Faculty of Science

Dynamical aspects of reaction networks

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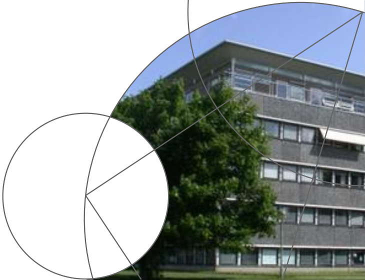


What we have seen so far!

- Framework to study reaction networks (stoichiometric matrix, stoichiometric compatibility classes...)
- Tools to study the steady state variety: Gröbner bases, linear elimination
- Multistationarity: injectivity theorem, multistationarity via Brouwer degree and the use of polyhedral geometry techniques and nonnegativity, binomial ideals and monomial parametrizations; partial parameter regions for multistationarity
- Special networks: complex balancing (one steady state that is asymptotically stable); MESSI systems; PTM systems
- Next: what about the dynamics?

Some dynamical aspects

$\dot{x} = f(x)$ an ODE system.

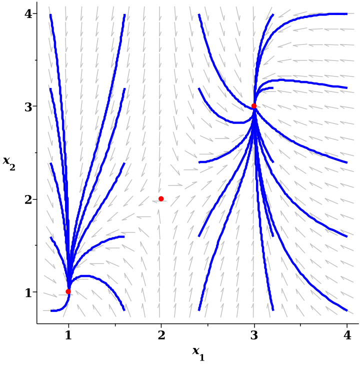
- If a trajectory $x(t)$ is defined for all $t \geq 0$ and converges to a point x^* when t goes to infinity, then x^* is a steady state.
- For a conservative network, trajectories are defined for all $t \geq 0$ and there exists a nonnegative steady state in each stoichiometric compatibility class.

  This is because the stoichiometric compatibility classes are compact and homeomorphic to a closed ball, and by the Brouwer fix point theorem.
- (Boros) All weakly reversible networks have at least a positive steady state in each stoichiometric compatibility class.
- Today: stability and Hopf bifurcations.

Why bistability and oscillations are interesting

Bistability

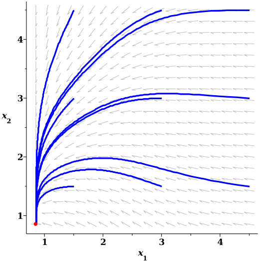
Robust switch-like behavior is important in cell signaling.



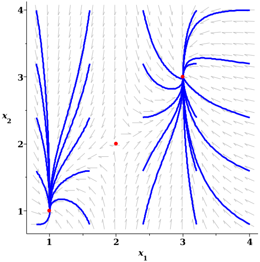
$$\frac{dx_1}{dt} = -x_1^3 + 6x_1^2 - 11x_1 + 6, \qquad \frac{dx_2}{dt} = x_1 - x_2.$$

Bistability

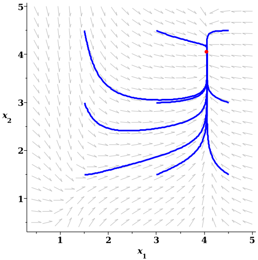
$$\frac{dx_1}{dt} = -x_1^3 + \kappa\, x_1^2 - 11x_1 + 6, \qquad \frac{dx_2}{dt} = x_1 - x_2.$$



$\kappa = 5.5$



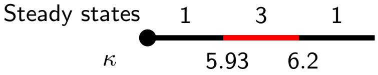
$\kappa = 6$

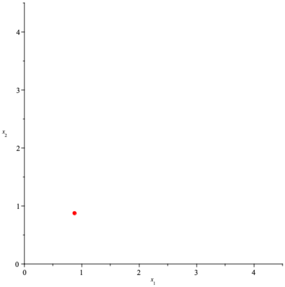


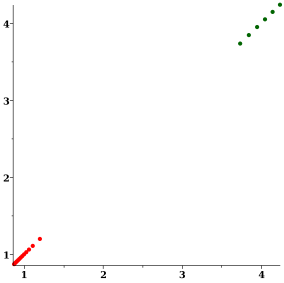
$\kappa = 6.4$

Bistability

$$\frac{dx_1}{dt} = -x_1^3 + \kappa\, x_1^2 - 11x_1 + 6$$
$$\frac{dx_2}{dt} = x_1 - x_2.$$







Bistability

$$\frac{dx_1}{dt} = -x_1^3 + \kappa\, x_1^2 - 11x_1 + 6$$
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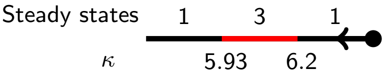

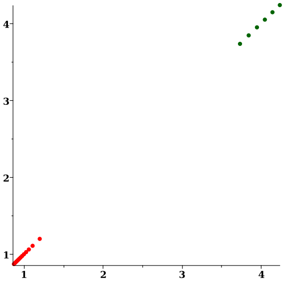

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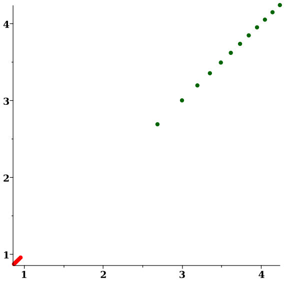

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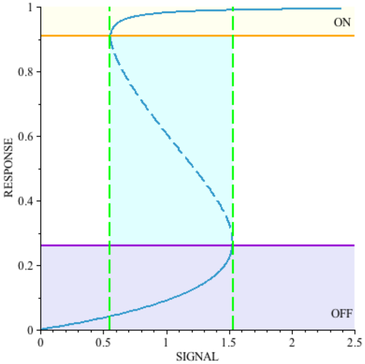
Bistability

Robust switch-like behavior is important in cell signaling via hysteresis

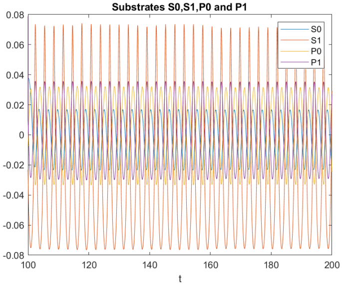


Response = Concentration of one of the species/proteins

Signal = One of the parameters of the system

Oscillations

Periodicity is abundant in biological systems: circadian rythm, cell cycle...



How to detect the presence of periodic solutions? Typical approaches for biochemical networks involve:

- Identification of a Hopf bifurcation.
- Identification of relaxation oscillations.

Some definitions

Exponential stability

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: trajectories starting nearby converge to the steady state.

- If at least one eigenvalue has positive real part, then x^* is unstable: there are always trajectories starting arbitrarily close to the steady state that diverge.

Hopf bifurcations

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.

At μ_0: $J_f(x^*(\mu_0))$ has a pair of purely imaginary eigenvalues.

In this case a periodic solution arises for systems with $\mu > \mu_0$. The periodic orbit can be stable or unstable.

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

Examples

1. Assume the Jacobian matrix evaluated at a steady state is

$$\begin{pmatrix} -1 & 2 & -4 \\ -5 & 3 & 2 \\ 5 & -2 & -7 \end{pmatrix}$$

The characteristic polynomial is

$$\det \begin{pmatrix} -1-y & 2 & -4 \\ -5 & 3-y & 2 \\ 5 & -2 & -7-y \end{pmatrix} = y^3 + 5y^2 + 17y + 13.$$

The roots are:

$$-1, -2-3i, -2+3i.$$

As all have negative real part, the steady state is exponentially stable and hence asymptotically stable.

2. Assume the Jacobian matrix evaluated at a steady state is

$$\begin{pmatrix} 5 & -2 & -8 \\ -1 & 1 & -2 \\ 7 & -4 & -7 \end{pmatrix}$$

The characteristic polynomial is

$$y^3 + y^2 + 19y + 9.$$

The roots are:

$$-1, -3i, 3i.$$

There is a pair of purely imaginary eigenvalues. There might be a Hopf bifurcation.

In our application

The matrices are symbolic, for instance

$$\begin{pmatrix} 5\lambda_1 & -2\lambda_2 & -8\lambda_3 \\ -\lambda_1 & \lambda_2 & -2\lambda_3 \\ 7\lambda_1 & -4\lambda_2 & -7\lambda_3 \end{pmatrix}$$

Is there λ_i such that this matrix has a pair of purely imaginary eigenvalues?

The characteristic polynomial is

$$p(y) = y^3 - (-7\lambda_3 + \lambda_2 + 5\lambda_1)y^2 - (-3\lambda_1\lambda_2 - 21\lambda_1\lambda_3 + 15\lambda_2\lambda_3)y + 9\lambda_1\lambda_2\lambda_3.$$

How to study the roots?

Is there a choice of parameters for which this solution consists of a pair of purely imaginary eigenvalues?

> *solve(p, y)*

$$\frac{1}{6}\Big(60 \lambda_1^2 \lambda_2 - 7980 \lambda_1^2 \lambda_3 + 12 \lambda_1 \lambda_2^2 + 48 \lambda_3 \lambda_1 \lambda_2 + 11172 \lambda_1 \lambda_3^2 + 372 \lambda_2^2 \lambda_3 - 2604 \lambda_2 \lambda_3^2 + 1000 \lambda_1^3 + 8 \lambda_2^3 - 2744 \lambda_3^3$$

$$+ 36\sqrt{-75 \lambda_1^4 \lambda_2^2 - 2550 \lambda_1^4 \lambda_2 \lambda_3 - 3675 \lambda_1^4 \lambda_3^2 + 6 \lambda_1^3 \lambda_2^3 + 1206 \lambda_1^3 \lambda_2^2 \lambda_3 + 23982 \lambda_1^3 \lambda_2 \lambda_3^2 + 22638 \lambda_1^3 \lambda_3^3 - 3 \lambda_1^2 \lambda_2^4 - 258 \lambda_1^2 \lambda_2^3 \lambda_3 - 9942 \lambda_1^2 \lambda_2^2 \lambda_3^2 - 57918 \lambda_1^2 \lambda_2 \lambda_3^3 - 7203 \lambda_1^2 \lambda_3^4 + 18 \lambda_1 \lambda_2^4 \lambda_3 + 1182 \lambda_1 \lambda_2^3 \lambda_3^2 + 26586 \lambda_1 \lambda_2^2 \lambda_3^3 + 14406 \lambda_1 \lambda_2 \lambda_3^4 - 75 \lambda_2^4 \lambda_3^2 - 3450 \lambda_2^3 \lambda_3^3 - 3675 \lambda_2^2 \lambda_3^4}\Big)^{1/3} - \Big(6\Big(-\frac{1}{9} \lambda_1 \lambda_2 + \frac{133}{9} \lambda_1 \lambda_3 -$$

$$-\frac{25}{9} \lambda_1^2 - \frac{1}{9} \lambda_2^2 - \frac{49}{9} \lambda_3^2\Big)\Big) \Big/ \Big(60 \lambda_1^2 \lambda_2 - 7980 \lambda_1^2 \lambda_3 + 12 \lambda_1 \lambda_2^2 + 48 \lambda_3 \lambda_1 \lambda_2 + 11172 \lambda_1 \lambda_3^2 + 372 \lambda_2^2 \lambda_3 - 2604 \lambda_2 \lambda_3^2 + 1000 \lambda_1^3 + 8 \lambda_2^3 - 2744 \lambda_3^3$$

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$$- 7980 \lambda_1^2 \lambda_3 + 12 \lambda_1 \lambda_2^2 + 48 \lambda_3 \lambda_1 \lambda_2 + 11172 \lambda_1 \lambda_3^2 + 372 \lambda_2^2 \lambda_3 - 2604 \lambda_2 \lambda_3^2 + 1000 \lambda_1^3 + 8 \lambda_2^3 - 2744 \lambda_3^3$$

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$$+ \frac{1}{2}\Big(I\sqrt{3}\Big(\frac{1}{6}\Big(60 \lambda_1^2 \lambda_2 - 7980 \lambda_1^2 \lambda_3 + 12 \lambda_1 \lambda_2^2 + 48 \lambda_3 \lambda_1 \lambda_2 + 11172 \lambda_1 \lambda_3^2 + 372 \lambda_2^2 \lambda_3 - 2604 \lambda_2 \lambda_3^2 + 1000 \lambda_1^3 + 8 \lambda_2^3 - 2744 \lambda_3^3$$

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We had from before that $\lambda_1 = \lambda_2 = \lambda_3 = 1$ works.

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

Problem: We cannot solve symbolically for x^* nor for the eigenvalues!

There are ways around!

For $n = 2$: $\dot{x}_1 = f_1(x), \dot{x}_2 = f_2(x)$,

$$J_f(x) = \begin{pmatrix} \frac{df_1}{dx_1} & \frac{df_1}{dx_2} \\ \frac{df_2}{dx_1} & \frac{df_2}{dx_2} \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

The characteristic polynomial is

$$\mathrm{ch}_f(y) = \det \begin{pmatrix} a - y & b \\ c & d - y \end{pmatrix} = y^2 - \mathrm{Tr}(J_f(x))y + \det J_f(x).$$

The roots α_1, α_2 are such that $\alpha_1\alpha_2 = \det J_f(x)$ and $\alpha_1 + \alpha_2 = \mathrm{Tr}(J_f(x))$.
This polynomial has:

- Two roots with negative real part if and only if $\det J_f(x) > 0$ and $\mathrm{Tr}(J_f(x)) < 0$.
- Two purely imaginary roots if and only if $\det J_f(x) > 0$ and $\mathrm{Tr}(J_f(x)) = 0$.

General case: Routh-Hurwitz criteria

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

$$H_1 = \alpha_1, \quad H_2 = \det \begin{bmatrix} \alpha_1 & \alpha_3 \\ \alpha_0 & \alpha_2 \end{bmatrix}, \quad H_3 = \det \begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 \\ \alpha_0 & \alpha_2 & \alpha_4 \\ 0 & \alpha_1 & \alpha_3 \end{bmatrix}$$

Hurwitz matrix: Stability criterion

$$H = \begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 & \dots & \dots & 0 \\ \alpha_0 & \alpha_2 & \alpha_4 & \alpha_6 & \dots & 0 \\ 0 & \alpha_1 & \alpha_3 & \alpha_5 & \dots & 0 \\ 0 & \alpha_0 & \alpha_2 & \alpha_4 & \dots & \\ \vdots & \vdots & \vdots & \vdots & \vdots & \alpha_n \end{bmatrix}$$

$H_i = i$-th leading principal minor

Criterion 1 (Routh-Hurwitz): Negative real part

- If $H_i > 0$ for all $i = 1, \dots, n-1$ and $\alpha_n > 0$, 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).

Example: $p(z) = z^2 - \mathrm{Tr}(J_f(x))z + \det J_f(x)$:

$$H_1 = -\mathrm{Tr}(J_f(x)), \quad \alpha_2 = \det J_f(x).$$

Hurwitz matrix: Stability criterion

$$H = \begin{bmatrix} \alpha_1 & \alpha_3 & \alpha_5 & \dots & \dots & 0 \\ \alpha_0 & \alpha_2 & \alpha_4 & \alpha_6 & \dots & 0 \\ 0 & \alpha_1 & \alpha_3 & \alpha_5 & \dots & 0 \\ 0 & \alpha_0 & \alpha_2 & \alpha_4 & \dots & \\ \vdots & \vdots & \vdots & \vdots & \vdots & \alpha_n \end{bmatrix}$$

H_i = i-th leading principal minor

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

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

Example: $p(z) = z^2 - \mathrm{Tr}(J_f(x))z + \det J_f(x)$:

$$H_1 = -\mathrm{Tr}(J_f(x)), \quad \alpha_2 = \det J_f(x).$$

Observation

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

Let $u_1, \ldots, u_n$ be the roots of p. It holds (Orlando's formula):

$$H_{n-1} = (-1)^{\frac{n(n-1)}{2}} \prod_{1 \leq i < j \leq n} (u_i + u_j).$$

So, if $H_{n-1} = 0$, then there exists a pair of roots u_i, u_j:

$$u_i + u_j = 0.$$

This implies

$$u_i = -u_j.$$

If both real, noninteresting... If both complex, they need to be purely imaginary roots.

For reaction networks

We apply these criteria to the characteristic polynomial of the Jacobian of $f_\kappa(x)$ evaluated at a parametrisation of the steady states, after removing $d = n - \mathrm{Rank}(N)$ zero roots, either of the positive steady state variety or using convex parameters:

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

The questions on stability and Hopf bifurcations reduce to deciding (determining when) some semi-algebraic sets are non-empty.

Stability:

$$\kappa > 0, x > 0 \quad \text{or} \quad \lambda > 0, h > 0$$
$$H_1 > 0, \dots, H_{s-1} > 0, a_s > 0$$

Hopf bifurcations:

$$\kappa > 0, x > 0 \quad \text{or} \quad \lambda > 0, h > 0$$
$$H_1 > 0, \dots, H_{s-2} > 0, \quad H_{s-1} = 0, \quad a_s > 0$$
$$\frac{dH_{s-1}(\mu_0)}{d\mu} \neq 0 \quad \text{for some parameter } \mu, \text{ and } \mu_0 \text{ satisfying the above inequalities}$$

Example: enzymatic transfer of calcium ions

$$0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_1 \quad X_1 + X_2 \xrightarrow{\kappa_3} 2X_1$$

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

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

With convex parameters λ, h: The polynomials H_1 and a_3 have positive coefficients. We also have

$$\begin{aligned}
&h_1^2h_2\lambda_1^2\lambda_2 + h_1^2h_2\lambda_1^2\lambda_3 + h_1^2h_2\lambda_1\lambda_2^2 + 2h_1^2h_2\lambda_1\lambda_2\lambda_3 + h_1^2h_2\lambda_1\lambda_3^2 - h_1^2h_3\lambda_1^2\lambda_2 - h_1^2h_3\lambda_1^2\lambda_3 - h_1^2h_3\lambda_1\lambda_2^2\\
&+ h_1^2h_3\lambda_1\lambda_3^2 + h_1^2h_3\lambda_2^2\lambda_3 + h_1^2h_3\lambda_2\lambda_3^2 + h_1^2h_4\lambda_1\lambda_2\lambda_3 + h_1^2h_4\lambda_1\lambda_3^2 + h_1^2h_4\lambda_2^2\lambda_3 + h_1^2h_4\lambda_2\lambda_3^2 + h_1h_2^2\lambda_1^3\\
&+ h_1h_2^2\lambda_1^2\lambda_2 + h_1h_2^2\lambda_1^2\lambda_3 + 2h_1h_2h_3\lambda_1^2\lambda_2 + 2h_1h_2h_3\lambda_1^2\lambda_3 + 2h_1h_2h_3\lambda_1\lambda_2^2 + 2h_1h_2h_3\lambda_1\lambda_2\lambda_3 + h_1h_2h_4\lambda_1^3\\
&+ 3h_1h_2h_4\lambda_1^2\lambda_2 + 2h_1h_2h_4\lambda_1^2\lambda_3 + 2h_1h_2h_4\lambda_1\lambda_2^2 + 2h_1h_2h_4\lambda_1\lambda_2\lambda_3 - h_1h_3^2\lambda_1^3 - 2h_1h_3^2\lambda_1^2\lambda_2\\
&+ h_1h_3^2\lambda_1^2\lambda_3 - h_1h_3^2\lambda_1\lambda_2^2 + 2h_1h_3^2\lambda_1\lambda_2\lambda_3 + h_1h_3^2\lambda_2^2\lambda_3 - h_1h_3h_4\lambda_1^3 - 2h_1h_3h_4\lambda_1^2\lambda_2 + 2h_1h_3h_4\lambda_1^2\lambda_3\\
&- h_1h_3h_4\lambda_1\lambda_2^2 + 4h_1h_3h_4\lambda_1\lambda_2\lambda_3 + 2h_1h_3h_4\lambda_2^2\lambda_3 + h_1h_4^2\lambda_1^2\lambda_3 + 2h_1h_4^2\lambda_1\lambda_2\lambda_3 + h_1h_4^2\lambda_2^2\lambda_3 + h_2^2h_3\lambda_1^3\\
&+ h_2^2h_3\lambda_1^2\lambda_2 + h_2^2h_4\lambda_1^3 + h_2^2h_4\lambda_1^2\lambda_2 + h_2h_3^2\lambda_1^3 + 2h_2h_3^2\lambda_1^2\lambda_2 + h_2h_3^2\lambda_1\lambda_2^2 + 2h_2h_3h_4\lambda_1^3\\
&+ 4h_2h_3h_4\lambda_1^2\lambda_2 + 2h_2h_3h_4\lambda_1\lambda_2^2 + h_2h_4^2\lambda_1^3 + 2h_2h_4^2\lambda_1^2\lambda_2 + h_2h_4^2\lambda_1\lambda_2^2
\end{aligned}$$

There are coefficients of both signs which are vertices of the Newton Polytope of H_2. There exist values of λ, h such that $H_2 = 0$. There is a pair of purely imaginary eigenvalues.

Also $\frac{dH_2}{dh_2} > 0$, so the extra condition holds. There is a Hopf bifurcation, hence the network displays periodic solutions.

Example: enzymatic transfer of calcium ions

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

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

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

$X_1 =$ 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 a parametrization of the positive steady state variety 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 $\mu = T = x_3 + x_4$ as bifurcation parameter, there is a Hopf bifurcation.

Gatermann, Eiswirth, Sensse, '05

Monostability

Networks with one positive steady state in each stoichiometric compatibility class:

(1)	$S_0 + E \rightleftharpoons S_0E \to S_1 + E$ $S_1 + F \rightleftharpoons S_1F \to S_0 + F$	**(2)**	$S_0 + E \rightleftharpoons S_0E \to S_1 + E$ $S_1 + E \rightleftharpoons S_1E \to S_0 + E$
(3)	$S_0 + E_1 \rightleftharpoons S_0E_1 \to S_1 + E_1$ $S_0 + E_2 \rightleftharpoons S_0E_2 \to S_1 + E_2$ $S_1 + F \rightleftharpoons S_1F \to S_0 + F$	**(4)**	$S_0 + E_1 \rightleftharpoons S_0E_1 \to S_1 + E_1$ $S_0 + E_2 \rightleftharpoons S_0E_2 \to S_1 + E_2$ $S_1 + F_1 \rightleftharpoons S_1F_1 \to S_0 + F_1$ $S_1 + F_2 \rightleftharpoons S_1F_2 \to S_0 + F_2$
(5)	$S_0 + E_1 \rightleftharpoons S_0E_1 \to S_1 + E_1$ $S_1 + E_2 \rightleftharpoons S_1E_2 \to S_2 + E_2$ $S_1 + F_1 \rightleftharpoons S_1F_1 \to S_0 + F_1$ $S_2 + F_2 \rightleftharpoons S_2F_2 \to S_1 + F_2$	**(6)**	$S_0 + E \rightleftharpoons S_0E \to S_1 + E$ $P_0 + E \rightleftharpoons P_0E \to P_1 + E$ $S_1 + F_1 \rightleftharpoons S_1F_1 \to S_0 + F_1$ $P_1 + F_2 \rightleftharpoons P_1F_2 \to P_0 + F_2$

For all these networks, the polynomials

$$H_1(\lambda, h) > 0, \dots, H_{s-1}(\lambda, h) > 0, a_s(\lambda, h) > 0$$

and this holds because the polynomials only have positive coefficients.
So, there is monostability.

Torres, Feliu (2021). Symbolic proof of bistability in reaction networks. SIADS

Bistability

Hybrid histidine kinase

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

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

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

$$\mathrm{Htp}_{\mathrm{p}} \xrightarrow{\kappa_6} \mathrm{Htp}$$

Multi $\Leftrightarrow \kappa_1 < \kappa_3$

Gene transcription network

$$X_1 \longrightarrow X_1 + P_1 \qquad P_1 \longrightarrow 0$$

$$X_2 \longrightarrow X_2 + P_2 \qquad P_2 \longrightarrow 0$$

$$X_2 + P_1 \rightleftharpoons X_2P_1 \qquad 2P_2 \rightleftharpoons P_2P_2$$

$$X_1 + P_2P_2 \rightleftharpoons X_1P_2P_2$$

Multi for all κ

These networks admit 3 positive steady states for some choice of parameter values. How can we guarantee that two are asymptotically stable?

Bistability vs. multistationarity

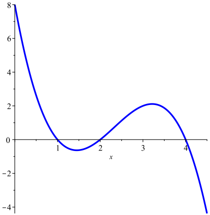
When can we assert that there is bistability whenever the network has 3 steady states?
How can we "prove" the existence of bistability (symbolically)?

For small networks we often have

- All Hurwitz determinants $H_1, \dots, H_{s-1}$ are positive. Then, the steady state is asymptotically stable if $a_s > 0$ and unstable if $a_s < 0$.
- It is possible to reduce the equations defining $C_{\kappa,c}$ to one polynomial equation $q_{\kappa,c}(x_i) = 0$, such that x_j are positive rational functions of x_i.
- For a steady state x^*

$$\operatorname{sign}(a_s(x^*)) = \operatorname{sign}(q'_{\kappa,c}(x_i^*)).$$

- "The stability of the steady states alternates with x_i".
- So, if the independent term of $q_{\kappa,c}(x_i) = 0$ is positive, and there are 3 steady states, two are asymptotically stable and one is unstable.



Torres, Feliu (2021). Symbolic proof of bistability in reaction networks. SIADS

Bistability

The following networks admit two asymptotically stable steady states and one unstable steady state:

Hybrid histidine kinase

$$\mathrm{HK_{00}} \to \mathrm{HK_{p0}} \to \mathrm{HK_{0p}} \to \mathrm{HK_{pp}} \qquad \mathrm{Htp_p} \to \mathrm{Htp}$$

$$\mathrm{HK_{pp}} + \mathrm{Htp} \to \mathrm{HK_{p0}} + \mathrm{Htp_p} \qquad \mathrm{HK_{0p}} + \mathrm{Htp} \to \mathrm{HK_{00}} + \mathrm{Htp_p}$$

Two substrate enzyme catalysis

$$\mathrm{E} + \mathrm{S_1} \rightleftharpoons \mathrm{ES_1} \qquad \mathrm{E} + \mathrm{S_2} \rightleftharpoons \mathrm{ES_2} \qquad \mathrm{ES_1S_2} \rightleftharpoons \mathrm{E} + \mathrm{P}$$

$$\mathrm{S_2} + \mathrm{ES_1} \rightleftharpoons \mathrm{ES_1S_2} \qquad \mathrm{S_1} + \mathrm{ES_2} \rightleftharpoons \mathrm{ES_1S_2}$$

Gene transcription network

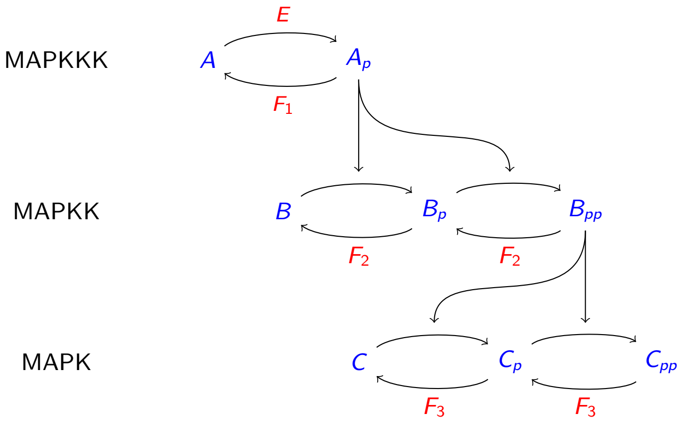
$$\mathrm{X_1} \to \mathrm{X_1} + \mathrm{P_1} \qquad \mathrm{X_2} \to \mathrm{X_2} + \mathrm{P_2} \qquad \mathrm{P_1} \to 0 \qquad \mathrm{P_2} \to 0$$

$$\mathrm{X_2} + \mathrm{P_1} \rightleftharpoons \mathrm{X_2P_1} \qquad 2\,\mathrm{P_2} \rightleftharpoons \mathrm{P_2P_2} \qquad \mathrm{X_1} + \mathrm{P_2P_2} \rightleftharpoons \mathrm{X_1P_2P_2}$$

Torres, Feliu (2021). Symbolic proof of bistability in reaction networks. SIADS

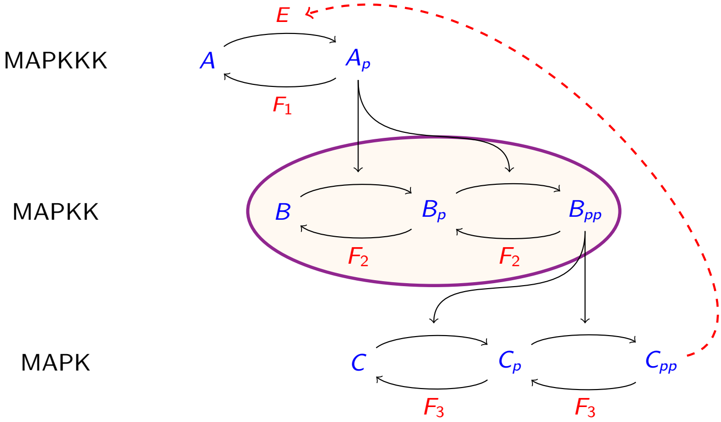
Two stories on the MAPK cascade

On the origin of oscillations in the MAPK cascade



Huang, Ferrell model, '99

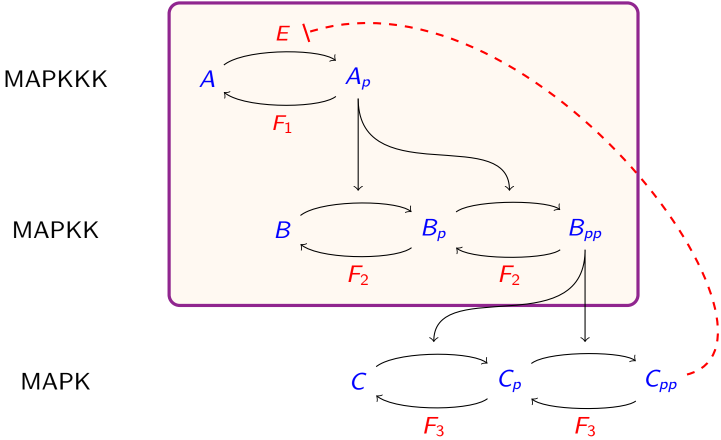
MAPK cascade. Bistability



Huang, Ferrell model, '99

Markevich, Hoeck, Kholodenko, '04

MAPK cascade. Oscillations

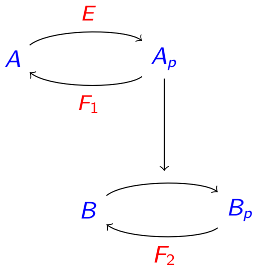


Suggest: Single-stage bistability is necessary for the oscillatory behavior

Kholodenko, '00

Qiao, Nachbar, Kevrekidis, Shvartsman, '07

A single-phosphorylation cascade admits oscillations!



Full model

$$
\begin{aligned}
A + E &\rightleftharpoons X_1 \longrightarrow A_p + E \\
A_p + F_1 &\rightleftharpoons X_2 \longrightarrow A + F_1 \\
B + A_p &\rightleftharpoons Y_1 \longrightarrow B_p + A_p \\
B_p + F_2 &\rightleftharpoons Y_2 \longrightarrow B + F_2
\end{aligned}
$$

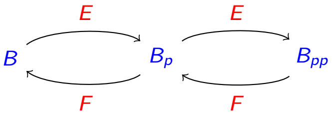
We make use of a model reduction technique.

H_4 has 37,235 terms in x and κ with both negative and positive coefficients.

(Torres, Feliu, In preparation)

Does the double-phosphorylation cycle admit oscillations?

$$B + E \rightleftharpoons X_1 \longrightarrow B_p + E \rightleftharpoons X_2 \longrightarrow B_{pp} + E$$
$$B_{pp} + F \rightleftharpoons Y_2 \longrightarrow B_p + F \rightleftharpoons Y_1 \longrightarrow B + F$$



$$H_1 > 0, \dots, H_{n-2} > 0, \qquad H_{n-1} \text{ and } \alpha_n \text{ have both positive and negative terms.}$$

- Several failed attempts to show the existence of Hopf bifurcations
- If F acts processively, the network has Hopf bifurcations (Conradi, Mincheva, Shiu '19)

- Reduced systems: irreversible reactions and keep two intermediates. For example

$$B + E \longrightarrow X_1 \longrightarrow B_p + E \longrightarrow B_{pp} + E$$
$$B_{pp} + F \longrightarrow Y_2 \longrightarrow B_p + F \longrightarrow B + F$$

- After a very detailed analysis of H_i: No reduced network with two intermediates admits a Hopf bifurcation (Conradi, Feliu, Mincheva (2019)). The same analysis extends to any choice of three intermediates (not published).
- Conjecture: The double-phosphorylation cycle does not admit Hopf bifurcations.

Appendix: computational approach

To work with Hurwitz determinants, we do as follows:

- Use N and B to find a matrix of conservation laws W, and the generators of $\ker(N) \cap \mathbb{R}^n_{\geq 0}$. Write the generators as columns of a matrix E.
- Construct the matrix $N \operatorname{diag}(E\lambda) B^\top \operatorname{diag}(h)$. Find the characteristic polynomial $\mathrm{ch}(y)$ of this matrix and divide it by y^{n-s}. Call the new polynomial $p(y)$, which has degree s.
- Find $s = \mathrm{rk}(N)$ and consider the general Hurwitz matrix of size s (see slides above, let the coefficients of the polynomial be symbols a_i for now). Compute the Hurwitz determinants $H_1, \dots, H_{s-1}$ by finding the principal minors of size $1, \dots, s-1$. Substitute the a_i by the actual coefficients of $p(y)$.
- Check the signs of the coefficients of $H_1, \dots, H_{s-1}$ and a_s.
  - If all positive, then all steady states are asymptotically stable.
  - If H_{s-1} has coefficients of both sign and the rest of the polynomials have only positive coefficients, decide whether there are vertices of the Newton polytope of H_{s-1} that have positive coefficients and some that have negative coefficients. If this is the case, check the derivative condition to conclude that there are Hopf bifurcations and hence periodic solutions.
  - If a_s has coefficients of both sign and the rest of the polynomials have only positive coefficients, decide whether the steady state equations can be reduced to one polynomial equation (see above).
- By working with a parametrization of the positive steady state variety instead of convex parameters, you can get parameter conditions for the existence of Hopf bifurcations or unstable steady states.