
Robustness
and
Complexity
John Doyle
Control and Dynamical Systems
Caltech

[02] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

Collaborators and contributors (partial list)

Biology: Csete, Yi, Borisuk, Bolouri, Kitano, Kurata, Khammash, El-Samad, …

Alliance for Cellular Signaling: Gilman, Simon, Sternberg, Arkin,…

HOT: Carlson, Zhou,…

Theory: Lall, Parrilo, Paganini, Barahona, D'Andrea, …

Web/Internet: Low, Effros, Zhu, Yu, Chandy, Willinger, …

Turbulence: Bamieh, Dahleh, Gharib, Marsden, Bobba,…

Physics: Mabuchi, Doherty, Marsden, Asimakapoulos,…

Engineering CAD: Ortiz, Murray, Schroder, Burdick, Barr, …

Disturbance ecology: Moritz, Carlson, Robert, …

Power systems: Verghese, Lesieutre,…

Finance: Primbs, Yamada, Giannelli,…

…and casts of thousands…

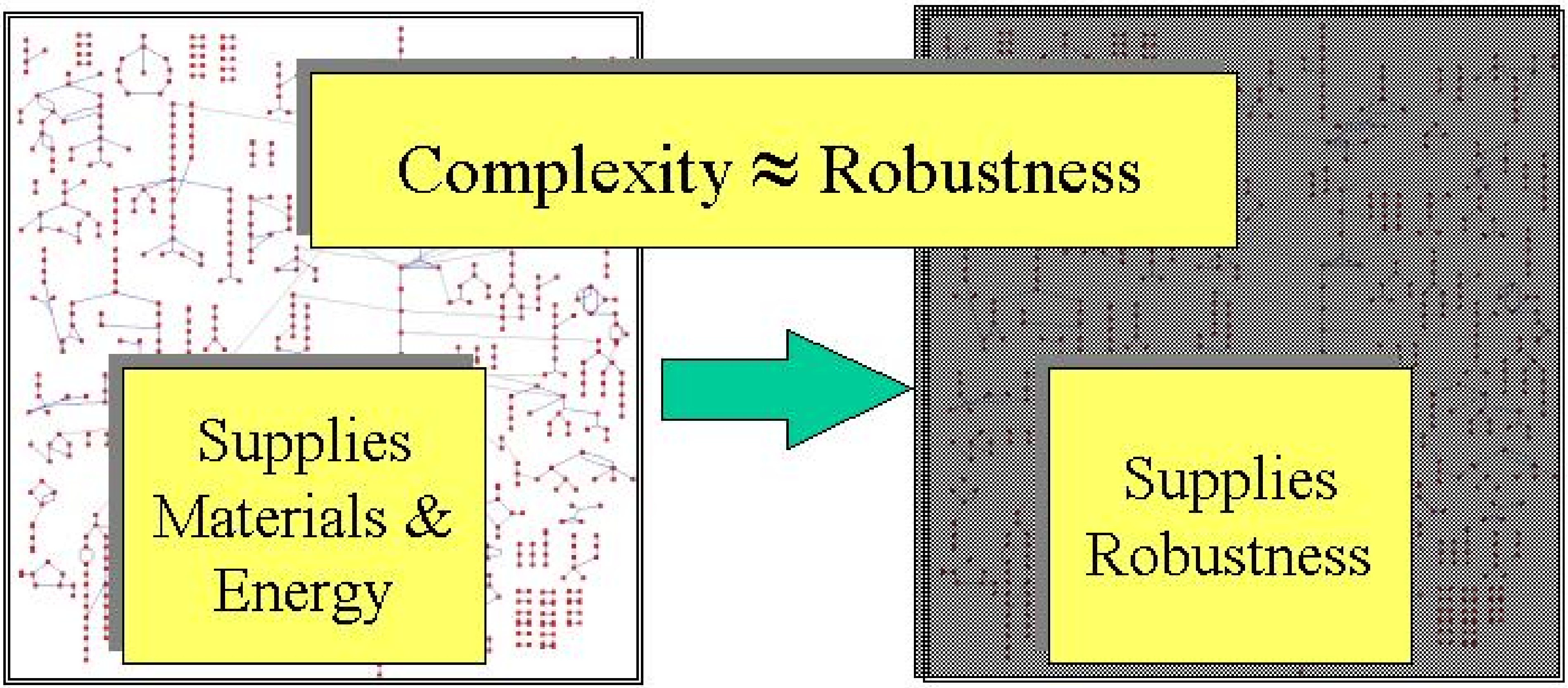
Background reading online

- On website accessible from my homepage
- http://www.cds.caltech.edu/~doyle/Networks/
- Papers with minimal math
  - Chemotaxis, Heat shock in E. Coli
  - HOT and power laws (w/ Jean Carlson, UCSB)
  - Web & Internet traffic, protocols, future issues
- Recommended books
  - **A course in Robust Control Theory**, Dullerud and Paganini, Springer
  - **Essentials of Robust Control**, Zhou, Prentice-Hall
  - **Cells, Embryos, and Evolution**, Gerhart and Kirschner
- Thesis: Structured semidefinite programs and semialgebraic geometry methods in robustness and optimization (Parrilo)

Biochemical Network: E. Coli Metabolism

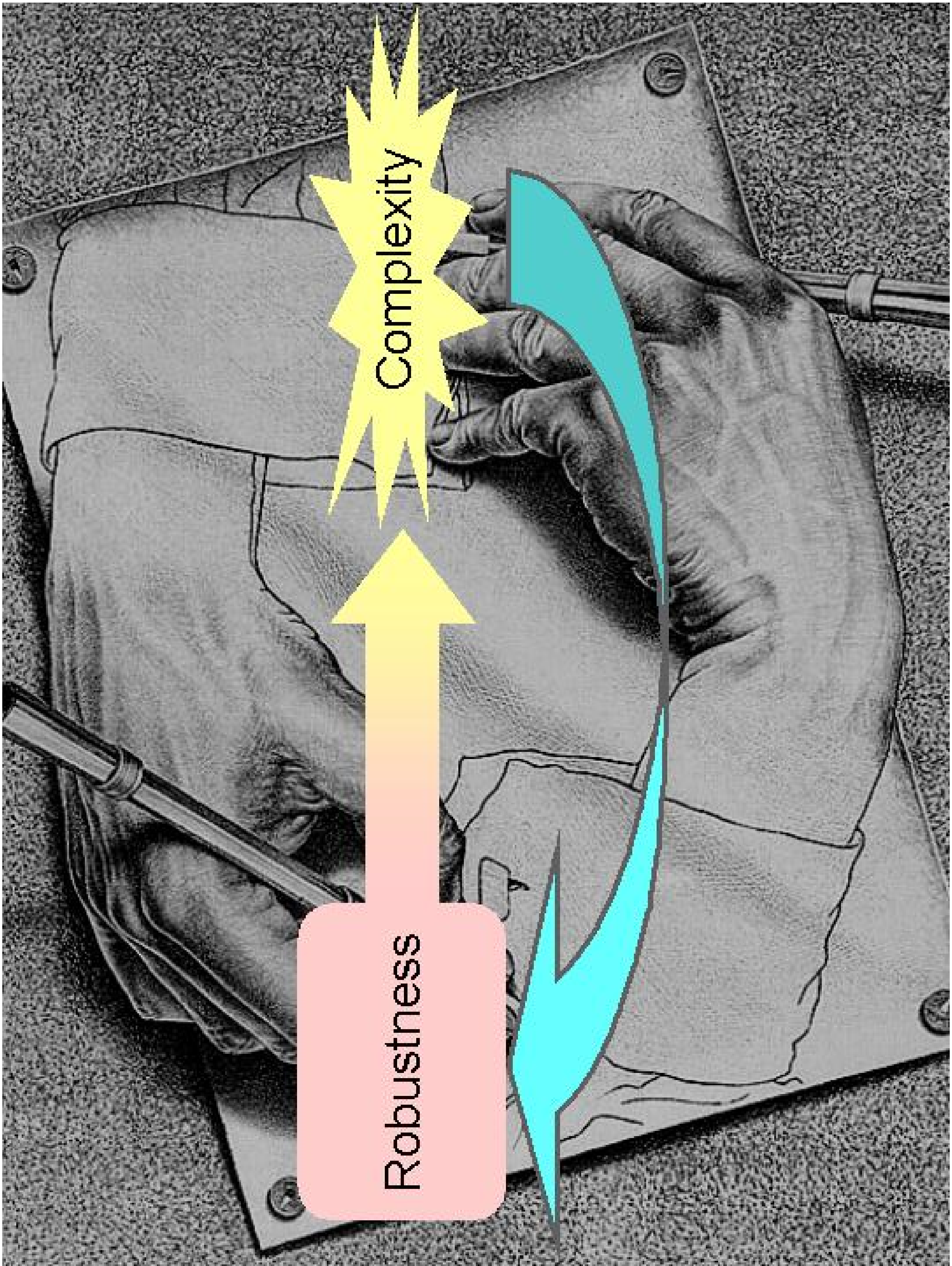
Mass Transfer in Metabolism*

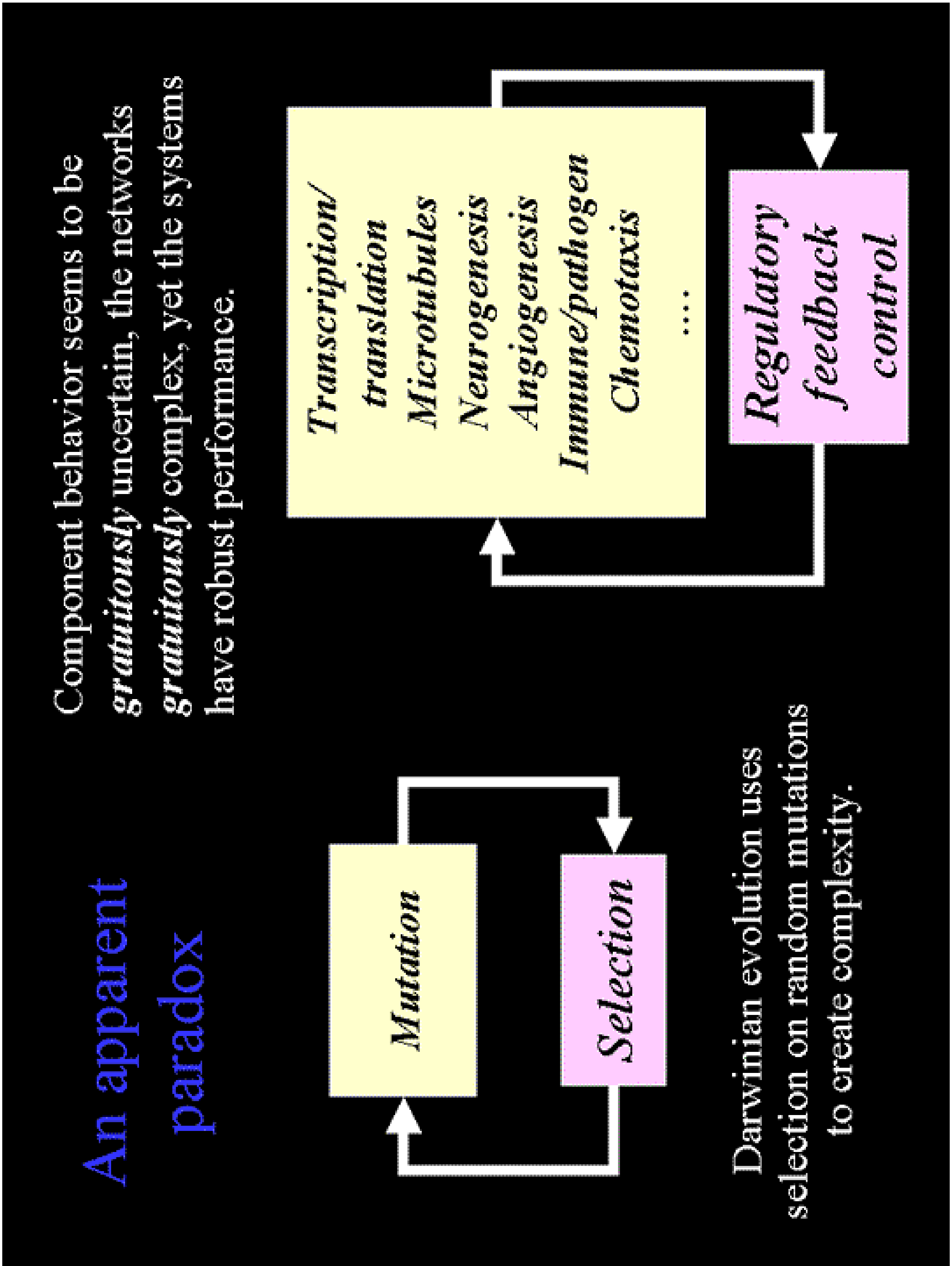
+ Regulatory Interactions

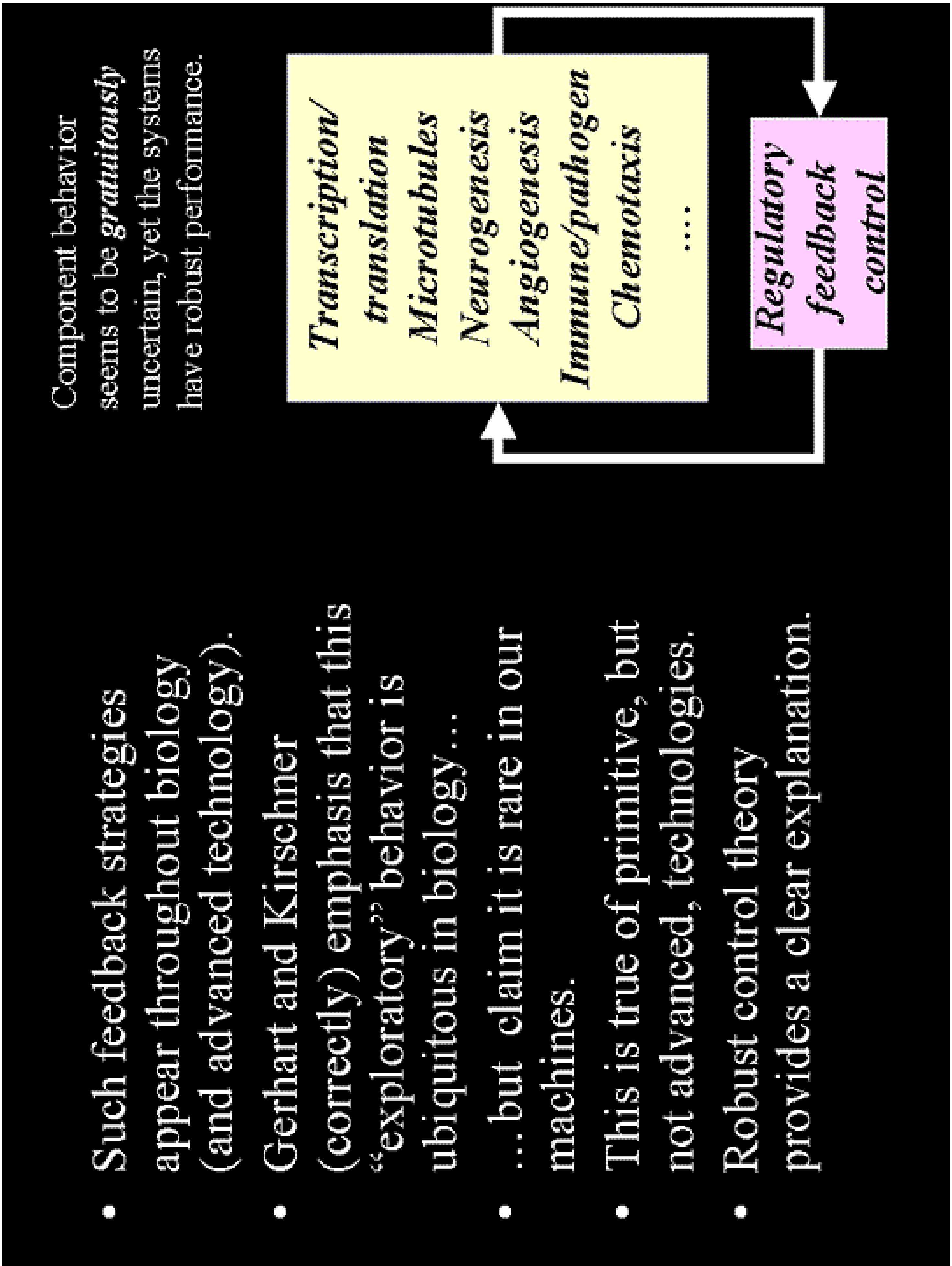


From Adam Arkin

* from: EcoCYC by Peter Karp


Complexity
Robustness


An apparent paradox
Mutation
Selection
Darwinian evolution uses selection on random mutations to create complexity.
Component behavior seems to be *gratuitously* uncertain, the networks *gratuitously* complex, yet the systems have robust performance.
Transcription/ translation
Microtubules
Neurogenesis
Angiogenesis
Immune/pathogen
Chemotaxis
….
Regulatory feedback control



Such feedback strategies appear throughout biology (and advanced technology).
Gerhart and Kirschner (correctly) emphasis that this "exploratory" behavior is ubiquitous in biology…
…but claim it is rare in our machines.
This is true of primitive, but not advanced, technologies.
Robust control theory provides a clear explanation.
Component behavior seems to be gratuitously uncertain, yet the systems have robust performance.
Transcription/ translation
Microtubules
Neurogenesis
Angiogenesis
Immune/pathogen
Chemotaxis
….
Regulatory feedback control

Motivation

- Continuing themes already discussed in this program…
- Without extensive engineering theory and math, even "reverse engineering" complex engineering systems would be hopeless.
- Modeling and simulation alone is inadequate
- Why should biology be much easier?
- We would not expect to have much success reverse engineering this laptop with:
  - Reductionism: try to find the single transistor or group of transistors responsible for ***this slide***
  - Emergence: "emerging" a random collection of silicon and metal

Engineering theory

- It turns out, that with respect to robustness and complexity, there is ***too much*** theory, not too little.
- Two great abstractions of the 20th Century:
  - Separate systems engineering into control, communications, and computing
    - Theory
    - Applications
  - Separate systems from physical substrate
- Facilitated massive, wildly successful, and explosive growth in both mathematical theory and technology…
- …but creating a new Tower of Babel where even the experts do not read papers or understand systems outside their subspecialty.

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Tower of Babel

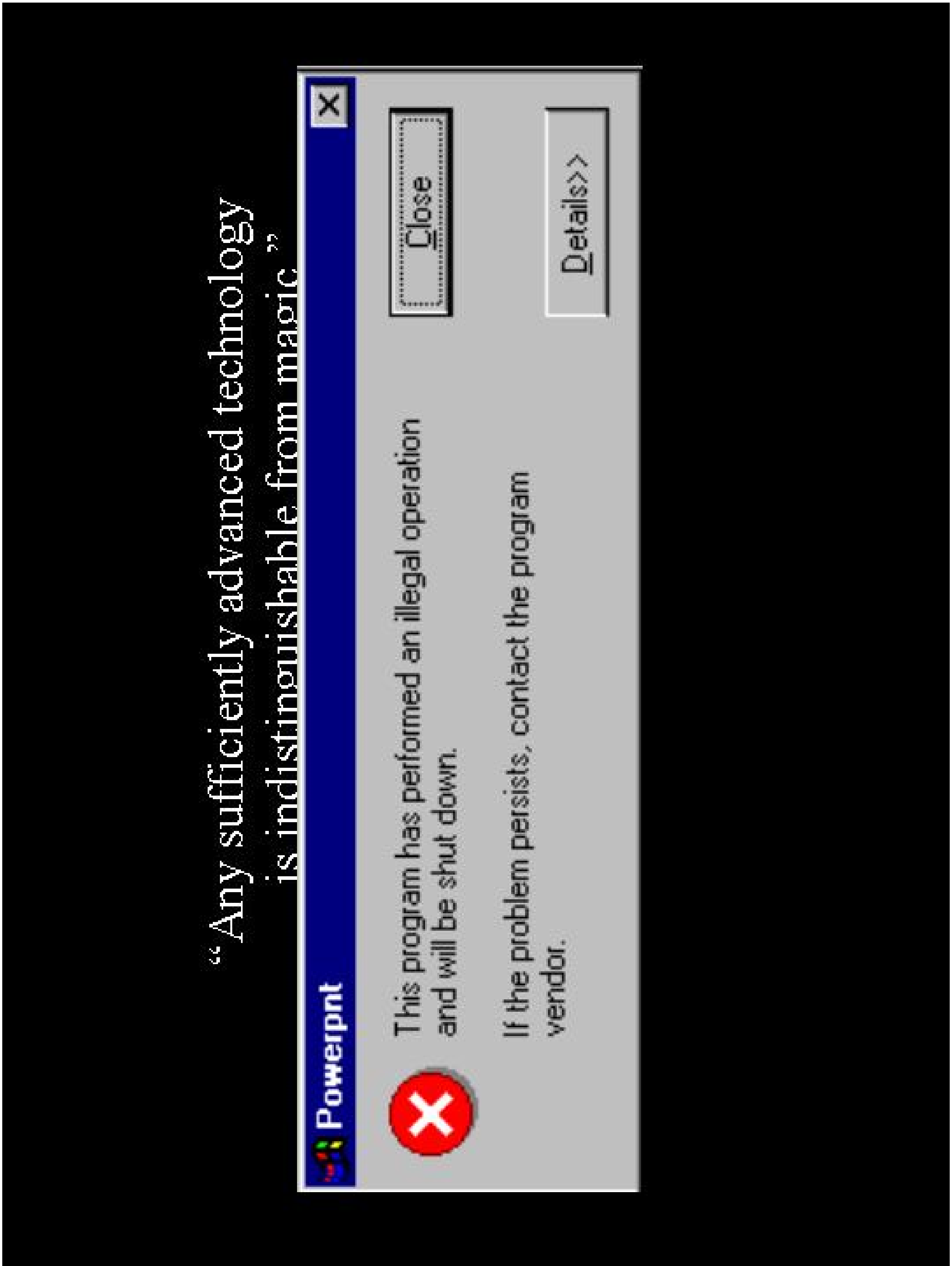
- Issues for theory
  - Rigor
  - Relevance
  - Accessibility
- Spectacular success on the first two
- Little success on the last one
- Perhaps all three is impossible?
- (In contrast, there are whole research programs in "complex systems" devoted exclusively to accessibility. They have been relatively "popular," but can be safely ignored in biology.)

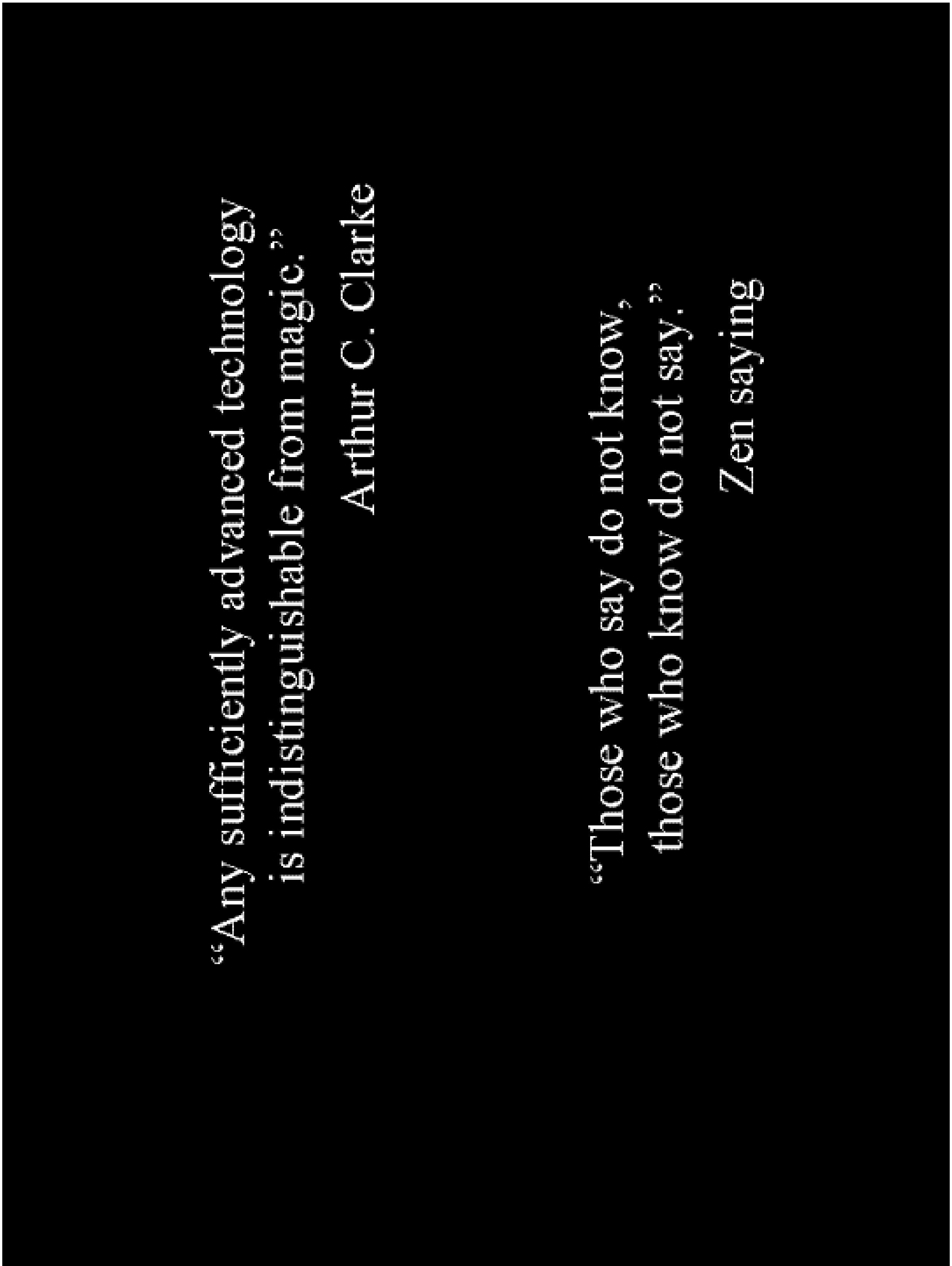
Today's goal

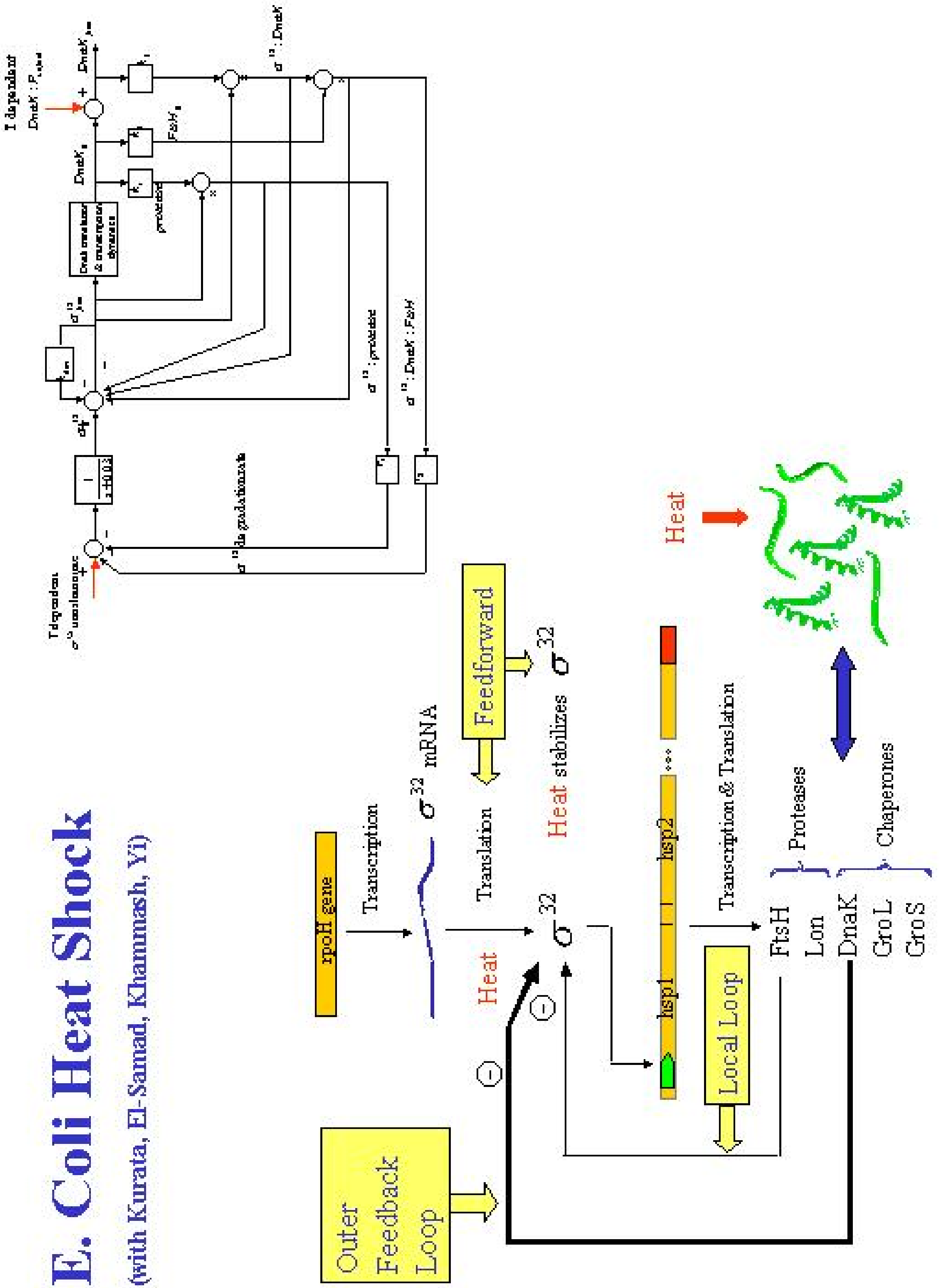
- Aim to tell you something not easily obtained elsewhere (papers online, other talks, texts, etc)
- Blending biology with math and engineering
- Introduce basic ideas about robustness and complexity
- Minimal math details, but still suggestive of what is possible
- Hopefully familiar (but unconventional) example systems, not requiring specialized expertise
  - Biology: Heat shock, chemotaxis
  - Engineering: Cars and planes

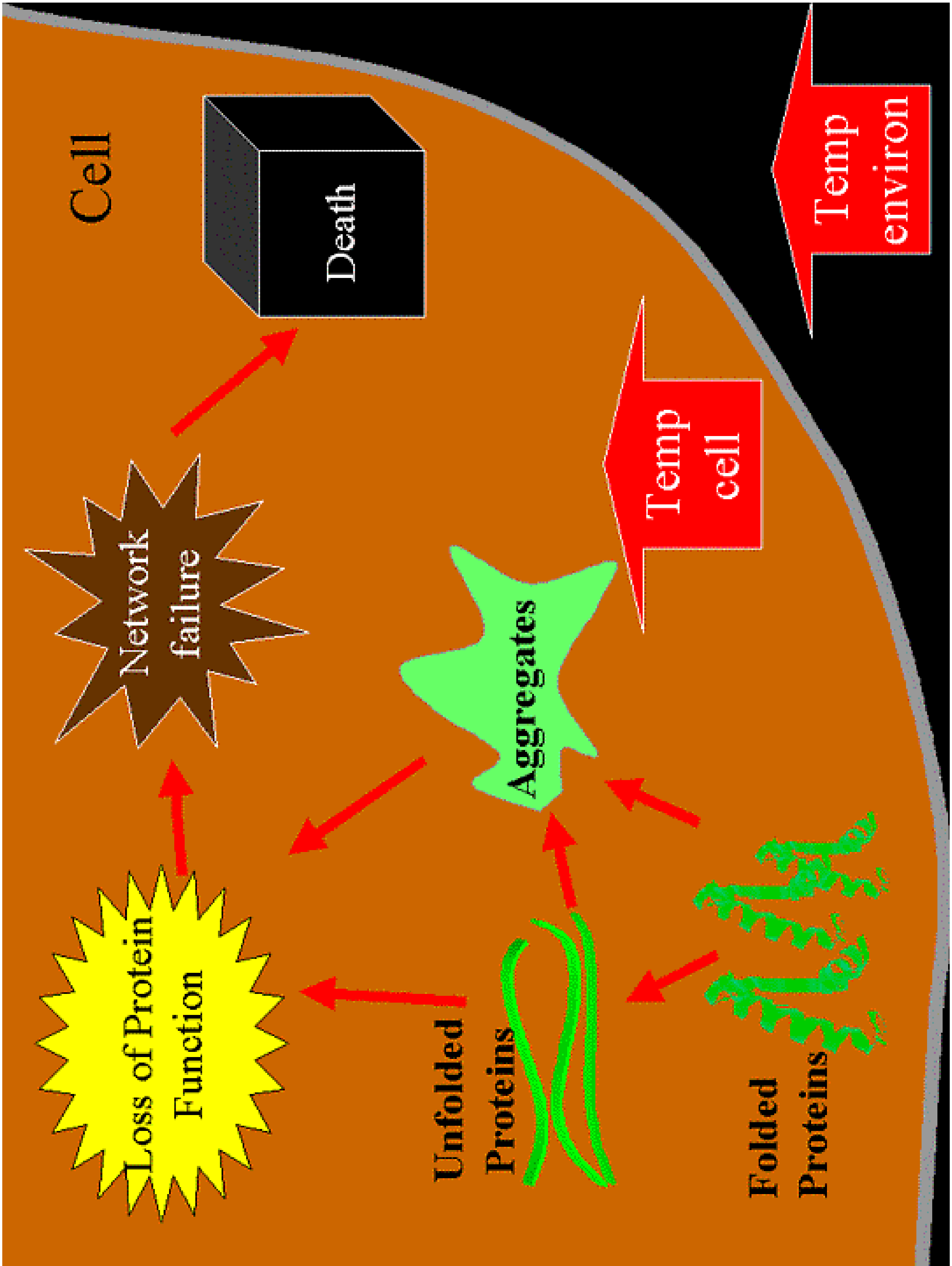
Caveats

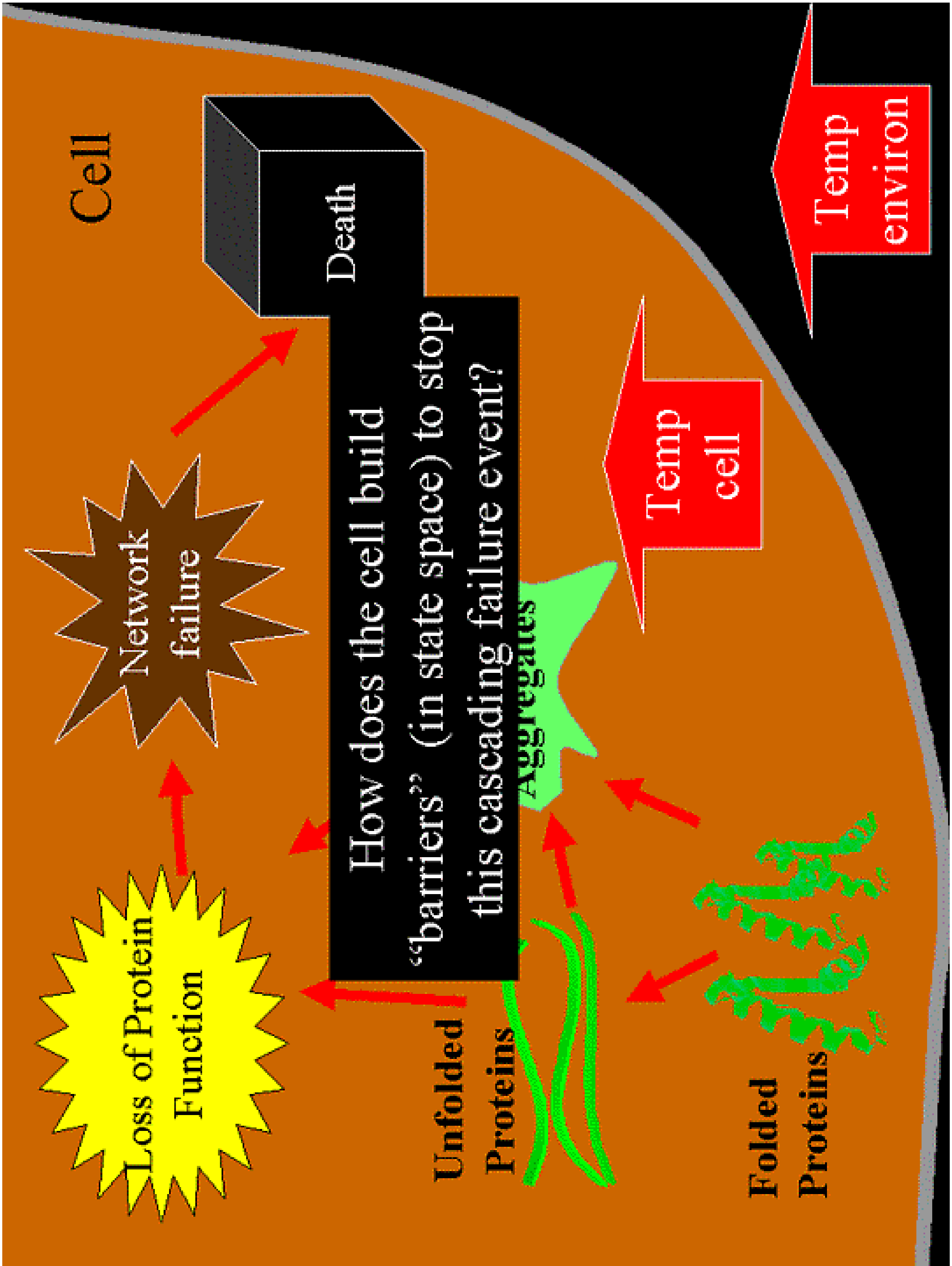
- The "real thing" is much more complicated
- I'm not a biologist (and I'm not ***really*** an engineer)
- Perhaps any accessible "simple story" is necessarily very misleading


"Any sufficiently advanced technology
is indistinguishable from magic."
Powerpnt
This program has performed an illegal operation
and will be shut down.
If the problem persists, contact the program
vendor.
Close
Details>>


"Any sufficiently advanced technology
is indistinguishable from magic."
Arthur C. Clarke
"Those who say do not know,
those who know do not say."
Zen saying


E. Coli Heat Shock
(with Kurata, El-Samad, Khammash, Yi)
Outer Feedback Loop
rpoH gene
Transcription
σ32 mRNA
Translation
Feedforward
σ32
Heat
σ32
Heat stabilizes σ32
hsp1
hsp2
Local Loop
Transcription & Translation
FtsH
Lon
DnaK
GroL
GroS
Proteases
Chaperones
Heat


Cell
Death
Network failure
Temp environ
Temp cell
Aggregates
Loss of Protein Function
Unfolded Proteins
Folded Proteins


Cell
Death
How does the cell build
"barriers" (in state space) to stop
this cascading failure event?
Network failure
Loss of Protein Function
Aggregates
Temp cell
Temp environ
Unfolded Proteins
Folded Proteins

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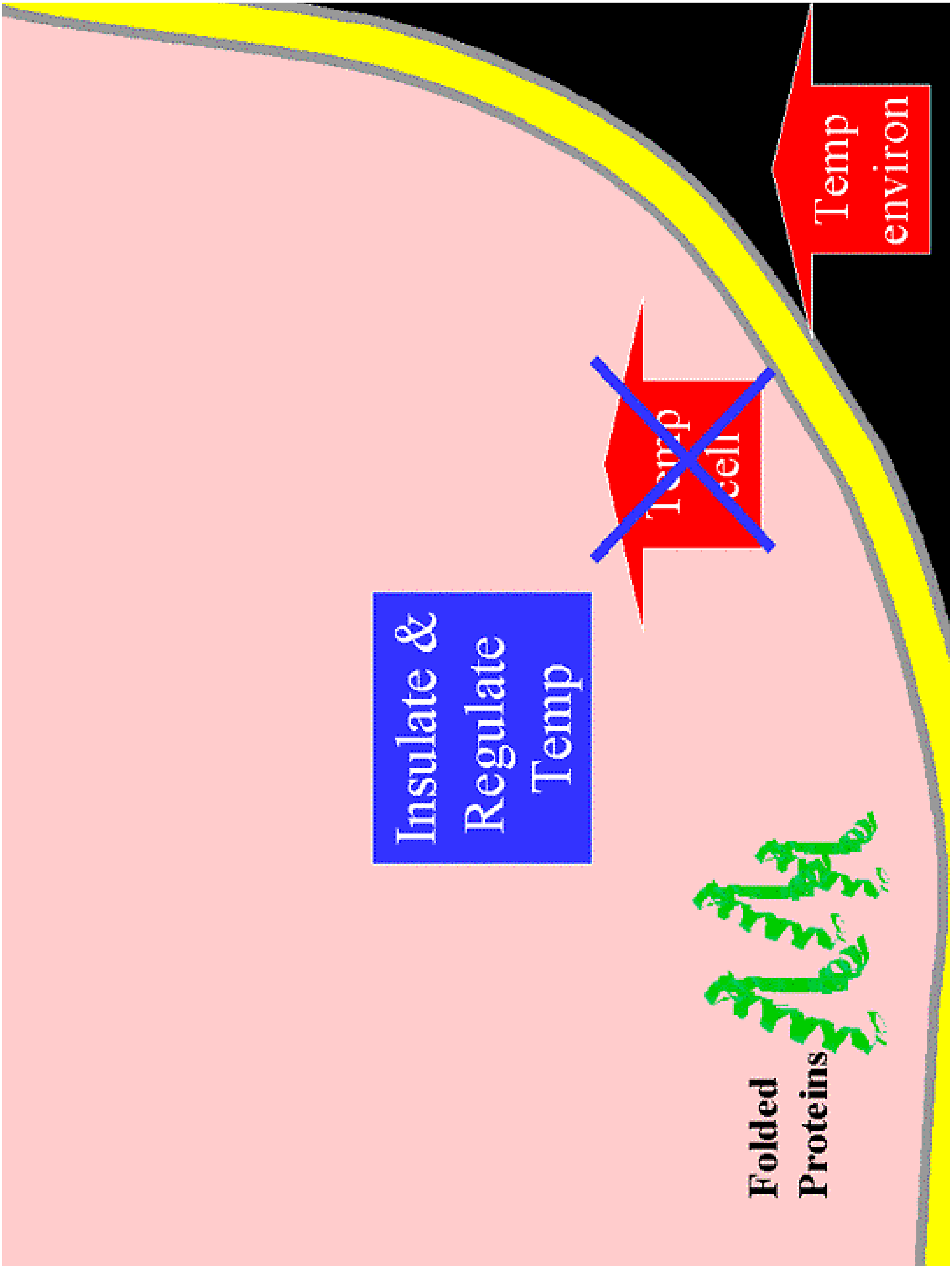
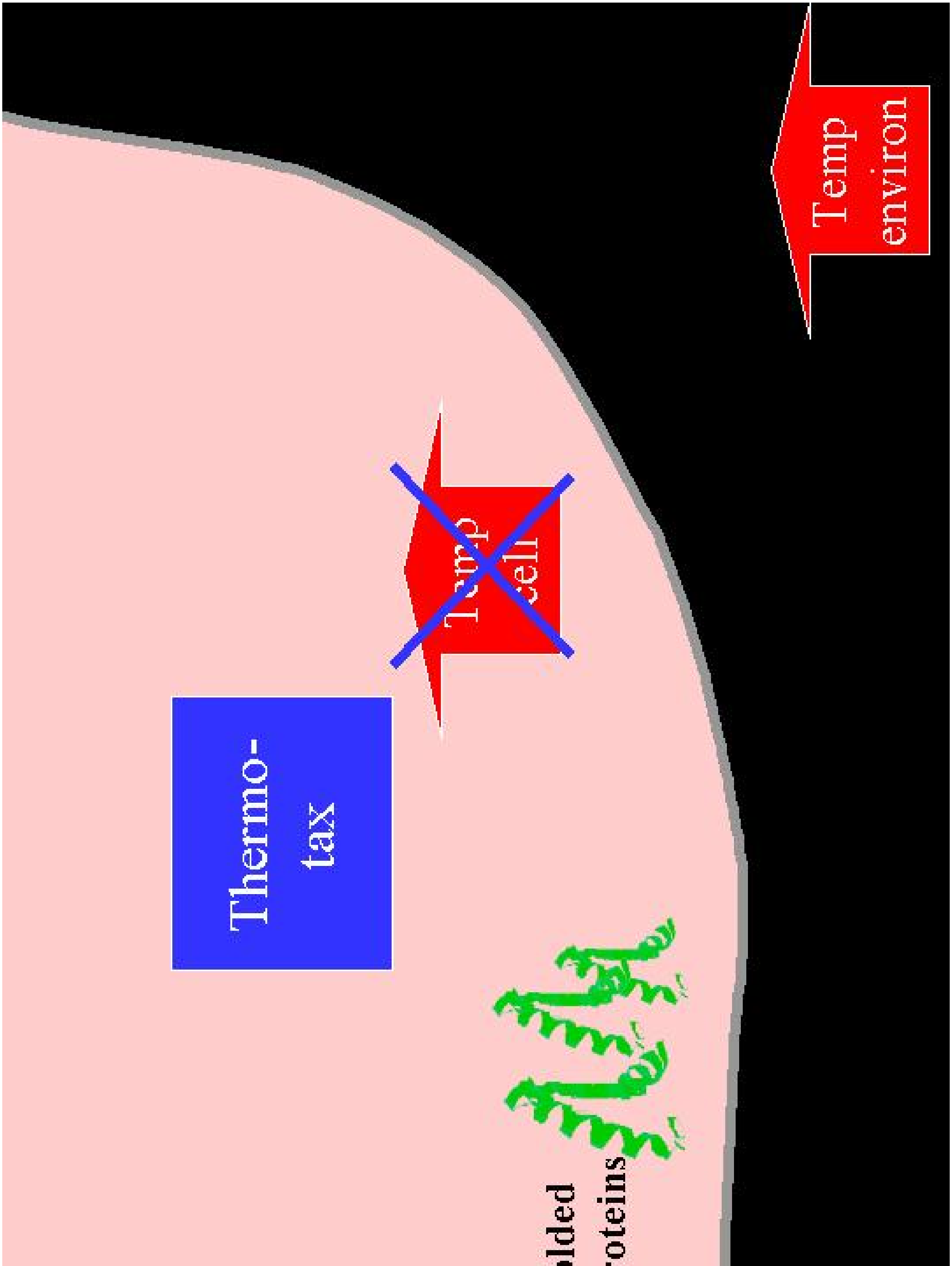
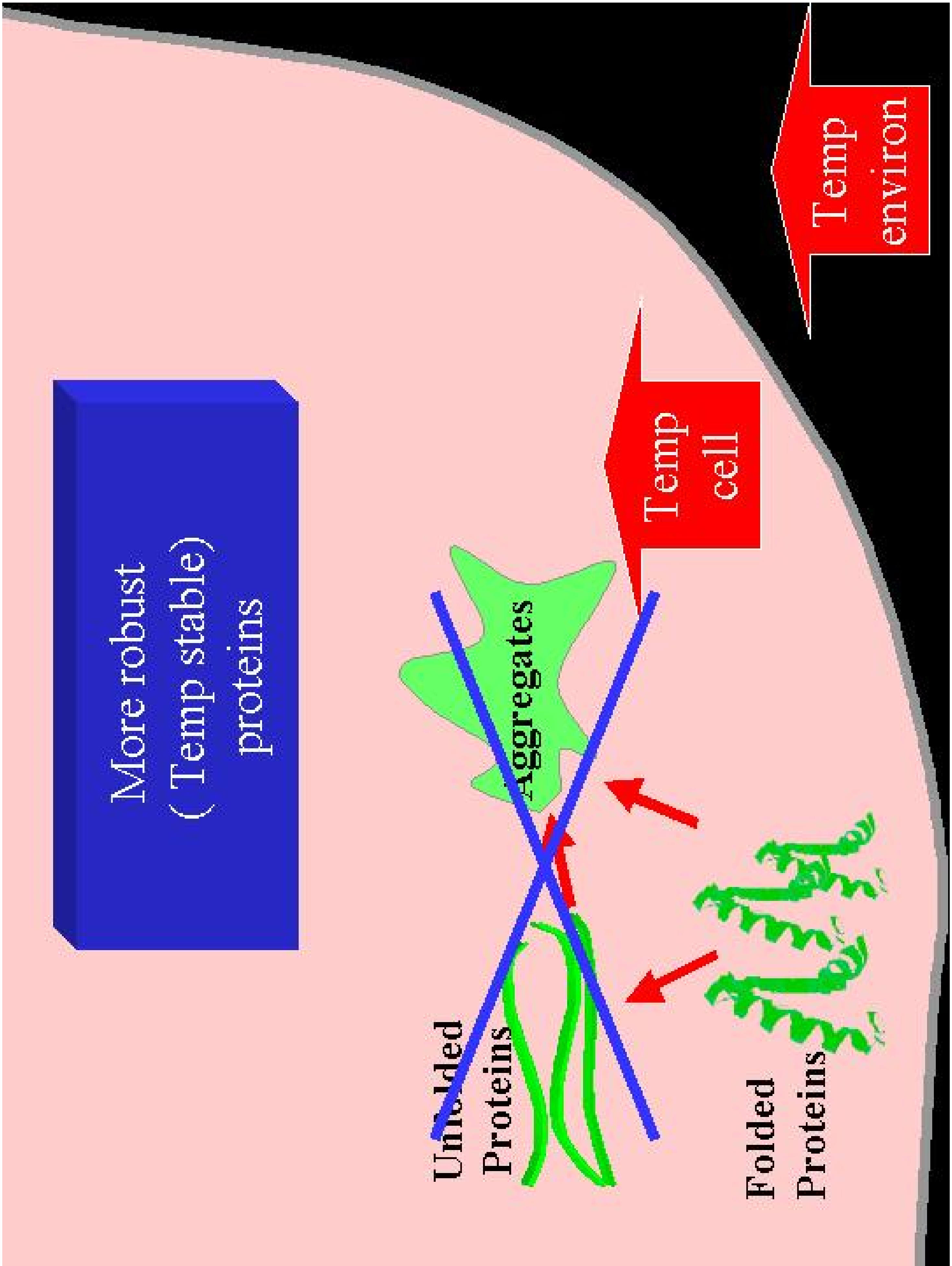
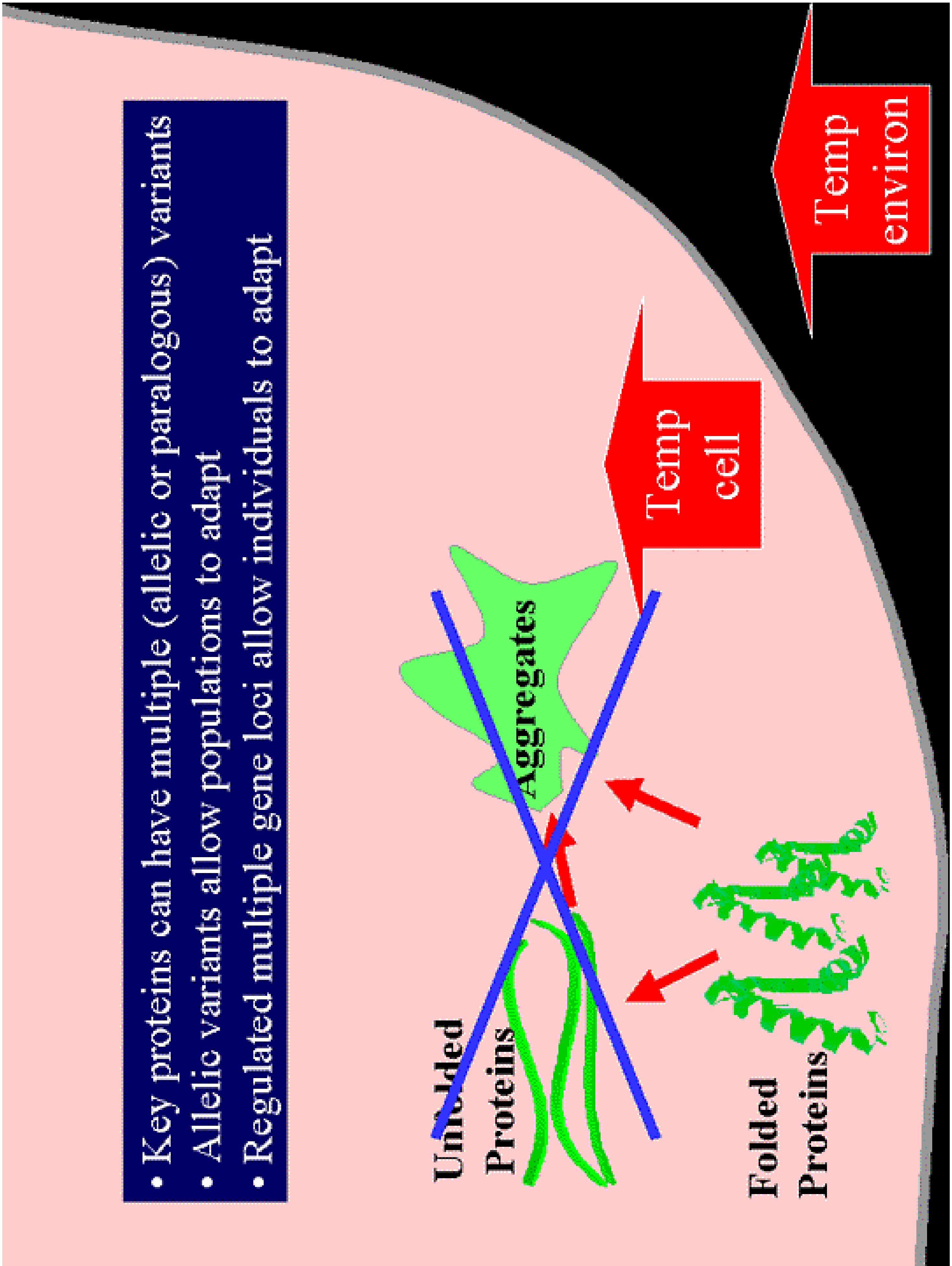
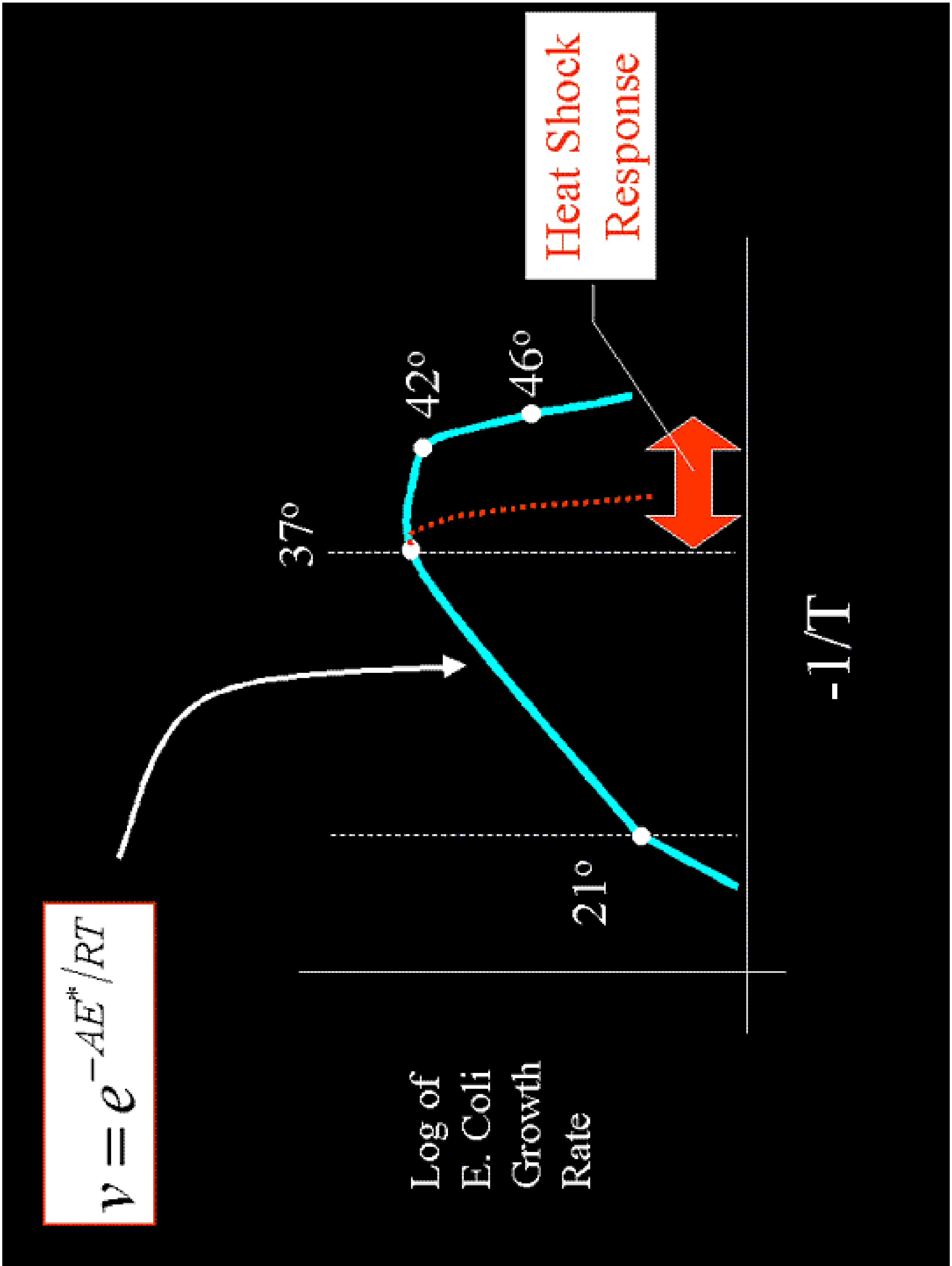
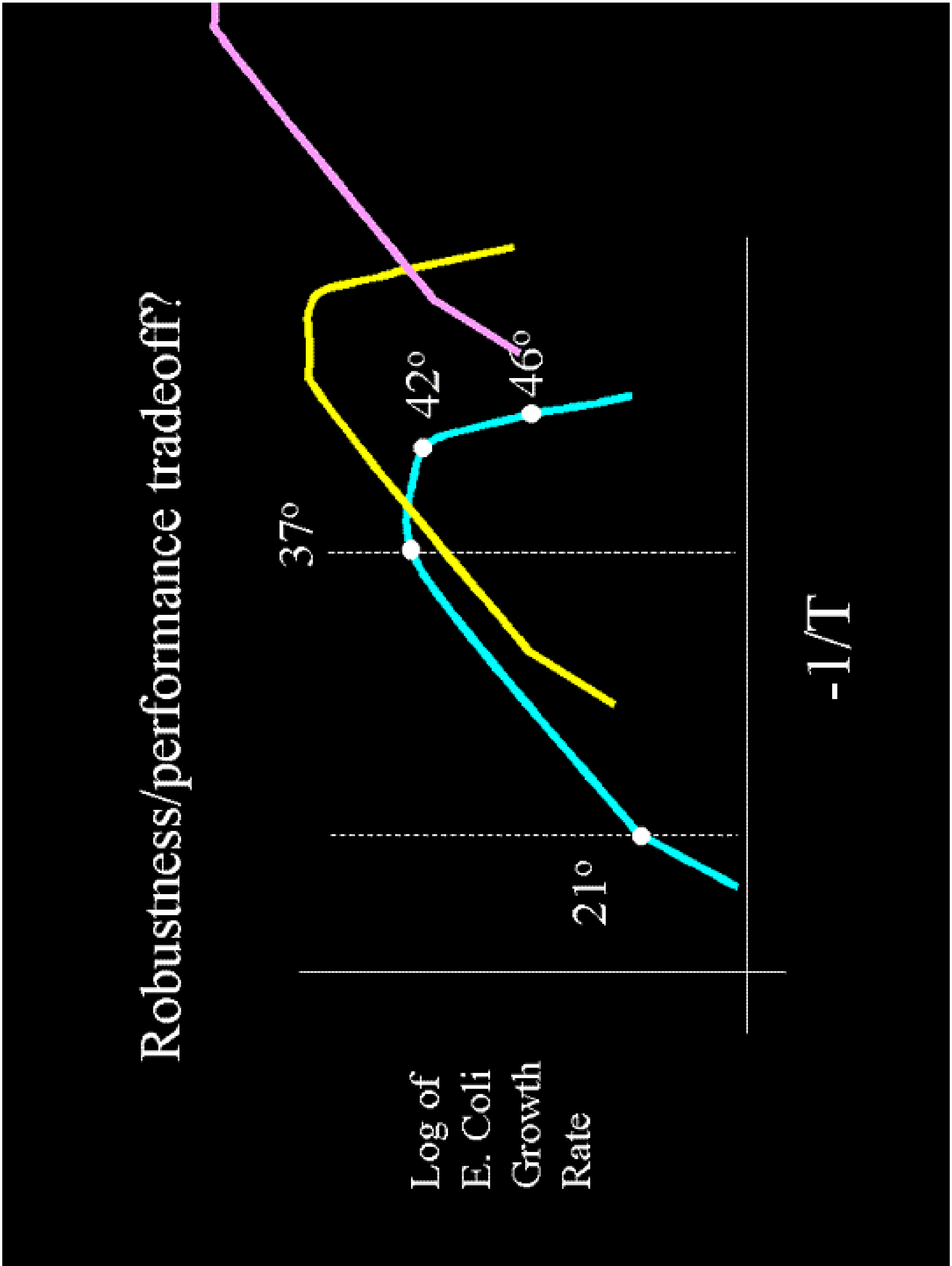


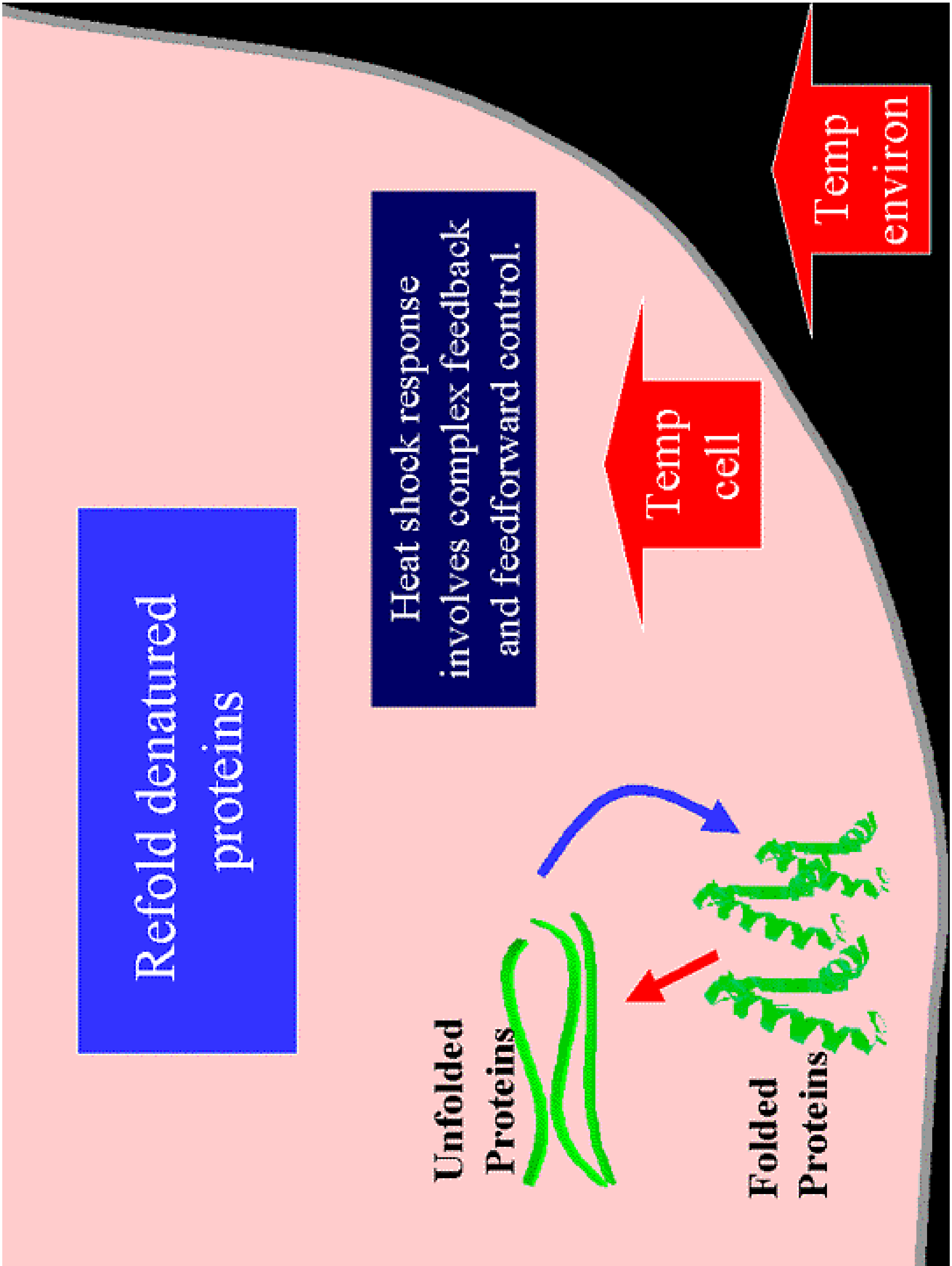

Temp
environ
Temp
cell
Thermo-
tax

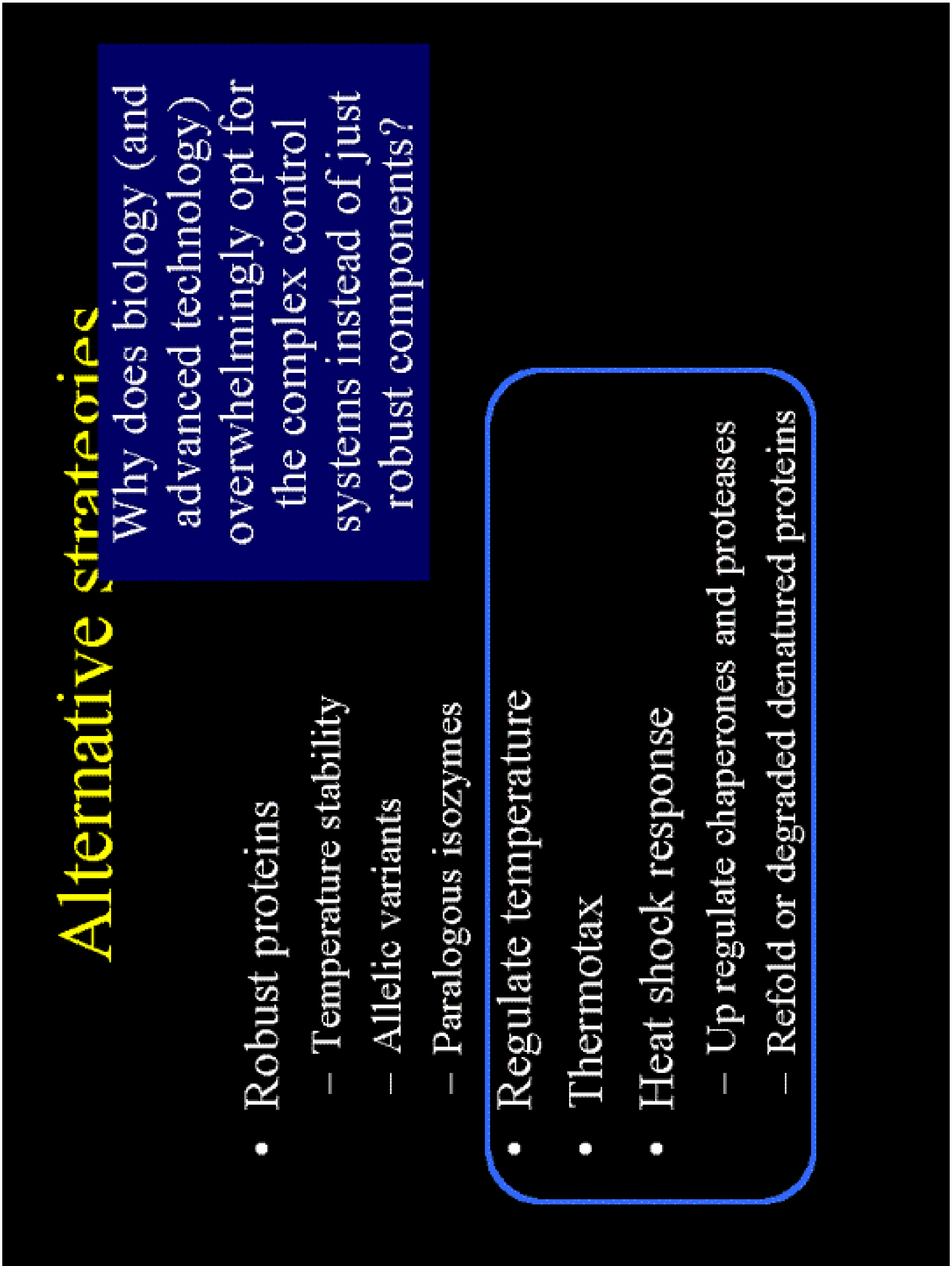

Temp
environ
Temp
cell
More robust
(Temp stable)
proteins
Aggregates
Proteins
Folded
Proteins

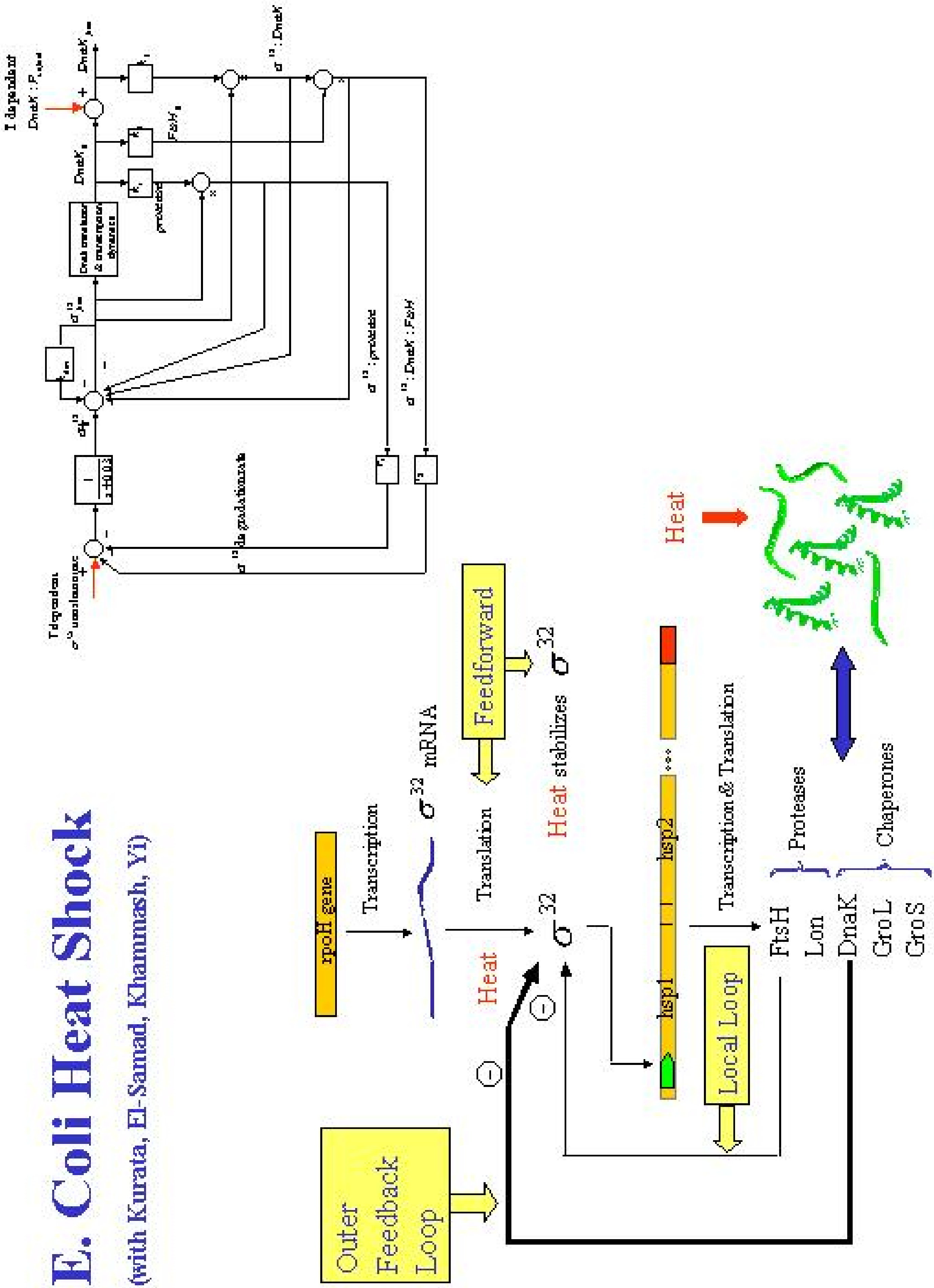

• Key proteins can have multiple (allelic or paralogous) variants
• Allelic variants allow populations to adapt
• Regulated multiple gene loci allow individuals to adapt
Temp environ
Temp cell
Aggregates
Unfolded Proteins
Folded Proteins


$v = e^{-AE^{*}/RT}$
Log of
E. Coli
Growth
Rate
-1/T
21°
37°
42°
46°
Heat Shock
Response

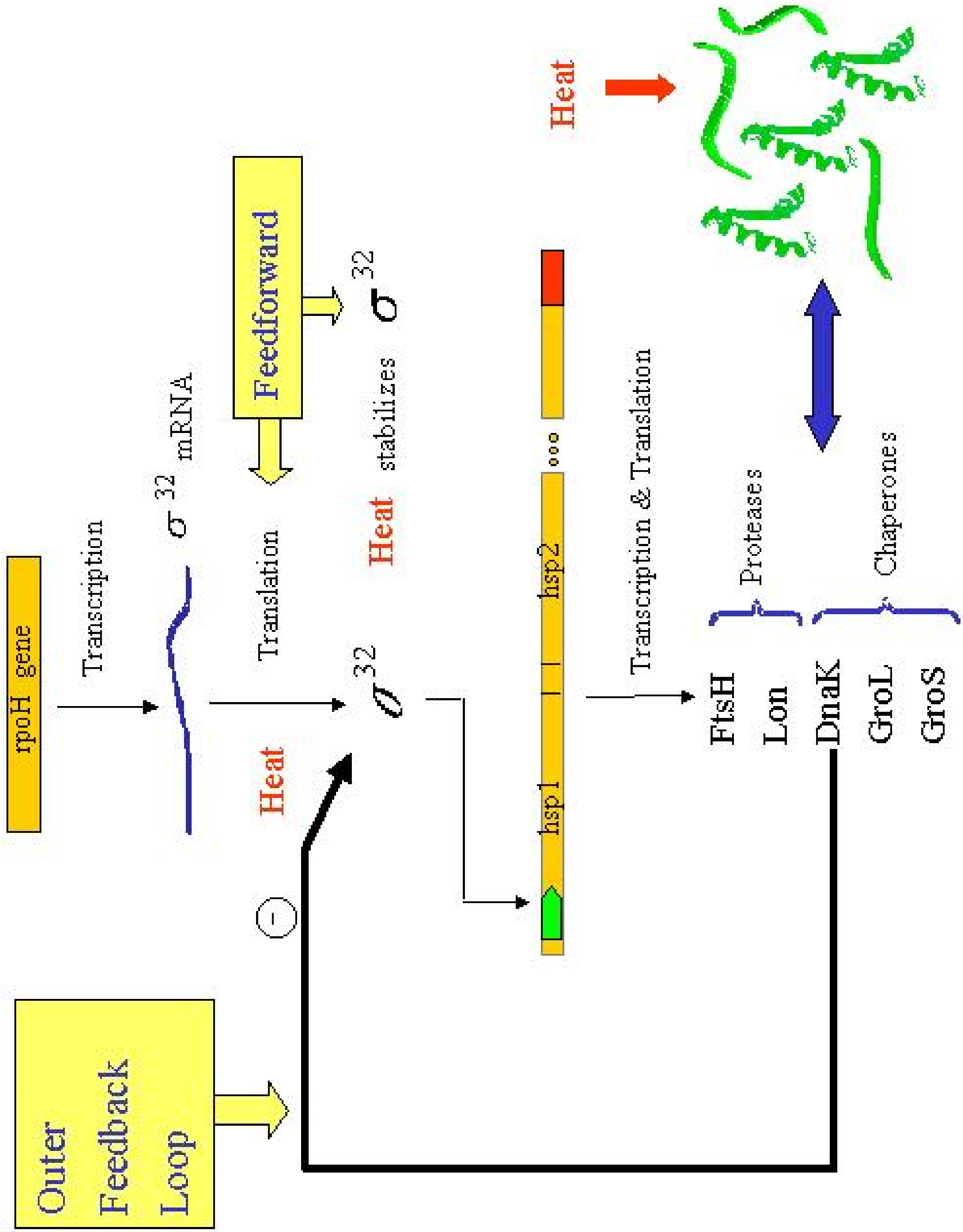

Robustness/performance tradeoff?
Log of
E. Coli
Growth
Rate
-1/T
21°
37°
42°
46°


Temp
environ
Temp
cell
Heat shock response
involves complex feedback
and feedforward control.
Refold denatured
proteins
Unfolded
Proteins
Folded
Proteins

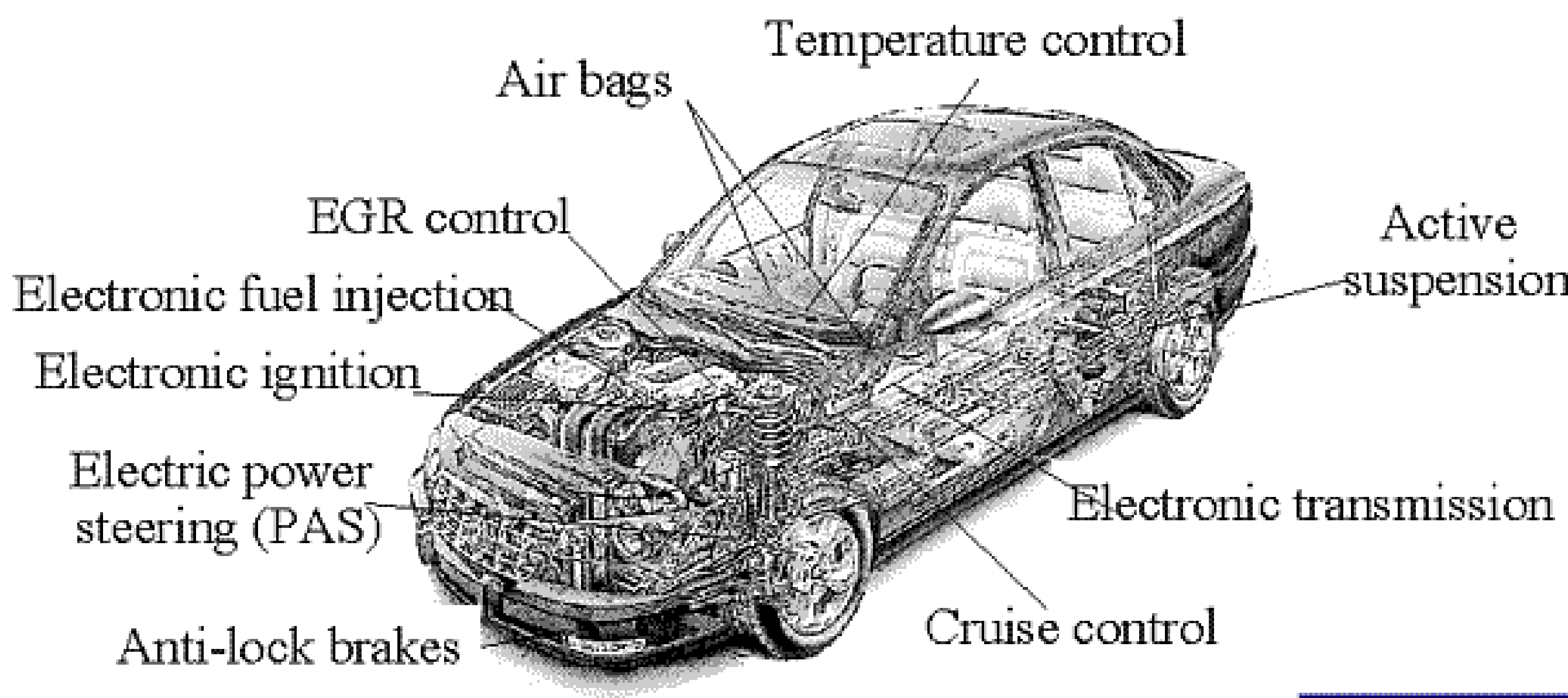

Alternative strategies
Why does biology (and advanced technology) overwhelmingly opt for the complex control systems instead of just robust components?
• Robust proteins
– Temperature stability
– Allelic variants
– Paralogous isozymes
• Regulate temperature
• Thermotax
• Heat shock response
– Up regulate chaperones and proteases
– Refold or degraded denatured proteins

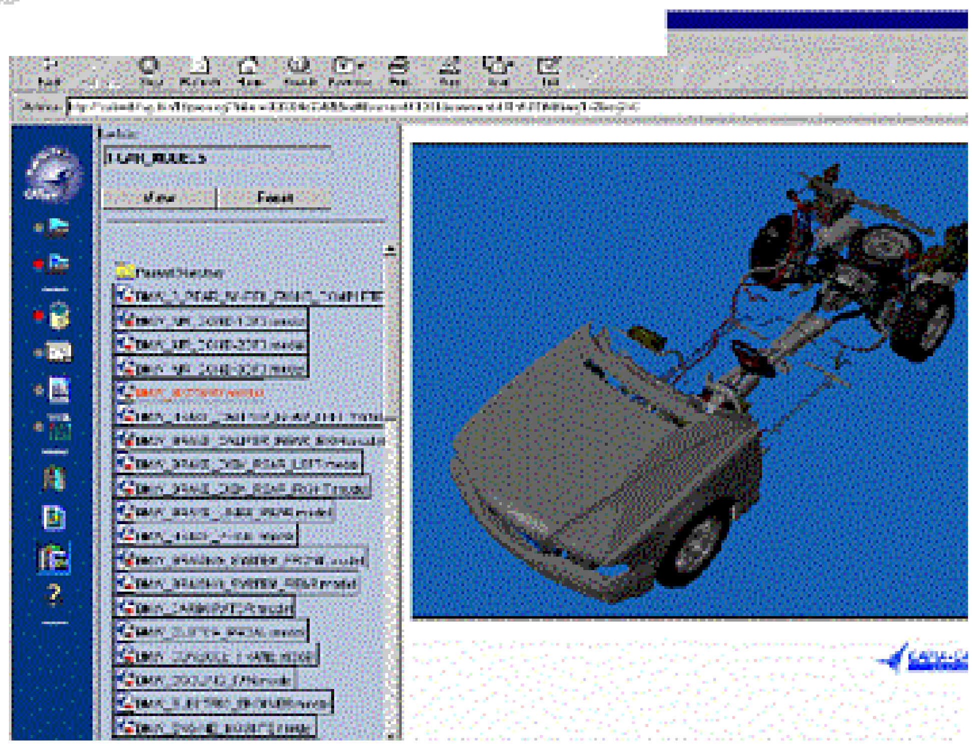


E. Coli Heat Shock
(with Kurata, El-Samad, Khammash, Yi)
Outer Feedback Loop
rpoH gene
Transcription
σ32 mRNA
Translation
Feedforward
Heat
σ32
Heat stabilizes σ32
hsp1
hsp2
Local Loop
Transcription & Translation
FtsH
Lon
DnaK
GroL
GroS
Proteases
Chaperones
Heat



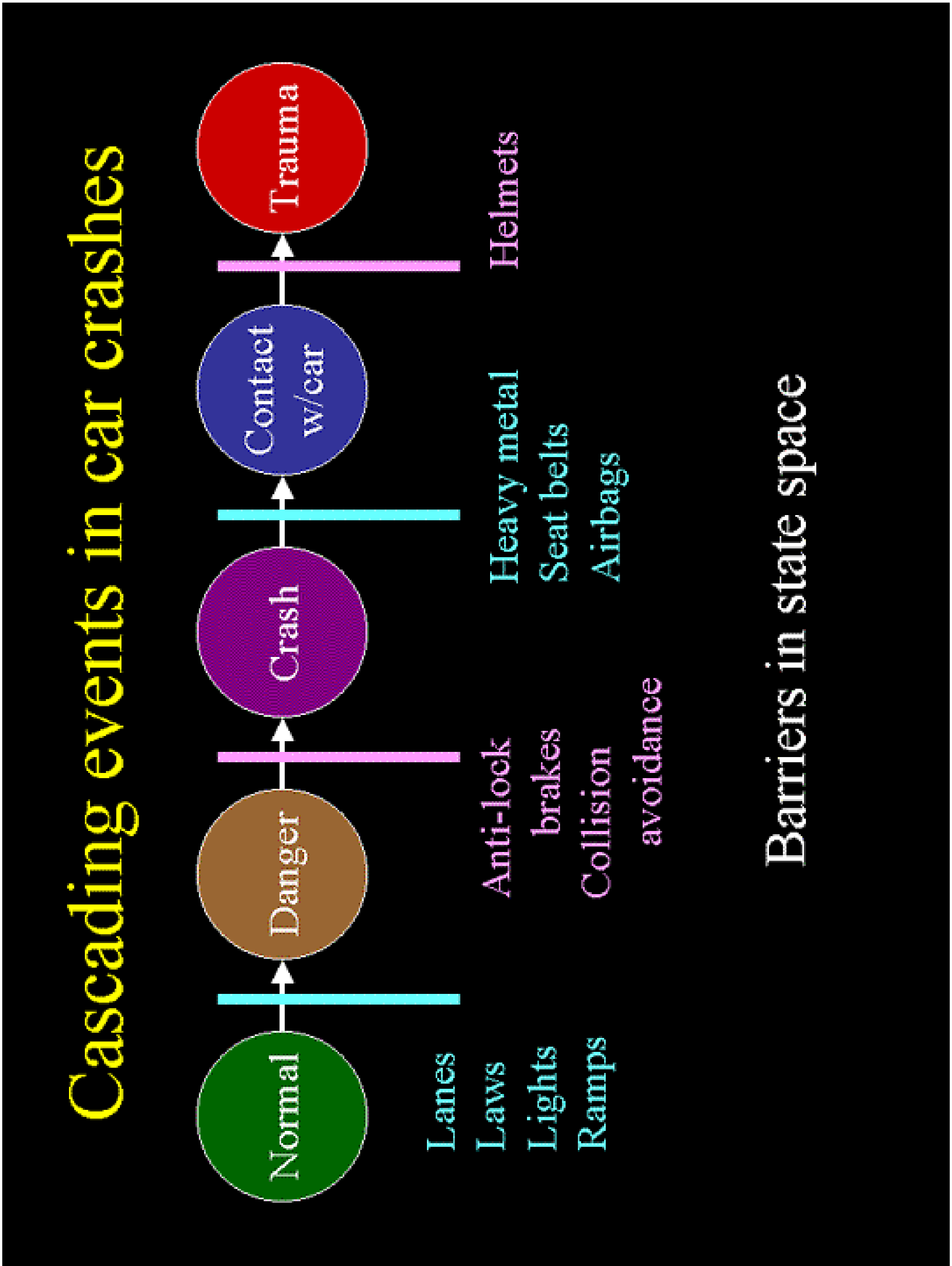
rpoH gene
Transcription
σ 32 mRNA
Translation
Heat
Feedforward
Heat
stabilizes σ 32
σ 32
hsp1
hsp2
Heat
Transcription & Translation
FtsH
Lon
DnaK
GroL
GroS
Proteases
Chaperones
Outer Feedback Loop
−



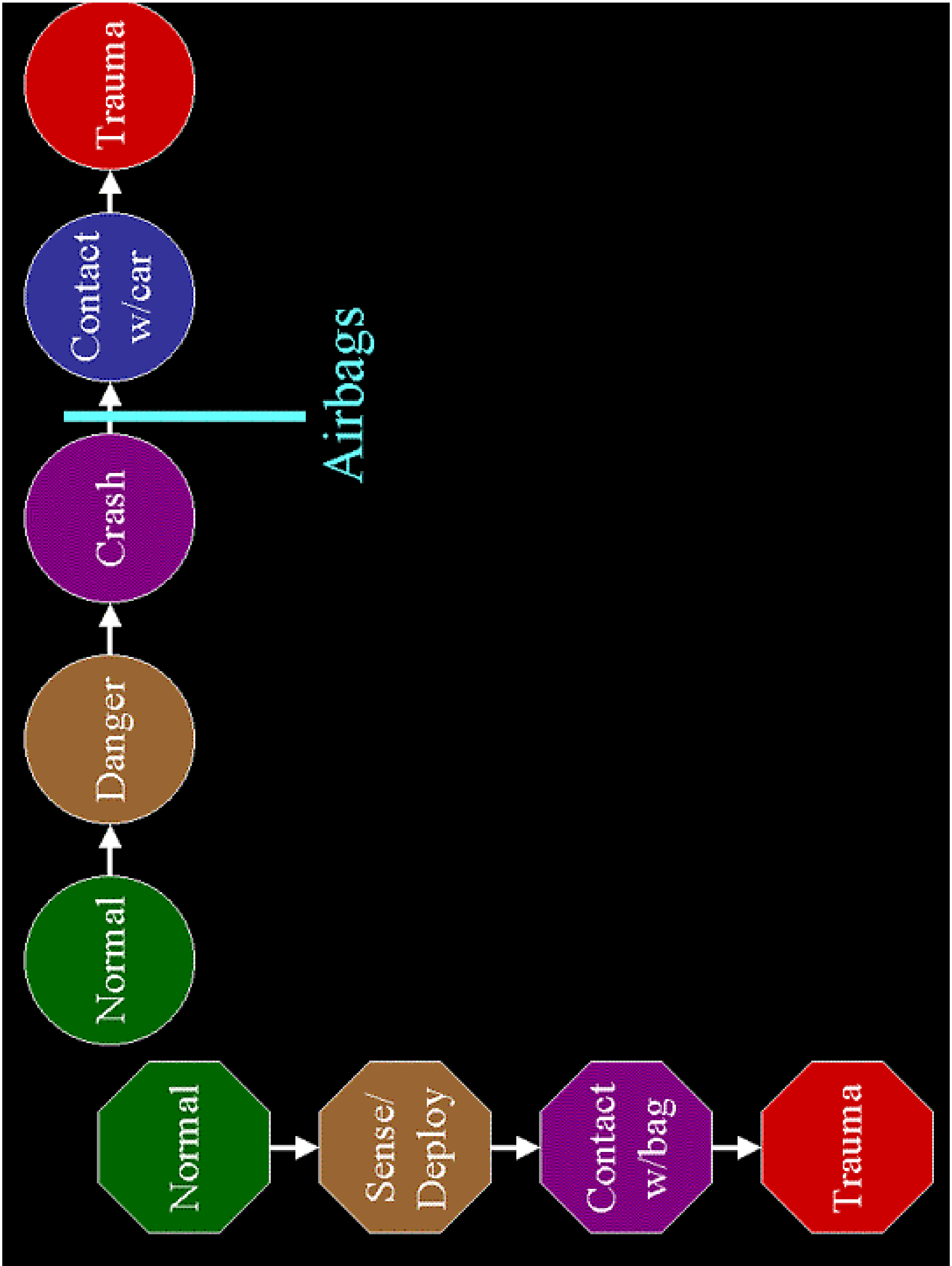


In development:

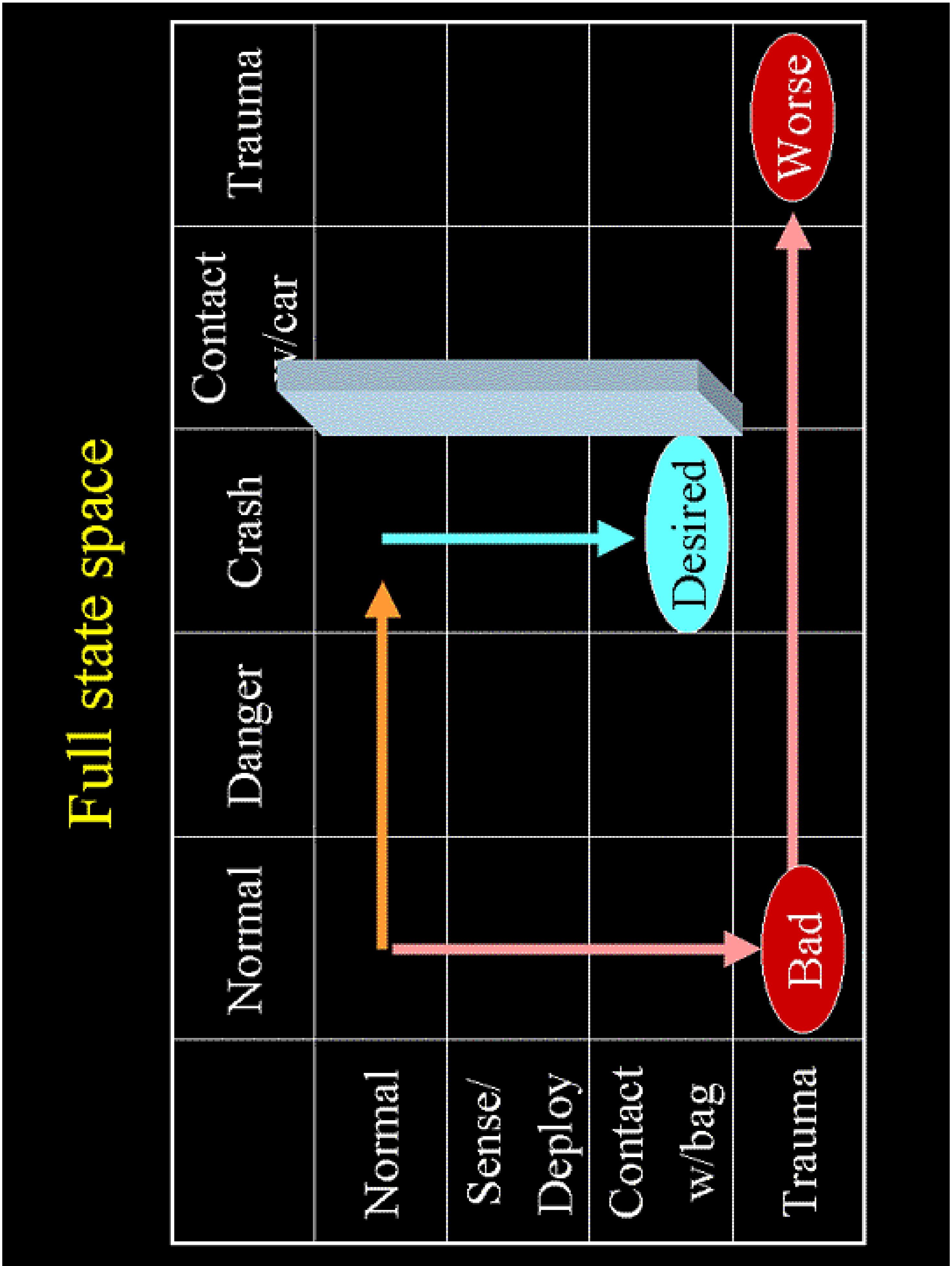
- drive-by-wire
- steering/traction control
- collision avoidance

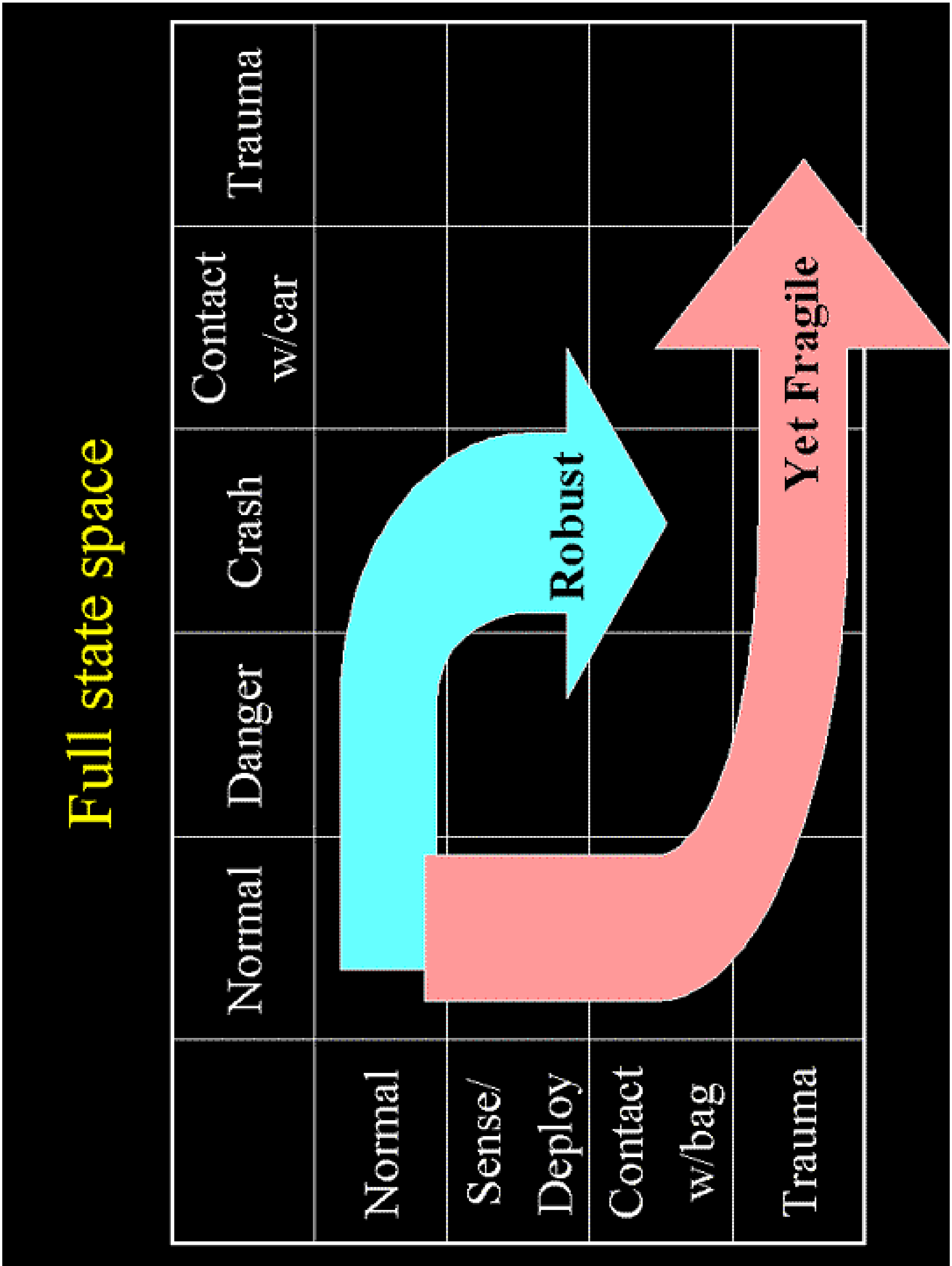

Cascading events in car crashes
Normal
Danger
Crash
Contact w/car
Trauma
Lanes
Laws
Lights
Ramps
Anti-lock brakes
Collision avoidance
Heavy metal
Seat belts
Airbags
Helmets
Barriers in state space

[31] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



[32] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



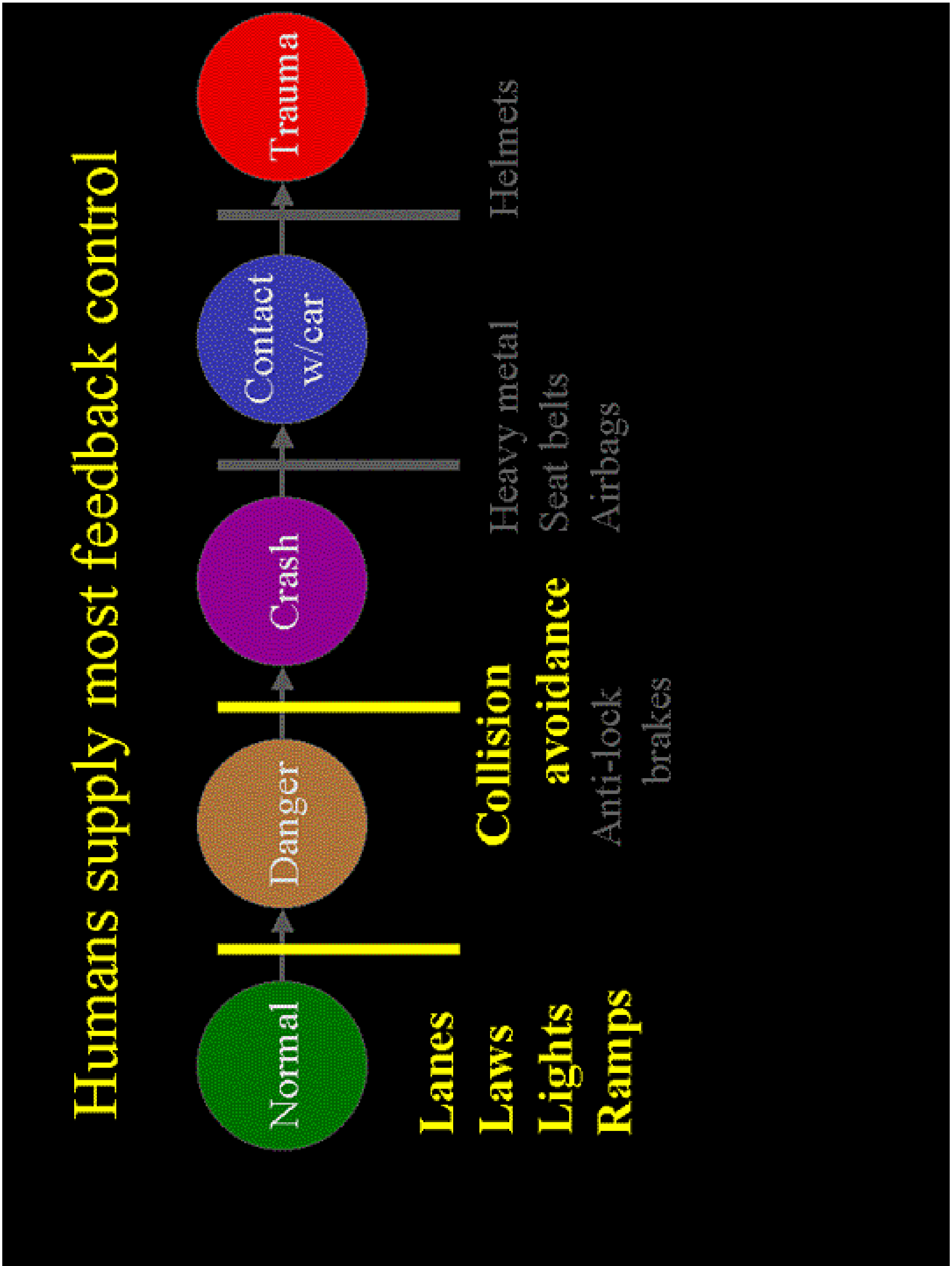

Full state space
Normal
Danger
Crash
Contact w/car
Trauma
Normal
Sense/ Deploy
Contact w/bag
Trauma
Robust
Yet Fragile

"Robust, yet fragile"

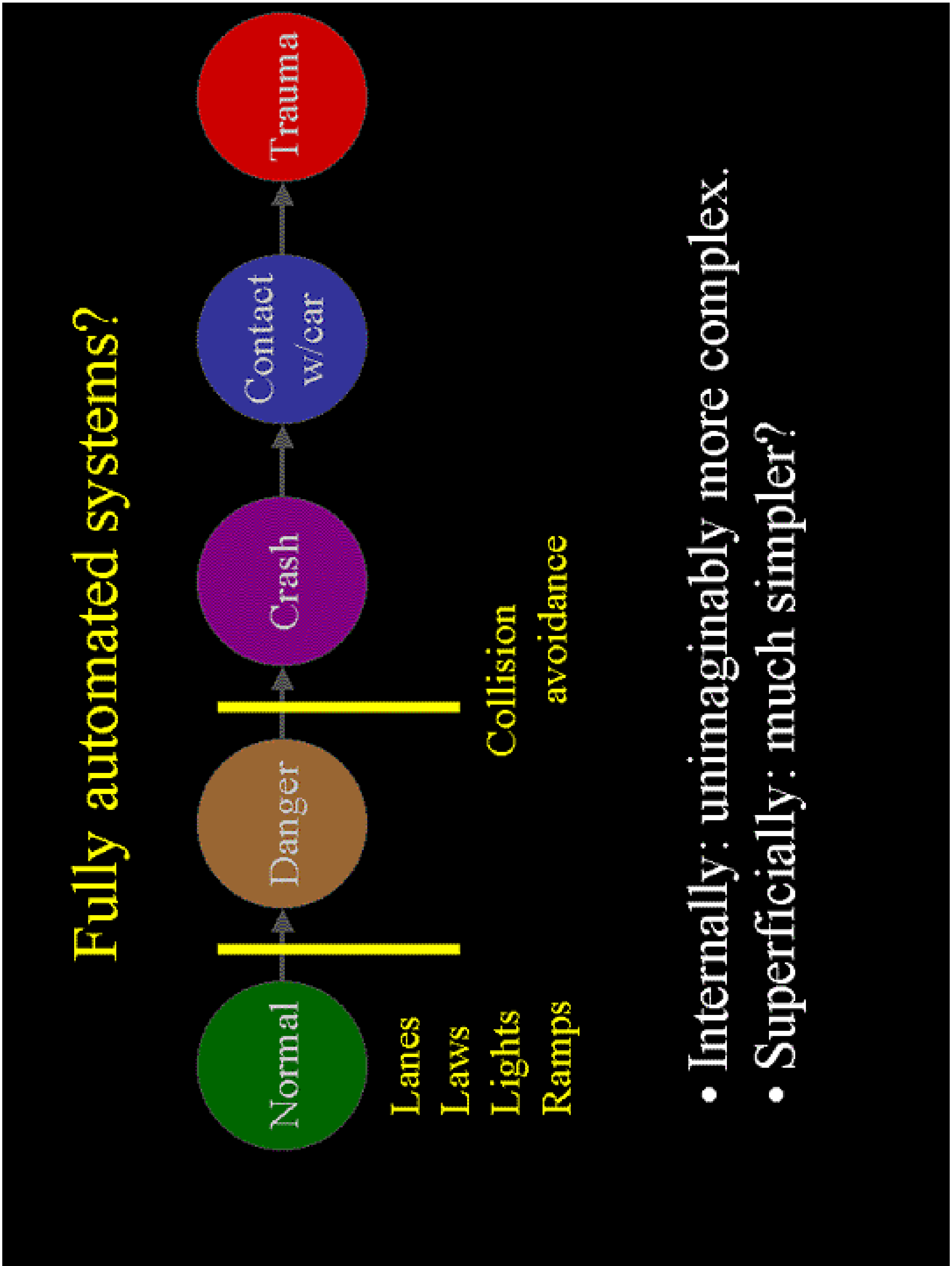
- **Robust** to uncertainties
  - that are common,
  - the system was designed for, or
  - has evolved to handle,
- **…yet fragile** otherwise

- This is *the* most important feature of complex systems (the essence of HOT).

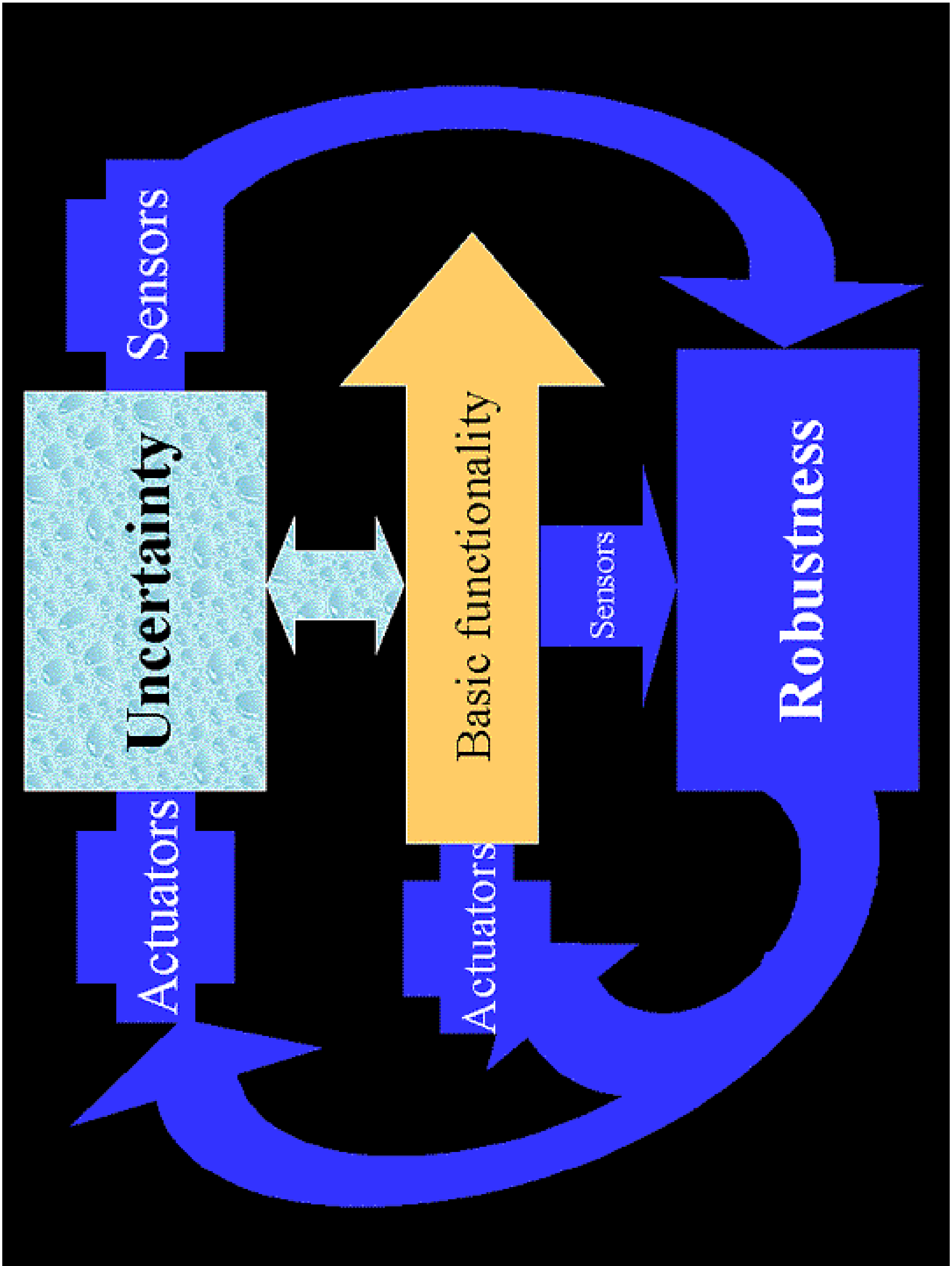
[35] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



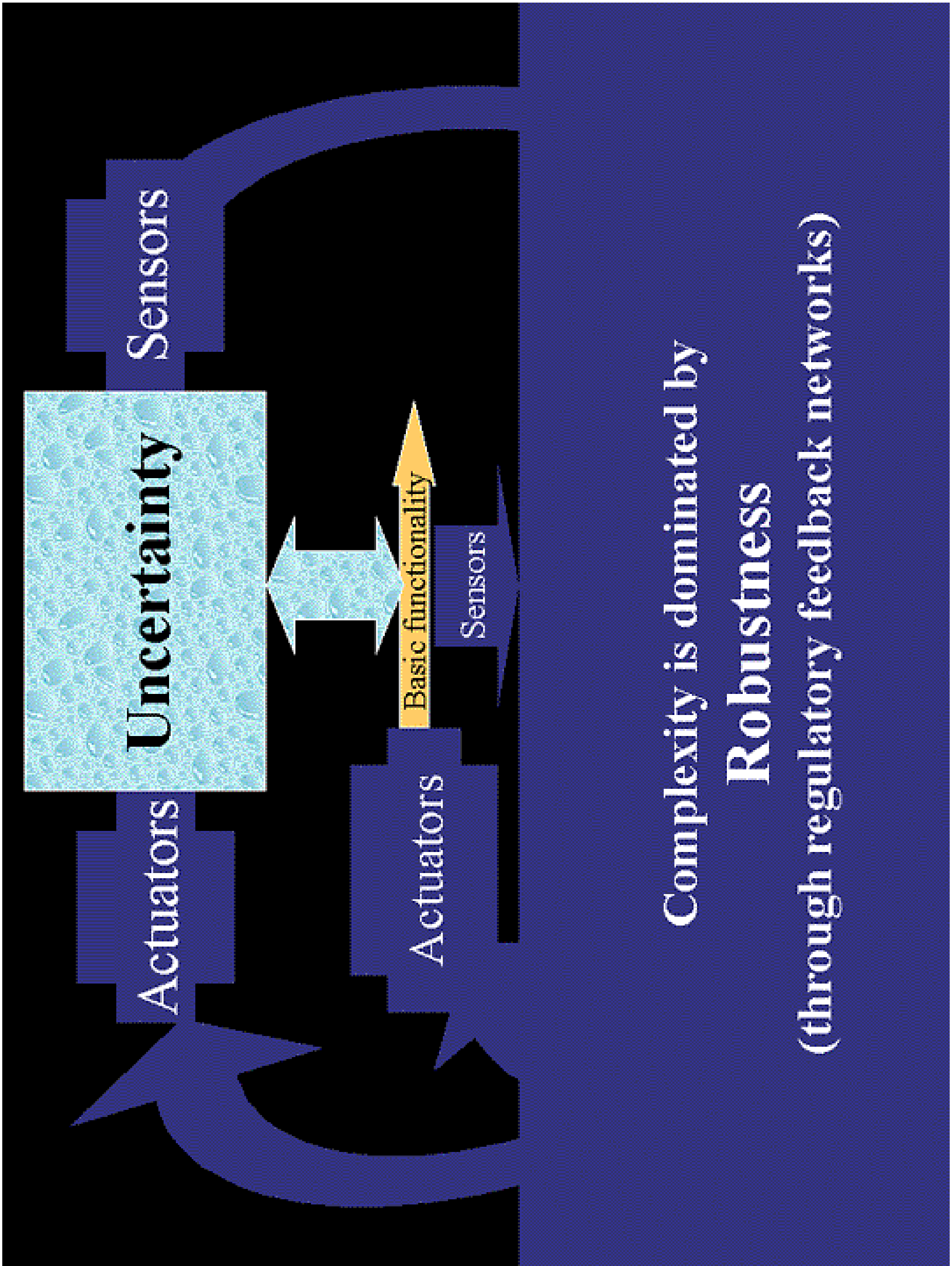
[36] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

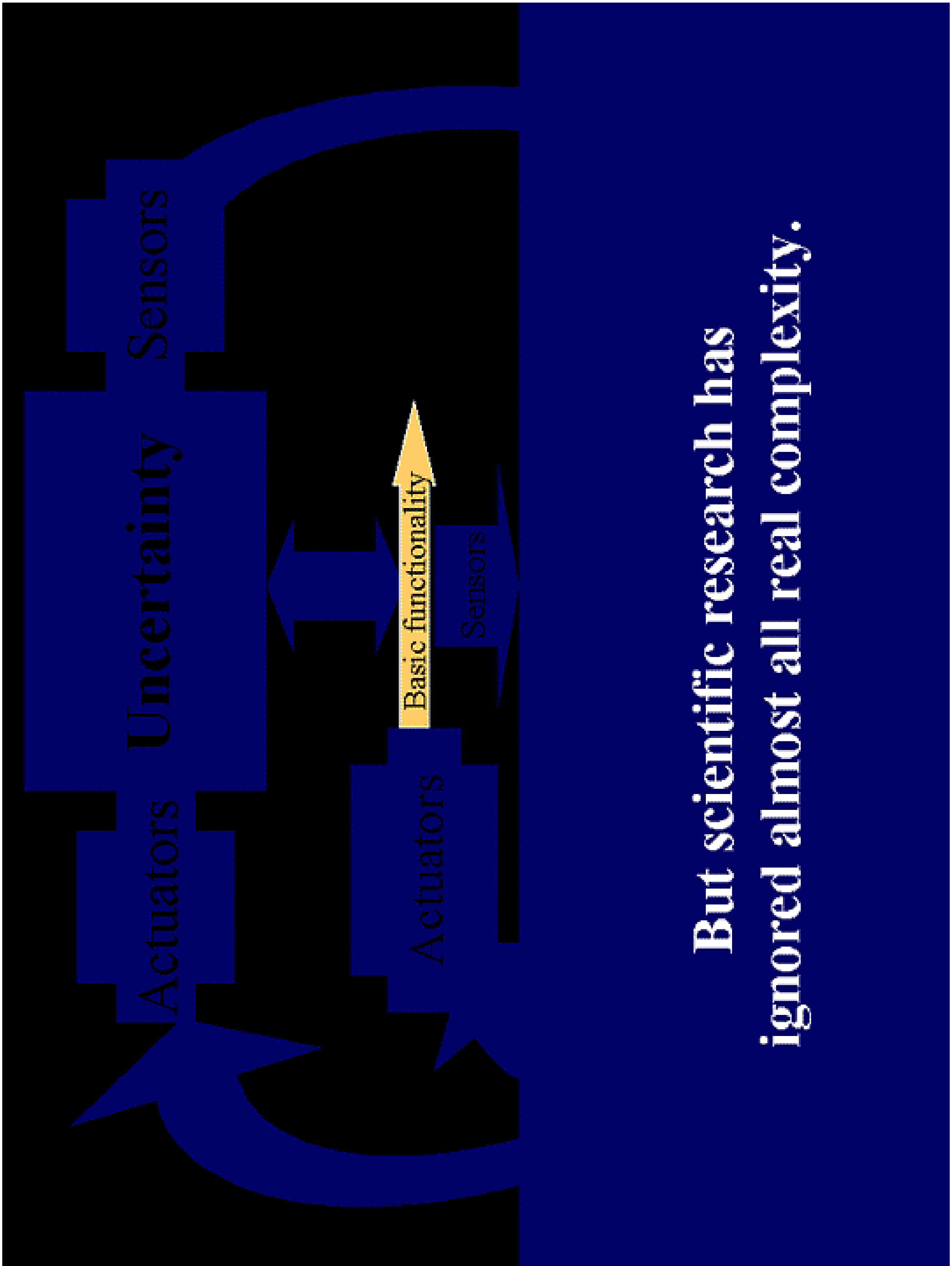


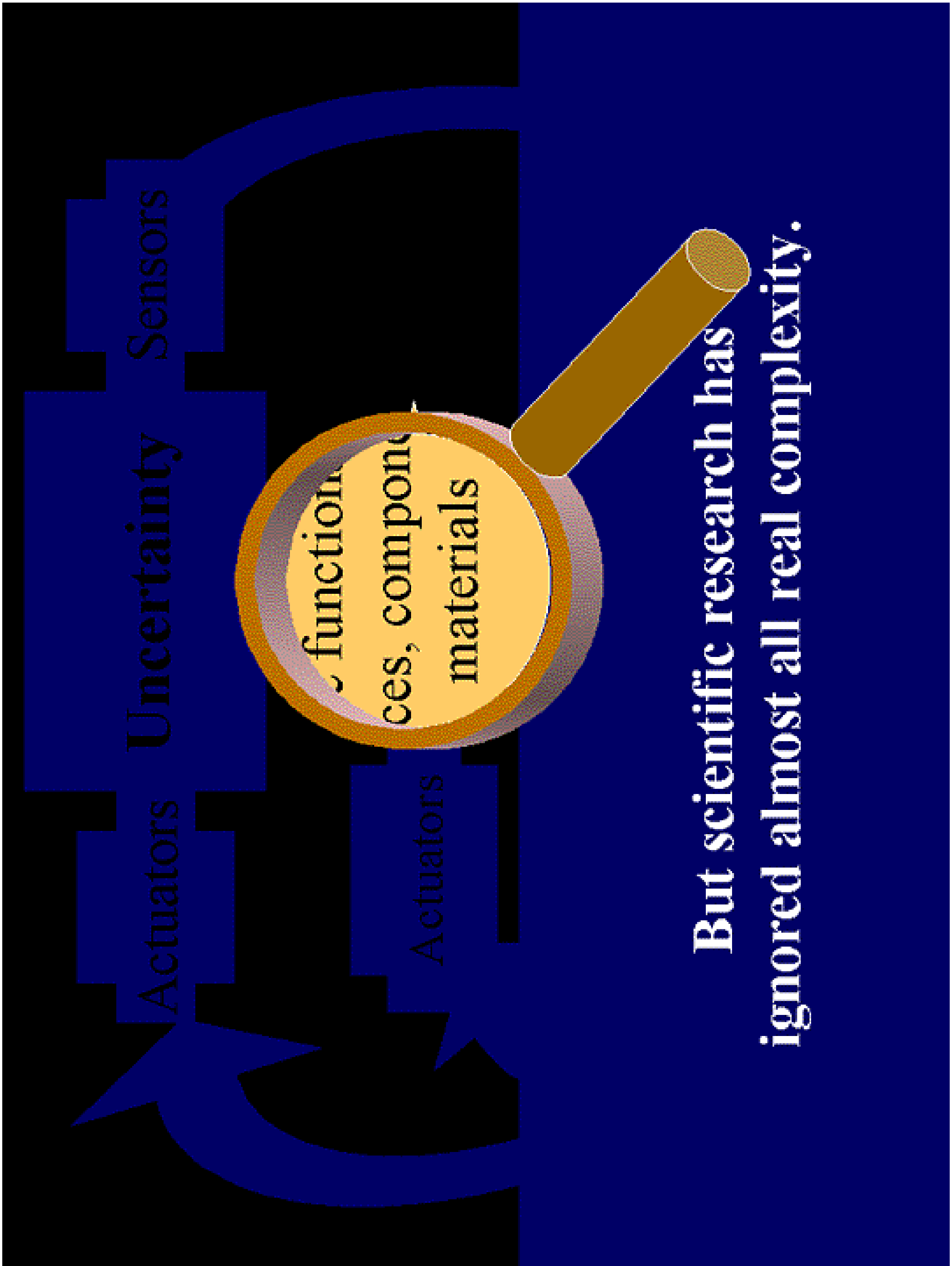
[37] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

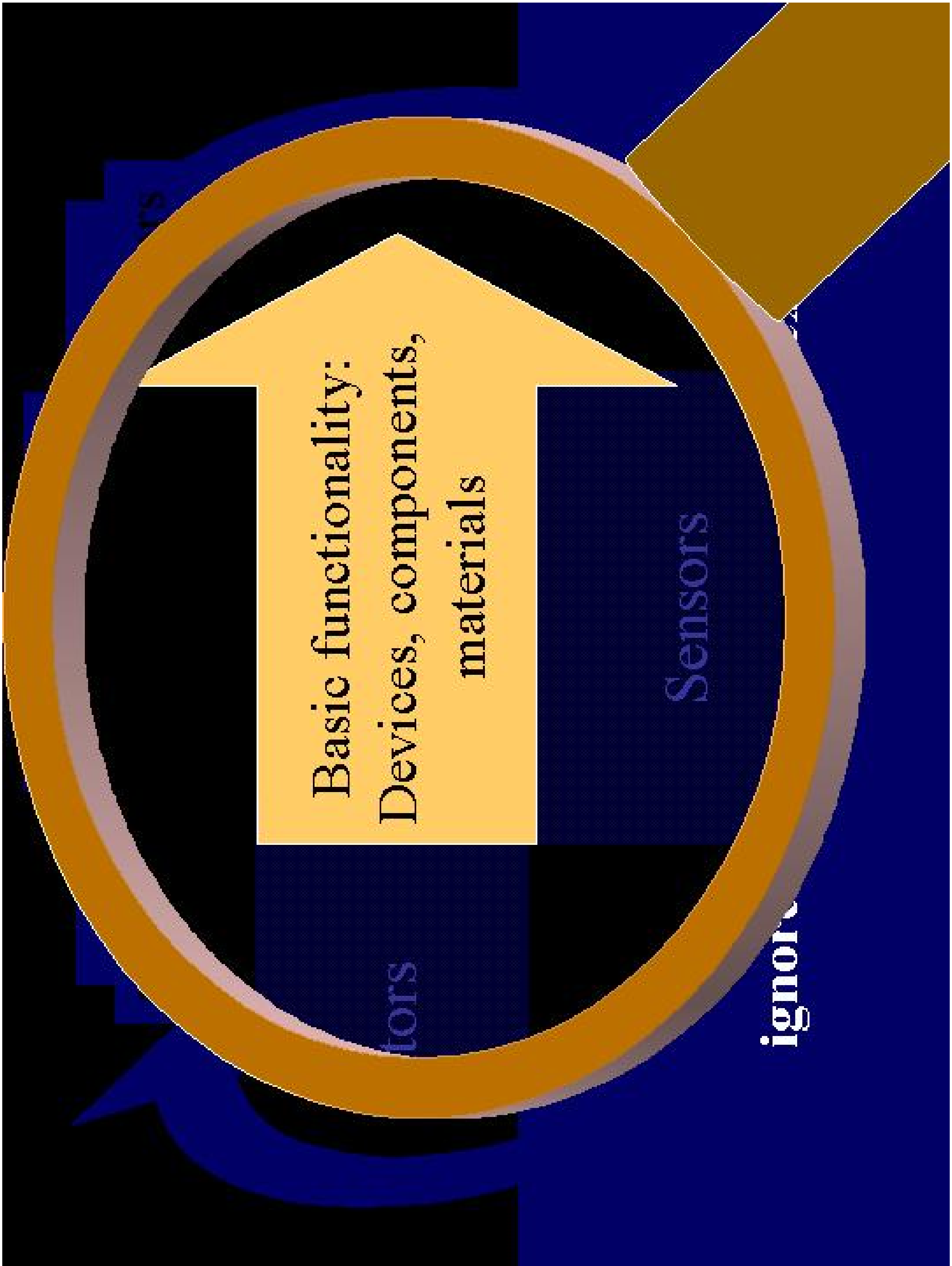


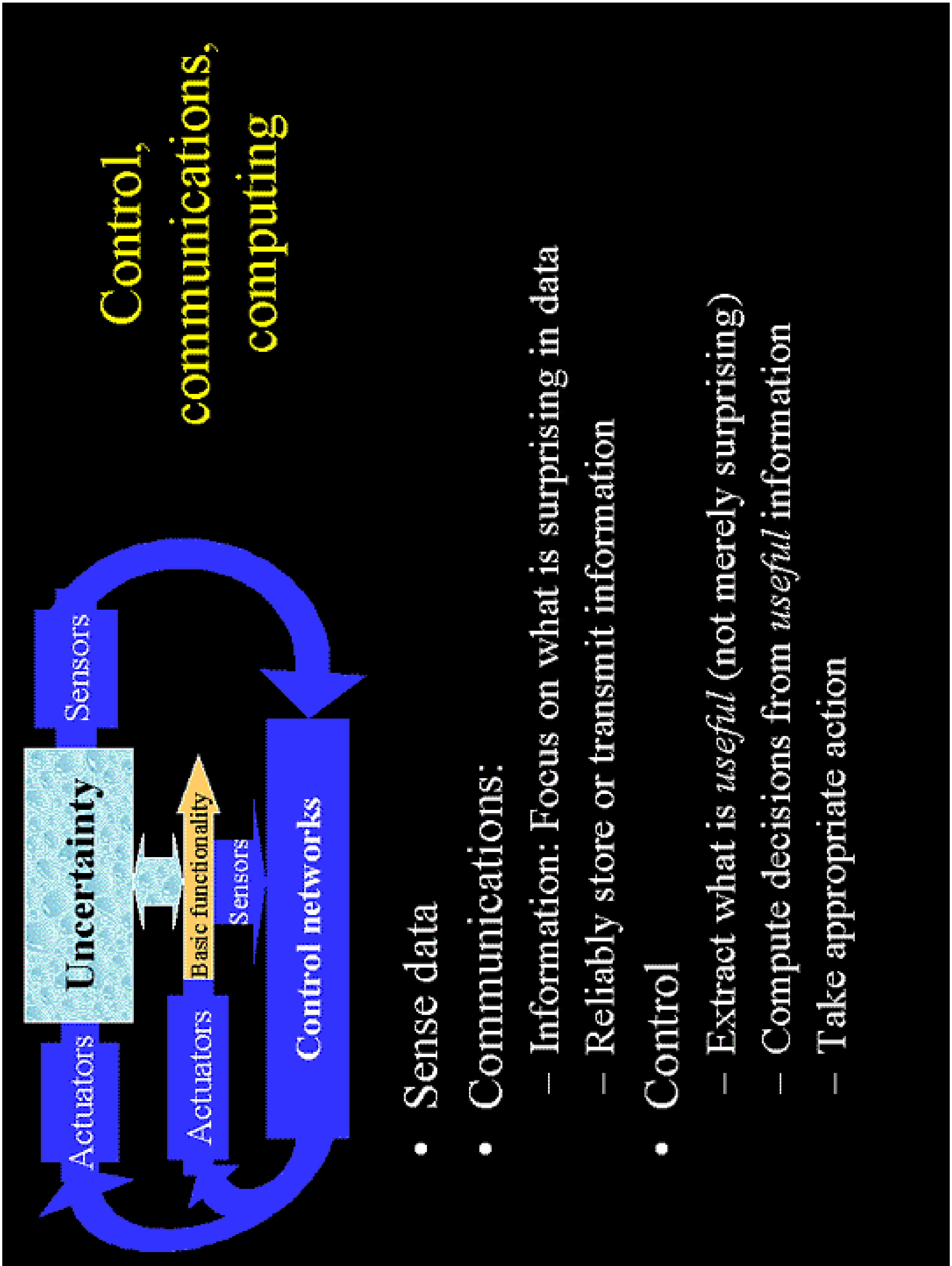
[38] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks




Sensors
Uncertainty
Actuators
Basic functionality
Sensors
Actuators
But scientific research has
ignored almost all real complexity.


Sensors
Uncertainty
Actuators
Actuators
materials
But scientific research has
ignored almost all real complexity.


Basic functionality:
Devices, components,
materials
Sensors


Control, communications, computing
Uncertainty
Sensors
Actuators
Basic functionality
Sensors
Actuators
Control networks
• Sense data
• Communications:
– Information: Focus on what is surprising in data
– Reliably store or transmit information
• Control
– Extract what is useful (not merely surprising)
– Compute decisions from useful information
– Take appropriate action

Theoretical foundations

- Control theory: feedback, optimization, games
- Information theory: source and channel coding
- Computational complexity: decidability, P-NP-coNP-…

- Dynamical systems: dynamics, bifurcation, chaos
- Statistical physics: phase transitions, critical phenomena, multiscale physics

- These are largely fragmented within isolated technical disciplines.
- Unified theory would be both intellectually satisfying and of enormous practical value.

Complexity and robustness

- Complexity ***phenotype*** : robust, yet fragile
- Complexity ***genotype***: internally complicated
- New theoretical framework: HOT (Highly optimized tolerance, with Jean Carlson, Physics, UCSB)
- Applies to biological and technological systems
  - Pre-technology: simple tools
  - Primitive technologies use simple strategies to build fragile machines from precision parts.
  - Advanced technologies use complicated architectures to create robust systems from sloppy components…
  - … but are also vulnerable to cascading failures…

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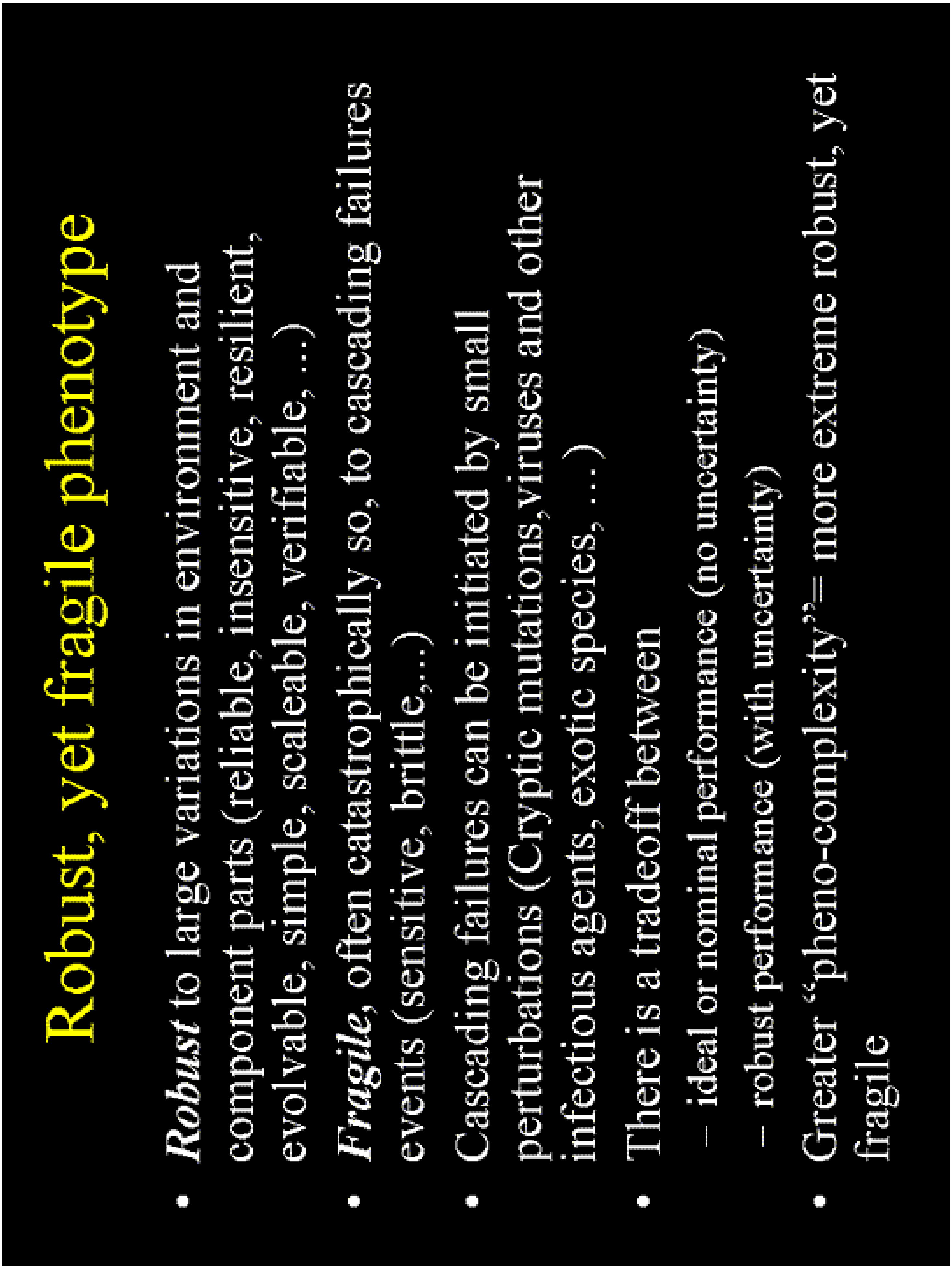
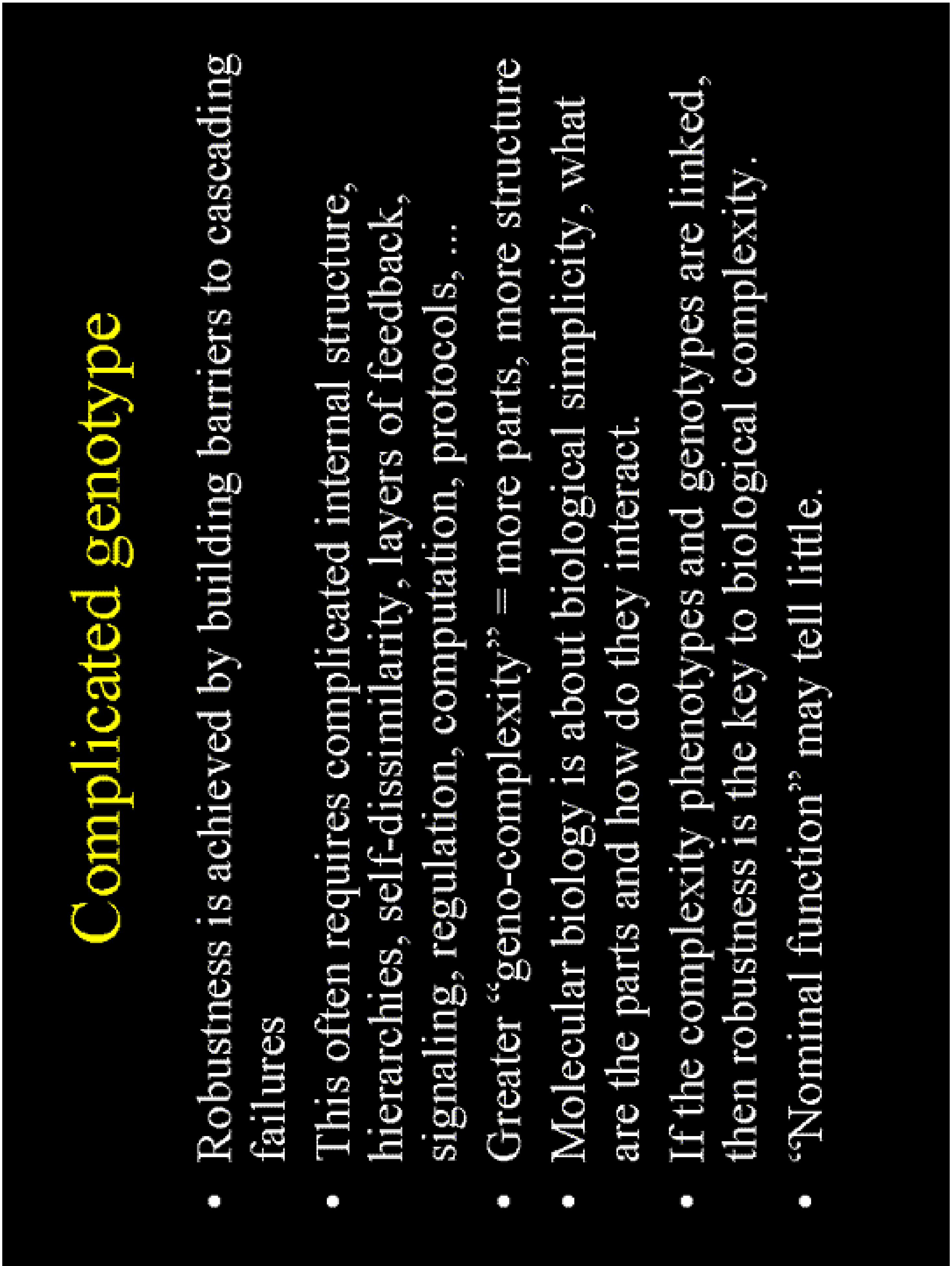
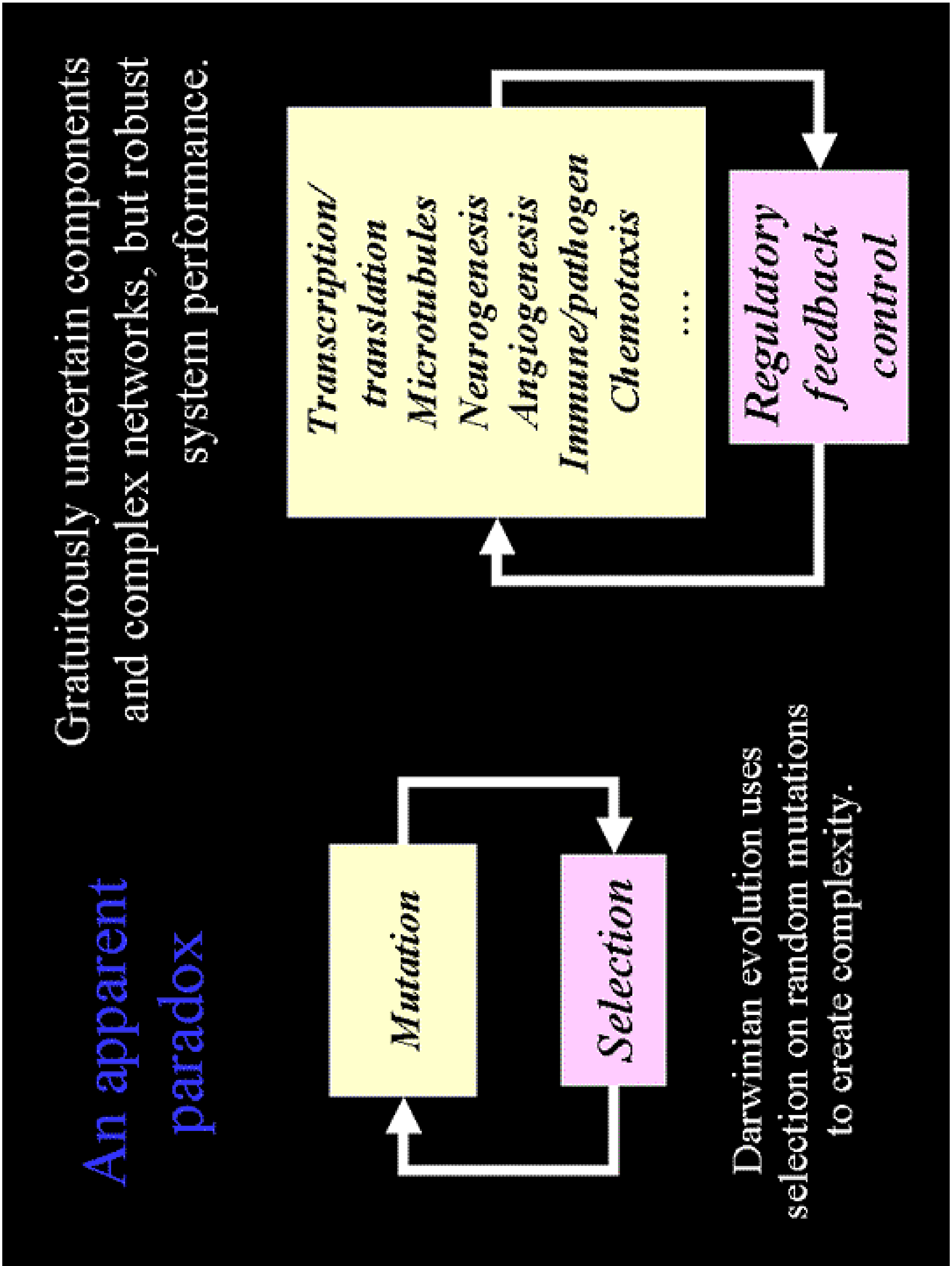
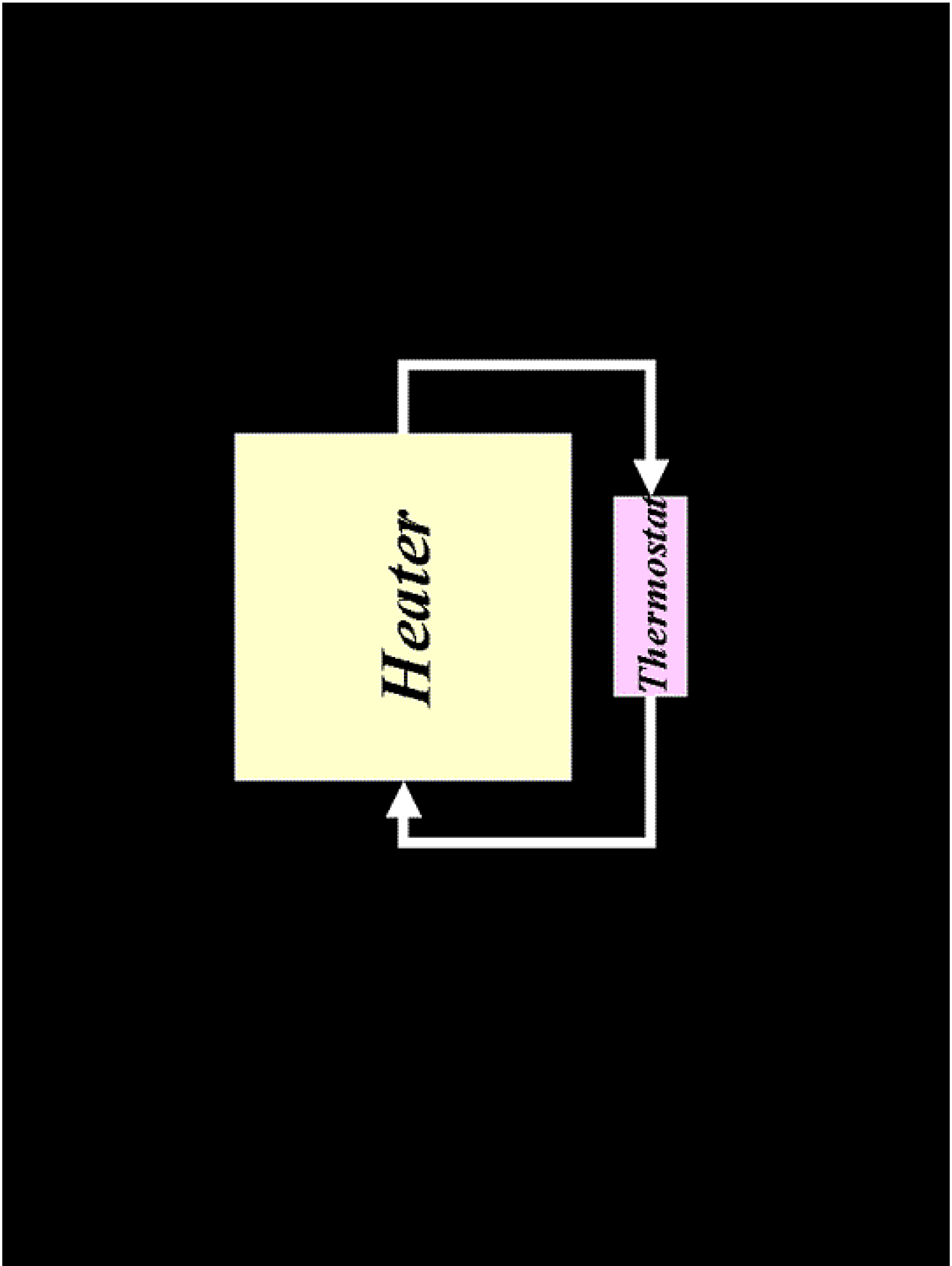


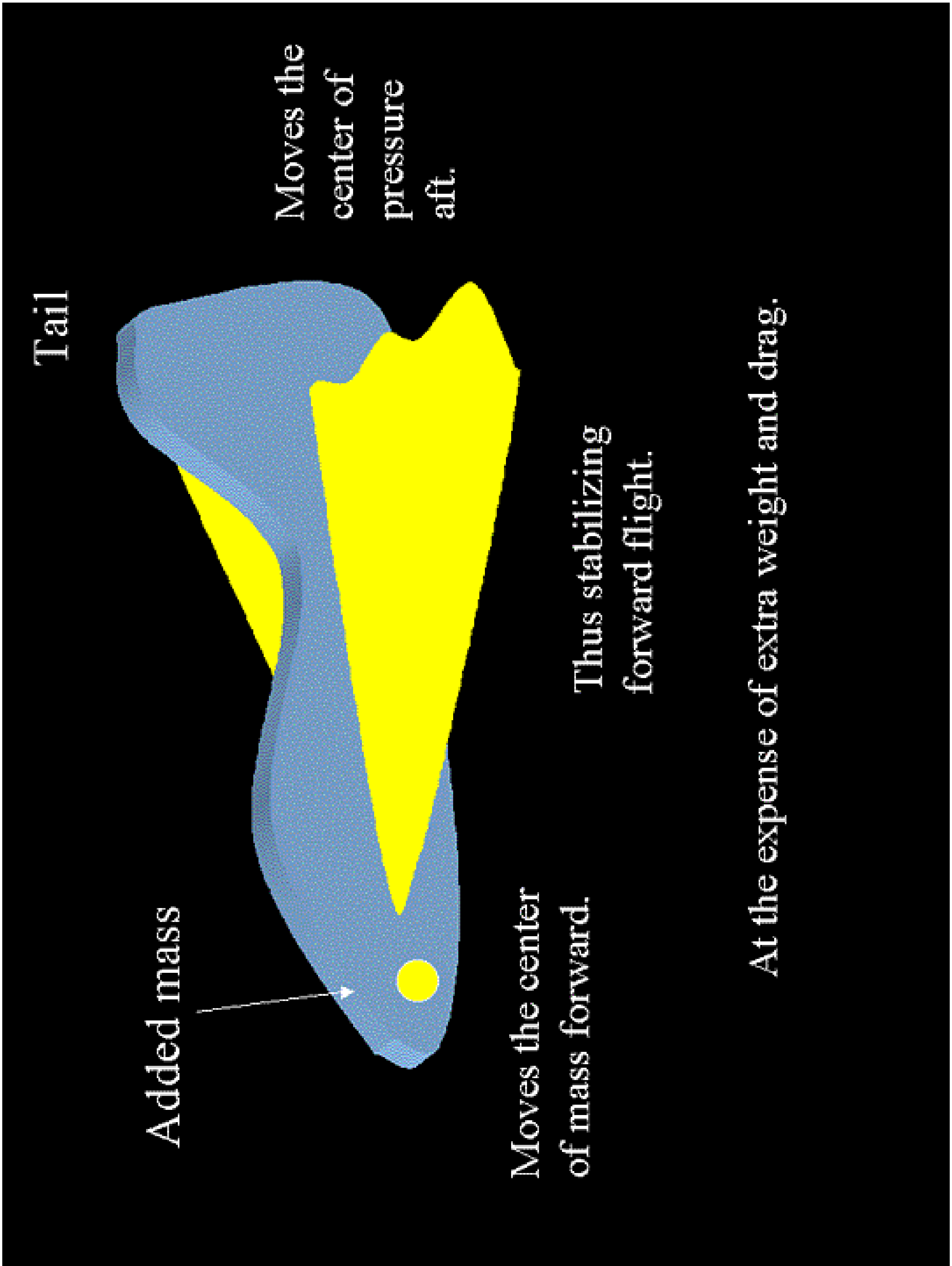
Robust, yet fragile phenotype

- Robustness is not just to genetic variation, but includes perturbations to both components and environment
- Cascading failures can be initiated by small perturbations (Cryptic mutations,viruses and other infectious agents, exotic species, …) or large
- In many complex systems, the size of cascading failure events are often unrelated to the size of the initiating perturbations
- Fragility is most interesting when it does not arise because of large perturbations, but catastrophic responses to small variations


Complicated genotype
• Robustness is achieved by building barriers to cascading failures
• This often requires complicated internal structure, hierarchies, self-dissimilarity, layers of feedback, signaling, regulation, computation, protocols, ...
• Greater "geno-complexity" = more parts, more structure
• Molecular biology is about biological simplicity, what are the parts and how do they interact.
• If the complexity phenotypes and genotypes are linked, then robustness is the key to biological complexity.
• "Nominal function" may tell little.

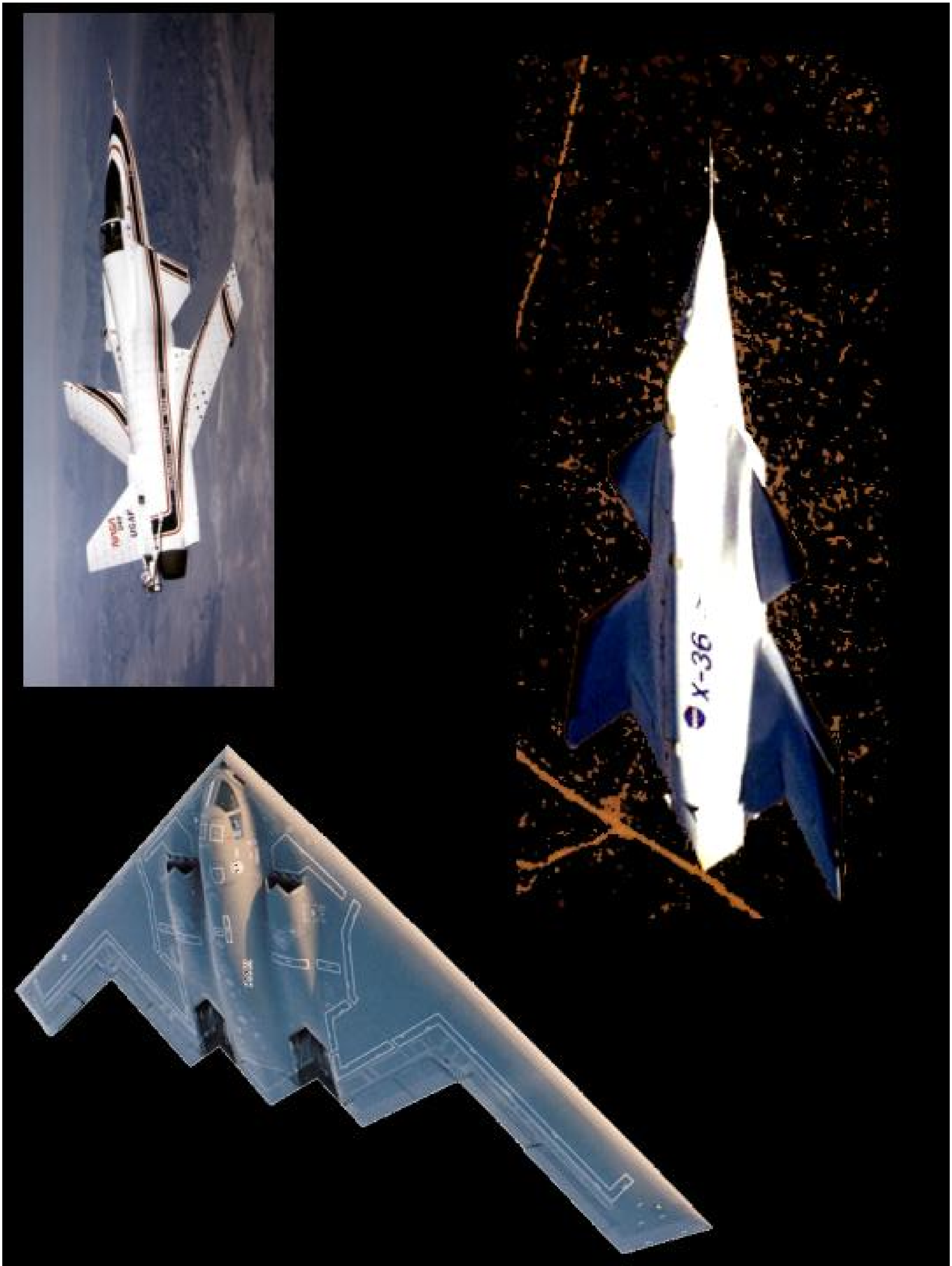

An apparent paradox
Gratuitously uncertain components and complex networks, but robust system performance.
Mutation
Selection
Darwinian evolution uses selection on random mutations to create complexity.
Transcription/
translation
Microtubules
Neurogenesis
Angiogenesis
Immune/pathogen
Chemotaxis
....
Regulatory
feedback
control


Heater
Thermostat


Tail
Moves the
center of
pressure
aft.
Added mass
Moves the center
of mass forward.
Thus stabilizing
forward flight.
At the expense of extra weight and drag.


For minimum weight & drag,
(and other performance issues)
eliminate fuselage and tail.

[52] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



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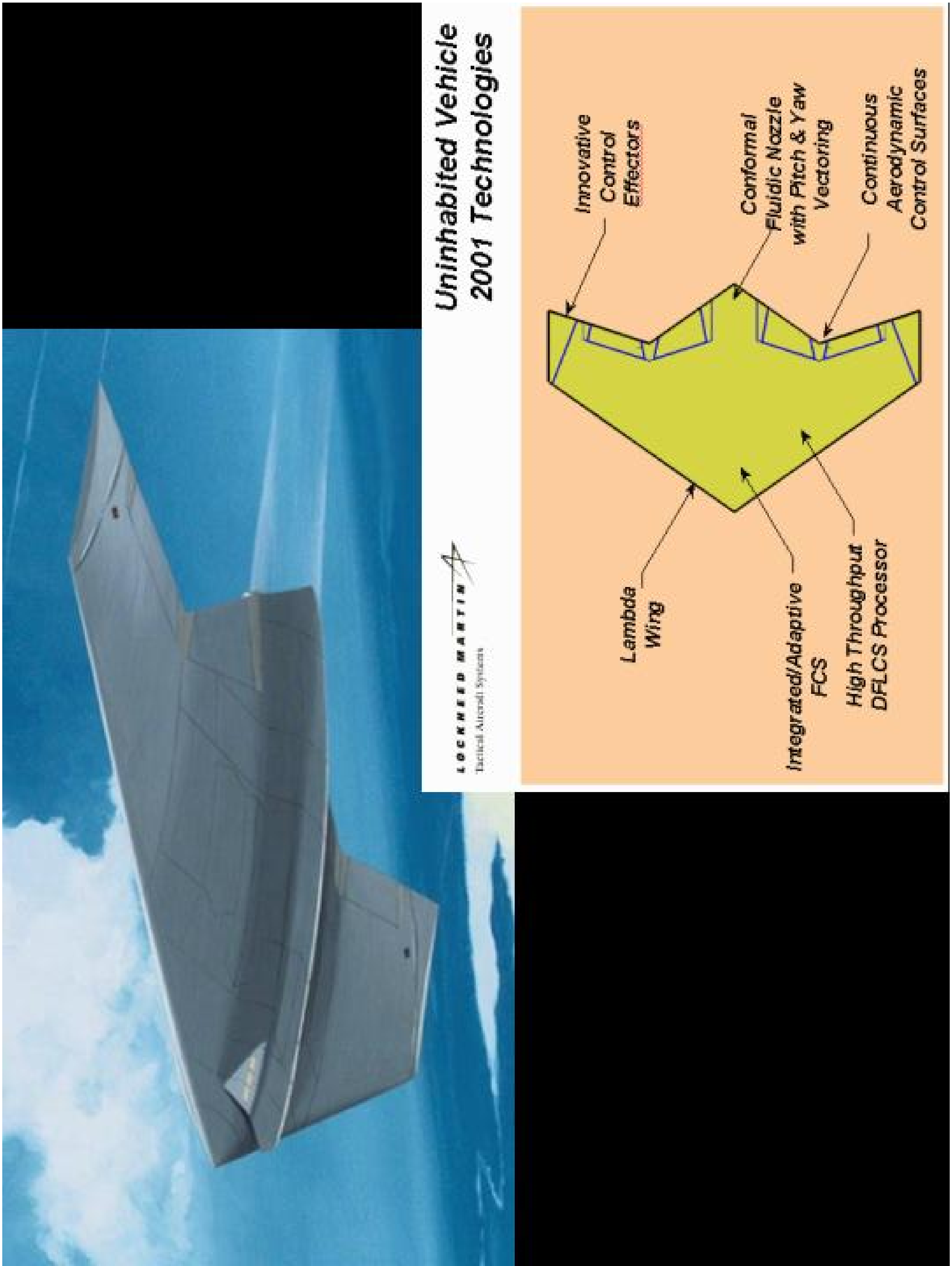
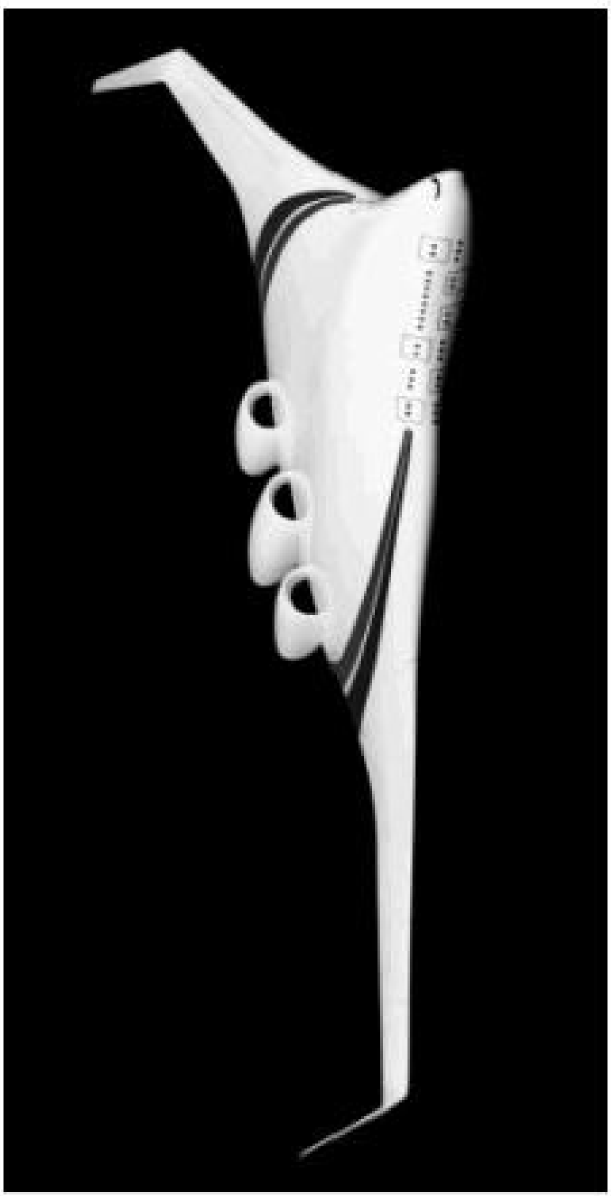
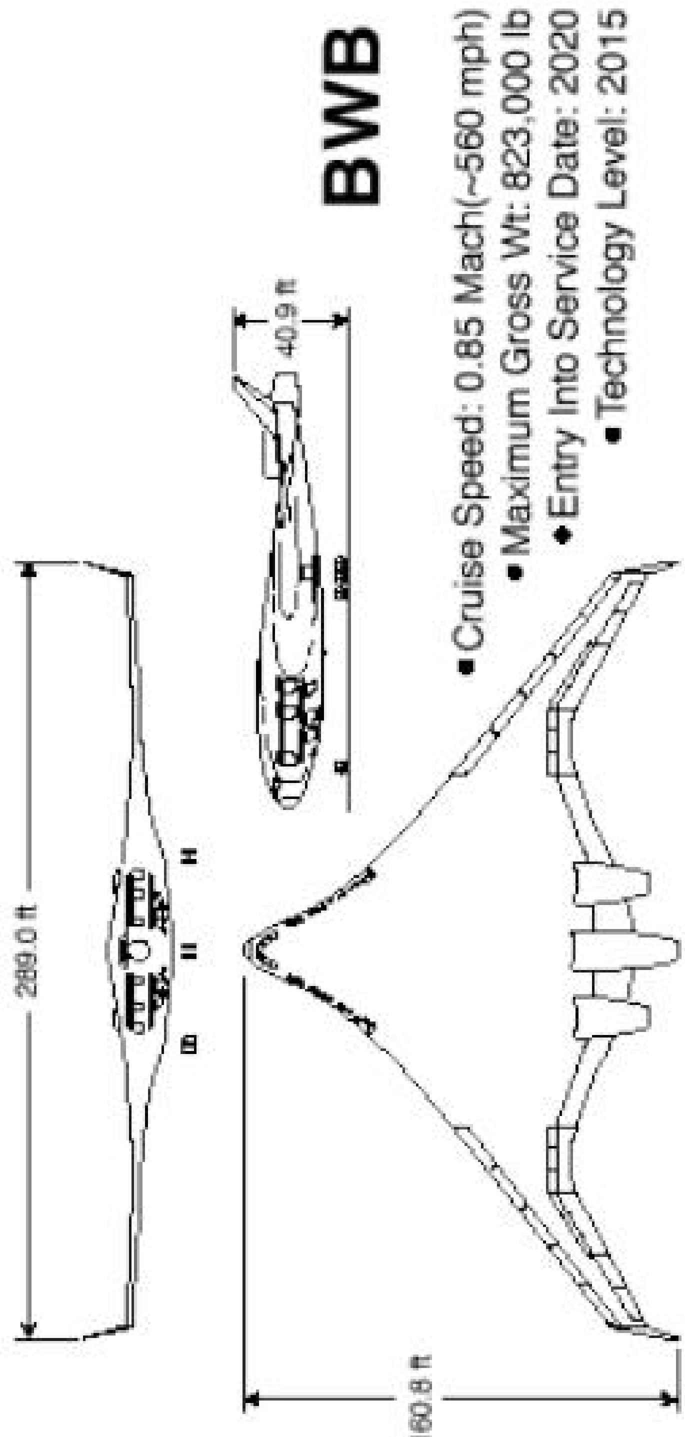
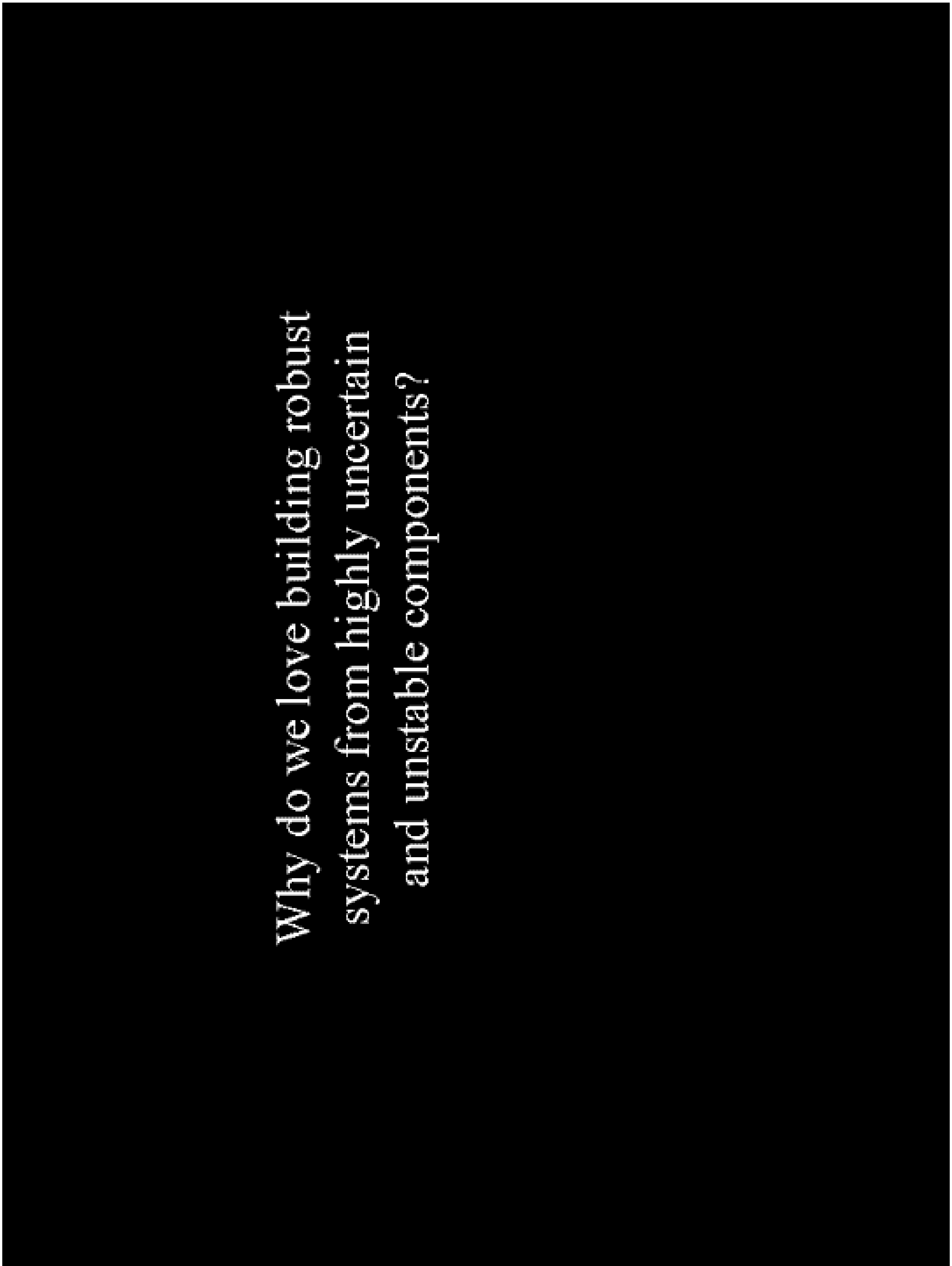
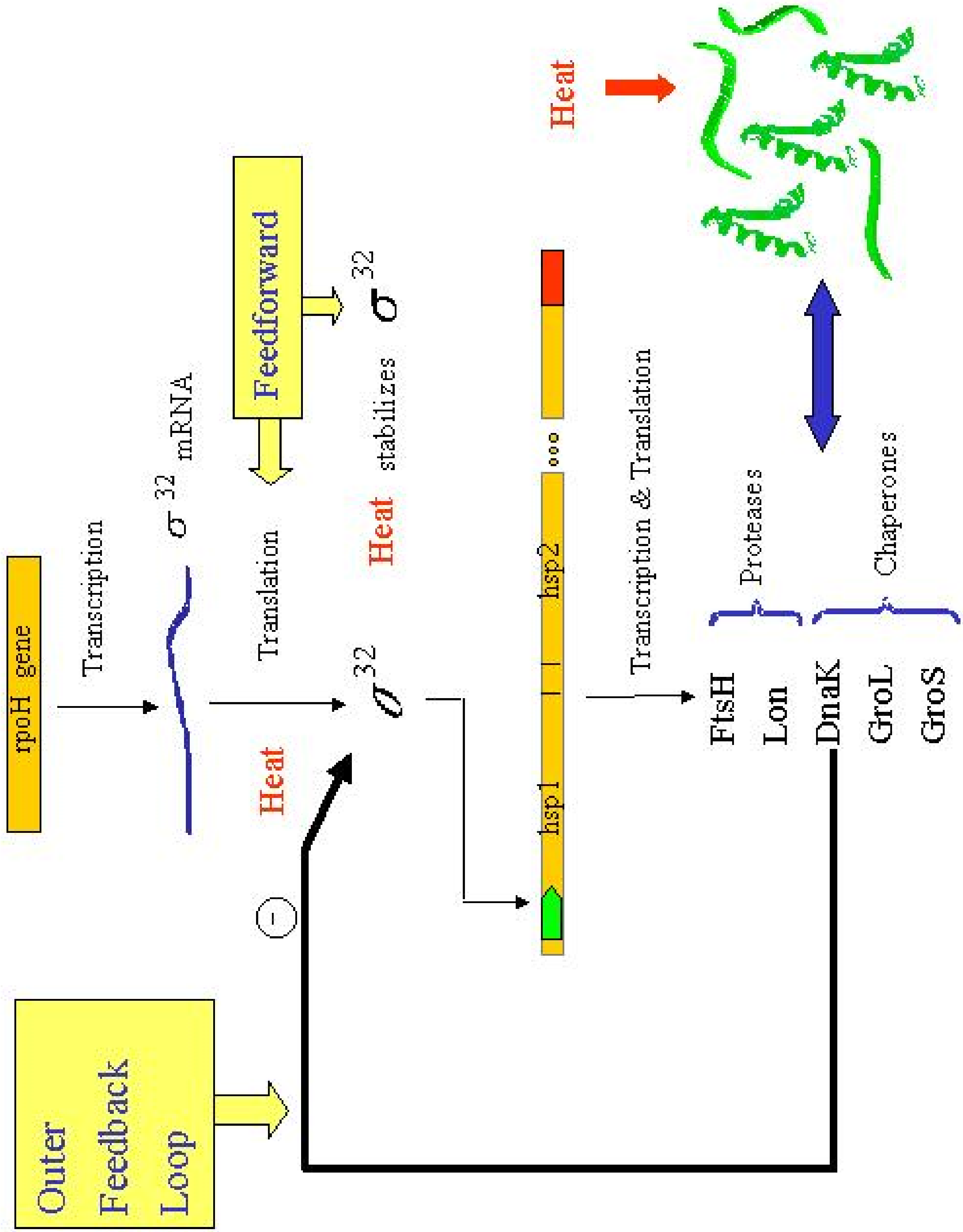
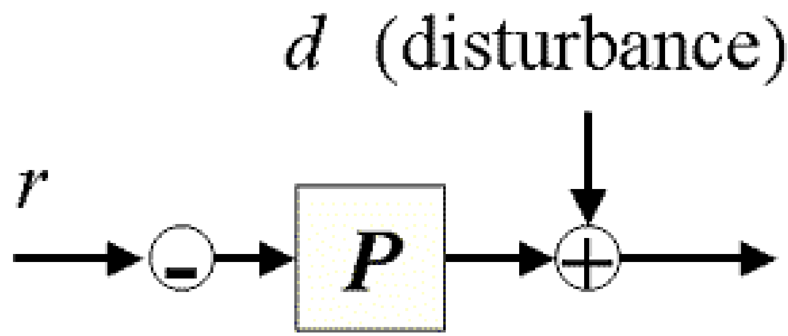





BWB
• Cruise Speed: 0.85 Mach(~560 mph)
• Maximum Gross Wt: 823,000 lb
• Entry Into Service Date: 2020
• Technology Level: 2015
40.9 ft
289.0 ft
160.8 ft


Why do we love building robust
systems from highly uncertain
and unstable components?


rpoH gene
Transcription
σ 32 mRNA
Translation
Heat
σ 32
Feedforward
Heat
stabilizes
σ 32
hsp1
hsp2
Heat
Transcription & Translation
Proteases
Chaperones
FtsH
Lon
DnaK
GroL
GroS
Outer
Feedback
Loop



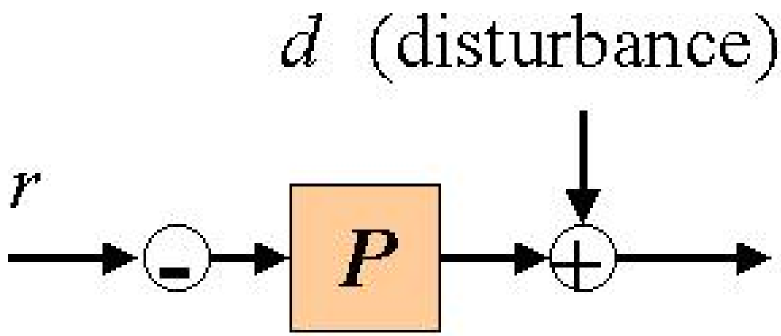
$$y = P(r) + d$$

Assumptions on components:

- Everything just numbers
- Uncertainty in P
- Higher gain = more uncertain

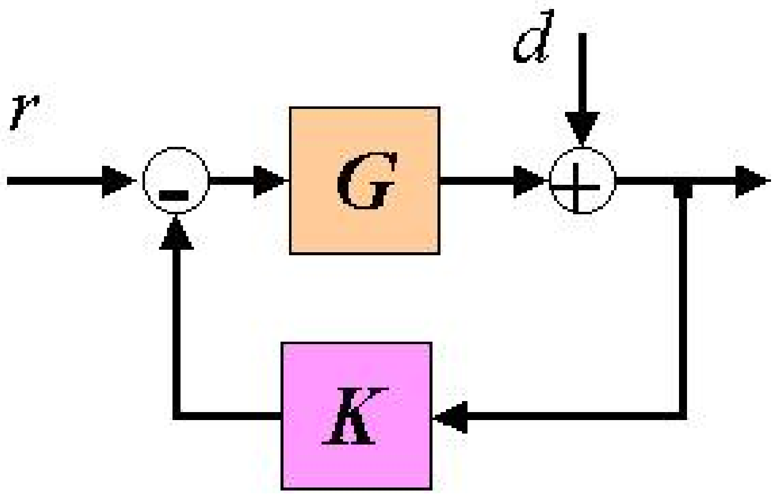
$$y = (P + \Delta P)r + d$$

$$P_1 > P_2 \Rightarrow \frac{\Delta P_1}{P_1} > \frac{\Delta P_2}{P_2}$$



$$y = P(r) + d$$

Negative feedback

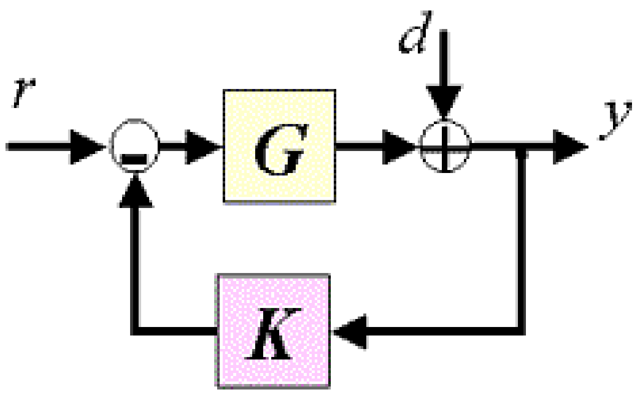


$$y = G\left(r - K(y + d)\right)$$

$$(1 + GK)y = G\left(r - Kd\right)$$

$$y = GSr + Sd = \frac{1}{K}(1 - S)r + Sd$$

$$S \,\square \left(\frac{1}{1 + GK}\right)$$



Design recipe:

- $1 >> K >> 1/G$
- $G >> 1/K >> 1$
- G maximally uncertain!
- K small, low uncertainty

$$G >> \frac{1}{K} > 1 \quad \Rightarrow \quad GK >> 1$$

$$\Rightarrow \quad S << 1 \quad \Rightarrow \quad y \approx \frac{1}{K} r$$

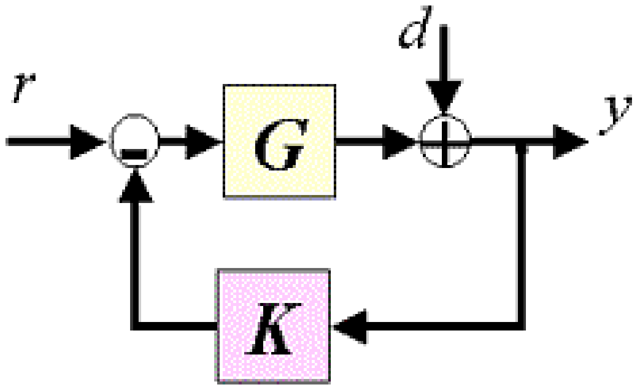
Results for $y \approx (1/K)r$:

- high gain
- low uncertainty
- d attenuated

$$y = GSr + Sd = \frac{1}{K}(1-S)r + Sd$$

$$S \square \left(\frac{1}{1+GK} \right)$$

S = sensitivity function



Design recipe:

- $1 >> K >> 1/G$
- $G >> 1/K >> 1$
- G maximally uncertain!
- K small, low uncertainty

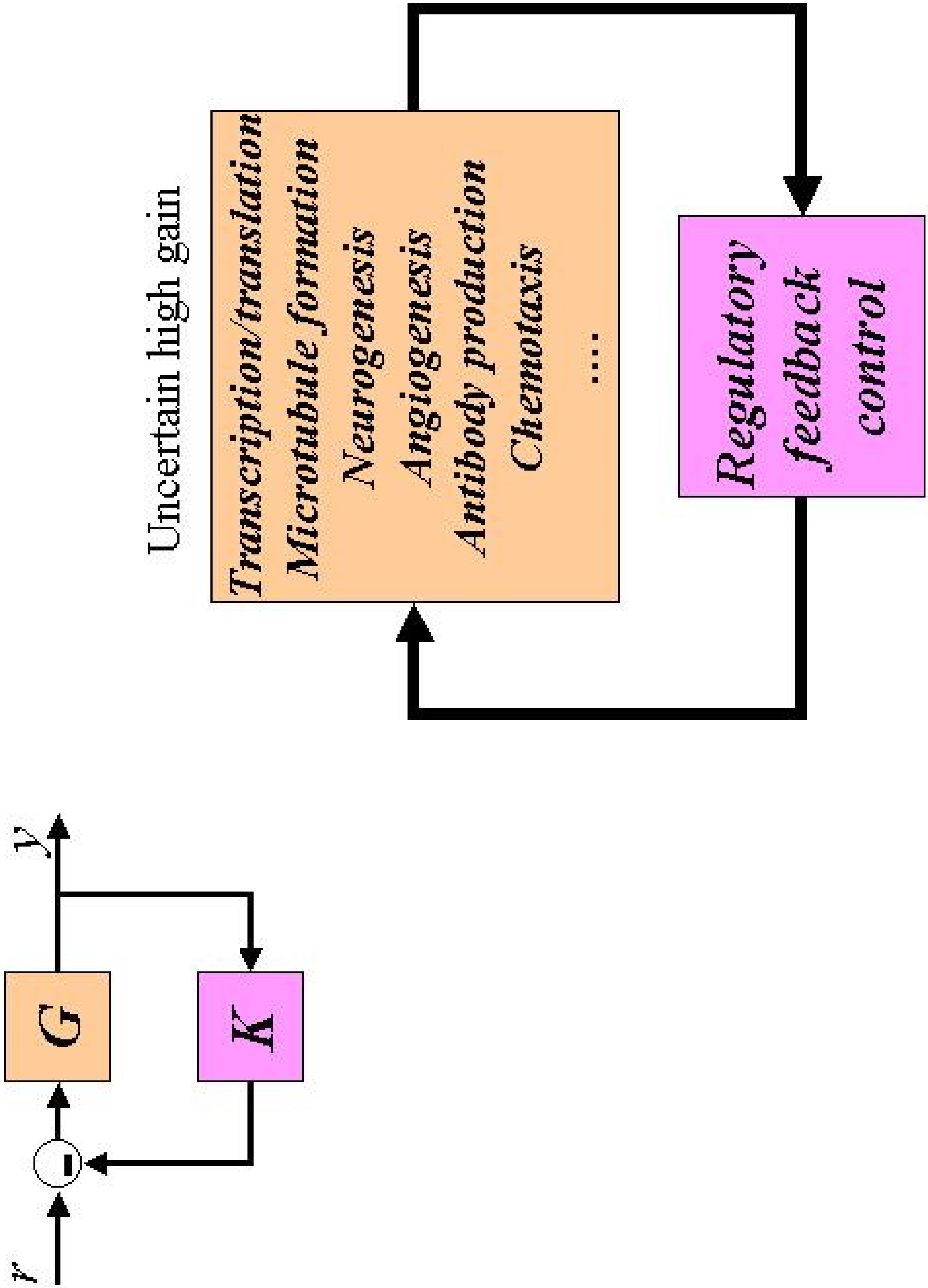
Extensions to:

- Dynamics
- Multivariable
- Nonlinear
- Structured uncertainty

All cost more computationally.

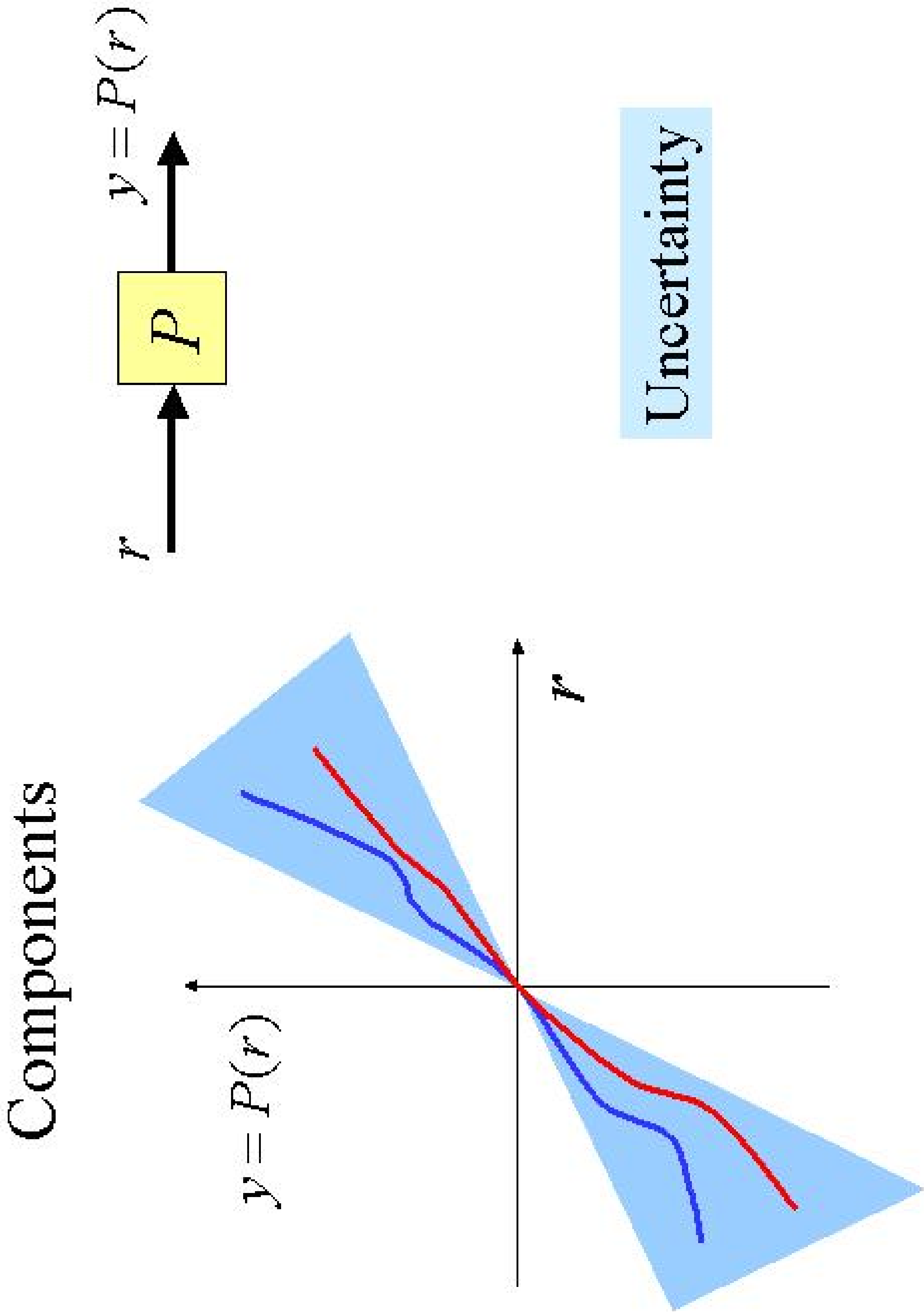
Results for $y \approx (1/K)r$:

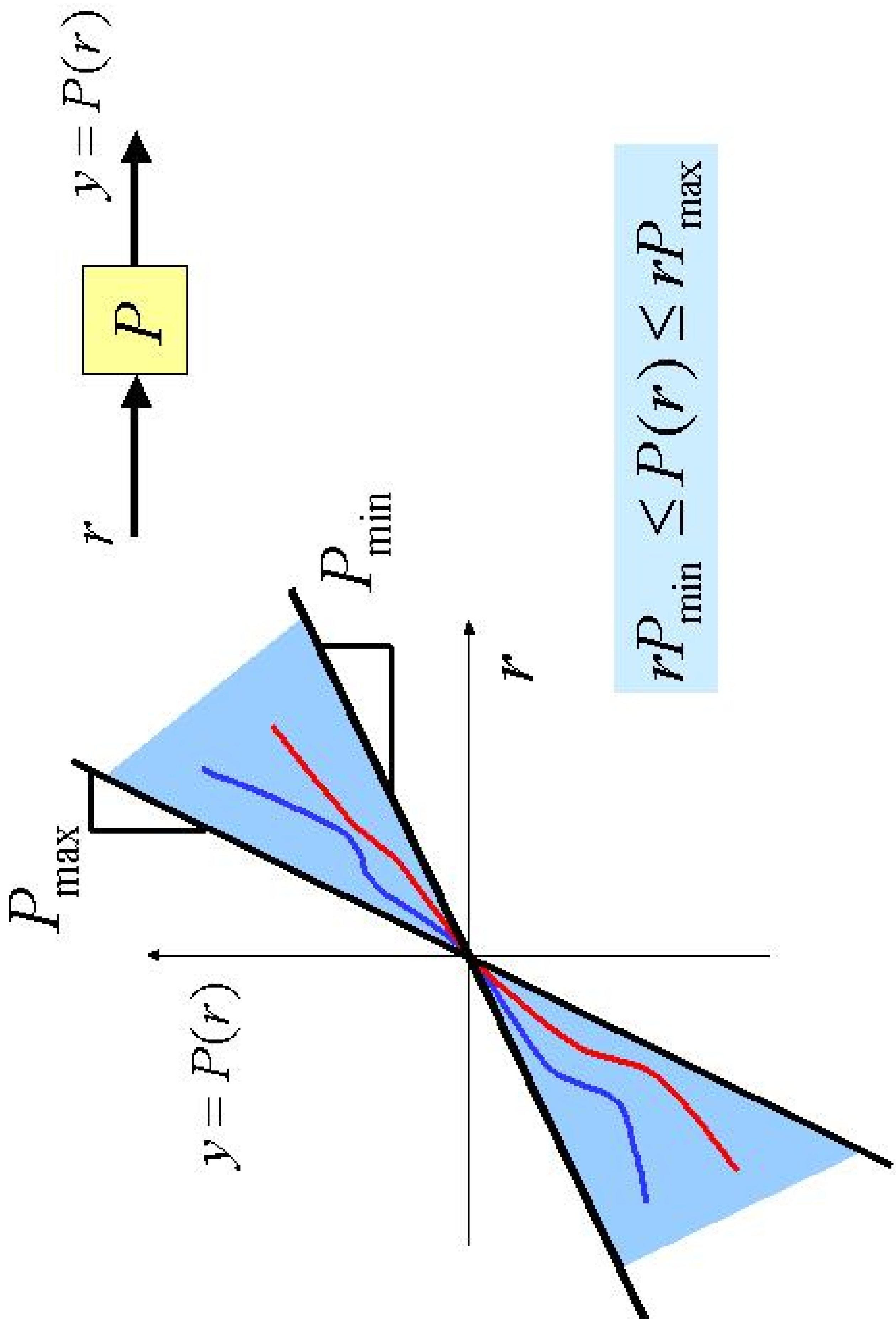
- high gain
- low uncertainty
- d attenuated


Uncertain high gain
Transcription/translation
Microtubule formation
Neurogenesis
Angiogenesis
Antibody production
Chemotaxis
….
Regulatory
feedback
control
r
G
K
y

[63] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

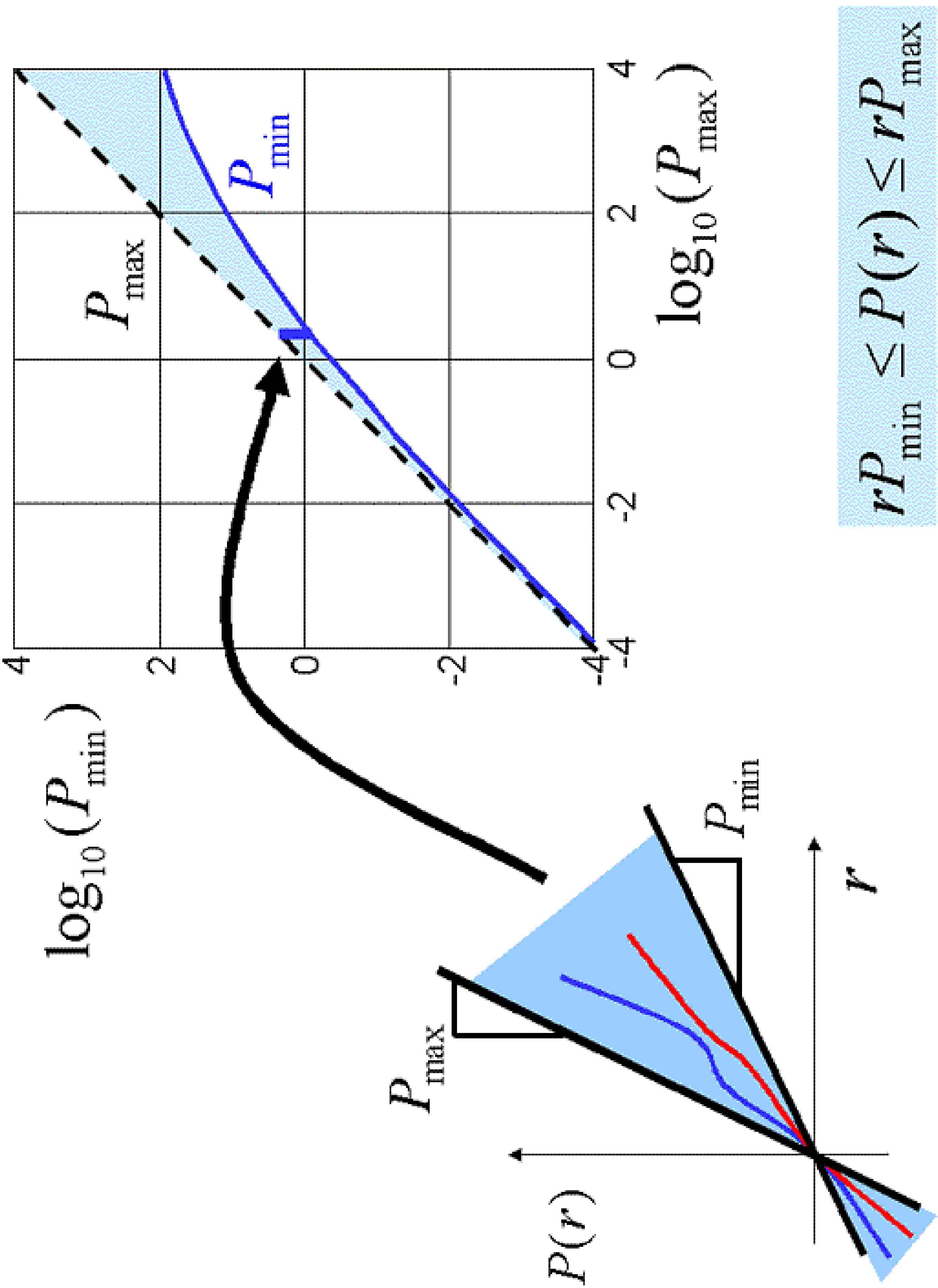
A slightly more detailed description….

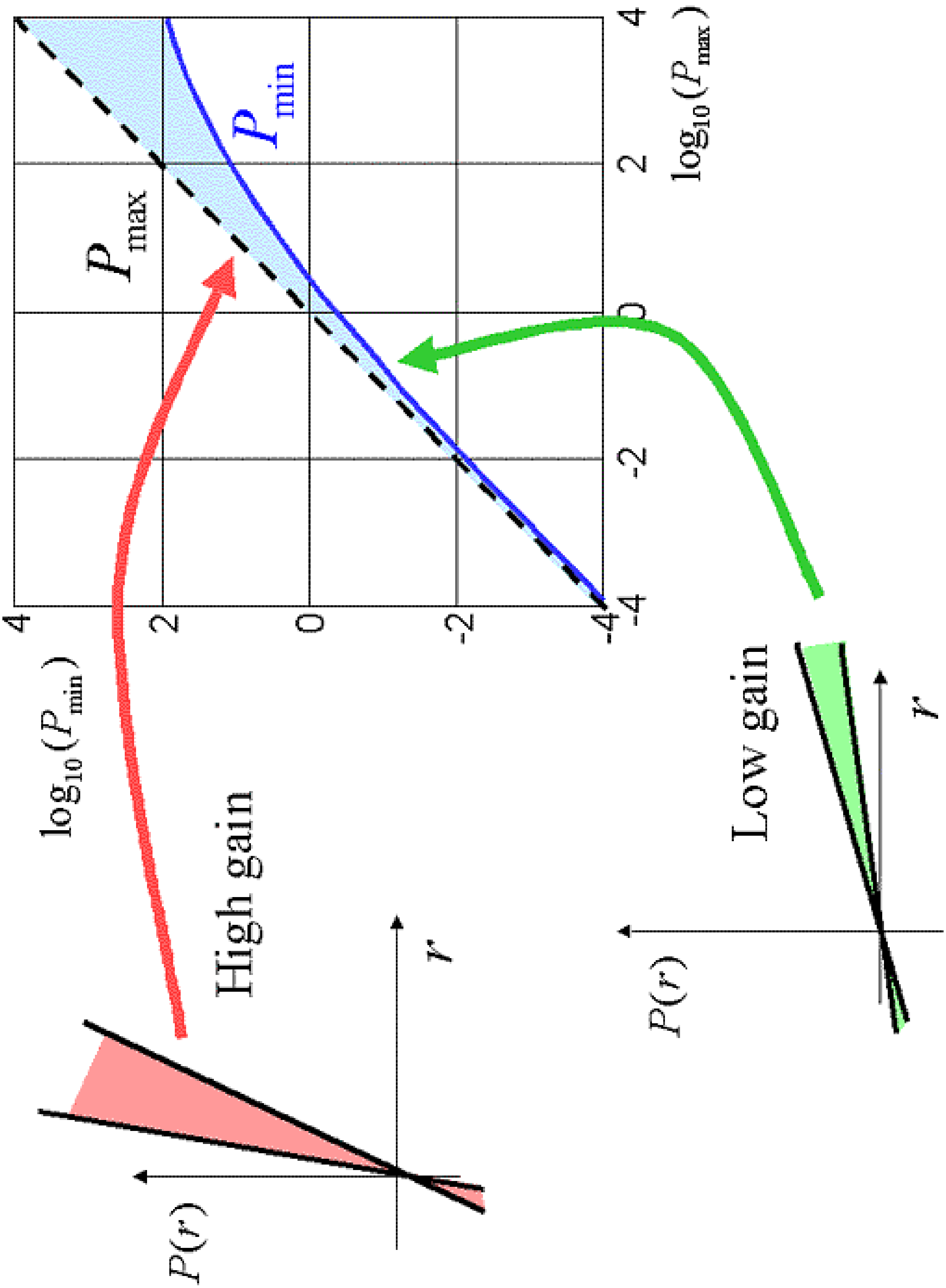

Components
Uncertainty
r
P
y = P(r)
y = P(r)
r



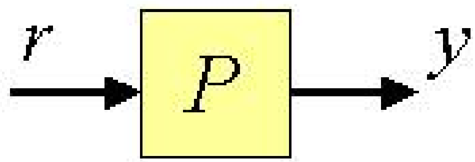
r
P
y = P(r)
P_max
P_min
r
y = P(r)
rP_min ≤ P(r) ≤ rP_max

[66] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



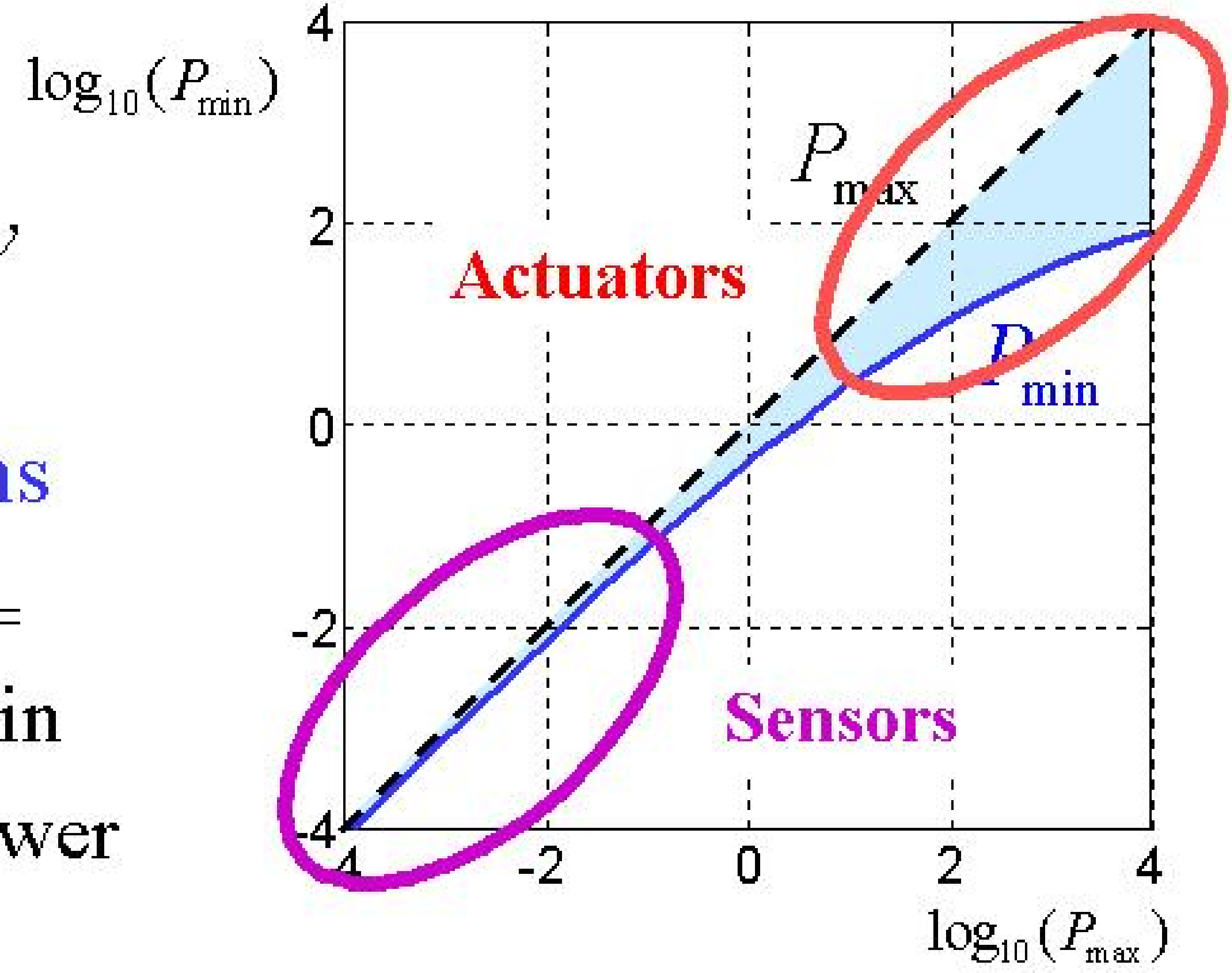


P_max
P_min
log10(P_max)
log10(P_min)
High gain
Low gain
P(r)
r
4
2
0
-2
-4

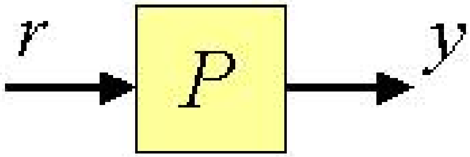


Assumptions

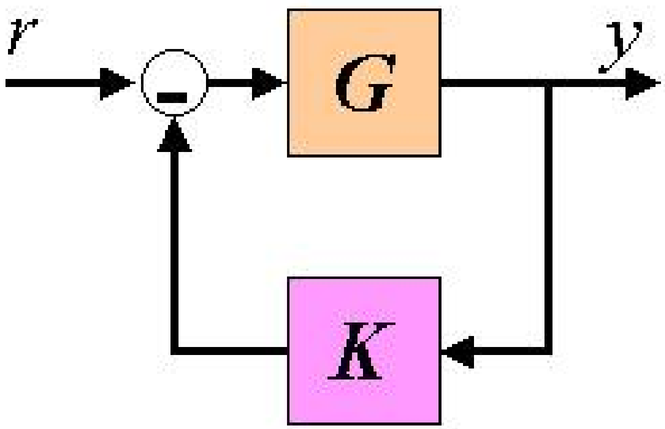
- Higher gain = more uncertain
- Upper and lower limits on achievable P_{max}



Negative feedback

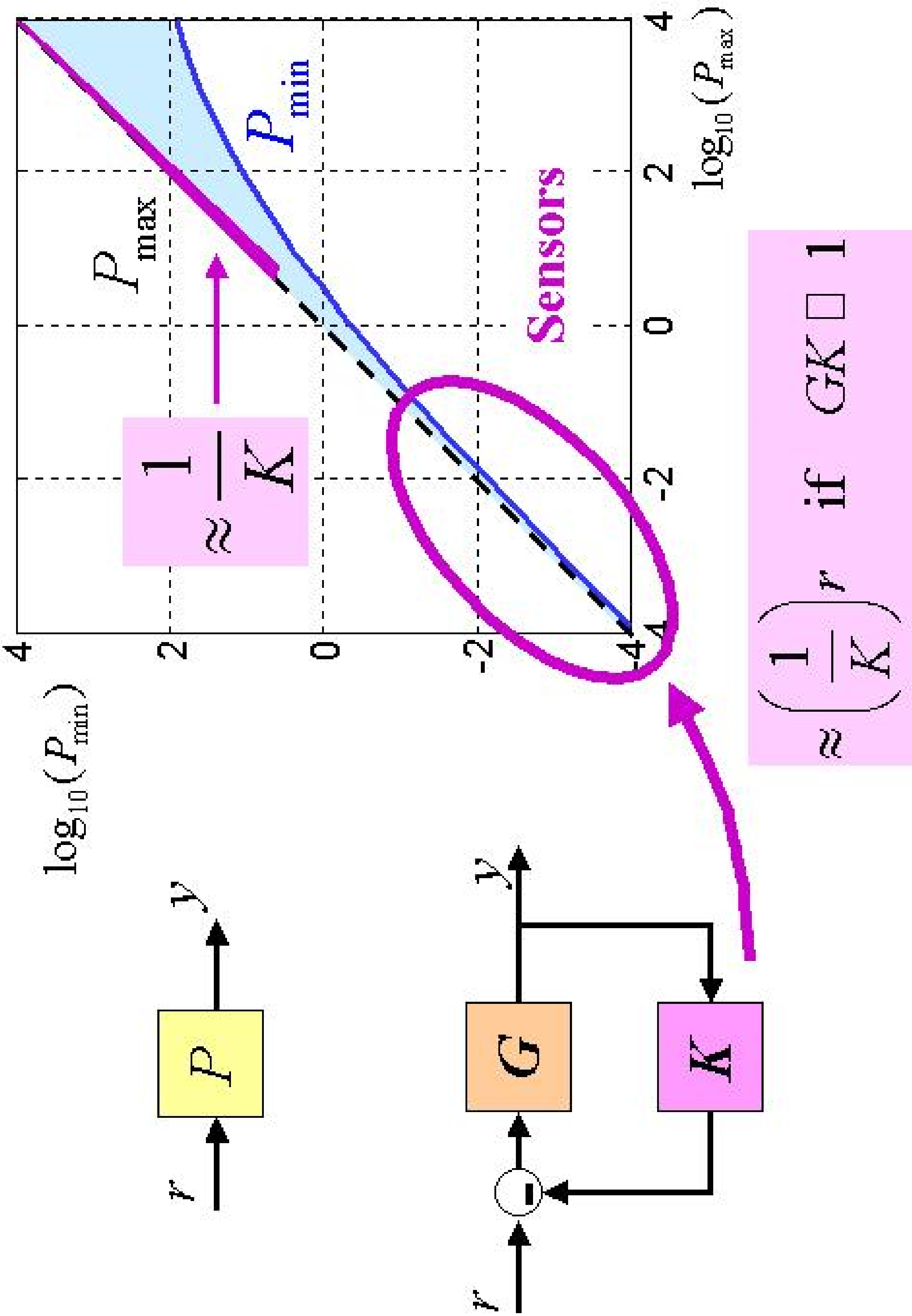


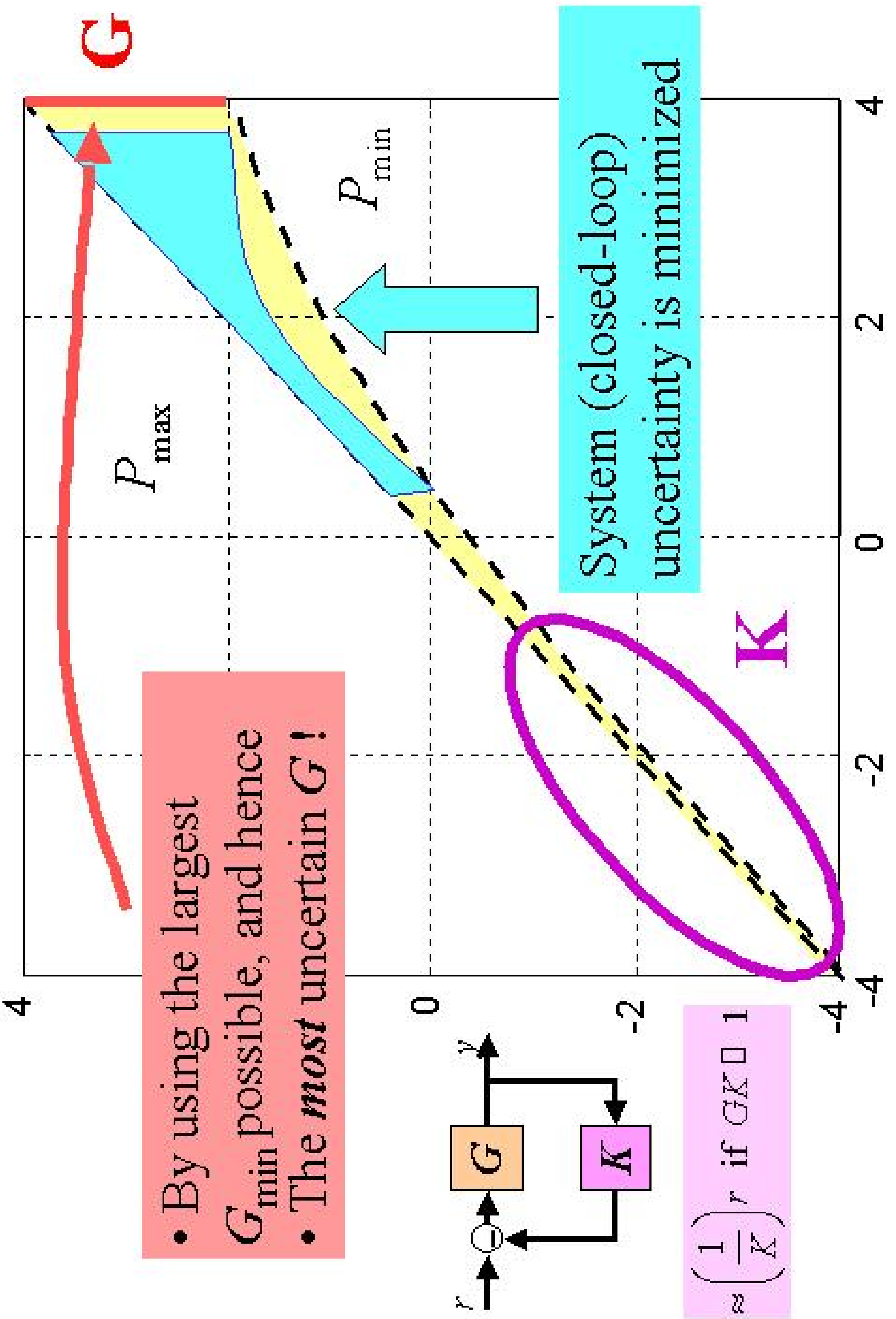
$$y = G\left(r - GK(y)\right)$$

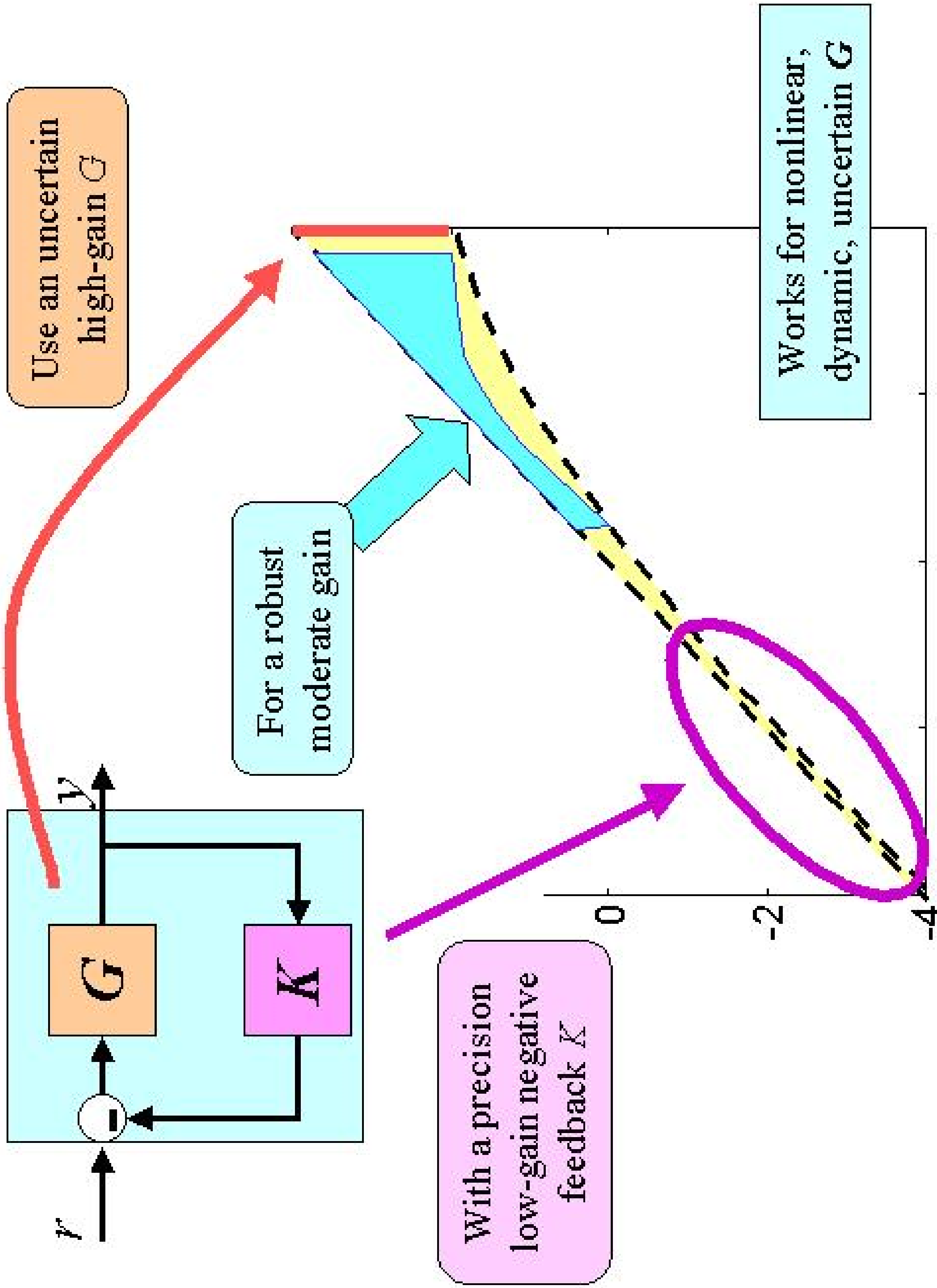


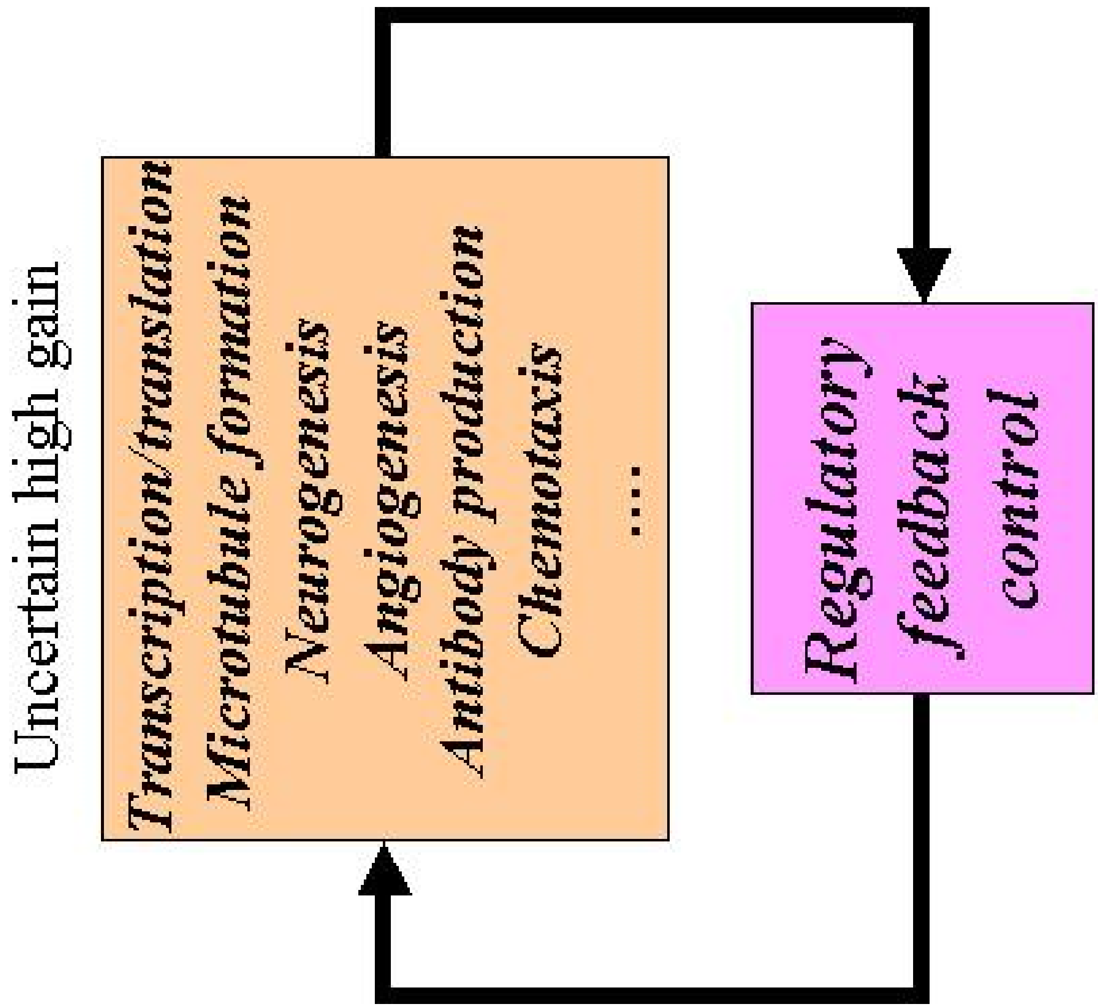
$$y \approx \left(\frac{G}{1+GK}\right)r = \left(\frac{1}{1/G+K}\right)r$$

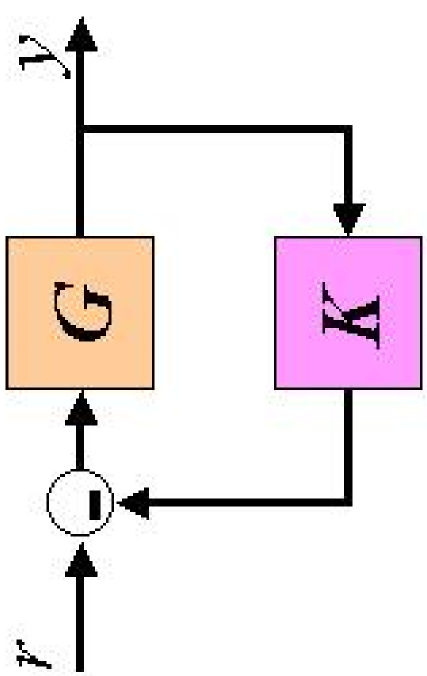
$$\approx \left(\frac{1}{K}\right)r \quad \text{if} \quad GK \gg 1$$

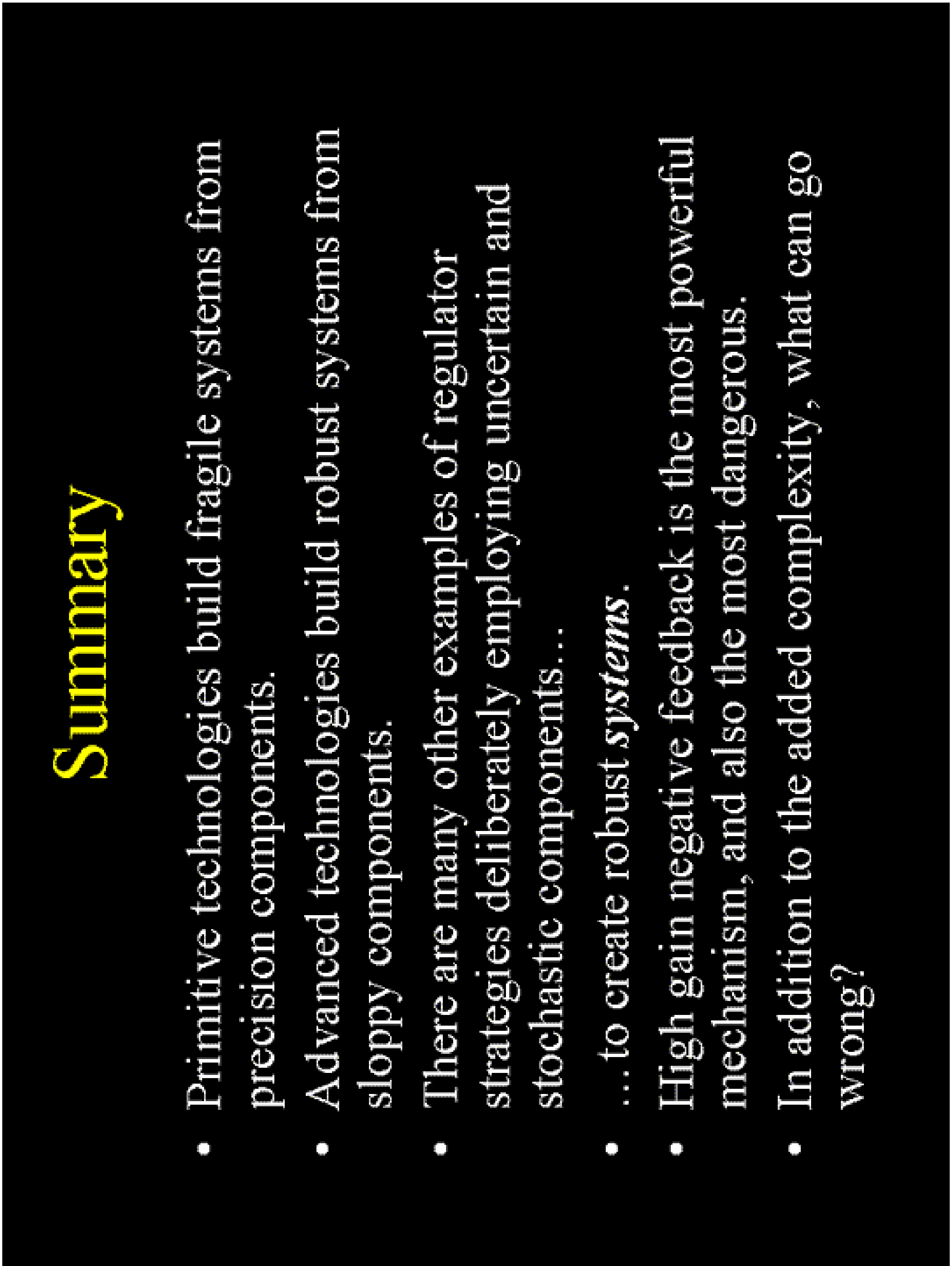

log10(Pmin)
log10(Pmax)
4
2
0
-2
-4
Pmax
Pmin
≈ 1/K
Sensors
≈ (1/K) r if GK □ 1
r
P
y
G
K
-

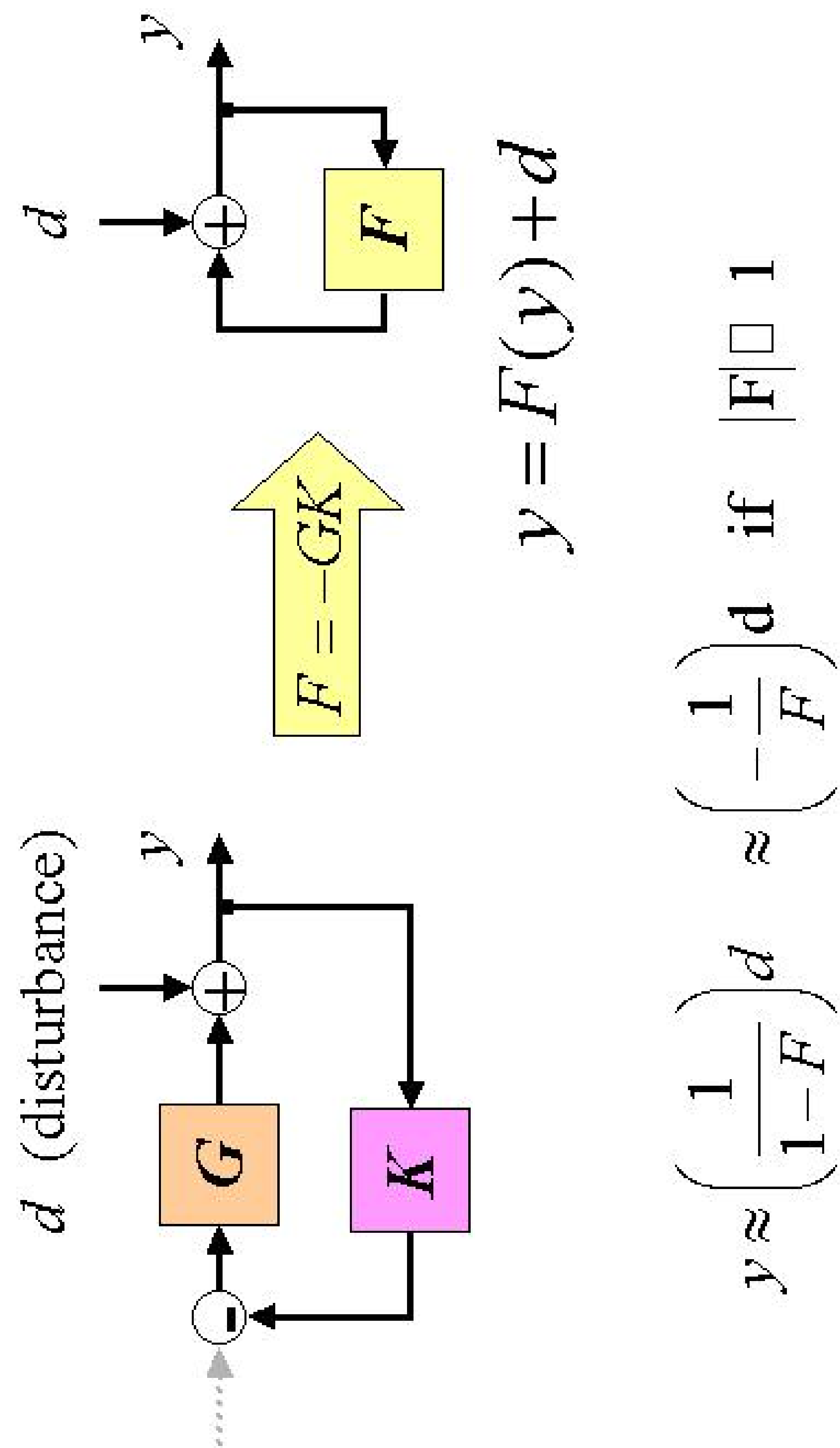

G
K
System (closed-loop) uncertainty is minimized
• By using the largest G_min possible, and hence
• The most uncertain G!
P_max
P_min
G
K
if GK 1


Use an uncertain high-gain G
For a robust moderate gain
With a precision low-gain negative feedback K
Works for nonlinear, dynamic, uncertain G
r
y
G
K
-4
-2
0
2
4

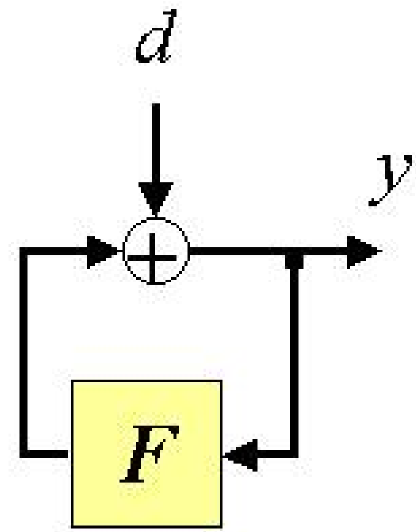

Uncertain high gain
Transcription/translation
Microtubule formation
Neurogenesis
Angiogenesis
Antibody production
Chemotaxis
....
Regulatory
feedback
control


y
G
K
-
r


Summary
• Primitive technologies build fragile systems from precision components.
• Advanced technologies build robust systems from sloppy components.
• There are many other examples of regulator strategies deliberately employing uncertain and stochastic components…
• …to create robust systems.
• High gain negative feedback is the most powerful mechanism, and also the most dangerous.
• In addition to the added complexity, what can go wrong?


d (disturbance)
y
G
K
F = −GK
d
y
F
y = F(y)+d
y ≈ (1/(1−F)) d ≈ (−1/F) d if |F| ≫ 1

$$y \approx \left(\frac{1}{1-F} \right) d$$



If y, d and F are just numbers:

$$S \equiv \frac{y}{d} = \frac{1}{1-F}$$

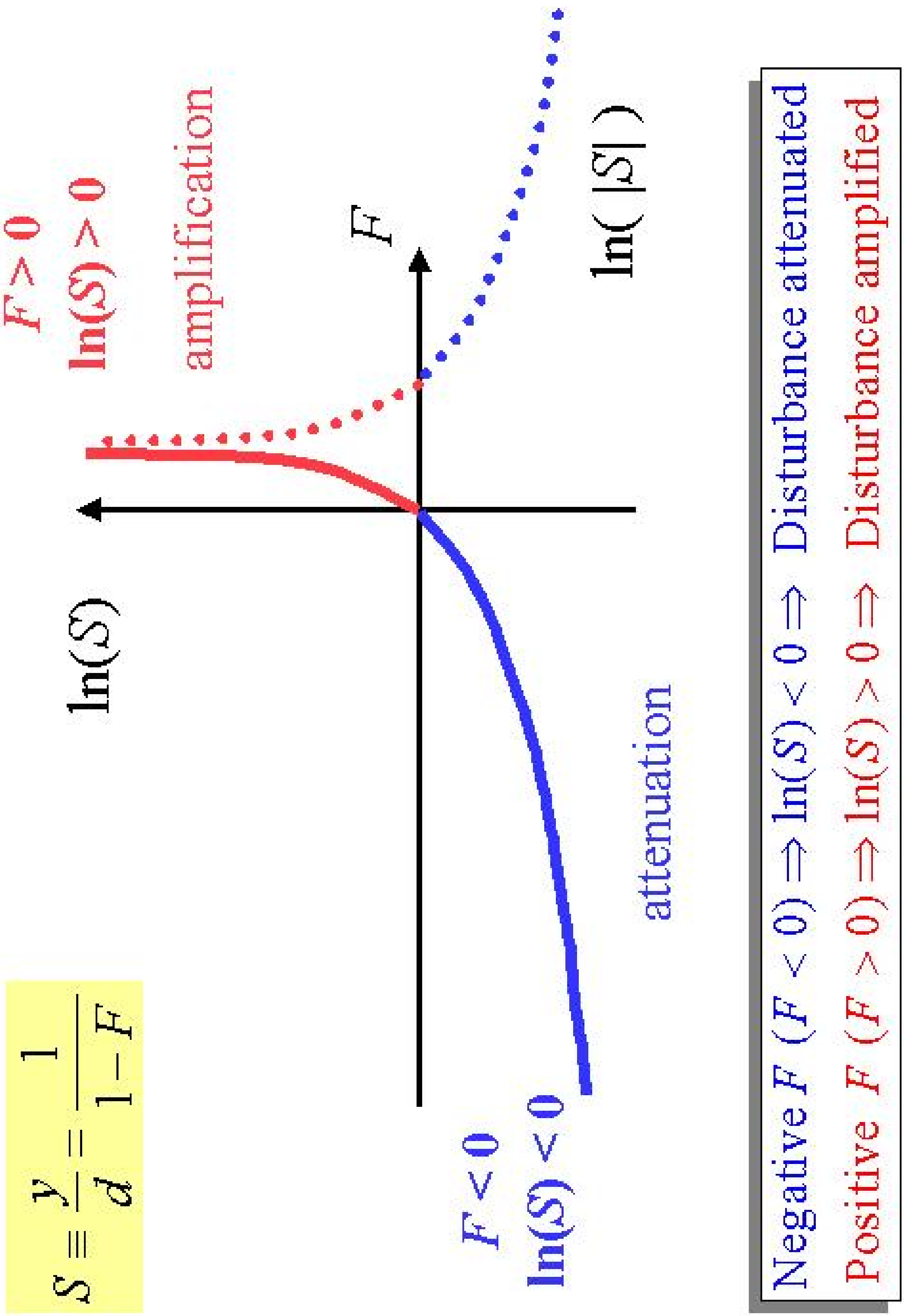
S measures disturbance rejection.

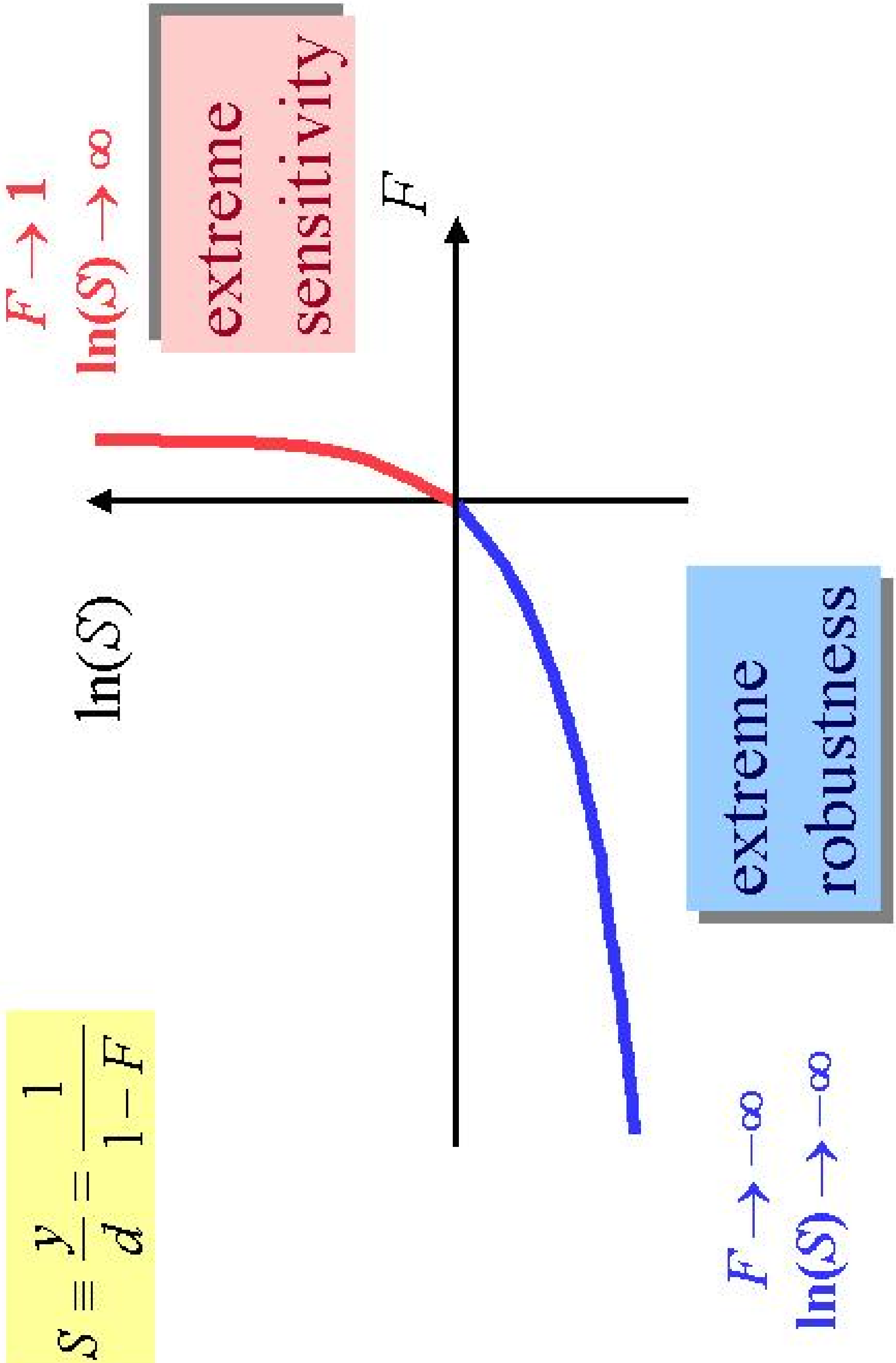
S = *sensitivity function*

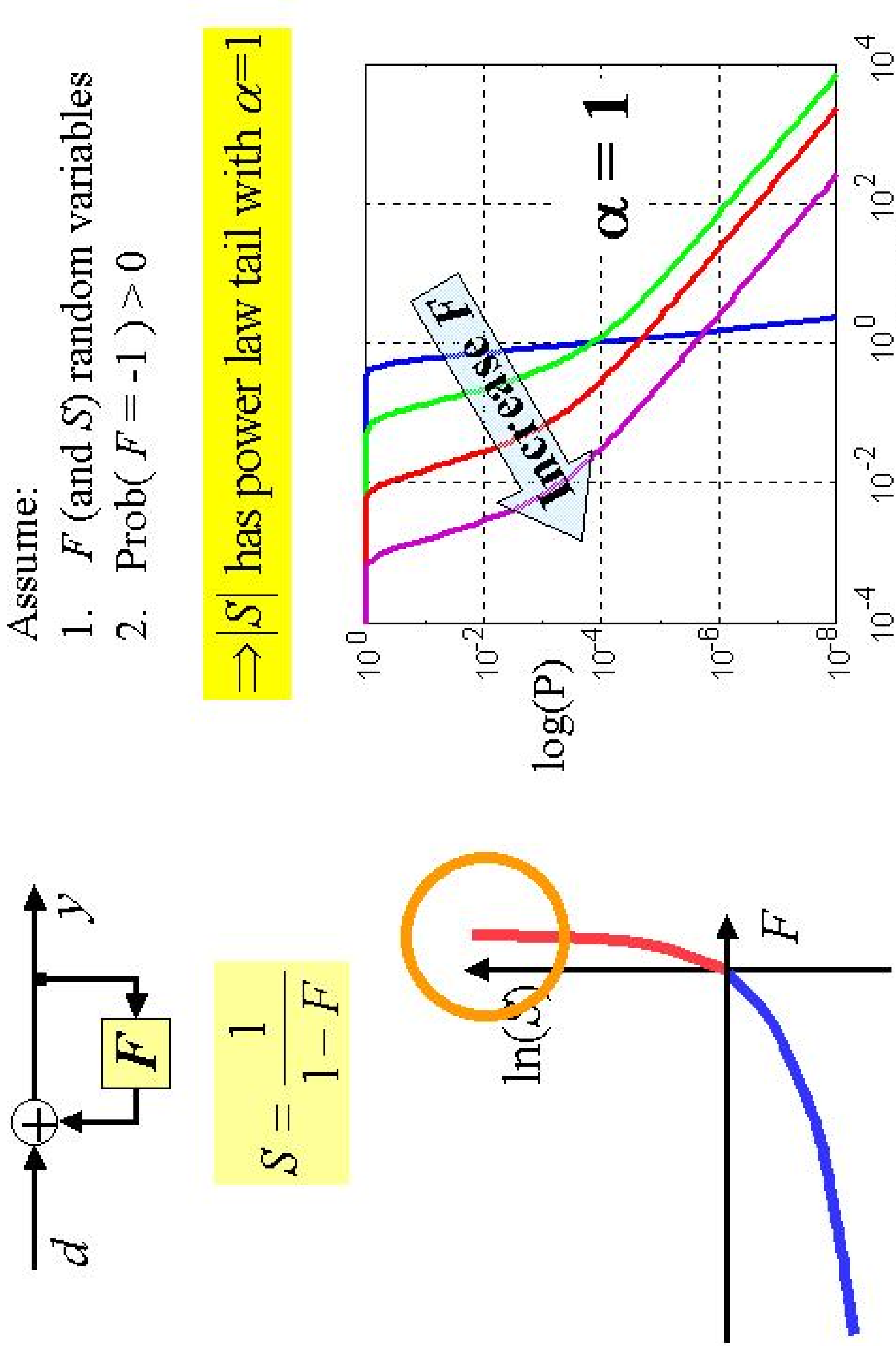
It's convenient to study $\ln(S)$.

Negative F $(F < 0) \Rightarrow \ln(S) < 0 \Rightarrow$ Disturbance attenuated

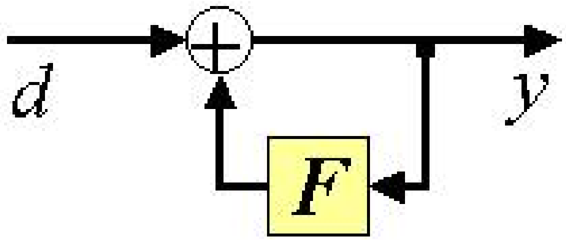
Positive F $(F > 0) \Rightarrow \ln(S) > 0 \Rightarrow$ Disturbance amplified


$F > 0$
$\ln(S) > 0$
amplification
F
$\ln(|S|)$
$\ln(S)$
attenuation
$F < 0$
$\ln(S) < 0$
$S \equiv \frac{y}{d} = \frac{1}{1-F}$
Negative F $(F < 0) \Rightarrow \ln(S) < 0 \Rightarrow$ Disturbance attenuated
Positive F $(F > 0) \Rightarrow \ln(S) > 0 \Rightarrow$ Disturbance amplified


$F \to 1$
$\ln(S) \to \infty$
extreme sensitivity
F
$\ln(S)$
extreme robustness
$F \to -\infty$
$\ln(S) \to -\infty$
$S \equiv \frac{y}{d} = \frac{1}{1-F}$



Assume:
1. F (and S) random variables
2. Prob(F = -1) > 0
⇒ |S| has power law tail with α=1
log(P)
10^0
10^-2
10^-4
10^-6
10^-8
10^-4
10^-2
10^0
10^2
10^4
log(S)
increase F
α = 1
d
y
F
S = 1/(1−F)
ln(S)
F



$$S = \frac{1}{1-F}$$

If these model physical processes, then d and y are signals and F is an operator. We can still define

$$S(\omega) = |Y(\omega)/D(\omega)|$$

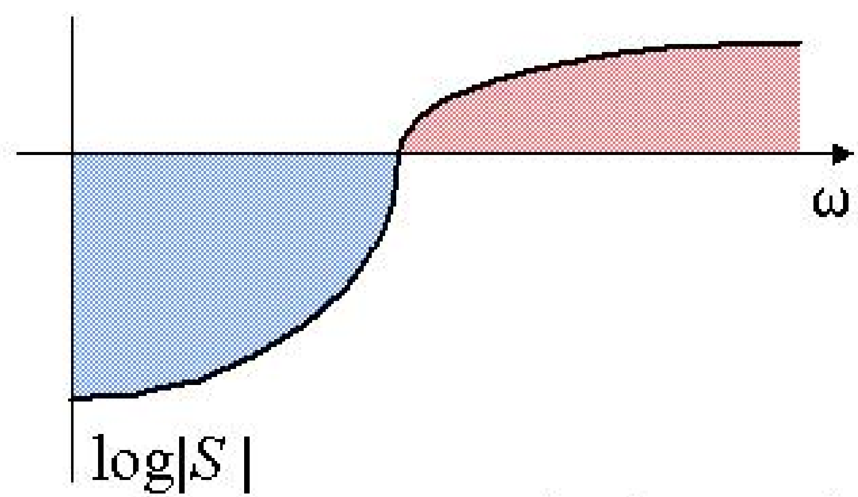
where E and D are the Fourier transforms of y and d. (If F is linear, then S is independent of D.)

Under assumptions that are consistent with F and d modeling physical systems (in particular, causality), it is possible to prove that:

$$\int \log |S(\omega)| d\omega \geq 0$$

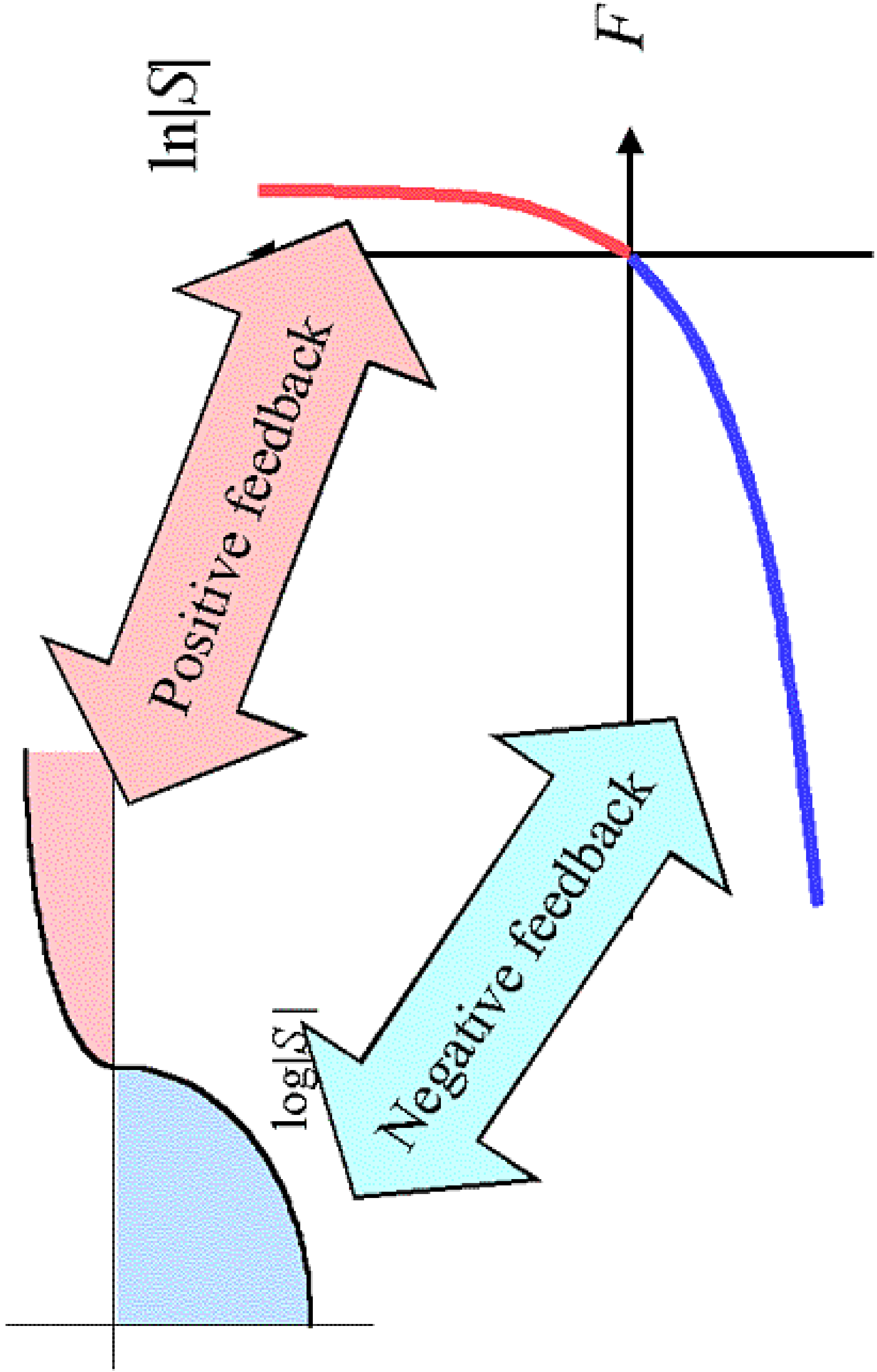
$(F < 0) \Rightarrow \ln(S) < 0 \Rightarrow$ attenuate

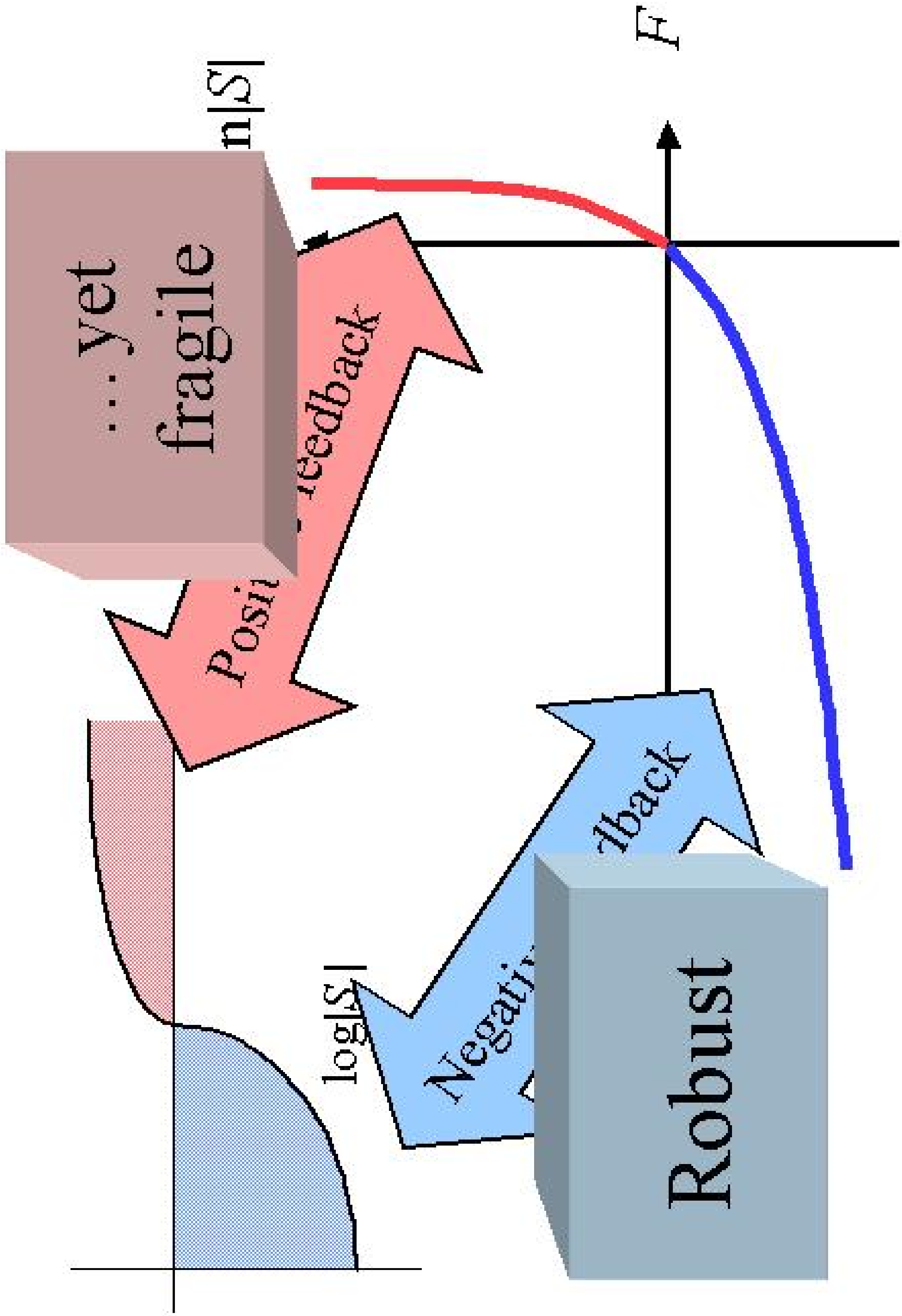
$(F > 0) \Rightarrow \ln(S) > 0 \Rightarrow$ amplify

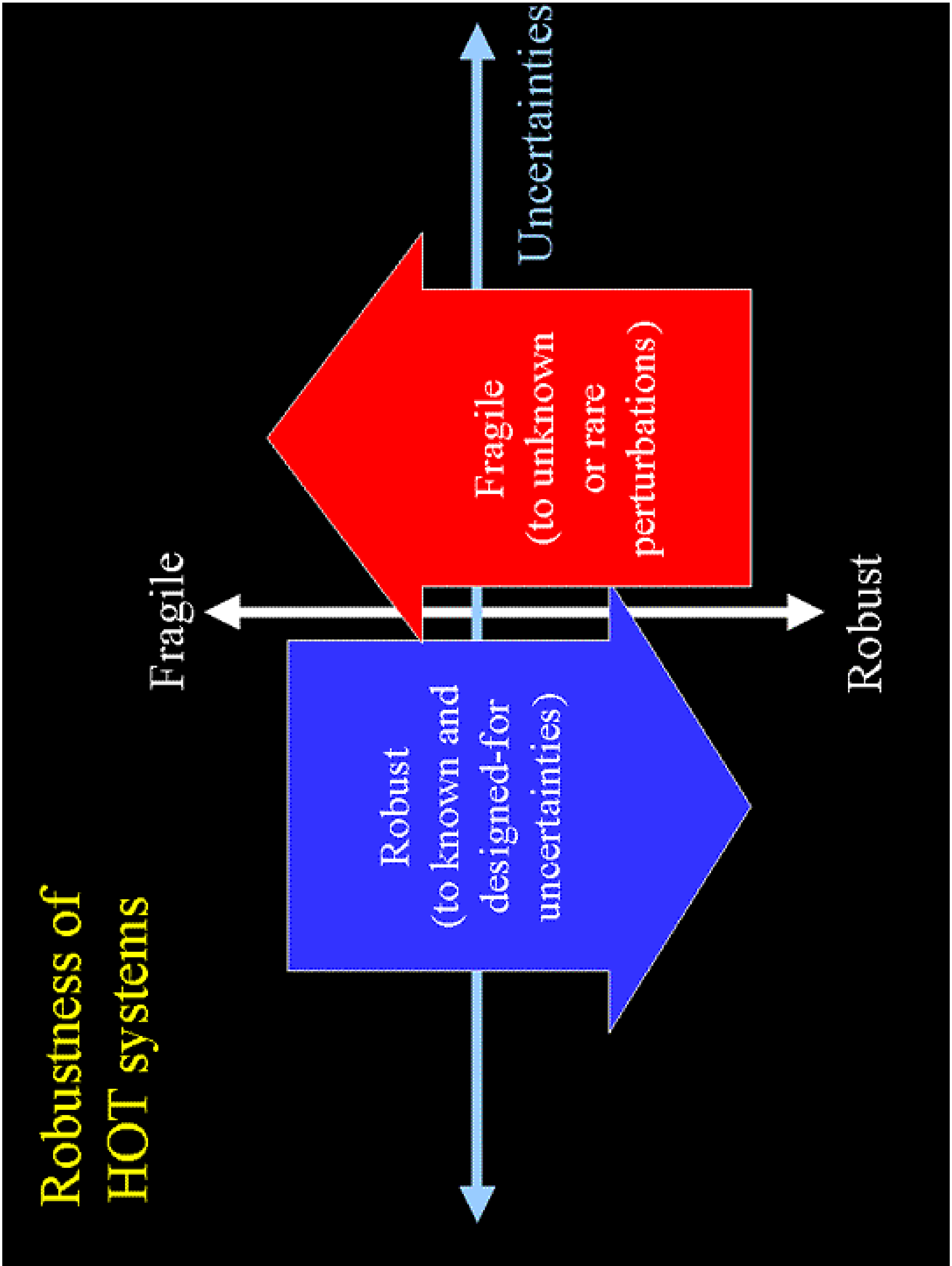


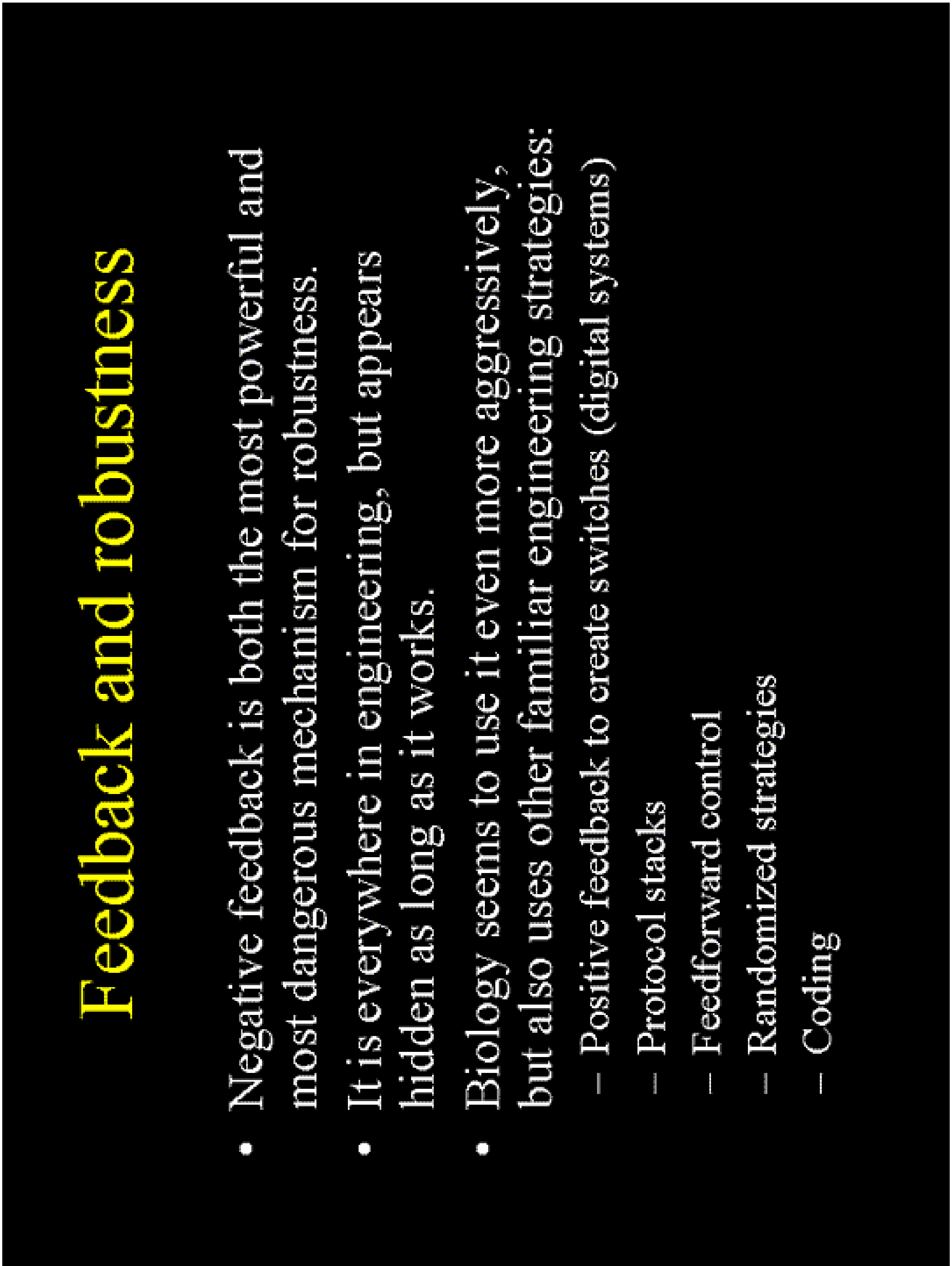
The amplification (F>0) must at least balance the attenuation (F<0).

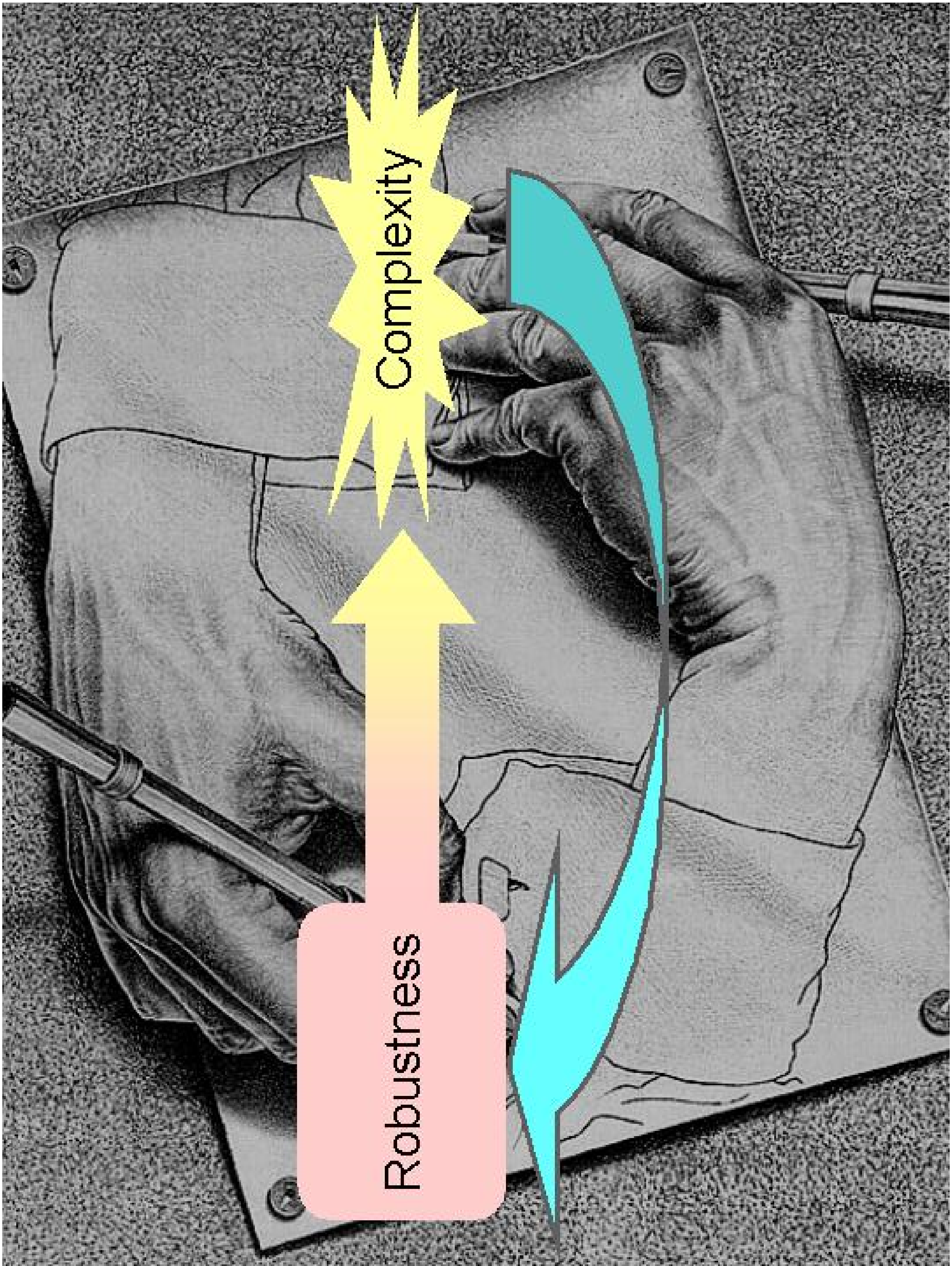
(Bode, ~1940)


ln|S|
F
Positive feedback
Negative feedback
log|S|


… yet
fragile
Robust
log|S|
F

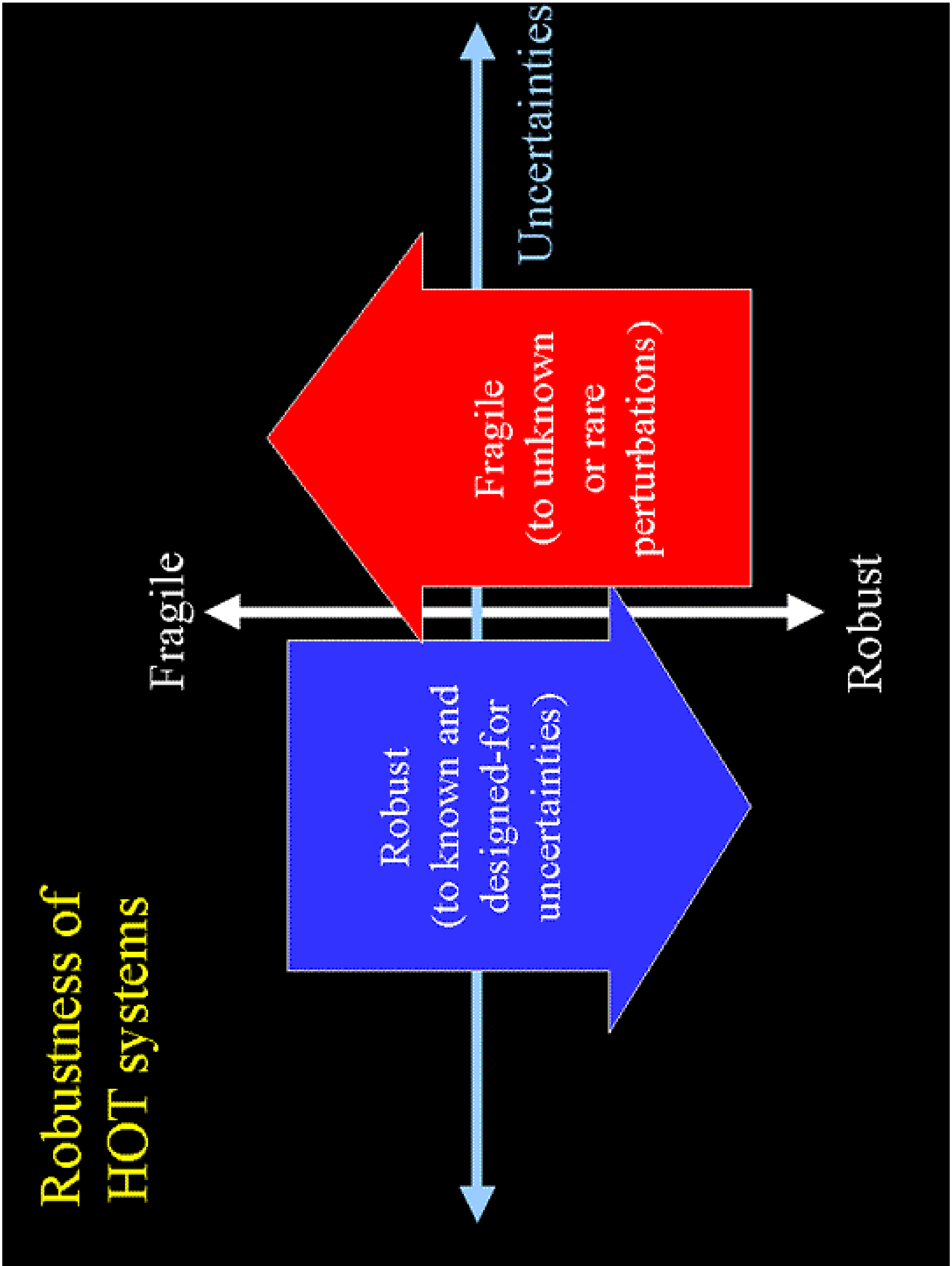

Robustness of
HOT systems
Uncertainties
Fragile
Robust
Fragile
(to unknown
or rare
perturbations)
Robust
(to known and
designed-for
uncertainties)

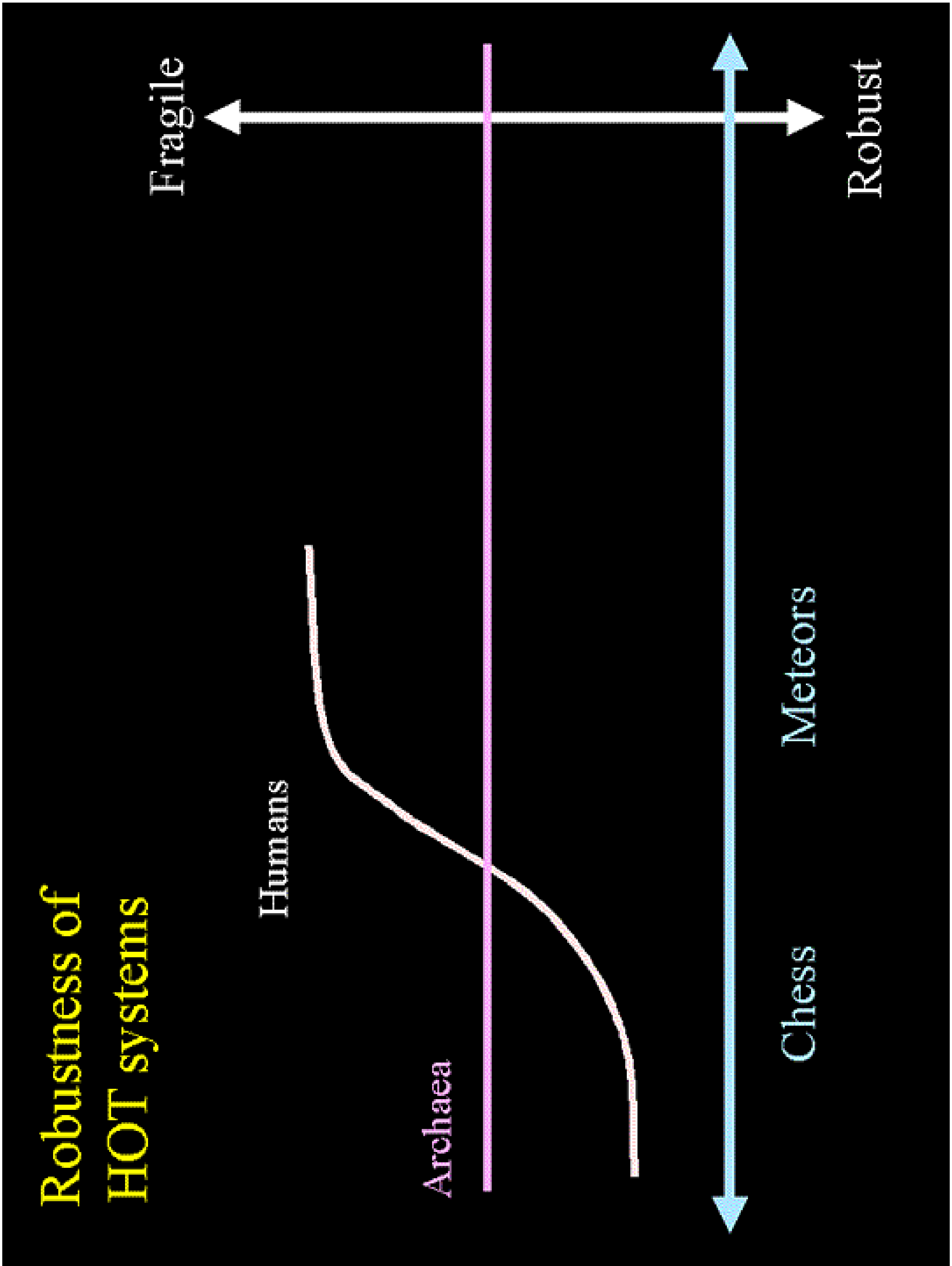

Feedback and robustness
• Negative feedback is both the most powerful and most dangerous mechanism for robustness.
• It is everywhere in engineering, but appears hidden as long as it works.
• Biology seems to use it even more aggressively, but also uses other familiar engineering strategies:
– Positive feedback to create switches (digital systems)
– Protocol stacks
– Feedforward control
– Randomized strategies
– Coding


Complexity
Robustness

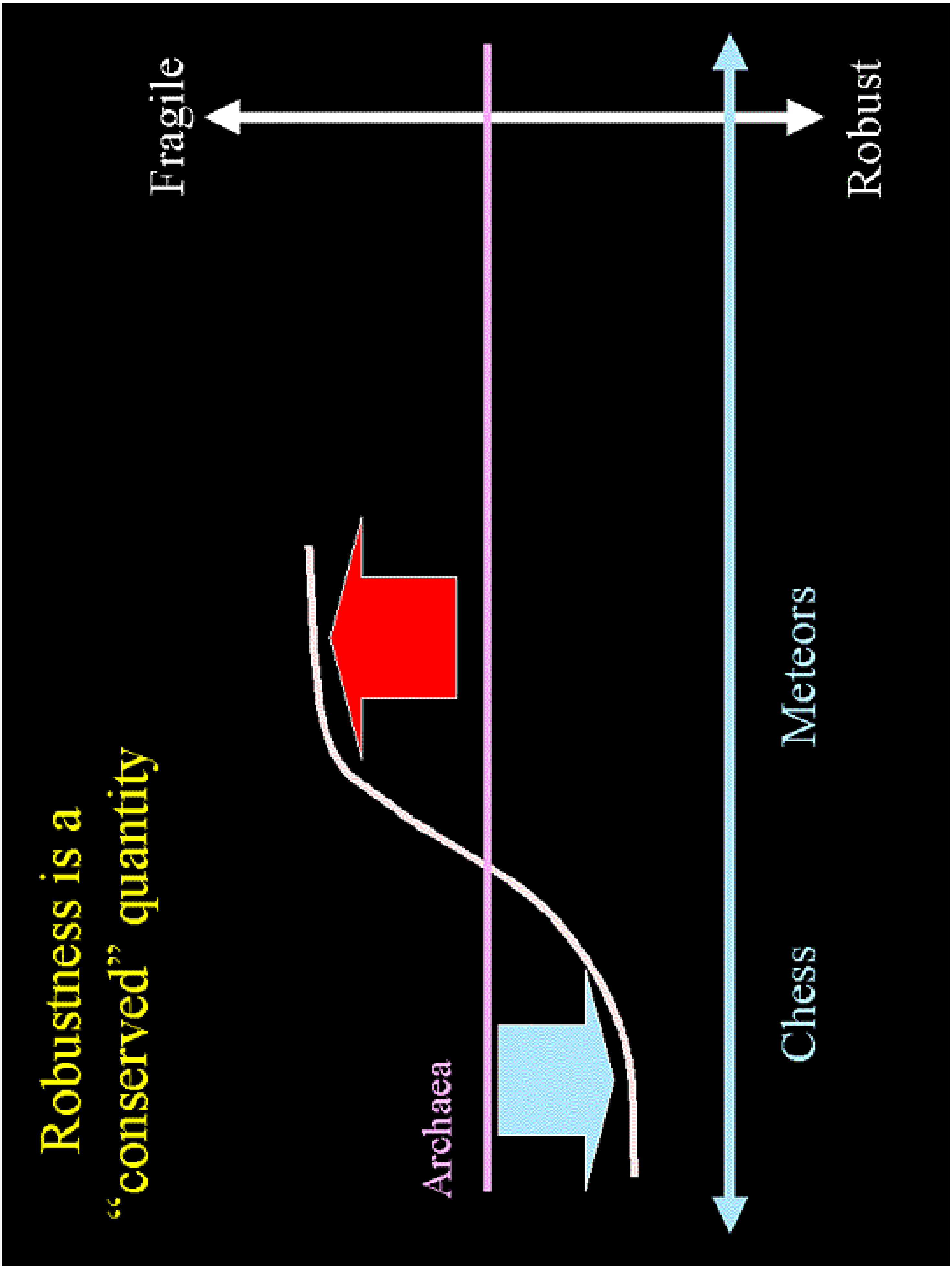
Current research

- So far, this is all undergraduate level material
- Current research involves lots of math not traditionally thought of as "applied"
- New theoretical connections between robustness, evolvability, and verifiability
- Beginnings of a more integrated theory of control, communications and computing
- Both biology and the future of ubiquitous, embedded networking will drive the development of new mathematics.

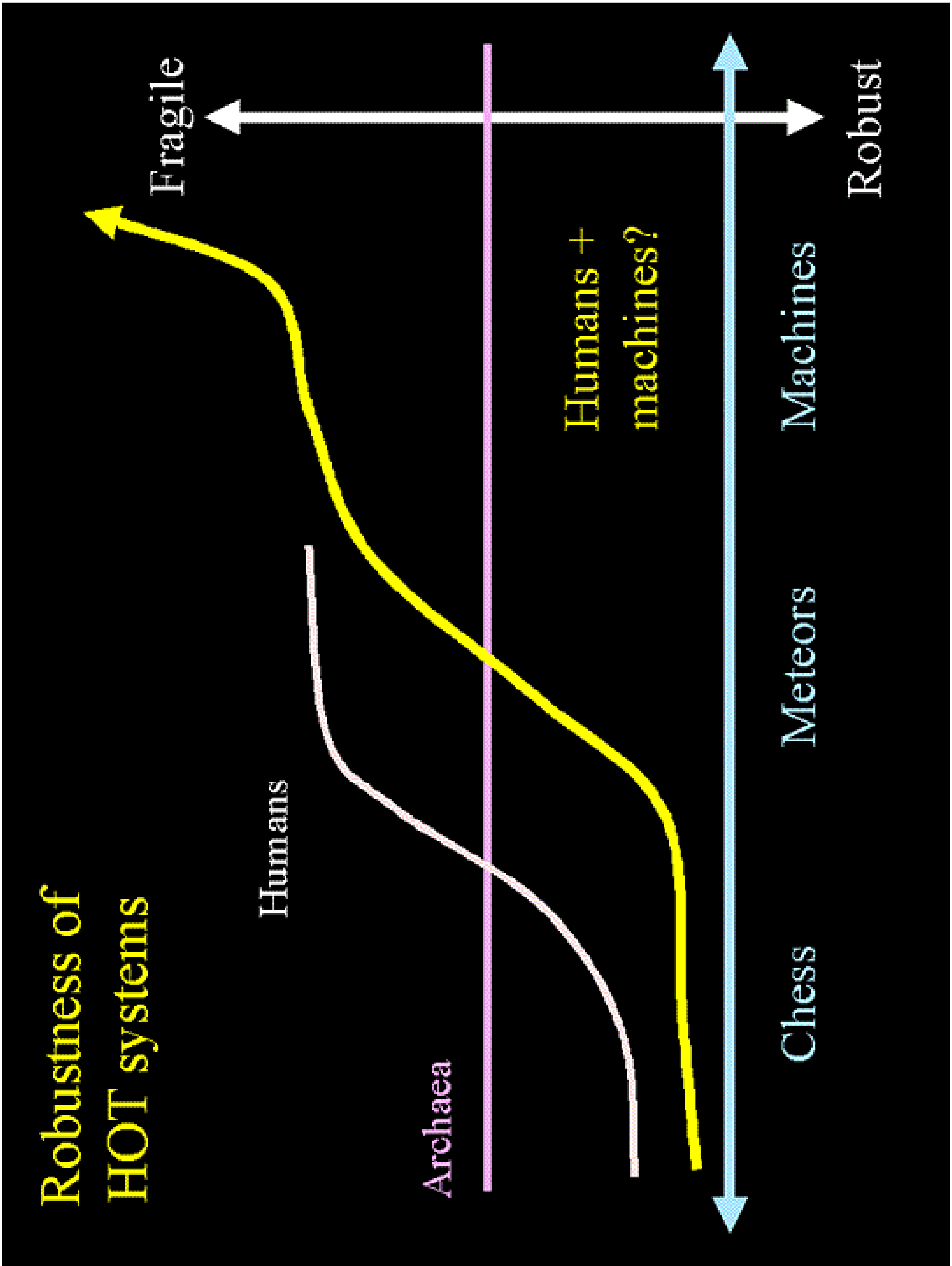

Robustness of
HOT systems
Uncertainties
Fragile
Robust
Fragile
(to unknown
or rare
perturbations)
Robust
(to known and
designed-for
uncertainties)



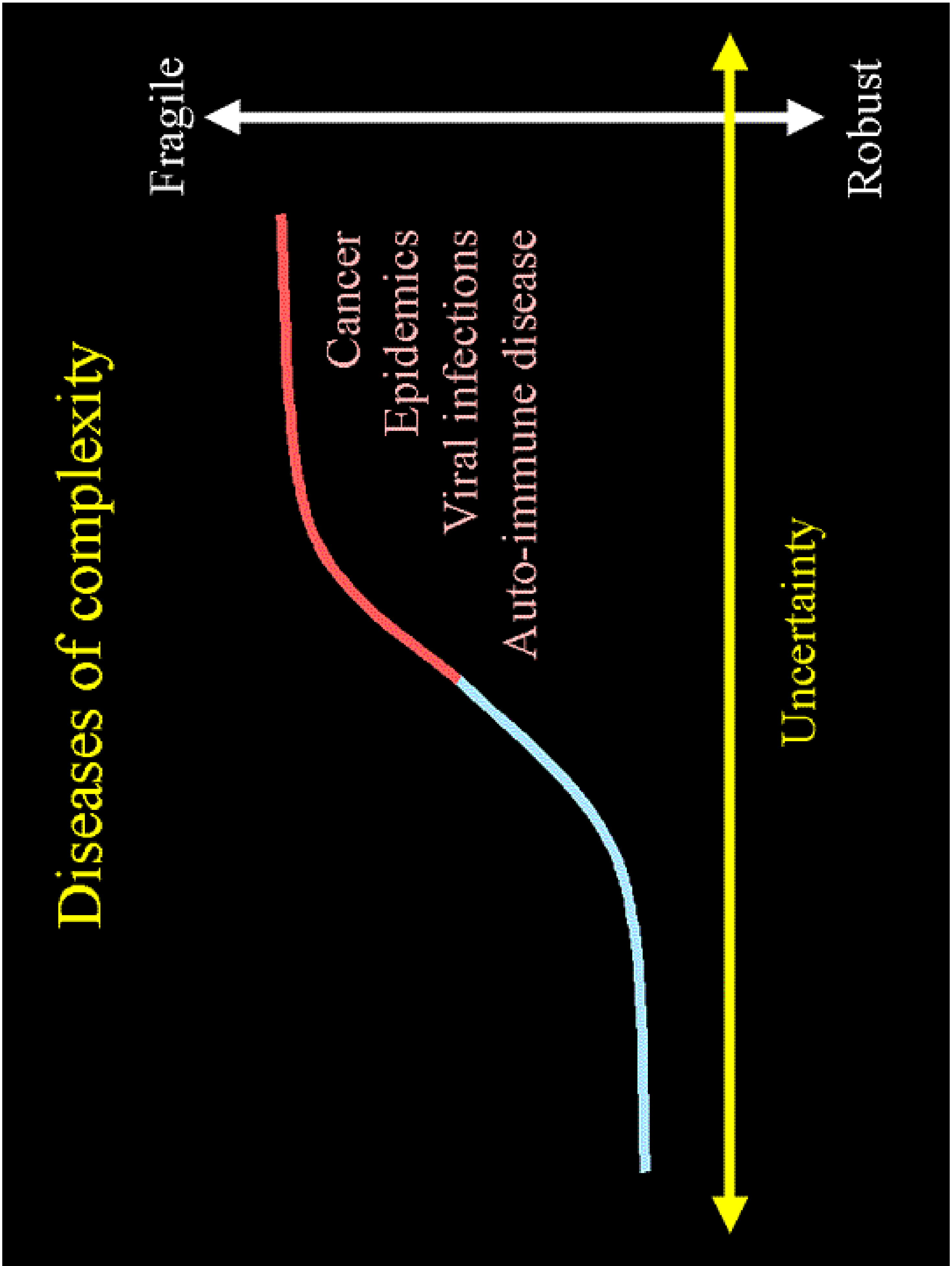
Robustness of
HOT systems
Fragile
Robust
Humans
Archaea
Meteors
Chess

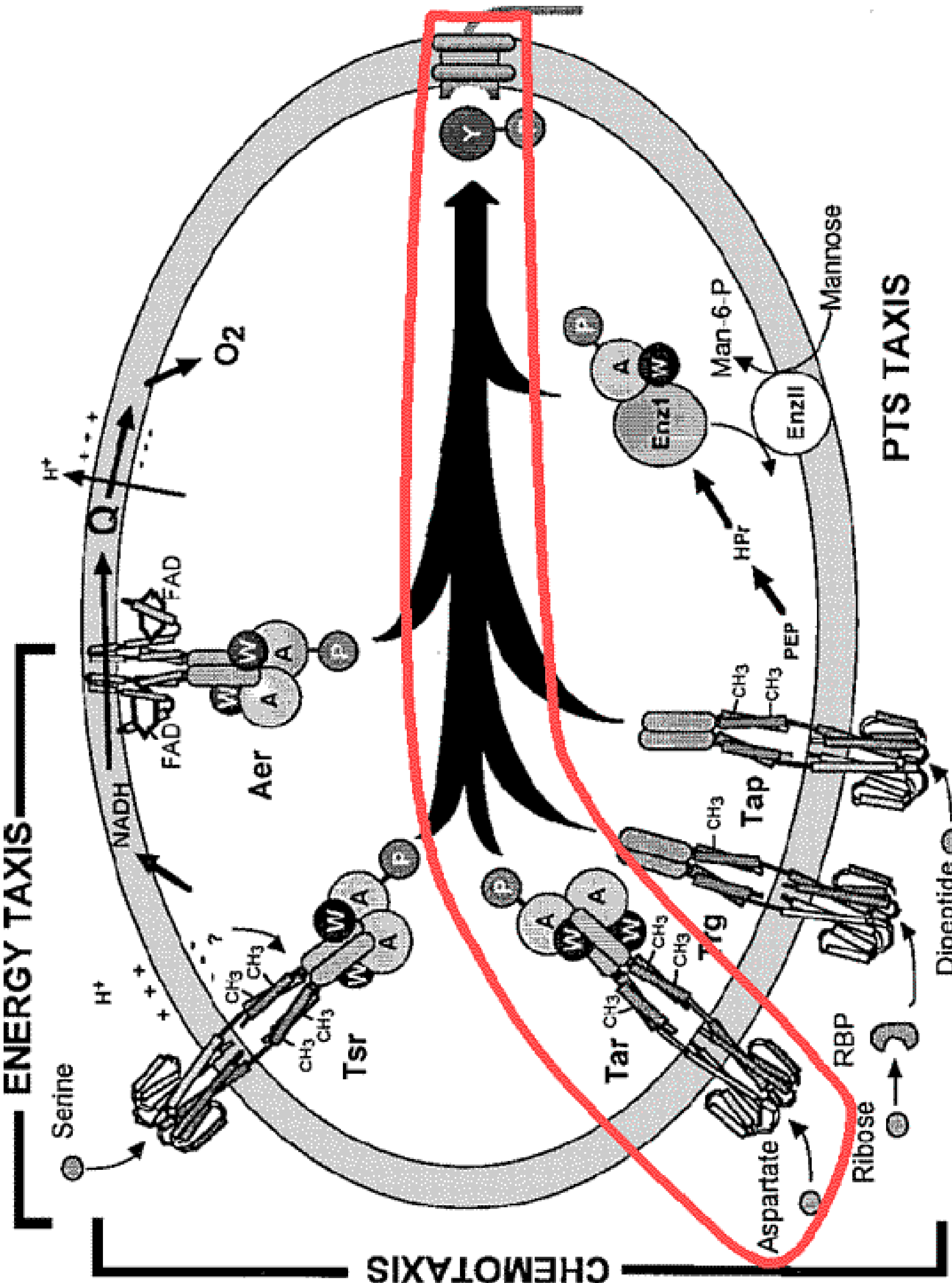

Robustness is a
“conserved” quantity
Fragile
Robust
Archaea
Chess
Meteors

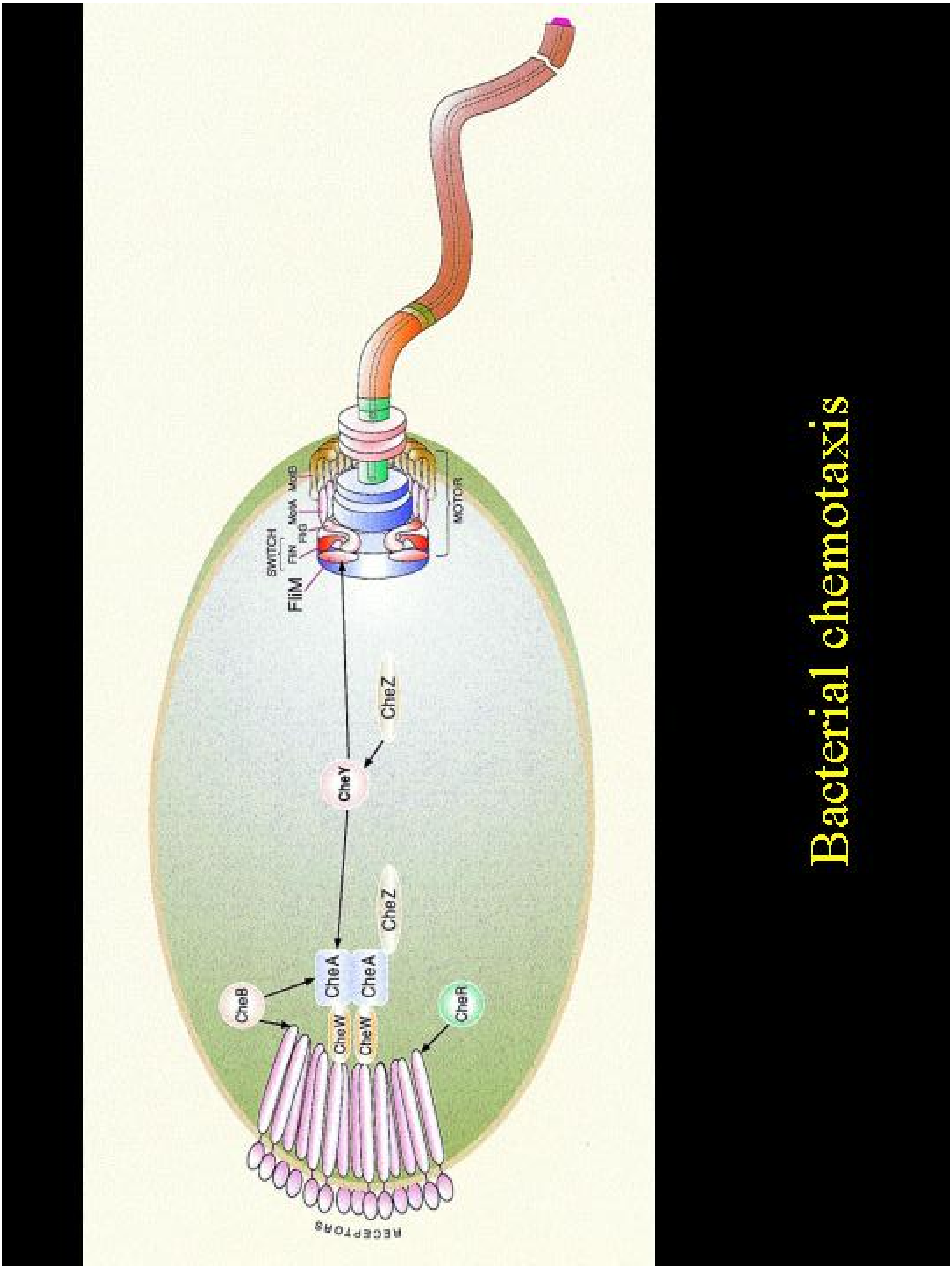
[90] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



[91] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks




ENERGY TAXIS
CHEMOTAXIS
PTS TAXIS
Serine
Aspartate
Ribose
RBP
Dipeptide
Mannose
Man-6-P
EnzI
EnzII
HPr
PEP
Tsr
Tar
Trg
Tap
Aer
NADH
FAD
Q
O_2
H^+
CH_3
A
W
P
Y

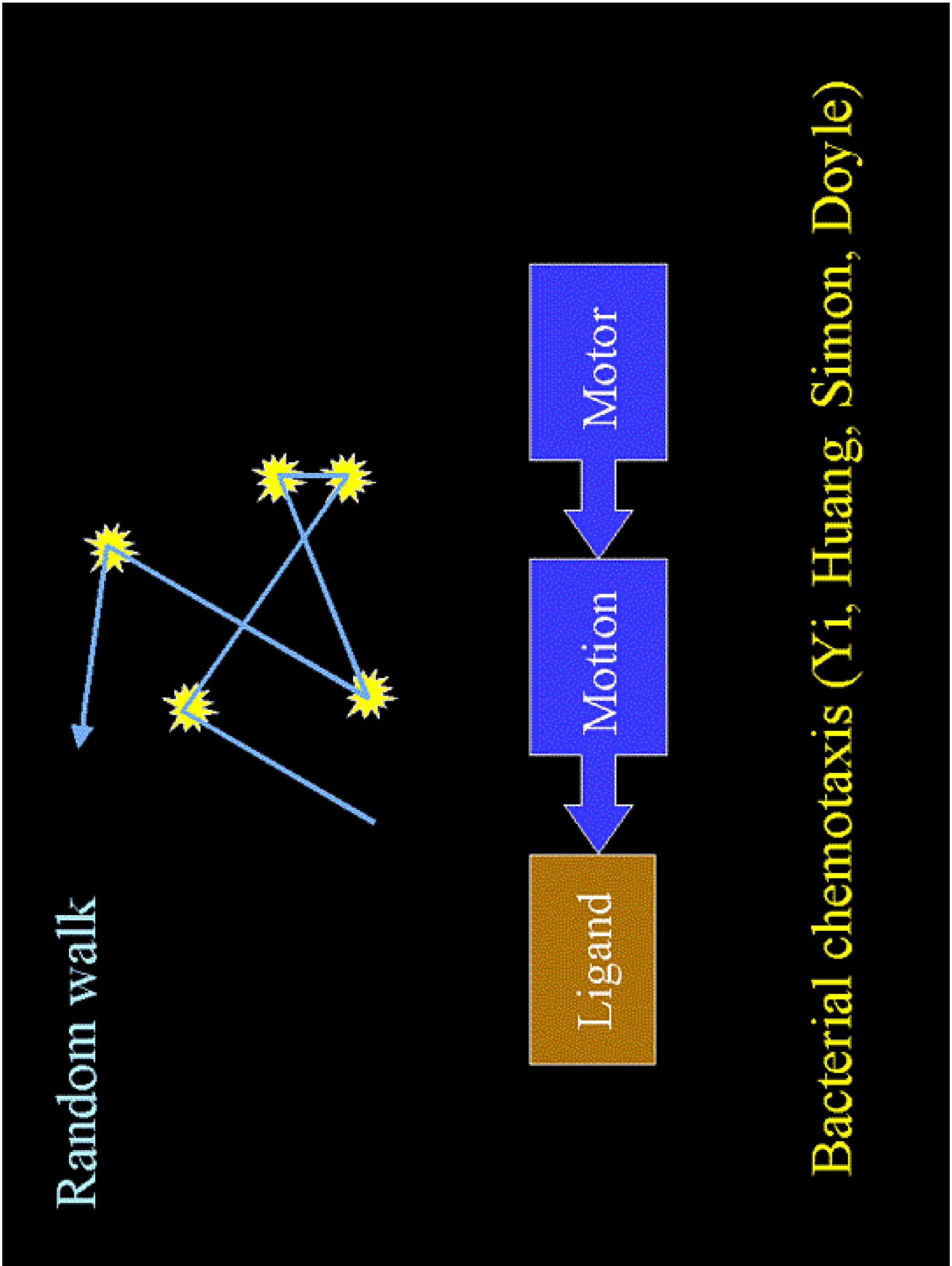

Bacterial chemotaxis
CheZ
CheY
CheZ
CheA
CheA
CheB
CheW
CheW
CheR
FliM
SWITCH
FliN
FliG
MotA
MotB
MOTOR
RECEPTORS

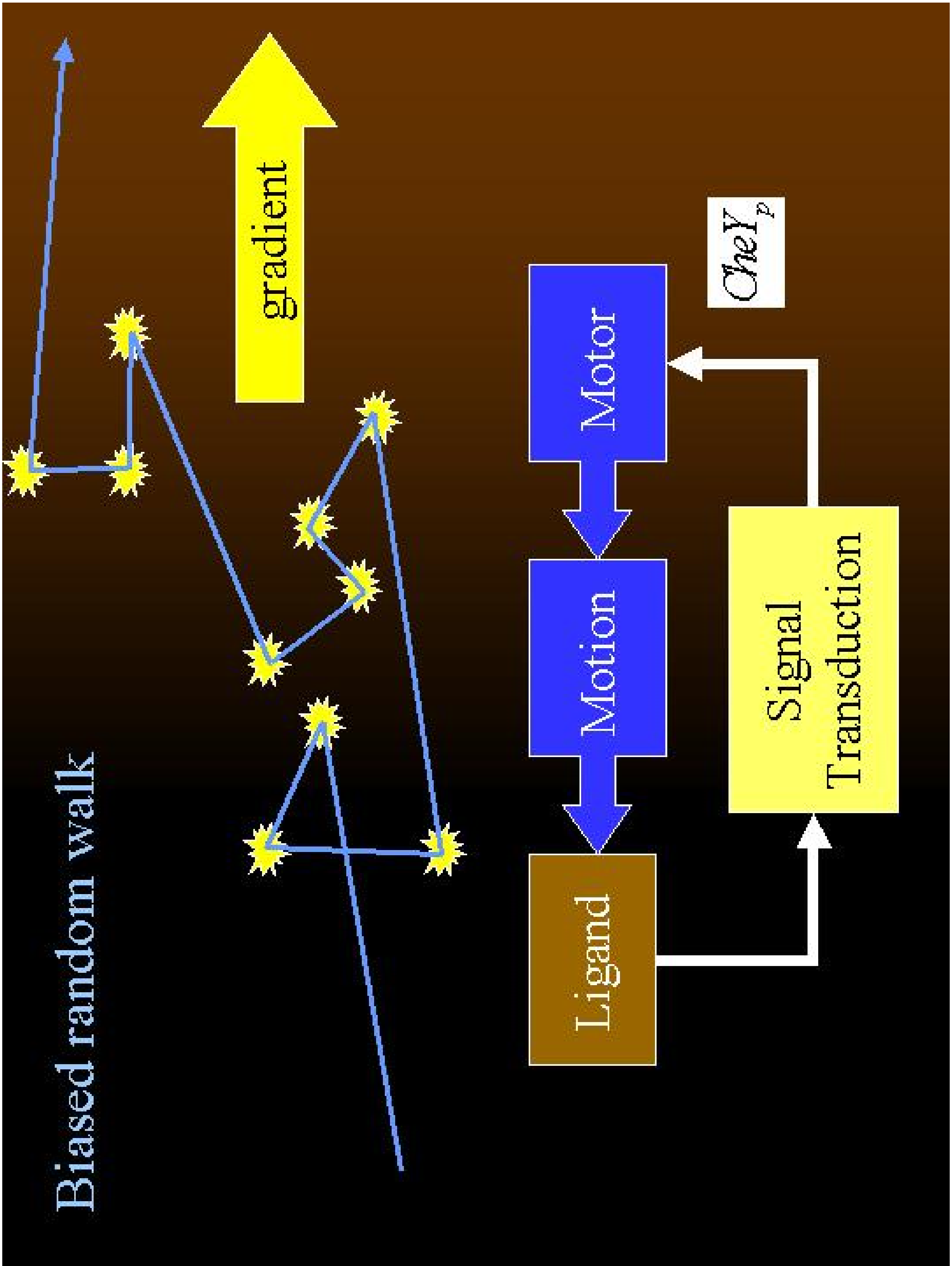
Proc. Natl. Acad. Sci. USA,
Vol. 97, Issue 9, 4649-4653, April 25, 2000

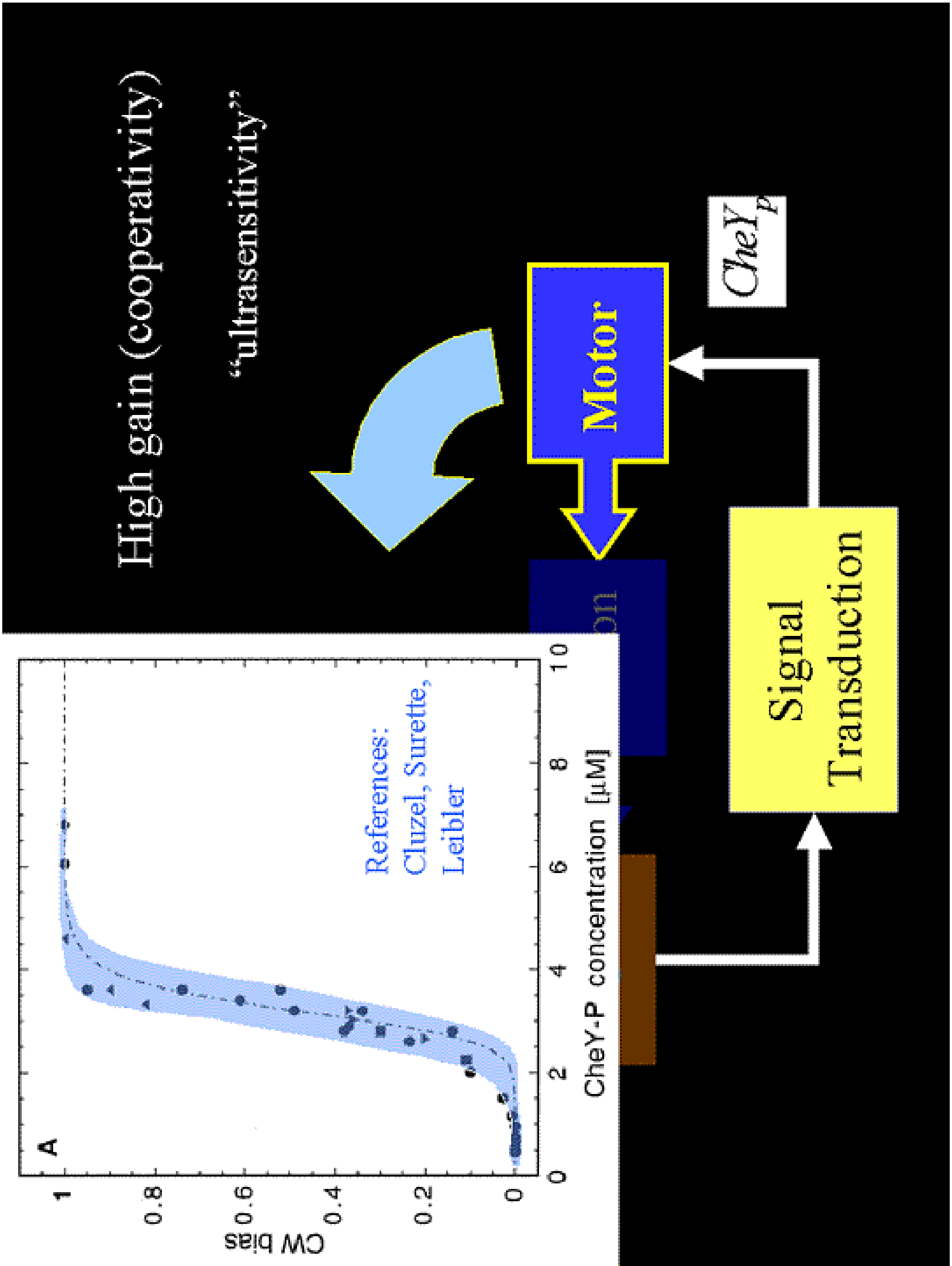
Biophysics

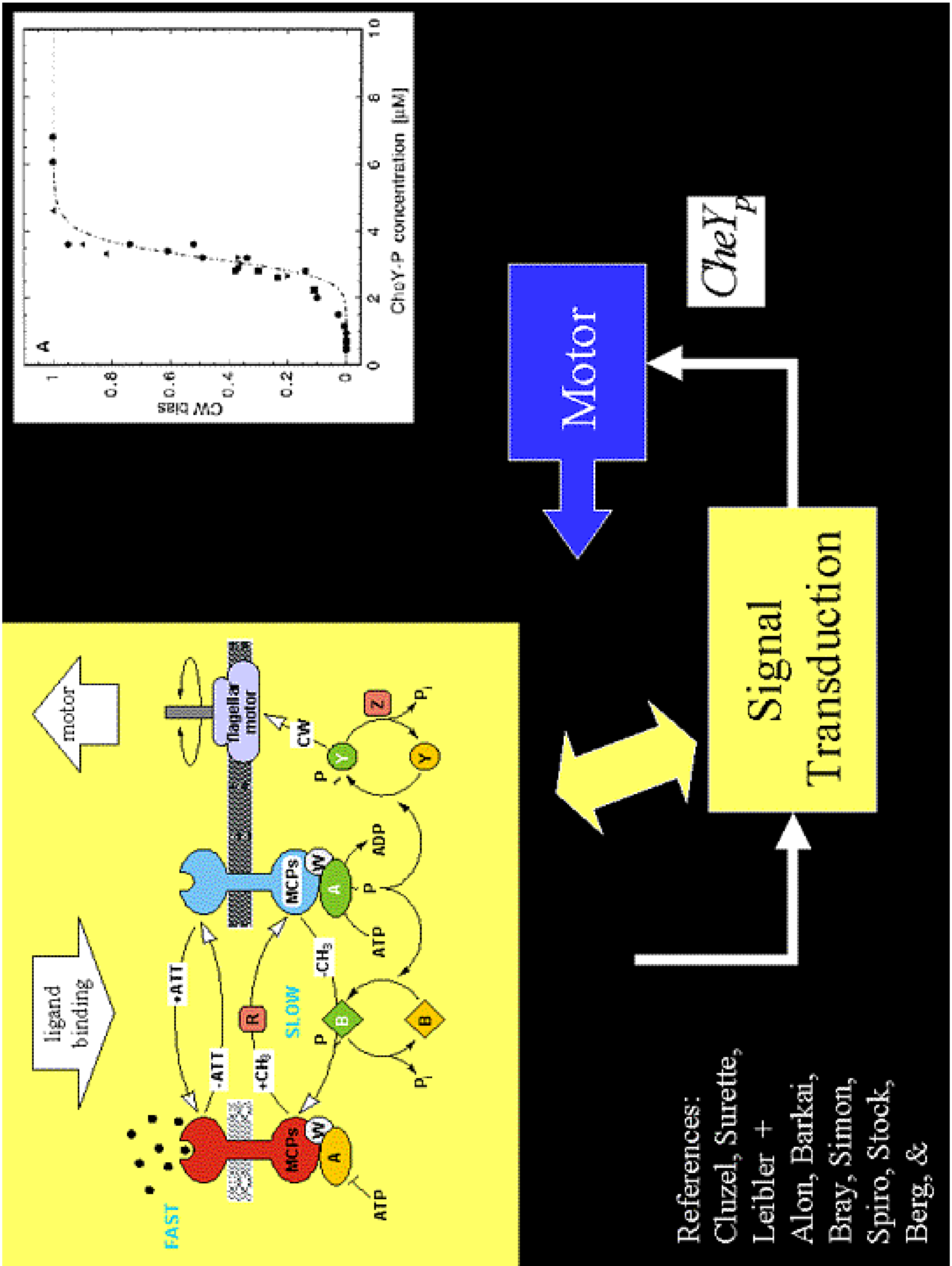
Robust perfect adaptation in bacterial chemotaxis through integral feedback control

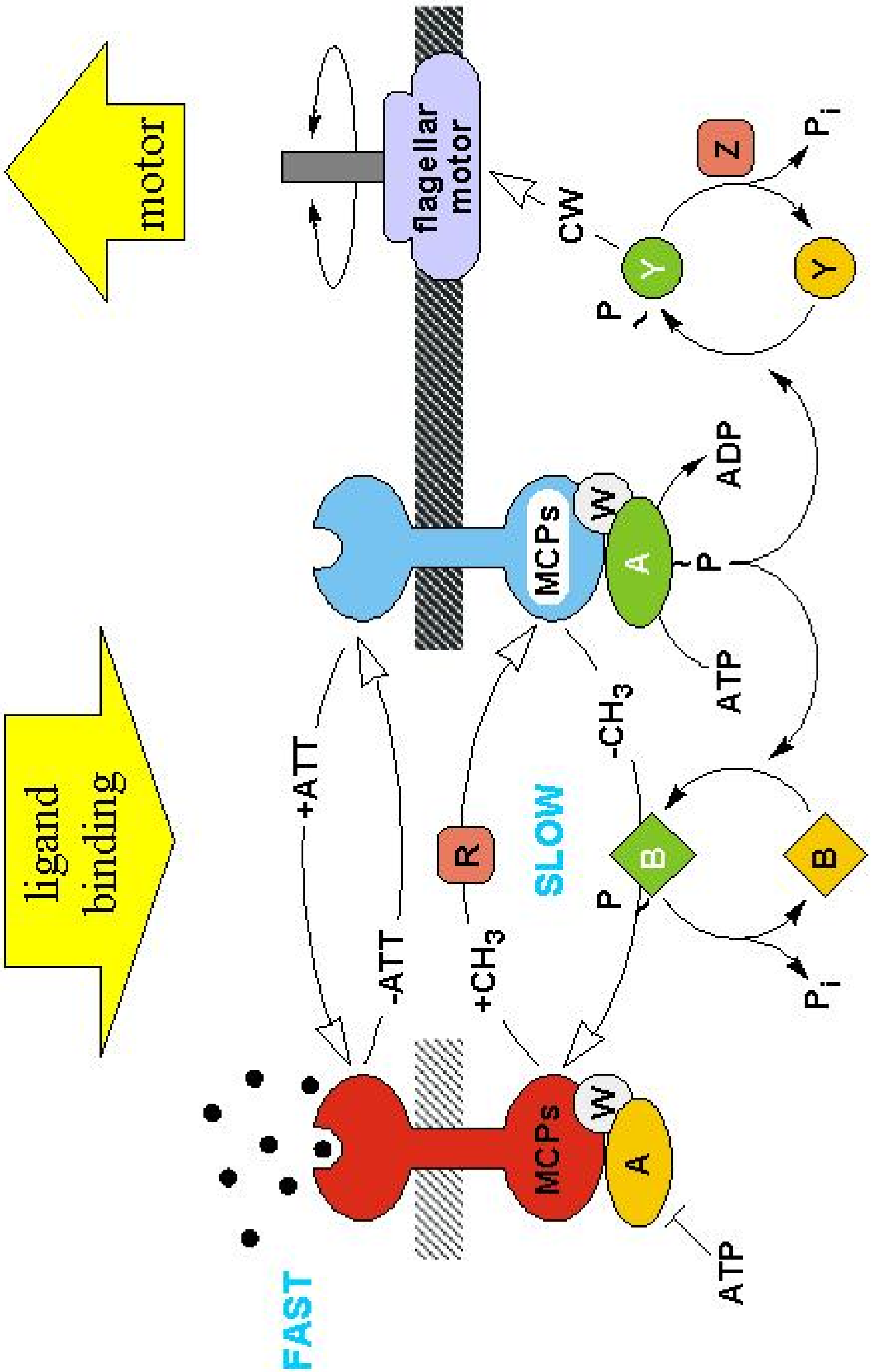
(Yi, Huang, Simon, Doyle)

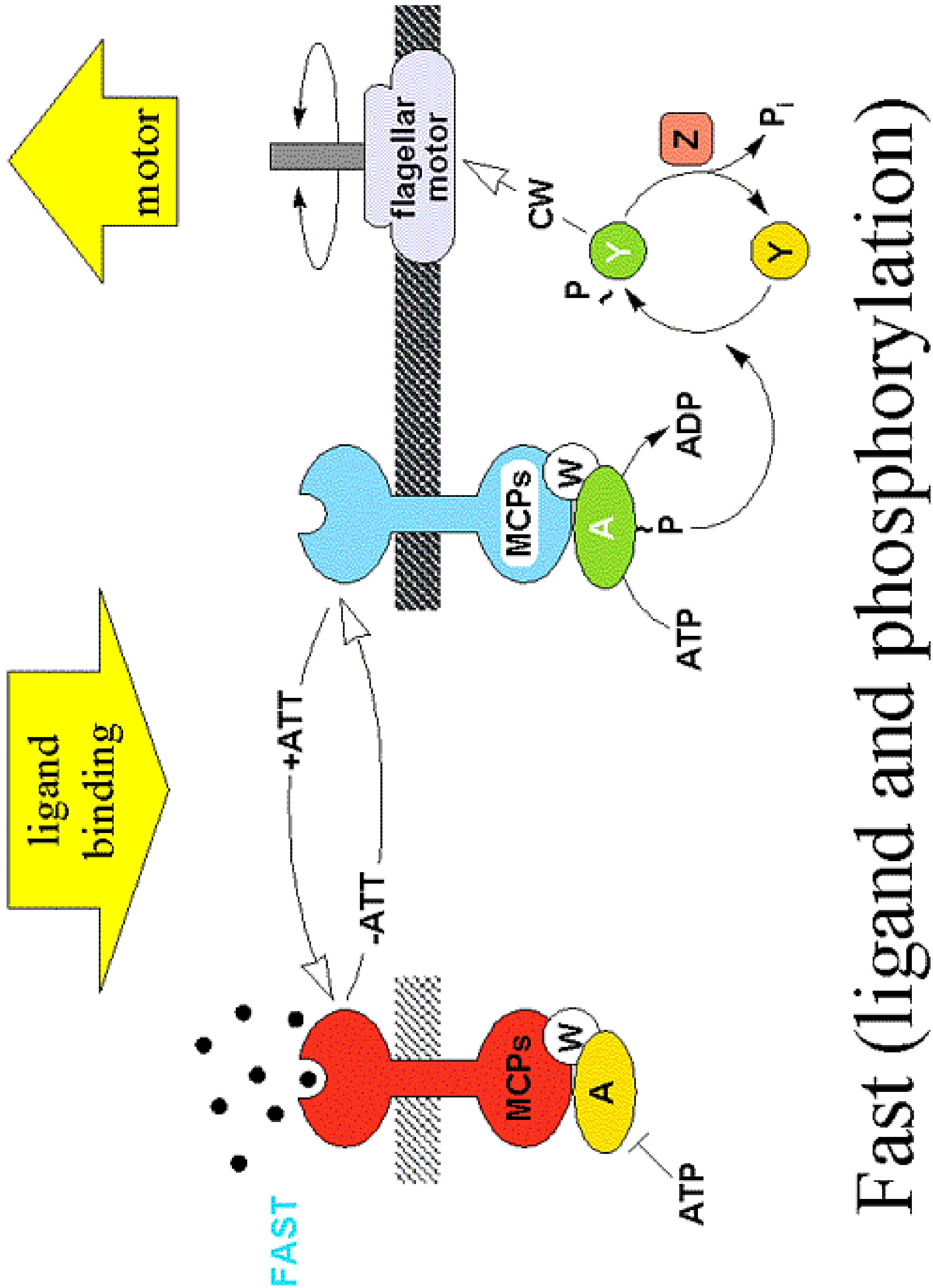

Random walk
Ligand
Motion
Motor
Bacterial chemotaxis (Yi, Huang, Simon, Doyle)

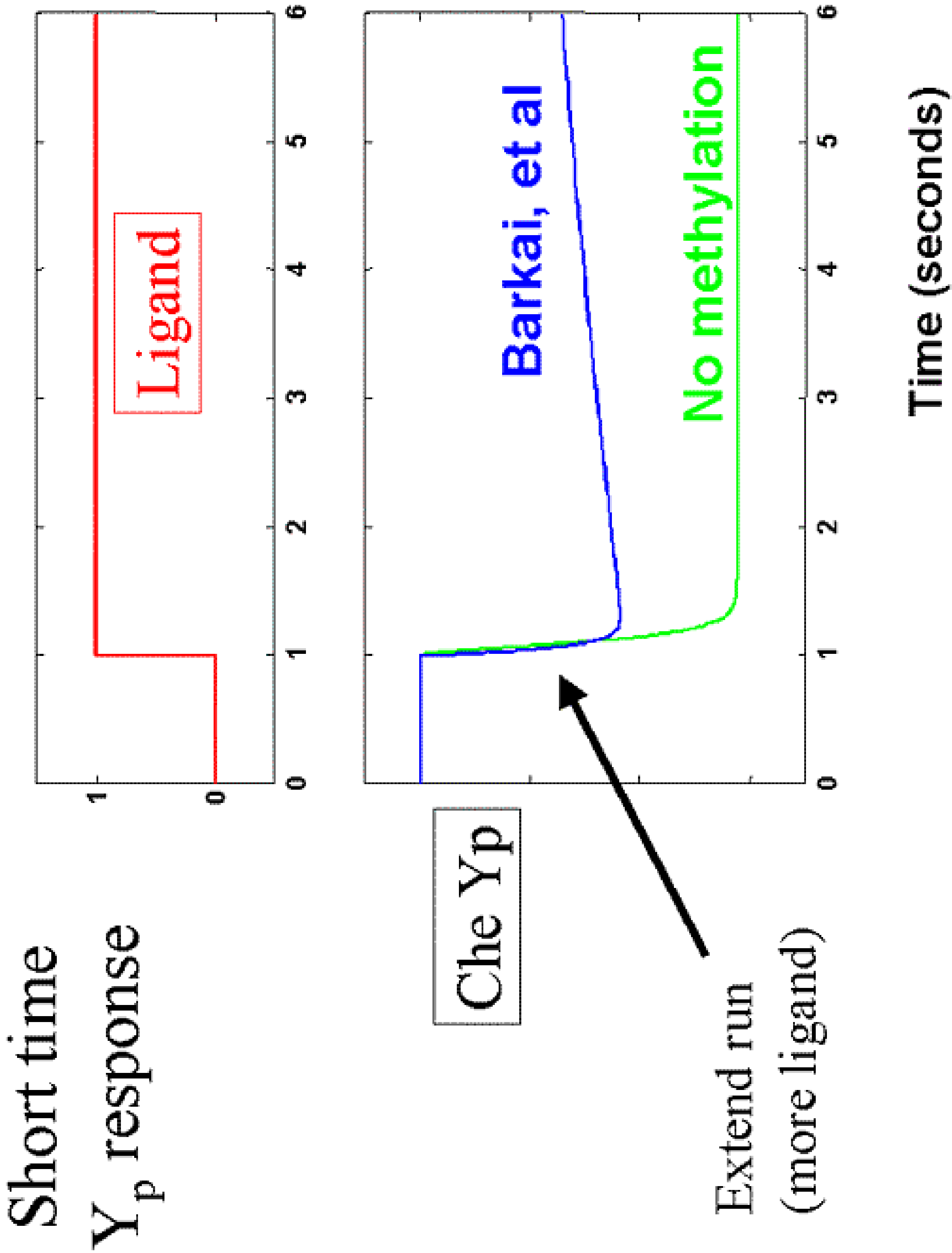

Biased random walk
gradient
Motor
Motion
Ligand
Signal
Transduction
CheY_p


High gain (cooperativity)
“ultrasensitivity”
Motor
CheY_p
Signal Transduction
References: Cluzel, Surette, Leibler
A
CW bias
CheY-P concentration [μM]
0
0.2
0.4
0.6
0.8
1
0
2
4
6
8
10


References:
Cluzel, Surette,
Leibler +
Alon, Barkai,
Bray, Simon,
Spiro, Stock,
Berg, &
Signal
Transduction
Motor
CheY_p
CW bias
CheY-P concentration [µM]
A
ligand
binding
motor
FAST
SLOW
MCPs
flagellar
motor
+ATT
-ATT
+CH3
-CH3
ATP
ADP
CW

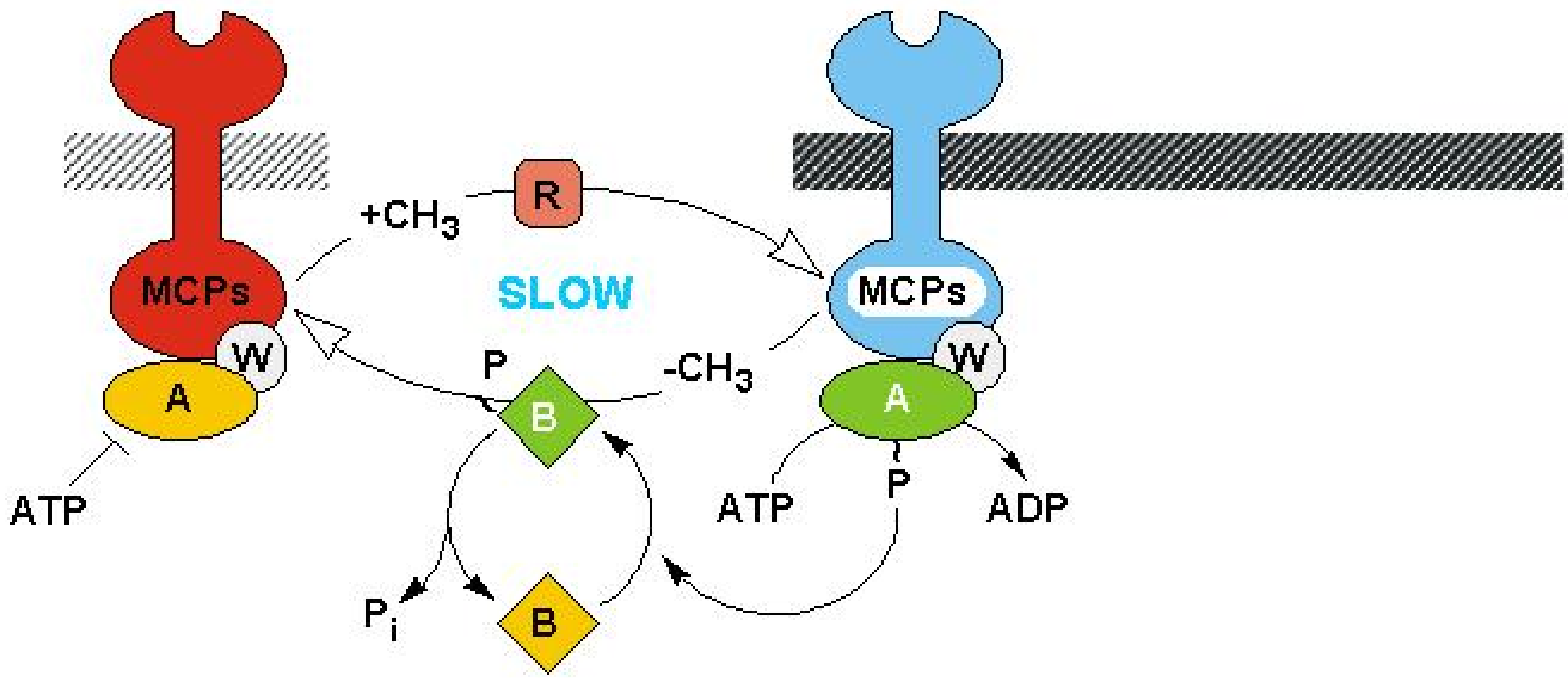

motor
ligand binding
flagellar motor
CW
Z
Y
P
P_i
MCPs
W
A
ADP
ATP
+ATT
-ATT
R
SLOW
$+CH_3$
$-CH_3$
B
FAST

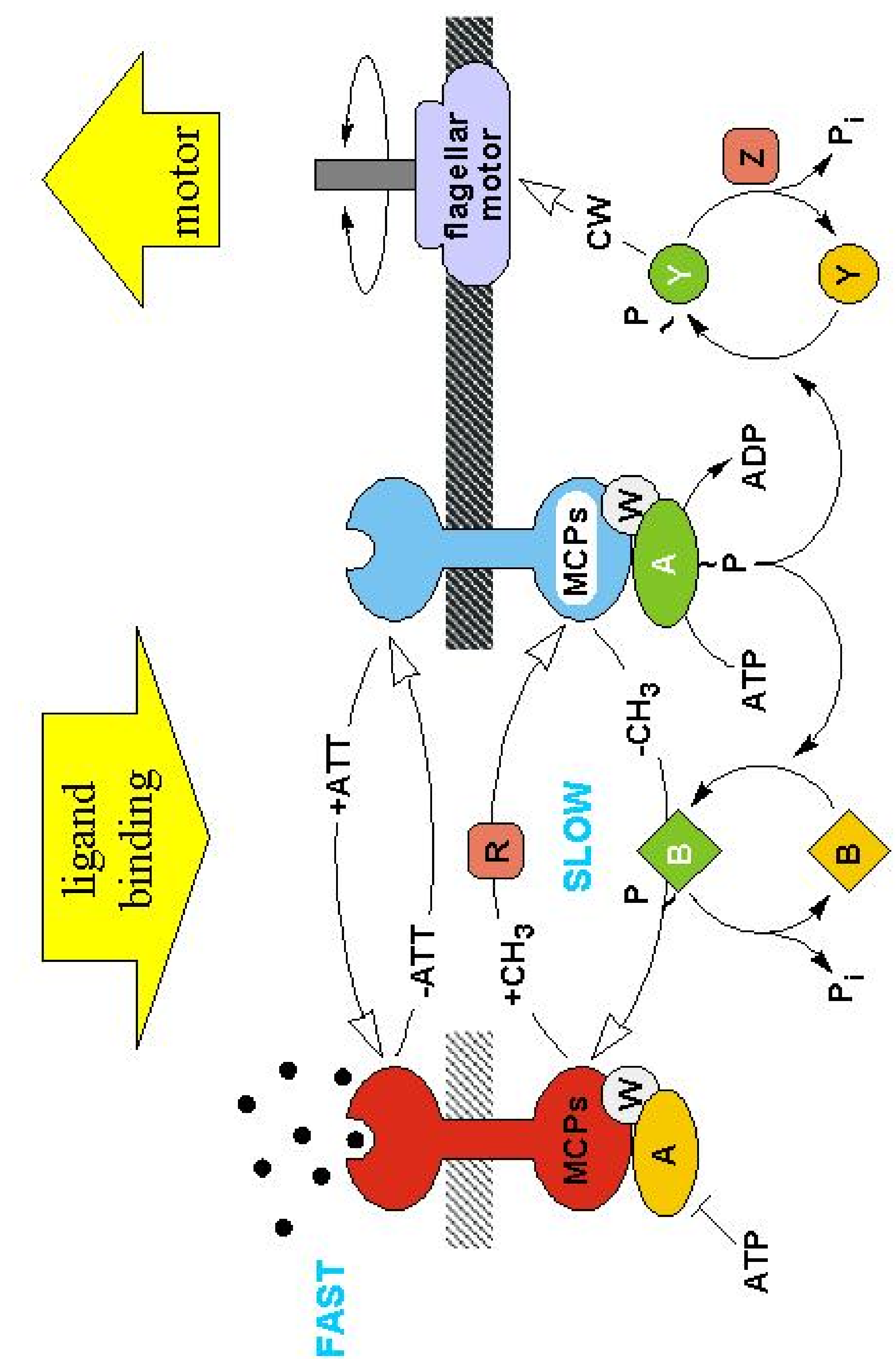

ligand binding
motor
FAST
MCPs
W
A
ATP
+ATT
-ATT
MCPs
W
A
P
ADP
ATP
flagellar motor
CW
Y
P
Z
P_i
Y
Fast (ligand and phosphorylation)

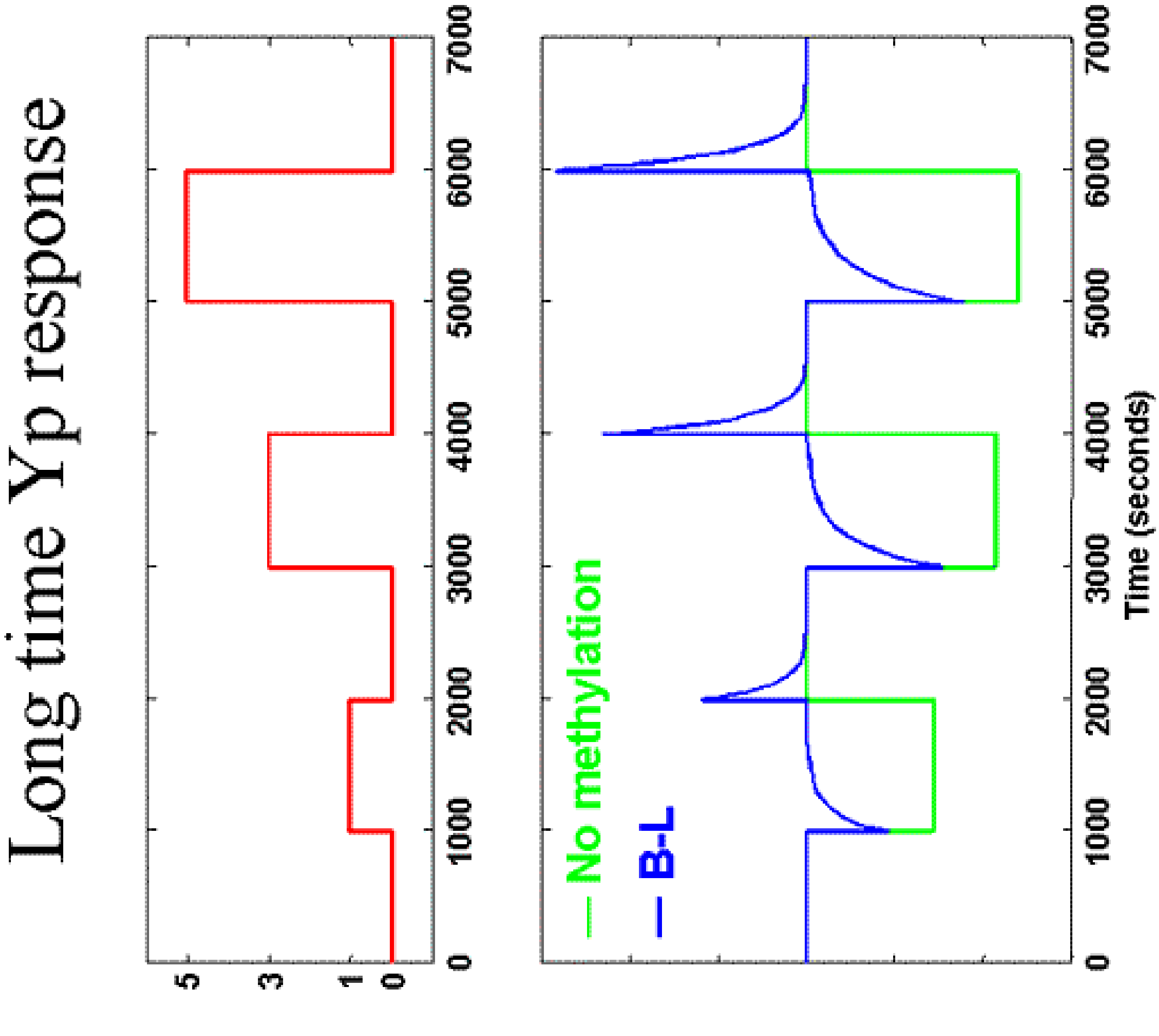


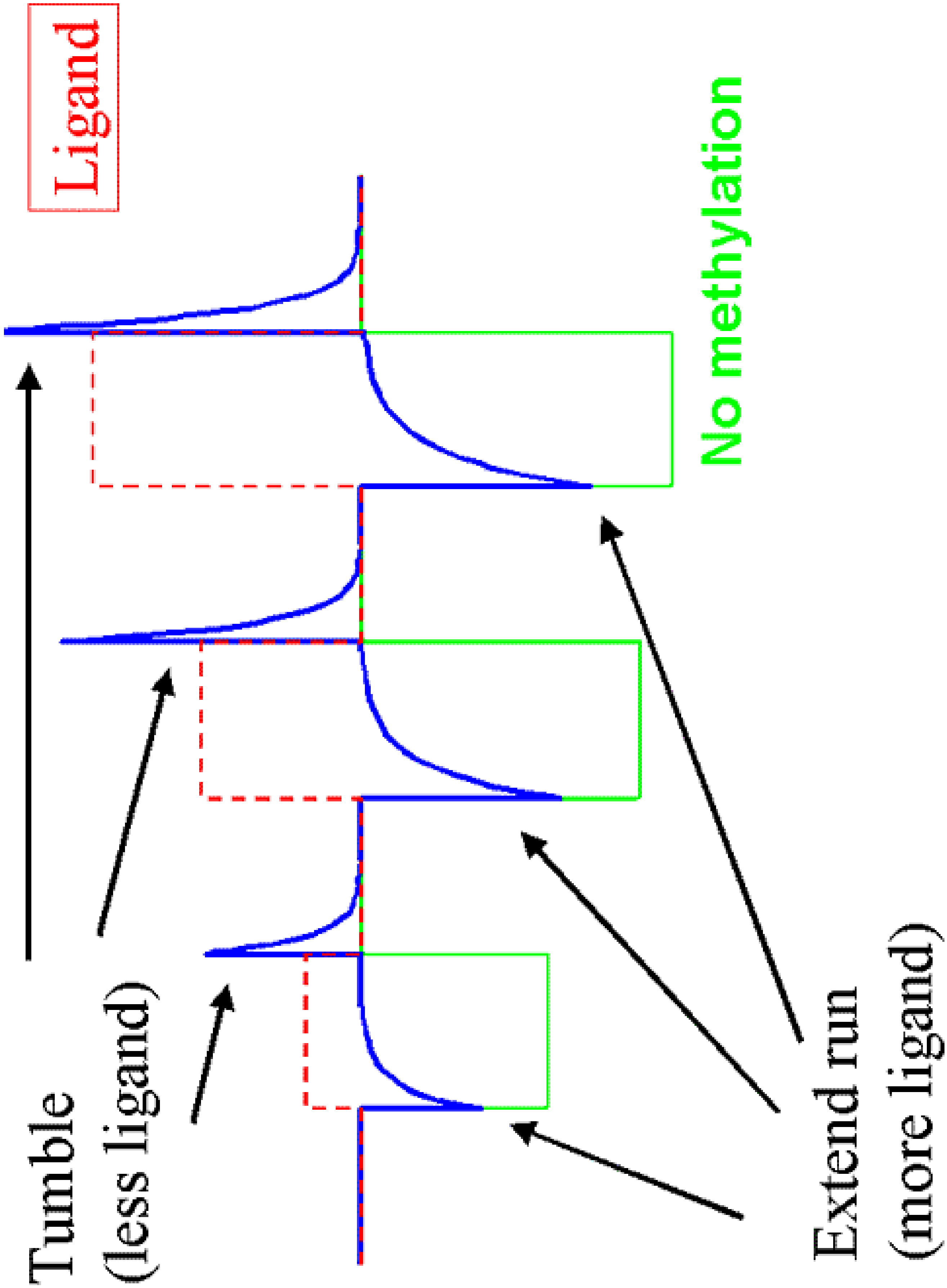
Short time
Yp response
Ligand
1
0
Che Yp
Barkai, et al
No methylation
Extend run
(more ligand)
0
1
2
3
4
5
6
Time (seconds)

Slow (de-) methylation dynamics

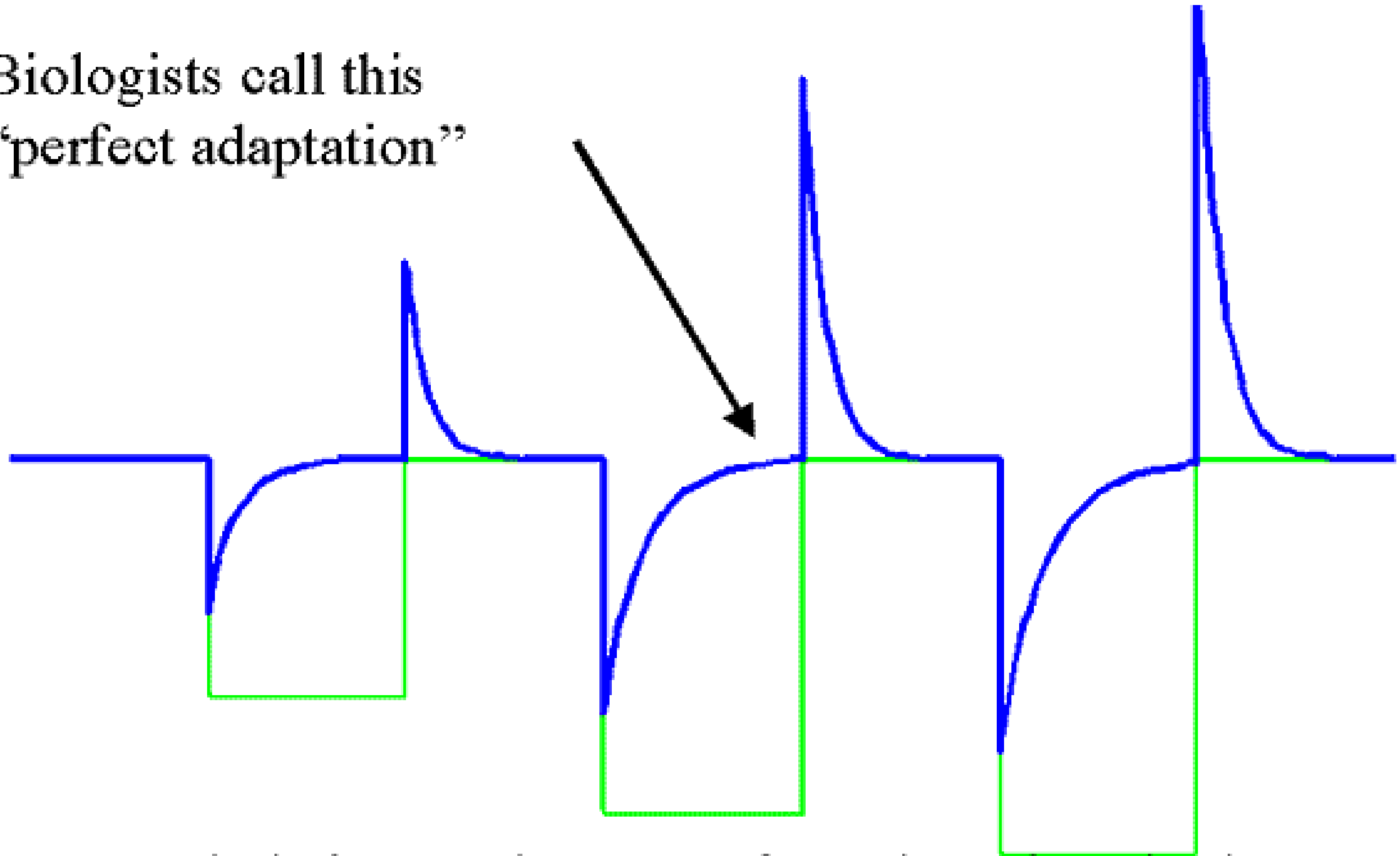



motor
ligand binding
flagellar motor
CW
Z
P
Y
Y
P_i
MCPs
W
A
ADP
ATP
$-CH_3$
+ATT
-ATT
R
SLOW
$+CH_3$
B
B
P_i
MCPs
W
A
ATP
FAST

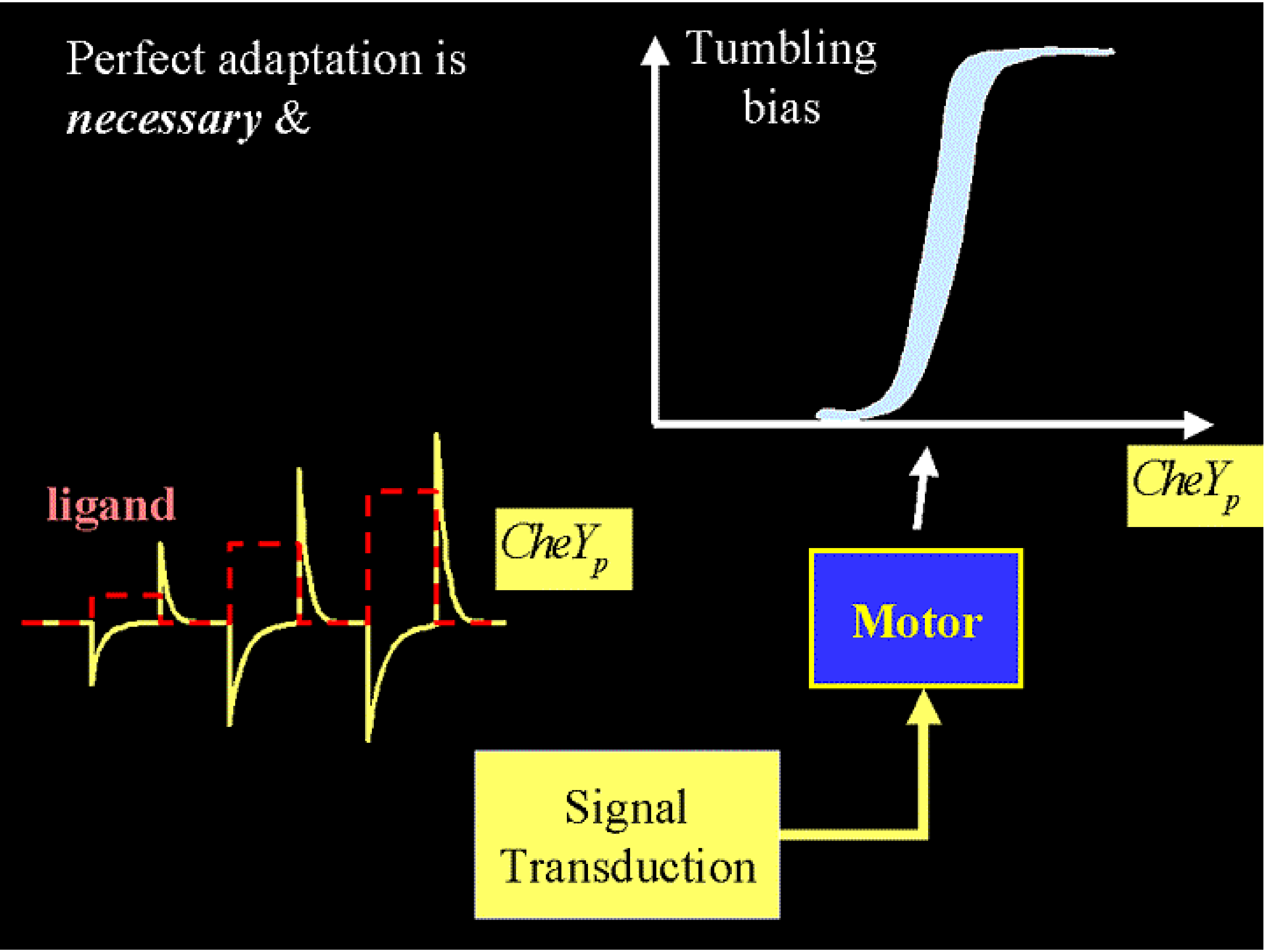

Long time Yp response
5
3
1
0
0
1000
2000
3000
4000
5000
6000
7000
— No methylation
— B-L
Time (seconds)

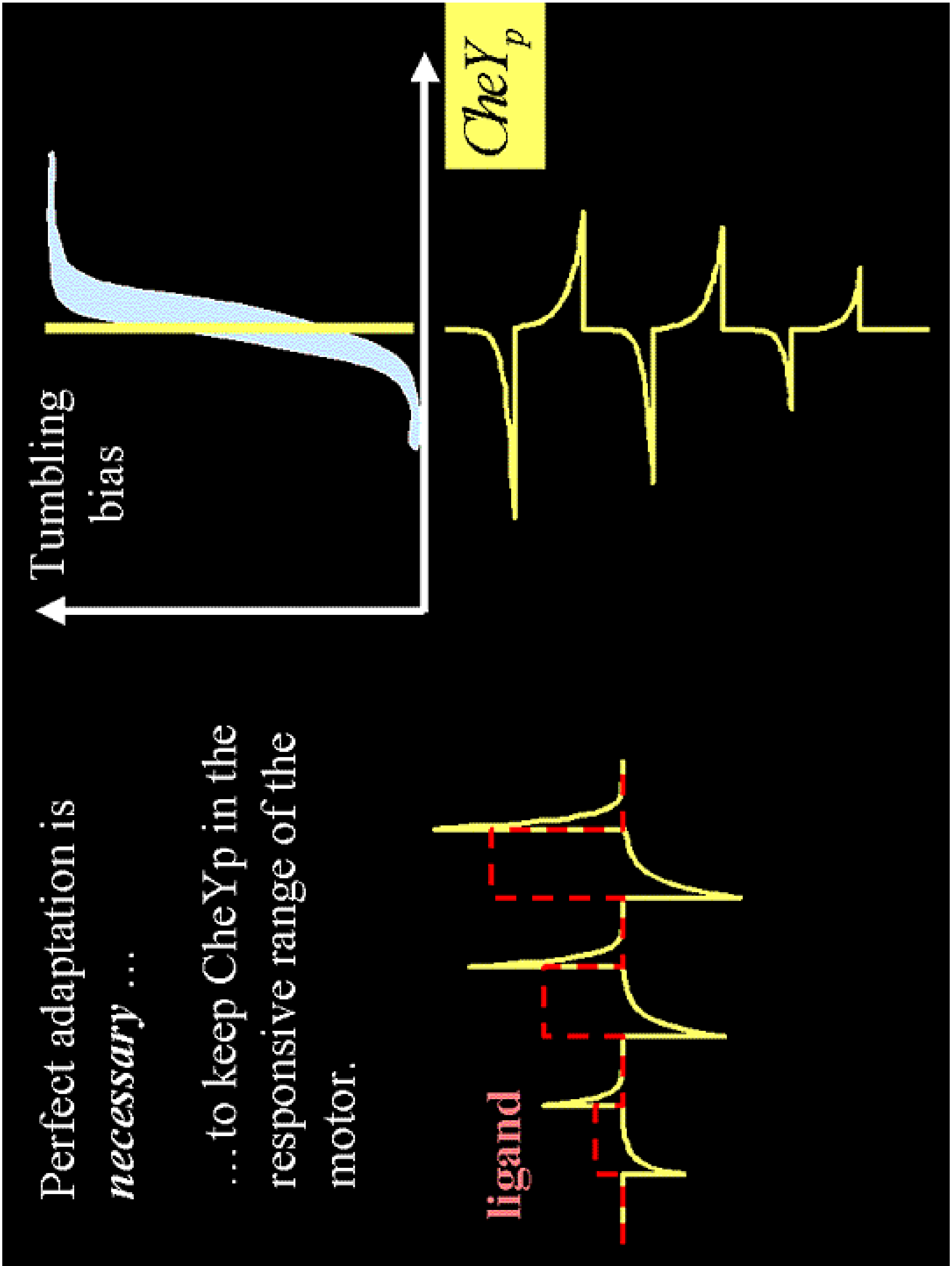

Ligand
No methylation
Tumble
(less ligand)
Extend run
(more ligand)

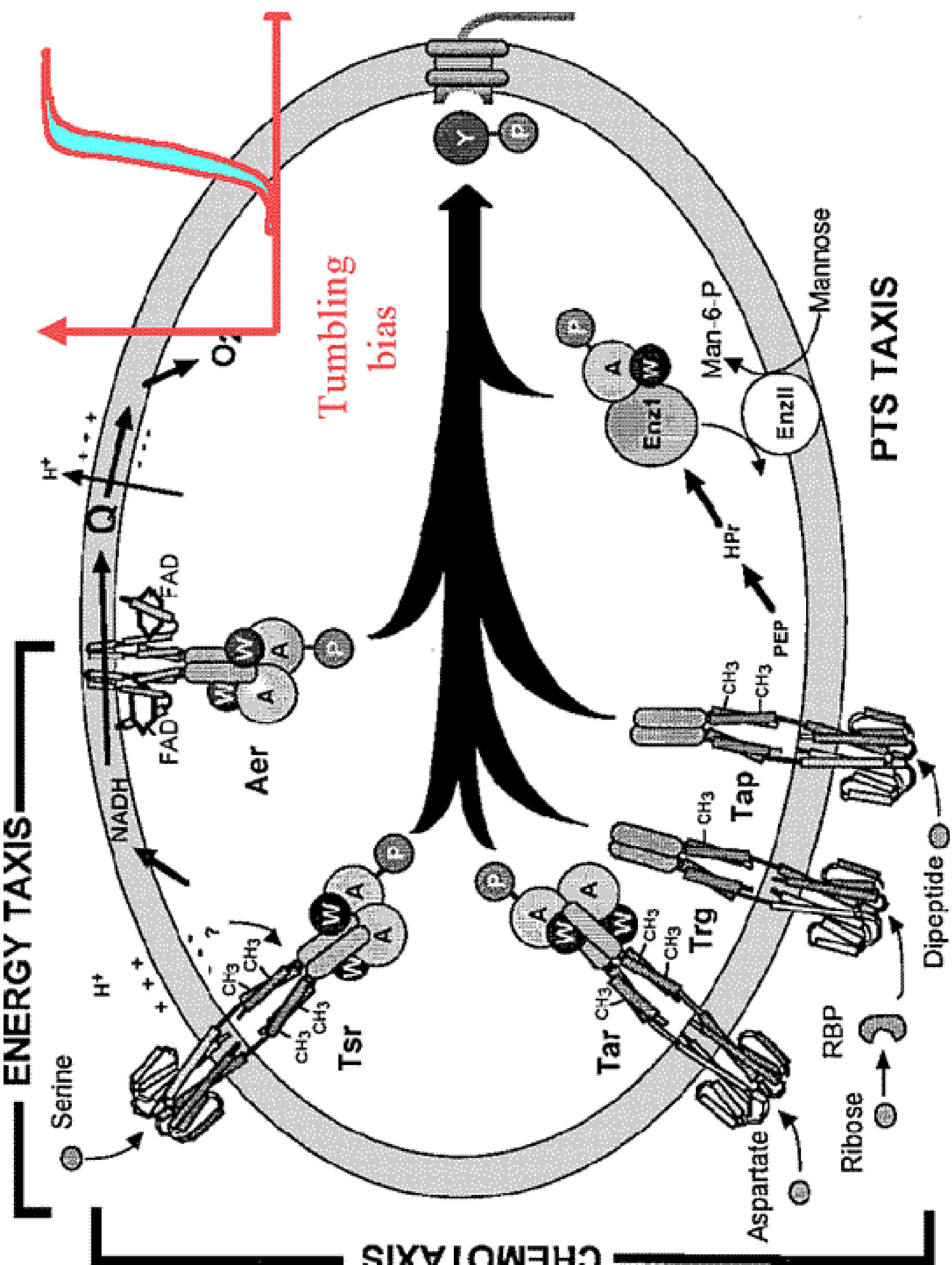
Biologists call this
"perfect adaptation"

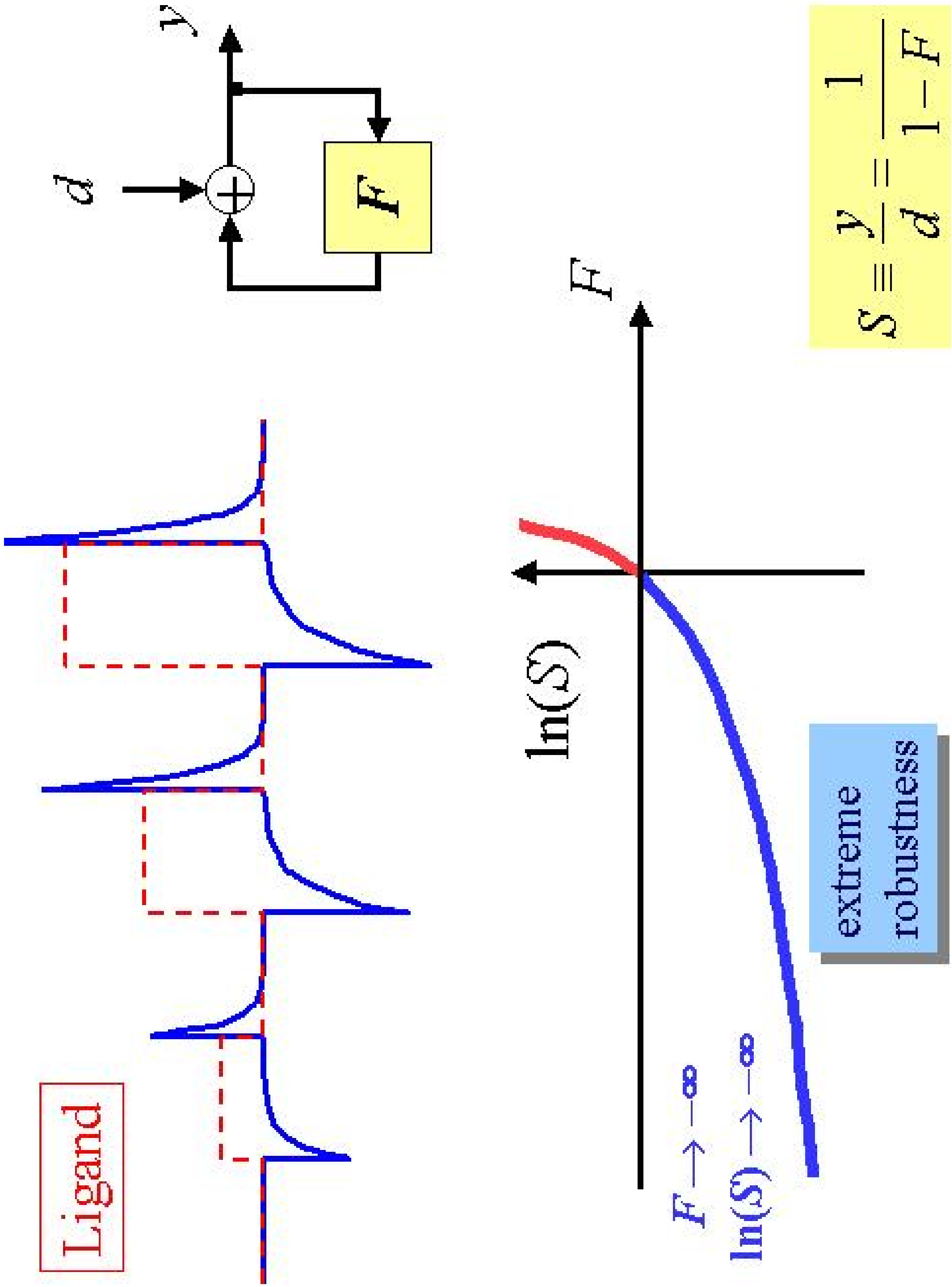


- Methylation produces "perfect adaptation" by ***integral feedback***.
- Integral feedback is ubiquitous in both engineering systems and biological systems.
- Integral feedback is ***necessary*** for ***robust*** perfect adaptation.

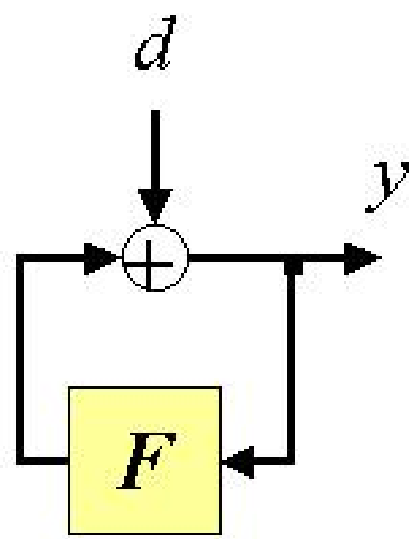

Perfect adaptation is
necessary &
Tumbling
bias
ligand
$CheY_p$
$CheY_p$
Motor
Signal
Transduction


Perfect adaptation is
necessary …
…to keep CheYp in the
responsive range of the
motor.
Tumbling
bias
CheY$_p$
ligand


ENERGY TAXIS
CHEMOTAXIS
PTS TAXIS
Tumbling bias
Serine
Aspartate
Ribose
RBP
Dipeptide
Mannose
Man-6-P
Tsr
Tar
Trg
Tap
Aer
NADH
FAD
Q
O_2
H^+
Enz1
EnzII
HPr
PEP
Y
P
A
W
CH_3



d
y
F
Ligand
ln(S)
F
extreme robustness
$S \equiv \frac{y}{d} = \frac{1}{1-F}$
$F \to -\infty$
$\ln(S) \to -\infty$



Integral feedback

$$F(s) = \frac{\hat{F}(s)}{s}, \quad \hat{F}(0) < 0$$

$$\Updownarrow$$

$$F(0) = -\infty$$

$$\Updownarrow$$

$$S(0) = 0$$

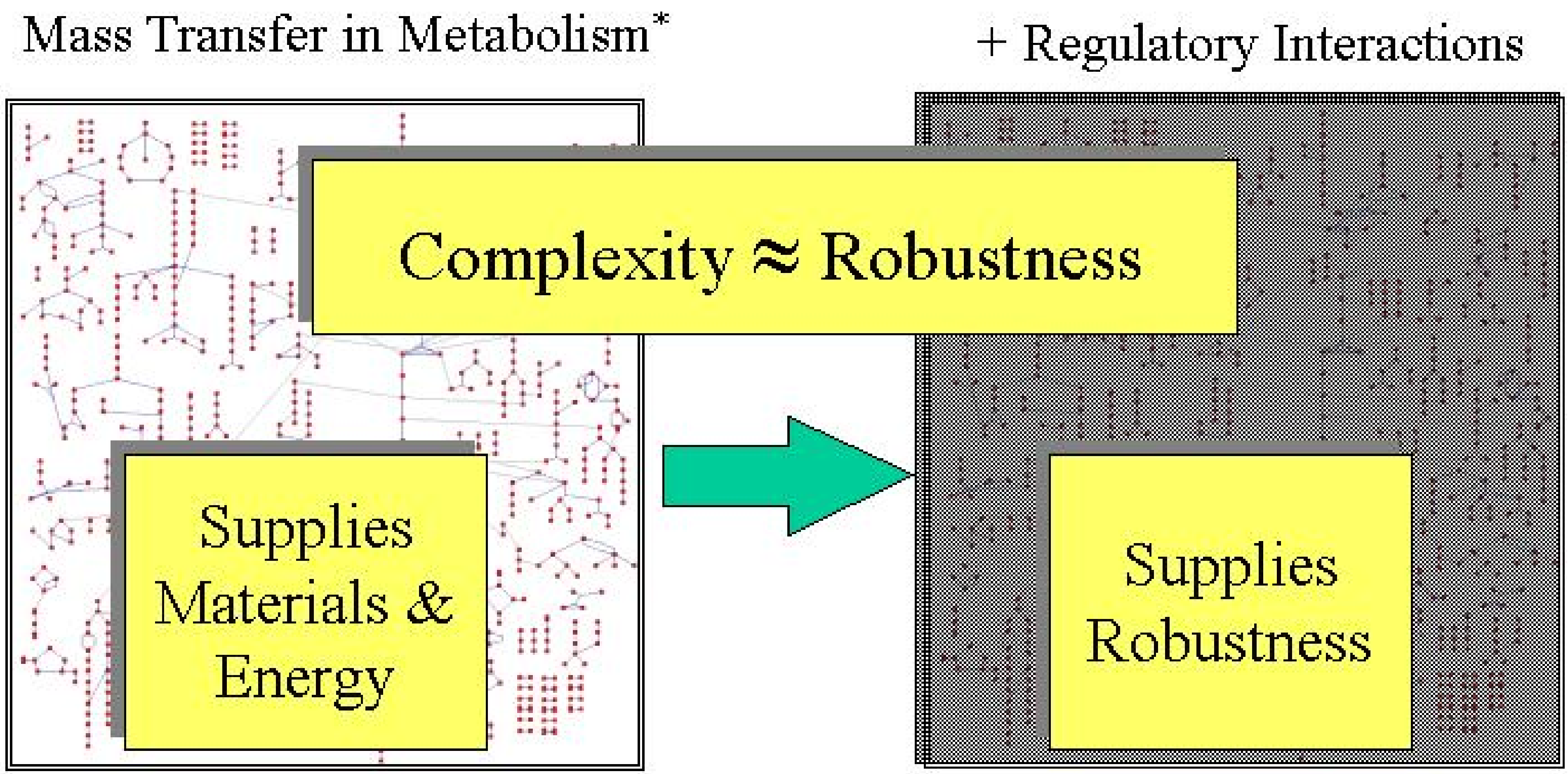
$$S \equiv \frac{y}{d} = \frac{1}{1-F}$$

$F \rightarrow -\infty$

$\ln(S) \rightarrow -\infty$

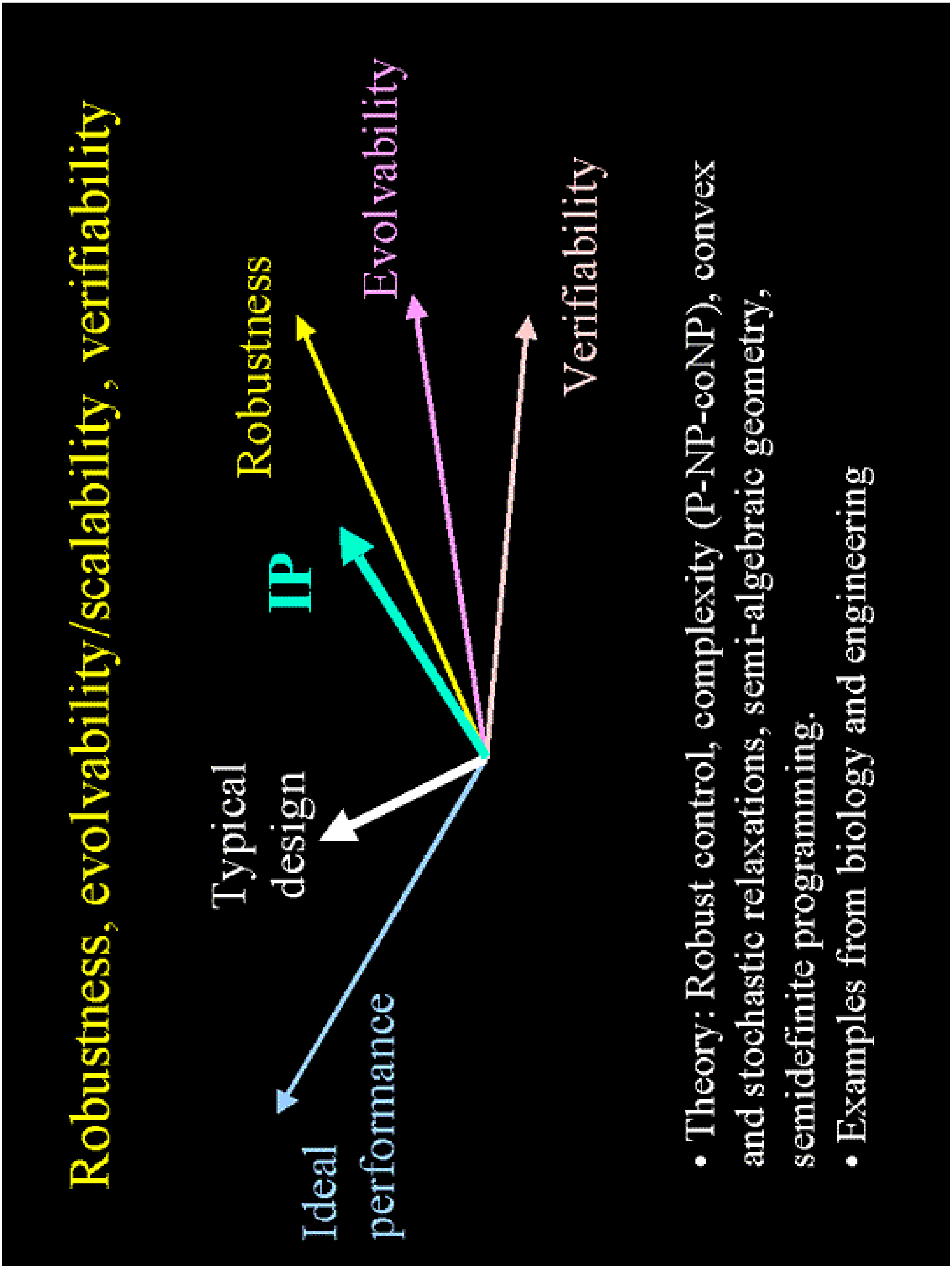

Fine tuned or robust ?
Maybe just not the right question.
Fine tuned *for* robustness…
…with resource costs and new fragilities as the price.
Necessity:
– How network *must* be (robustness)
– Price to pay (fragility)

Biochemical Network: E. Coli Metabolism



From Adam Arkin

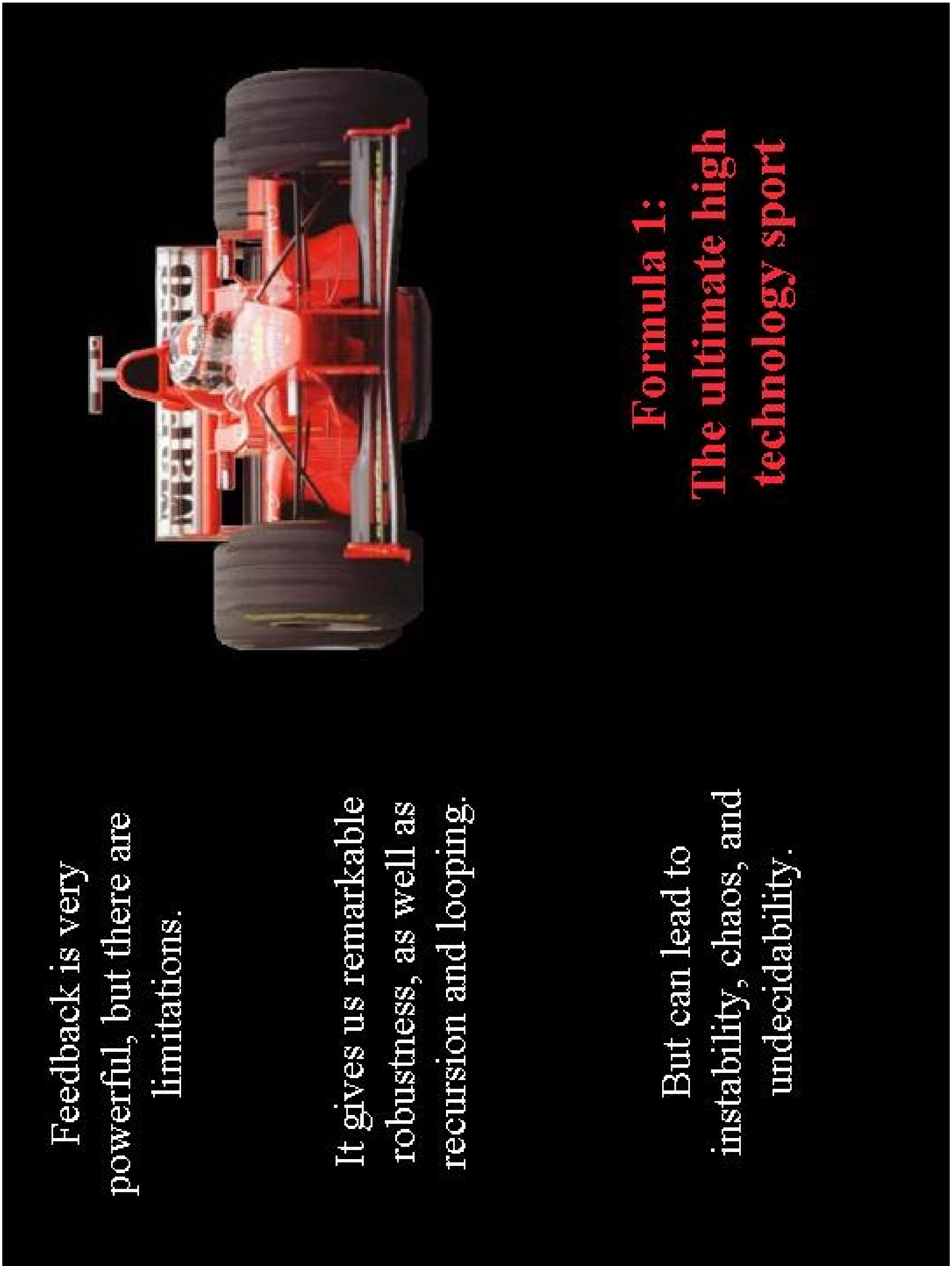
* from: EcoCYC by Peter Karp

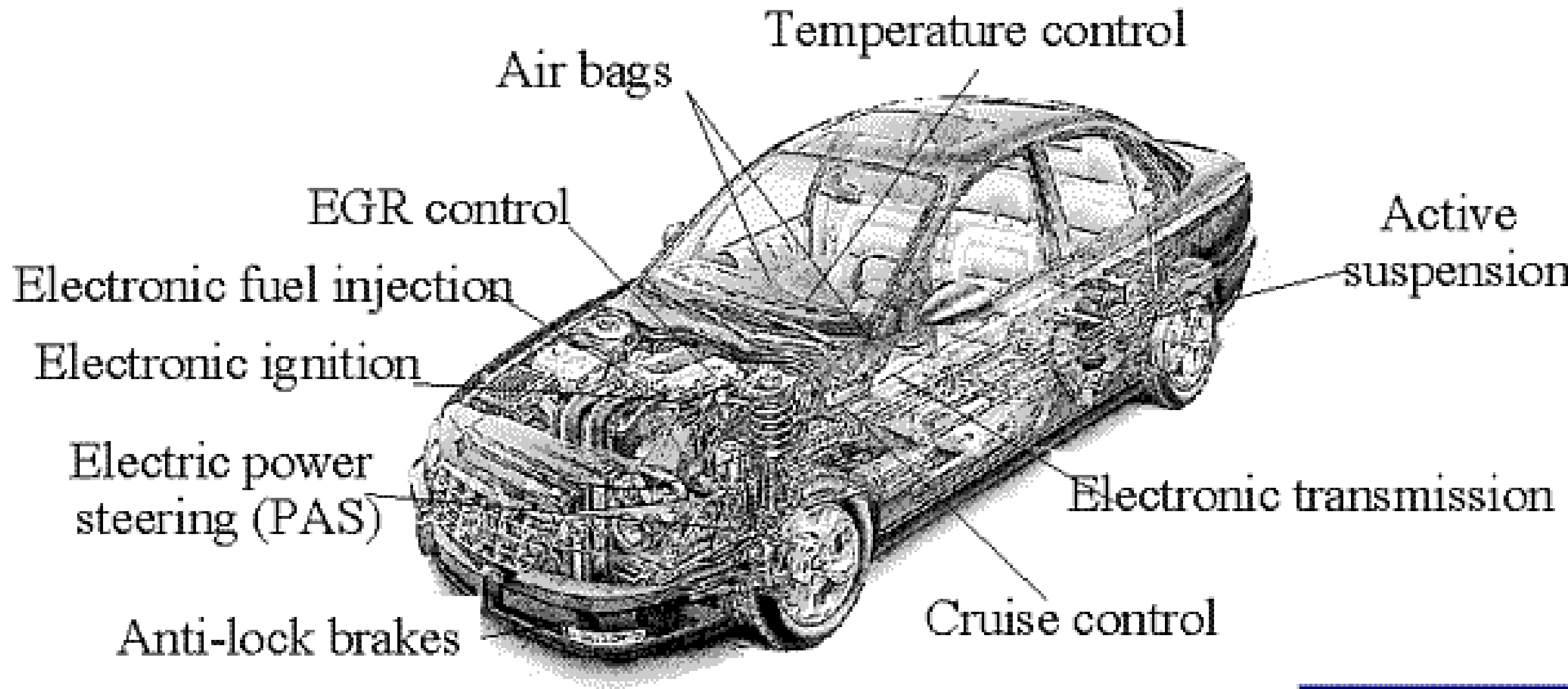

Robustness, evolvability/scalability, verifiability
Robustness
Evolvability
Verifiability
IP
Typical design
Ideal performance
• Theory: Robust control, complexity (P-NP-coNP), convex and stochastic relaxations, semi-algebraic geometry, semidefinite programming.
• Examples from biology and engineering

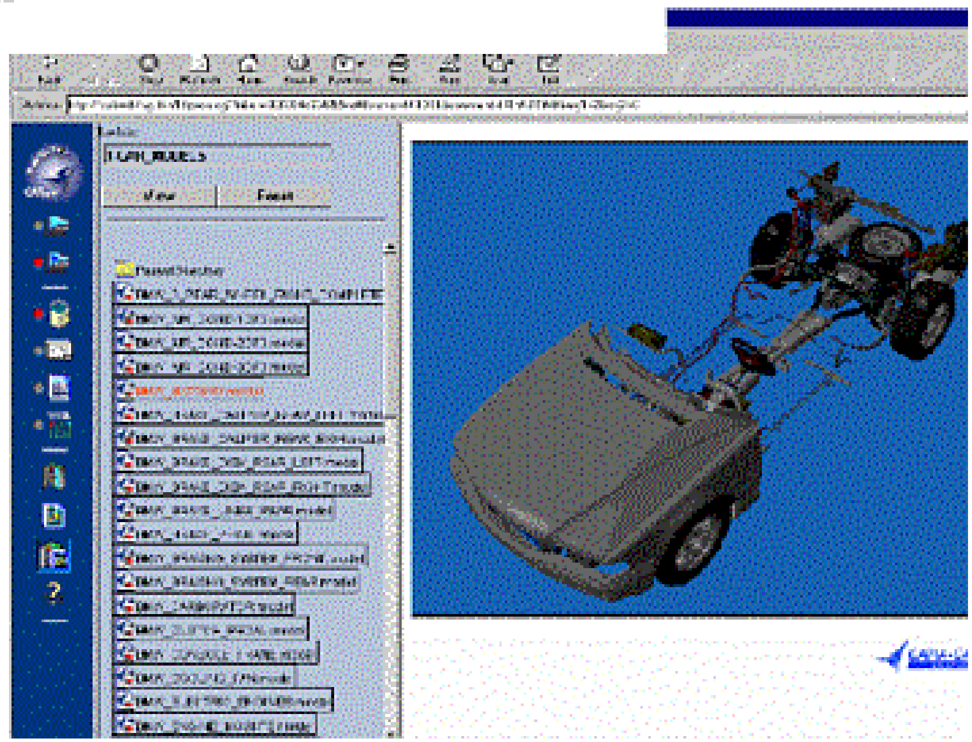
What about ?

- Information & entropy
- Fractals & self-similarity
- Chaos
- Criticality and power laws
- Undecidability
- Fuzzy logic, neural nets, genetic algorithms
- Emergence
- Self-organization
- Complex adaptive systems
- New science of complexity

- Not really about complexity
- These concepts themselves are "robust, yet fragile"
- Powerful in their niche
- Brittle (break easily) when moved or extended
- Some are relevant to biology and engineering systems
- Comfortably reductionist
- Remarkably useful in getting published

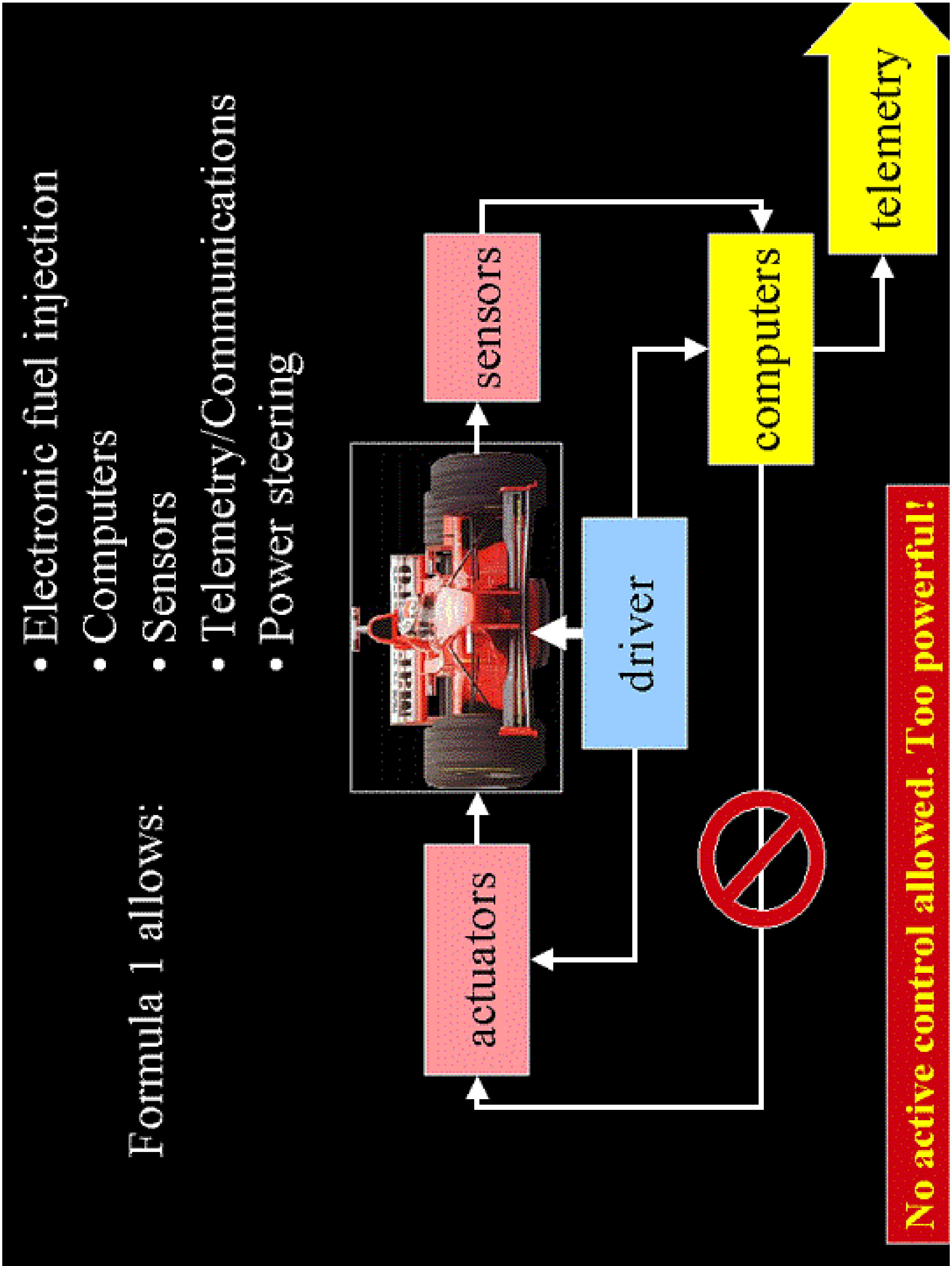

Formula 1:
The ultimate high
technology sport
Feedback is very
powerful, but there are
limitations.
It gives us remarkable
robustness, as well as
recursion and looping.
But can lead to
instability, chaos, and
undecidability.

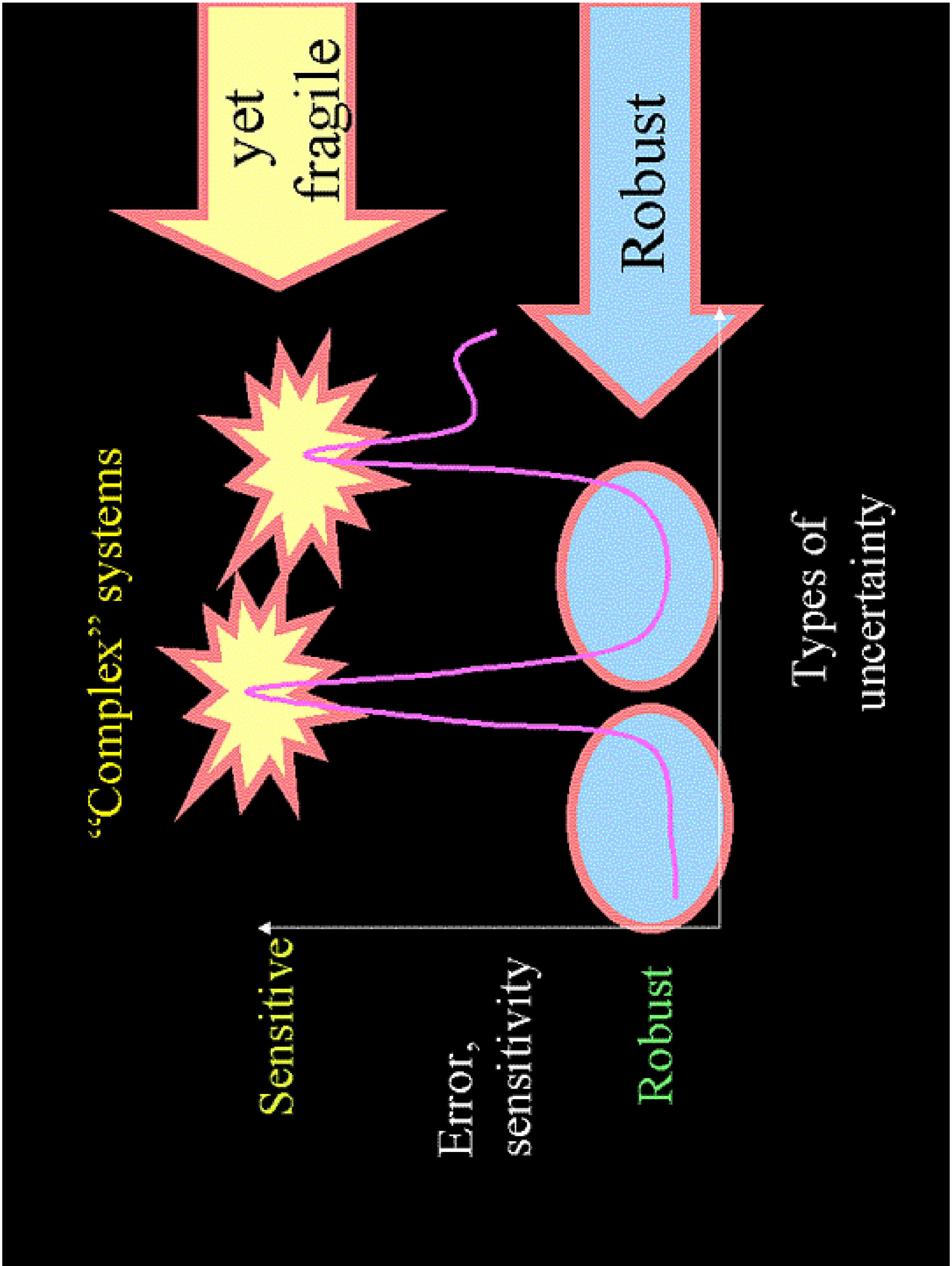




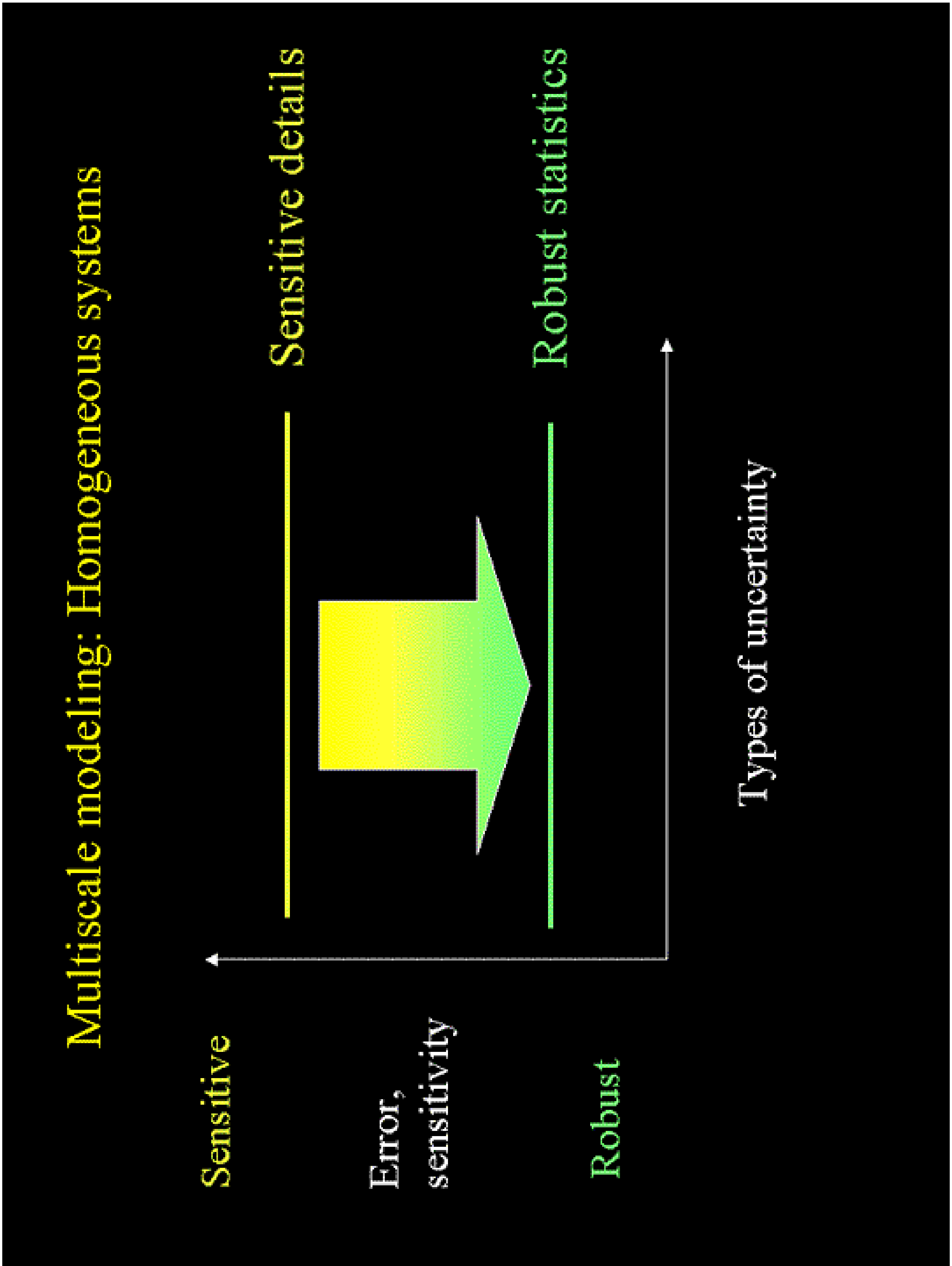
In development:

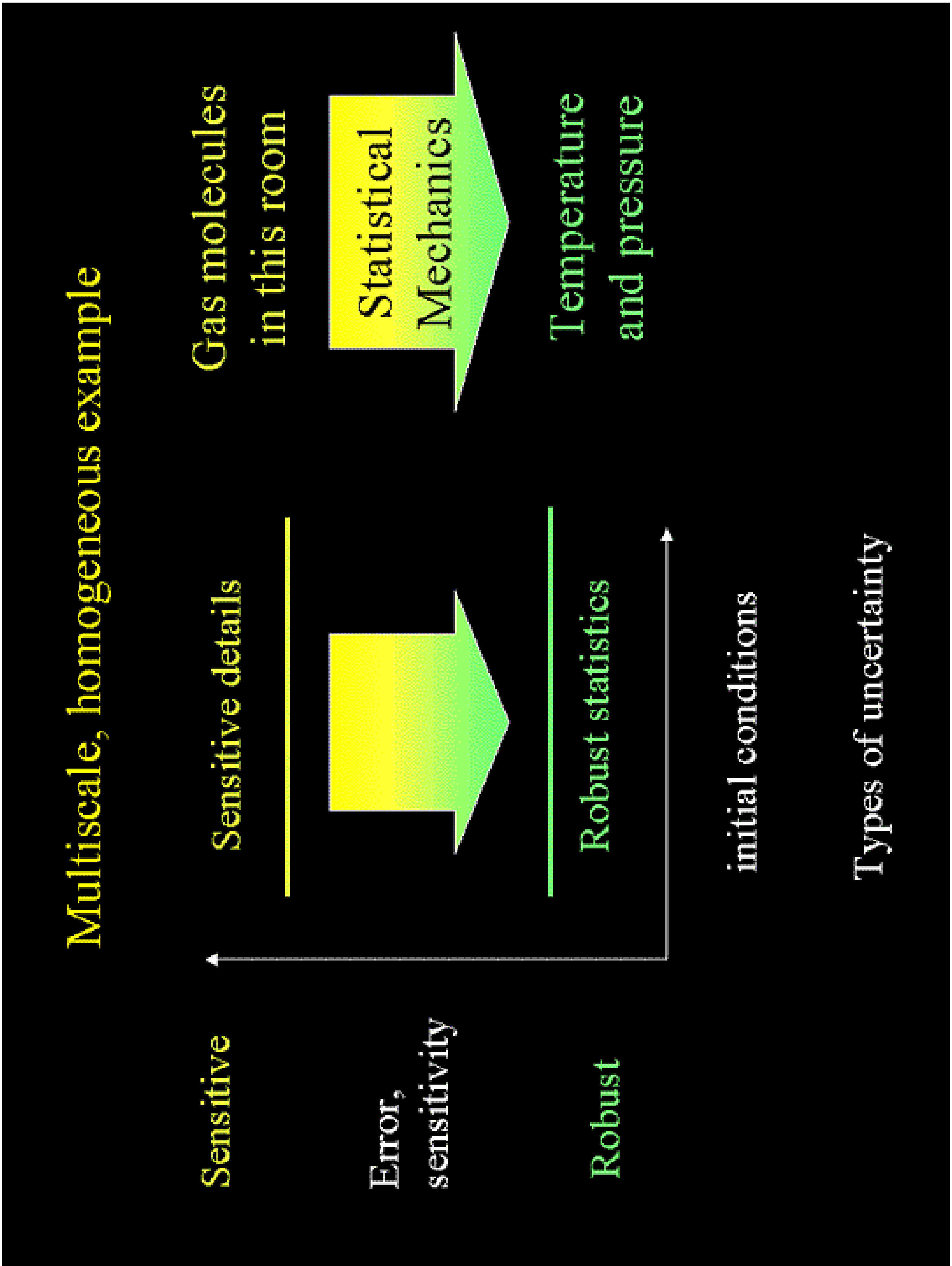
- drive-by-wire
- steering/traction control
- collision avoidance

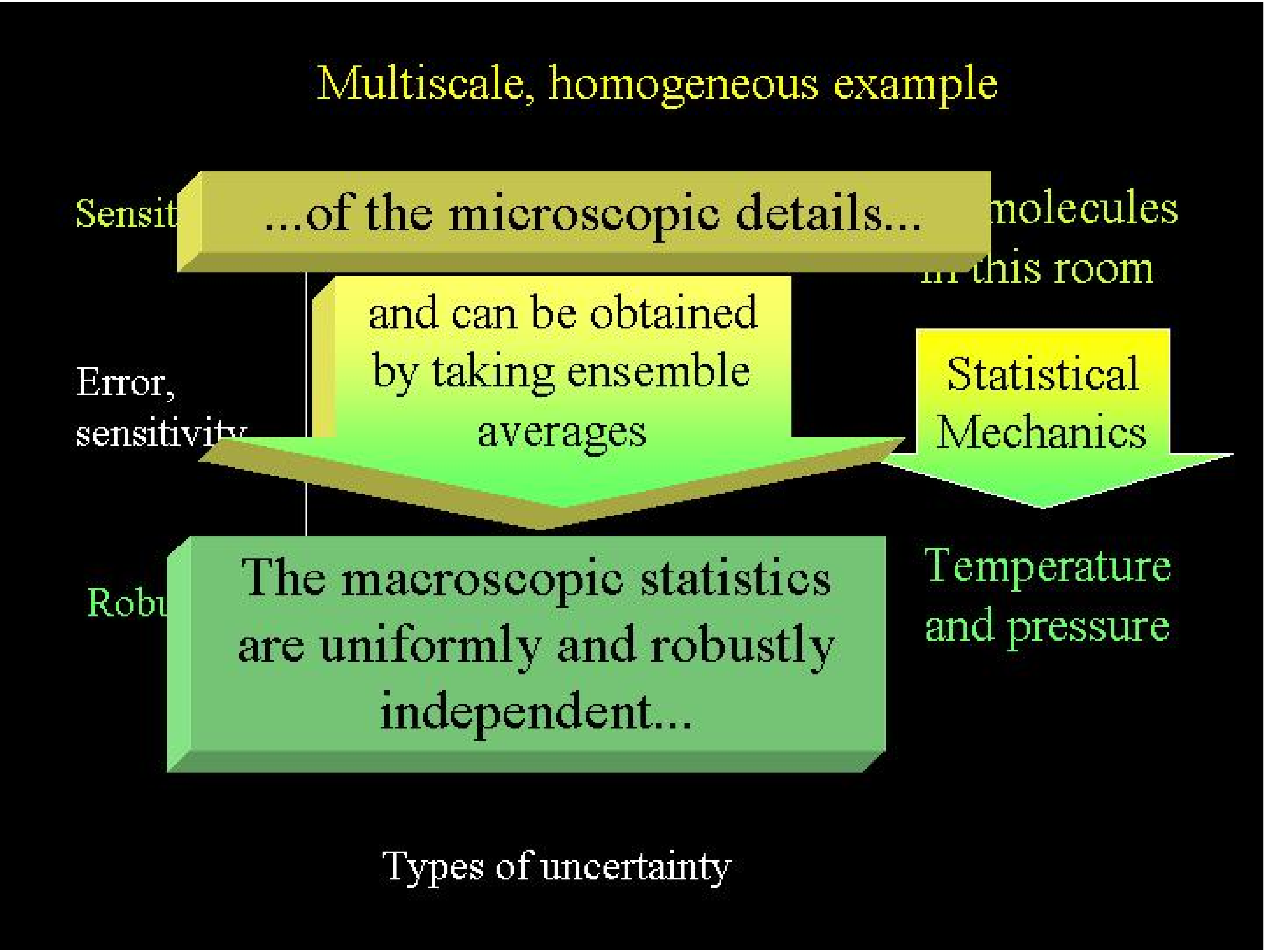

Formula 1 allows:
• Electronic fuel injection
• Computers
• Sensors
• Telemetry/Communications
• Power steering
actuators
sensors
driver
computers
telemetry
No active control allowed. Too powerful!

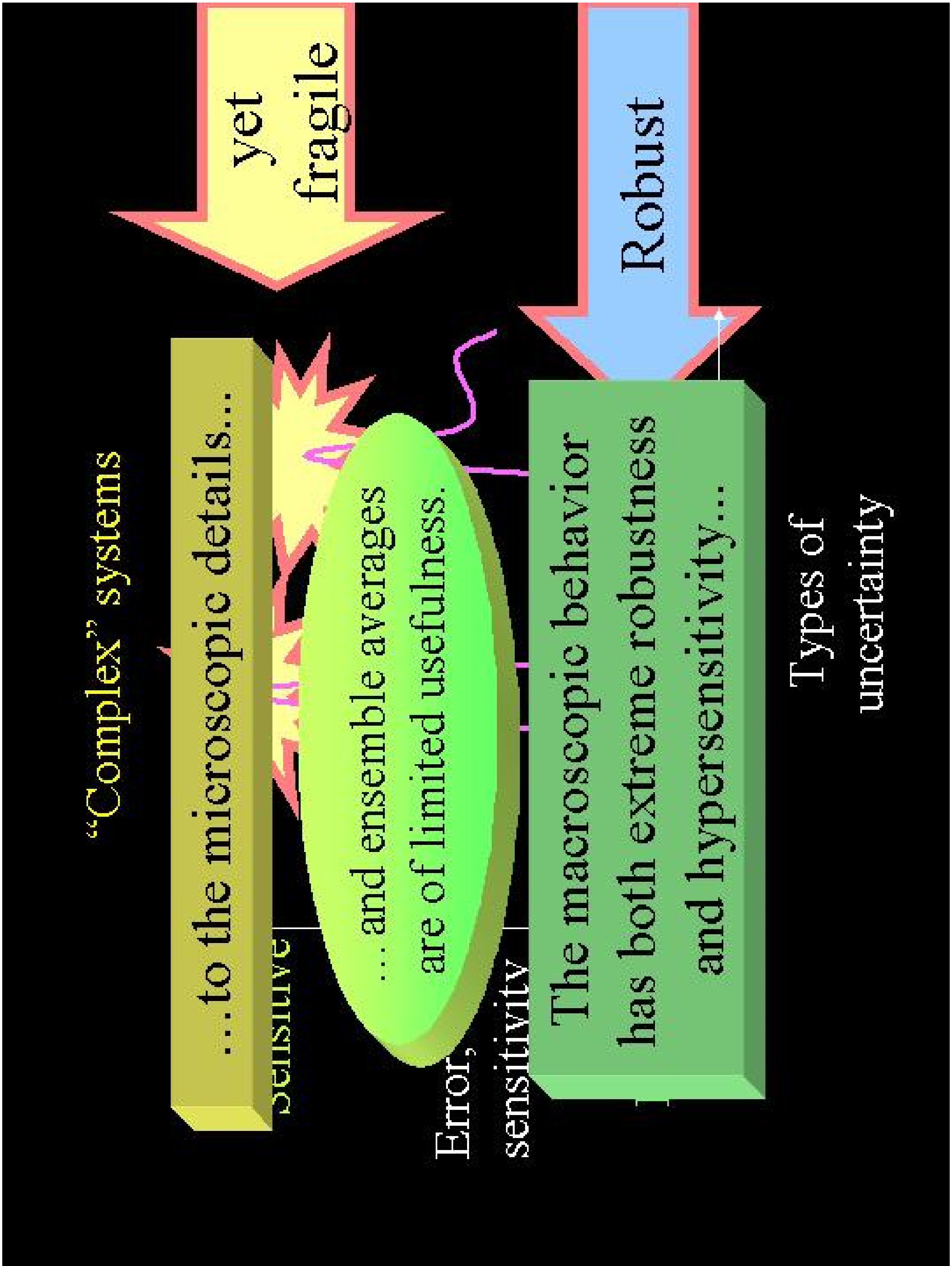


yet
fragile
Robust
“Complex” systems
Types of
uncertainty
Sensitive
Error,
sensitivity
Robust

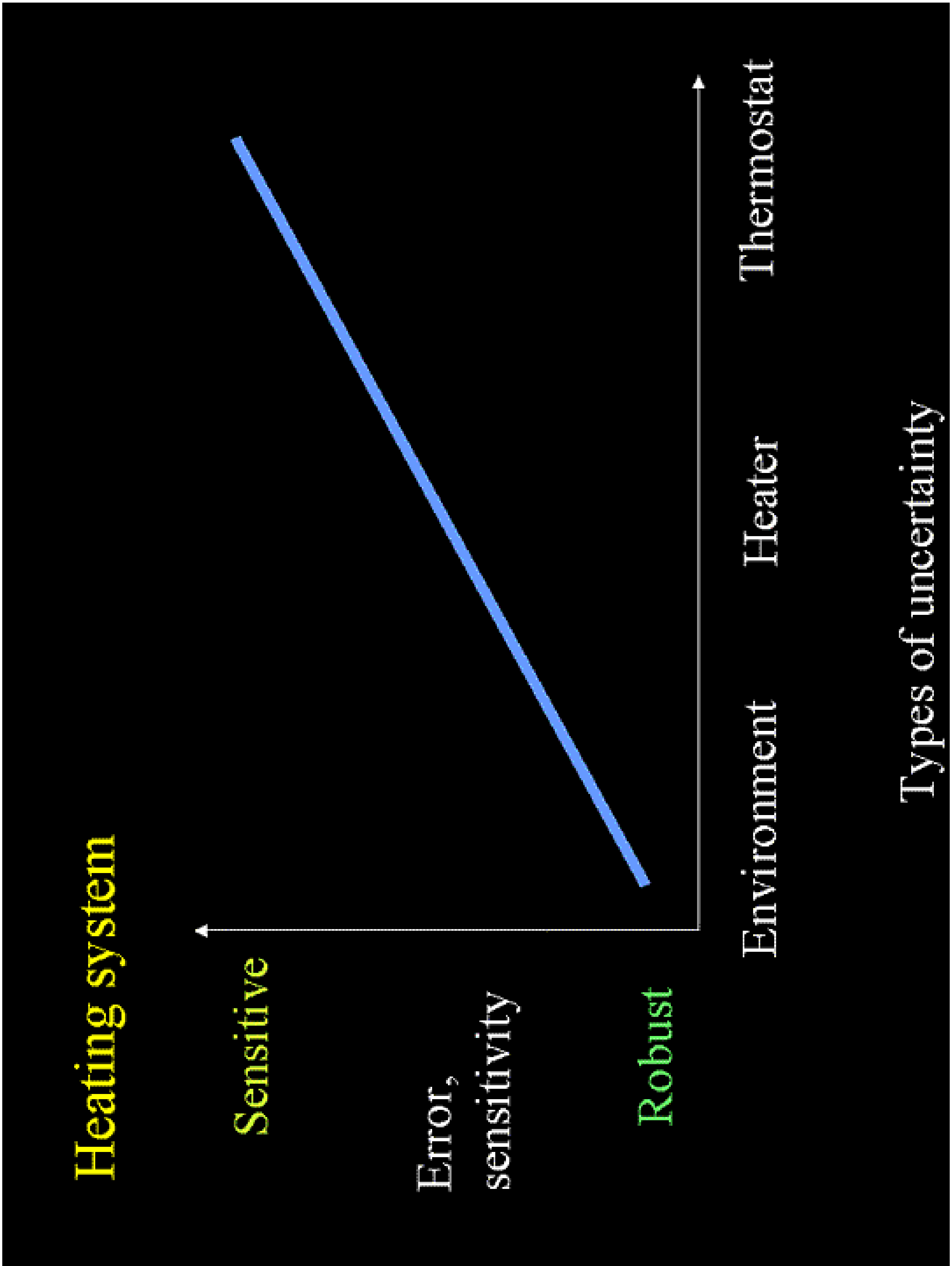

Multiscale modeling: Homogeneous systems
Sensitive details
Robust statistics
Sensitive
Error,
sensitivity
Robust
Types of uncertainty

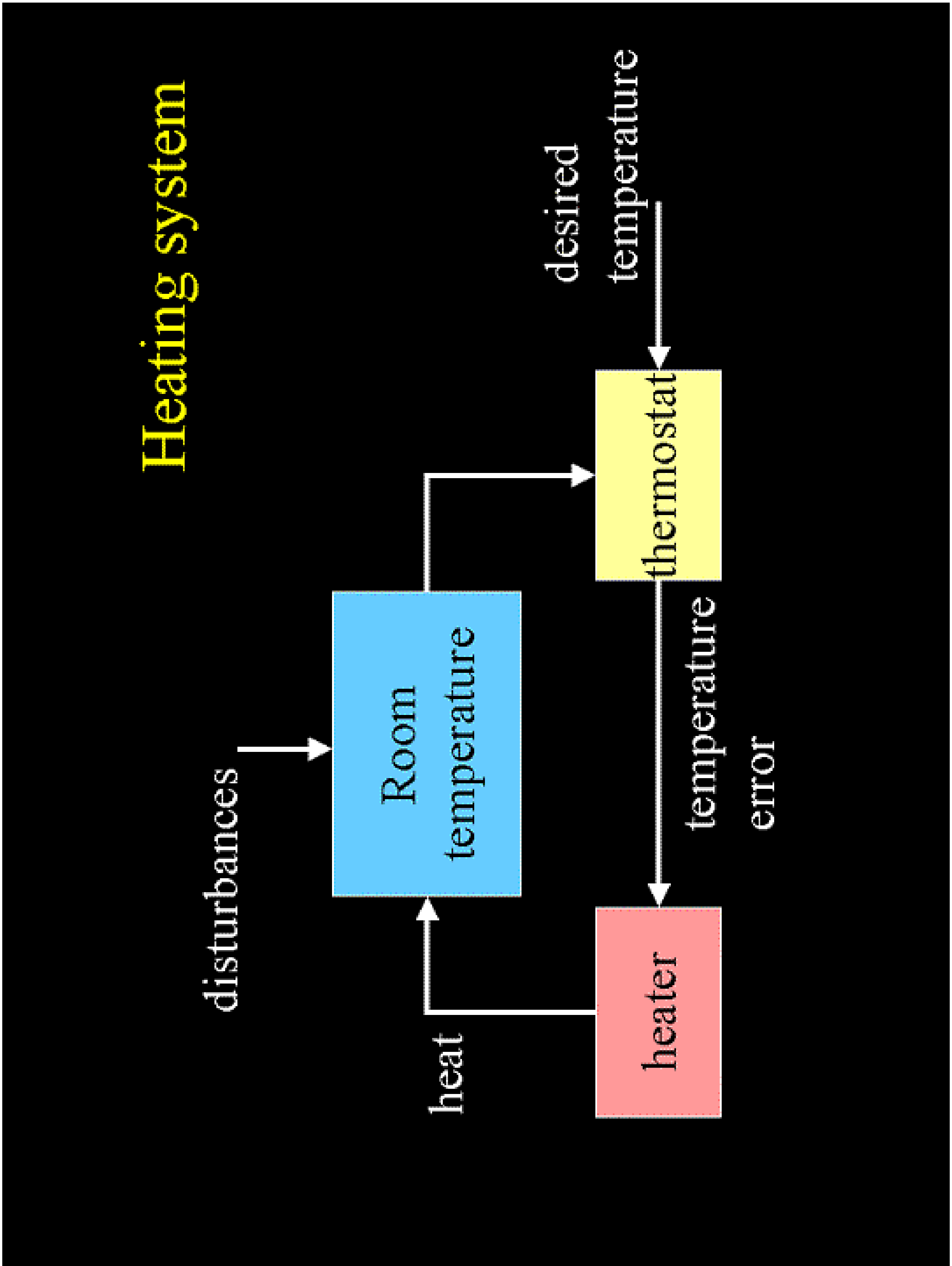

Multiscale, homogeneous example
Sensitive
Error, sensitivity
Robust
Sensitive details
Robust statistics
initial conditions
Types of uncertainty
Gas molecules in this room
Statistical Mechanics
Temperature and pressure


Multiscale, homogeneous example
Sensit
...of the microscopic details...
molecules
in this room
and can be obtained
by taking ensemble
averages
Statistical
Mechanics
Error,
sensitivity
Temperature
and pressure
Robu
The macroscopic statistics
are uniformly and robustly
independent...
Types of uncertainty

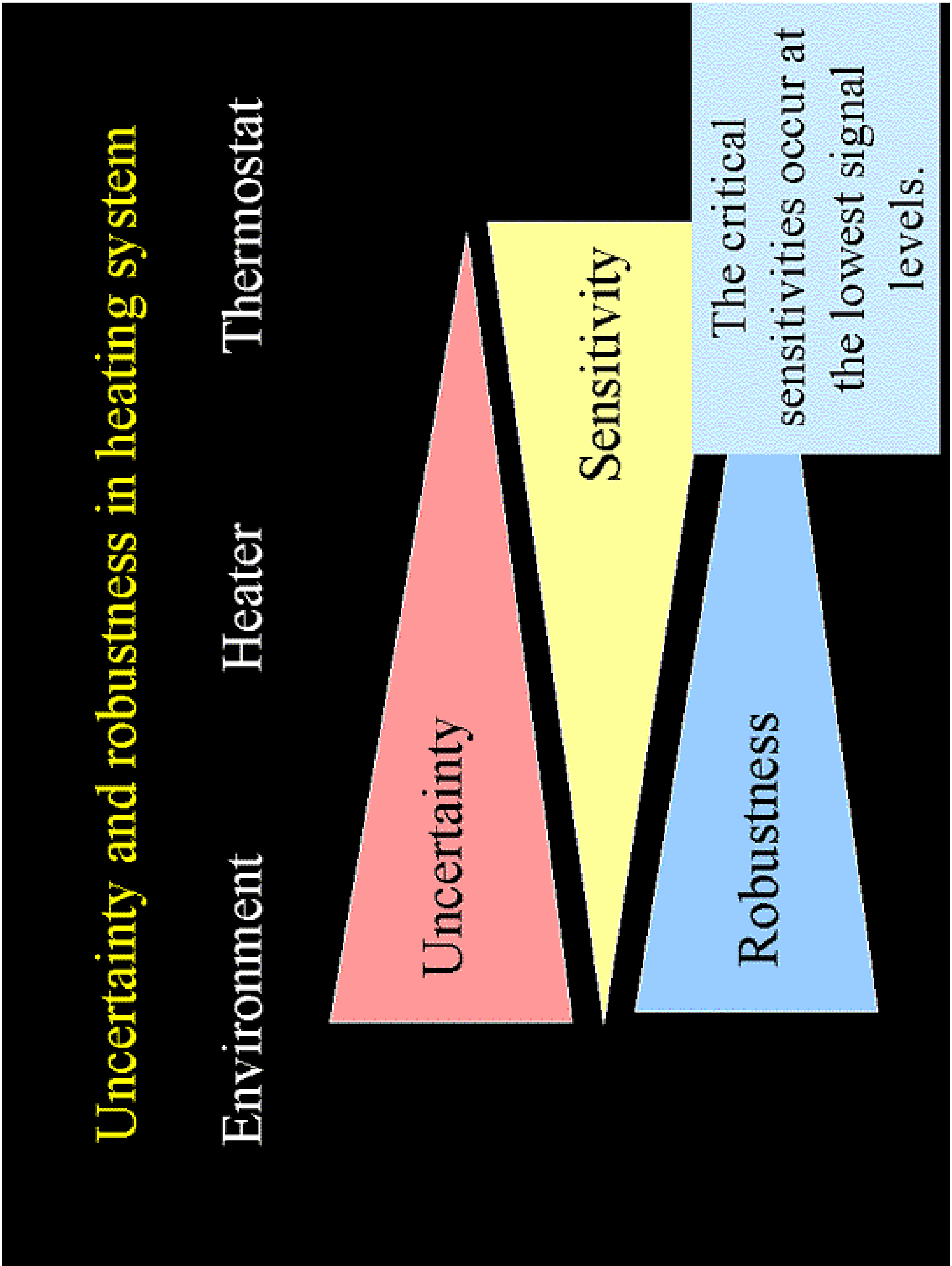


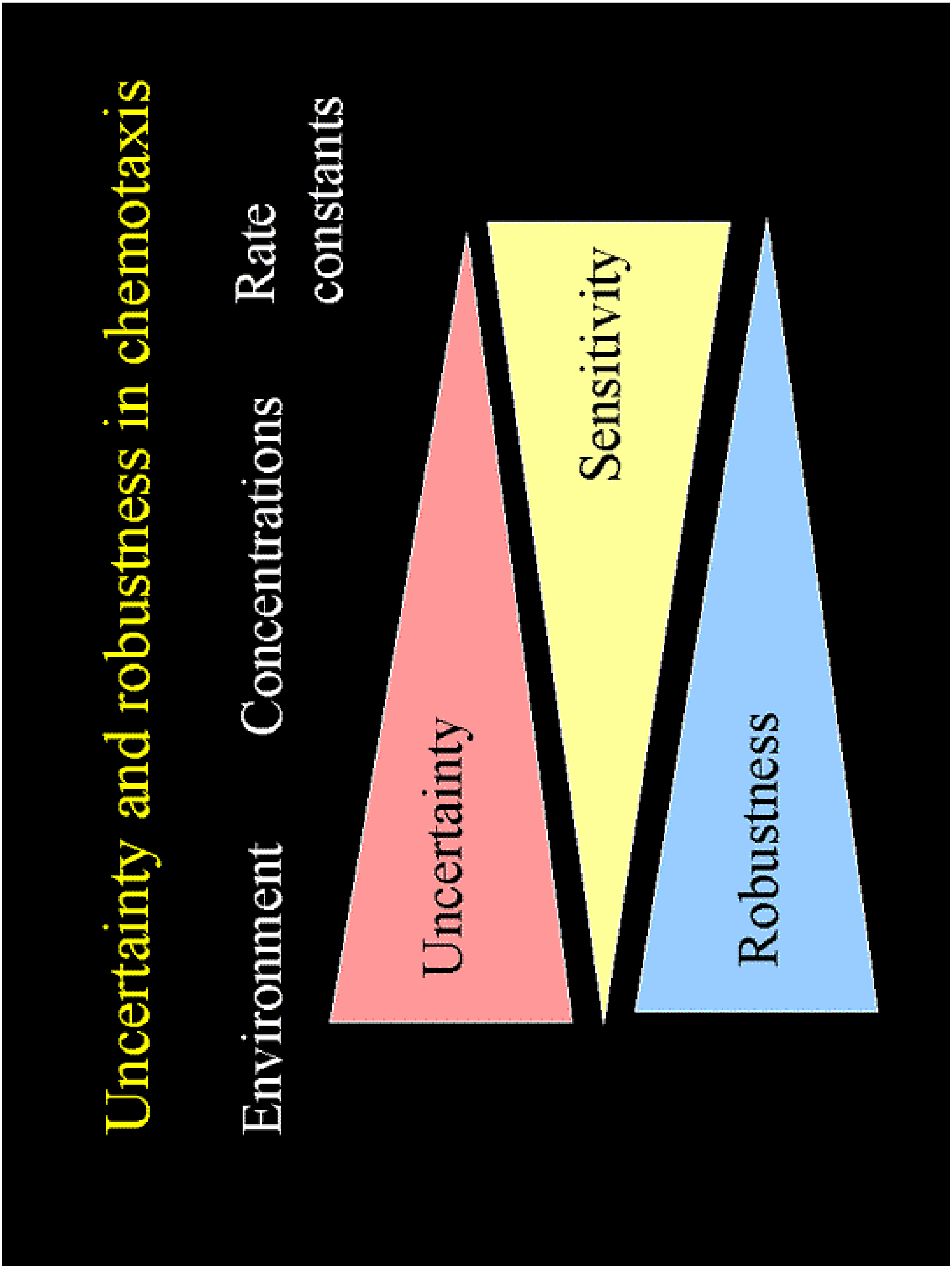
"Complex" systems
…to the microscopic details…
yet fragile
…and ensemble averages are of limited usefulness.
Error, sensitivity
Robust
The macroscopic behavior has both extreme robustness and hypersensitivity…
Types of uncertainty


Heating system
Sensitive
Error,
sensitivity
Robust
Environment
Heater
Thermostat
Types of uncertainty

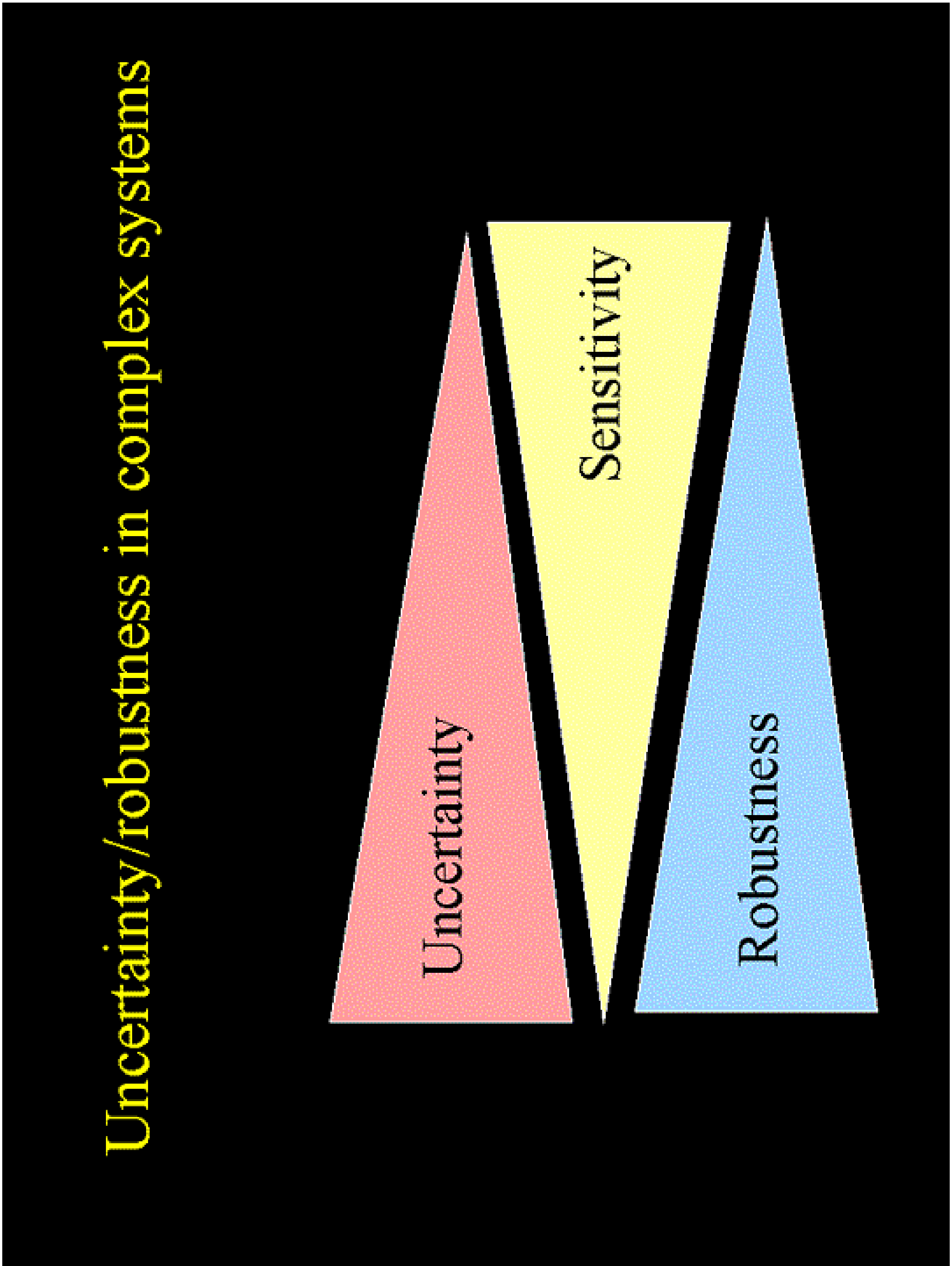

Heating system
desired
temperature
thermostat
Room
temperature
disturbances
temperature
error
heat
heater

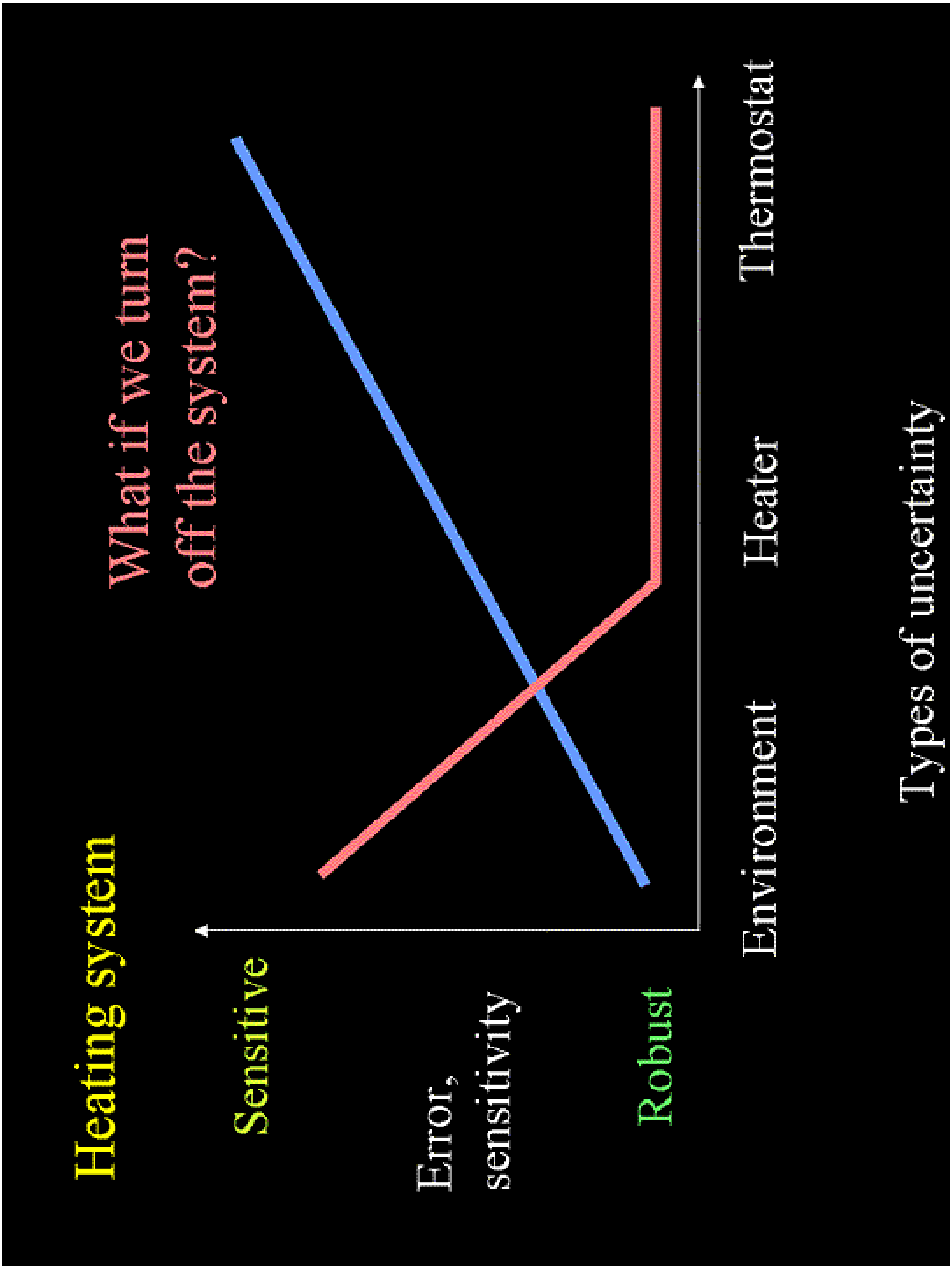
[126] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

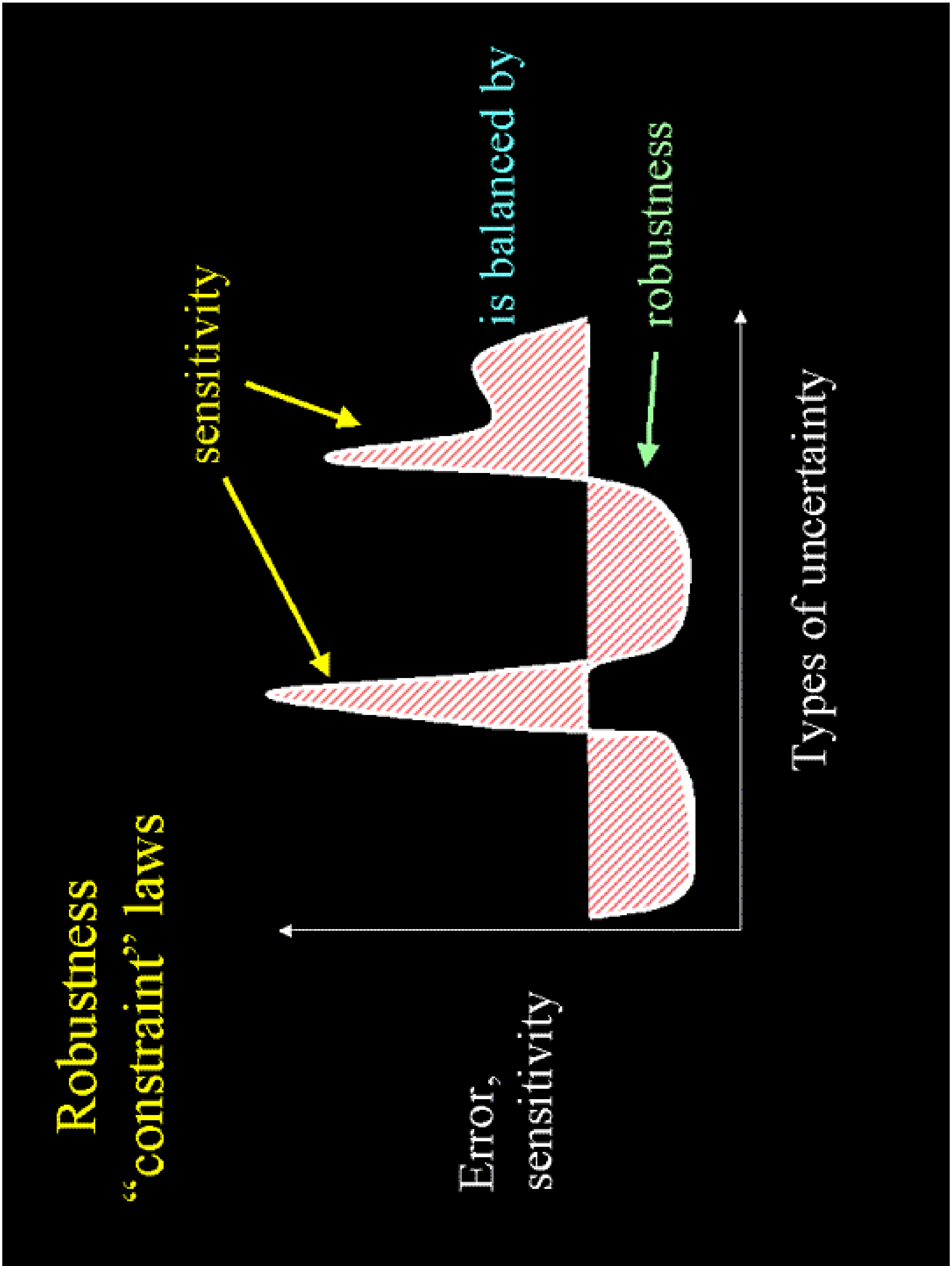


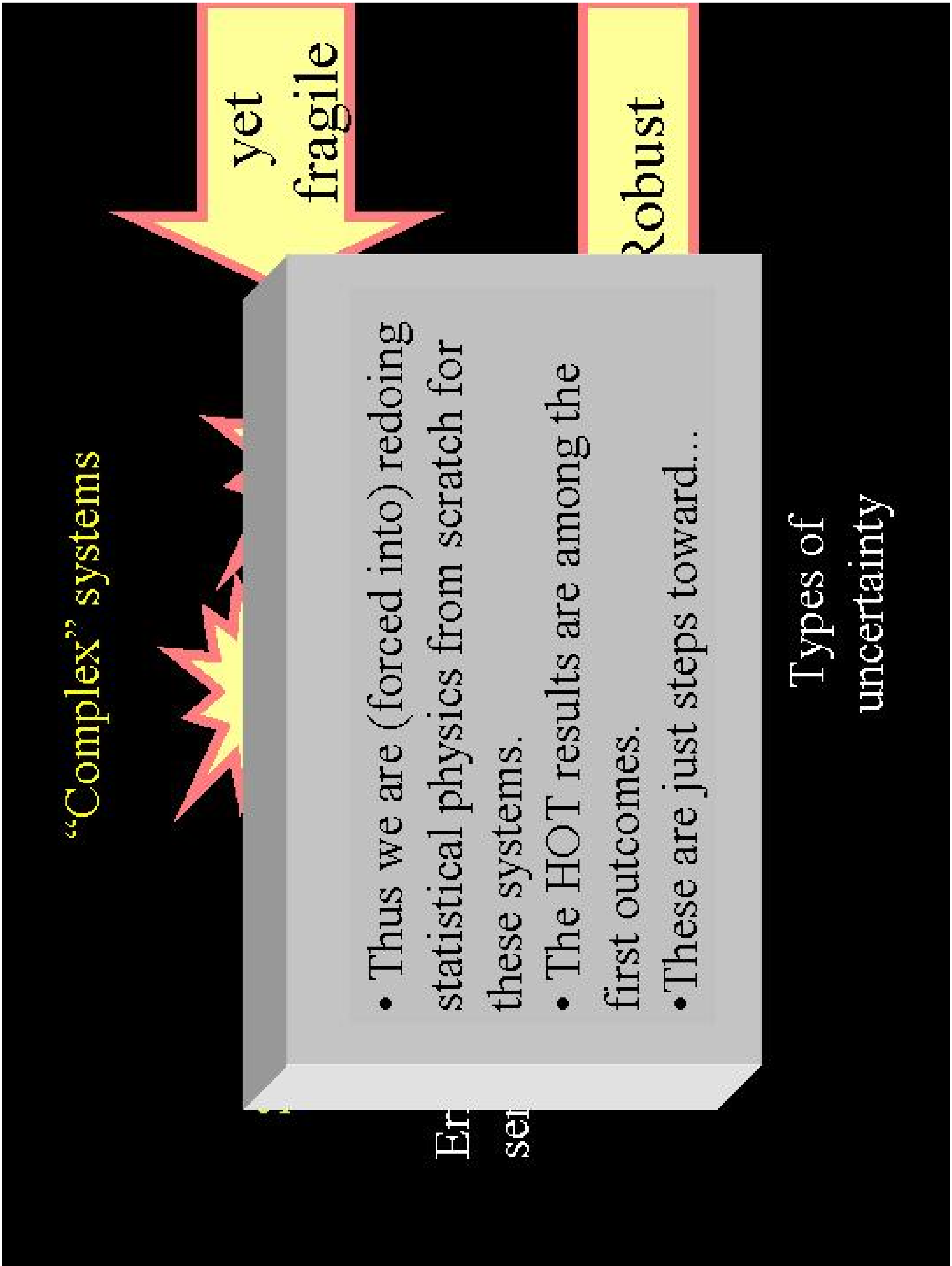

Uncertainty and robustness in chemotaxis
Environment
Concentrations
Rate constants
Uncertainty
Sensitivity
Robustness

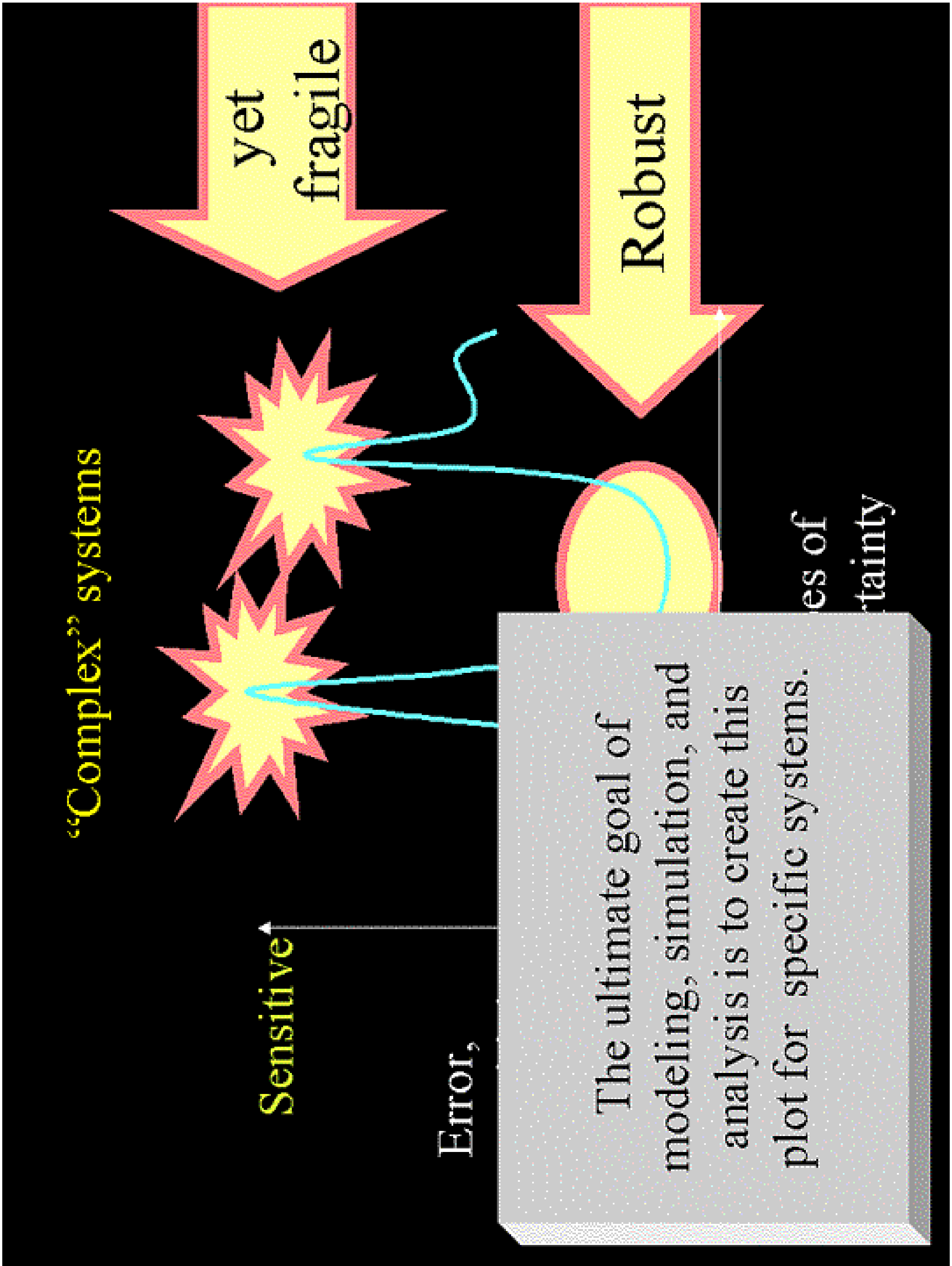
[128] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

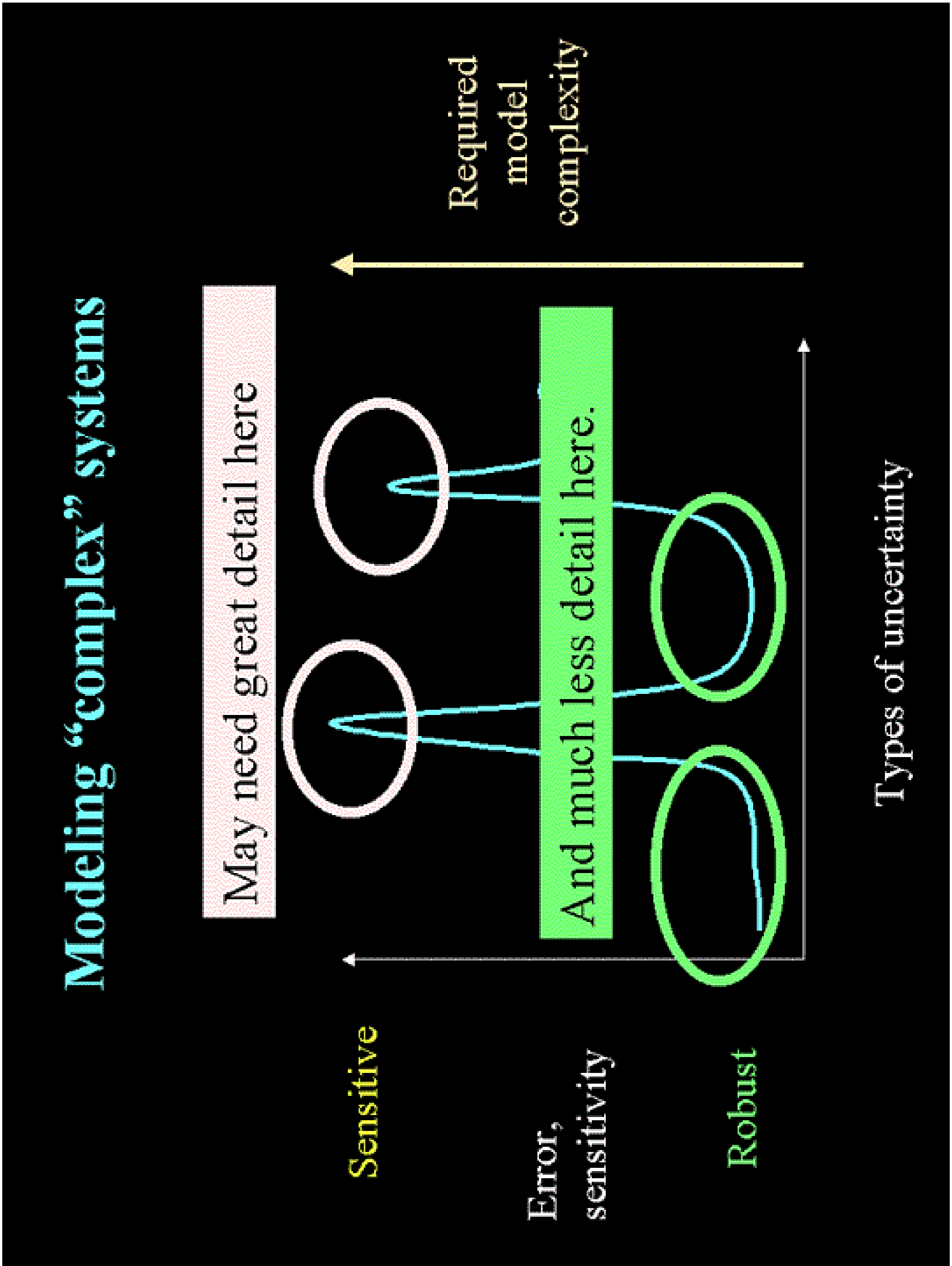


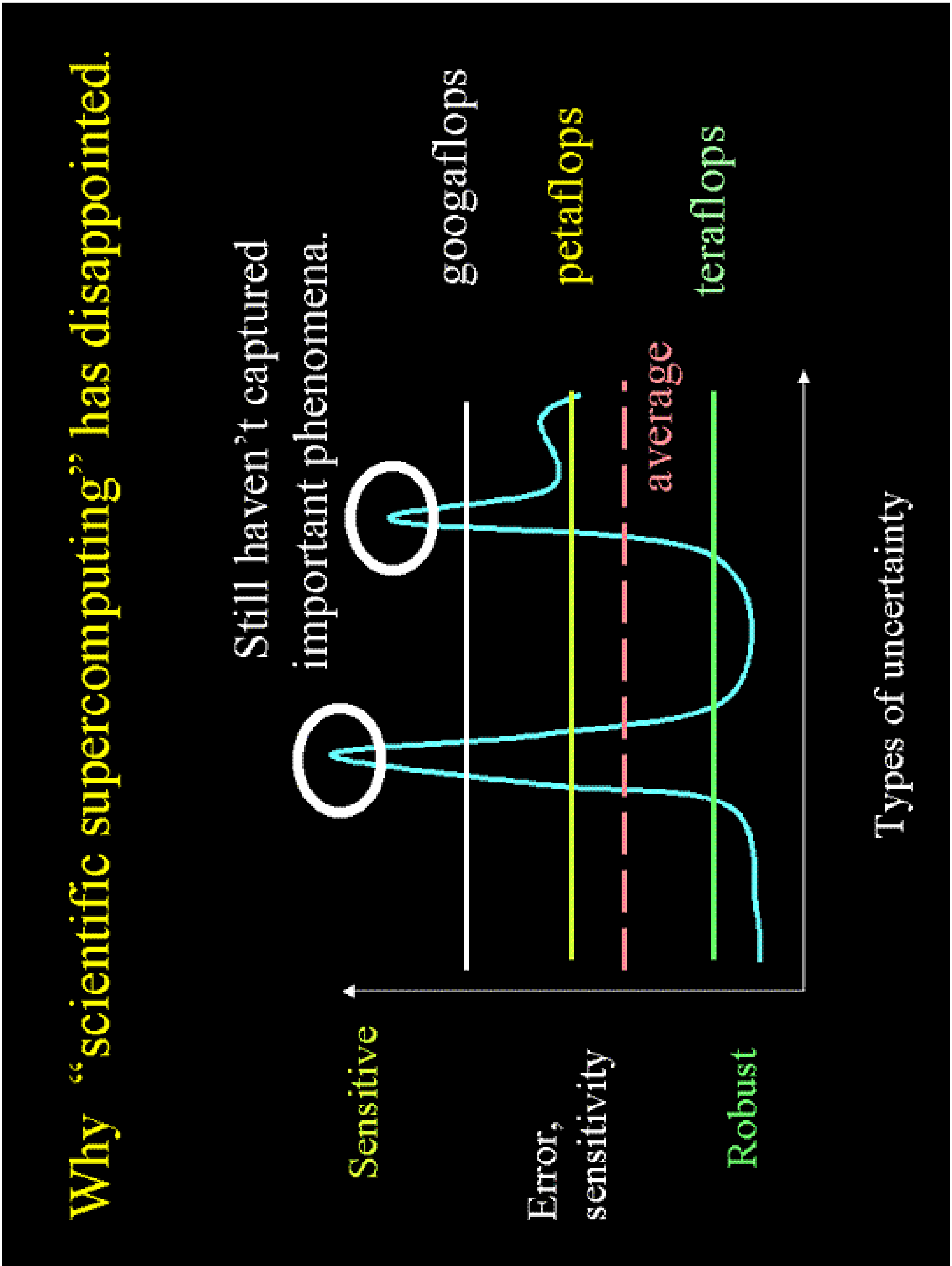

Heating system
Sensitive
Error, sensitivity
Robust
What if we turn off the system?
Environment
Heater
Thermostat
Types of uncertainty

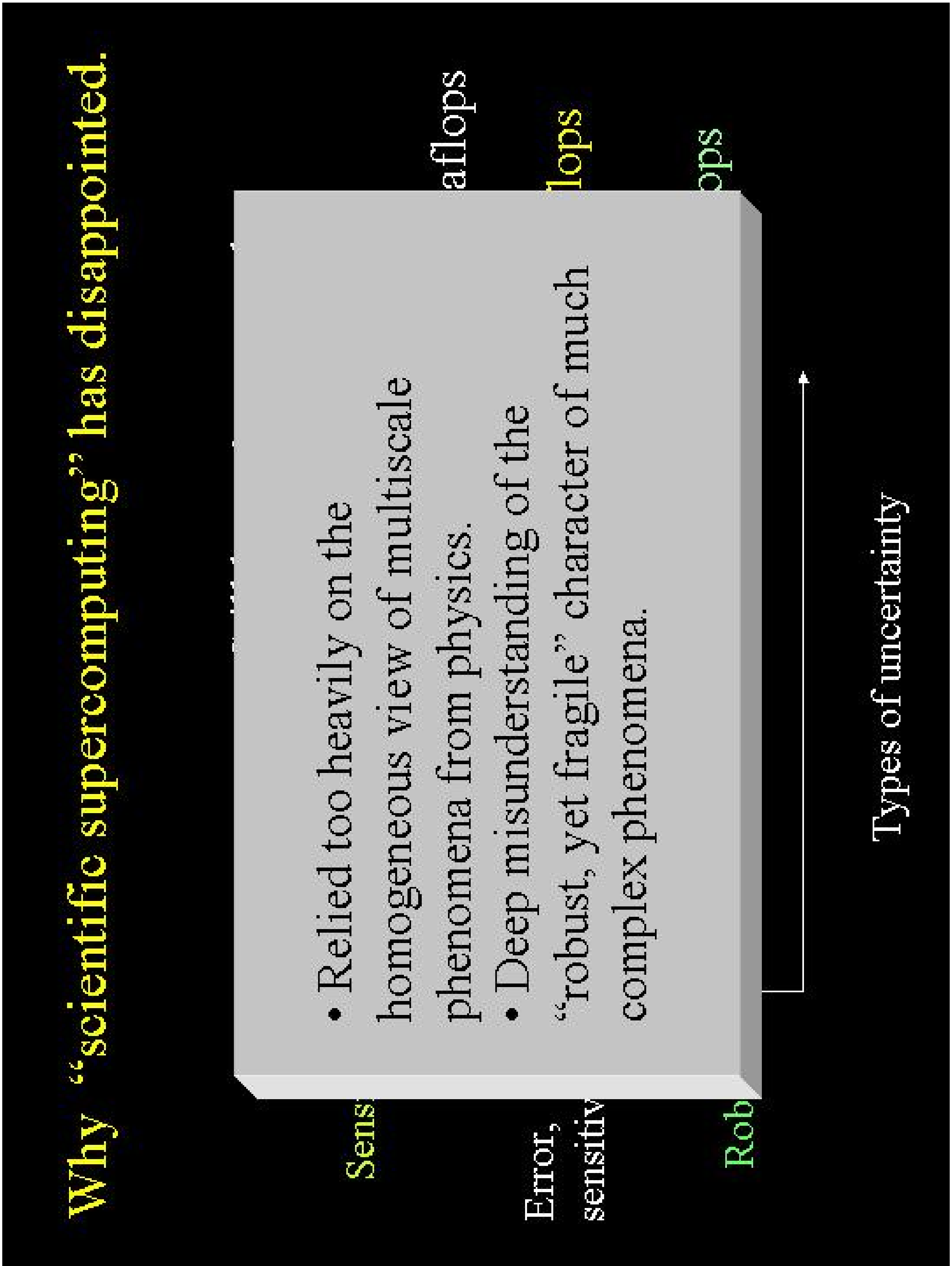

Robustness
“constraint” laws
Error,
sensitivity
sensitivity
is balanced by
robustness
Types of uncertainty


“Complex” systems
Robust
yet fragile
• Thus we are (forced into) redoing statistical physics from scratch for these systems.
• The HOT results are among the first outcomes.
•These are just steps toward…
Types of uncertainty

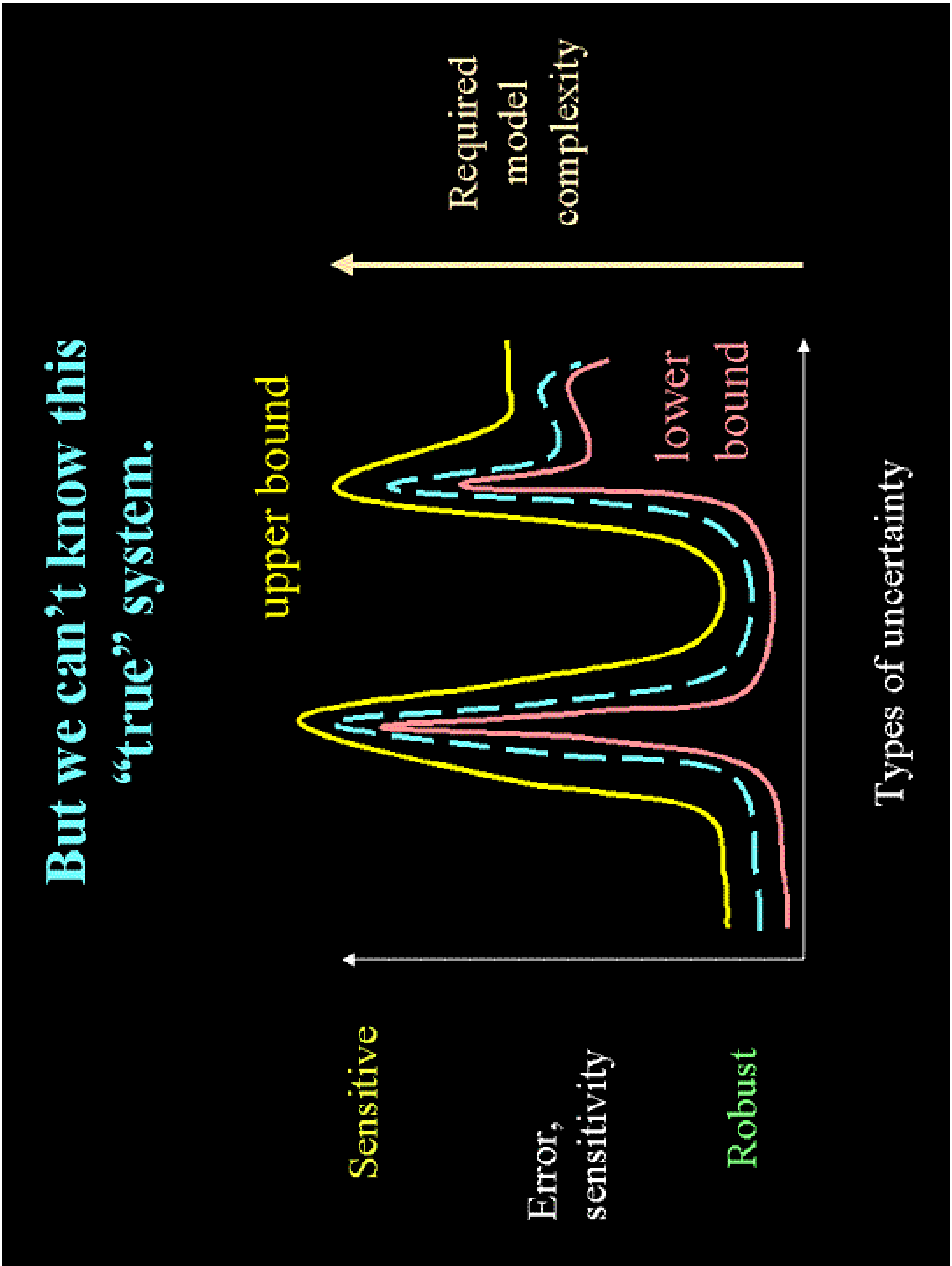

“Complex” systems
yet fragile
Robust
Sensitive
Error,
The ultimate goal of modeling, simulation, and analysis is to create this plot for specific systems.

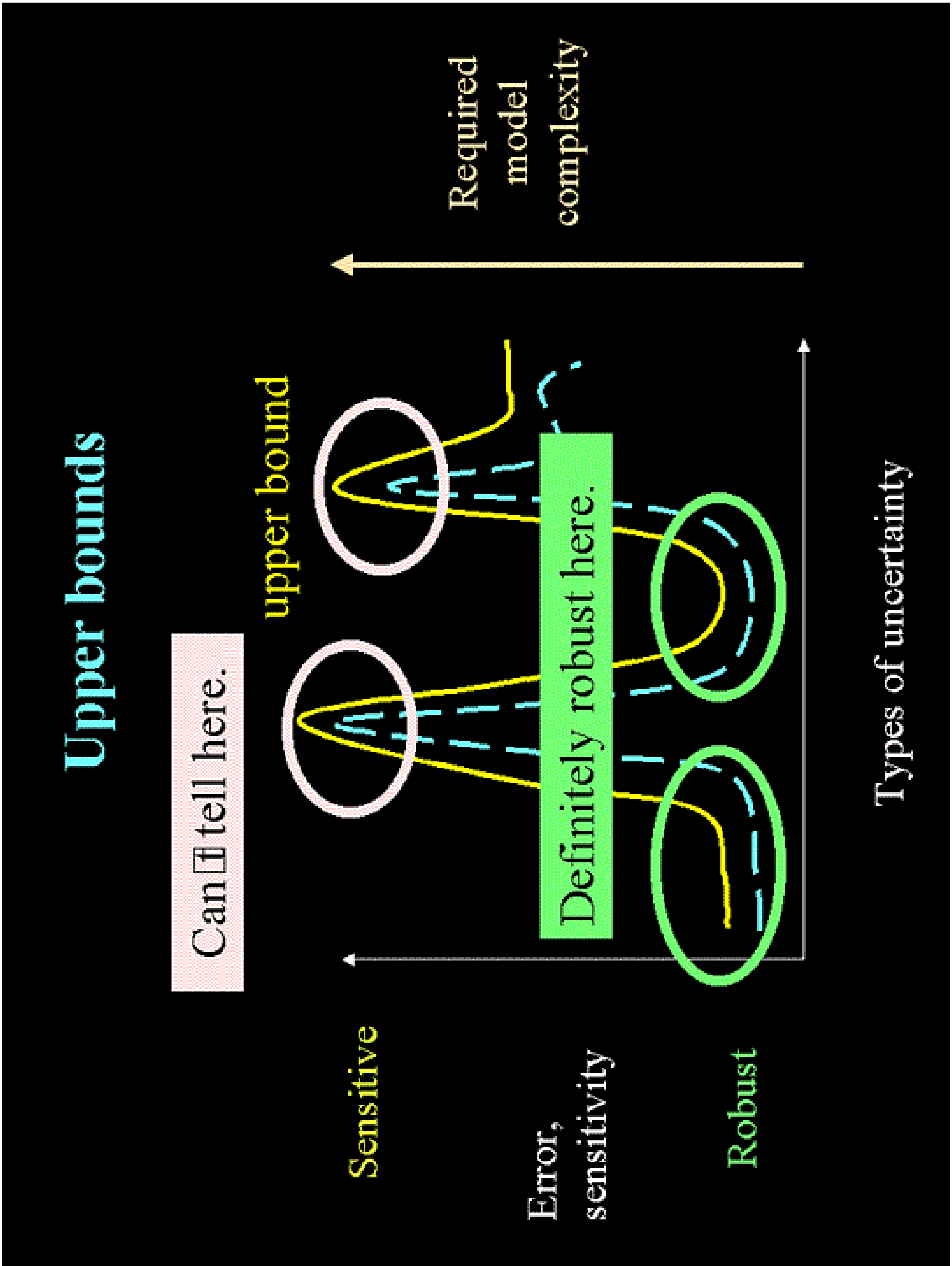

Modeling “complex” systems
May need great detail here
And much less detail here.
Required
model
complexity
Types of uncertainty
Sensitive
Error,
sensitivity
Robust

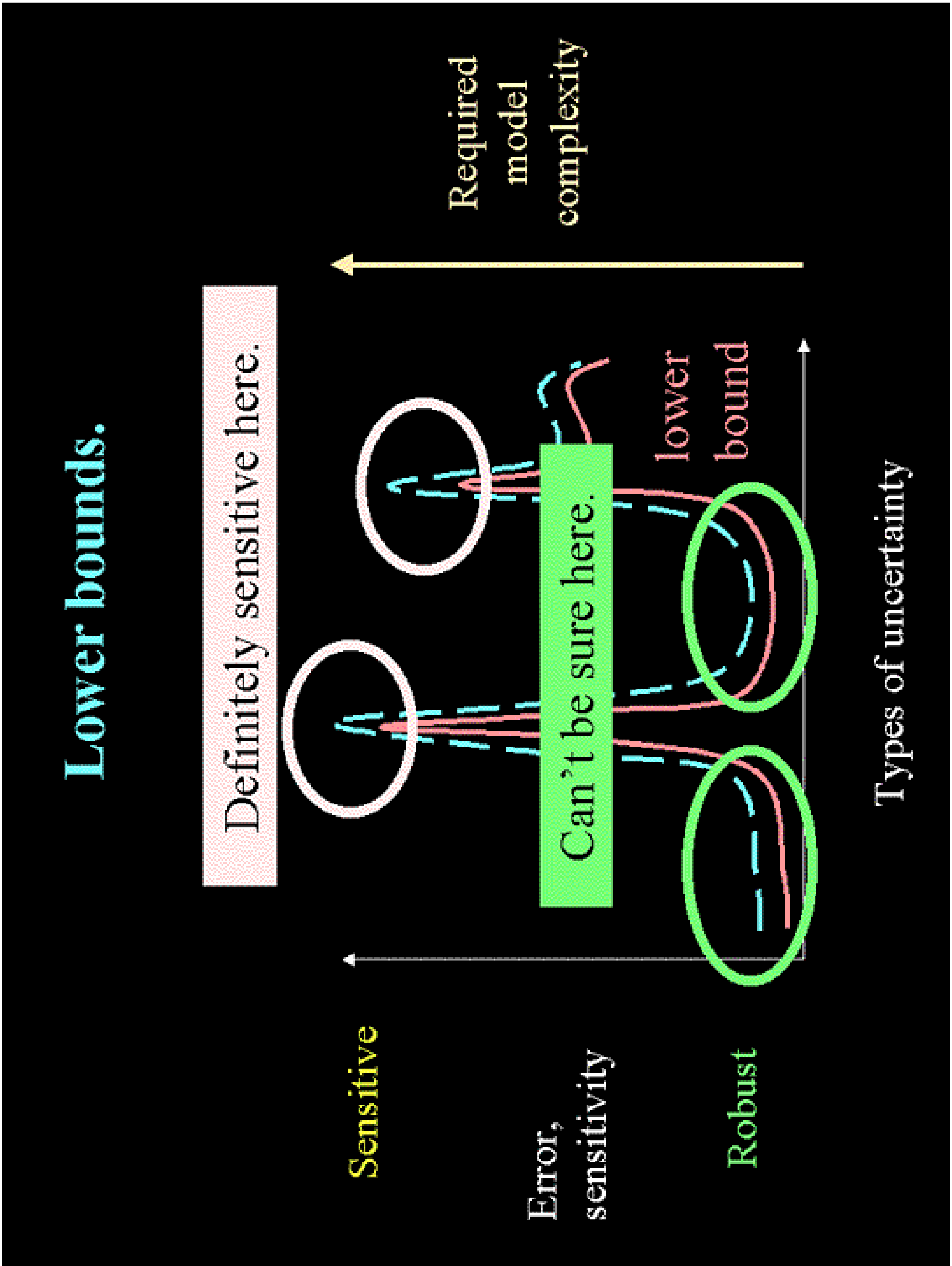

Why "scientific supercomputing" has disappointed.
Still haven't captured important phenomena.
googaflops
petaflops
average
teraflops
Sensitive
Error, sensitivity
Robust
Types of uncertainty

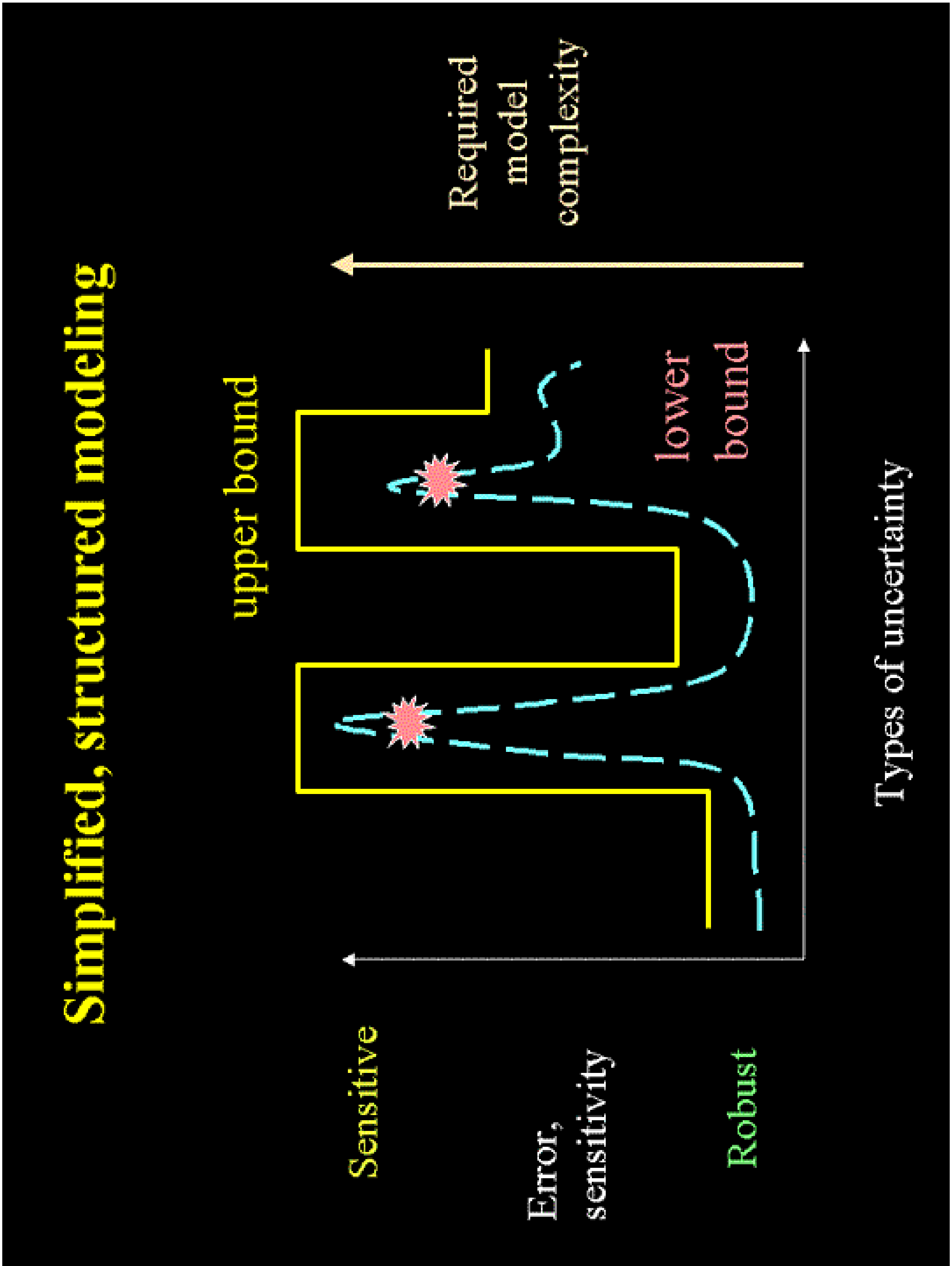

Why "scientific supercomputing" has disappointed.
• Relied too heavily on the homogeneous view of multiscale phenomena from physics.
• Deep misunderstanding of the "robust, yet fragile" character of much complex phenomena.
Types of uncertainty
aflops
flops
ops
Sens
Error,
sensitiv
Rob

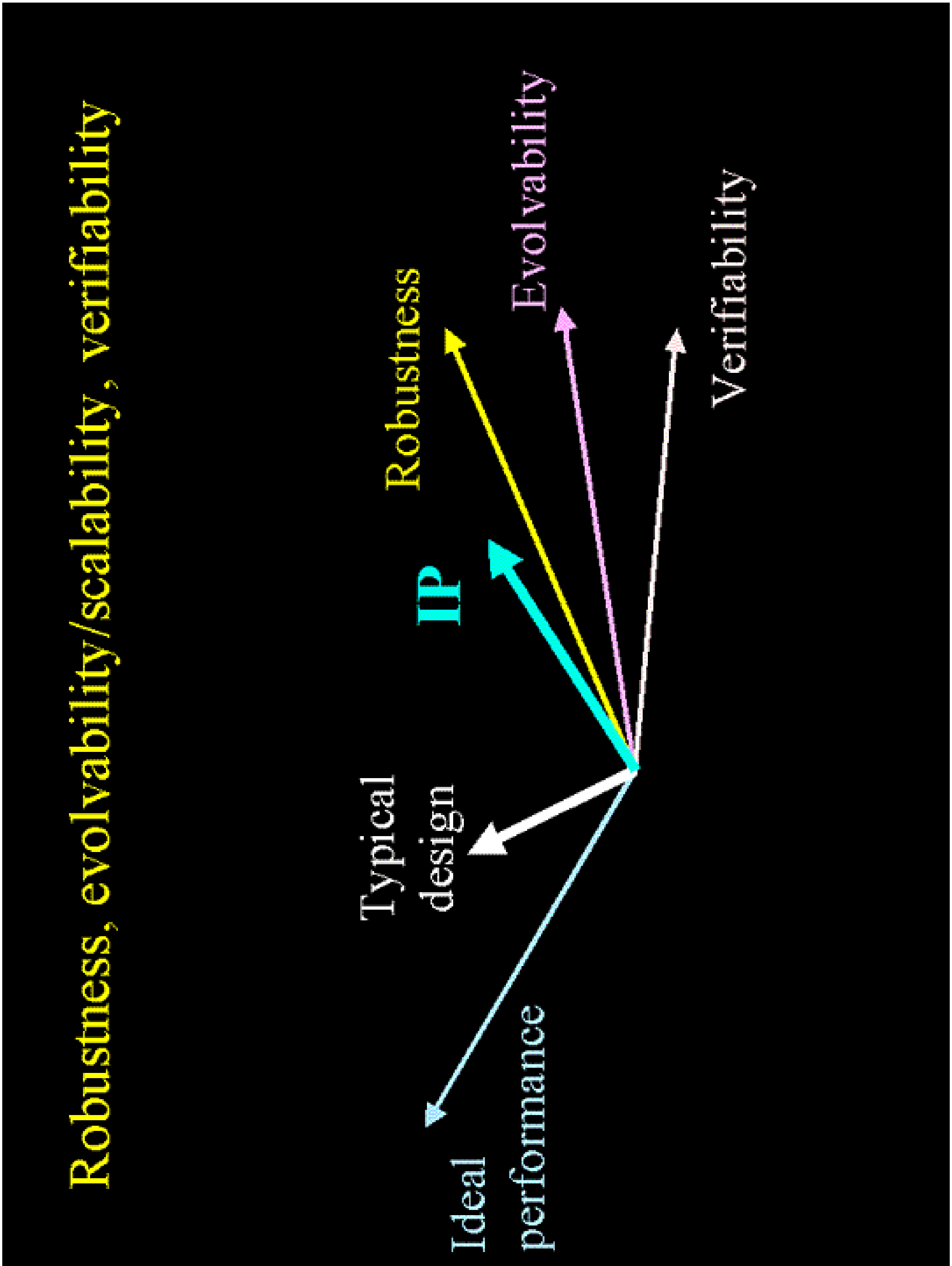
[136] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks



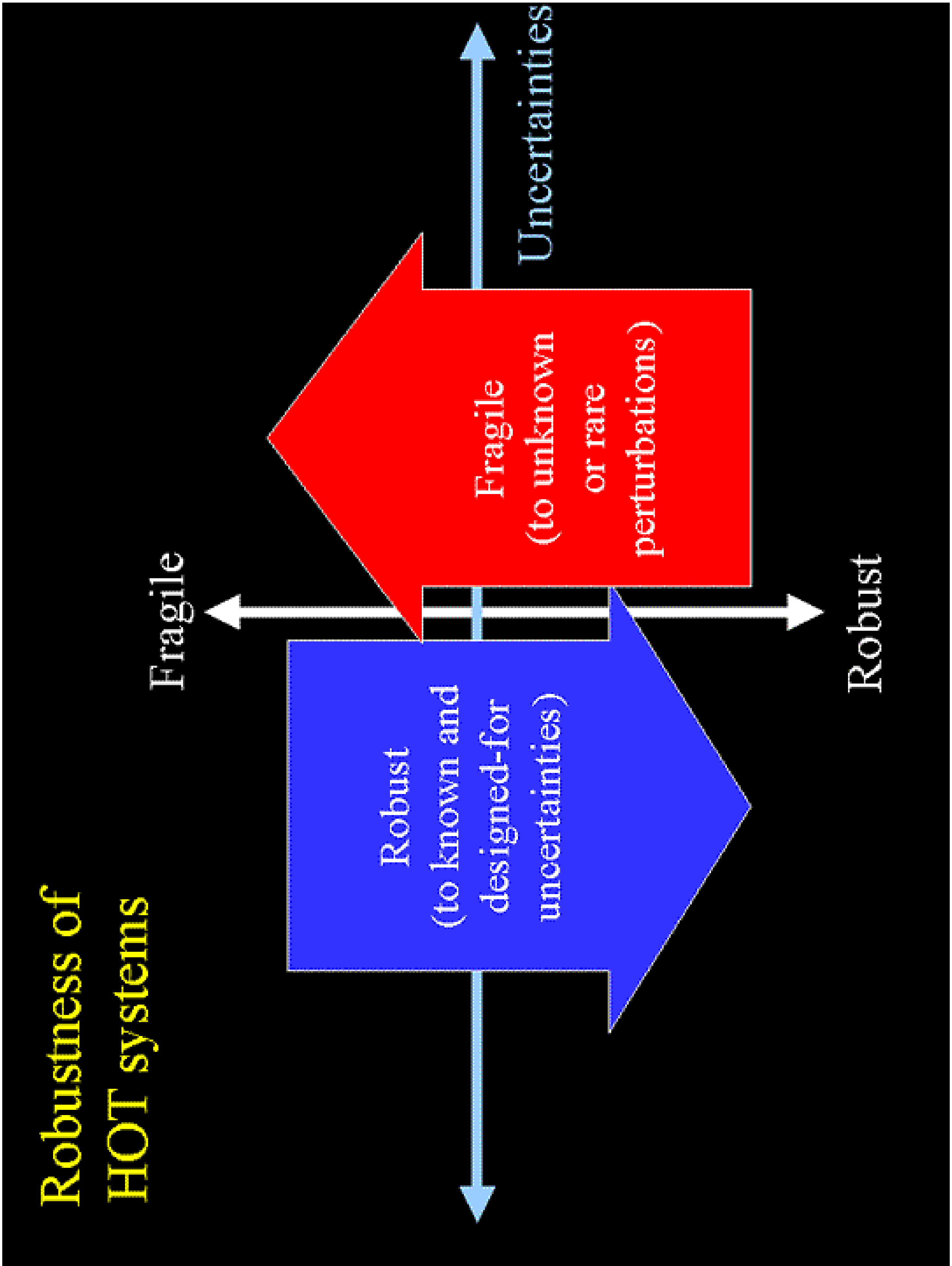

Upper bounds
Can't tell here.
upper bound
Definitely robust here.
Required model complexity
Sensitive
Error, sensitivity
Robust
Types of uncertainty

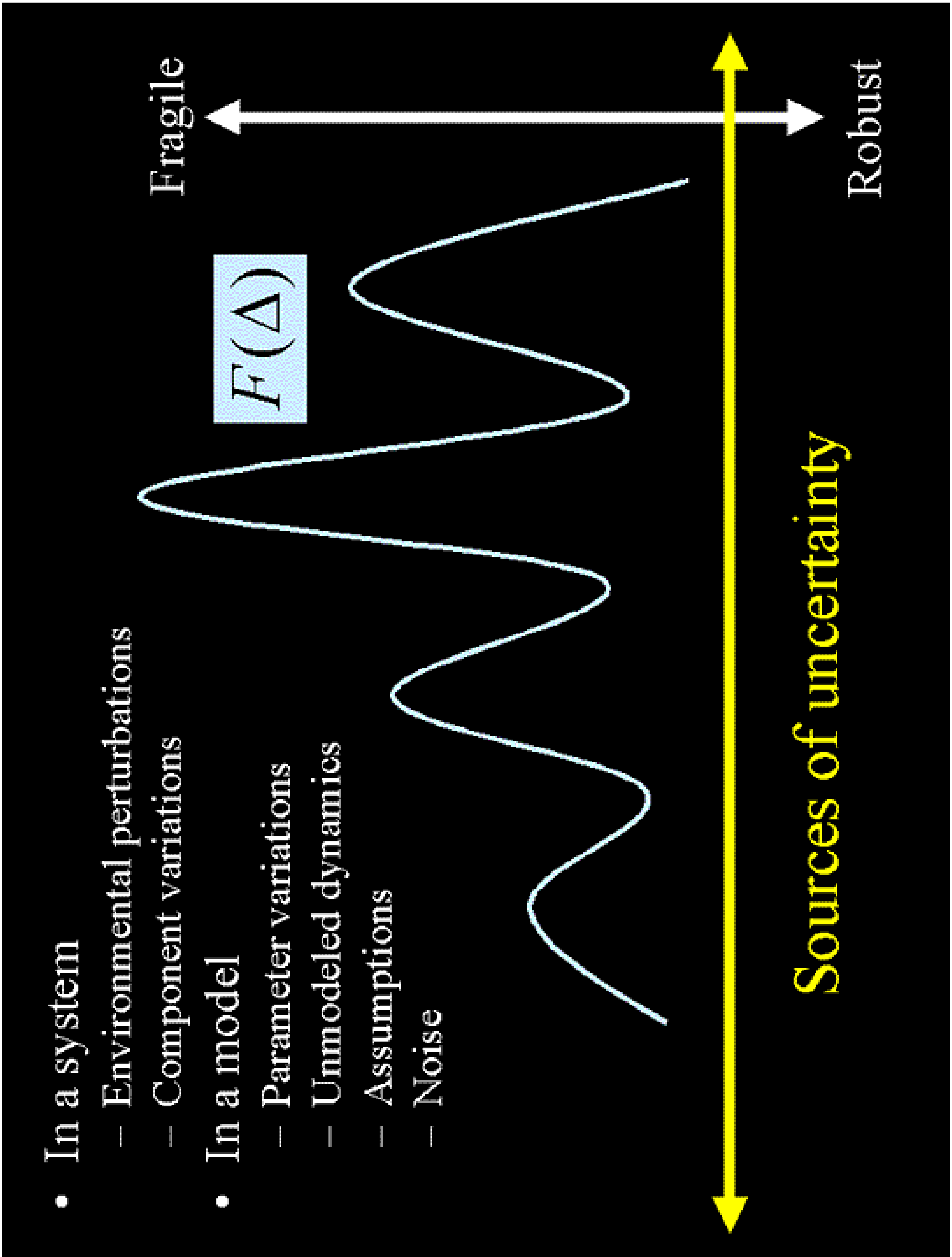

Lower bounds.
Definitely sensitive here.
Required model complexity
Can't be sure here.
lower bound
Types of uncertainty
Sensitive
Error, sensitivity
Robust

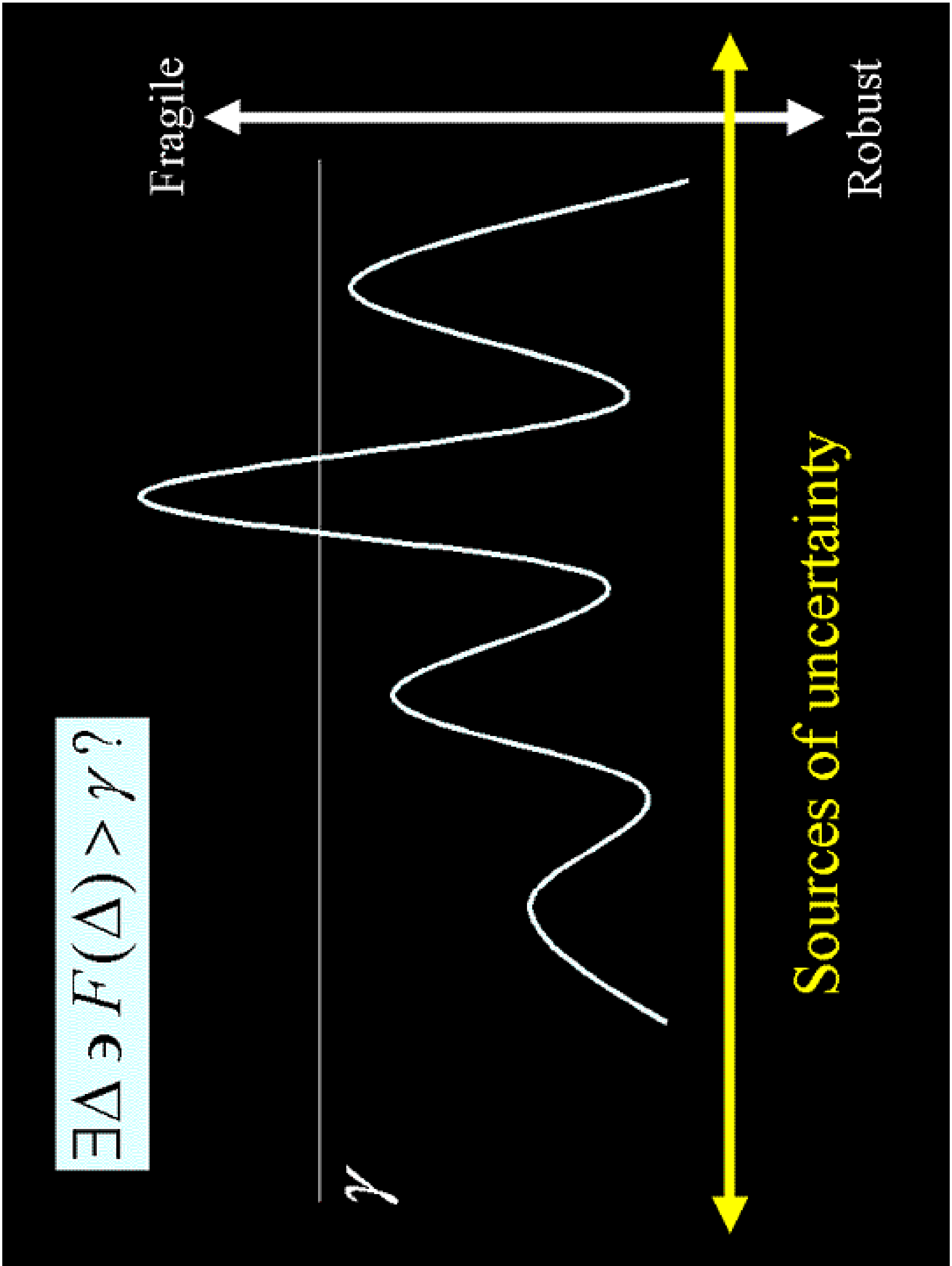

Simplified, structured modeling
Required
model
complexity
upper bound
lower
bound
Sensitive
Error,
sensitivity
Robust
Types of uncertainty

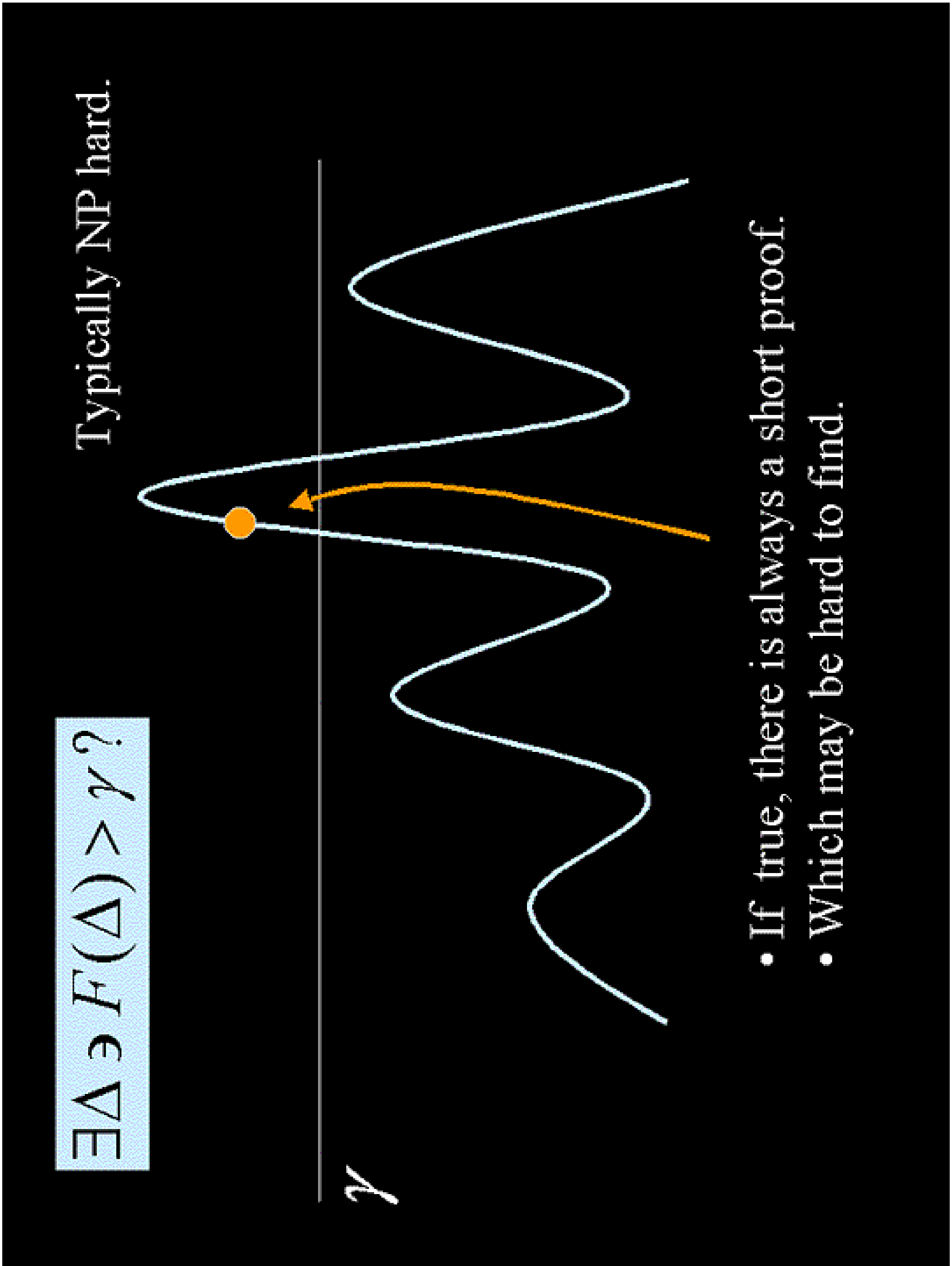

Robustness, evolvability/scalability, verifiability
Robustness
Evolvability
Verifiability
IP
Typical design
Ideal performance

[141] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks

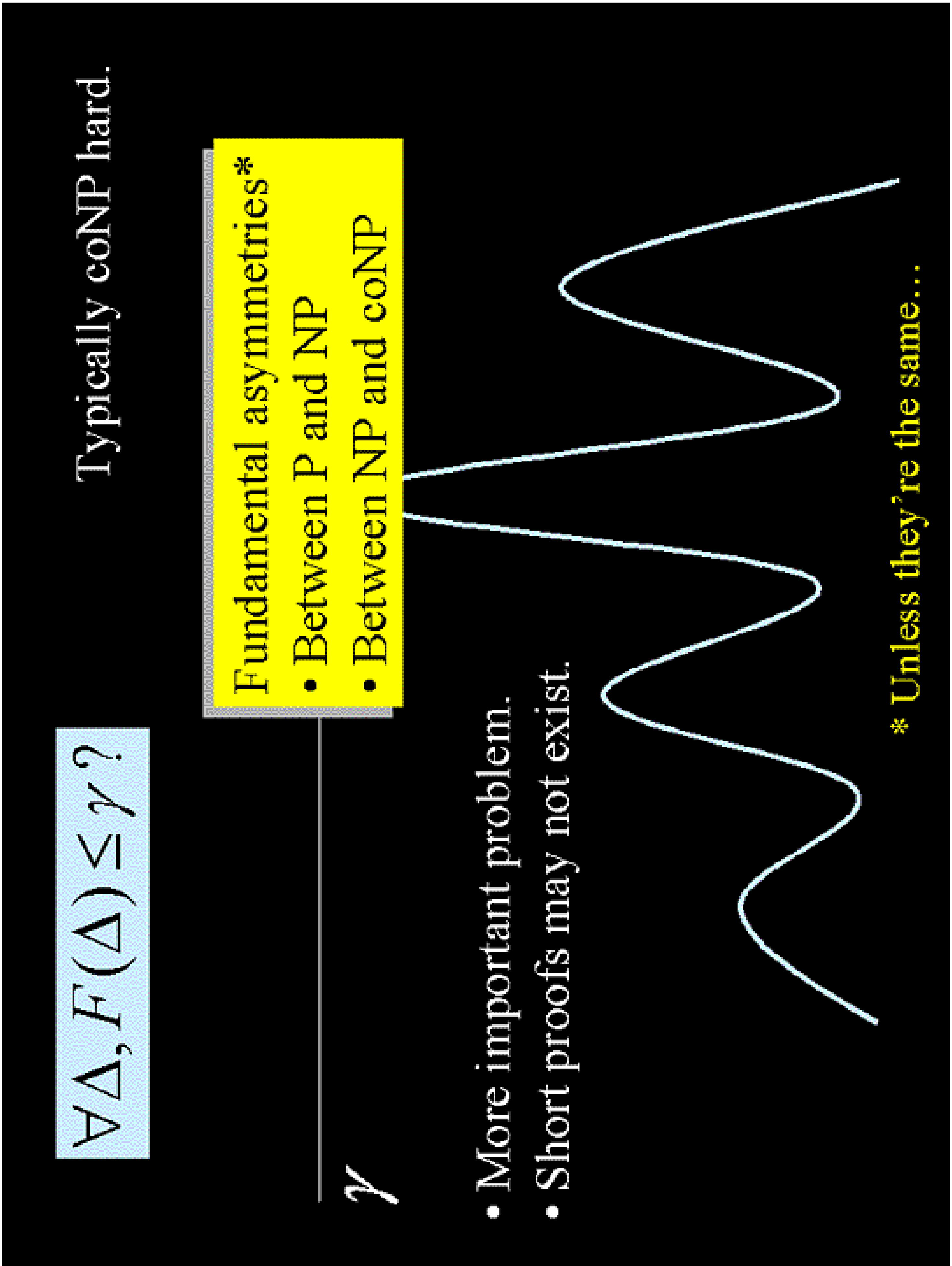



Fragile
Robust
$F(\Delta)$
Sources of uncertainty
• In a system
– Environmental perturbations
– Component variations
• In a model
– Parameter variations
– Unmodeled dynamics
– Assumptions
– Noise


Fragile
Robust
Sources of uncertainty
∃Δ ∋ F(Δ) > γ ?
γ

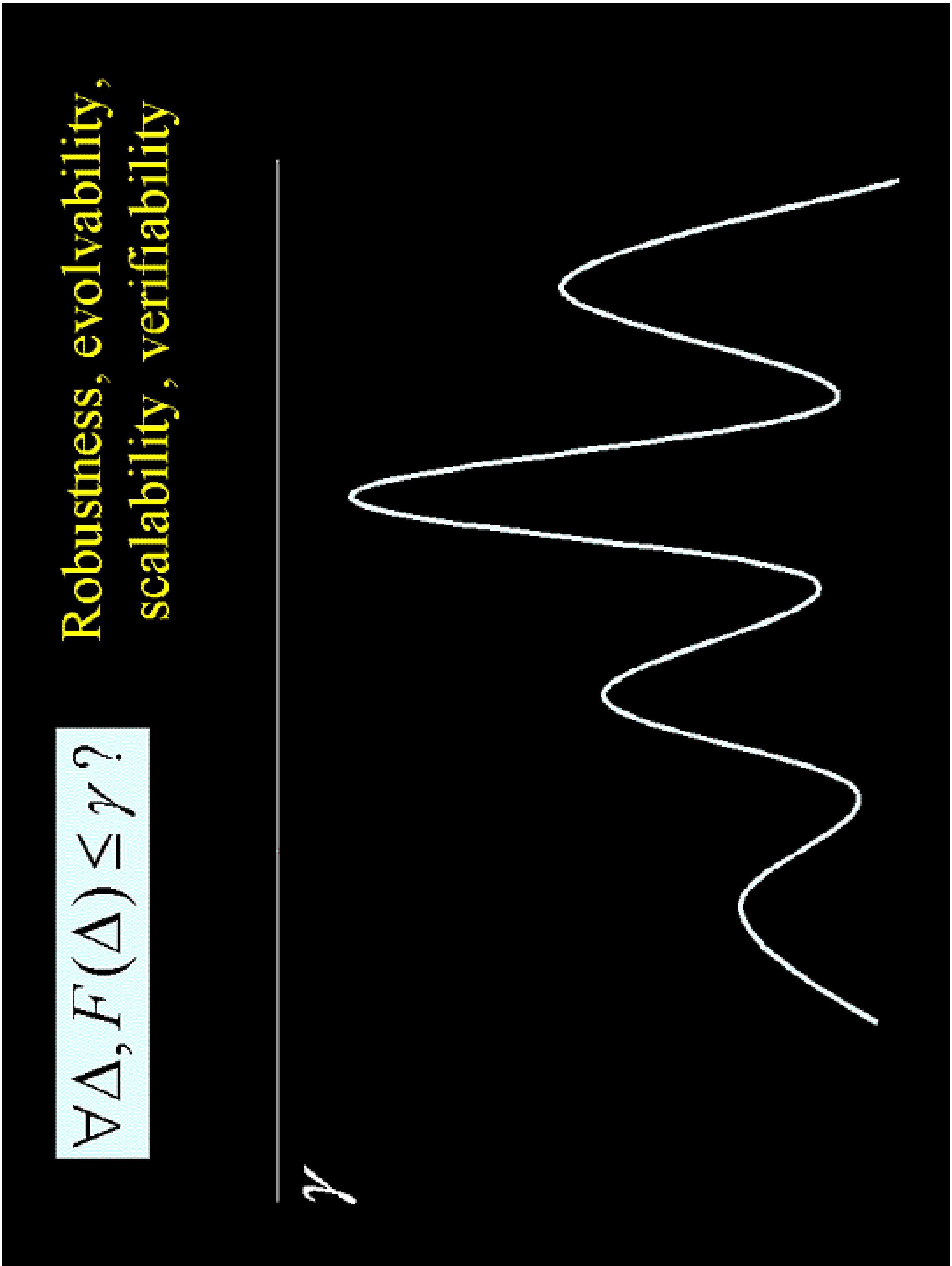


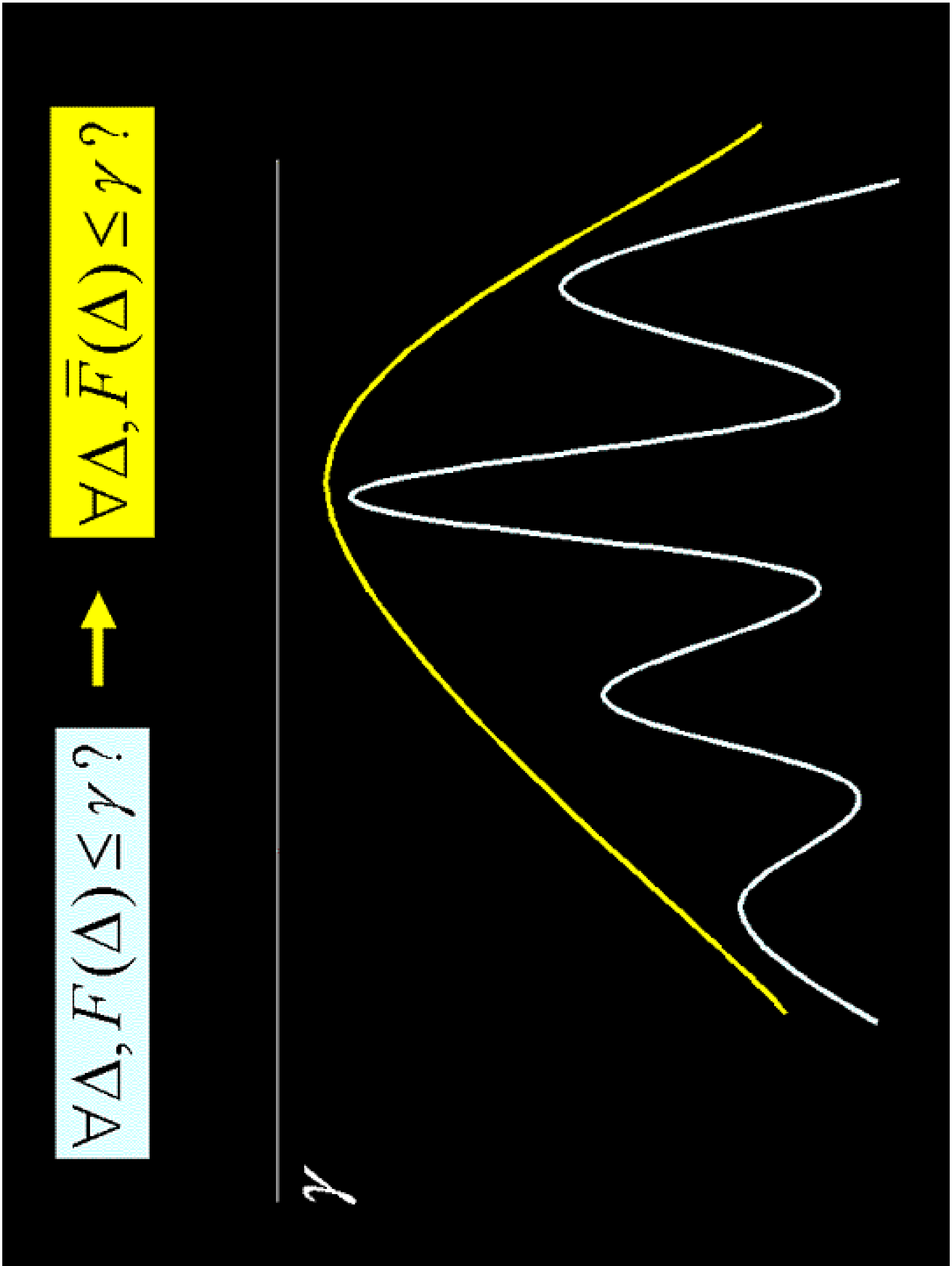
$\exists \Delta \in \mathbf{\Delta} \ni F(\Delta) > \gamma$?
Typically NP hard.
γ
• If true, there is always a short proof.
• Which may be hard to find.

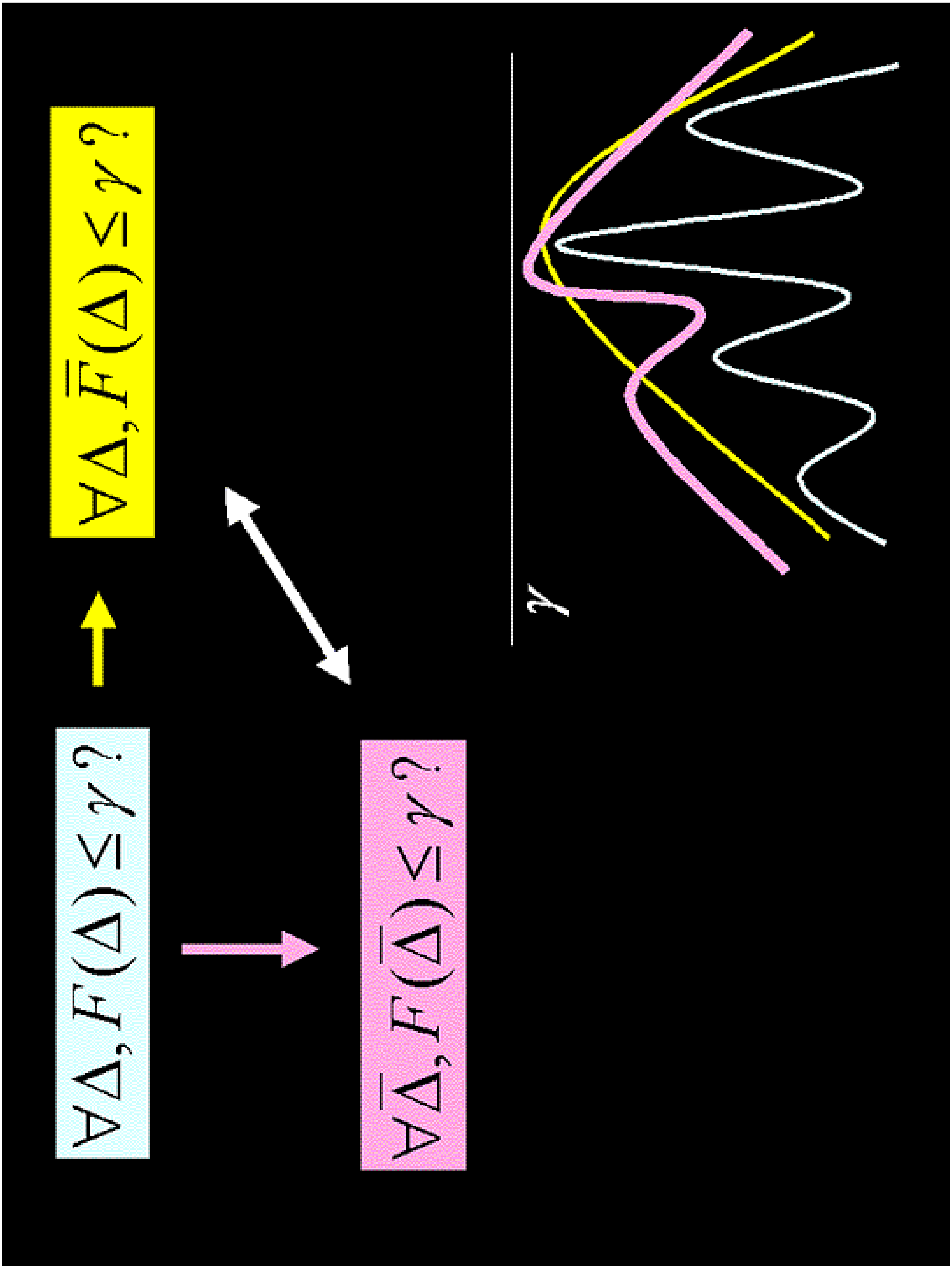

Typically coNP hard.
$\forall \Delta, F(\Delta) \leq \gamma$?
Fundamental asymmetries*
• Between P and NP
• Between NP and coNP
γ
• More important problem.
• Short proofs may not exist.
* Unless they're the same…

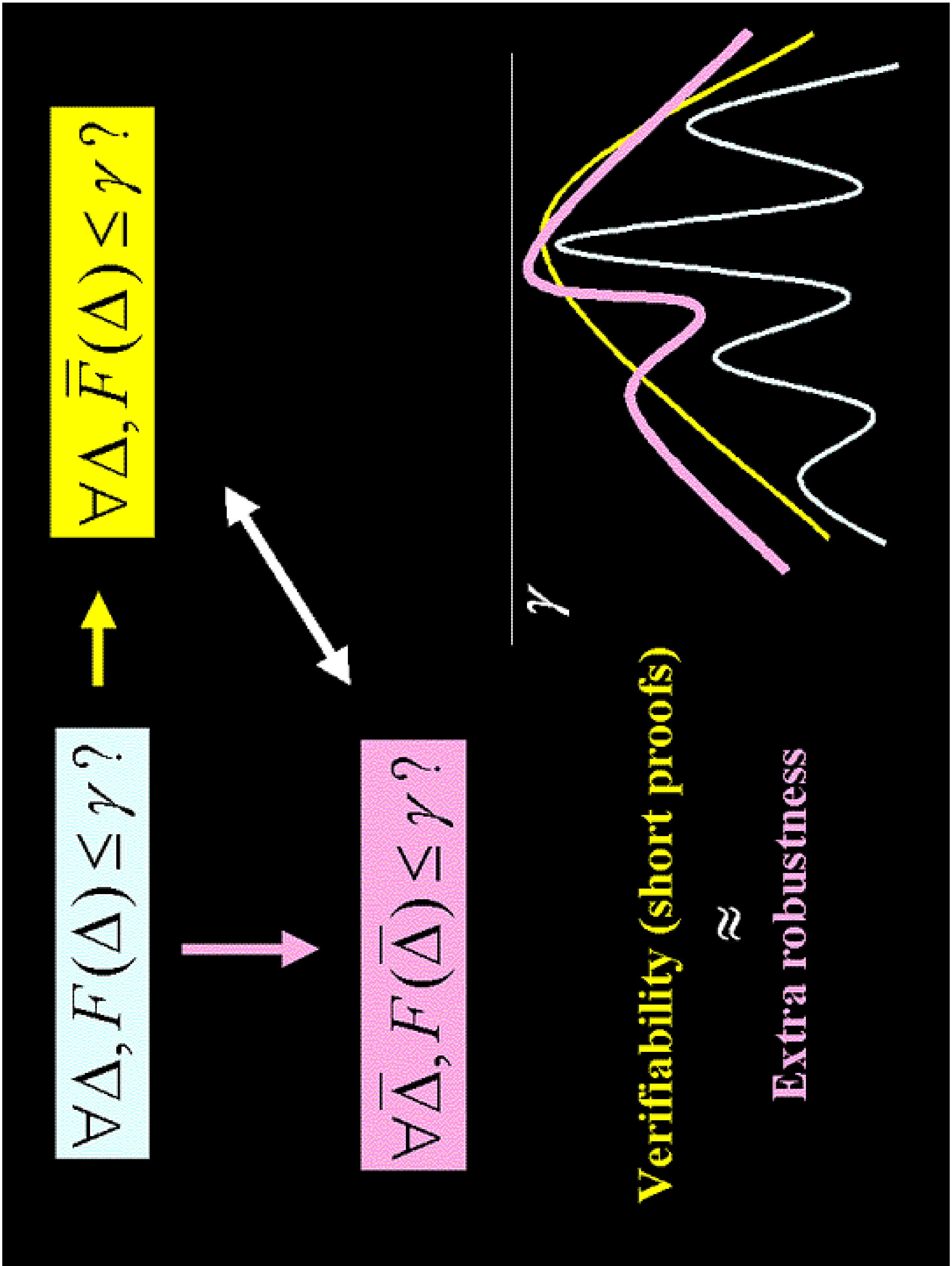
How do we *prove* that $\forall \Delta, F(\Delta) \leq \gamma$?

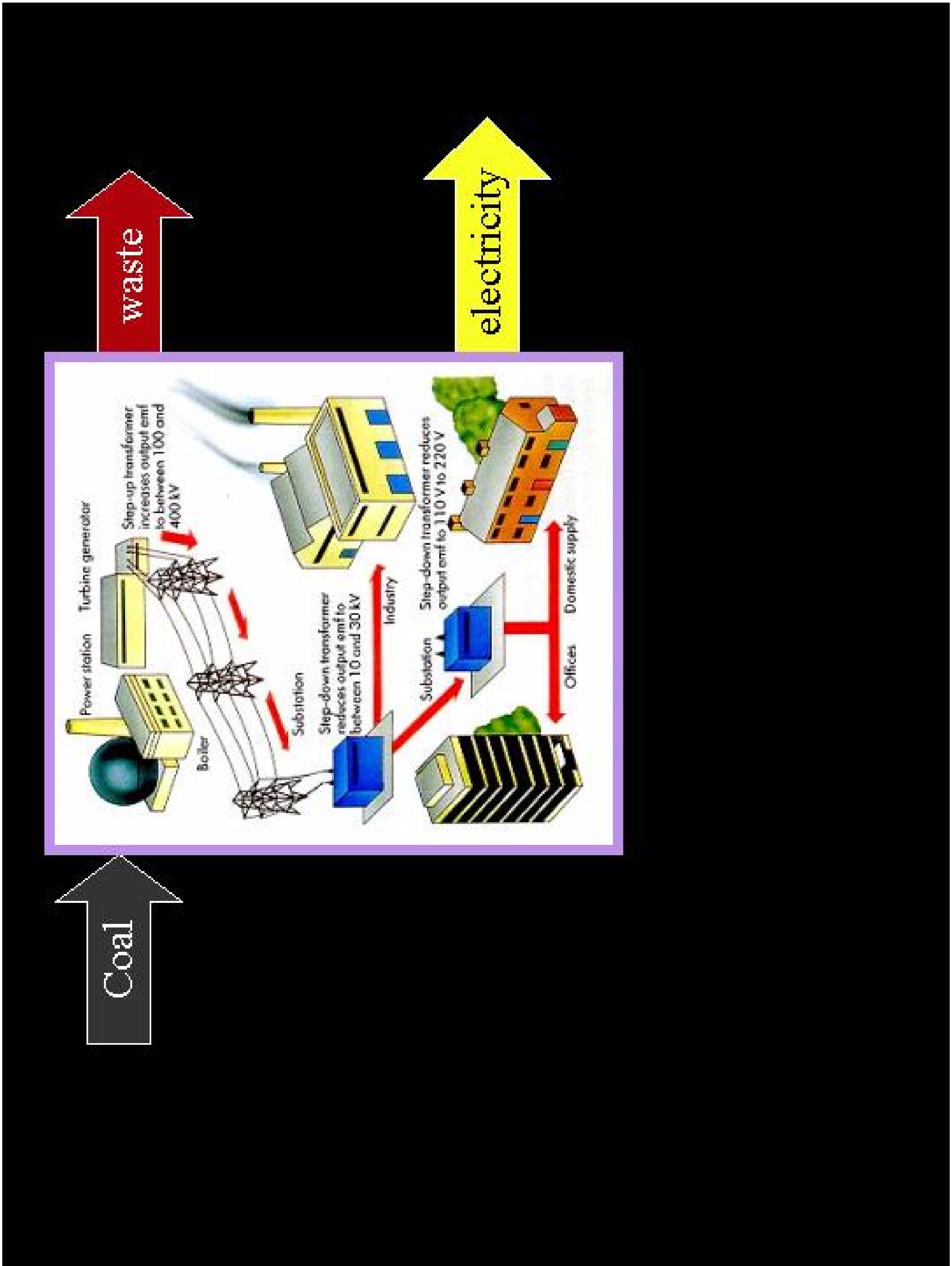
- Standard techniques include relaxations, Grobner bases, resultants, numerical homotopy, etc…
- Powerful new method based on real algebraic geometry and semidefinite programming (Parrilo, Shor, …)
- Nested series of polynomial time relaxations search for polynomial sized certificates
- Exhausts coNP (but no uniform bound)
- Relaxations have both computational and physical interpretations
- Beats gold standard algorithms (eg MAX CUT) handcrafted for special cases
- Completely changes the P/NP/coNP picture

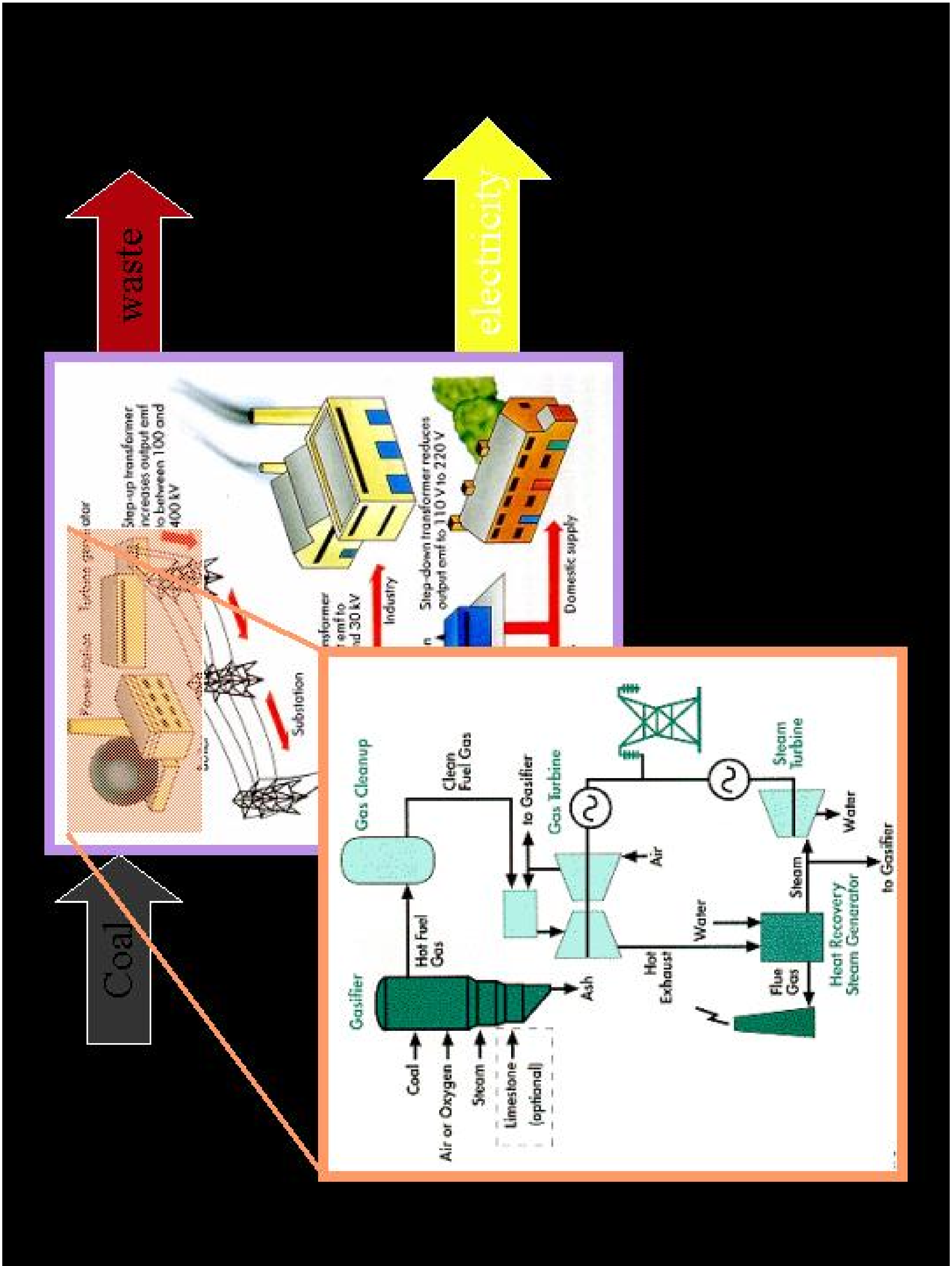

Robustness, evolvability,
scalability, verifiability
$\forall \Delta, F(\Delta) \leq \gamma$?
γ


$\forall\Delta, F(\Delta) \le \gamma$?
$\forall\Delta, \bar{F}(\Delta) \le \gamma$?
γ


$\forall \Delta, \bar{F}(\Delta) \leq \gamma ?$
$\forall \Delta, F(\Delta) \leq \gamma ?$
$\forall \underline{\Delta}, F(\underline{\Delta}) \leq \gamma ?$
γ


∀Δ, F(Δ) ≤ γ ?
∀Δ, F̄(Δ) ≤ γ ?
∀Δ̲, F(Δ̲) ≤ γ ?
γ
Verifiability (short proofs)
≈
Extra robustness


waste
electricity
Coal
Power station
Turbine generator
Step-up transformer increases output emf to between 100 and 400 kV
Boiler
Substation
Step-down transformer reduces output emf to between 10 and 30 kV
Industry
Substation
Step-down transformer reduces output emf to 110 V to 220 V
Offices
Domestic supply


waste
electricity
Coal
Step-up transformer increases output emf to between 100 and 400 kV
Step-down transformer reduces output emf to 110 V to 220 V
Industry
Domestic supply
Substation
Gasifier
Gas Cleanup
Clean Fuel Gas
Hot Fuel Gas
to Gasifier
Gas Turbine
Steam Turbine
Air
Water
Steam
Ash
Hot Exhaust
Flue Gas
Heat Recovery Steam Generator
Coal
Air or Oxygen
Steam
Limestone (optional)

[153] Dr. J. Doyle, Caltech 4/12/01) Robustness of Signal Transduction Networks