Dynamics of chemical reaction networks and positivity of polynomials

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Goal

GOAL
Give an insight on how studying the positivity of a polynomial $p(x_1, \ldots, x_n)$ in $\mathbb{R}^n_{>0}$, is used to detect different dynamic behaviors in a Chemical Reaction Network.

Outline

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What is a Chemical Reaction Network?

$$\mathsf{HK} \longrightarrow \mathsf{HK_P} \qquad \mathsf{HK_p} + \mathsf{RR} \longrightarrow \mathsf{HK} + \mathsf{RR_p} \qquad \mathsf{RR_p} \longrightarrow \mathsf{RR}.$$

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We study the change of concentration of the species, through time.

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$$\mathsf{X}_1 \longrightarrow \mathsf{X}_2 \qquad \mathsf{X}_2 + \mathsf{X}_3 \longrightarrow \mathsf{X}_1 + \mathsf{X}_4 \qquad \mathsf{X}_4 \longrightarrow \mathsf{X}_3$$

In this example $n = 4$ and $\mathcal{S} = \{X_1, X_2, X_3, X_4\}$.

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What happens when each reaction occurs?

$$N_1 = \begin{pmatrix} -1 \\ 1 \\ 0 \\ 0 \end{pmatrix} \qquad N_2 = \begin{pmatrix} 1 \\ -1 \\ -1 \\ 1 \end{pmatrix} \qquad N_3 = \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \end{pmatrix}$$

The subspace $S = \mathrm{Span}\{N_1, N_2, N_3\}$ is called the stoichiometric subspace.

System of ODEs

$$X_1 \longrightarrow X_2 \qquad X_2 + X_3 \longrightarrow X_1 + X_4 \qquad X_4 \longrightarrow X_3$$

Under mass action kinetics, we assume that the rate of occurrence of each reaction is proportional to the product of the species in the origin of the reaction.

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The dynamics of the system are given by

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \begin{pmatrix} N_1 & N_2 & N_3 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix} = \begin{pmatrix} -\kappa_1 x_1 + \kappa_2 x_2 x_3 \\ \kappa_1 x_1 - \kappa_2 x_2 x_3 \\ -\kappa_2 x_2 x_3 + \kappa_3 x_4 \\ \kappa_2 x_2 x_3 - \kappa_3 x_4 \end{pmatrix}$$

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In general...

- N is a $n \times m$ matrix, where m is the amount of reactions. Its column span is the stoichiometric subspace.

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In general...

- N is a $n \times m$ matrix, where m is the amount of reactions. Its column span is the stoichiometric subspace.
- The function f(x)=Nv is called the rate function.
- The reaction rate constants $\kappa_1, \ldots \kappa_m$ are positive.

Steady states

The steady states are the non-negative points where the vector of derivatives of the concentrations is zero.

$$\dot{x} = 0 = f(x).$$

The positive steady states are the solutions to $0 = f(x)$ that are in the positive orthant.

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$$\begin{aligned} 0 &= -\kappa_1 x_1 + \kappa_2 x_2 x_3 \\ 0 &= \kappa_1 x_1 - \kappa_2 x_2 x_3, \\ 0 &= -\kappa_2 x_2 x_3 + \kappa_3 x_4 \\ 0 &= \kappa_2 x_2 x_3 - \kappa_3 x_4 \end{aligned}$$

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$$\phi(x_2, x_4) = \left(\frac{\kappa_3 x_4}{\kappa_1}, x_2, \frac{\kappa_3 x_4}{\kappa_2 x_2}, x_4 \right). \tag{1}$$

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The vector Wx_0 is denoted by T and is called the *vector of total amounts*.

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Conservation laws

$$\begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} T_1 \\ T_2 \\ T_3 \\ T_4 \end{pmatrix}.$$

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Conservation laws

$$x_1 + x_2 = T_1 \qquad x_3 + x_4 = T_2$$

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STABILITY

Consider a system of differential equations $\frac{dx}{dt} = f(x)$, with $f \in \mathcal{C}^1$, and a steady state x^*.

The steady state x^* is *asymptotically stable* if all the eigenvalues of $J_f(x^*)$ have negative real part. If one of the eigenvalues of $J_f(x^*)$ has positive real part, then x^* is *unstable*.

Stability: Hurwitz criterion.

Let $p(x) = a_n x^n + a_{n-1} x^{n-1} + \ldots + a_1 x + a_0$ be a polynomial with $a_i \in \mathbb{R}$, $a_n > 0$ and $a_0 \neq 0$. The Hurwitz matrix associated to p is

$$H = \begin{pmatrix} a_{n-1} & a_n & 0 & 0 & \cdots & 0 \\ a_{n-3} & a_{n-2} & a_{n-1} & a_n & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & a_{6-n} & \cdots & a_2 \\ 0 & 0 & 0 & 0 & \cdots & a_0 \end{pmatrix}$$

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Example

In our example

$$\mathrm{X}_1 \xrightarrow{\kappa_1} \mathrm{X}_2 \qquad \mathrm{X}_2 + \mathrm{X}_3 \xrightarrow{\kappa_2} \mathrm{X}_1 + \mathrm{X}_4 \qquad \mathrm{X}_4 \xrightarrow{\kappa_3} \mathrm{X}_3.$$

We compute J_f and evaluate at $\phi(x_2, x_4)$.

$$J_f(\phi(x_2,x_4)) = \begin{pmatrix} -\kappa_1 & \frac{\kappa_3 x_4}{x_2} & \kappa_2 x_2 & 0 \\ \kappa_1 & -\frac{\kappa_3 x_4}{x_2} & -\kappa_2 x_2 & 0 \\ 0 & -\frac{\kappa_3 x_4}{x_2} & -\kappa_2 x_2 & \kappa_3 \\ 0 & \frac{\kappa_3 x_4}{x_2} & \kappa_2 x_2 & -\kappa_3 \end{pmatrix}$$

Example

The characteristic polynomial of $J_f(x^*)$, $p_{J_f}(\lambda)$, and factor λ^d, where d is the amount of conservation laws.

$$p_{J_f}(\lambda) = \lambda^4 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda^3 + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}\lambda^2$$

$$= \lambda^2 \left(\lambda^2 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}\right)$$

Example

The polynomial we have to study is.

$$q_f(\lambda) = \lambda^2 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}$$

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The Hurwitz determinants are

$$H_1 = \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}$$

$$H_2 = \frac{(\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4)(\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4)}{x_2^2}$$

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For all choice of reaction rate constants and total amounts, the steady state is asymptotically stable.

A second example

Consider the following network

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

In this case the characteristic polynomial of $J_f(\varphi)$, has degree 4 which means that we have to analyse 4 Hurwitz determinants.

A second example

H_1, H_2 and H_3 are polynomials with positive coefficients.

$$H_4 = \frac{1}{\kappa_3}\left((\kappa_1+\kappa_2)\kappa_3\kappa_4\kappa_5\kappa_6 x_5^2 + \kappa_2\kappa_4\kappa_5^2(\kappa_1-\kappa_3)x_4x_5^2 \right.$$
$$+ 2\kappa_2\kappa_2\kappa_3\kappa_4\kappa_5 x_4 x_5 + \kappa_1(\kappa_2+\kappa_3)\kappa_3\kappa_5\kappa_6 x_5 + \kappa_1\kappa_2\kappa_3^2\kappa_5 x_4 +$$
$$\left.\kappa_1\kappa_2\kappa_3^2\kappa_6\right) H_3$$

Stability depends on the sign of the first factor.

A second example

The Newton polytope of

$$p(x_4, x_5) = \frac{1}{\kappa_3}\Big((\kappa_1+\kappa_2)\kappa_3\kappa_4\kappa_5\kappa_6 x_5^2 + \kappa_2\kappa_4\kappa_5^2(\kappa_1-\kappa_3)x_4x_5^2 + 2\kappa_2\kappa_2\kappa_3\kappa_4\kappa_5 x_4 x_5 + \kappa_1(\kappa_2+\kappa_3)\kappa_3\kappa_5\kappa_6 x_5 + \kappa_1\kappa_2\kappa_3^2\kappa_5 x_4 + \kappa_1\kappa_2\kappa_3^2\kappa_6\Big)$$

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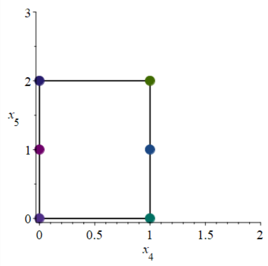

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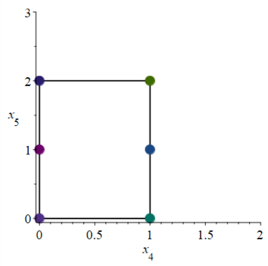

If $\kappa_3 > \kappa_1$ it is possible to find one unstable steady state. Otherwise, all the steady states are asymptotically stable.

What do we need for bigger networks?

When using algebraic parameterizations, computing the Hurwitz determinants and studying their sign is computationally expensive.

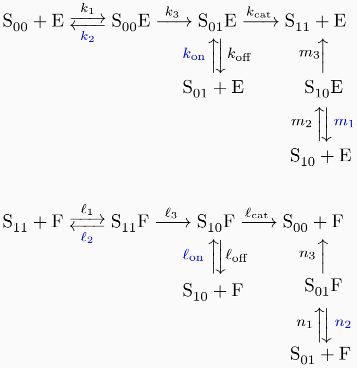

Figure 1: Model of ERK regulation

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Model or ERK regulation

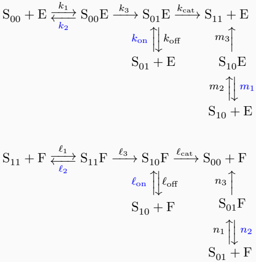

Figure 2: Model of ERK regulation

N. Obatake, A. Shiu, X. Tang, ·

- There is a set of parameters where the model of ERK regulation is bistable.
- Bistability arises only if $\kappa_{on} > 0$ or $\ell_{on} > 0$.

Bistability in a CRN

	Network	Reduced network
(a)	$S_0 + E \rightleftharpoons S_0E \rightarrow S_1 + E$	$S_0 + E \rightarrow S_0E \rightarrow S_1 + E$
	$S_1 + E \rightleftharpoons S_1E \rightarrow S_2 + E$	$S_1 + E \rightarrow S_1E \rightarrow S_2 + E$
	$S_1 + F_1 \rightleftharpoons S_1F_1 \rightarrow S_0 + F_1$	$S_1 + F_1 \rightarrow S_0 + F_1$
	$S_2 + F_2 \rightleftharpoons S_2F_2 \rightarrow S_1 + F_2$	$S_2 + F_2 \rightarrow S_1 + F_2$

E. Feliu, ·
Procedure to detect bistability by studying model reductions of a network.

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	$S_1 + F_1 \rightleftharpoons S_1F_1 \to S_0 + F_1$	$S_1 + F_1 \to S_0 + F_1$
	$S_2 + F_2 \rightleftharpoons S_2F_2 \to S_1 + F_2$	$S_2 + F_2 \to S_1 + F_2$

E. Feliu, ·
Procedure to detect bistability by studying model reductions of a network.

THANK YOU!