I/O monotone dynamical systems

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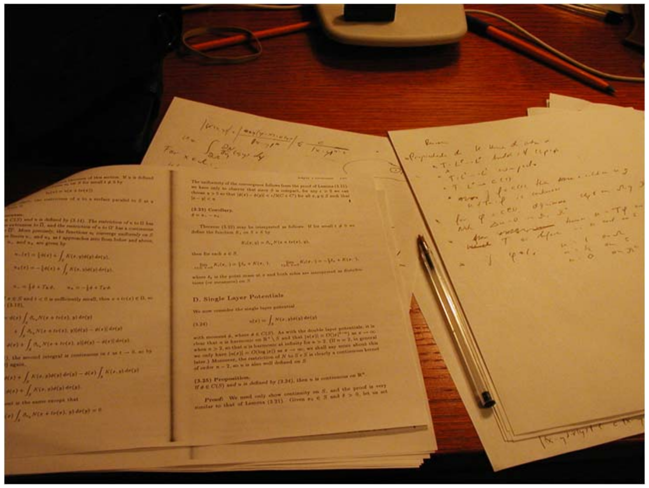
BEFORE:
Santa Barbara, January 2003
Having handed to me a photocopied paper by one Morris Hirsch, to be deciphered for weeks…

DURING DISSERTATION WORK:
Lots of reading, and regular meetings



Words of encouragement

Teaching by example how to interact with future colleagues:

From: "Eduardo Sontag" <sontag@feedback.rutgers.edu>
To: elranoquecroa@yahoo.com

So, I put this in a email to [redacted]:

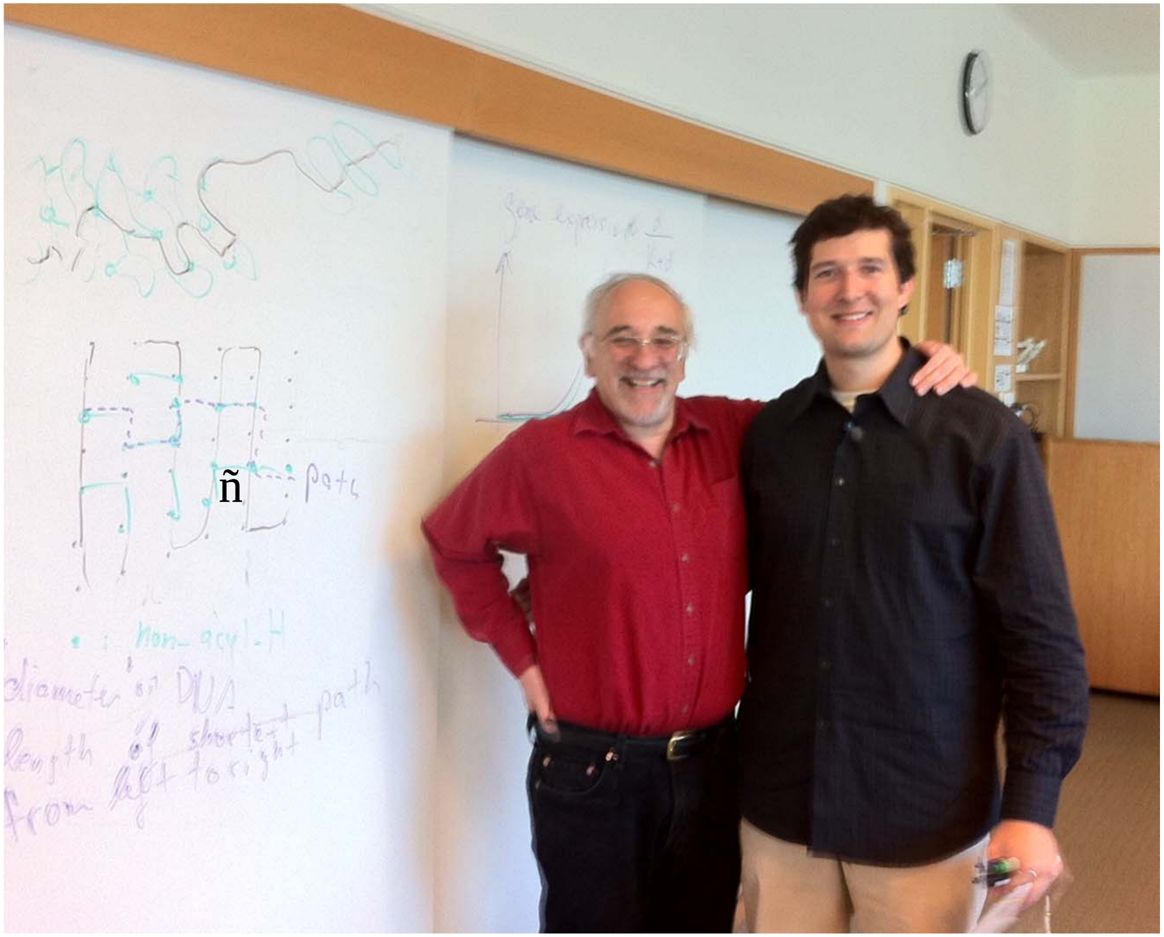
> >This last paragraph is here as a test. I suspect that you only read the
> >first few lines in emails (since often I say things later on, but in
> >subsequent emails you don't seem to be aware that I said such things). I
> >wonder if you will read this paragraph. (A simple "Y" will suffice.) ;-)

Guess what happened.

LOL.

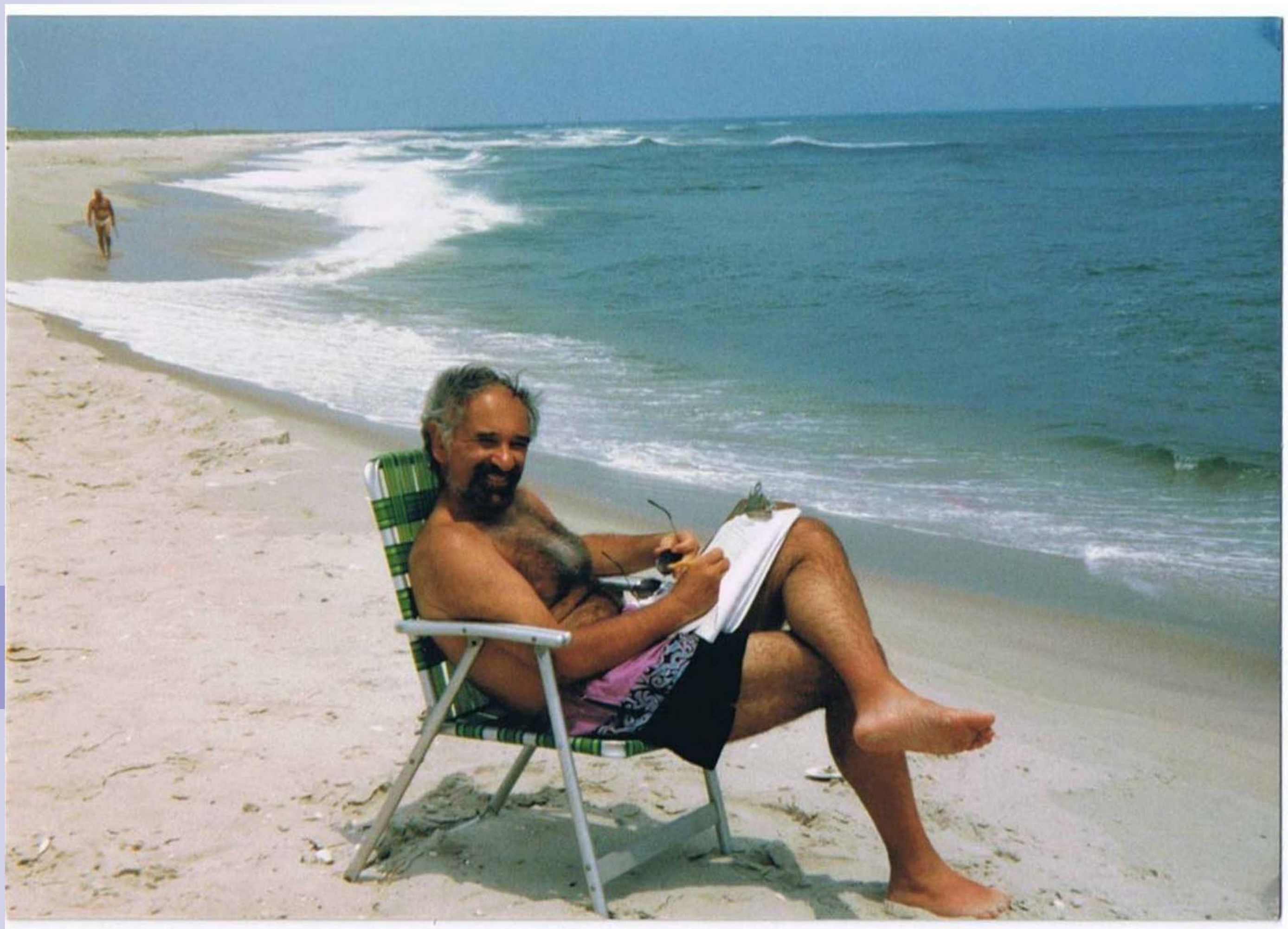
AFTER:
Boston, April 15^{th} 2011

Last day before 60^{th} birthday
(birthday cake pictured below)



Feliz cumpleaños Eduardo!

Summer 1999, Jersey Shore – by Misha Krichman

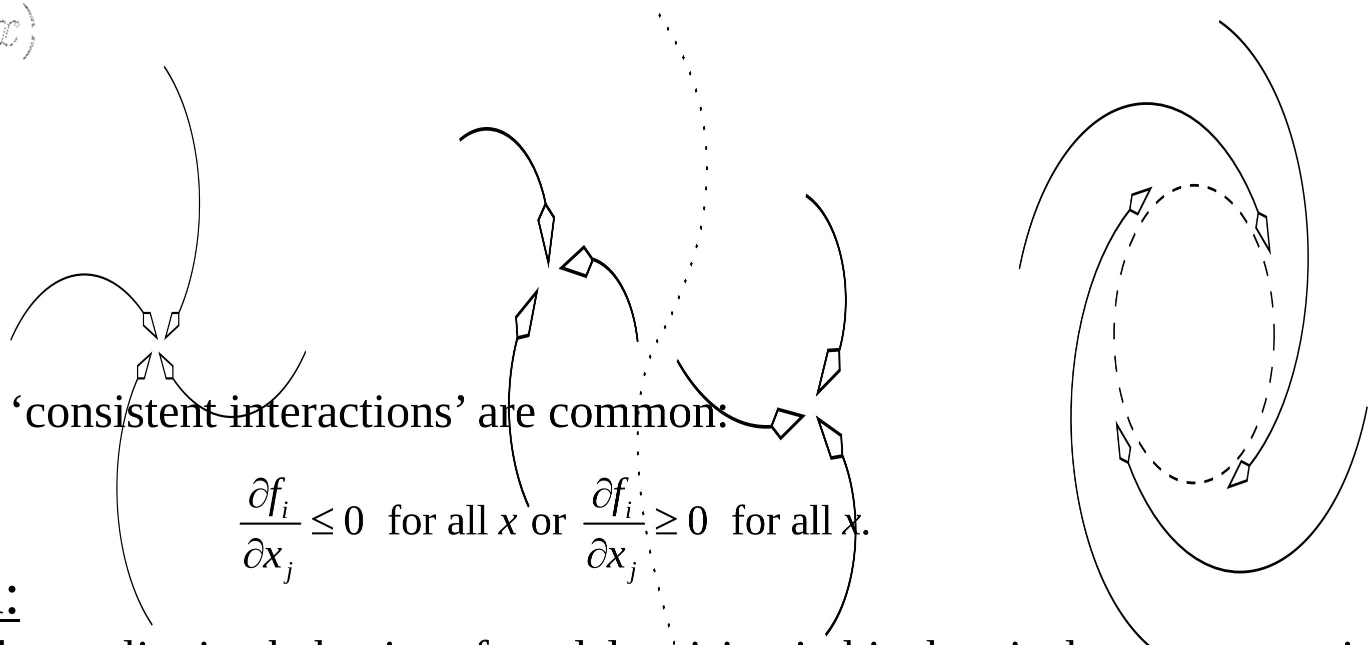


Please use YY-filter to zoom in and find out whose dissertation this is

Introduction: gene and protein networks

- systems of molecular interactions inside a cell, modeled using dynamical systems
- strongly nonlinear, high dimensional, and noisy
- many of the parameters are unknown
- but: often the phase space dynamics is one of the following:

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



- Also: ‘consistent interactions’ are common:

$$\frac{\partial f_i}{\partial x_j} \leq 0 \text{ for all } x \text{ or } \frac{\partial f_i}{\partial x_j} \geq 0 \text{ for all } x.$$

Problem:

To study the qualitative behavior of models arising in biochemical processes, using as little quantitative knowledge as possible

Monotone Input/Output Systems

$$\dot{x} = f(x,u), \quad y = h(x), \; h: X \to U$$

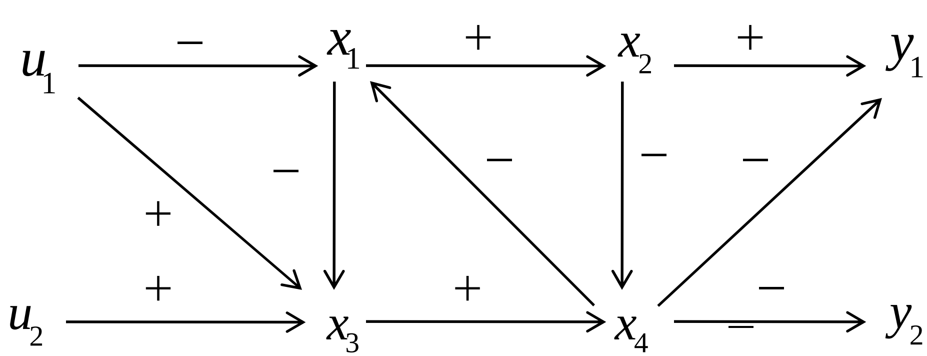
- Order defined on both the state space *X* and the input space *U*
- I/O system is *monotone* if $u(t) \leq v(t) \; \forall t, \; x(0) \leq z(0)$, implies $x(t) \leq z(t) \; \forall t$
- Positive Feedback Output: $x \leq z \;\; \to \; h(x) \; \leq \; h(z)$

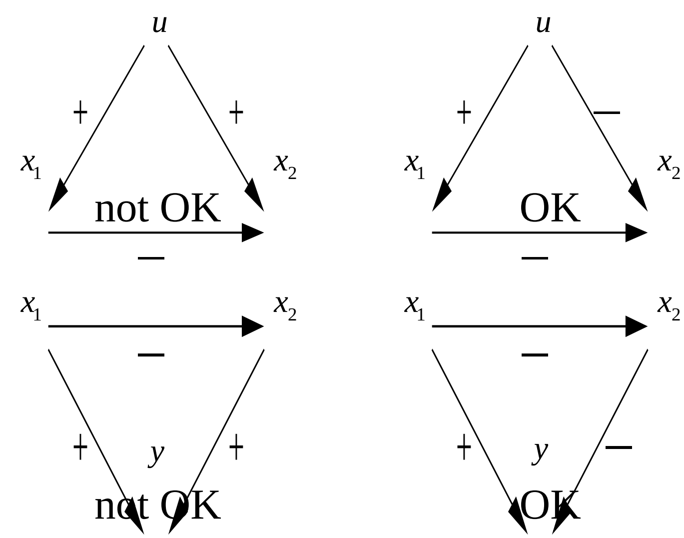
  Negative Feedback Output: $x \leq z \;\; \to \; h(x) \; \geq \; h(z)$
- Assume that the I/S characteristic is well defined, and define *S(u)* as the I/O characteristic

Example: Orthant I/O Monotone Systems

Recall orthant order: for some fixed $\delta \in (1,-1)^n$, $x \le z$ iff $x_i \delta_i \le z_i \delta_i \ \forall i$

$$\dot{x} = f(x,u), \quad y = h(x)$$

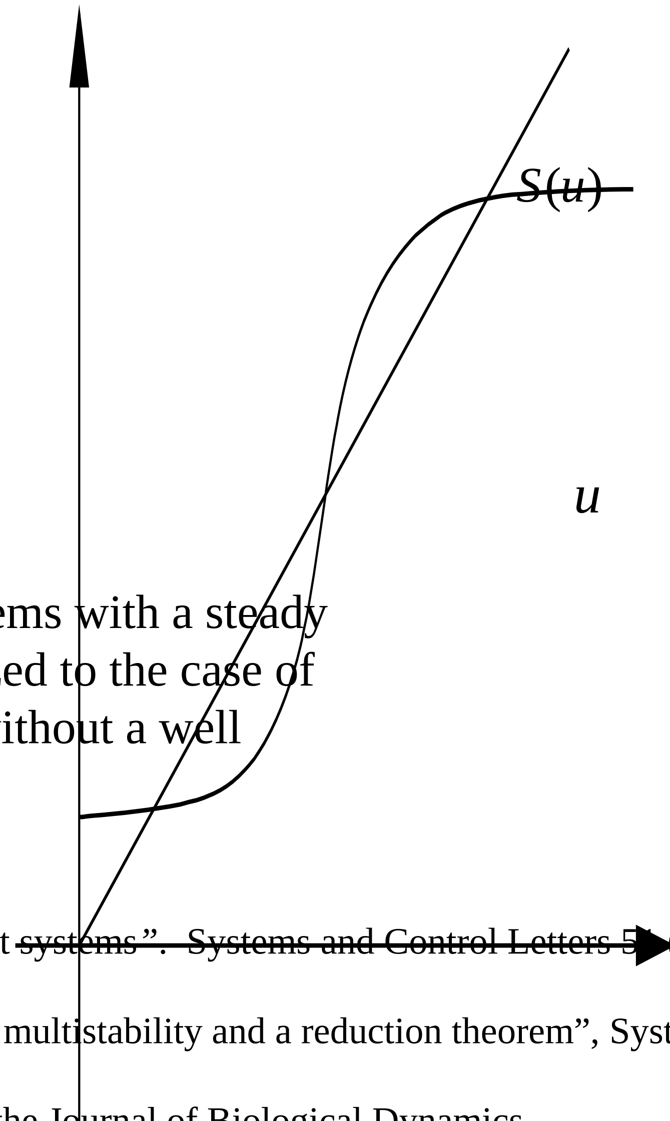




- Positive parity for all *undirected* feedback loops, including those involving inputs, states and/or outputs
- Positive feedback: all paths from any input to any output have positive parity
- Negative feedback: all paths from any input to any output have negative parity

Positive Feedback Multistability Theorem

Theorem: In the SISO positive feedback case, each equilibrium of the closed loop system $x' = f(x,h(x))$ corresponds to a fixed point of $S(u)$. Moreover, the stable equilibria correspond to the fixed points such that $S'(u) < 1$.



This result is proved for arbitrary monotone systems with a steady state response function $S(u)$ in [1]. It is generalized to the case of multiple inputs and outputs [2], and to systems without a well defined response function $S(u)$ [3].

[1] D. Angeli, E. Sontag, "Multistability in monotone input/output systems". Systems and Control Letters 51 (2004), 185-202.
[2] GAE, E. Sontag, "Monotone systems under positive feedback: multistability and a reduction theorem", Systems and Control Letters 51(2):185-202, 2005.
[3] GAE, E. Sontag, "Monotone bifurcation graphs", to appear in the Journal of Biological Dynamics.

Comments:

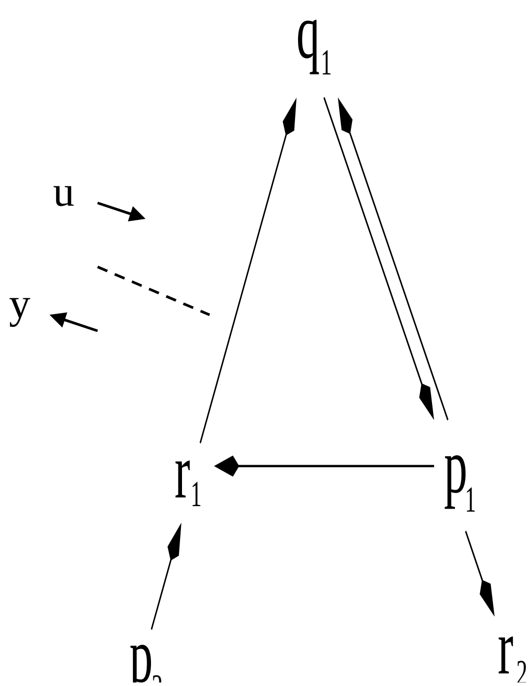
- Only use the general topology of the interaction digraph, plus quantitative information about the function *S(u)* -- no need to know all parameter values!
- The function *S(u)* can potentially be measured in the lab, without precise knowledge of parameter values
- This analysis also stresses the robustness of the system: small parameter changes will only affect the number of equilibria etc only to the extent that they alter the steady state response.

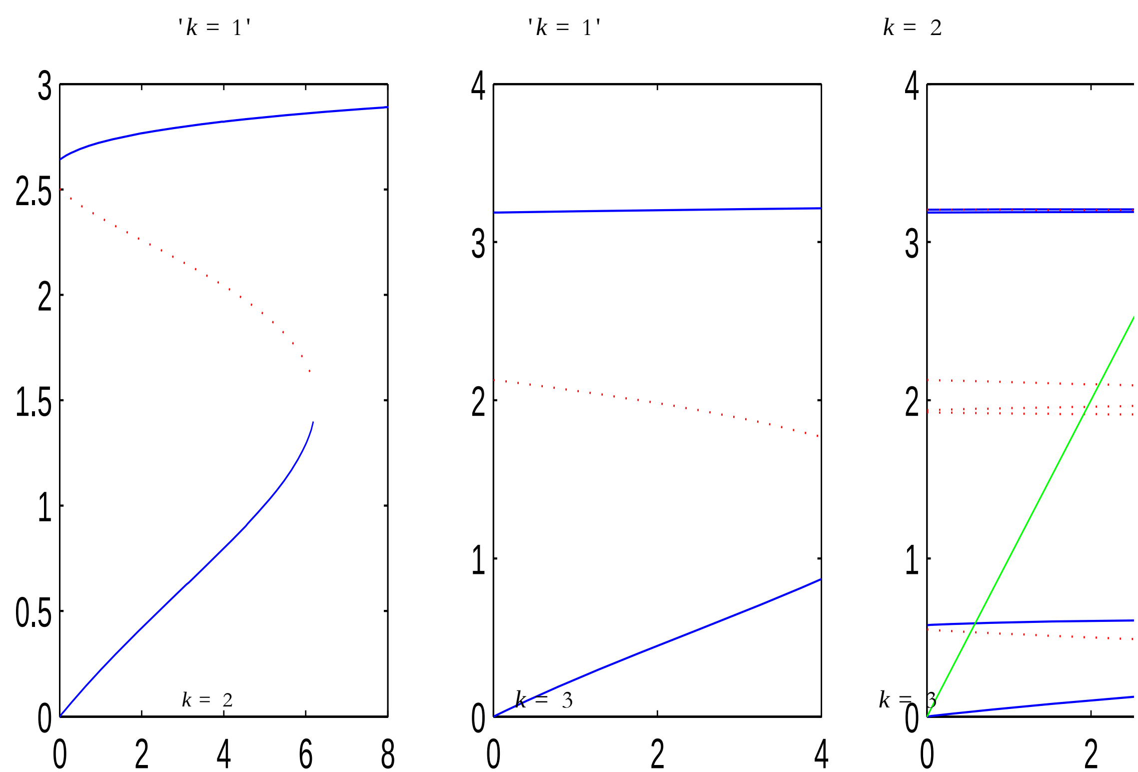
Positive Feedback - Example

Consider the following gene regulatory network of *k* genes:

$$\dot{p}_i = K_{imp,i}(q_i) - K_{exp,i}(p_i) - a_{2,i}p_i$$
$$\dot{q}_i = T(r_i) - K_{imp,i}(q_i) + K_{exp,i}(p_i) - a_{3,i}q_i$$
$$\dot{r}_i = H(p_i, p_{i-1}) - a_{1,i}r_i$$
$$i=1\ldots k,\; p_0 := p_k$$

p_i : protein *i*, located in the nucleus
r_i: messenger RNA
q_i: protein i in the cytoplasm





Negative feedback and the Small Gain Theorem (SGT)

Given a SISO I/O monotone system under negative feedback, assume that the I/O characteristic *S(u)* is well defined.   Suppose that the following condition holds:

Small Gain Condition (SGC): the function *S(u)* forms a discrete system

$$u_{n+1} = S(u_n)$$

which is globally attractive towards a unique equilibrium.

Then the closed loop of the system converges globally towards an equilibrium.

D. Angeli, E. Sontag, *Monotone control systems,* IEEE Trans. on Automatic Control 48 (10): 1684-1698, 2003.

Negative feedback and the Small Gain Theorem (SGT)

A generalization to abstract Banach spaces yields an analog result for:

- Multiple inputs and outputs [1]
- Delays of arbitrary length [1]
- Spatial models of reaction-diffusion equations [2]

Also, using a computational algorithm [3] one can efficiently decompose *any* sign-definite system as the closed loop of a I/O monotone system under negative feedback.

[1] GAE, E. Sontag, "On the global attractivity of abstract dynamical systems satisfying a small gain hypothesis, with application to biological delay systems", to appear in J. Discrete and Continuous Dynamical Systems.
[2] GAE, H. Smith, E. Sontag, "Non-monotone systems decomposable into monotone systems with negative feedback", Journal of Differential Equations 224:205-227, 2006.
[3] B. DasGupta, GAE, E. Sontag, Y. Zhang, Algorithmic and complexity results for decompositions of biological networks into monotone subsystems, Lecture Notes in Computer Science 4007: Experimental Algorithms, pp. 253-264, Springer Verlag, 2006.

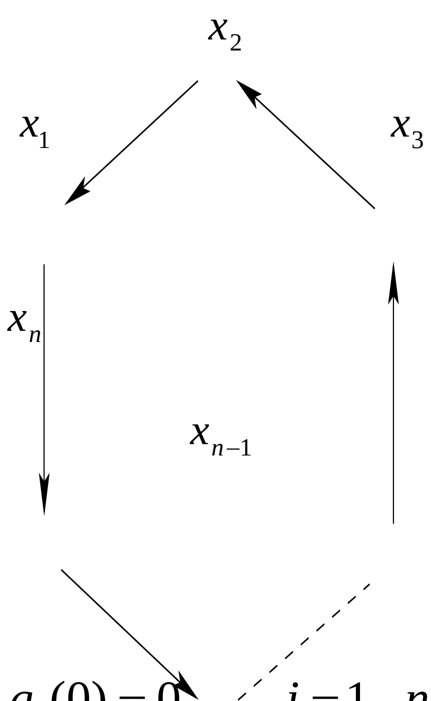
Comments

- Monotone systems can also be used to establish the global asymptotic behavior of certain *non-monotone* systems
- Once again, the result only uses the general topology of the interaction digraph, plus quantitative information about the function *S(u)* -- no need to know all parameter values
- This theorem can also be extended to delay and reaction-diffusion equations

Example: stability and oscillations under time delay

Consider the nonlinear delay system

$$\dot{x}_1 = g_1(x_2) - \alpha_1 x_1$$
$$\dot{x}_2 = g_2(x_3) - \alpha_2 x_2$$
$$....$$
$$\dot{x}_n = g_n(x_1(t-\tau)) - \alpha_n x_n$$

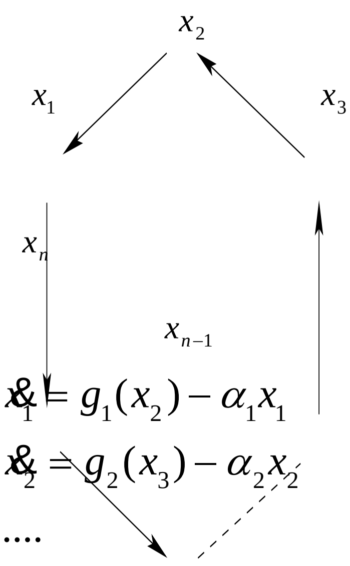


under the assumptions

$$\alpha_i > 0, \quad i = 1 \ldots n,$$
$$\partial_i g_i'(x) \geq 0, \quad \partial_i = 1, -1, \quad \partial_1 \cdot \ldots \cdot \partial_n = -1, \quad g_i(0) = 0, \quad i = 1 \ldots n.$$

- Can allow for multiple delays and $g_i(\overline{x}_{i+1}) = \alpha_i \overline{x}_i$, after a change of variables
- The dynamics of this system is governed by a Poincare-Bendixson theorem
- Recent examples of this system in the biology literature: Elowitz & Leibler 2000, Monk 2003, Lewis 2003.

Example: stability and oscillations under time delay



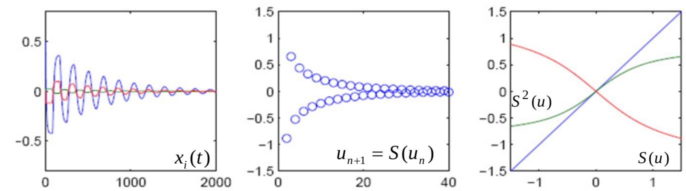
$$\dot{x}_1 = g_1(x_2) - \alpha_1 x_1$$
$$\dot{x}_2 = g_2(x_3) - \alpha_2 x_2$$
....
$$\dot{x}_n = g_n(x_1(t-\tau)) - \alpha_n x_n$$

$$g_i(x) = \frac{a x^m}{b + x^m} + c, \quad \text{or}$$
$$g(x) = \frac{a}{b + x^m} + c$$

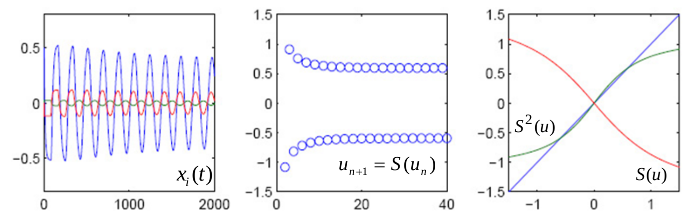
Theorem:

Consider a cyclic time delay system under negative feedback, with *Hill function nonlinearities*. Then exactly one of the following holds:

I. If the iterations of S(u) are globally convergent, then all solutions of the cyclic system converge towards the equilibrium, for every value of the delay (SGT):



II. Else, periodic solutions exist for some values of the delay, due to a Hopf bifurcation on the delay parameter.



If some nonlinearities $g_i(x)$ have nonnegative Schwarzian derivative, then both I. and II. might be violated. This is possible even for some (non-Hill) sigmoidal nonlinearites.

GAE, "A dichotomy for a class of cyclic delay systems", Mathematical Biosciences 208:63-75, 2007.

Unique fixed point for characteristic of negative feedback systems

Question: is it possible to generalize SGT to the case of bistability as in the positive feedback case, even for MIMO systems?

Theorem: assume

- $x' = f(x,u),\ \ y = h(x)$ I/O monotone, negative feedback
- $S : \mathbb{R}^n \to \mathbb{R}^n$ bounded, C^2 I/O characteristic ($u \le v \to S(u) \ge S(v)$)
- $-S'(u_0)$ strongly monotone, hyperbolic for every fixed point u_0
- a.e. iteration of $u_{i+1} = S(u_i)$ is convergent to *some* s.s. (weak small gain condition)

Then: S(u) has a unique fixed point.

Answer: cannot generalize SGT to the case of bistability for MIMO systems, at least using the weak small gain condition

On the other hand, this result allows to unify MIMO positive and negative feedback cases (following slide)

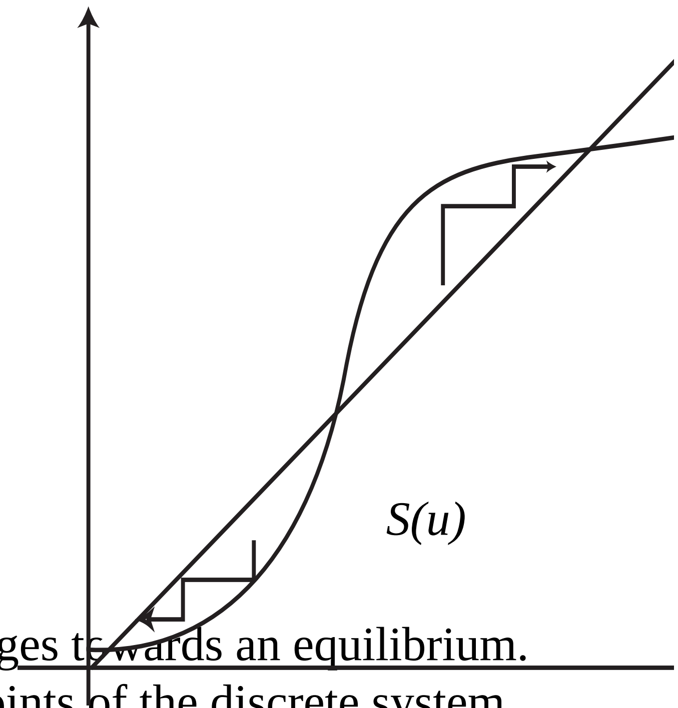
Monotone I/O systems: a unified framework

Theorem: Consider a MIMO I/O monotone control system under positive or negative feedback, and a I/O characteristic function *S(u)* with strongly (anti)monotone and hyperbolic linearization around fixed points.
Assume:

Weak small gain condition: every solution of the discrete system

$$u_{n+1} = S(u_n)$$

converges towards an equilibrium (which may depend on the initial condition)



Then almost every solution of the closed loop system converges towards an equilibrium. Moreover, the stable equilibria correspond to the stable fix points of the discrete system.

Note: Proof in the MIMO negative feedback case follows from the uniqueness of the fixed point by previous result

Mixed Feedback? It has been shown that I/O systems that satisfy small gain condition in the mixed feedback case can be unstable (Angeli et al, work in preparation).

Boolean Monotone Systems

$$x_i(t+1) = f_i(x(t)), \quad f_i : \{0, 1\}^n \to \{0, 1\}, \quad i = 1 \ldots n$$

- system is monotone with respect to the standard order iff each f_i can be written in terms of AND, OR, with no negations

Which properties of monotone systems hold in the Boolean case?

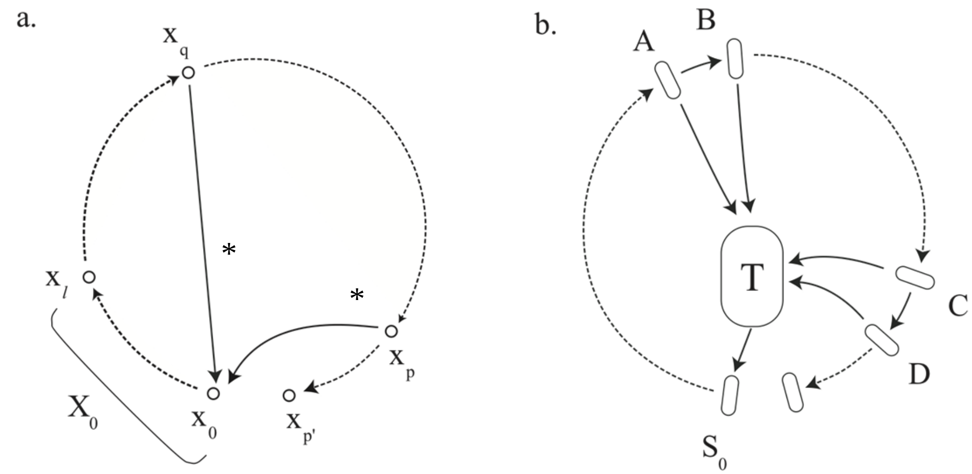
- On average, Boolean monotone systems tend to have shorter periodic orbits than arbitrary Boolean systems (Sontag, Laubenbacher et al.)
- Can any hard bounds be shown for such systems?

Boolean Monotone Systems

Additive lagged Fubini generator:

$$z(t) = z(t-p) + z(t-q) \bmod 2$$
$$= z(t-p) \text{ XOR } z(t-q)$$

For appropriate choices of p>q, the iterations of this system have period 2^p – 1.



Theorem: (Just, GAE 2011) For arbitrary 1<c<2, there exists a Boolean monotone system of dimension n with a solution of period at least c^n. Moreover, the system is irreducible and has at most two inputs for each variable.

Proof: imitate the non-monotone Boolean network above with a monotone Boolean network which reproduces its dynamics.

THE UNIVERSITY OF CALIFORNIA
LET THERE BE LIGHT
1868

Thanks!

- Eduardo Sontag, of course
- Hal Smith
- Moe Hirsch
- Patrick de Leenheer
- DIMACS

Questions?

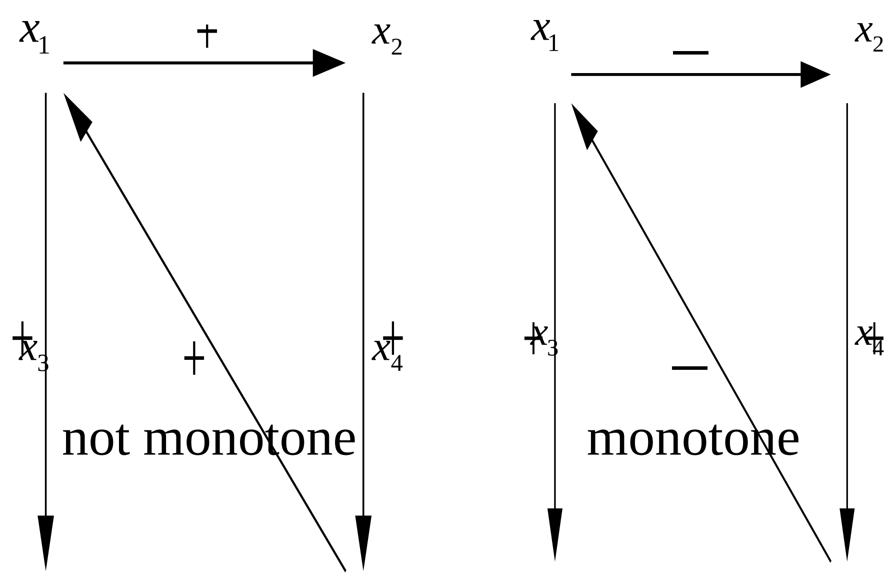
Monotone systems: a definition

Write every variable in the system as a node in a graph, and denote:

$$x_j \xrightarrow{+} x_i \text{ if the interaction is promoting, i.e. } \frac{\partial f_i}{\partial x_j} \geq 0$$

$$x_j \xrightarrow{-} x_i \text{ if the reaction is inhibitory, i.e. } \frac{\partial f_i}{\partial x_j} \leq 0$$

A dynamical system is *monotone* (with respect to some orthant order) iff every loop of the interaction graph has an even number of –'s (i.e. positive feedback), regardless of arc orientation:



Monotone systems: some notes

- Monotone systems have very strong stability properties: almost every solution converges towards an equilibrium [1],[2]
- Monotonicity can be established using only ‘qualitative’ information, i.e. without knowledge of exact parameter values or nonlinearities
- Notice: monotonicity is a very strong assumption, which is usually only satisfied on *subsystems* of a given network!
- Also: given the digraph of the system alone, it is not possible to determine the number of equilibria and their stability.

[1] M. Hirsch, “Systems of differential equations that are competitive or cooperative II: convergence almost everywhere”, SIAM J. Math. Anal. 16:423-439, 1985.

[2] GAE, M. Hirsch, H. Smith, “Prevalent behavior of strongly order preserving semiflows”, submitted.