The ISS Philosophy

as a Unifying Framework

for Stability-Like Behavior

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I would like to begin by thanking the Control Systems Society for awarding me this honor.

Our field attracts a unique blend of bright and knowledgeable researchers, any of whom are equally deserving of this Prize.

So, I am especially grateful to have been selected as the speaker.

What is “ISS”?

The main part of the talk will deal with the ISS notion.

Sorry, not ISS . . .

You are at the wrong lecture if you thought that ISS is an acronym for International Space Station,

Nor (Google)

Indonesian Skeptic Society
International Superstar Soccer
Imprinted Sportswear Shows
Intelligence Studies Section
Internet Security Systems
Internet Support Service
Institute of Social Studies
International Summer School
Information Systems Support
Istituto Superiore di Sanita'
Industry Solutions & Services
Institute of Social Science
International Shared Services
International Sound Symposium
. . .

or for that matter any of these others that you find when you search the web (I am not making them up!).

Outline

- *Input to State Stability*
  - Motivation, Definition, Feedback Redesign
  - Robust Stability, Superposition, Dissipation
  - I/O Stability & Detectability; Relationships
  - Other Notions: iSS, Minphase
  - Taste of Theory: DI's, Viscosity
  - Some Open Problems & Applics; Summary
- *Systems Molecular Biology*
  - E.g.: MAPK Cascades, Stability Questions
  - E.g.: *E.coli* Chemotaxis, IMP
  - New Tools: Measurements, System Perturbations
  - Discussion
- *Acknowledgments*

My plan for this talk is to first introduce input to state stability, including its role in feedback design, and to provide statements of the main theoretical results about ISS.

I will then discuss associated notions such as input to output stability, detectability, and integral ISS,

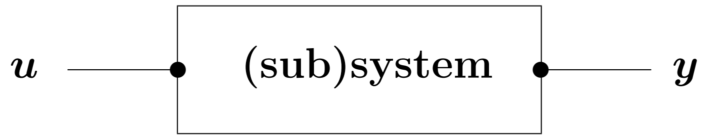
and will conclude with a brief sampler of theoretical tools,

as well as a mention of some of the many open problems that remain, and a couple of sample applications.

In a second part of the lecture, I will spend a few minutes talking about Systems Molecular Biology, a subject which, I believe, has the potential of becoming, in the long term, one of the most important areas of application for systems and control ideas (including, of course, input to state stability :), and which presents huge challenges to our field.

Overall Theme: ISSomics

stability-type questions for i/o systems



motivations include:

- **adding to system theorist's "toolkit" for studying systems via decompositions**
- **quantify response to external signals**
- **unify state-space and i/o stability theory**

In the spirit of biology, which studies genomics, proteomics, and so forth, the overall theme of this talk will be that of ISSomics, which deals with stability-like questions for systems with inputs and outputs.

There are many reasons for studying such questions:

one of the strengths of systems theory is in providing a methodology for analyzing complex systems, when viewed as an interconnection of simpler devices, and ISS tools are often useful in that context;

in particular, ISS provides one way to quantify system responses;

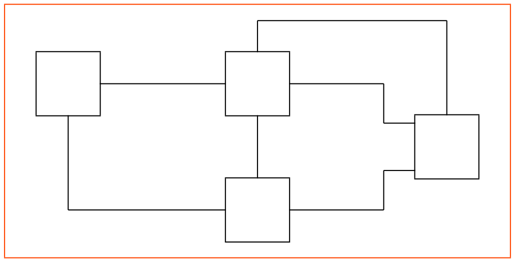
and yet another motivation is more purely mathematical, namely the unification of state space and input/output stability notions.

Decompositions

even if original system is "autonomous"

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

must study "systems with i/o signals"

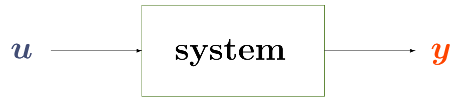


(otherwise, how to interconnect?)

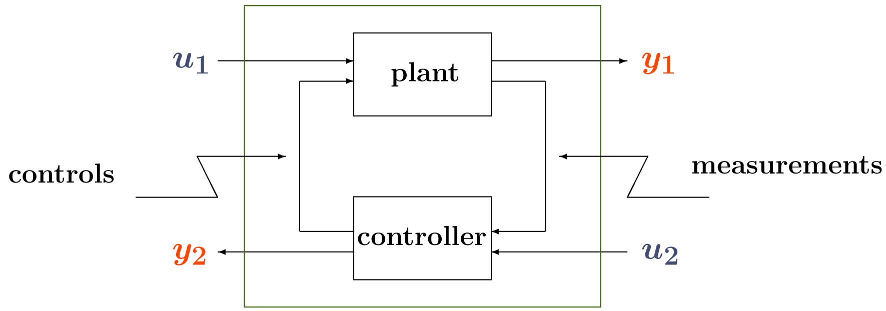
Regarding the first motivation, the study of systems through decompositions,

note that, even if we wish to study a *closed* or autonomous system, we must allow the subsystems to have inputs and outputs, since, otherwise, one cannot even *define* "interconnection".

Response to External Signals



typically:



$u = (u_1, u_2)$ = noise, disturbances, tracking signals, ...
$y = (y_1, y_2)$ = distance to desired states, tracking error, ...

Regarding the motivation of studying responses to external signals,

of course, the "inputs" to the system may represent disturbances, or tracking signals, in a regulator problem, and outputs might be measurements, or error signals.

Defining ISS

formalization of "stability" of $u(\cdot) \mapsto y(\cdot)$,
accounting for initial states & transients

talk concentrates on notions relative to globally attractive steady states

but, general "philosophy":

- more arbitrary attractors
- local theory
- robust/adaptive versions ...

(for applications: talks, papers, books, ...)

Our first objective will be to provide a definition of input to output stability which takes into account internal states and transient behavior;

actually, for simplicity, I will initially only talk about input *to state* stability and will introduce outputs later.

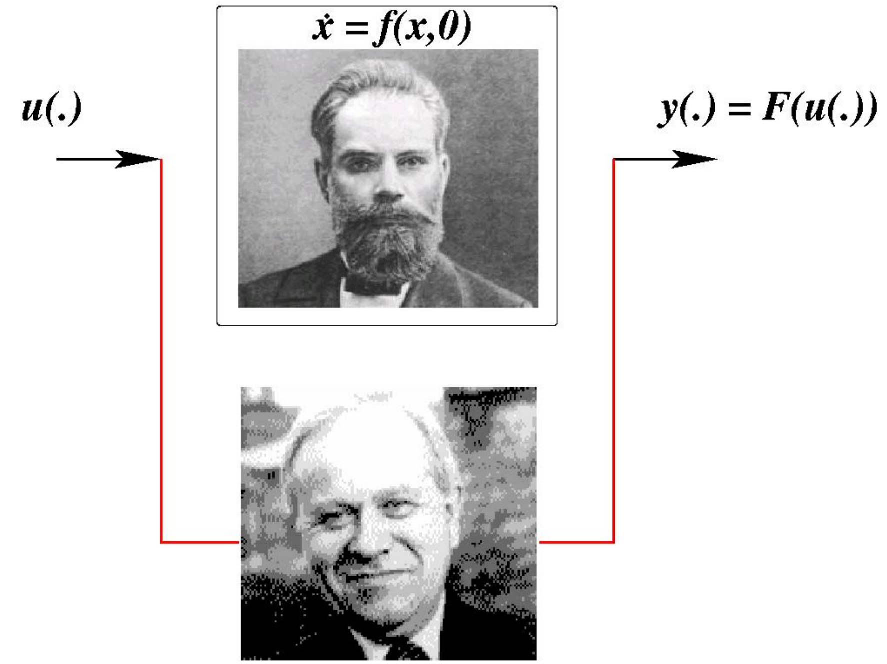
In addition, I will only address notions of *global* stability with respect to *equilibria*,

but many of the concepts and results may be extended to local stability, and to stability of attracting sets, such as periodic orbits,

and there are robust stability versions as well.

The talk will focus on *theoretical* results and I will not cover in any detail the many applications, which can be found in papers and textbooks.

Merge Lyapunov/Zames ?



For systems *without* inputs and outputs, the classical notions of stability were introduced by Lyapunov, well over a hundred years ago;

on the other hand, George Zames, and many others, developed a rich theory of stability for input/output operators, starting in the mid 1960's.

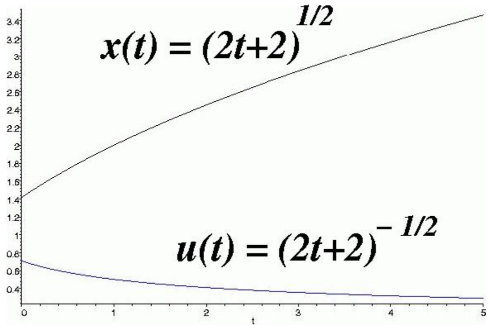
The notion of ISS allows us to combine features of both.

$\dot{x} = f(x, 0)$ Stable <u>not</u> Enough

for *linear* $\dot{x} = Ax + Bu$, A Hurwitz $\Rightarrow$

$u \to 0 \Rightarrow x \to 0$; BIBS; finite $u(\cdot) \mapsto x(\cdot)$ norm

but false for nonlinear: $\boxed{\dot{x} \;=\; -x + (x^2 + 1)u}$



even though with $u = 0$ is GAS: $\boxed{\dot{x} = -x}$

(even worse: $u \equiv 1 \Rightarrow$ explosion !)

For *linear* systems, the combination is not an issue, because internal stability implies all types of input to state stability, such as convergence of states to zero when inputs converge to zero, bounded-input bounded-state stability, and finiteness of operator norms.

But for *non*linear systems, matters are more complicated, as illustrated by this example which is exponentially stable when the input u is identically zero, but which exhibits unstable behavior when forced by an input which converges to zero.

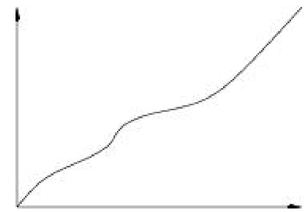
The x-squared term affects the system when the input is not zero, dominating the stable linear part, but has no effect on the unforced system.

So Require I/O Boundedness

bound $|x(t, x^0, u)|$ in "nonlinear gain" sense

$$\boxed{|x(t)| \,(\text{"ultimately"}) \;\leq\; \gamma\left(\|u(\cdot)\|_\infty\right)}$$

$\gamma \in \mathcal{K}_\infty$:
$\gamma(0){=}0$
$\mathcal{C}^0$, $\nearrow +\infty$



(defining concepts for "input $\longrightarrow$ state" map
but may also apply to "input $\longrightarrow$ output", *IOS*

for now, sup norms; later integral norms)

So we must explicitly impose boundedness by asking that the amplitude of the state be ultimately bounded; we express this condition by means of K-infinity functions, that is to say using a nonlinear increasing function of the amplitude of the input.

I will mostly talk about input *to state* behavior, but I will later mention extensions to the more general case of outputs, and I will also discuss other norms than sup norms.

$\dot{x} = f(x, 0)$ GAS

global asymptotic stability (GAS) **of origin means:**

$$\boxed{|x(t, x^0)| \leq \beta(|x^0|, t)} \qquad (\forall\, x^0,\ \forall\, t \geq 0)$$

for some $\beta(\nearrow, \searrow) \in \mathcal{KL} \quad (\beta(0, \cdot) = 0,\ \mathcal{C}^0)$

$$|x(t, x^0)| \leq \beta(|x^0|, 0) \rightsquigarrow \text{stab (small overshoot)}$$

$$|x(t, x^0)| \leq \beta(|x^0|, t) \underset{t\to\infty}{\longrightarrow} 0 \rightsquigarrow \text{ attractivity}$$

In order to finish introducing the notion of ISS, let me first remind you of some formalism: global asymptotic stability of the origin of an unforced system is usually given as an epsilon-delta definition,

but a totally equivalent way of defining it is using "KL functions".

That is, one postulates that the solution must be bounded above by a function which increases in its first variable, the norm of the state, and decreases in its second variable, time;

this restricts overshoot and forces solutions to converge to the origin.

Input-to-State Stability

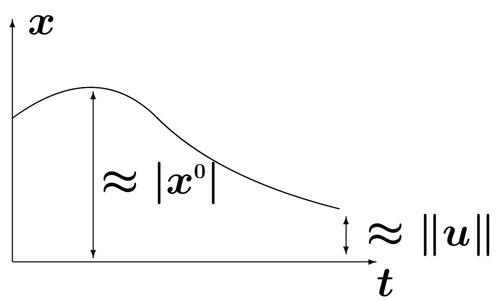
Definition of ISS:

$(\exists\ \beta \in \mathcal{KL},\ \gamma \in \mathcal{K}_\infty)$

$$\boxed{|x(t,x^0,u)| \ \leq\ \max\left\{\beta(|x^0|,t), \gamma\left(\|u\|_\infty\right)\right\}}$$

t large: $x(t)$ bounded by $\gamma(\|u\|_\infty)$ indep of x^0

but transient (overshoot) depends on x^0



We can now define ISS: we just ask that an estimate like this holds:

The state is bounded by the maximum (a sum could be used, equivalently) of a KL-term, that handles the effect of initial states when t is small, and an input gain term, that is effective when t is large;

this gives exactly global asymptotic stability if there are no inputs and, in general, says that the overshoot depends on the initial state and the asymptotic behavior, depends on the size of the input.

Linear Case, for Comparison

$$\dot{x} = Ax + bu \rightsquigarrow \boxed{|x(t)| \leq \beta(t)\,|x^0| + \gamma\,\|u\|_\infty}$$

$$\beta(t) = \left\|e^{tA}\right\| \;\rightarrow\; 0$$

$$\gamma = \|B\| \int_0^\infty \left\|e^{sA}\right\| ds \;<\; \infty$$

is particular case of ISS estimate

$$\boxed{|x(t)| \;\leq\; \beta(|x^0|, t) \;+\; \gamma\,(\|u\|_\infty)}$$

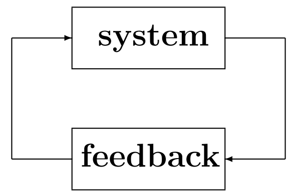
[equiv defn ($\neq\ \beta, \gamma$) using "+" instead of "max"]

ISS is obvious, for stable linear systems, since variation of parameters gives us an ISS estimate using linear gains.

The estimate has an additive form, but one can equally well define ISS using a sum instead of a max, just changing slightly the beta and gamma functions.

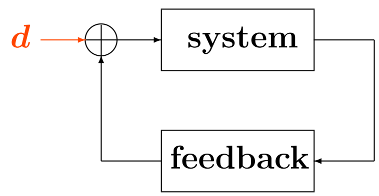
Feedback Redesign

suppose $\dot{x} = f(x, u)$ stabilized under $u = k(x)$:



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

what is effect of actuator disturbances $d(\cdot)$?



$$\dot{x} = f(x, k(x) + d)$$

noise may destabilize (not ISS) !

To show why ISS plays an important role in feedback redesign, let me consider the following problem:

suppose that a system has been stabilized under feedback in the sense that a closed-loop system is stable.

But it may well happen that actuator disturbances destabilize the system.

Example

may happen under feedback linearization design:

$$\dot{x} = x + (x^2+1)u$$

$$\Downarrow \qquad u := \frac{-2x}{x^2+1} + d$$

$$\dot{x} = -x + (x^2+1)\,d$$

$$\boxed{\text{not ISS: } d(t) = \frac{1}{\sqrt{2t+2}} \not\to x(t) \to 0}$$

but if, instead:

$$\dot{x} = x + (x^2+1)u$$

$$\Downarrow \qquad u := \frac{-2x}{x^2+1} \boxed{-x} + d$$

$$\dot{x} = -2x + \boxed{-x^3} + (x^2+1)\,d$$

this is still stable when $d \equiv 0$

$\boxed{\textit{but in addition} \text{ is ISS: } -x^3 \text{ dominates } (x^2+1)d}$

This can happen even in a simple feedback linearization example:

suppose we cancel the nonlinearity and feed back a linear function of the state.

This works fine if there is no disturbance d. But if there *is* a disturbance, then we are back to the counterexample, that I mentioned earlier, in which a stable input destabilizes the system.

The interesting thing is that, if we *redesign* our feedback law by just adding a linear term,

then the new closed-loop system is *still* stable when there are no disturbances, but, in addition, it is now ISS, because the cubic term dominates the disturbance.

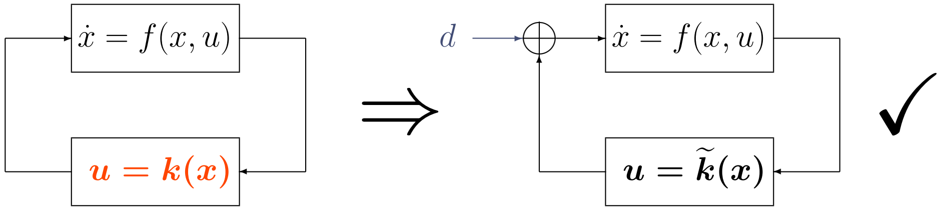
General Theorem (EDS, TAC'89)

$$\dot{x} = f(x,u) = g_0(x) + \sum_{i=1}^{m} u_i g_i(x) \qquad (g_0(0) = 0)$$

if $\dot{x} = f(x, k(x))$ has $x = 0$ as GAS equilibrium

then $\exists$ feedback $u = \widetilde{k}(x)$ s.t.

$\dot{x} = f(x, \widetilde{k}(x) + d)$ is ISS with input $d(\cdot)$



Corollary: fdbk linearizable $\Rightarrow$ ISS-stabilizable
Kokotovic *et.al.*: recursive design, backstepping

In fact, a general theorem says that, whenever one can stabilize a system, it is possible to redesign the control law so that the closed-loop system is input to state stable with respect to actuator disturbances.

In particular, every feedback linearizable system can be made ISS.

This is just tip of the iceberg: there is a beautiful theory of recursive design, based on backstepping and other techniques, that exploits these ideas.

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- ***Systems Molecular Biology***
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- ***Acknowledgments***

Now that I introduced ISS, let me discuss some of the basic theory.

Natural Notion?

a mathematical concept is "natural" ($\Rightarrow$ useful !) if it has many *equivalent* characterizations

ISS turns out to be equivalent to:

- *$\exists$ proper robustness margins*
- *dissipativity (in "input – state" form)*
- *separation: AS + asymptotic gain*
- *energy-like stability*

and many other properties
next part of talk will explain these

One may argue that a mathematical notion will be useful if it is *natural*, in that it can take many equivalent forms.

So, let me briefly discuss how ISS is exactly equivalent, among other properties, to the existence of robust margins of stability, to dissipativity, to a combination of stability and finite asymptotic gain, and to an energy-like stability notion.

Fine Print Stuff

unless otherwise stated, all results hold for arbitrary (finite dimensional) systems

$$\dot{x}(t) = f(x(t), u(t)) \qquad (x(t) \in \mathbb{R}^n)$$

inputs are Lebesgue-measurable locally (essentially) bounded

$$u(\cdot) : [0, \infty) \to \mathbb{R}^m$$

the map $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ is locally Lipschitz, $f(0,0) = 0$

when outputs appear, output map is continuous
when feedbacks appear, they are loc. Lipschitz, $k(0) = 0$

partial results available (but not discussed here)
for time-varying and discrete-time systems,
various classes of infinite-dimensional systems, etc

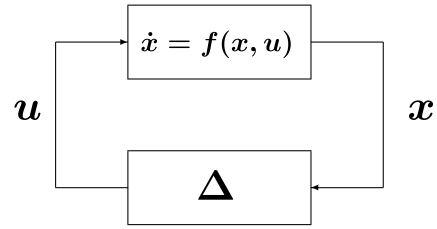
The theorems that I will mention all hold under minimal assumptions, for finite-dimensional and time invariant continuous time systems.

Generalizations to time-varying systems, to stability of more complicated attractors than equilibria, to discrete time systems, and so forth, have been also pursued to various degrees, but I will restrict attention to this case.

ISS $\equiv$ Robust Stability

ISS $\iff$ $\exists$ "margin of stability" $\rho \in \mathcal{K}_\infty$:

$$\boxed{\dot{x} \;=\; f(x, \Delta(t,x))}$$



has origin uniformly globally asympt stable
$\forall$ t-v feedback laws Δ s.t. $|\Delta(t,x)| \leq \rho(|x|)$
(Yuan Wang and EDS, SCL'95)

compare: A Hurwitz $\Rightarrow$ $A + \Delta A$ too

intuition: $|x(t)| \leq \max\left\{\beta(|x^0|,t), \gamma\left(\|u\|_\infty\right)\right\}$
β term dominates, provided $u \ll x$

The first theorem says that ISS is equivalent to *robust* stability, in the sense that there is a *margin of stability* , which is large for states far from the origin (that's what "K infinity" means), and the system remains globally stable under all feedbacks whose magnitude is bounded by this margin.

Observe that for *linear* systems, a matrix remains Hurwitz under small perturbations, so margins always exist;

in that sense, ISS is a better generalization of linear stability than plain global asymptotic stability.

ISS Superposition Principle

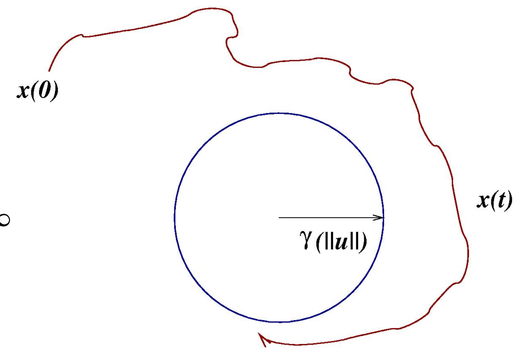
$$\boxed{|x(t)| \;\leq\; \max\left\{\beta(|x^0|, t), \gamma\left(\|u\|_\infty\right)\right\}}$$

$\Rightarrow |x(t)| \leq \beta(|x^0|, t)$

when $u \equiv 0$ (GAS) &

$\exists$ ***asymptotic gain*** $\gamma \in \mathcal{K}_\infty$

$\overline{\lim\limits_{t \to +\infty}} |x(t, x^0, u)| \leq \gamma\left(\|u\|_\infty\right)$



$$\boxed{\text{ISS} \iff \exists \text{ asympt gain \& unforced sys stable}}$$

(Wang and EDS, TAC'96)

sufficiency hard: non-uniform on controls; no (even weak) compactness

As we already saw, if a system is ISS then the unforced system is stable,

and it is also clear, since the overshoot term dies out for large t, that the state approaches a ball whose radius is determined by the size of the input.

It is a surprising and nontrivial result that the conjunction of these two properties is in fact equivalent to ISS.

Mathematically, the challenge lies in the fact that the ultimate bound is not required to be uniform on inputs, and there is no convexity and compactness to help, even in the sense of weak topologies.

Dissipation Characterization

$$\boxed{\text{ISS} \iff \exists\ \text{ISS-Lyapunov function}}$$

(Wang and EDS, SCL'95)

V smooth, proper, pos def; $\exists\, \gamma, \alpha \in \mathcal{K}_\infty$:

$$\boxed{\dot{V}(x,u) = \nabla V(x)\, f(x,u) \;\leq\; -\alpha(|x|) + \gamma(|u|)}$$

i.e., dissipation inequality

$$V(x(t_2)) - V(x(t_1)) \;\leq\; \int_{t_1}^{t_2} w(u(s), x(s))\, ds$$

holds along all trajectories of the system,
with "supply" function $w(u,x) = \gamma(|u|) - \alpha(|x|)$

generalizes converse Lyapunov: $u{=}0 \rightsquigarrow$ Lyap function

A third theorem says that ISS is equivalent to the existence of an ISS-Lyapunov function,

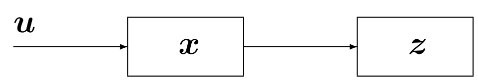
which amounts to a dissipation property, with a smooth storage, or energy-like, function which is allowed to increase at a rate bounded by the instantaneous input magnitude and which otherwise decreases.

Note that for systems without inputs, the u term vanishes, and the theorem reduces to the classical converse Lyapunov theorem of Massera.

Cascades OK (EDS, TAC'89)

cascades of ISS are ISS ($u{\equiv}0$: GAS & ISS $\Rightarrow$ GAS)

$$\begin{aligned}\dot z &= f(z,x) \quad \text{ISS } (x \text{ input})\\ \dot x &= g(x,u) \quad \text{ISS } (u \text{ input})\end{aligned}$$



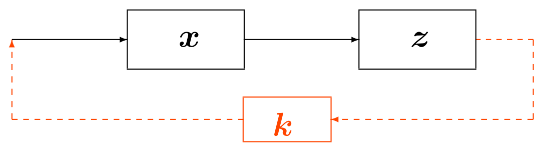
$$\begin{aligned}\dot V_1(z,x) &\le \quad\;\; \theta(|x|) - \alpha(|z|)\\ \dot V_2(x,u) &\le -2\,\theta(|x|) + \gamma(|u|)\end{aligned}$$

matching ISS-Lyapunov fncs (Teel and EDS, TAC'95)

$\rightsquigarrow W(x,z) := V_1(z) + V_2(x)$ is ISS-Lyap for cascade:

$$\dot W(x,z) \;\le\; -\theta(|x|) - \alpha(|z|) + \gamma(|u|) \quad \checkmark$$

generalization:
$u = k(z)$, k small



$\gamma(|u|) \le (1{-}\varepsilon)\alpha(|z|) \;\rightsquigarrow\; \dot W(x,z) \le -\theta(|x|){-}\varepsilon\alpha(|z|) \;< 0 \;\checkmark$

small-gain theorem **(Jiang-Teel-Praly, MCSS'94)**

Another way, in which ISS is natural as a notion of stability, is that every serial connection of ISS systems is again an ISS system.

In particular, driving an ISS system by a stable system produces a stable system.

This fact can be easily proved directly, but it is especially evident from a dissipation characterization

given appropriate storage functions for each system, their sum is a storage function for the cascade

(the positive input term of the z system is canceled by the negative stability term of the x system).

More generally, feedback does not destroy stability, if the feedback is small enough that V still decreases

which leads to a most useful *small-gain* theorem for ISS.

E.g. of ISS Design

toy example, just for illustration of ideas, angular momentum stabilization of rigid body:

$$I\dot{\omega} = \begin{pmatrix} 0 & \omega_3 & -\omega_2 \\ -\omega_3 & 0 & \omega_1 \\ \omega_2 & -\omega_1 & 0 \end{pmatrix} I\omega + \begin{pmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} v$$

controls = two torques acting along principal axes;
$\omega = (\omega_1, \omega_2, \omega_3)$ angular velocity, body-attached frame,
$I = \mathrm{diag}(I_1, I_2, I_3)$ principal moments of inertia; assume $I_2 \neq I_3$

change coordinates $\rightsquigarrow$

$$\dot{x}_1 = x_2 x_3$$
$$\dot{x}_2 = u_1$$
$$\dot{x}_3 = u_2$$

$(I_2 - I_3)x_1 = I_1\omega_1, x_2 = \omega_2,\ x_3 = \omega_3,\ I_2 u_1 = (I_3 - I_1)\omega_1\omega_3 + v_1,\ I_3 u_2 = (I_1 - I_2)\omega_1\omega_2 + v_2$

It is worth looking at a simple toy example to understand how ISS ideas can help in feedback design.

Let us take the textbook problem, of angular velocity stabilization of a rigid body, with two torques as controls,

which under a coordinate change becomes the cascade of a one-dimensional system (described by x1) and a linear system.

Change State & Input Coords

$$\boxed{\dot{x}_1 = x_2 x_3 \quad \dot{x}_2 = u_1 \quad \dot{x}_3 = u_2}$$

globally stabilizing feedback:

$$u_1 = -x_1 - x_2 - x_2 x_3 + d_1$$
$$u_2 = -x_3 + x_1^2 + 2x_1 x_2 x_3 + d_2$$

because, with $z_2 := x_1 + x_2$, $z_3 := x_3 - x_1^2$:

$$\dot{x}_1 = -x_1^3 + \alpha(x_1, z_2, z_3)$$
$$\dot{z}_2 = -z_2 + d_1$$
$$\dot{z}_3 = -z_3 + d_2$$

x_1-subsys ISS: $\deg_{x_1} \alpha \leq 2$ so cubic dominates

thus cascade ISS $\quad$ ($\therefore$ GAS when $d_1 = d_2 \equiv 0$)

The x1 system is clearly stabilizable when thinking of x2 and x3 as inputs, so the basic redesign theorem says that we can make it ISS, which then implies, because of the cascade result, that the complete system can be made ISS as well.

If one carries out this idea, the net result is that the feedback law shown here globally stabilizes the rigid body model, and, moreover, does so in an ISS manner.

This is shown, by looking at the closed-loop system in slightly different coordinates, in which the system can be seen as a cascade of two ISS systems.

The cubic term provides the margin of stability for the x1 system, and z2,z3 give a stable linear system.

This is just a simple example of a systematic approach to constructive feedback design based on ISS ideas.

Energy-Like Norms (EDS, SCL'98)

$$\int_0^t \gamma_1(|x(s)|)\,ds \;\leq\; \max\left\{\kappa(|x^0|)\,,\, \int_0^t \gamma_2(|u(s)|)ds\right\}$$

for all trajectories ($\exists\ \gamma_i, \kappa \in \mathcal{K}_\infty$)

compare: everything quadratic, "H_∞"

$\boxed{\text{ISS} \iff \exists \text{ such an } \int \to \int \text{ estimate}}$

on the other hand, mixed energy/sup:

$$\gamma_1\left(|x(t)|\right) \;\leq\; \max\left\{\beta(|x^0|, t)\,,\, \int_0^t \gamma_2(|u(s)|)\,ds\right\}$$

leads to *new* notion: ***iISS*** (***integral*** ISS)

Finally, in this brief discussion of characterizations of ISS, let me mention a last theorem, namely that ISS is also equivalent to the existence of estimates of an integral-to-integral type,

analogous to an H-infinity estimate if all nonlinearities were quadratic.

On the other hand, and very surprisingly, a genuinely *new* concept finally arises if we mix integral and sup norm estimates.

This concept of *integral* input to state stability is *strictly weaker* that ISS, and I'll say a few words about it later.

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- *Input to State Stability*
  - Motivation, Definition, Feedback Redesign
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  - I/O Stability & Detectability; Relationships
  - Other Notions: iISS, Minphase
  - Taste of Theory: DI's, Viscosity
  - Some Open Problems & Applics; Summary
- *Systems Molecular Biology*
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Let me now turn to input/output and detectability properties.

Input/Output Stability

IOS: input to *output* stability defined for systems with outputs $\dot{x} = f(x,u)$, $y = h(x)$

$$u \to 0 \longrightarrow \boxed{\; x \;} \longrightarrow \;\Rightarrow\; y \to 0$$

$$\boxed{|y(t)| \;\leq\; \max\left\{\beta(|x^0|,t)\,,\,\gamma(\|u\|_\infty)\right\}}$$

overshoot bounded by a function of $|x^0|$,
just as in linear regulator theory;
related to "partial stability" (subset of vars)

$\Longleftrightarrow$ **dissipation: Wang and EDS, SICON'01**

The notion of input to *output* stability is defined for systems with outputs, in a manner totally analogous to ISS.

One just replaces the estimate on states, by an estimate on outputs, using KL functions to bound initial-state dependent, transient behavior and a K-infinity function to express the influence of input amplitudes.

ISS is a special case, of course, when the output is just the state.

Observe that the overshoot is controlled by the initial state, and this is what we want, since in regulator problems, for instance, the mismatch between an internal model and an external signal determines the transient behavior.

One may characterize IOS in dissipation terms, but let me skip the technicalities.

IOSS (Krichman-Wang-EDS, SICON'01)

zero-detectability typically: $u \equiv y \equiv 0 \Rightarrow x(t) \to 0$

— but this is weak for nonlinear systems:
not "well-posed" (what happens if $u, y \approx 0$?)

input/output to state **stability (IOSS):**

$$\boxed{|x(t)| \;\leq\; \max\left\{\beta(|x^0|, t)\,,\, \gamma_1(\|u\|)\,,\, \gamma_2(\|y\|)\right\}}$$

(more precisely: sup norms restricted to $[0, t]$)

"stability *from the i/o data to the state*"
u & y small $\Rightarrow$ x eventually small

$$\boxed{\begin{array}{c}\text{IOSS} \iff \exists\ \text{IOSS-Lyapunov function:}\\ \nabla V(x)\, f(x,u) \leq -\alpha_1(|x|) + \alpha_2(|u|) + \alpha_3(|y|)\end{array}}$$

Yet another ingredient of the theory is a notion of ***zero-detectability***.

One *might* define detectability by asking that identically zero input and output signals imply that the internal state converges to zero.

However, it is far more reasonable, and *not* equivalent when dealing with nonlinear systems, to ask that small inputs and outputs should imply asymptotically small internal states.

The notion of IOSS makes this precise, including, as always, a term that quantifies the transient behavior, and incorporating a term for the amplitudes of inputs and outputs.

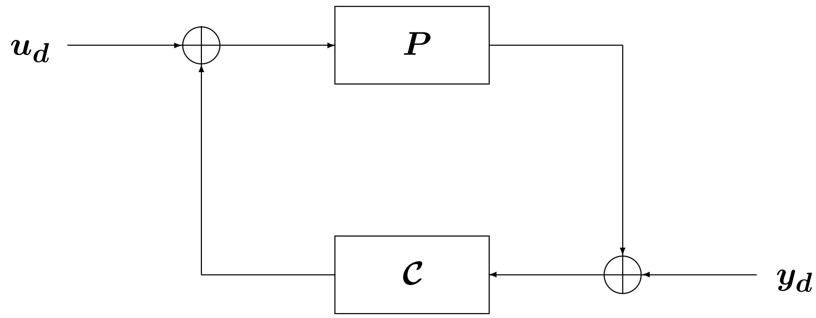
For large t, the beta term goes to zero, so, if u and y are small, then the state is eventually small as well.

IOSS stands for input and output *to* state stability, consistent with the idea that small inputs and outputs imply small internal states.

Also here, a fundamental theorem states that IOSS is *equivalent* to dissipativity, with smooth storage functions, in the expected sense.

Output Stabilization $\Rightarrow$ IOSS

Remark:



$\exists\, \mathcal{C}$ **ISS stabilizing w.r.t. external "disturbances"** u_d **and** y_d

$\Rightarrow$ **original system is IOSS**

assuming $y_e \equiv 0 \;\Rightarrow\; u_e \equiv 0$
for any initial state ξ and control u, pick $u_d := u$ and $y_d := -y_{\xi,u}$

One can prove that the IOSS property is in fact ***necessary*** **for stabilization under partial observations.**

Fundamental Relationships

very easy, *given the definitions:*

$$\boxed{\text{IOS} \ \& \ \text{IOSS} \iff \text{ISS}}$$

i.e., intuitively:

external stab & detectab $\iff$ internal stab

$$\begin{tikzcd} u \to 0 \arrow[r] & \boxed{x \to 0} \arrow[r] & y \to 0 \end{tikzcd}$$

if $u \to 0$ then $y \to 0$ (by external stability),
and this then implies $x \to 0$ (by detectability)

converse: if internally stable, then $u \to 0 \Rightarrow x \to 0$,
so in particular this happens when $y(t) \to 0$ (detectability)
and it always holds that $y(t) \to 0$ (i/o stability)

There is a fundamental relationship among the three concepts which I introduced, saying basically that external stability and detectability together are equivalent to internal stability.

Intuitively, if inputs are small, then input/output stability tells us that outputs are also small, and then, detectability insures that the internal states are small.

But the main point is that the equivalence holds for IOS, IOSS, and ISS as we defined.

This is yet another indication that these are the right notions.

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There are many other subjects which I could cover regarding the ISS formulation of systems properties. Let me mention a couple of them.

iISS (Angeli-Wang-EDS, TAC'00)

$$\gamma_1(|x(t)|) \;\le\; \beta(|x^0|, t) + \int_0^t \gamma_2(|u(s)|)\, ds$$

iISS: ***integral input*** $\rightarrow$ **(sup-norm) state stab**

nonlinear analog of "H_2" ($L^2 \rightarrow L^\infty$) gain

$$\boxed{\text{iISS} \iff \exists \text{ iISS-Lyapunov function}}$$

iISS-Lyap function: $\alpha > 0$, **not nec.** $\alpha \notin \mathcal{K}_\infty$

$$\dot V(x,u) = \nabla V(x)\, f(x,u) \;\le\; -\alpha(|x|) + \gamma(|u|)$$

ISS $\underset{\not\Leftarrow}{\Rightarrow}$ **iISS**

e.g.: bilinear: $\dot x = (A + \sum_{i=1}^m u_i A_i)x + Bu$

A **Hurwitz** $\Rightarrow$ **iISS, but in general not ISS**

(or even BIBS): $\dot x = -x + ux, u \equiv 2$

As I said before, mixing integral and pointwise estimates results in a genuinely new notion, that of integral ISS.

There is a dissipativity characterization that goes along with integral ISS,

and one can prove that this property is strictly weaker than ISS.

For instance, bilinear systems which are stable when inputs are zero are always integral ISS, but are seldom ISS.

iISS & Output Dissipation

useful if dissipation only wrt some variables

system *dissipative wrt output function* $y = h(x)$**:**

$$\nabla V(x)\, f(x,u) \;\leq\; -\alpha(h(x)) + \gamma(|u|)$$

***h-detectable*:**

$y(t) = h(x(t)) \equiv 0 \Rightarrow x(t) \to 0$ **as** $t \to \infty$

$$\boxed{\text{iISS} \iff (\exists\, h)\ h\text{-detectable \& } h\text{-dissipative}}$$

(Angeli-Wang-EDS, TAC'00)

e.g.'s with tracking control, iISS wrt time-varying signals in larger class than designed for; V **= energy,** y **= velocities**

Integral ISS corresponds to a sort of partial dissipativity, together with weak detectability,

and it has proved useful when studying mechanical tracking problems, where the dissipativity property can be checked using energy functions.

Bode's Minphase

a nonlinear, global, well-posed, notion of Bode's minimum phase systems:

$$\boxed{\text{OIS} = \text{output to input stability}}$$

("inverse system is ISS")

$$\Rightarrow\ u \to 0 \longrightarrow \boxed{\Rightarrow\ x \to 0} \longrightarrow y \to 0$$

Liberzon-Morse-EDS, TAC'02

- "zero dynamics" ISS
- applics to adaptive control

Finally, let me point out that one can define a notion of *minimum phase* system, generalizing Bode's concept for linear systems.

This property is defined via input to output stability of the inverse system, or equivalently as an ISS property for the zero dynamics.

This notion plays a role in adaptive control, for instance.

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I did not discuss *proofs* of theorems, nor do not intend to so,

but let me show you a couple of examples of some of the issues involved, to give you a flavor of parts of the theory.

Differential Inclusions

$$\boxed{\dot{x}(t) \in F(x(t))}$$

e.g. for ISS system:

$F(x)=\{f(x,u), |u|\leq\gamma(|x|)\}$ (stability margin)

one key ingredient: characterize uniform GAS:

$$|x(t)| \;\leq\; \beta(|x^0|\,, t)$$

$$\boxed{\begin{array}{c}\text{UGAS} \iff (\exists\ V \in C^\infty,\ \alpha \in \mathcal{K}_\infty) \\ \nabla V(x) \cdot v + \alpha(|x|) \leq 0 \quad \forall\ v \in F(x)\end{array}}$$

(Lin-Wang-EDS, SICON'96)

Corollary: dissipation characterization of ISS

Teel-Praly, COCV'00: $\exists\, V$ more general DI's

For ISS systems, *differential inclusions* arise when inputs are constrained by a stability margin.

A key ingredient in the theory is the characterization of uniform global asymptotic stability, by Lyapunov functions.

A Hamilton-Jacobi partial differential inequality, forcing directional derivatives to be negative along all constrained motions, is shown to have smooth solutions.

This leads, in turn, to the dissipation characterization of ISS.

DI's, ctd'

another key ingredient: **relaxations**

can approx sols of $\dot{x} \in \mathrm{co}(F(x))$ by $\dot{x} \in F(x)$ on *infinite intervals* **(Wang-EDS, TAC'96)**

Corollary: **GAS (+stability) $\Rightarrow$ uniform GAS**

[$F(x) = \{f(x,u)\}$ generally not convex in u, so $u(\cdot) \mapsto x(\cdot)$ not $\mathcal{C}^0$ wrt weak topology!]

Corollary: **superposition principle for ISS**

(Ingalls-Wang-EDS, Proc.Amer.Math.Soc.'02: extended to arbitrary locally Lipschitz DI's)

Another central ingredient is a relaxation theorem for differential inclusions, extending Filippov's theorem to infinite intervals.

This gives, as a corollary, the equivalence of non-uniform and uniform global asymptotic stability for non-convex differential inclusions,

and the superposition theorem for ISS then follows.

Taste of Theory: Viscosity

often *nonsmooth* V's useful:

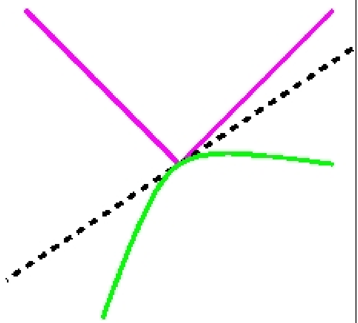
"$\nabla V(x) \cdot v + \alpha(|x|) \leq a \quad \forall\, v \in F(x)$" $\rightsquigarrow$

$$\boxed{\zeta \cdot v + \alpha(|x|) \leq 0 \quad \forall\, v \in F(x) \ \&\ \zeta \in \partial_{\mathrm{V}} V(x)}$$

(HJB PDE in viscosity form)

viscosity subgradients: $\zeta = \nabla \varphi$
$\forall\, \varphi =$ *supporting* $\mathcal{C}^1$ *function*

e.g. $\partial_{\mathrm{V}} V(0) = [-1, 1]$
for $V(x) = |x|$



discont stab (EDS, SICON'82; Clarke-Ledyaev-Subbotin-EDS, TAC'97),
and "$\dot{x} = f(x, k(x+e))$" (see below), local, discont k (EDS, COCV'99)

Nonsmooth analysis is also beginning to play a role in ISS theory.

Although all the results that I mentioned until now were stated in terms of smooth V's, nonsmooth V appear when discontinuous feedback is used, or when studying ISS properties with respect to observation errors, or in "measurement to error stability", a property that I will mention when I discuss open problems.

For nonsmooth storage functions V, dissipation inequalities are understood in a viscosity sense.

This means, in simple terms, that one must replace the gradient of V by *generalized gradients*, which amounts to using the gradients of differentiable functions that just touch the graph of V, like the green one in the picture, which has the dotted line as tangent, and there are many of these at those points where V has a corner.

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I believe that the area of ISS is still very much in its infancy, as evidenced by the huge number of open problems that remain.

Let me mention a couple of them.

Some Open Problems

structure of Lyap funcs for $\dot{x} \in F(x)$ *(and ISS-Lyap)*

for n (dimension of state space) $\neq 4, 5$,
$\exists$ coordinate change $\rightsquigarrow V$ quadratic

(Grüne-Wirth-EDS, SCL'99)

("coord change": $\mathcal{C}^0(\mathbb{R}^n)$, $\mathcal{C}^\infty(\mathbb{R}^n \setminus \{0\})$)

open: is result true for dim $n = 4$ and/or 5?

($\sim$ relations ISS & H_∞ gains)

(Poincaré & Smale/Milnor cobordism)

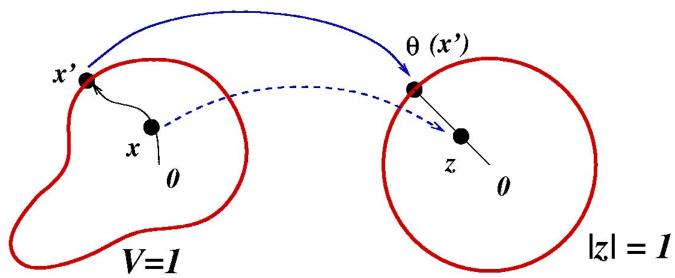
The first one is purely mathematical, but a lot of fun: it has to do with the structure of storage functions.

It is known that, for all systems of dimension *different from* 4 and 5, one can find, up to coordinate changes, *quadratic* storage functions, but the result is still open in dimensions exactly 4 and 5.

This is all totally useless in practice, since the coordinate changes are impossible to construct explicitly, but knowing if the result is always true would clarify certain theoretical issues concerning the relationships between ISS and H-infinity control.

Proof Sketch: V's Quadratic

levels $S := \{V(x) = 1\}$ homotopically equivalent to $\mathbb{S}^{n-1}$:
$S \simeq S \times \mathbb{R}$ ($\mathbb{R}$ contractible) & $S \times \mathbb{R} \approx \mathbb{R}^n \setminus 0 \simeq \mathbb{S}^{n-1}$ (flow)
$\Rightarrow \{V(x) = 1\}$ diffeomorphic to $\mathbb{S}^{n-1}$, provided $n \neq 4, 5$
(enough room to "untangle" curves; ad-hoc in low dims)



go to level set via an appropriate normalized gradient flow and then use diffeomorphism $\theta : \{V = 1\} \simeq \{|z| = 1\}$

(h-cobordism; Poincaré would give homeomorphism if $n \neq 4$)
must adjust s.t. smooth away from 0 and $\mathcal{C}^0$ at 0; must apply robustness characterization to $\rightsquigarrow$ UGAS problem
for $n \geq 6$ sublevel set is compact, connected smooth manifold with a simply connected boundary $\rightsquigarrow$ diffeo to ball

The proof is based on the fact that sublevel sets of Lyapunov functions are smooth connected manifolds whose boundaries are homotopically equivalent to spheres, which implies, as a consequence of Smale's and Milnor's work on the Poincare' conjecture, that level sets are diffeomorphic to spheres, and one can then use a normalized flow to produce the coordinate change.

The problem is that the needed differential-topology results are still open in dimensions 4 and 5.

Some Open Problems, ctd'

ISS wrt observation errors, separation principle

recall: $\exists$ ($\mathcal{C}^0$) stabilizing feedback

$\Rightarrow$ redesign s.t. $\dot{x} = f(x, k(x) + d)$ ISS wrt d

(robustness to actuator errors/noise)

what about observation error?

$$\dot{x} = f(x, k(x+e))$$

if OK: may use *any* unbiased state estimator:

$$\dot{x} = f(x, k(\hat{x}))) = f(x, k(x + e))$$

and $x \to 0$ if estimation error $e = \hat{x} - x \to 0$

but(!): Freeman, TAC'96: *redesign impossible*

using continuous time-invariant state feedback

open: theory for t-v, dynamic, hybrid, . . .

Coming back to earth,

we said that one can redesign feedbacks to get ISS with respect to *actuator* errors.

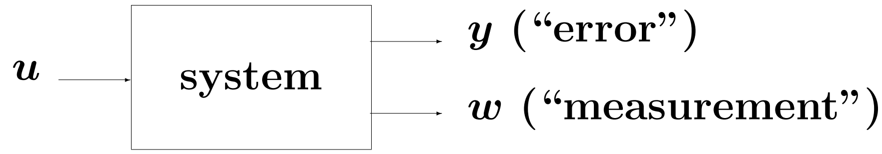
The open problem is, if one can also get ISS with respect to *observation* errors.

If this were always possible, the output stabilization problem would be much easier, since any unbiased state estimator could be used for feedback.

ISS would tell us, that when the estimation error goes to zero, the state converges to zero.

Unfortunately, there are counterexamples, showing that redesign using continuous, time-invariant, feedback is not always possible, but there are no general results using hybrid or dynamic controllers.

Relative ISS & Regulation



$$\dot{x} = f(x,u) \qquad y = h(x),\ \ w = g(x)$$

input-measurement to error stable (IMES):
$\exists\ \beta \in \mathcal{KL}$ & $\gamma_1, \gamma_2 \in \mathcal{K}_\infty$ s.t.

$$|y(t)| \leq \max\{\beta(|x^0|\,, t), \gamma_1(\|w\|), \gamma_2(\|u\|)\}$$

in particular: IOS: $w = 0$, IOSS: $y = x$

property is key to regulator questions

(partial) nonsmooth Lyapunov characterizations
(Ingalls-Wang-EDS, CDC'02) open: smooth

One last problem that I would like to mention, concerns a variant of ISS for systems with two types of outputs, which we may call "errors" and "measurements".

This notion arises in regulator problems, where it makes sense to ask that small inputs and measurements should imply small errors.

When the error is the state, we recover the detectability or IOSS property, and when the measurement function is not there, we get input/output stability.

We do not, as yet, have a satisfactory characterization of this property. For now, we only have partial results involving nonsmooth dissipation functions.

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I do not intend to talk about applications in any detail, but let me just give you the *flavor* of a couple of recent ones.

An Example of "ISSomics"

Arcak and Kokotovic, Automatica Dec. 2001: jet engine stall; axial compressor model

single-mode approx. of Moore-Greitzer PDE

$$\dot{\phi} = -\psi + \tfrac{3}{2}\phi + \tfrac{1}{2} - \tfrac{1}{2}(\phi+1)^3 - 3(\phi+1)R$$

$$\dot{\psi} = \frac{1}{\beta^2}(\phi + 1 - u)$$

$$\dot{R} = \sigma R(-2\phi - \phi^2 - R) \qquad (R \geq 0)$$

ϕ = mass flow relative to setpoint
ψ = pressure rise relative to setpoint
R = magnitude of first stall mode

objective: **stabilize using only $y = \psi$ (pressure)**

One example of the general ISSomics philosophy concerns the control of jet engine stall, modeled by a reduced Moore-Greizer equation; and using only *pressure* as a measured output.

A&K'01, ctd'

general framework:

$$\dot{x} = f(x, z, u)$$
$$\dot{z} = g(x, z)$$

only output $y = h(x)$ available for stabilization
z-subsystem (R) is unknown (robust design)

design state-feedback $u = k(x)$ and observer, producing estimate $\widehat{x}$ such that:

- error $e = x - \widehat{x}$ is ISS(z)
- $\dot{x} = f(x, z, k(\widehat{x})) = F(x, z, e)$ is ISS(e, z)
- $\dot{z} = g(x, z)$ is ISS(x)

$\rightsquigarrow$ (w/small-gain cond) stab of entire system

The authors achieve this objective by viewing the problem as a robust stabilization one, with the first stall mode as unknown dynamics.

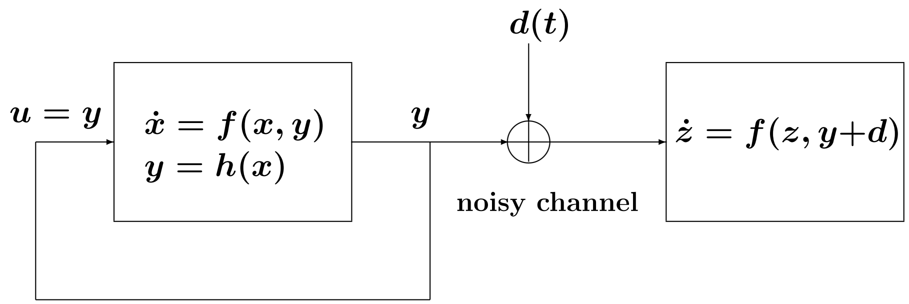
Their method relies upon a novel observer algorithm, coupled with a state feedback law designed so that *three* ISS properties are satisfied:

the estimation error is ISS with respect to the unmodeled dynamics z; the rest of the state is ISS with respect to the error and z; and the unmodeled part is ISS with respect to the rest of the system.

An ISS small gain argument is used to prove that the design works.

Appl: Chaos Synchronization

Angeli, TAC'02: driven copy of system



("master-slave" configuration; secure communications)

states synchronize:

$$|x(t) - z(t)| \;\leq\; \max\{\beta(|x^0 - z^0|, t)\,,\; \|d\|\}$$

provided that $\dot{x} = f(x, u)$ ***is*** Δ***-ISS :***

The next two applications of ISS are quite nontraditional.

The first concerns synchronization of chaotic systems, a technique proposed in the context of secure communications.

It is interesting that ISS ideas may be used in validating designs.

One wants a copy of the original system, driven by the same input, plus channel noise, and starting at a different initial state, to synchronize with the transmitter, provided the noise is not too large.

Incremental ("Δ") ISS

$$\|x(t)-z(t)\| \leq \max\{\beta(|x^0-z^0|,t),\gamma_1(\|u-v\|\}$$

for any two sols $\dot{x} = f(x,u)$, $\dot{z} = f(z,v)$

e.g. Lorentz attractor:

$$\begin{aligned}
\dot{x}_1 &= -\beta x_1 + \mathrm{sat}(x_2)\mathrm{sat}(x_3)\\
\dot{x}_2 &= \sigma(x_3 - x_2)\\
\dot{x}_3 &= -x_3 + u\\
y &= \rho x_2 - x_1 x_2
\end{aligned}$$

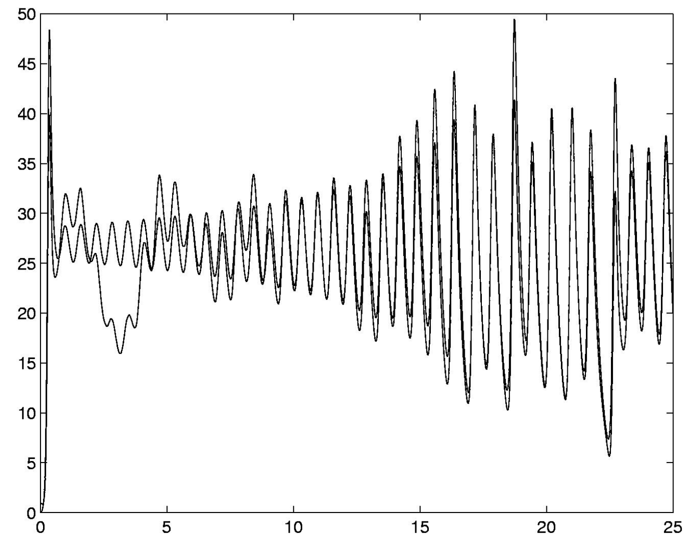
where $\beta = 8/3$, $\sigma = 10$, $\rho = 28$

(saturation here for technical reasons - does not affect application)

cascade of Δ-ISS $\Rightarrow$ Δ-ISS, so OK!

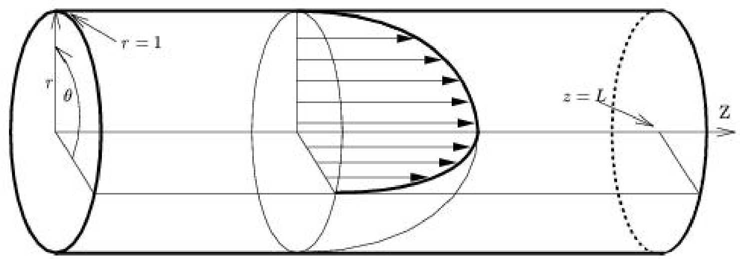
One can state this objective as one of *incremental* ISS, and the *preservation of incremental ISS under cascades* shows easily that, for example, the Lorentz chaotic attractor works.

e.g.: z_1 tracks x_1



The second systems tracks even though the signals are chaotic.

IOSS in Pipe Flow Mixing



Aamo & Krstic, Springer, 2002:

want: ***de*stabilize flow (to enhance mixing)**

input = wall velocity(position,time)

blowing/suction actuators distributed on wall

output = pressure differences across pipe

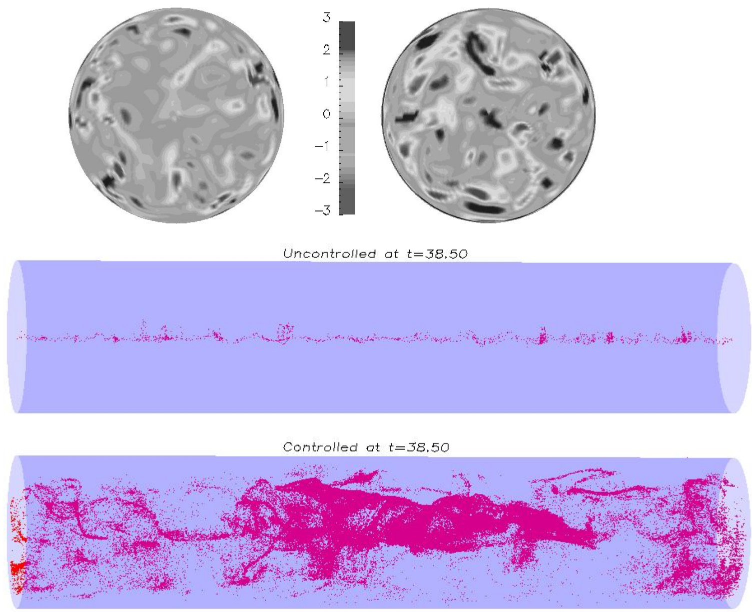
***output feedback*, based on IOSS estimates**

(Navier-Stokes eqn. IMES to turbulent kinetic energy & dissipation)

The last example is also very nontraditional: it involves *de*stabilization rather than stabilization, in the context of mixing of fluids in a pipe.

A central role is played by IOSS "detectability type" estimates, using as inputs the wall velocities, and as outputs, certain pressure differences.

Results



Here are cross-section, and longitudinal pictures showing the enhancement of mixing under the designed control laws.

Of course, the authors did far more than just checking ISS properties, but IOSS helped them formulate goals and organize thoughts.

Summary of ISS part

- *natural blend of Lyapunov & I/O*
- *suitable for analyzing interconnections and as basis for recursive design*
- *many equivalent characterizations*
- *elegant connections to detectability, etc*
- *rich mathematical theory*
- *many open problems remain incl extend to broader systems classes*
- *applications: see wide literature*

Before I turn to biology, let me summarize the ISS part of the talk.

I argued that ISS is a natural blend of Lyapunov and input/output notions, suitable for the stability analysis of interconnected systems;

that it can be characterized in many very different manners, through dissipation, stability margins, and so on,

and that other systems theoretic notions, such as detectability, can be formulated in an similar fashion, leading to an elegant and consistent theory.

The theory, although deep and well-developed, is far from complete, and many exciting open problems remain.

I have not talked about applications in any serious way;

many in the audience, are far better qualified than me to describe applications, and I refer you to their lectures and papers.

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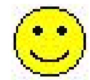
  - Discussion
- ***Acknowledgments***

I would like to say a few words now about Systems Molecular Biology, a subject which, I believe, may become one of the most important areas of application for systems and control ideas.

Systems Molecular Biology

- source of theory questions [similar, but $\neq$!]

  fascinating "playground"
  for control theory (including ISS )

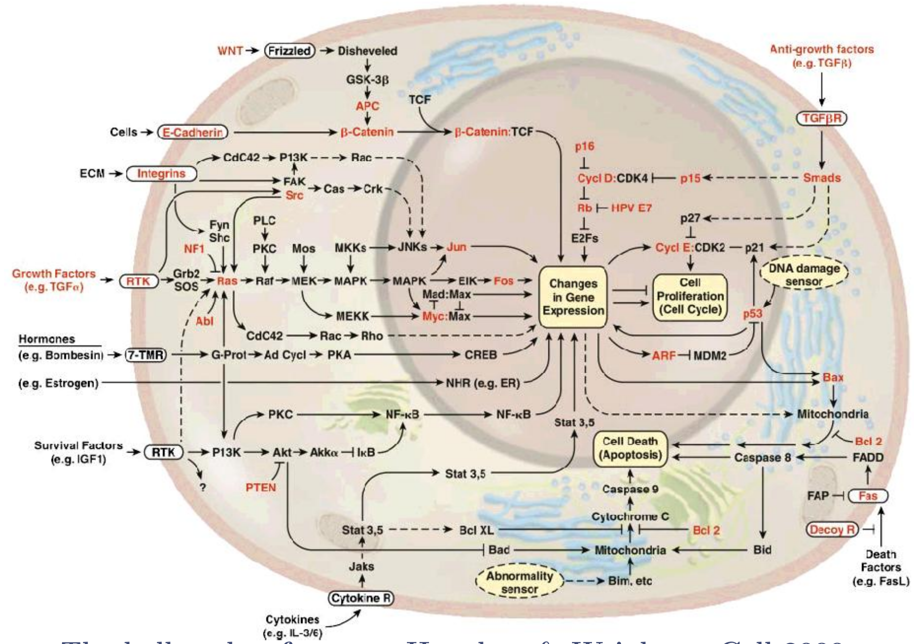
- huge potential societal impact

  - scientific knowledge
  - pharmaceutical research
  - gene therapies
  - engineered "viruses"

The field raises a tremendous number of exciting theoretical questions, and in that sense, it is a great "playground";

but more importantly, of course, our contributions as a community have the potential to have a major impact upon society, adding to scientific knowledge, drug design, and gene therapies.

e.g. System: Cancer Network



The hallmarks of cancer, Hanahan & Weinberg, Cell 2000

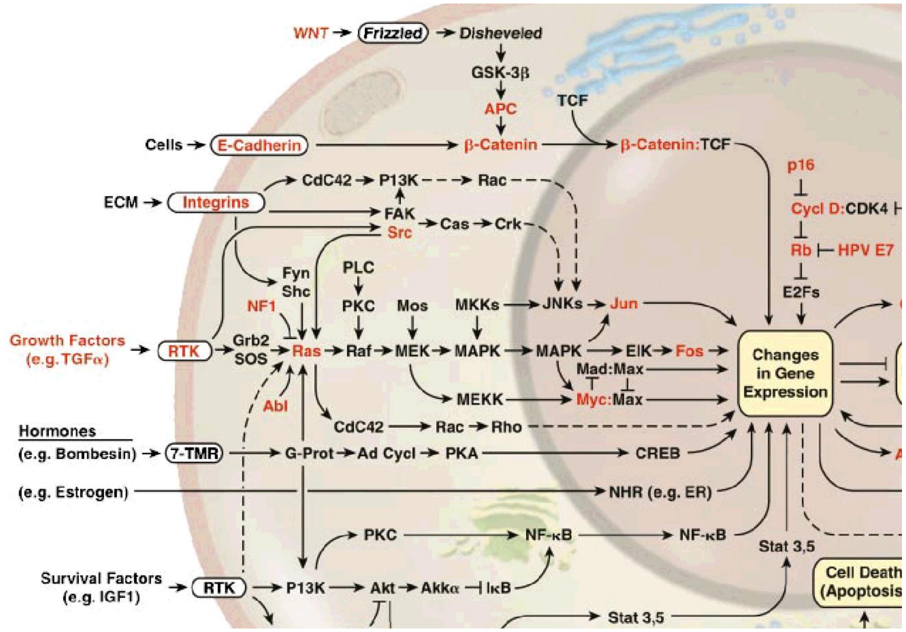
This picture, from a well-known paper in cancer research, shows the network inside cells which is responsible for the control of cell division.

The breakdown of this control system leads to cancer.

The arrows indicate chemical interconnections through which the cell carries out its information processing tasks.

Let me zoom-in so you can see better.

Inputs ⟶ Gene Expression



The inputs to the system are external signals such as growth factors, hormones, and various other chemicals.

The outputs are chemical signals to other cells as well as signals to the reproduction machinery inside the cell.

Of course, much of the system has not been identified yet: there are surely other, so far unknown, components, and the numerical values of most parameters are only known very approximately.

However, data is being collected at an amazing rate, and better and better models are being constantly obtained.

As a systems theorist, one cannot help but to be fascinated by all this.

Many Challenging Questions

- ***information-processing (i/o)?***
- ***signal transduction pathways?***
- ***reverse engineering (inverse problem)***
  - parameters (reaction constants)?
  - protein expression levels (state $\in \mathbb{R}^{100,000}$)?
- ***what "modules" appear repeatedly?***
- ***why cascades and feedback loops?***
- ***dynamical properties?***
  - stability, oscillations, ...
- ***how to control using external inputs?***

Moreover, the *questions* that we would normally ask are precisely those that the best biologists are asking:

what type of information processing is being carried out?

how do the different signal transduction pathways interact?

how do we identify system parameters?

if we know parameters, how do we estimate internal states?

(which, for an entire cell, might involve knowing the concentrations of thousands of proteins, as a function of time)

what subsystems appear repeatedly?

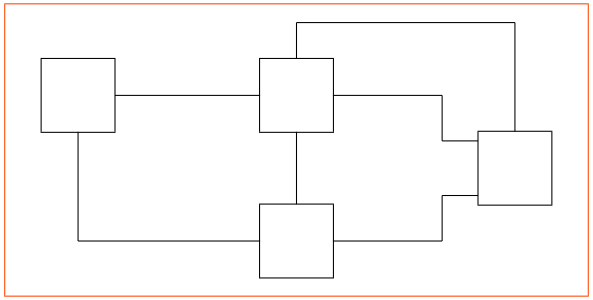
what is the reason that there are cascades and feedback loops?

more generally, what can one say, if anything, about stability and other dynamical properties of such complex systems?

and finally, how can we *control* cellular systems?

Systems Theorists' Heaven

decomposition questions central
***and* recognized as such**



(buzzword: "modules")

It is amazing that one of the buzzwords in current molecular biology is the word *module*, which may be understood as *subsystem*:

biologists are attempting to understand cell behavior as arising from an interconnection of common subsystems which perform standarized tasks.

Q's Similar but $\neq$ Engineering!

e.g.:

- identify "network graph" from *steady state* data [DNA chips, etc] (or a *very small* # time samples)
  Kholodenko *et.al.*-EDS, PNAS'02

- limited freedom in inputs for identification (e.g. step responses only)
  EDS, J. Nonlinear Science'02

next: a couple of e.g.'s in more detail

Having said all this, one of the messages that I'd like to leave you with is that, while the questions that biologists ask *sound* like those that we are accustomed to,

technically, in my experience, they end up being *very different* than those that are common in many areas of engineering.

I have been looking at a number of such questions,

dealing with issues such as systems identification based on small amounts of steady-state data;

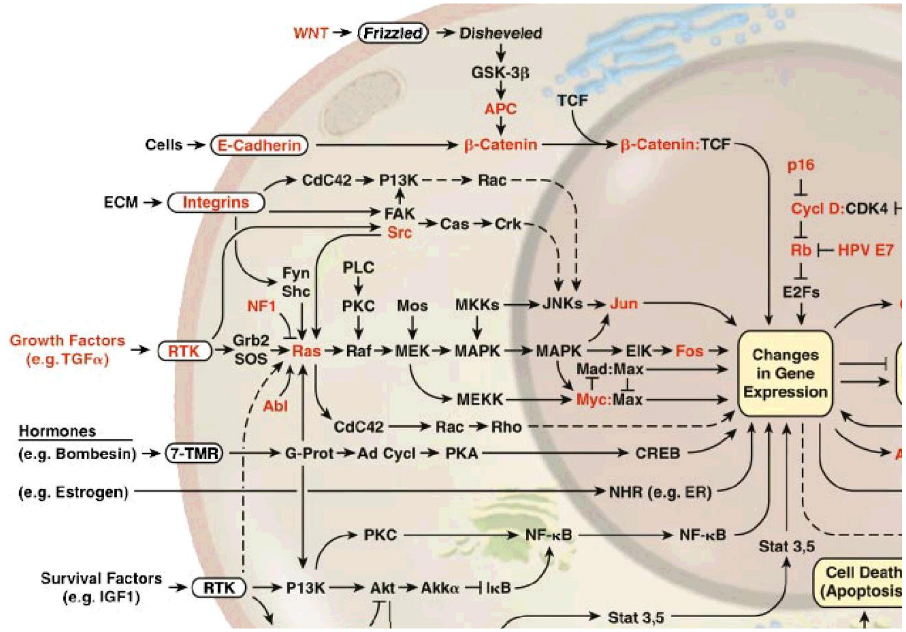
or the fact that, typically, one cannot apply rich enough inputs to a cell for identification purposes.

Outline

- *Input to State Stability*
  - Motivation, Definition, Feedback Redesign
  - Robust Stability, Superposition, Dissipation
  - I/O Stability & Detectability; Relationships
  - Other Notions: iSS, Minphase
  - Taste of Theory: DI's, Viscosity
  - Some Open Problems & Applics; Summary
- *Systems Molecular Biology*
  - E.g.: MAPK Cascades, Stability Questions
  - E.g.: *E.coli* Chemotaxis, IMP
  - New Tools: Measurements, System Perturbations
  - Discussion
- *Acknowledgments*

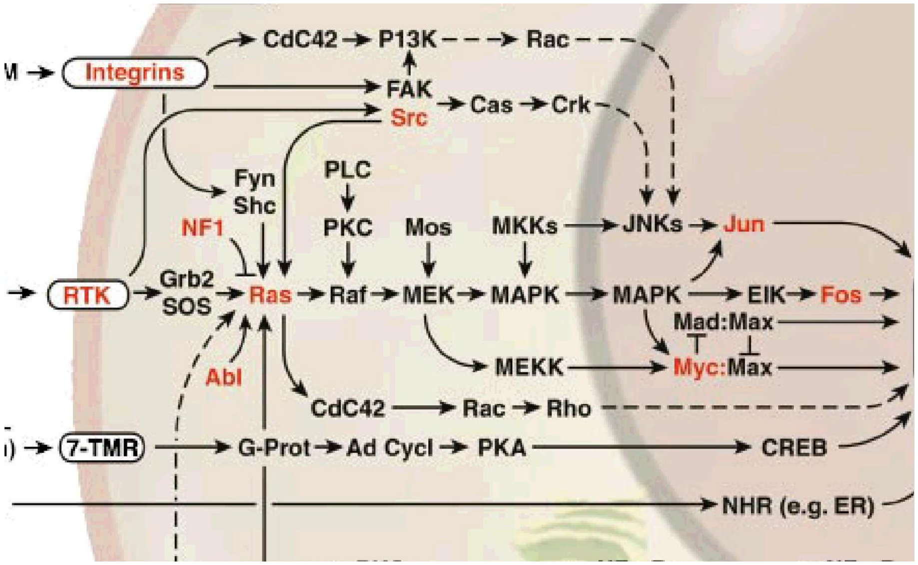
For the rest of this talk, let me describe a couple of "short stories" that illustrate this point.

Zoom-in Cancer Net



This is part of the cancer network that I showed earlier.

Zoom More: MAPK Cascades

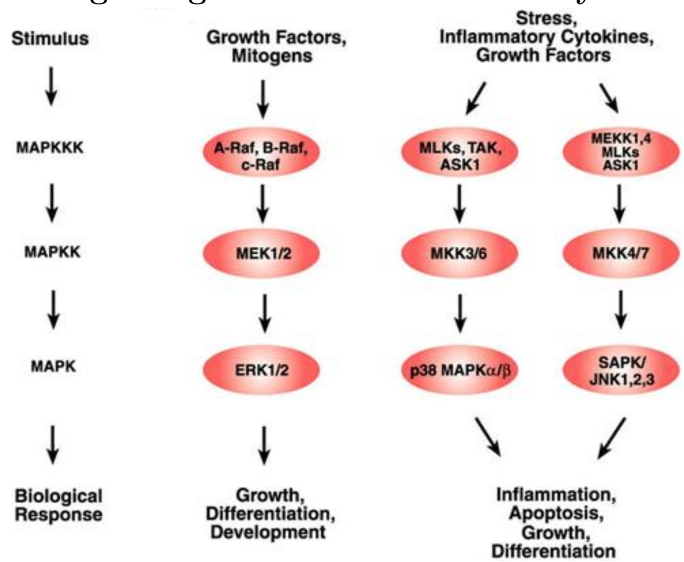


Let me zoom in even more, and draw your attention to the middle of this slide.

These reactions are an example of a *mitogen activated protein kinase* or “MAPK” cascade.

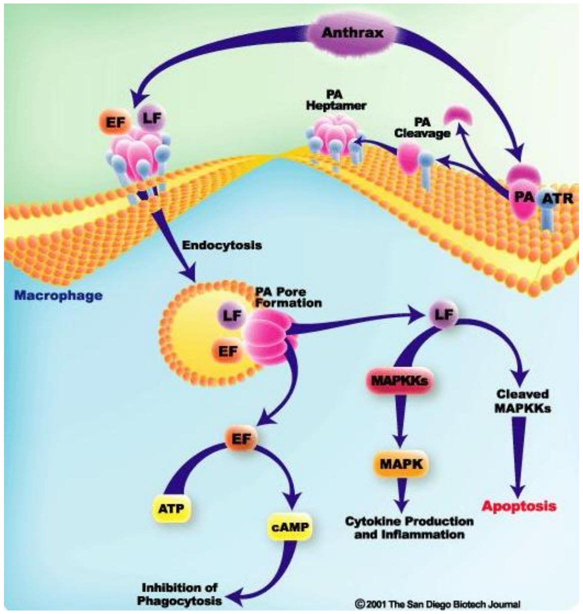
MAPK 3-Level Cascades

mitogen-activated protein kinase cascades
ubiquitous "signaling "submodule" in eukaryotes



These are always cascades of three subsystems, each one driving the next one through a phosphorylation reaction; they appear everywhere, with apparently minor variations, and have a role in the most important cellular processes.

Even: Role in Anthrax



Lethal Factor (LF) is a toxin secreted by Bacillus anthracis. It is a highly specific protease that cleaves members of a MAPKK near their amino-termini, removing the docking sequence for the down-stream cognate MAP kinase

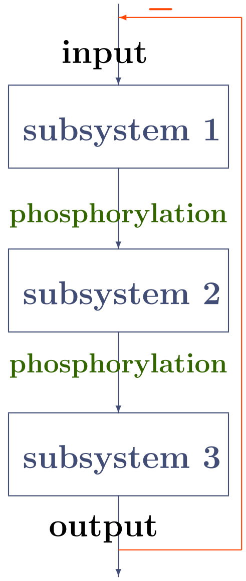
It was even discovered that *anthrax* attacks by breaking the communication link between the second and third subsystem in this cascade.

Example: 2-3-3 cascade

$$
\begin{aligned}
\frac{dx_1}{dt} &= \frac{v_2\,x_2}{k_2 + x_2} - \frac{g_1\,u}{(k_1 + x_1)} \\
\frac{dx_2}{dt} &= \frac{g_1\,u}{(k_1 + x_1)} - \frac{v_2\,x_2}{k_2 + x_2} \\
\frac{dy_1}{dt} &= \frac{v_6\,y_2}{k_6 + y_2} - \frac{\kappa_3\,x_2\,y_1}{k_3 + y_1} \\
\frac{dy_2}{dt} &= \frac{\kappa_3\,x_2\,y_1}{k_3 + y_1} + \frac{v_5\,y_3}{k_5 + y_3} - \frac{\kappa_4\,x_2\,y_2}{k_4 + y_2} - \frac{v_6\,y_2}{k_6 + y_2} \\
\frac{dy_3}{dt} &= \frac{\kappa_4\,x_2\,y_2}{k_4 + y_2} - \frac{v_5\,y_3}{k_5 + y_3} \\
\frac{dz_1}{dt} &= \frac{v_{10}\,z_2}{k_{10} + z_2} - \frac{\kappa_7\,y_3\,z_1}{k_7 + z_1} \\
\frac{dz_2}{dt} &= \frac{\kappa_7\,y_3\,z_1}{k_7 + z_1} + \frac{v_9\,z_3}{k_9 + z_3} - \frac{\kappa_8\,y_3\,z_2}{k_8 + z_2} - \frac{v_{10}\,z_2}{k_{10} + z_2} \\
\frac{dz_3}{dt} &= \frac{\kappa_8\,y_3\,z_2}{k_8 + z_2} - \frac{v_9\,z_3}{k_9 + z_3}
\end{aligned}
$$

This is a typical set of equations, taken from the literature, describing a cascade with systems of dimensions 2,3,3 respectively.

Oscillations



Kholodenko, Europ.J.Biochem.'00:
inhibitory feedback (to turn-off response?)
may induce oscillations (Hopf)
if too strong . . . but *how* strong?

obvious approach: small-gain
ask "loop gain $\boxed{}$ less than 1"
but gain in what sense?

in biology, equilibrium location may depend on feedback gain!

e.g.: $\dot{x} = -x + \frac{4}{3+x} \Rightarrow$ equil moves $x = 0 \rightsquigarrow 1$

Let me show one example of a question about MAPK cascades which led to some interesting new control theory.

There is some evidence that inhibitory feedback loops from the bottom level of the cascade to the top play a role in "turning off" a response after a signal has been transmitted (keeping a signal "on" is too expensive, metabolically).

Simulations published in the biochemical literature showed Hopf bifurcations for large negative gains.

It is thus an interesting question to try to predict for what ranges of feedback gains there are no oscillations.

As control theorists, we immediately think "small gain theorem" but, as far as I could see, no classical version applies in this case.

One of the complications is that the magnitude of the gain affects the location of the steady state, a situation which is typical in biological feedback.

⇝ New Control Theory Q's

- "Cauchy gains" theory developed to provide tight estimates of Hopf bifurcations
  [EDS, SCL'02 & CDC'02]

- "monotone control systems" theory and rich SGT's ("ISS with order")
  [Angeli-EDS, CDC'02 & submitted to TAC]

- also: "+"feedback, hysteresis, multi-stability ISS-like properties of open loop subsystems
  $\Rightarrow$ global convergence to *some* equilibrium
  [Angeli-EDS, in preparation]

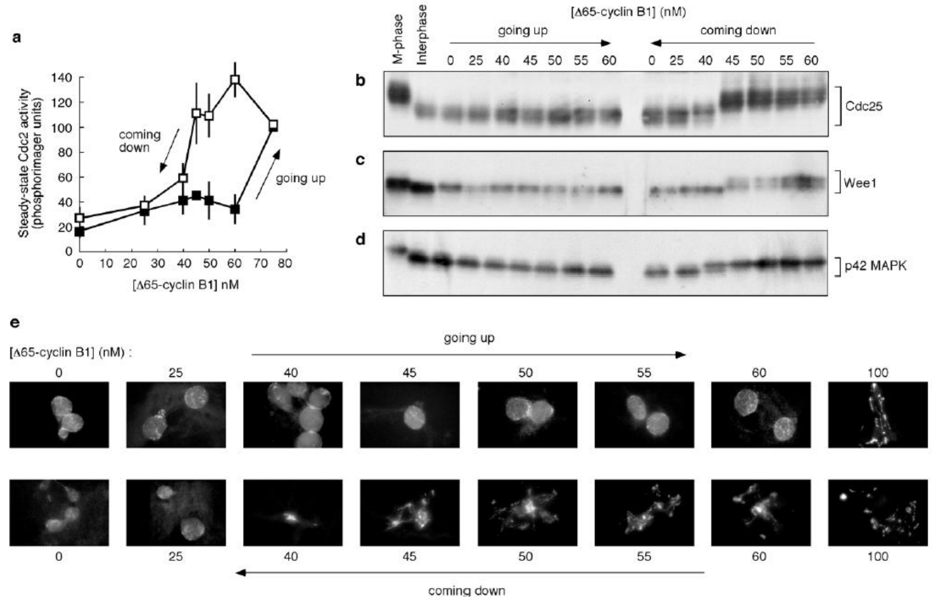
In any event, studying this problem led to the development of a new type of "gain" for nonlinear systems, related to, but quite different from, both classical and ISS gains.

One gets a tight estimate of gains that don't produce oscillations;

and further research into biochemical models of MAPK cascades, gave rise to yet another theoretical development, this one concerning an ISS property on ordered spaces,

including an extension to the characterization of hysteresis and multi-stable behavior, which play a central role in molecular biology.

Bi-Stable Behavior



(Pomerening & Ferrell, 2002, unpublished)

Bistable phenomena are not at all a purely mathematical game; these experimental results show bistable behavior in cdc2-cyclin B activity in mitosis.

We see the hysteresis in MAPK and other enzymes, when inputs change up or down,

and the effect is evident both in the Western blot that measures protein phosphorylation, and in microscope photographs of the nucleii of cells undergoing cell cycle.

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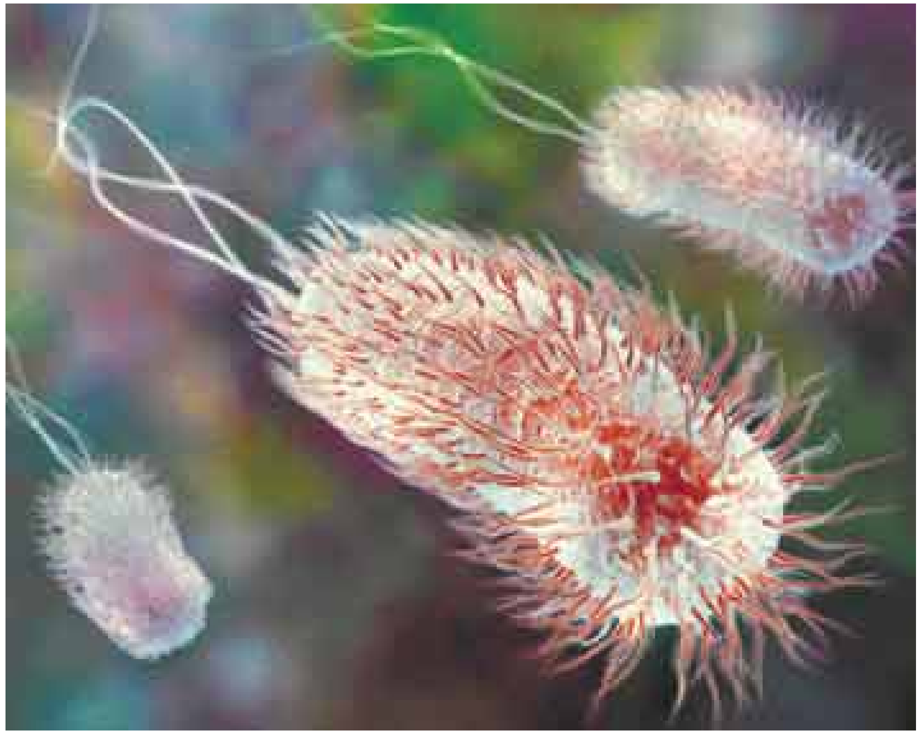
I want to emphasize that really exciting new theoretical questions appear as soon as one looks into such problems.

Hopefully, the theory will be useful to biologists.

But, if nothing else, molecular biology in the 21st century may well play the role that physics played in the last two centuries, in generating new mathematics.

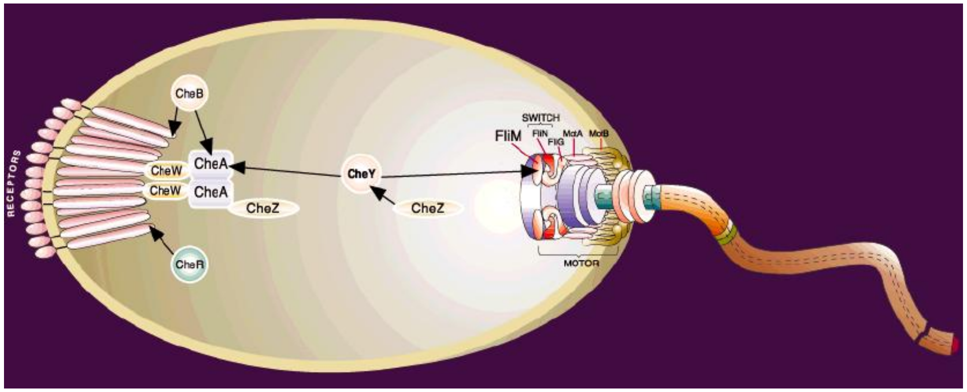
The second "short story" that I want to tell, concerns the movements of E-coli bacteria.



The bacteria that make you sick if you eat under-cooked hamburgers.

E.coli Chemotaxis

E.coli **moves (taxis), propelled by flagella, in response to chemical attractants/repellents**



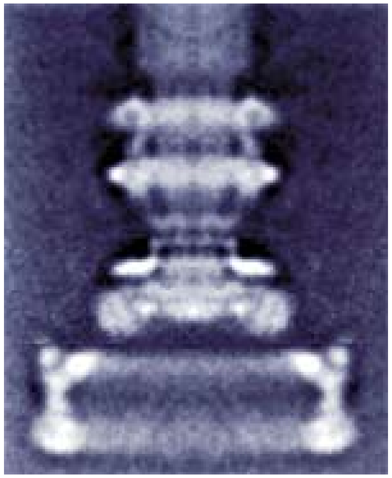
sense nutrient $\longrightarrow$ $\boxed{\text{signaling system}}$ $\longrightarrow$ signal motors

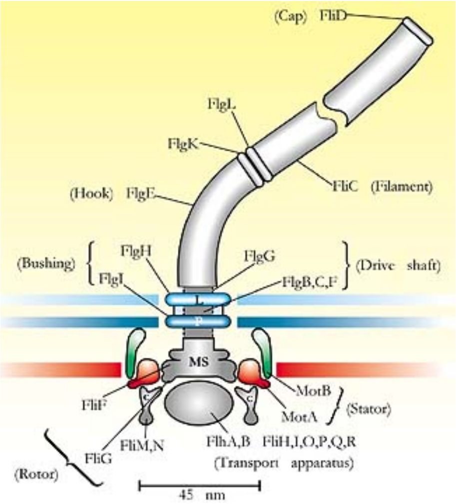
Berg: typical cell has up to six flagella and hundreds of porins (channels for nutrients); cell body is 2 μm long

E-coli bacteria move in response to chemical gradients, towards food and away from poisons.

They have a subsystem which is resposible for detecting nutrients and signaling motors to turn propellers.

Motor: Micrograph, Diagram





engines, propellers, particle counters, rate meters, gear boxes
"a nanotechnologist's dream" (Berg, Physics Today, 2000)

The motors are marvels of nanotechnology: to the left is an *actual photograph* of a motor, and to the right a parts diagram.

- transient signal ("run toward food")
  issued in response to a change in concentration
- but then adapt, stop running

(actually, opposite: tumble/random gradient search)

behavior consistent with regulation with respect to constant signals (chemical gradient) plus nontrivial I/O

indeed, experimental measurements of impulse-response (local, small amplitude, wrt default tumbling signal) fit perfectly to transfer function having a zero at $s = 0$

further, integral of i/r fit is itself fit perfectly by data:

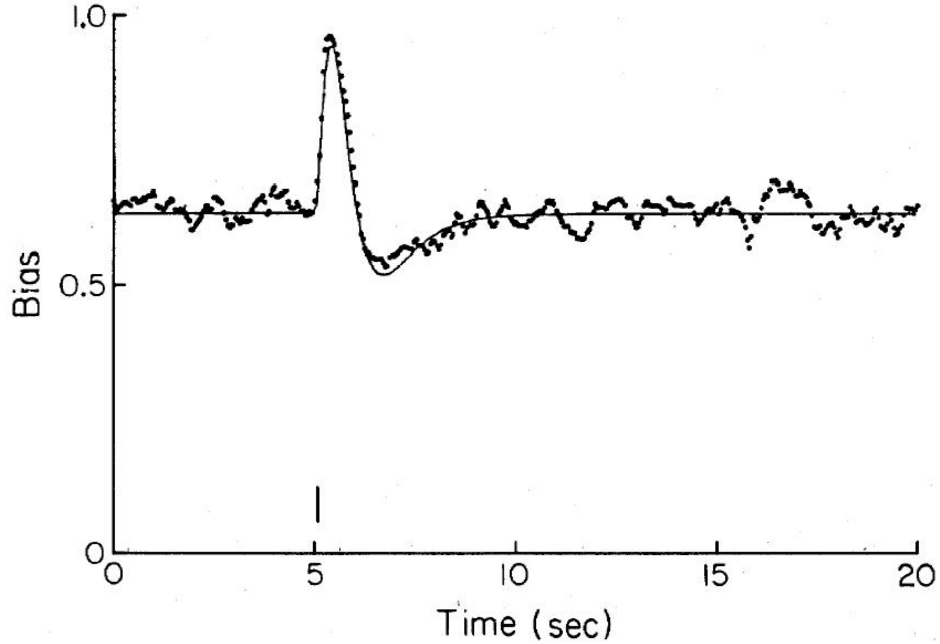
There are many questions for control theory, but let's mention just one:

E-coli detects *gradients* rather than absolute concentrations: it runs towards food if there is a change in concentration but when the concentration does not change, it stops

(actually, there is a far more complicated stochastic search algorithm going on, but let me skip the details).

So there is regulation against constant signals.

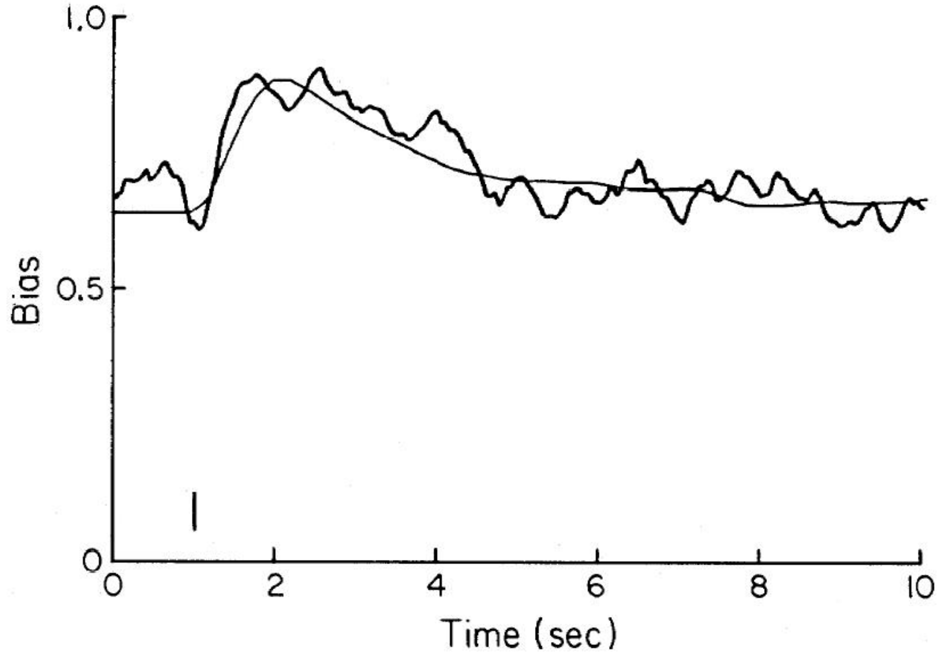
Zero DC Gain



impulse response (population avg), Segall, Block, Berg, PNAS 1986

There have been measurements of the impulse response, and indeed, for small signals, one checks that the system has zero DC gain.

Step Response, Indeed $\int$



step response (population avg), Segall, Block, Berg, PNAS 1986

Fitting and then integrating gives the same as the experimental step response, which is amazing if you think of the complicated biology going on.

Internal Model Principle

if system Σ regulates w.r.t. all inputs $u(\cdot) \in \mathcal{U}$
($\mathcal{U}$ = some predetermined class, e.g. constants)
then Σ *must* contain an IM generating $\mathcal{U}$

Wonham, Francis, Hepburn: if robust
(structurally stable; center manifold techniques)

Bio IMP Technically $\neq$ Usual

small overshoot desirable in engineering
— e.g. cruise-control, active suspension

but here ***want*** to detect sudden change in $u(\cdot)$

$\therefore$ desirable theorem:

signal detect & adapt $\Rightarrow$ internal model

This suggests, by the Internal Model Principle, that there should be some sort of integrator inside the system.

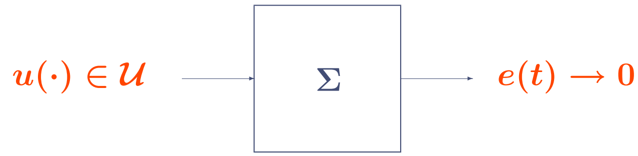
In contrast to standard disturbance rejection, however, one ***wants*** a large transient, that allows signal detection before adaptation kicks in (sort of a mixture of fault detection and regulation).

This is quite different from, say, active suspension design – we would not want passengers in a car to hit the roof as hard as possible before the car adapts to a bump in the road!

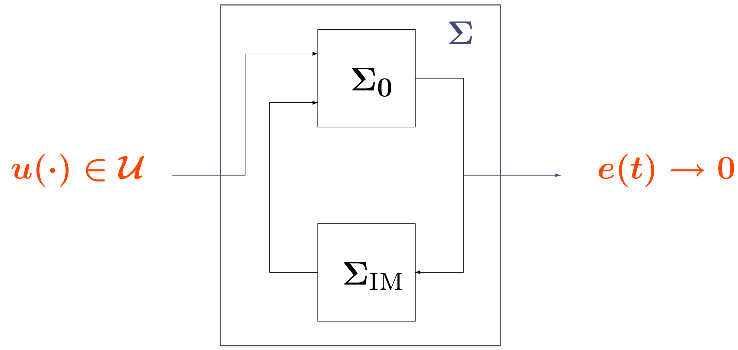
One is led to an internal model theorem which is different in spirit to the classical ones of Francis and coauthors (which assume robustness instead of signal detection).

Again, I wish to emphasize the point that a problem which is very similar to a classical one, on closer inspection differs in subtle ways from the analogous engineering problem, and new concepts and results need to be developed.

One Theorem (EDS'02, to appear)



$\Rightarrow$ **decomposition:**



where the subsystem Σ_{IM} is driven by the "error" $y(\cdot) - y^*$ and can generate all possible "disturbances" $u(\cdot) \in \mathcal{U}$

One simple theorem along those lines states that if a system regulates against all disturbances generated by an exosystem, and if a relative degree condition holds, which models the "signal detection" property,

then there is a decomposition of the system which exhibits a subsystem that is driven by errors and which is capable of generating all the possible exosystem signals.

More Precisely:

suppose $\dot{x}(t) = f(x(t)) + u(t)g(x(t))$, $y(t) = h(x(t))$
adapts to $\mathcal{U}$ = generated by Poisson-stable exosystem

f & g smooth vf's; h smooth $\mathbb{R}^n \to \mathbb{R}$, $f(0) = h(0) = 0$

assume finite uniform relative degree:

$(\exists\, r) \quad L_g L_f^k h \equiv 0 \quad \forall\, k < r-1, \quad L_g L_f^{r-1} h(x) \neq 0 \quad \forall\, x \in \mathbb{R}^n$

and vf's $\tau_i := \mathrm{ad}_{\widetilde{f}}^{i-1}\widetilde{g}$, complete and pairwise commutative

$$\widetilde{g}(x) = \frac{1}{L_g L_f^{r-1} h(x)} g(x), \;\; \widetilde{f}(x) = f(x) - \left(L_f^r h(x)\right)\widetilde{g}(x),$$

(linear systems: $\equiv$ nonzero transfer function)

then $\exists$ diffeomorphism $\rightsquigarrow$

$$\begin{aligned} \dot{z}_1 &= f_1(z_1, z_2) + u g_1(z_1, z_2)\,, \qquad & y &= \kappa(z_1) \\ \dot{z}_2 &= f_2(y, z_2) \end{aligned}$$

and $\exists$ smooth scalar $\varphi(z_2)$ s.t., $\forall\, u \in \mathcal{U}$, $\exists$ solution of

$$\dot{z}_2 = f_2(0, z_2) \qquad \text{s.t. } \varphi(z_2(t)) \equiv u(t)$$

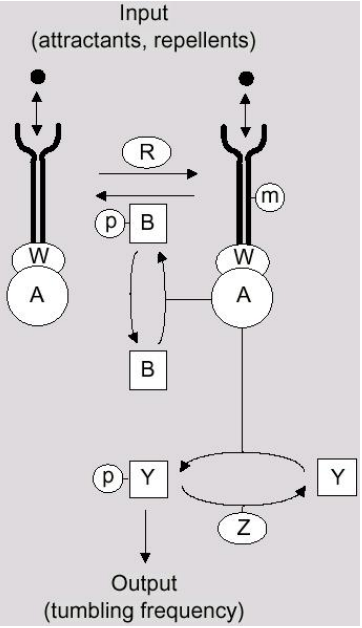
The precise statement involves a Poisson stability assumption on the exosystem and a decomposition based on center manifold types of techniques.

Internal Model (Integrator)

Yi/Huang/Simon/Doyle
(PNAS 2000):

IMP ⇒ integral feedback
in molecular mechanism of
Barkai&Leibler, Nature 1997

(also: Iglesias & Levchenko,
CDC 2001)



Integrators have been found, indeed, in the subsystem responsible for E-coli chemotaxis and a specific methylation reaction has been interpreted as playing the role of integrator.

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In the last few minutes, let me tell you quickly why I believe that the field may be ripe for a quantitative study.

Enabling Technologies

- bioinformatics: genomics & proteomics
- measurement tools, e.g. genechips, GFP
- system perturbations, e.g. mutations

Besides the advances in decoding the genome, which provides a "parts list" for life,

and the ongoing work on finding what these parts look like, that is to say, finding the shapes of proteins,

several other technological advances make quantitative modeling possible.

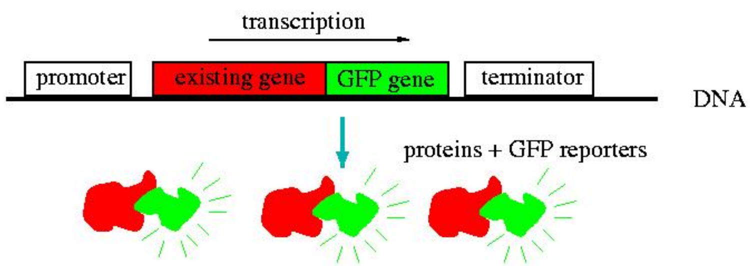
One is the advent of sophisticated methods for measuring what is going on inside a cell,

and another is the development of techniques for performing system perturbations.

E.g. of Measurement Tools

scalar outputs: Green Fluorescent Protein

GFP gene inserted adjacent to gene coding for protein to be measured



genes are expressed simultaneously, measure intensity of the GFP light emitted

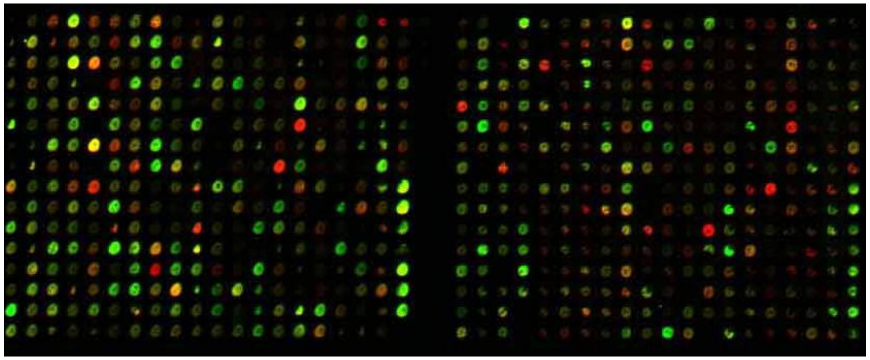
One example of measurement tool is the use of ***green fluorescent protein***.

A mutation inserts a GFP gene next to the gene of interest, so that both are expressed simultaneously;

the quantity being produced of the protein of interest correlates with the total amount of light emitted by GFP.

Gene Chips

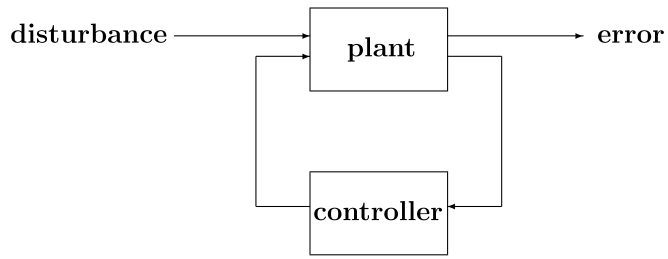
vector output measurement:
snapshot of current state of system
activity levels of many [all] genes



***Gene chips*, or *DNA microarrays*, are a technique which gives a snapshot of overall gene expression and provides a read-out of thousands of genes simultaneously.**

E.g. of System Perturbations

one can use genetic engineering in order to experimentally answer if, at the molecular level, cells employ neg feedback to reduce uncertainty



higher feedback gain $\Rightarrow$ smaller (ISS, etc) gain?

Not only can one attach sensors, so to speak, but genetic engineering can help study the effect of feedback loops.

A recent paper in the molecular biology literature dealt with the use of negative feedback in uncertainty reduction.

Specifically, the authors asked if a higher feedback gain resulted in better disturbance attenuation.

Let me describe the experiment, to give you an idea of what is becoming possible in this area.

Becskei and Serrano, Engineering Stability in Gene Networks by Autoregulation, *Nature* 2000

in *E.coli*, about 40% of transcription factors self-regulate

TetR, or tetracycline repressor protein, defends *E.coli* against tetracycline, and is a major source of antibiotic resistance

TetR regulates its own formation through a feedback loop

protein level measured by splicing GFP gene to gene coding for TetR

experiment: "loop gain" ↘ by mutations/replace operator (feedback loop partially or almost totally disabled)

lower "gain" ⇒ more variability in protein expression

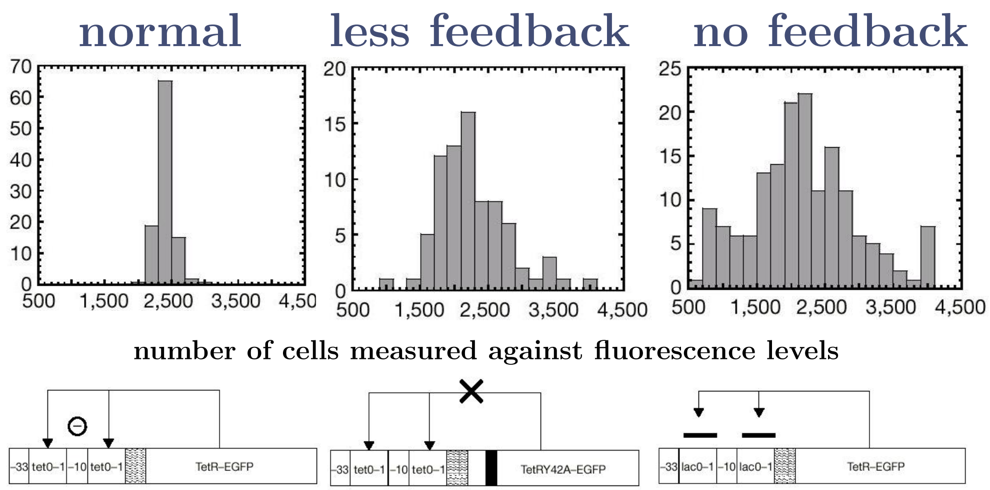
In E-coli bacteria, about 40% of transcription factors regulate themselves.

TetR, or tetracycline repressor protein, defends E-coli against tetracycline, and is a major source of antibiotic resistance.

TetR tightly regulates its own level through a negative feedback loop.

An experiment showed that lowering the gain results in more variability.

Experimental results



number of cells measured against fluorescence levels

"negative feedback" in biology typically *not* additive "$x - ke$" (!)
but rather inhibition: multiplication by small factor $\left(\frac{1}{1+ke}\right) x$

In these three plots, the first one is of normal expression levels, while the second and third show a higher variance due to lower feedback gain.

The feedback was changed by mutations which blocked regulation. These types of experiments, although still expensive and nontrivial, are becoming commonplace in molecular biology research.

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let me make a couple of closing remarks about systems biology and systems and control theory.

On Sysbio & Math/Control

feedback control deals, in principle, with issues central to postgenomic (systems) molecular bio

avoid "pseudo-exactness": relevant values (rate constants, concentrations) may vary over orders of magnitude: require robustness to large parameter variations

expect principles of feedback theory useful in guiding experimental work

other parts (e.g. identification, observers): role in experimental design, instrumentation

also: extremely interesting research areas in mathematics arise studying these problems

There is no question that our field deals with the fundamental issues of postgenomic, or "systems" molecular biology.

But it is not going to be easy: a unique aspect of life, is that it performs well under a tremendous amount of uncertainty, far more than allowed by our favorite robustness/identification tools.

The precision and optimality results that we are accustomed to, have to be extended to allow for large of parameter variations.

Still, theoretical principles will help guide and interpret experiments, while other parts of our field play a central role in instrumentation, and new and challenging open problems will arise for us theoreticians.

Outline

- ***Input to State Stability***
  - **Motivation, Definition, Feedback Redesign**
  - **Robust Stability, Superposition, Dissipation**
  - **I/O Stability & Detectability; Relationships**
  - **Other Notions: iISS, Minphase**
  - **Taste of Theory: DI's, Viscosity**
  - **Some Open Problems & Applics; Summary**
- ***Systems Molecular Biology***
  - **E.g.: MAPK Cascades, Stability Questions**
  - **E.g.:** *E.coli* **Chemotaxis, IMP**
  - **New Tools: Measurements, System Perturbations**
  - **Discussion**
- ***Acknowledgments***

Acknowledgments

- *AFOSR for long-standing support*
- *many colleagues (too many to list!)*

but especially:

In closing, I wish to thank the Air Force Office of Scientific Research, and especially, the recently retired program director, Marc Jacobs, for many years of support for foundational research;

and, of course, I should thank a huge number of people, many of whom were mentioned in the slides, such as David Angeli, for many years of collaboration, encouragement, and discussions.

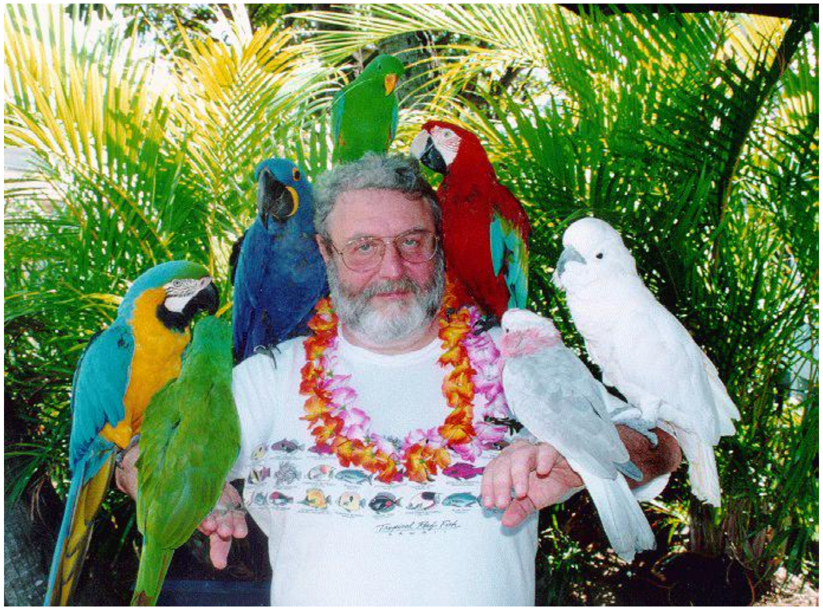
I would like to single out three people, especially:

Advisor: Rudolf Kalman

the Kalman gang

My advisor, Rudolf Kalman, who taught me the importance of asking fundamental conceptual questions.

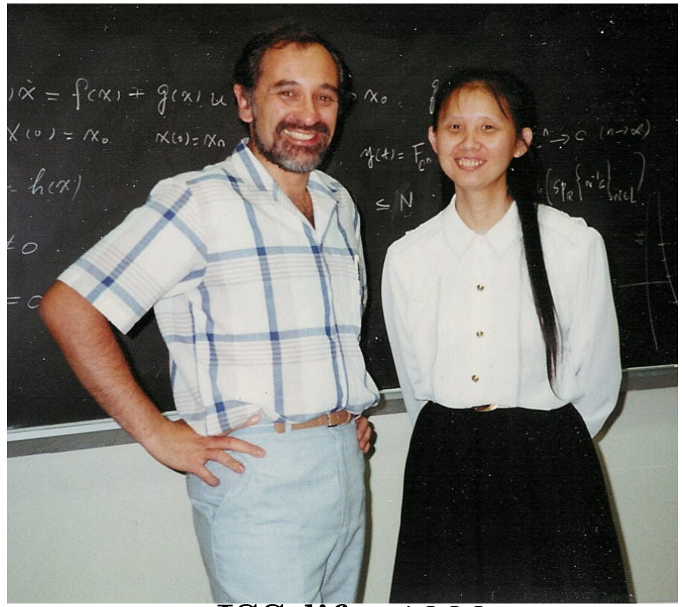
Colleague: Héctor Sussmann



scouting next CDC's site

My colleague, Hector Sussmann, who provided me with many of the tools needed to attack these fundamental questions.

Student: Yuan Wang



pre-ISS life, 1990

And my former graduate student, and long-time collaborator, Yuan Wang, who was instrumental in answering many of these fundamental questions.

http://www.math.rutgers.edu/~sontag

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Thank you very much.