CDS 212

2011 website:
https://www.cds.caltech.edu/wiki/index.php/CDS_212_Fall_2011

The two primary texts for the course (available via the online) are


The following additional texts may be useful for some students:

“Universal laws and architectures?”

- Universal “conservation laws” (constraints)
- Universal architectures (constraints that deconstrain)
- Start a dialog
- Mention recent papers*
- Focus on broader context not in papers
- Lots of case studies (motivate & illustrate)
- You can have all of the slides

*try to get you to read them?
“Universal laws and architectures?”

- Universal “conservation laws” (constraints)
- Universal architectures (constraints that deconstrain)
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*try to get you to read them?
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

John C. Doyle\textsuperscript{a,1} and Marie Csete\textsuperscript{b,1}

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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.
Sensory
Motor
Prefrontal
Striatum
Reflex
Catabolism
AA
RN
A
transl.
Proteins
xRNA
transc.
Precursors
DNA
Repl.
Gene
ATP
Ribosome
RNAp
DNAP
Gene
Horizontal Gene Transfer
Horizontal App Transfer
Software
Hardware
Digital
Analog
Horizontal Meme Transfer
Learning
Prefrontal
Sensory
Striatum
Reflex
Horizontal App Transfer
ATP
A
transl.
A
transl.
DNAp
Gene
Ribosome
xRNA
RN
Horizontal Gene Transfer
Horizontal Meme Transfer
Catabolism
Precursors
ATP
NAD
AA
• Cell biology
• Networking
• Neuroscience
• Medical physiology
• Smartgrid, cyber-phys
• Wildfire ecology
• Earthquakes
• Lots of aerospace
• Physics:
  – turbulence,
  – stat mech (QM?)
• “Toy”:
  – Lego,
  – clothing,
• Buildings, cities
• **Synesthesia**
Case studies (recent focus)

- Bacterial biosphere
- Internet, PC, smartphone, etc technology
- Human brain and mind
- Human physiology

- *Amazing* evolvability (sustainability?)
- Illustrate universal laws and architecture in (hopefully) accessible way
Case studies (purpose)

• Illustrate/motivate theory and universals
  – Laws (constraints, hard limits, tradeoffs)
  – Architectures (design, forward and reverse engineering, organization)
  – Otherwise publish in eng/systems/math journals

• Impact for domain experts
  – Frameworks to organize existing, isolated facts
  – Suggests new experiments
  – Publish in core domain journals (Science, Cell, PNAS, ACM Sigcomm, Science Trans Med, …)
Universal “laws” (constraints)

- Constraints “bottom up” from physics/chemistry
  - Gravity, speed of light
  - Energy, carbon, …
  - Small moieties (redox, …)… more later?

- **But**, the most universal laws for bio&tech are largely *independent* of physics
- Most scientists and many engineers don’t understand and/or believe this is even possible
- So skepticism is warranted
- We’ll come back to this after we discuss universal architectures
When concepts fail, words arise

Faust, Goethe

Mephistopheles. …Enter the templed hall of Certainty.

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

Mephistopheles. Quite true! But don't torment yourself too anxiously;
For at the point where concepts fail, 
At the right time a word is thrust in there…
Requirements on systems and architectures

accessible accountable accurate adaptable administrable affordable auditable autonomy available credible process capable compatible composable configurable correctness customizable debuggable degradable determinable demonstrable dependable deployable discoverable distributable durable effective efficient **evolvable** extensible failure transparent fault-tolerant fidelity flexible inspectable installable Integrity interchangeable interoperable predictable productive provable recoverable relevant reliable repeatable reproducible resilient responsive responsive reusable robust safety scalable seamless self-sustainable serviceable supportable securable sustainable simplicity stable standards compliant survivable sustainable tailorable testable timely traceable ubiquitous understandable understandable usable usable
Requirements on systems and architectures

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

**Long term**

evolvable sustainable
Lumping requirements into simple groups

- accessible
- accountable
- accurate
- adaptable
- administrable
- affordable
- auditable
- autonomous
- available
- compatible
- composable
- configurable
- correct
- customizable
- debugable
- degradable
- determinable
- demonstrable

- dependable
- deployable
- discoverable
- distributable
- durable
- effective
- failure
- transparent
- fault-tolerant
- fidelity
- flexible
- inspectable
- installable
- Integrity
- interchangeable
- interoperable
- learnable
- maintainable

- manageable
- mobile
- modifiable
- modular
- nomadic
- operable
- orthogonality
- portable
- precision
- predictable
- producible
- provable
- recoverable
- relevant
- reliable
- repeatable
- reproducible
- resilient
- responsive
- reusable

- safety
- scalable
- seamless
- self-sustainable
- serviceable
- supportable
- securable
- simple
- stable
- standards
- survivable
- tailorable
- testable
- timely
- traceable
- ubiquitous
- understandable
- upgradable
- usable

- efficient
- sustainable
- robust
Requirements on systems and architectures

- efficient
- robust
- sustainable
Requirements on systems and architectures

- Efficient
- Robust
- Sustainable
Requirements on systems and architectures

- Efficient
- Robust
- Sustainable
- Fragile
- Wasteful
Requirements on systems and architectures

- efficient
- robust
- fragile
- wasteful
- sustainable
Requirements on systems and architectures

- Efficient
- Robust
- Sustainable
- Fragile
- Wasteful

Ideally, systems and architectures should be sustainable and robust, while avoiding being fragile and wasteful. The diagram shows the tension between these qualities, with sustainability and robustness on one axis and efficiency and wastefulness on the other. The line marked 'Achievable' indicates the boundary of what is practically attainable.
At best we get one

Current Technology?
Often neither
Future evolution of the “smart” grid?
Bad theory?

Bad architectures?

fragile

efficient

robust

wasteful

gap?
laws and architectures?

- Sharpen hard bounds
- Case studies

- fragile
- robust

- efficient
- wasteful

Hard limit
Even with a murky picture

Find and fix bugs

Sharpen hard bounds

Case studies

Bad 😞
Flow of materials and energy

Efficient Resource

Wasteful Resource

Efficient Waste

Wasteful Waste

efficient wasteful
Perfect = all conserved resources are converted into product
Efficient Resources

Product
Waste

Impossible Resources

Product
Waste

Wasteful Resources

Product
Waste
Flow of materials and energy

Efficient Resource

Wasteful

Waste

efficient wasteful

Product

Resource

Product

Resource
Efficient Resource Product Waste
efficient wasteful Perturb

Product Efficient Resource
Waste

efficient wasteful
Efficient
Resource
Product
Waste
Components
System
Efficient
Perturb
fragile
robust
efficient
wasteful
Feedbacks for robustness and efficiency
Theory?
Deep, but fragmented, incoherent, incomplete

Control, OR

Comms
Compute
Godel
Shannon
Turing
Von Neumann
Nash
Bode
Pontryagin
Kalman
Carnot
Boltzmann
Heisenberg
Einstein
Physics
Each theory $\approx$ one dimension
- Laws=hard limits
- Architectures fixed
- Scalable algorithms for design in comp/comm/cont
• Each theory $\approx$ one dimension
• Tradeoffs across dimensions
• Assume architectures a priori
• Progress is encouraging, but…
• Stovepipes are an obstacle…
• Limited “universality”
Control, OR

Compute

Turing

Delay is *most* important

Communicate

Shannon

Delay is *least* important

Bode

Physics

Carnot

Boltzmann

Heisenberg

Einstein

Delay is most important

Delay is least important
delay=death

sense

move

Spine
Flexor Reflex

- Pain receptor
- Sharp tack
- Alpha motor neurons
- Excitatory interneurons
- SN

Diagram showing the pathway of the flexor reflex involving pain receptor, alpha motor neurons, and excitatory interneurons.
Vestibulo-ocular reflex

1. Detection of rotation

2. Inhibition of extraocular muscles on one side.

2. Excitation of extraocular muscles on the other side

3. Compensating eye movement
Same actuators
Delay is limiting

Move head
Sense

Fast
Act

Move hand
Sense

Fast?

Slow

Slow

Act
\[ x_{t+1} = px_t + w_t + u_{t-a} \]

\( p > 1 \)
No delay or no uncertainty

\[ u_{t-a} = -\left( px_t + w_t \right) \]

\[ \Rightarrow \| x \| \approx 0 \quad \| u \| \approx \| w \| \]

\[ x_{t+1} = px_t + w_t + u_{t-a} \]

\[ p > 1 \]
No delay or no uncertainty

\[ u_{t-a} = -(px_t + w_t) \]

\[ \Rightarrow \|x\| \approx 0 \quad \|u\| \approx \|w\| \]

With delay and uncertainty

\[ x_{t+1} = px_t + w_t + u_{t-a} \]

\[ \Rightarrow \|x\| \approx \|u\| \approx p^a \|w\| \]

\( p > 1 \)
Delay is most important

New progress!

Lowering the barrier
Resource

Waste

Function

Process

Control

Recycle

& autocatalysis

Case studies

Wasteful

efficient

robust

fragile

Sharpen

hard

bounds
Glycolytic Oscillations and Limits on Robust Efficiency

Fiona Chandra, Genti Buzi, and John Doyle

www.sciencemag.org  SCIENCE  VOL 333  8 JULY 2011

Case studies

Most important paper so far.
Theorem! \[
\frac{1}{\pi} \int_0^\infty \frac{1}{S(j\omega)} \ln \left( \frac{z}{z^2 + \omega^2} \right) d\omega \geq \ln \left( \frac{z + p}{z - p} \right)
\]

\(z\) and \(p\) functions of enzyme complexity and amount

Fragility

\[\ln \left( \frac{z + p}{z - p} \right)\]

Simple enzyme

Complex enzyme

Enzyme amount

Savageaumics
Hard tradeoff/constraint in glycolysis
- resolves central, persistent mystery
- **robustness vs efficiency**
- **autocatalysis** has crucial role
- oscillations are side effects w/o “purpose”
- new experiments, directions, questions,…

\[
\frac{1}{\pi} \int_0^\infty \ln |S(j\omega)| \left| \frac{z}{z^2 + \omega^2} \right| d\omega \\
\geq \ln \left| \frac{z + p}{z - p} \right|
\]
What (some) reviewers say

• “...to establish universality for all biological and physiological systems is **simply wrong**. It cannot be done...

• ... a mathematical scheme **without any real connections to biological or medical**...

• ...universality is well justified in physics... for biological and physiological systems ...a **dream that will never be realized**, due to the vast diversity in such systems.

• ...**does not seem to understand or appreciate** the vast diversity of biological and physiological systems...

• ...**a high degree of abstraction, which ...make[s] the model useless** ...
This picture is very general

Fragile

Simple tech

Robust

Complex tech

Cheap

Large delay $\tau$

Fast multiply


Metabolic expensive

Small $\tau$

Slow
I recently found this paper, a rare example of exploring an explicit tradeoff between robustness and efficiency. This seems like an important paper but it is rarely cited.
Phage lifecycle

Survive

Multiply

Lyse

Infect
slow
fragile
fast
robust
Survive
thin
small
Good architectures?
Capsid Genome
thick
big
Hard limits?
Multiply
fast
slow
fragile
Survive
robust
Efficiency in Evolutionary Trade-Offs
Elad Noor and Ron Milo
Science 336, 1114 (2012);

Evolutionary Trade-Offs, Pareto Optimality, and the Geometry of Phenotype Space
O. Shoval et al.
Science 336, 1157 (2012);

Multidimensional Optimality of Microbial Metabolism
Robert Schuetz, Nicola Zamboni, Mattia Zampieri, Matthias Heinemann, Uwe Sauer*
\[
\frac{1}{\pi} \int_{0}^{\infty} \ln|S(j\omega)|d\omega = 0
\]

\[
\frac{1}{\pi} \int_{0}^{\infty} \ln|S(j\omega)|d\omega = \frac{1}{\pi} \int_{0}^{\infty} \left( \ln|E(j\omega)| - \ln|D(j\omega)| \right) d\omega
\]
Linearized pendulum on a cart

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

\[q = J(M + m) + Mml^2\]
\[(M + m) \ddot{x} + ml(\ddot{\theta} \cos \theta - \dot{\theta}^2 \sin \theta) = u\]
\[\ddot{x} \cos \theta + l\ddot{\theta} + g \sin \theta = 0\]
\[y = x + \alpha l \sin \theta\]

**linearize**

\[(M + m) \ddot{x} + ml\ddot{\theta} = u\]
\[\ddot{x} + l\ddot{\theta} \pm g \theta = 0\]
\[y = x + \alpha l \theta\]
Robust
= agile and balancing
Robust
= agile and balancing
Efficient = length of pendulum (artificial)
\[
\begin{bmatrix}
x \\
\theta
\end{bmatrix} = \frac{1}{D(s)} \begin{bmatrix}
l s^2 \pm g \\
- s^2
\end{bmatrix} u
\]

\[D(s) = s^2 \left(M l s^2 \pm (M + m) g\right)\]

\[y = x + \alpha l \theta = \frac{\varepsilon l s^2 \pm g}{D(s)}\]

\[\varepsilon = 1 - \alpha\]

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

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

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

\[y = x + \alpha l \theta\]
Delay $\tau$

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

$|T(j\omega)| = \left| \frac{E}{N} \right|$
\[
\frac{1}{\pi} \int_{0}^{\infty} \ln |T(j\omega)| d\omega \geq 0
\]

\[
\frac{1}{\pi} \int_{0}^{\infty} \ln |S(j\omega)| d\omega \geq 0
\]

Easy, even with eyes closed
No matter what the length

Proof: Standard UG control theory:
    Easy calculus, easier contour integral,
easiest Poisson Integral formula
\[ \frac{1}{\pi} \int_{0}^{\infty} \ln |S(j\omega)| \, d\omega = 0 \]

\[ \frac{1}{\pi} \int_{0}^{\infty} \ln |S(j\omega)| \, d\omega = \frac{1}{\pi} \int_{0}^{\infty} \left( \ln |E(j\omega)| - \ln |D(j\omega)| \right) \, d\omega = 0 \]
Harder if delayed or short

Delay

Short
Also harder if sensed low (details later)

\[ r = \frac{m}{M} \]
Delay $\tau$

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

$|T(j\omega)| = \left| \frac{E}{N} \right|$
\[
\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \cdot \frac{2p}{p^2 + \omega^2} \, d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
Delay $\tau$ is hard

Any controller so is an intrinsic constraint on the difficulty of the problem.

\[
\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
\[
\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
We would like to tolerate large delays (and small lengths), but large delays severely constrain the achievable robustness.
Delay $\tau$

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

$M$

Short is hard

$$\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}$$
\[
\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}
\]

For fixed delay

Why oscillations?
Side effects of hard tradeoffs

Fragility

Too fragile

\[p \propto \sqrt{\frac{1}{l}}\]
The ratio of delay between people is proportional to the lengths they can stabilize.

\[ \frac{1}{\pi} \int_{0}^{\infty} \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}} \]
Eyes moved down is harder (RHP zero)
Similar to delay
Suppose $r = \frac{m}{M} \ll 1$

Units $\Rightarrow M = g = 1$

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

$$p \approx \sqrt{\frac{g}{l}} \quad z = \sqrt{\frac{g}{l} \frac{1}{\varepsilon}} \Rightarrow \frac{z + p}{z - p} = \frac{1 + \sqrt{\varepsilon}}{1 - \sqrt{\varepsilon}}$$
Compare

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

Move eyes

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

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

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

\[ = p \left(1 + \frac{1-\alpha}{3}\right) \]
\[ \frac{1}{\pi} \int_0^\infty \ln |S(j\omega)| \left( \frac{2z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right| \]
\[ \frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \left( \frac{2p}{p^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right| \]

\[ \varepsilon = \frac{1}{1 + r} \]

\[ \frac{z + p}{z - p} = \frac{1 + \sqrt{\varepsilon}}{1 - \sqrt{\varepsilon}} \]

This is a cartoon, but can be made precise.
Hard limits on the \textit{intrinsic} robustness of control \textit{problems}.

Must (and do) have algorithms that achieve the limits, and architectures that support this process.

\[
\frac{\ln \left| \frac{z + p}{z - p} \right|}{z - p} \leq \frac{1}{\pi} \int_{0}^{\infty} \ln |S(j\omega)| \left( \frac{2z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right|
\]
How general is this picture?


fragile

robust

efficient

wasteful

simple tech

complex tech
I recently found this paper, a rare example of exploring an explicit tradeoff between robustness and efficiency. This seems like an important paper but it is rarely cited.
Phage lifecycle

- Multiply
- Survive
- Lyse
- Infect
Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,1* Gentian Buzi,2 John C. Doyle2

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.
Theorem!

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

\( z \) and \( p \) functions of enzyme complexity and amount

Fragility

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

Savageaumics

simple enzyme

complex enzyme

Enzyme amount
Hard tradeoff in glycolysis is

- too fragile with simple control
- plausibly robust with complex control
- too fragile without autocatalysis
- absent without robustness vs efficiency

Simple, but too fragile

No tradeoff

expensive

$\ln \left| \frac{z}{z-p} \right| \leq \ln \left| \frac{z}{z+p} \right| + \frac{1}{\pi} \int_{0}^{\infty} \ln |S(j\omega)| \left| \frac{z}{z^2 + \omega^2} \right| d\omega$
This picture is very general


Fragile
- simple tech

Robust
- complex tech

Cheap
- large delay $\tau$
- fast multiply

Metabolic expensive
- small $\tau$
- slow
### Domain specific costs/tradeoffs

<table>
<thead>
<tr>
<th>Aspect</th>
<th>cheap</th>
<th>expensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic overhead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS reaction time $\tau$ (delay)</td>
<td>large $\tau$</td>
<td>small $\tau$</td>
</tr>
<tr>
<td>Phage multiplication rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This picture is very general

- fragile
- robust

- simple tech
- complex tech

- metabolic cost
- reaction time $\tau$
- phage x rate

- cheap ↔ expensive
- large $\tau$ ↔ small $\tau$
- fast ↔ slow

Domain specific costs/tradeoffs
Survive

fragile

robust

thin small

Capsid thickness Genome size

Good architectures?

Hard limits?

fast multiply slow

slow multiply
\[ \frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq p\tau \propto \tau \sqrt{\frac{1}{l}} \]
\[
\frac{1}{\pi} \int_0^\infty \ln |S(j\omega)| \left( \frac{2z}{z^2 + \omega^2} \right) d\omega \geq \ln \left| \frac{z + p}{z - p} \right|
\]

This is a cartoon, but can be made precise.
Hard tradeoff in glycolysis is

- **robustness vs efficiency**
- **absent without autocatalysis**
- **too fragile with simple control**
- **plausibly robust with complex control**
Turing has the original “universal law”. 

Really slow computational complexity.

Decidable: Flexible/General

NP: Inflexible/Specific

P
This is about speed and flexibility of computation.

How do these two constraints (laws) relate?

Computation delay adds to total delay.

Computation is a component in control.

This is about speed and flexibility of computation.
Delay comes from sensing, communications, computing, and actuation. Delay limits robust performance.

\[ \frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}} \]
Delay makes control hard.

Computation delay adds to total delay.

Computation is a component in control.

\[
\frac{1}{\pi} \int_0^\infty \ln|T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
This needs formalization:

What *flexibility* makes control hard?

Large, structured uncertainty?
Fragility

Limitations on hard limits

- General
- Rigorous
- First principle

Overhead, waste

• Simple
• Complex

Plugging in domain details

- Domain specific
- Ad hoc
- Phenomenological
Components of robustnessness

- Robust
- Efficient
- Wasteful
- Fragile

Achievable
Not
Components of robustness

fragile  fragile

robust  robust
Speed and flexibility

- Robust
- Inflexible
- Fragile

- Solve problems
- Make decisions
- Take actions

- Fast
- Slow

- Flexible
- Inflexible
Laws and architectures

- Fast
- Slow
- Flexible
- Inflexible

Architecture (constraints that deconstrain)

Architecture (laws, constraints)
# Architecture case studies comparison

<table>
<thead>
<tr>
<th></th>
<th>Bacteria+</th>
<th>Internet+</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understood?</td>
<td>😊</td>
<td>😊😊</td>
<td>😓</td>
</tr>
<tr>
<td>By scientists?</td>
<td>😊</td>
<td>😓😊😊</td>
<td>😓</td>
</tr>
<tr>
<td>Live demos?!?</td>
<td>😓</td>
<td>😊</td>
<td>😊😊</td>
</tr>
<tr>
<td>Who cares?</td>
<td>😓*</td>
<td>😊</td>
<td>😊😊</td>
</tr>
<tr>
<td>Design quality?</td>
<td>😊😊😊</td>
<td>😊😊😊</td>
<td>😊😊实实在</td>
</tr>
<tr>
<td>∃ Math?</td>
<td>😊</td>
<td>😊😊😊</td>
<td>😊😊实实在</td>
</tr>
</tbody>
</table>

*Except for a few bacteriophiles (LC, SR, JD, ?)  
*See also “Bacterial Internet” (LC)
“vertical” + “horizontal” evolution in Bacteria/Internet/Brain in Genes/Apps/Memes

• Vertical (lineages)
  – accumulation of small increments
  – de novo invention
  – Accelerated RosenCaporalian evolution

• Horizontal
  – Swap existing gene/app/meme
  – Source of most individual change?

• Both essential to large scale (r)evolution
“vertical” + “horizontal” evolution in Bacteria/Internet/Brain in Genes/Apps/Memes

- Evolution is *not* only (or even primarily) due to slow accumulation of random mutations

- Effective architectures facilitate *all* aspects of “evolvability”

- Lamarckian and Darwinian
“Evolvability”

• Robustness of lineages to large changes on long timescales

• Essentially an architectural question
  – What makes an architecture evolvable?
  – What does “architecture” mean here?

• What are the limits on evolvability?

• How does architecture, evolvability, robustness, and complexity relate?

• Key: tradeoffs, robustness, layering
“Nothing in biology makes sense except in the light of evolution.”

T Dobzhansky

“Nothing in evolution makes sense except in the light of biology.”

Tony Dean (U Minn) paraphrasing T Dobzhansky
### big picture from high level with a bit of Internet

<table>
<thead>
<tr>
<th></th>
<th>Bacteria</th>
<th>Internet</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understood?</td>
<td>😊</td>
<td>😊 😊 😊</td>
<td>😐</td>
</tr>
<tr>
<td>By scientists?</td>
<td>😊 😊 😊</td>
<td>😐 😐 😐</td>
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<td>😊 😊 😊 🐱</td>
<td>😊 😊 😊</td>
<td>😐 😐 😐</td>
</tr>
</tbody>
</table>
Familiar layered architecture: PC, smartphone, router, etc
Any application can run on any hardware provided they are compatible with the OS.
“hourglass”

Many applications can run on this hardware.
Any application can run on any hardware almost.
Any application can run on any hardware.
OS

Deconstrained (Hardware)

Constrained (Applications)

"hourglass"

Virus

Perturb

Constrained

HW

App

HW

App

HW

App

HW

App

HW

App

HW

App

HW

App

HW

App
Layered architectures

Deconstrained (Applications)

OS

Constrained

Deconstrained (Hardware)

Few global variables

Don't cross layers

Control, share, virtualize, and manage resources

Processing
Memory
I/O

Essentials CS 101
Diverse applications

TCP
IP

Diverse

Physical
Any application can run on any hardware provided they are compatible with the OS or TCP/IP.
Tradeoffs:
PC, smartphone, router, etc

Apps
OS
HW
Digital
Lumped
Distrib.
Tradeoffs:
PC, smartphone, router, etc

- Apps
- OS
- HW
- Digital
- Lumped
- Distrib.
Tradeoffs:
PC, smartphone, router, etc

- Apps
- OS
- HW
- Digital
- Lumped
- Distrib.

- Fast
- Slow

Flexible
- Inflexible

Accident or necessity?
Architecture?

Slow

Apps
OS
HW
Digital
Lumped
Distrib.

OS
HW
Digital
Lumped
Distrib.

Digital
Lumped
Distrib.

Lumped
Distrib.

Fast

Flexible

Inflexible
Shared architecture and infrastructure is and must be mostly hidden.
Slow
Flexible

Software
Hardware

Digital
Analog

Fast
Inflexible

Efficiency?
Bacteria and brains have similar:
- layered architectures
- tradeoffs and constraints

Need
- Details
- Theorems
Flexible/Adaptable/Evolvable

Horizontal Mem Transfer

Sensory

Prefrontal

Striatum

Learning

Catabolism

RN

AA

xRNA

transc.

Precursors

Software

Hardware

Reflex

Horizontal App Transfer

Digital

Analog

Depends crucially on layered architecture

Horizontal Gene Transfer

RNAP

DNAp

Ribosome

RNAp

Gene

Rep

Repl

Precursors

ATP

Precursors

Hotel

Gene

Transfer

ATP

Nuc.

AA

AA

AA
Sequence ~100 E Coli (not chosen randomly)
- ~ 4K genes per cell
- ~20K different genes in total
- ~ 1K universally shared genes
- ~ 300 essential (minimal) genes

See slides on bacterial biosphere
Mechanisms in molecular biology

0. HGT (Horizontal Gene Transfer)
1. DNA replication
2. DNA repair
3. Mutation
4. Transcription
5. Translation
6. Metabolism
7. Signal transduction
8. ...

Think of this as a “protocol stack”
Think of this as a “protocol stack”

Control 1.0

0. HGT
1. DNA replication
2. DNA repair
3. Mutation
4. Transcription
5. Translation
6. Metabolism
7. Signal transduction
8. ...

Highly controlled
Control 2.0

Think of this as a “protocol stack”
Control 2.0

- HGT
- DNA replication
- DNA repair
- Mutation
- Transcription
- Translation
- Metabolism
- Sig. transduct.

- Fast
- Slow

- Flexible
- Inflexible

- Cheap
- Expensive
Central nervous system

CNS “stack”

Prosencephalon

Telencephalon
Hippocampus, Neocortex, Basal ganglia, Lateral ventricles

Diencephalon
Epithalamus, Thalamus, Hypothalamus, Subthalamus, Pituitary gland, Pineal gland, Third ventricle

Mesencephalon
Tectum, Cerebral peduncle, Pretectum, Mesencephalic duct

Rhombencephalon
Metencephalon
Pons, Cerebellum

Myelencephalon
Medulla oblongata

Brain stem

Brain

Spinal cord
Are these “emergent” properties?
"Laws" = hard limits, tradeoffs
The “whole” is constrained to be **much less** than the possible sum of all parts.

“Laws” = hard limits, tradeoffs

Are these “emergent” properties?
Universal architectures

What can go wrong?
Exploiting layered architecture

Virus

Horizontal Bad Gene Transfer

Horizontal Bad App Transfer

Horizontal Bad Meme Transfer

Fragility?

Parasites & Hijacking

Virus
Unfortunately, not intelligent design

Ouch.
Why?

left recurrent laryngeal nerve
Why? Building humans from fish parts.

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.
It could be worse.
Global and direct access to physical address!
Robust?

- Secure
- Scalable
- Verifiable
- Evolvable
- Maintainable
- Designable
- …

Global and direct access to physical address!

IP addresses interfaces (not nodes)
Naming and addressing need to have **scope** and
bullet resolved within layer
bullet translated between layers
bullet not exposed outside of layer

Related “issues”
- VPNs
- NATS
- Firewalls
- Multihoming
- Mobility
- Routing table size
- Overlays
- …
Until late 1980s, no congestion control, which led to “congestion collapse”
Original design challenge?

TCP/IP

Deconstrained (Applications)

Constrained

Deconstrained (Hardware)

Networked OS

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

Facilitated wild evolution

Created

- whole new ecosystem
- completely opposite
Next layered architectures

Deconstrained (Applications)

Deconstrained (Hardware)

Constrained

? Control, share, virtualize, and manage resources

Few global variables

Don’t cross layers

Comms
Memory, storage
Latency
Processing
Cyber-physical
Persistent errors and confusion ("network science")

Every layer has different diverse graphs.

Architecture is \textit{least} graph topology.

Architecture facilitates arbitrary graphs.
The "robust yet fragile" nature of the Internet

John C. Doyle*, David L. Alderson*, Lun Li*, Steven Low*, Matthew Roughan†, Stanislav Shalunov§, Reiko Tanaka‖, and Walter Willinger‖

*Engineering and Applied Sciences Division, California Institute of Technology, Pasadena, CA 91125; †Applied Mathematics, University of Adelaide, South Australia 5005, Australia; §Internet2, 3025 Boardwalk Drive, Suite 200, Ann Arbor, MI 48108; ‡Bio-Mimetic Control Research Center, Institute of Physical and Chemical Research, Nagoya 463-0003, Japan; and ††AT&T Labs–Research, Florham Park, NJ 07932

Edited by Robert M. May, University of Oxford, Oxford, United Kingdom, and approved August 29, 2005 (received for review February 18, 2005)

The search for unifying properties of complex networks is popular, challenging, and important. For modeling approaches that focus on no self-loops or parallel edges) having the same graph degree We will say that graphs $g \in G(D)$ have scaling-degree sequen
Mathematics and the Internet: A Source of Enormous Confusion and Great Potential

Walter Willinger, David Alderson, and John C. Doyle
Reactions

Assembly

DNA/RNA

control

control

DNA

Outside

Inside

Ligands & Receptors

Transmitter

Receiver

Responses

control

control

Protein

Assembly

DNA/RNA

Cross-layer control

- Highly organized
- Naming and addressing

Coming later:
contrast with cells
Ashby & Crossley

- Acquire
- Translate/integrate
- Automate

Thanks to Bassett & Grafton
Ashby & Crossley

- Acquire
- Translate/integrate
- Automate
Fast
Inflexible
Slow
Flexible

from cortex
glutamatergic (excitatory)

back to cortex
 glutamatergic (excitatory)

Learning
Fast
Inflexible

Striatum

GABAergic (dopamine)

GABAergic (glutamate)

GABAergic (GABA)

GABAergic (inhibitory)

Thalamus

Internal globus pallidus

External globus pallidus

Subthalamic nucleus

Substantia nigra

pars compacta

pars reticulata

dopaminergic

GABAergic (dopamine)

GABAergic (glutamate)

GABAergic (GABA)

GABAergic (inhibitory)
Build on Turing to show what is necessary to make this work.

- Acquire
- Translate/integrate
- Automate

Slow Flexible

Fast Inflexible

Prefrontal

Motor Learning

Sensory Striatum

Reflex
Prefrontal

Motor

Learning

Sensory

Striatum

Reflex
Cyber-physical: decentralized control with internal delays.
Decentralized, but initially assume computation is fast and memory is abundant.
Plant is also distributed with its own component dynamics
Internal delays between components, and their sensor and actuators, and also externally between plant components
Going beyond black box: control is decentralized with internal delays.

Huge theory progress in last decade, year, mo., ...
“Evolvability”

- **Robustness** of lineages to large changes on long timescales
- Essentially an *architectural* question
  - What makes an architecture evolvable?
  - What does “architecture” mean here?
- What are the limits on evolvability?
- How does architecture, evolvability, robustness, and complexity relate?
- Key: tradeoffs, robustness, layering
Unfortunately, not intelligent design

Ouch.
Human evolution

weak fragle slow

strong robust fast

hands feet skeleton muscle skin gut long helpless childhood

All very different.

How is this progress?
This much seems pretty consistent among experts regarding circa 1.5-2 Mya. Roughly modern Homo Erectus?

So how did H. Erectus survive and expand globally?

- Hands
- Feet
- Skeleton
- Muscle
- Skin
- Gut

Very fragile

Weak and fragile

Strong and robust

Efficient (slow)

Inefficient, wasteful
weak
fragile

strong
robust
(fast)

efficient
(slow)

endurance

speed &
strength

inefficient
wasteful

Apes

Biology
Human evolution

weak fragile (slow)

strong robust (fast)

efficient (slow)

inefficient wasteful

dashed line connects human to apes

humans:
- hands
- feet
- skeleton
- muscle
- skin
- gut

apes:
- Biology

human evolution
From weak prey to invincible predator?

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

From weak prey to invincible predator

Before much brain expansion?

Plausible but speculation?
Today

2Mya

Gap?

Cranial capacity (cubic centimetres)

Before much brain expansion?
Key point:

Our physiology, technology, and brains have co-evolved

Probably true no matter what

Huge implications.

From weak prey to invincible predator

Before much brain expansion?

weak

fragile

strong

robust

efficient (slow)

hands
feet
skeleton
muscle
skin
gut

+ sticks
stones
fire

From weak prey to invincible predator

Before much brain expansion?
Cranial capacity

Greatest brain size increase

Today

2Mya

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

From weak prey to invincible predator

Before much brain expansion?

Huge implications.
inefficient
wasteful
weak
fragile
strong
robust

+ sticks
+ stones
+ fire

Architecture?

Biology

+Technology

efficient (slow)

inefficient wasteful
From weak prey to invincible predator
Before much brain expansion?
weak
fragile

strong
robust

efficient (slow)
inefficient wasteful

Architecture?

Biology

+ Technology

- sticks
- stones
- fire
Human complexity?

Consequences of our evolutionary history?

- sticks
- stones
- fire

- Fragile
- Robust
- Efficient
- Wasteful

Biology

± Technology
A streamwise constant model of turbulence in plane Couette flow

D. F. Gayme¹†, B. J. McKeon¹, A. Papachristodoulou², B. Bamieh³ and J. C. Doyle¹

Streamlined Laminar Flow

Flow

Turbulence and drag?

Transition to Turbulence

Increasing Drag, Fuel/Energy Use and Cost

Turbulent Flow
Amplification and nonlinear mechanisms in plane Couette flow

Dennice F. Gayme, Beverley J. McKeon, Bassam Bamieh, Antonis Papachristodoulou, and John C. Doyle

Coherent structures and turbulent drag

- High-speed region
- Upflow
- Downflow
- Low speed streak
- 3D coupling

Blunted turbulent velocity profile

Turbulent

Laminar
Blunted turbulent velocity profile

Laminar

Turbulent

“turbulence is a highly nonlinear phenomena”

Really?
\[
\frac{\partial u}{\partial t} + u \cdot \nabla u = -\nabla p + \frac{1}{R} \Delta u
\]

\[\nabla \cdot u = 0\]

<table>
<thead>
<tr>
<th>Robust</th>
<th>Small</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple</td>
<td>Organized Computer</td>
</tr>
<tr>
<td></td>
<td>2d, linear</td>
<td></td>
</tr>
<tr>
<td>Fragile</td>
<td>chaocritical mildy nonlinear</td>
<td>Irreducible?</td>
</tr>
<tr>
<td></td>
<td>3d, nonlinear</td>
<td>highly nonlinear</td>
</tr>
</tbody>
</table>
\[ \frac{\partial u}{\partial t} + u \cdot \nabla u = -\nabla p + \frac{1}{R} \Delta u \]
\[ \nabla \cdot u = 0 \]

- Numerical simulations can be **highly predictive** of real phenomena, yet still leave gaps in **understanding**
- Our research is all about this deeper understanding
- The “highly organized” computer on which the simulations are run are truly “highly nonlinear”
- The PDEs that are simulated are mildly nonlinear

<table>
<thead>
<tr>
<th>Robust</th>
<th>Simple (2d, \text{linear})</th>
<th><strong>Organized Computer</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile</td>
<td>mildly (3d, \text{nonlinear})</td>
<td><strong>Irreducible</strong>?</td>
</tr>
</tbody>
</table>
∃ coherent story here, but haven’t figured out best way to explain... working on it...
Universal reward systems

VTA dopamine

Constraints that deconstrain

Blood
Glucose
Oxygen

Universal metabolic system

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules

Sports
Music
Dance
Crafts
Art
Toolmaking
Sex
Food
food

Blood
Glucose
Oxygen

Organ
Tissue
Cell
Molecule

Other nutrients

Universal metabolic system
Universal reward systems

VTA dopamine

Reward Drive Control Memory

Other neuro-endocrine signals

- sports
- music
- dance
- crafts
- art
- toolmaking
- sex
- food
Universal reward systems

VTA dopamine

Constraints that deconstrain

Blood
Glucose
Oxygen

Universal metabolic system

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules

food

art
toolmaking
sex
dance
music
sports
Modularity 2.0 Architecture

that deconstrain

Extreme evolvability

Reward Drive Control Memory

Organs Tissues Cells Molecules

sports music dance crafts art toolmaking sex food
Universal reward/metabolic systems

Robust and adaptive, yet ...

work
family
community
nature

food
sex
toolmaking
sports
music
dance
dance
crafts
art

Blood

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules

dopamine
Yet Fragile

Vicarious

money
salt
sugar/fat
nicotine
alcohol

Glucose
Oxygen

VOA

dopamine

high sodium

hyper-tension

athero-sclerosis

immune suppression

coronary, cerebro-vascular, reno-vascular

cancer

cirrhosis

accidents/homicide/suicide

robust

drug abuse

alcoholism

Yet Fragile
"Laws" = hard limits, tradeoffs

Architecture = Constraints (that deconstrain)

Four types of constraints

Components
“Laws” = hard limits, tradeoffs

Components

Protocols

Blood
Glucose
Oxygen

VTA dopamine

Constraints that deconstrain

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules

System

Sports
Music
Dance
Crafts
Art
Toolmaking

Constraints

“Laws” = hard limits, tradeoffs
Human complexity

Robust

😊 Metabolism
😊 Regeneration & repair
😊 Healing wound /infect

Fragile

😊 Obesity, diabetes
😊 Cancer
😊 AutoImmune/Inflame
😊 Infectious diseases

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**
Controlled Dynamic

Low mean

High variability

- Fat accumulation
- Insulin resistance
- Proliferation
- Inflammation
Controlled Dynamic
Low mean
High variability

Uncontrolled Chronic
High mean
Low variability

- Death
- Fat accumulation
- Insulin resistance
- Proliferation
- Inflammation
## Mechanism?

<table>
<thead>
<tr>
<th>Robust</th>
<th>Fragile</th>
</tr>
</thead>
<tbody>
<tr>
<td>☺ Metabolism</td>
<td>☹ Obesity, diabetes</td>
</tr>
<tr>
<td>☺ Regeneration &amp; repair</td>
<td>☹ Cancer</td>
</tr>
<tr>
<td>☺ Healing wound /infect</td>
<td>☹ AutoImmune/Inflame</td>
</tr>
</tbody>
</table>

Mainstream view is health

- = good genes (reductionist)
- = emergent, edge of chaos, fractals,…

- *no* physiology, homeostasis, tradeoffs, constraints, architecture, etc etc
- change is hopefully coming
Restoring robustness?

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

Controlled Dynamic
- Low mean
- High variability

Uncontrolled Chronic
- High mean
- 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?
- 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?
Some features robust to some perturbations

Other features or other perturbations
Some features robust to some perturbations

Other features or other perturbations

Increased complexity?