Distributions for stochastically modelled biochemical reaction systems

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Imperial College Biomathematics Seminar
April 26th, 2016
Overview

Biochemical interaction systems are typically modeled in one of two ways:

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

**Type of mathematical question I am interested in:**

Can we prove general theorems relating the structure of the interaction network to dynamical properties of the mathematical model.

- Focus on two results – one is about stationary distributions, one is about possible extinctions/medium time behavior.
- This work is part of chemical reaction network theory (CRNT).

**Collaborators:** Gheorghe Craciun, Tom Kurtz, German Enciso, Matthew Johnston, Daniele Cappelletti, and Simon Cotter

**Funding:** Army Research Office, grant W911NF-14-1-0401
Focus is on reaction networks.

\[ A + B \rightarrow 2B \]
\[ B \rightarrow A \]

or

\[ E + S \Leftrightarrow ES \rightarrow E + P \]
\[ E \Leftrightarrow \emptyset \]
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\textsubscript{i} denotes phosphate ion. (B) The mass-action model underlying (A). [T] denotes the ATP concentration, assumed fixed. Terminal nodes are colored pink, and nonterminal nodes are colored blue. (C) A schematic diagram of an EnvZ-OmpR model in which ADP is the cofactor in phospho-OmpR dephosphorylation. (D) The mass-action model underlying (C). [D] denotes the ADP concentration, assumed fixed.

\[^1\] Guy Shinar and Martin Feinberg, Structural Sources of Robustness in Biochemical Reaction Networks, Science, 2010
Definition
A chemical reaction network, \( \{S, C, R\} \), consists of:

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

2. **Complexes**, \( C \): linear combinations of the species representing those used, and produced, in each reaction.

3. A set of **reactions**, \( R := \{y_k \rightarrow y'_k\} \).

Denote reaction vectors
\[
\zeta_k = y'_k - y_k.
\]
Reaction networks: \( \{S, C, R\} \)

Example:

\[
\begin{align*}
A & \overset{\text{\Huge \rightarrow}}{\underset{\text{\Huge \rightarrow}}{\leftrightarrow}} 2B \\
A + C & \overset{\text{\Huge \rightarrow}}{\underset{\text{\Huge \rightarrow}}{\leftrightarrow}} D \\
B + E &
\end{align*}
\]

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

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

Reactions:
\( R = \{A \rightarrow 2B, 2B \rightarrow A, A + C \rightarrow D, D \rightarrow A + C, D \rightarrow B + E, B + E \rightarrow A + C\} \).

\[
\begin{align*}
\zeta_1 &= \begin{bmatrix}
-1 \\
2 \\
0 \\
0 \\
0
\end{bmatrix}, \\
\zeta_2 &= \begin{bmatrix}
1 \\
-2 \\
0 \\
0 \\
0
\end{bmatrix}, \\
\zeta_3 &= \begin{bmatrix}
-1 \\
0 \\
-1 \\
1 \\
0
\end{bmatrix}, \ldots
\end{align*}
\]
Stochastic models

The usual stochastic model is a continuous time Markov chain:

- could simulate with the Gillespie algorithm or next reaction method.

- could understand via the forward equation (chemical master equation):

  \[
  \frac{d}{dt} p_\mu(x, t) = \sum_k p_\mu(x - \zeta_k, t) \lambda_k(x - \zeta_k) - \sum_k p_\mu(x, t) \lambda_k(x),
  \]

  where \( p_\mu(x, t) = P_\mu(X(t) = x) \).

- Could understand via stochastic equations of Kurtz

  \[
  X(t) = X(0) + \sum_k Y_k \left( \int_0^t \lambda_k(X(s)) ds \right) \zeta_k.
  \]

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

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

\[
X_G(t) = X_G(0) + Y_1 \left( \int_0^t X_T(s)ds \right) - Y_2 \left( 0.025 \int_0^t X_G(s)ds \right) - Y_6 \left( 7.5 \times 10^{-6} \int_0^t X_G(s)X_S(s)ds \right) \\
X_S(t) = X_S(0) + Y_3 \left( 1000 \int_0^t X_T(s)ds \right) - Y_5 \left( 2 \int_0^t X_S(s)ds \right) - Y_6 \left( 7.5 \times 10^{-6} \int_0^t X_G(s)X_S(s)ds \right) \\
X_T(t) = X_T(0) + Y_2 \left( 0.025 \int_0^t X_G(s)ds \right) - Y_4 \left( 0.25 \int_0^t X_T(s)ds \right) \\
X_V(t) = X_V(0) + Y_6 \left( 7.5 \times 10^{-6} \int_0^t X_G(s)X_S(s)ds \right).
\]
**Story #1: stationary distributions**

Stationary distributions play a central role in understanding (all) stochastic models. They:

1. Characterize the long-time behavior of the model.

2. Are used heavily in stochastic averaging (and, therefore, transient dynamics).

They are a fixed point of the chemical master equation:

\[
\frac{d}{dt}p_{\mu}(x, t) = \sum_k p_{\mu}(x - \zeta_k, t)\lambda_k(x - \zeta_k) - \sum_k p_{\mu}(x, t)\lambda_k(x),
\]

Thus, they solve

\[
\sum_k \lambda_k(x - \zeta_k)\pi(x - \zeta_k) = \sum_k \lambda_k(x)\pi(x).
\]

**Problems:**

1. There is one such equation for each state, \(x\), in the state space.

2. The functions \(\lambda_k\) are often nonlinear.
A motivating example

Consider

\[ A \overset{N_{\kappa_1}}{\rightleftharpoons} \emptyset, \quad A + C \overset{\beta}{\rightarrow} A + D. \]

Very easy!

\[ A \sim \text{Poisson}(\frac{\kappa_2}{\kappa_1}), \] so effective model for \( C \) and \( D \):

\[ C \overset{\beta \cdot \frac{\kappa_2}{\kappa_1}}{\rightarrow} D. \]

\((\kappa_2 = 2, \kappa_1 = 1, \beta = 1, \text{ and } X_C(0) = 1000, X_D(0) = 0.\)
A motivating example

Consider

$$A \xleftrightarrow{N_{\kappa_1}} B, \quad A + C \xrightarrow{\beta} A + D.$$  

Very easy!

$$A \sim \text{Binomial}(X_A(0) + X_B(0), \frac{\kappa_2}{\kappa_1 + \kappa_2}), \text{ so effective model for } C \text{ and } D:$$

$$C \xrightarrow{\beta \cdot X_{\text{Tot}} \cdot \frac{\kappa_2}{\kappa_1 + \kappa_2}} D.$$  

where $X_{\text{Tot}} = X_A(0) + X_B(0)$. 

A motivating example

Consider

\[ A \xrightarrow{N_{\kappa_1}} B \xrightarrow{N_{\kappa_2}} \emptyset, \quad A + C \xrightarrow{\beta} A + D. \]

Very easy!

\[ A \sim \text{Poisson}(\frac{\kappa_2 \kappa_4}{\kappa_1 \kappa_3}), \text{ so effective model for } C \text{ and } D: \]

\[ C \xrightarrow{\beta \cdot \frac{\kappa_2 \kappa_4}{\kappa_1 \kappa_3}} D. \]
A motivating example

Consider

\[ A \xrightleftharpoons[\kappa_2]{\kappa_1} 2B, \quad A + C \xrightarrow[\beta]{} A + D. \]

Not quite as easy.

1. Nonlinearity (in 2B), makes this trickier.
2. Stationary distribution can certainly still be calculated for this model, however.
A motivating example

Consider

\[ A \xrightleftharpoons[N_{\kappa_2}]{N_{\kappa_1}} 2B, \]

\[ ES \xrightleftharpoons[N_{\kappa_4}]{N_{\kappa_3}} E + S \]

\[ ES + S_p \xrightleftharpoons[N_{\kappa_6}]{N_{\kappa_5}} ES_p S \xrightleftharpoons[N_{\kappa_8}]{N_{\kappa_7}} A, \quad A + C \xrightarrow{\beta} A + D. \]

Very hard without general theory.
Motivation

- Closed form solutions for stationary distributions of linear (first order) systems have been known for a long while.

- No general theory for nonlinear systems. We hope to find classes of models for which we can say something, but this is still a wide open area!

- Multiple computational strategies have been developed which attempt to overcome this problem, such as:
  - Nested stochastic simulation algorithm of Weinen E, D. Liu, and Eric Vanden-Eijnden.
  - Slow scale SSA of Yang Cao, Dan Gillespie, and Linda Petzold.
  - Myriad QSSA methods and constrained QSSA methods.

- This is a great place where theoretical mathematics can help a lot. With formula, you would no longer need to estimate distribution with expensive inner loop.
Theorem (Anderson, Craciun, Kurtz, 2010)

Let \( \{S, C, R\} \) be a chemical reaction network with rate constants \( \kappa_k \).
Suppose:

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

Then, for any irreducible communicating equivalence class, \( \Gamma \), the stochastic system has a product form stationary distribution

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

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

Connectivity

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

Example

\[ A + B \xrightarrow{\alpha} 2B \]  
\[ B \xrightarrow{\beta} A \]  
(Linkage Class 1)
(Linkage Class 2)

Has two linkage classes.
Connectivity

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

A network is called **reversible** if \( y'_k \rightarrow y_k \in \mathcal{R} \) whenever \( y_k \rightarrow y'_k \in \mathcal{R} \).
Connectivity

The following is not weakly reversible:

Neither is the following:

\[ A + B \xrightarrow{\alpha} 2B \] (Linkage Class 1)

\[ B \xrightarrow{\beta} A \] (Linkage Class 2)
Network properties

Definition

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

is the **stoichiometric subspace** of the network.

Denote

\[ \text{dim}(S) = s. \]

**Implication:** Solutions bound to translations of \( S \).

**Example:** Reaction network

\[ A + B \rightleftharpoons 2B \]
\[ B \rightleftharpoons A \]
Deficiency.

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

where

1. \(n = \# \text{ of complexes.}\)
2. \(\ell = \# \text{ of linkage classes.}\)
3. \(s = \text{dimension of span of reaction vectors.}\)

So it is easy to check.

**Example**

\[
\begin{align*}
A + B & \rightleftharpoons 2B \\
B & \rightleftharpoons A
\end{align*}
\]

(R1) \hspace{1cm} (R2)

\(n = 4, \ell = 2, s = 1 \implies \delta = 1.\)
Deficiency

Example

\[
\begin{align*}
A & \quad \leftrightarrow \quad 2B \\
A + C & \quad \leftrightarrow \quad D \\
B + E &
\end{align*}
\]

\[
\begin{align*}
n &= 5 \\
\ell &= 2 \\
s &= 3 \\
\implies \delta &= 5 - 2 - 3 = 0.
\end{align*}
\]
Of course, you are thinking I have no idea what deficiency is – that was pointless.

In reality,

\[ \dot{x} = f(x) = YA_\kappa \psi(x), \]

where

1. \( Y \) and \( A_\kappa \) are matrices,
2. and

\[ \text{deficiency} = \delta = \dim(\ker(Y) \cap \text{image}A_\kappa). \]
Deficiency Zero Theorem - stochastic

Theorem (Anderson, Craciun, Kurtz, 2010)

Let \( \{S, C, R\} \) be a chemical reaction network with rate constants \( \kappa_k \). Suppose:

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

Then, for any irreducible communicating equivalence class, \( \Gamma \), the stochastic system has a product form stationary distribution

\[
\pi(x) = \frac{1}{Z^V} \prod_{i=1}^{d} e^{-c_i} \frac{c_i^{x_i}}{x_i!}, \quad x \in \Gamma,
\]  
(2)

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

Consider the possible model of enzyme kinetics given by

\[ E + S \rightleftharpoons ES \rightleftharpoons E + P , \quad E \rightleftharpoons \emptyset \rightleftharpoons S \]

- Easy to see that deficiency is 0 and that \( \Gamma = \mathbb{Z}_{\geq 0}^4 \).

- Thus, in distributional equilibrium, the species numbers are independent and have Poisson distributions.
Consider the slightly different enzyme kinetics given by

\[ E + S \rightleftharpoons ES \rightleftharpoons E + P, \quad E \rightleftharpoons \emptyset \]

- We see \( S + ES + P = N_{\text{Tot}} \).

- In distributional equilibrium:
  - \( E \) has Poisson distribution,
  - \( S, \ ES, \ P \) have a multinomial distribution, and
  - \( E \) is independent from \( S, \ ES, \) and \( P \).
is

\[ L + R \xrightleftharpoons[k_{\text{off}}]{k_{\text{on}}} C_0 \]

\[ k_{\text{off}} \uparrow \quad \downarrow k_p \]

\[ C_2 \xrightleftharpoons[\omega k_p]{\phi k_p} C_1. \]
Generalizations

Simon Cotter (Manchester) introduced me to his constrained approach\(^2\) to stochastic averaging, which leads to non-mass action kinetics.

\[
2P \xrightleftharpoons[kD]{\lambda_1(P)} D,
\]

with

\[
\lambda_1(P) = k_1 P(P - 1) + k_2 1(P \geq 2).
\]

Can write

\[
\lambda_1(P) = k_1 P(P - 1) + k_2 1(P \geq 1) 1(P - 1 \geq 1)
\]

\[
= \varphi^1(P) \varphi^1(P - 1) + \varphi^2(P) \varphi^2(P - 1),
\]

where

\[
\varphi^1(p) = \sqrt{k_1} p,
\]

\[
\varphi^2(p) = \sqrt{k_2} 1(p \geq 1).
\]

Generalizations

Suppose rates are:

\[ \lambda_k(x) = \kappa_k \prod_{i=1}^{d} \sum_{\ell=1}^{L_i} \prod_{j=0}^{y_{ki}-1} \varphi_i^\ell (x_i - j), \]  

(3)

where \( y_{ki} \) is \# of molecules of species \( S_i \) required for reaction \( k \) to occur.

Theorem (Anderson and Cotter, to appear soon)

Let \( \{S, \mathcal{C}, \mathcal{R}\} \) be a chemical reaction network with rate kinetics given above.

Suppose:

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

Then, for any irreducible communicating equivalence class, \( \Gamma \), the stochastic system has a product form stationary distribution

\[ \pi(x) = \frac{1}{Z^V} \prod_{i=1}^{d} \frac{c_i^{x_i}}{\prod_{j=0}^{\lfloor x_i/y_i \rfloor - 1} \sum_{\ell=1}^{L_i} \prod_{b=0}^{y_i-1} \varphi_i^\ell (x_i - jy_i - b)} \]  

(4)

where \( Z^V \) is a normalizing constant and \( c \) is a complexed-balanced equilibrium of the corresponding ODE.
Story 2: Absolute concentration robustness


\[ A + B \xrightarrow{\alpha} 2B \]  \hspace{1cm} (R1)

\[ B \xrightarrow{\beta} A \]  \hspace{1cm} (R2)

\[
\begin{align*}
\dot{x}_A(t) &= -\alpha x_A(t)x_B(t) + \beta x_B(t) \\
\dot{x}_B(t) &= \alpha x_A(t)x_B(t) - \beta x_B(t)
\end{align*}
\]

\[ M \overset{\text{def}}{=} x_A(0) + x_B(0), \]

Solving for equilibria:

\[ \bar{x}_A = \frac{\beta}{\alpha}, \]

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

Network has absolute concentration robustness in species A.
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.

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 $S$. 
Differing in one species

Examples:

1. \( A, \ A + B \)
   differ in species \( B \).

2. \( XT, \ XT + Y_p \)
   differ in species \( Y_p \).

3. \( T, \ T + G \)
   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


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.

What about stochastically modeled systems?

Theorem (A., Enciso, Johnston – stochastic)

Consider a reaction network satisfying the following:

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

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

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Example

Reaction network

\[ A + B \rightarrow 2B \]

\[ B \rightarrow A \]

has state space
Example

\[ X_{\text{tot}} := X + XD + XT + X_p + X_p Y + XDY_p \]
\[ Y_{\text{tot}} := Y + X_p Y + XDY_p + Y_p. \]
Bifunctional enzyme acting on a substrate with one modification site

Example (Model ix)

\[ E + S_p \rightleftharpoons ES_p \rightarrow E + S \]
\[ ES_p + S \rightleftharpoons ES_pS \rightarrow ES_p + S_p \]

Example (Model x)

\[ E + S \rightleftharpoons ES \rightarrow E + S_p \]
\[ ES + S_p \rightleftharpoons ES_pS \rightarrow ES + S \]

---

Idea of proof

1. **Suppose not true:** then there is a positive recurrent state for which a nonterminal complex has positive intensity (rate).

2. This provides a series of stopping times, $\tau_N \to \infty$.

3. Use stochastic equation:

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

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

4. In limit $N \to \infty$, find something in kernel of $YA_{\kappa}$ that can not be there.
Extinction can be a rare event. What’s the real behavior?

\[ A + B \xrightarrow{\alpha} 2B \]
\[ B \xrightarrow{\beta} A \]
\[ X_A(0) + X_B(0) = M, \]

**MATLAB** \[ \beta = 10, \alpha = 1, M \text{ big} \]

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

\[ \pi^Q_M(x) \rightarrow e^{-\left(\frac{\beta}{\alpha}\right)} \left(\frac{\beta}{\alpha}\right)^x \frac{1}{x!}, \quad \text{as } M \rightarrow \infty. \]
Quasi-stationary distribution: EnvZ-OmpR signaling system

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

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4 Guy Shinar and Martin Feinberg, *Structural Sources of Robustness in Biochemical Reaction Networks*, Science, 2010
Quasi-stationary distribution

Molecules of $Y_p$

Quasi-stationary probabilities

$X_{\text{tot}} = 100$
$Y_{\text{tot}} = 3500$

$X_{\text{tot}} = 1000$
$Y_{\text{tot}} = 35000$

$X_{\text{tot}} = 10000$
$Y_{\text{tot}} = 350000$

Poisson
Behavior on compact time intervals

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

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

$$J \sim \text{Poisson}(q).$$  \hspace{1cm} (5)

Theorem (Anderson, Cappelletti, Kurtz, 2016\textsuperscript{5})

Suppose $T > 0$ and that some technical assumptions hold on the reaction network and let $J$ be as in (5). Then, for any bounded function $\hat{g} : \mathbb{R}_{\geq 0}^{\chi_{ACR}} \rightarrow \mathbb{R}$ we have

$$\sup_{t \leq T} E[\hat{g}(X_{ACR}^N(t))] \rightarrow E[\hat{g}(J)], \quad \text{as } N \rightarrow \infty.$$

That is, for $k \geq 0$,

$$P(X_{ACR,i}^N(t) = k) \rightarrow P(J_i = k) = e^{-q_i} \frac{q_i^k}{k!}.$$  

\textsuperscript{5}David F. Anderson, Daniele Cappelletti, and Thomas G. Kurtz, Finite time distributions of stochastically modeled chemical systems with absolute concentration robustness, submitted, 2016
That is the story. Thanks!

Main References:


