

Homotopy Methods for Counting Reaction Network Equilibria

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<http://www.math.ucsd.edu/~williams/reactionnet/chw.pdf>

Dynamical System Models

DS models of chemical reaction networks have form

$$\dot{c} = f(c) \quad (1)$$

where f is a smooth $\mathbb{R}^n$ -valued function defined on a subset of $\mathbb{R}_{\geq 0}^n$.

Typically such DS are high-dimensional, nonlinear, and parameters defining f are not well known.

Focus here on positive equilibria for (1), i.e., on $c^* \in \mathbb{R}_{> 0}^n$ for which $f(c^*) = 0$.

Some References

Positive Equilibria for Chemical Reaction Networks

*Sufficient Conditions for Uniqueness of Positive Equilibria for **All Values** of Model Parameters:* Recent work of Craciun, Feinberg et al. using graph-theoretical methods (assumes **mass-action kinetics**).

*Examples of Reaction Networks Admitting Multiple Positive Equilibria for **Some Values** of the Parameters:* Recent work of Craciun, Feinberg et al. with **mass-action kinetics**.

Here we describe **methods** based on homotopy invariance of degree for determining how the number of positive equilibria for a chemical reaction network depends on the parameters of the model.

Key Condition

The determinant of the Jacobian $\frac{\partial f}{\partial c}(\cdot)$ of f is either strictly positive or strictly negative everywhere on its domain of definition.

(Craciun and Feinberg et al. consider situations where this holds for **all values** of the rate constants.)

(Note: Under this condition, the absolute value of the topological degree of f counts the number of zeros of f .)

Advantages of Homotopy Method

- Don't need conditions for *all* rate constants
- Can obtain *existence* of positive equilibria
- Kinetics can be *more general than mass-action*

OUTLINE

- Consequence of Homotopy Invariance of Degree
- Example: Bounded State Space, Not Mass Action
- Application to a Conservative Reaction Network with Inflows and Outflows (CFSTR)
- Examples: Mass Action

Consequence of Homotopy Invariance of Degree

For a **bounded** domain $\Omega \subset \mathbb{R}_{>0}^n$, consider

$$\dot{c} = f_\lambda(c), \quad c \in \Omega,$$

where $f_\lambda : \bar{\Omega} \rightarrow \mathbb{R}^n$ for $\lambda \in [0, 1]$ is a continuously varying family of smooth functions.

Suppose that

- (i) f_λ does not have any zeros on $\partial\Omega$ for all $\lambda \in [0, 1]$,
- (ii) $\det \left(\frac{\partial f_\lambda}{\partial c}(c) \right) \neq 0$ for all $c \in \Omega$, for $\lambda = 0, 1$.

Then the number of zeros of f_0 in Ω equals the number of zeros of f_1 in Ω .

Example of Arcak and Sontag (not mass action)

Simplified model of mitogen activated protein kinase (MAPK) cascades with inhibitory feedback:

$$\begin{aligned}\dot{c}_1 &= -\frac{b_1 c_1}{c_1 + a_1} + \frac{d_1(1 - c_1)}{e_1 + (1 - c_1)} \frac{\mu}{1 + k c_3} \\ \dot{c}_2 &= -\frac{b_2 c_2}{c_2 + a_2} + \frac{d_2(1 - c_2)}{e_2 + (1 - c_2)} c_1 \\ \dot{c}_3 &= -\frac{b_3 c_3}{c_3 + a_3} + \frac{d_3(1 - c_3)}{e_3 + (1 - c_3)} c_2.\end{aligned}$$

The variables $c_j \in [0, 1]$, $j = 1, 2, 3$ denote the (normalized) concentrations of the active forms of the proteins.

Confirm result of AS that there is a unique positive equilibrium for any choice of the strictly positive parameters, $a_1, a_2, a_3, b_1, d_1, e_1, b_2, d_2, e_2, b_3, d_3, e_3, \mu, k$.

Continuous Flow Stirred Tank Reactor

Conservative dynamical system augmented with inflows and outflows:

$$\dot{c} = f(c) := c_{in} - c + g(c) \quad (2)$$

where $c_{in} \in \mathbb{R}_{\geq 0}^n$, and the function $g : \mathbb{R}_{\geq 0}^n \rightarrow \mathbb{R}^n$ is a species formation rate function for a conservative chemical reaction network:

$$g(c) = Sr(c) \quad \text{for } c \in \mathbb{R}_{\geq 0}^n.$$

In particular, g is assumed to be a smooth function such that

- (i) for each $j \in \{1, \dots, n\}$, $g_j(c) \geq 0$ whenever $c_j = 0$ (*positive invariance*),
- (ii) there is $m \in \mathbb{R}_{\geq 0}^n$ such that $m \cdot g(c) = 0$ for all $c \in \mathbb{R}_{\geq 0}^n$ (*mass conservation*).

Theorem

The augmented dynamical system

$$\dot{c} = f(c) := c_{in} - c + g(c)$$

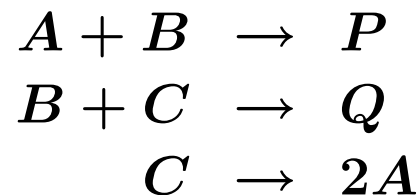
has no equilibria on the boundary of $\mathbb{R}_{\geq 0}^n$. Furthermore, if

$$\det \left(\frac{\partial f}{\partial c} \right) \neq 0 \quad \text{on } \mathbb{R}_{> 0}^n,$$

then there is exactly one equilibrium point in $\mathbb{R}_{> 0}^n$.

Example

Consider the chemical reaction network



Associated DS for mass-action kinetics (augmented with inflows and outflows):

$$\begin{aligned}\dot{c}_A &= k_{0 \rightarrow A} - k_{A \rightarrow 0}c_A - k_{A+B \rightarrow P}c_Ac_B + 2k_{C \rightarrow 2A}c_C \\ \dot{c}_B &= k_{0 \rightarrow B} - k_{B \rightarrow 0}c_B - k_{A+B \rightarrow P}c_Ac_B - k_{B+C \rightarrow Q}c_Bc_C \\ \dot{c}_C &= k_{0 \rightarrow C} - k_{C \rightarrow 0}c_C - k_{B+C \rightarrow Q}c_Bc_C - k_{C \rightarrow 2A}c_C \\ \dot{c}_P &= k_{0 \rightarrow P} - k_{P \rightarrow 0}c_P + k_{A+B \rightarrow P}c_Ac_B \\ \dot{c}_Q &= k_{0 \rightarrow Q} - k_{Q \rightarrow 0}c_Q + k_{B+C \rightarrow Q}c_Bc_C.\end{aligned}$$

By work of Craciun and Feinberg, the dynamical system has multiple positive equilibria for some values of the reaction rate parameters.

Example (cont.)

For simplicity, assume outflow rates $k_{A \rightarrow 0}, \dots, k_{Q \rightarrow 0}$ are all equal to 1. The determinant of the Jacobian of the reaction rate function has the following expansion:

$$\begin{aligned} \det(\partial f / \partial c) = & -1 - k_{A+B \rightarrow P} c_A - k_{B+C \rightarrow Q} c_C \\ & - k_{B+C \rightarrow Q} c_B \\ & - k_{B+C \rightarrow Q} k_{A+B \rightarrow P} c_A c_B - k_{C \rightarrow 2A} \\ & - k_{C \rightarrow 2A} k_{A+B \rightarrow P} c_A \\ & - k_{C \rightarrow 2A} k_{B+C \rightarrow Q} c_C - k_{A+B \rightarrow P} c_B \\ & - k_{A+B \rightarrow P} k_{C \rightarrow 2A} c_B \\ & - k_{A+B \rightarrow P} k_{B+C \rightarrow Q} c_B^2 \\ & - k_{A+B \rightarrow P} k_{B+C \rightarrow Q} c_B c_C \\ & + k_{A+B \rightarrow P} k_{B+C \rightarrow Q} k_{C \rightarrow 2A} c_B c_C. \end{aligned}$$

There is only one (anomalous sign) in the determinant expansion (with monomial $c_B c_C$).

Example (cont.)

Combining all terms with this monomial gives

$$[-k_{A+B \rightarrow P}k_{B+C \rightarrow Q} + k_{A+B \rightarrow P}k_{B+C \rightarrow Q}k_{C \rightarrow 2A}]c_Bc_C.$$

If $k_{C \rightarrow 2A} \leq 1$, then $\det(\partial f / \partial c) < 0$ for this network, everywhere on $\mathbb{R}_{>0}^5$.

The reaction network before augmentation with inflows and outflows satisfies positive invariance and the vector $(m_A, m_B, m_C, m_P, m_Q) = (1, 1, 2, 2, 3)$ is a conserved mass vector.

Hence, the dynamical system, augmented with inflows and unit rate outflows, has a unique positive equilibrium for all positive values of the reaction rates such that $k_{C \rightarrow 2A} \leq 1$.

Some Further Examples of Craciun & Feinberg

	Reaction network	Num. of “anomalous” signed terms in det expansion
(i)	$A + B \rightleftharpoons P \quad B + C \rightleftharpoons Q$ $C \rightleftharpoons 2A$	1
(ii)	$A + B \rightleftharpoons P \quad B + C \rightleftharpoons Q$ $C + D \rightleftharpoons R \quad D \rightleftharpoons 2A$	0
(iii)	$A + B \rightleftharpoons P \quad B + C \rightleftharpoons Q$ $C + D \rightleftharpoons R \quad D + E \rightleftharpoons S$ $E \rightleftharpoons 2A$	1
(iv)	$A + B \rightleftharpoons P \quad B + C \rightleftharpoons Q$ $C \rightleftharpoons A$	0
(v)	$A + B \rightleftharpoons F \quad A + C \rightleftharpoons G$ $C + D \rightleftharpoons B \quad C + E \rightleftharpoons D$	1
(vi)	$A + B \rightleftharpoons 2A$	1
(vii)	$2A + B \rightleftharpoons 3A$	1
(viii)	$A + 2B \rightleftharpoons 3A$	1

Some examples of reaction networks with mass action kinetics and the signs of coefficients in their Jacobian determinant expansion when augmented with inflows and outflows. For recent work on counting the number of plus and minus signs in Jacobian determinant expansions, see Helton, Klep and Gomez (2008), Math Arxiv.

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