Stochastic analysis of biochemical reaction networks with absolute concentration robustness

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Big picture

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

**Example 1:** \( A + B \rightarrow C \).

**Example 2:** \( A + B \rightarrow 2B \) or \( S + I \rightarrow 2I \)

- \( B \rightarrow A \)
- \( I \rightarrow S \)

**Example 3:** Gene transcription & translation:

\[
\begin{align*}
G & \xrightarrow{\kappa_1} G + M \quad \text{transcription} \\
M & \xrightarrow{\kappa_2} M + P \quad \text{translation} \\
M & \xrightarrow{\kappa_3} \emptyset \quad \text{degradation} \\
P & \xrightarrow{\kappa_4} \emptyset \quad \text{degradation} \\
G + P & \xrightarrow{\kappa_5} B \quad \text{Binding/unbinding of Gene}
\end{align*}
\]

Cartoon representation:

\[\text{Cartoon image showing gene transcription, mRNA production, and protein synthesis.}\]

\[^1\text{J. Paulsson, Physics of Life Reviews, 2, 2005 157 – 175.}\]
Big picture

Example 4: EnvZ/OmpR signaling system

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

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

Metabolic Pathways
Big picture

- For complex models, simulation is often used to explore the possible dynamics (for both deterministic and stochastic models).

- Key system parameters are oftentimes unknown, or known only up to an order of magnitude.

- Want an alternative approach: discover what pieces of the network architecture determine overall system behavior.

- Best if results do not depend upon particular choices of rate constants (which are never really known).

  - how can we cut through the bewildering complexity of biological systems and say something sensible?

  - Mathematics.

- This story is far from complete – really just at beginning stages.
Big picture

Will tell two stories:

   1.1 When will deterministic and stochastic models give similar behavior?

2. (2014 - A., Enciso, Johnston, Royal Society Interface) Provide network conditions that guarantee deterministic model has component which is “Absolutely robust”, stochastic model has extinction event!
   2.1 When will deterministic and stochastic models give different behavior?
   2.2 Characterizing recurrence/transience of the states of the Markov model.
   2.3 Isolated examples abound (Keizer’s paradox, models in ecology, etc). We characterize broad class.

This research is part of chemical reaction network theory, which is part of systems biology.
Reaction Networks: $\{S, C, R\}$

Example:

$$A \rightarrow B$$

- $S = \{A, B\}$.
- $C = \{A, B\}$.
- $R = \{A \rightarrow B\}$.

Example:

$$A + B \rightarrow 2B$$

$$B \rightarrow A$$

- $S = \{A, B\}$.
- $C = \{A + B, 2B, B, A\}$.
- $R = \{A + B \rightarrow 2B, B \rightarrow A\}$. 
Network of complexes and state space of discrete model

Reaction network

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

has the network of complexes

\[ C_1 \rightarrow C_2 \]
\[ C_3 \rightarrow C_4 \]

and state space
Network of complexes and state space of discrete model

Reaction network

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

has the network of complexes

\[ C_1 \rightarrow C_2 \]
\[ C_3 \rightarrow C_4 \]

and state space
Dynamics: stochastic

Example:

\[ A + B \xrightarrow{\alpha} 2B \]  \hspace{1cm} (R1)
\[ B \xrightarrow{\beta} A \]  \hspace{1cm} (R2)

\[ X(t) = X(0) + R_1(t) \left( \begin{bmatrix} 0 \\ 2 \end{bmatrix} - \begin{bmatrix} 1 \\ 1 \end{bmatrix} \right) + R_2(t) \left( \begin{bmatrix} 1 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 1 \end{bmatrix} \right) \]

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

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.
Dynamics: stochastic

For general system, we have $S = \{X_1, \ldots, X_d\}$, with

$$R : \sum_{i=1}^{d} y_{ki} X_i \xrightarrow{\kappa_k} \sum_{i=1}^{d} y'_{ki} X_i \text{ or } y_k \rightarrow y'_k$$

and complexes found at either end of reaction arrow: $C = \{y_k, y'_k\}$.

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

- As before:

$$X(t) = X(0) + \sum_{k} R_k(t)(y'_k - y_k),$$

with

$$X(t) = X(0) + \sum_{k} Y_k \left( \int_{0}^{t} \lambda_k(X(s))ds \right) (y'_k - y_k),$$

$Y_k$ are independent, unit-rate Poisson processes.
Mass-action kinetics

The standard intensity function chosen is mass-action kinetics:

\[ \lambda_k(x) = \kappa_k \left( \prod_i y_{ik}! \right) \left( \frac{x}{y_k} \right) = \kappa_k \prod_i \frac{x_i!}{(x_i - y_{ik})!}. \]

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

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

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

\[ p'_t(x) = \sum_k \lambda(x - \zeta_k)p_t(x - \zeta_k) - p_t(x) \sum_k \lambda_k(x) \]
Neuronal models: Morris-Lecar

Voltage satisfying

\[
\frac{dV}{dt} = f(V(t), N(t))
\]

\[
= \frac{1}{C} \left( I_{app} - g_{Ca} m_{\infty}(V(t))(V(t) - V_{Ca}) - V_K \right) - g_L(V - V_L) - g_K N(t)(V(t)) .
\]

with number of open potassium channels following

\[
\alpha(V(t)) \quad \overset{\leftrightarrow}{\underset{\beta(V(t))}{\text{Open}}} \quad \text{Closed}
\]
Voltage satisfying

\[
\frac{dV}{dt} = \frac{1}{C} \left( I_{\text{app}} - g_{\text{Ca}} m_\infty(V(t))(V(t) - V_{\text{Ca}}) - V_K \right) - g_L (V - V_L) - g_K^o N(t)(V(t)) .
\]

with number of open potassium channels following

\[
N(t) = N(0) - Y_{\text{close}} \left( \int_0^t \beta(V(s))N(s)ds \right) + Y_{\text{open}} \left( \int_0^t \alpha(V(s))(N_{\text{tot}} - N(s))ds \right).
\]
Dynamics: deterministic model

Assuming:

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

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

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

so a good approximation is solution to

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

where

$$u^V = u_1^{V_1} \cdots u_d^{V_d},$$

is standard mass-action kinetics. See Tom Kurtz’s works...
Dynamics. Example

\[ A + B \xrightarrow{\alpha} 2B \quad (R1) \]
\[ B \xrightarrow{\beta} A \quad (R2) \]

**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

\[ \dot{x}(t) = \alpha x_ax_b \begin{bmatrix} -1 \\ 1 \end{bmatrix} + \beta x_B \begin{bmatrix} 1 \\ -1 \end{bmatrix} \]

or

\[ \dot{x}_A(t) = -\alpha x_A x_B + \beta x_B \]
\[ \dot{x}_B(t) = \alpha x_ax_B - \beta x_B. \]
Story 1: special stability for both models

Network reversibility conditions

Definition
Let $S = \{S_i\}$, $\mathcal{C} = \{y_k\}$, and $\mathcal{R} = \{y_k \rightarrow y'_k\}$ denote the sets of species, complexes, and reactions, respectively. The triple $\{S, \mathcal{C}, \mathcal{R}\}$ is called the chemical reaction network.

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

Example

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

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

Has two linkage classes.
Network reversibility conditions

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

That is, if each connected component of network of complexes is strongly connected.

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

Definition

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

is the *stoichiometric subspace* of the network.

Denote

\[ \dim(S) = s. \]

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

**Example:** Reaction network

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

Definition
The *deficiency* of a chemical reaction network, \( \{S, C, R\} \), is

\[
\delta = |C| - \ell - s,
\]

where \(|C|\) is the number of complexes, \(\ell\) is the number of linkage classes of the network graph, and \(s\) is the dimension of the stoichiometric subspace of the network.

Example

\begin{align*}
A + B &\rightleftharpoons 2B & (R1) \\
B &\rightleftharpoons A & (R2)
\end{align*}

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

\begin{align*}
A + B &\rightleftharpoons C & (R1) \\
B &\rightleftharpoons A & (R2)
\end{align*}

\(n = 4, \ell = 2, s = 2 \implies \delta = 0\).
Theorem (The Deficiency Zero Theorem - Deterministic)

Let \( \{S, C, R\} \) be a weakly reversible, deficiency zero chemical reaction network with mass action kinetics. Then, for any choice of rate constants \( \kappa_k \), within each invariant manifold there is precisely one equilibrium value \( c \),

\[
\sum_k \kappa_k c^y_k (y'_k - y_k) = 0,
\]

and that equilibrium value is locally asymptotically stable relative to its compatibility class.

Actually have stronger result: for each \( \eta \in C \),

\[
\sum_{k: y_k = \eta} \kappa_k c^y_k = \sum_{k: y'_k = \eta} \kappa_k c^y_k.
\]

(1)

c is said to be a complex balanced equilibrium.
Theorem (A., Craciun, Kurtz, 2010)

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

Suppose that the deterministic system is complex balanced with equilibrium \( c \in \mathbb{R}^m_0 \). Then, for any irreducible communicating equivalence class, \( \Gamma \), the stochastic system has a product form stationary measure

\[
\pi(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!}, \quad x \in \Gamma,
\]

where \( M \) is a normalizing constant.

Greatly generalizes known results for first-order, or linear, models.
Consider the possible enzyme kinetics given by

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

Not too difficult to see that \( \Gamma = \mathbb{Z}_0^4 \). Therefore, in distributional equilibrium the specie numbers are independent and have Poisson distributions.
Consider the simple reversible system

\[ S_1 \xrightleftharpoons[\kappa_2]{\kappa_1} S_2. \]

Suppose that \( X_1(0) + X_2(0) = N \iff X_1(t) + X_2(t) = N \) for all \( t \).

\[ \delta = n - \ell - s = 2 - 1 - 1 = 0. \]

An equilibrium to the system that satisfies the complex balance equation is

\[ c = \left( \frac{\kappa_2}{\kappa_1 + \kappa_2}, \frac{\kappa_1}{\kappa_1 + \kappa_2} \right), \]

and the product form stationary distribution for the system is

\[ \pi(x) = M \frac{c_1^{x_1} c_2^{x_2}}{x_1! x_2!}, \quad x \in \Gamma. \]
Non-independence

Using that $X_1(t) + X_2(t) = N$ for all $t$ yields

$$
\pi_1(x_1) = M \frac{c_1^{x_1}}{x_1!} \frac{c_2^{N-x_1}}{(N-x_1)!} = \frac{M}{x_1!(N-x_1)!} c_1^{x_1} (1 - c_1)^{N-x_1}.
$$

After setting $M = N!$, we see that $X_1$ is binomially distributed. Similarly,

$$
\pi_2(x_2) = \binom{N}{x_2} c_2^{x_2} (1 - c_2)^{N-x_2}.
$$
Consider the slightly different enzyme kinetics given by

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

- 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 \( P \).
Story 2: Absolute Concentration Robustness


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

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

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

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

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.
We say that two complexes, $y_1, y_2$, differ in species $S_i$ if

$$y_1 = y_2 + \alpha e_i$$

for some $\alpha > 0$.

Examples:

1. $A$, $A + B$
   
   differ in species $B$.

2. $XT$, $XT + Y_p$
   
   differ in species $Y_p$. 
Terminal and non-terminal complexes
Viewing complexes as states of a Markov chain (network of complexes),

\[
\begin{align*}
XD & \quad \xrightarrow{k_1} \quad X \quad \xleftarrow{k_2} \quad Xp + Y \\
\quad & \quad \xrightarrow{k_3[T]} \quad XT \quad \xrightarrow{k_5} \quad Xp \\
Xp + Y & \quad \xrightarrow{k_6} \quad XpY \quad \xleftarrow{k_7} \quad XD + Yp \\
XD + Yp & \quad \xleftarrow{k_{10}} \quad XDY_p \quad \xrightarrow{k_11} \quad XD + Y
\end{align*}
\]

becomes

\[
\begin{align*}
C_1 & \iff C_2 \iff C_3 \to C_4 \\
C_5 & \iff C_6 \to C_7 \\
C_8 & \iff C_9 \to C_{10}.
\end{align*}
\]

- A complex is called **terminal** if it is recurrent in network of complexes.
- “Transient complexes” are called **non-terminal**.
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 for every positive recurrent state of the Markov model the intensity of each non-terminal complex is zero.
Example

Reaction network

\[ A + B \rightarrow 2B \]

\[ B \rightarrow A \]

has state space
\( X_{\text{tot}} := X + XD + XT + X_p + X_p Y + XDY_p \)
\( Y_{\text{tot}} := Y + X_p Y + XDY_p + Y_p. \)
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 \( \pi^Q_M \) so that for \( \tau \) absorption time and \( x \in \) transient states,

\[ \lim_{t \to \infty} P_{\nu}(X(t) = x \mid \tau > t) = \pi^Q_M(x). \]

Satisfies

\[ \pi^Q_M(x) = P_{\pi^Q_M}(X(t) = x \mid \tau > t). \]

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

\[ \pi^Q_M(x) \to e^{-\left(\frac{\beta}{\alpha}\right)} \left(\frac{\beta}{\alpha}\right)^x \frac{x^x}{x!}, \quad \text{as } M \to \infty. \]
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.

3 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
How to prove: an example

\[ A + B \xrightarrow{\alpha} 2B \quad \text{(R1)} \]
\[ B \xrightarrow{\beta} A \quad \text{(R2)} \]
How to prove: an example

\[ A + B \xrightarrow{\alpha} 2B \quad (\text{R1}) \]
\[ B \xrightarrow{\beta} A \quad (\text{R2}) \]
\[ 2A \leftrightarrow B + C. \quad (\text{R3}) \]

- Note \(|C| = 6, \ell = 3, 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 $\text{ker}(YA_\kappa)$.

▶ 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 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 $\text{ker}(YA_\kappa)$ which is impossible.
Flavor of proof

<table>
<thead>
<tr>
<th>General Case:</th>
<th>Example: $A + B \overset{\kappa_1}{\iff} 2B \overset{\kappa_2}{\iff} 2A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{x} = f(x) = Y \circ A_\kappa \circ \psi(x)$</td>
<td>$\dot{x} = \kappa_1 x_A x_B \begin{bmatrix} -1 \ 1 \end{bmatrix} + \kappa_2 x_B^2 \begin{bmatrix} 1 \ -1 \end{bmatrix} + \kappa_3 x_A^2 \begin{bmatrix} -2 \ 2 \end{bmatrix}$</td>
</tr>
<tr>
<td>$\psi: \mathbb{R}^d \rightarrow \mathbb{R}^c$</td>
<td>$\psi(x) = \begin{bmatrix} x_A x_B \ x_B^2 \ x_A^2 \end{bmatrix}$</td>
</tr>
<tr>
<td>$\psi(x)_y = x^y$</td>
<td>$\psi(x) = \begin{bmatrix} x_A x_B \ x_B^2 \ x_A^2 \end{bmatrix}$</td>
</tr>
<tr>
<td>$A_\kappa: \mathbb{R}^c \rightarrow \mathbb{R}^c$</td>
<td>$A_\kappa =$ $\begin{bmatrix} -\kappa_1 &amp; \kappa_2 &amp; 0 \ \kappa_1 &amp; -\kappa_2 &amp; \kappa_3 \ 0 &amp; 0 &amp; -\kappa_3 \end{bmatrix}$</td>
</tr>
<tr>
<td>$A_{ij}^\kappa = \begin{cases} -\kappa_j \rightarrow_{i} &amp; \text{for } j \neq i \ -\sum_{\ell \neq j} \kappa_j \rightarrow_{\ell} &amp; \text{for } i = j \end{cases}$</td>
<td></td>
</tr>
<tr>
<td>$Y: \mathbb{R}^c \rightarrow \mathbb{R}^d$ is linear:</td>
<td>$Y =$ $\begin{bmatrix} 1 &amp; 0 &amp; 2 \ 1 &amp; 2 &amp; 0 \end{bmatrix}$</td>
</tr>
<tr>
<td>$Ye_i = y_i$</td>
<td></td>
</tr>
<tr>
<td>$\dot{x} =$ $\begin{bmatrix} 1 &amp; 0 &amp; 2 \ 1 &amp; 2 &amp; 0 \end{bmatrix}$ $\begin{bmatrix} -\kappa_1 &amp; \kappa_2 &amp; 0 \ \kappa_1 &amp; -\kappa_2 &amp; \kappa_3 \ 0 &amp; 0 &amp; -\kappa_3 \end{bmatrix}$ $\begin{bmatrix} x_A x_B \ x_B^2 \ x_A^2 \end{bmatrix}$</td>
<td></td>
</tr>
</tbody>
</table>
Flavor of proof

- Can use that the deficiency of model is one to characterize basis of kernel of $YA_\kappa$.

$$\ker(YA_\kappa) = \text{span}\{\bar{c}, b_1, \ldots, b_T\},$$

- The terms $\{b_1, \ldots, b_T\}$ have support on terminal complexes. Recall: $A_T^\kappa$ is the infinitesimal generator for the CTMC on network of complexes.

- The term $\bar{c}$ has support on *all* complexes.

- Now consider reduced model. I.e.

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

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

$$2A \overset{\kappa_3}{\leftrightarrow} B + C.$$  

becomes

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

$$2A \overset{\kappa_3}{\leftrightarrow} B + C.$$
flavor of proof

Only work with $A + B$ – reduced network. Call it $\{S, C, R^*\}$. 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 $N$th return time to $X_0$ as $t_N$. It follows that we have 

$$X^*(t_N) = X^*(0)$$

for all $N$ so that 

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

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

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

- 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

\[
\lim_{N \to \infty} \frac{1}{t_N} \int_0^{t_N} (X^*(s))^{y_k} ds = \sum_{x \in \mathcal{I}} \pi_x(X)X^{y_k}, \quad (5)
\]

- Define the vector \( G_\pi \in \mathbb{R}^C \) via

\[
[G_\pi]_y := \sum_{x \in \mathcal{I}} \pi_x(X)X^{y}, \quad (6)
\]

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). \( \square \)
Generalization

Can generalize to models with a higher deficiency.

Theorem

Let \((S, \mathcal{C}, \mathcal{R})\) be a conservative chemical reaction network for which the following assumptions hold:

1. There are non-empty sets of non-terminal complexes \(\mathcal{C}^*\) and \(\mathcal{C}^{**}\) such that, if \(y \in \mathcal{C}^*\) then there exists a \(y' \in \mathcal{C}^{**}\) such that \(y \ll y'\).

2. For some choice of rate constants \(\{k_i\}_{i=1}^r\), the following property holds: if \(\Psi \in \ker(YA_k)\) and \(\Psi_y = 0\) for all \(y \in \mathcal{C}^*\), then \(\Psi_{\bar{y}} = 0\) for all non-terminal \(\bar{y}\).

Then, for any choice of stoichiometrically admissible kinetics, all non-terminal complexes of the network are off at each positive recurrent state of the stochastically modeled system.

Remark: The second condition in assumption 2 above may also be formulated in the following way, which may be more intuitive to some readers.

2'. For some choice of rate constants \(\{k_i\}_{i=1}^r\), the following property holds: if \(\Psi \in \ker(YA_k)\) has support on a non-terminal complex, then \(\Psi\) has support on some \(y \in \mathcal{C}^*\).
Generalization, example

\[
\begin{align*}
XD & \overset{k_1}{\Leftrightarrow} X \overset{k_3[T]}{\Leftrightarrow} XT \overset{k_5}{\rightarrow} X_p \\
& \overset{k_2[D]}{\Leftrightarrow} k_4
\end{align*}
\]

\[
\begin{align*}
X_p + Y & \overset{k_6}{\Leftrightarrow} X_p Y \overset{k_8}{\rightarrow} X + Y_p \\
& \overset{k_7}{\Leftrightarrow}
\end{align*}
\]

\[
\begin{align*}
XD + Y_p & \overset{k_9}{\Leftrightarrow} XDY_p \overset{k_{11}}{\rightarrow} XD + Y \\
& \overset{k_{10}}{\Leftrightarrow}
\end{align*}
\]

\[
\begin{align*}
XT + Y_p & \overset{k_{12}}{\Leftrightarrow} XTY_p \overset{k_{14}}{\rightarrow} XT + Y_p.
\end{align*}
\]

(7)

Deficiency is two.

\[
XD + Y_p \ll XD, \quad \text{and} \quad XT + Y_p \ll XT.
\]

Ordering non-terminal complexes as

\[
\{ XD, X, XT, X_p + Y, X_p Y, XD + Y_p, XDY_p, XT + Y_p, XTY_p \}. \quad (8)
\]

there are \textit{two} basis vectors of \( YA_k \) with non-zero support on the complexes as ordered in (8);

\[
\{ [2, 2, 1, 2, 1, 2, 1, 0, 0], [2, 2, 1, 2, 1, 0, 0, 2, 1] \}. \]
That is the story. Thanks!

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