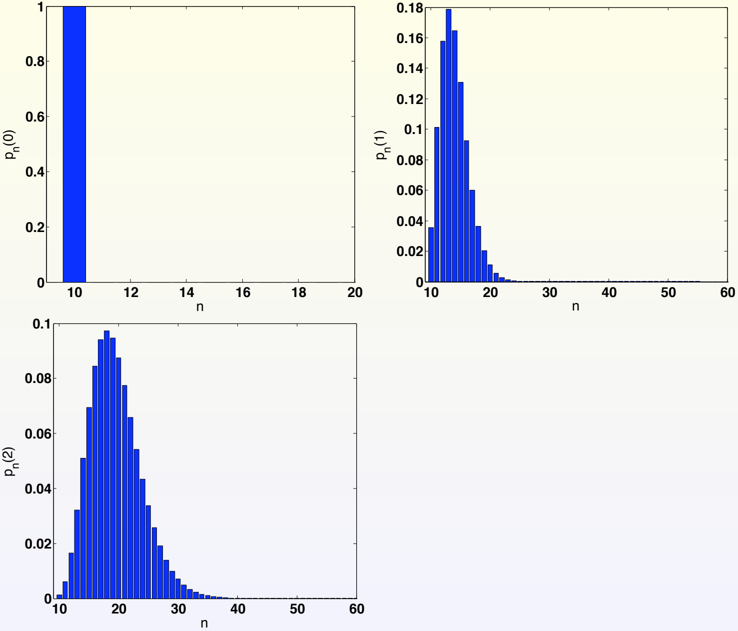

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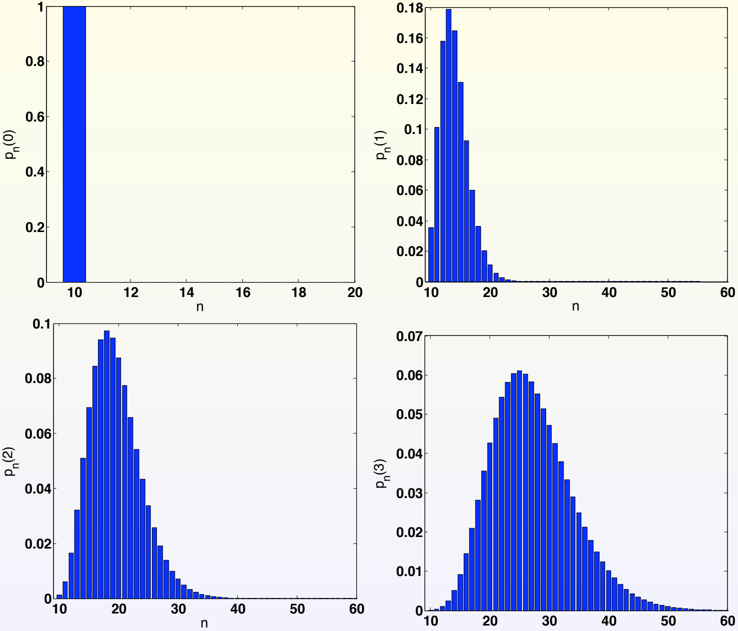

Section 3

The notion of equilibrium in the stochastic setting

Stationary distribution

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$$\begin{cases} p(x,0) = P(X_0 = x) \\ \dfrac{dp(x,t)}{dt} = \displaystyle\sum_{y \to y' \in \mathbb{R}} p(x - y' + y, t)\lambda_{y \to y'}(x - y' + y) - p(x,t) \sum_{y \to y' \in \mathbb{R}} \lambda_{y \to y'}(x) \end{cases}$$

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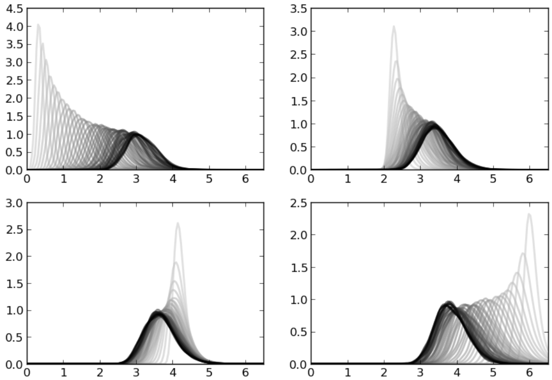
The probabilities $\pi(x)$ that are equilibrium points for the above ODE, that is such that

$$\sum_{y \to y' \in \mathbb{R}} \pi(x - y' + y)\lambda_{y \to y'}(x - y' + y) - \pi(x) \sum_{y \to y' \in \mathbb{R}} \lambda_{y \to y'}(x) = 0 \qquad \forall x \in \mathbb{N}^{|\mathcal{S}|},$$

are the stationary distributions of the system.

Stochastic: convergence of distribution to equilibria



Properties of the stationary distributions

- If the initial distribution $\pi(x)$ of the system is stationary, then

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- As for equilibrium points in the deterministic case, we often have

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  with $\pi(x)$ stationary.
- The stationary distribution are concentrated on the irreducible components.
- If we restrict X_t to an irreducible component, then the stationary distribution, if it exists, is unique.

If a SRN has a stationary distribution π, then (if the model is restricted to an irreducible component)

- for any state x
$$P(X_t = x) \xrightarrow[t\to\infty]{} \pi(x);$$
- for any state x
$$\frac{N_x(t)}{t} \xrightarrow[t\to\infty]{} \pi(x),$$
where $N_x(t)$ is the time spent by the process in state x up to time t;

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We can use stationary distributions to

- know what is the long-term behaviour of a system;
- know what is the average expression of some protein over a long time;
- approximate multi-scale models by assuming that the faster systems are always at stationary regime;

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:

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

Then, for any irreducible set Γ, the stochastic system has a product form stationary distribution

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

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

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Converse proved by Carsten Wiuf and me.

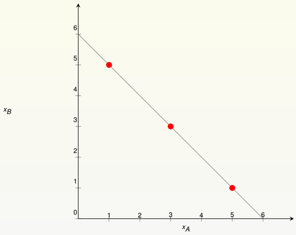
Theorem

If the stationary distribution on enough states is the distribution above, then the ODE model is complex-balanced with complex-balanced equilibrium c.

Consider

$$2A \xrightarrow{\kappa_1} 2B \qquad A + 3B \xrightarrow{\kappa_2} 3A + B$$

on



The dynamics are the same of

$$2A \underset{3\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} 2B \qquad 7A \qquad\qquad 0$$

Formulas for stationary distributions via reaction graph structure

- Anderson, Craciun, Kurtz, Product-form stationary distributions for deficiency zero chemical reaction networks, 2010;
- Anderson, C., Koyama, Kurtz, Non-explosivity of stochastically modeled reaction networks that are complex balanced, 2017;
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Formulas for stationary distributions via reaction graph structure

- Hornos, Schultz, Innocentini, Wang, Walczak, Onuchic, Wolynes Self-regulating gene: an exact solution, 2005;
- Mélykúti, Hespanha, Khammash Equilibrium distributions of simple biochemical reaction systems for time-scale separation in stochastic reaction networks, 2014;
- Anderson, Craciun, Gopalkrishnan, Wiuf Lyapunov functions, stationary distributions, and non-equilibrium potential for reaction networks, 2015;
- Anderson, Cotter Product-form stationary distributions for deficiency zero networks with non-mass action kinetics, 2016;
- Hong, Kim, Al-Radhawi, Sontag, Kim Derivation of stationary distributions of biochemical reaction networks via structure transformation, 2021;

Approximation of stationary distributions

There are techniques to approximate the stationary distributions! As an example, state space truncation techniques [1]

[1] Gupta, Mikelson, Khammash, A finite state projection algorithm for the stationary solution of the chemical master equation, 2017; Kuntz, Thomas, Stan, Barahona, Stationary distributions of continuous-time Markov chains: a review of theory and truncation-based approximations, 2021]

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They assume a stationary distribution exists!

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Existence of stationary distribution via reaction graph structure

Some works connect graphical properties with existence of stationary distributions:

- Gupta, Briat, Khammash, A Scalable Computational Framework for Establishing Long-Term Behavior of Stochastic Reaction Networks, 2013;
- Anderson, Kim Some network conditions for positive recurrence of stochastically modeled reaction networks, 2018;
- Anderson, C., Kim, Stochastically modeled weakly reversible reaction networks with a single linkage class, 2020;
- Anderson, C., Kim, Nguyen Tier structure of strongly endotactic reaction networks, 2020;
- Xu, Hansen, Wiuf, Full classification of dynamics for one-dimensional continuous time Markov chains with polynomial transition rates, pre-print;
- C., Pal Majumder, Wiuf, The dynamics of stochastic mono-molecular reaction systems in stochastic environments, 2021.

The chemical recurrence conjecture

Conjecture

If a network is weakly reversible, the associated stochastic mass-action system has a stationary distribution for ***any choice of rate constants****.*

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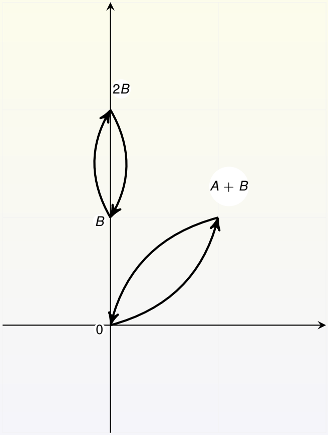
If a network is weakly reversible, the associated stochastic mass-action system has a stationary distribution for ***any choice of rate constants****.*

To prove the conjecture, we only need to prove there is no drift towards infinity.

The idea

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} A + B$$

$$B \underset{\kappa_4}{\overset{\kappa_3}{\rightleftarrows}} 2B$$



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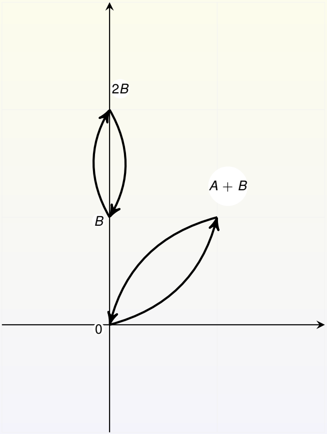

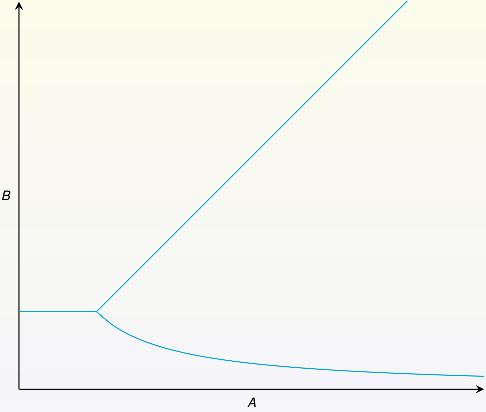

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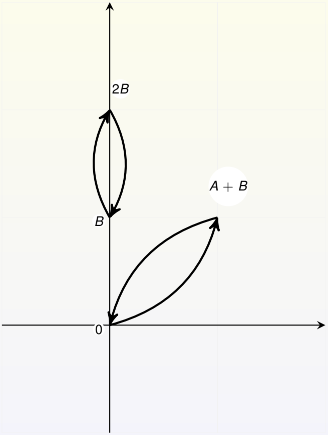

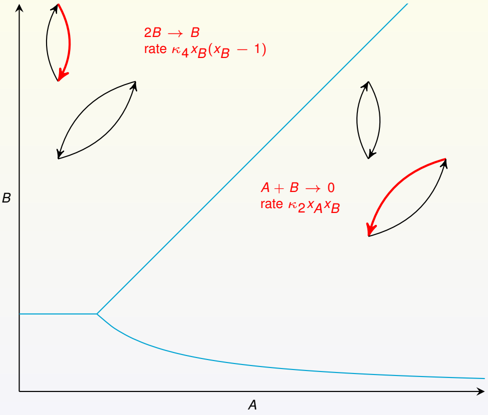

Section 4

Foster-Lyapunov criteria

The generator of a Markov process

Given a function V, the generator of the process X applied to the function V is a function defined by

$$\mathcal{L}V(x) = \lim_{h \to 0} \frac{E[V(X_h)|X_0 = x] - V(x)}{h}$$

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Given a function V, the generator of the process X applied to the function V is a function defined by

$$\mathcal{L}V(x) = \lim_{h \to 0} \frac{E[V(X_h)|X_0 = x] - V(x)}{h} = \frac{d}{dt} E[V(X_t)](x)$$

Consider a stochastic mass-action system $\{X(t) : t \geq 0\}$.

Theorem (Meyn and Tweedie, Stability of Markovian Processes III : Foster-Lyapunov Criteria for Continuous-Time Processes, 1993)

If there exists a scalar function V such that

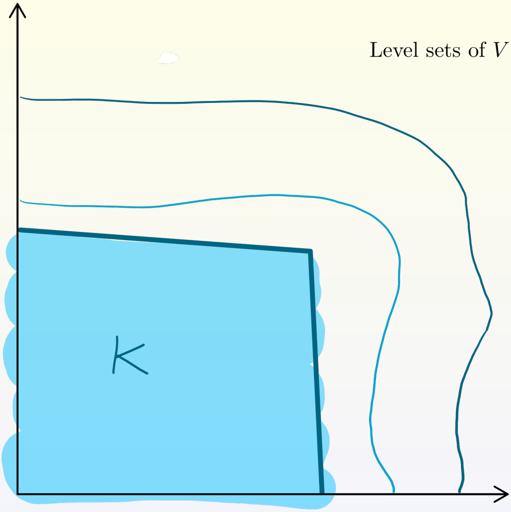
- $V(x) > 0$ *for all* x;
- $\lim_{x\to\infty} V(x) = \infty$;
- *there exists a compact set* K *and* $c > 0$ *such that*

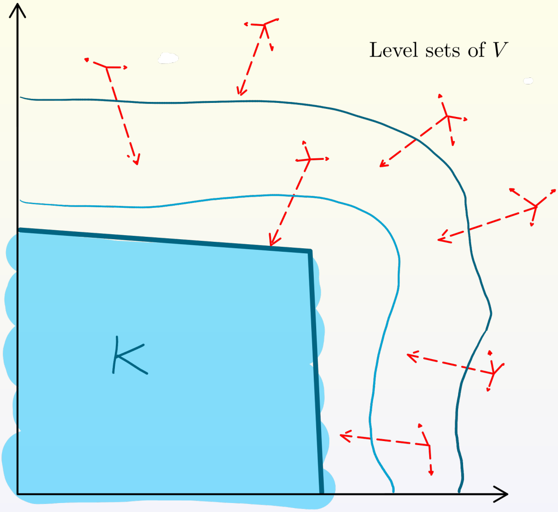
$$\mathcal{L}V(x) = \sum_{y\to y'} \lambda_{y\to y'}(x)\Big(V(x+y'-y) - V(x)\Big) < -c$$

  for all $x \notin K$.

Then, X *has a stationary distribution.*

Foster-Lyapunov criterium




Level sets of V
K

In order to have

$$\mathcal{L}V(x) = \sum_{y \to y'} \lambda_{y \to y'}(x) \Big(V(x + y' - y) - V(x) \Big) < -c \tag{2}$$

we can try to construct a function V that decreases along the most likely transitions, given by the dominant reactions.

Usual strategy

In order to have

$$\mathcal{L}V(x) = \sum_{y\to y'} \lambda_{y\to y'}(x)\Big(V(x+y'-y) - V(x)\Big) < -c \tag{2}$$

we can try to construct a function V that decreases along the most likely transitions, given by the dominant reactions.

This strategy is used, for example, in Anderson, Kim Some network conditions for positive recurrence of stochastically modeled reaction networks, 2018; Anderson, C., Kim, Stochastically modeled weakly reversible reaction networks with a single linkage class, 2020; Anderson, C., Kim, Nguyen Tier structure of strongly endotactic reaction networks, 2020.

The boundary is often a problem

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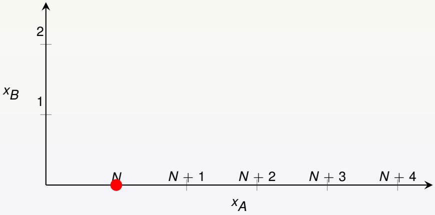

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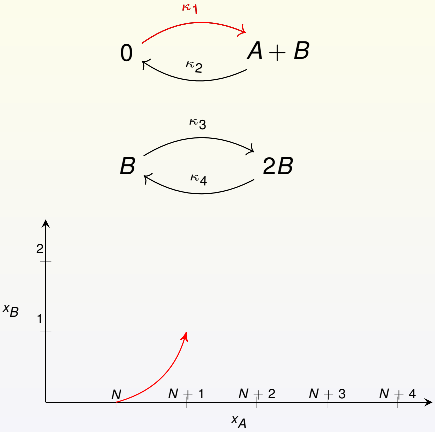

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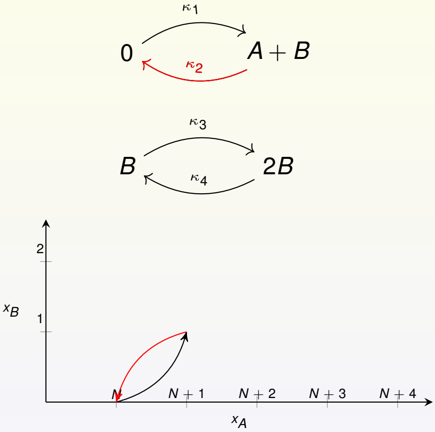

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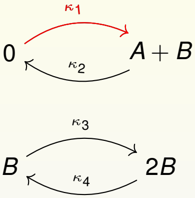

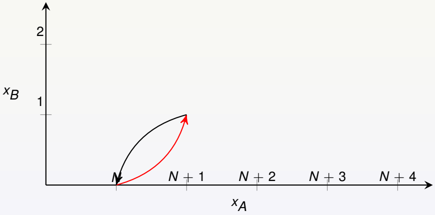

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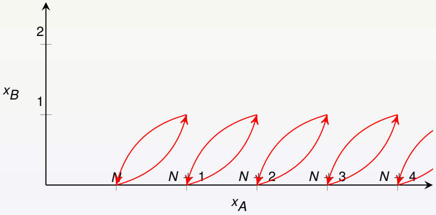

Section 5

Discrepancies between the long-term behaviour of deterministic and stochastic models

Consider the mass-action system

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

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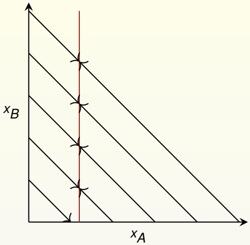

- In the deterministic setting, if $z_A(0) + z_B(0) = N$ with $N > \frac{\kappa_2}{\kappa_1}$, then $\lim_{t\to\infty} z(t) = \left(\frac{\kappa_2}{\kappa_1}, N - \frac{\kappa_2}{\kappa_1}\right)$.

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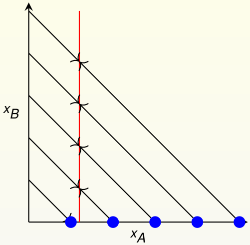

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- In the stochastic setting, the extinction of the species B will eventually occur, and almost surely $\lim_{t\to\infty} X(t) = (N, 0)$

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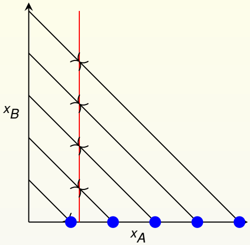

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- If N is large, $\left(\frac{\kappa_2}{\kappa_1}, N - \frac{\kappa_2}{\kappa_1}\right)$ and $(N, 0)$ are very different!

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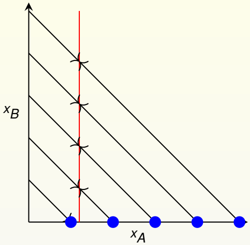

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Also: the deterministic model does not give the mean values of the stochastic process!

Section 6

Boundary Equilibria and Absorption

Idea! Since there is a boundary steady state, and the stochastic model explores around, it will be found!

[2] David F. Anderson, Daniele Cappelletti, *Discrepancies between extinction events and boundary equilibria in reaction networks*

Idea! Since there is a boundary steady state, and the stochastic model explores around, it will be found!
However we proved by example[2] that

Lack of positive equilibria $\quad\not\Rightarrow\quad$ Extinction

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Idea! Since there is a boundary steady state, and the stochastic model explores around, it will be found!
However we proved by example[2] that

Lack of positive equilibria	$\not\Rightarrow$	Extinction
Existence of stationary distribution on every state	$\not\Rightarrow$	Positive equilibria

[2] David F. Anderson, Daniele Cappelletti, *Discrepancies between extinction events and boundary equilibria in reaction networks*

$$
\begin{aligned}
A+B &\xrightarrow{\kappa_1} B+C \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} 2B \\
C &\xrightarrow{\kappa_4} A \xleftarrow{\kappa_5} E \\
A+D &\xrightarrow{\kappa_6} D+E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} 2D
\end{aligned}
$$

$$
\begin{array}{ccccc}
\text{A+B} & \xrightarrow{\kappa_1} & \text{B+C} & \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} & \text{2B} \\
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\end{array}
$$

- $A + B + C + D + E$ is conserved;

$$
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$$

- $A + B + C + D + E$ is conserved;
- There is no positive equilibrium unless

$$\frac{\kappa_3 \kappa_4}{\kappa_1 \kappa_2} = \frac{\kappa_5 \kappa_8}{\kappa_6 \kappa_7}.$$

$$\mathrm{A+B} \xrightarrow{\kappa_1} \mathrm{B+C} \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} \mathrm{2B}$$

$$\mathrm{C} \xrightarrow{\kappa_4} \mathrm{A} \xleftarrow{\kappa_5} \mathrm{E}$$

$$\mathrm{A+D} \xrightarrow{\kappa_6} \mathrm{D+E} \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{2D}$$

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$$\frac{\kappa_3\kappa_4}{\kappa_1\kappa_2} = \frac{\kappa_5\kappa_8}{\kappa_6\kappa_7}.$$

- There is a stationary distribution with mass on all states: The sets $\{B = 0\}$ and $\{D = 0\}$ are absorbing, but cannot be reached.

Section 7

Strongly Endotactic Networks

Strongly endotactic networks

Definition

Let H be the convex hull formed by the source complexes. A network is called strongly endotactic if

- all the reactions point inside or along the faces of H;
- for each face of H there is at least one reaction originated in the face and pointing away from it.

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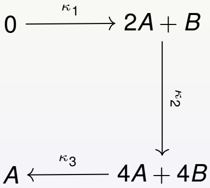

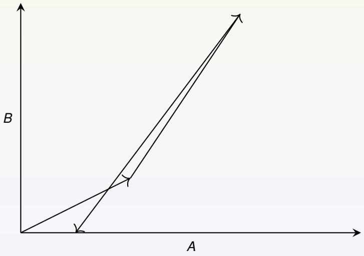

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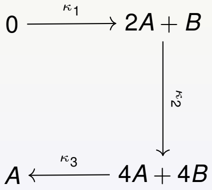

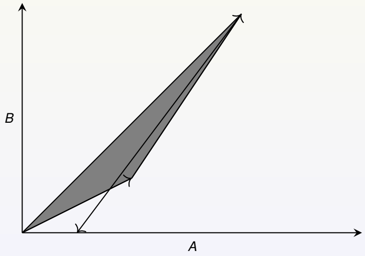

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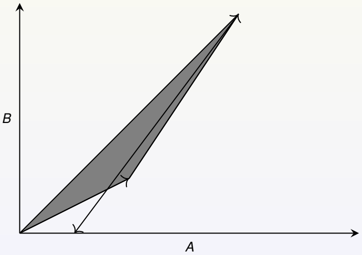
$$0 \xrightarrow{\kappa_1} 2A + B$$

$$2A + B \xrightarrow{\kappa_2} 4A + 4B$$

$$A \xleftarrow{\kappa_3} 4A + 4B$$



The network is strongly endotactic!

Theorem (Gopalkrishnan, Miller, and Shiu, SIAM J. Appl. Dyn. Syst., 2014)

Consider a deterministic mass-action system which is strongly endotactic. Then, there exists a compact global attractor within each stoichiometric compatibility class, for any choice of rate constants (permanence).

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If a network is strongly endotactic and no subset of the state space boundary is absorbing, then the rescaled stochastic mass-action system satisfies a sample path Large Deviation Principle in the supremum norm.

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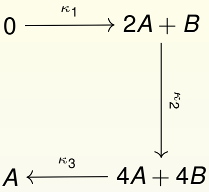
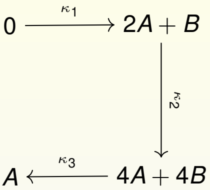
What about stationary distributions?
When stochastically modeled, the network of the previous example is transient!


0
κ1
2A + B
κ2
A
κ3
4A + 4B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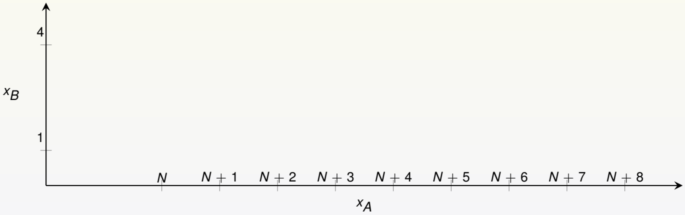
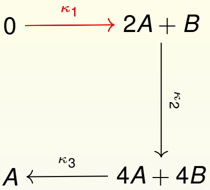
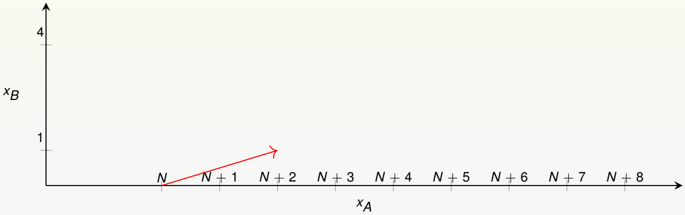
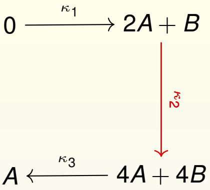
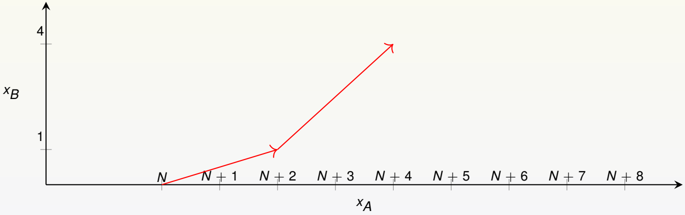

4
x_B
1
N
N + 1
N + 2
N + 3
N + 4
N + 5
N + 6
N + 7
N + 8
x_A



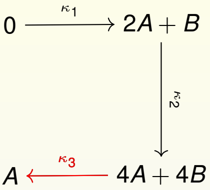


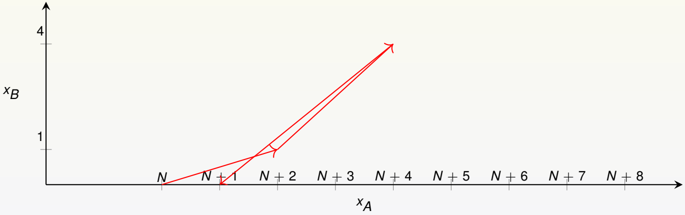
Probability $\approx$ 1 ·



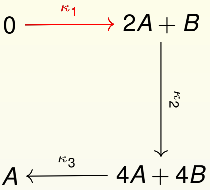


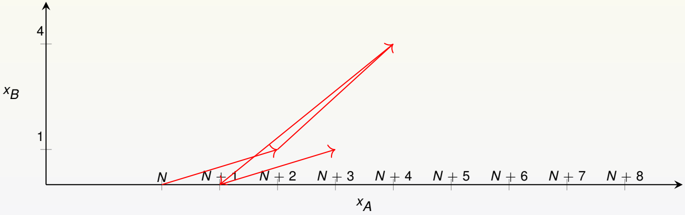
Probability $\approx 1 \cdot \frac{\kappa_2(N+2)^2}{\kappa_2(N+2)^2+\kappa_1}$.





Probability $\approx 1 \cdot \frac{\kappa_2(N+2)^2}{\kappa_2(N+2)^2+\kappa_1} \cdot \frac{\kappa_3(N+4)^4}{\kappa_3(N+4)^4+\kappa_2(N+4)^2+\kappa_1}$.





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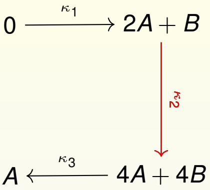
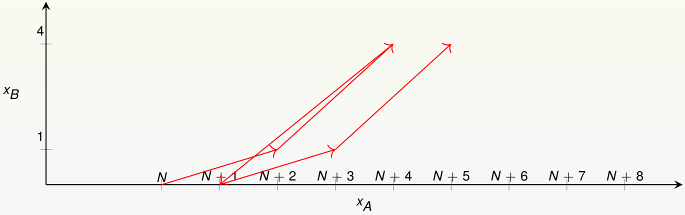
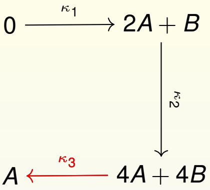
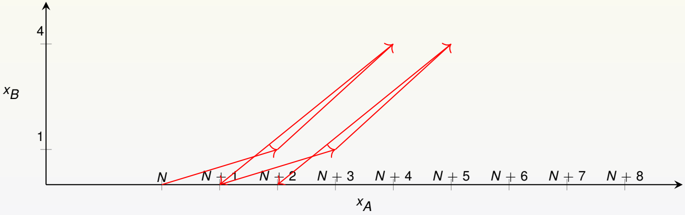


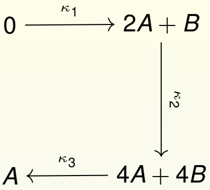


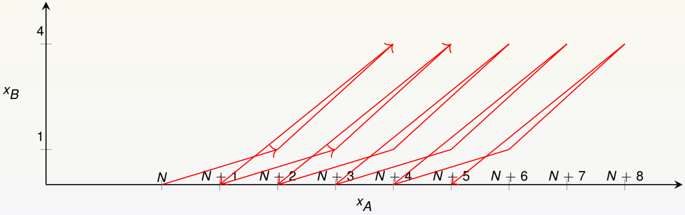
Probability $\approx 1 \cdot \frac{\kappa_2(N+2)^2}{\kappa_2(N+2)^2+\kappa_1} \cdot \frac{\kappa_3(N+4)^4}{\kappa_3(N+4)^4+\kappa_2(N+4)^2+\kappa_1} \cdot 1 \cdot \frac{\kappa_2(N+3)^2}{\kappa_2(N+3)^2+\kappa_1} \cdots$





$$\text{Probability} \approx 1 \cdot \frac{\kappa_2(N+2)^2}{\kappa_2(N+2)^2+\kappa_1} \cdot \frac{\kappa_3(N+4)^4}{\kappa_3(N+4)^4+\kappa_2(N+4)^2+\kappa_1} \cdot 1 \cdot \frac{\kappa_2(N+3)^2}{\kappa_2(N+3)^2+\kappa_1} \cdots$$





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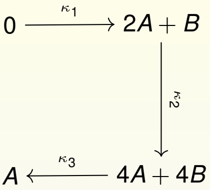

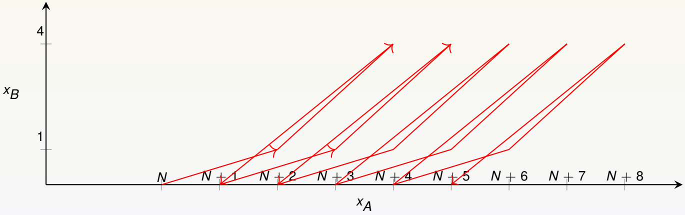

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Strongly endotactic networks

Theorem (Anderson, C., Kim and Tung, SPA 2020)

If a network is strongly endotactic, then it is positive recurrent after adding outflows and inflows for every species, that is reactions of the type $mS \to 0$ *and* $0 \to m'S$*, for specific choices of* m *(it should be bigger than the maximum stoichiometricity minus 1).*

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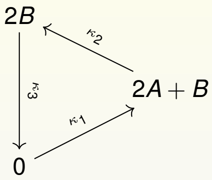
If a bimolecular network is strongly endotactic, then it is positive recurrent after adding reactions of the type $S \to 0$ and $0 \to S$ for all species.

Union of networks, an open problem

When is it true that the union of two positive recurrent networks is positive recurrent?

Union of networks, an open problem

The stochastic mass-action system



is complex balanced (hence positive recurrent) for any choice of rate constants.

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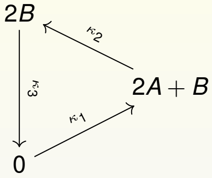
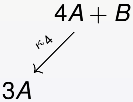
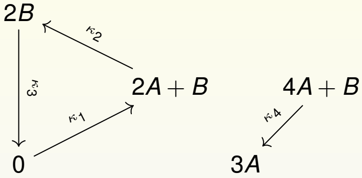


is complex balanced (hence positive recurrent) for any choice of rate constants.
If we add the reaction



which may seem innocent enough (it consumes both A and B), the model becomes transient (for any choice of rate constants).

Union of networks, a warning



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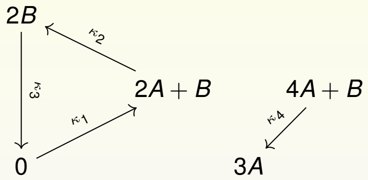

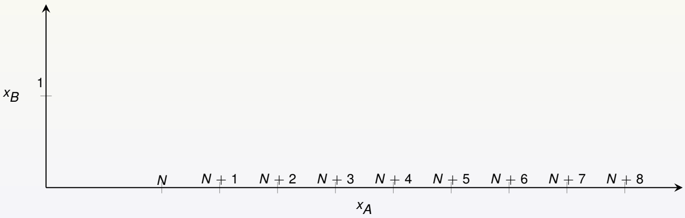

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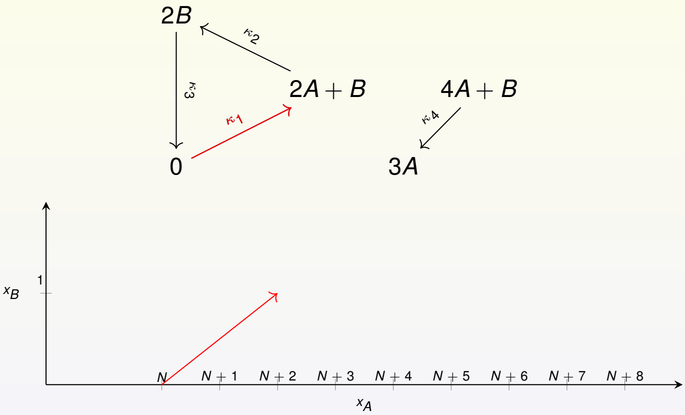

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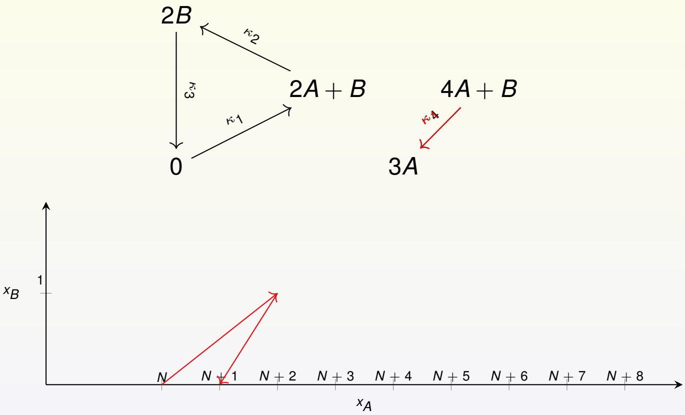

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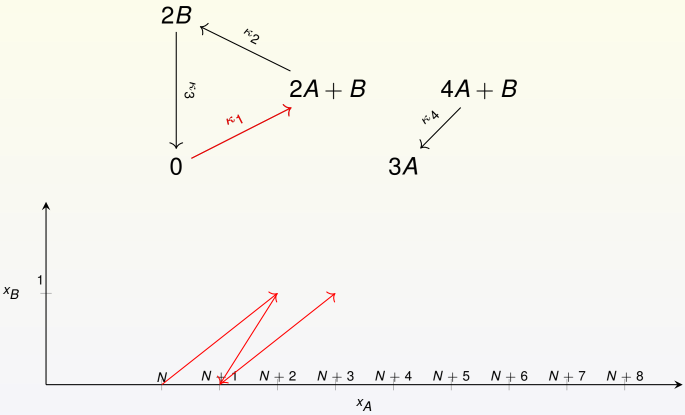

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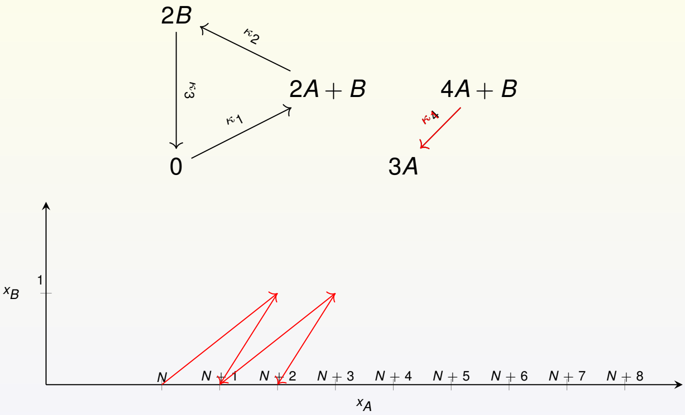

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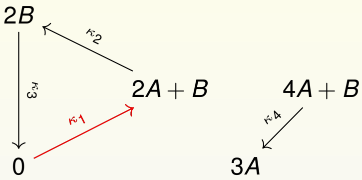

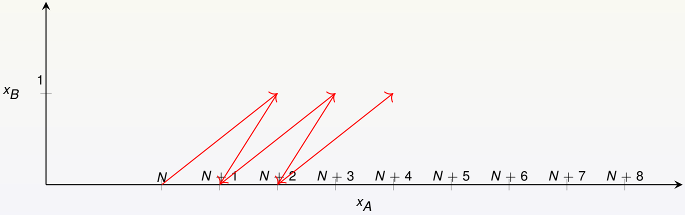

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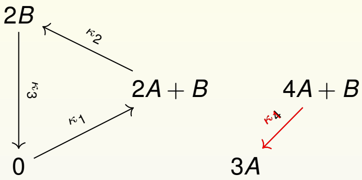

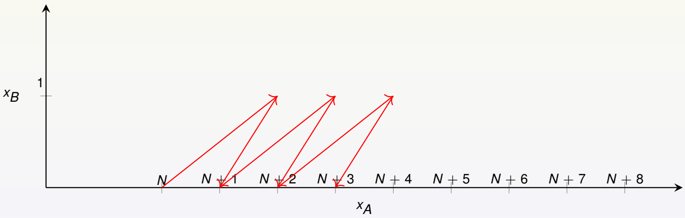

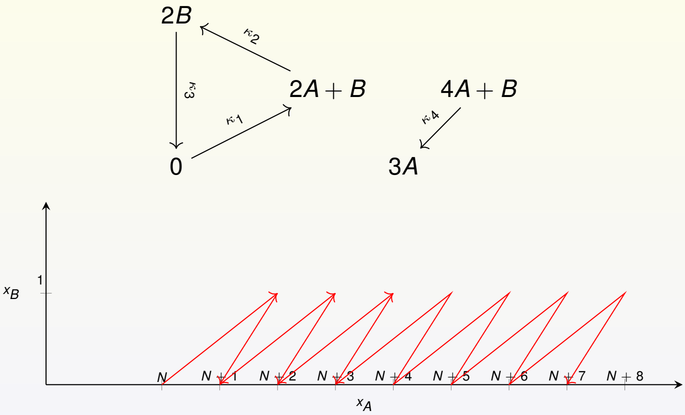
2B
κ_2
κ_3
2A + B
4A + B
κ_1
κ_4
0
3A
x_B
1
N
N + 1
N + 2
N + 3
N + 4
N + 5
N + 6
N + 7
N + 8
x_A

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Consider a deterministic mass-action system that

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Differing in one species

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1. $$A, \qquad A + B$$

   differ in species B.

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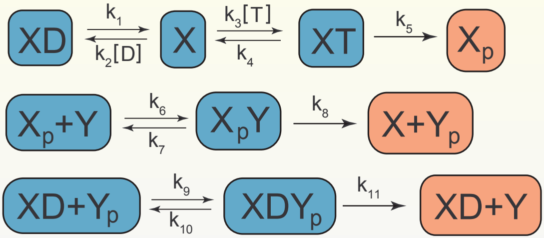
3. $$G, \quad 2G$$

   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

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Time until absorption

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$$A + B \xrightarrow{\kappa_1} 2B \qquad B \xrightarrow{\kappa_2} A$$

and imagine the initial condition $X(0)$ is near to the deterministic equilibrium $(q, N - q)$.

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The above reaction system has Poisson stationary distribution!

Results

$$A + B \xrightarrow{\kappa_1} 2B \qquad B \xrightarrow{\kappa_2} A$$

[2] David F. Anderson, Daniele Cappelletti, and Thomas G. Kurtz, *Finite time distributions of stochastically modeled chemical systems with absolute concentration robustness*, SIAM Journal on Applied Dynamical Systems 2017, vol. 16(3)

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For any fixed time points $T > \delta > 0$ and any continuous bounded φ,

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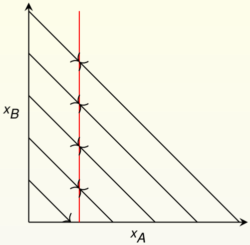

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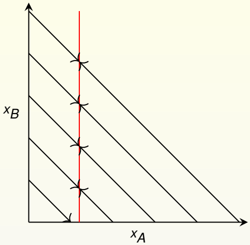

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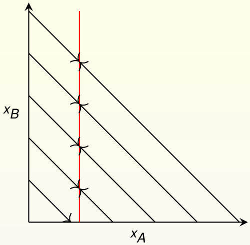

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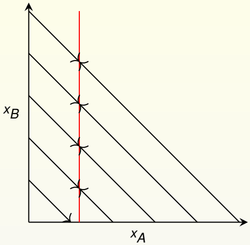

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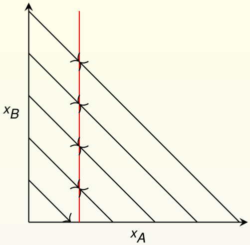

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Conjecture

Consider a stochastic mass-action system that is ACR, if deterministically modeled. Then, with probability one it undergoes an extinction.

Theorem (Anderson, Enciso, Johnston, 2014)

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Hence ACR (+ bimolecularity, mass conservation etc.) does not imply extinction.

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