(Some) Challenges in the study of algebraic models of biochemical reaction networks

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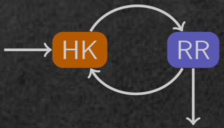
The big picture

A reaction network

Two-component system (used by bacteria to transfer cellular signal)

$$
\begin{aligned}
\mathrm{HK} &\longrightarrow \mathrm{HK_p} \\
\mathrm{HK_p} + \mathrm{RR} &\rightleftharpoons \mathrm{HK} + \mathrm{RR_p} \\
\mathrm{RR_p} &\longrightarrow \mathrm{RR}
\end{aligned}
$$



HK = histidine kinase; RR = response regulator

The evolution of the concentrations in time is modelled using a system of ordinary differential equations:

$$
\begin{aligned}
\dot{x}_1 &= -\kappa_1 x_1 + \kappa_2 x_2 x_3 - \kappa_3 x_1 x_4 \\
\dot{x}_2 &= \kappa_1 x_1 - \kappa_2 x_2 x_3 + \kappa_3 x_1 x_4 \\
\dot{x}_3 &= -\kappa_2 x_2 x_3 + \kappa_3 x_1 x_4 + \kappa_4 x_4 \\
\dot{x}_4 &= \kappa_2 x_2 x_3 - \kappa_3 x_1 x_4 - \kappa_4 x_4
\end{aligned}
$$

where
$x_1 = [\mathrm{HK}]$, $x_2 = [\mathrm{HK}_p]$,
$x_3 = [\mathrm{RR}]$, $x_4 = [\mathrm{RR}_p]$.

Here $\kappa_1, \kappa_2, \kappa_3, \kappa_4$ are parameters (generally unknown).

Two approaches

- Quantitative: find approximate values for the parameters, and then study the resulting system in detail.

  Numerical simulations are often part of this approach.

- Qualitative: study the system for all parameter values, focusing on questions of the type
  - Does there exist a choice of parameters such that the system displays ...?
  - Where in the parameter space does the system display ...?
  - Why do specific parameters display ...?

  Strategies:
  - Sample parameters and decide upon the property (often numerically).
  - Theoretical study, often symbolical.

Mathematical framework

Reaction networks

A reaction network over a set of species $\mathcal{X} = \{X_1, \dots, X_n\}$ consists of a finite set of reactions of the form

$$r_j: \sum_{i=1}^{n} b_{ij} X_i \to \sum_{i=1}^{n} c_{ij} X_i, \qquad b_{ij}, c_{ij} \in \mathbb{Z}_{\geq 0}$$

$$X_1 \xrightarrow{\kappa_1} X_2$$
$$2X_2 \xrightarrow{\kappa_2} 2X_1$$
$$X_1 + X_2 \xrightarrow{\kappa_3} 2X_2$$

Dynamical system:
(x_i= concentration of species X_i)

$$\dot{x} = N\, v_\kappa(x).$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix}$$

- N is the stoichiometric matrix, where entry (i,j) is the net production of species i in reaction j: $N_{ij} = (c_{ij} - b_{ij})$.
- Mass-action: $v_{\kappa,j}(x) = \kappa_j x_1^{b_{1j}} \cdot \dots \cdot x_n^{b_{nj}}$. $\kappa_j > 0$, reaction rate constants.
- $\mathbb{R}^n_{>0}$ and $\mathbb{R}^n_{\geq 0}$ are forward invariant.

Stoichiometric compatibility classes

$$[1 \quad 1] \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = [1 \quad 1] \begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix} = 0$$

We obtain

$$\dot{x}_1 + \dot{x}_2 = 0 \qquad \Rightarrow \qquad x_1 + x_2 \text{ constant along trajectories.}$$

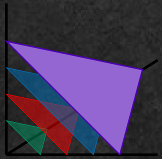
Trajectories are confined to linear subspaces $x_1 + x_2 = c$ with c depending on the initial condition.

W: matrix whose rows form a basis of the left kernel of N, $\ker(N^T) = \mathrm{Im}(N)^\perp$

Stoichiometric compatibility classes:

$$Wx = c, \qquad x \in \mathbb{R}^n_{\geq 0}$$

with c vector of total amounts.



Every trajectory is confined to one of these classes, depending on the initial condition.

Steady states

The steady states or equilibrium points of the ODE system are given as the solutions to

$$Nv_\kappa(x) = 0.$$

In particular: we are concerned with positive solutions in each stoichiometric compatibility class:

$$x \in \mathbb{R}^n_{>0} \qquad \text{such that} \qquad Nv_\kappa(x) = 0 \qquad \text{and} \qquad Wx = c$$

Two types of parameters, κ, c, treated as unknown.

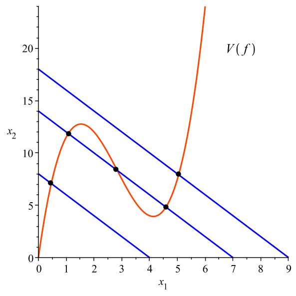
$$C_{\kappa,c} = \{x \in \mathbb{R}^n_{>0} |\ Nv_\kappa(x) = 0, \quad Wx = c\}.$$

Steady states and stoichiometric compatibility classes

In the example,

$$C_{\kappa,c} = \left\{ x \in \mathbb{R}^2_{>0} \;\middle|\; \begin{array}{r} -\kappa_1 x_1 + 2\kappa_2 x_2^2 - \kappa_3 x_1 x_2 = 0, \\ \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2 = 0 \\ \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2 = 0 \\ x_1 + x_2 = c \end{array} \right\}.$$

These sets are parameterised by $\kappa = (\kappa_1, \dots, \kappa_m)$ and $c = (c_1, \dots, c_d)$.



Expected: each of these sets contains a finite number of points.

The number of elements might depend on the parameters.

Qualitative properties of interest

$$C_{\kappa,c} = \{x \in \mathbb{R}^n_{>0} |\ Nv_\kappa(x) = 0, \quad Wx = c\}.$$

We are interested in the existence, where and why for:

(Multistationarity) Presence of two positive steady states

$$\#C_{\kappa,c} \geq 2 \quad ? \qquad\qquad \text{(existence essentially solved)}$$

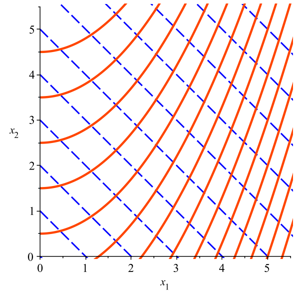
(Bistability) Presence of two asymptotically stable positive steady states

(Oscillations) Presence of periodic solutions

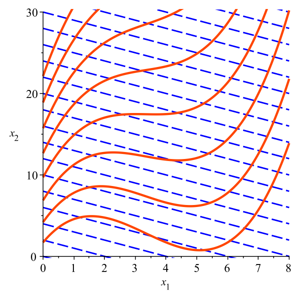
Question

(answer using this link (click on it): `http://etc.ch/XwNY`)

The following figures show the family of steady state curves (red, solid) for varying κ, together with the invariant linear subspaces (blue, dashed) for varying c, for two different networks.



(1)



(2)

According to the figures, which network(s) display(s) multistationarity?

(A) Network (1) (B) Network (2) (C) Both networks

Parametrizations

A positive parametrization of the (positive) steady states is an injective function

$$\phi\colon \mathbb{R}^d_{>0} \to \mathbb{R}^n_{>0} \qquad \xi \mapsto \phi(\xi)$$

such that the image is exactly the set of positive steady states (solutions to $N\, v_\kappa(x) = 0$).

For the two-component system:

$$\phi(x_2, x_4) = \left(\tfrac{\kappa_4}{\kappa_1} x_4, x_2, \tfrac{(\kappa_1 + \kappa_3 x_4)\kappa_4 x_4}{\kappa_1 \kappa_2 x_2}, x_4 \right)$$

$$X_1 \xrightarrow{\kappa_1} X_2$$
$$X_2 + X_3 \xrightarrow{\kappa_2} X_1 + X_4$$
$$X_1 + X_4 \xrightarrow{\kappa_3} X_2 + X_3$$
$$X_4 \xrightarrow{\kappa_4} X_3$$

Multistationarity

Understand for what κ, c, the system

$$Nv_\kappa(x) = 0, \qquad Wx = c$$

has at least two positive solutions.

Generic tools like Cylindrical Algebraic Decomposition can theoretically answer this question, but are impractical.

The number of variables and parameters is typically too large for these approaches

There are many methods to decide whether multistationarity exists

Parameter regions for multistationarity

Goal:

find a full or partial description of the parameter that give multistationarity, or a given number of steady states.

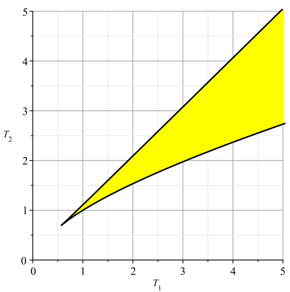


Figure by Amirhosein Sadeghimanesh

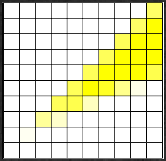
- Can we find computationally feasible approaches by using the specific structure of systems arising from reaction networks?

Some approaches to understand parameter regions

- Classical: reduction to one polynomial and analysis of the polynomial (Descartes' rule of signs, Sturm sequences...).

Recently (2016-20):

- Real triangularization, cylindrical algebraic decomposition and sampling with small number of parameters (England, Errami, Grigoriev, Radulescu, Sturm, Weber & more...).
- Numerical algebraic geometry: homotopy continuation methods (with very few parameters).
- Kac-Rice formula: computation of the expected number of steady states in a box. Works with larger number of parameters (Sadeghimanesh, Feliu).



The answer might be too complex...

$$\mathrm{HK_{00}} \xrightarrow{\kappa_1} \mathrm{HK_{p0}} \xrightarrow{\kappa_2} \mathrm{HK_{0p}} \xrightarrow{\kappa_3} \mathrm{HK_{pp}}$$
$$\mathrm{HK_{0p}} + \mathrm{RR} \xrightarrow{\kappa_4} \mathrm{HK_{00}} + \mathrm{RR_p}$$
$$\mathrm{HK_{pp}} + \mathrm{RR} \xrightarrow{\kappa_5} \mathrm{HK_{p0}} + \mathrm{RR_p}$$
$$\mathrm{RR_p} \xrightarrow{\kappa_6} \mathrm{RR}$$

The network has three positive steady states if and only if

$$a_2 > 0 \qquad 9a_0a_3 + a_1a_2 < 0$$
$$27a_0^2a_3^2 + 18a_0a_1a_2a_3 - 4a_0a_2^3 + 4a_1^3a_3 - a_1^2a_2^2 < 0 \qquad -6a_0a_2 + 2a_1^2 > 0,$$

where

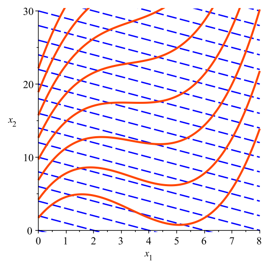
$$\begin{aligned}
a_0 &= (\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 > 0 \\
a_1 &= (\kappa_1(c_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - c_2(\kappa_1 + \kappa_2)\kappa_4\kappa_6)\kappa_5 \\
a_2 &= (\kappa_1\kappa_2\kappa_3(c_1\kappa_5 + \kappa_6) - c_2\kappa_1(\kappa_2 + \kappa_3)\kappa_5\kappa_6) \\
a_3 &= -c_2\kappa_1\kappa_2\kappa_3\kappa_6 < 0.
\end{aligned}$$

Kothamanchu, Feliu, Cardelli, Soyer (2015)

Partial answer

We say a reaction rate constant κ enables multistationarity if can we find a vector of total amounts c such that there are at least two positive steady states.

What values of κ enable multistationarity?



Theorem. Consider a network such that ... (some technical conditions). Fix κ. There exists a (computable) polynomial $p(x)$ such that

(A) Uniqueness. If

$$\text{sign}(p(x)) = + \quad \text{for all positive } x,$$

then there is exactly one positive steady state in each class.

(B) Multistationarity. If

$$\text{sign}(p(x^*)) = - \quad \text{for some positive } x^*,$$

then there are at least two positive steady states in the class of x^*.

Extra info: The result is based on Brouwer degree theory. The polynomial $p(x)$ is the determinant of the Jacobian of the system of equations evaluated at a parameterisation of the steady state variety. The technical conditions are no boundary steady states and dissipativity.

Conradi C, Feliu E, Mincheva M, Wiuf C (2017) Identifying parameter regions for multistationarity. PloS Computational Biology.

Example: Hybrid two-component system

If $\mathrm{sign}(p(x)) = +$ for all positive x, **one steady state** in each class.	If $\mathrm{sign}(p(x^*)) = -$ for one positive x^*, then there is **multistationarity** in the class of x^*.

$$\begin{aligned} \mathrm{HK}_{00} &\xrightarrow{\kappa_1} \mathrm{HK}_{p0} \xrightarrow{\kappa_2} \mathrm{HK}_{0p} \xrightarrow{\kappa_3} \mathrm{HK}_{pp} \\ \mathrm{HK}_{0p} + \mathrm{RR} &\xrightarrow{\kappa_4} \mathrm{HK}_{00} + \mathrm{RR}_p \\ \mathrm{HK}_{pp} + \mathrm{RR} &\xrightarrow{\kappa_5} \mathrm{HK}_{p0} + \mathrm{RR}_p \\ \mathrm{RR}_p &\xrightarrow{\kappa_6} \mathrm{RR} \end{aligned}$$

$$\begin{aligned} p_\kappa(x) = {} & \kappa_1\kappa_2\kappa_3\kappa_6 + (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^2 \\ & + \kappa_2\kappa_4\kappa_5^2\left(\frac{\kappa_1}{\kappa_3} - 1\right) x_4 x_5^2 + 2\kappa_1\kappa_2\kappa_4\kappa_5 x_4 x_5 \\ & + (\kappa_2+\kappa_3)\kappa_1\kappa_5\kappa_6 x_5 + \kappa_1\kappa_2\kappa_3\kappa_5 x_4 \end{aligned}$$

- If $\kappa_1 \geq \kappa_3$: sign$= +$ for all $x_4, x_5 > 0$. There exists a unique positive steady state in each class.
- If $\kappa_1 < \kappa_3$, let $x_i = T$ and T be arbitrarily large. Then sign$= -$. There is multistationarity.

κ enables multistationarity $\quad\Leftrightarrow\quad \kappa_1 < \kappa_3$

Original problem of multistationarity: Understand for what κ, c, the system

$$Nv_\kappa(x) = 0, \qquad Wx = c$$

has at least two positive solutions.

New problem: For which κ does it hold

$$p_\kappa(x^*) < 0, \qquad \text{for some positive } x^*?$$

We deal now with the question of deciding whether a polynomial is non-negative over the positive orthant.

Techniques from sum-of-squares optimization (SOS), or sums of non-negative circuits (SONC), might be employed. Still, $p_\kappa(x)$ has parametric coefficients.

Other partial answers (employing polyhedral geometry techniques):

- Partial parameter regions involving total amounts and some κ (Bihan, Dickenstein, Giaroli).
- Partial parameter regions on only total amounts for systems where $Nv_\kappa(x) = 0$ in $\mathbb{R}^n_{>0}$ is cut out by binomials (Conradi, Iosif, Kahle).

Bistability and oscillations

Exponential stability and Hopf bifurcations

Consider a system of ordinary differential equations

$$\dot{x} = f(x)$$

and x^* a steady state. Let $J_f(x^*)$ be the Jacobian of f at x^*.

- The steady state x^* is exponentially stable if all eigenvalues of $J_f(x^*)$ have negative real part. Exponential stability implies asymptotic stability.
- If at least one eigenvalue has positive real part, then x^* is unstable.
- Assume the system is parametric in μ: $\dot{x} = f_\mu(x)$. Given a non-singular steady state x^* for μ_0, there exists a curve of steady states $x^*(\mu)$ around μ_0.

  A Hopf bifurcation arises at μ_0 if a pair of eigenvalues of $J_f(x^*(\mu))$ crosses the imaginary axis, and $x^*(\mu)$ goes from stable to unstable at μ_0.

  In this case a periodic solution arises for systems with $\mu > \mu_0$.

Goal: Study the sign of the real part of the eigenvalues of $J_{f_\kappa}(x^*)$ for x^* a steady state of $\dot{x} = Nv_\kappa(x)$.

Hurwitz matrix

Given a real polynomial

$$p(z) = \alpha_0 z^n + \alpha_1 z^{n-1} + \cdots + \alpha_{n-1} z + \alpha_n, \qquad \alpha_0 > 0,$$

How many roots have positive real part and how many have negative real part?

Does it have a pair of imaginary roots?

$$H = \begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 & \dots & \dots & 0 \\ \alpha_0 & \alpha_2 & \alpha_4 & \alpha_6 & \dots & 0 \\ 0 & \alpha_1 & \alpha_3 & \alpha_5 & \dots & 0 \\ 0 & \alpha_0 & \alpha_2 & \alpha_4 & \dots & \\ \vdots & \vdots & \vdots & \vdots & \vdots & \alpha_n \end{bmatrix} \qquad H_i = i\text{-th leading principal minor.}$$

(note $H_{n-1} = \alpha_n H_{n-1}$.)

Hurwitz matrix

$$H = \begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 & \dots & \dots & 0 \\ \alpha_0 & \alpha_2 & \alpha_4 & \alpha_6 & \dots & 0 \\ 0 & \alpha_1 & \alpha_3 & \alpha_5 & \dots & 0 \\ 0 & \alpha_0 & \alpha_2 & \alpha_4 & \dots & \\ \vdots & \vdots & \vdots & \vdots & \vdots & \alpha_n \end{bmatrix} \qquad H_i = i\text{-th leading principal minor}$$

Criterion 1 (Routh-Hurwitz): Negative real part

- If $H_i > 0$ for all i, then all roots of $p(z)$ have negative real part.
- If not, if none is zero, then the number of roots with positive real part can be determined (and there is at least one).

Criterion 2 (Liu): Imaginary roots

- $p(z)$ has a simple pair of imaginary roots and the rest of the roots have negative real part, if and only if

$$H_1 > 0, \dots, H_{n-2} > 0, \qquad H_{n-1} = 0, \qquad \alpha_n > 0.$$

For reaction networks

We apply these criteria to the characteristic polynomial of the Jacobian of $Nv_\kappa(x)$ evaluated at a parametrisation of the steady states, after removing $d = n - \mathrm{Rank}(N)$ zero roots:

$$\mathrm{ch}_\kappa(\lambda) = \lambda^d \left(a_0(\kappa)\lambda^s + a_1(\kappa)\lambda^{s-1} + \cdots + a_{s-1}(\kappa)\lambda + a_s(\kappa) \right)$$

The questions on stability and Hopf bifurcation reduce to decide (determine when) the following semi-algebraic sets are non-empty:

$$\kappa_1, \ldots, \kappa_m > 0$$

$$H_1(\kappa) > 0, \ldots, H_{s-1}(\kappa) > 0, a_s(\kappa) > 0 \qquad \text{(for stability)}$$

$$H_1(\kappa) > 0, \ldots, H_{s-2}(\kappa) > 0, \quad H_{s-1}(\kappa) = 0, \quad a_s(\kappa) > 0 \quad \text{(for Hopf bifurcations)}$$

Example: enzymatic transfer of calcium ions

$X_1 =$ cytosolic calcium Ca^{++},
$X_2 = \mathrm{Ca}^{++}$ in the endoplasmic reticulum,
$X_3 =$ enzyme catalyzing the transport

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1$$

$$X_1 + X_2 \xrightarrow{\kappa_3} 2X_1$$

$$X_1 + X_3 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} X_4 \xrightarrow{\kappa_6} X_2 + X_3$$

The set of steady states is parametrized by x_4

$$x_1 = \frac{\kappa_1}{\kappa_2}, \qquad x_2 = \frac{\kappa_2\kappa_6 x_4}{\kappa_1\kappa_3}, \qquad x_3 = \frac{\kappa_2(\kappa_5+\kappa_6)x_4}{\kappa_1\kappa_4}$$

Gatermann, Eiswirth, Sensse, '05

Question

(answer using this link: http://etc.ch/XwNY)

$$\kappa_1, \dots, \kappa_m > 0$$

$$H_1(\kappa) > 0, \dots, H_{s-1}(\kappa) > 0, a_s(\kappa) > 0 \qquad \text{(for stability)}$$

$$H_1(\kappa) > 0, \dots, H_{s-2}(\kappa) > 0, \quad H_{s-1}(\kappa) = 0, \quad a_s(\kappa) > 0 \qquad \text{(for Hopf bifurcations)}$$

Here $s = 3$. The Hurwitz determinants of the characteristic polynomial of the Jacobian of the system evaluated at this parametrization are ($b_1(\kappa), \dots, b_5(\kappa) > 0$)

$$\begin{aligned}
H_1 &= b_1(\kappa)(\kappa_2^2\kappa_5 x_4 + \kappa_1^2\kappa_3 + \kappa_1^2\kappa_4 + \kappa_1\kappa_2^2 + \kappa_1\kappa_2\kappa_5 + \kappa_1\kappa_2\kappa_6) \\
H_2 &= b_2(\kappa)(\kappa_2^4\kappa_5(\kappa_3\kappa_5 + \kappa_3\kappa_6 - \kappa_4\kappa_6)x_4^2 + b_5(\kappa)x_4 + b_3(\kappa)) \\
a_3 &= b_4(\kappa)(\kappa_1\kappa_3(\kappa_1\kappa_4 + \kappa_2\kappa_5 + \kappa_2\kappa_6))
\end{aligned}$$

This network has exactly one positive steady state in each stoichiometric compatibility class. Which of the following statements is true (only one)?

(1) For all κ, the steady state in each class is asymptotically stable.

(2) For all κ, the network admits Hopf bifurcations.

(3) For some κ the steady state in all classes is asymptotically stable, and for other κ, there is a Hopf bifurcation in some class.

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1$$

$$X_1 + X_2 \xrightarrow{\kappa_3} 2X_1$$

$$X_1 + X_3 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} X_4 \xrightarrow{\kappa_6} X_2 + X_3$$

$X_1 =$ cytosolic calcium Ca^{++},
$X_2 = \mathrm{Ca}^{++}$ in the endoplasmic reticulum
$X_3 =$ enzyme catalyzing the transport

The Hurwitz determinants of the characteristic polynomial of the Jacobian of the system evaluated at this parametrization are $(b_1(\kappa), \dots, b_5(\kappa) > 0)$

$$H_1 = b_1(\kappa)(\kappa_2^2\kappa_5 x_4 + \kappa_1^2\kappa_3 + \kappa_1^2\kappa_4 + \kappa_1\kappa_2^2 + \kappa_1\kappa_2\kappa_5 + \kappa_1\kappa_2\kappa_6)$$
$$H_2 = b_2(\kappa)(\kappa_2^4\kappa_5(\kappa_3\kappa_5 + \kappa_3\kappa_6 - \kappa_4\kappa_6)x_4^2 + b_5(\kappa)x_4 + b_3(\kappa))$$
$$a_3 = b_4(\kappa)(\kappa_1\kappa_3(\kappa_1\kappa_4 + \kappa_2\kappa_5 + \kappa_2\kappa_6))$$

$H_2 = 0$ for some steady state x_4, and hence there is a pair of imaginary eigenvalues if and only if $(\kappa_3\kappa_5 + \kappa_3\kappa_6 - \kappa_4\kappa_6) < 0$, or equivalently

$$\kappa_3 < \frac{\kappa_6\kappa_4}{\kappa_5+\kappa_6}.$$

With $T = x_3 + x_4$ as bifurcation parameter, there is a Hopf bifurcation for almost all parameter values (extra condition is satisfied).

Challenges

- High computational complexity: The polynomials are HUGE (millions of terms). Often not computable.
- If the polynomials have both positive and negative terms, how do we decide the signs they attain?
- The use of convex coordinates simplifies slightly the computational cost.

Model reduction

Results relating qualitative properties of two networks F and G:

(Provided ...) if F has property X for some choice of parameter values, then so does G.

Property X can be:

- X1 Having at least ℓ positive/asymptoticaly stable/unstable (...) steady states.
- X2 Having a periodic solution.

Many such operations are known

(At least: Craciun, Feinberg, Conradi et al., Joshi, Shiu, Feliu, Cappelletti, Wiuf, Banaji, Pantea...)

- Make a reaction reversible

$$F: S + E \longrightarrow S^* + E \qquad G: S + E \rightleftharpoons S^* + E$$

Joshi, Shiu (for X1), Banaji (for X2)

- Add intermediates

$$F: S + E \longrightarrow S^* + E \qquad G: S + E \rightleftharpoons X \longrightarrow S^* + E$$

Feliu, Wiuf (for X1)

Example

This network admits 3 positive steady states

$$\mathrm{HK}_{00} \xrightarrow{\kappa_1} \mathrm{HK}_{\mathrm{p0}} \xrightarrow{\kappa_2} \mathrm{HK}_{\mathrm{0p}} \xrightarrow{\kappa_3} \mathrm{HK}_{\mathrm{pp}}$$
$$\mathrm{HK}_{\mathrm{0p}} + \mathrm{RR} \xrightarrow{\kappa_4} \mathrm{HK}_{00} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{HK}_{\mathrm{pp}} + \mathrm{RR} \xrightarrow{\kappa_5} \mathrm{HK}_{\mathrm{p0}} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{RR}_{\mathrm{p}} \xrightarrow{\kappa_6} \mathrm{RR}$$

and from here we conclude that this more realistic network also does:

$$\mathrm{HK}_{00} \xrightarrow{\kappa_1} \mathrm{HK}_{\mathrm{p0}} \xrightarrow{\kappa_2} \mathrm{HK}_{\mathrm{0p}} \xrightarrow{\kappa_3} \mathrm{HK}_{\mathrm{pp}}$$
$$\mathrm{HK}_{\mathrm{0p}} + \mathrm{RR} \underset{\kappa_7}{\overset{\kappa_4}{\rightleftharpoons}} Y_1 \xrightarrow{\kappa_8} \mathrm{HK}_{00} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{HK}_{\mathrm{pp}} + \mathrm{RR} \underset{\kappa_9}{\overset{\kappa_5}{\rightleftharpoons}} Y_2 \xrightarrow{\kappa_{10}} \mathrm{HK}_{\mathrm{p0}} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{RR}_{\mathrm{p}} \xrightarrow{\kappa_6} \mathrm{RR}$$

If $p(x)$ has a negative coefficient, is $p(x)$ negative for some $x > 0$?

$$x^2 - 2xy + y^2 = (x-y)^2 \geq 0$$

$$\text{Multivariate polynomial} \qquad f(x) = \sum_{v \in \mathbb{N}^n} \alpha_v x^v,$$

where $x^v = x_1^{v_1} \cdots x_n^{v_n}$ and $\alpha_v \in \mathbb{R}$, for which only a finite number are non-zero.

The Newton polytope of $f(x)$, $\mathcal{N}(f)$, is the convex hull of the exponents $v \in \mathbb{N}^n$ for which $\alpha_v \neq 0$.

Proposition: For every vertex v of $\mathcal{N}(f)$, there exists $x^* \in \mathbb{R}^n_{>0}$ such that

$$\operatorname{sign}(f(x^*)) = \operatorname{sign}(\alpha_v).$$

For non-vertices: the coefficient plays a role:

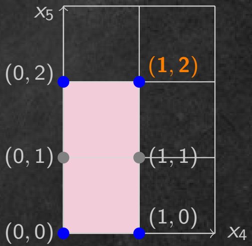
$$x^2 - 2xy + y^2 = (x-y)^2 \geq 0$$

but

$$x^2 - 3xy + y^2 = (x-y)^2 - xy < 0, \qquad \text{whenever } x = y$$

Signs and the Newton polytope

$$p(x) = \kappa_1\kappa_2\kappa_3\kappa_6 + (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^2 + \kappa_2\kappa_4\kappa_5^2\left(\frac{\kappa_1}{\kappa_3} - 1\right) x_4 x_5^2$$
$$+ 2\kappa_1\kappa_2\kappa_4\kappa_5 x_4 x_5 + (\kappa_2+\kappa_3)\kappa_1\kappa_5\kappa_6 x_5 + \kappa_1\kappa_2\kappa_3\kappa_5 x_4$$



Good news: the computation of the vertices of the Newton polytope can be "easily" carried on even for huge polynomials.

Conclusion

A recurrent problem in the study of biochemical models is to determine the parameter regions where

a semi-algebraic set has a certain number of points.

The specific structure of the systems of interest (quadratic system, linearity in the parameters) has been proven useful to give an answer, even when generic tools fail.

Some methods for precluding and asserting multistationarity

- Injectivity: Nv_κ is injective on all stoichiometric compatibility classes for all κ implies no multistationarity.
  (At least: Craciun, Feinberg, Baigent, Banaji, Conradi, Dickenstein, Donnell, Feliu, Joshi, Müller, Pantea, Pérez-Millán, Regensburger, Shinar, Shiu, Wiuf, ...)

  Easy to implement determinant-based criterion and sign-based criterion. Can also be used to assert multistationarity.
- Sign vectors: toric steady states, generalised complex balancing, sign pattern analysis (related to injectivity). (At least: Conradi, Dickenstein, Müller, Pérez-Millán, Regensburger, Shiu ...)
- Deficiency based results (including complex-balancing). Partly based on sign compatibility and solving systems of linear inequalities. (mostly Feinberg's group)
- Case-by-case approaches. Fx. reduce the problem to find the positive solutions to a polynomial in one variable, and then apply Descartes' rule of sign, Sturm sequences, adhoc results...
- User-friendly interfaces: CRNT toolbox, Windows interface, closed-source (http://www.crnt.osu.edu/CRNTWin), CoNtRol. Web interface, open-source (http://reaction-networks.net/control/)

(... and more)

Selected references for further reading

Reaction networks (algebraic perspective)

- Dickenstein, *Biochemical reaction networks: an invitation for algebraic geometers* (2016)
- Cox, *Applications of polynomials systems. Chapter 5* (2020)

Network reduction

- Joshi, Shiu, *Atoms of multistationarity* (2013)
- Feliu, Wiuf, *Simplifying Biochemical Models With Intermediate Species* (2013)
- Banaji, Pantea, *The inheritance of nondegenerate multistationarity in chemical reaction networks* (2018)
- Banaji, *Inheritance of oscillation in chemical reaction networks* (2018)
- Cappelletti, Feliu, Wiuf, *Addition of flow reactions preserving multistationarity and bistability* (2020)

Selected references for further reading

Multistationarity (algebraic/polyhedral perspective)

- Conradi, Feliu, Mincheva, Wiuf, *Identifying parameter regions for multistationarity* (2017)
- Conradi, Iosif, Kahle, *Multistationarity in the space of total concentrations for systems that admit a monomial parametrization* (2019)
- Bihan, Dickenstein, Giaroli, *Lower bounds for positive roots and regions of multistationarity in chemical reaction networks* (2020)
- Feliu, Kaihnsa, de Wolff, Yürük, *The kinetic space of multistationarity in dual phosphorylation* (2020)

Stability and Hopf bifurcations

- Kahoui, Weber, *Deciding Hopf Bifurcations by Quantifier Elimination in a Software-component Architecture* (2000)
- Conradi, Mincheva, Shiu, *Emergence of oscillations in a mixed-mechanism phosphorylation system* (2019)
- Conradi, Feliu, Mincheva, *On the existence of Hopf bifurcations in the sequential and distributive double phosphorylation cycle* (2019)
- Torres, Feliu, *Detecting parameter regions for bistability in reaction networks* (2020)

Thank you all for
your attention

(I hope to meet you all in the non-virtual Banff one day)