Multistationarity in Biochemical Networks

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Objectives

What does the set of rate constants $(k_1, k_2, ...)$ (or, with networks involving conservation laws, $(k_1, k_2, T...)$) for which there are multiple positive equilibria (MPE) look like? I investigate this mathematical problem by:

- Analyzing 3 specific examples of smaller reaction networks
- Investigating their unique conditions for potential existence/number of equilibria
- Studying the system of ordinary differential equations that model the steady-state equations of each reaction network
- Investigating the roots of the equations with Descartes' Rule of Signs to determine the number of positive roots
- Applying the Discriminant to determine the parameters of the reaction rate constants of each network that give multiple positive roots

Introduction

1. **Biochemical networks** are complex objects that contain **nonlinear interactions** among a large number of chemical species.
2. Understanding the **interaction** requires strategies more subtle than an interaction diagram, which leads to the relevance of **multistationarity**
3. **Instabilities** of different types are probable for small biological structures; an important class of instabilities are the ones that lead to **multiple positive steady states** (equilibria)
4. Defined as **multistationarity**, these instabilities are visible as **irreversible switch-like behavior**.
5. **Multistationarity** is significant in **crucial cell behaviors**, ranging from differentiation, generating oscillatory responses, and remembering transitory stimuli.
6. To improve our understanding of multistationarity, it is necessary to define the **number/conditions** of the set of **rate constants** that give MPE for a specific network.
7. To find **positive equilibria**, we set the right-hand side of the **steady-state equations** (differential equations) equal to zero and solve.
8. We can also graph the differential equations in the x_A, x_B plane if there are only two species in the network.
9. If there are more than A, B species in the network, it is difficult to graph the steady state equations to visually see the equilibria points in each compatibility class, which demonstrates why *theorems characterizing conditions of MPE* for a network are important.
10. For a **different choice** of rate constants, the network could have MPE.

Significant Definitions and Notations

1. **Chemical Reaction Network (CRN)**: list of reactions that involve a finite list of species
2. **Ordinary Differential Equation (ODE)**: equality involving a function and its derivatives
3. **Rate Constant**: reaction-dependent quantity written on top of the reaction arrow, $k > 0$; aggregating contributions of all reactions in a network gives system of ODE of CRN
4. **Stoichiometry Classes**: affine spaces parallel to the *stoichiometric subspace*; classes are spaces where dynamical behaviors of CRNs are researched for existence/uniqueness of equilibria
5. **Equilibrium**: a point in the phase space at which its vector field vanishes; single-point trajectory of the dynamics of a CRN
6. **Discriminant**: portion of quadratic formula under square root; use relationship between discriminant and roots to determine number of solutions to a polynomial
7. **Descartes's Rule of Signs**: number of positive roots is greater than/equal to the number of sign changes of coefficients; use to determine the greatest number of *equilibria* & how number depends on constant k or T

Mathematical Theorem 1

In my research, I prove **three total theorems** for the characterization of multiple positive equilibria (MPE) for 3 unique networks. I walk through the outline of proving Theorem 1 for my first network example below.

1. **Theorem 1**: Consider Network 1:

$$2A + B \xrightarrow{k_1} 3A \qquad A \xrightarrow{k_2} B \tag{1}$$

and its *Conservation Law* $x_A + x_B = T$. Then, MPE $\Leftrightarrow T^2 > \frac{4k_2}{k_1}$.

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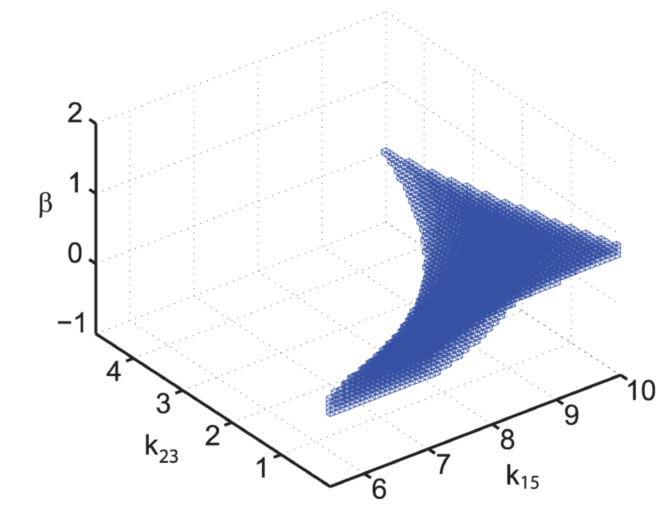

Figure 1:Example of a Region of Multistationarity in a Network

Network 1: Proof Outline of Theorem 1

1. **Step 1:** Using **Network (1):**
   - The *steady-state equations* are $\dot{x_A} = k_1 x_A^2 x_B - k_2 x_A$ & $\dot{x_B} = -k_1 x_A^2 x_B + k_2 x_A$.
   - Letting $x = x_A$ and $y = x_B$, we get $k_1 x^2 y - k_2 x = 0$.
   - Since the *conservation law* is $x_A + x_B = T$, we let $x = x_A$ and $y = x_B$ to get $x + y = T$.
   - Then, substitute $y = T - x$ into y in the steady state for $g = -k_1 x^2 + k_1 T x - k_2$.
2. **Step 2:** Calculating the **discriminant** of our quadratic polynomial, we get $\triangle = k_1^2 T^2 - 4k_1 k_2$.
   - We want to check when $\triangle = k_1^2 T^2 - 4k_1 k_2 > 0$.
   - Assuming $k_1, k_2, T > 0$, we get:

$$\begin{aligned} &\text{g has two real roots} \\ \Leftrightarrow\ &\triangle = k_1^2 T^2 - 4k_1 k_2 > 0 \\ \Leftrightarrow\ &k_1 T^2 - 4k_2 > 0 \\ \Leftrightarrow\ &T^2 > \frac{4k_2}{k_1} \end{aligned}$$

   - We can also determine the second case: if g has *at most one* real root:

$$T^2 \leq \frac{4k_2}{k_1} \Leftrightarrow \text{g has at most one real root.}$$

3. **Step 3:** We can find the **roots** of $-k_1 x^2 + k_1 T x - k_2$.
   - If $\triangle \leq 0$, then there are no MPE.
   - We can check the remaining case, $\triangle > 0$, to conclude that there are two positive roots (MPE).
   - The two roots x^* and x^{**} are:

$$\begin{aligned} x^* &= \frac{k_1 T + \sqrt{k_1^2 T^2 - 4k_2 k_1}}{2k_1} \Rightarrow y^* = T - x^* \\ &= \frac{k_1 T - \sqrt{k_1^2 T^2 - 4k_2 k_1}}{2k_1} \Rightarrow y^{**} = T - x^{**}. \end{aligned} \tag{2}$$

4. **Step 4:** We must identify if the **set of points** (x^*, y^*) and (x^{**}, y^{**}) are *two positive equilibria.*
   - We know that $0 < x^{**} < x^*$, but we must find if $y^* > 0$ and $y^{**} > 0$ to determine whether $0 < x^{**} < x^* < T$ by:

$$\begin{aligned} x^* &= \frac{k_1 T}{2k_1} + \frac{\sqrt{k_1^2 T^2 - 4k_1 k_2}}{2k_1} \\ &= \frac{T}{2} + \frac{\sqrt{k_1^2 T^2 - 4k_1 k_2}}{2k_1} \\ &= \frac{T k_1 + \sqrt{k_1^2 T^2 - 4k_1 k_2}}{2k_1} \\ &= \frac{T k_1 + \sqrt{(T k_1)^2 - 4k_1 k_2}}{2k_1} \\ &< \frac{T k_1 + \sqrt{(T k_1)^2 - 0}}{2k_1} \\ &= \frac{2T k_1}{2k_1} = T. \end{aligned} \tag{3}$$

   Therefore, we have proved **Theorem 1**.

Mathematical Theorems 2 and 3

I enhanced the validity of **Theorem 1** with two additional examples of specific biochemical networks. Like in the network one example, **MPE is characterized by a single inequality** for networks two and three below. In my research, I proved, similarly as I did in the proof outline for Theorem 1, two additional theorems.

1. **Theorem 2**: Consider Network 2:

$$0 \xrightarrow{k_1} A \qquad A \xrightarrow{k_2} 0 \qquad 2A \xrightarrow{k_3} 3A \tag{4}$$

. Then, MPE $\Leftrightarrow k_2 > 2\sqrt{k_1 k_3}$.

2. **Theorem 3**: Consider Network 3:

$$0 \xleftarrow{k_1} A \qquad 2A \xrightarrow{k_2} 3A \qquad 4A \xrightarrow{k_3} 3A \tag{5}$$

Then, MPE $\Leftrightarrow \frac{4k_2^3}{27k_1^2} > k_3$.

Conclusions & Future Works

After exploring **three unique theorems that characterized the parameters**, or rate constants, in which **a specific network displayed multiple positive equilibria**, I will explore another important mathematical concept related to Multistationarity: *path connectedness*.

1. **Path connected:** given points x and y of a space X, a *path* in X from x to y is a continuous map $f : [a, b] \to X$ of a closed interval in the real line into X such that $f(a) = x$ and $f(b) = y$. A space X is **path connected** if every pair of points of X can be joined by a path in X.
2. I want to determine if the space X, defined by

$$X = \{(k_1, ..., k_r) \in \mathbb{R}^r > 0 | \text{Network has MPE}\},$$

is **path connected**.

3. With networks involving *conservation laws*, I will discover whether the space Y, defined by

$$Y = \{(k_1, ..., k_r, T) | \text{Network has MPE}\},$$

is **path connected**.

4. I will continue my research on *multistationarity in biochemical networks* by examining the three network examples shown in the poster to determine if each condition, or **theorem**, I found characterizing MPE for the specific network is **path-connected**.

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