Multistationarity in Biochemical Networks
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Objectives
What does the set of rate constants \((k_1, k_2, \ldots)\) (or, with networks involving conservation laws, \((k_1, k_2, T, \ldots)\)) 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/nature 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
- Biochemical networks are complex objects that contain nonlinear interactions among a large number of chemical species.
- Understanding the interaction requires strategies more subtle than an interaction diagram, which leads to the relevance of multistationarity.
- 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).
- Multistationarity is significant in crucial cell behaviors, ranging from differentiation, generating oscillatory responses, and remembering transitory stimuli.
- 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.
- To find positive equilibria, we set the right-hand side of the steady-state equations (differential equations) equal to zero and solve.
- We can also graph the differential equations in the \(x_1, x_2\) plane if there are only two species in the network.
- 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.
- For a different choice of rate constants, the network could have MPE.

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.

**Theorem 1** Consider Network 1:
\[
2A + B \overset{k_1}{\rightarrow} 3A
\]
\[
A \overset{k_2}{\rightarrow} B
\]
and its Conservation Law \(\Delta A = x_B = T\). Then, MPE \(T^2 > \frac{4k_2}{k_1}\)

**Step 1: Using Network (1):**
- The steady-state equations are \(x_A = k_2x_B - k_2x_A, x_B = -k_2x_A + k_2x_B\).
- Letting \(x = x_A\) and \(y = x_B\), we get \(k_2y = k_2 = 0\).
- Since the conservation law is \(x_B = x_A = T\), we let \(x = x_A\) and \(y = x_B = T\).
- Then, substitute \(y = T - x\) into the steady state for \(x = -k_2x + k_2T - k_2B\).

**Step 2: Calculating the discriminant** of our quadratic polynomial, we get \(\Delta = k_2T^2 - 4k_2B\).

**Step 3: We can find the roots** of \(-k_2x + k_2T - k_2B = 0\).
- If \(\Delta \leq 0\), there are no MPE.
- We can check the remaining case \(\Delta > 0\), to conclude that there are two positive roots (MPE).

**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 \(0 < x^* < x^*\) or \(y^* > 0\).

Therefore, we have proved Theorem 1.

Significant Definitions and Notations
- **Chemical Reaction Network (CRN)**: list of reactions that involve a finite list of species.
- **Ordinary Differential Equation (ODE)**: equation involving a function and its derivatives.
- **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
- **Stoichiometry Classes**: affine spaces parallel to the stoichiometric subspace; classes are spaces where dynamical behaviors of CRNs are resource for existence/uniqueness of equilibria.
- **Equilibrium**: a point in the phase space at which its vector field vanishes; single-point trajectory of the dynamics of a CRN
- **Discriminant**: portion of quadratic formula under square root; use relationship between discriminant and number of positive roots to determine the number of solutions to a polynomial.
- **Descartes’ 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 \(T\)

References