

# **Universal laws and architecture 3:**

Constraints on robust efficiency

John Doyle

John G Braun Professor

Control and Dynamical Systems, EE, BE

Caltech

## Turing on layering

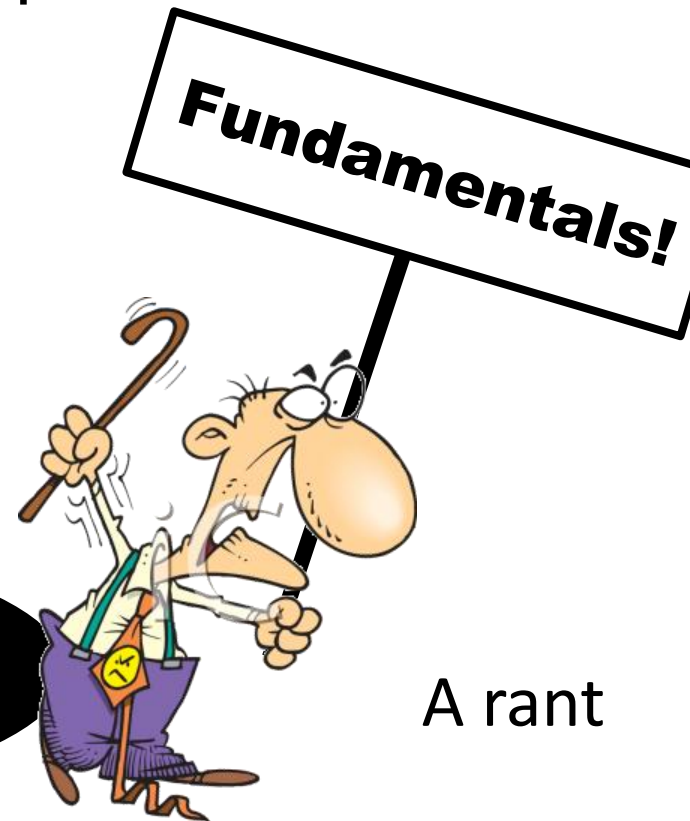
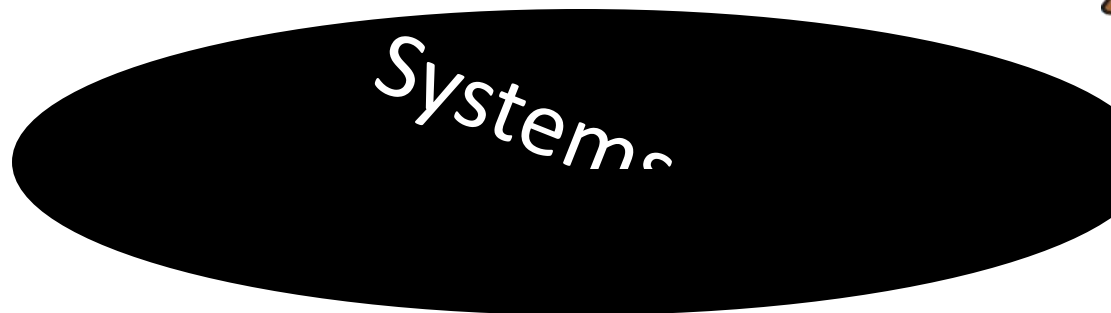
The 'skin of an onion' analogy is also helpful. In considering the functions of the mind or the brain we find certain operations which we can explain in purely mechanical terms. This we say does not correspond to the real mind: it is a sort of skin which we must strip off if we are to find the real mind. But then in what remains we find a further skin to be stripped off, and so on. Proceeding in this way do we ever come to the 'real' mind, or do we eventually come to the skin which has nothing in it? In the latter case the whole mind is mechanical.

1950, Computing Machinery and Intelligence, *Mind*

# “Universal laws and architectures?”

- **Universal “conservation laws” (constraints)**
- Universal architectures (constraints that deconstrain)
- Mention recent papers\*
- Focus on broader context not in papers
- Lots of case studies for motivation

\*try to get you  
to read them?



A rant

- Turing 100<sup>th</sup> birthday in 2012
- Turing
  - machine (math, CS)
  - test (AI, neuroscience)
  - pattern (biology)
- Arguably greatest\*
  - all time math/engineering combination
  - WW2 hero
  - “invented” software

**Turing (1912-1954)**

**Compute**

\*Also world-class runner.

# Key papers/results

- Theory (1936): Turing machine (TM), computability, (un)decidability, universal machine (UTM)
- Practical design (early 1940s): code-breaking, including the design of code-breaking machines
- Practical design (late 1940s): general purpose digital computers and software, layered architecture
- Theory (1950): Turing test for machine intelligence
- Theory (1952): Reaction diffusion model of morphogenesis, plus practical use of digital computers to simulate biochemical reactions

Control

Comms

Bode

Shannon

fragile?

slow?

wasteful?

?

- Each theory  $\approx$  one dimension
- Tradeoffs **across** dimensions
- Assume architectures a priori
- Progress is encouraging, but...
- Stovepipes are an obstacle...

Carnot

Turing

Boltzmann

Godel

Heisenberg

Compute

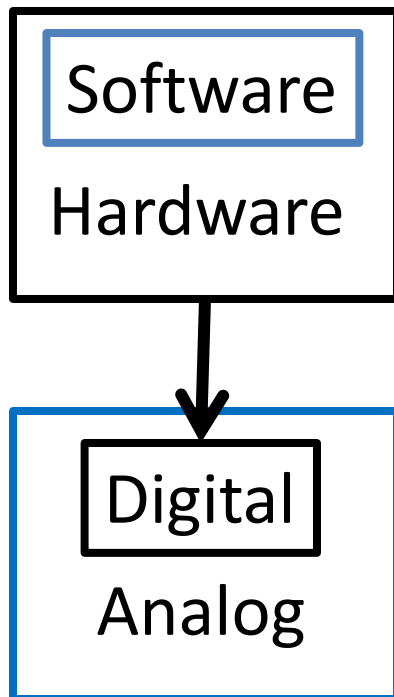
Einstein

Physics

Turing as  
“new”  
starting  
point?

## Essentials:

0. Model
1. Universal laws
2. Universal architecture
3. Practical implementation



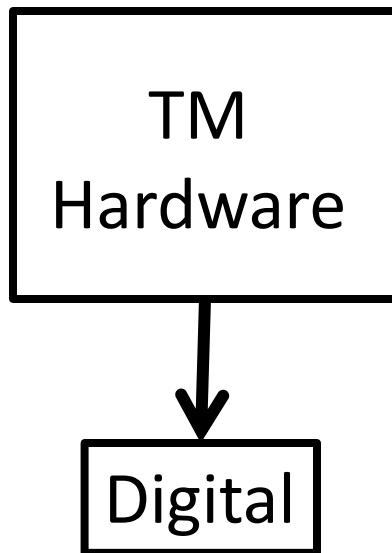
## Turing's 3 step research:

0. Virtual (TM) machines
1. hard limits, (un)decidability using standard model (TM)
2. Universal architecture achieving hard limits (UTM)
3. Practical implementation in digital electronics (biology?)

Essentials:

0. **Model**

1. Universal laws
2. Universal architecture
3. Practical implementation

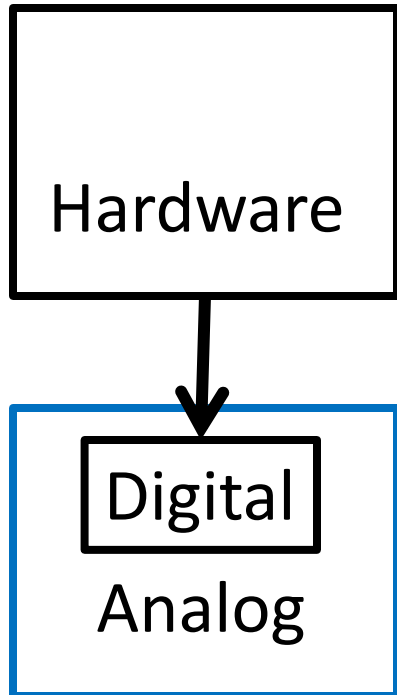


Turing's 3 step research:

0. **Virtual (TM) machines**

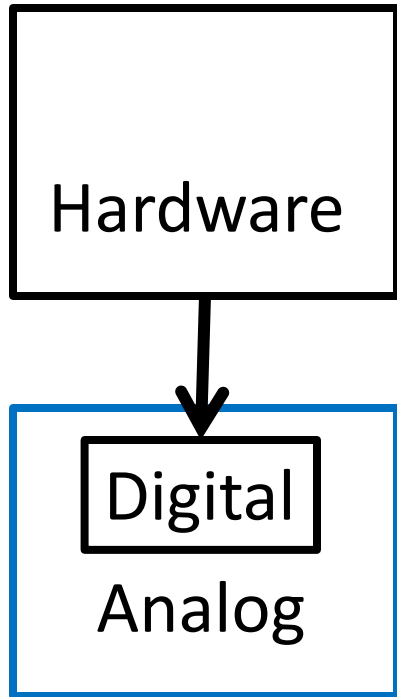
1. hard limits, (un)decidability using standard model (TM)
2. Universal architecture achieving hard limits (UTM)
3. Practical implementation in digital electronics (biology?)





- ...being digital should be of greater interest than that of being electronic. That it is electronic is certainly important because these machines owe their high speed to this... But this is virtually all that there is to be said on that subject.
- That the machine is digital however has more subtle significance. ... One can therefore work to any desired degree of accuracy.

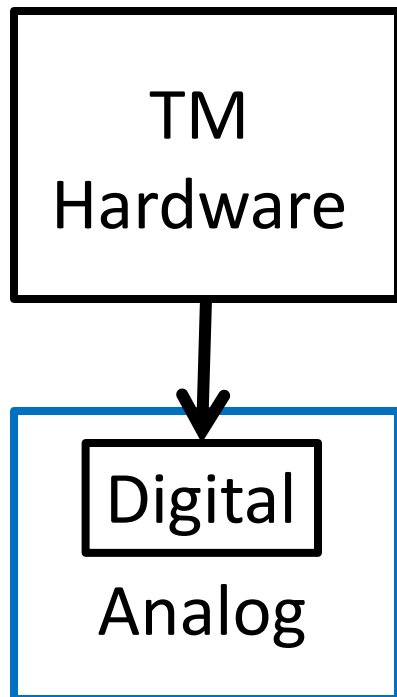
1947 Lecture to LMS



- ... digital ... of greater interest than that of being electronic ...
- ...any desired degree of accuracy...
- This accuracy is not obtained by more careful machining of parts, control of temperature variations, and such means, but by a slight increase in the amount of equipment in the machine.

1947 Lecture to LMS

- Digital more important than electronic...
- Robustness: accuracy and repeatability.
- Achieved more by internal hidden complexity than precise components or environments.



Turing Machine (TM)

- Digital
- Symbolic
- Logical
- Repeatability

*avalanche*

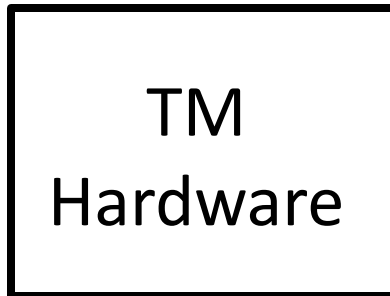
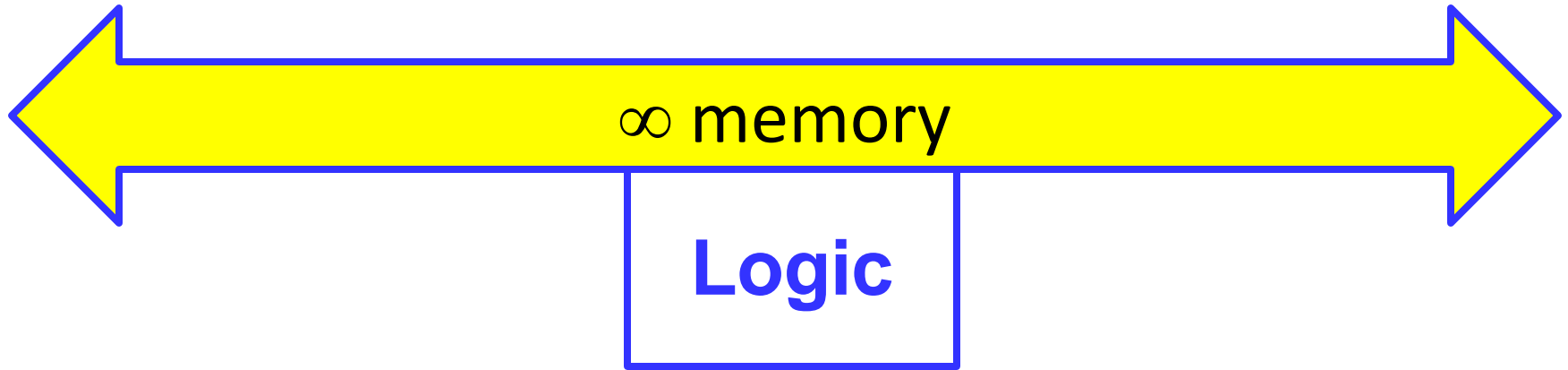
## The ~~butterfly~~ effect

- ... quite small errors in the initial conditions can have an overwhelming effect at a later time. The displacement of a single electron by a billionth of a centimetre at one moment might make the difference between a man being killed by an avalanche a year later, or escaping.

1950, Computing Machinery and Intelligence,  
*Mind*

- ... quite small errors in the initial conditions can have an overwhelming effect at a later time....
- It is an essential property of the mechanical systems which we have called 'discrete state machines' that this phenomenon does not occur.
- Even when we consider the actual physical machines instead of the idealised machines, reasonably accurate knowledge of the state at one moment yields reasonably accurate knowledge any number of steps later.

1950, Computing Machinery and Intelligence, *Mind*



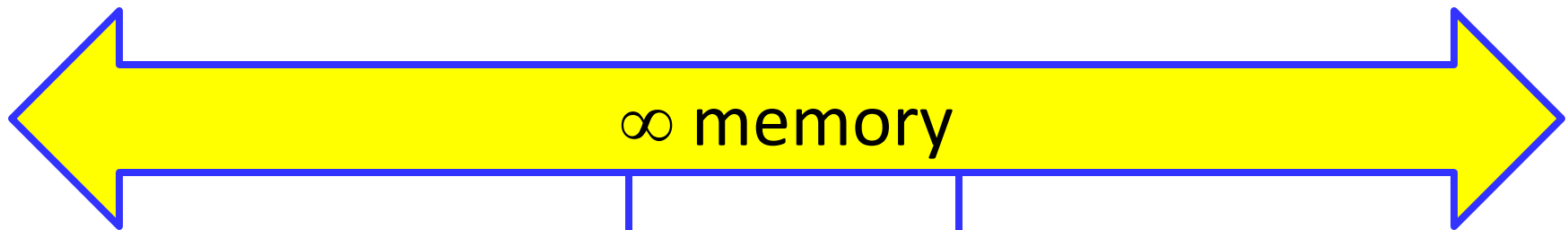
Turing's 3 step research:

0. Virtual (TM) machines

**1. hard limits, (un)decidability  
using standard model (TM)**

2. Universal architecture  
achieving hard limits (UTM)

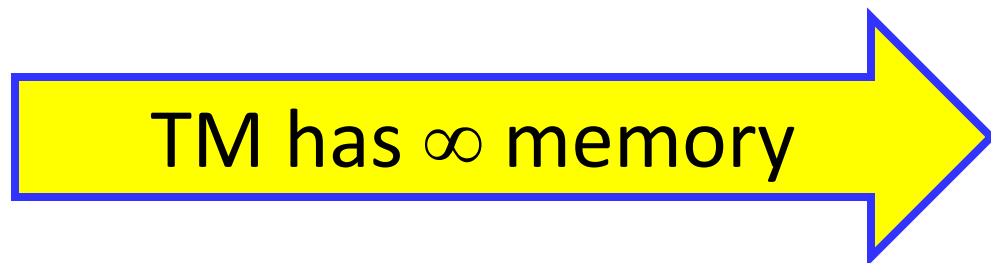
3. Practical implementation in  
digital electronics (biology?)



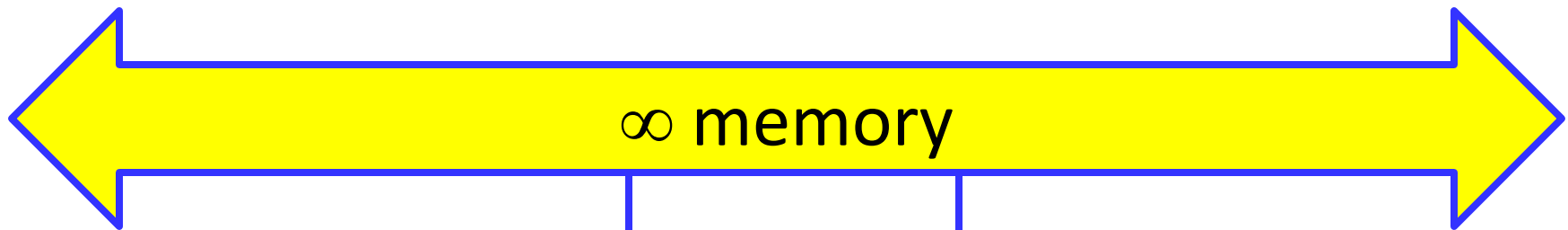
slow

time

fast



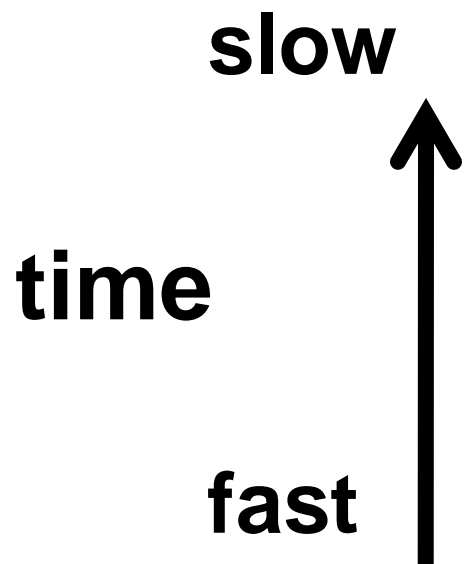
large  
space



$\infty$  memory



Logic

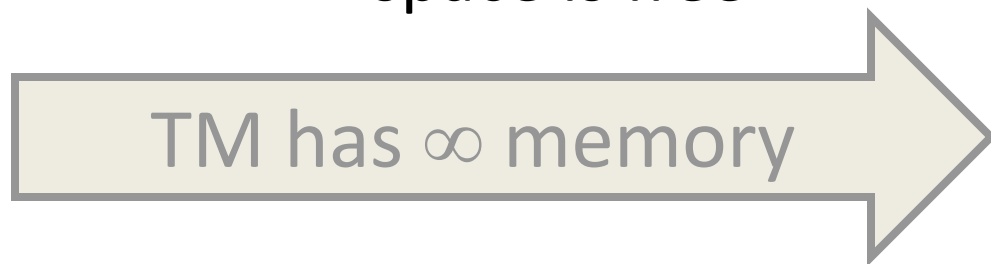


slow

time

fast

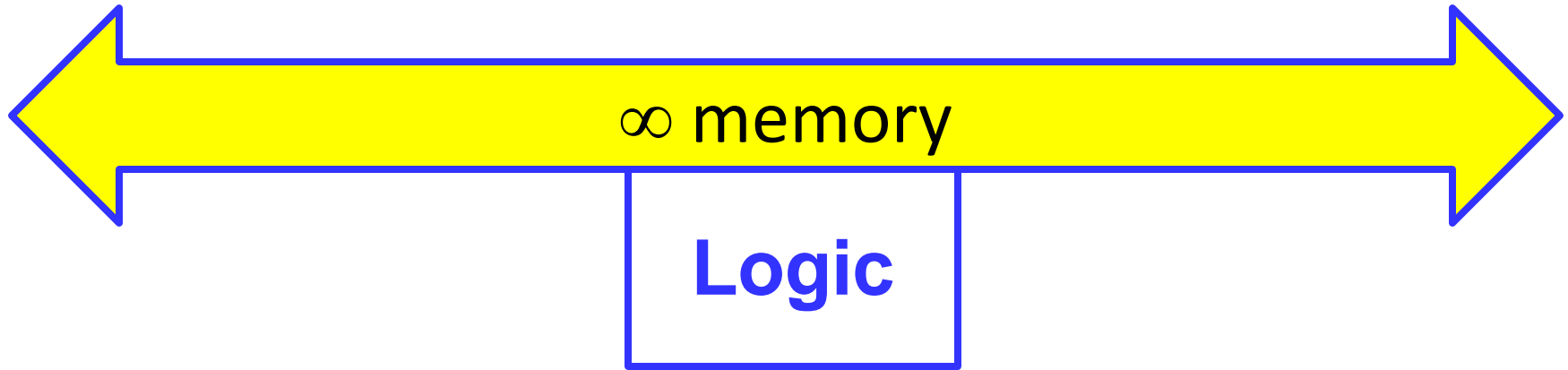
space is free



TM has  $\infty$  memory

large  
space

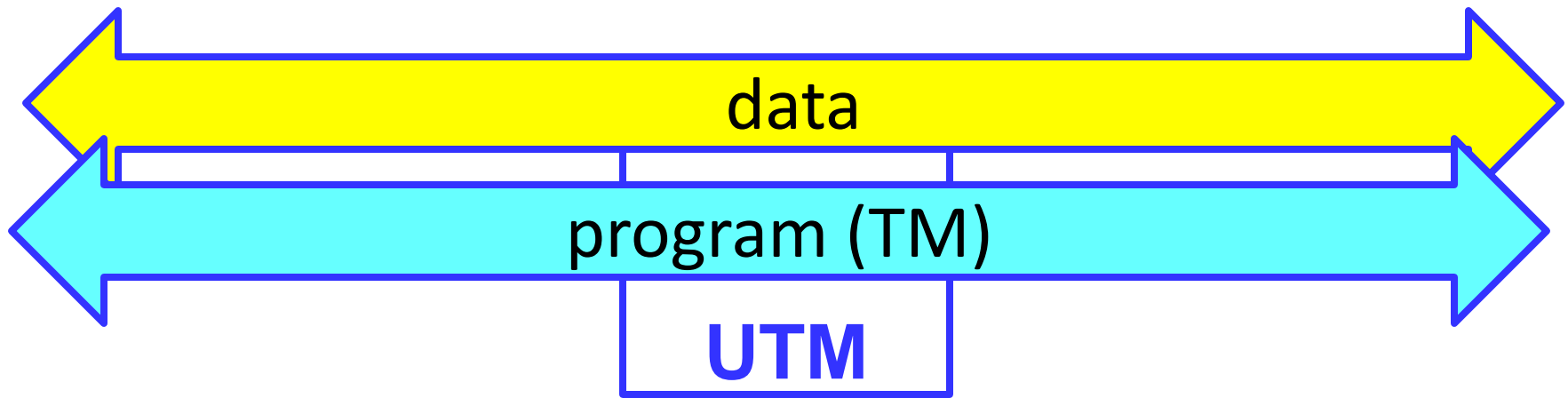




**time?**

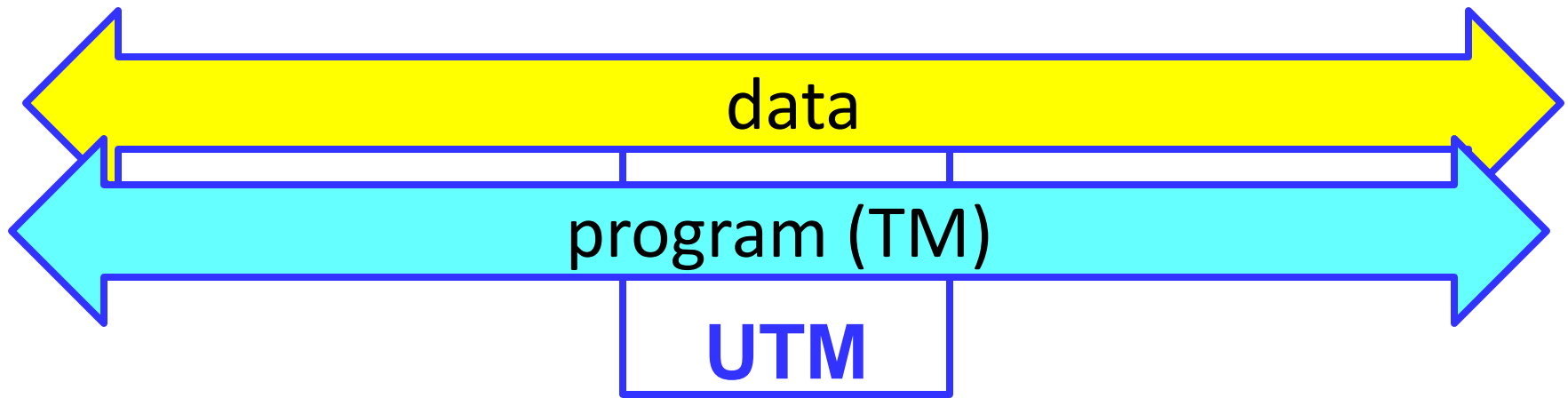
**Decidable problem** =  $\exists$  algorithm that solves it

Most naively posed problems are undecidable.



Turing's 3 step research:

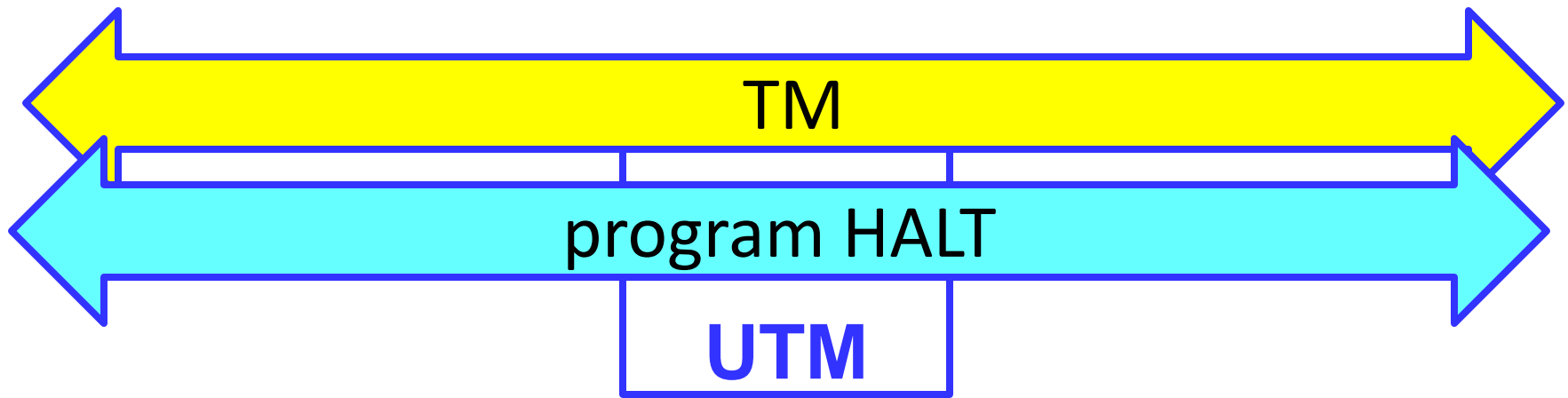
0. Virtual (TM) machines
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using standard model (TM)
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achieving hard limits (UTM)**
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digital electronics (biology?)



Software  
Hardware

## 2. Universal architecture achieving hard limits (UTM)

- Software: A Turing machine (TM) can be data for another Turing machine
- A Universal Turing Machine can run any TM
- A UTM is a virtual machine.
- There are lots of UTMs, differ only (but greatly) in speed and programmability (space assumed free)



## The halting problem

- Given a TM (i.e. a computer program)
- Does it halt (or run forever)?
- Or do more or less anything in particular.
- Undecidable! There does not exist a special TM that can tell if any other TM halts.
- i.e. the program HALT does not exist. ☹️

**Thm:** TM H=HALT does not exist.

That is, there does not exist a program like this:

$$H(TM, input) \triangleq \begin{cases} 1 & \text{if } TM(input) \text{ halts} \\ 0 & \text{otherwise} \end{cases}$$

**Proof** is by contradiction. Sorry, don't know any alternative. And Turing is a god.

$$H(TM, input) \triangleq \begin{cases} 1 & \text{if } TM(input) \text{ halts} \\ 0 & \text{otherwise} \end{cases}$$

**Thm:** No such H exists.

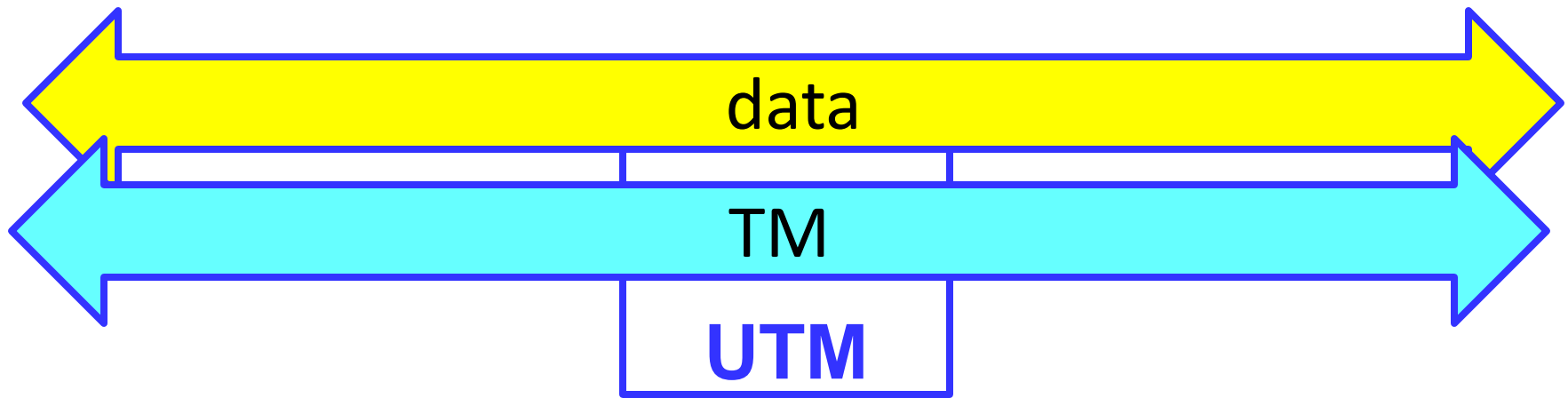
**Proof:** Suppose it does. Then define 2 more programs:

$$H'(TM, input) \triangleq \begin{cases} 1 & \text{if } H(TM, input) = 0 \\ \text{loop forever} & \text{otherwise} \end{cases}$$

$$H^*(TM) \triangleq H'(TM, TM)$$

$$\begin{aligned} \text{Run } H^*(H^*) &= H'(H^*, H^*) \\ &= \begin{cases} \text{halt} & \text{if } H^*(H^*) \text{ loops forever} \\ \text{loop forever} & \text{otherwise} \end{cases} \end{aligned}$$

**Contradiction!**



## Implications

- TMs and UTMs are perfectly repeatable
- But perfectly unpredictable
- Undecidable: Will a TM halt? Is a TM a UTM? Does a TM do X (for almost any X)?
- Easy to make UTMs, but hard to recognize them.
- Is anything decidable? Yes, many questions NOT about TMs.
- Large, thin, nonconvex everywhere...

# Issues for engineering

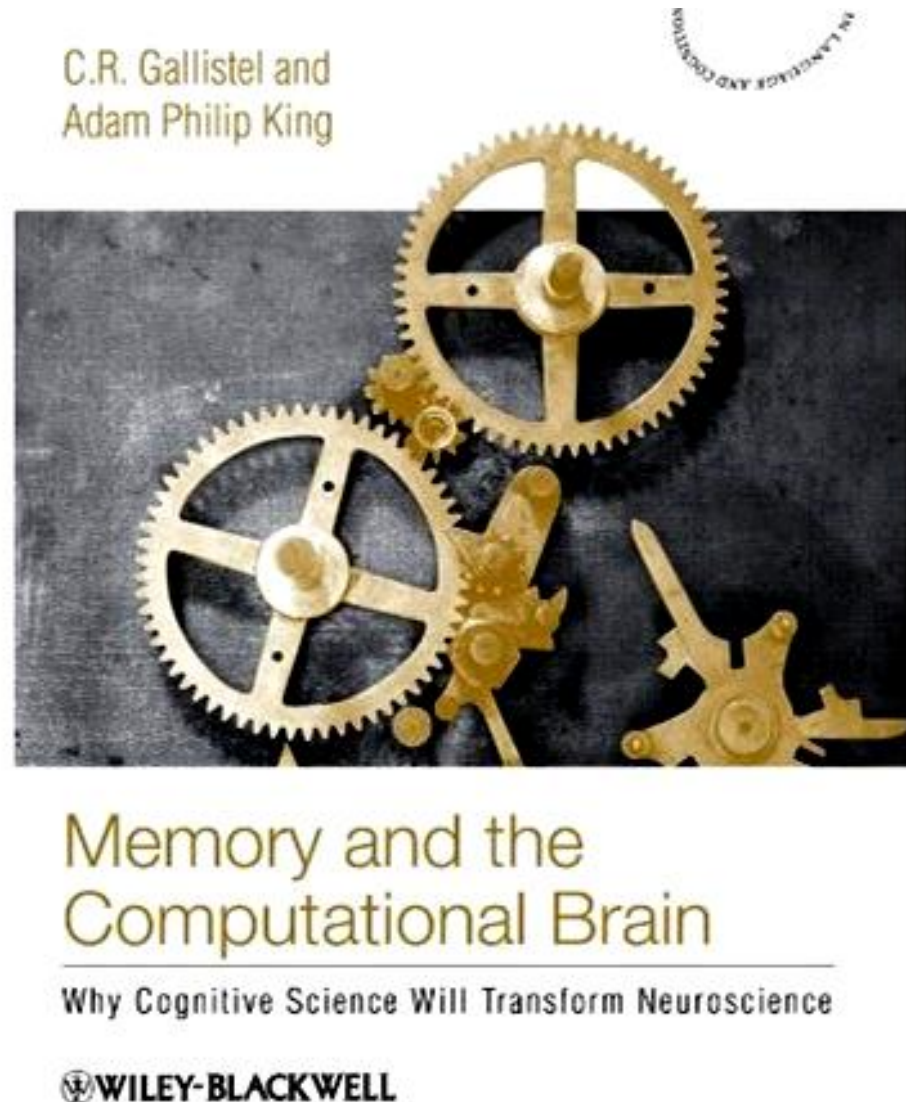
- Turing remarkably relevant for 76 years
- UTMs are  $\approx$  implementable
  - Differ only (but greatly) in speed and programmability
  - Time/speed/delay is most critical resource
  - Space (memory) almost free for most purposes
- Read/write random access memory hierarchies
- Further gradations of decidable (P/NP/coNP)
- **Most crucial:**
  - UTMs differ vastly in speed, usability, and programmability
  - You can fix bugs but it is hard to automate finding/avoiding them



# Issues for neuroscience

- Brains and UTMs?
  - Time is most critical resource?
  - Space (memory) almost free?
- Read/write random access memory hierarchies?
- Brain >> UTM?

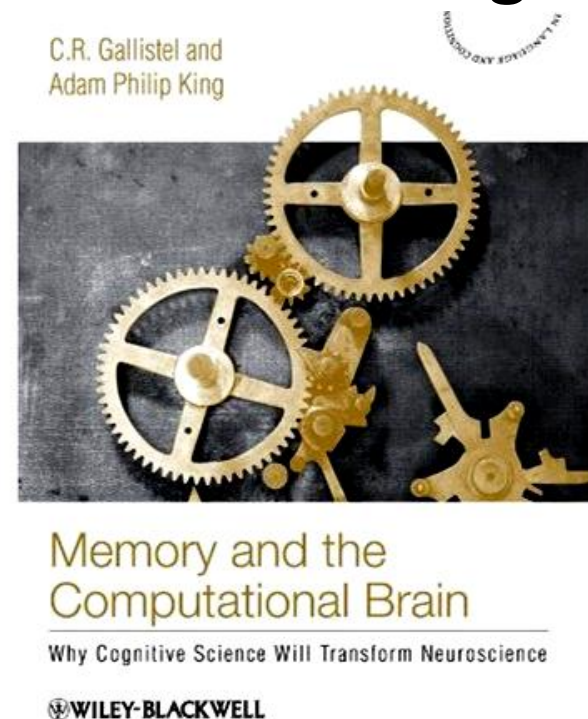
## Gallistel and King



# Conjecture

- Memory potential  $\approx \infty$
- Examples
  - Insects
  - Scrub jays
  - Autistic Savants

## Gallistel and King



- But why so rare and/or accidental?
- Large memory, computation of limited value?
- Selection favors fast robust ***action***?

**Compute**

Turing

**Delay is  
*most*  
important**

Bode

**Control, OR**

**Communicate**

Shannon

**Delay is  
*least*  
important**

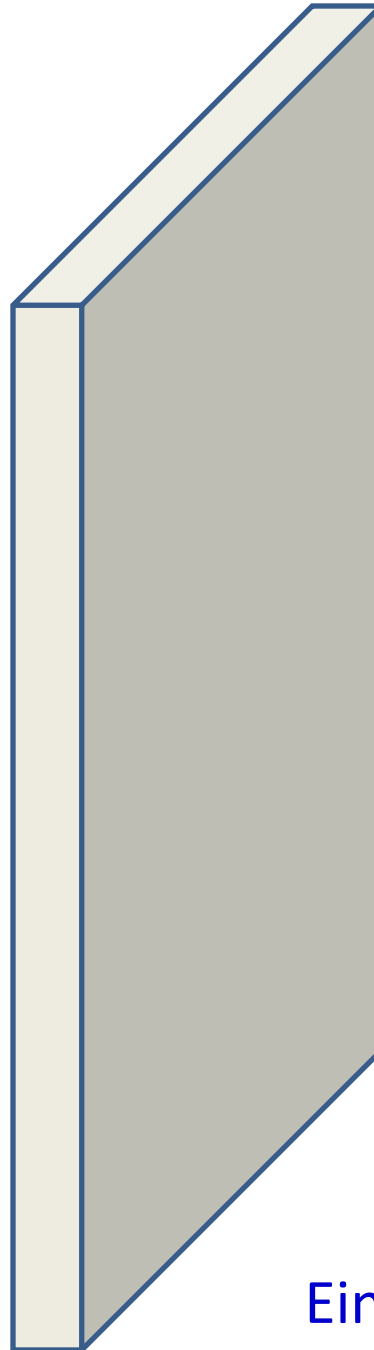
Carnot

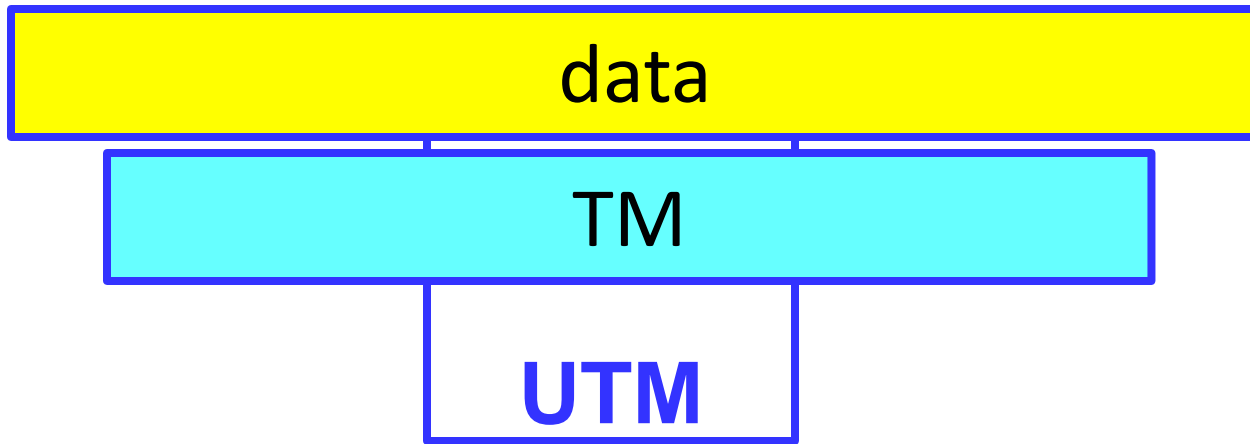
Boltzmann

Heisenberg

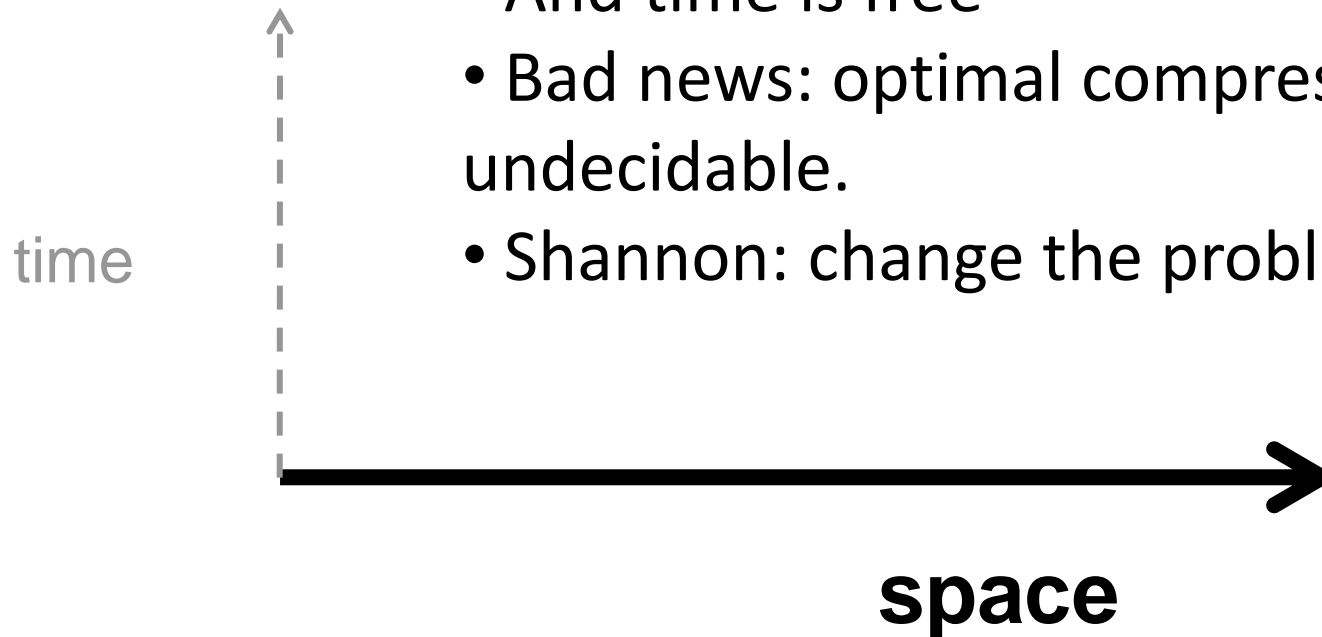
Einstein

**Physics**





- Suppose we only care about space?
- And time is free
- Bad news: optimal compression is undecidable.
- Shannon: change the problem!



# Communications

Shannon

Shannon's brilliant insight

- Don't worry about time or delay!
- Don't compress and code files, worry only about *infinite random ensembles*
- Information theory is most popular and accessible topic in systems engineering
- ***Fantastic*** for engineering, almost useless for biology (But see Lestas, Vinnicombe, Paulsson)
- (And largely irrelevant to Internet architecture)
- Mised and distracted generations of biologists and neuroscientists
- New generation of information theorists are putting delay back in. (Cheer!)

**Compute**

Turing

Delay is  
*most*  
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Bode

**Control, OR**

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Shannon

Delay is  
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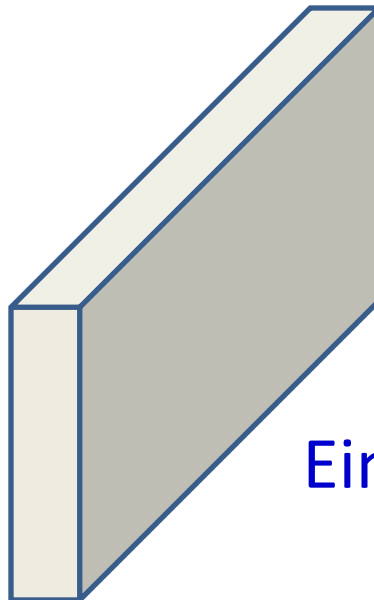
Carnot

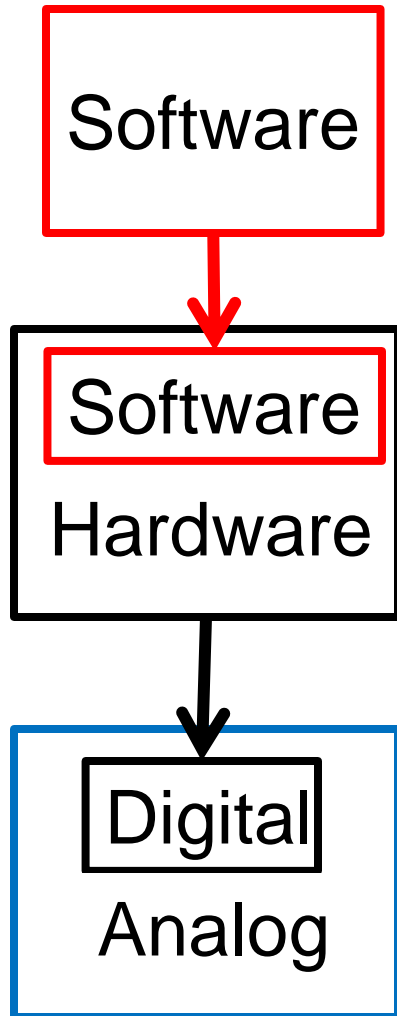
Boltzmann

Heisenberg

Einstein

**Physics**

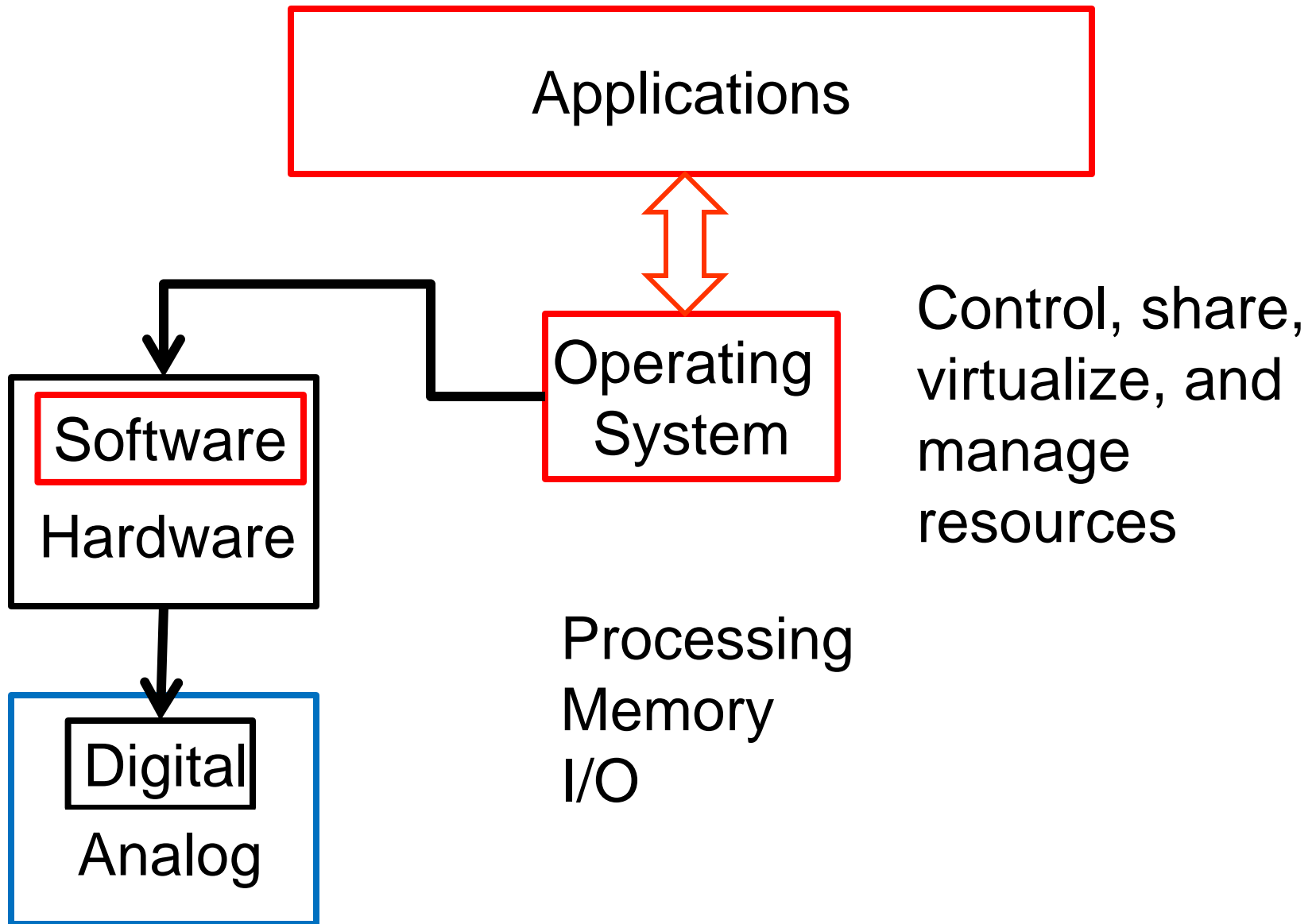




**Slow execution**  
**Flexible reprogramming**

**Faster execution**  
**Less flexible**

Modern technology gives lots  
of intermediate alternatives.



Want to emphasize the differences between these two types of layering.



**Applications**



**Operating System**

**Software**

Hardware

**Digital**

Analog

**Outfit**

**Garment**

**Cloth**

**Cloth**

**Thread**

**Thread**

**Fiber**

**Garment**

**Cloth**

**Cloth**

**Thread**

**Thread**

**Fiber**

**Garment**

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**Thread**

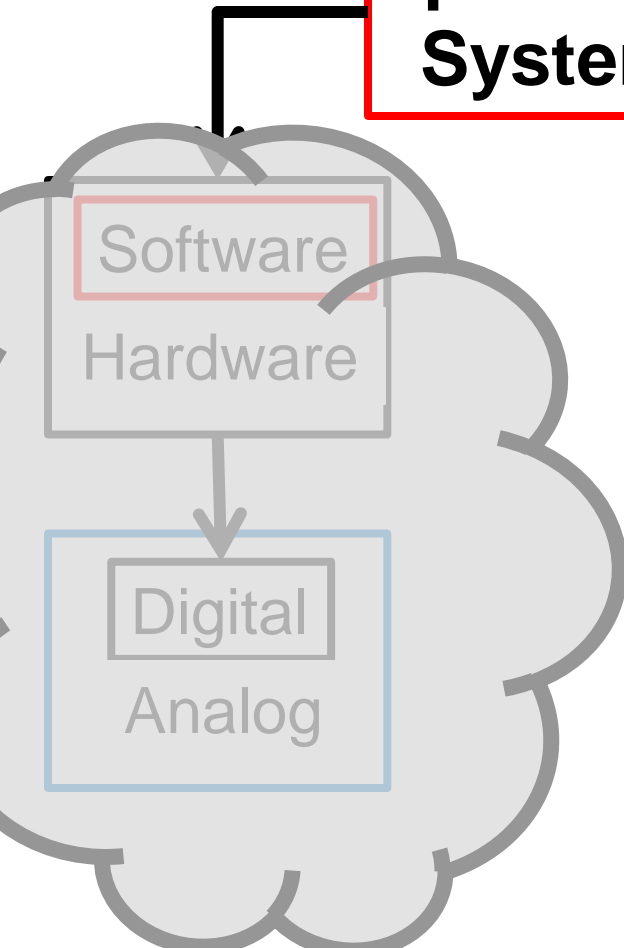
**Thread**

**Fiber**

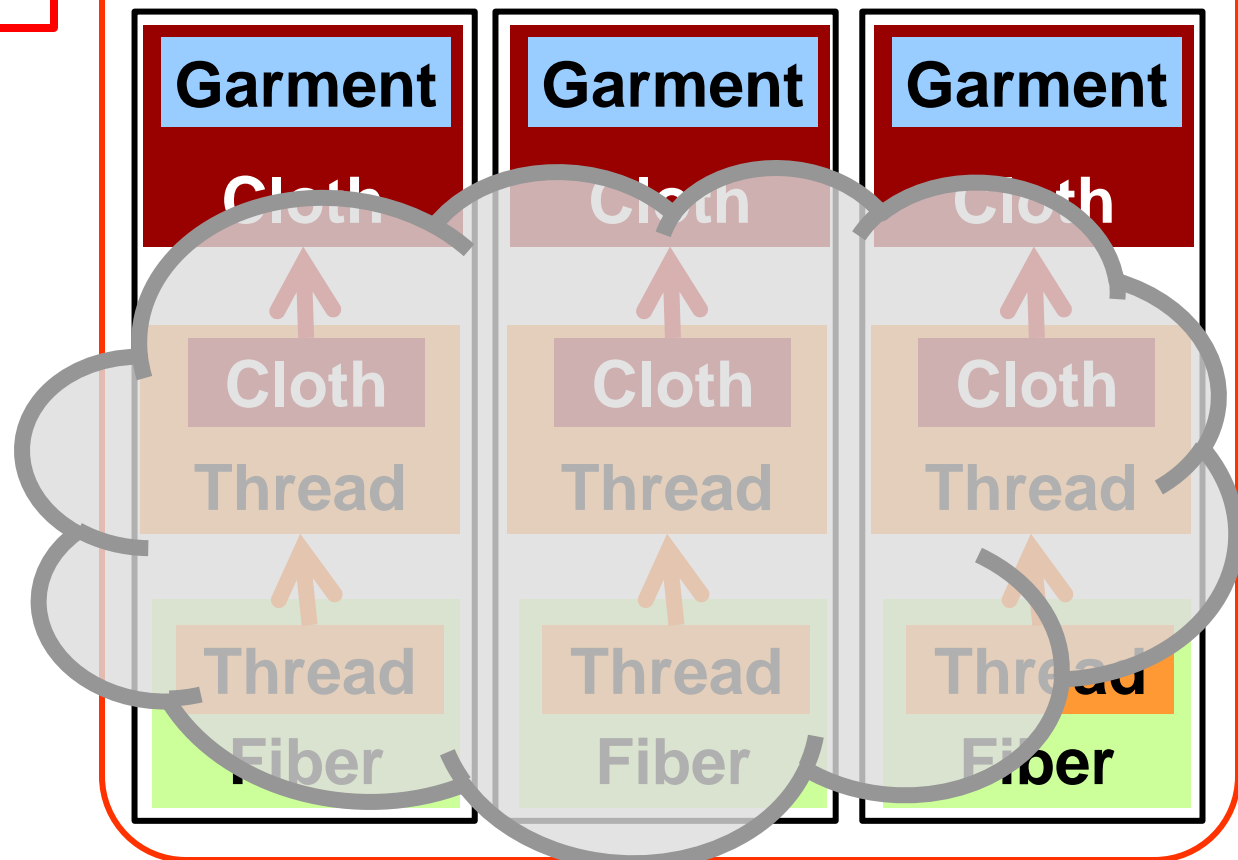
**Applications**

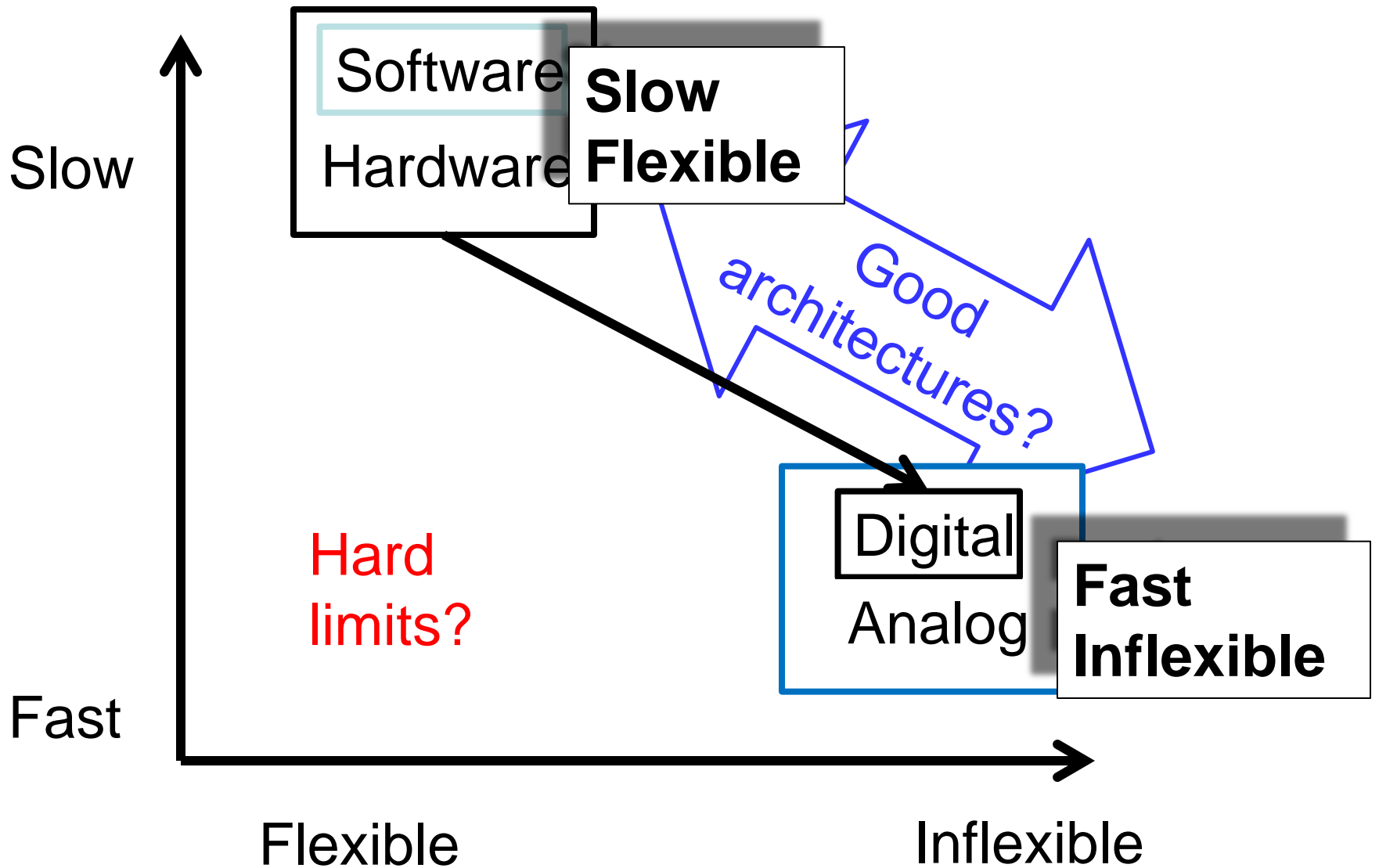
The virtual is more  
“real” than the  
implementation

**Operating  
System**

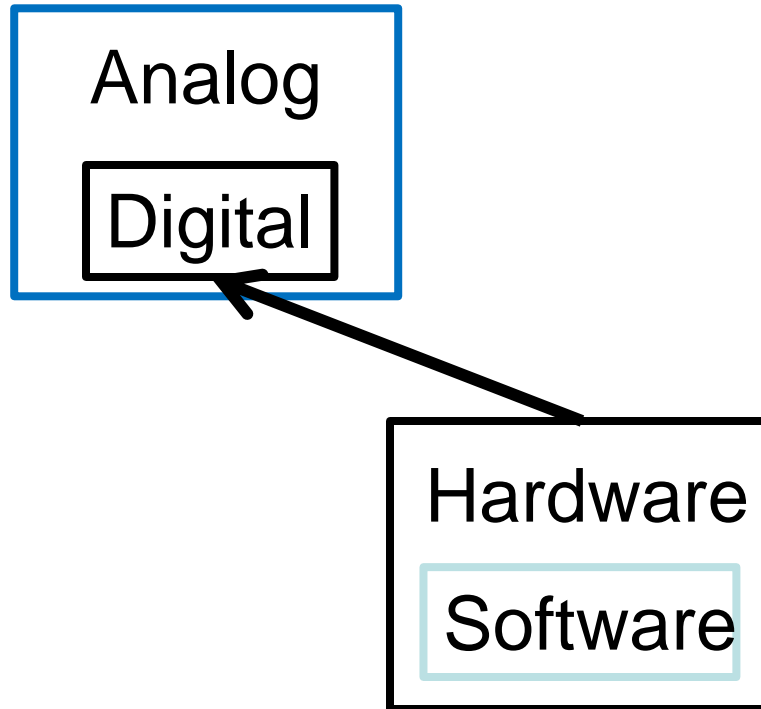


**Outfit**



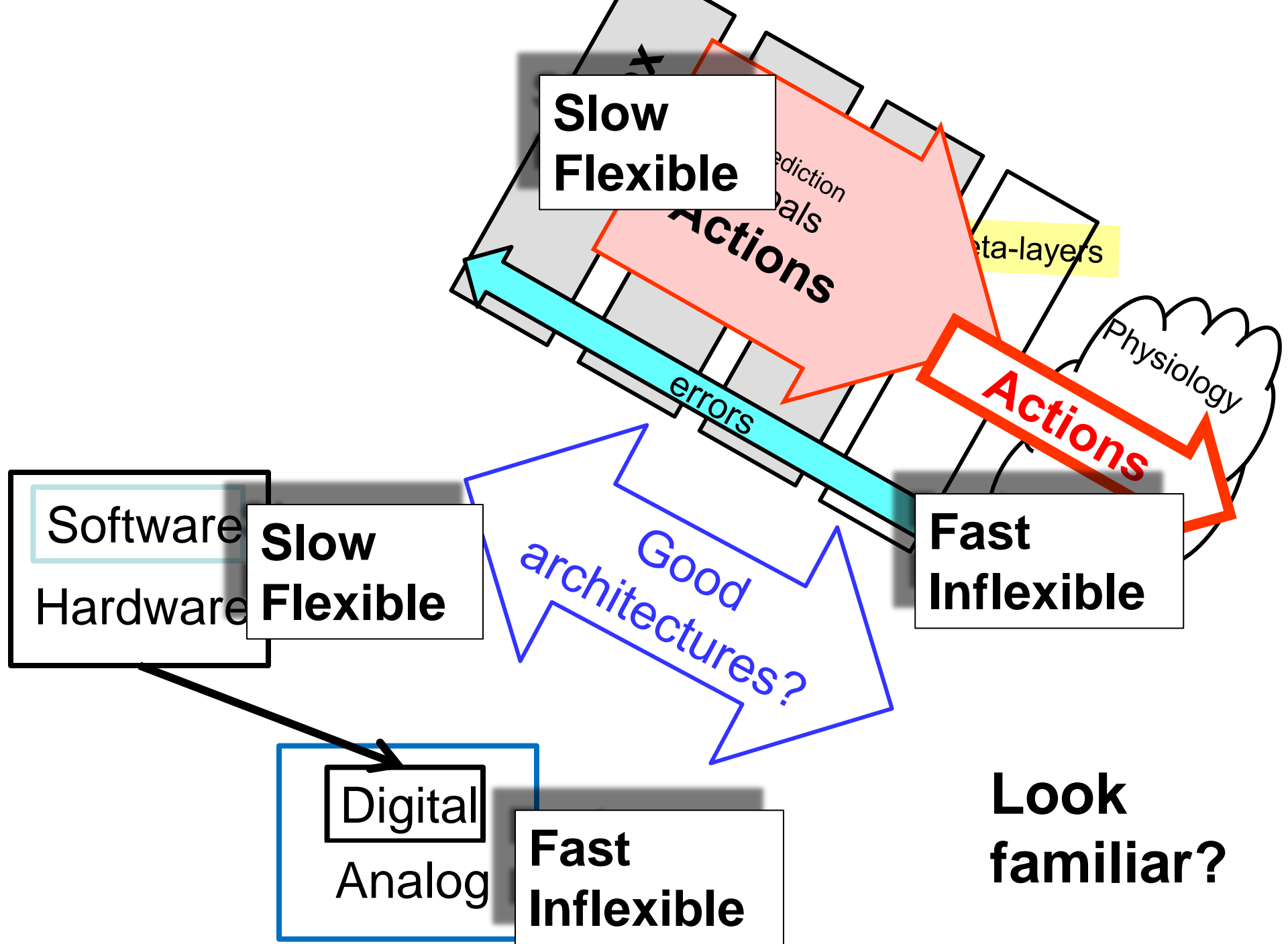


**Fast  
Inflexible**

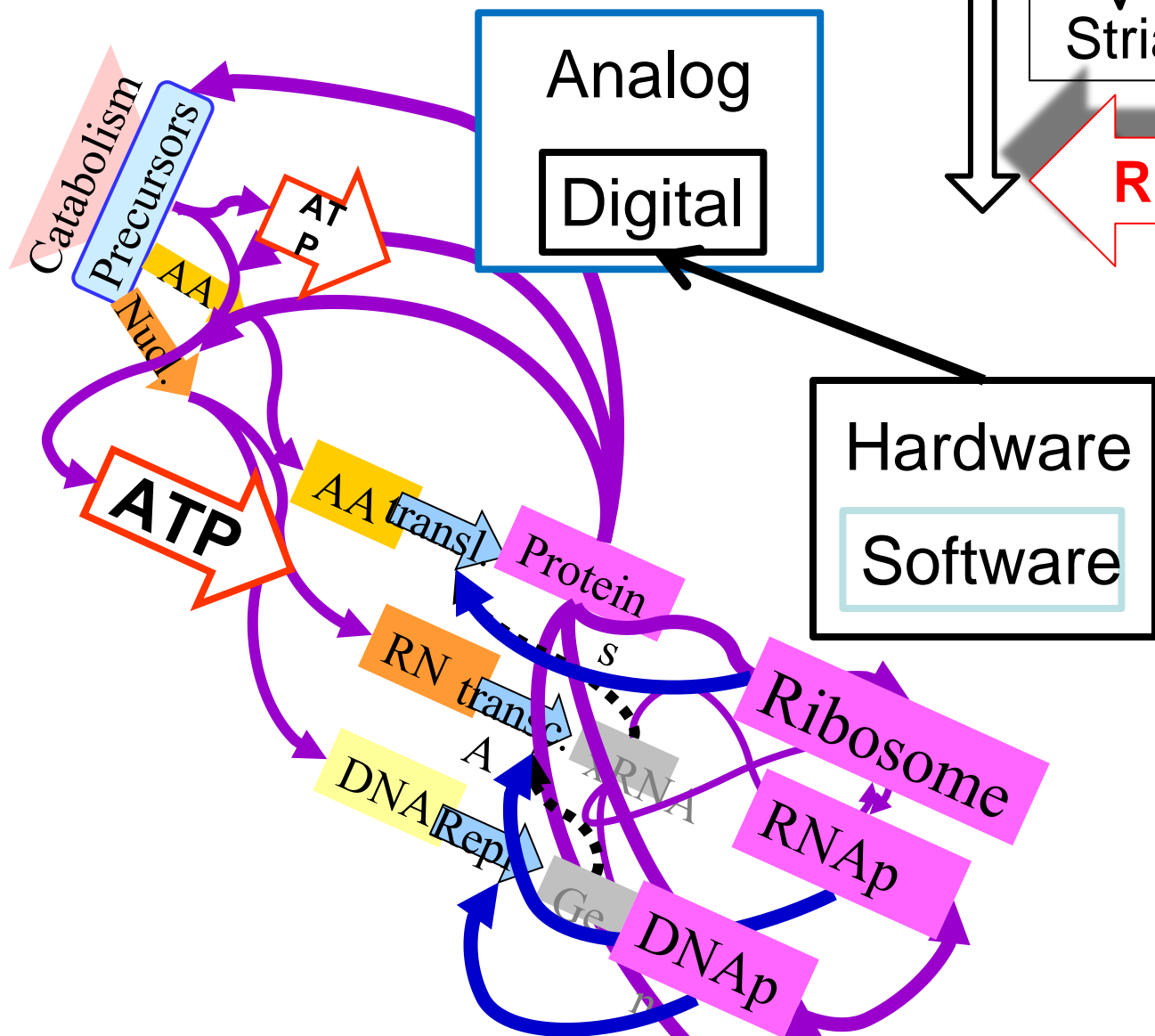


**It will be convenient later,  
for comparison with  
biology, to flip the picture  
this way to show tradeoffs.**

**Slow  
Flexible**



**Fast  
Inflexible**



Where  
we're  
ultimately  
heading

**Slow  
Flexible**

**Fast  
Inflexible**

Prefrontal

Striatum

**Reflex**

**Slow  
Flexible**

**Learning**

THINKING,  
FAST AND SLOW



DANIEL  
KAHNEMAN

WINNER OF THE NOBEL PRIZE IN ECONOMICS

**WHO'S IN CHARGE?**

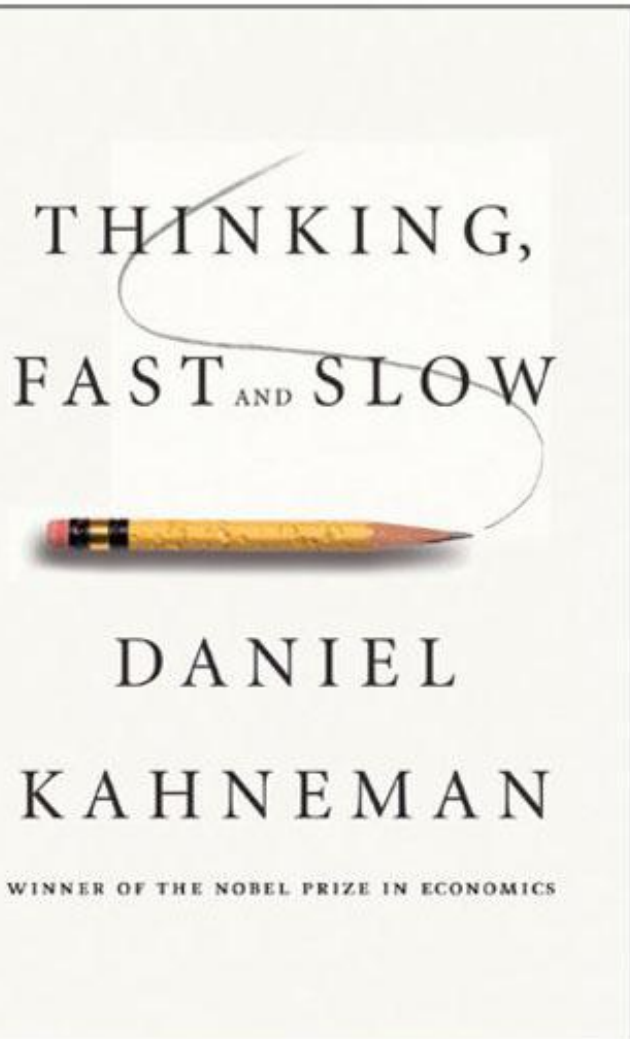
FREE WILL AND THE  
SCIENCE OF THE BRAIN

**MICHAEL S. GAZZANIGA**

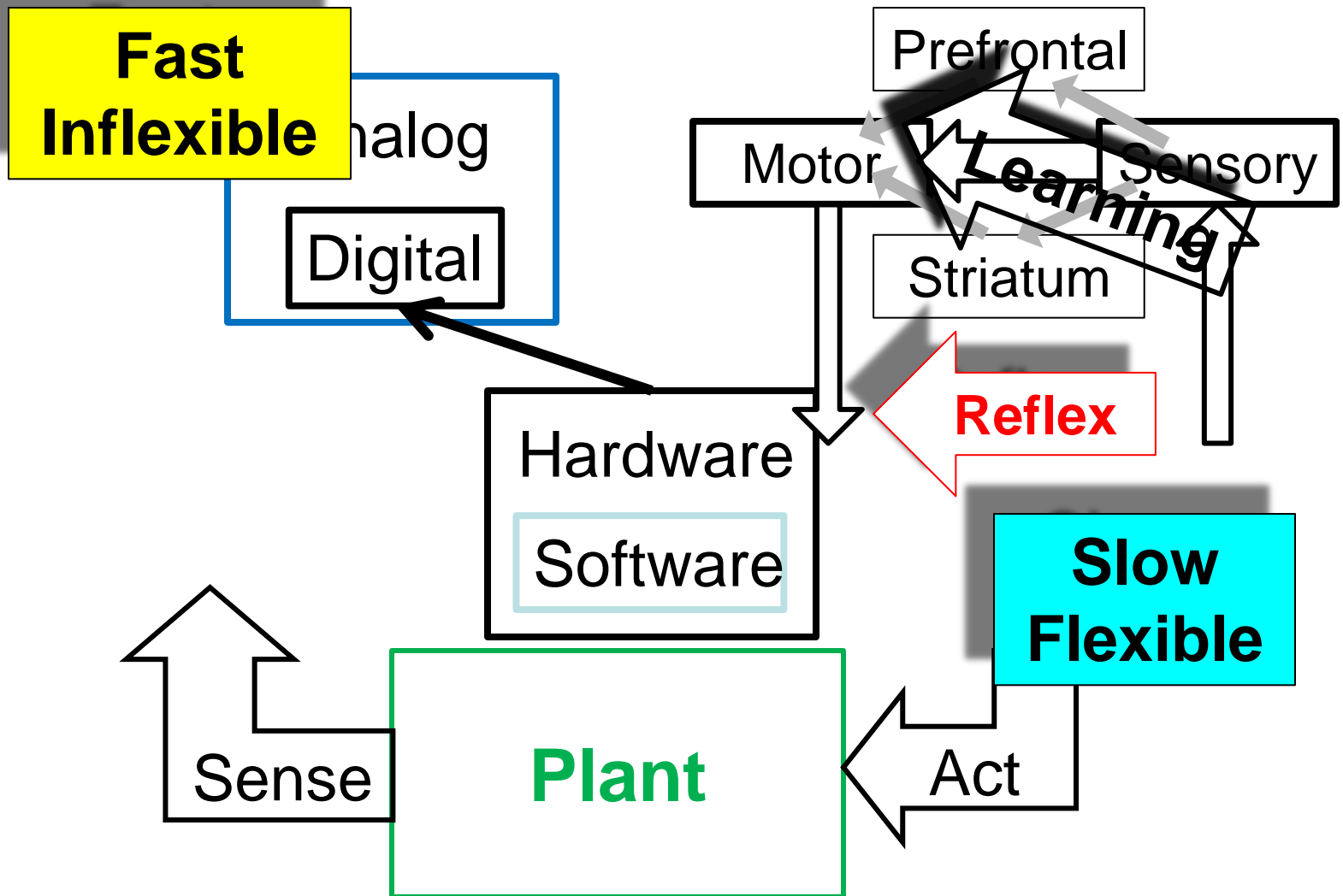
author of HUMAN and THE ETHICAL BRAIN

# Essentials To Do

- Reyna/Brainerd: Gist, false memory
- Ashby: Automaticity, multiple memory systems,...
- Cosmides/Tooby: Risk, uncertainty, cooperation, evolution,...





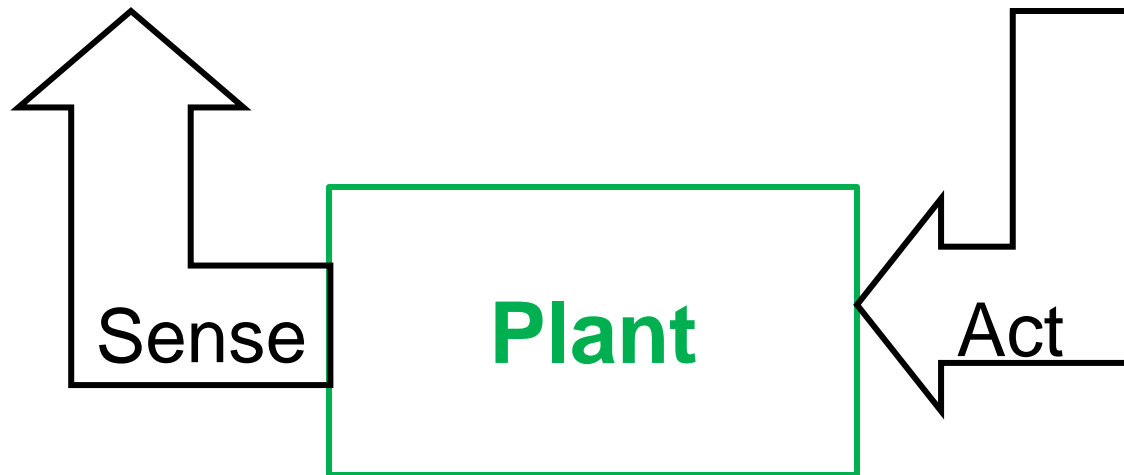


Speed and flexibility are crucial to implementing robust controllers.

Wolpert, Grafton, etc

*robust*

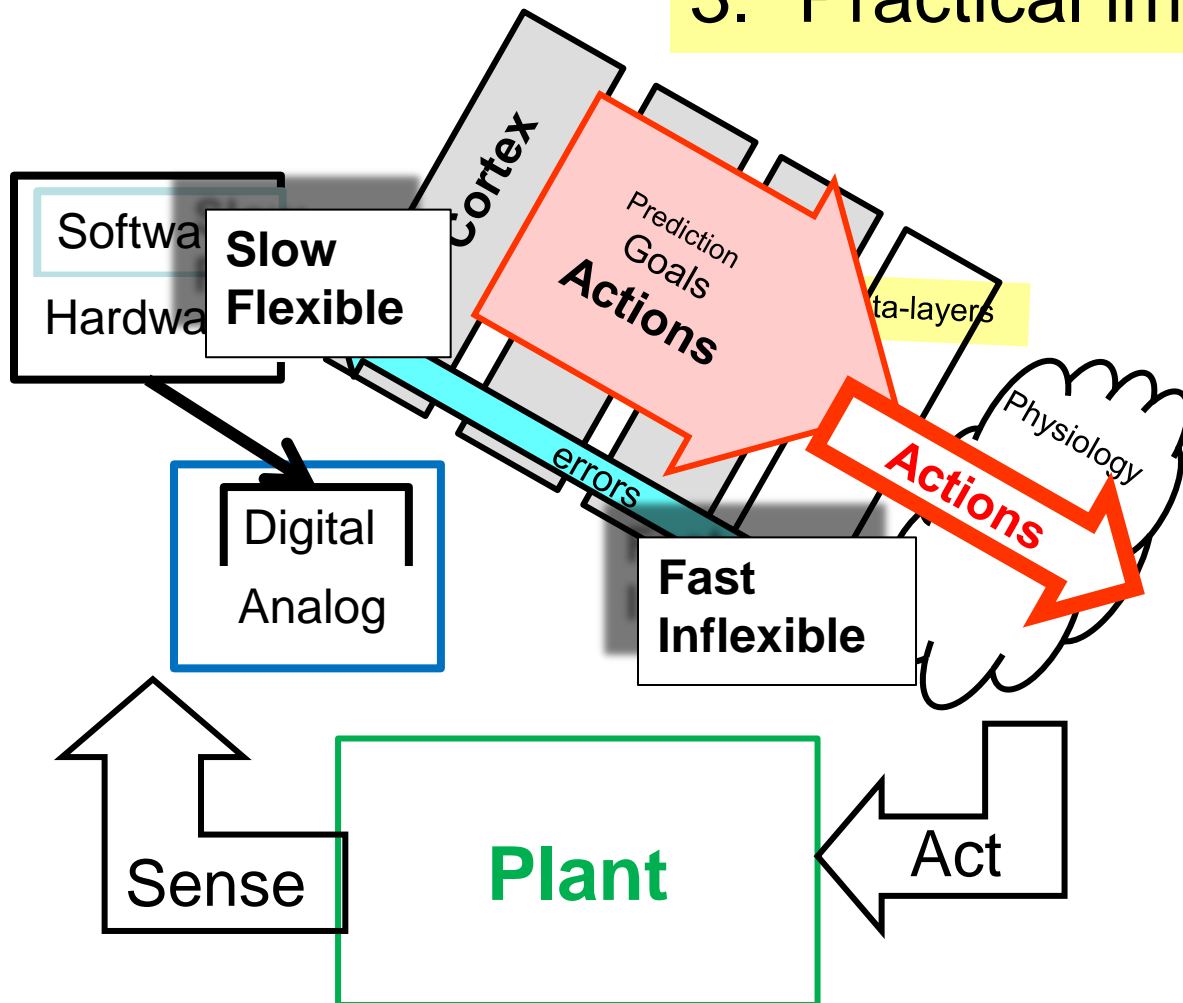
Brain as ~~optimal~~ controller

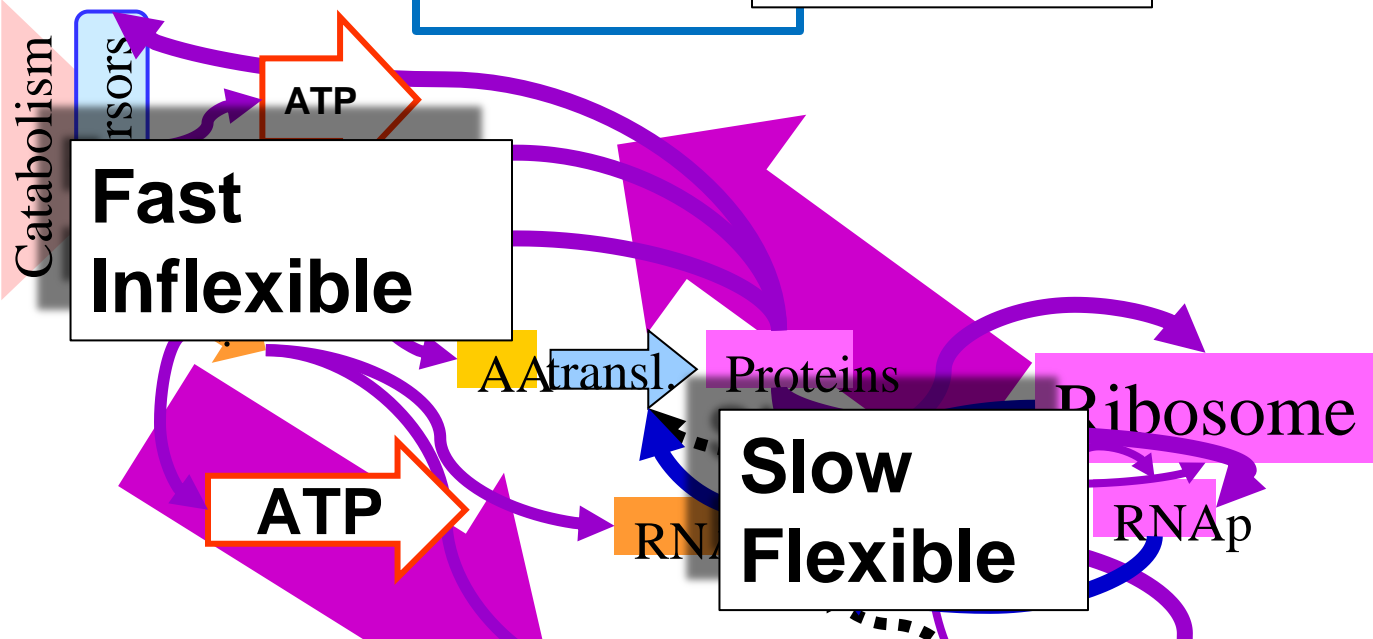
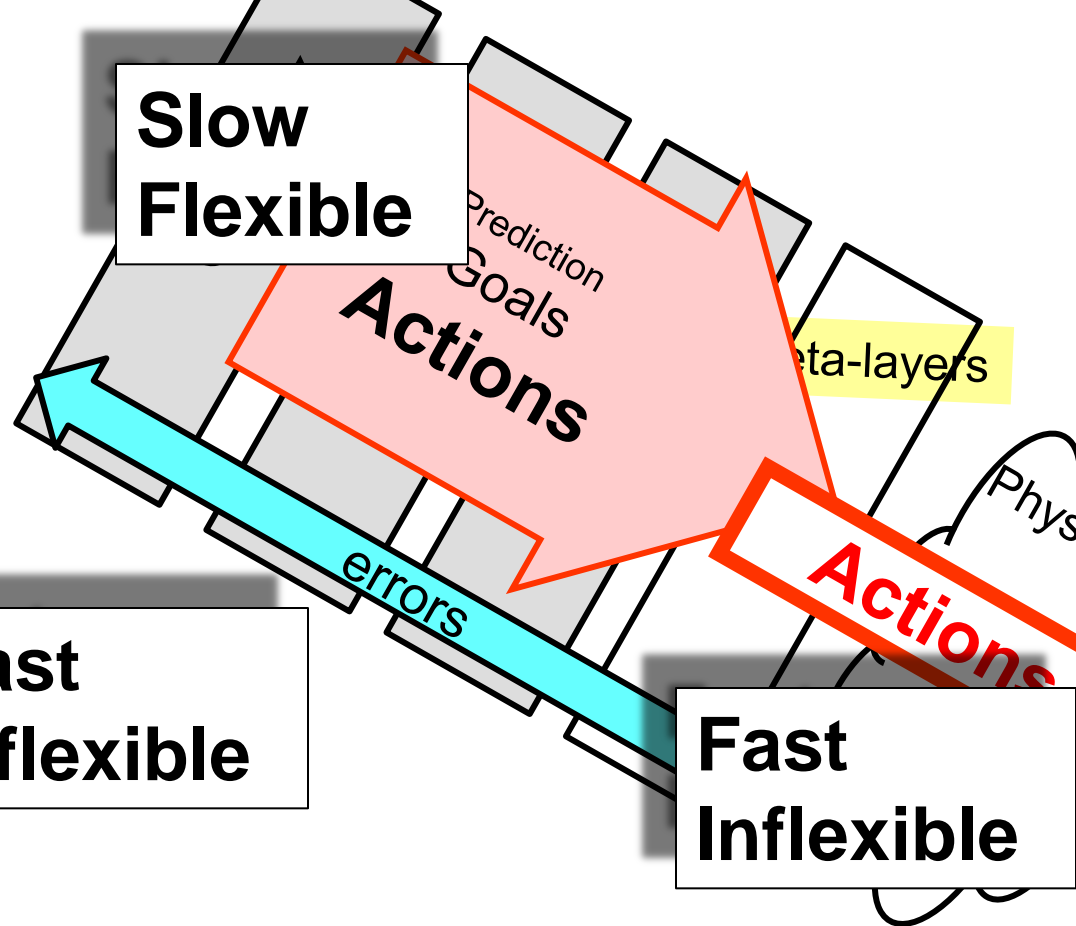
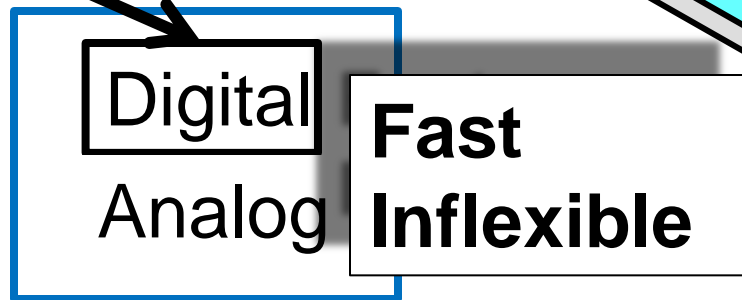
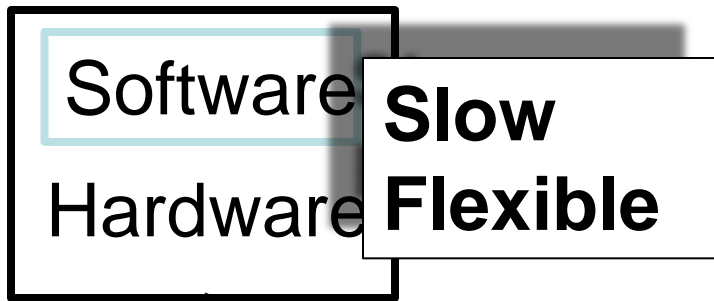


Speed and flexibility are crucial to implementing robust controllers.

# Beyond black boxes: Putting brain physiology back in the picture

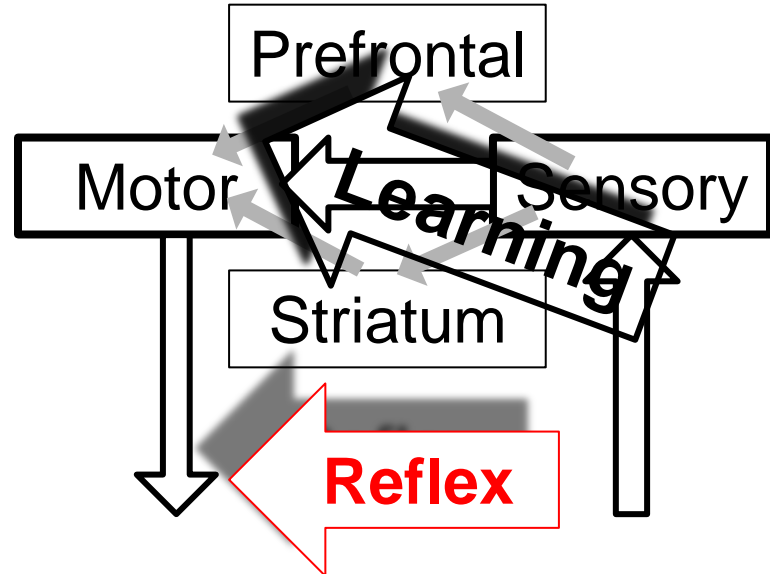
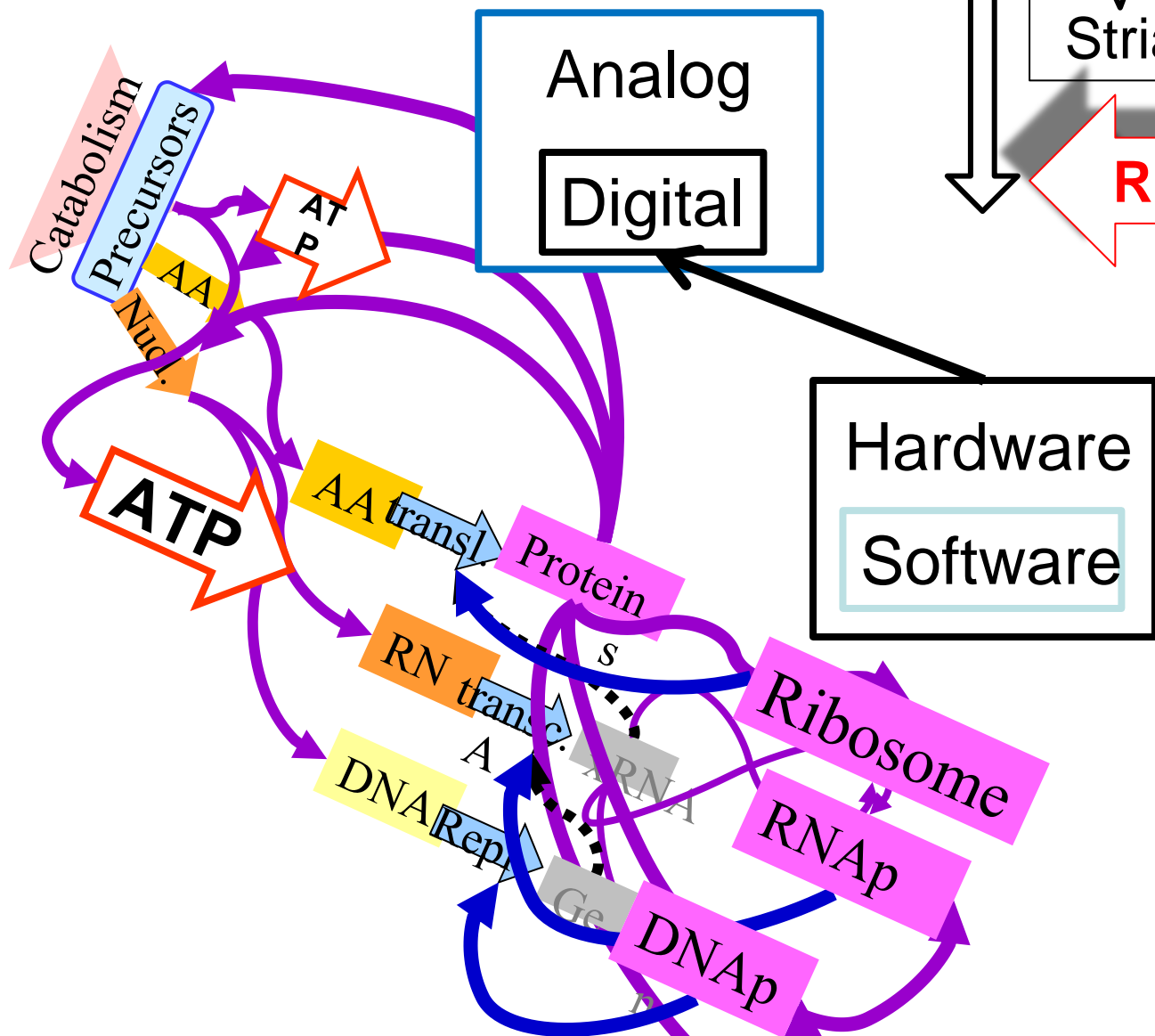
- Essentials (following Turing)
0. Model
  1. Universal laws
  2. Universal architecture
  3. Practical implementation





Want to make  
these look  
more similar

**Fast  
Inflexible**

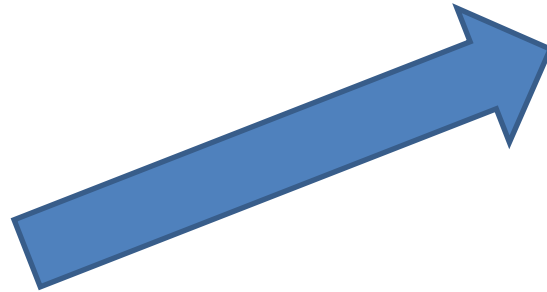
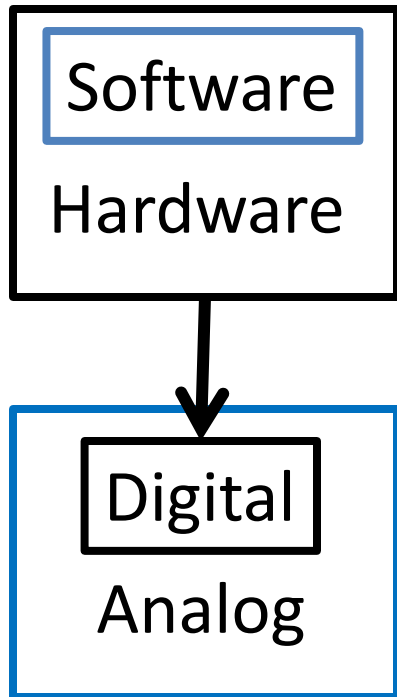


**Slow  
Flexible**

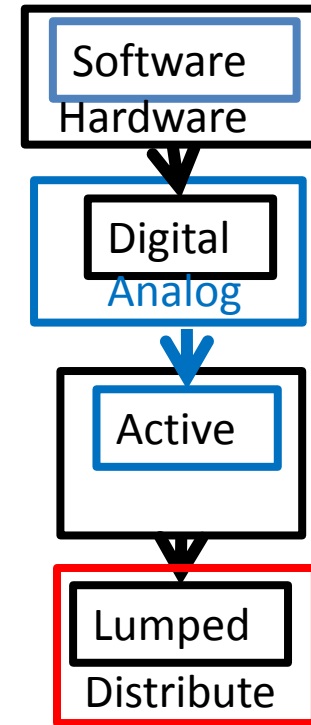


# Cyberphysical

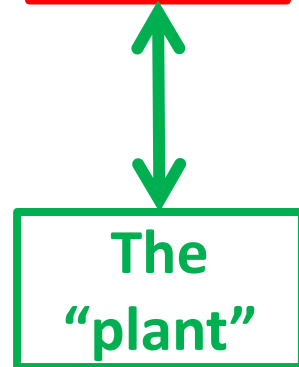
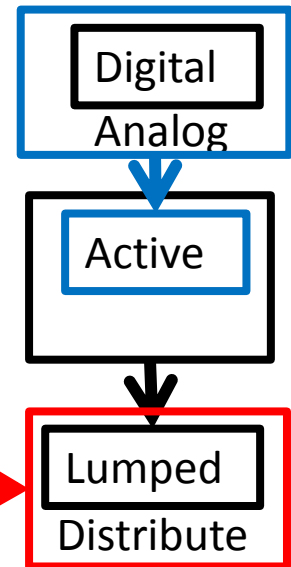
## Starting point



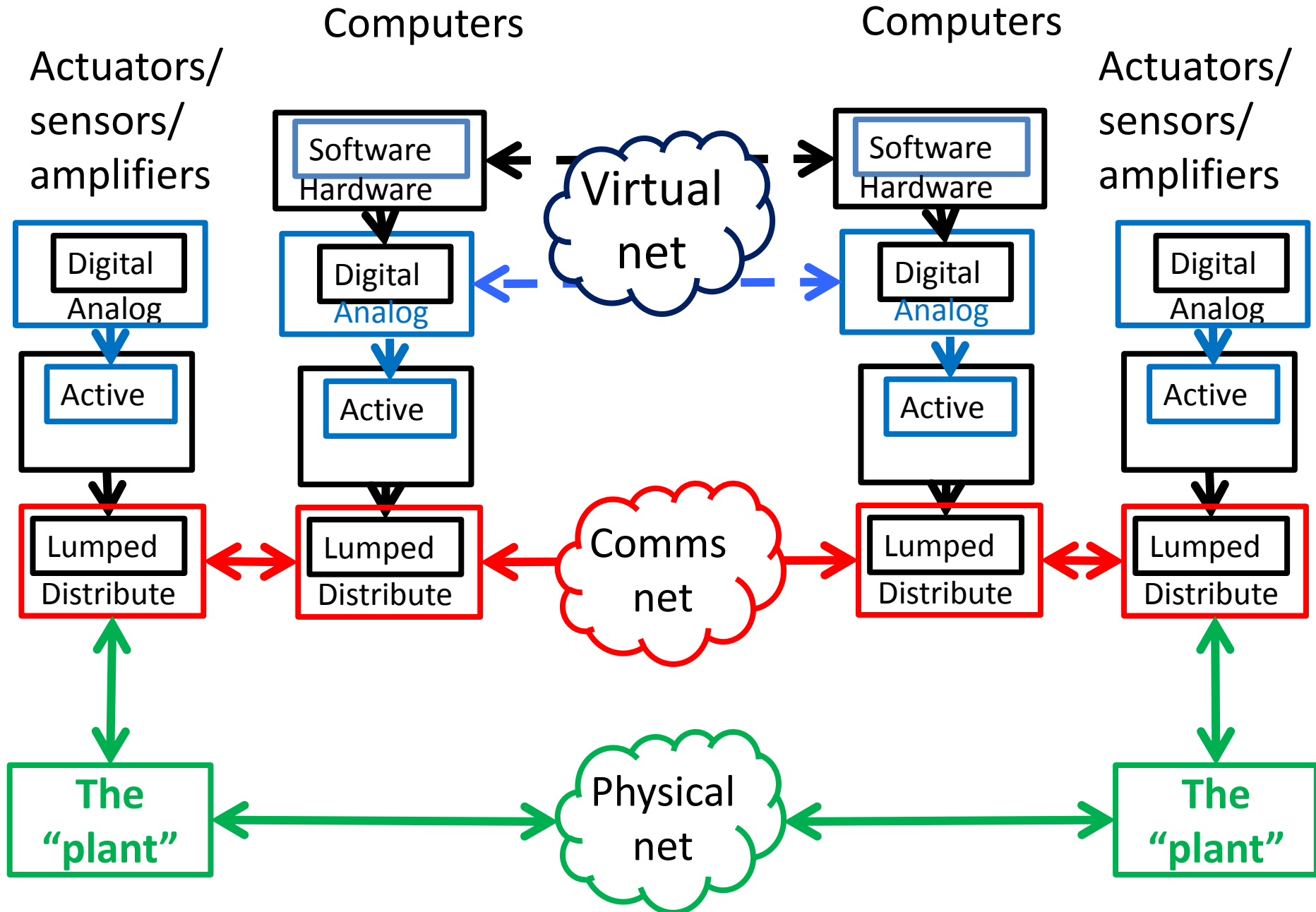
## Computers



## Actuators/ sensors/ amplifiers



# Cyberphysical

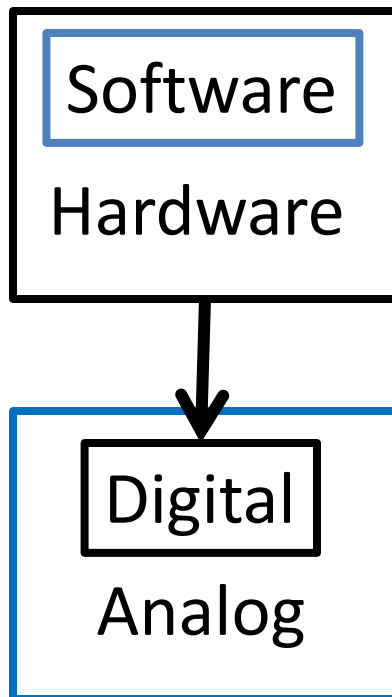




Turing as  
“new”  
starting  
point?

## Essentials:

0. Model
1. Universal laws
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**Maybe start from here with  
Turing’s 3 step research:**

1. hard limits, (un)decidability  
using standard model (TM)
2. Universal architecture  
achieving hard limits (UTM)
3. Practical implementation in  
digital electronics (biology?)

Control

Comms

Bode

Shannon

fragile?

slow?

?

wasteful?

- Each theory  $\approx$  one dimension
- Tradeoffs ***across*** dimensions
- Assume architectures a priori
- Progress is encouraging, but...
- Stovepipes are an obstacle...

Carnot

Turing

Boltzmann

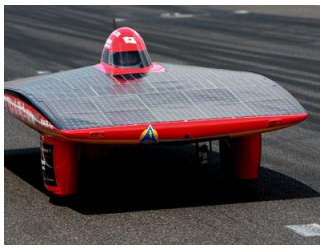
Godel

Heisenberg

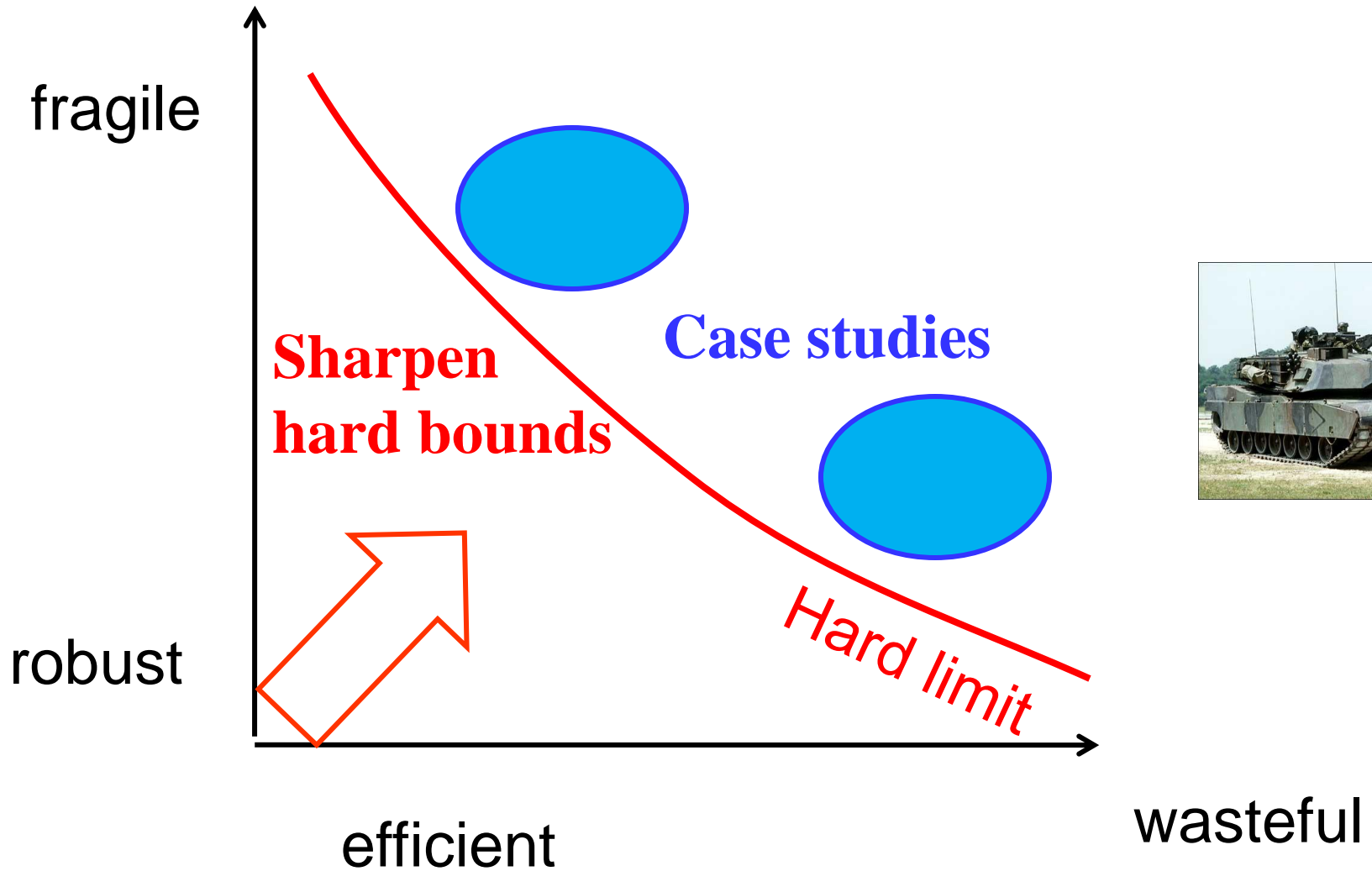
Compute

Einstein

Physics



# laws and architectures?



# Viruses' Life History: Towards a Mechanistic Basis of a Trade-Off between Survival and Reproduction among Phages

**Marianne De Paepe, François Taddei\***

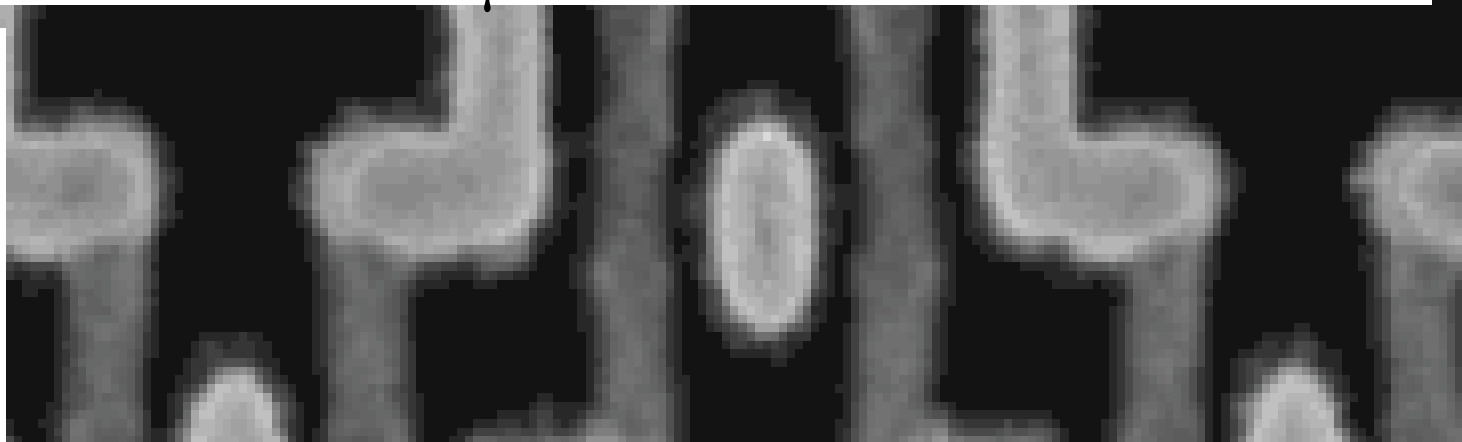
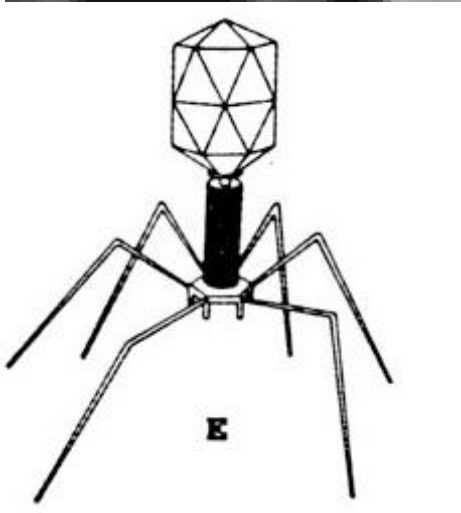
Laboratoire de Genetique Moleculaire, Evolutive et Medicale, University of Paris 5, INSERM, Paris, France

**Marianne De Paepe, François Taddei\***

Laboratoire de Genetique Moleculaire, Evolutive et Medicale, University of Paris 5, INSERM, Paris, France

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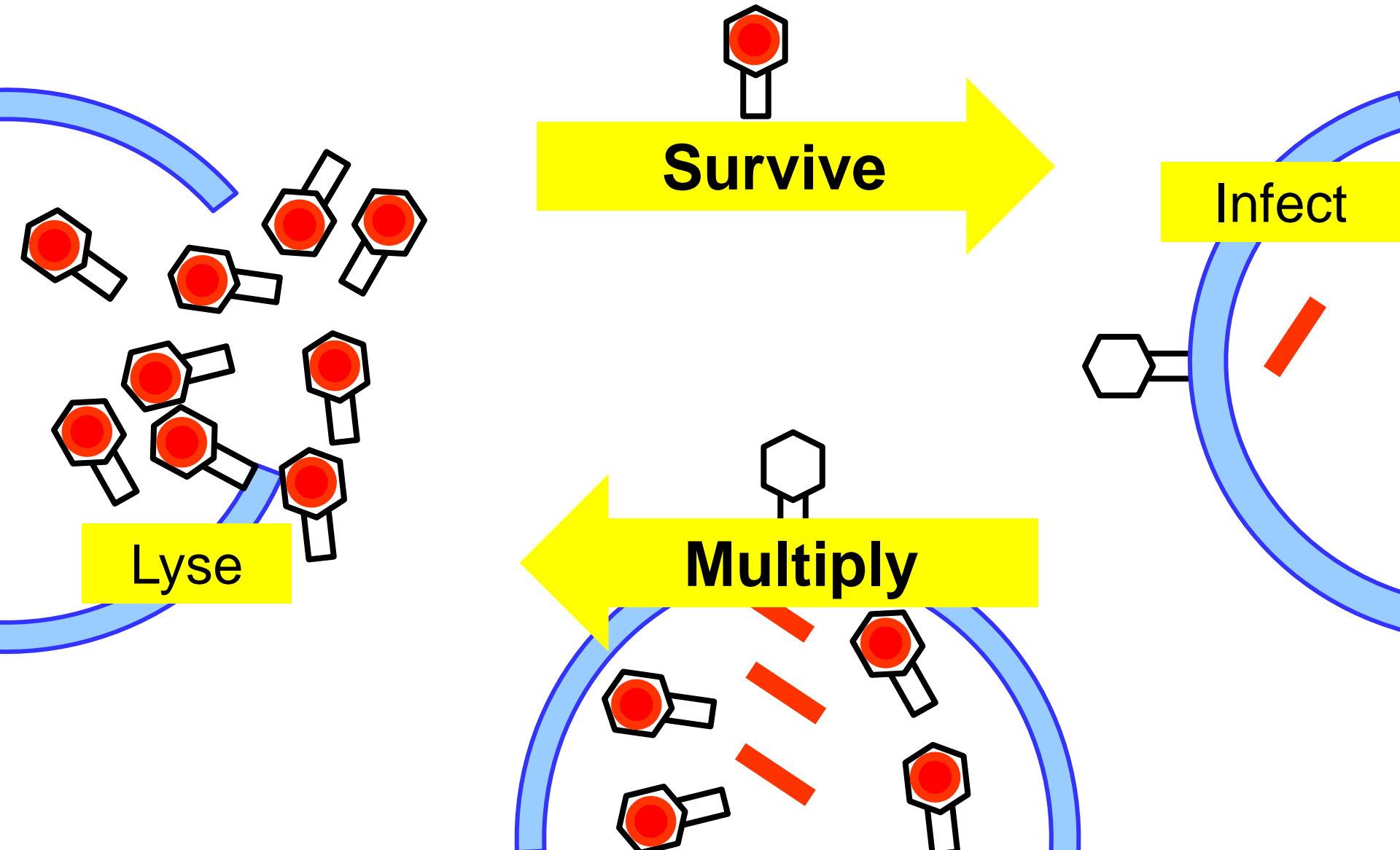
1  $\mu\text{m}$



**Phage**

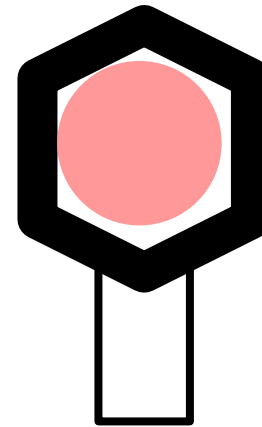
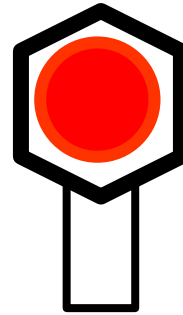
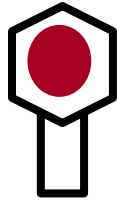
**Bacteria**

# Phage lifecycle



antagonistic  
pleiotropy

fragile



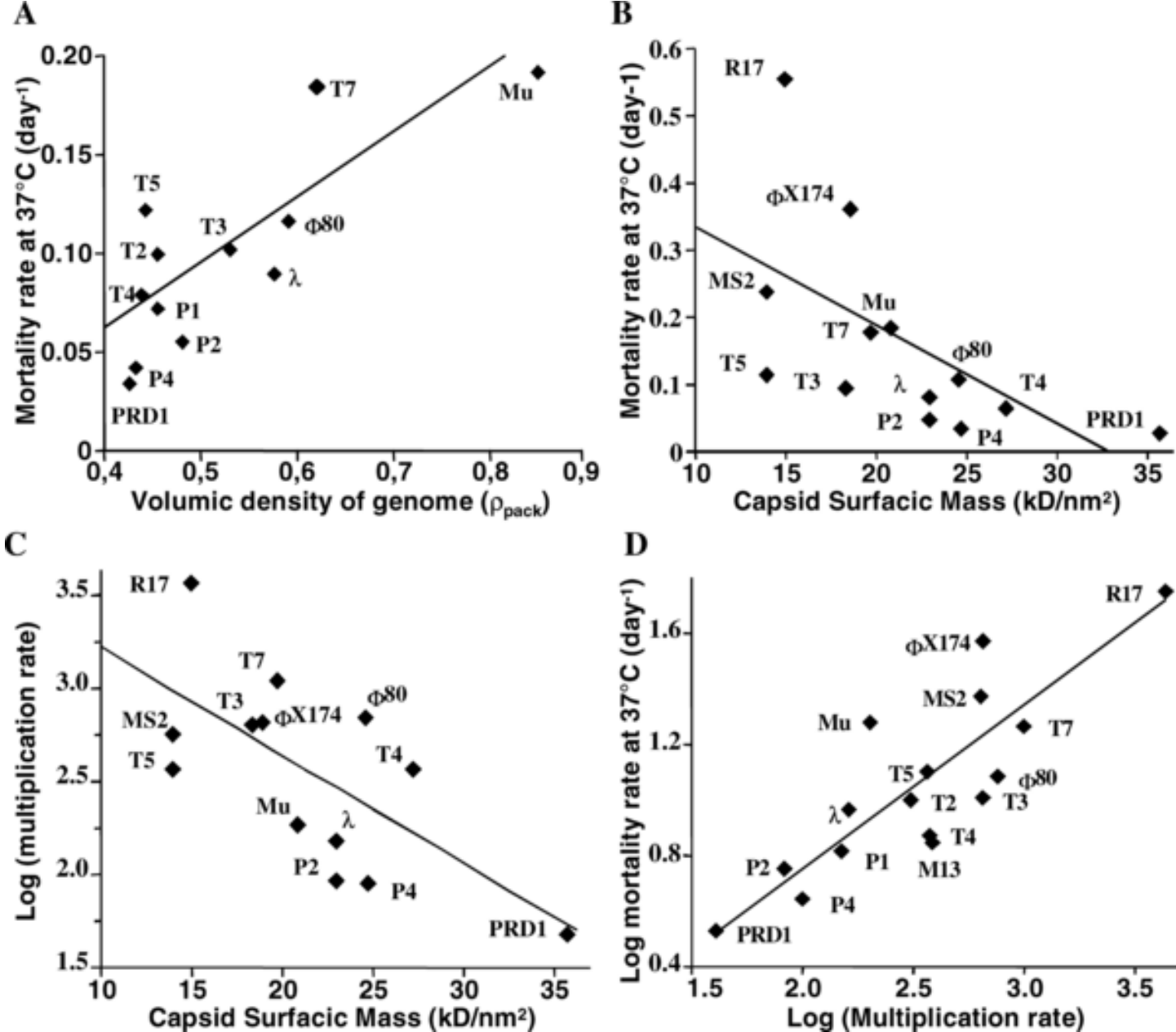
**Survive**

robust

fast  
efficient

**Multiply**

slow



**Figure 4.** Correlations between Phage Life History Traits and Phage Particle Characteristics



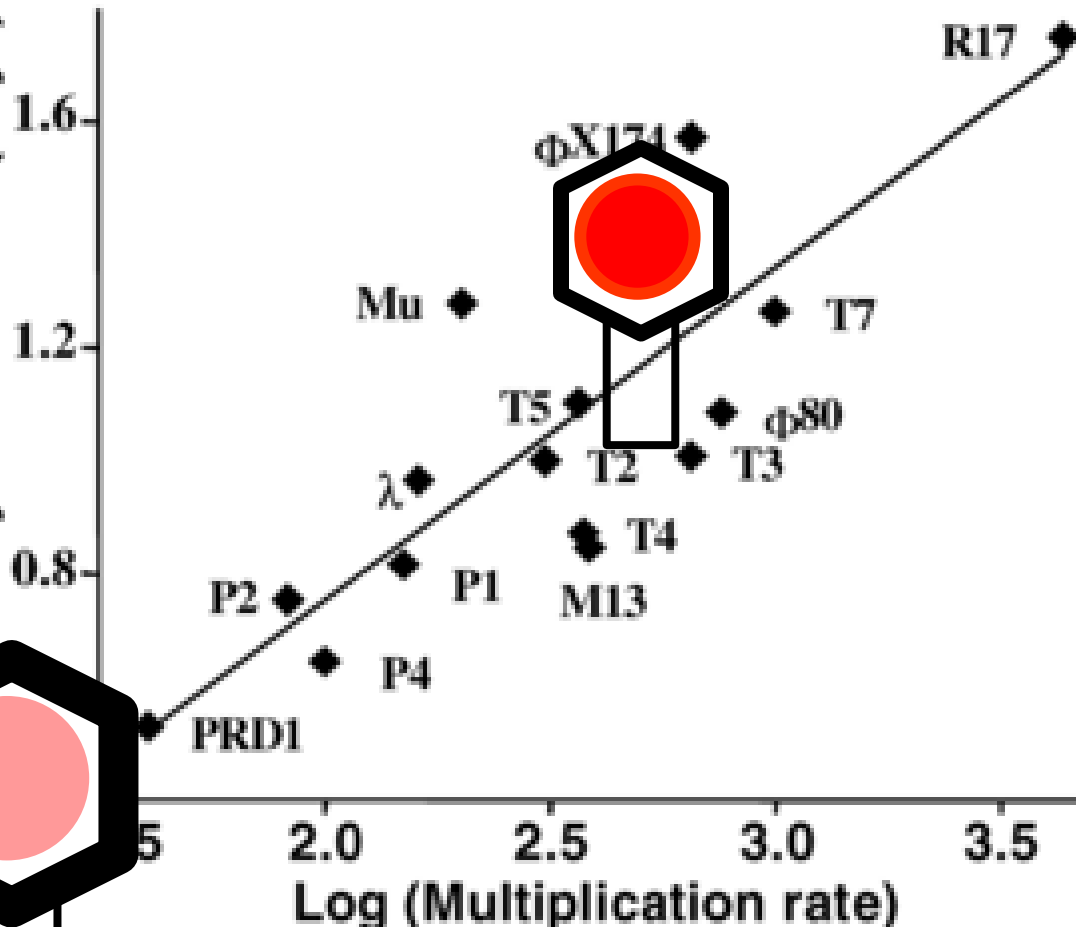
fragile

**Survive**

robust

slow

mortality rate at 37°C (day<sup>-1</sup>)



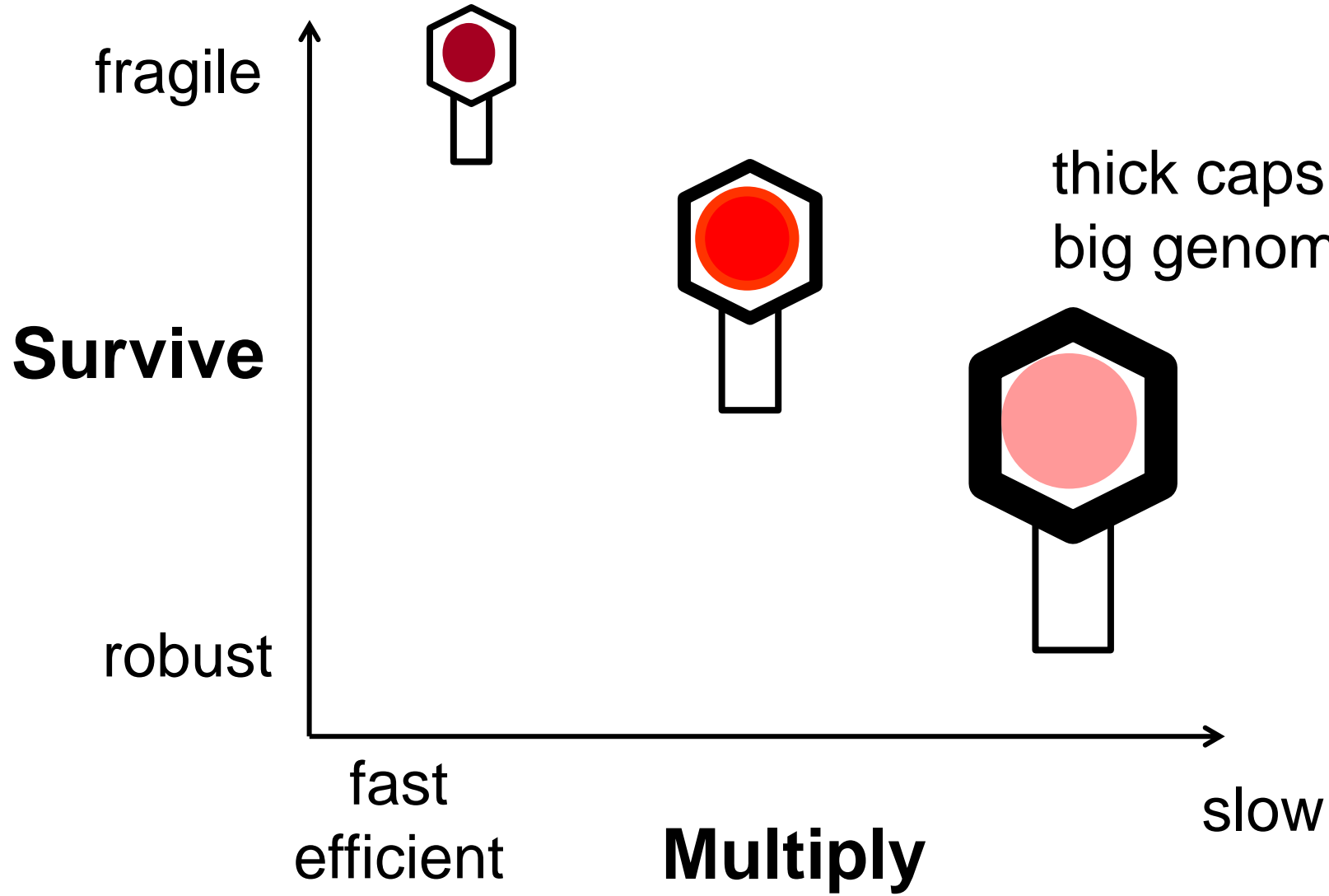
**Multiply**

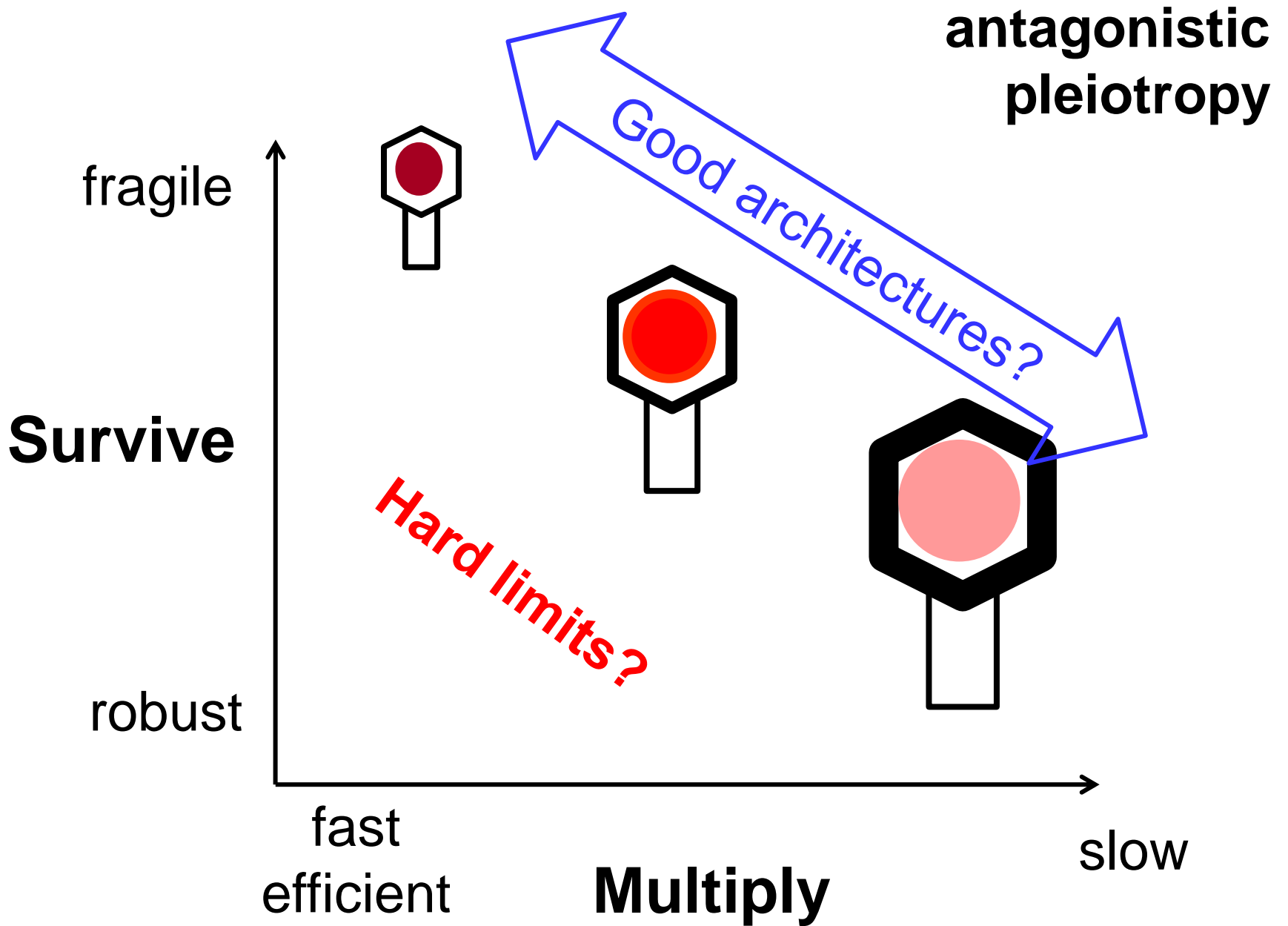
fast  
efficient

**Mechanism?**

thin capsid  
small genome

thick capsid  
big genome





Name	Type of Phage		Measured Life Cycle Characteristics						Published Structural Properties			Calculated Ratio	
	Family	Life Cycle	Decay Rate (d)	Burst Size	Latency Period (min)	Multiplication Rate <sup>a</sup> (h <sup>-1</sup> )	Adsorption Rate (min <sup>-1</sup> )	E <sub>a</sub> <sup>b</sup> (kJ/mol)	Genome Size (kb)	Ext. Diameter <sup>c</sup> (nm)	Capsid MW <sup>d</sup> (kDa)	Surfacic Mass <sup>e</sup> (kDa/nm <sup>2</sup> )	ρ <sub>pack</sub> <sup>f</sup>
λ	Siphoviridae	T	0.072	115	42	162	4.5 × 10 <sup>-10</sup>	142	49 [37]	63 [24]	22,500 [38]	22.7	0.572
M13	Inoviridae	Chronic	0.074			413	9.0 × 10 <sup>-11</sup>	125	6 [37]	6.5x90 [37]	15,700 [39]	8.7	
MS2	Leviviridae	L	0.250	400	40	669	6.5 × 10 <sup>-10</sup>	99	4 [37]	27 [40]	2,500 [41]	13.7	
Mu	Myoviridae	T	0.290	200	60	200	ϕ	111	43 [37]	54 [42]	15,000 [43]	20.6	0.845
P1	Myoviridae	T	0.077	400	60	149	2.2 × 10 <sup>-10</sup>	119	100 [37]	85 [44]			0.435
P2	Myoviridae	T	0.041	160	48	88	5.5 × 10 <sup>-11</sup>	123	34 [37]	60 [45]	20,400 [46]	22.7	0.468
P4	Myoviridae	T	0.045	300	60	101	2.2 × 10 <sup>-10</sup>	105	12 [37]	45 [46]	12,400 [46]	24.5	0.429
φ80	Siphoviridae	T	0.120	600	55	776	3.8 × 10 <sup>-10</sup>	114	45	61		24.3	0.585
φX174	Microviridae	L	0.200	180	15	697	2.9 × 10 <sup>-9</sup>	136	5 [37]	32 [47]	4,700 [48]	18.4	
PRD1	Tectiviridae	L	0.037	50	48	50	4.6 × 10 <sup>-10</sup>	171	15 [49]	65 [49]	33,000 [49]	35.5	0.421
T2	Myoviridae	L	0.068	135	23	335	4.0 × 10 <sup>-10</sup>		170 [37]	85x110 [50]		19.9	0.451
T3	Podoviridae	L	0.102	200	17	700	1.6 × 10 <sup>-9</sup>	105	38 [51]	60 [52]		18.1	0.525
T4	Myoviridae	L	0.068	150	23	400	5.0 × 10 <sup>-10</sup>	96	170 [37]	85x110 [50]	65,600 [50]	26.9	0.421
T5	Siphoviridae	L	0.120	290	44	399	2.0 × 10 <sup>-10</sup>	115	122 [53]	65 [53]	27,500 [53]	13.7	0.439
T7	Podoviridae	L	0.187	260	13	1,131	3.0 × 10 <sup>-9</sup>	100	40 [37]	60 [52]	16,300 [54]	19.4	0.615
R17	Leviviridae	L	0.520	3,570	53	4,288	3.7 × 10 <sup>-9</sup>	99	4 [37]	27 [55]	2,600 [41]	14.7	

Mortality rate, burst size, latency period, and adsorption rate were measured as described in Material and Methods. Each value is the mean of at least three independent experiments. Genome size, diameter, and molecular weight were collected from published results. The internal volume used to calculate ρ<sub>pack</sub> has either been collected in structural studies of phage capsids or calculated by subtracting the thickness of the shell from the external diameter. Empty cells in the table correspond to data that were either not available or not measured.

<sup>a</sup>Mean of the ratio obtained by dividing the burst size by the latency period, calculated for each experiment.

<sup>b</sup>E<sub>a</sub>: energy of activation of the reaction leading to inactivation of virions, obtained from the Arrhenius equation linking mortality rate and temperature between 30 °C and 45 °C. The energy of activation represents the energy the system has to overcome so that the reaction occurs.

<sup>c</sup>Ext. diameter: external diameter of the capsid.

<sup>d</sup>Molecular weight of the proteins constituting the capsid.

<sup>e</sup>Capsid molecular weight divided by the surface of the capsid; this ratio represents the thickness of the shell.

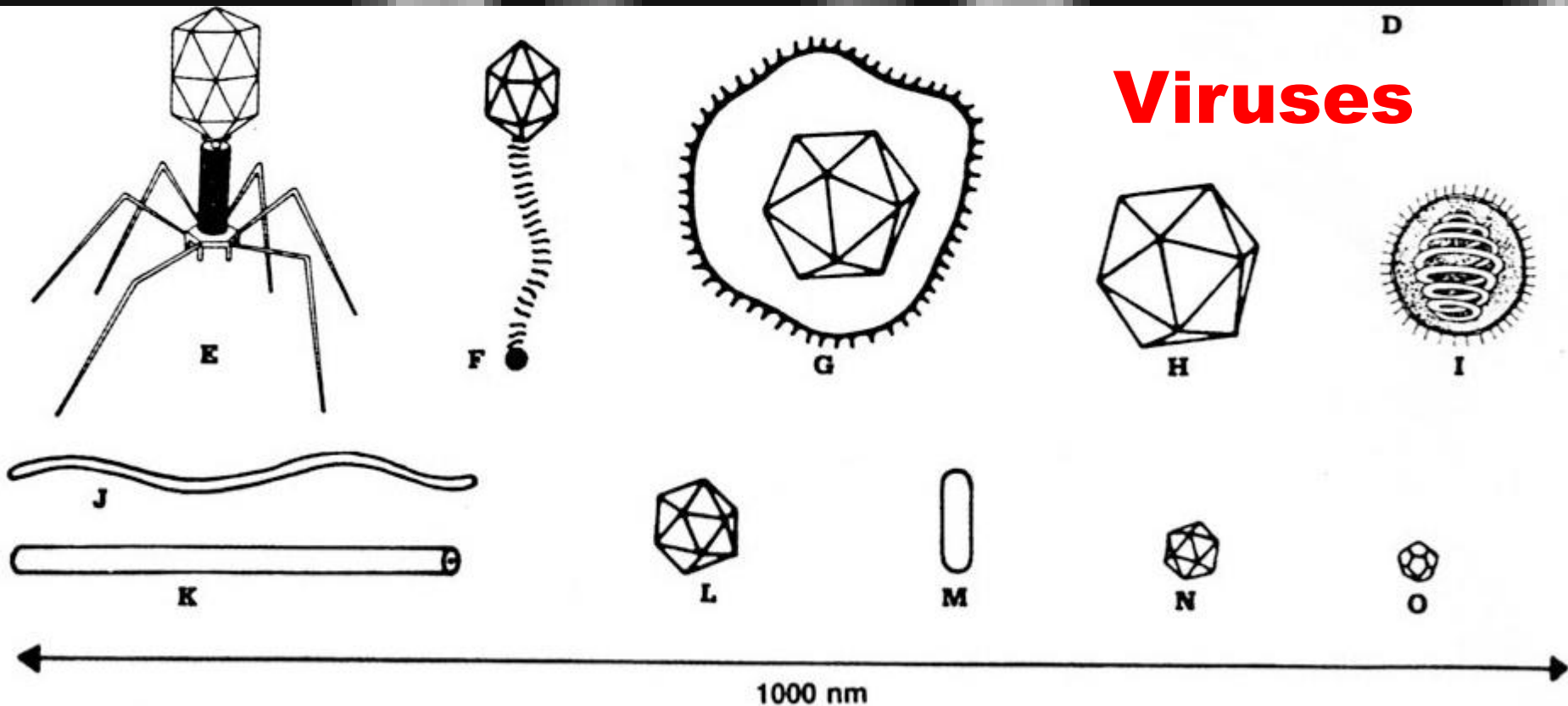
<sup>f</sup>Volume occupied by the genome divided by the internal volume of the capsid.

T: Temperate phage, L: Virulent Phage, Chronic: creates a chronic infection

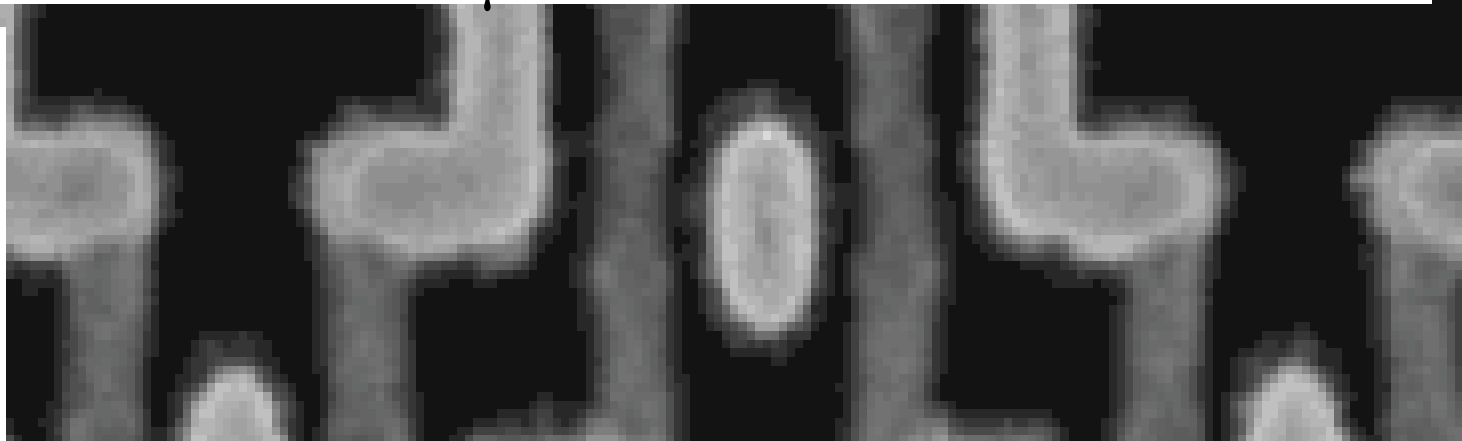
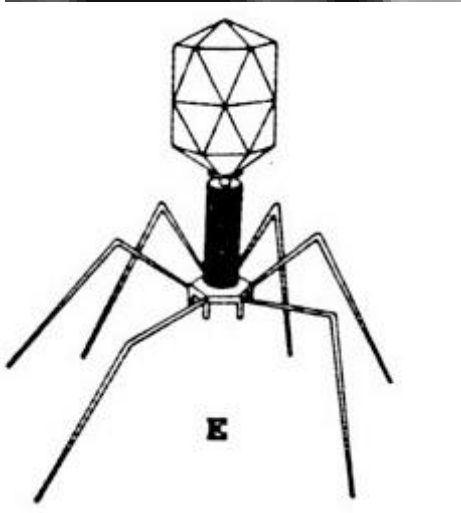
DOI: 10.1371/journal.pbio.0040193.t001

1  $\mu\text{m}$

# Viruses

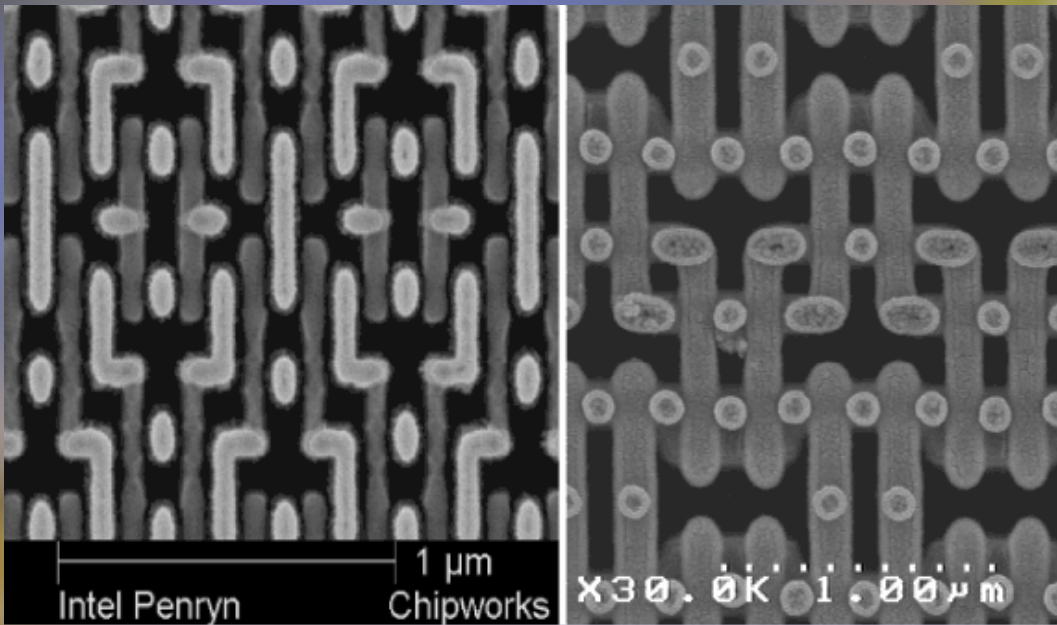


1  $\mu\text{m}$



**Phage**

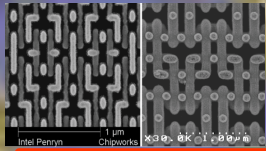
**Bacteria**



1  $\mu\text{m}$

why computer memory is almost “free”



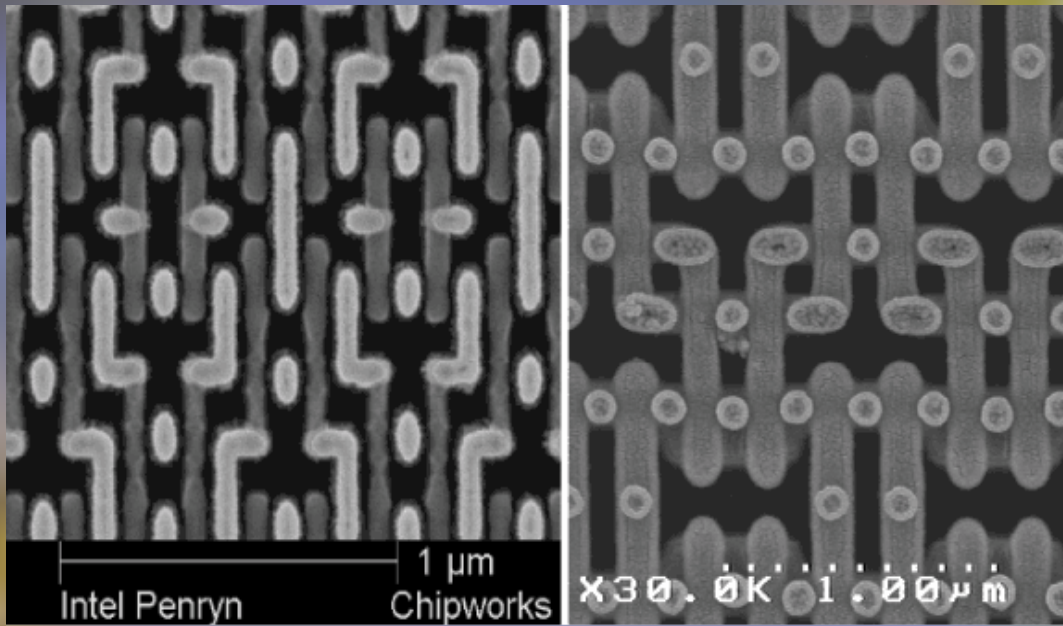


5 μm

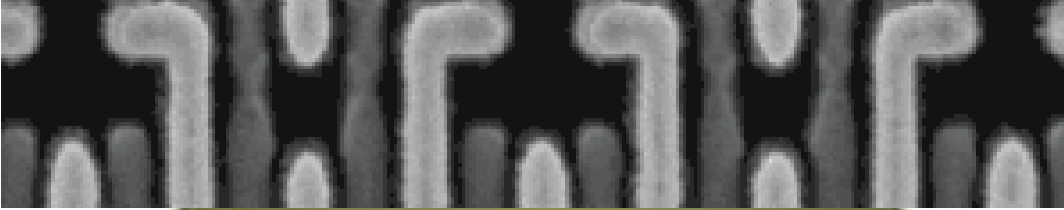
Gallistel: where is our read/write memory?  
Conjecture: it's digital and much smaller than this.

5 μm





1  $\mu\text{m}$



1  $\mu\text{m}$

Bacterium  
(Staph. aureus)



Bacterium  
(Chlamydia)



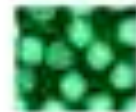
Pox  
virus



Herpes



Influenza

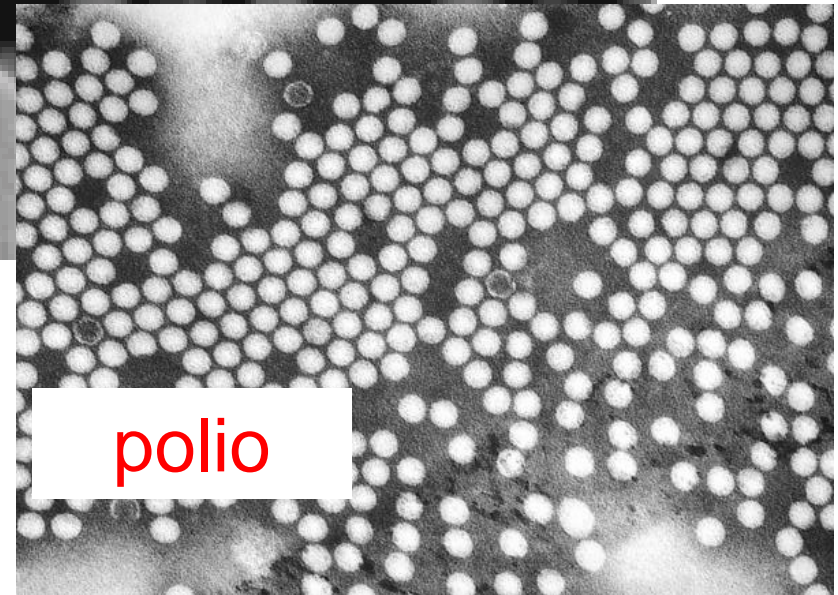
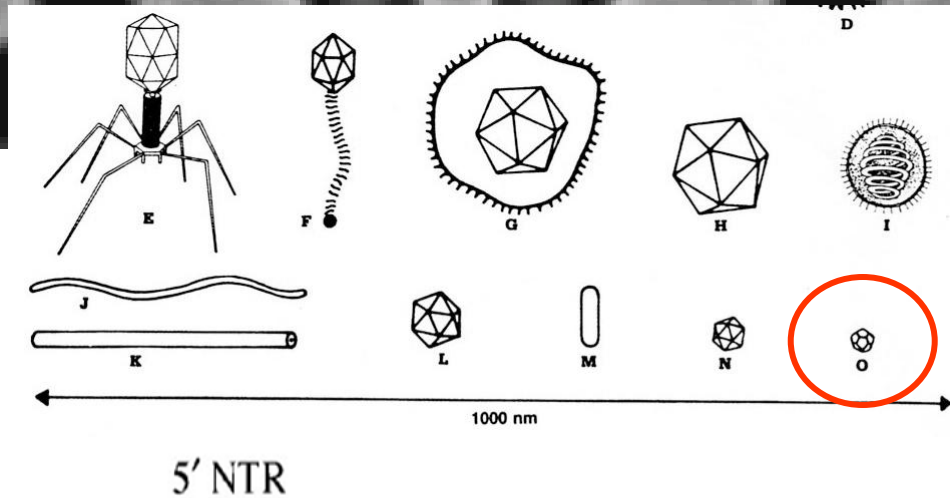


Polio

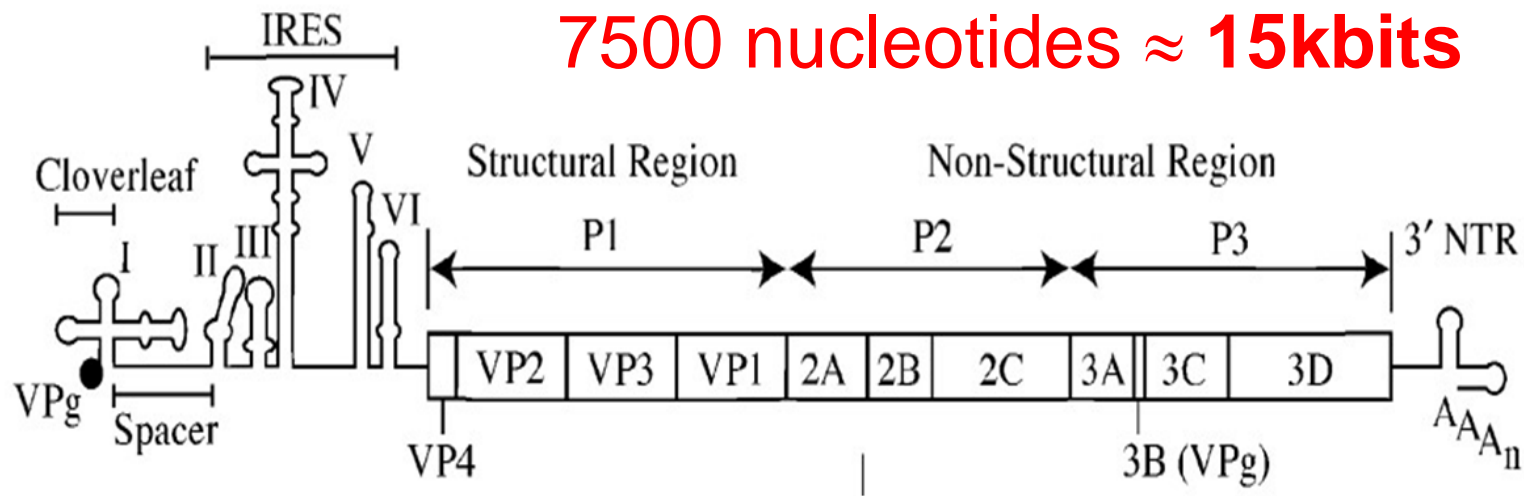
Bacterium (Staphylococcus  
aureus)

**1 bit**

$1\mu\text{m}$



**7500 nucleotides  $\approx$  15kbits**



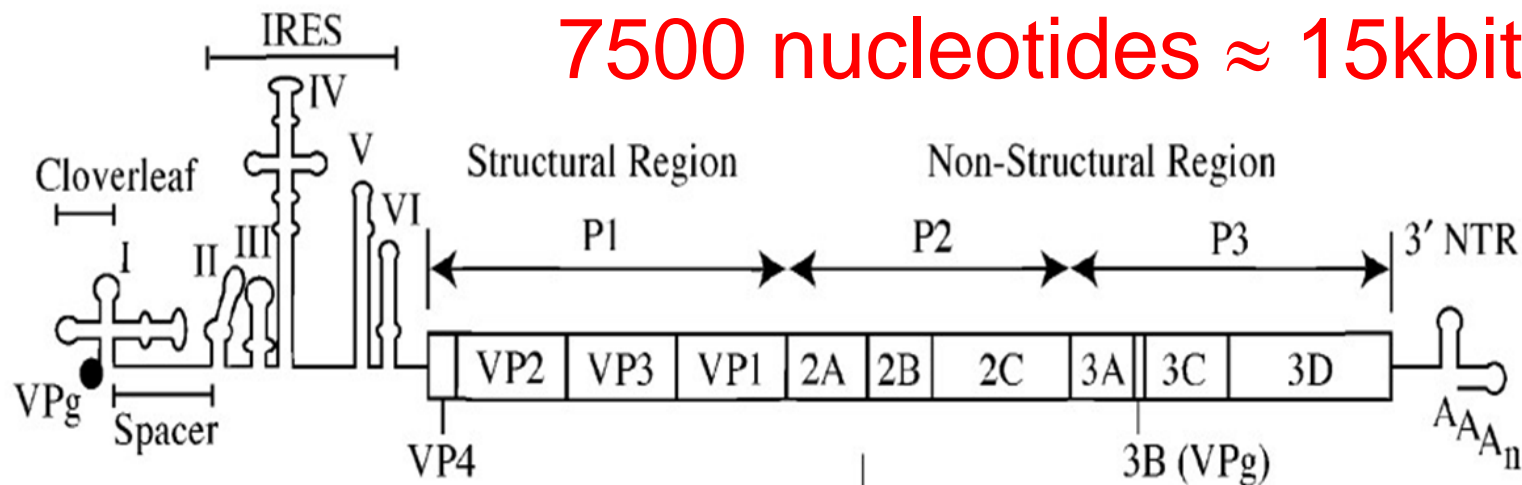
**1 bit fast**

**1  $\mu\text{m}$**

Memory is (almost) free  
Speed is what matters

**polio**

5' NTR



**7500 nucleotides  $\approx$  15kbits slow**



UG biochem, math,  
control theory

# Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,<sup>1\*</sup> Gentian Buzi,<sup>2</sup> John C. Doyle<sup>2</sup>

Both engineering and evolution are constrained by trade-offs between efficiency and robustness, but theory that formalizes this fact is limited. For a simple two-state model of glycolysis, we explicitly derive analytic equations for hard trade-offs between robustness and efficiency with oscillations as an inevitable side effect. The model describes how the trade-offs arise from individual parameters, including the interplay of feedback control with autocatalysis of network products necessary to power and catalyze intermediate reactions. We then use control theory to prove that the essential features of these hard trade-off “laws” are universal and fundamental, in that they depend minimally on the details of this system and generalize to the robust efficiency of any autocatalytic network. The theory also suggests worst-case conditions that are consistent with initial experiments.

un-  
fo-  
w-  
the cell's use of ATP. In glycolysis, two ATP molecules are consumed upstream and four are produced downstream, which normalizes to  $q = 1$  (each  $y$  molecule produces two downstream) with kinetic exponent  $a = 1$ . To highlight essential trade-offs with the simplest possible analysis, we normalize the concentration such that the unperturbed ( $\delta = 0$ ) steady states are  $\bar{y} = 1$  and  $\bar{x} = 1/k$  [the system can have one additional steady state, which is unstable when  $(1, 1/k)$  is stable]. [See the supporting online material (SOM) part I]. The basal rate of the PFK reaction and the consumption rate have been normalized to 1 (the 2 in the numerator and feedback coefficients of the reactions come from these normalizations). Our results hold for more general systems as discussed below and in SOM, but the analysis

Chandra, Buzi, and Doyle

Most important paper so far.



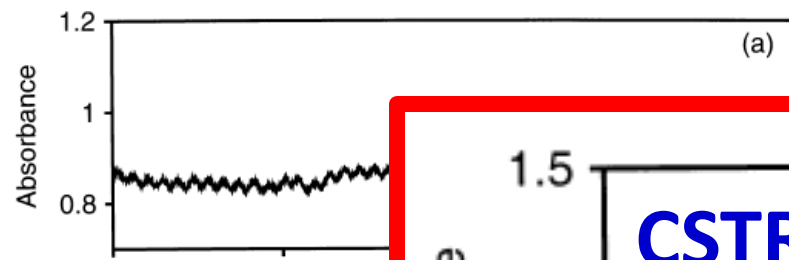
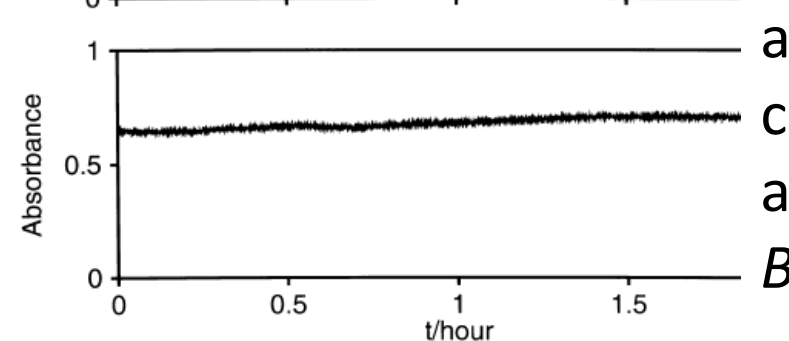
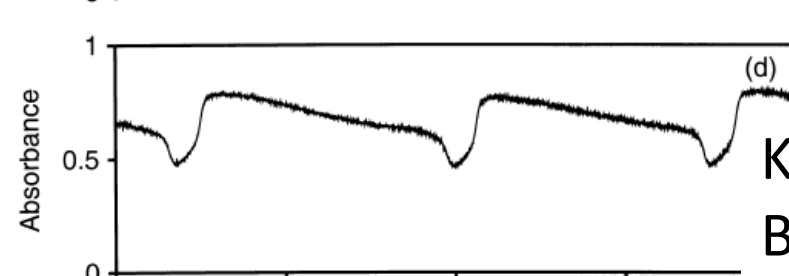
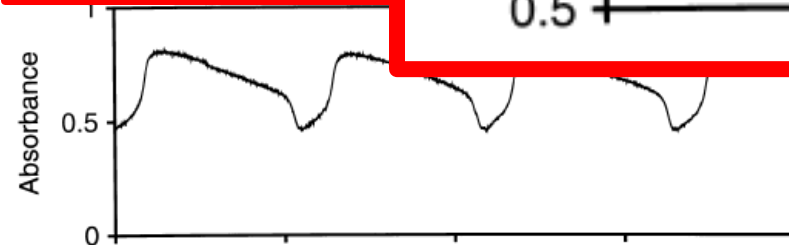
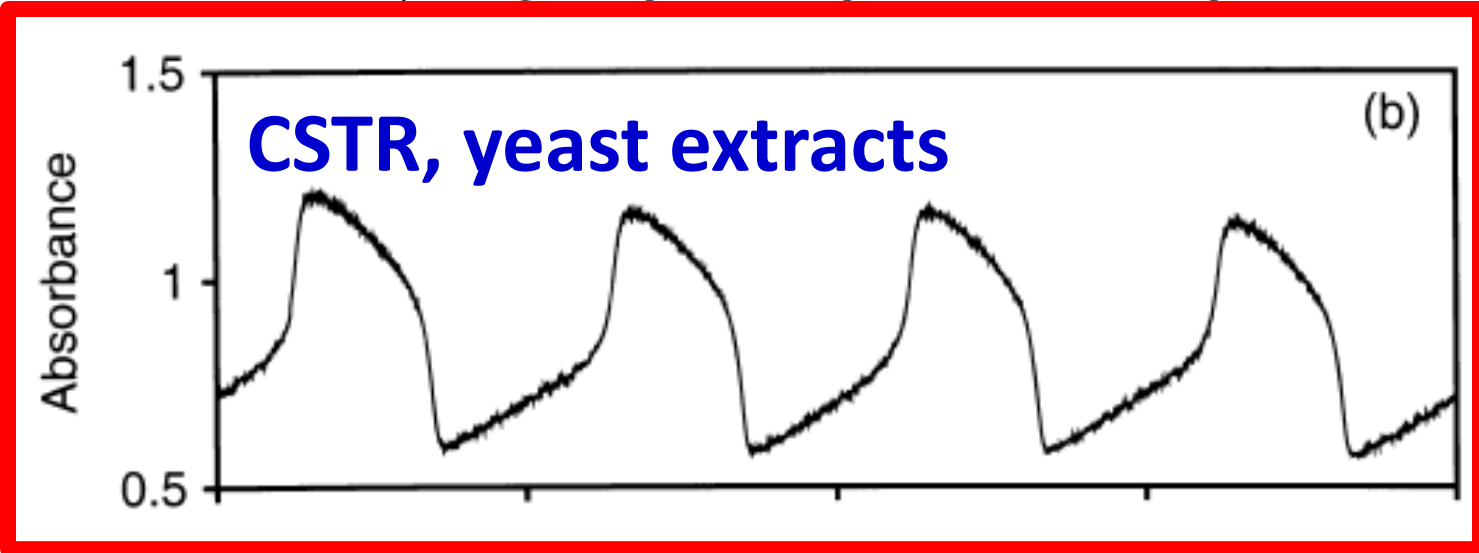
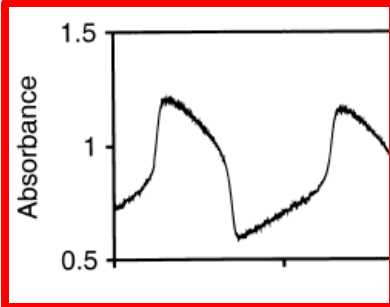


Fig. 2. Dependence of pattern on flow rate. Experimental time

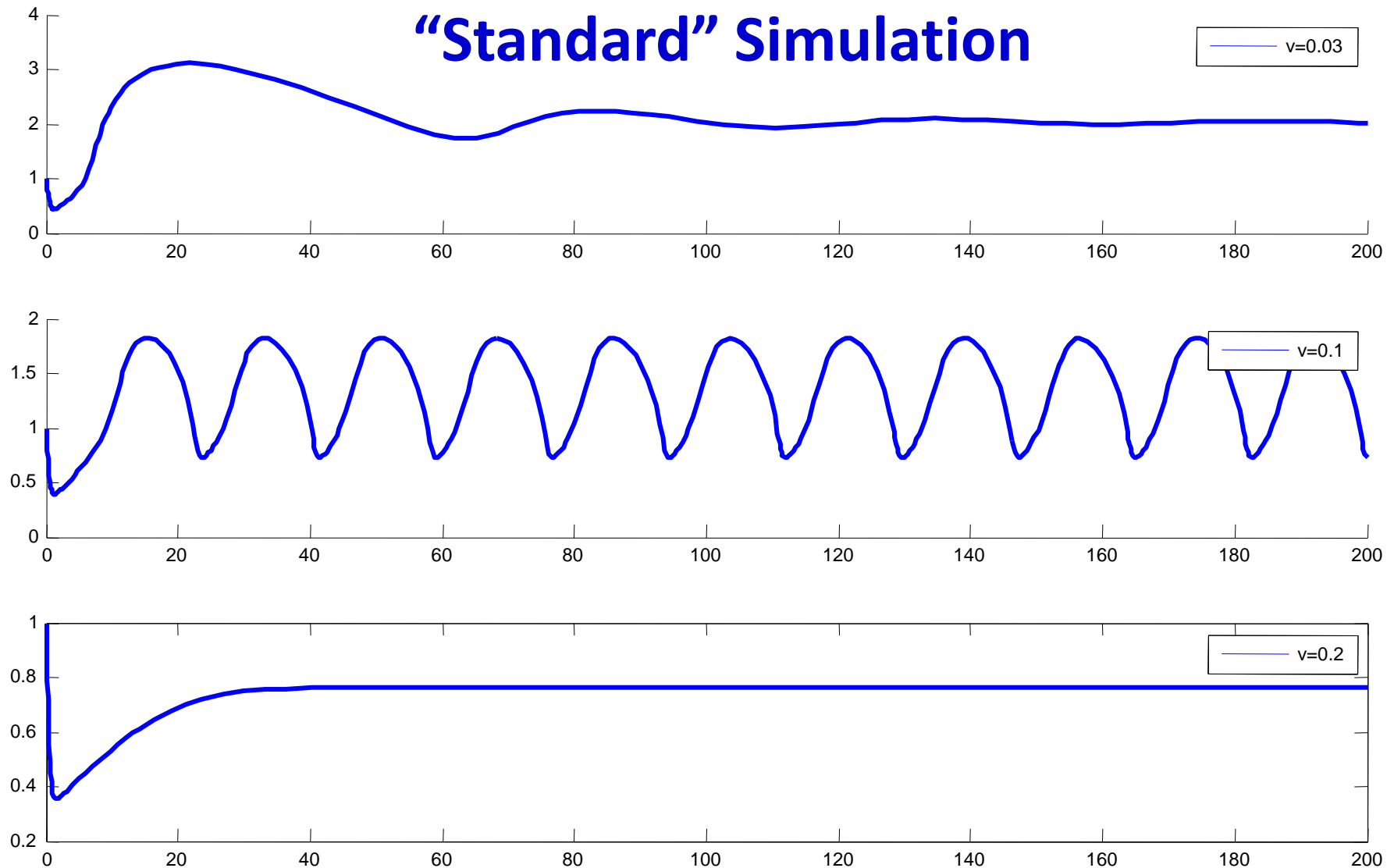


tion becomes longer (b–d), and at the highest flow rate (e), the state is stationary.

Experiments

K Nielsen, PG Sorensen, F Hynne, H-G Busse. **Sustained oscillations in glycolysis:** an experimental and theoretical study of chaotic and complex periodic behavior and of quenching of simple oscillations. *Biophys Chem* 72:49-62 (1998).

# “Standard” Simulation

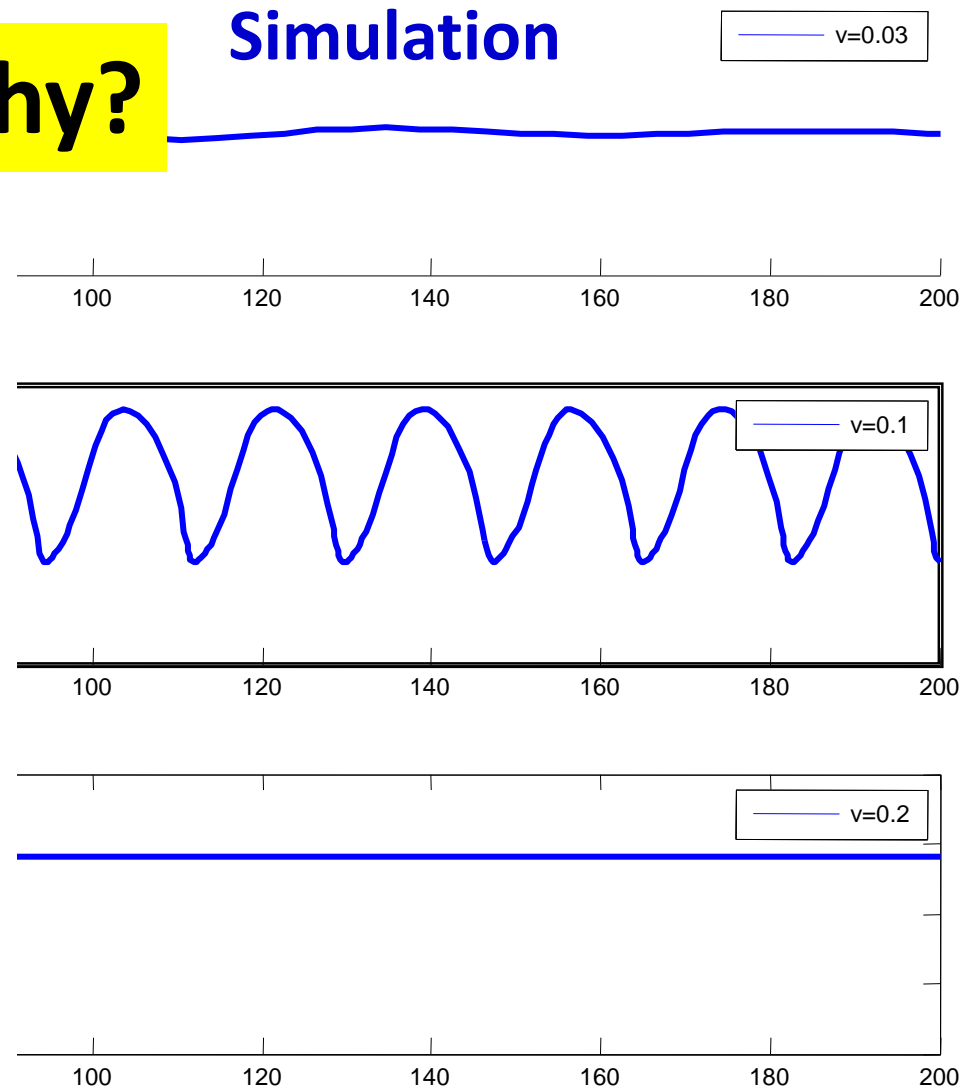
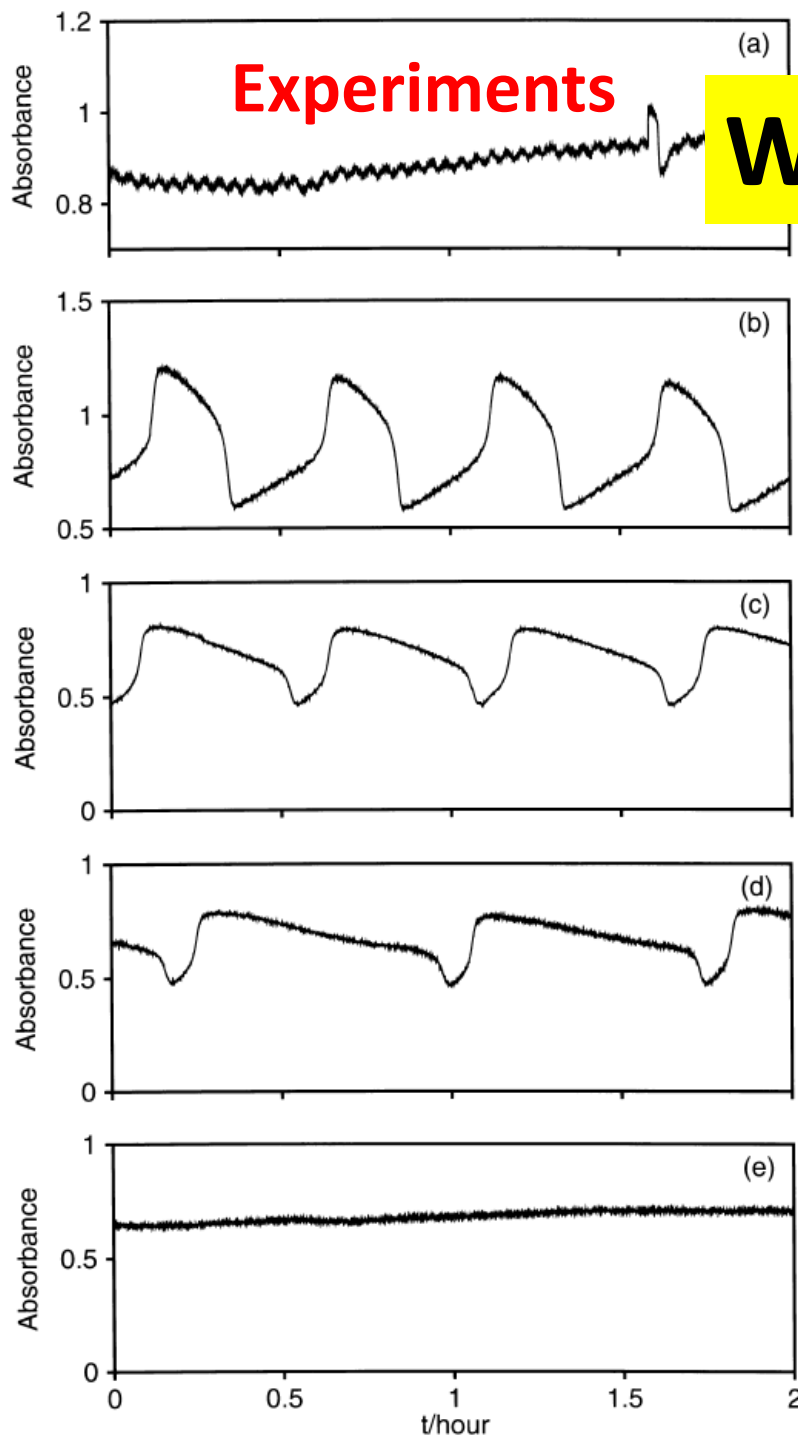


**Figure S4.** Simulation of two state model (S7.1) qualitatively recapitulates experimental observation from CSTR studies [5] and [12]. As the flow of material in/out of the system is increased, the system enters a limit cycle and then stabilizes again. For this simulation, we take  $q=a=Vm=1$ ,  $k=0.2$ ,  $g=1$ ,  $u=0.01$ ,  $h=2.5$ .

Experiments

Why?

Simulation



Model (S7.1) qualitatively recapitulates studies [5] and [12]. As the flow of material in the system enters a limit cycle and then we take  $q=a=Vm=1$ ,  $k=0.2$ ,  $g=1$ ,  $u=0.01$ ,  $h=2.5$ .



# Why?

Levels of explanation:

1. Possible

2. Plausible

3. Actual

Science

4. Mechanistic

5. Necessary

Engineering

Medicine

# Glycolytic “circuit” and oscillations

- Most studied, persistent mystery in cell dynamics
- End of an old story (why oscillations)
  - side effect of hard robustness/efficiency tradeoffs
  - no purpose per se
  - just needed a theorem
- Beginning of a new one
  - robustness/efficiency tradeoffs
  - complexity and architecture
  - need more theorems and applications



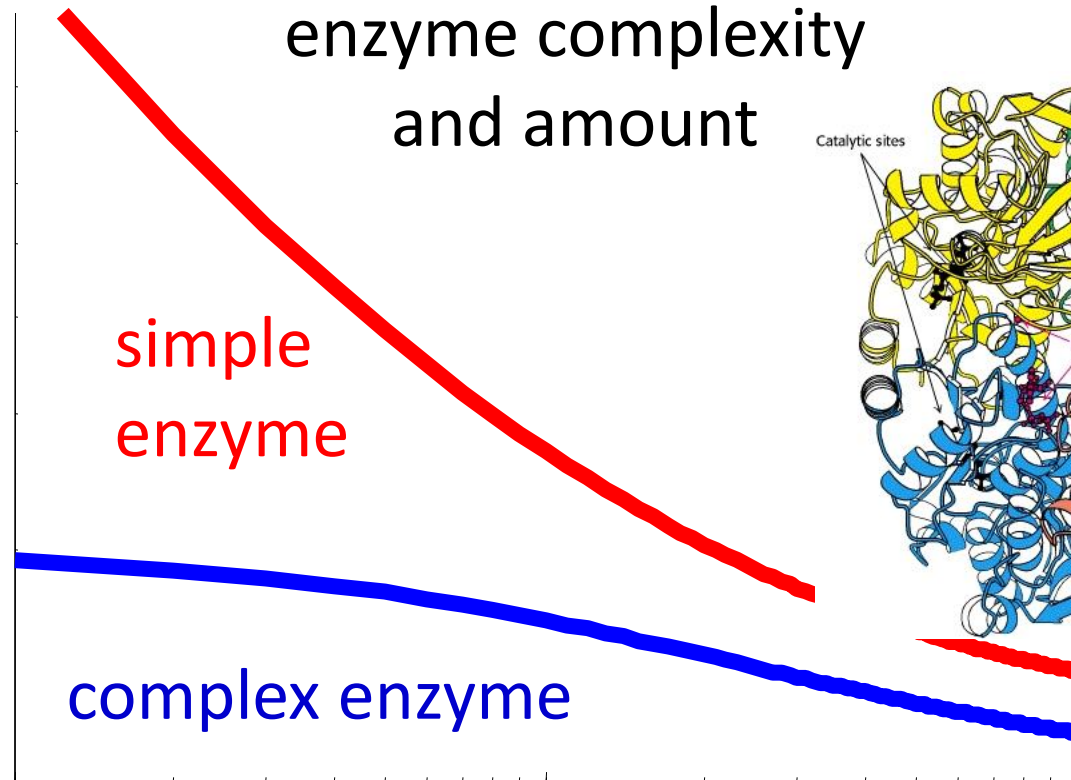
**Theorem!**

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right|$$

$z$  and  $p$  functions of  
enzyme complexity  
and amount

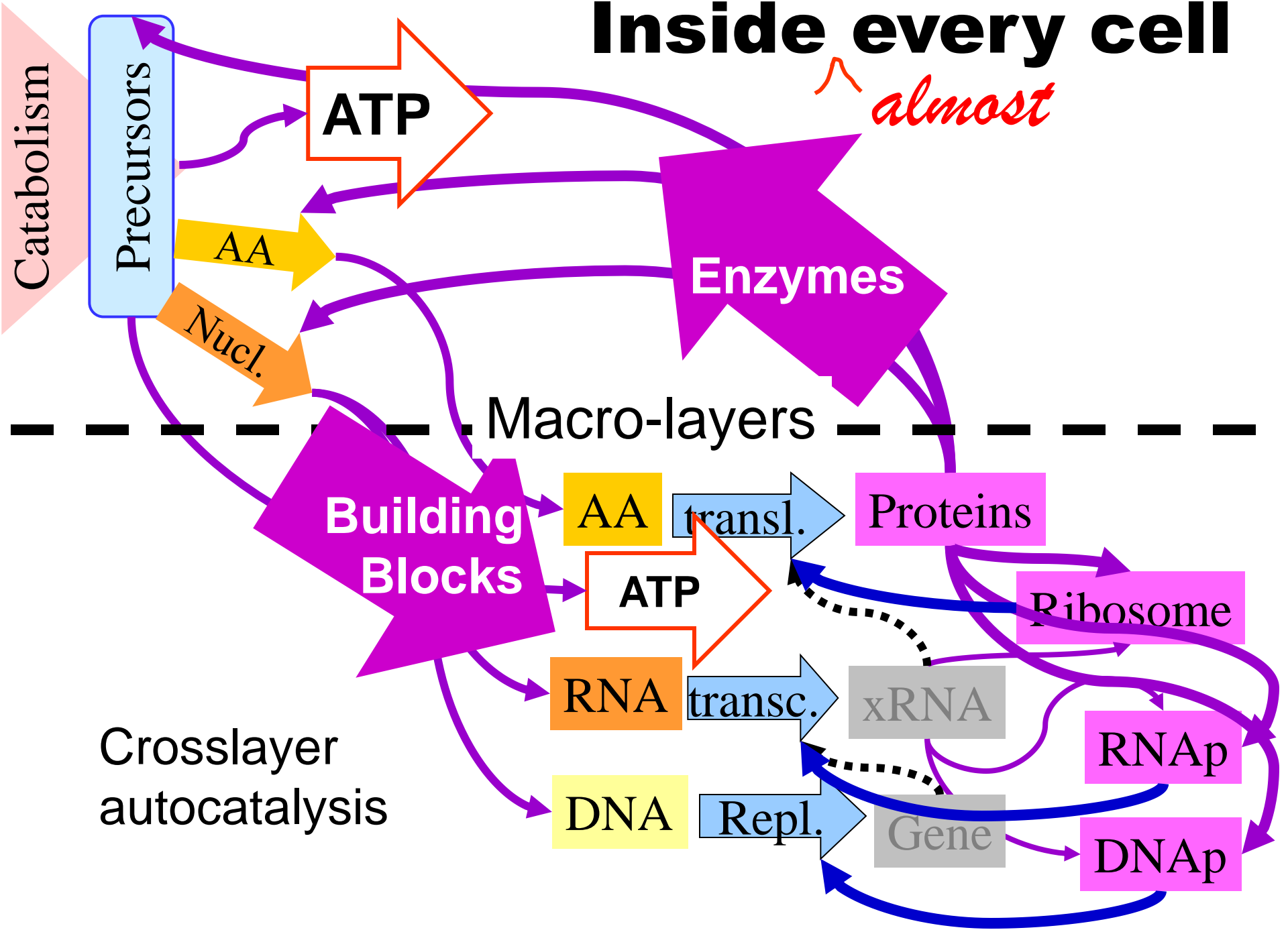
Fragility

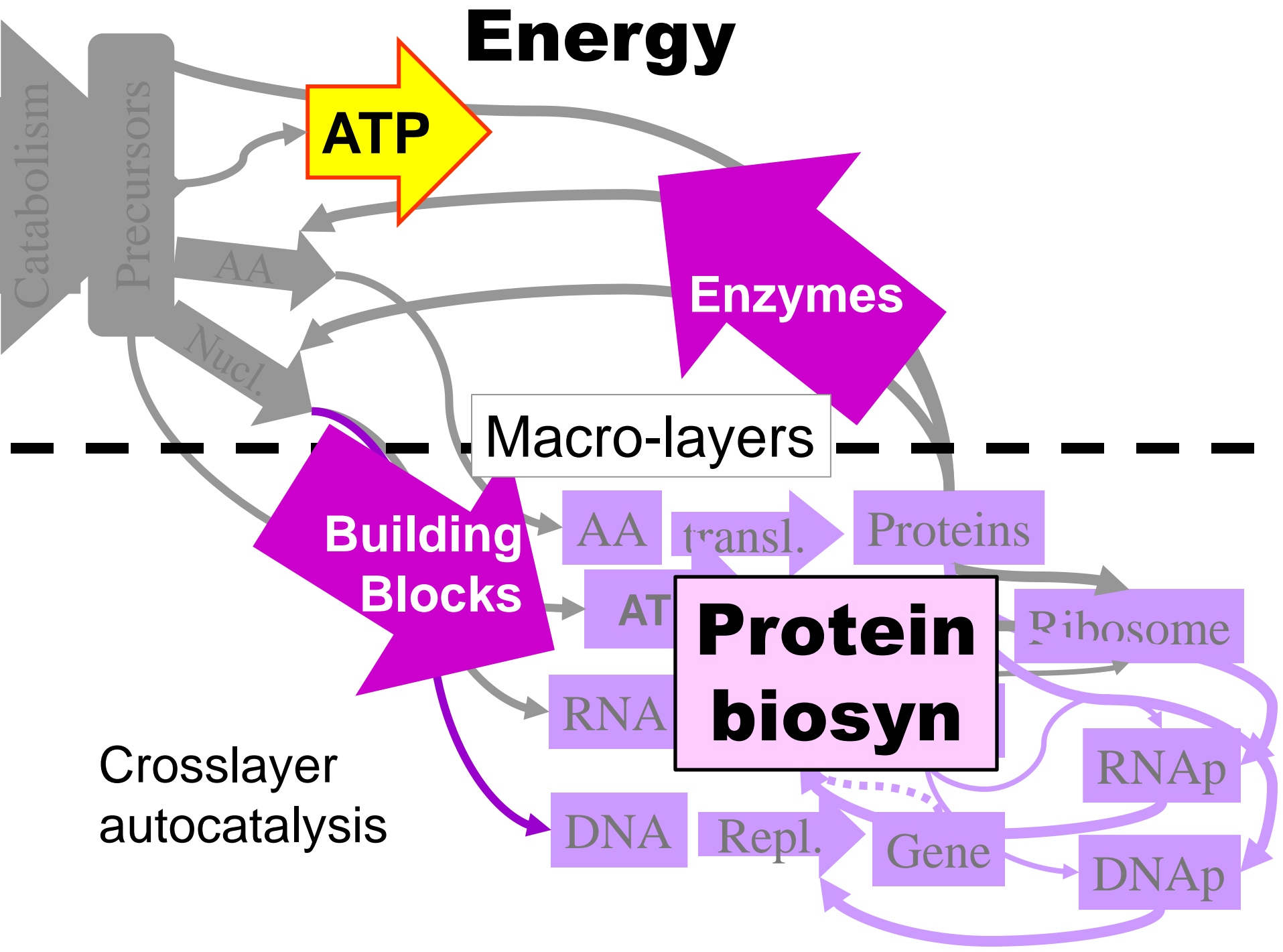
$$\ln \left| \frac{z + p}{z - p} \right|$$

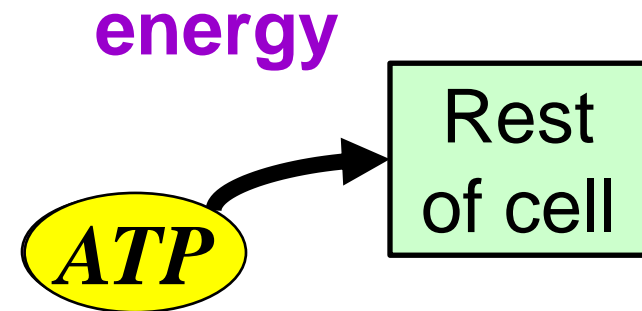
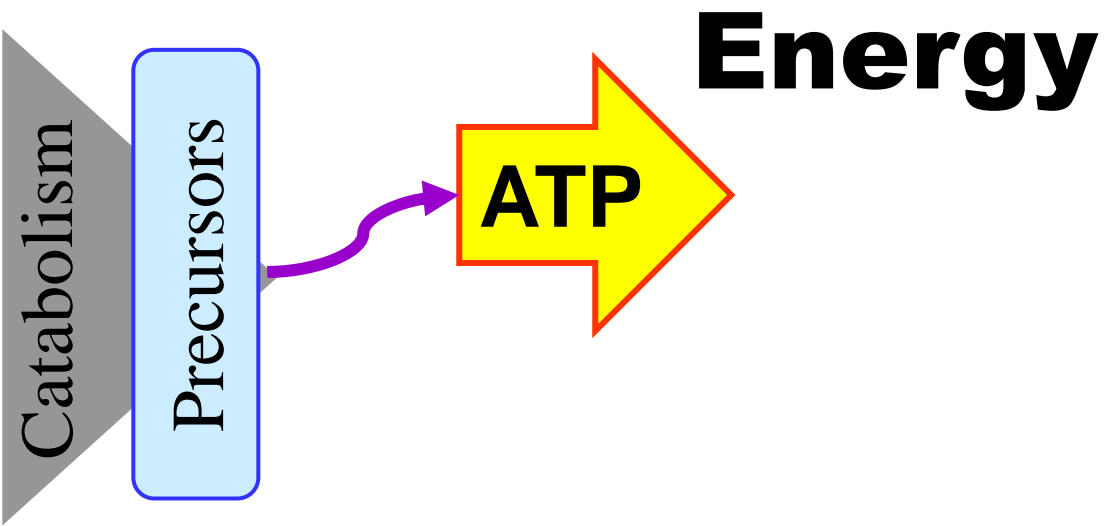


Enzyme amount

# Inside every cell

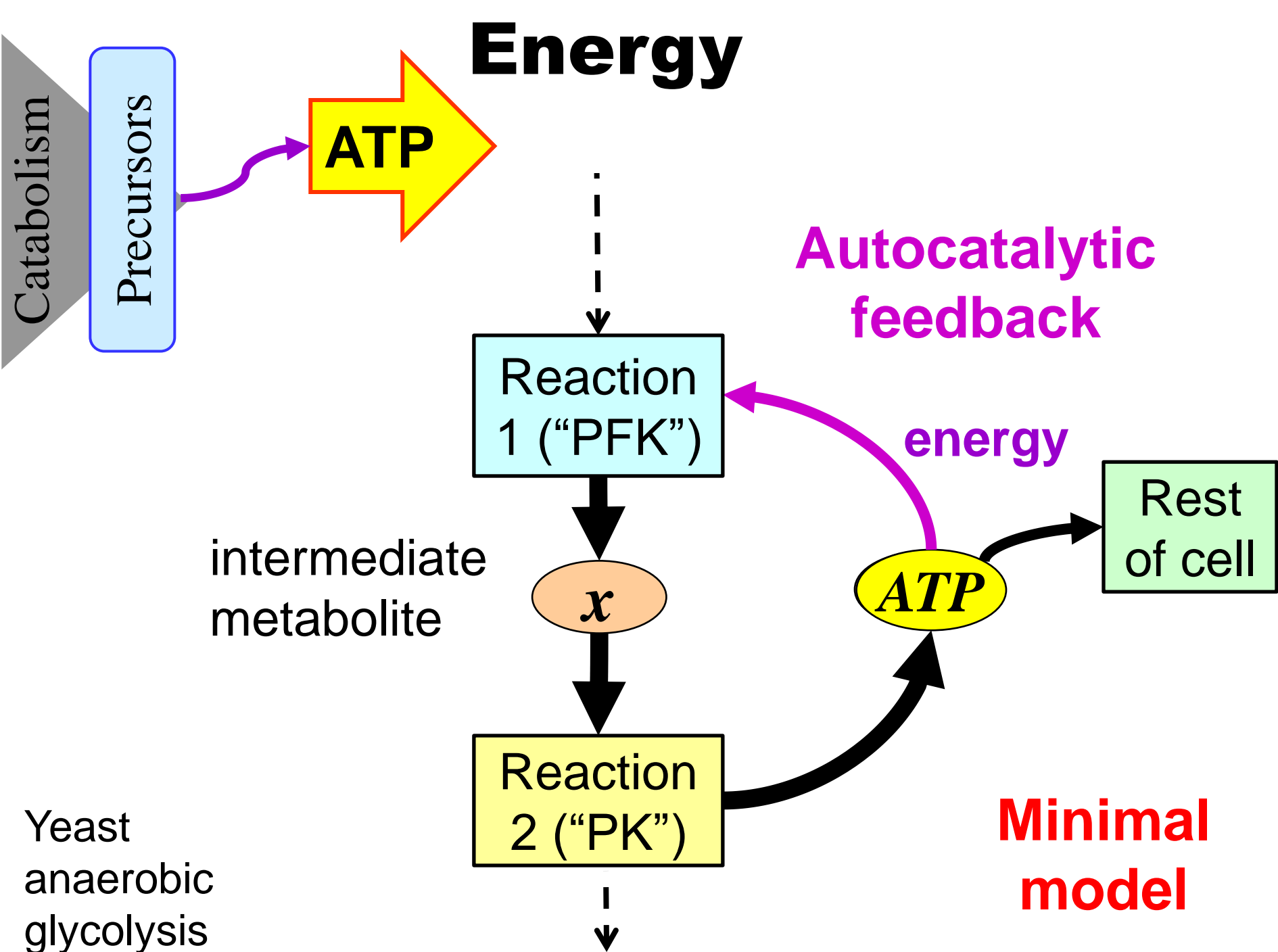




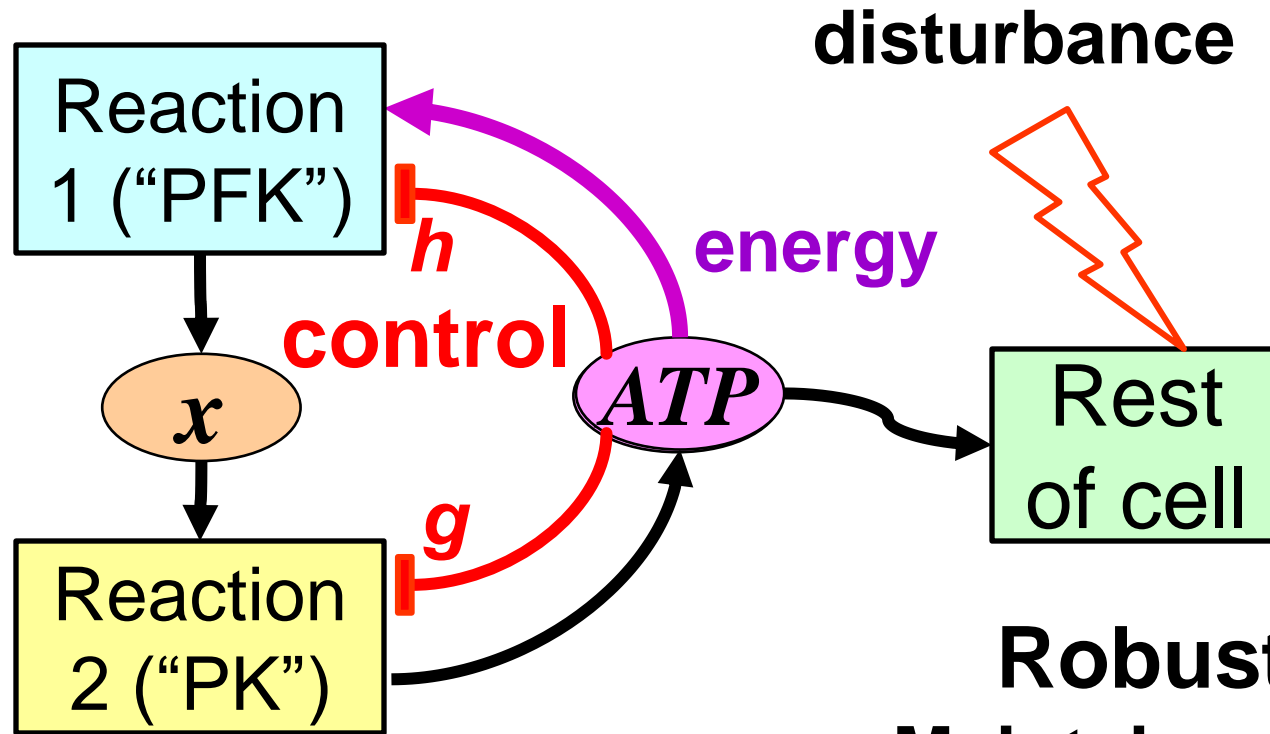


Yeast  
anaerobic  
glycolysis

**Minimal  
model**



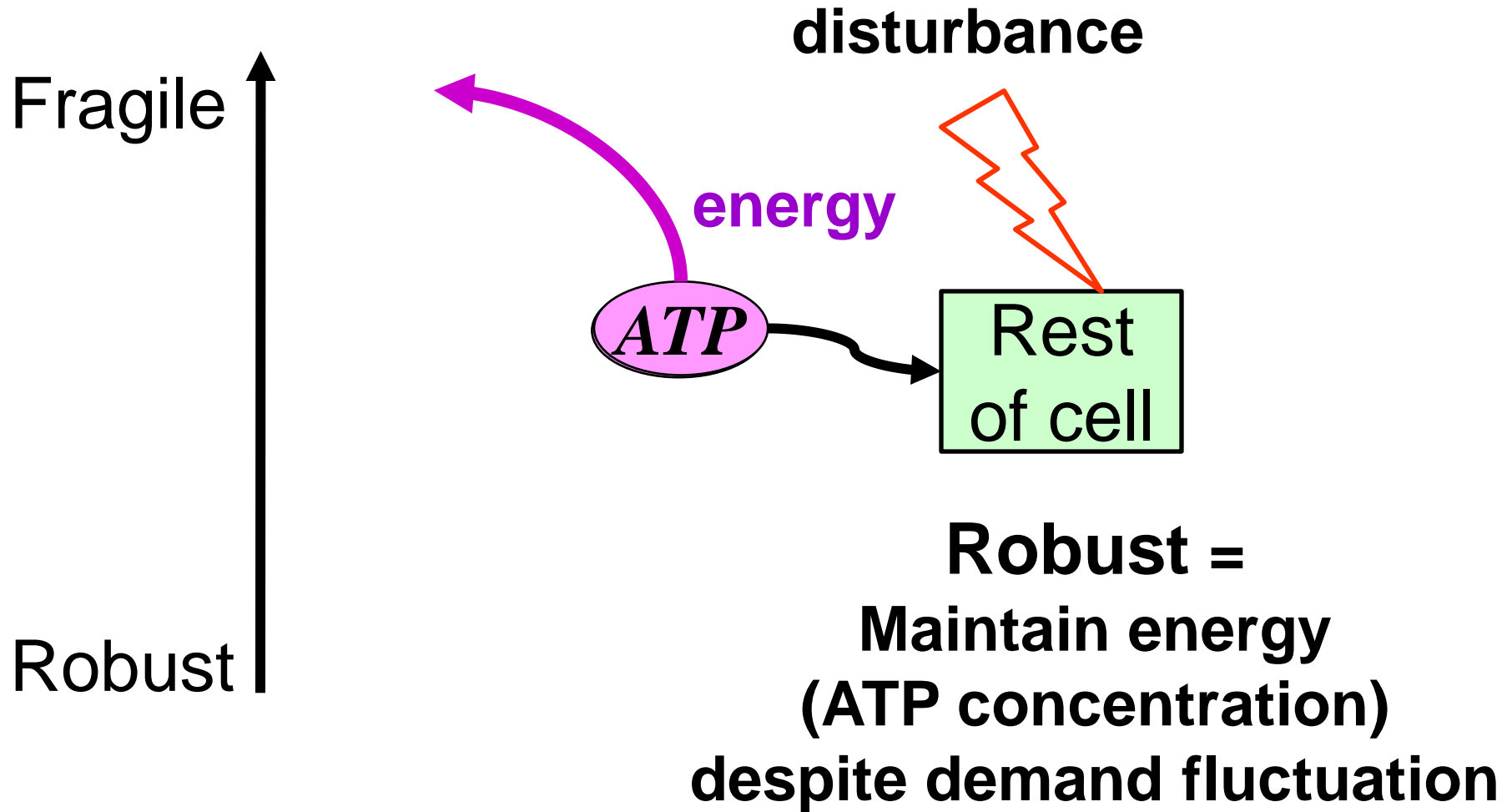
## control feedback



**Robust =**  
**Maintain energy**  
**(ATP concentration)**  
**despite demand fluctuation**

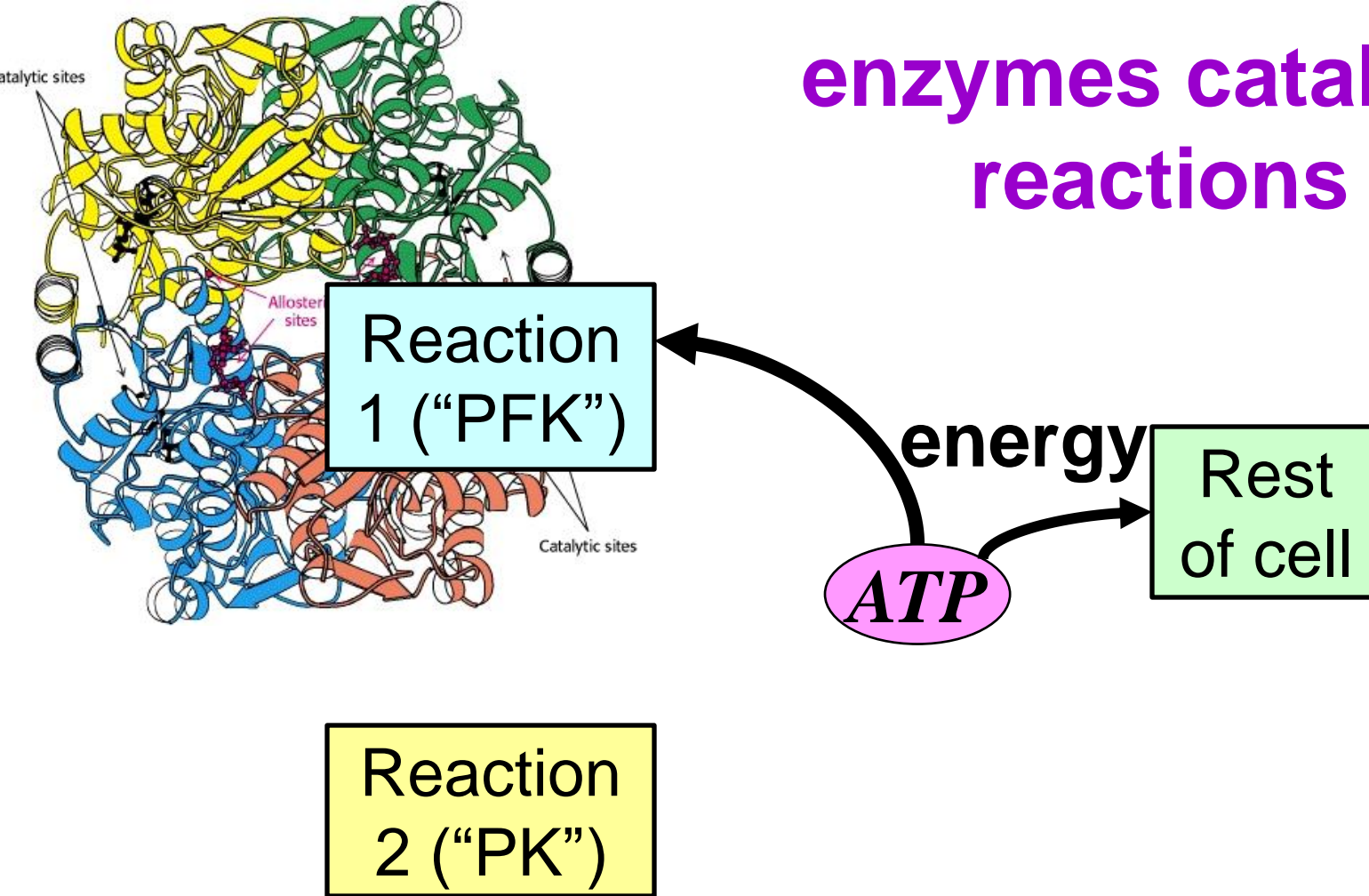
Tight control creates “weak linkage”  
between power supply and demand



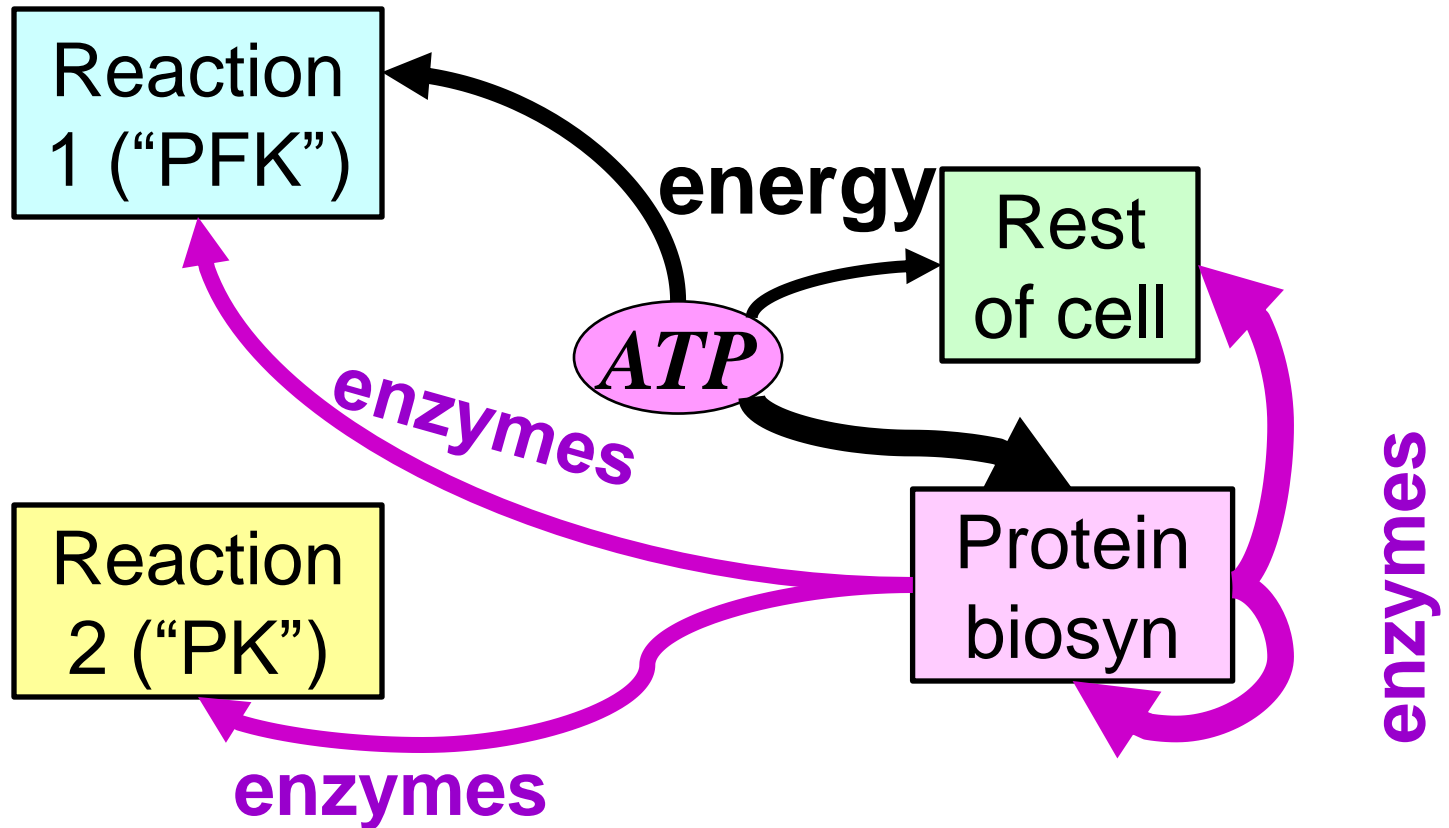


Tight control creates “weak linkage”  
between power supply and demand

# enzymes catalyze reactions

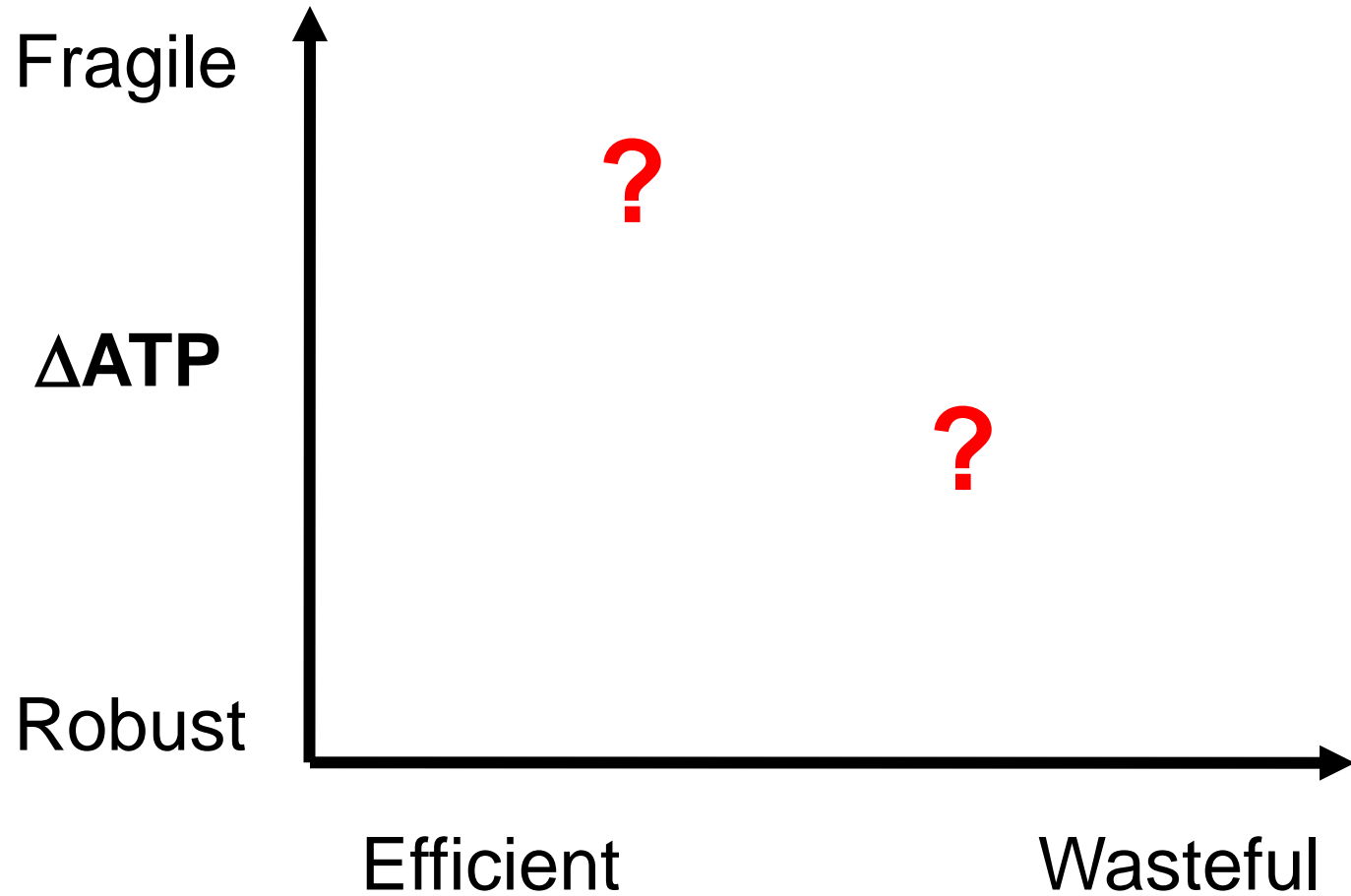


# enzymes catalyze reactions



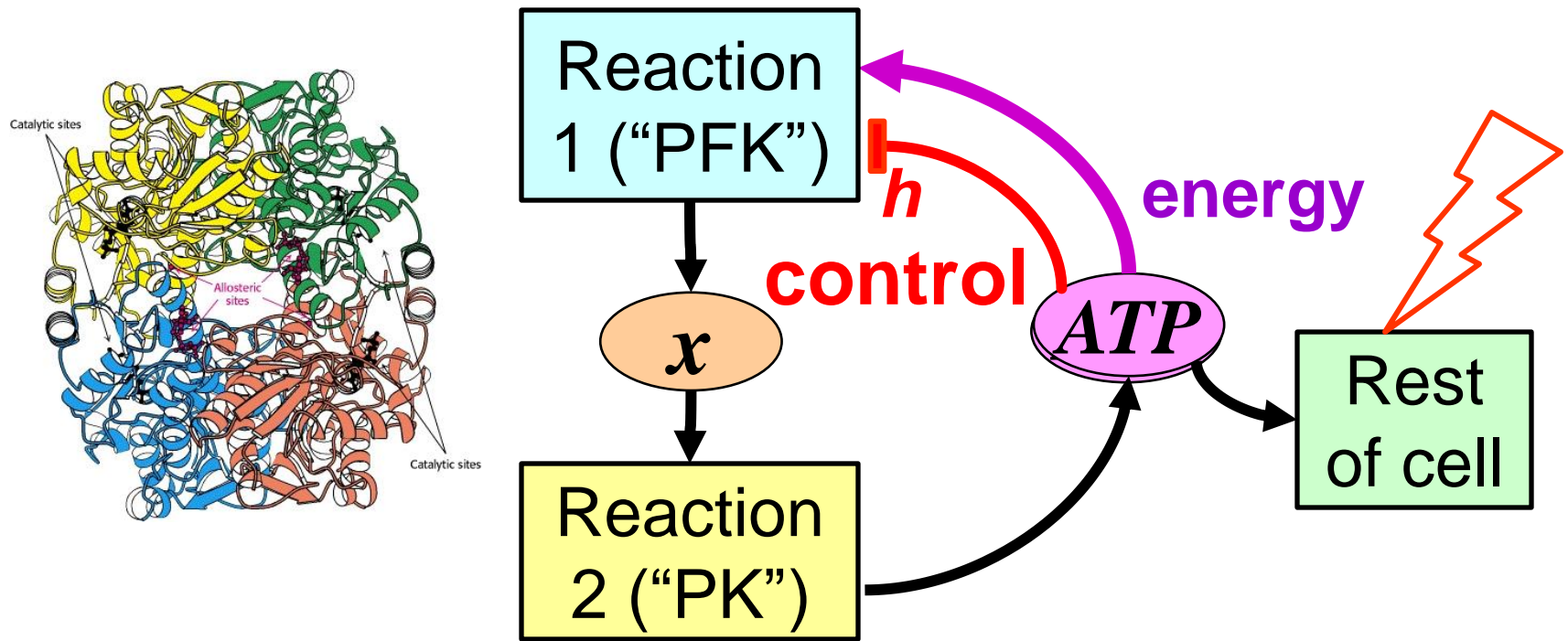
**Efficient =**  
**low metabolic overhead**  
**≈ low enzyme amount**

**Robust =  
Maintain  
ATP**



$\Delta$ ATP

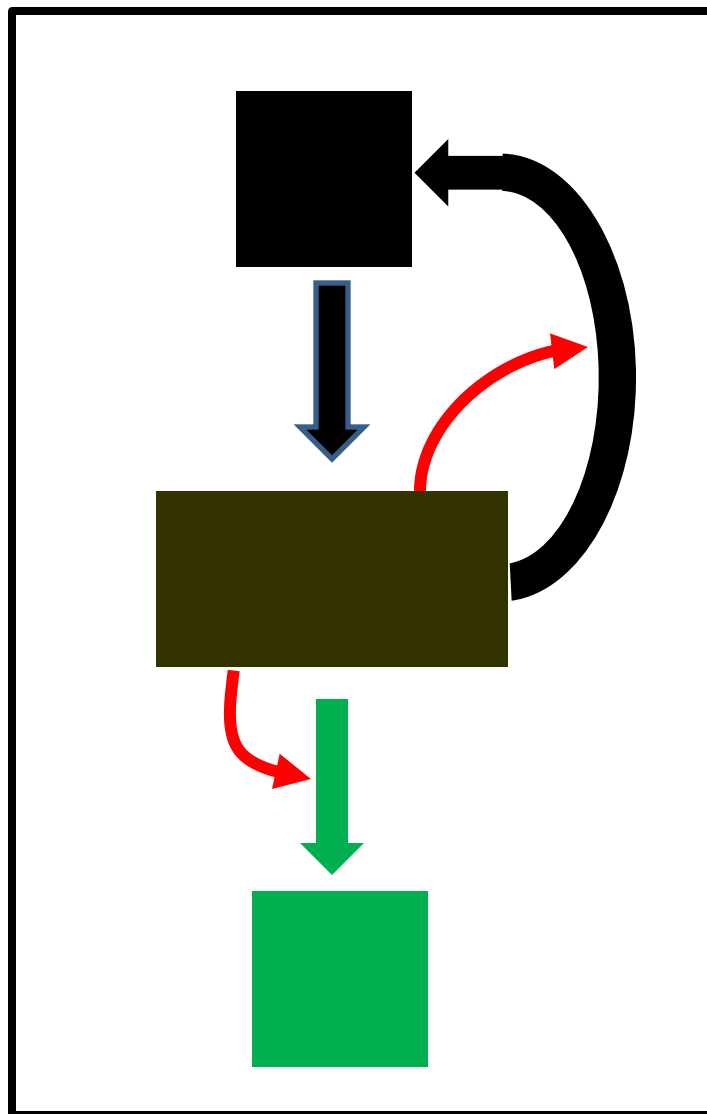
**Efficient =  
low enzyme amount**



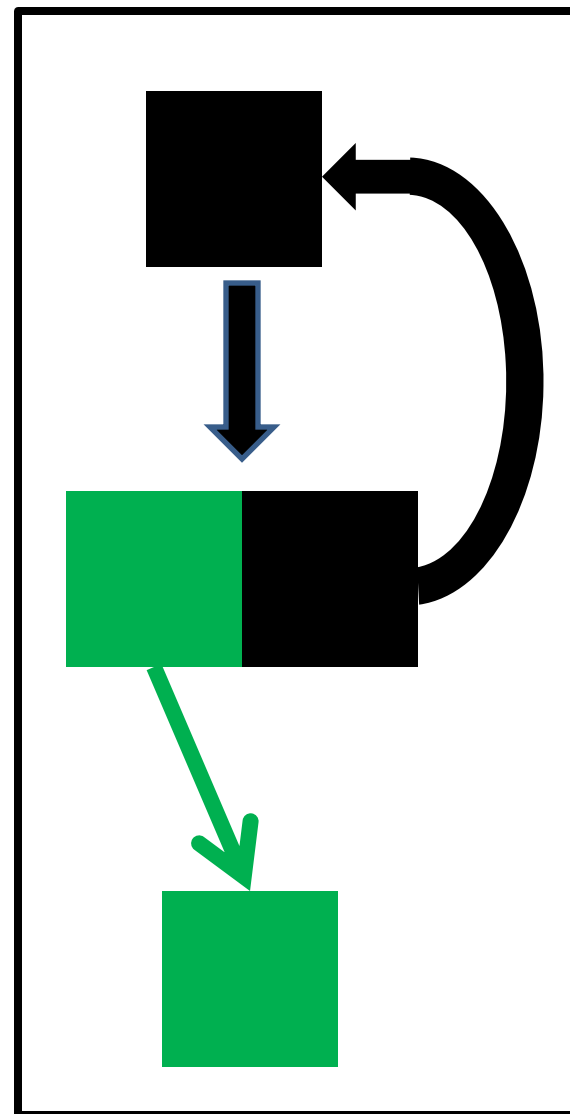
**Standard story:**  
**Autocatalytic** plus **control** feedback  
*necessary and sufficient*  
for oscillations

Proof: Dynamical systems model,  
simulation, bifurcation analysis

## Control feedback



## Autocatalytic feedback

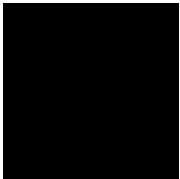


Year

1

2

Seed



Harvest



Product

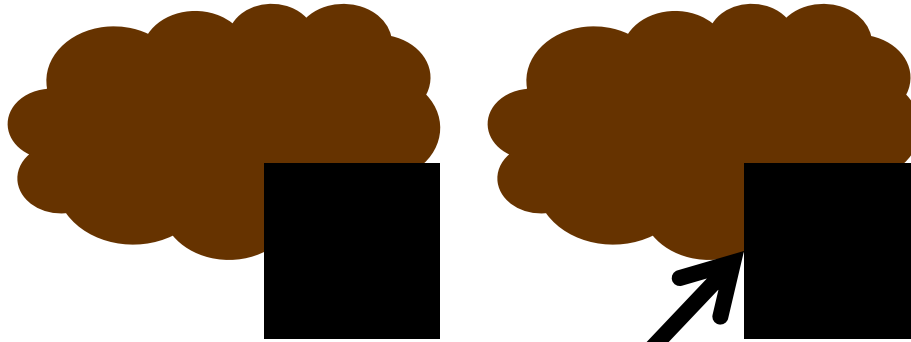


Year

1

2

Seed



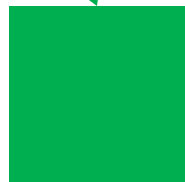
**There may be  
other resources  
needed that  
aren't recycled**

**which we'll  
ignore for now**

Harvest



Product

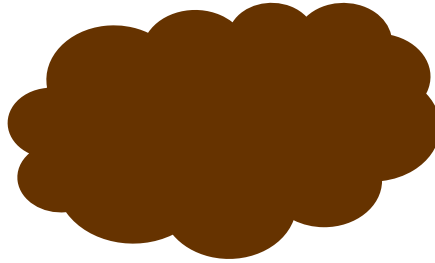
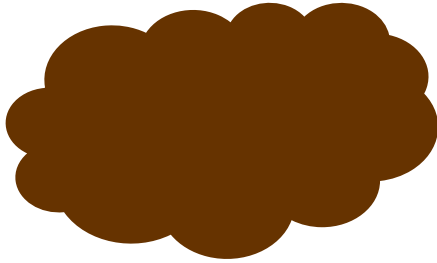




Year

1

2



Harvest



Product



**Some processes  
don't require  
autocatalysis**

Year

1

2

Seed



Harvest



Product



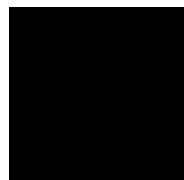
Year

1

2

3

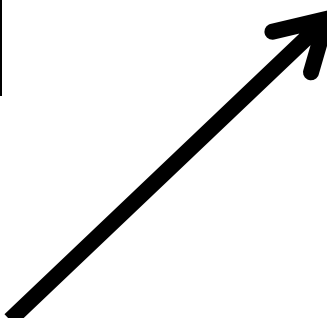
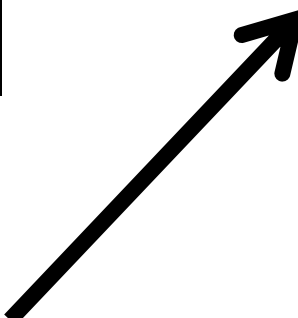
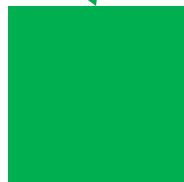
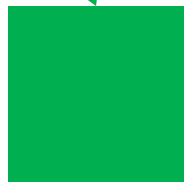
Seed



Harvest



Product



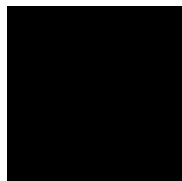
Year

1

2

**Autocatalytic  
feedback**

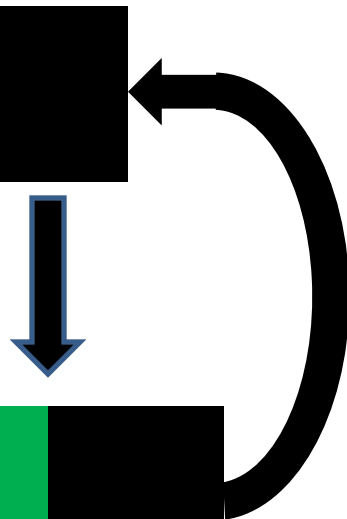
Seed



Harvest



Product



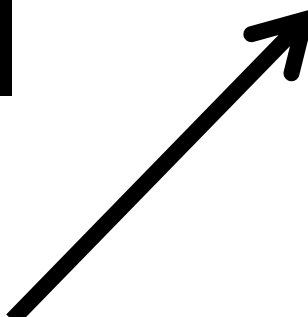
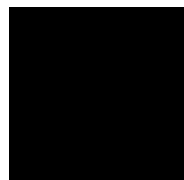
Year

1

2

3

Seed



?

Harvest



Bad harvest?



Product

?

# Maintain product?

Year

1

2

3

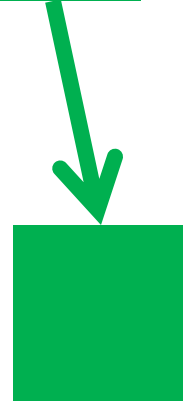
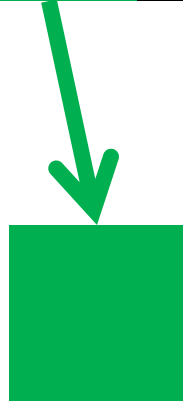
Seed



Harvest



Product

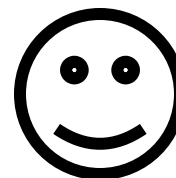
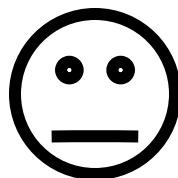
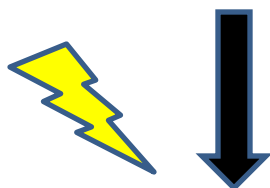


Year

1

2

Harvest



**Without  
autocatalysis**

Product

# Cut back product

Year

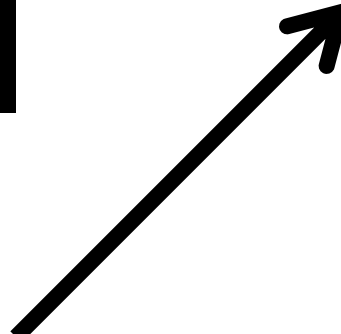
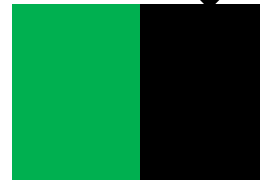
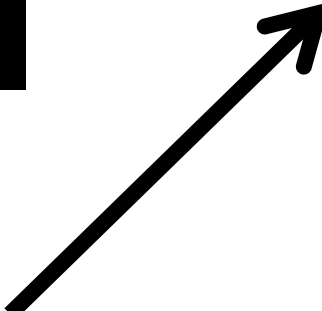
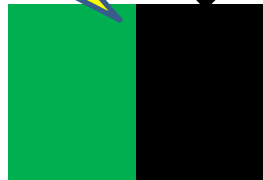
1

2

Seed



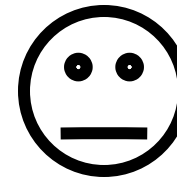
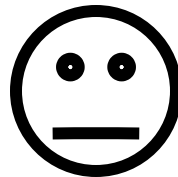
Harvest



...

**Better, but...**

Product





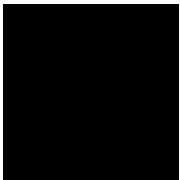
Cut back product more

Year

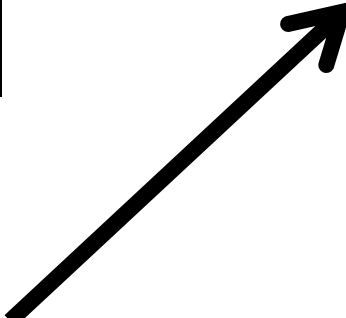
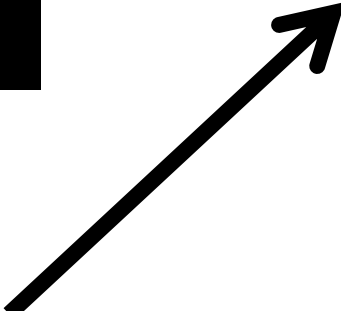
1

2

Seed



Harvest



...

Product



# Over-react and oscillate

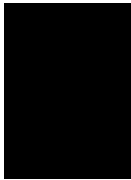
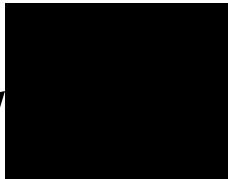
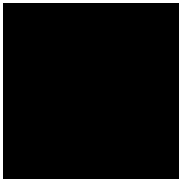
Year

1

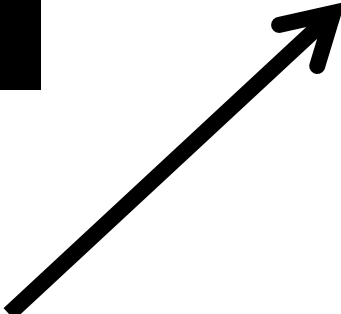
2

3

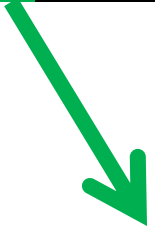
Seed



Harvest



Product



Year

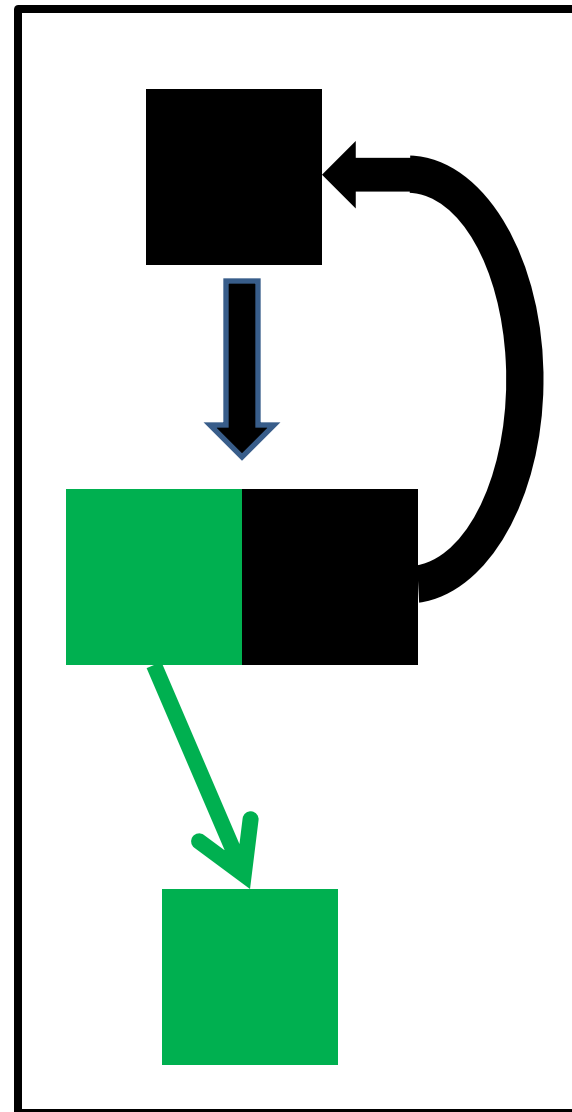
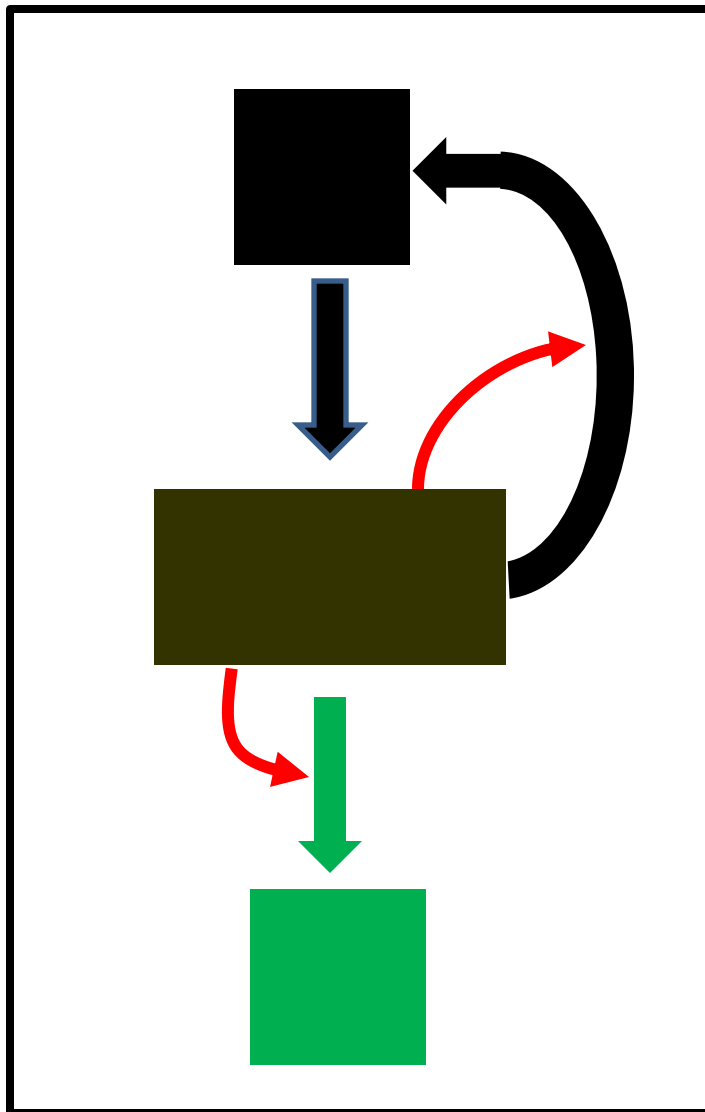
## Control feedback

## Autocatalytic feedback

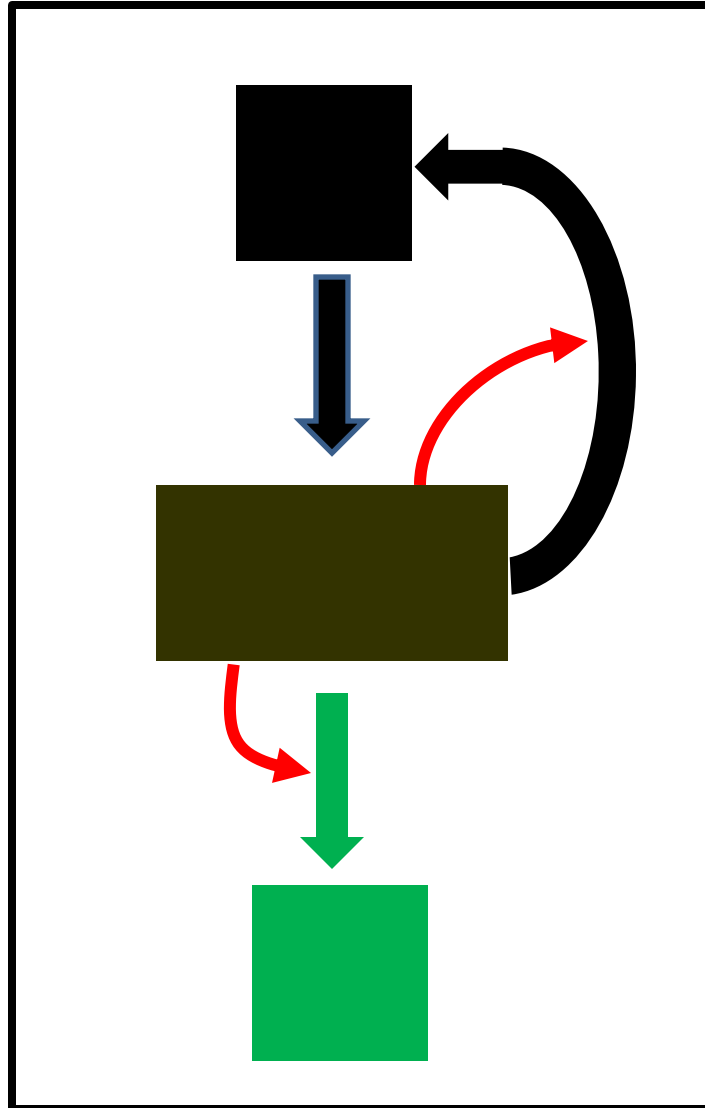
Seed

Harvest

Product

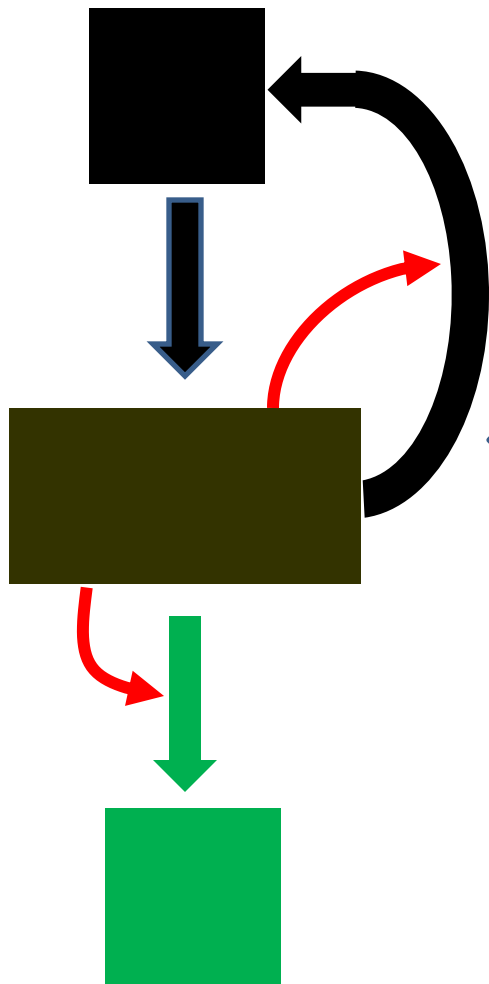


**Control  
feedback**

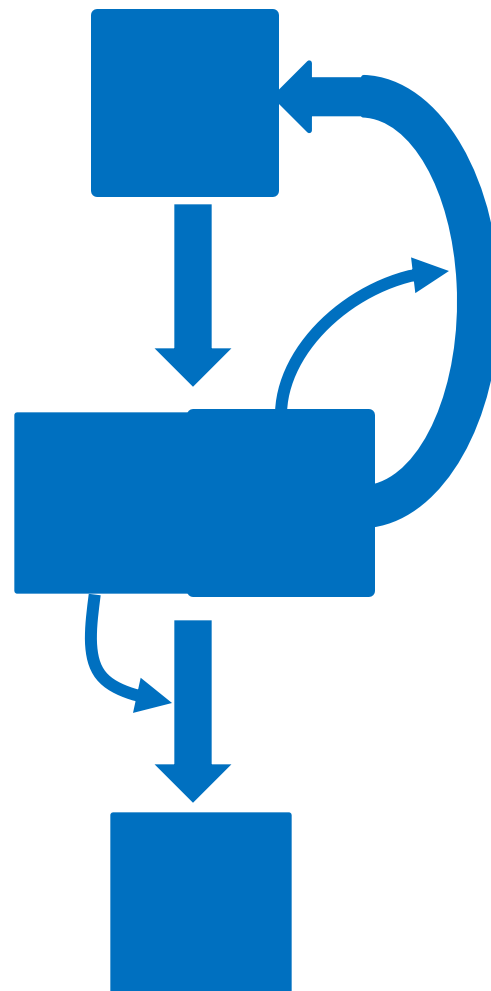


**Autocatalytic  
feedback  
makes  
control  
harder**

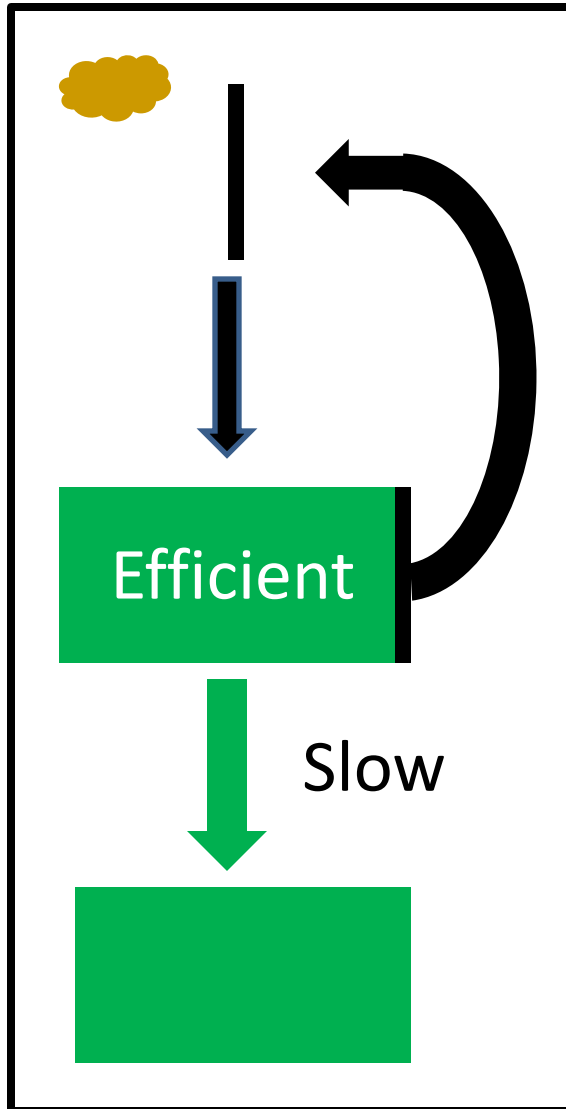
## Production



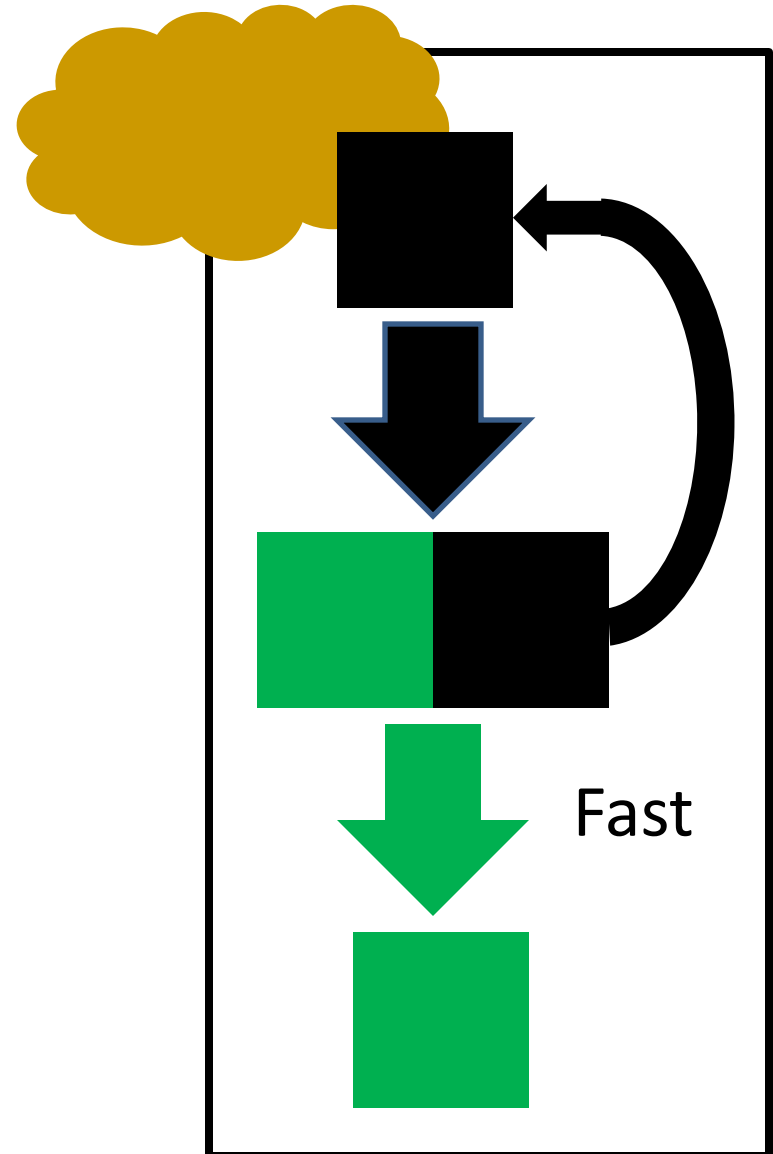
## Finance



## With oxygen

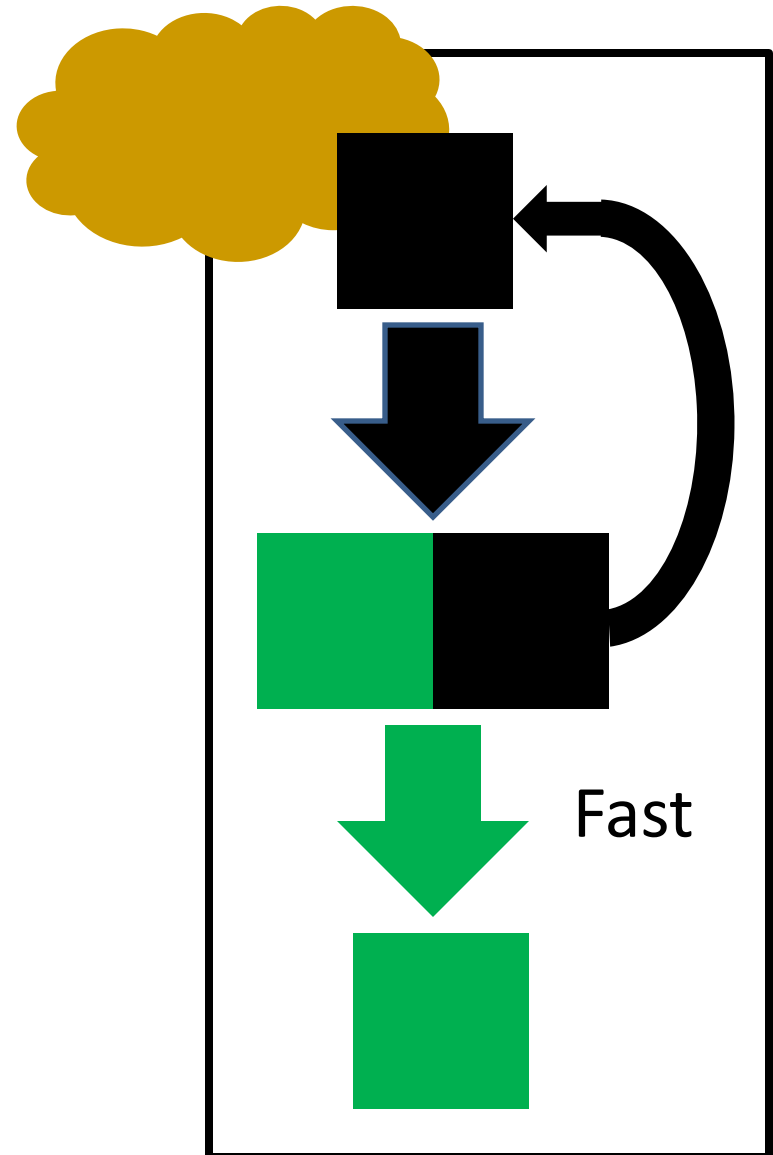


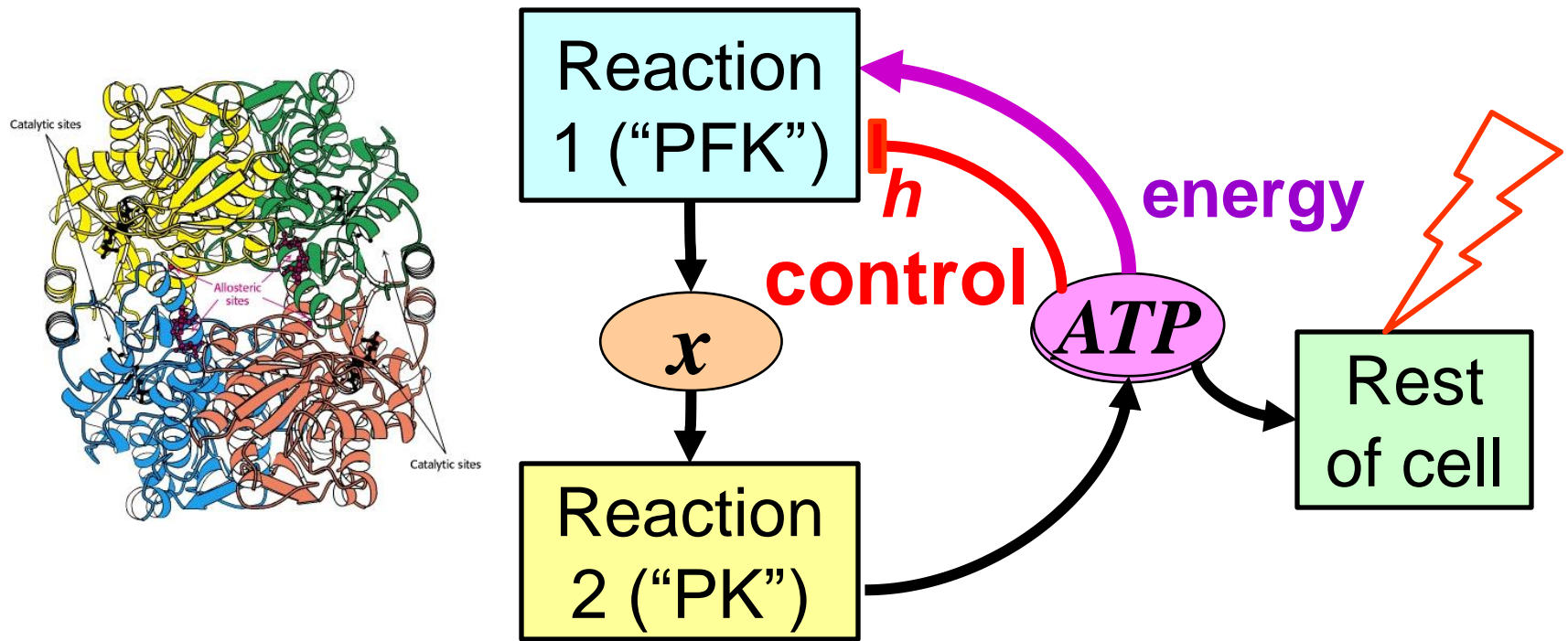
## Without oxygen



**Without  
oxygen**

This is why we focus on  
anaerobic glycolysis, to  
maximize the  
autocatalytic feedback.





**Standard story:**  
**Autocatalytic** plus **control** feedback  
*necessary and sufficient*  
for oscillations

Proof: Dynamical systems model,  
simulation, bifurcation analysis



**Theorem!**

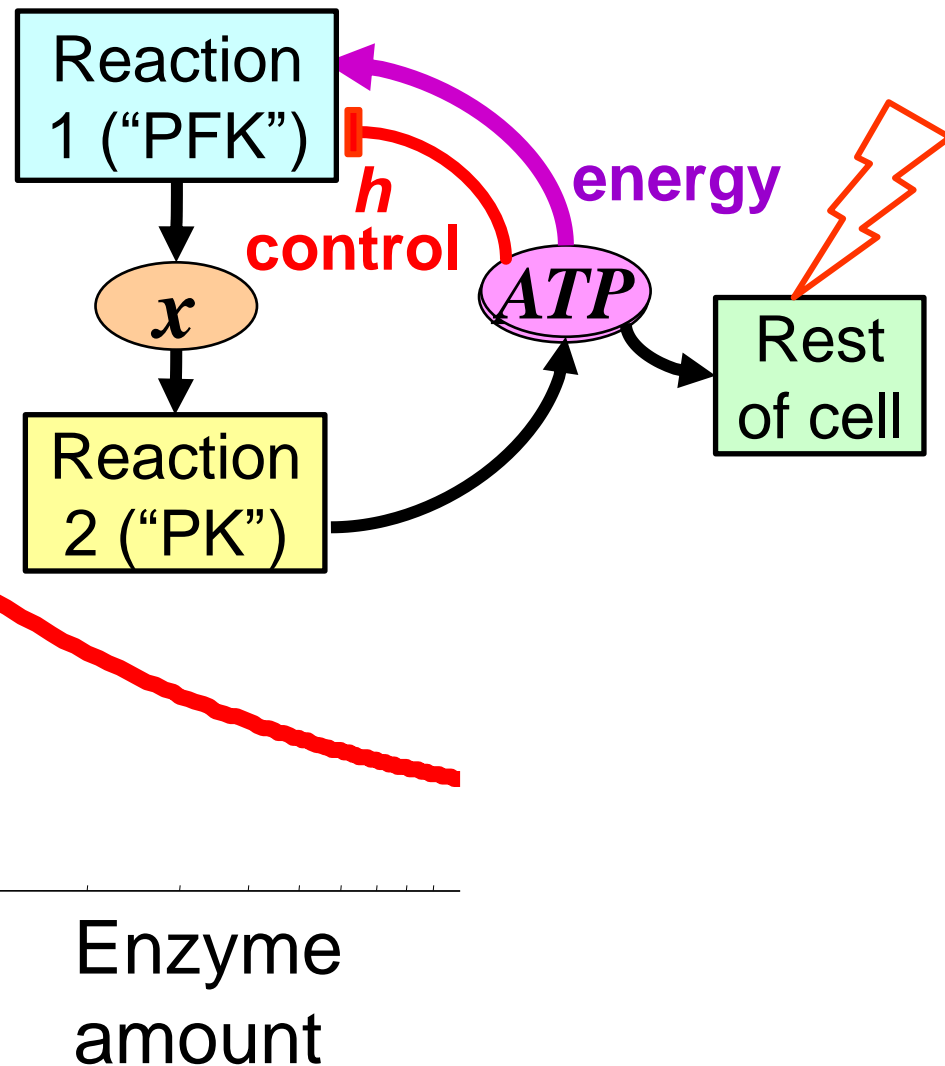
**DS  $\rightarrow$  CDS**

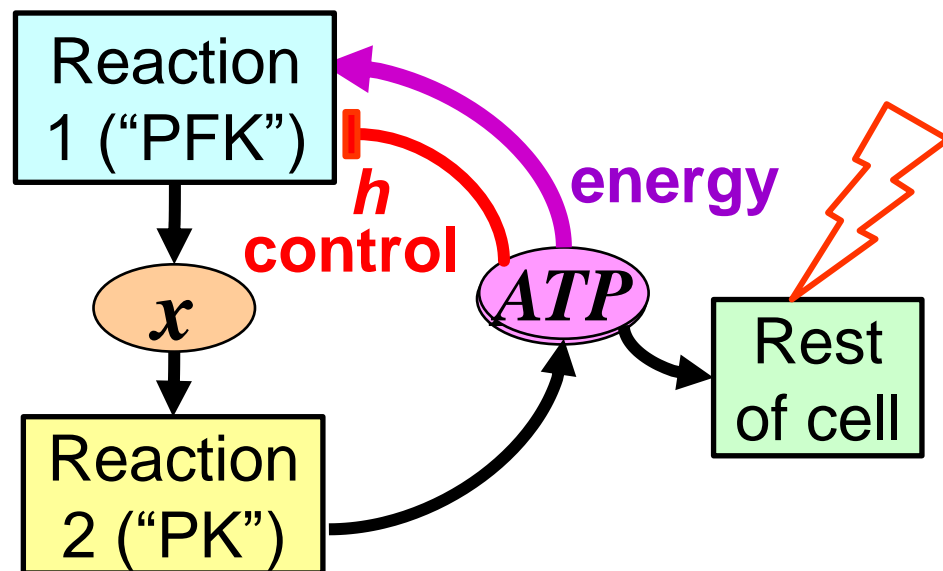
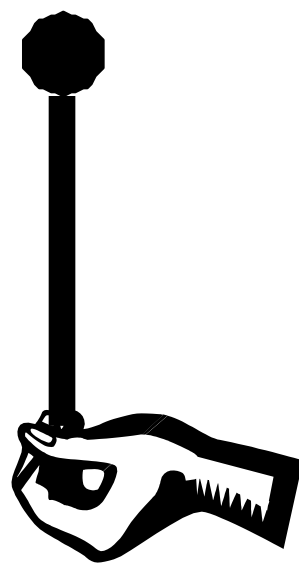
$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$

Fragility

$$\ln \left| \frac{z+p}{z-p} \right|$$

**New story:  
Tradeoffs**





Fragile

$$\ln \left| \frac{z+p}{z-p} \right|$$

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega$$

$$\geq \ln \left| \frac{z+p}{z-p} \right|$$

**New story:  
Tradeoffs =  
"Universal laws"**

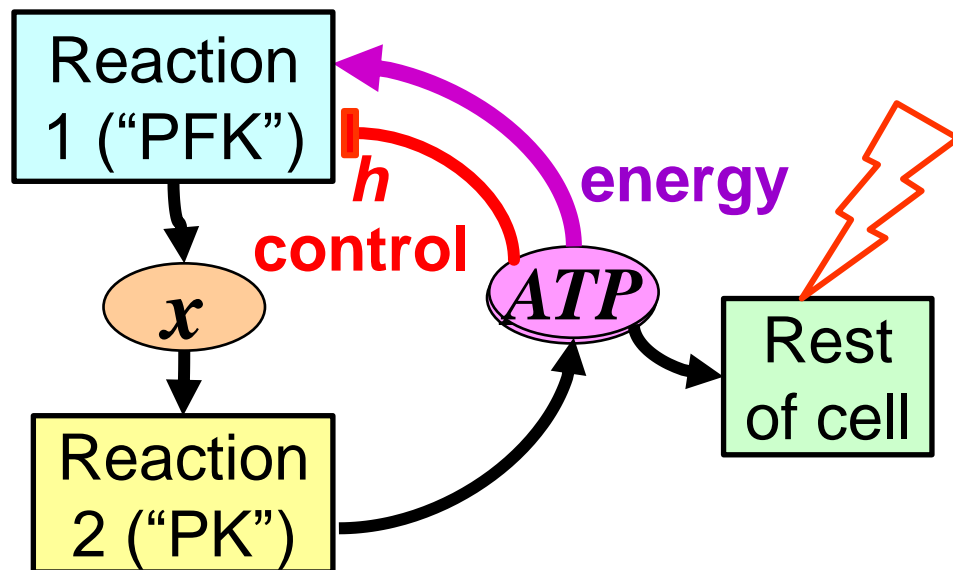
Cheap

Expensive

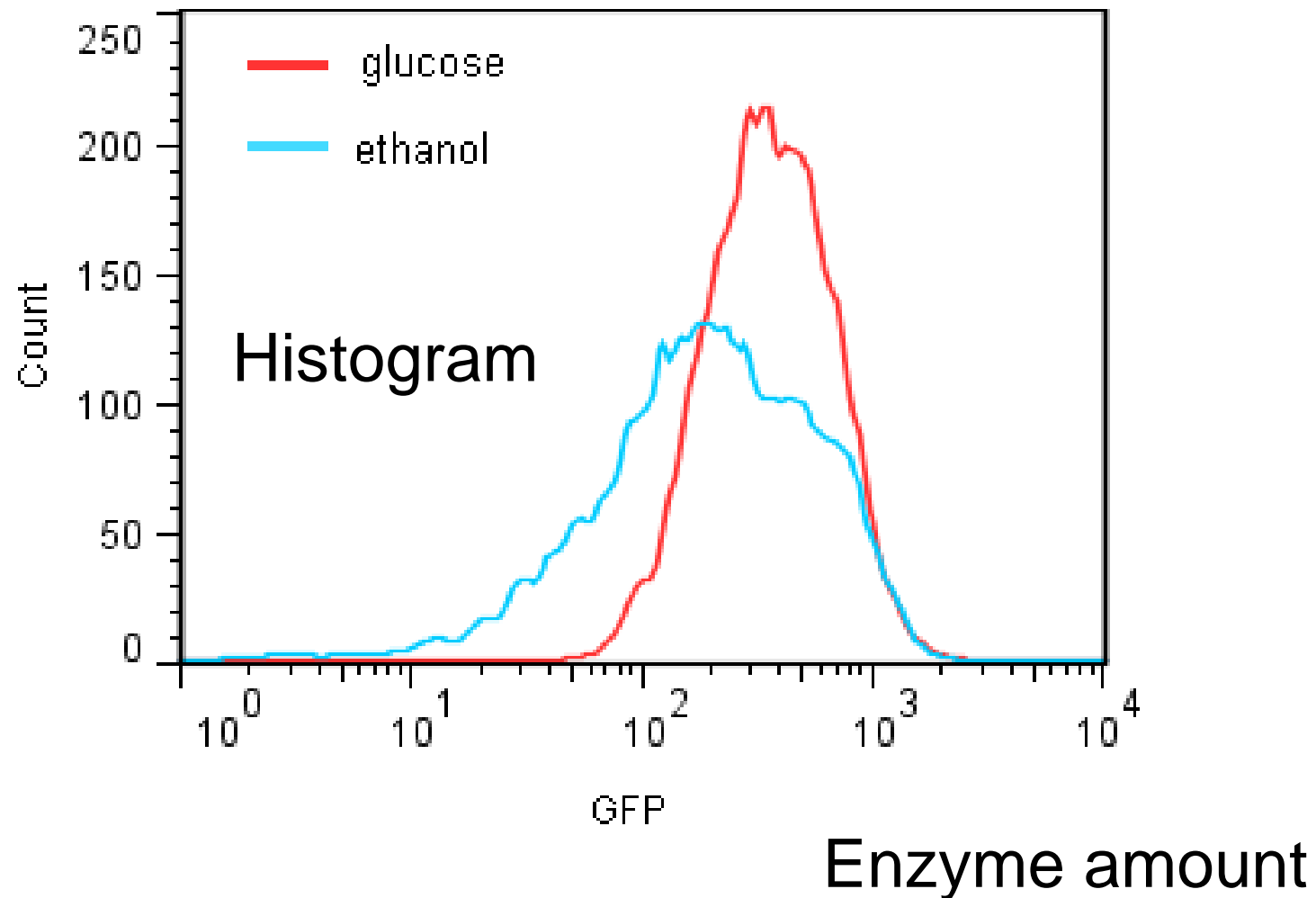
Fragility

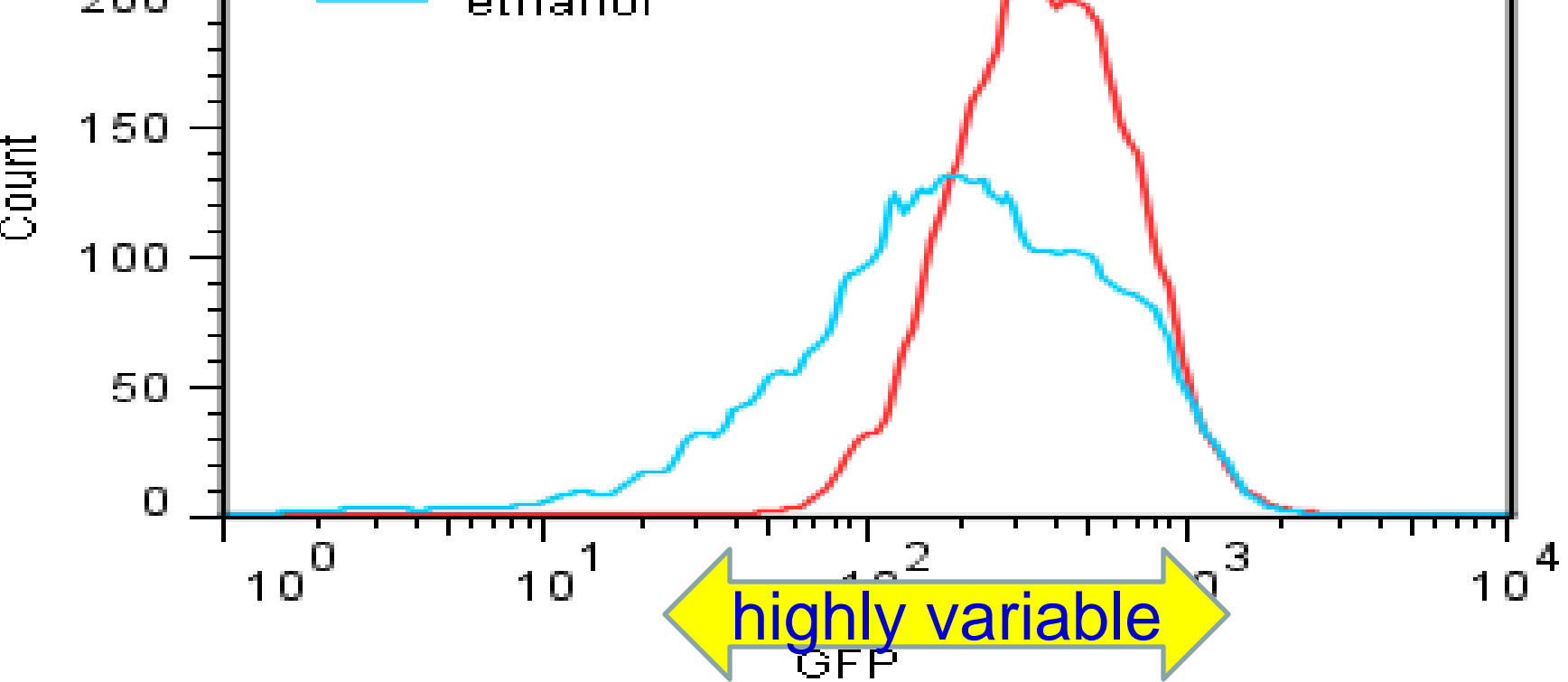
Plausible?

Enzyme  
amount



Fluorescence histogram (fluorescence vs. cell count) of GFP-tagged Glyceraldehyde-3-phosphate dehydrogenase (TDH3). Cells grown in ethanol have lower mean and median and higher variability.





10<sup>1</sup>

10<sup>2</sup>

10<sup>3</sup>

$\propto k$

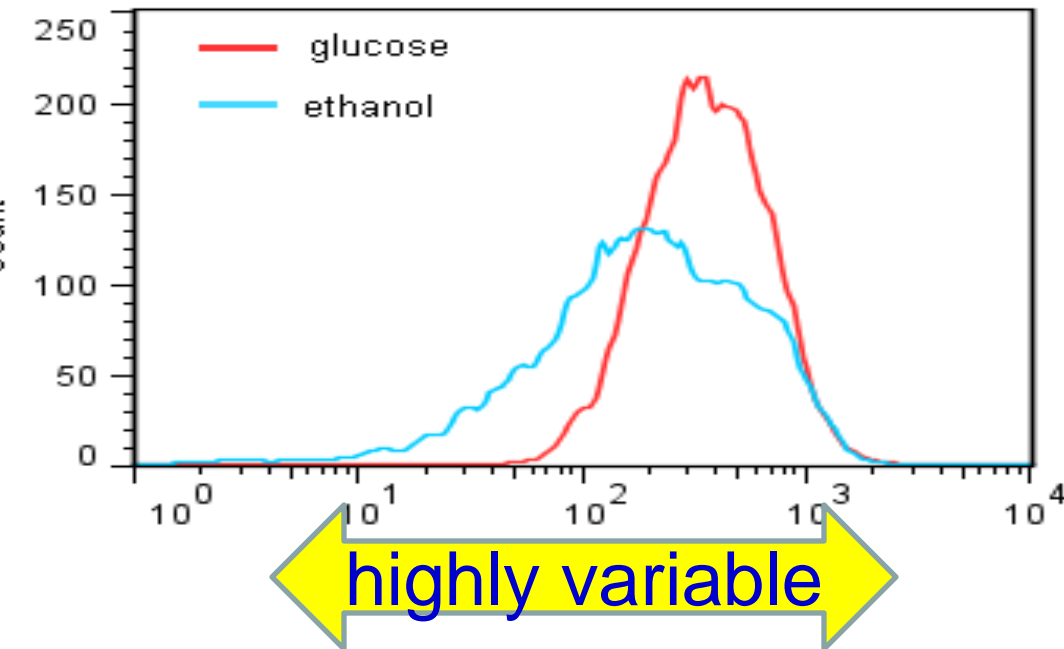
Metabolic  
Overhead

See Lestas, Vinnicombe, Paulsson, *Nature*

# Communicate

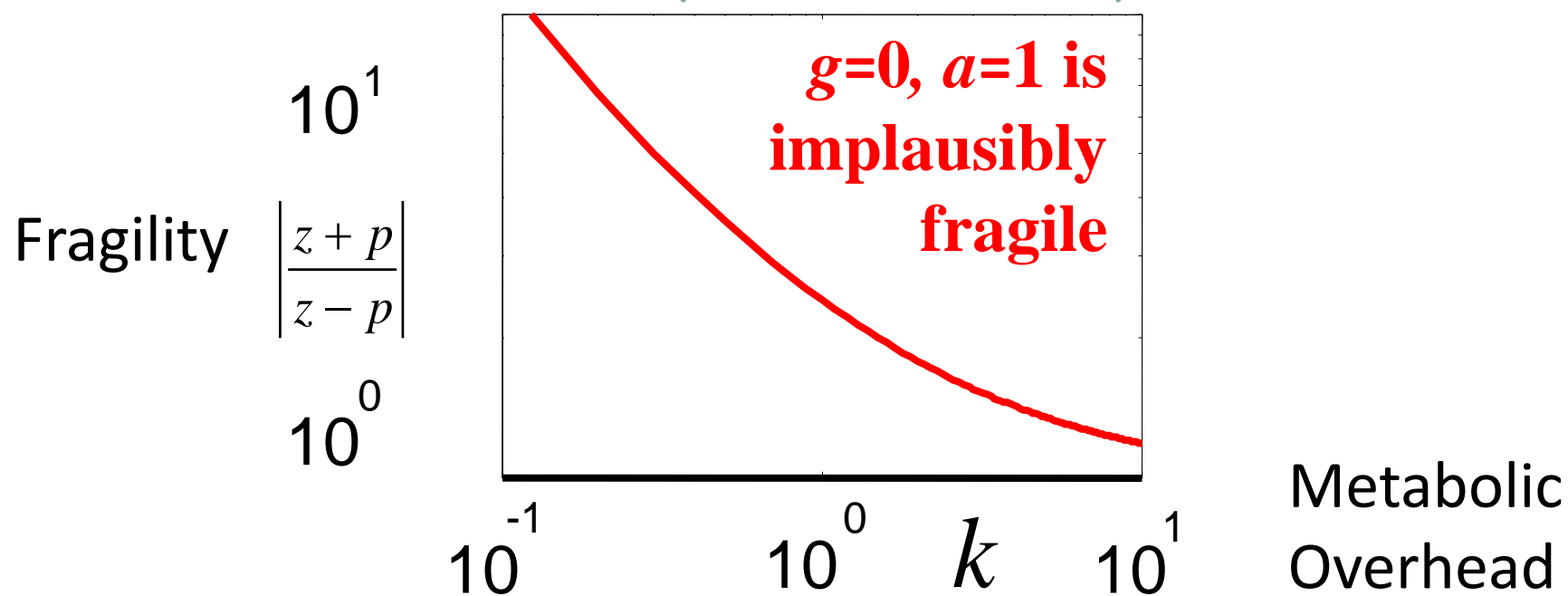
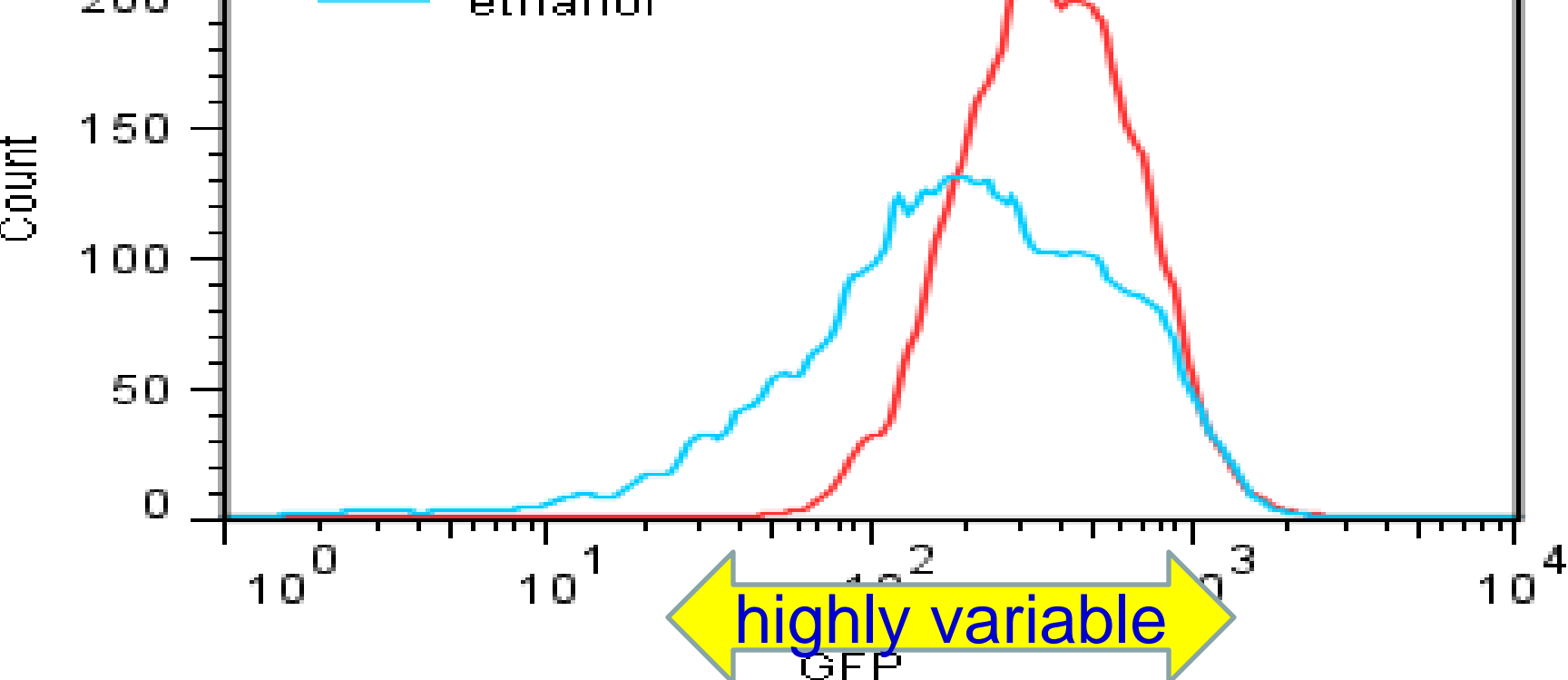
Shannon

**Delay is  
*least*  
important**



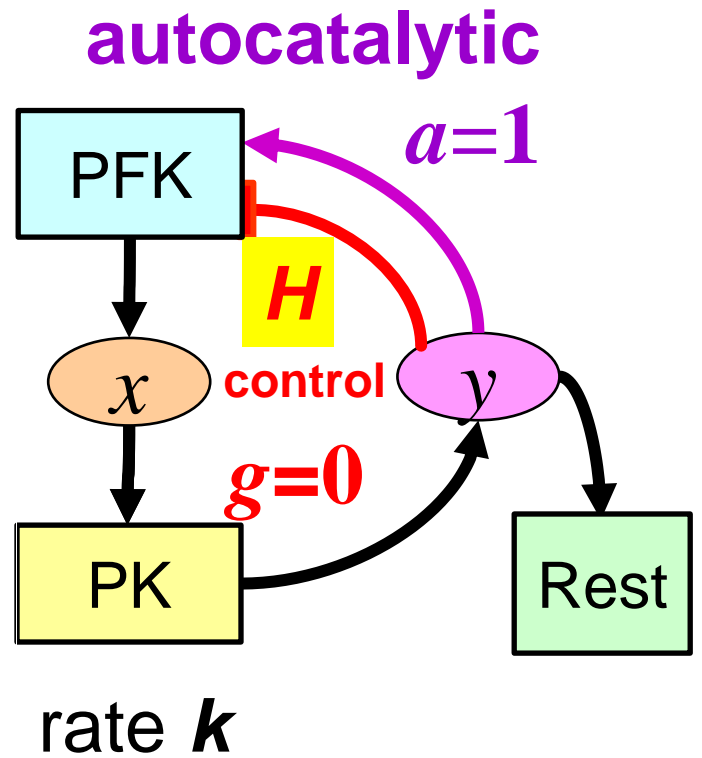
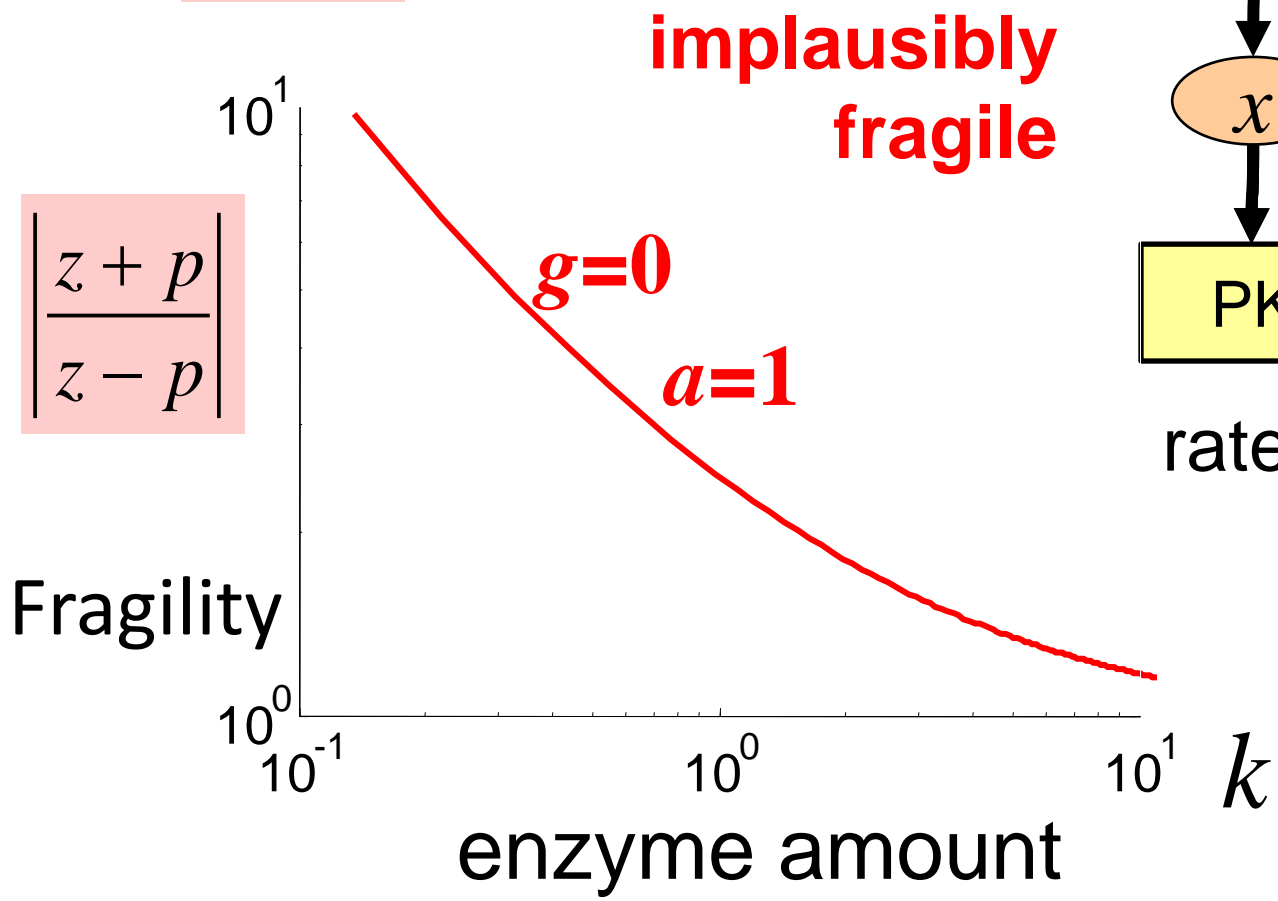
- Transcription is highly variable
- Even if you allow  $\infty$  delay!
- So information theory applies

See Lestas, Vinnicombe, Paulsson, *Nature*



$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega$$

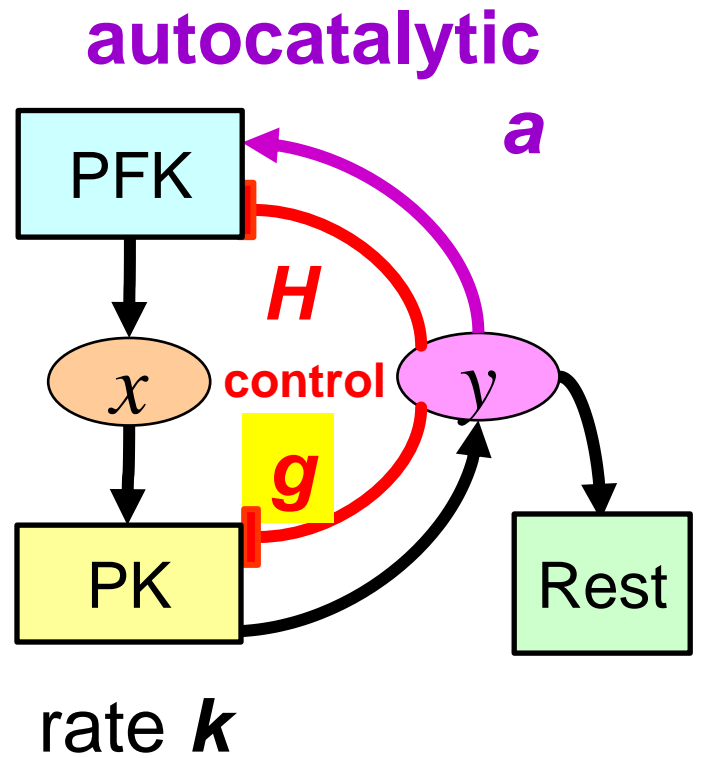
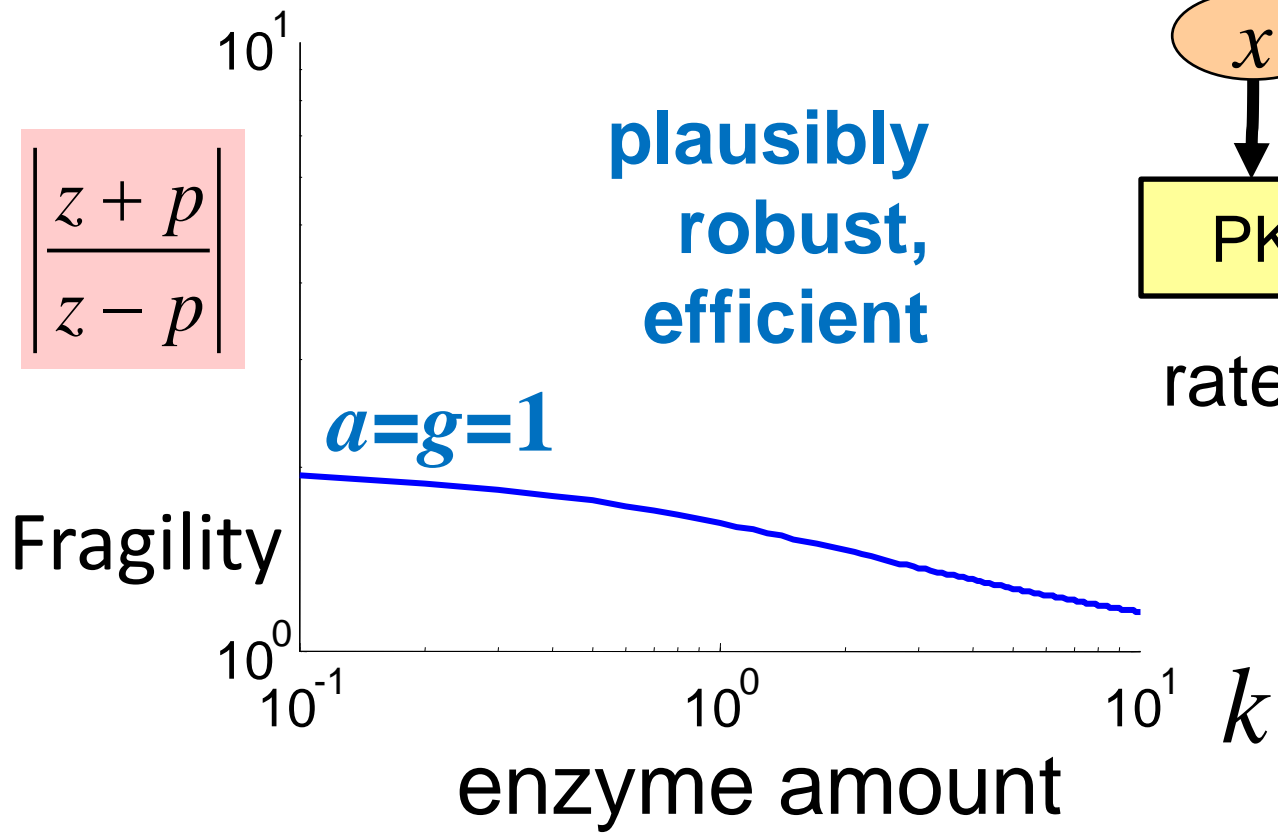
$$\geq \ln \left| \frac{z + p}{z - p} \right|$$





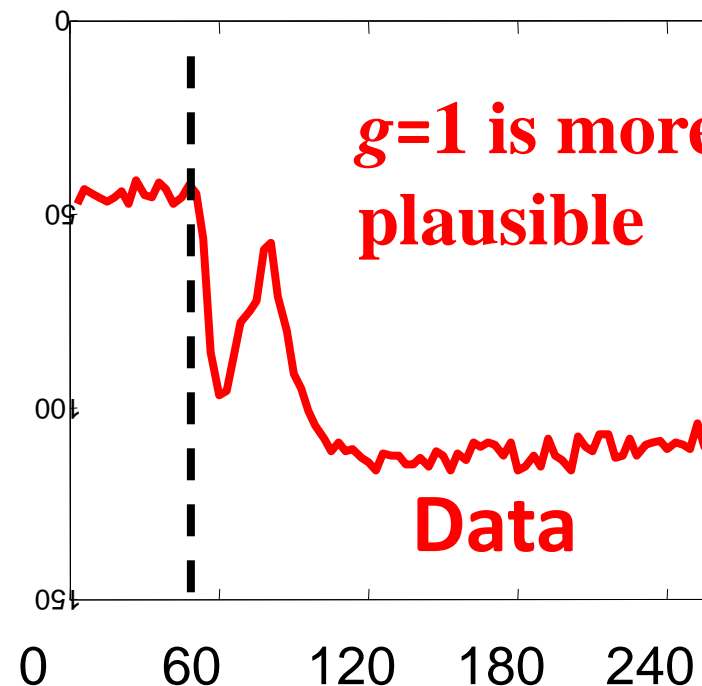
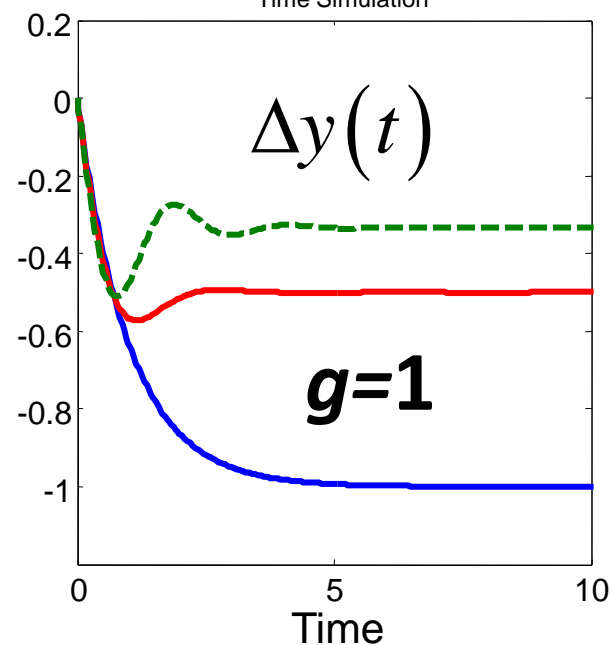
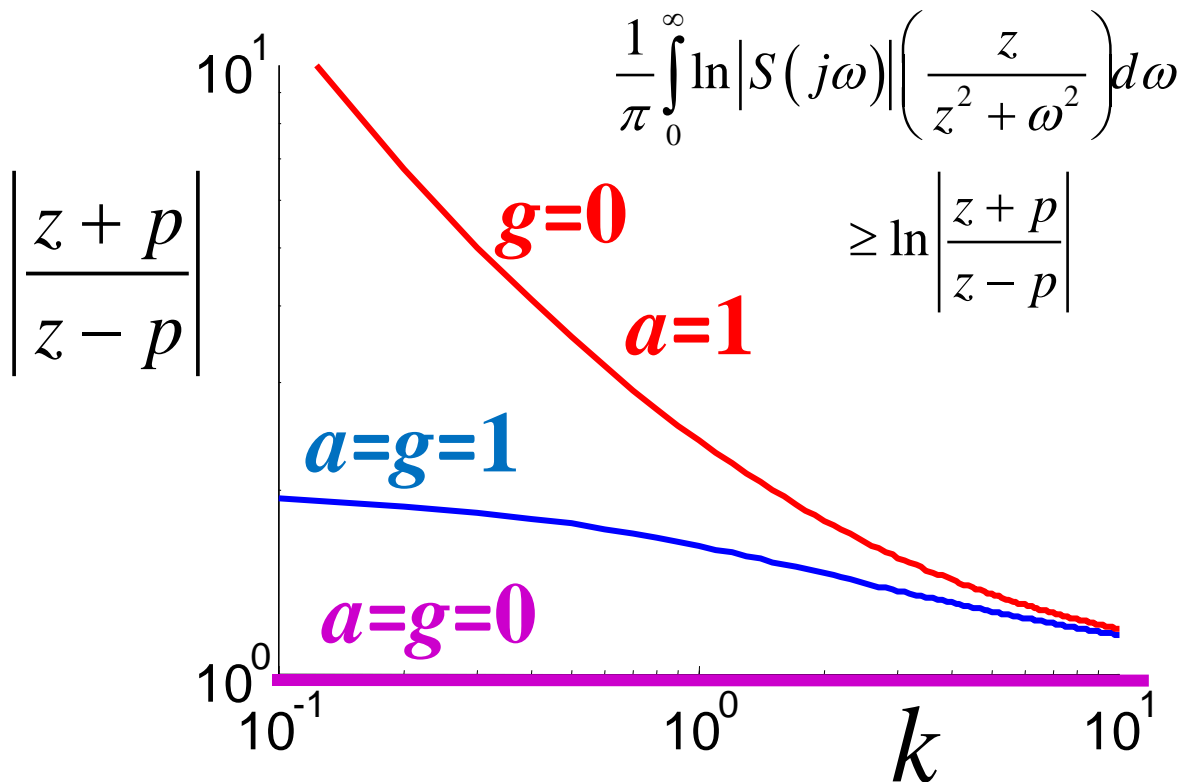
$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega$$

$$\geq \ln \left| \frac{z + p}{z - p} \right|$$



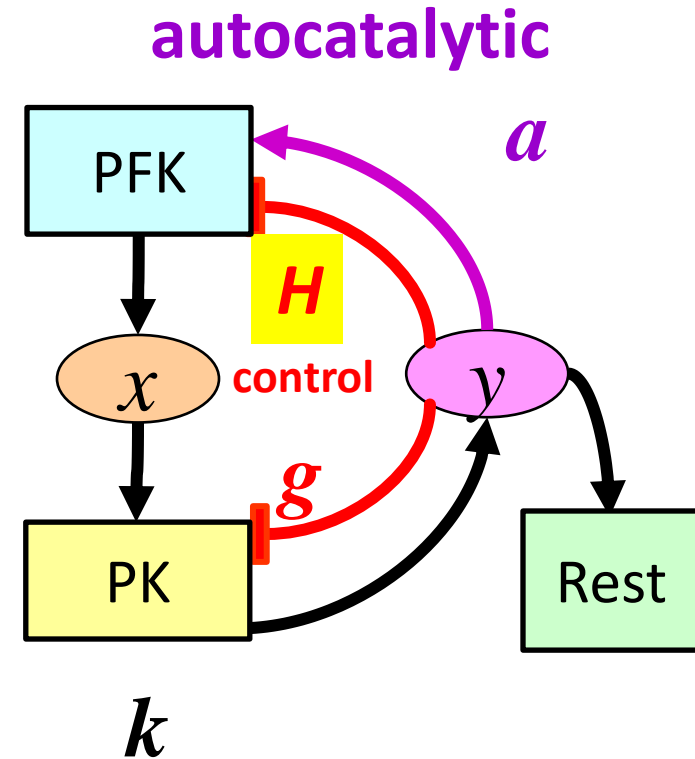
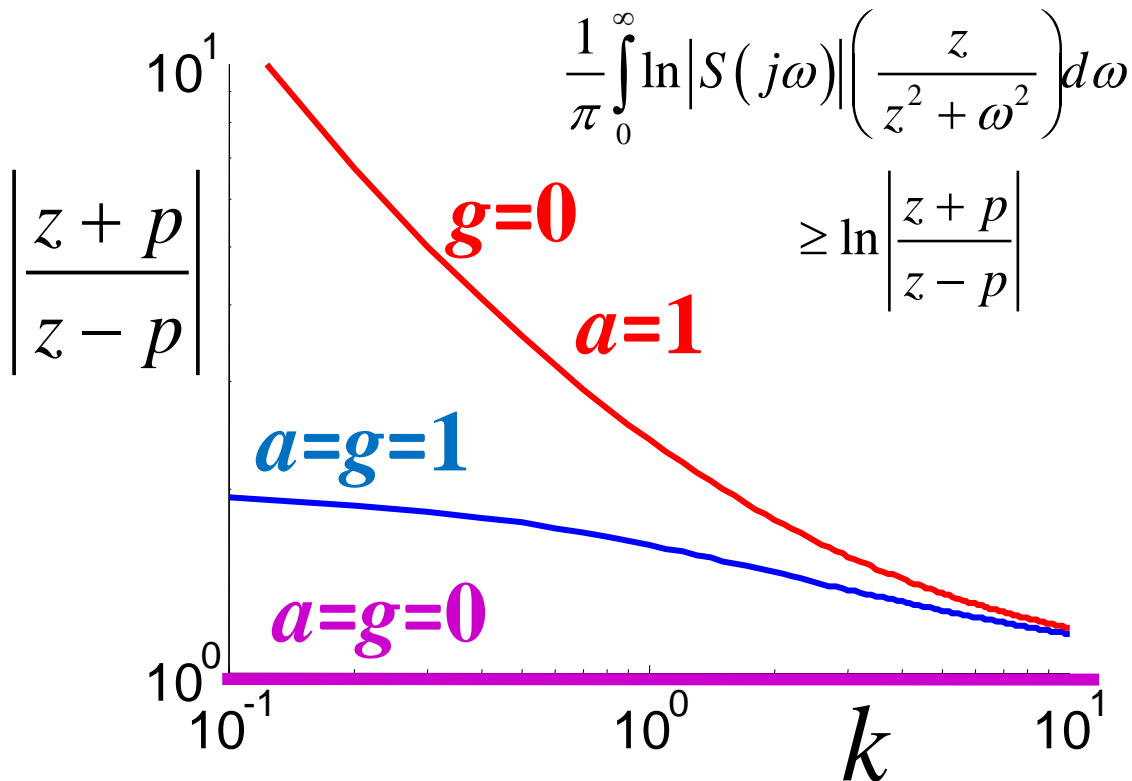
***a=1 sufficient for oscillations  
(and is actual)***

***g=1 necessary for robust  
efficiency (and is actual)***



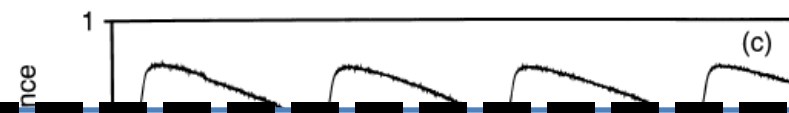
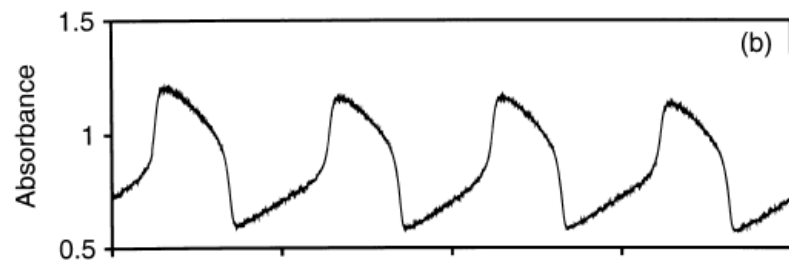
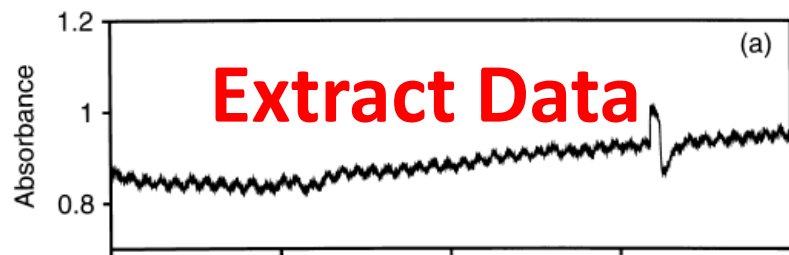
***a=1 sufficient*** for oscillations  
(and is *actual*)

***g=1 necessary*** for robust  
efficiency (and is *actual*)

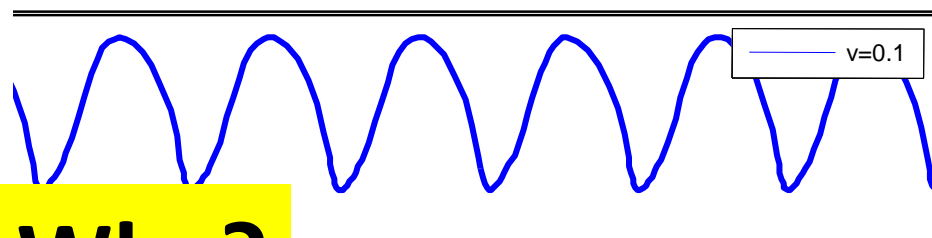
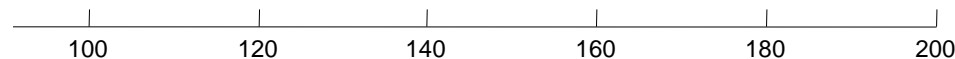


# What (some) reviewers say

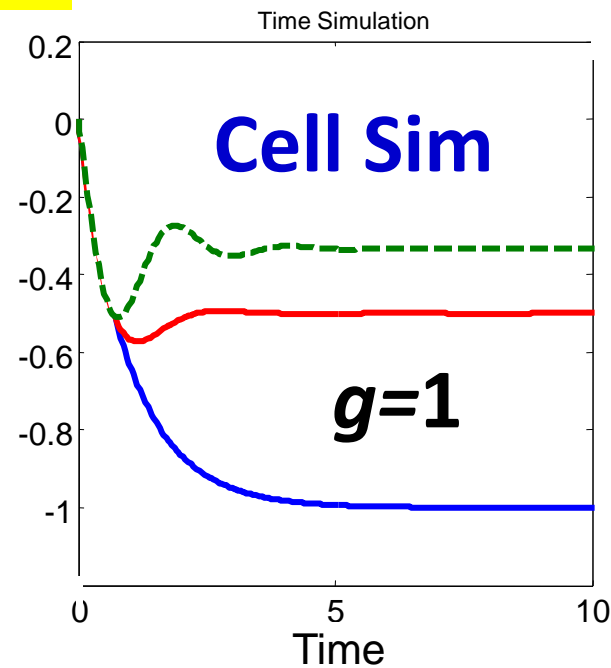
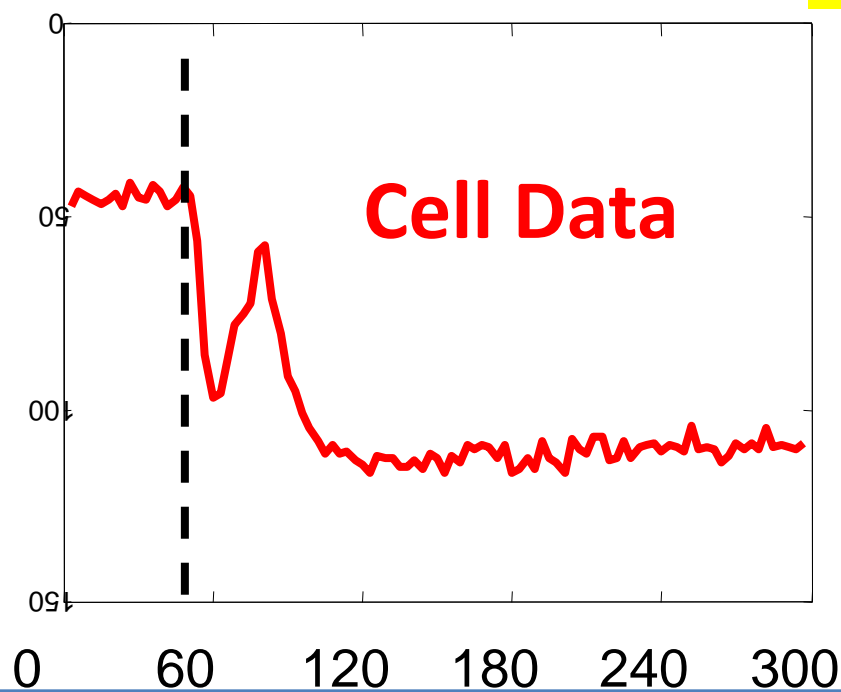
- “...to establish universality for all biological and physiological systems is **simply wrong**. It cannot be done...”
- “... a mathematical scheme **without any real connections to biological or medical...**”
- “If such oscillations are indeed optimal, why are they not universally present?”
- “...universality is well justified in physics... for biological and physiological systems ...**a dream that will never be realized**, due to the vast diversity in such systems.”
- “...**does not seem to understand or appreciate** the vast diversity of biological and physiological systems...”
- “...a high degree of abstraction, which ...make[s] **the model useless** ...”



**Extract Simulation**  $\approx 0.03$



**Why?**



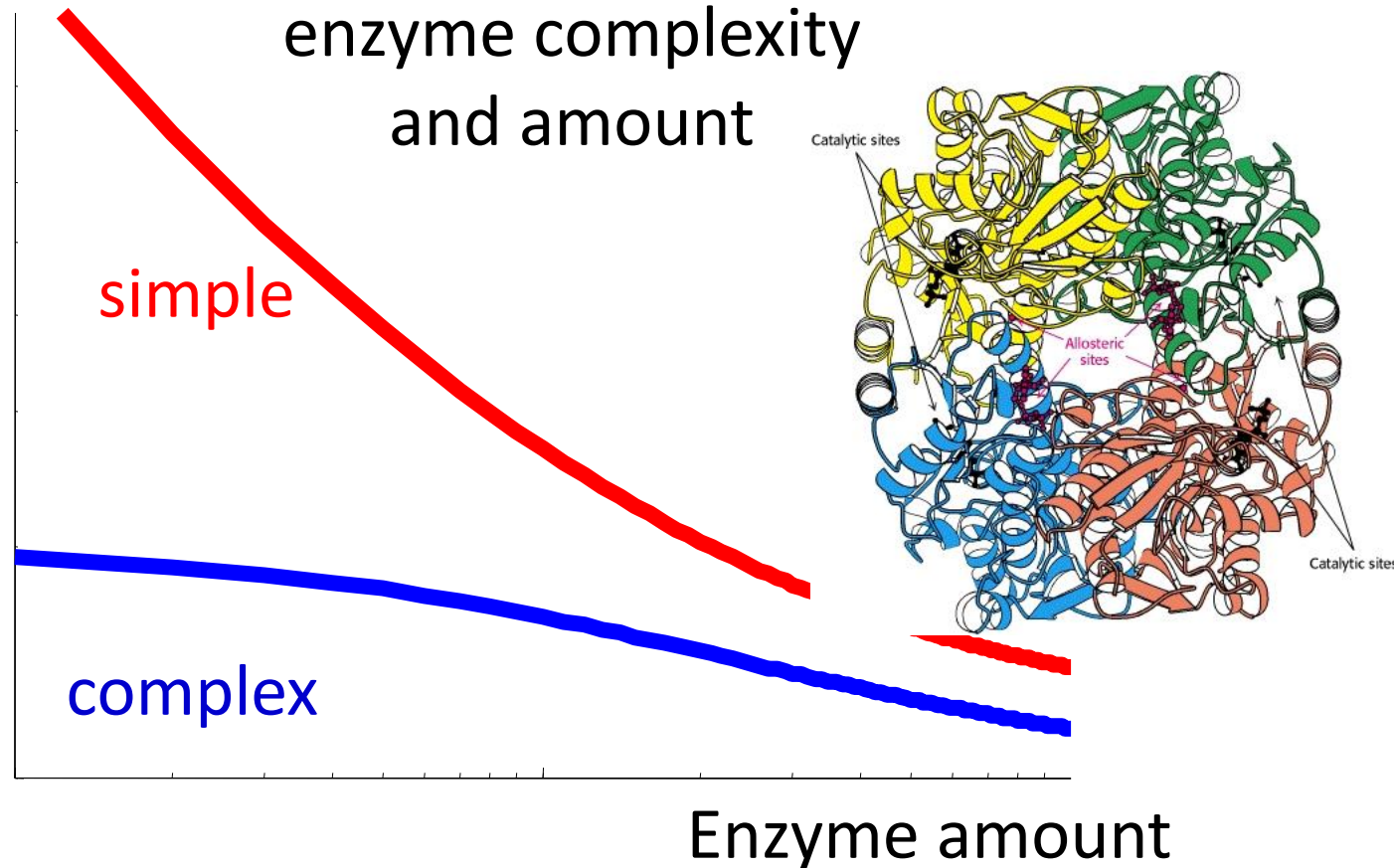
**Theorem!**

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right|$$

$z$  and  $p$  functions of  
enzyme complexity  
and amount

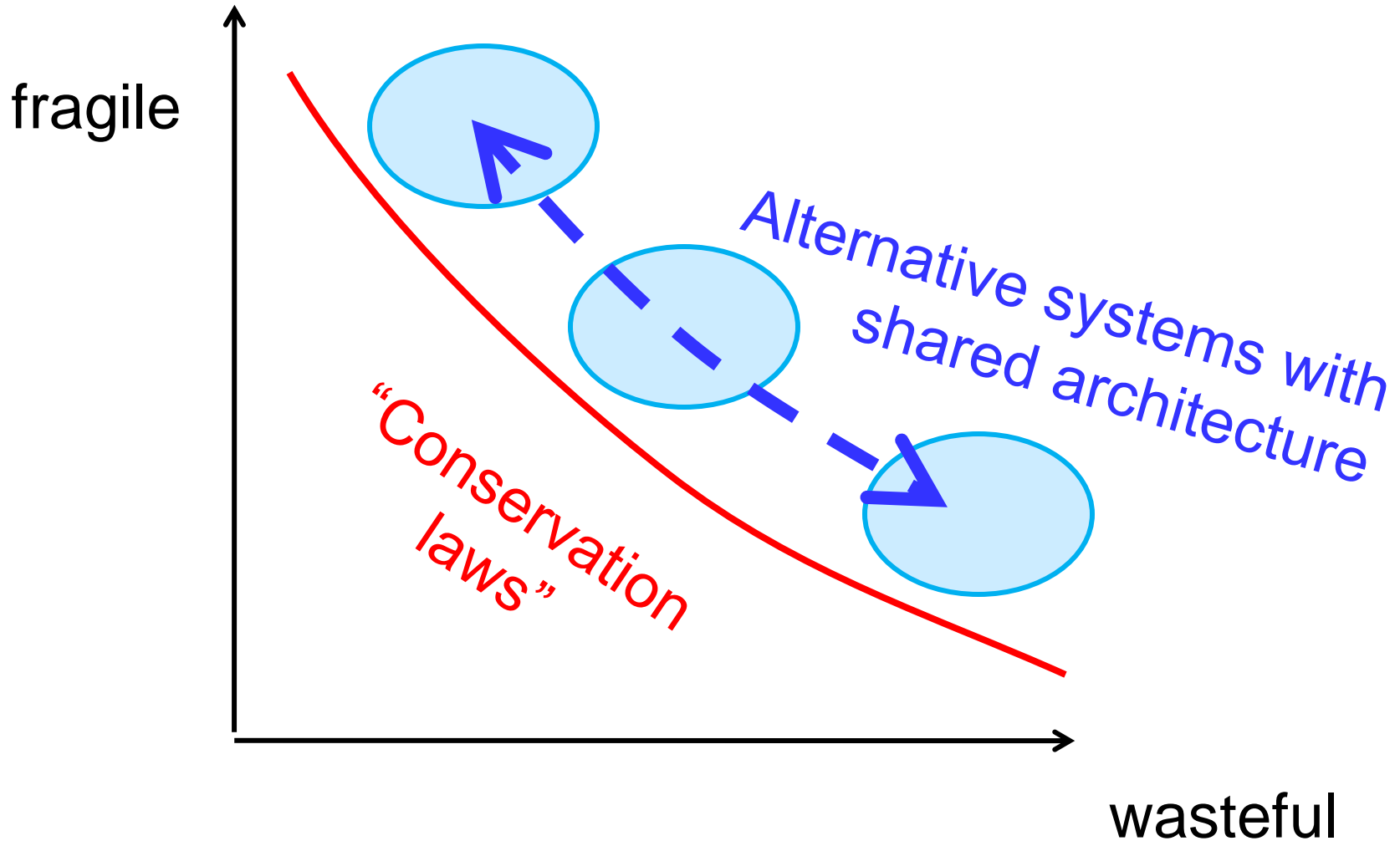
Fragility

$$\ln \left| \frac{z + p}{z - p} \right|$$

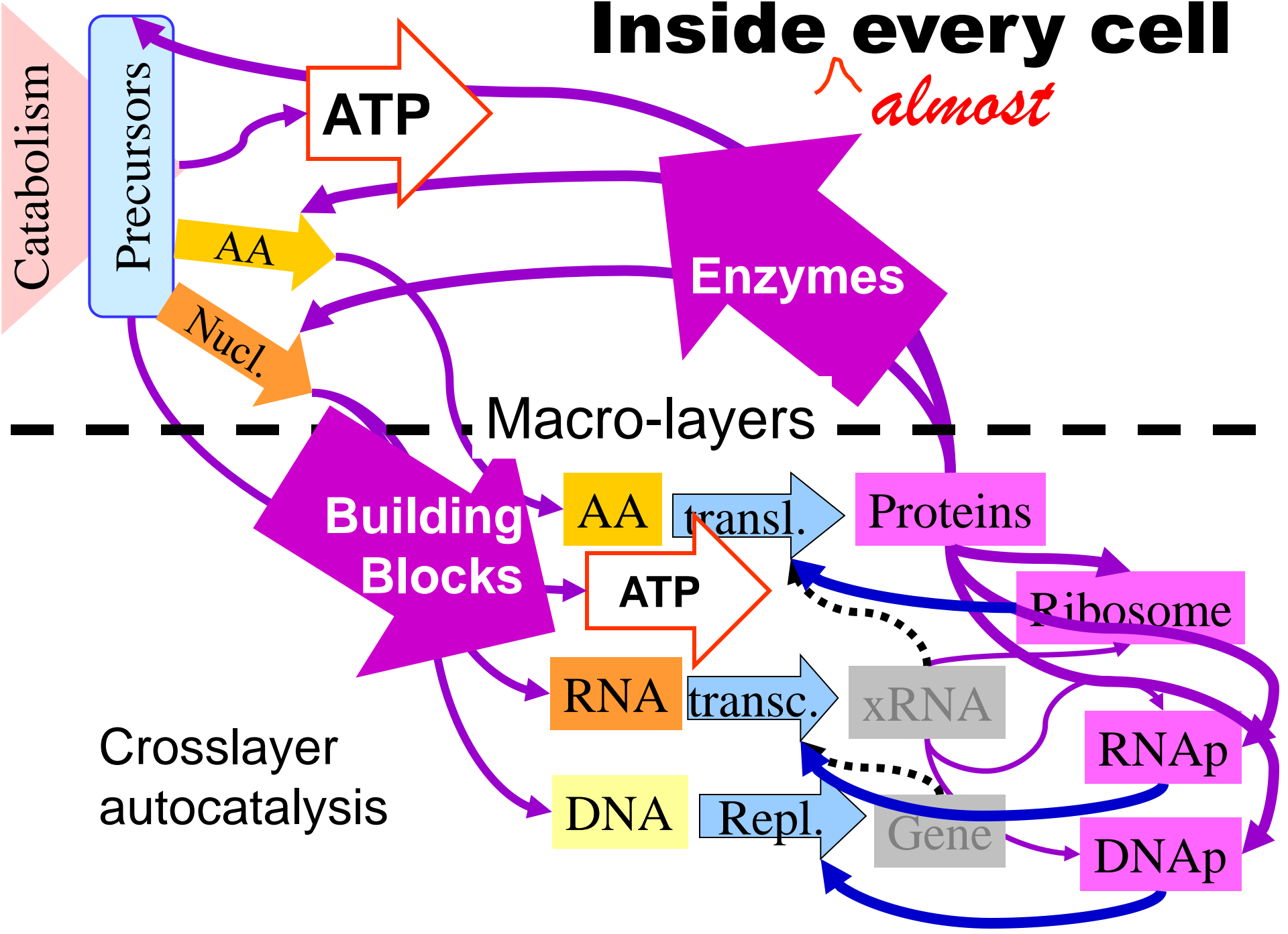


# Architecture

Good architectures  
allow for effective  
tradeoffs



# Inside every cell





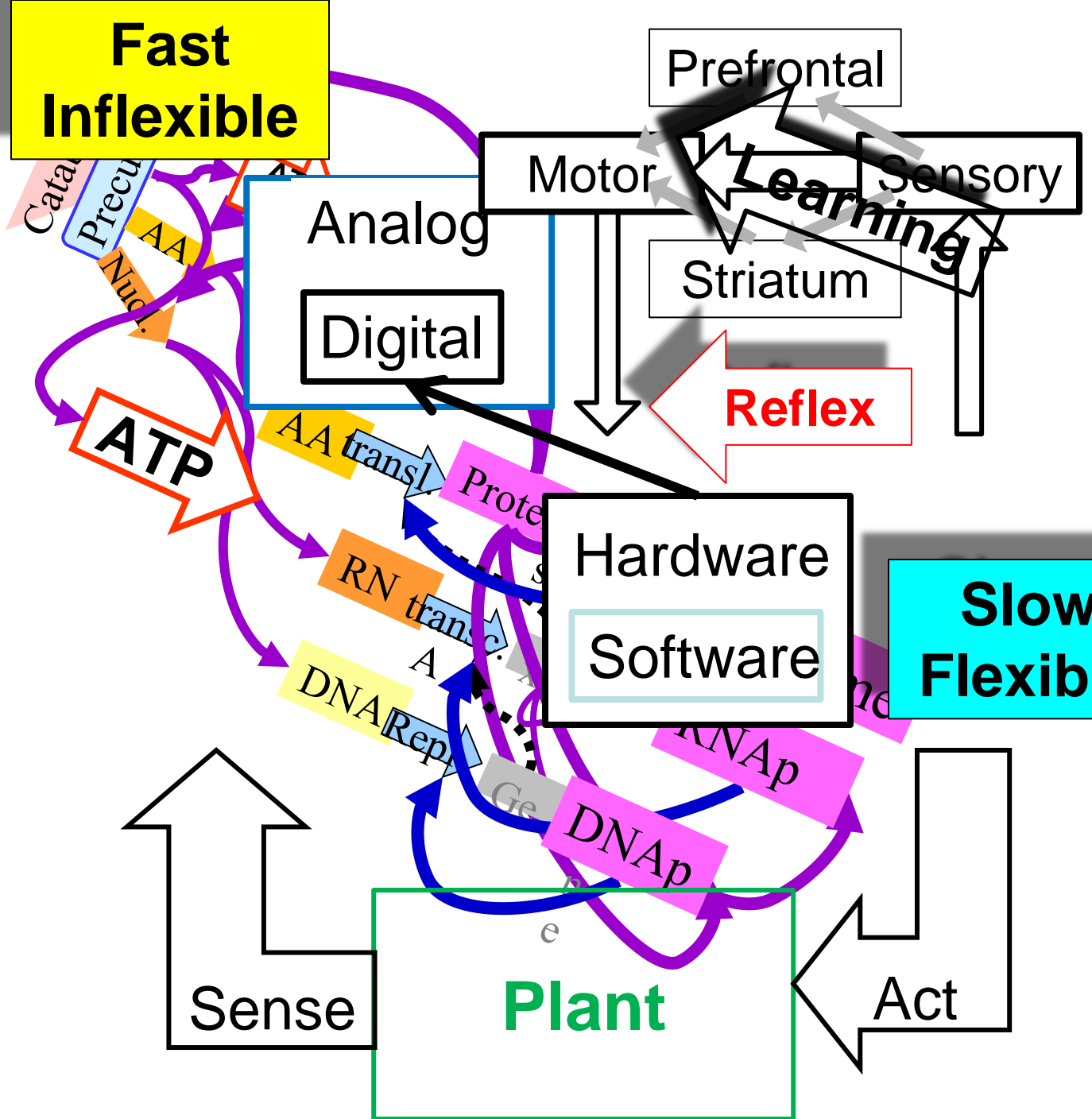
**Compute**

Turing

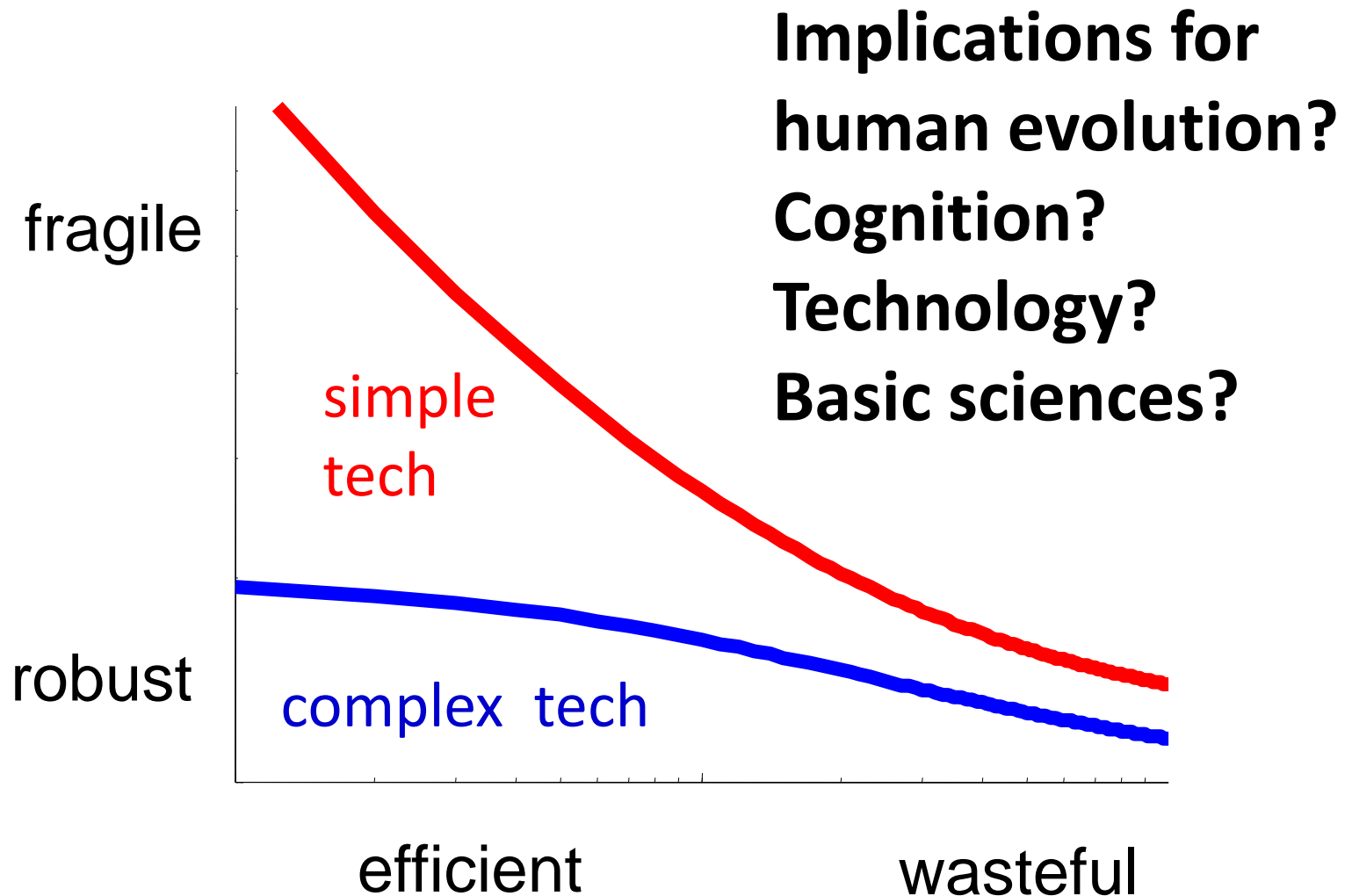
Delay is  
*most*  
important

Bode

**Control**



# How general is this picture?



Supplementary materials has a demo.

# Architecture, constraints, and behavior

John C. Doyle<sup>a,1</sup> and Marie Csete<sup>b,1</sup>

<sup>a</sup>Control and Dynamical Systems, California Institute of Technology, Pasadena, CA 91125; and <sup>b</sup>Department of Anesthesiology, University of California, San Diego, CA 92103

Edited by Donald W. Pfaff, The Rockefeller University, New York, NY, and approved June 10, 2011 (received for review March 3, 2011)

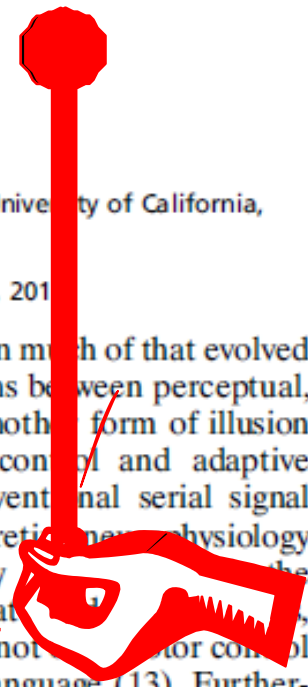
This paper aims to bridge progress in neuroscience involving sophisticated quantitative analysis of behavior, including the use of robust control, with other relevant conceptual and theoretical frameworks from systems engineering, systems biology, and mathematics. Familiar and accessible case studies are used to illustrate concepts of robustness, organization, and architecture (modularity and protocols) that are central to understanding complex networks. These essential organizational features are hidden during normal function of a system but are fundamental for understanding the nature, design, and function of complex biologic and technologic systems.

evolved for sensorimotor control and retain much of that evolved architecture, then the apparent distinctions between perceptual, cognitive, and motor processes may be another form of illusion (9), reinforcing the claim that robust control and adaptive feedback (7, 11) rather than more conventional serial signal processing might be more useful in interpreting neurophysiology data (9). This view also seems broadly consistent with the arguments from grounded cognition that behavior is not a disembodied state, but is embodied in the body and situated in the world (12), including language (13). Furthermore, the myriad constraints involved in the evolution of circuit

*m*

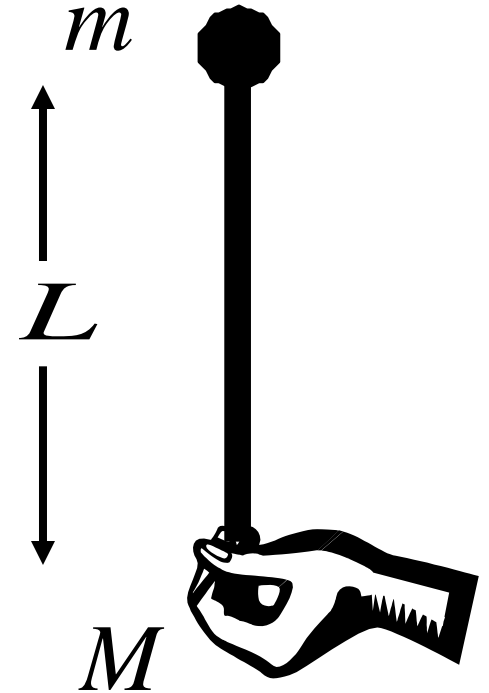
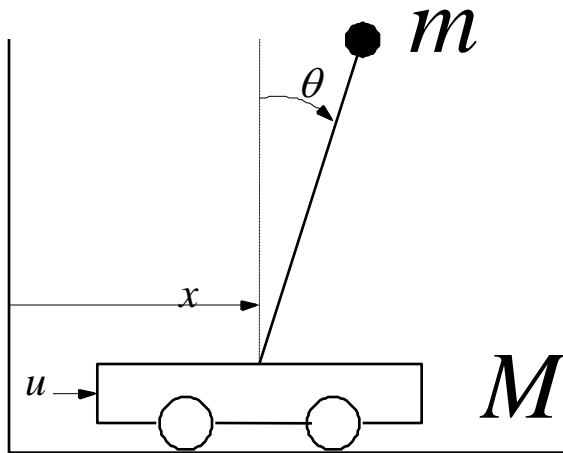


*M*



Doyle and Csete, *Proc Nat Acad Sci USA*, online JULY 25 2011

# Linearized pendulum on a cart



$$\frac{d}{dt} \begin{bmatrix} x \\ \theta \\ \dot{x} \\ \dot{\theta} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & \frac{m^2 g l^2}{q} & \frac{-(J + m l^2) b}{q} & 0 \\ 0 & \frac{m g l (M + m)}{q} & \frac{-m l b}{q} & 0 \end{bmatrix} \begin{bmatrix} x \\ \theta \\ \dot{x} \\ \dot{\theta} \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ \frac{J + m l^2}{q} \\ \frac{m l}{q} \end{bmatrix} u$$

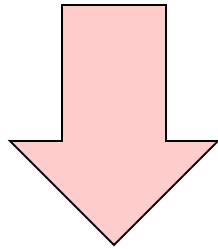
$$q = J(M + m) + M m l^2$$

$$(M + m)\ddot{x} + ml(\ddot{\theta} \cos \theta - \dot{\theta}^2 \sin \theta) = u$$

$$\ddot{x} \cos \theta + l\ddot{\theta} + g \sin \theta = 0$$

$$y = x + \alpha l \sin \theta$$

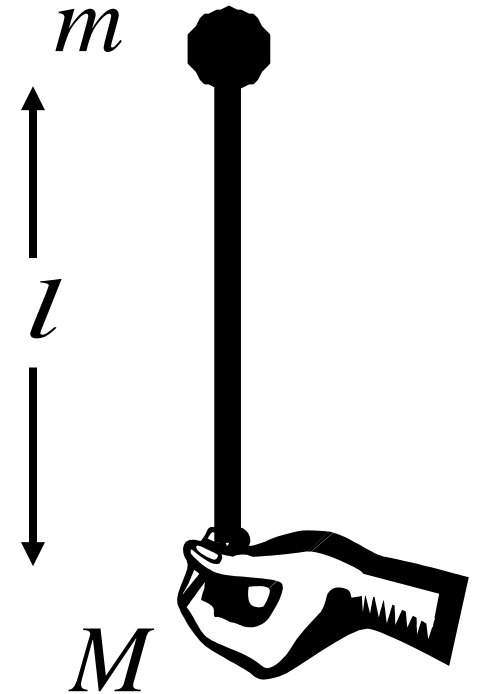
linearize



$$(M + m)\ddot{x} + ml\ddot{\theta} = u$$

$$\ddot{x} + l\ddot{\theta} \pm g\theta = 0$$

$$y = x + \alpha l \theta$$



**Robust**  
=agile and  
balancing

fragile?

robust?

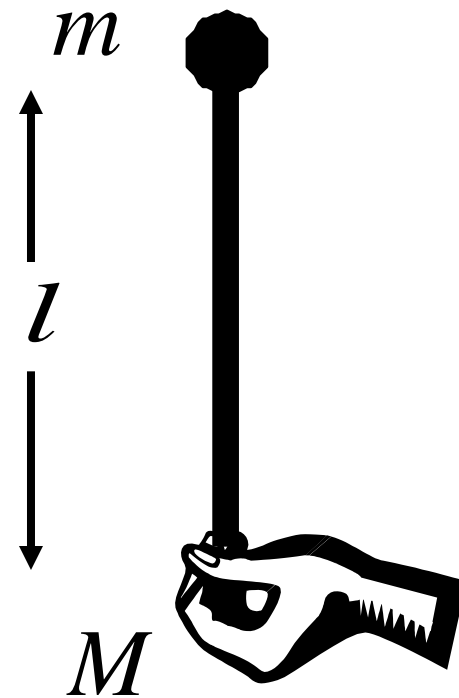
Tradeoffs?

Hard limit?

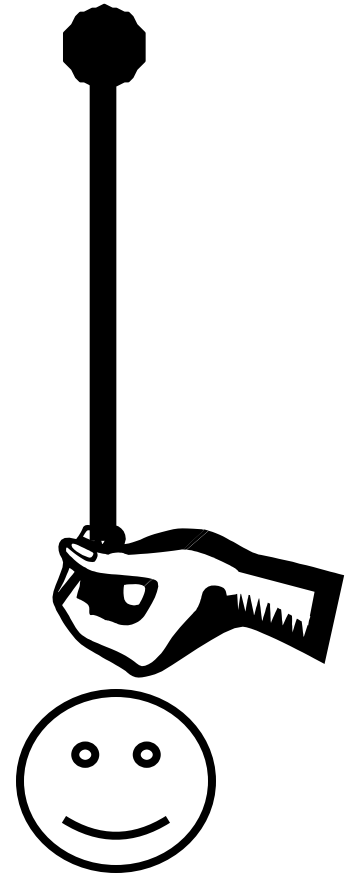
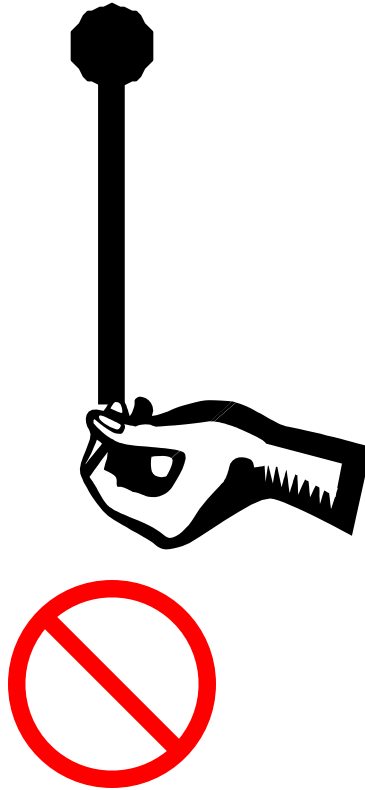
efficient?

wasteful?

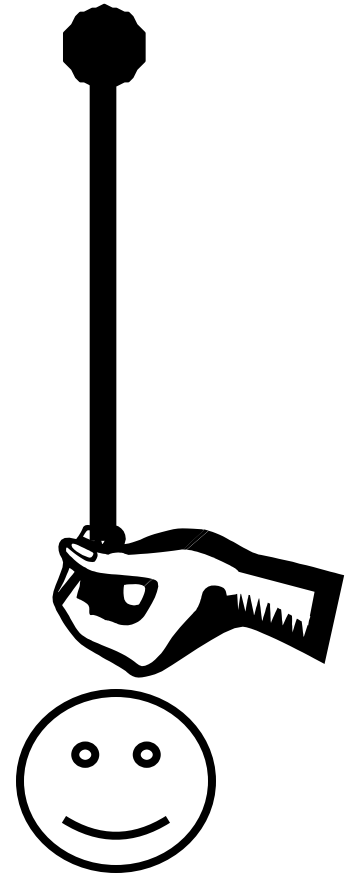
**Efficient**=length of  
pendulum (artificial)



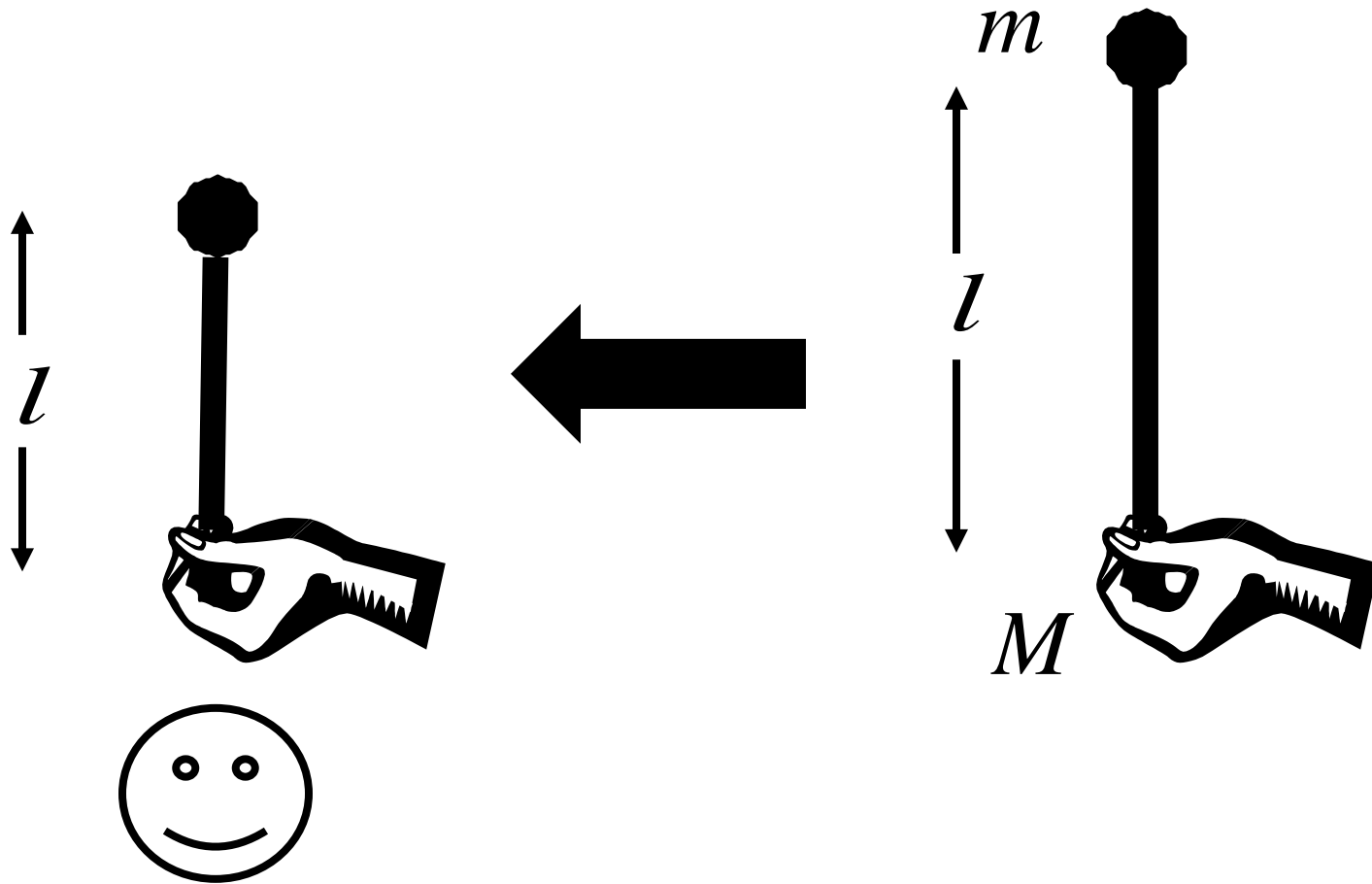
**Robust**  
=agile and  
balancing



**Robust**  
=agile and  
balancing







**Efficient**=length of  
pendulum (artificial)

**Robust**  
=agile and  
balancing

fragile?

robust?

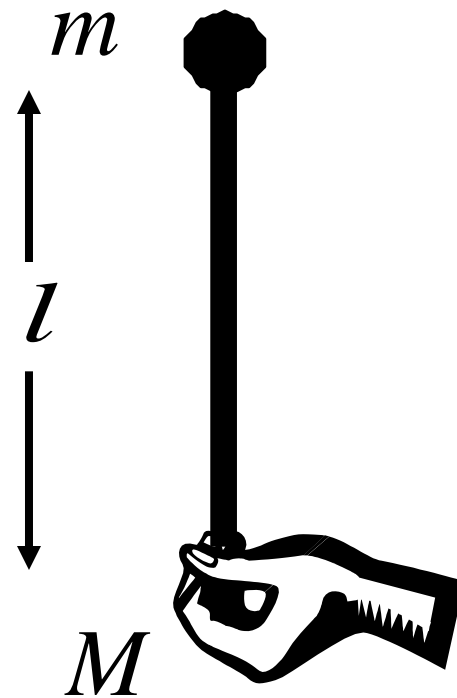
Tradeoffs?

Hard limit?

efficient?

wasteful?

**Efficient**=length of  
pendulum (artificial)

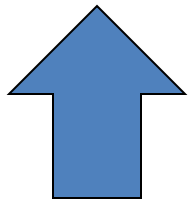


$$\begin{bmatrix} x \\ \theta \end{bmatrix} = \frac{1}{D(s)} \begin{bmatrix} ls^2 \pm g \\ -s^2 \end{bmatrix} u$$

$$D(s) = s^2 (Mls^2 \pm (M + m)g)$$

$$y = x + \alpha l \theta = \frac{(1 - \alpha)ls^2 \pm g}{D(s)}$$

$$p = \sqrt{\frac{g}{l}} \sqrt{1 + r} \quad r = \frac{m}{M} \quad z = \sqrt{\frac{g}{l}} \sqrt{\frac{1}{(1 - \alpha)}}$$



transform+algebra

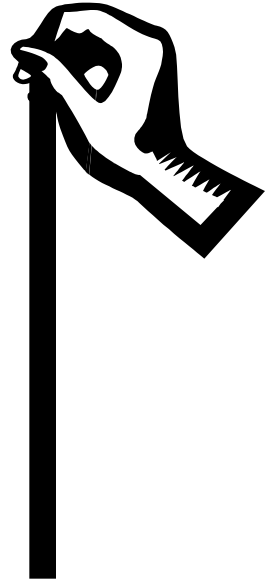
$$(M + m)\ddot{x} + ml\ddot{\theta} = u$$

$$\ddot{x} + l\ddot{\theta} \pm g\theta = 0$$

$$y = x + \alpha l \theta$$



$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$

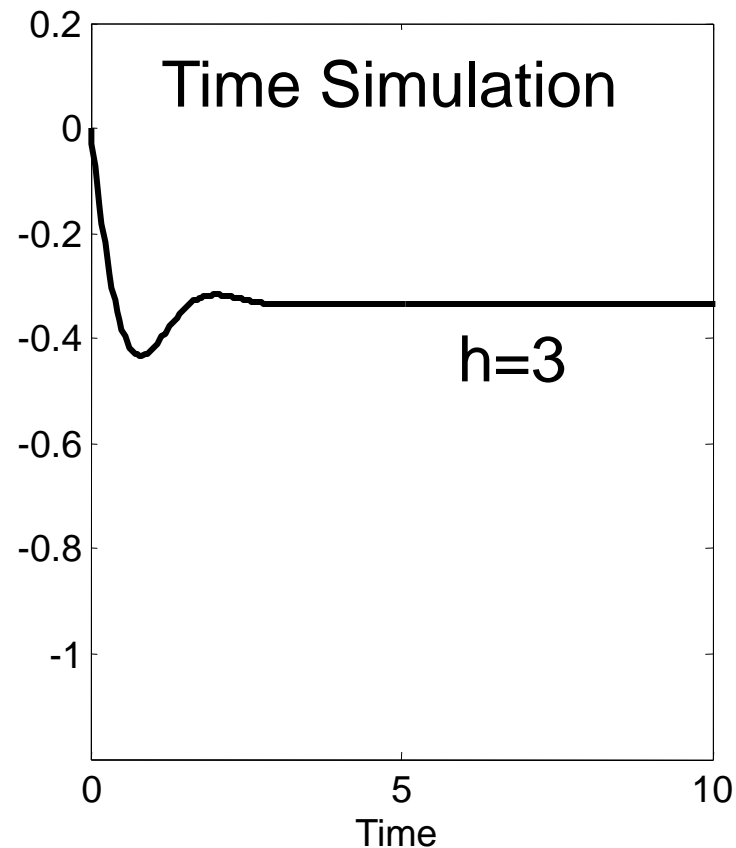
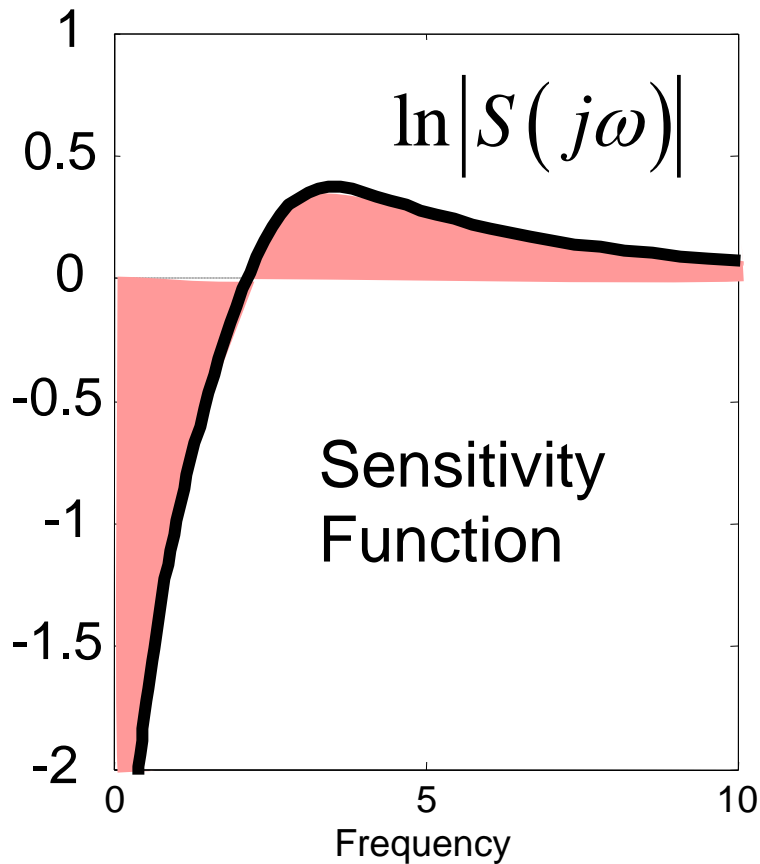
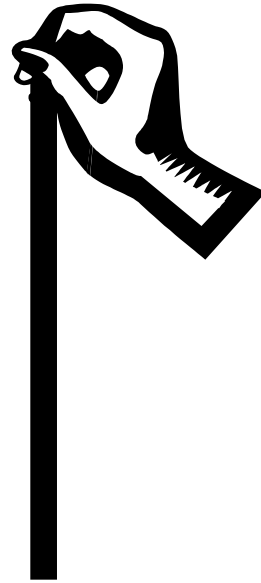


Easy, even with eyes closed  
No matter what the length

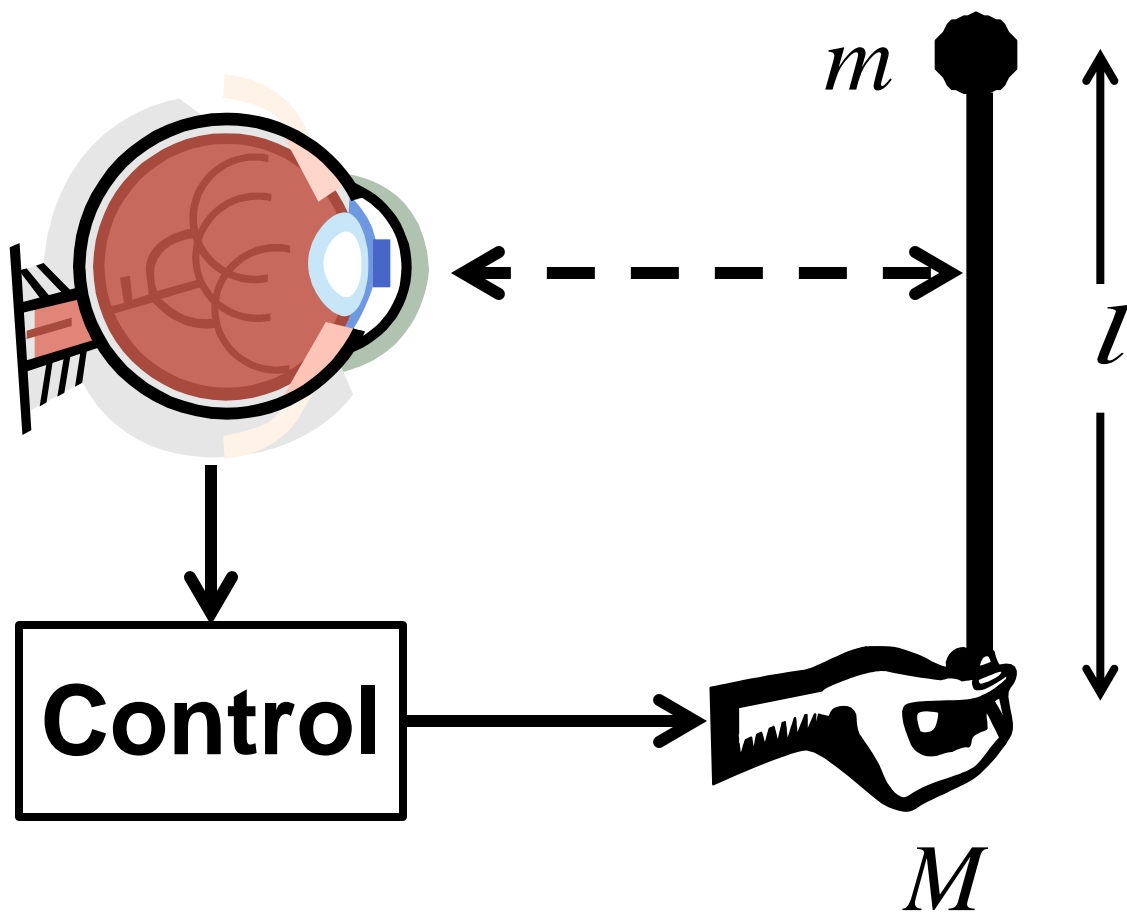
Proof: Standard UG control theory:  
Easy calculus, easier contour integral,  
easiest Poisson Integral formula

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$

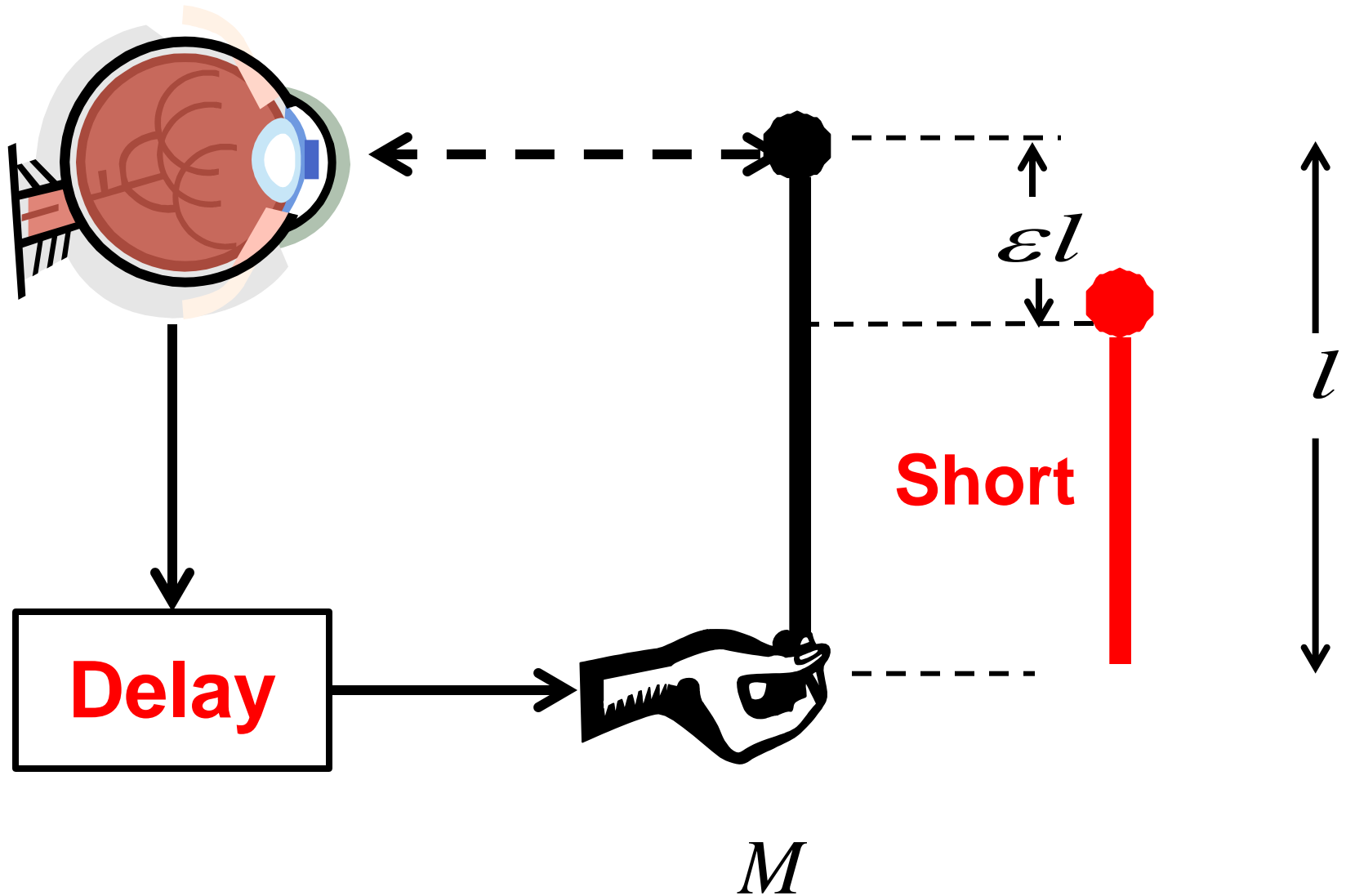
≈ simple metabolism without autocatalysis



Need vision

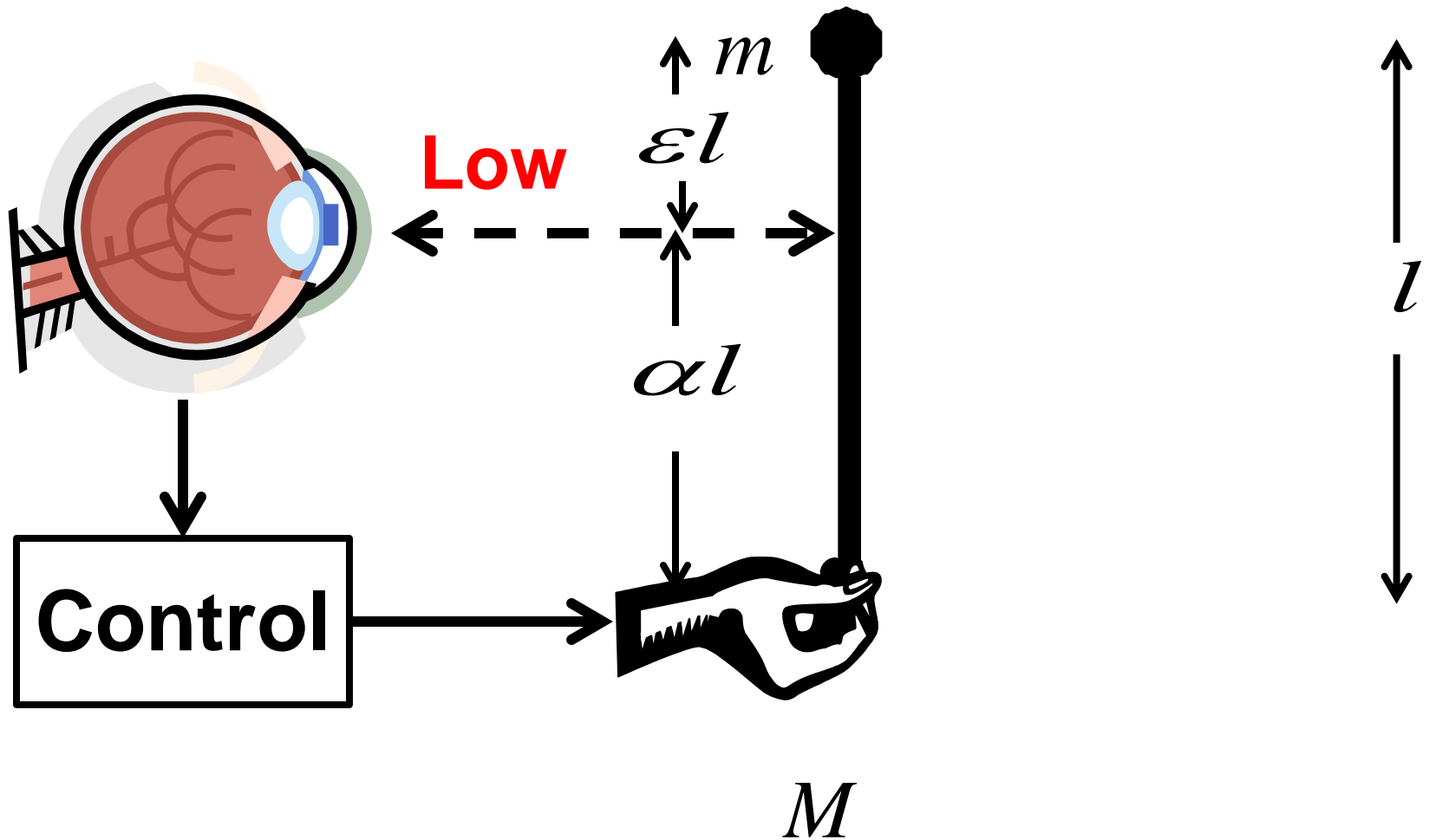


Harder if delayed or short



Also harder if low

$$r = \frac{m}{M}$$





Gratuitous fragility  
versus  
fragile robustness

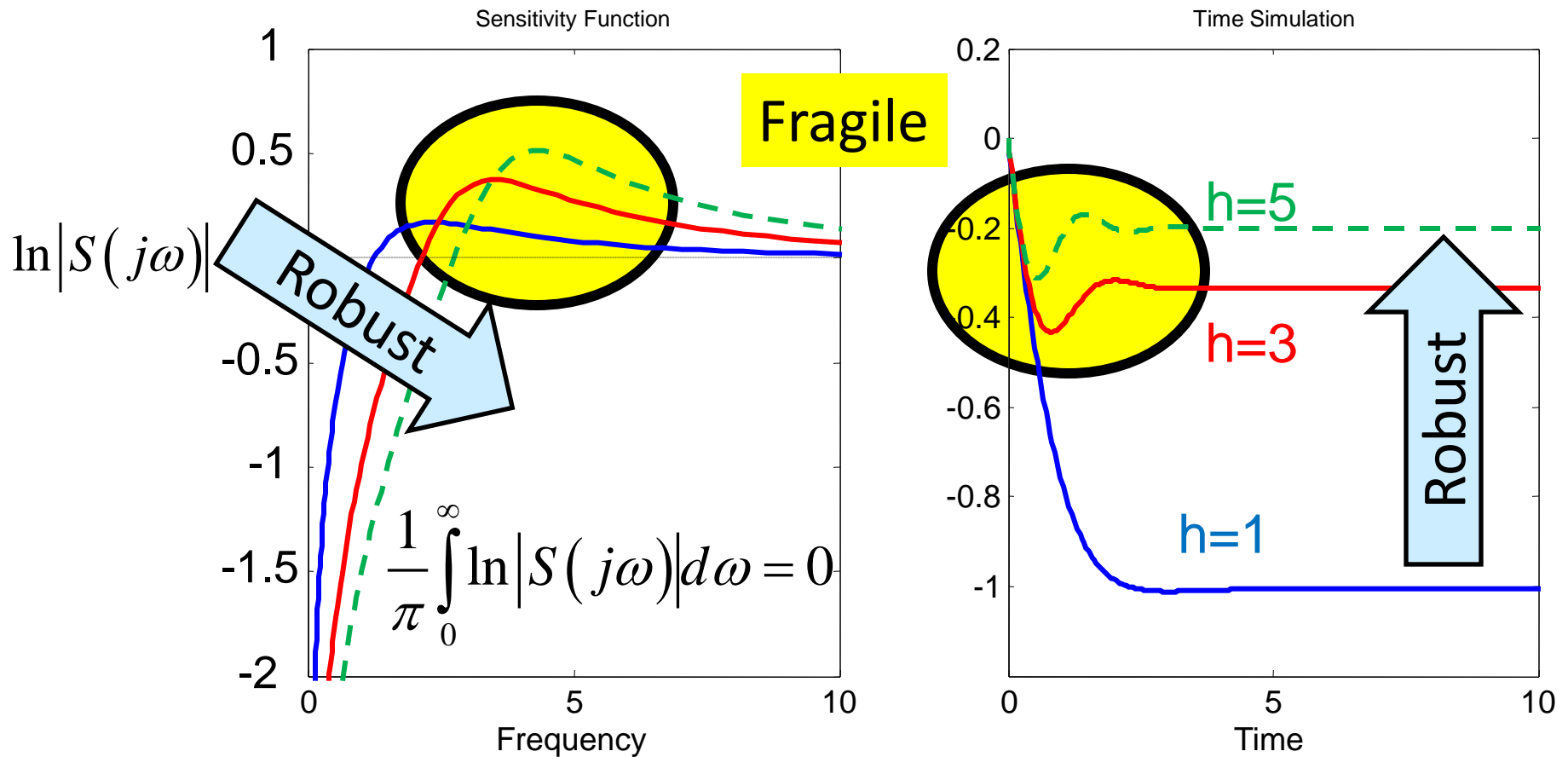
$$\int_0^{\infty} \ln |S(j\omega)| d\omega \geq 0$$

$\gg \Rightarrow$  Gratuitous fragility

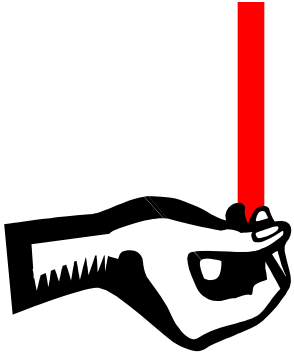
$= \Rightarrow$  Fragile robustness

Theorem is independent  
of control implementation.

# Simple metabolism without autocatalysis

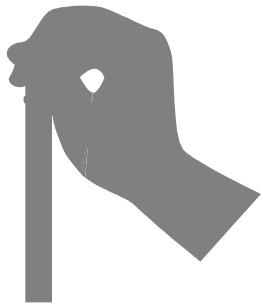
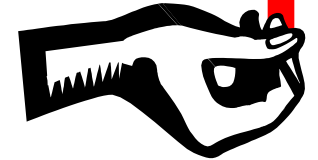


Up is hard for shorter lengths (RHP pole)

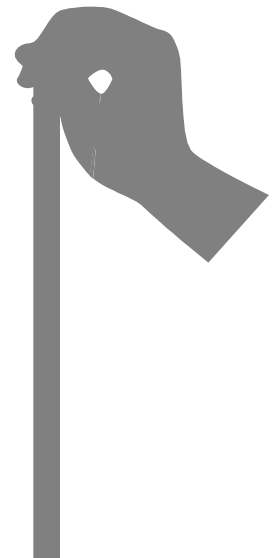


$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq |p|$$

$$p = \sqrt{\frac{g}{l}(1+r)} \quad r = \frac{m}{M}$$



$$p \text{ small} \Leftrightarrow l \text{ large}$$

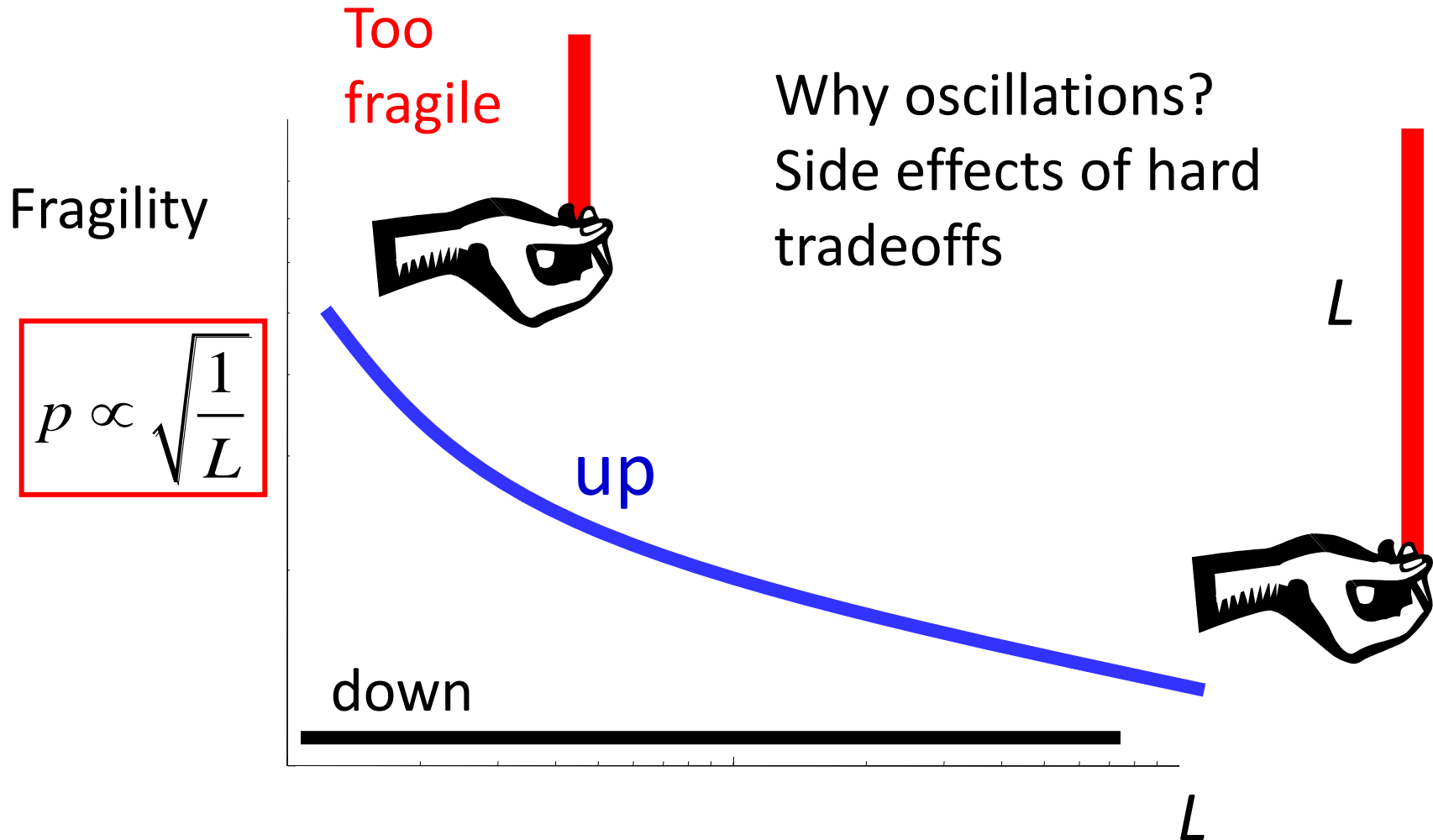


Down easy, even with

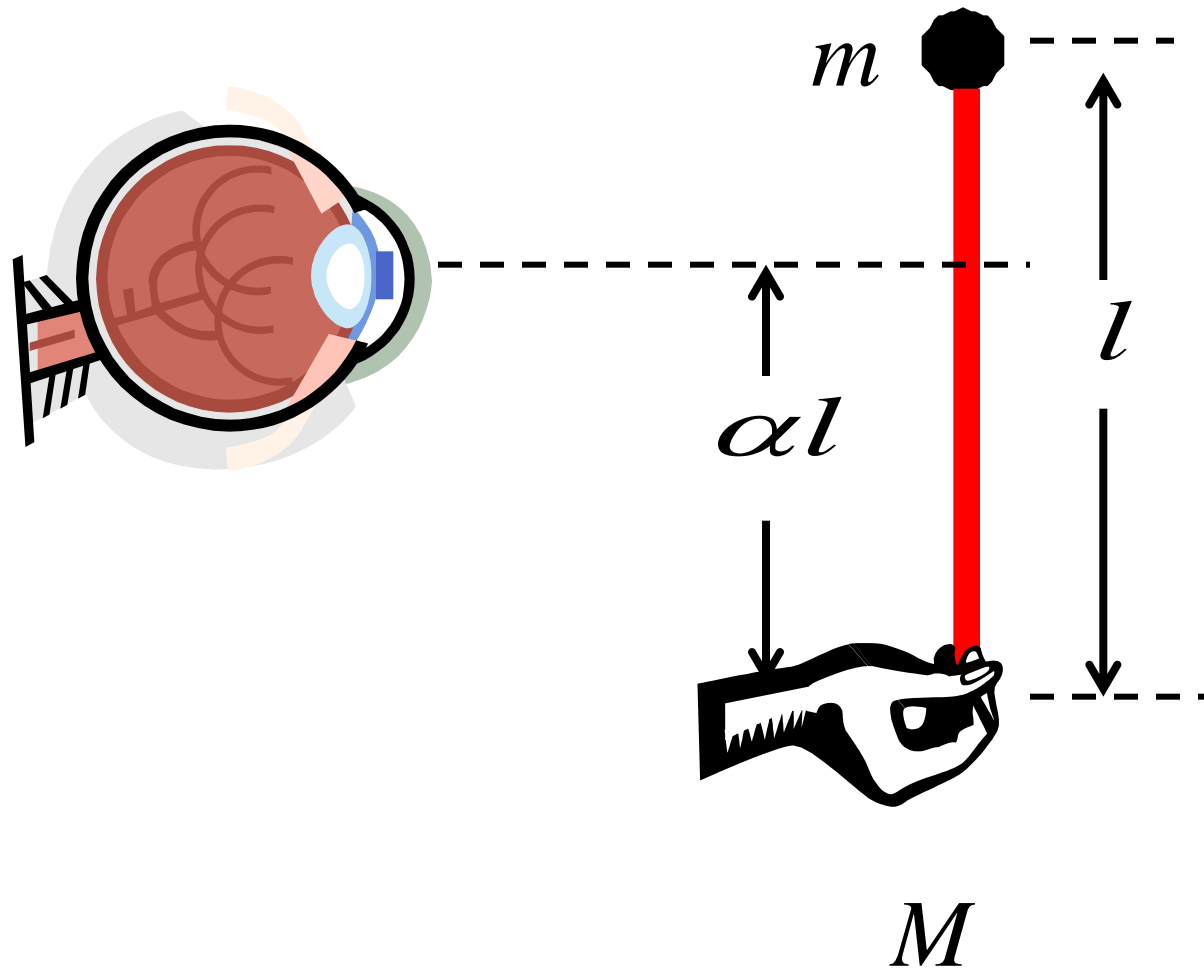
- eyes closed
- all lengths

$$\frac{1}{\pi} \int_0^{\infty} \ln |S(j\omega)| d\omega \geq |p|$$

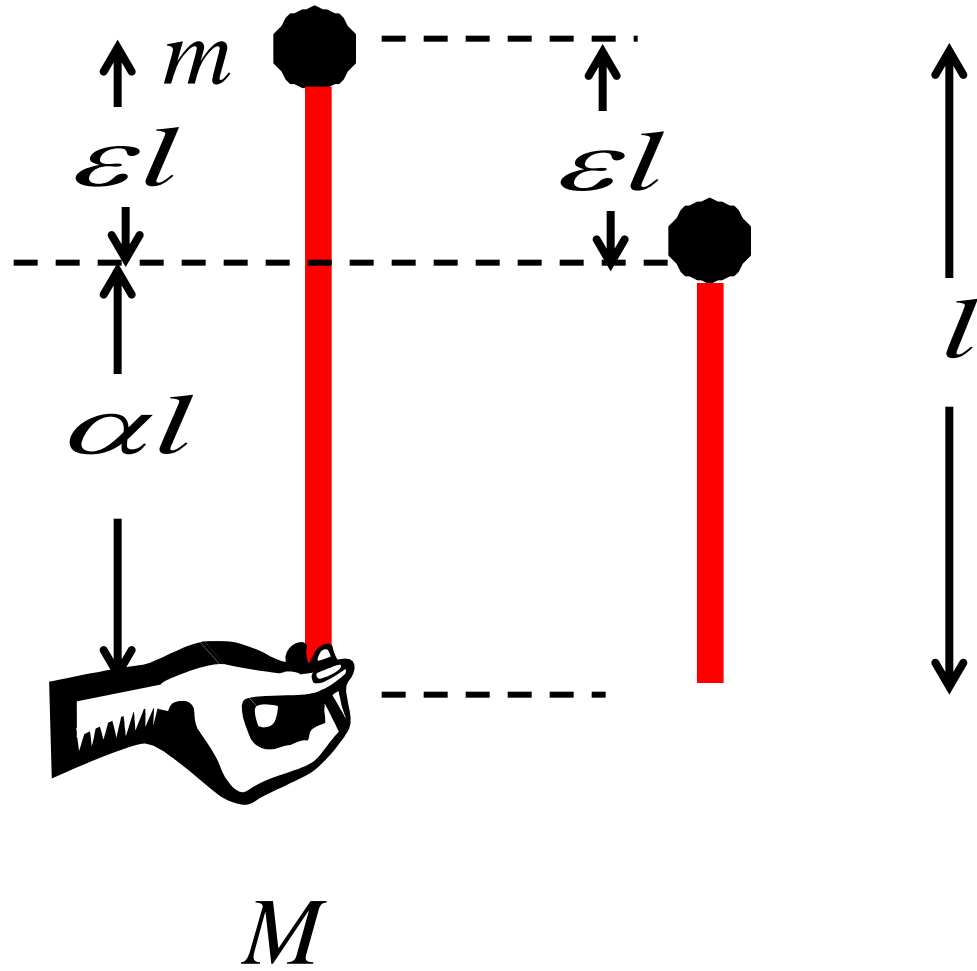
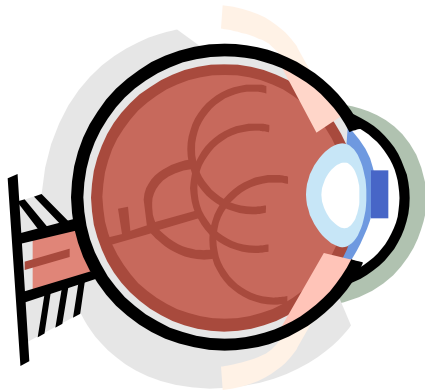
This is a cartoon,  
but can be made  
precise.



Eyes moved down is harder  
(RHP zero)  
Similar to delay



$$r = \frac{m}{M}$$



Compare

$$p = \sqrt{\frac{g}{l(1-\varepsilon)}} \sqrt{1+r} = p_0 \sqrt{\frac{1}{(1-\varepsilon)}} \approx p_0 \left(1 + \frac{\varepsilon}{2}\right)$$

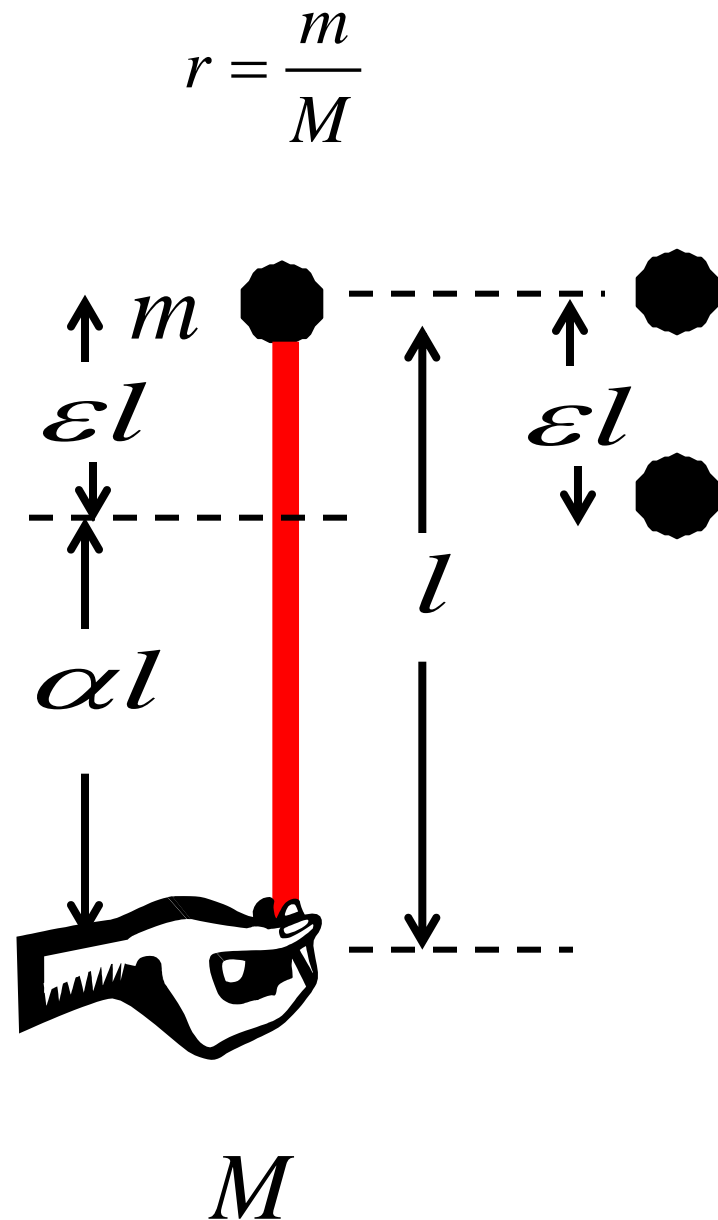
Move eyes

$$p = \sqrt{\frac{g}{l}} \sqrt{1+r} \quad r = \frac{m}{M} \quad z = \sqrt{\frac{g}{l}} \sqrt{\frac{1}{\varepsilon}}$$

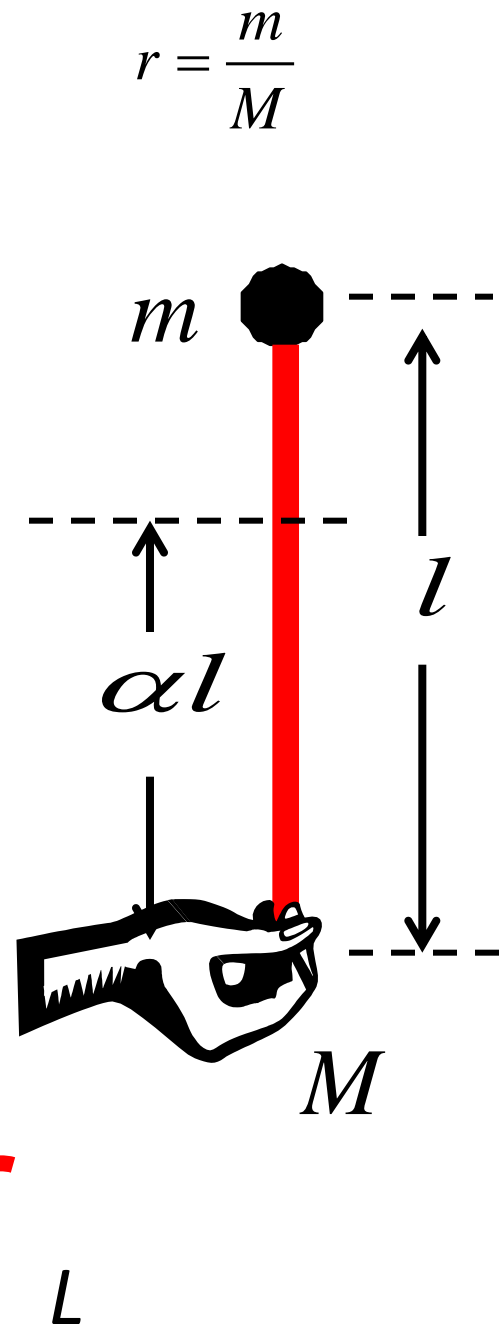
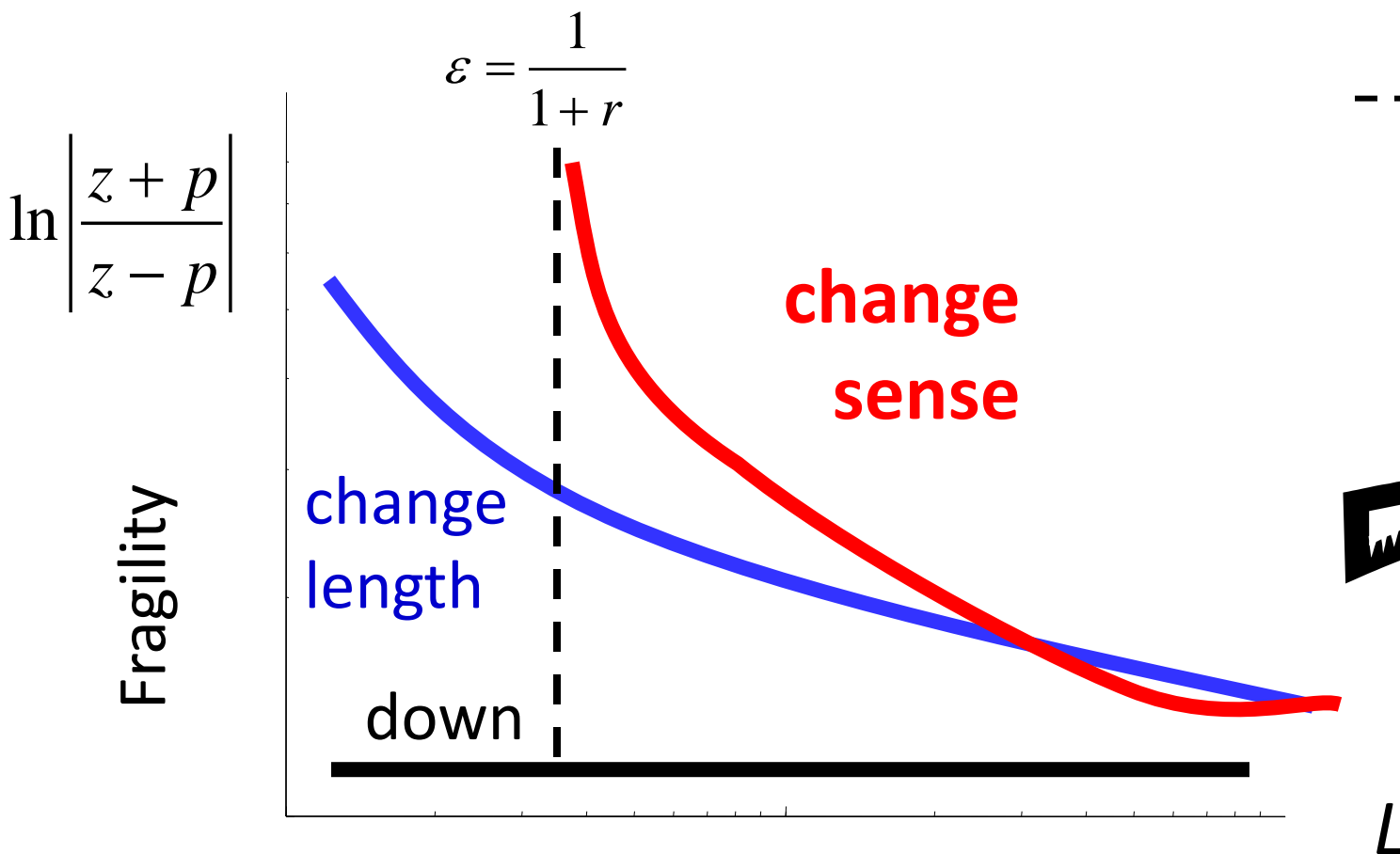
$$p = z \Rightarrow 1+r = \frac{1}{\varepsilon} \Rightarrow \varepsilon = \frac{1}{1+r}$$

$$p \left(1 + \frac{1}{3} \frac{p^2}{z^2}\right) = \sqrt{\frac{g}{l}} \sqrt{1+r} \left(1 + \frac{1}{3} \varepsilon\right) = p \left(1 + \frac{\varepsilon}{3}\right)$$

$$= p \left(1 + \frac{1-\alpha}{3}\right)$$



$$\frac{1}{\pi} \int_0^\infty \ln |S(j\omega)| \left( \frac{2z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z+p}{z-p} \right|$$



This is a cartoon, but can be made precise.



# Next (and last) time

- Universal laws in more depth
- Universal architectures revisited/compared
  - Computers and networks
  - Cells
  - Brains and minds
- Architecture & laws at the extremes
  - evolution
  - eusociality

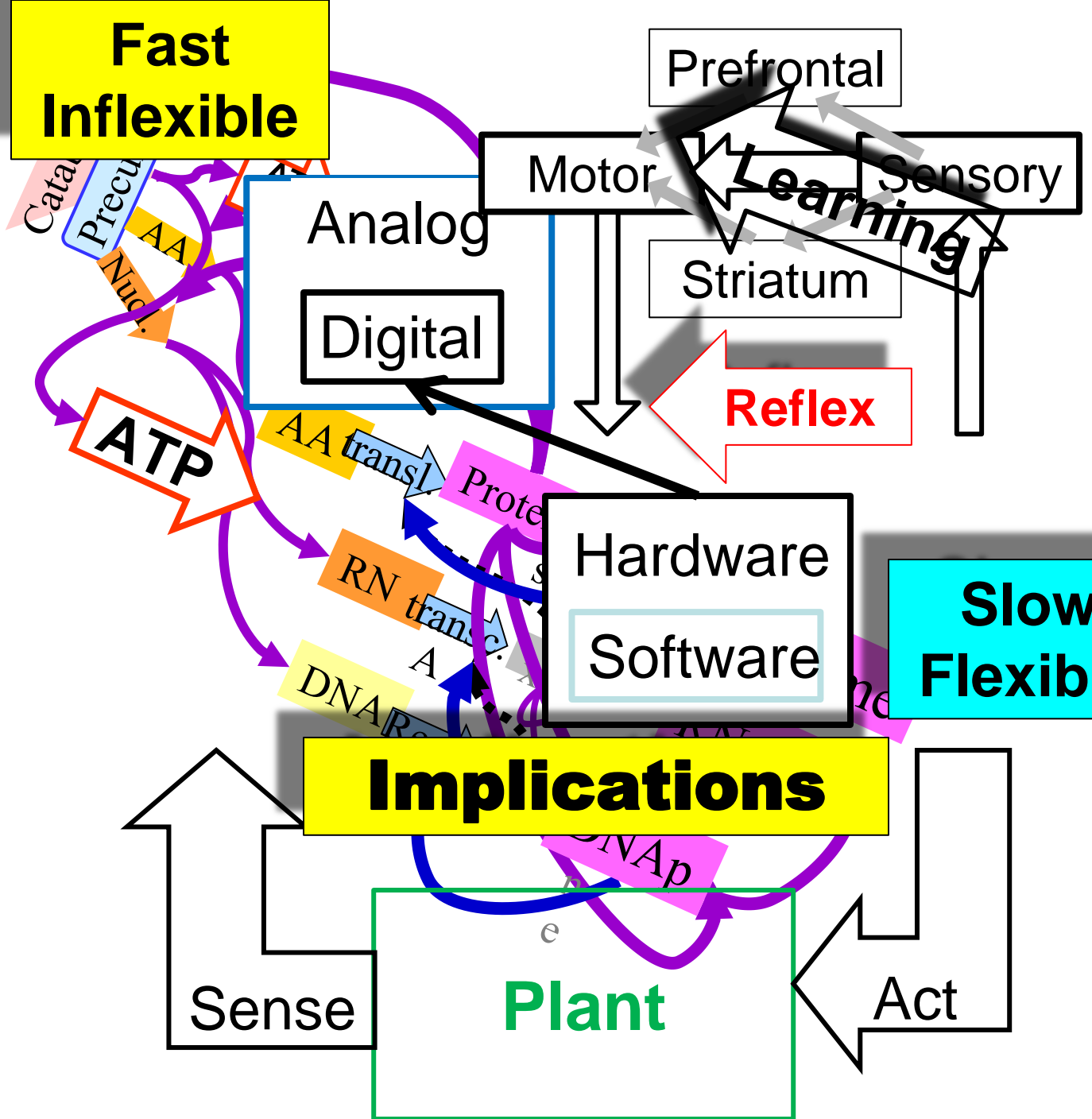
**Compute**

Turing

Delay is  
*most*  
important

Bode

**Control**

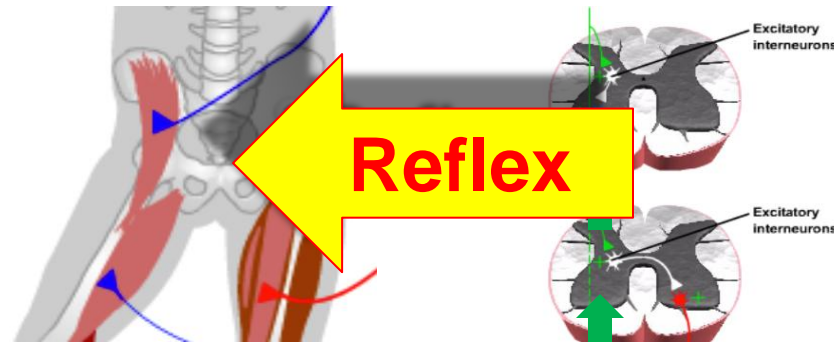


Wolpert, Grafton, etc

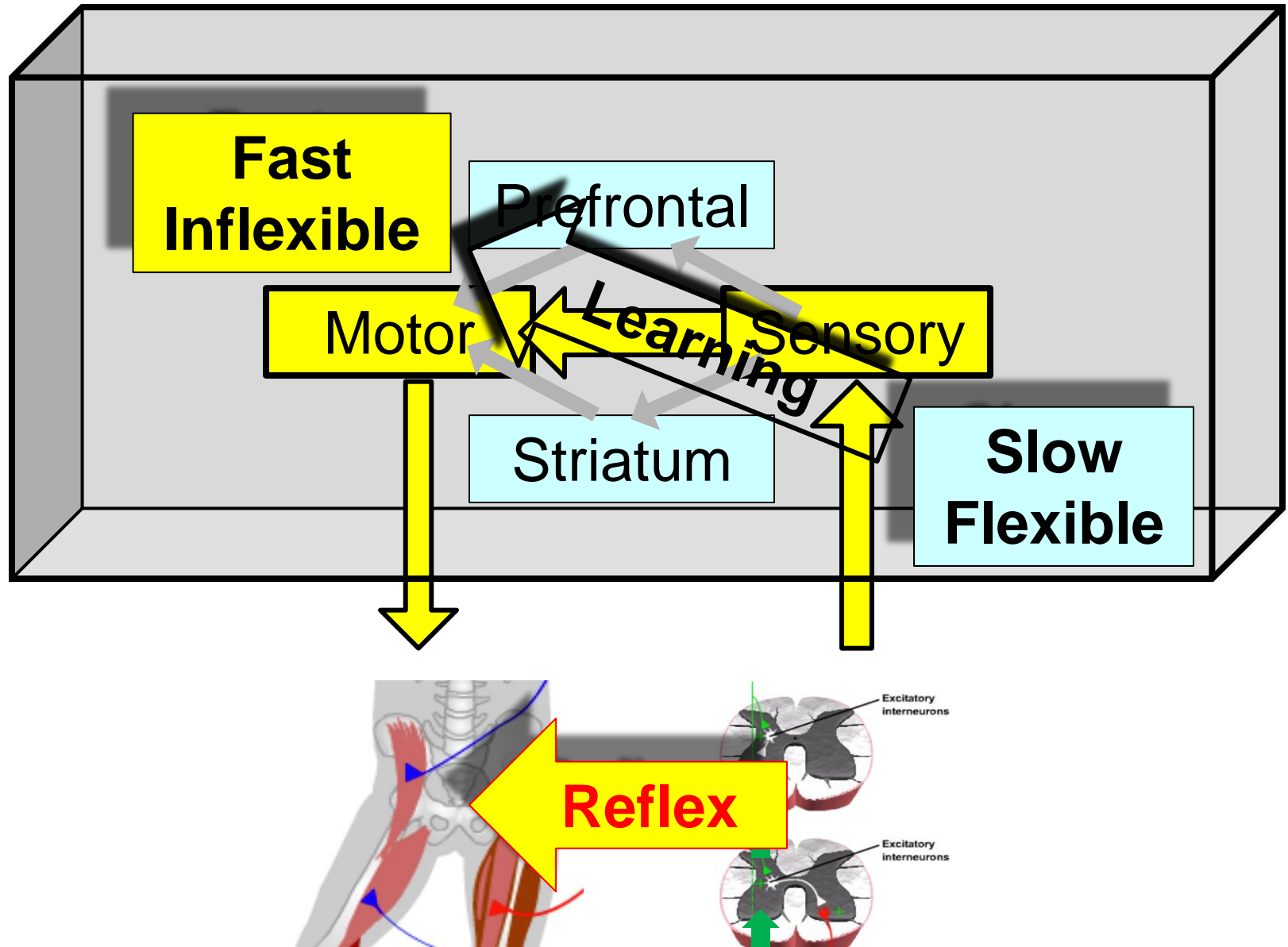
*robust*

Brain as ~~optimal~~ controller

- Acquire
- Translate/  
integrate
- **Automate**



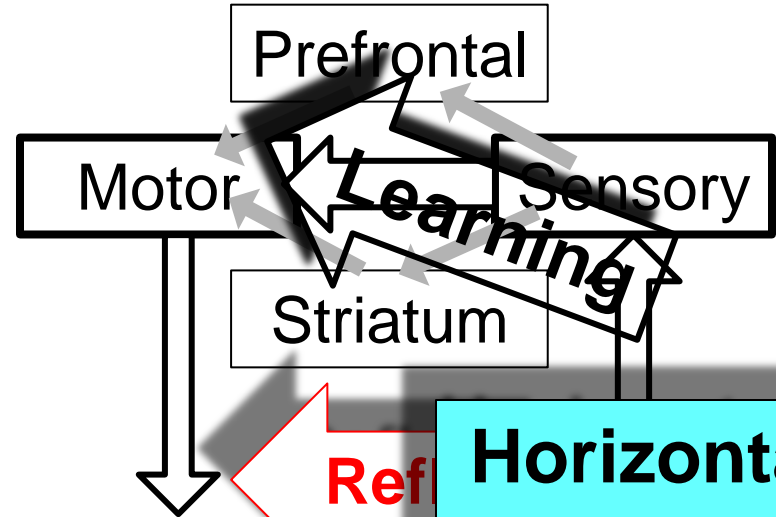
Going beyond black box: control is decentralized with internal delays.



**Depends  
crucially on  
layered  
architecture**

Analog

Digital



**Horizontal  
Meme  
Transfer**

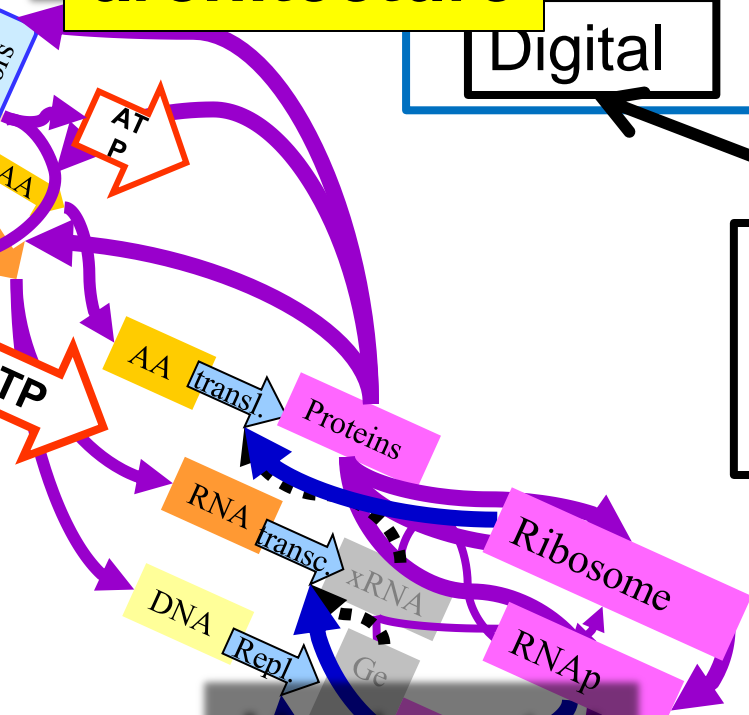
Hardware

Soft

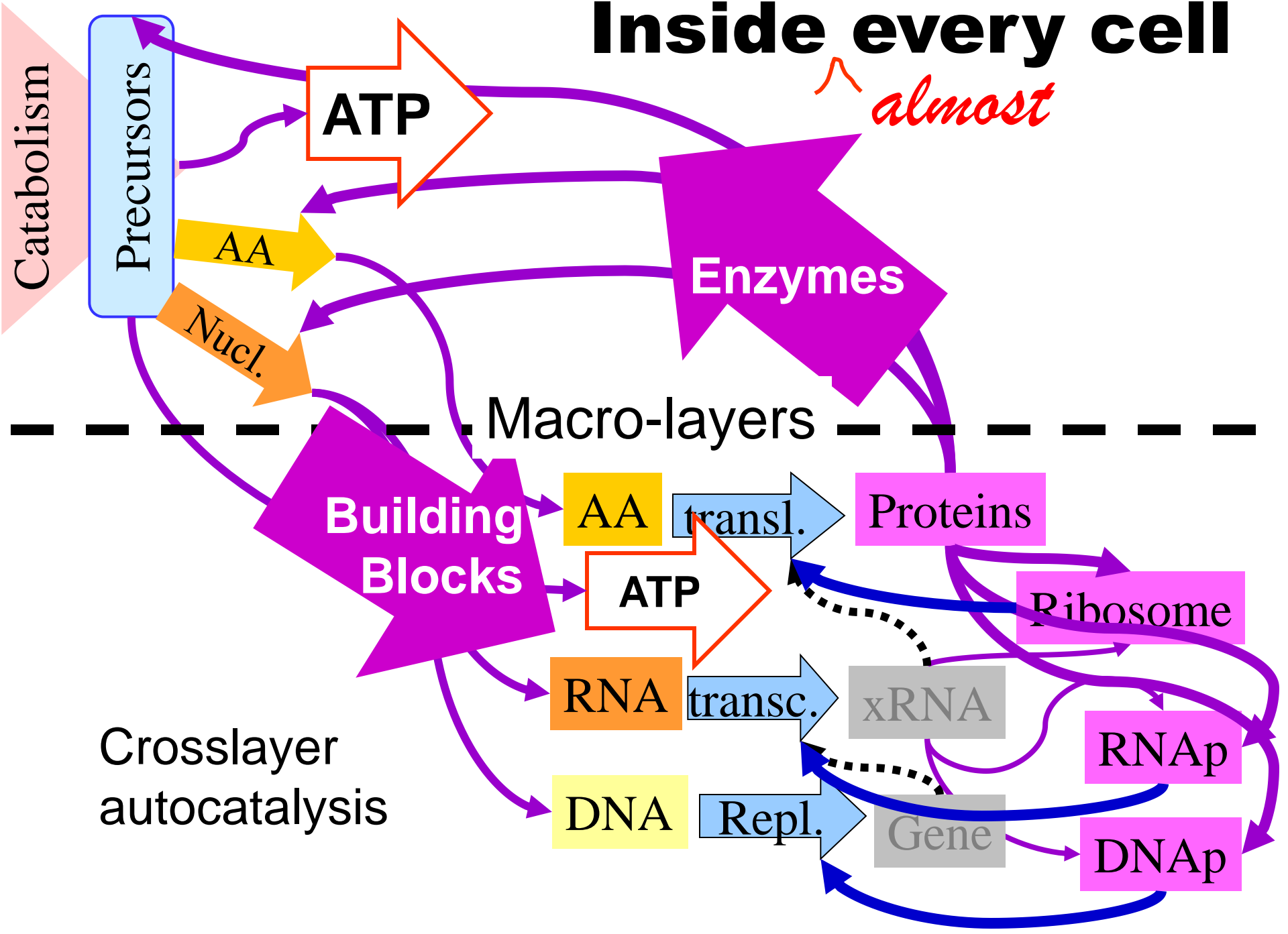
**Horizontal  
App  
Transfer**

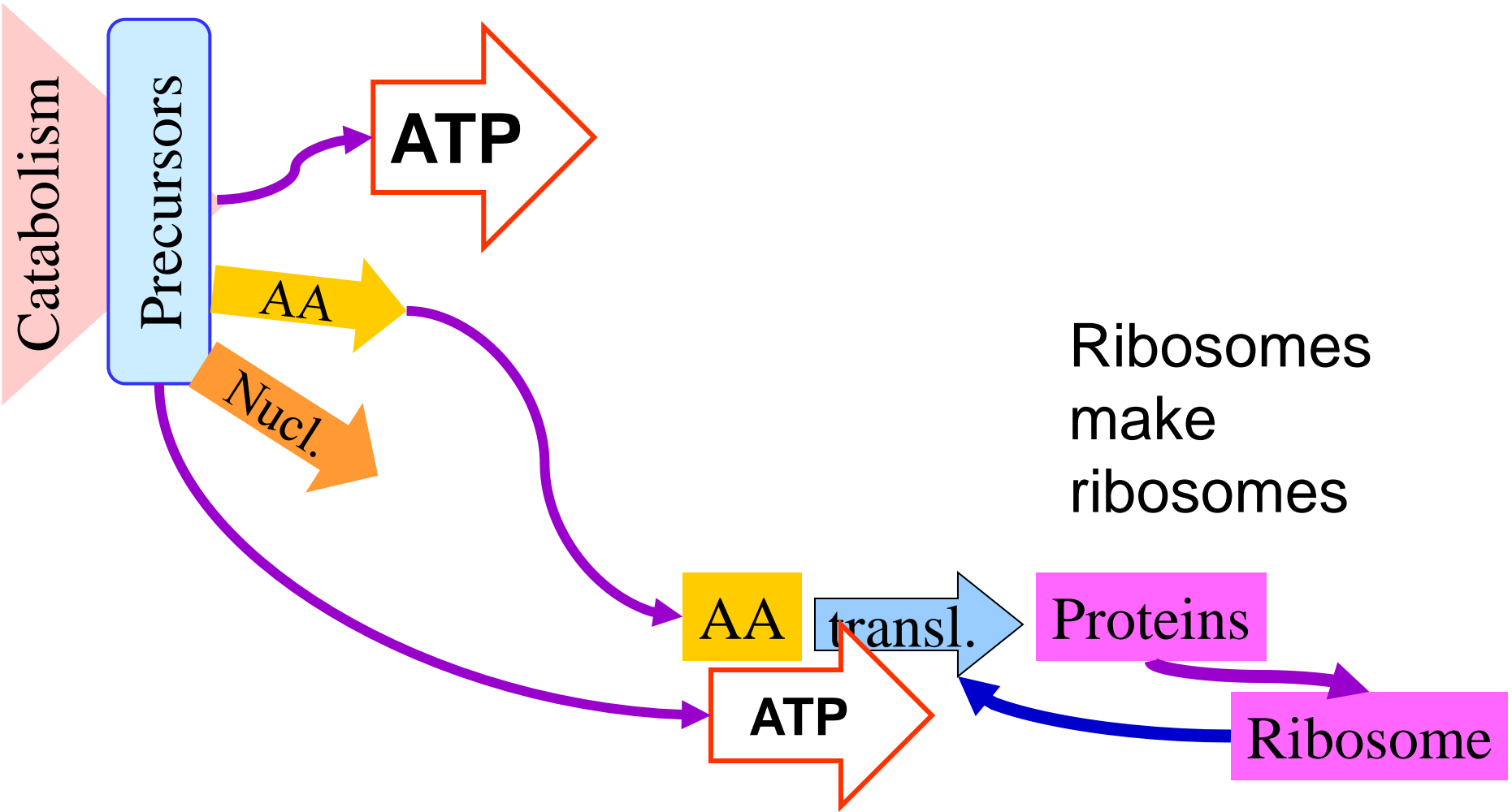
**Horizontal  
Gene  
Transfer**

**Amazingly  
Flexible/  
Adaptable**

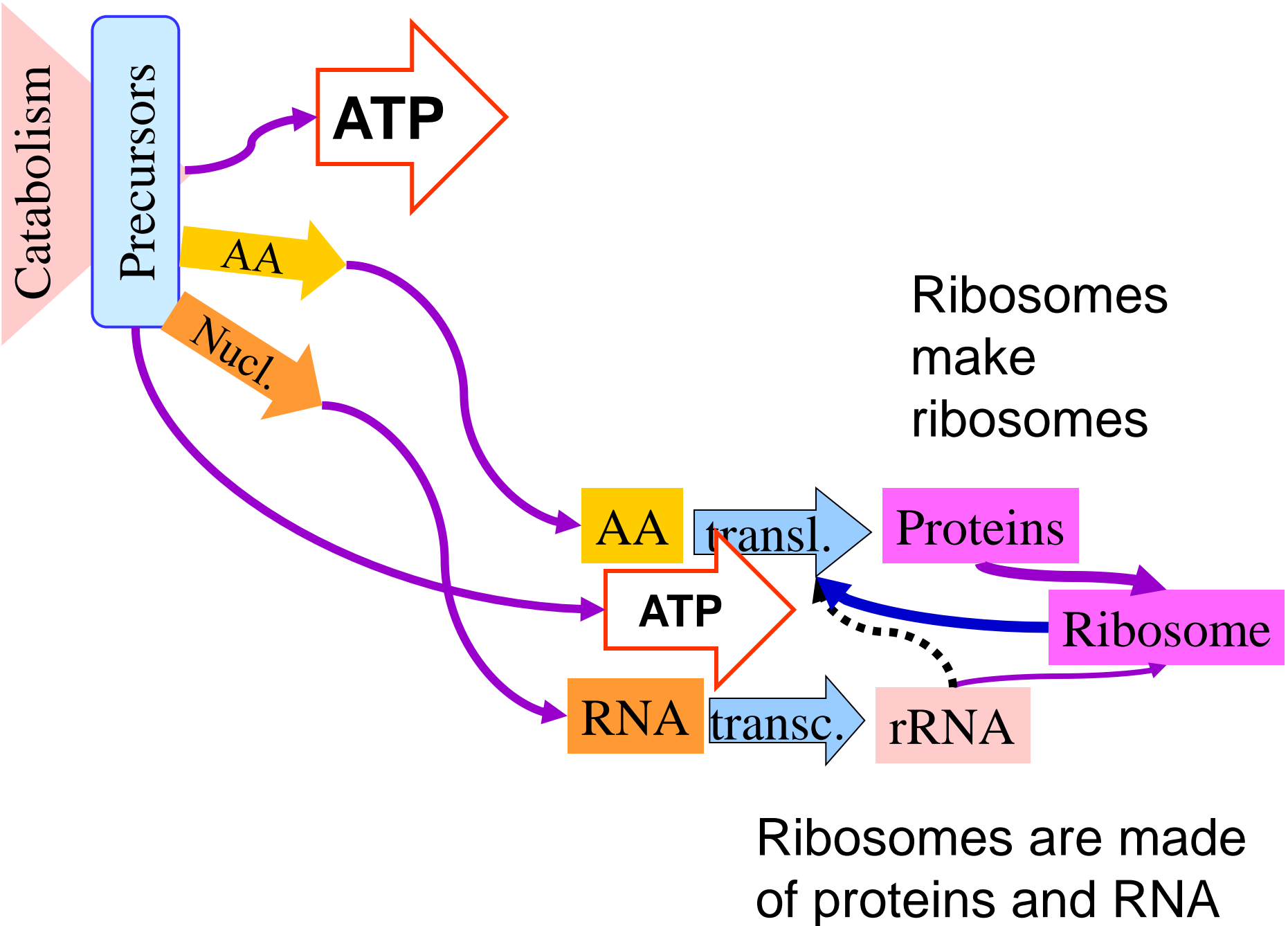


# Inside every cell





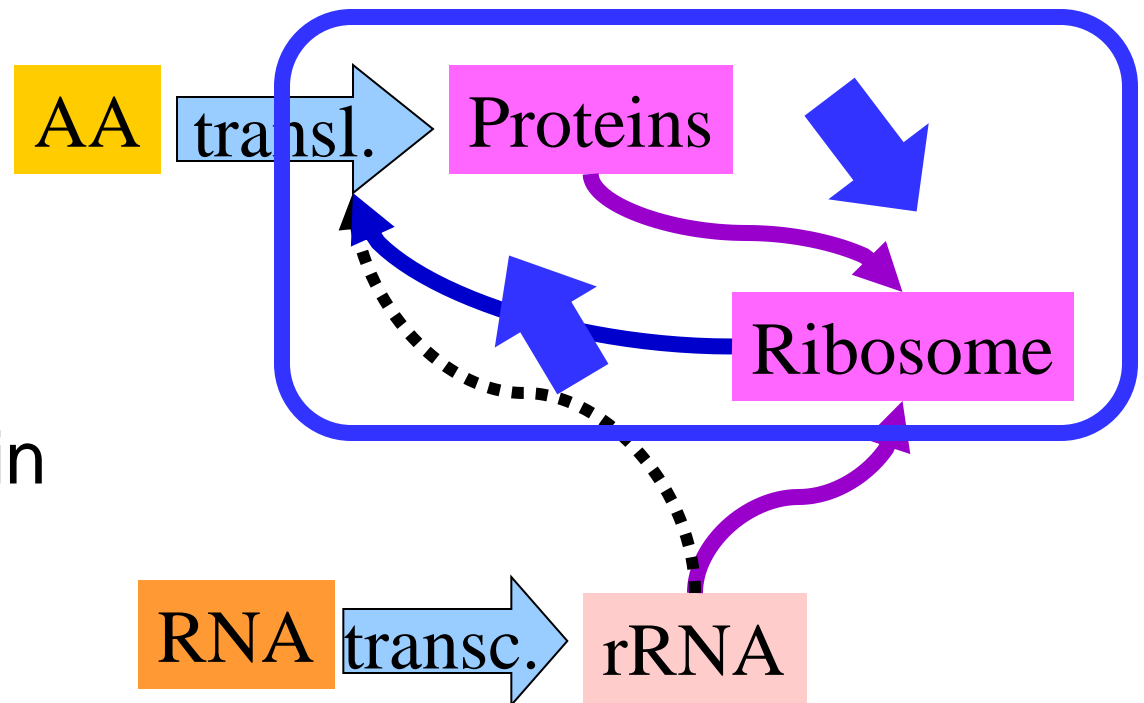
Translation: Amino acids  
polymerized into proteins





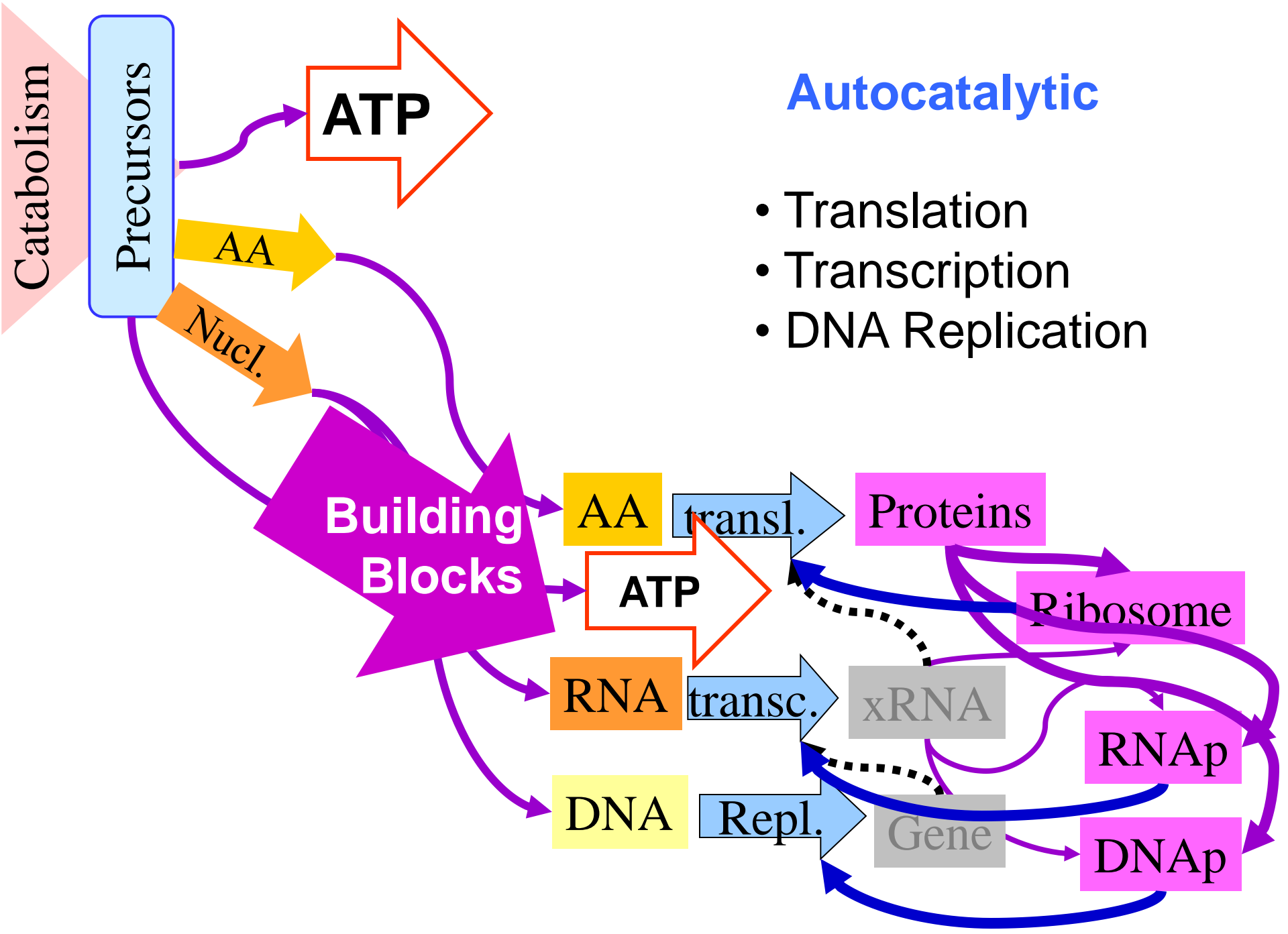
Ribosomes  
make  
ribosomes

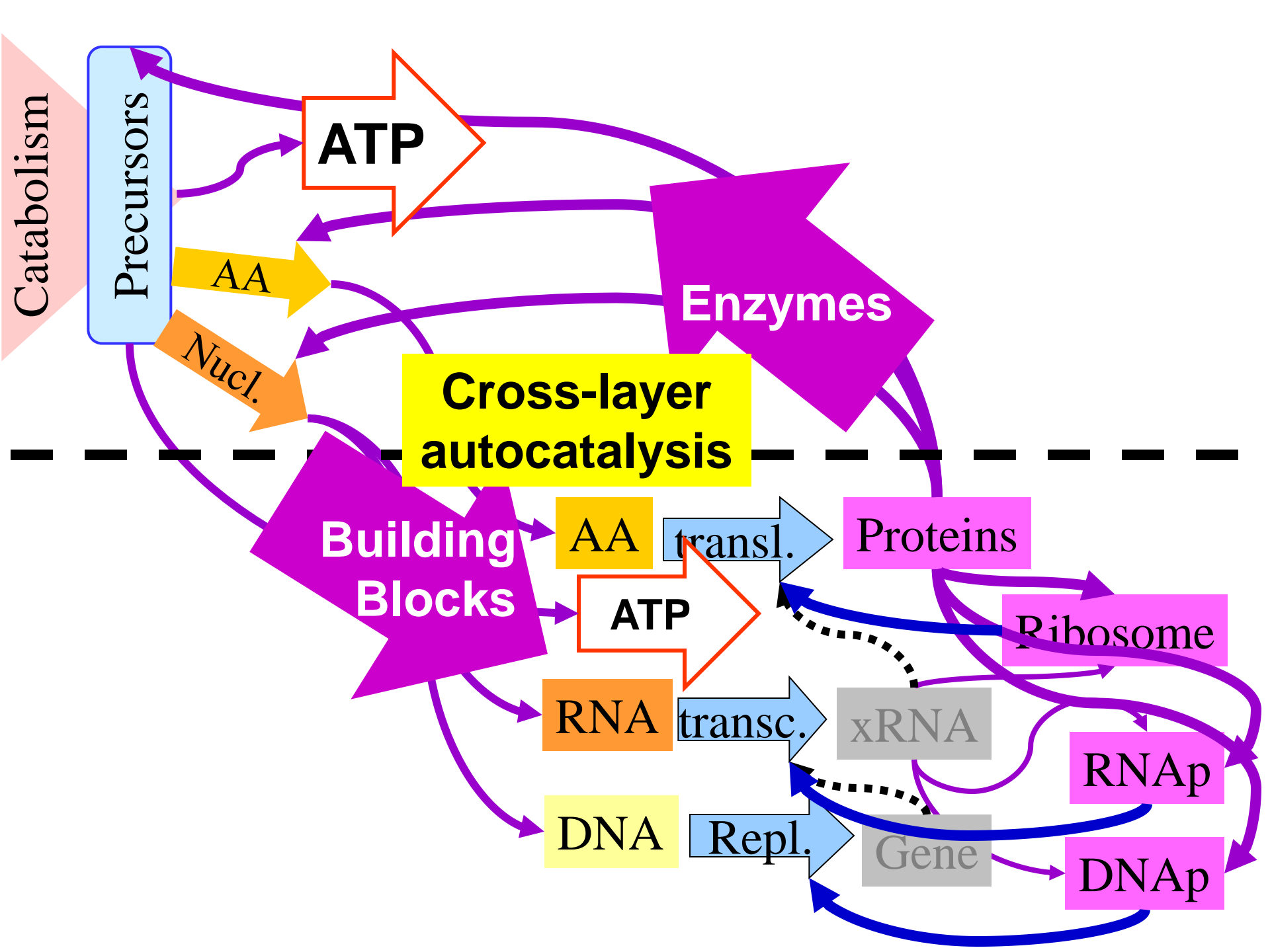
**Autocatalytic**

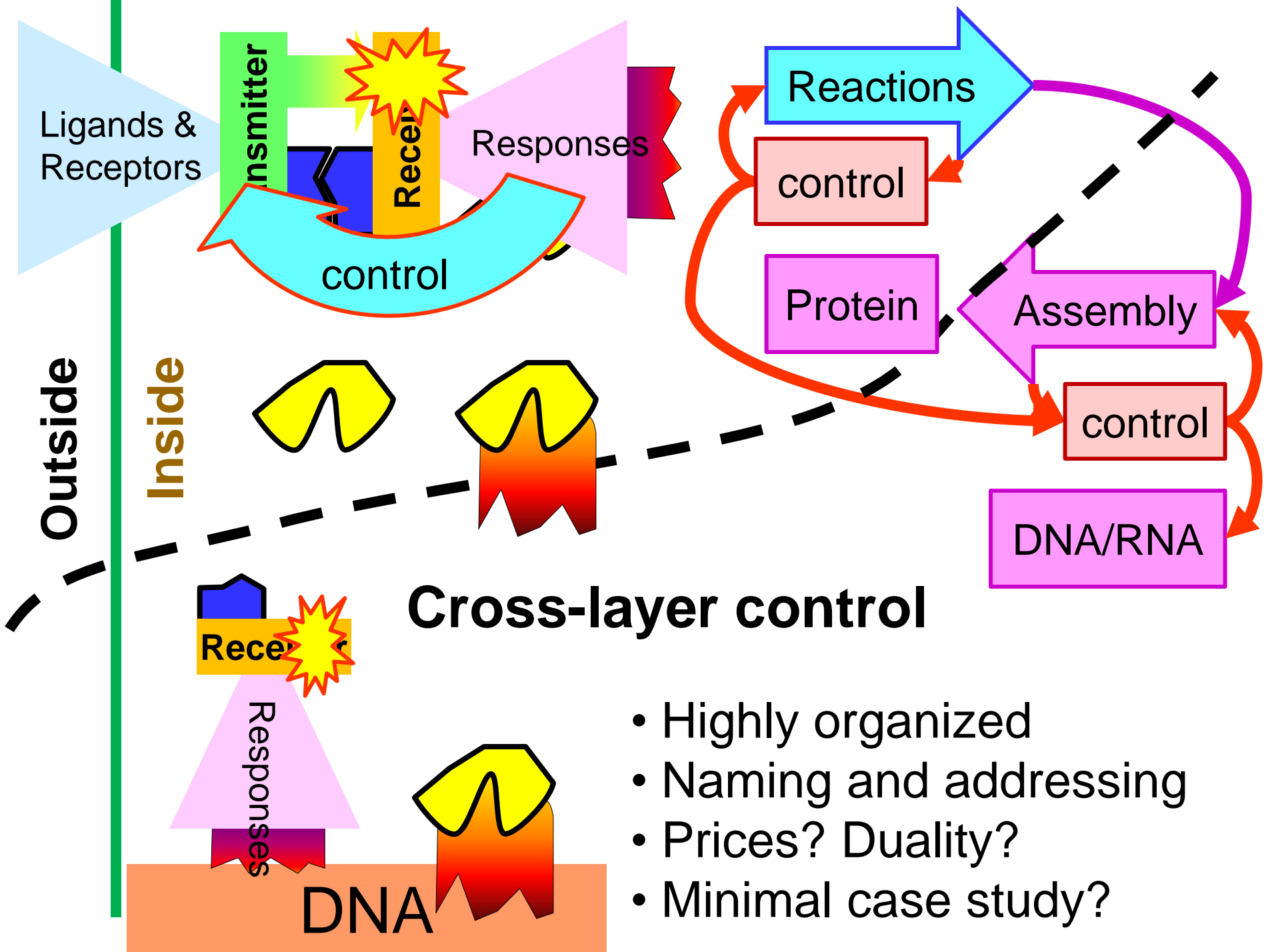


Organisms differ in  
the proportion of  
ribosomal protein  
vs rRNA

Ribosomes are made  
of proteins and rRNA





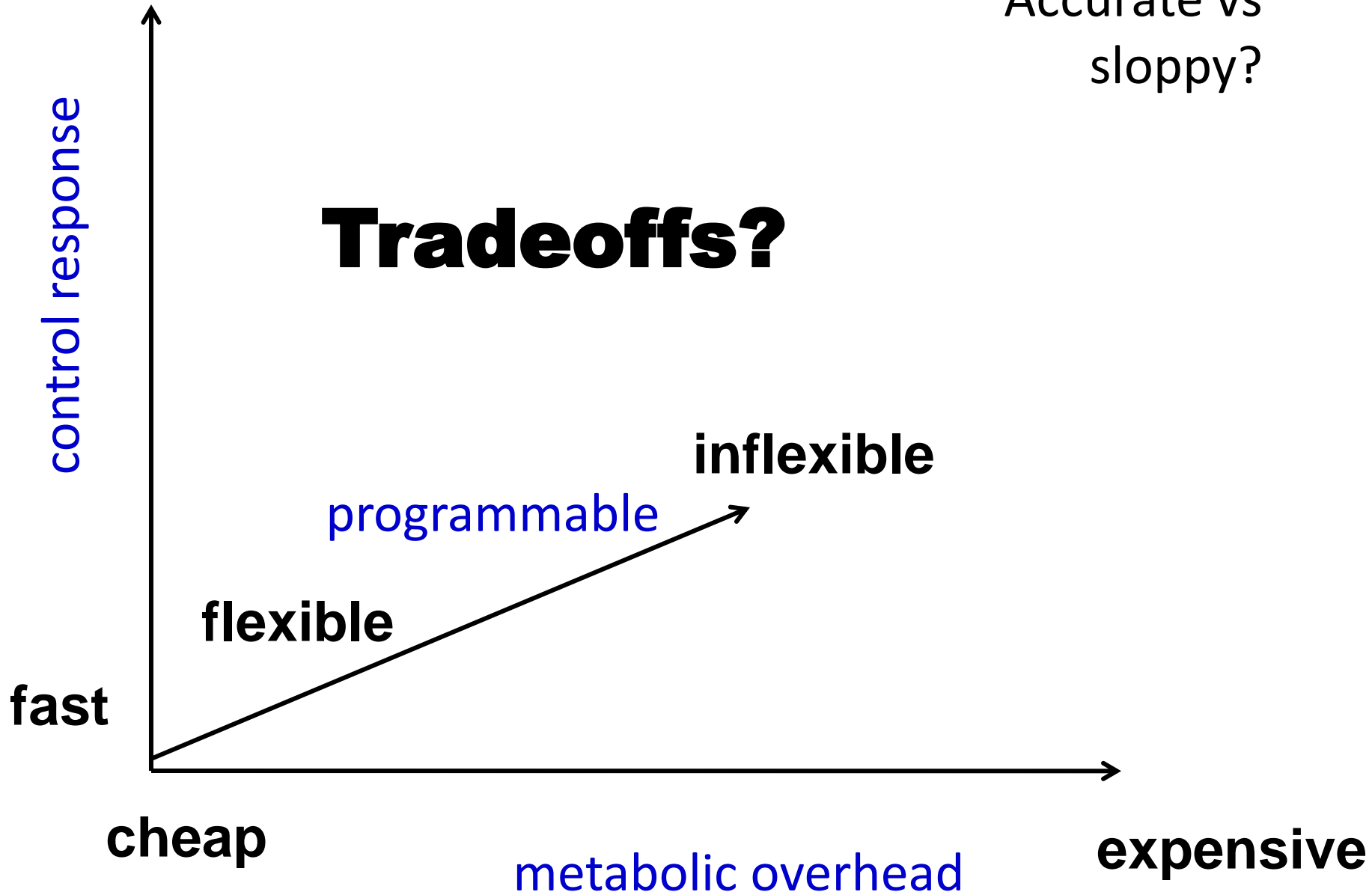


- Highly organized
- Naming and addressing
- Prices? Duality?
- Minimal case study?

**slow (  $\approx$  fragile)**

Accurate vs  
sloppy?

# Tradeoffs?



# Evolution and architecture

Nothing in biology makes sense except in the light of evolution

Theodosius Dobzhansky  
(see also de Chardin)

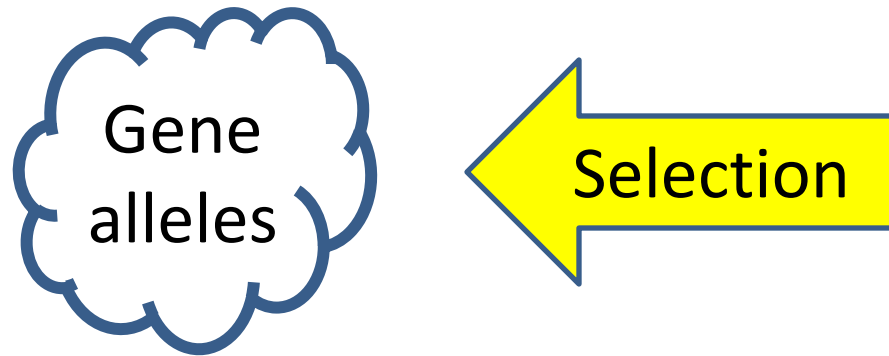
Nothing in evolution makes sense except in the light of biology

?????

Standard theory:

natural selection + genetic drift  
+ mutation + gene flow

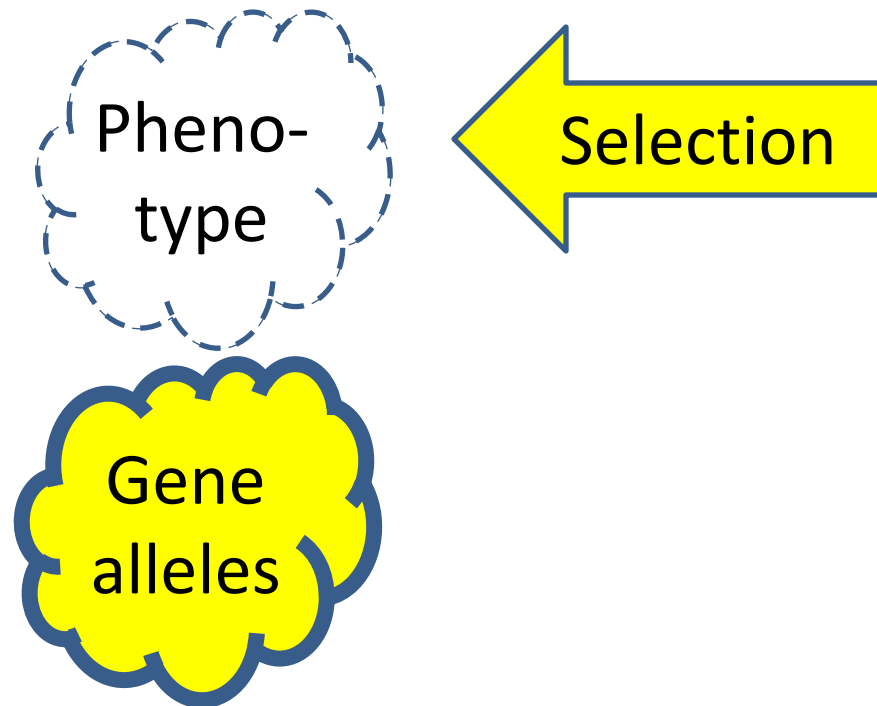
Greatly abridged cartoon here



Shapiro explains well what this is and why it's incomplete (but Koonin is more mainstream)

Standard theory:

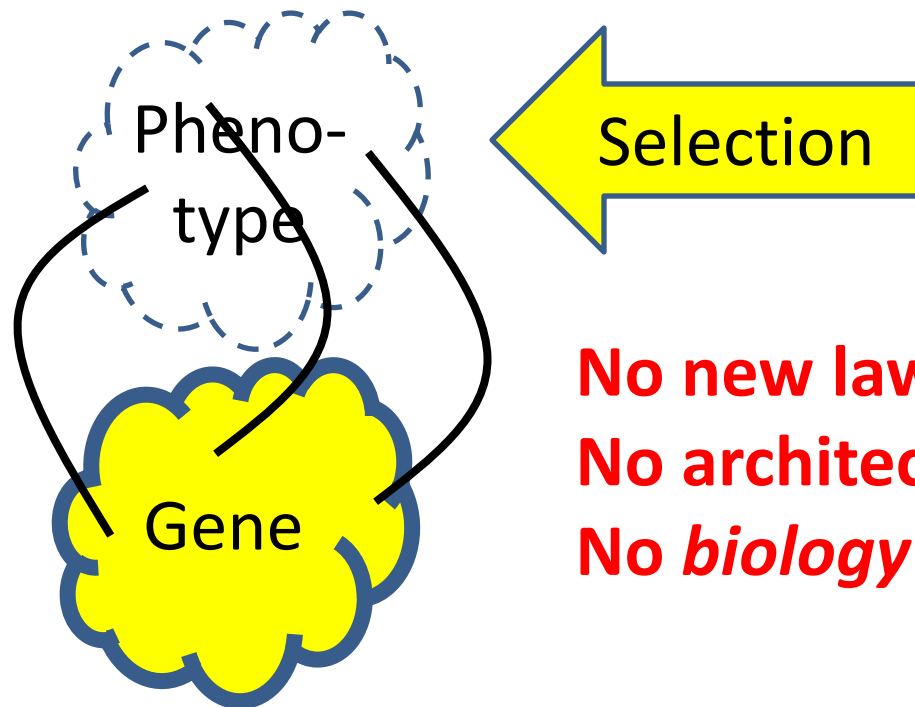
selection + drift + mutation + gene flow





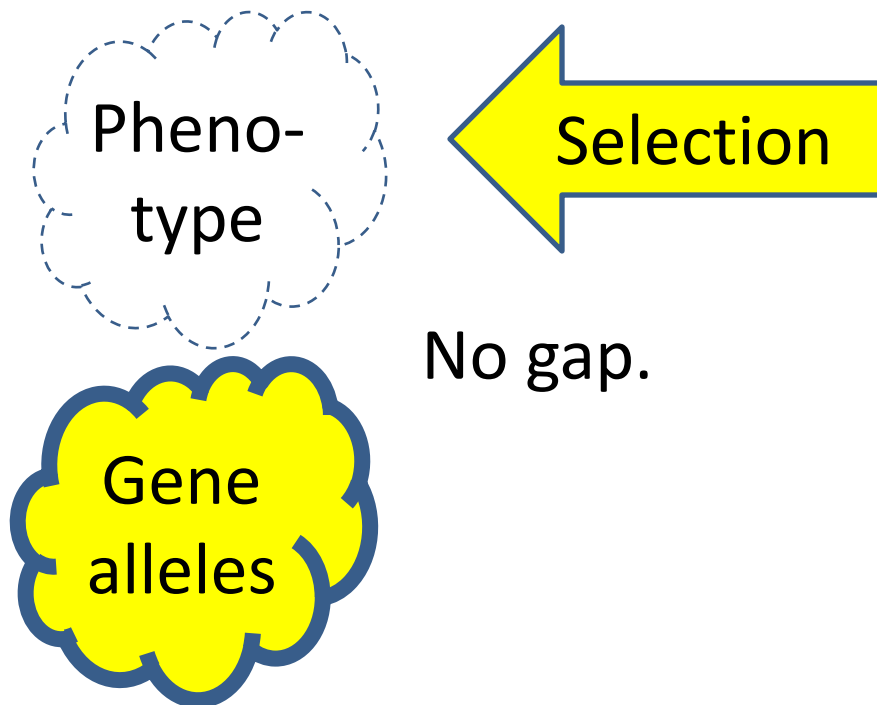
Standard theory:

selection + drift + mutation + gene flow



**No new laws.**  
**No architecture.**  
**No *biology*.**

selection +  
drift +  
mutation +  
gene flow



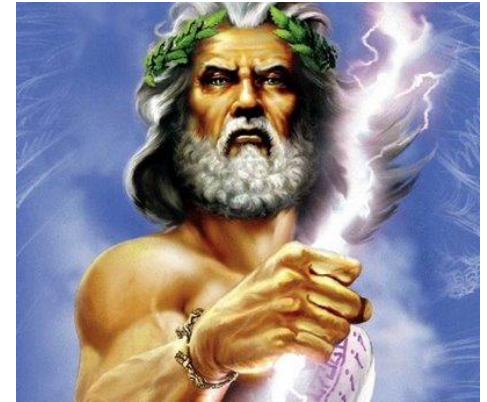
***All complexity is emergent from random ensembles with *minimal* tuning .***

**No new laws.**

**No architecture.**

# The battleground

Pheno-  
type



Huge gap.  
Need  
supernatural

Genes?

Pheno-  
type

No gap.  
Just physics.

Gene  
alleles

# What they agree on

**No new laws.**  
**No architecture.**  
**No biology.**

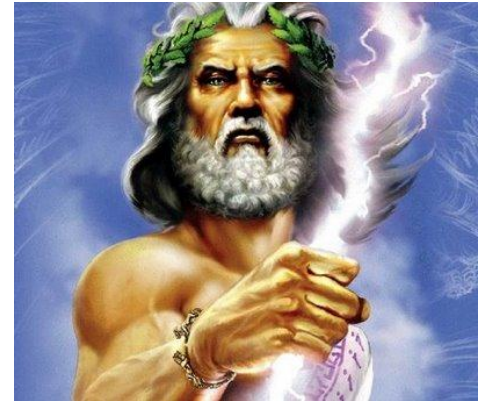
Pheno-  
type

Pheno-  
type

No gap.

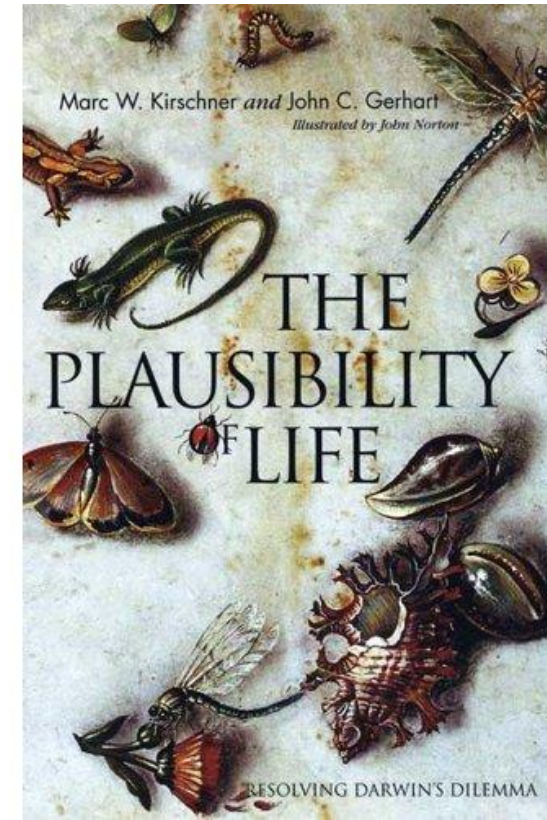
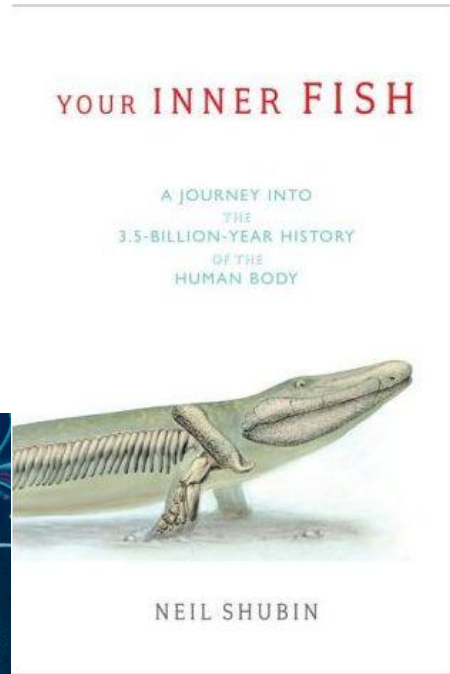
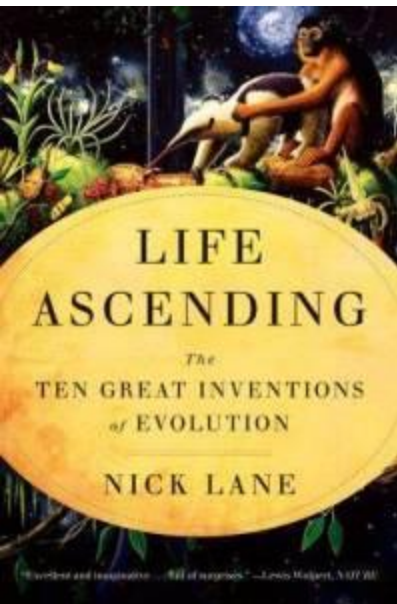
Gene  
alleles

Huge  
gap.

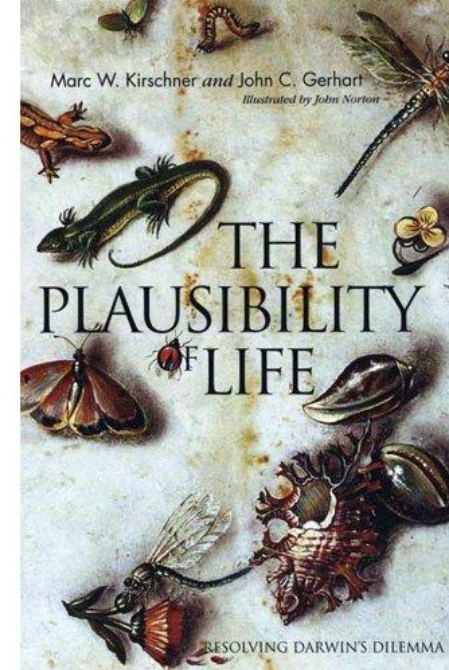
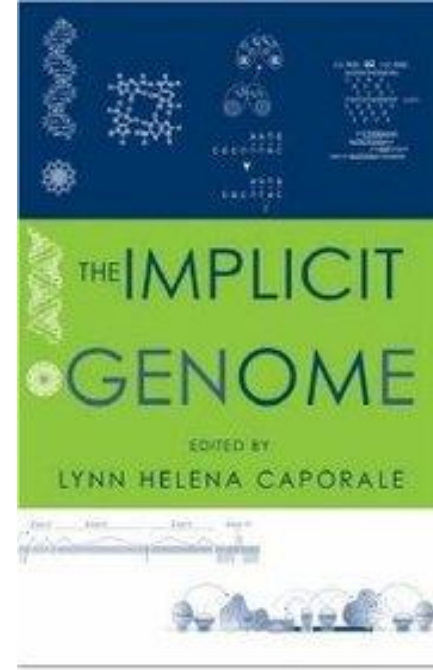
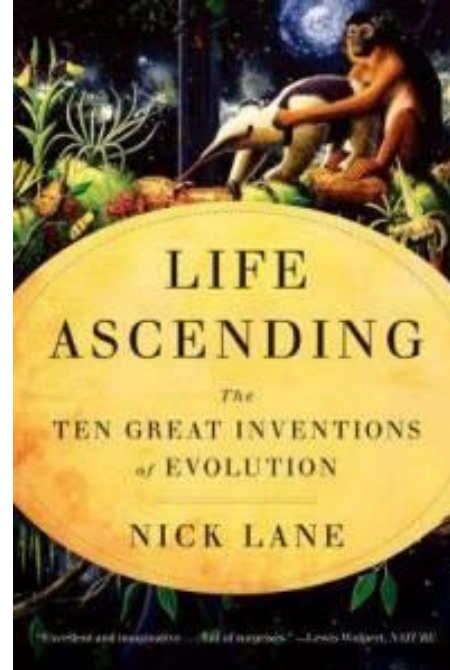
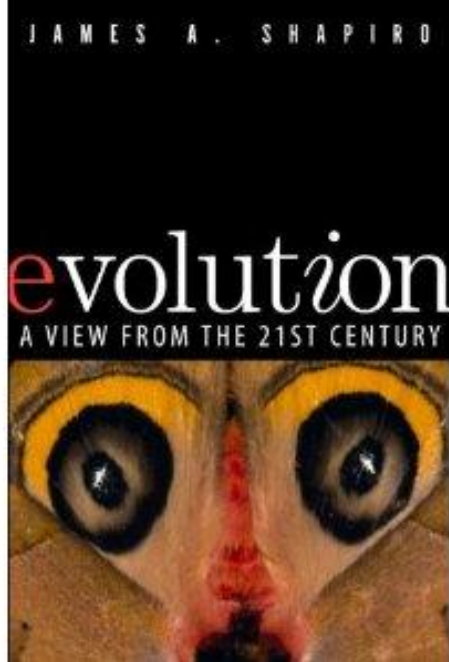


Genes

# Putting biology back into evolution







## The heresies

- Many mechanisms for “horizontal” gene transfer
- Many mechanisms to create large, functional mutations
- At highly variable rate, can be huge, global
- Selection alone is a very limited filtering mechanism
- Mutations **can** be “targeted” within the genomes
- **Can** coordinate DNA change w/ useful adaptive needs
- Viruses **can** induce DNA change giving heritable resistance
- Still myopic about future, still produces the grotesque

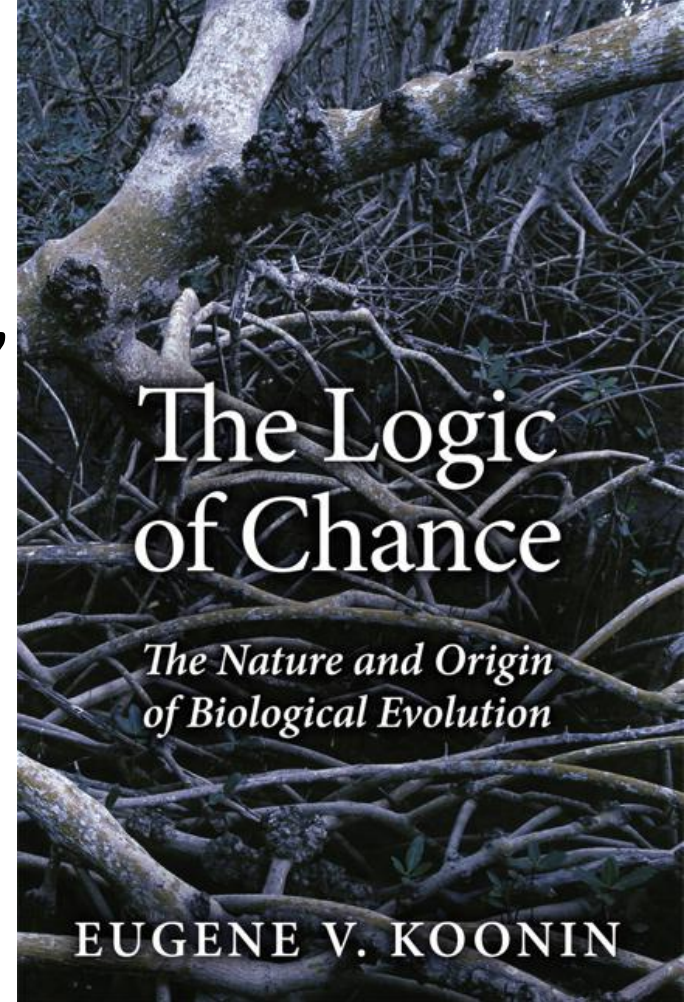
# THE SOCIAL CONQUEST OF EARTH



EDWARD  
O. WILSON

WINNER of the PULITZER PRIZE

**Surprising  
heresies from  
“conservatives”**



## The Logic of Chance

*The Nature and Origin  
of Biological Evolution*

EUGENE V. KOONIN

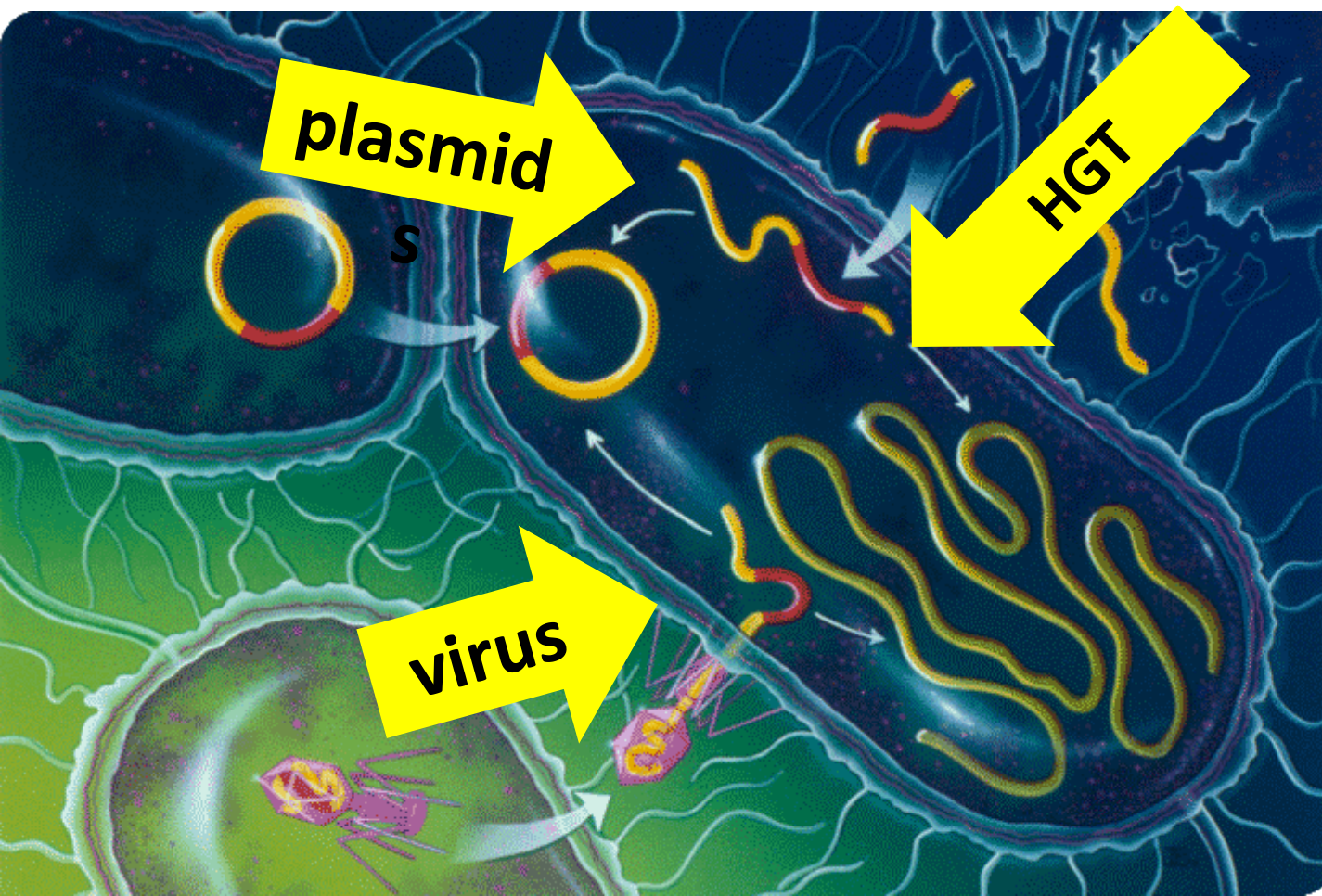
~~kin selection~~

~~modern synthesis~~





selection + drift + mutation + gene flow  
**+ facilitated *variation***

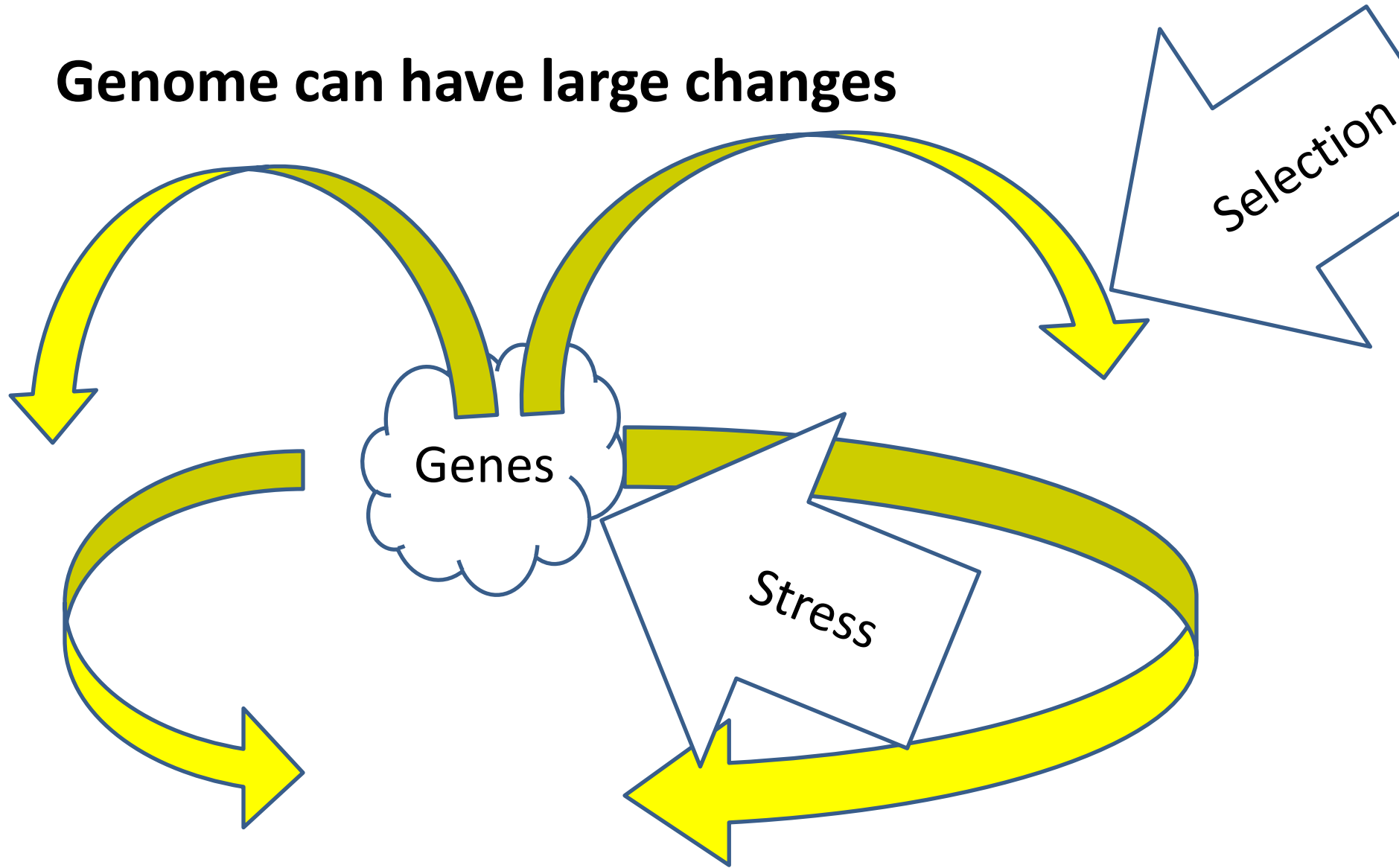


large  
functional  
changes in  
genomes

HGT  
= horizontal  
gene transfer

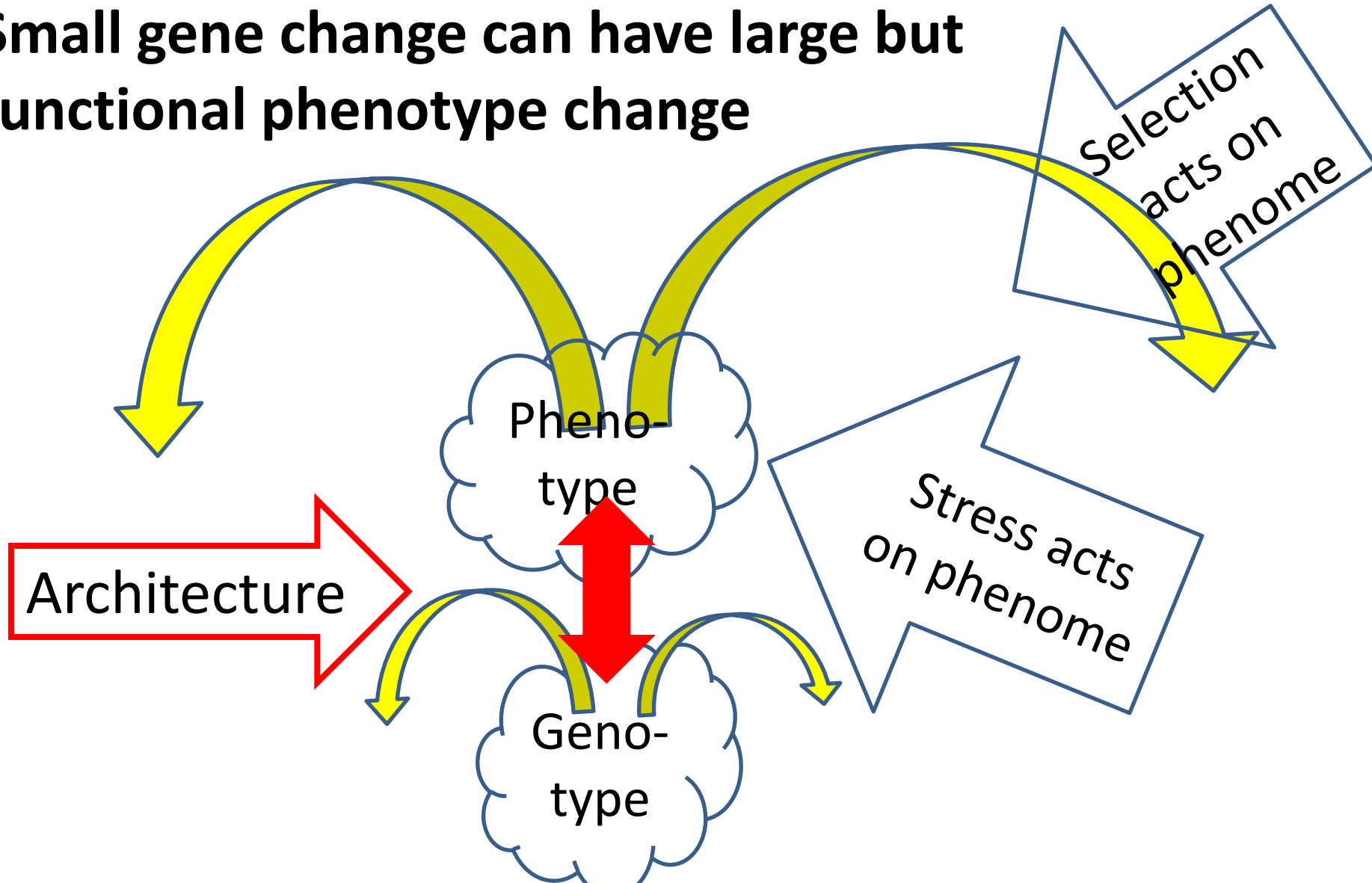
natural selection + genetic drift + mutation + gene flow  
+ facilitated *variation*

**Genome can have large changes**



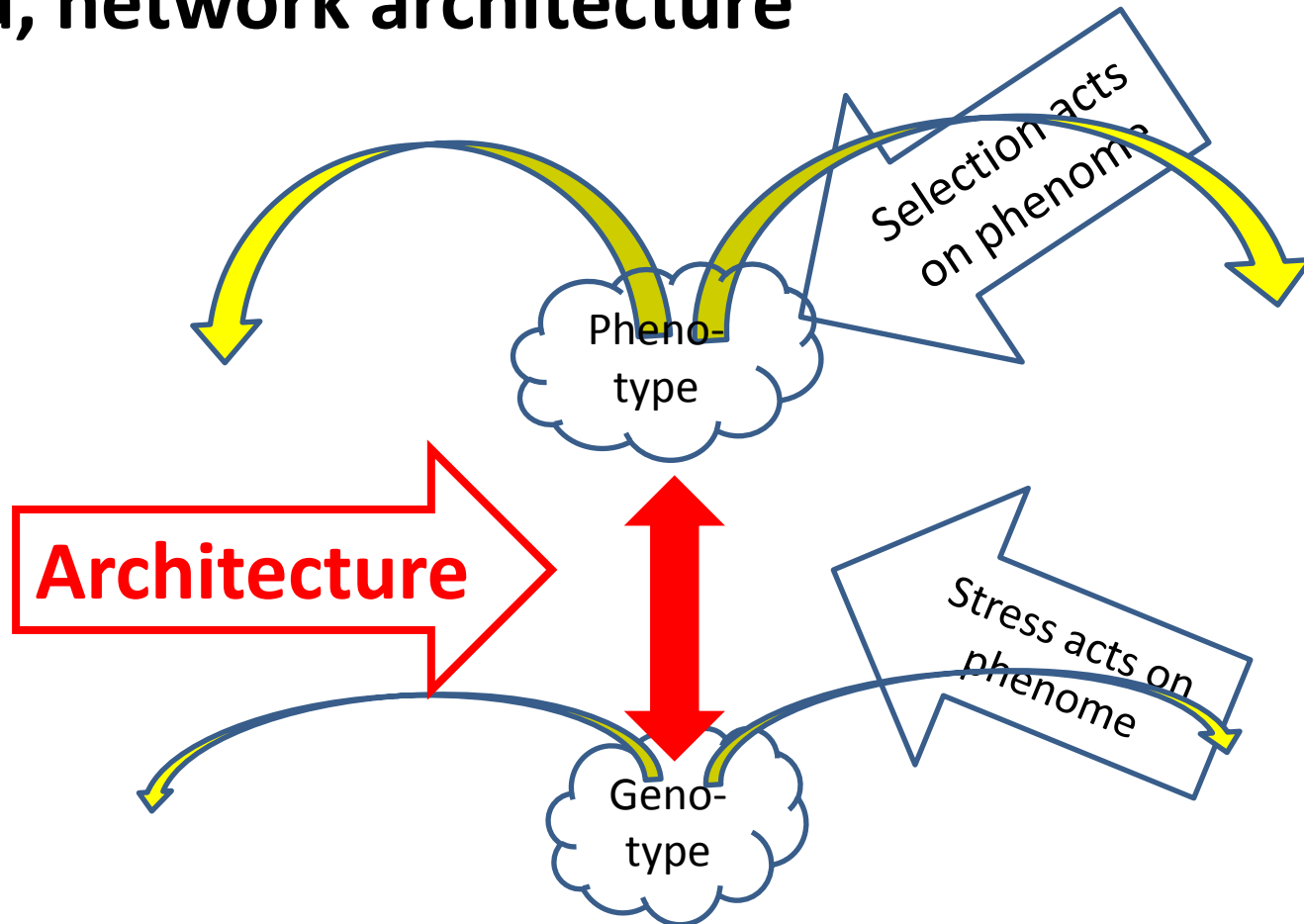
natural selection + genetic drift + mutation + gene flow  
+ facilitated *variation*

**Small gene change can have large but  
functional phenotype change**



natural selection + genetic drift + mutation + gene flow  
+ facilitated *variation*

**Only possible because of shared,  
layered, network architecture**



# Reading?

- See refs in 2011 *PNAS* paper but also...
- Turing: Gallistel (+ Wolpert on control/bayes)
- Brain/Mind: Gazzaniga, Kahneman + Reyna/Brainerd, Ashby, Cosmides/Tooby,...
- Evolution: Gerhart & Kirschner, Shapiro, Lane, Koonin, Caporale (+ fire + running)
- Apes: De Waal (Bonobos), Sapolsky (Baboons)
- Eusociality: Wilson
- Juarrero