Universal laws and architecture:

Theoretical foundations for complex networks relevant to biology, medicine, and neuroscience?

John Doyle

John G Braun Professor

Control and Dynamical Systems, EE, BE

Caltech

Thanks

Lectures

1) Concrete motivation
2-3) Universal laws and architectures*
4) A teensy bit of math

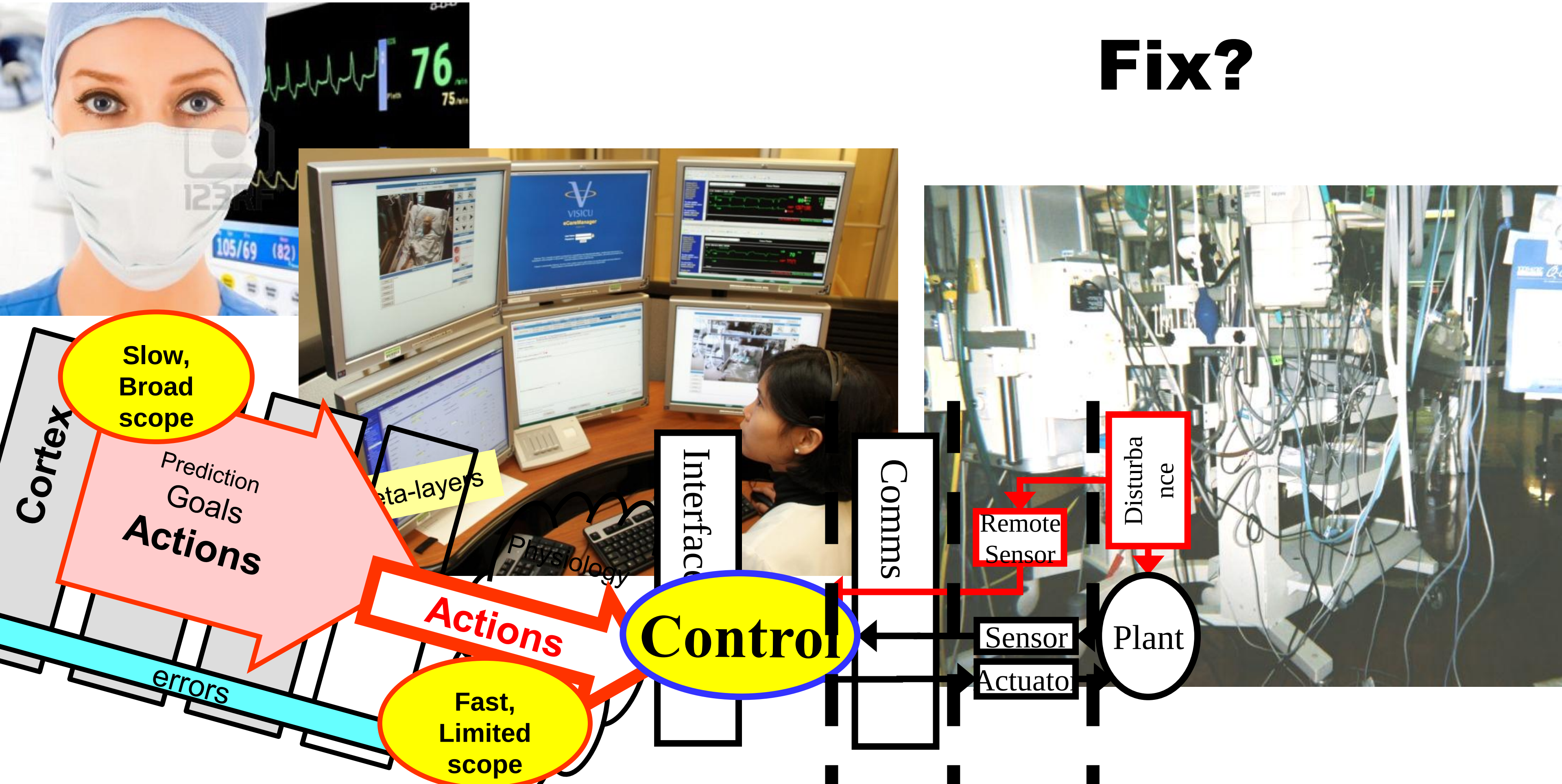
*have you ever heard of anything more pretentious?

Seriously?

1) Irresponsible speculation
(Feedback from audience)
2-3) Slightly less speculative?
4) A teensy bit of math?

Existing design frameworks
- Sophisticated components
- Poor integration
- Limited theoretical framework

Fix?



Lectures

1) Concrete motivation
2-3) Universal laws and architectures
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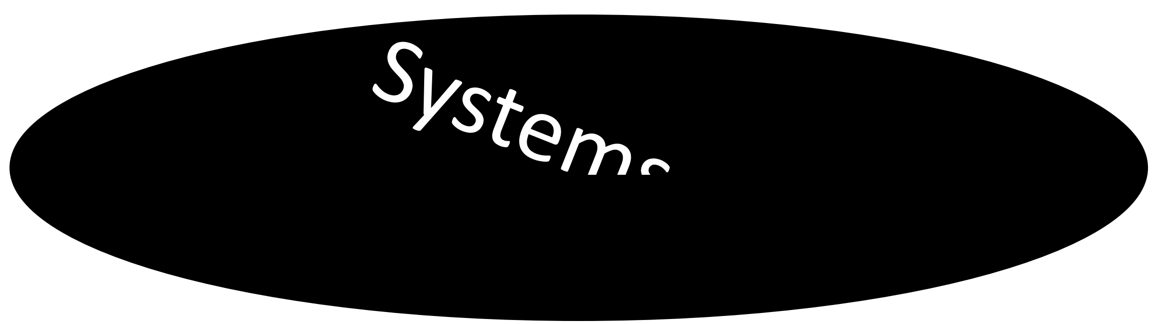
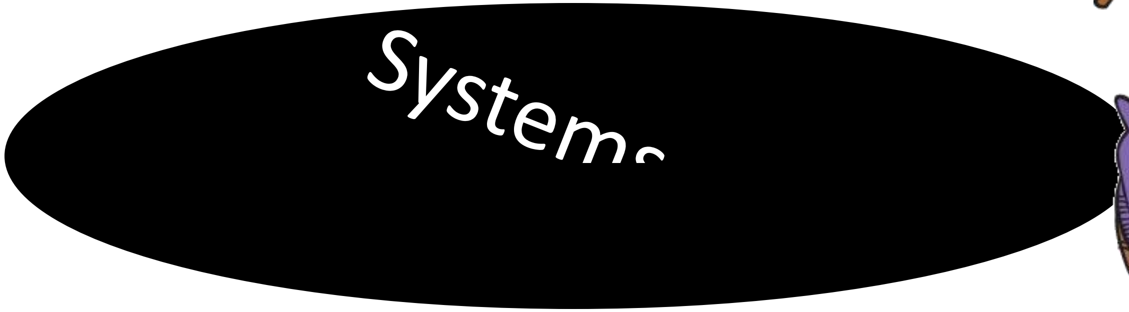
A rant

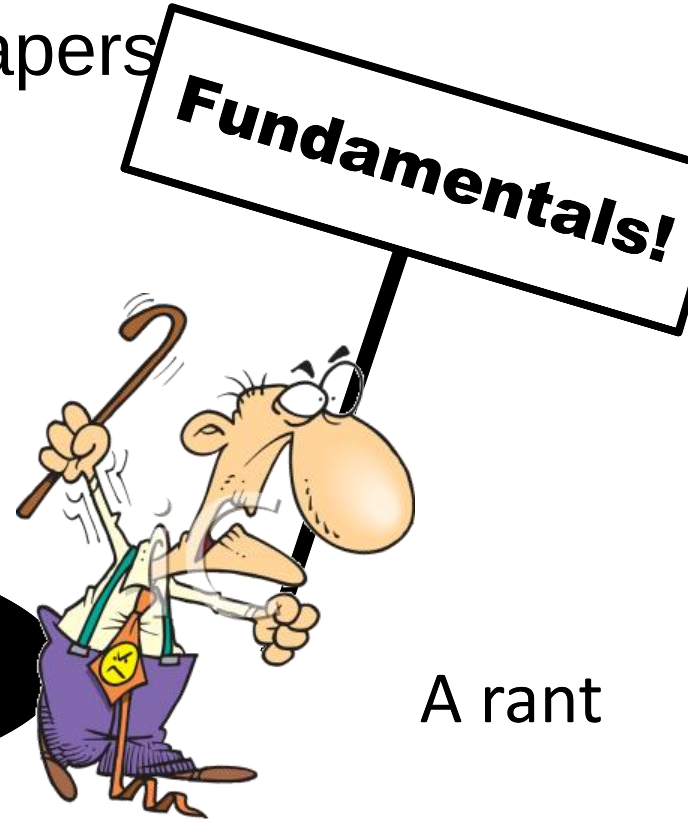


“Universal laws and architectures?”

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

*try to get you to read them?





A rant

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.**

Very accessible
No math

Architecture, constraints, and behavior

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

evolved for sensorimotor control and retain much of that evolved architecture, then the apparent distinctions between perceptual, cognitive, and motor processes may be another form of illusion (9), reinforcing the claim that robust control and adaptive feedback (7, 11) rather than more conventional serial signal processing might be more useful in interpreting neurophysiology data (9). This view also seems broadly consistent with the arguments from grounded cognition that modal simulations, bodily states, and situated action underlie not only 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,* JULY 25 2011

Human complexity

Robust

Fragile

Human complexity

Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Healing wound /infect	☹ AutoImmune/Inflame

Start with physiology

Lots of triage

Benefits

Robust

- ☺ Metabolism
- ☺ Regeneration & repair
- ☺ Healing wound /infect

- ☺ Efficient
- ☺ Mobility
- ☺ Survive uncertain food supply
- ☺ Recover from moderate trauma and infection

Mechanism?

Robust

- ☺ Metabolism
- ☺ Regeneration & repair
- ☺ Healing wound /infect
  - ☹ Fat accumulation
  - ☹ Insulin resistance
  - ☹ Proliferation
  - ☹ Inflammation

Fragile

- ☹ Obesity, diabetes
- ☹ Cancer
- ☹ AutoImmune/Inflame
  - ☹ Fat accumulation
  - ☹ Insulin resistance
  - ☹ Proliferation
  - ☹ Inflammation

What's the difference?

Robust

- ☺ Metabolism
- ☺ Regeneration & repair
- ☺ Healing wound /infect

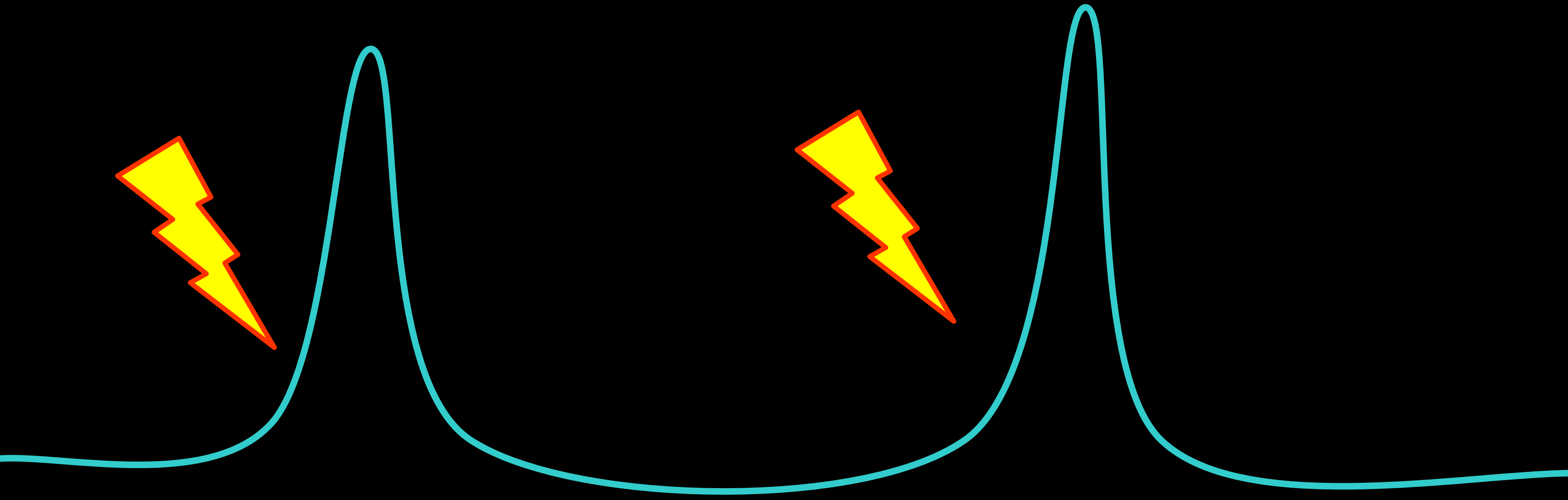
Fragile

- ☹ Obesity, diabetes
- ☹ Cancer
- ☹ AutoImmune/Inflame

- ☹ Fat accumulation
- ☹ Insulin resistance
- ☹ Proliferation
- ☹ Inflammation

Controlled
Dynamic

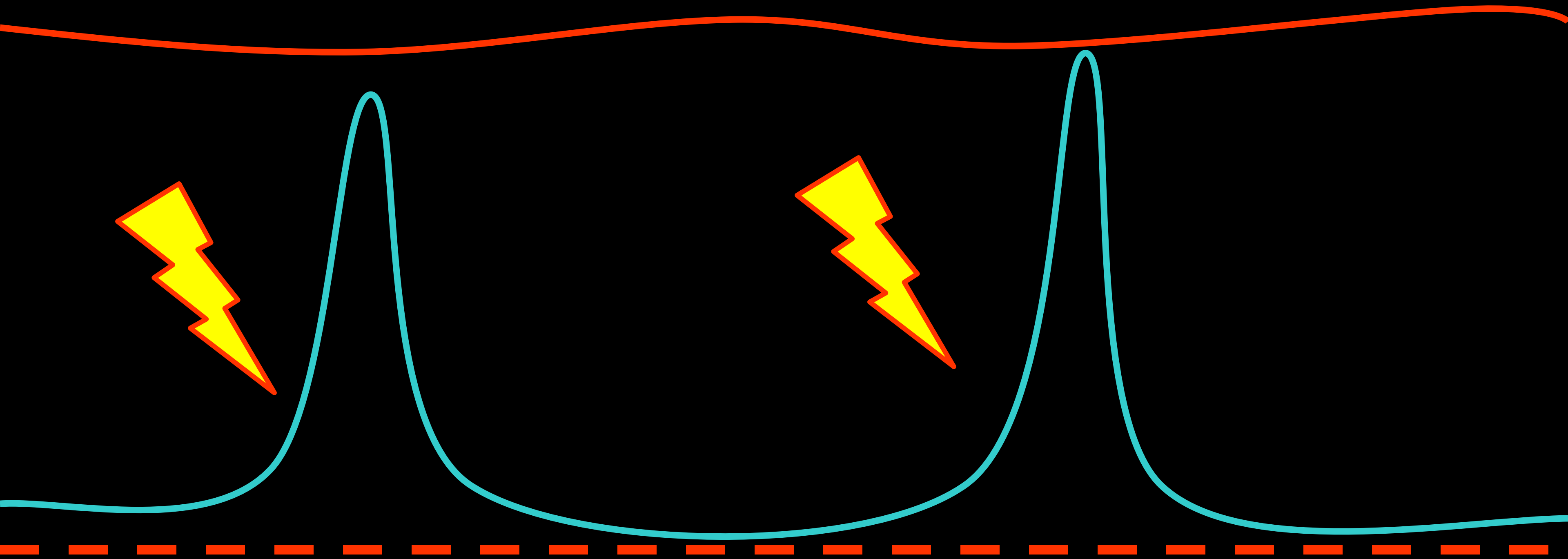
Uncontrolled
Chronic



☹ Fat accumulation
☹ Insulin resistance
☹ Proliferation
☹ Inflammation

Controlled
Dynamic

Low mean
High variability



Death

☹ Fat accumulation
☹ Insulin resistance
☹ Proliferation
☹ Inflammation

Controlled
Dynamic

Low mean
High variability

Uncontrolled
Chronic

High mean
Low variability

Restoring robustness?

Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Healing wound /infect	☹ AutoImmune/Inflame
☹ Fat accumulation	☹ Fat accumulation
☹ Insulin resistance	☹ Insulin resistance
☹ Proliferation	☹ Proliferation
☹ Inflammation	☹ Inflammation
Controlled	Uncontrolled
Dynamic	Chronic
Low mean	High mean
High variability	Low variability

Human complexity

Robust

☺ Metabolism
☺ Regeneration & repair
☺ Immune/inflammation
☺ Microbe symbionts
☺ Neuro-endocrine
🗐 Complex societies
🗐 Advanced technologies
🗐 Risk “management”

Yet Fragile

☹ Obesity, diabetes
☹ Cancer
☹ AutoImmune/Inflame
☹ Parasites, infection
☹ Addiction, psychosis,…
☠ Epidemics, war,…
💣 Disasters, global &!%$#
💣 Obfuscate, amplify,…

Accident or necessity?

Robust | Fragile

☺ Metabolism
☺ Regenerati
☺ Healing wo

☹ Obesity, diabetes

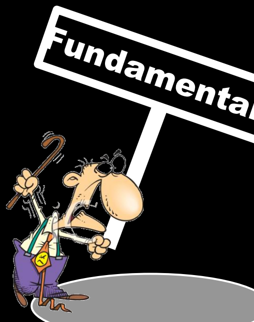
une/Inflame

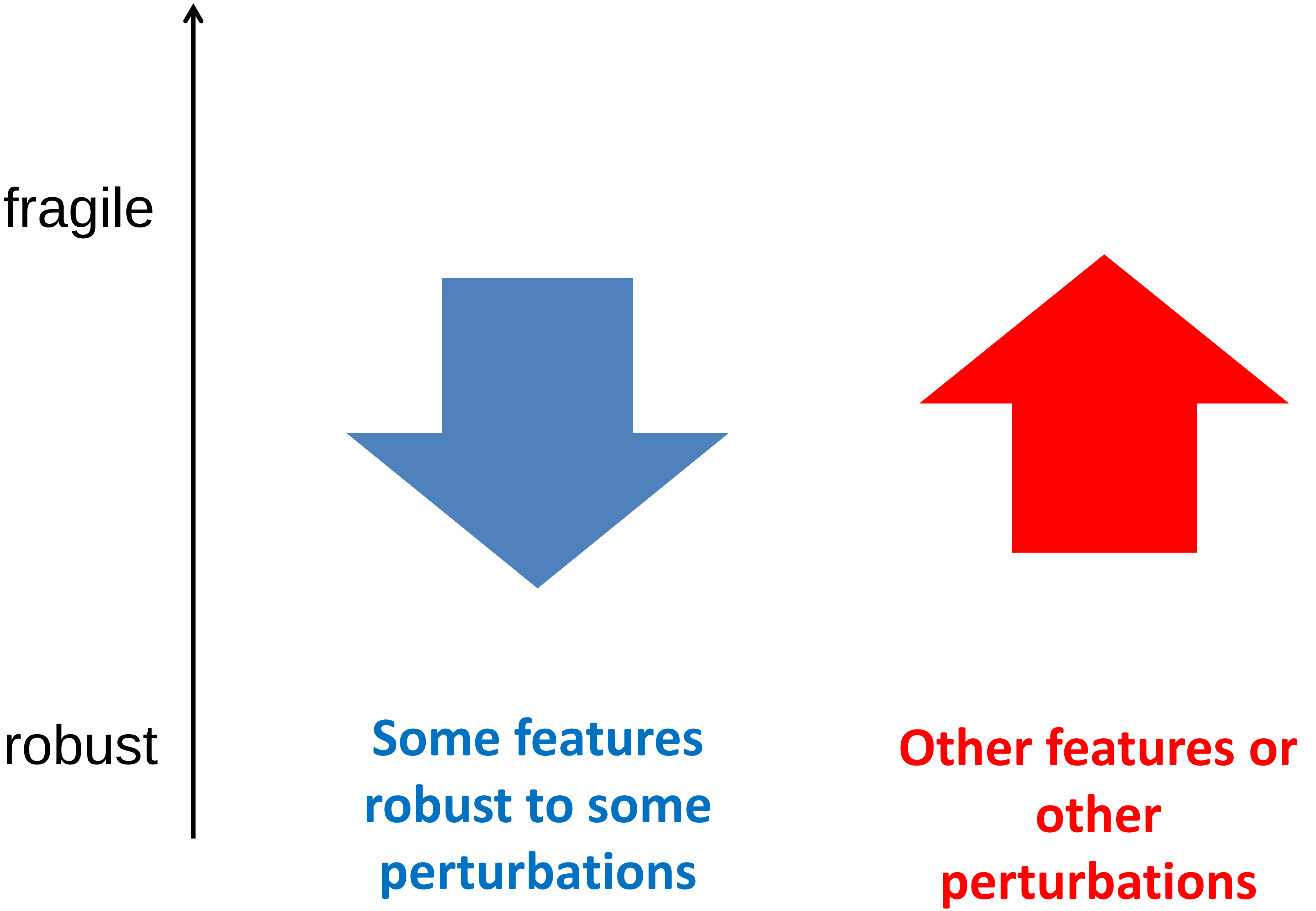
☹ Fat accumulation
☹ Insulin resistance
☹ Proliferation
☹ Inflammation

- Fragility ← Hijacking, side effects, unintended…
- Of mechanisms evolved for robustness
- Complexity ← control, robust/fragile tradeoffs
- Math: robust/fragile constraints (“conservation laws”)

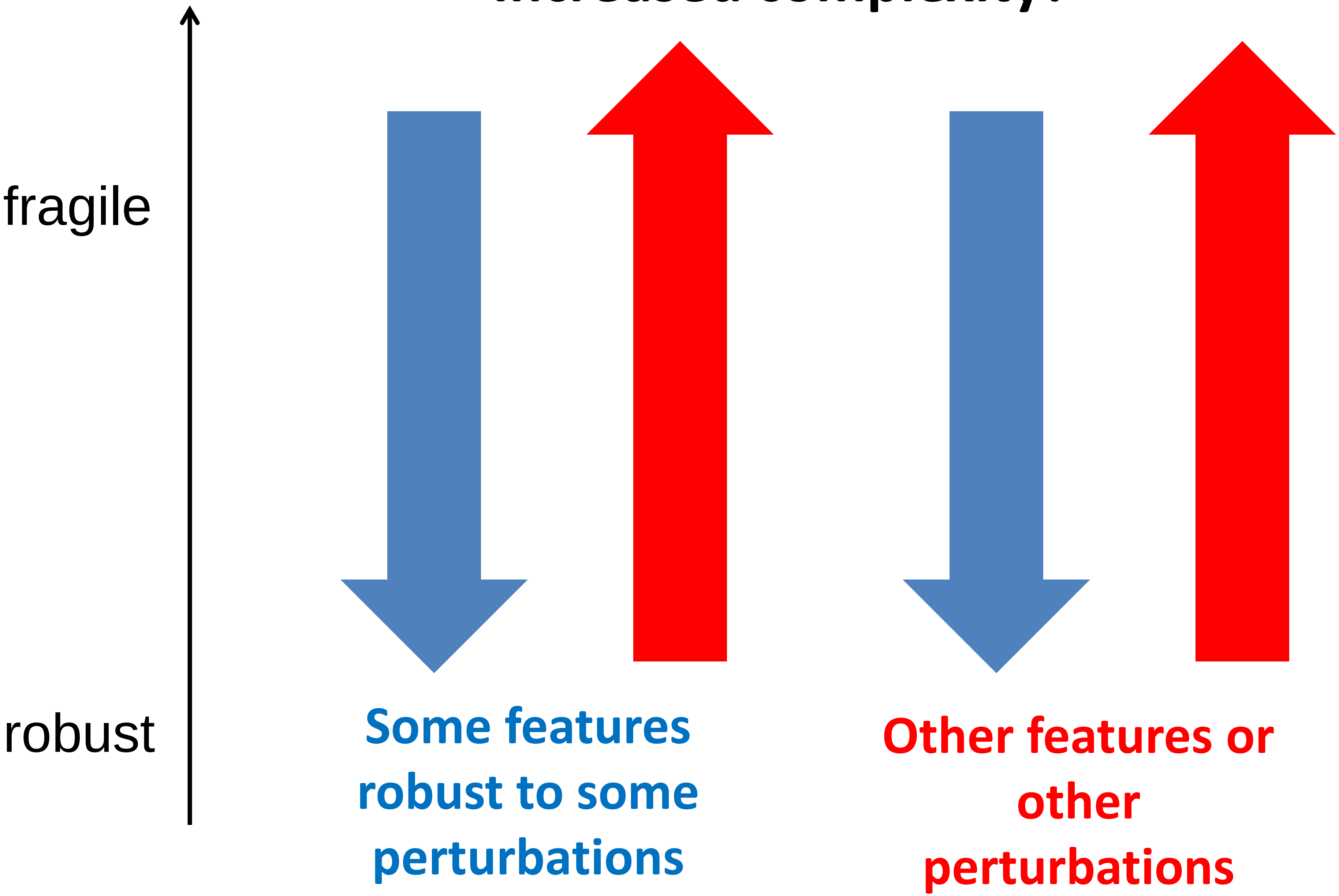
Both

Accident or necessity?




fragile
robust
Some features robust to some perturbations
Other features or other perturbations

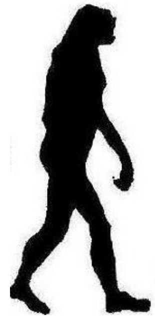
Increased complexity?



Robust		Fragile
Modular	*and*	Distributed
Simple	~~***xor***~~	Complex
Plastic		Frozen
Evolvable		Frozen

tradeoffs

weak
fragile
slow



hands
feet
skeleton
muscle
skin
gut
long helpless childhood

All very different.

Human evolution

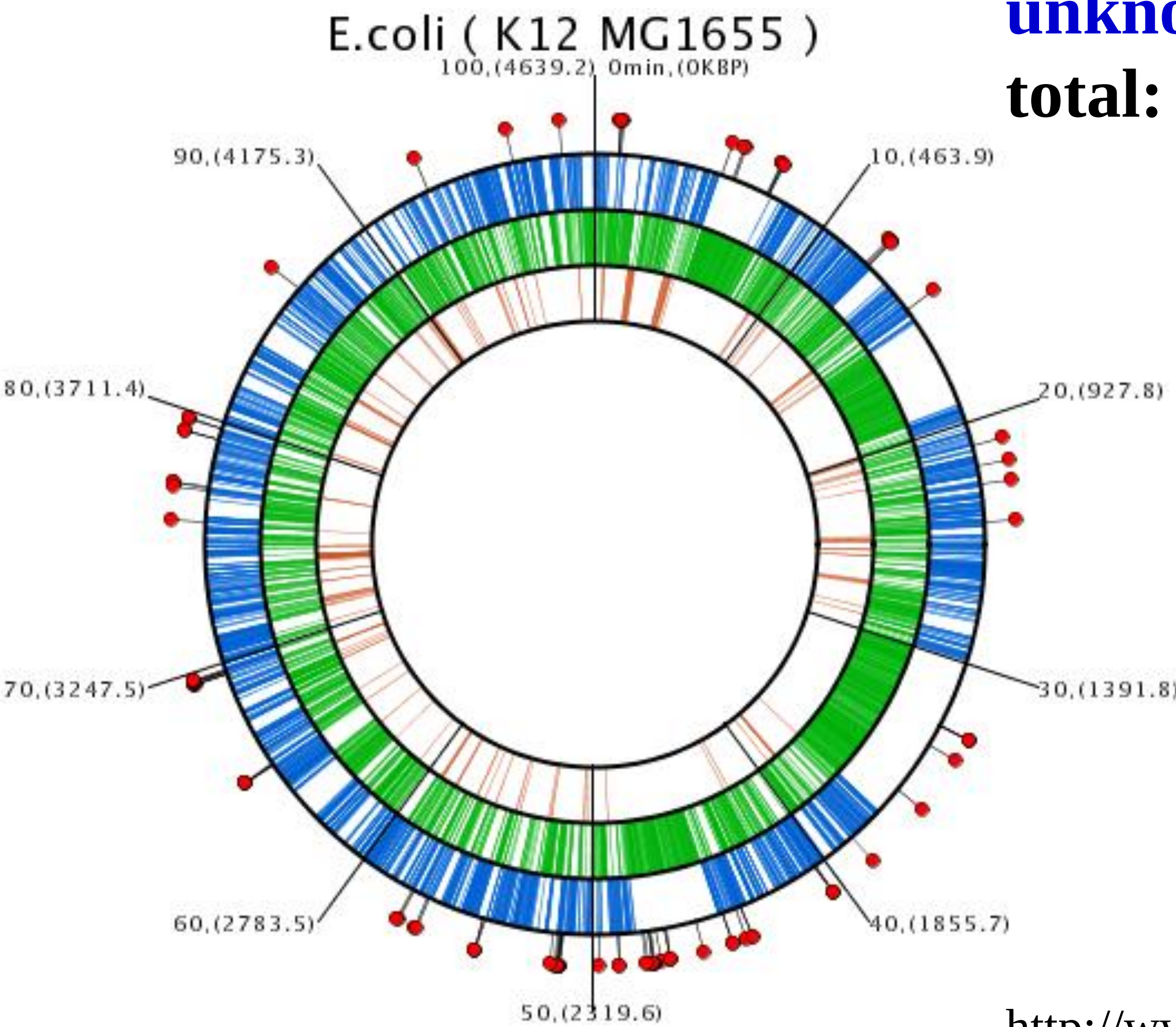
Apes

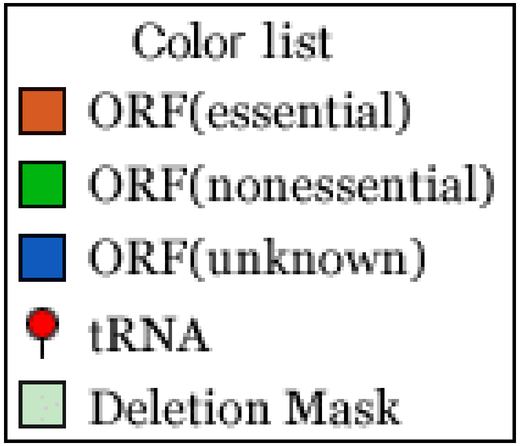
strong
robust
fast

How is this progress?

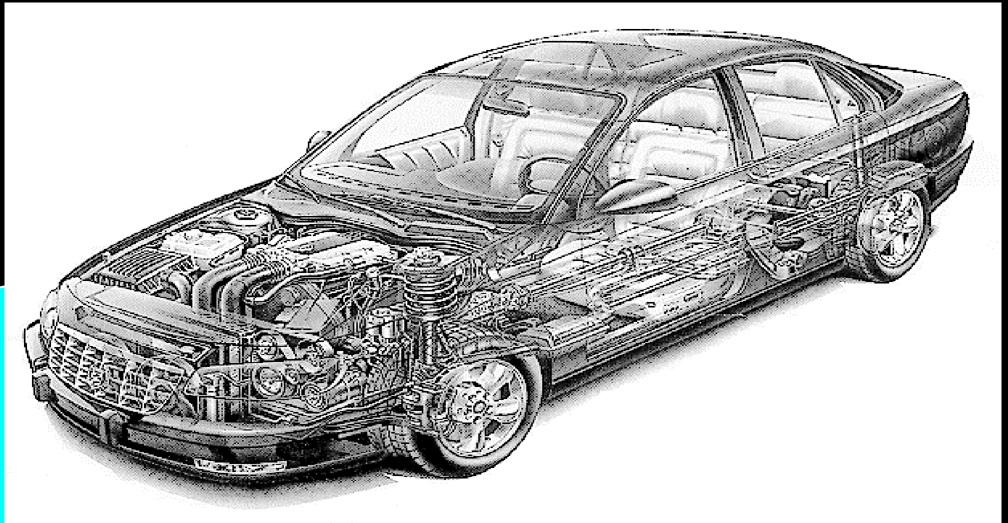
Gene networks?

essential:	230
nonessential:	2373
unknown:	1804
total:	4407





http://www.shigen.nig.ac.jp/ecoli/pec



Steering

Brakes Anti-skid

Cruise control

Traction control

Shifting

Electronic ignition

Temperature control

Electronic fuel injection

Seatbelts

Bumpers Fenders

Suspension (control)

Airbags

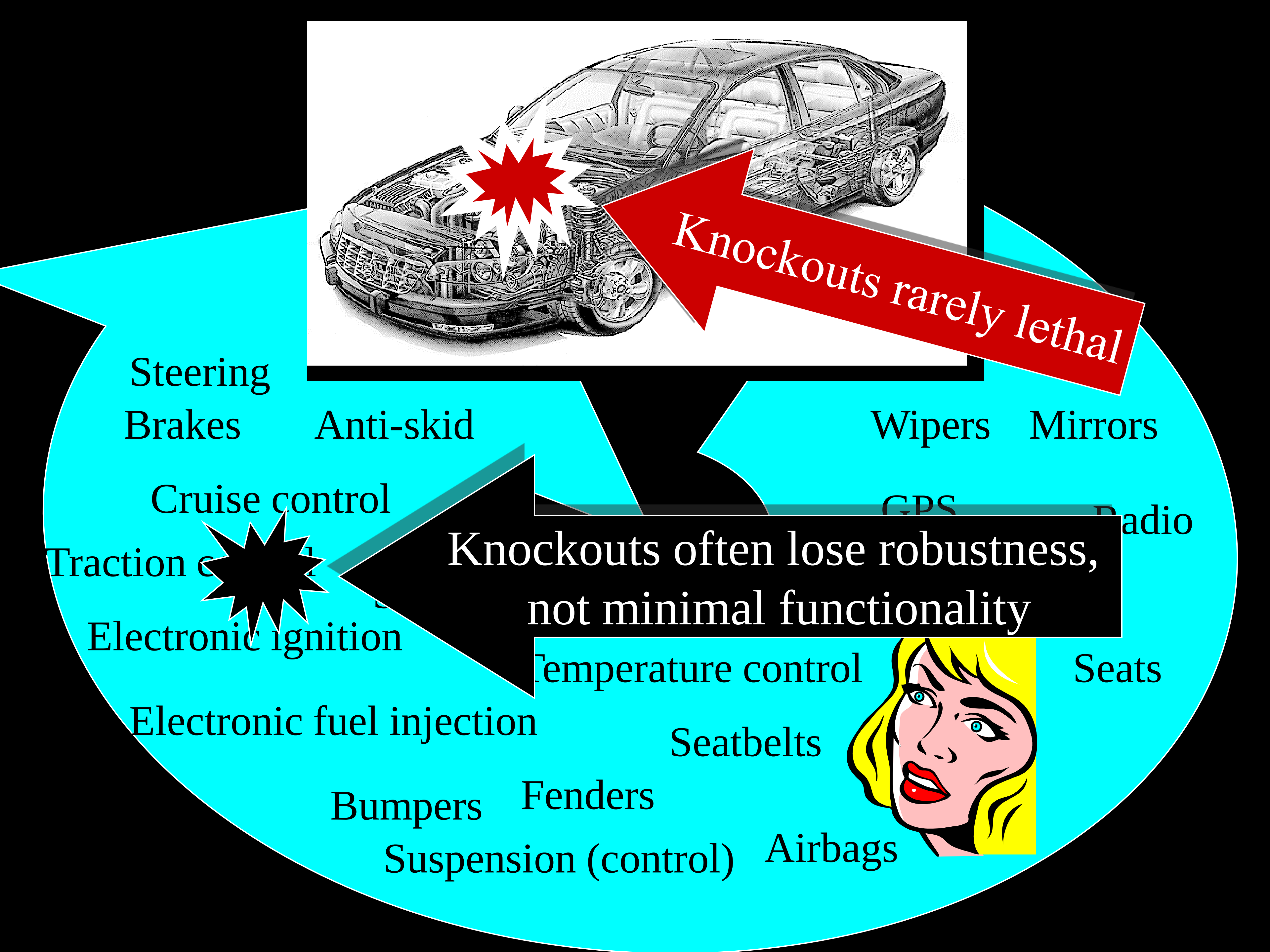
Wipers Mirrors

GPS

Radio

Headlights

Seats


Knockouts rarely lethal
Steering
Brakes
Anti-skid
Wipers
Mirrors
Cruise control
Knockouts often lose robustness,
not minimal functionality
Electronic ignition
Temperature control
Seats
Electronic fuel injection
Seatbelts
Bumpers
Fenders
Suspension (control)
Airbags

- Lots from cell biology
  - glycolytic oscillations for hard limits
  - bacterial layering for architecture
- Networking and “clean slate” architectures
  - wireless end systems
  - info or content centric application layer
  - integrate routing, control, scheduling, coding, caching
  - control of cyber-physical
  - PC, OS, VLSI, antennas, etc (IT components)

my case studies

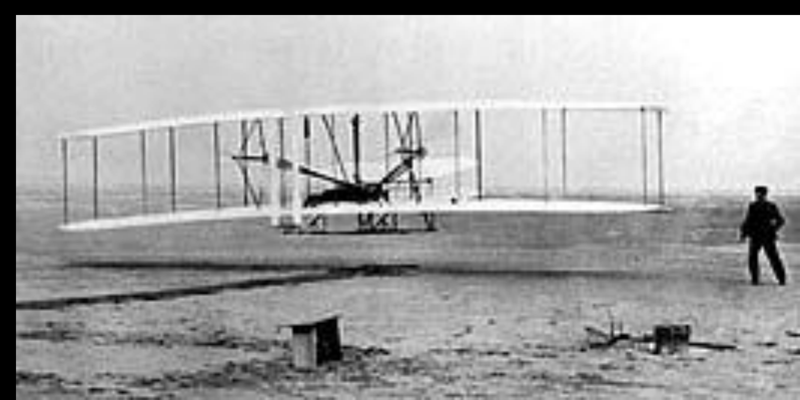
- Cell biology
- Networking &“clean slate” architectures
- Neuroscience
- Medical physiology
- Smartgrid, cyber-phys
- Wildfire ecology
- Earthquakes
- Lots of aerospace
- Physics:
  - turbulence,
  - stat mech (QM?)
- “Toy”:
  - Lego,
  - clothing,
  - buildings, …

my case studies

The dangers of naïve biomemetics

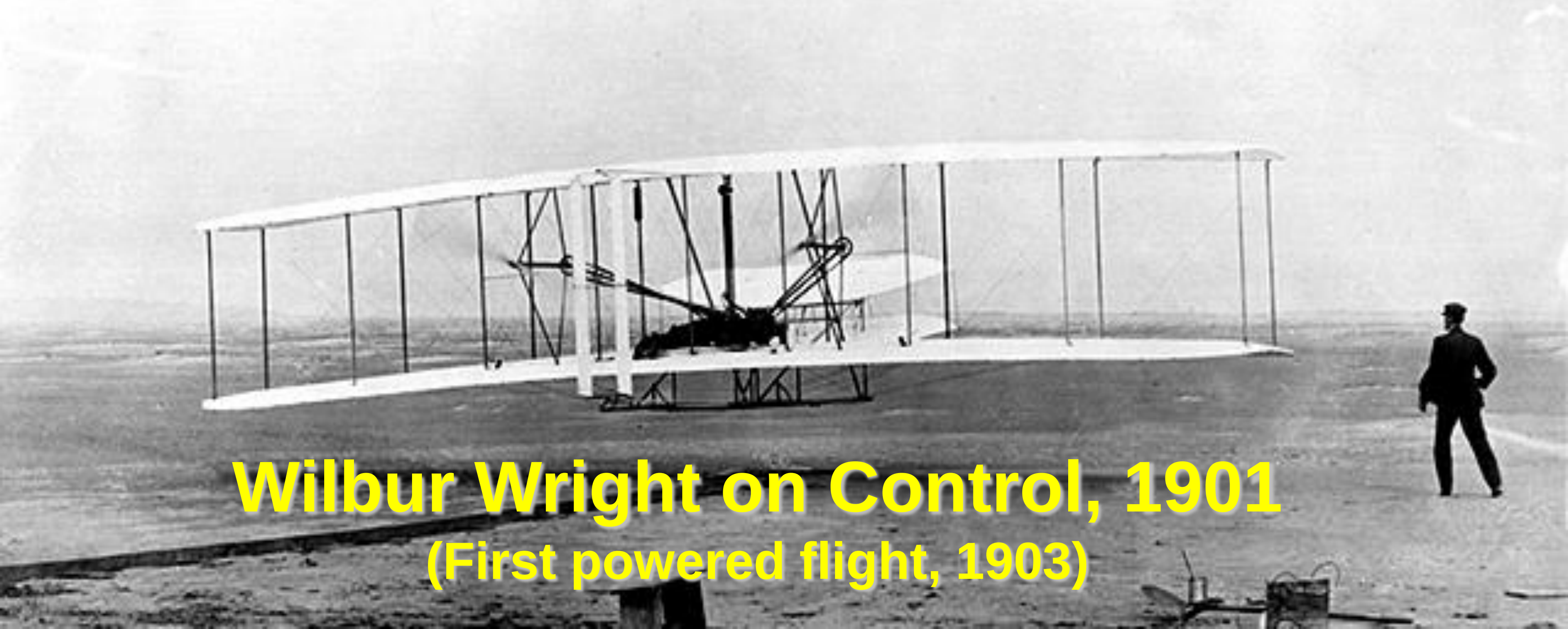
Feathers
and
flapping?

Or lift, drag, propulsion,
and ***control***?



Getting it (W)right, 1901

- “We know how to construct airplanes...” (lift and drag)
- “… also know how to build engines.” (propulsion)
- “When... balance and steer[ing]... has been worked out, the age of flying will have arrived, for all other difficulties are of minor importance.” (control)



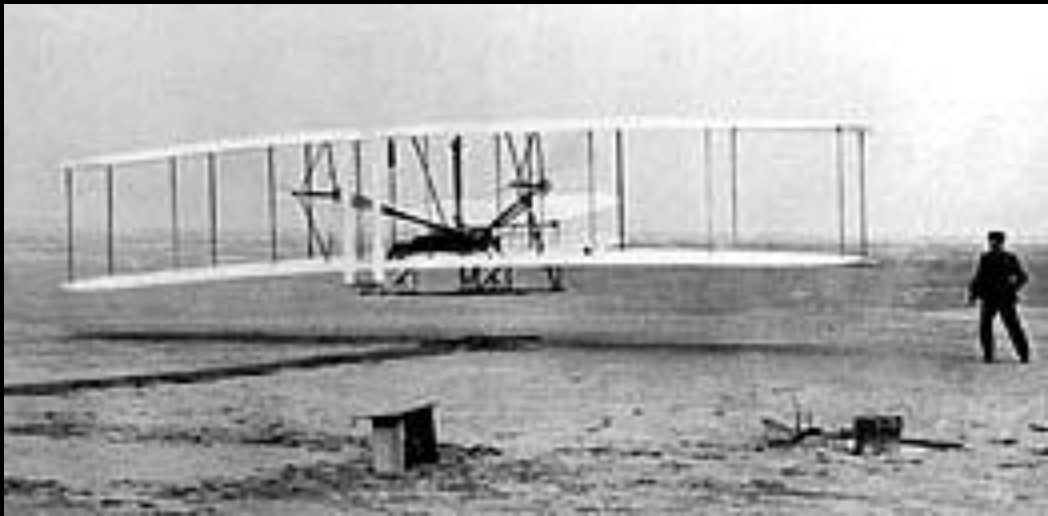
Wilbur Wright on Control, 1901

(First powered flight, 1903)

Universals?

Feathers and flapping?

Lift, drag, propulsion, and ***control***?

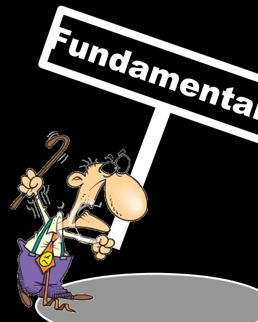


Universals?

- Complexity $\leftarrow$ control, robust/fragile tradeoffs
- Fragility $\leftarrow$ Hijacking, side effects, unintended…
- Of mechanisms evolved for robustness
- Math: robust/fragile constraints ("conservation laws")

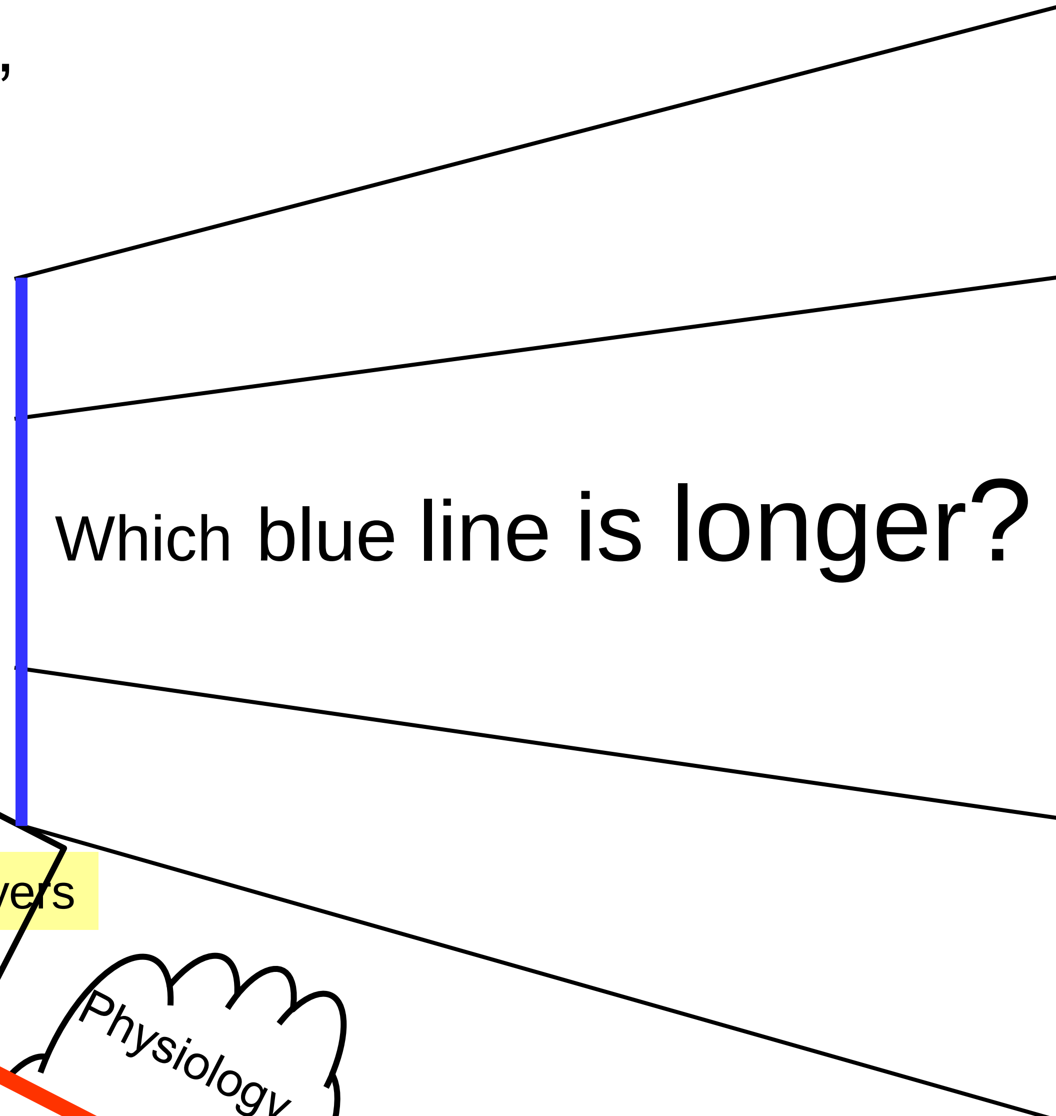
Both

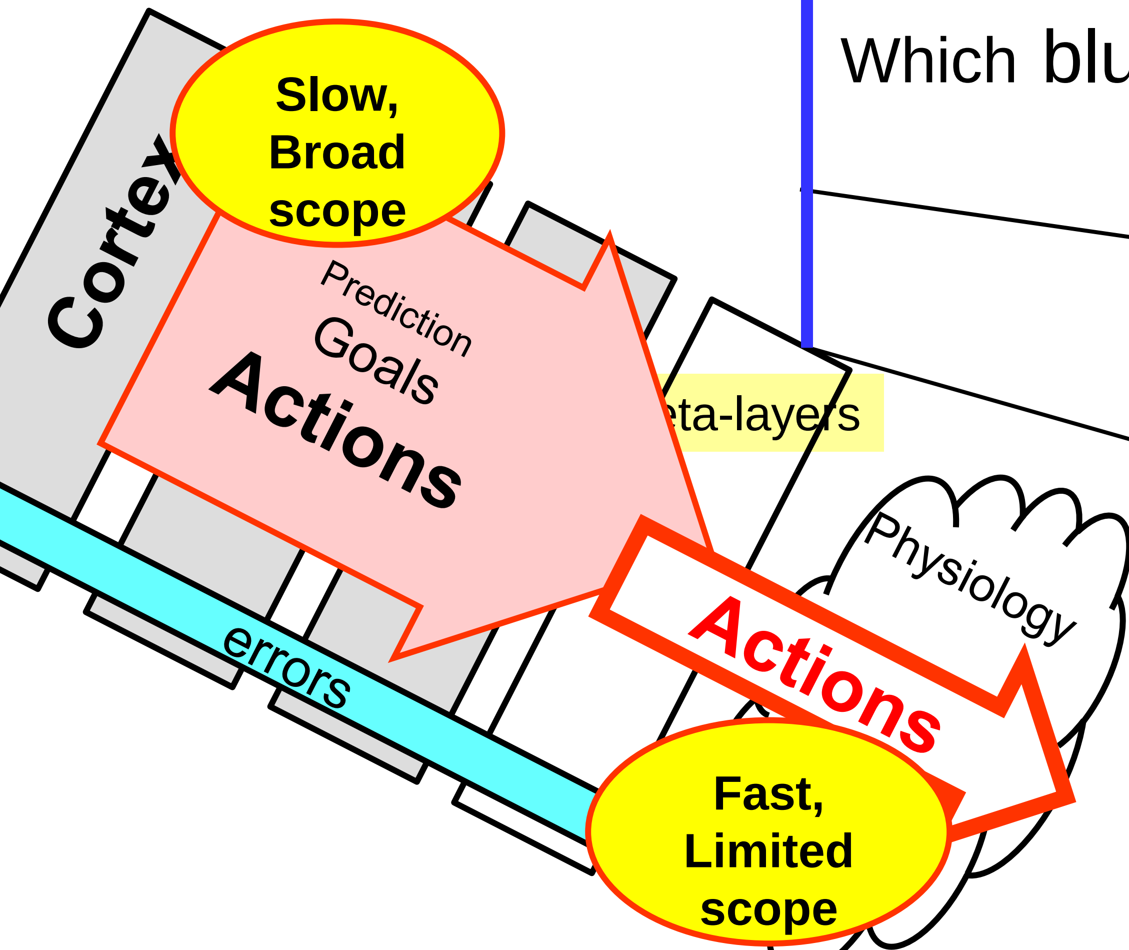
Accident or necessity?

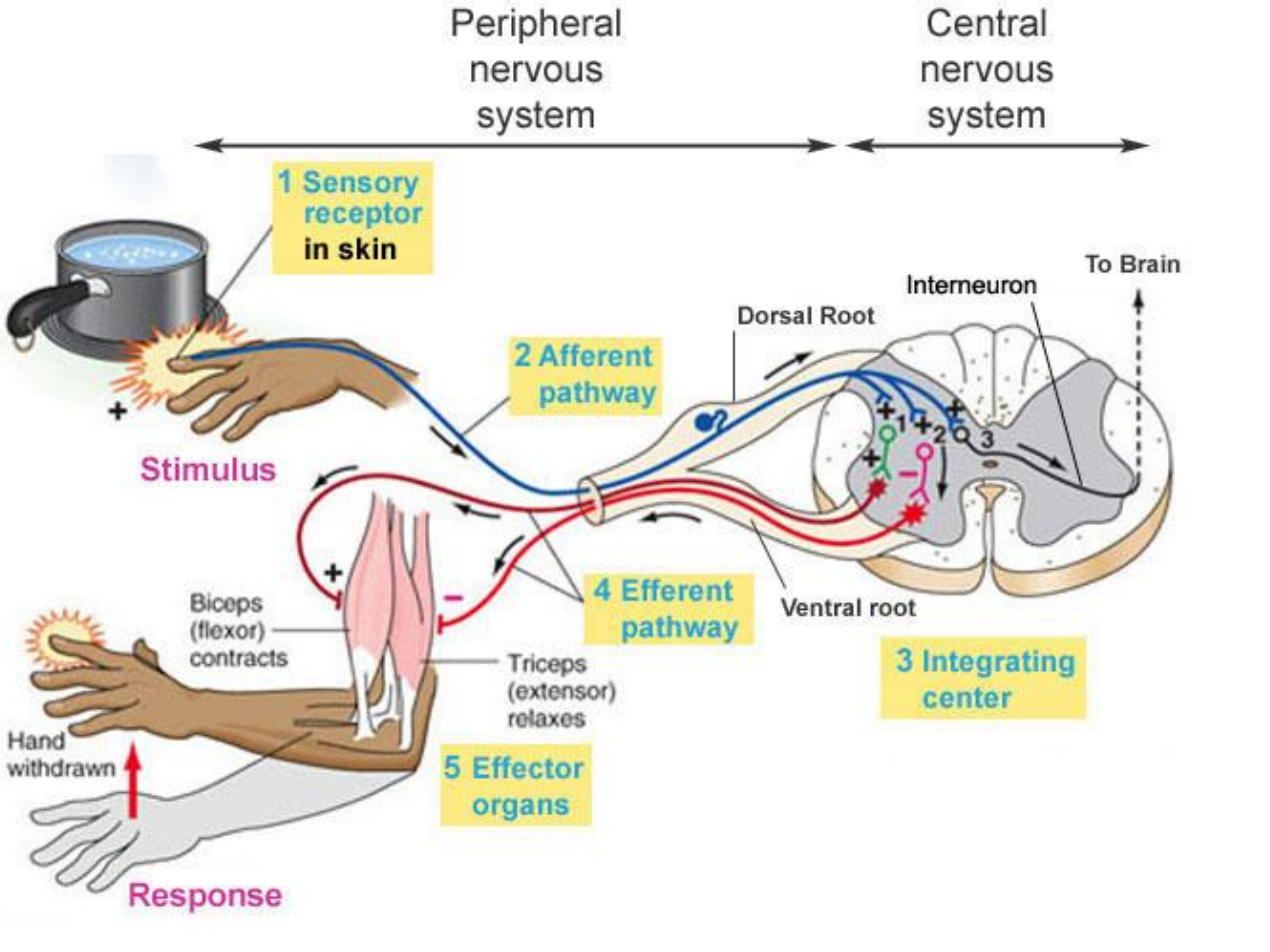


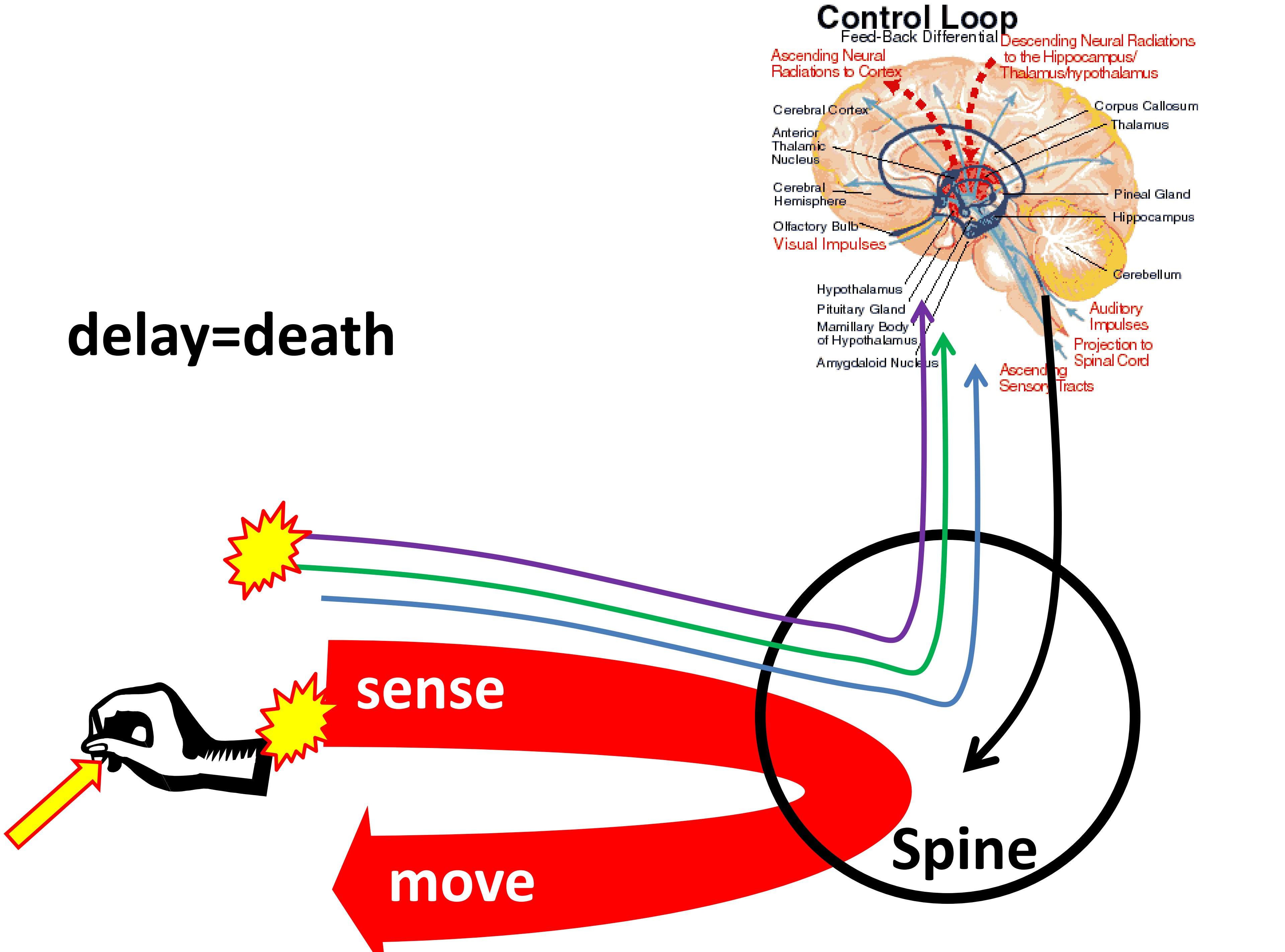
“Seeing is dreaming?”

“Seeing is believing?”



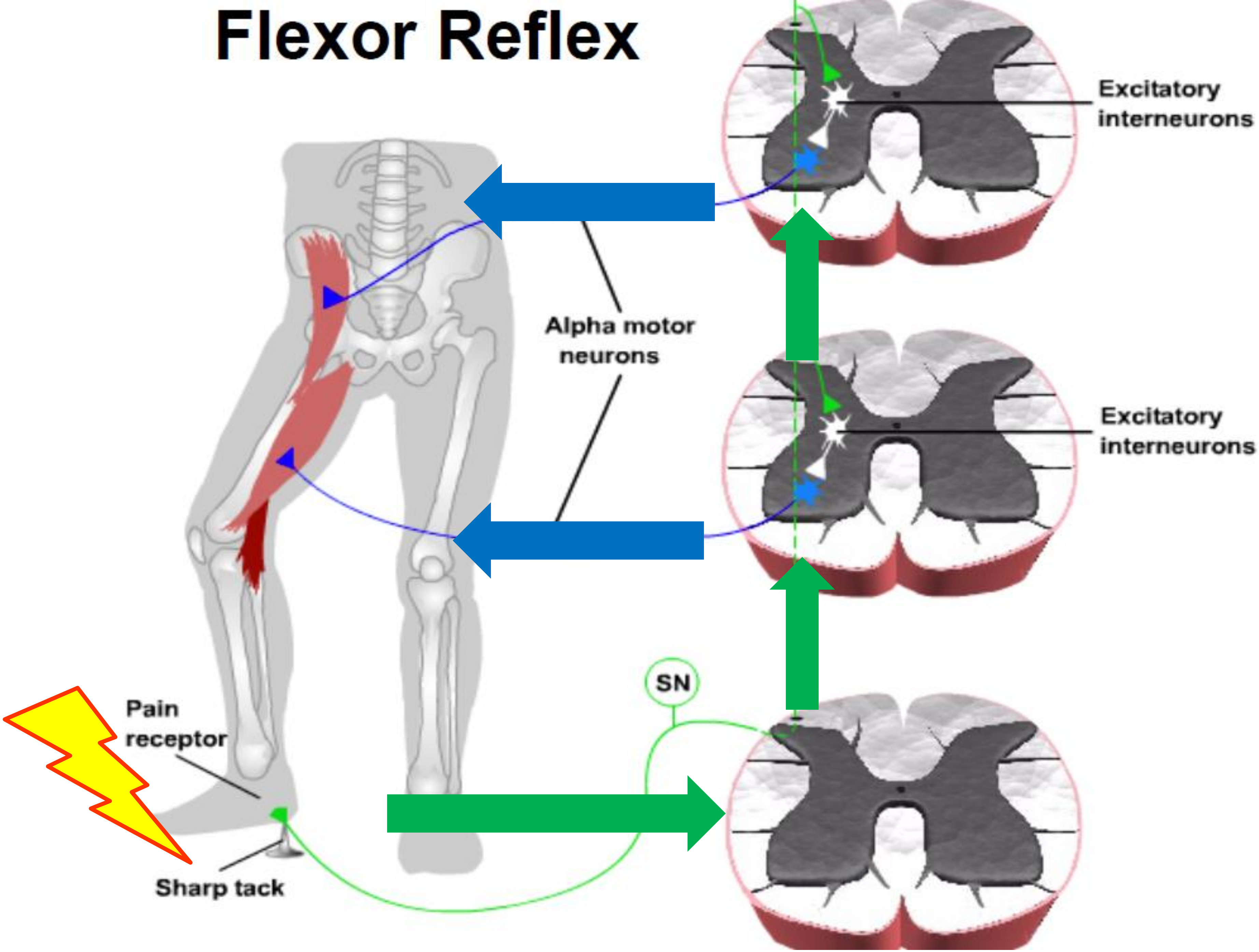


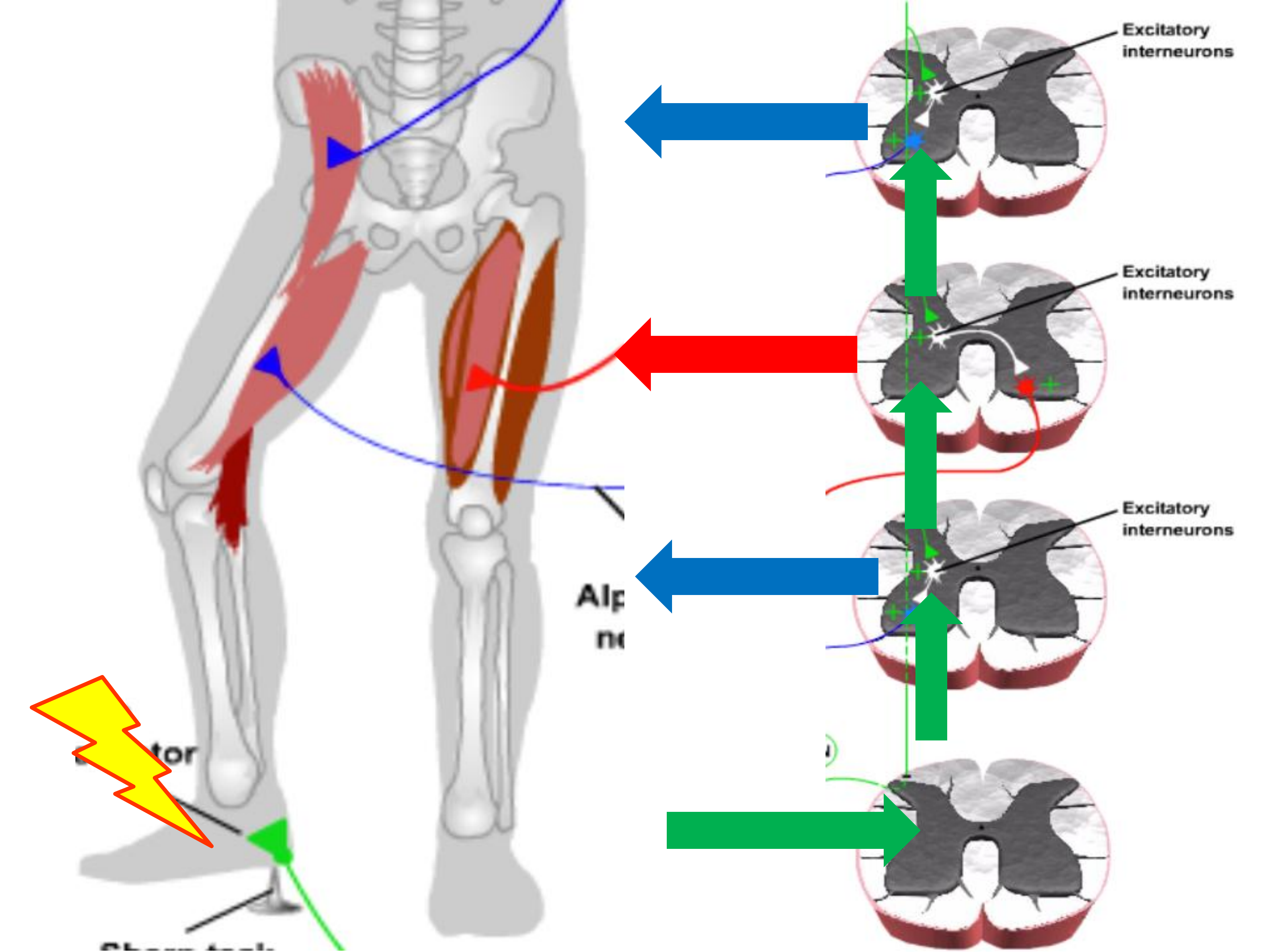

Peripheral nervous system
Central nervous system
1 Sensory receptor in skin
Stimulus
2 Afferent pathway
Dorsal Root
Interneuron
To Brain
1
2
3
3 Integrating center
4 Efferent pathway
Ventral root
Biceps (flexor) contracts
Triceps (extensor) relaxes
5 Effector organs
Hand withdrawn
Response

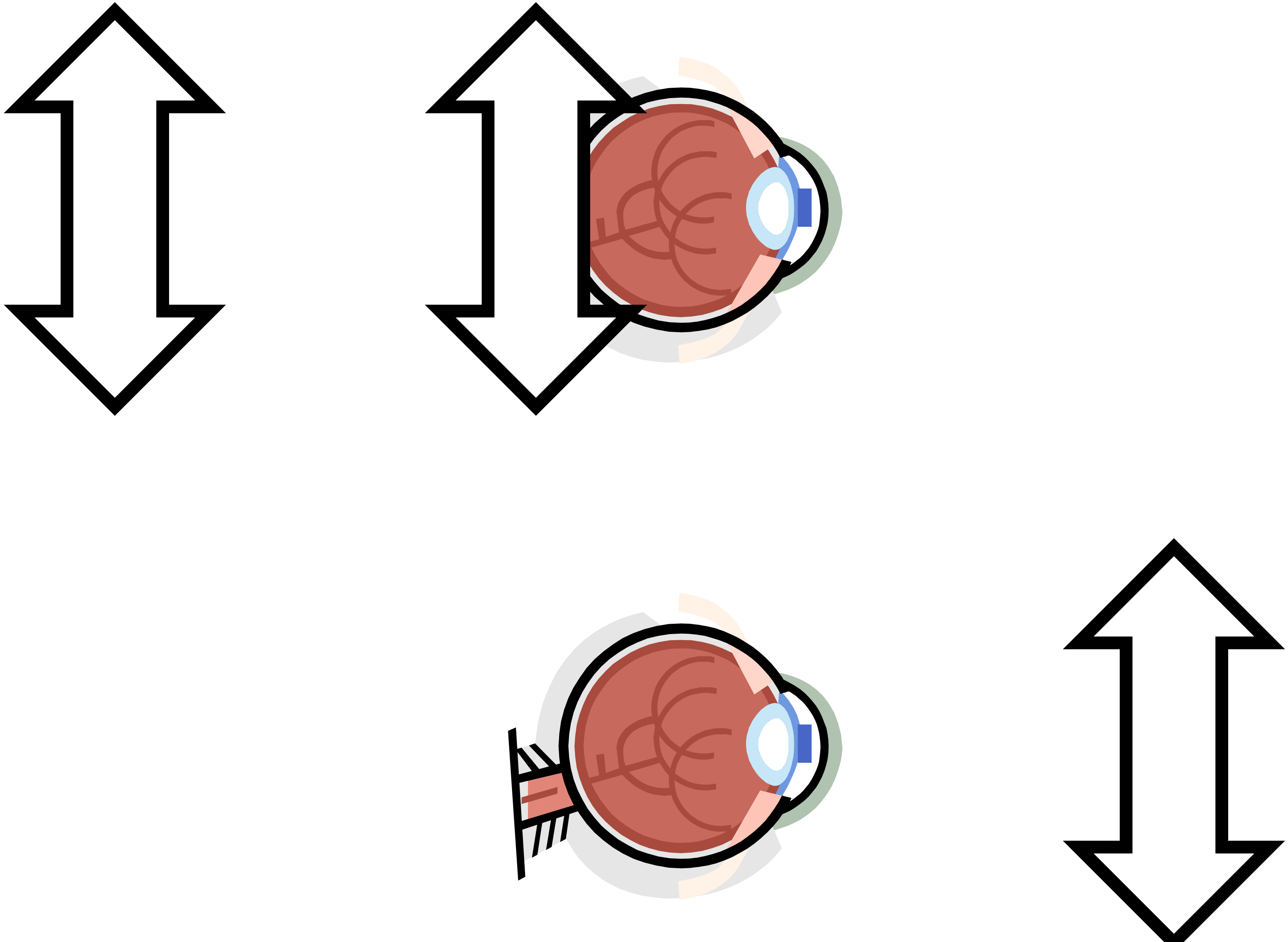


Control Loop
Feed-Back Differential
Ascending Neural Radiations to Cortex
Descending Neural Radiations to the Hippocampus/ Thalamus/hypothalamus
Cerebral Cortex
Anterior Thalamic Nucleus
Cerebral Hemisphere
Olfactory Bulb
Visual Impulses
Corpus Callosum
Thalamus
Pineal Gland
Hippocampus
Cerebellum
Hypothalamus
Pituitary Gland
Mamillary Body of Hypothalamus
Amygdaloid Nucleus
Auditory Impulses
Projection to Spinal Cord
Ascending Sensory Tracts
delay=death
sense
move
Spine

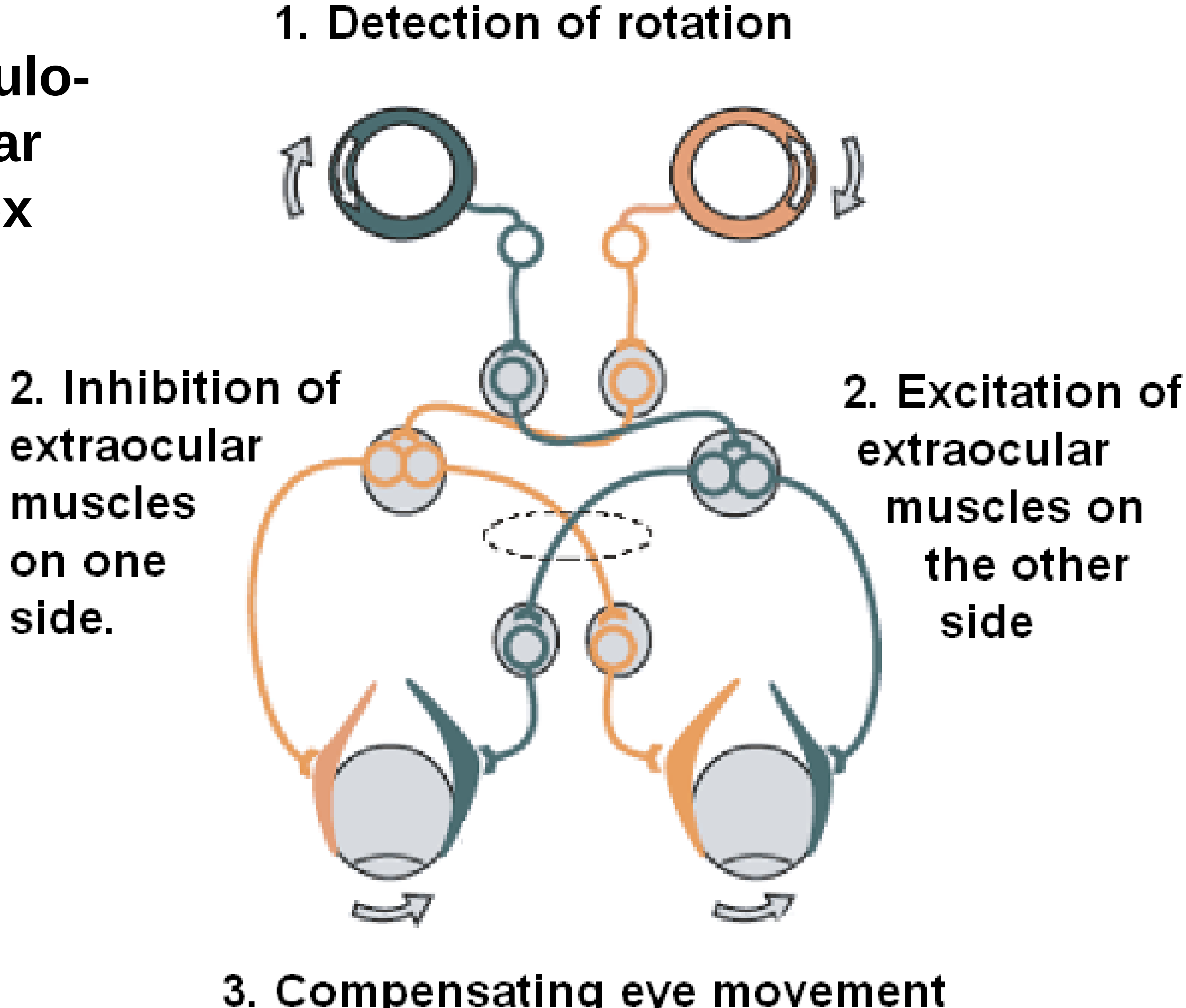
Flexor Reflex

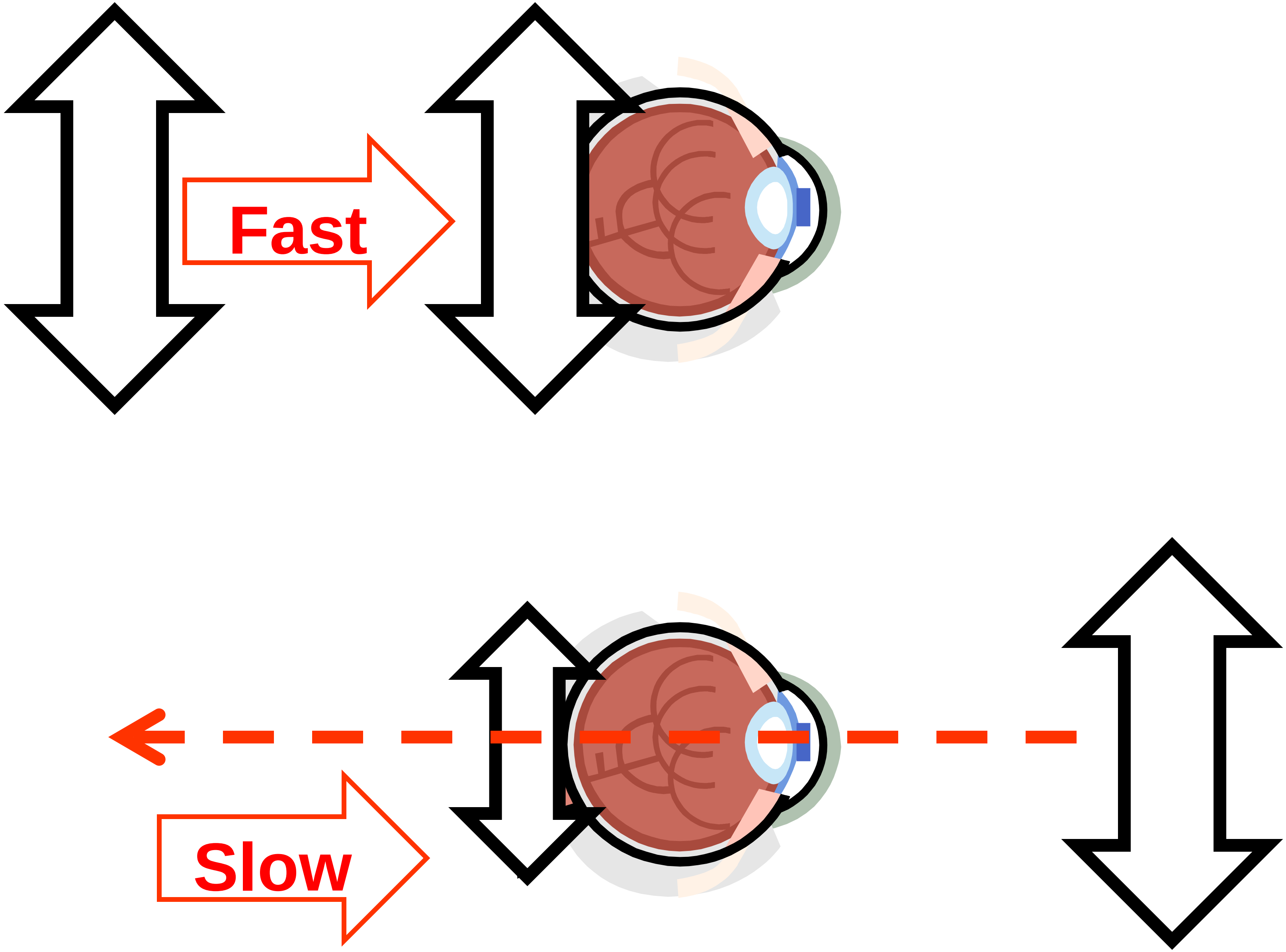



Excitatory interneurons
Excitatory interneurons
Excitatory interneurons

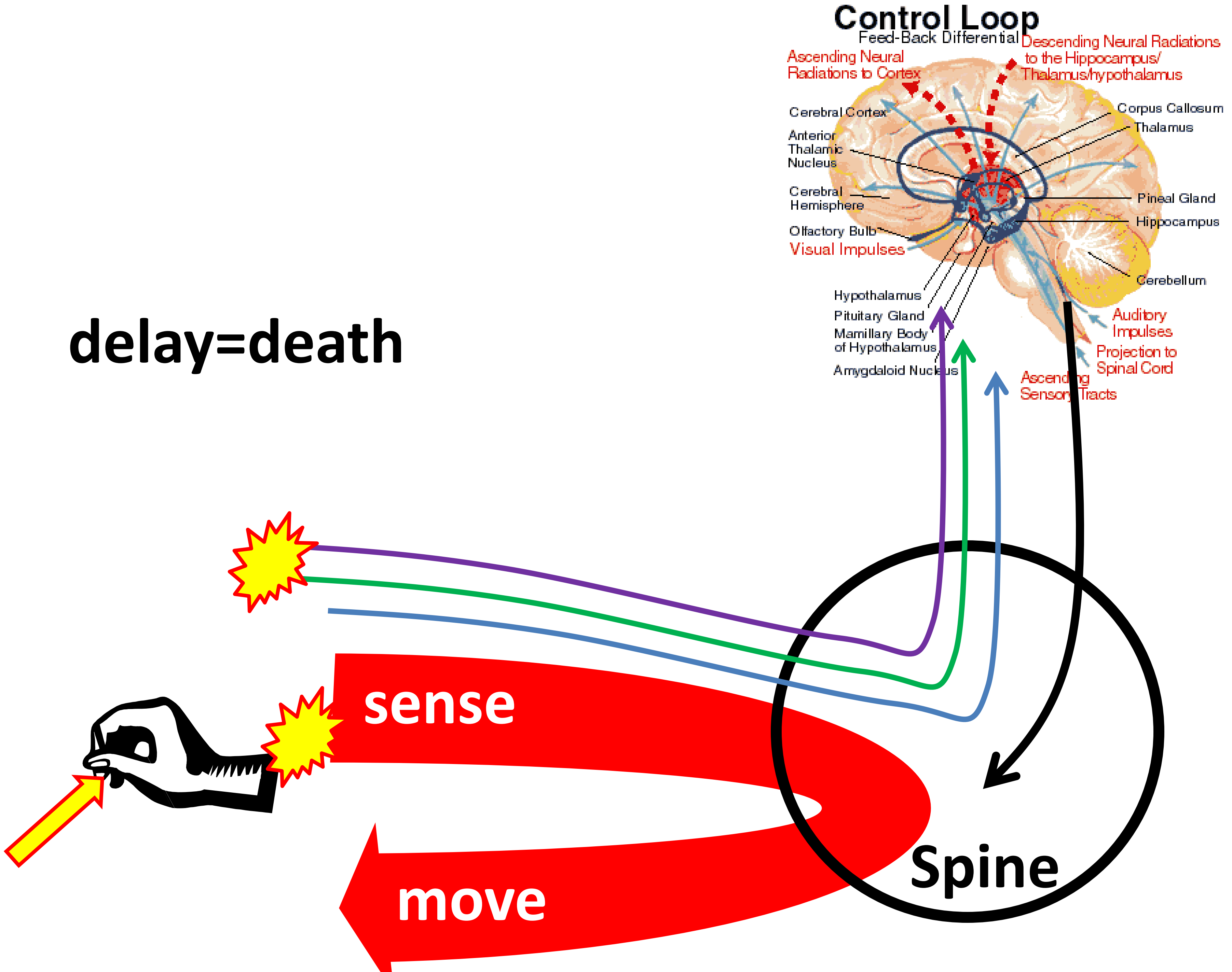


Vestibulo-ocular reflex




Fast
Slow

delay=death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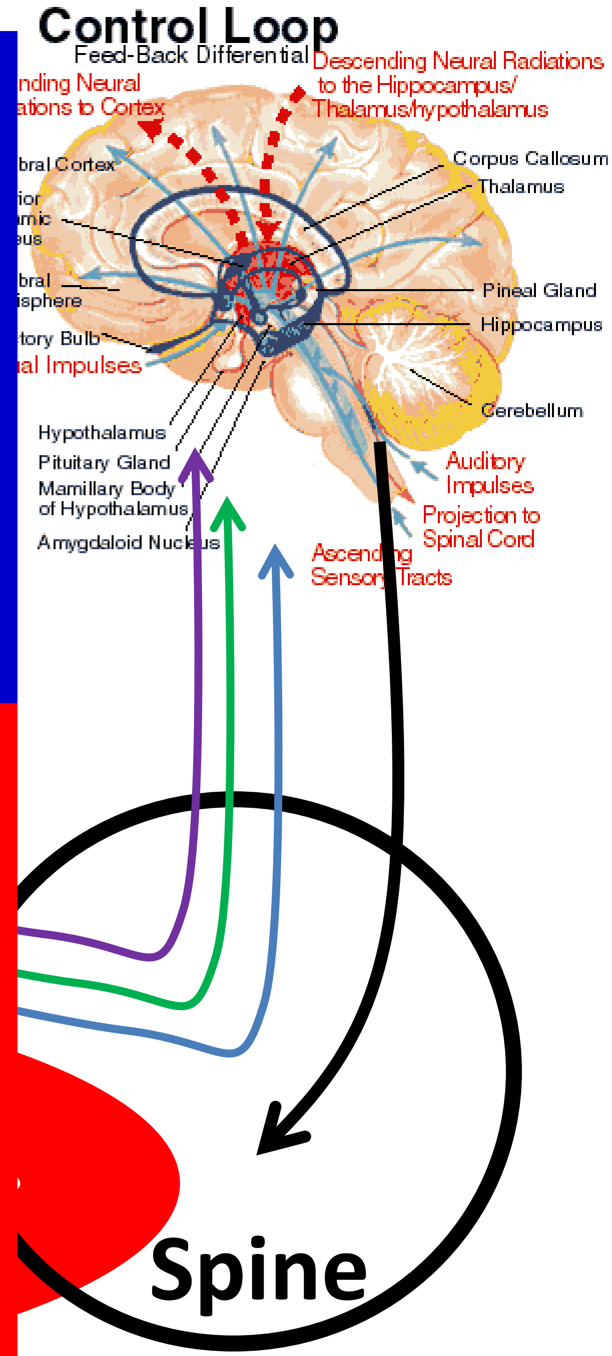
Cerebellum
Hypothalamus
Pituitary Gland
Mamillary Body of Hypothalamus
Amygdaloid Nucleus
Auditory Impulses
Projection to Spinal Cord
Ascending Sensory Tracts
sense
move
Spine

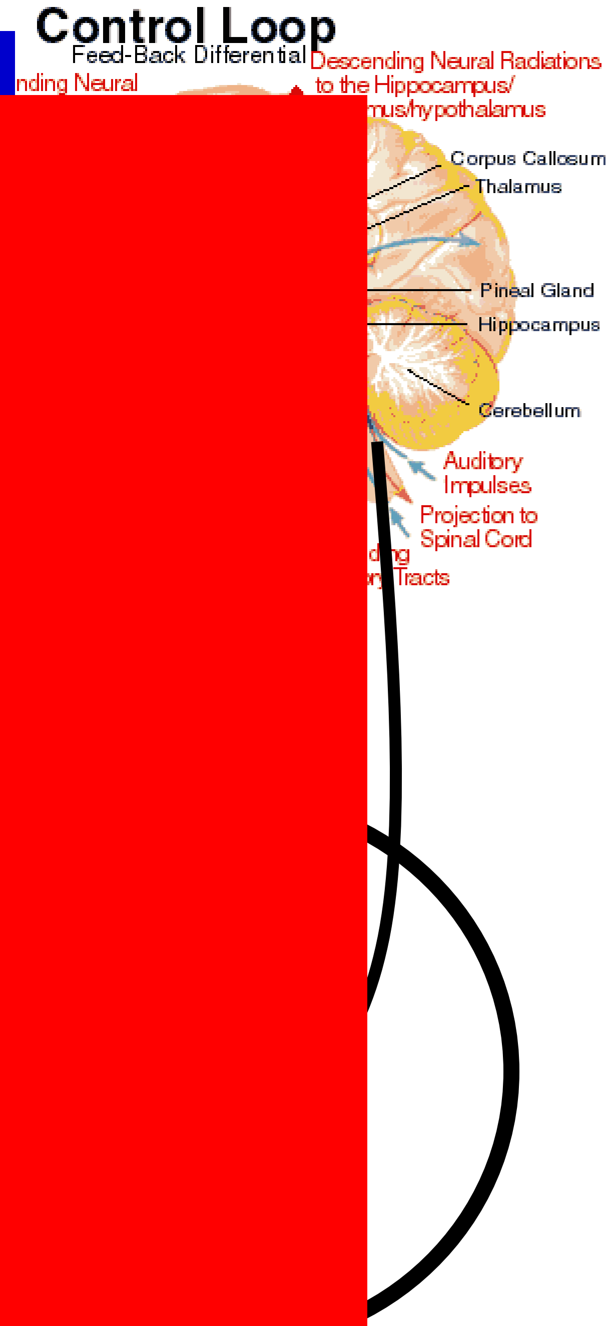
Reflect

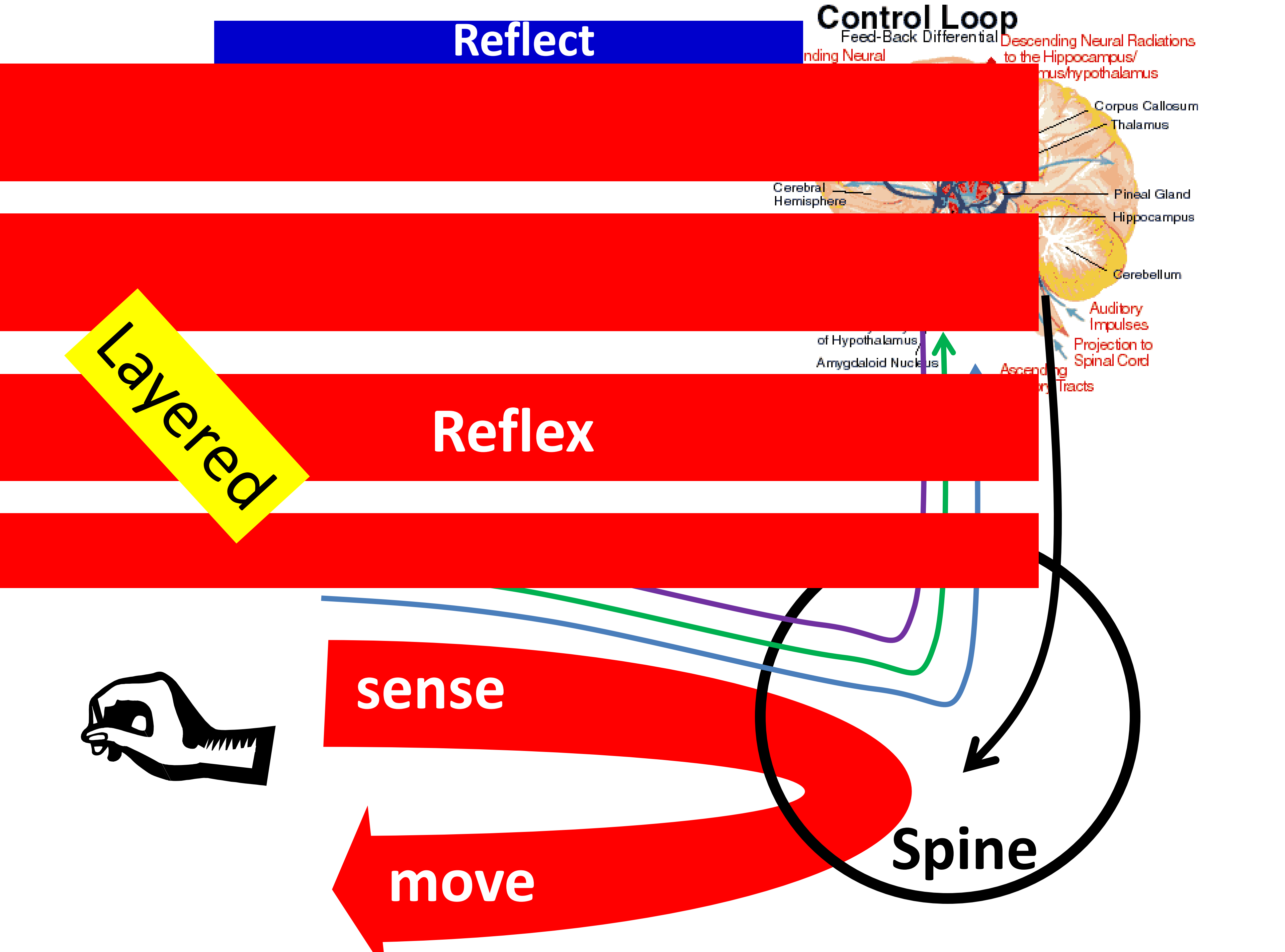
Reflex



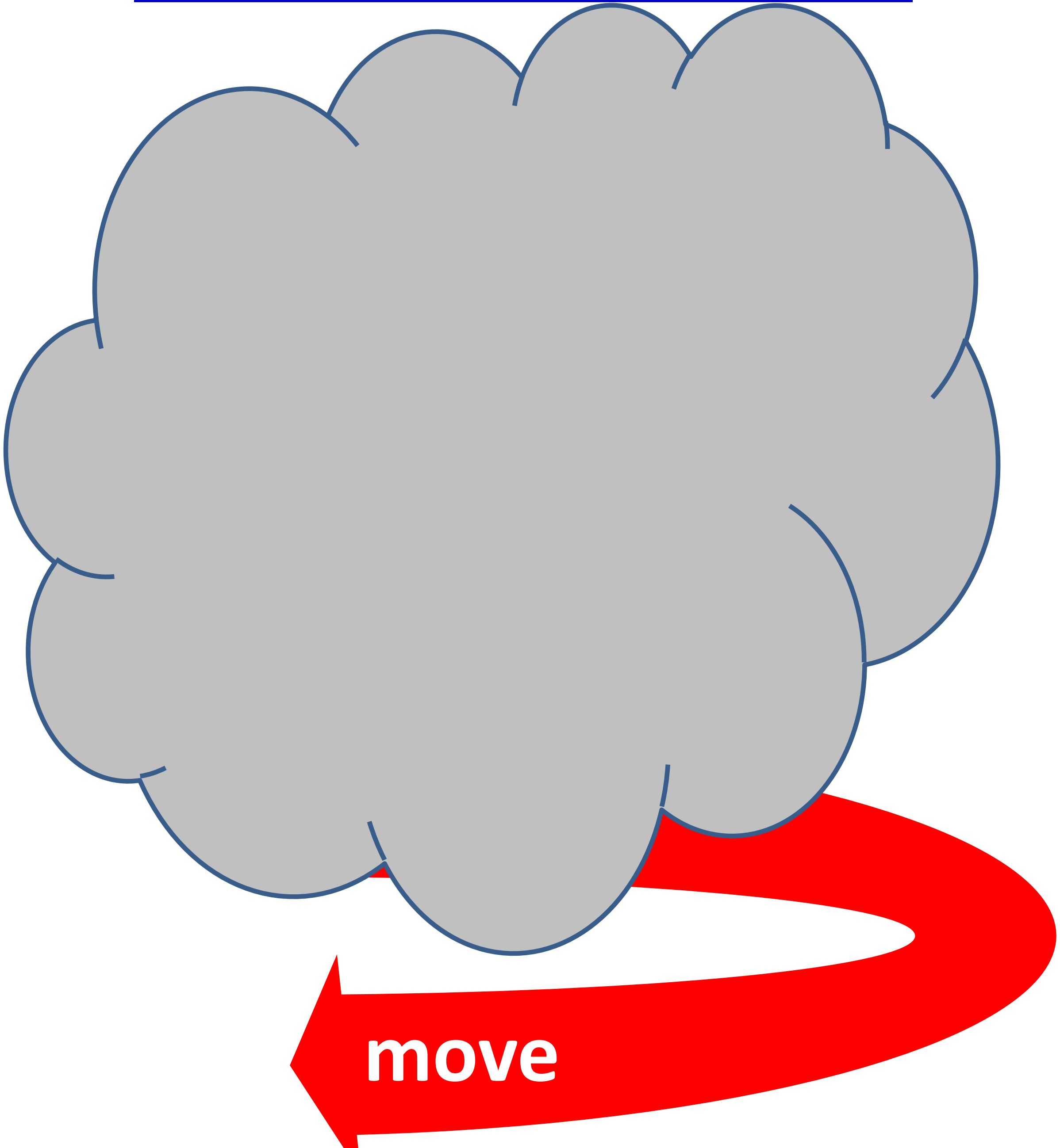
Reflect

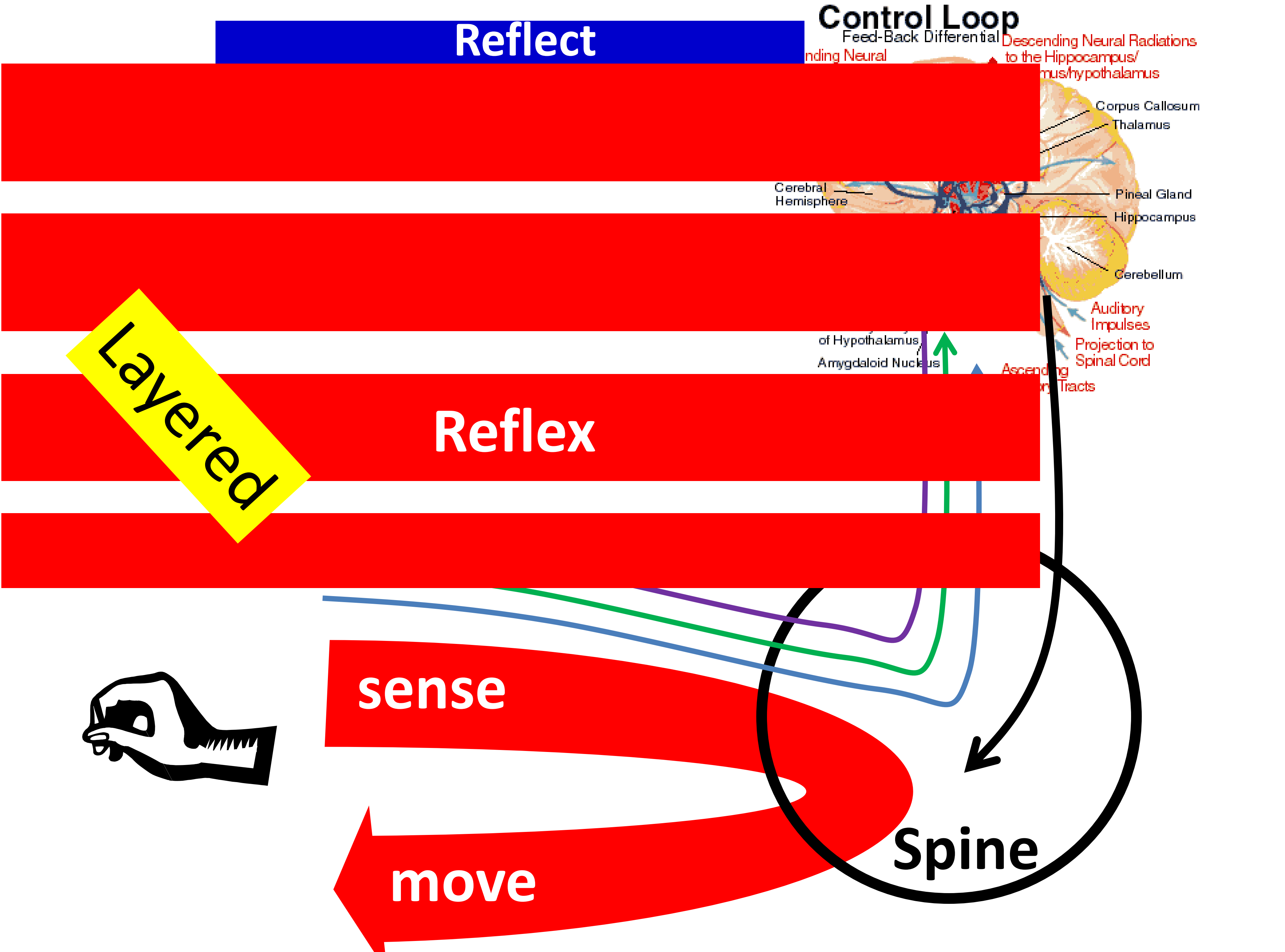
Reflex




Reflect
Control Loop
Feed-Back Differential
Descending Neural Radiations
to the Hippocampus/
mus/hypothalamus
nding Neural
Corpus Callosum
Thalamus
Cerebral
Hemisphere
Pineal Gland
Hippocampus
Cerebellum
Auditory
Impulses
of Hypothalamus
Amygdaloid Nucleus
Projection to
Spinal Cord
Layered
Reflex
sense
move
Spine

Reflect




Reflect
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Hippocampus
Cerebellum
Auditory
Impulses
Projection to
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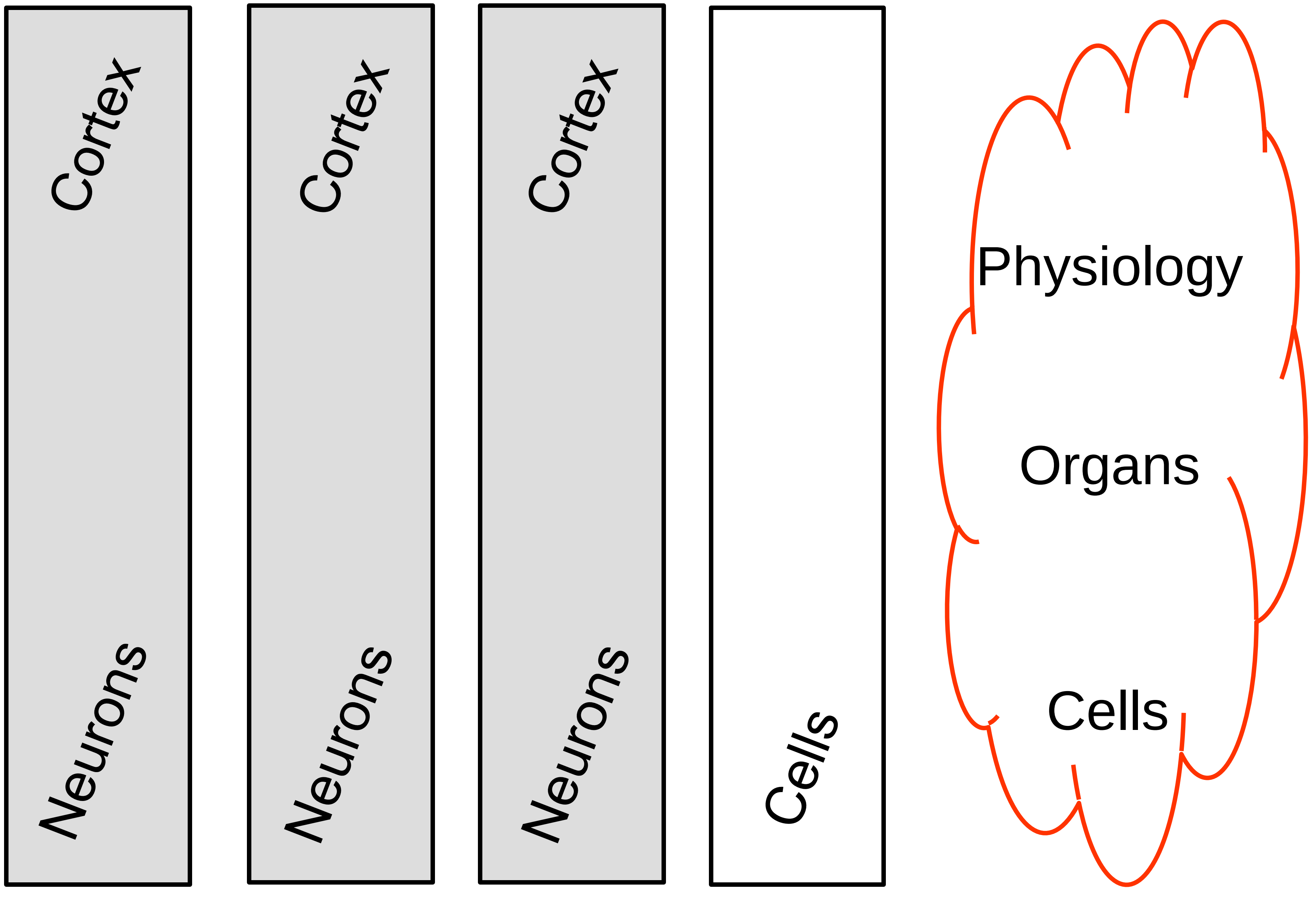
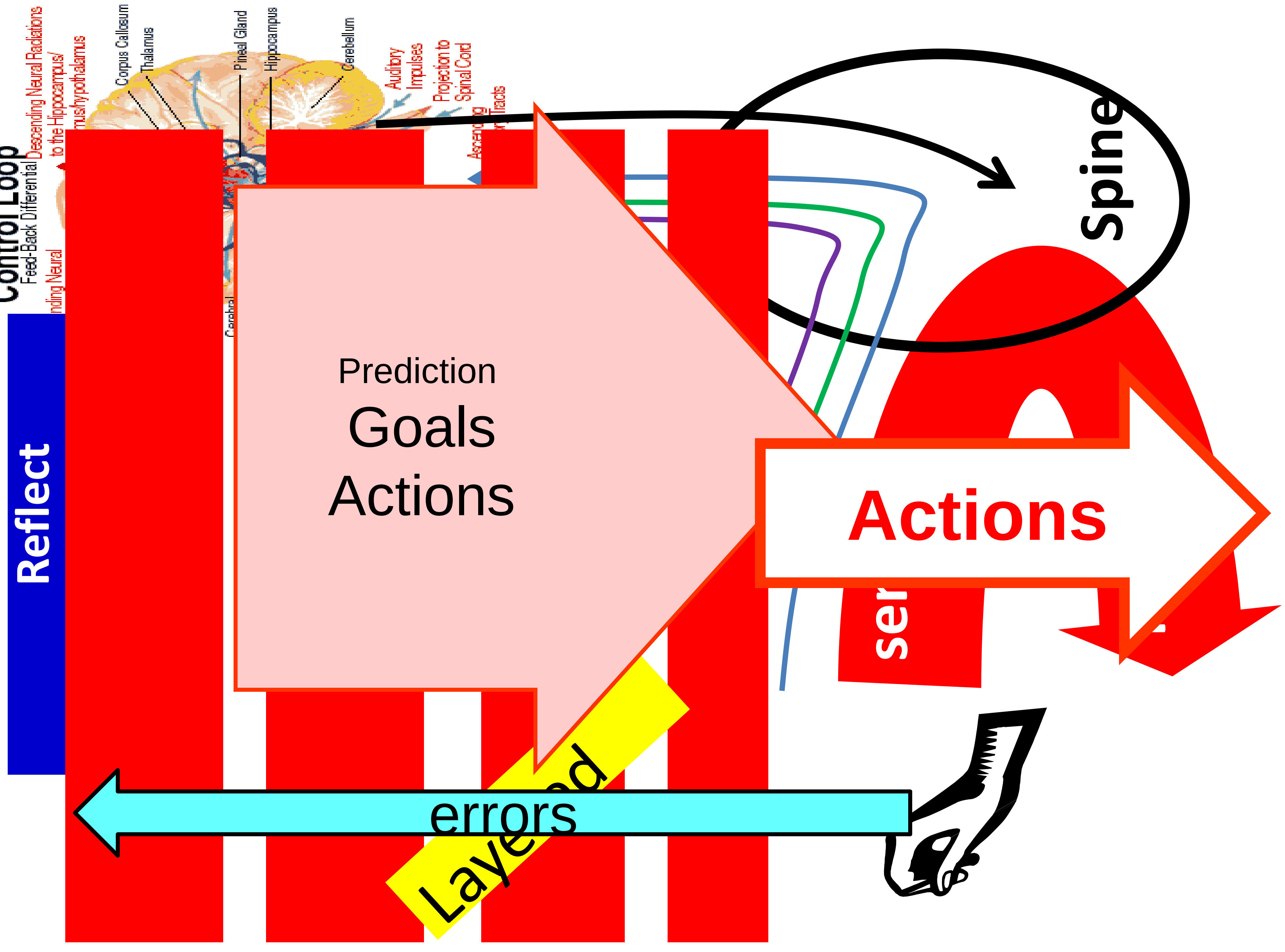
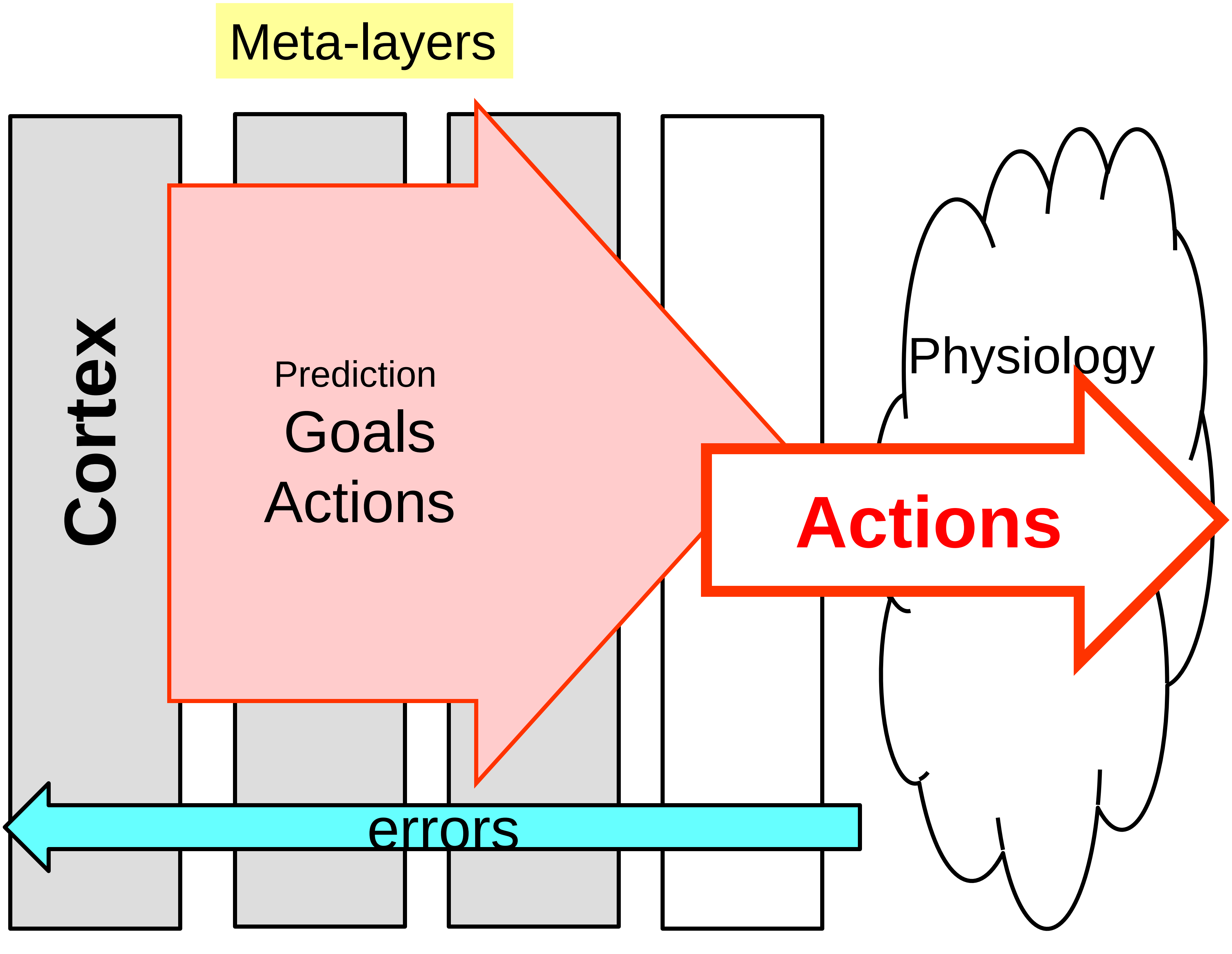
Amygdaloid Nucleus
Layered
Reflex
sense
move
Spine

Layered architectures

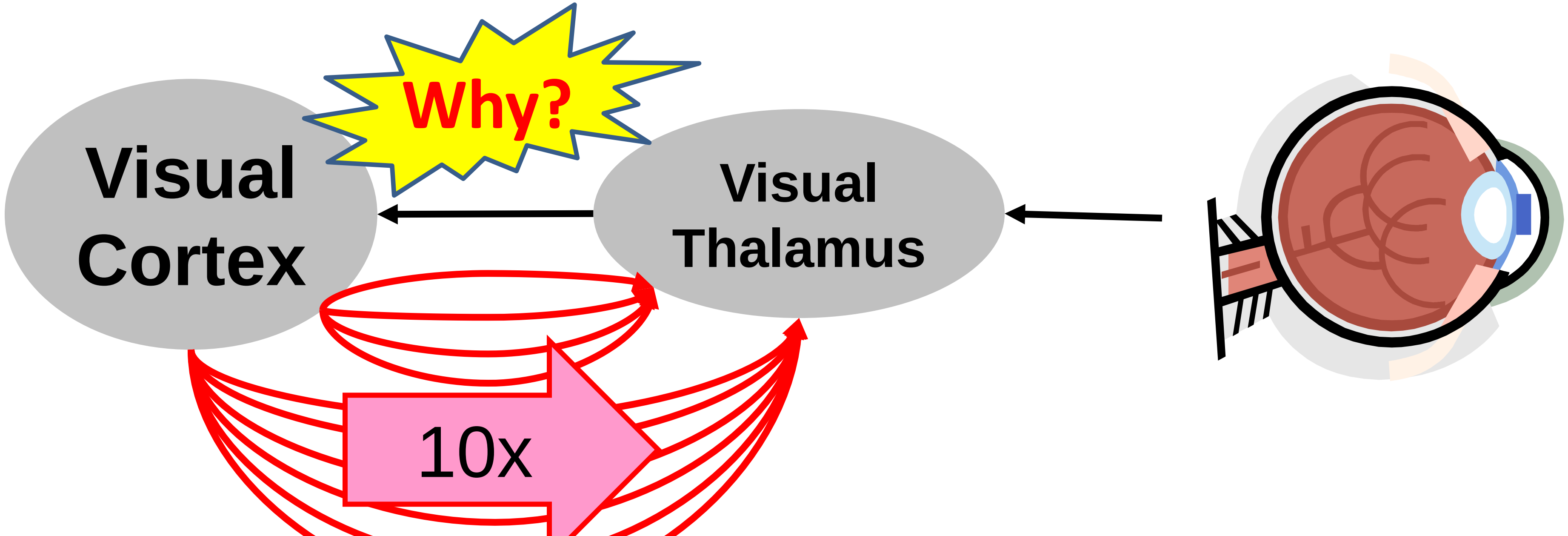


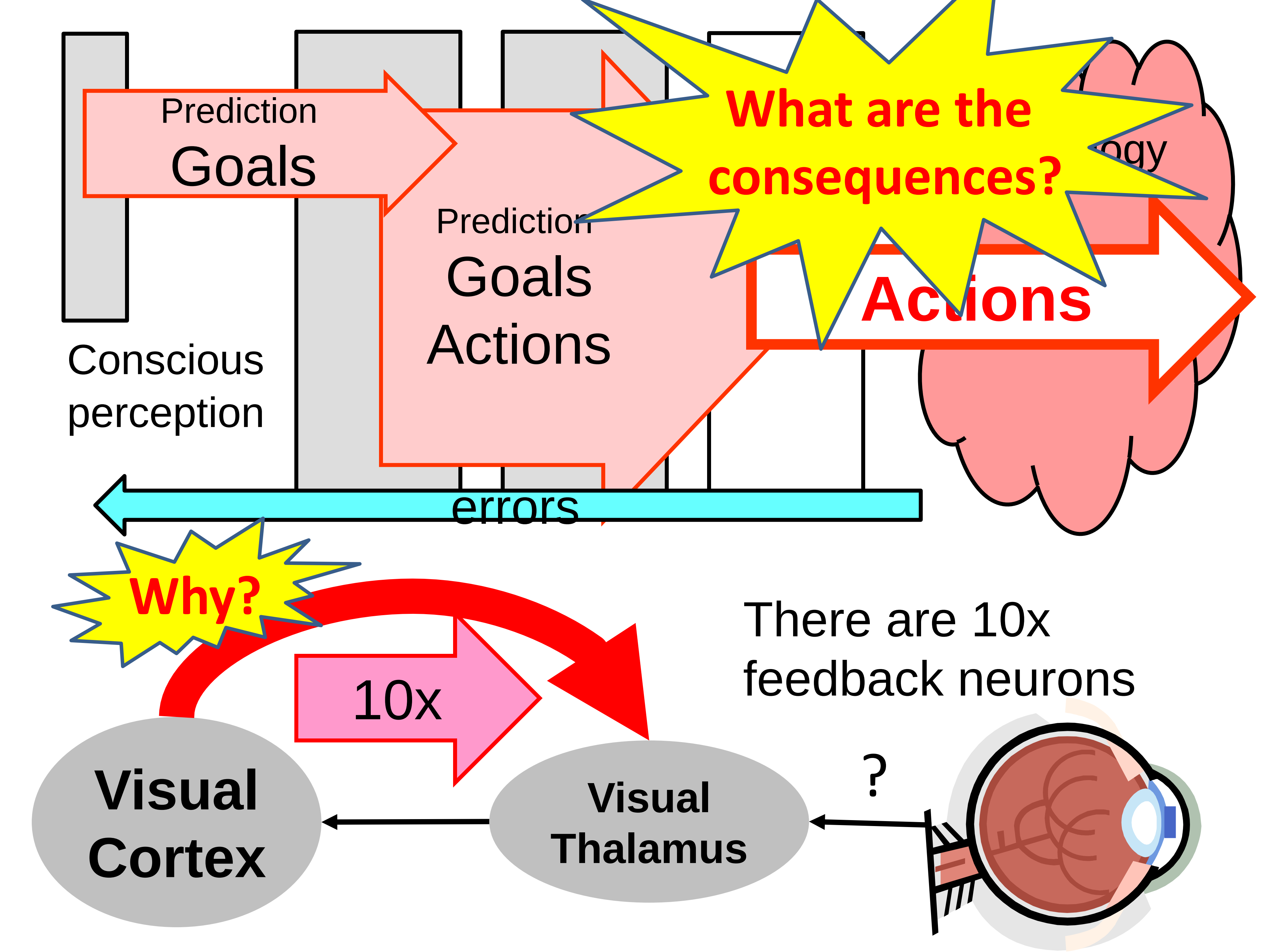


Corpus Callosum
Thalamus
Pineal Gland
Hippocampus
Cerebellum
Auditory Impulses
Projection to Spinal Cord
Feed-Back Differential
Spine
Prediction
Goals
Actions
Actions
Reflect
errors


Meta-layers
Cortex
Prediction
Goals
Actions
Physiology
Actions
errors

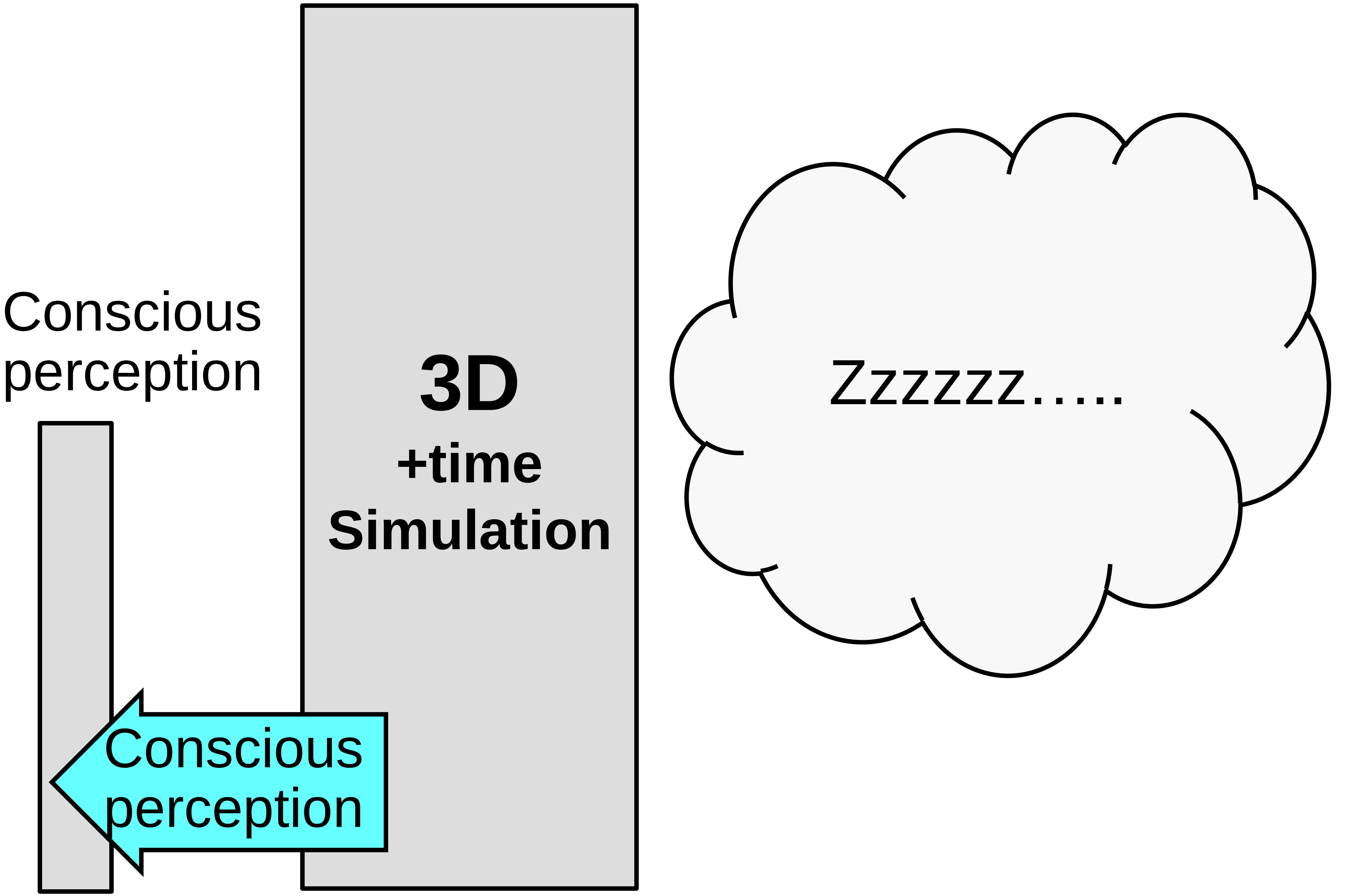
There are 10x feedback neurons

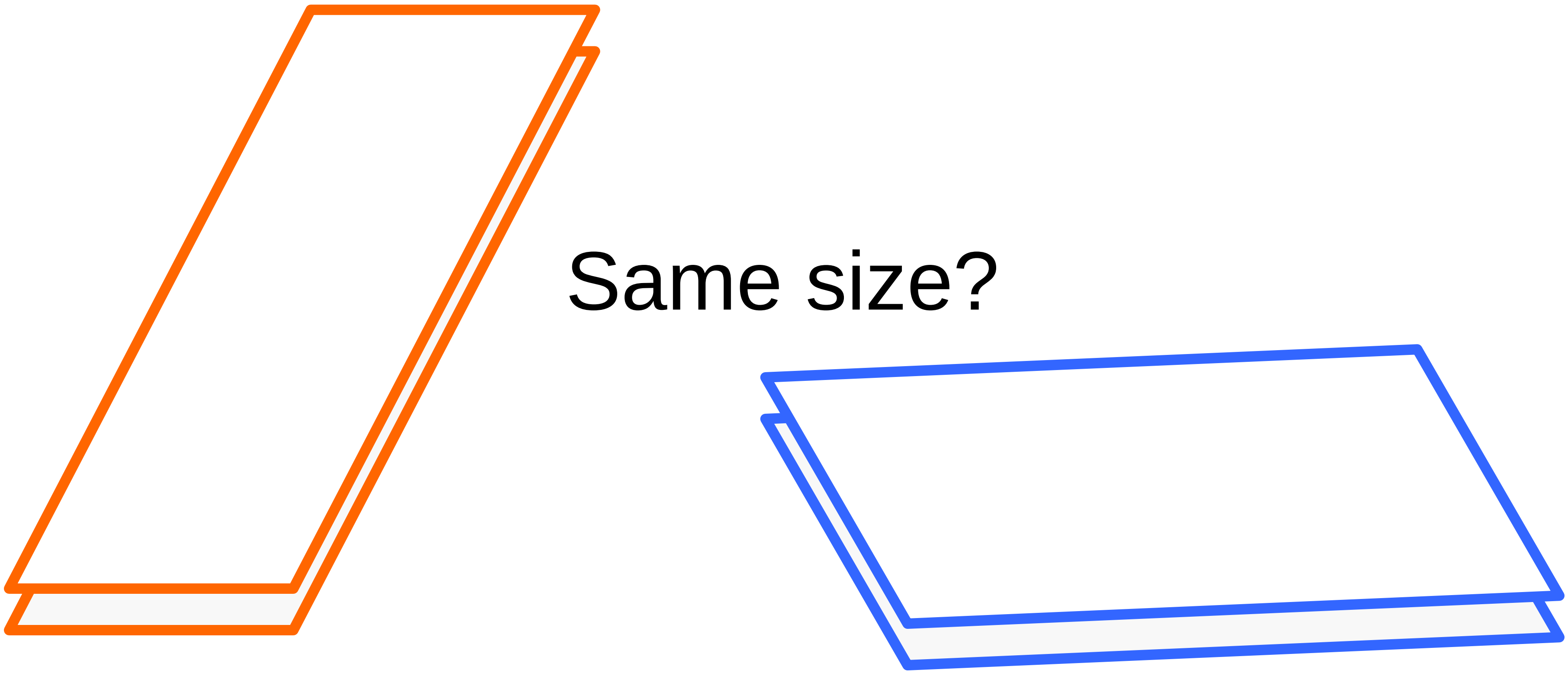


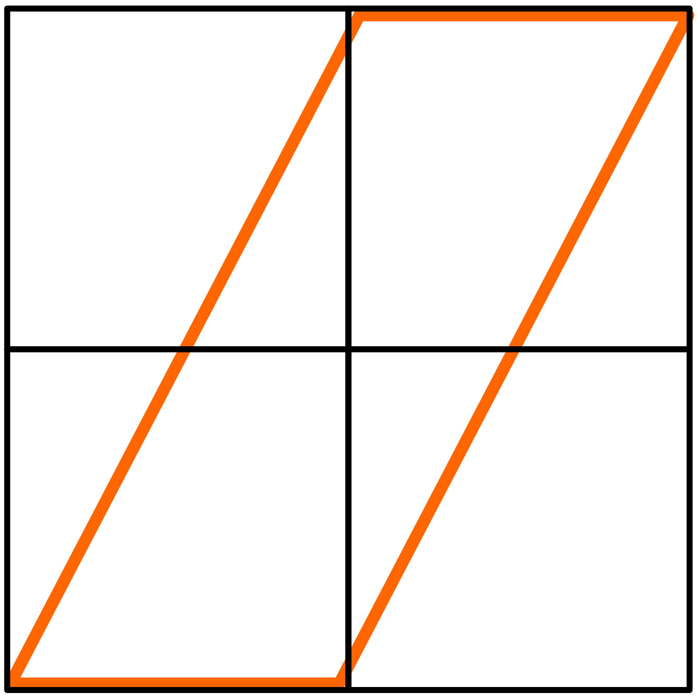


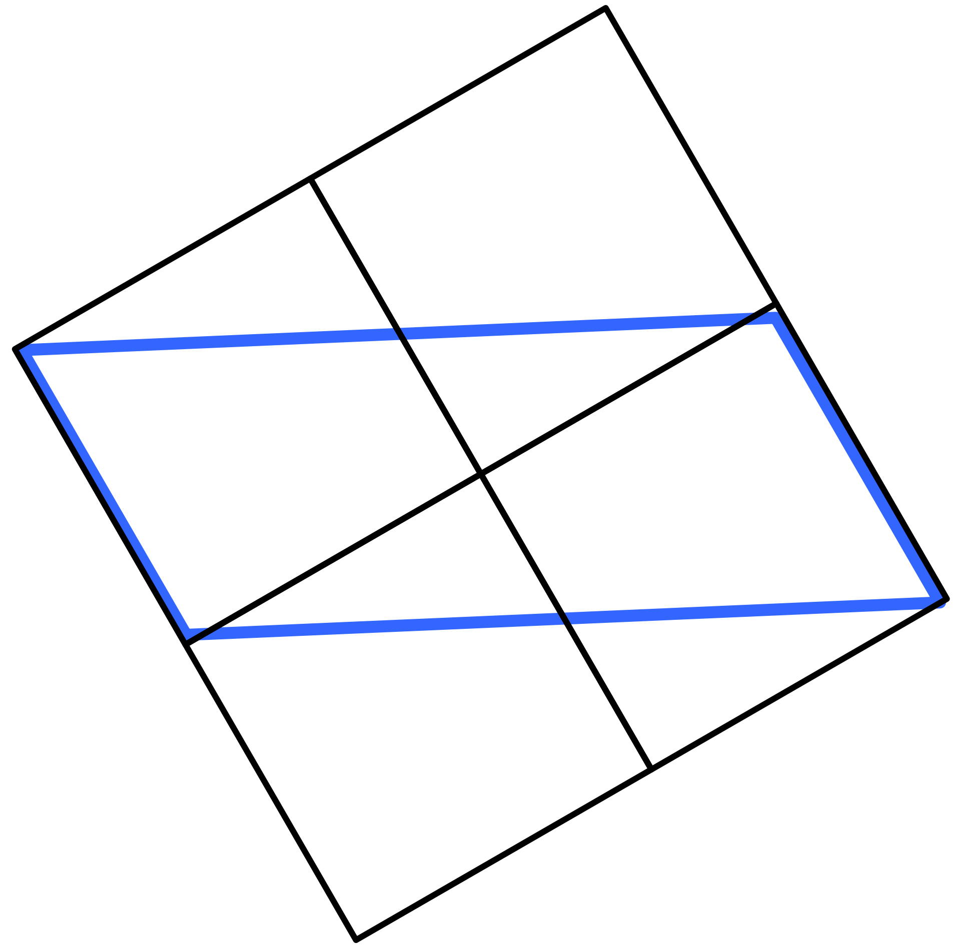
Prediction
Goals
Prediction
Goals
Actions
What are the consequences?
Actions
Conscious perception
errors
Why?
10x
There are 10x feedback neurons
?
Visual Cortex
Visual Thalamus

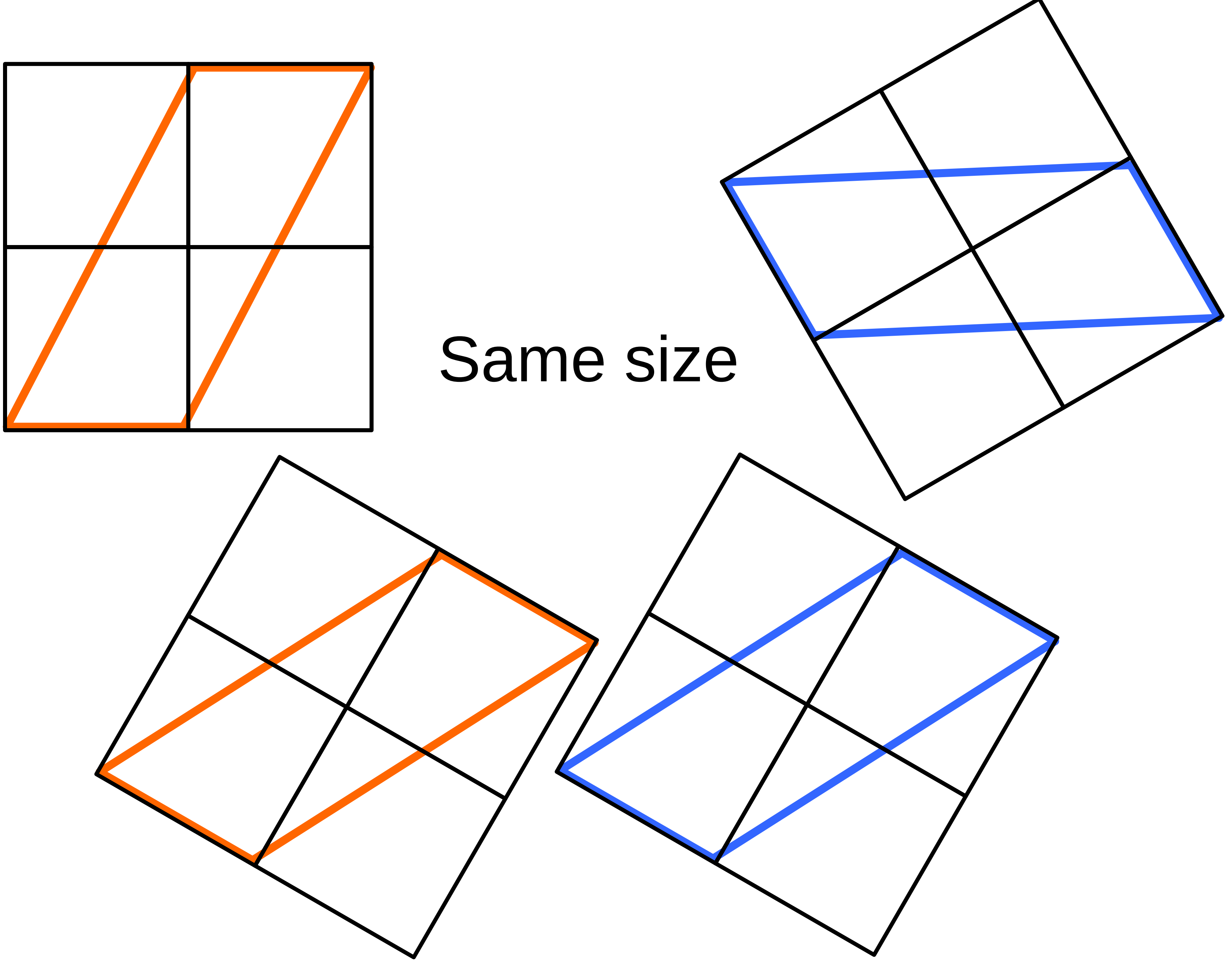
Seeing is ***dreaming***

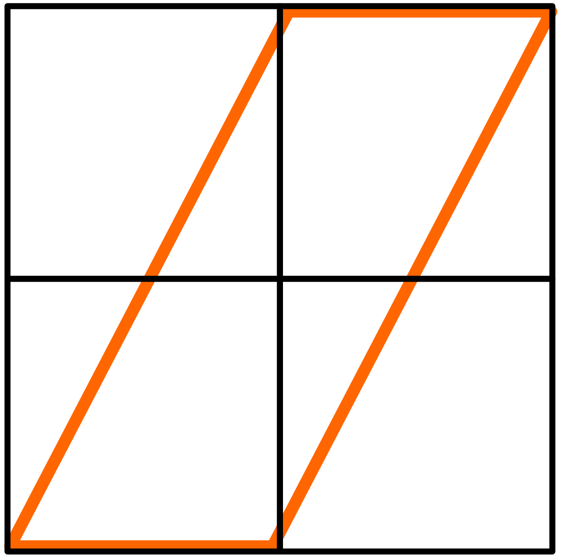



Same size?






Same size



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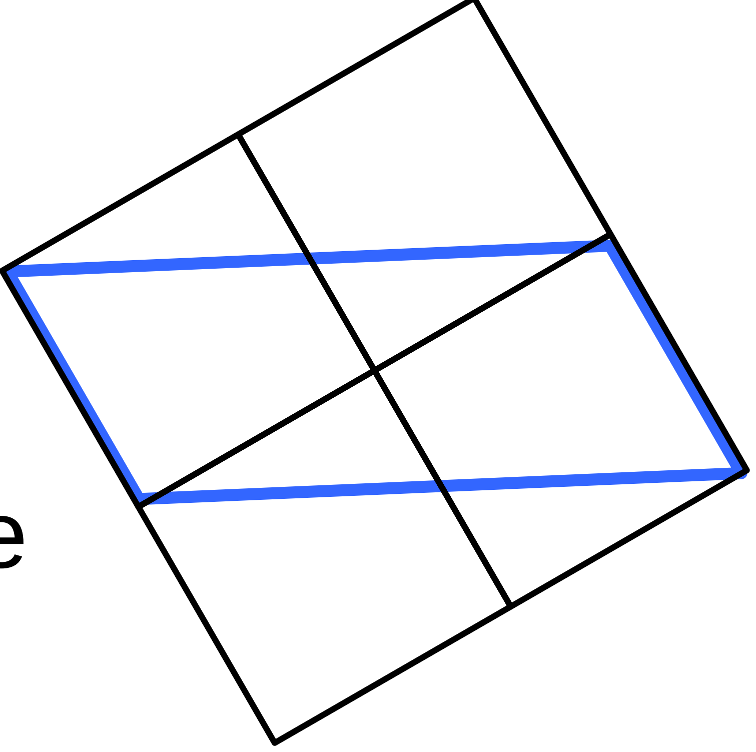


Same size

Toggle between this slide and the ones before and after

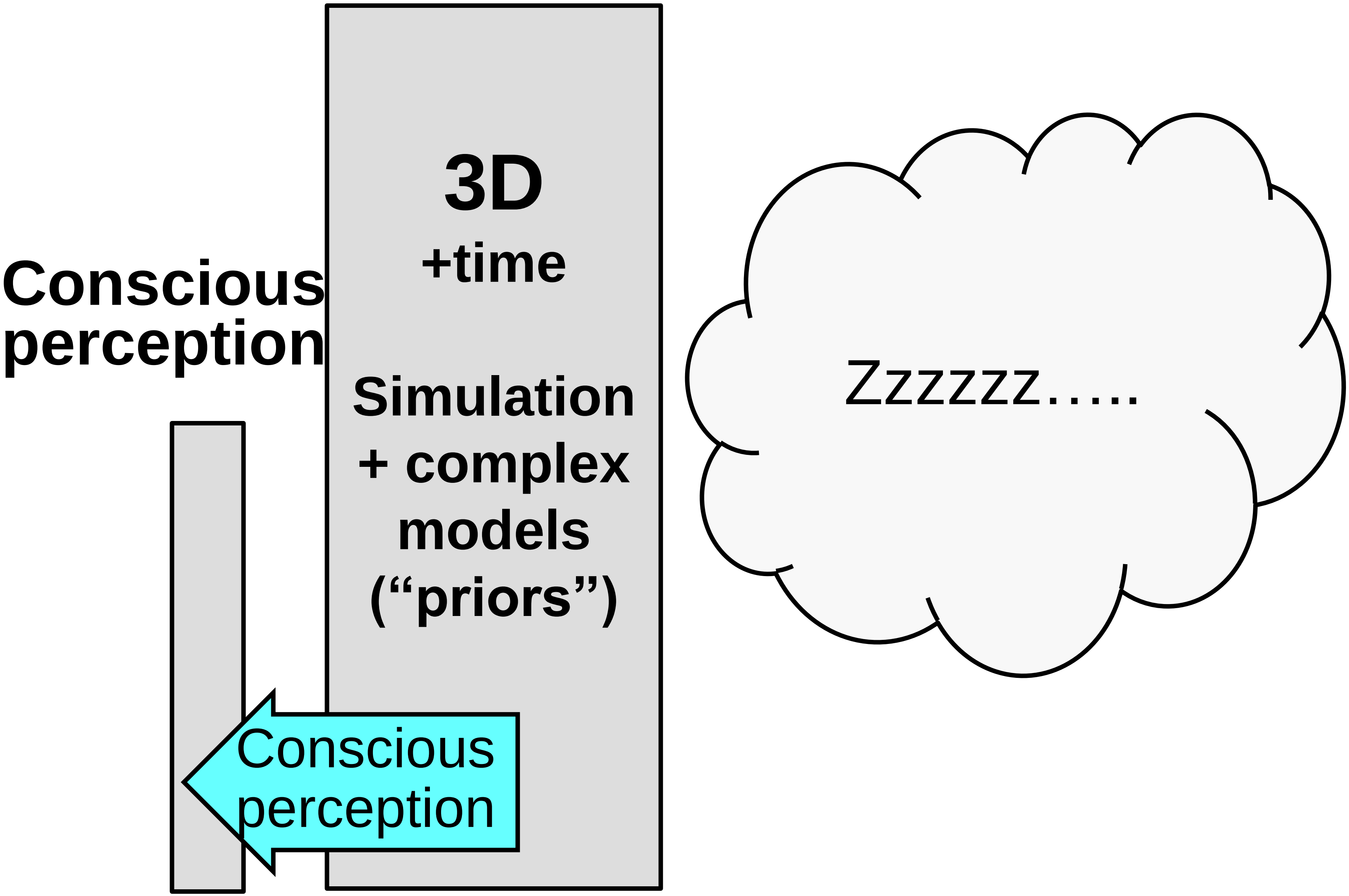
Even when you “know” they are the same, they appear different

Same size?

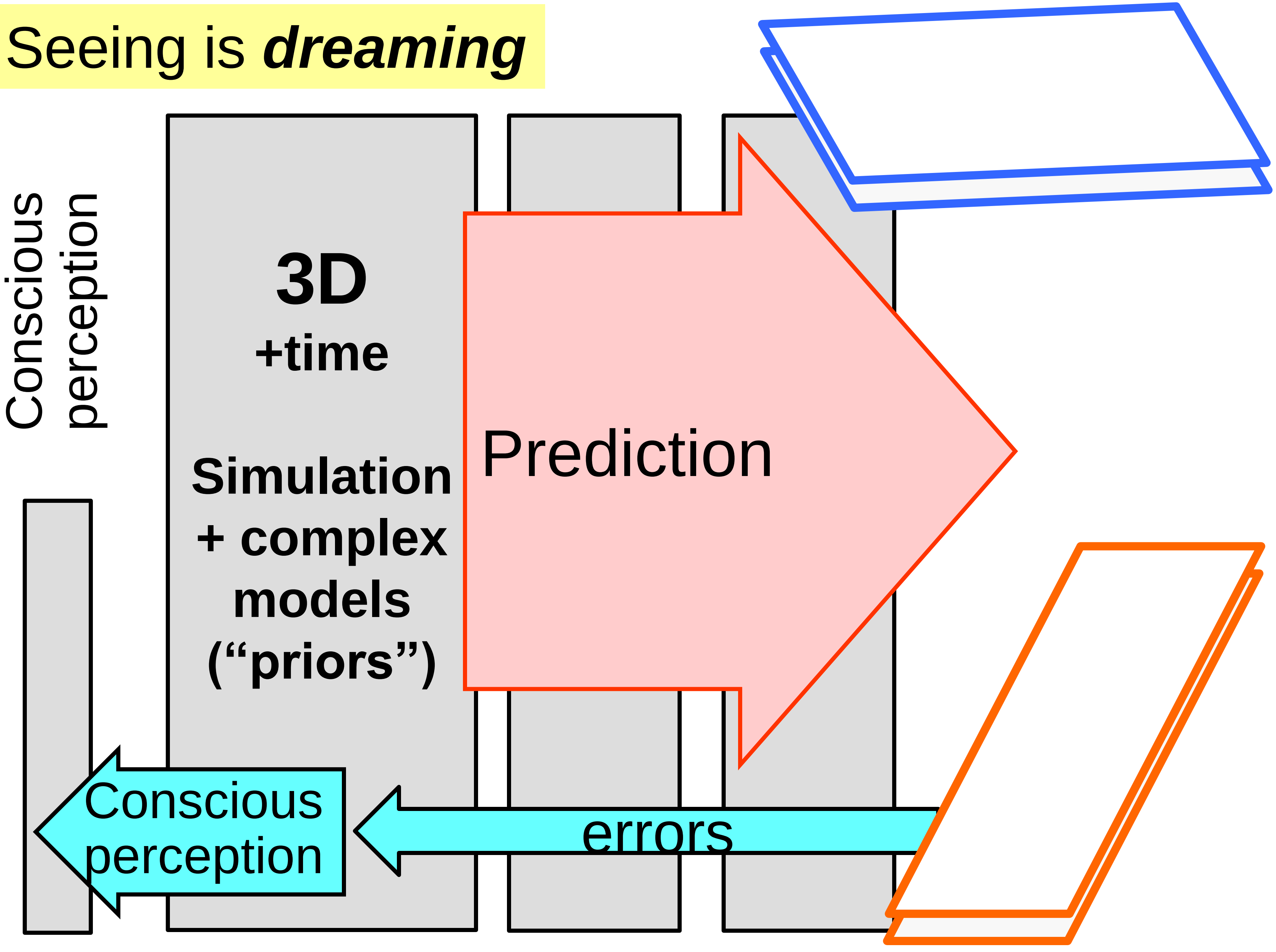
Vision: evolved for complex simulation and control, not 2d static pictures

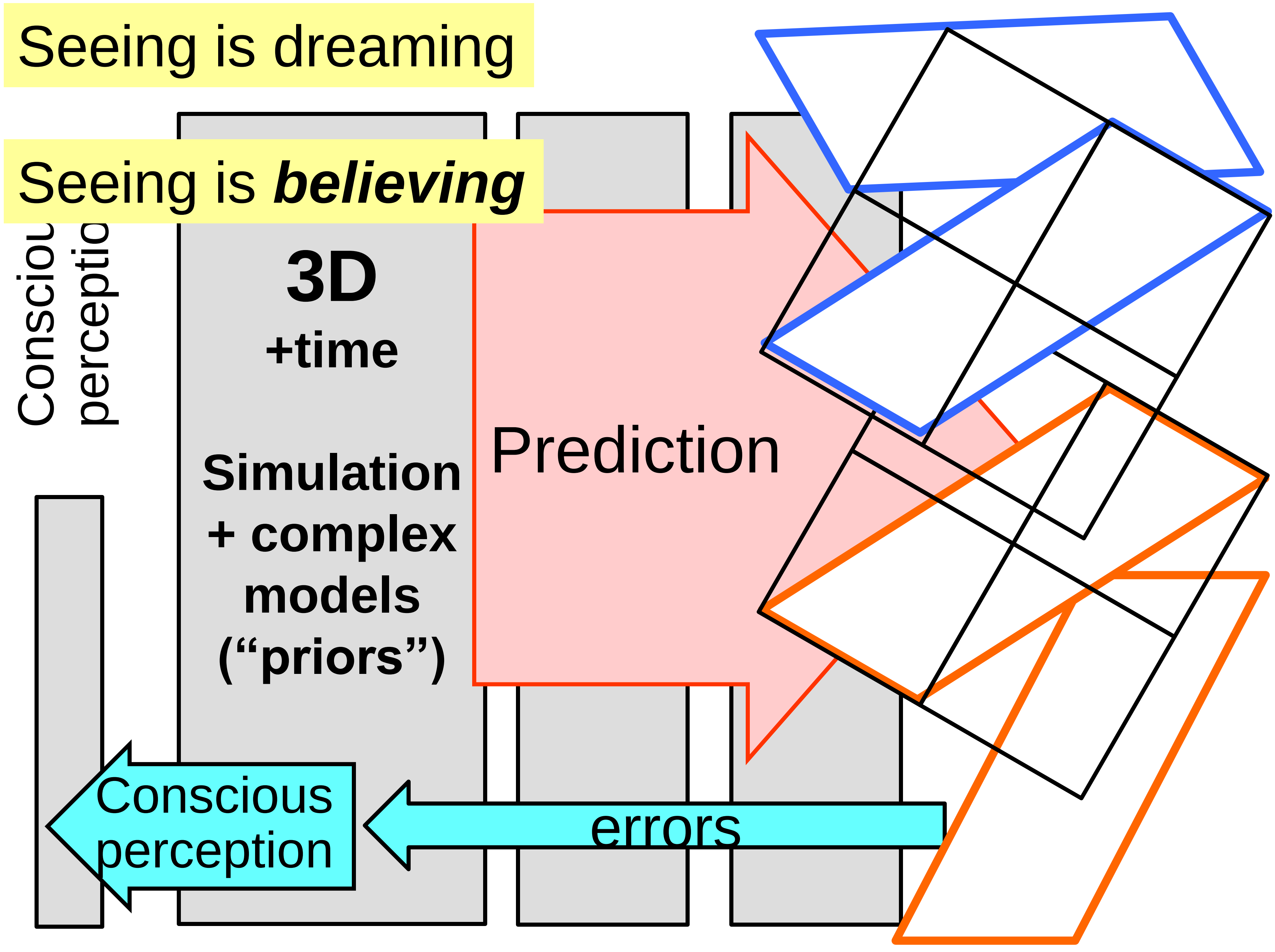
Even when you “know” they are the same, they appear different

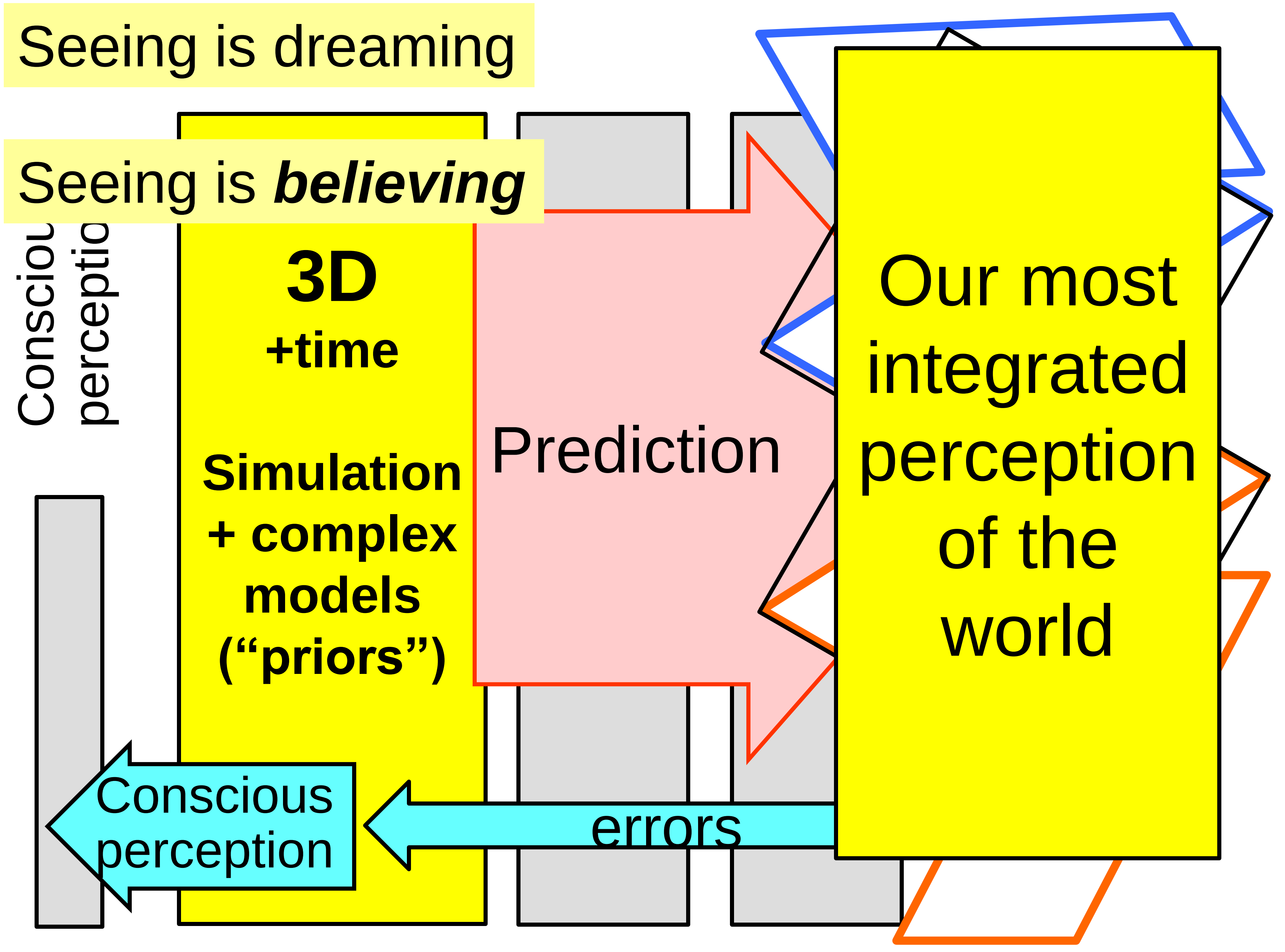
Seeing is ***dreaming***



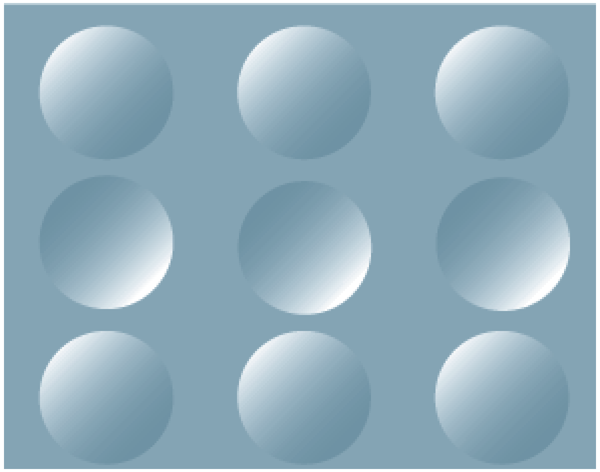
Seeing is ***dreaming***

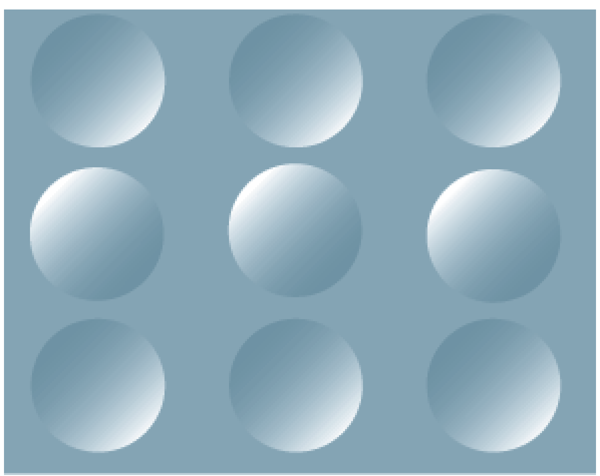


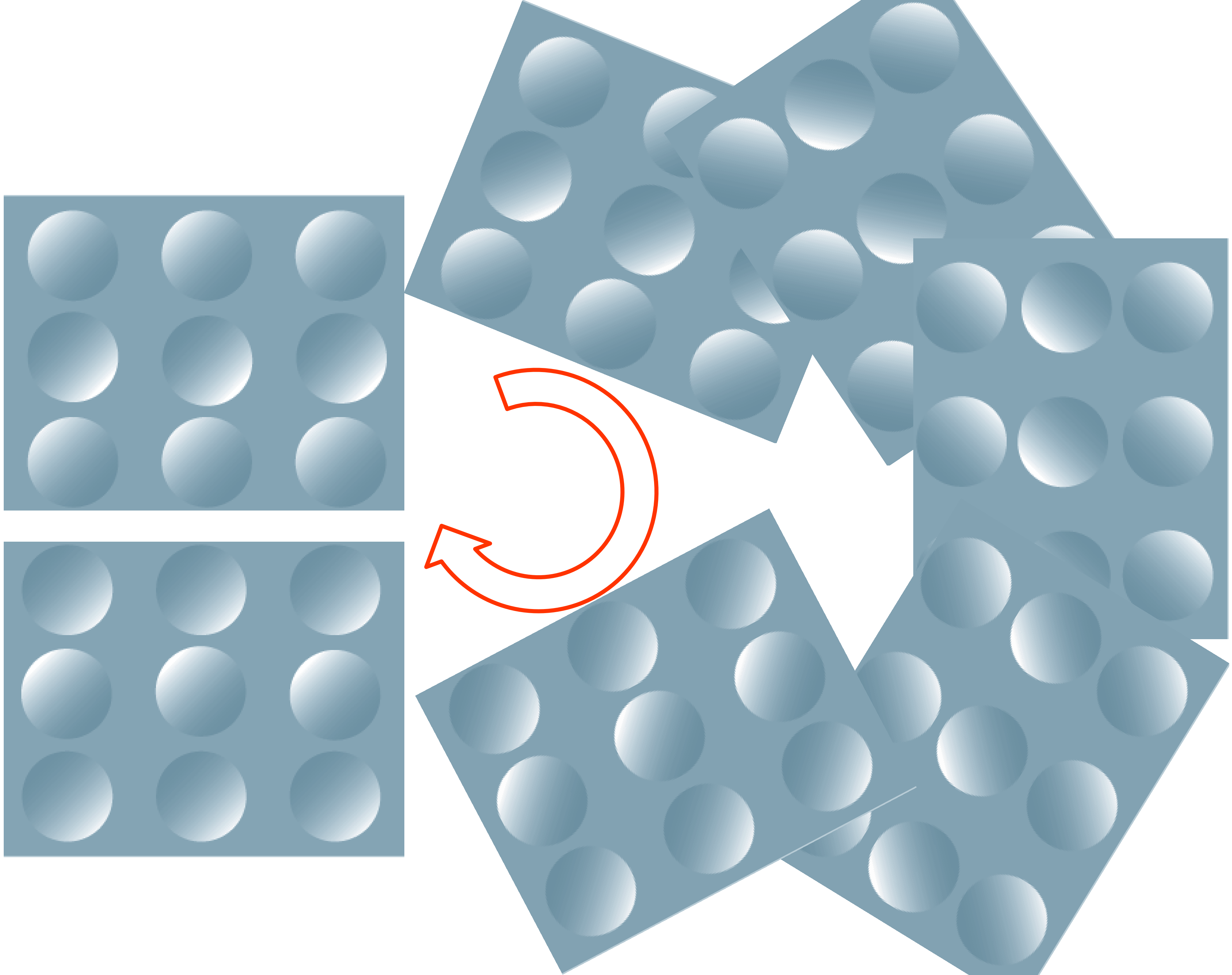

Seeing is dreaming
Seeing is ***believing***
3D
+time
Simulation
+ complex
models
(“priors”)
Prediction
Conscious
perception
errors



Seeing is dreaming
Seeing is ***believing***
Consciou
perceptio
3D
+time
Simulation
+ complex
models
(“priors”)
Prediction
Our most integrated perception of the world
Conscious perception
errors

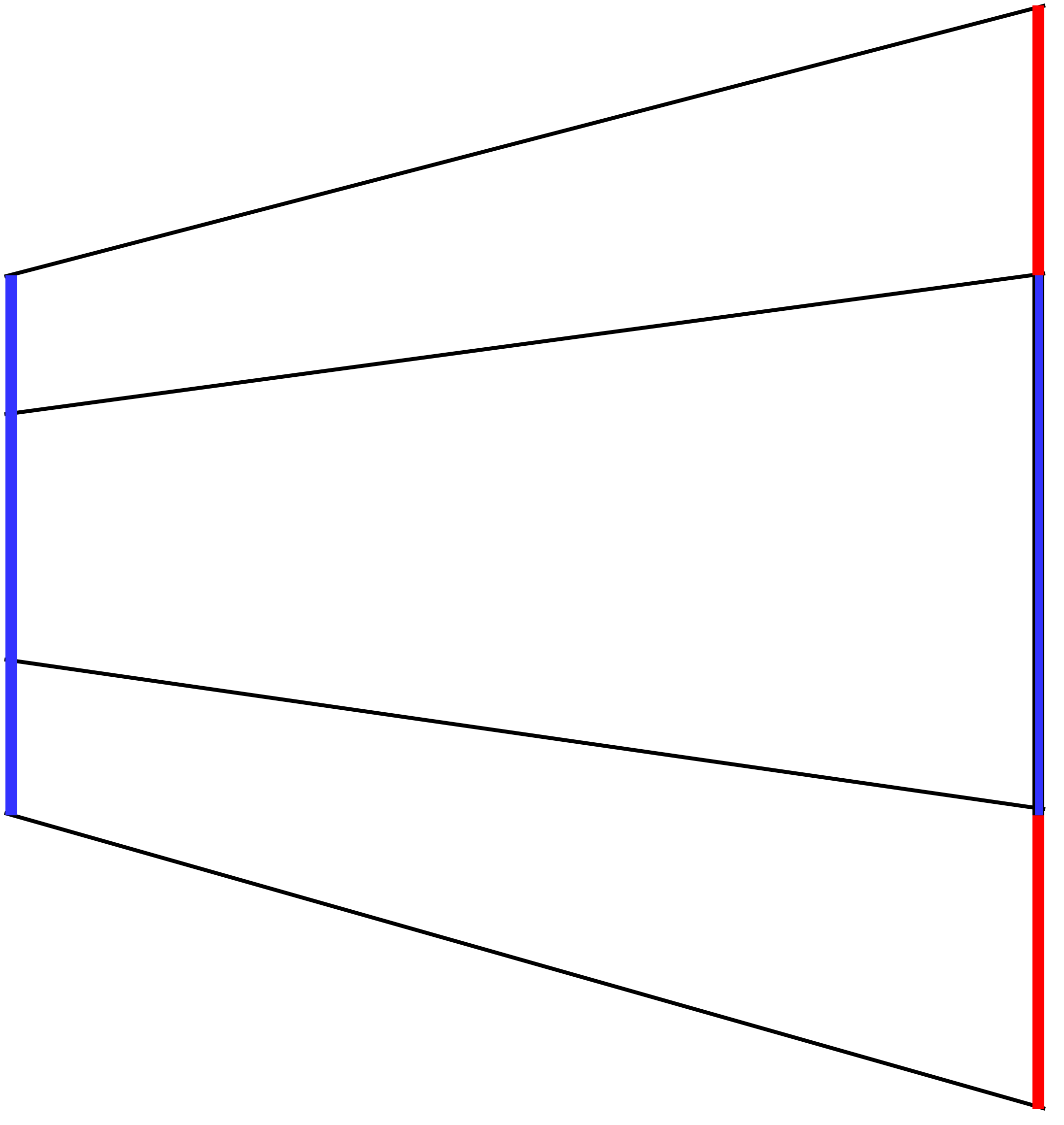




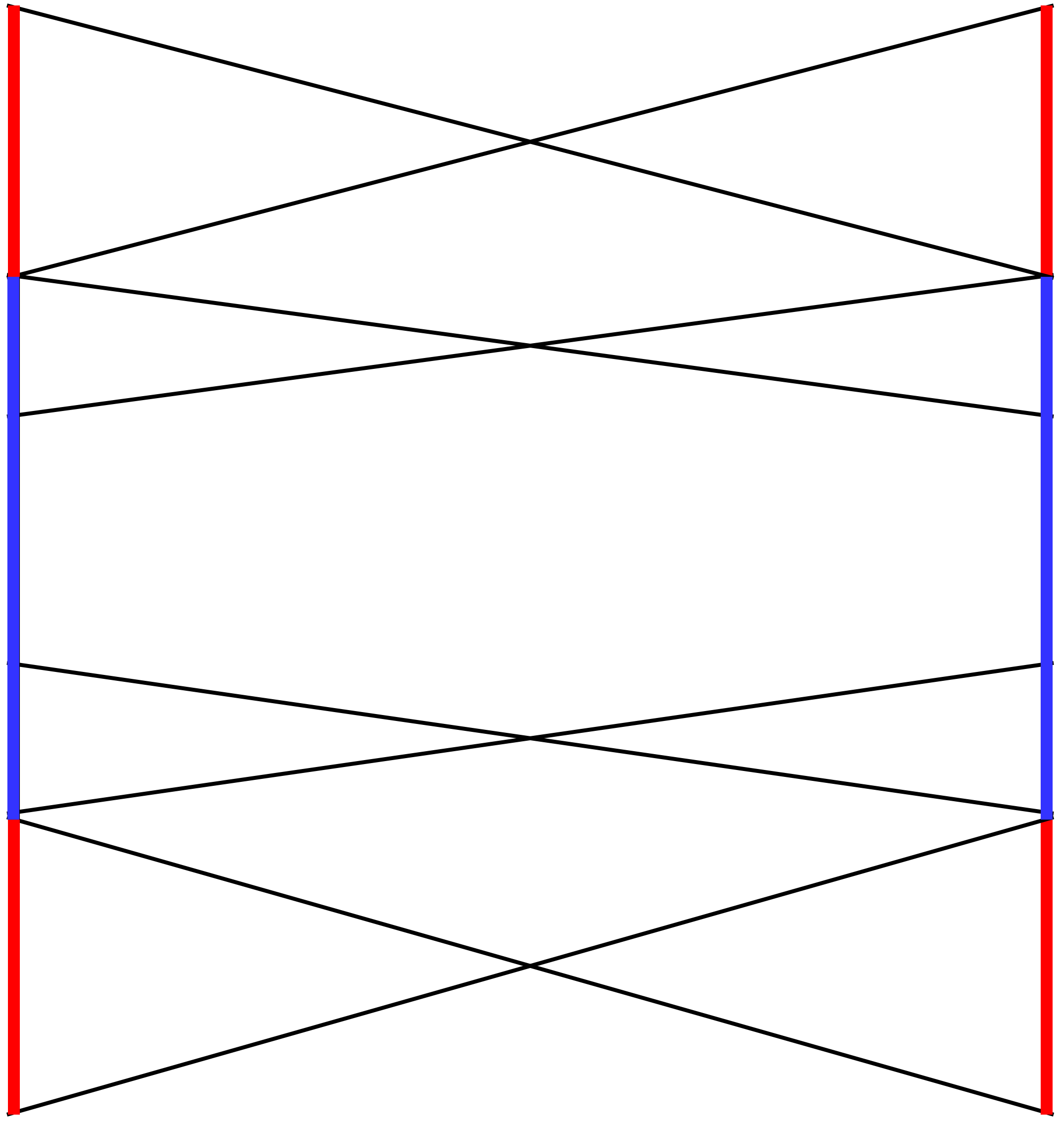


Which blue line is longer?

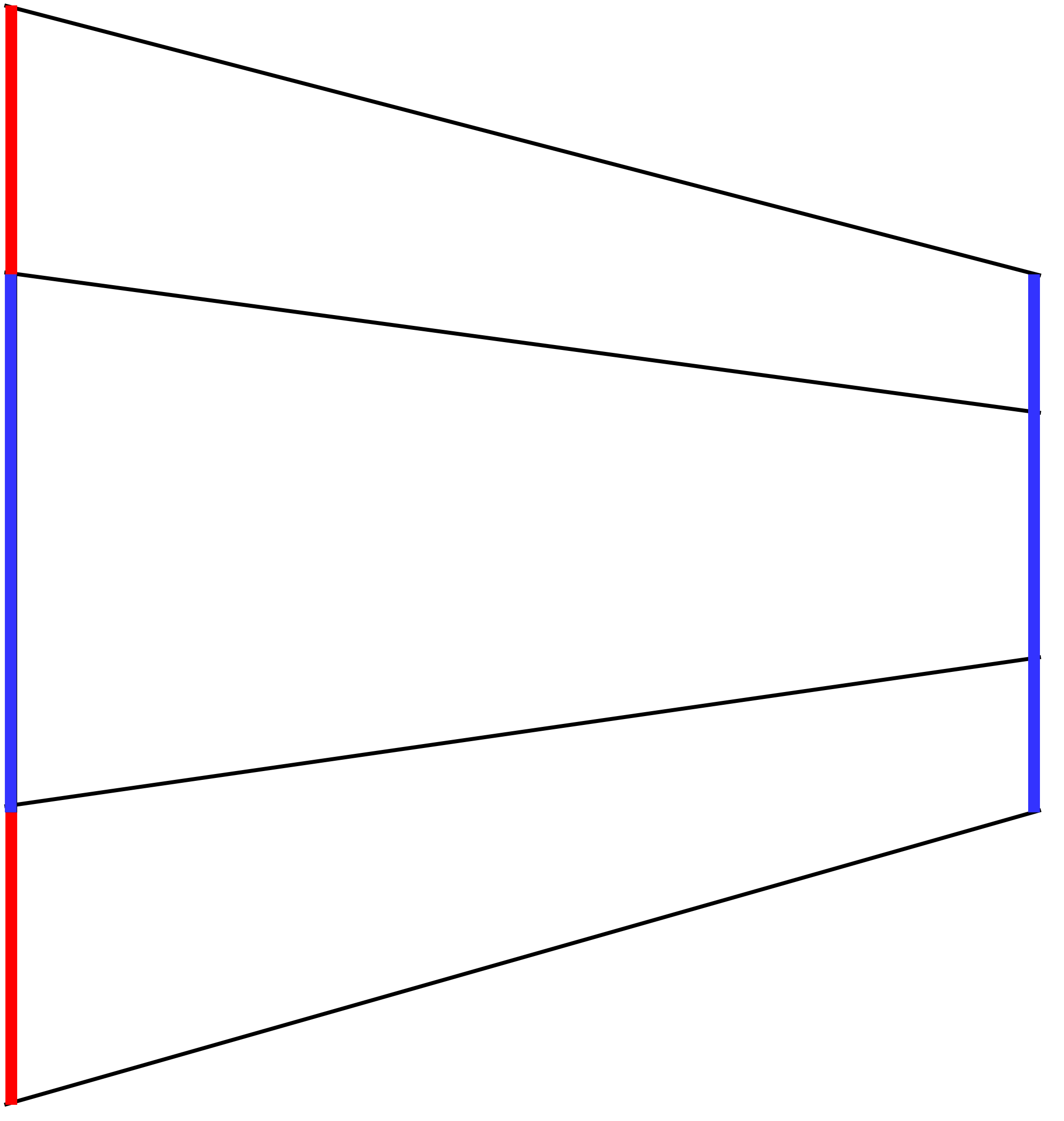
Which blue line is longer?



Which blue line is longer?



Which blue line is longer?



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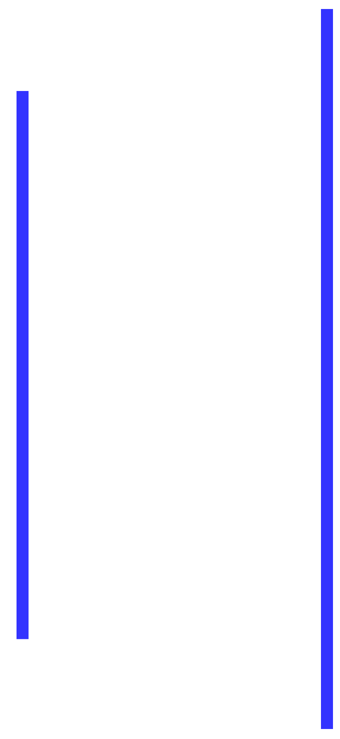

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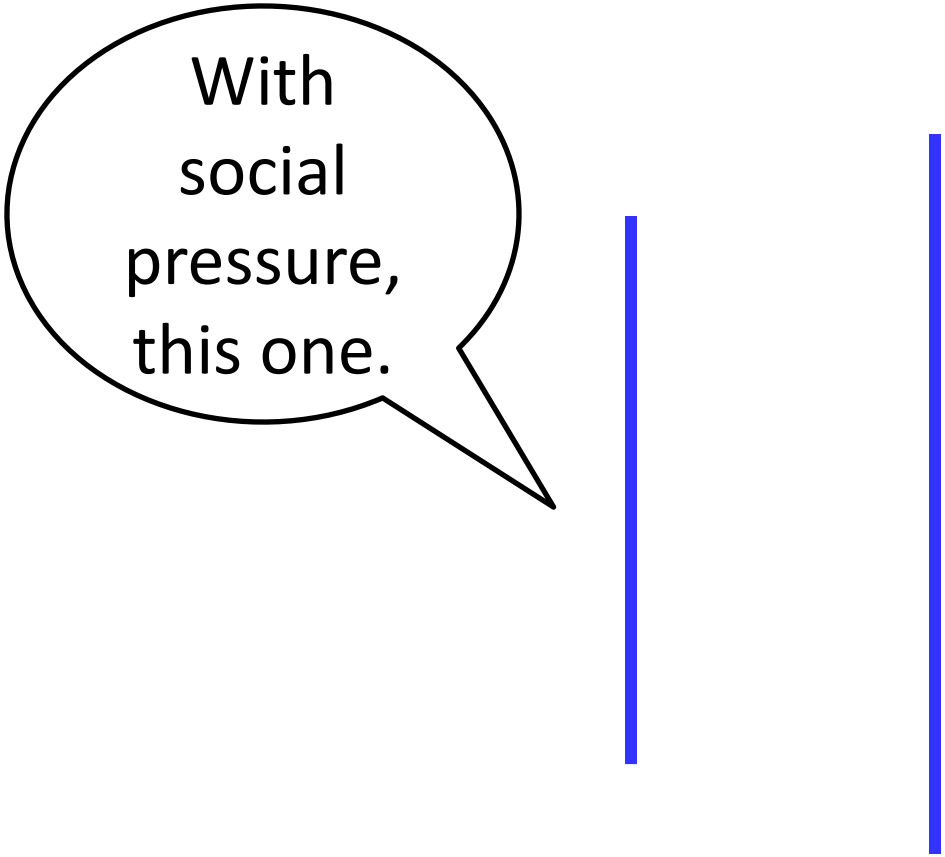
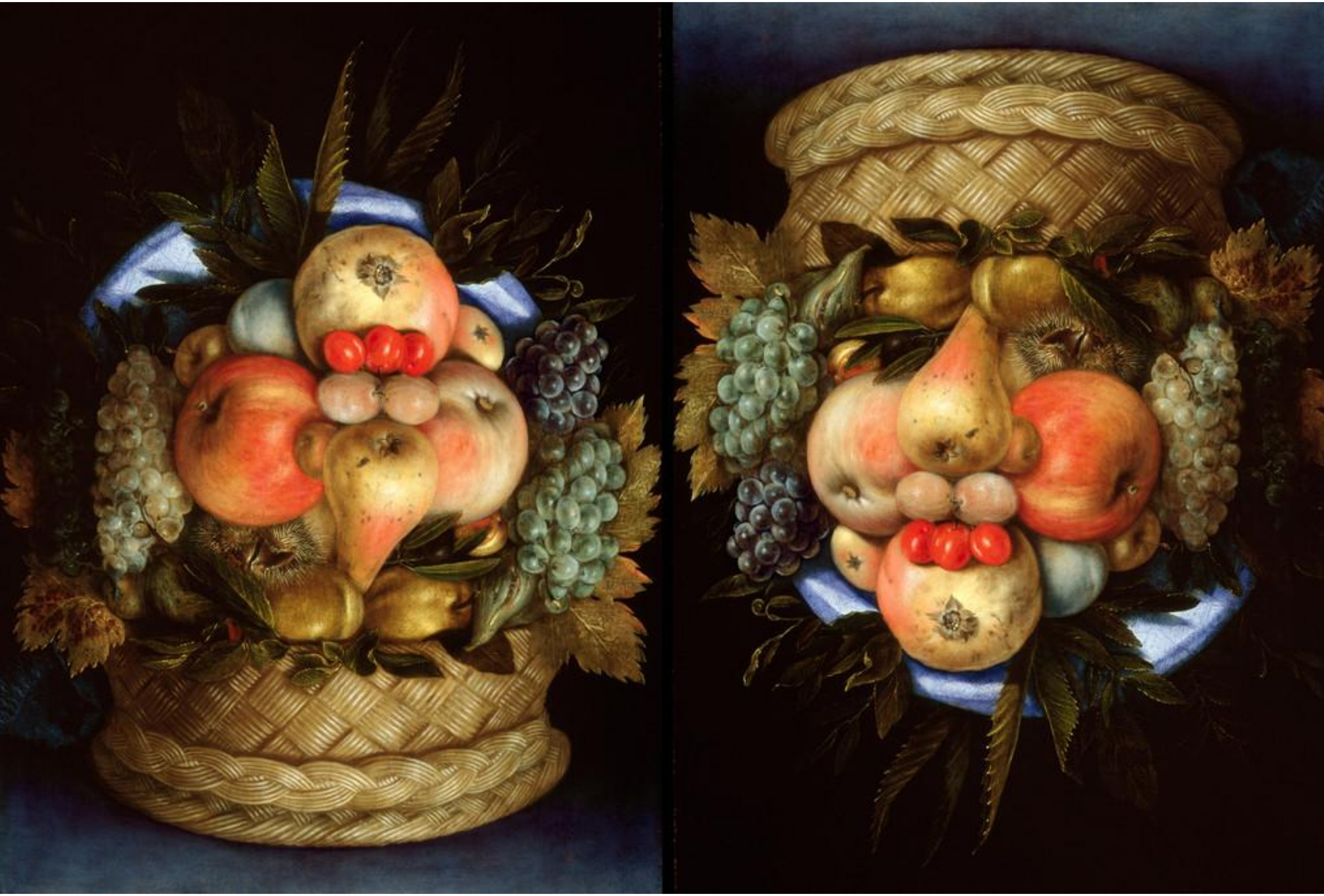


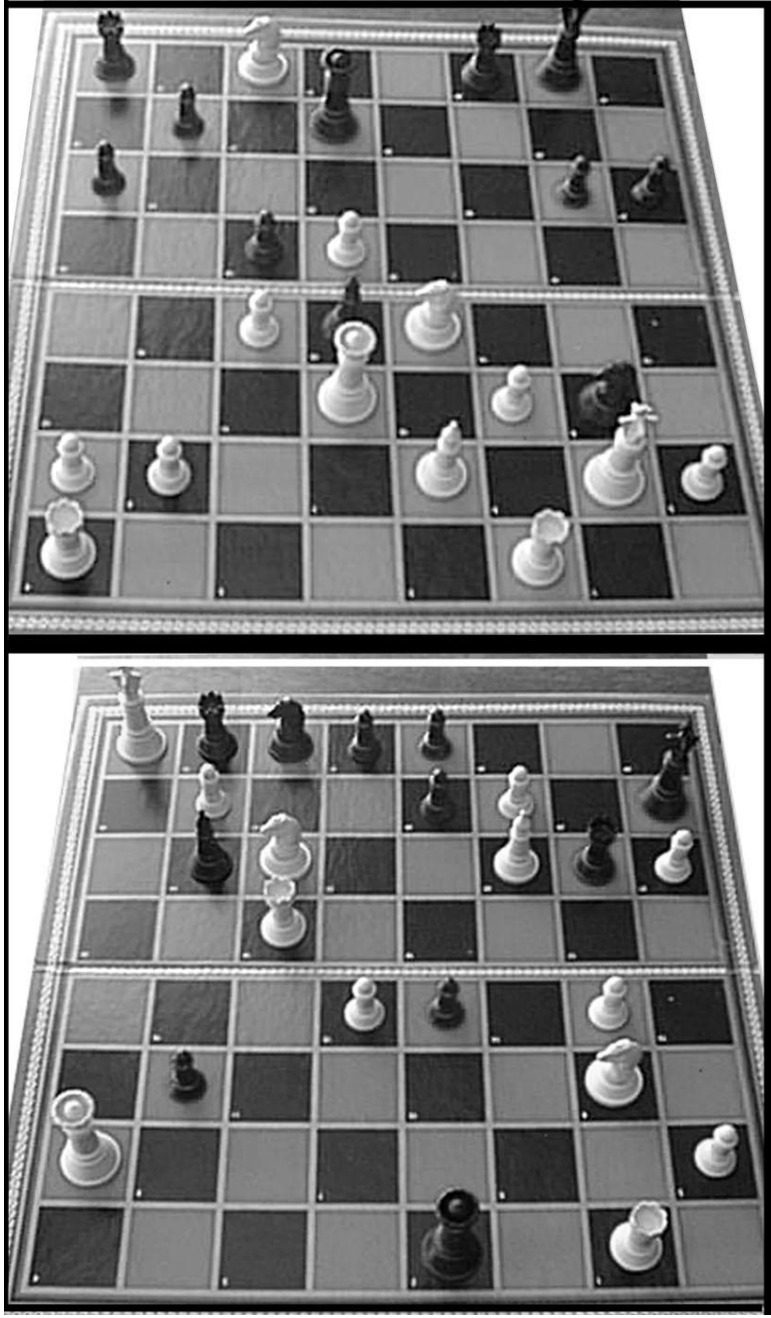
Standard social psychology experiment.



Chess experts

- can reconstruct entire chessboard with < ~ 5s inspection
- can recognize 1e5 distinct patterns
- can play multiple games blindfolded and simultaneous
- are no better on random boards

(Simon and Gilmartin, de Groot)



www.psywww.com/intropsych/ch07_cognition/expertise_and_domain_specific_knowledge.html

Specialized Face Learning Is Associated with Individual Recognition in Paper Wasps

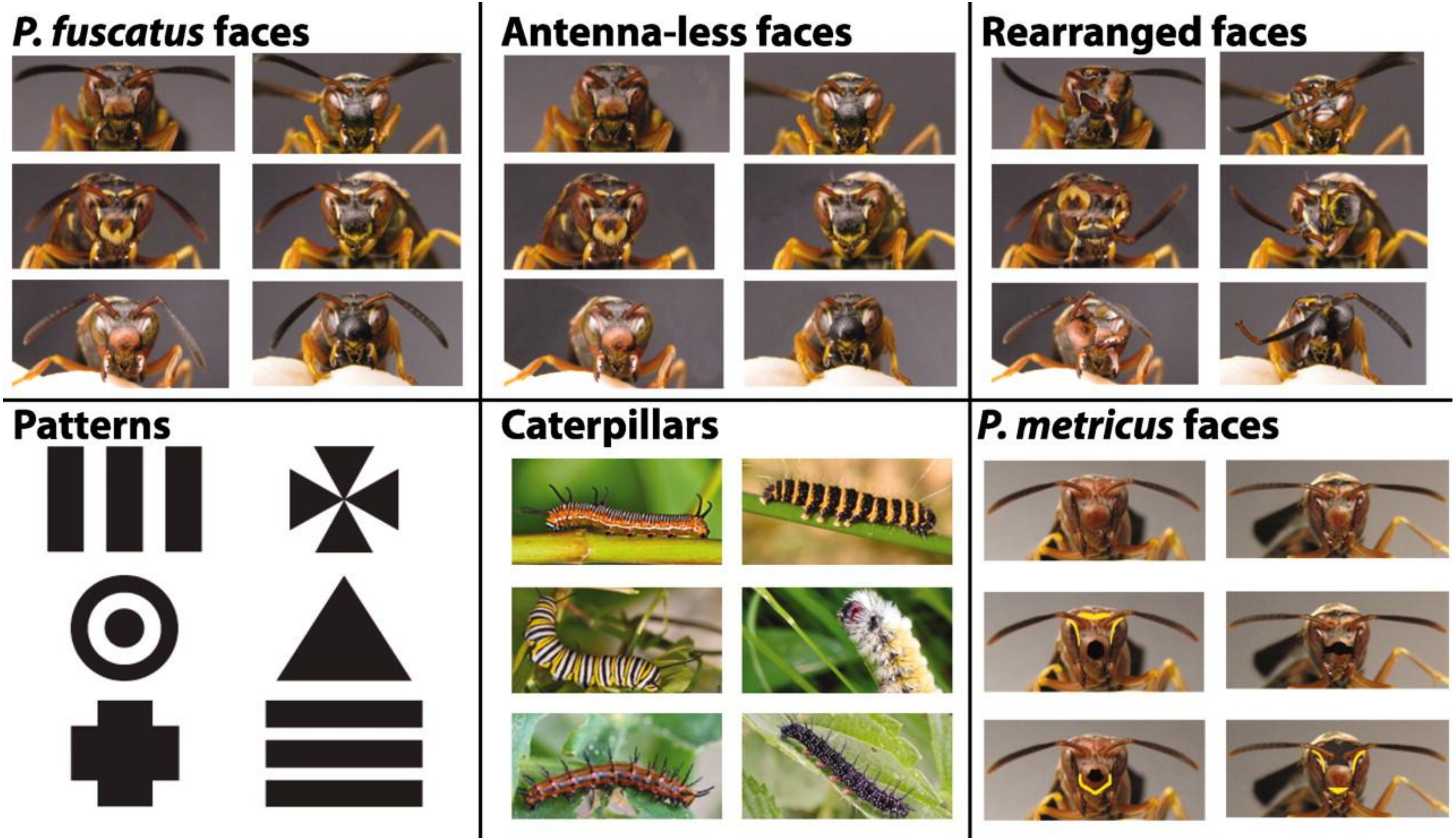
Science AAAS

Michael J. Sheehan* and Elizabeth A. Tibbetts

We demonstrate that the evolution of facial recognition in wasps is associated with specialized face-learning abilities. *Polistes fuscatus* can differentiate among normal wasp face images more rapidly and accurately than nonface images or manipulated faces. A close relative lacking facial recognition, *Polistes metricus*, however, lacks specialized face learning. Similar specializations for face learning are found in primates and other mammals, although *P. fuscatus* represents an independent evolution of specialization. Convergence toward face specialization in distant taxa as well as divergence among closely related taxa with different recognition behavior suggests that specialized cognition is surprisingly labile and may be adaptively shaped by species-specific selective pressures such as face recognition.

- *Polistes fuscatus* can differentiate among normal wasp face images more rapidly and accurately than nonface images or manipulated faces.
- *Polistes metricus* is a close relative lacking facial recognition and specialized face learning.
- Similar specializations for face learning are found in primates and other mammals, although *P. fuscatus* represents an independent evolution of specialization.
- Convergence toward face specialization in distant taxa as well as divergence among closely related taxa with different recognition behavior suggests that specialized cognition is surprisingly labile and may be adaptively shaped by species-specific selective pressures such as face recognition.

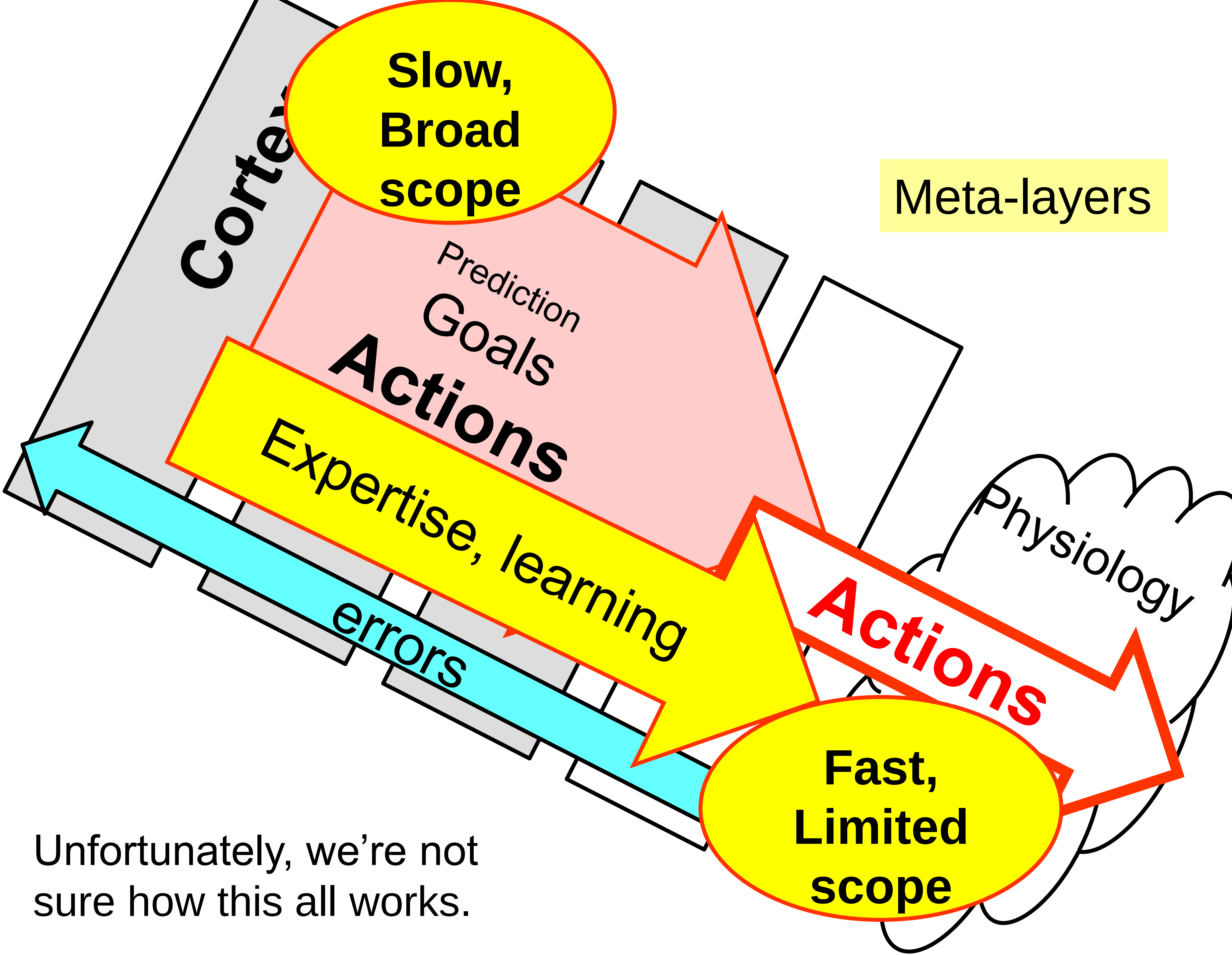
Fig. 1 Images used for training wasps.



M J Sheehan, E A Tibbetts Science 2011;334:1272-1275

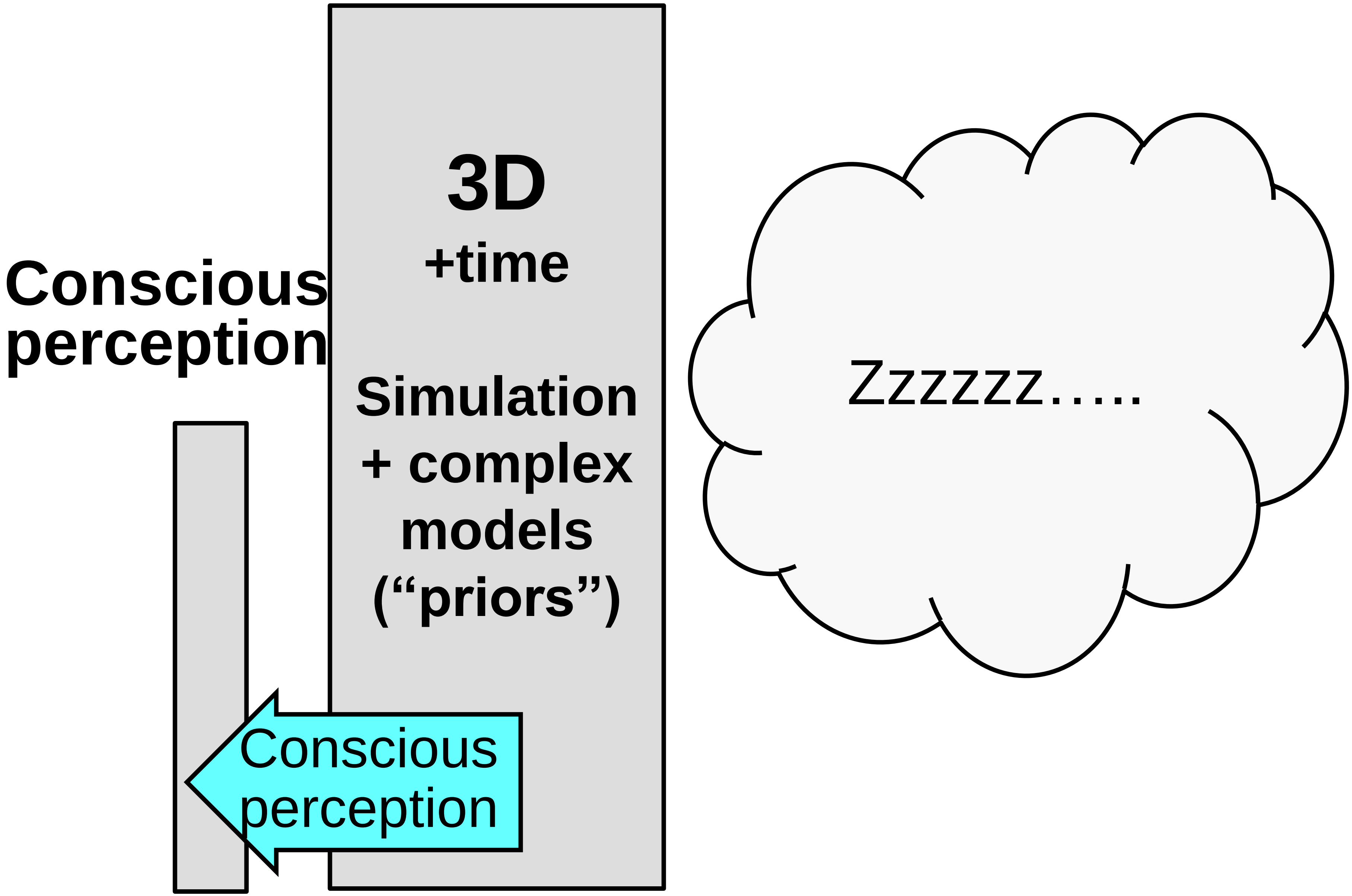
Published by AAAS

Science AAAS



Unfortunately, we're not sure how this all works.

Seeing is ***dreaming***



Seeing is dreaming

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Consciou
perceptio

3D
+time

Simulation
+ complex
models
("priors")

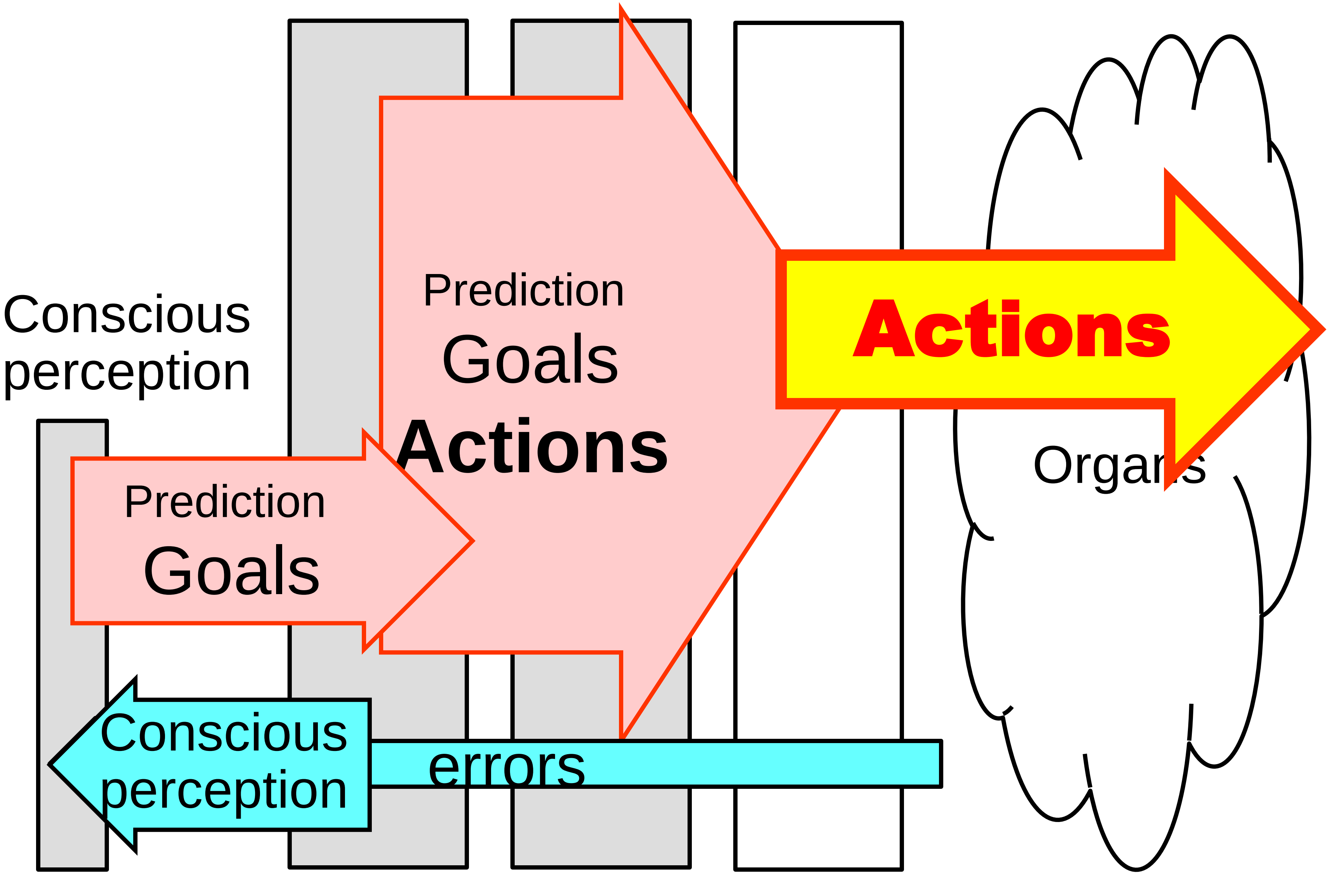
Pred

Our most
integrated
perception
of the world

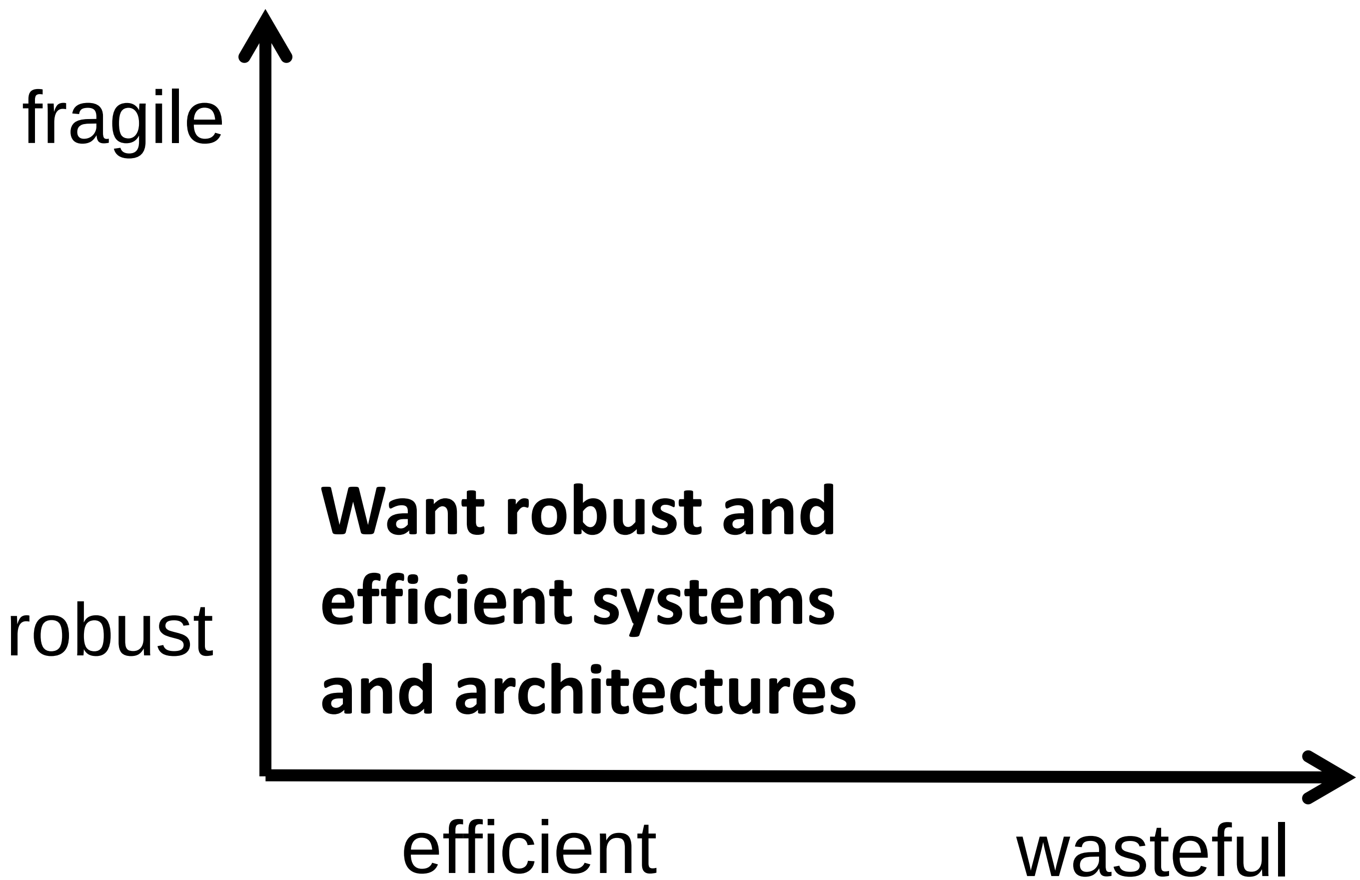
Conscious
perception

errors

But ultimately, only actions matter.



Want to understand the space of systems/architectures



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
failure transparent
fault-tolerant
fidelity
flexible
inspectable
installable
Integrity
interchangeable
interoperable
learnable
maintainable
manageable
mobile
modifiable
modular
nomadic
operable
orthogonality
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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

Simplified, minimal requirements

accessible
accountable
accurate
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affordable
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credible
process capable
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upgradable
usable

Requirements on systems and architectures

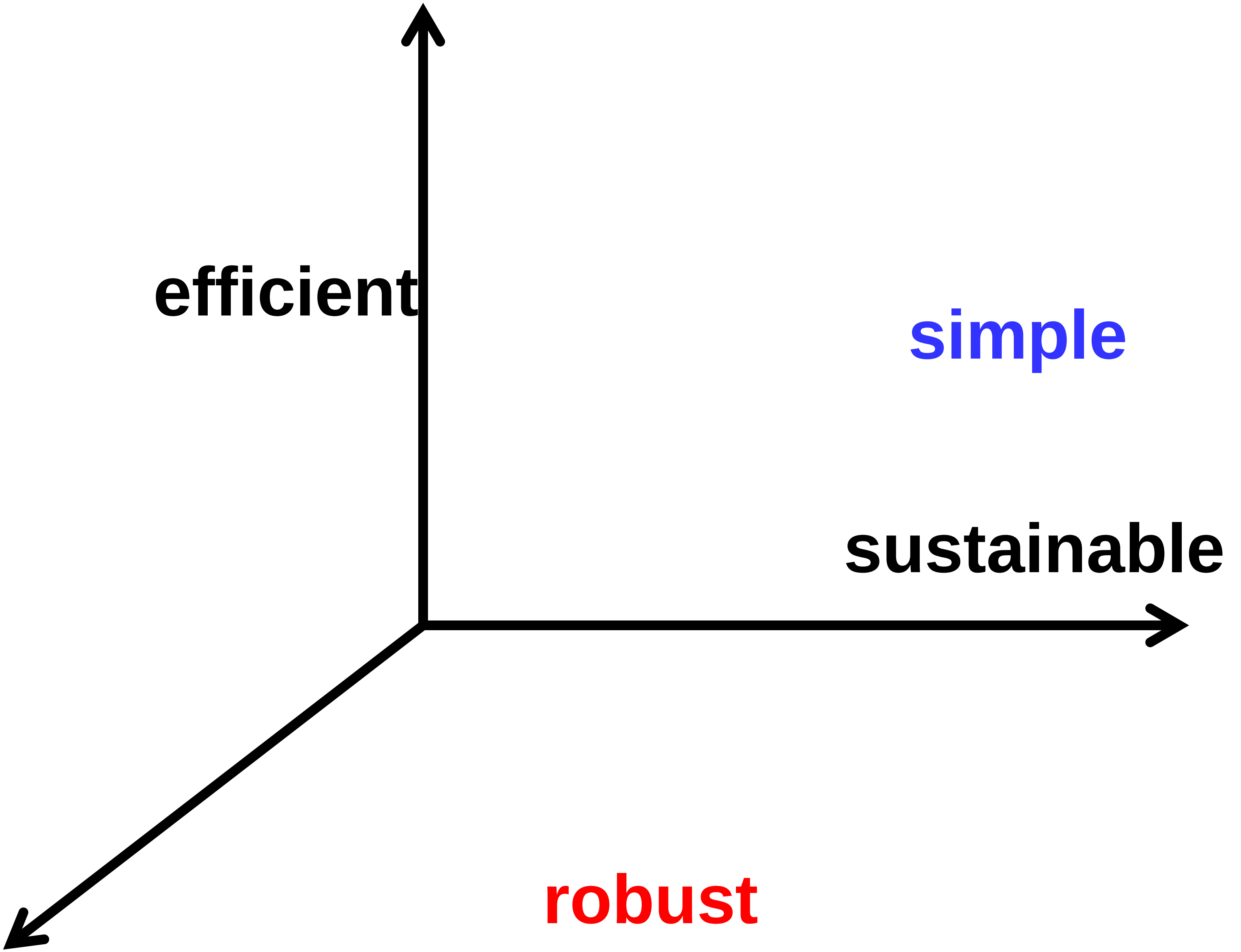
efficient

simple

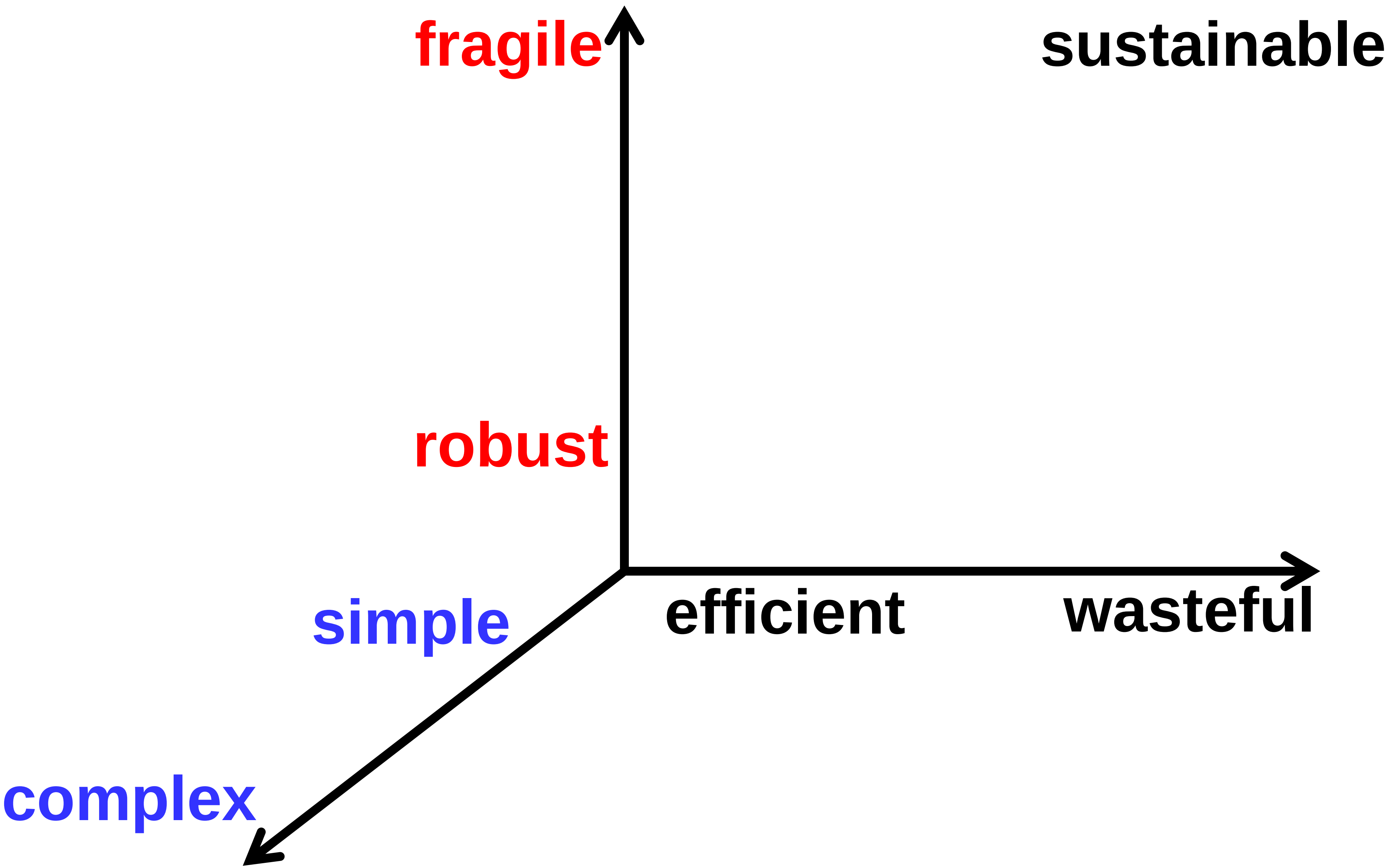
sustainable

robust

Requirements on systems and architectures

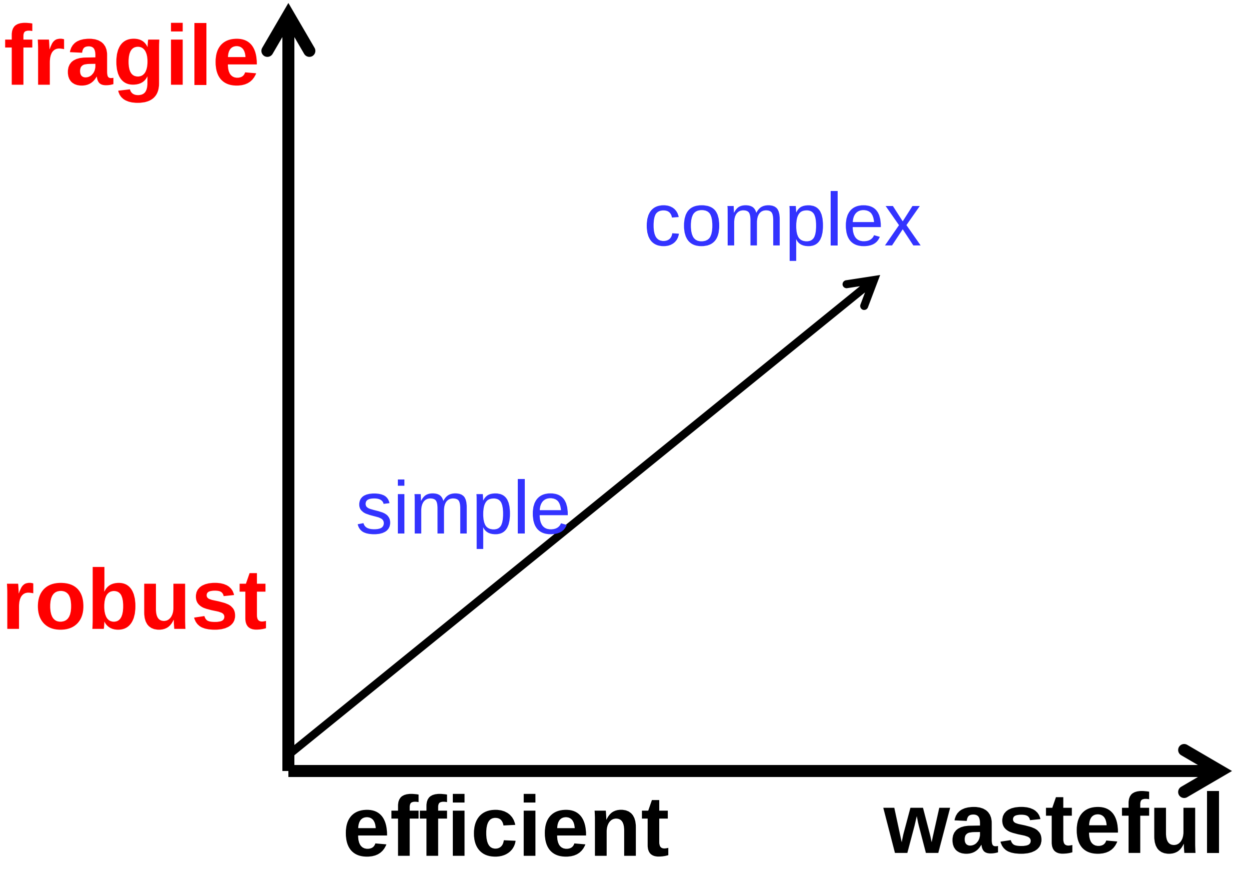


Requirements on systems and architectures



Requirements on systems and architectures

sustainable



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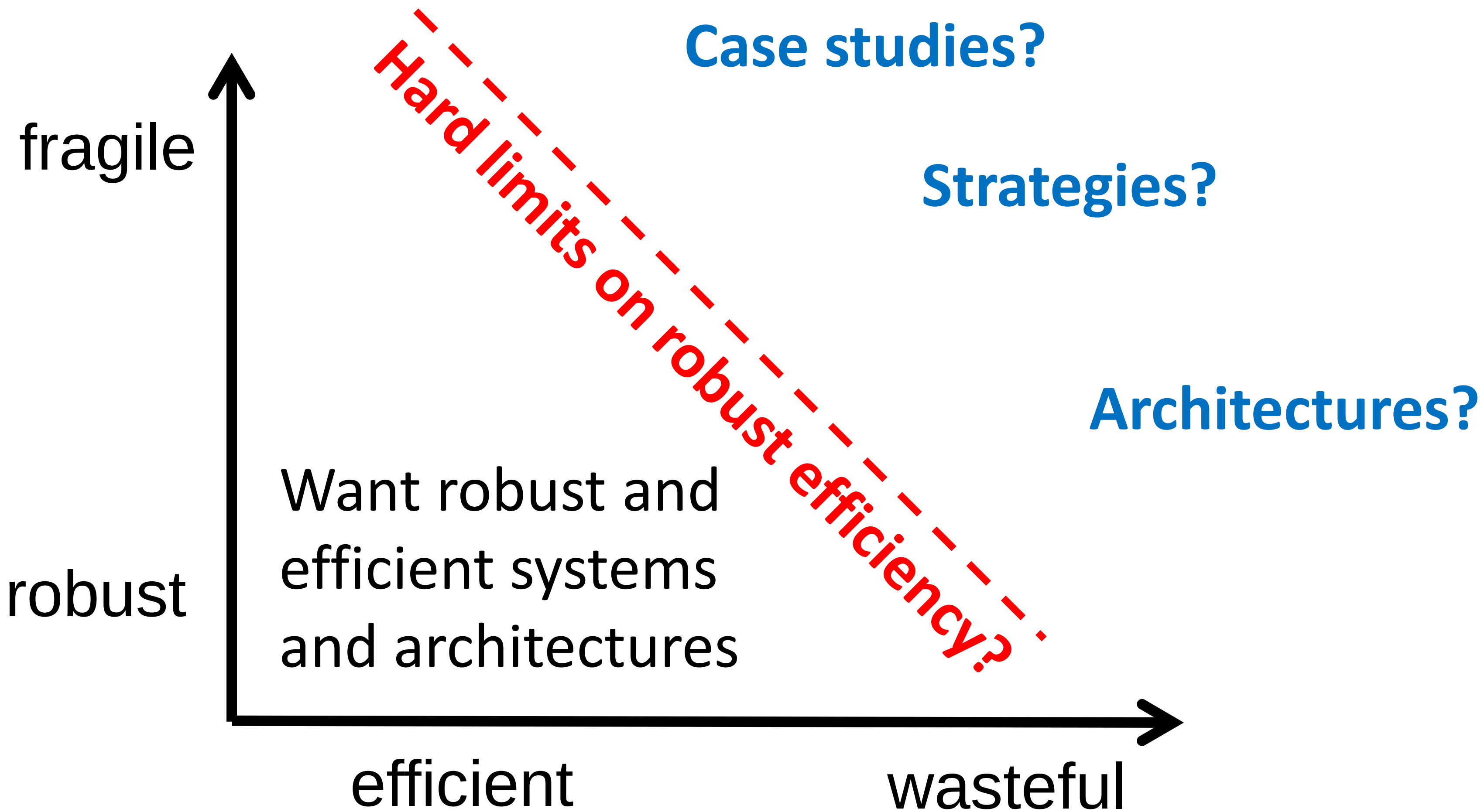

WHAT WE GET

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avai...

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Rocky Mountain Institute®

Amory B. Lovins,
Reinventing Fire

Fire in the Earth System

I'm interested in fire…

David M. J. S. Bowman,[1*] Jennifer K. Balch,[2,3,4*†] Paulo Artaxo,[5] William J. Bond,[6] Jean M. Carlson,[7] Mark A. Cochrane,[8] Carla M. D'Antonio,[9] Ruth S. DeFries,[10] John C. Doyle,[11] Sandy P. Harrison,[12] Fay H. Johnston,[13] Jon E. Keeley,[14,15] Meg A. Krawchuk,[16] Christian A. Kull,[17] J. Brad Marston,[18] Max A. Moritz,[16] I. Colin Prentice,[19] Christopher I. Roos,[20] Andrew C. Scott,[21] Thomas W. Swetnam,[22] Guido R. van der Werf,[23] Stephen J. Pyne[24]

Fire is a worldwide phenomenon that appears in the geological record soon after the appearance of terrestrial plants. Fire influences global ecosystem patterns and processes, including vegetation distribution and structure, the carbon cycle, and climate. Although humans and fire have always coexisted, our capacity to manage fire remains imperfect and may become more difficult in the future as climate change alters fire regimes. This risk is difficult to assess, however, because fires are still poorly represented in global models. Here, we discuss some of the most important issues involved in developing a better understanding of the role of fire in the Earth system.

Very accessible
No math

Science AAAS

www.sciencemag.org SCIENCE VOL 324 24 APRIL 2009

Wildfires, complexity, and highly optimized tolerance

Max A. Moritz*, Marco E. Morais[†], Lora A. Summerell[‡], J. M. Carlson[§¶], and John Doyle[‖]

*Department of Environmental Science, Policy, and Management, University of California, Berkeley, CA 94720; Departments of [†]Geography and [§]Physics, University of California, Santa Barbara, CA 93106; [‡]Department of Earth Sciences, California Polytechnic State University, San Luis Obispo, CA 93407; and [‖]Department of Control and Dynamical Systems, California Institute of Technology, Pasadena, CA 91125

Communicated by James S. Langer, University of California, Santa Barbara, CA, October 19, 2005 (received for review July 26, 2004)

Recent, large fires in the western United States have rekindled debates about fire management and the role of natural fire regimes in the resilience of terrestrial ecosystems. This real-world experience parallels debates involving abstract models of forest fires, a central metaphor in complex systems theory. Both real and modeled fire-prone landscapes exhibit roughly power law statistics in fire size versus frequency. Here, we examine historical fire catalogs and a detailed fire simulation model; both are in agreement with a highly optimized tolerance model. Highly optimized tolerance suggests robustness tradeoffs underlie resilience in different fire-prone ecosystems. Understanding these mechanisms may provide new insights into the structure of ecological systems and be key in evaluating fire management strategies and sensitivities to climate change.

Highly optimized tolerance (HOT) is a conceptual framewo for examining organization and structure in complex systen (18). Theoretically, HOT builds on models and mathemati from physics and engineering, and identifies robustness tradeof as a principle underlying mechanism for complexity and pow law statistics. HOT has been discussed in the context of a varie of technological and natural systems, including wildfires (18, 22 A quantitative prediction for the distribution of fire sizes h come from an extremely simple analytical HOT model, referre to as the PLR (probability–loss–resource) model (22). As precursor to results presented later in this article, Fig. 2 der onstrates the PLR prediction and truncated power law statisti (23) for several fire history catalogs. This plot represents the ra data as rank or cumulative frequency of fires $P(l)$ greater tha

Accessible ecology
UG math

17912–17917 | PNAS | December 13, 2005 | vol. 102 | no. 50

Wildfire ecosystem as ideal example

- Cycles on years to decades timescale
- Regime shifts: grass vs shrub vs tree
- Fire= keystone “specie”
  - Metabolism: consumes vegetation
  - Doesn’t (co-)evolve
  - Simplifies co-evolution spirals and metabolisms
- 4 ecosystems globally with convergent evo
  - So Cal, Australia, S Africa, E Mediterranean
  - Similar vegetation mix
  - Invasive species

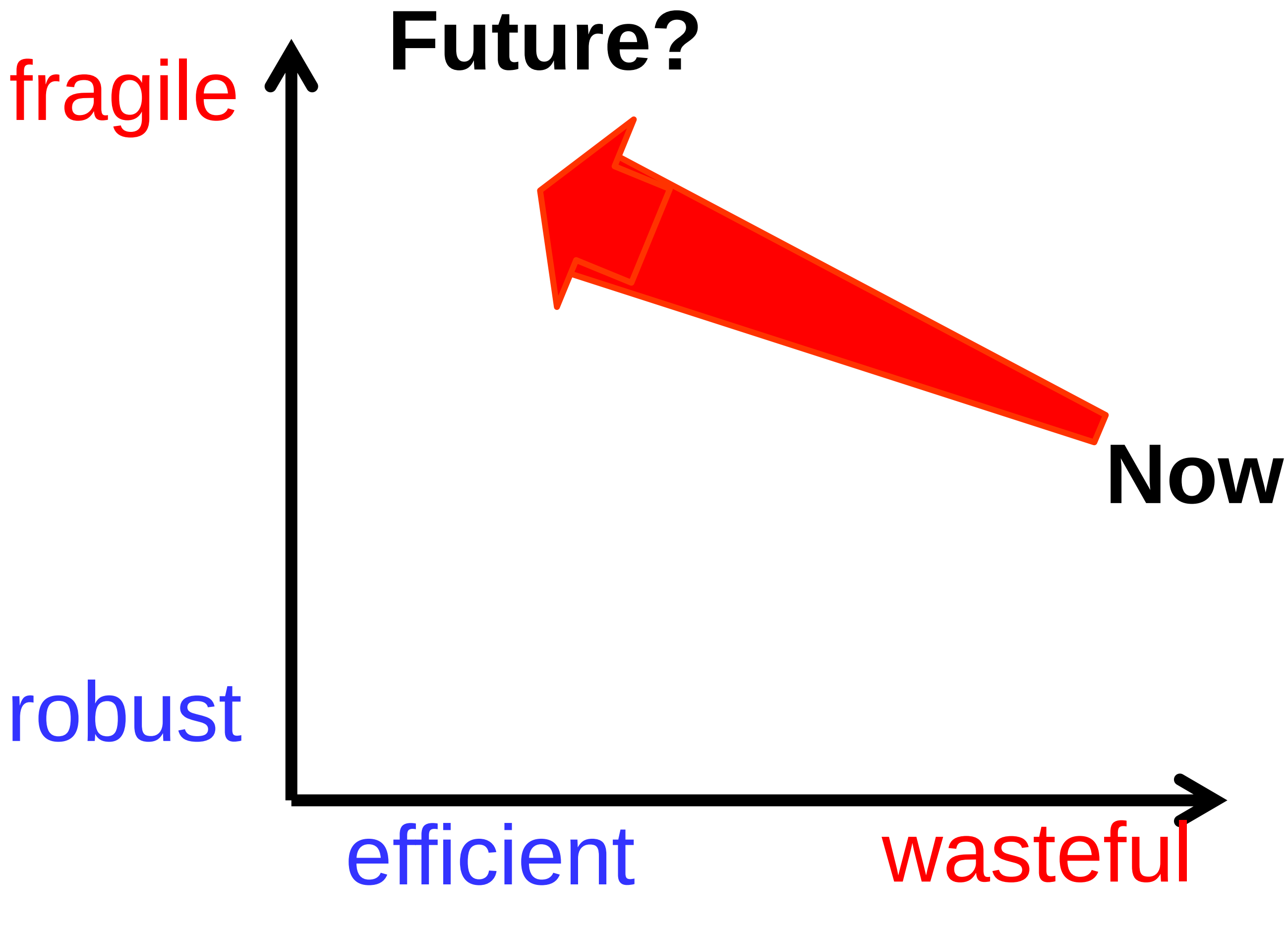
2050

Today

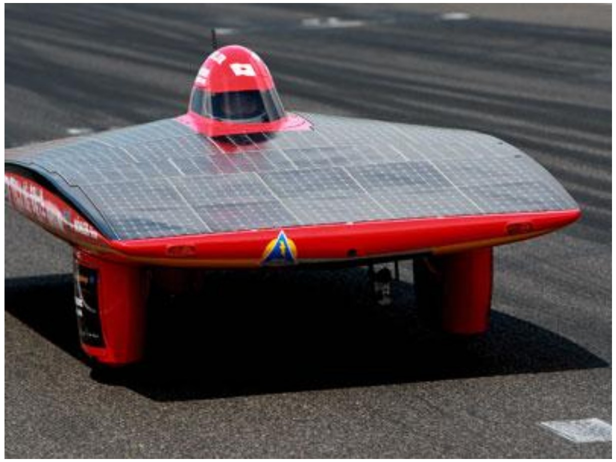
efficient → wasteful

“Physics”

Future evolution of the "smart" grid?



Current Technology?



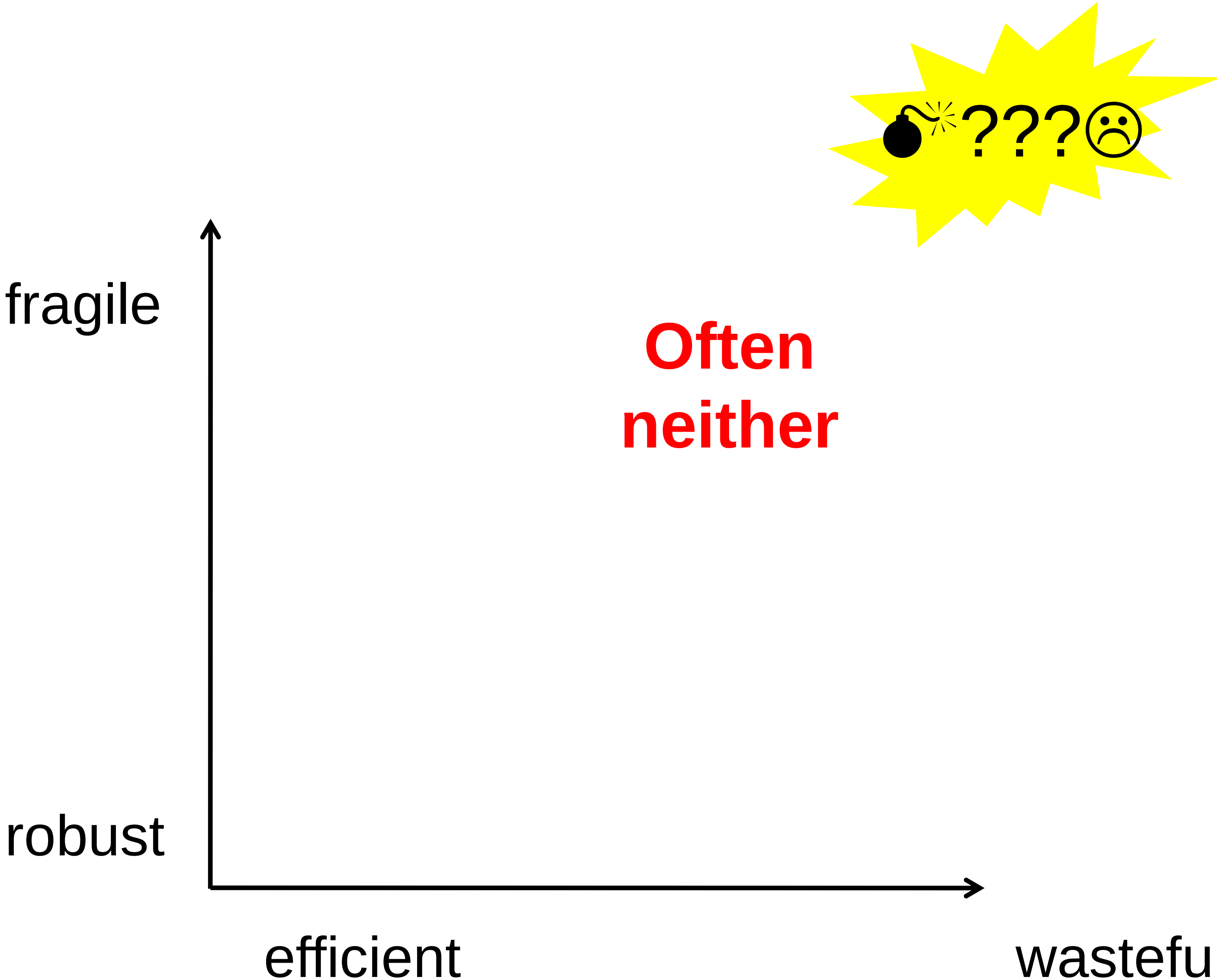
fragile

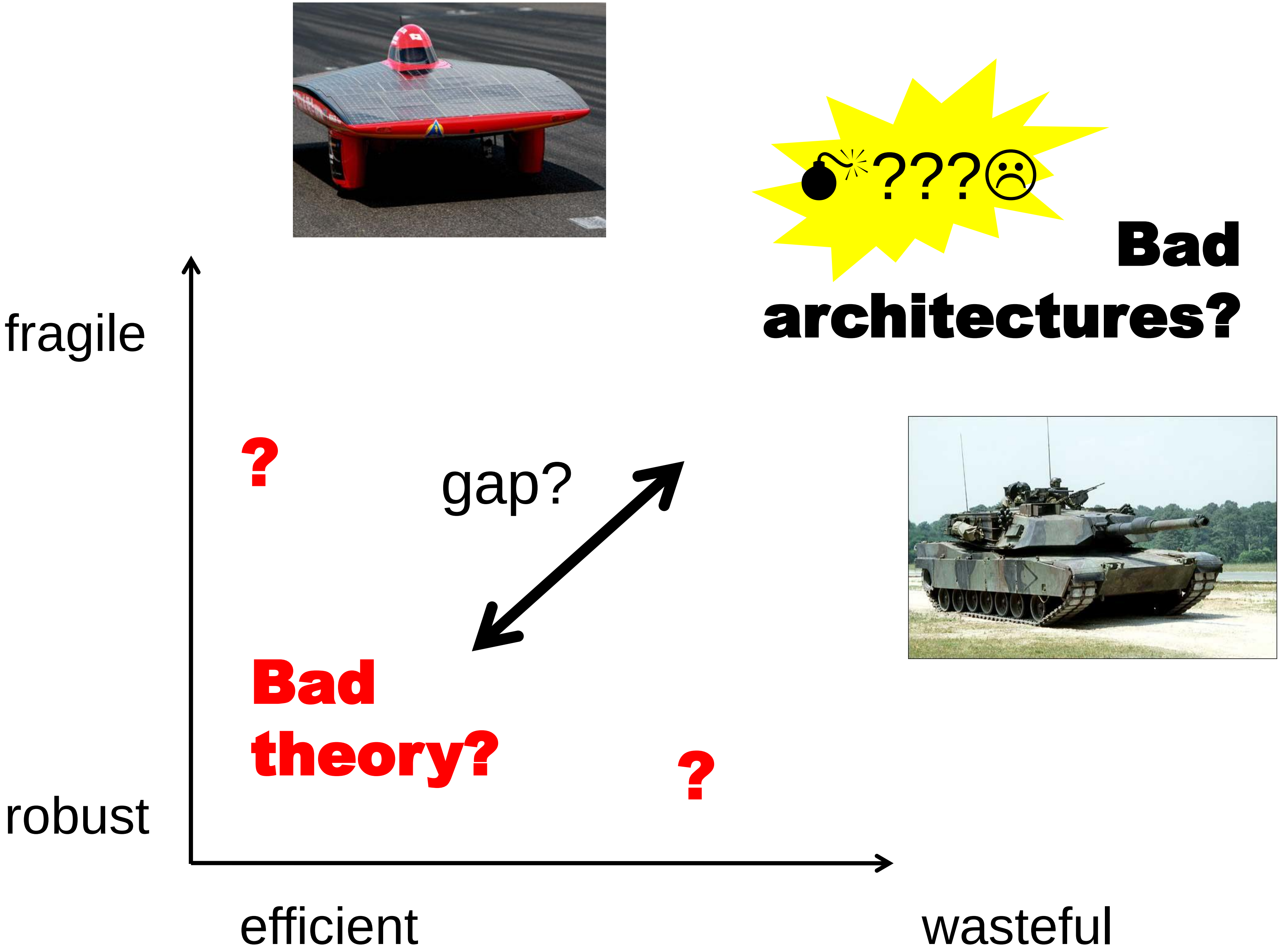
At best we get one

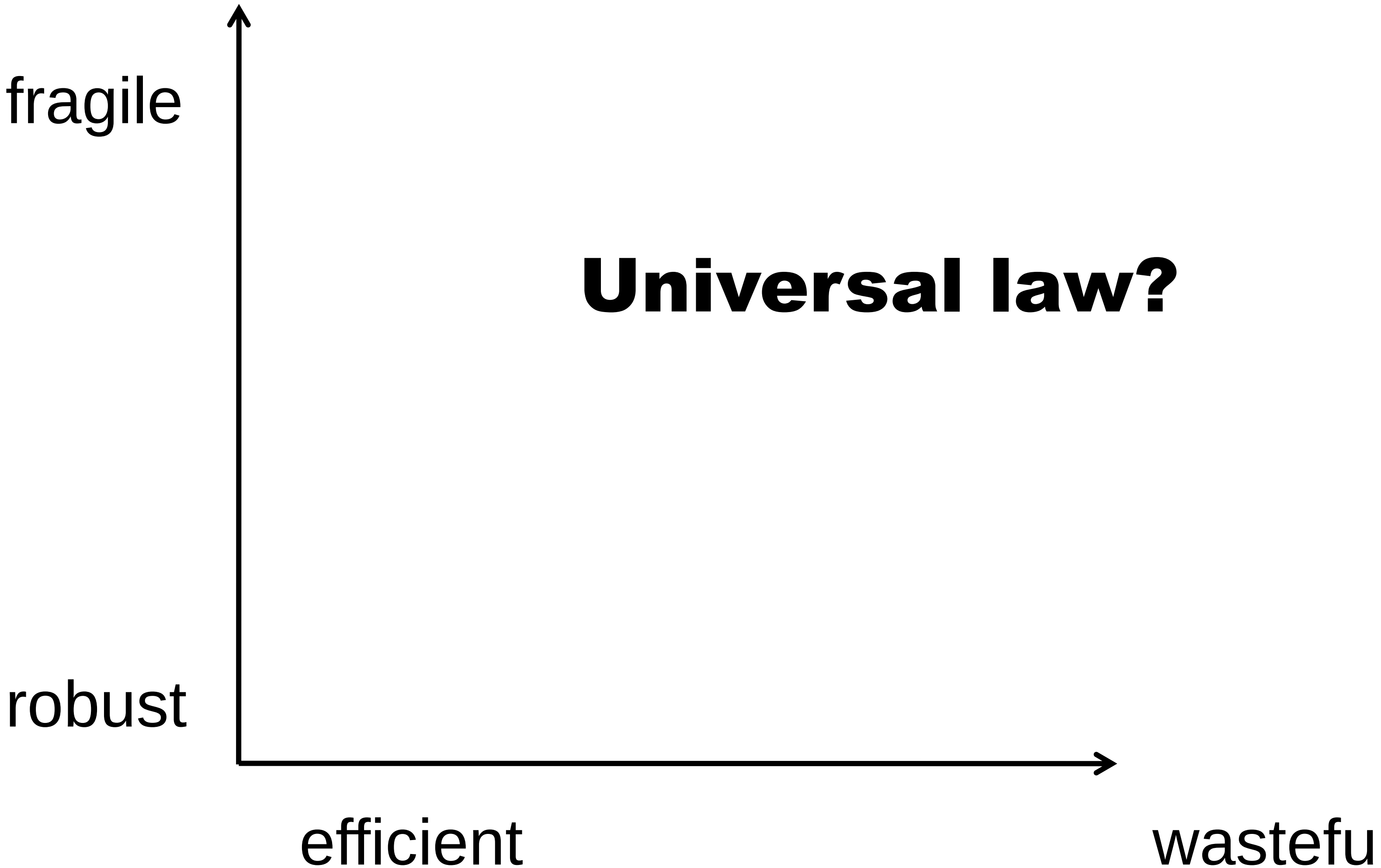
robust

efficient

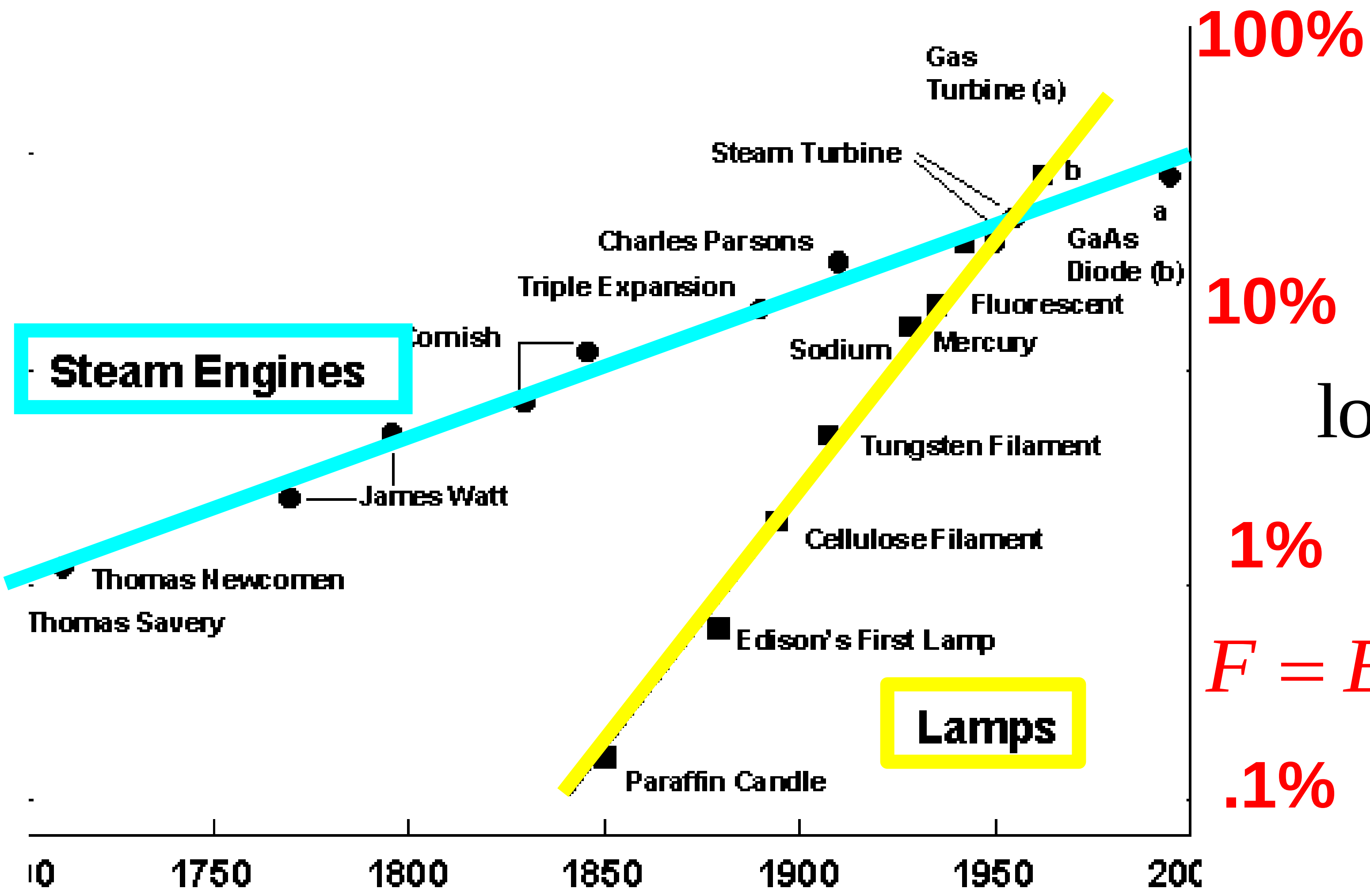
wasteful


fragile
robust
efficient
wasteful
Often neither
💣???☹


💣???☹
Bad architectures?
fragile
robust
?
gap?
Bad theory?
?
efficient
wasteful


fragile
Universal law?
robust
efficient
wasteful

Exponential improvement in efficiency *F*

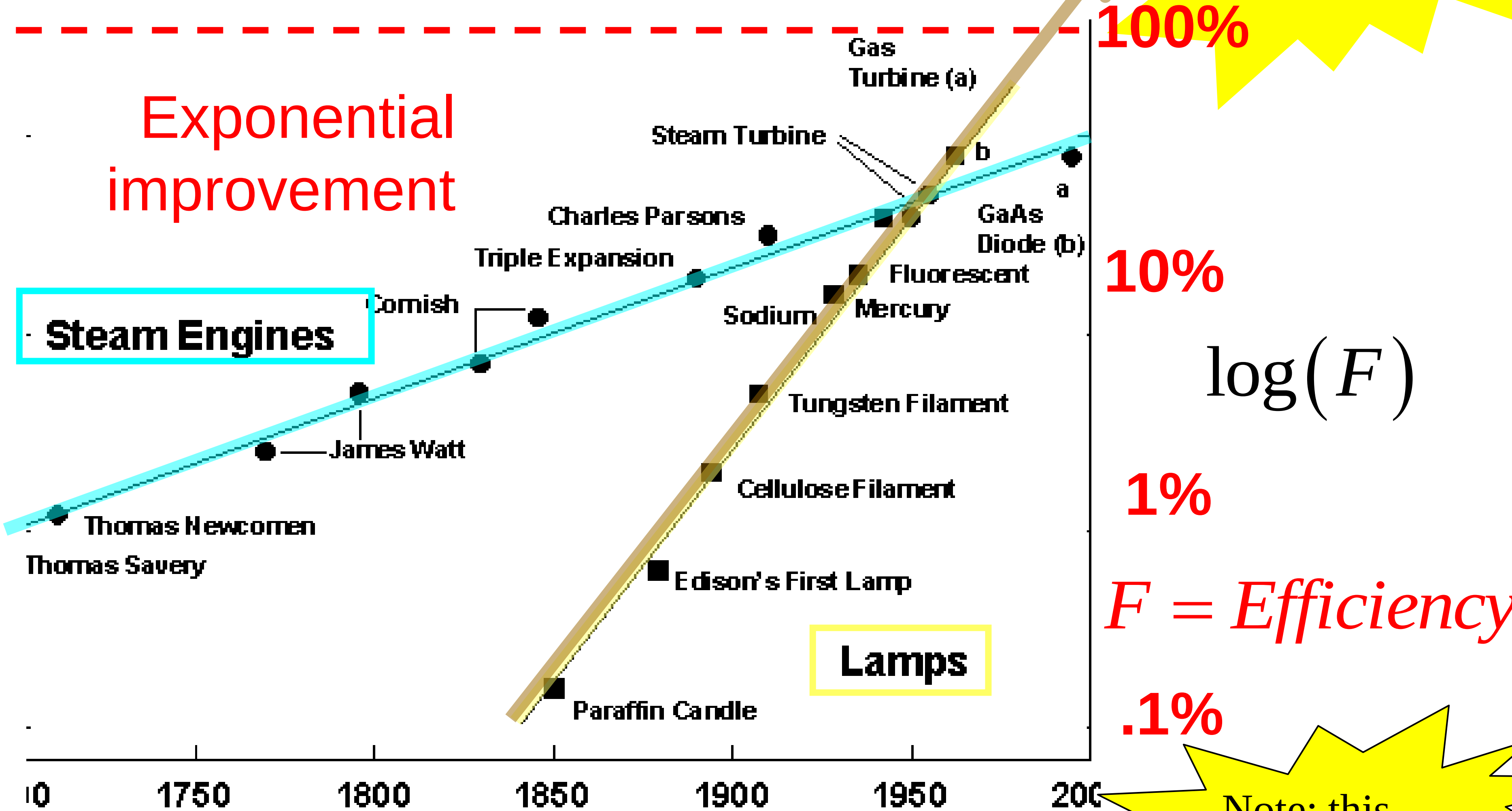


$$\log(F)$$

$$F = Efficiency$$

http://phe.rockefeller.edu/Daedalus/Elektron/

When will lamps be 200% efficient?

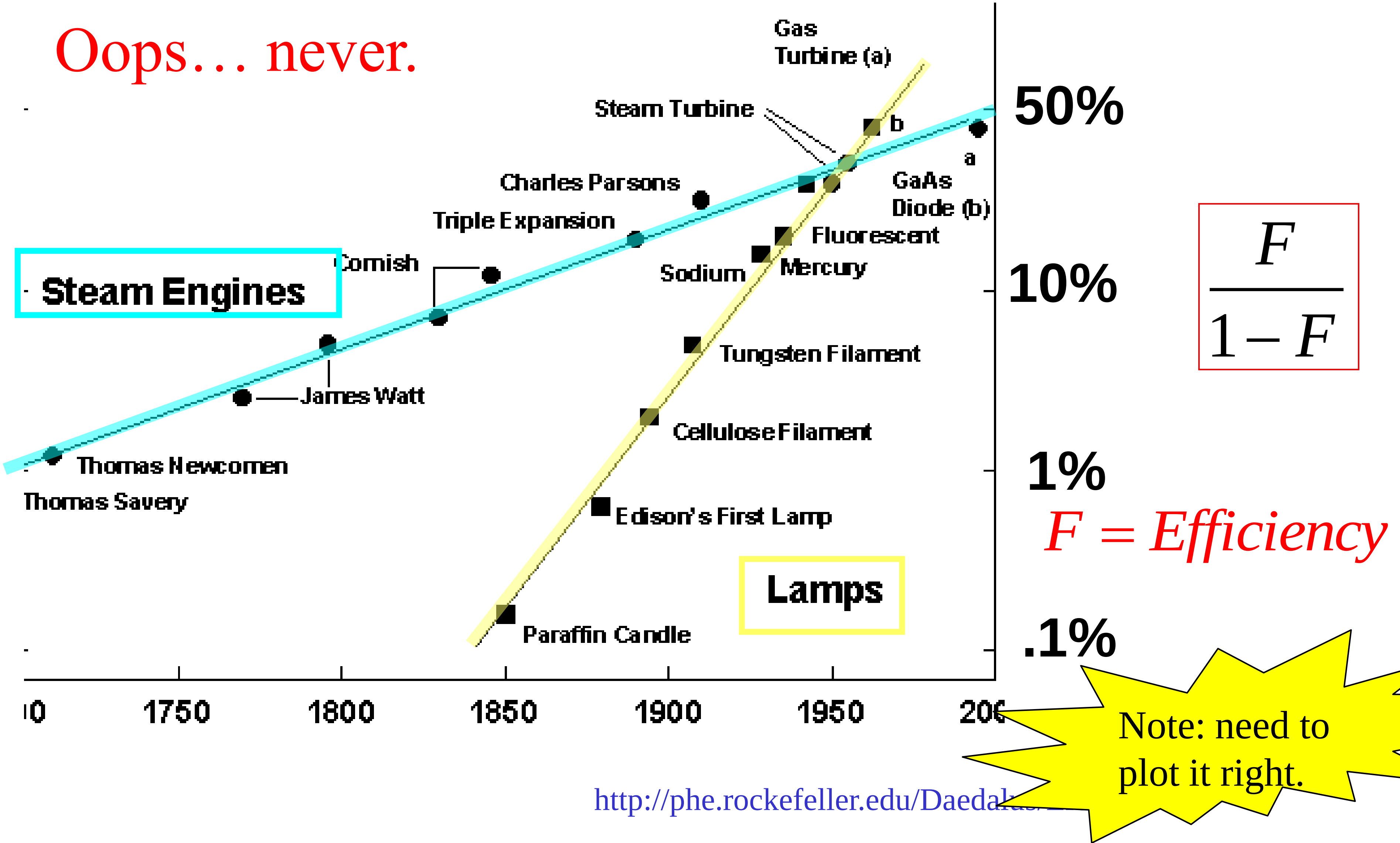


Solving all energy problems?

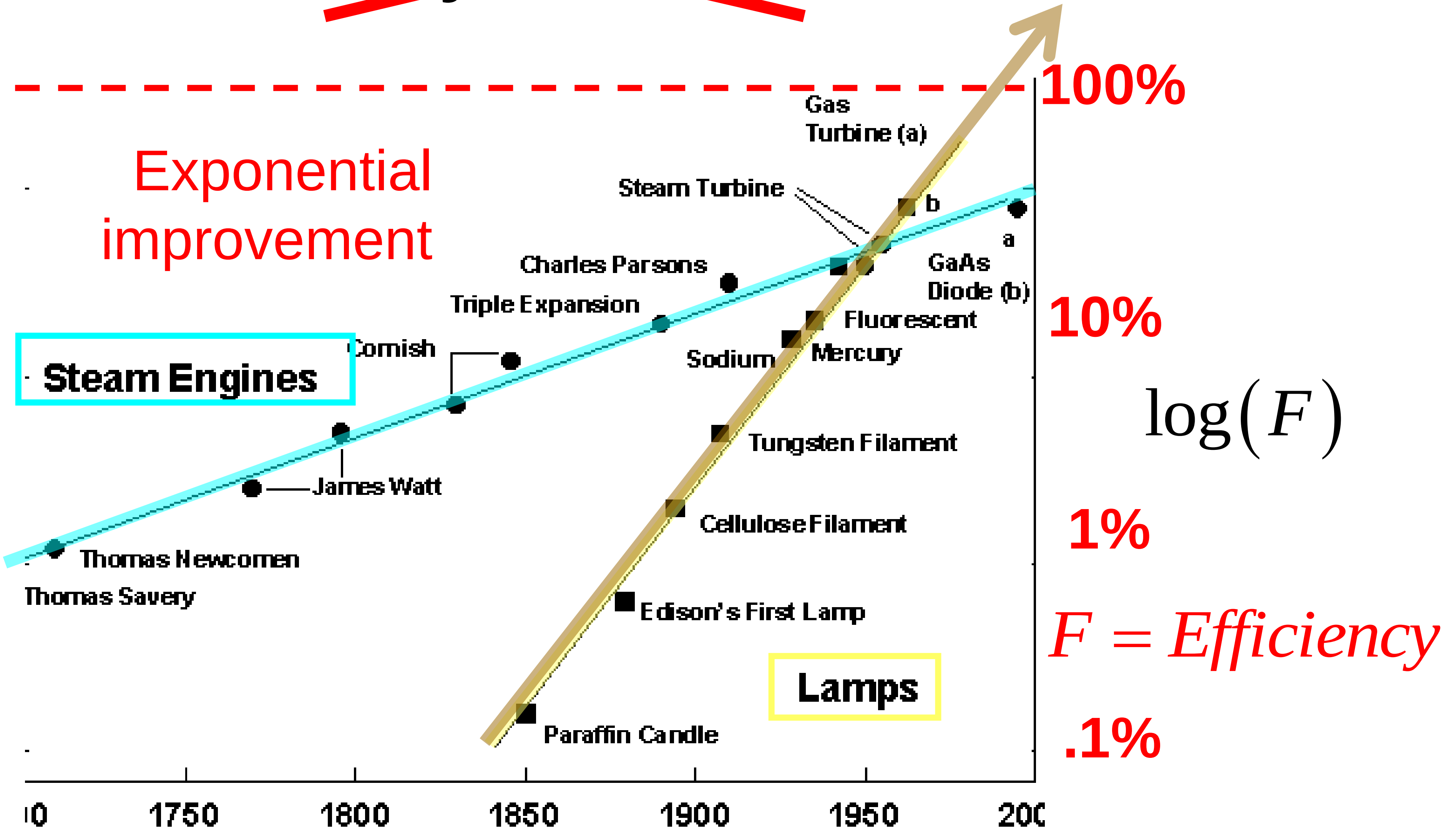
Note: this is real data!

http://phe.rockefeller.edu/Daedalus/Elektron/

When will lamps be 200% efficient?



~~Doyle's law?~~



http://phe.rockefeller.edu/Daedalus/Elektron/

Universal law

100%

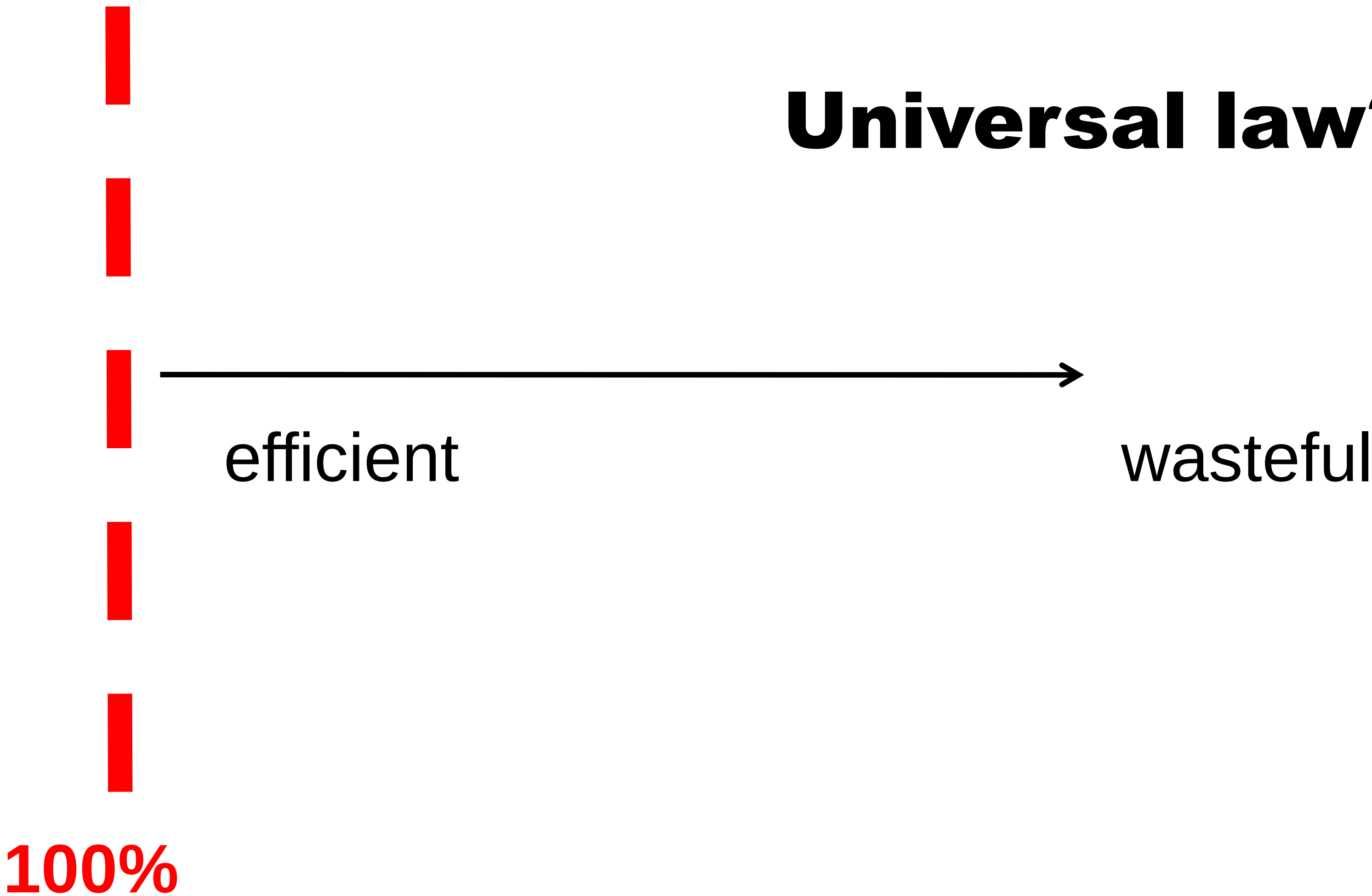
10%

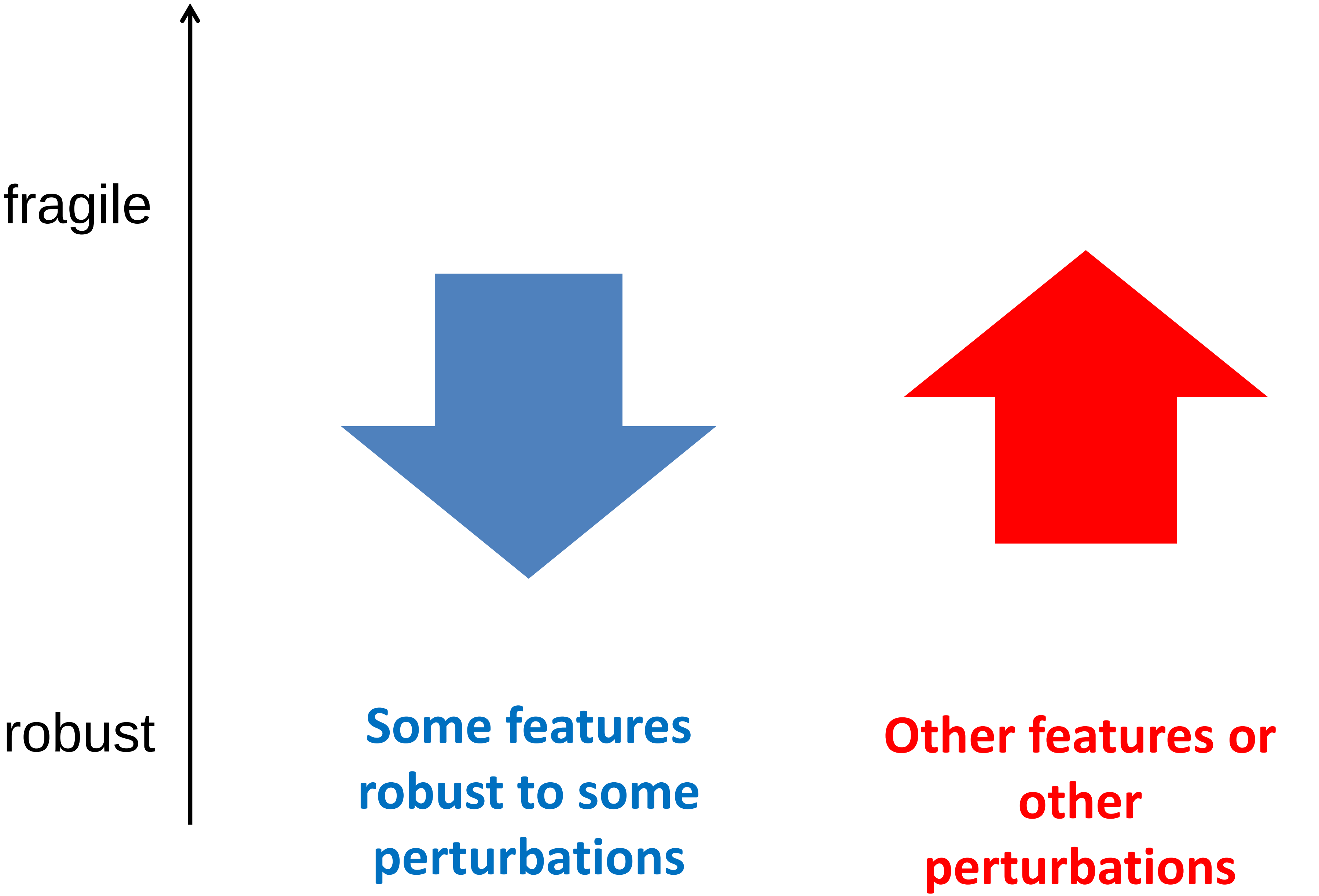
1%

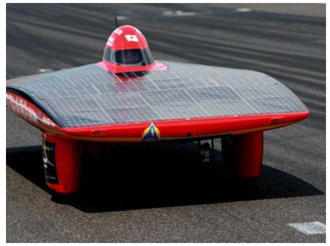
$$F = Efficiency$$

.1%

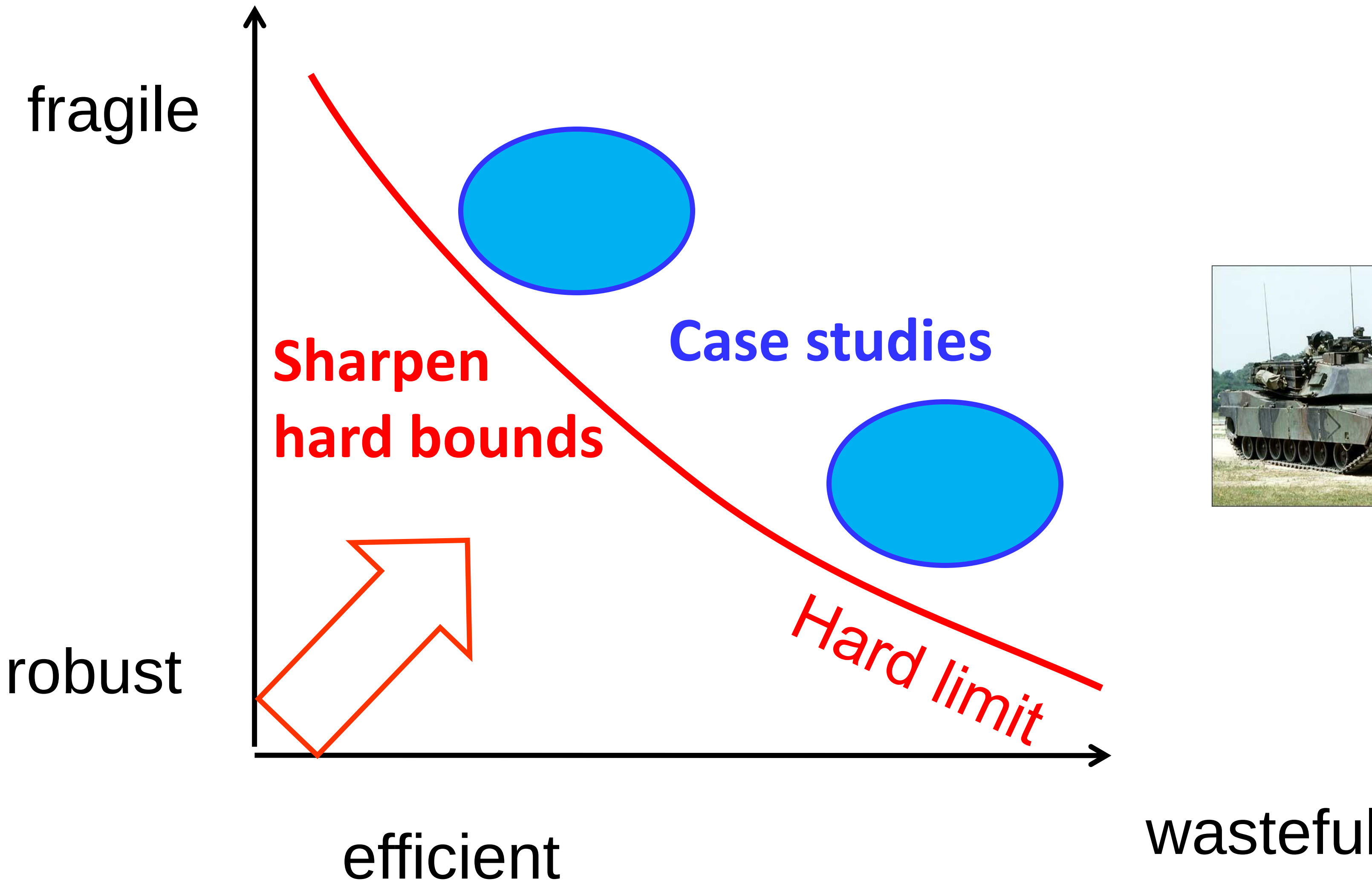
Universal law?




fragile
robust
Some features robust to some perturbations
Other features or other perturbations



laws and architectures?



Control, OR

Kalman

Comms

Pontryagin

Bode

Shannon

Nash

Theory?

Deep, but fragmented, incoherent, incomplete

Von Neumann

Carnot

Turing

Boltzmann

Godel

Heisenberg

Compute

Einstein

Physics

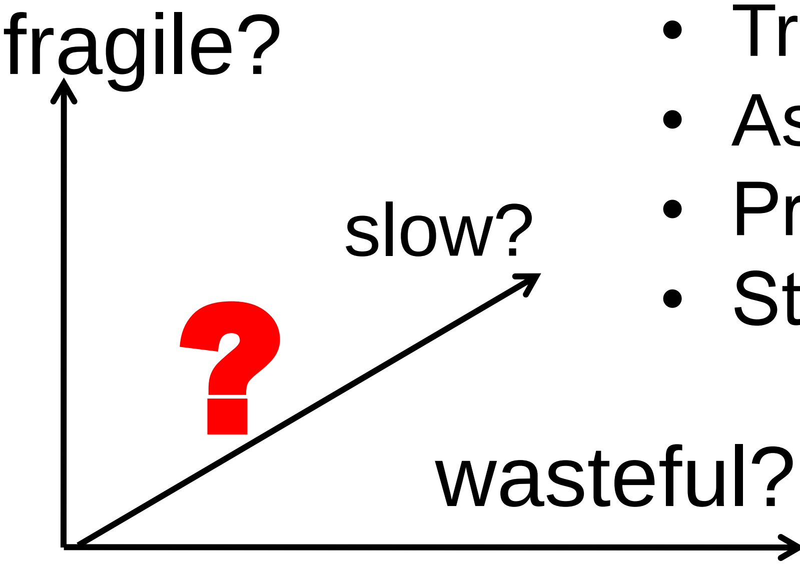
Control

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

- 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

Cyberphysical theories

Cyber (digital)

- Turing computation (time)
- Shannon compression (space)
- Content centric nets (time, space, location)

Physical (analog)

- Bode (latency)
- Shannon (channels)
- Networked control (AndyL)
- Redo StatMech and efficiency

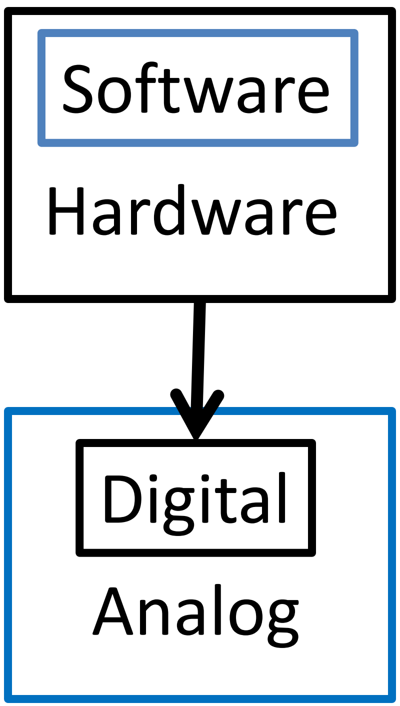
Lots of challenges not yet addressed
(e.g. Smartgrid, biology, neuro,..)

Layering as optimization?

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?)

Control

Bode

Comms

Shannon

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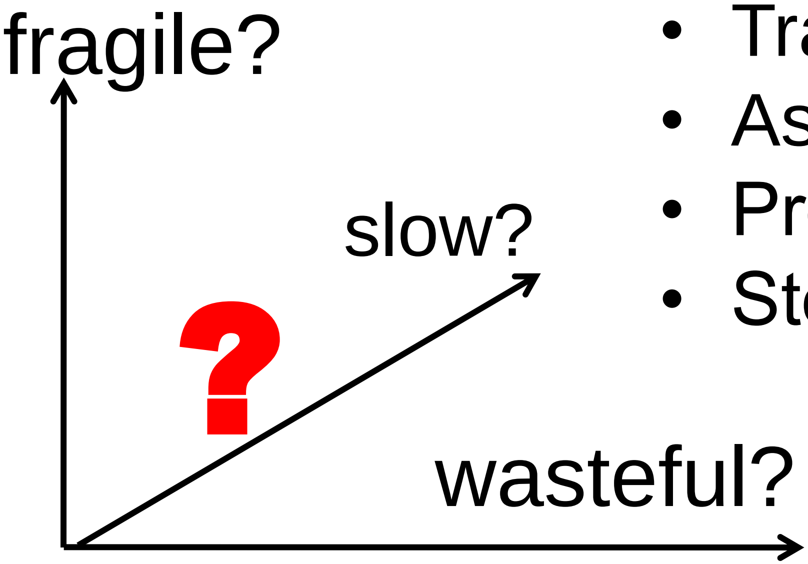
- Tradeoffs ***across*** dimensions
- Assume architectures a priori
- Progress is encouraging, but…
- Stovepipes are an obstacle…



Carnot

Boltzmann

Turing

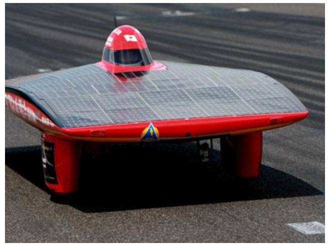
Godel

Heisenberg

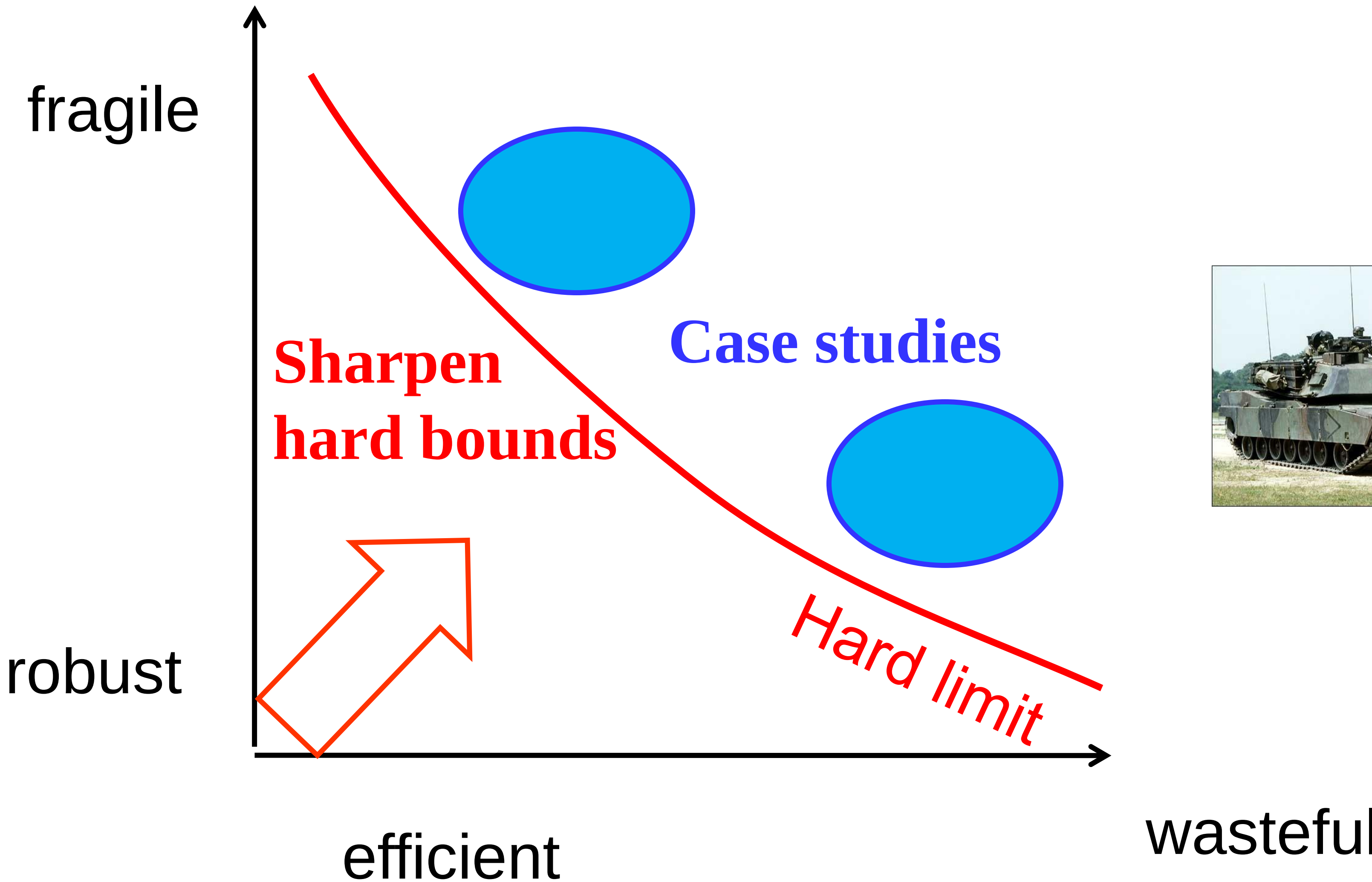
Compute

Physics

Einstein



laws and architectures?



REVIEW

Reverse Engineering of Biological Complexity

Marie E. Csete[1] and John C. Doyle[2*]

Advanced technologies and biology have extremely different physical implementations, but they are far more alike in systems-level organization than is widely appreciated. Convergent evolution in both domains produces modular architectures that are composed of elaborate hierarchies of protocols and layers of feedback regulation, are driven by demand for robustness to uncertain environments, and use often imprecise components. This complexity may be largely hidden in idealized laboratory settings and in normal operation, becoming conspicuous only when contributing to rare cascading failures. These puzzling and paradoxical features are neither accidental nor artificial, but derive from a deep and necessary interplay between complexity and robustness, modularity, feedback, and fragility. This review describes insights from engineering theory and practice that can shed some light on biological complexity.

ty in components or the
Biologists and biophy
ing complex networks ofte
a biological network's
(*15*). They find that "per
homeostatic regulation are
networks (*16, 17*), despite
anisms" that can seem g
(*18–20*). Some even concl
anisms and their resulting
in engineering (*20, 21*). H
is in the nature of their rob
ity that biology and adva

Science
AAAS

Csete and Doyle

1 MARCH 2002 VOL 295 SCIENCE www.sciencemag.org

UG biochem, math, control theory

Glycolytic Oscillations and Limits on Robust Efficiency

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

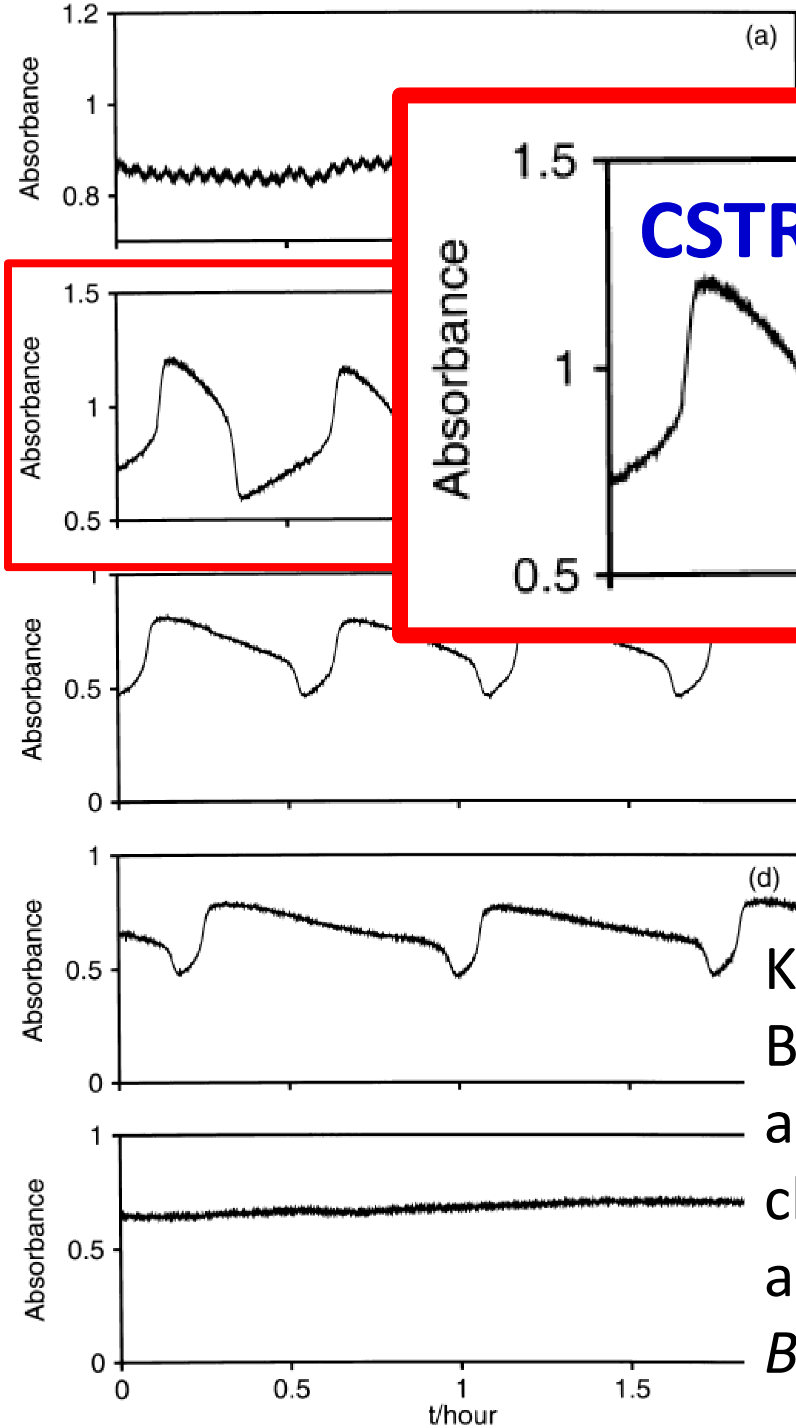
Both engineering and evolution are constrained by trade-offs between efficiency and robustness, but theory that formalizes this fact is limited. For a simple two-state model of glycolysis, we explicitly derive analytic equations for hard trade-offs between robustness and efficiency with oscillations 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

Science AAAS

Most important paper so far.



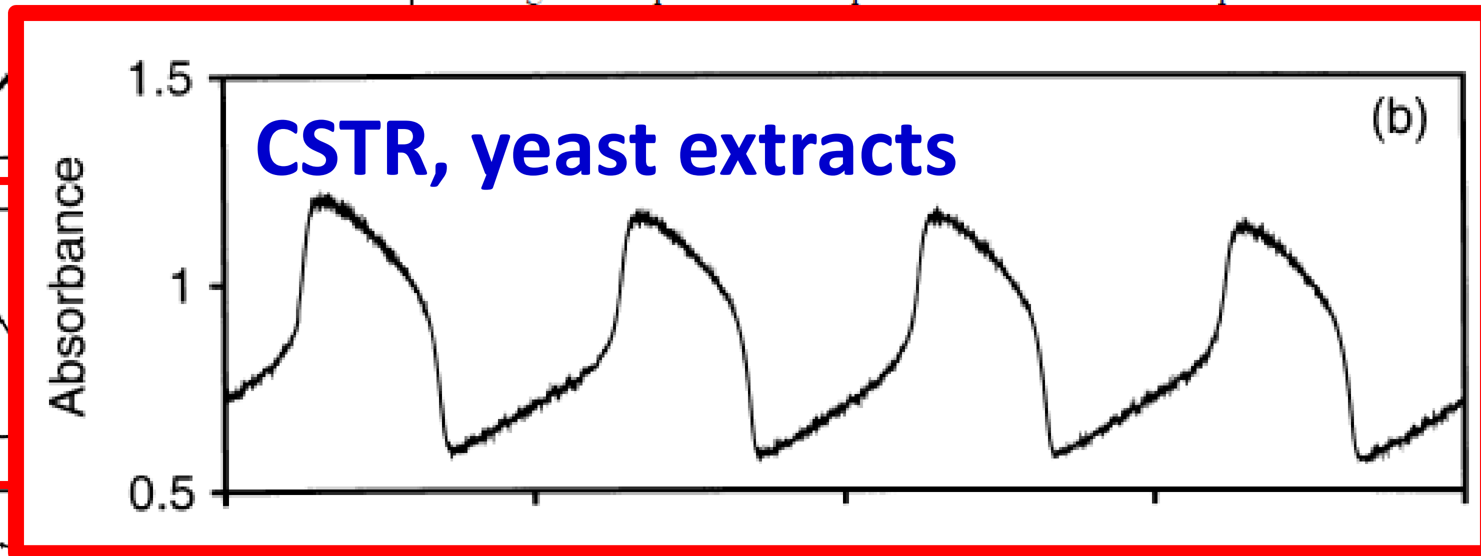


Fig. 2. Dependence of pattern on flow rate. Experimental time

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

Experiments

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

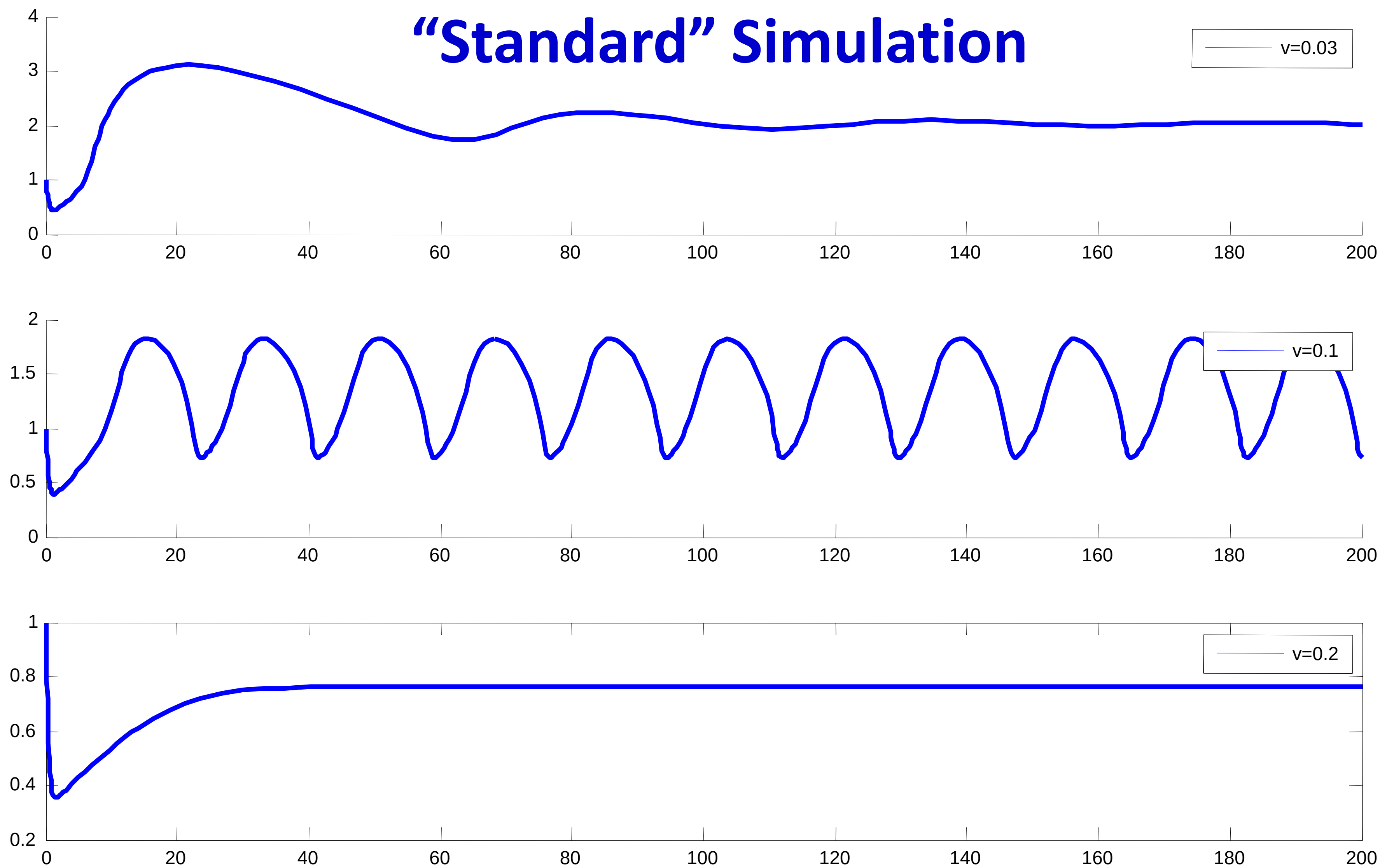
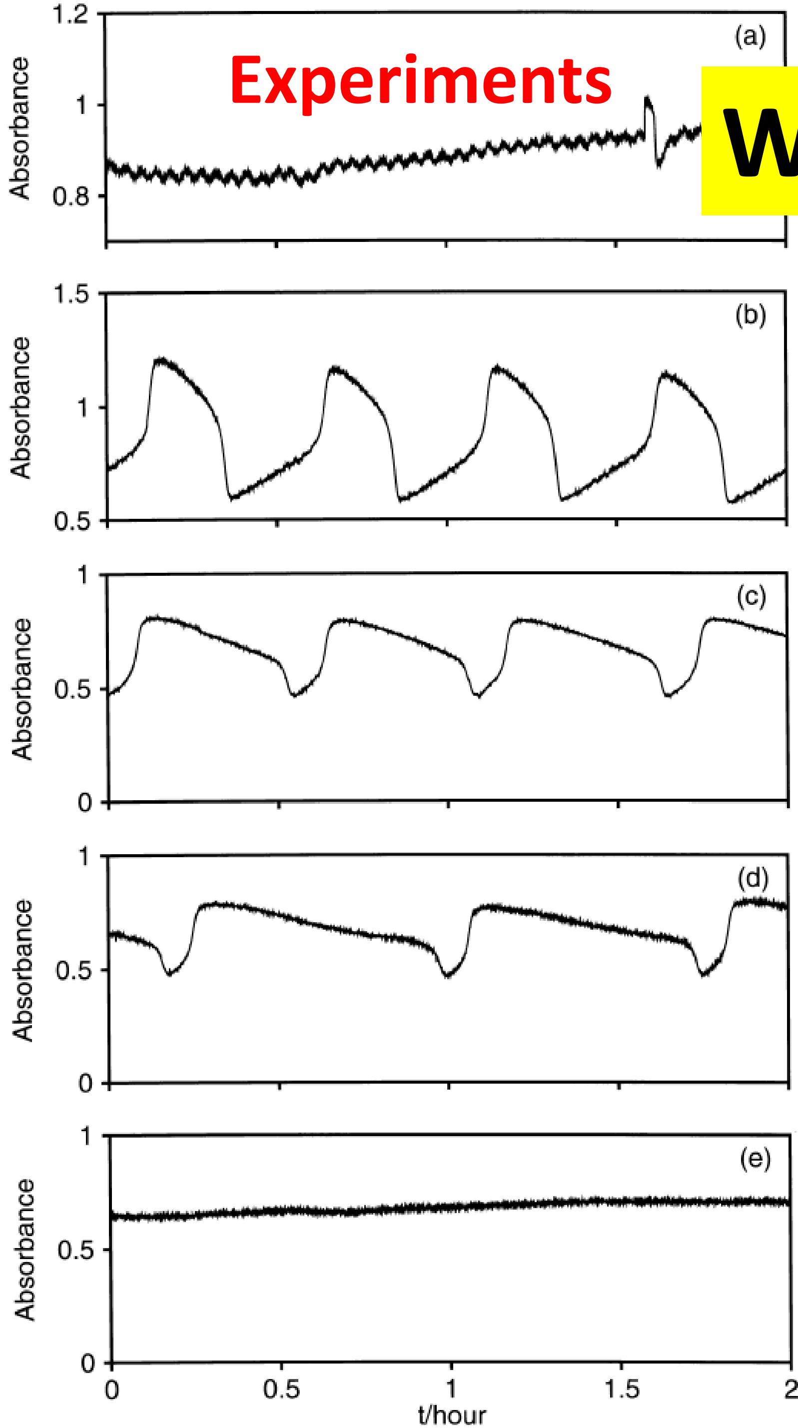
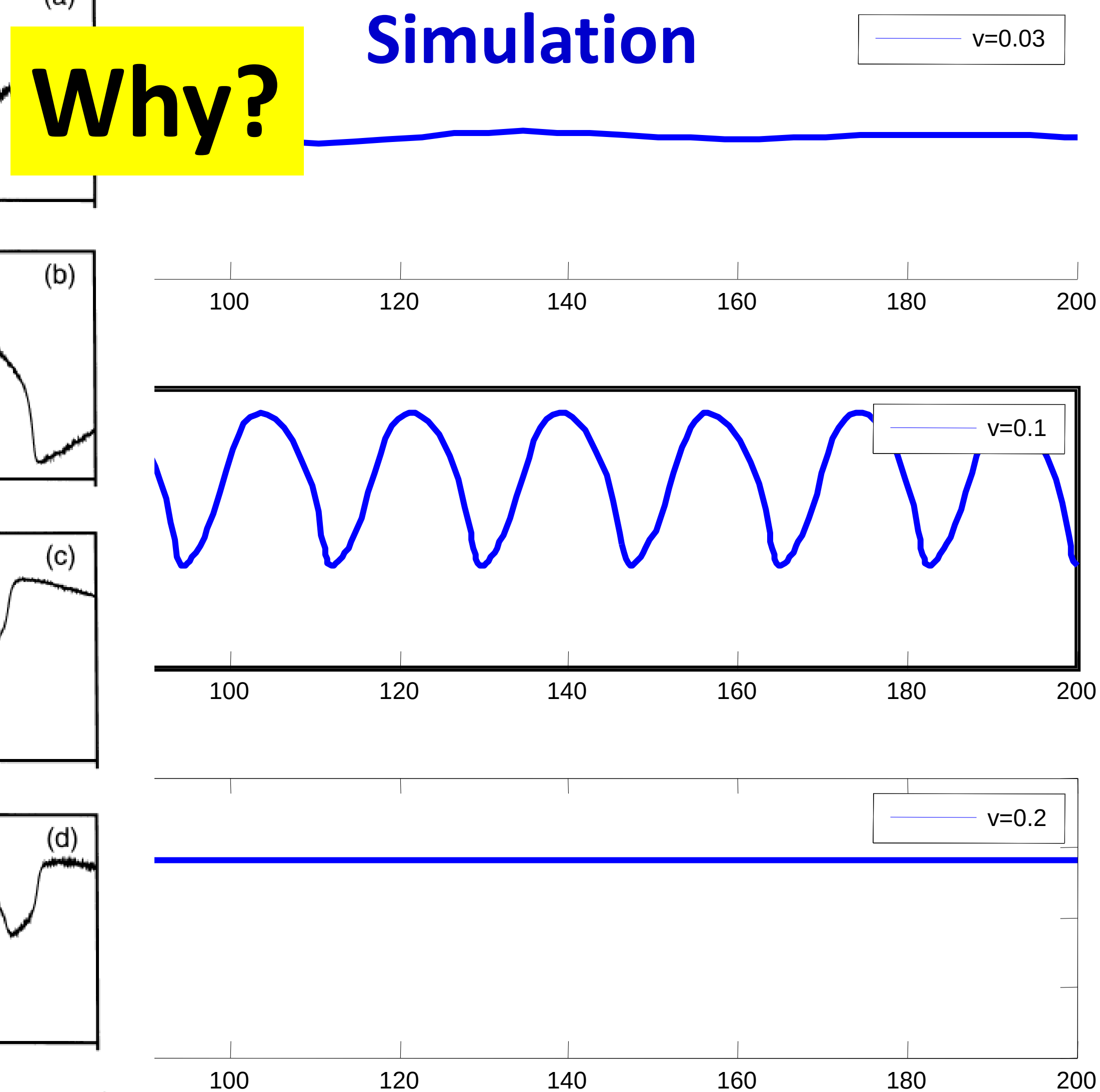


Figure S4. Simulation of two state model (S7.1) qualitatively recapitulates experimental observation from CSTR studies [5] and [12]. As the flow of material in/out of the system is increased, the system enters a limit cycle and then stabilizes again. For this simulation, we take *q=a=Vm=1, k=0.2, g=1,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





odel (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

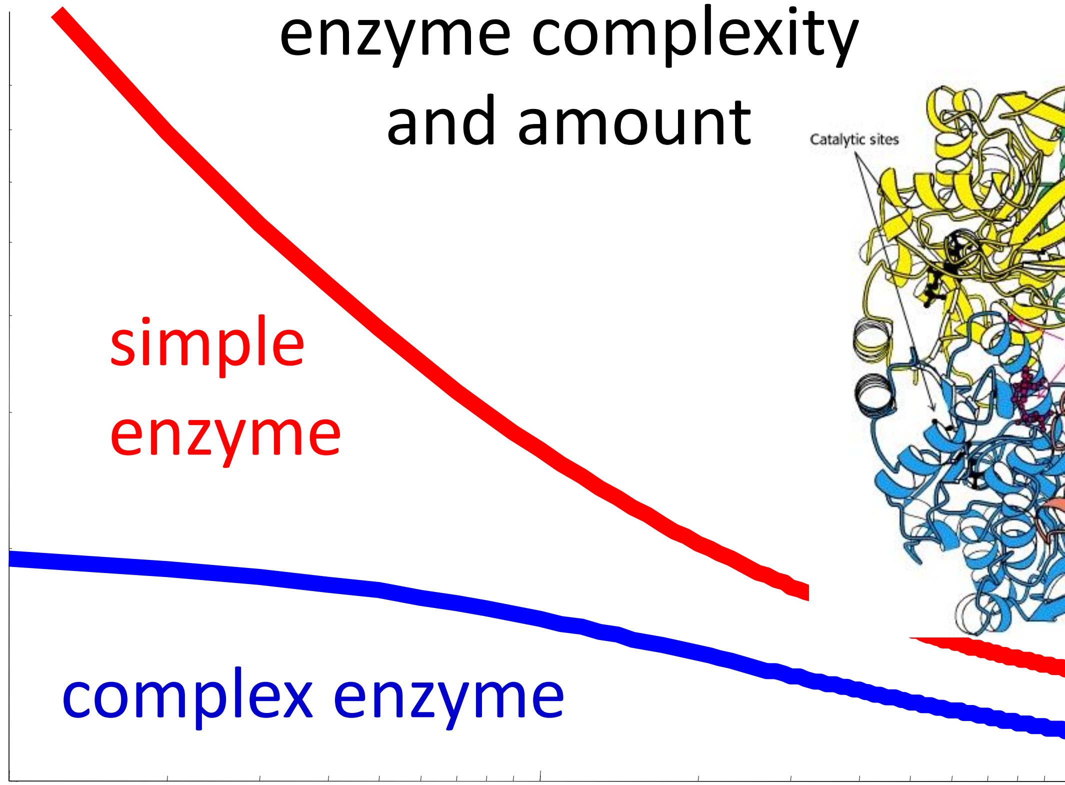
- Most studied, persistent mystery in cell dynamics
- End of an old story (why oscillations)
  - side effect of hard robustness/efficiency tradeoffs
  - no purpose per se
  - just needed a theorem
- Beginning of a new one
  - robustness/efficiency tradeoffs
  - complexity and architecture
  - need more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

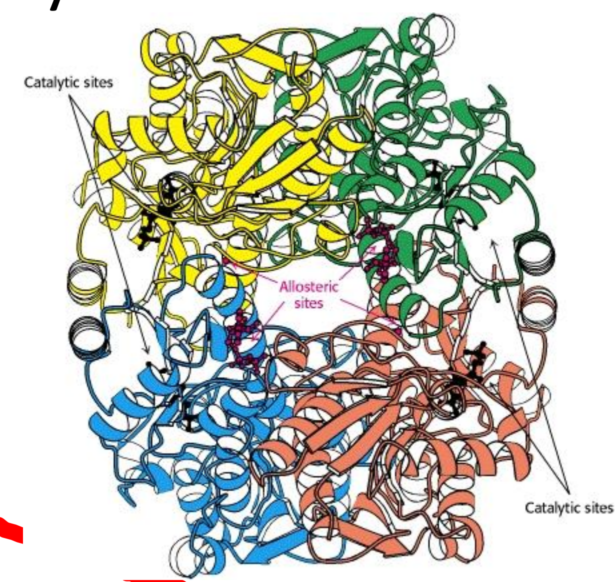
Theorem! $$\frac{1}{\pi}\int_0^{\infty}\ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

z and *p* functions of enzyme complexity and amount

Fragility

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

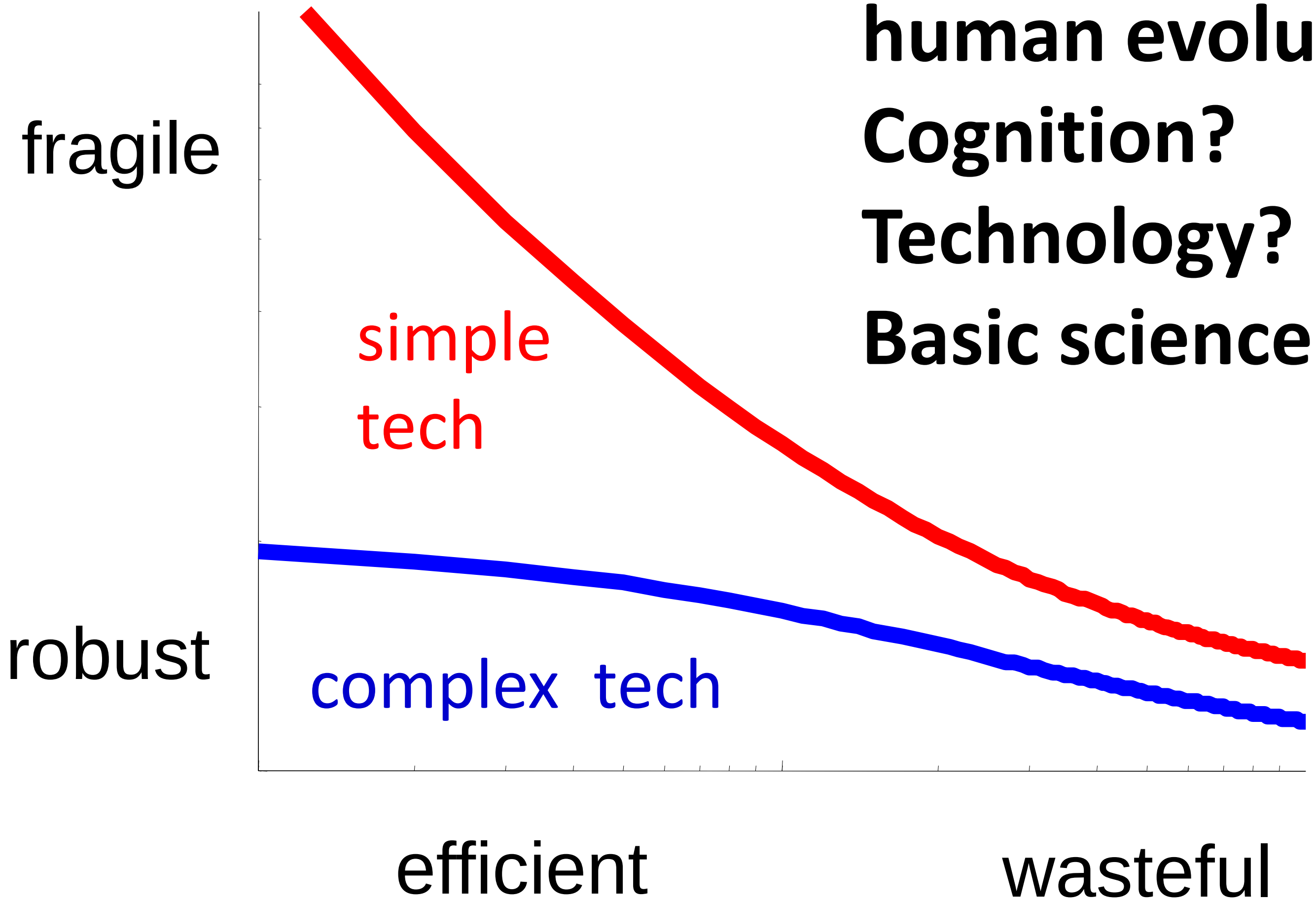




Enzyme amount

Savageaumics

How general is this picture?



Implications for human evolution?

Cognition?

Technology?

Basic sciences?

Evolution and architecture

Nothing in biology makes sense except in the light of evolution

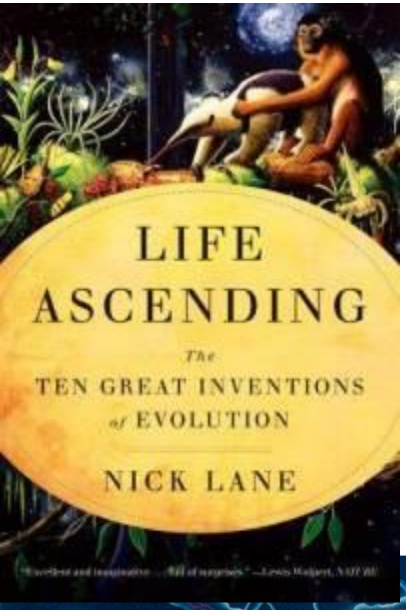
Theodosius Dobzhansky

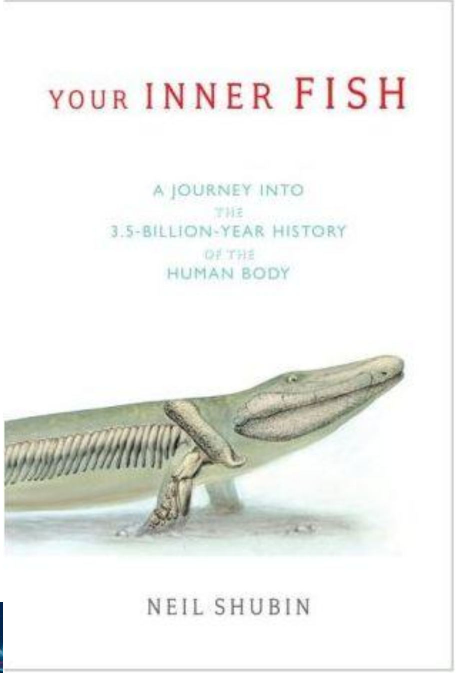
(see also de Chardin)

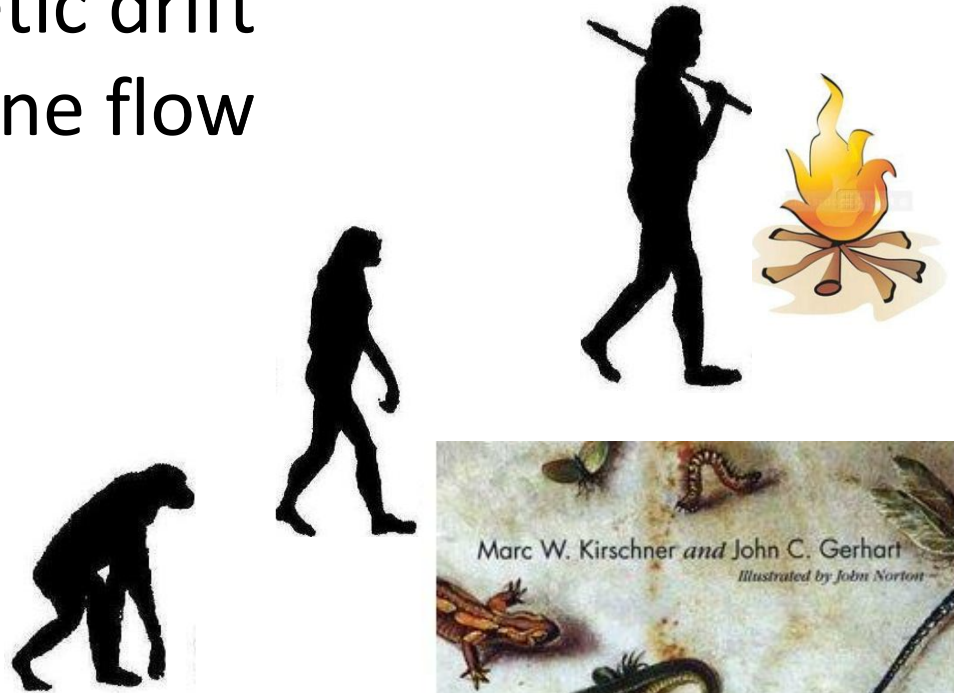
Nothing in evolution makes sense except in the light of biology

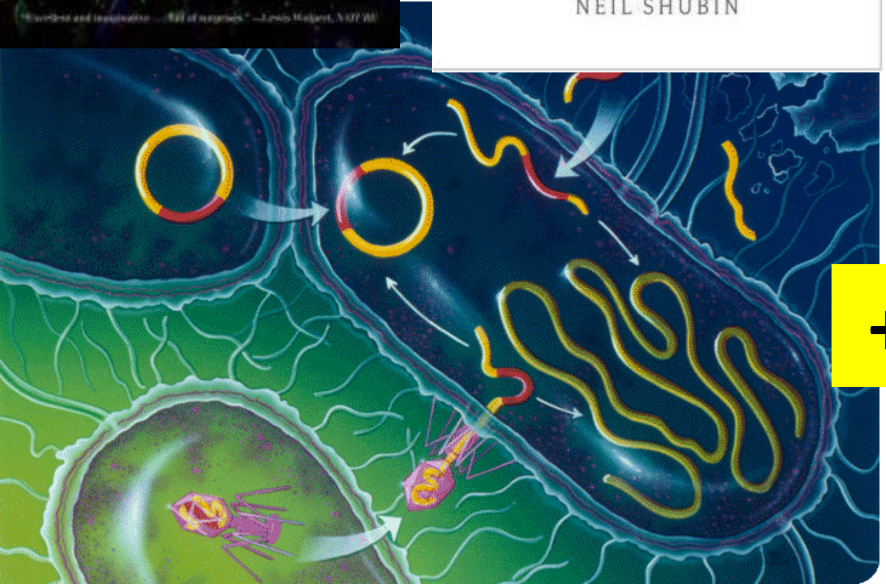
?????

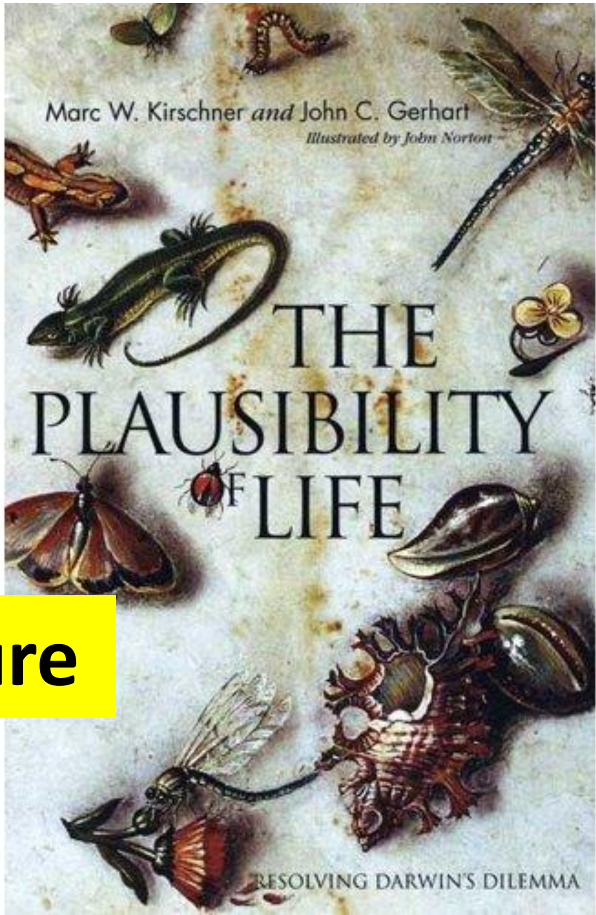
natural selection + genetic drift
+ mutation + gene flow











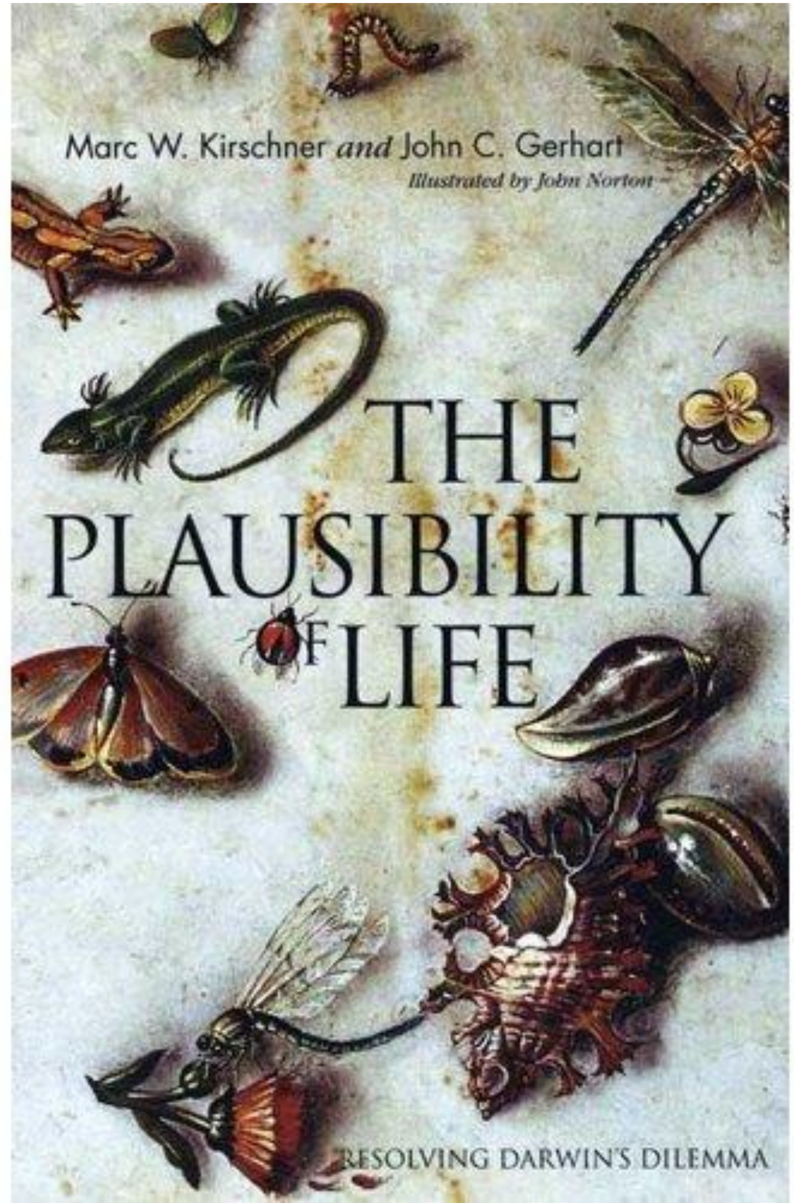
++ architecture

Gerhart and Kirschner

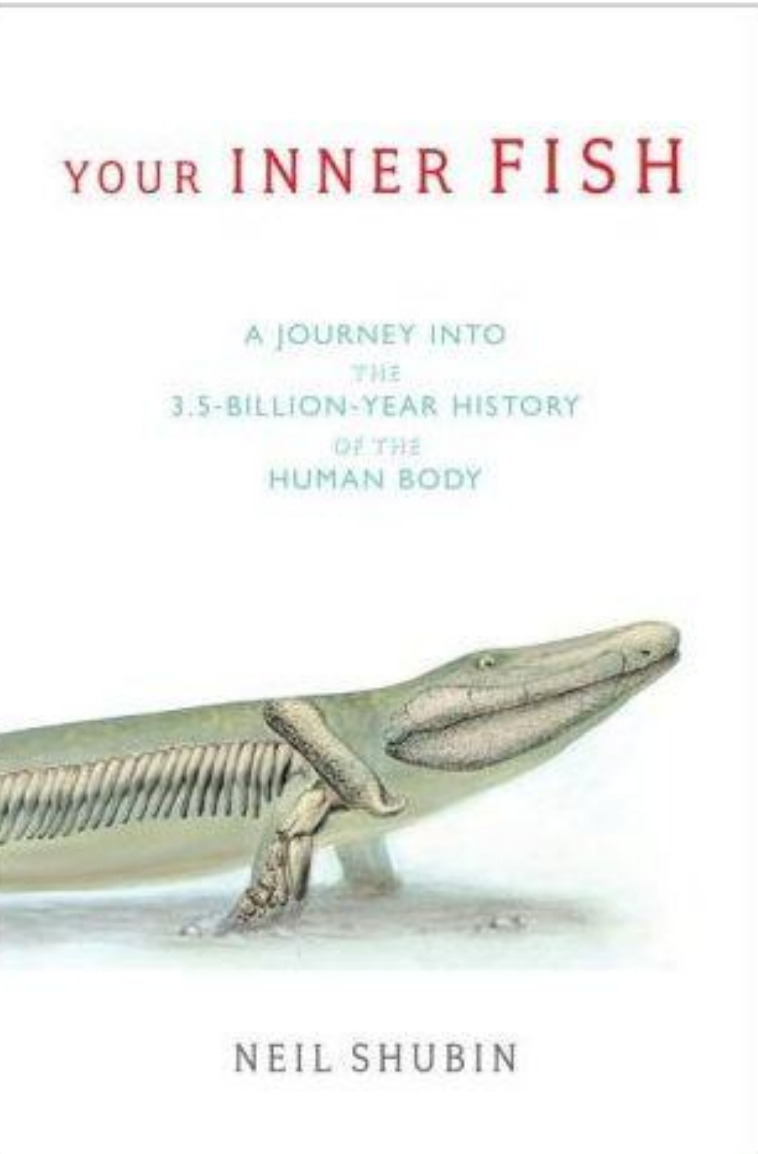
Facilitated variation

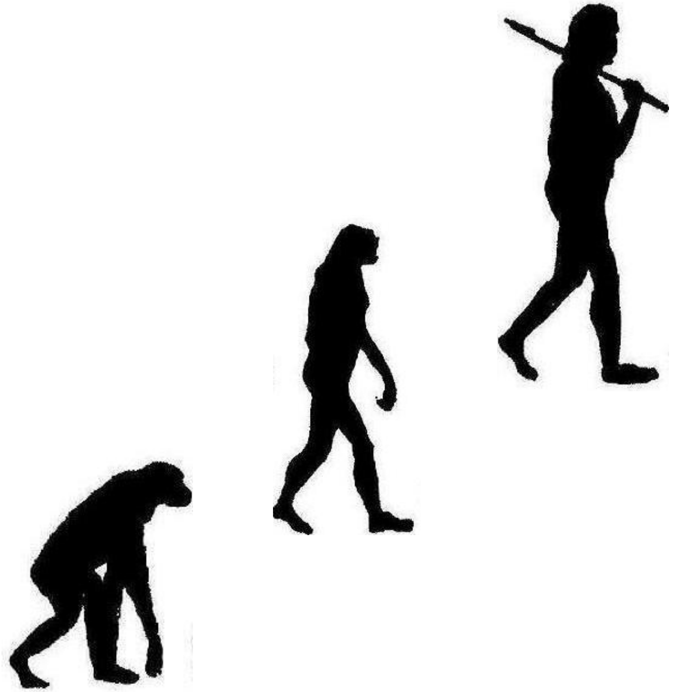
Architecture =
Constraints that deconstrain

- Weak linkage
- Exploratory mechanisms
- Compartmentalization

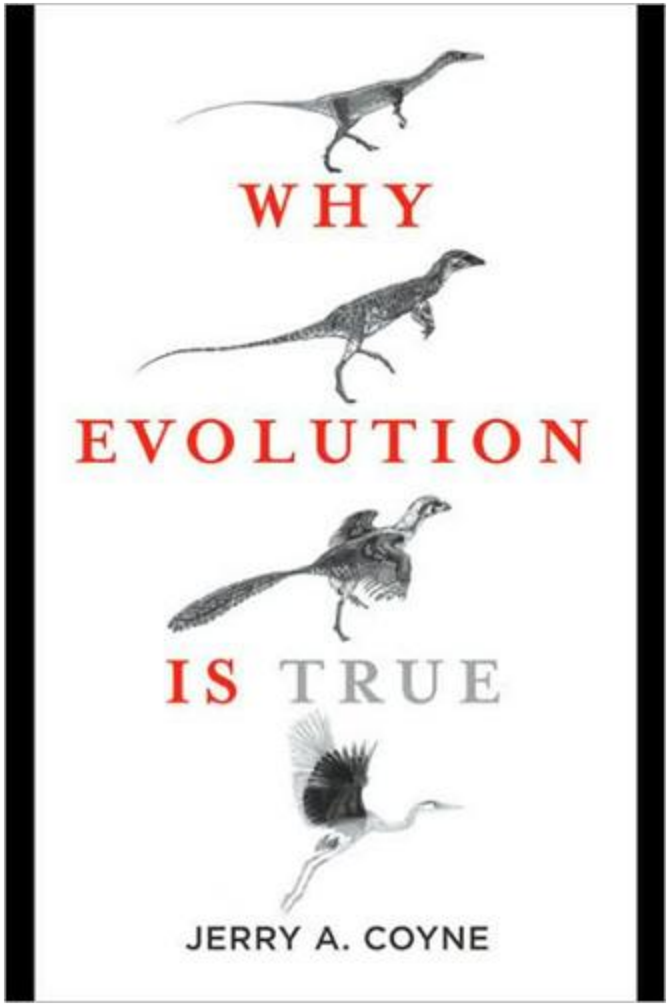


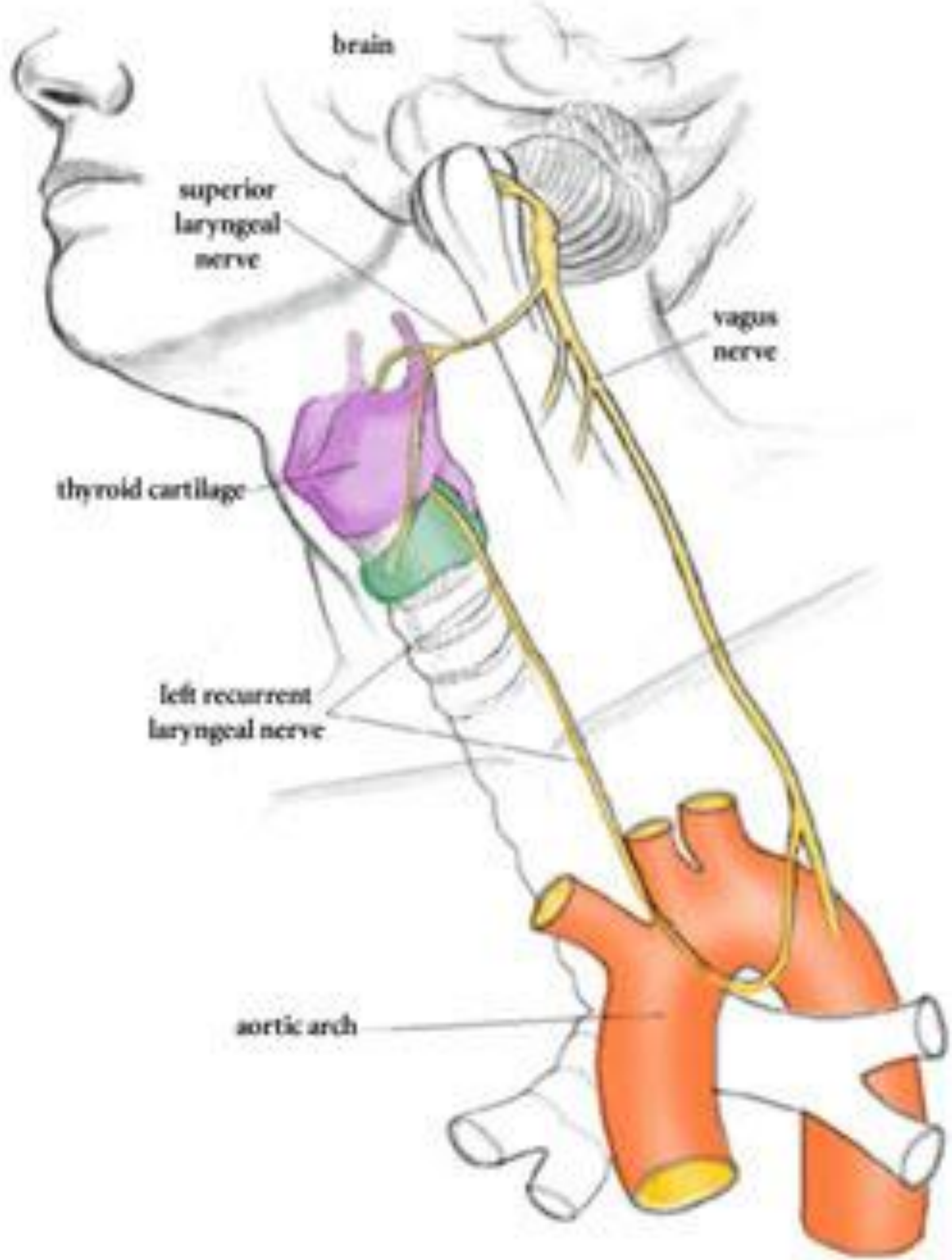
Unfortunately, not intelligent design





Ouch.


WHY
EVOLUTION
IS TRUE
JERRY A. COYNE


brain
superior
laryngeal
nerve
vagus
nerve
thyroid cartilage
left recurrent
laryngeal nerve
aortic arch

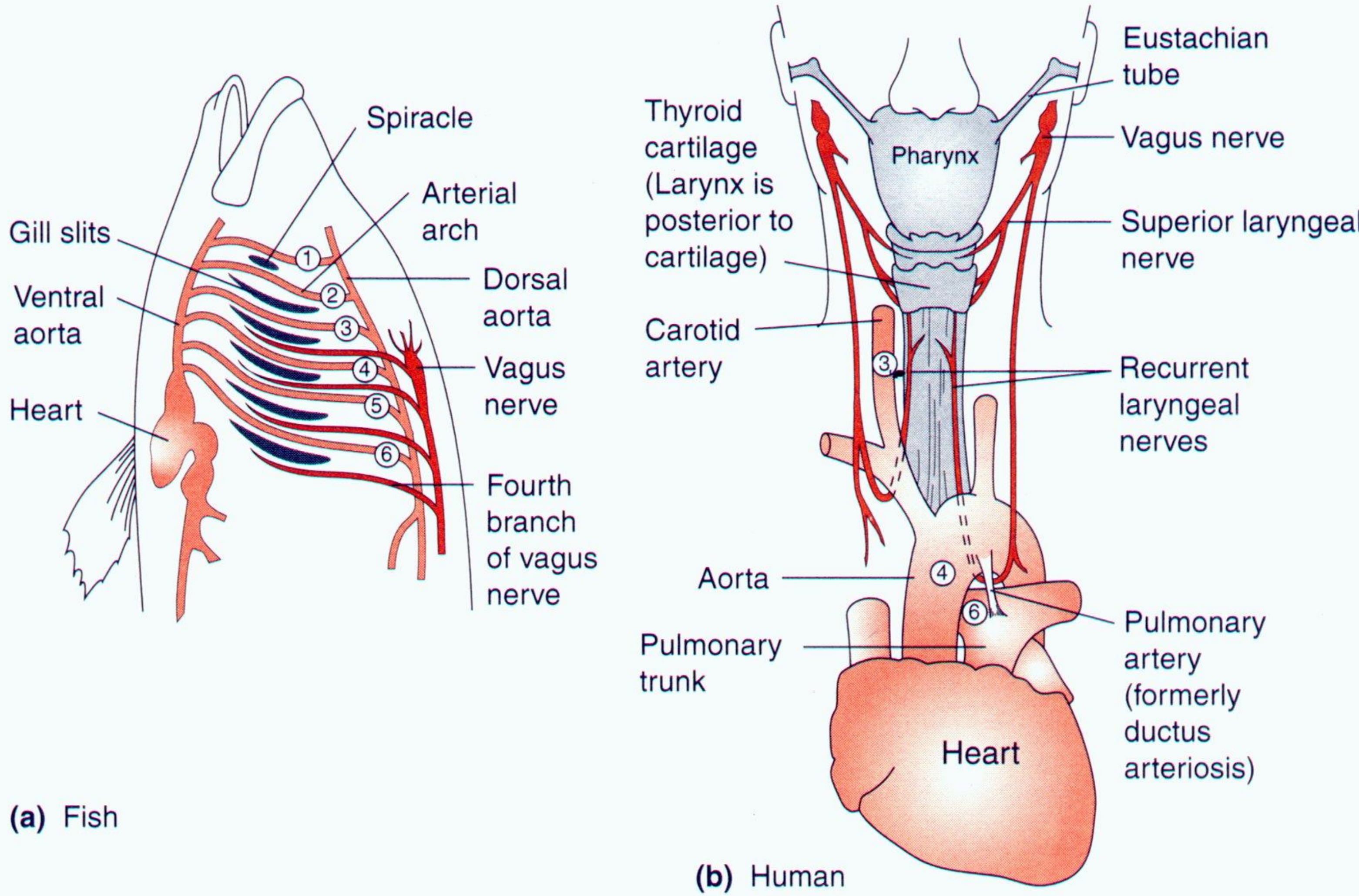
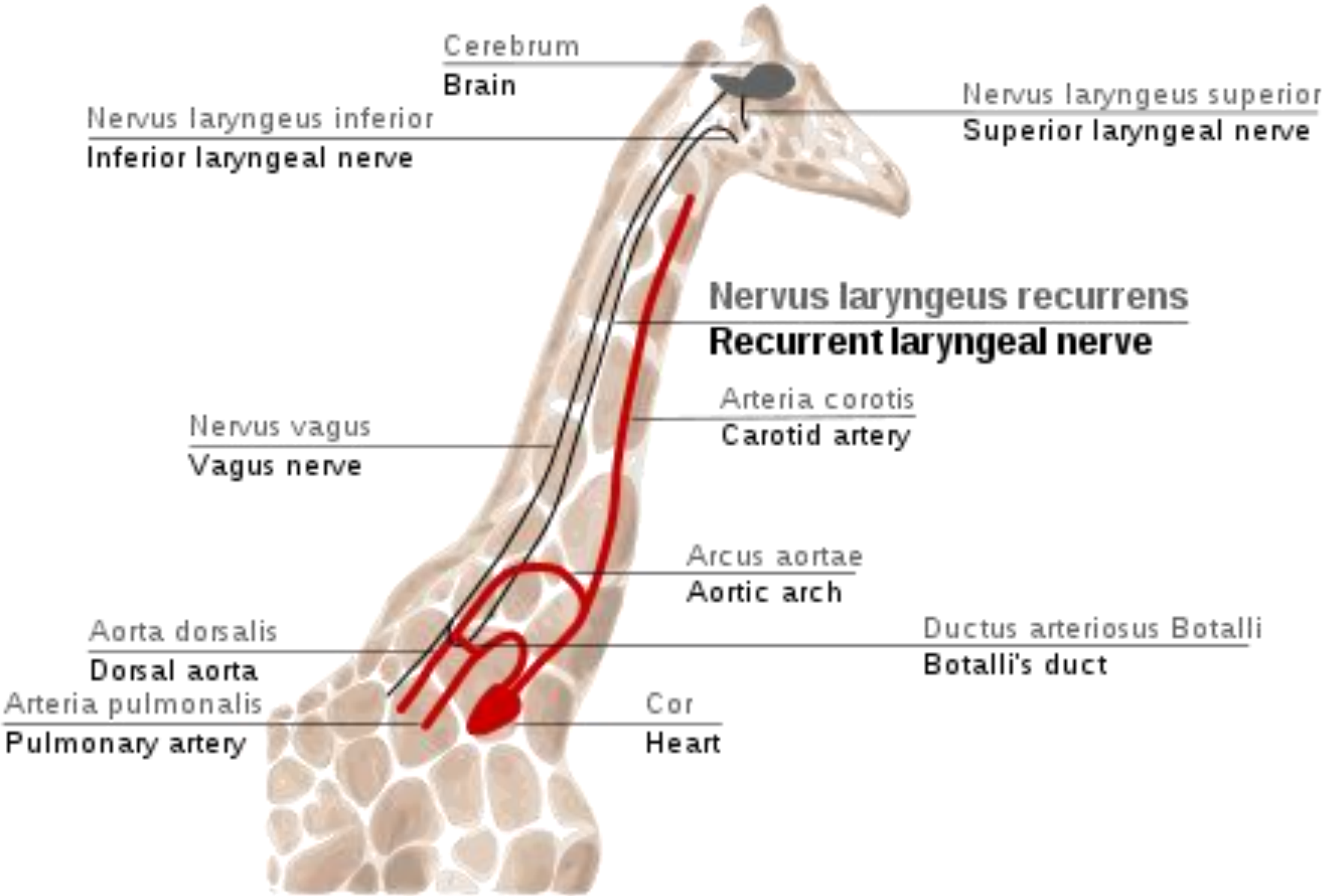
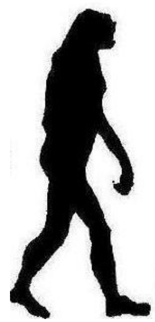


FIGURE 3–11 Schematic diagram showing the relationship between the vagus cranial nerve and the arterial arches in fish (*a*) and human (*b*). Only the third, fourth, and part of the sixth arterial arches remain in placental mammals, the sixth acting only during fetal development to carry blood to the placenta. The fourth vagal nerve in mammals (the recurrent laryngeal nerve) loops around the sixth arterial arch just as it did in the original fishlike ancestor, but must now travel a greater distance since the remnant of the sixth arch is in the thorax.



Cerebrum
Brain
Nervus laryngeus inferior
Inferior laryngeal nerve
Nervus laryngeus superior
Superior laryngeal nerve
Nervus laryngeus recurrens
Recurrent laryngeal nerve
Arteria corotis
Carotid artery
Nervus vagus
Vagus nerve
Arcus aortae
Aortic arch
Aorta dorsalis
Dorsal aorta
Ductus arteriosus Botalli
Botalli's duct
Arteria pulmonalis
Pulmonary artery
Cor
Heart

weak
fragile
slow



Human evolution

hands
feet
skeleton
muscle
skin
gut
long helpless childhood

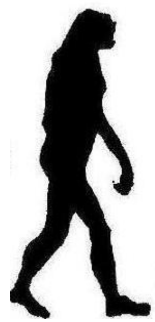
All very different.

Apes

strong
robust
fast

How is this progress?

Homo Erectus?



hands
feet
skeleton
muscle
skin
gut

Roughly modern

Very fragile

weak
fragile

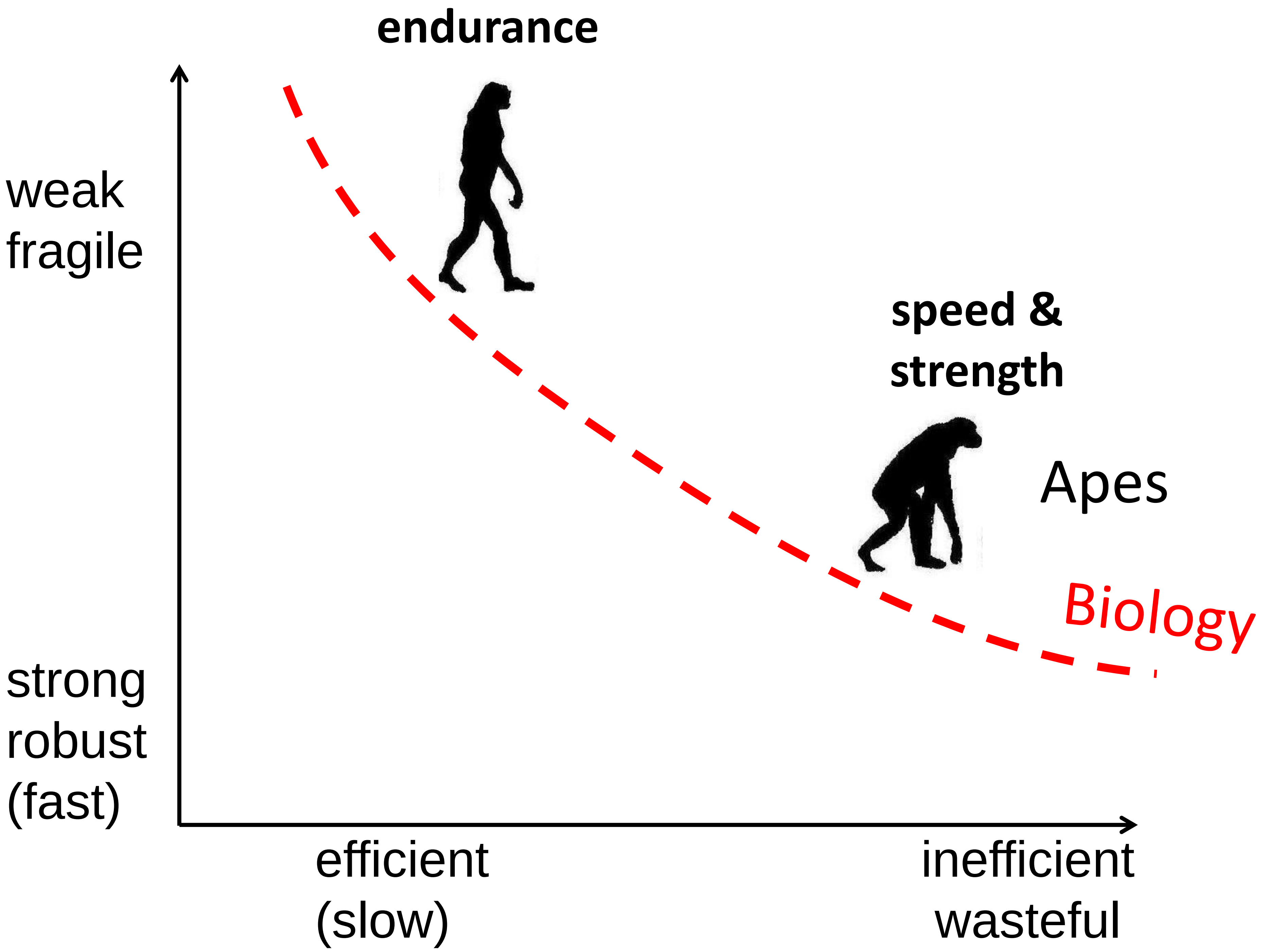
This much seems pretty consistent among experts regarding circa 1.5-2Mya

strong
robust

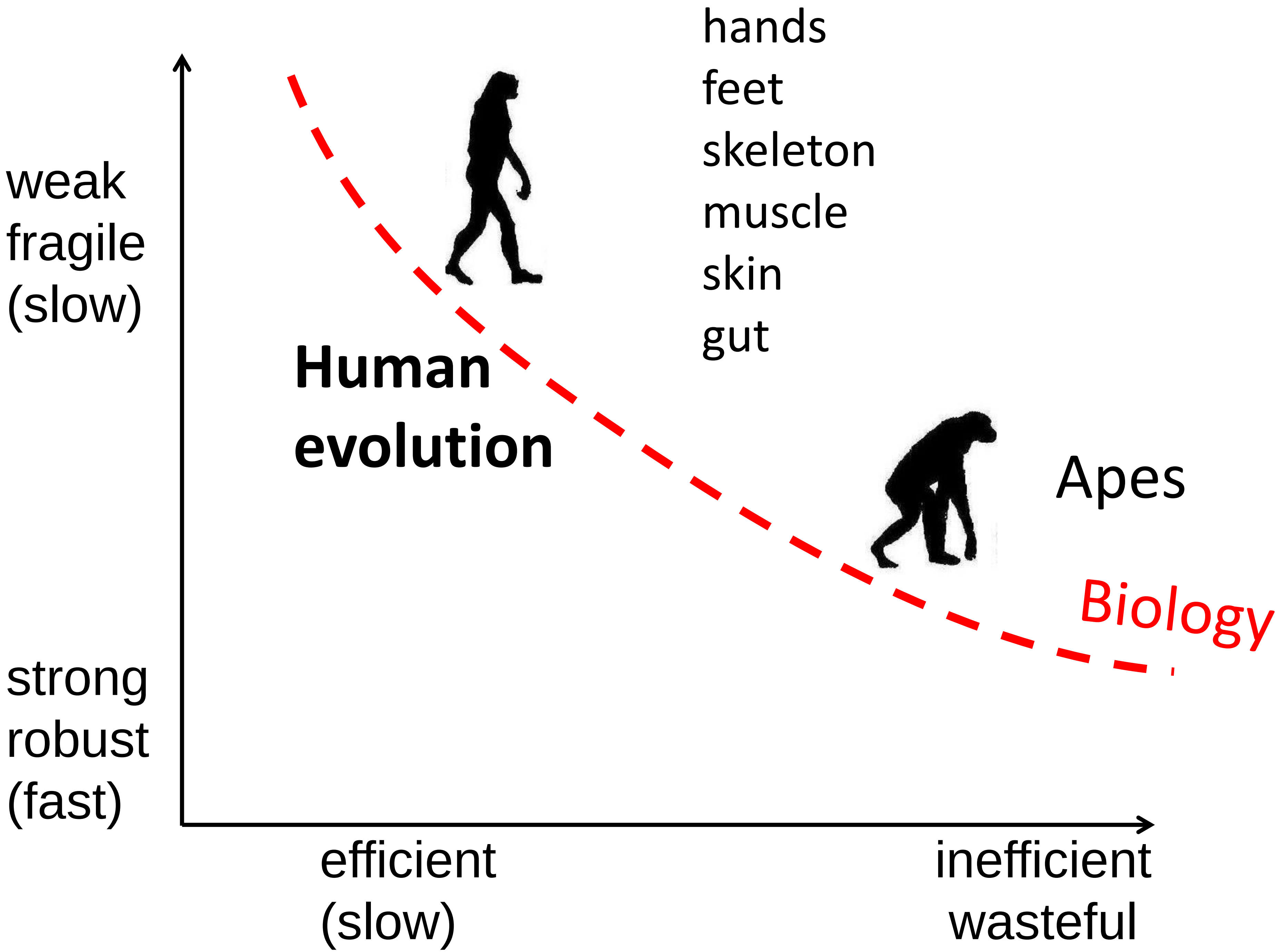
So how did H. Erectus survive and expand globally?

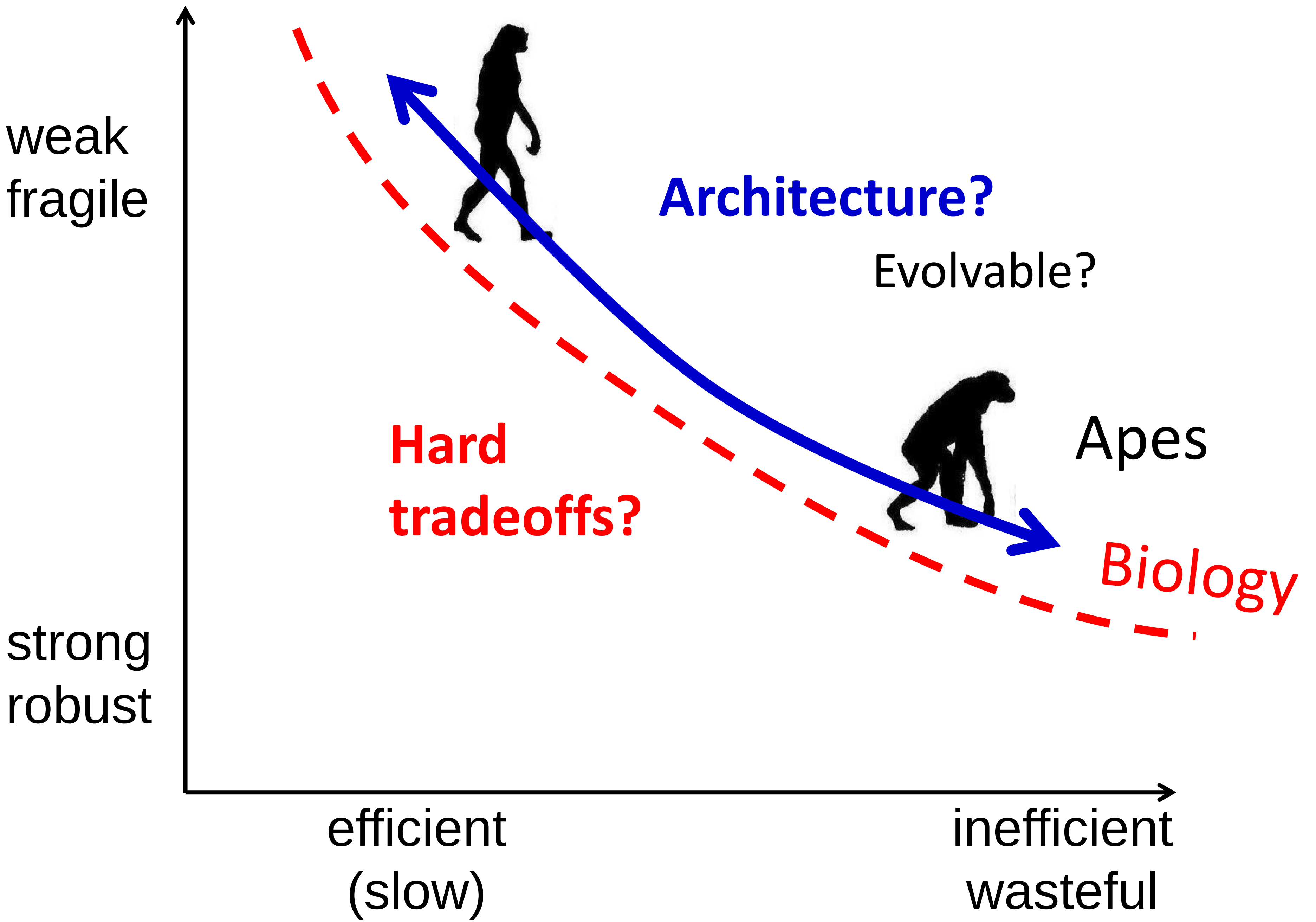
efficient
(slow)

inefficient
wasteful

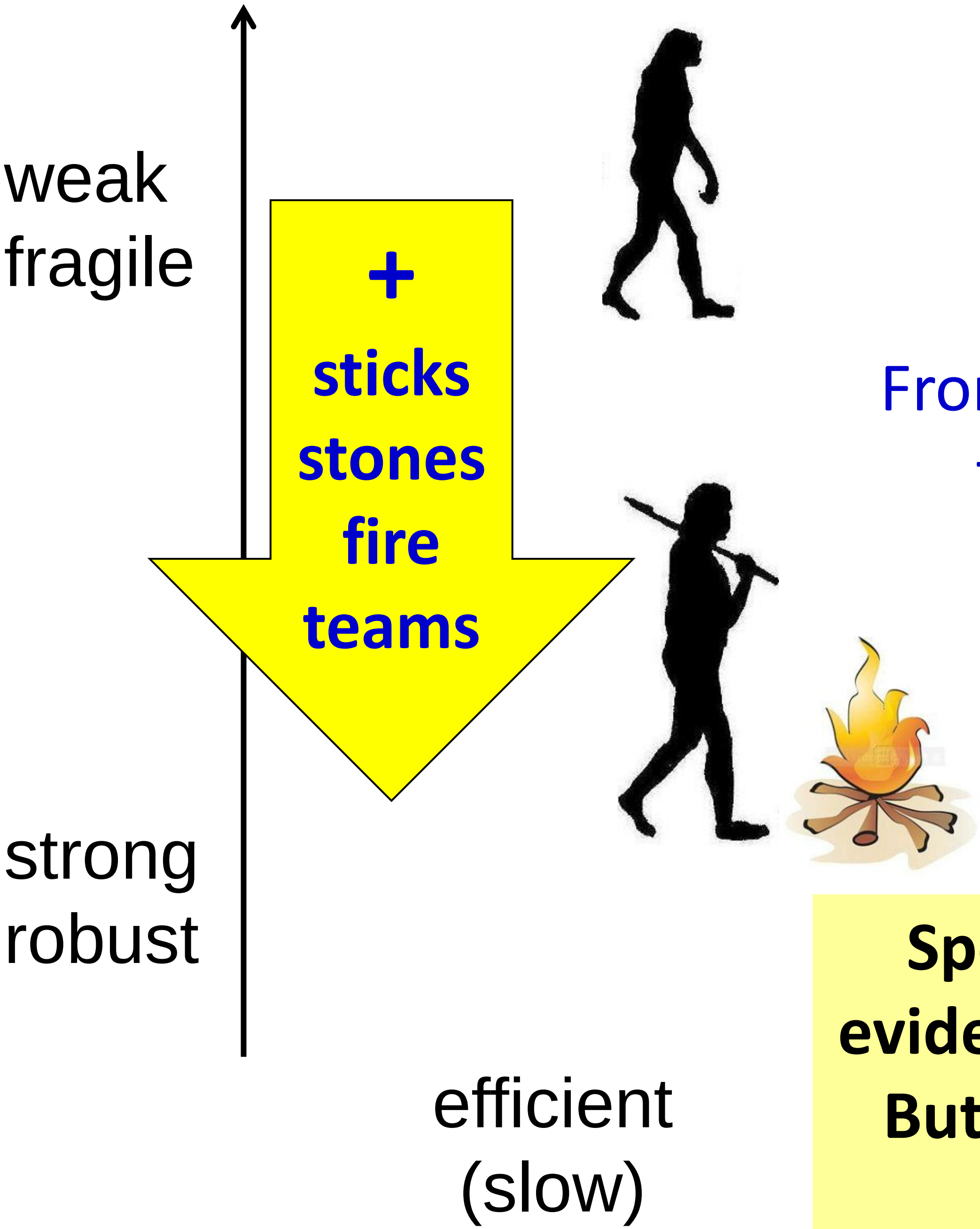


endurance
weak
fragile
speed &
strength
Apes
Biology
strong
robust
(fast)
efficient
(slow)
inefficient
wasteful


hands
feet
skeleton
muscle
skin
gut
weak
fragile
(slow)
Human
evolution
Apes
Biology
strong
robust
(fast)
efficient
(slow)
inefficient
wasteful


weak
fragile
strong
robust
Architecture?
Evolvable?
Hard
tradeoffs?
Apes
Biology
efficient
(slow)
inefficient
wasteful

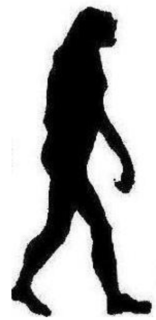
endurance



From weak prey
to invincible
predator?

Speculation? There is only evidence for crude stone tools. But sticks, fire, teams might not leave a record?

weak
fragile



Speculation? With only evidence for crude stone tools. But sticks and fire might not leave a record?

+
sticks
stones
fire
teams

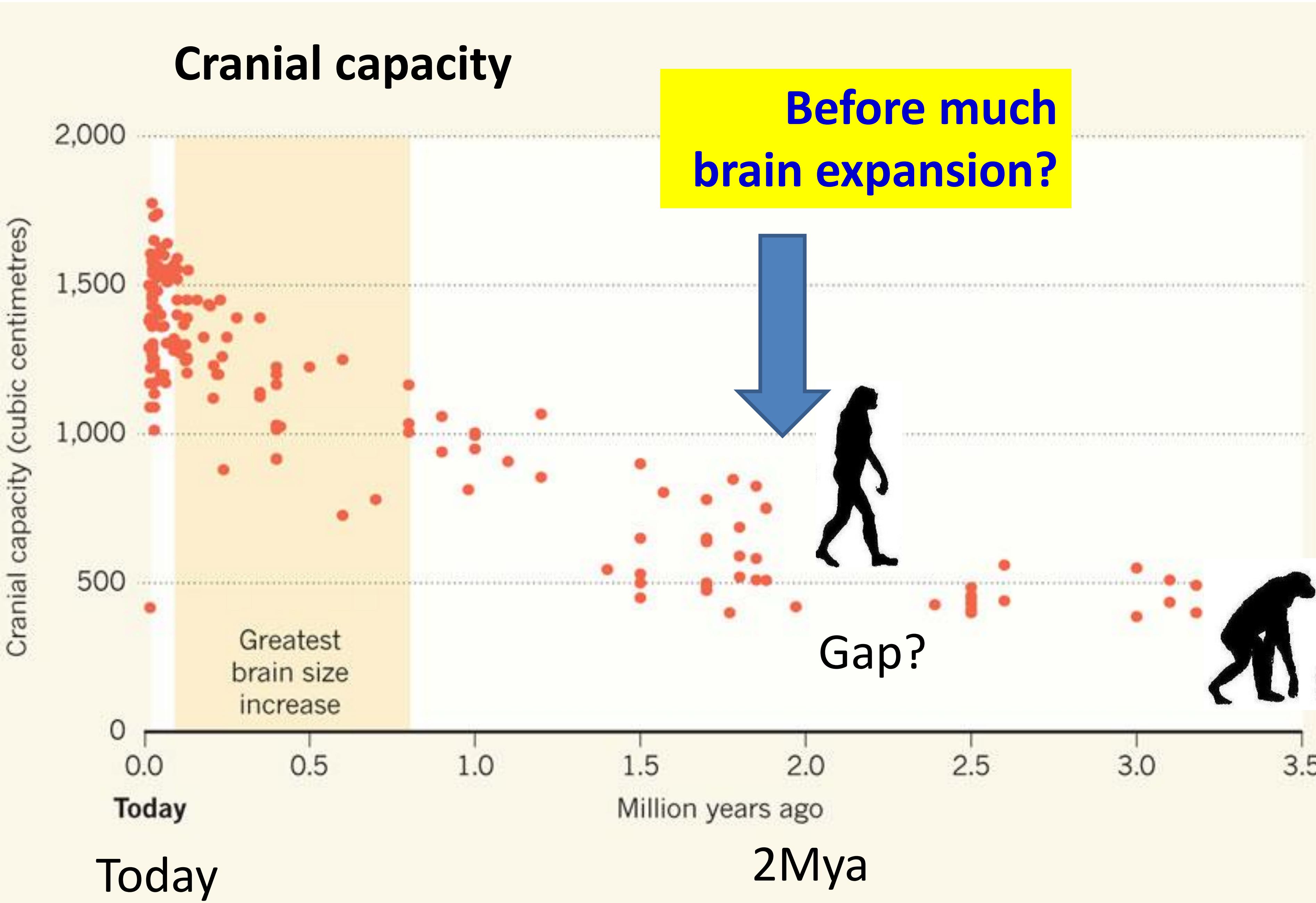
From weak prey to invincible predator

Before much brain expansion?

strong
robust

Plausible but speculation?

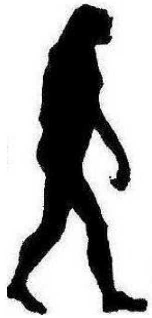
efficient
(slow)



Cranial capacity
Before much brain expansion?
2,000
1,500
1,000
500
0
Cranial capacity (cubic centimetres)
Greatest brain size increase
Gap?
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Today
Million years ago
Today
2Mya

weak
fragile

strong
robust



hands
feet
skeleton
muscle
skin
gut

+
sticks
stones
fire

From weak prey
to invincible
predator

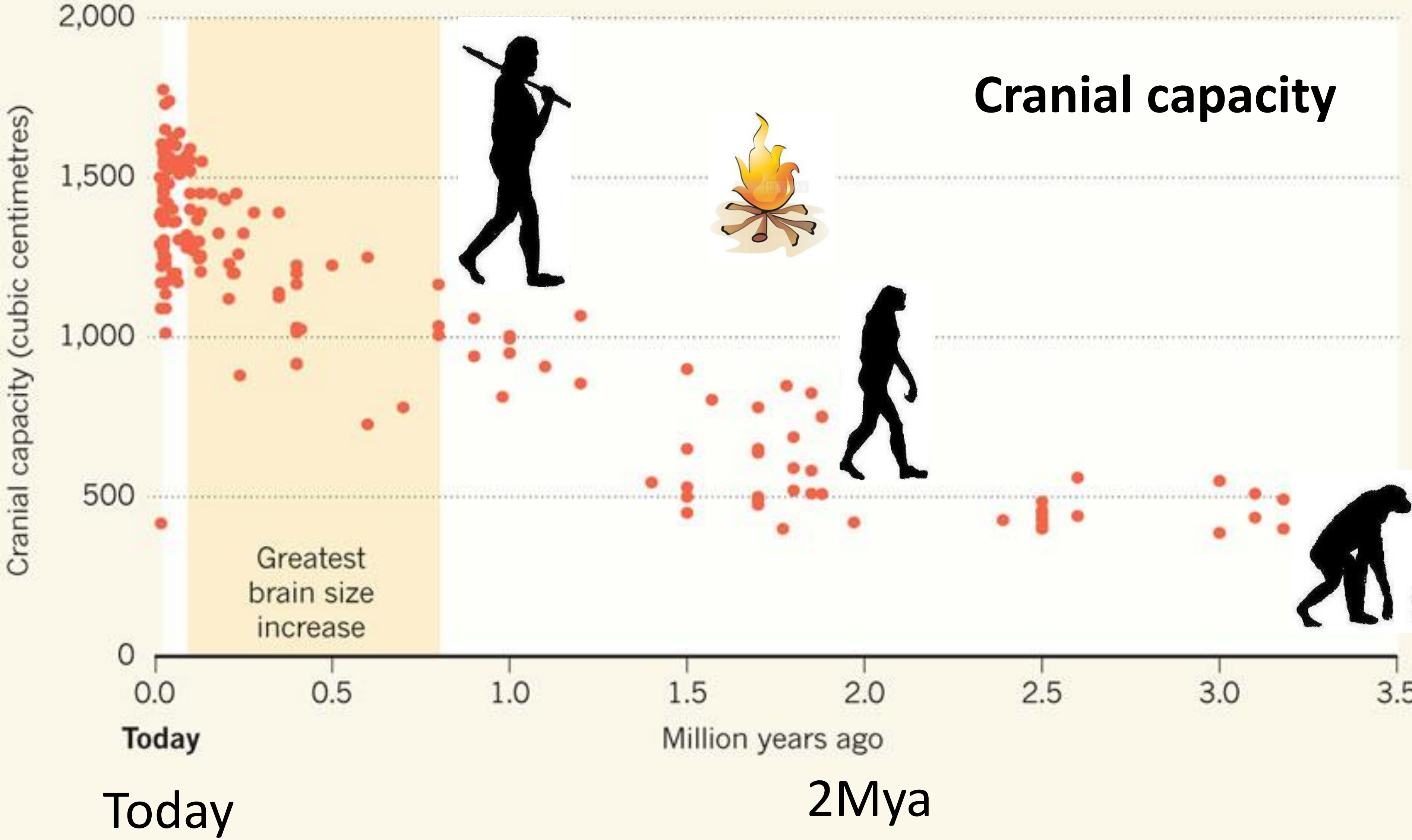
Before much
brain expansion?

efficient
(slow)

Key point:
Our physiology,
technology,
and brains
have co-
evolved

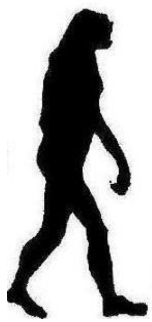
Probably true
no matter what

Huge
implications.



Cranial capacity
2,000
1,500
1,000
500
0
Cranial capacity (cubic centimetres)
Greatest
brain size
increase
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Today
Million years ago
Today
2Mya

weak
fragile



hands
feet
skeleton
muscle
skin
gut

Key point needing more discussion:
The evolutionary challenge of big brains is ***homeostasis***, not basal metabolic load.

From weak prey to invincible predator

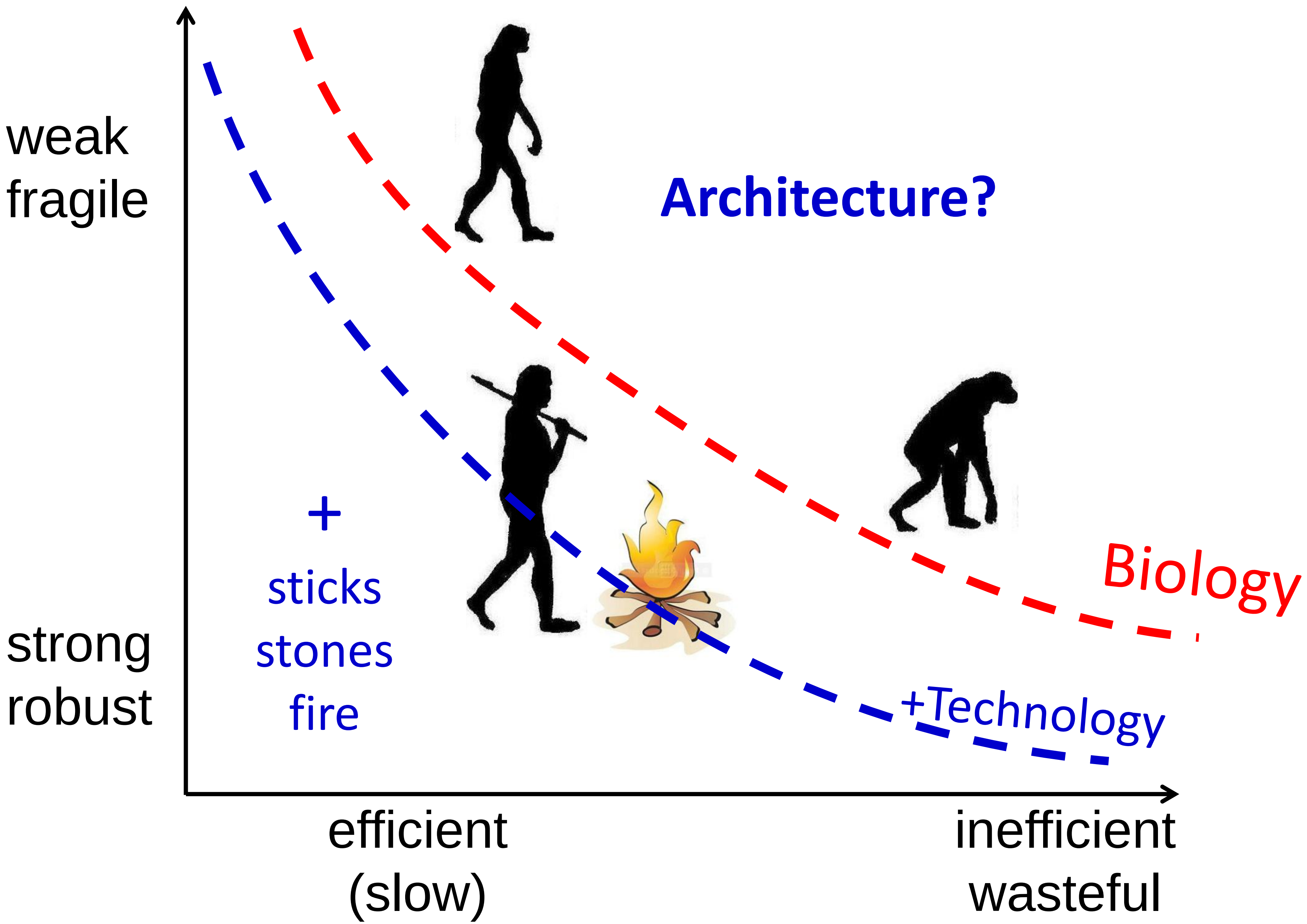
+
sticks
stones
fire

strong
robust

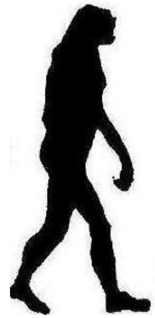
Before much brain expansion?

efficient
(slow)

Huge implications.


weak
fragile
strong
robust
Architecture?
+
sticks
stones
fire
Biology
+Technology
efficient
(slow)
inefficient
wasteful

weak
fragile



hands
feet
skeleton
muscle
skin
gut

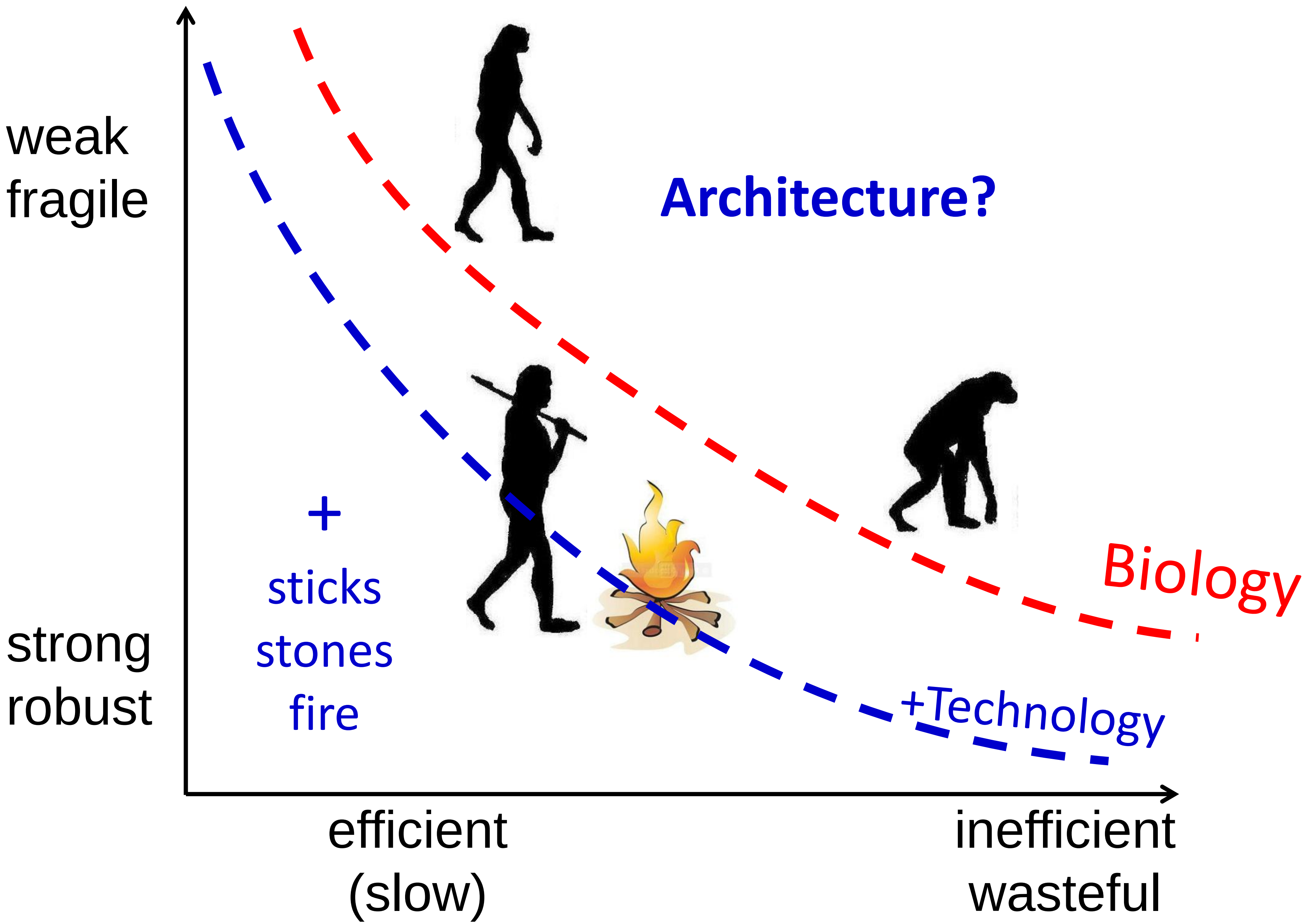
From weak prey
to invincible
predator

+
sticks
stones
fire

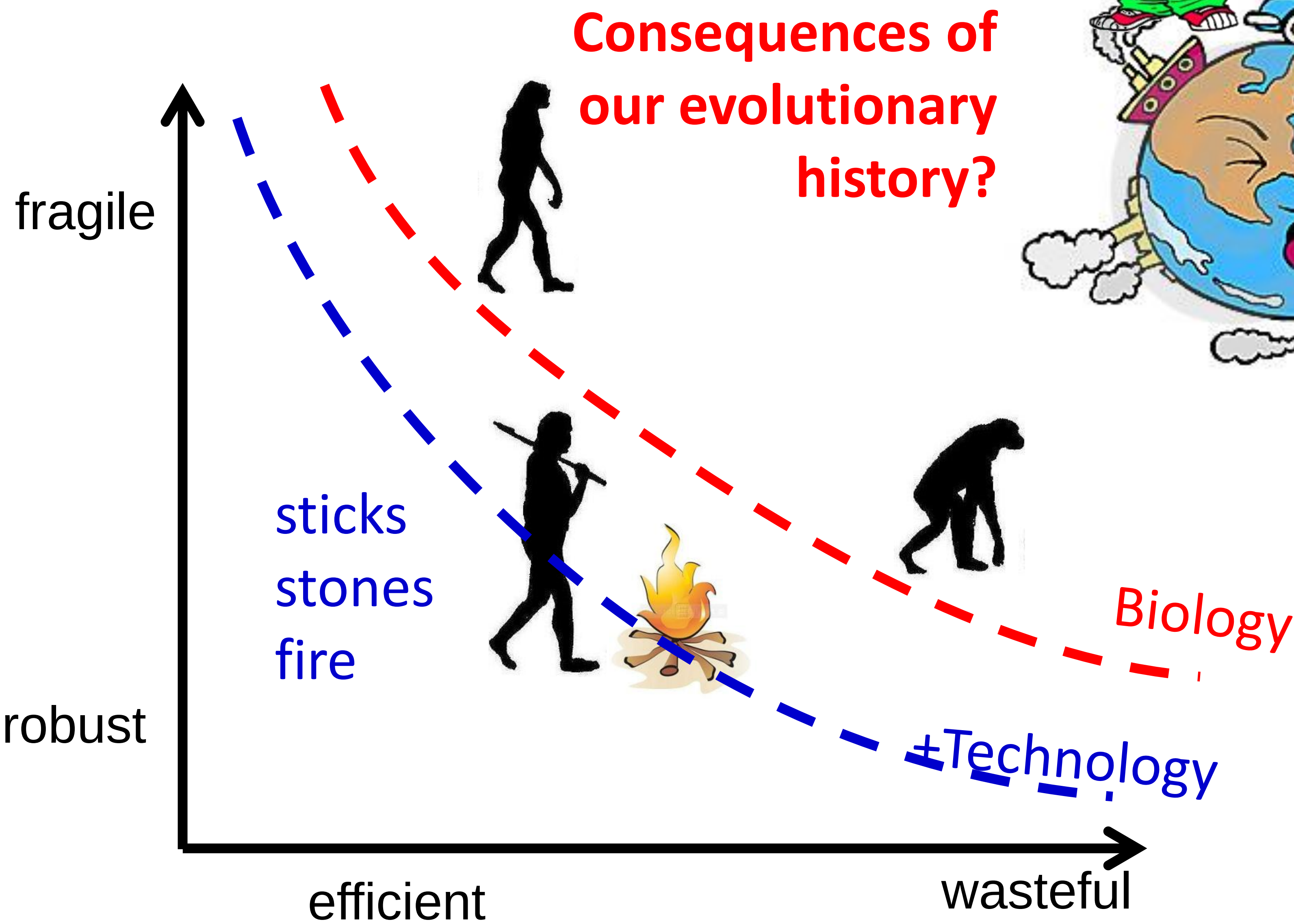
strong
robust

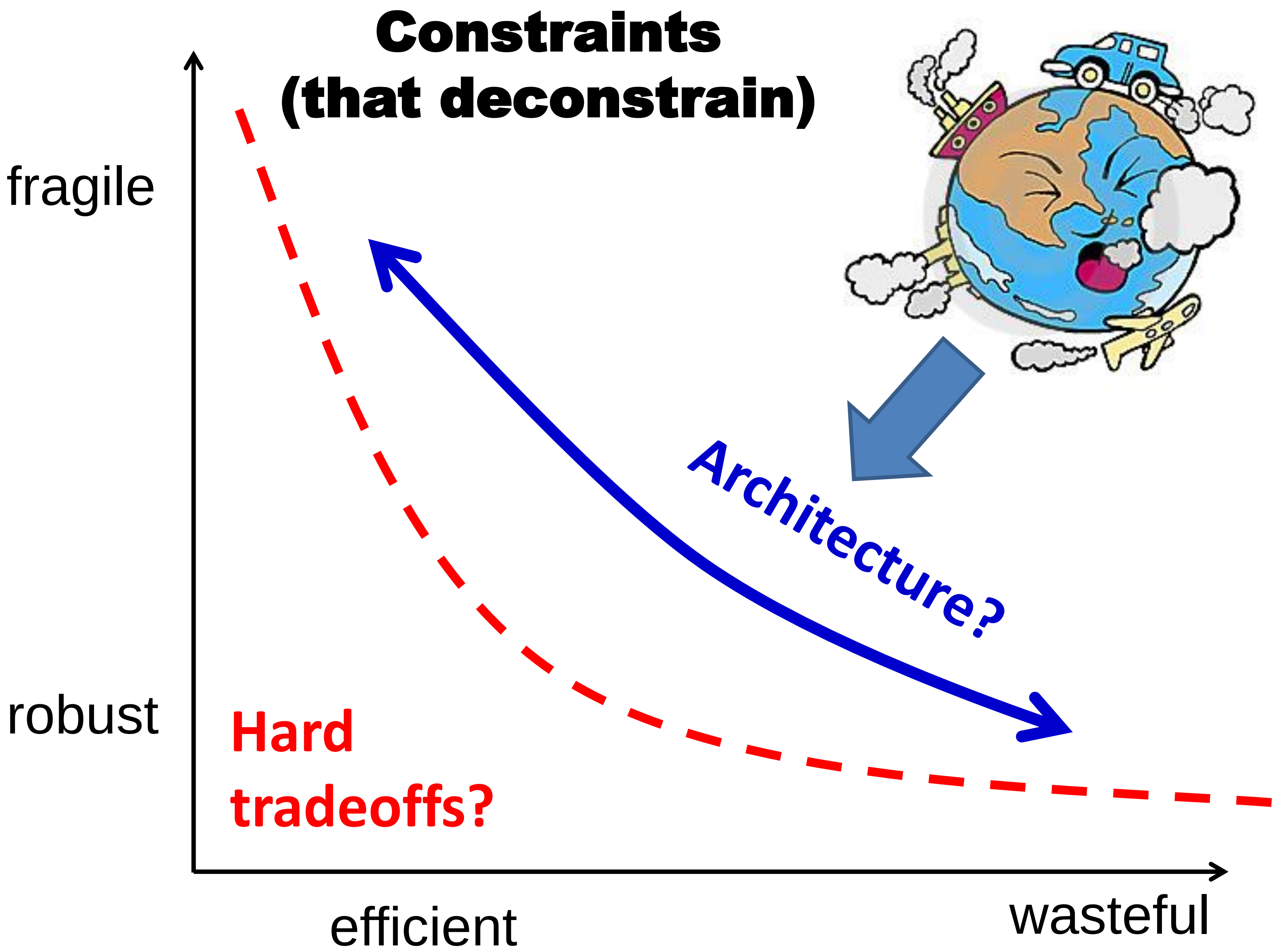
efficient
(slow)

Before much
brain expansion?


weak
fragile
strong
robust
Architecture?
+
sticks
stones
fire
Biology
+Technology
efficient
(slow)
inefficient
wasteful

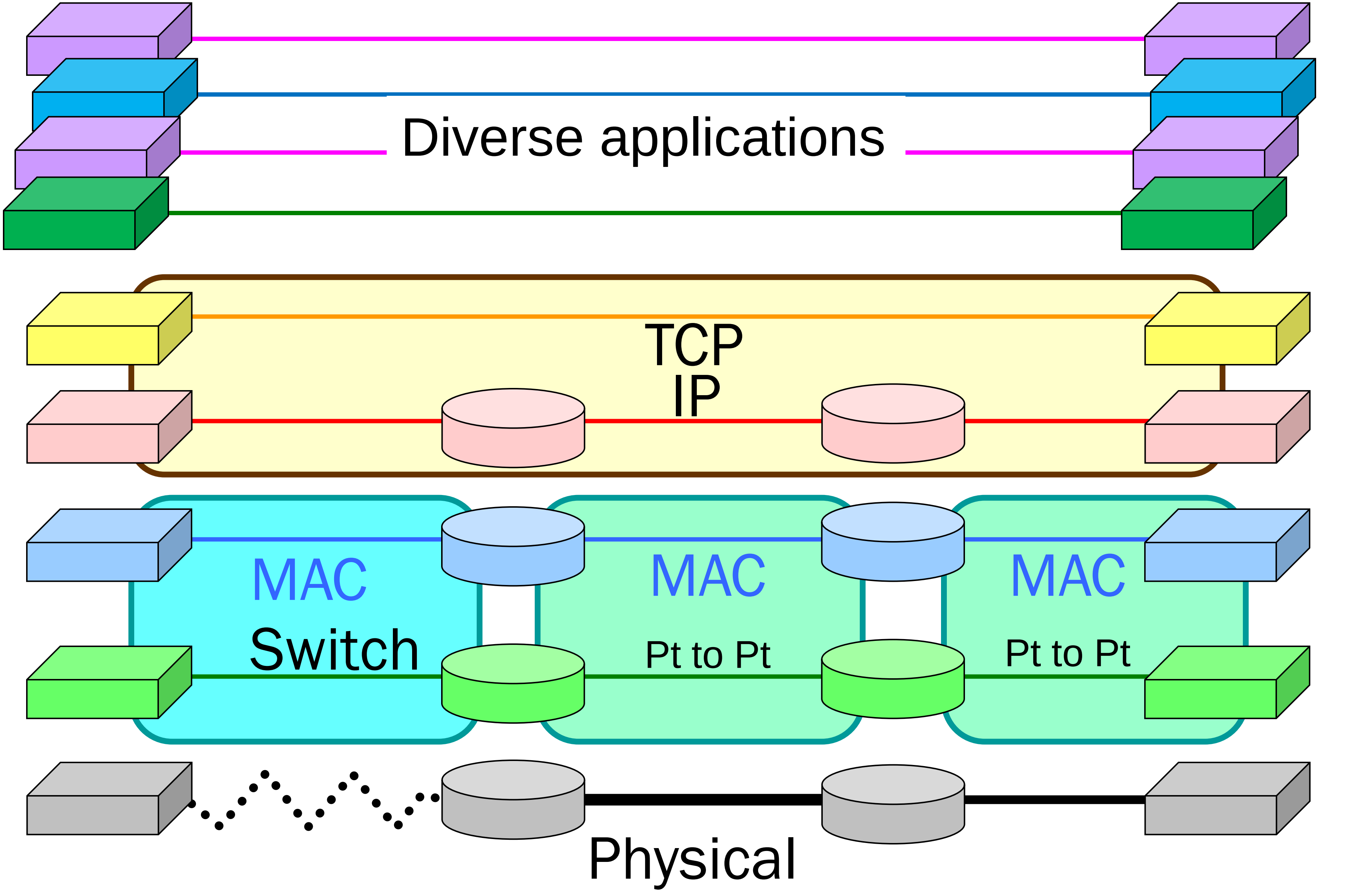
Human complexity?





Constraints
(that deconstrain)
fragile
robust
Architecture?
Hard
tradeoffs?
efficient
wasteful

Layered architectures



Proceedings of the IEEE, Jan 2007

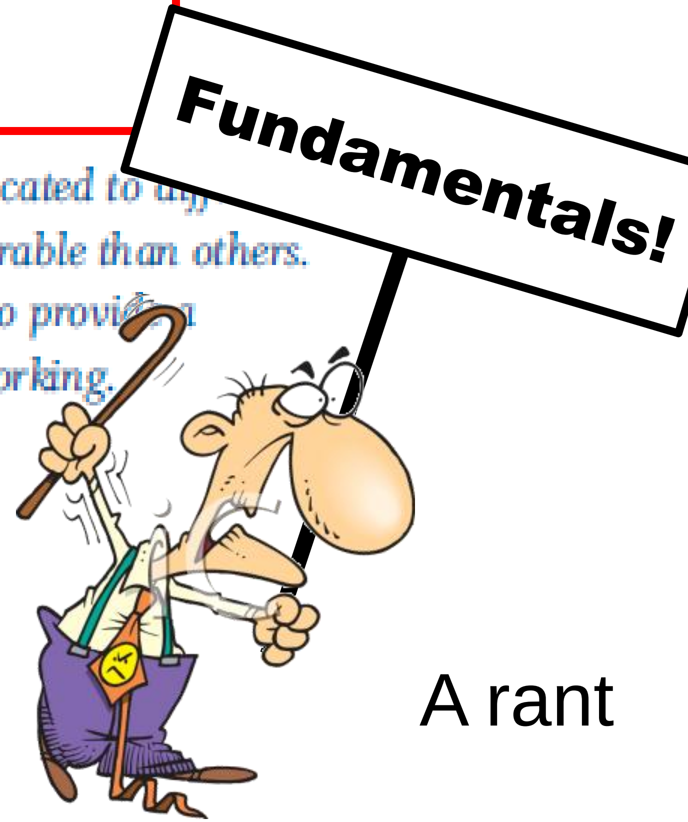
OR optimization

Layering as Optimization Decomposition: A Mathematical Theory of Network Architectures

What's next?

There are various ways that network functionalities can be allocated to different layers and to different network elements, some being more desirable than others. The intellectual goal of the research surveyed by this article is to provide a theoretical foundation for these architectural decisions in networking.

By MUNG CHIANG, *Member IEEE*, STEVEN H. LOW, *Senior Member IEEE*, A. ROBERT CALDERBANK, *Fellow IEEE*, AND JOHN C. DOYLE



Chang, Low, Calderbank, Doyle

A rant

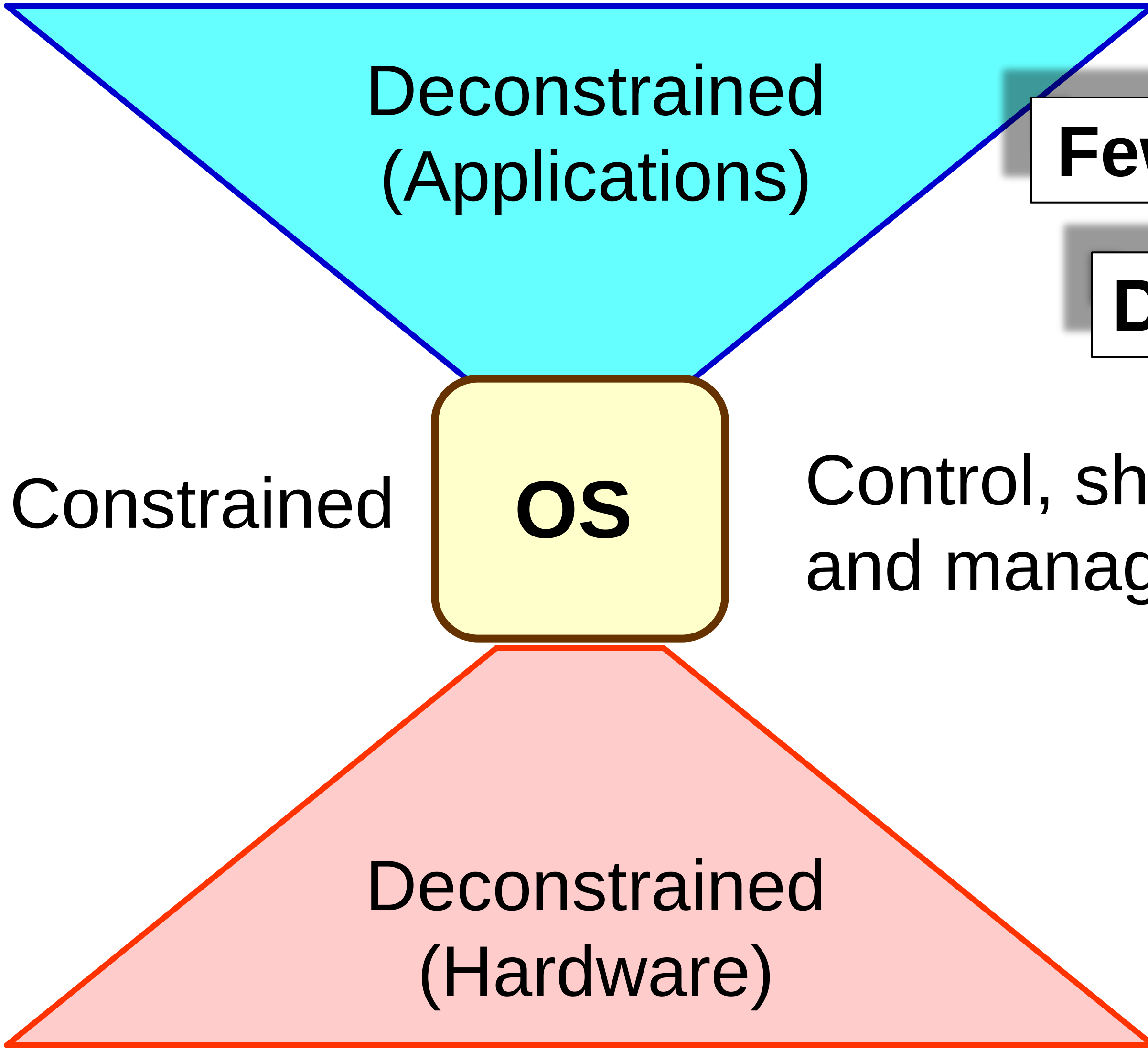
Layered architectures

Essentials

Few global variables

Don't cross layers

Constrained



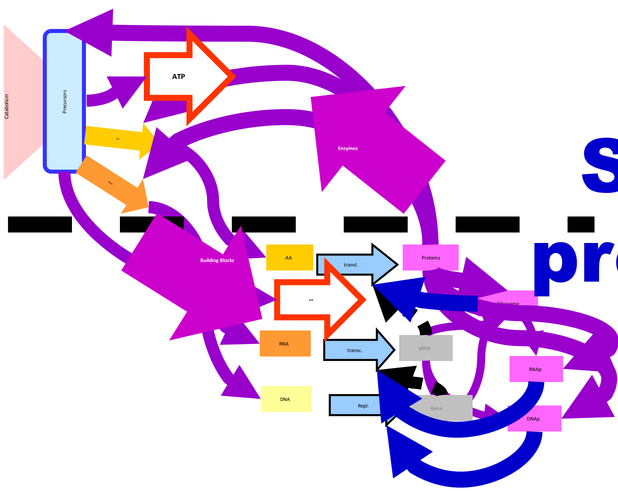
Control, share, virtualize,
and manage resources

Processing
Memory
I/O

Layered architectures

Bacterial biosphere

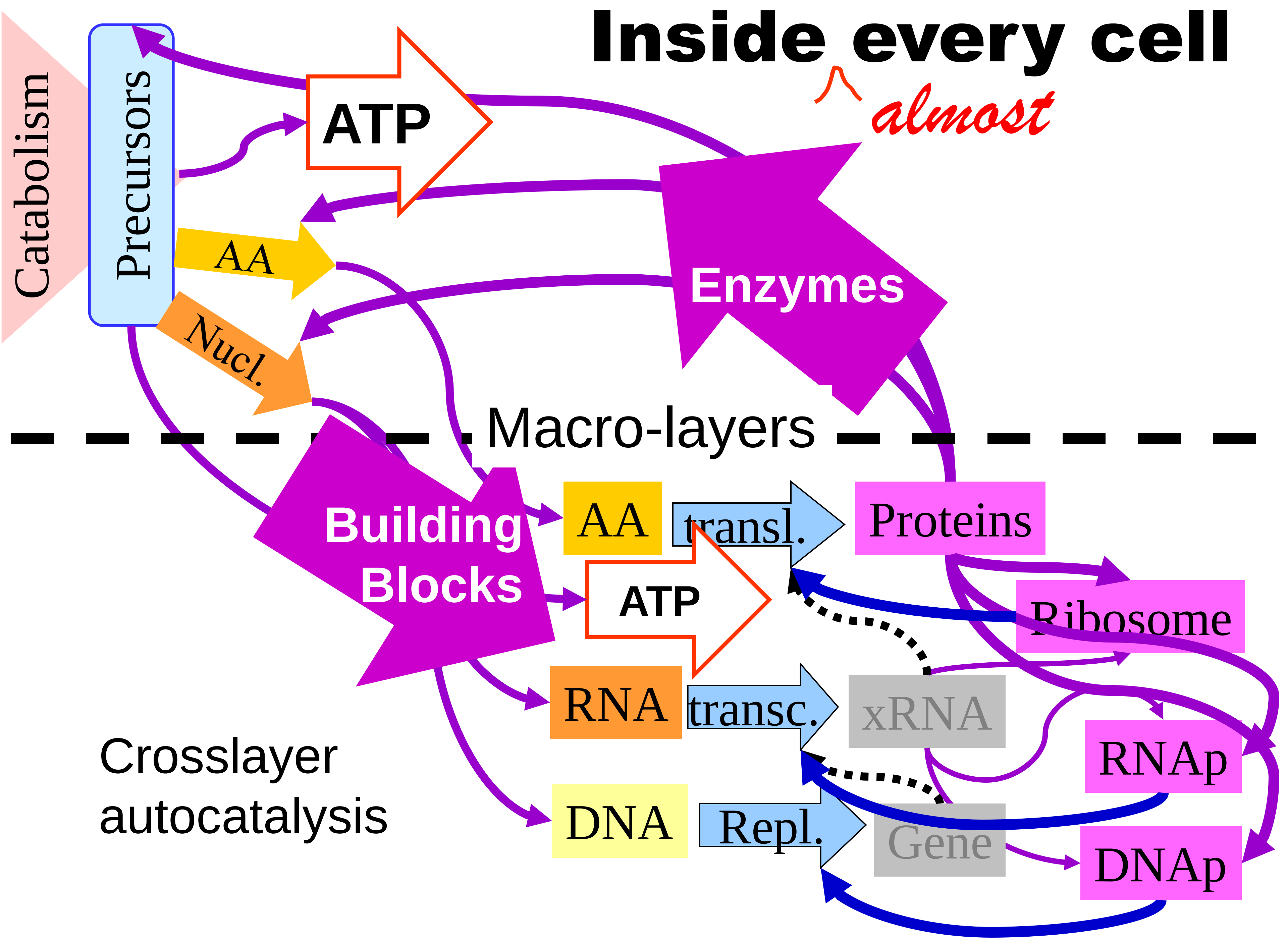
Deconstrained (diverse) Environments



Shared protocols

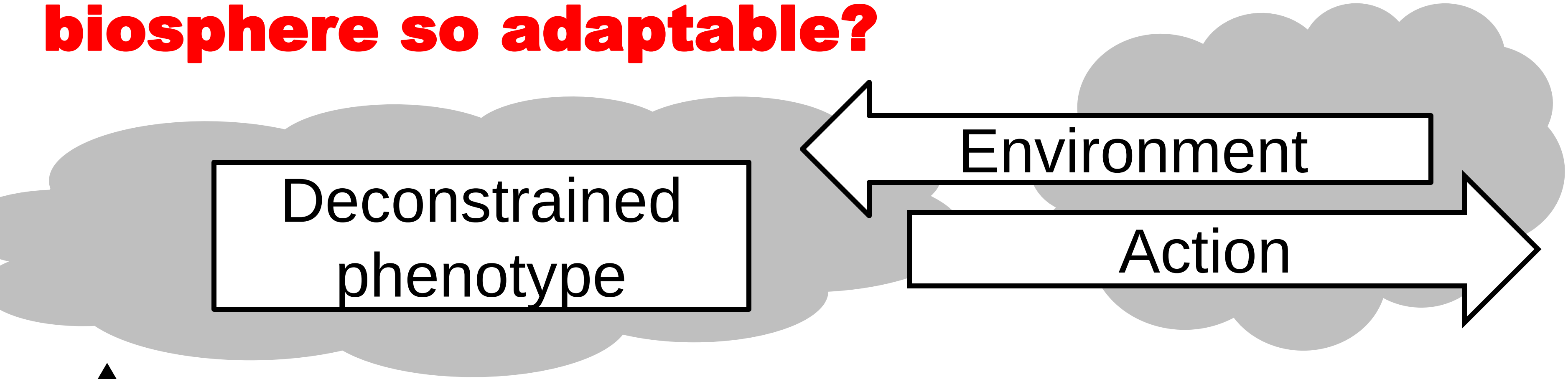
Architecture = Constraints that Deconstrain

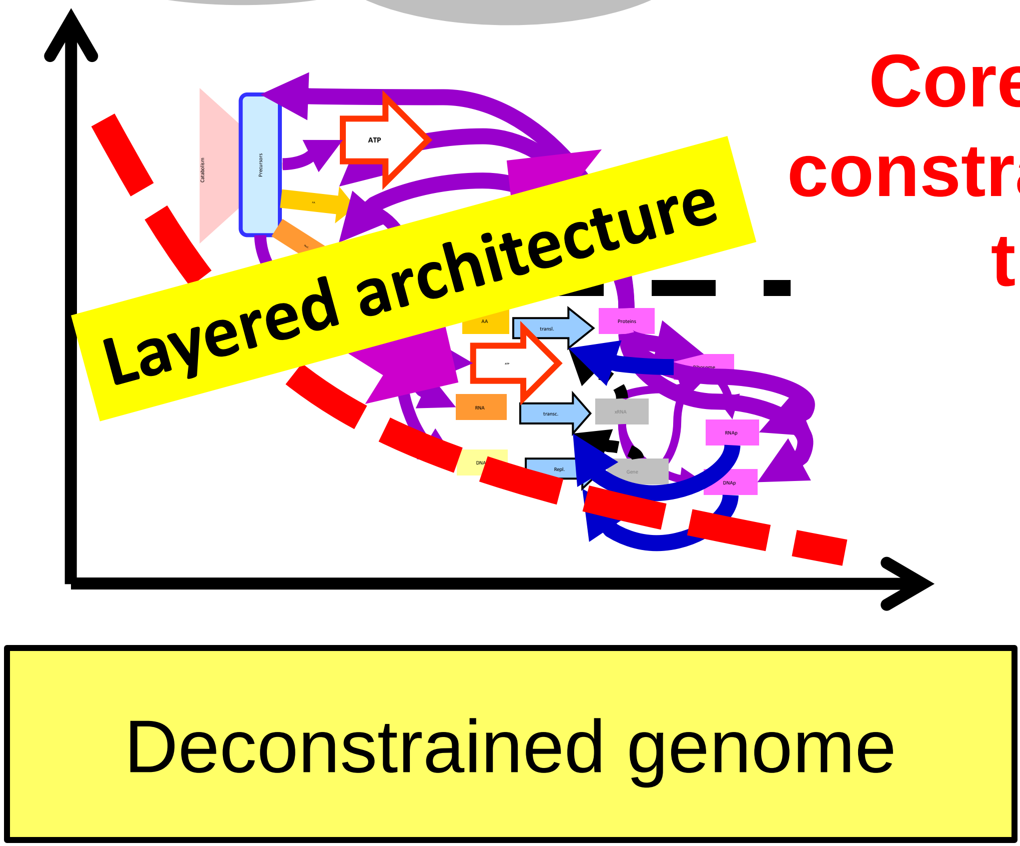
Deconstrained (diverse) Genomes



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

What makes the bacterial biosphere so adaptable?



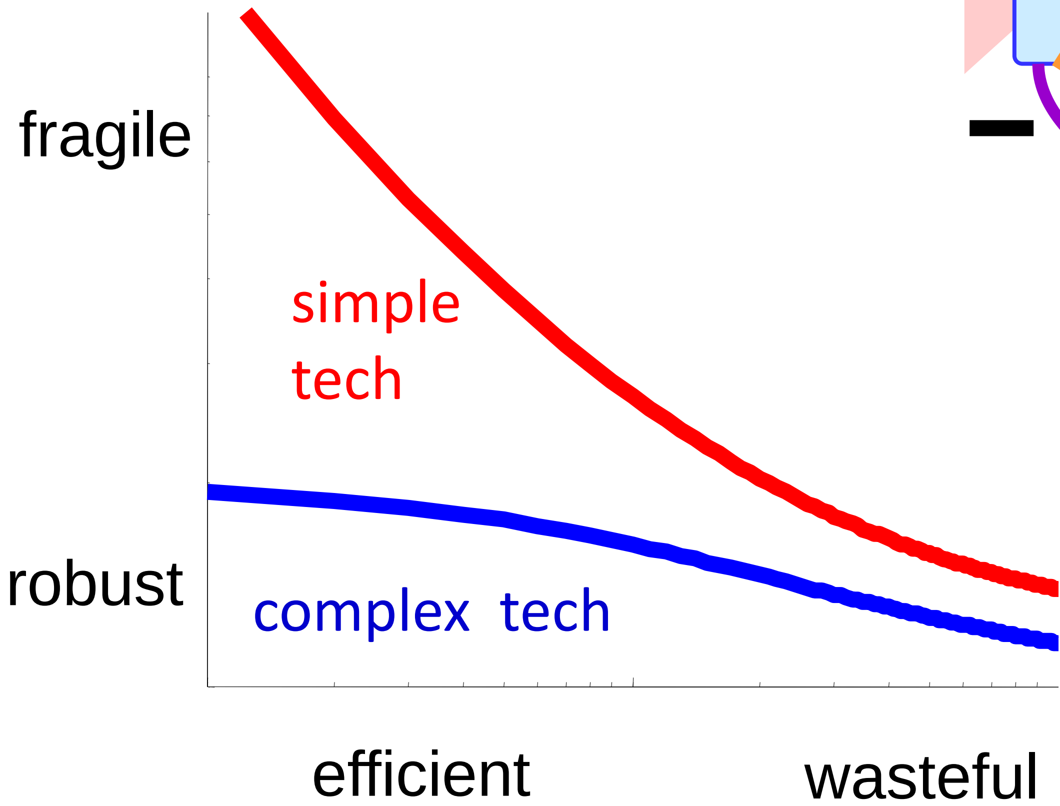


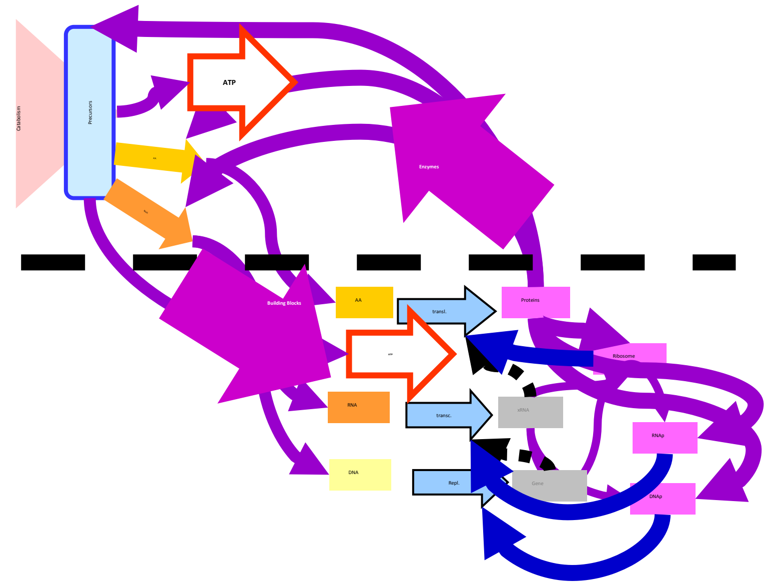
Core conserved constraints facilitate tradeoffs

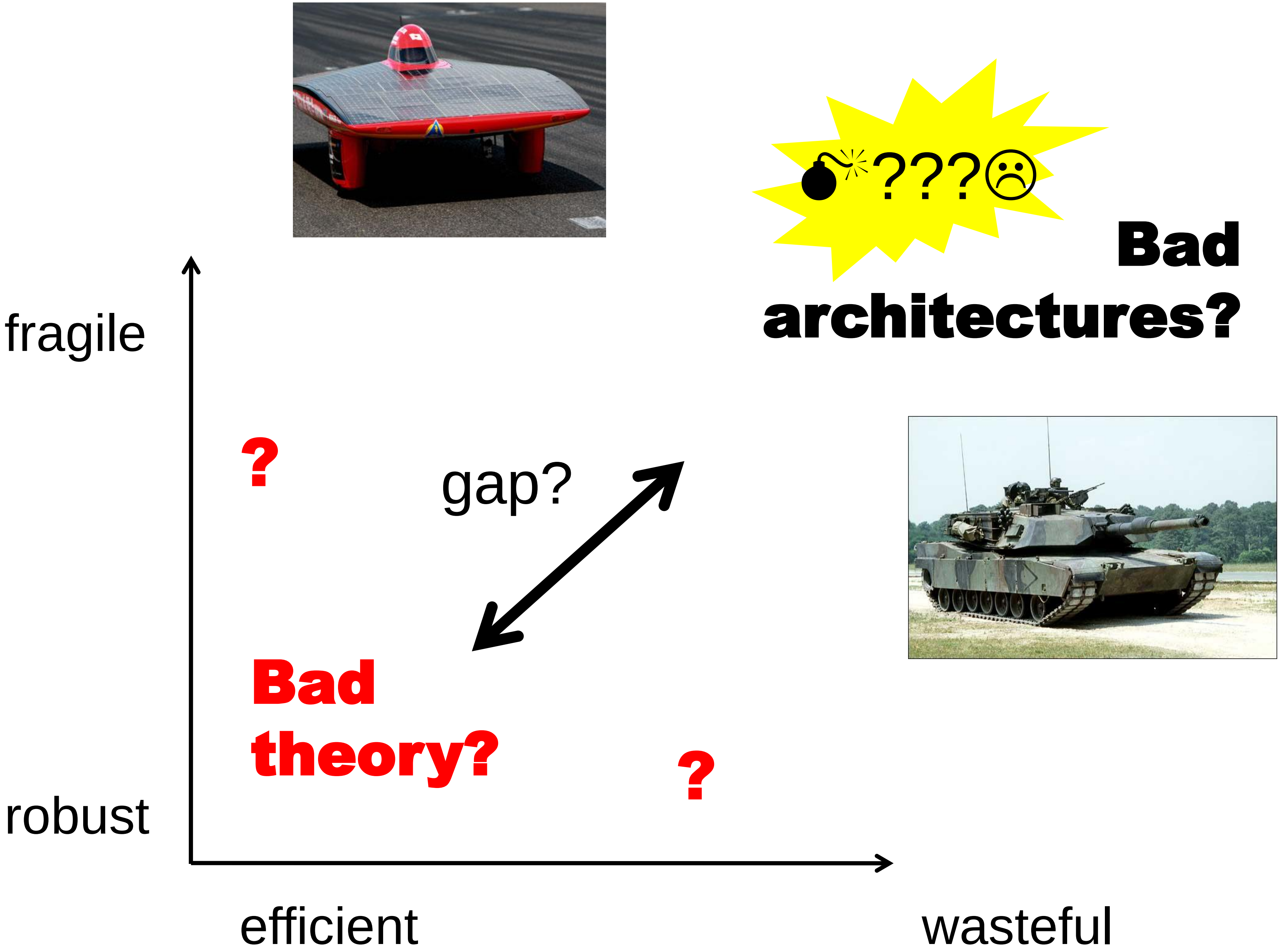
+

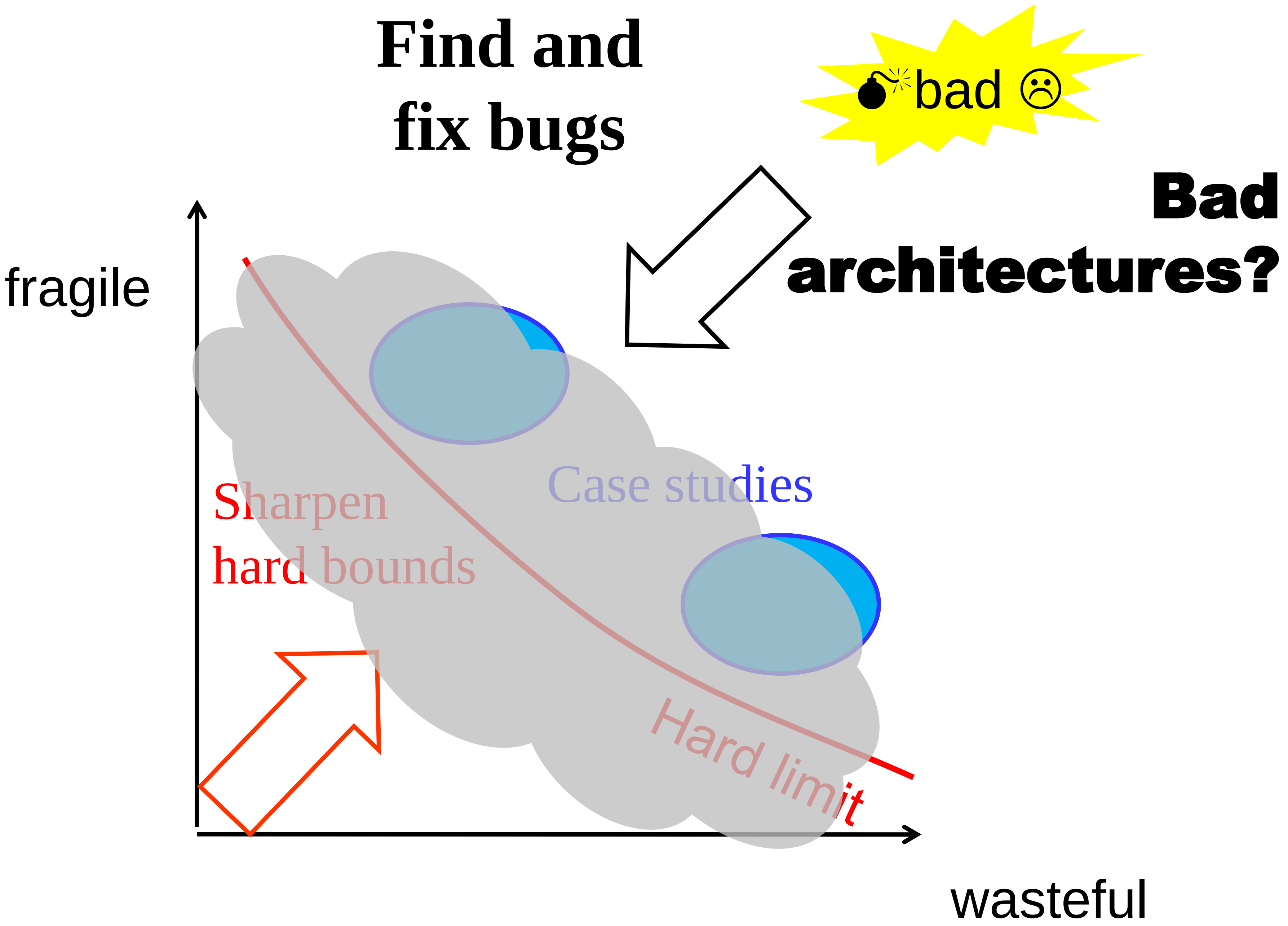
Active control of the genome (facilitated variation)

How general is this picture?
Very! Constraints!
i.e. hard limits and architecture






???☹
Bad architectures?
fragile
robust
?
gap?
Bad theory?
?
efficient
wasteful


Find and
fix bugs
bad ☹
Bad
architectures?
fragile
Sharpen
hard bounds
Case studies
Hard limit
wasteful

“New sciences” of “complexity” and “networks”?

Science as

- Pure fashion
- Ideology
- Political
- Evangelical
- Nontech trumps tech

- Edge of chaos
- Self-organized criticality
- Scale-free “networks”
- Creation “science”
- Intelligent design
- Financial engineering
- Risk management
- “Merchants of doubt”
- …

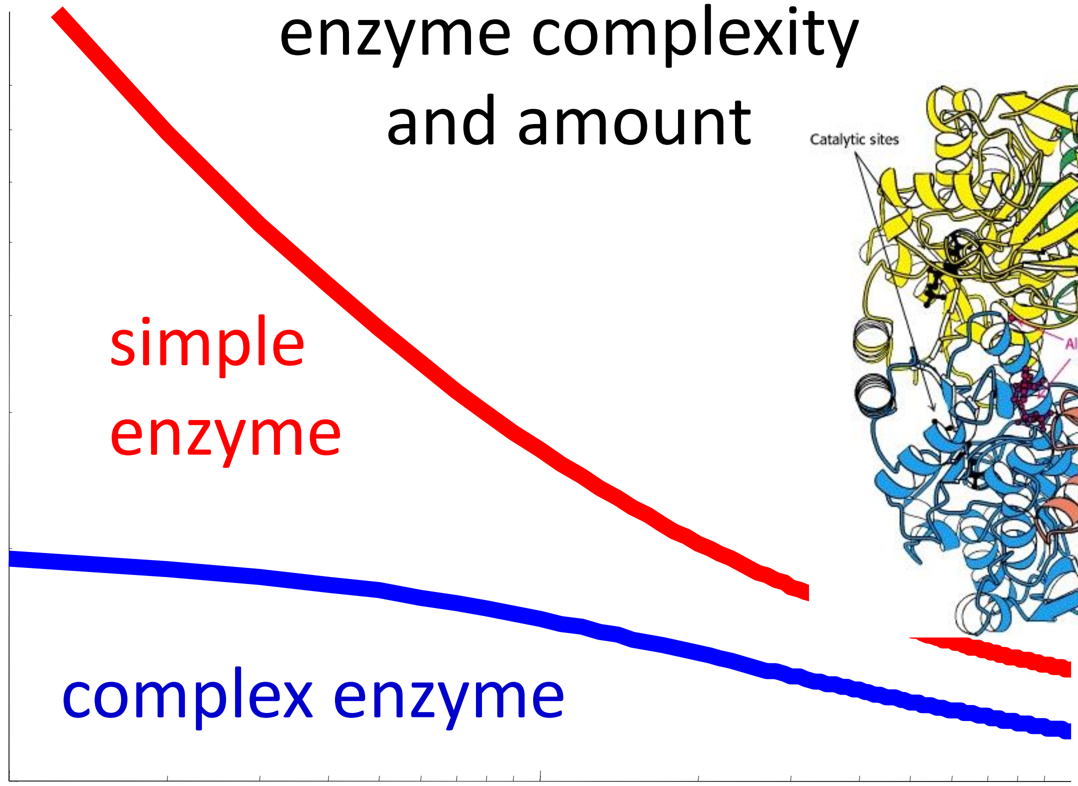
Theorem!

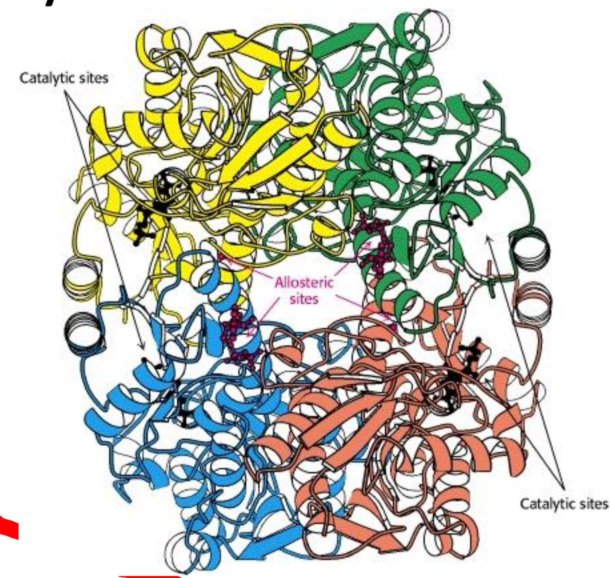
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \ge \ln\left|\frac{z+p}{z-p}\right|$$

z and p functions of enzyme complexity and amount

Fragility

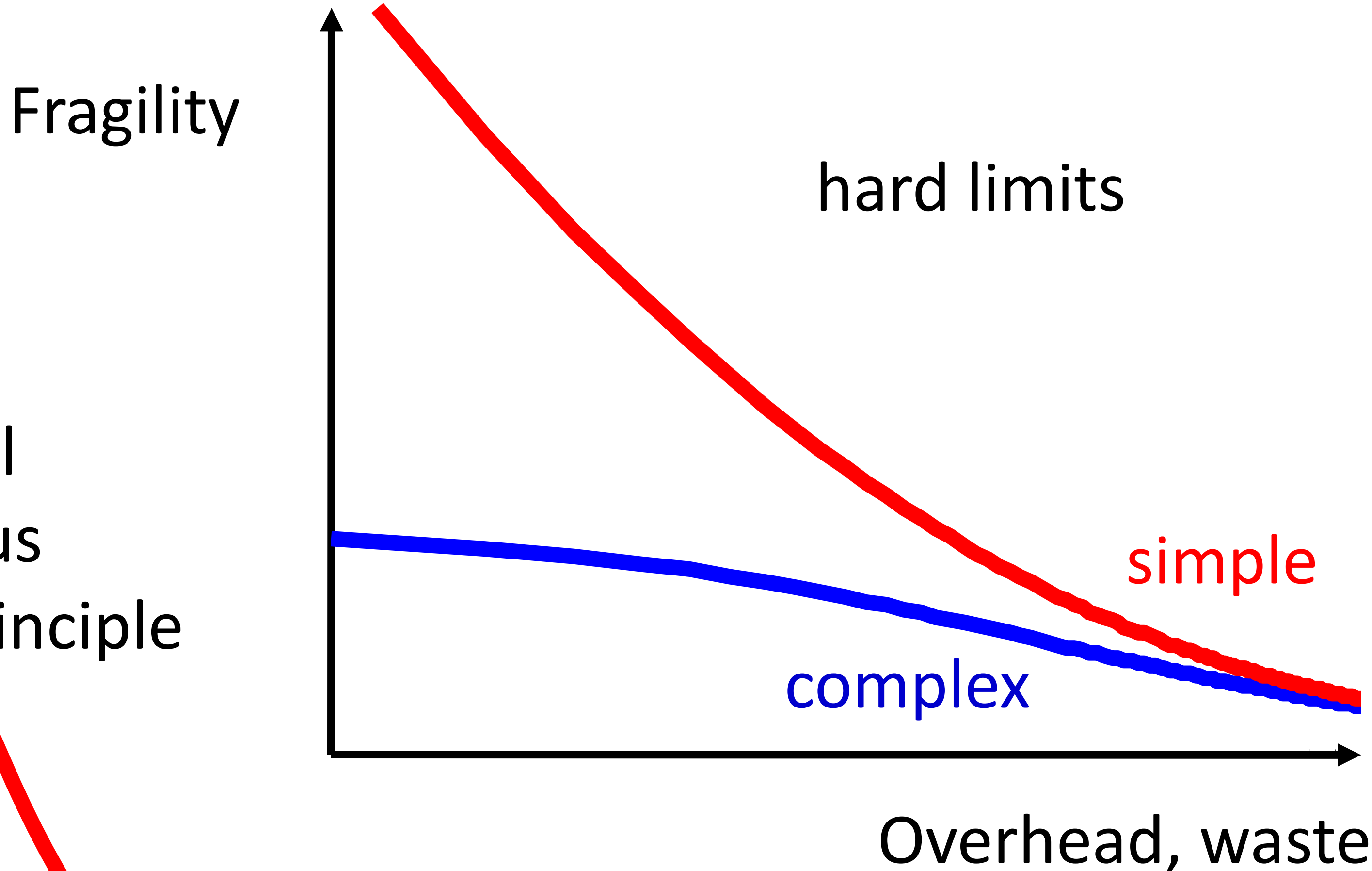
$$\ln\left|\frac{z+p}{z-p}\right|$$





Enzyme amount

Savageaumics



- General
- Rigorous
- First principle

Plugging in domain details

- Domain specific
- Ad hoc
- Phenomenological

Control Wiener **Comms**

Bode

robust control

Shannon

Kalman

- General
- Rigorous
- First principle

- Fundamental multiscale physics
- Foundations, origins of
  - noise
  - dissipation
  - amplification
  - catalysis

?

Carnot

Boltzmann

Heisenberg

Physics

Control **Comms**

Complex networks

Wildly "successful"

Compute

"New sciences" of complexity and networks
edge of chaos, self-organized criticality, scale-free,...

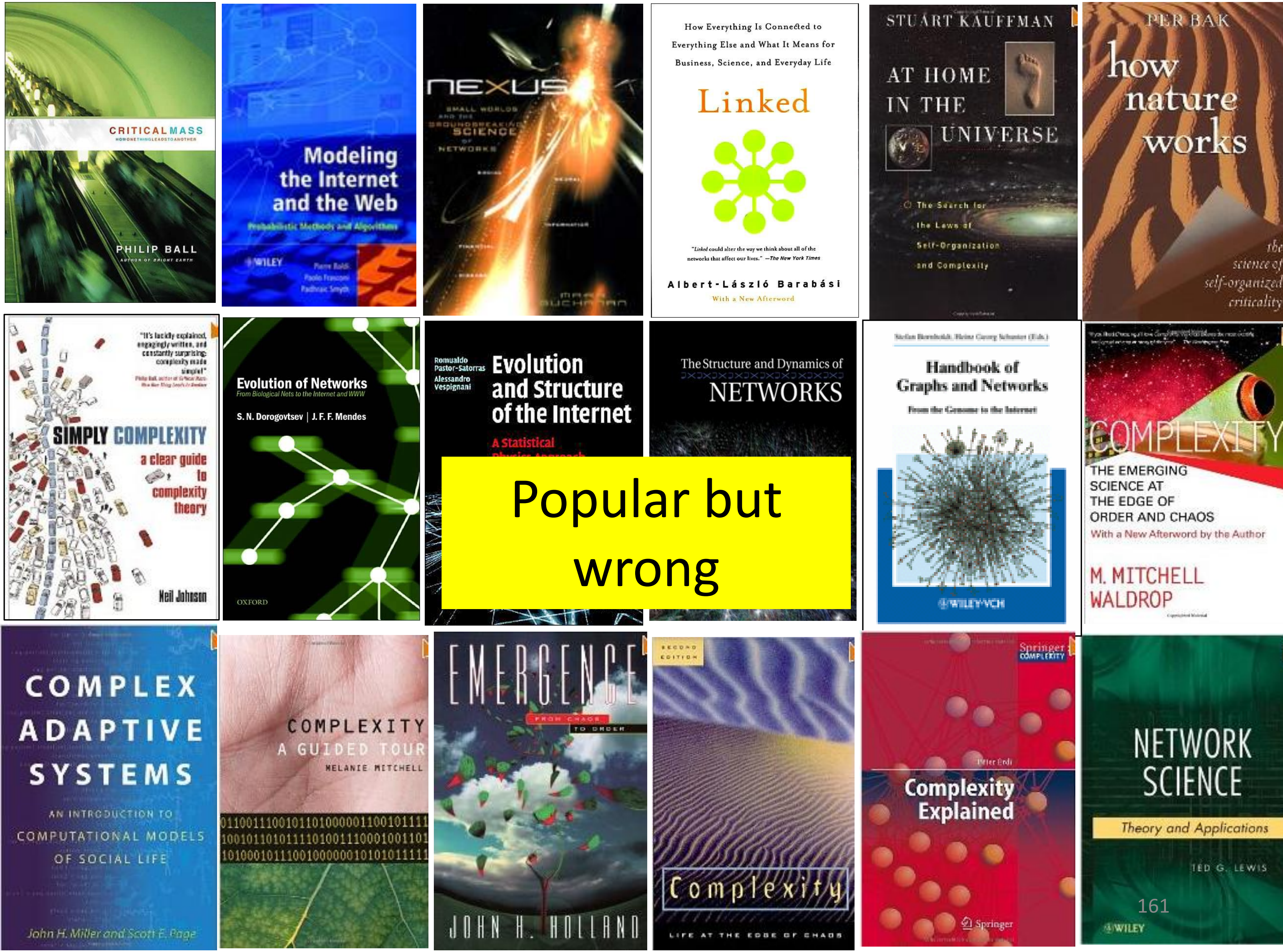
Stat physics

Carnot

Boltzmann

Heisenberg

Physics



Popular but wrong

Complex systems?

Even small amounts can create bewildering complexity

Fragile

- Scale
- Dynamics
- Nonlinearity
- Nonequlibrium
- Open
- Feedback
- Adaptation
- Intractability
- Emergence
- …

Complex systems?

Robust

- Scale
- Dynamics
- Nonlinearity
- Nonequlibrium
- Open
- Feedback
- Adaptation
- Intractability
- Emergence
- …

Fragile

- Scale
- Dynamics
- Nonlinearity
- Nonequlibrium
- Open
- Feedback
- Adaptation
- Intractability
- Emergence
- …

Complex systems?

Robust complexity

- Scale
- Dynamics
- Nonlinearity
- Nonequlibrium
- Open
- Feedback
- Adaptation
- Intractability
- Emergence
- …

- Resources
- Controlled
- Organized
- Structured
- Extreme
- ***Architected***
- …

New words

Emergulent

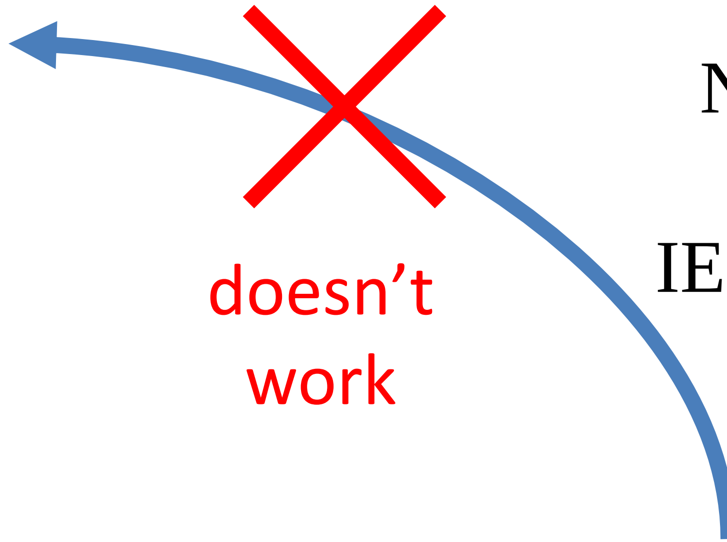
Emergulence at the edge of chaocritiplexity

Fragile complexity

- Scale
- Dynamics
- Nonlinearity
- Nonequlibrium
- Open
- Feedback
- Adaptation
- Intractability
- Emergence
- …

Alderson & Doyle, Contrasting Views of Complexity and Their Implications for Network-Centric Infrastructure, IEEE TRANS ON SMC, JULY 2010

Complex networks



doesn't work

Stat physics

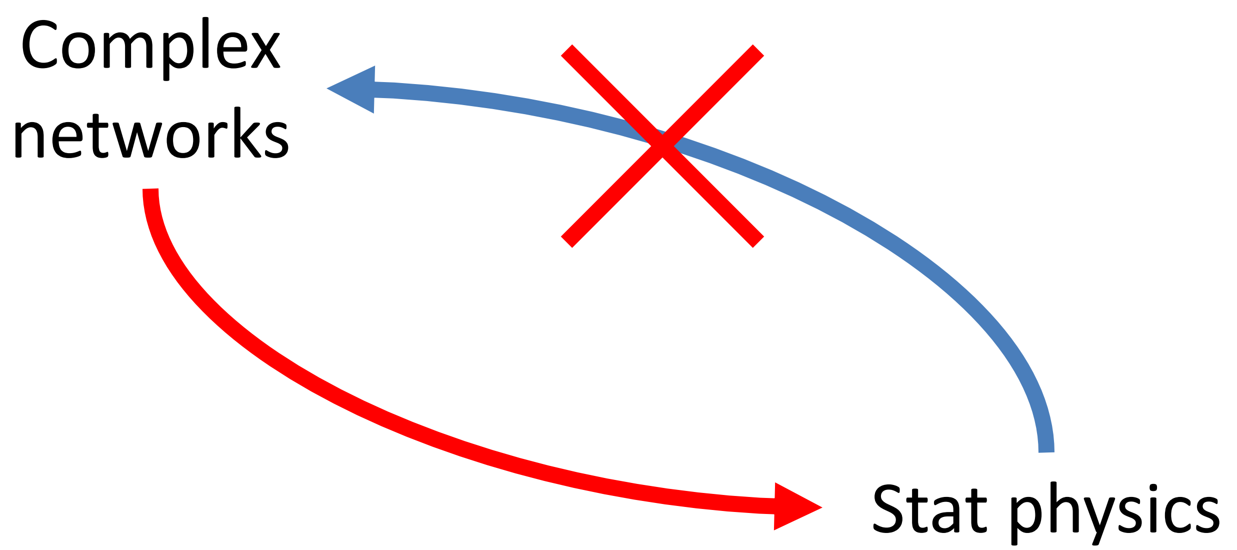
"New sciences" of complexity and networks

edge of chaos, self-organized criticality, scale-free,…

Complex systems?

Control

Comms



Compute

Carnot

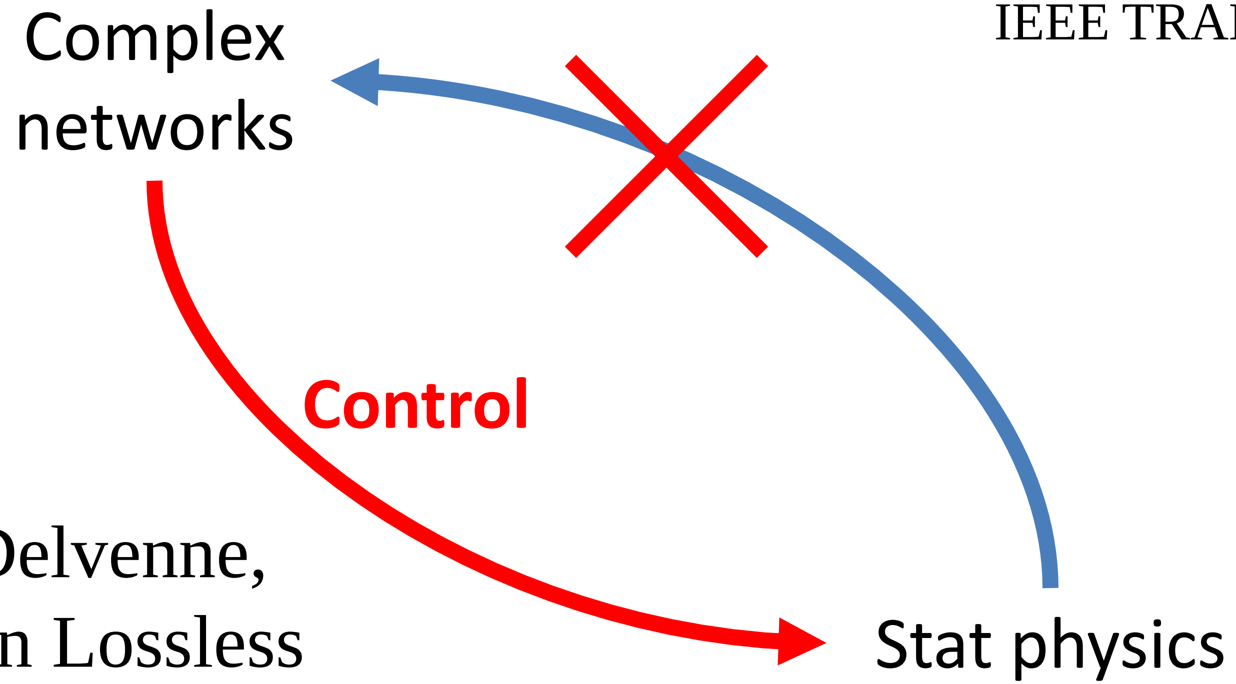
Boltzmann

Heisenberg

Jean Carlson, UCSB Physics

Physics

Alderson &Doyle, Contrasting Views of Complexity and Their Implications for Network-Centric Infrastructure, IEEE TRANS ON SMC, JULY 2010



Sandberg, Delvenne, & Doyle, On Lossless Approximations, the Fluctuation-Dissipation Theorem, and Limitations of Measurement, IEEE TRANS ON AC, FEBRUARY, 2011

Carnot

Boltzmann

Heisenberg

Physics

"The last 70 years of the 20th century will be viewed as the dark ages of theoretical physics." (Carver Mead)

Complex networks

"orthophysics"

From prediction to mechanism to control

Stat physics, fluids, QM

Carnot

Boltzmann

Heisenberg

Physics

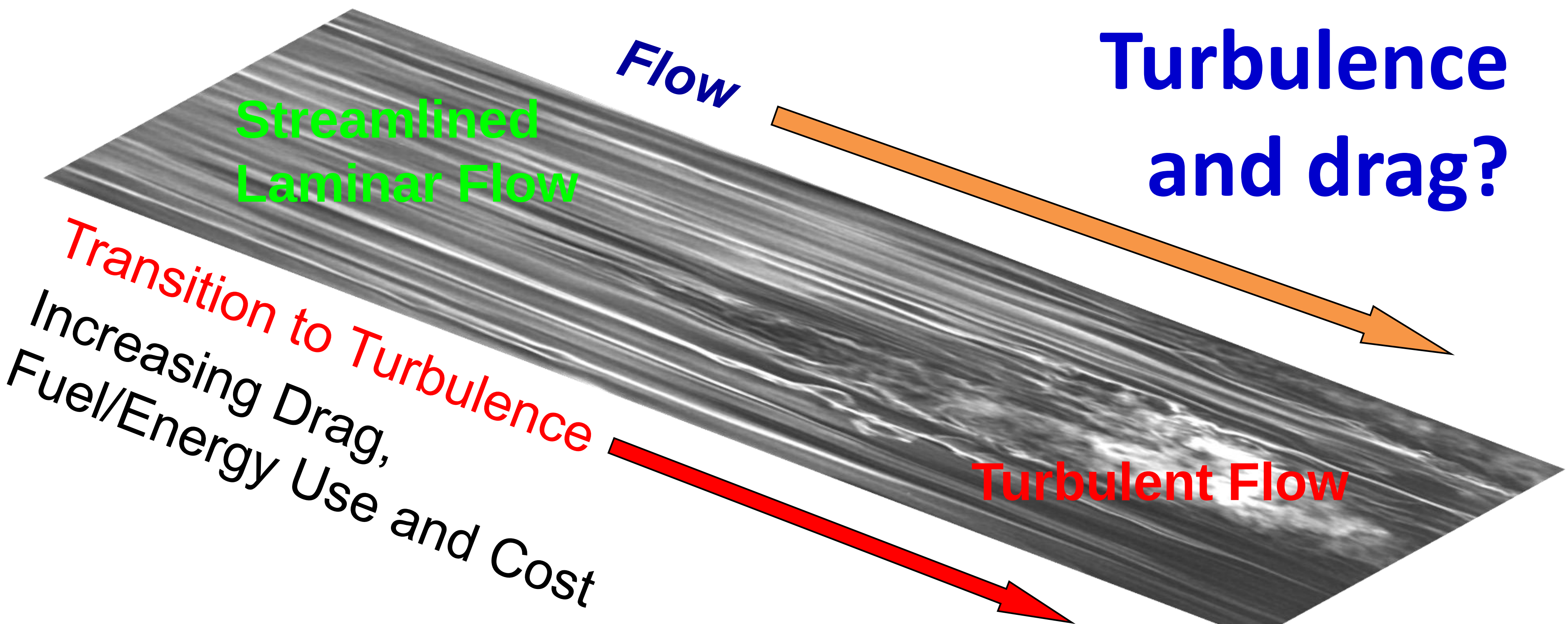
Sandberg, Delvenne, & Doyle, On Lossless Approximations, the Fluctuation-Dissipation Theorem, and Limitations of Measurement, IEEE TRANS ON AC, FEBRUARY, 2011

J. Fluid Mech. (2010), *vol.* 665, *pp.* 99–119. © Cambridge University Press 2010
doi:10.1017/S0022112010003861

J. Fluid Mech (2010)

A streamwise constant model of turbulence in plane Couette flow

D. F. GAYME[1]†, B. J. McKEON[1], A. PAPACHRISTODOULOU[2], B. BAMIEH[3] AND J. C. DOYLE[1]



Physics of Fluids (2011)

PHYSICS OF FLUIDS **23**, 065108 (2011)

Amplification and nonlinear mechanisms in plane Couette flow

Dennice F. Gayme,[1] Beverley J. McKeon,[1] Bassam Bamieh,[2] Antonis Papachristodoul
and John C. Doyle[3]

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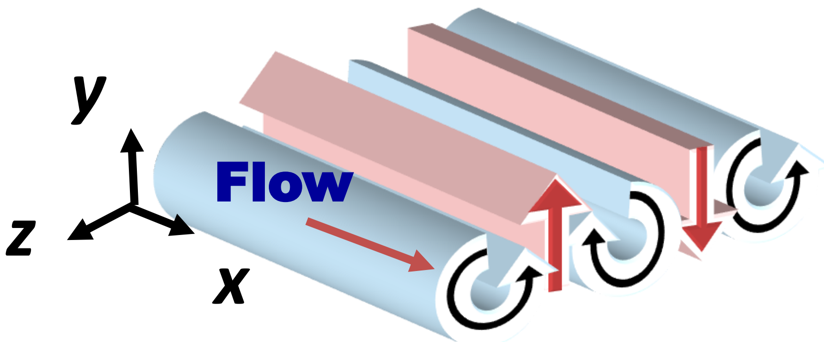
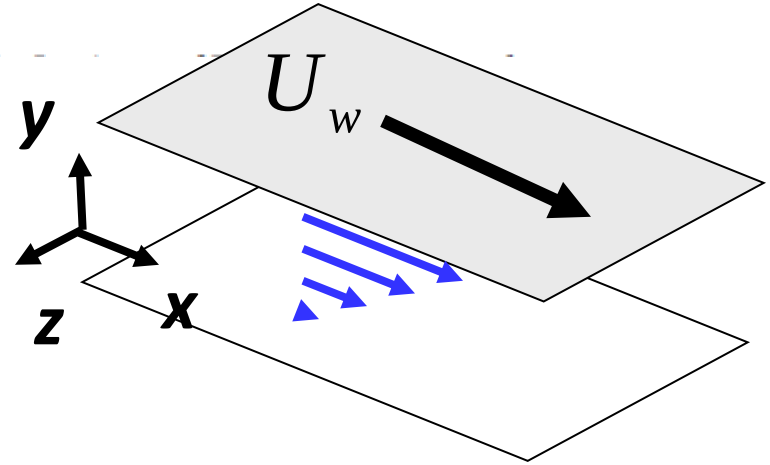
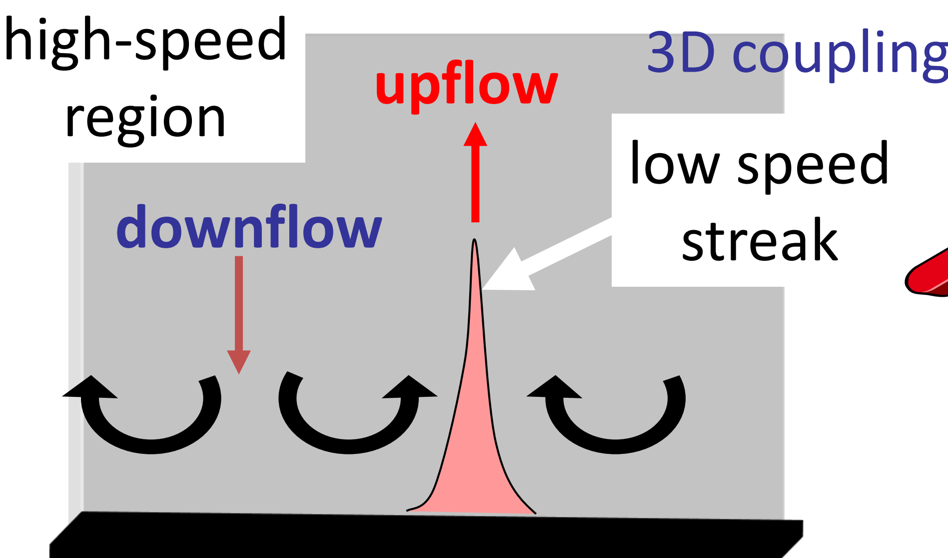
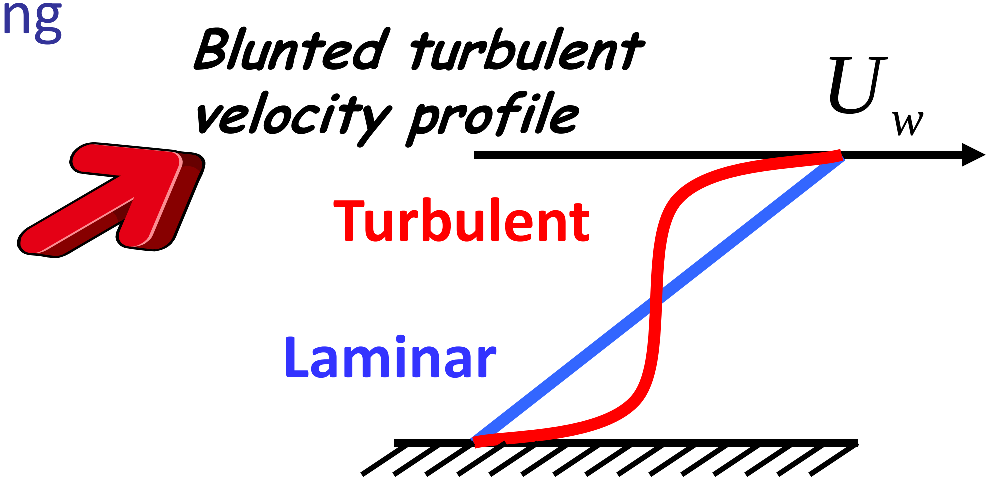
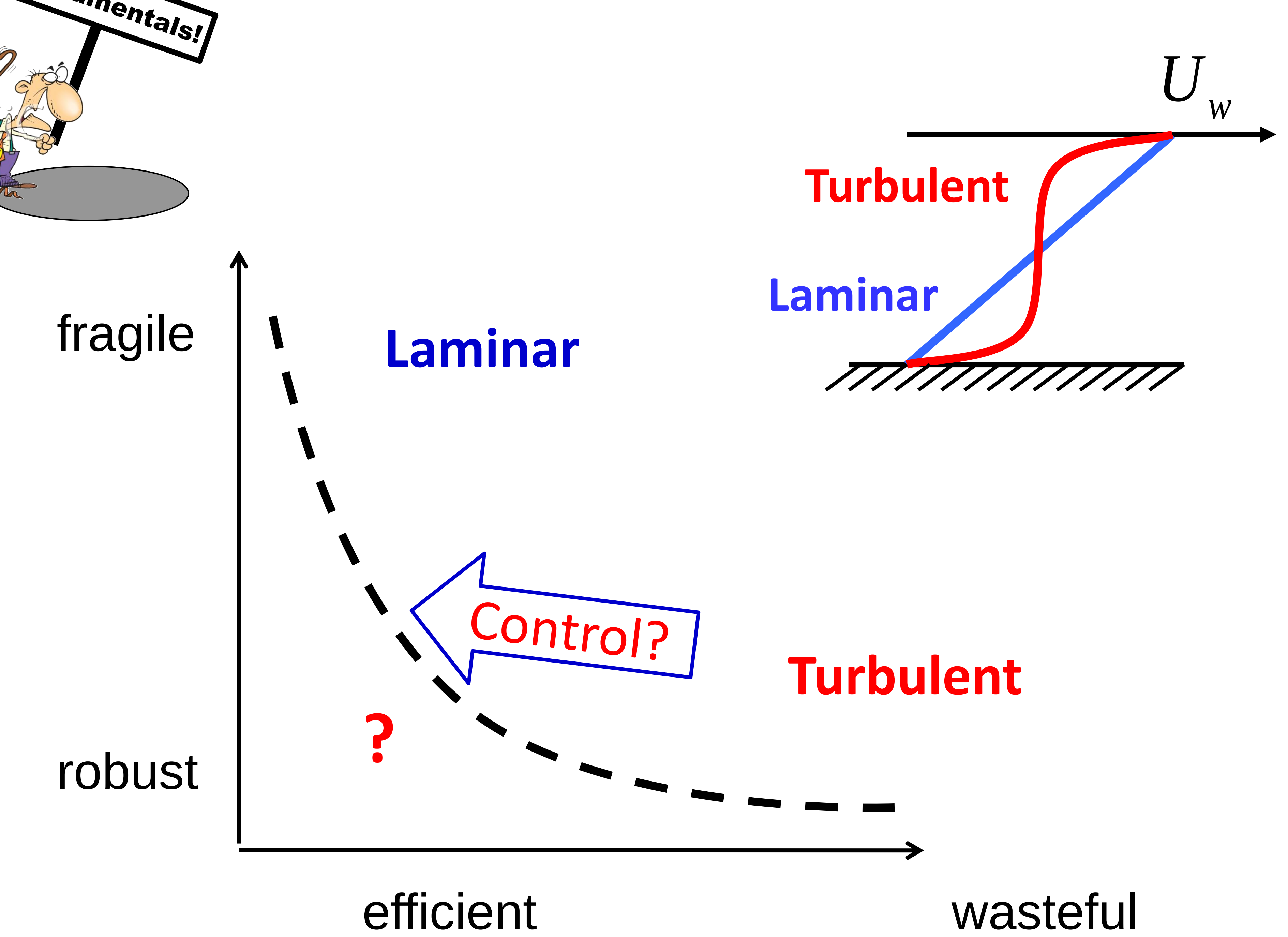




Coherent structures and turbulent drag







U_w
Turbulent
Laminar
fragile
Laminar
Control?
?
Turbulent
robust
efficient
wasteful

Existing design frameworks

- Sophisticated components
- Poor integration
- Limited theoretical framework