Universal laws and architectures:

Theory and lessons from

brains, bugs, nets, grids,
planes, docs, fire, bodies, fashion,
earthquakes, turbulence, music, buildings, cities,
art, running, throwing, Synesthesia, spacecraft, statistical mechanics

John Doyle 道陽
Jean-Lou Chameau Professor
Control and Dynamical Systems, EE, & BioE
Ca#1tech

Requirements on systems and architectures

accessible
accountable
accurate
adaptable
administrable
affordable
auditable
autonomy
available
credible
process capable
compatible
composable
configurable
correctness
customizable
debugable
degradable
determinable
demonstrable
dependable
deployable
discoverable
distributable
durable
effective
efficient
evolvable
extensible
fail transparent
fast
fault-tolerant
fidelity
flexible
inspectable
installable
Integrity
interchangeable
interoperable
learnable
maintainable
manageable
mobile
modifiable
modular
nomadic
operable
orthogonality
portable
precision
predictable
producible
provable
recoverable
relevant
reliable
repeatable
reproducible
resilient
responsive
reusable
robust
safety
scalable
seamless
self-sustainable
serviceable
supportable
securable
simplicity
stable
standards compliant
survivable
sustainable
tailorable
testable
timely
traceable
ubiquitous
understandable
upgradable
usable

Requirements on systems and architectures

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accountable
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capable
compatible
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manageable
mobile
modifiable
modular
nomadic
operable
provable
recoverable

safety
scalable
seamless
self-sustainable
serviceable
supportable
survivable
sustainable

When concepts fail, words arise.

Mephistopheles, *Faust*, Goethe

Mephistopheles. …Enter the templed hall of Certainty.

Student. Yet in each word some concept there must be.

Mephistopheles. Quite true!

But don't torment yourself too anxiously;
For at the point where concepts fail,
At the right time a word is thrust in there…

- **Concrete case studies**
- **Theorems**

When concepts fail, ~~words~~ arise.

Mephistopheles, *Faust*, Goethe

Sorry, still too many
words and slides.

Hopefully read later?

- Concrete case studies
- Theorems

> When concepts fail, ~~words~~ arise.
> **Mephistopheles,** *Faust*, Goethe

"Laws and Architecture"

- Few words more misused
- Few concepts more confused

What's the best/simplest fix?

- **Concrete case studies**
- **Theorems**

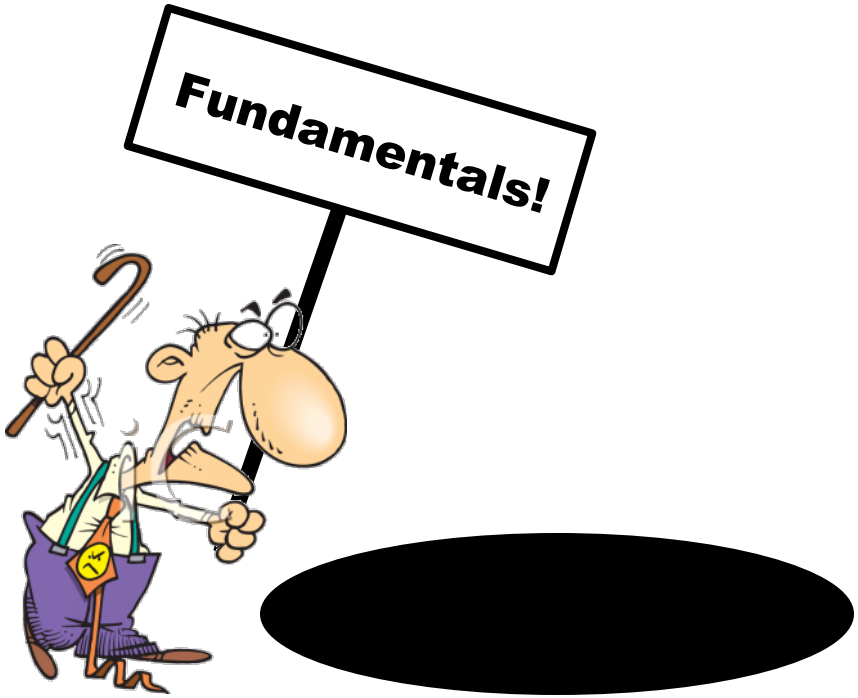
and words

Reality is a crutch for people who can't do math.

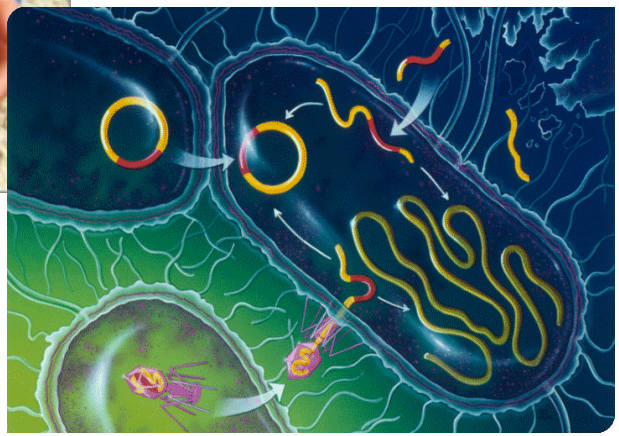
***Anon*, Berkeley, 70's**

$\bigcap$ {Case Study}

- **Brains**
- Nets/Grids (cyberphys)
- Bugs (microbes, ants)
- Medical physiology



- Lots of aerospace
- Wildfire ecology
- Earthquakes
- Physics:
  - –turbulence,
  - –stat mech (QM?)
- "Toy":
  - –Lego
  - –clothing, fashion
- Buildings, cities
- **Synesthesia**



Focus today:

- **Neuroscience**
  - **+ People care**
  - **+ Live demos**
- Cell biology (esp. bacteria)
  - **+** Perfection
  - **±** Some people care
- Internet (of everything) (& Cyber-Phys)
  - **+** Understand the details
  - **-** Flawed designs
  - -Everything you've read is wrong (in science)*
- Medical physiology (esp. HRV)
  - + People care, somewhat familiar
  - - Demos more difficult

* Mostly high impact "journals"

Focus today:

- Neuroscience
  - + People care
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- Medical physiology
  - + People care, somewhat familiar
  - - Demos more difficult

* Mostly high impact "journals"

What we want to build but can't, yet.

The zombie apocalypse is already here…

Sustainable ≈ robust + efficient

accessible
accountable
accurate
adaptable
administrable
affordable
auditable
autonomy
available
compatible
composable
configurable
correctness
customizable
debugable
degradable
determinable
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relevant
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repeatable
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reusable

robust

safety
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seamless
self-sustainable
serviceable
supportable
securable
simple
stable
standards
survivable

sustainable

tailorable
testable
timely
traceable
ubiquitous
understandable
upgradable
usable

Priorities

- Functionality (behavior, semantics)
- **Robustness**
  - –Uncertain environment and components
  - –Fast (sense, decide, act)
  - –Flexible (adaptable, evolvable)
- **Efficiency**
  - –Energy
  - –Other resources (make and maintain)

Simple, apparent, obvious

- **Functionality**
- Robustness
  - ponents
  - –Flexible (adaptable, evolvable)
- **Efficiency**

Complexity ⇔ Robustness

- Functionality (behavior, semantics)
- **Robustness**
  - –Uncertain environment and components
  - –Fast (sense, decide, act)
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- Efficiency
  - –Energy
  - –Other resources (make and maintain)

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ubiquitous
understandable
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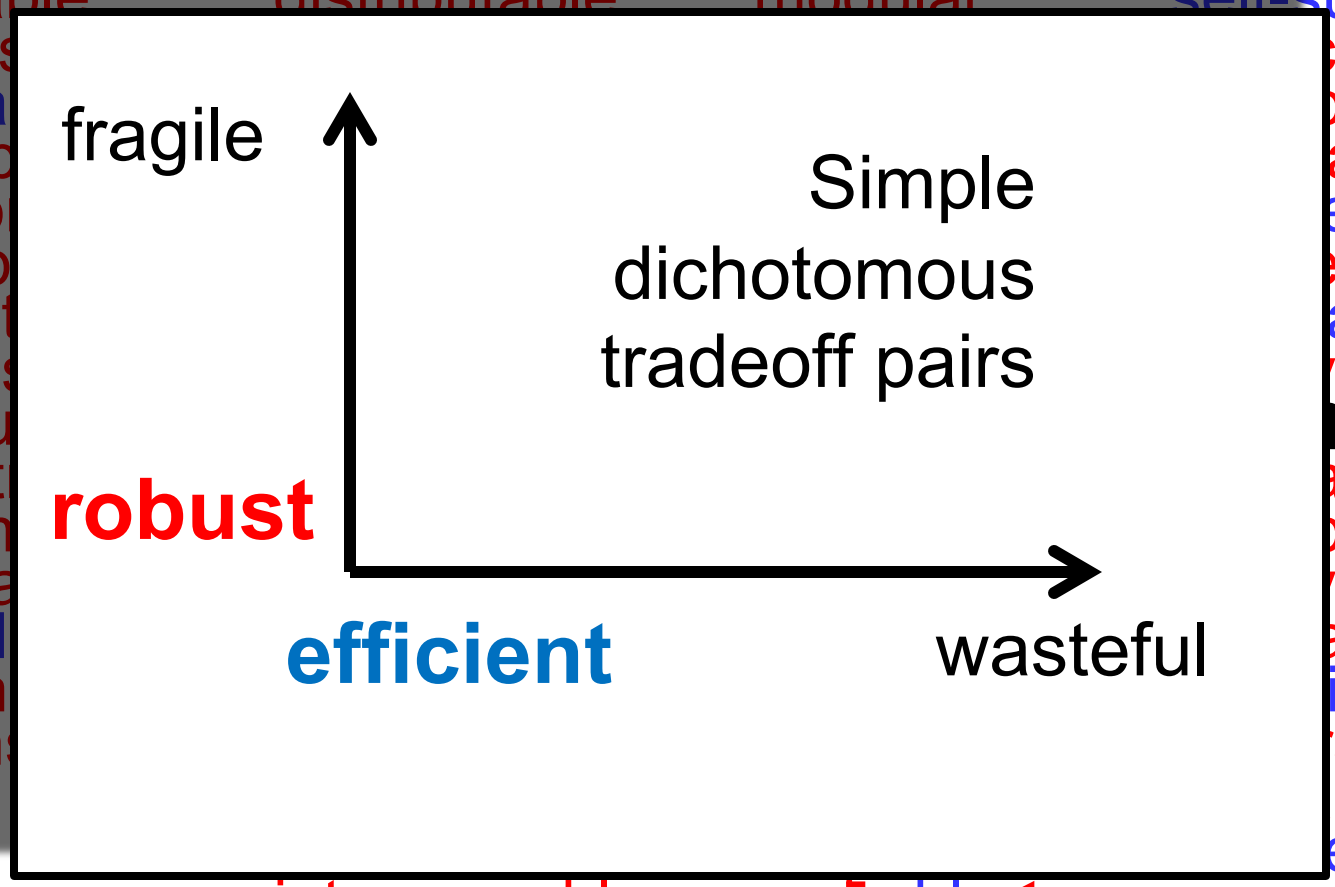
usable

PCA ≈ Principal ***Concept*** Analysis ☺

With ***function*** given



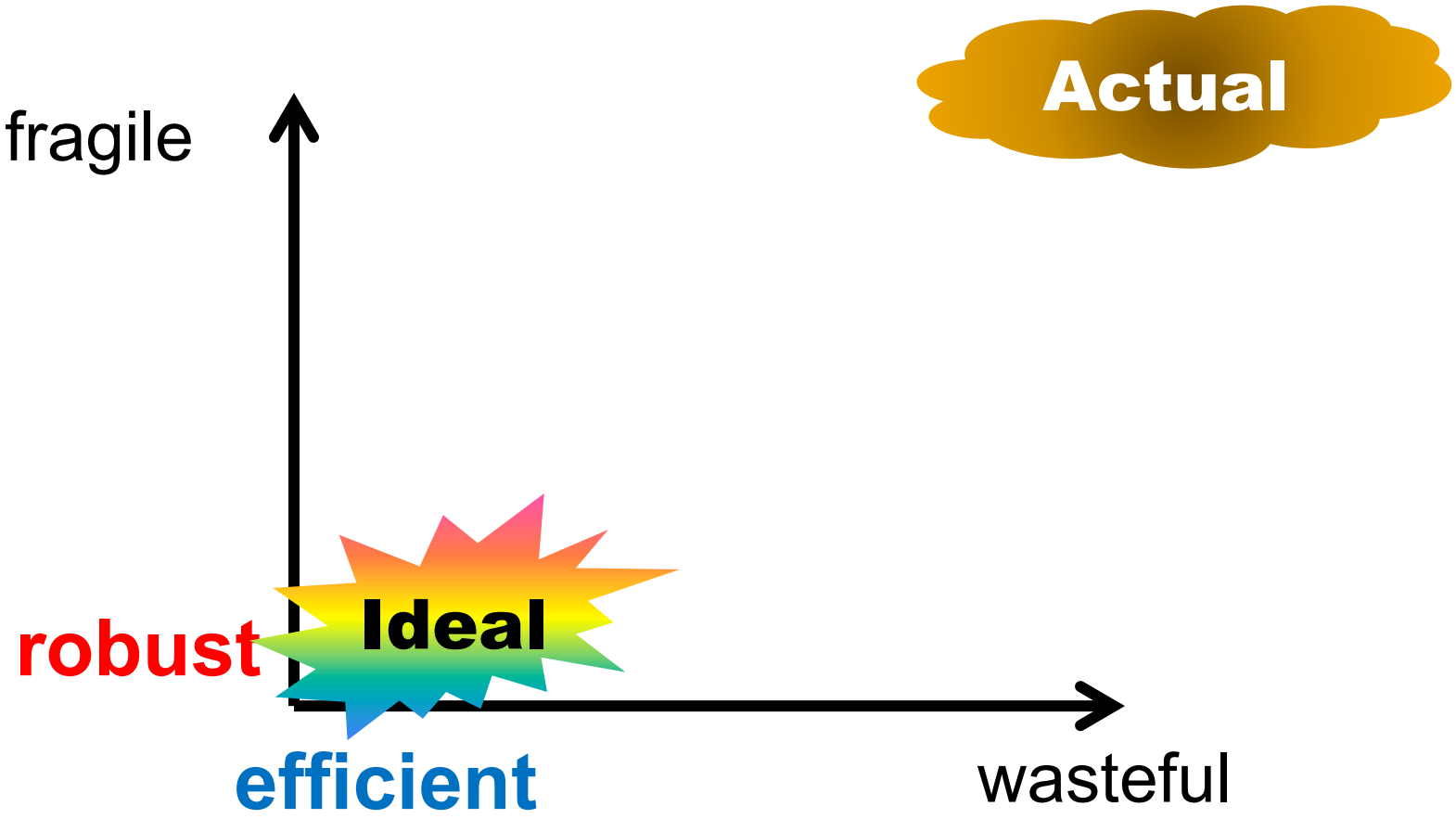
accurate
adaptable
adminis
afforda
auditab
autono
availab
compat
compos
configu
correct
custom
debuga
degrad
determ
demons

manageable
mobile
modifiable
modular
safety
scalable
seamless
self-sustainable

interoperable
learnable
maintainable

robust

The main tradeoff

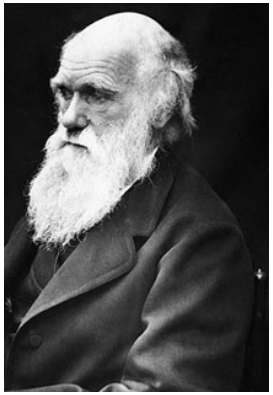


Efficiency/instability/layers/feedback

- New efficiencies but also instability/fragility
- New distributed/layered/complex/active control

- Sustainable infrastructure? (e.g. smartgrids)
- Money/finance/lobbyists/etc
- Industrialization
- Society/agriculture/weapons/etc
- **Bipedalism**
- Maternal care
- Warm blood
- Flight
- Mitochondria
- Oxygen
- Translation (ribosomes)
- Glycolysis (2011 *Science*)

Live demo?

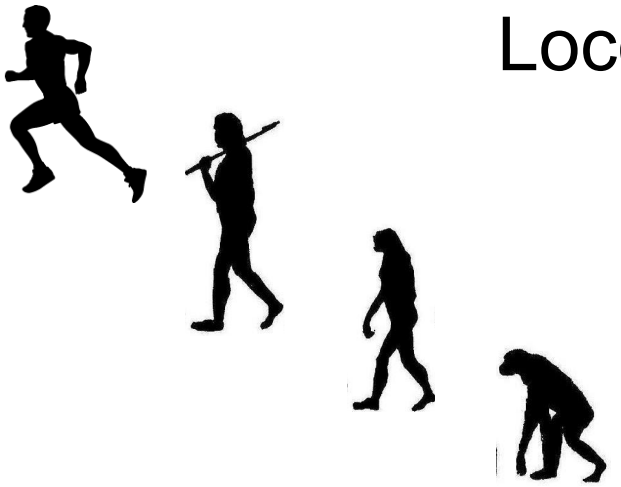


Tradeoffs

(swim/crawl to run/bike)

Function=
Locomotion

fragile

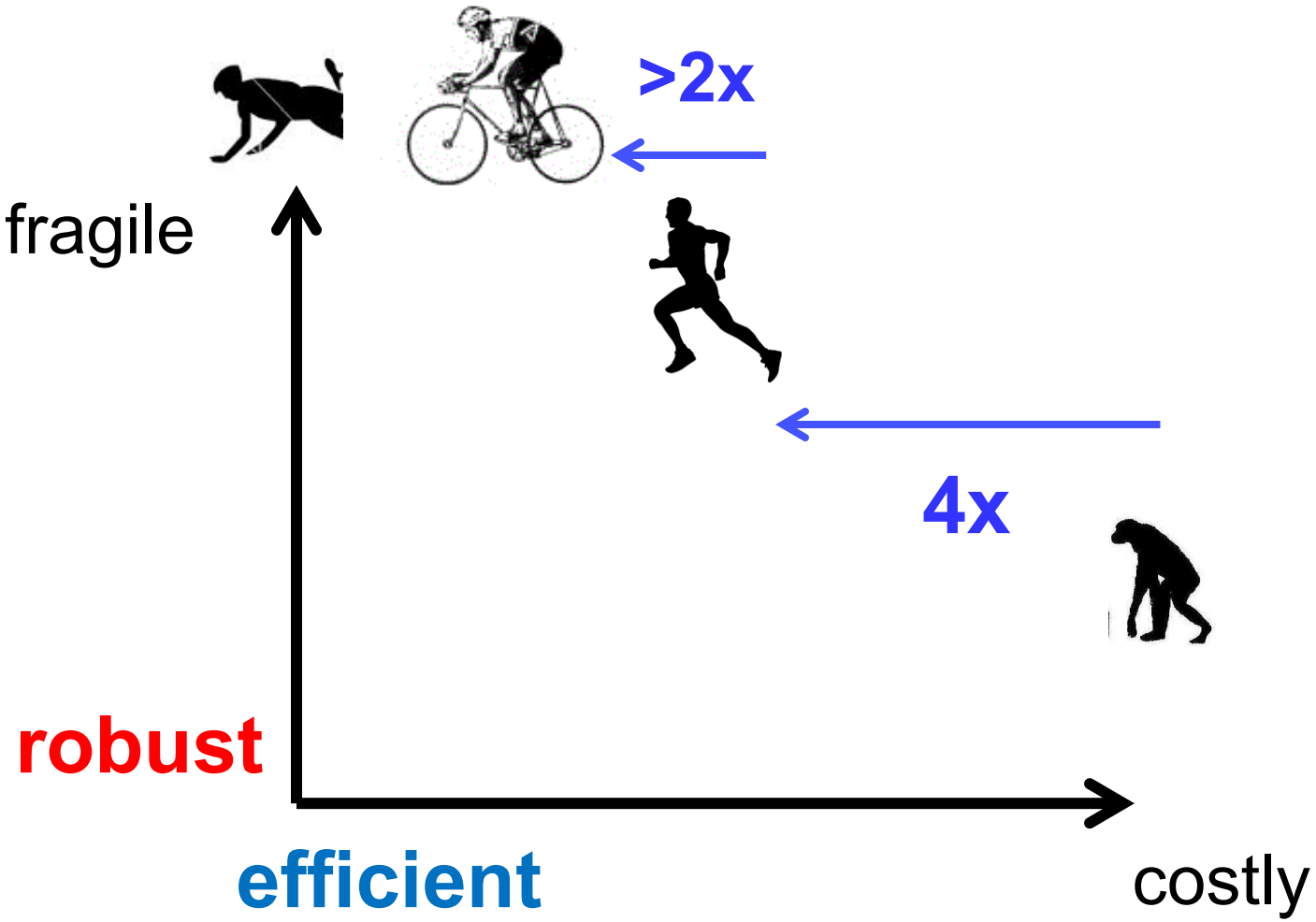


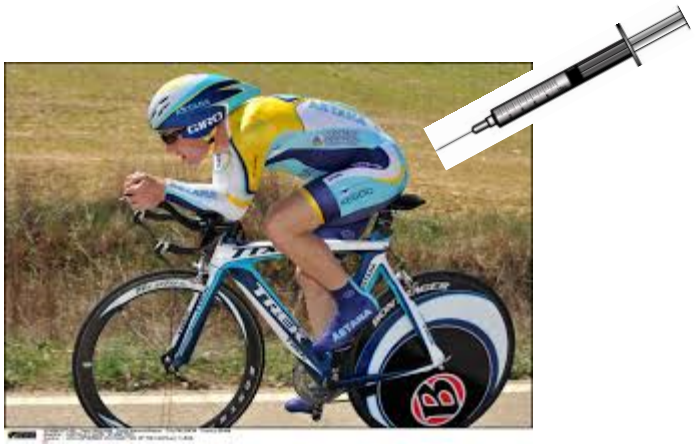
robust

efficient

costly

Tradeoffs





fragile

robust

efficient

costly

How does a layered architecture, including an “executive,” trade off robustness and efficiency?

fragile

robust

efficient

costly

How does a layered architecture, including an “executive,” trade off robustness and efficiency?

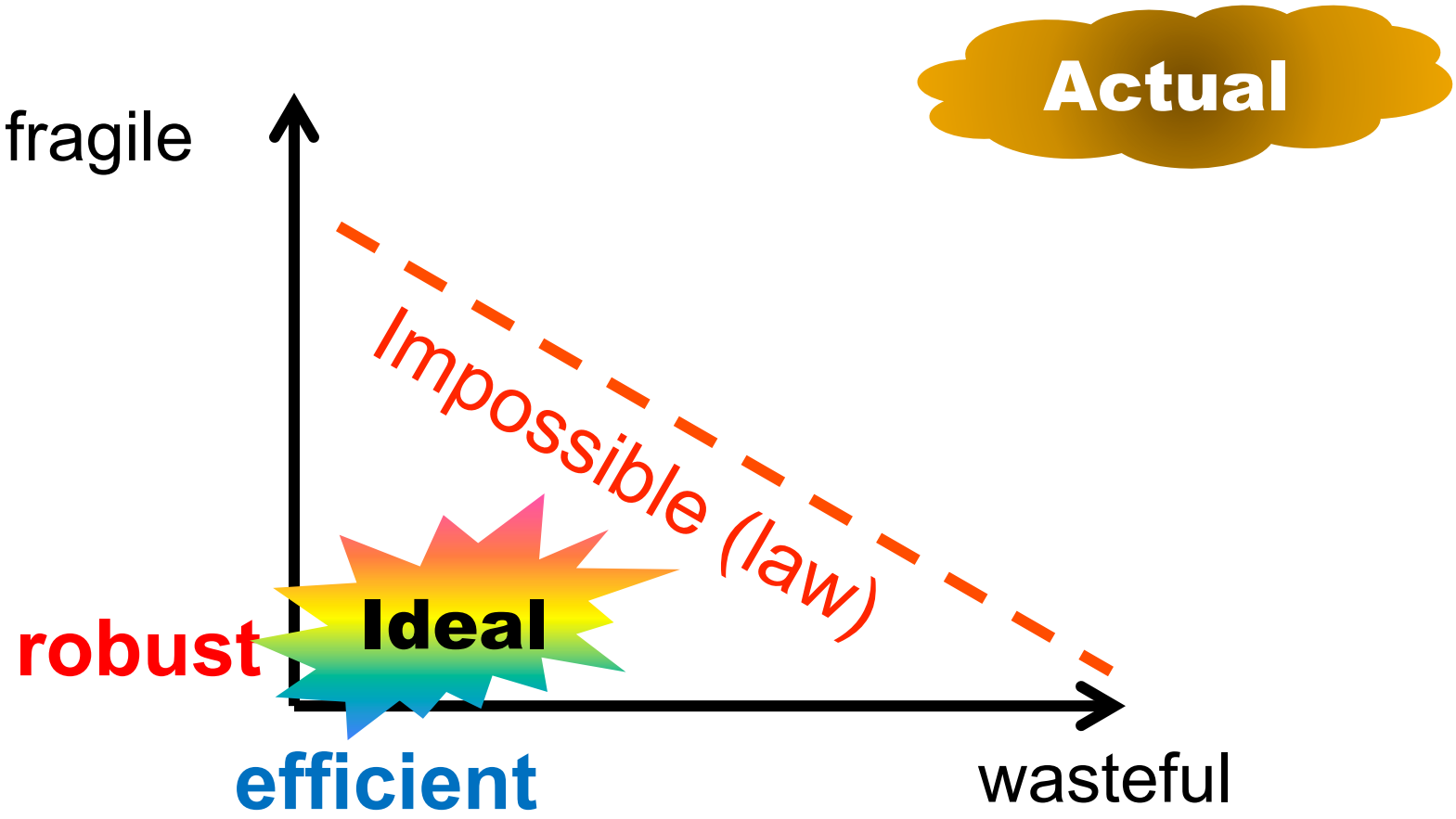
fragile

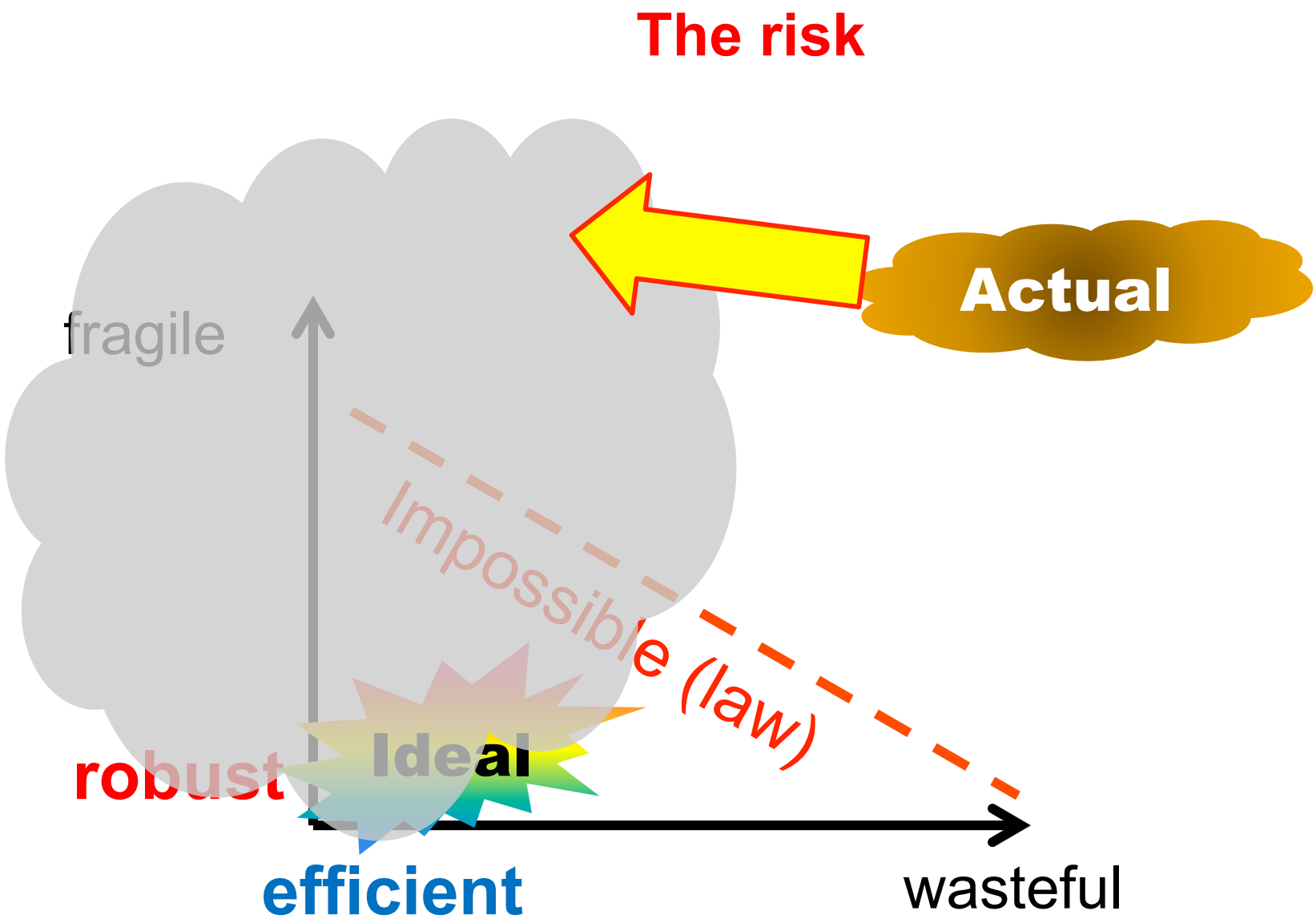
robust

efficient

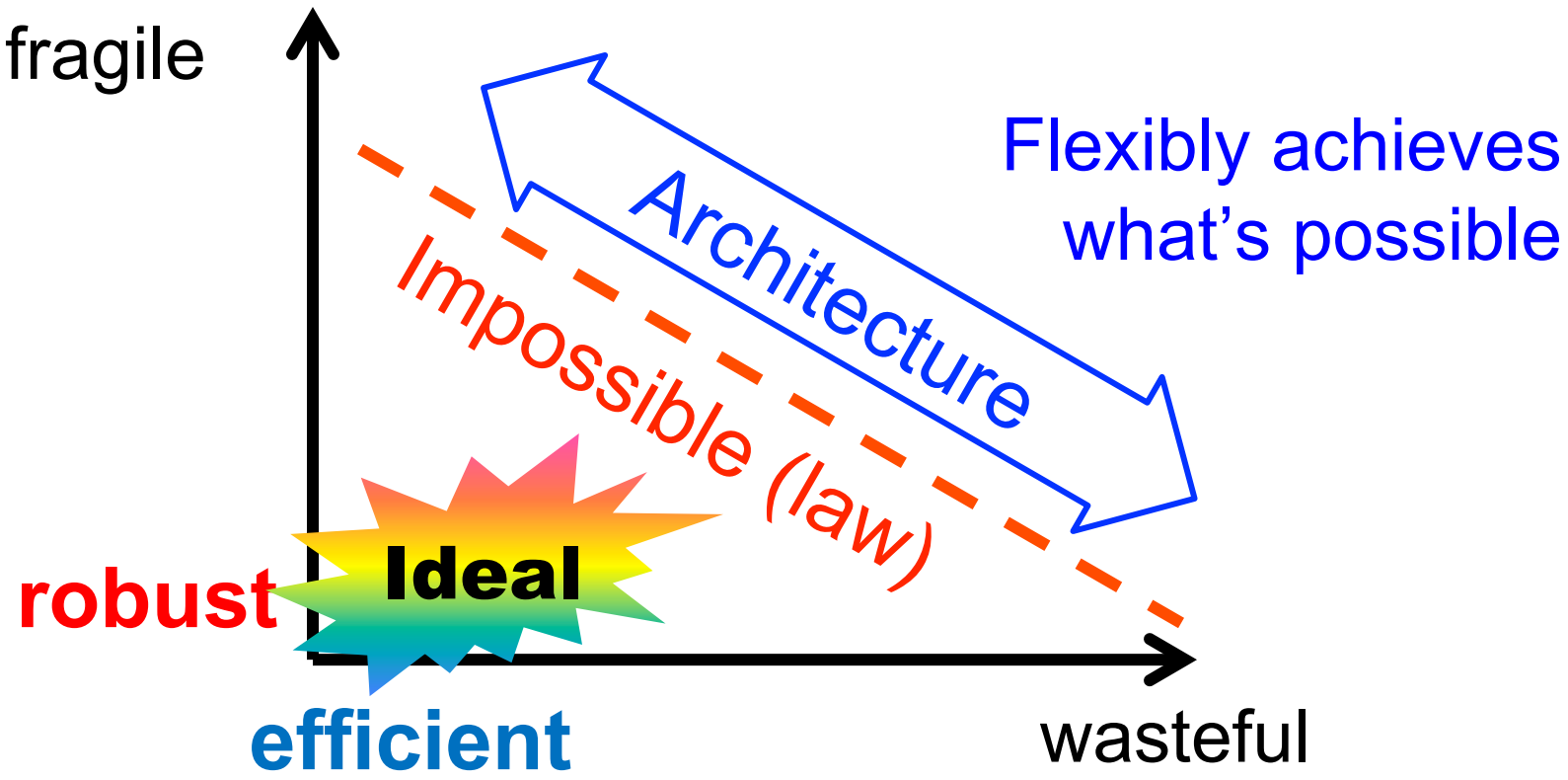
costly

Universal laws



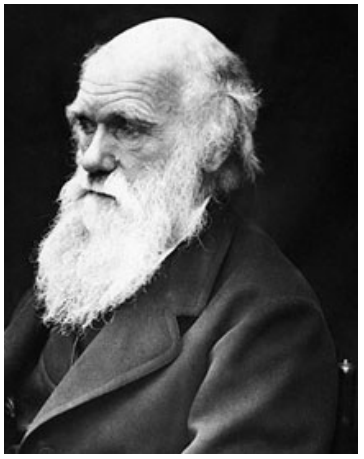

The risk
Actual
fragile
Impossible (law)
robust
Ideal
efficient
wasteful

Universal laws and architectures

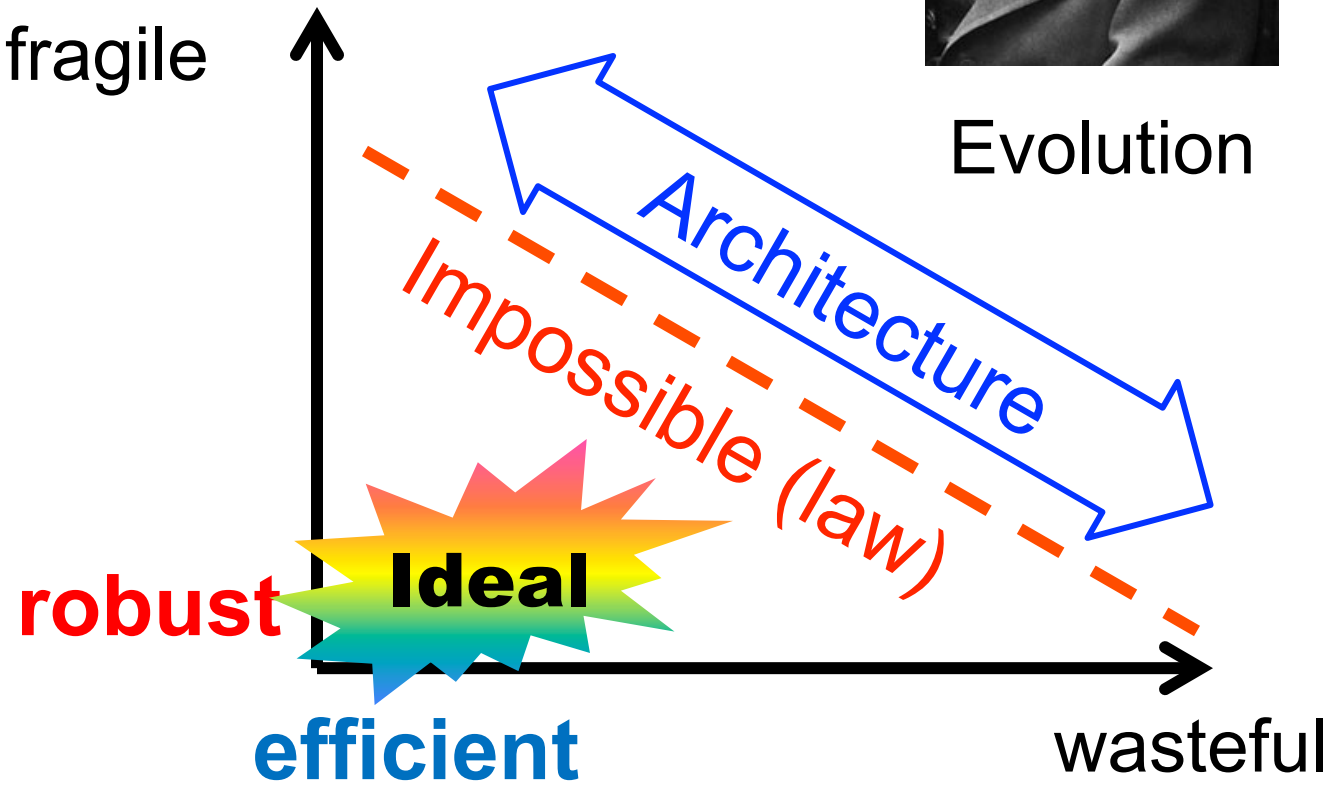


Universal laws and architectures

Our heroes



Evolution Complexity



Efficiency/instability/layers/feedback

- All create new efficiencies but also instabilities
- Needs new distributed/layered/complex/active control

- Sustainable infrastructure? (e.g. smartgrids)
- Money/finance/lobbyists/etc
- Industrialization
- Society/agriculture/weapons/etc
- Bipedalism
- Maternal care
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- Translation (ribosomes)
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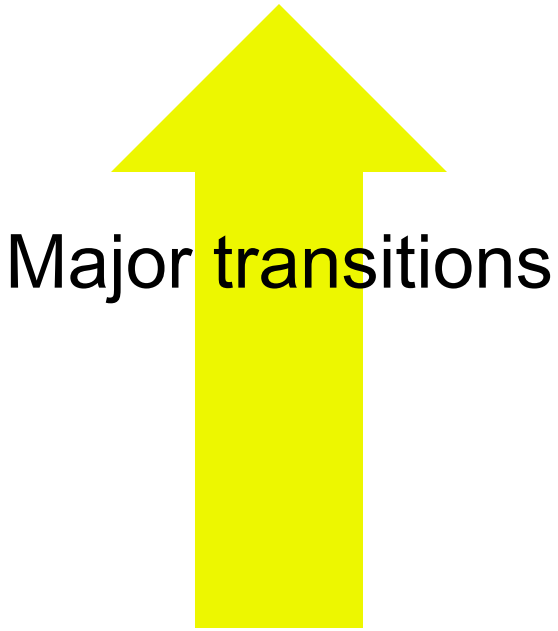


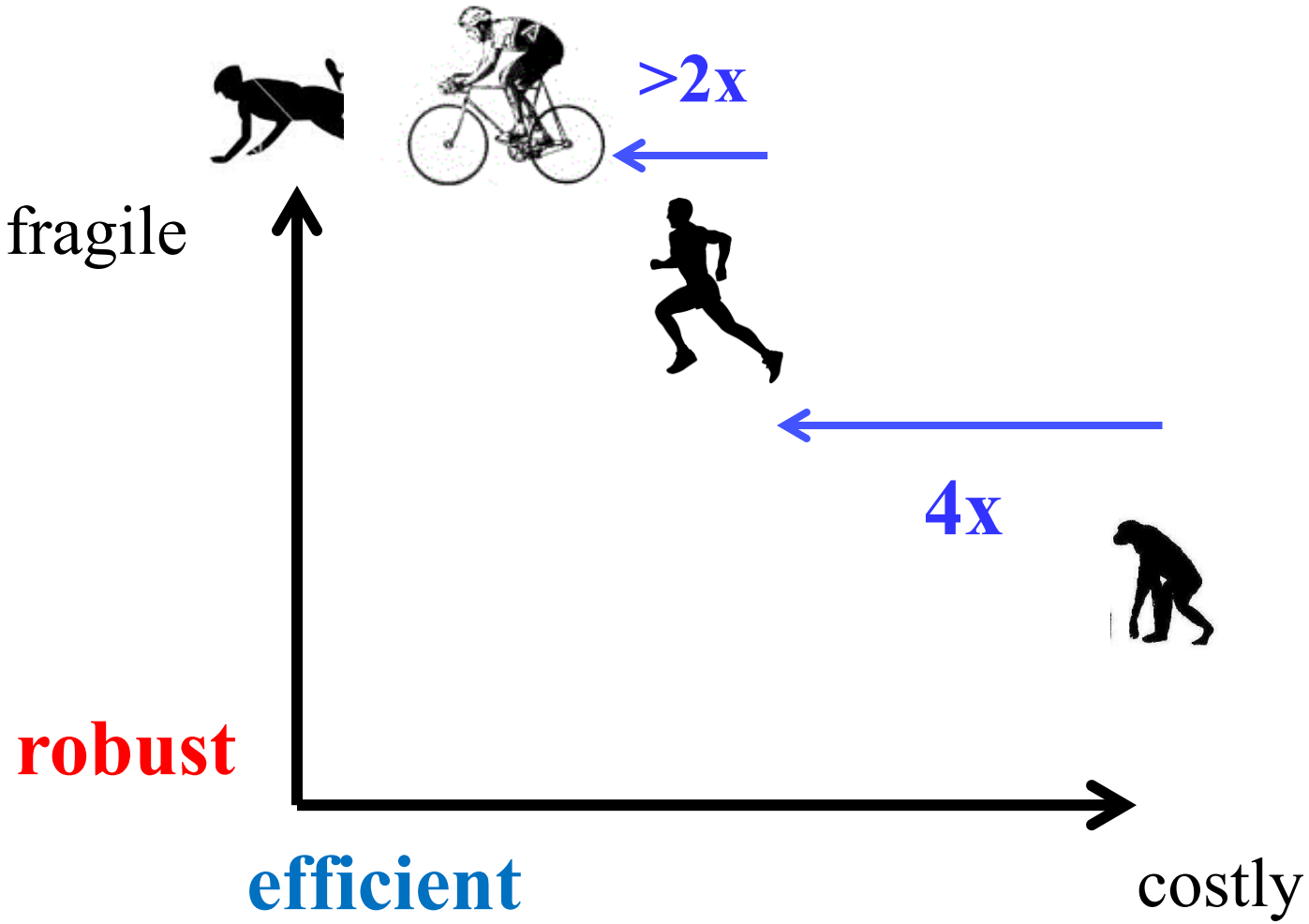
"Nothing in *biology* makes sense except in the light of *evolution*."

T Dobzhansky

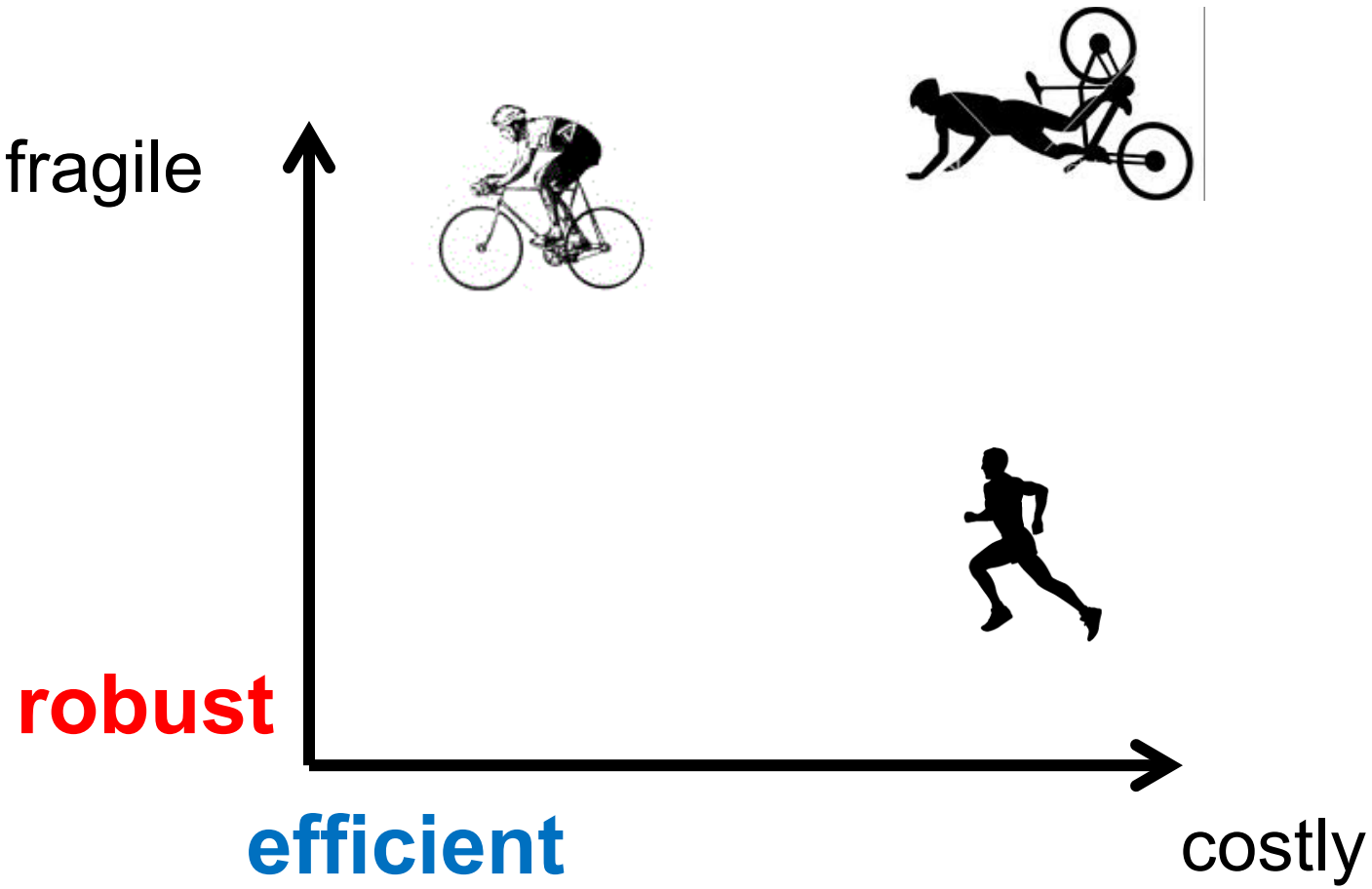
"Nothing in *evolution* makes sense except in the light of *biology*."

Tony Dean (U Minn) paraphrasing T Dobzhansky

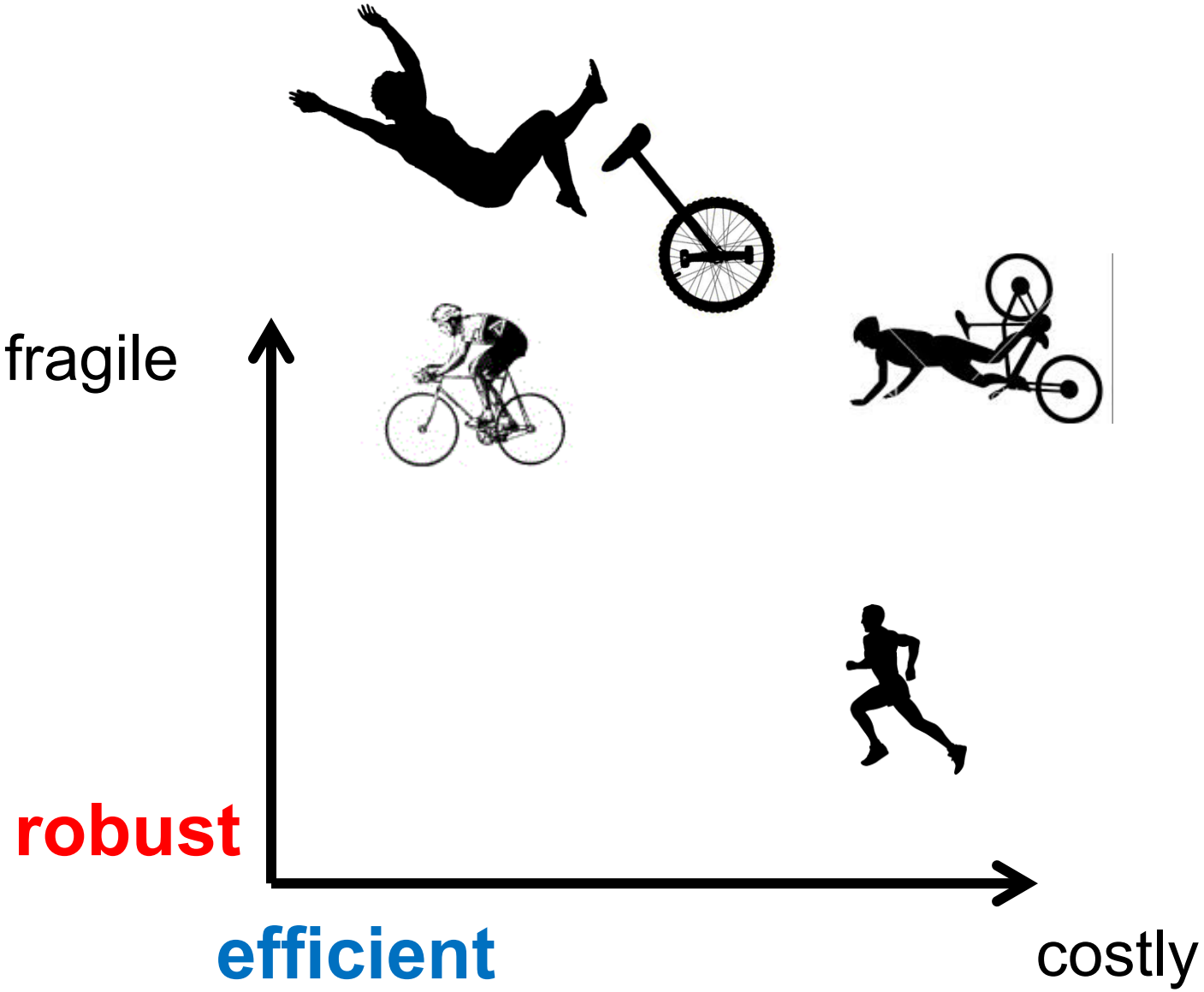
Tradeoffs



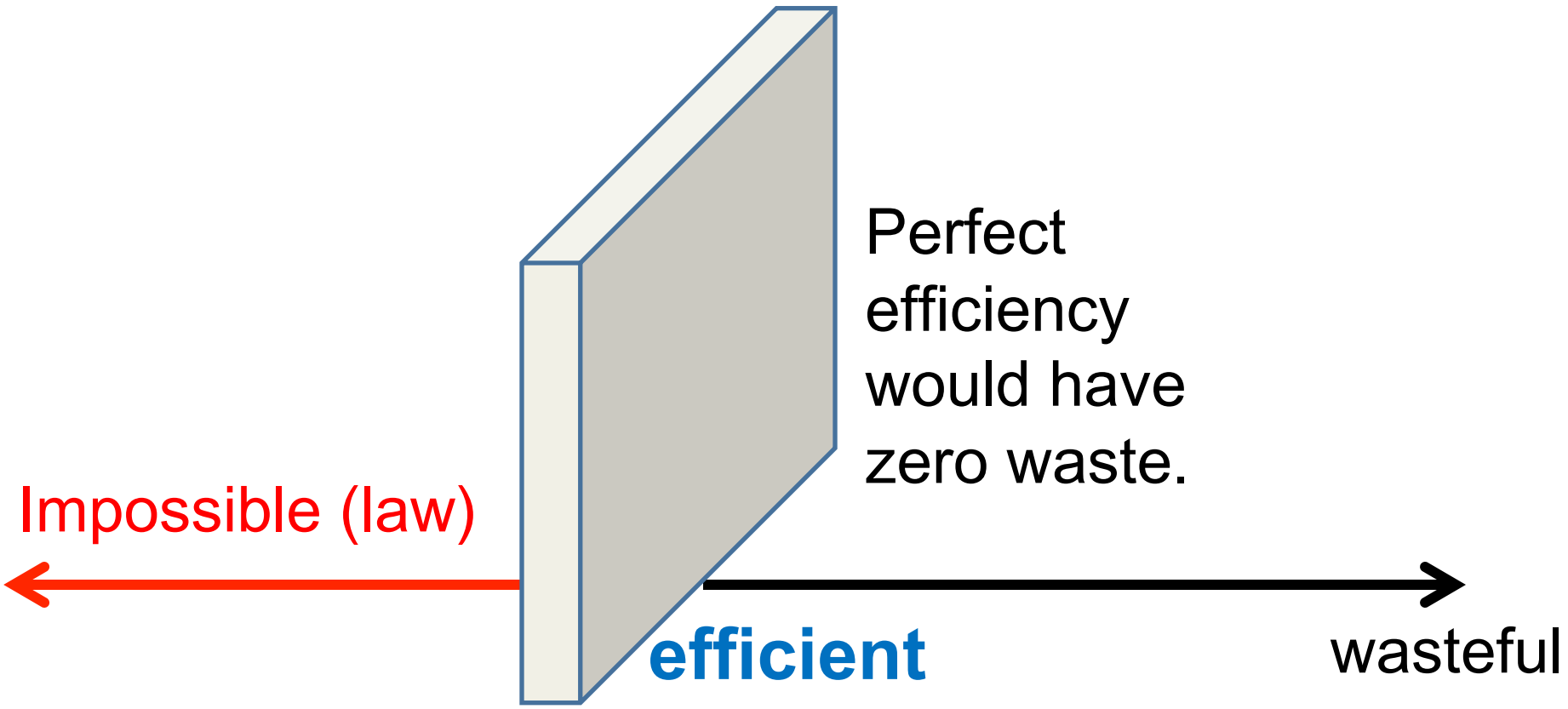
Tradeoffs



Tradeoffs

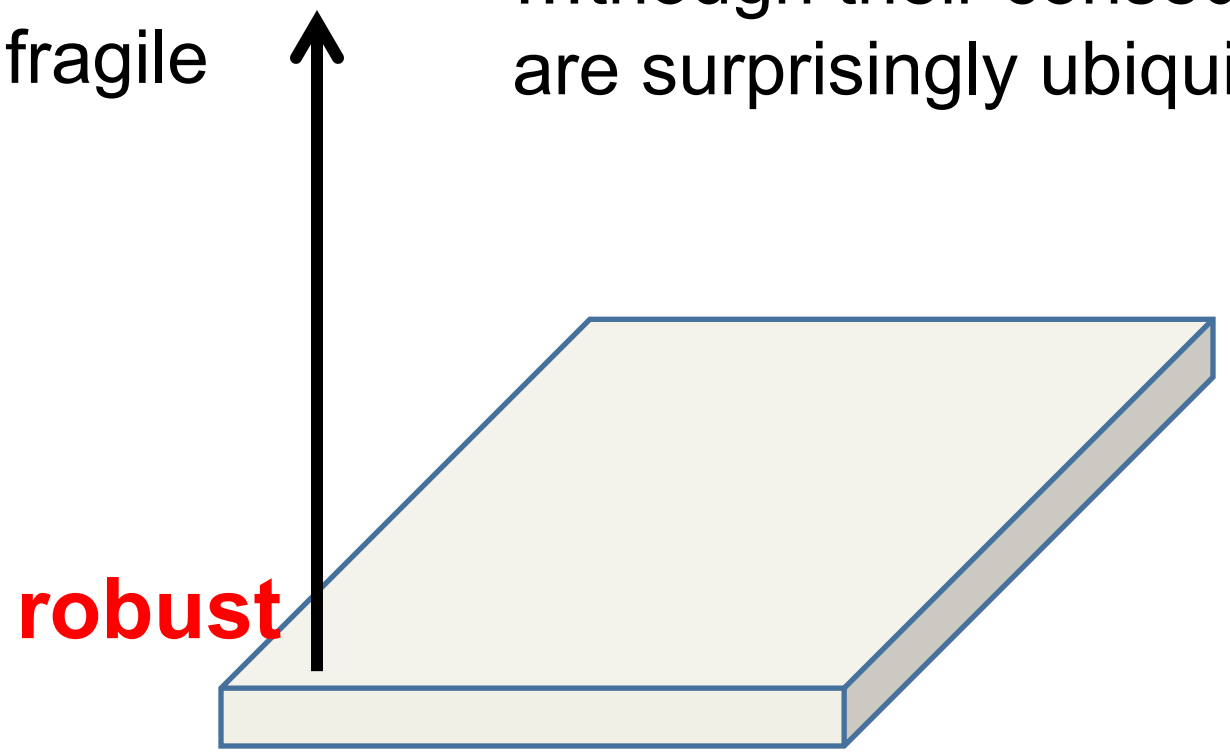


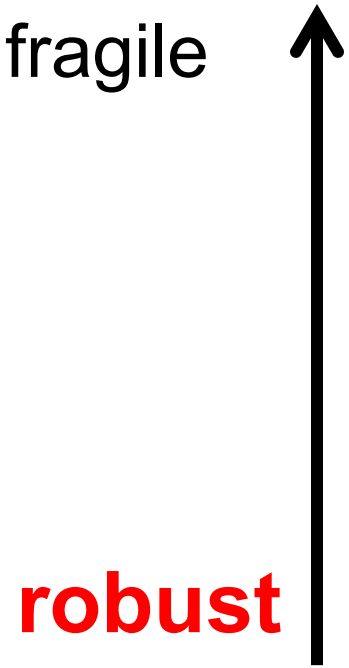
Materials and energy have many "universal conservation laws" that limit achievable efficiency.



Robustness also has
“universal conservation laws”
that are less familiar…

…though their consequence
are surprisingly ubiquitous.





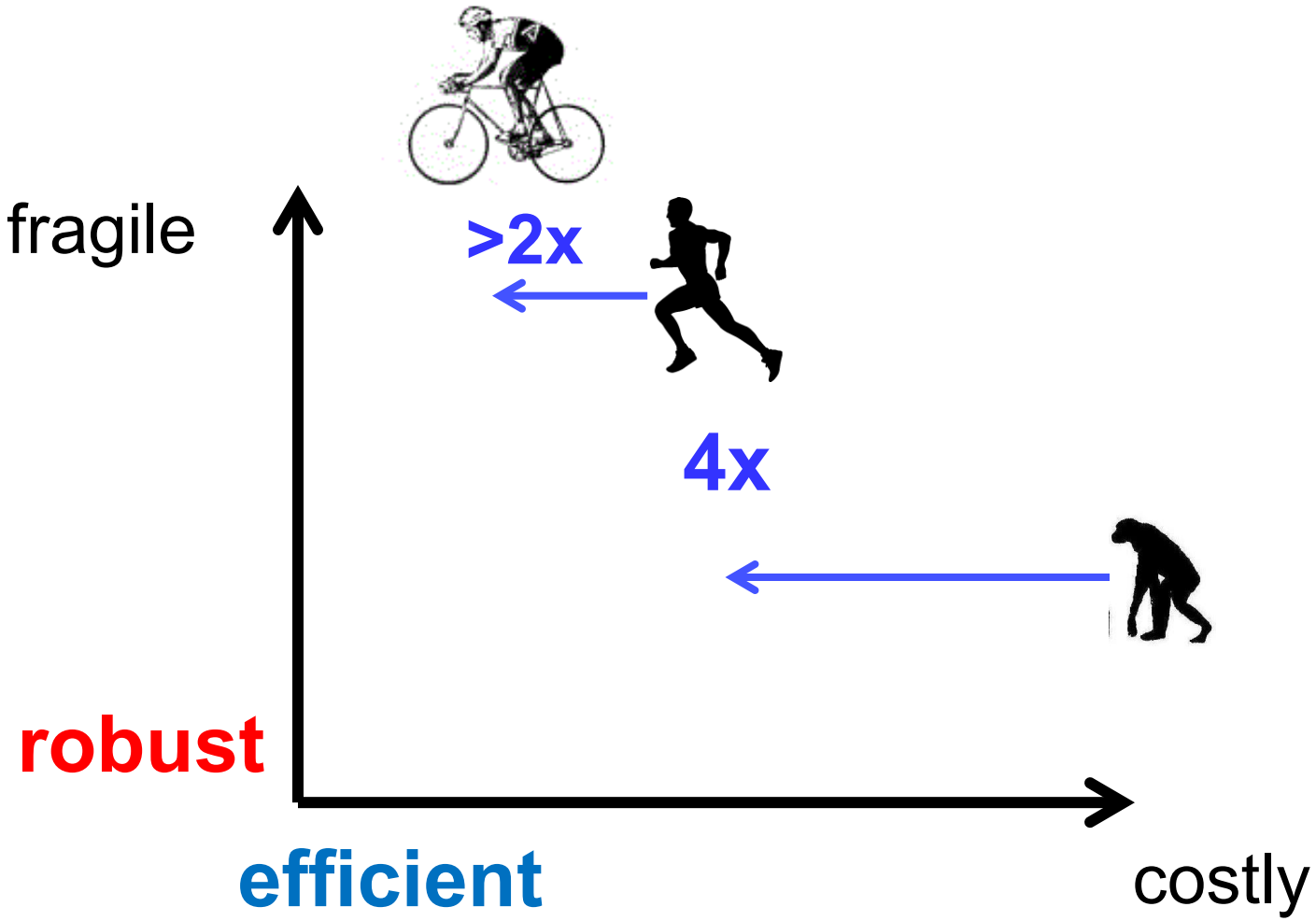
- **Brains**
- Nets/Grids (cyberphys)
- Bugs (microbes, ants)
- Medical physiology
- Lots of aerospace
- Wildfire ecology
- Earthquakes
- Physics:
  - –turbulence,
  - –stat mech (QM?)
- “Toy”:
  - –Lego
  - –clothing, fashion
- Buildings, cities
- **Synesthesia**

- **Neuroscience**
  + People care
  +Live demos!

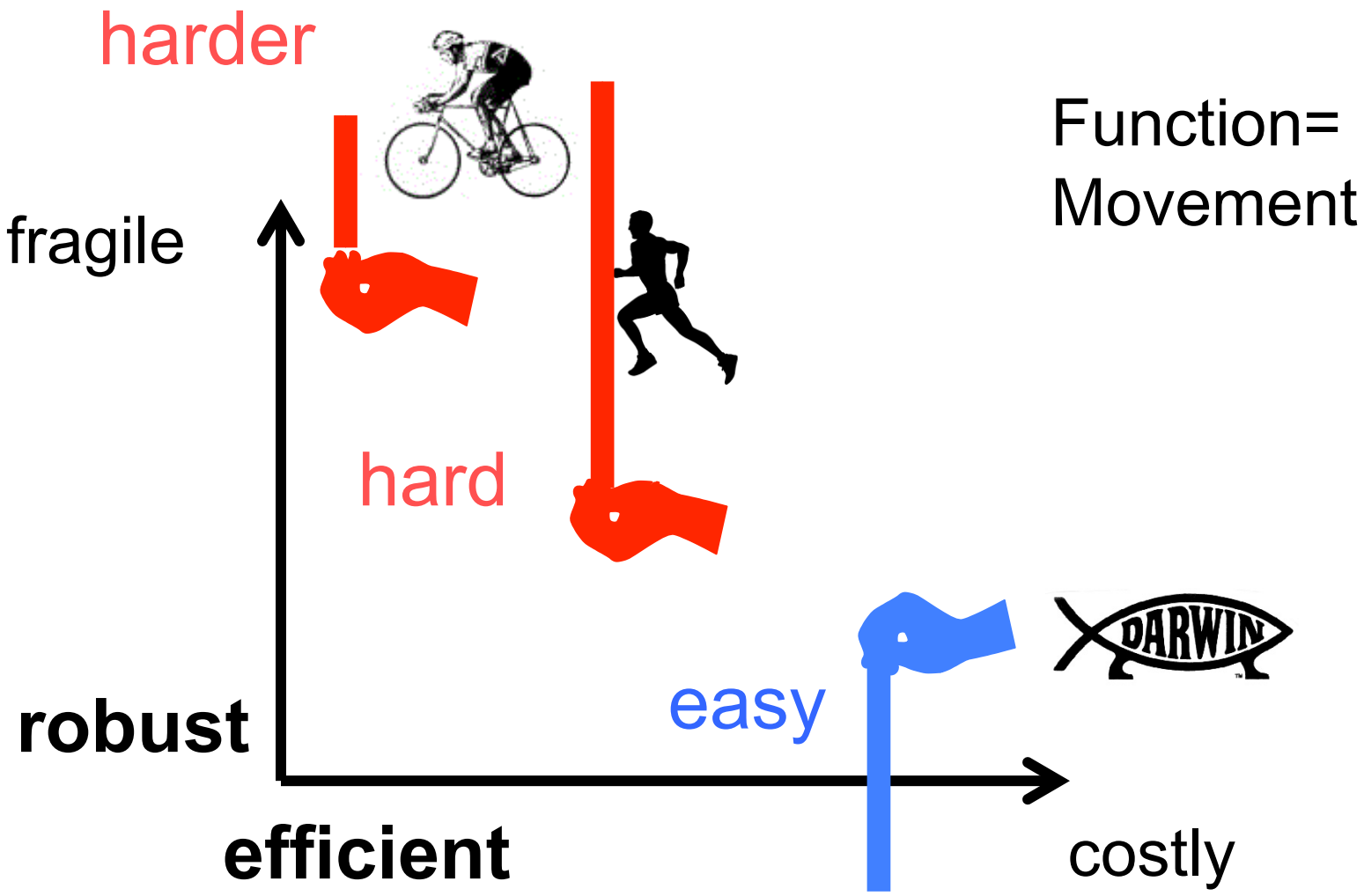
1. experiments
2. data
3. theory
4. universals

Simpler demo?

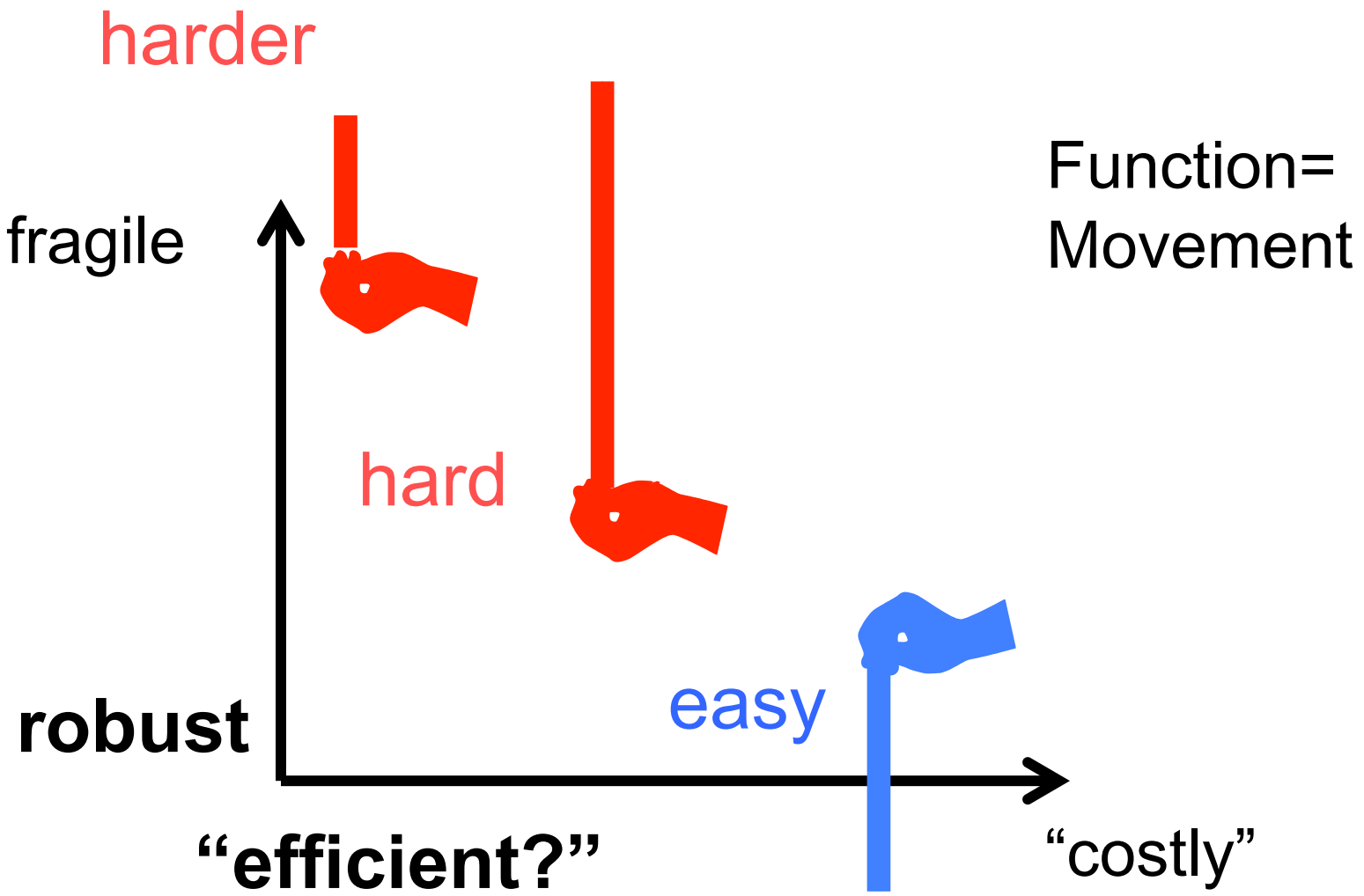
Tradeoffs



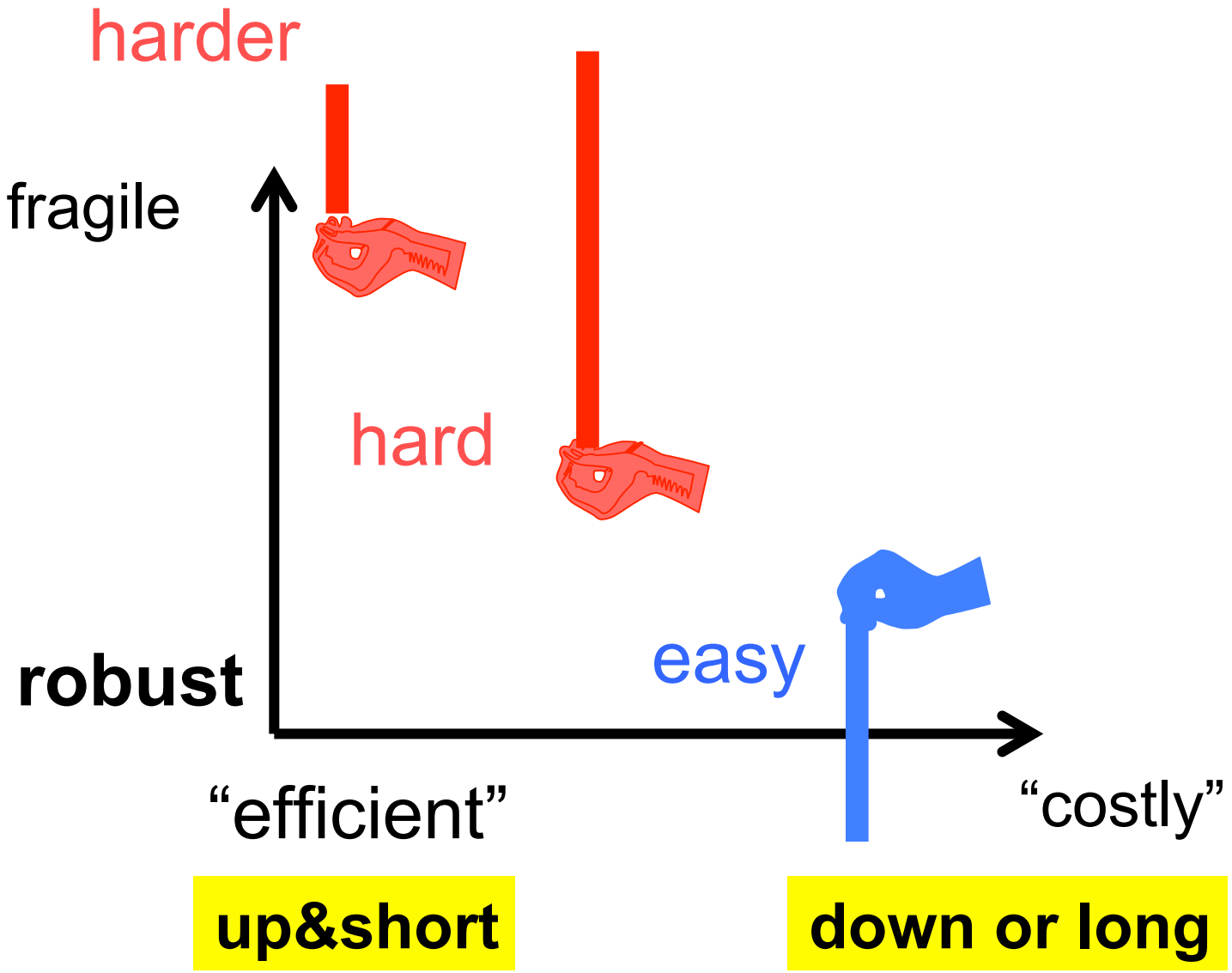
A convenient cartoon



A convenient cartoon demo

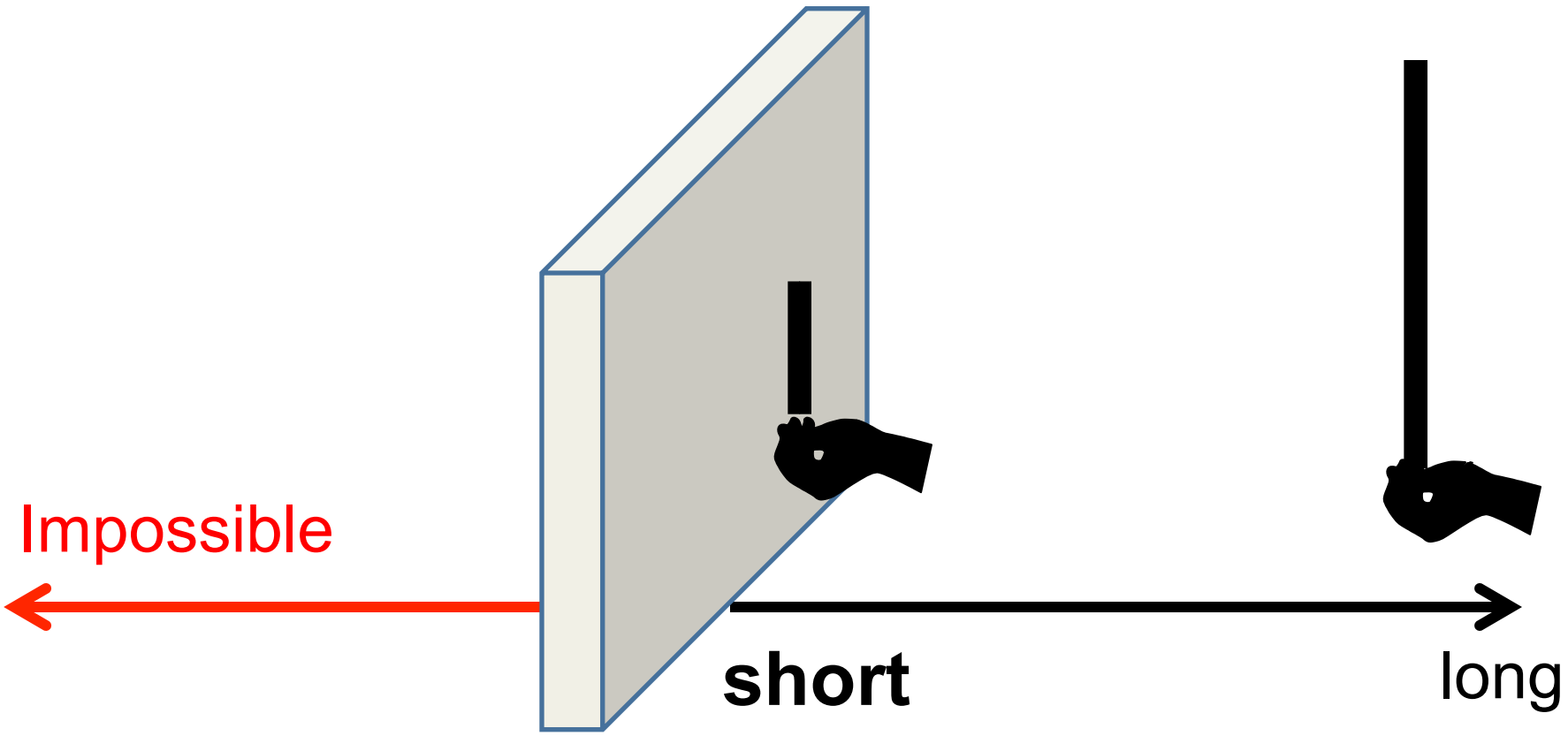


cartoon demo



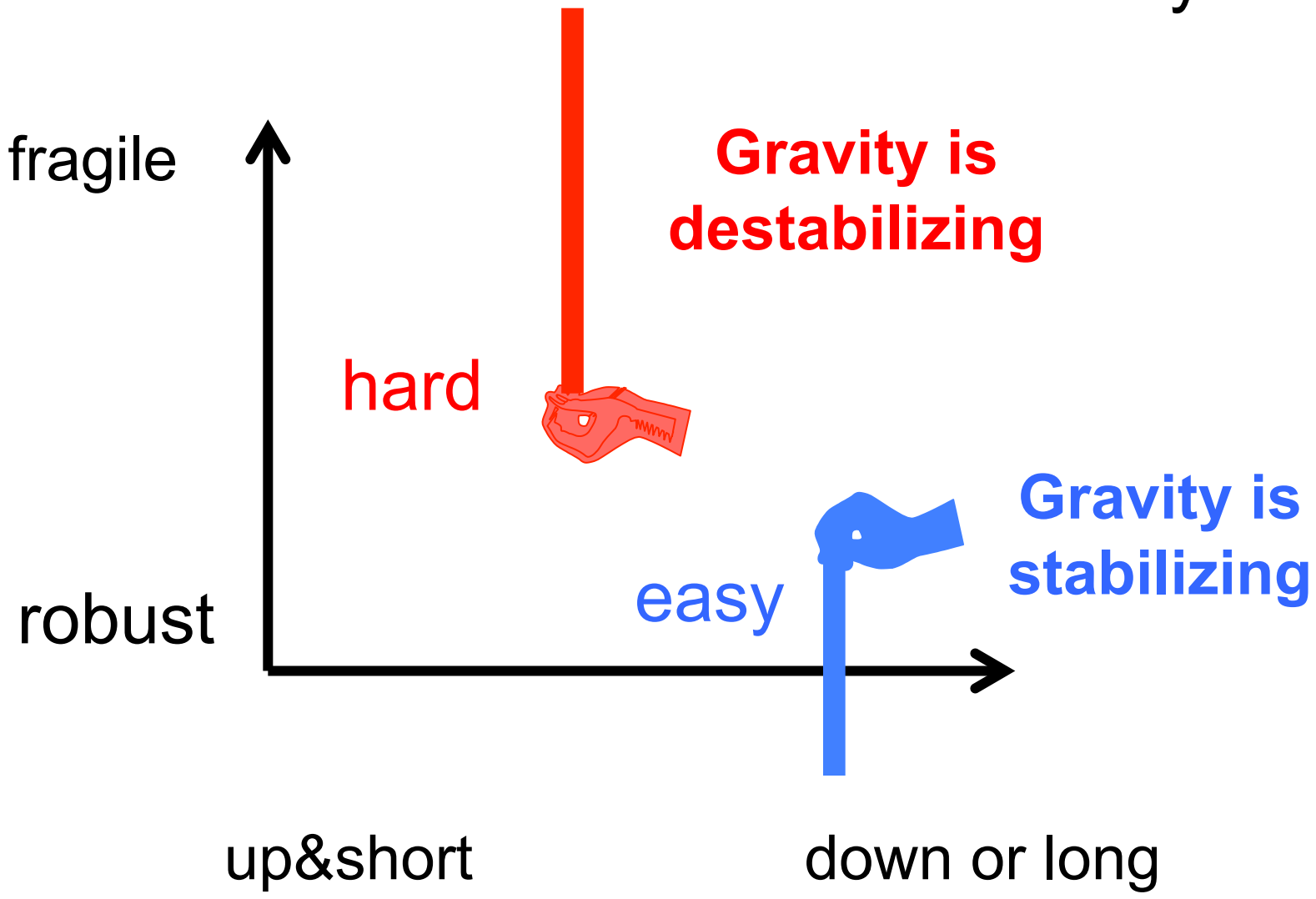
cartoon demo

Length is positive
(not “waste,” but a cartoon)



Universal laws?

Law #1 : Mechanics
Law #2 : Gravity



Efficiency/instability/layers/feedback

- New efficiencies but also instabilities
- New distributed/layered/complex/active control

cartoon demo

- Sustainable infr[illegible]ure? (e.g. smartgrids)
- Money/fin[illegible]bbyists/etc
- Indus[illegible]ion
- Societ[illegible]/agriculture/weapons/etc
- **Bipedalism**
- Maternal care
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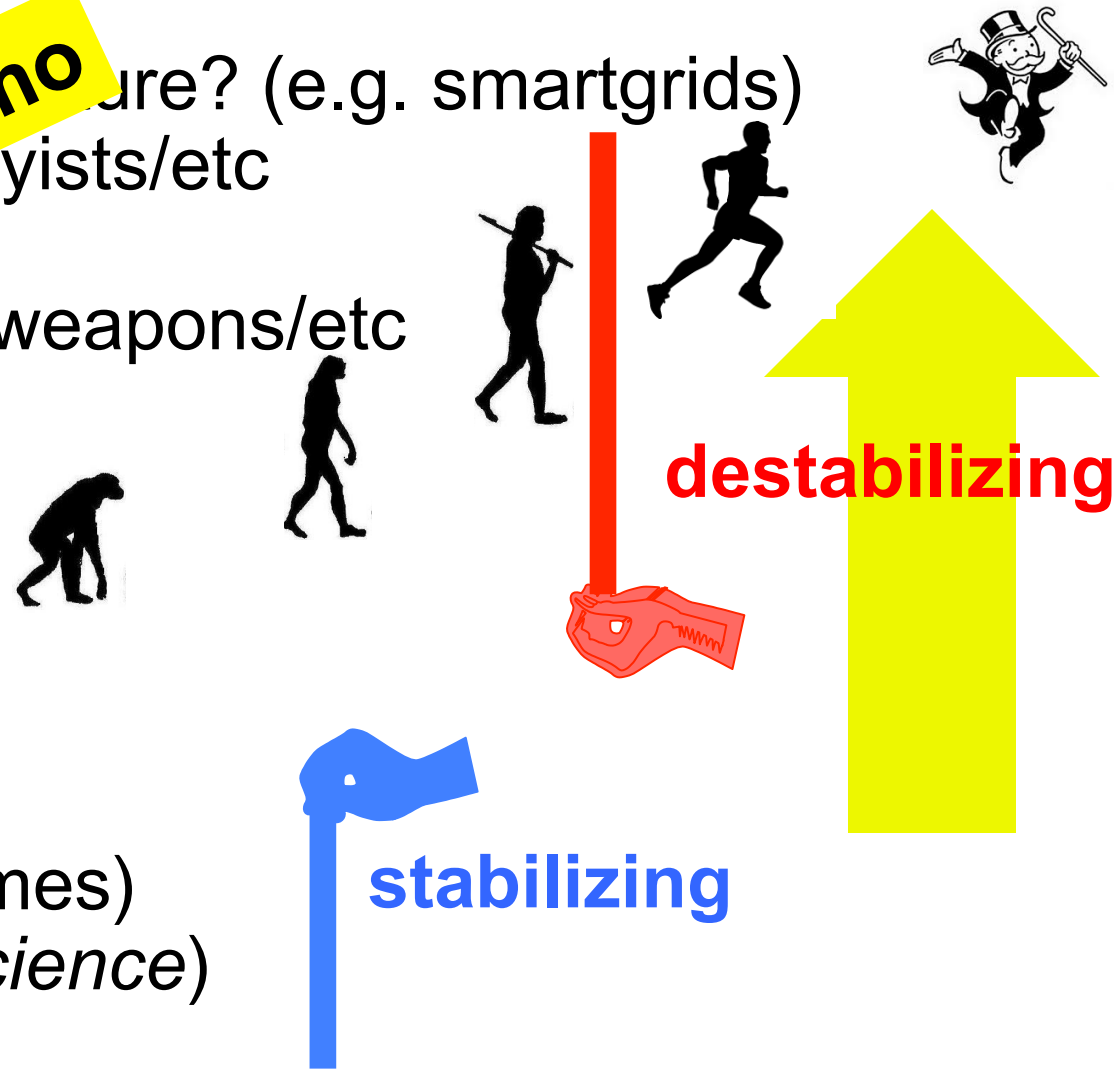
- Oxygen
- Translation (ribosomes)
- Glycolysis (2011 *Science*)

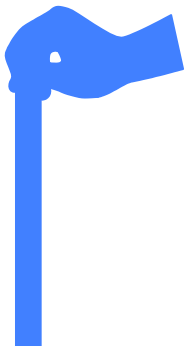


Universal laws?

Law #1 : Mechanics
Law #2 : Gravity

We think of
mechanics and gravity as
"obeying universal *laws*."

Gravity is destabilizing



Gravity is stabilizing

But both "universal" and "law"
are confused and overloaded,
so unfortunate terminology.

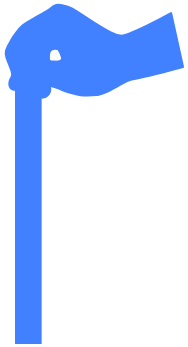
Universal laws?

Law #1 : Mechanics
Law #2 : Gravity

We think of
mechanics and gravity as
"obeying universal *laws*."

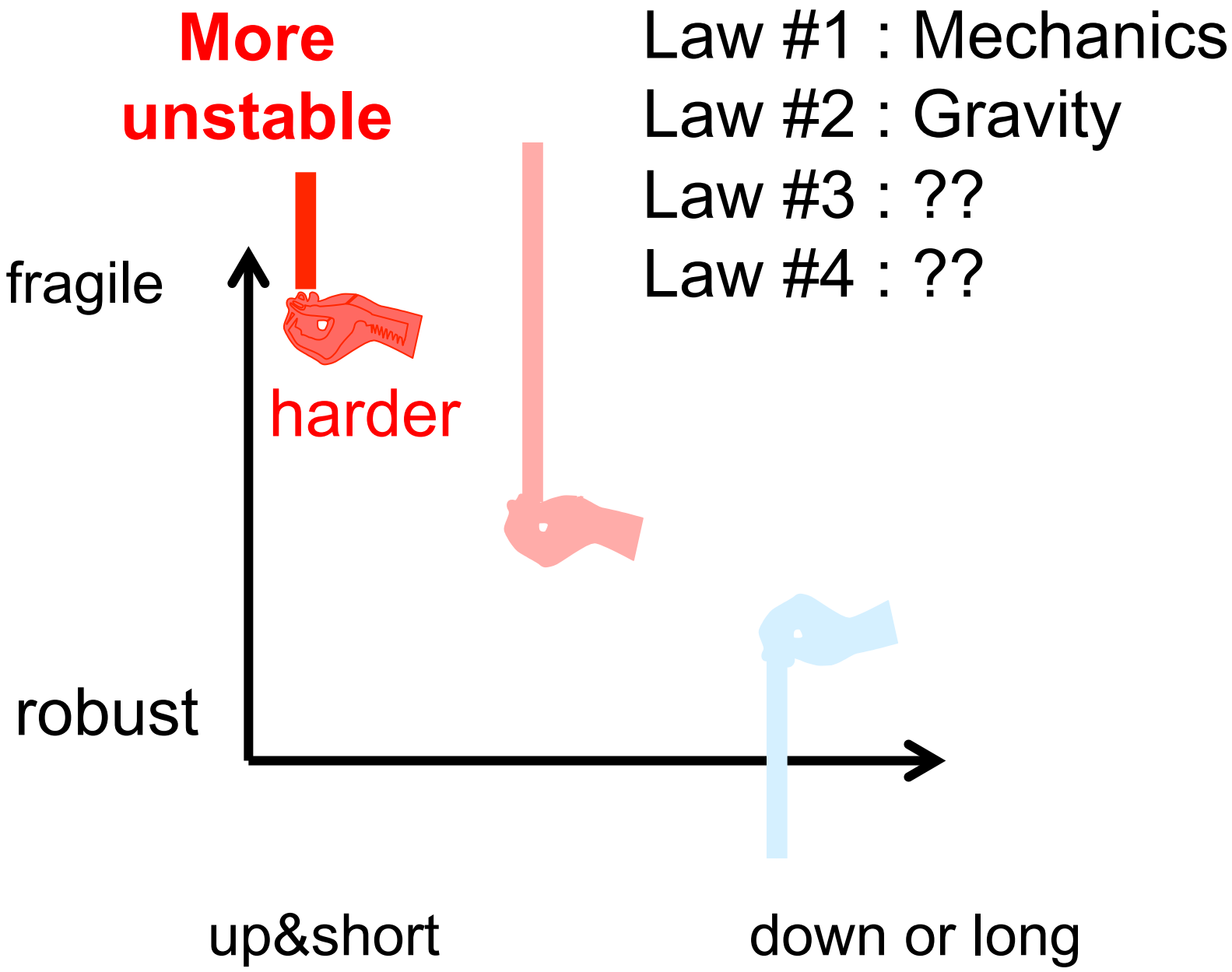
(Generally: ***constraints***)

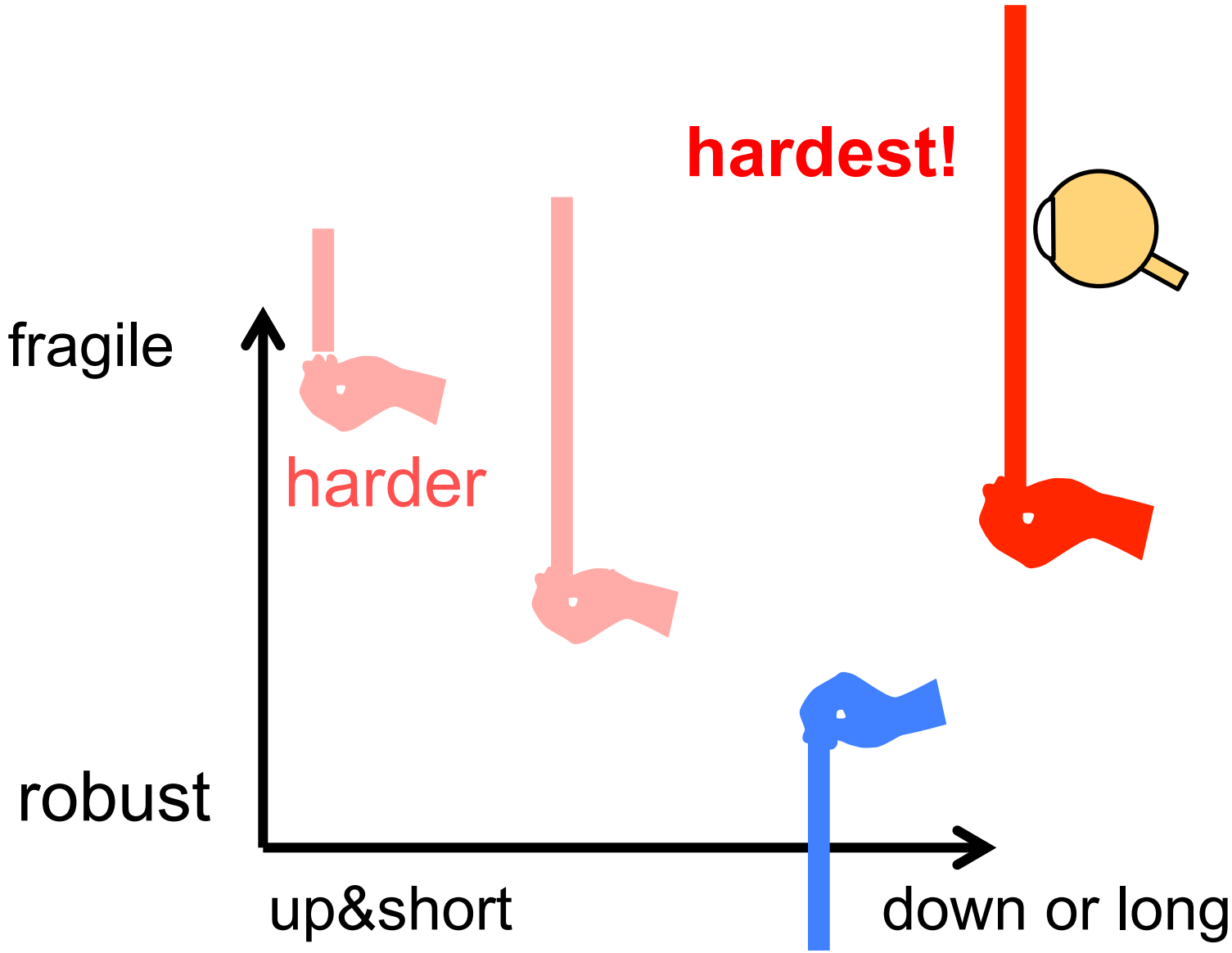
Gravity is destabilizing



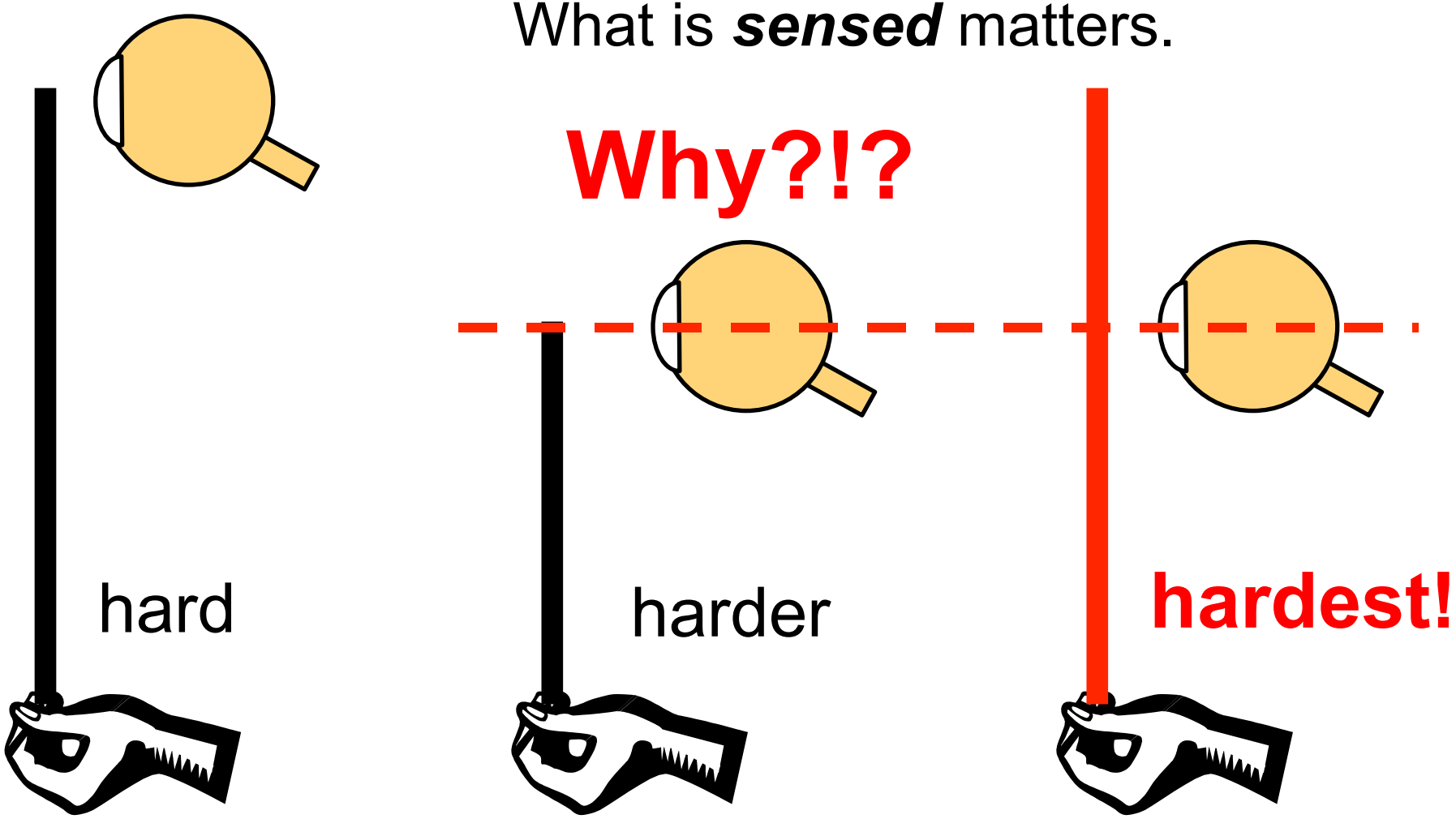
Gravity is stabilizing

But the *consequences* (even of gravity) depend on other constraints.


More
unstable
Law #1 : Mechanics
Law #2 : Gravity
Law #3 : ??
Law #4 : ??
fragile
harder
robust
up&short
down or long


hardest!
fragile
harder
robust
up&short
down or long

What is ***sensed*** matters.

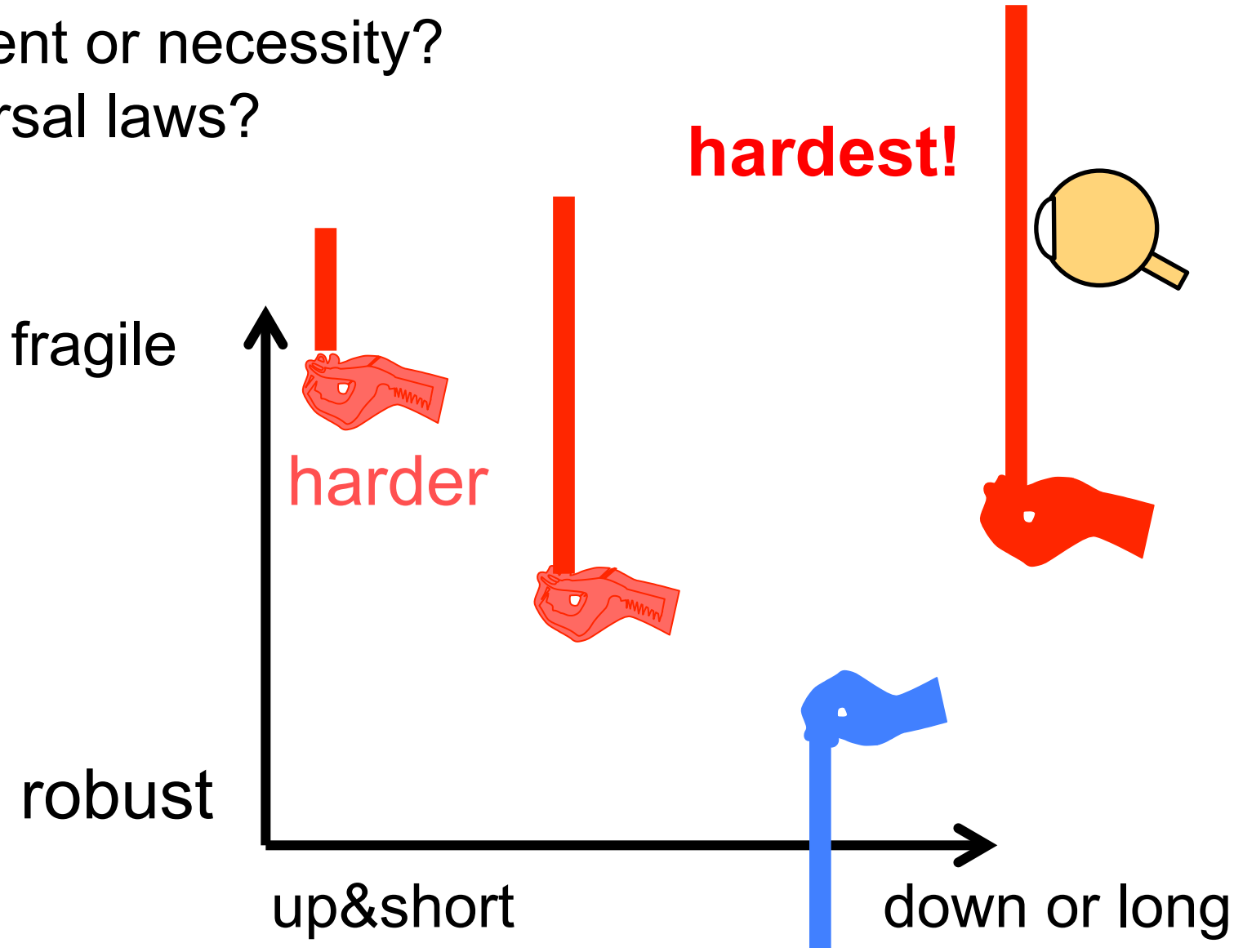


Why?

Easy to ***prove*** using simple models.

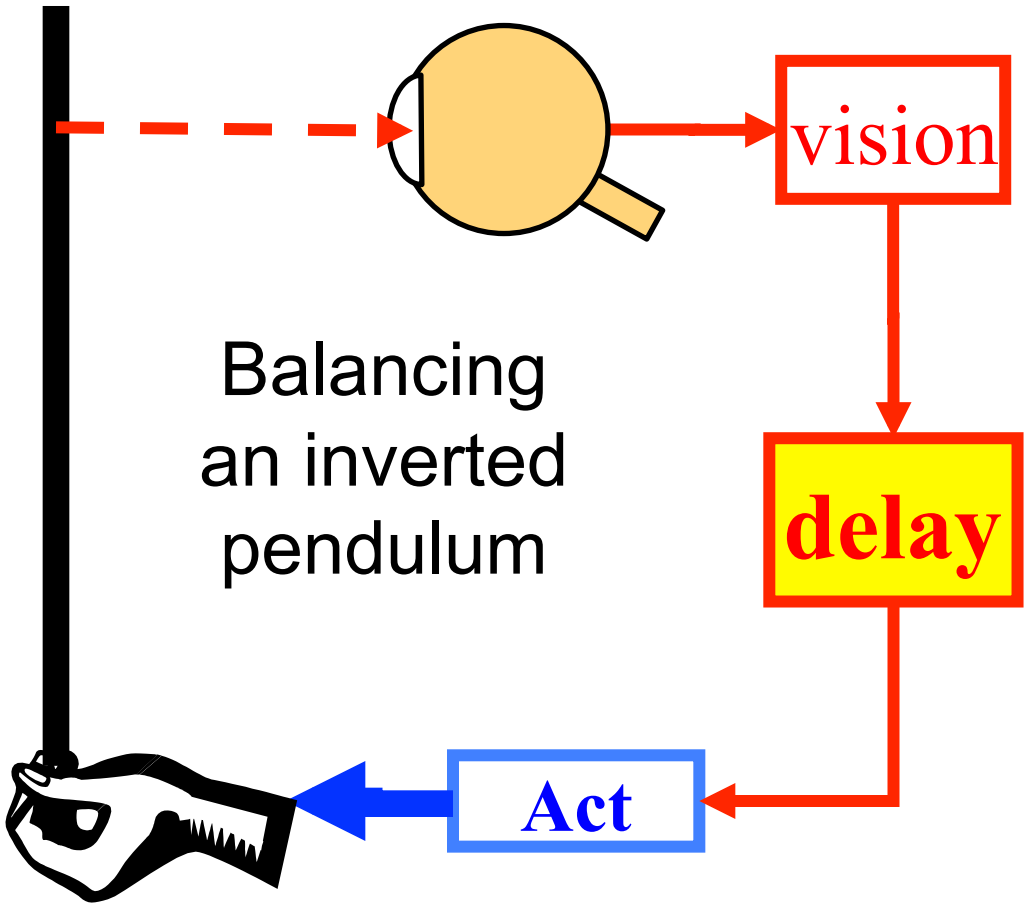
Why?

Accident or necessity?
Universal laws?



Some minimal math details

(4) Universal laws +

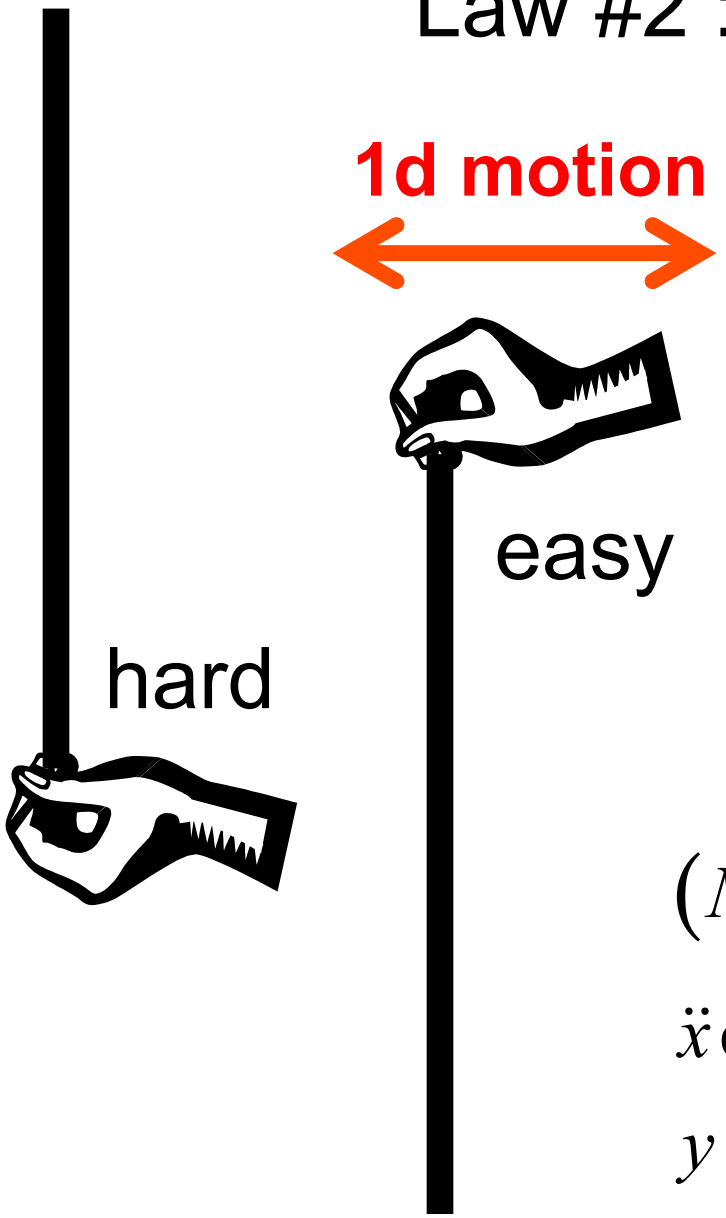


Mechanics+
Gravity +
Light +

$$\|T\|_\infty \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$

+ Neuroscience

Law #1 : Mechanics
Law #2 : Gravity



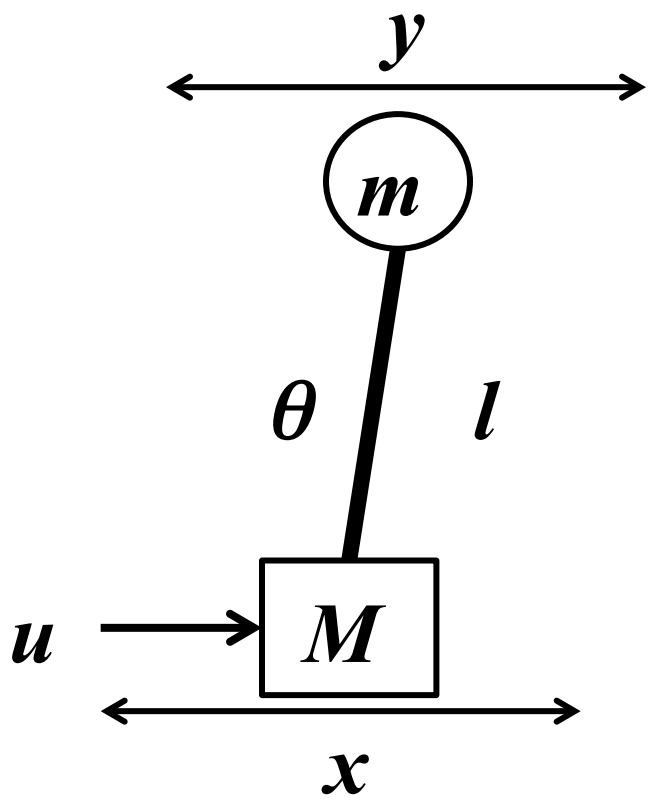
Use “conservation laws”

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

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

$$y = x + l_o\sin\theta$$

Standard inverted pendulum



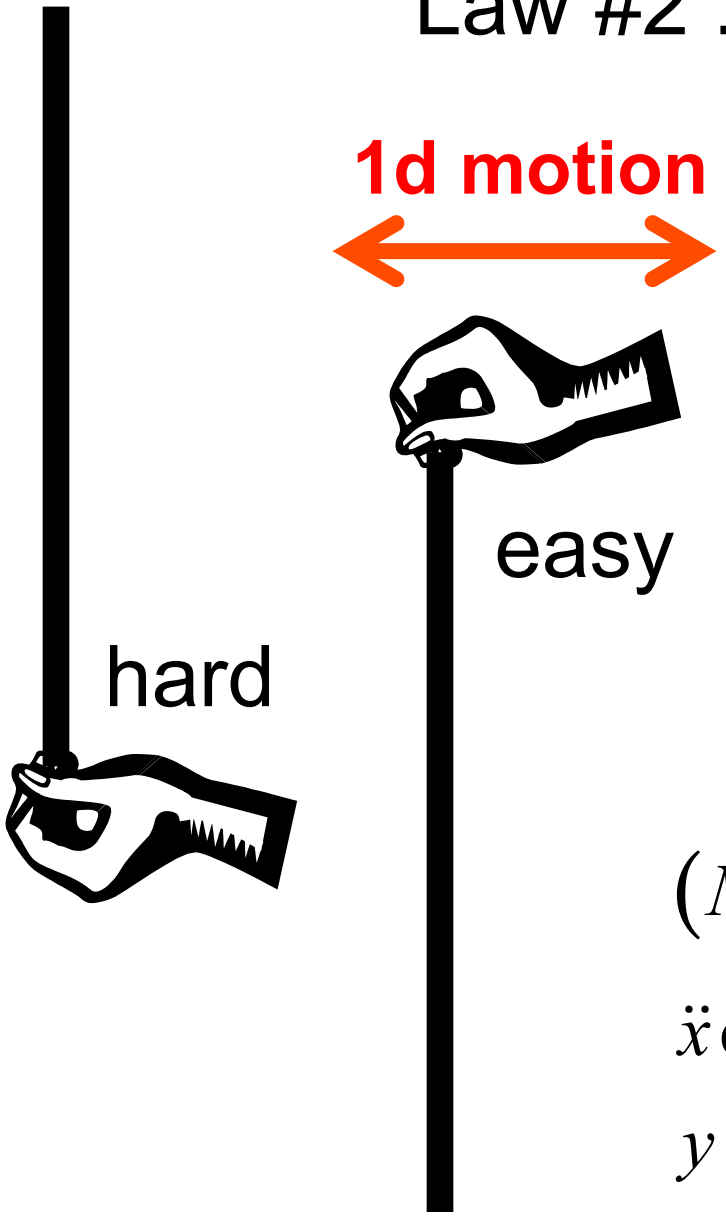
l	***length***
m	***mass***
M	***mass***
g	***gravity***
u	***control force***

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

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

$$y = x + l_o\sin\theta$$

Law #1 : Mechanics
Law #2 : Gravity



linearize

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

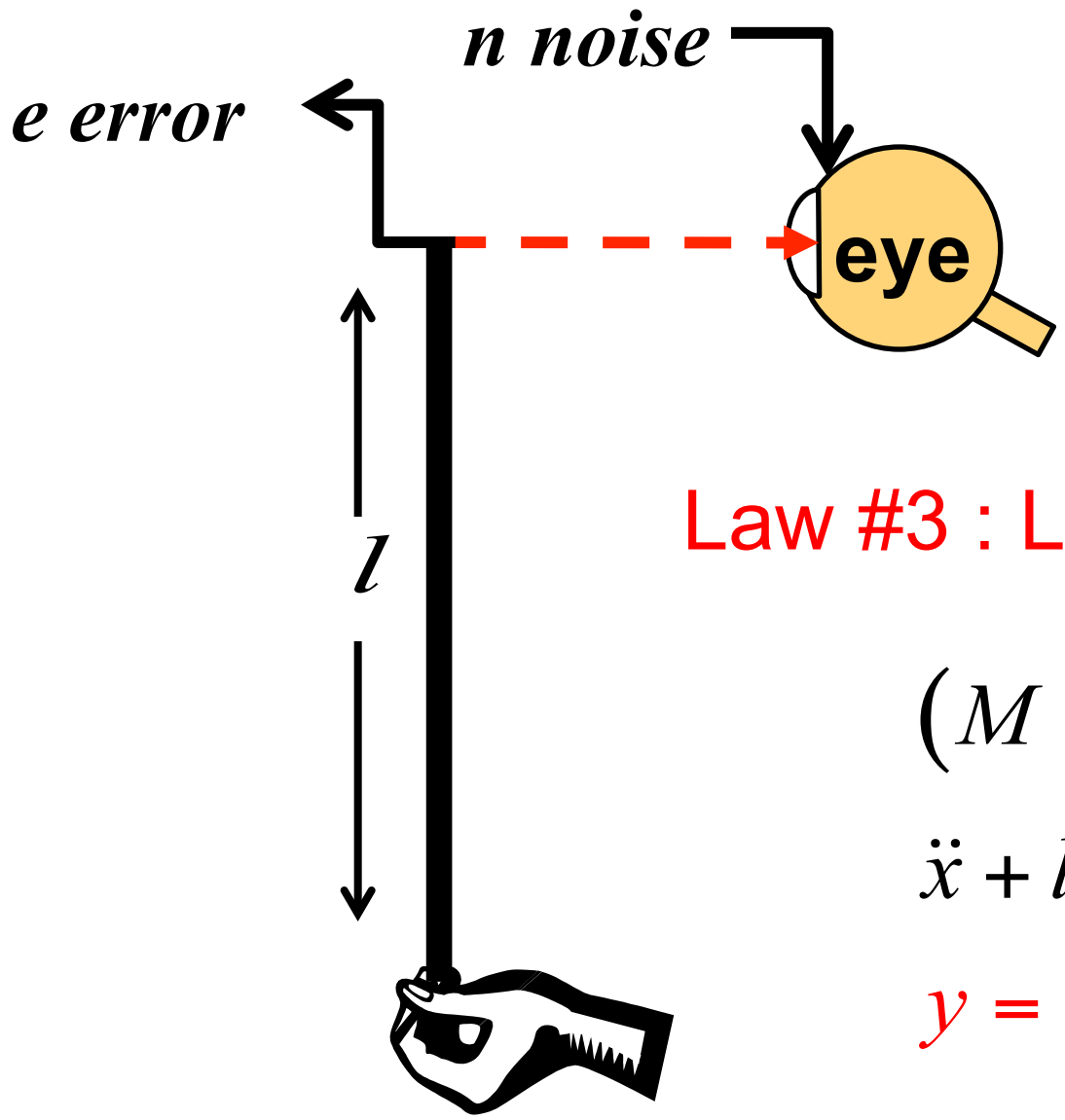
$$\ddot{x} + l\ddot{\theta} \pm g\theta = 0$$

$$y = x + l_o\theta$$

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

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

$$y = x + l_o\sin\theta$$



Law #3 : Light (vision)

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

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

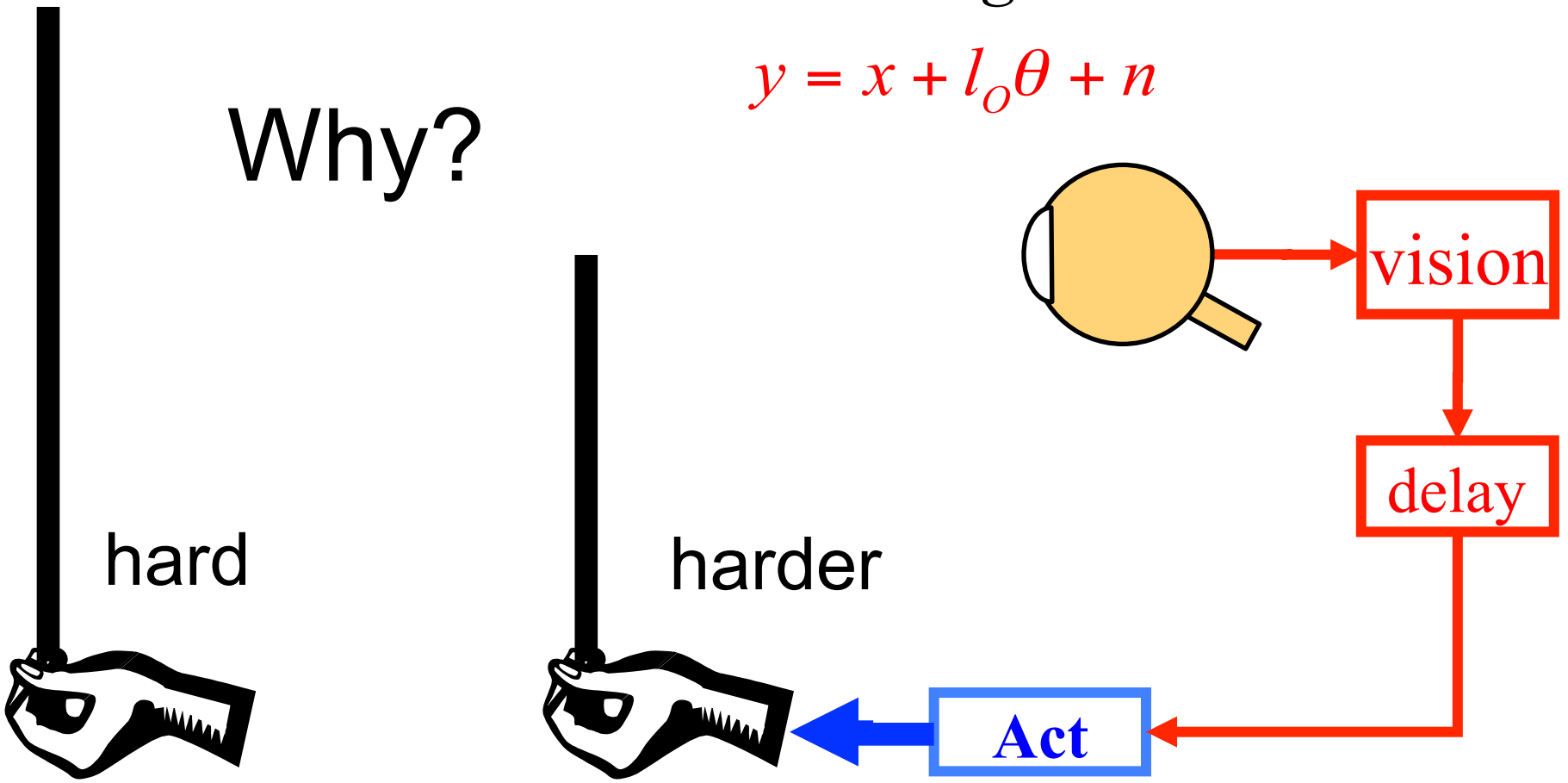
$$y = x + l_o\theta + n$$

Law #3 : Light $(M+m)\ddot{x} + ml\ddot{\theta} = u$

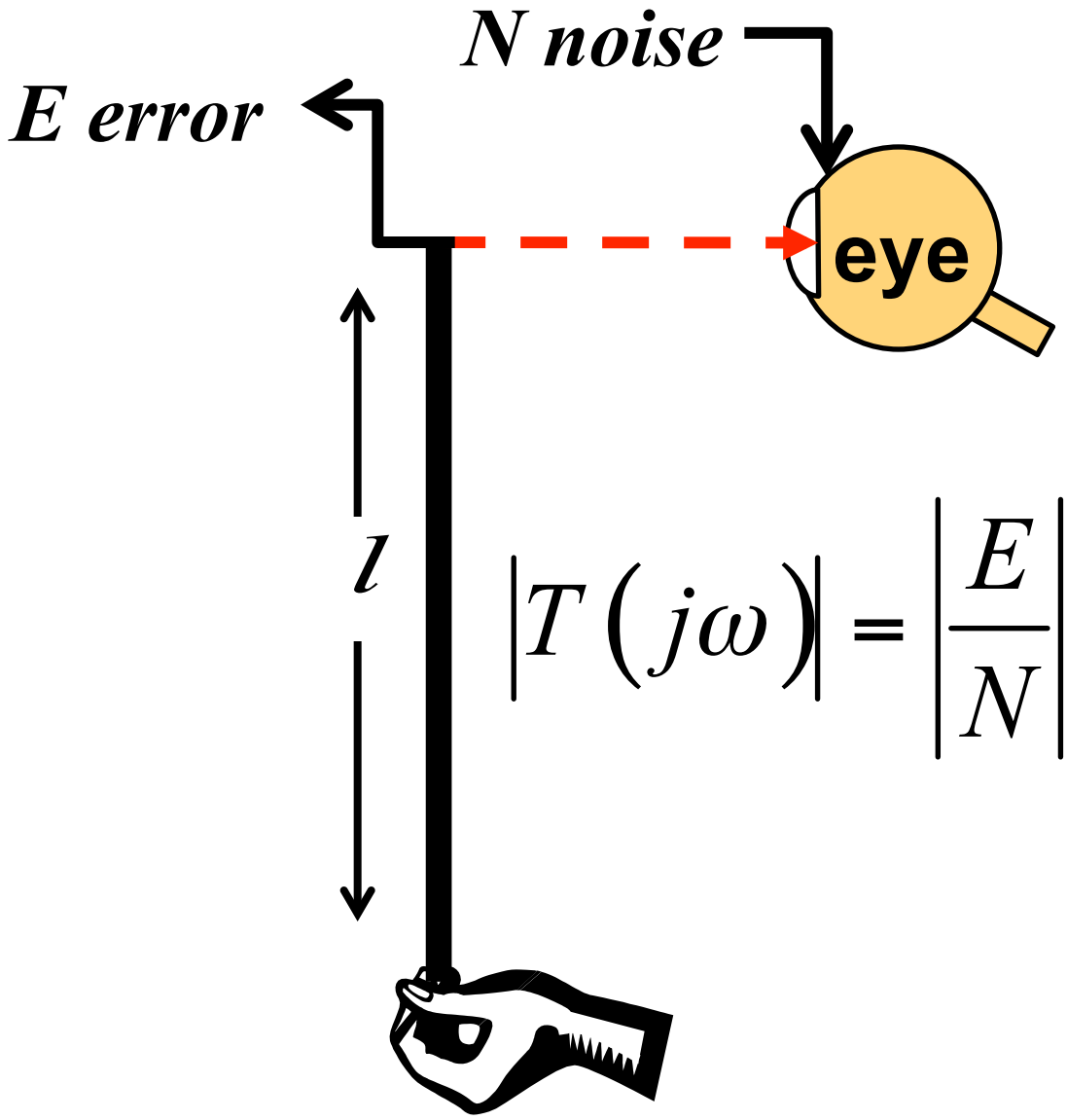
$\ddot{x} + l\ddot{\theta} \pm g\theta = 0$

$y = x + l_o\theta + n$

Why?



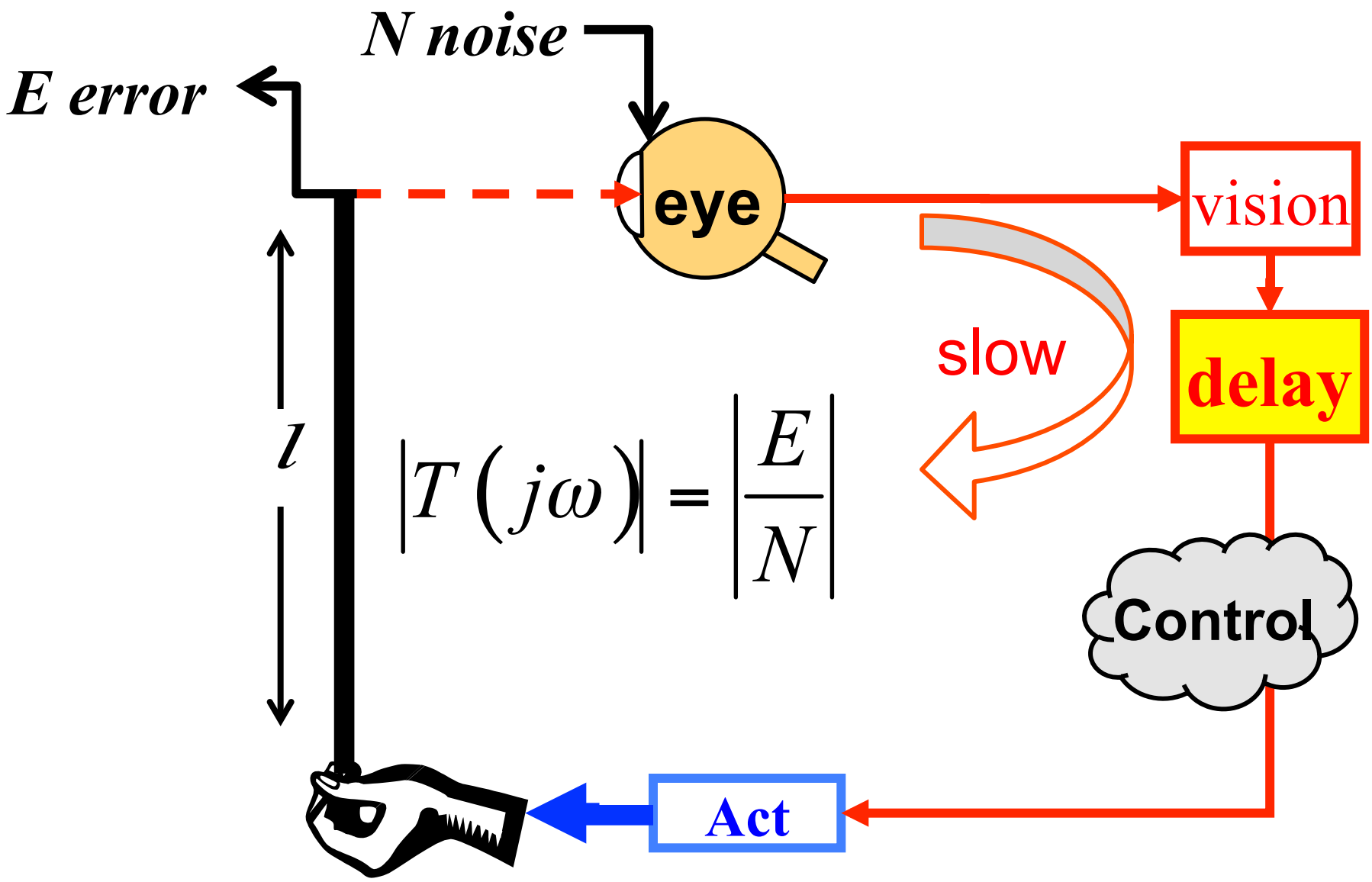
Easy to ***prove*** using simple models.



$$\left|T(j\omega)\right| = \left|\frac{E}{N}\right|$$

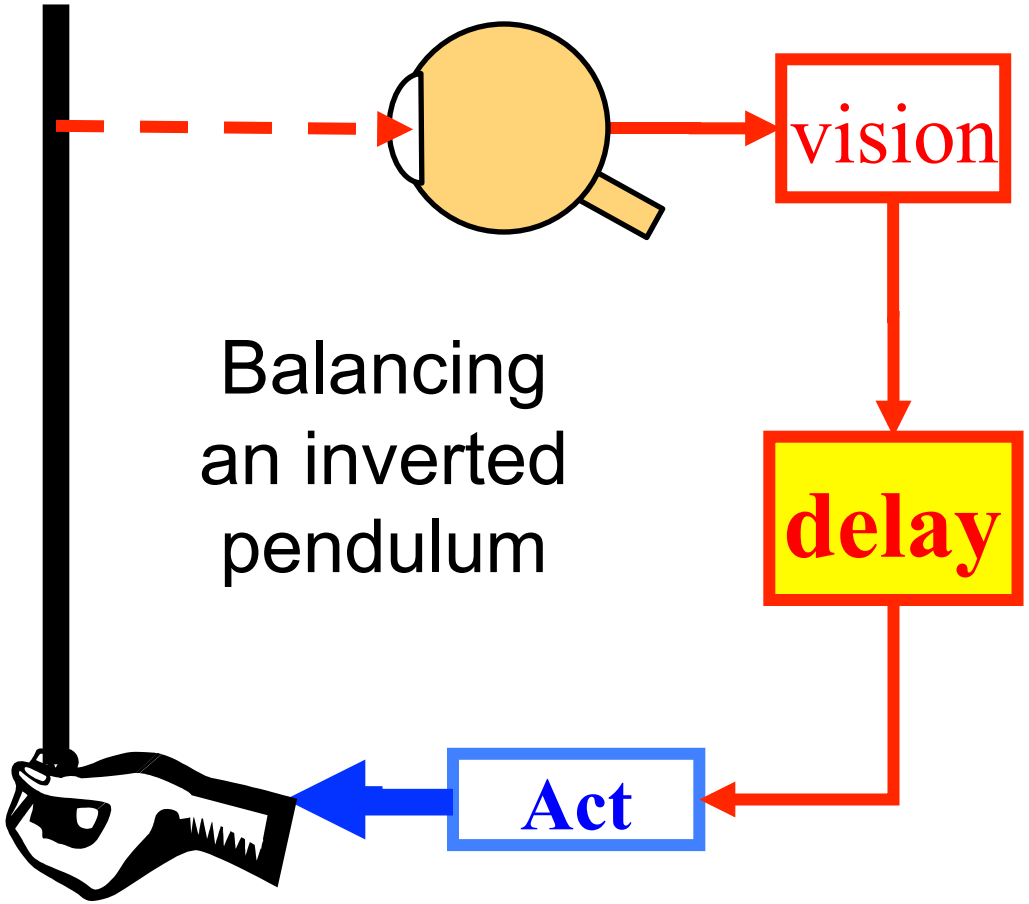
$$\left\|T\right\|_{\infty} \geq ?$$

Frequency domain


N noise
E error
eye
vision
slow
delay
l
$|T(j\omega)| = \left|\frac{E}{N}\right|$
Control
Act

Universal laws

Mechanics+
Gravity +
Light +



Balancing
an inverted
pendulum

$$\|T\|_\infty \geq \exp(p\tau)$$

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

$$\tau \approx .3s$$

Laplace transform
(One complex variable)

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

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

$$y = x + l_O\theta + n$$

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

$$y = x + l_O\theta = \left[\frac{(l-l_O)s^2 \pm g}{D(s)}\right] u$$

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

Fragility two ways (~ Bode* and Zames):

$$\exp\left(\int \ln|T|\right) \triangleq \exp\left(\frac{1}{\pi}\int_0^\infty \ln|T(j\omega)|\left(\frac{p}{p^2+\omega^2}\right)d\omega\right)$$

$$\|T\|_\infty = \sup_\omega |T(j\omega)|$$

$$\left.\exp\left(\int \ln|T|\right)\right|_{\|T\|_\infty} \geq \exp(p\tau)$$

* With key help from Freudenberg and Seron et al

$$\exp\left(\int \ln|T|\right) \triangleq \exp\left(\frac{1}{\pi}\int_0^{\infty} \ln\left|T(j\omega)\right|\left(\frac{p}{p^2+\omega^2}\right)d\omega\right)$$

$$\|T\|_{\infty} = \sup_{\omega}\left|T(j\omega)\right|$$

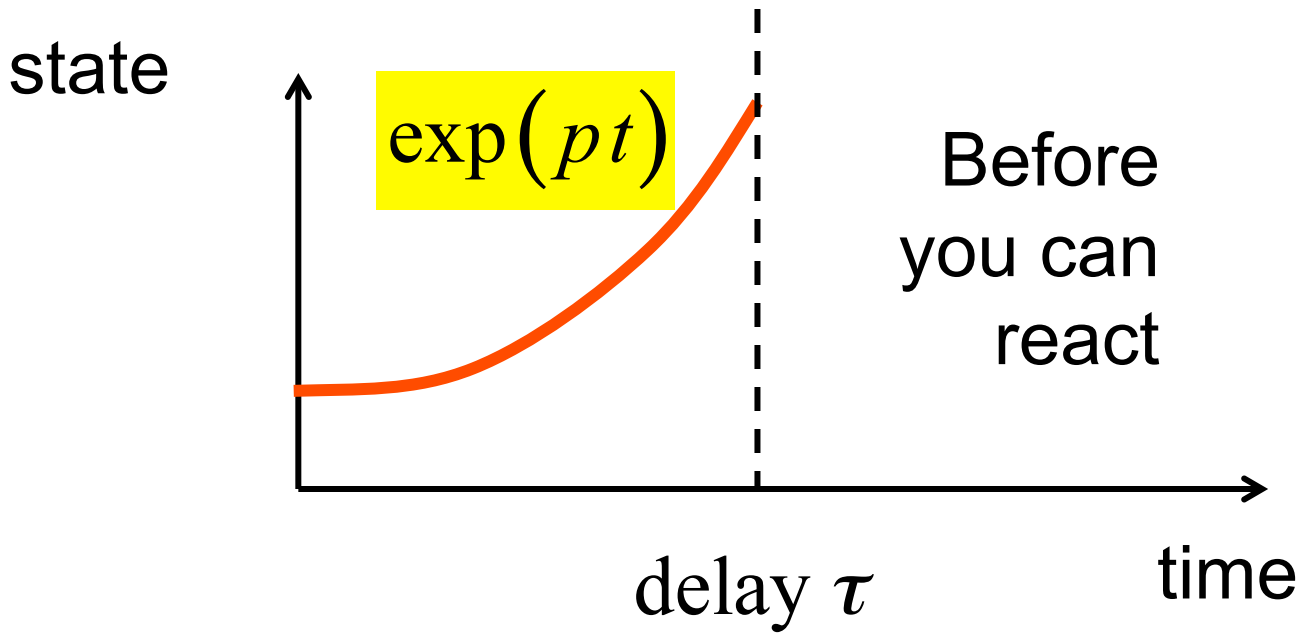
Amplification (noise to error)

Entropy rate

Energy (L2)

$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_{\infty}\end{matrix}\right\} \geq \exp(p\tau)$$

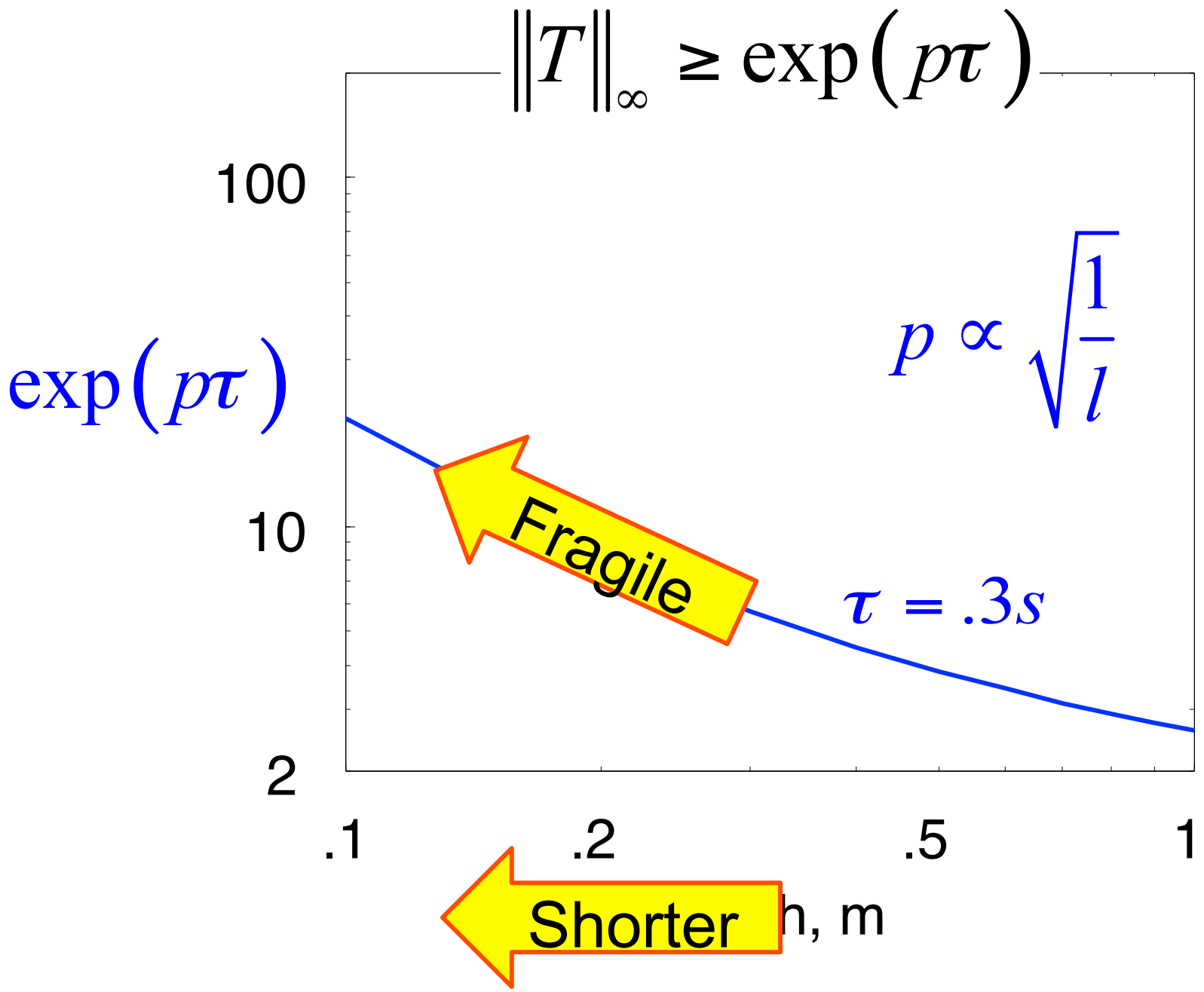
intuition

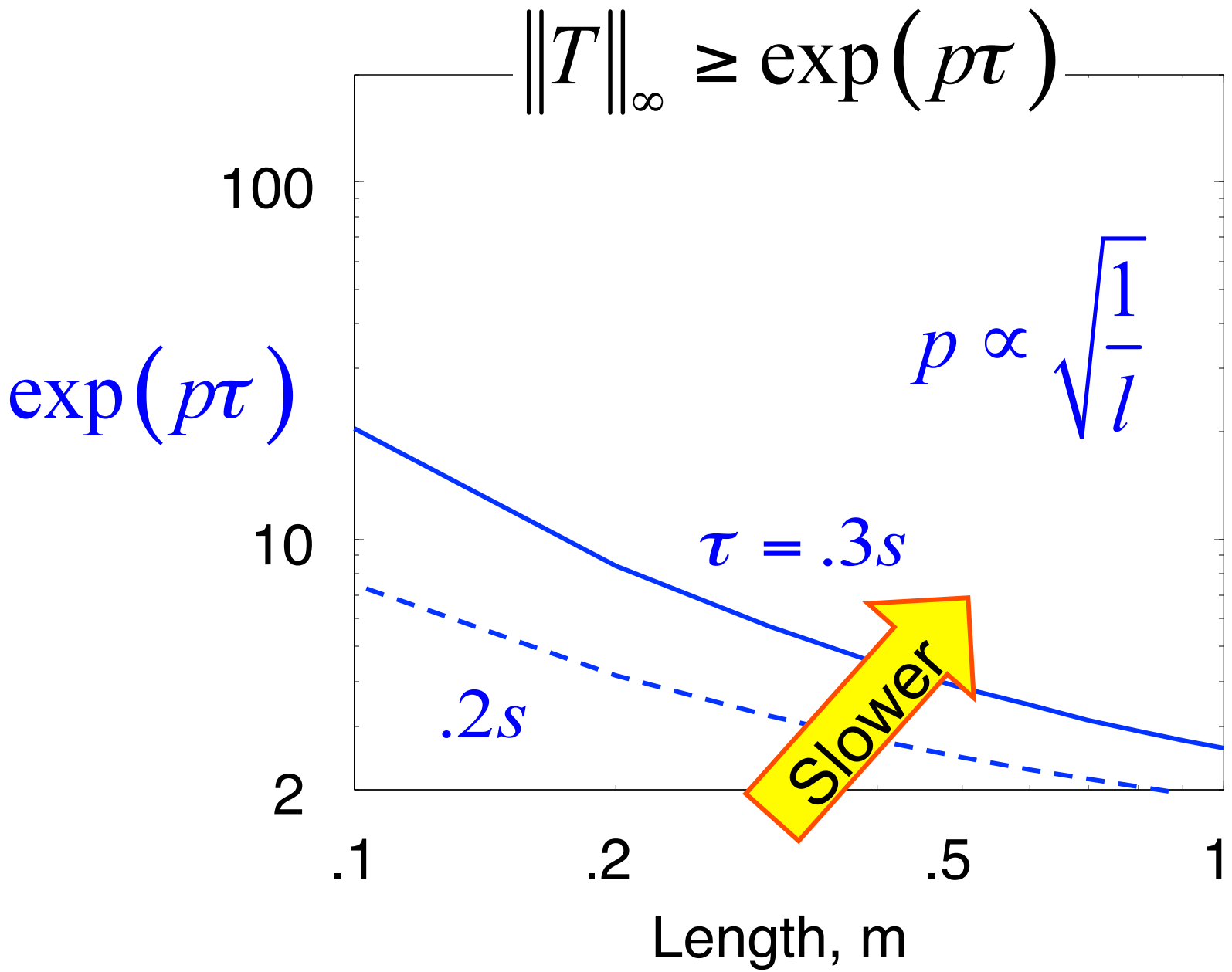


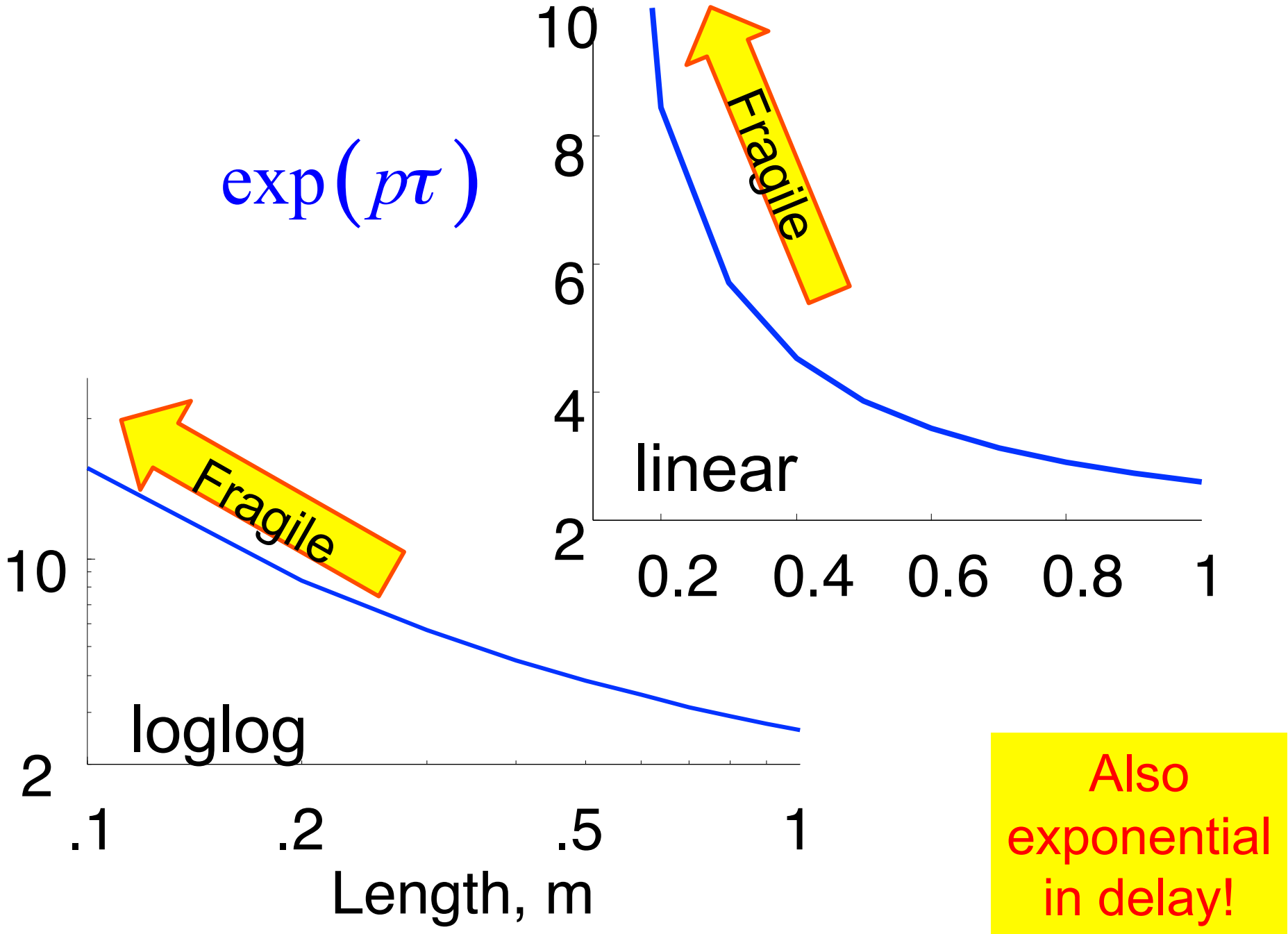
Entropy rate

Energy (L2)

$$\left.\begin{matrix} \exp\left(\int \ln|T|\right) \\ \|T\|_\infty \end{matrix}\right\} \geq \exp(p\tau)$$

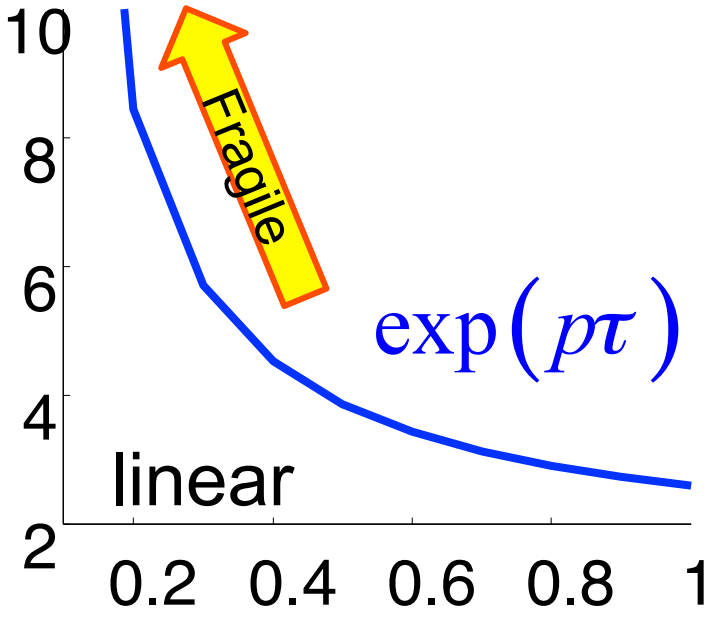

$\|T\|_\infty \geq \exp(p\tau)$
100
10
2
$\exp(p\tau)$
$p \propto \sqrt{\frac{1}{l}}$
Fragile
$\tau = .3s$
.1
.2
.5
1
Shorter
h, m


$\|T\|_\infty \geq \exp(p\tau)$
100
10
2
$\exp(p\tau)$
$p \propto \sqrt{\frac{1}{l}}$
$\tau = .3s$
$.2s$
Slower
.1
.2
.5
1
Length, m

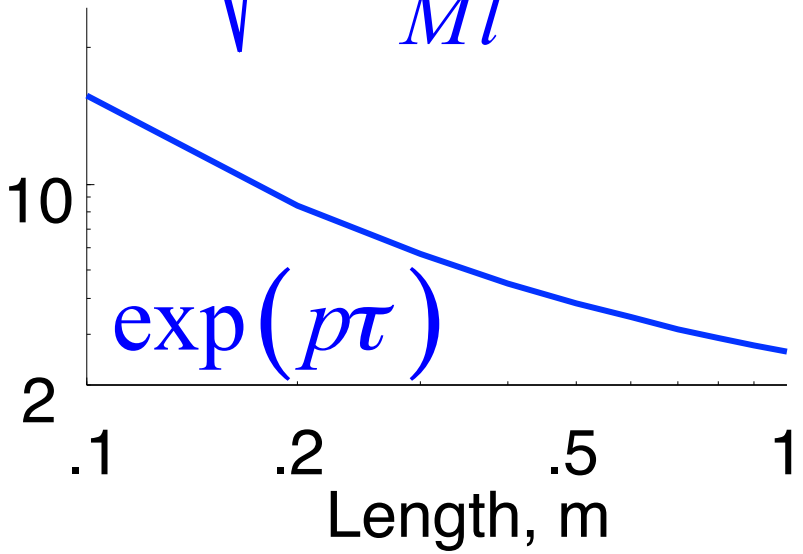


Also exponential in delay!

l	***length***
m	***mass***
M	***mass***
g	***gravity***

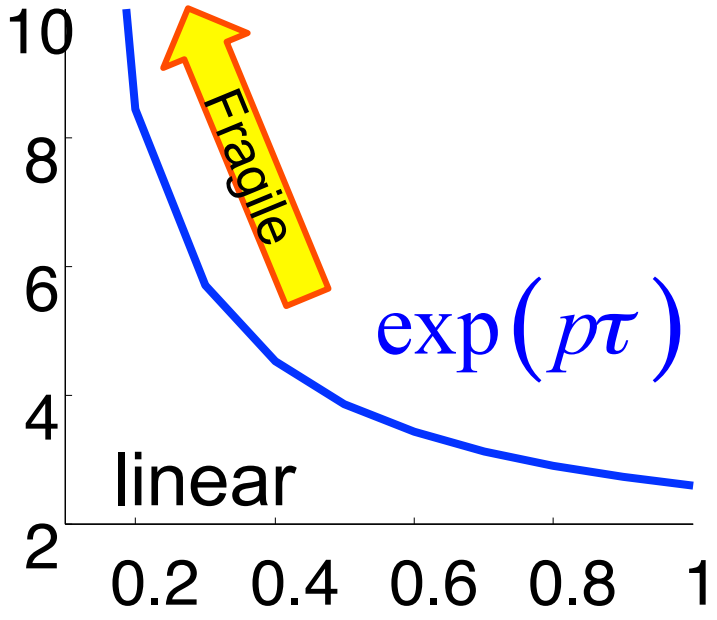


$$p = \sqrt{\frac{(M+m)g}{Ml}}$$

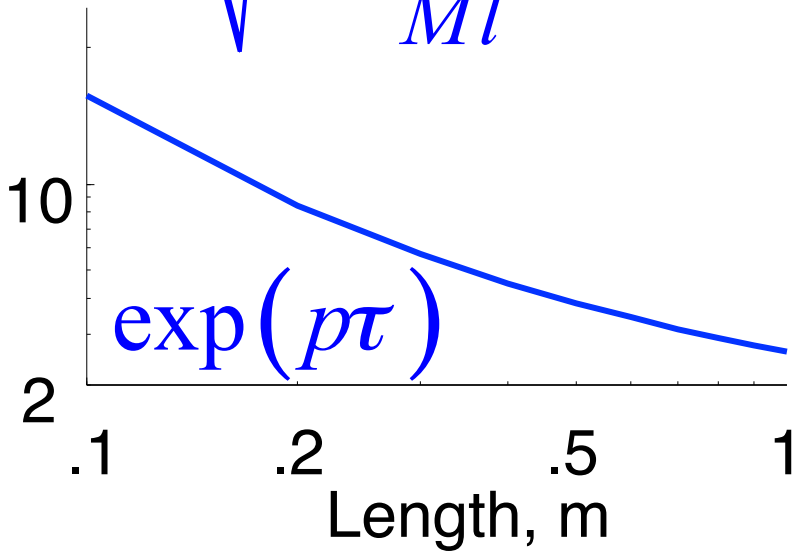


Idealized model

l	*length*
m	*mass*
M	*mass*
g	*gravity*



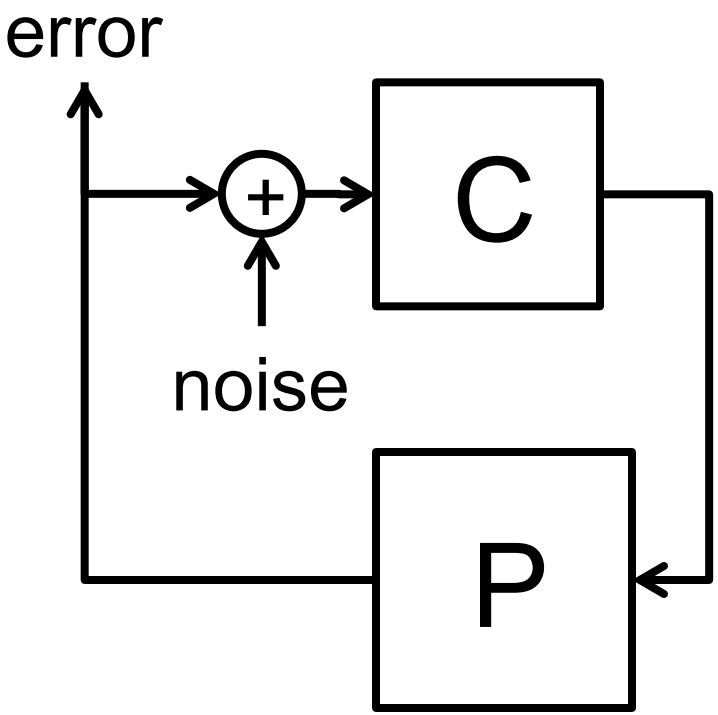
$$p = \sqrt{\frac{(M+m)g}{Ml}}$$

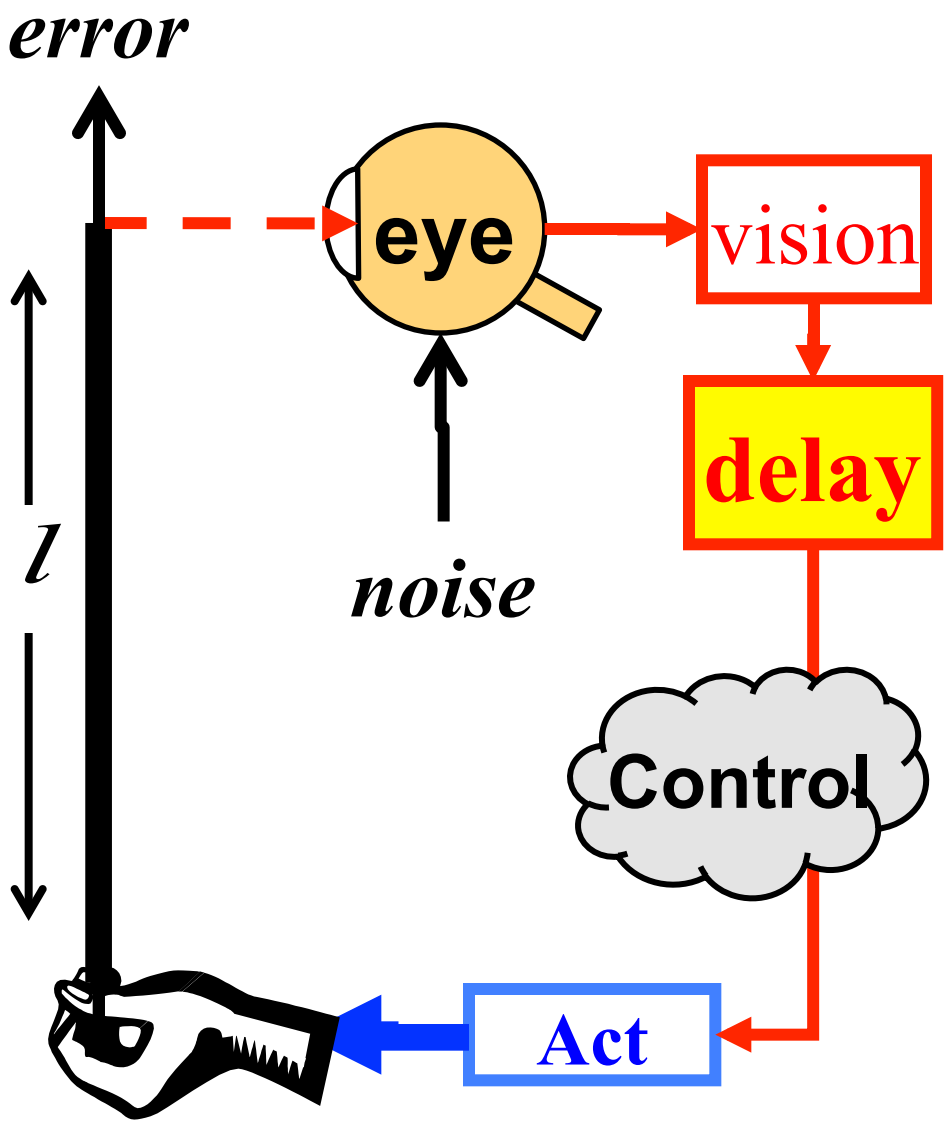


Essential constraint ("law"):

$$\left\{ \exp\left(\int \ln|T| \right) \right\}_{\|T\|_\infty} \geq \exp(p\tau)$$

$$\left|T\left(j\omega\right)\right| = \left|\frac{E}{N}\right|$$

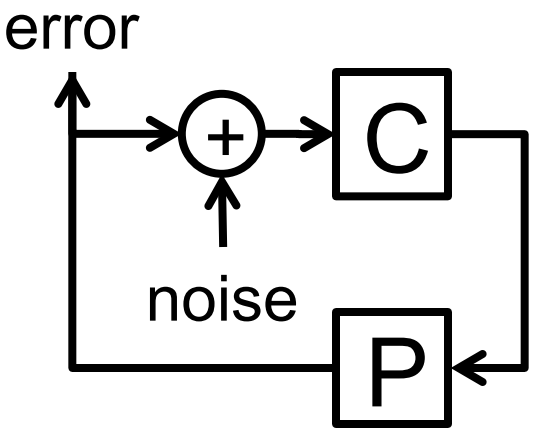




Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$

Max modulus



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

$$\Theta(s) = \exp(-\tau s)$$

$$|T(j\omega)| = \left|\frac{E}{N}\right|$$

$$P(p) = \infty \Rightarrow T(p) = 1$$

$$\Rightarrow M(p) = \Theta(p)^{-1}$$

$$P(s) = P_M(s)\exp(-\tau s) \Rightarrow$$

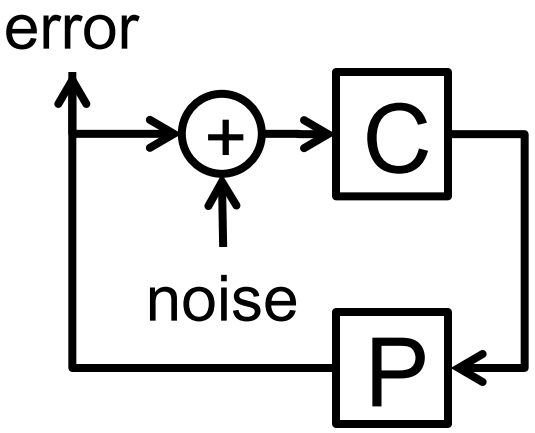
$$\|T\|_\infty = \|M\|_\infty \geq |M(p)| \geq |\Theta(p)^{-1}| \geq \exp(\tau p)$$

$$\Rightarrow \|T\|_\infty \geq \exp(\tau p)$$

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$

Max modulus



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

$$\Theta(s) = \exp(-\tau s)$$

$$|T(j\omega)| = \left|\frac{E}{N}\right|$$

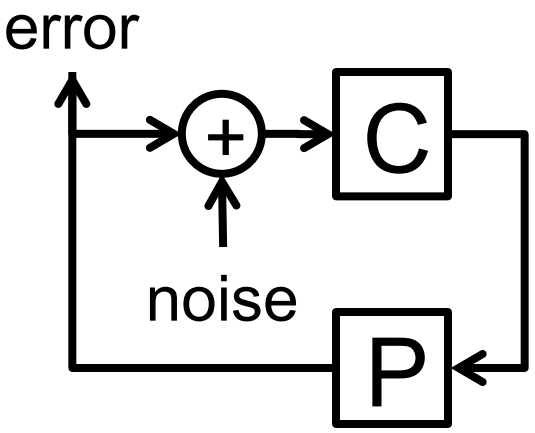
M "minimum phase" (stably invertible)

Θ "all pass"

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$

Max modulus



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

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$$|T(j\omega)| = \left|\frac{E}{N}\right|$$

$$P(p) = \infty \Rightarrow T(p) = 1$$

$$\Rightarrow M(p) = \Theta(p)^{-1}$$

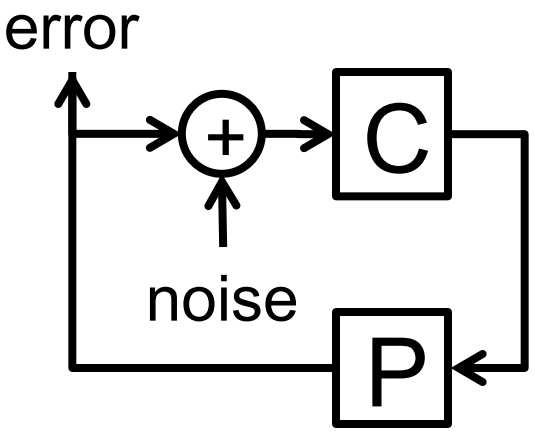
$$T = \frac{PC}{1 + PC}$$

$$\text{so } P(p) = \infty \Rightarrow T(p) = 1$$

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$

Max modulus



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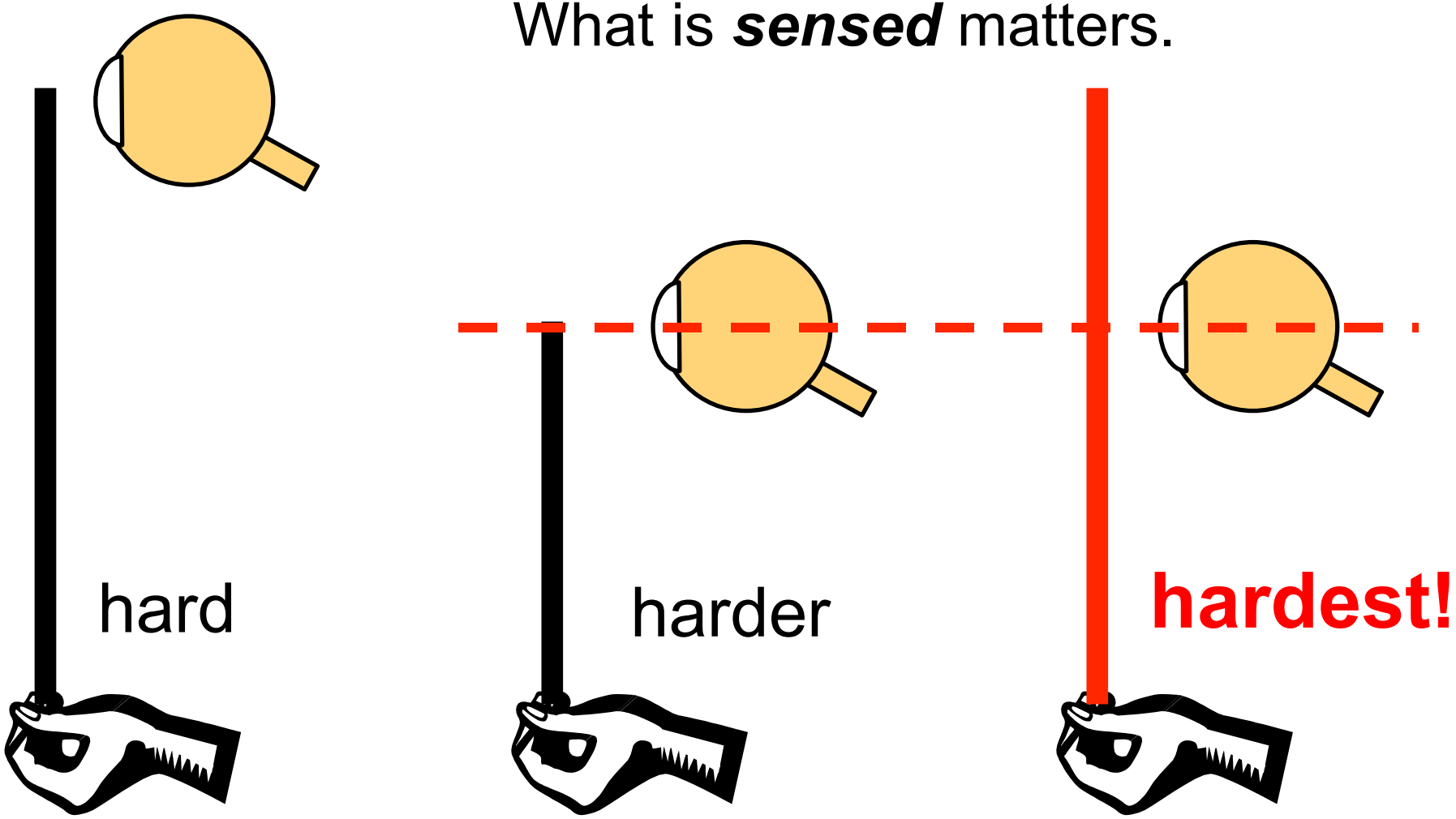
$$\|T\|_\infty = \|M\|_\infty \geq |M(p)| \geq |\Theta(p)^{-1}| \geq \exp(\tau p)$$

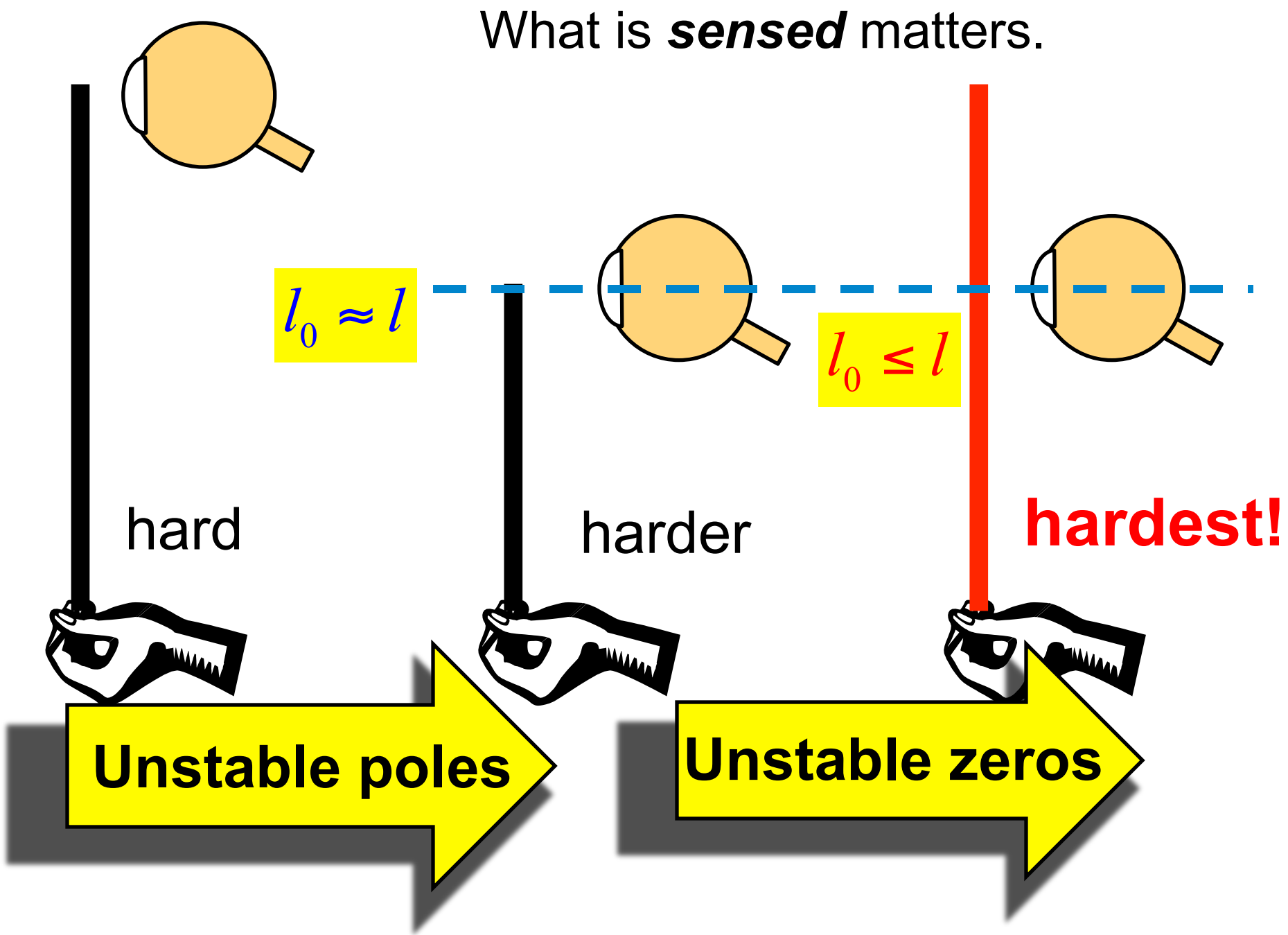
$$\Rightarrow \|T\|_\infty \geq \exp(\tau p)$$

What is ***sensed*** matters.



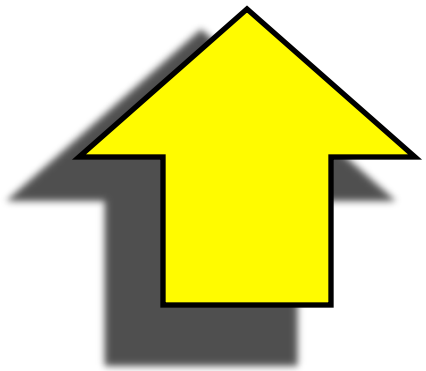
Why?

Easy to ***prove*** using simple models.


What is *sensed* matters.
$l_0 \approx l$
$l_0 \leq l$
hard
harder
hardest!
Unstable poles
Unstable zeros

Fragility two ways (Bode* and Zames):

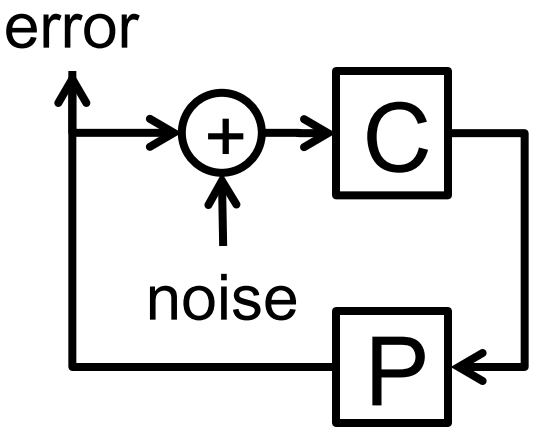
$$\left.\begin{matrix} \exp\left(\int \ln|T|\right) \\ \|T\|_\infty \end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$



Unstable zeros

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

$$\Theta(s) = \exp(-\tau s)\frac{s-z}{s+z}$$

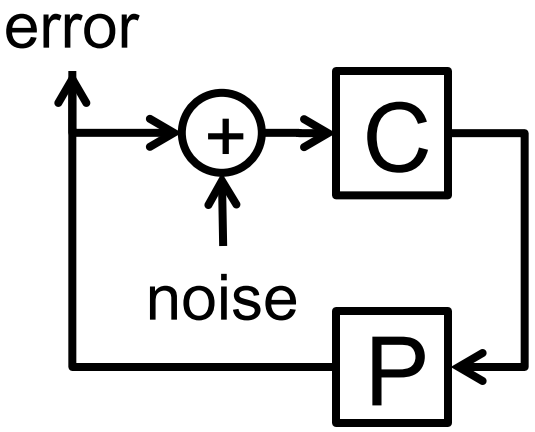
$$P(s) = P_M(s)\left[\exp(-\tau s)\frac{s-z}{s+z}\right] \Rightarrow$$

$$\|T\|_\infty = \|M\|_\infty \geq |M(p)| \geq \left|\Theta(p)^{-1}\right| \geq \exp(\tau p)\left|\frac{z+p}{z-p}\right|$$

$$\Rightarrow \|T\|_\infty \geq \exp(\tau p)\left|\frac{z+p}{z-p}\right|$$

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

$$\Theta(s) = \exp(-\tau s)\frac{s - z}{s + z}$$

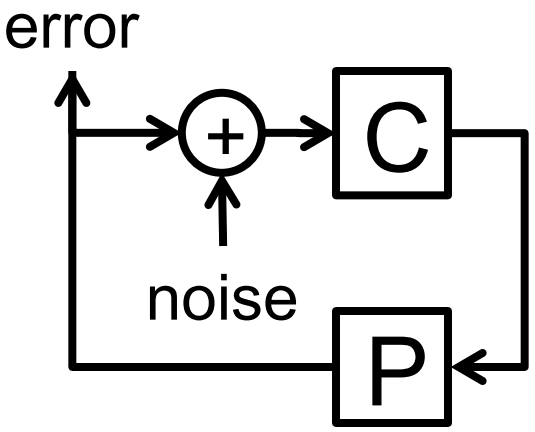
$$T = \frac{PC}{1 + PC}$$

$$\text{so } P(p) = \infty \Rightarrow T(p) = 1$$

$$\& \;\; P(z) = 0 \Rightarrow T(z) = 0$$

Proof?

$$\|T\|_\infty = \sup_\omega |T(j\omega)| = \sup \{ |T(s)| \mid \mathrm{Re}(s) \geq 0 \}$$



$$T(s) = M(s)\Theta(s) \quad |\Theta(j\omega)| = 1$$

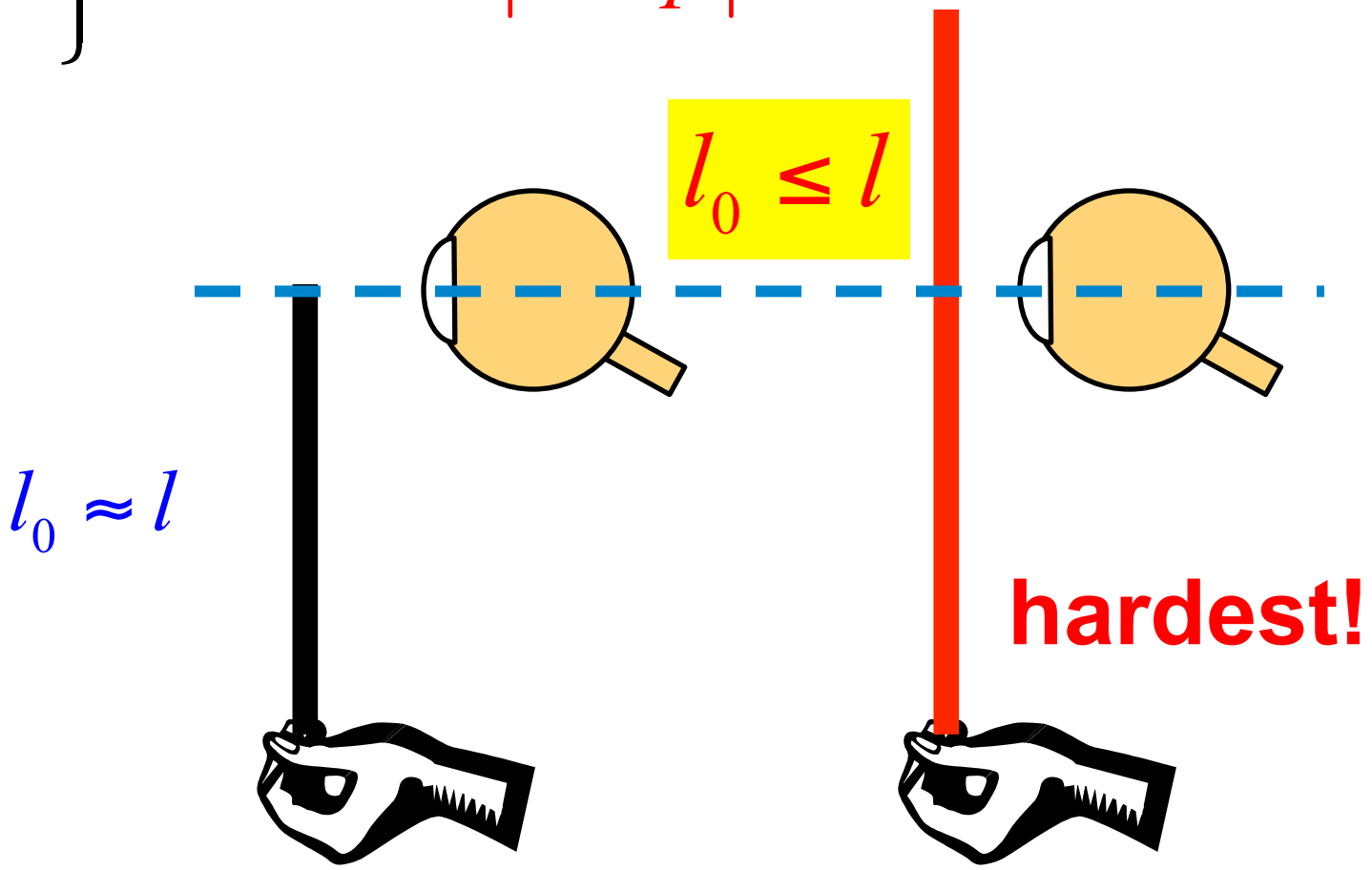
$$\Theta(s) = \exp(-\tau s)\frac{s-z}{s+z}$$

$$P(s) = P_M(s)\left[\exp(-\tau s)\frac{s-z}{s+z}\right] \Rightarrow$$

$$\|T\|_\infty = \|M\|_\infty \geq |M(p)| \geq \left|\Theta(p)^{-1}\right| \geq \exp(\tau p)\left|\frac{z+p}{z-p}\right|$$

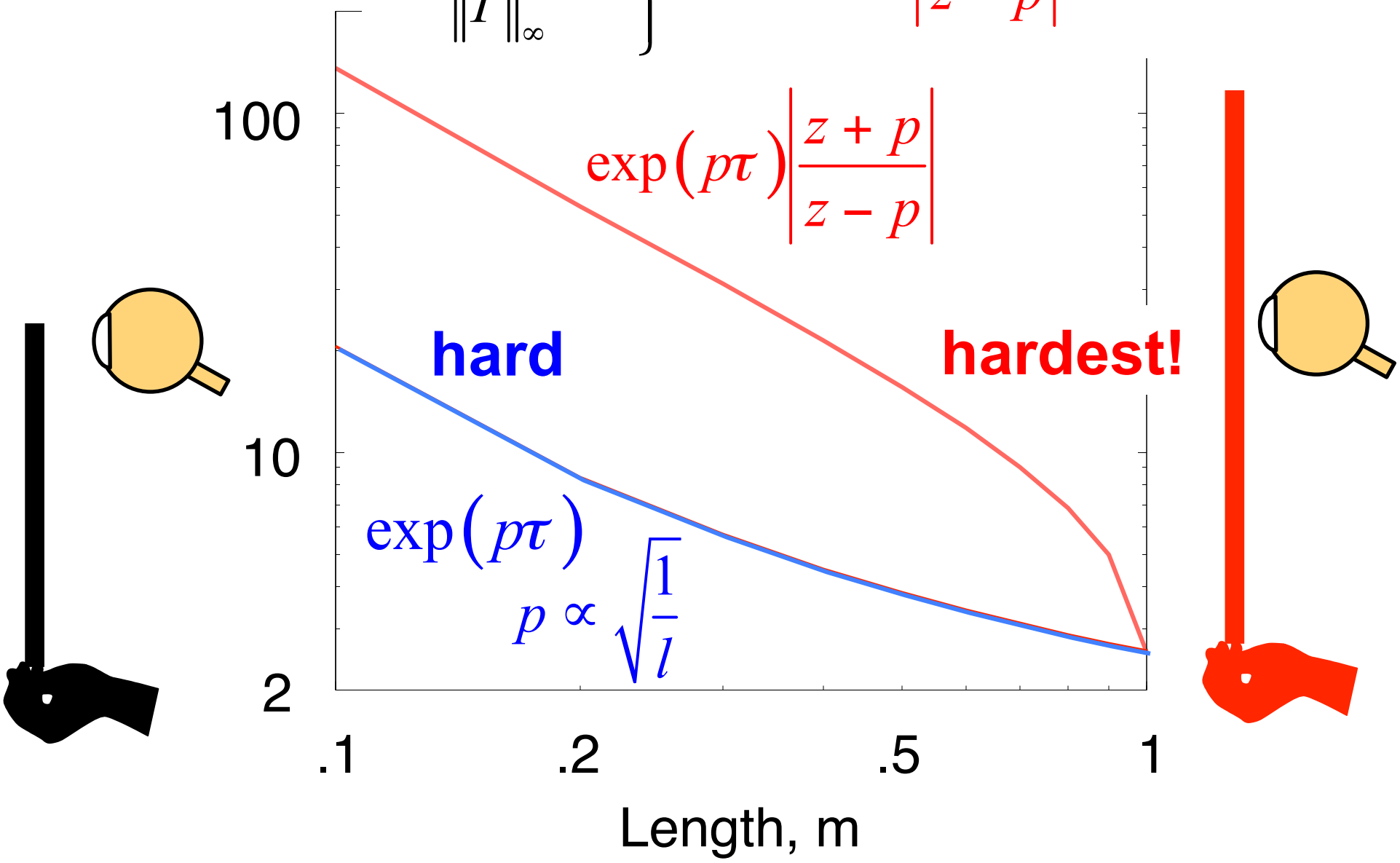
$$\Rightarrow \|T\|_\infty \geq \exp(\tau p)\left|\frac{z+p}{z-p}\right|$$

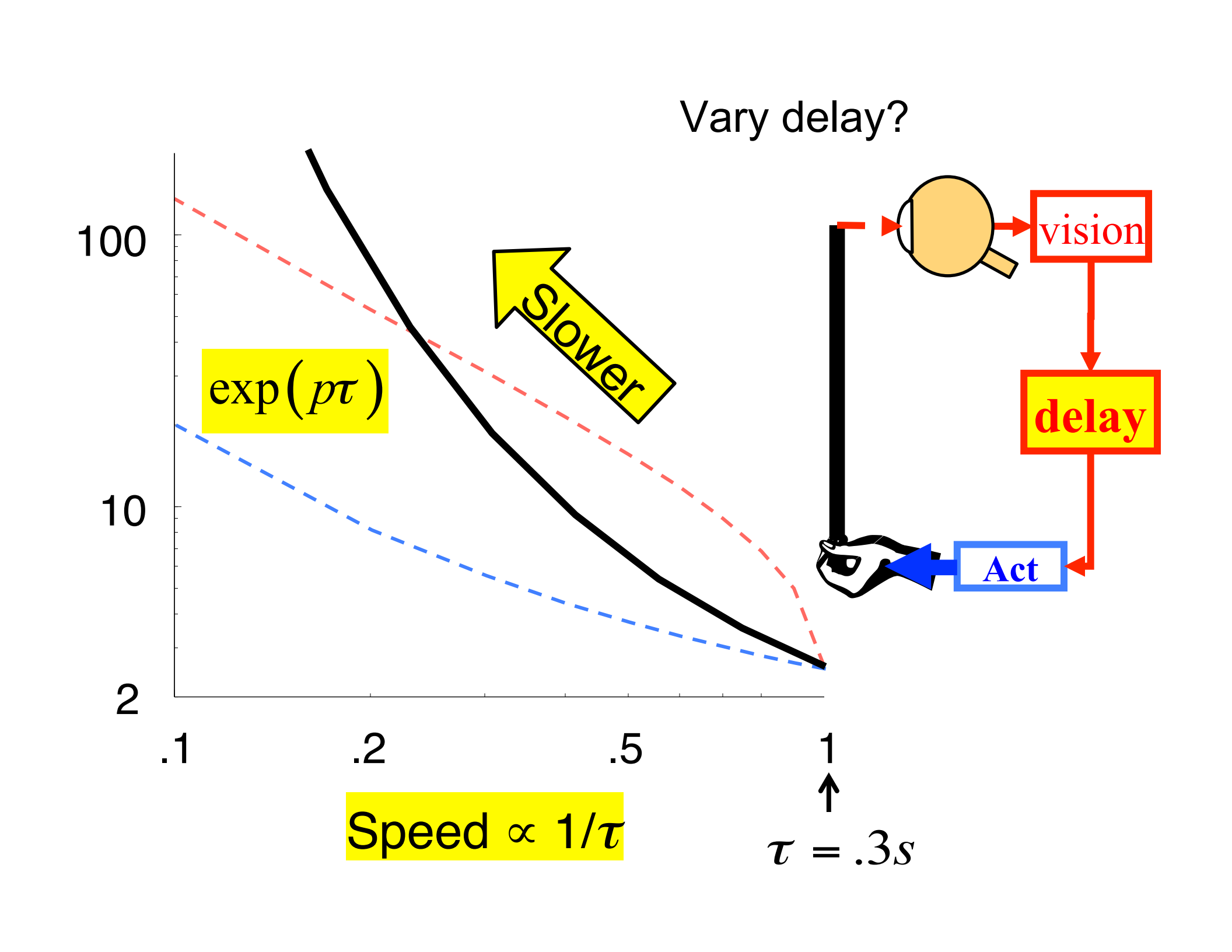
$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_\infty\end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right| \geq \exp(p\tau)$$



$\tau = .3s$

$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_\infty\end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right| \geq \exp(p\tau)$$

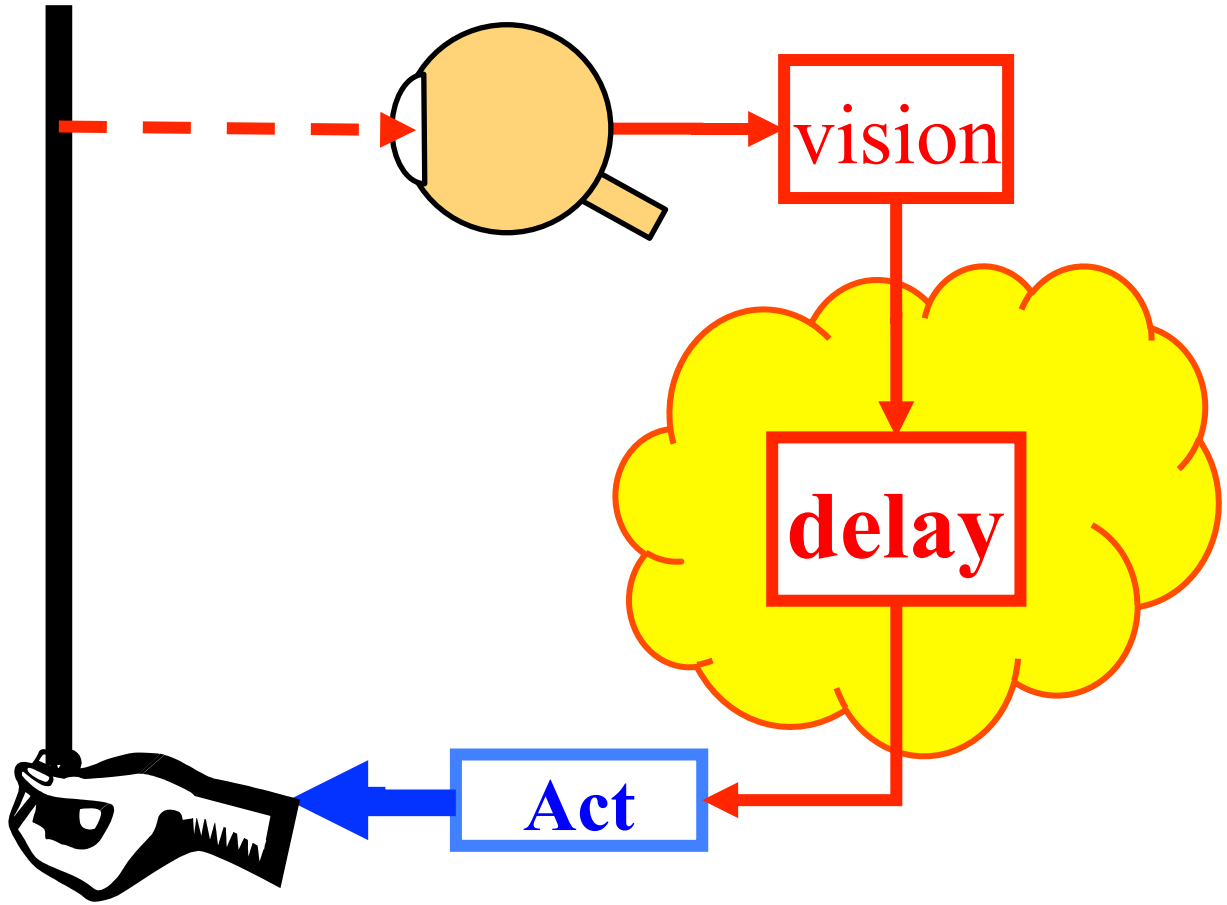


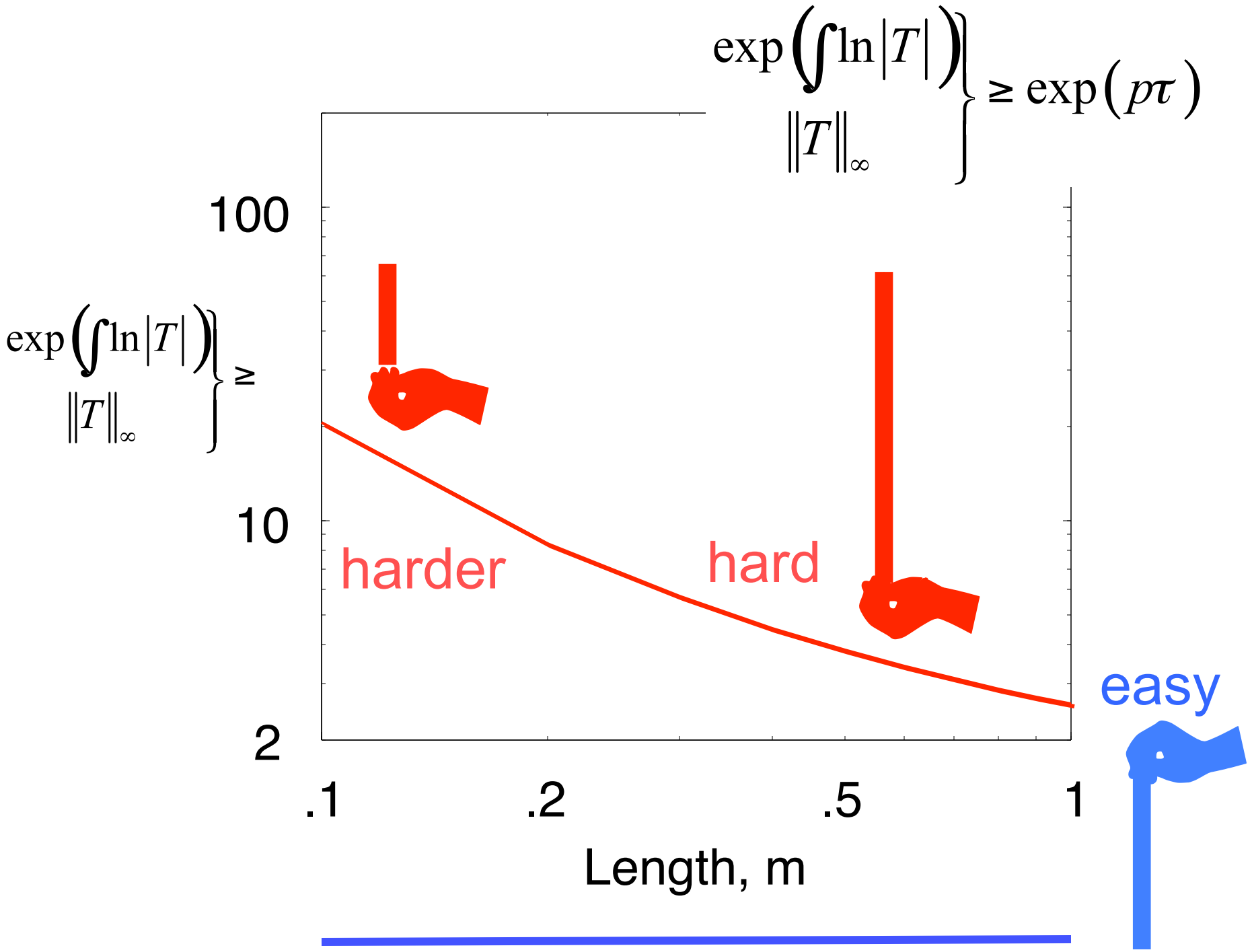

Vary delay?
100
10
2
.1
.2
.5
1
$\exp(p\tau)$
Slower
vision
delay
Act
Speed $\propto 1/\tau$
$\tau = .3s$

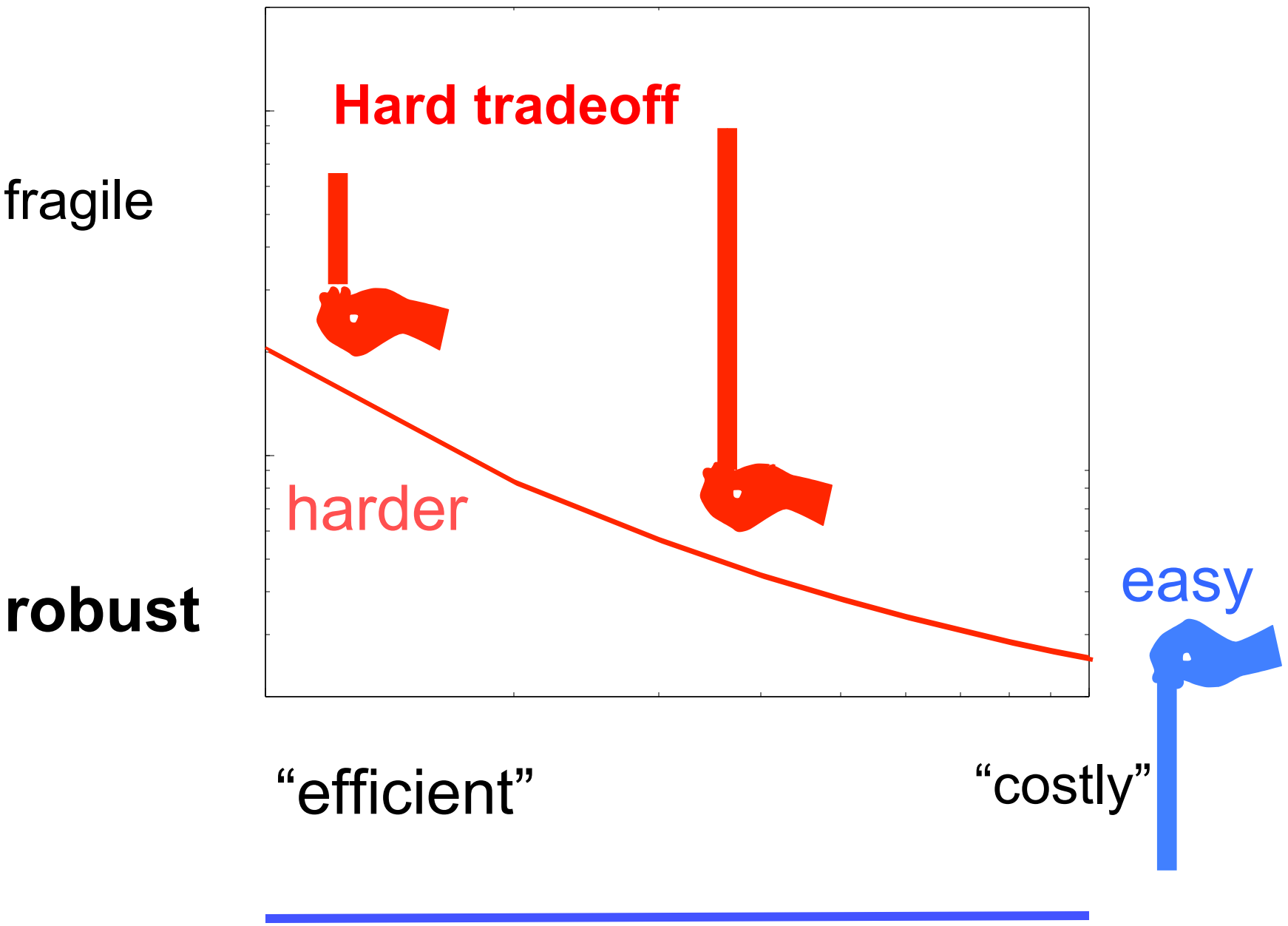
Holds for *all* controllers.

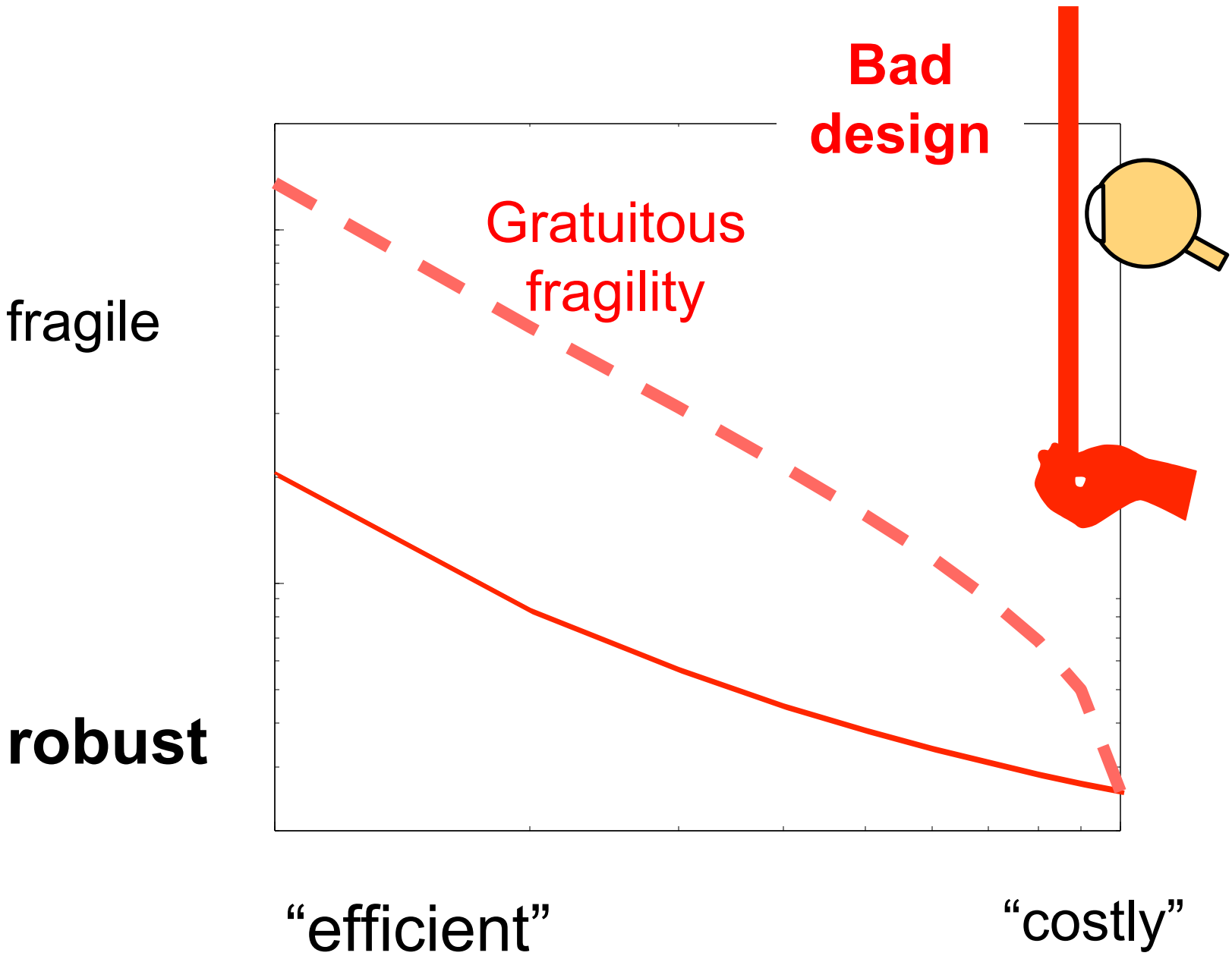
$$\|T\|_\infty \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$

A "law" about *intrinsic* problem difficulty (a la Turing).




$\exp\left(\int \ln|T|\right)$
$\|T\|_\infty$
≥ exp(pτ)
100
10
2
.1
.2
.5
1
Length, m
harder
hard
easy

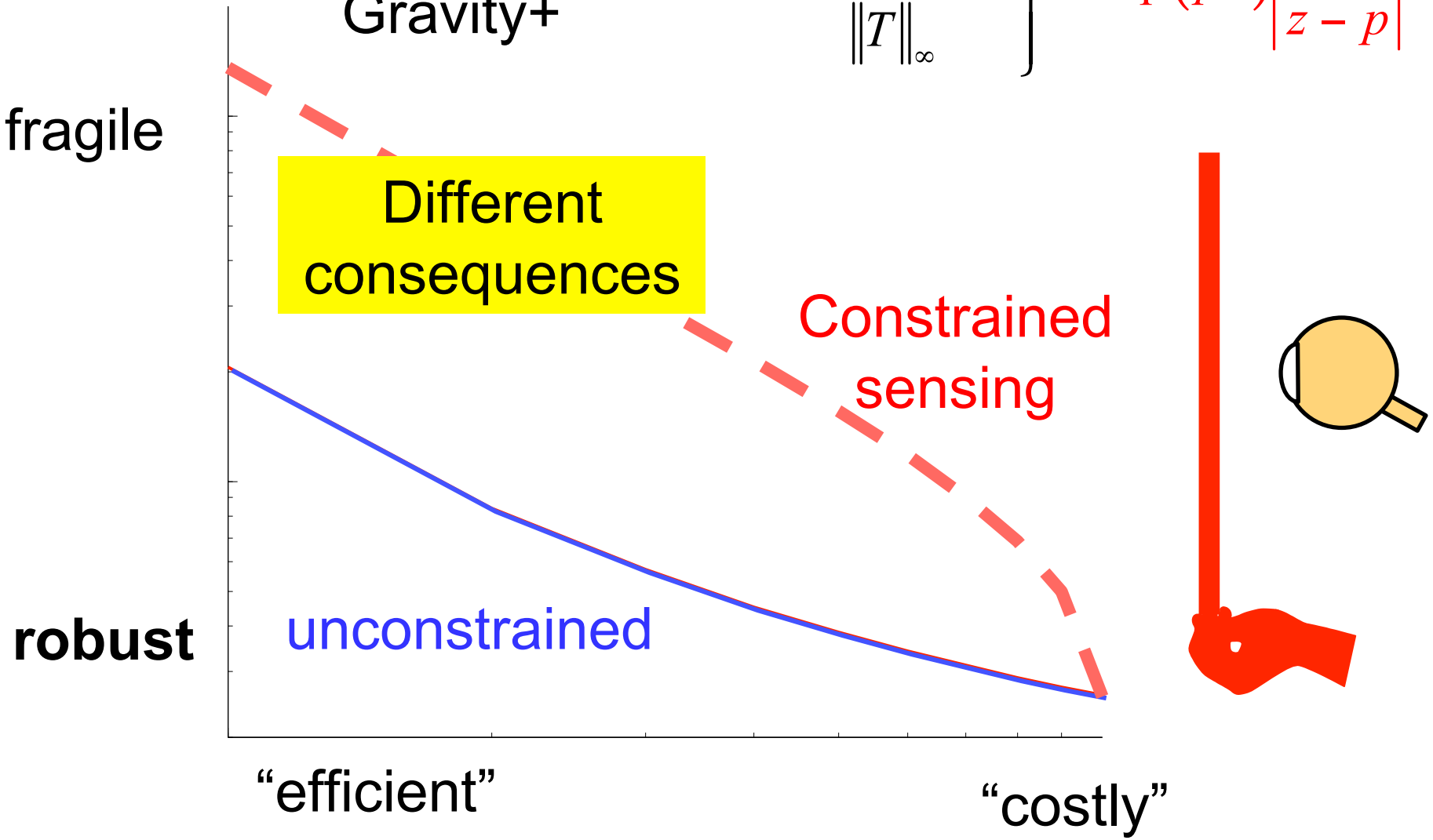

Hard tradeoff
fragile
harder
robust
easy
“efficient”
“costly”

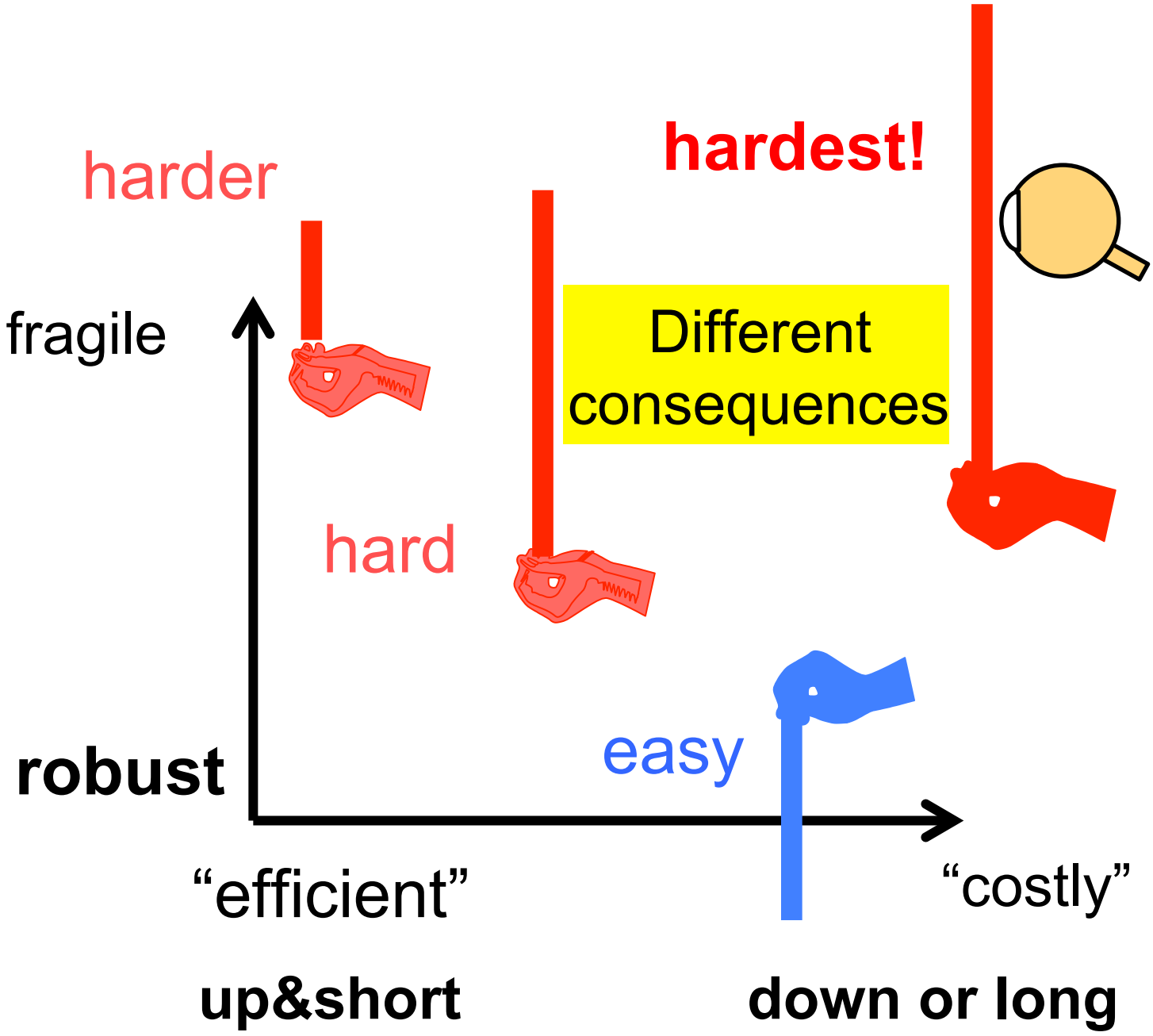

Bad design
Gratuitous fragility
fragile
robust
“efficient”
“costly”

The nature of “laws”

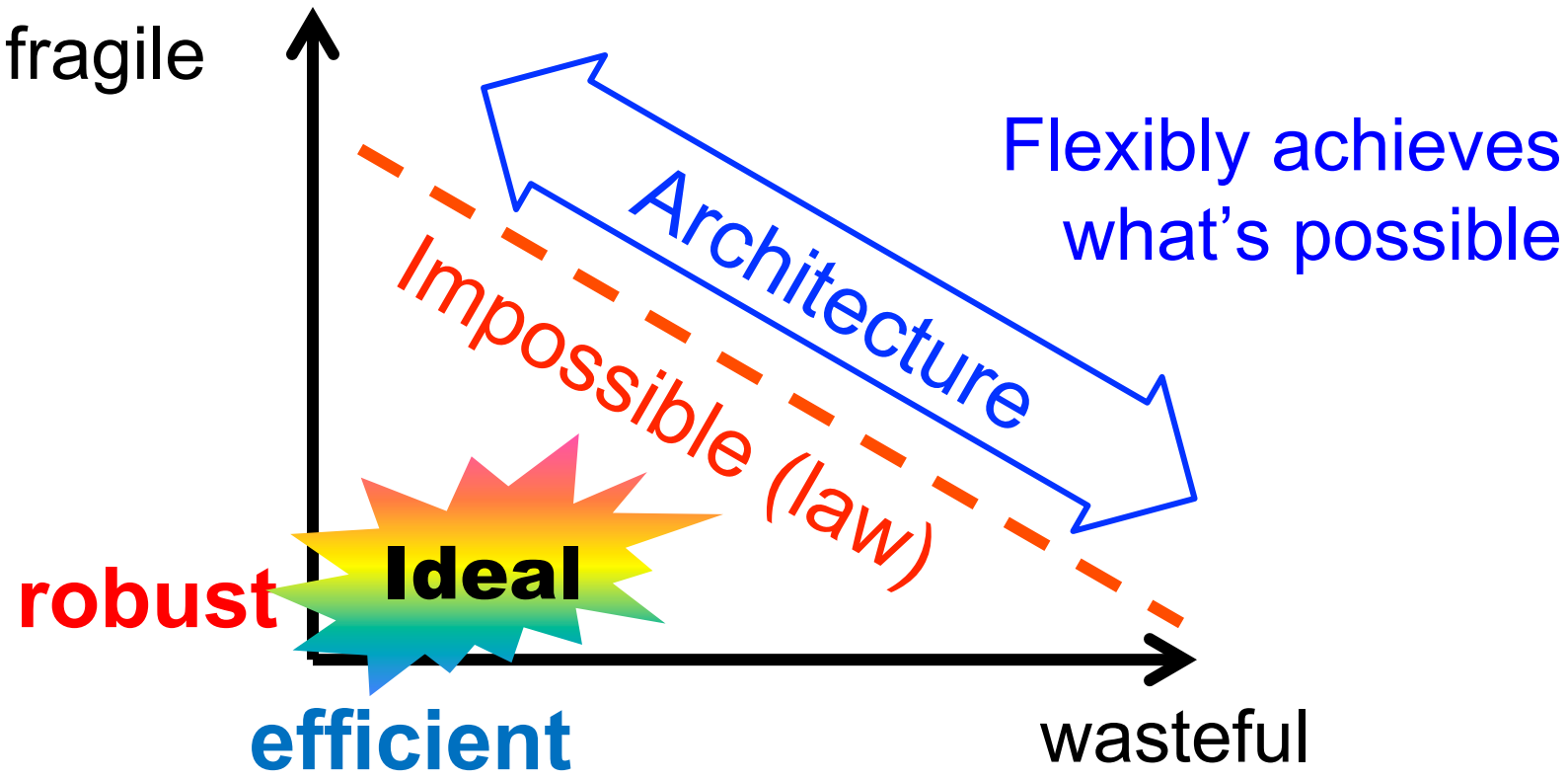
Same constraints:
Mechanics+
Gravity+

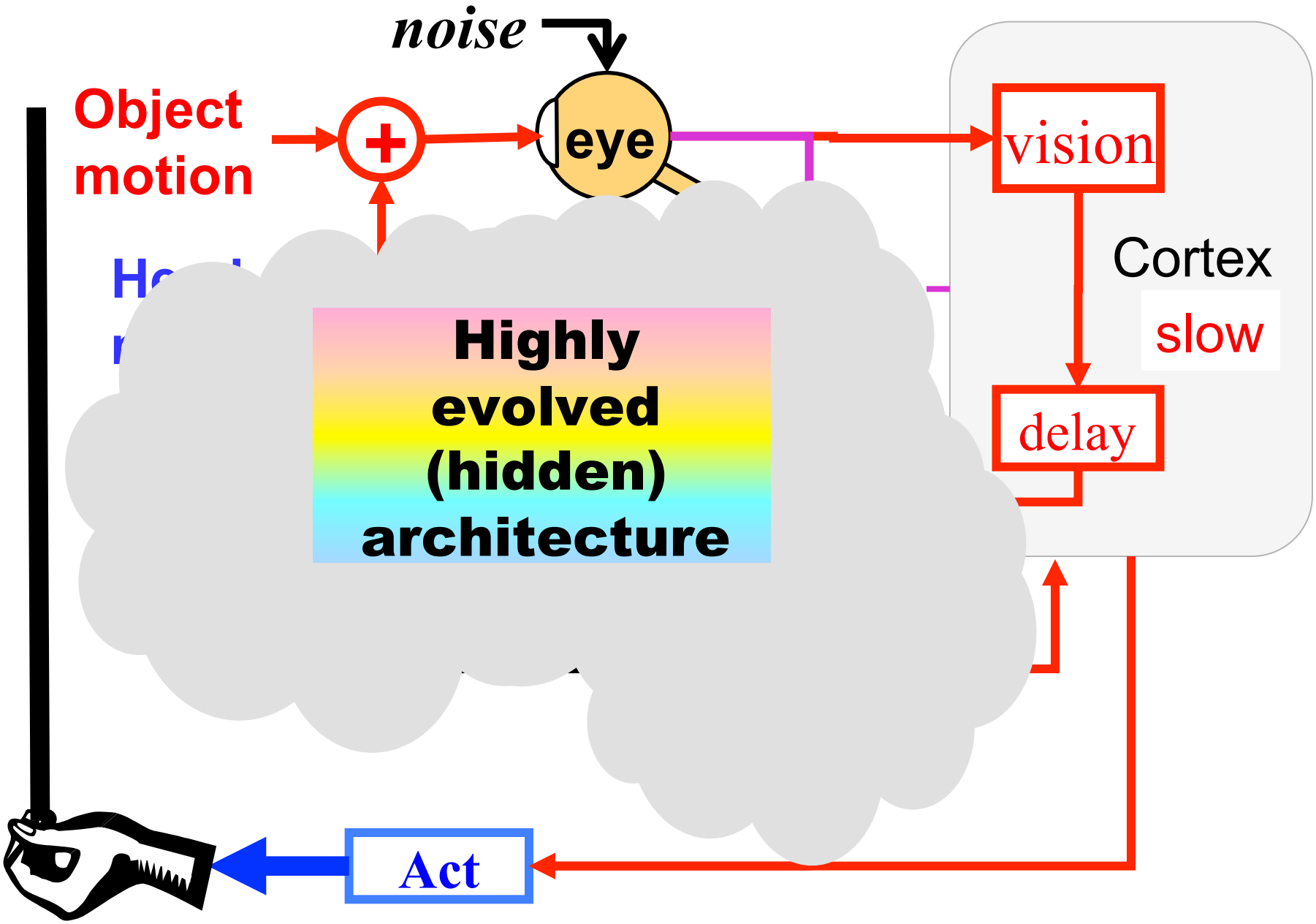
$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_\infty\end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$



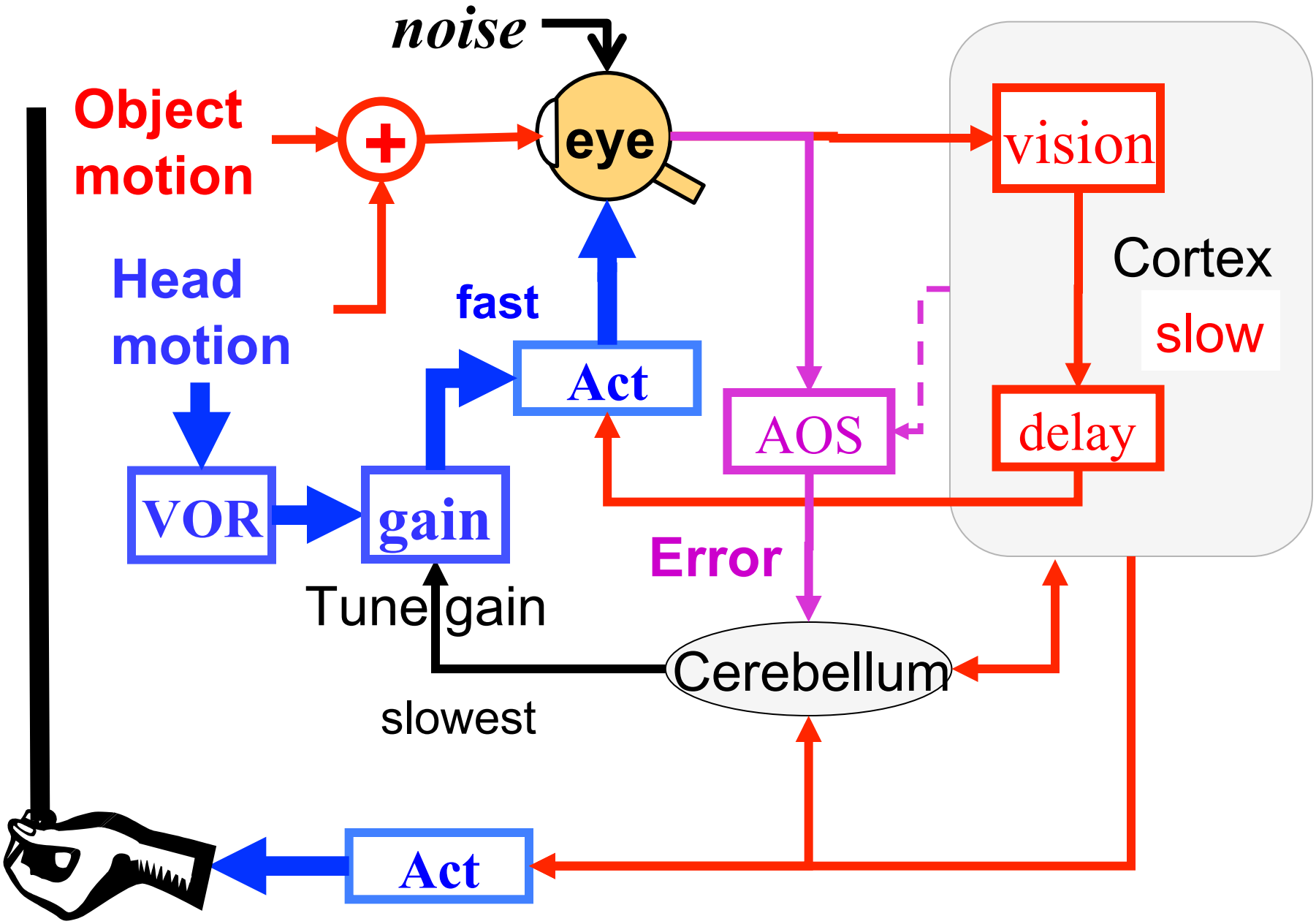

harder
hardest!
fragile
Different consequences
hard
easy
robust
“efficient”
“costly”
up&short
down or long

Universal laws and architectures

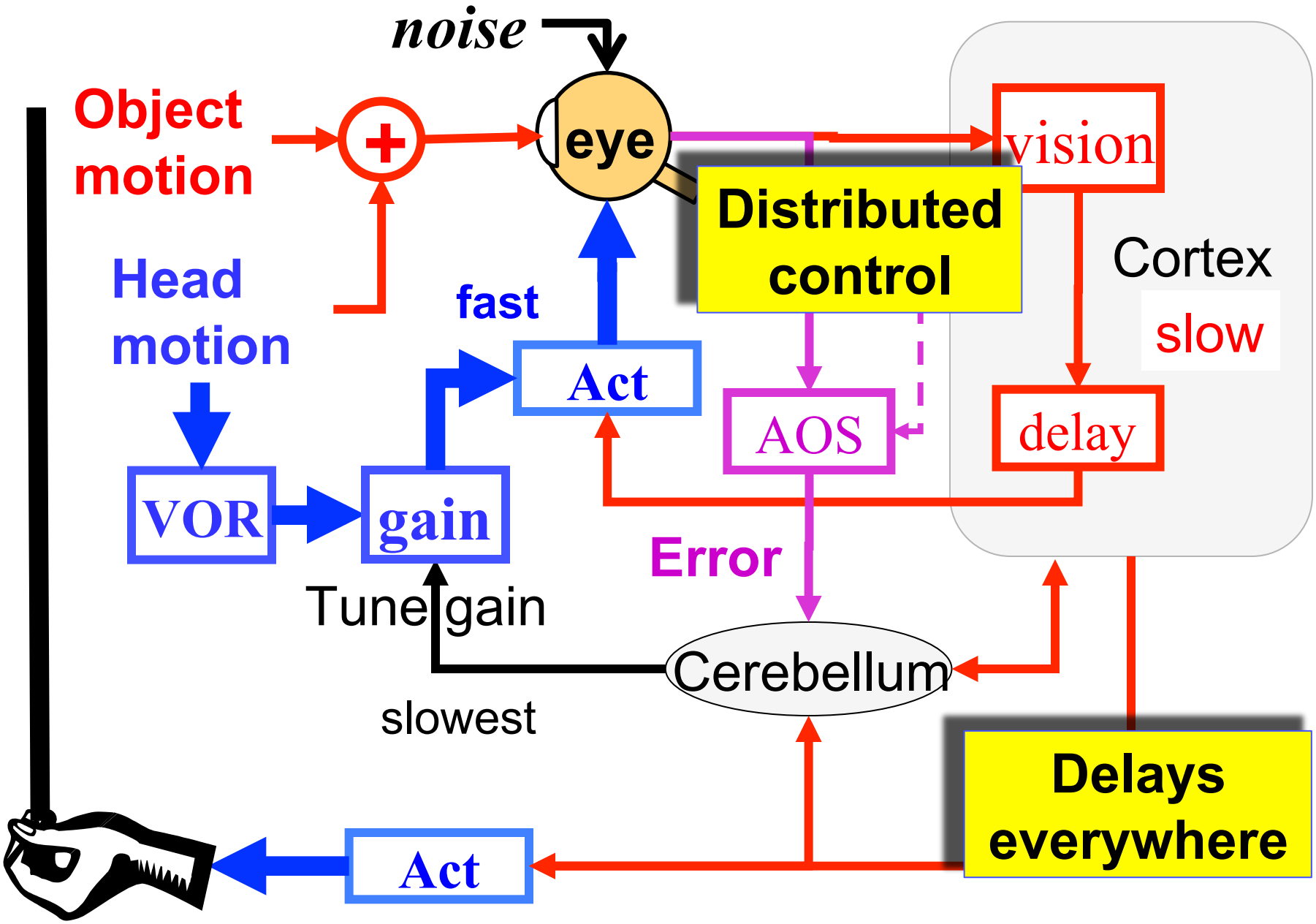




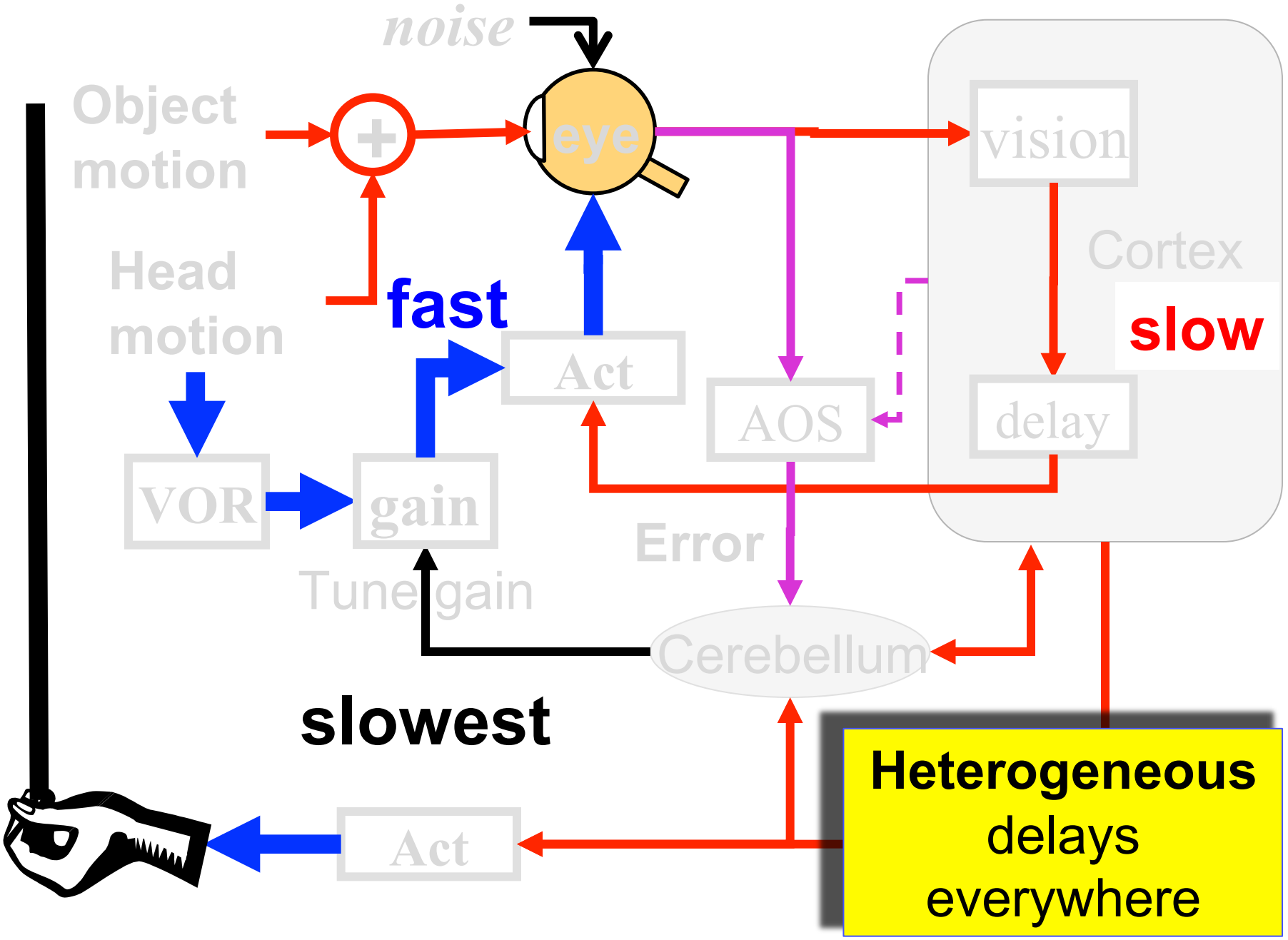
AOS = Accessory Optical system



AOS = Accessory Optical system



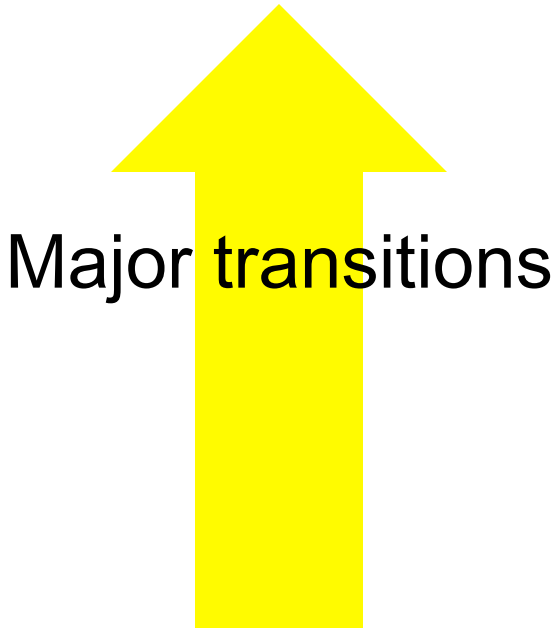
AOS = Accessory Optical system


noise
Object motion
eye
vision
Head motion
fast
Cortex
slow
Act
AOS
delay
VOR
gain
Error
Tune gain
Cerebellum
slowest
Act
Heterogeneous delays everywhere

Efficiency/instability/layers/feedback

How universal? Very.

- Sustainable infrastructure? (e.g. smartgrids)
- Money/finance/lobbyists/etc
- Industrialization
- Society/agriculture/weapons/etc
- Bipedalism
- Maternal care
- Warm blood
- Flight
- Mitochondria
- Oxygen
- Translation (ribosomes)
- **Glycolysis (2011 *Science*)**



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.

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

Chandra, Buzi, and Doyle

Insight
Accessible
Verifiable

Science
AAAS

Glycolytic oscillations

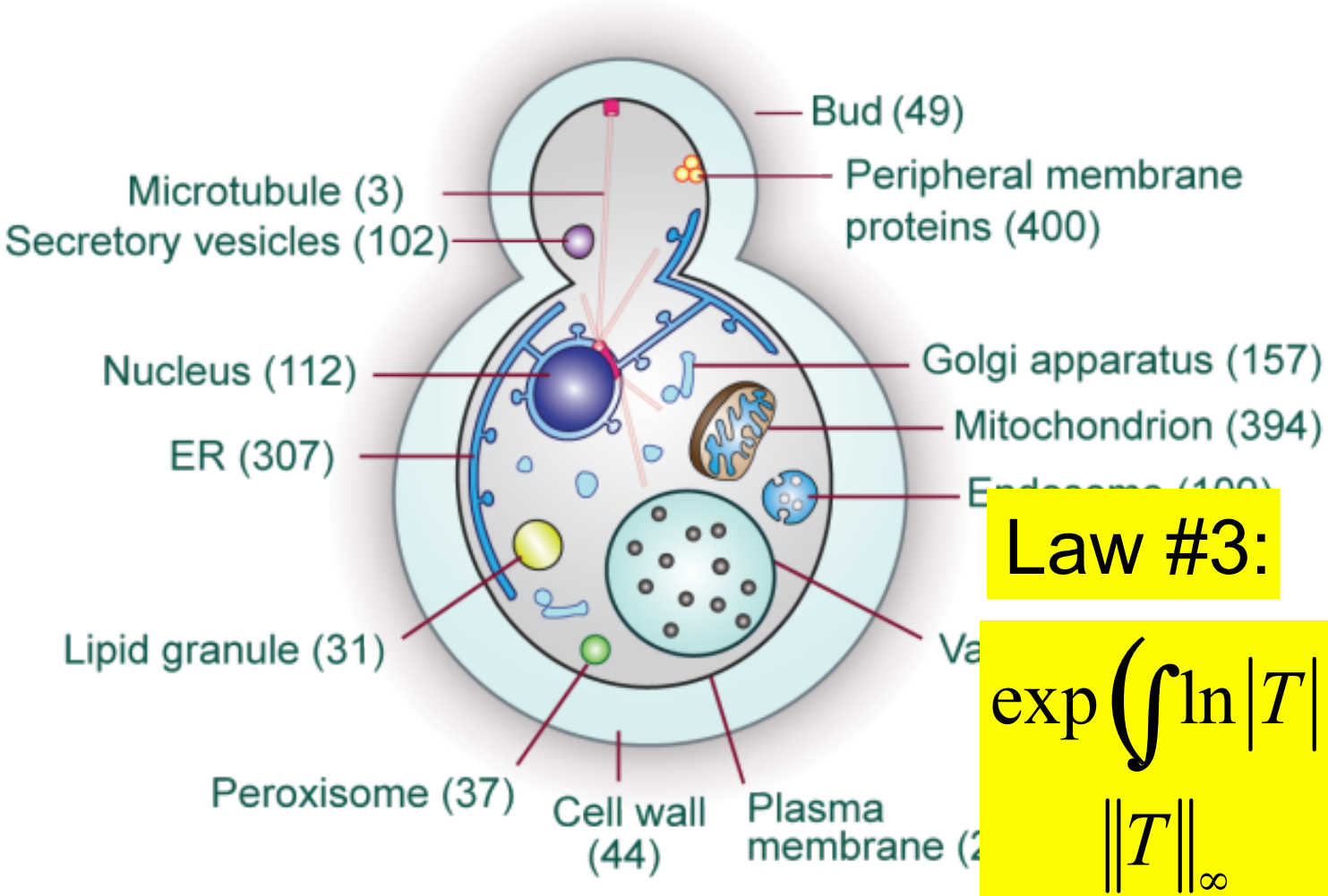
- Exhaustively studied
  - –Extensive experiments and data
  - –Detailed models and simulations
  - –Great! But all just deepen the mystery
- Perfectly illustrates “conservation law”
- Without which? Bewilderment.

$$\exp\left(\int_{\|T\|_\infty} \ln|T|\right) \geq \left|\frac{z+p}{z-p}\right|$$

Law #1 : Chemistry (vs mechanics)

Law #2 : Autocatalysis (vs gravity)

(→ RHP *p* and *z*)



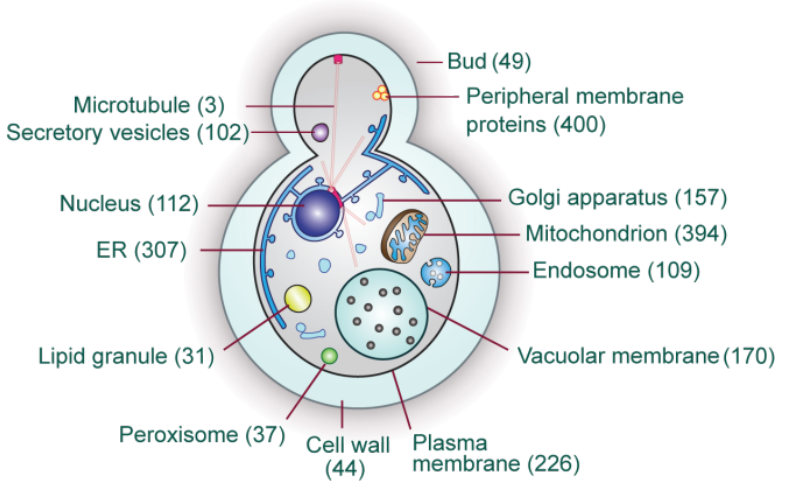
Law #3:

$$\exp\left\{\frac{\int \ln|T|}{\|T\|_\infty}\right\} \geq \left|\frac{z+p}{z-p}\right|$$

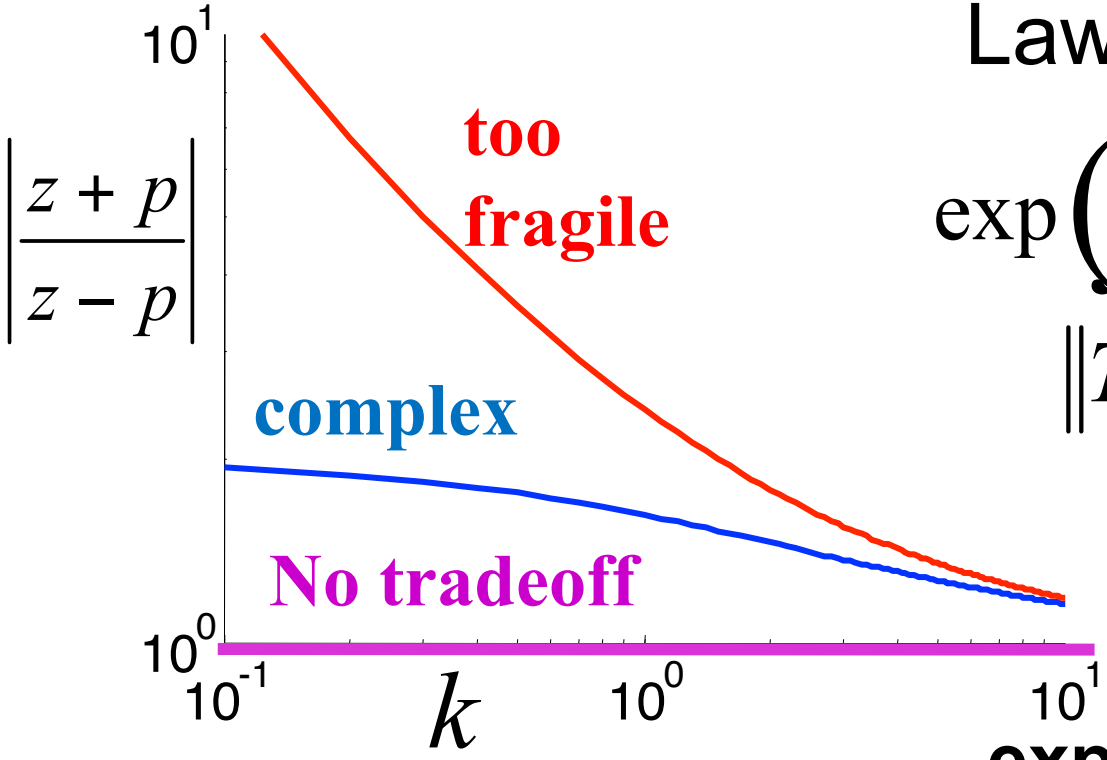
Law #1 : Chemistry

Law #2 : Autocatalysis

(→ RHP *p* and *z*)



fragile



expensive

Law #3:

$$\exp\left\{\int \ln|T| \Big/ \|T\|_\infty\right\} \geq \left|\frac{z+p}{z-p}\right|$$

Robust Efficiency in Energy Supply

fragile

Robust to Δ in supply and demand

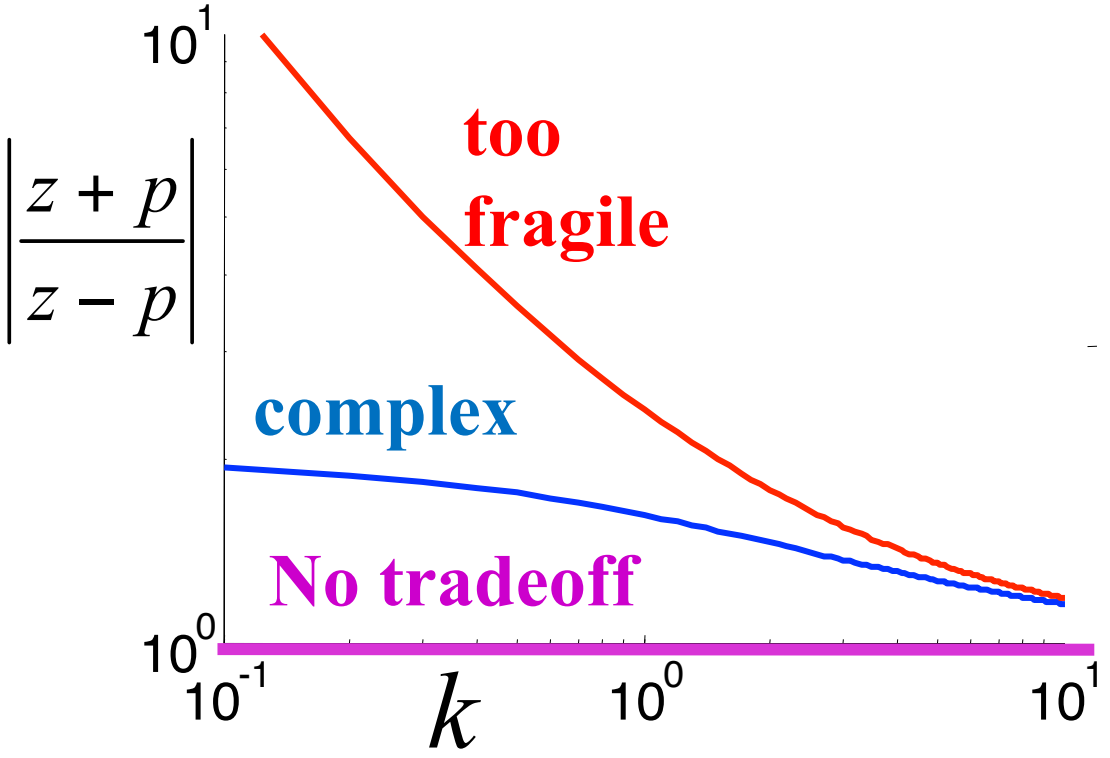
Metabolic overhead to make enzymes

Robust Efficiency in Energy Supply

$$\left.\begin{matrix} \exp\left(\int \ln|T|\right) \\ \|T\|_\infty \end{matrix}\right\} \geq \left|\frac{z+p}{z-p}\right|$$

fragile

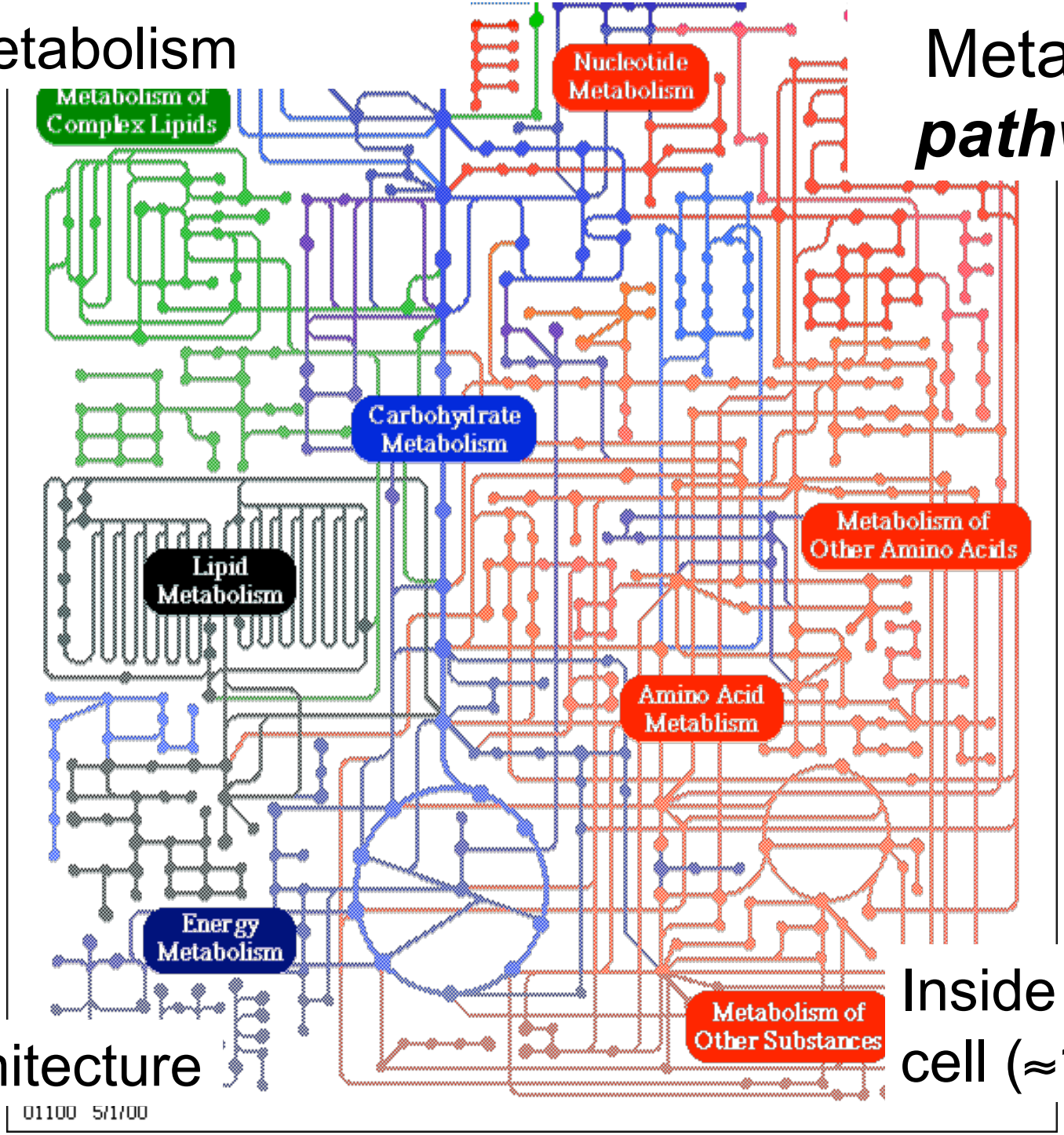
Robust to Δ in supply and demand



Metabolic overhead to make enzymes

Core metabolism

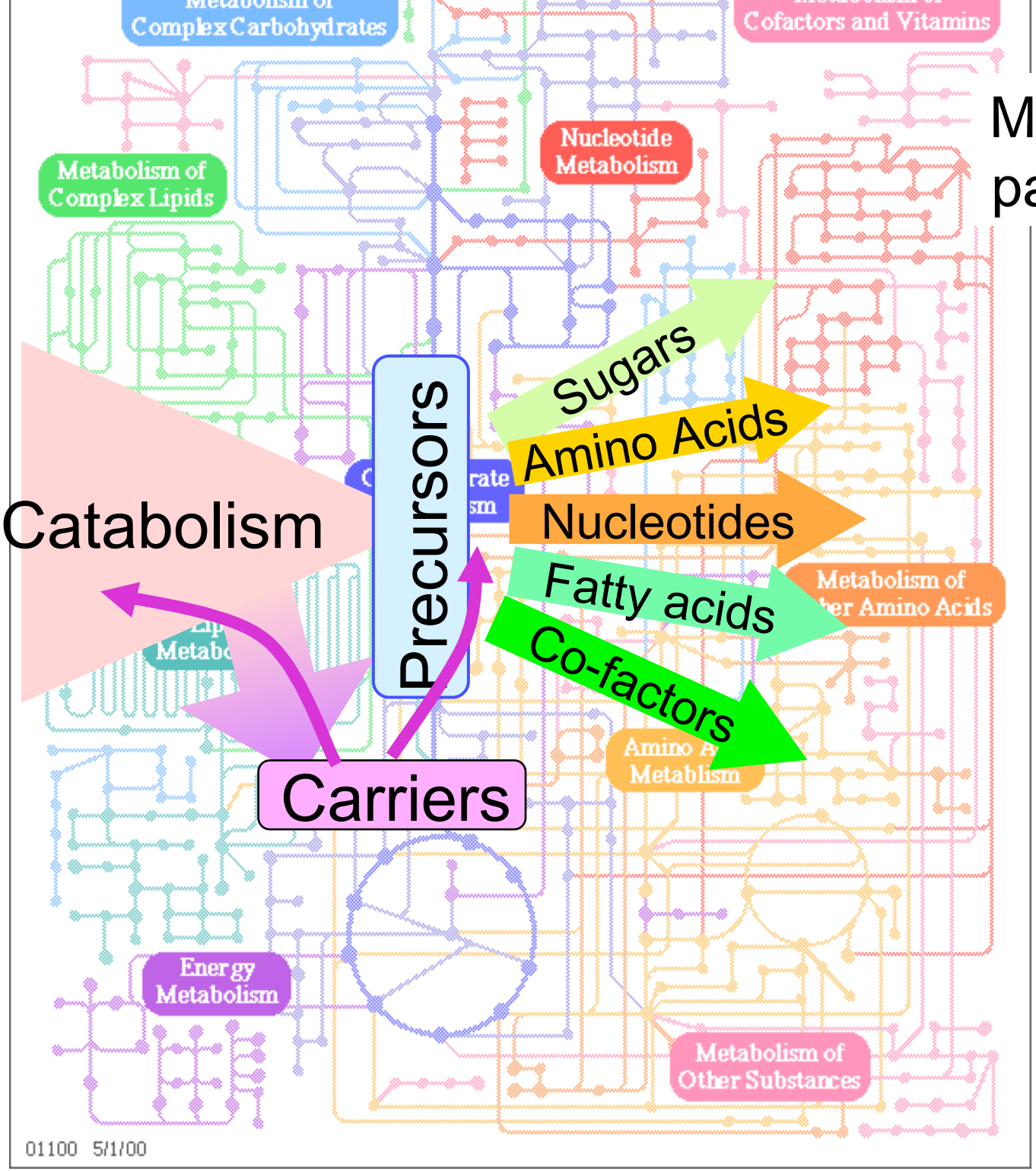
Metabolic ***pathways***

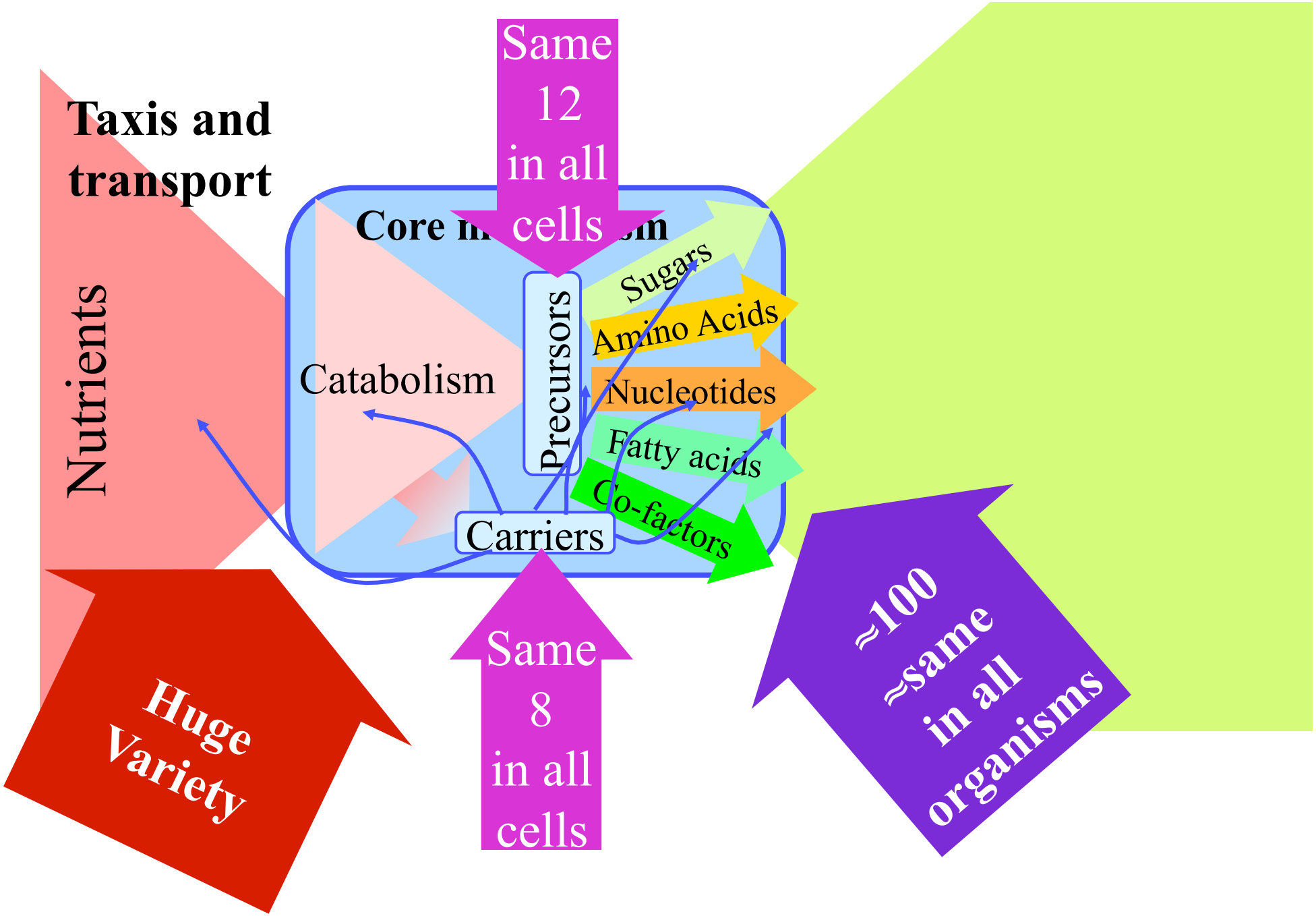


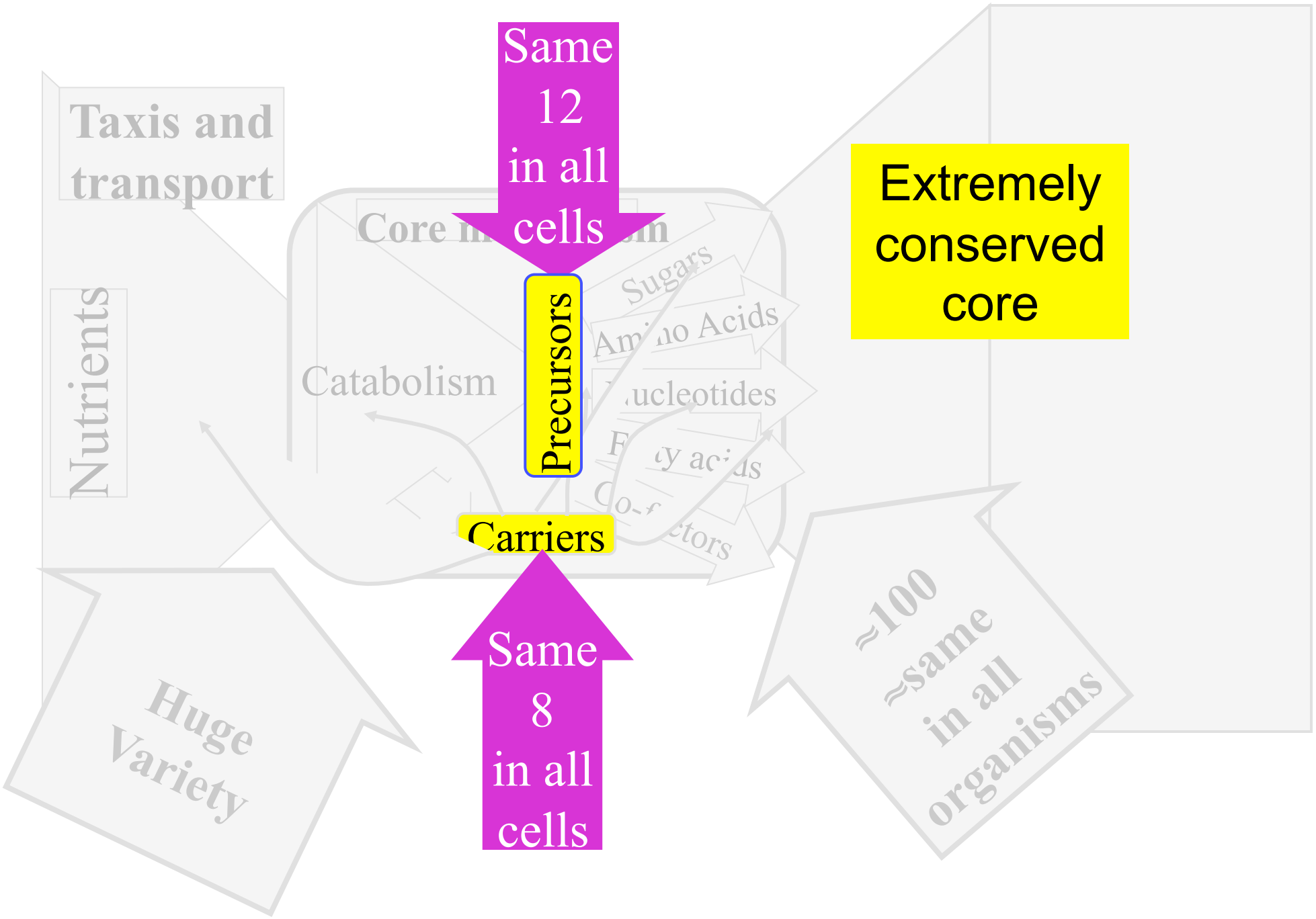
No architecture

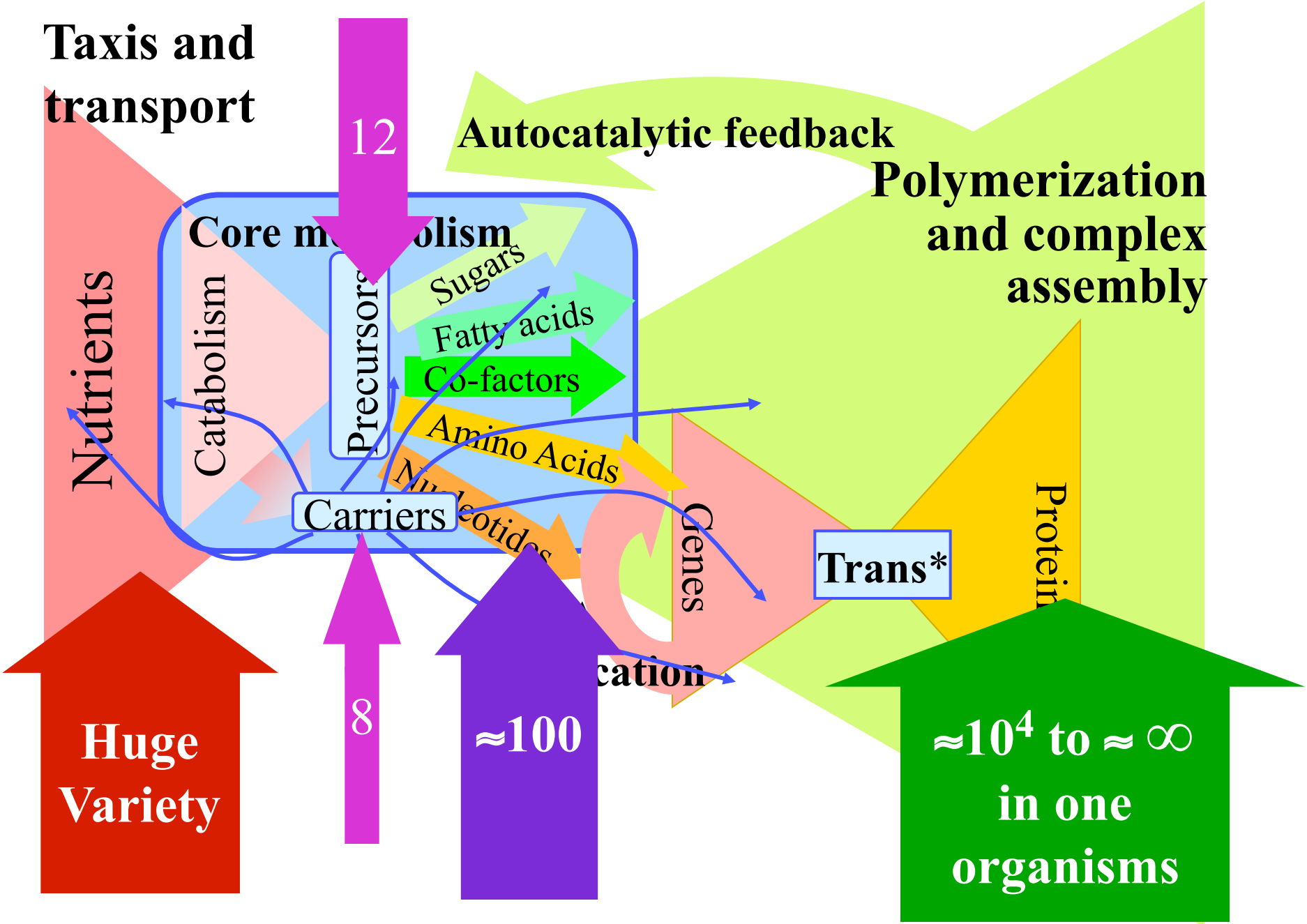
Inside every cell ($\approx 10^{30}$)

Metabolic pathways

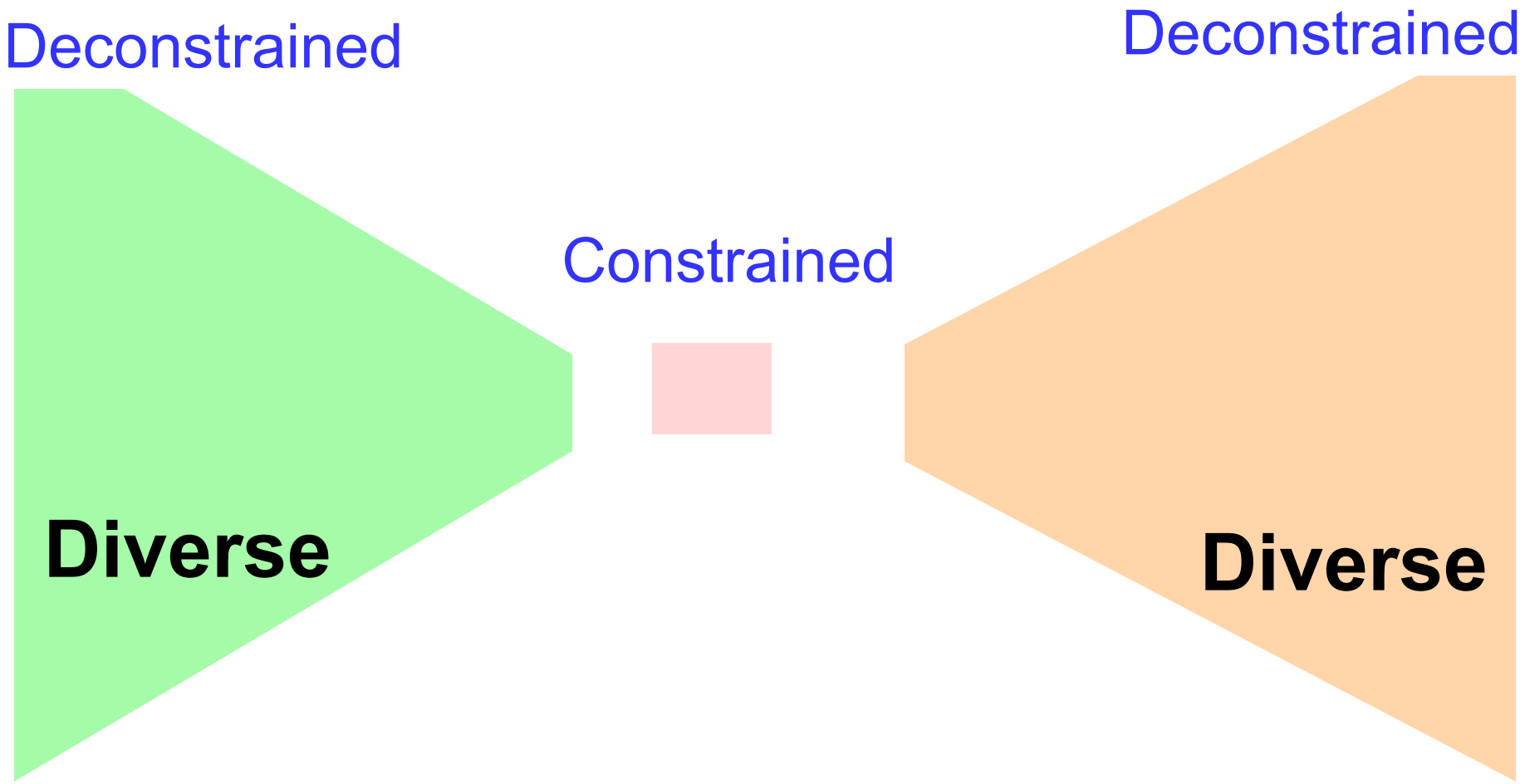



Taxis and transport
Nutrients
Same 12 in all cells
Core
Catabolism
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Carriers
Same 8 in all cells
Huge Variety
≈100 ≈same in all organisms

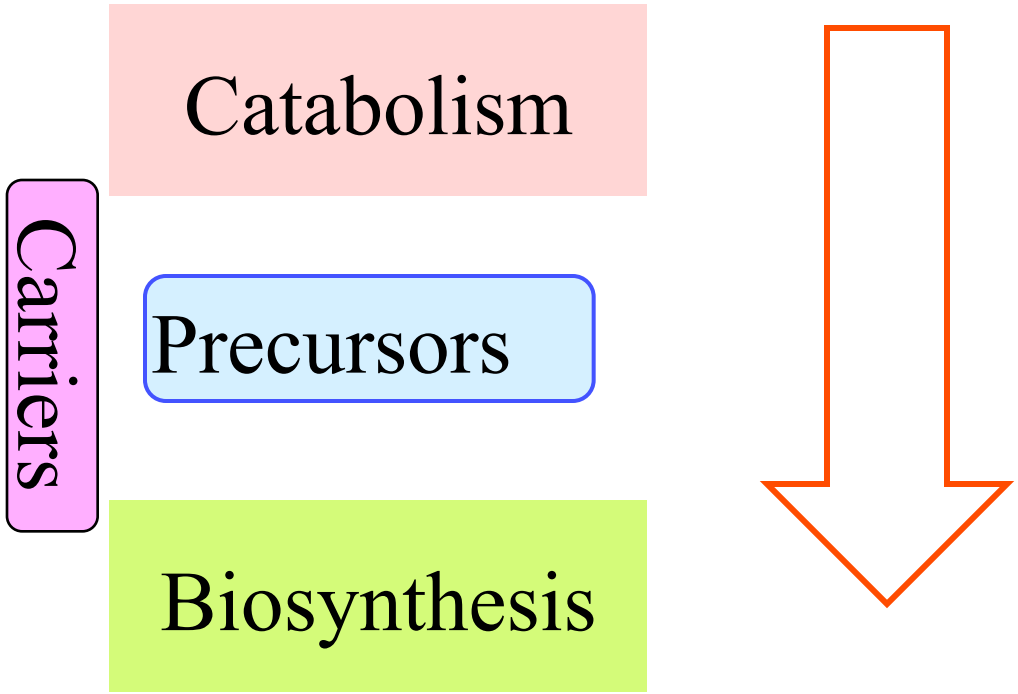

Same 12 in all cells
Precursors
Carriers
Same 8 in all cells
Extremely conserved core
Taxis and transport
Nutrients
Catabolism
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Huge Variety
≈100 ≈same in all organisms


Taxis and transport
12
Autocatalytic feedback
Polymerization and complex assembly
Core m olism
Nutrients
Catabolism
Precursors
Sugars
Fatty acids
Co-factors
Amino Acids
Carriers
Genes
Trans*
Protein
Huge Variety
8
≈100
≈10^4 to ≈ ∞ in one organisms

Efficient
Robust
Evolvable

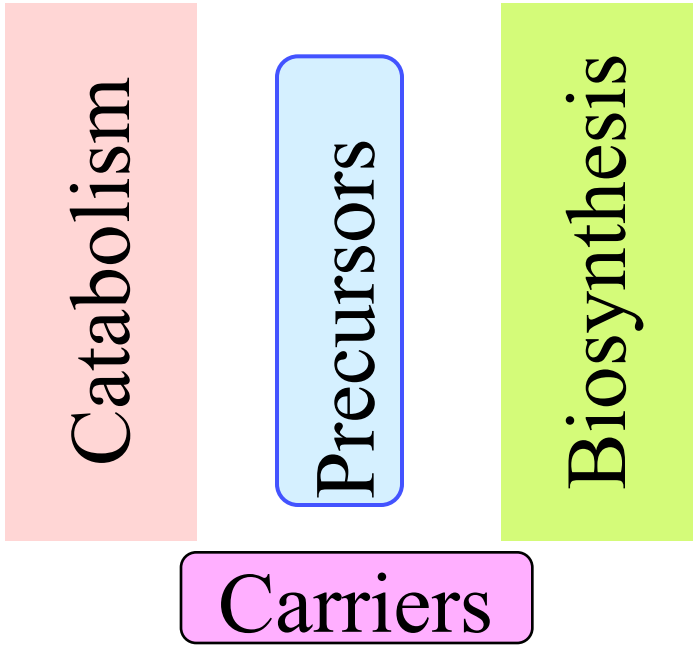


Inside every cell

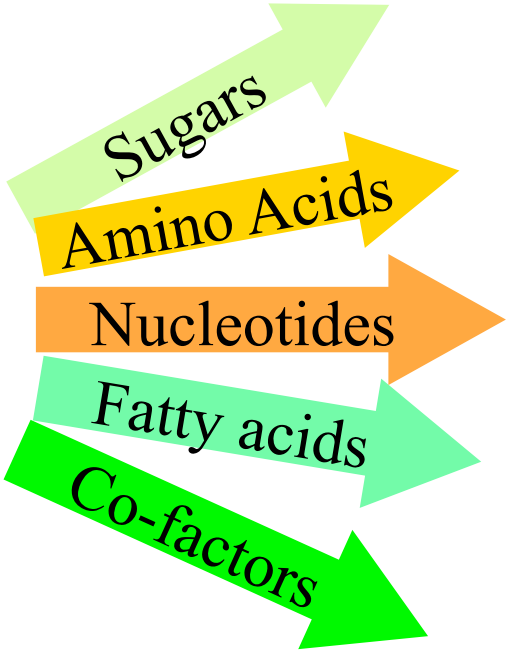


Layered architecture

Inside every cell

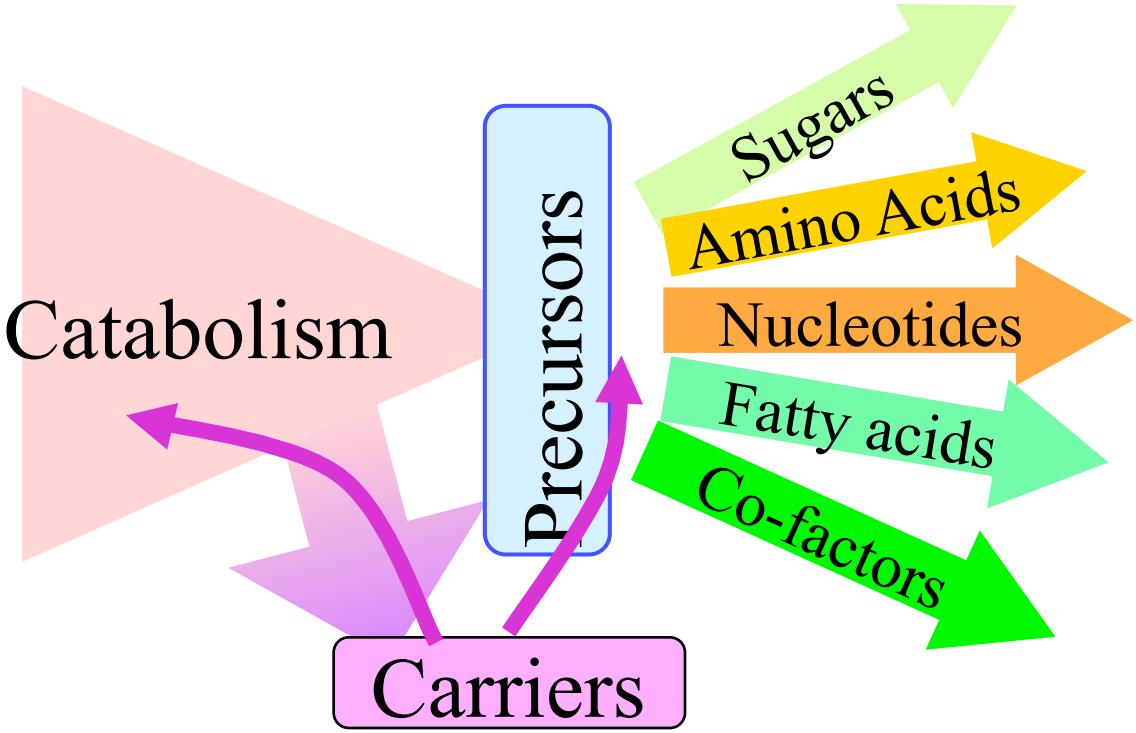


Layered architecture



Biosynthetic Pathways

Inside every cell



Core metabolic bowtie
Layered architecture

Efficient
Robust
Evolvable

food

Blood

Glucose

Oxygen

Organs
Tissues
Cells
Molecules

Universal metabolic system

Efficient
Robust
Evolvable

Deconstrained

food

Constrained

Blood

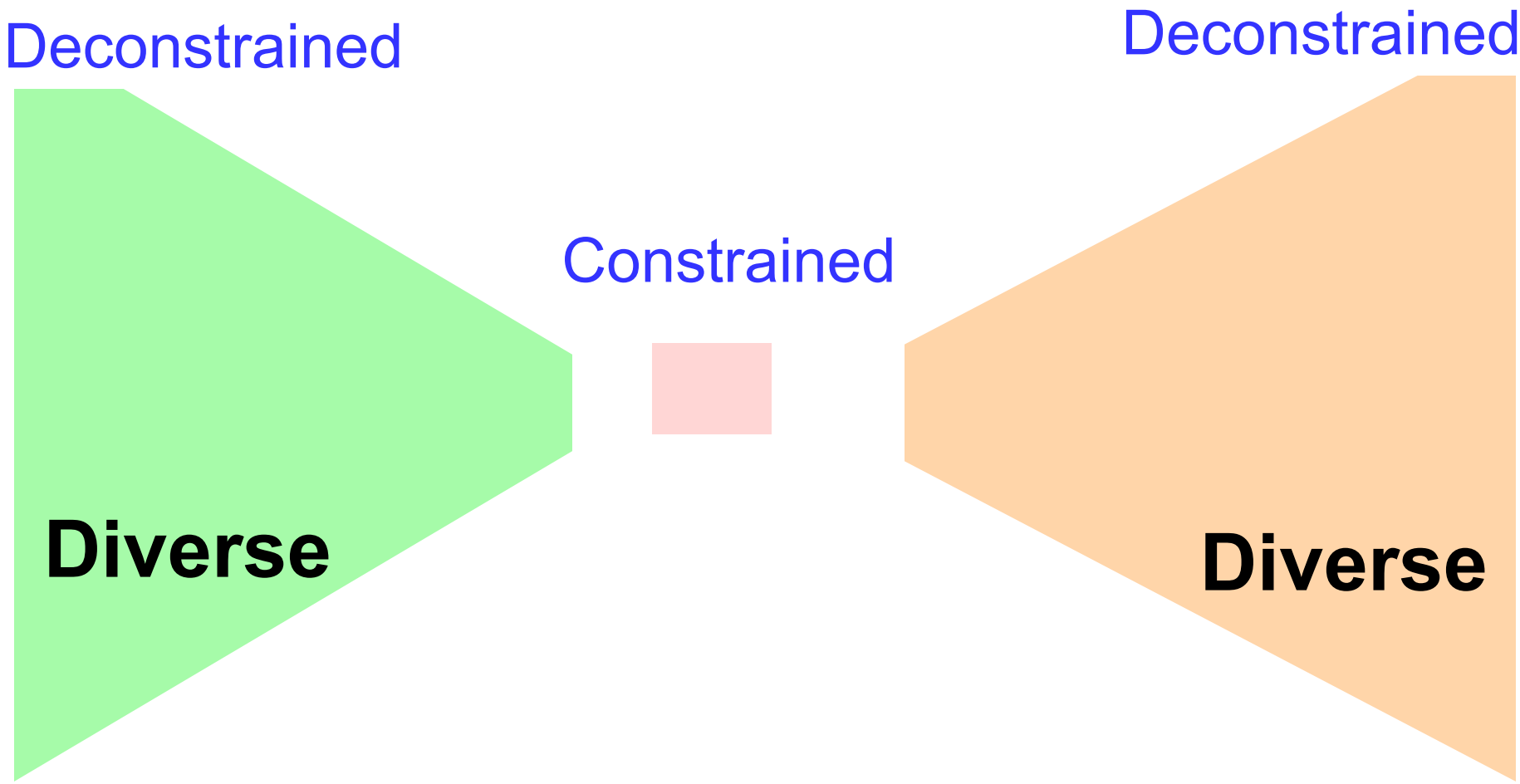
Glucose

Oxygen

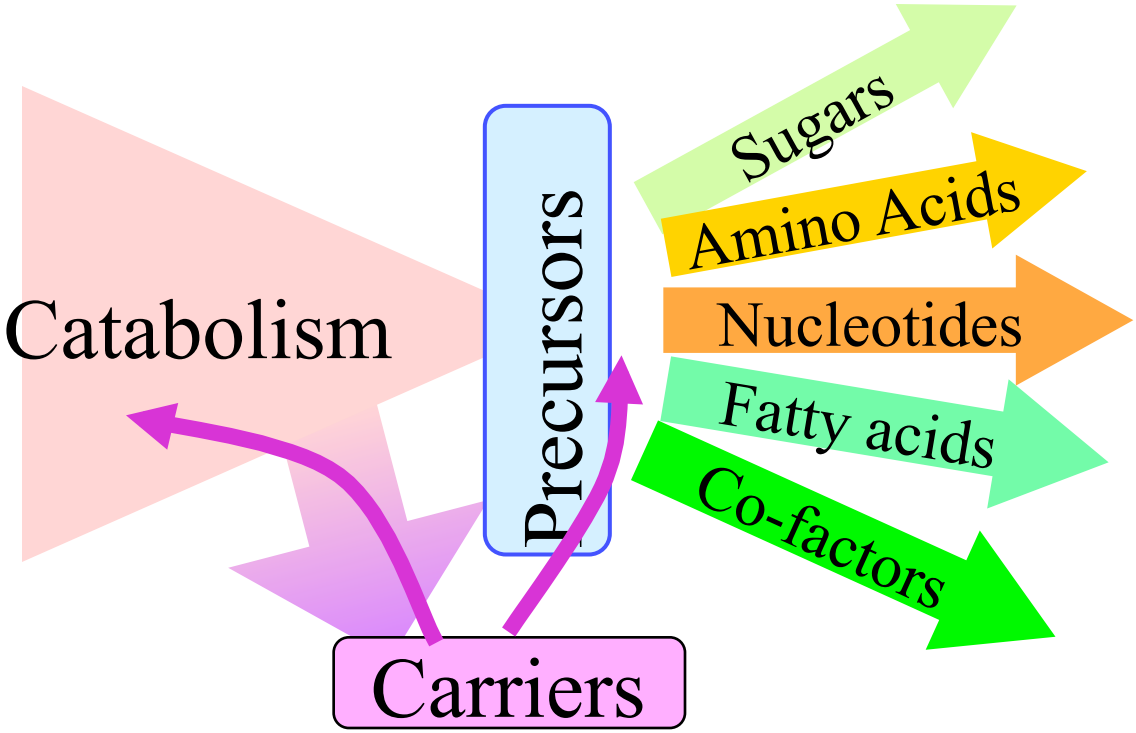
Deconstrained

Organs
Tissues
Cells
Molecules

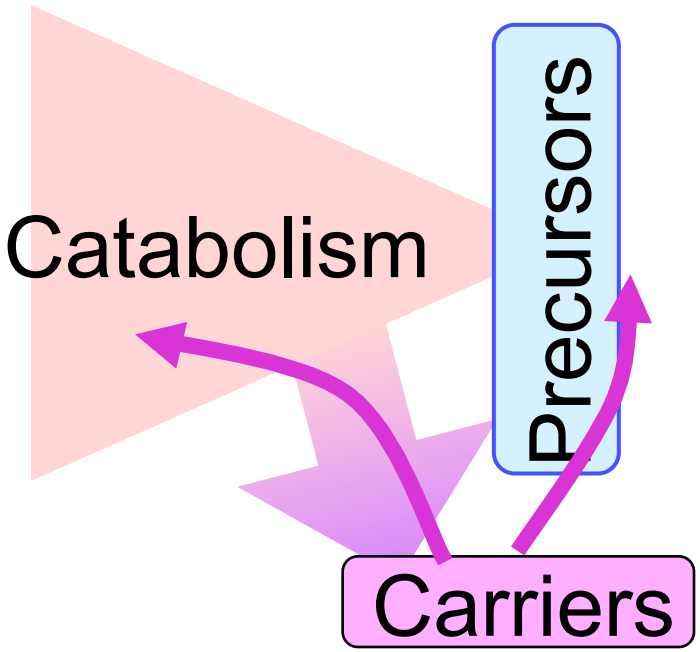
Efficient
Robust
Evolvable

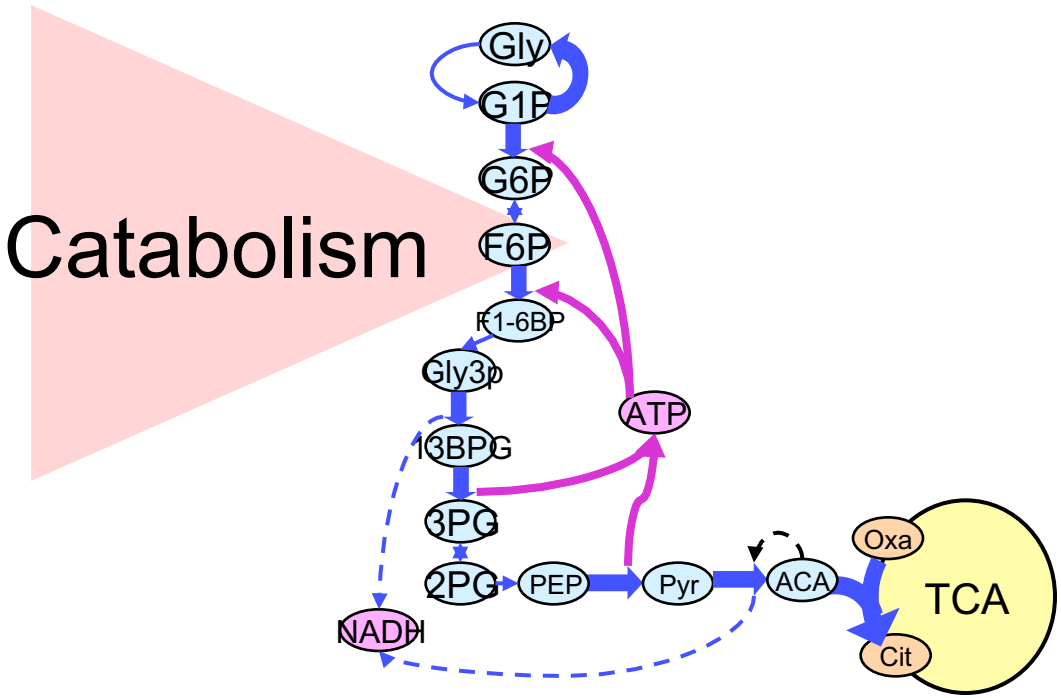


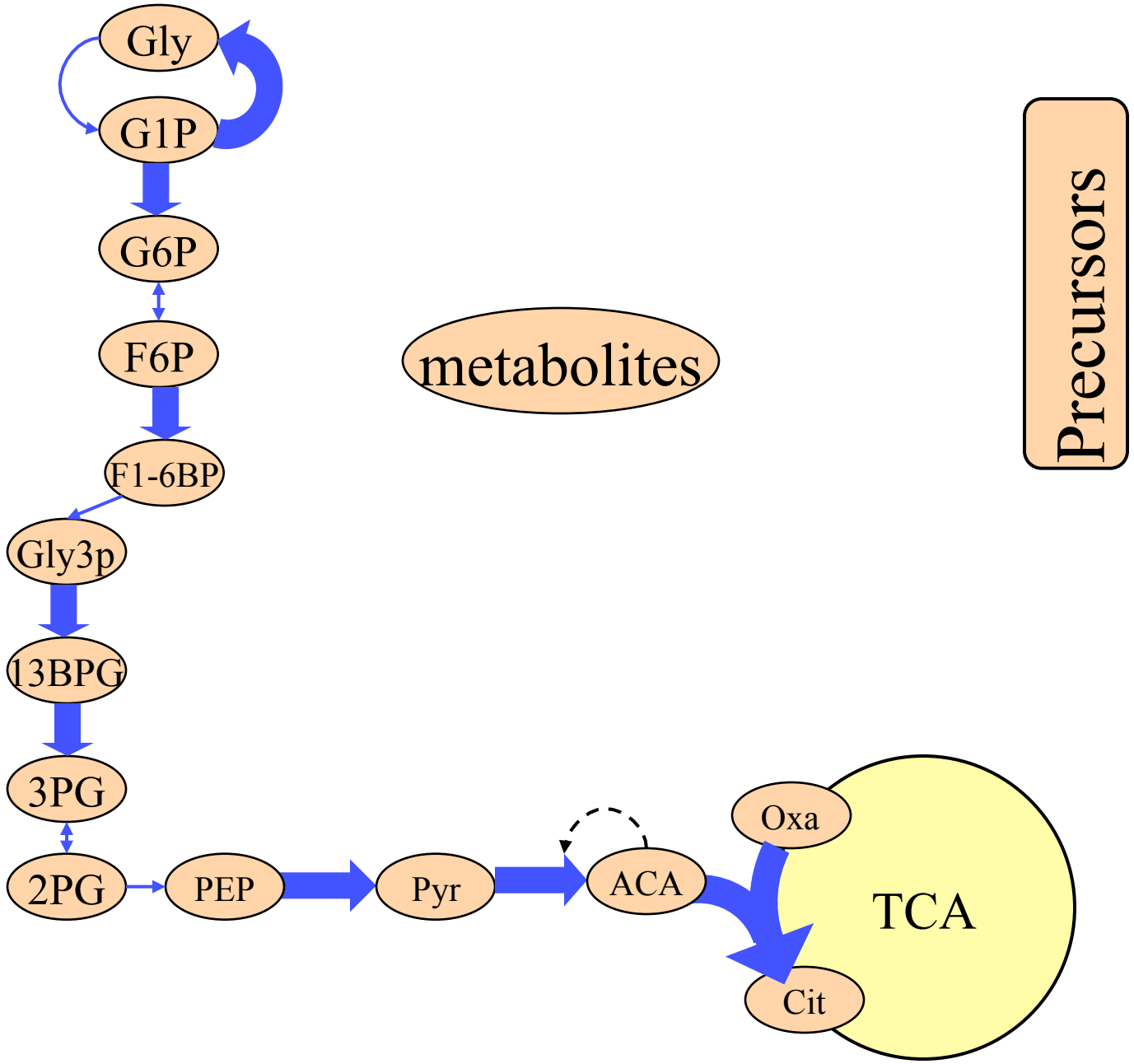
Inside every cell

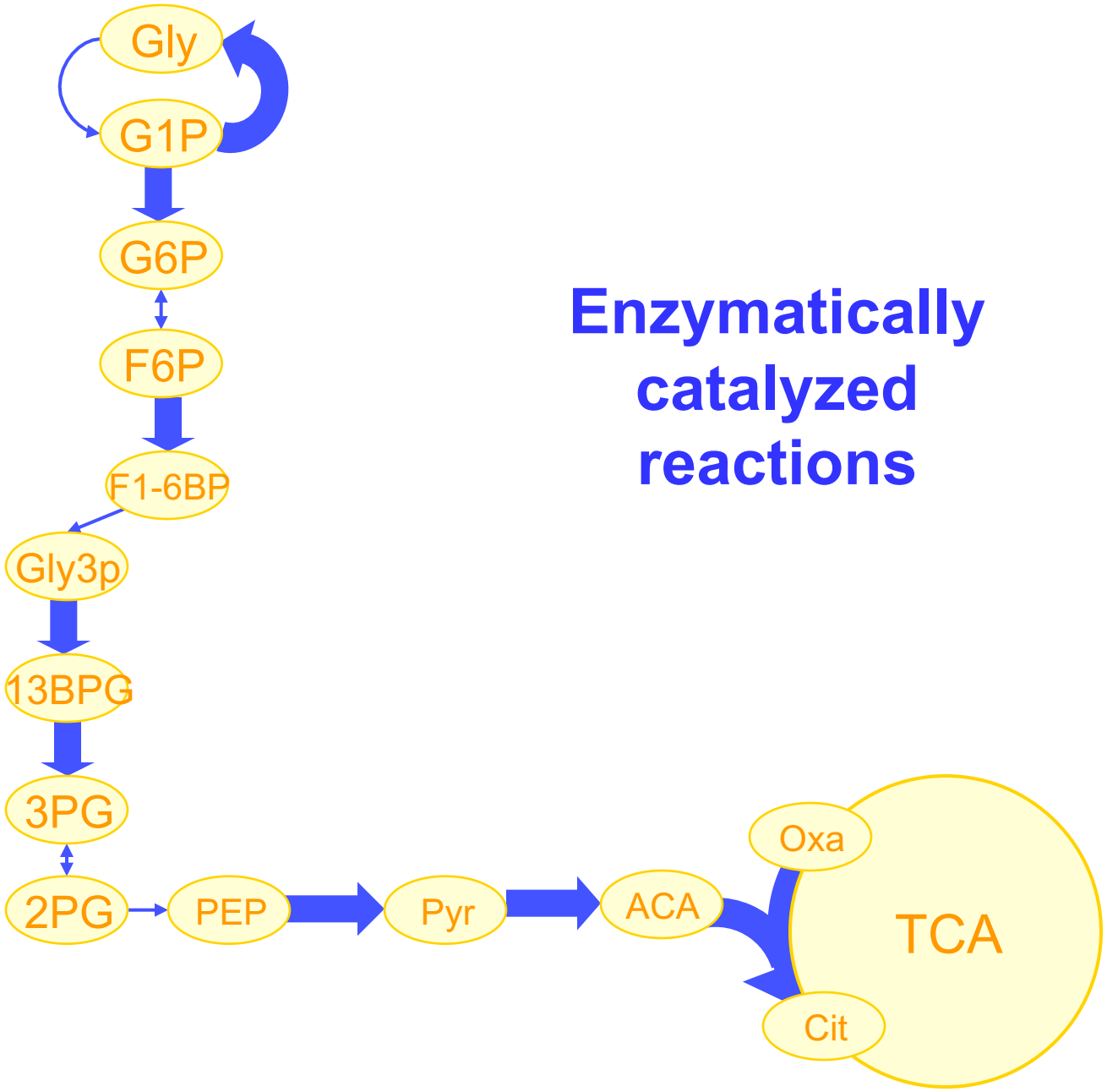


Core metabolic bowtie
Layered architecture

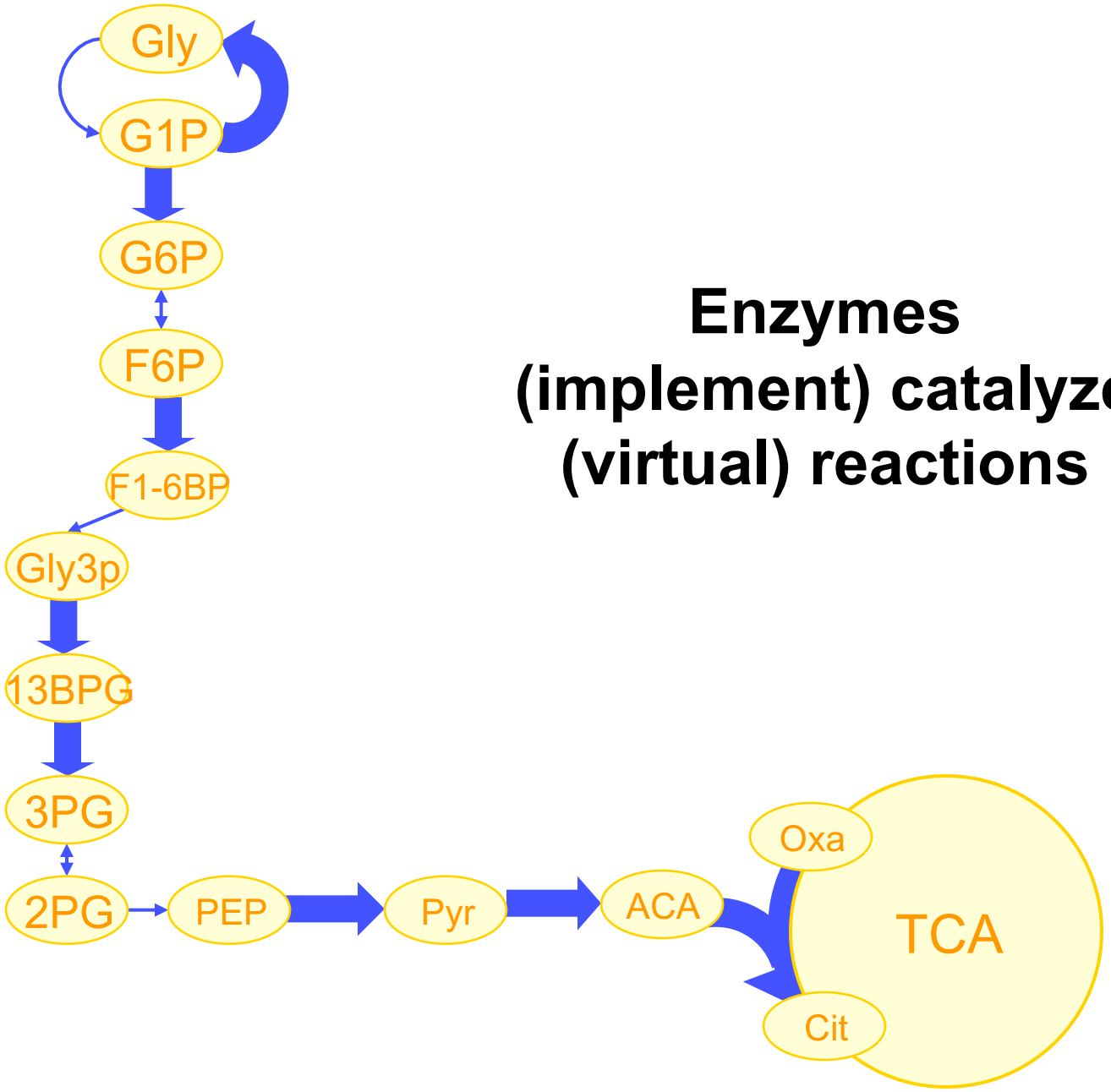

Catabolism
Precursors
Carriers


Catabolism
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
ATP
NADH

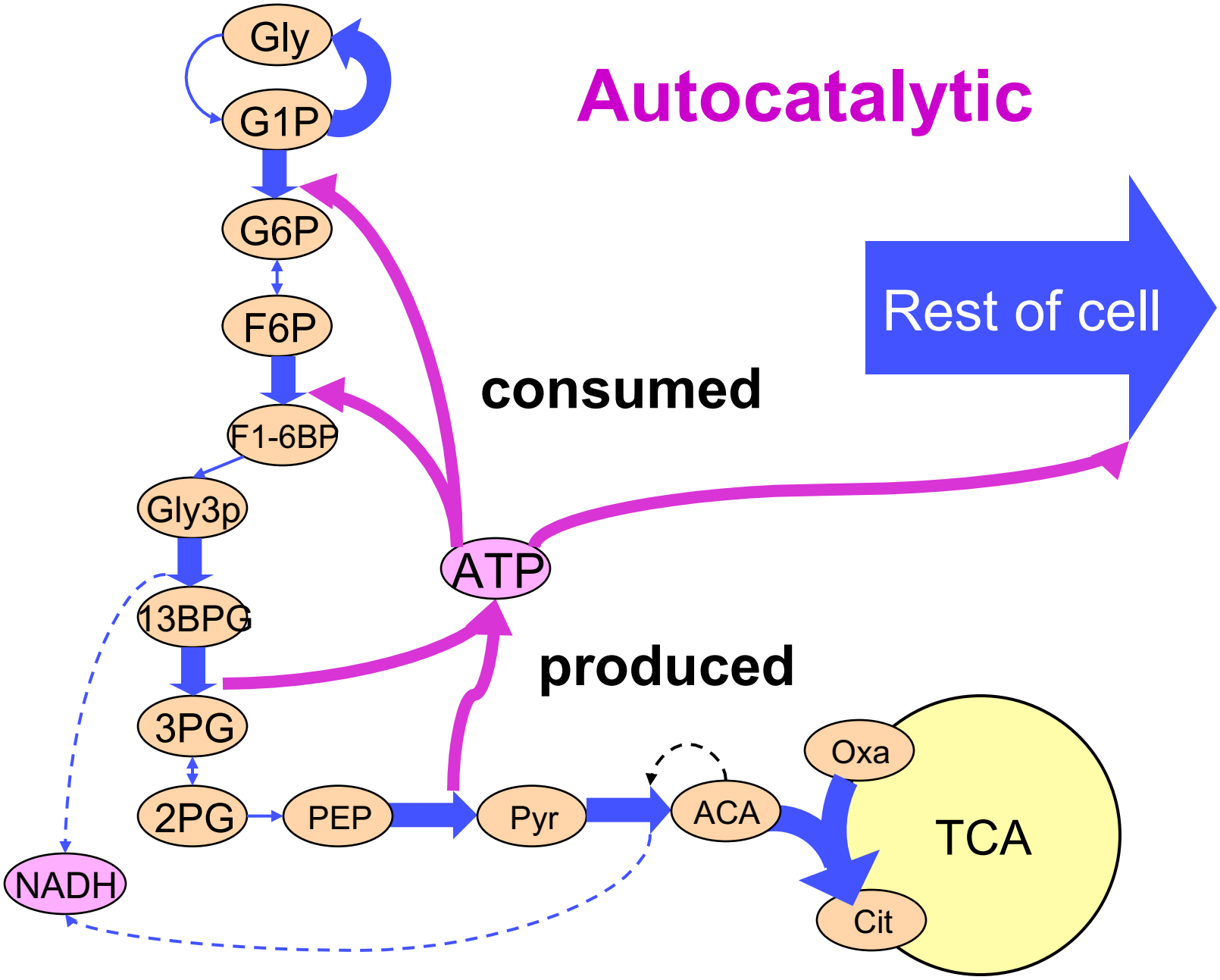

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
metabolites
Precursors

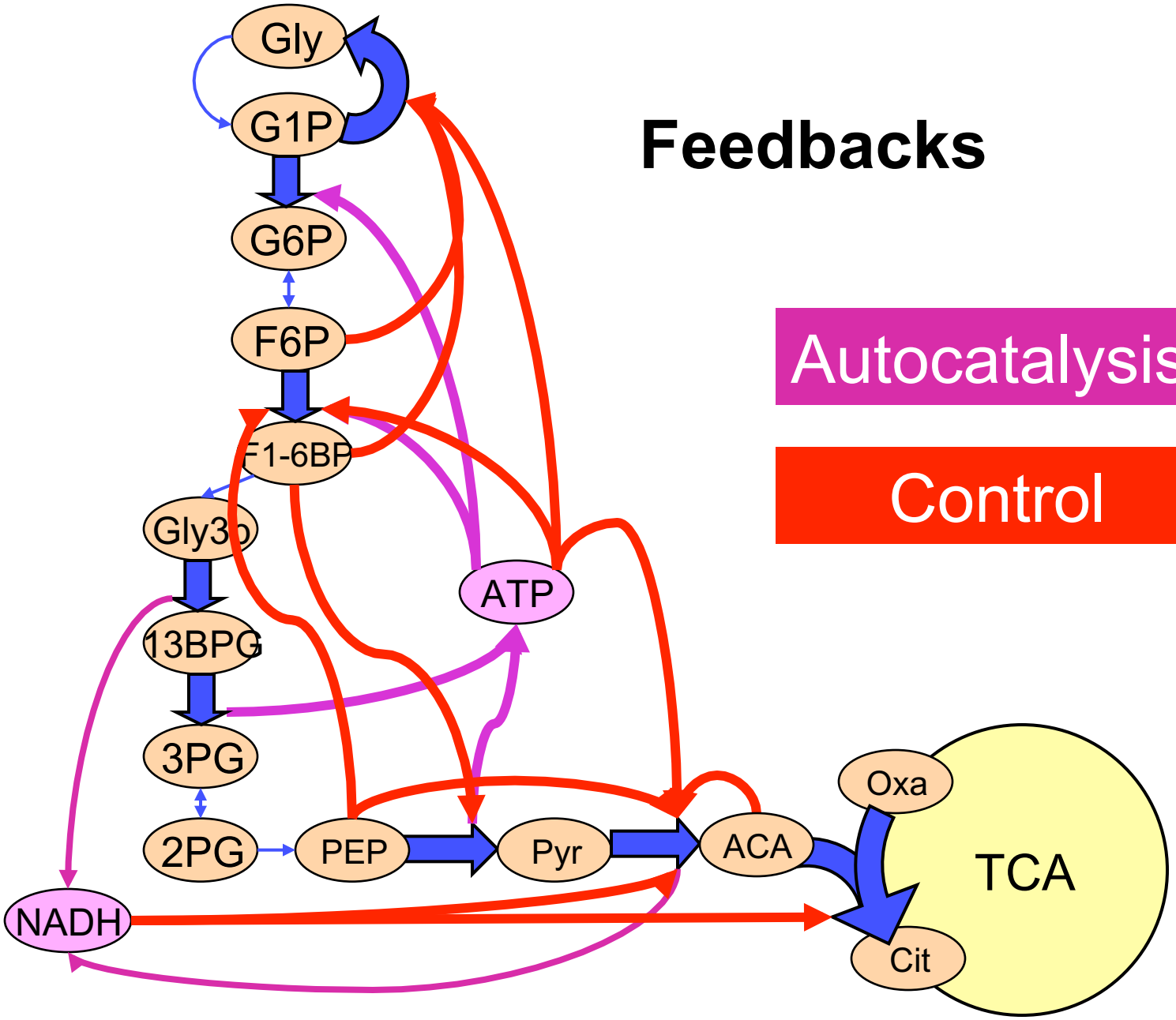


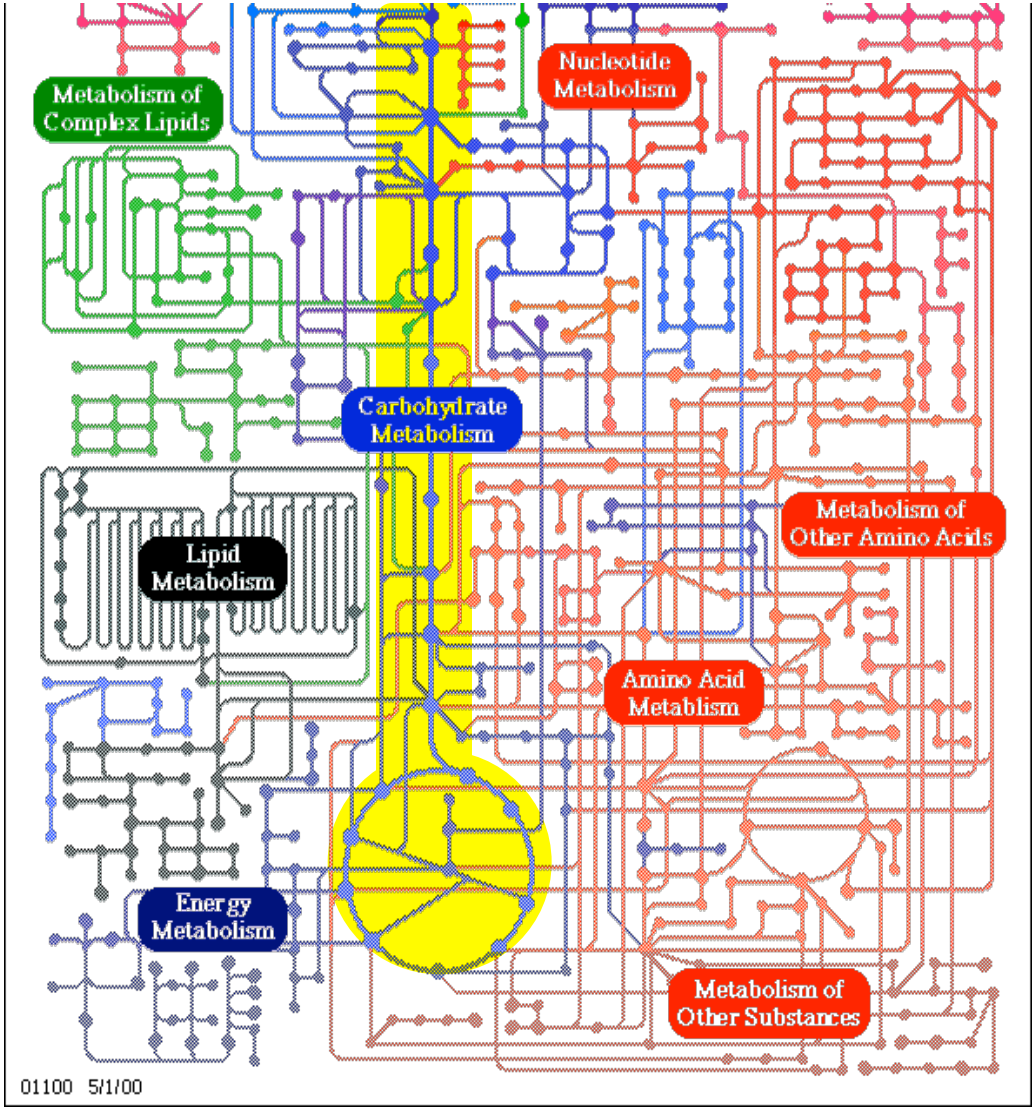
Enzymatically catalyzed reactions

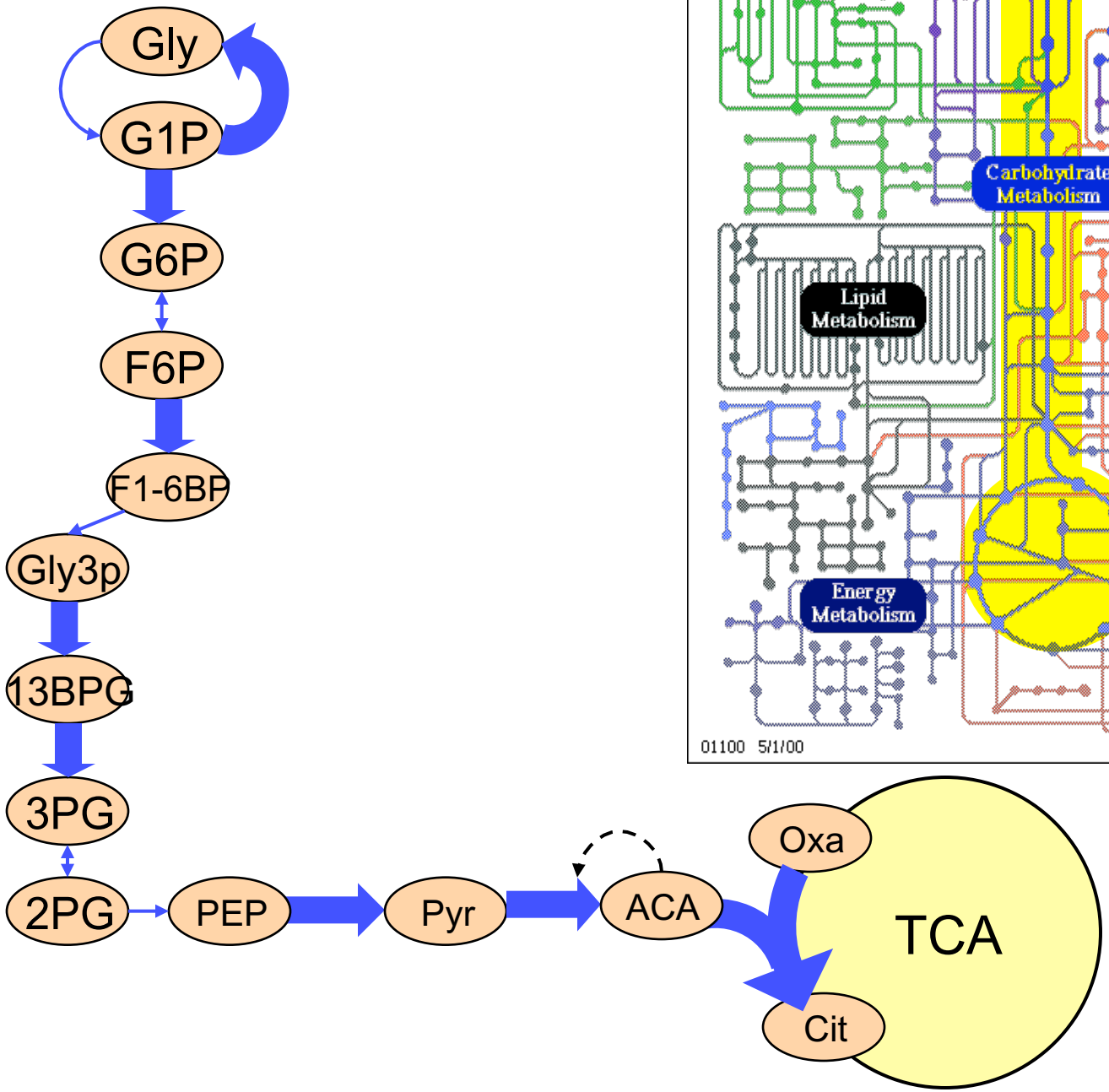


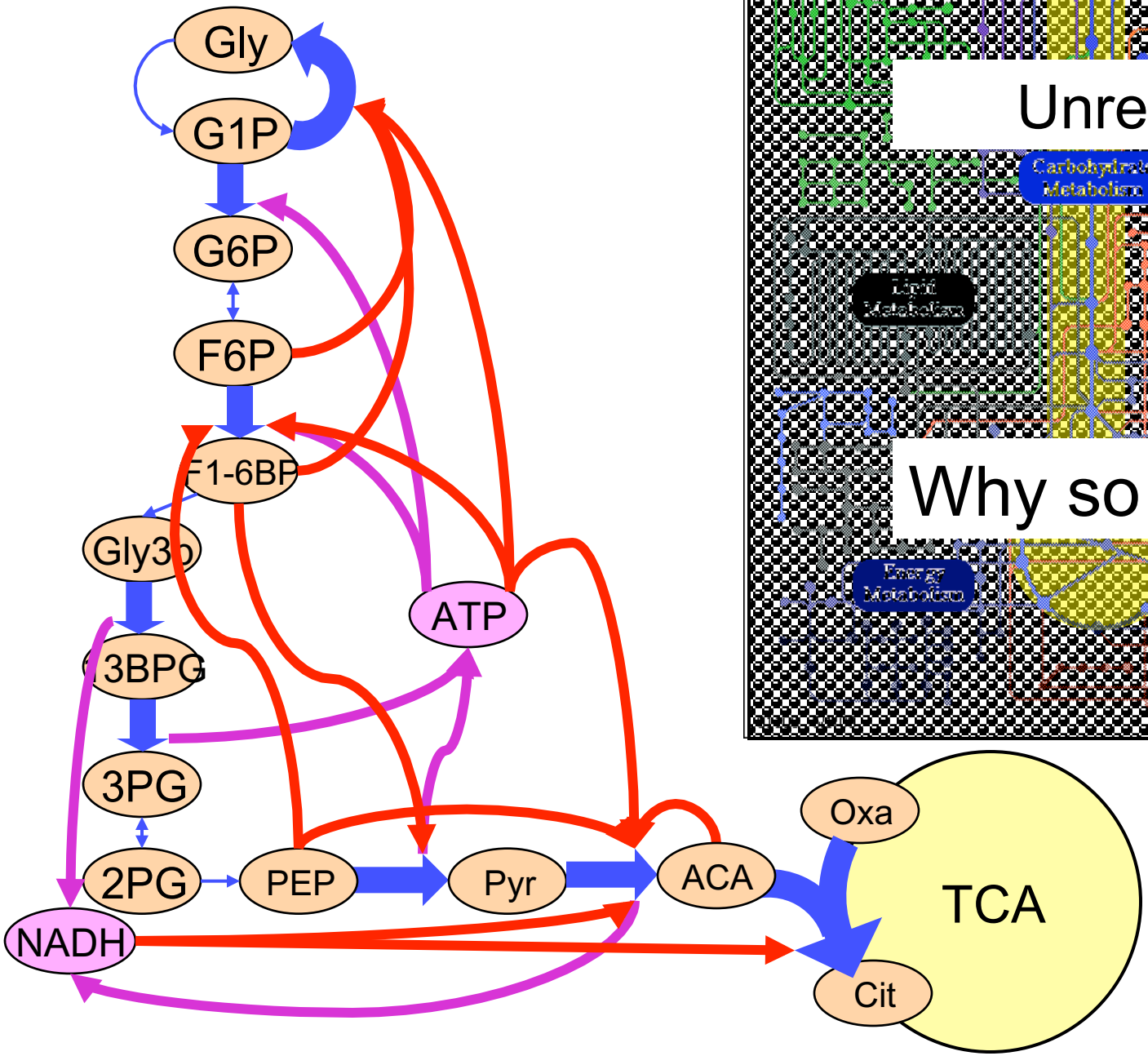
Enzymes (implement) catalyze (virtual) reactions

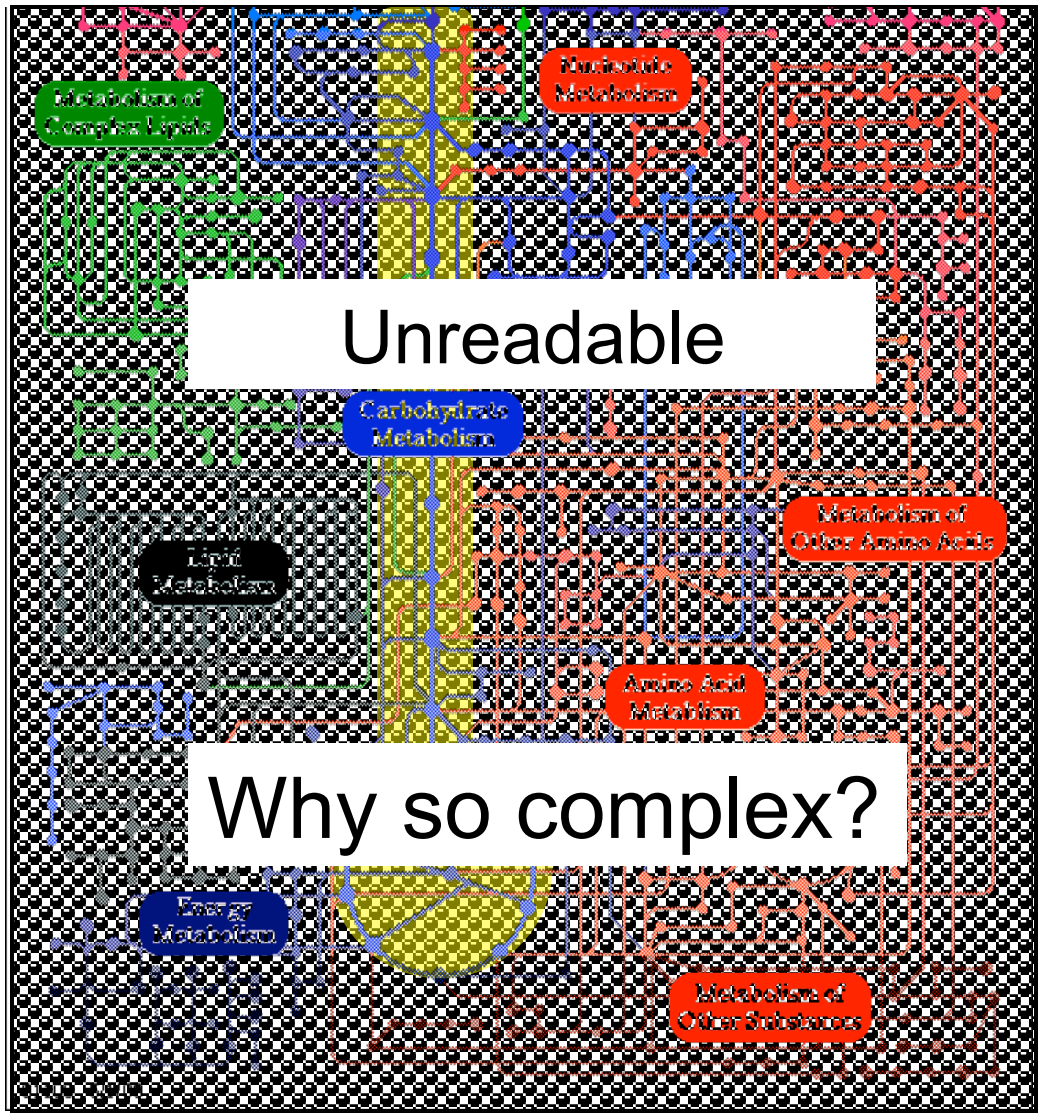

Autocatalytic
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
NADH
ATP
consumed
produced
Rest of cell


Feedbacks
Autocatalysis
Control
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
TCA
Cit


Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00


Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit

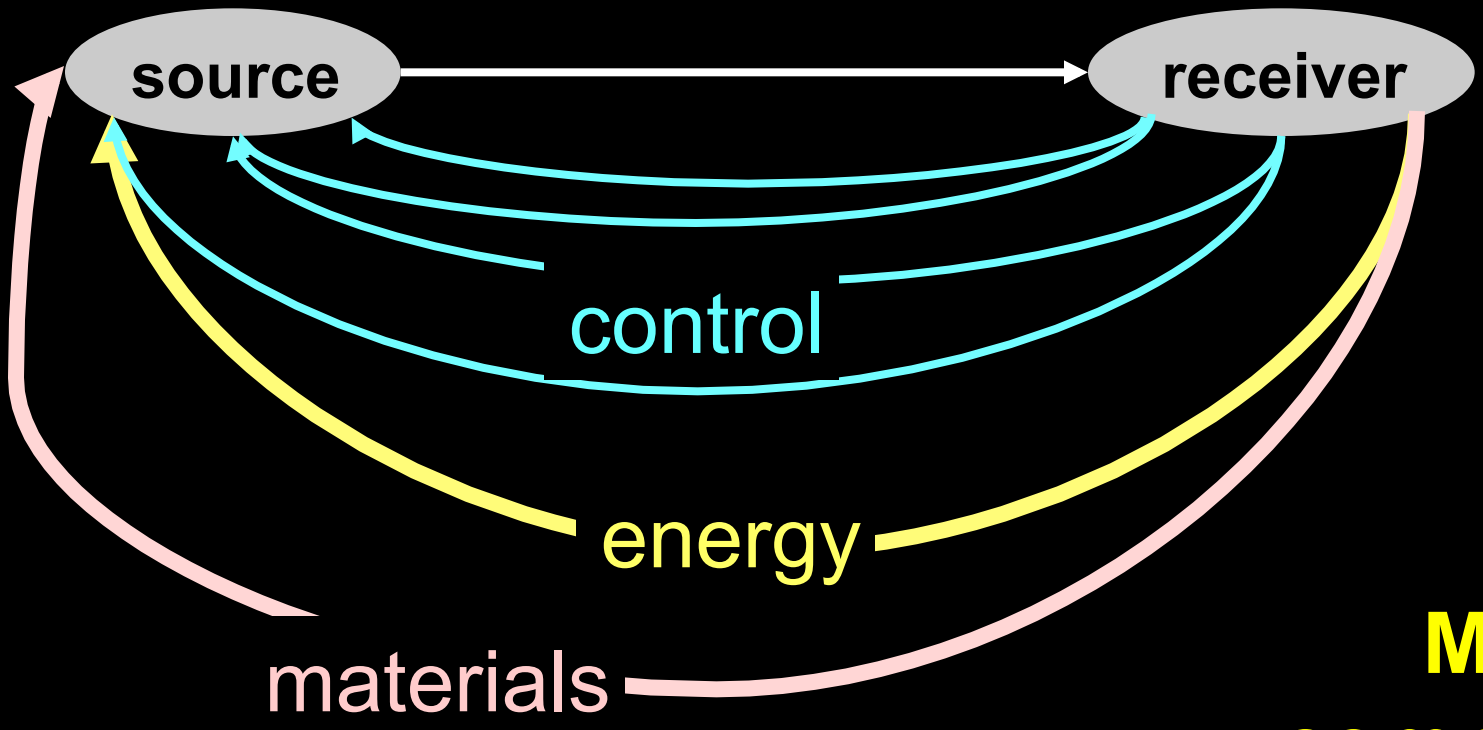

Gly
G1P
G6P
F6P
F1-6BP
Gly3P
3BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
Cit
TCA


Unreadable
Why so complex?

signaling
gene expression
metabolism
lineage

Biological pathways

signaling
gene expression
metabolism
lineage



More complex feedback

UG biochem, math, control theory

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

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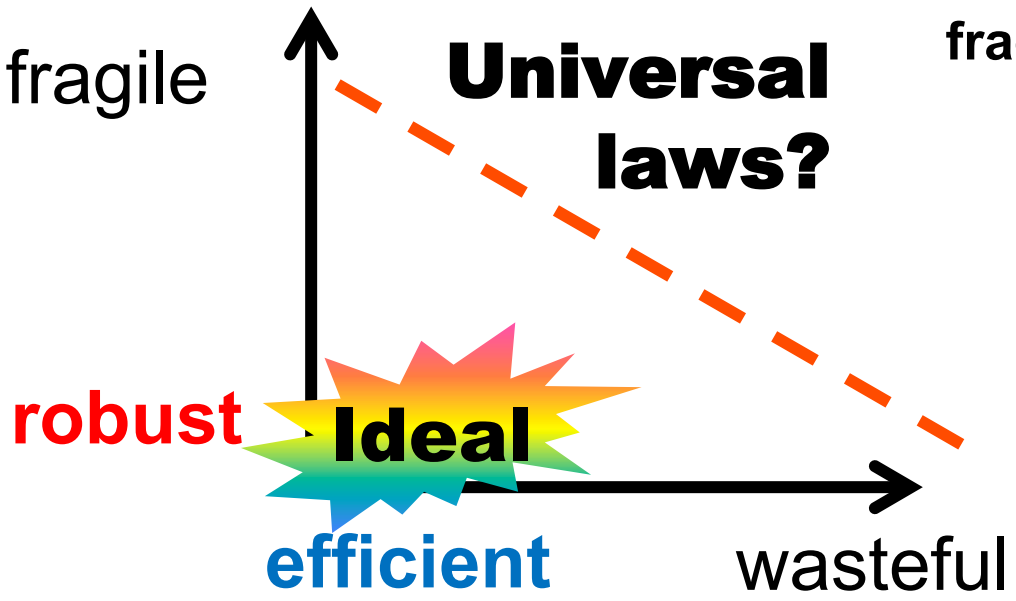
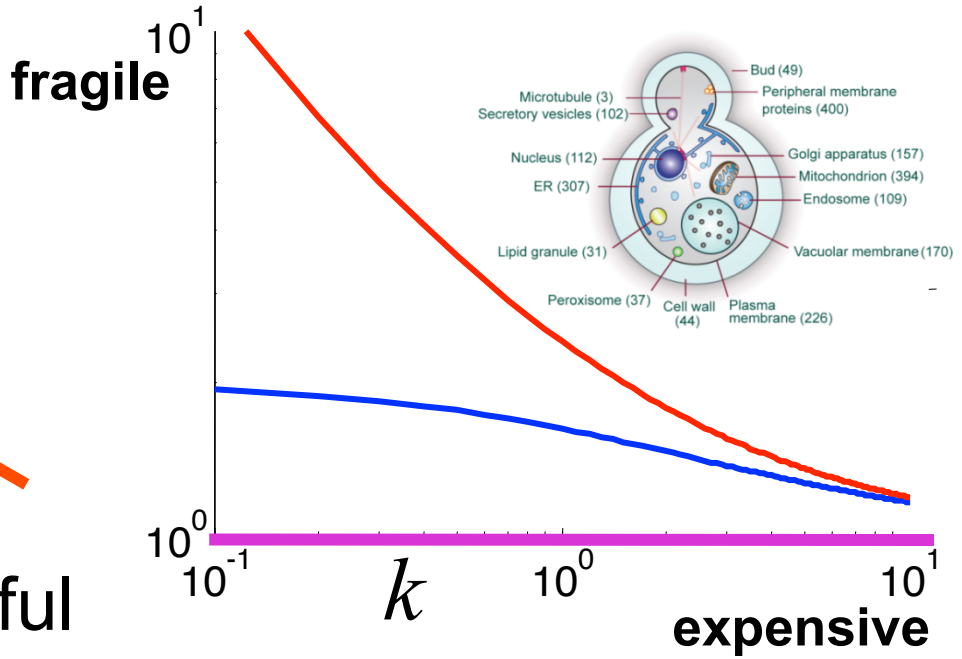
molecules are consumed upstream and four are produced downstream, which normalizes to $q = 1$ (each y molecule produces two downstream) with kinetic exponent $a = 1$. To highlight essential trade-offs with the simplest possible analysis, we normalize the concentration such that the unperturbed ($\delta = 0$) 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

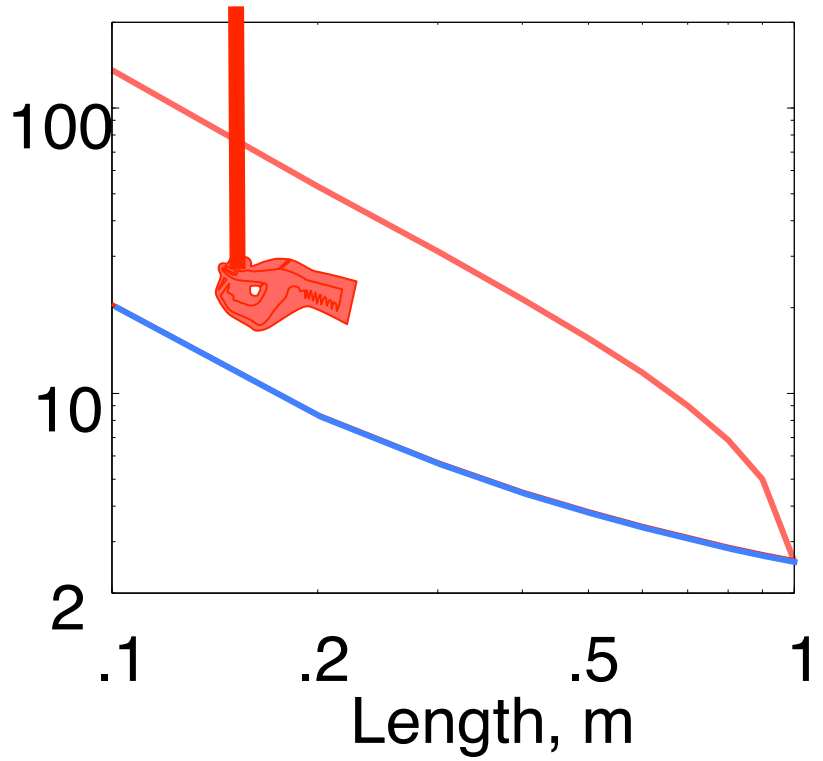
Chandra, Buzi, and Doyle

Most important paper so far.

www.sciencemag.org SCIENCE VOL 333 8 JULY 2011



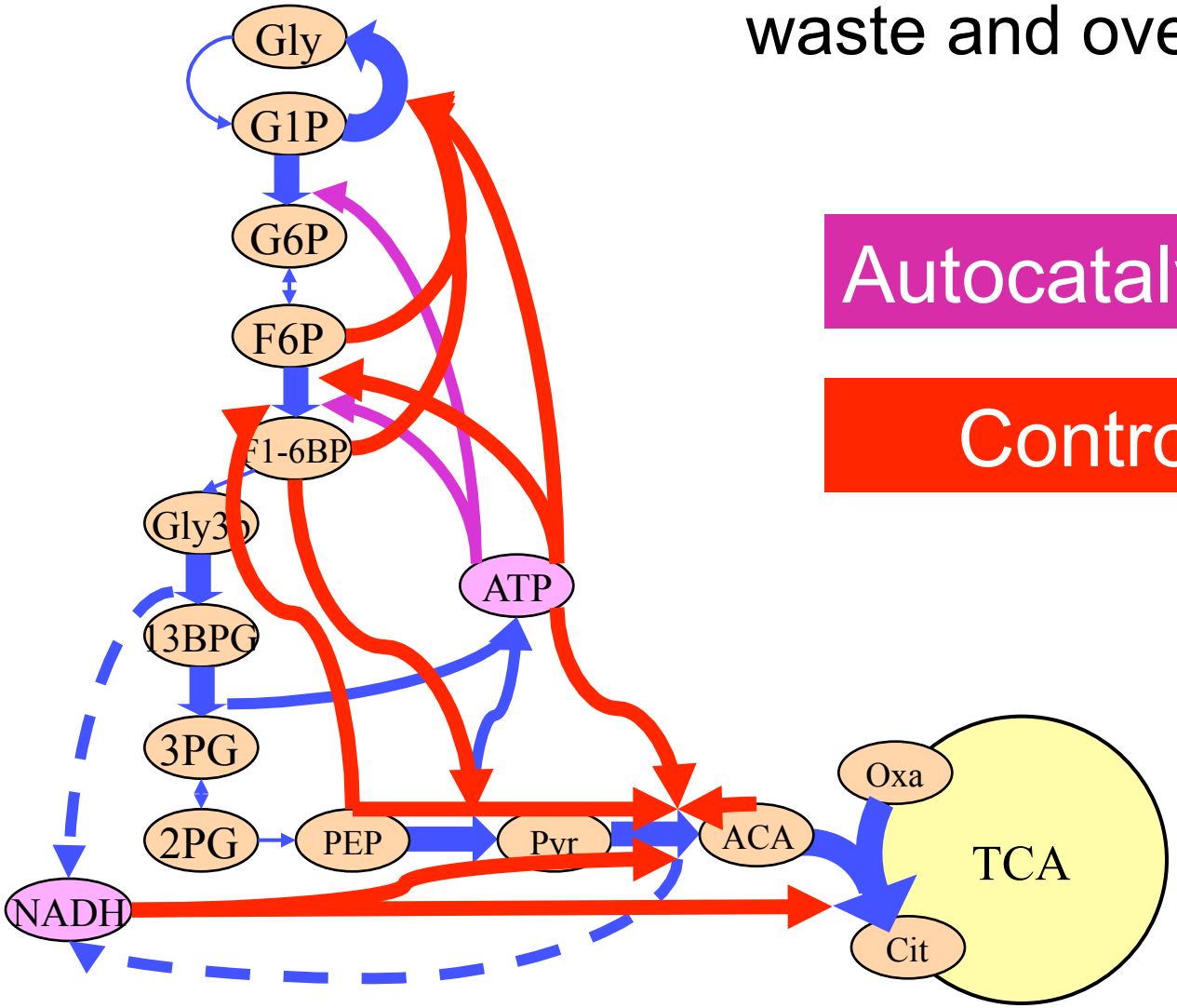




$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_\infty\end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$

Robust=maintain energy charge w/fluctuating cell demand

Efficient=minimize metabolic waste and overhead

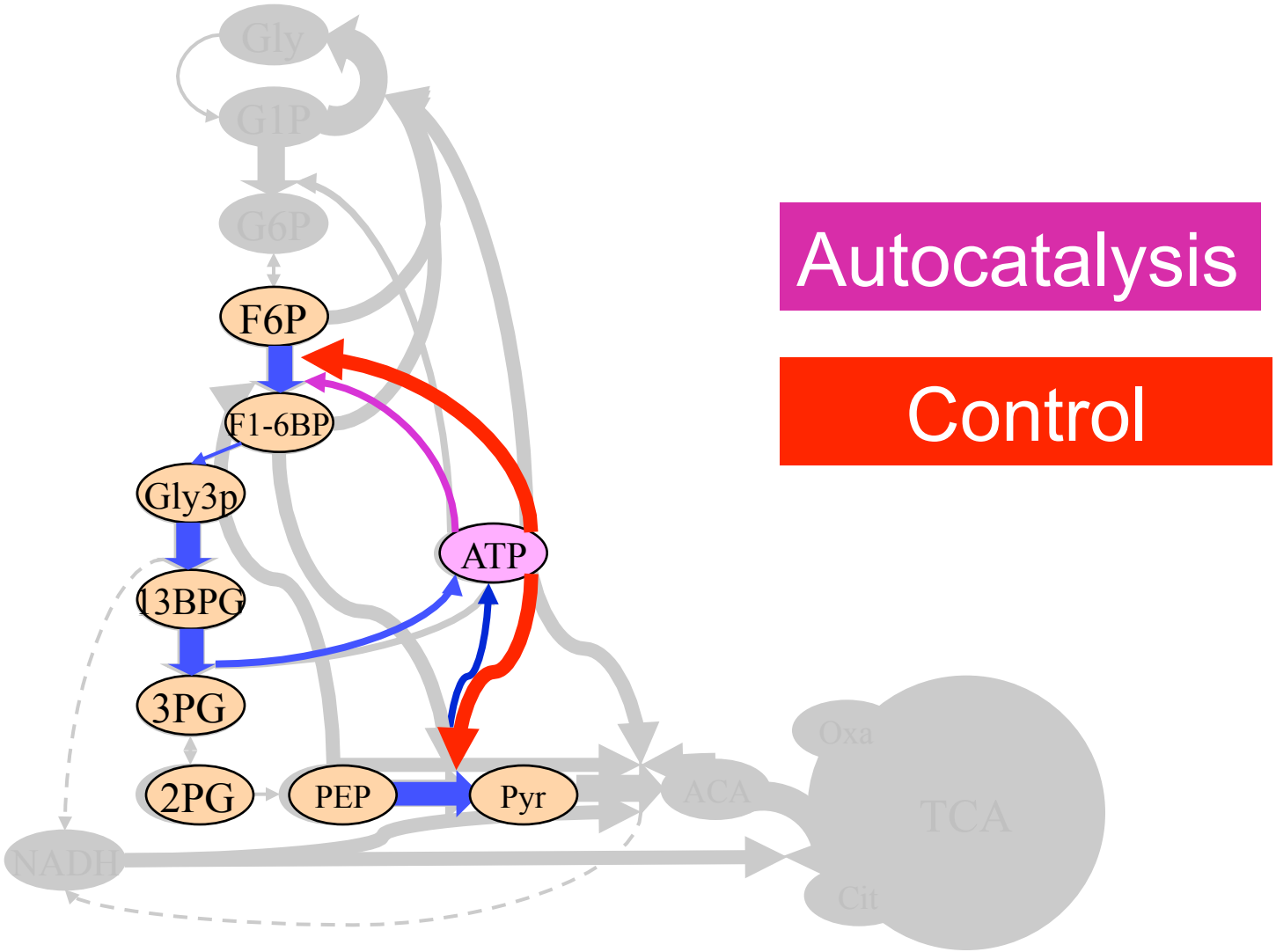


Autocatalysis

Control

Feedbacks

Minimal model?

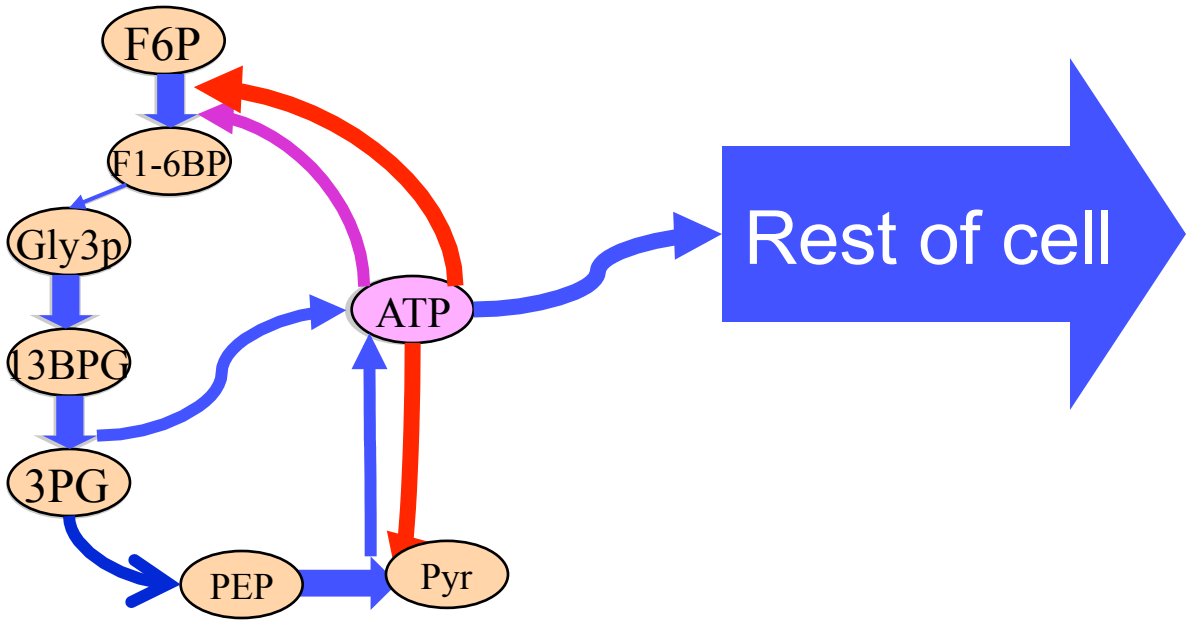


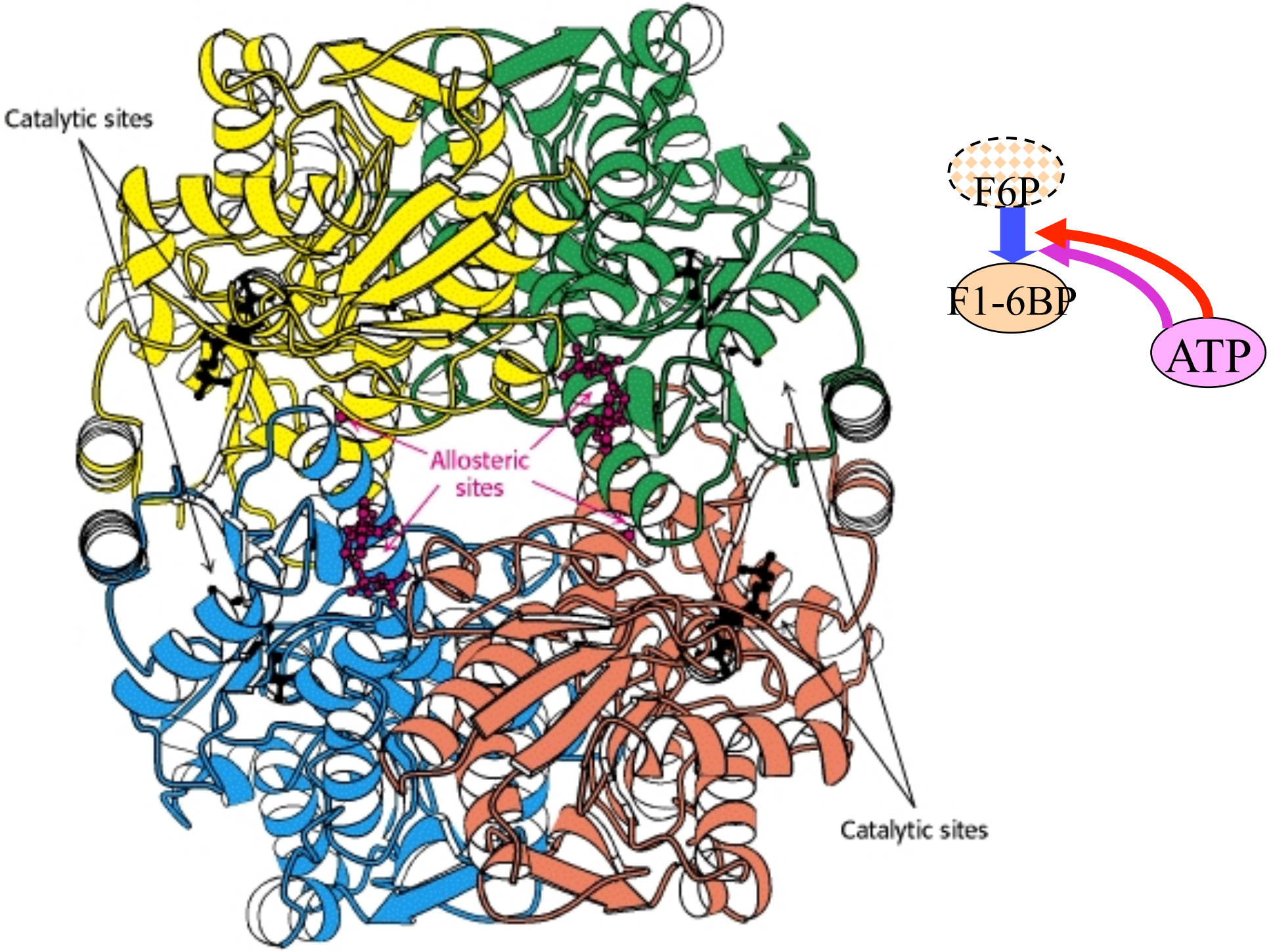
Autocatalysis

Control

Minimal model
~1 equilibrium
2 metabolites
3 “reactions”

Control
Plus
Autocatalytic
Feedback



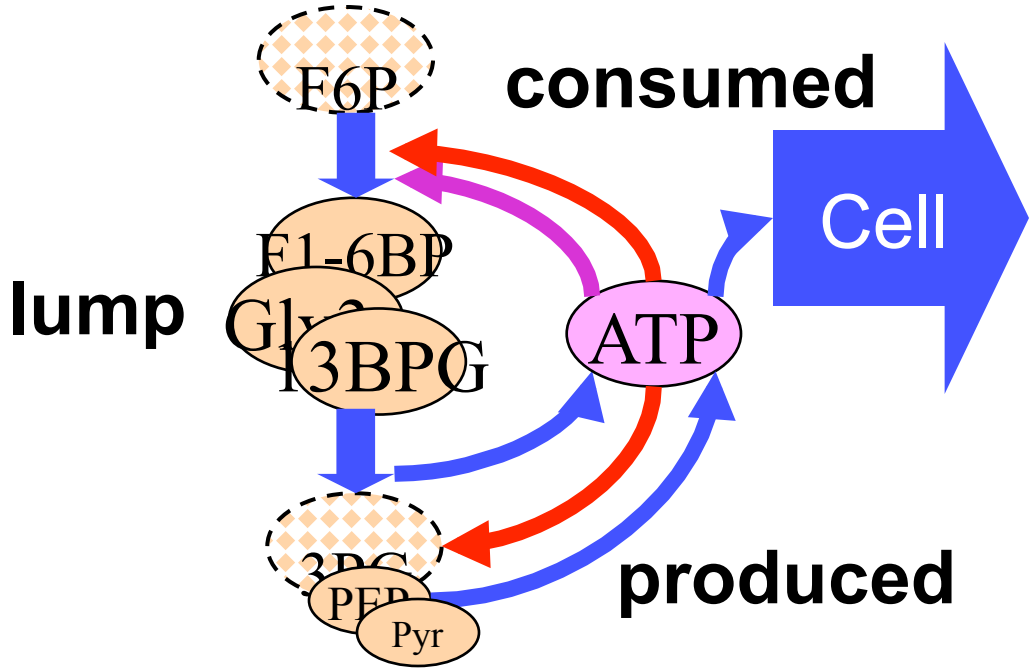

Catalytic sites
Allosteric sites
Catalytic sites
F6P
F1-6BP
ATP

Minimal model

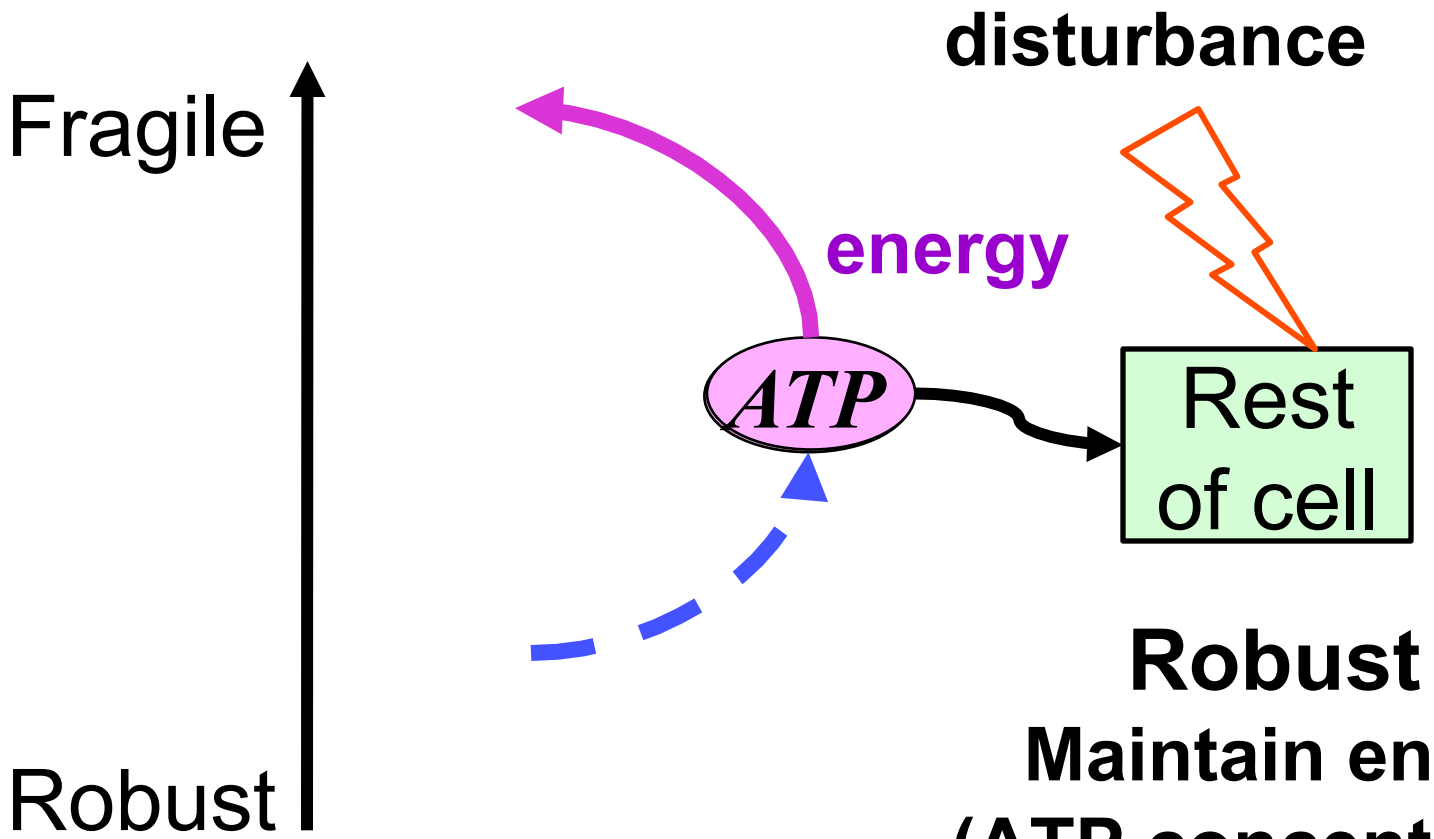
~1 equilibrium

2 metabolites

3 “reactions”



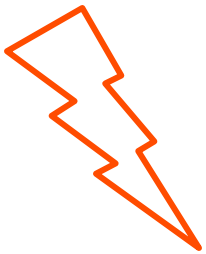
Hard tradeoff in glycolysis



Robust =
Maintain energy
(ATP concentration)
despite demand fluctuation

disturbance

Accurate vs sloppy



Fragile

Robust

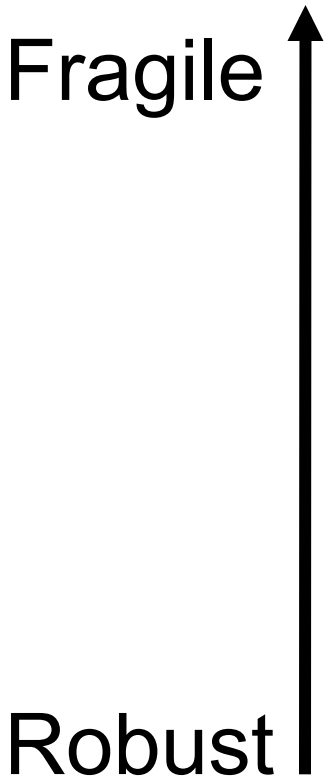
What makes this hard?

1. Instability (autocatalysis)
2. Delay (enzyme amount)

Robust

≈Disturbance rejection

≈ Accurate

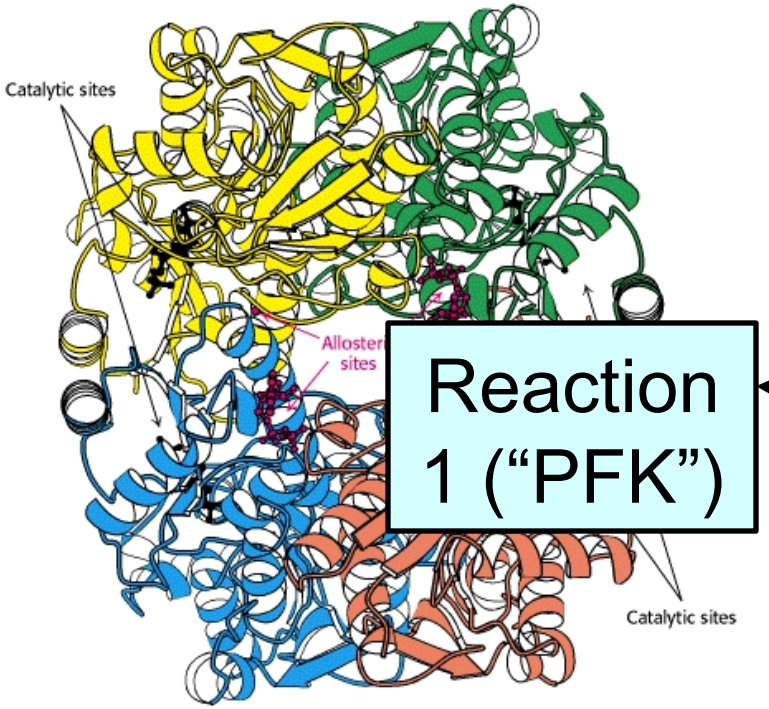


What makes this hard?

1. Instability
2. Delay

The CNS must cope with both!

enzymes catalyze reactions



Reaction 1 ("PFK")

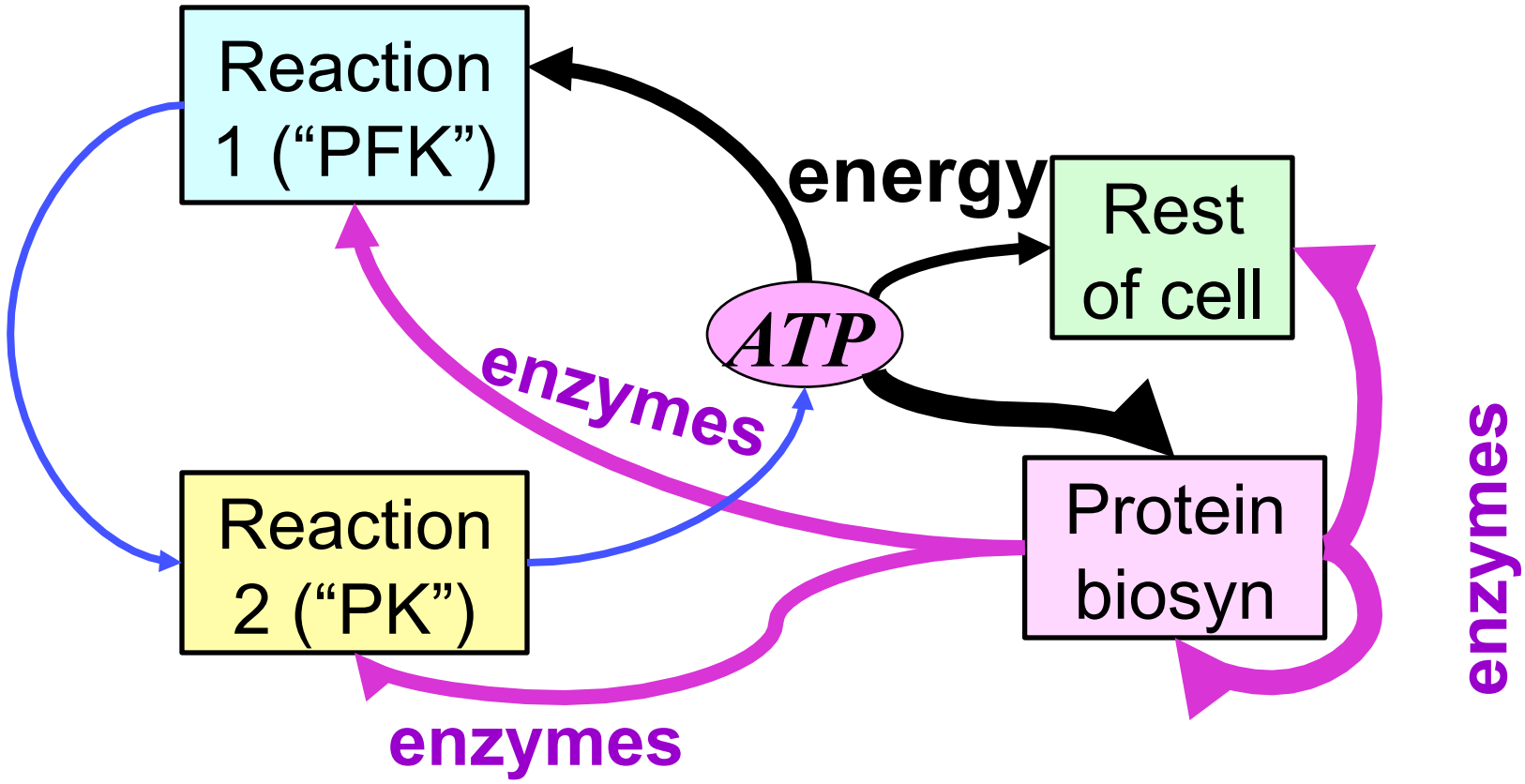
energy

Rest of cell

ATP

Reaction 2 ("PK")

enzymes catalyze reactions, another source of autocatalysis



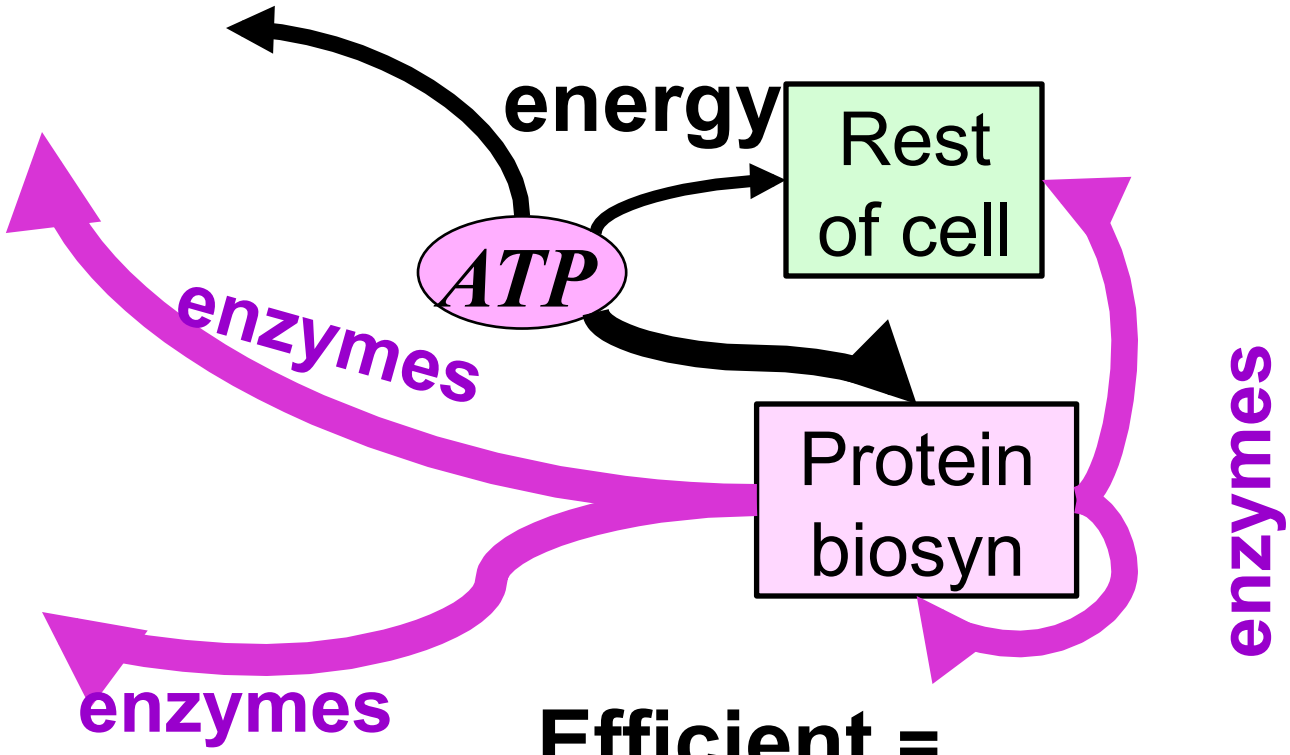
Efficient =
low metabolic overhead
≈ low enzyme amount

enzymes catalyze reactions, another source of autocatalysis

reaction rates

∝

enzyme amount



Can't make too many enzymes here, need to supply rest of the cell.

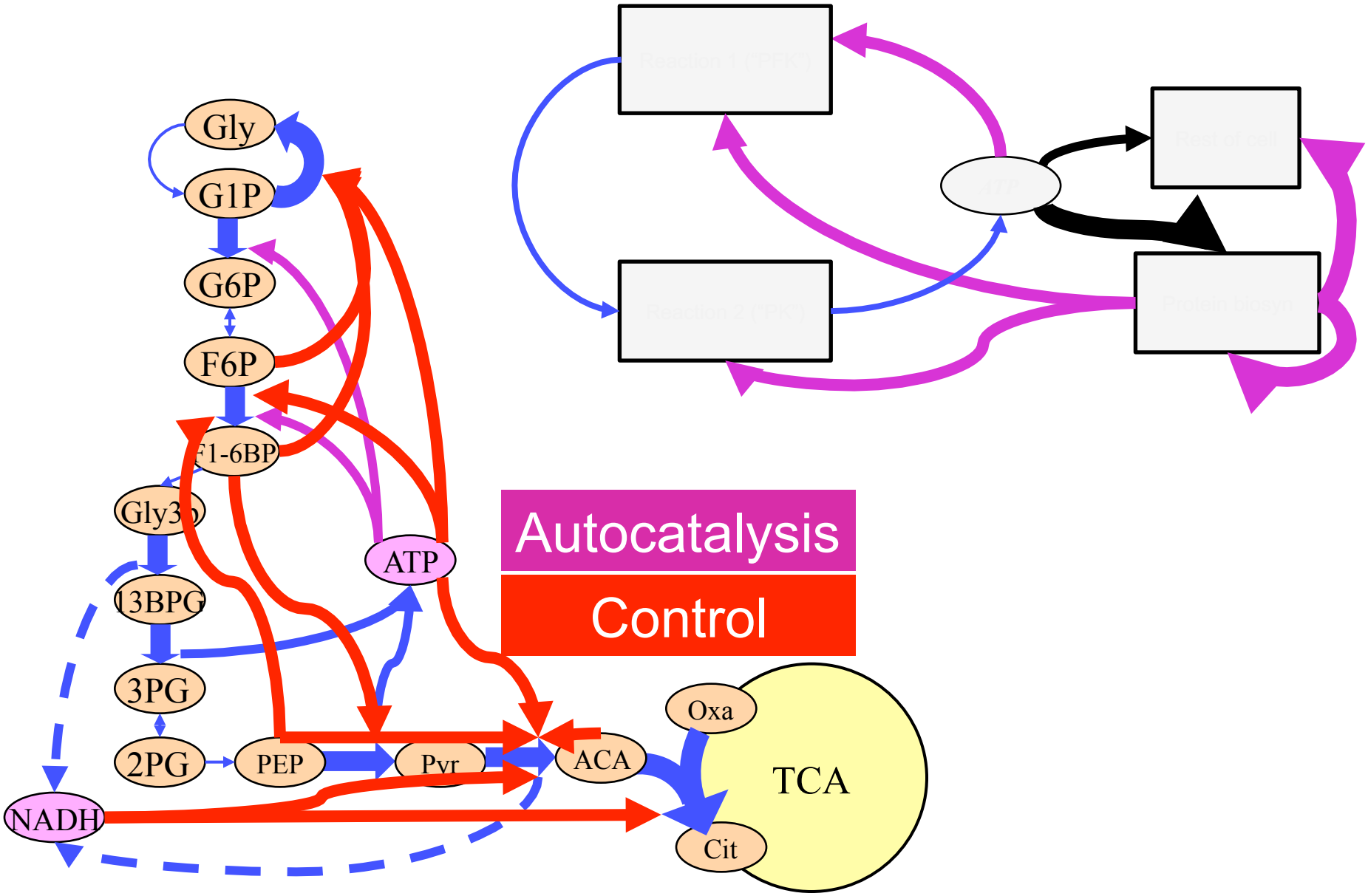
Efficient =

low metabolic overhead

≈ low enzyme amount

(⇒ slow reactions)

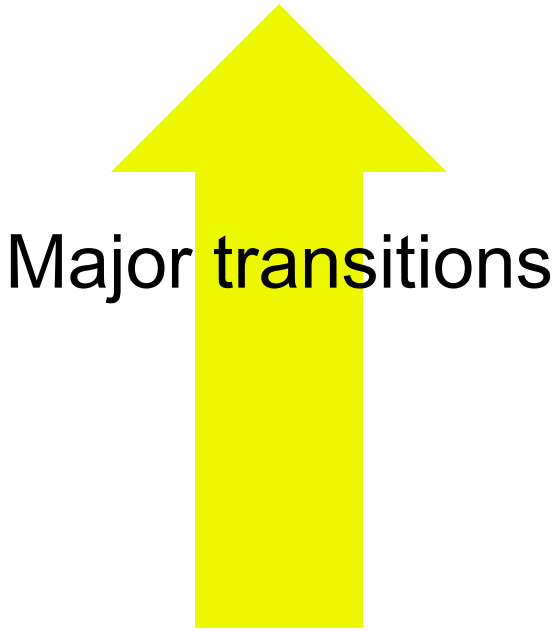
Autocatalysis



Autocatalysis

- New forms important in most transitions
- Major and poorly studies source of instability

- Sustainable infrastructure? (e.g. smartgrids)
- Money/finance/lobbyists/etc
- Industrialization
- Society/agriculture/weapons/etc
- Bipedalism
- Maternal care
- Warm blood
- Flight
- Mitochondria
- Oxygen
- Translation (ribosomes)
- Glycolysis (2011 *Science*)

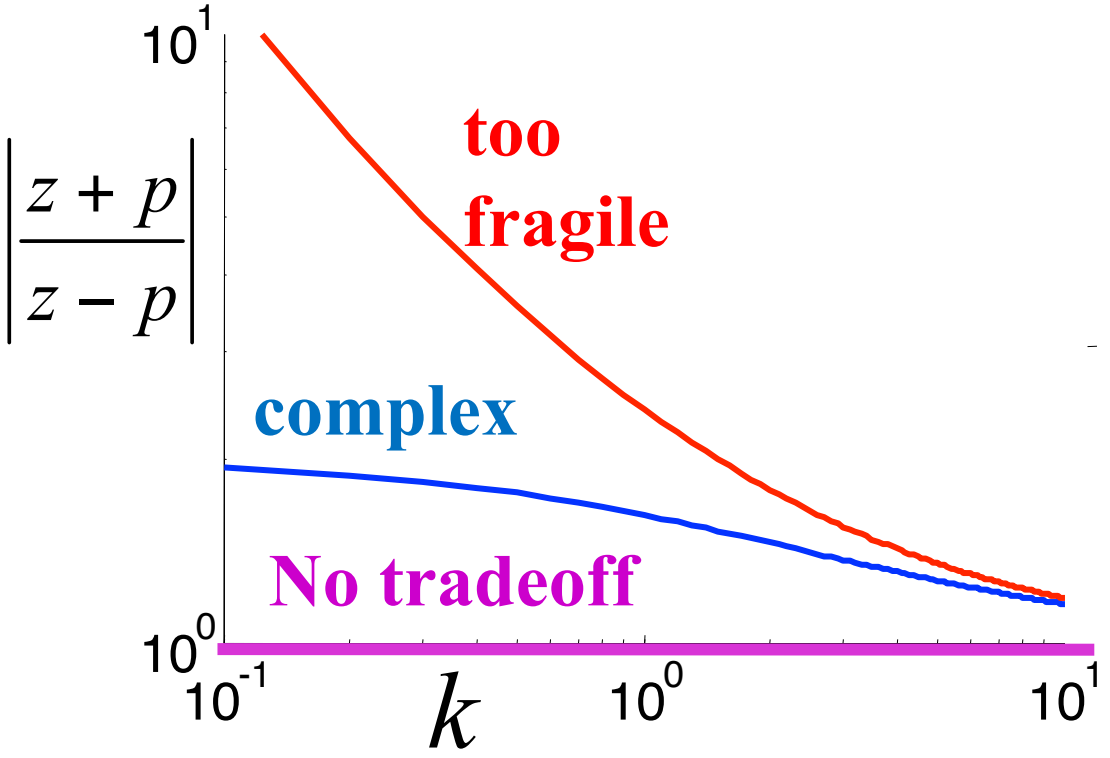


Robust Efficiency in Energy Supply

$$\left.\begin{matrix} \exp\left(\int \ln|T|\right) \\ \|T\|_\infty \end{matrix}\right\} \geq \left|\frac{z+p}{z-p}\right|$$

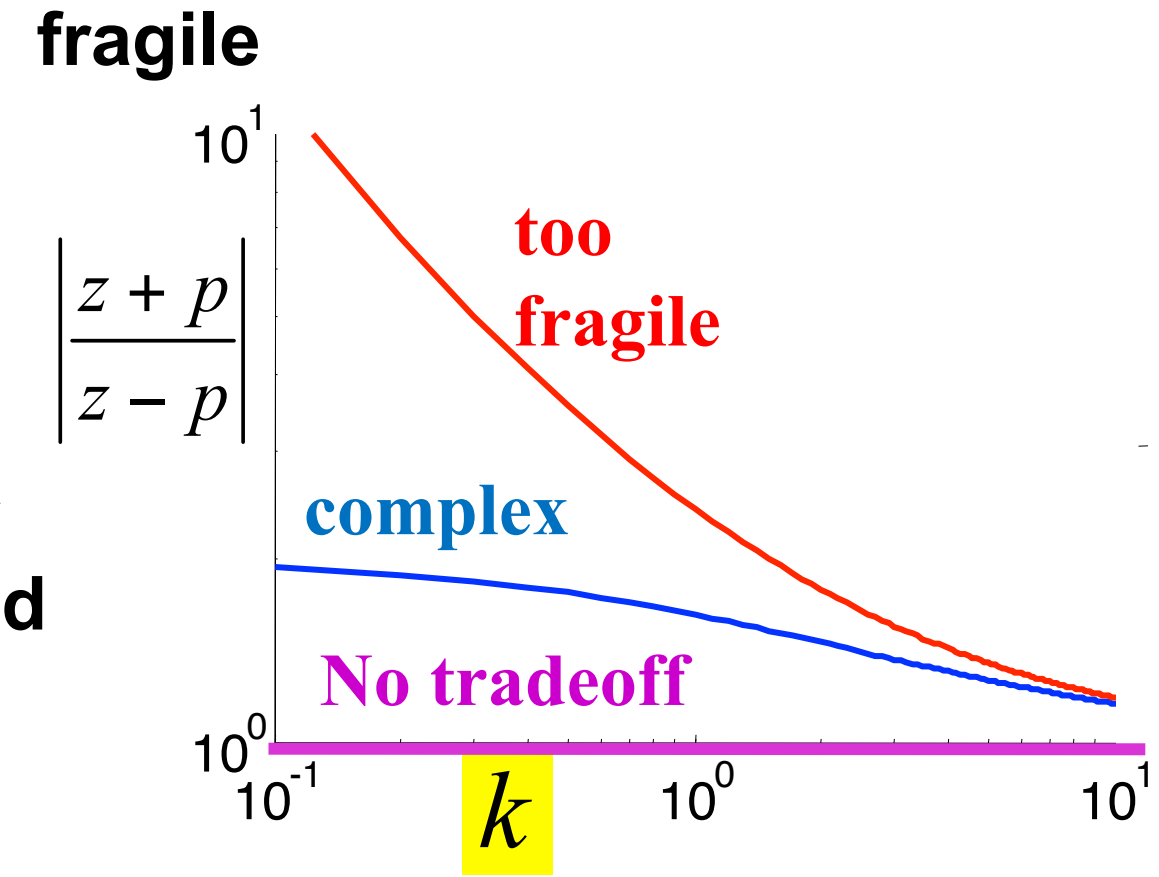
fragile

Robust to Δ in supply and demand



Metabolic overhead to make enzymes

Robust to Δ in supply and demand



What (some) reviewers say

- "…to establish universality … is **simply wrong**. It cannot be done…
- … a mathematical scheme **without any real connections to biological or medical**…
- …universality is well justified in physics… for biological and physiological systems …**a dream …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** …

What (some) reviewers say

- "…to establish universality … is **simply wrong**. It cannot be done…
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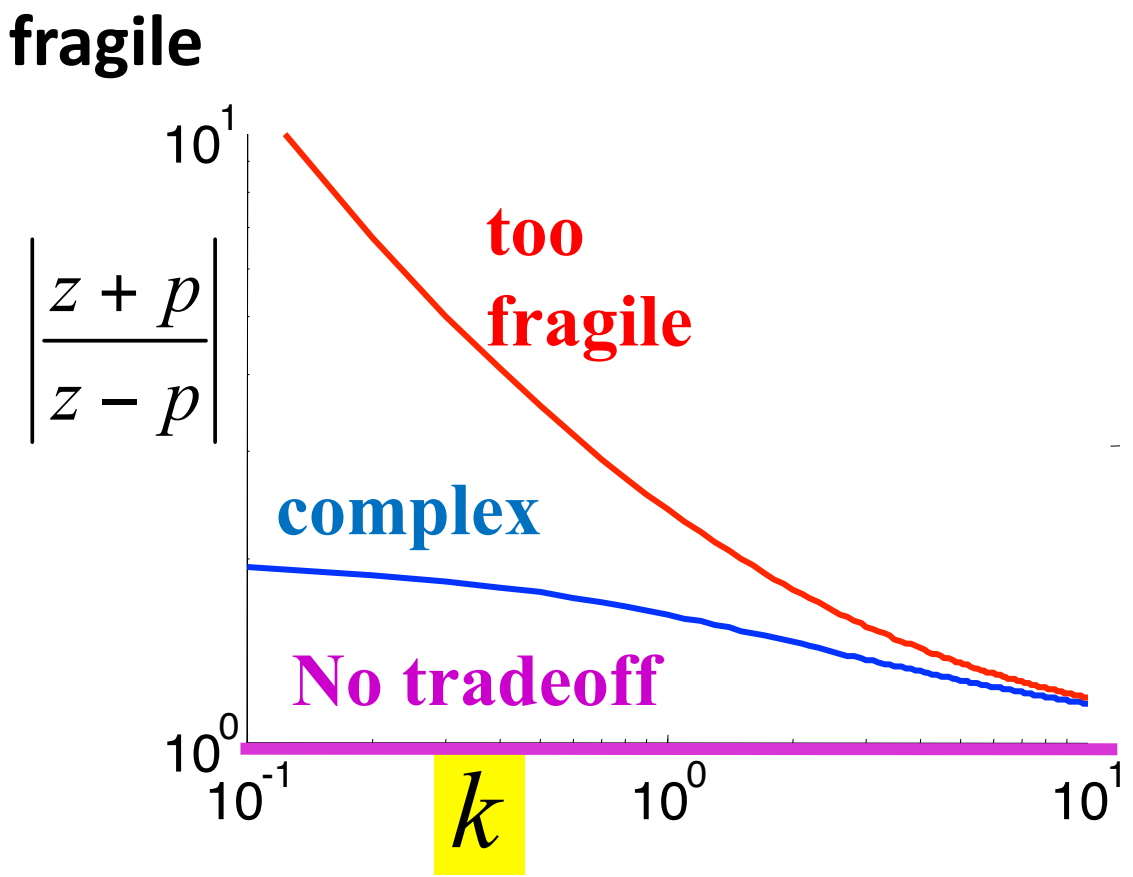
- …unive… for biolog… **dream …neve**…rsity in such s…
- …**does not seem to understand or appreciate** the vast diversity of biological and physiological systems…
- …a high degree of abstraction, which …make[s] the model **useless** …

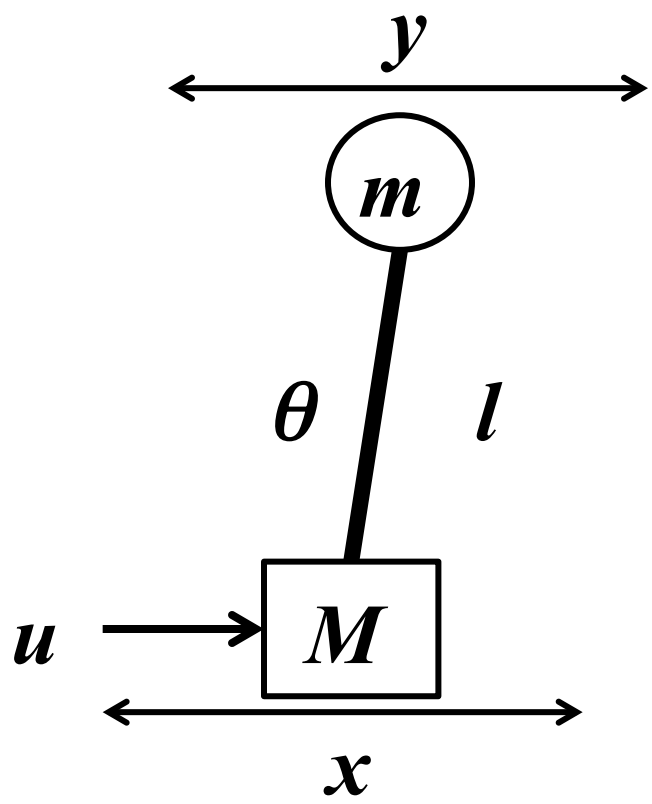
If you agree
- You're in good company
- Stay off commercial aircraft

Robust to Δ in supply and demand



Uncertainty?

Standard inverted pendulum



l	*length*
m	*mass*
M	*mass*
g	*gravity*
u	*control force*

$$y = x + l_O \sin\theta + n$$

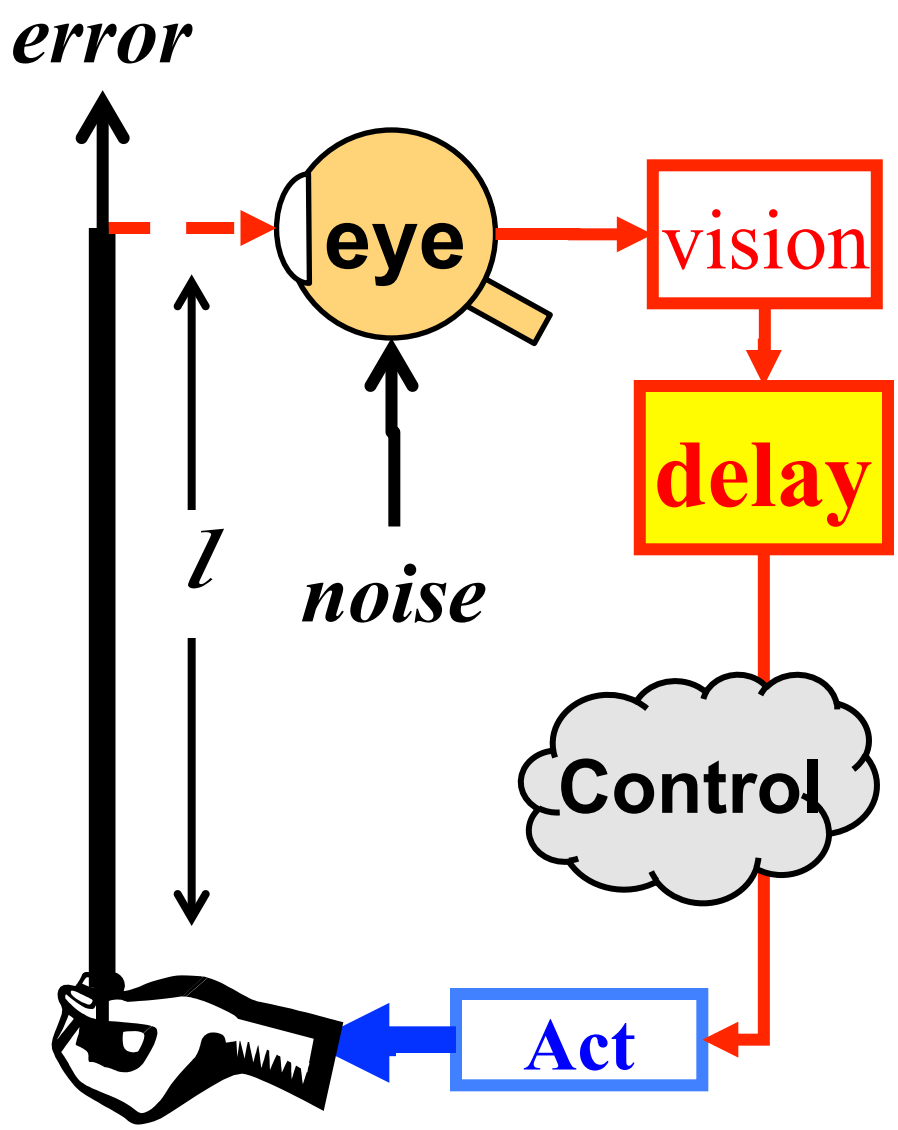
$$\ddot{x}\cos\theta + l\ddot{\theta} + g\sin\theta = 0$$

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

Uncertainty?

In our model?
In our brain?
In our brain's model?

- Parameters
- Noise
- Unmodeled dynamics



$$y = x + l_o \sin\theta + n$$

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

Uncertainty?

In our model?
In our brain?
In our brain's model?

Analysis
Limits/laws
Synthesis

- **Parameters (real)**
- **Noise (additive)**
- **Unmodeled dynamics (complex)**
- **Nonlinear dynamics**

$$y = x + l_O \sin\theta + n$$

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

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

Homeostasis and HRV

controls

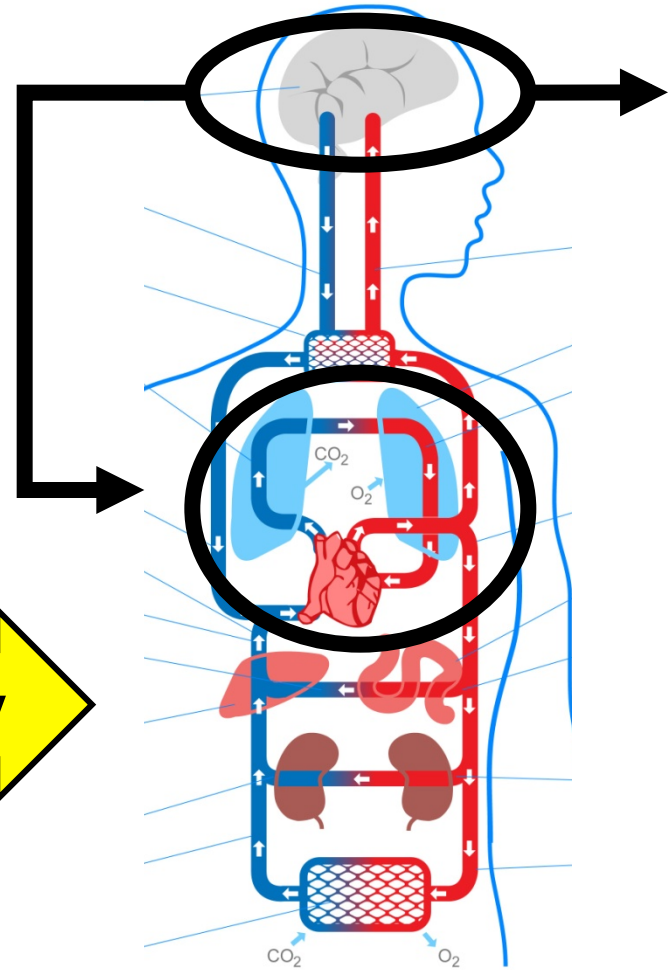
heart rate

ventilation

errors

O2

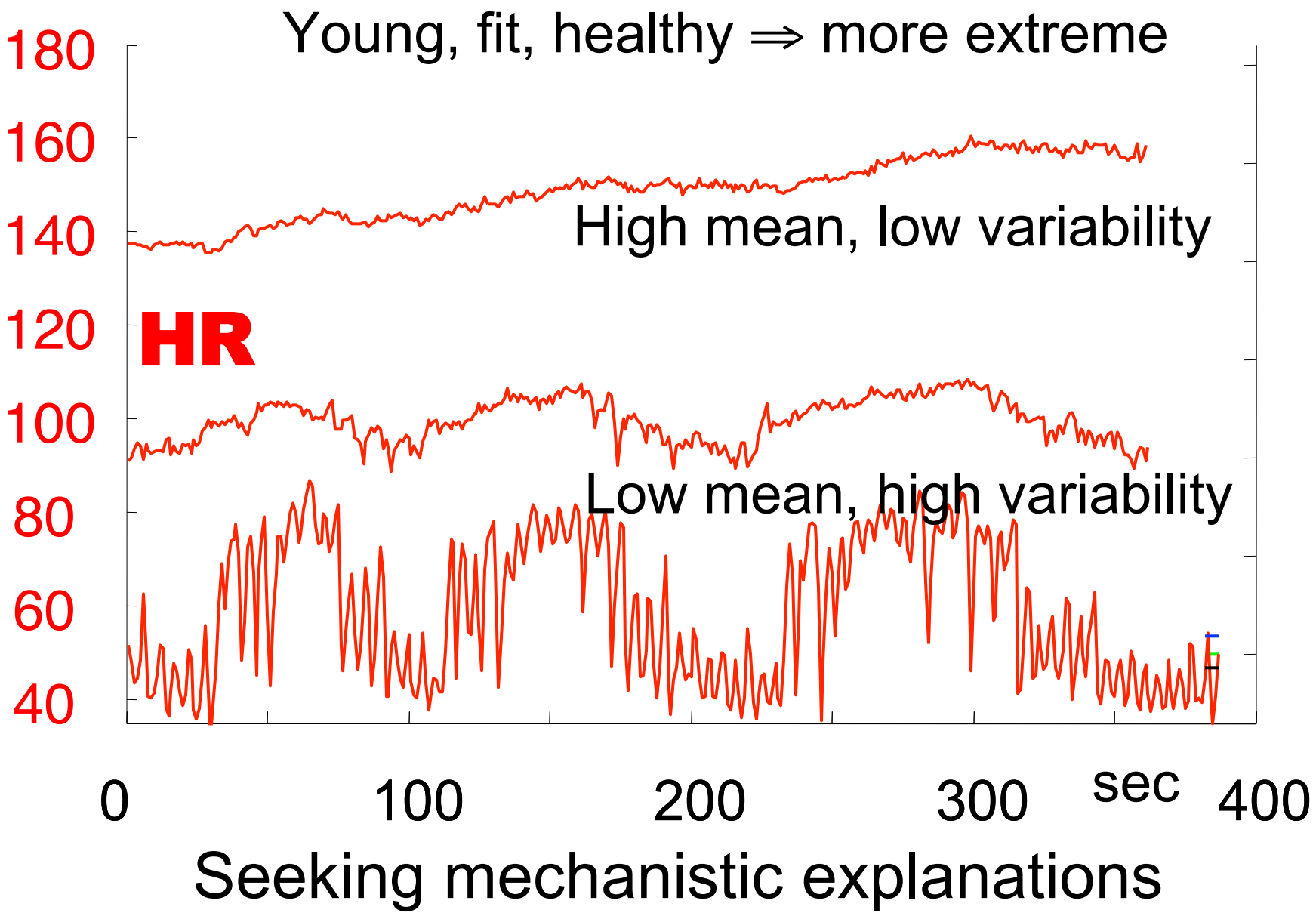
BP



energy

external disturbances

The persistent mystery



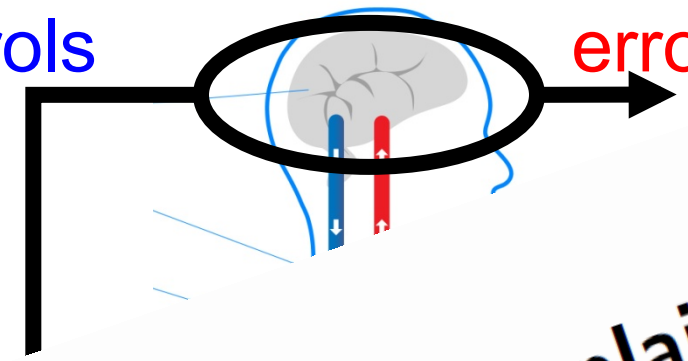
Seeking mechanistic explanations

Homeostasis and HRV

controls

errors

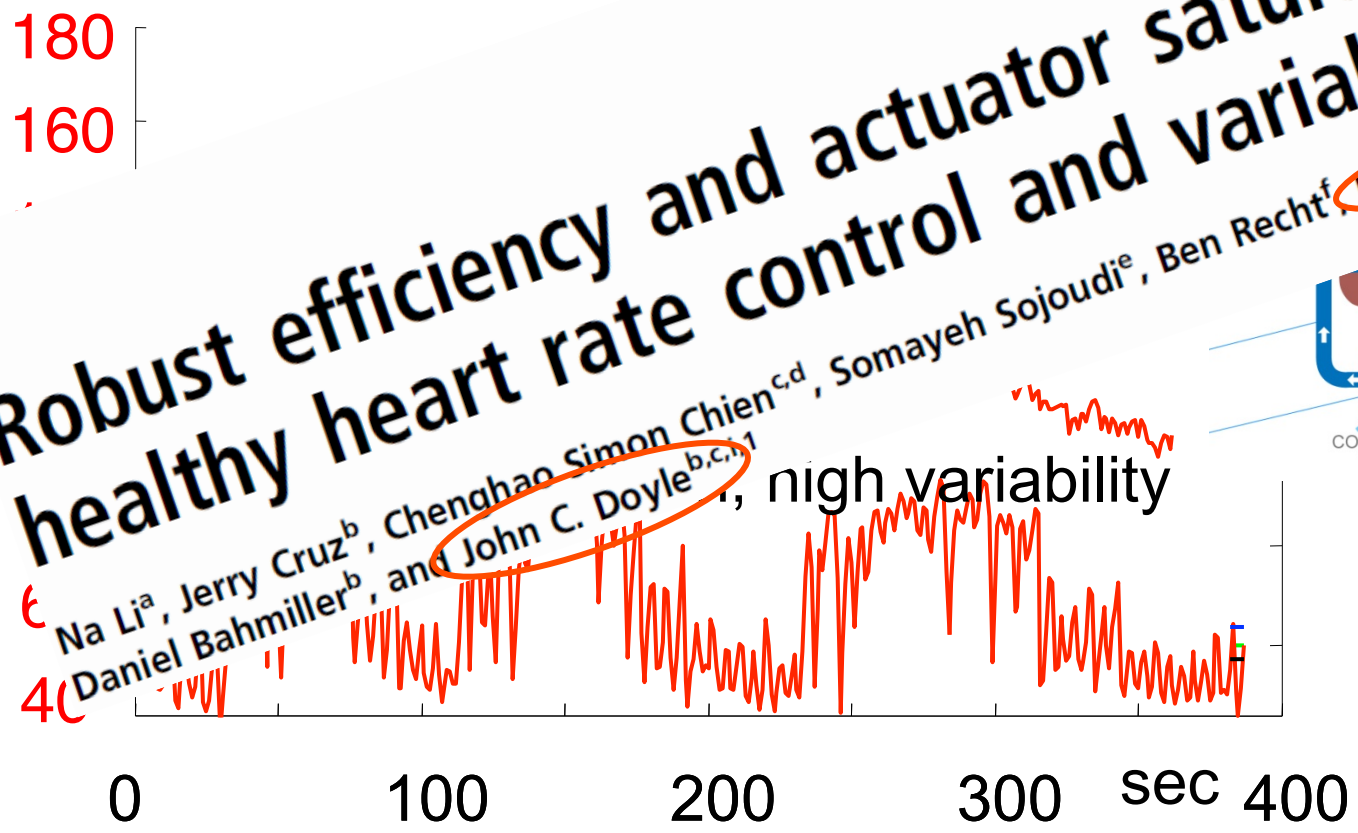
heart rate
ventilation



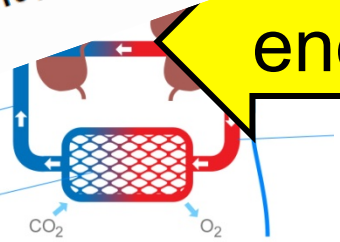
Finally!

Robust efficiency and actuator saturation explain healthy heart rate control and variability

Na Li[a], Jerry Cruz[b], Chenghao Simon Chien[c,d], Somayeh Sojoudi[e], Ben Recht[f], David Stone[g], Marie Csete[h], Daniel Bahmiller[b], and John C. Doyle[b,c,1]



energy



external disturbances

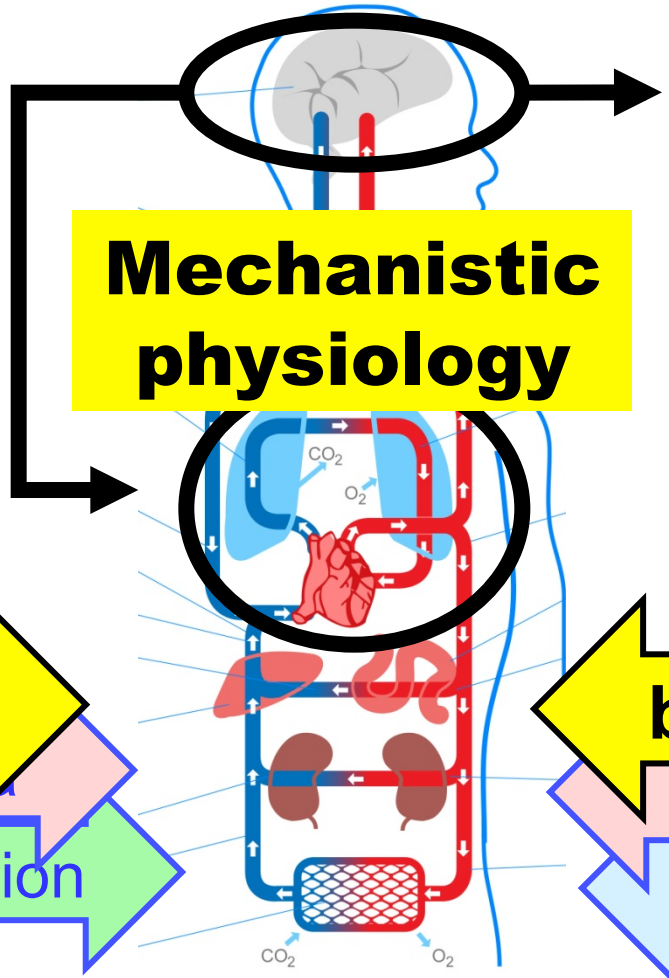
Homeostasis and robust efficiency

controls

heart rate
ventilation
vasodilation
coagulation
inflammation
digestion
storage
…

errors

O2
BP
pH
Glucose
Energy store
Blood volume
…



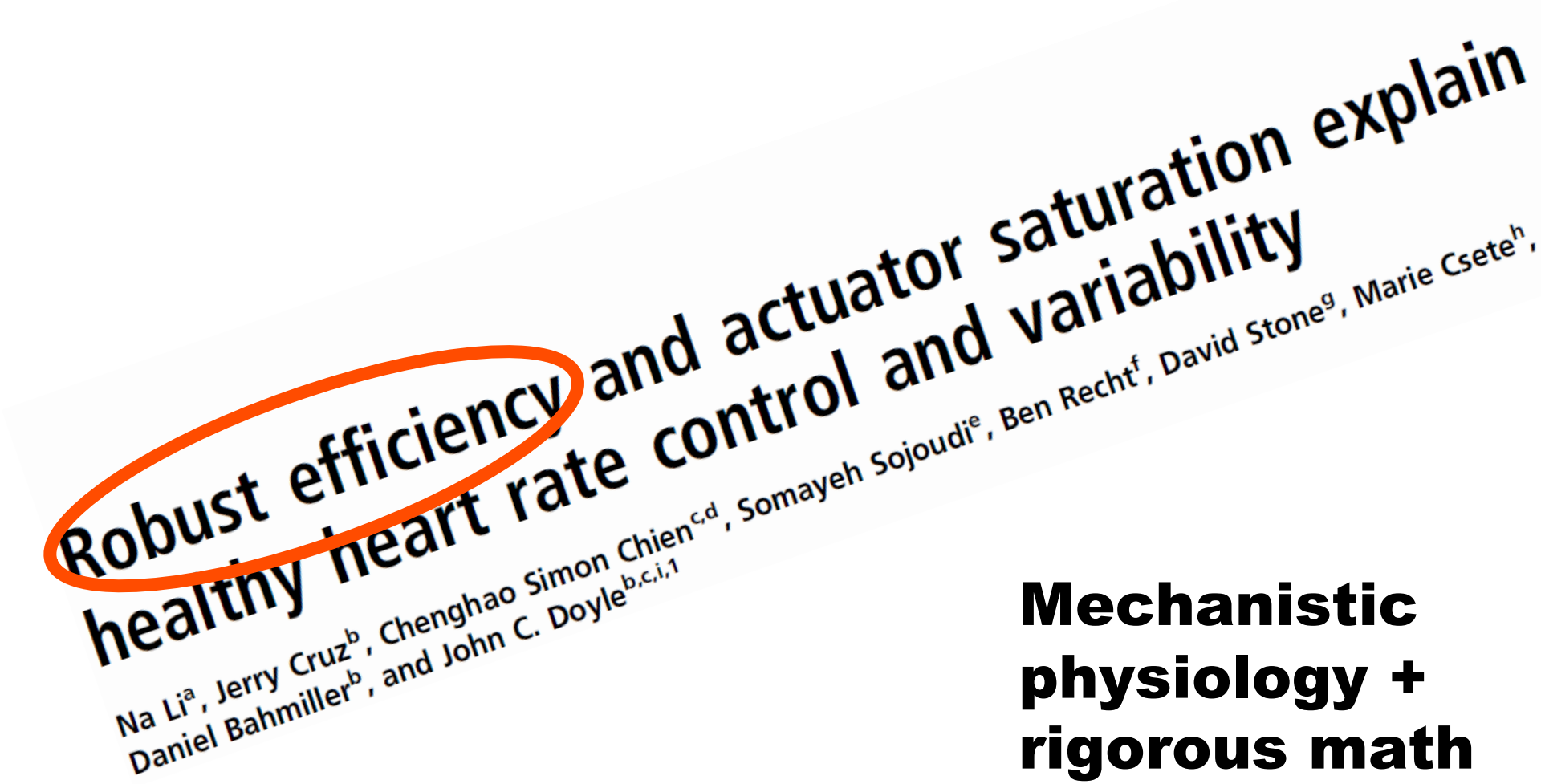
energy
trauma
infection

breath
heart beat
sensor

external disturbances

internal noise

The main tradeoff: Robust efficiency



Robust efficiency and actuator saturation explain healthy heart rate control and variability

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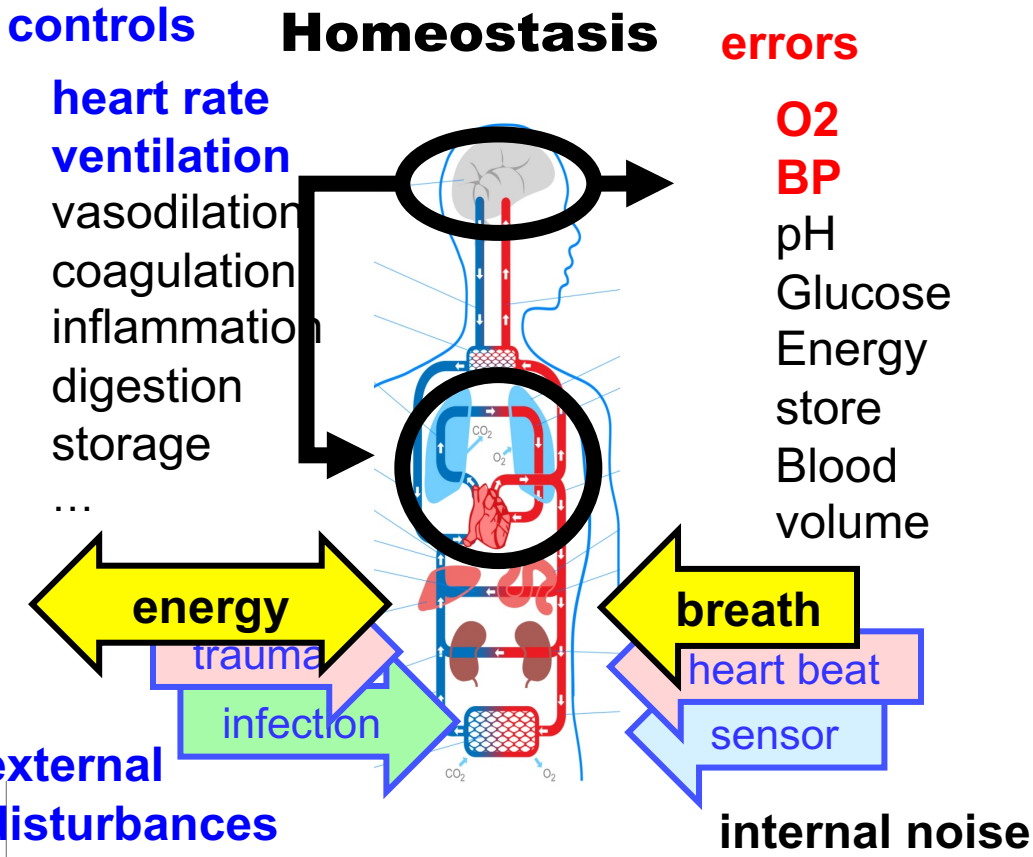
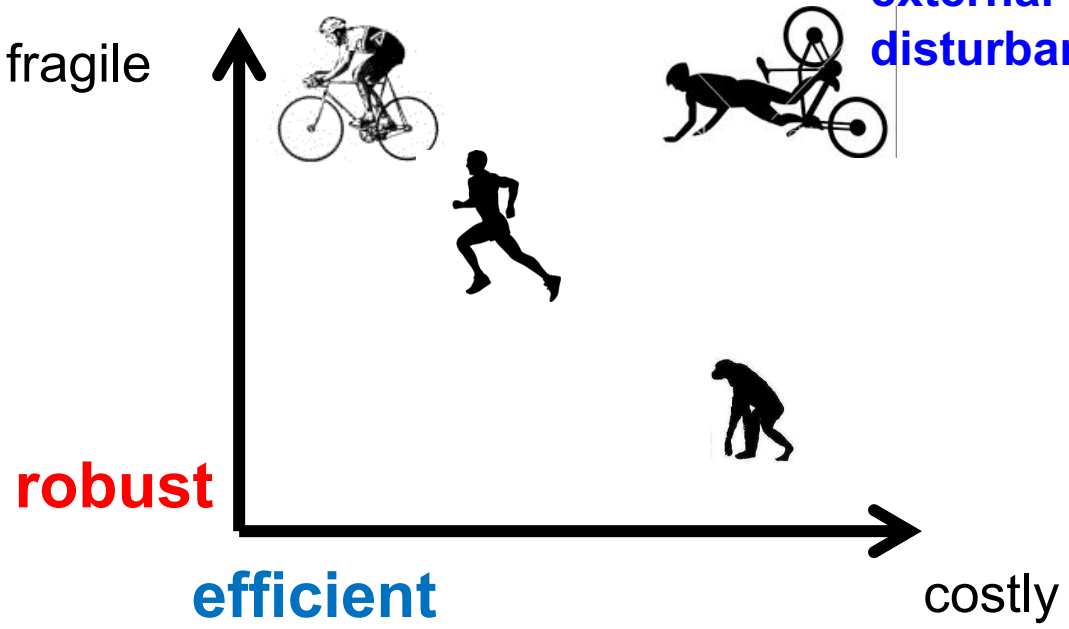
Mechanistic physiology + rigorous math and stats

Tradeoffs:

- physiology
- evolution
- ecologically relevant





Mechanistic physiology + rigorous math and stats

Homeostasis

controls

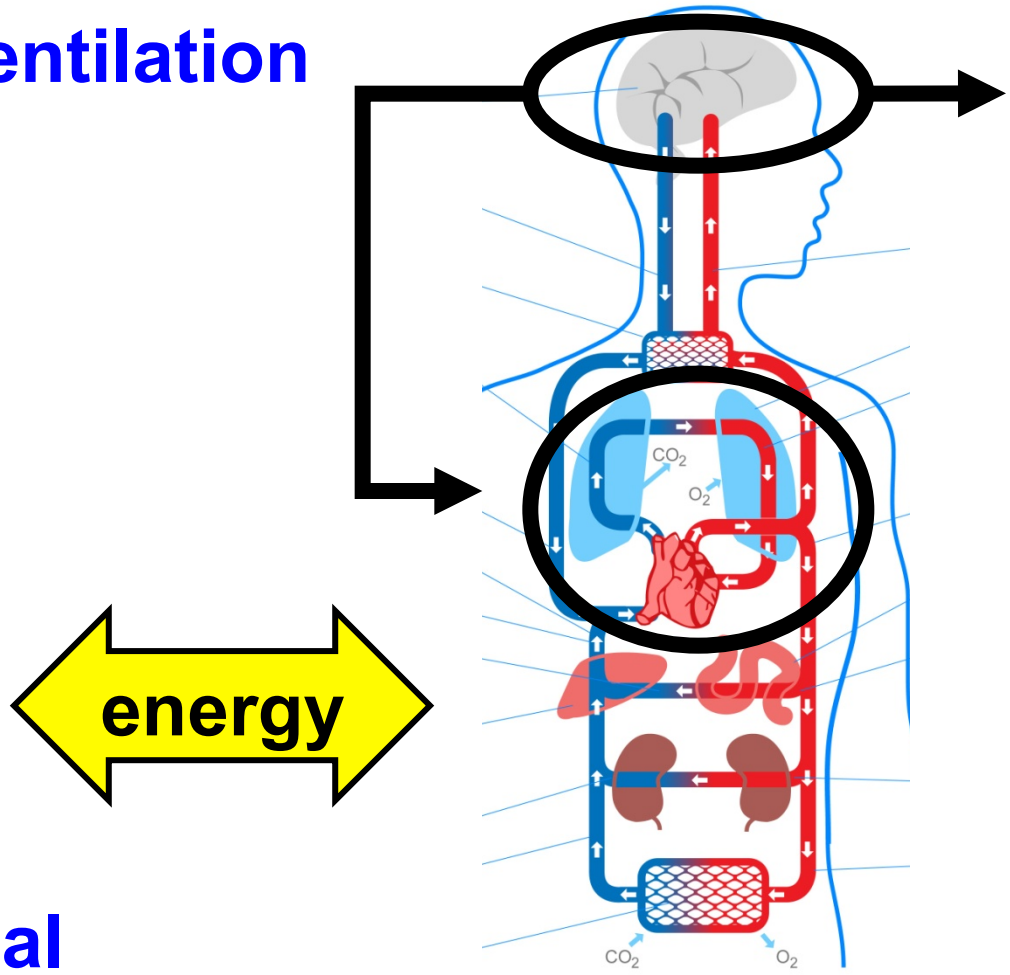
heart rate

ventilation

errors

O2

BP



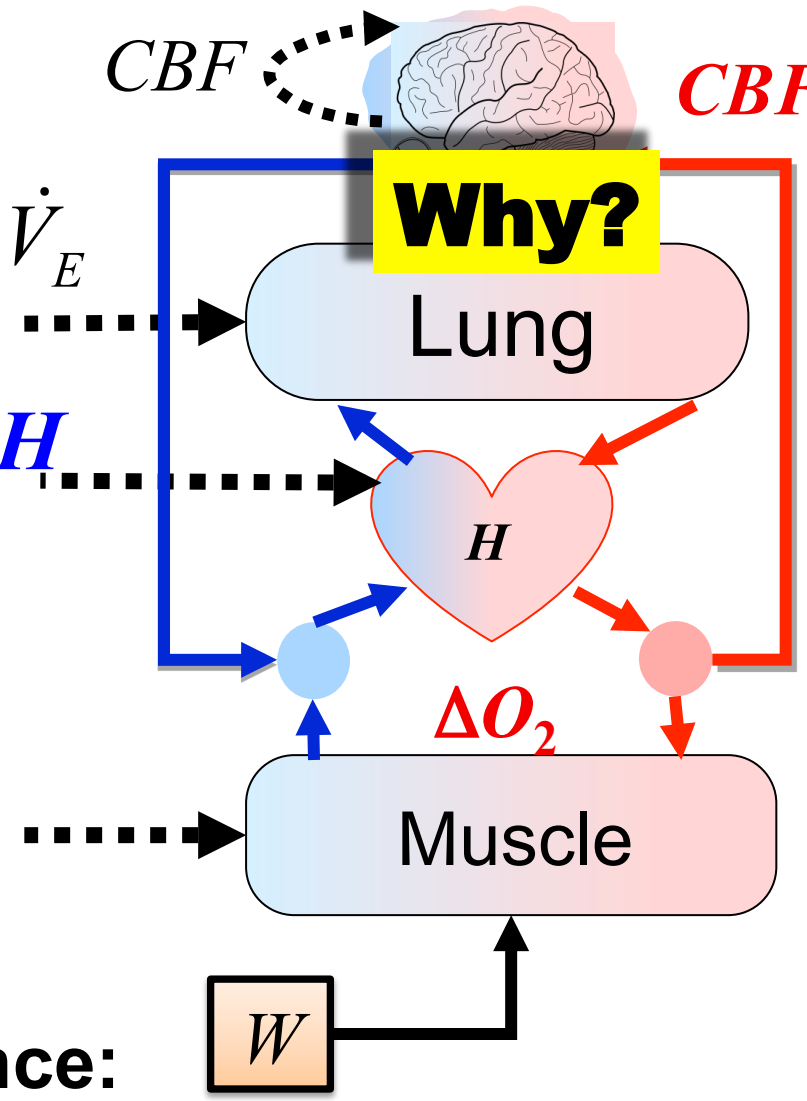
energy

external disturbances

high variability

Health

low variability



dilate

pump

pump

dilate

Disturbance:
W

CBF

flow

SaO_2

O_2

P_{as}

pressure

O_2

Minimal cartoon

high variability

Healthy homeostasis

low variability

regulated variables

flow

O_2

pressure

O_2

dilate

pump

pump

dilate

actuators

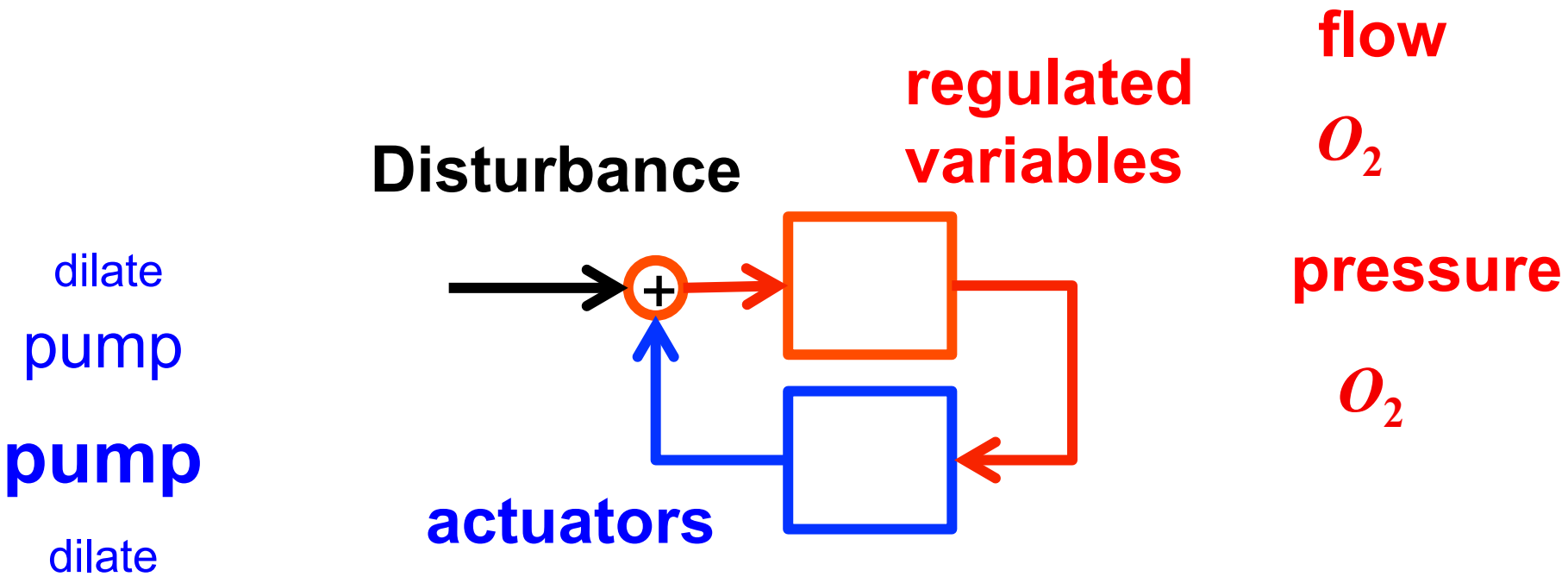
Disturbance: run

Minimal cartoon

high variability

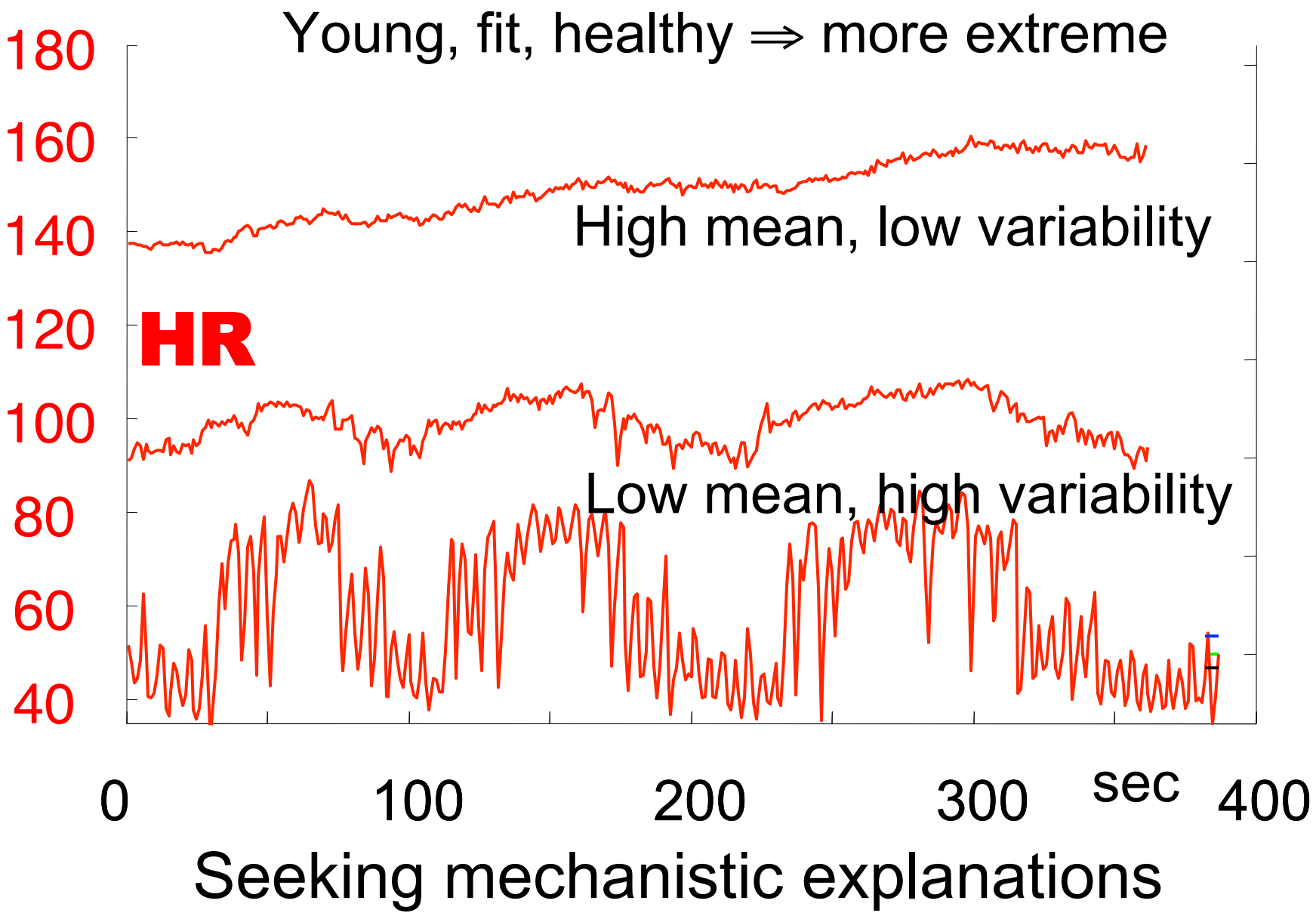
Healthy homeostasis

low variability



Minimal cartoon

The persistent mystery



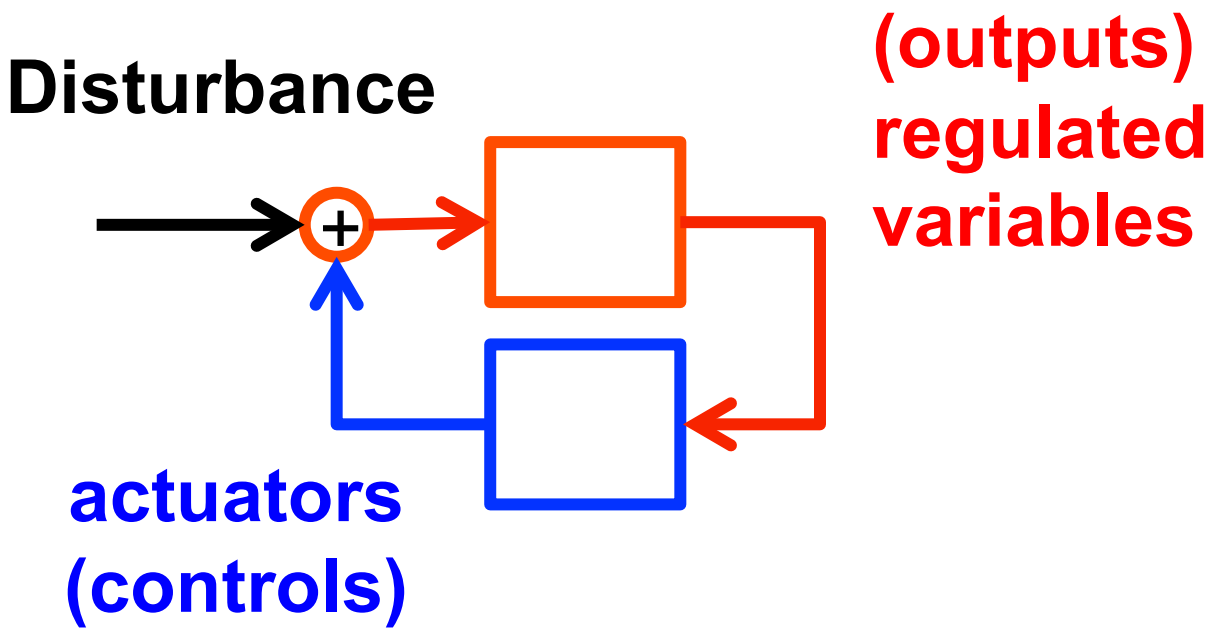
Seeking mechanistic explanations

Universals

low variability errors

\+ ***large*** disturbances

⇒ ***high*** variability controls



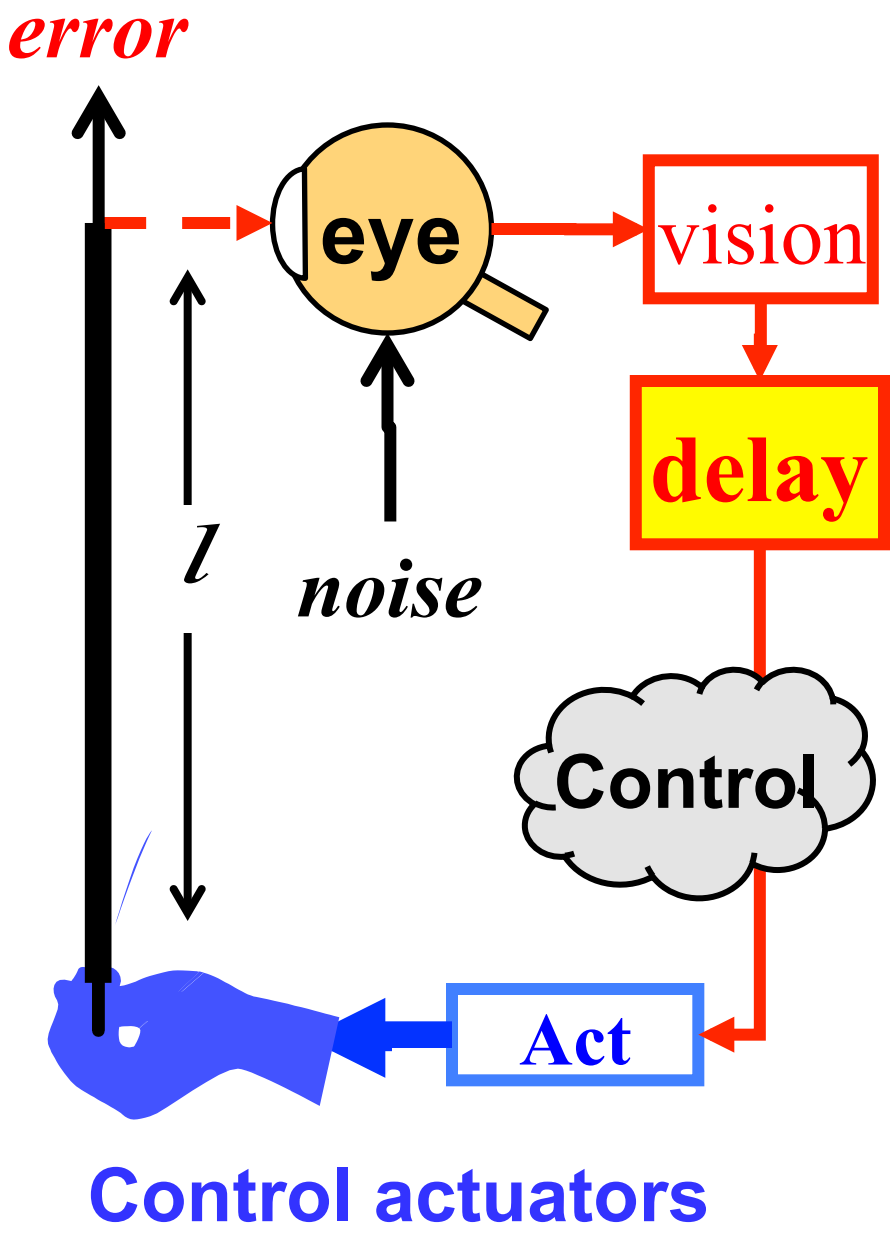
Universals

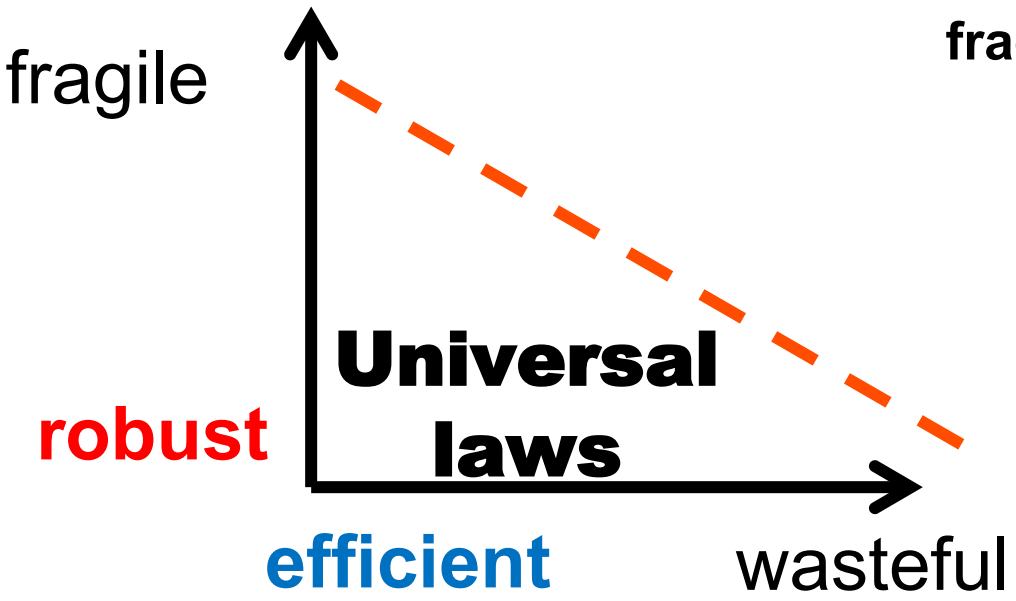
low variability ***errors***

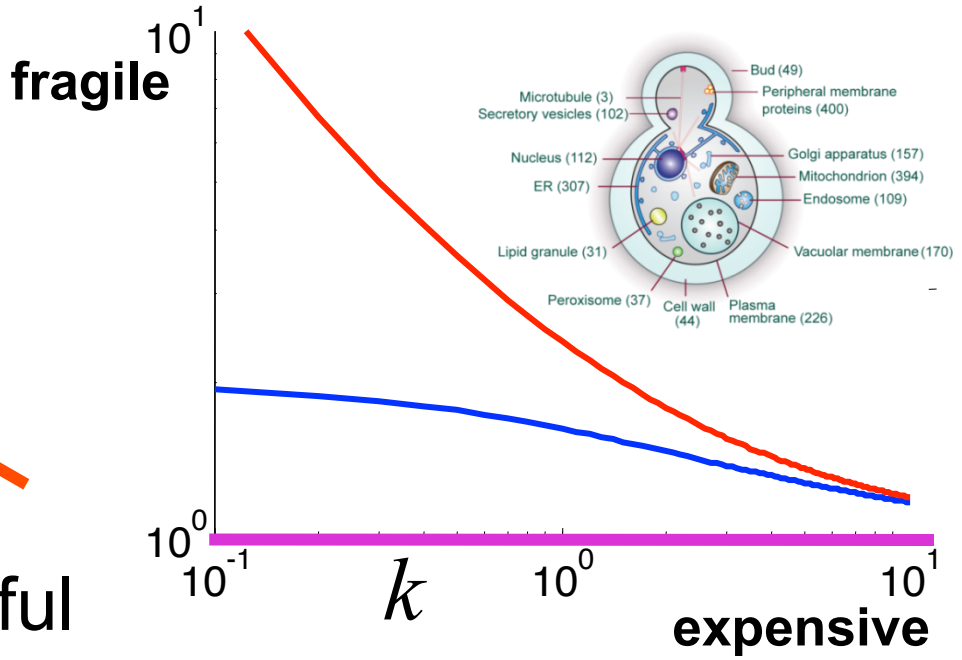
\+ ***large noise/delay***

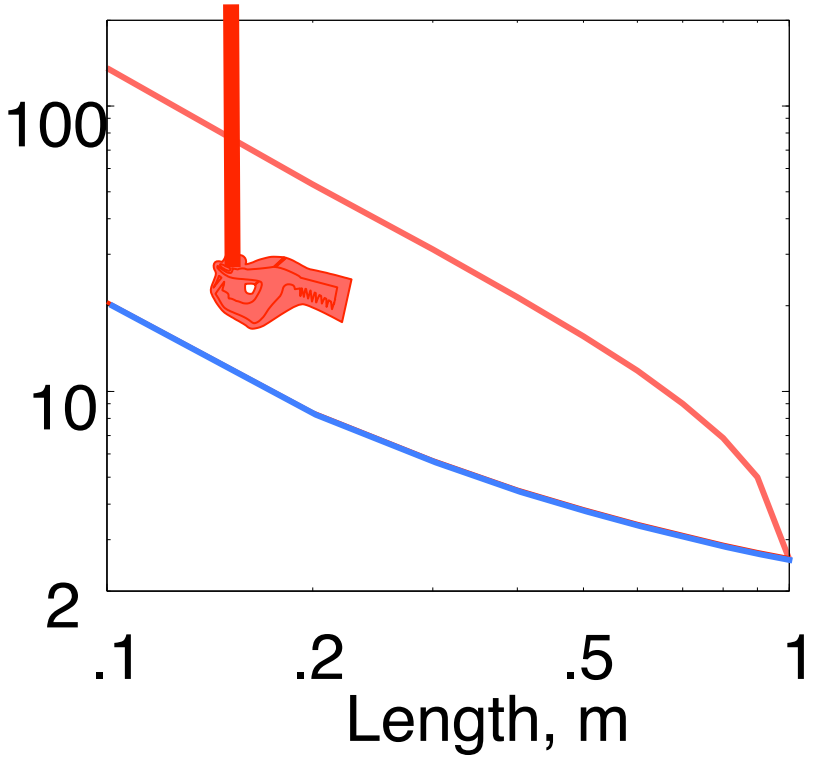
⇒ ***high*** variability controls

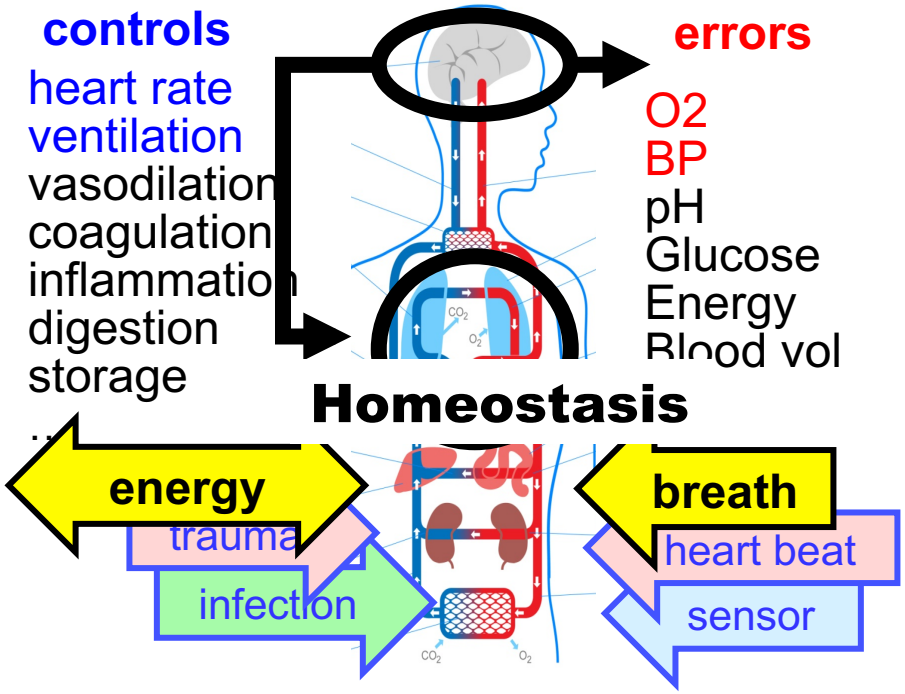
Is loss of actuator variability a precursor of a crash?

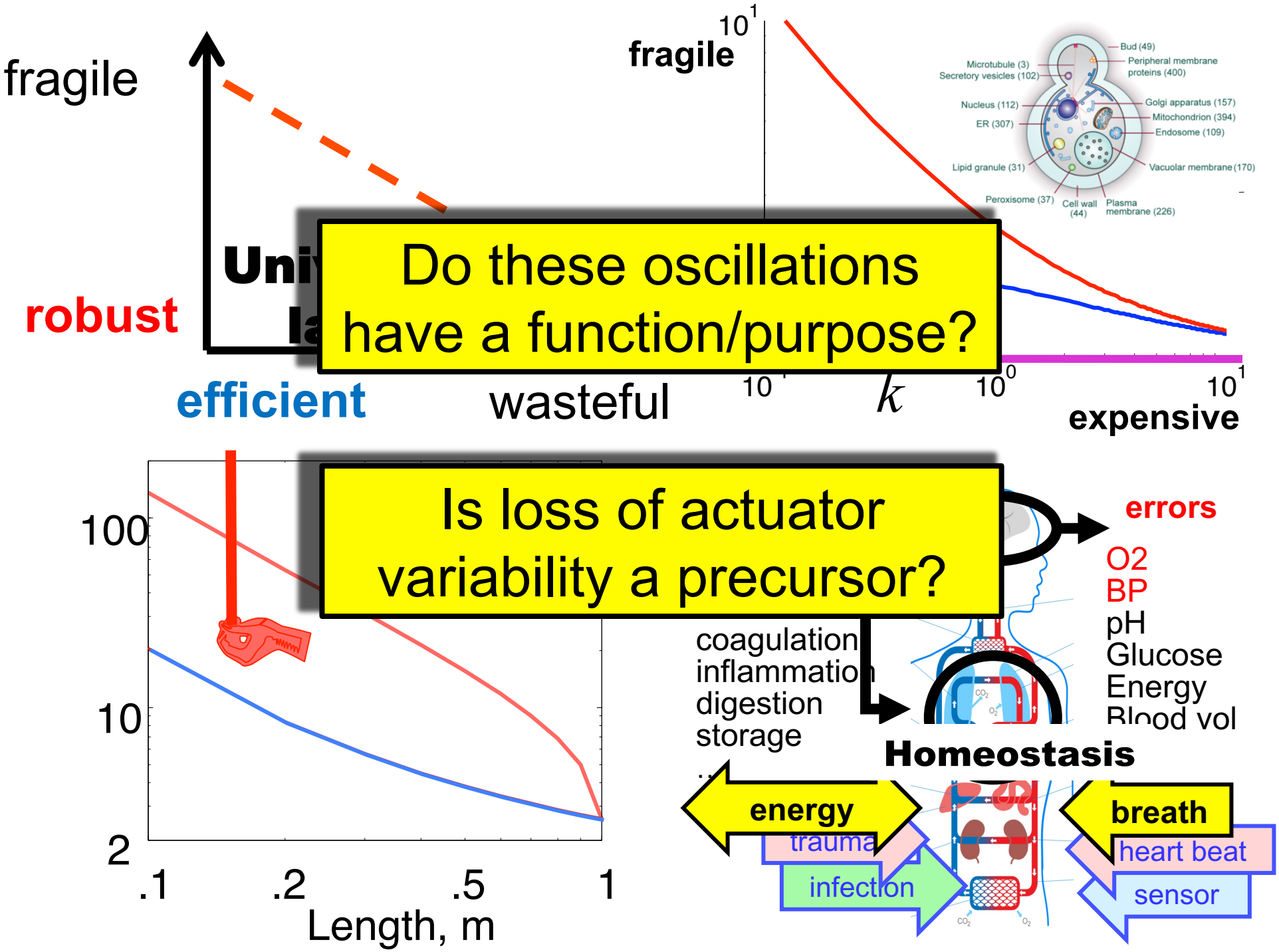



fragile
Universal
laws
robust
efficient
wasteful


fragile
10^1
10^0
10^{-1}
k
10^0
10^1
expensive
Bud (49)
Peripheral membrane proteins (400)
Microtubule (3)
Secretory vesicles (102)
Nucleus (112)
Golgi apparatus (157)
ER (307)
Mitochondrion (394)
Endosome (109)
Lipid granule (31)
Vacuolar membrane (170)
Peroxisome (37)
Cell wall (44)
Plasma membrane (226)


100
10
2
.1
.2
.5
1
Length, m


controls
heart rate
ventilation
vasodilation
coagulation
inflammation
digestion
storage
errors
O2
BP
pH
Glucose
Energy
Blood vol
Homeostasis
energy
trauma
infection
breath
heart beat
sensor


fragile
robust
efficient
wasteful
fragile
expensive
10^1
10^0
10^{-1}
k
Bud (49)
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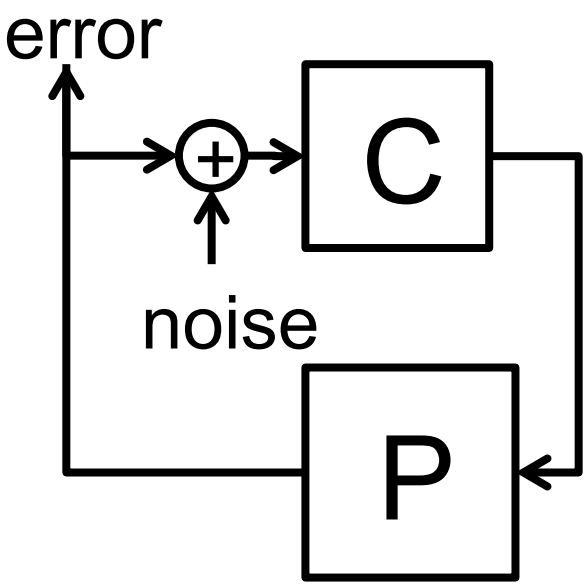
Mitochondrion (394)
Endosome (109)
Lipid granule (31)
Vacuolar membrane (170)
Peroxisome (37)
Cell wall (44)
Plasma membrane (226)
Do these oscillations have a function/purpose?
Is loss of actuator variability a precursor?
100
10
2
.1
.2
.5
1
Length, m
errors
O2
BP
pH
Glucose
Energy
Blood vol
coagulation
inflammation
digestion
storage
Homeostasis
energy
trauma
infection
breath
heart beat
sensor

Understand this more deeply?

$$\exp\left\{\int \ln|T|\right\}_{\|T\|_\infty} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$

Mechanics+
Gravity +
Light +
Control theory

$$|T(j\omega)| = \left|\frac{E}{N}\right|$$



+ Neuroscience