Universal laws and architecture 3:
Constraints on robust efficiency

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Outline

• Review Turing, universal laws and architectures
• Compare with cells and brains
• Horizontal gene, app, and meme transfer
• Laws, constraints, tradeoffs
  – phage survival and multiply rate
  – glycolytic oscillations, robust efficiency, and autocatalysis
  – stabilizing an inverted pendulum
“Universal laws and architectures?”

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

*try to get you to read them?
• Turing 100th birthday in 2012
• Turing
  – machine (math, CS)
  – test (AI, neuroscience)
  – pattern (biology)
• Arguably greatest*
  – all time math/engineering combination
  – WW2 hero
  – “invented” software

Turing (1912-1954)

*Also world-class runner.
Key papers/results

• Theory (1936): Turing machine (TM), computability, (un)decidability, universal machine (UTM)
• Practical design (early 1940s): code-breaking, including the design of code-breaking machines
• Practical design (late 1940s): general purpose digital computers and software, layered architecture
• Theory (1950): Turing test for machine intelligence
• Theory (1952): Reaction diffusion model of morphogenesis, plus practical use of digital computers to simulate biochemical reactions
Fast and flexible

Solve problems
Make decisions
Take actions
Laws and architectures

- Fast
- Slow
- Flexible
- Inflexible

Architecture (constraints that deconstrain)

Architecture (constraints)
- Each theory $\approx$ one dimension
- Tradeoffs *across* dimensions
- Assume architectures a priori
- Progress is encouraging, but…
- Stovepipes are an obstacle…
Control, OR Compute

Turing

Delay is *most* important

Bode

Communicate

Shannon

Delay is *least* important

Carnot

Boltzmann

Physics

Einstein

Heisenberg
Turing as “new” starting point?

Compute
- Turing

Delay is most important

Bode

Control, OR

Software

Hardware

Digital

Analog
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?)

Essentials:
0. Model
1. Universal laws
2. Universal architecture
3. Practical implementation

Turing as “new” starting point?
Turing’s 3 step research:
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Essentials:
0. **Model**
1. Universal laws
2. Universal architecture
3. Practical implementation
• ...being digital should be of greater interest than that of being electronic. That it is electronic is certainly important because these machines owe their high speed to this... But this is virtually all that there is to be said on that subject.
• That the machine is digital however has more subtle significance. ... One can therefore work to any desired degree of accuracy.

1947 Lecture to LMS
• ... digital ... of greater interest than that of being electronic ...
• ...any desired degree of accuracy...
• This accuracy is not obtained by more careful machining of parts, control of temperature variations, and such means, but by a slight increase in the amount of equipment in the machine.

1947 Lecture to LMS
• Digital more important than electronic…
• Robustness: accuracy and repeatability.
• Achieved more by internal hidden complexity than precise components or environments.

Turing Machine (TM)
• Digital
• Symbolic
• Logical
• Repeatable
… quite small errors in the initial conditions can have an overwhelming effect at a later time. The displacement of a single electron by a billionth of a centimetre at one moment might make the difference between a man being killed by an avalanche a year later, or escaping.

1950, Computing Machinery and Intelligence, Mind
• ... quite small errors in the initial conditions can have an overwhelming effect at a later time....

• It is an essential property of the mechanical systems which we have called 'discrete state machines' that this phenomenon does not occur.
• Even when we consider the actual physical machines instead of the idealised machines, reasonably accurate knowledge of the state at one moment yields reasonably accurate knowledge any number of steps later.

1950, Computing Machinery and Intelligence, *Mind*
Turing’s 3 step research:
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?)
TM has $\infty$ memory.
Logic

- Time: fast → slow
- Memory: small → large

TM has $\infty$ memory

Space is free

Large space
time?

Decidable problem = \exists \text{ algorithm that solves it}

Most naively posed problems are undecidable.
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?)
2. Universal architecture achieving hard limits (UTM)

- Software: A Turing machine (TM) can be data for another Turing machine.
- A Universal Turing Machine can run any TM.
- A UTM is a virtual machine.
- There are lots of UTMs, differ only (but greatly) in speed and programmability (space assumed free).
The halting problem

• Given a TM (i.e. a computer program)
• Does it halt (or run forever)?
• Or do more or less anything in particular.
• Undecidable! There does not exist a special TM that can tell if any other TM halts.
• i.e. the program HALT does not exist. 😞
**Thm:** TM $H =$HALT does not exist.

That is, there does not exist a program like this:

$$H(TM, input) \triangleq \begin{cases} 
1 & \text{if } TM(input) \text{ halts} \\
0 & \text{otherwise}
\end{cases}$$

**Proof** is by contradiction. Sorry, don’t know any alternative. And Turing is a god.
\[ H(TM, input) \triangleq \begin{cases} 1 & \text{if } TM(input) \text{ halts} \\ 0 & \text{otherwise} \end{cases} \]

**Thm:** No such H exists.

**Proof:** Suppose it does. Then define 2 more programs:

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

\[
H*(TM) \triangleq H'(TM, TM)
\]

Run \( H*(H*) = H'(H*, H*) \)

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

**Contradiction!**
Implications
• TMs and UTMs are perfectly repeatable
• But perfectly unpredictable
• Undecidable: Will a TM halt? Is a TM a UTM? Does a TM do X (for almost any X)?
• Easy to make UTMs, but hard to recognize them.
• Is anything decidable? Yes, many questions NOT about TMs.
• Large, thin, nonconvex everywhere...
These are hard limits on the *intrinsic* computational complexity of *problems*.

Must still seek algorithms that achieve the limits, and architectures that support this process.
Delay is even more important in control

Computational complexity of
- *Designing* control algorithms
- *Implementing* control algorithms

Control
- Sense
- Plant
- Act

Compute
- Designing
- Implementing

Digital
- Software
- Hardware

Analog
Slow Flexible

Fast Inflexible

Most UTMs here

Hopeless fragility

Unachievable robustness

Hard limits

Fast Inflexible
Issues for engineering

• Turing remarkably relevant for 76 years
• UTM s are \( \approx \) implementable
  – Differ only (but greatly) in speed and programmability
  – Time/speed/delay is most critical resource
  – Space (memory) almost free for most purposes
• Read/write random access memory hierarchies
• Further gradations of decidable (P/NP/coNP)
• Most crucial:
  – UTM s differ vastly in speed, usability, and programmability
  – You can fix bugs but it is hard to automate finding/avoiding them
Issues for neuroscience

• Brains and UTMs?
  – Time is most critical resource?
  – Space (memory) almost free?
• Read/write random access memory hierarchies?
• Brain >> UTM?
Conjecture

• Memory potential $\approx \infty$

• Examples
  – Insects
  – Scrub jays
  – Autistic Savants

• But why so rare and/or accidental?
• Large memory, computation of limited value?
• Selection favors fast robust action?
• Suppose we only care about space?
• And time is free
• Bad news: optimal compression is undecidable.
• Shannon: change the problem!
Shannon’s brilliant insight
• Forget time
• Forget files, use *infinite random ensembles*

**Good news**
• Laws and architecture!
• Info theory most popular and accessible topic in systems engineering
• *Fantastic* for some engineering problems
Shannon’s brilliant insight
• Forget time
• Forget files, use *infinite random ensembles*

**Bad news**
• Laws and architecture very brittle

• Less than zero impact on internet architecture
• Almost useless for biology (But see Lestas et al, 2010)
• Misled, distracted generations of biologists (and neuroscientists)
Delay is most important

Lowering the barrier

New progress!

Delay is least important

Compute
  Turing

Communicate
  Shannon

Delay is least important

Lowering the barrier

Computing and communication: New progress!

Control, OR

Bode

Physics
  Einstein
  Heisenberg
  Carnot
  Boltzmann
The virtual is more “real” than the implementation.
Turing architecture

- Slow
  - Flexible
- Fast
  - Inflexible

- Softwate
- Hardware

- Digital
- Analog

Fast limits?
Essentials To Do

• Reyna/Brainerd: Gist, false memory
• Ashby: Automaticity, multiple memory systems,…
• Cosmides/Tooby: Risk, uncertainty, cooperation, evolution,…
Speed and flexibility are crucial to implementing robust controllers.
Software

Hardware

"Vertical" App Migration

Fast result

Very Slow Process

Fast

Inflexible

Inflexible

Flexible

Flexible

Horizontal App Transfer

Slow

Slow
• Acquire
• Translate/integrate
• Automate

Horizontal Meme Transfer

Very Slow Process

“Vertical” App Migration

Fast Inflexible

Slow Flexible

Prefrontal

Motor

Sensory

Striatum

Reflex

Horizontal Meme Transfer

Very Slow Process

“Vertical” App Migration

Fast Inflexible

Slow Flexible

Prefrontal

Motor

Sensory

Striatum

Reflex
Horizontal Gene Transfer

Most
- software and hardware
- new ideas (humans)
- new genes (bacteria)

is acquired by “horizontal” transfer, though sometimes it is evolved locally
Sequence ~100 E Coli *(not chosen randomly)*
- ~4K genes per cell
- ~20K *different* genes in total
- ~1K universally shared genes

See slides on bacterial biosphere
Exploiting layered architecture

Horizontal Bad Gene Transfer

Horizontal Bad App Transfer

Horizontal Bad Meme Transfer

Fragility?

Parasites & Hijacking

Virus
Build on Turing to show what is *necessary* to make this work.

- Acquire
- Translate/integrate
- Automate

- Amazingly Flexible/
  Adaptable

- Layered architecture

- Build on Turing to show what is necessary to make this work.

- Acquire
- Translate/integrate
- Automate

- Amazingly Flexible/Adaptable
Delay is even more important

Computational aspects:
- Turing
- Universal laws and architectures

Control components:
- Sense
- Plant
- Act

Physical aspects:
- Slow Flexible:
  - Software
- Fast Inflexible:
  - Hardware
- Digital
- Analog

Bode's control theory
The starting point is software, hardware, digital, and analog. This leads to computers with digital, analog, active, lumped, and distribute. The "plant" is actuators/sensors/amplifiers.
Each theory \( \approx \) one dimension

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

laws and architectures?

robust

fragile

efficient

wasteful

Case studies
Viruses’ Life History: Towards a Mechanistic Basis of a Trade-Off between Survival and Reproduction among Phages

Marianne De Paepe, François Taddei

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

July 2006 | Volume 4 | Issue 7 | e193
Bacteria

Phage

Bacteria
Phage lifecycle

- Multiply
- Survive
- Infect
- Lyse
fragile, fast, efficient

antagonistic pleiotropy

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

- Robust
- Fragile

Multiply

- Fast
- Efficient
- Slow

Mechanism?

- Thin capsid, small genome
- Thick capsid, big genome
fragile

Survive

robust

fast efficient

Multiply

slow

Good architectures?

Hard limits?

antagonistic pleiotropy
<table>
<thead>
<tr>
<th>Name</th>
<th>Type of Phage</th>
<th>Measured Life Cycle Characteristics</th>
<th>Published Structural Properties</th>
<th>Calculated Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Family</td>
<td>Life Cycle</td>
<td>Decay Rate (d)</td>
<td>Burst Size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.072</td>
<td>115</td>
</tr>
<tr>
<td>M13</td>
<td>Inoviridae</td>
<td>Chronic</td>
<td>0.074</td>
<td>413</td>
</tr>
<tr>
<td>MS2</td>
<td>Leviriviridae</td>
<td>L</td>
<td>0.250</td>
<td>400</td>
</tr>
<tr>
<td>Mu</td>
<td>Myoviridae</td>
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<td>0.290</td>
<td>200</td>
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<td>T</td>
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<td>160</td>
</tr>
<tr>
<td>P4</td>
<td>Myoviridae</td>
<td>T</td>
<td>0.045</td>
<td>300</td>
</tr>
<tr>
<td>φ80</td>
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<td>L</td>
<td>0.120</td>
<td>600</td>
</tr>
<tr>
<td>ϕX174</td>
<td>Microviridae</td>
<td>L</td>
<td>0.200</td>
<td>180</td>
</tr>
<tr>
<td>PRD1</td>
<td>Tectiviridae</td>
<td>L</td>
<td>0.037</td>
<td>50</td>
</tr>
<tr>
<td>T2</td>
<td>Myoviridae</td>
<td>L</td>
<td>0.068</td>
<td>135</td>
</tr>
<tr>
<td>T3</td>
<td>Podoviridae</td>
<td>L</td>
<td>0.102</td>
<td>200</td>
</tr>
<tr>
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<td>Myoviridae</td>
<td>L</td>
<td>0.068</td>
<td>150</td>
</tr>
<tr>
<td>T5</td>
<td>Siphoviridae</td>
<td>L</td>
<td>0.120</td>
<td>290</td>
</tr>
<tr>
<td>T7</td>
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<td>260</td>
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<td>R17</td>
<td>Leviriviridae</td>
<td>L</td>
<td>0.320</td>
<td>3,570</td>
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</tbody>
</table>

Mortality rate, burst size, latency period, and adsorption rate were measured as described in Material and Methods. Each value is the mean of at least three independent experiments. Genome size, diameter, and molecular weight were collected from published results. The internal volume used to calculate $\rho_{pack}$ has either been collected in structural studies of phage capsids or calculated by subtracting the thickness of the shell from the external diameter. Empty cells in the table correspond to data that were either not available or not measured.

*$E_a$: energy of activation of the reaction leading to inactivation of virions, obtained from the Arrhenius equation linking mortality rate and temperature between 30 °C and 45 °C. The energy of activation represents the energy the system has to overcome so that the reaction occurs.

*Ext. diameter: external diameter of the capsid.
*Molecular weight of the proteins constituting the capsid.
*Capsid molecular weight divided by the surface of the capsid; this ratio represents the thickness of the shell.
*Volume occupied by the genome divided by the internal volume of the capsid.
**T: Temperate phage, L: Virulent Phage, Chronic: creates a chronic infection

DOI: 10.1371/journal.pbio.0040193.t001
Viruses
Bacteria

Phage

Bacteria

1μm
why computer memory is almost “free”
Gallistel: where is our read/write memory? Conjecture: it’s digital and much smaller than this.
Bacterium (Staph. aureus)

Pox virus

Herpes

Influenza

Polio

Bacterium (Chlamydia)
7500 nucleotides ≈ 15kbits
Memory is (almost) free
Speed is what matters

7500 nucleotides $\approx$ 15kbits slow

1 bit fast

1 $\mu$m

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

Levels of explanation:

1. Possible
2. Plausible
3. Actual
4. Mechanistic
5. Necessary

Science
Engineering
Medicine
Glycolytic “circuit” and oscillations

- Most studied, persistent mystery in cell dynamics

- End of an old story (why oscillations)
  - side effect of hard robustness/efficiency tradeoffs
  - no purpose per se
  - just needed a theorem

- Beginning of a new one
  - robustness/efficiency tradeoffs
  - complexity and architecture
  - need more theorems and applications
Theorem!

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

Fragility

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

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

Enzyme amount

Savageaumics
Inside every cell

Catabolism

Precursors

ATP

AA

Enzymes

RNA

Proteins

Ribosome

RNAp

DNA

DNAP

Building Blocks

AA transl.

xRNA

Gene

Macro-layers

Crosslayer autocatalysis

ATP

transc.

Enzymes

Repl.

Repl.
Yeast anaerobic glycolysis

Energy

ATP

Rest of cell

Minimal model
ATP

Autocatalytic feedback

Rest of cell

Catabolism

Precursors

ATP

Energy

Reaction 1 (“PFK”)

Reaction 2 (“PK”)

Intermediate metabolite

Yeast anaerobic glycolysis

Minimal model
Robust = Maintain energy (ATP concentration) despite demand fluctuation

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

Robust = Maintain energy (ATP concentration) despite demand fluctuation
enzymes catalyze reactions

Reaction 1 ("PK")

Reaction 2 ("PFK")

ATP

Rest of cell
Enzymes catalyze reactions.

Efficient = low metabolic overhead \approx low enzyme amount
Robust = Maintain ATP

\[ \Delta \text{ATP} \]

Efficient = low enzyme amount
**Standard story:**

**Autocatalytic** plus **control** feedback

*necessary and sufficient* for oscillations

Proof: Dynamical systems model, simulation, bifurcation analysis
There may be other resources needed that aren’t recycled which we’ll ignore for now.
Some processes don’t require autocatalysis
Autocatalytic feedback

Seed

Harvest

Product

Year

1

2
Seed

Year

1

2

3

Bad harvest?

Harvest

Product

??
Maintain product?

Year
- 1
- 2
- 3

Seed
- 1
- 2

Harvest
- 1
- 2

Product
- 1
- 2

Seed

Maintain product?
Harvest

Year 1

Without autocatalysis

Year 2

Product
Cut back product

Year

Seed

Harvest

Product

Better, but...
Cut back product more

Year
1 2

Seed

Harvest

Product

Cut back product more
Over-react and oscillate

Year

Seed

Harvest

Product
Autocatalytic feedback makes control harder.
With oxygen

Efficient

Slow

Without oxygen

Fast
This is why we focus on anaerobic glycolysis, to maximize the autocatalytic feedback.
Standard story: Autocatalytic plus control feedback necessary and sufficient for oscillations

Proof: Dynamical systems model, simulation, bifurcation analysis
Theorem!  
DS $\rightarrow$ CDS

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

New story: Tradeoffs
New story: Tradeoffs = “Universal laws”

\[
\frac{1}{\pi} \int_{0}^{\infty} \ln|S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega \\
\geq \ln \left| \frac{z + p}{z - p} \right|
\]
ATP

Rest of cell

energy

control

React 1 ("PFK")

x

React 2 ("PK")

ATP

Rest of cell

Fragility

Plausible?

Enzyme amount
Fluorescence histogram (fluorescence vs. cell count) of GFP-tagged Glyceraldehyde-3-phosphate dehydrogenase (TDH3). Cells grown in ethanol have lower mean and median and higher variability.
highly variable

$10^1 \quad 10^2 \quad 10^3$

$\propto k$

Metabolic Overhead

See Lestas, Vinnicombe, Paulsson, *Nature*
Transcription is highly variable
Even if you allow $\infty$ delay!
So information theory applies

See Lestas, Vinnicombe, Paulsson, *Nature*
$g=0, a=1$ is implausibly fragile.

**Fragility**

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

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

implausibly fragile

\[ \frac{z + p}{z - p} \]

Fragility

\[ 10^1 \]

\[ 10^0 \]

\[ 10^{-1} \]

enzyme amount

\[ k \]

autocatalytic

\( a=1 \)

control

\( g=0 \)

Rest

PK

Rate \( k \)

PFK

H

enzyme amount

implausibly fragile

\( g=0 \)

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

Fragility

\[a = g = 1\]

enzyme amount

a = g = 1

autocatalytic

plausibly robust, efficient

rate k

Rest

control

PK

PFK

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

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

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

\(a=g=1\)
\(a=g=0\)

\(g=1\) is more plausible
\[ a = 1 \text{ sufficient for oscillations (and is actual)} \]

\[ g = 1 \text{ necessary for robust efficiency (and is actual)} \]

\[ \frac{1}{\pi} \int_{0}^{\infty} \ln|S(j\omega)| \left( \frac{z}{z^2 + \omega^2} \right) d\omega \]

\[ \frac{|z + p|}{|z - p|} \]

\[ a = g = 1 \]

\[ a = g = 0 \]

\[ k \]
What (some) reviewers say

• “...to establish universality for all biological and physiological systems is simply wrong. It cannot be done...”
• “…a mathematical scheme without any real connections to biological or medical...”
• “If such oscillations are indeed optimal, why are they not universally present?”
• “…universality is well justified in physics... for biological and physiological systems ...a dream that will never be realized, due to the vast diversity in such systems.”
• “...does not seem to understand or appreciate the vast diversity of biological and physiological systems...”
• “...a high degree of abstraction, which ...make[s] the model useless ...”
Simulation of two state model (S7.1) qualitatively recapitulates experimental observation from CSTR studies [5] and [12]. As the flow of material in/out of the system is increased, the system enters a limit cycle and then stabilizes again. For this simulation, we take $q = a = V_m = 1$, $k = 0.2$, $u = 0.01$, $h = 2.5$. Why?
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

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

simple

complex

Enzyme amount

Savageaumics
Good architectures allow for effective tradeoffs.

Alternative systems with shared architecture are less fragile and less wasteful.
Inside every cell

Almost

Precursors

ATP

Catabolism

AA

Enzymes

Building Blocks

RNA

Proteins

Ribosome

DNA

RNAP

DNAp

Repl.

Gene

transl.

transc.

Crosslayer autocatalysis

Macro-layers
**Compute**

Turing

**Delay is most important**

Bode

**Control**

**Fast Inflexible**

**Hardware Software**

**Sensory**

**Prefrontal**

**Learning**

**Motor**

**Striatum**

**Reflex**

**Plant**

**Sense**

**Act**

**AtP**

**DNA Rep**

**RNAP**

**AA translation**

**Protein**

**Slow Flexible**

**Bode**

**Digital**

**Sensory**

**Prefrontal**

**Act**

**Control**

**Digital**

**Analog**

**Fast Inflexible**

**Delay is most important**

**Bode**

**Control**

**AtP**

**DNA Rep**

**RNAP**

**AA translation**

**Protein**

**Slow Flexible**

**Bode**

**Control**

**AtP**

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**Bode**

**Control**
How general is this picture?

Supplementary materials has a demo.

Architecture, constraints, and behavior

John C. Doyle and Marie Csete

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.

Doyle and Csete, *Proc Nat Acad Sci USA*, online JULY 25 2011
\[ x_{t+1} = px_t + w_t + u_{t-a} \]

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

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

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

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

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

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

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

With delay and uncertainty

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

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

\[ p > 1 \]
Linearized pendulum on a cart

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

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

\(\ddot{x}\cos \theta + l\dot{\theta} + g \sin \theta = 0\)

\(y = x + \alpha l \sin \theta\)

linearize

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

\(\ddot{x} + l\dot{\theta} \pm g \theta = 0\)

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

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

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

\[\varepsilon = 1 - \alpha\]

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

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

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

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

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

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

Easy, even with eyes closed
No matter what the length

Proof: Standard UG control theory:
Easy calculus, easier contour integral,
easiest Poisson Integral formula
Harder if delayed or short
Also harder if sensed low

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

\[
\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
This holds for any controller so is an intrinsic constraint on the difficulty of the problem.

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

We would like to tolerate large delays (and small lengths), but large delays severely constrain the achievable robustness.

large \( \tau \) \quad small \( \tau \)

small \( 1/\tau \) \quad large \( 1/\tau \)
Delay $\tau$

$$\frac{1}{\pi} \int_0^\infty \ln |T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}$$
\[
\frac{1}{\pi} \int_0^{\infty} \ln|T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln|T_{mp}(p)| = p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
The ratio of delay between people is proportional to the lengths they can stabilize.
Eyes moved down is harder (RHP zero)
Similar to delay
Suppose \( r = \frac{m}{M} \ll 1 \)

Units \( \Rightarrow M = g = 1 \)

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

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

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

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

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

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

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

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

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

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

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

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

This is a cartoon, but can be made precise.
How do these two constraints (laws) relate?

\[
\frac{1}{\pi} \int_0^\infty \ln |S(j\omega)| \left(\frac{2z}{z^2 + \omega^2}\right) d\omega \geq \ln \left|\frac{z + p}{z - p}\right|
\]
Delay comes from sensing, communications, computing, and actuation. Delay limits robust performance.

\[
\frac{1}{\pi} \int_{0}^{\infty} \ln |T(j \omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq \ln |T_{mp}(p)| = p \tau \propto \tau \sqrt{\frac{l}{l}}
\]
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.

Control

Delay $\tau$

This is about speed and flexibility of computation.

Flexible

Inflexible

Large delay

Small delay

Hard limits

l

Noise
Delay makes control hard.

Computation delay adds to total delay.

Computation is a component in control.

Fragility

\[
\frac{1}{\pi} \int_0^\infty \ln|T(j\omega)| \frac{2p}{p^2 + \omega^2} d\omega \geq p\tau \propto \tau \sqrt{\frac{1}{l}}
\]
How general is this picture?


<table>
<thead>
<tr>
<th>fragile</th>
<th>robust</th>
</tr>
</thead>
<tbody>
<tr>
<td>simple tech</td>
<td>complex tech</td>
</tr>
</tbody>
</table>

efficient | wasteful
Next (and last) time

• Universal laws in more depth
• Universal architectures revisited/compared
  – Computers and networks
  – Cells
  – Brains and minds
• Architecture & laws at the extremes
  – evolution
  – eusociality
• Acquire
• Translate/integrate
• Automate

Wolpert, Grafton, etc

Robust

Brain as optimal controller

Reflex
Going beyond black box: control is decentralized with internal delays.
Depends crucially on layered architecture.

Amazingly Flexible/Adaptable

Horizontal Gene Transfer

Horizontal App Transfer

Horizontal Meme Transfer

Prefrontal

Motor

Sensory

Striatum

Learning

Reflex

Hardware

Software

Digital

Analog
Catabolism

Inside every cell

Enzymes

ATP

Precursors

AA

Nucl.

Building Blocks

Macro-layers

Crosslayer autocatalysis

ATP

RNA

AA transl.

Ribosome

Proteins

xRNA

RNA transc.

RNAP

DNA

Repl.

Gene

DNAP

ATP

RNAp
Catabolism

Precursors

ATP

AA

Nucl.

Ribosomes

Ribosomes make ribosomes

ATP

AA transl.

Proteins

Ribosome

Translation: Amino acids polymerized into proteins
Catabolism

Precursors

ATP

AA

Nucl.

RNA

transl.

Proteins

Ribosome

Ribosomes make ribosomes

Ribosomes are made of proteins and RNA

Ribosomes

ATP

transc.

rRNA
Ribosomes make ribosomes

Organisms differ in the proportion of ribosomal protein vs rRNA

Ribosomes are made of proteins and rRNA
Catabolism

Precursors → ATP

AA → ATP

Nucl. → ATP

Building Blocks

AA transl. → ATP

RNA transc. → ATP

DNA → ATP

ATP → Repl.

Building Blocks

Proteins

Ribosome

xRNA

RNAp

RNAP

DNAp

Gene

ATP

• Translation
• Transcription
• DNA Replication

Autocatalytic
Cross-layer control

- Highly organized
- Naming and addressing
- Prices? Duality?
- Minimal case study?
Evolution and architecture

Nothing in biology makes sense except in the light of evolution

Theodosius Dobzhansky
(see also de Chardin)

Nothing in evolution makes sense except in the light of biology
Standard theory:
natural selection + genetic drift
+ mutation + gene flow

Greatly abridged cartoon here

Shapiro explains well what this is and why it’s incomplete (but Koonin is more mainstream)
Standard theory:
selection + drift + mutation + gene flow
Standard theory:
selection + drift + mutation + gene flow

No new laws.
No architecture.
No biology.
All complexity is emergent from random ensembles with minimal tuning.

No new laws.

No architecture.
The battleground

Phenotype

No gap. Just physics.

Huge gap. Need supernatural

Genes?

Gene alleles
What they agree on

No new laws.
No architecture.
No biology.

Huge gap.

No gap.
Putting biology back into evolution
The heresies

• Many mechanisms for “horizontal” gene transfer
• Many mechanisms to create large, functional mutations
• At highly variable rate, can be huge, global
• Selection alone is a very limited filtering mechanism
• Mutations can be “targeted” within the genomes
• Can coordinate DNA change w/ useful adaptive needs
• Viruses can induce DNA change giving heritable resistance
• Still myopic about future, still produces the grotesque
Surprising heresies from “conservatives”

kin selection

modern synthesis
What matters is the OS.
Sensory

Motor

Prefrontal

Striatum

Reflex

Catabolism

AA

RN

transl.

Proteins

xRNA transc.

Precursors

DNA

Repl.

Gene

ATP

ATP

Nucel.

AA

Ribosome

RNAp

DNAp

Flexible/Adaptable/Evolvable

Horizontal Meme Transfer

Software

Hardware

Horizontal App Transfer

Digital

Analog

Depends crucially on layered architecture

Transcrip.
Sequence ~100 E Coli (*not* chosen randomly)
- ~ 4K genes per cell
- ~20K *different* genes in total
- ~ 1K universally shared genes

See slides on microbial biosphere laws and architectures.
selection + drift + mutation + gene flow + facilitated variation

HGT = horizontal gene transfer

large functional changes in genomes
natural selection + genetic drift + mutation + gene flow
+ facilitated variation

Genome can have large changes
natural selection + genetic drift + mutation + gene flow + facilitated variation

Small gene change can have large but functional phenotype change

Architecture

Phenotype

Genotype
natural selection + genetic drift + mutation + gene flow + facilitated variation

Only possible because of shared, layered, network architecture
Reading?

• See refs in 2011 *PNAS* paper but also…
• Turing: Gallistel (+ Wolpert on control/bayes)
• Brain/Mind: Gazzaniga, Kahneman + Reyna/Brainerd, Ashby, Cosmides/Tooby,…
• Evolution: Gerhart & Kirschner, Shapiro, Lane, Koonin, Caporale (+ fire + running)
• Apes: De Waal (Bonobos), Sapolsky (Baboons)
• Eusociality: Wilson
• Juarrero