Universal laws and architecture 3:
Foundations for Sustainable Infrastructure

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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.

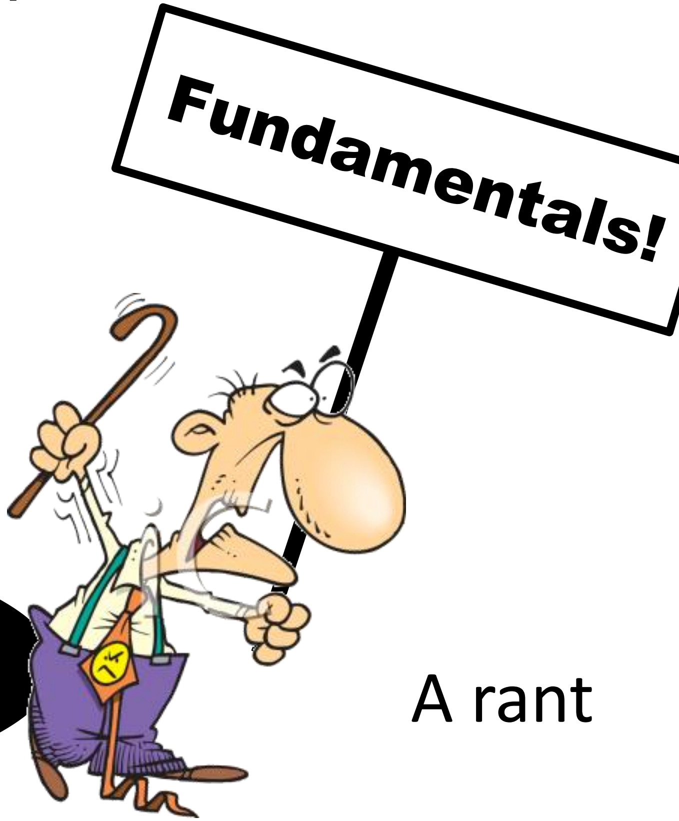
1950, Computing Machinery and Intelligence, *Mind*

“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?

Systems



A rant

- Turing 100th 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

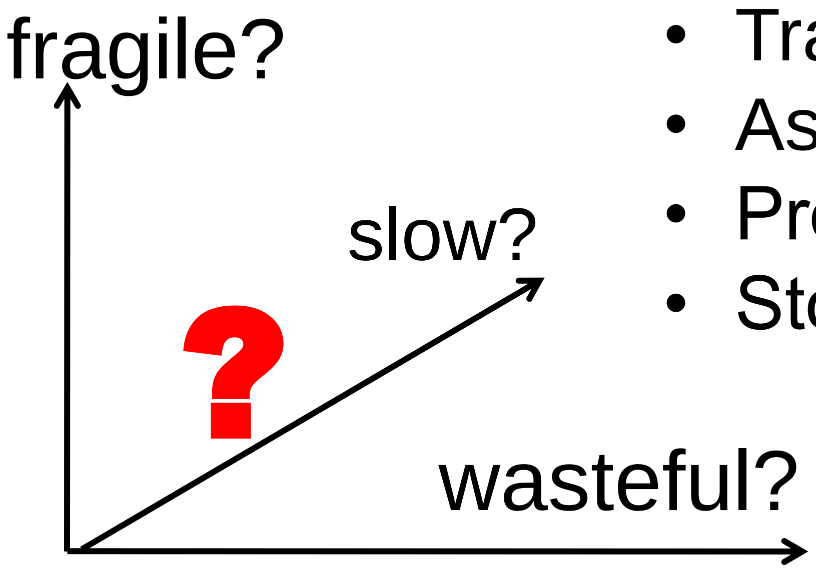
Control

Comms

Bode

Shannon

- Each theory ≈ one dimension
- Tradeoffs ***across*** dimensions
- Assume architectures a priori
- Progress is encouraging, but…
- Stovepipes are an obstacle…



Carnot

Turing

Boltzmann

Godel

Heisenberg

Compute

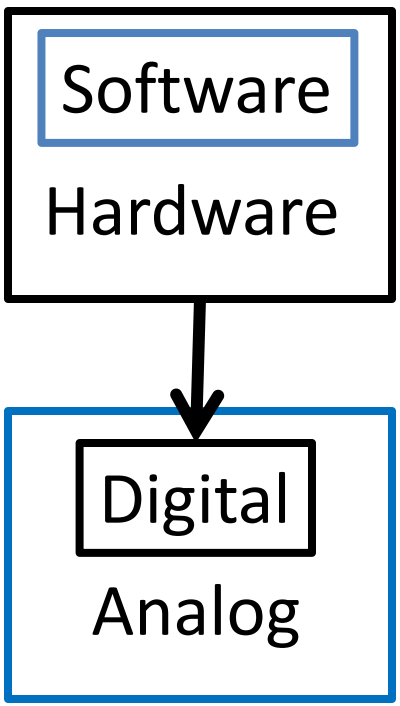
Physics

Einstein

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?)

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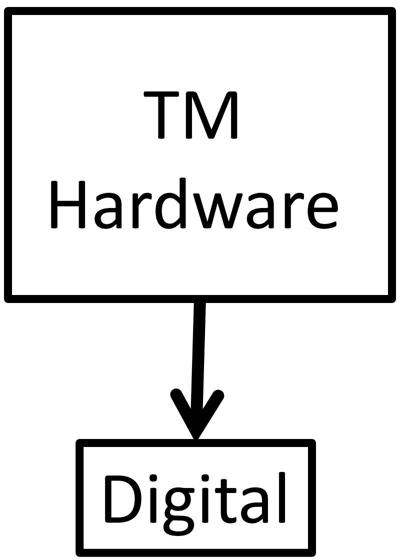

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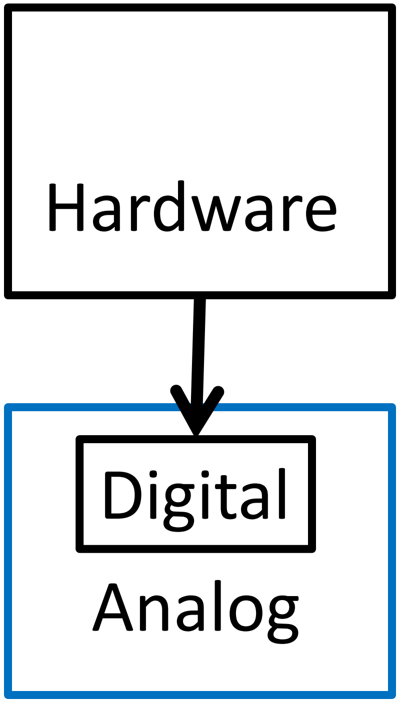
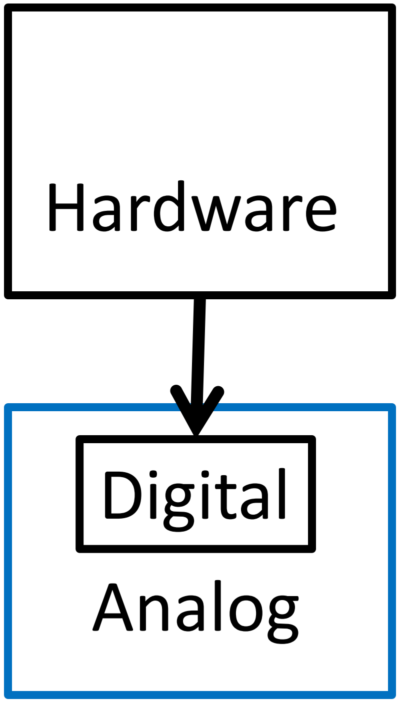


- …being digital should be of greater interest than that of being electronic. That it is electronic is certainly important because these machines owe their high speed to this… But this is virtually all that there is to be said on that subject.
- That the machine is digital however has more subtle significance.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

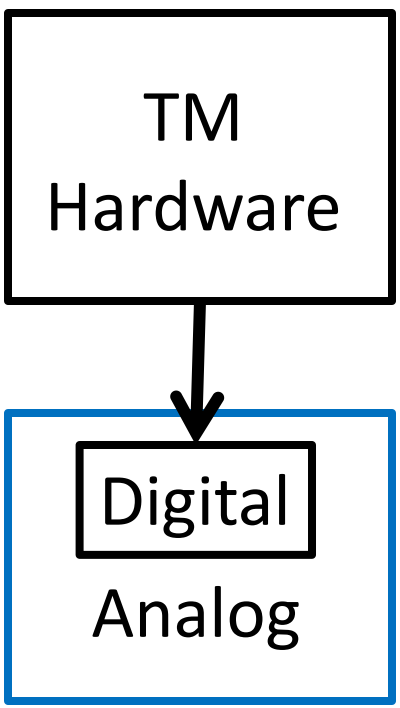
1947 Lecture to LMS



- … 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
- Repeatable

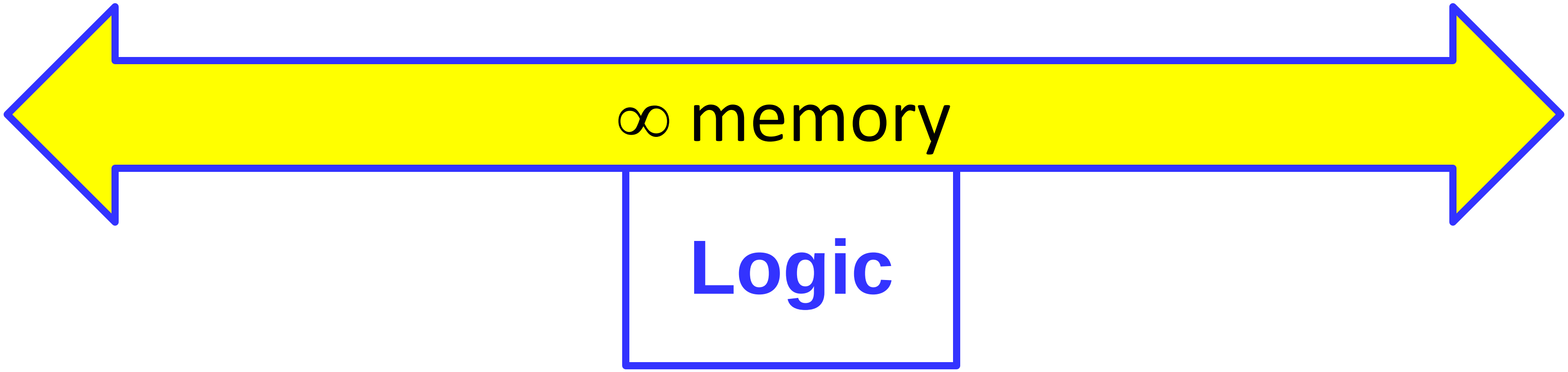
- … quite small errors in the initial conditions can have an overwhelming effect at a later time. The displacement of a single electron by a billionth of a centimetre at one moment might make the difference between a man being killed by an avalanche a year later, or escaping.

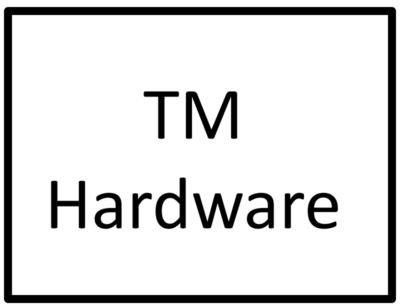
1950, Computing Machinery and Intelligence, *Mind*

- … 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:

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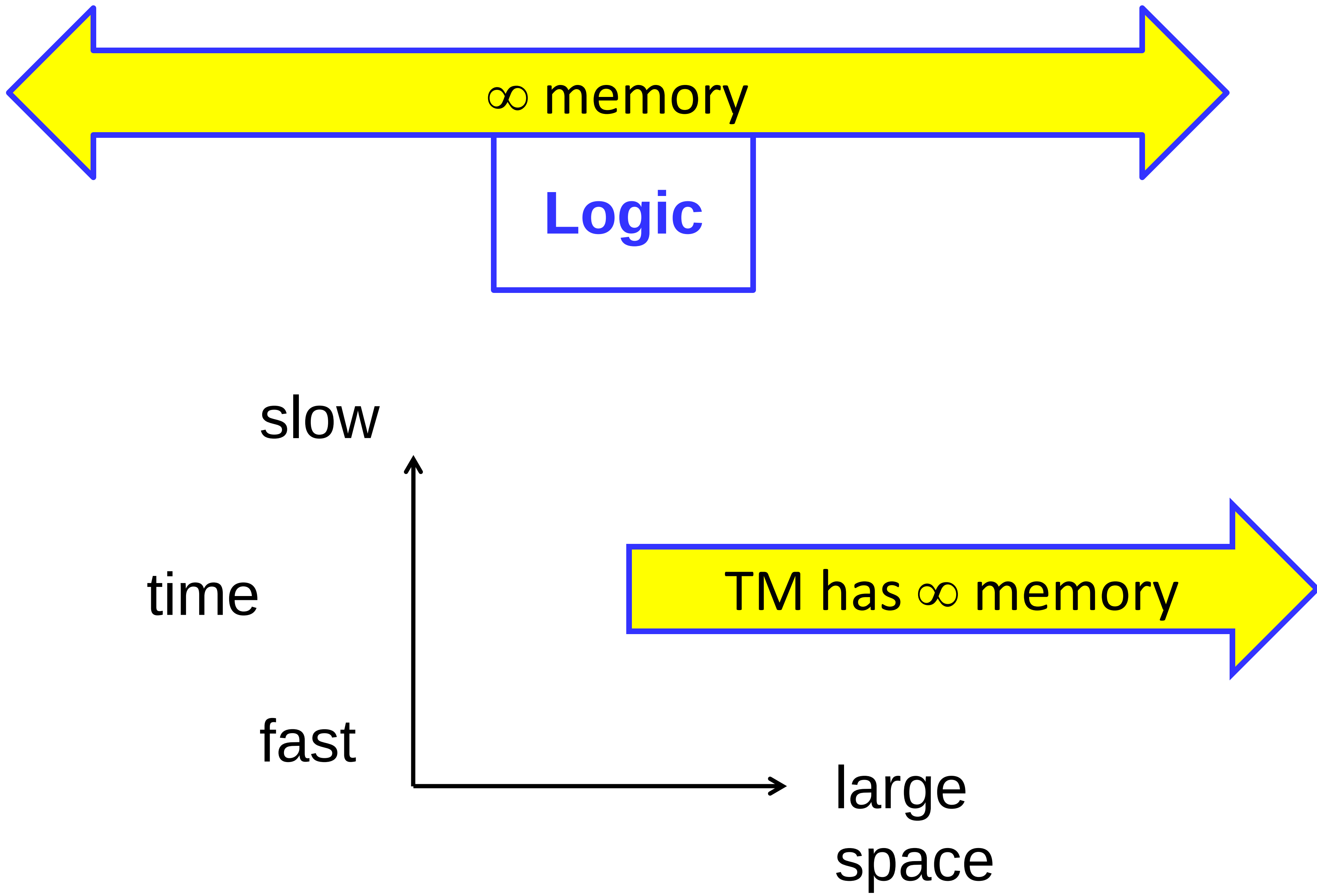
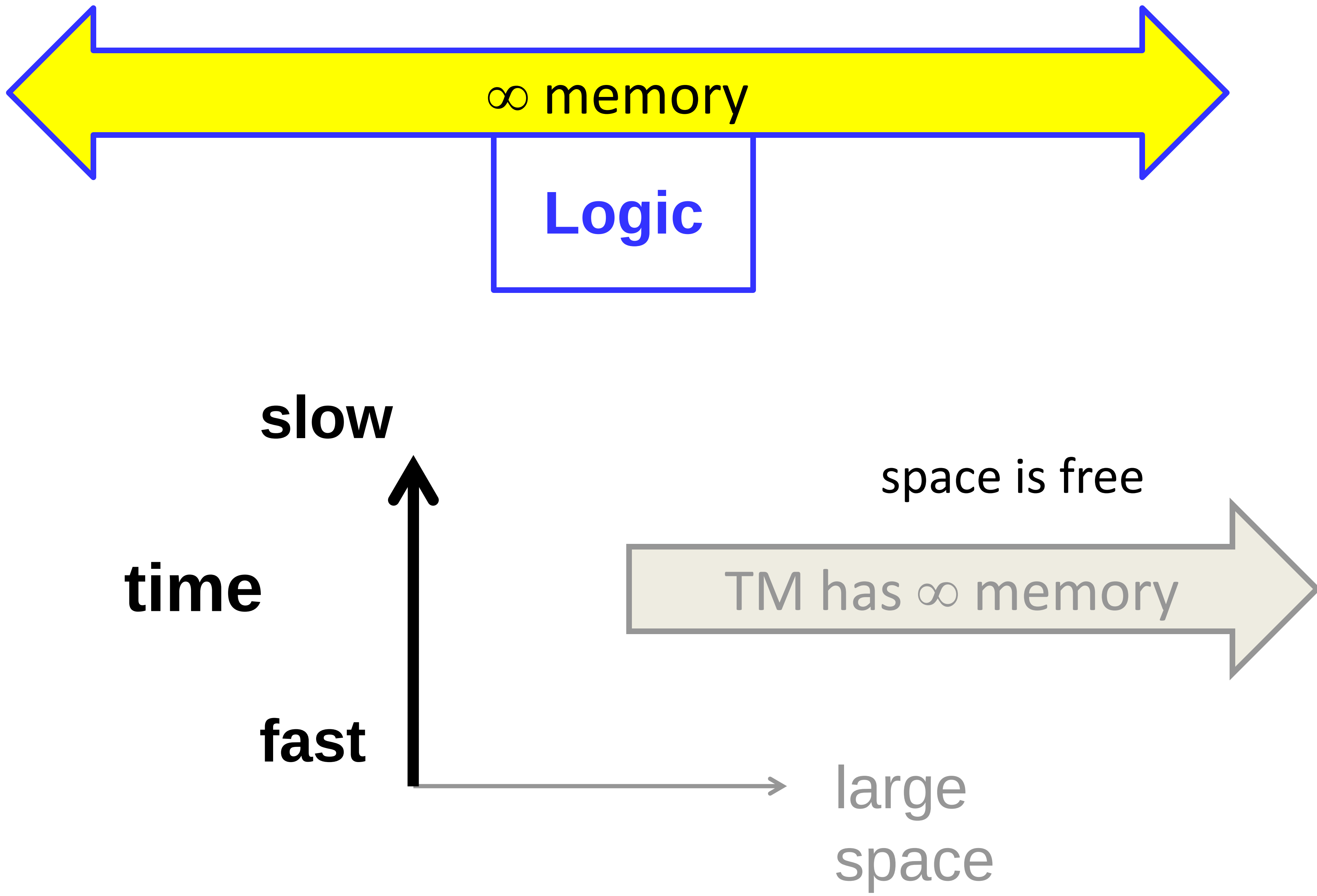
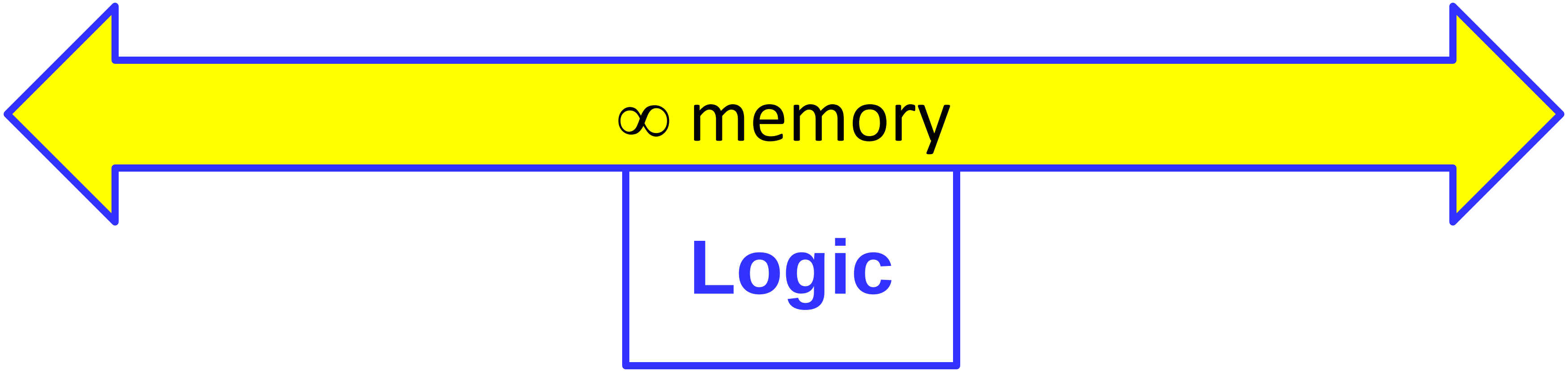

∞ memory
Logic
slow
time
fast
TM has ∞ memory
large
space

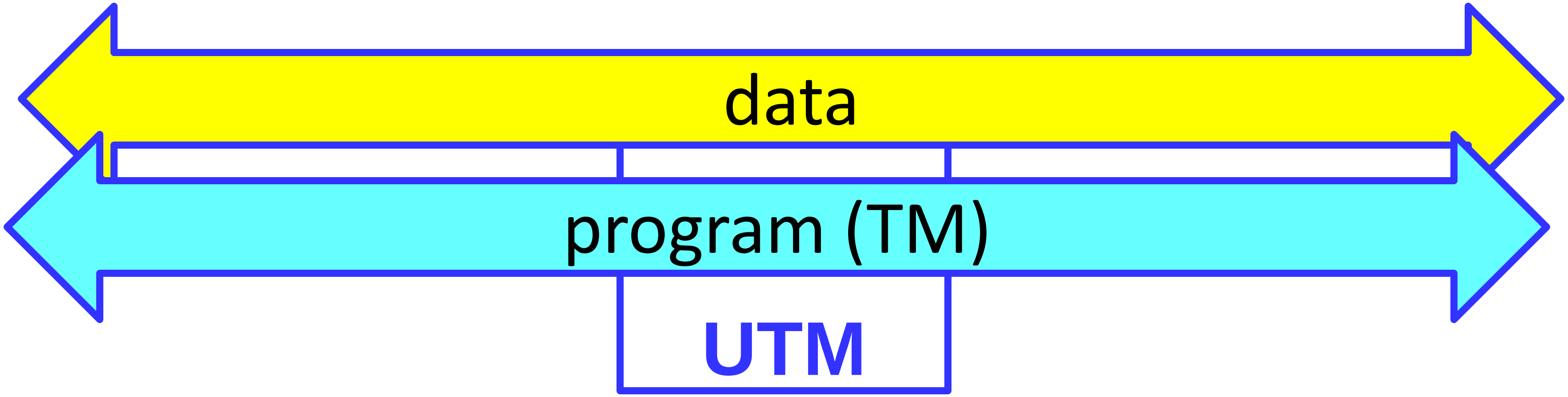

∞ memory
Logic
slow
time
fast
space is free
TM has ∞ memory
large
space



time?

Decidable problem = ∃ algorithm that solves it

Most naively posed problems are undecidable.



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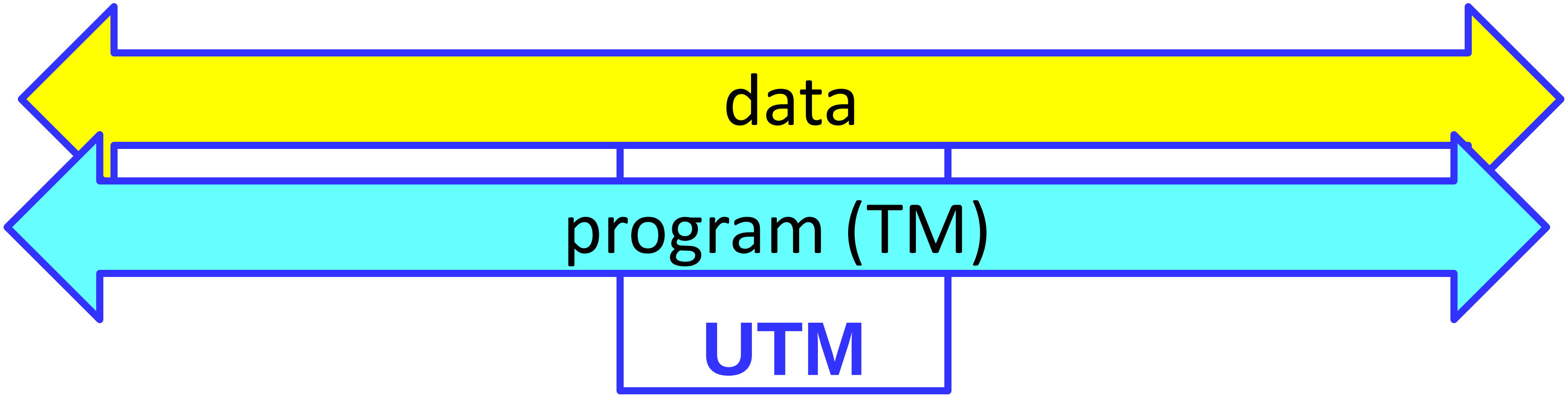
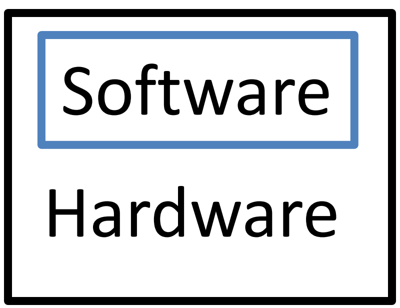
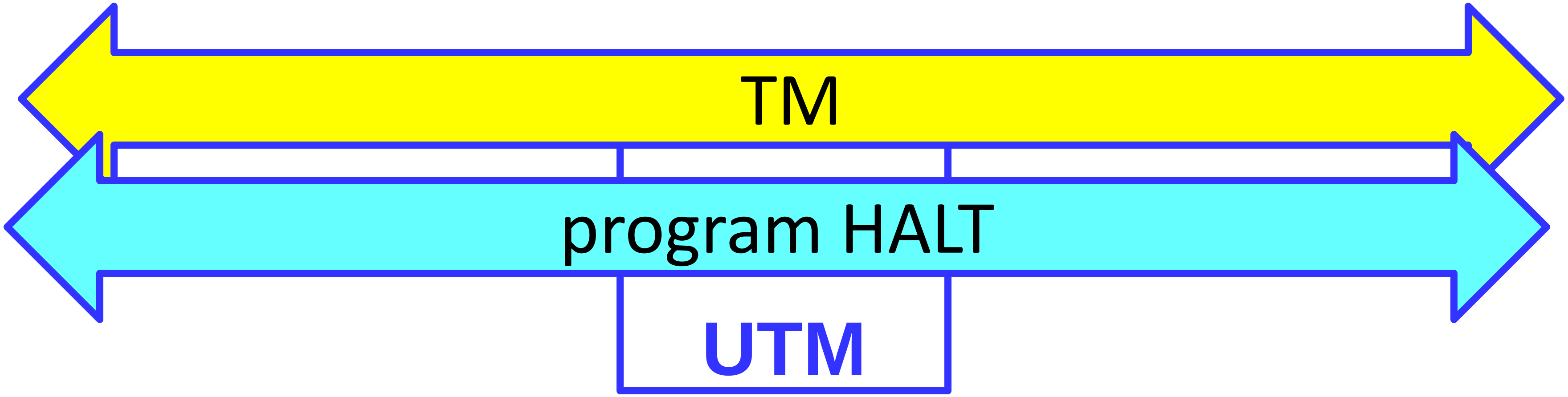




2. Universal architecture achieving hard limits (UTM)

- 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.



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:

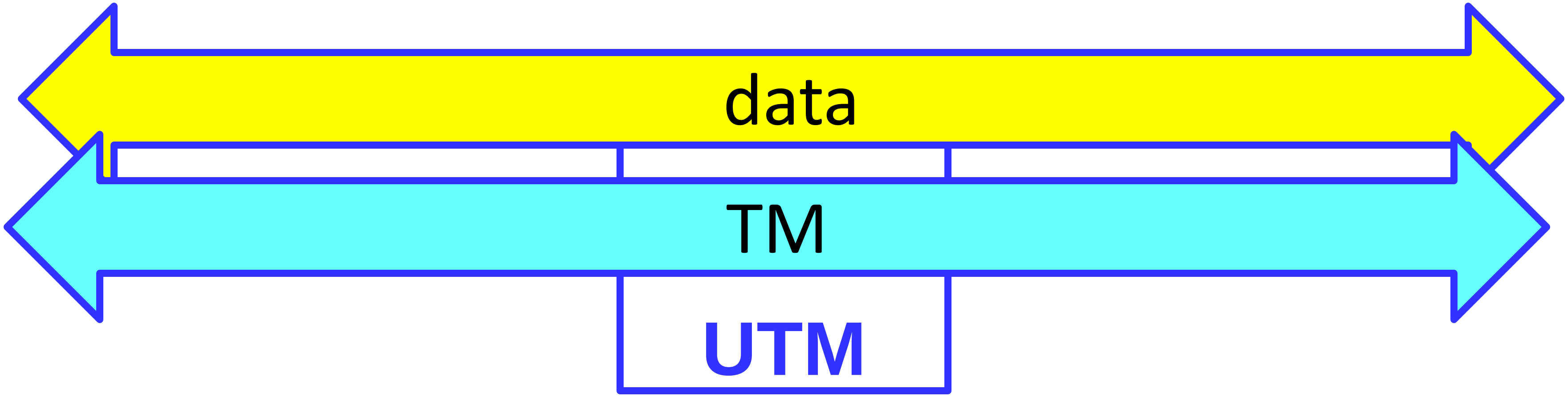
$$H'(TM, input) \triangleq \begin{cases} 1 \text{ if } H(TM, input) = 0 \\ \text{loop forever otherwise} \end{cases}$$

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

$$\text{Run } H^*(H^*) = H'(H^*, H^*)$$

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

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

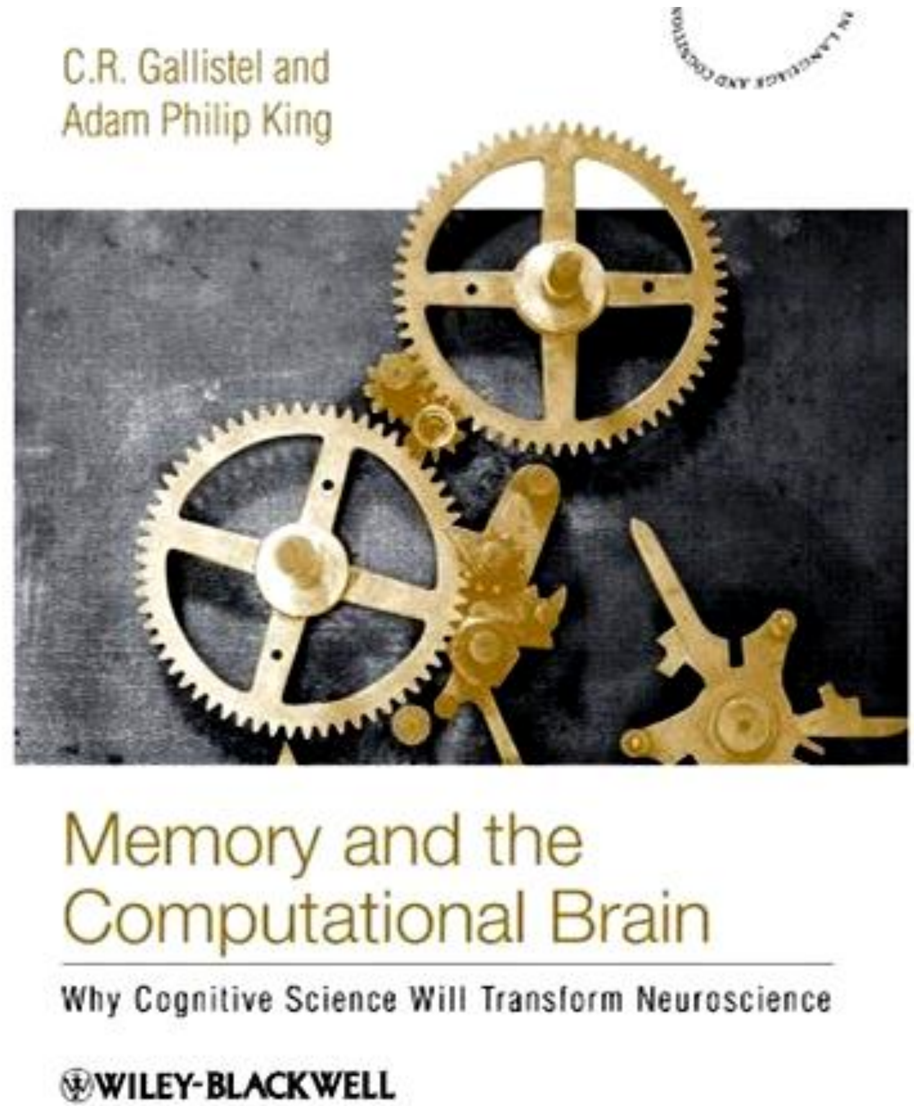
- Turing remarkably relevant for 76 years
- UTMs are ≈ implementable
  - Time is most critical resource
  - Space (memory) almost free
- Read/write random access memory hierarchies
- Further gradations of decidable (P/NP/coNP)

- Must crucial: 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?

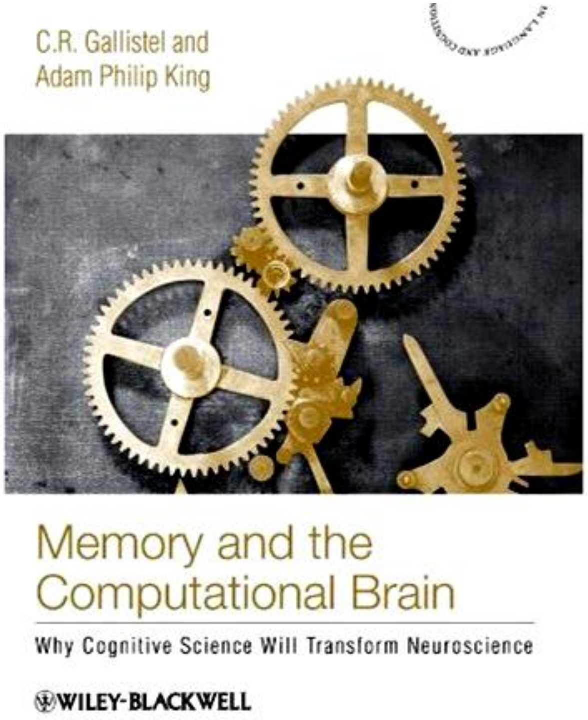
Gallistel and King



Conjecture

Gallistel and King

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



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

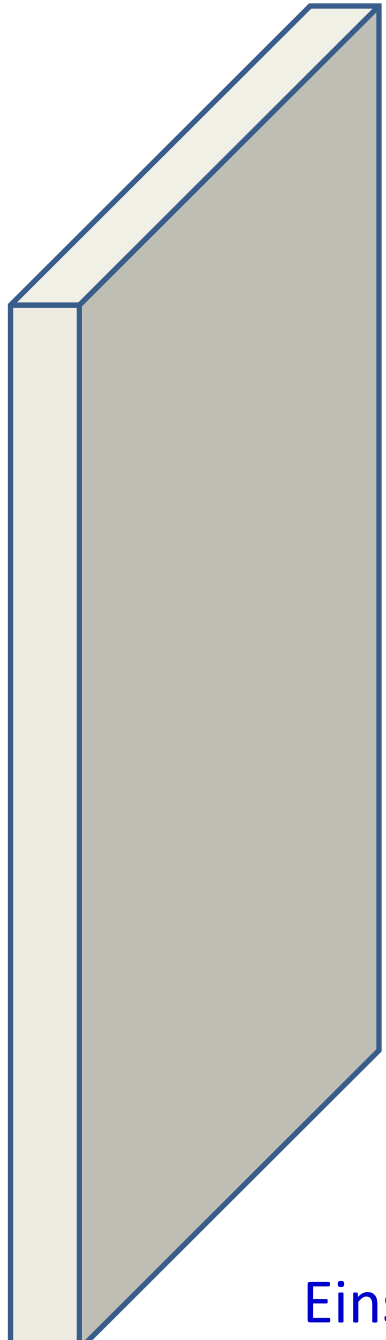
Compute

Turing

Delay is *most* important

Bode

Control, OR



Communicate

Shannon

Delay is *least* important

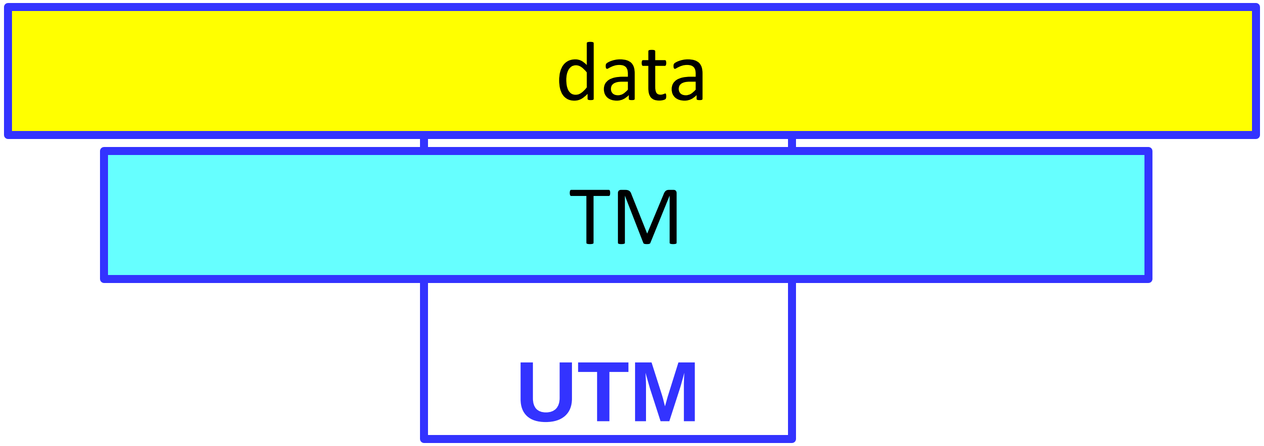
Carnot

Boltzmann

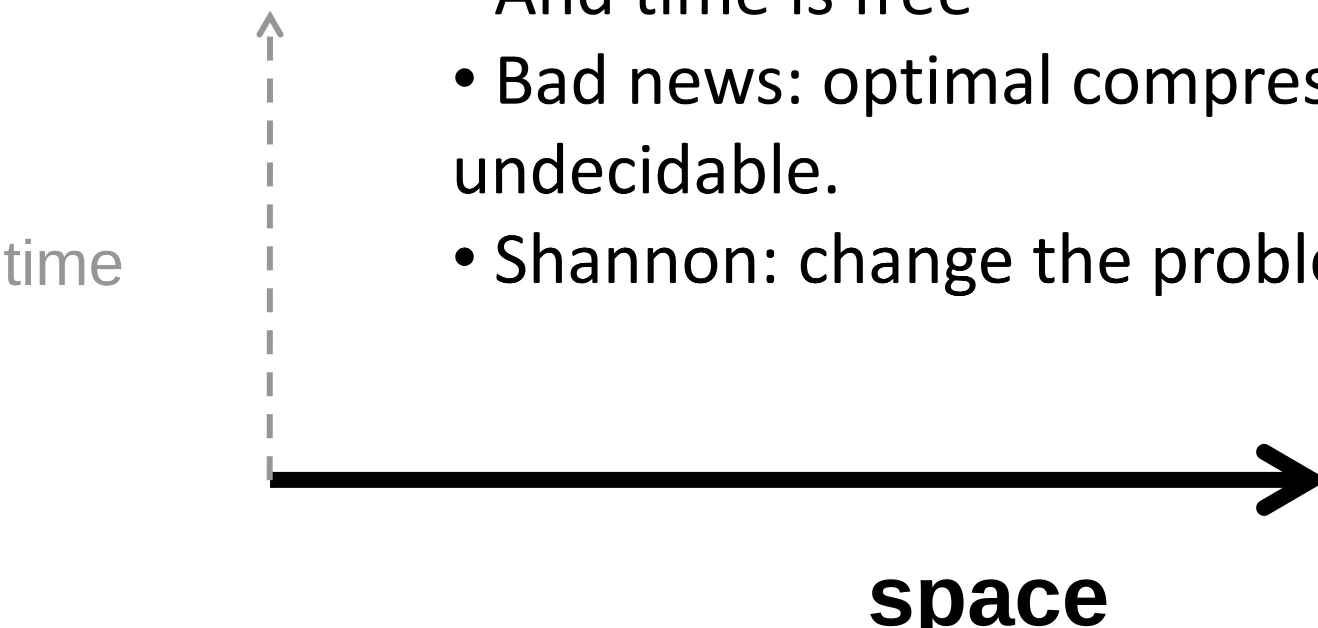
Heisenberg

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)
- Misled and distracted generations of biologists and neuroscientists
- New generation of information theorists are putting delay back in. (Cheer!)

Compute

Turing

Delay is *most* important

Communicate

Shannon

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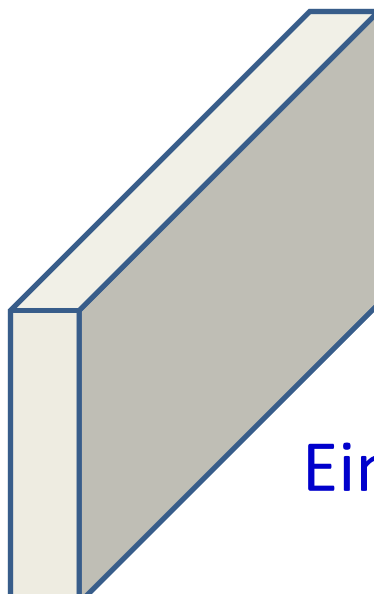


Einstein

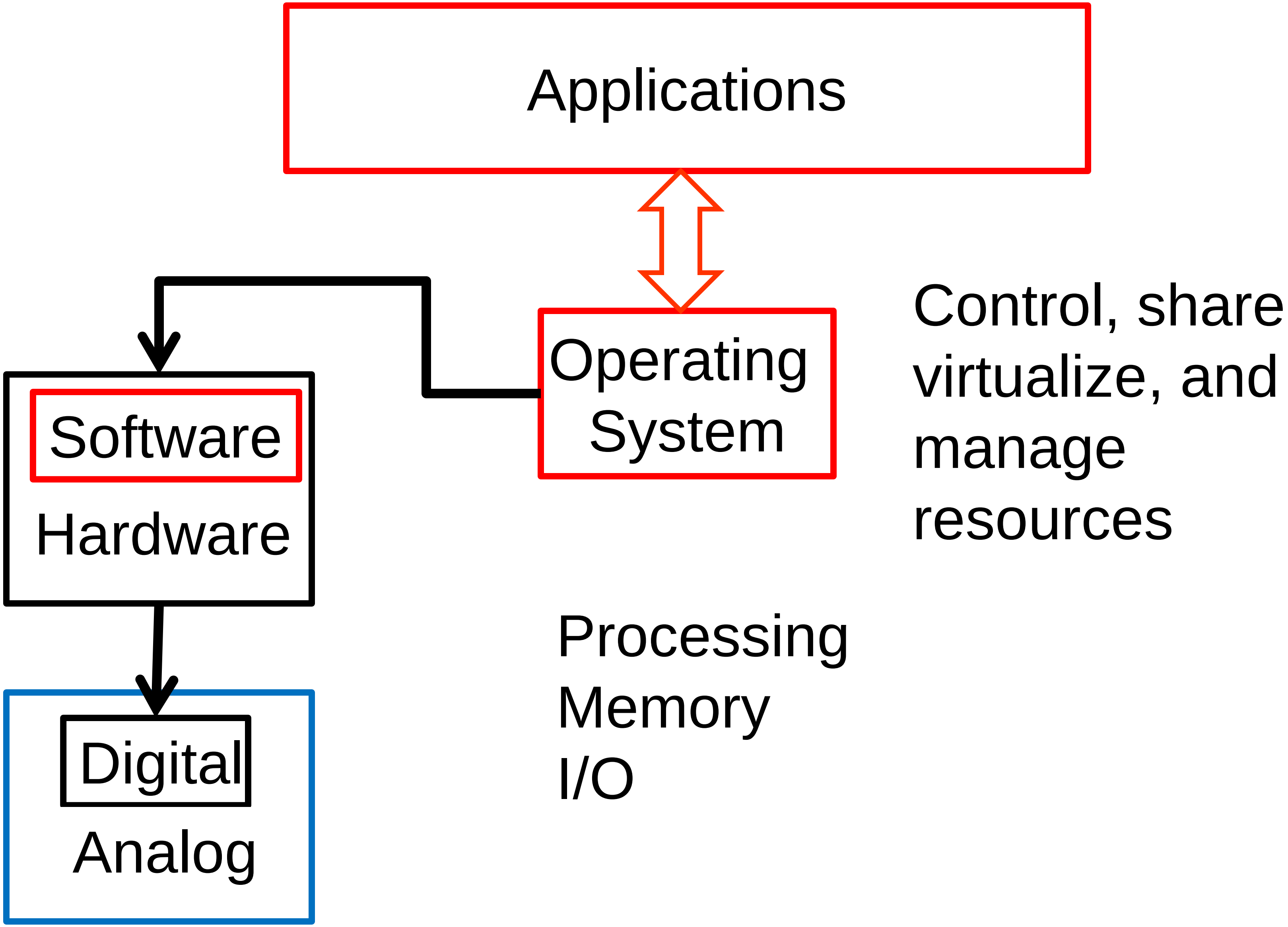
Control, OR

Physics

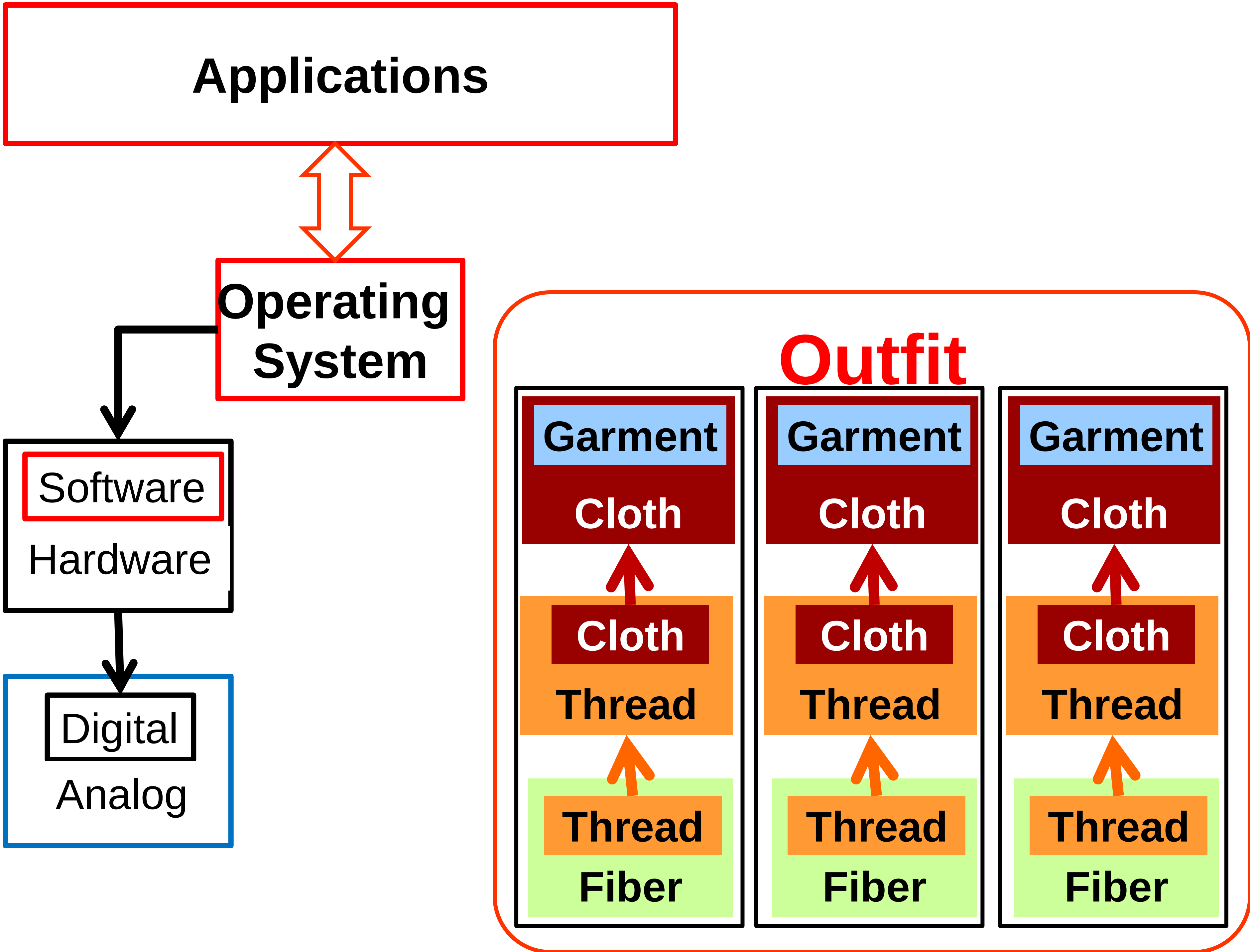
Slow execution
Flexible reprogramming

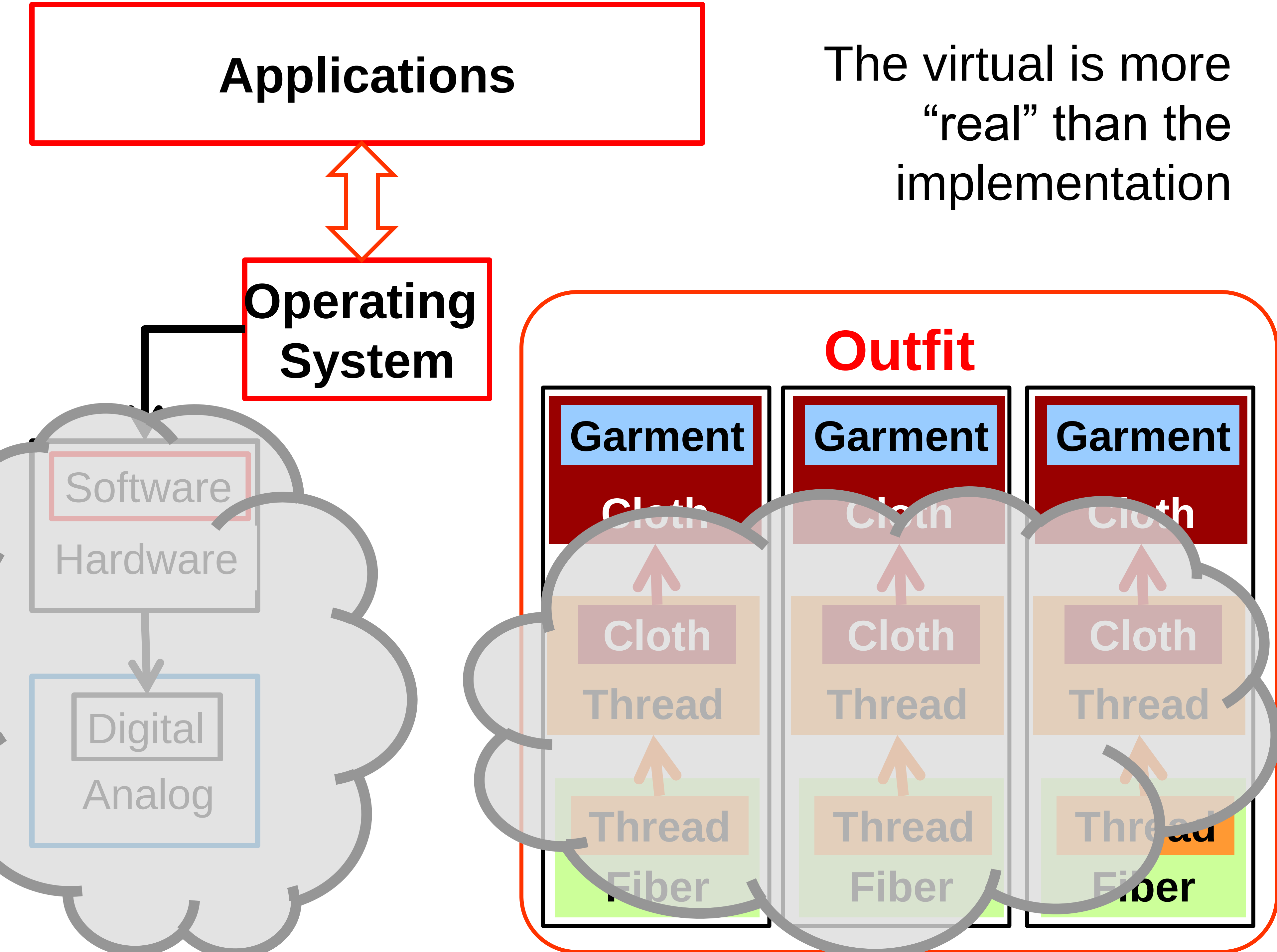
Faster execution
Less flexible

Modern technology gives lots of intermediate alternatives.

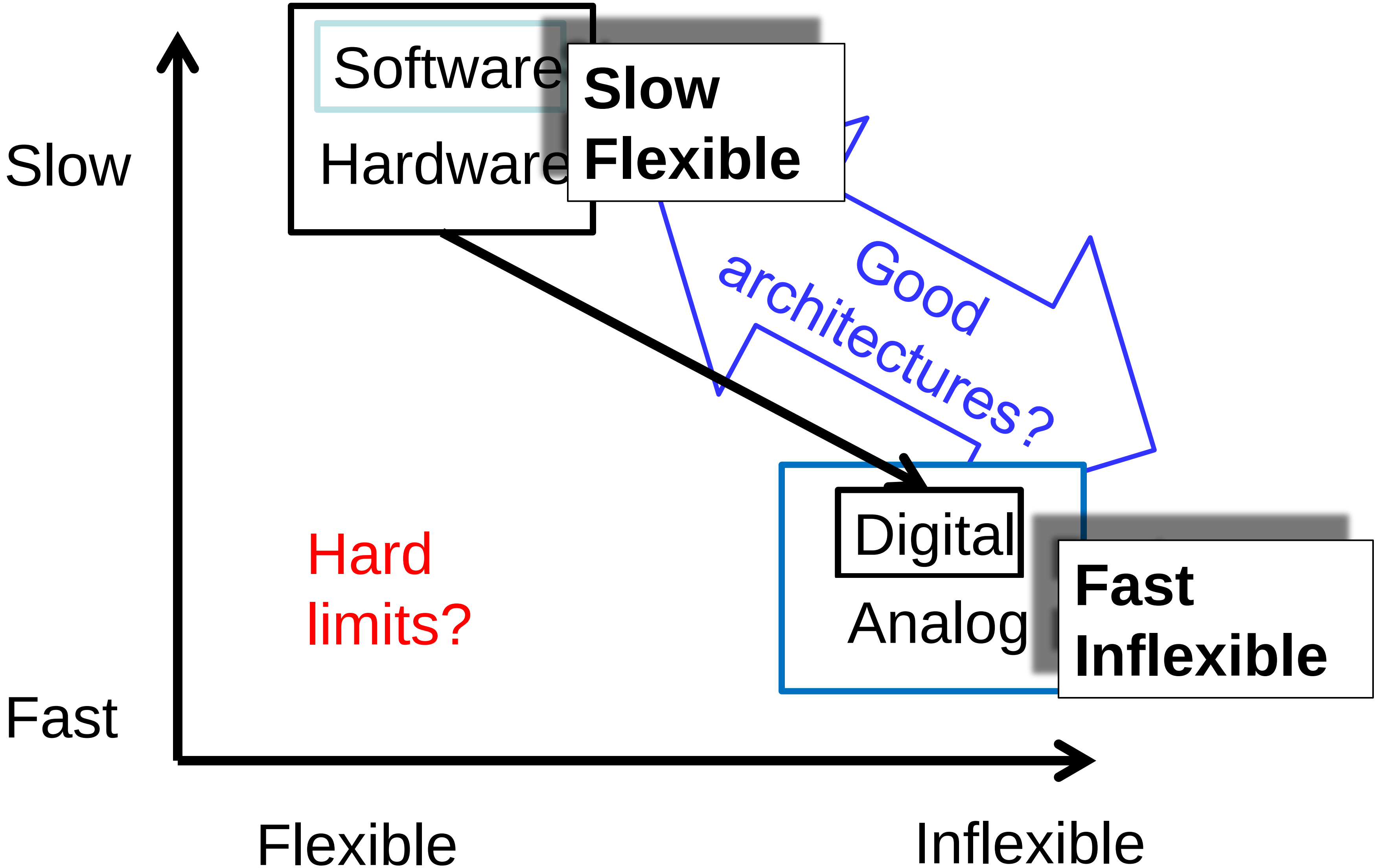


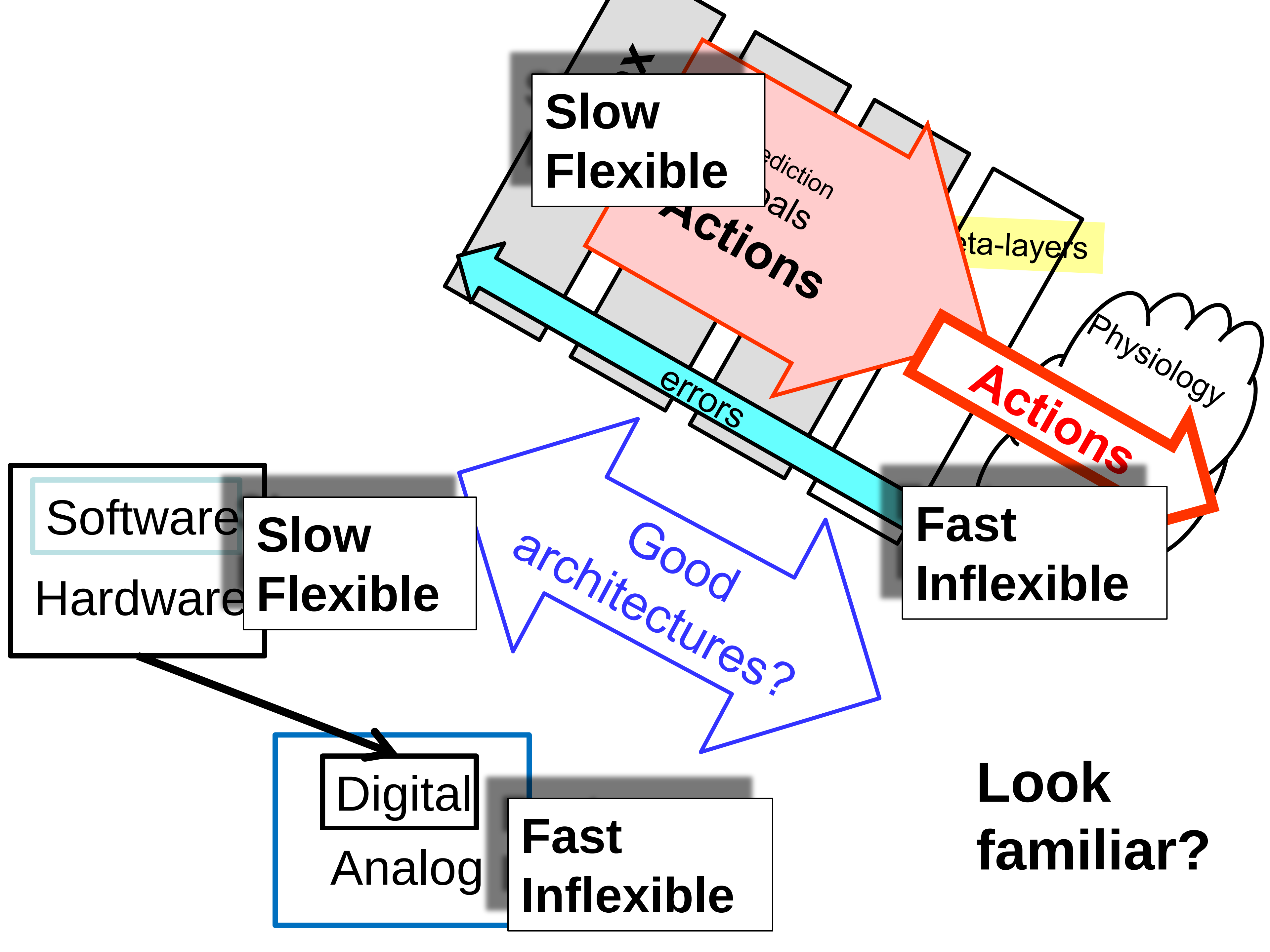
Want to emphasize the differences between these two types of layering.

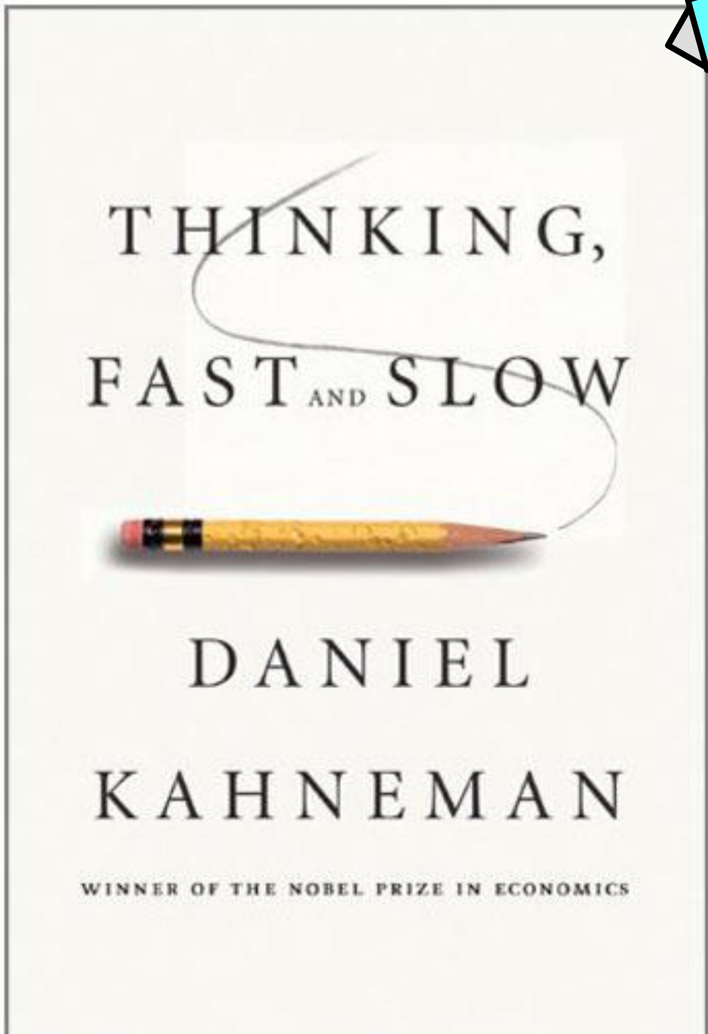

Applications
Operating System
Software
Hardware
Digital
Analog
Outfit
Garment
Cloth
Cloth
Thread
Thread
Fiber
Garment
Cloth
Cloth
Thread
Thread
Fiber
Garment
Cloth
Cloth
Thread
Thread
Fiber

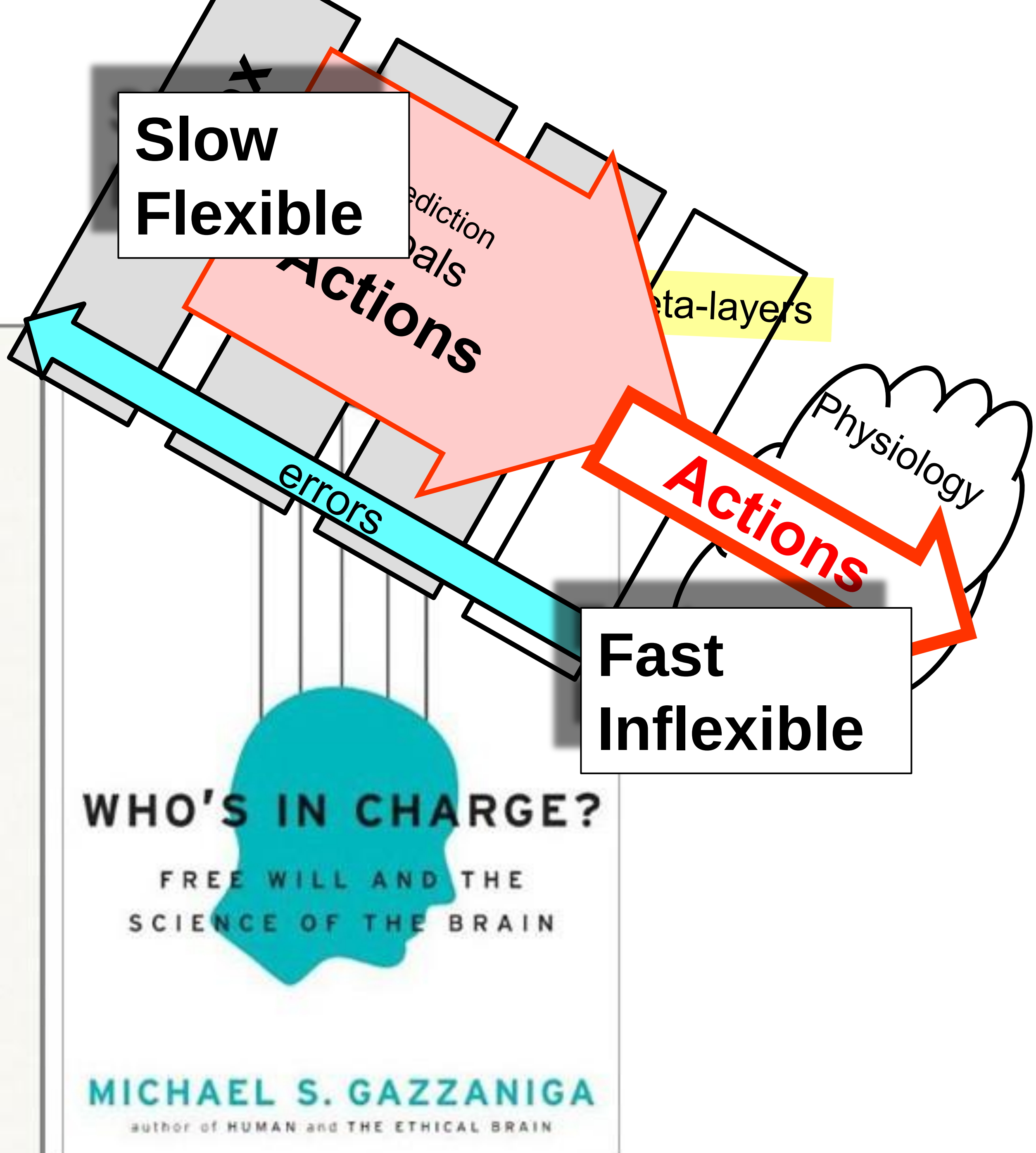


The virtual is more "real" than the implementation

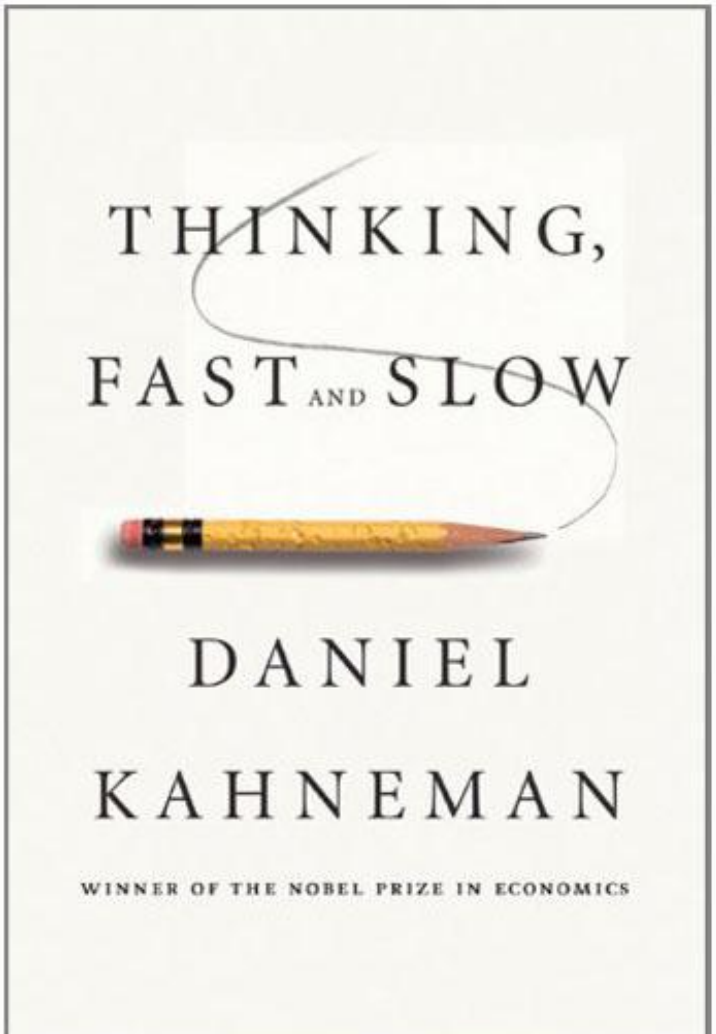

Slow
Fast
Flexible
Inflexible
Software
Hardware
Slow
Flexible
Good architectures?
Digital
Analog
Fast
Inflexible
Hard limits?


Slow
Flexible
Actions
errors
Physiology
Actions
Fast
Inflexible
Software
Hardware
Slow
Flexible
Good
architectures?
Digital
Analog
Fast
Inflexible
Look
familiar?

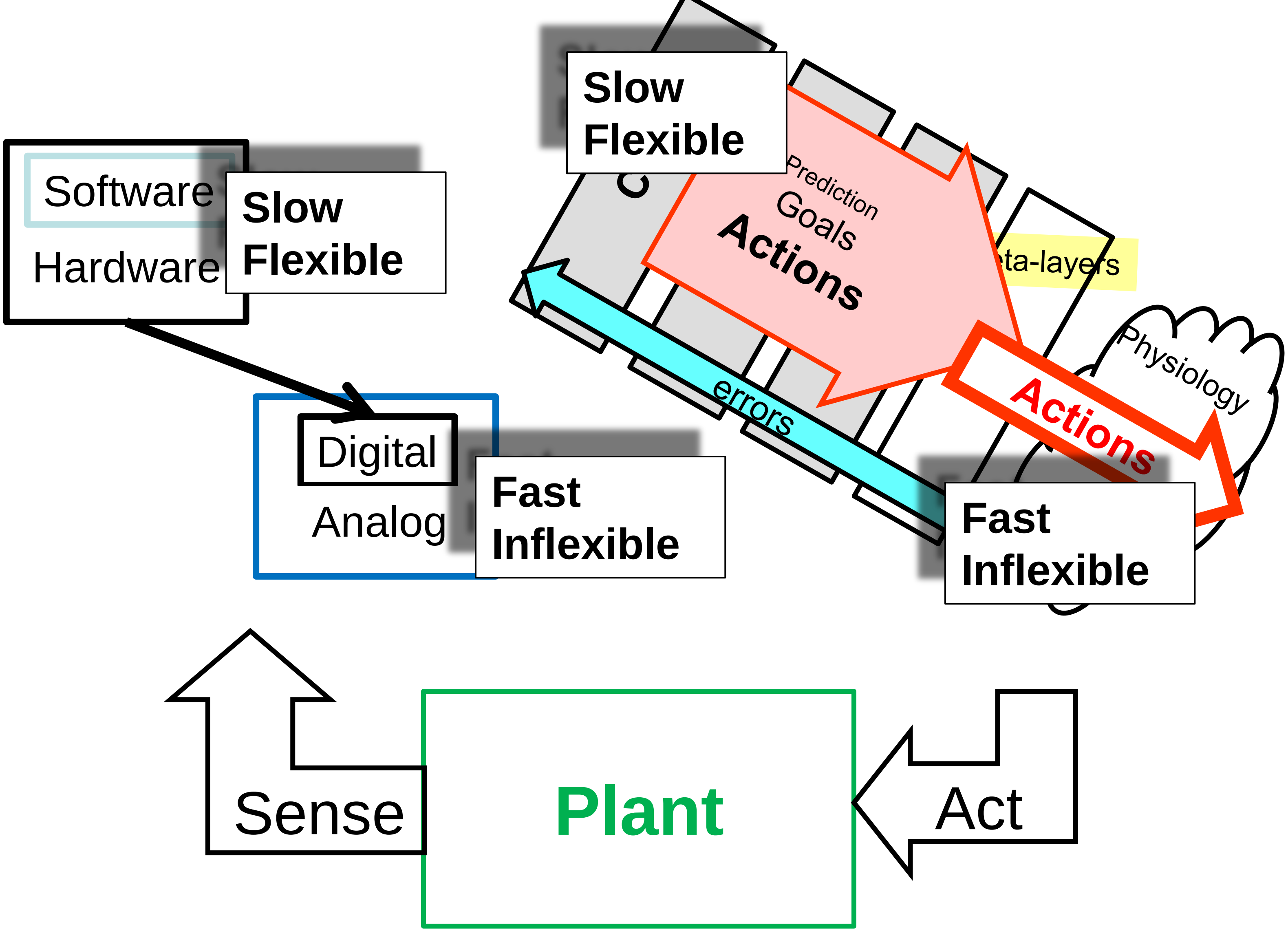

THINKING,
FAST AND SLOW
DANIEL
KAHNEMAN
WINNER OF THE NOBEL PRIZE IN ECONOMICS


Slow
Flexible
Actions
Actions
errors
Physiology
Fast
Inflexible
WHO'S IN CHARGE?
FREE WILL AND THE
SCIENCE OF THE BRAIN
MICHAEL S. GAZZANIGA
author of HUMAN and THE ETHICAL BRAIN

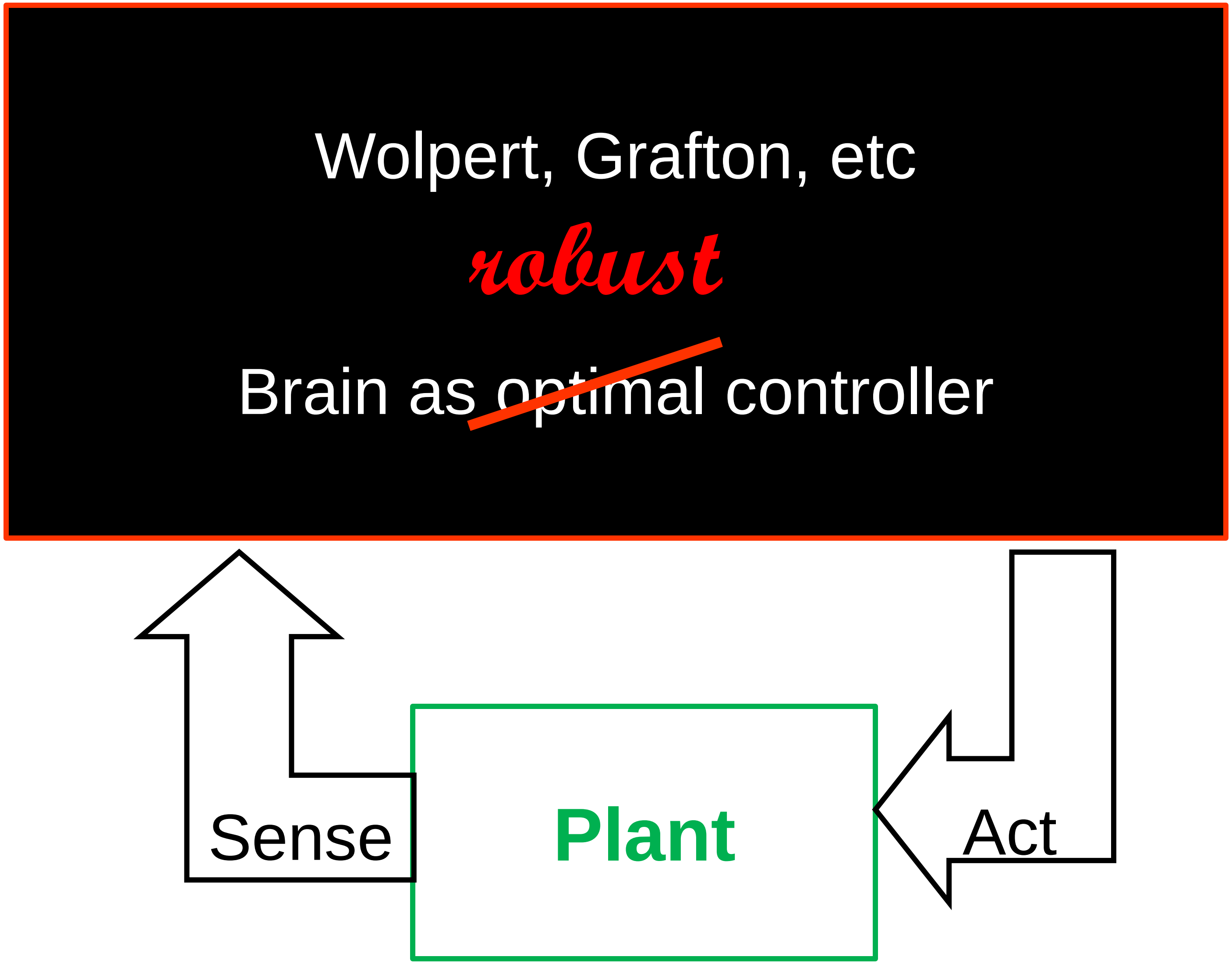
Essentials To Do



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



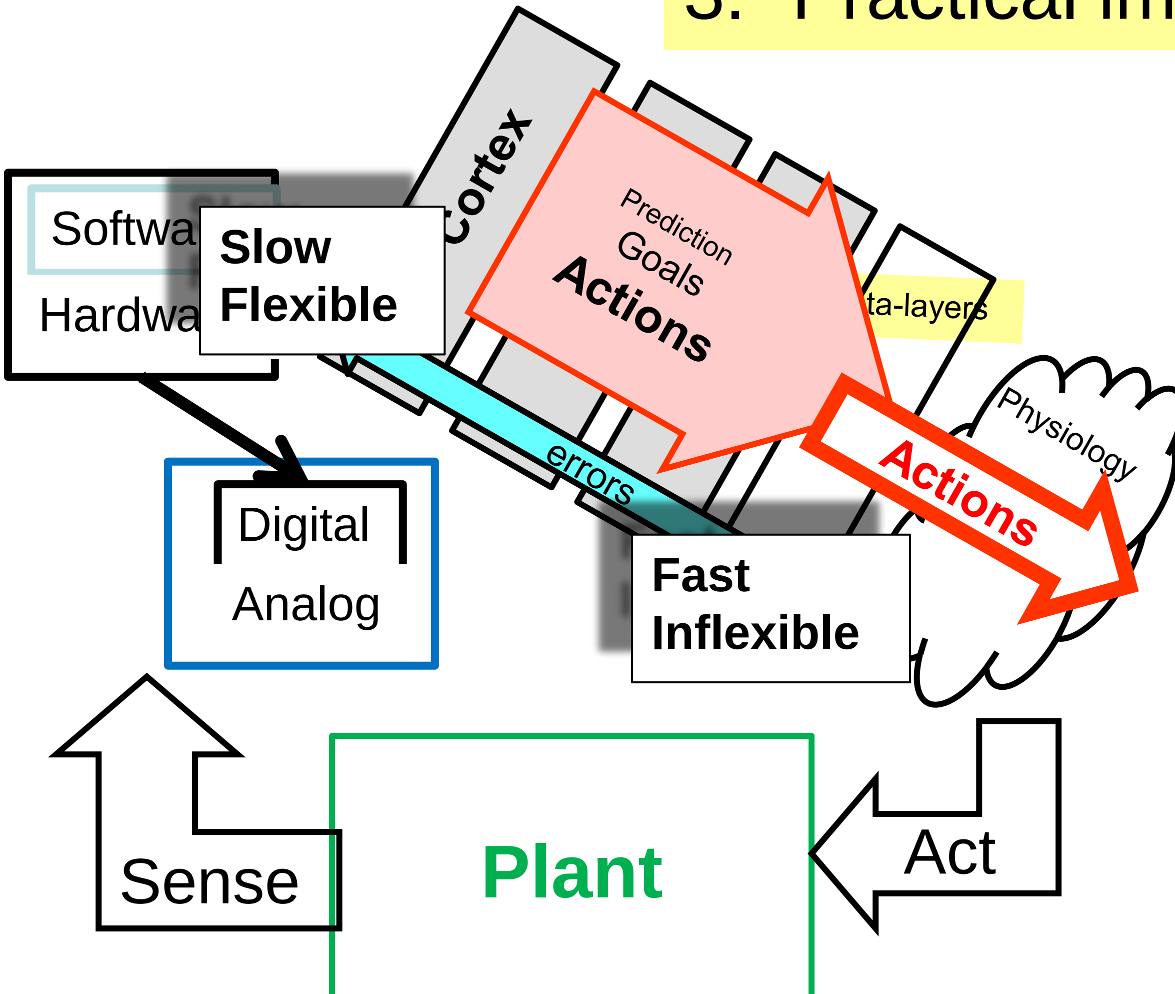
Speed and flexibility are crucial to implementing robust controllers.

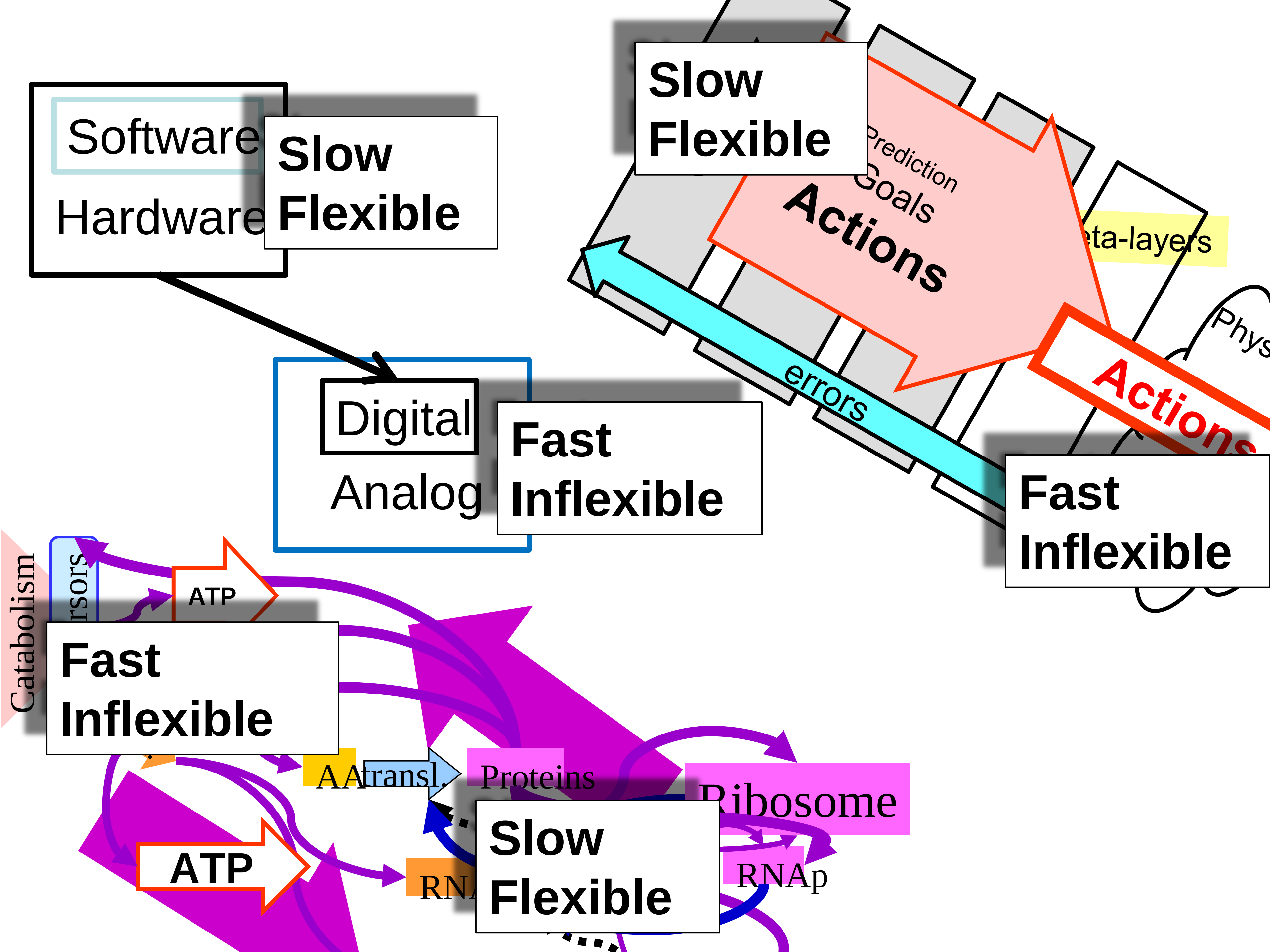


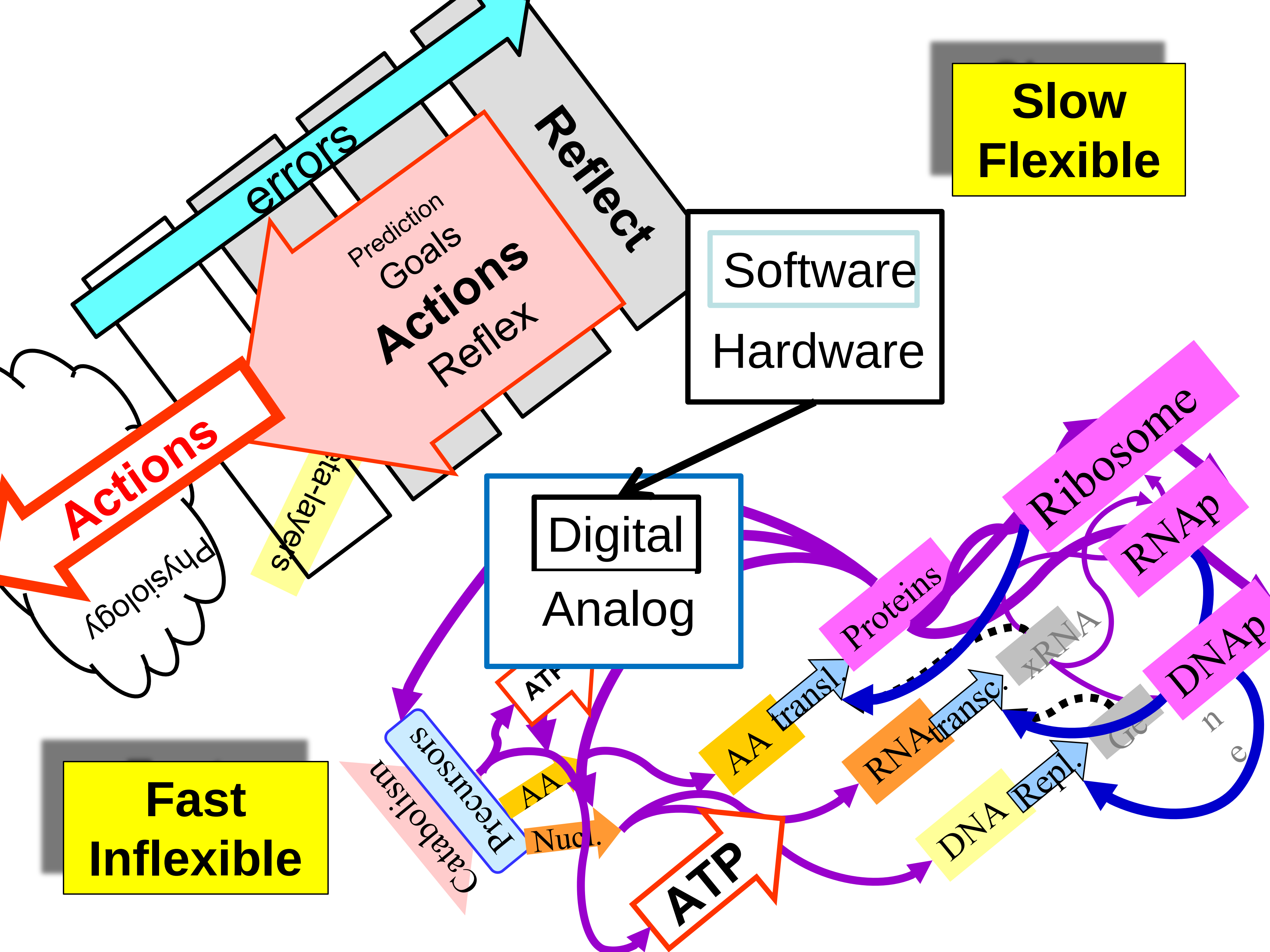
Speed and flexibility are crucial to implementing robust controllers.

Beyond black boxes:
Putting brain physiology back in the picture

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




Software
Hardware
Slow
Flexible
Digital
Analog
Fast
Inflexible
Slow
Flexible
Prediction
Goals
Actions
errors
Actions
Fast
Inflexible
Catabolism
ATP
Fast
Inflexible
AAtransl.
Proteins
Ribosome
ATP
RNAp
Slow
Flexible

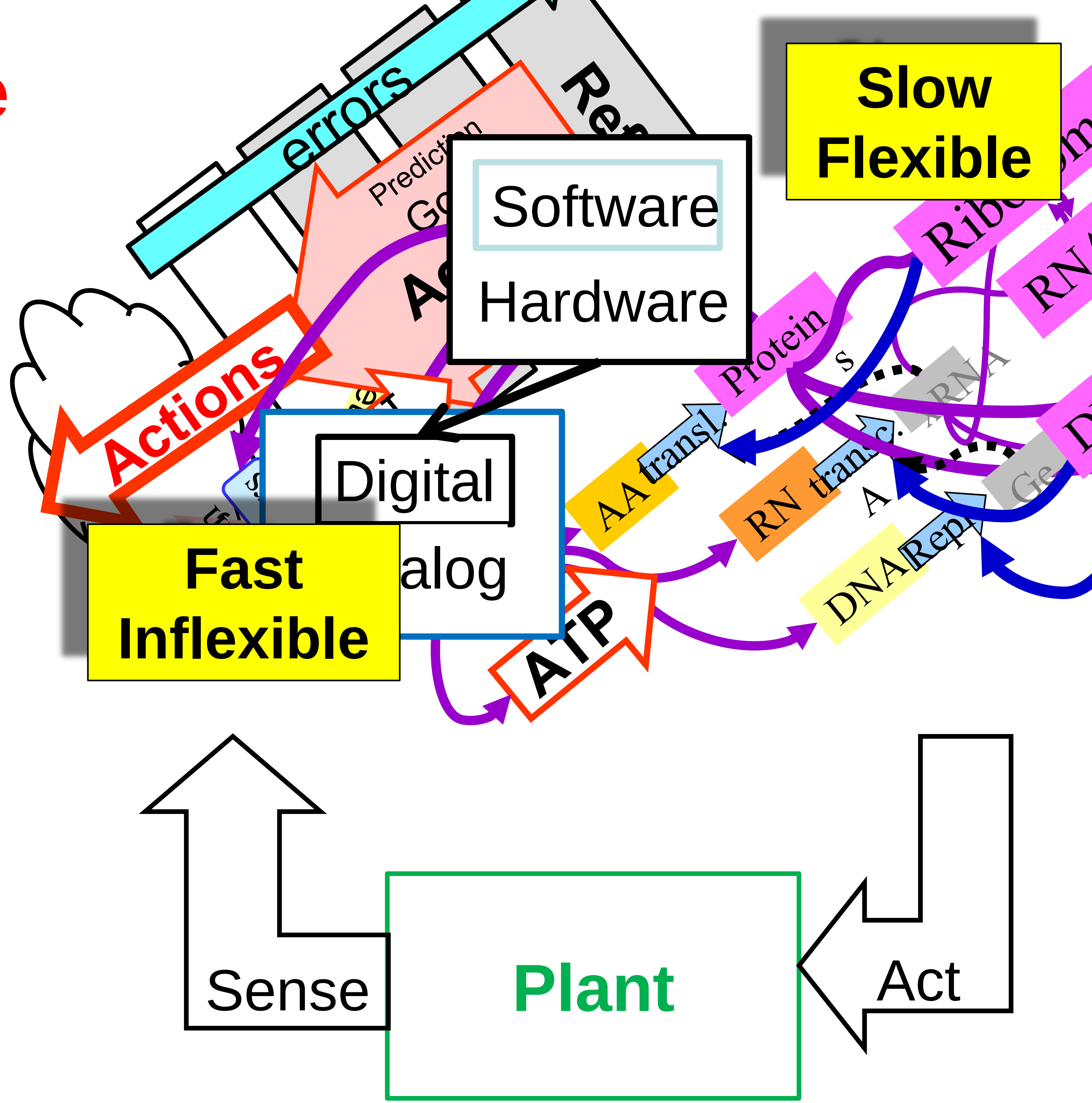


Slow
Flexible
errors
Reflect
Prediction
Goals
Actions
Reflex
Actions
Physiology
Meta-layers
Software
Hardware
Digital
Analog
Ribosome
RNAp
DNAp
Proteins
xRNA
AA transl.
RNA transc.
DNA Repl.
Precursors
Catabolism
AA
Nucl.
ATP
Fast
Inflexible

Compute

Turing

Delay is *most* important

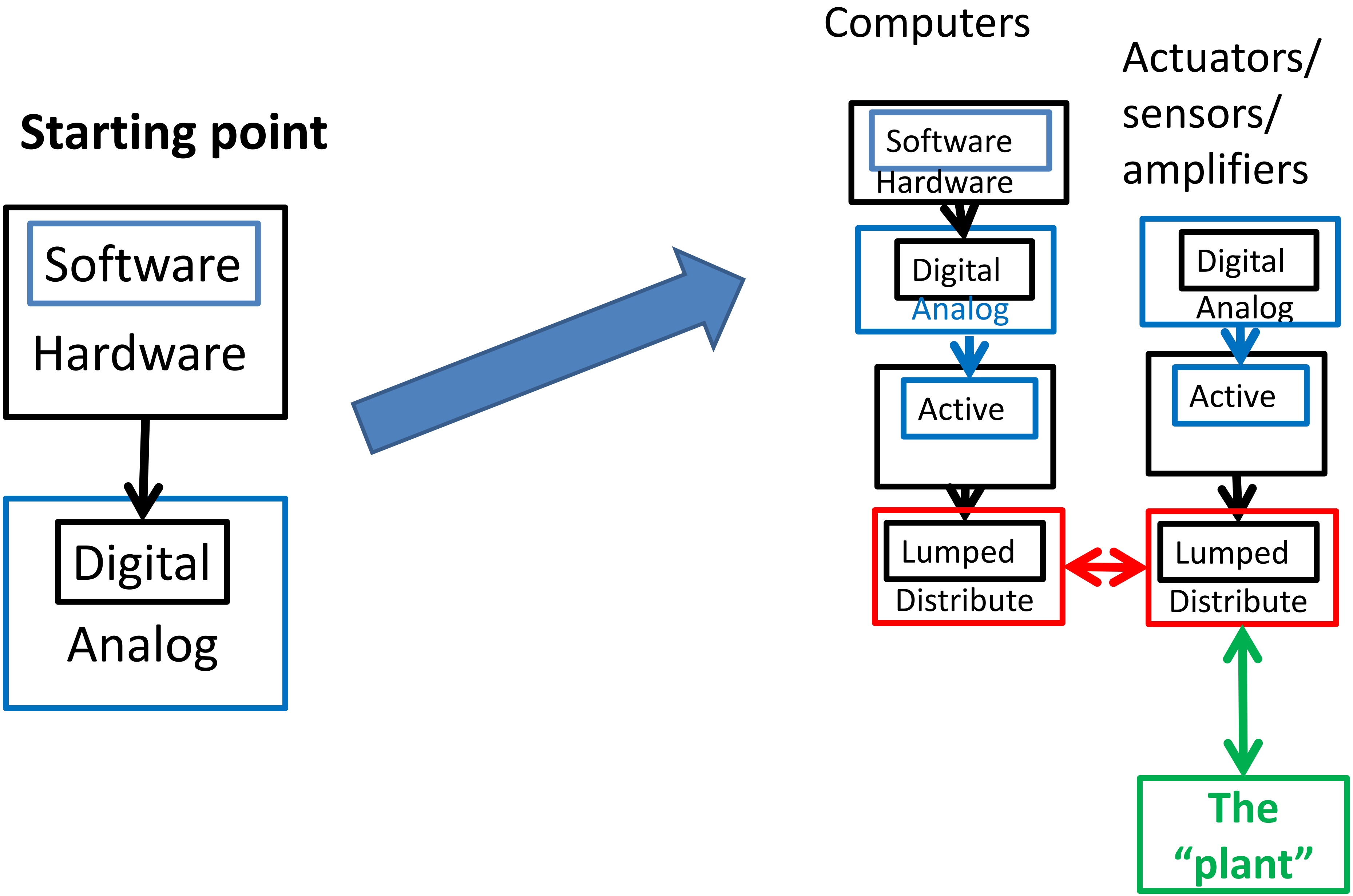


Bode

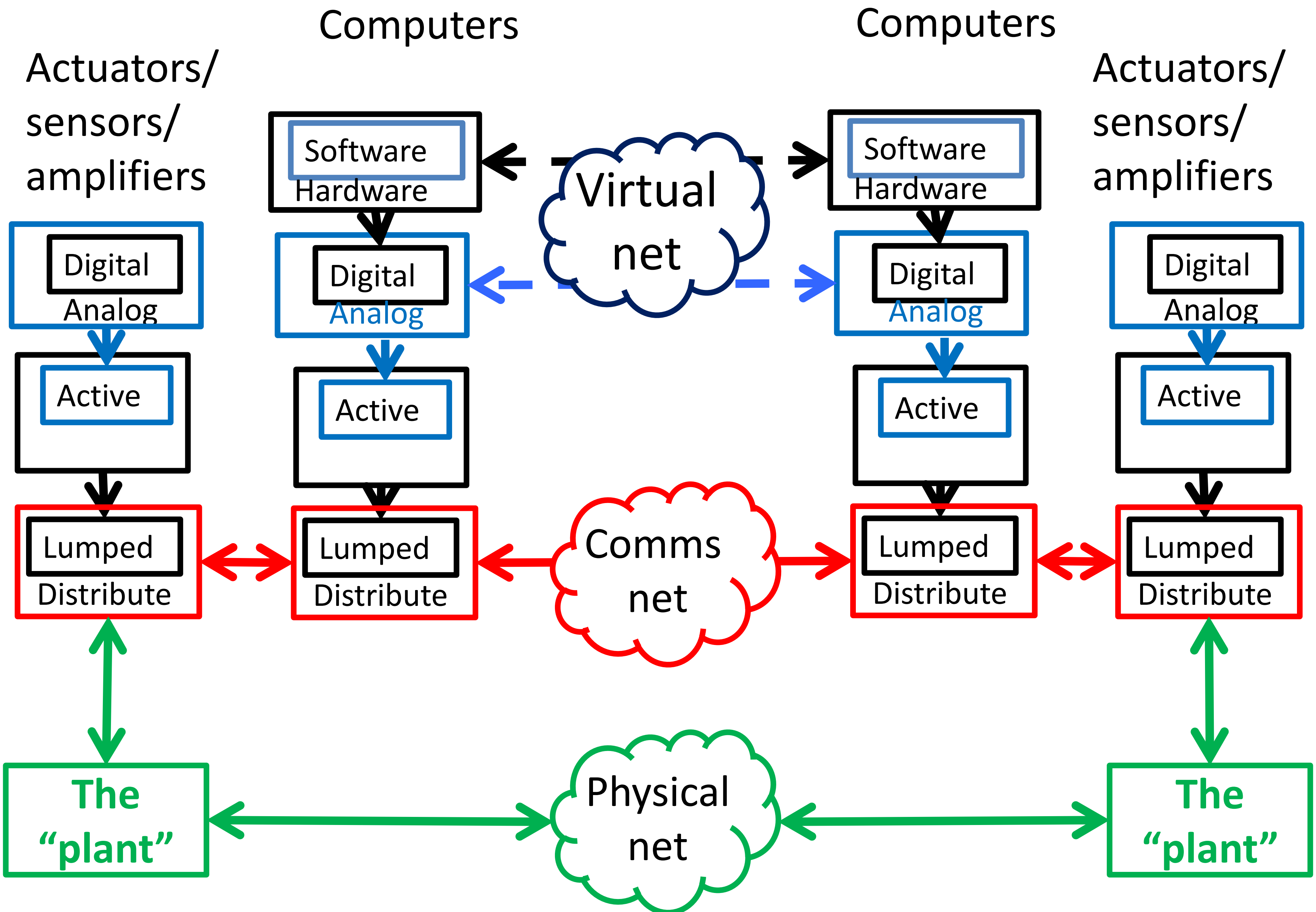
Control

Cyberphysical

Starting point



Cyberphysical



Turing as "new" starting point?

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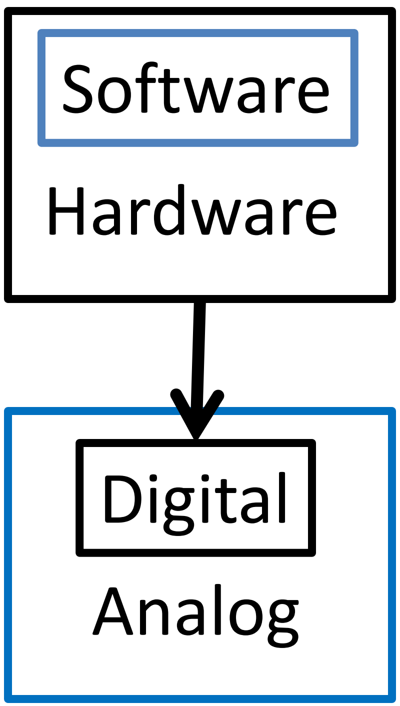
2. **Universal architecture**
3. **Practical implementation**



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?)

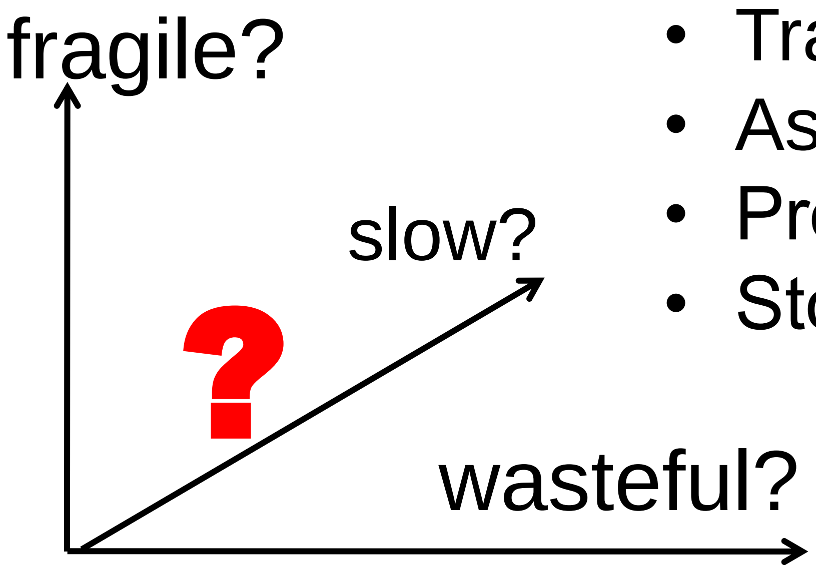
Control

Bode

Comms

Shannon

- Each theory ≈ one dimension
- Tradeoffs ***across*** dimensions
- Assume architectures a priori
- Progress is encouraging, but…
- Stovepipes are an obstacle…



Carnot

Boltzmann

Turing

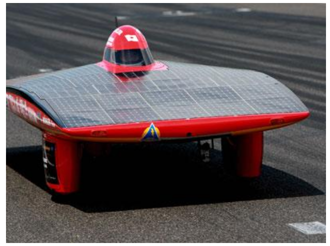
Godel

Heisenberg

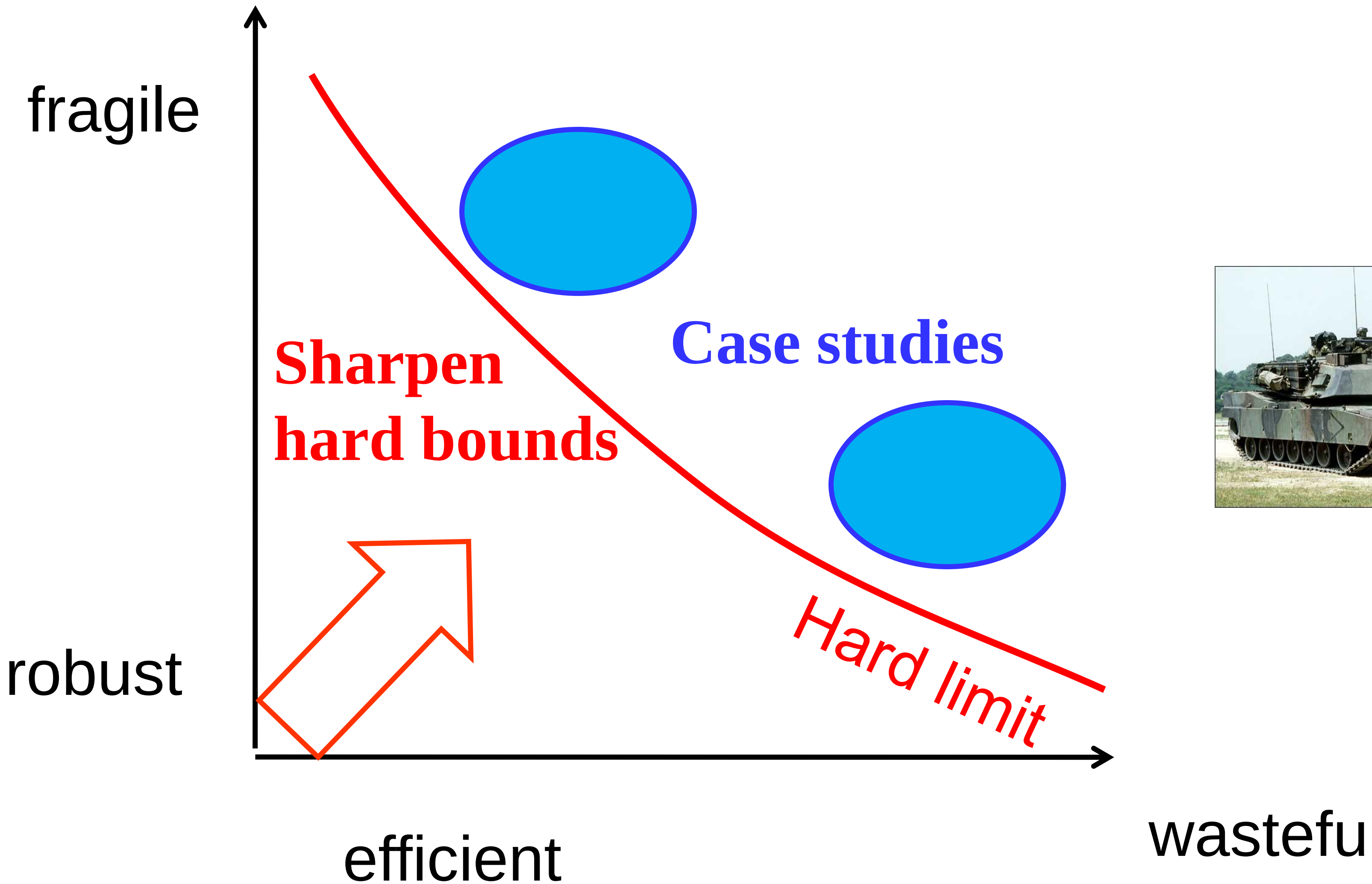
Compute

Physics

Einstein



laws and architectures?



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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

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

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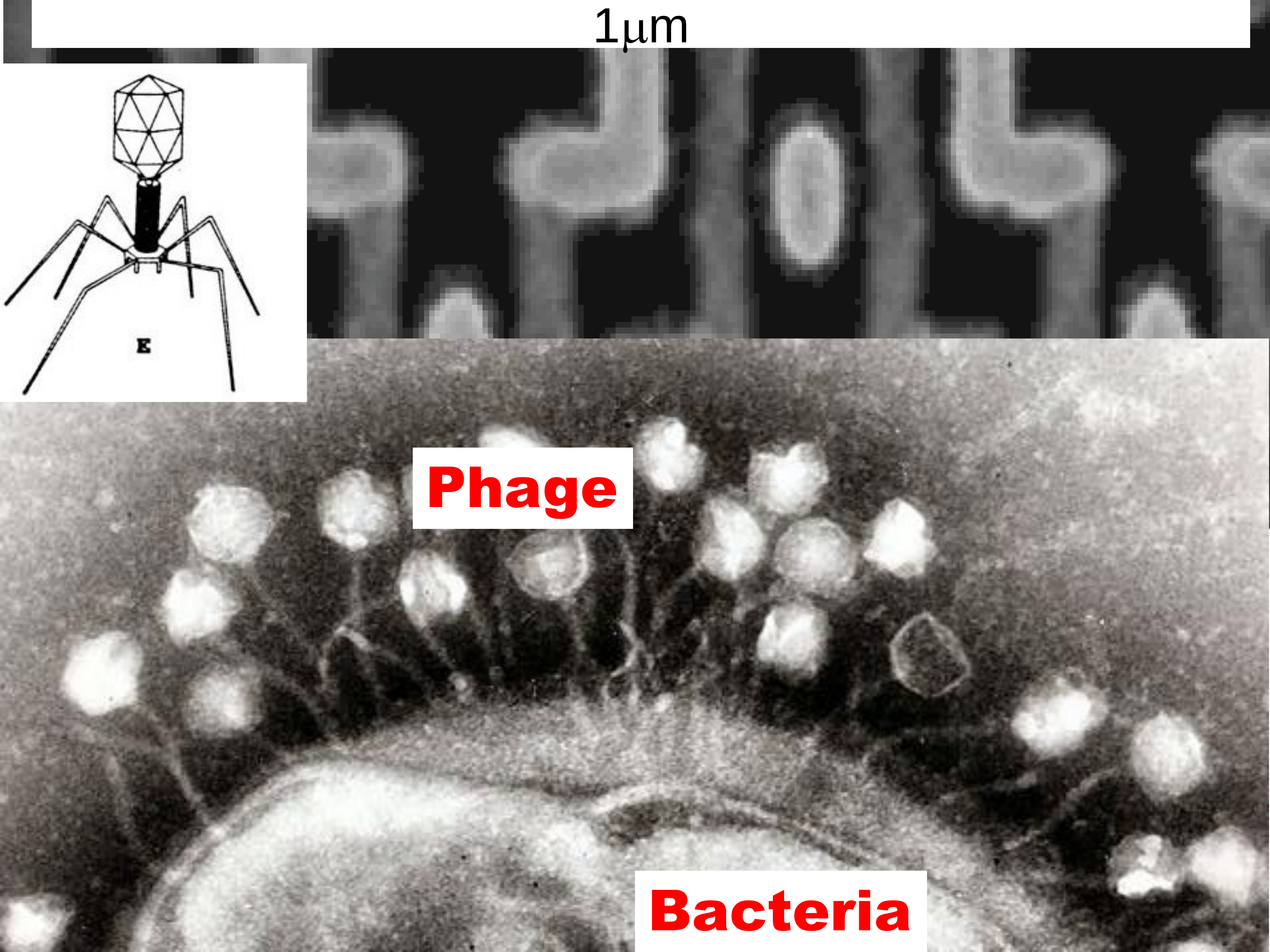
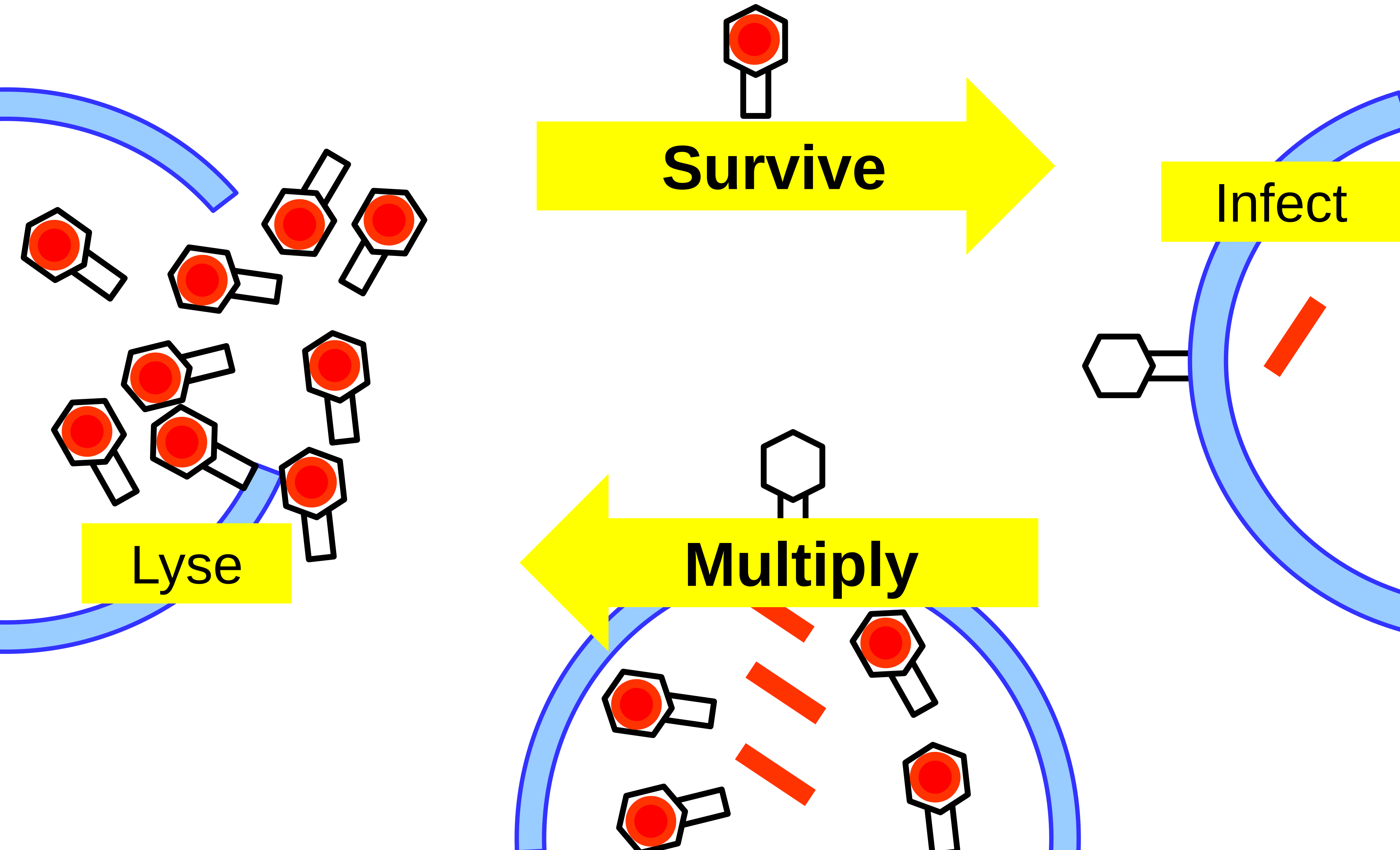
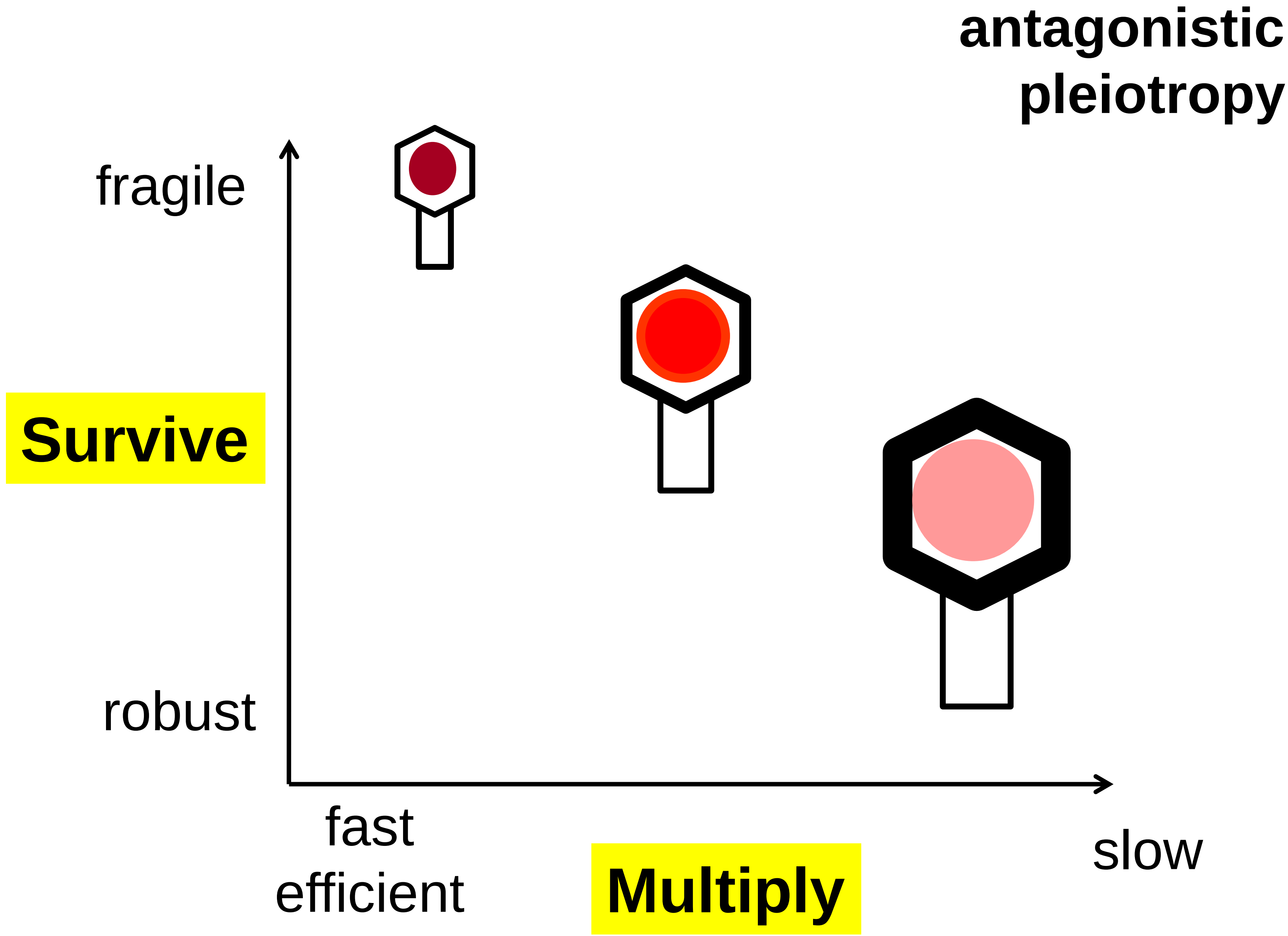

1μm
E
Phage
Bacteria

Phage lifecycle




antagonistic pleiotropy
fragile
Survive
robust
fast
efficient
Multiply
slow

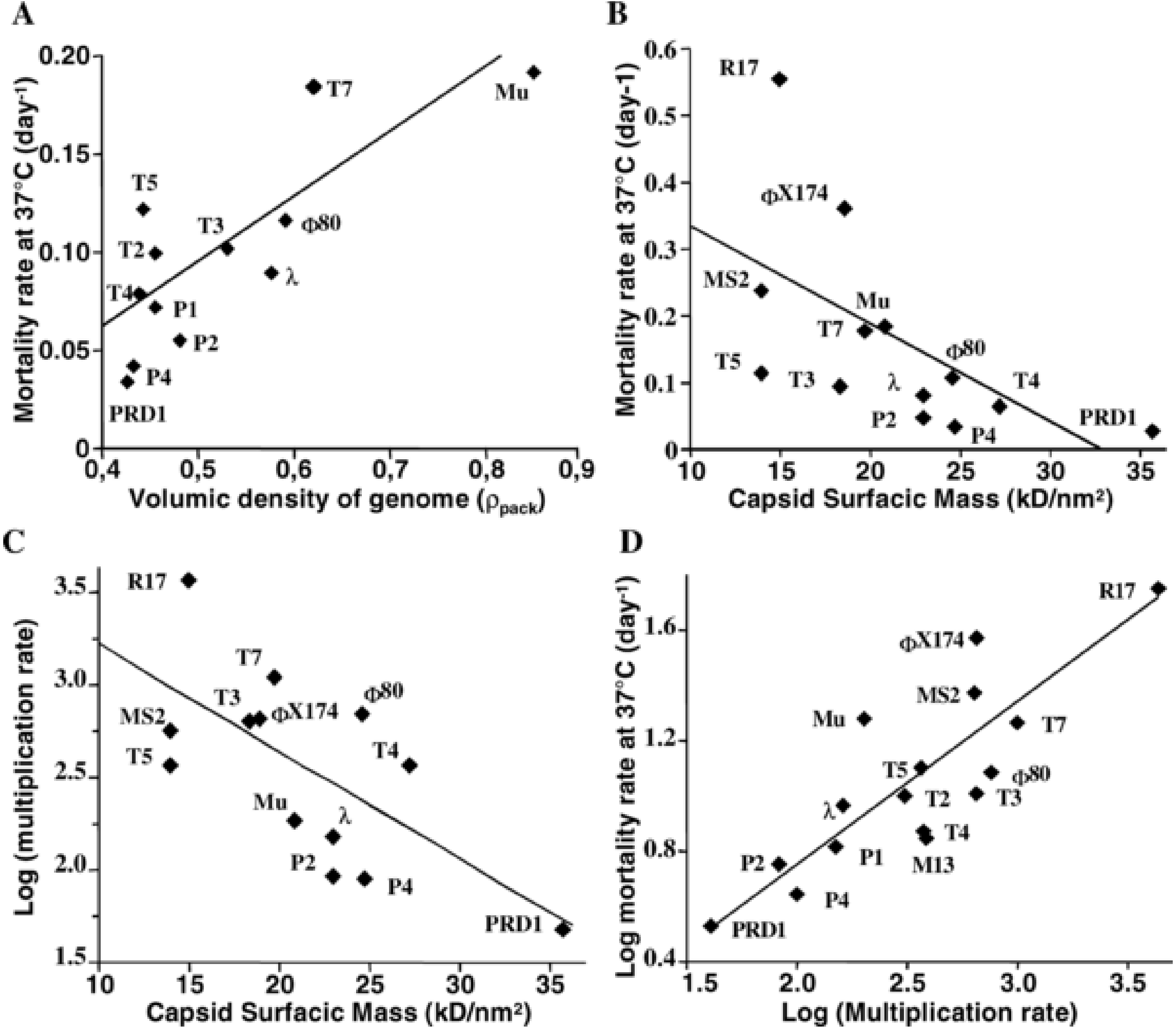
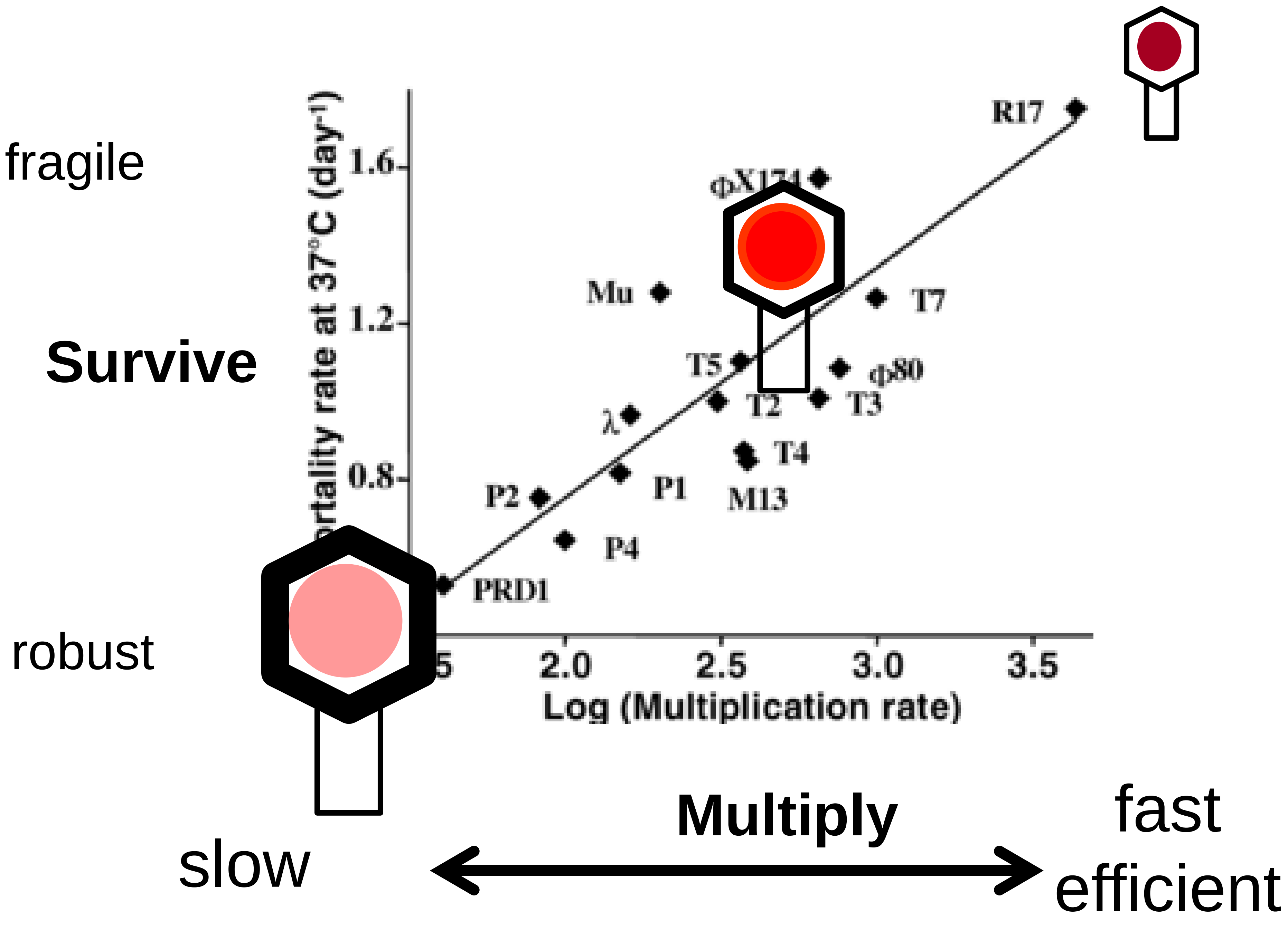
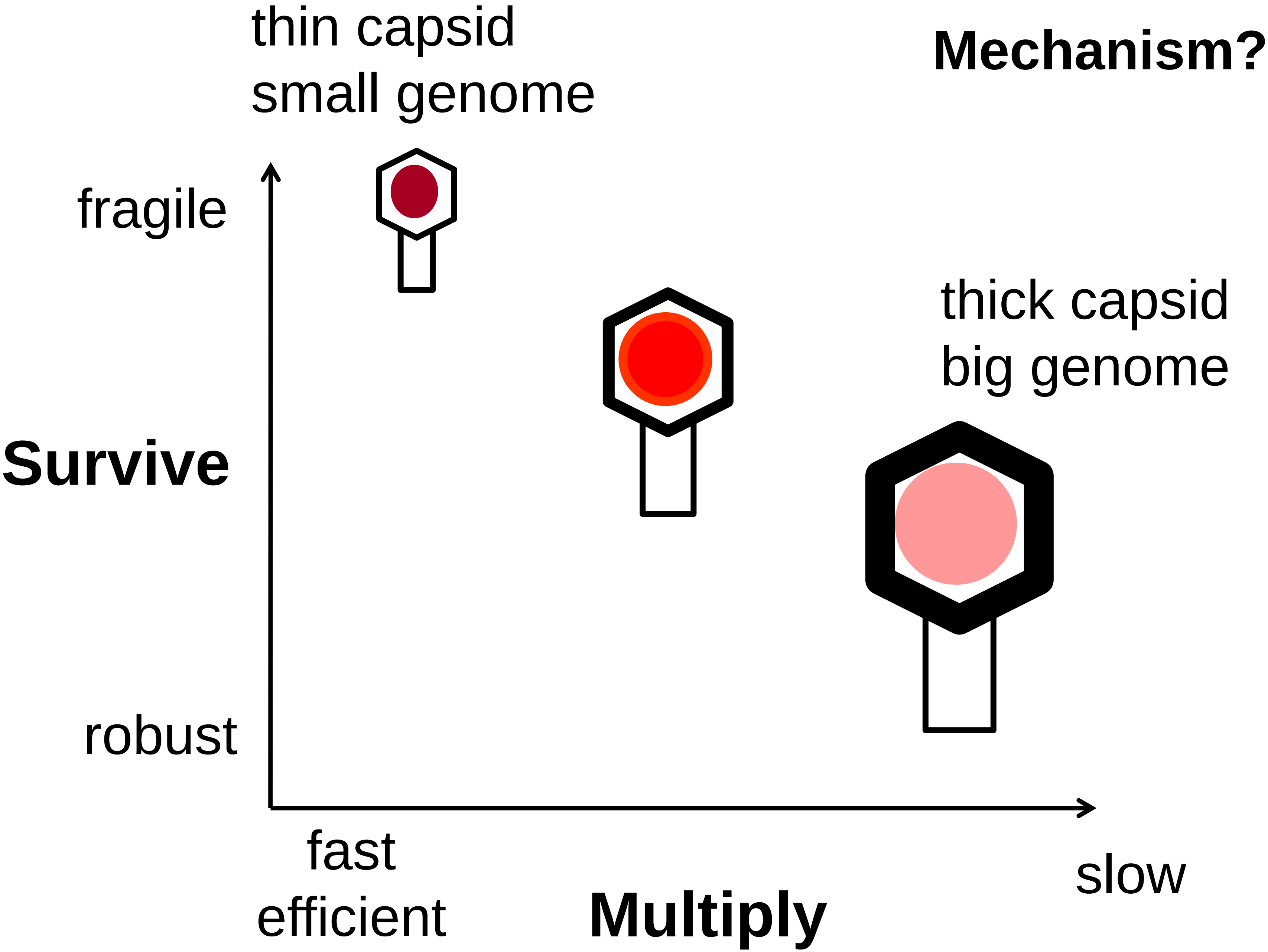
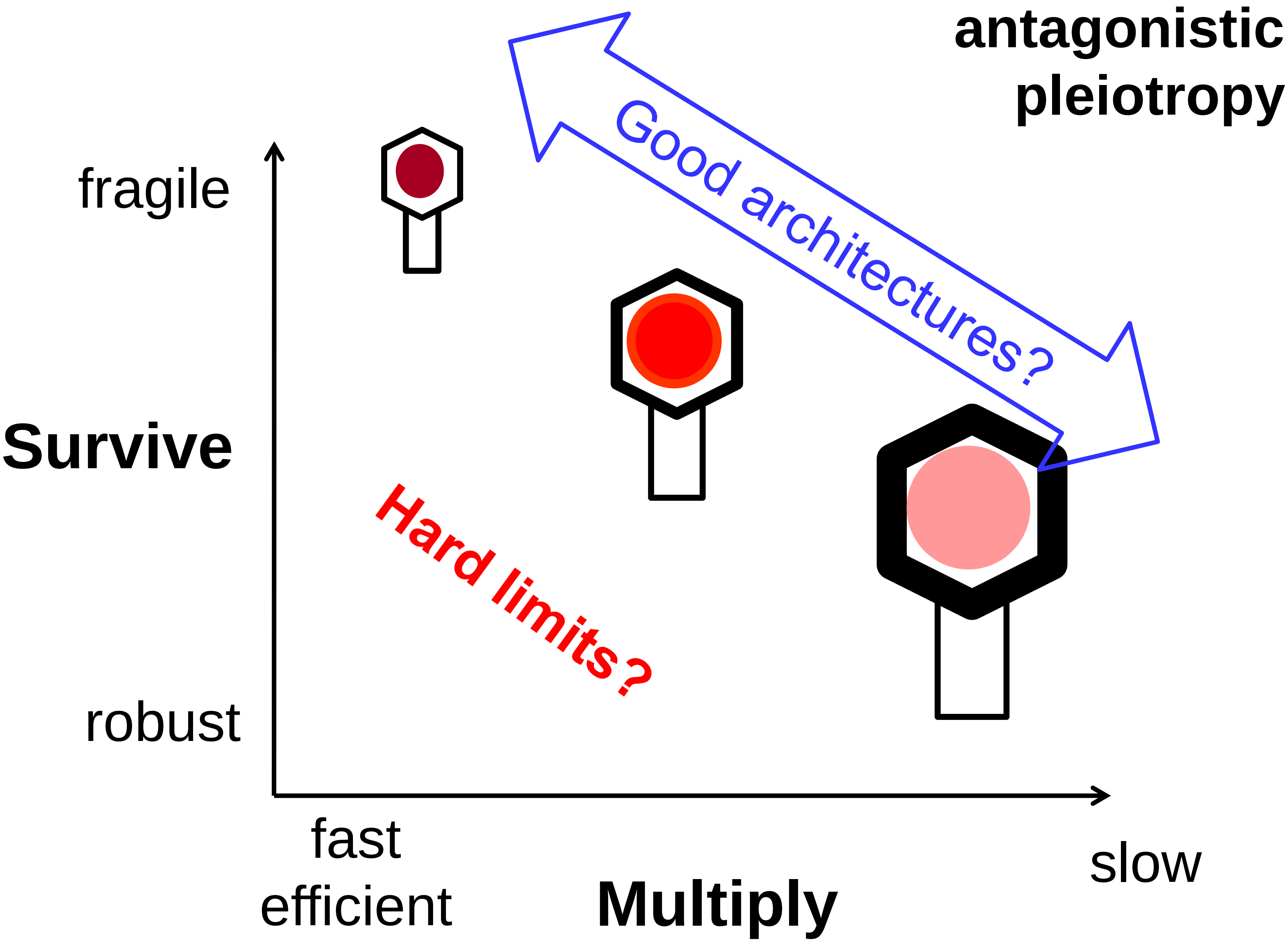


Figure 4. Correlations between Phage Life History Traits and Phage Particle Characteristics



fragile
Survive
robust
rtality rate at 37°C (day-1)
1.6
1.2
0.8
R17
Mu
T7
T5
φ80
T2
T3
λ
T4
P1
M13
P2
P4
PRD1
5
2.0
2.5
3.0
3.5
Log (Multiplication rate)
slow
Multiply
fast
efficient


thin capsid
small genome
Mechanism?
fragile
thick capsid
big genome
Survive
robust
fast
efficient
Multiply
slow


antagonistic
pleiotropy
Good architectures?
fragile
Survive
Hard limits?
robust
fast
efficient
Multiply
slow

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[a] (h^{-1})	Adsorption Rate (min^{-1})	E_a[b] (kJ/mol)	Genome Size (kb)	Ext. Diameter[c] (nm)	Capsid MW[d] (kDa)	Surfacic Mass[e] (kDa/nm^2)	ρ_{pack}[f]
λ	Siphoviridae	T	0.072	115	42	162	4.5×10^{-10}	142	49 [37]	63 [24]	22,500 [38]	22.7	0.572
M13	Inoviridae	Chronic	0.074			413	9.0×10^{-11}	125	6 [37]	6.5x90 [37]	15,700 [39]	8.7	
MS2	Leviviridae	L	0.250	400	40	669	6.5×10^{-10}	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^{-10}	119	100 [37]	85 [44]			0.435
P2	Myoviridae	T	0.041	160	48	88	5.5×10^{-11}	123	34 [37]	60 [45]	20,400 [46]	22.7	0.468
P4	Myoviridae	T	0.045	300	60	101	2.2×10^{-10}	105	12 [37]	45 [46]	12,400 [46]	24.5	0.429
φ80	Siphoviridae	T	0.120	600	55	776	3.8×10^{-10}	114	45	61		24.3	0.585
φX174	Microviridae	L	0.200	180	15	697	2.9×10^{-9}	136	5 [37]	32 [47]	4,700 [48]	18.4	
PRD1	Tectiviridae	L	0.037	50	48	50	4.6×10^{-10}	171	15 [49]	65 [49]	33,000 [49]	35.5	0.421
T2	Myoviridae	L	0.068	135	23	335	4.0×10^{-10}		170 [37]	85x110 [50]		19.9	0.451
T3	Podoviridae	L	0.102	200	17	700	1.6×10^{-9}	105	38 [51]	60 [52]		18.1	0.525
T4	Myoviridae	L	0.068	150	23	400	5.0×10^{-10}	96	170 [37]	85x110 [50]	65,600 [50]	26.9	0.421
T5	Siphoviridae	L	0.120	290	44	399	2.0×10^{-10}	115	122 [53]	65 [53]	27,500 [53]	13.7	0.439
T7	Podoviridae	L	0.187	260	13	1,131	3.0×10^{-9}	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^{-9}	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_{pack} 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.

[a]Mean of the ratio obtained by dividing the burst size by the latency period, calculated for each experiment.

[b]E_a: 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.

[c]Ext. diameter: external diameter of the capsid.

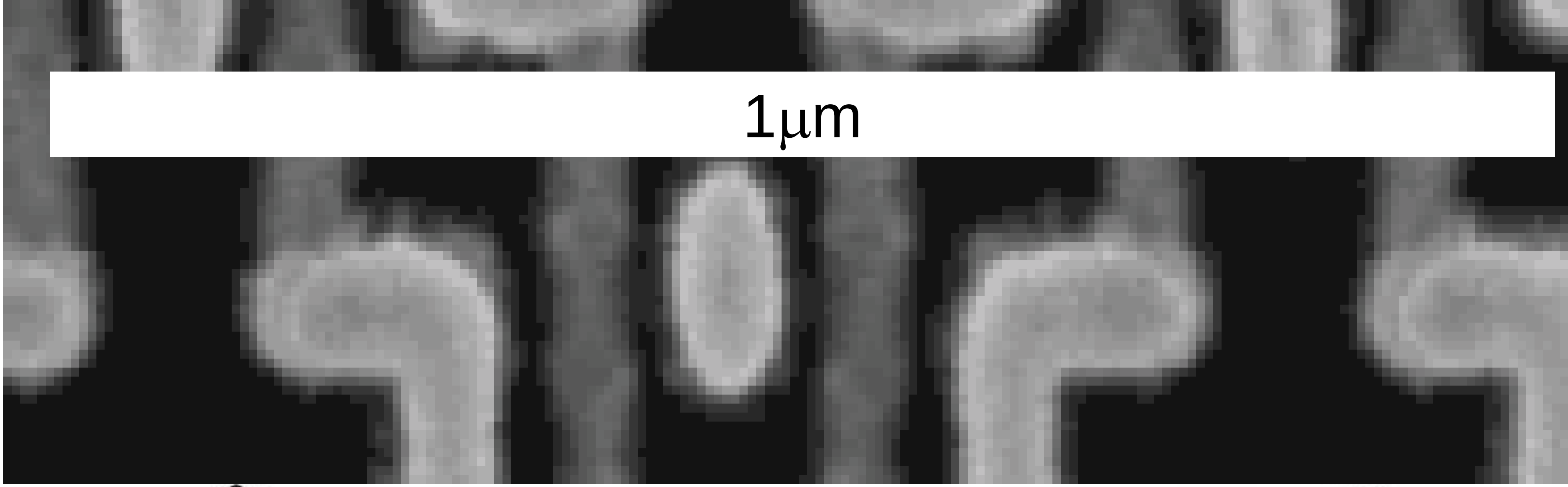
[d]Molecular weight of the proteins constituting the capsid.

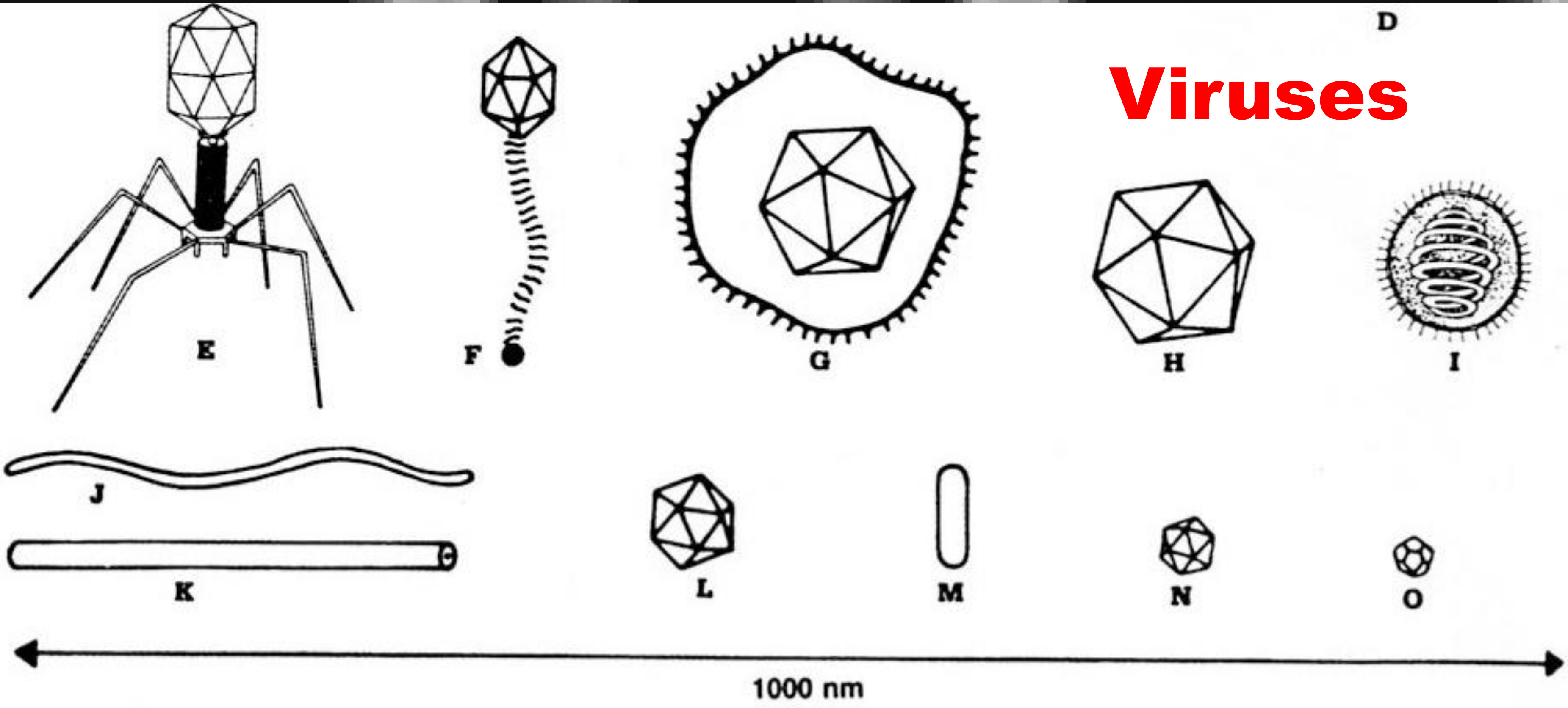
[e]Capsid molecular weight divided by the surface of the capsid; this ratio represents the thickness of the shell.

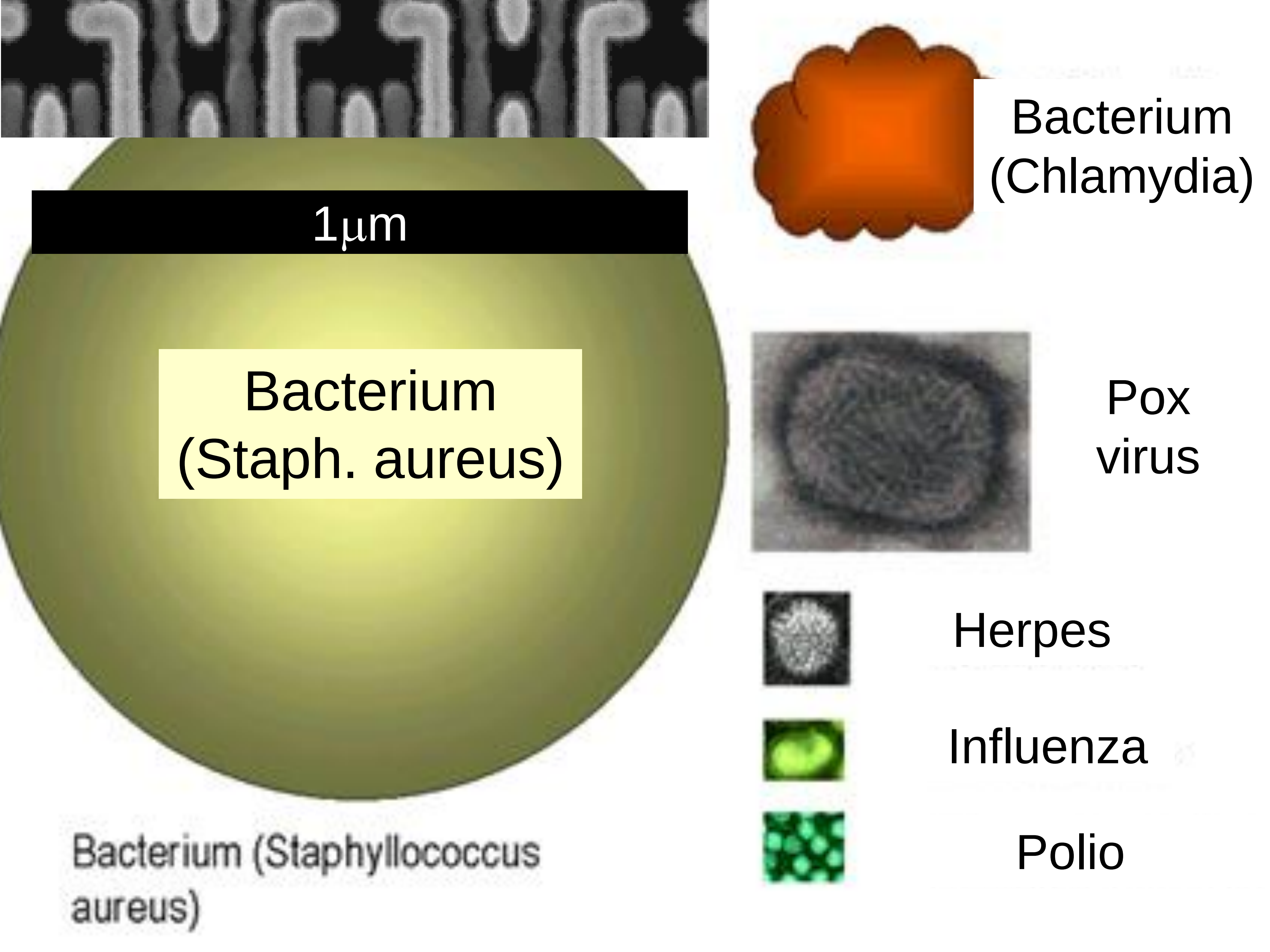
[f]Volume occupied by the genome divided by the internal volume of the capsid.

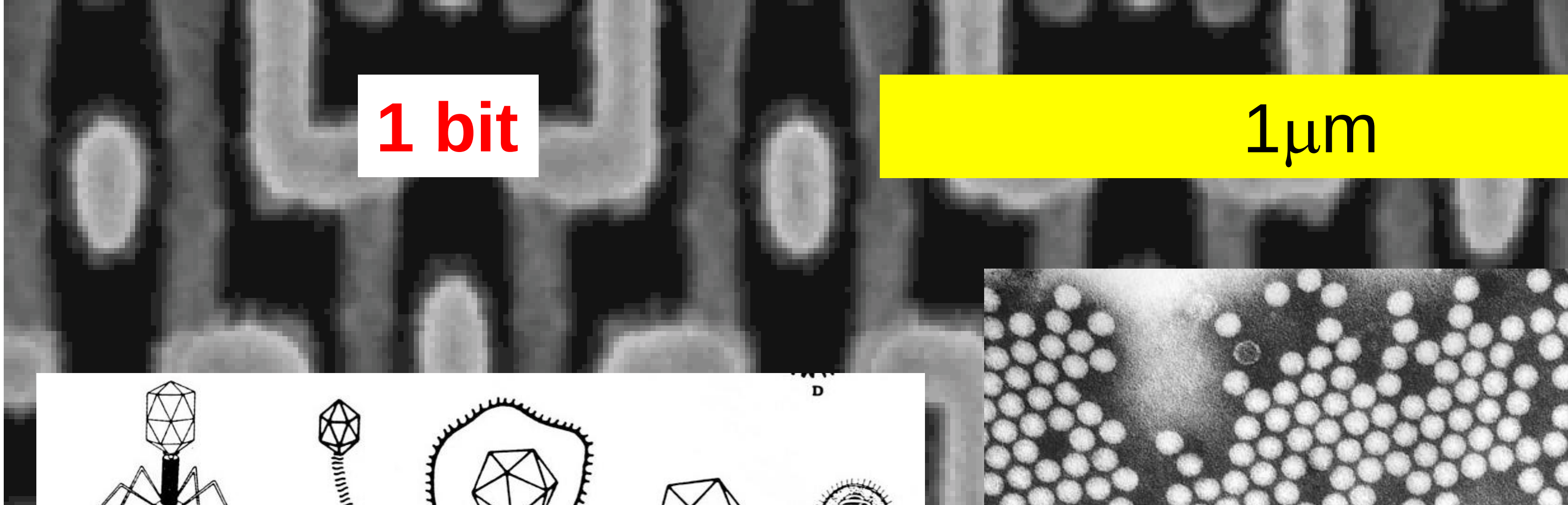
T: Temperate phage, L: Virulent Phage, Chronic: creates a chronic infection

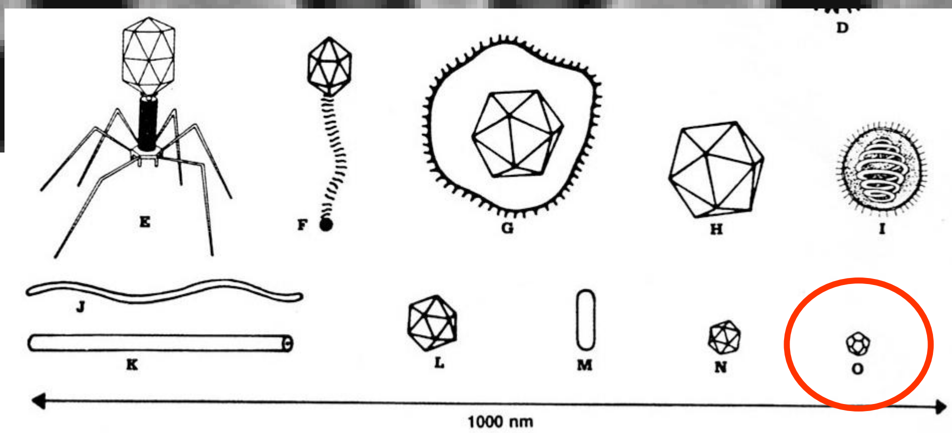
DOI: 10.1371/journal.pbio.0040193.t001

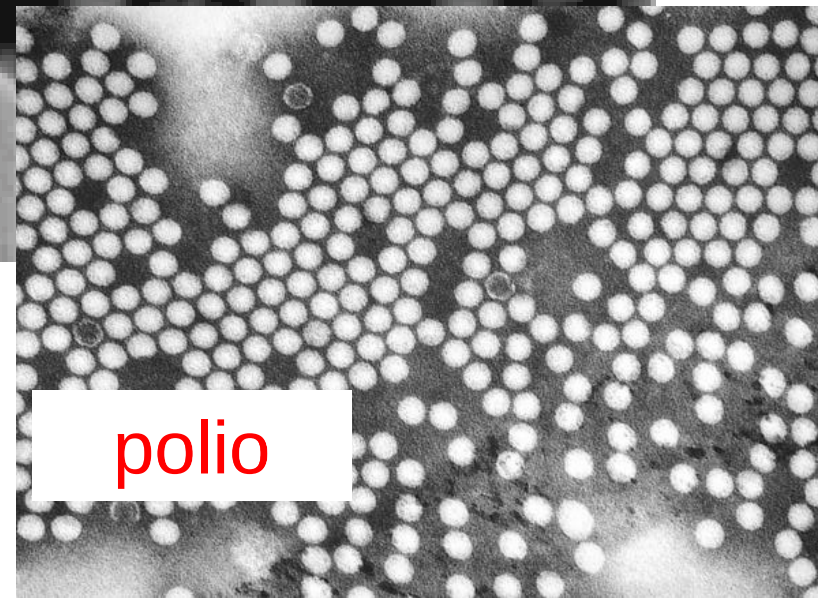

1μm


D
Viruses
E
F
G
H
I
J
K
L
M
N
O
1000 nm

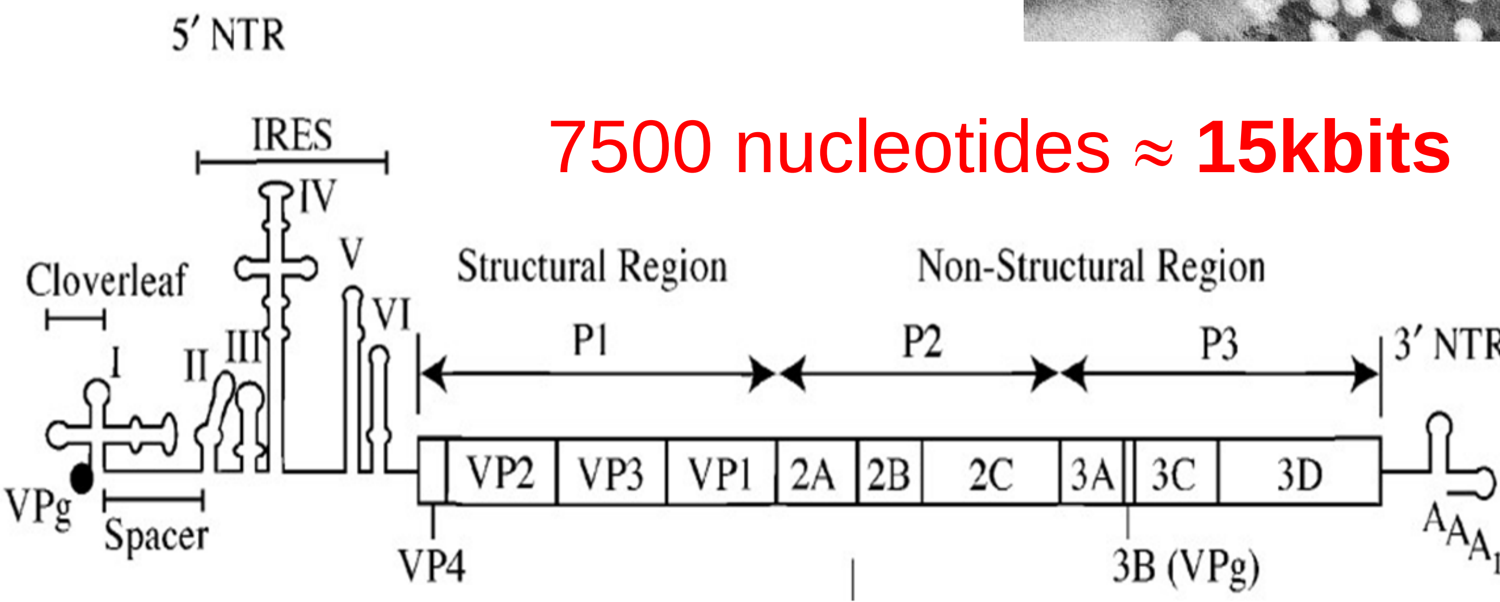

1μm
Bacterium
(Staph. aureus)
Bacterium (Staphyllococcus
aureus)
Bacterium
(Chlamydia)
Pox
virus
Herpes
Influenza
Polio

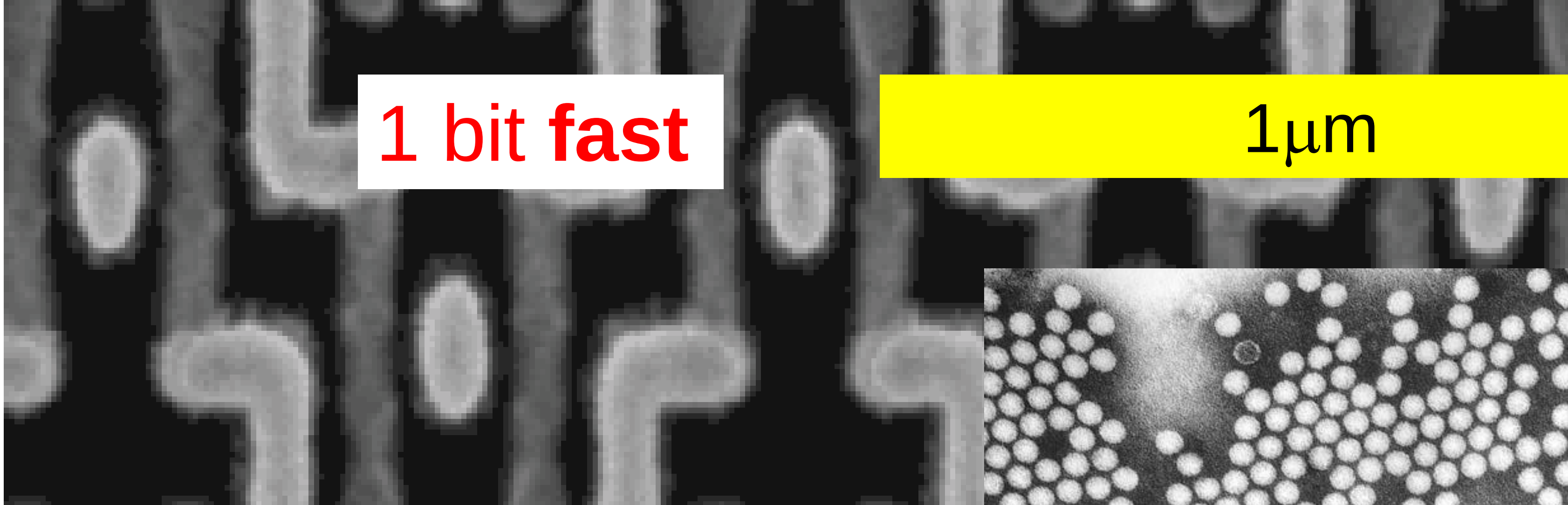


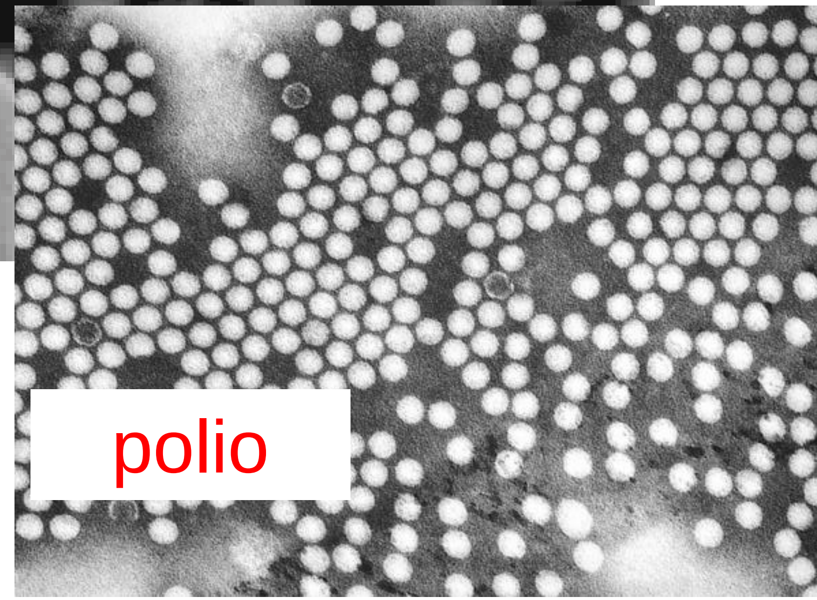




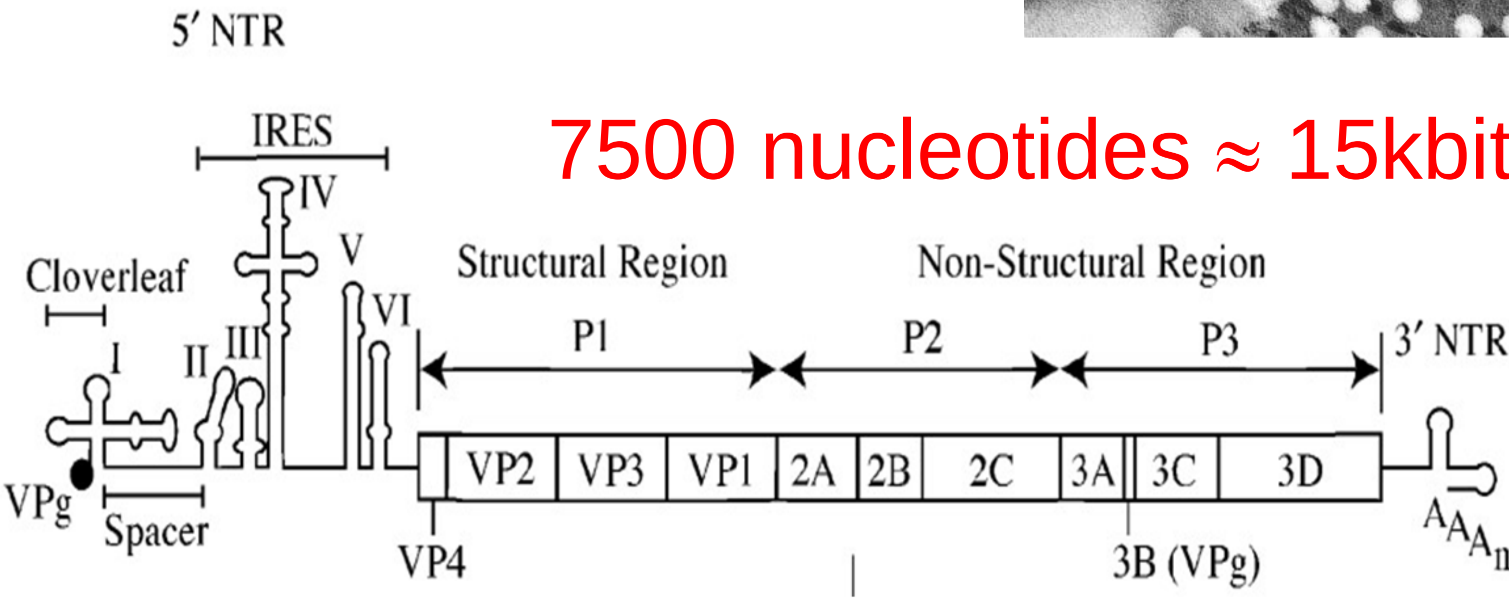
7500 nucleotides ≈ **15kbits**







7500 nucleotides ≈ 15kbits **slow**



UG biochem, math, control theory

Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,[1]* Gentian Buzi,[2] John C. Doyle[2]

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.

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.

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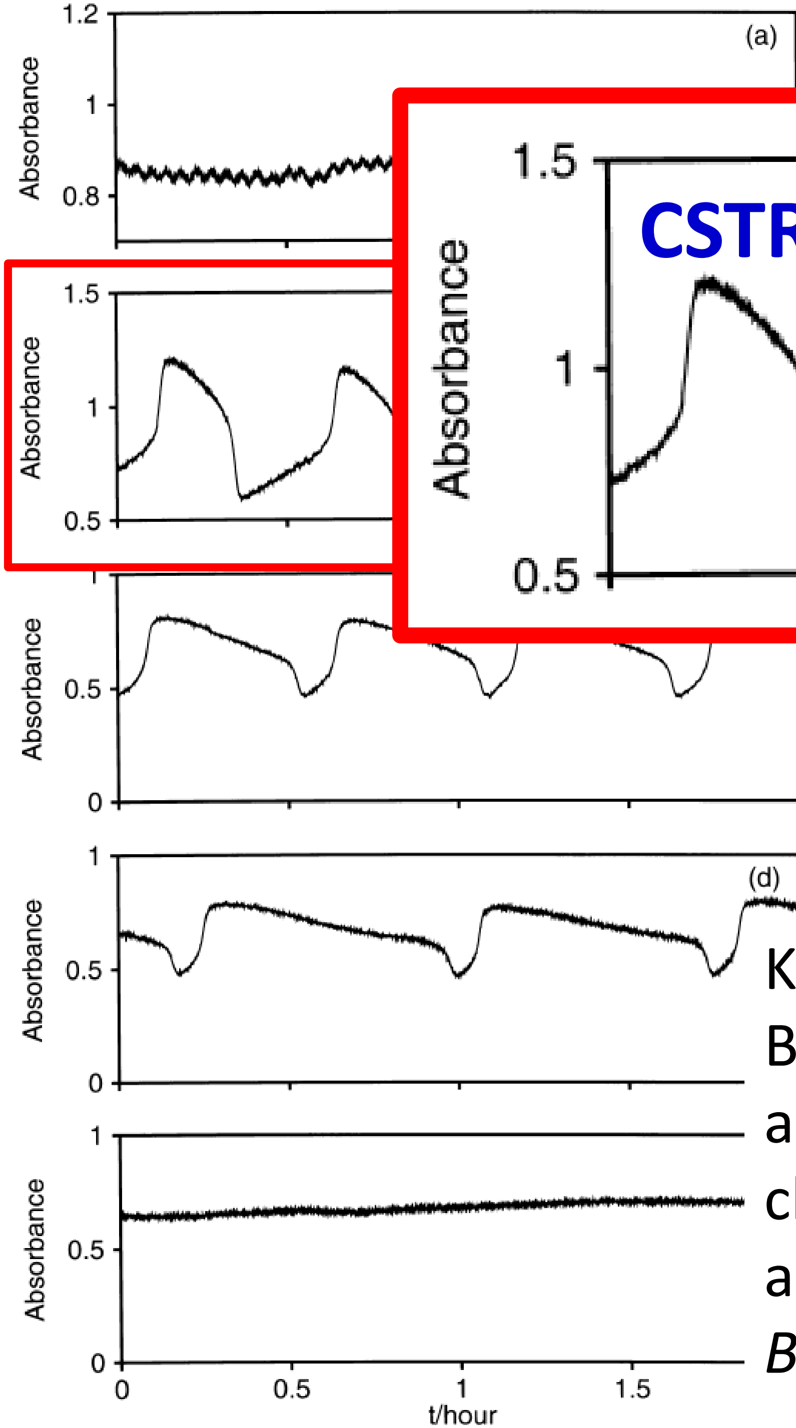


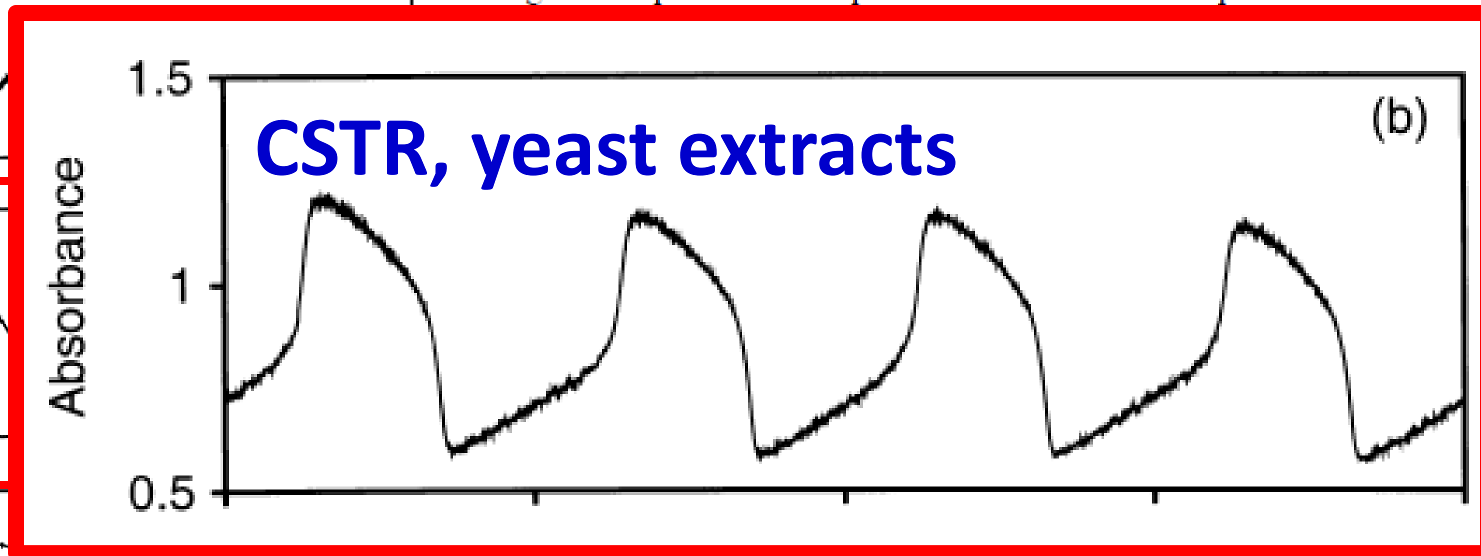


Fig. 2. Dependence of pattern on flow rate. Experimental time

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

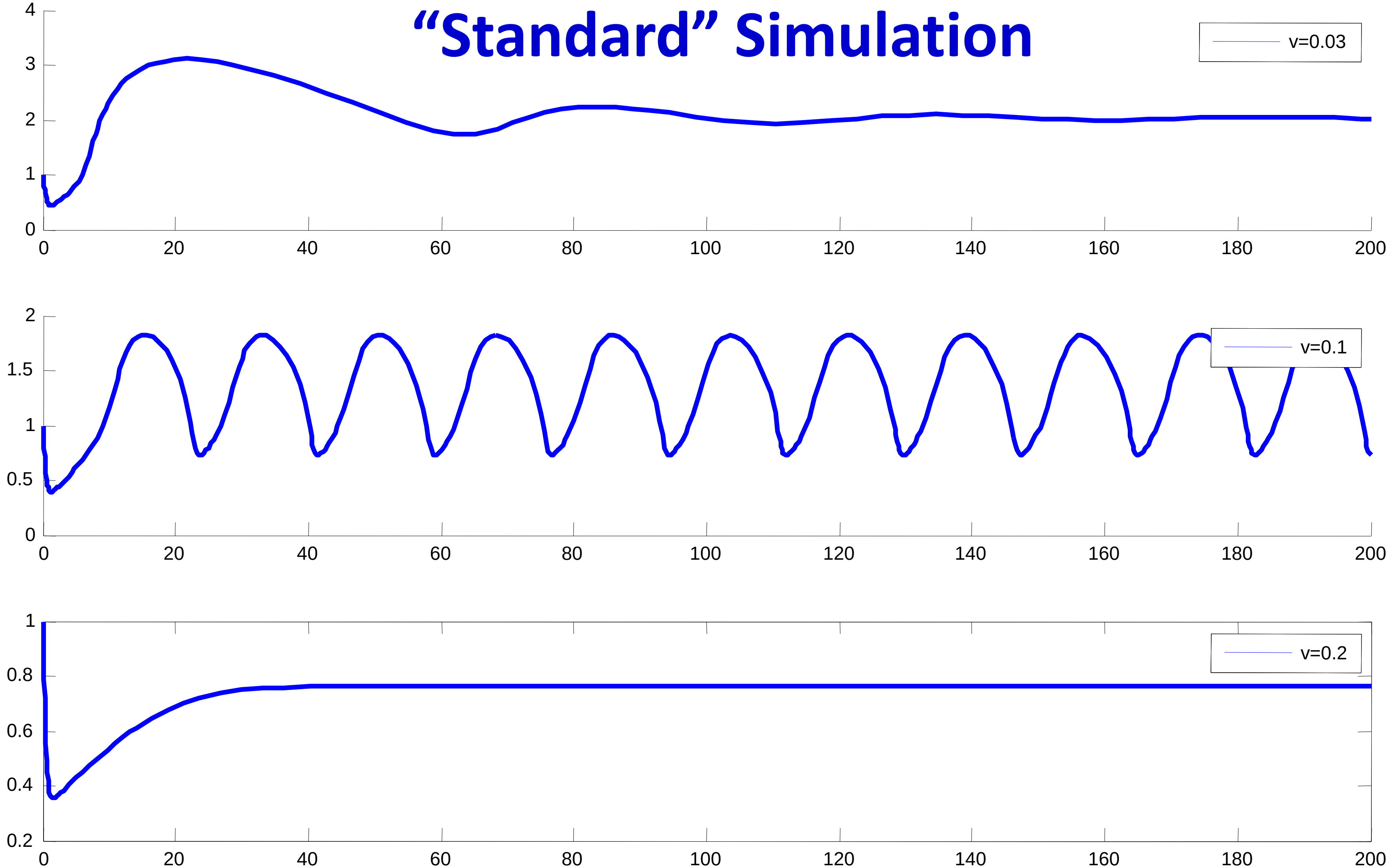
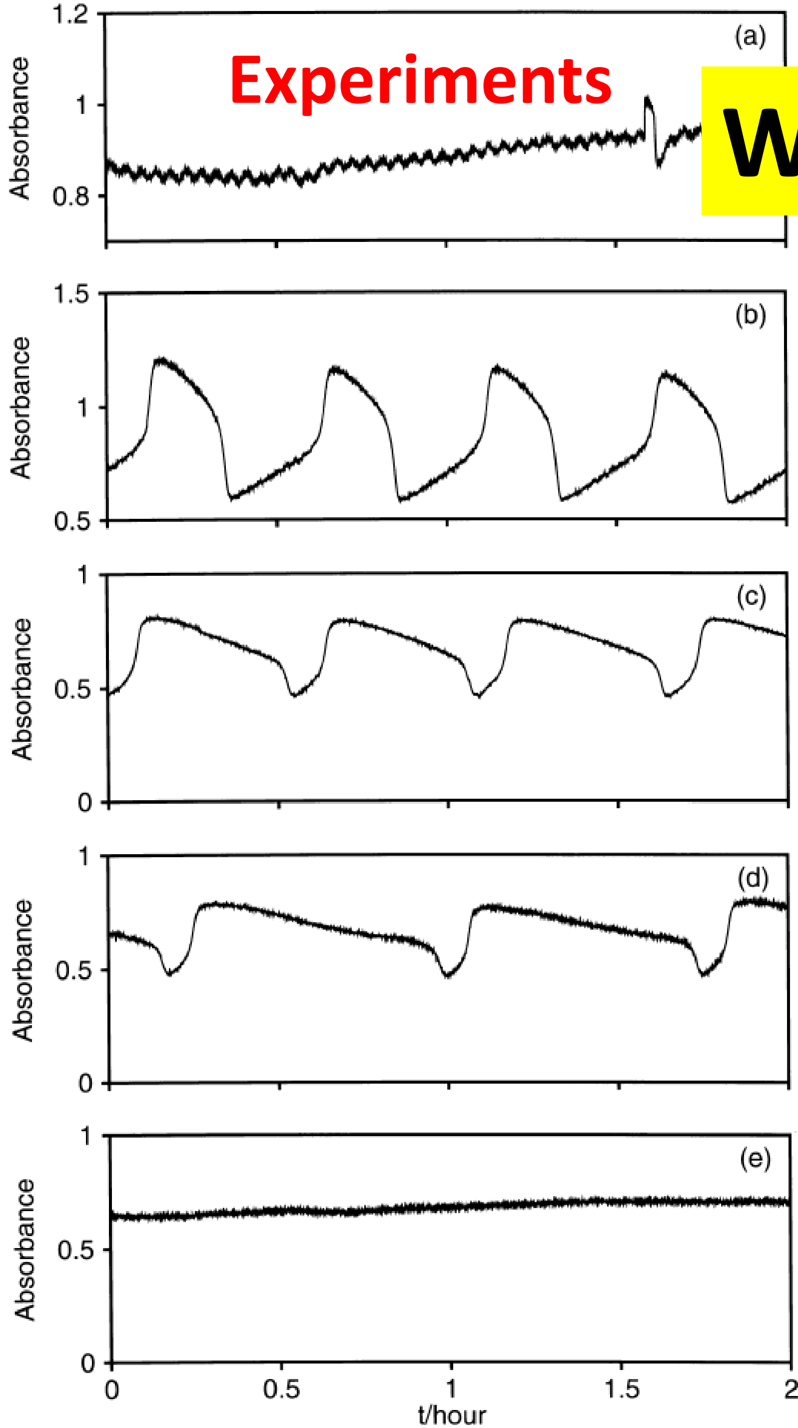
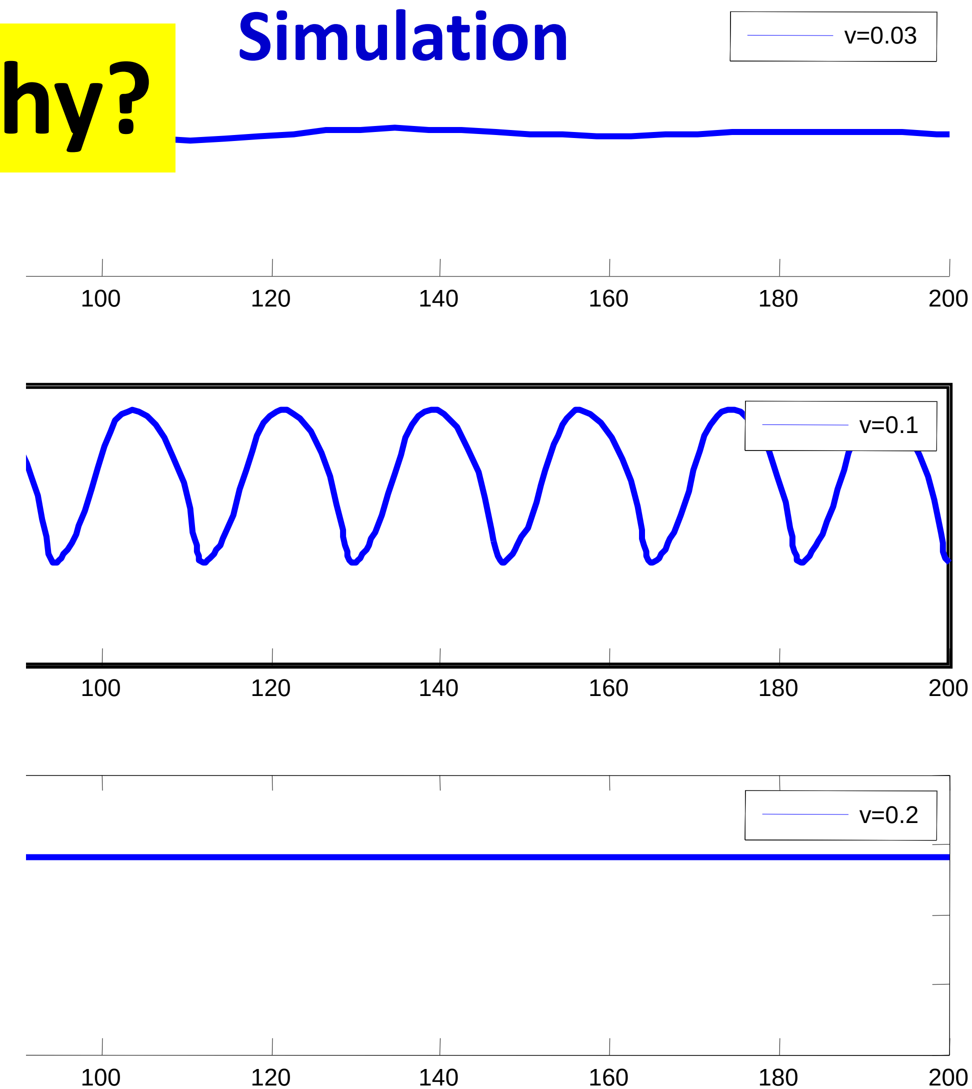


Figure S4. Simulation of two state model (S7.1) qualitatively recapitulates experimental observation from CSTR studies [5] and [12]. As the flow of material in/out of the system is increased, the system enters a limit cycle and then stabilizes again. For this simulation, we take *q=a=Vm=1, k=0.2, g=1,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



Why?



ɔdel (S7.1) qualitatively recapitulates
studies [5] and [12]. As the flow of material
: system enters a limit cycle and then
ve 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

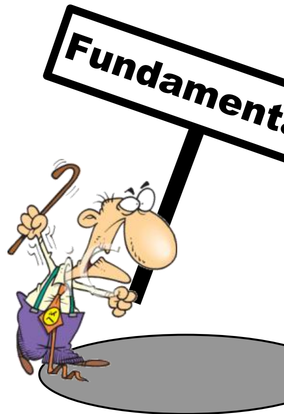
Science

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

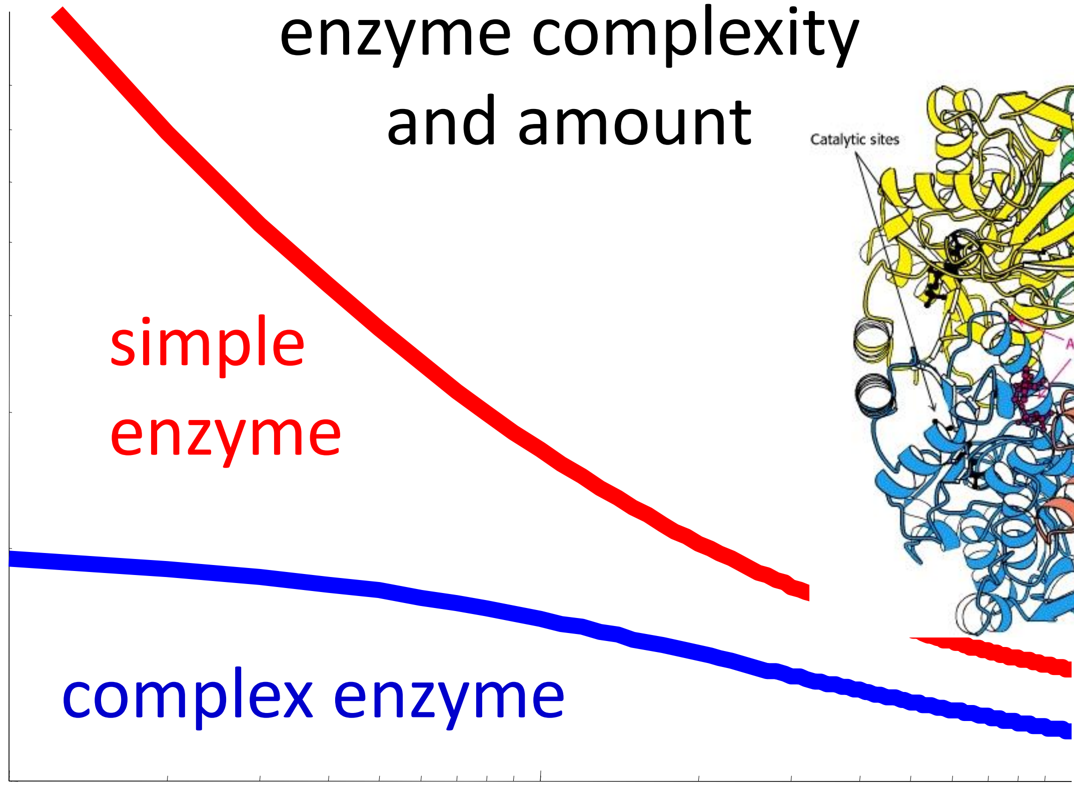


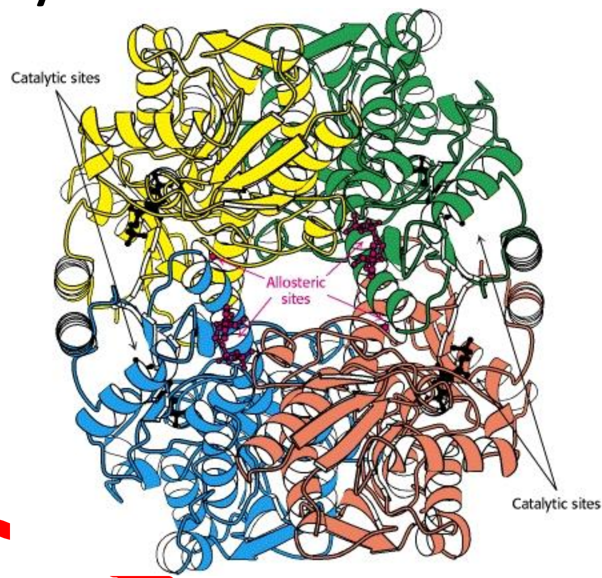
Theorem!

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

z and *p* functions of enzyme complexity and amount

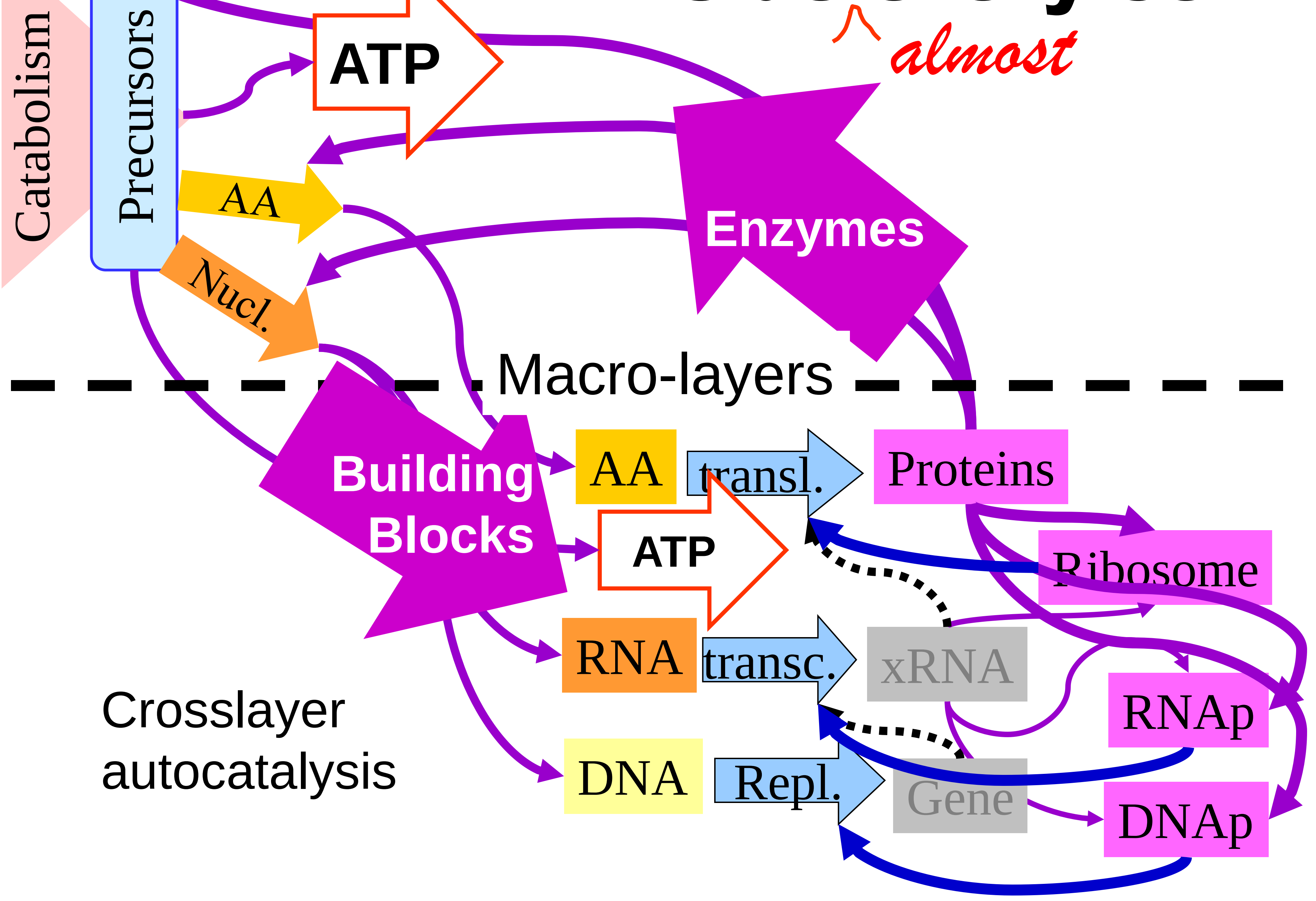
$$\ln\left|\frac{z+p}{z-p}\right|$$

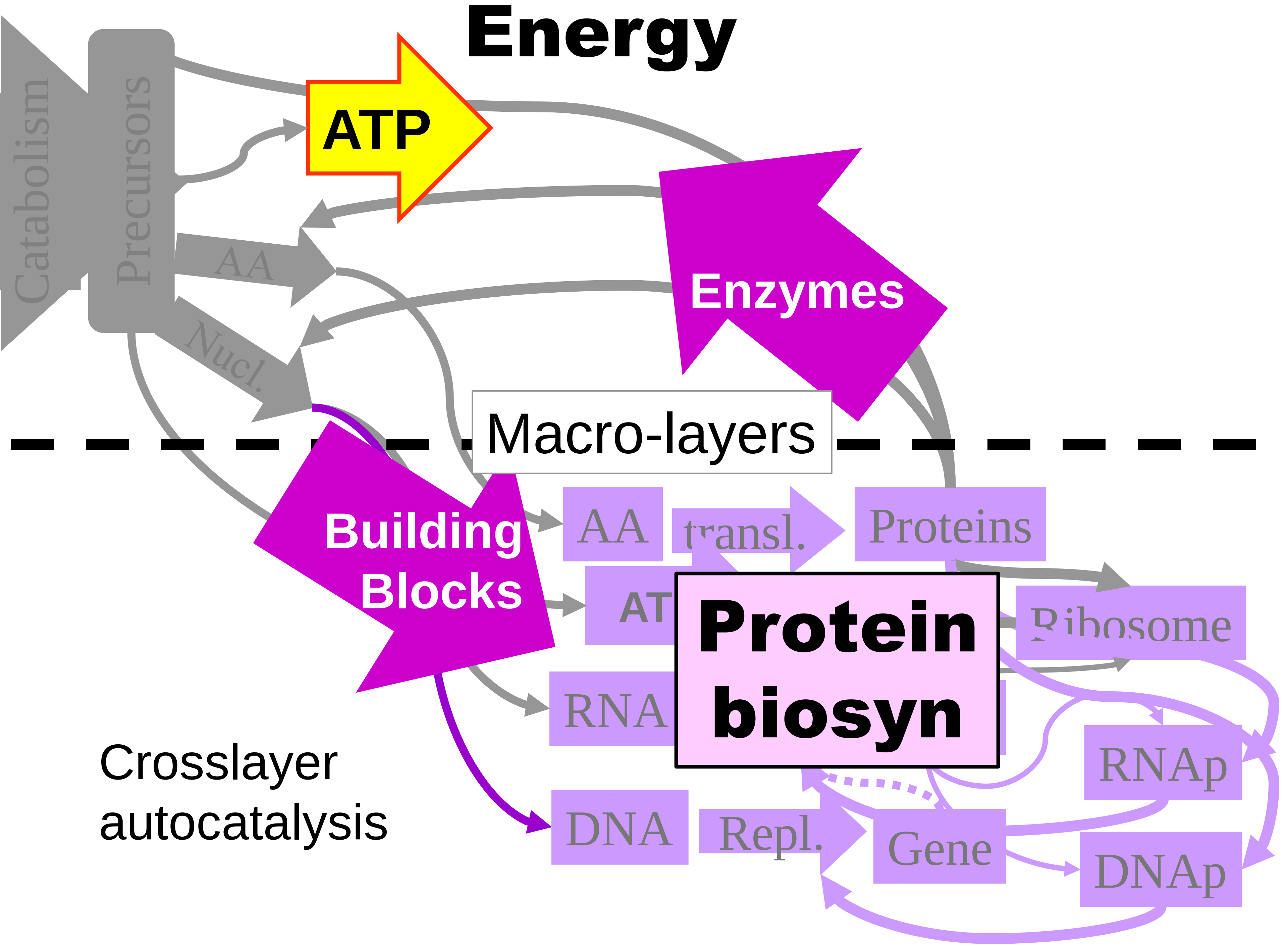




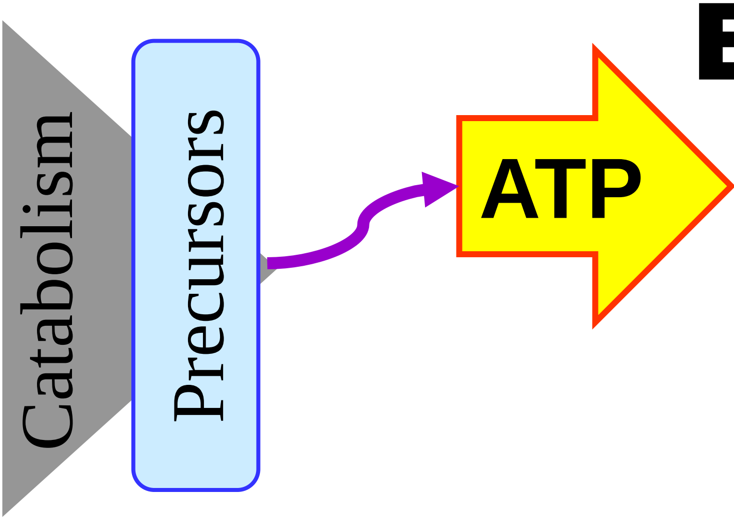
Savageaumics

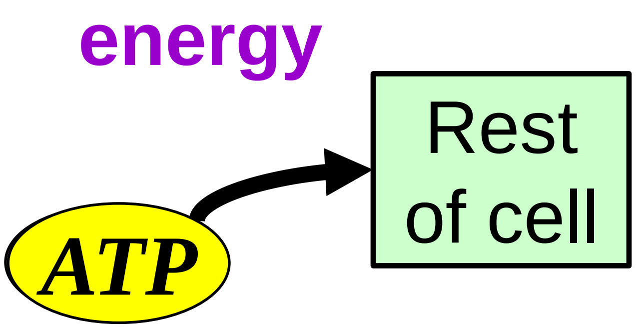
Inside every cell




Energy
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
Ribosome
RNA
RNAp
DNA
Repl.
Gene
DNAp
Protein biosyn
Crosslayer autocatalysis

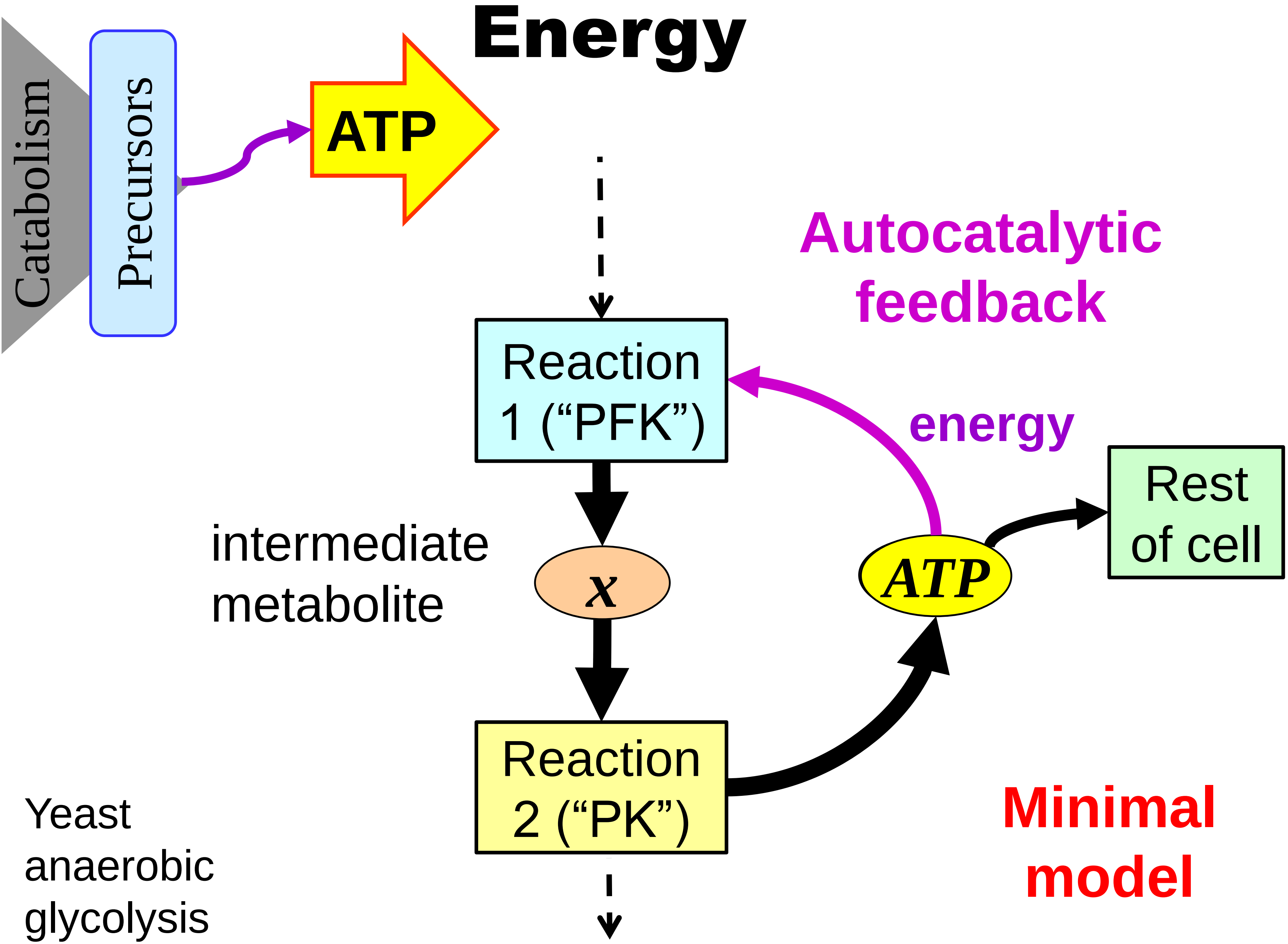
Energy





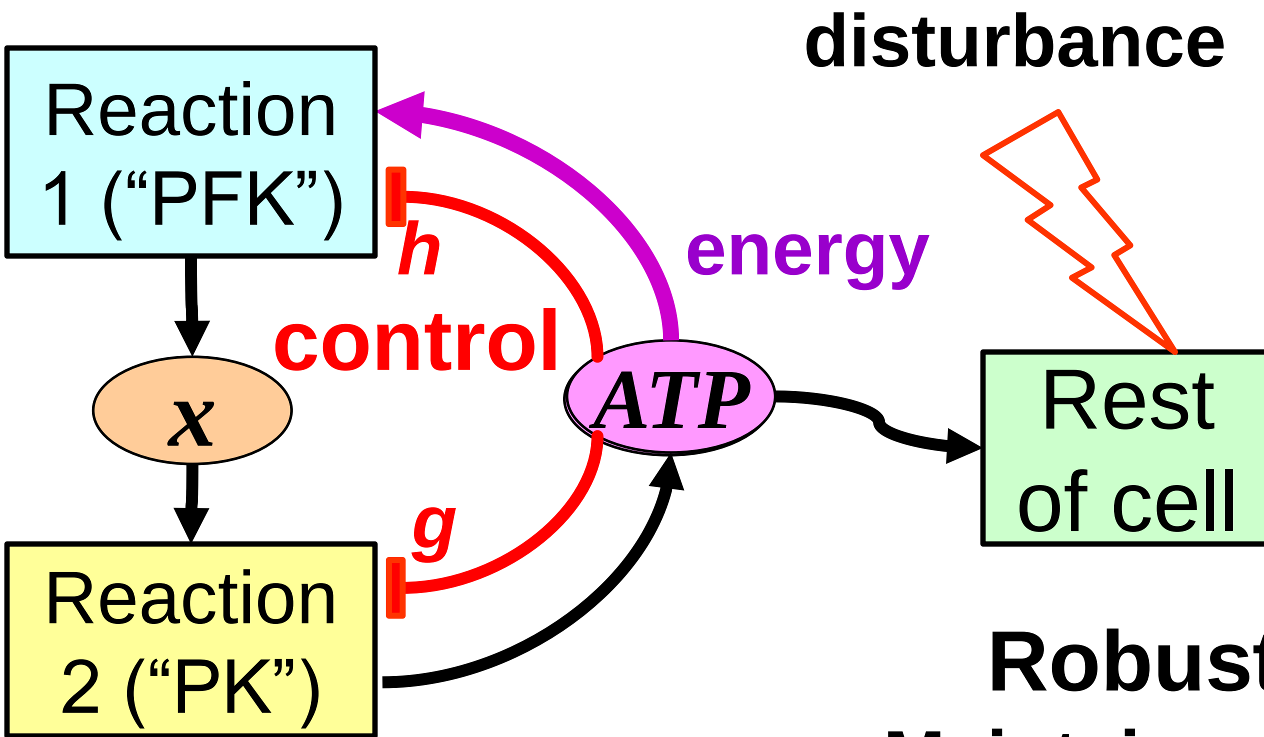
Yeast anaerobic glycolysis

Minimal model



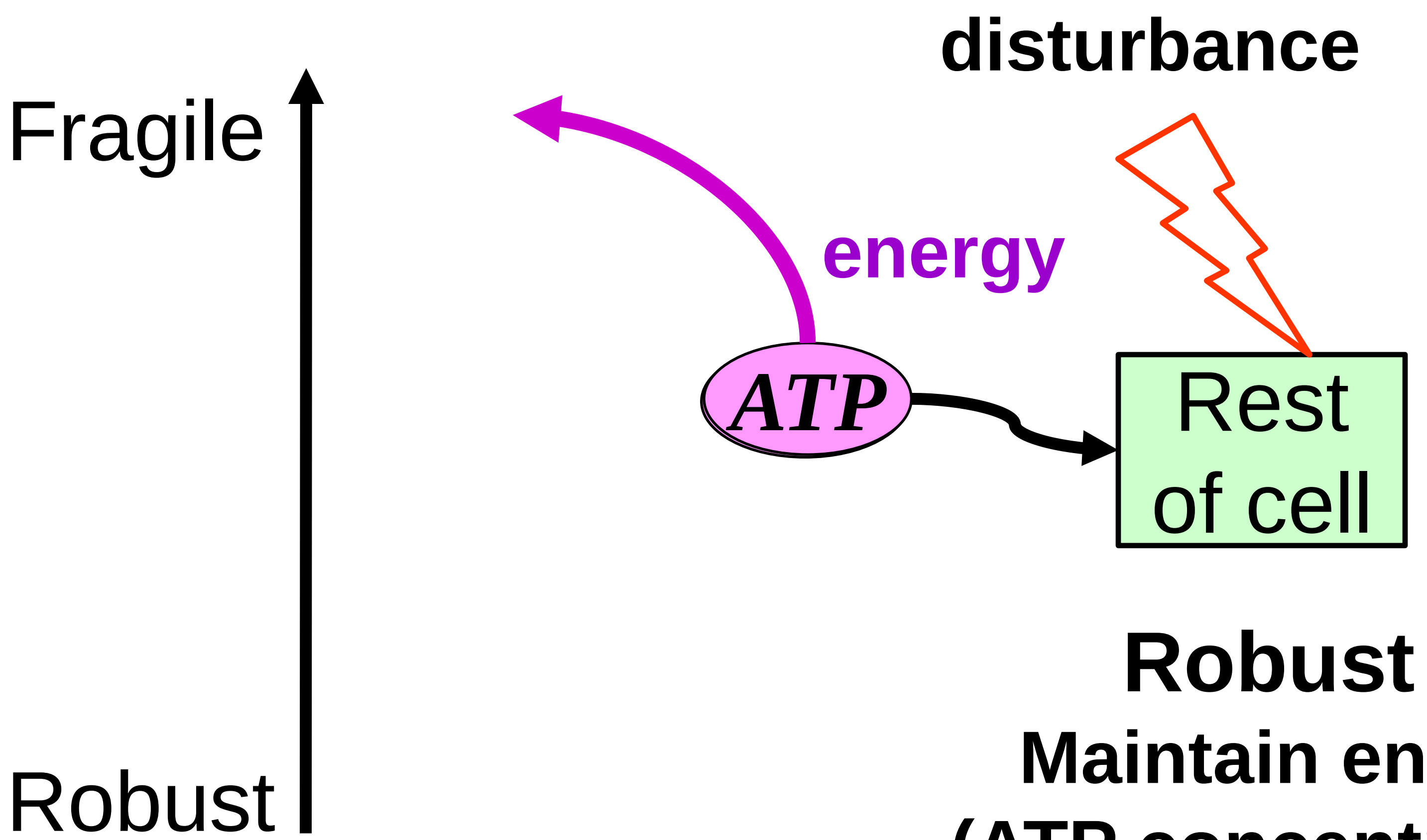
Energy
Catabolism
Precursors
ATP
Autocatalytic feedback
Reaction 1 ("PFK")
energy
intermediate metabolite
x
ATP
Rest of cell
Reaction 2 ("PK")
Yeast anaerobic glycolysis
Minimal model

control feedback



Robust =
Maintain energy
(ATP concentration)
despite demand fluctuation

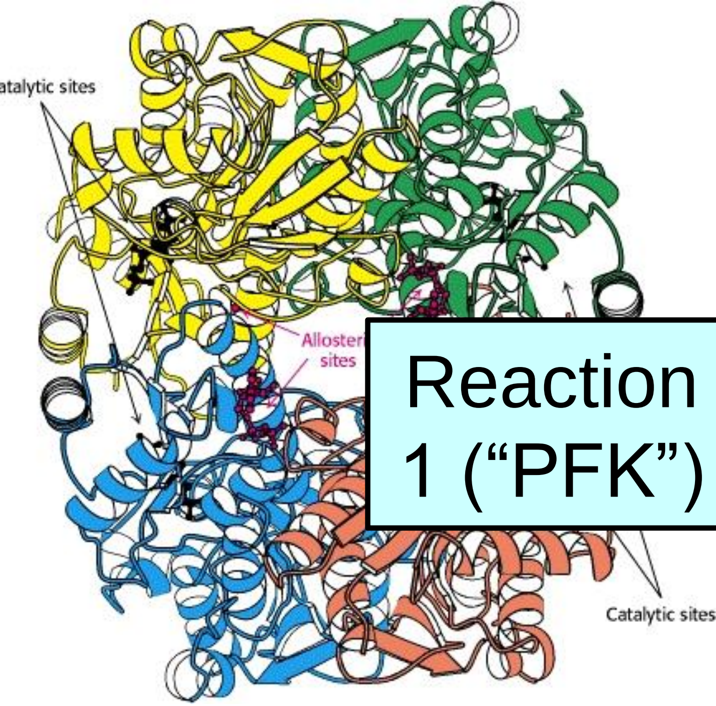
Tight control creates "weak linkage" between power supply and demand



Robust =
Maintain energy
(ATP concentration)
despite demand fluctuation

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

enzymes catalyze reactions



Reaction 1 (“PFK”)

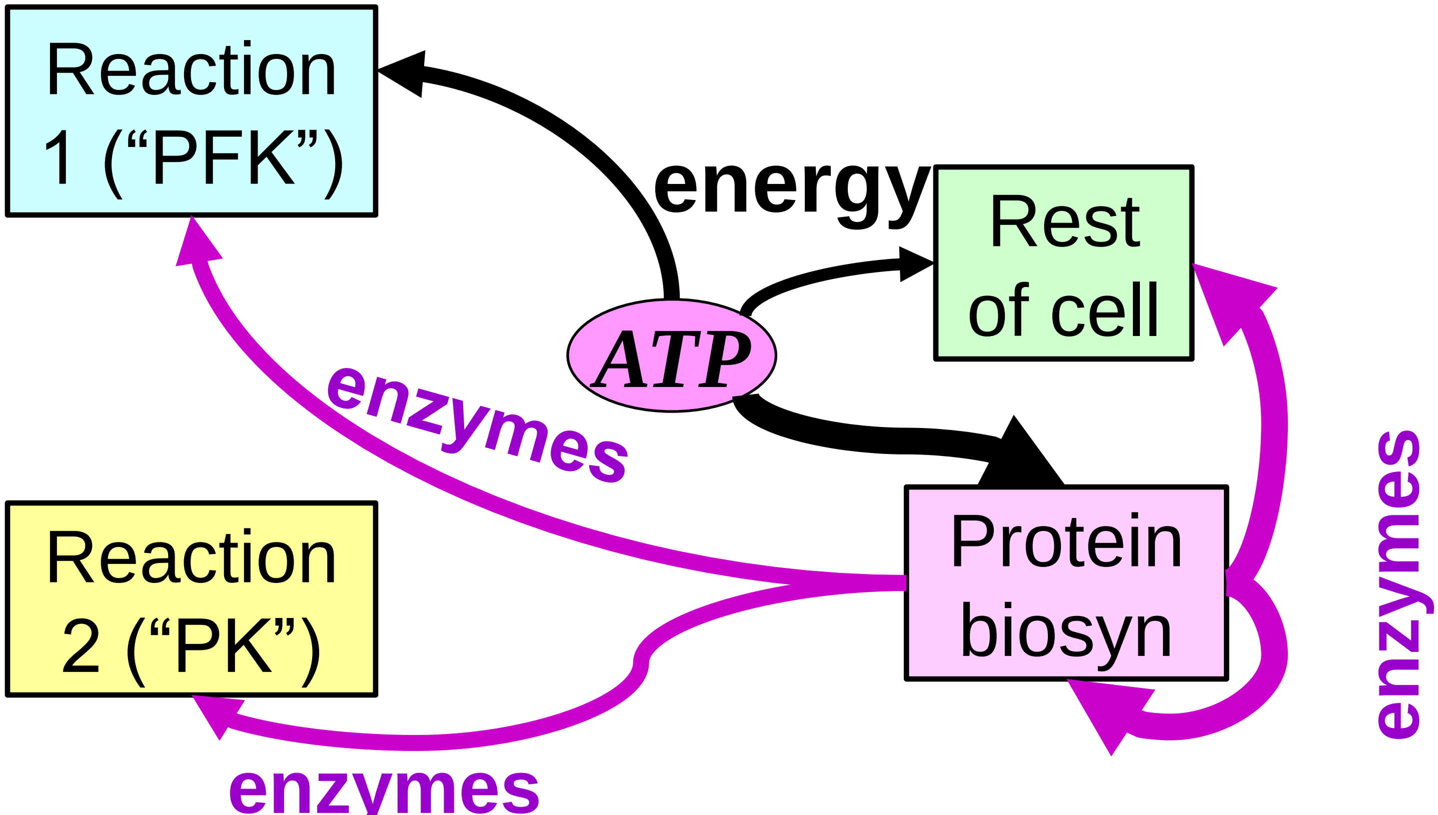
energy

ATP

Rest of cell

Reaction 2 (“PK”)

enzymes catalyze reactions

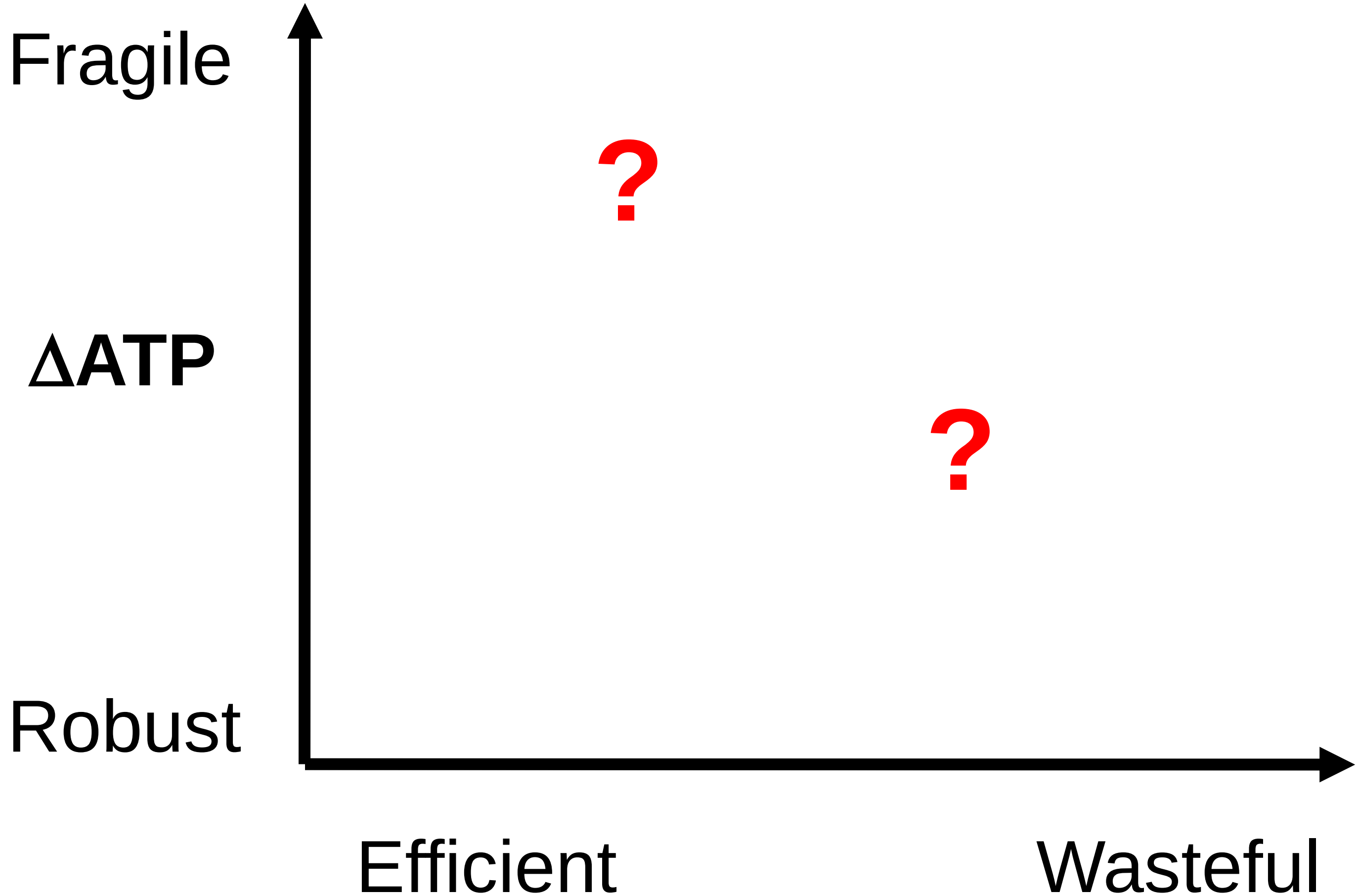


Efficient =

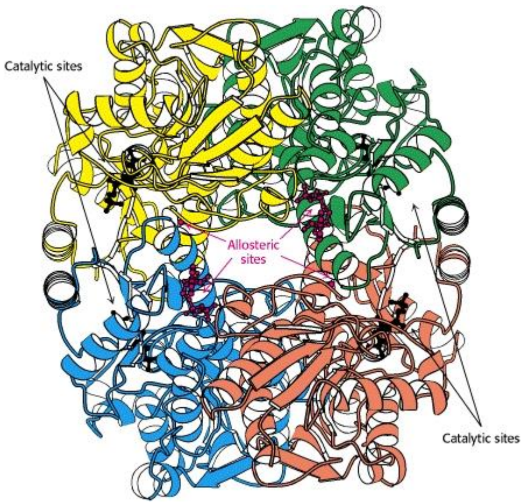
low metabolic overhead

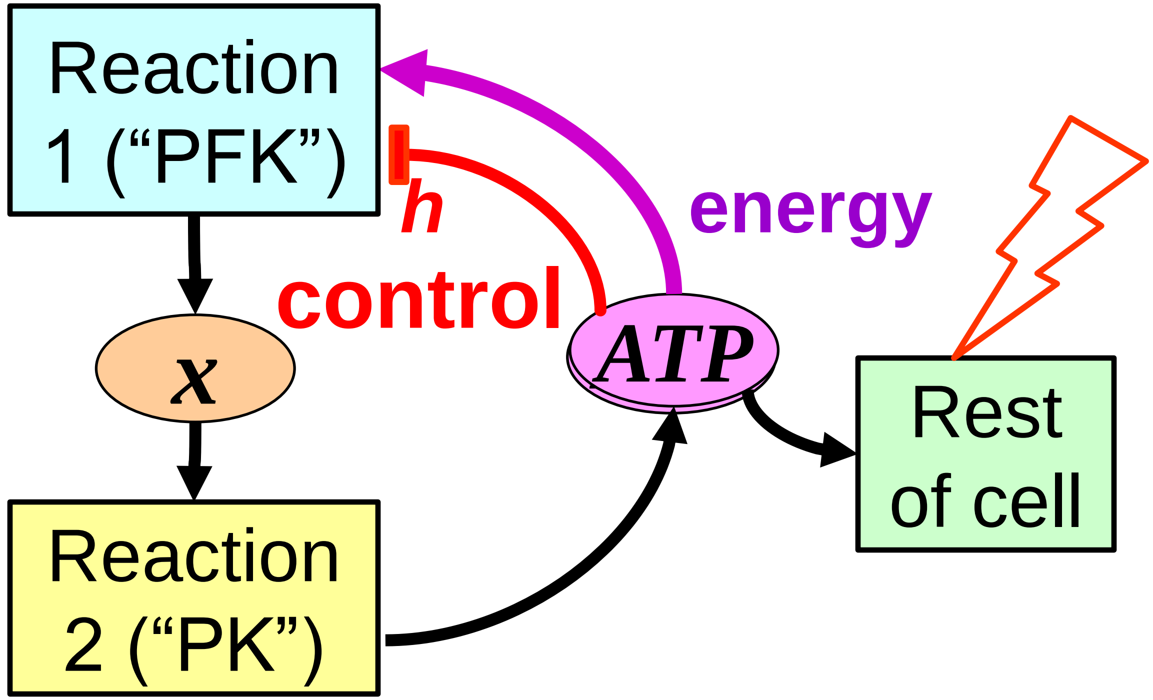
≈ low enzyme amount

Robust = Maintain ATP



Efficient = low enzyme amount





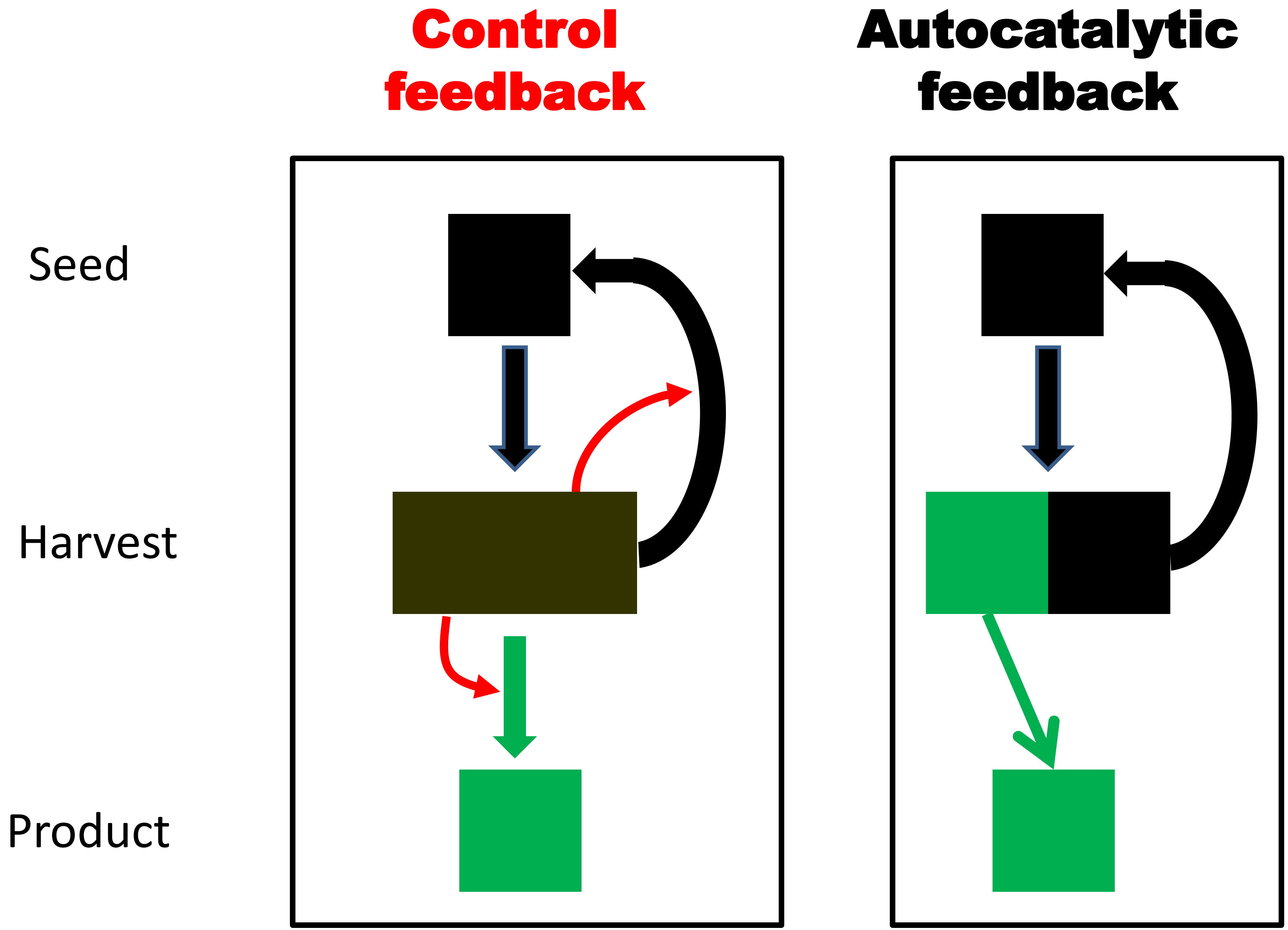
Standard story:

Autocatalytic plus control feedback

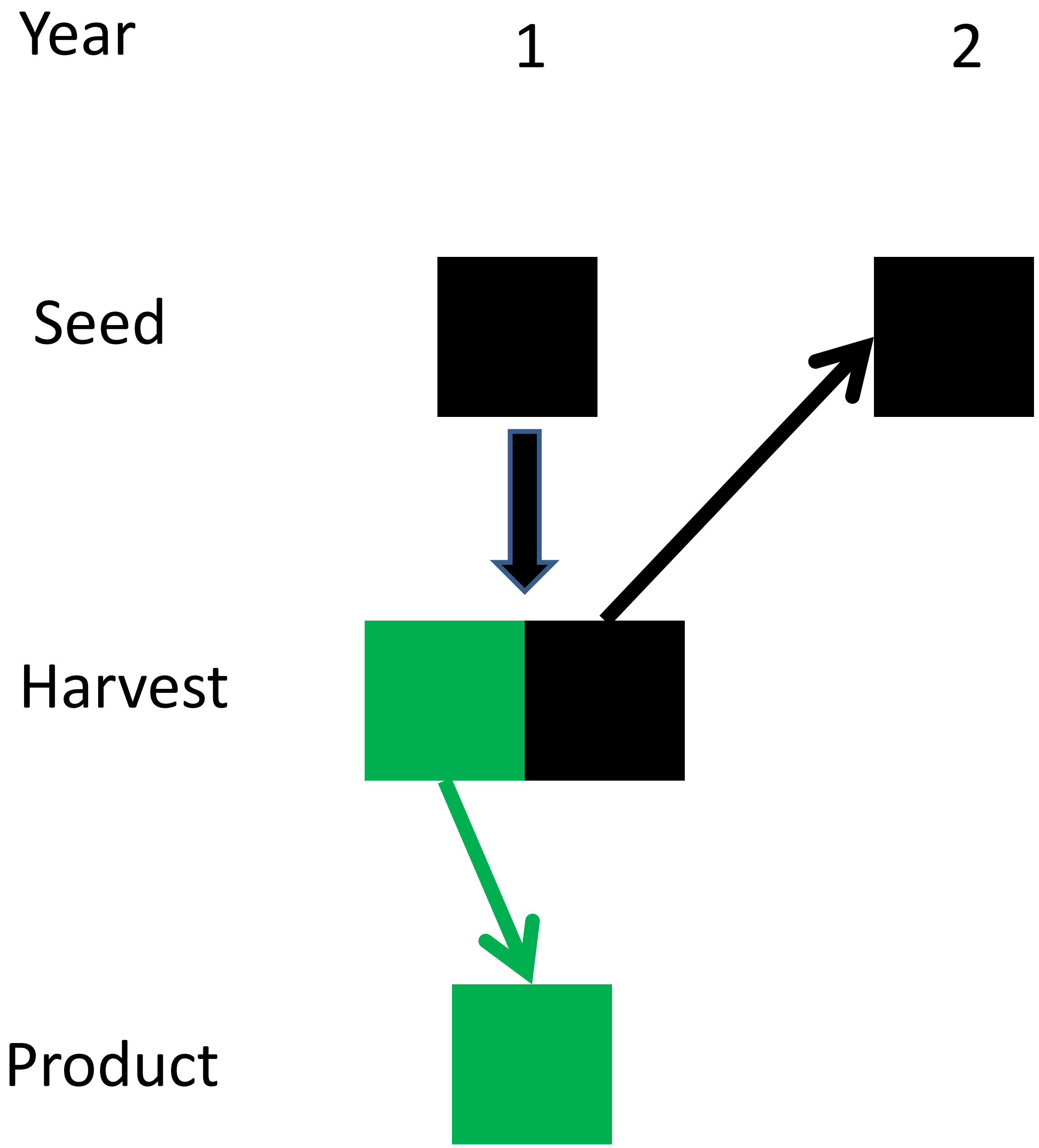
necessary and sufficient

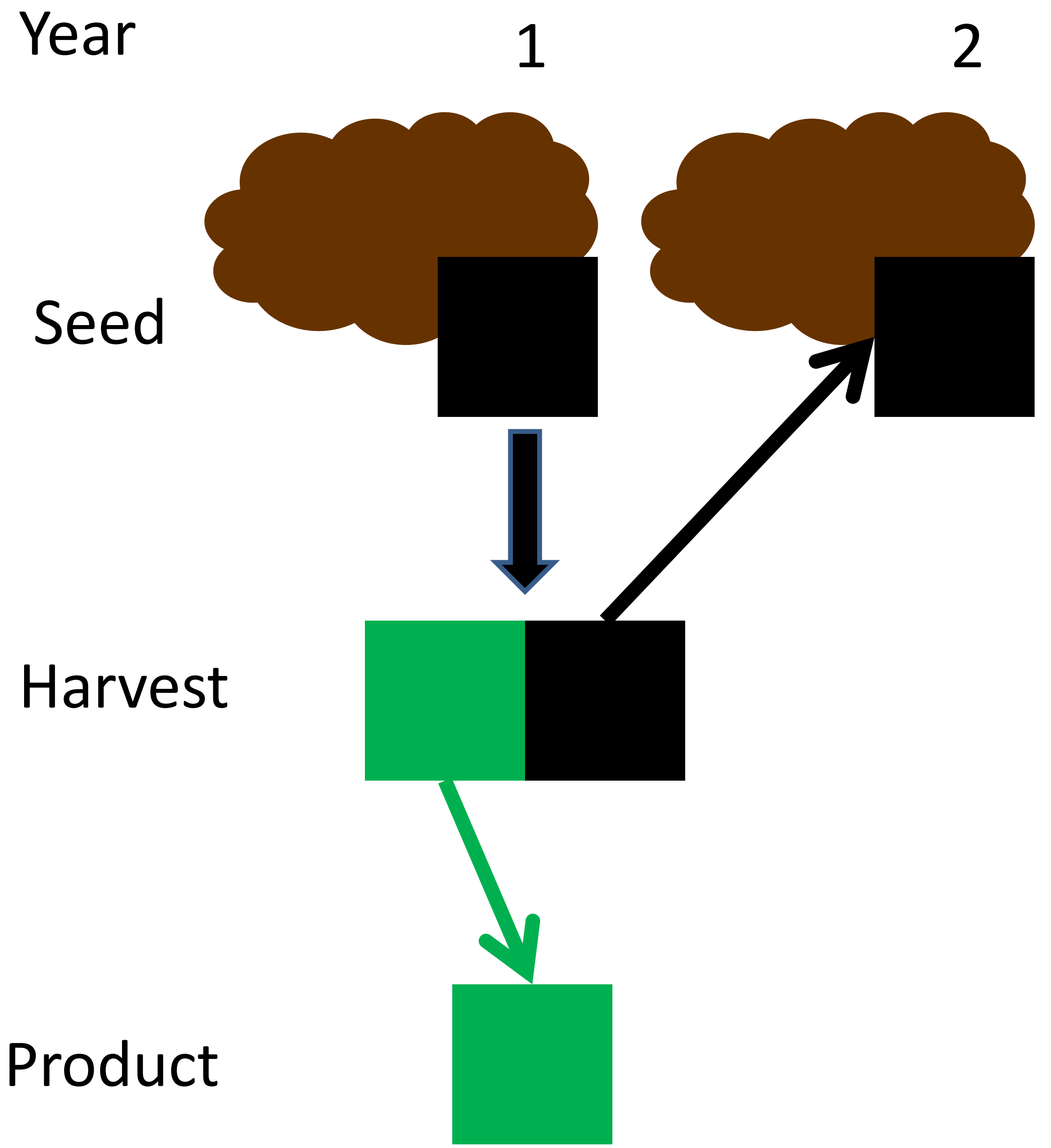
for oscillations

Proof: Dynamical systems model, simulation, bifurcation analysis



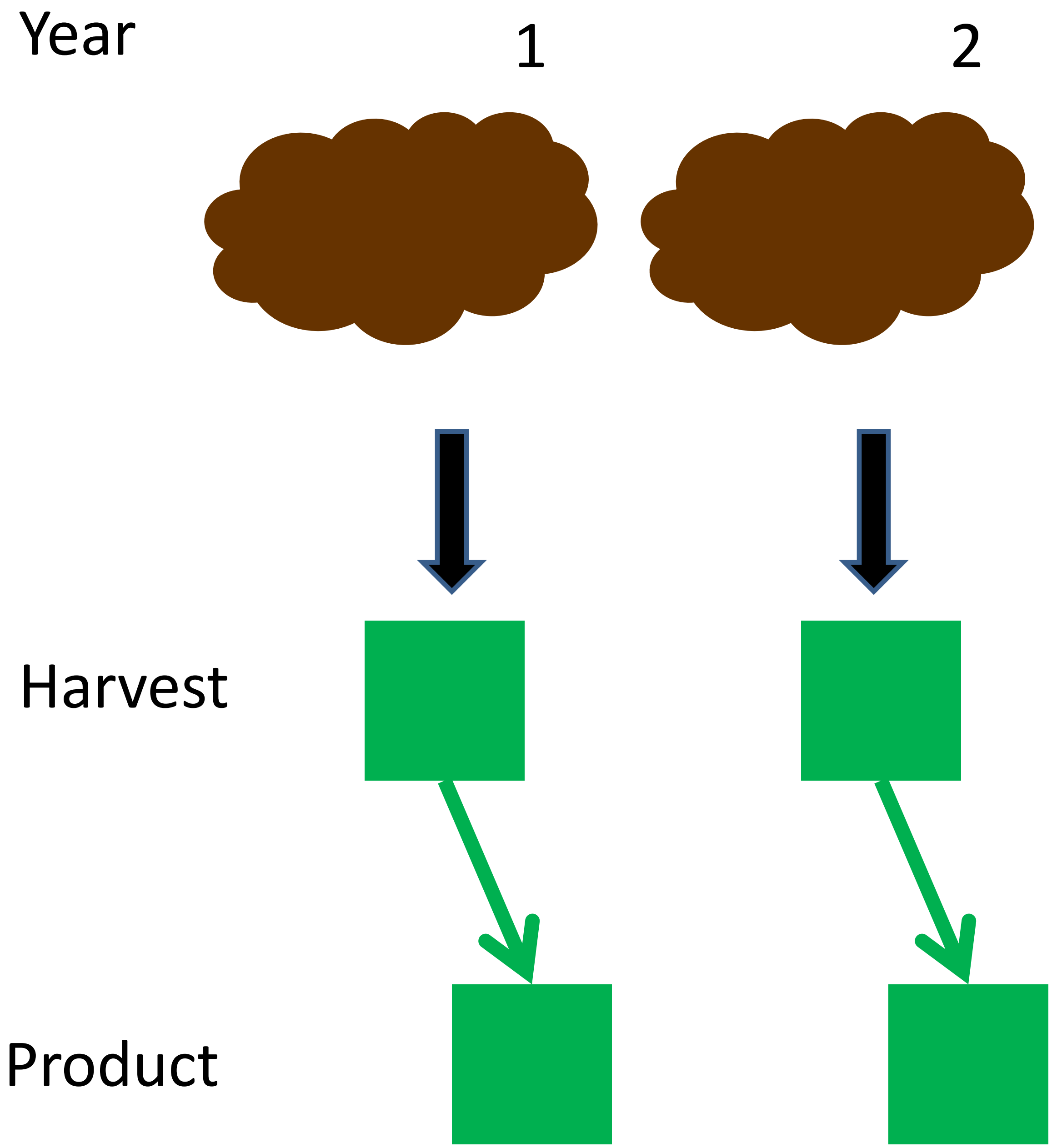
Control feedback
Autocatalytic feedback
Seed
Harvest
Product


Year
1
2
Seed
Harvest
Product

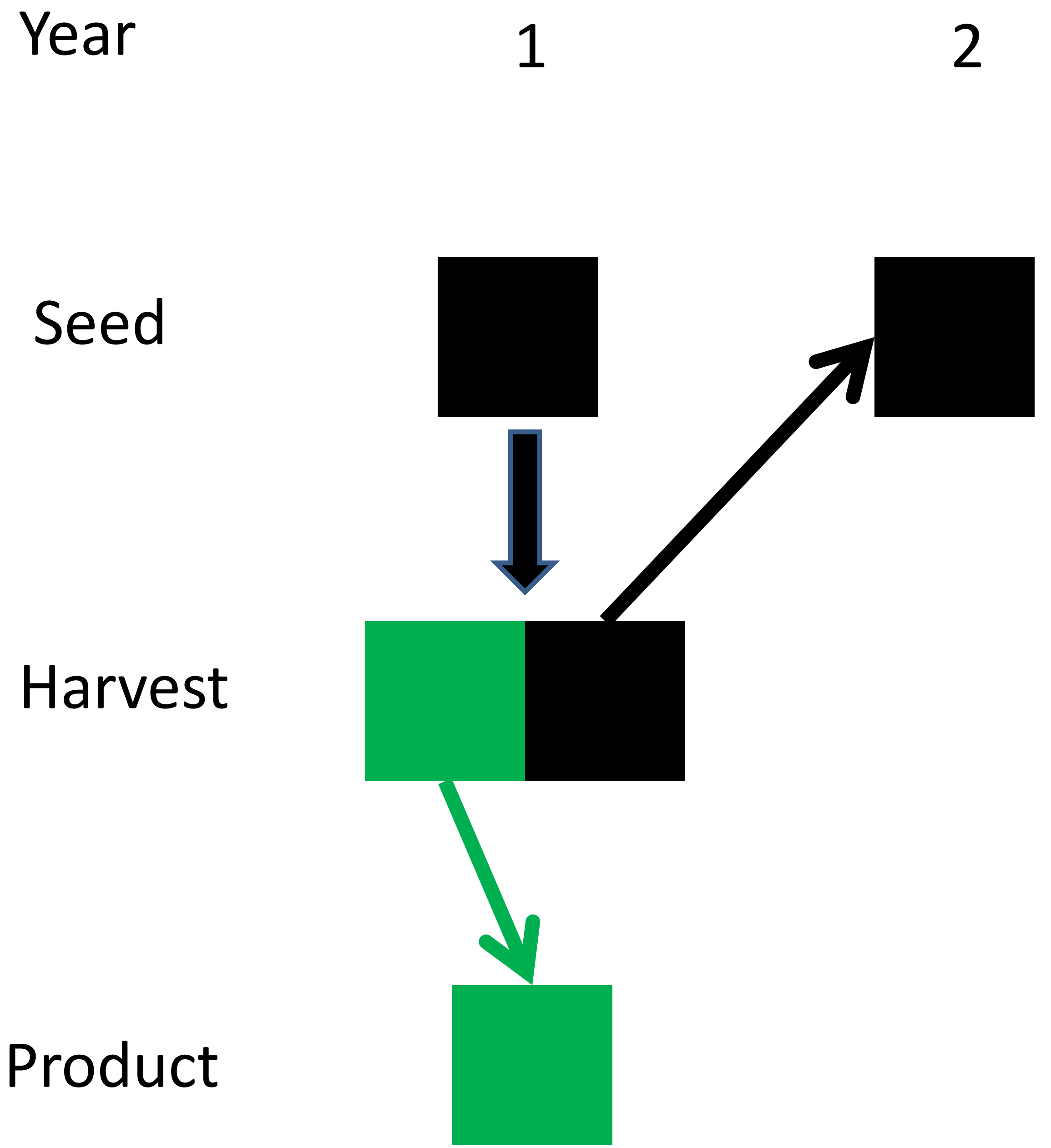


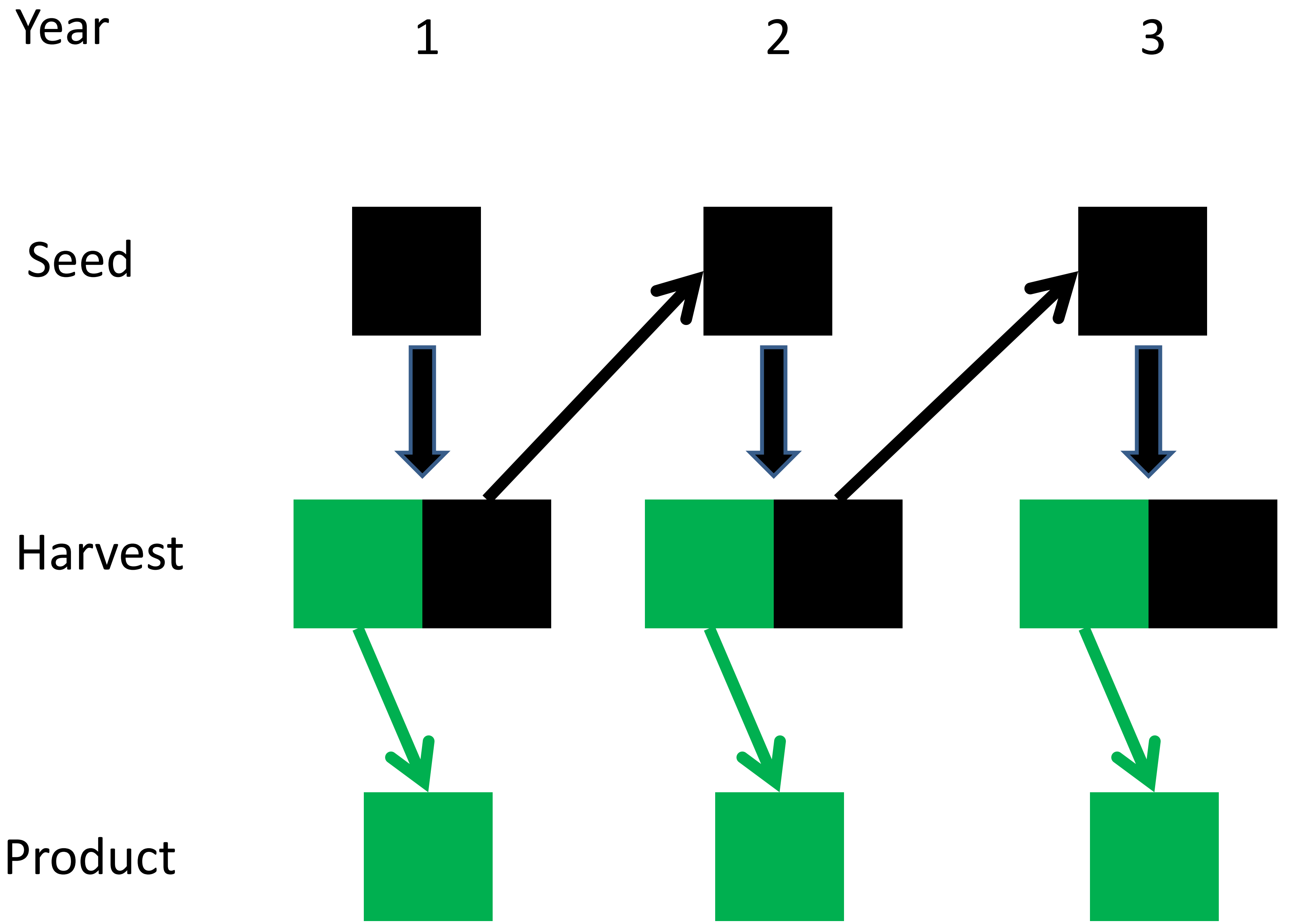
There may be other resources needed that aren't recycled

which we'll ignore for now

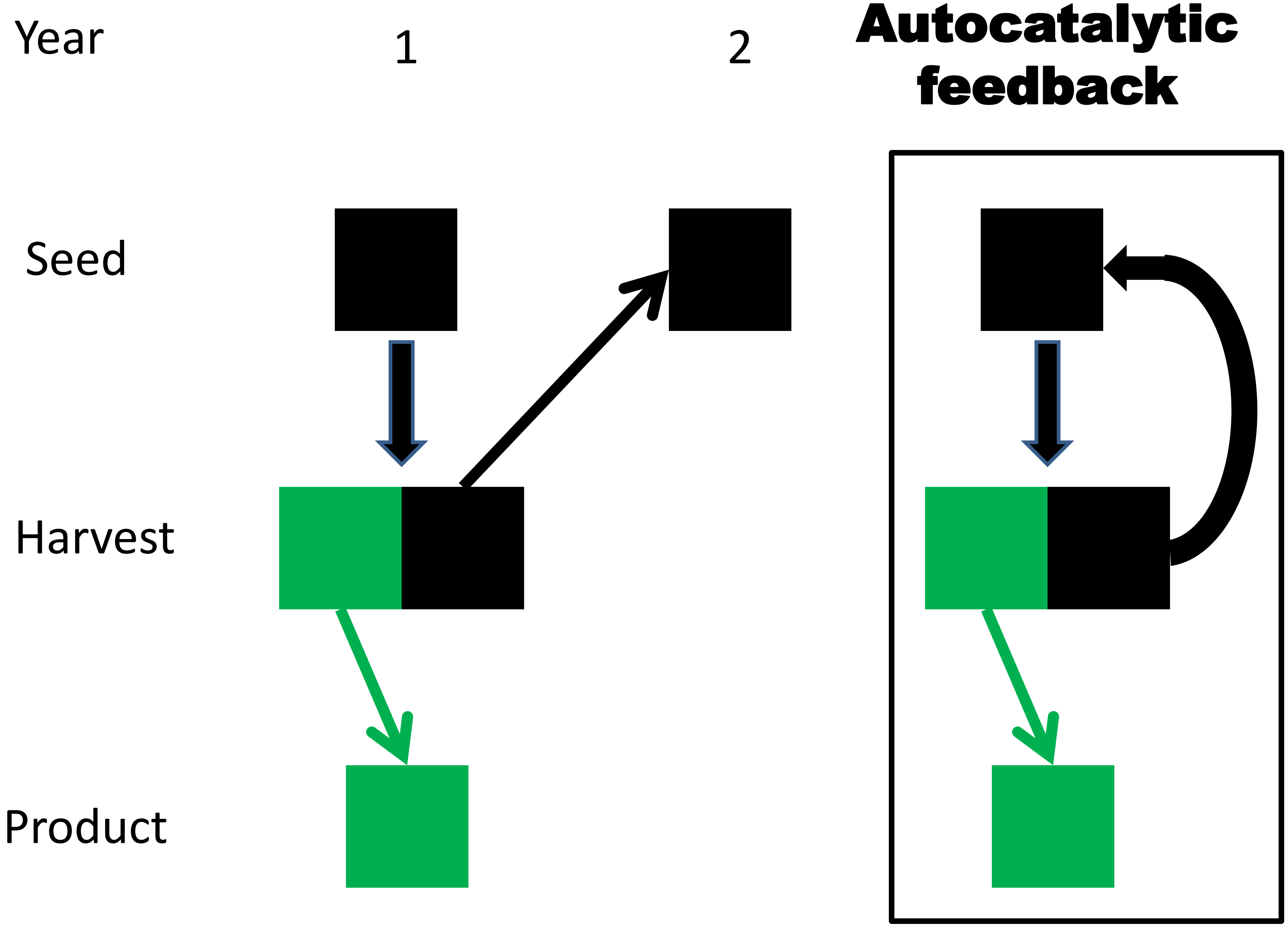


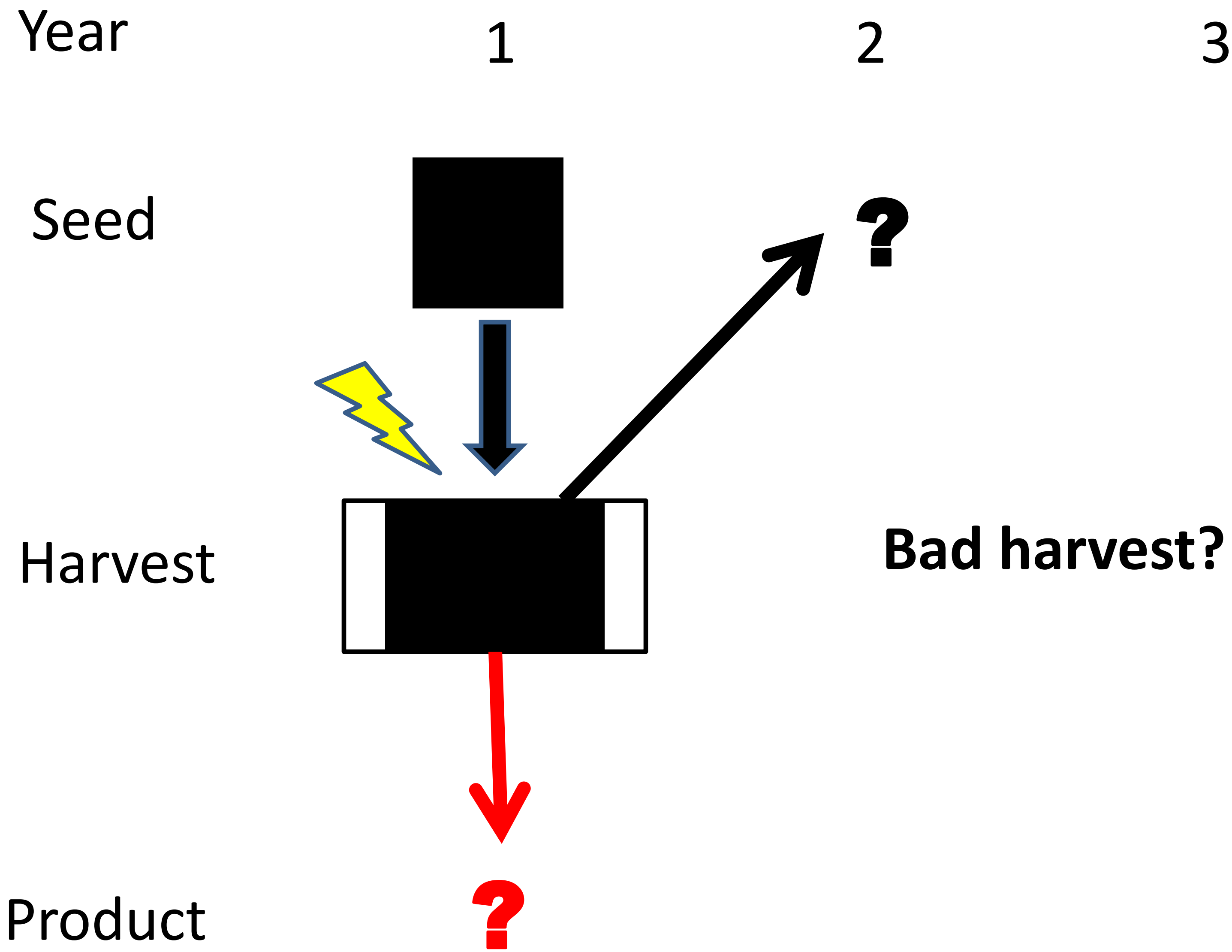
Some processes don't require autocatalysis


Year
1
2
Seed
Harvest
Product

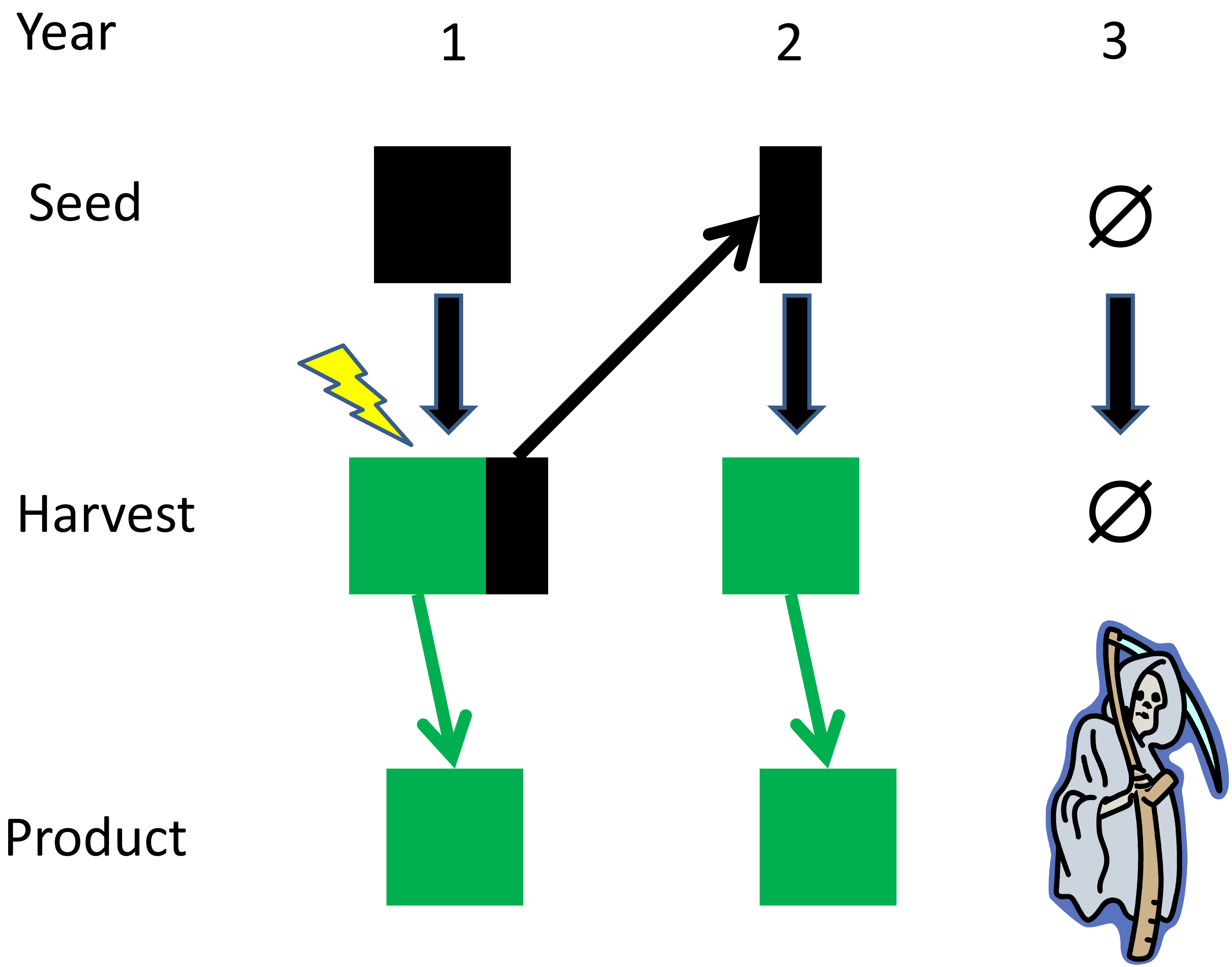


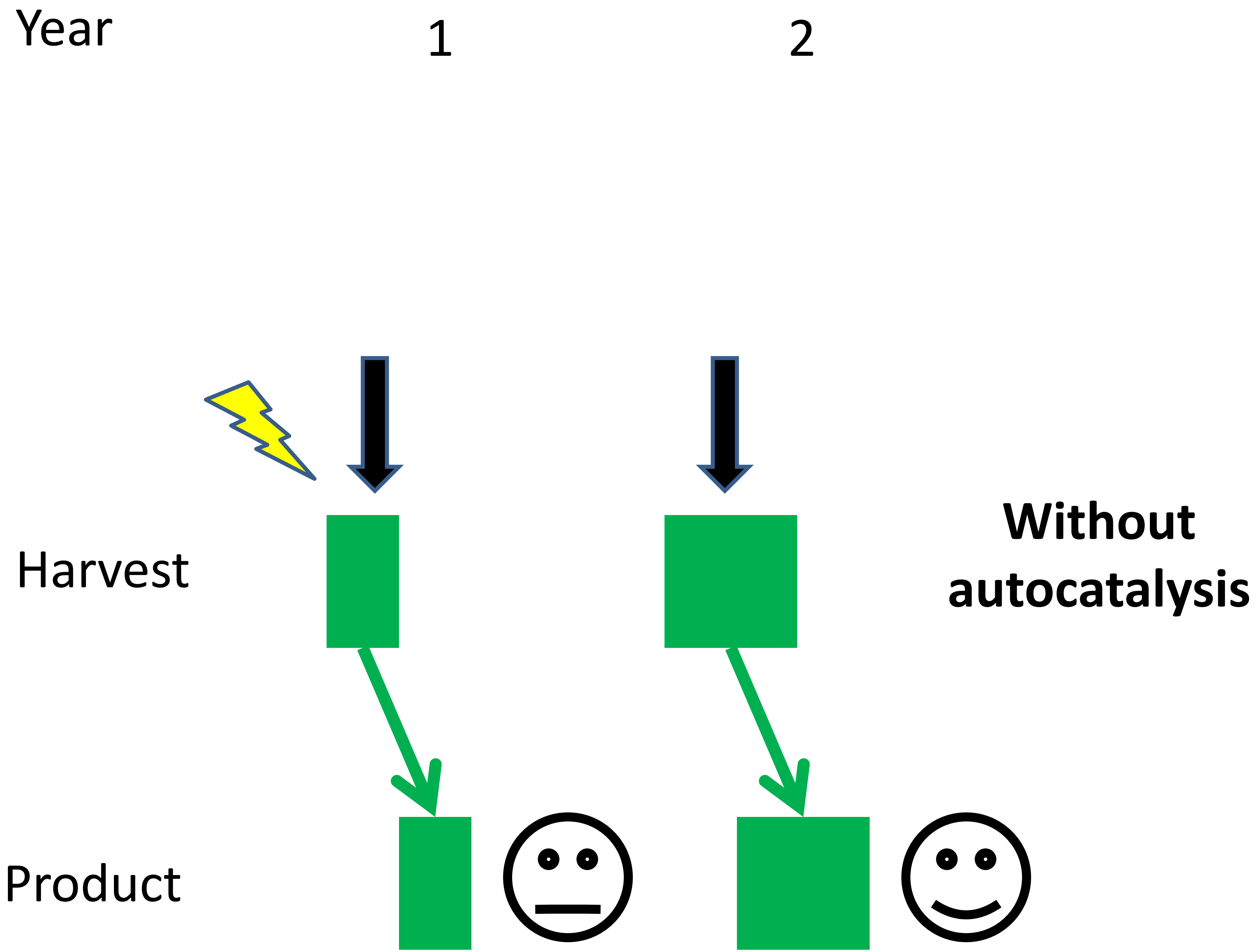
Year
1
2
3
Seed
Harvest
Product


Year
1
2
Autocatalytic feedback
Seed
Harvest
Product

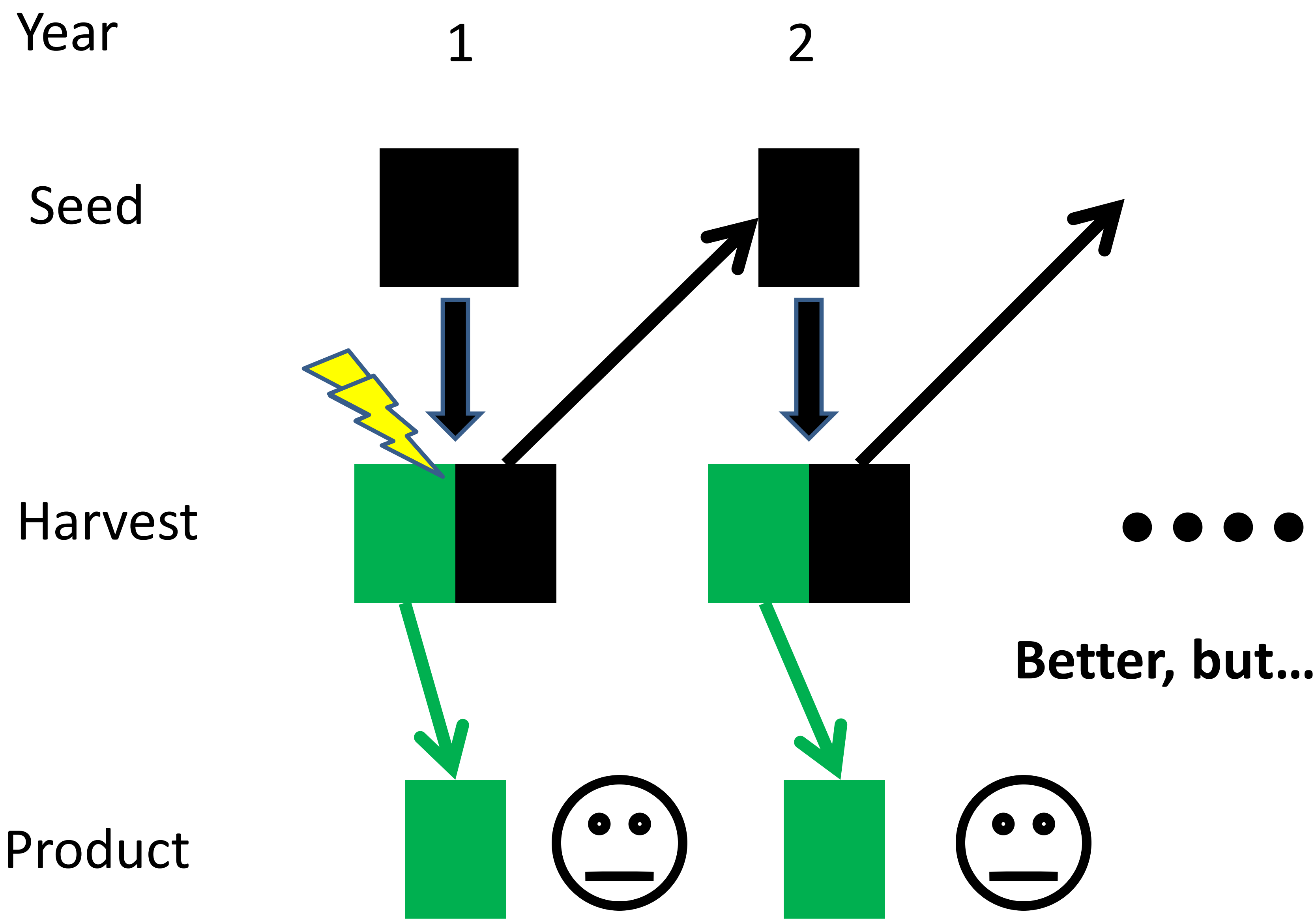

Year
1
2
3
Seed
?
Harvest
Bad harvest?
Product
?

Maintain product?

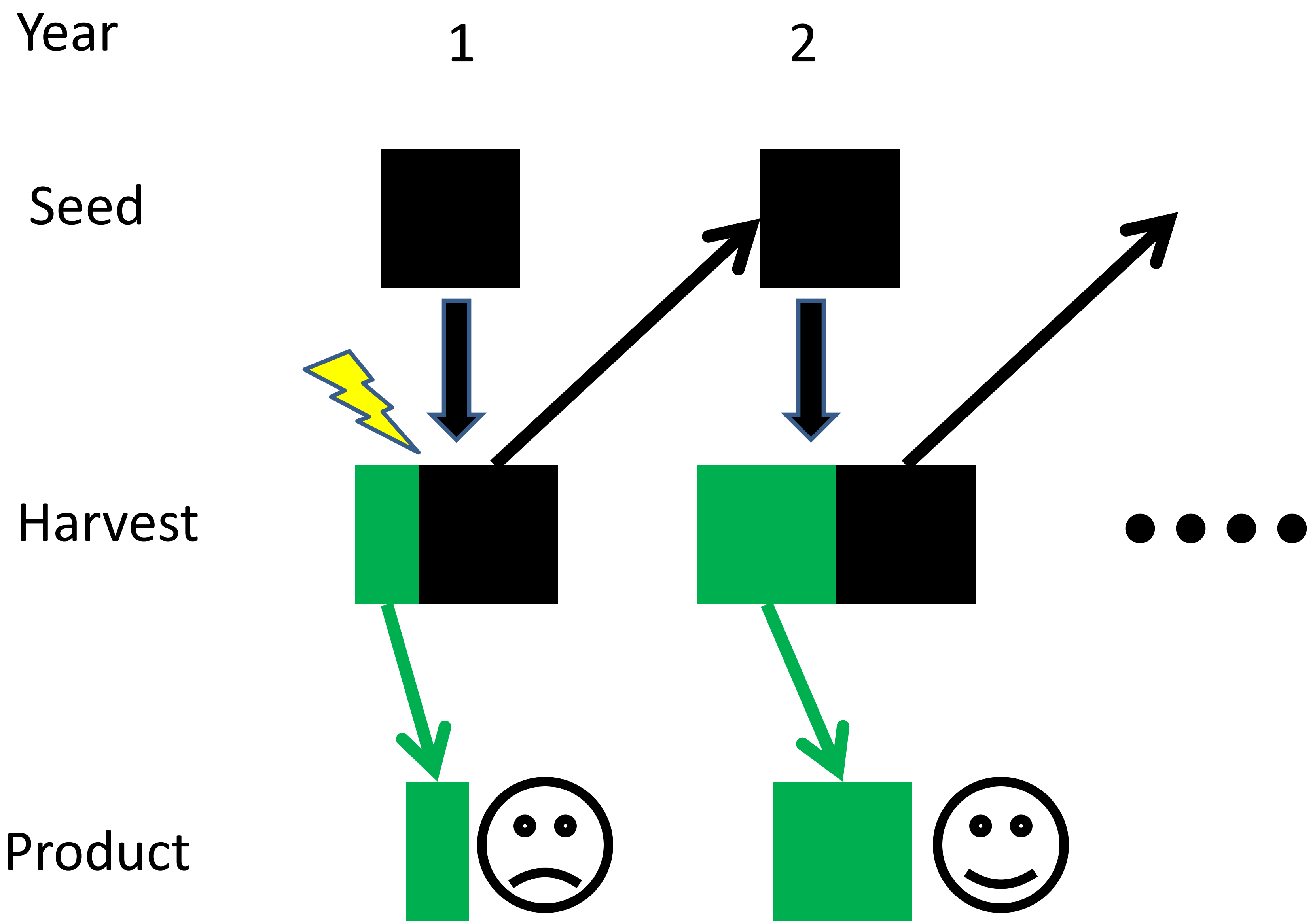



Year
1
2
Harvest
Without autocatalysis
Product

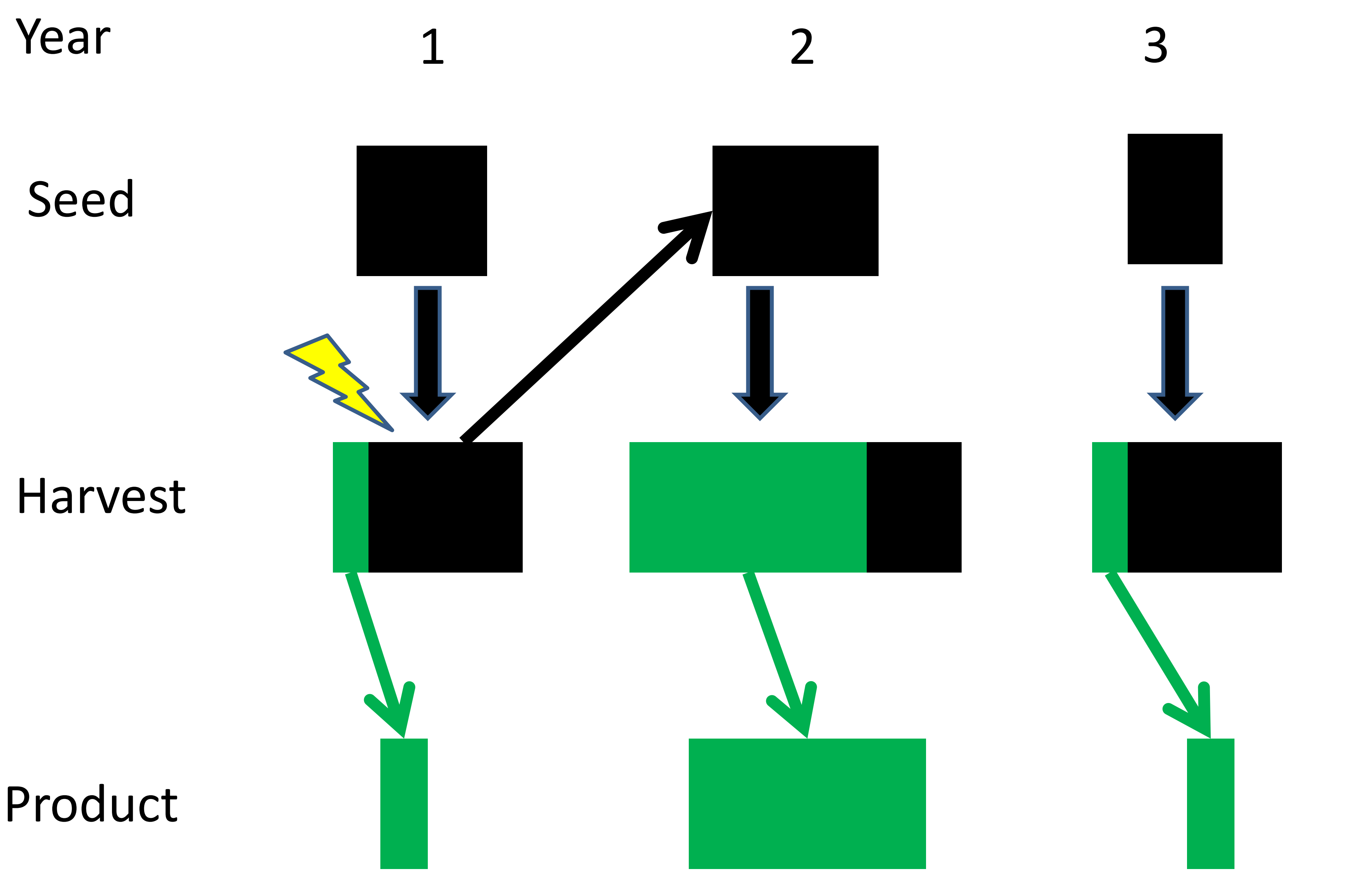
Cut back product

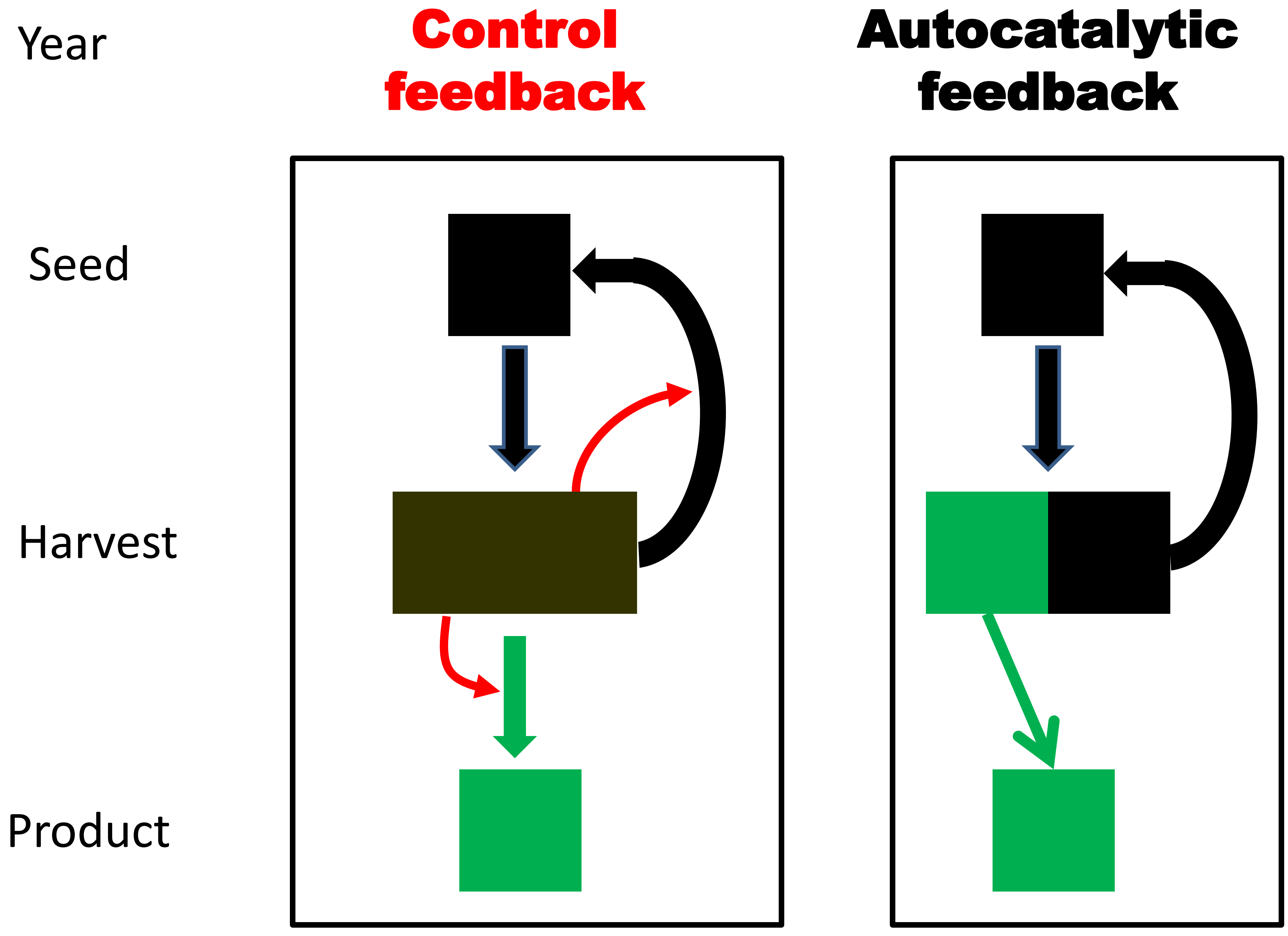


Cut back product more

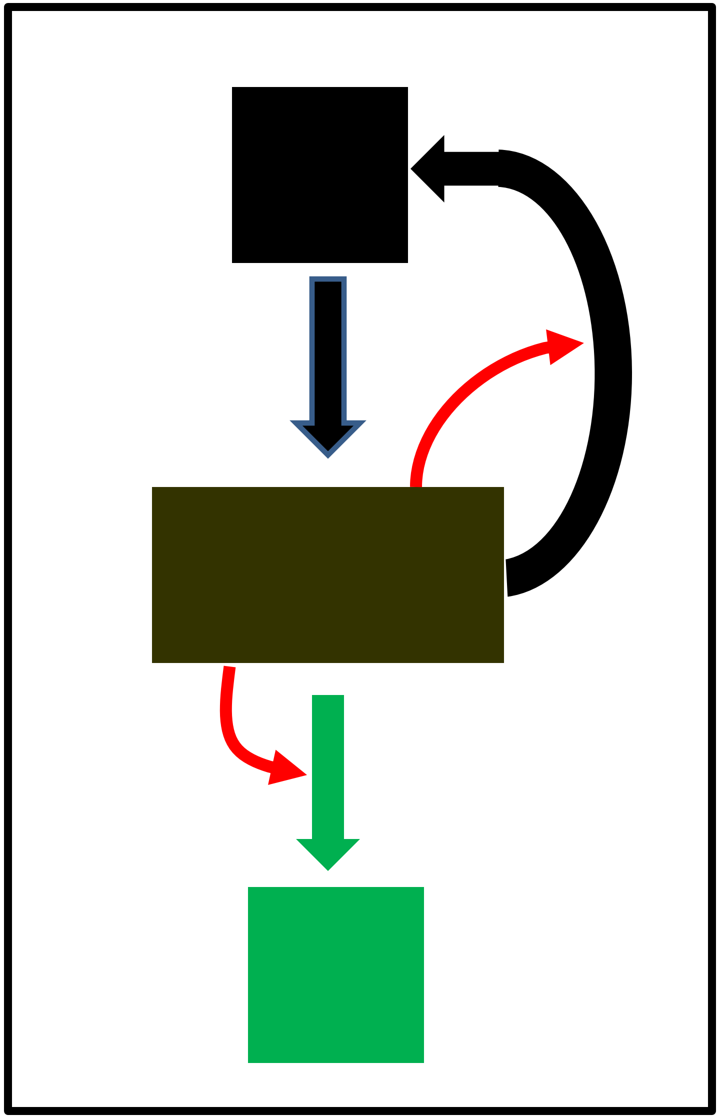


Over-react and oscillate

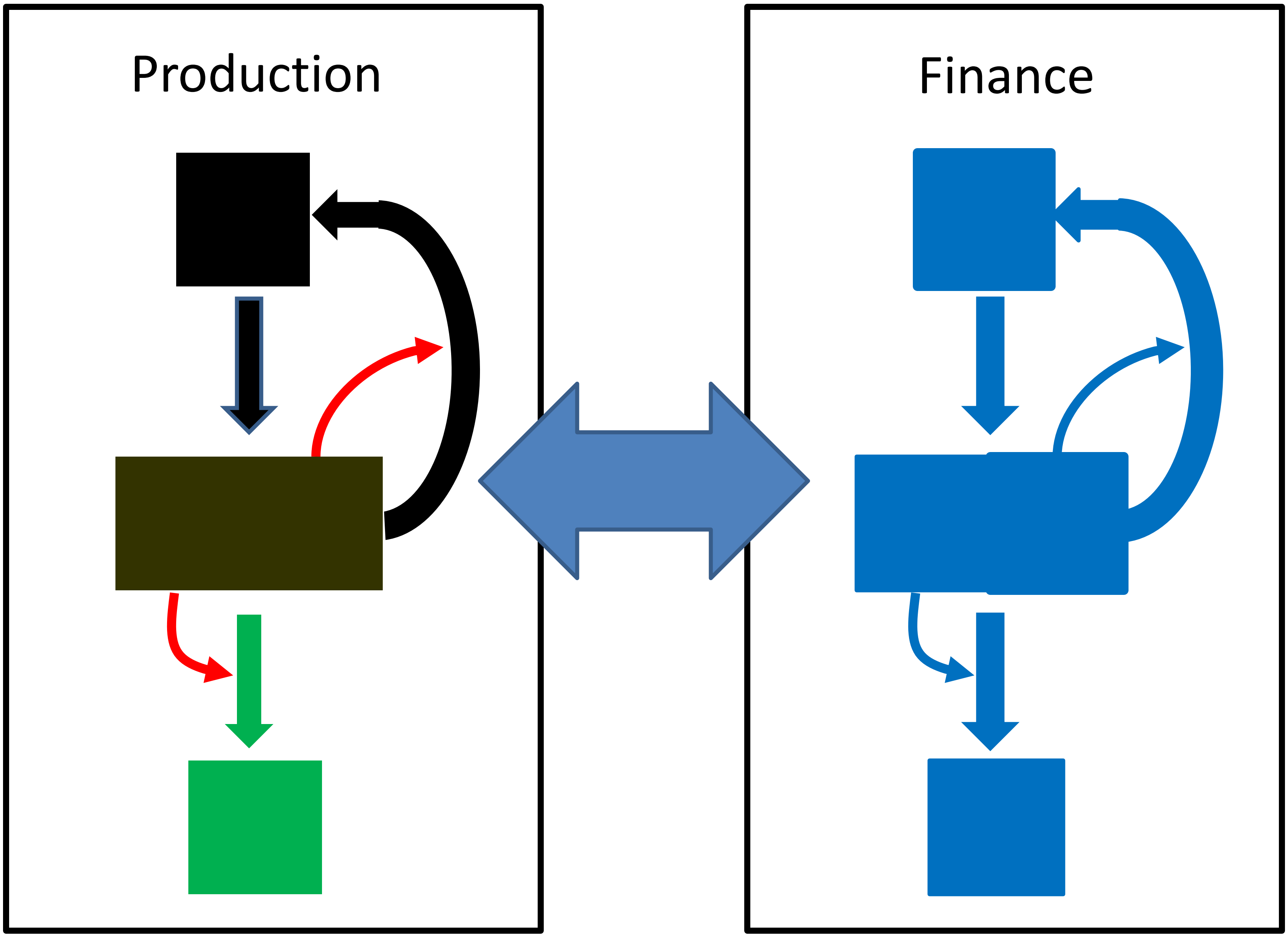


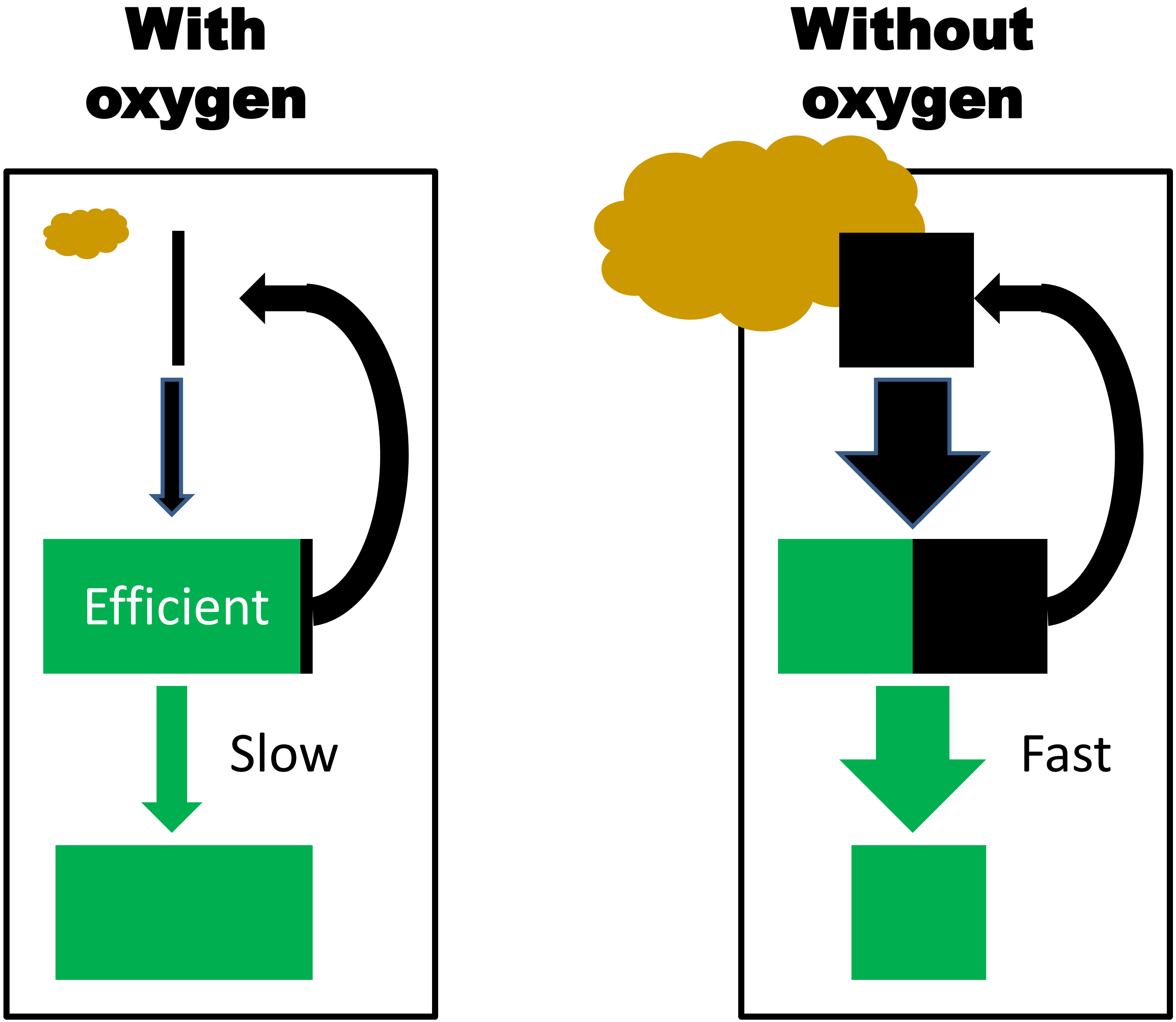

Year
Control feedback
Autocatalytic feedback
Seed
Harvest
Product

Control feedback

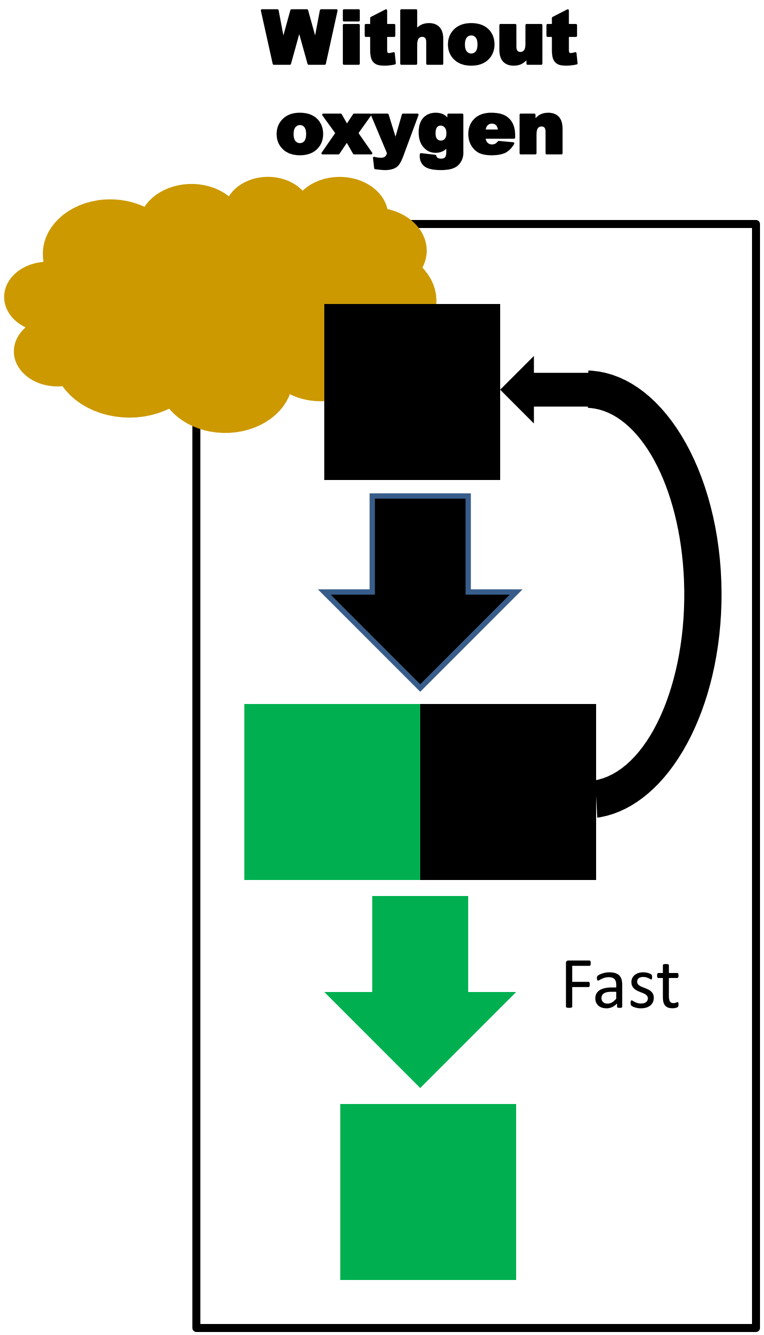


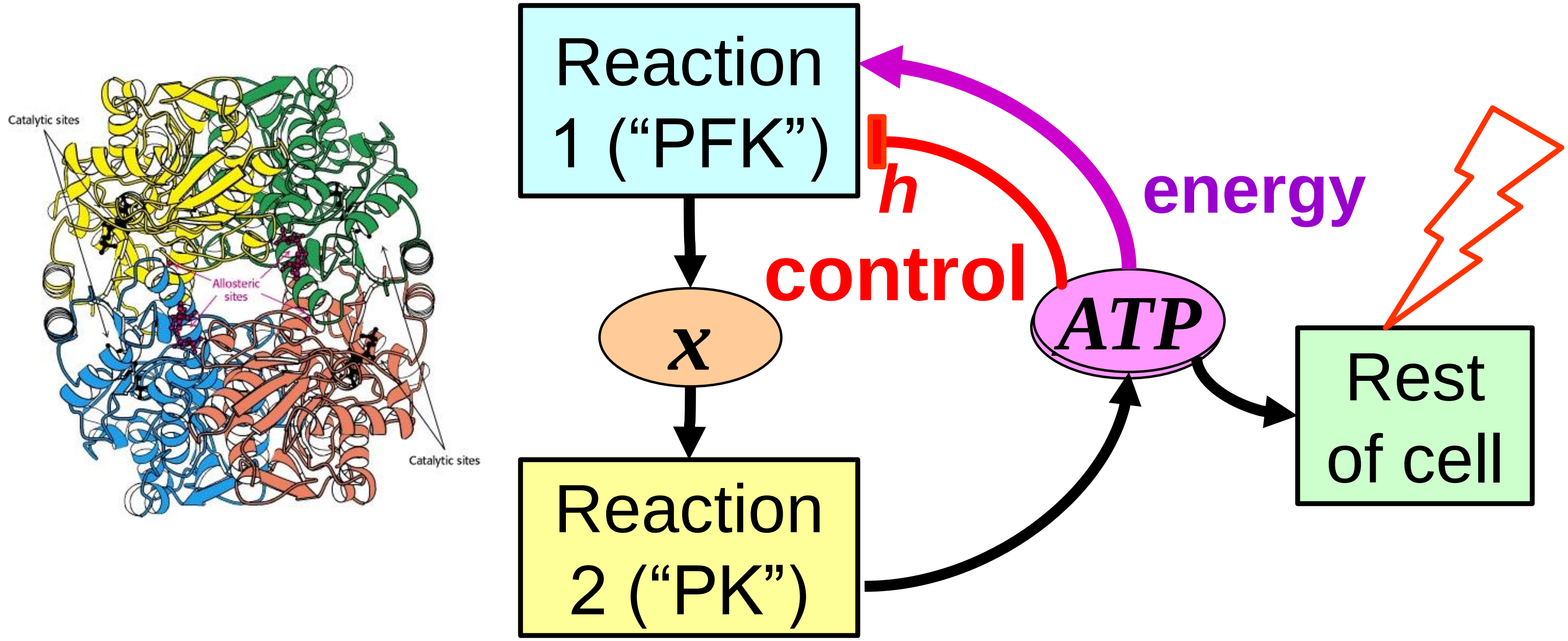
Autocatalytic feedback makes control harder


Production
Finance


With oxygen
Efficient
Slow
Without oxygen
Fast

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





Standard story:

Autocatalytic plus **control** feedback

necessary and sufficient

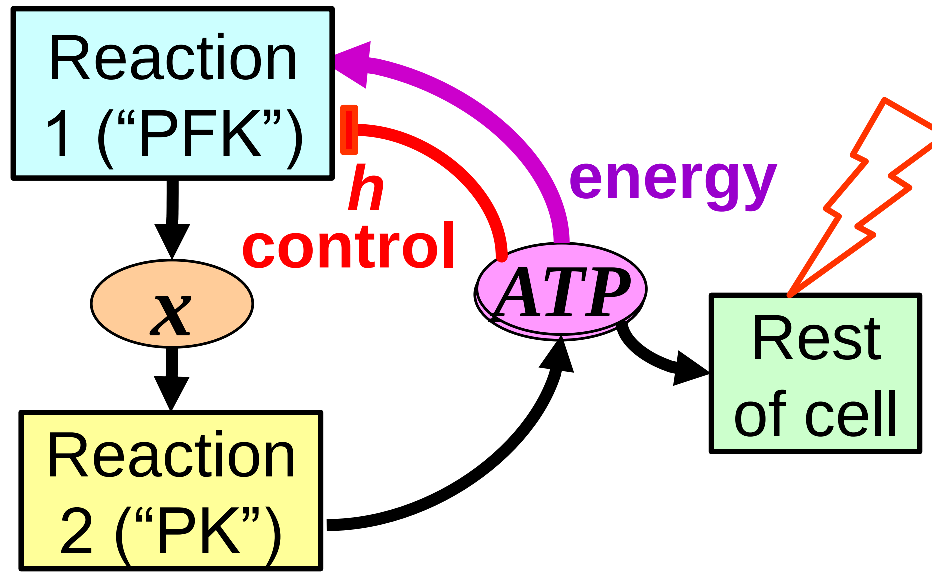
for oscillations

Proof: Dynamical systems model, simulation, bifurcation analysis

Theorem!

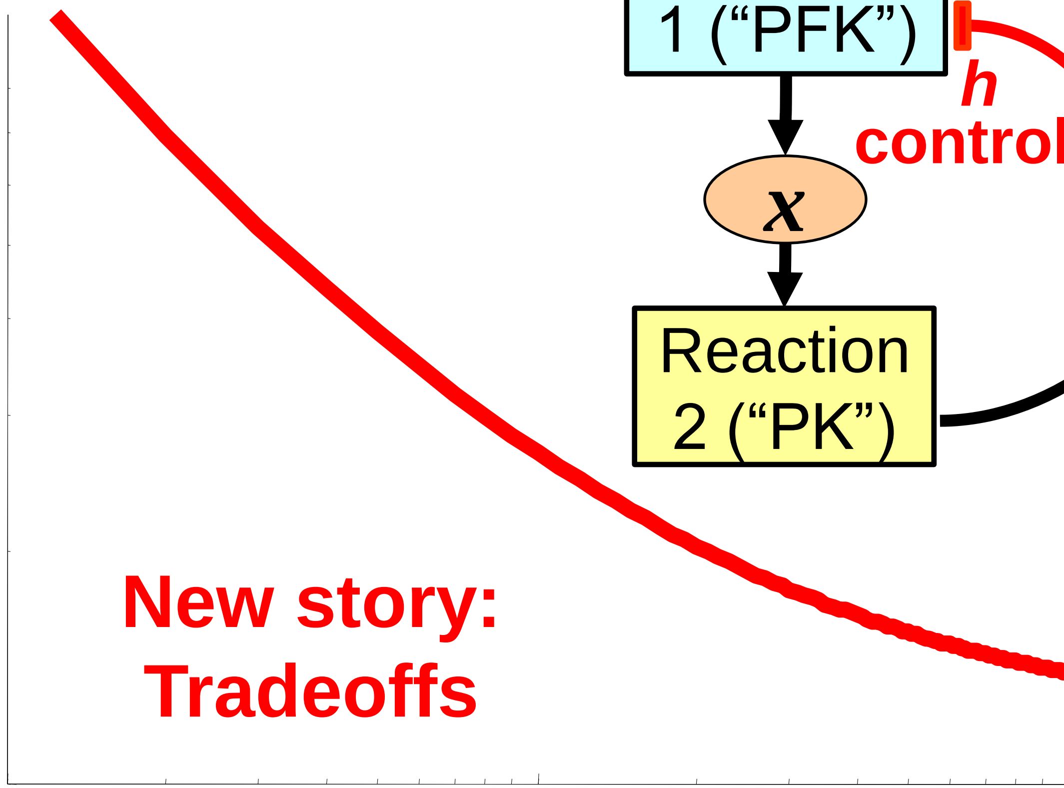
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \ge \ln\left|\frac{z+p}{z-p}\right|$$

DS → CDS

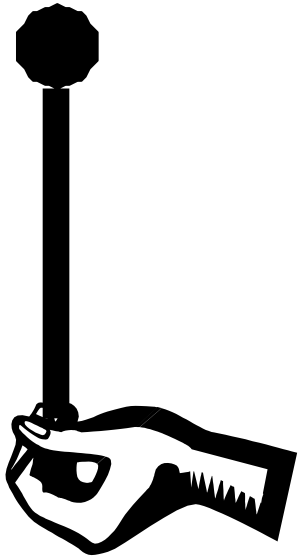


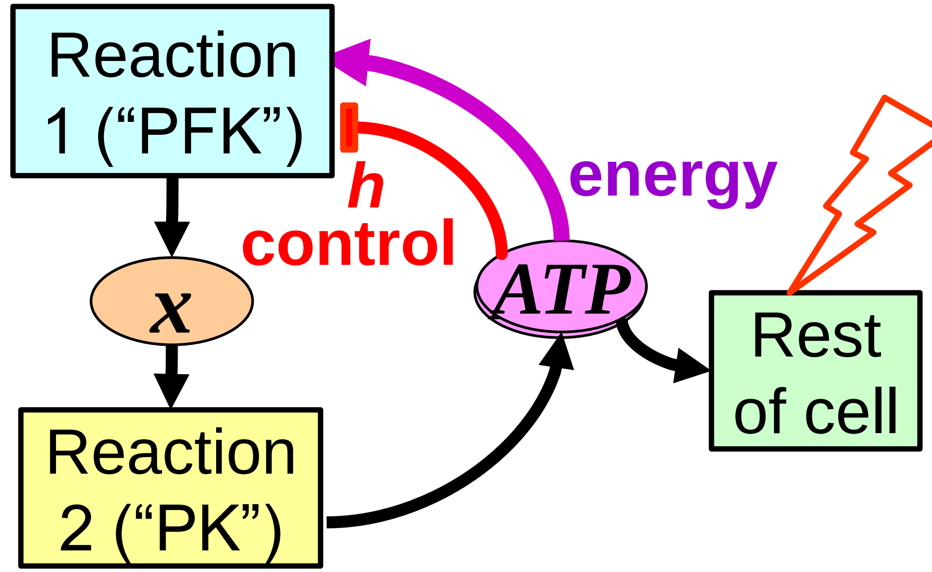
Fragility

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



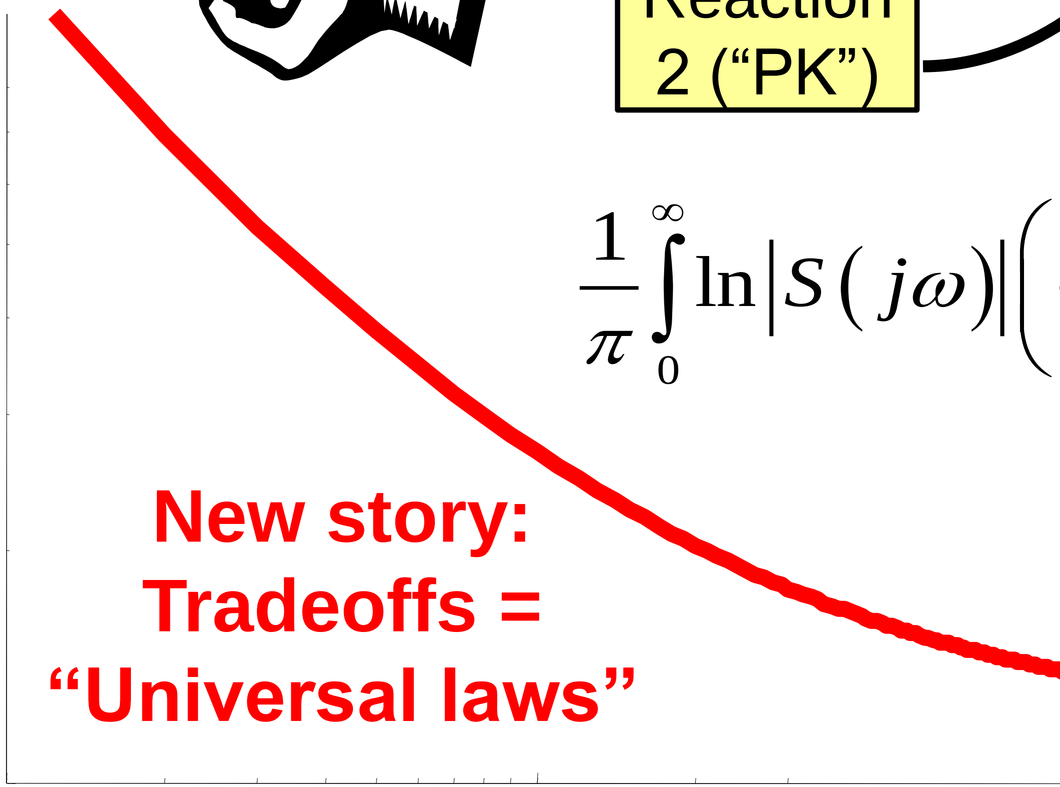
Enzyme amount





Fragile

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

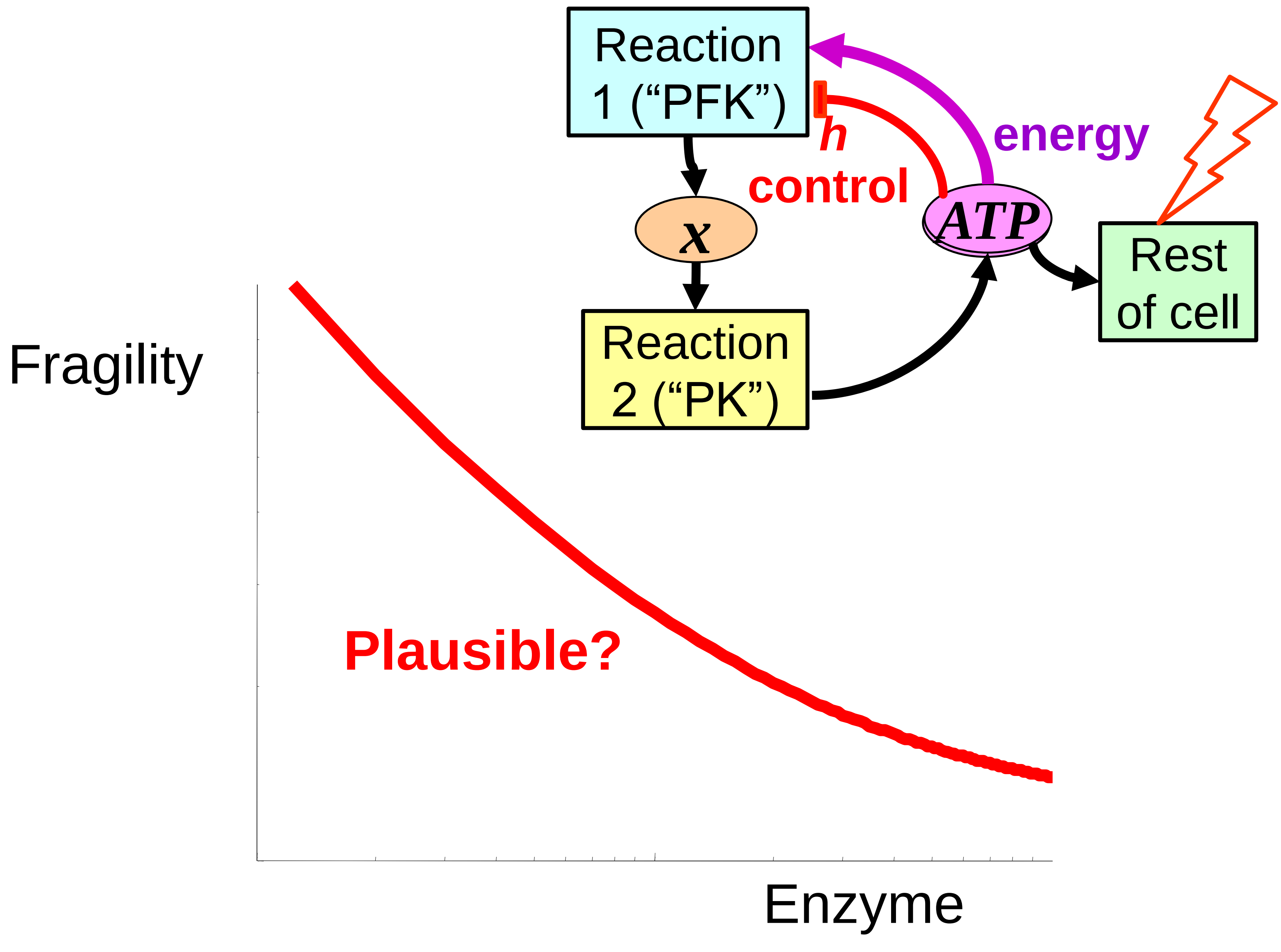


$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega$$

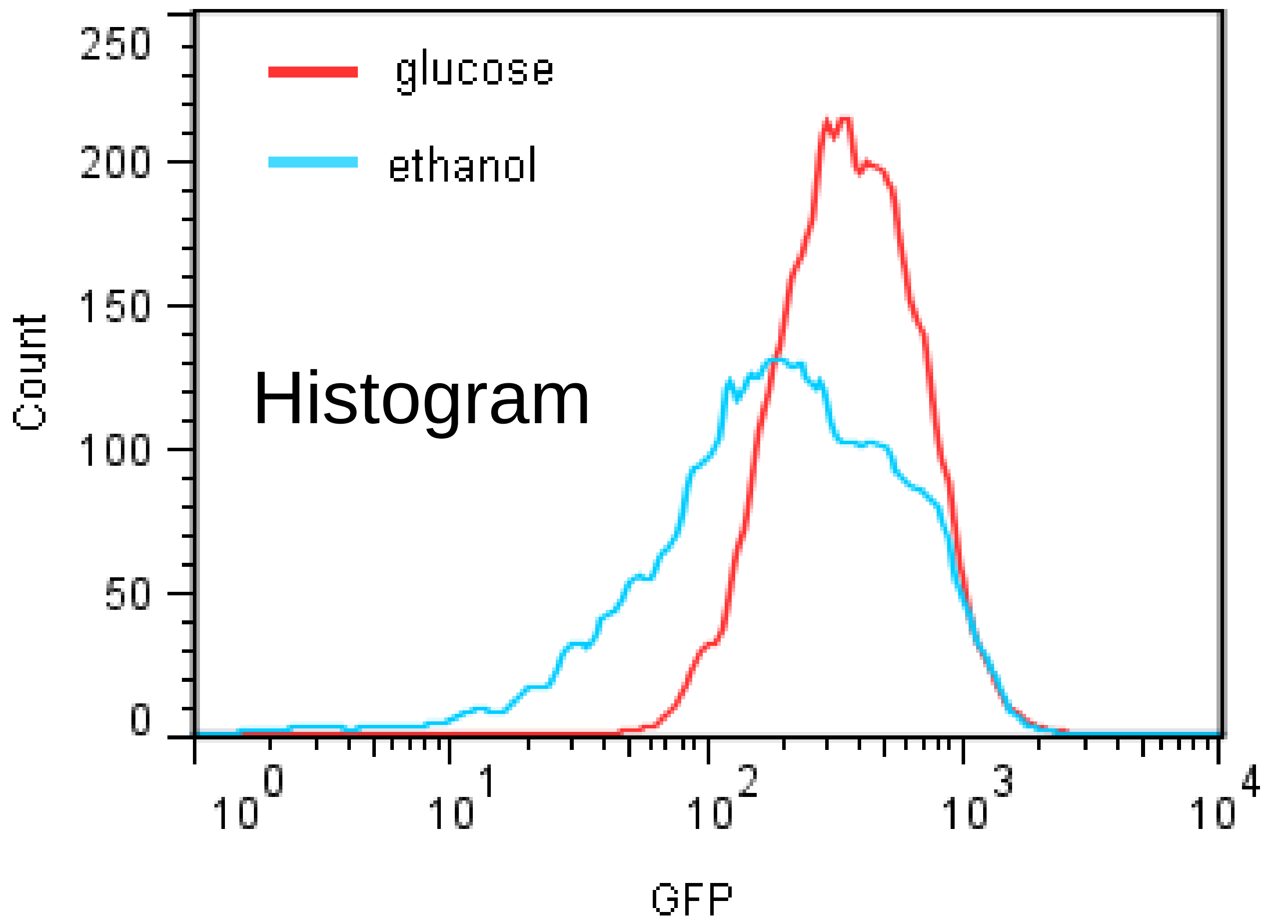
$$\geq \ln\left|\frac{z+p}{z-p}\right|$$

Cheap

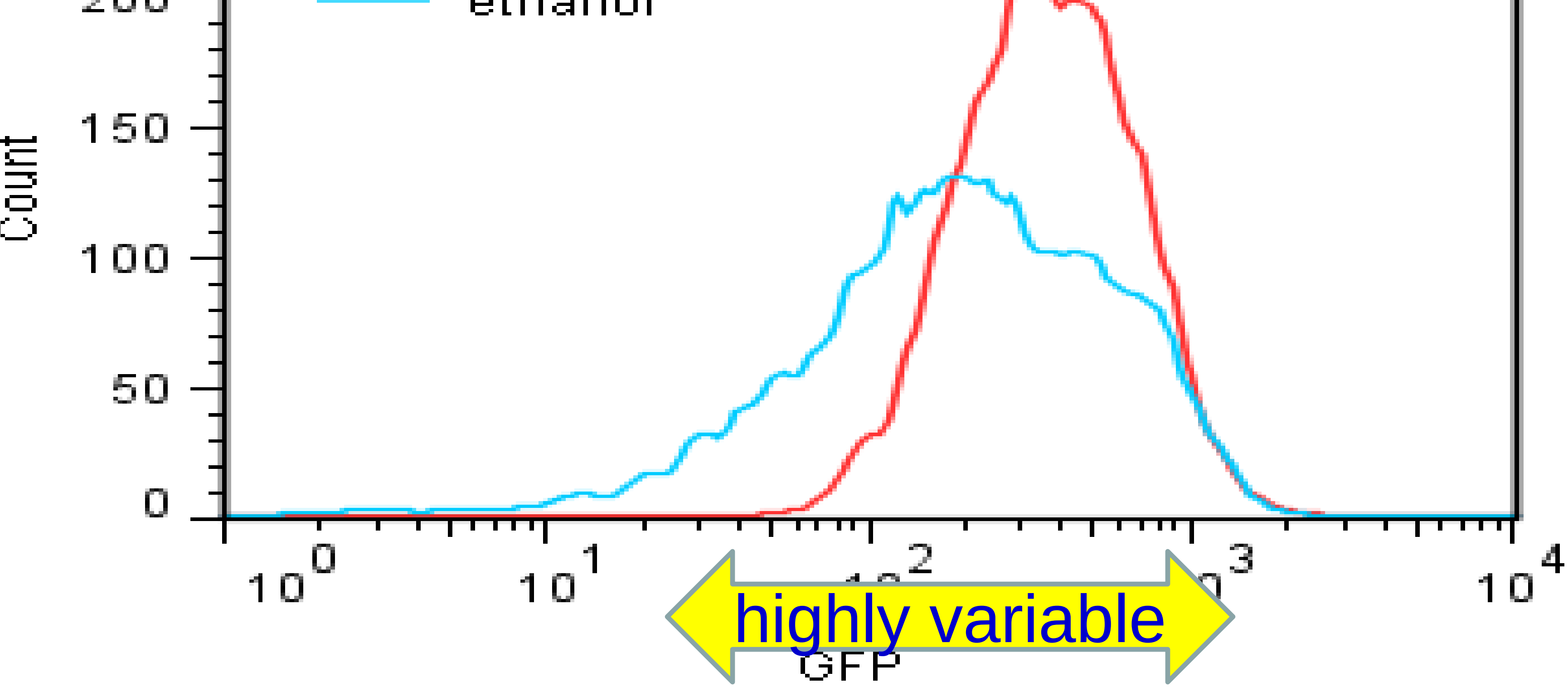
Expensive


Reaction 1 ("PFK")
x
Reaction 2 ("PK")
h
control
energy
ATP
Rest of cell
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.



Enzyme amount

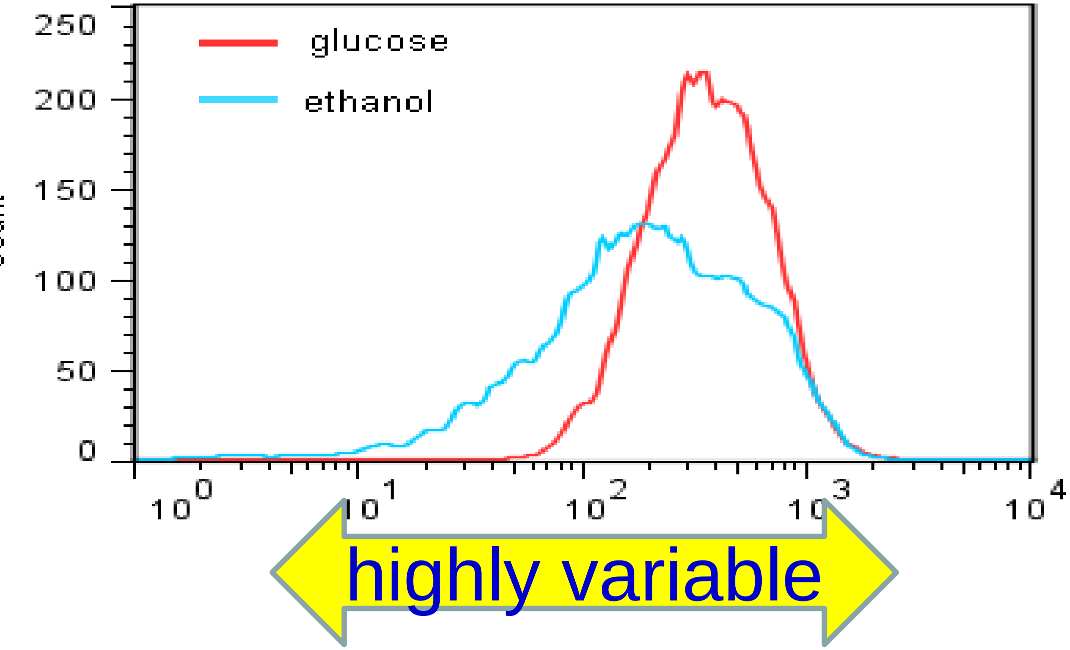


10^1 10^2 10^3

$\propto k$

Metabolic
Overhead

See Lestas, Vinnicombe, Paulsson, *Nature*



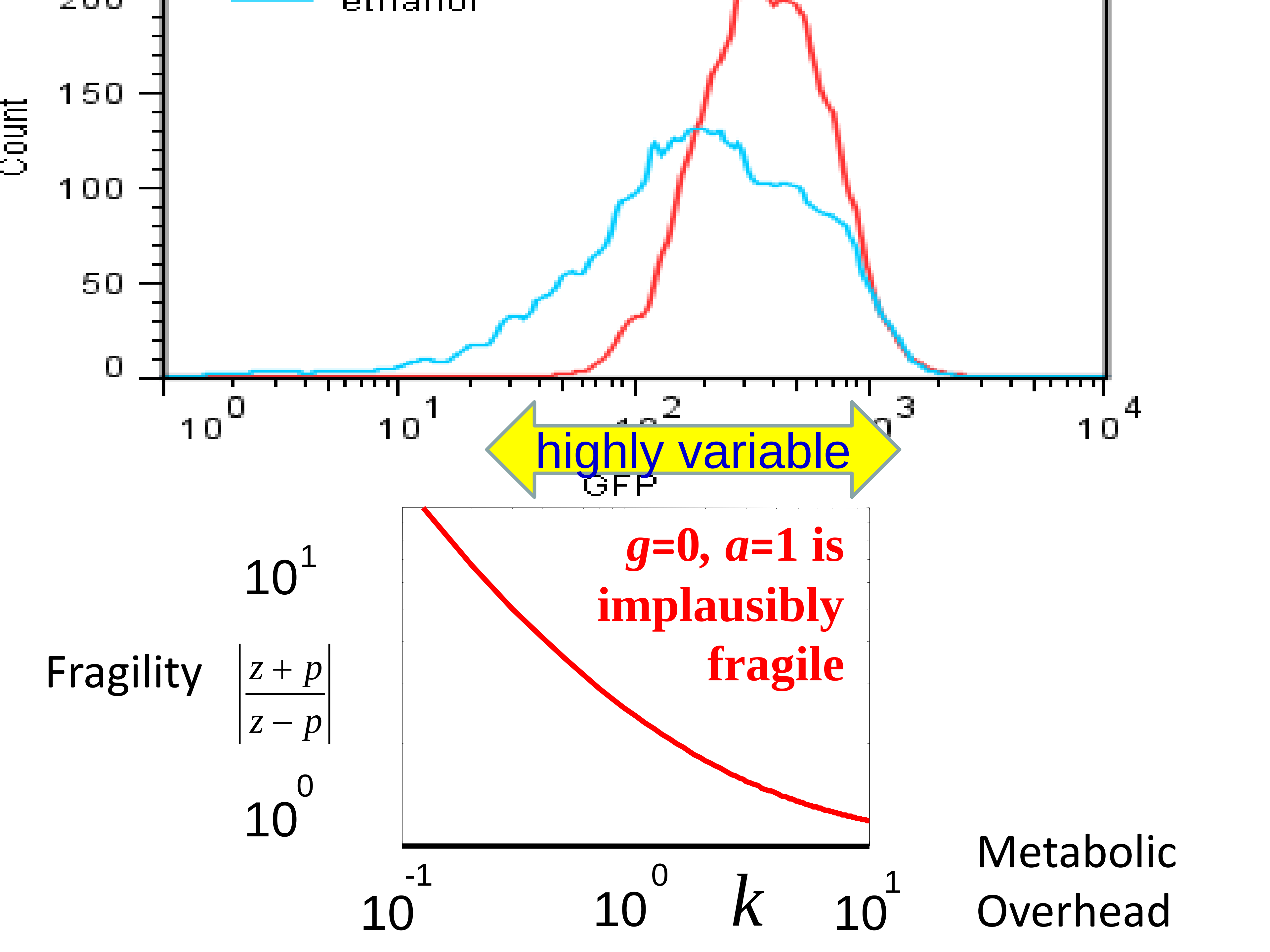
Communicate

Shannon

Delay is *least* important

- Transcription is highly variable
- Even if you allow ∞ delay!
- Information theory applies

See Lestas, Vinnicombe, Paulsson, *Nature*



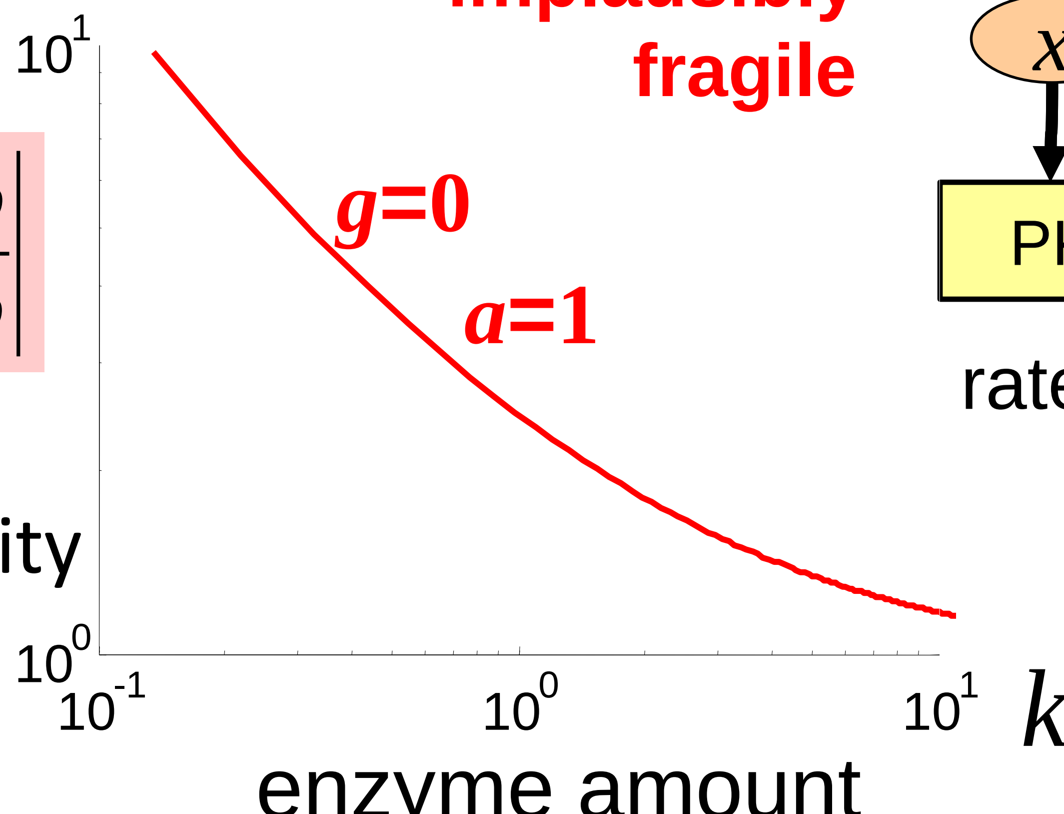
ethanol
Count
200
150
100
50
0
10^0
10^1
10^2
10^3
10^4
GFP
highly variable
g=0, a=1 is implausibly fragile
Fragility
|z + p / z − p|
10^1
10^0
10^-1
10^0
k
10^1
Metabolic Overhead

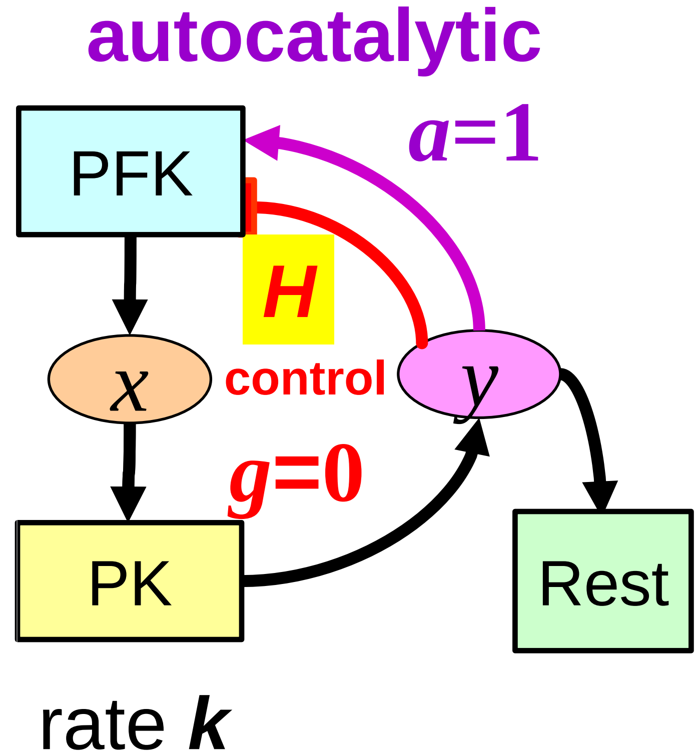
$$\frac{1}{\pi}\int_0^{\infty}\ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega$$

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

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

implausibly fragile

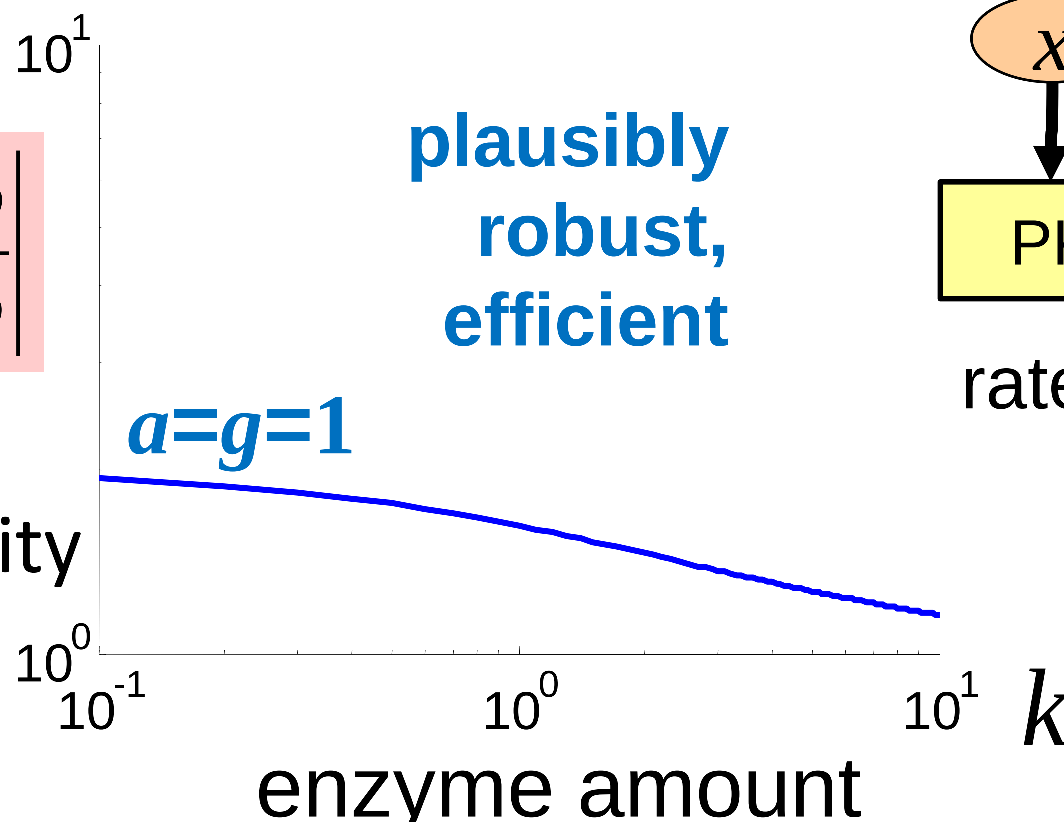


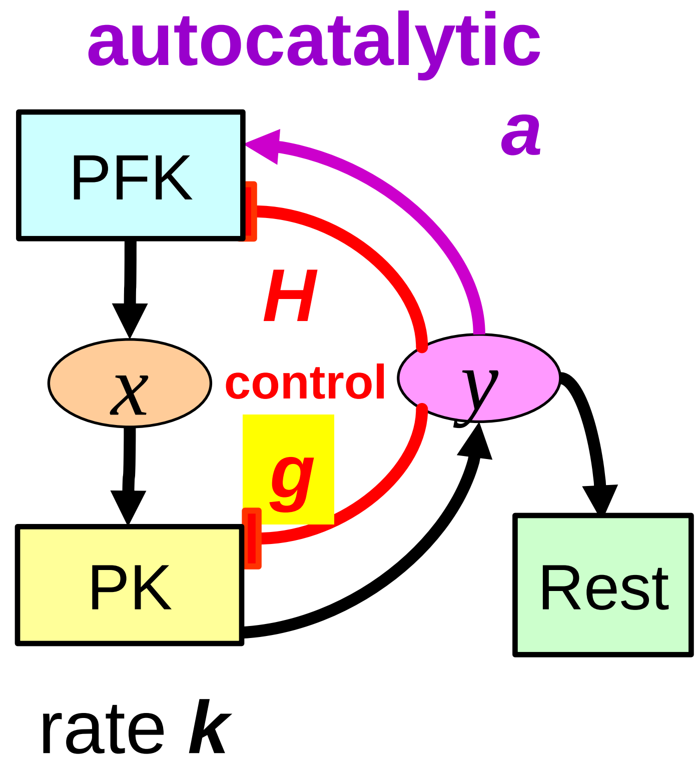


$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

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

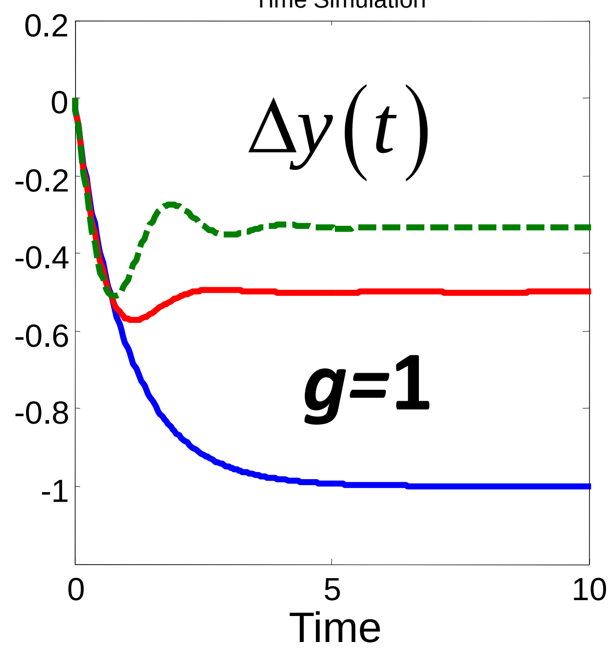
Fragility



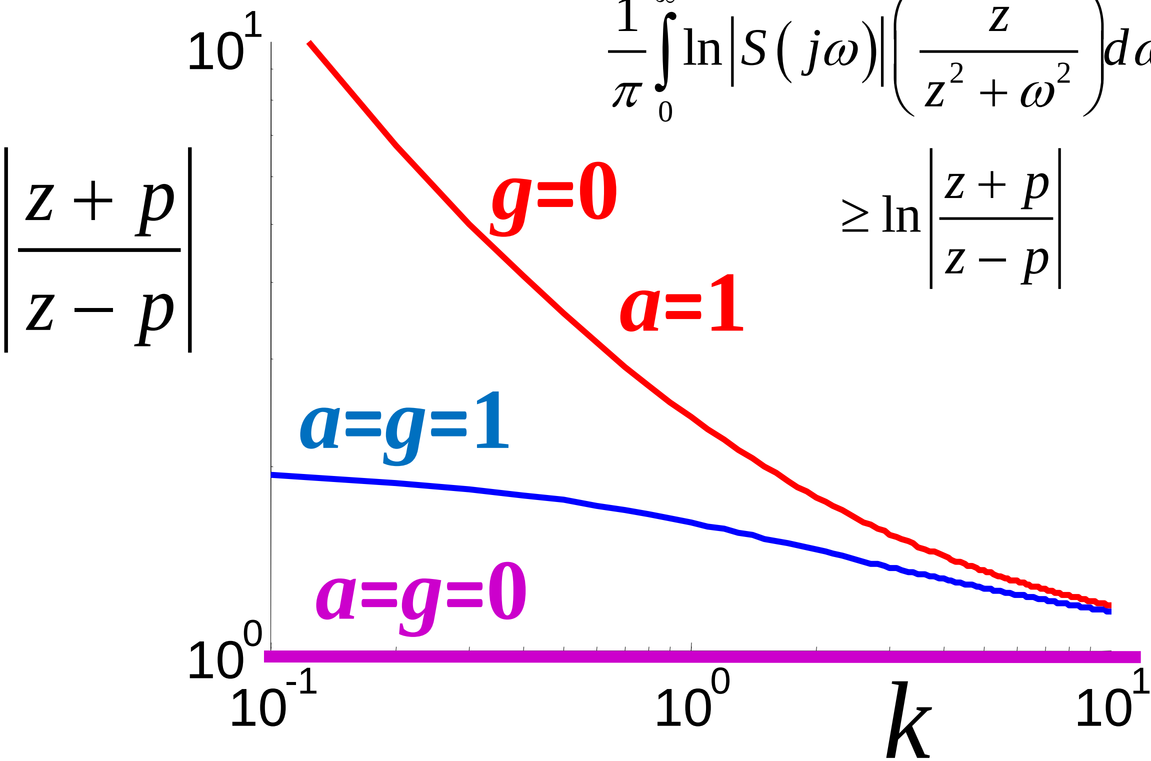


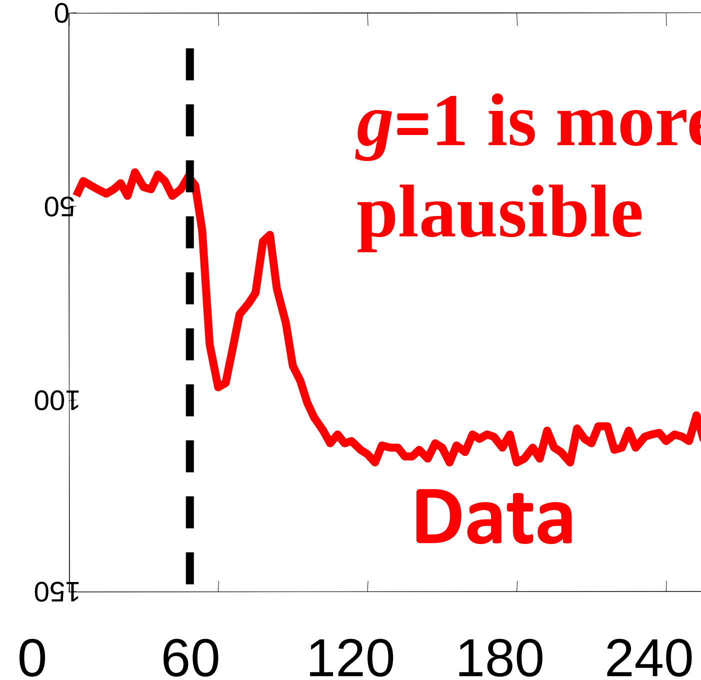
***a*=1 *sufficient* for oscillations (and is *actual*)**

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



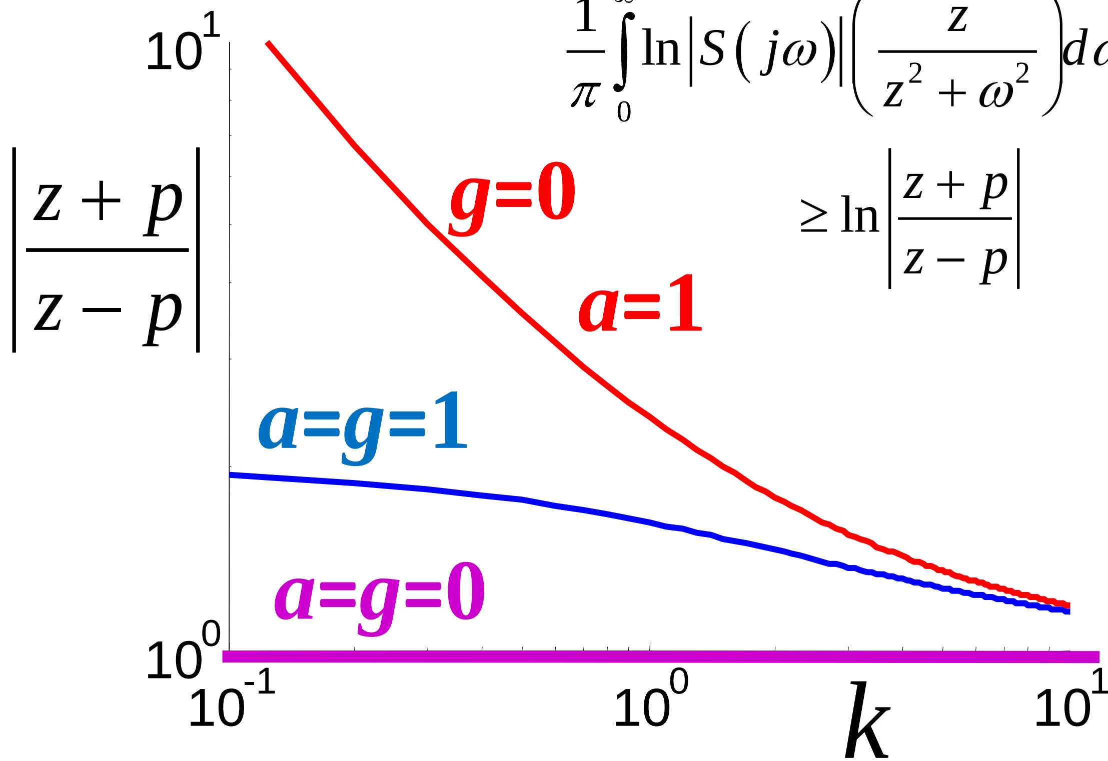
$$\frac{1}{\pi}\int_0^\infty \ln|S(j\omega)|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

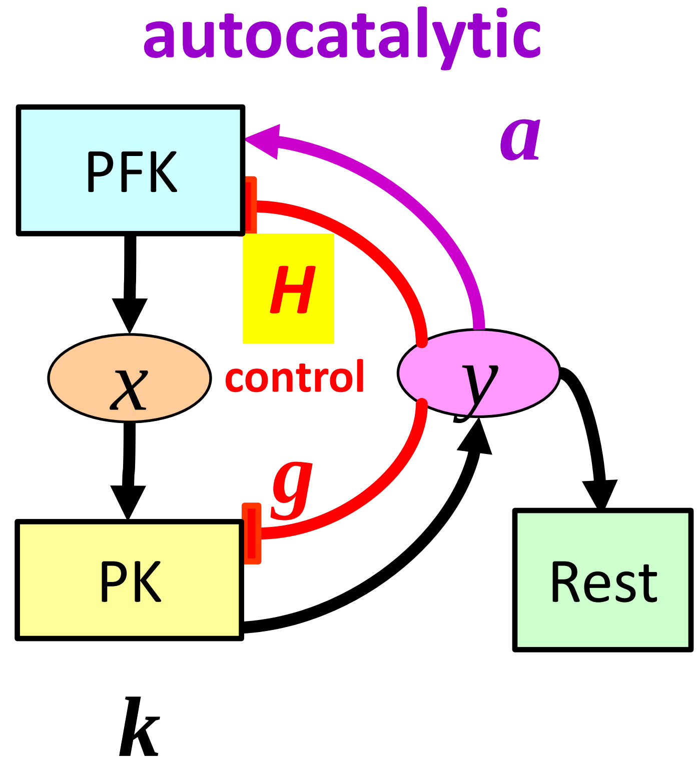




a=1 *sufficient* for oscillations (and is *actual*)
g=1 *necessary* for robust efficiency (and is *actual*)

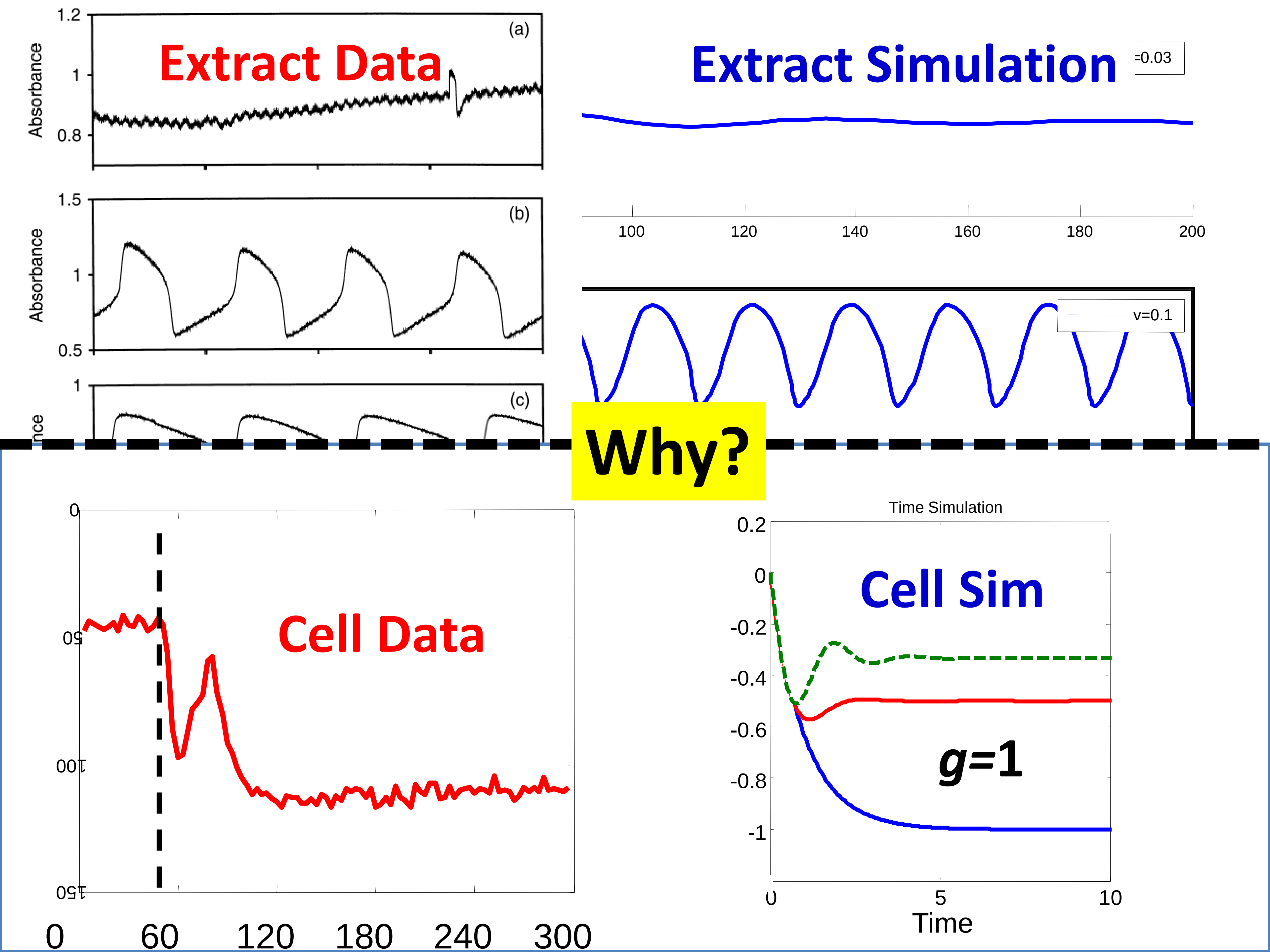
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$





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 Data
Absorbance
1.2
1
0.8
(a)
1.5
1
0.5
(b)
(c)
Extract Simulation
=0.03
100
120
140
160
180
200
v=0.1
Why?
Cell Data
0
50
100
150
0
60
120
180
240
300
Cell Sim
Time Simulation
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
g=1
0
5
10
Time

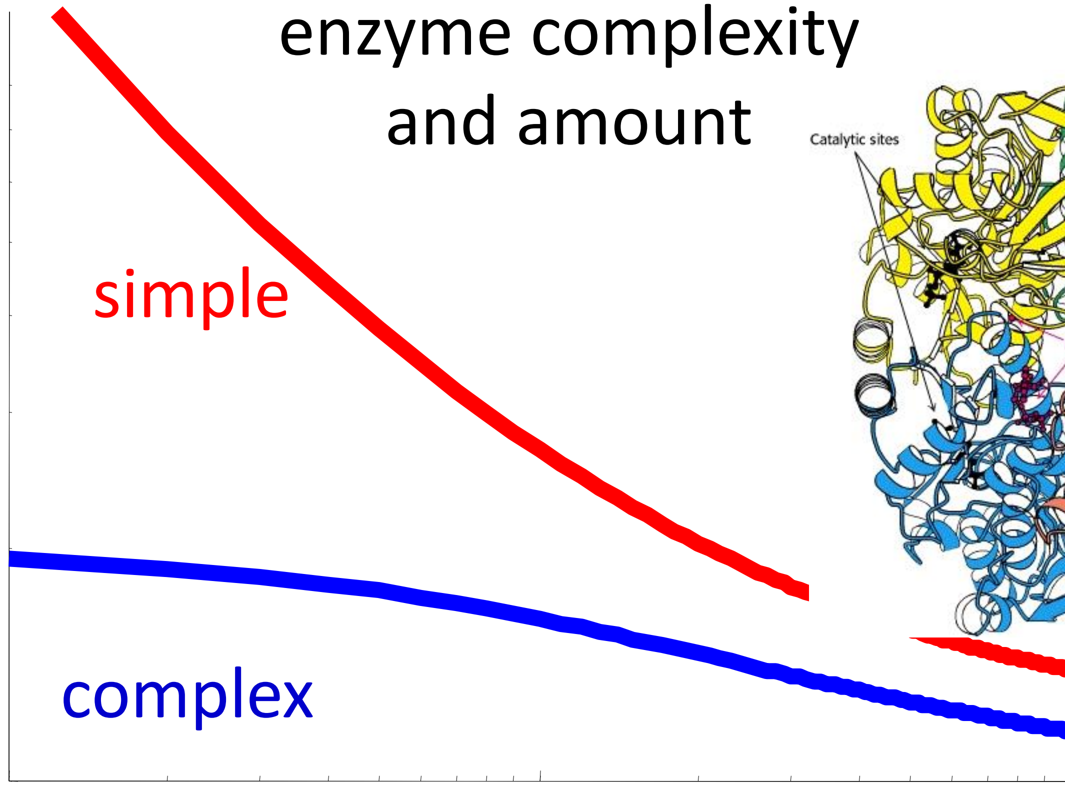
Theorem!

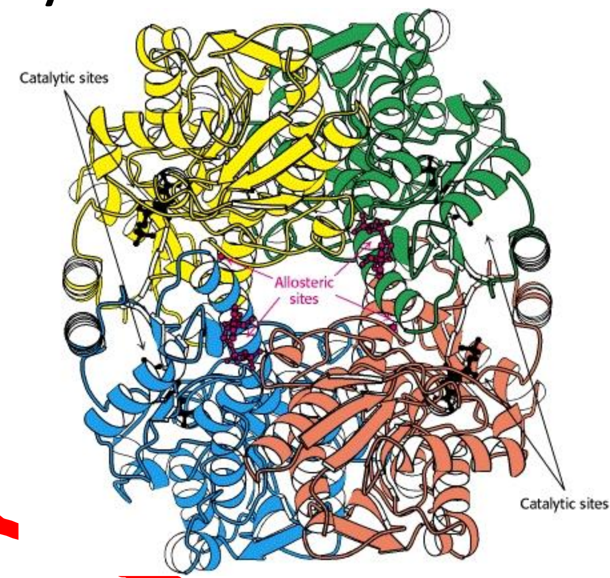
$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

z and *p* functions of enzyme complexity and amount

Fragility

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



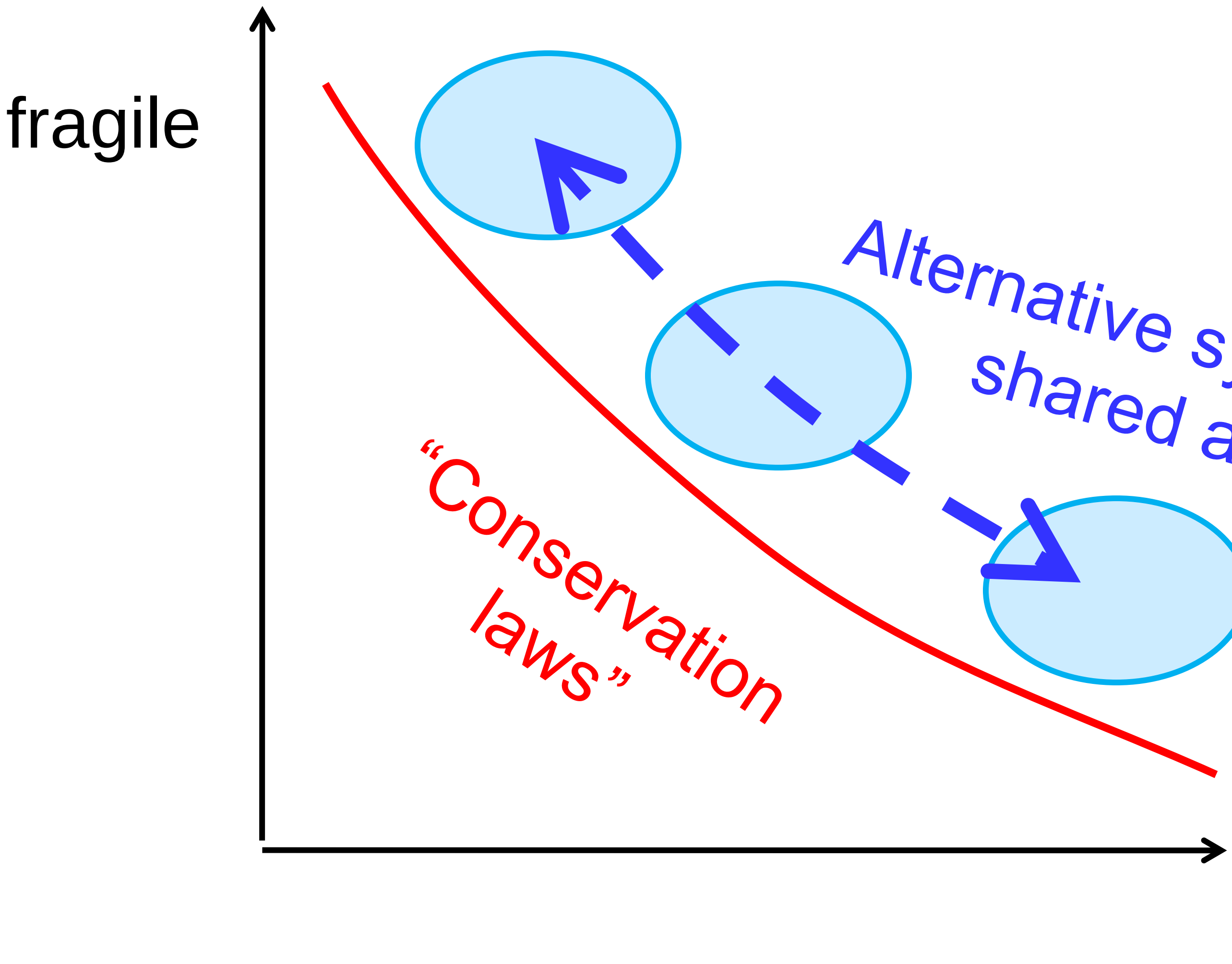


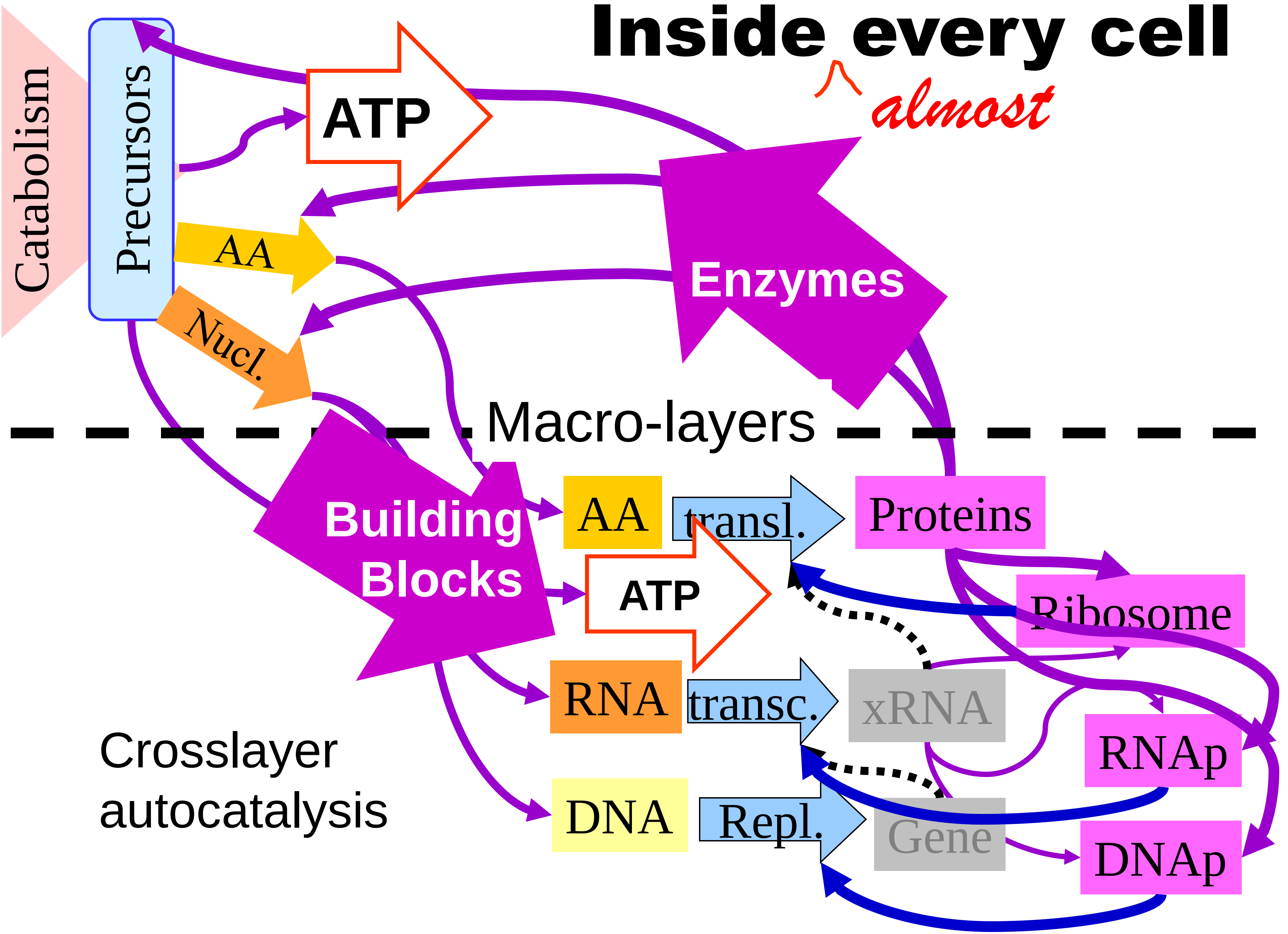
Enzyme amount

Savageaumics

Architecture

Good architectures allow for effective tradeoffs





Inside every cell
almost
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis

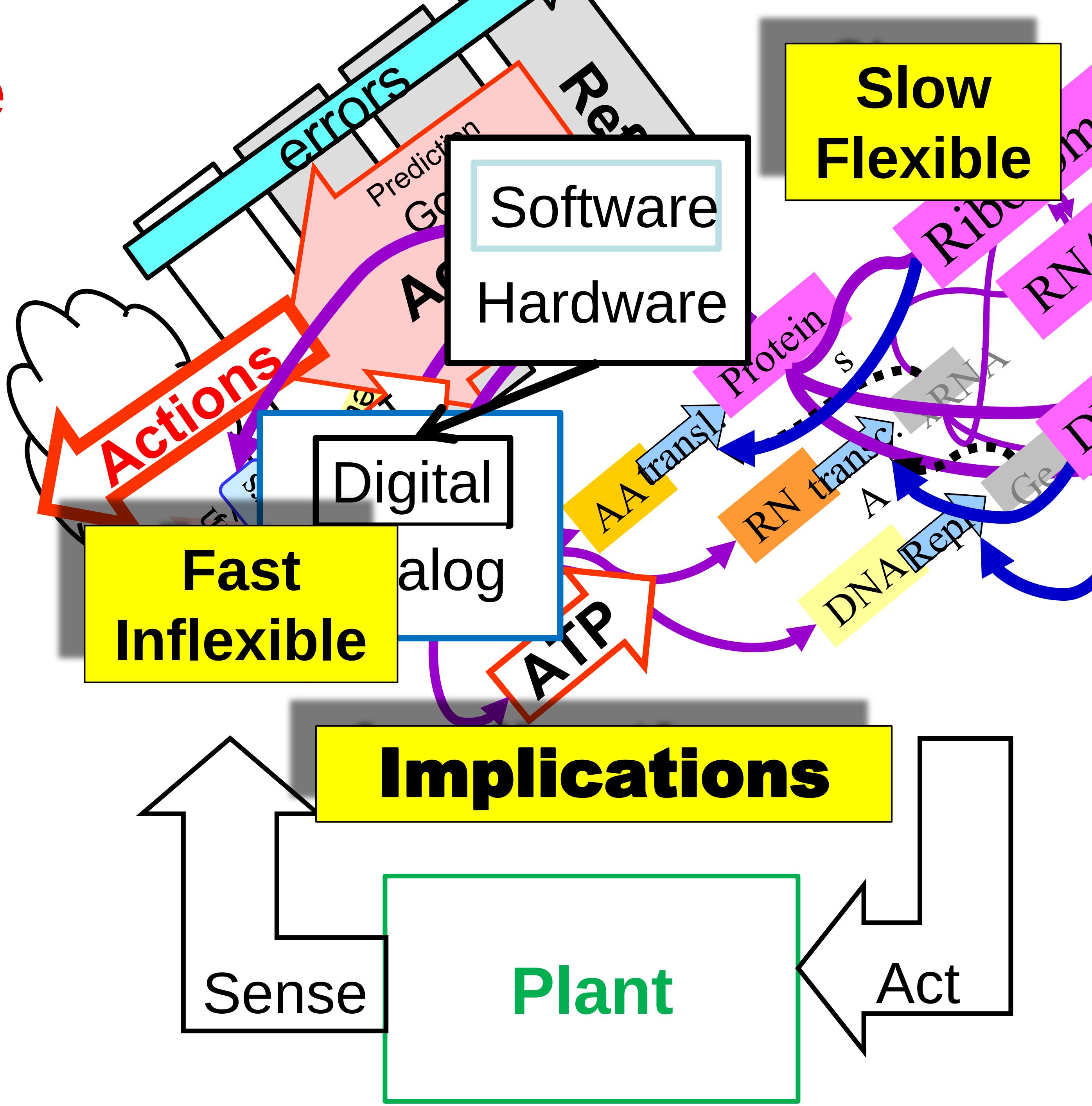
Compute

Turing

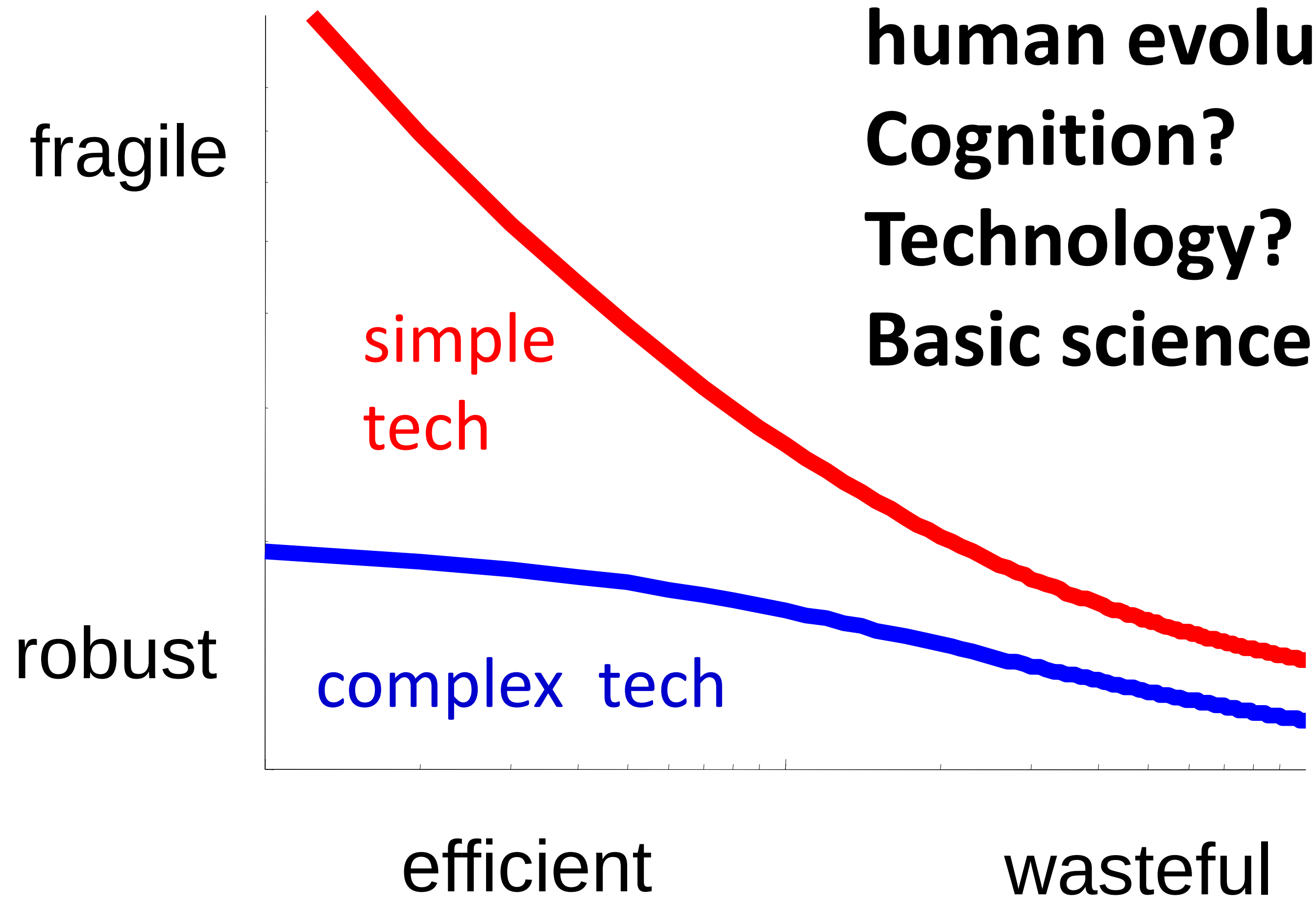
Delay is *most* important

Bode

Control



How general is this picture?



Implications for human evolution?
Cognition?
Technology?
Basic sciences?

Supplementary materials has a demo.

Architecture, constraints, and behavior

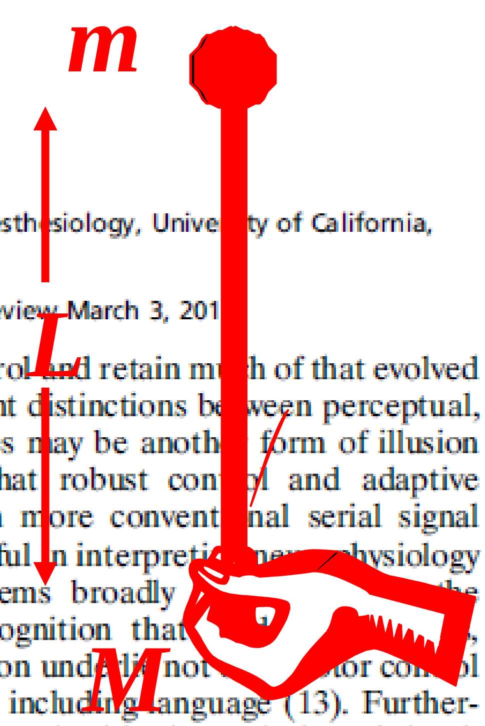
John C. Doyle[a,1] and Marie Csete[b,1]

[a]Control and Dynamical Systems, California Institute of Technology, Pasadena, CA 91125; and [b]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, 201

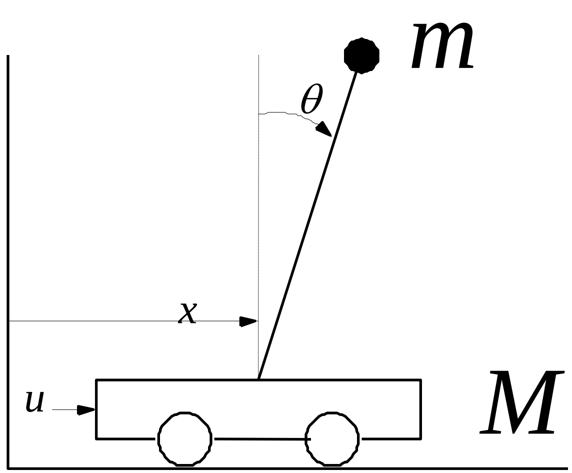
This paper aims to bridge progress in neuroscience involving sophisticated quantitative analysis of behavior, including the use of robust control, with other relevant conceptual and theoretical frameworks from systems engineering, systems biology, and mathematics. Familiar and accessible case studies 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.

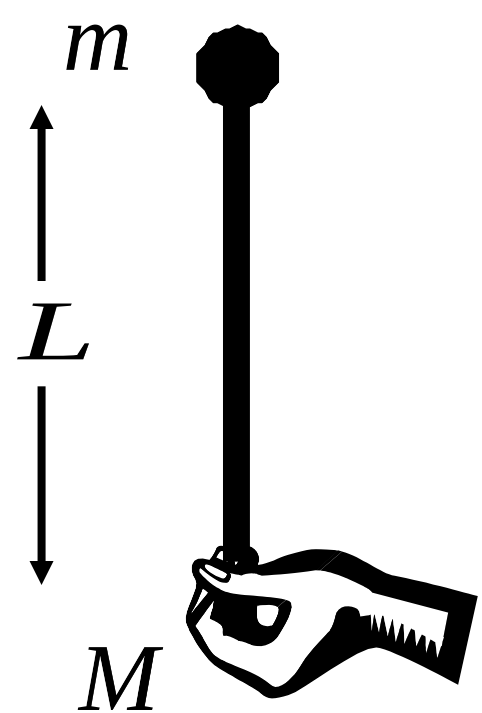
evolved for sensorimotor control and retain much of that evolved architecture, then the apparent distinctions between perceptual, cognitive, and motor processes may be another form of illusion (9), reinforcing the claim that robust control and adaptive feedback (7, 11) rather than more conventional serial signal processing might be more useful in interpreting neurophysiology data (9). This view also seems broadly [illegible] arguments from grounded cognition that [illegible] bodily states, and situated action underlie not [illegible] motor control but cognition in general (12), including language (13). Furthermore, the myriad constraints involved in the evolution of circuit



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

Linearized pendulum on a cart





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

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

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

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

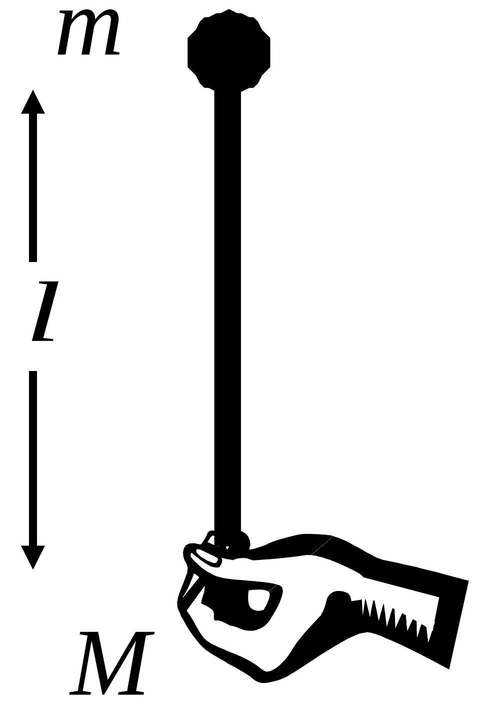
$$y=x+\alpha l\sin\theta$$

linearize

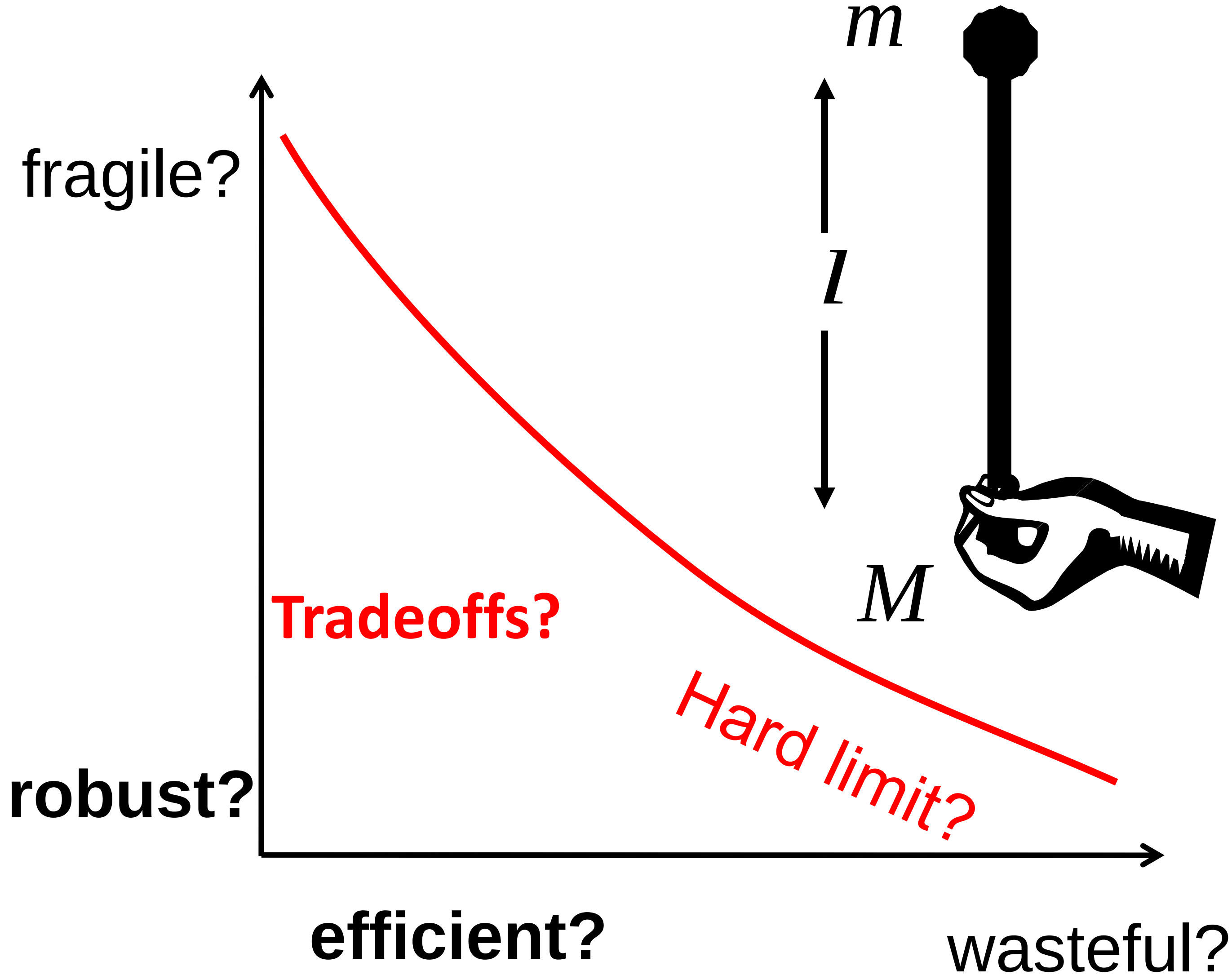
$$(M+m)\ddot{x}+ml\ddot{\theta}=u$$

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

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



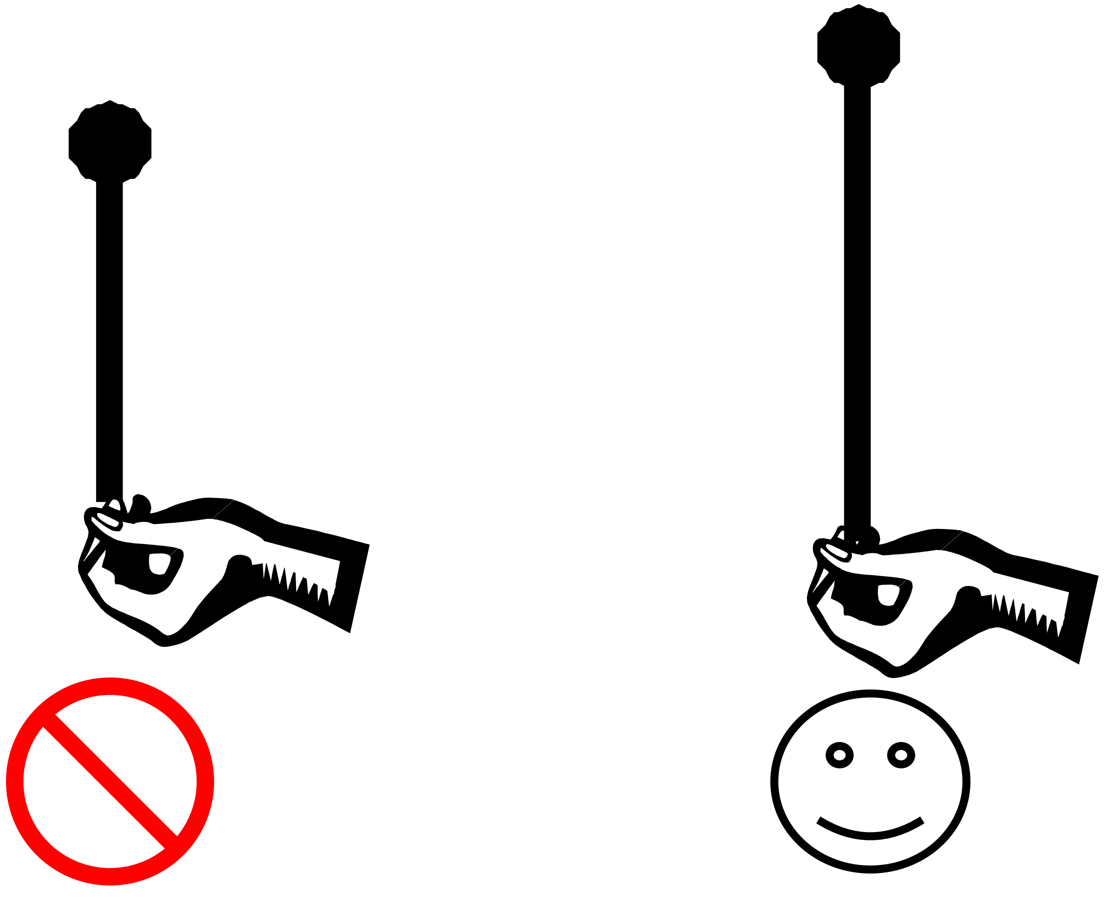
Robust
=agile and
balancing

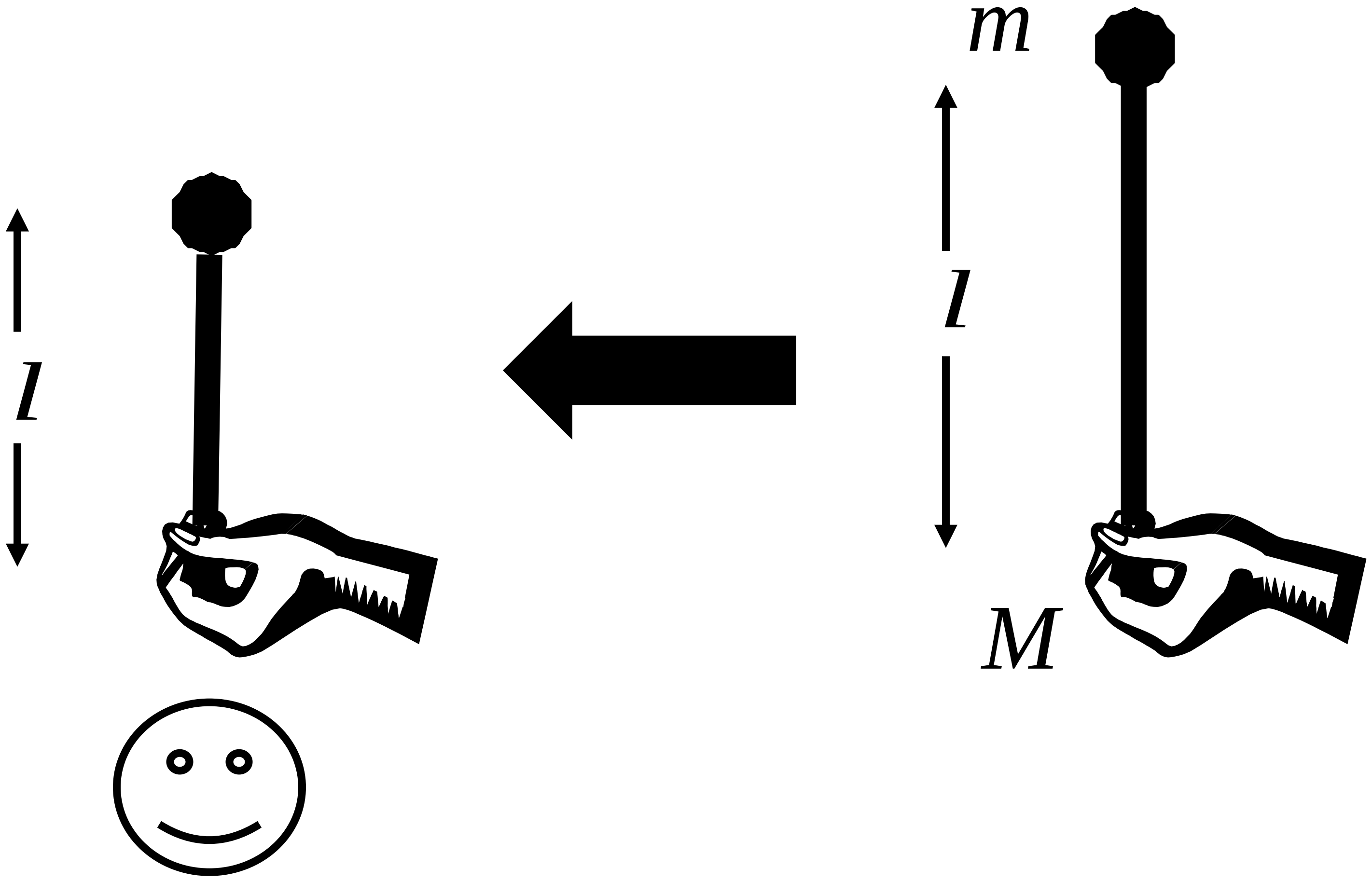


Efficient=length of
pendulum (artificial)

Robust

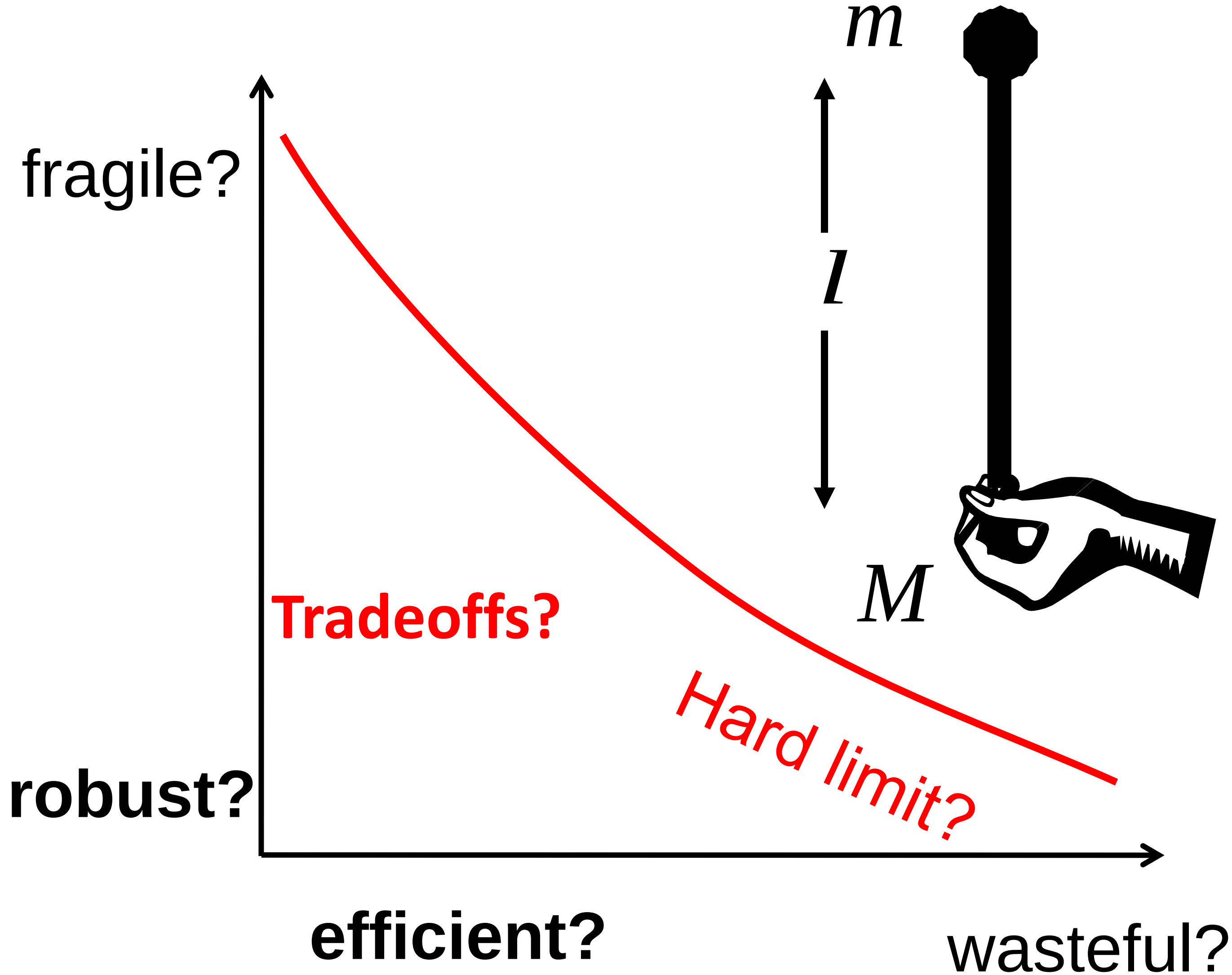
=agile and balancing





Efficient=length of pendulum (artificial)

Robust
=agile and balancing

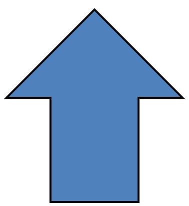


Efficient=length of pendulum (artificial)

$$\begin{bmatrix} x \\ \theta \end{bmatrix} = \frac{1}{D(s)} \begin{bmatrix} ls^2 \pm g \\ -s^2 \end{bmatrix} u \qquad D(s) = s^2 \left(Mls^2 \pm (M+m) g \right)$$

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

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



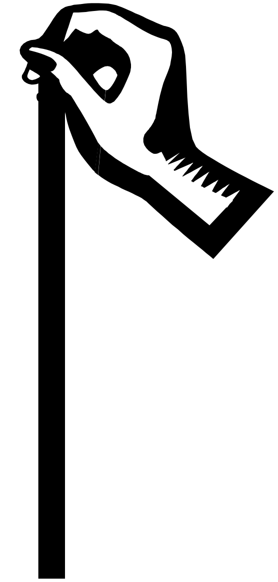
transform+algebra

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

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

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

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

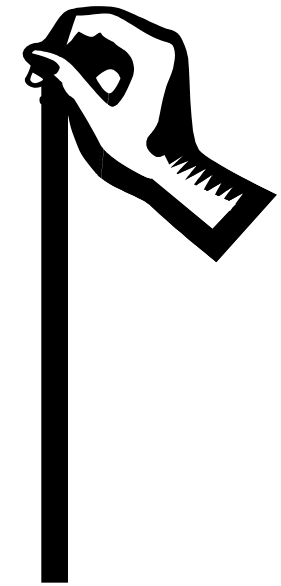


Easy, even with eyes closed
No matter what the length

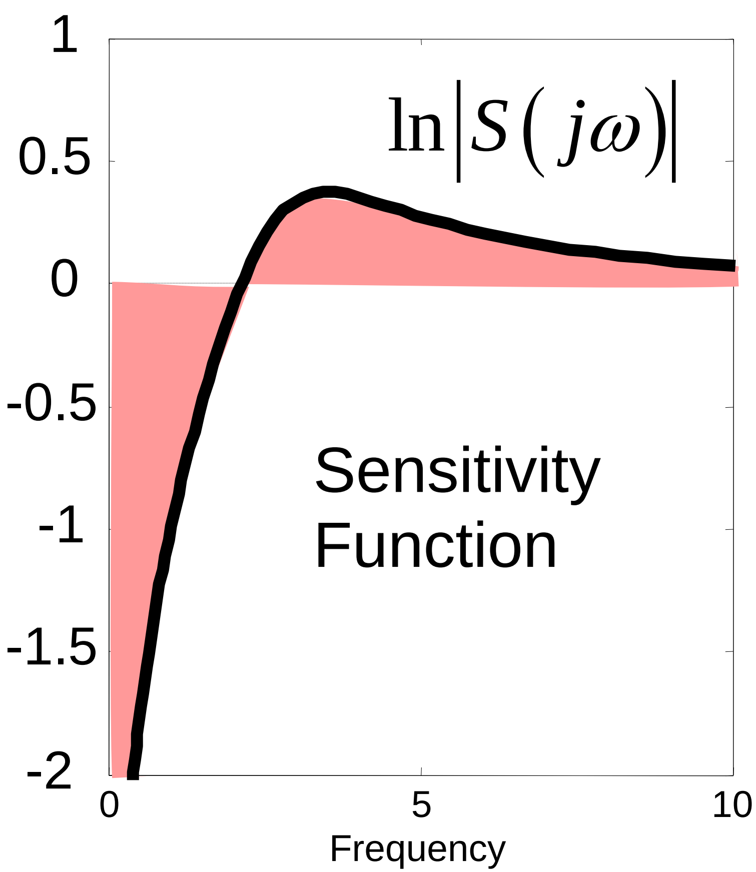
Proof: Standard UG control theory:

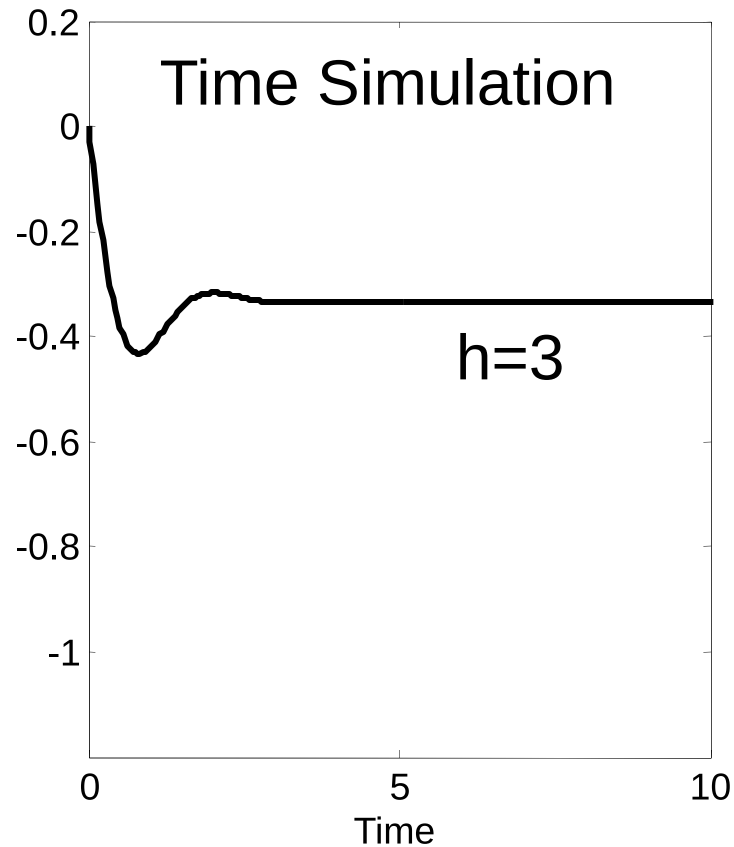
Easy calculus, easier contour integral,
easiest Poisson Integral formula

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

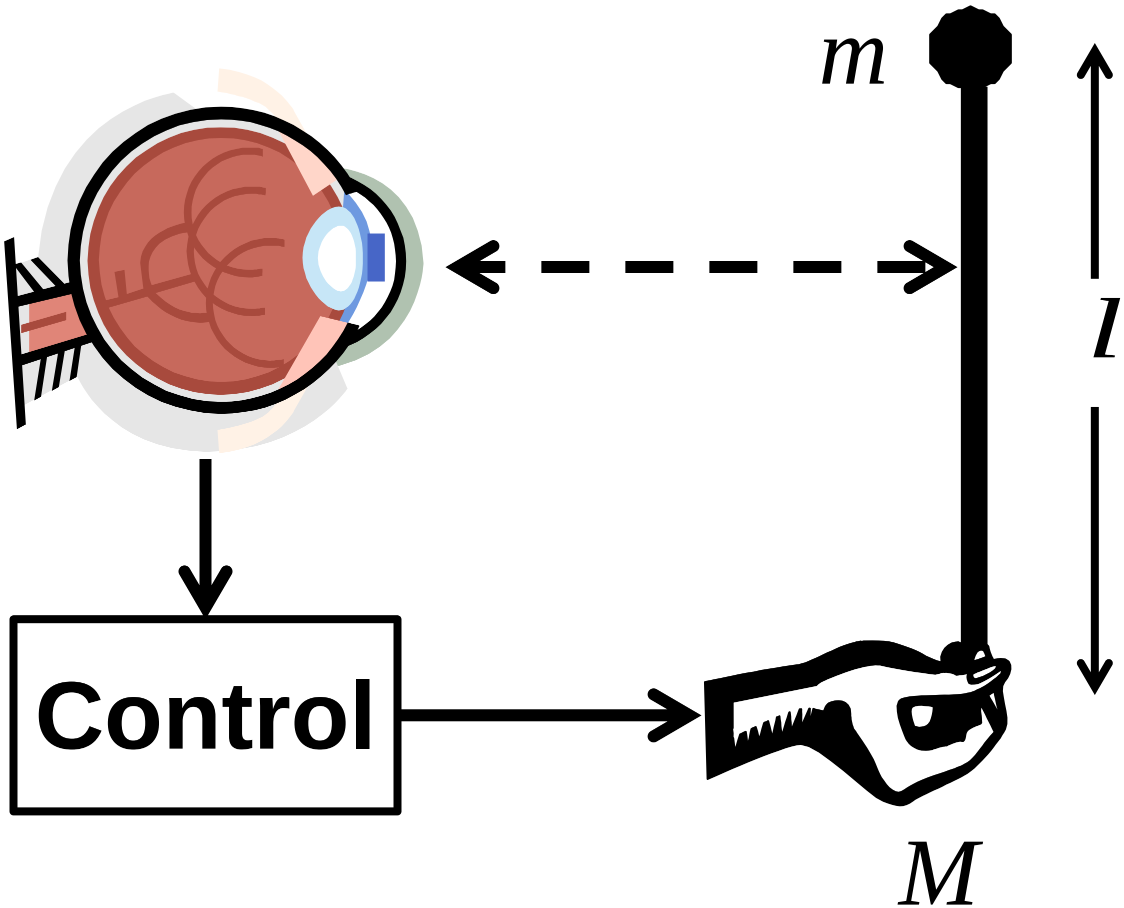


≈ simple metabolism without autocatalysis

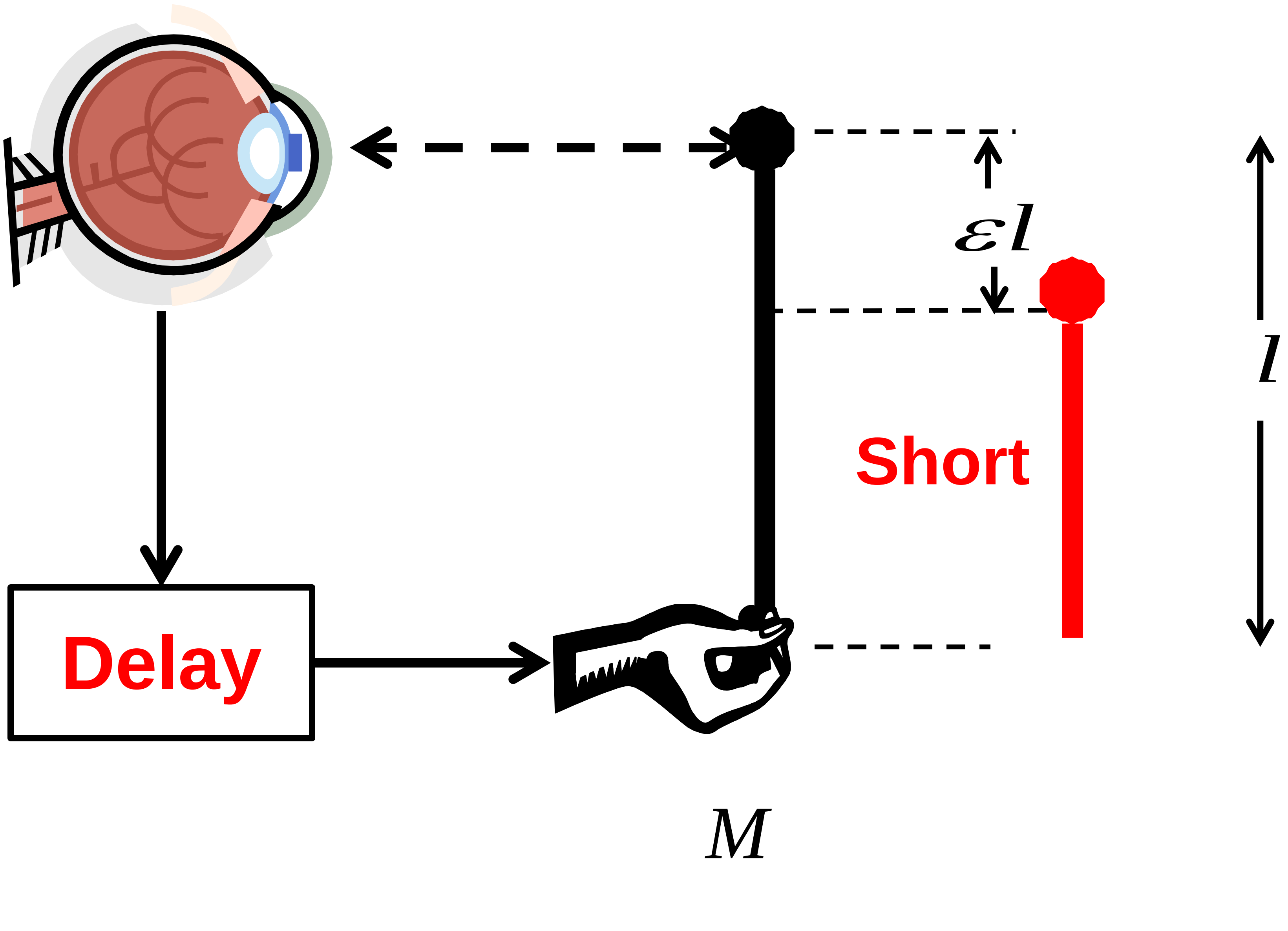




Need vision

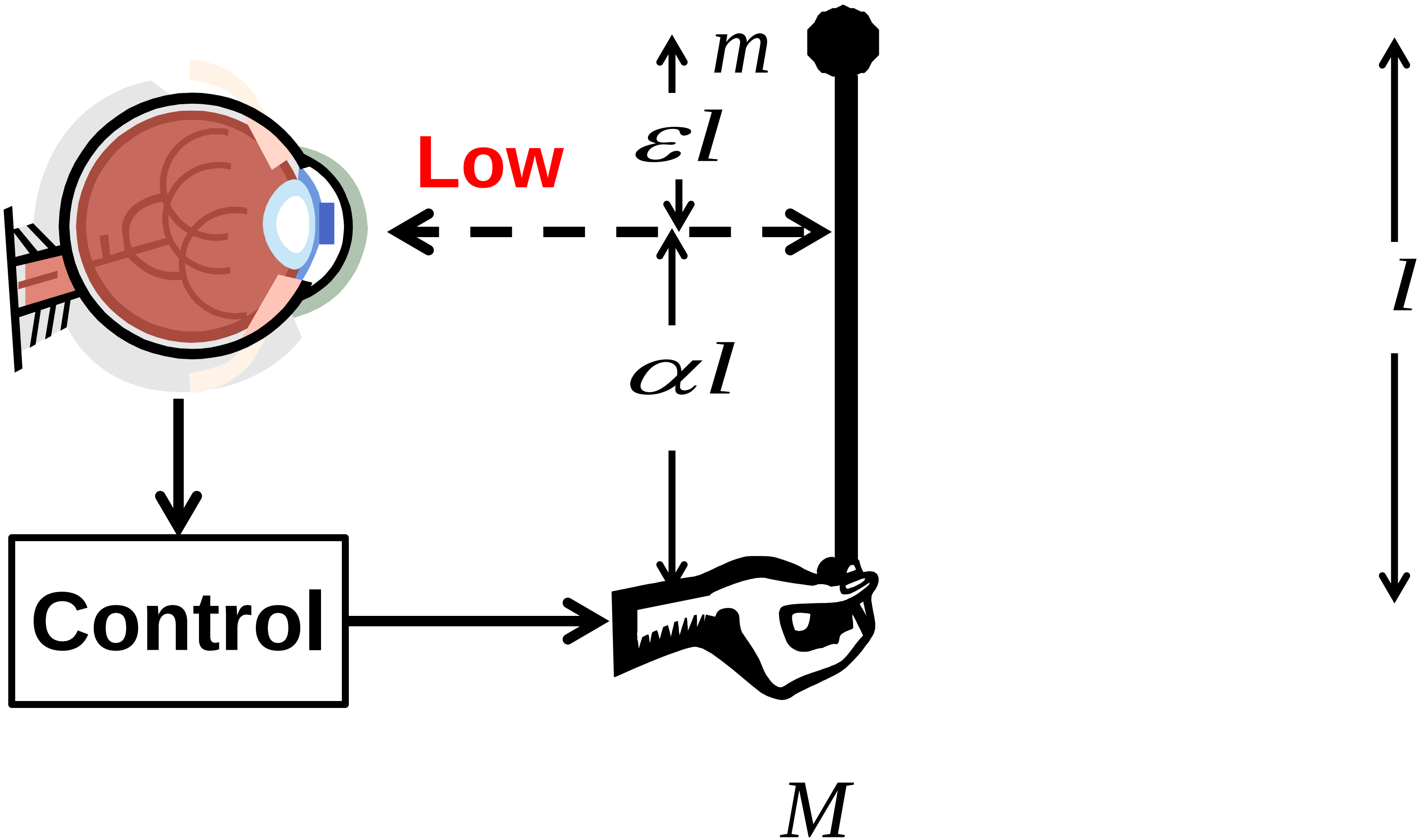


Harder if delayed or short



Also harder if low

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



Gratuitous fragility
versus
fragile robustness

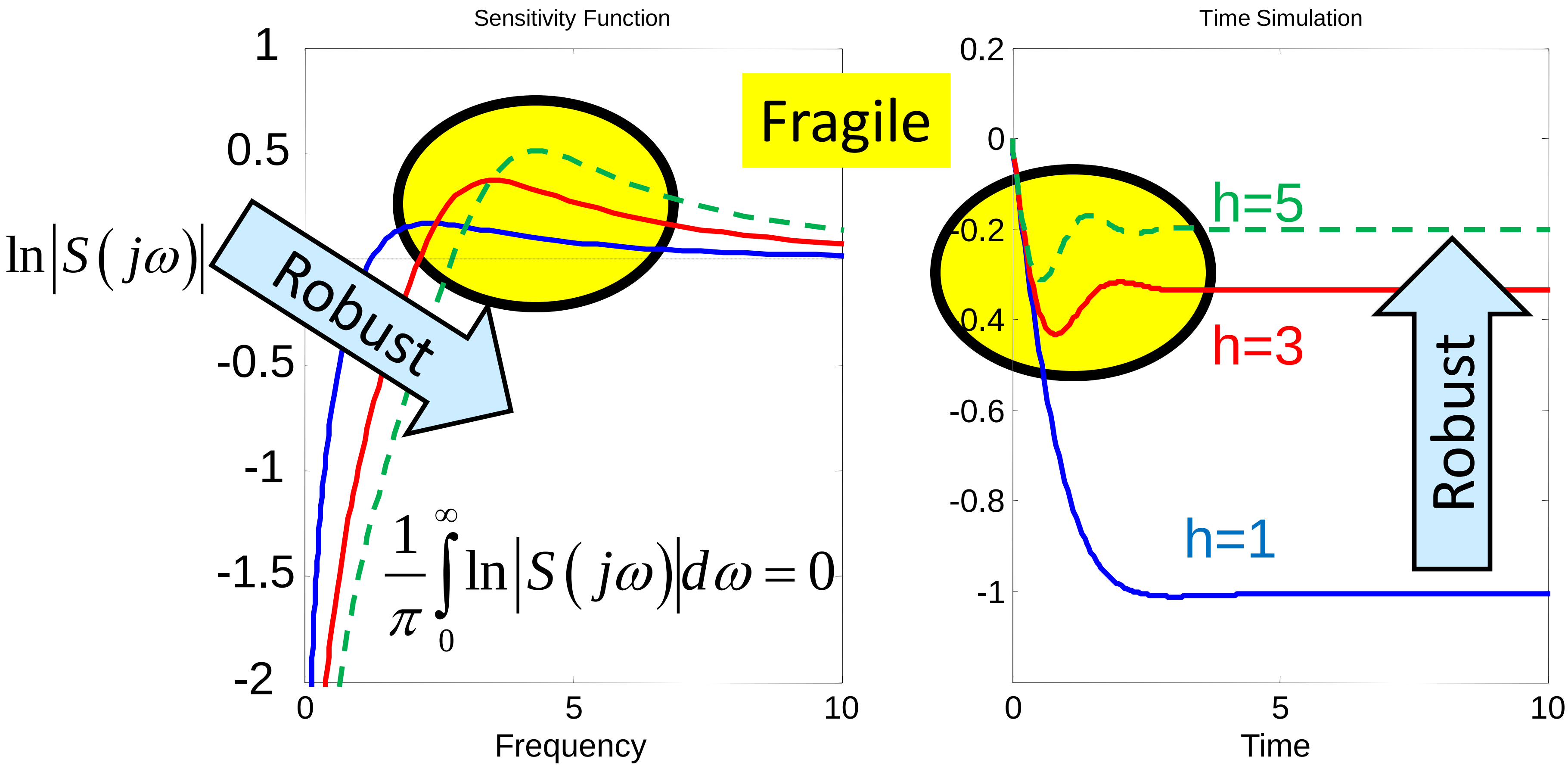
$$\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq 0$$

$$\gg \quad \Rightarrow \quad \text{Gratuitous fragility}$$

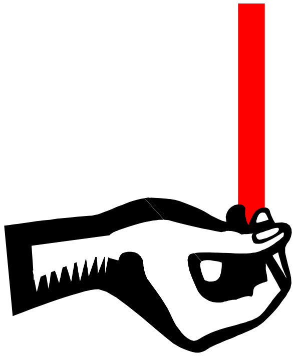
$$= \quad \Rightarrow \quad \text{Fragile robustness}$$

Theorem is independent
of control implementation.

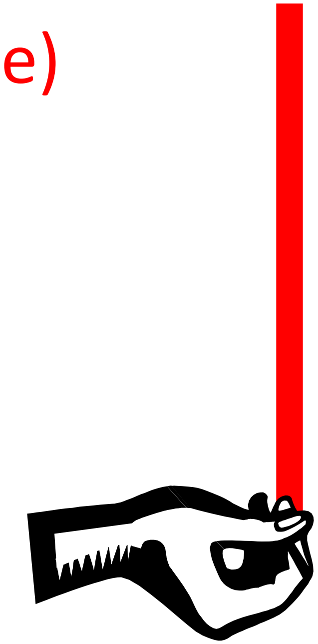
Simple metabolism without autocatalysis



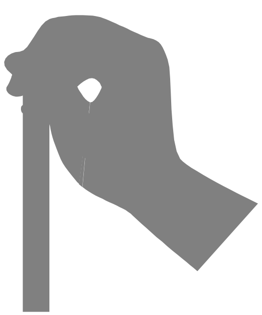
Up is hard for shorter lengths (RHP pole)



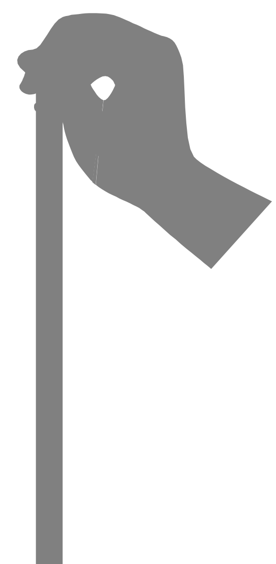
$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq |p|$$



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



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



Down easy, even with

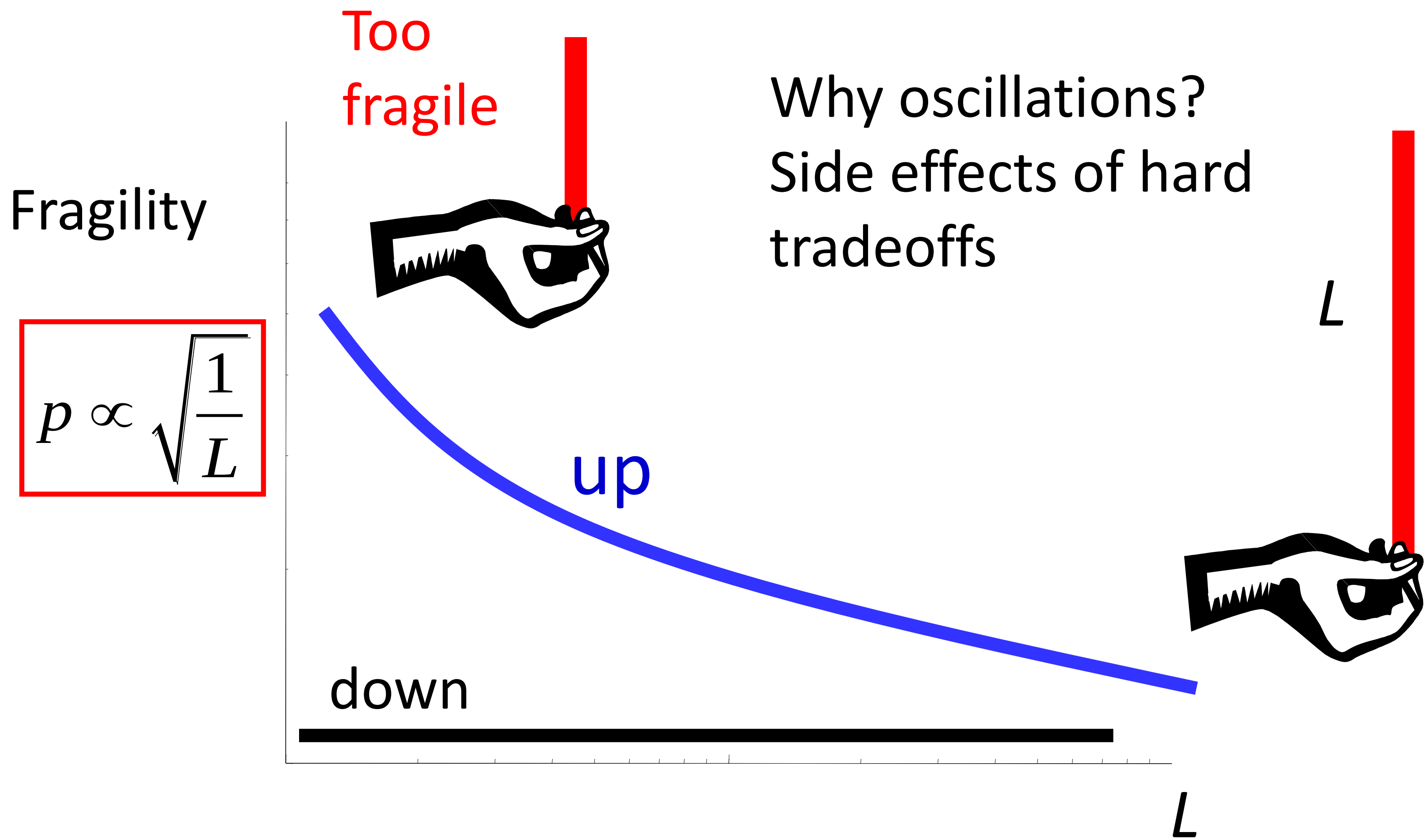
- eyes closed
- all lengths

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

This is a cartoon, but can be made precise.

Why oscillations? Side effects of hard tradeoffs

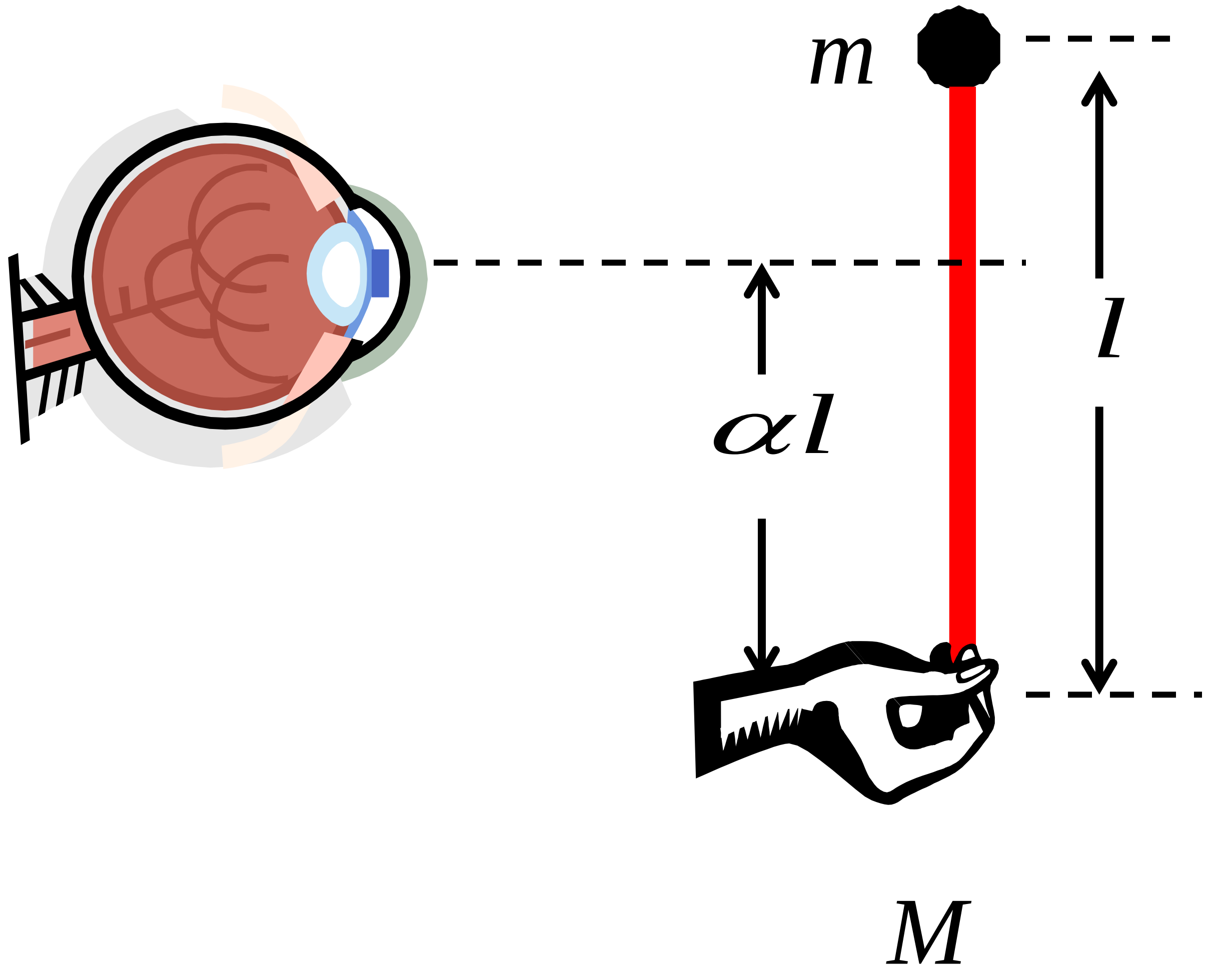
$$p \propto \sqrt{\frac{1}{L}}$$



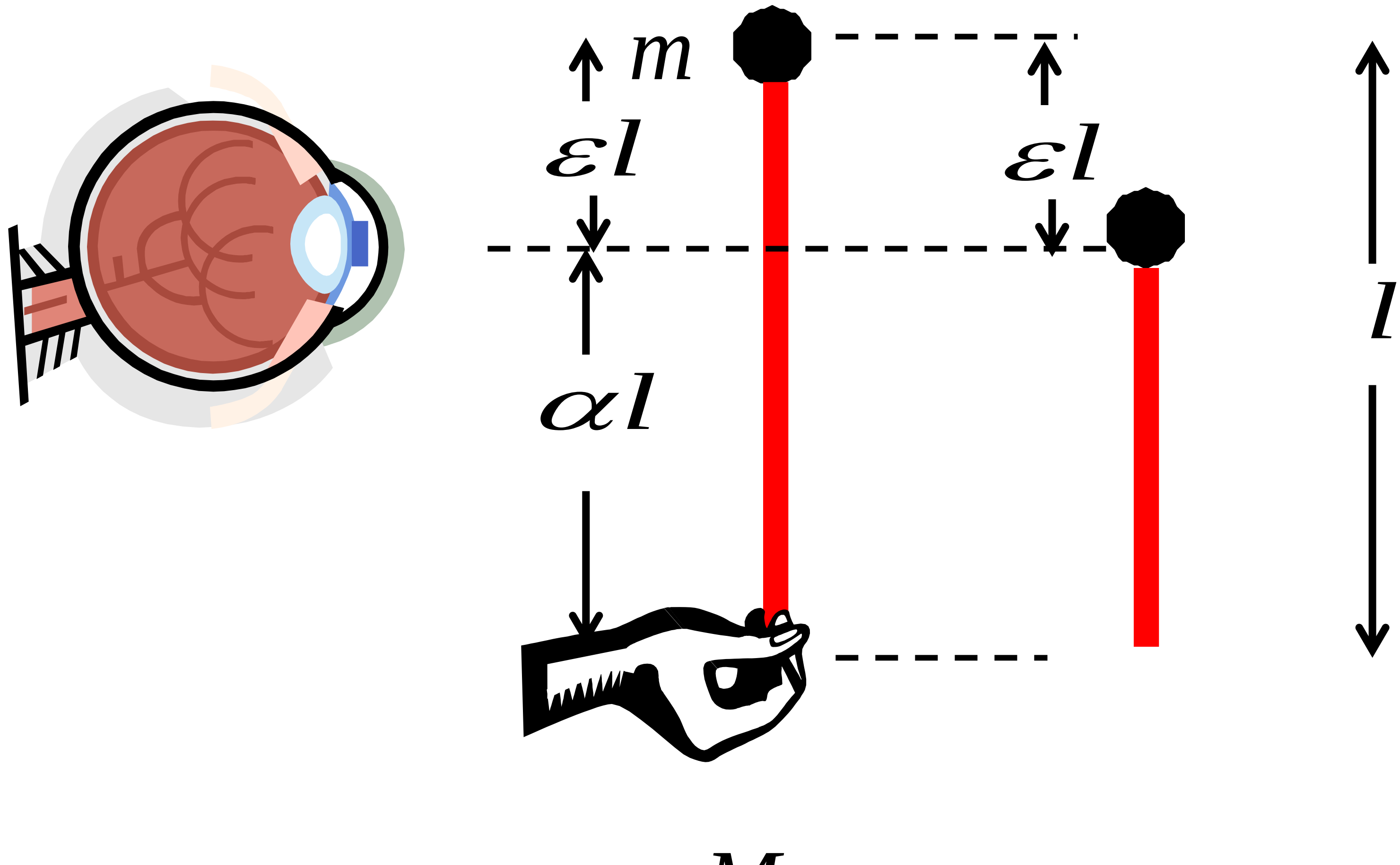
Eyes moved down is harder

(RHP zero)

Similar to delay



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



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

Compare

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

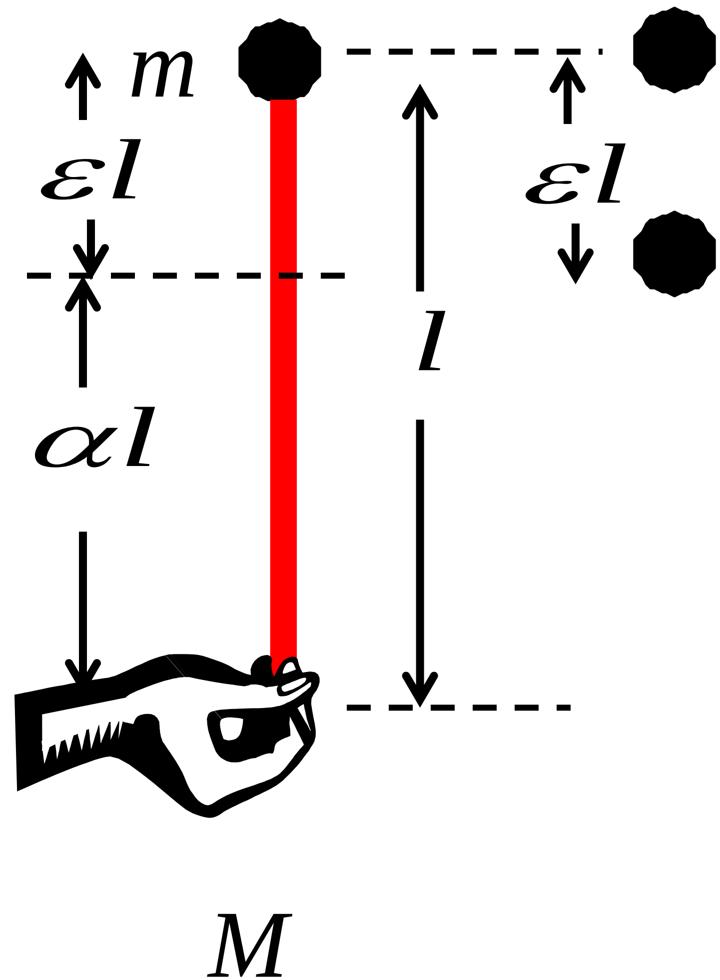
Move eyes

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

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

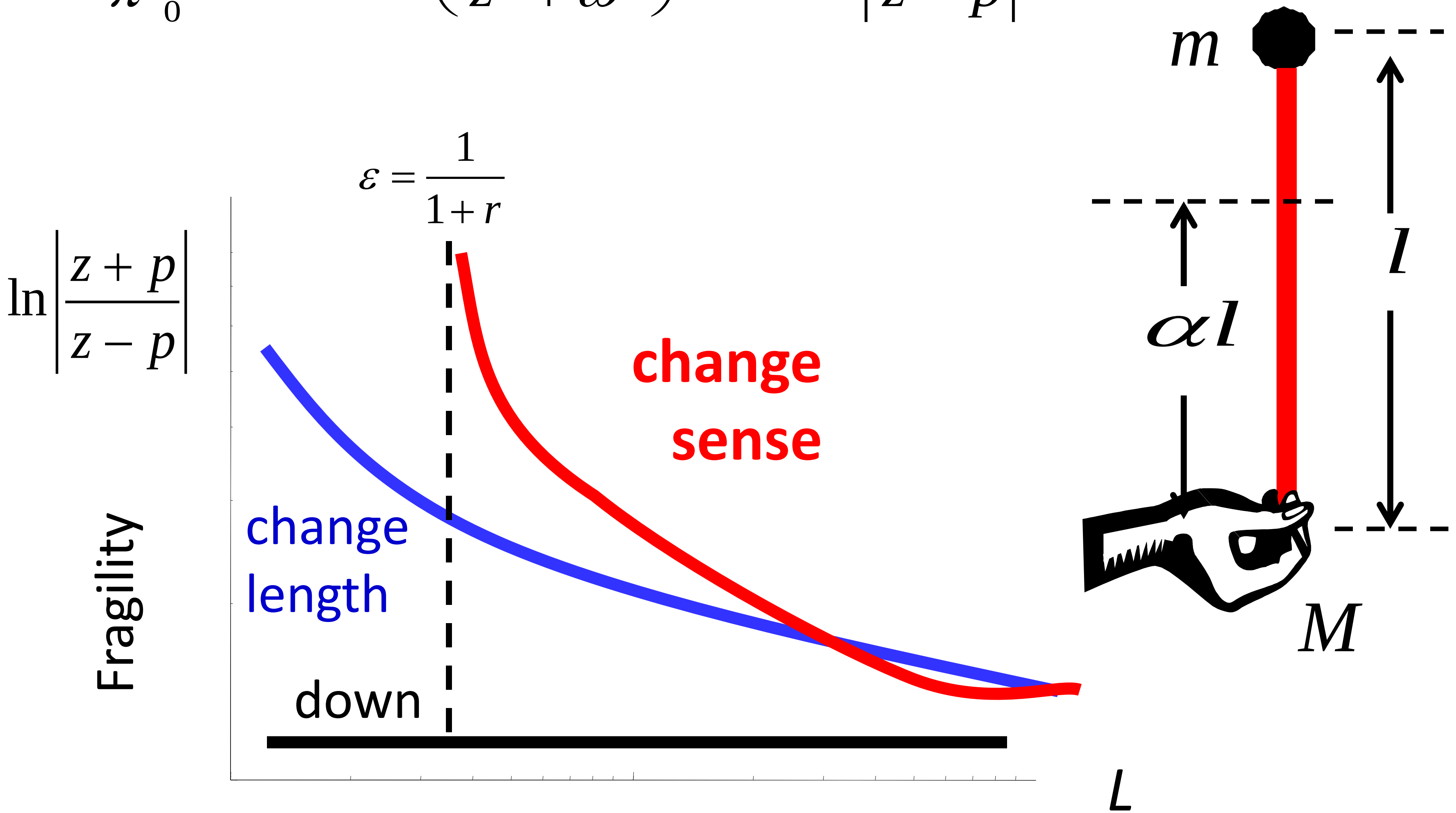
$$p\left(1+\frac{1}{3}\frac{p^2}{z^2}\right) = \sqrt{\frac{g}{l}}\sqrt{1+r}\left(1+\frac{1}{3}\varepsilon\right) = p\left(1+\frac{\varepsilon}{3}\right)$$

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



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

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



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

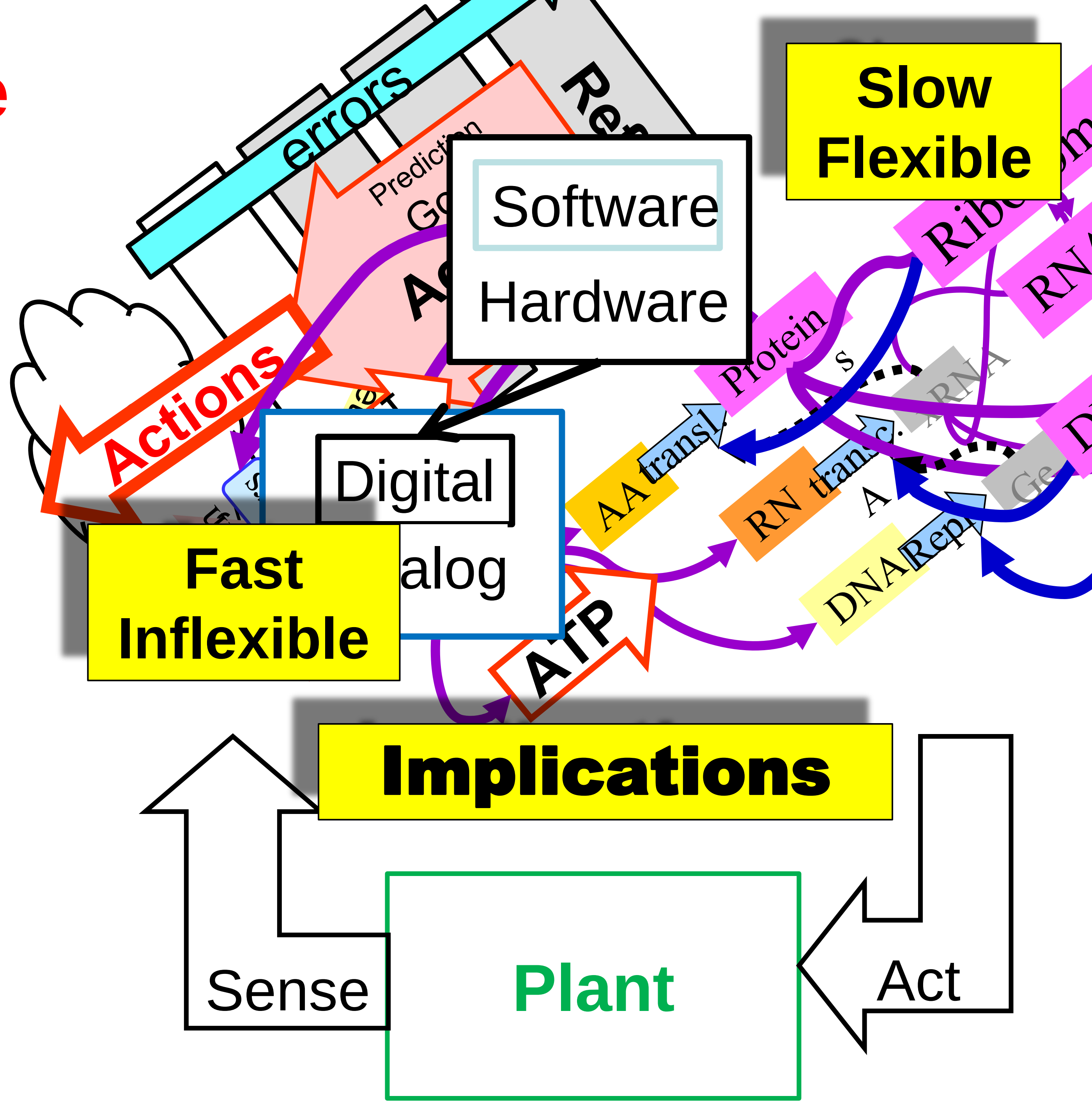
Compute

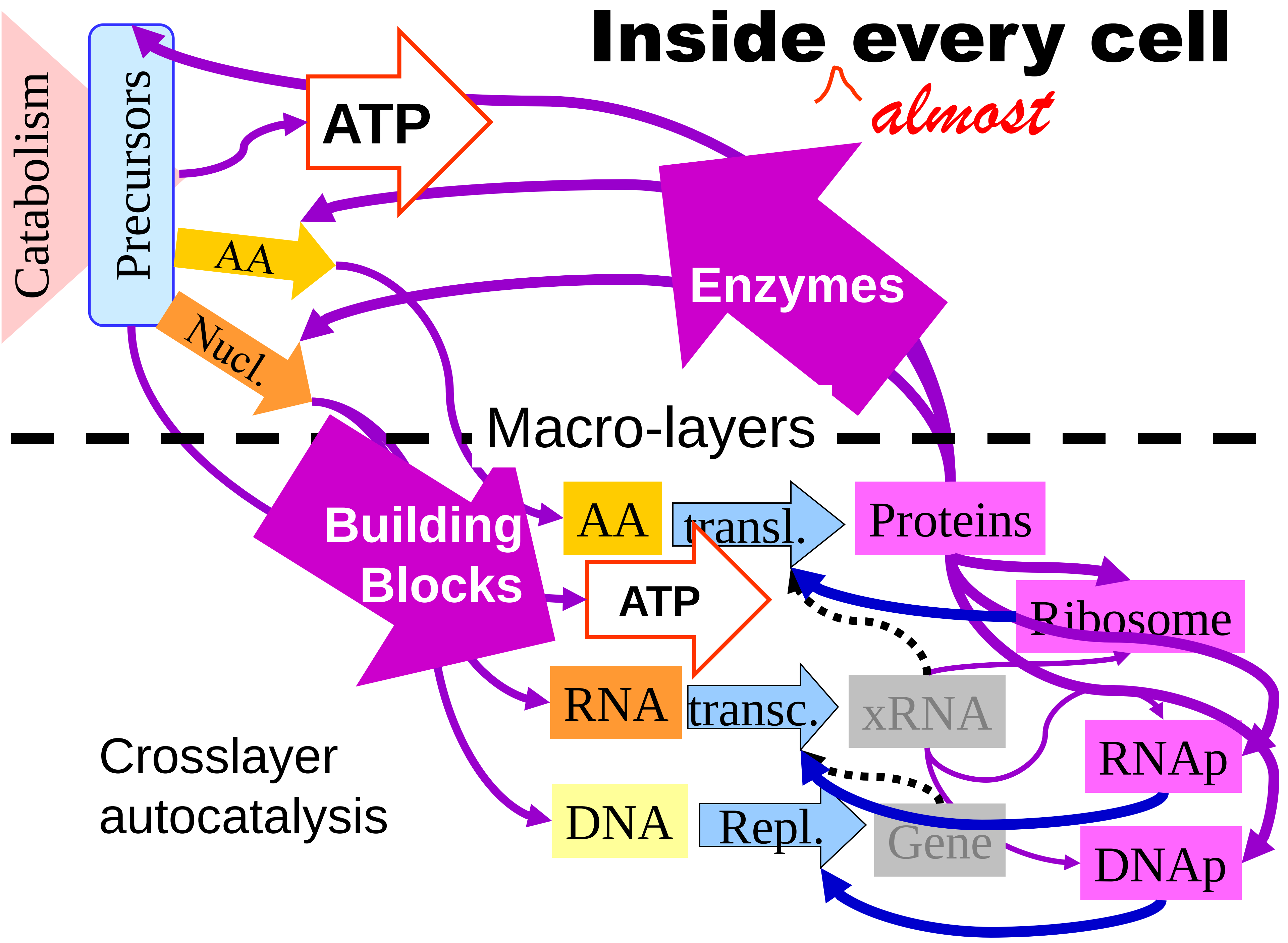
Turing

Delay is *most* important

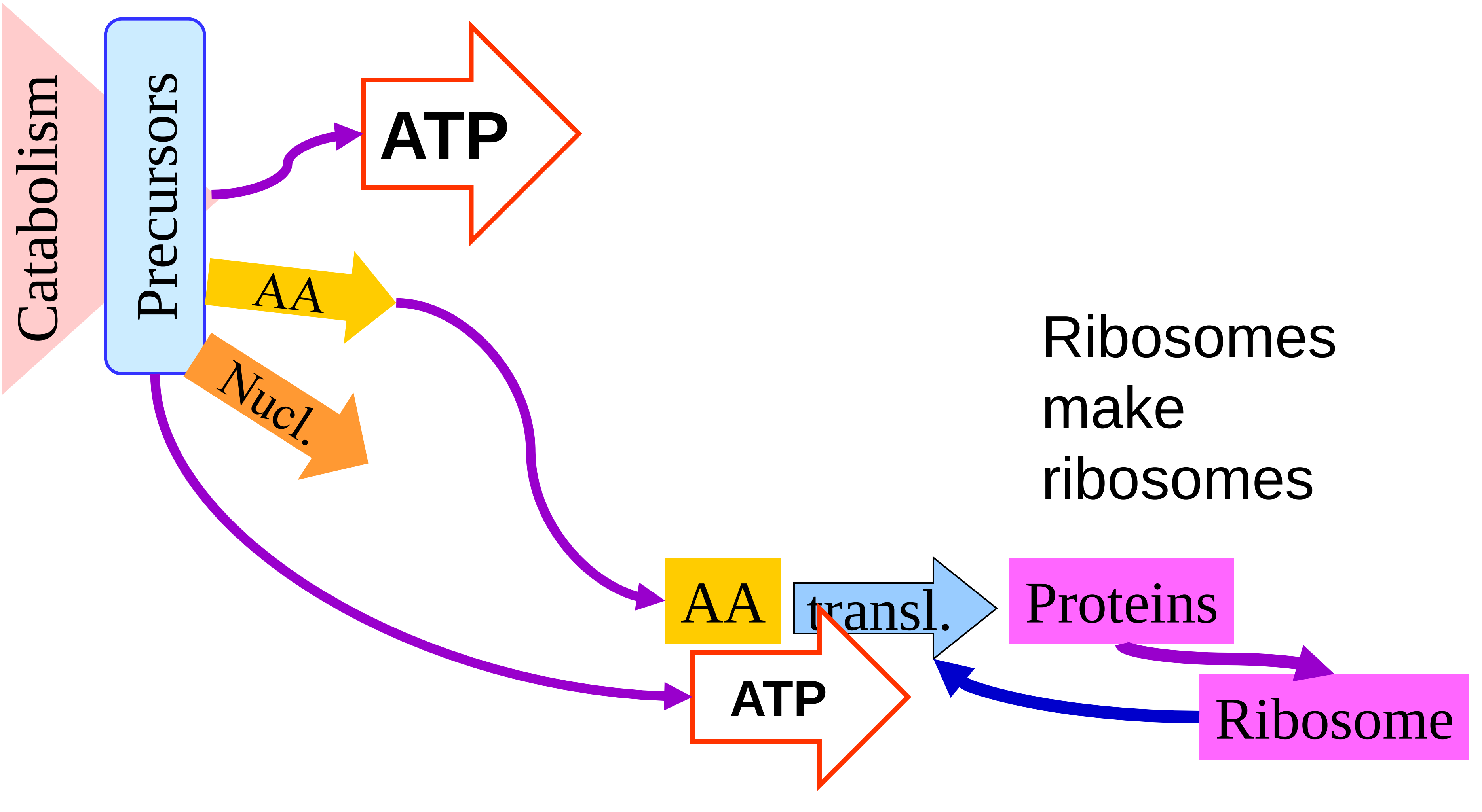
Bode

Control



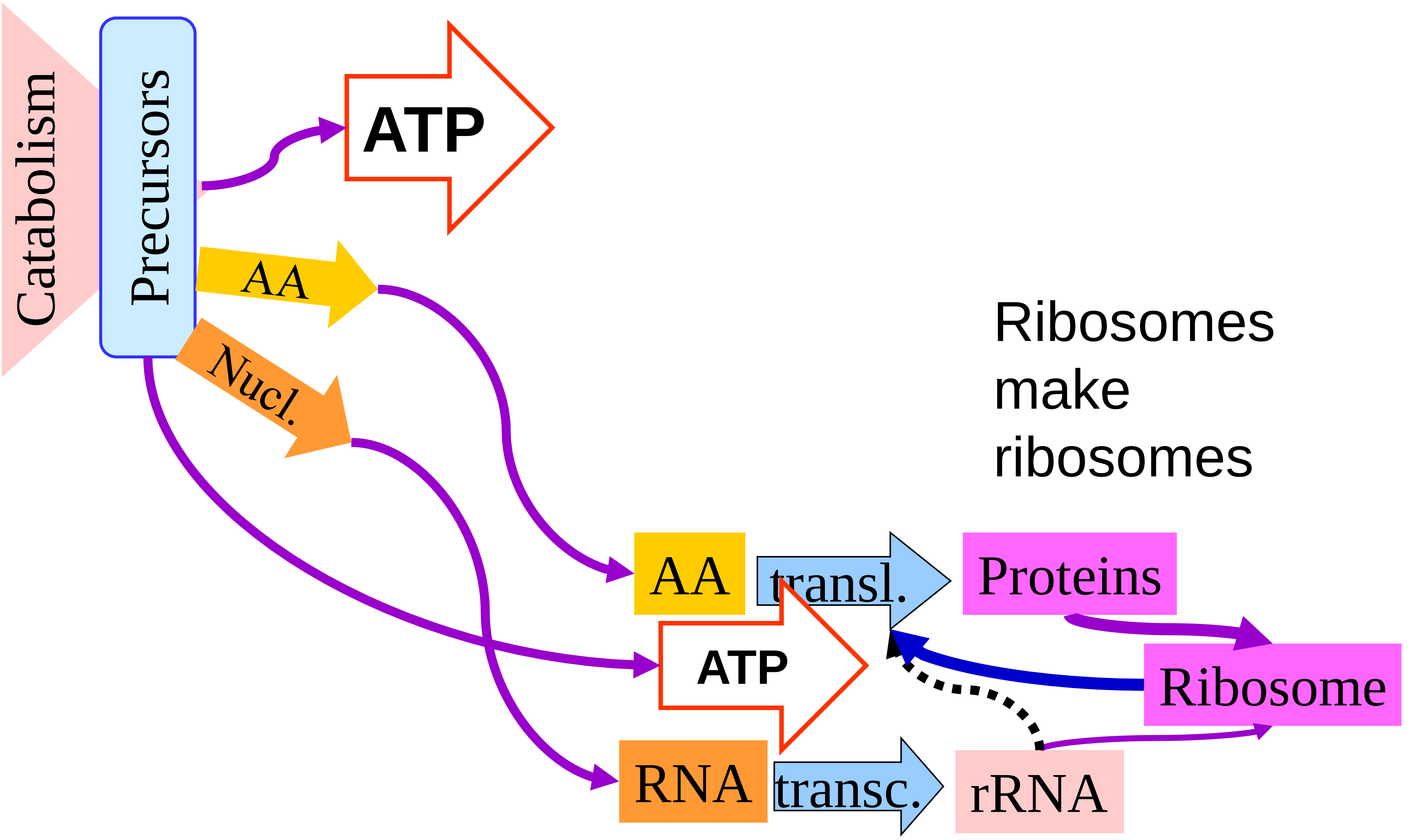


Inside every cell
almost
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis



Ribosomes make ribosomes

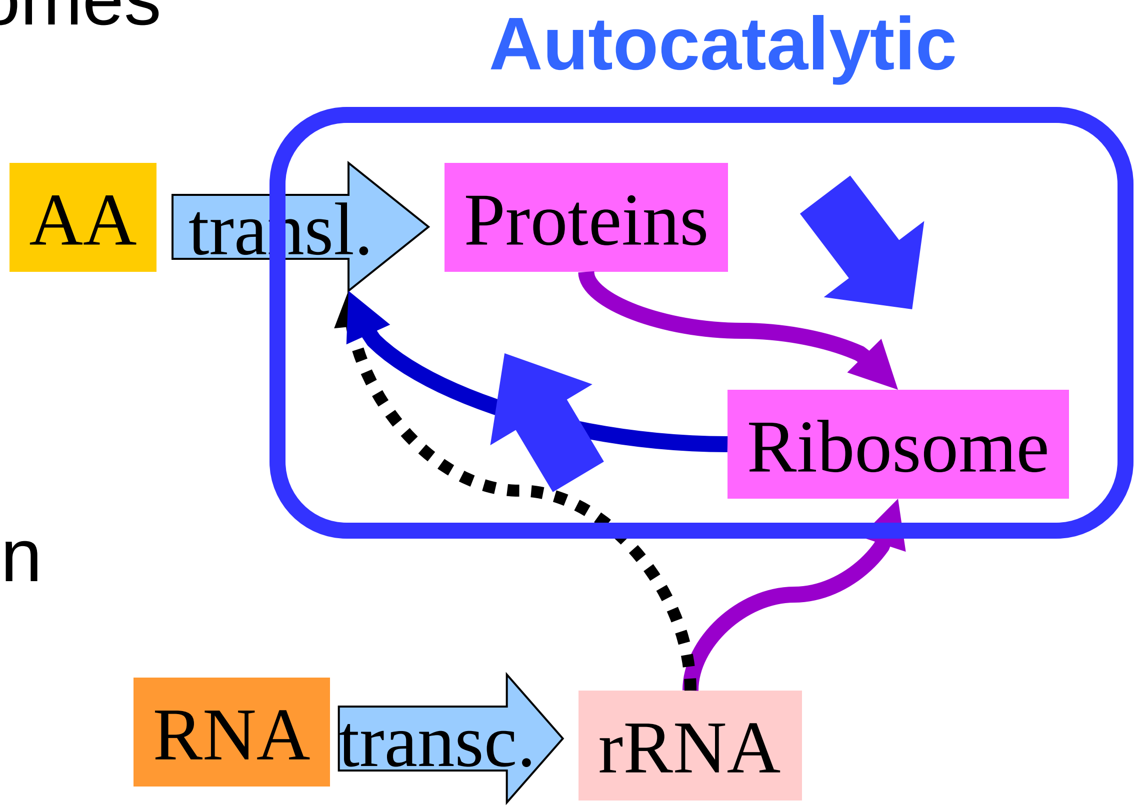
Translation: Amino acids polymerized into proteins



Ribosomes
make
ribosomes

Ribosomes are made
of proteins and RNA

Ribosomes make ribosomes

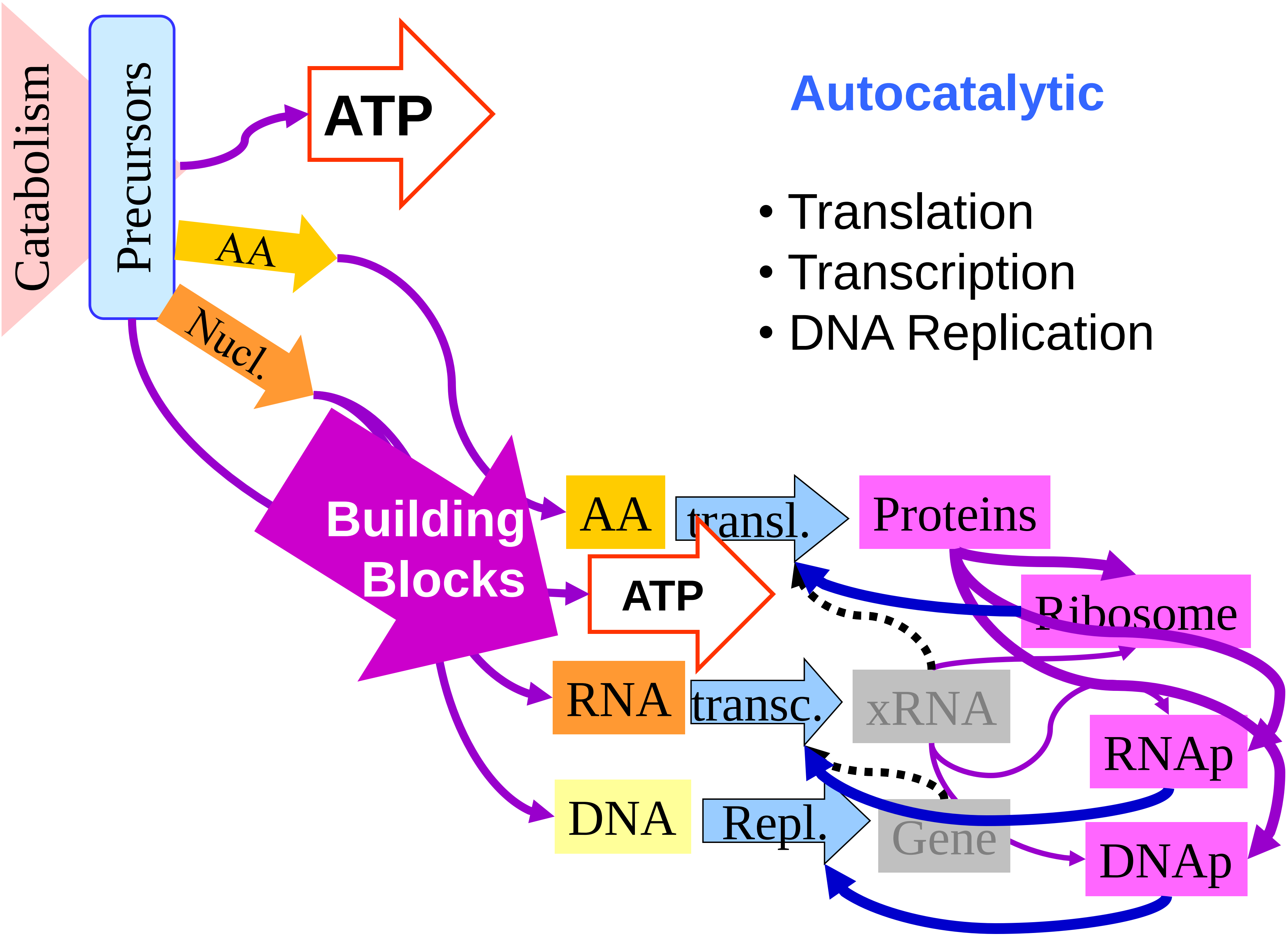


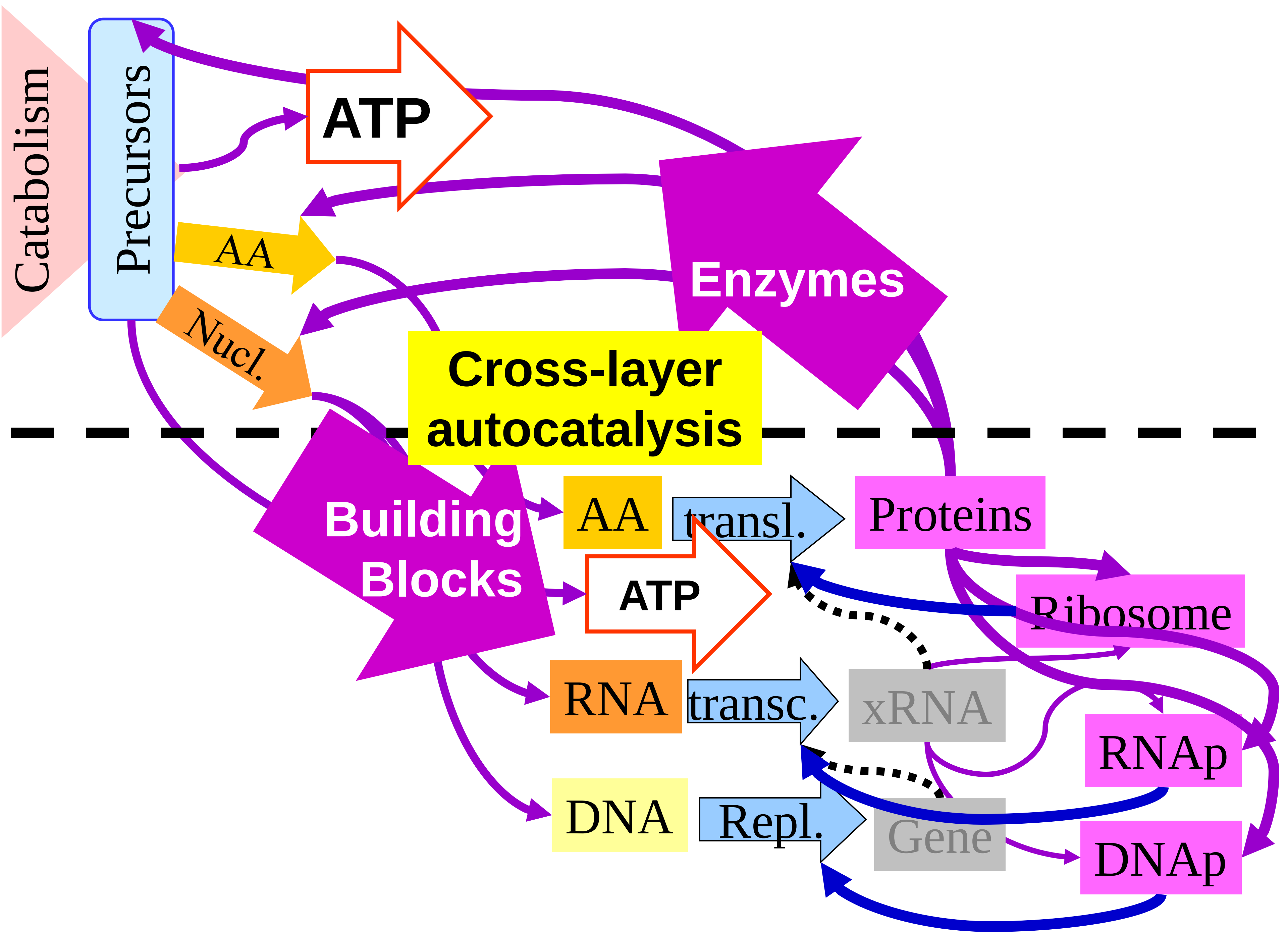
Organisms differ in the proportion of ribosomal protein vs rRNA

Ribosomes are made of proteins and rRNA

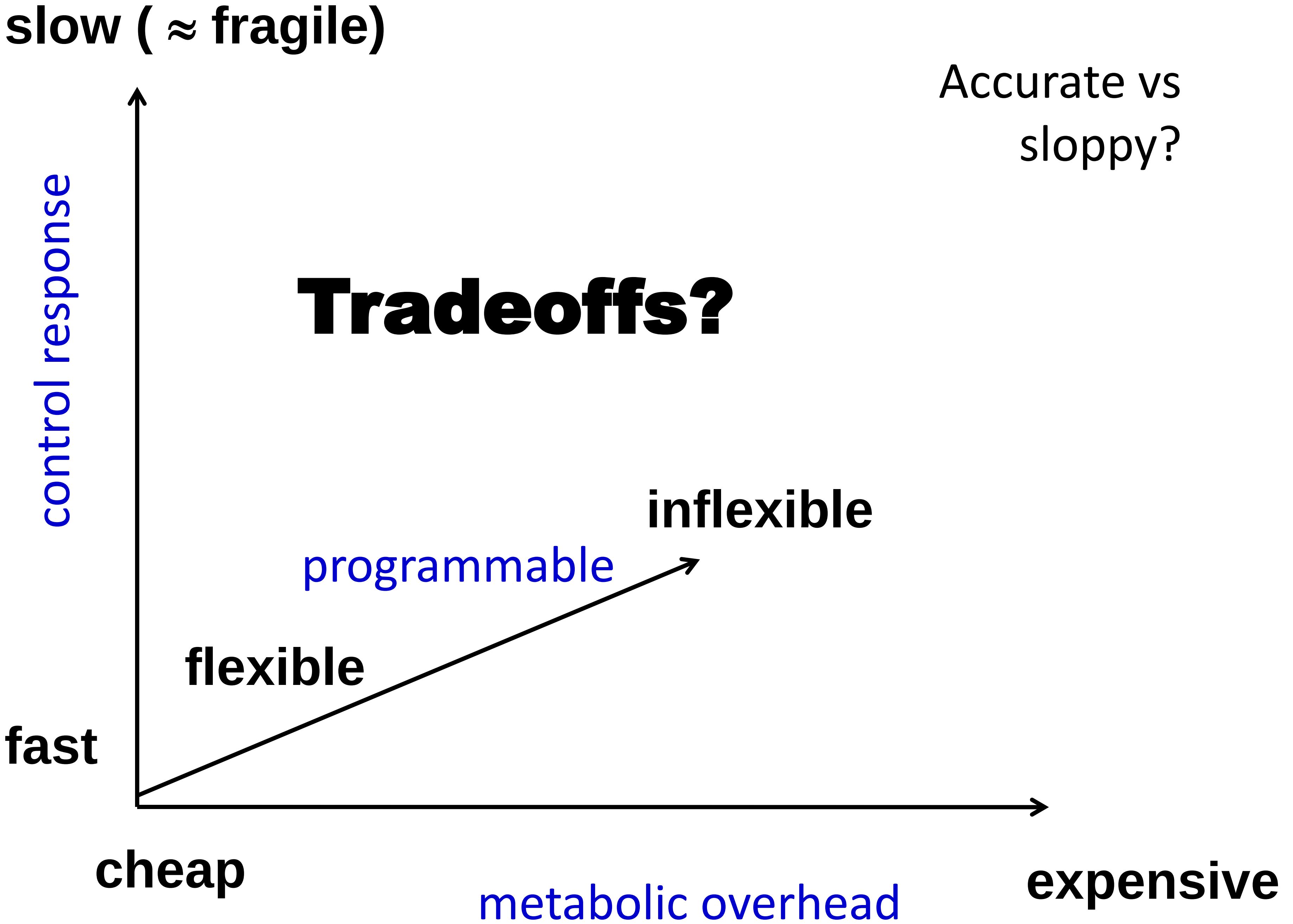
Autocatalytic

- Translation
- Transcription
- DNA Replication





Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Cross-layer
autocatalysis
Building
Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp


slow (≈ fragile)
Accurate vs sloppy?
control response
Tradeoffs?
inflexible
programmable
flexible
fast
cheap
metabolic overhead
expensive

Evolution and architecture

Nothing in biology makes sense except in the light of evolution

Theodosius Dobzhansky

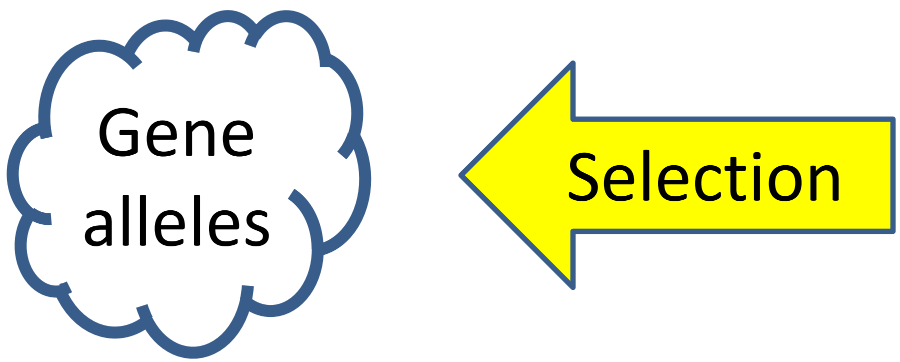
(see also de Chardin)

Nothing in evolution makes sense except in the light of biology

?????

Standard theory:
natural selection + genetic drift
+ mutation + gene flow

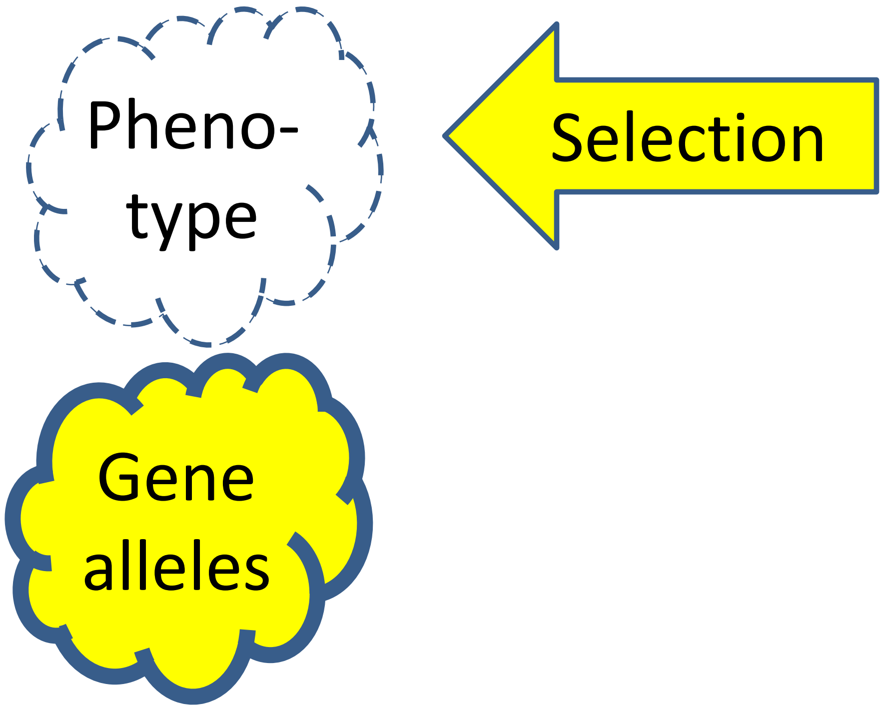
Greatly abridged cartoon here



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

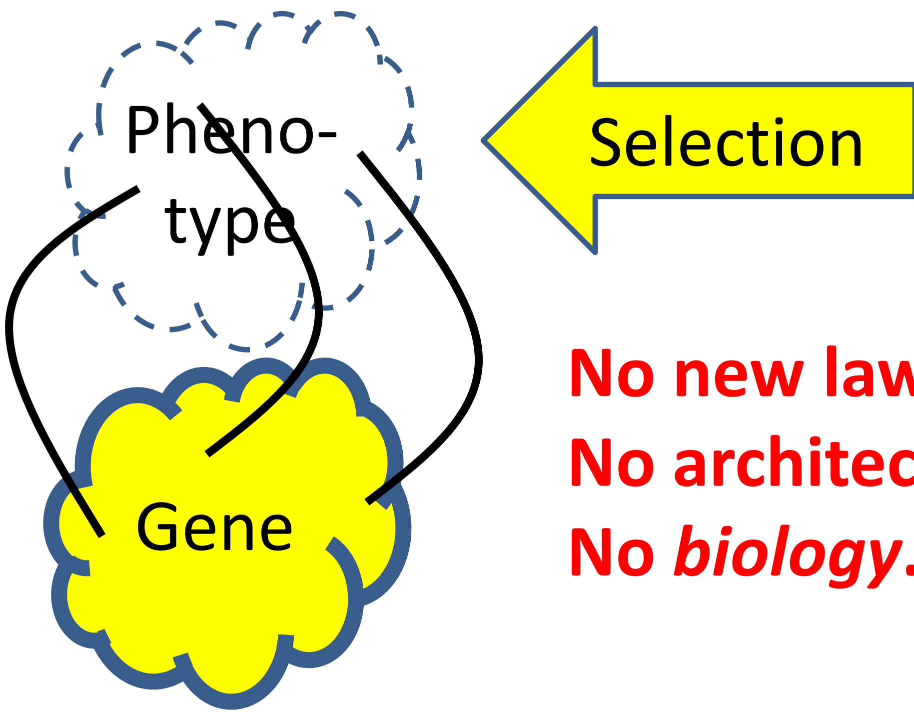
Standard theory:

selection + drift + mutation + gene flow



Standard theory:

selection + drift + mutation + gene flow

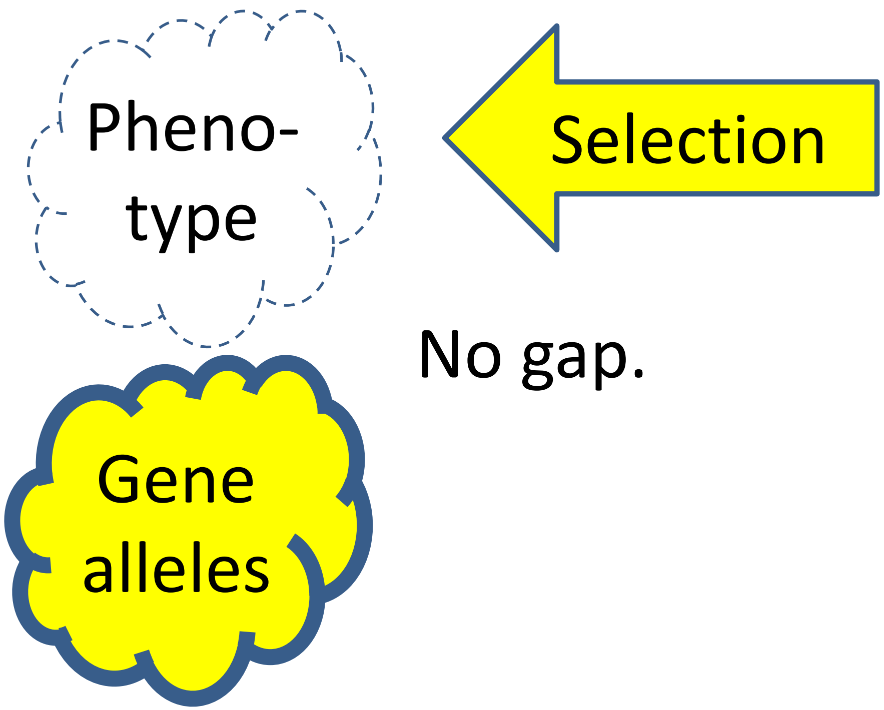


No new laws.

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

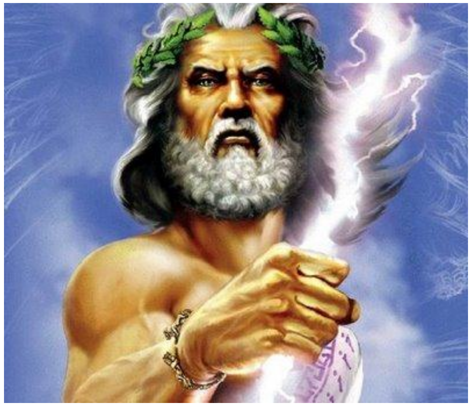
Pheno-
type

Pheno-
type

Gene
alleles

No gap.
Just physics.

Huge gap.
Need
supernatural



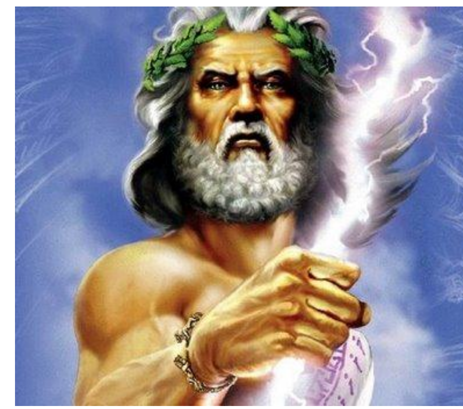
Genes?

What they agree on

Pheno-
type

No new laws.
No architecture.
No biology.

Huge
gap.

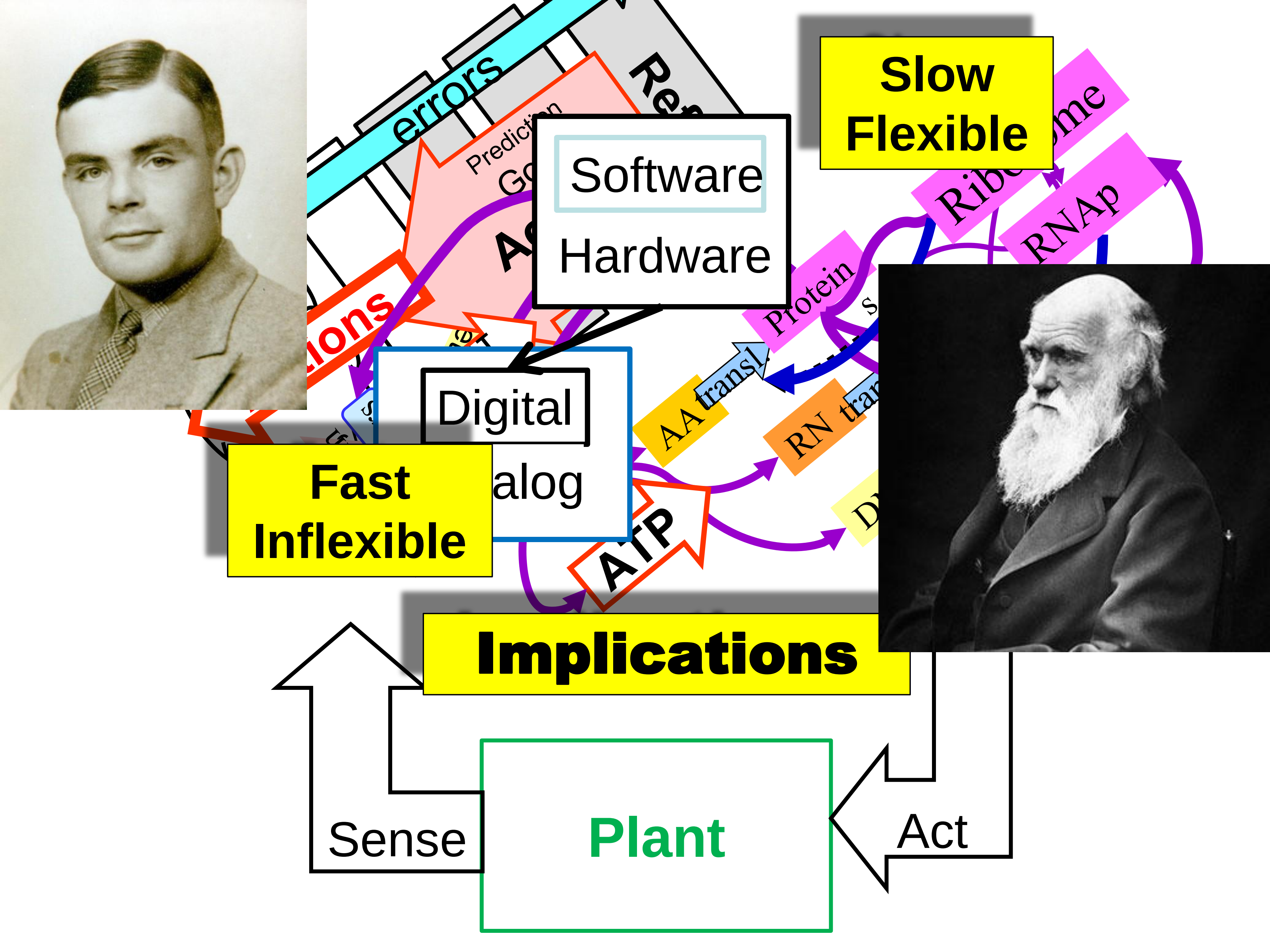


Pheno-
type

No gap.

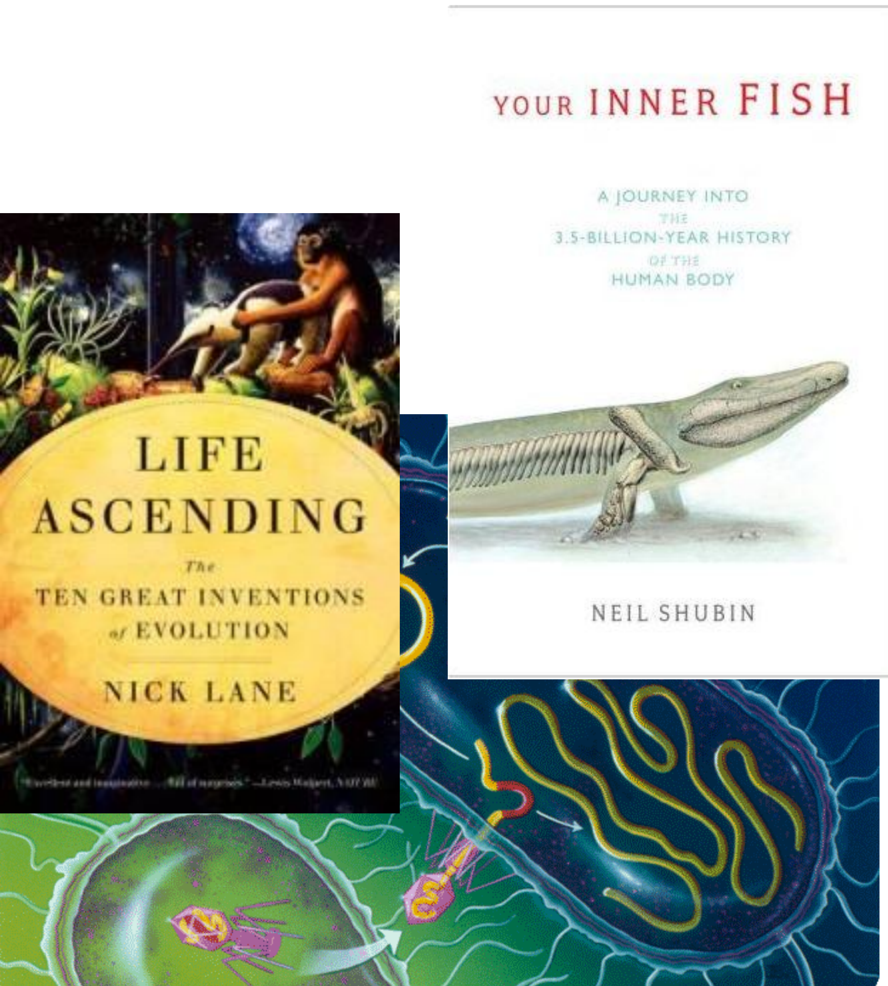
Gene
alleles

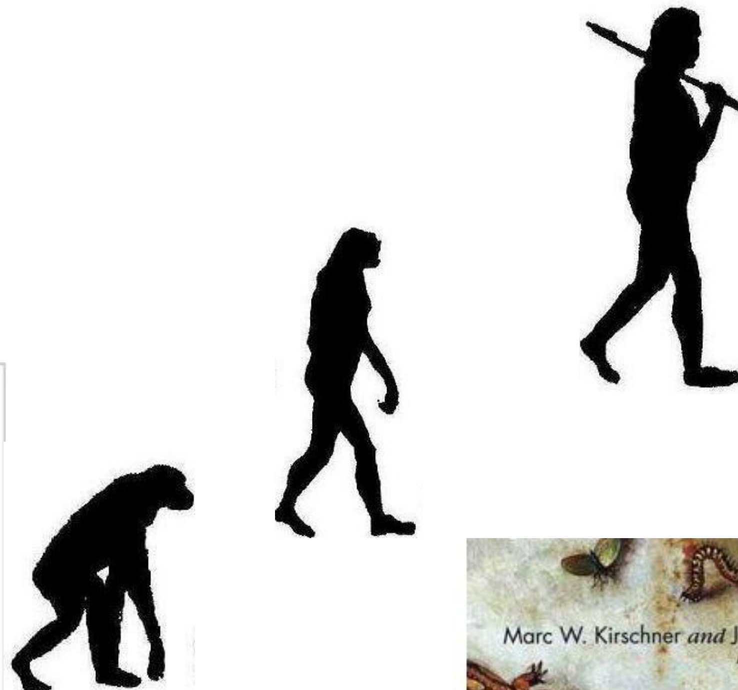
Genes

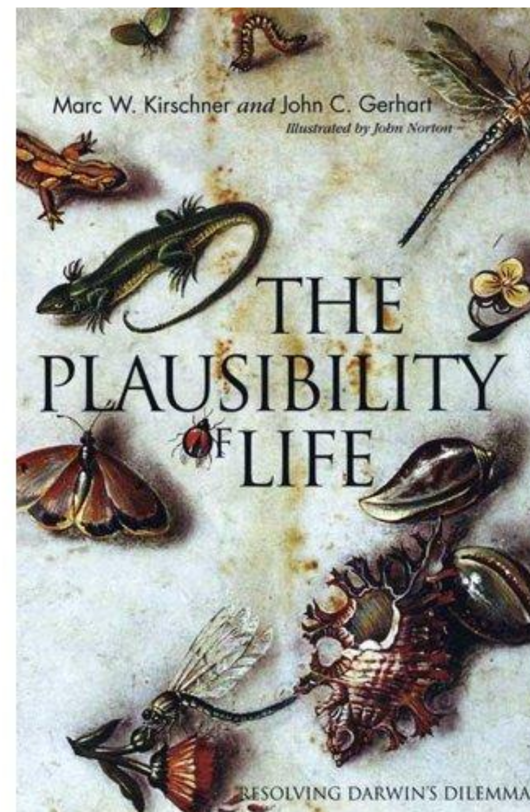


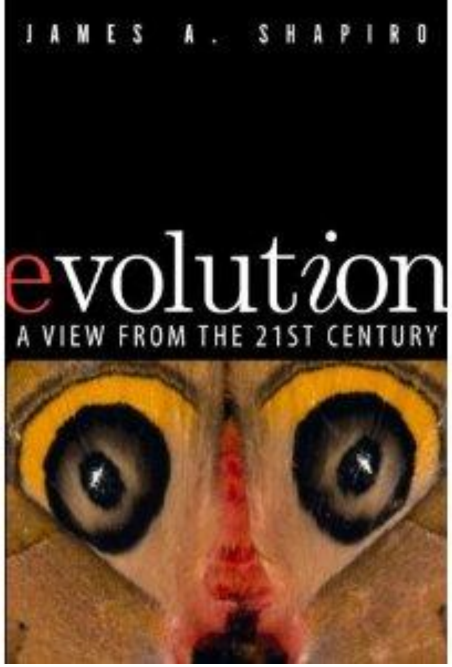
errors
Prediction
Software
Hardware
Slow
Flexible
Protein
RNAp
AA transl.
RN tran
Digital
alog
ATP
Fast
Inflexible
Implications
Sense
Plant
Act

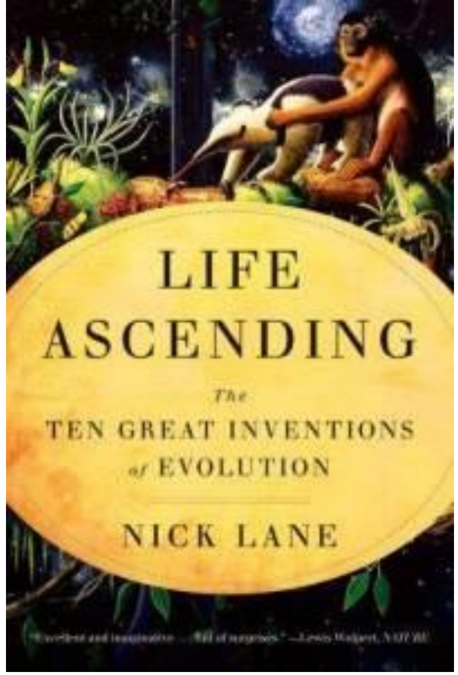
Putting biology back into evolution

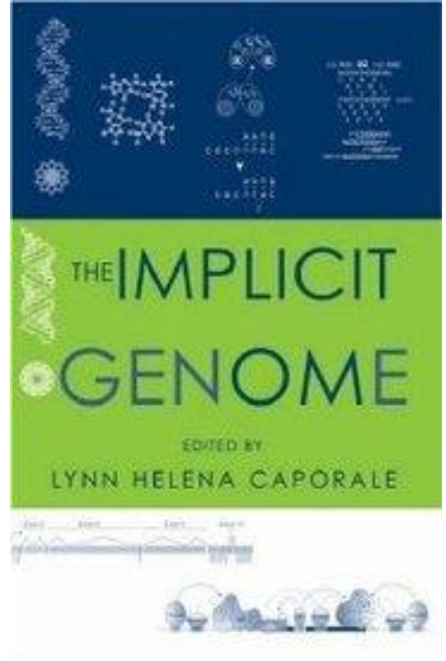


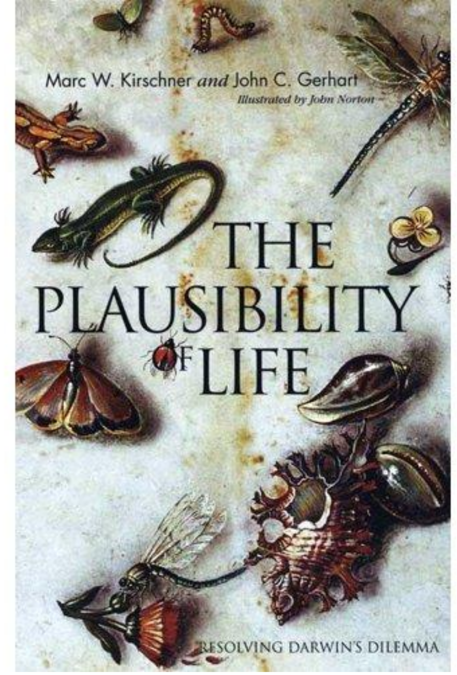






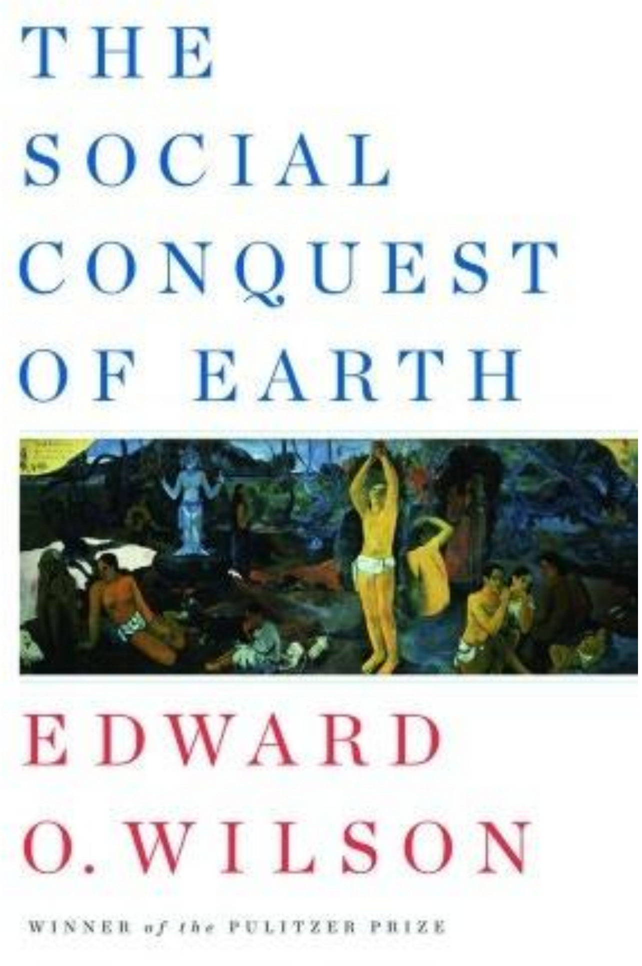




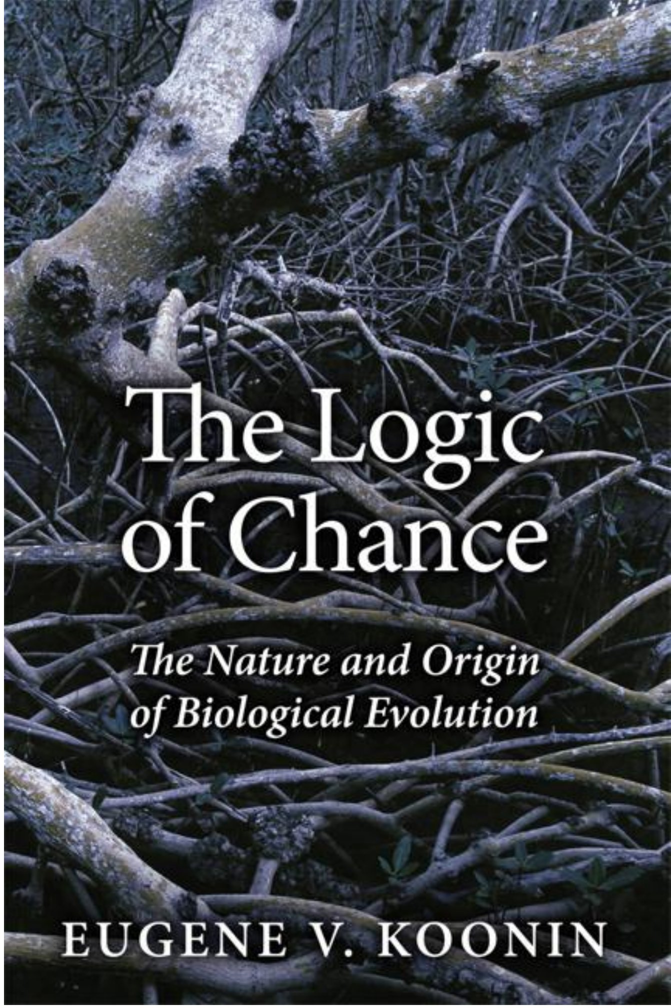


The heresies

- 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



Surprising heresies from “conservatives”

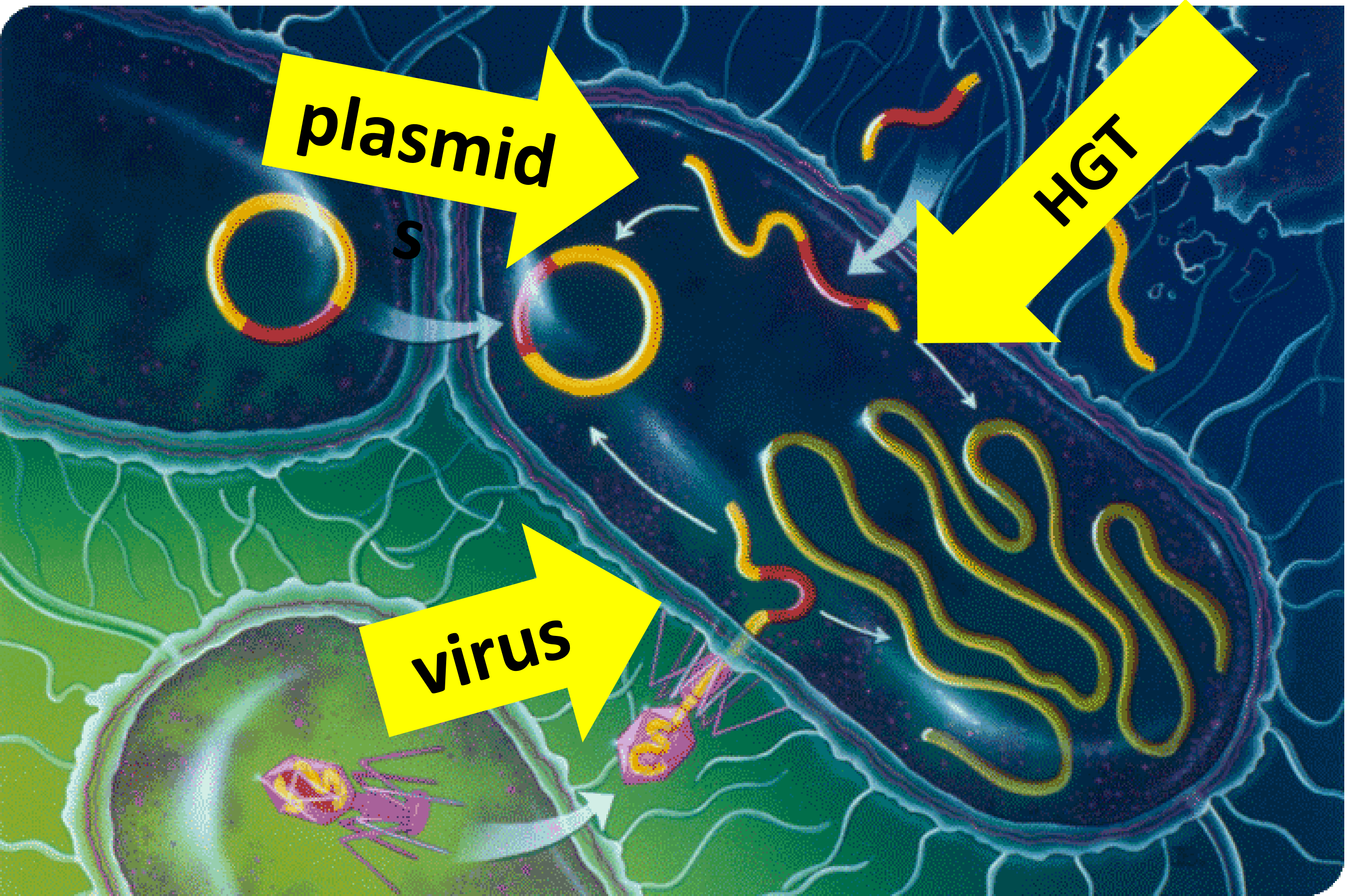


~~kin selection~~

~~modern synthesis~~

selection + drift + mutation + gene flow

+ facilitated *variation*



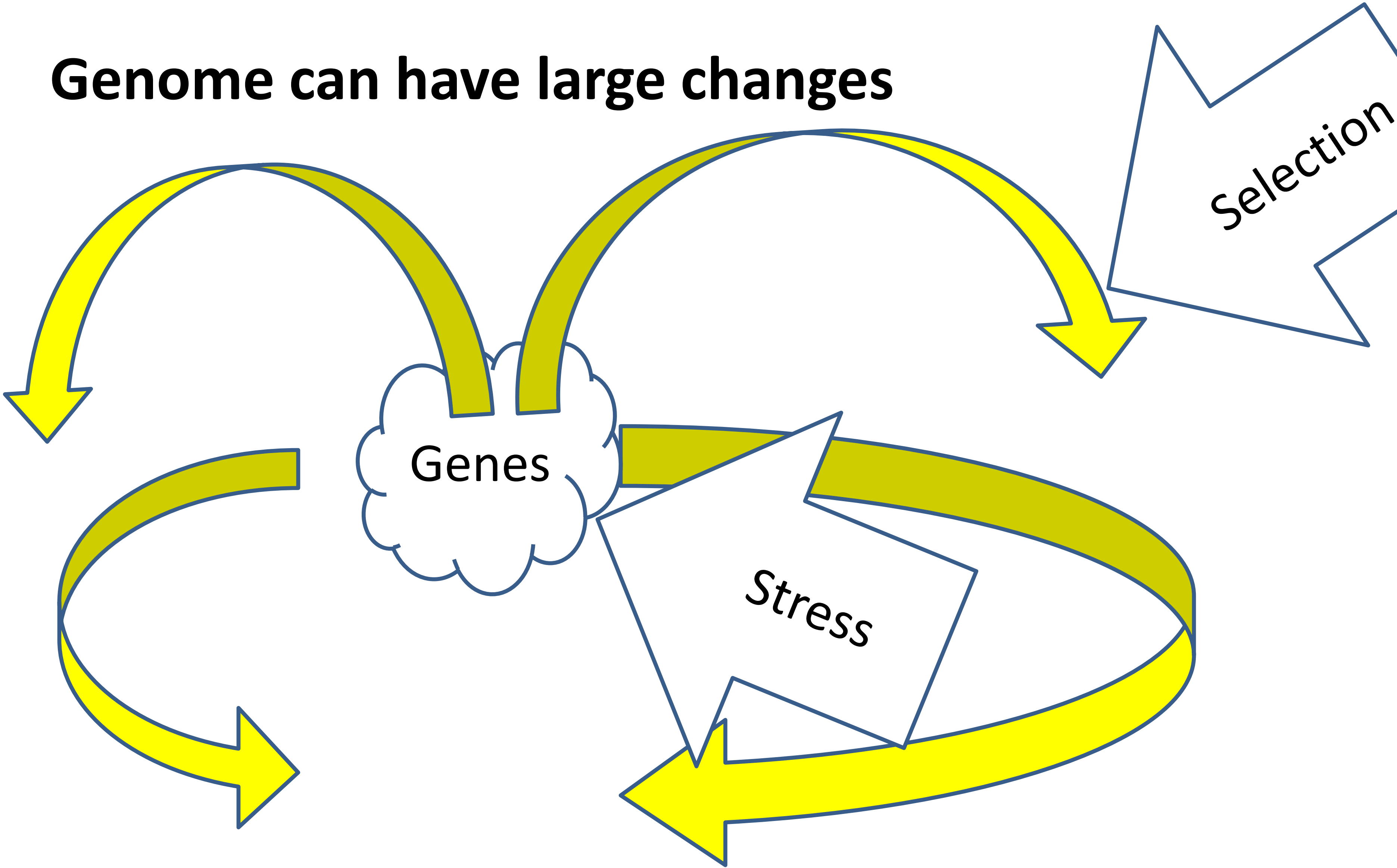
large functional changes in genomes

HGT
= horizontal gene transfer

natural selection + genetic drift + mutation + gene flow

+ facilitated *variation*

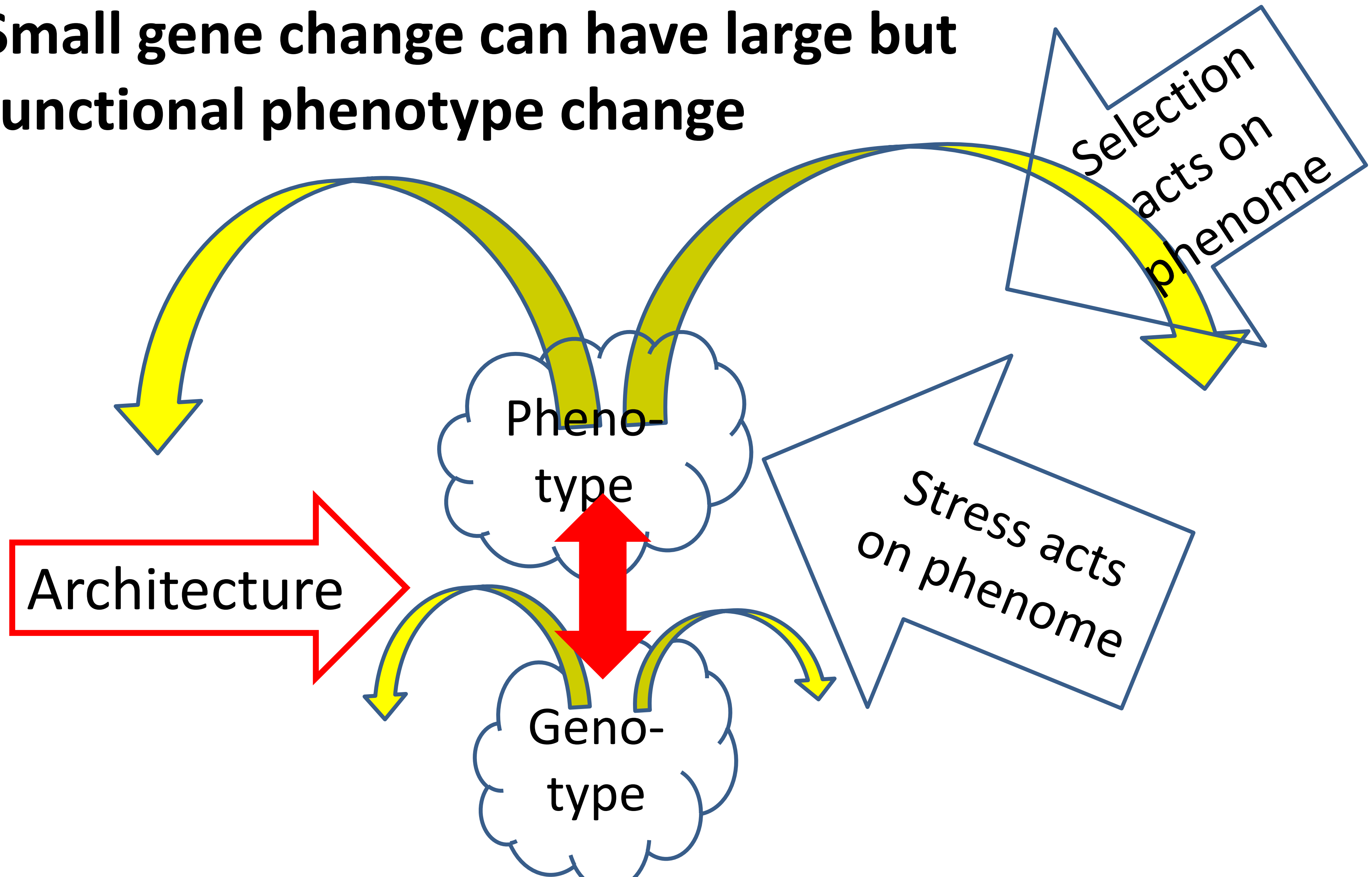
Genome can have large changes



natural selection + genetic drift + mutation + gene flow

+ facilitated *variation*

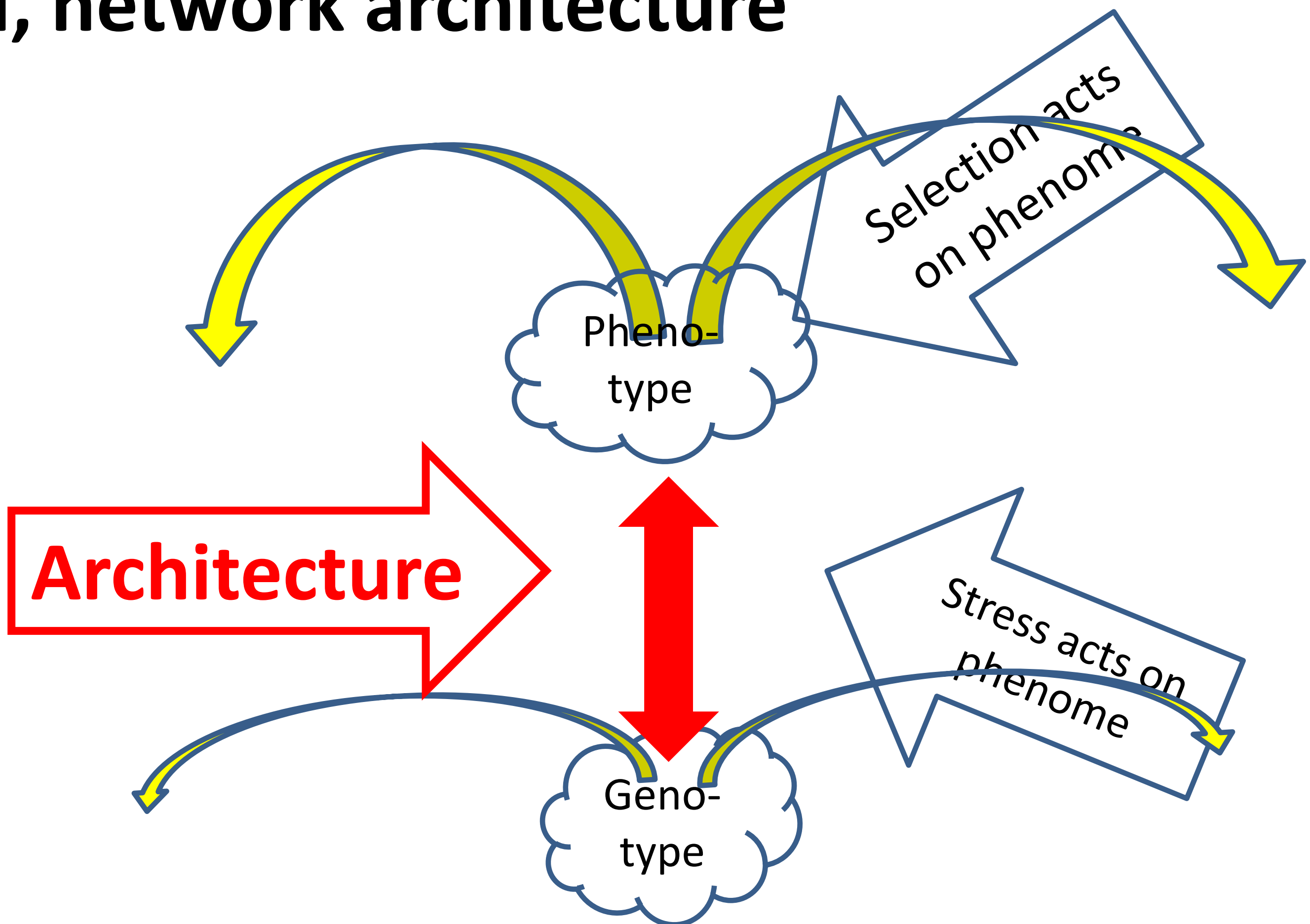
Small gene change can have large but functional phenotype change



natural selection + genetic drift + mutation + gene flow

+ facilitated *variation*

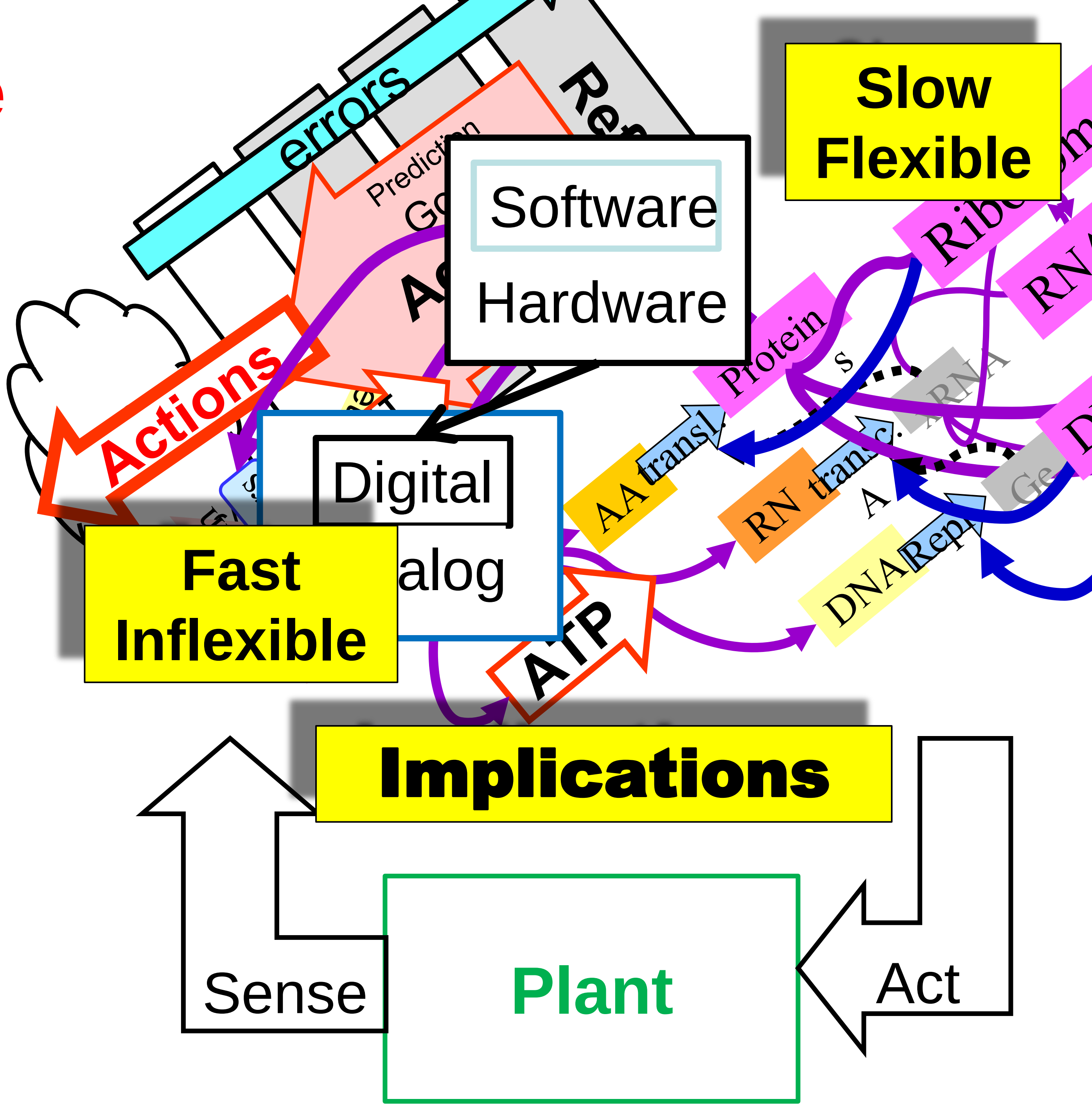
Only possible because of shared, layered, network architecture



Compute

Turing

Delay is *most* important



Bode

Control

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