Feedback Control Theory

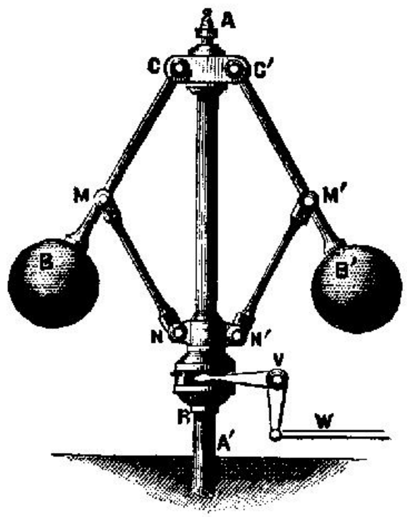
and the challenges of postgenomic

Molecular Biology

Eduardo D. Sontag

Introduction

feedback control systems played
a central role in the industrial revolution
(through Watt's steam engine governor),
made possible long-distance communications
(by means of Black's feedback amplifier),
were a key enabler of the aerospace industry
(e.g.: Kalman filters, optimal control),
and are embedded in contemporary
consumer and industrial technology



governor
higher speed ⇒ balls raised
⇒ valve closes, lowering speed

feedback control theory arose from the need to analyze the stability and performance of technological systems, and developed into one of the deepest and most useful areas of applied mathematics and engineering

this talk: review a few central "themes" of feedback control, and speculate upon their roles in modern molecular biology

Postgenomic Biology

today's work in genomics is providing a complete parts list for life

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gcacgagtaa acatgcactt cccaggccac agcagcaaga aggaggaatc tgcccaagcg
gccctcacga agctgaactc ctggttcccc accaccaaga accccgtcat catcagcgcc
cccatgtatc tcatcgccaa cggcactctt gcggccgagg tatccaaggc cggcggtatt
ggctttgtcg ccggcggctc cgacttccgc cccggctcct cccacctaac cgccctctct
accgaactcg cctccgcccg cagccgcctc ggtcttaccg accgccccct cacccctctc
cccggcattg gcgtcggcct cattttaacc cacaccatct ccgttcccta cgtaaccgac
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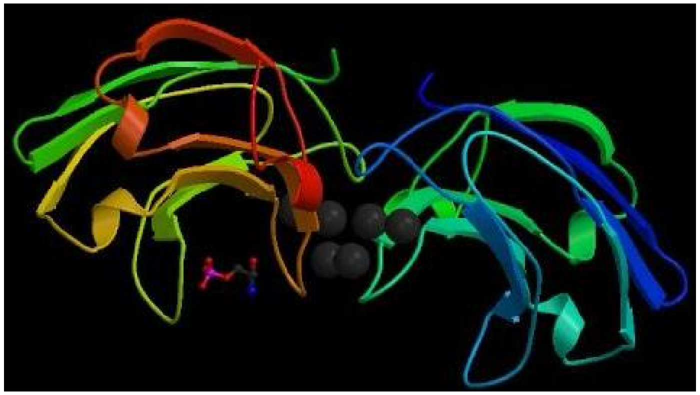
task of proteomics: determine three-dimensional shapes of the parts so described (proteins) — their shape, in turn, largely determines their function



interactions among proteins induce conformational changes, allowing release of signaling molecules or lock&key binding

or enhancing/repressing gene expression via DNA binding

cell life ≡ huge "wireless network" of such interactions driven by external physical (UV radiation, temperature) and chemical signals (drugs, hormones, nutrients)

E.g.: A Cancer Network

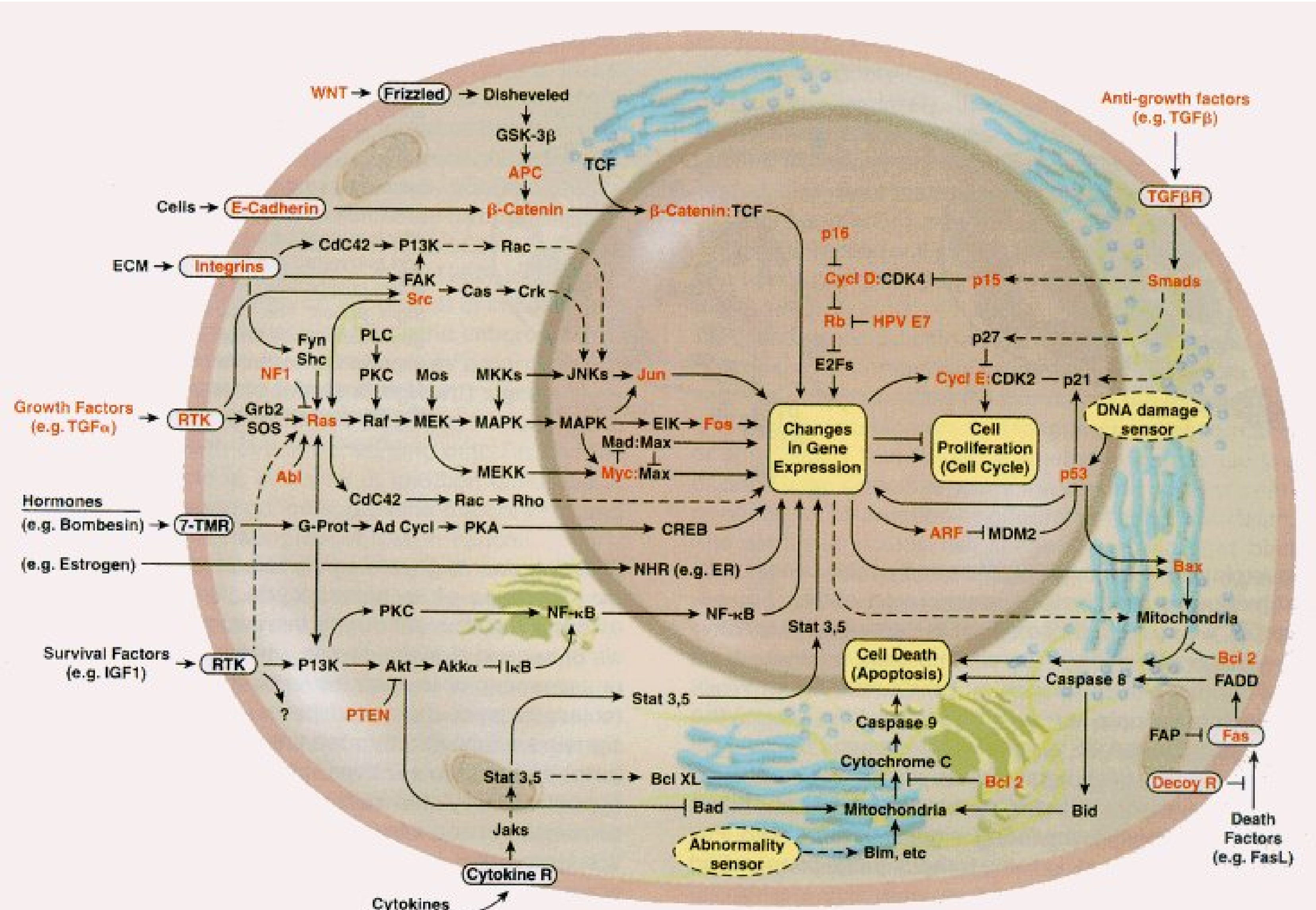


Figure from: Hanahan and Weinberg, *2000*. Cell *100*, p. 57-70

from TRANSPATH database. Outputs: proteins for structure, or as signals to other cells or regulating gene expression

Challenging Questions

- *information-processing (i/o)?*
- *signal transduction pathways?*
- *reverse engineering (inverse problem)*
  - parameters (reaction constants)?
  - protein expression levels (state $\in \mathbb{R}^{30,000}$)?
- *what "modules" appear repeatedly?*
- *why cascades and feedback loops?*
- *dynamical properties?*
  - stability, oscillations, . . .
- *how to control using external inputs?*

The Role of Math Modeling

need for mathematical models long recognized

- 1950s Cybernetics, Wiener, Ashby; "homeostasis"
- dynamics, feedback, of molecular networks in 1970s (e.g. Tyson, Othmer, Kauffman, Savageau, Glass)

what is different now:

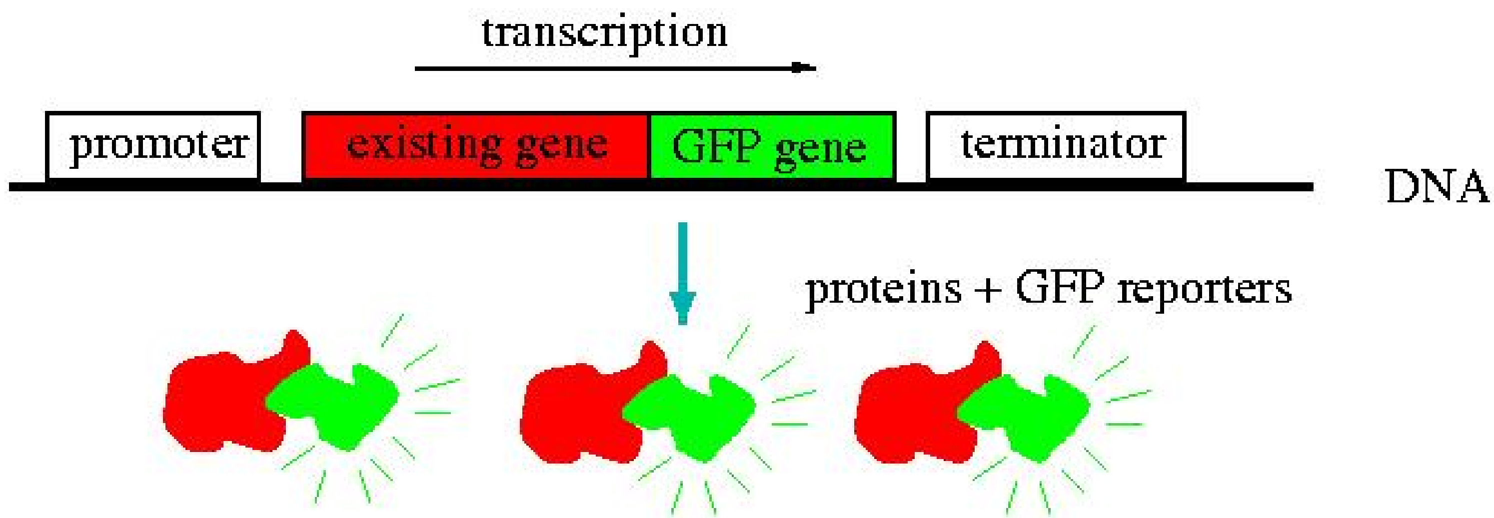
- lots of data
- new experimental design techniques
  - gene knock-outs, mutations, mass copying (PCR)
  - measurement tools ("outputs"): gene chips, GFP

  allow hypotheses testing & falsification

(next: examples of measurement technology)

Scalar Outputs: GFP

one inserts a Green Fluorescent Protein gene, adjacent to the gene that codes for the protein one wishes to measure



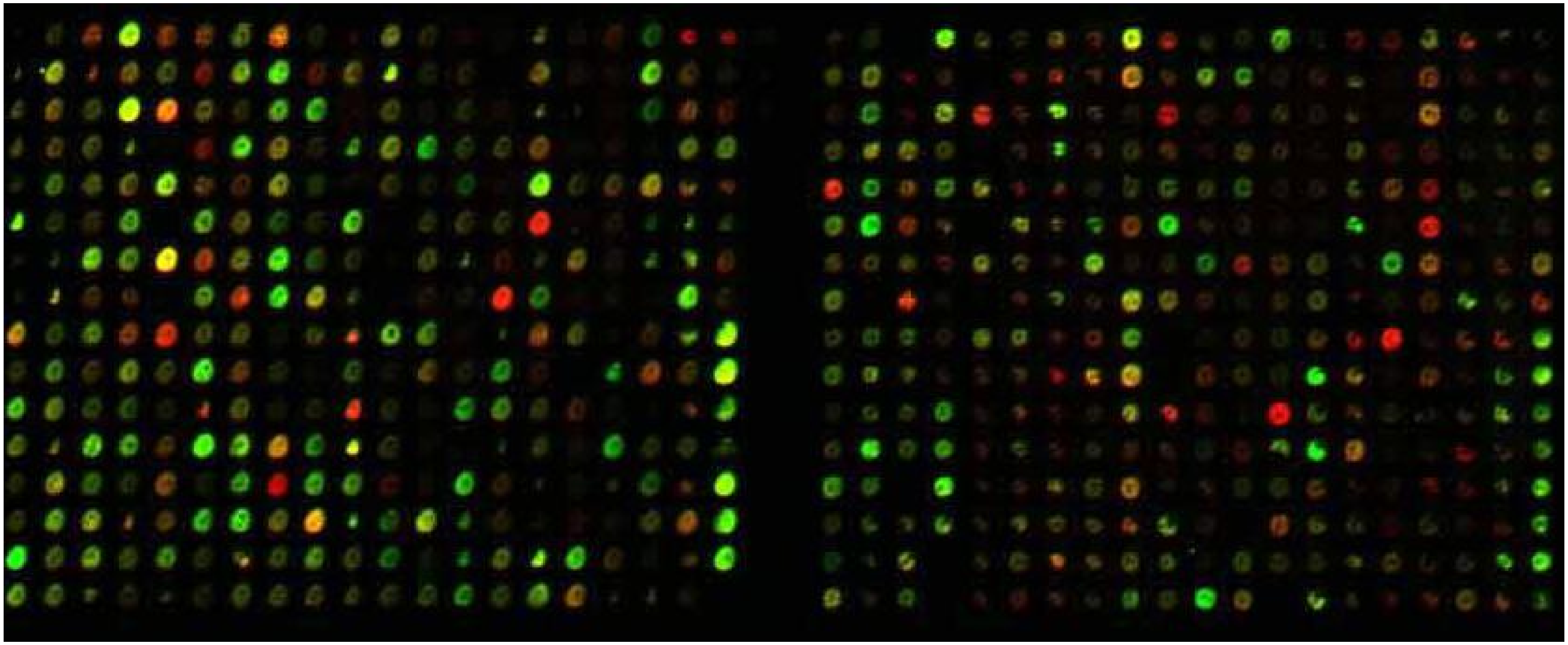
in this manner, both genes are expressed simultaneously, one simply measures intensity of the GFP light emitted

source of GFP: Aequoria victoria, Pacific NW jellyfish

GFP = aequorin used as “reporter” green fluorescence when UV irradiated

Vector Outputs: Gene Chips

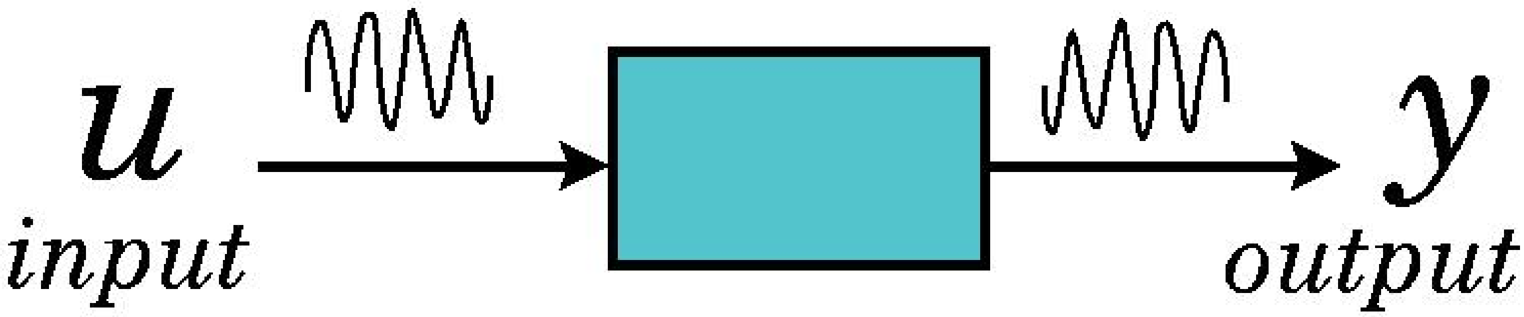
A newer technology, gene arrays, allows simultaneous measurement of activity levels of thousands of genes basically by spreading a sample on an array which has, in each spot, a detector "tuned" to a different possible gene $\rightsquigarrow$ more complete snapshot of the current state of the system



gene → (nucleus) messenger RNA → (ribosomes) proteins ; technology: estimate mRNA (proportional to protein); too unstable, so reverse-transcribed to complementary DNA spread sample on chip; bind specific DNA at each "pixel"

The Basic Paradigm

in broad terms, control systems theory deals with interconnections of devices which process input signals into output signals



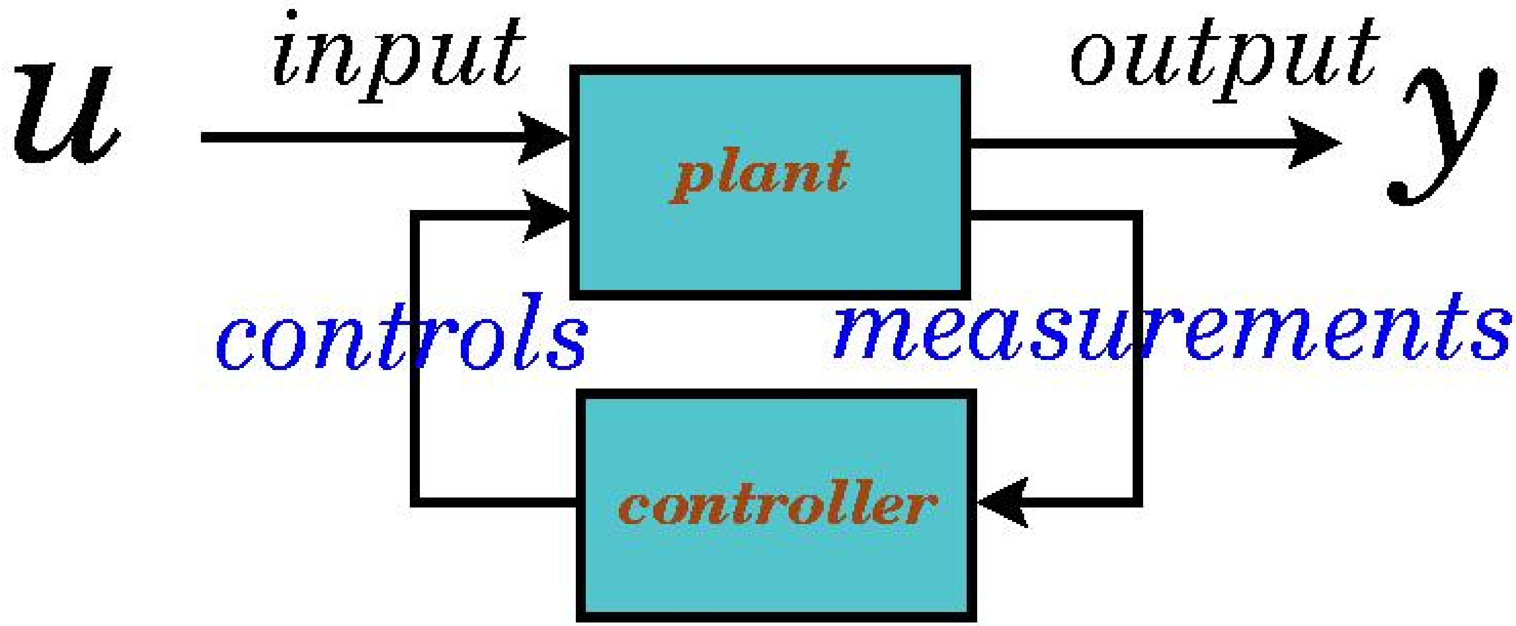
various subfields address the "challenges" mentioned earlier

for instance, identification and realization theory study reconstruction of internal structure and parameters from i/o

and observer/filtering theory, problems of state estimation

but in this talk, I'll discuss only questions of feedback

Feedback



feedback theory deals with the design of feedback laws
in order to achieve a desired behavior,

gives limits to performance under any possible controller,

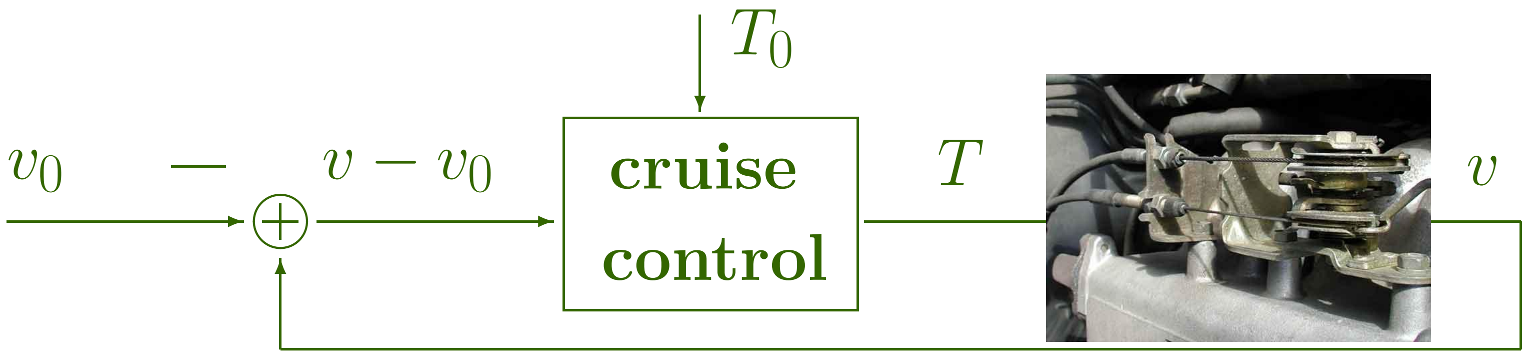
and, for existing systems, provides necessity statements
regarding the existence of embedded control structures
— which could then be tested experimentally

Disturbance Attenuation

a basic role of feedback is to ensure signal tracking, and to decrease "uncertainty" due to noise and other disturbances

let us take the simple example of speed controls for cars, which keep the velocity $v(t)$ at a fairly constant level v_0, independently of disturbances $d(t)$ (wind, up/downhill grade)

we start with the obvious idea, adjusting the throttle in proportion to the error in speed $v - v_0$ $(\Delta T = -k(v - v_0))$



velocity error $v - v_0$ is fed to controller, which regulates engine air intake w/cable parallel to that from gas pedal

with forces due to engine, disturbances, and drag, Newton's law gives diff eqn for the error e in speed:

(for small displacements, after nondimensionalizing and linearizing around an equilibrium v_0 with corrresponding throttle opening T_0)

$$\dot{e} \;=\; -e \;-\; ke \;+\; d \qquad \left[\, e := v - v_0 \,\right]$$

from which clear: error $e(t)$ asymptotically small, i.e. $v \approx v_o$ **provided the feedback gain k is large**

e.g. for *constant* **disturbances** $d(t) \equiv d$**,** $e(t) \to \frac{1}{1+k}\, d$ **as** $t \to \infty$

more generally, for any d, $\exists$ **analogous L^2 and L^∞ estimates:**

$$\limsup_{t\to\infty} \int_t^\infty |e(s)|^2\, ds \;\leq\; \left(\frac{1}{1+k}\right)^2 \int_t^\infty |d(s)|^2\, ds$$

$$\limsup_{t\to\infty} |e(t)| \;\leq\; \left(\frac{1}{1+k}\right) \sup_{0\leq t\leq\infty} |d(t)|$$

and, for white noise d, a similar bound $(2+2k)^{-1}\sigma_d$ **holds on the asymptotic variance of the (Ornstein-Uhlenbeck) error e**

**(but high-gain dangerous & imposes trade-offs . . .
back to that later)**

Non-Steady State Analysis

general principle: negative feedback helps decrease asymptotic error – the higher the gain, the smaller the error

we discussed this only for a first-order linear system, but the theory addresses such issues in great generality, and in addition deals with non-equilibrium behavior

for this purpose, one introduces appropriate structures on spaces of input signals "u" (such as disturbances $d(\cdot)$) and output signals y (such as errors to be made small), and the solution operator $u(\cdot) \mapsto y(\cdot)$ is studied

its "norm", in an appropriate sense, tells us how the size of the output depends on the size of the disturbances

(actually, one studies $(x(0), u(\cdot)) \mapsto y(\cdot)$, to account for effect of initial conditions on transients and overshoot behavior)

Gain Quantification

among the main approaches to quantifying gains:

$L^2 \to L^2$: ("H_∞") measures energy gain
sophisticated design of norm-minimization controllers

$L^\infty \to L^\infty$: quantifies overshoot, max deviations

ISS: coordinate-free version of above ("$L^\alpha \to L^\beta$")

stochastic: (e.g. "H_2"): random inputs, variation of $y(\cdot)$

game theory: view disturbances as opponent (Ashby, 1956)

$$\min_{\text{controller}} \max_{\text{input}} \|y\|$$

(for L^2 norms, leads to H_∞ via Hamilton-Jacobi-Isaacs PDE)

H_2 , H_∞ $\rightsquigarrow$ Riccati Equations

RICCATI DIFFERENTIAL EQUATIONS

WILLIAM T. REID
Department of Mathematics
University of Oklahoma, Norman, Oklahoma

is Volume 86 in
THEMATICS IN SCIENCE AND ENGINEERING
ries of monographs and textbooks
ed by RICHARD BELLMAN, *University of Southern California*

complete listing of books in this series is available from the Publisher
request.

ACADEMIC PRESS New York and London 1972

An Experiment

the cellular environment is extremely noisy, but, on the other hand, large variations in levels of certain chemicals, (such as transcriptional regulators) may be lethal to the cell

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

since we know that negative feedback decreases uncertainty, reasonable to expect cells use feedback for that purpose

let's discuss recent experiments validating the hypothesis that naturally occurring feedback loops are responsible for reduced variation of gene expression, and that

increasing the feedback gain $k \gg 1$ decreases variability

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

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

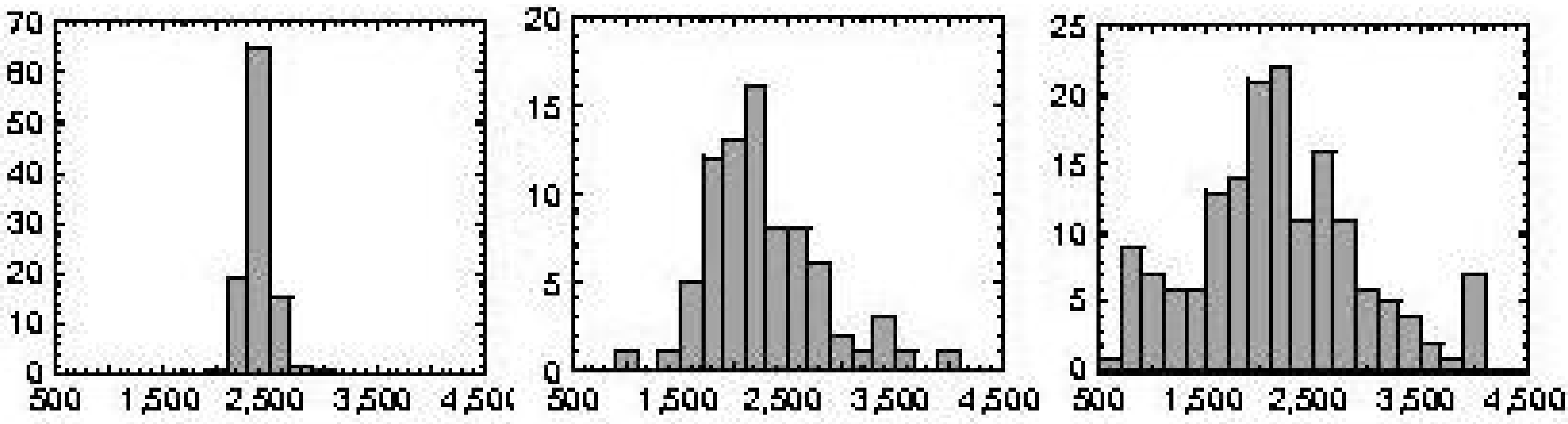
the authors showed that, indeed, lowering the "gain" in this loop results in more variability in protein expression

they managed to lower the "gain" by creating mutant bugs in which the feedback loop was partially or totally disabled

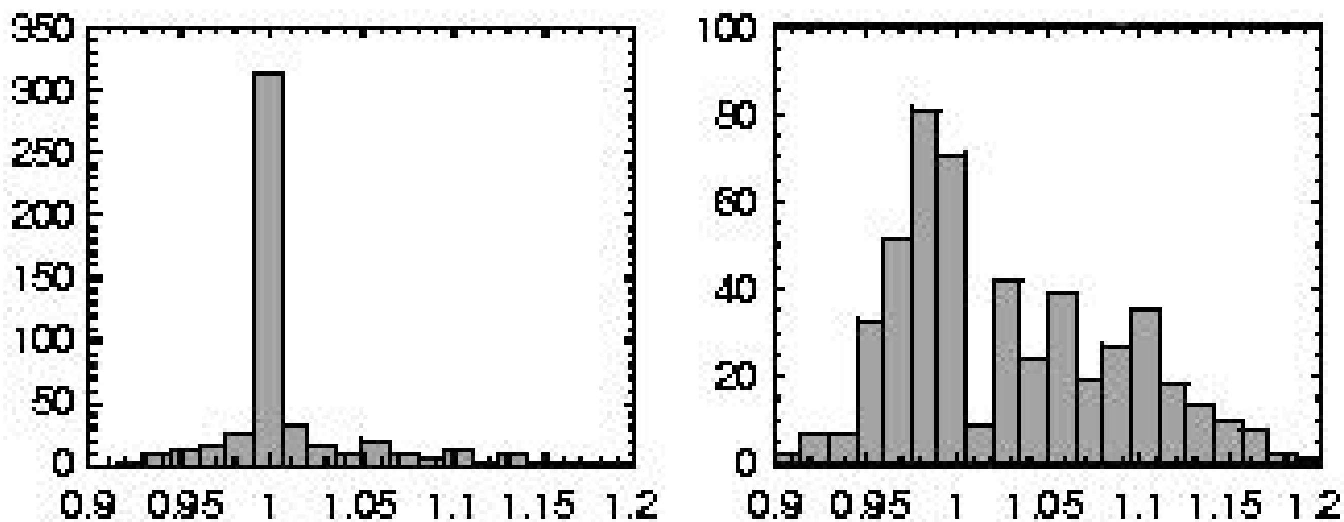
protein level measured by splicing GFP gene to gene coding for TetR

Experimental results

normal **less feedback** **no feedback**



number of cells measured against fluorescence levels



stochastic ODE simulation: normal & mutated (cells/concentration)

Too Much of a Good Thing is Bad

before proceeding, let us note that high-gain feedback is often undesirable, for several reasons, including the facts that they

- may not be physically implementable, due to limitations of actuators
- may induce instabilities
- may increase sensitivity to measurement errors

this last point can be understood in the context of our simple speed control example . . .

Measurement Errors with High Gain

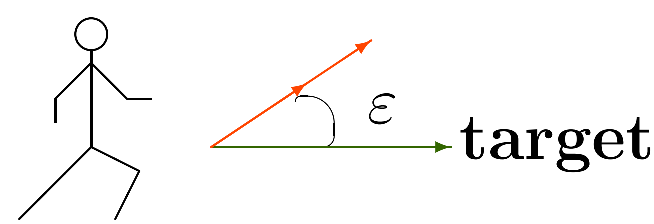
let us suppose that velocity sensing is inaccurate, and our controller feeds back a corrupted velocity measurement

$$-k\,(\underbrace{v+\varepsilon(t)}_{\textbf{measured}} - v_d) \quad \rightsquigarrow \quad \dot{e} = -e - k\,(e+\varepsilon) + d$$

we see high gain $k \gg 1$ improves disturbance attenuation, but increases sensitivity to measurement errors

$$\underbrace{\varepsilon(t) \equiv \varepsilon, d(t) \equiv d}_{\textbf{assume for simplicity}} \quad \Rightarrow \quad \textbf{steady state} = \underbrace{\frac{1}{1+k}}_{\approx 0} d + \underbrace{\frac{k}{1+k}}_{\approx 1} \varepsilon$$

reacting and moving too fast
in perceived direction of target
magnifies errors in perception
move too far before realizing mistake



we'll return later to the subject of measurement errors

Integral Control

for the cruise control model, using proportional feedback, we had the following equation for the error in velocity:

$$\dot{e} \;=\; -e - ke + d$$

for the special case of constant disturbances, this means that the steady state error is $e(+\infty) = \frac{1}{1+k}\,d$, which is nonzero for nonzero disturbances, and is not even small unless k is large

since huge gains k are undesirable,
one would like to know if it is possible to attain small,
or even zero steady state error without using large k

one solution is to use integral control, where the controller feeds back the integral of the error as well as the error:

$$\Delta T(t) \;=\; -\,k(v(t) - v_0) - \ell \int_0^t [v(s) - v_0]\, ds$$

intuition behind idea: if $e(t)$ is nonzero (even if small) for a long time, then its integral will be large, and thus the controller will apply a large correction

with constant disturbances d, introducing $y := \int e \rightsquigarrow$

$$\begin{aligned} \dot{e} &= -(1+k)e - \ell y + d \\ \dot{y} &= e \end{aligned}$$

for which $e = 0$, $y = (1/\ell)d$ is a global attractor

thus the error converges to zero, no matter what d is

the controller now includes an integrator (to compute y) (plus a linear combination device to compute k, ℓ)

note that the controller is robust,
in the sense that precise values of $k, \ell > 0$ are irrelevant
— the structure of the controller is what matters

robust vs nonrobust analogy: "find α, β s.t. $\alpha\, e^{\beta t} \to 0$"
non-robust solution: β arbitrary, α exactly $= 0$
robust solution: α arbitrary, β arbitrary < 0

Deeper Story:

the integrator worked precisely because disturbances were assumed constant; otherwise there is no reason for $e(t) \to 0$

Q: but what if, say, disturbances are linear: $a + bt$?

A: controller must incorporate an *internal model* of system producing disturbances, in this case a *double* integrator $\ddot{y} = 0$

or harmonic oscillators for periodic $d(t)$'s, etc

regulator theory provides a sophisticated toolkit of control algorithms based upon internal models and error feedback

and the internal model principle states that,
in order to achieve robust regulation, controllers must contain embedded internal models driven by "errors"

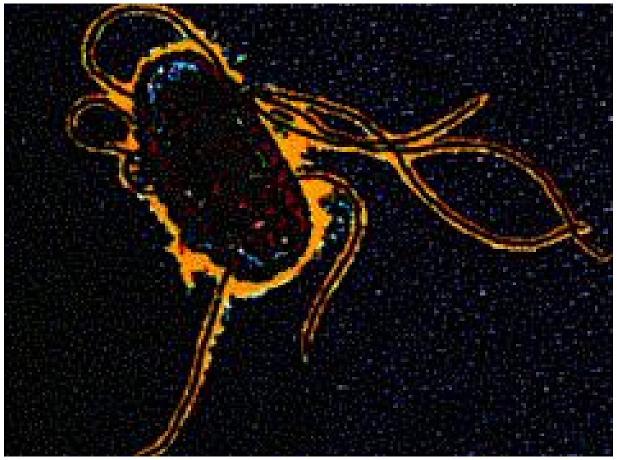
"robust" = structurally stable/Whitney topo, model = flow embedding
Wonham-Francis 1970s: linear; Wonham-Hepburn 1981: Center Mfld's

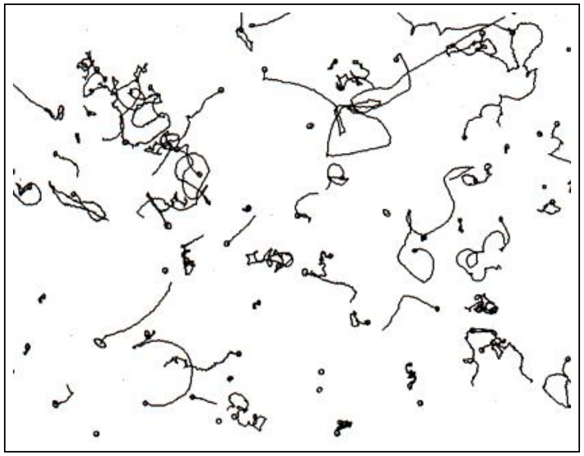
next: a biological illustration of this phenomenon . . .

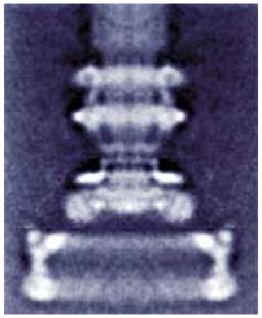
Chemotaxis in *E.coli*

E.coli **moves (*taxis*), propelled by flagella,**
in response to gradients of *chem*ical attractants or repellents

it can perform two basic types of motions:
tumbles (erratic turns, displacement ≈ 0) and runs







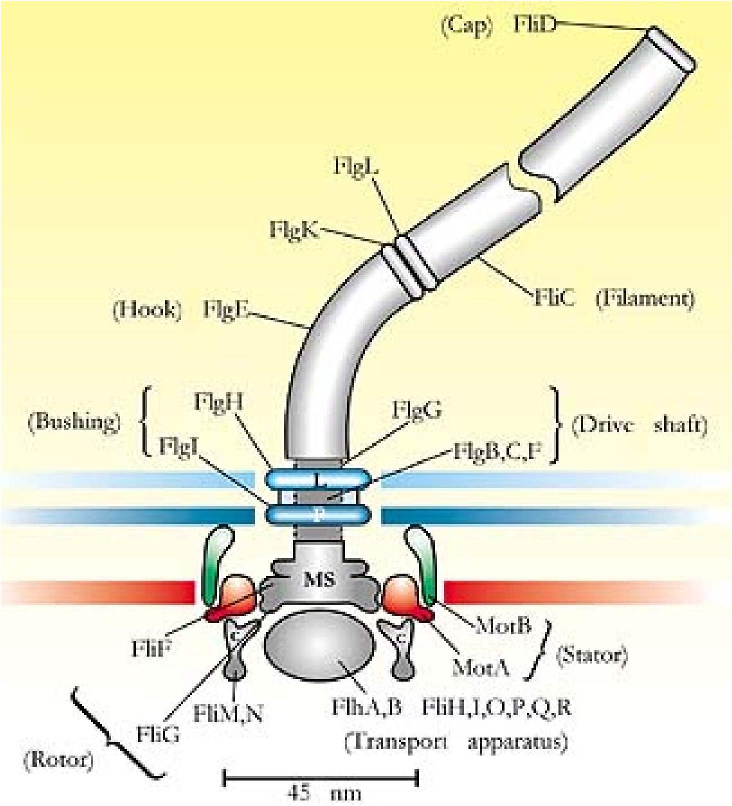
a flagellar motor
(electron micrograph)

E.coli **carries out a stochastic gradient search strategy:**

sense increased concentration $\rightarrow$ stop tumbling (and run)
∇ concentration ≈ 0 $\rightarrow$ resume tumble ("search mode")

runs caused by filaments coordinated in bundle (turning CCW); tumbles occur when they turn CW, resulting in independent moves (lack of symmetry). runs are biased, drifting about 30 deg/s due to viscous drag and asymmetry; no inertia (low Reynolds); mean run interval about 1 s, mean tumble interval about 0.1 s

Side Remark: Motor



actuation & sensing molecular mechanisms well-understood

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

the chemotactic signaling system, which detects chemicals and directs motor actions, behaves (roughly) as follows:

after a transient nonzero ("stop tumbling, run towards food") signal, issued in response to a change in concentration,

system adapts and signal converges to zero ("OK, tumble")

the adaptation happens for any constant nutrient level, even over large ranges of scale and system parameters, and may be interpreted as robust rejection of constant disturbances

if this interpretation is correct, one would expect (IMP), to find an integral feedback controller inside the system

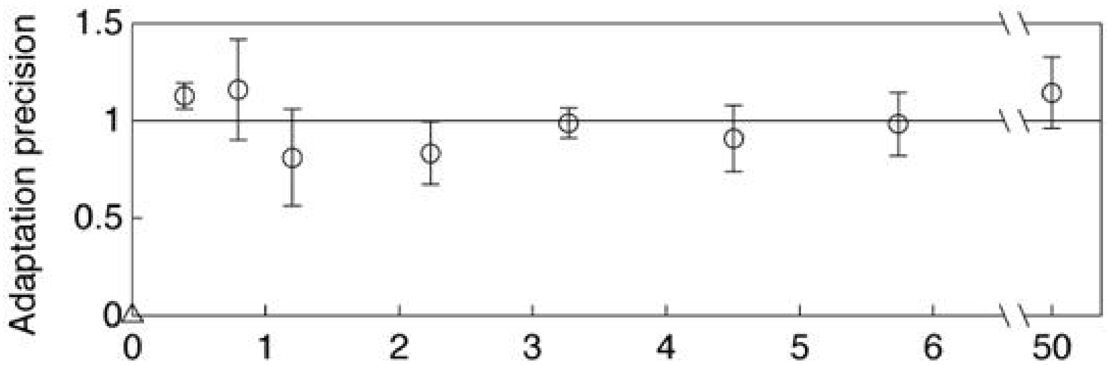
indeed(!): Barkai and Leibler (*Nature*, 1997), came up with molecular mechanism which includes integral error feedback

d(methylated receptors)/dt $= a - by/(k+y) \approx a - by$, $y =$ "activity" so of form "$v_0 - v$, $v = by$, $v_0 = a$ basal activity level

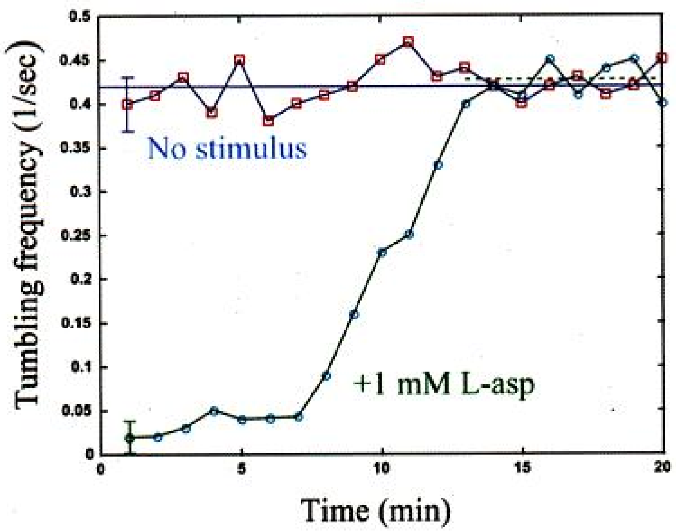
(cf. discussion in Yi, Huang, Simon, Doyle *PNAS* 2000)

Alon, Surette, Barkai, Leibler *Nature* 1999

more recent research experimentally confirmed robustness of adaptation



robustness: system parameters (here, protein CheR) were varied up to 100-fold, with no significant change in disturbance rejection capability



input $\Rightarrow$ transient "stop tumbling signal" ($e(0) \neq 0$), but $e(t) \to 0$ as $t \to \infty$

A Mathematical Vignette

just as the internal model principle forces an embedded structure in controllers, two recent theorems characterize necessity/sufficiency of other controller features, namely:

switching & memory

their proofs rely upon a series of papers by several authors

Hermes (1967 measurement errors),
Hájek (1979 relation Hermes, Krasovskii, Filippov),
Sussmann (1979 examples of the necessity of discontinuous feedback),
Sussmann-EDS (1980 memory sufficient, 1-dim),
EDS 1981 ($\mathcal{C}^0$ clf's),
Artstein 1983 ($\mathcal{C}^1$ clf's),
Brockett 1983 (Lie conditions, Krasnosel'ski's theo),
Coron 1992 (time-varying, no drift),
Lin-EDS-Wang 1993 (converse Lyapunov),
Coron-Rosier (converse, measurable selections),
Clarke-Ledyaev-EDS-Subbotin 1997 (general existence theorem),
Ledyaev-EDS 1998 (measurement error obstructions),
EDS 1999 (clocks sufficient)

we'll discuss the theorems very informally

Nonlinear Systems

the results apply to arbitrary systems of controlled ordinary differential equations,

$$\frac{dx_1(t)}{dt} = f_1(\underbrace{x_1(t), \ldots, x_n(t)}_{\text{states}}, \underbrace{u_1(t), \ldots, u_m(t)}_{\text{controls}})$$

$$\vdots$$

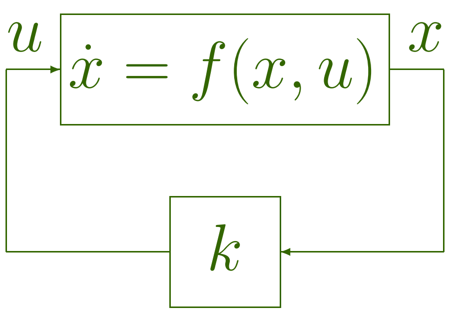
$$\frac{dx_n(t)}{dt} = f_n(x_1(t), \ldots, x_n(t), u_1(t), \ldots, u_m(t))$$

which we write as "$\dot{x} = f(x, u)$"

we assume that $f(0,0) = 0$ and f locally Lipschitz

the objective is to find a feedback law $u = k(x)$ such that the closed-loop system

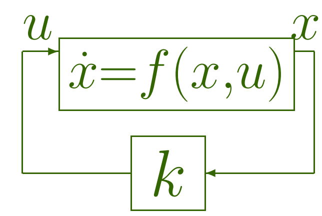
$$\dot{x} = f(x, k(x))$$



obtained when substituting the feedback into the original system has the origin as a globally asymptotically stable point

Feedback Stabilization

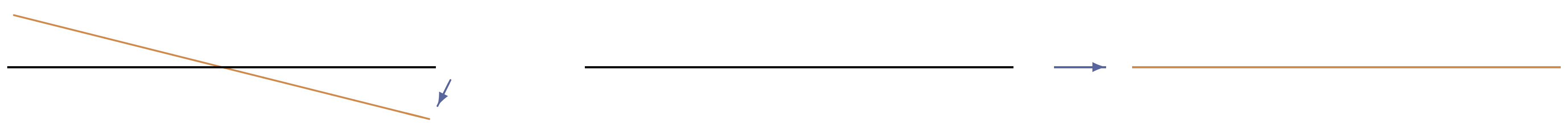
first result says this is always possible, under the obvious "asymptotic controllability" conditions, but that switching or memory in control laws are unavoidable for highly nonlinear systems



necessity characterized by means of Lyapunov-like functions;

for mechanical systems, result is: switching is required if controllability of system depends on nontrivial Lie motions

to illustrate, let us consider a stick which can either rotate around its center or displace along its axis

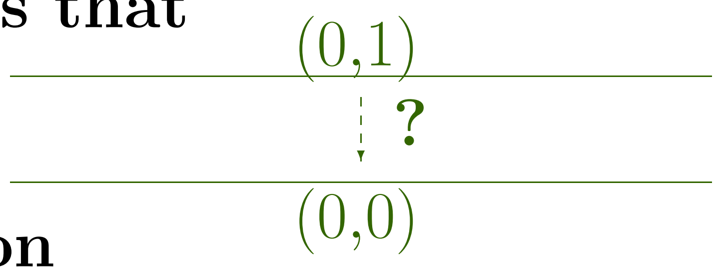


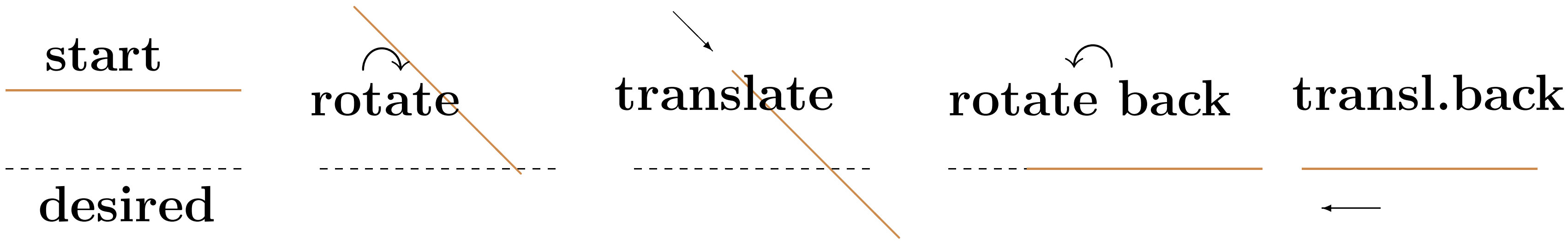
we'll call it the turn and drive (or "tumble and run") system

think of it as 3-dimensional system: state specified by orientation and coordinates of the center, and angular and linear velocities as controls

Nonholonomy

note: "no parallel translations" means that going from the configuration $x_0 = (0,0,1)$ to the origin $(0,0,0)$ needs a "parallel-parking" type motion





i.e., Lie (commutator) motions are required (r t $\mathbf{r}^{-1}$ $\mathbf{t}^{-1}$)

indeed any memoryless control law must be discontinuous e.g. if "turn clockwise from CW positions, CCW otherwise" $\rightsquigarrow$ by intermediate-value theorem, *continuity* would imply horizontal positions are equilibria for closed-loop system

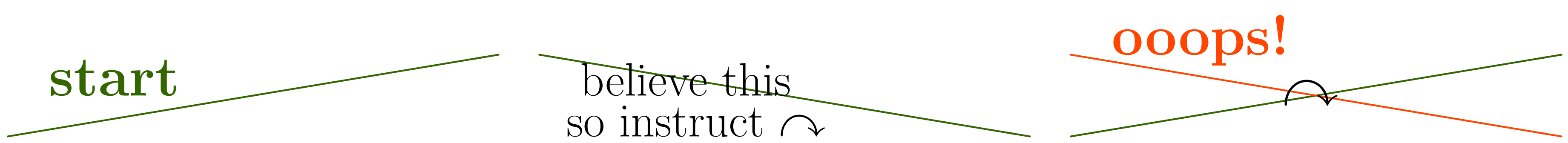
in contrast, for stick model modified to allow slipping, Lie brackets are not needed, and continuous stabilizers *do* exist

proved by index theory (Brockett'83), exposition in EDS MCT textbook

Measurement Errors

still with turn-and-drive example, suppose a (discontinuous) strategy instructs the system: when starting from a nearly horizontal configuration, keep turning counter-clockwise if the angle is already positive, and clockwise otherwise:

if we start with a small CCW position, but measurement noise fools us into believing the opposite is true, a rotation in the wrong direction takes us back towards horizontal:



a malicious disturbance might consistently fool us, leading to a high-frequency oscillation (chattering)

A "Hysteresis" Theorem

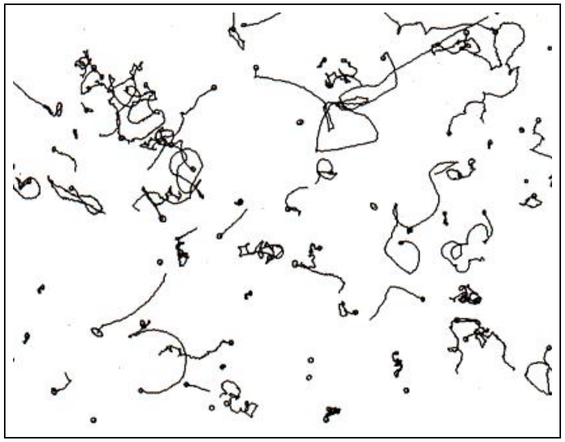
a second general result for nonlinear systems shows that:

- **with noise, there is in general no possible** (even non-$\mathcal{C}^0$) **memoryless controller which prevents chattering**
- **but it is always possible to stabilize under noise, provided one uses a hybrid stay the course strategy**

Ledyaev-EDS *Nonl. Analysis*'98, EDS *Control, Optim, Calc. Var.*'99

intuitive idea: use same control, not re-estimating the state, for some minimal period (how long, depends on the system equations, Lipschitz constants, etc)

the Lie-algebraic conditions, under which such strategies are required, apply to the turn-and-drive example, — so that long "tumbles" and "runs" are consistent with the general theory



Outline: Impossibility Proof *

the impossibility result is based on proving that, if some controller k stabilizes under small measurement errors,

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

then there must also be a continuous stabilizer, and hence the usual necessary conditions apply

this is done by showing that an associated usc differential inclusion is strongly stable,

$$\dot{x} \in \bigcap_{\delta>0} \overline{\mathrm{co}} f(x, k(x+\delta B))$$

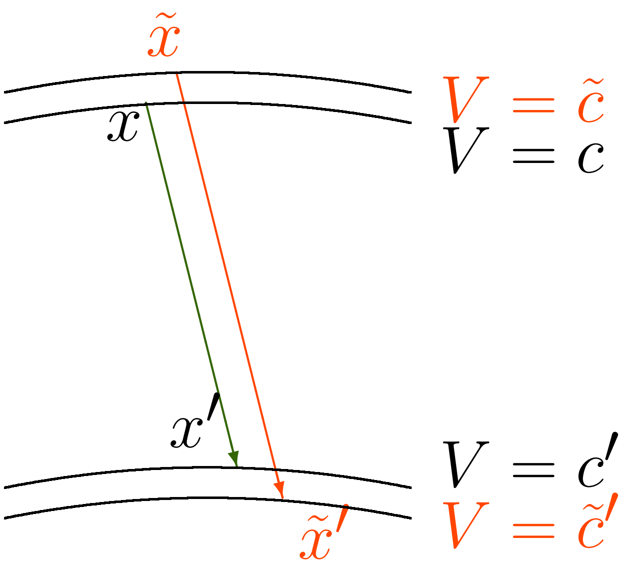
so converse theorem provides smooth Lyapunov function V, which is then a smooth cLf for the original system and thus a continuous stabilizer exists

Outline: "Stay the Course" Construction

one first shows, for any asymptotically controllable system, the existence of a continuous control-Lyapunov function V, as value function of appropriate optimal control problem

then V is regularized using a Iosida-Moreau inf-convolution and the feedback k is obtained by solving an associated (viscosity) Hamilton-Jacobi partial differential inequality

let $\tilde{x} := x + \varepsilon \approx x$, use $u := k(\tilde{x})$ for time long enough s.t. $\tilde{c}' \ll \tilde{c}$
controller thinks $\rightsquigarrow \tilde{x}'$ but really $\rightsquigarrow x'$
continuity on initial conds $\Rightarrow c' \approx \tilde{c}'$
$\therefore\; c' \approx \tilde{c}' \ll \tilde{c} \approx c$ i.e. V decreases



among other technical issues in the theory, one has to give a precise meaning to the concept of solution of the closed loop system $\dot{x} = f(x, k(x))$ when k is discontinuous, and this is done in ways reminiscent of Itô solutions of stochastic ode's

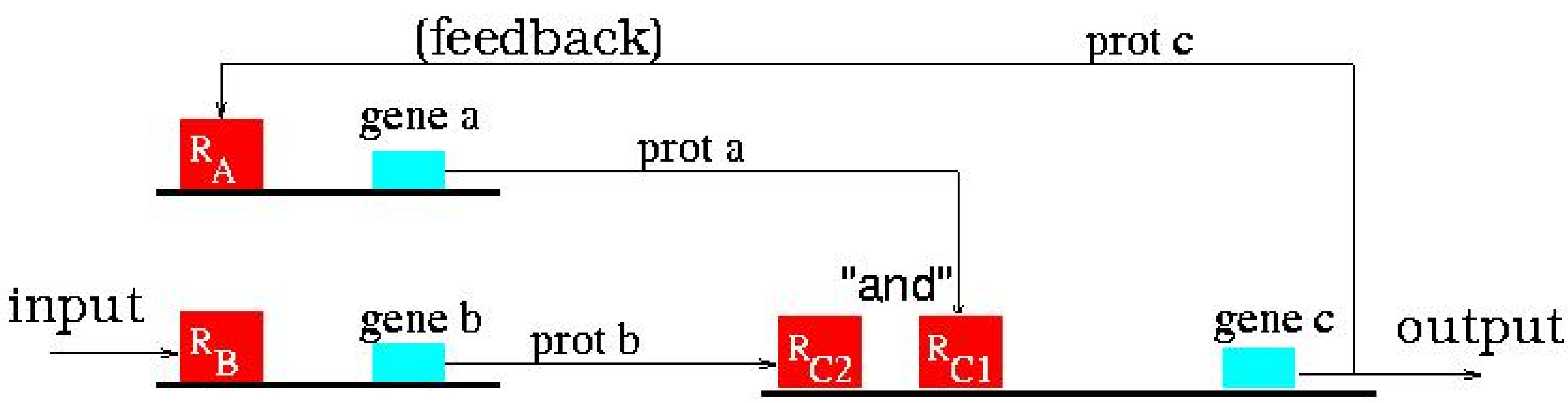
Hybrid Systems

we saw discontinuities in feedback laws may be unavoidable,

and indeed, control mechanisms in cells involve switching,
e.g. when a protein blocks production of a gene

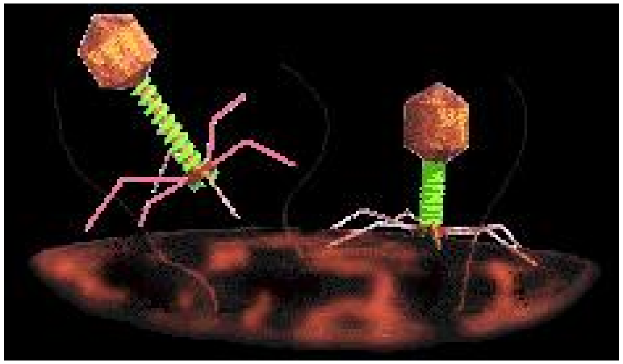
one can model switches by bistable differential equations operating at a faster time scale than rest of system

but, at a higher level of resolution, it might be more natural to use hybrid models which combine discrete and continuous components, and combinatorial logic to implement Boolean operations on the discrete components



E.g.: λ Control Circuit Model

bacteriophage viruses
(Twort & d'Hérelle, 1915/7)
are extremely well-studied examples
of hybrid control systems



T4

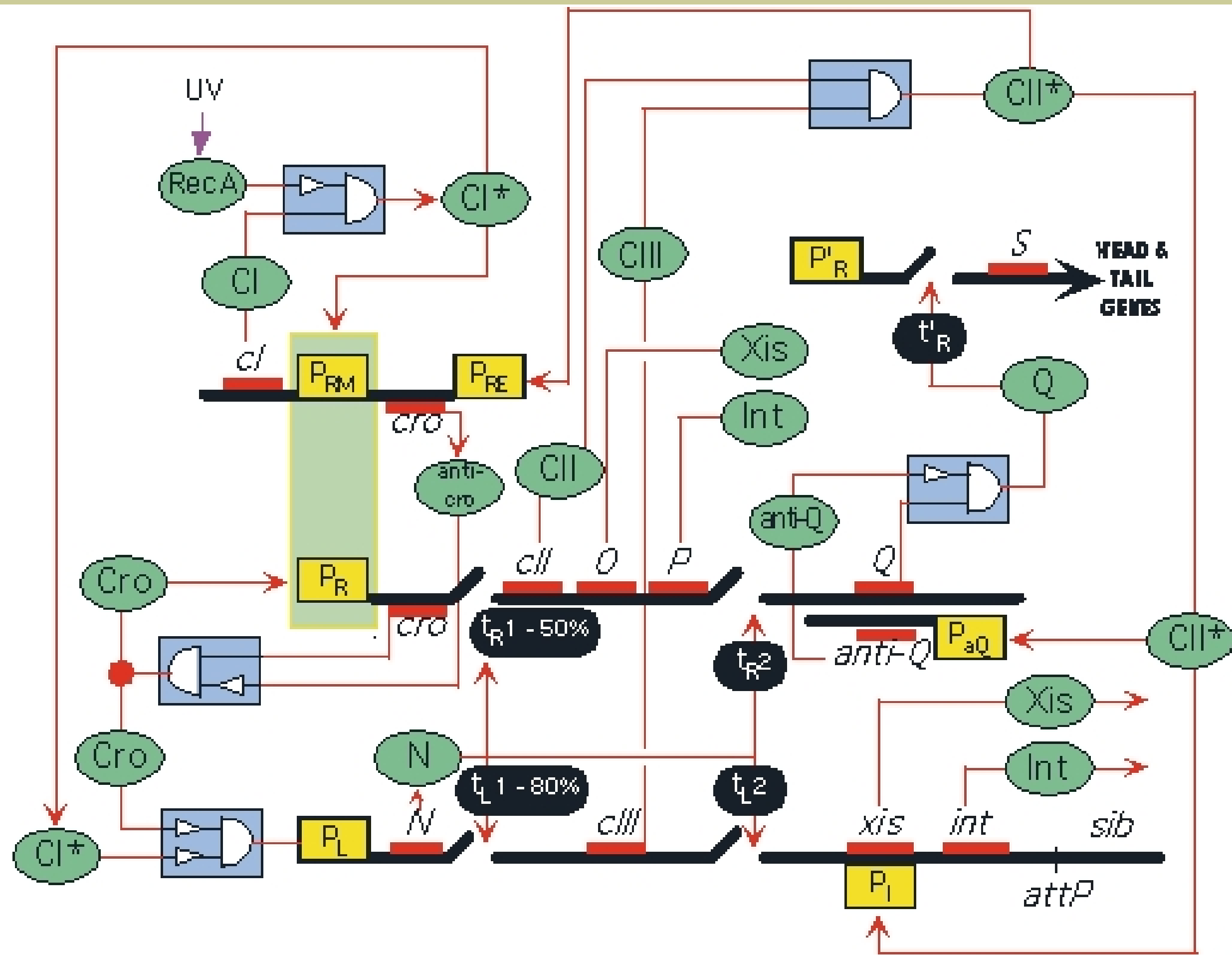
bacteriophage λ infects *E.coli*; and it lies dormant (lysogeny) until it senses lethal danger to its host – e.g. UV radiation – at which point it "abandons the ship" (lysis) and infects other bacteria

the binary lysogeny/lysis state is decided by competition for binding sites between Cro and λ repressor proteins

UV $\Rightarrow$ RecA (repair) protein activated $\Rightarrow$ degrade repressor; otherwise, λ keeps control

a by now "classic" paper published in 1995 presented a complete, and biologically-based, hybrid simulation model of the lysogeny/lysis decision subsystem in λ

McAdams and Shapiro, Circuit Simulation of Genetic Networks, *Science* 1995



goal: obtain complete wiring diagrams for larger systems (systems ID?)

engineering goal: build artificial circuits (realization?)

– e.g. “designer bugs” for therapeutic purposes

(small circuits already implemented and “alive”)

High-Gain and Instability

returning to the subject of trade-offs in feedback . . .
we mentioned high gain may not be physically implementable and discussed the effect of measurement noise

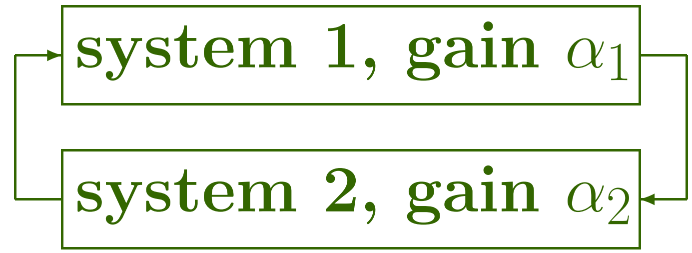
another potential problem: emergence of instabilities

even for linear systems, (in dimension at least 3), large negative feedback may make a system unstable
e.g. $y''' + 2y'' + 2y' + y = u$ with feedback $u = -ky$ $(k > 0)$ must have $k < 3$, else unstable

feedback around high order dynamics in effect introduces delays, which might cause oscillation – a familiar example of delay-induced oscillations: control of water temperature in shower (delay: water travel from faucet to shower head)

much of feedback theory deals with conditions which guarantee stability of feedback loops and cascades

Small-Gain Principle



small gain theorems are based upon the principle that the interconnection of two stable systems is stable

provided loop  *gain be less than one*

i.e.: first system amplifies signals by factor α_1, second by α_2 then round trip results in contraction by factor $\rho = \alpha_1 \alpha_2 < 1$

intuitively clear: signals keep getting contracted as they go around the loop, eventually converging to zero

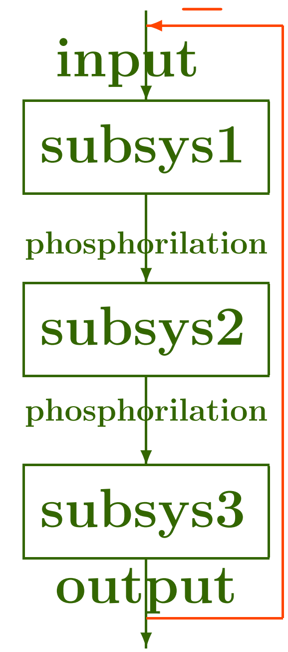
one way to make precise: introduce norms on signal spaces in such a manner that closed-loop operator a contraction

but theory is far more sophisticated: transient behavior, unbounded operators w/abstract "gains", asymptotic gains

E.g.: MAPK Cascades

illustration of small gain ideas in a molecular bio context:
MAPK (mitogen-activated protein kinase) cascades

common signaling "submodule" in eukaryotes, involved in cell proliferation, differentiation, movement, death



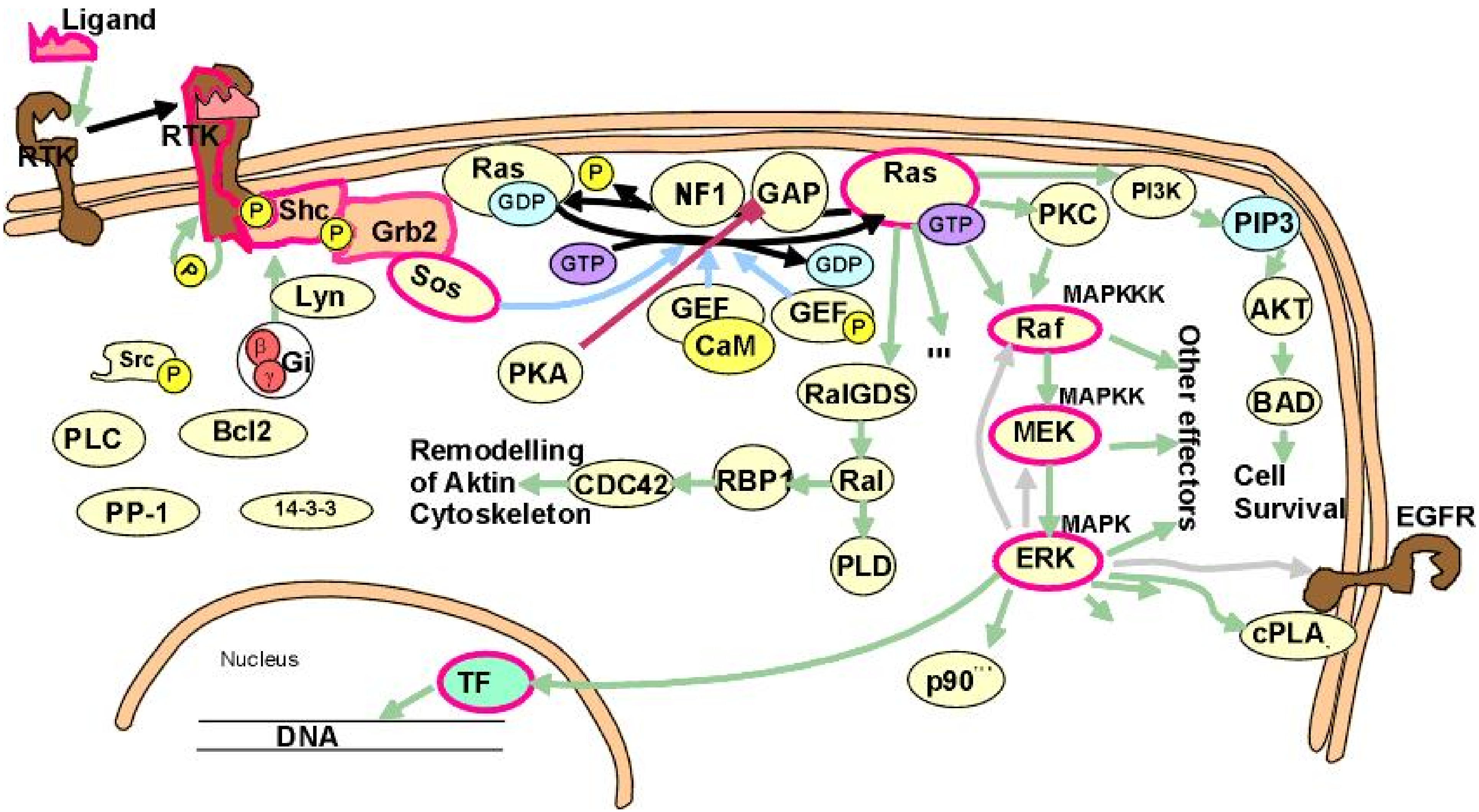
basic mechanism (with variations):
cascade of three subsystems,
each foliated into 1-dim invariant manifolds
($\therefore$ 3-dim inv manifolds in cascade)
phosphorylation drives reactions

in each subsystem, phosphates attached e.g. to aminoacid tyrosine; degradation by phostphatase (phosphate-removing enzyme) produces reversibility and interesting dynamics

much current research deals with MAPK cascades

sometimes $\exists$ negative feedback (to turn-off response?)
— and recent work pointed out this may induce oscillations
Kholodenko, European J.Biochem., 2000: Hopf bifurcations in model

A MAPK Example



Ras Cascade *from TRANSPATH database*

receptor tyrosine kinase and epidermal growth factor receptor as inputs; control of transcription factors

OK if Small Enough Feedback

bifurcation analysis characterizing onset of oscillations in a MAPK cascade model was recently carried out
Shvartsman-Wiley-Lauffenburger, MIT Report, 2001
and one might ask whether small gain theorems could provide good estimates of stable regions for parameters

it appears that standard theorems do not apply, because of the existence of multiple equilibria and the highly nonlinear character of the system

however, it is possible to introduce a new notion of input-to-state-stability incremental asymptotic gain, prove a small-gain type of theorem for this notion, and show extremely tight agreement between the estimates provided by the theorem and parameters which result in oscillations
Shvartsman-EDS, in preparation

Summary

- feedback control as technology enabler
- the challenge: molecular biological networks
- measuring outputs (GFP, Gene Chips)
- disturbance attenuation, and gain quantification
- experiments: large gain decreases variability
- limitations of feedback & measurement errors
- internal models, integral control, and chemotaxis
- Lie obstructions to continuous feedback, switches
- chattering and observation error - general theorems
- the need for hybrid models, bacteriophage λ
- small-gain theorems, MAPK

Some Remarks: ODE's

concentrations of chemicals may be viewed as real numbers, interpreted as population averages (or as expectations), and "steady state" $f(x) = 0$ does not mean lack of activity, but rather a balance between creation and absorption rates (or equilibrium probability distributions)

however, since as little as a few hundred (or less) molecules might participate in a cellular reaction, mean approximations may not be valid (e.g. stochastic stability?), may need stochastic simulations quite a controversial topic!

spatial homogeneity in concentrations (ode vs pde's): although some processes tend to be localized (e.g. at cell membrane, nucleus, or ribosomes), for small (intracellular) volumes, diffusion plays a major role

On Models and Theory

avoid "pseudo-exactness"!

in engineering (including bioengineering, e.g. heart control, prostheses), it makes sense to develop high-precision models

but in molecular biology, relevant values (rate constants, concentrations) may vary over orders of magnitude

∴ interest in results robust to large parameter variations
– conclusions not meaningful if depending on exact values

structure should provide robustness of desired behavior

e.g. Von Dassow et.al., Nature'2000, segment polarity network in *Drosophila* embryos: topology encodes function, even under huge changes in constants and even functional forms of connections

[cellular output & organism-level quantities precise: body temperature and pressure, glucose concentrations, frequencies of circadian clocks]

e.g. optimal control: good algorithms not as useful as general theory - *types* of solutions: bang-bang, singular?

role of optimality: evolution produced "*locally* optimal" solutions??

Conclusions

feedback control theory is an extremely deep and rich area dealing with many of the problems which are, in principle, of interest in postgenomic ("systems") molecular biology

one may expect that many principles of feedback theory will be of great use in guiding experimental work

while parts of the theory (e.g. identification, observers) may play a role in experimental design and instrumentation

talk to be posted to:

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