Universal laws and architecture 4:
Layering, learning, and decentralized control

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Outline: Laws and architectures

• Motivating case studies
  – Brains
  – Computers, networks
  – Cells
  – Physiology

• Layered architecture of the cell
  – replication, transcription, translation
  – metabolism, signaling, chemotaxis
  – 2CST and cross layer control
Delay is most important

Closing the loop
- On the “plant”
- On the “story”
Neuro motivation

Reflex

Fast Inflexible
Ashby & Crossley

- Acquire
- Translate/integrate
- Automate

Thanks to Bassett & Grafton
Ashby & Crossley

- Acquire
- Translate/integrate
- Automate
Fast
Inflexible

Slow
Flexible

Learning

Fast
Inflexible

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

- Acquire
- Translate/integrate
- Automate

Slow Flexible

Motor Learning Prefrontal Striatum

Fast Inflexible

Reflex
Slow Flexible

Fast Inflexible

Turing architecture

Software Hardware

Digital Analog

Hard limits?

Fast Inflexible
Wolpert, Grafton, etc

**robust**

Brain as optimal controller

- Acquire
- Translate/integrate
- **Automate**

Reflex
What I’m not going to talk about

- Connections between robustness and risk sensitivity
- Asymmetry between false positives and negatives
- Risk aversion and risk seeking
- Uncertainty is more in models than in probabilities
- Life is not like a casino
Going beyond black box: control is decentralized with internal delays.

Huge theory progress in last decade, year, mo., ...

2nd hour (after break)
- Andy Lamperski
- Nikolai Matni
Going beyond black box: control is decentralized with internal delays.

Mammal NS seems organized to reduce delays in motor control.
Move head

Move hand

Bigger error
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
Slow
Act

Fast?

Slow
Versus standing on one leg

- Eyes open vs closed
- Contrast
  - young surfers
  - old football players
Delay is even more important in control.

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

Control

Sense

Plant

Act

Software

Hardware

Digital

Analog

Compute

Designing

Implementing
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
- Sensori-motor memory potential $\approx \infty$ (Ashby)
- Limits are on *speed* of
  - nerve propagation delays
  - learning
- But control is *never* centralized
- Is there a random access read/write memory?
• Sensori-motor memory potential $\approx \infty$ (Ashby)
• Limits are on *speed* of
  – nerve propagation delays *(fish parts?*)
  – learning ???
• I’m probably confused
• What about robust learning
Horizontal Meme Transfer

Sensory Learning

Prefrontal

Striatum

Relex

Catabolism

AA

RN

tranx.

Precursors

DNA

Repl.

Gene

Horizontal App Transfer

Software

Hardware

Flexible/Adaptable/Evolvable

Depends crucially on layered architecture
What I’m not going to talk about

• It’s true that most “really smart scientists” think almost everything in this talk is nonsense
• Why they think this
• Why they are wrong

• Time (not space) is our problem, as usual
• Don’t have enough time for what is true, so have to limit discussion of what isn’t
• No one ever changes a made up mind (almost)
What I’m not going to talk about

Compute
- Turing
- Delay is most important
- Bode
- Control, OR

Communicate
- Shannon
- Delay is least important
- Carnot
- Boltzmann
- Physics

Shannon
Inside every cell

Catabolism

Precursors → ATP (Catabolism)

AA → ATP (Building Blocks)

RNA → xRNA (Transcript)

DNA → Gene (Replication)

Ribosome → Proteins

Enzymes

Macro-layers

Crosslayer autocatalysis
Mature red blood cells live 120 days or “metabolism first” origins of life?
Core metabolism

Inside every cell

Catabolism

Precursors

ATP

AA

Nucl.

Building Blocks

Macro-layers

Enzymes

ATP

RNA transl.

xRNA

DNA Repl.

Gene

Proteins

Ribosome

RNAP

DNAP

ATP

Repl.

DNA

RNA transc.

xRNA

RNAP

DNAP
Core metabolism

Metabolic pathways

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

Catabolism

Precursors

Taxis and transport

Core metabolism

Carriers

Same 12 in all cells

Same 8 in all cells

Nutrients

Huge Variety

Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors

≈100 ≈same in all organisms
Genes

Co-factors

Polymerization and complex assembly

Proteins

Precursors

Autocatalytic feedback

Taxis and transport

Nutrients

Core metabolism

Catabolism

Sugars

Fatty acids

Co-factors

Amino Acids

Nucleotides

Carriers

Huge Variety

≈100

≈10^4 to ≈ ∞ in one organisms

Trans*
Universal reward systems

VTA dopamine

Constraints that deconstrain

Blood

Glucose

Oxygen

Universal metabolic system

Sports

Music

Dance

Crafts

Art

Toolmaking

Sex

Food

Reward

Drive

Control

Memory

Organs

Tissues

Cells

Molecules
Modularity 2.0

Constraints

dopamine

Blood

Glucose
Oxygen
Modularity 2.0

That deconstrain

Sports
Music
Dance
crafts
Art
Toolmaking
Sex
Food

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules
Universal reward/metabolic systems

work
family
community
nature

food
sex
toolmaking
sports
music
dance
crafts
art

dopamine

Blood

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules

Robust and adaptive, yet ...
Blood

cocaine
amphetamine

doamine

work
family
community
nature

sex
food
toolmaking
sports
music
dance
dance
crafts
art

Reward
Drive
Control
Memory

Organs
Tissues
Cells
Molecules
Vicarious

money
salt
sugar/fat
nicotine
alcohol

high sodium
obesity
overwork
smoking
alcoholism
drug abuse

hypertension
averoseclerosis
diabetes
inflammation
immune suppression

coronary, cerebrovascular, renovascular
cancer
cirrhosis
accidents/homicide/suicide

From Sterling
Universal reward systems

Prefrontal cortex
Accumbens

VTA dopamine

Universal metabolic system

Blood
Glucose
Oxygen

Organs
Tissues
Cells
Molecules

sports
music
dance
crafts
art
toolmaking
sex
food
Yet Fragile
Inside every cell

Layered architecture

Catabolism

Precursors

Biosynthesis
Inside every cell

Layered architecture

Catabolism
Precursors
Biosynthesis
Carriers

Biosynthetic Pathways

Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Inside every cell

Catabolism
Precursors
Carriers

Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors

Core metabolic bowtie
Layered architecture
Catabolism

Precursors

Carriers
Catabolism

Gly
G1P
G6P
F6P
F1-6BP
Gly3P
13BPG
3PG
2PG
ATP
PEP
Pyr
ACA
TCA
NADH
Oxa
Cit
Gly → G1P → G6P → F6P → F1-6BP → Gly3p → 13BPG → 3PG → 2PG → PEP → Pyr → ACA → TCA

Precursors

metabolites
Enzymatically catalyzed reactions

TCA

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

Oxa
Cit
Enzymes (implement) catalyze (virtual) reactions
Autocatalytic

Rest of cell

consumed

produced

TCA

Gly

G1P

G6P

F6P

F1-6BP

Gly3p

ATP

3BPG

3PG

2PG

PEP

Pyr

ACA

Oxa

Cit

NADH

produced

consumed
Biological pathways
signaling

gene expression

metabolism

lineage

energy

control

materials

More complex feedback

modalities

feedback
Feedbacks

Autocatalysis

Control
Constrained (conserved):
1. Total NAD moiety
2. Total Adenylate moiety
3. Total Carbon moiety
4. Total phosphate moiety
5. Total oxygen moiety
6. Oxidized state of metabolites
7. Reduced state of metabolites
8. High energy potential release
Constrained ("conserved"): Moieties

1. NAD
2. Adenylate
3. Carbon
4. phosphate
5. oxygen
6. Oxidized state of metabolites
7. Reduced state of metabolites
8. High energy potential release

(P1) Total NAD moiety: \([\text{NAD}^+] + [\text{NADH}]\)
Robust = maintain energy charge with fluctuating cell demand
Efficient = minimize metabolic waste and overhead

Autocatalysis

Control

Feedbacks
Minimal model?

Autocatalysis

Control
Minimal model
~1 equilibrium
2 metabolites
3 “reactions”

Control
Plus
Autocatalytic Feedback

Rest of cell
Minimal model
~1 equilibrium
2 metabolites
3 “reactions”
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.
(May 21): Hard tradeoff in glycolysis

Robust = Maintain energy (ATP concentration) despite demand fluctuation
What makes this hard?
1. Instability (autocatalysis)
2. Delay (enzyme amount)

$$\approx$$ Disturbance rejection
$$\approx$$ Accurate
What makes this hard?

1. Instability
2. Delay

The CNS must cope with both

Today's important point
enzymes catalyze reactions

Reaction 1 ("PK")

ATP

Rest of cell

Reaction 2 ("PFK")
Efficient = low metabolic overhead ≈ low enzyme amount
Can’t make too many enzymes here, need to supply rest of the cell.

Efficient =
low metabolic overhead
≈ low enzyme amount
(⇒ slow reactions)

reaction rates
$\propto$
enzyme amount

enzymes catalyze reactions, another source of autocatalysis

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

Efficient =
low metabolic overhead
≈ low enzyme amount
(⇒ slow reactions)

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

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

Efficient =
low metabolic overhead
≈ low enzyme amount
(⇒ slow reactions)
Robust = Maintain ATP

Efficient = low enzyme amount
(⇒ slow reactions)
(May 21): Hard tradeoff in glycolysis is
- **robustness vs efficiency**
- **absent without autocatalysis**
- **too fragile with simple control**
- **plausibly robust with complex control**
(May 21): Hard tradeoff in glycolysis is
• robustness vs efficiency
• absent without autocatalysis
• too fragile with simple control
• plausibly robust with complex control

• Evolution can
• increase complexity
• to improve robustness tradeoffs.
• But this complexity creates new fragilities
• so there is always more to this story.
Constrained ("conserved"): Moieties

1. NAD
2. Adenylate
3. Carbon
4. phosphate
5. oxygen
6. Oxidized state of metabolites
7. Reduced state of metabolites
8. High energy potential release

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

\[+ [\text{PYR}] + [\text{ADP}] + 2[\text{AMP}] + [\text{H}_2\text{O}]\]
What makes the bacterial biosphere so adaptable?

Deconstrained

Environment

Action

Core conserved constraints facilitate tradeoffs

Layered architecture

Active control of the genome (facilitated variation)
What makes the bacterial biosphere so adaptable?

Core conserved constraints facilitate tradeoffs

Active control of the genome (facilitated variation)
Deconstrained Environments

Bacterial biosphere

Architecture = Constraints that Deconstrain

Deconstrained Genomes

Shared protocols

Precursors

DNA

ATP

Building Blocks

Enzymes

Arrows:

AA
Ribosome
RNA
RNAp
transl.
Proteins
xRNA
tランス

Repl.
Gene
ATP
Bacterial biosphere

Architecture = Constraints that Deconstrain

Deconstrained Genomes
"Emergent": "Nontrivial" consequences of other constraints

Architecture = Constraints

System

Protocols

Components
Components and materials: "Chemistry"

Constraints

Systems requirements: Survive in hostile environments
Constrained ("conserved"): Moieties
1. NAD
2. Adenylate
3. Carbon
4. phosphate
5. oxygen
6. Oxidized state of metabolites
7. Reduced state of metabolites
8. High energy potential release
Bacterial biosphere
• carriers: ATP, NADH, etc
• Precursors, ...
• Enzymes
• Translation
• Transcription
• Replication
• ...

Architecture = protocols
= “constraints that deconstrain”
Systems requirements: functional, efficient, robust, evolvable

Constraints:
- Hard constraints: Thermo (Carnot), Info (Shannon), Control (Bode), Compute (Turing)

Components and materials:
- Energy, moieties

Diverse
- Universal Control
- Protocols

Co-factors
Components and materials: Energy, moieties

Constraints

Hard constraints:

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

Protocols

Universal Control

Diverse

Diverse

Systems requirements: functional, efficient, robust, evolvable
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.
Bacteria

Phage

Bacteria
Phage lifecycle

- **Survive**
- **Infect**
- **Multiply**
- **Lyse**
Tradeoffs?

Accurate vs sloppy is now an implicit dimension of robust/fragile

- Inflexible
- Programmable?
- Flexible

- Fast
- Control response?
- Metabolic overhead?

- Cheap
- Expensive

慢 (≈ 脆弱)
Conjecture: human brain tradeoffs dominated by fast vs flexible more than robust vs cheap

1. For hunter/gatherer metabolism is far above basal, and dominated by active muscle
2. Brain homeostasis is a much greater challenge than basal metabolic demands

Creates new fragilities in modern lifestyle

Not true for sedentary organisms with limited nutrient diets (e.g. Koala, Panda, ...
**Conjecture:** human brain tradeoffs dominated by fast vs flexible more than robust vs cheap

Fragility dimensions with most important tradeoffs:
1. latency/delay/speed of control vs.
2. flexibility/adaptability
Consistent tradeoff across very different systems:
- nervous system
- cell
- computer
  (that have some shared architecture)

Expense is a complicated tradeoff between:
- design effort
- fabrication cost
- energy use
- etc etc
• Sensori-motor memory potential $\approx \infty$ (Ashby)
• Limits are on *speed* of
  – nerve propagation delays
  – learning
• But control is *never* centralized
• Is there a random access read/write memory?
- Acquire
- Translate/integrate
- Automate

Horizontal Meme Transfer

Very Slow Process

“Vertical” App Migration

Fast Inflexible

Slow Flexible

Prefrontal

Motor

Sensory

Striatum

Reflex

Excitatory interneurons

Excitatory interneurons
Sensory
Motor
Prefrontal
Striatum

Learning
Reflex

Slow Flexible

Horizontal App Transfer

Hardware

Software

Fast Inflexible

Universal Architecture

Horizontal HW Transfer

Digital
Analog

Fast
Flexible

App Migration

Universal Architecture
Catabolism

Precursors

DNAp

RNAP

Ribosome

xRNA

transc

RN

transl

AA

ATP

Horizontal App Transfer

Horizontal Meme Transfer

Digital

Analog

Horizontal Gene Transfer

Software

Hardware

Flexible/Adaptable/Evolvable

Reflex

Learning

Sensory

Striatal

Frontal

Depends crucially on layered architecture
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

Virus

Horizontal Bad App Transfer

Fragility?

Parasites & Hijacking

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

- Acquire
- Translate/integrate
- Automate

**Horizontal Meme Transfer**

**Horizontal App Transfer**

**Horizontal Gene Transfer**

Depends crucially on layered architecture
Compute

Turing

Delay is even more important

Bode

Control

Plant

Sense

Control

Universal laws and architectures

Slow Flexible

Software

Hardware

Fast Inflexible

Digital

Analog
Inflexible slow

But efficiency tradeoffs are different.
Cell metabolic expense lines up nicely
Usually draw it this way…


What you see:
The hardware interface and the application function

Need shared architecture and infrastructure
(mostly hidden)
Amazingly Flexible/Adaptable

Need shared architecture and infrastructure (mostly hidden)
Need shared architecture and infrastructure (mostly hidden)
Net
Large Memory

Software

Hardware

Amazingly Flexible/
Adaptable

Horizontal App Transfer

Need shared architecture and infrastructure (mostly hidden)

App

Fast Memory

CPU

App

App

OS

App
More Large Memory

New I/O

Horizontal Hardware Transfer

Fast Memory

CPU

OS

New Hardware

Need shared architecture and infrastructure (mostly hidden)

Amazingly Flexible/Adaptable
Layered architectures

Deconstrained (Applications)

Deconstrained (Hardware)

Constrained

OS

Control, share, virtualize, and manage resources

Processing Memory I/O

Few global variables

Don’t cross layers

Essentials
Tradeoff across multiple layers
• Distributed
• Analog
• ASICs
• FPGA
• …
• Compiled
• Interpreted
Slow
Flexible
Fast
Inflexible
Software
Hardware
Digital
Analog
Technology Evolution
Fast
Inflexible
Scientists have always relied on hypothesis and experimentation. Now, in the era of massive data, there’s a better way.

"All models are wrong, and increasingly you can succeed without them."
Save our children, stop Peta-philia.

There is a treatment.
computers

log(/system)

or log(speed)
transistors or synapses*1e6

log(#/system)

log(speed)

log(#/system)

or log(speed)

computers

biology?

log(speed)

time
transistors or synapses

log(speed)

log(#/system)

computers

linear(time)

biology?

So different architectures?
How general is this picture?