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Passivity-Based Analysis of Biochemical Reaction Networks

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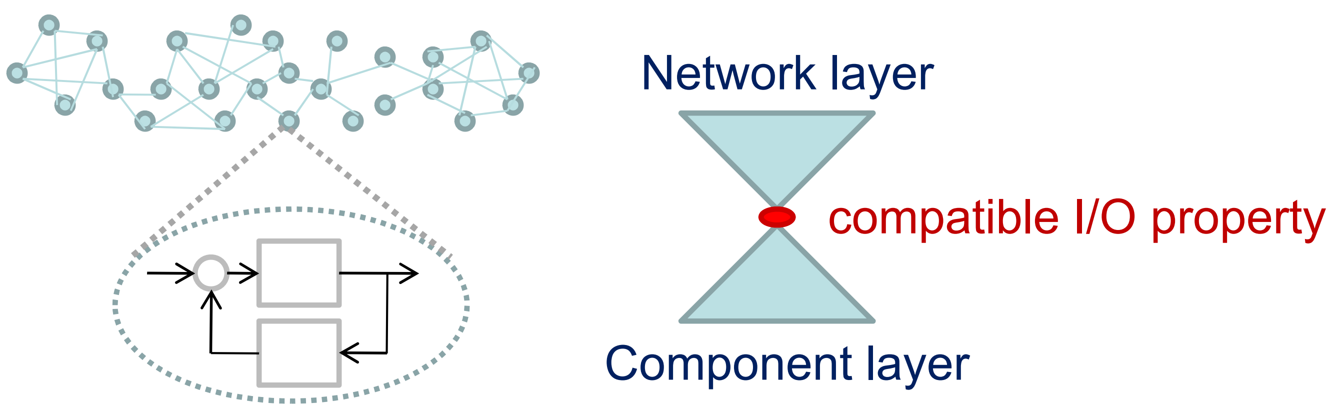
Divide the stability analysis into two layers:

1) Network layer: Represent components with I/O properties, such as passivity, as abstractions of their detailed dynamic models.

Determine which I/O properties are compatible with the network structure:

(Moylan and Hill, 1978), (Vidyasagar, 1981), (Megretski & Rantzer, 1997)

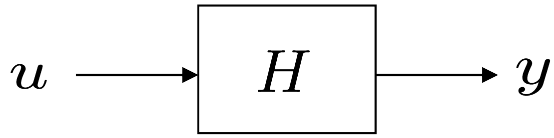


2) Component layer: Verify the relevant I/O properties without relying on further knowledge of the network.

Outline:

- Overview of Passivity
- Secant Criterion for Cyclic Networks
- From Cyclic to Other Network Structures
- Extension to Reaction-Diffusion Systems
- From Stability to Synchronization

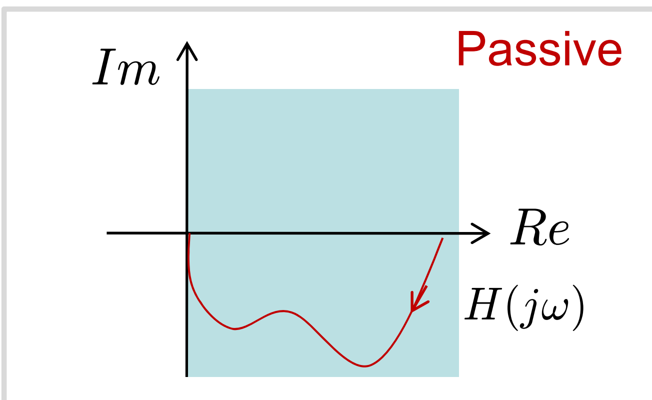
Overview of Passivity

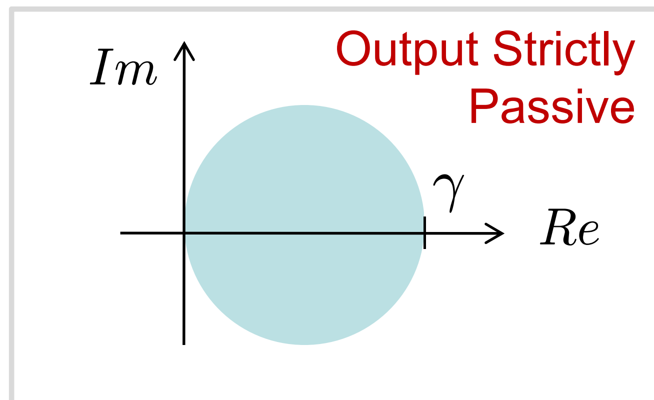


The dynamic system H is called *passive* if it admits a "*storage function*"

$S(x) \geq 0$ s.t. $\dot{S} \leq u^T y$. Output strictly passive if $\dot{S} \leq \gamma u^T y - ||y||^2$

Example: Stable LTI systems with phase restrictions:





Example: The Euler-Lagrange system:

$$M(q)\ddot{q} + C(q,\dot{q})\dot{q} + \frac{dP}{dq} = \tau$$

is passive with $u = \tau$, $y = \dot{q}$, $S(q,\dot{q}) = \frac{1}{2}\dot{q}^T M(q)\dot{q} + P(q)$

Cyclic Biochemical Reaction Networks

Cellular Signaling: Kholodenko (2000, 2006); Shvartsman *et al.* (2001)

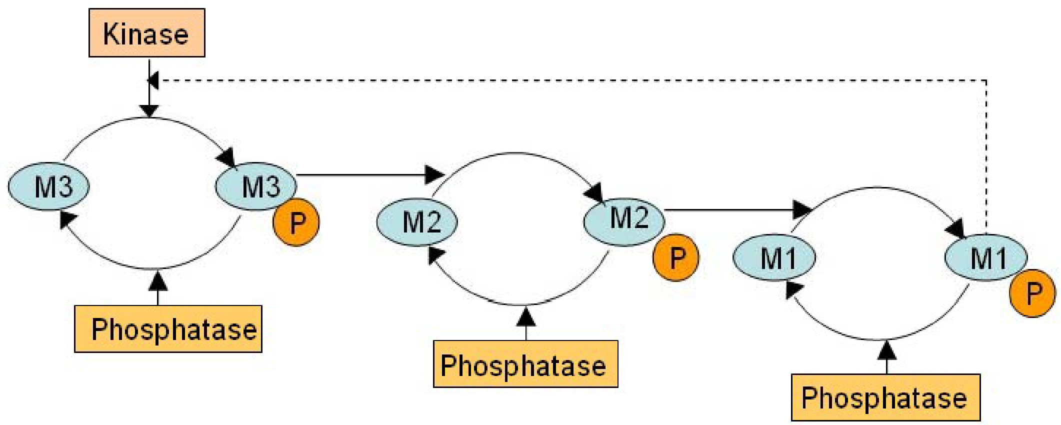
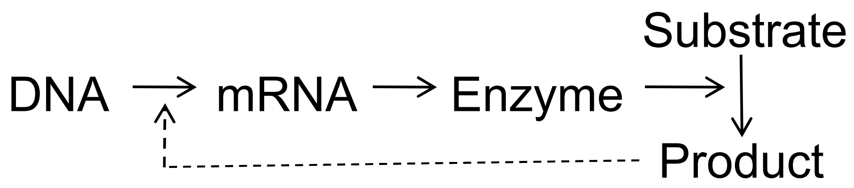


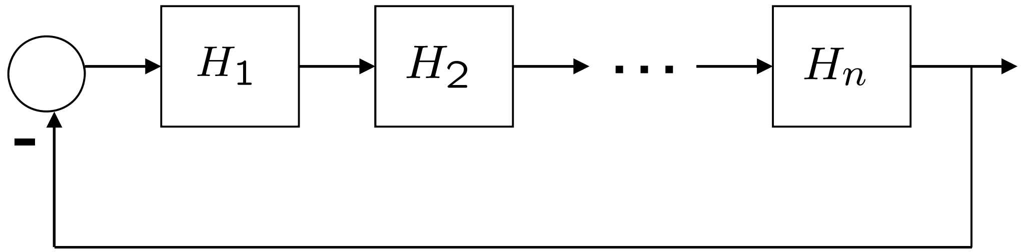
Figure: Kholodenko (2006)

Gene Regulation: Jacob & Monod (‘61), Goodwin (‘65), Elowitz & Leibler (2000)



Metabolic Pathways: Morales (’67), Dibrov *et al.* (‘82), Stephanopoulos *et al.* (‘98)

Secant Criterion for Local Stability: (Tyson & Othmer, 1978; Thron, 1991)

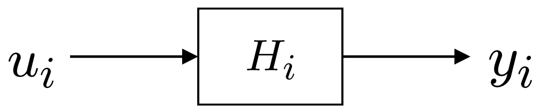


The cyclic interconnection of linear blocks $H_i: \;\; \tau_i \dot{y}_i = -y_i + \gamma_i u_i$

is asymptotically stable if:

$$\gamma_1 \ldots \gamma_n < \sec(\pi/n)^n$$ **--- (secant)**

Extension to Nonlinear Blocks via Passivity: (Arcak and Sontag, 2006)

If each block 

is output strictly passive:

$$\dot{S}_i \leq -||y_i||^2 + \gamma_i \, u_i^T y_i$$

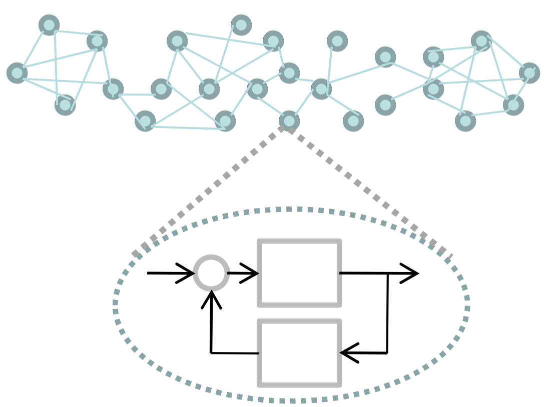
with pos. def. S_i and if (secant) holds then global stability with Lyap. function:

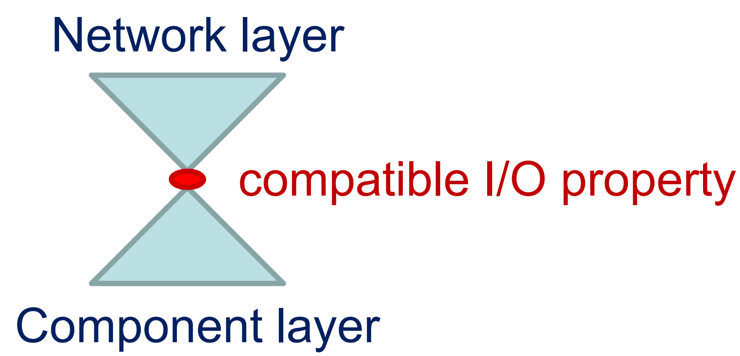
$$V = \sum_{i=1}^n d_i S_i$$

This approach divides analysis/design procedures into two layers:

1) Network layer: Represent components with I/O properties, such as passivity, as abstractions of their detailed dynamic models.

Determine which I/O properties are compatible with network structure: (Moylan and Hill, 1978), (Vidyasagar, 1981), (Megretski & Rantzer, 1997)





2) Component layer: Verify or assign the relevant I/O properties without relying on further knowledge of the network.

Component Analysis of the Cyclic Reaction Network:

$$
\begin{aligned}
\dot{x}_1 &= f_1(x_1) - g_1(x_1)h_n(x_n) \\
\dot{x}_2 &= f_2(x_2) + g_2(x_2)h_1(x_1) \\
&\vdots \\
\dot{x}_n &= f_n(x_n) + g_n(x_n)h_{n-1}(x_{n-1})
\end{aligned}
$$

$h_i(\cdot)$: increasing functions

Task: Verify that each subsystem H_i :

$$
u_i - u_i^* \longrightarrow \boxed{\begin{aligned} \dot{x}_i &= f_i(x_i) + g_i(x_i)u_i \\ y_i &= h_i(x_i) \end{aligned}} \longrightarrow y_i - y_i^*
$$

is output strictly passive relative to fixed point x_i^* and calculate gain γ_i

Challenge: The network fixed point x^* and consequently u_i^* and y_i^* depend on all other components and are highly uncertain

Equilibrium-Independent Passivity (Hines, Arcak and Packard, 2009)

Suppose the system: $\dot{x} = f(x,u) \quad y = h(x,u)$ is such that, for every $u^* \in \mathcal{U}$ there exists unique x^* satisfying $f(x^*,u^*) = 0$

Definition: The system is **equilibrium-independent passive** if for every $u^* \in \mathcal{U}$ there exists storage function $S_{u^*}(x) > 0 \quad \forall x \neq x^*$ satisfying:

$$\nabla_x S_{u^*} f(x,u) \leq (u-u^*)^T(y-y^*) - \frac{1}{\gamma}\|y-y^*\|^2 \qquad \textbf{EIP}(\gamma)$$

Necessary &sufficient conditions for EIP of scalar input-affine systems:

$$\dot{x} = f(x) + g(x)u \quad y = h(x) \quad g(x) \neq 0$$

1) $\mathrm{sign}(g(x))h(x)$ is a strictly increasing function

2) The steady-state map $y^* = k_y(u^*)$ satisfies:

$$0 \leq k_y'(u^*) \leq \gamma \quad \forall u^* \in \mathcal{U}$$

$$S_{u^*}(x) = \int_{x^*}^{x} \frac{h(\sigma)-h(x^*)}{g(\sigma)} d\sigma$$

Equilibrium-Independent Passivity (Hines, Arcak and Packard, 2009)

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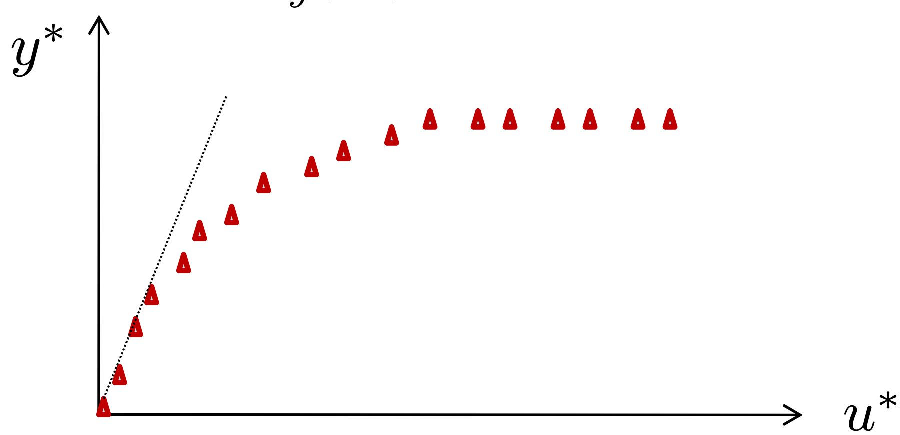


Example: MAPK Cascade with Inhibitory Feedback

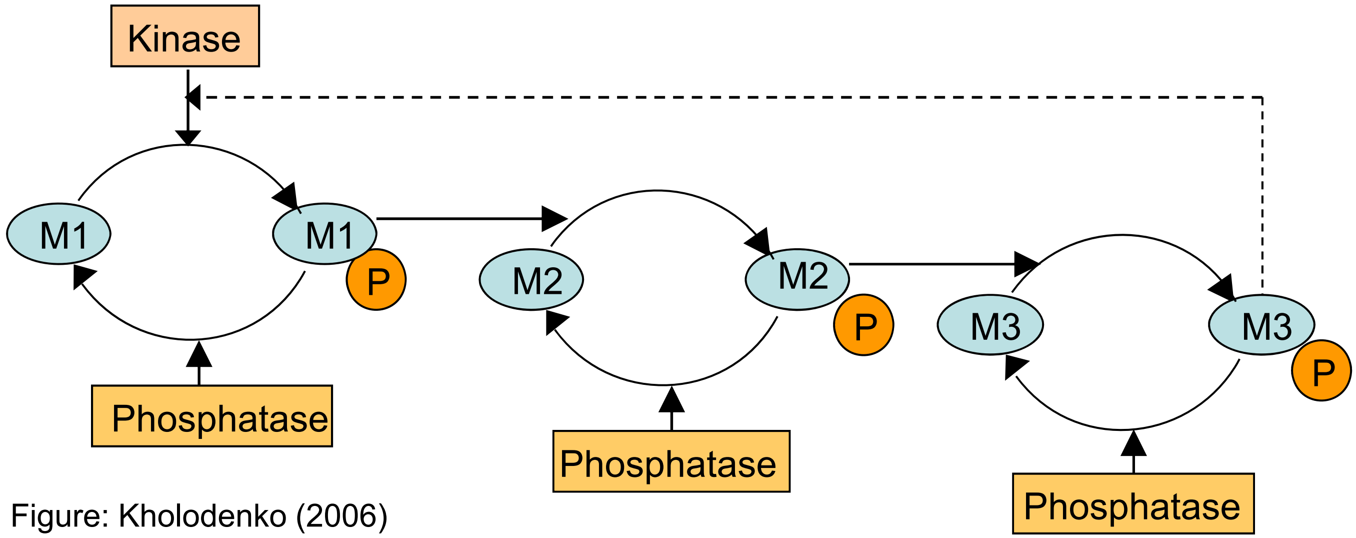


Figure: Kholodenko (2006)

$$
\begin{aligned}
\dot{x}_1 &= -\frac{b_1 x_1}{c_1 + x_1} + \frac{d_1(1-x_1)}{e_1 + (1-x_1)} \frac{\mu}{1 + k x_3} \\
\dot{x}_2 &= -\frac{b_2 x_2}{c_2 + x_2} + \frac{d_2(1-x_2)}{e_2 + (1-x_2)} x_1 \\
\dot{x}_3 &= -\frac{b_3 x_3}{c_3 + x_3} + \frac{d_3(1-x_3)}{e_3 + (1-x_3)} x_2 .
\end{aligned}
$$

Shvartsman *et al.* (2001):

$b_1 = e_1 = c_1 = b_2 = 0.1$

$c_2 = e_2 = c_3 = e_3 = 0.01$

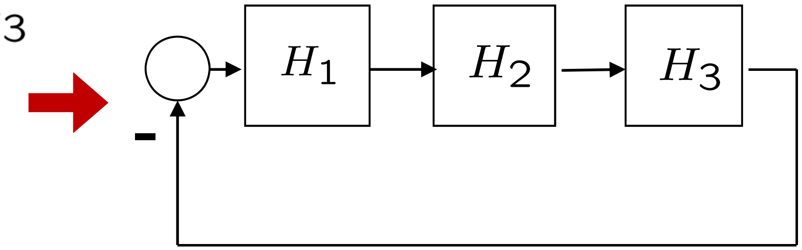
$d_1 = d_2 = d_3 = 1$

$b_3 = 0.5 \quad \mu = 0.3$

- Secant estimate for global asymptotic stability: $k \leq 4.35$
- Small-gain estimate: $k \leq 3.9$ Bifurcation at: $k = 5.1$

Example: MAPK Cascade with Inhibitory Feedback

$$\dot{x}_1 = -\frac{b_1 x_1}{c_1 + x_1} + \frac{d_1(1-x_1)}{e_1 + (1-x_1)}\frac{\mu}{1+kx_3}$$
$$\dot{x}_2 = -\frac{b_2 x_2}{c_2 + x_2} + \frac{d_2(1-x_2)}{e_2 + (1-x_2)}x_1$$
$$\dot{x}_3 = -\frac{b_3 x_3}{c_3 + x_3} + \frac{d_3(1-x_3)}{e_3 + (1-x_3)}x_2.$$



H1: $f_1(x_1) = -\frac{b_1 x_1}{c_1 + x_1}$ $g_1(x_1) = \frac{d_1(1-x_1)}{e_1 + (1-x_1)}$ $h_1(x_1) = x_1$

H2: $f_2(x_2) = -\frac{b_2 x_2}{c_2 + x_2}$ $g_2(x_2) = \frac{d_2(1-x_2)}{e_2 + (1-x_2)}$ $h_2(x_2) = x_2$

H3: $f_3(x_3) = -\frac{b_3 x_3}{c_3 + x_3}$ $g_3(x_3) = \frac{d_3(1-x_3)}{e_3 + (1-x_3)}$ $h_3(x_2) = -\frac{\mu}{1+kx_3}$

To estimate γ_i , solve for $k_{y_i}(\cdot)$ from:

$$f_i(x_i^*) + g_i(x_i^*)u_* = 0 \quad \Rightarrow \quad x_i^* = k_{x_i}(u^*)$$
$$y_i^* = k_{y_i}(u^*) = h_i(k_{x_i}(u^*))$$

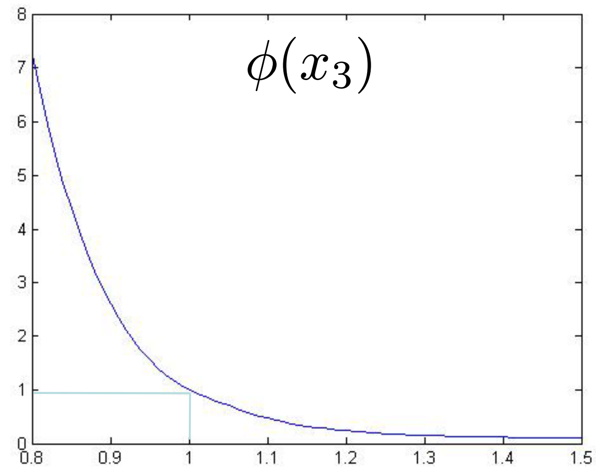
and obtain an upper bound on the slope. Secant criterion: $\gamma_1\gamma_2\gamma_3 < 8$

Local vs. Global Secant Criteria

Local secant criterion does not rule out the possibility of periodic orbits.

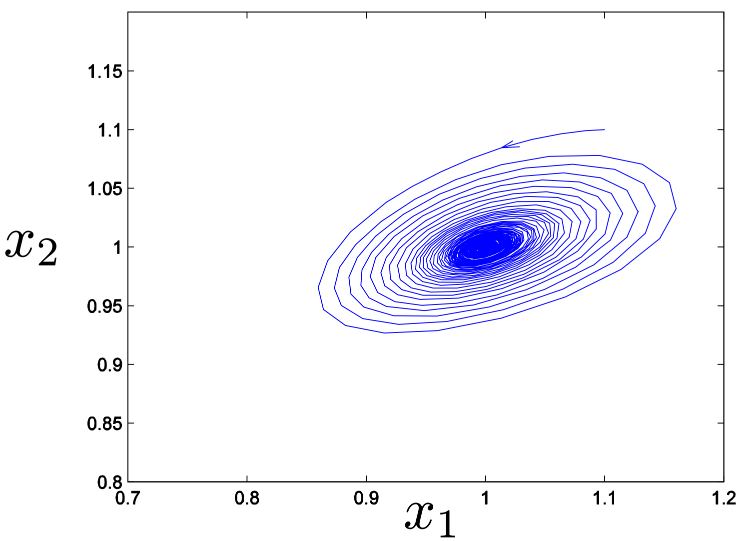
Example:

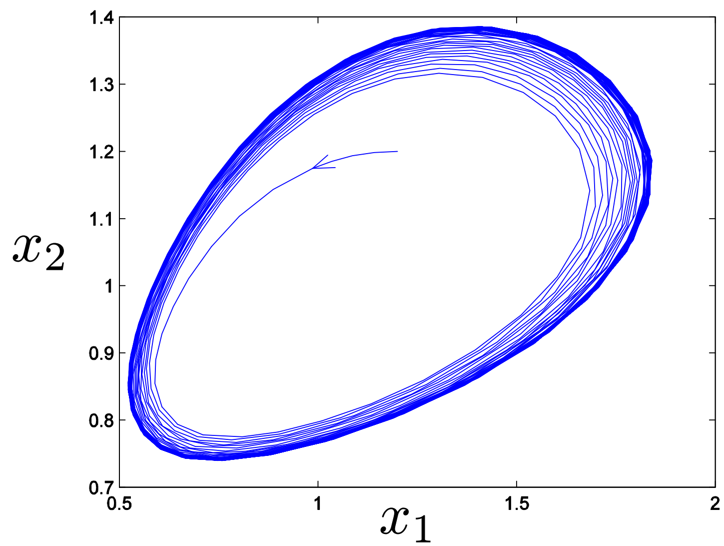
$$\begin{aligned}\dot{x}_1 &= -x_1 + \phi(x_3)\\ \dot{x}_2 &= -x_2 + x_1\\ \dot{x}_3 &= -x_3 + x_2\end{aligned}$$



Because $\phi'(1) = 7.5 < 8$ local secant criterion guarantees asymptotic stability of $x^* = (1,1,1)$

An attractive limit cycle exists in addition to x^*:





From Cyclic to Other Network Structures

$$\begin{aligned} \dot{x}_i &= f_i(x_i) + g_i(x_i)u_i \\ y_i &= h_i(x_i) \end{aligned} \qquad u = Ky$$

(Arcak and Sontag, 2008): Suppose each subsystem is EIP(γ_i) and a fixed point x^* exists for the network. Then x^* is asymptotically stable if

$$E = K - \mathrm{diag}\left\{\frac{1}{\gamma_1}, \cdots, \frac{1}{\gamma_n}\right\}$$

is diagonally stable ; that is, $E^T D + DE < 0$ for some diagonal $D > 0$

Cyclic Structure as a Special Case:

$$E_{cyclic} = \begin{bmatrix} -1/\gamma_1 & 0 & \cdots & -1 \\ 1 & -1/\gamma_2 & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 \\ 0 & \cdots & 1 & -1/\gamma_n \end{bmatrix}$$

is diagonally stable if and only if $\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n$

Example: MAPK Network Topologies in PC-12 Cells (Santos *et al*., 2007)

X_1 : Raf-1 X_2 : Mek1/2 X_3 : Erk1/2

(a) When activated with epidermal growth factors (EGFs)

(b) When activated with neuronal growth factors (NGFs)

$$E_a = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix}$$

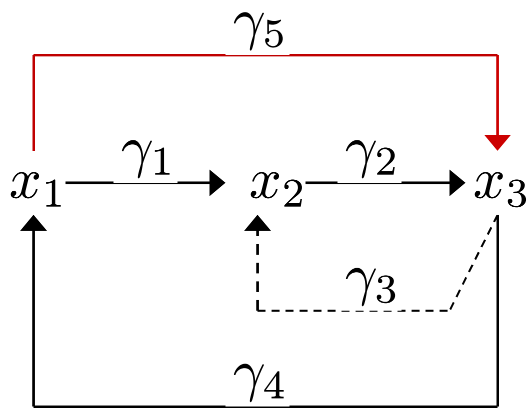
$$E_b = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix}$$

Lemma: E_a is diagonally stable iff:

$$\gamma_1\gamma_2\gamma_4 < 8$$

E_b is diagonally stable iff:

$$\gamma_1\gamma_2\gamma_4 < 1$$



(c) Increased connectivity from Raf-1 to Erk1/2 when NGF activation observed over a longer period of time

$$E_c = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 & 0 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 1 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} & 1 \\ 0 & 0 & 0 & 1 & -\frac{1}{\gamma_5} \end{bmatrix}$$

Principal submatrix obtained by deleting row-3 and column-3 diagonally stable iff:

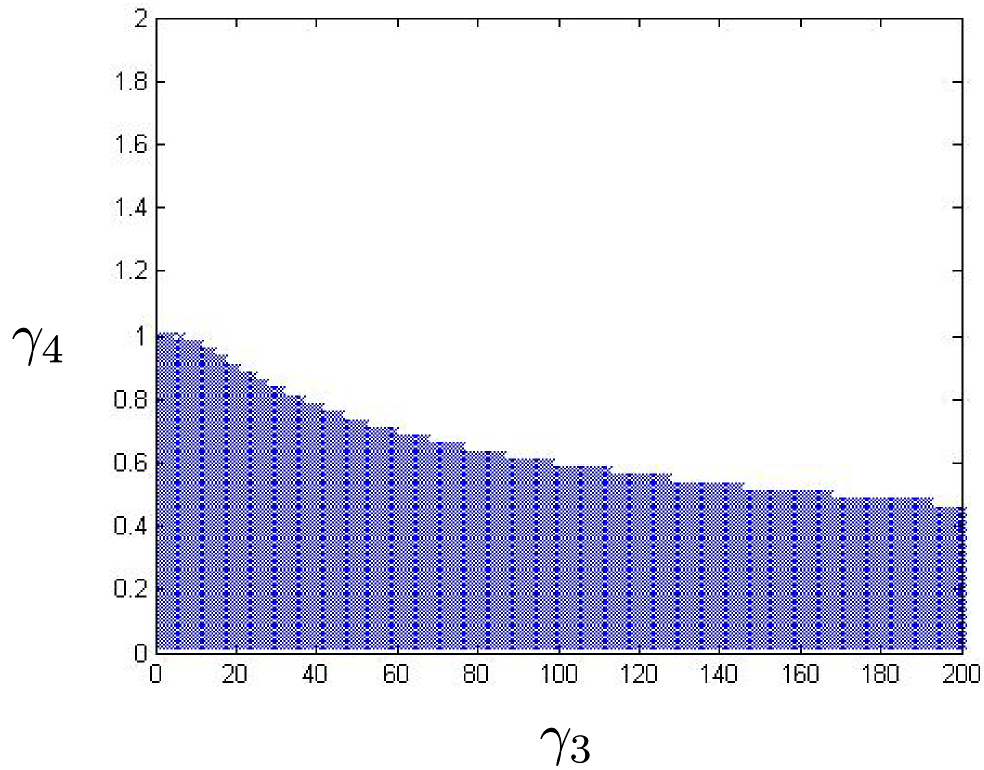
$$\gamma_1\gamma_2\gamma_4 + \gamma_4\gamma_5 < 1$$

➡ necessary (but not sufficient) condition for diagonal stability of E_c

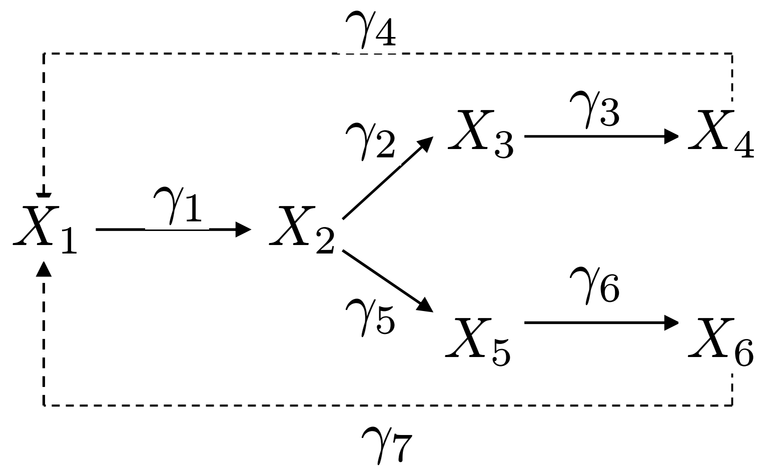
Exact diagonal stability region (determined numerically) in (γ_3, γ_4) -plane:

$$\gamma_1 = 1$$

$$\gamma_2 = \gamma_5 = 0.5$$



Example: Branched Pathways with Feedback Inhibition



Lemma: The matrix

$$E = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -\frac{1}{\gamma_4} & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -\frac{1}{\gamma_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_7} \end{bmatrix}$$

is diagonally stable if and only if:

$$\gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7 < \sec(\pi/4)^4 = 4$$

Extension to Reaction-Diffusion Systems

$$\dot{x} = f(x) \quad x \in R^n$$ **(R)**

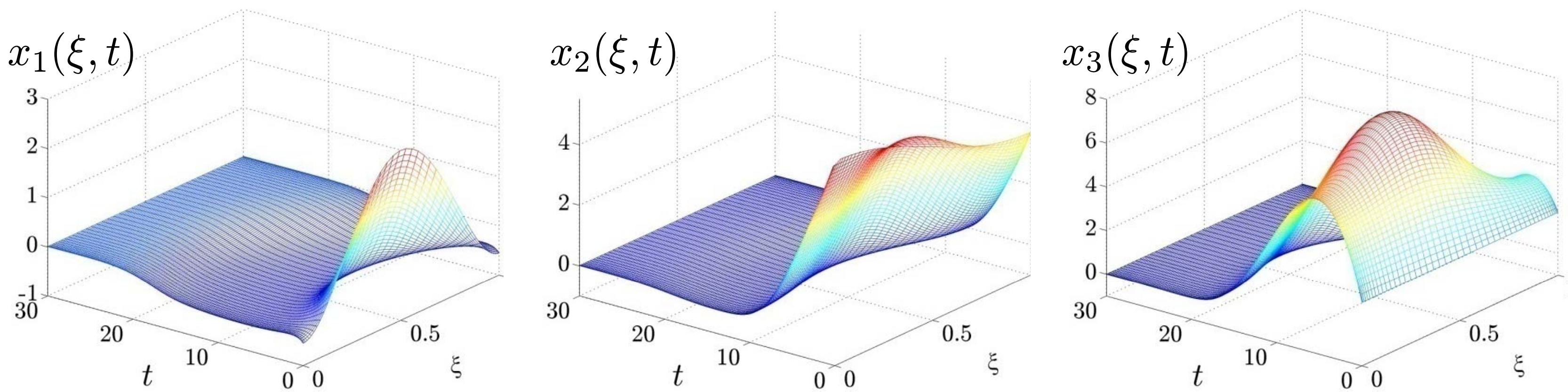
$$\frac{\partial x}{\partial t} = f(x) + \mathcal{D}\nabla^2 x$$ on domain Ω with Neumann boundary condition **(RD)**

Diffusion-Driven Instability (Turing, 1952): Stability of x^* in (R) does not imply stability of the uniform steady-state $x(\xi) \equiv x^*$ in (RD).

(Jovanovic, Arcak, Sontag, 2008; Wang 2008):

The diagonal stability test for (R) decomposed into EIP subsystems guarantees (upon mild technical conditions) global stability for uniform steady-state in (RD).

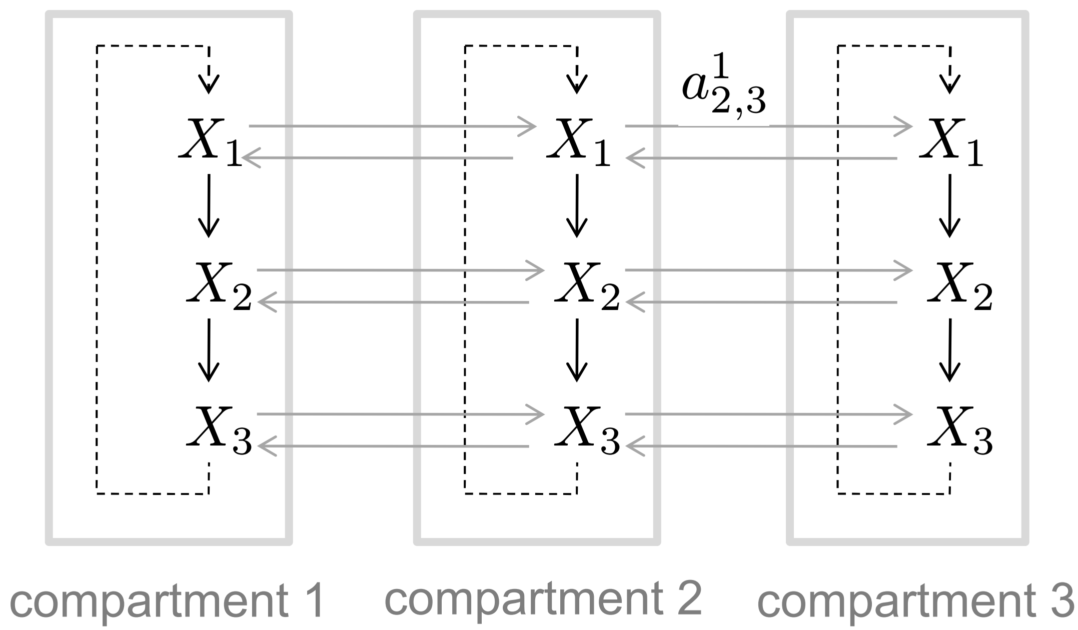
MAPK Cascade Example with Diffusion:



From Stability to Synchronization

Species i in compartment k:

$$\dot{x}_{i,k} = \underbrace{f_i(x_{i,k}) + g_i(x_{i,k})u_{i,k}}_{\text{identical model in each compartment}} + \sum_{j \neq k} \underbrace{a^i_{j,k}(x_{i,j} - x_{i,k})}_{\text{diffusive coupling btw compartments}}$$



Diffusion graph for species i represented with Laplacian:

$$L^i_{j,k} = \begin{cases} \sum_{p \neq j} a^i_{j,p} & j = k \\ -a^i_{j,k} & j \neq k \end{cases}$$

Algebraic connectivity:

$$\lambda_i = \min_{\substack{\|z\|=1 \\ z \perp 1_n}} \frac{z^T L_i z}{z^T z}$$

(Scardovi, Arcak and Sontag, 2009): Replace EIP with "co-coercivity" and modify the dissipativity matrix as:

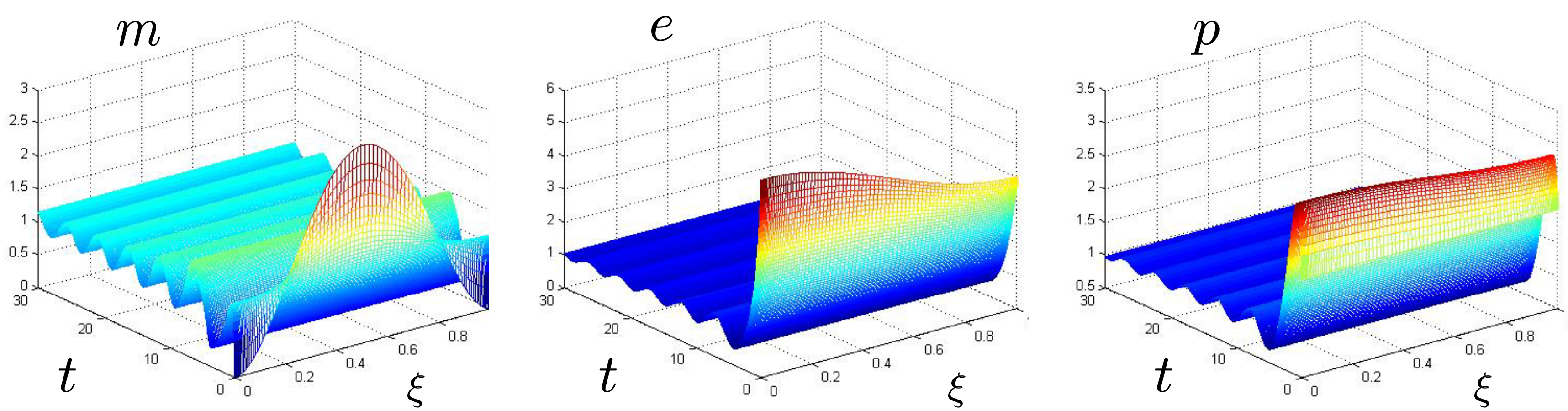
$$E_{\text{sync}} = E - \text{diag}\{\lambda_1, \cdots, \lambda_n\}$$

If E_{sync} is diagonally stable then $x_{i,k}(t) - x_{i,j}(t) \to 0$ for each species i

Example: For cyclic coupling, E_{sync} is diagonally stable if and only if:

$$\frac{\gamma_1}{1+\gamma_1\lambda_1} \cdots \frac{\gamma_n}{1+\gamma_n\lambda_n} < \sec(\pi/n)^n$$

Goodwin Oscillator with Diffusion:



Conclusions

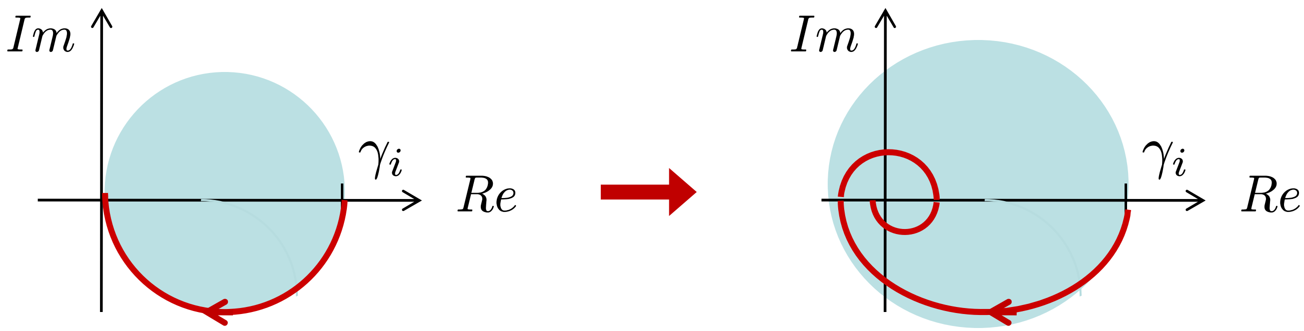
Passivity approach used to extend the classical secant criterion:

- From local, linear models to nonlinear models;
- From cyclic networks to general interconnection structures.

Modified criteria developed for stability and synchronization in the presence of diffusion.

Remaining problems:

- Verifying EIP for higher order blocks.
- Accounting for time delays:



Papers Discussed in this Talk

M. Arcak and E.D. Sontag. Diagonal stability of a class of cyclic systems and its connection with the secant criterion. *Automatica*, September 2006.

M. Jovanovic, M. Arcak and E.D. Sontag. A passivity-based approach to stability of spatially distributed systems with a cyclic interconnection structure. *IEEE Transactions on Automatic Control and IEEE Transactions on Circuits and Systems (Joint Special Issue on Systems Biology)*, January 2008.

M. Arcak and E.D. Sontag. A passivity-based stability criterion for a class of biochemical reaction networks. *Mathematical Biosciences and Engineering,* January 2008.

L. Scardovi, M. Arcak and E.D. Sontag. Synchronization of interconnected systems with an input/output approach. To appear in *IEEE Transactions on Automatic Control,* 2009.

G. Hines, M. Arcak and A. Packard. Equilibrium-independent passivity: A new definition and implications. Submitted.