Lecture 10: Deciding upon multistationarity

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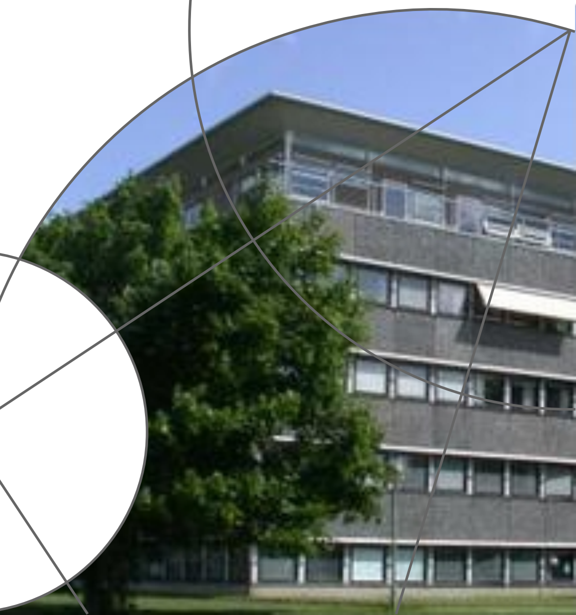

Recall some notation

- Mass-action system for $\kappa \in \mathbb{R}^r_{>0}$:

$$\dot{x} = f_\kappa(x), \qquad f_\kappa(x) = N \operatorname{diag}(\kappa) x^B,$$

  with $N \in \mathbb{R}^{n\times r}$ the stoichiometric matrix.

- $s = \operatorname{rk}(N)$, $d = n - s$.

- Matrix of conservation laws $W \in \mathbb{R}^{d\times n}$ ($W\,N = 0$ and W has full rank d.)

- Equations for the stoichiometric compatibility class given a total amount $T \in \mathbb{R}^d$:

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

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- Equations for the stoichiometric compatibility class given a total amount $T \in \mathbb{R}^d$:
$$Wx - T = 0, \qquad x \in \mathbb{R}^n_{\geq 0}.$$

- Positive steady states in a stoichiometric compatibility class are solutions to
$$F_{\kappa,T}(x) = 0, \qquad x \in \mathbb{R}^n_{>0}.$$
The function $F_{\kappa,T}$ has d rows equal to $Wx - T$, and s linearly independent polynomials among $f_\kappa(x)$.

- $C_{\kappa,T} = \{x \in \mathbb{R}^n_{>0} |\ F_{\kappa,T}(x) = 0\}$.

Multistationarity

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- Deficiency one theorem precludes multistationarity (conditions for which there is a monomial parametrization of the steady states, with exponent matrix W, as in complex balancing) (Feinberg).

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- The deficiency one algorithm to assert/preclude multistationarity (Feinberg).
- The higher deficiency algorithm decides upon multistationarity "for almost" all networks (Ellison, Feinberg, Ji, Knight). Implemented in the CRNT toolbox of Feinberg for Windows (https://cbe.osu.edu/chemical-reaction-network-theory).

Today (and next Tuesday)

Explorations of these two questions:

(1) Is there a choice of parameters $\kappa \in \mathbb{R}^r_{>0}$ and $T \in \mathbb{R}^d$ such that the set $C_{\kappa,T}$ contains at least two positive points?

(2) If the network admits multistationarity, for which values of κ, T does this occur?

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How to address the questions:

- General approaches coming from semialgebraic geometry.
- Direct approaches using ideas from univariate polynomials.
- Other methods involving the Jacobian (from semialgebraic geometry to polyhedral geometry).

A bit more on injectivity

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Recall:

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But the reverse implication holds when the positive steady state variety can be parametrized by monomials!

Monomials and injectivity

Assume:

- Monomial parametrization. There exists a matrix $M \in \mathbb{Z}^{n\times p}$ such that

$$f_\kappa(x) = 0,\ x \in \mathbb{R}^n_{>0} \quad \Leftrightarrow \quad x^M = \gamma(\kappa)$$

  (this holds for example if the ideal generated by $f_\kappa(x)$ is binomial, or if $V_{>0}(f_\kappa)$ admits a monomial parametrization for all κ.)

- The network is consistent (that is, $\ker N \cap \mathbb{R}^r_{>0} \neq \emptyset$).

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Then:

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Checkable using the sign condition $\sigma(\ker M^\top) \cap \sigma(S) = \{0\}$ or the determinant condition if $p = \dim S$

Monomials and injectivity: Proof

$f_\kappa(x) = N \operatorname{diag}(\kappa)\, x^B$

- There exists a matrix $M \in \mathbb{Z}^{n\times p}$ such that

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- The network is consistent (that is, $\ker N \cap \mathbb{R}^r_{>0} \neq \emptyset$).

x^M not injective with respect to S implies the network is multistationary

$\exists\, x, y \in \mathbb{R}^n_{>0},\ x - y \in S,\ x \neq y \quad x^M = y^M$ (*)

$\exists\, \kappa$ st $\operatorname{diag}(\kappa)\, x^B = z$, where $z \in \ker N \cap \mathbb{R}^r_{>0}$

$\hookrightarrow f_\kappa(x) = 0$

$f_\kappa(x) = 0 \iff x^M = \gamma(\kappa) \overset{(*)}{\iff} y^M = \gamma(\kappa) \iff f_\kappa(y) = 0$

$\Rightarrow$ Multist.

Recall

Our hybrid histidine kinase example:

$$\mathrm{HK}_{00} \xrightarrow{\kappa_1} \mathrm{HK}_{\mathrm{p}0} \xrightarrow{\kappa_2} \mathrm{HK}_{0\mathrm{p}} \xrightarrow{\kappa_3} \mathrm{HK}_{\mathrm{pp}}$$

$$\mathrm{HK}_{0\mathrm{p}} + \mathrm{Htp} \xrightarrow{\kappa_4} \mathrm{HK}_{00} + \mathrm{Htp}_{\mathrm{p}}$$

$$\mathrm{HK}_{\mathrm{pp}} + \mathrm{Htp} \xrightarrow{\kappa_5} \mathrm{HK}_{\mathrm{p}0} + \mathrm{Htp}_{\mathrm{p}}$$

$$\mathrm{Htp}_p \xrightarrow{\kappa_6} \mathrm{Htp}$$

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

$$X_3 + X_5 \xrightarrow{\kappa_4} X_1 + X_6$$

$$X_4 + X_5 \xrightarrow{\kappa_5} X_2 + X_6$$

$$X_6 \xrightarrow{\kappa_6} X_5$$

This network admits multistationarity.

General approaches

Semialgebraic sets

Semialgebraic sets.
A semialgebraic set in $\mathbb{R}^n$ is a finite union of sets defined by a finite number of polynomial equations and inequalities:

$$p_i(x_1,\dots,x_n) > 0, \quad i=1,\dots,r_1, \qquad q_i(x_1,\dots,x_n) = 0, \quad i=1,\dots,r_2.$$

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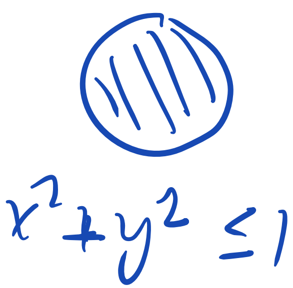
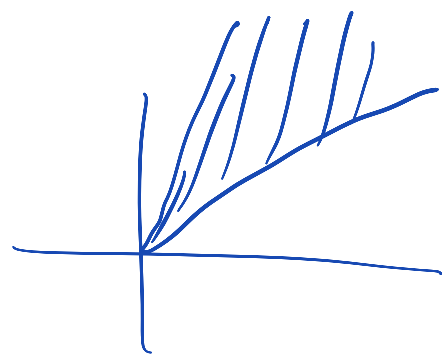
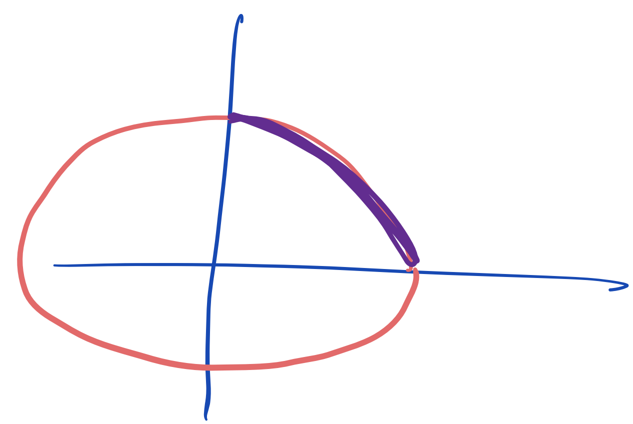
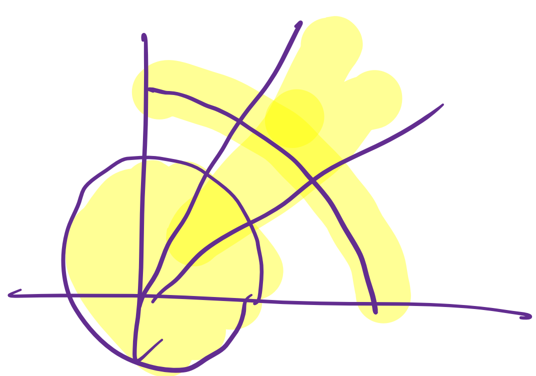
Examples:









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Any example relevant to "us"?

- $V_{>0}(f_\kappa)$
- $\mathcal{P}_{x_0}$

Semialgebraic sets

Let $\pi\colon \mathbb{R}^{n+1} \to \mathbb{R}^n$ be the projection map sending $(x_1, \dots, x_n, x_{n+1})$ to $(x_1, \dots, x_n)$.

Theorem. (Tarski-Seidenberg) If X is a semialgebraic set in $\mathbb{R}^{n+1}$ for some $n \geq 1$, then $\pi(X)$ is a semialgebraic set in $\mathbb{R}^n$.

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How can we use this?

- Nonemptyness. Consider the set of positive steady states

$$V_\kappa := \{x \in \mathbb{R}^n_{>0} \colon f_\kappa(x) = 0\}$$

and the set $K := \{\kappa \in \mathbb{R}^r_{>0} : V_\kappa \neq \emptyset\}$. Is $K \neq \emptyset$?

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K is the projection onto the κ's of the semialgebraic set

$$\mathcal{V} := \{(\kappa, x) \in \mathbb{R}^r_{>0} \times \mathbb{R}^n_{>0} \colon f_\kappa(x) = 0\}.$$

By the Tarski-Seidenberg Theorem, K is semialgebraic.

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Rephrasing: M is the projection onto the κ's of the semialgebraic set

$$\{(\kappa, x, y) \in \mathbb{R}^r_{>0} \times \mathbb{R}^n_{>0} \times \mathbb{R}^n_{>0} \colon f_\kappa(x) - f_\kappa(y) = 0, W(x-y) = 0, (x-y)^2 > 0\}$$

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- The proof of the theorem is constructive, although the way to obtain defining equations with high complexity.
- A method called Cylindrical Algebraic Decomposition of Collins gives a better approach to find the projection, but it has also high complexity.

Conclusion: we can decide upon for which κ's the steady state variety is nonempty, upon multistationarity, and to find the parameter region of multistationarity (theoretically).

Cylindrical Algebraic Decomposition (CAD)

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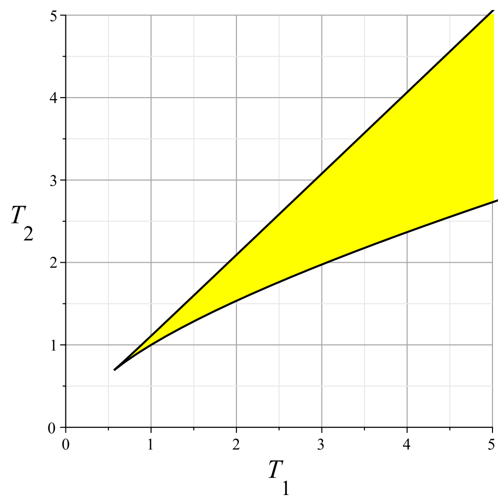

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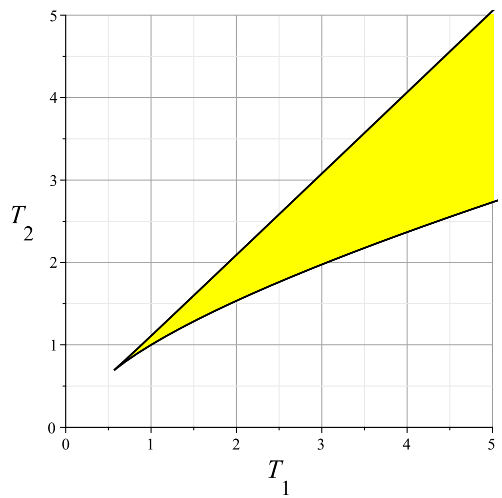
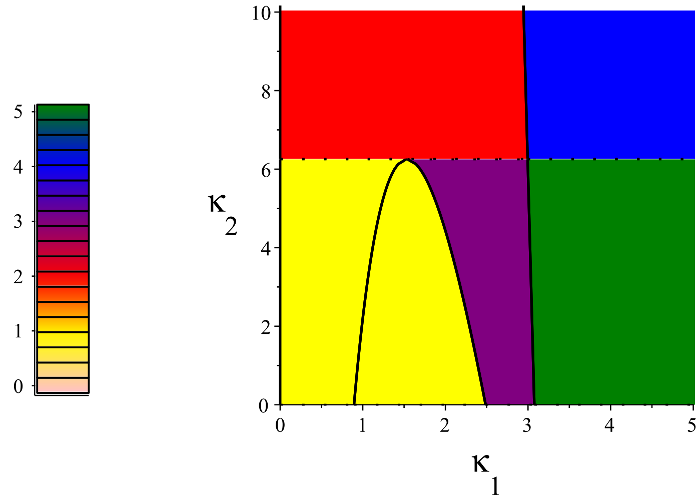


Hybrid Histidine Kinase parameter region with 3 positive steady states, for some fixed values of the κ's and only T_1, T_2 free.



Partition of the parameter region of

$$
\begin{aligned}
p_\kappa(t) = t^5 - (\kappa_1 + \tfrac{9}{2})t^4 \\
+ (\tfrac{9}{2}\kappa_1 + \tfrac{21}{4})t^3 + (-\tfrac{23}{4}\kappa_1 + \tfrac{3}{8})t^2 \\
+ (\tfrac{15}{8}\kappa_1 - \tfrac{23}{8})t + (\tfrac{1}{100}\kappa_2 - \tfrac{1}{16}).
\end{aligned}
$$

according to the number of positive roots.

Quantifier Elimination language

The Tarski-Seidenberg theorem can be expressed in terms of quantifier elimination:

For every first-order formula over the reals there exists an equivalent quantifier-free formula. Furthermore, there is an explicit algorithm to compute this quantifier-free formula.

- Example 1:

$$\exists x \in \mathbb{R} \text{ such that } x^2 + b\,x + c = 0$$

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$$b^2 - 4c \geq 0$$

- Example 2:

$$\forall x \in \mathbb{R} \text{ it holds } x^2 - c\,x + 1 > 0$$

  is transformed into a formula without quantifiers

$$c > 2$$

Discriminant

Univariate approaches

Case Study

Our hybrid histidine kinase example:

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

$$X_1 \xrightarrow{\kappa_1} X_2 \xrightarrow{\kappa_2} X_3 \xrightarrow{\kappa_3} X_4$$
$$X_3 + X_5 \xrightarrow{\kappa_4} X_1 + X_6$$
$$X_4 + X_5 \xrightarrow{\kappa_5} X_2 + X_6$$
$$X_6 \xrightarrow{\kappa_6} X_5$$

This network admits multistationarity.

Manual approach

Recall that we had the following relations:

$$
\begin{aligned}
0 &= \kappa_4 x_3 x_5 - \kappa_1 x_1 \\
0 &= \kappa_5 x_4 x_5 + \kappa_1 x_1 - \kappa_2 x_2 \\
0 &= \kappa_2 x_2 - \kappa_3 x_3 - \kappa_4 x_3 x_5 \\
0 &= \kappa_6 x_6 - \kappa_4 x_3 x_5 - \kappa_5 x_4 x_5 \\
T_1 &= x_1 + x_2 + x_3 + x_4 \\
T_2 &= x_5 + x_6 .
\end{aligned}
$$

$$
\begin{aligned}
x_1 &= \frac{\kappa_2\kappa_4\kappa_5 T_1 x_5^2}{(\kappa_1+\kappa_2\kappa_4)\kappa_5 x_5^2 + \kappa_1(\kappa_2+\kappa_3)\kappa_5 x_5 + \kappa_1\kappa_2\kappa_3} \\
x_2 &= \frac{\kappa_1(\kappa_4 x_5 + \kappa_3)\kappa_5 T_1 x_5}{(\kappa_1+\kappa_2\kappa_4)\kappa_5 x_5^2 + \kappa_1(\kappa_2+\kappa_3)\kappa_5 x_5 + \kappa_1\kappa_2\kappa_3} \\
x_3 &= \frac{\kappa_1\kappa_2\kappa_5 T_1 x_5}{(\kappa_1+\kappa_2\kappa_4)\kappa_5 x_5^2 + \kappa_1(\kappa_2+\kappa_3)\kappa_5 x_5 + \kappa_1\kappa_2\kappa_3} \\
x_4 &= \frac{\kappa_1\kappa_2\kappa_3 T_1}{(\kappa_1+\kappa_2\kappa_4)\kappa_5 x_5^2 + \kappa_1(\kappa_2+\kappa_3)\kappa_5 x_5 + \kappa_1\kappa_2\kappa_3} \\
x_6 &= T_2 - x_5 .
\end{aligned}
$$

These expressions into the remaining equation give the polynomial:

$$
\begin{aligned}
q_6(x_5) = {} & (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^3 + (\kappa_1(T_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - T_2(\kappa_1+\kappa_2)\kappa_4\kappa_6)\kappa_5 x_5^2 \\
& + (\kappa_1\kappa_2\kappa_3(T_1\kappa_5 + \kappa_6) - T_2\kappa_1(\kappa_2+\kappa_3)\kappa_5\kappa_6)x_5 - T_2\kappa_1\kappa_2\kappa_3\kappa_6 .
\end{aligned}
$$

Any positive root of q_6 provides a positive steady state.

(all roots of $q_6(x_5)$ are smaller than T_2).

Simple idea to assert multistationarity

Write the polynomial as

$$q_6(x_5) = a_3(\kappa, T)x_5^3 + a_2(\kappa, T)x_5^2 + a_1(\kappa, T)x_5 + a_0(\kappa, T)$$

- Choose any polynomial with three positive roots, e.g.

$$q(x) = (x-1)(x-2)(x-3) = x^3 - 6x^2 + 11x - 6.$$

- Find κ, T such that

$$a_3(\kappa, T) = 1, \quad a_2(\kappa, T) = -6, \quad a_1(\kappa, T) = 11, \quad a_0(\kappa, T) = -6.$$

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We find:

$$\begin{array}{llll} \kappa_1 = 0.06, & \kappa_2 = 1, & \kappa_3 = 1, & \kappa_4 = 7.5, \\ \kappa_5 = 0.12, & \kappa_6 = 1, & T_1 = 1660, & T_2 = 100. \end{array}$$

Therefore, there exist κ, T such that $q_6(x_5)$ has three positive roots. The network is multistationary.

Descartes' rule of signs

Descartes' rule of signs: if the polynomial has n positive roots, then the coefficients alternate signs and none of them are zero.

In our example

$$q_6(x_5) = (\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^3 + (\kappa_1(T_1\kappa_2\kappa_4+\kappa_2\kappa_6+\kappa_3\kappa_6) - T_2(\kappa_1+\kappa_2)\kappa_4\kappa_6)\kappa_5 x_5^2 + (\kappa_1\kappa_2\kappa_3(T_1\kappa_5+\kappa_6) - T_2\kappa_1(\kappa_2+\kappa_3)\kappa_5\kappa_6)x_5 - T_2\kappa_1\kappa_2\kappa_3\kappa_6$$

Necessary conditions for 3 positive steady states:

$$a_2(\kappa, T) = (\kappa_1(T_1\kappa_2\kappa_4+\kappa_2\kappa_6+\kappa_3\kappa_6) - T_2(\kappa_1+\kappa_2)\kappa_4\kappa_6)\kappa_5 < 0$$

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$$\begin{aligned} q_6(x_5) = &(\kappa_1+\kappa_2)\kappa_4\kappa_5\kappa_6 x_5^3 + (\kappa_1(T_1\kappa_2\kappa_4+\kappa_2\kappa_6+\kappa_3\kappa_6) - T_2(\kappa_1+\kappa_2)\kappa_4\kappa_6)\kappa_5 x_5^2 \\ &+ (\kappa_1\kappa_2\kappa_3(T_1\kappa_5+\kappa_6) - T_2\kappa_1(\kappa_2+\kappa_3)\kappa_5\kappa_6)x_5 - T_2\kappa_1\kappa_2\kappa_3\kappa_6 \end{aligned}$$

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Descartes' rule of signs

$\downarrow$

$p(x)$ of degree n has n positive roots	$\Rightarrow$ / $\not\Leftarrow$	signs of the coefficients of $p(x)$ alternate

Sturm's theorem

$p(x)$ real univariate polynomial.

- Sturm sequence:

$$p_0(x) = p(x),\ p_1(x) = p'(x), \quad \text{and} \quad p_{i+1}(x) = -\mathrm{rem}(p_{i-1}, p_i),$$

  for $i \geq 1$. The sequence stops when $p_{i+1} = 0$. p_m last nonzero polynomial.
- For $c \in \mathbb{R}$, let

$$\sigma(c) = \text{number of sign changes in } p_0(c), \ldots, p_m(c).$$

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Sturm's theorem. Let $a < b$ and assume that neither a nor b are multiple roots of $p(x)$. Then

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- For positive roots, $(0, +\infty)$, $p_i(+\infty)$ = coefficient of highest degree.
- If degree of p is n and $m = n$, then p has n positive roots if and only if

$$\sigma(0) = n, \qquad \sigma(+\infty) = 0.$$

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$$p_0(x) = p(x),\ p_1(x) = p'(x), \quad \text{and} \quad p_{i+1}(x) = -\mathrm{rem}(p_{i-1}, p_i), \qquad i \geq 1$$
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Example 2. $p(x) = x^3 - 3x^2 - 3x + 1$.

$$p_0(0) = 1, \qquad p_1(0) = -3, \qquad p_2(0) = 0, \qquad p_3(0) = 3$$

$$p_0(+\infty) = 1, \qquad p_1(+\infty) = 3, \qquad p_2(+\infty) = 4, \qquad p_3(+\infty) = 3.$$

$\sigma(0) = 2$

$\sigma(\infty) = 0$

roots in $(0, +\infty)$ is

$2 - 0 = 2$

Sturm's theorem

$p_0(x) = a_3x^3 + a_2x^2 + a_1x + a_0$. The sequence is:

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$$p_1(x) = 3a_3x^2 + 2a_2x + a_1 \qquad p_3(x) = -\frac{9a_3(27a_3^2a_0^2 - 18\,a_3a_2a_1a_0 + 4a_0a_2^3 + 4a_1^3a_3 - a_2^2a_1^2)}{4(3a_3a_1 - a_2^2)^2}.$$

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In our case, the coefficients are:

$$\begin{aligned}
a_3 &= (\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 > 0 \\
a_2 &= (\kappa_1(T_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - T_2(\kappa_1 + \kappa_2)\kappa_4\kappa_6)\kappa_5 \\
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a_0 &= -T_2\kappa_1\kappa_2\kappa_3\kappa_6 < 0.
\end{aligned}$$

Three positive steady states if and only if

$$a_1 > 0 \qquad 27a_3^2a_0^2 - 18\,a_3a_2a_1a_0 + 4a_0a_2^3 + 4a_1^3a_3 - a_2^2a_1^2 < 0$$

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$$9a_0a_3 - a_1a_2 > 0 \qquad -3a_1a_3 + a_2^2 > 0$$

If we can show that the solution set of these inequalities (a semialgebraic set!) is nonempty, then we will have three positive solutions.

Problem: The expressions coming from Sturm's Theorem can be difficult to work with when coefficients are parametric...

Real rooted polynomials

Definition. A univariate polynomial $p(x)$ is said to be real rooted if all its roots are real.

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Newton Inequalities. Let $p(x) = a_n x^n + \cdots + a_1 x + a_0$, with $a_i \geq 0$, $i = 0, \dots, n$ (all coefficients nonnegative). If $p(x)$ is real rooted, then

$$\frac{a_k^2}{\binom{n}{k}^2} \geq \frac{a_{k-1}}{\binom{n}{k-1}} \cdot \frac{a_{k+1}}{\binom{n}{k+1}}$$

These give necessary conditions for being real rooted. But they are not sufficient!

Kurtz Theorem

A theorem on real rooted polynomials (Kurtz '92)

Let $p(x) = x^{2m+1} - a_{2m}x^{2m} + a_{2m-1}x^{2m-1} - \cdots + a_1 x - a_0$ with $a_i \geq 0$, and let $a_{2m+1} = 1$ (a polynomial with alternating signs).

If

$$a_i^2 - 4a_{i-1}a_{i+1} > 0, \qquad i = 1, \ldots, 2m$$

then $p(x)$ has $2m+1$ distinct positive real roots.

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Examples.

- $q(x) = x^3 - 6x^2 + 8x - 1$: $a_3 = 1$, $a_2 = 6$, $a_1 = 8$, $a_0 = 1$.
  Kurtz inequalities are satisfied:

  $$0 < a_1^2 - 4a_0a_2 = 8^2 - 4 \cdot 1 \cdot 6 = 40, \qquad 0 < a_2^2 - 4a_1a_3 = 6^2 - 4 \cdot 8 \cdot 1 = 4.$$

  So the polynomial has three positive real roots.

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  So the polynomial has three positive real roots.
- $q(x) = x^3 - 6x^2 + 11x - 6$: $a_3 = 1$, $a_2 = 6, a_1 = 11, a_0 = 6$.
  Kurtz inequalities are not satisfied
  $$0 < a_1^2 - 4a_0a_2 = 11^2 - 4 \cdot 6 \cdot 6 = -23 \text{ !!}$$

Kurtz Theorem for hybrid HK

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Imposing the conditions from Descartes Rule of Signs to the Hybrid HK network:

$$\begin{aligned} a_2(\kappa, T) &= (\kappa_1(T_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - T_2(\kappa_1 + \kappa_2)\kappa_4\kappa_6)\kappa_5 < 0 \\ a_1(\kappa, T) &= (\kappa_1\kappa_2\kappa_3(T_1\kappa_5 + \kappa_6) - T_2\kappa_1(\kappa_2 + \kappa_3)\kappa_5\kappa_6) > 0 \end{aligned}$$

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Kurtz Theorem tells me that if

$$a_2(\kappa, T)^2 - 4(\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 a_1(\kappa, T) > 0, \qquad a_1(\kappa, T)^2 - 4a_2(\kappa, T)\, T_2\kappa_1\kappa_2\kappa_3\kappa_6 > 0,$$

then the polynomial will have 3 positive real roots.

Recall:

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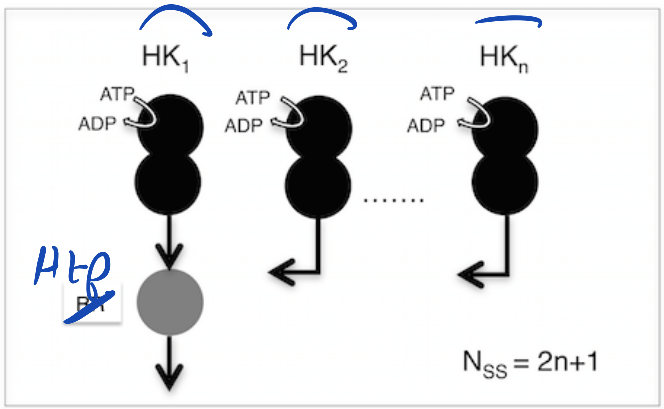
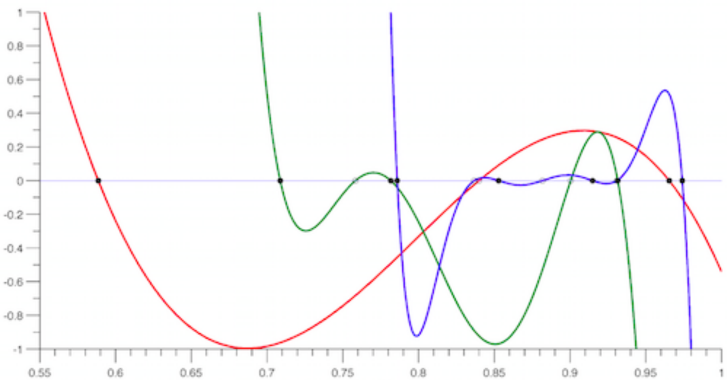
With some work, it is possible to show that this semialgebraic set is nonempty

General system





Steady states are in one-to-one correspondence with the positive roots of:

$$p_n(x) = a_{2n+1}(\kappa, T)x^{2n+1} + \cdots + a_1(\kappa, T)x + a_0(\kappa, T) \qquad x = [\mathrm{Htp}]$$

- One can construct parameters κ, T such that the coefficients $a_i(\kappa, T)$ fulfil the conditions of Kurtz theorem.

The system can have up to $2n+1$ steady states

(further: alternating ones are unstable)

Kothamanchu VB, Feliu E, Cardelli L, Soyer OS (2015) Unlimited multistability and Boolean logic in microbial signaling. Journal of the Royal Society Interface. 12:108, 20150234

Parameter regions

$$\Omega := \{(\kappa, T) \in \mathbb{R}^6_{>0} \times \mathbb{R}^2_{>0} \colon q_6 \text{ has 3 positive roots}\}.$$

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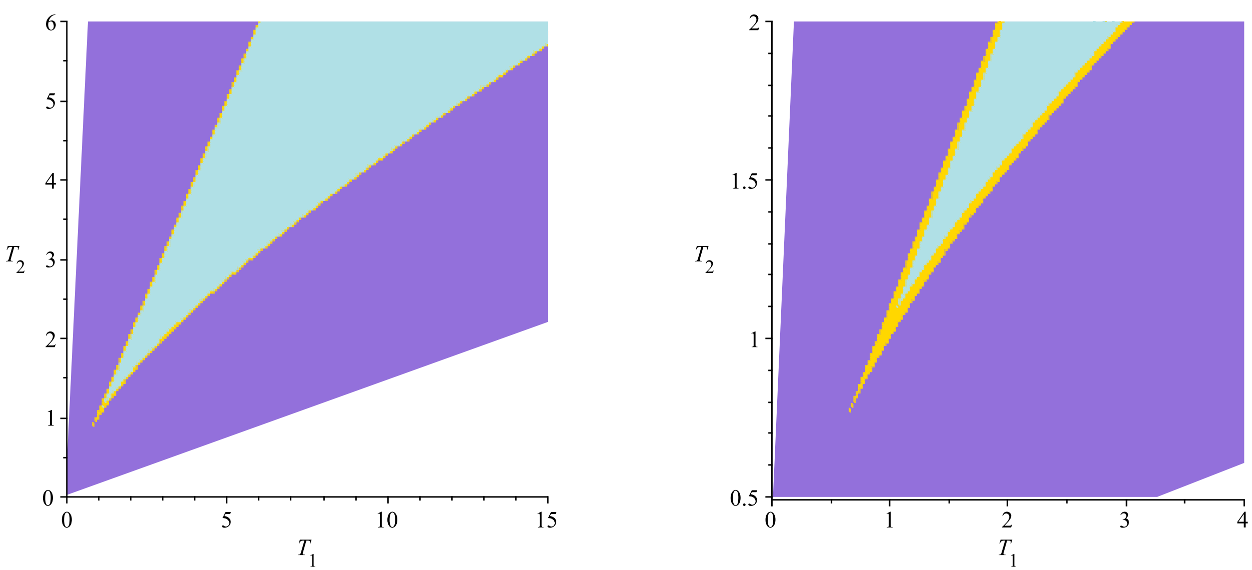
- Kurtz theorem gives a region contained in Ω.

Illustration in 2D



Purple: Descartes' rule of signs; Yellow: exact region; Blue: Kurtz theorem.

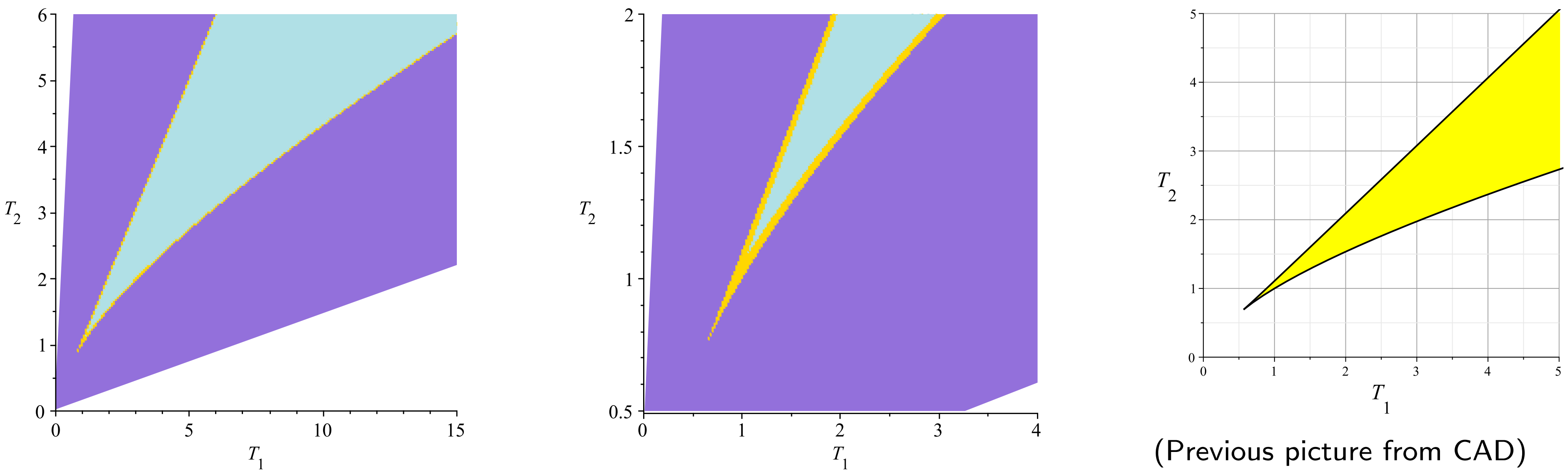
Reaction rate constants: $\kappa_1 = \frac{7329}{10000}, \kappa_2 = 100, \kappa_3 = \frac{7329}{100}, \kappa_4 = 50, \kappa_5 = 100, \kappa_6 = 5.$

Parameter regions

$$\Omega := \{(\kappa, T) \in \mathbb{R}^6_{>0} \times \mathbb{R}^2_{>0} \colon q_6 \text{ has 3 positive roots}\}.$$

- Sturm's theorem gives Ω.
- Descartes' rule of signs gives a set that contains Ω.
- Kurtz theorem gives a region contained in Ω.

Illustration in 2D



(Previous picture from CAD)

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Reaction rate constants: $\kappa_1 = \frac{7329}{10000}, \kappa_2 = 100, \kappa_3 = \frac{7329}{100}, \kappa_4 = 50, \kappa_5 = 100, \kappa_6 = 5.$

Sturm's theorem

$p_0(x) = a_3 x^3 + a_2 x^2 + a_1 x + a_0.$

$$
\begin{aligned}
a_3 &= (\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 > 0 \\
a_2 &= (\kappa_1(T_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - T_2(\kappa_1 + \kappa_2)\kappa_4\kappa_6)\kappa_5 \\
a_1 &= \kappa_1\kappa_2\kappa_3(T_1\kappa_5 + \kappa_6) - T_2\kappa_1(\kappa_2 + \kappa_3)\kappa_5\kappa_6 \\
a_0 &= -T_2\kappa_1\kappa_2\kappa_3\kappa_6 < 0.
\end{aligned}
$$

Three positive steady states if and only if

$$
\begin{aligned}
a_1 &> 0 & 27a_3^2a_0^2 - 18\, a_3 a_2 a_1 a_0 + 4a_0 a_2^3 + 4a_1^3 a_3 - a_2^2 a_1^2 &< 0 \\
9a_0 a_3 - a_1 a_2 &> 0 & -3a_1 a_3 + a_2^2 &> 0
\end{aligned}
$$

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\end{aligned}$$

Three positive steady states if and only if

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$$9a_0a_3 - a_1a_2 > 0 \qquad -3a_1a_3 + a_2^2 > 0$$

What if I tell you that the projection onto the κ-space
is the region with $\kappa_3 > \kappa_1$?

Jacobian-based methods

Jacobian criterion

Injectivity and Jacobians:
Let $F \colon U \to \mathbb{R}^n$, $U \subseteq \mathbb{R}^n$ continuously differentiable, such that each coordinate of F is either a polynomial of degree 1 or 2. Then F is injective if

$$\det(J_F(x)) \neq 0 \qquad x \in U.$$

(Bass), (Pantea, Koeppl, Craciun)

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Example.

$$F_{\kappa,T} = (\kappa_4 x_3 x_5 - \kappa_1 x_1, \kappa_5 x_4 x_5 + \kappa_1 x_1 - \kappa_2 x_2, \kappa_2 x_2 - \kappa_3 x_3 - \kappa_4 x_3 x_5,$$
$$\kappa_6 x_6 - \kappa_4 x_3 x_5 - \kappa_5 x_4 x_5, x_1 + x_2 + x_3 + x_4 - T_1, x_5 + x_6 - T_2)$$

Then

$$J_{F_{\kappa,T}}(x) = \begin{pmatrix} -\kappa_1 & 0 & \kappa_4 x_5 & 0 & \kappa_4 x_3 & 0 \\ \kappa_1 & -\kappa_2 & 0 & \kappa_5 x_5 & \kappa_5 x_4 & 0 \\ 0 & \kappa_2 & -\kappa_4 x_5 - \kappa_3 & 0 & -\kappa_4 x_3 & 0 \\ 0 & 0 & -\kappa_4 x_5 & -\kappa_5 x_5 & -\kappa_4 x_3 - \kappa_5 x_4 & \kappa_6 \\ 1 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}$$

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Example.

$$F_{\kappa,T} = (\kappa_4 x_3 x_5 - \kappa_1 x_1, \kappa_5 x_4 x_5 + \kappa_1 x_1 - \kappa_2 x_2, \kappa_2 x_2 - \kappa_3 x_3 - \kappa_4 x_3 x_5, \kappa_6 x_6 - \kappa_4 x_3 x_5 - \kappa_5 x_4 x_5, x_1 + x_2 + x_3 + x_4 - T_1, x_5 + x_6 - T_2)$$

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$$\det(J_{F_{\kappa,T}}(x)) = -(\kappa_1 - \kappa_3)\kappa_2\kappa_4\kappa_5 x_3 x_5 - \kappa_1\kappa_2\kappa_3\kappa_4 x_3 - \kappa_1\kappa_2\kappa_4\kappa_5 x_4 x_5 - \kappa_1\kappa_2\kappa_3\kappa_5 x_4 - (\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 x_5^2 - (\kappa_2 + \kappa_3)\kappa_1\kappa_5\kappa_6 x_5 - \kappa_1\kappa_2\kappa_3\kappa_6$$

If $\kappa_1 \geq \kappa_3$, then no multistationarity.

So, $\kappa_1 < \kappa_3$ is necessary for multistationarity.

(Bass), (Pantea, Koeppl, Craciun)

Teaser for next Tuesday

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

(A) Uniqueness. If

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

then $\#C_{\kappa,T} = 1$ for all T.

(B) Multistationarity. If

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

then $\#C_{\kappa,T} \geq 2$ for some T.

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With this we will be able to prove that there exists T such that the hybrid HK network is multistationary if and only if $\kappa_3 > \kappa_1$.

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With this we will be able to prove that there exists T such that the hybrid HK network is multistationary if and only if $\kappa_3 > \kappa_1$.

Need: Understand how to decide whether a polynomial attains negative values over the positive orthant. You'll learn about this on Monday!