Stability of biochemical reactions with a cyclic interconnection structure

Mihailo Jovanović
www.umn.edu/∼mihailo

joint work with:
Murat Arcak
Eduardo Sontag

University of Minnesota

The University of California · Let There Be Light · 1868

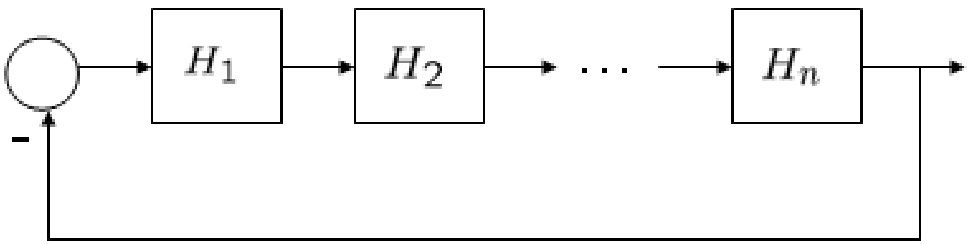
Rutgers The State University of New Jersey · 1766 · Sol Iustitiae et Occidentem Illustra

ECE Bio Seminar Lunch; May 6, 2009

Motivating example for cyclic systems

SEQUENCE OF BIOCHEMICAL REACTIONS

end product inhibits the first reaction



$$
\begin{aligned}
\dot{\psi}_1 &= -f_1(\psi_1) - g_n(\psi_n) \\
\dot{\psi}_2 &= -f_2(\psi_2) + g_1(\psi_1) \\
&\vdots \\
\dot{\psi}_n &= -f_n(\psi_n) + g_{n-1}(\psi_{n-1})
\end{aligned}
$$

LINEARIZATION (Tyson & Othmer '78, Thron '91)

$$
A = \begin{bmatrix}
-a_1 & 0 & \cdots & 0 & -b_n \\
b_1 & -a_2 & \ddots & & 0 \\
0 & b_2 & -a_3 & \ddots & \vdots \\
\vdots & \ddots & \ddots & \ddots & 0 \\
0 & \cdots & 0 & b_{n-1} & -a_n
\end{bmatrix}
\qquad
\begin{aligned}
a_i &> 0 \\
b_i &> 0
\end{aligned}
$$

SECANT CRITERION:

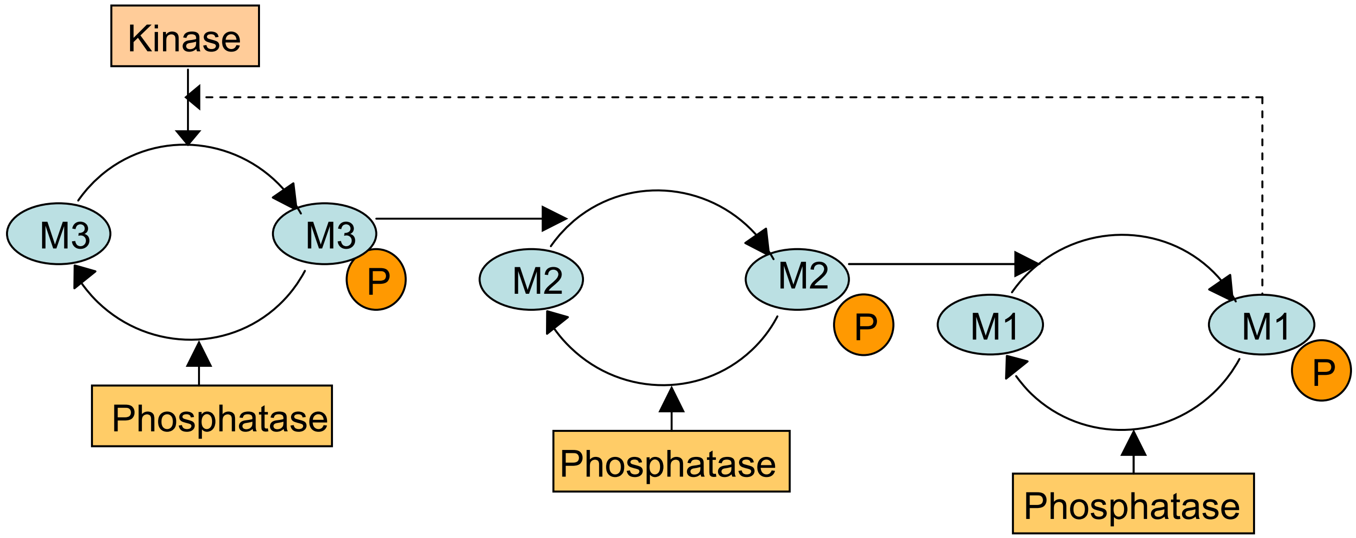
$$\frac{b_1 \cdots b_n}{a_1 \cdots a_n} < \sec(\pi/n)^n \Rightarrow \text{stability}$$

a_i's equal $\Rightarrow$ necessary as well

Cyclic biochemical networks with inhibitory feedback

CELLULAR SIGNALING

Kholodenko ’00; Shvartsman *et al.* ’01



GENE REGULATION

Jacob & Monod ’61; Goodwin ’65; Elowitz & Leibler ’00

$$S_0 \to S_1 \to S_2 \to \cdots \to S_n \to$$

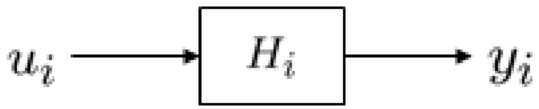
S_0: DNA S_1: mRNA S_2: enzyme S_n: endproduct

METABOLIC PATHWAYS

Morales & McKay ’67; Stephanopoulos *et al.* ’98

Stability via output strict passivity (Sontag '06)

OUTPUT STRICT PASSIVITY:



$$\gamma_i \langle u_i, y_i \rangle - \|y_i\|^2 \geq -\mu_i$$

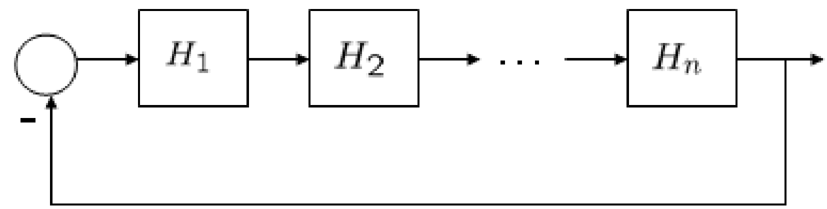
+

SECANT CRITERION:

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n$$

$\Rightarrow$

STABILITY:



TYSON & OTHMER, THRON: $H_i(s) = \dfrac{b_i}{s + a_i}, \ \gamma_i := \dfrac{b_i}{a_i}$

LESS RESTRICTIVE THAN SMALL-GAIN

LYAPUNOV-BASED CHARACTERIZATION (Arcak & Sontag '06):

exhibits classes of nonlinear cyclic systems

provides sharp stability estimates from secant criterion

Modeling issues

ODE MODELS:

suitable for 'well-mixed' environments

neglect exchange of chemical species between spatial domains

MORE APPROPRIATE MODELS: Reaction-Diffusion PDEs

SURPRISE: diffusion can introduce instability and pattern formation
Turing '52

QUESTION: identify classes of systems where diffusion doesn't lead to instability
Jovanović, Arcak, Sontag; IEEE TAC'08, *Special Issue on Systems Biology*

Diffusion driven instability (Turing '52)

$$\begin{bmatrix} \psi_{1t} \\ \psi_{2t} \end{bmatrix} = \left(\begin{bmatrix} c_1 \partial_{xx} & 0 \\ 0 & c_2 \partial_{xx} \end{bmatrix} + \begin{bmatrix} \alpha & \beta \\ \gamma & \delta \end{bmatrix} \right) \begin{bmatrix} \psi_1 \\ \psi_2 \end{bmatrix}, \quad x \in \mathbb{R}$$

stability $\Leftrightarrow$ $A(\kappa) := \begin{bmatrix} \alpha - c_1\kappa^2 & \beta \\ \gamma & \delta - c_2\kappa^2 \end{bmatrix}$ Hurwitz for all $\kappa \in \mathbb{R}$

A HAS UNSTABLE E-VALUES:

corresponding e-functions $\rightsquigarrow$ exp. growing spatio-temporal patterns

$$A(\kappa)\boldsymbol{\varphi}_n(\kappa) = \lambda_n(\kappa)\boldsymbol{\varphi}_n(\kappa)$$

$\downarrow$ SOLVE

$$\boldsymbol{\psi}(\kappa, t) = \mathrm{e}^{\lambda_n(\kappa)t}\boldsymbol{\varphi}_n(\kappa)$$

$\downarrow$ BACK TO PHYSICAL SPACE

$$\boldsymbol{\psi}(x, t) = \mathrm{Re}\left\{\mathrm{e}^{\lambda_n(\kappa)t + \mathrm{i}\kappa x}\boldsymbol{\varphi}_n(\kappa)\right\}$$

Outline

❶ Classes of systems

- ⋆ cyclic interconnection of n reaction-diffusion equations

❷ Linear reaction-diffusion equations

- ⋆ secant criterion and exponential stability
- ⋆ existence of decoupled quadratic Lyapunov function

❸ Nonlinear reaction-diffusion equations

- ⋆ passivity-based approach
- ⋆ convex Lyapunov-function

❹ Biological example

- ⋆ simplified MAPK cascade model

❺ Remarks

Linear cyclic reaction-diffusion systems

$$
\begin{aligned}
\psi_{1t} &= c_1\,\psi_{1xx} - a_1\psi_1 - b_n\psi_n \\
\psi_{2t} &= c_2\,\psi_{2xx} - a_2\psi_2 + b_1\psi_1 \\
&\vdots \\
\psi_{nt} &= c_n\,\psi_{nxx} - a_n\psi_n + b_{n-1}\psi_{n-1}
\end{aligned}
$$

STATE OF H_i: $\psi_i(x,t),\ x \in [0,\,1]$

NEUMANN BCS: $\psi_{ix}(0,t) = \psi_{ix}(1,t) = 0$

SPECTRAL DECOMPOSITION OF DIFFUSION OPERATOR:

e-functions: $\varphi_0(x) = 1, \quad \varphi_l(x) = \sqrt{2}\cos l\pi x, \quad l \in \mathbb{N}$

e-values: $\lambda_0 = 0, \quad \lambda_l = -(l\pi)^2, \quad l \in \mathbb{N}$

$$
\psi_i(x,t) = \sum_{k=0}^{\infty} z_{i,k}(t)\varphi_k(x)
$$

decoupled system on l_2^n: $\dot{z}_k = A_k z_k, \quad k = 0, 1, \ldots$

$$A_k := \begin{bmatrix} -\alpha_{1,k} & 0 & \cdots & 0 & -b_n \\ b_1 & -\alpha_{2,k} & \ddots & & 0 \\ 0 & b_2 & -\alpha_{3,k} & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -\alpha_{n,k} \end{bmatrix}$$

$$\left.\begin{array}{c} \alpha_{i,k} := a_i + c_i (k\pi)^2 \\ \Downarrow \\ \dfrac{b_1 \cdots b_n}{\alpha_{1,k} \cdots \alpha_{n,k}} \leq \dfrac{b_1 \cdots b_n}{a_1 \cdots a_n} < \sec(\pi/n)^n \end{array}\right\} \Rightarrow \text{ each } A_k \text{ Hurwitz}$$

LYAPUNOV-BASED PROOF:

$\exists$ a decoupled Lyapunov function: $V(\psi) := \sum_{i=1}^{n} d_i \langle \psi_i, \psi_i \rangle$

$\Updownarrow$

secant criterion holds

Nonlinear cyclic reaction-diffusion systems

$$
\begin{aligned}
\psi_{1t} &= (h_1(\psi_1)\,\psi_{1x})_x - f_1(\psi_1) - g_n(\psi_n) \\
\psi_{2t} &= (h_2(\psi_2)\,\psi_{2x})_x - f_2(\psi_2) + g_1(\psi_1) \\
&\vdots \\
\psi_{nt} &= (h_n(\psi_n)\,\psi_{nx})_x - f_n(\psi_n) + g_{n-1}(\psi_{n-1})
\end{aligned}
$$

GLOBAL ASYMPTOTIC STABILITY:

$$\sigma f_i(\sigma) > 0, \quad \sigma g_i(\sigma) > 0, \quad \forall\, \sigma \in \mathbb{R} \setminus \{0\} \qquad \text{(C1)}$$

$$g_i(\sigma)/f_i(\sigma) \leq \gamma_i, \quad \forall\, \sigma \in \mathbb{R} \setminus \{0\} \qquad \text{(C2)}$$

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n \qquad \text{(C3)}$$

$$\lim_{|\psi_i| \to \infty} \int_0^{\psi_i} g_i(\sigma)\, \mathrm{d}\sigma = \infty \qquad \text{(C4)}$$

$$h_i \geq 0, \quad g_{i\sigma} := \partial g_i/\partial \sigma \geq 0, \quad \forall\, \sigma \in \mathbb{R} \qquad \text{(C5)}$$

☞ (C5) $\Rightarrow$ convexity of: $V(\psi) = \sum_{i=1}^{n} d_i \gamma_i \int_0^1 \left(\int_0^{\psi_i(x)} g_i(\sigma)\, \mathrm{d}\sigma \right) \mathrm{d}x$

Stability proof (sketch)

$$H_i : \begin{cases} \psi_{it} = (h_i(\psi_i)\,\psi_{ix})_x - f_i(\psi_i) + u_i \\ y_i = g_i(\psi_i) \end{cases}$$

KEY:

H_i – Output Strictly Passive with storage function:

$$V_i(\psi_i) := \gamma_i \int_0^1 \left(\int_0^{\psi_i(x)} g_i(\sigma)\,\mathrm{d}\sigma \right) \mathrm{d}x$$

$$\begin{aligned} \dot{V}_i &= \gamma_i \langle g_i(\psi_i),\, \psi_{it} \rangle \\ &= \gamma_i \langle g_i(\psi_i),\, (h_i(\psi_i)\,\psi_{ix})_x - f_i(\psi_i) + u_i \rangle \\ &= -\gamma_i \langle g_{i\psi_i}\,\psi_{ix},\, h_i\,\psi_{ix} \rangle - \gamma_i \langle g_i, f_i \rangle + \gamma_i \langle g_i, u_i \rangle \end{aligned}$$

$\downarrow$ (C1,C2,C5)

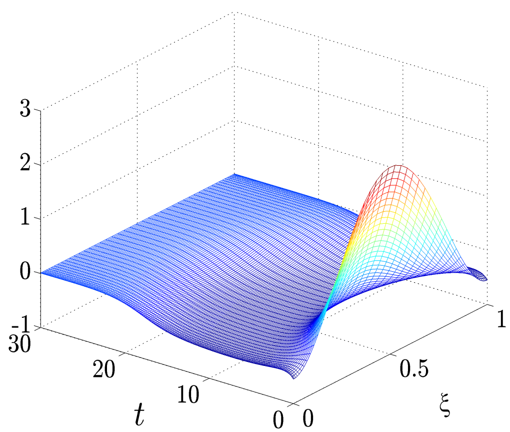
$$\begin{aligned} \dot{V}_i &\le -\langle g_i,\, g_i \rangle + \gamma_i \langle g_i,\, u_i \rangle \\ &= -\|y_i\|^2 + \gamma_i \langle y_i,\, u_i \rangle \end{aligned}$$

An example

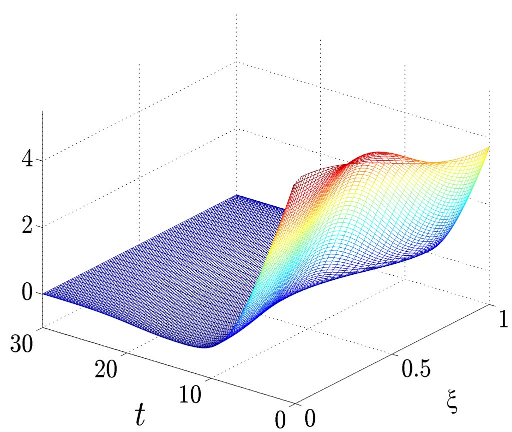
MAPK CASCADES: responsible for cell proliferation and growth

$$
\begin{aligned}
\phi_{1t} &= 0.001\,\phi_{1xx} - \frac{\phi_1}{1+\phi_1} + \frac{0.4}{1+\phi_3} \\
\phi_{2t} &= 0.001\,\phi_{2xx} - \frac{\phi_2}{1+\phi_2} + 0.4\phi_1 \\
\phi_{3t} &= 0.001\,\phi_{3xx} - \frac{\phi_3}{1+\phi_3} + 0.4\phi_2
\end{aligned}
$$

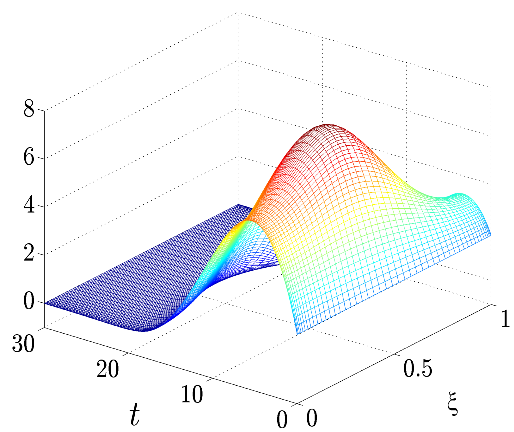
$\psi_1(x,t)$:



$\psi_2(x,t)$:



$\psi_3(x,t)$:



Remarks

PDEs with a cyclic interconnection structure

⋆ identied classes where diffusion doesn't lead to instability

Linear reaction-diffusion equations

⋆ secant criterion and exponential stability
⋆ existence of decoupled quadratic Lyapunov function

Nonlinear reaction-diffusion equations

⋆ passivity-based approach
⋆ convex Lyapunov-function