Emergence of oscillations in a two-layer cascade

Angélica Torres
Joint work with Elisenda Feliu

MPI MiS

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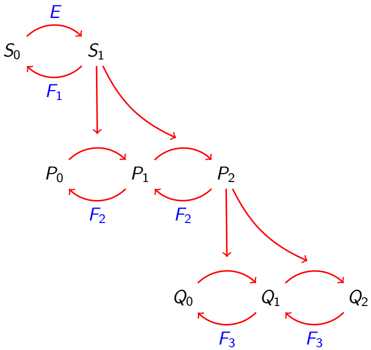
MAPK cascade



- The mitogen-activated protein kinase (MAPK) cascades are processes of cell signalling, present in all eukaryotic cells.

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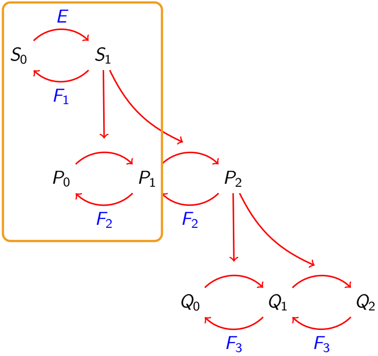
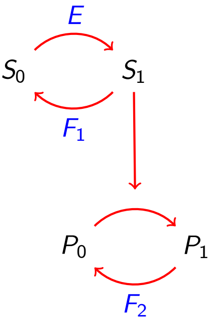


- The mitogen-activated protein kinase (MAPK) cascades are processes of cell signalling, present in all eukaryotic cells.
- The Huang and Ferrell model consists on several layers where the activated kinase at each level, phosphorylates the kinase in the next one

MAPK Cascade



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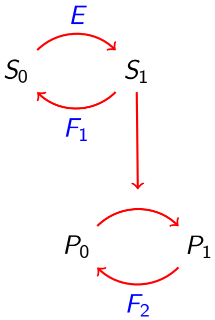


Chemical Reaction Network

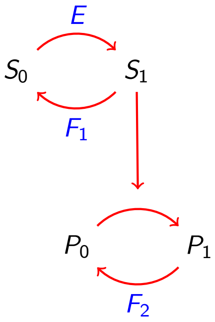
$$\mathrm{S}_0 + \mathrm{E} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{Y}_1 \xrightarrow{\kappa_3} \mathrm{S}_1 + \mathrm{E}$$

$$\mathrm{S}_1 + \mathrm{F}_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{Y}_2 \xrightarrow{\kappa_6} \mathrm{S}_0 + \mathrm{F}_1$$

$$\mathrm{P}_0 + \mathrm{S}_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{Y}_3 \xrightarrow{\kappa_9} \mathrm{P}_1 + \mathrm{S}_1$$

$$\mathrm{P}_1 + \mathrm{F}_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} \mathrm{Y}_4 \xrightarrow{\kappa_{12}} \mathrm{P}_0 + \mathrm{F}_2.$$

MAPK Cascade



Chemical Reaction Network

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- Finite directed graph with no loops.
- Nodes: nonnegative integer linear combinations of the species.

ODEs for Reaction Networks

The evolution of the concentration of the species can be modelled with a system of ODEs that, under mass action kinetics, are polynomial. The coefficients of the polynomial equations are $\{\kappa_1, \dots, \kappa_m\} \subset \mathbb{R}^n_{>0}$ which are called *rate constants*.

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Key characteristics of the system of ODEs

- One autonomous differential equation per species.
- As many monomials as linear combinations appearing in the nodes.
- As many parameters as rate constants.

ODEs for Reaction Networks

For our system

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} Y_1 \xrightarrow{\kappa_3} S_1 + E$$

$$S_1 + F_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} Y_2 \xrightarrow{\kappa_6} S_0 + F_1$$

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\begin{aligned}
\dot{s_0} &= -\kappa_1 s_0 e + \kappa_2 y_1 + \kappa_6 y_2 \\
\dot{s_1} &= -\kappa_4 s_1 f_1 - \kappa_7 s_1 p_0 + \kappa_3 y_1 + \kappa_5 y_2 + \kappa_8 y_3 + \kappa_9 y_3 \\
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$$\dot{s_0} = -\kappa_1 s_0 e + \kappa_2 y_1 + \kappa_6 y_2$$

Hopf bifurcations

Consider a system of ODEs parametrized by $\mu \in \mathbb{R}$:

$$\dot{x} = f_\mu(x),$$

where $x \in \mathbb{R}^n$, and $f_\mu(x)$ varies smoothly in μ and x. Assume that $f_{\mu_0}(x_0) = 0$, and assume that there is a smooth curve of steady states:

$$\mu \;\mapsto\; x(\mu)$$

(that is, $f_\mu\left(x(\mu)\right) = 0$ for all μ) such that $x(\mu_0) = x_0$.

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A simple Hopf bifurcation occurs at μ_0 if the matrix $J_f(x_0, \mu_0)$ has a simple pair of imaginary eigenvalues, while all other eigenvalues remain with negative real part.

Hopf bifurcations

Example

Consider the system of ODEs

$$\dot{x} = -y + x(\mu - x^2 - y^2)$$
$$\dot{y} = x + y(\mu - x^2 - y^2)$$

The only steady state is $(0, 0)$ which is independent of μ.

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The only steady state is $(0, 0)$ which is independent of μ. We have

$$J_f((0,0),\mu) = \begin{bmatrix} \mu & -1 \\ 1 & \mu \end{bmatrix}$$

with eigenvalues $-i + \mu$ and $i + \mu$.

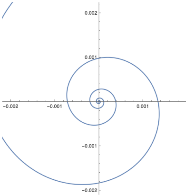
Hopf bifurcations

Example

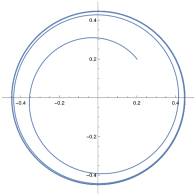
Consider the system of ODEs

$$\dot{x} = -y + x(\mu - x^2 - y^2)$$
$$\dot{y} = x + y(\mu - x^2 - y^2)$$

The dynamics of the system change depending on the value of μ.



$\mu \leq 0$



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Decide whether there are values for the parameters such that a Hopf bifurcation arises in the subsystem.

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- Equilibria
- Are the dynamics constrained to a lower-dimensional space?
- Eigenvalues of the Jacobian of the polynomials defining the ODEs at equilibrium

Equilibria for CRN

The positive steady states are defined as equilibrium points of the ODE that have positive entries. That is, the points in $\mathbb{R}^n_{>0}$ such that $\dot{x} = 0$.

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Example

For our system, the positive steady states are defined by the equations

$$
\begin{aligned}
0 &= -\kappa_1 s_0 e + \kappa_2 y_1 + \kappa_6 y_2 \\
0 &= -\kappa_4 s_1 f_1 - \kappa_7 s_1 p_0 + \kappa_3 y_1 + \kappa_5 y_2 + \kappa_8 y_3 + \kappa_9 y_3 \\
0 &= -\kappa_7 s_1 p_0 + \kappa_8 y_3 + \kappa_{12} y_4 \\
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&s_0, s_1, p_0, p_1, e, f_1, f_2, y_i \in \mathbb{R}^n_+
\end{aligned}
$$

Equilibria por CRN

The steady states can be parameterized as

$$\varphi(s_0, s_1, p_1, f_1, y_3) = \left(s_0, s_1, \frac{(k_8 + k_9)\, y_3}{k_7 s_1}, p_1, \frac{(k_2 + k_3)\, k_4 k_6 s_1 f_1}{k_1 k_3 (k_5 + k_6)\, s_0}, f_1, \frac{k_9 (k_{11} + k_{12})\, y_3}{k_{10} k_{12} p_1}, \right.$$
$$\left. \frac{\kappa_4 \kappa_6 s_1 f_1}{\kappa_3 (\kappa_5 + \kappa_6)}, \frac{\kappa_4 s_1 f_1}{\kappa_5 + \kappa_6}, y_3, \frac{\kappa_9 y_3}{\kappa_{12}}\right)$$

Conservation laws in CRN

Given an initial solution x_0 for the system of ODEs, the trajectories containing x_0, remain in $x_0 + \mathrm{S}$ for a linear space S (*Stoichiometric compatibility class*). Therefore, we study the dynamics of the network within $x_0 + S$.

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Example

In our system the compatibility classes are defined by the equations

$$
\begin{aligned}
s_0 + s_1 + y_1 + y_2 + y_3 &= T_1 \\
p_0 + p_1 + y_3 + y_4 &= T_2 \\
e + y_1 &= T_3 \\
f_1 + y_2 &= T_4 \\
f_2 + y_4 &= T_5 .
\end{aligned}
$$

These come precisely from the linear relations among the equations defining the system of ODEs.

Conservation laws in CRN

Indeed, consider the conservation law

$$f_2 + y_4 = T_5.$$

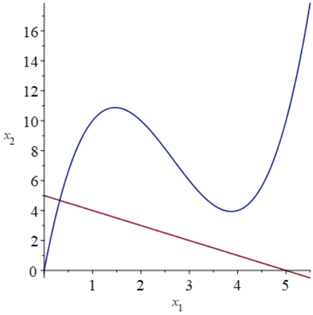
The ODEs associated with f_2 and y_4 are

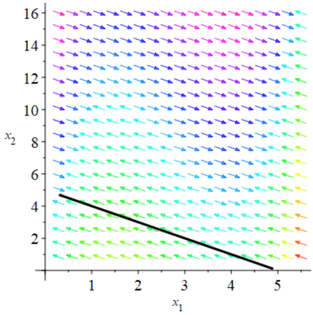
$$\begin{aligned}\dot{f}_2 &= -\kappa_{10} p_1 f_2 + \kappa_{11} y_4 + \kappa_{12} y_4 \\ \dot{y}_4 &= \kappa_{10} p_1 f_2 - \kappa_{11} y_4 - \kappa_{12} y_4\end{aligned}$$

whose sum vanishes, that is, $\dot{f}_2 + \dot{y}_4 = 0$, which implies the conservation law above.

Dynamics of CRN

Intuitively...





Hopf bifurcations in two-layer cascade

Establish the system of ODEs $\dot{x} = f_\kappa(x)$ of the network.

→

Compute the Jacobian $J_f(x^*)$ for an equilibria x^*

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For which parameter values does J_f have a pair of pure imaginary eigenvalues?

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Challenges

The equilibria are given by a parameterization.

We cannot compute the eigenvalues of J_f

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There is hope!

There is no need to compute the exact value of the eigenvalues

Liu's criterion for Hopf bifurcations

Hopf Bifurcations in two-layer Cascade

Denote the characteristic polynomial of $J_{f_\mu}(x(\mu))$ as

$$p_\mu(\lambda) := \det\left(\lambda I - J_{f_\mu}\right)|_{x=x(\mu)} = \lambda^n + b_1(\mu)\lambda^{n-1} + \cdots + b_n(\mu).$$

Since the coefficients of $p_\mu(\lambda)$ depend on μ, its Hurwitz determinants depend on μ as well. We denote each determinant by $H_i(\mu)$, for $i = 1, \ldots, n$.

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Liu's criterion

There is a simple Hopf bifurcation at x_0 with respect to μ if and only if the following conditions hold:

1. $b_n(\mu_0) > 0$,
2. $H_1(\mu_0) > 0$, $H_2(\mu_0) > 0$, ..., $H_{n-2}(\mu_0) > 0$, and
3. $H_{n-1}(\mu_0) = 0$ and $\frac{d(H_{n-1}(\mu))}{d\mu}|_{\mu=\mu_0} \neq 0$.

Hopf bifurcations in two-layer Cascade

Definition (Hurwitz determinants)

Let $p(x) = a_s x^s + a_{s-1}x^{s-1} + \ldots + a_1 x + a_0$ be a polynomial with $a_i \in \mathbb{R}$, $a_s > 0$ and $a_0 \neq 0$. Define the Hurwitz matrix associated with p, as the matrix H whose entries are defined by $h_{i,j} = a_{s-2i+j}$ for $i, j = 1, \ldots, s$ and $a_k = 0$ if $k < 0$ or $k > s$:

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

The i-th Hurwitz determinant of H, denoted by H_i, is defined as $H_i = \det(H_{I,I})$, with $I = \{1, \ldots, i\}$.

Hopf Bifurcations in two-layer Cascade

Results

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Hopf Bifurcations in two-layer Cascade

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- We computed 6 Hurwitz determinants: $\{H_1, \ldots, H_6\}$ and evaluated them at the parameterization of the steady states.

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A Hopf bifurcation appears if there is a set of parameters κ^* and an steady state x^* such that

$$H_4(k^*, x^*) \geq 0 \text{ and } H_5(k^*, x^*) = 0.$$

Hopf bifurcations in two-layer Cascade

Proposition

For a real, multivariate polynomial

$$p(x) = a_1 x^{\alpha_1} + a_2 x^{\alpha_2} + \cdots + a_\ell x^{\alpha_\ell} \in \mathbb{R}[x_1, \ldots, x_n],$$

if α_i is a vertex of $Newt(p)$, then there exists $x^* \in \mathbb{R}^n_{>0}$ such that $sign(p(x^*)) = sign(a_i)$.

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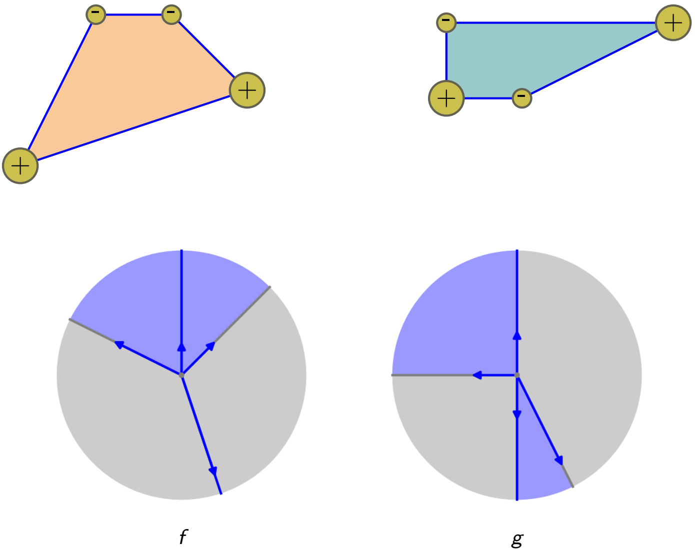
Proposition

Let $f, g \in \mathbb{R}[x_1, x_2, \ldots x_s]$. Assume that α is a positive vertex of $\mathrm{Newt}(f)$, β_+ is a positive vertex of $\mathrm{Newt}(g)$, and β_- is a negative vertex of $\mathrm{Newt}(g)$. Then, if $\mathrm{int}(N_f(\alpha)) \cap \mathrm{int}(N_g(\beta_+))$ and $\mathrm{int}(N_f(\alpha)) \cap \mathrm{int}(N_g(\beta_-))$ are both nonempty, then there exists $x^* \in \mathbb{R}^s_{>0}$ such that $f(x^*) > 0$ and $g(x^*) = 0$.

Hopf bifurcations in a two-layer cascade



Hopf bifurcations in a two-layer cascade

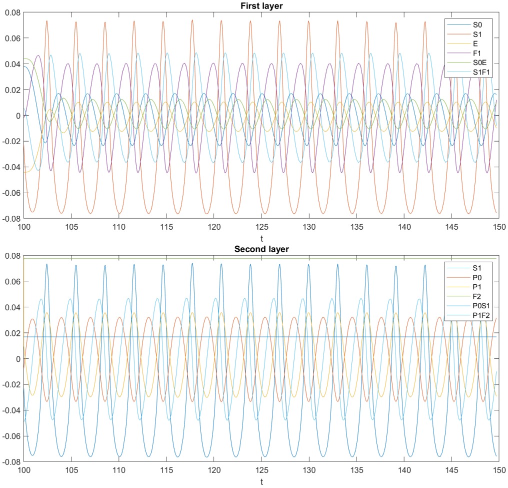
Applying the previous propositions in a reduced version of H_4 and H_5 we found the following parameters that satisfy Liu's criterion.

$$
\begin{aligned}
s_0 =& 0.008221823730, s_1 = 8.670580350 \times 10^{-7}, p_0 = 1, p_1 = 197868.6638,\\
e =& 0.007561436673, f_1 = 1, f_2 = 0.007884719363, y_1 = 0.001238422300,\\
y_2 =& 0.001238422300, y_3 = 0.5461508658, y_4 = 780.0694426
\end{aligned}
$$

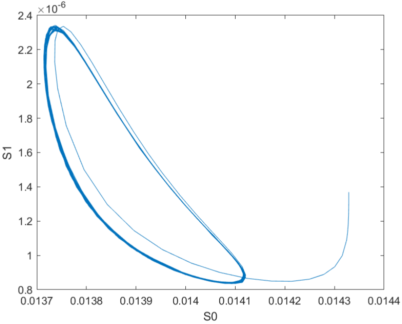
with parameters

$$
\begin{aligned}
\kappa_1 =& 20, \kappa_2 = 0.004, \kappa_3 = 1, \kappa_4 = 1428.303957, \kappa_5 = 9.941572972 \times 10^{-8}\\
\kappa_6 =& 1, \kappa_7 = 9.941572972 \times 10^{8}, \kappa_8 = 150, \kappa_9 = 1428.303957,\\
\kappa_{10} =& 1, \kappa_{11} = 1, \kappa_{12} = 1,\\
T_1 =& 0.5568504012, T_2 = 198650.2794,\\
T_3 =& 0.008799858973, T_4 = 1.001238422, T_5 = 780.0773273
\end{aligned}
$$

Hopf Bifurcations in a two-layer cascade



Hopf Bifurcations in a two-layer cascade



Remaining questions

- Are these parameters meaningful biologically?
- Is there a good implementation to speed up computations of Hurwitz determinants?

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References

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Danke!