# **Universal laws and architecture 2:**

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 again

### Lectures

# Concrete motivation Universal laws and architectures\*

4) A teensy bit of math

\*have you ever heard of anything more pretentious?

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**.

# Architecture, constraints, and behavior

Very accessible No math

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

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

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

This paper aims to bridge progress in neuroscience involving sophisticated quantitative analysis of behavior, including the use of robust control, with other relevant conceptual and theoretical frameworks from systems engineering, systems biology, and mathematics. Familiar and accessible case studies are used to illustrate concepts of robustness, organization, and architecture (modularity and protocols) that are central to understanding complex networks. These essential organizational features are hidden during normal function of a system but are fundamental for understanding the nature, design, and function of complex biologic and technologic systems. evolved for sensorimotor control and retain much of that evolved architecture, then the apparent distinctions between perceptual, cognitive, and motor processes may be another form of illusion (9), reinforcing the claim that robust control and adaptive feedback (7, 11) rather than more conventional serial signal processing might be more useful in interpreting neurophysiology data (9). This view also seems broadly consistent with the arguments from grounded cognition that 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

#### Lectures

# Concrete motivation (recap) Universal laws and architectures\* A teensy bit of math

\*have you ever heard of anything more pretentious?

# Human complexity

# Robust

# Yet Fragile

- Metabolism
- Regeneration & repair
- Immune/inflammation
- ③ Microbe symbionts
- Seuro-endocrine
- Complex societies
- Advanced technologies
- Risk "management"

- Obesity, diabetes
- Cancer
- AutoImmune/Inflame
- Parasites, infection
- ⊗ Addiction, psychosis,...
- Epidemics, war,...
- ♦ Obfuscate, amplify,...

# Accident or necessity?

# **Human complexity**

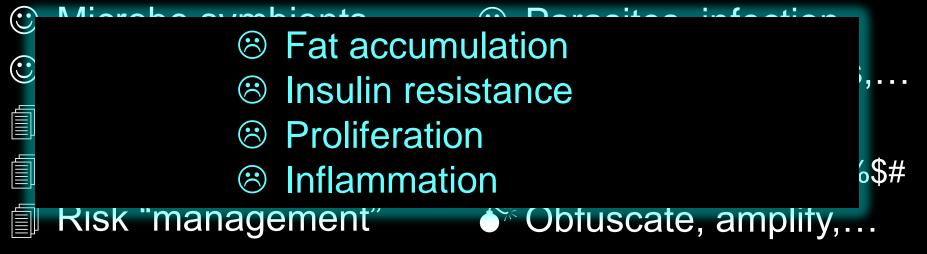
## Robust

# Yet Fragile

- ③ Metabolism
- Regeneration & repair
- Immune/inflammation



- Cancer
- AutoImmune/Inflame



# Accident or necessity?

# Robust

Metabolism

#### Fragile Obesi<u>ty, diabetes</u>

- Segenerati
- Healing wo
- Set accumulation

 $\odot$ 

- Insulin resistance
- Proliferation
- Inflammation

une/Inflame

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

# Both

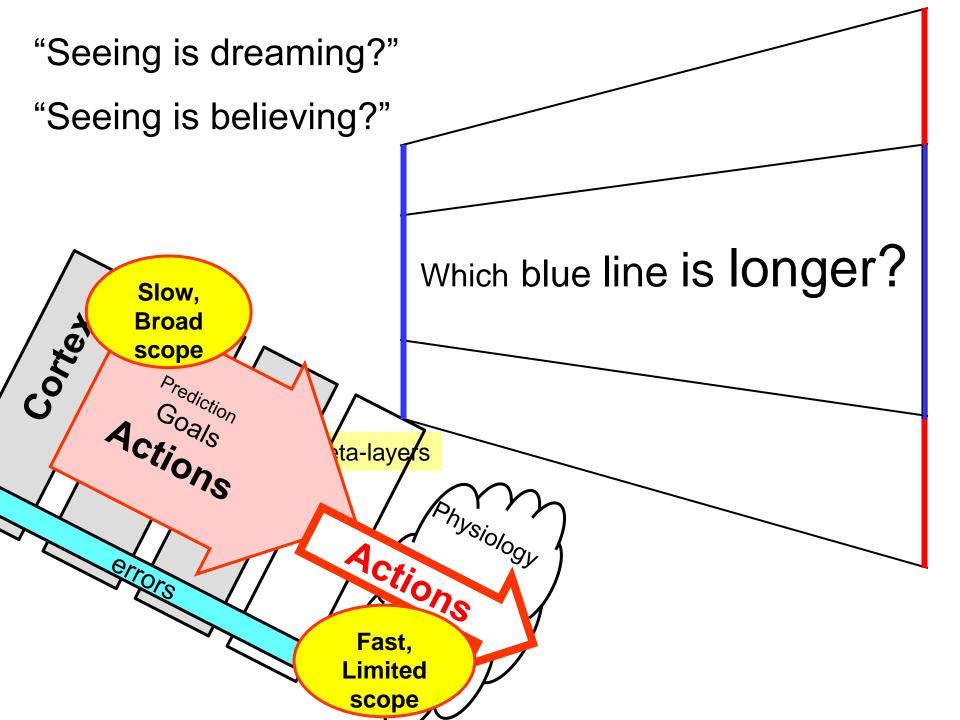
Accident or necessity?

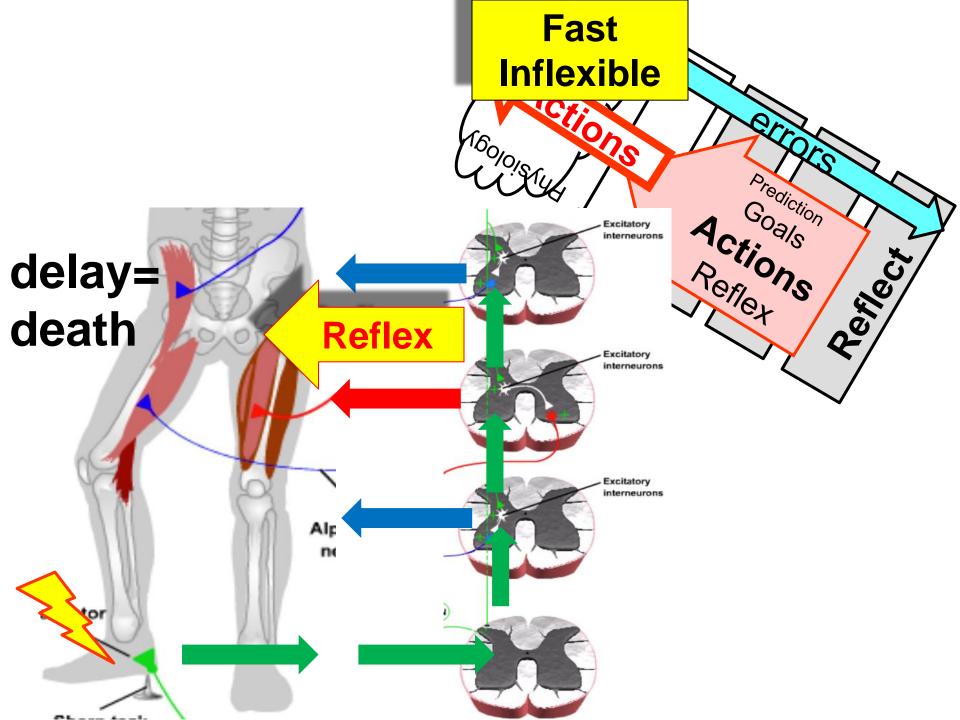


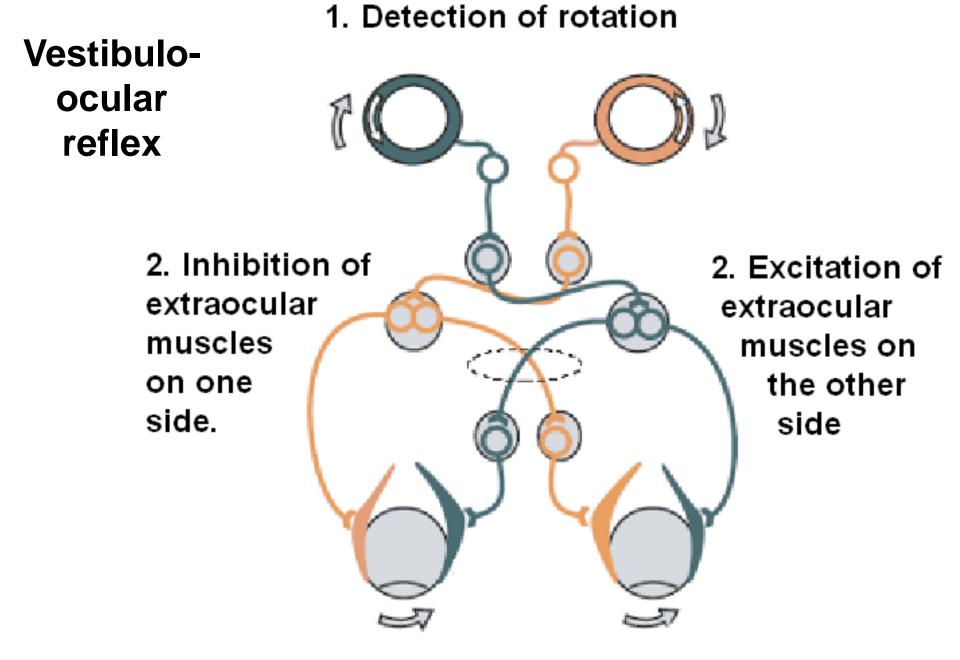
Robust Modular Simple Plastic Evolvable Fragile Distributed Complex Frozen Frozen

tradeoffs

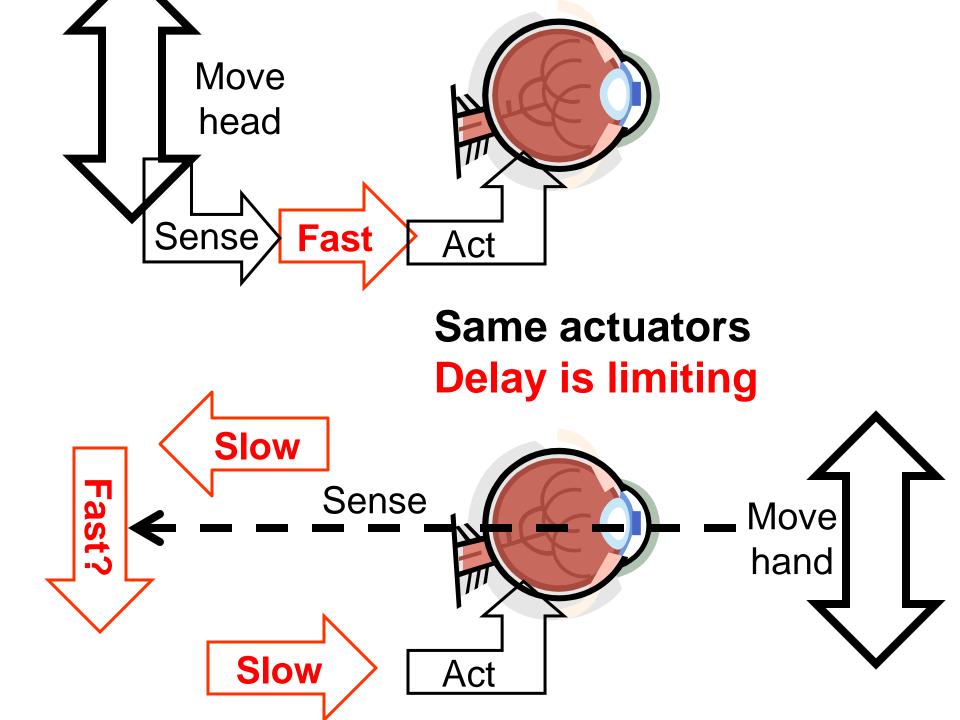
and







3. Compensating eye movement



#### Reflect

Control Loop Feed-Back Differential Descending Neural Radiations to the Hippocampus/ mus/hypothalamus

Corpus Callosum Thalamus

> Pineal Gland Hippocampus

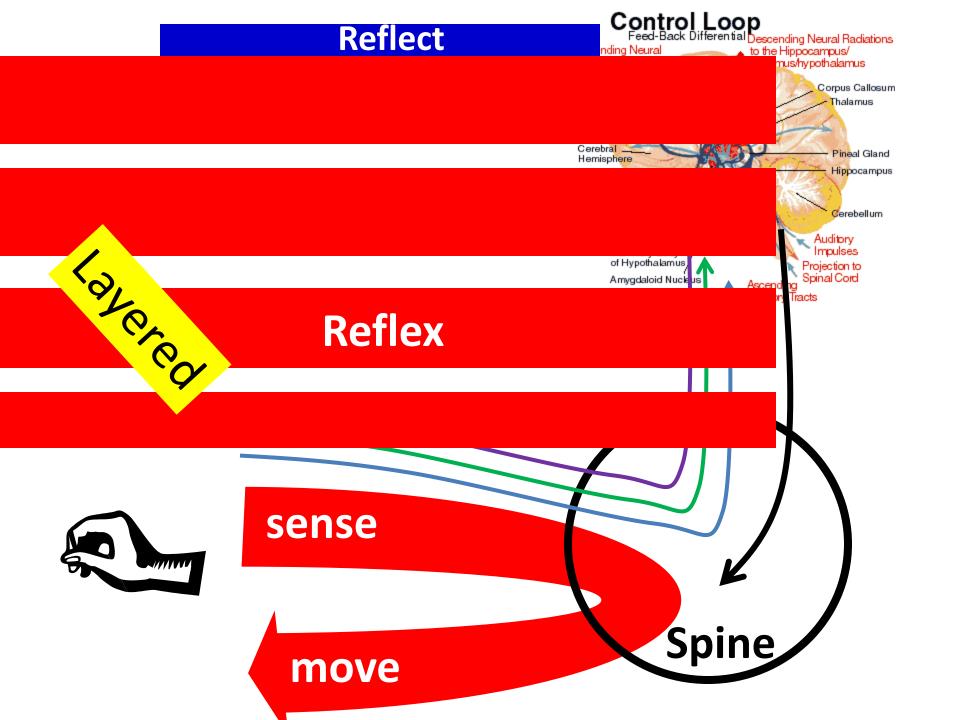
Cerebellum

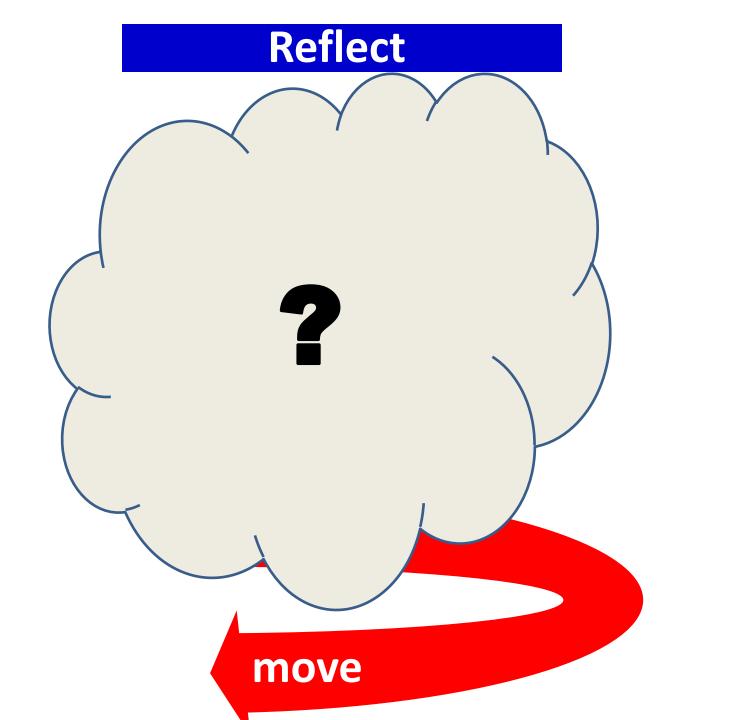
Auditory Impulses

Projection to Spinal Cord

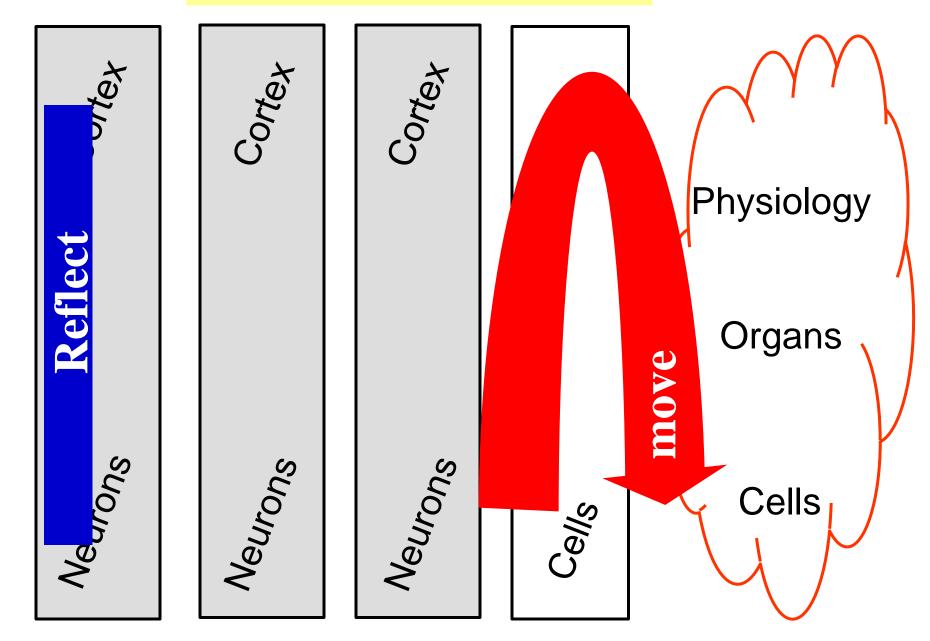
ng Tracts

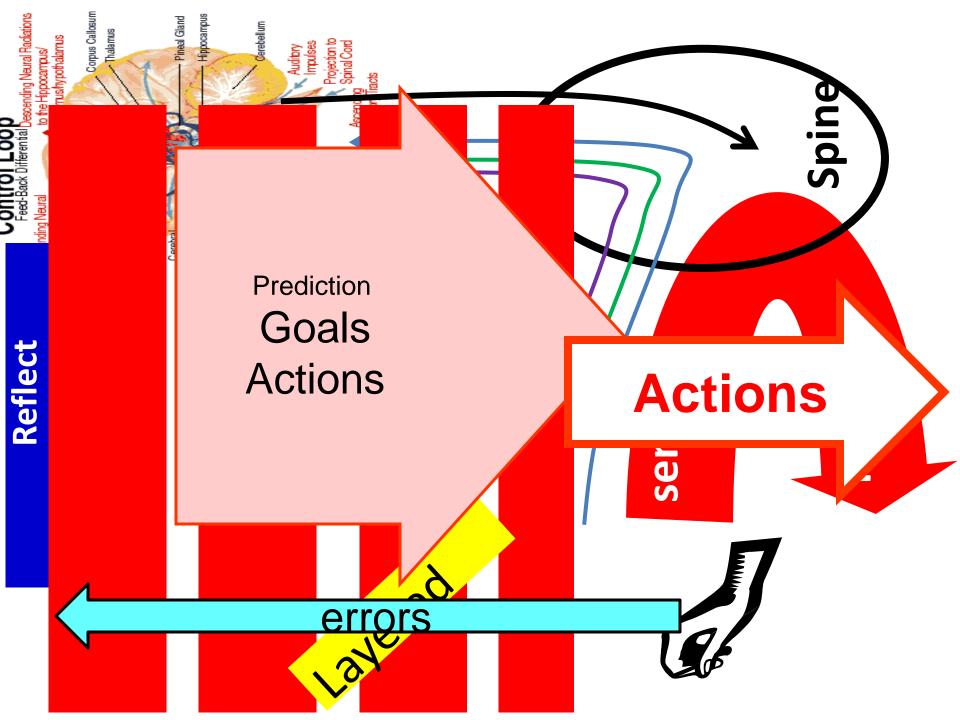
## **Reflex**



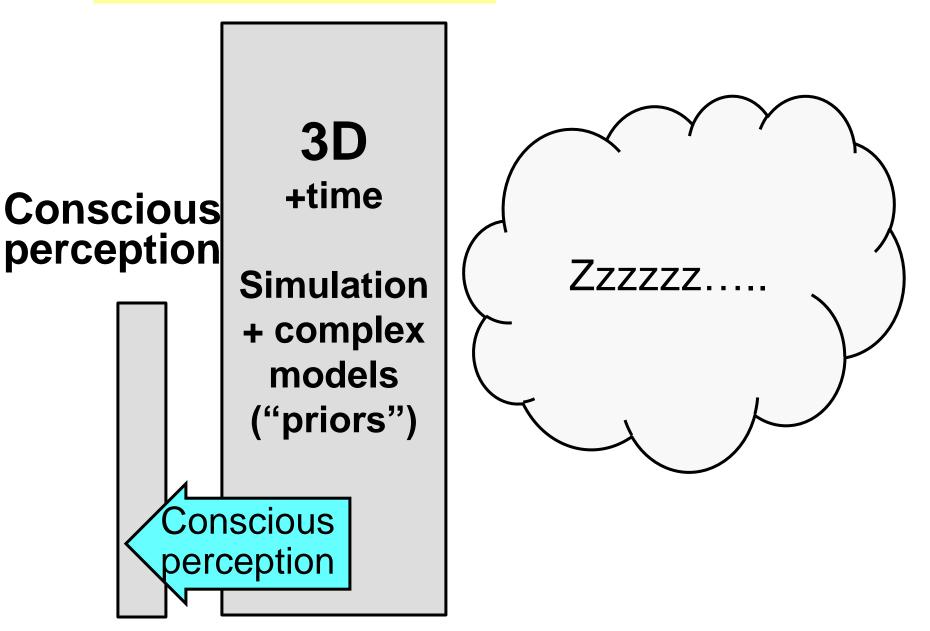


## **Layered architectures**

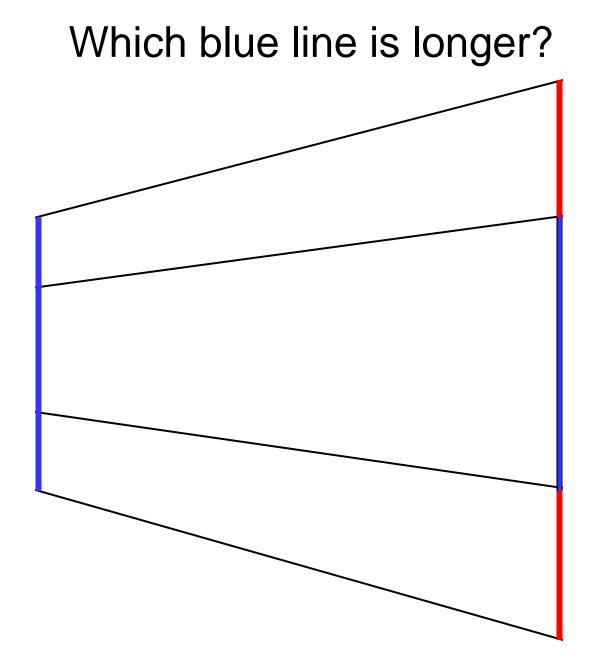


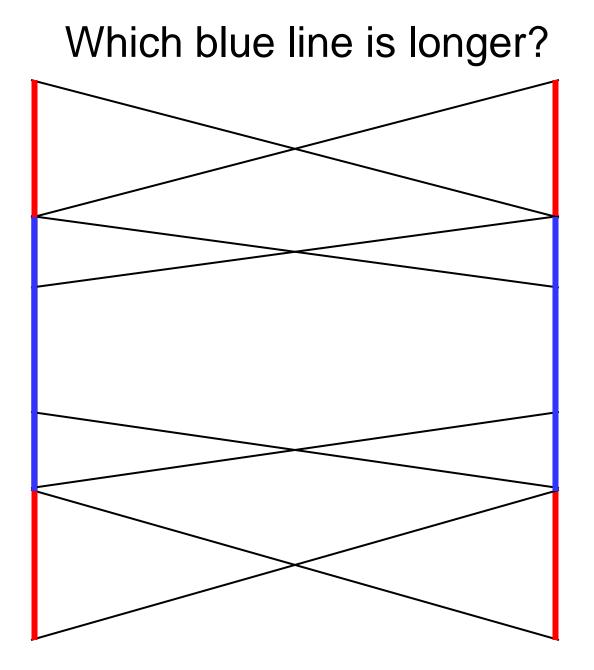


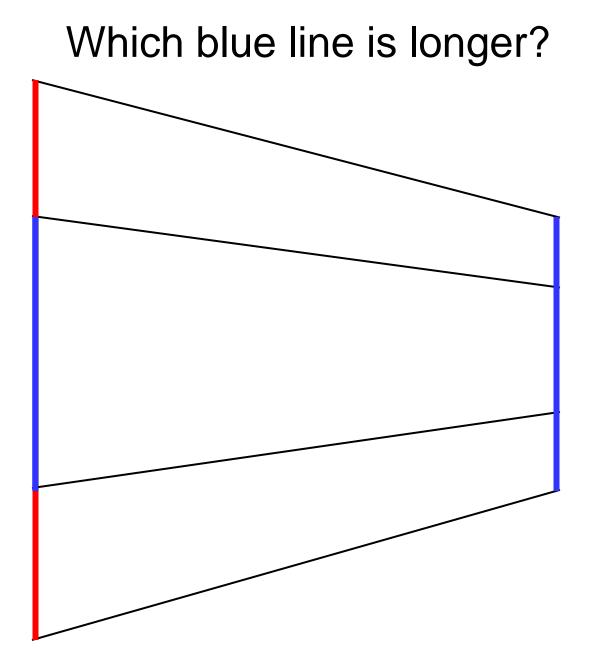
# Seeing is *dreaming*



### Which blue line is longer?





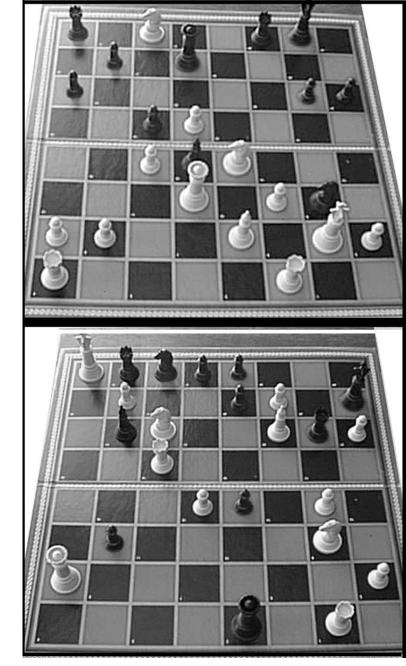




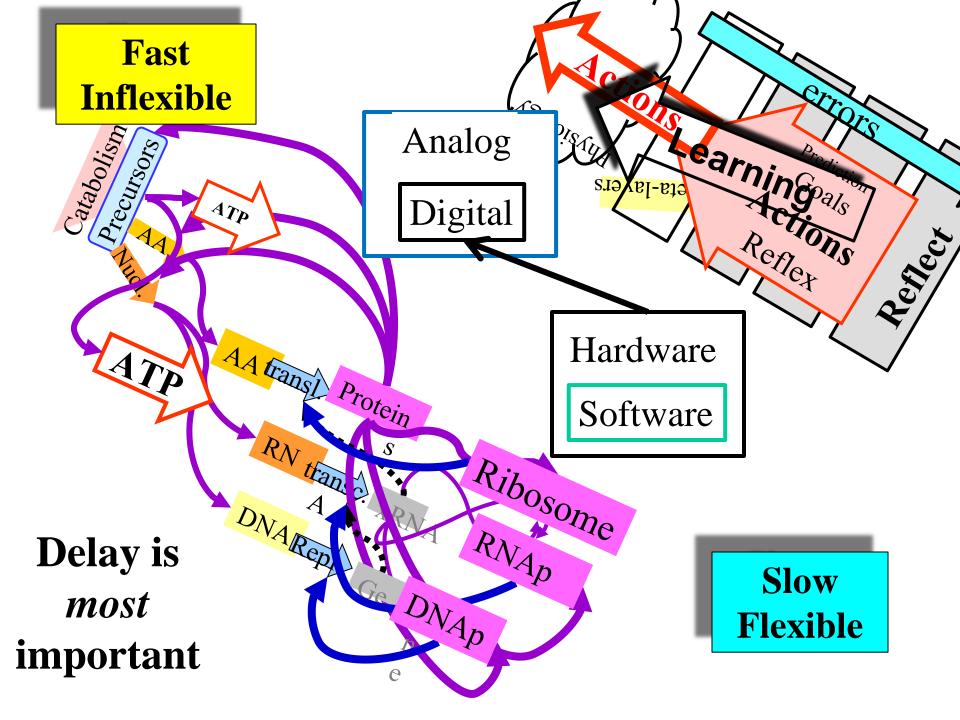
## **Chess experts**

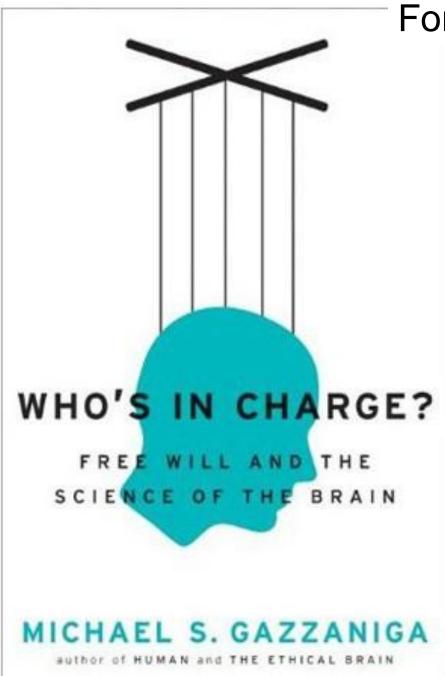
- can reconstruct entire chessboard with < ~ 5s inspection
- can recognize 1e5 distinct patterns
- can play multiple games
   blindfolded and simultaneous
- are no better on random boards

(Simon and Gilmartin, de Groot)



www.psywww.com/intropsych/ch07\_cognition/expertise\_and\_domain\_specific\_knowledge.html





For more



#### INCOGNITO

OF THE BRAIN

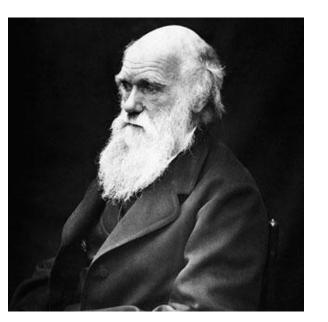
DAVID EAGLEMAN

AUTHOR OF SUM

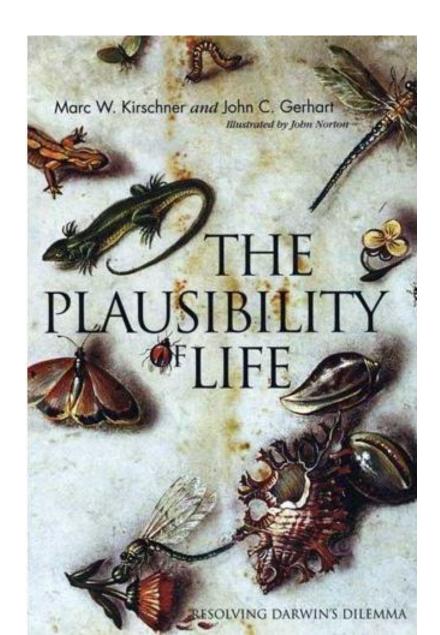
#### Evolution

Facilitated variation

- Architecture =
  - Constraints that deconstrain
  - Weak linkage
  - Exploratory mechanisms
  - Compartmentalization



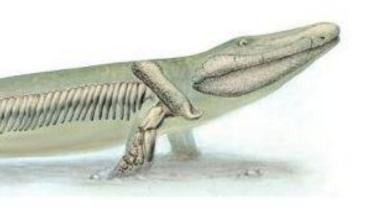
#### Kirschner and Gerhart



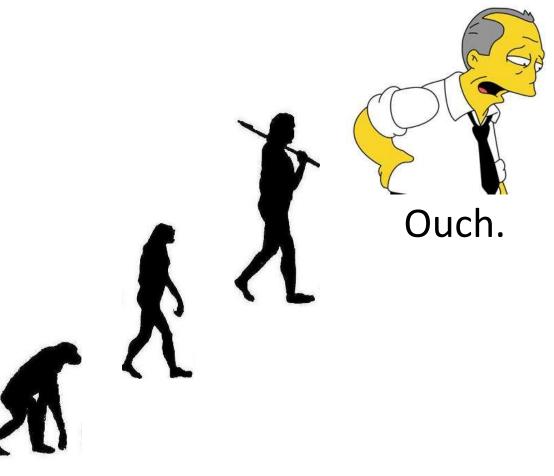
# Unfortunately, not intelligent design

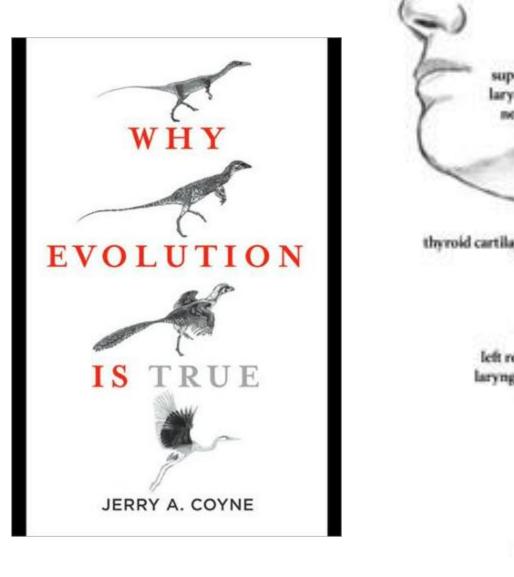
### YOUR INNER FISH

A JOURNEY INTO THE 3.5-BILLION-YEAR HISTORY OF THE HUMAN BODY



NEIL SHUBIN

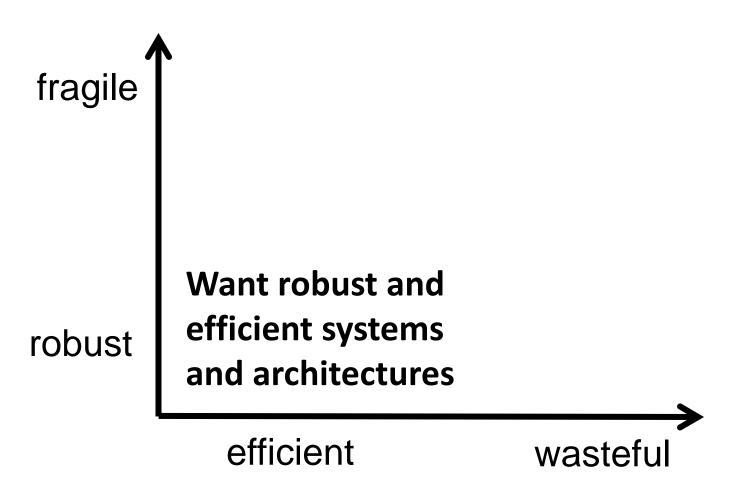




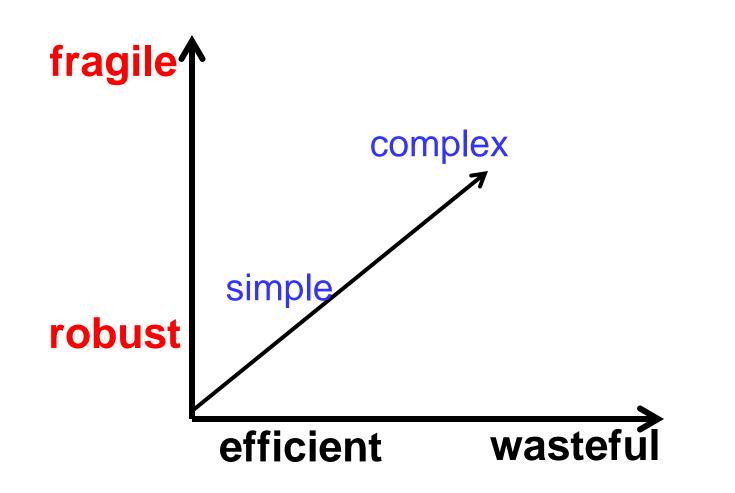
# superior laryngeal INTRO vagus nerve thyroid cartilage left recurrent laryngeal nerve

Making humans from fish parts.

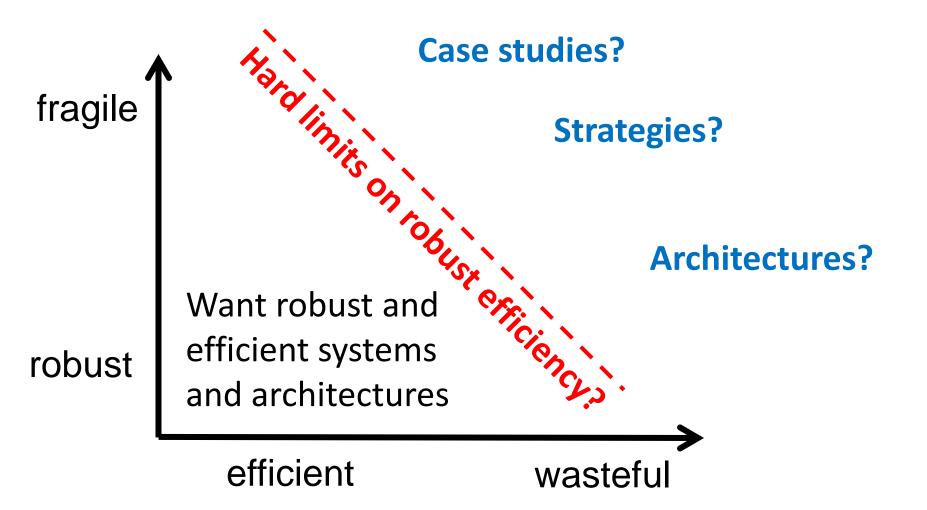
# Want to understand the space of systems/architectures

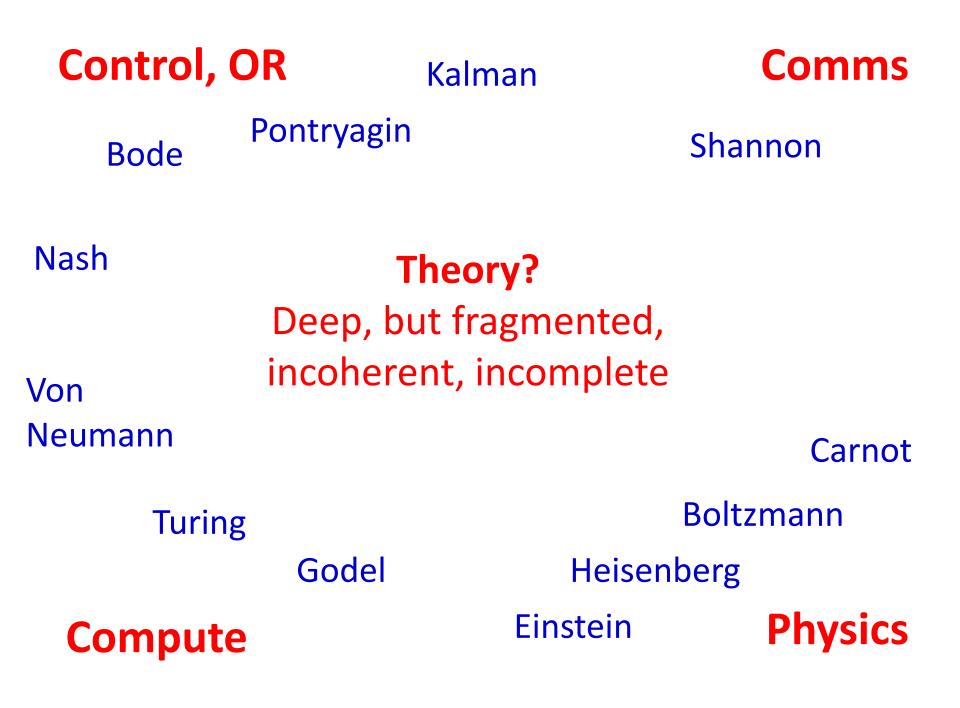


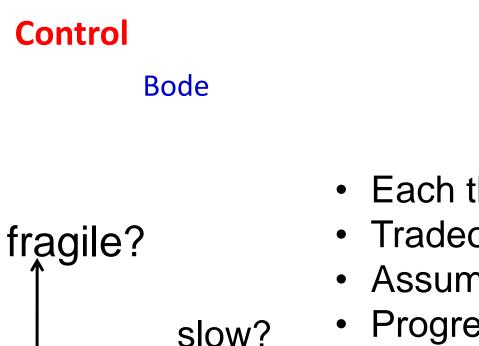
#### **Requirements on systems and architectures**



# Want to understand the space of systems/architectures

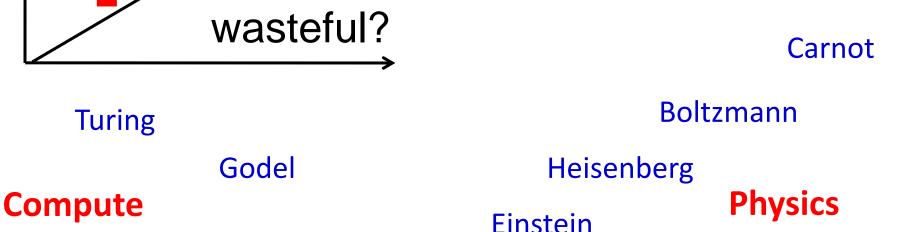








- Each theory  $\approx$  one dimension
- Tradeoffs *across* dimensions
- Assume architectures a priori
- Progress is encouraging, but...
- Stovepipes are an obstacle...



#### Glycolytic Oscillations and Limits on Robust Efficiency

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

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

#### Chandra, Buzi, and Doyle

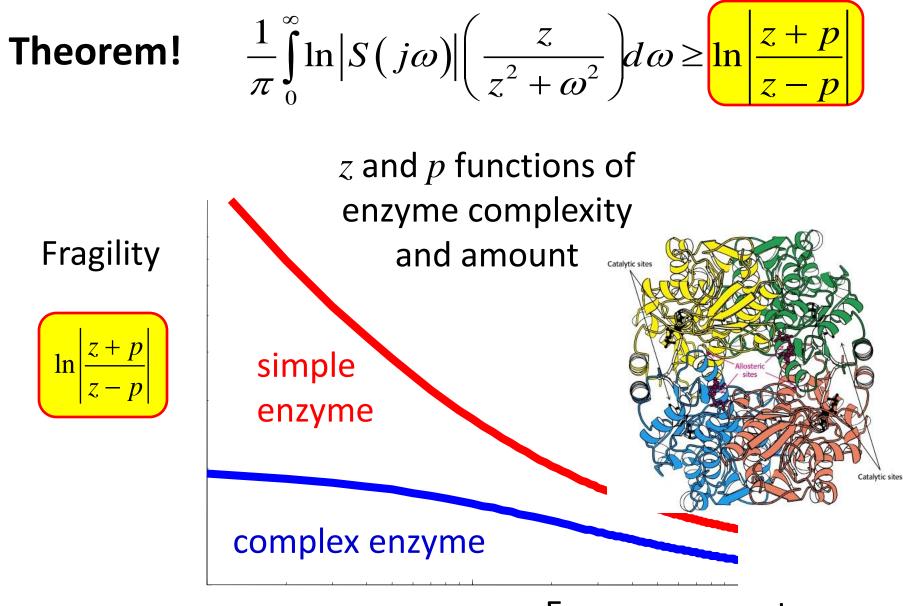
Most important paper so far.

#### UG biochem, math, control theory

the cen's use of ATF. In giveorysis, 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  $\overline{y} = 1$  and  $\overline{x} = 1/k$  [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



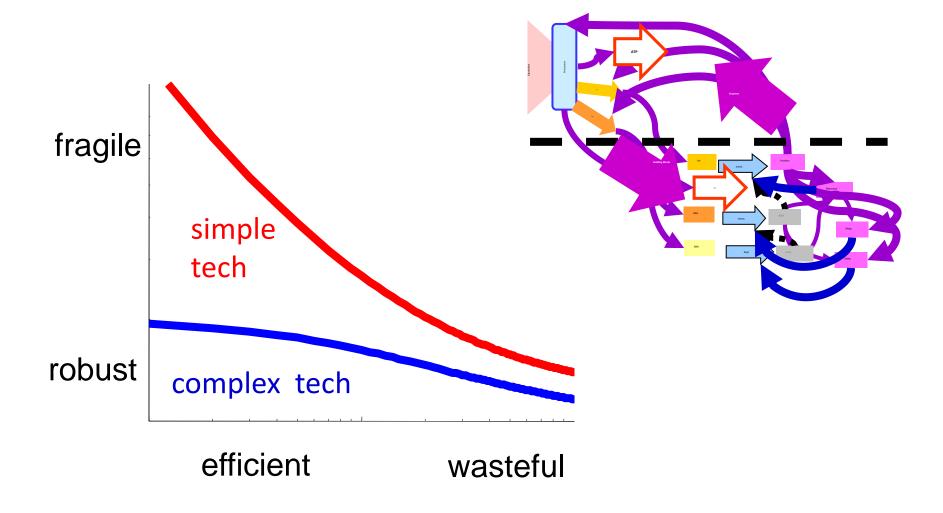
www.sciencemag.org SCIENCE VOL 333 8 JULY 2011

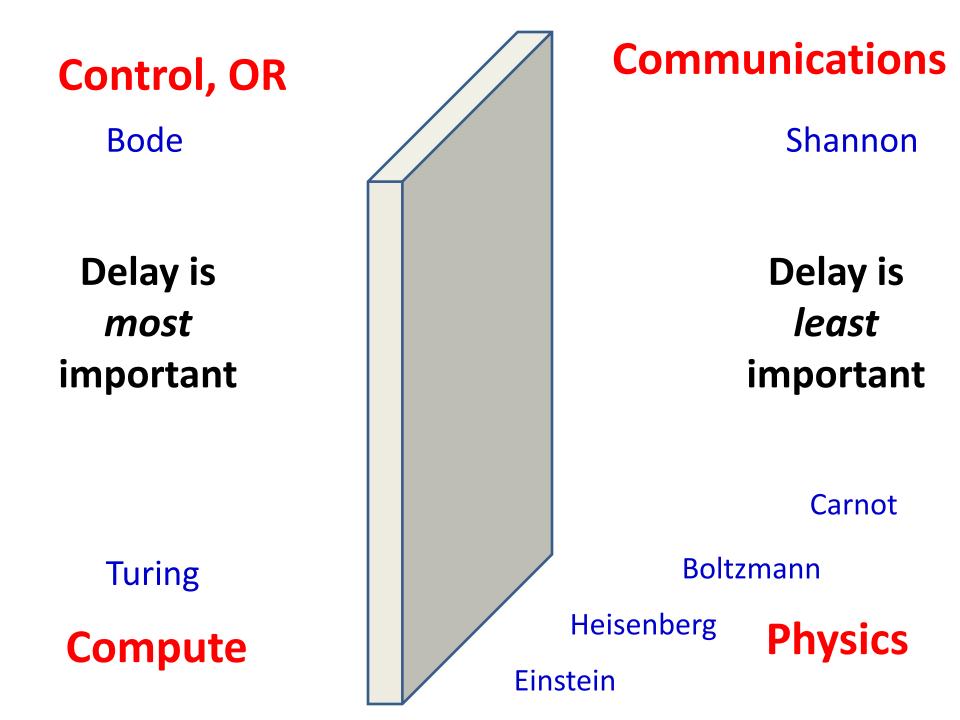


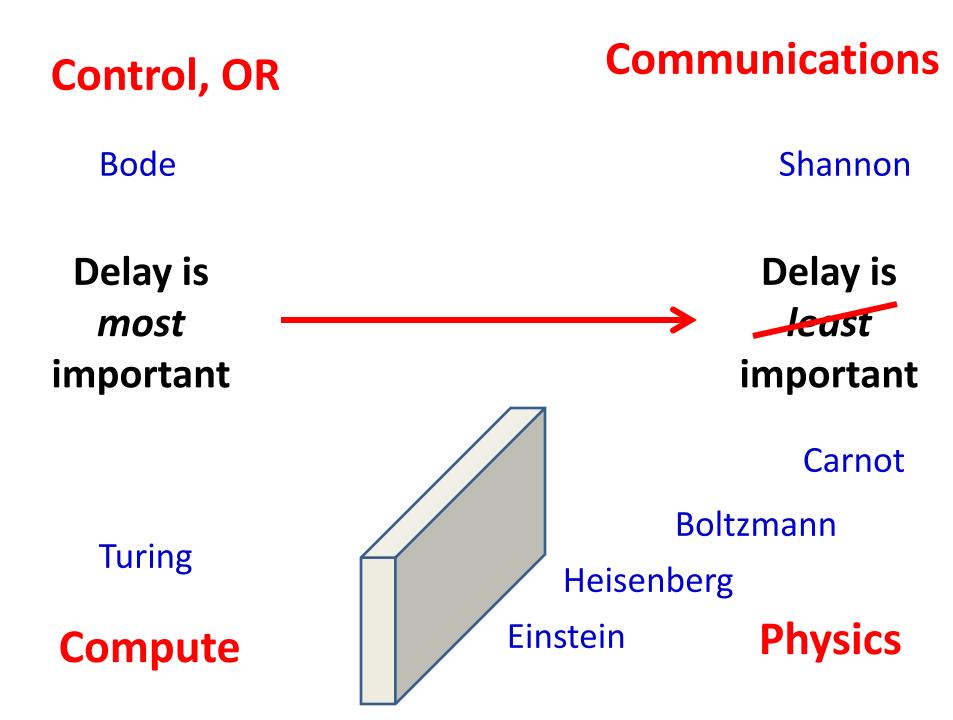
Enzyme amount

**Savageaumics** 

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







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

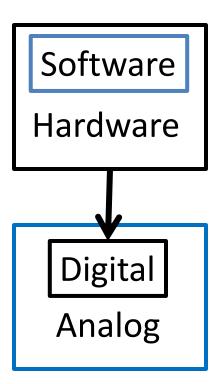
## Turing (1912-1954)





\*Also world-class runner.

Turing as "new" starting point?

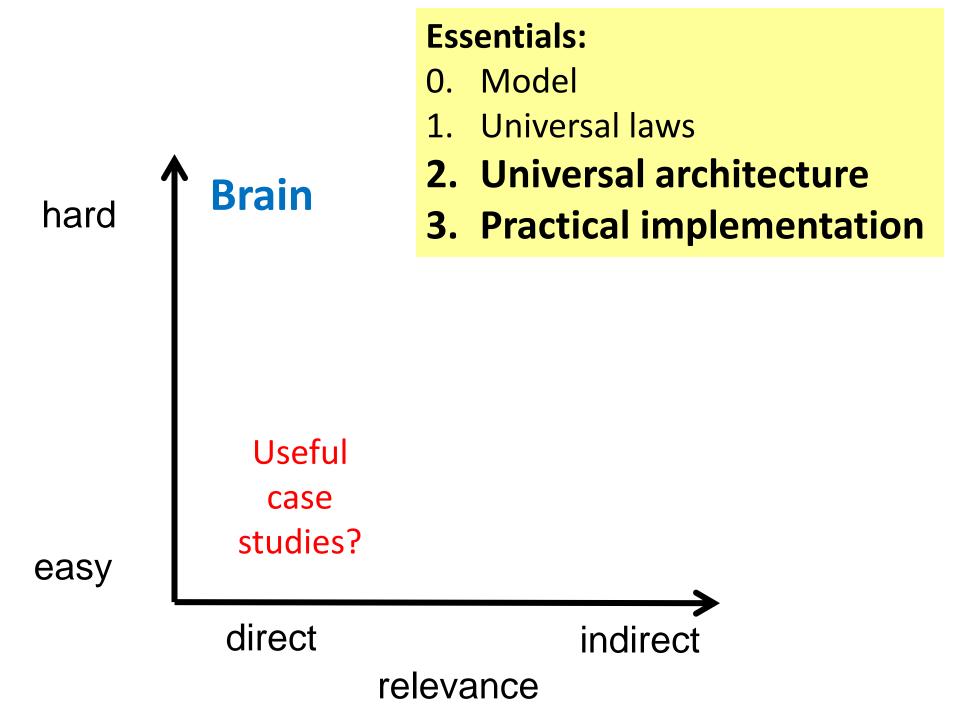


#### **Essentials:**

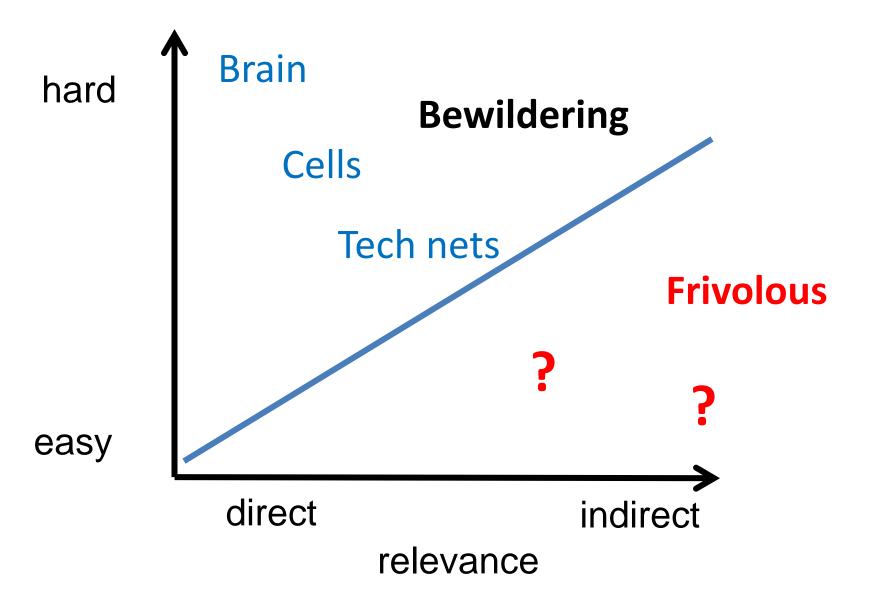
- 0. Model
- 1. Universal laws
- 2. Universal architecture
- 3. Practical implementation

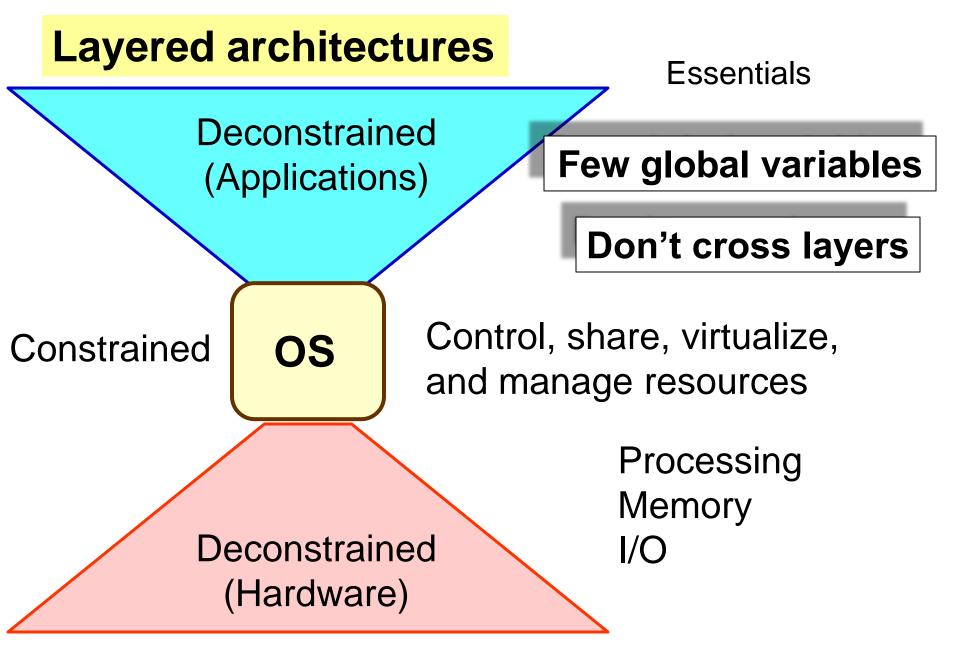
### Turing's 3 step research:

- 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?)



- 3. Universal architecture
- 4. Practical implementation





#### Layered architectures

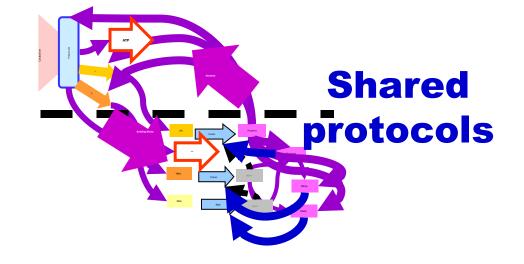
Deconstrained (diverse) Environments

# Bacterial biosphere

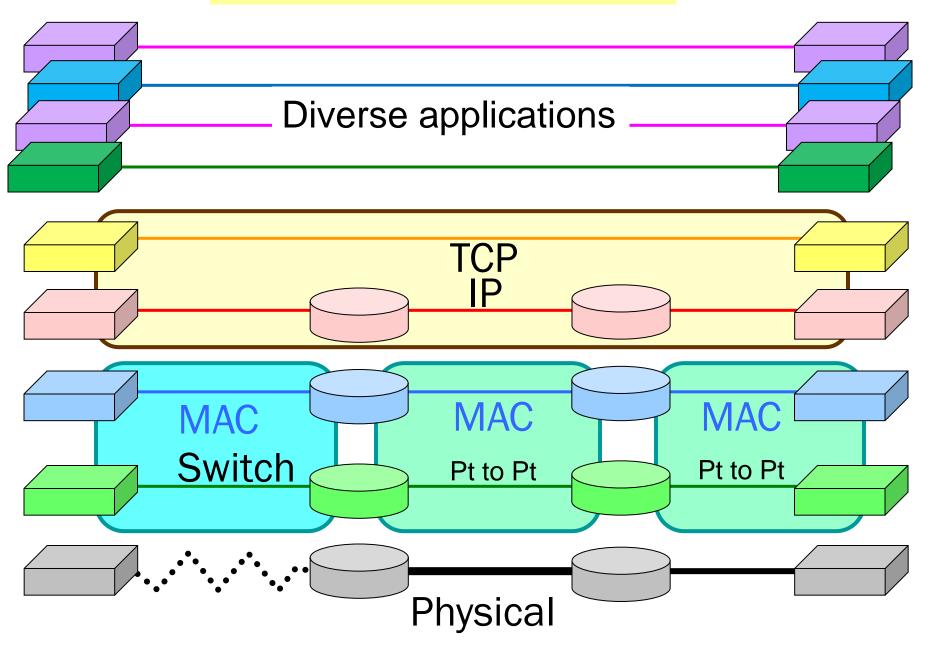
Architecture

Constraints that Deconstrain

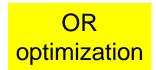
Deconstrained (diverse) Genomes



## **Layered architectures**



## Proceedings of the IEEE, Jan 2007



A rant

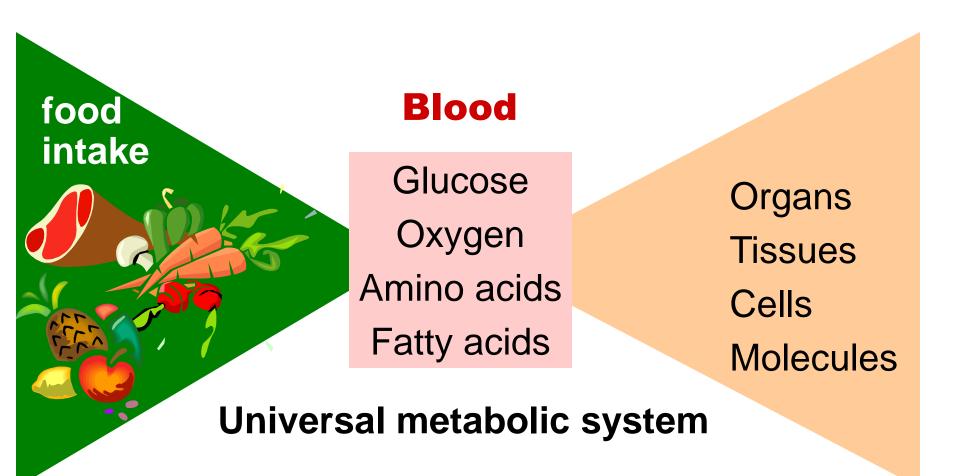
## Layering as Optimization Decomposition: A Mathematical Theory of Network Architectures

There are various ways that network functionalities can be allocated to an entails? 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 theoretical foundation for these architectural decisions in networking.

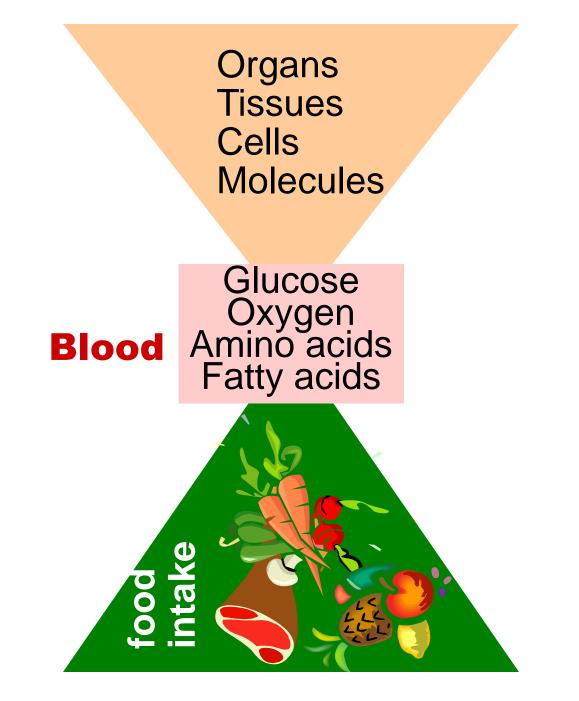
By MUNG CHIANG, Mombor IEEE, STEVEN H. LOW, Senior Mombor IEEE, A. ROBERT CALDERBANK, Fellow IEEE, AND JOHN C. DOYLE

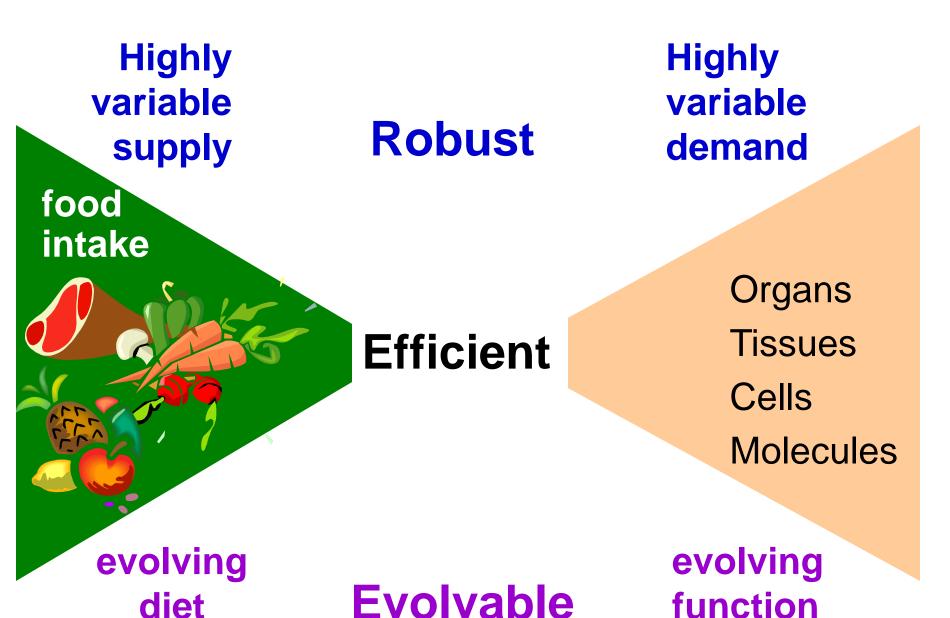
Chang, Low, Calderbank, Doyle

Peter Sterling and Allostasis



Organs Tissues Blood Cells Glucose Molecules Oxygen Amino acids food intake Fatty acids





Highly variable supply

food intake Conserved core building blocks

Glucose

Oxygen

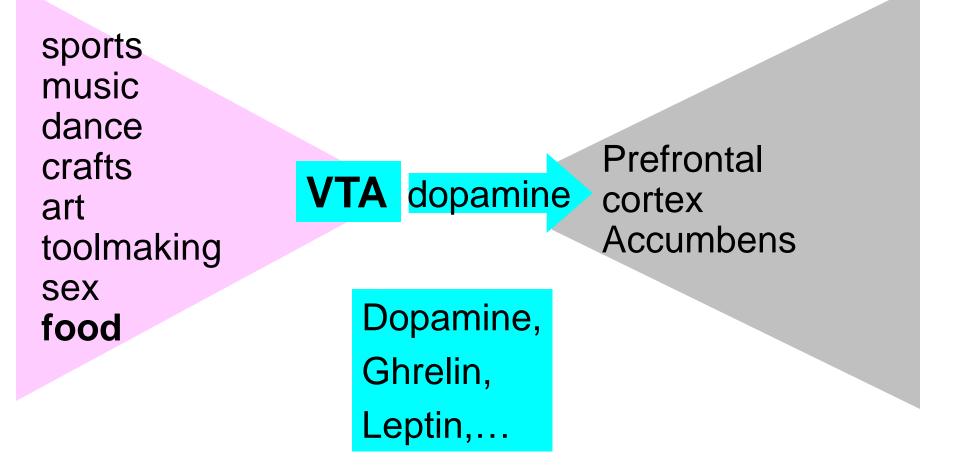
Highly variable demand

> Organs Tissues Cells Molecules

evolving diet Blood

evolving function

#### **Universal reward systems**

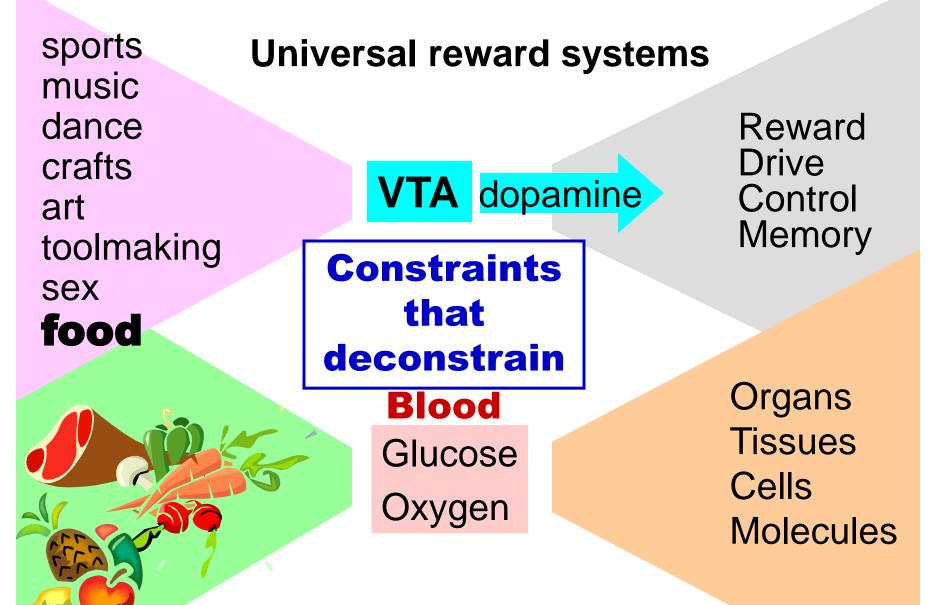


**Ridiculous oversimplification** 

#### **Universal reward systems**

sports music	PFC CG	Reward
dance crafts	OFC NAcc	Drive
art	VTA dopamine Amyg	Control
toolmaking sex	STR TH PIT	Memory
food	HIP	-
	SN	

#### **Robust and evolvable**



**Universal metabolic system** 

## Modularity 2.0





Blood

Glucose Oxygen

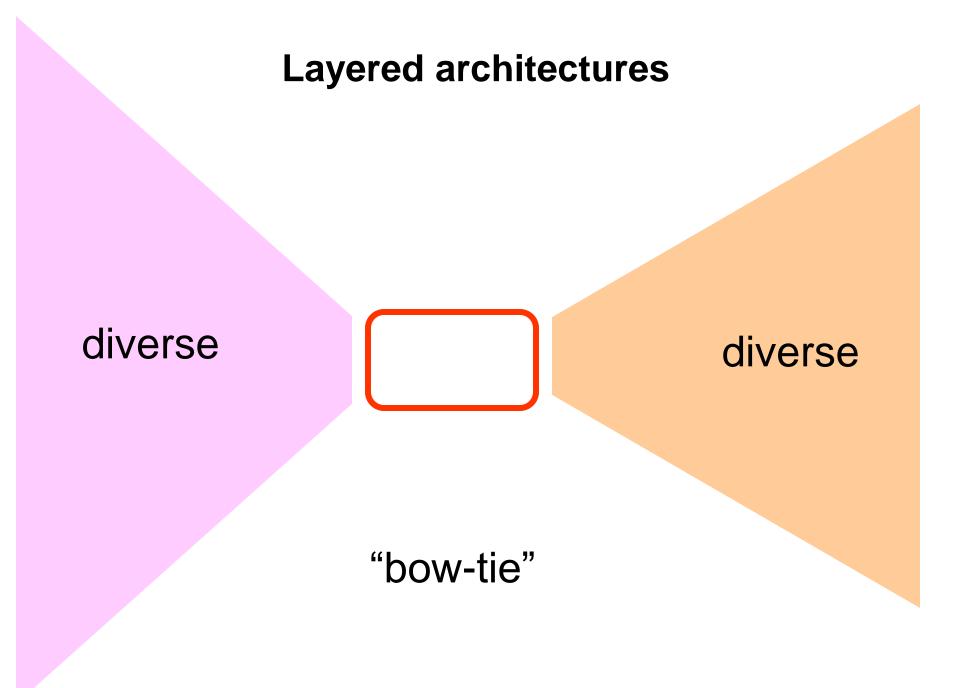
sports music dance crafts art toolmaking Sex food

# Modularity 2.0

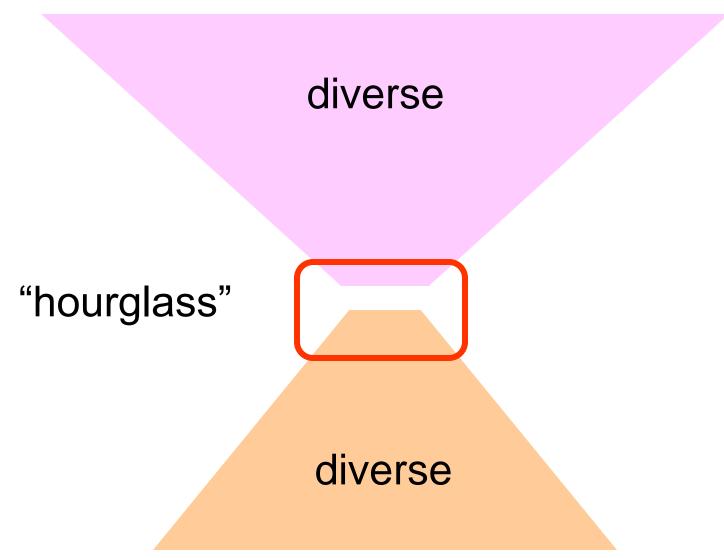
Reward Drive Control Memory

#### that deconstrain

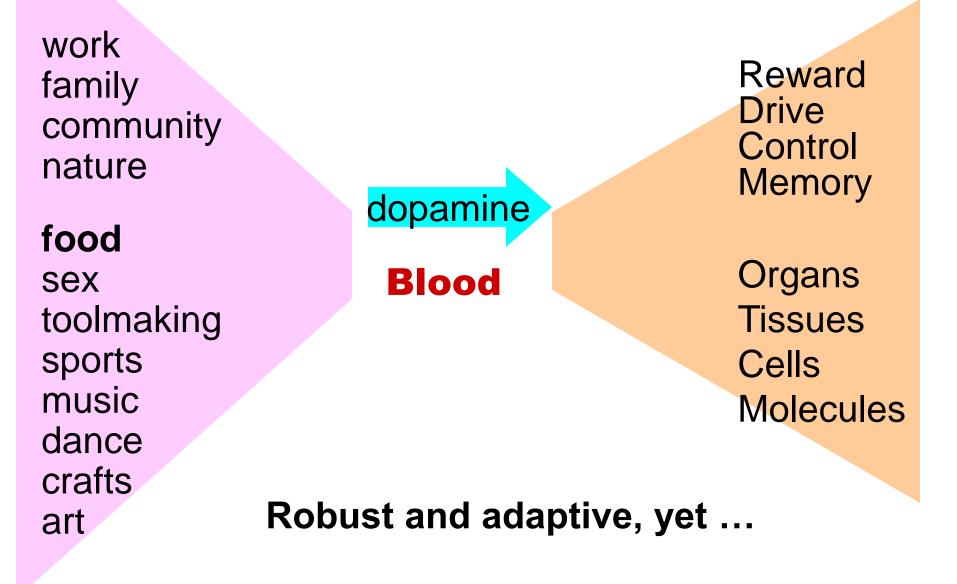
Organs Tissues Cells Molecules



#### Layered architectures



#### **Universal reward/metabolic systems**



## Modularity 1.0

- work family community nature
- food sex toolmaking sports music dance crafts art

Reward Drive Control Memory

Organs Tissues Cells Molecules

## "Weak linkage"

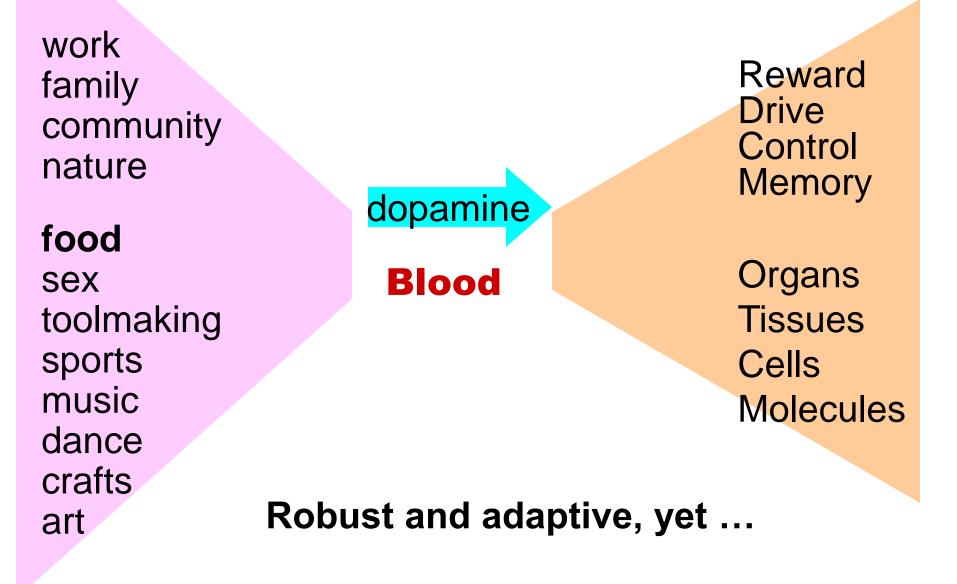
## Modularity 2.0

#### Most important "modules"



Not weakly connected to others, but highly connected

#### **Universal reward/metabolic systems**



work family community nature sex food toolmaking sports

music

dance

crafts

art

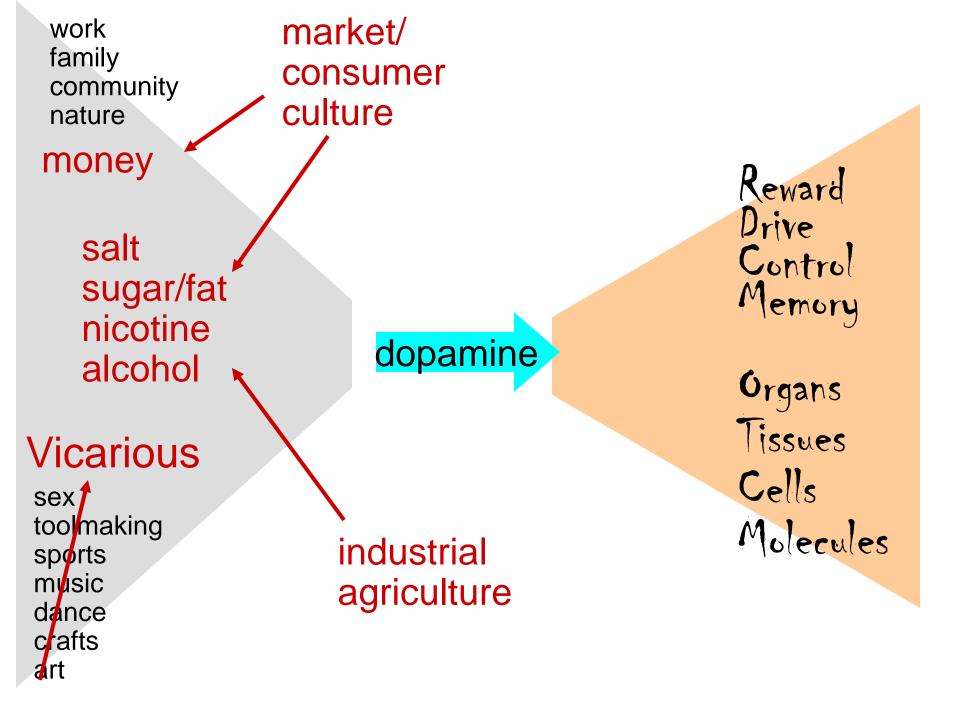
cocaine amphetamine

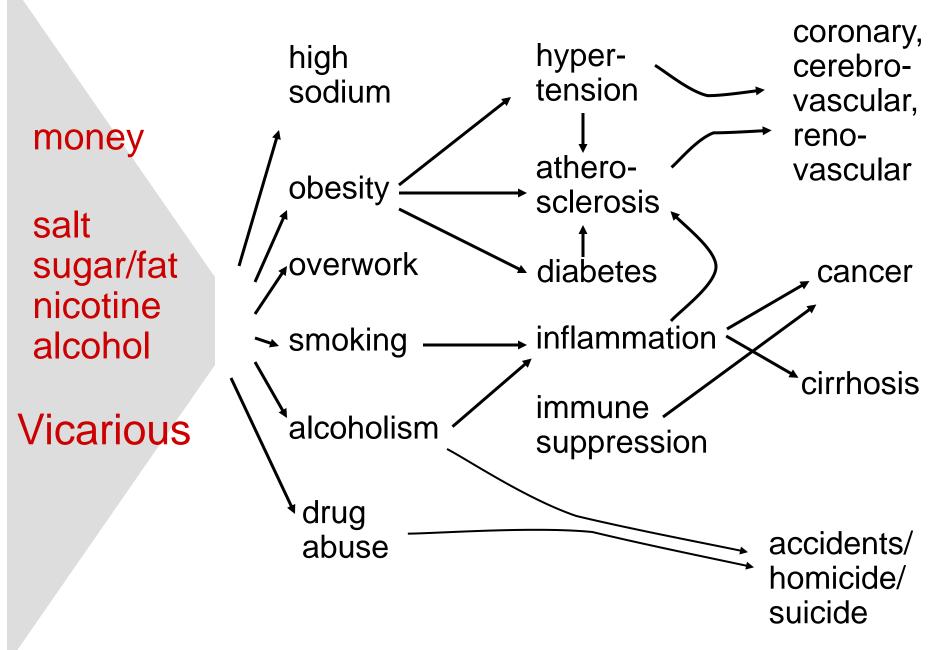
dopamine

Blood

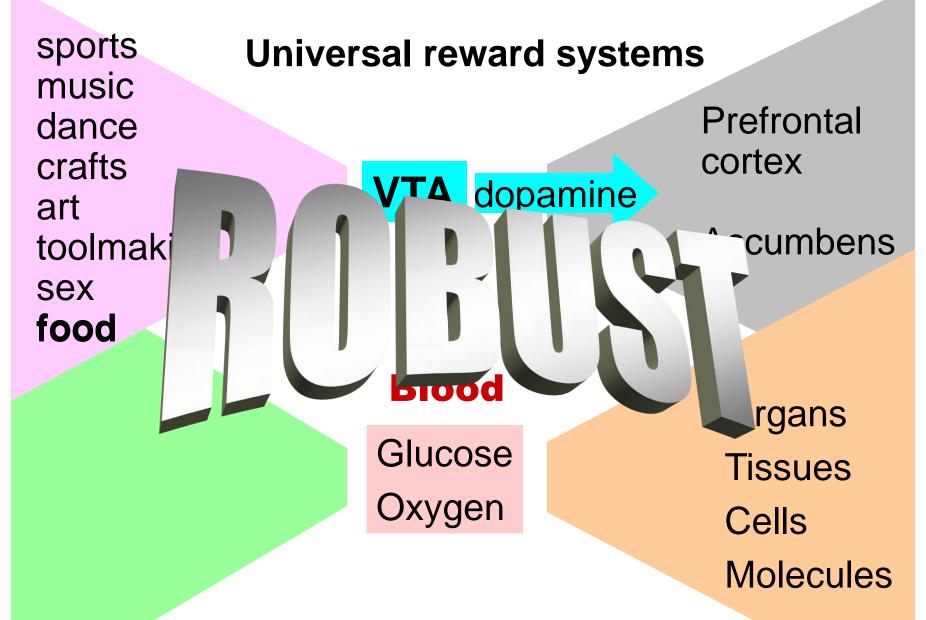
Reward Drive Control Memory

Organs Tissues Cells Molecules

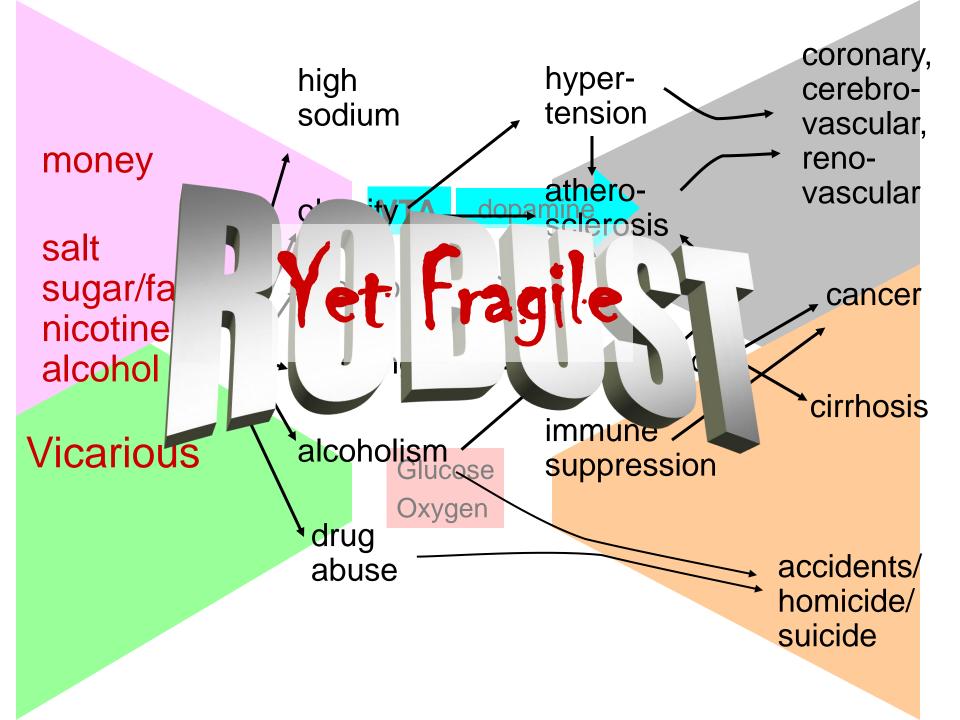




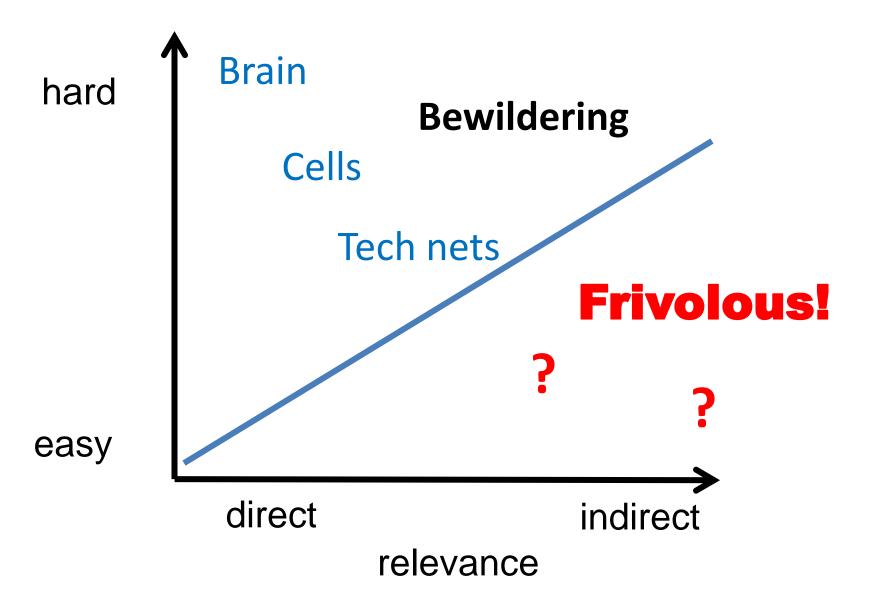
**From Sterling** 



**Universal metabolic system** 



- 3. Universal architecture
- 4. Practical implementation





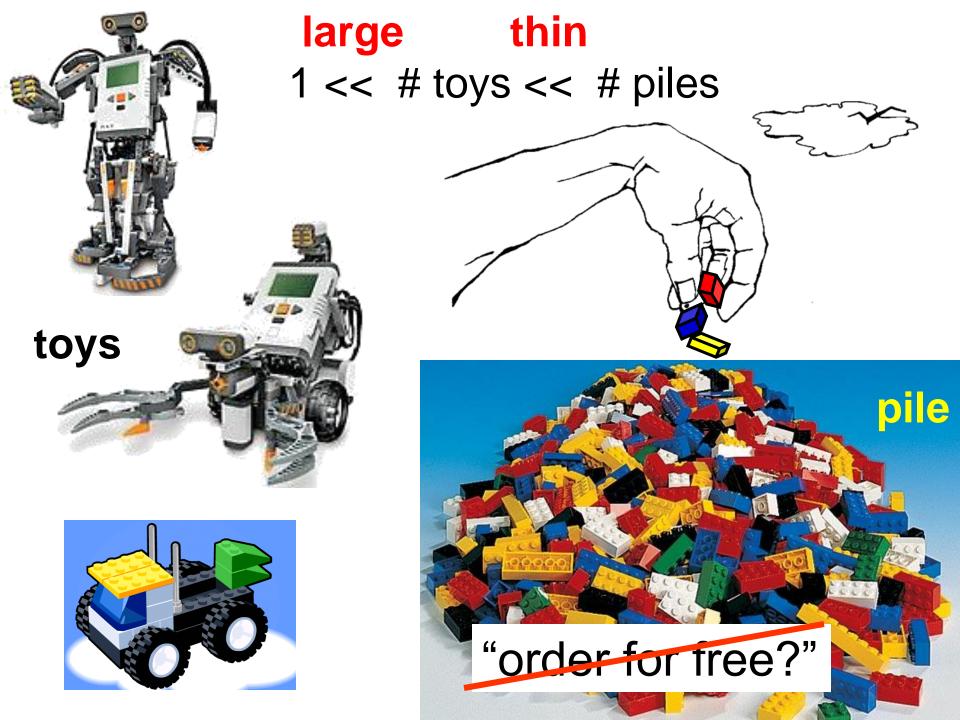
## **Other examples**

Words Lego Clothing **Cell biology** Internet Cyberphysical Money

# Letters and words

- 9 letters: adeginorz
- 9!= 362,880 sequences of 9 letters
- Only "organized" is a word

1 << (# words) << (# non-words) large thin





edge of chaos self-organized criticality scale-free ???

statistical physics random ensembles minimally tuned phase transitions bifurcations



REVIEW

# Reverse Engineering of Biological Complexity

Marie E. Csete<sup>1</sup> and John C. Doyle<sup>2\*</sup>

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 advar



#### **Csete and Doyle**

1 MARCH 2002 VOL 295 SCIENCE www.sciencemag.org

#### wardrobe

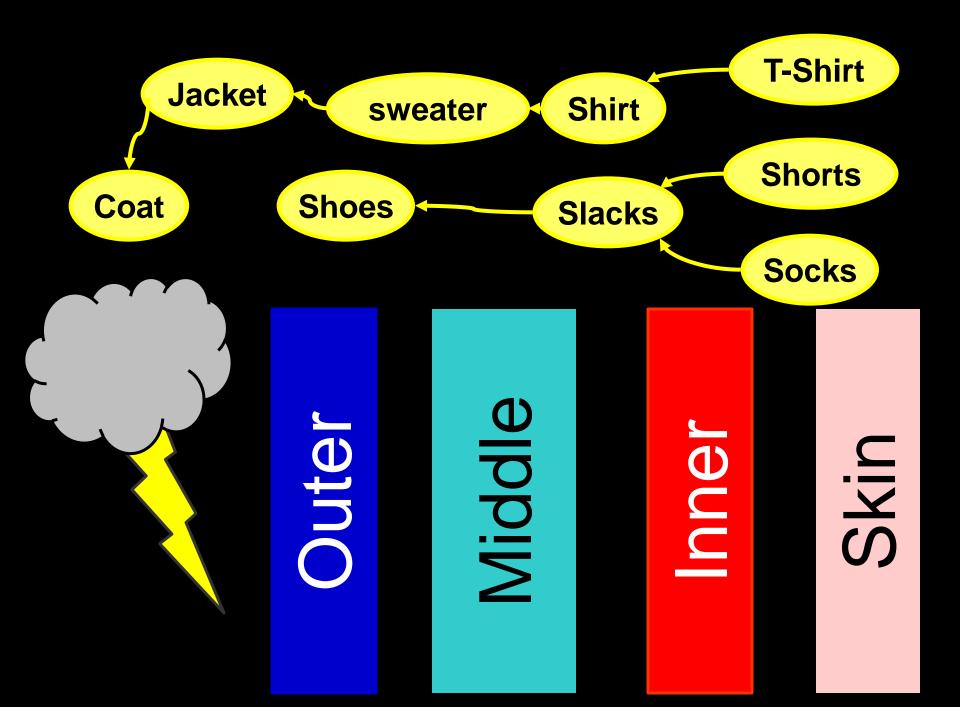


# outfit

# largethin1 << # outfits</td><< # heaps</td>







# System constraints

Robust to variations and requirements in

- weather
- activity
- appearance
- wear and tear
- washing

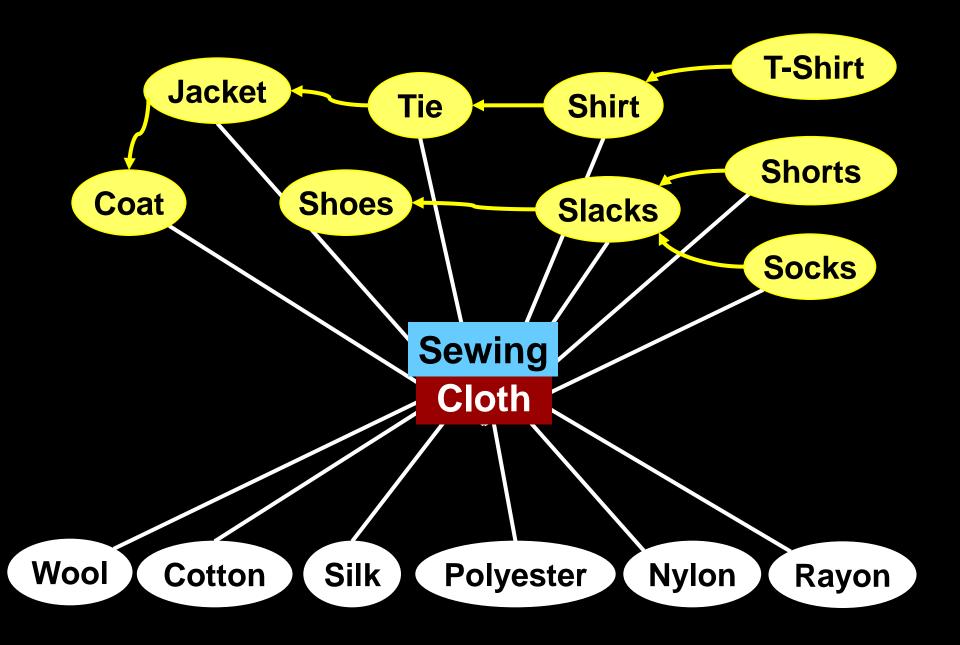
# Hidden

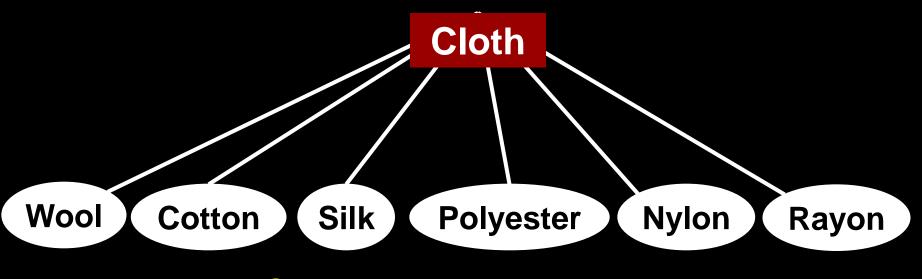
outer

Middle

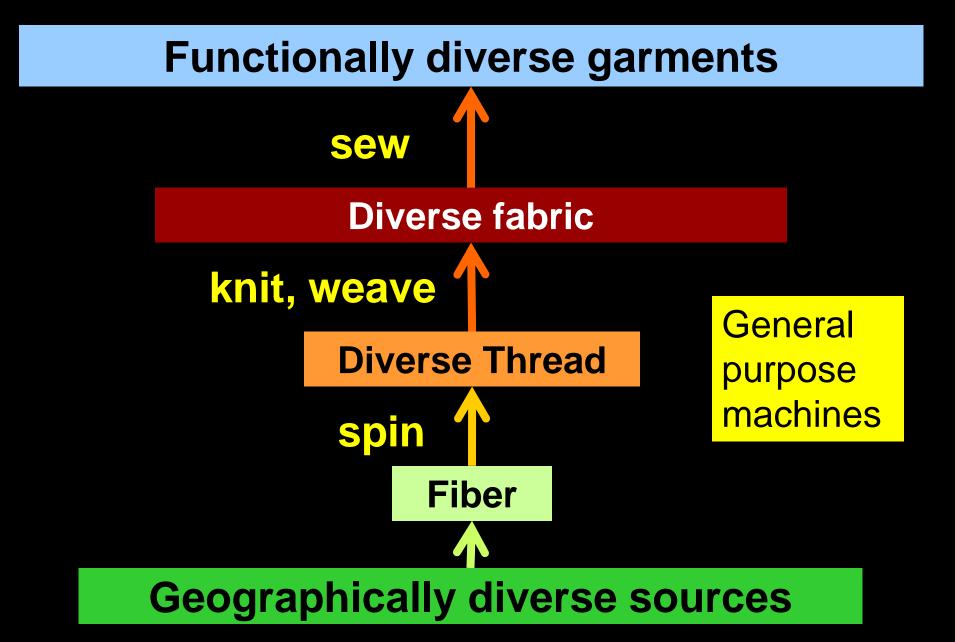
Inner

Skin

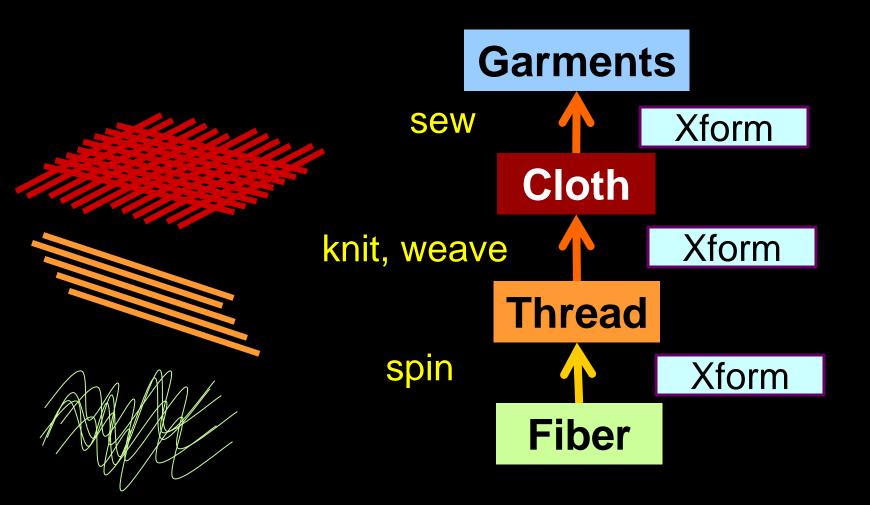




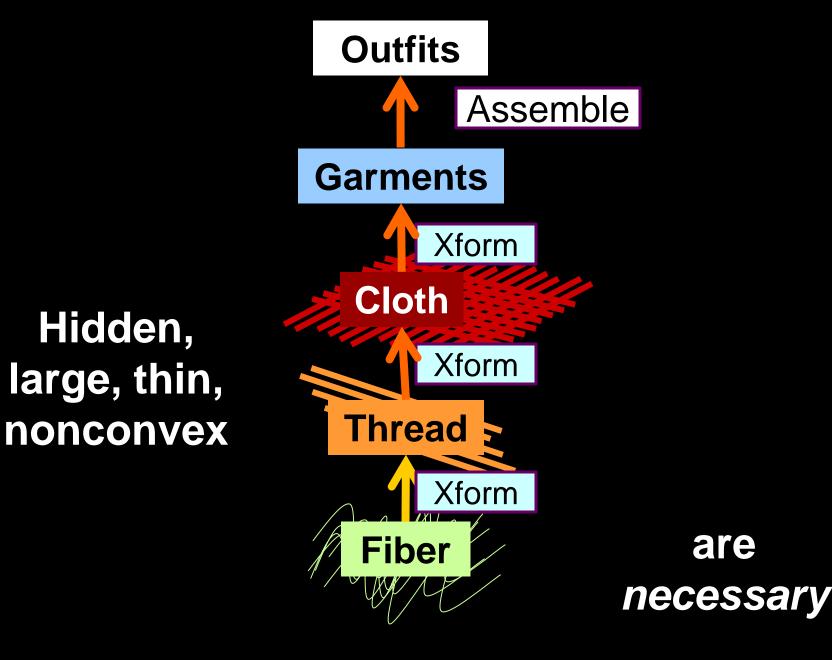
# **Component constraints**



# **Architecture and Modularity 2.0**



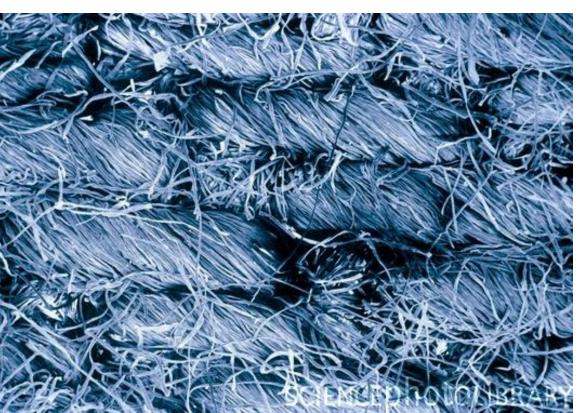
Prevents unraveling of lower layers



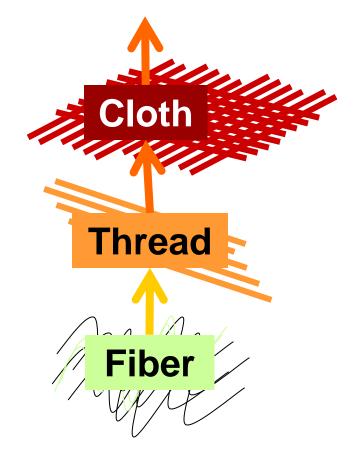


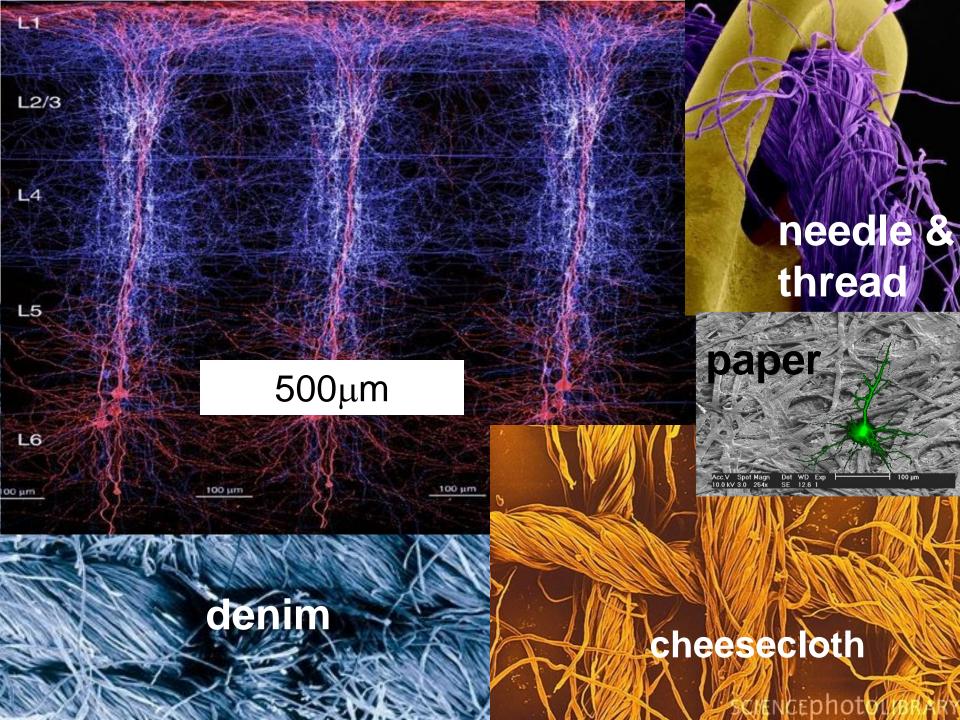


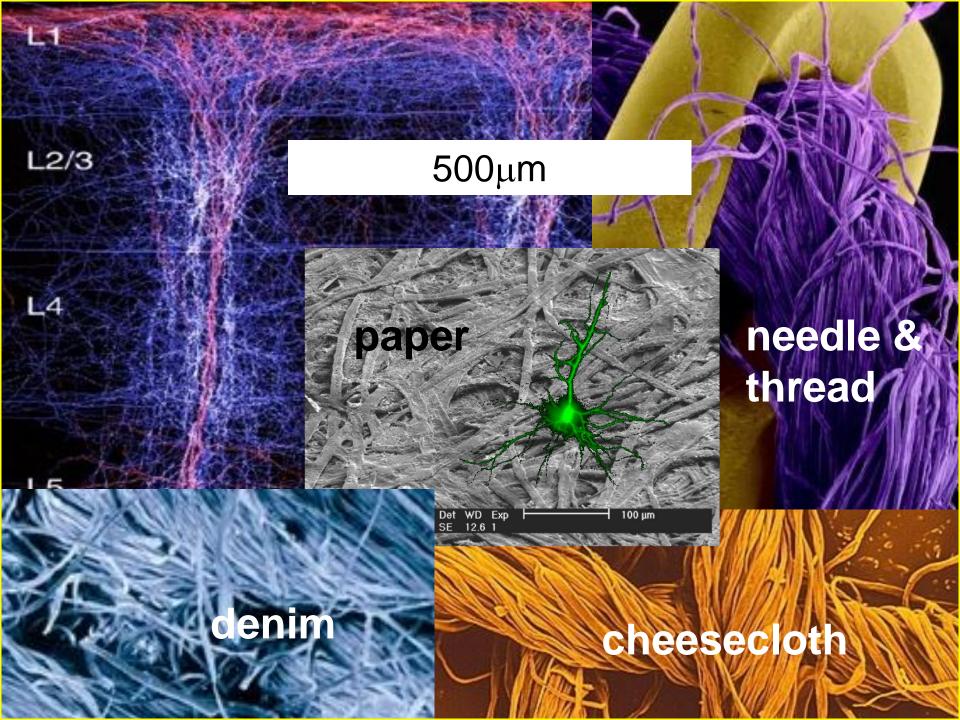
# denim



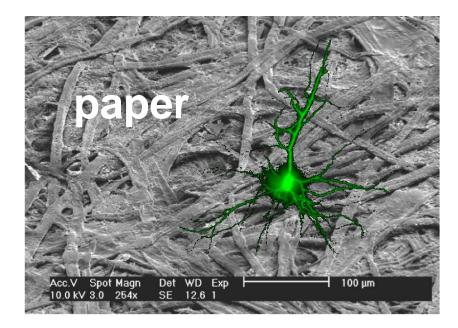


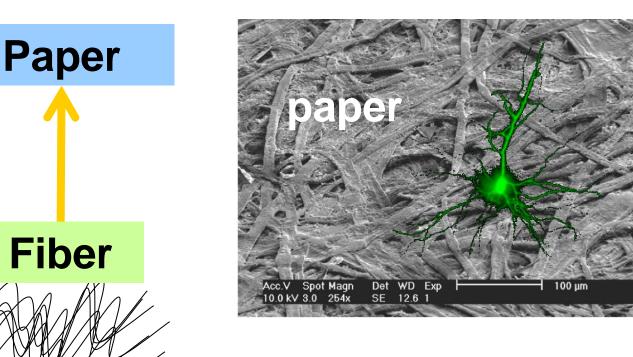




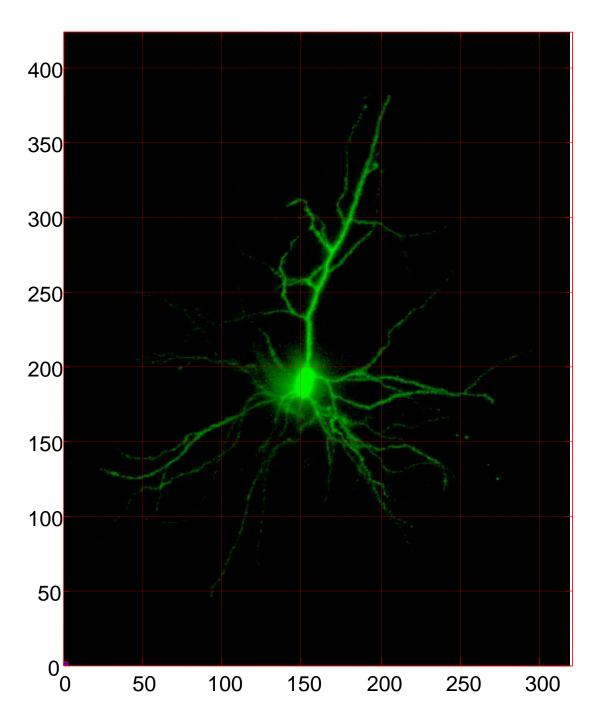


# .5mm x .35 mm cotton paper

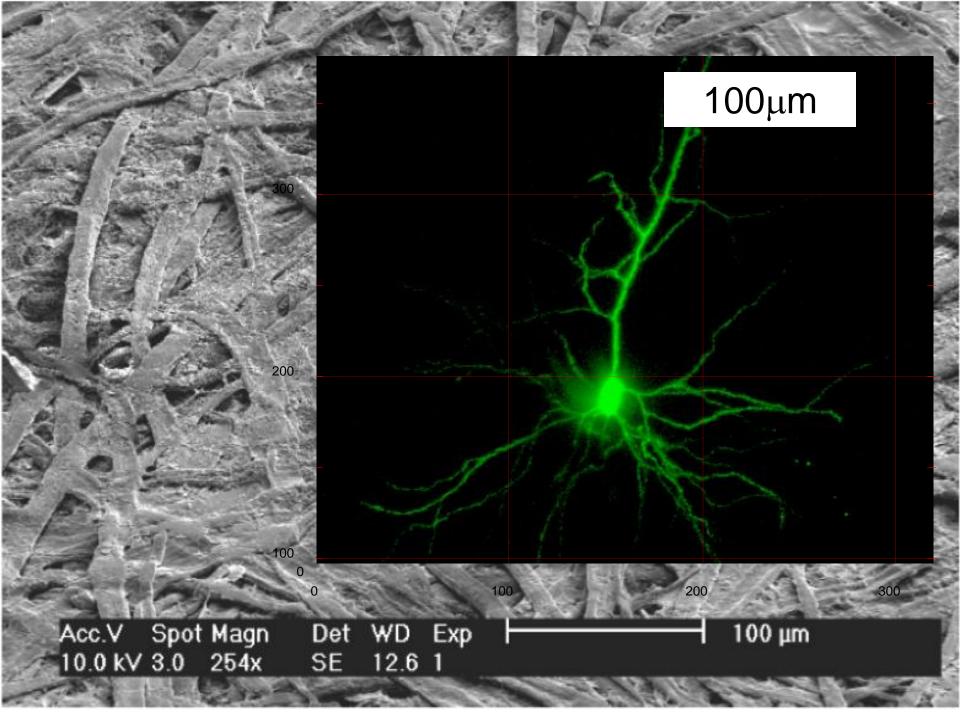




# **Minimal architecture**



#### A neonatal rat pyramidal neuron filled with Lucifer Yellow imaged on the BioRad MRC600 confocal microscope using a 20X oil objective, NA=0.8. Image size is 320 x 425 x 120 µm.

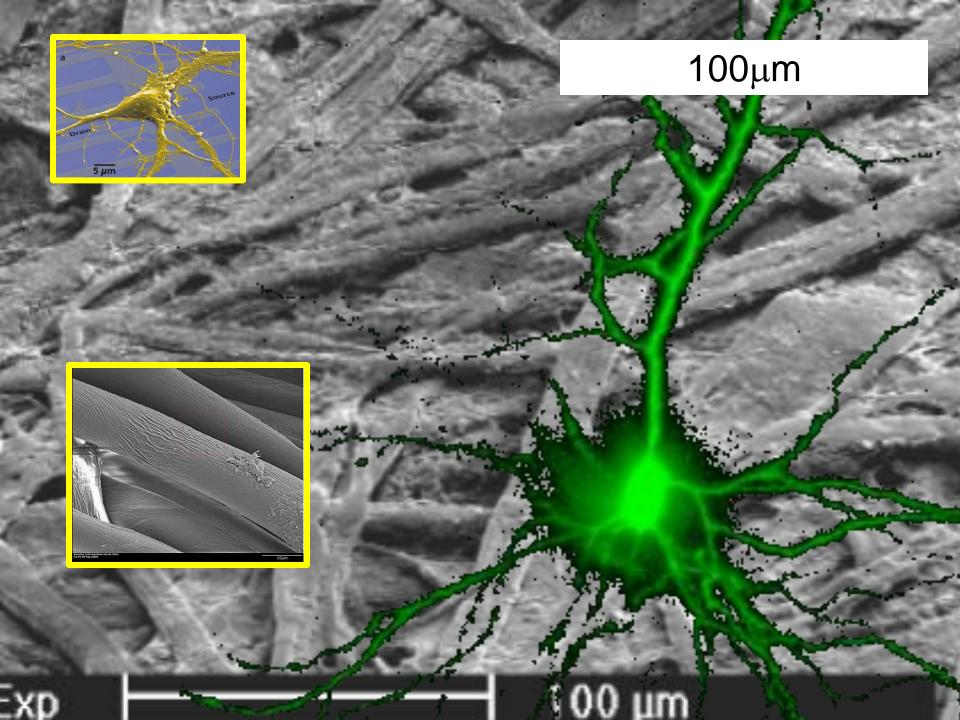


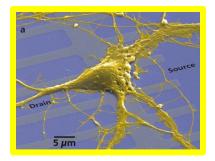
# .5mm x .35 mm cotton paper

# 100µm

Acc.V Spot Magn Det WD Exp 10.0 kV 3.0 254x SE 12.6 1

100 μm .5mm x .35 mm cotton paper

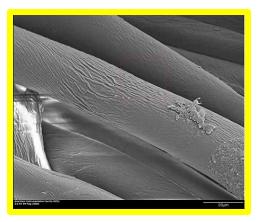




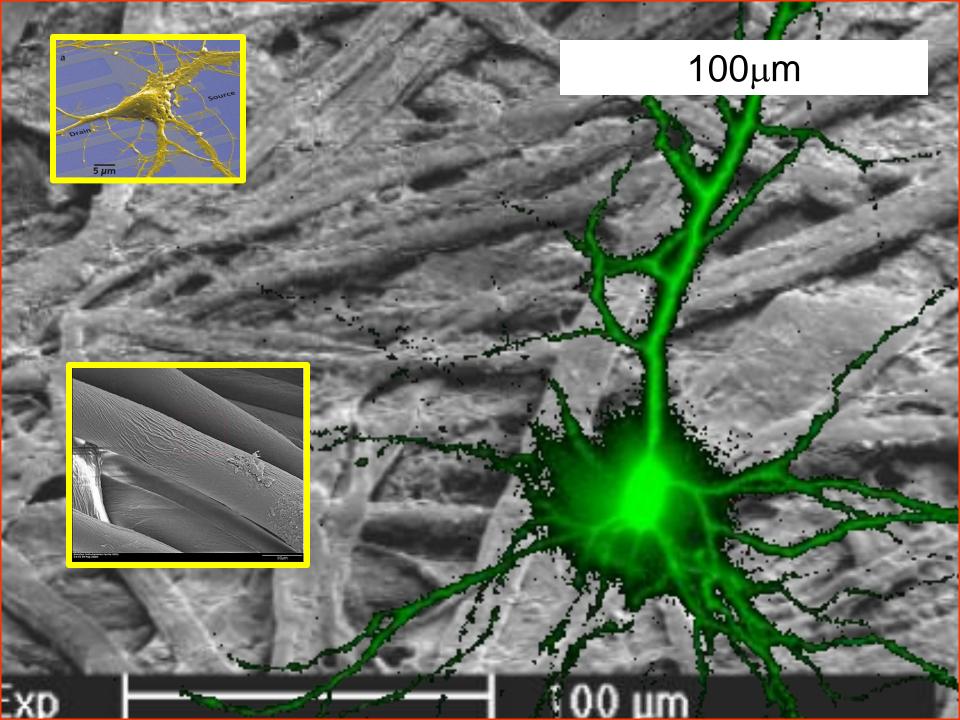
#### 47x35 micron

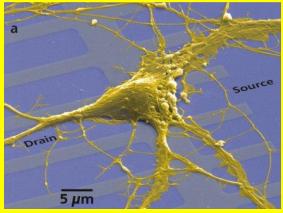
# 100µm

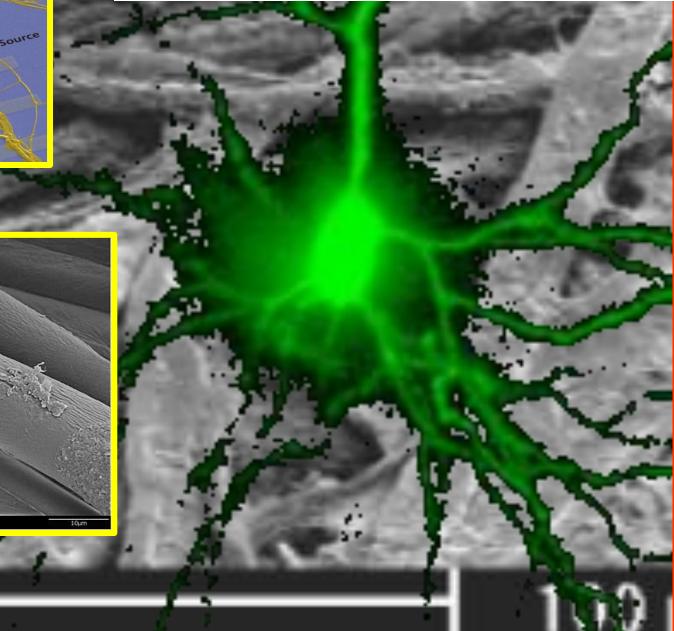
#### cotton fibers

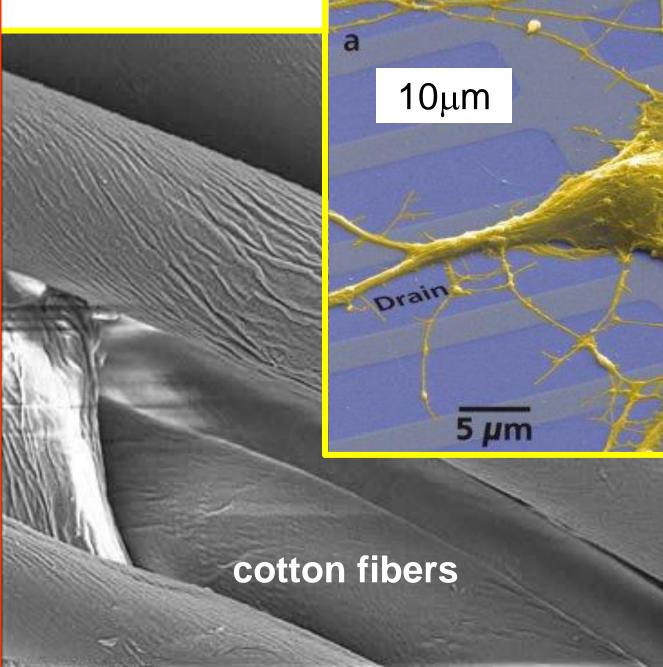


#### 60x50 microns

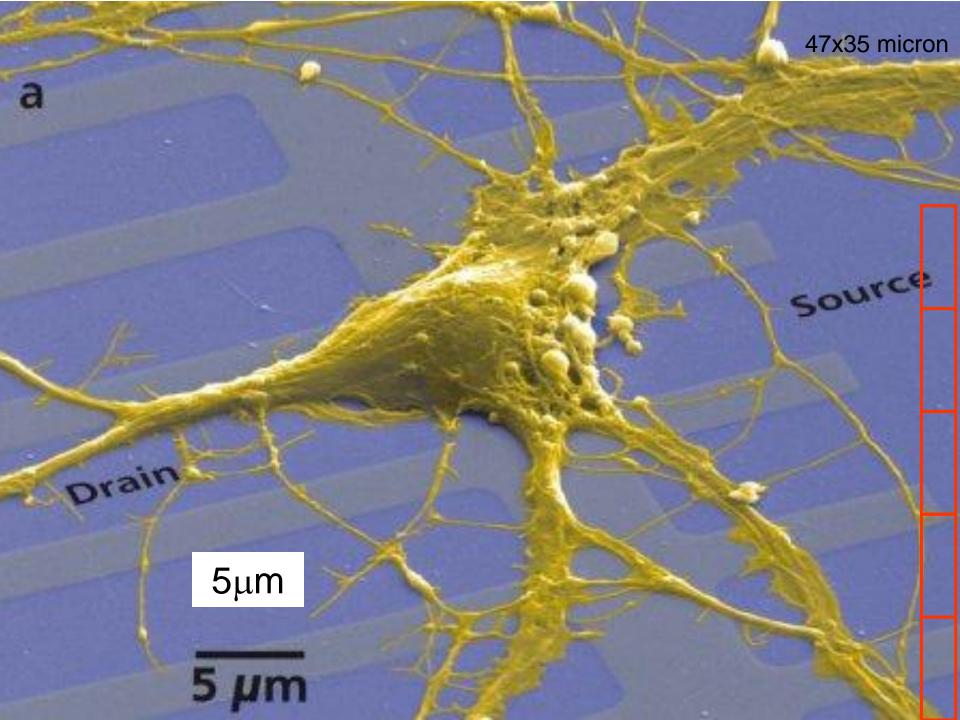


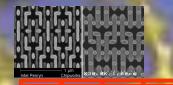


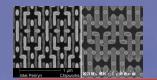


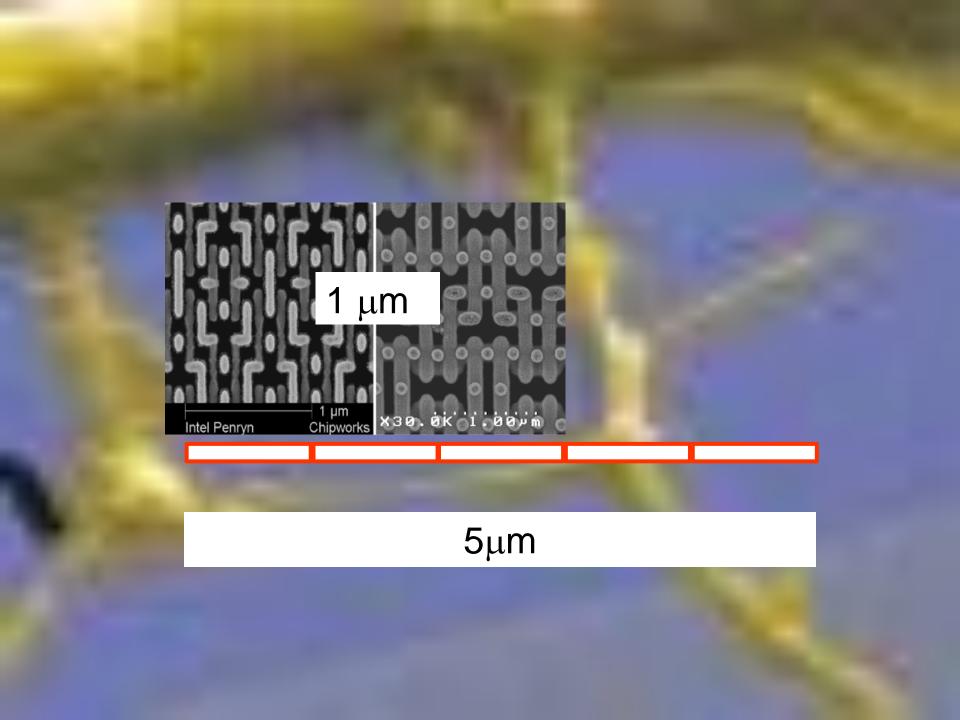


Analytical that/umentation Pacifity NCSU 5.0 KV EM Mag 2000X Source

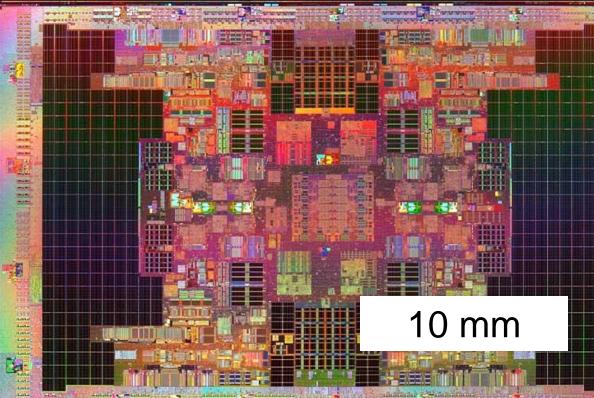


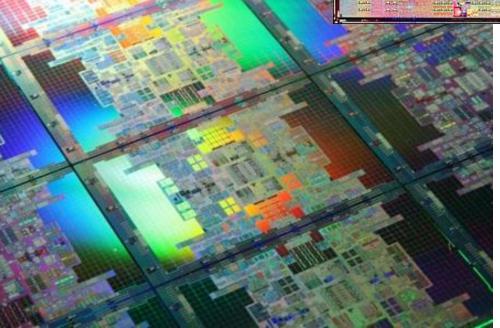


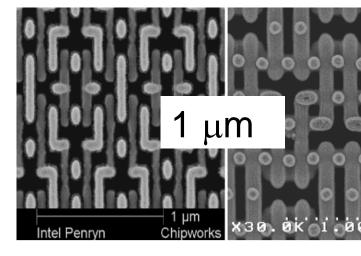


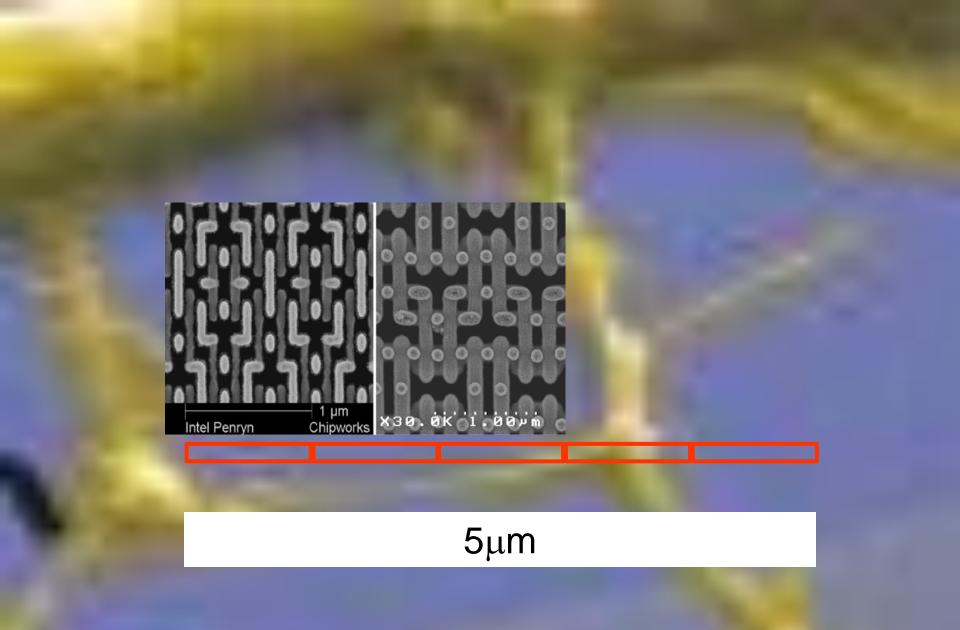


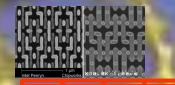
Intel Tukwila quad core chip with more than 2 billion transistors

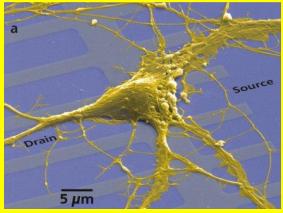


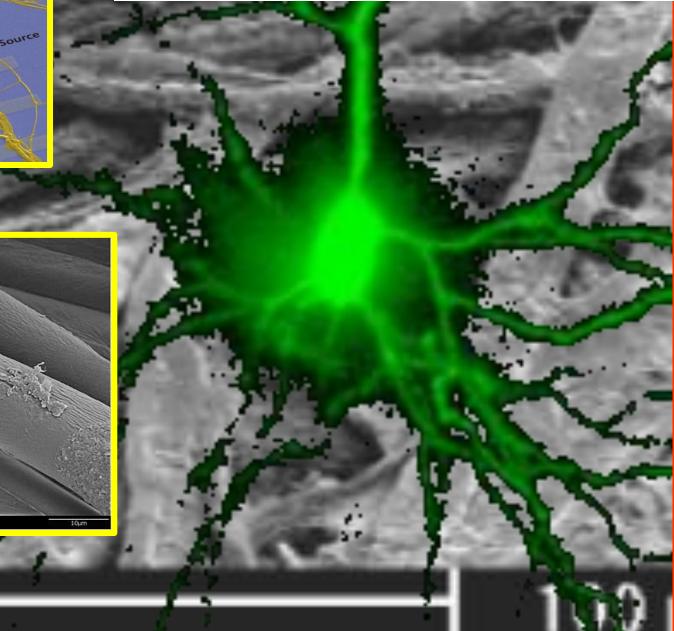












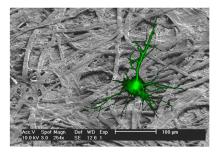
# .5mm x .35 mm cotton paper

# 100µm

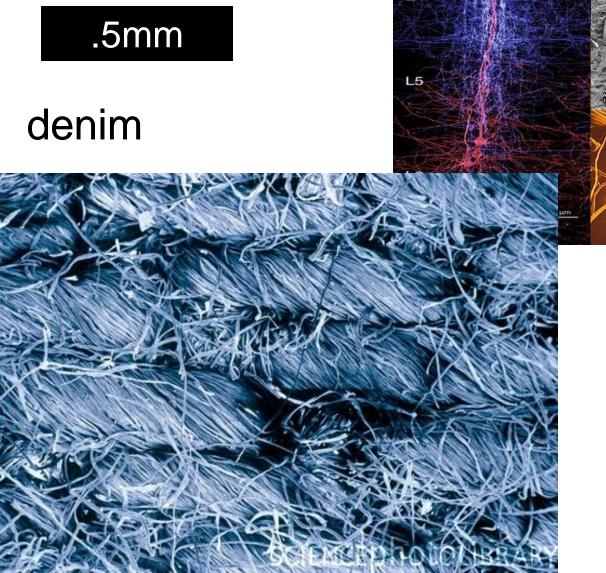
Acc.V Spot Magn Det WD Exp 10.0 kV 3.0 254x SE 12.6 1

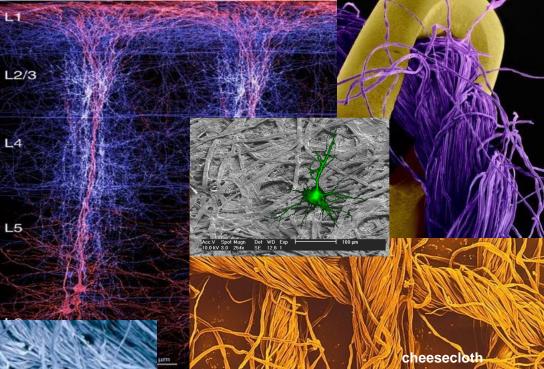
100 μm .5mm x .35 mm cotton paper

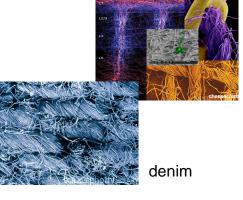








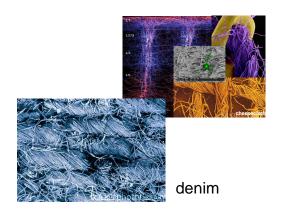




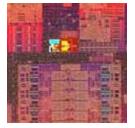


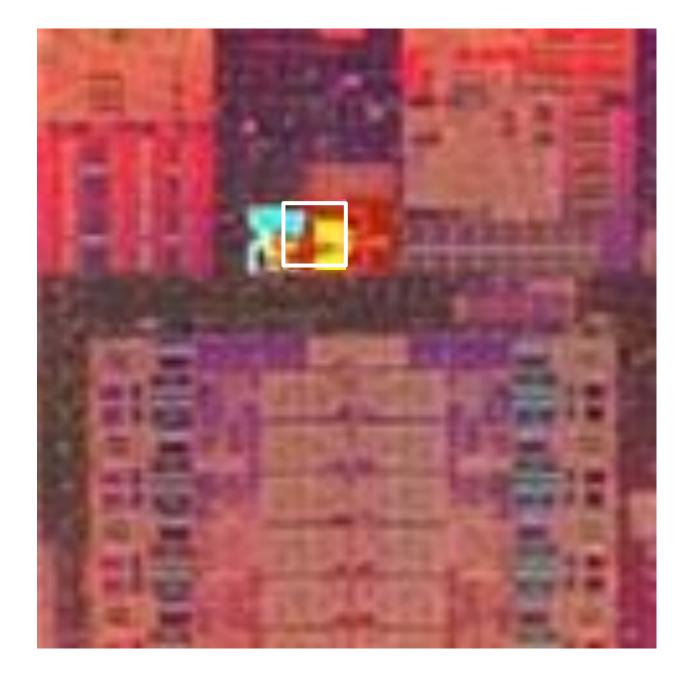
#### 500×500µm

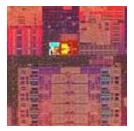
## .5×.5mm

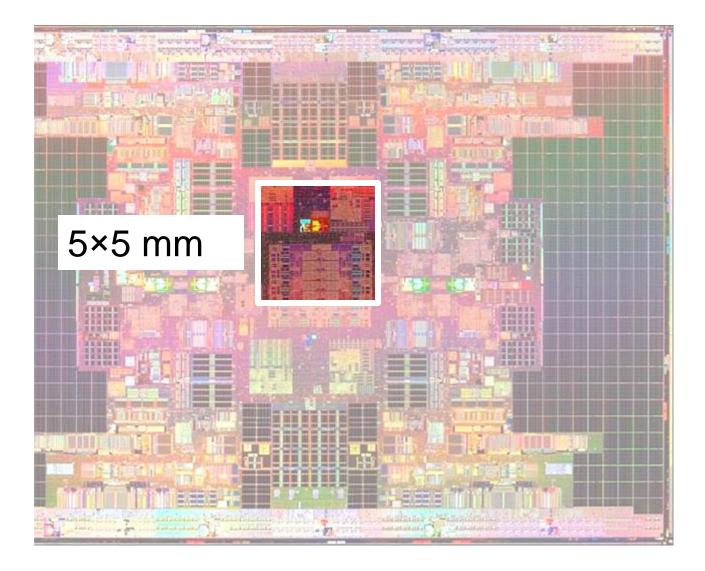


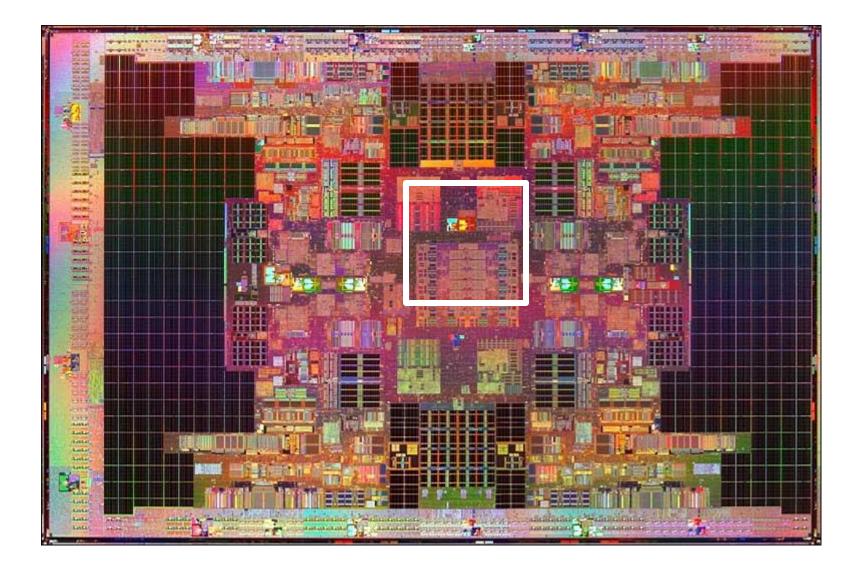
# 500×500µm .5×.5mm

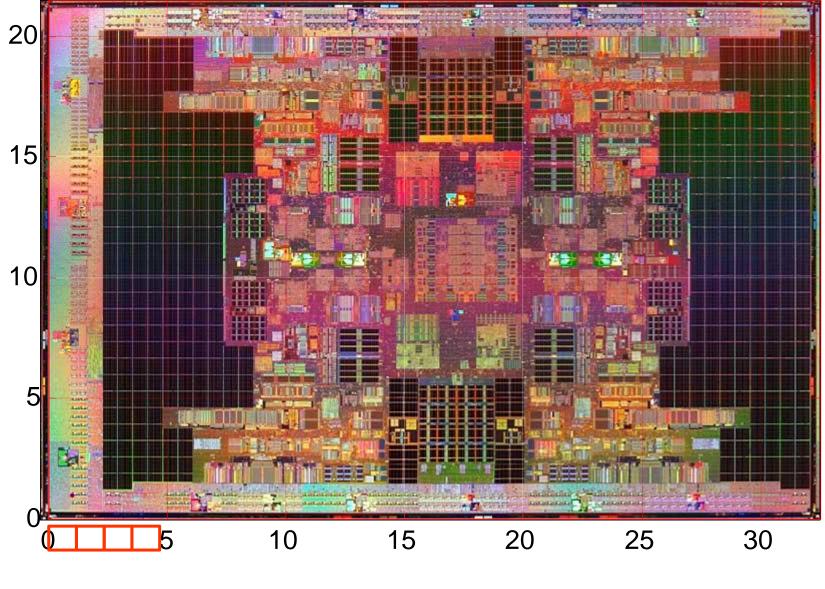












21.5×32.5 mm

Intel Tukwila quad core chip with more than 2 billion transistors

Sitt Internation

- El

Luite Luite Luite Luite

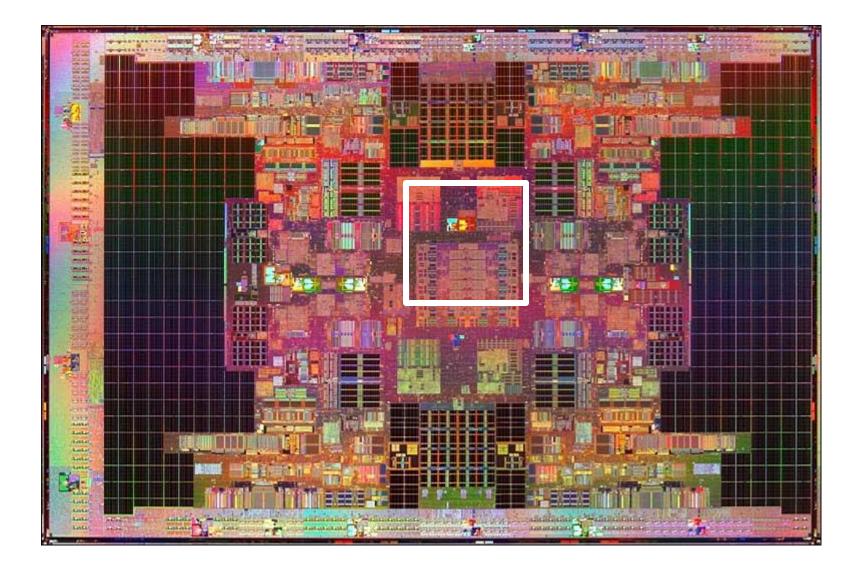
21.5×32.5 mm

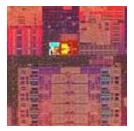
1000

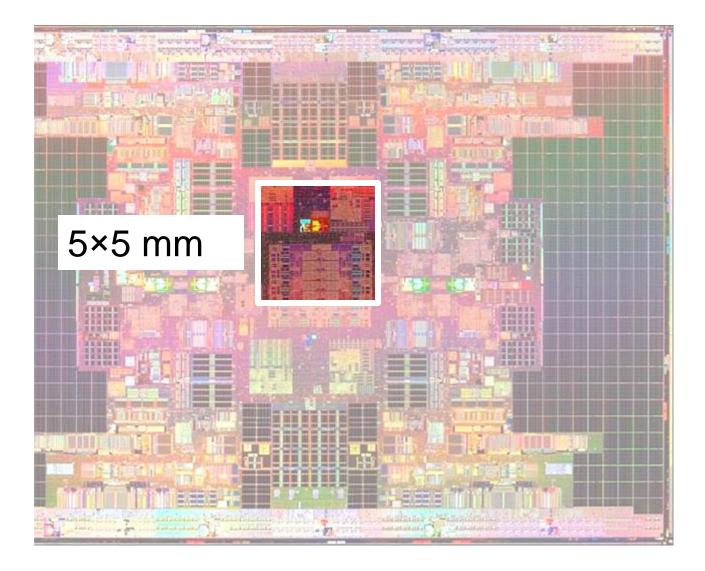
λ.

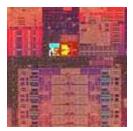
£ 3

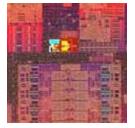
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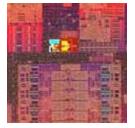


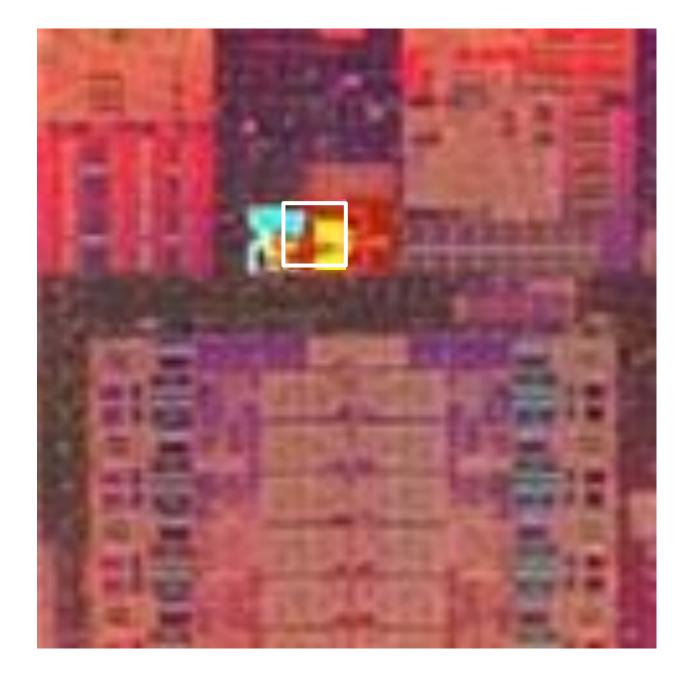










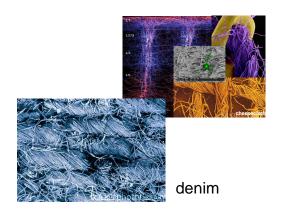


# 500×500µm .5×.5mm



#### 500×500µm

## .5×.5mm

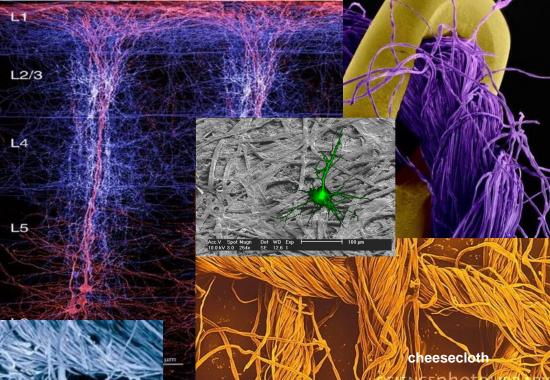


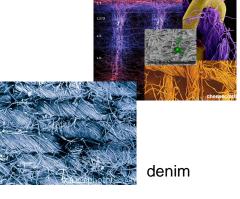


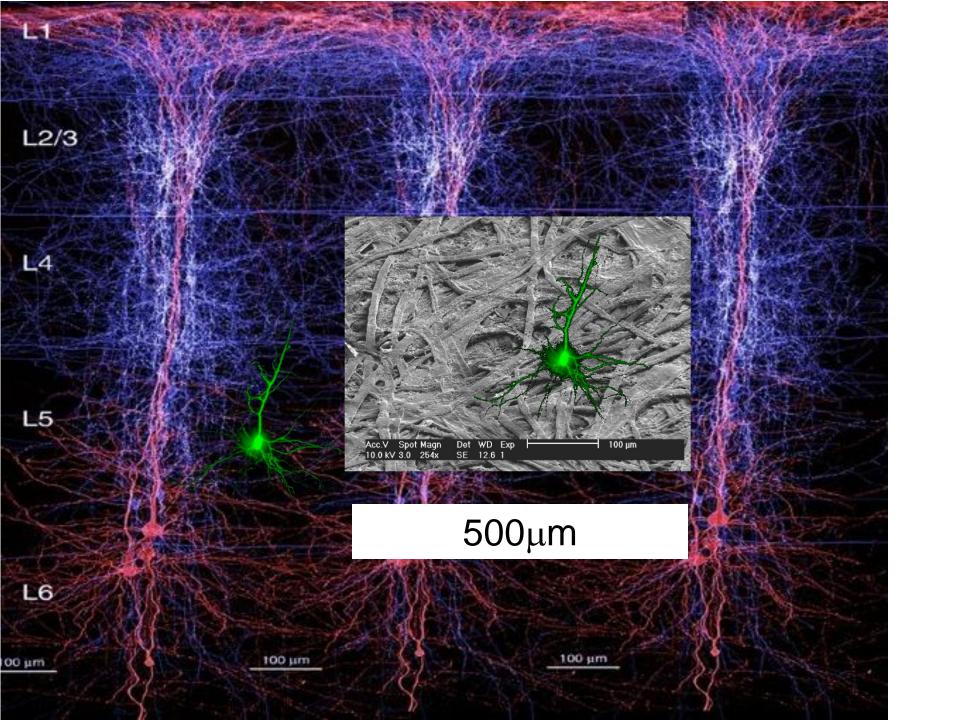
#### .5mm

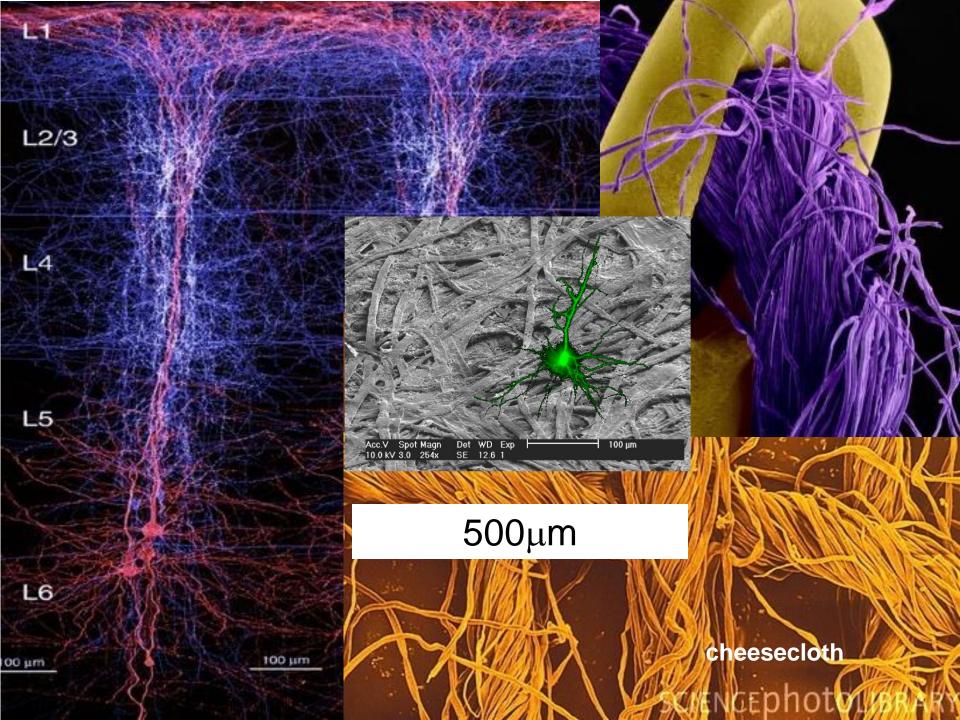
#### denim

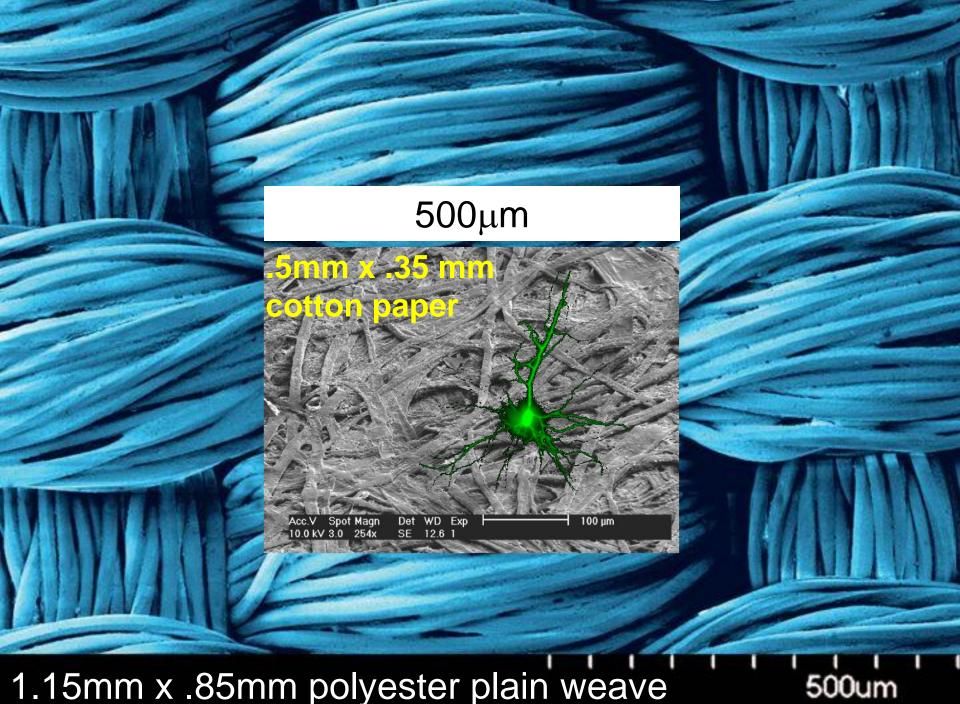












#### 1.15mm x .85mm polyester plain weave

#### polyester plain weave

#### 500µm

Acc.V Spot Magn Det WD Exp 10.0 kV 3.0 254x SE 12.6 1

paper

100 µm

# needle & thread

#### cheesecloth

### denim

#### polyester plain weave

L4

L5

# needle & thread

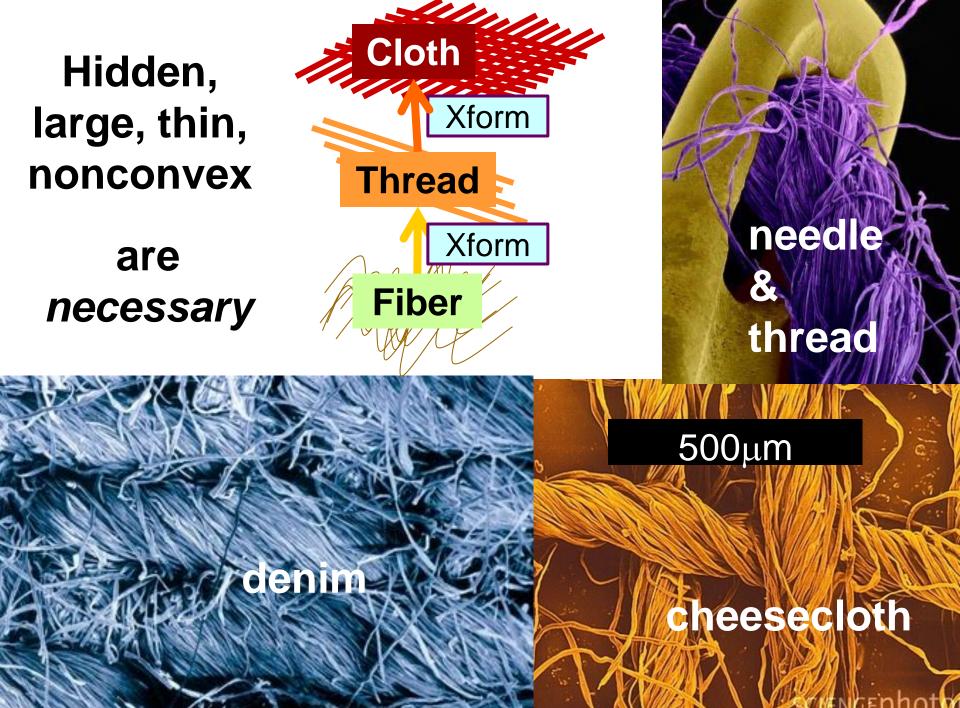
#### 500µm

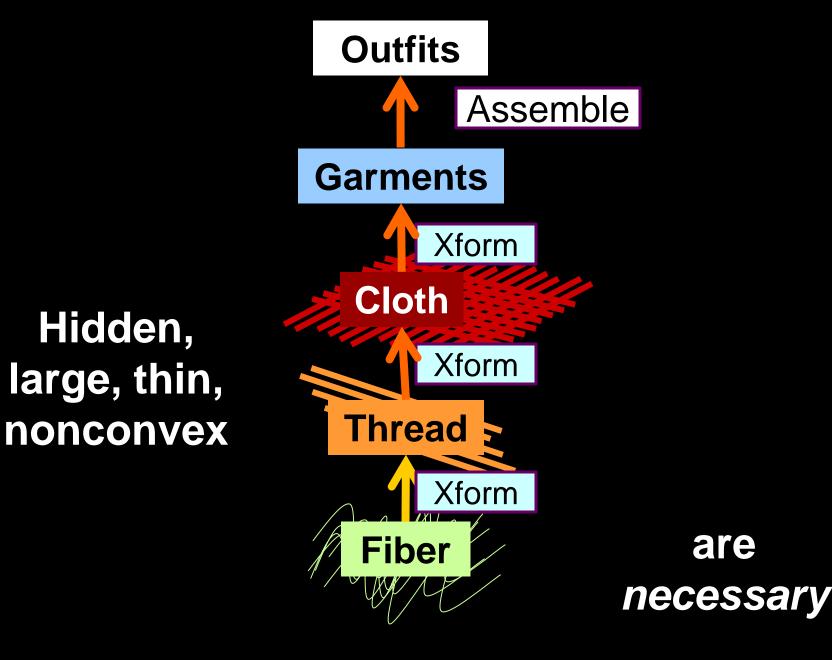
paper

### denim

Acc.V Spot Magn Det WD Exp 100 µm 10.0 kV 3.0 254x SE 12.6 1

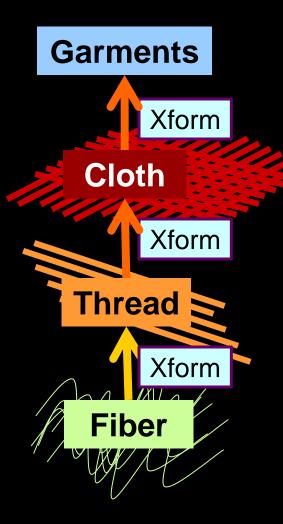
#### cheesecloth





#### **Universal strategies?**

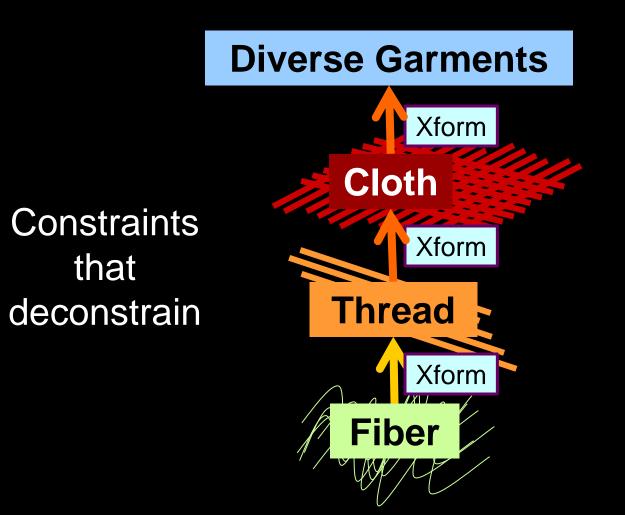
Even though garments seem analog/continuous quantization for robustness



Garments have limited access to threads and fibers

constraints on cross-layer interactions

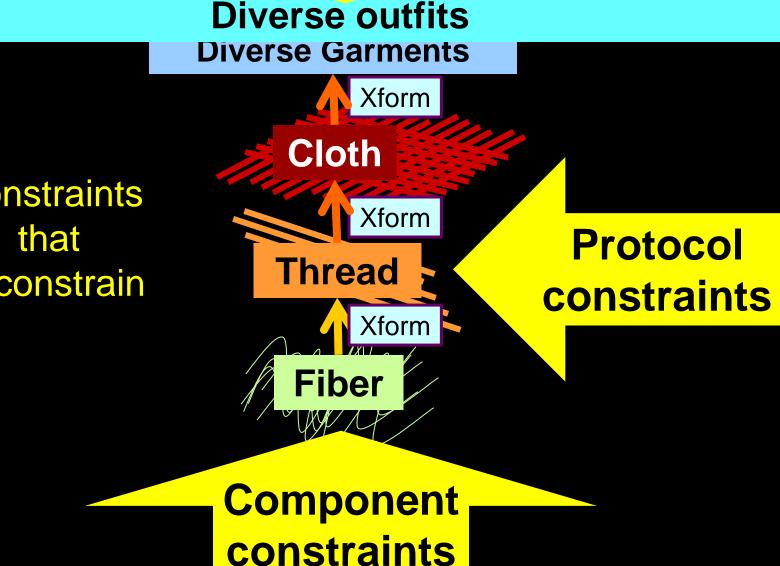
Prevents unraveling of lower layers

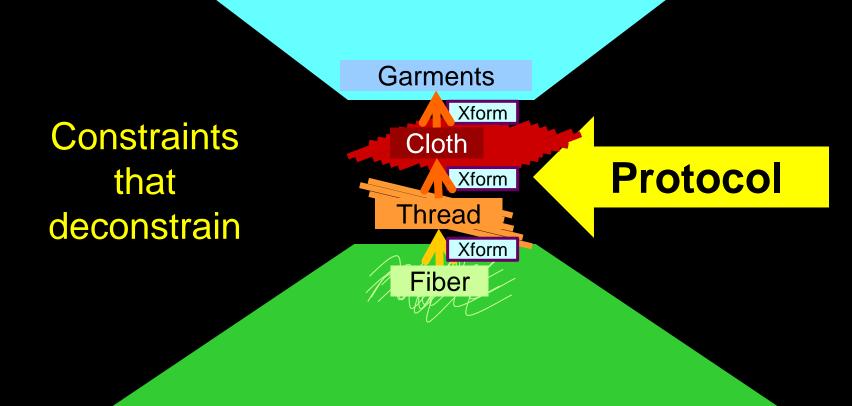


#### **Geographically diverse sources**

#### **System constraints**

#### **Constraints** that deconstrain





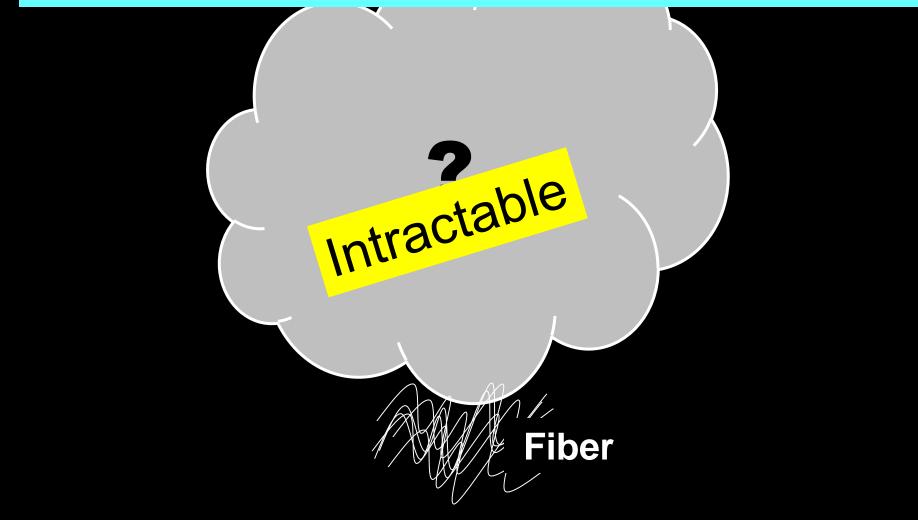
#### **Diverse sources**



?



Fiber







#### SOC/EOC?

## Random

Self-Organized Clothing Edge of Couture Scale-Free Fashion



Standard error



#### **Diverse outfits**

#### Small gap No architecture

Fiber

Self-Organized Clothing

Edge of Couture

**Scale-Free Fashion** 







Standard error

#### **Diverse outfits**



#### Huge gap No architecture Supernatural





#### Mysteries in the gaps No architecture

**Diverse outfits** 



Huge gap Supernatural



Small gap Emergence Self-organized Phase transition Edge-of Scale-free

#### **Diverse outfits**

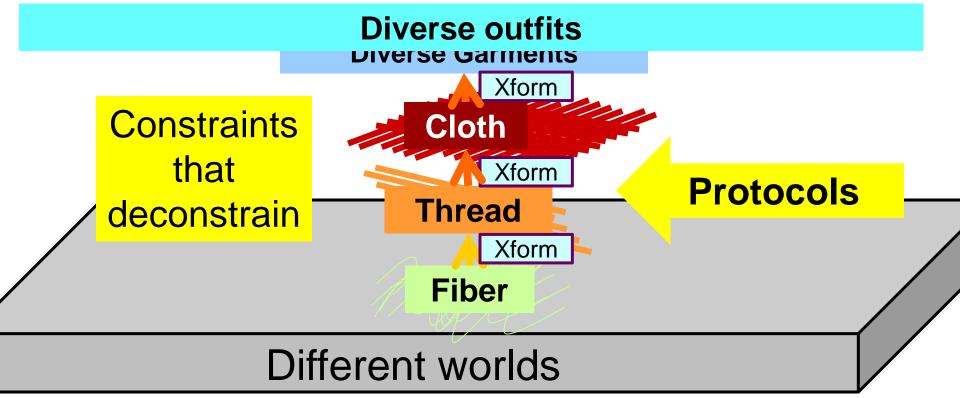
M/

W



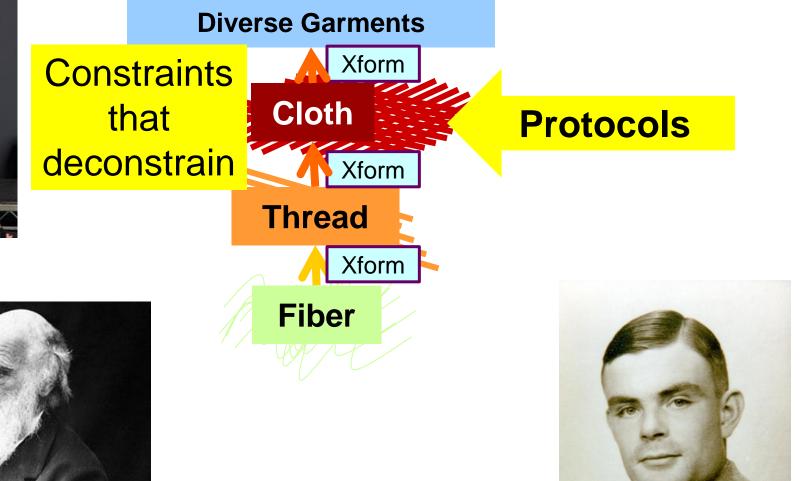


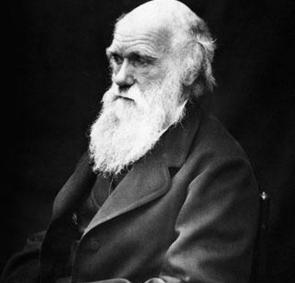
Huge gap **Supernatural** 

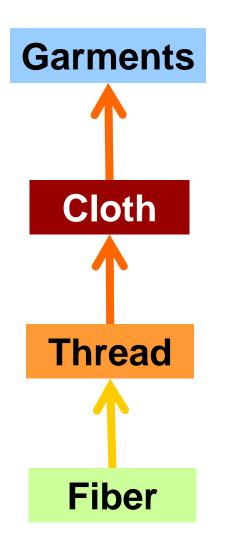


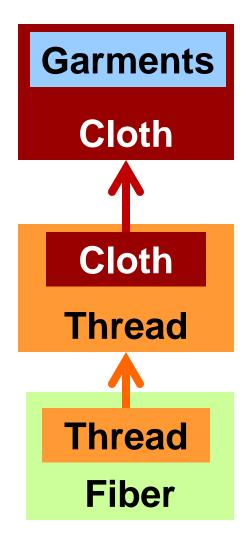




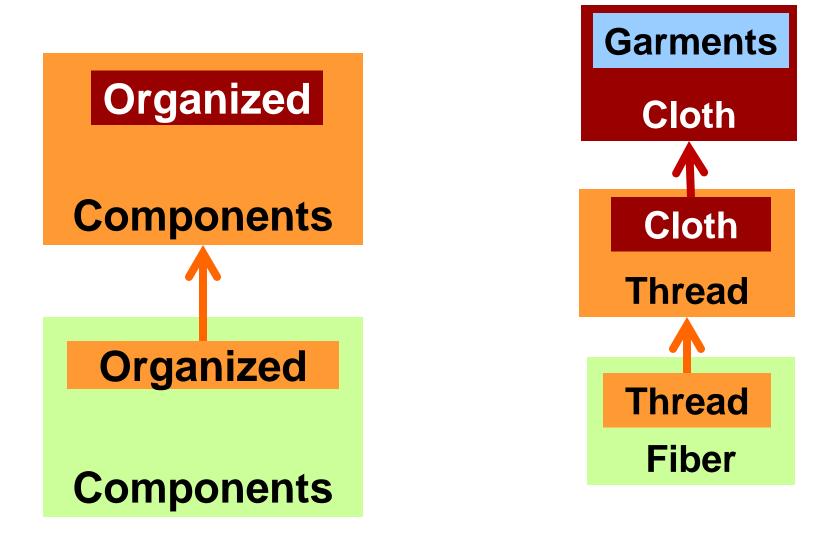








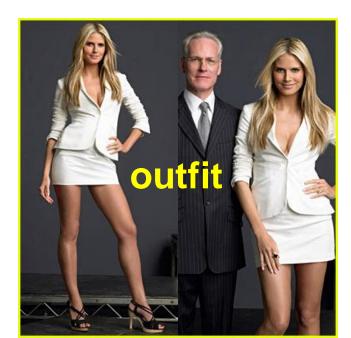
## Layered, large, thin



# largethin1 << # outfits</td><< # heaps</td>

## Organized

### Components







# largethin1 << # outfits</td><< # heaps</td>

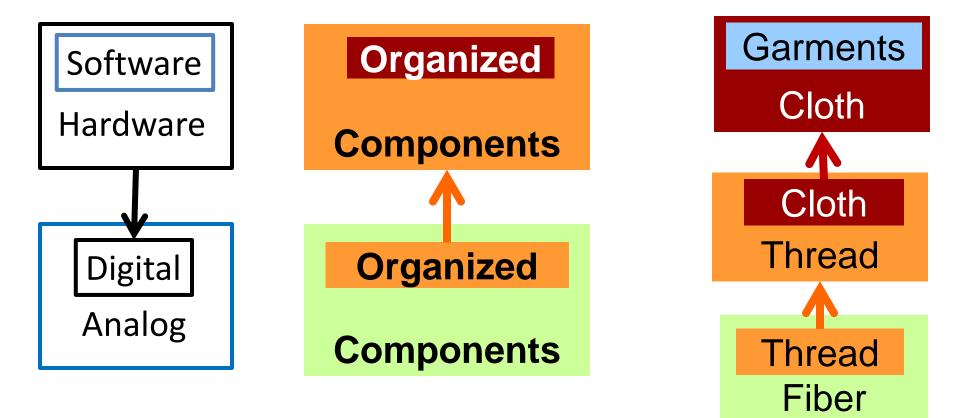
#### Organized

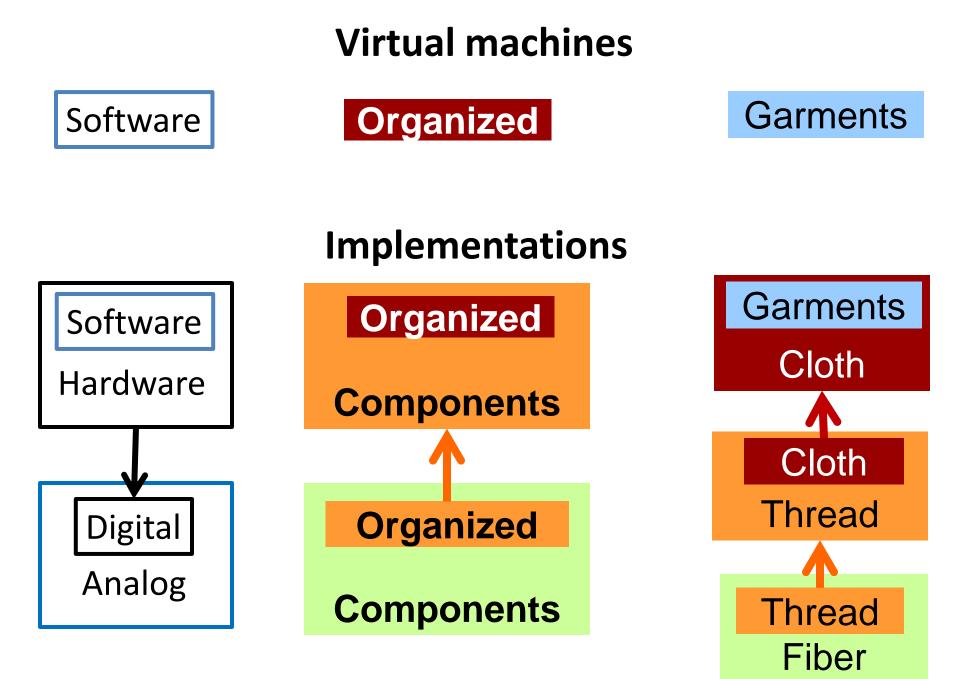
### **Components**

















### **Virtual machines**



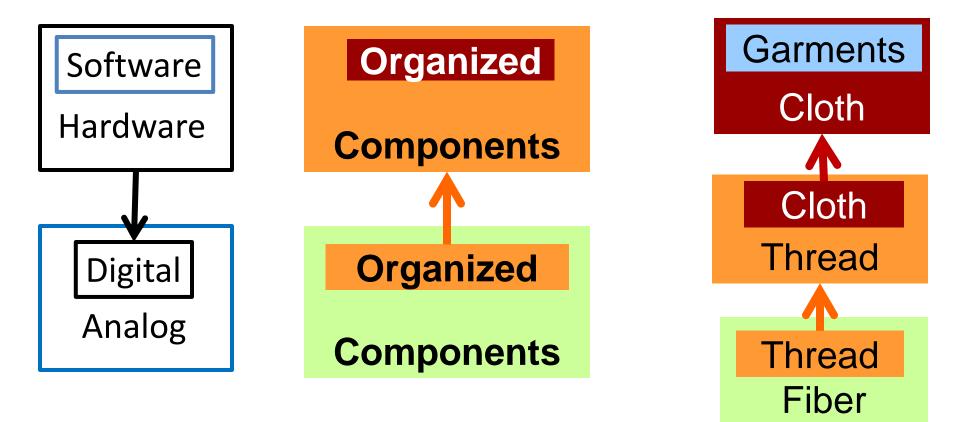


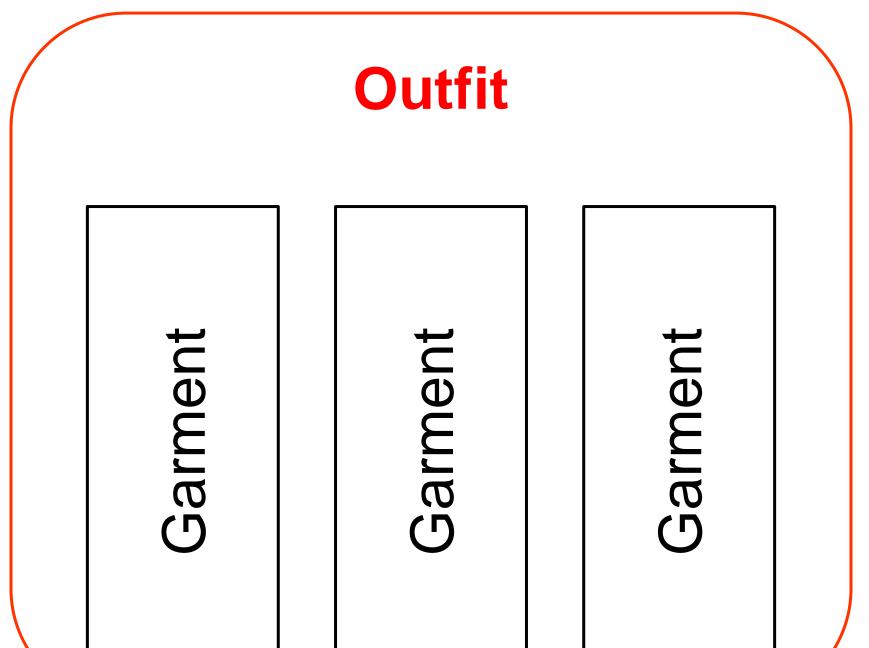


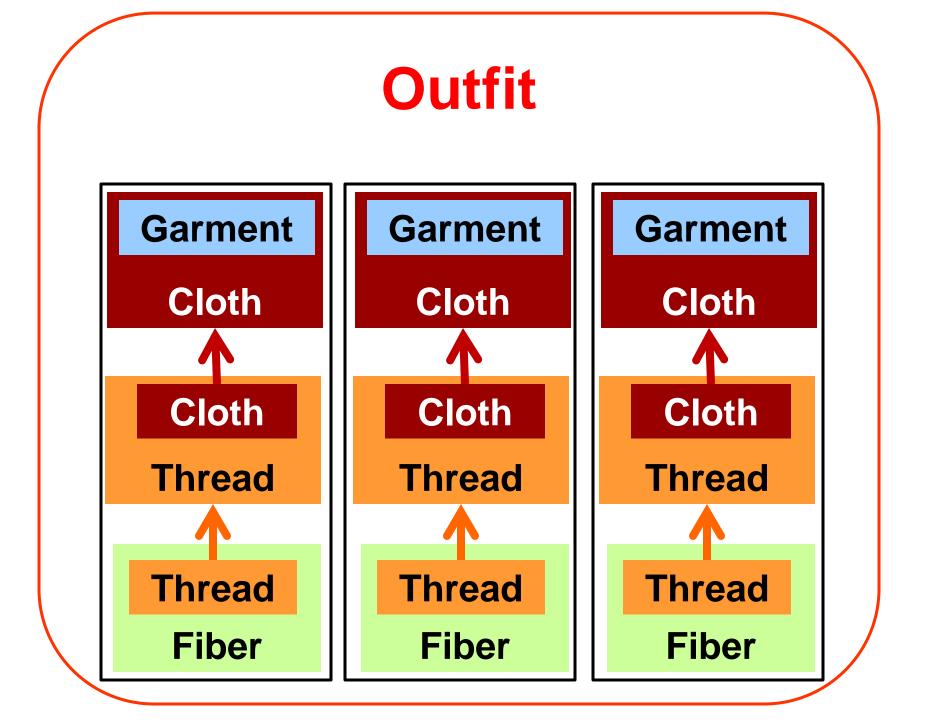
### Implementations



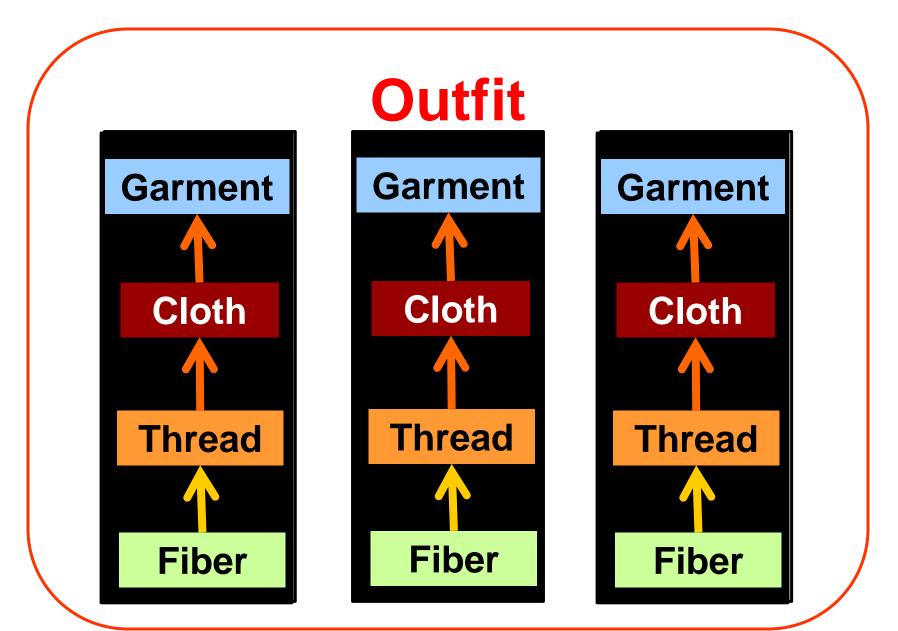
## Layered, large, thin Hidden Virtualized

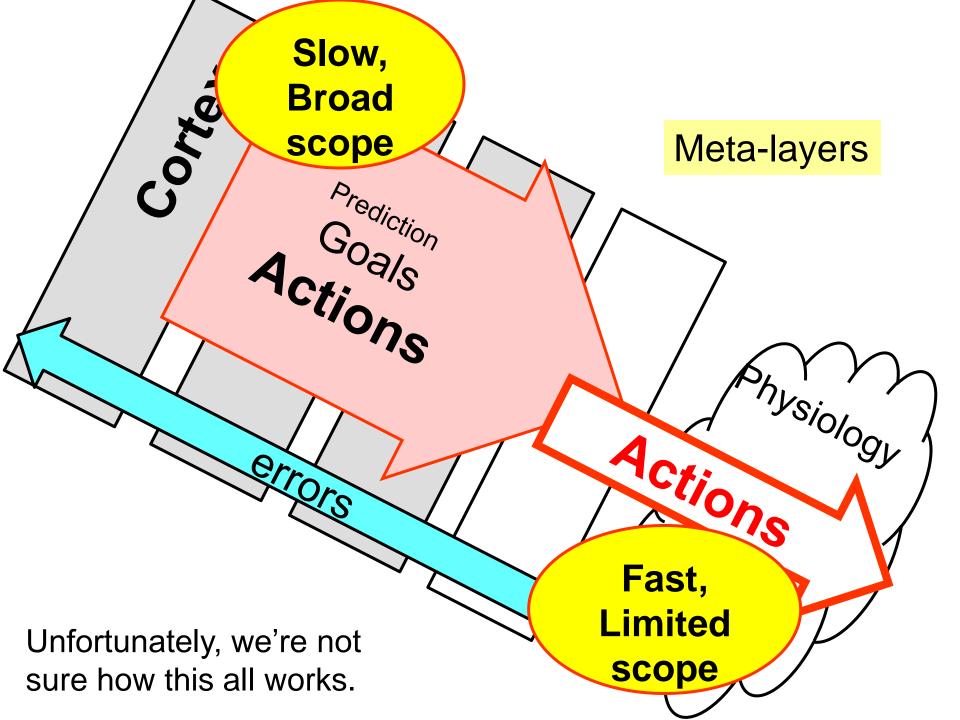




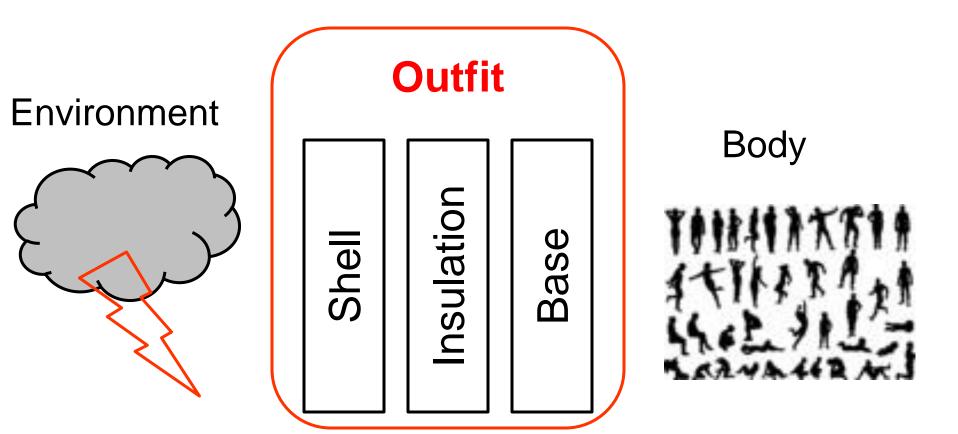


### Layering within garments (textiles)

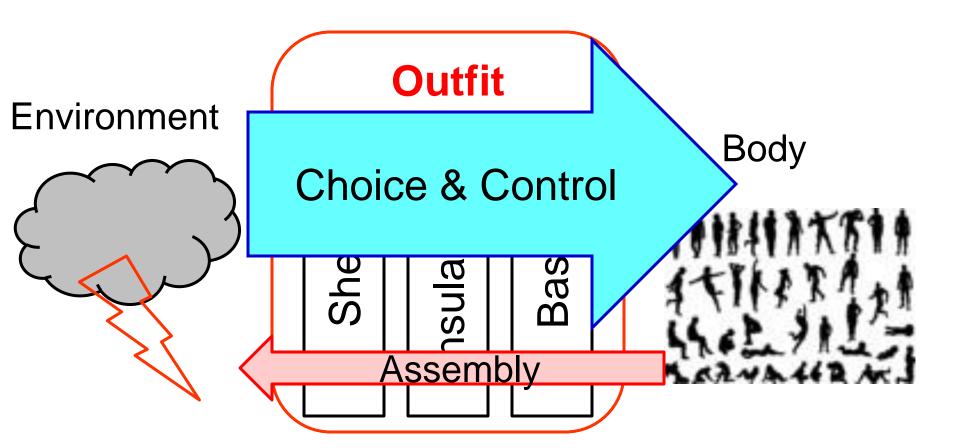


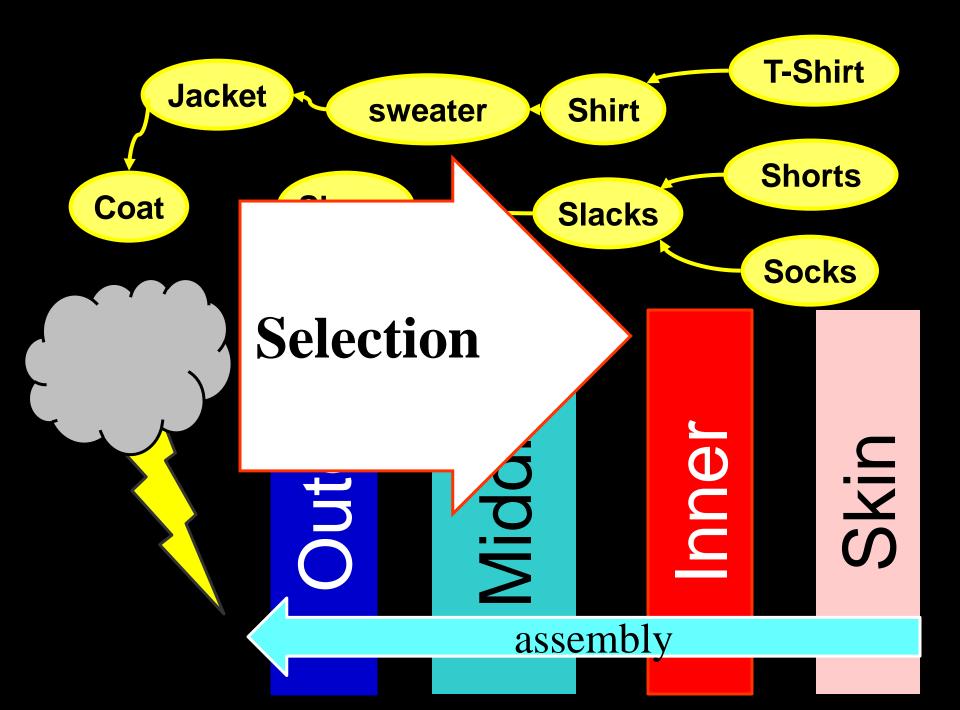




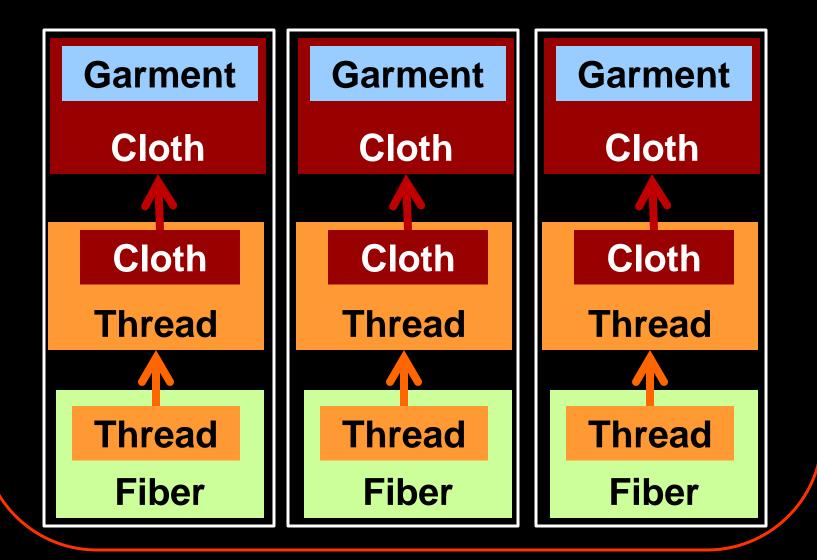


- Complexity  $\Leftrightarrow$  Robustness
- Layers must be hidden to be robust
- Choice (management and control) is more complex than assembly

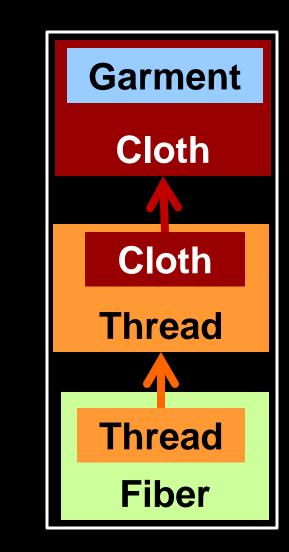




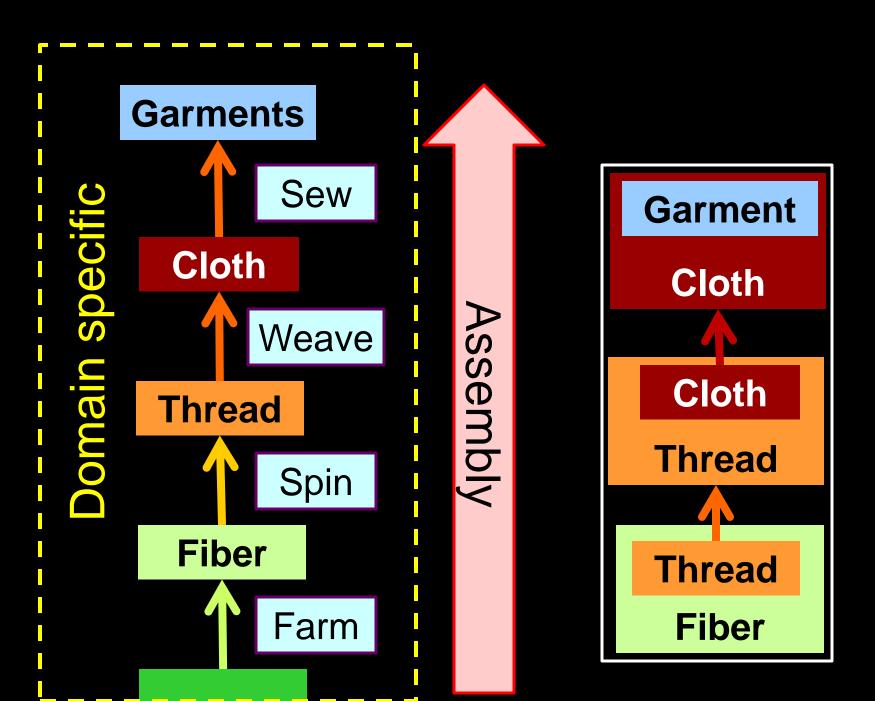
# Outfit

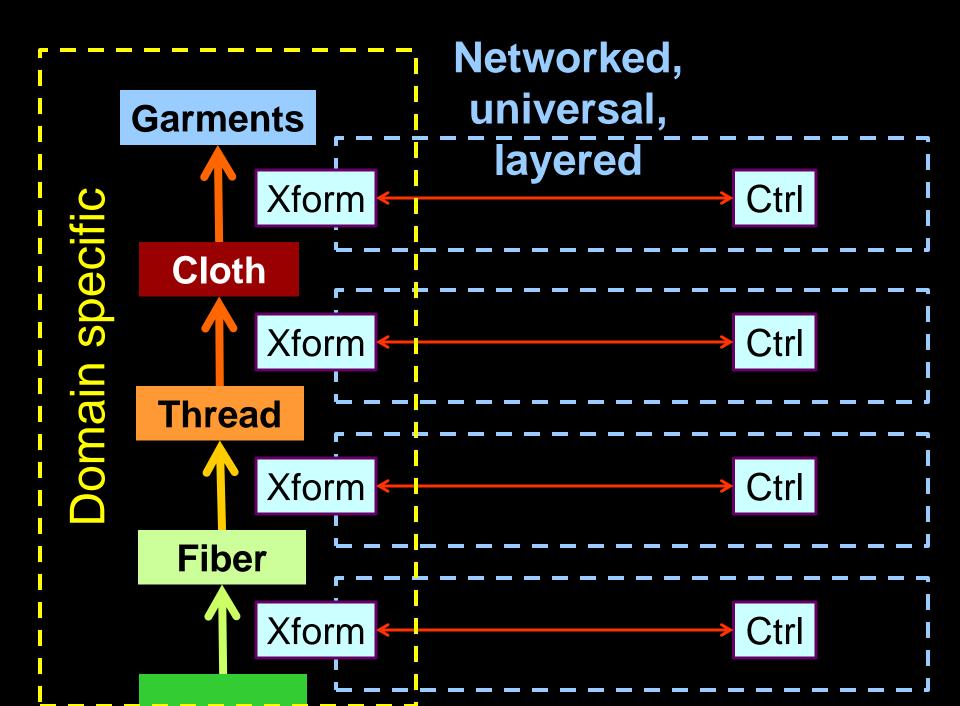


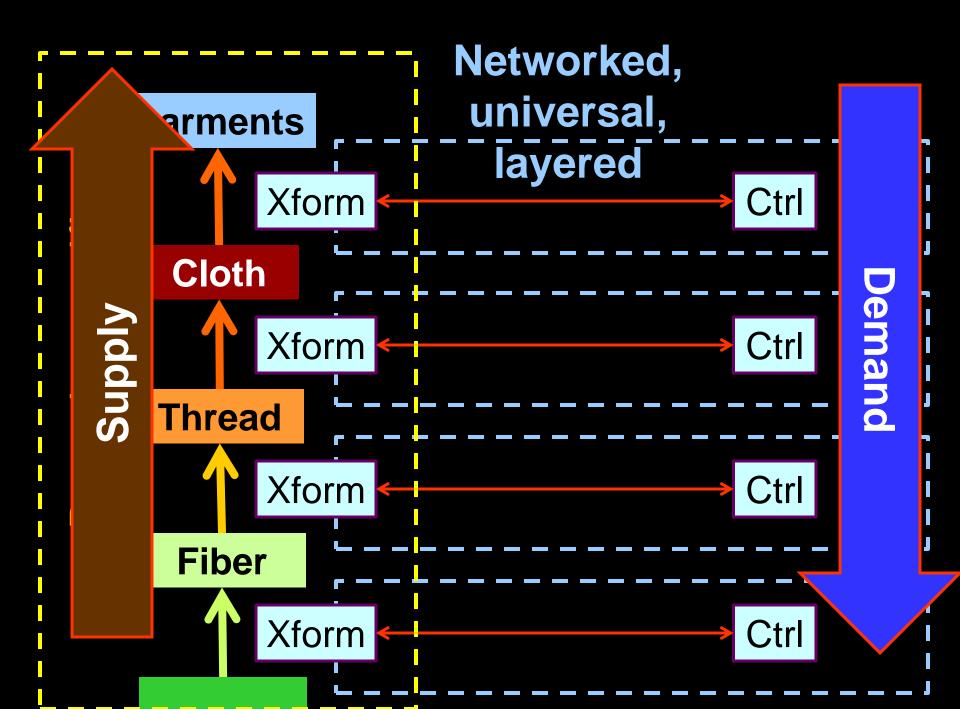


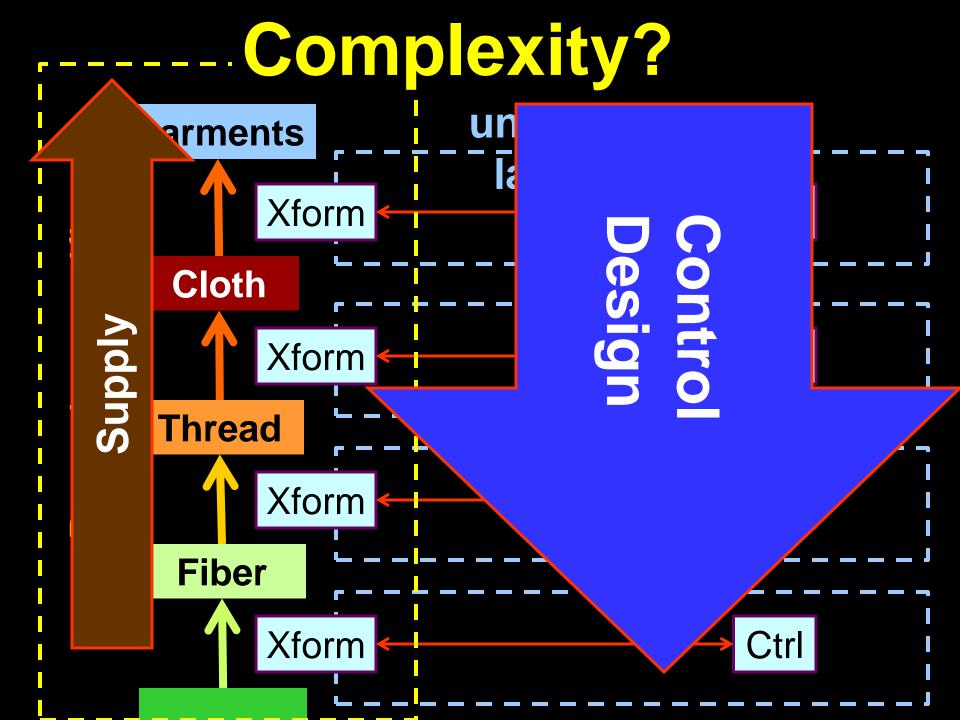


# Assembly

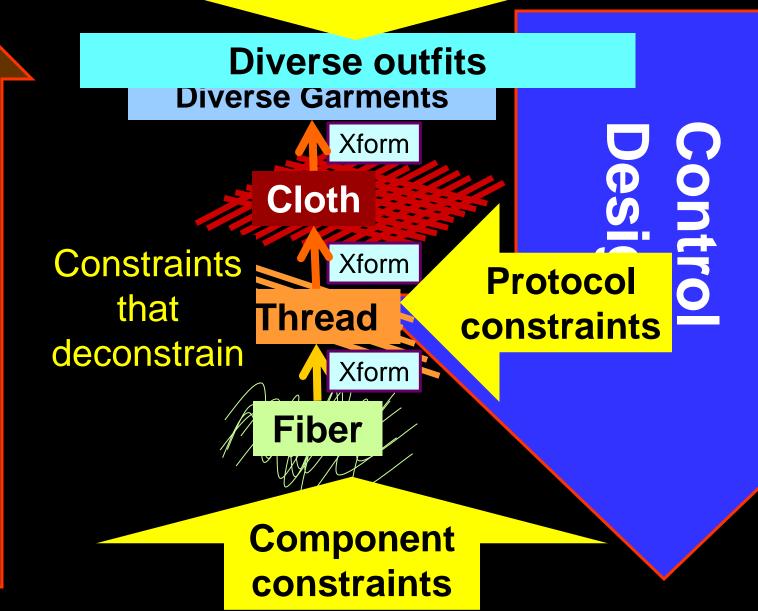






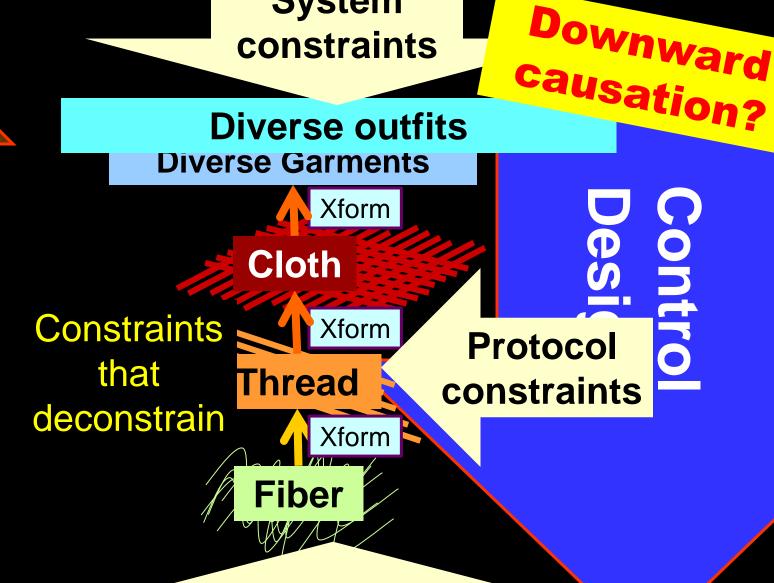


### System constraints



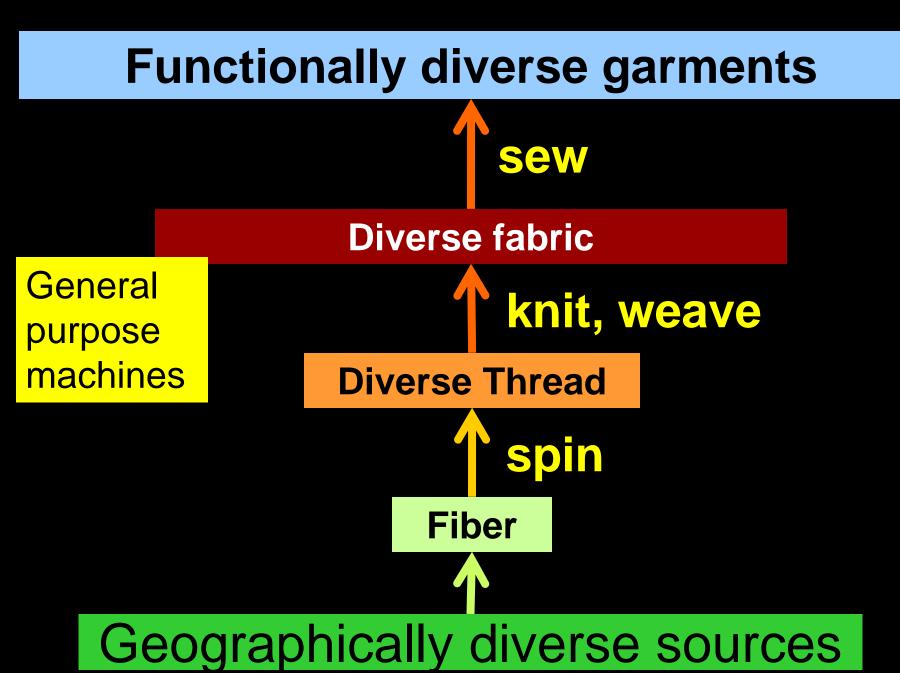
Assembly

### System constraints



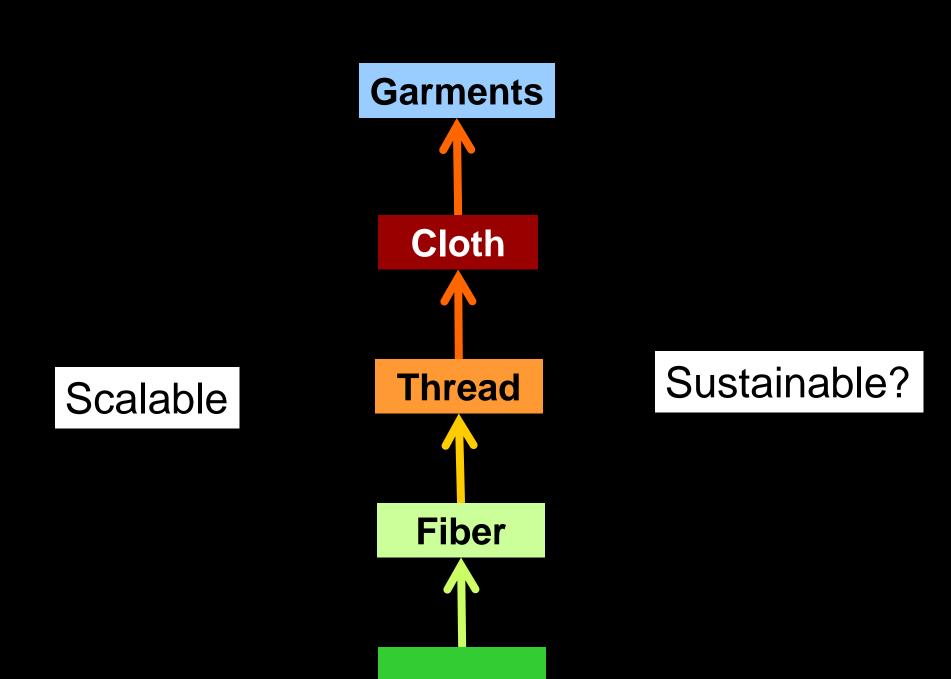
Assembly

Component constraints

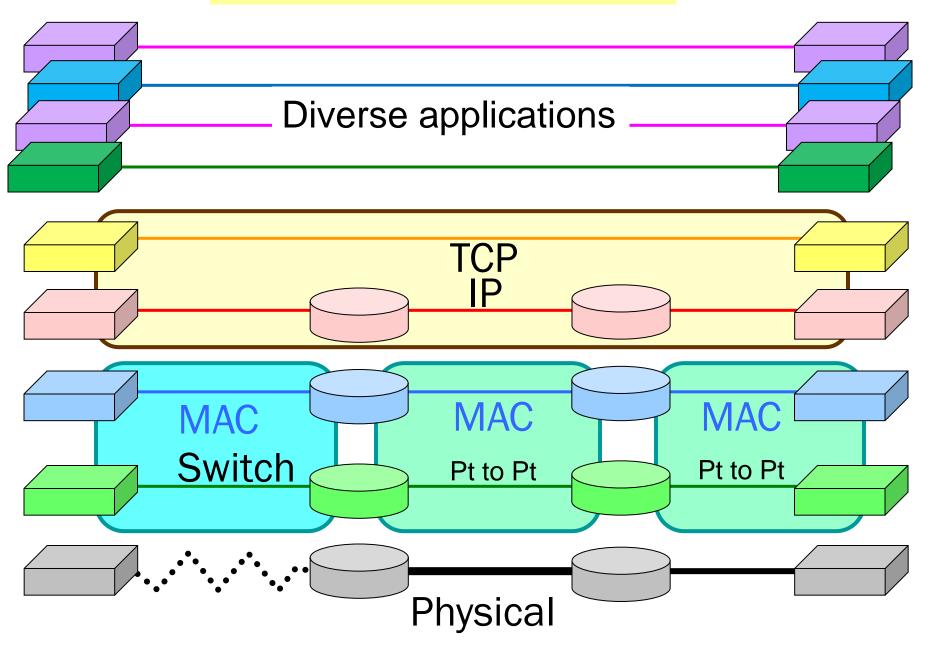


# **Functionally diverse garments**

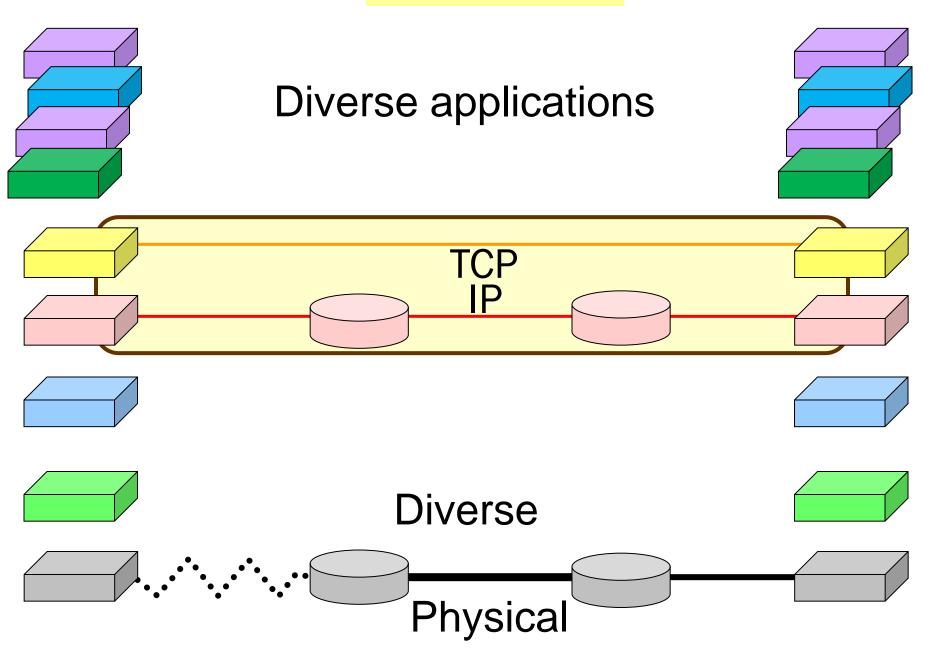




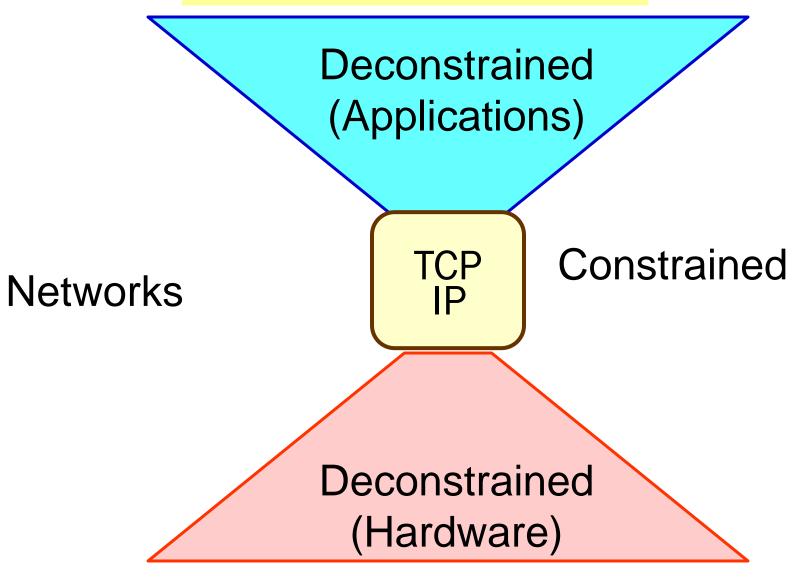
### **Layered architectures**



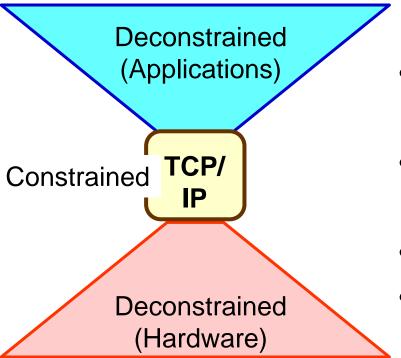
**Too clever?** 



### Layered architectures



"constraints that deconstrain" (Gerhart and Kirschner)



# Networked OS

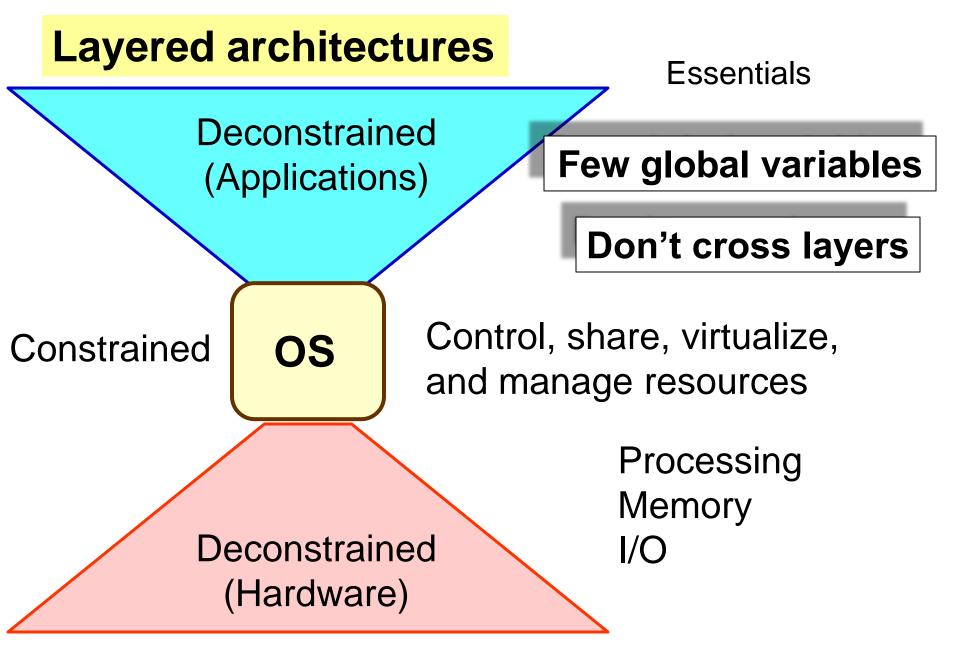
- OS better starting point than
   phone/comms systems
- Extreme robustness confers surprising evolvability
- Creative engineers
- Rode hardware evolution

### Facilitated wild evolution Created

- whole new ecosystem
- completely opposite



### Architecture



### **Layered architectures**

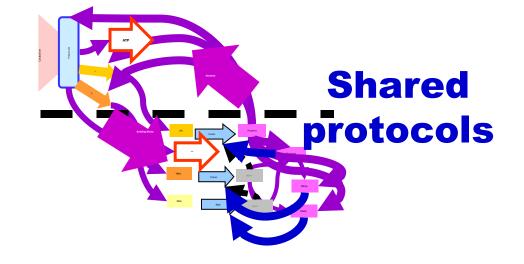
Deconstrained (diverse) Environments

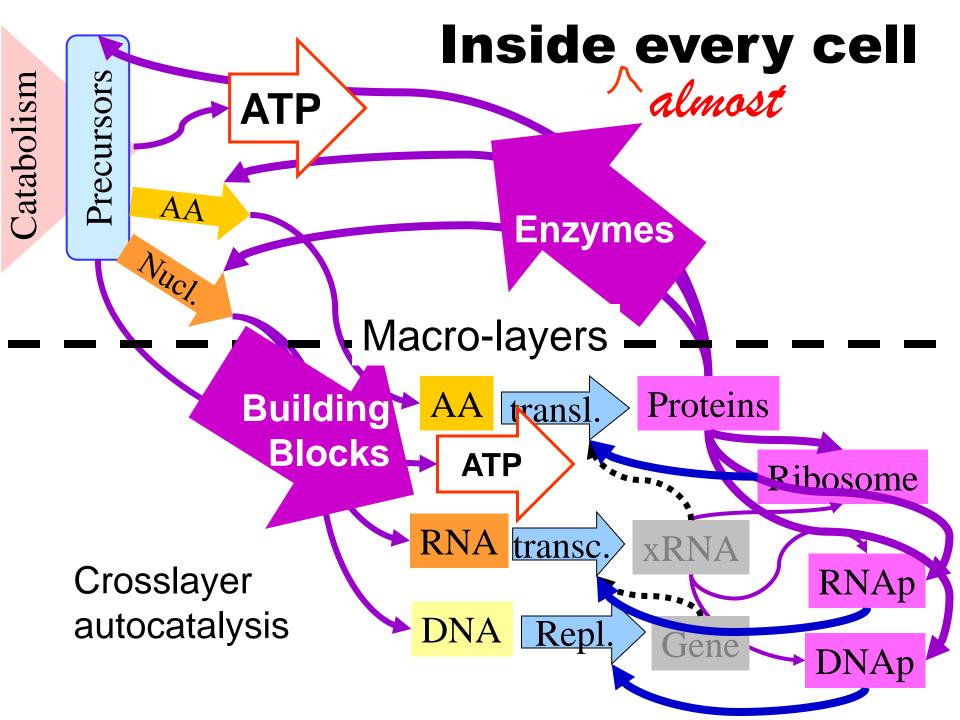
# Bacterial biosphere

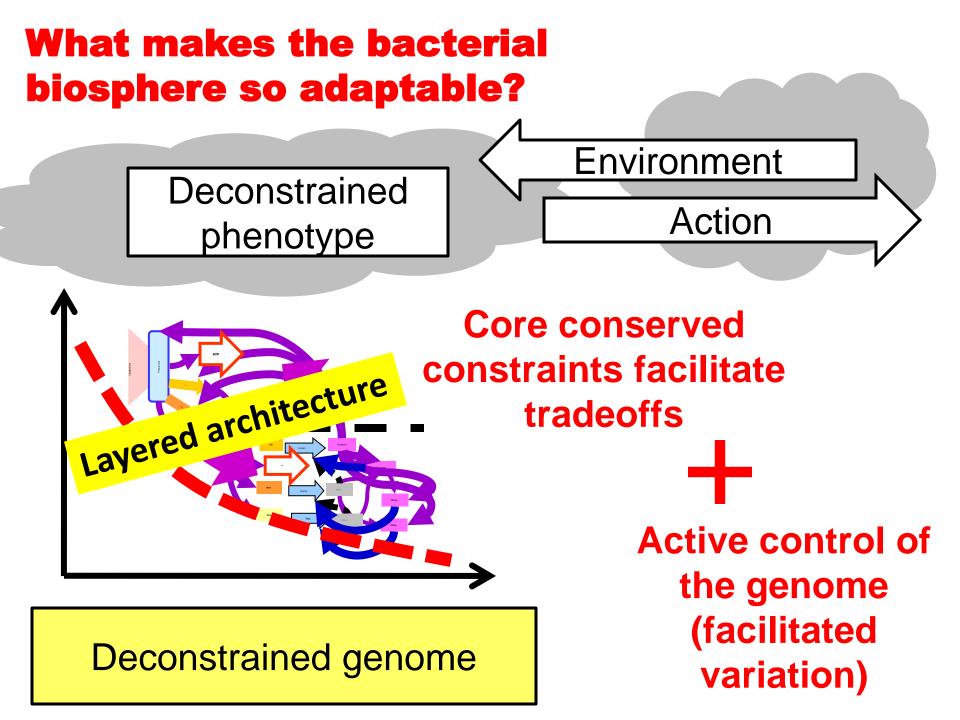
Architecture

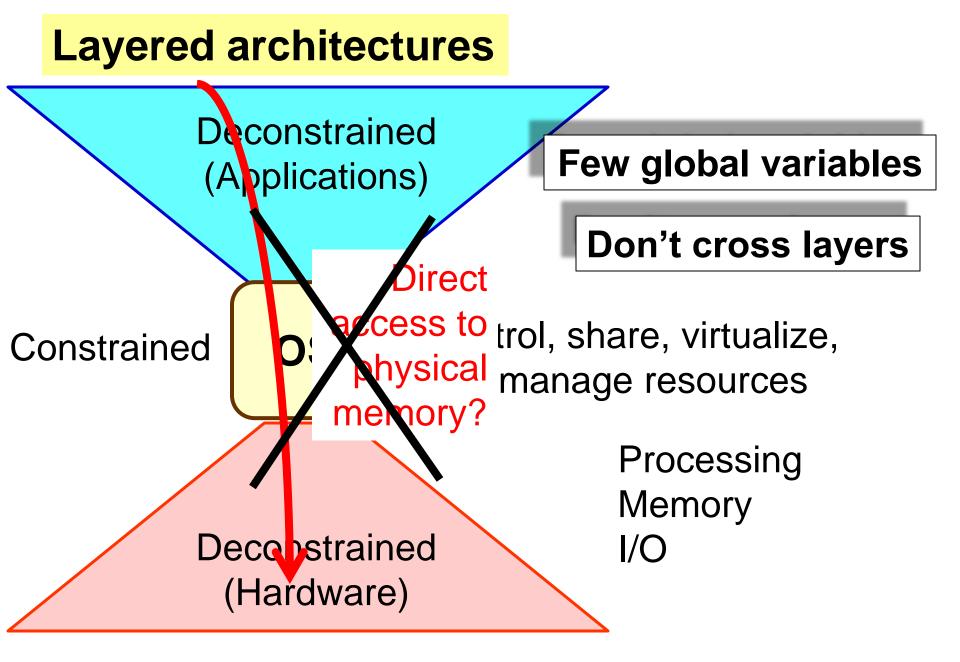
Constraints that Deconstrain

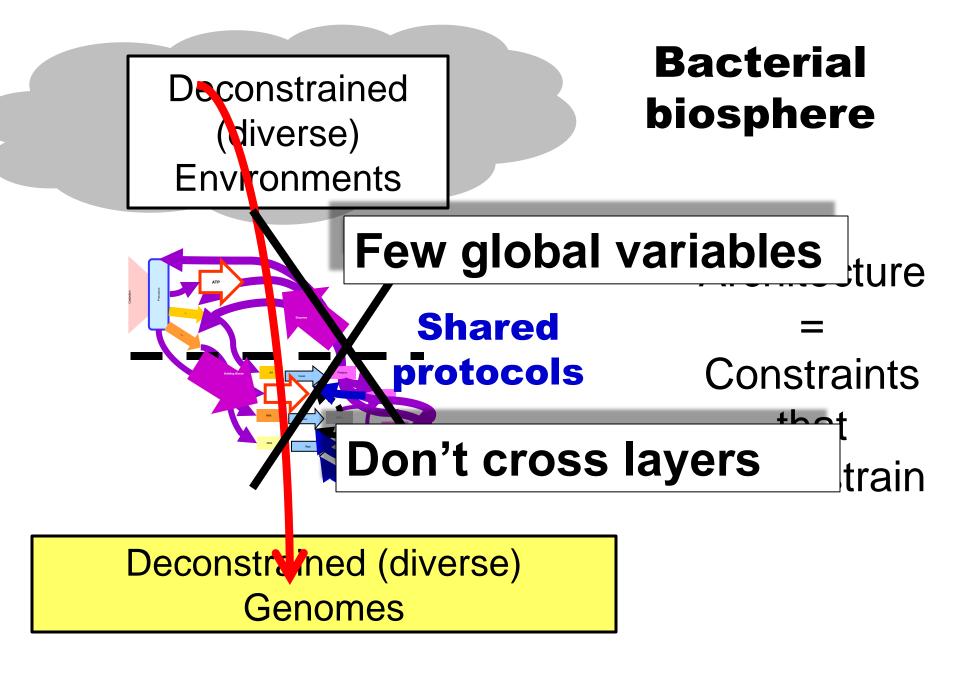
Deconstrained (diverse) Genomes











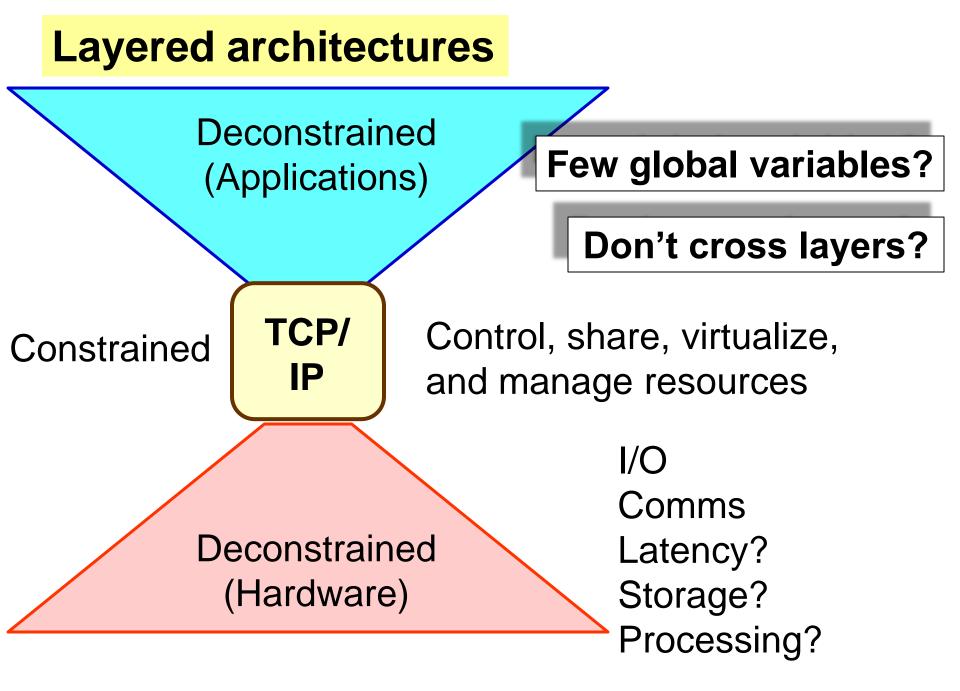
## Problems with *leaky* layering

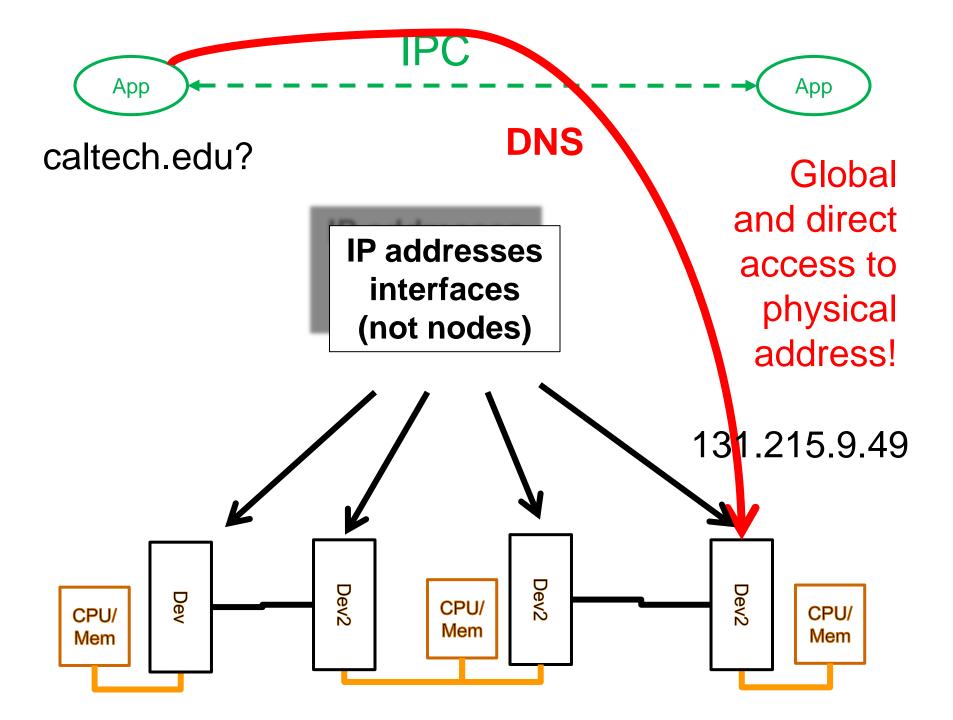
Modularity benefits are lost

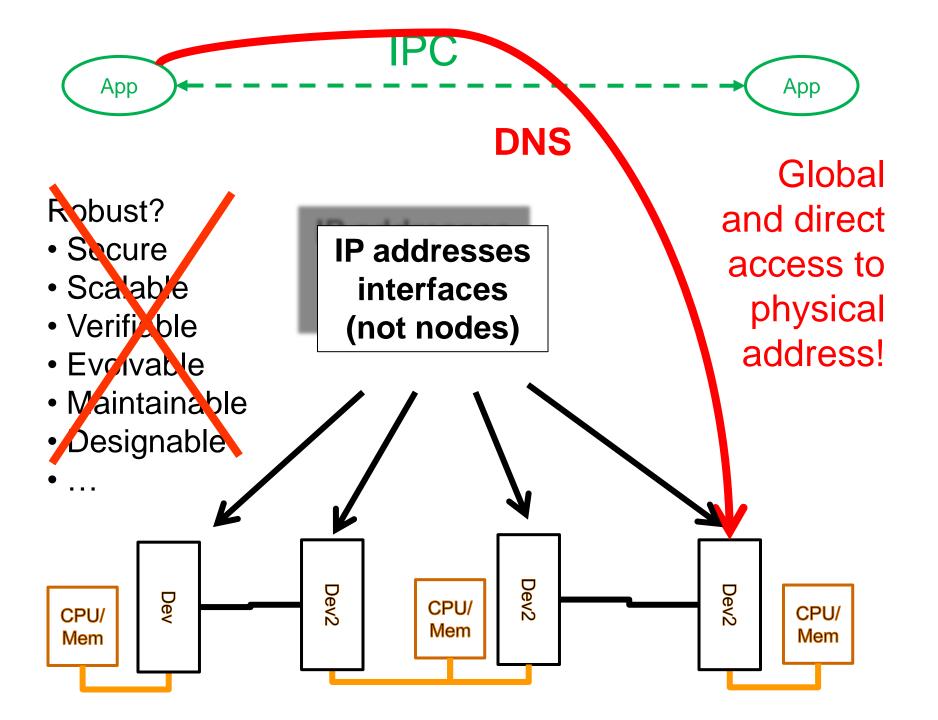
- Global variables? @\$%\*&!^%@&
- Poor portability of applications
- Insecurity of physical address space
- Fragile to application crashes
- No scalability of virtual/real addressing
- Limits optimization/control by duality?

## Fragilities of layering/virtualization

- "Universal" fragilities that must be avoided
- Hijacking, parasitism, predation
  - Universals are vulnerable
  - Universals are valuable
- Cryptic, hidden
  - breakdowns/failures
  - unintended consequences
- Hyper-evolvable but with frozen core





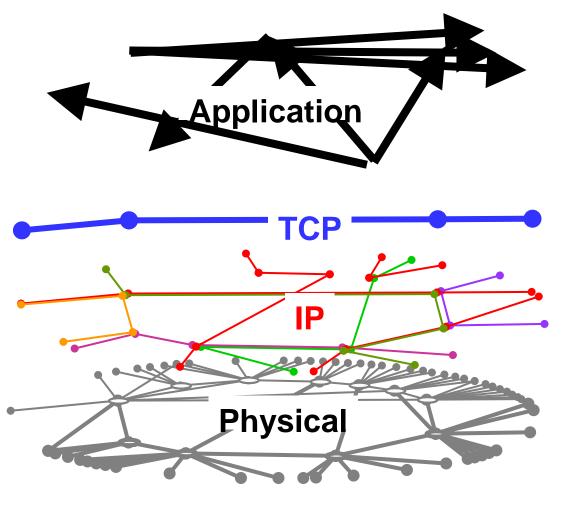


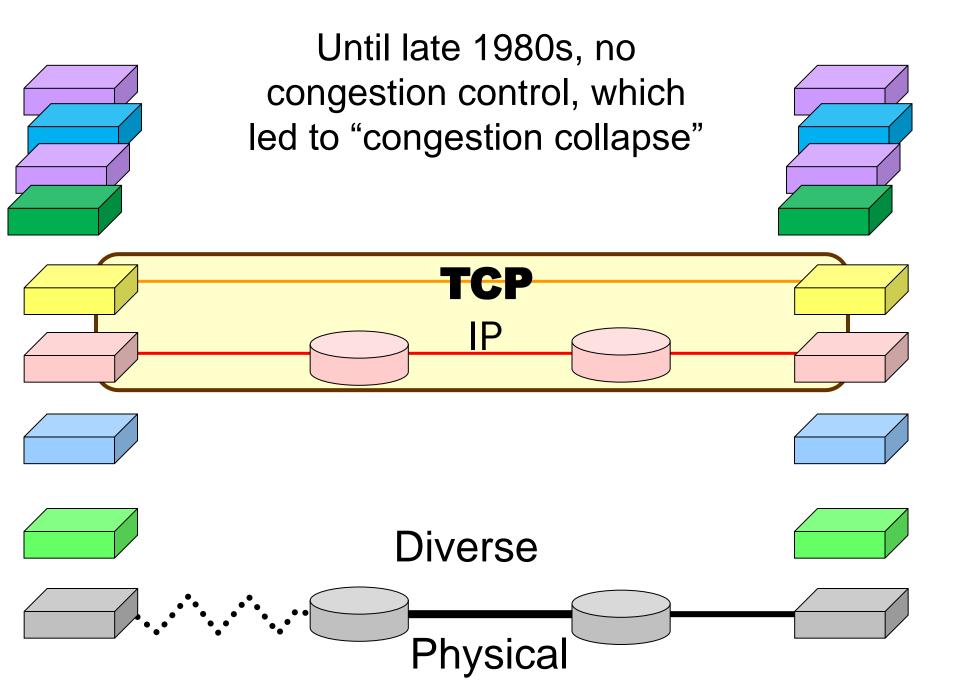
Naming and addressing need to be

- resolved within layer
- translated between layers
- not exposed outside of layer

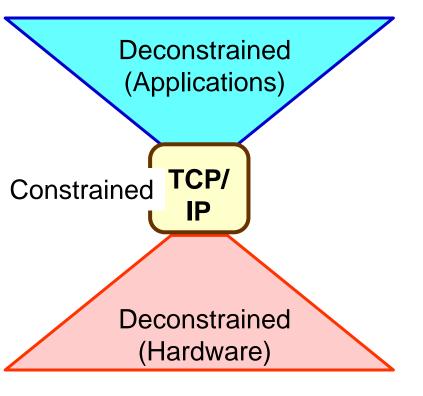
### Related "issues"

- VPNs
- NATS
- Firewalls
- Multihoming
- Mobility
- Routing table size
- Overlays





## **Original design challenge?**

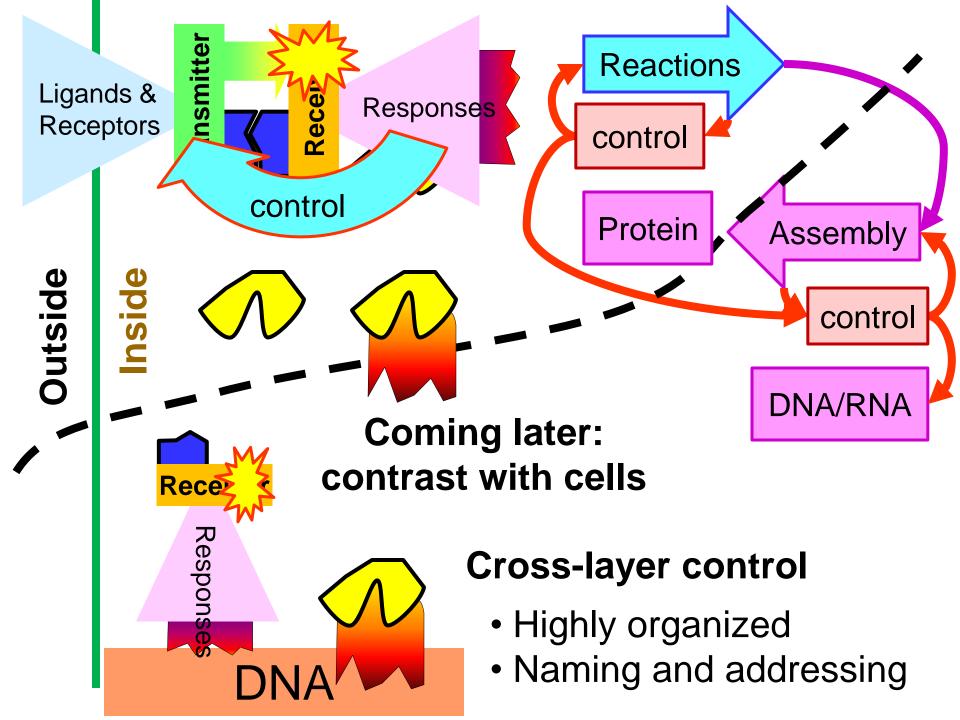


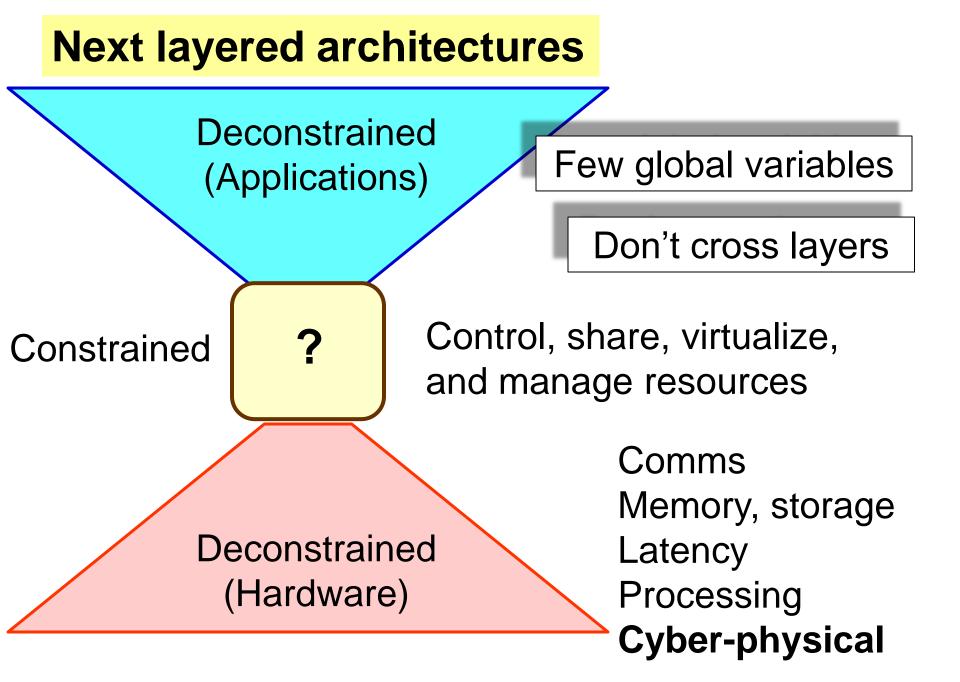
### Networked OS

- Expensive mainframes
- Trusted end systems
- Homogeneous
- Sender centric
- Unreliable comms

Facilitated wild evolution Created

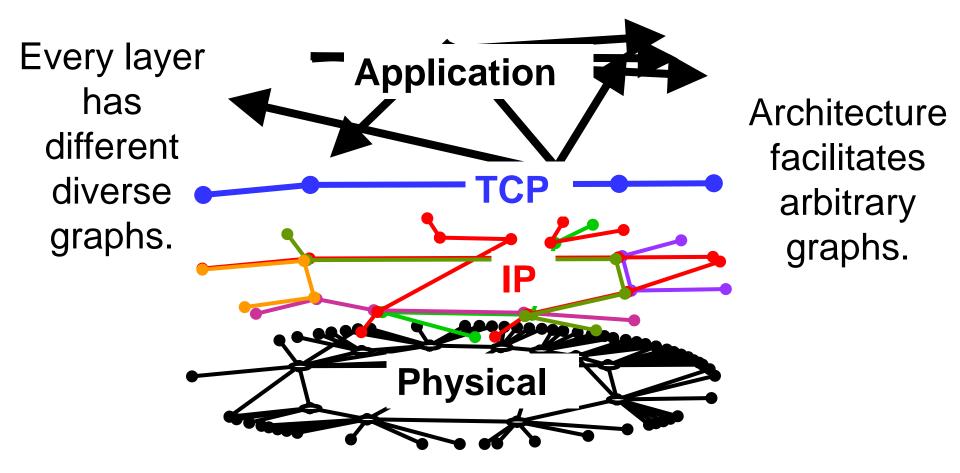
- whole new ecosystem
- completely opposite





#### Persistent errors and confusion ("network science")

Architecture is *least* graph topology.



# The "robust yet fragile" nature of the Internet

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The search for unifying properties of complex networks is popular, challenging, and important. For modeling approaches that focus on

SVNJ

no self-loops or parallel edges) having the same graph degree We will say that graphs  $g \in G(D)$  have scaling-degree sequen

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