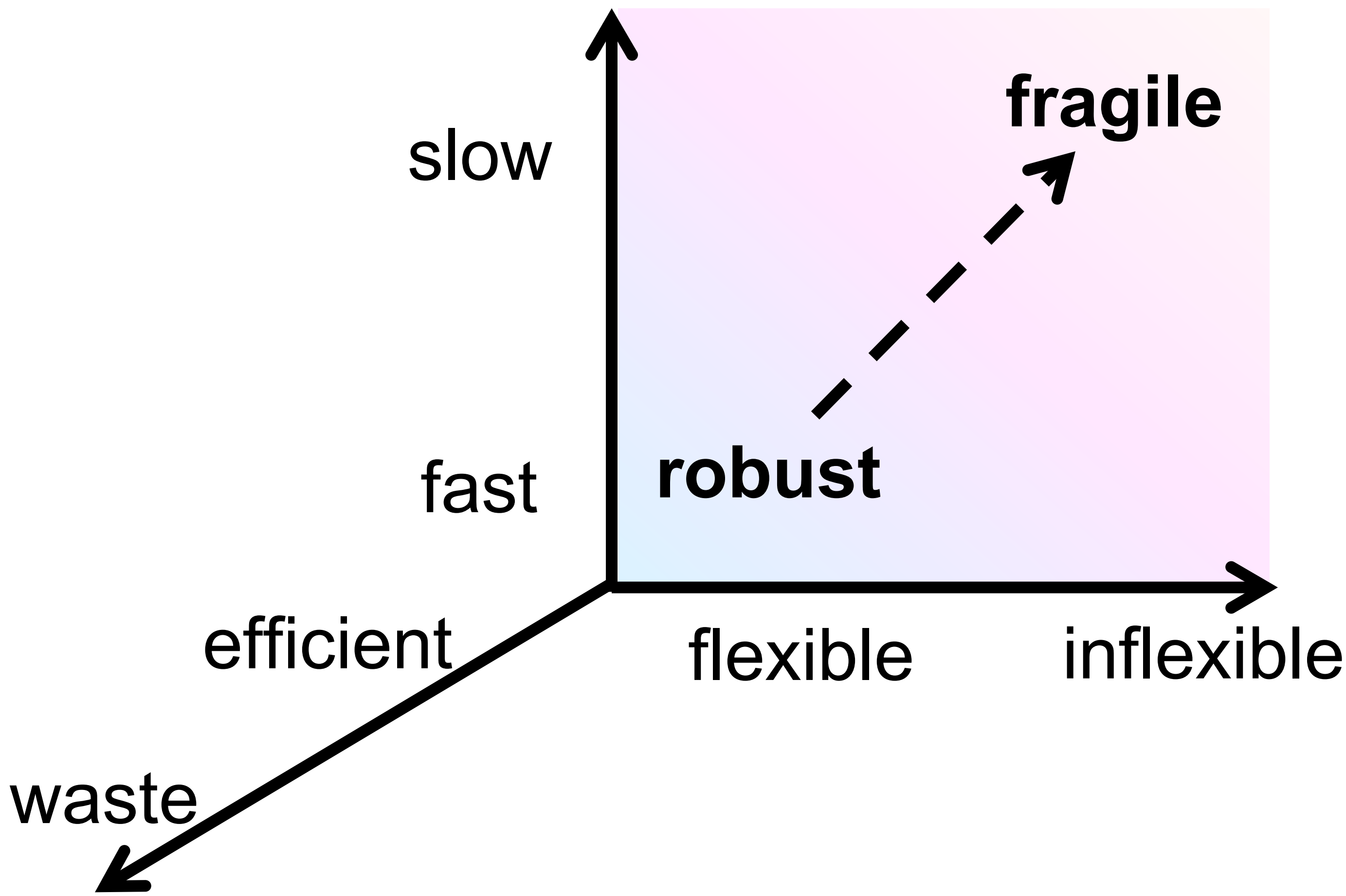
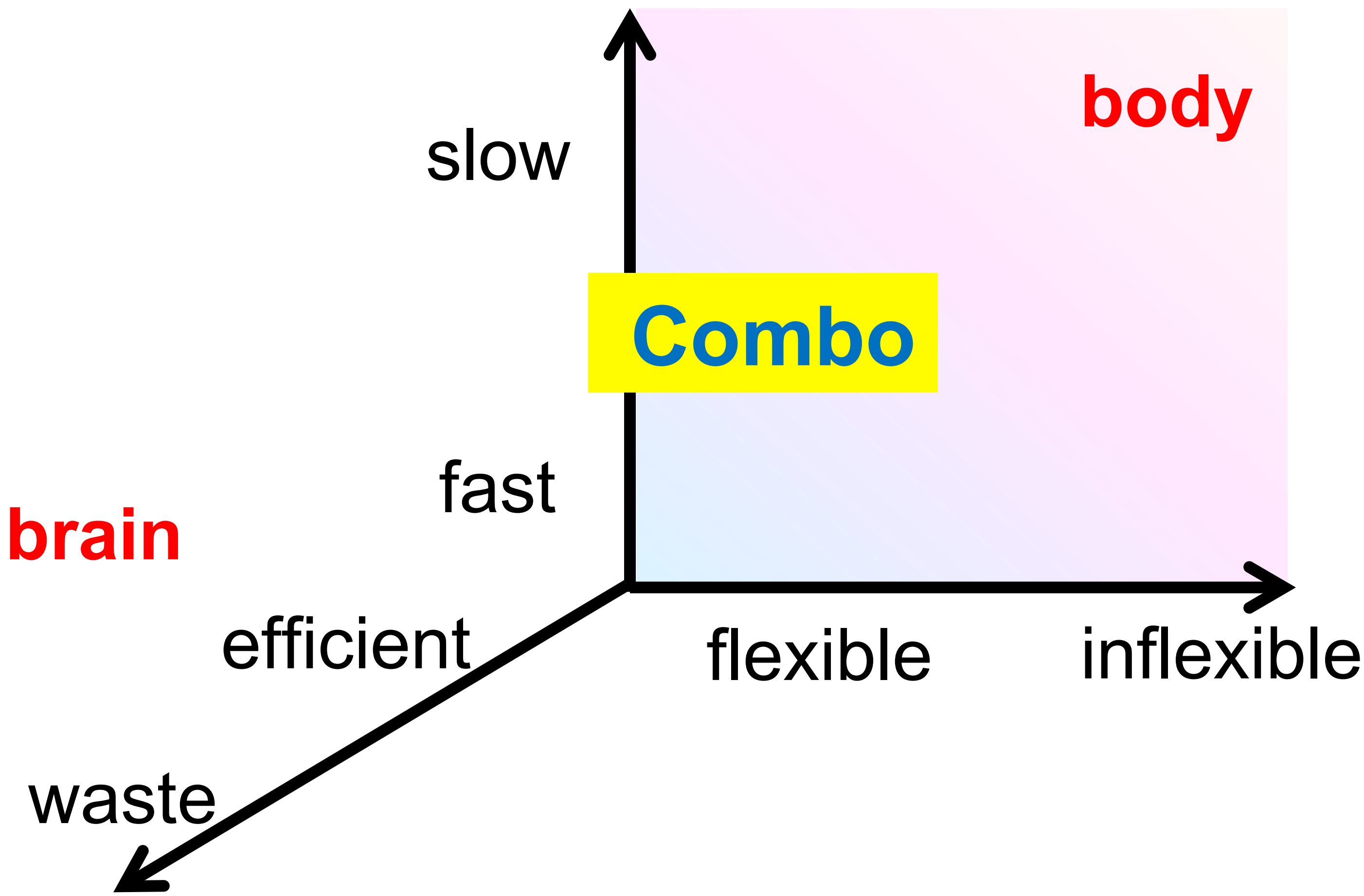
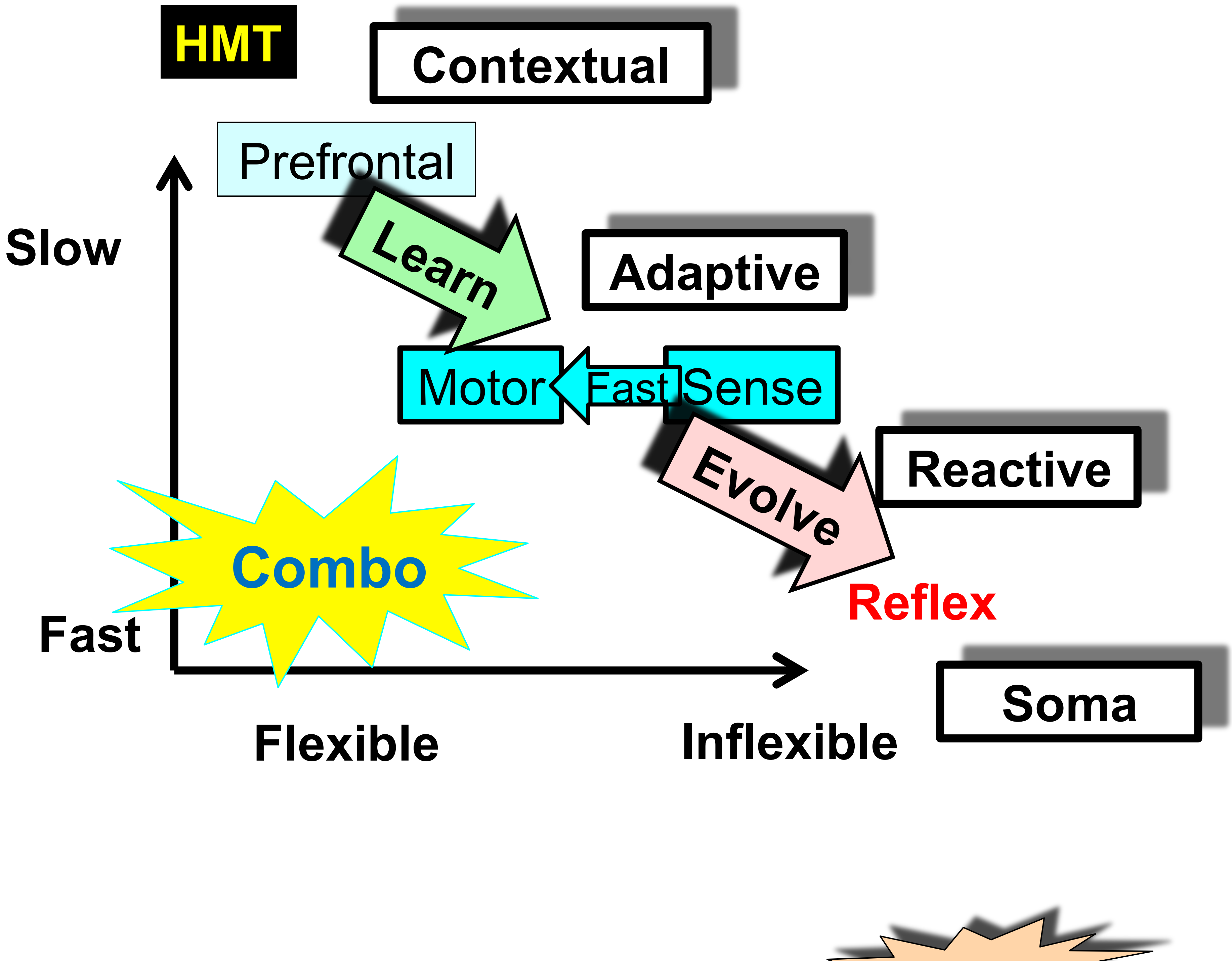
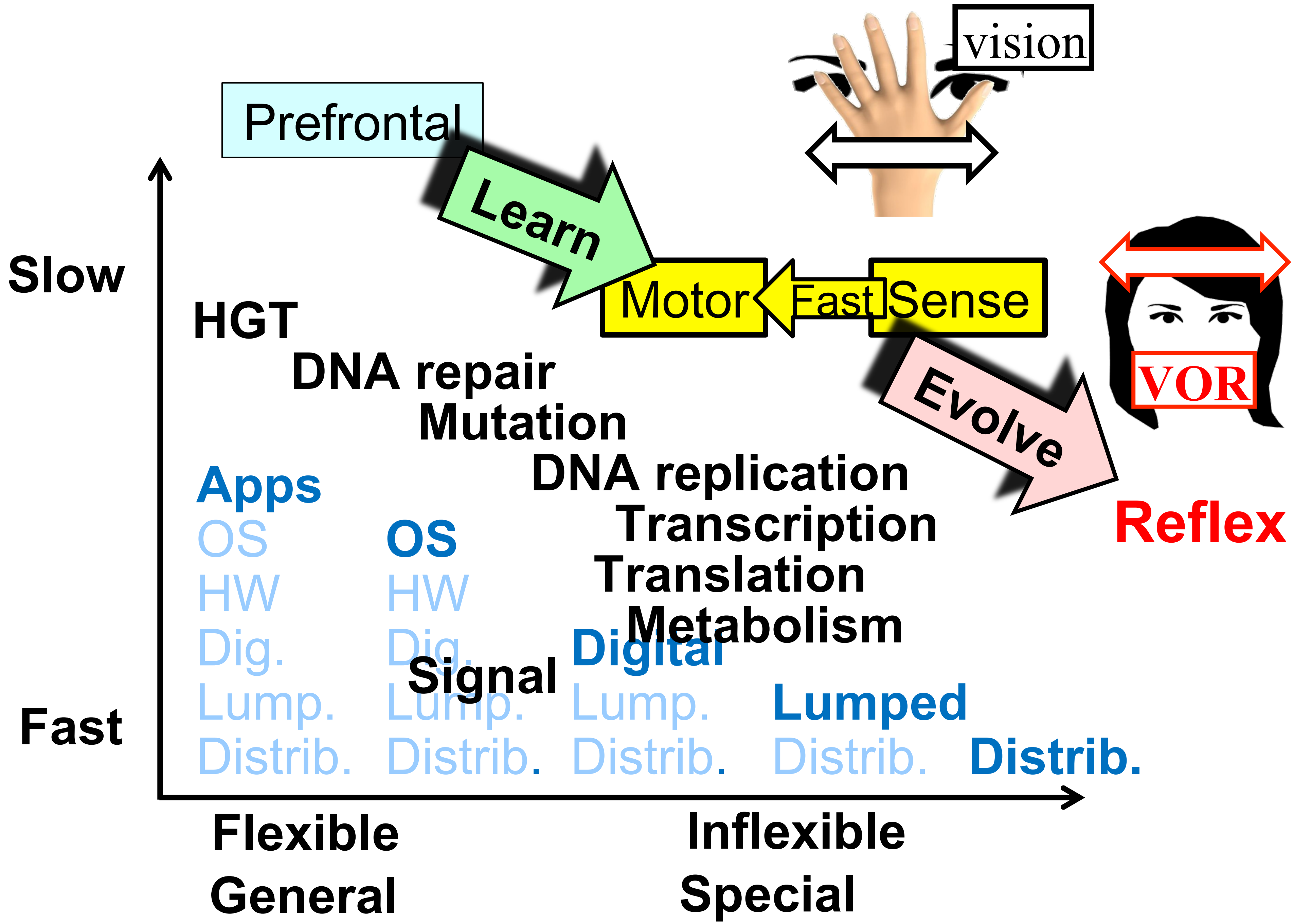


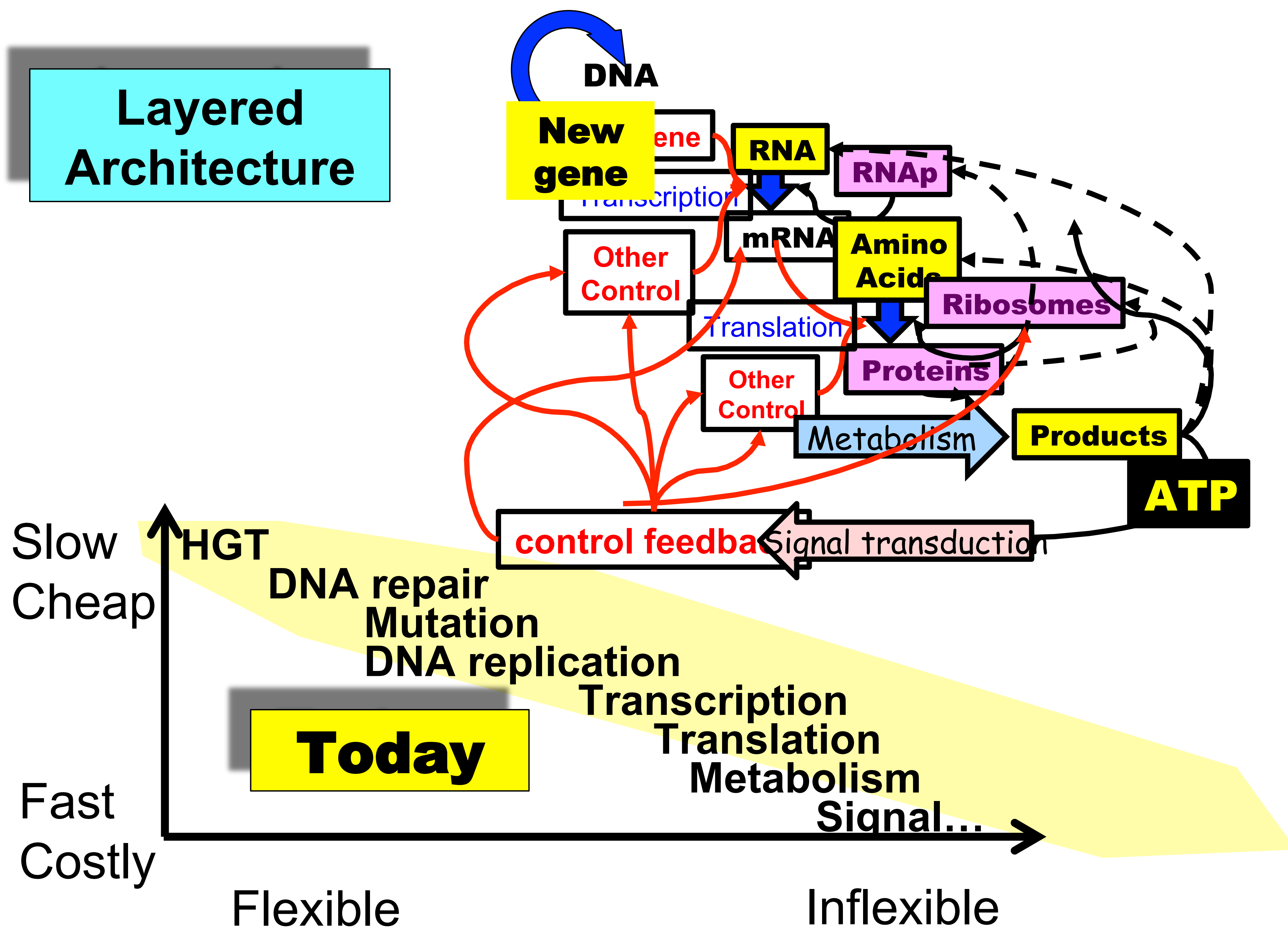
fragile
slow
robust
fast
efficient
flexible
inflexible
waste


body
slow
Combo
fast
brain
efficient
flexible
inflexible
waste


HMT
Contextual
Prefrontal
Learn
Adaptive
Motor
Fast
Sense
Evolve
Reactive
Reflex
Slow
Fast
Combo
Flexible
Inflexible
Soma



Prefrontal
Learn
vision
Motor
Fast
Sense
Evolve
VOR
Reflex
Slow
Fast
HGT
DNA repair
Mutation
DNA replication
Transcription
Translation
Metabolism
Signal
Apps
OS
HW
Dig.
Lump.
Distrib.
OS
HW
Dig.
Lump.
Distrib.
Digital
Lump.
Distrib.
Lumped
Distrib.
Distrib.
Flexible
General
Inflexible
Special

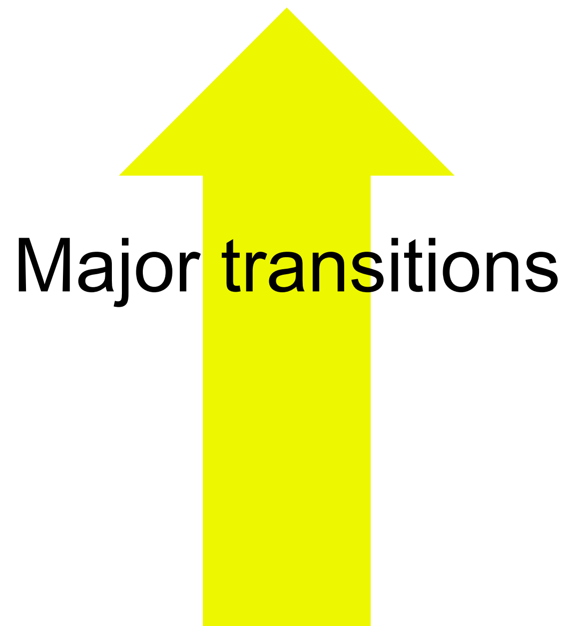


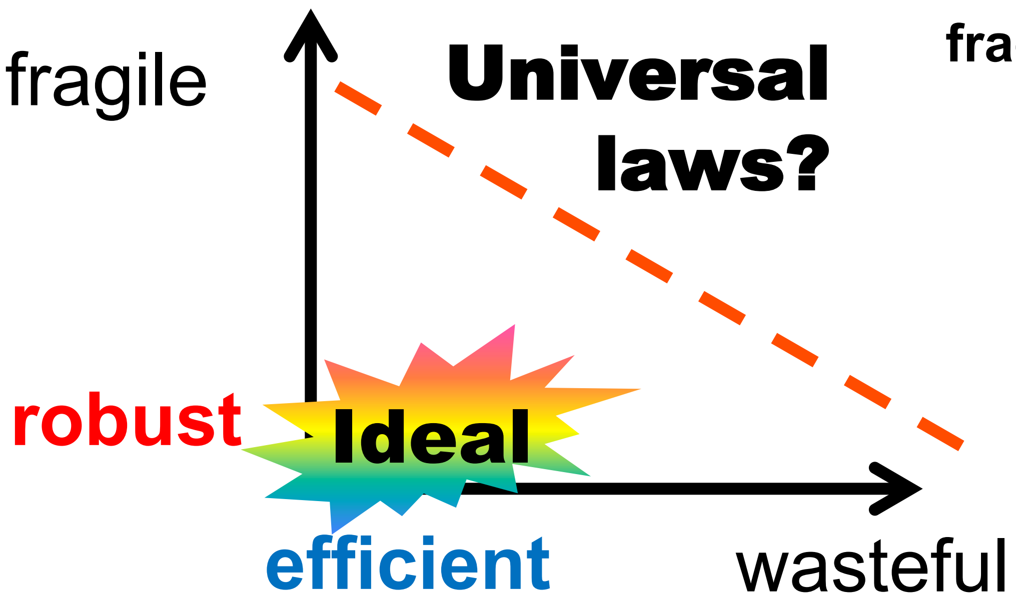
Layered Architecture
DNA
New gene
ene
Transcription
RNA
RNAp
mRNA
Amino Acids
Other Control
Translation
Ribosomes
Proteins
Other Control
Metabolism
Products
ATP
control feedba
Signal transduction
Slow
Cheap
HGT
DNA repair
Mutation
DNA replication
Transcription
Translation
Metabolism
Signal…
Today
Fast
Costly
Flexible
Inflexible

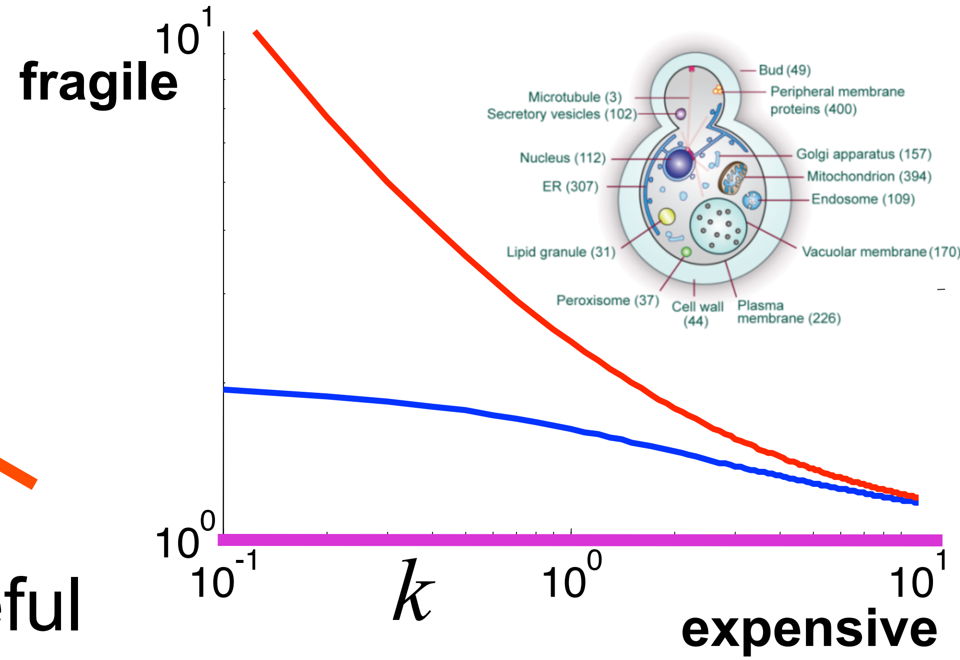
Efficiency/instability/layers/feedback

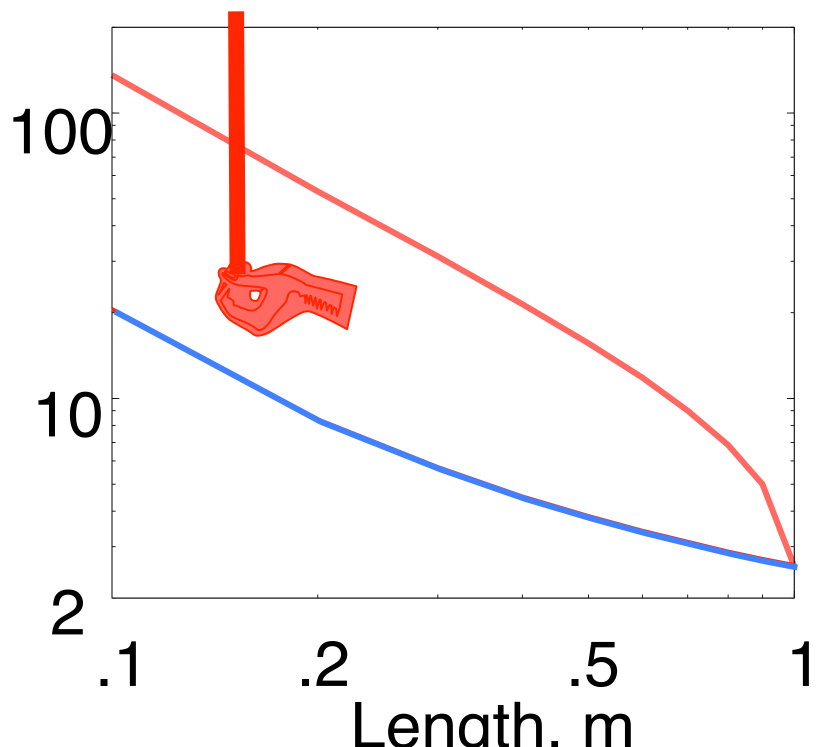
- All create new efficiencies but also instabilities
- Needs new distributed/layered/complex/active control

- Sustainable infrastructure? (e.g. smartgrids)
- Money/finance/lobbyists/etc
- Industrialization
- Society/agriculture/weapons/etc
- Bipedalism
- Maternal care
- Warm blood
- Flight
- Mitochondria
- Oxygen
- Translation (ribosomes)
- Glycolysis (2011 *Science*)





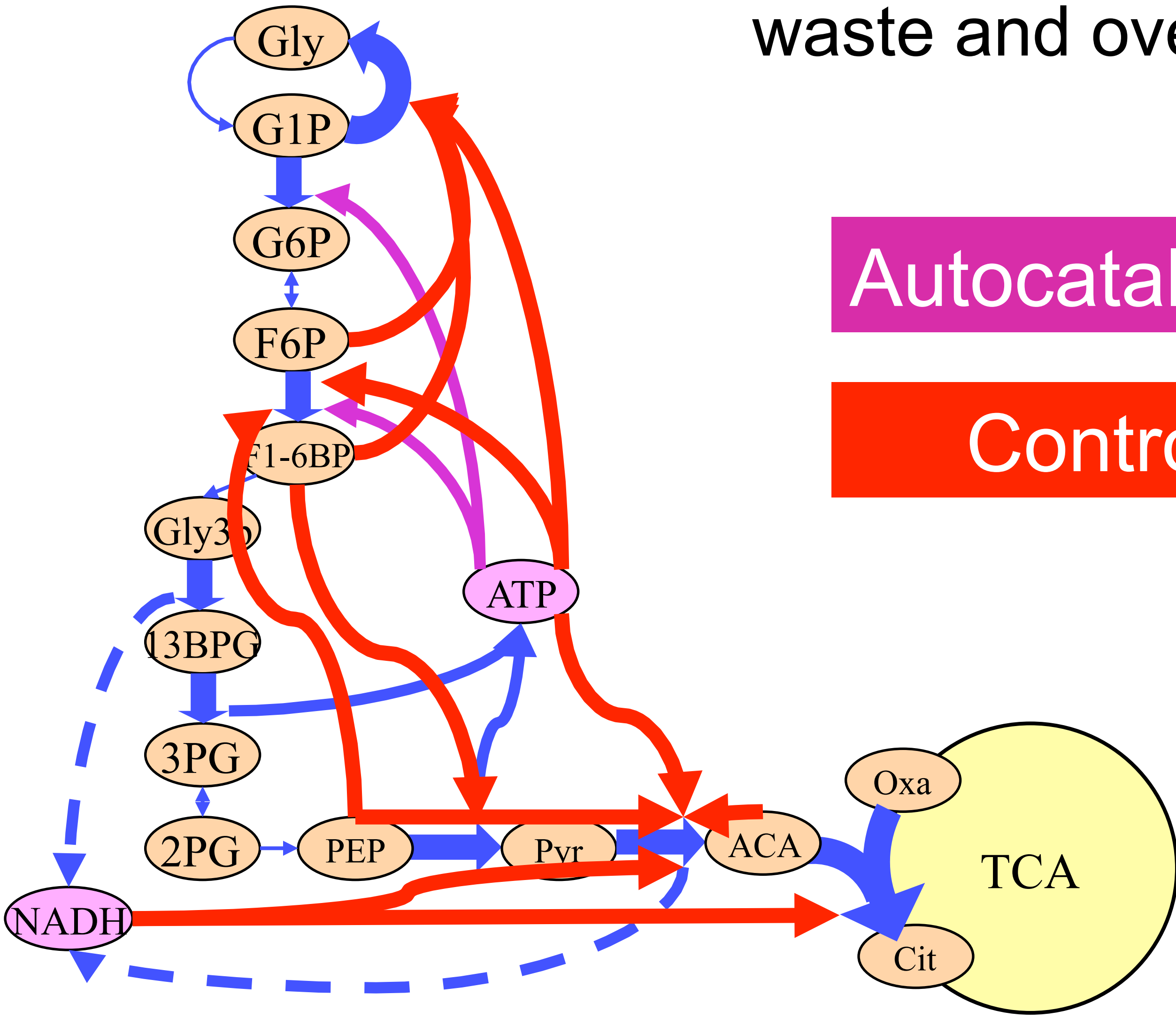




$$\left.\begin{matrix}\exp\left(\int \ln|T|\right) \\ \|T\|_\infty\end{matrix}\right\} \geq \exp(p\tau)\left|\frac{z+p}{z-p}\right|$$

Robust=maintain energy charge w/fluctuating cell demand

Efficient=minimize metabolic waste and overhead

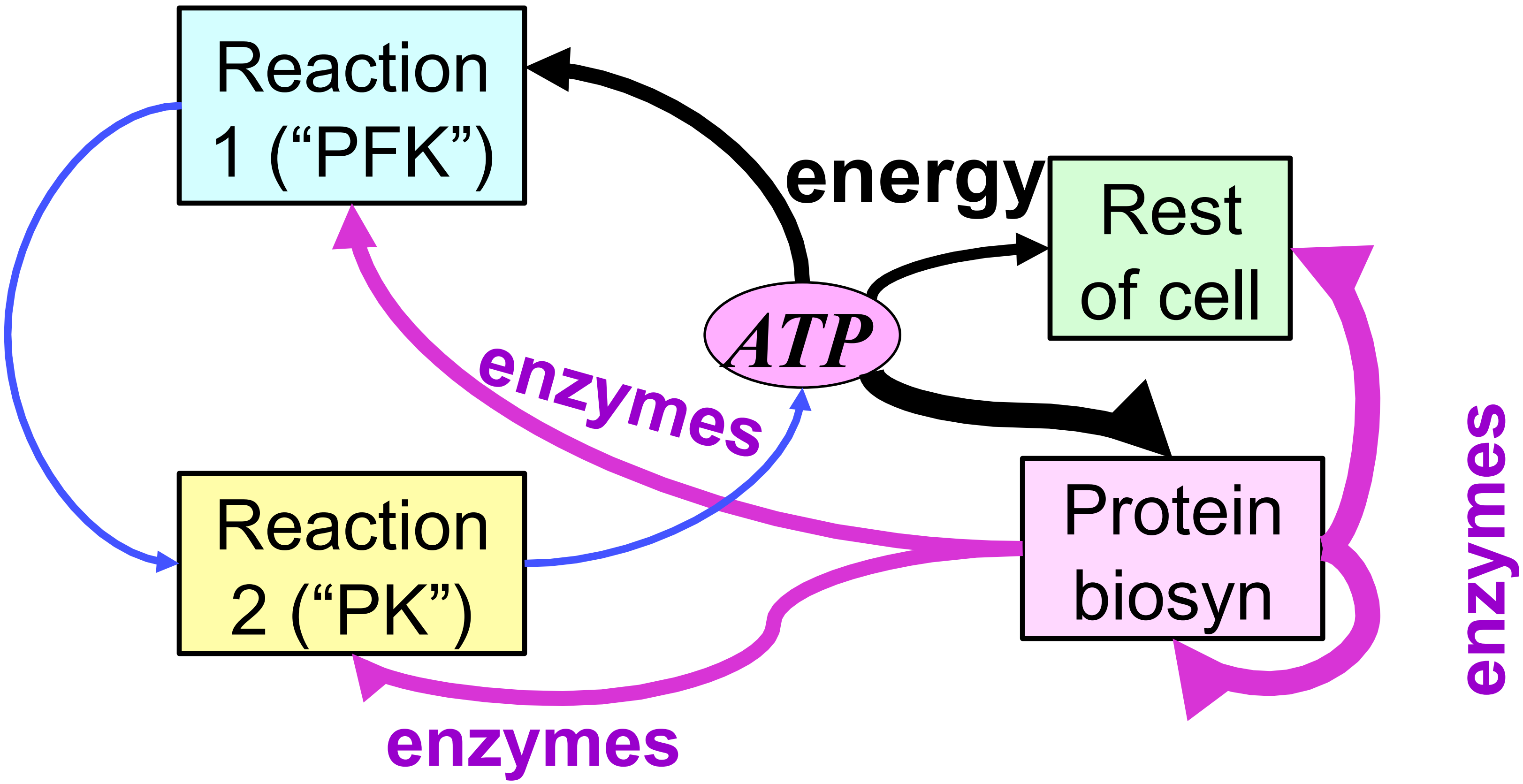


Autocatalysis

Control

Feedbacks

enzymes catalyze reactions, another source of autocatalysis



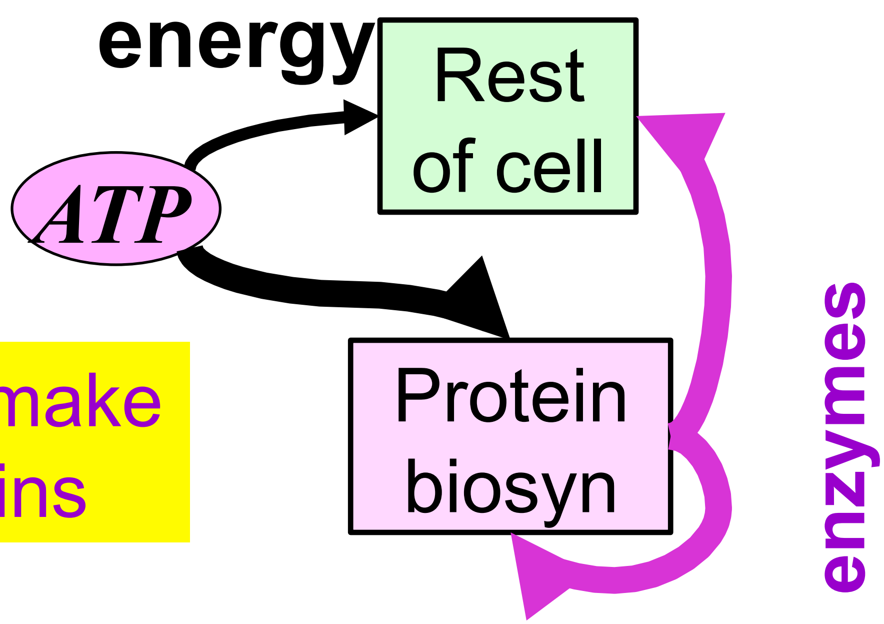
Efficient =

low metabolic overhead

≈ low enzyme amount

enzymes catalyze reactions, another source of autocatalysis

Autocatalysis

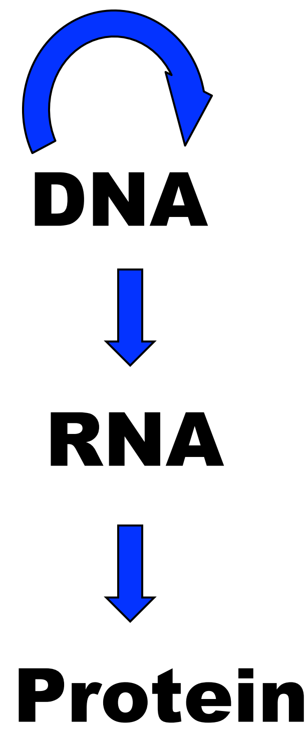


Ribosomes must make ribosomal proteins

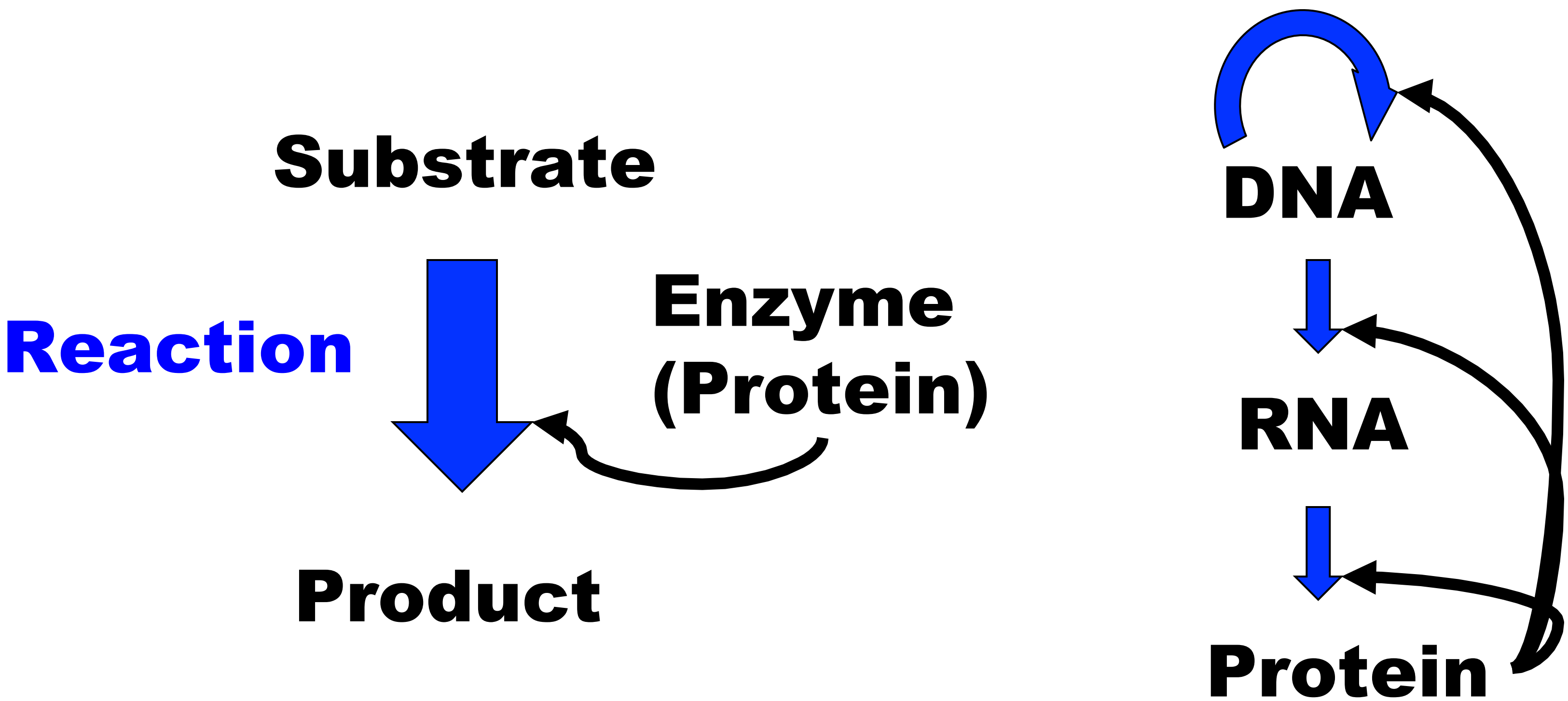
Ribosomal protein content:
Mitochondria >> Bacteria

A pathway view

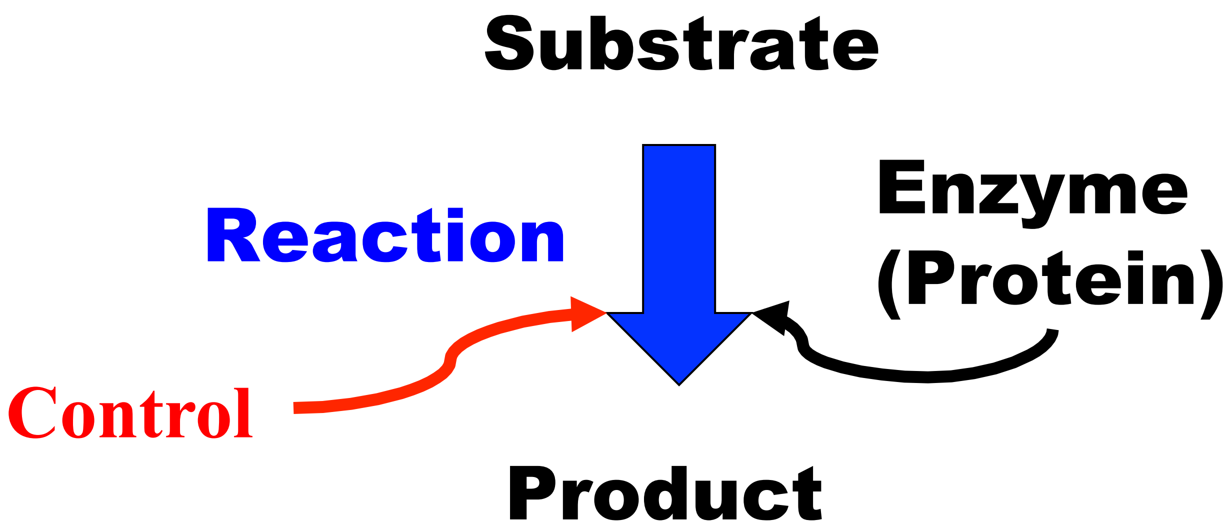
1. DNA repair
2. **Mutation**
3. **DNA replication**
4. Transcription
5. Translation
6. Metabolism
7. Signal transduction
8. …

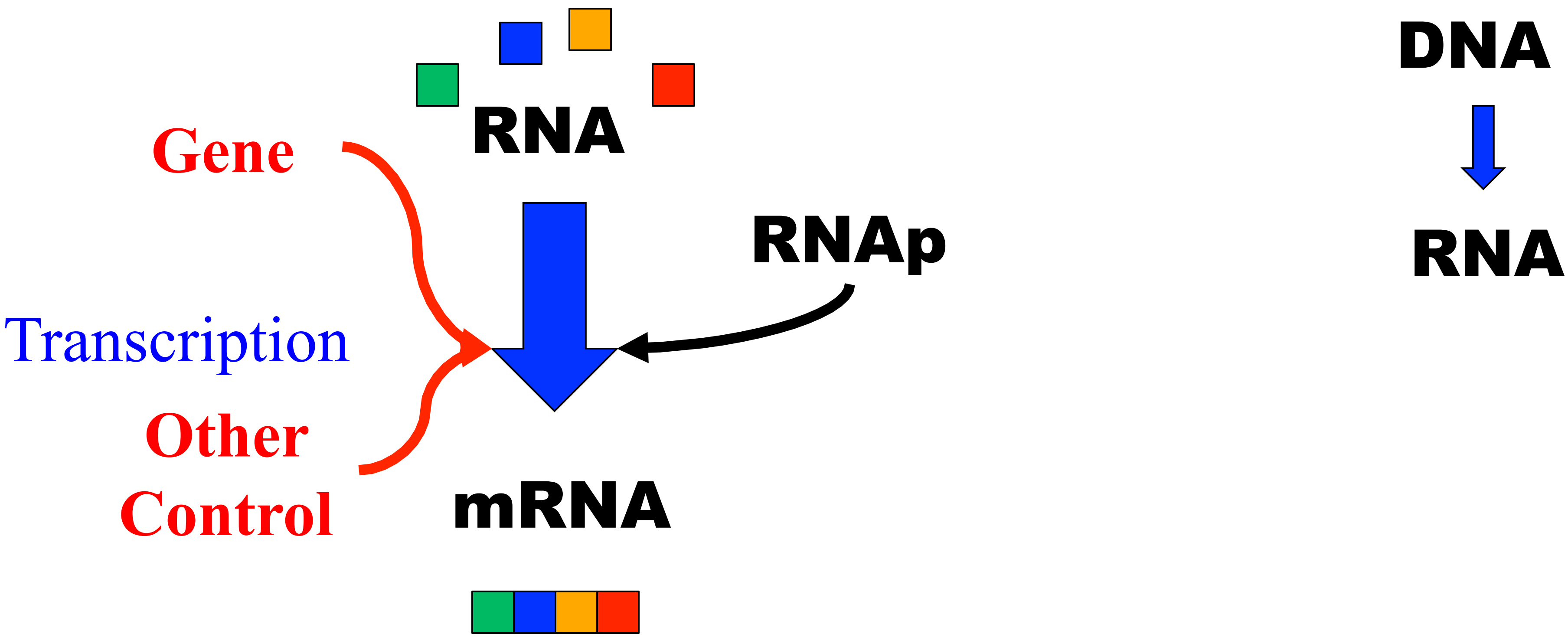


A pathway view

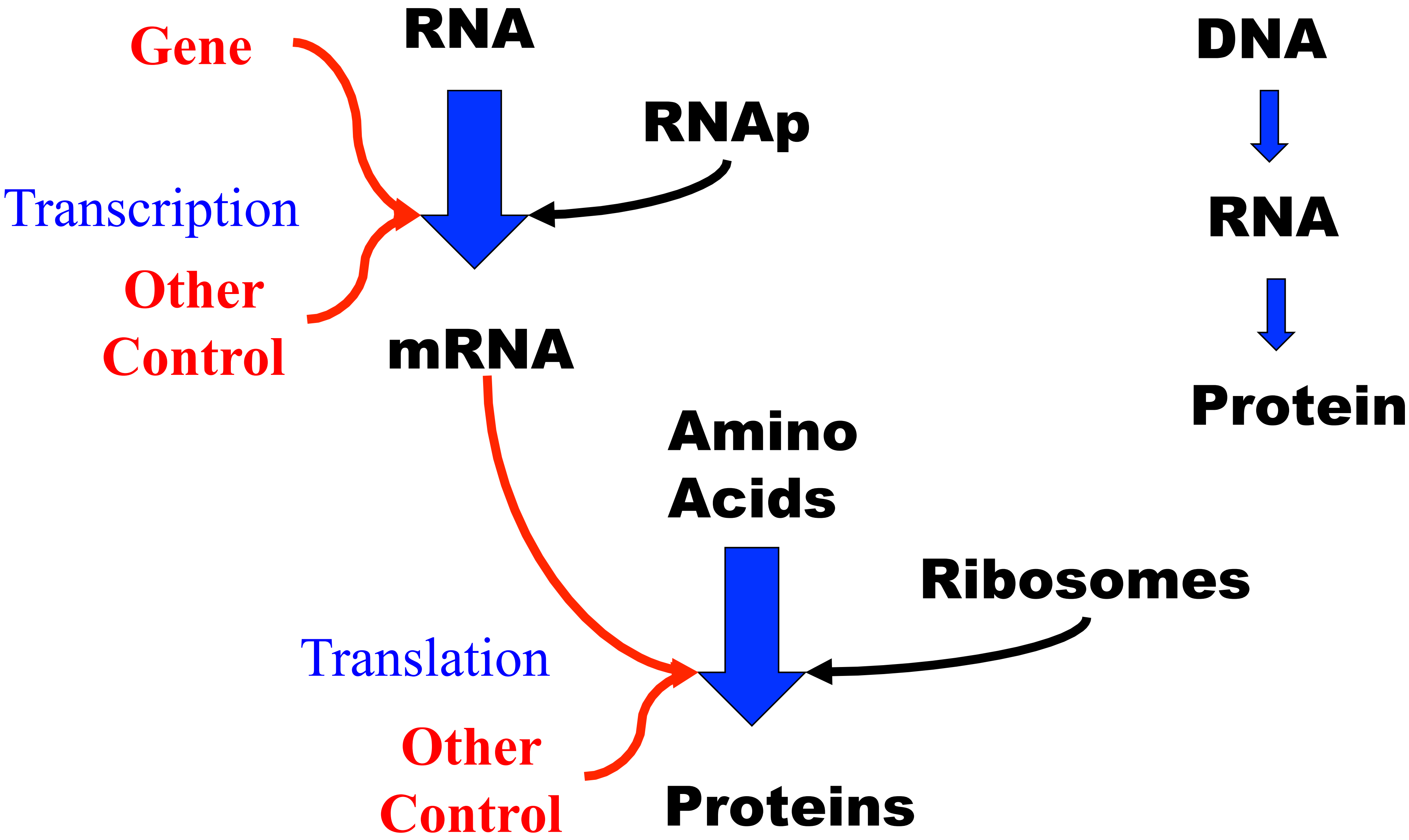


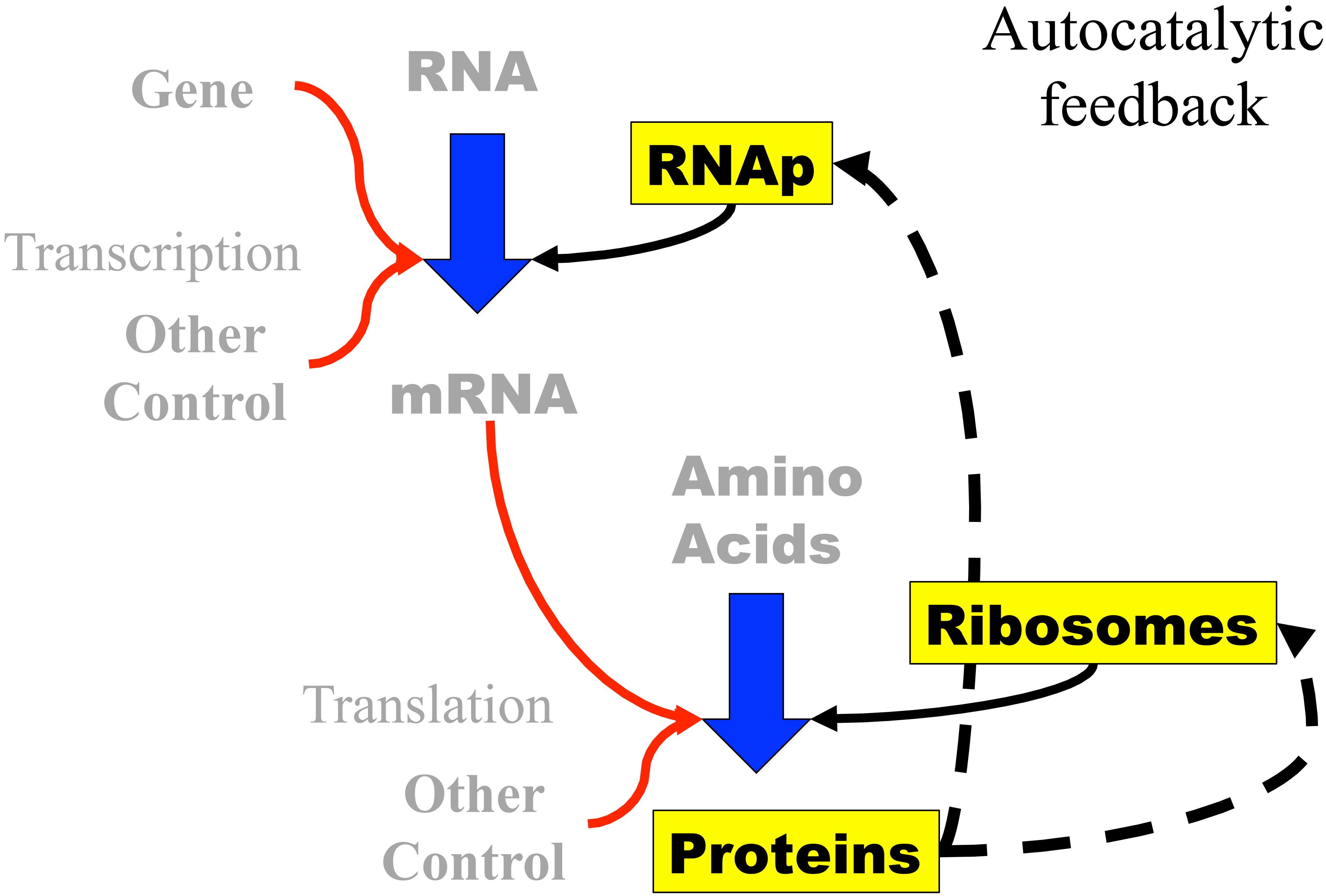
A pathway view



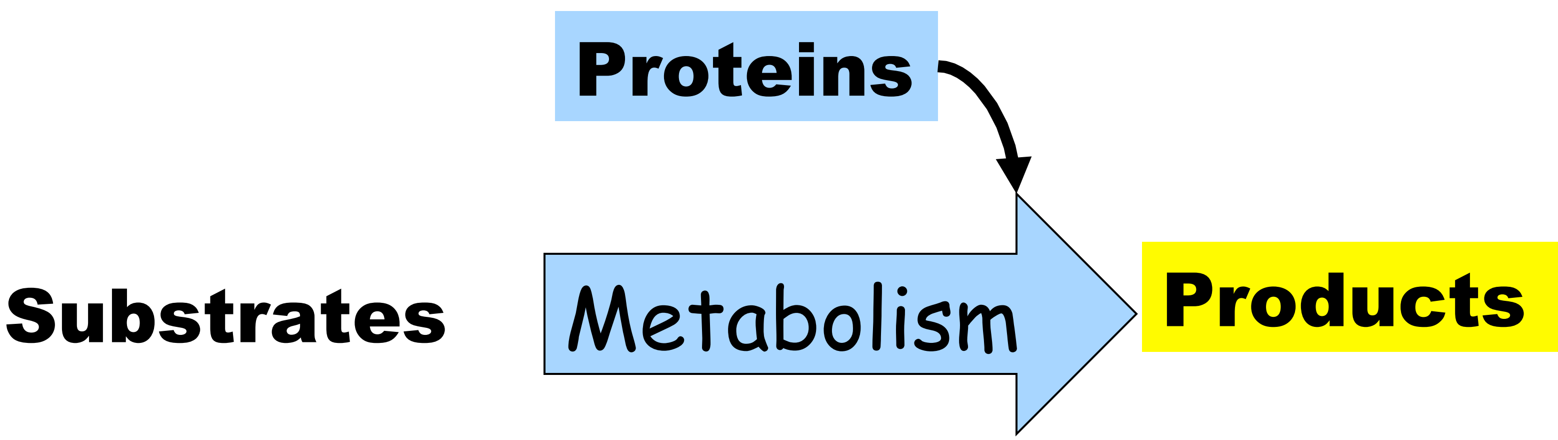


Polymerization

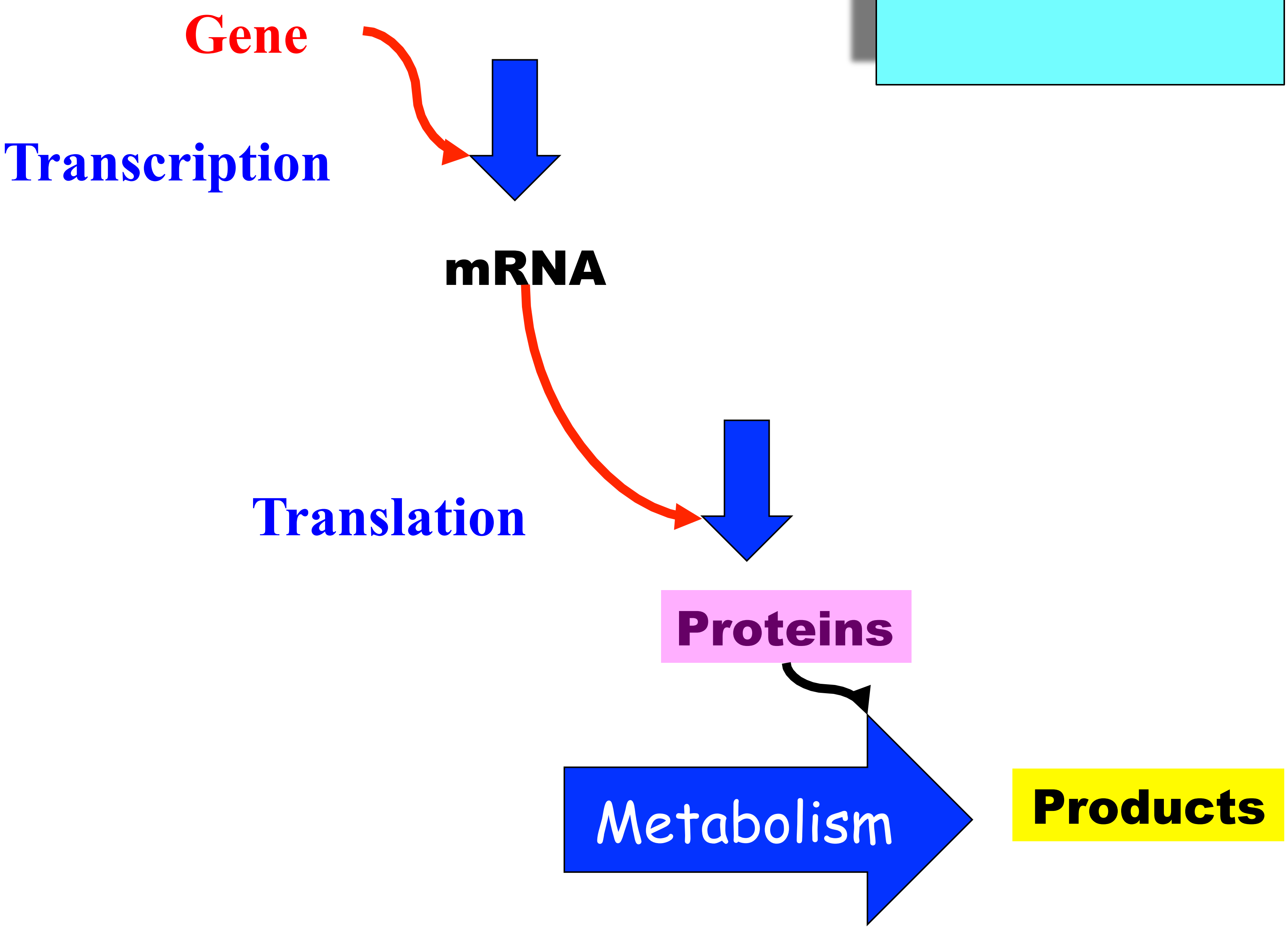

RNA
Gene
RNAp
Transcription
Other
Control
mRNA
Amino
Acids
Ribosomes
Translation
Other
Control
Proteins
DNA
RNA
Protein

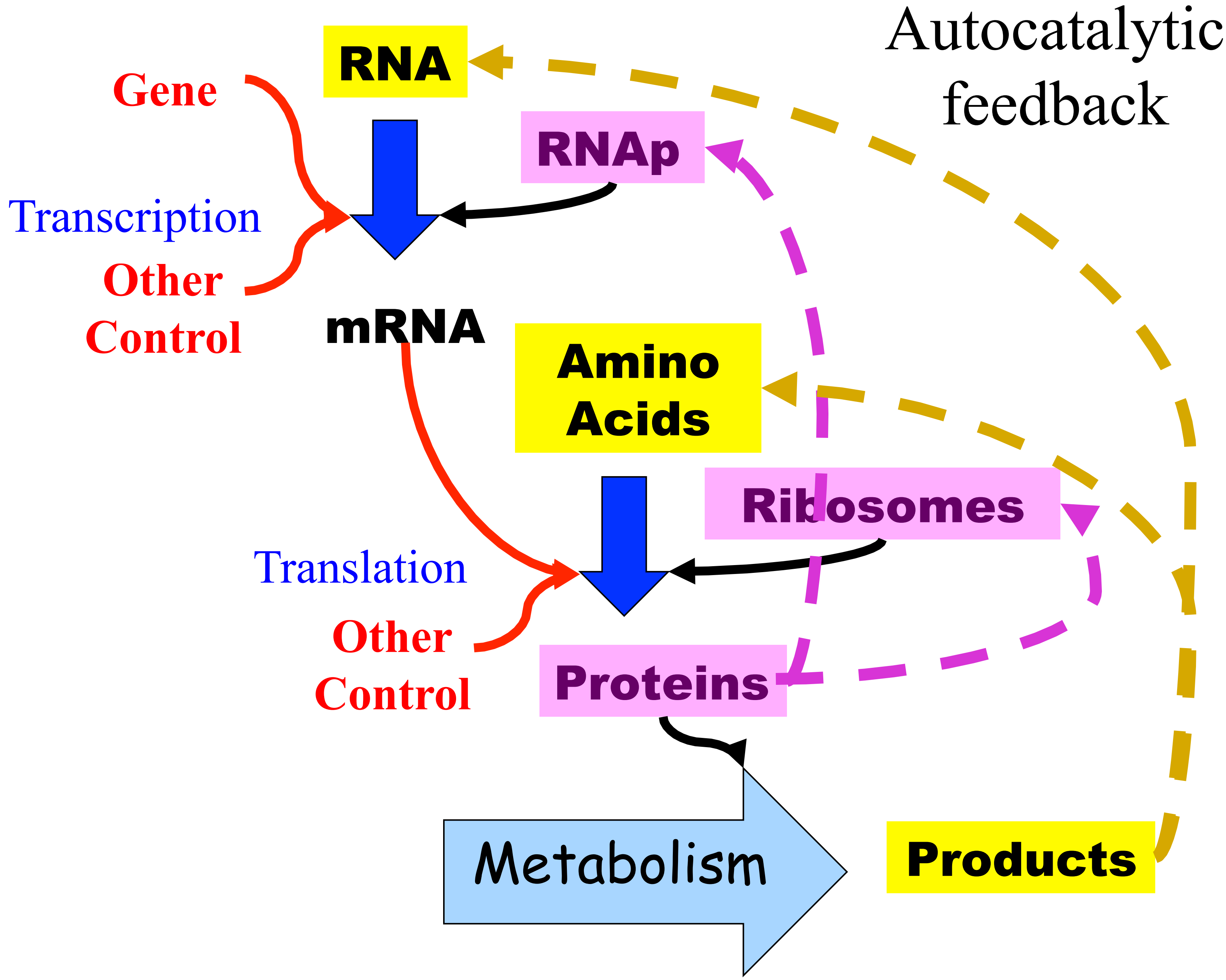


Autocatalytic feedback
Gene
RNA
Transcription
Other Control
RNAp
mRNA
Amino Acids
Ribosomes
Translation
Other Control
Proteins

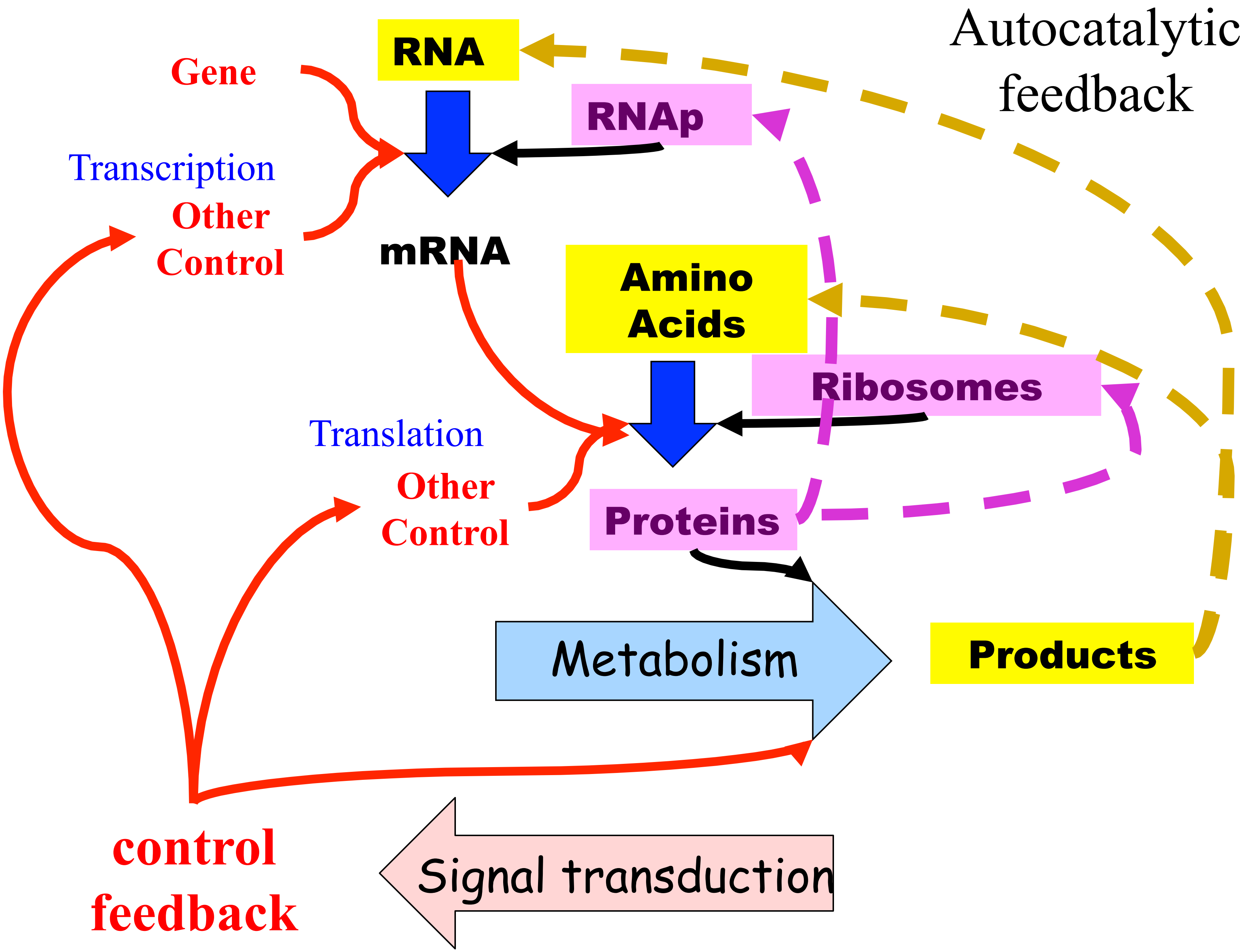

Proteins
Substrates
Metabolism
Products

Core Protocols

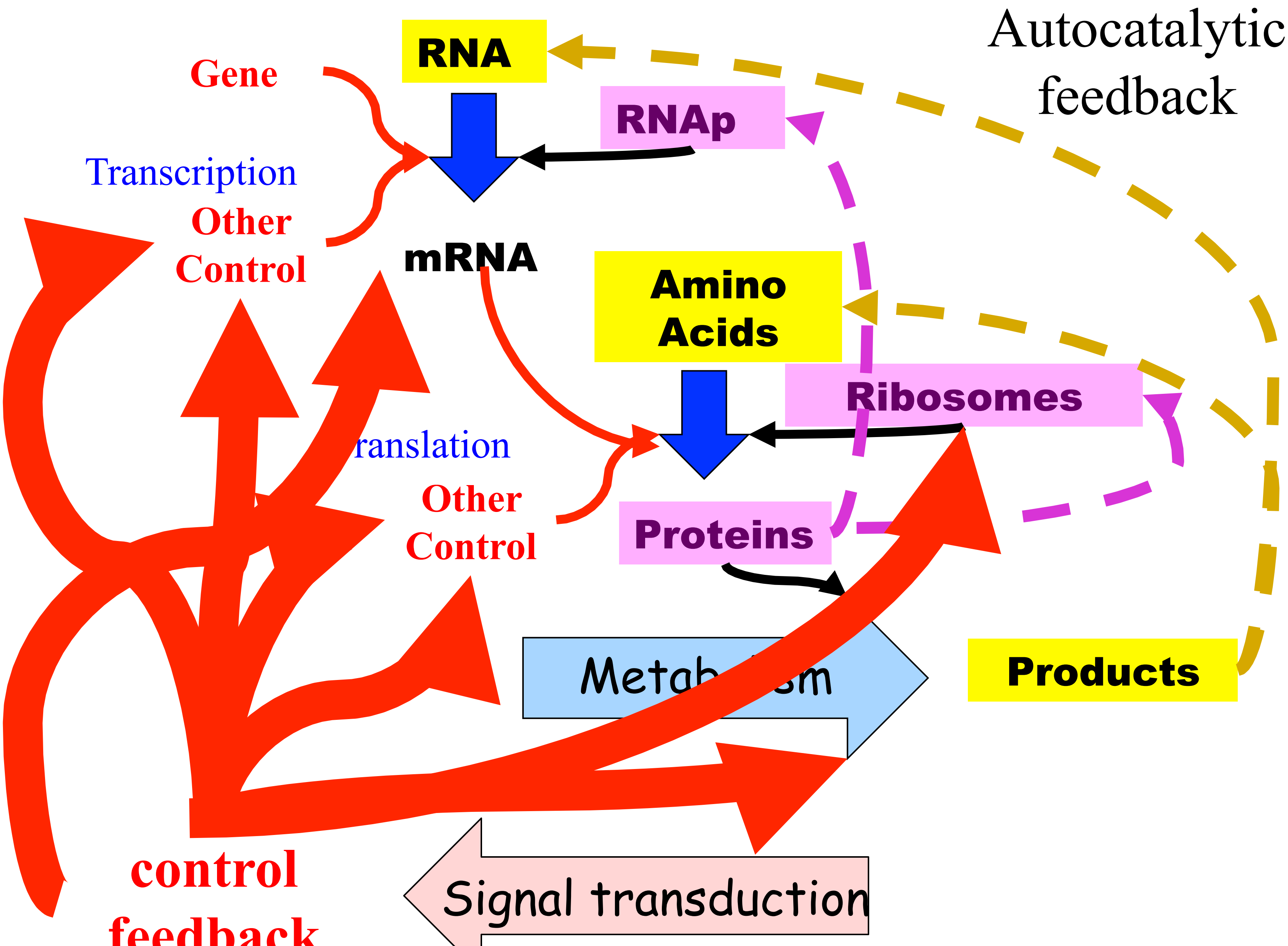


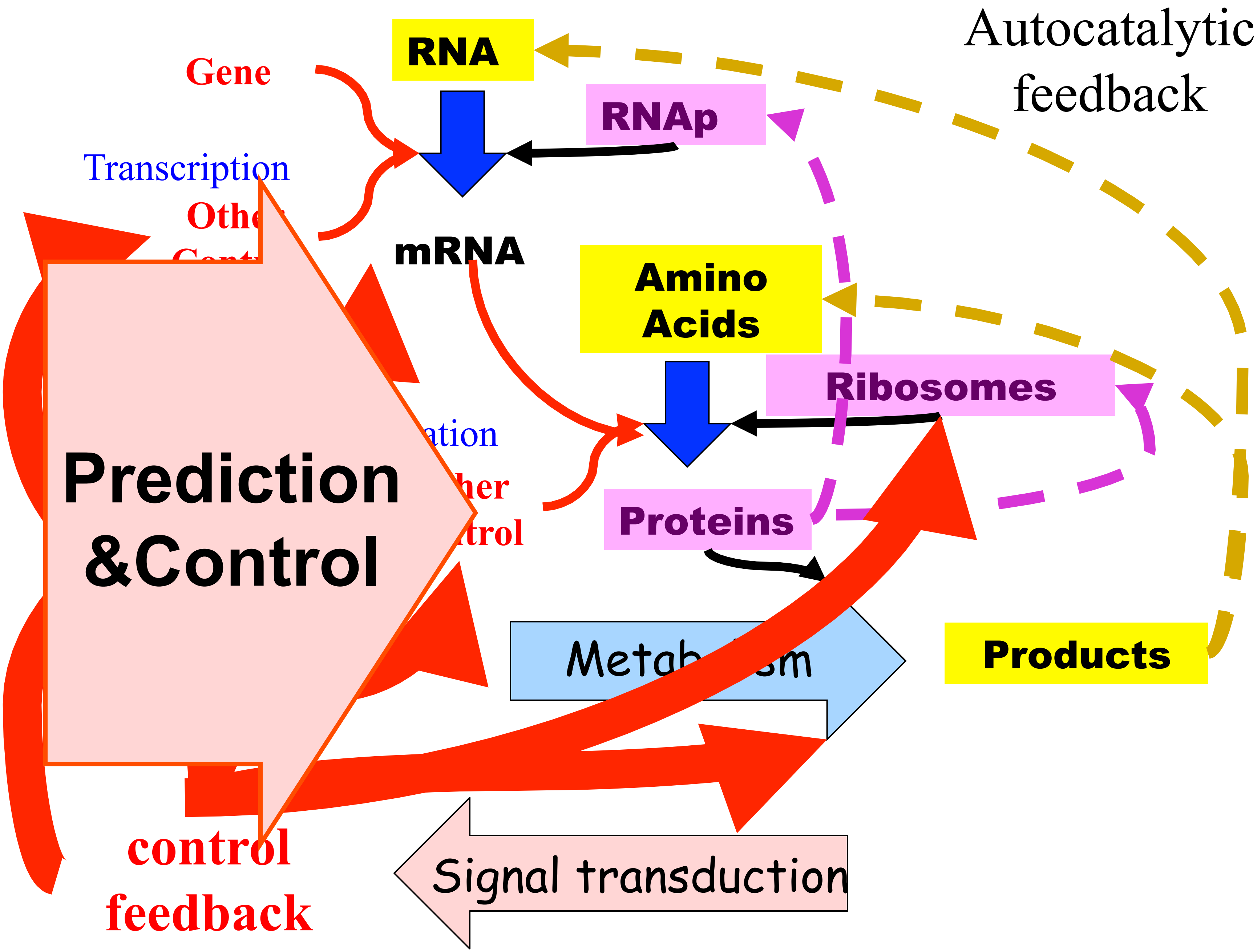


Autocatalytic feedback
RNA
Gene
RNAp
Transcription
Other Control
mRNA
Amino Acids
Ribosomes
Translation
Other Control
Proteins
Metabolism
Products



Autocatalytic
feedback
RNA
Gene
RNAp
Transcription
Other
Control
mRNA
Amino
Acids
Ribosomes
Translation
Other
Control
Proteins
Metabolism
Products
control
feedback
Signal transduction

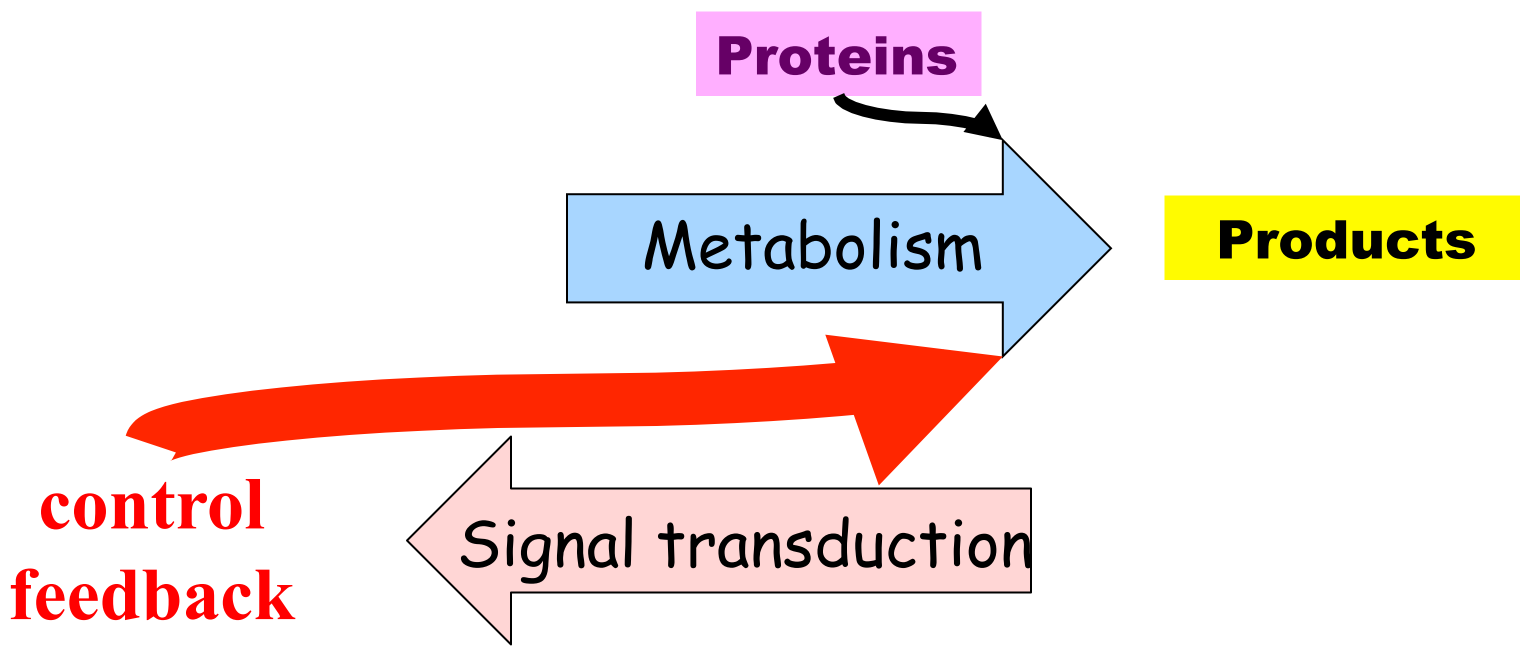

RNA
Gene
RNAp
Autocatalytic feedback
Transcription
Other Control
mRNA
Amino Acids
Ribosomes
ranslation
Other Control
Proteins
Metab sm
Products
control feedback
Signal transduction

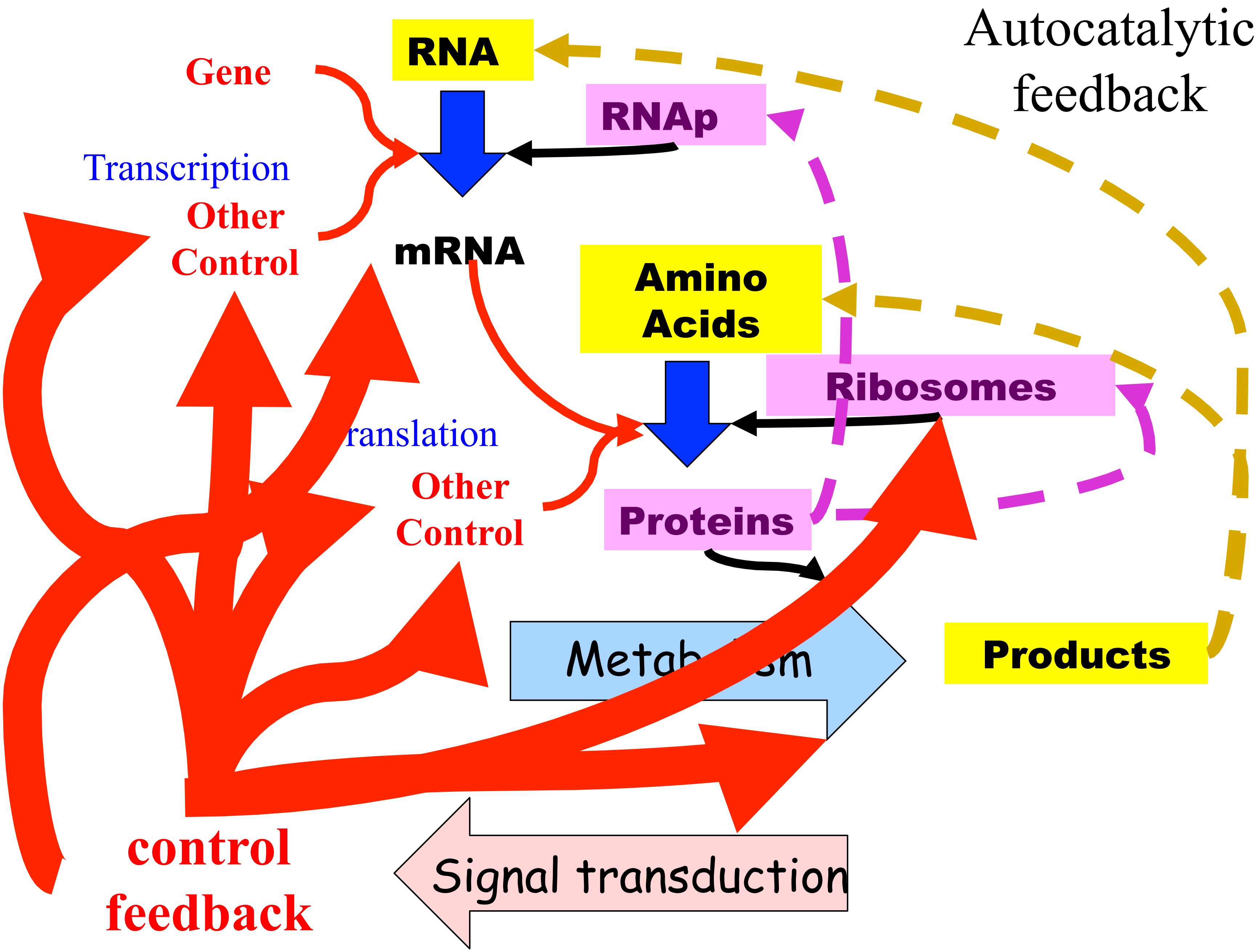


Autocatalytic feedback
Gene
RNA
RNAp
Transcription
mRNA
Amino Acids
Ribosomes
Proteins
Prediction &Control
Metab
sm
Products
control feedback
Signal transduction

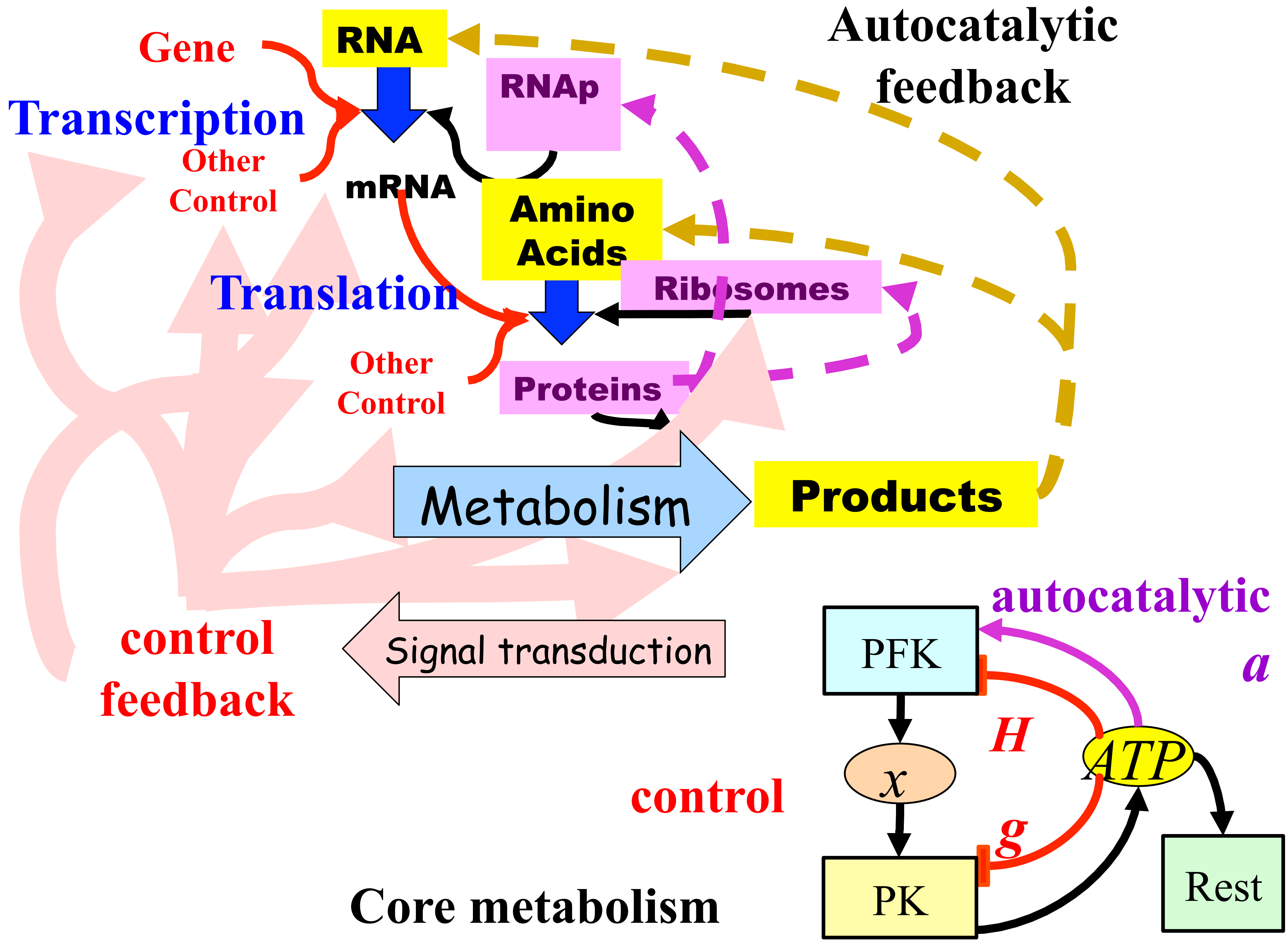
1. DNA repair
2. Mutation
3. DNA replication
4. Transcription
5. Translation
6. **Metabolism**
7. **Signal transduction**
8. **…**

Red blood cells





Autocatalytic feedback
RNA
Gene
RNAp
Transcription
Other Control
mRNA
Amino Acids
Ribosomes
ranslation
Other Control
Proteins
Metab sm
Products
control feedback
Signal transduction



Gene
RNA
RNAp
Autocatalytic feedback
Transcription
Other Control
mRNA
Amino Acids
Translation
Ribosomes
Other Control
Proteins
Metabolism
Products
control feedback
Signal transduction
autocatalytic
a
PFK
H
x
ATP
control
g
PK
Rest
Core metabolism

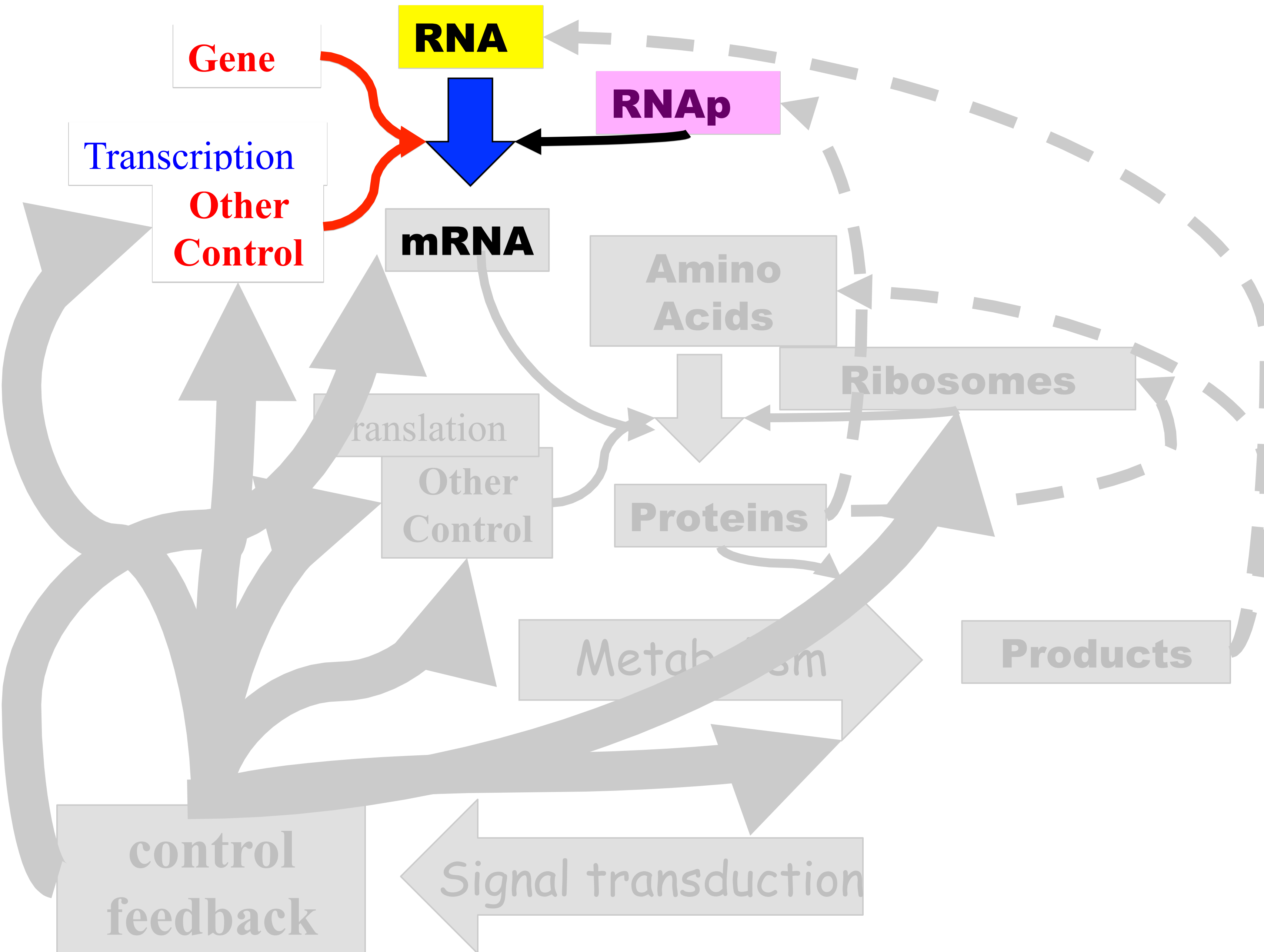
Control 1.0

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

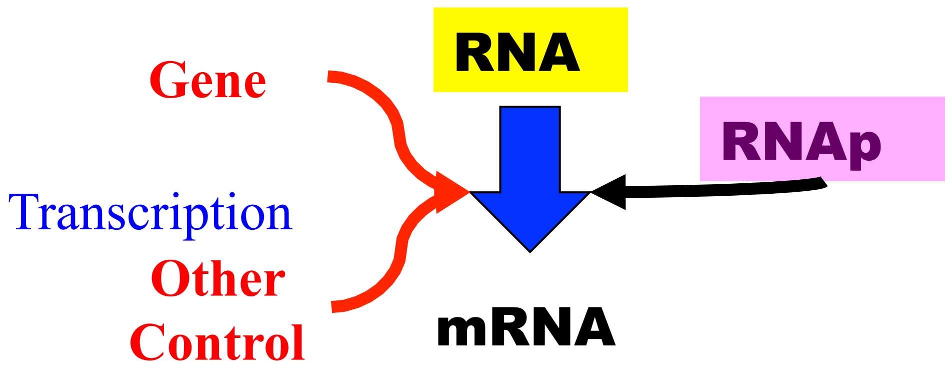
}

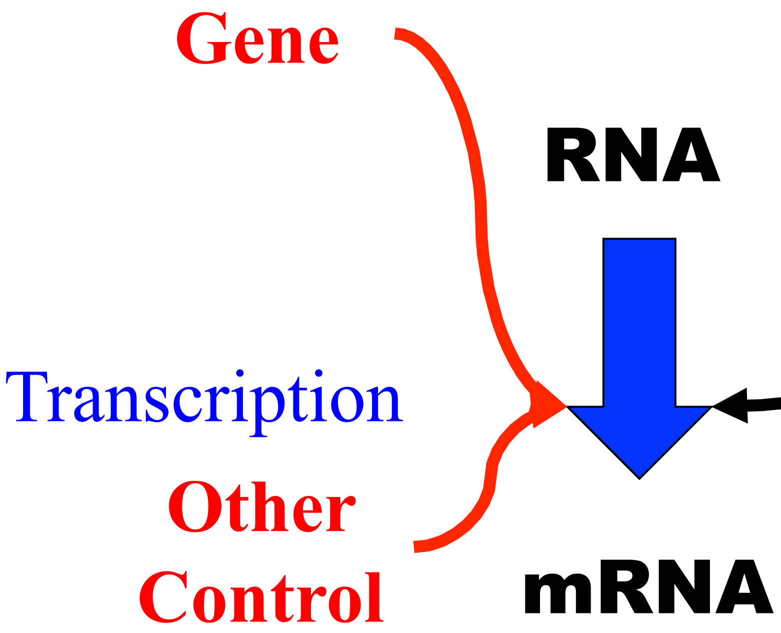
Highly controlled

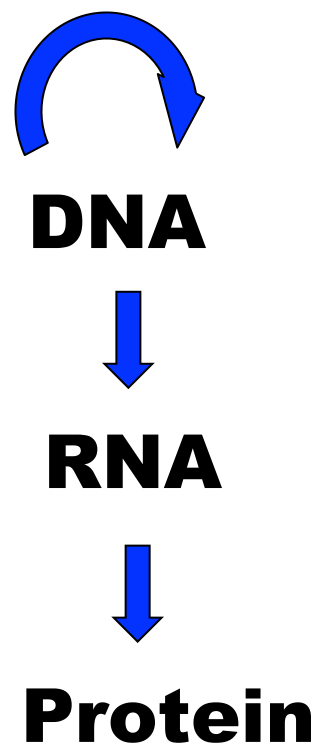
Think of this as a "protocol stack"

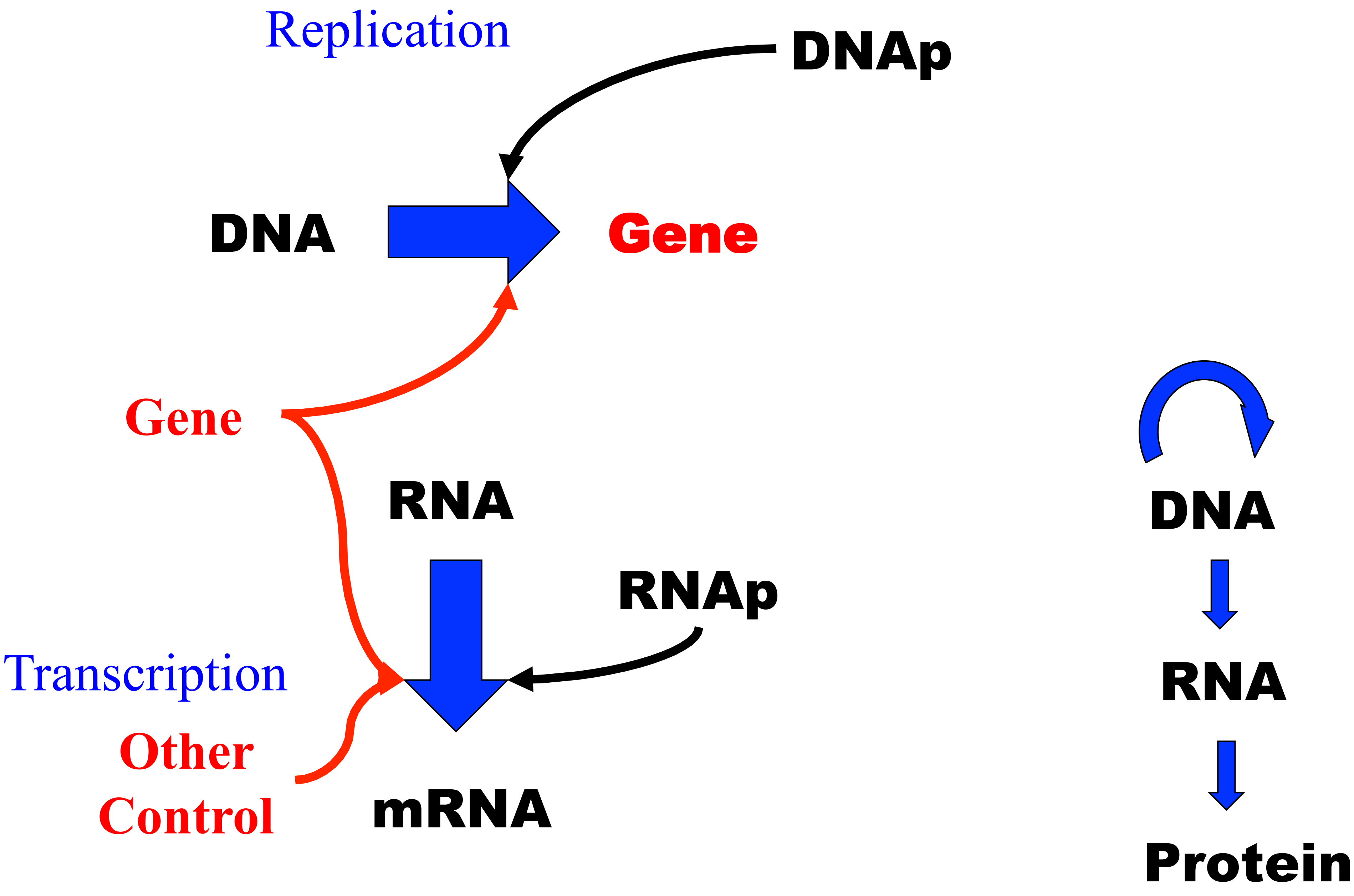


Gene
RNA
RNAp
Transcription
Other
Control
mRNA
Amino
Acids
Ribosomes
Translation
Other
Control
Proteins
Products
control
feedback
Signal transduction

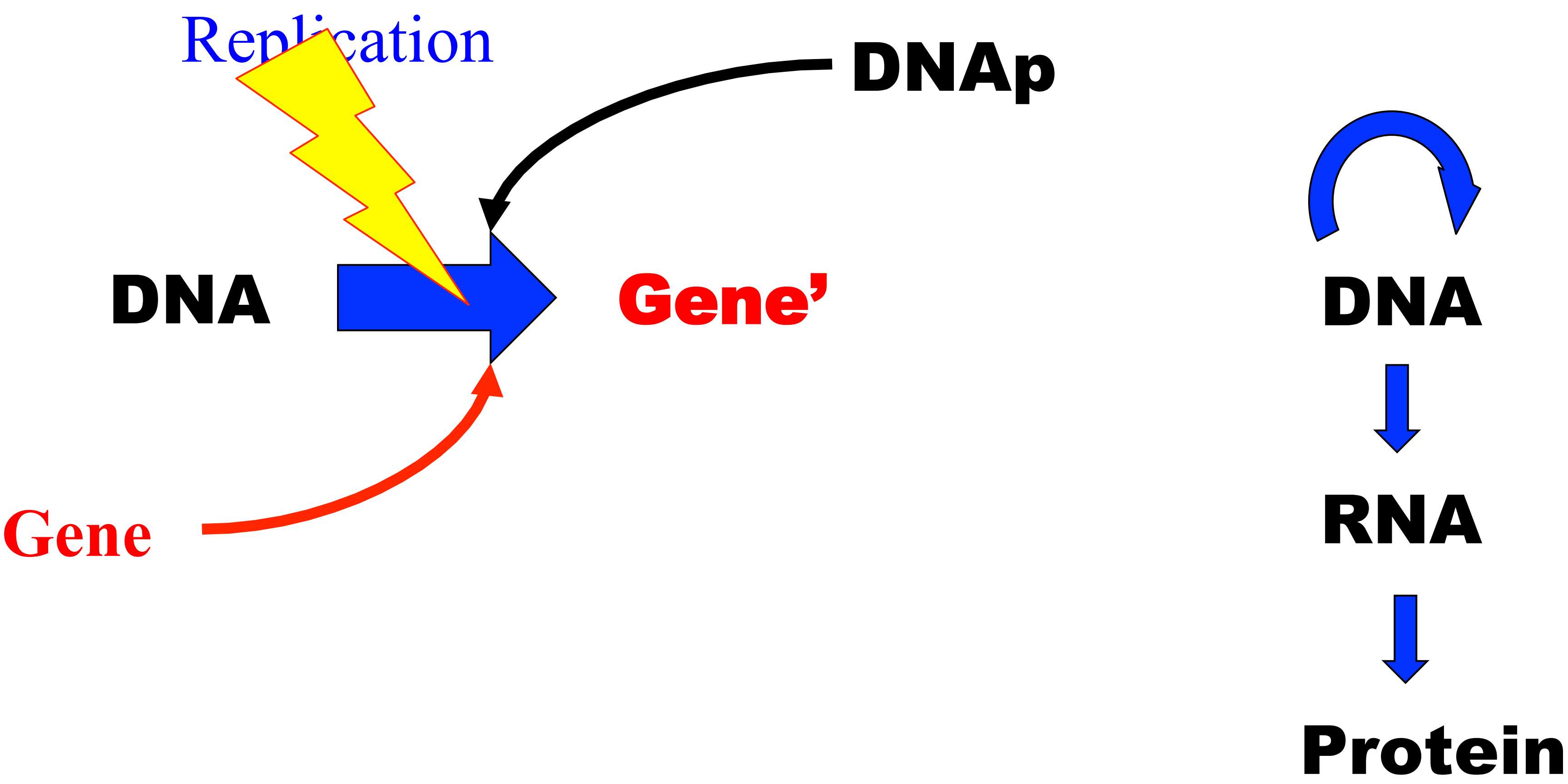

RNA
Gene
RNAp
Transcription
Other
Control
mRNA


Gene
RNA
RNAp
Transcription
Other
Control
mRNA


DNA
RNA
Protein


Replication
DNAp
DNA
Gene
Gene
RNA
RNAp
Transcription
Other
Control
mRNA
DNA
RNA
Protein

Mutation and repair



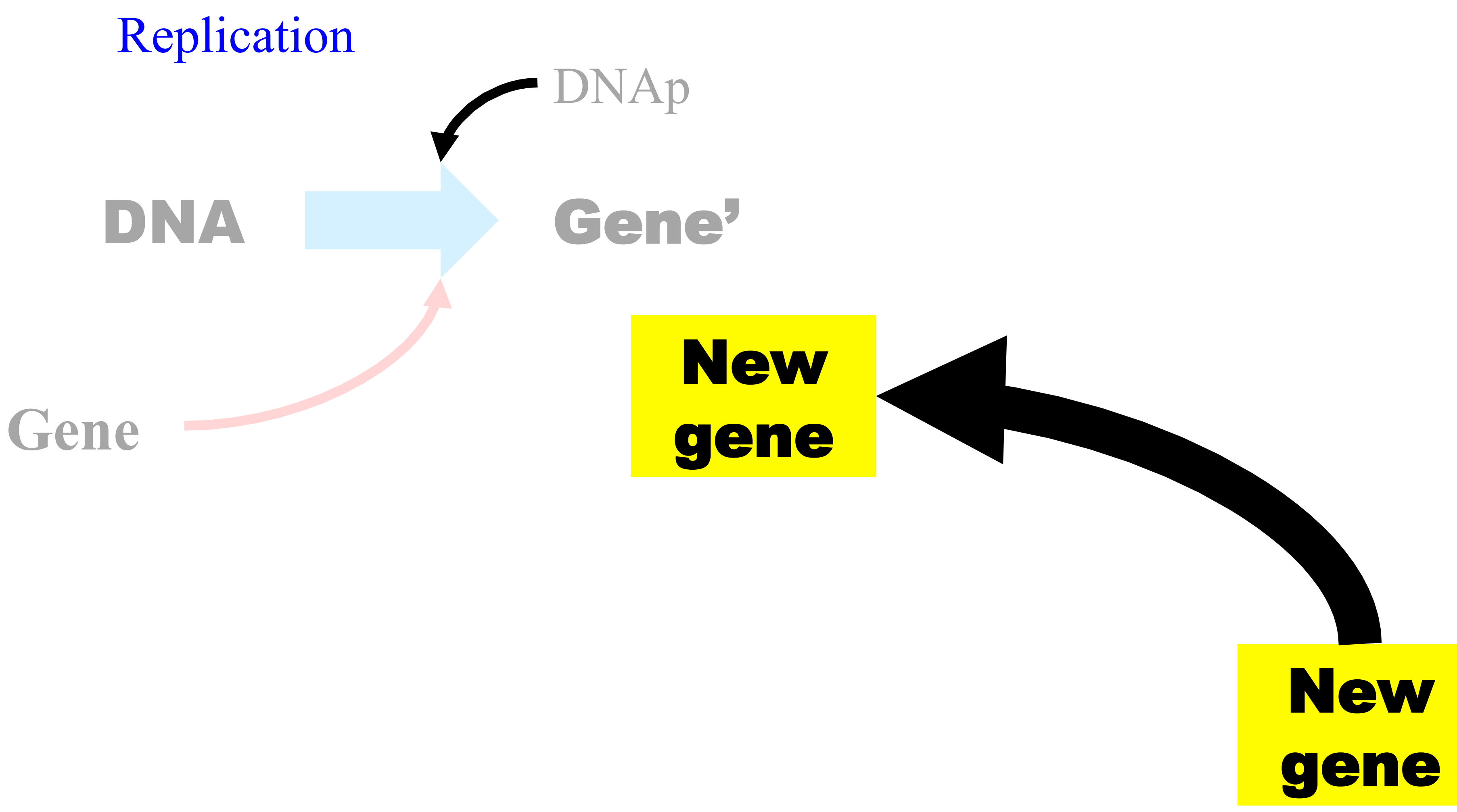
Control 1.0

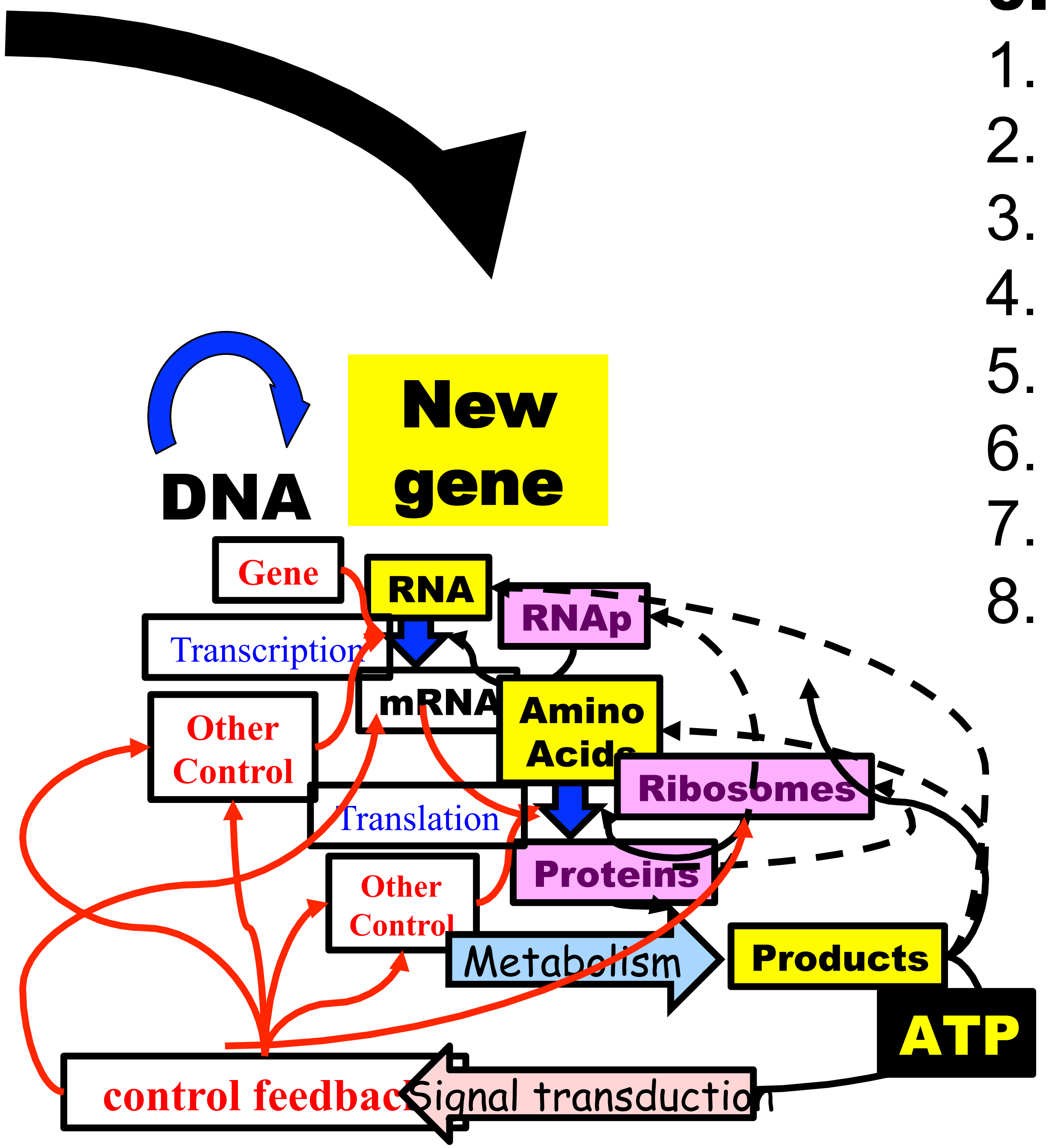
1. DNA repair
2. Mutation
3. DNA replication
4. Transcription
5. Translation
6. Metabolism
7. Signal transduction
8. …

Highly controlled

Think of this as a “protocol stack”

Horizontal gene transfer (HGT)





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

Control 1.0

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

Highly controlled (items 4–8)

Think of this as a "protocol stack"

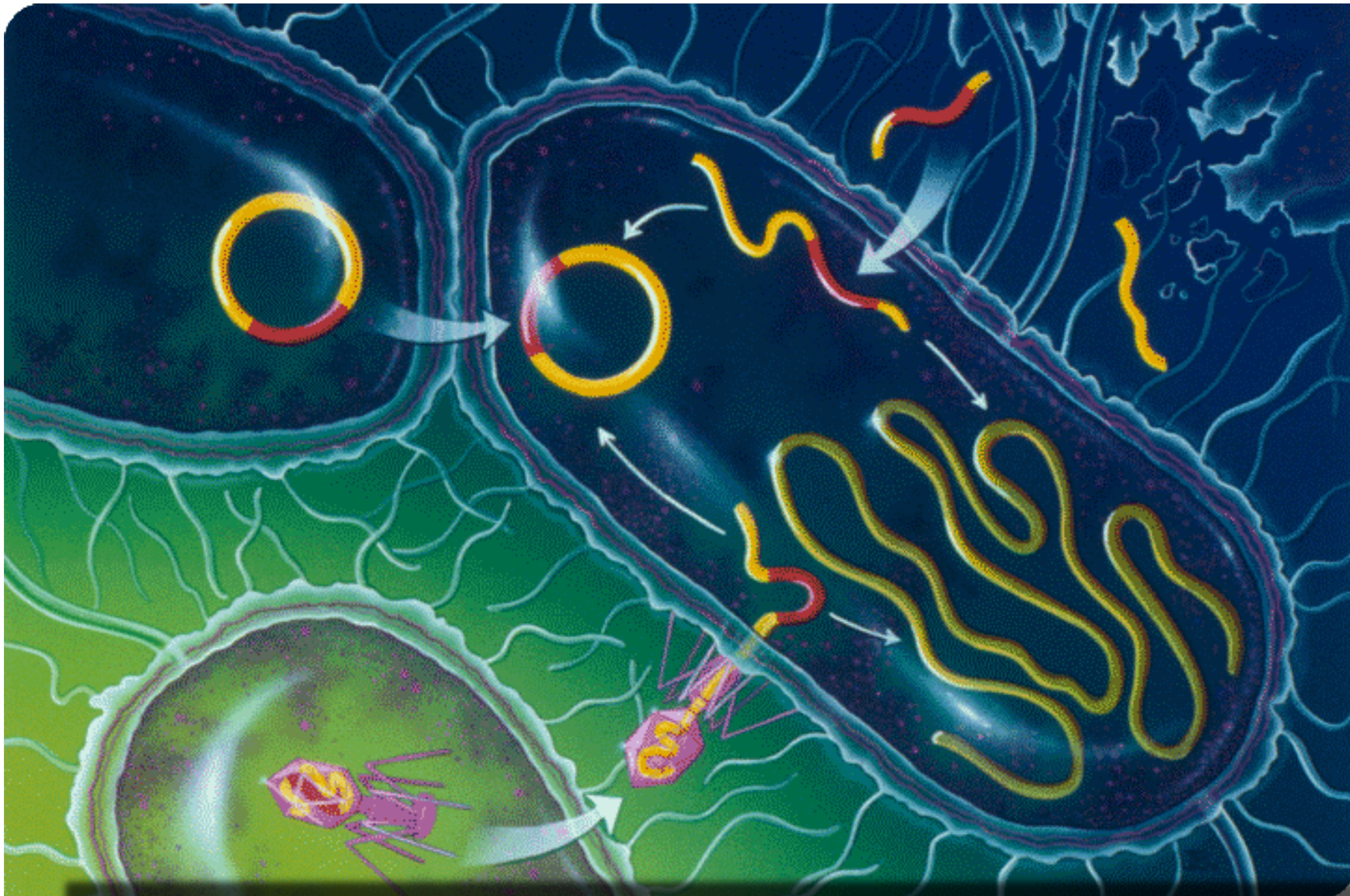
Control 2.0 Evolution ⊂ Adaptation ⊂ Control

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

Items 0–3: Highly controlled (slow)

Items 4–8: Highly controlled (fast)

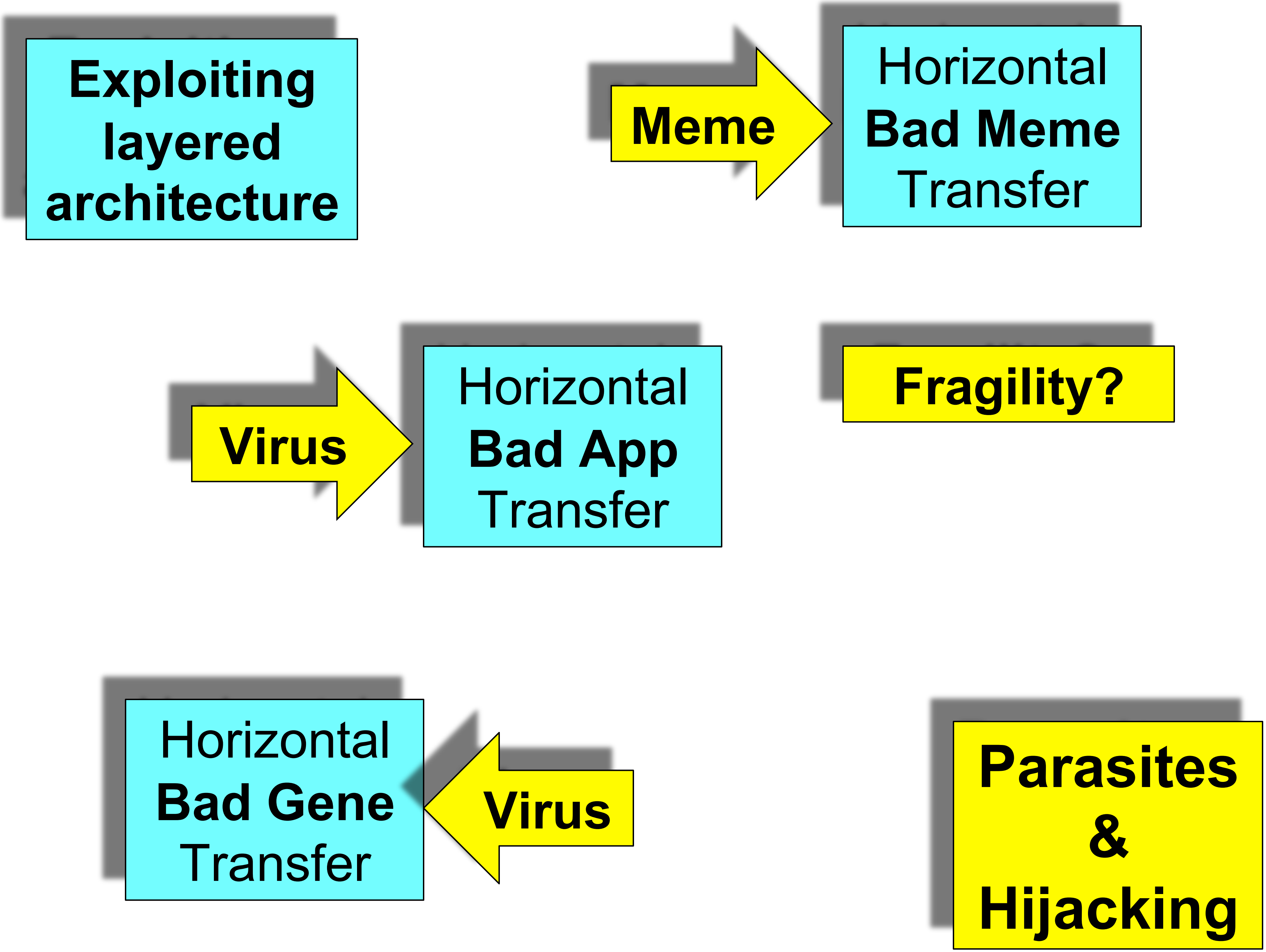
Think of this as a "protocol stack"

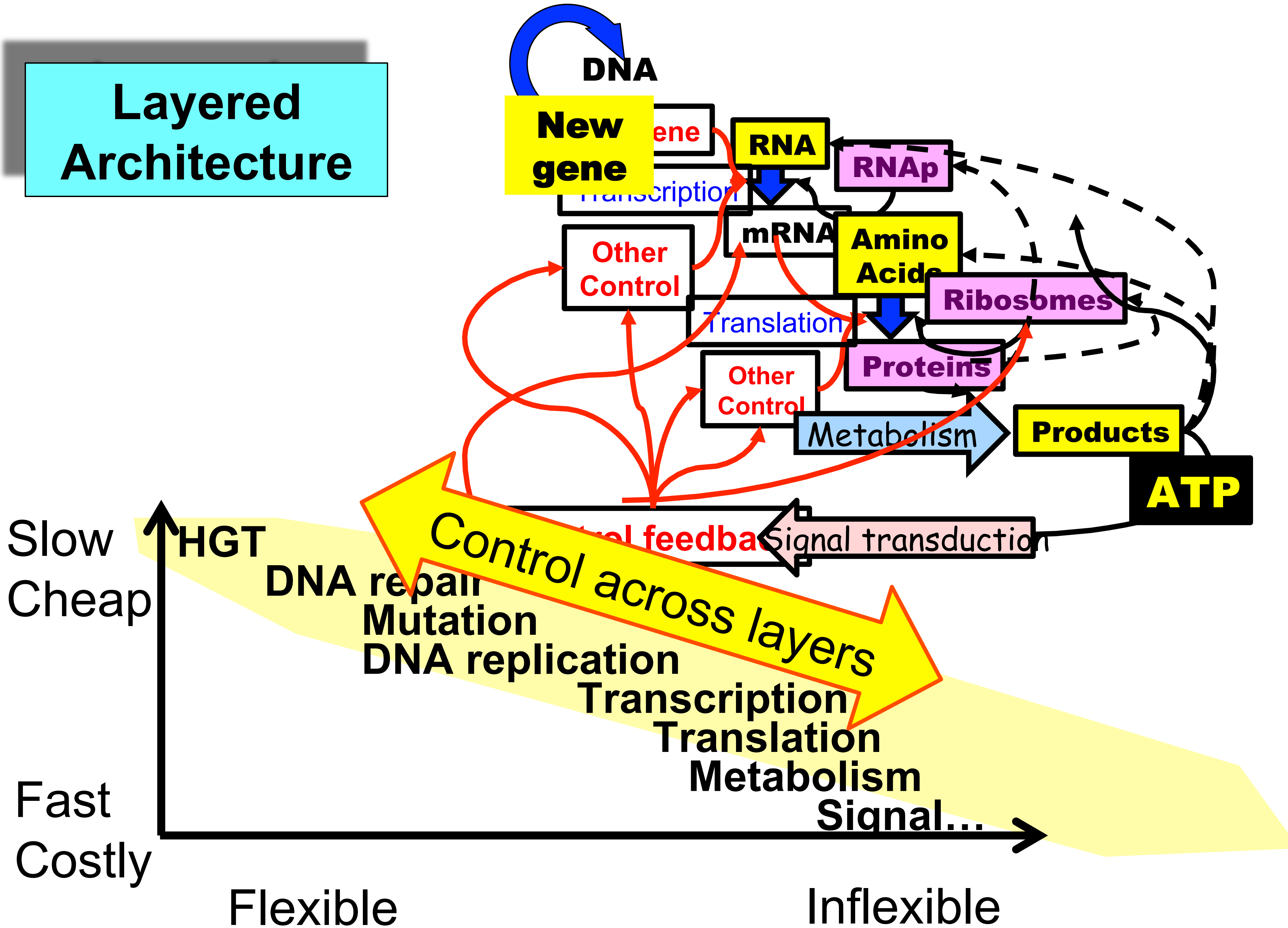


Horizontal Gene Transfer

Sequence ~100 E Coli (*not* chosen randomly)

- ~ 4K genes per cell
- ~20K *different* genes in total (pangenome)
- ~ 1K universally shared genes
- ~ 300 essential (minimal) genes

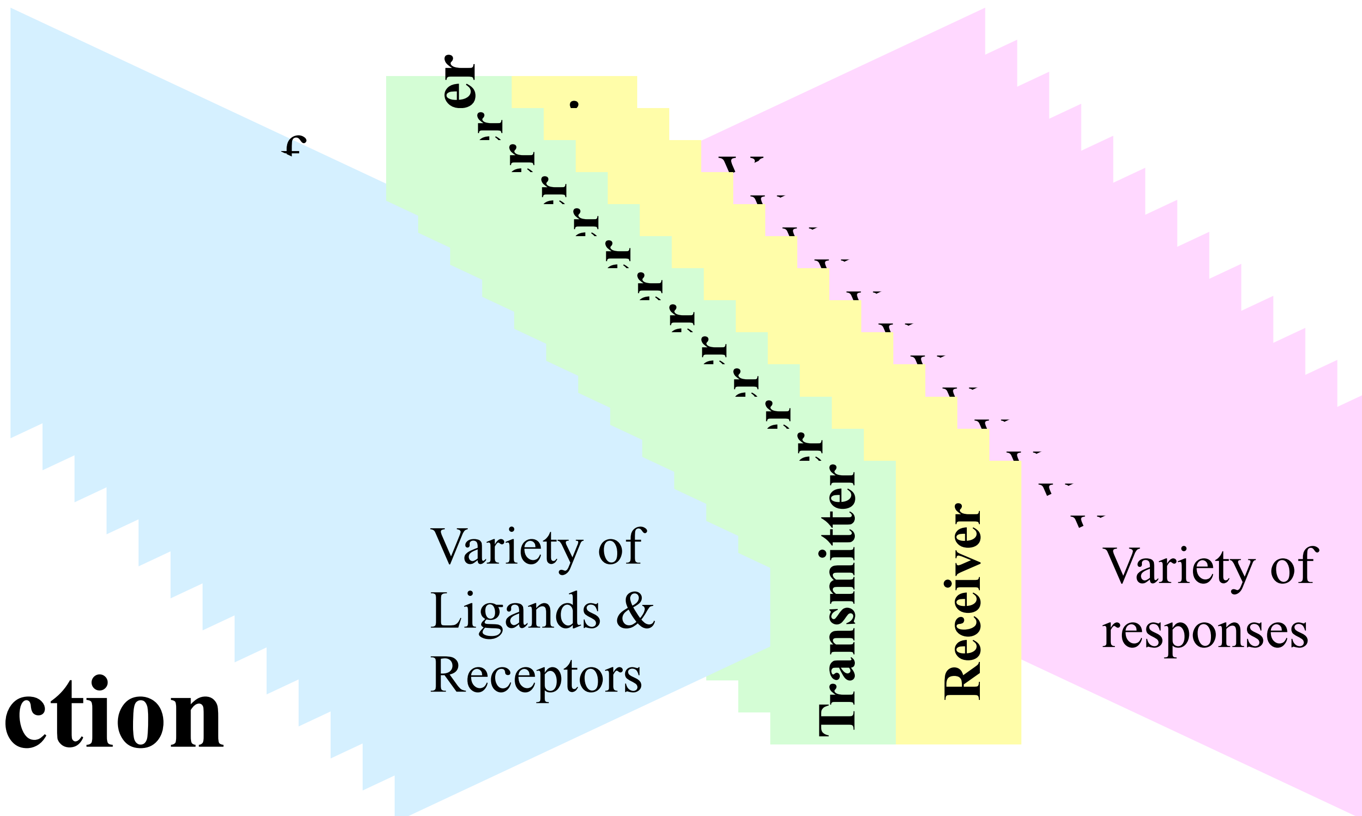

Exploiting layered architecture
Meme
Horizontal Bad Meme Transfer
Virus
Horizontal Bad App Transfer
Fragility?
Horizontal Bad Gene Transfer
Virus
Parasites & Hijacking

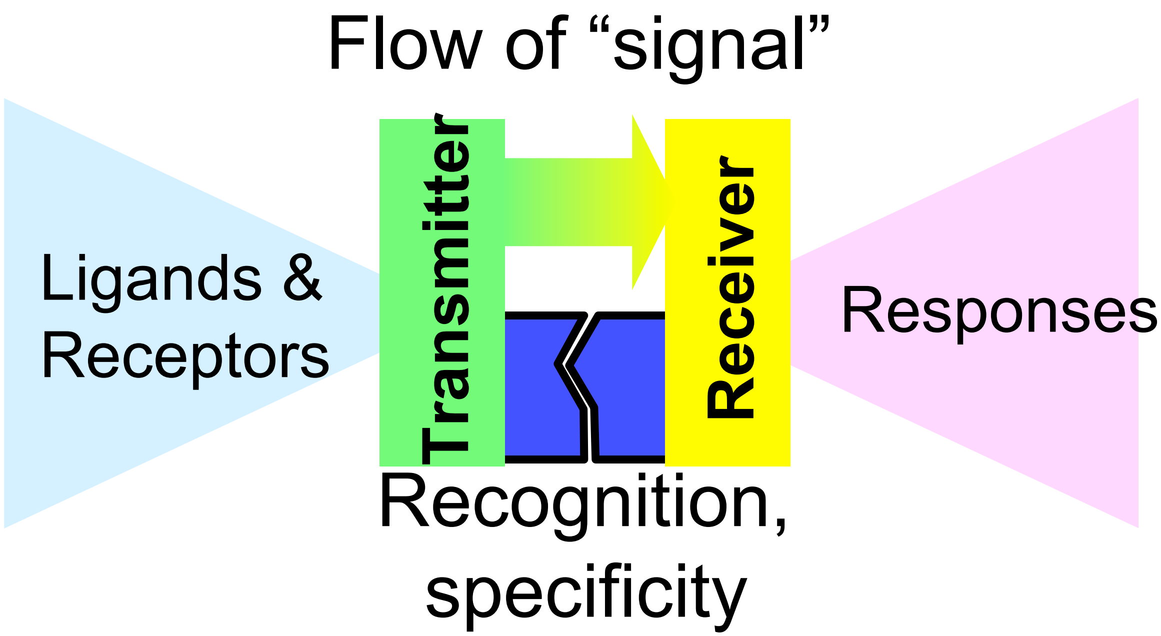


Layered Architecture
DNA
New gene
RNA
RNAp
Transcription
mRNA
Amino Acids
Other Control
Ribosomes
Translation
Other Control
Proteins
Metabolism
Products
ATP
Signal transduction
Control across layers
Slow
Cheap
Fast
Costly
HGT
DNA repair
Mutation
DNA replication
Transcription
Translation
Metabolism
Signal…
Flexible
Inflexible

- ≈50 such "two component" systems in *E. Coli*
- All use the same protocol
  - Histidine autokinase transmitter
  - Aspartyl phospho-acceptor receiver
- Huge variety of receptors and responses
- Also multistage (phosphorelay) versions

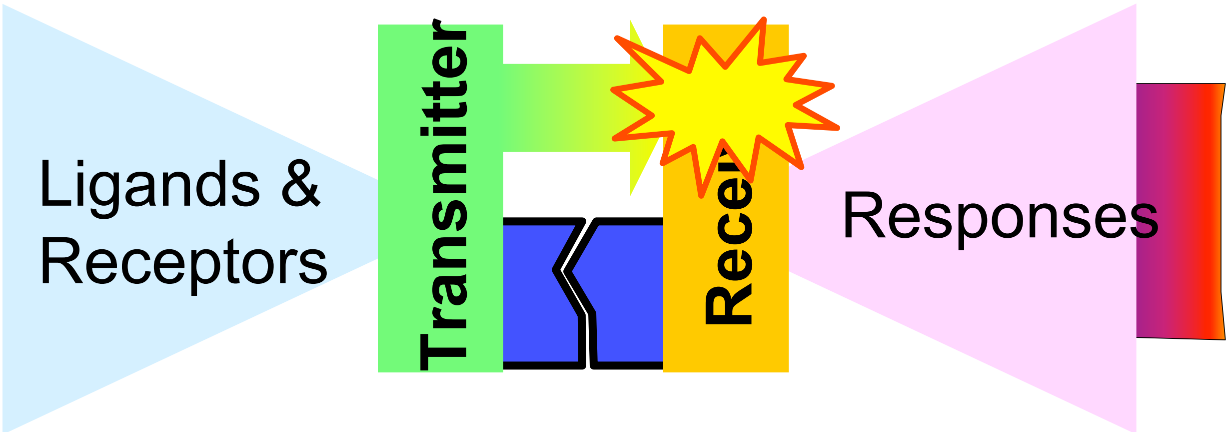
Signal transduction





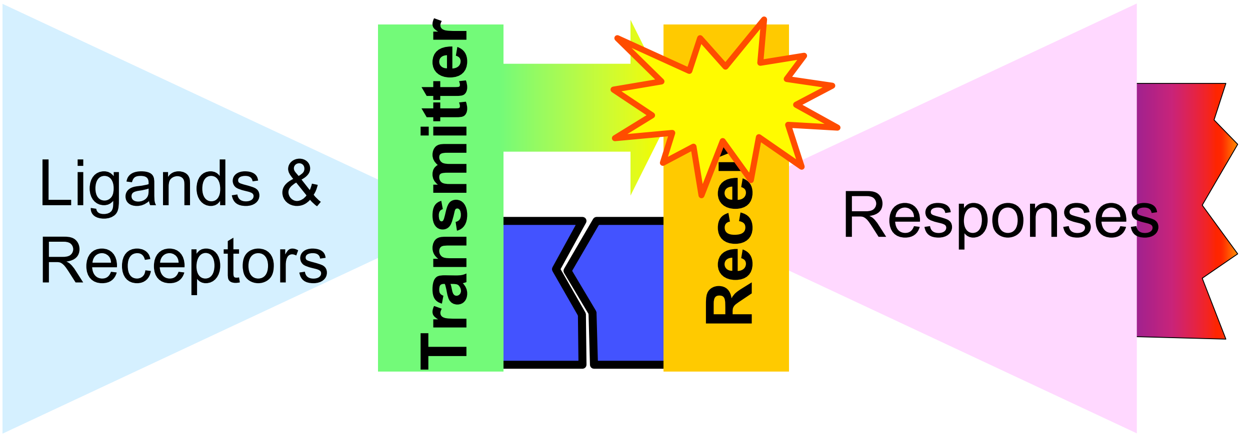
Shared
protocols

• "Name resolution" within signal transduction
• Transmitter must locate "cognate" receiver and avoid non-cognate receivers
• Global search by rapid, local diffusion
• Limited to very small volumes



"Name" recognition
= molecular recognition
= localized functionally
= global spatially

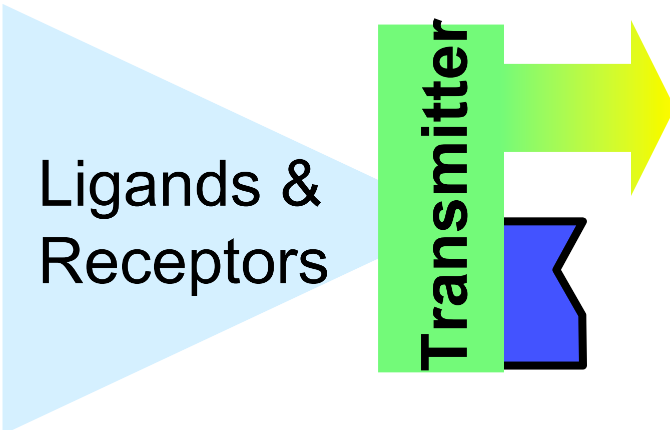
Transcription factors
do "name" to "address"
translation



“Name” recognition
= molecular recognition
= localized functionally

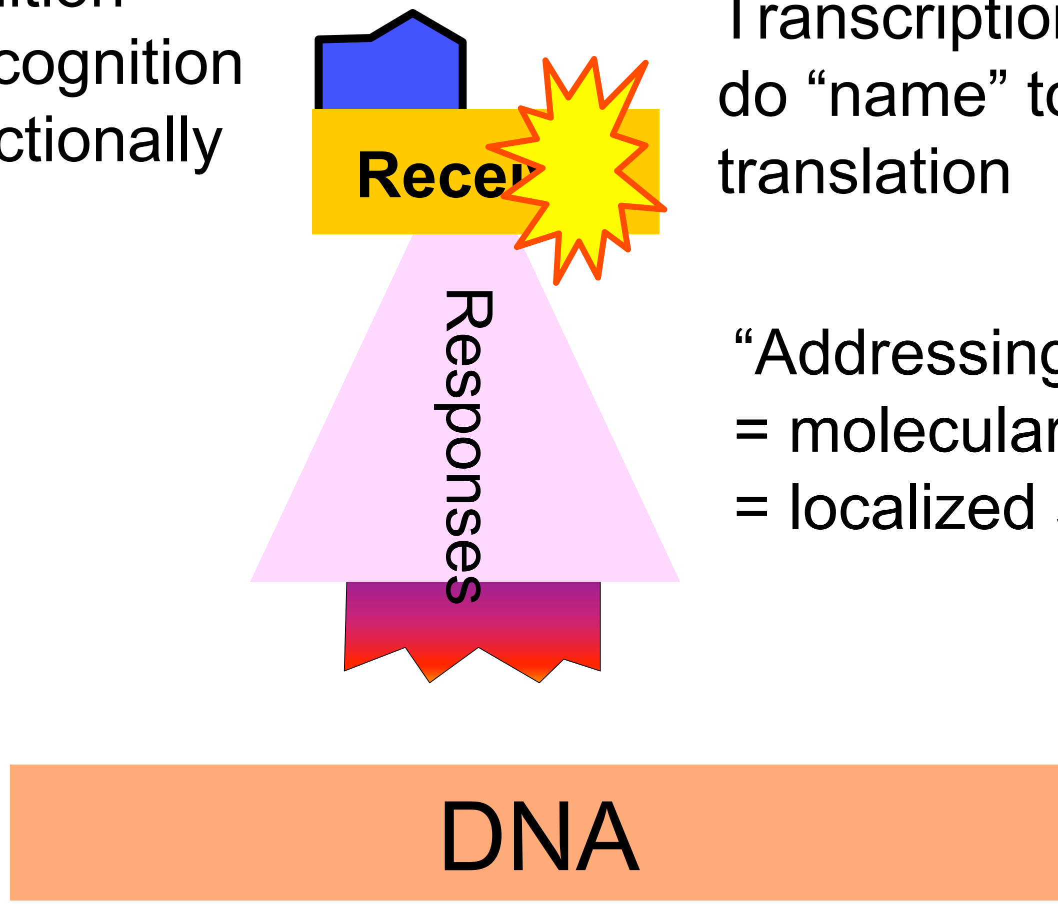
Transcription factors
do “name” to “address”
translation

DNA



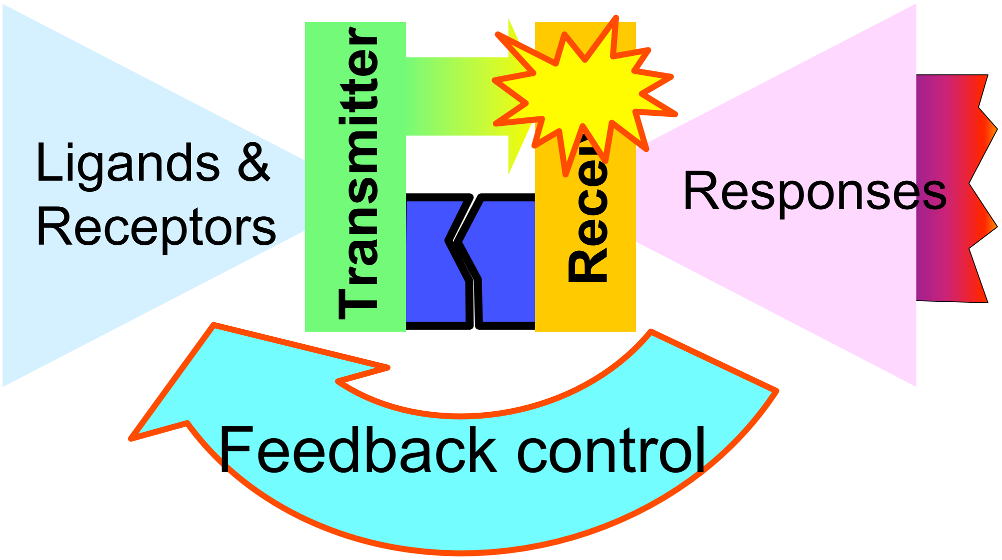
“Name” recognition
= molecular recognition
= localized functionally

Transcription factors do “name” to “address” translation

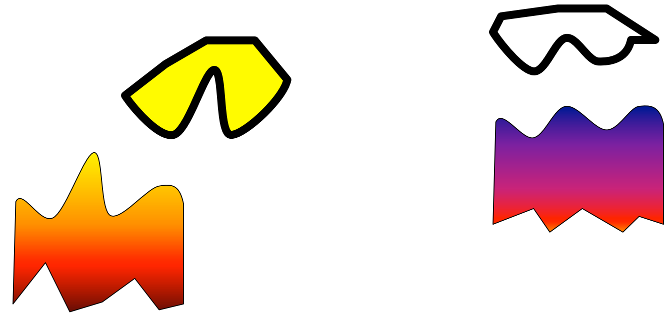


“Addressing”
= molecular recognition
= localized spatially

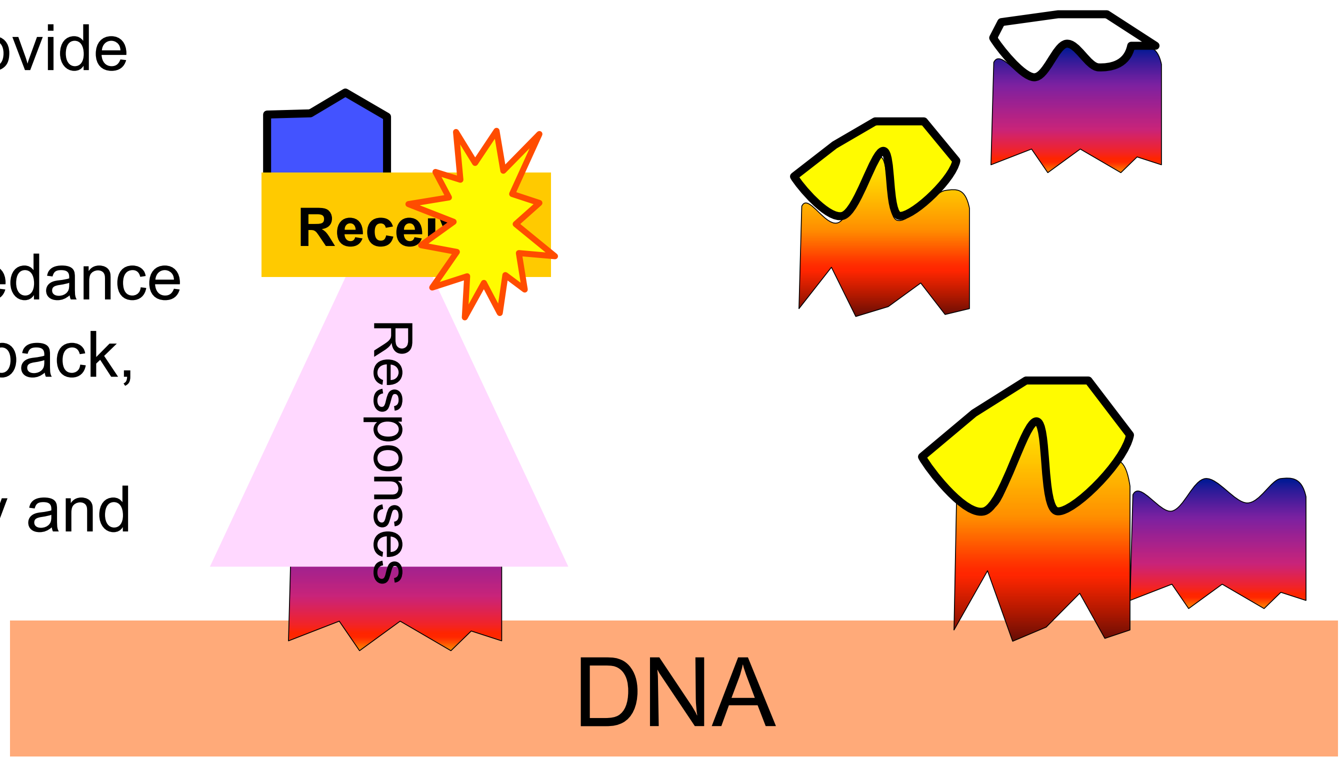
Both are
• Almost digital
• Highly programmable



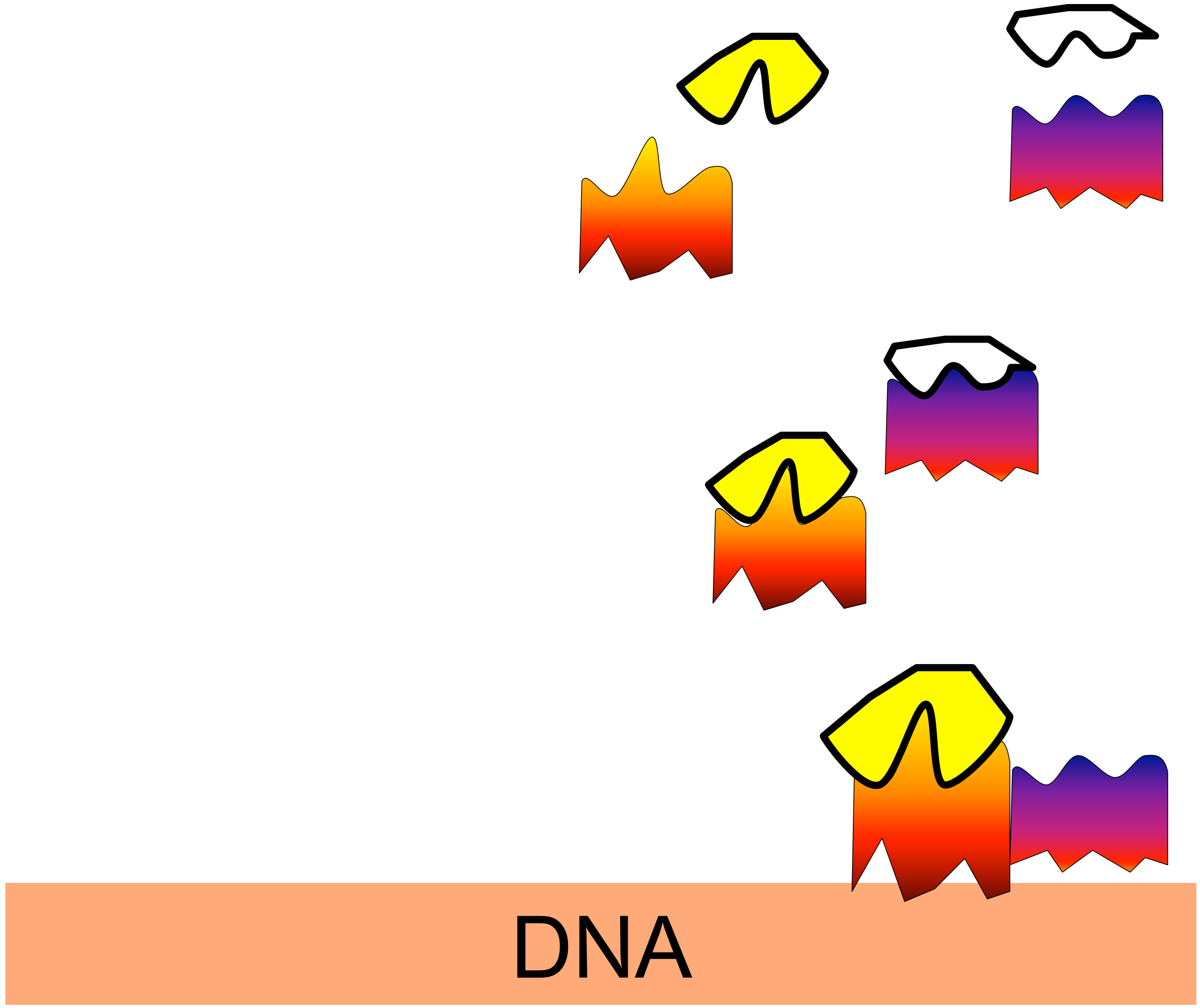
There are simpler transcription factors for sensing internal states



2CST systems provide speed, flexibility, external sensing, computation, impedance match, more feedback, but
greater complexity and overhead



There are simpler transcription factors for sensing internal states

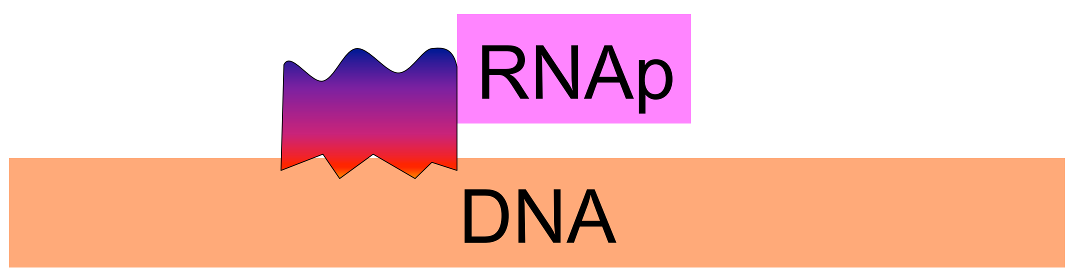


There are simpler transcription factors for sensing internal states

Domains can be evolved independently or coordinated.

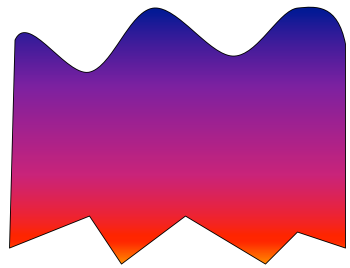
Application layer cannot access DNA directly.

Highly evolvable architecture.



This is like a "name to address" translation.

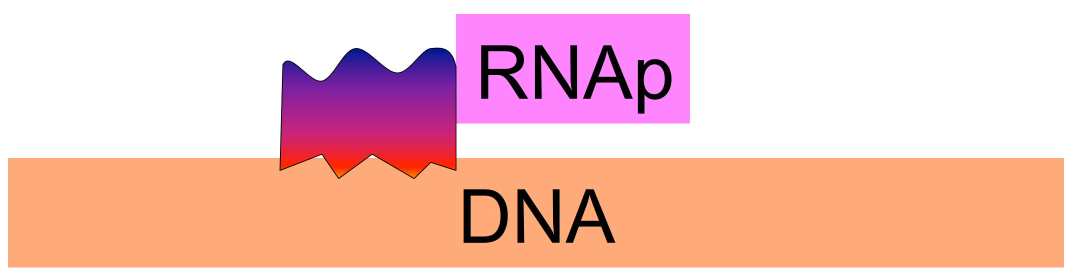
Sensor domains

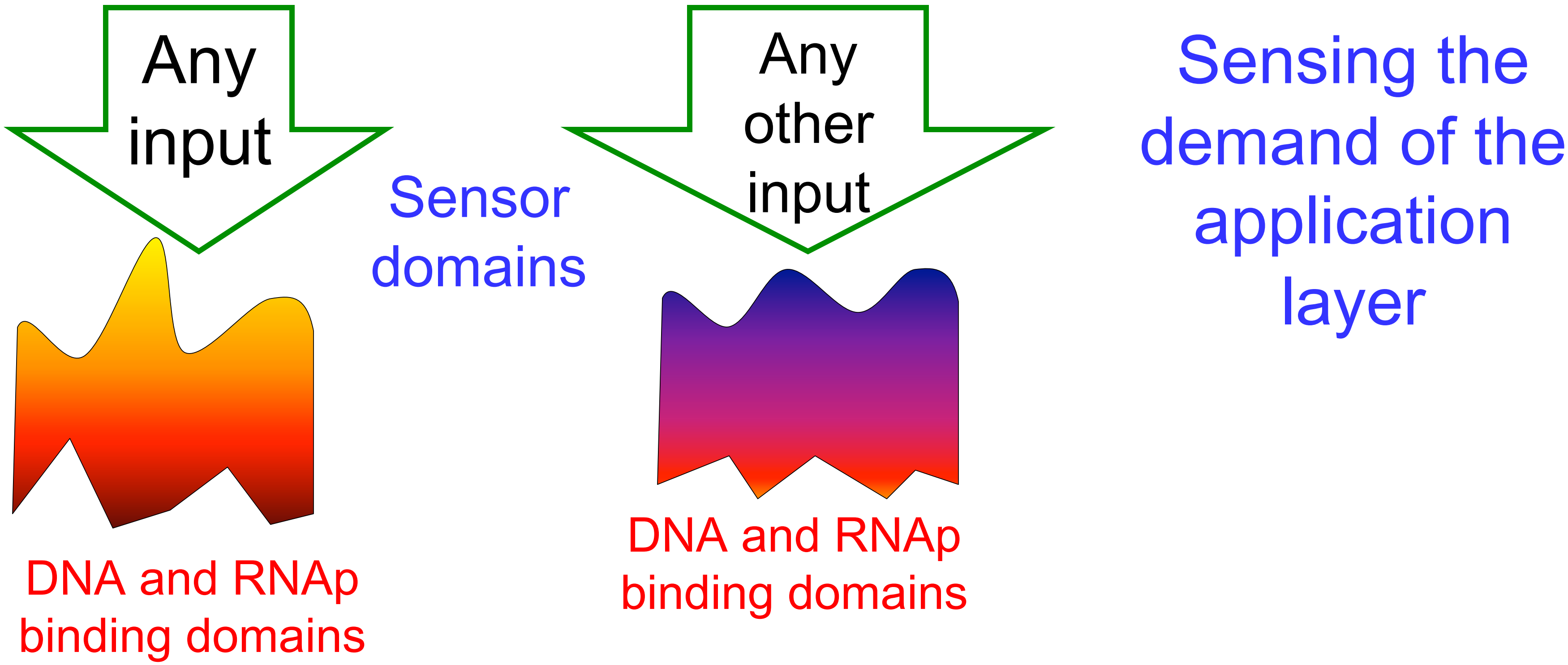


DNA and RNAp binding domains

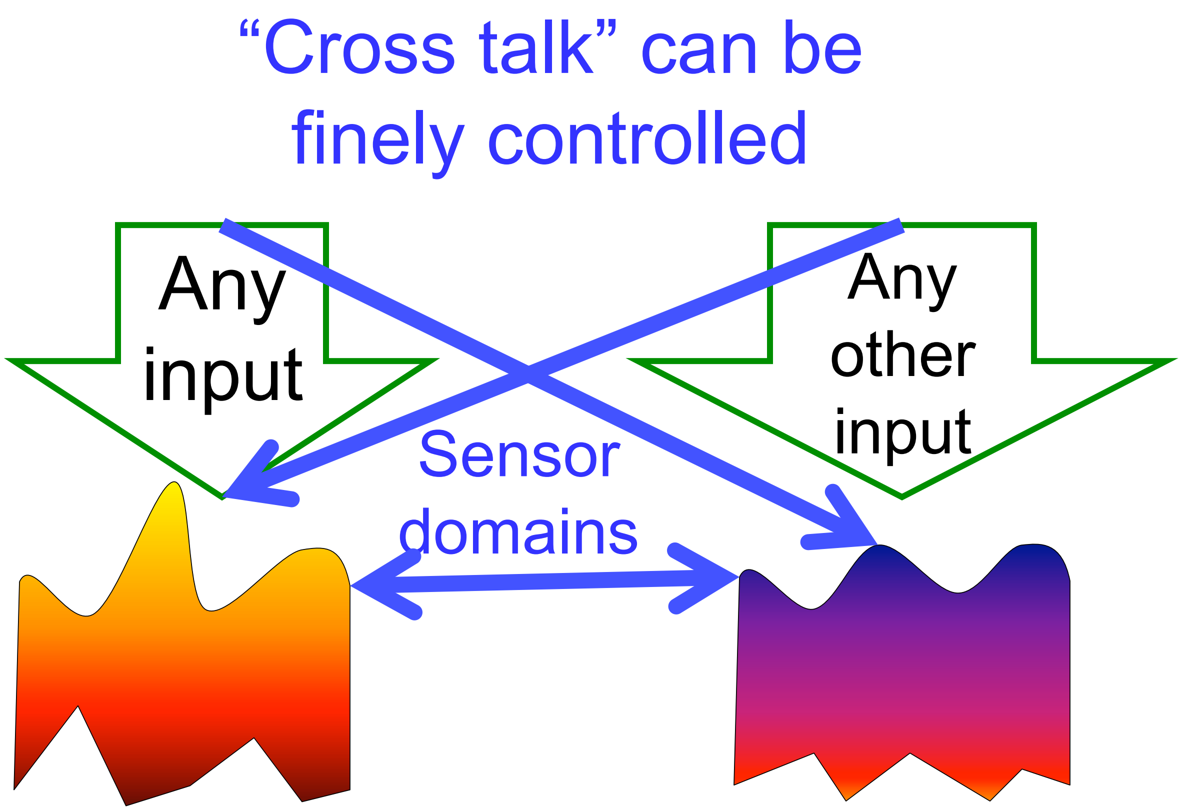
Sensing the demand of the application layer

Initiating the change in supply



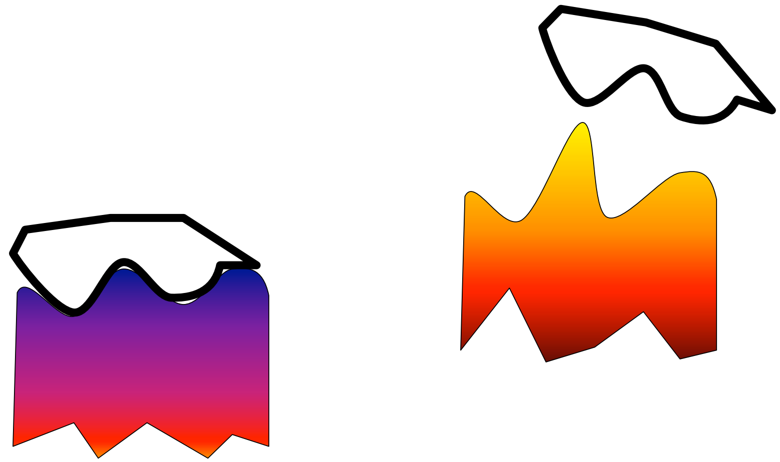


- Sensor sides attach to metabolites or other proteins
- This causes an allosteric (shape) change
- (Sensing is largely analog (# of bound proteins))
- Effecting the DNA/RNAp binding domains
- Protein and DNA/RNAp recognition is more digital
- Extensively discussed in both Ptashne and Alon

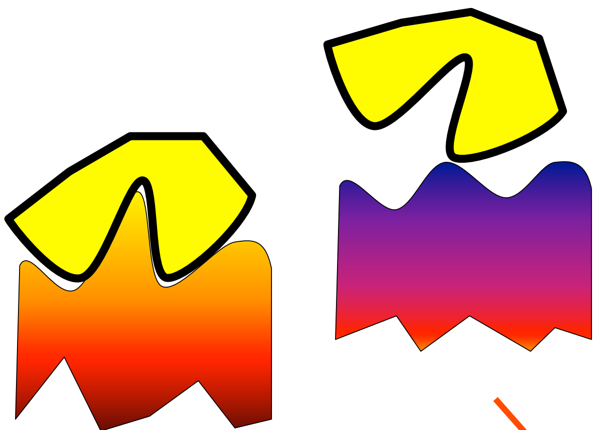


- Application layer signals can be integrated or not
- Huge combinatorial space of (mis)matching shapes
- A functionally meaningful "name space"
- Highly adaptable architecture
- Interactions are fast (but expensive)
- Return to this issue in "signal transduction"

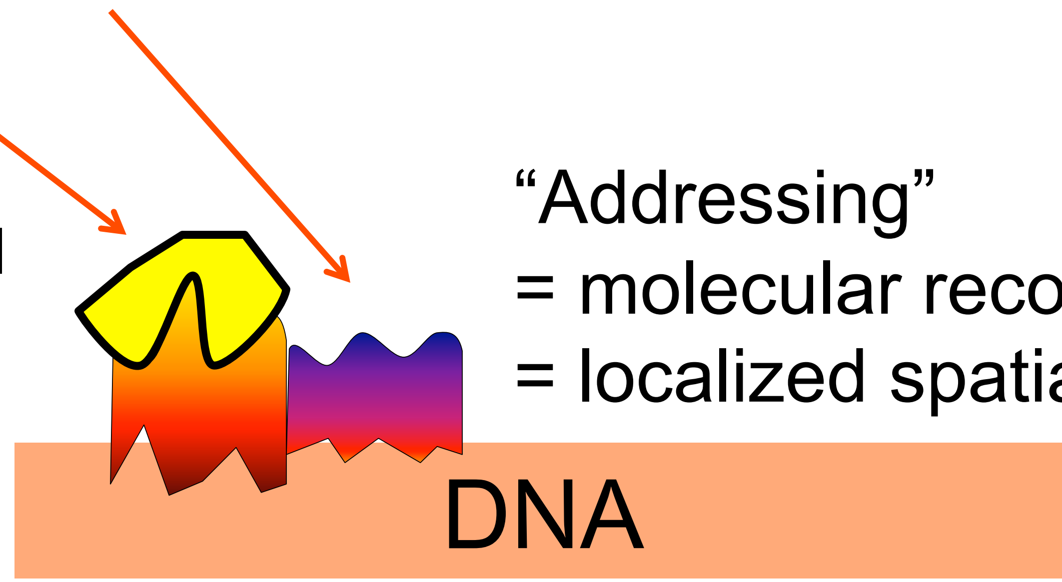
“Name” recognition
= molecular recognition
= localized functionally
= global spatially



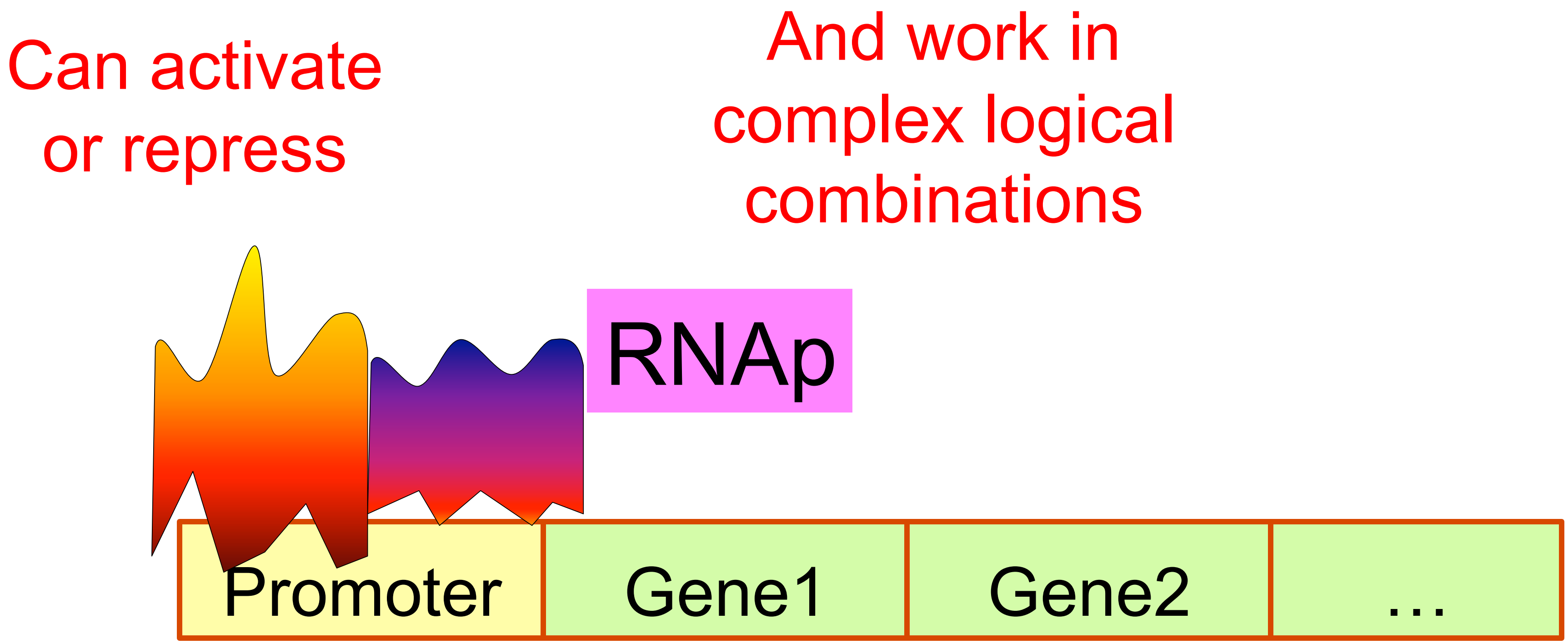
Transcription factors do “name” to “address” translation



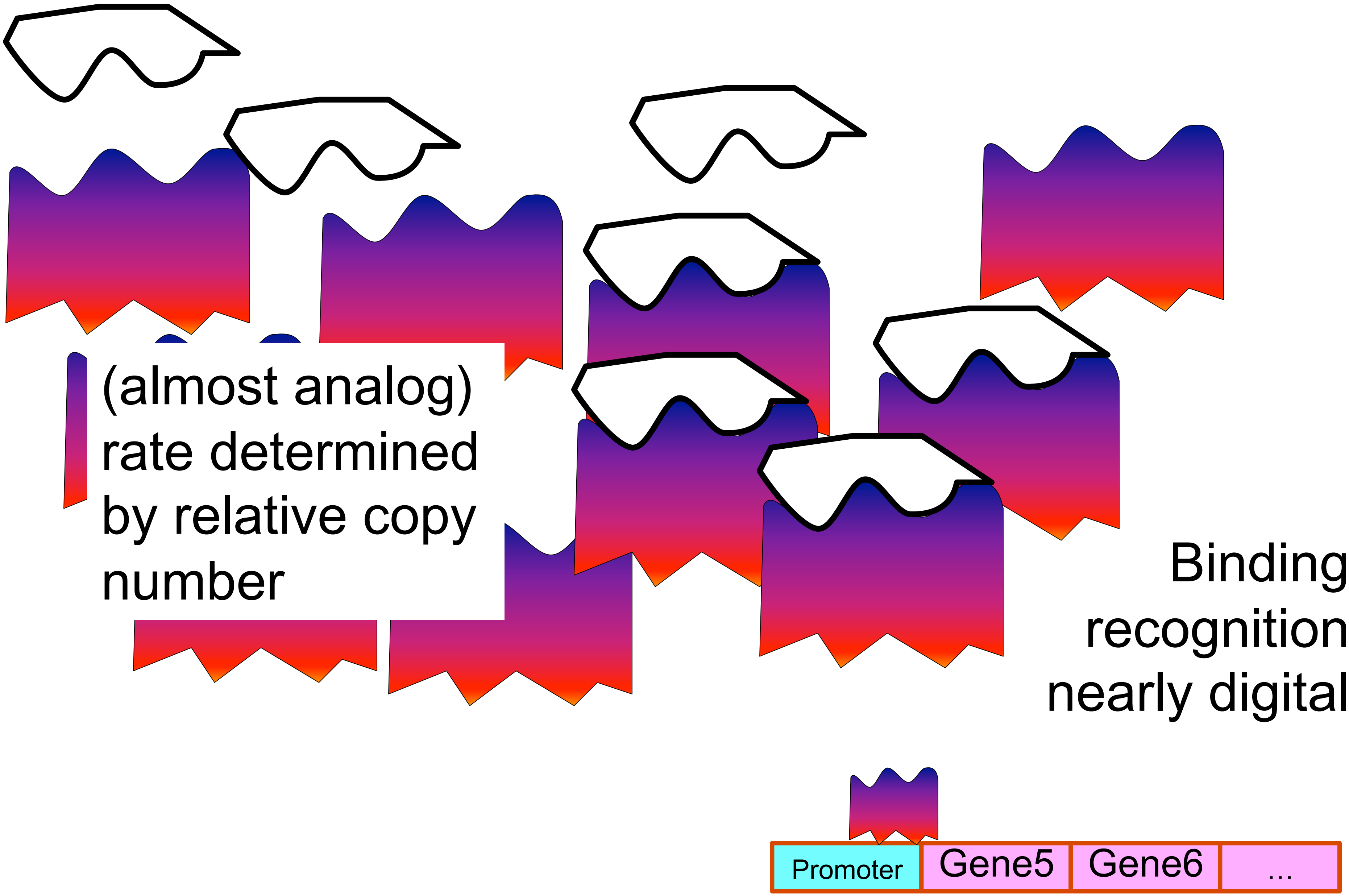
Both are
- Almost digital
- Highly programmable

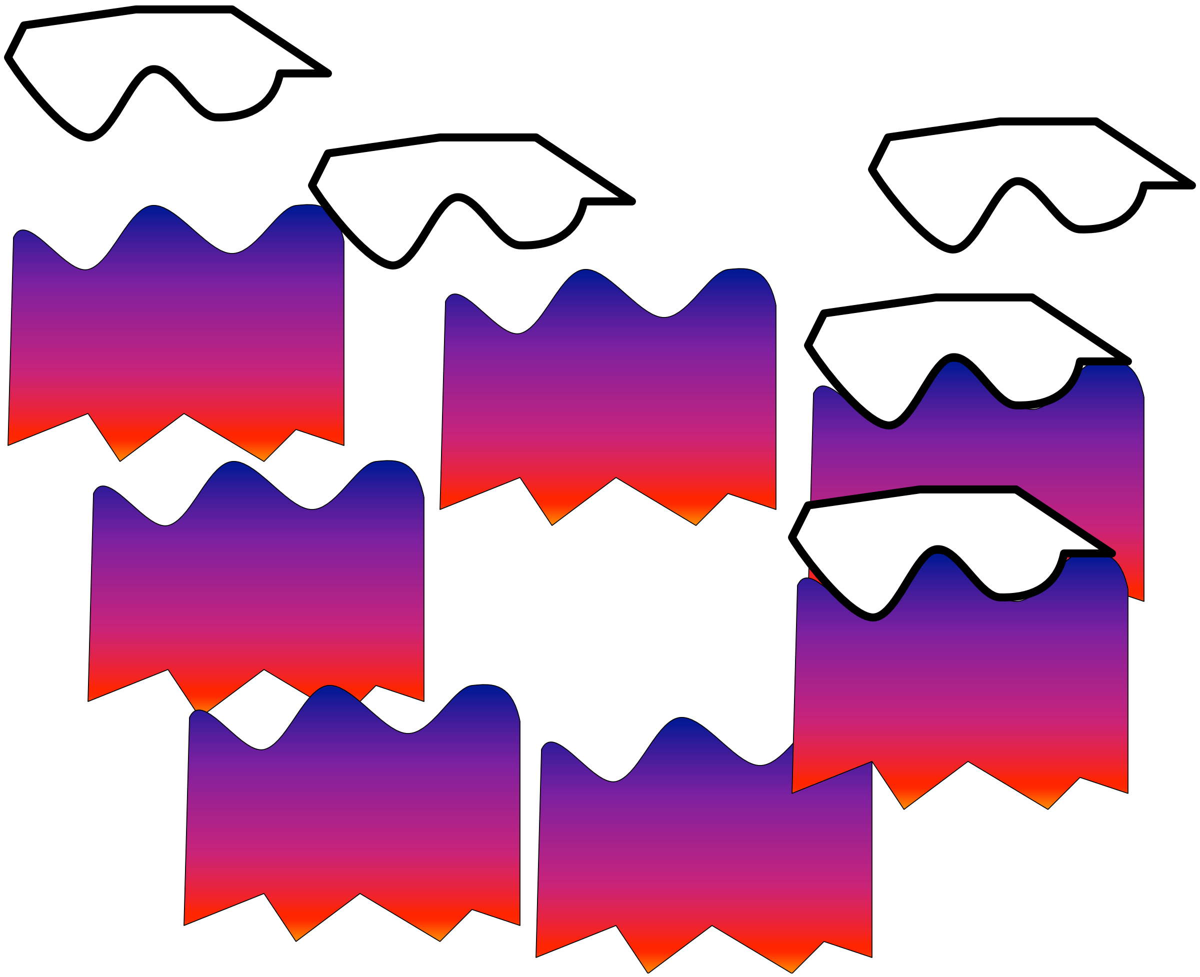


“Addressing”
= molecular recognition
= localized spatially



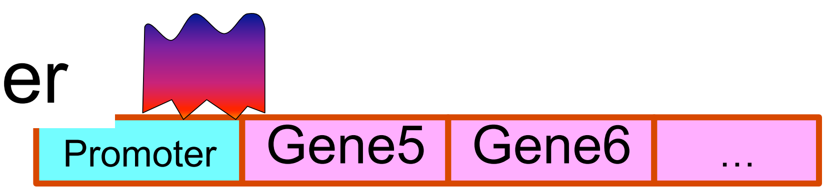
- Both protein and DNA sides have sequence/shape
- Huge combinatorial space of “addresses”
- Modest amount of “logic” can be done at promoter
- Transcription is very noise (but efficient)
- Extremely adaptable architecture

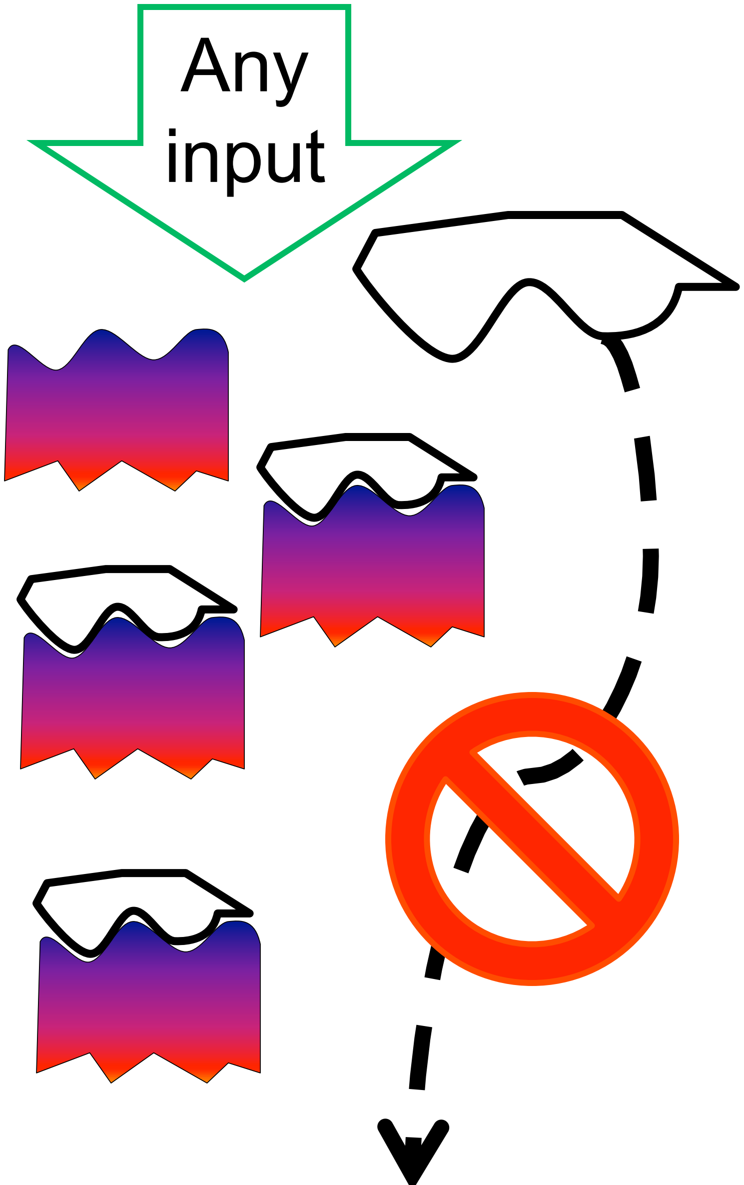

(almost analog) rate determined by relative copy number
Binding recognition nearly digital
Promoter
Gene5
Gene6
...



Recall: can work by pulse code modulation so for small copy number does digital to analog conversion

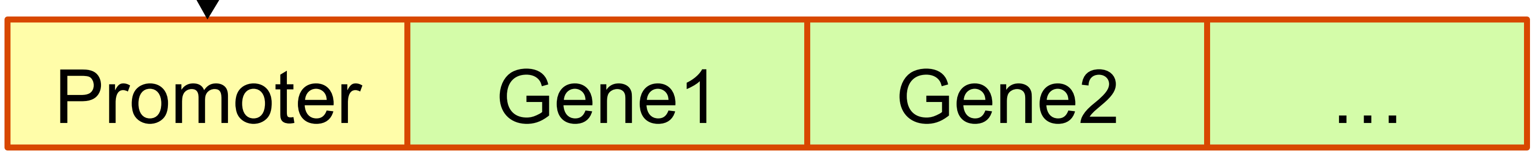
rate (almost analog) determined by copy number

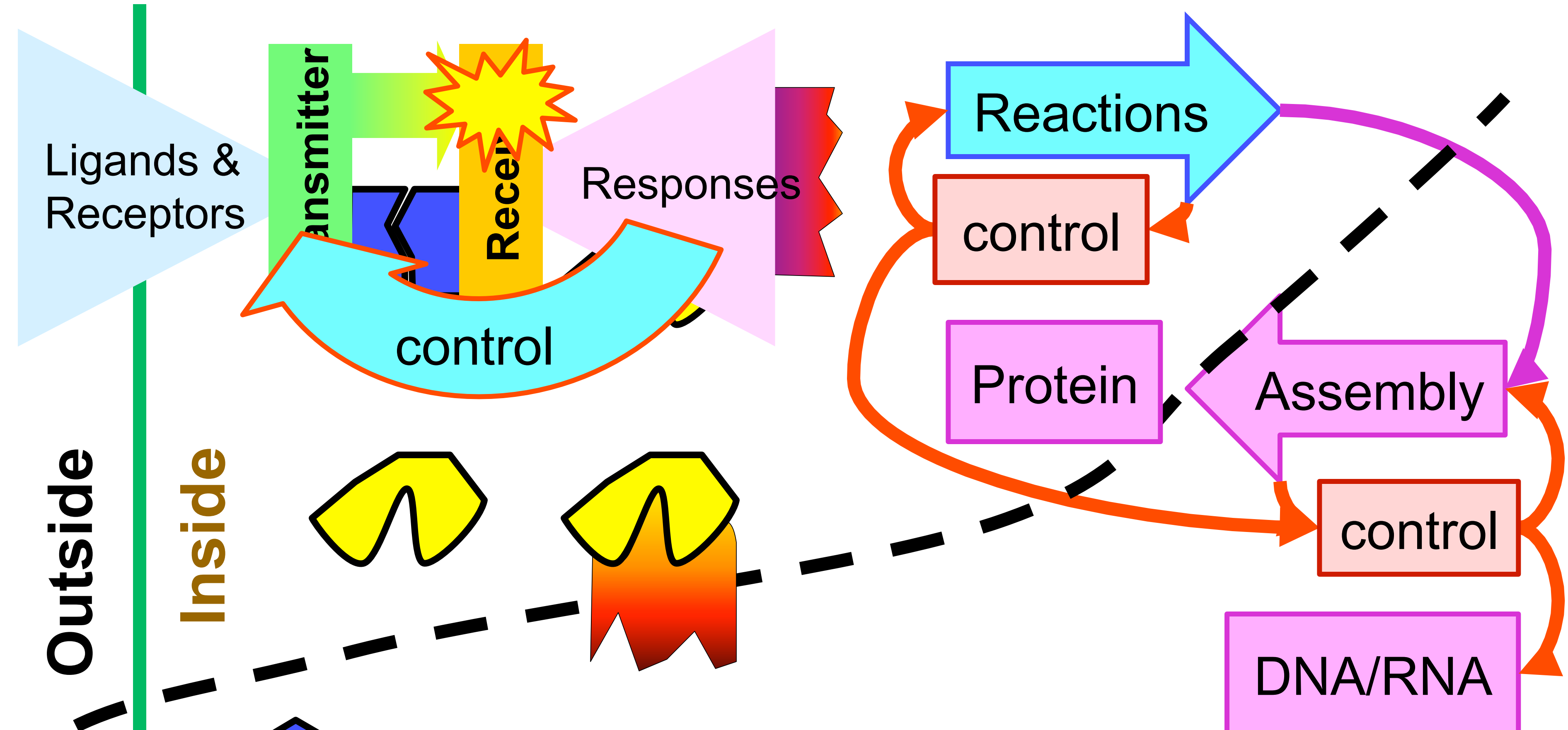




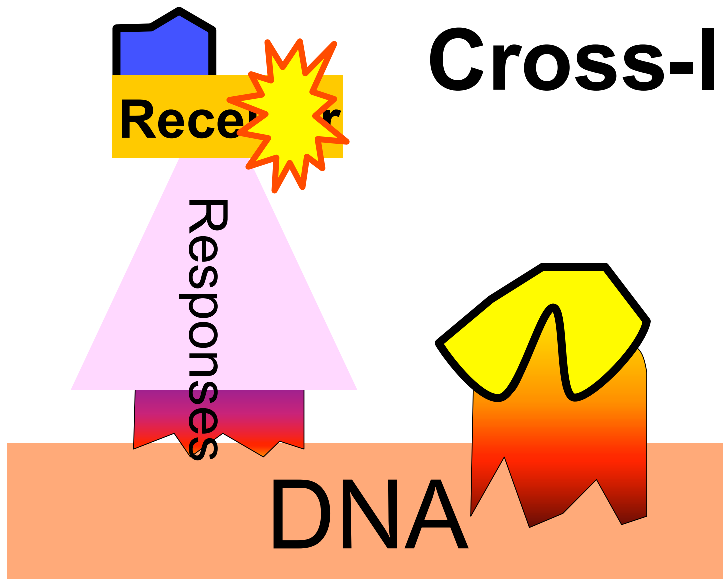
No crossing layers

- Highly structured interactions
- Transcription factor proteins control all cross-layer interactions
- DNA layer details hidden from application layer
- Robust ***and*** evolvable
- Functional (and global) demand mapped logically to local supply chain processes





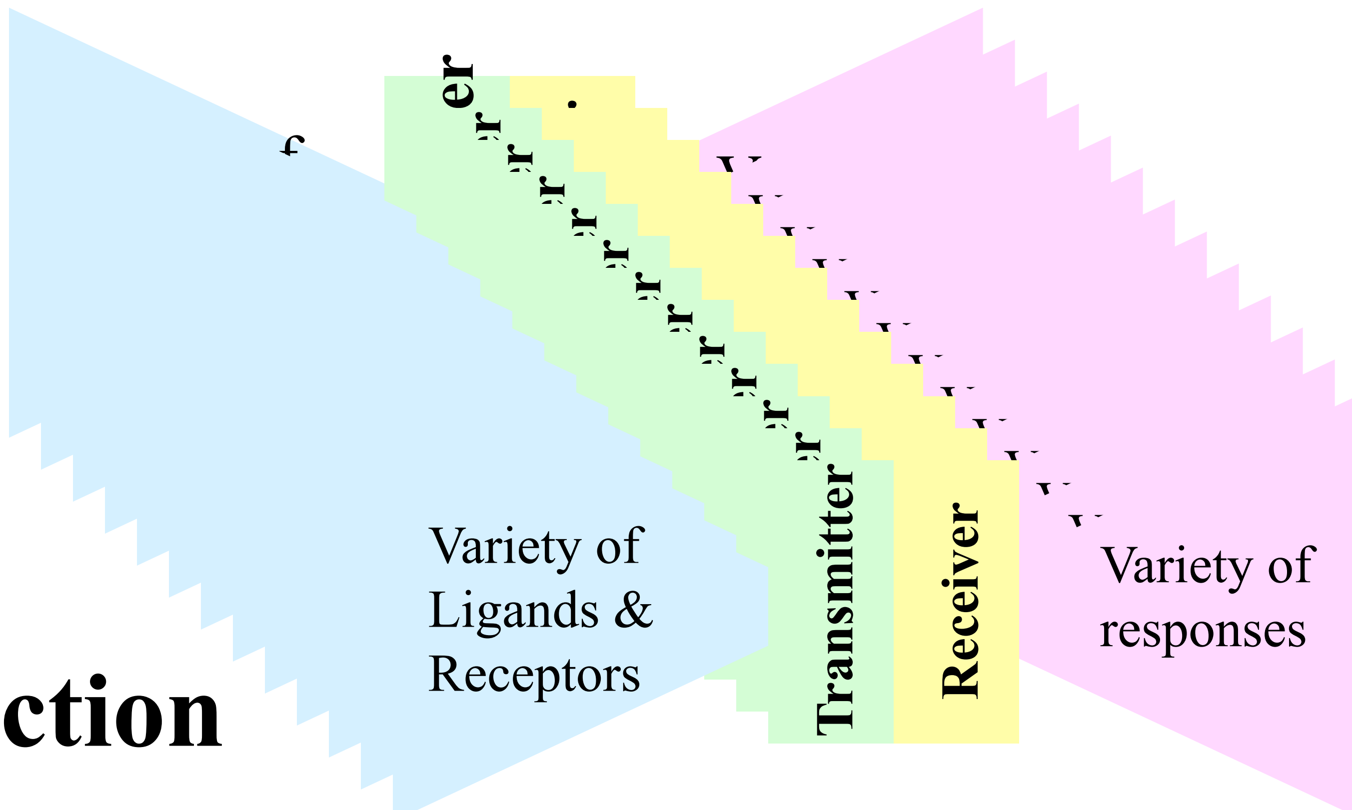
Cross-layer control



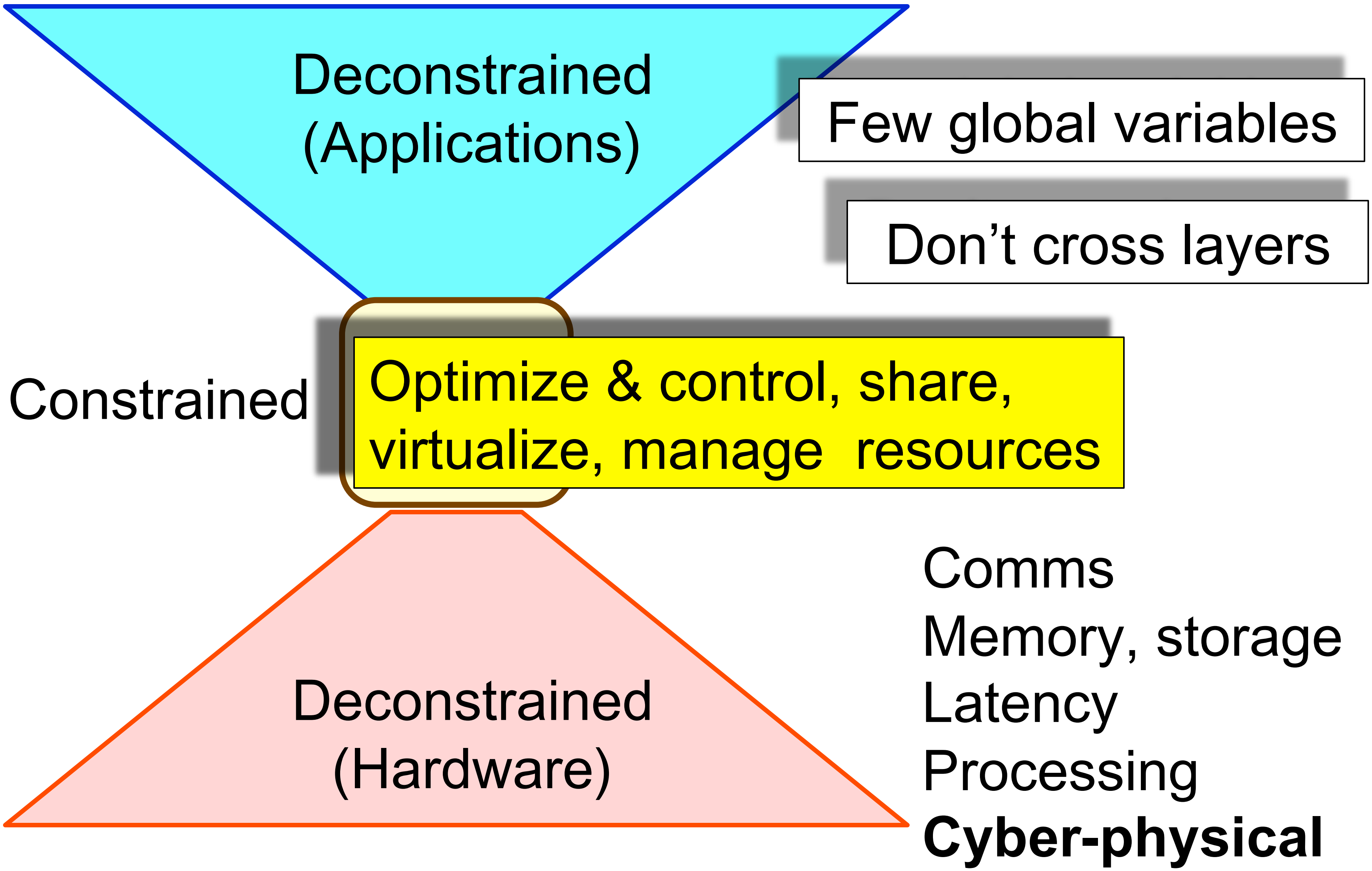
- Highly organized
- Naming and addressing
- Prices? Duality?
- Minimal case study?

- ≈50 such “two component” systems in *E. Coli*
- All use the same protocol
  - Histidine autokinase transmitter
  - Aspartyl phospho-acceptor receiver
- Huge variety of receptors and responses
- Also multistage (phosphorelay) versions

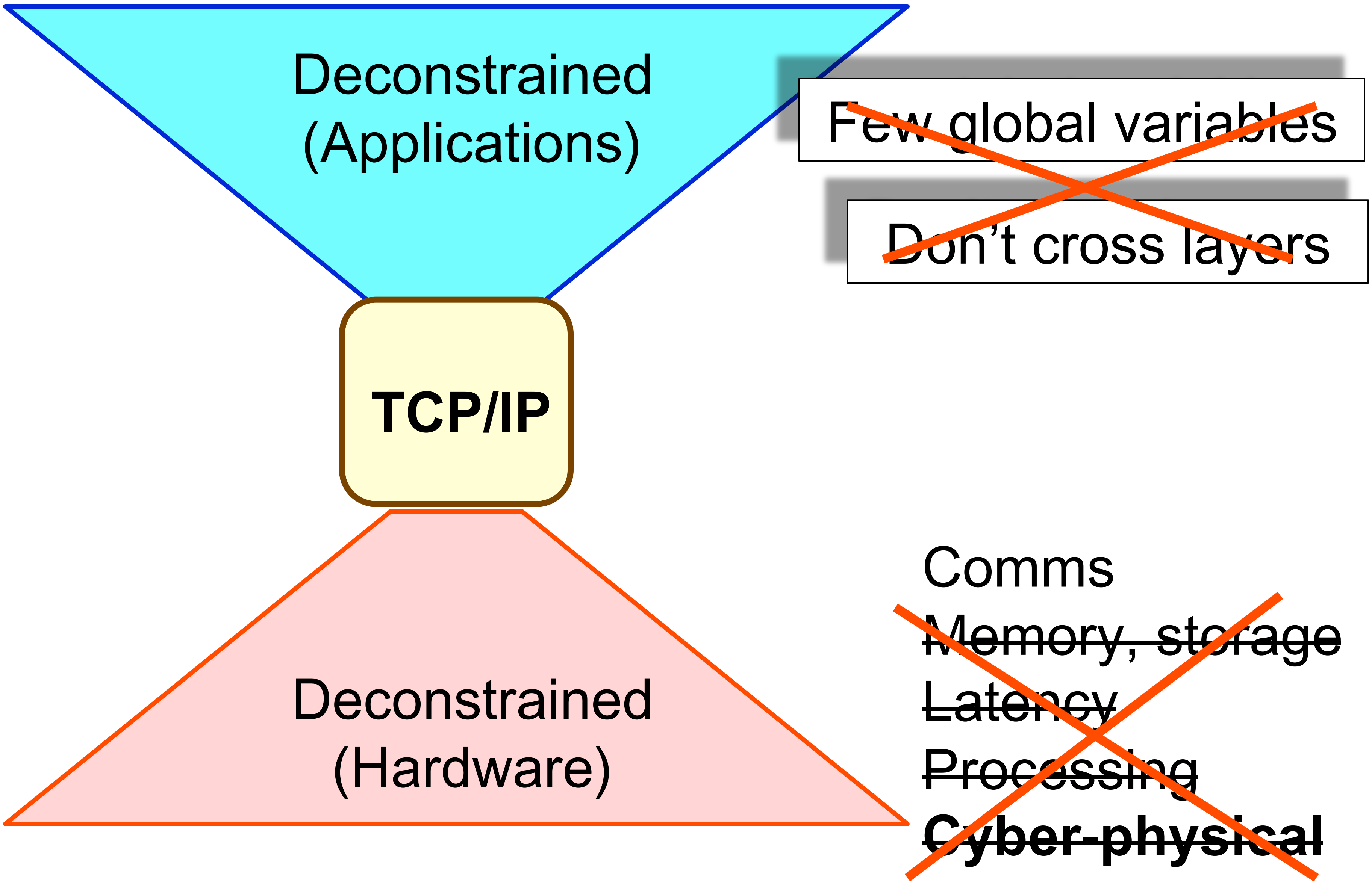
Signal transduction

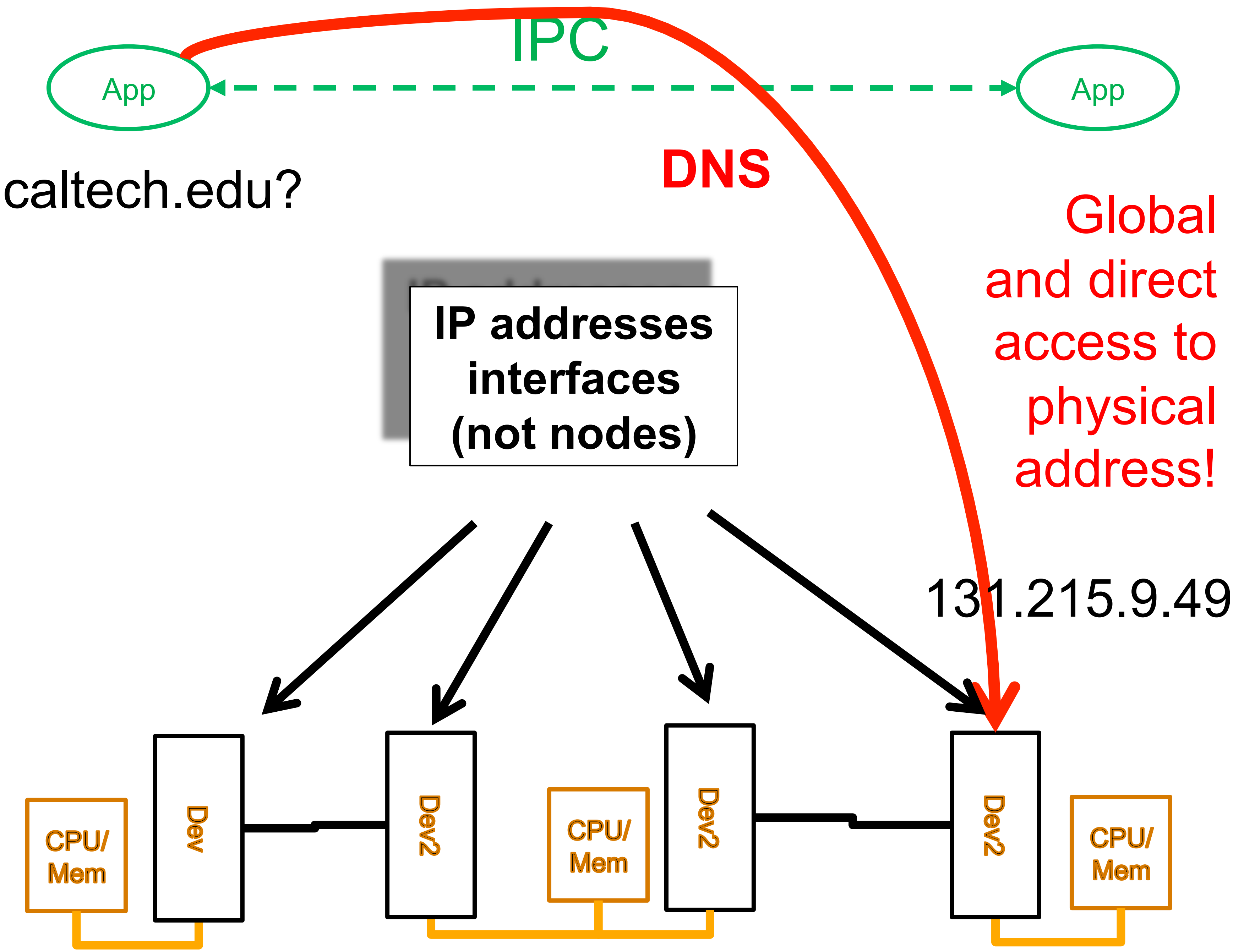


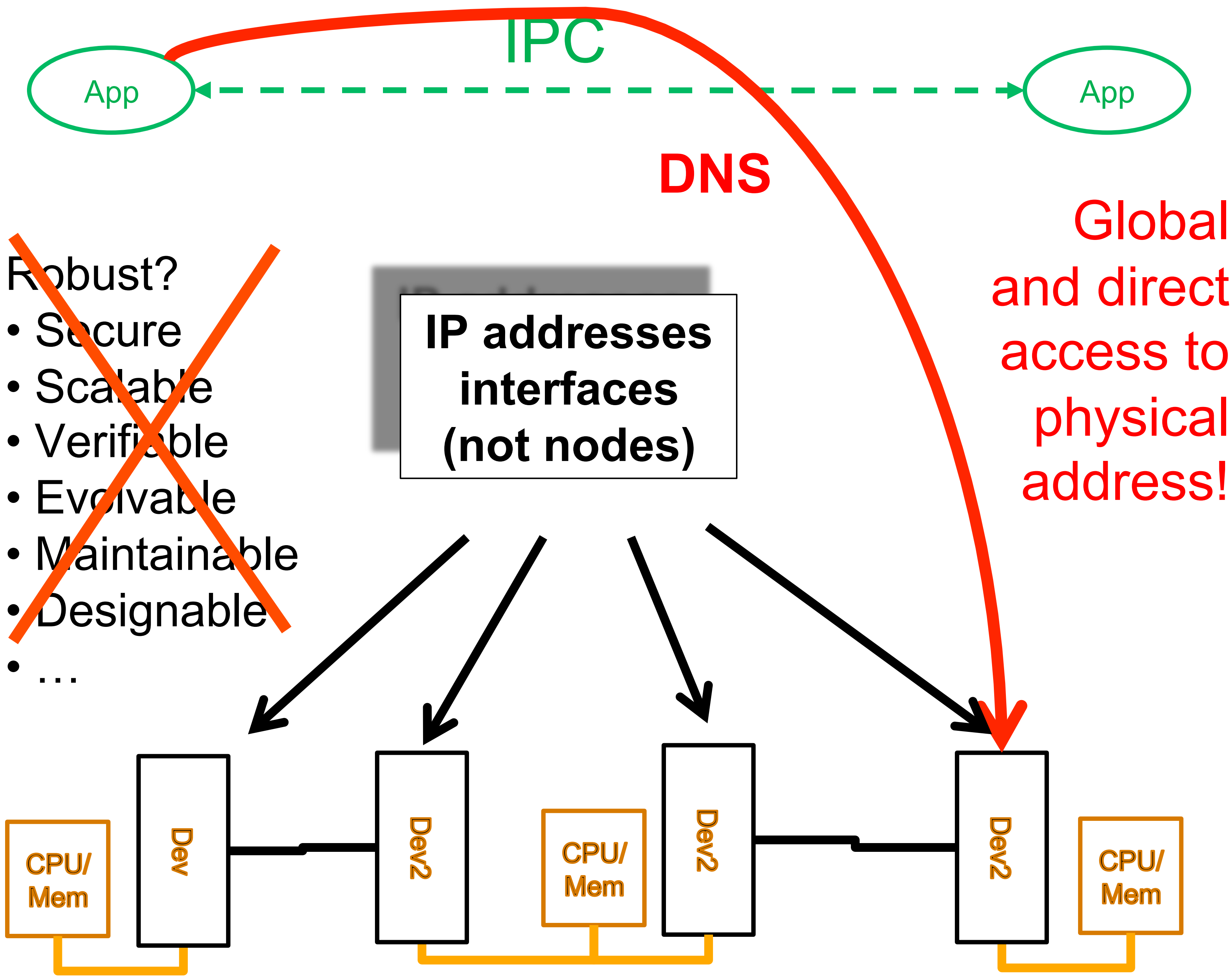
Next layered architectures (SDN)



TCP/IP architecture?

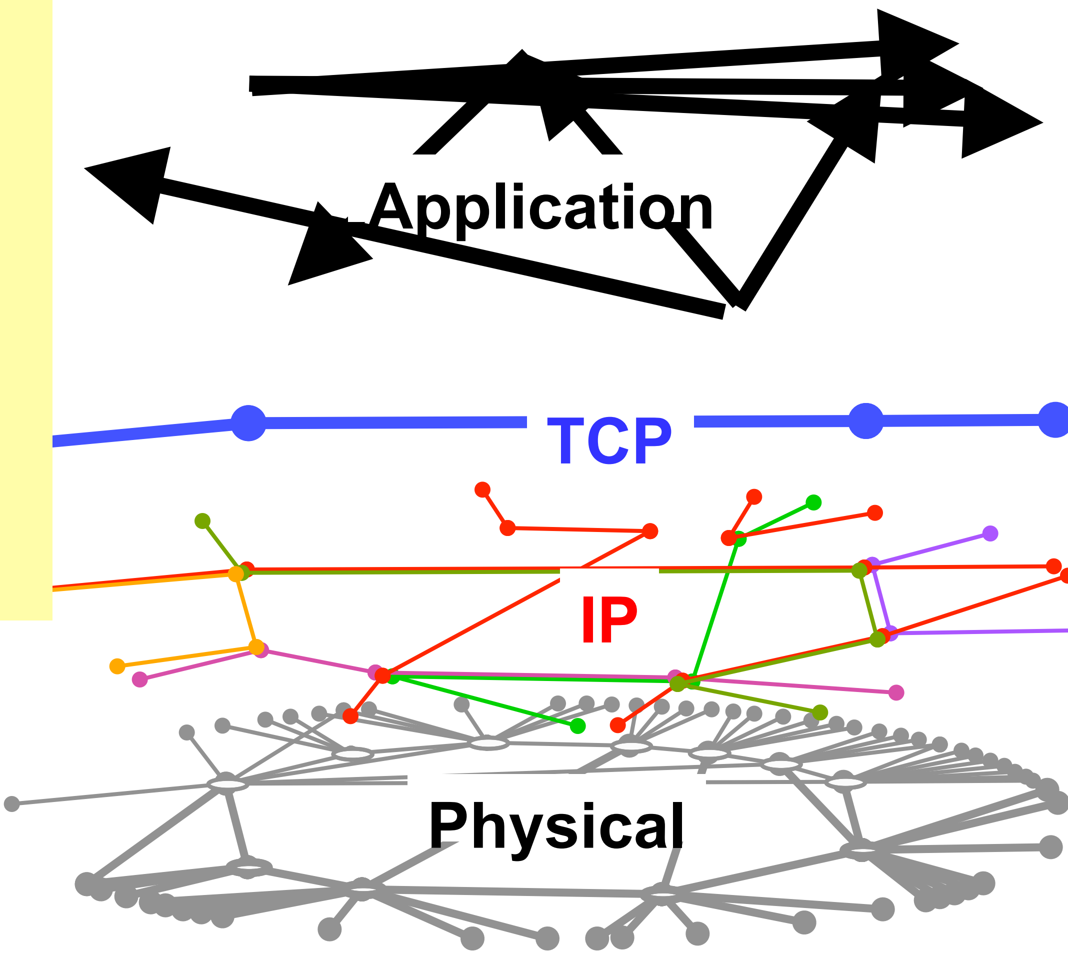



IPC
App
App
caltech.edu?
DNS
Global and direct access to physical address!
IP addresses interfaces (not nodes)
131.215.9.49
CPU/ Mem
Dev
Dev2
CPU/ Mem
Dev2
Dev2
CPU/ Mem



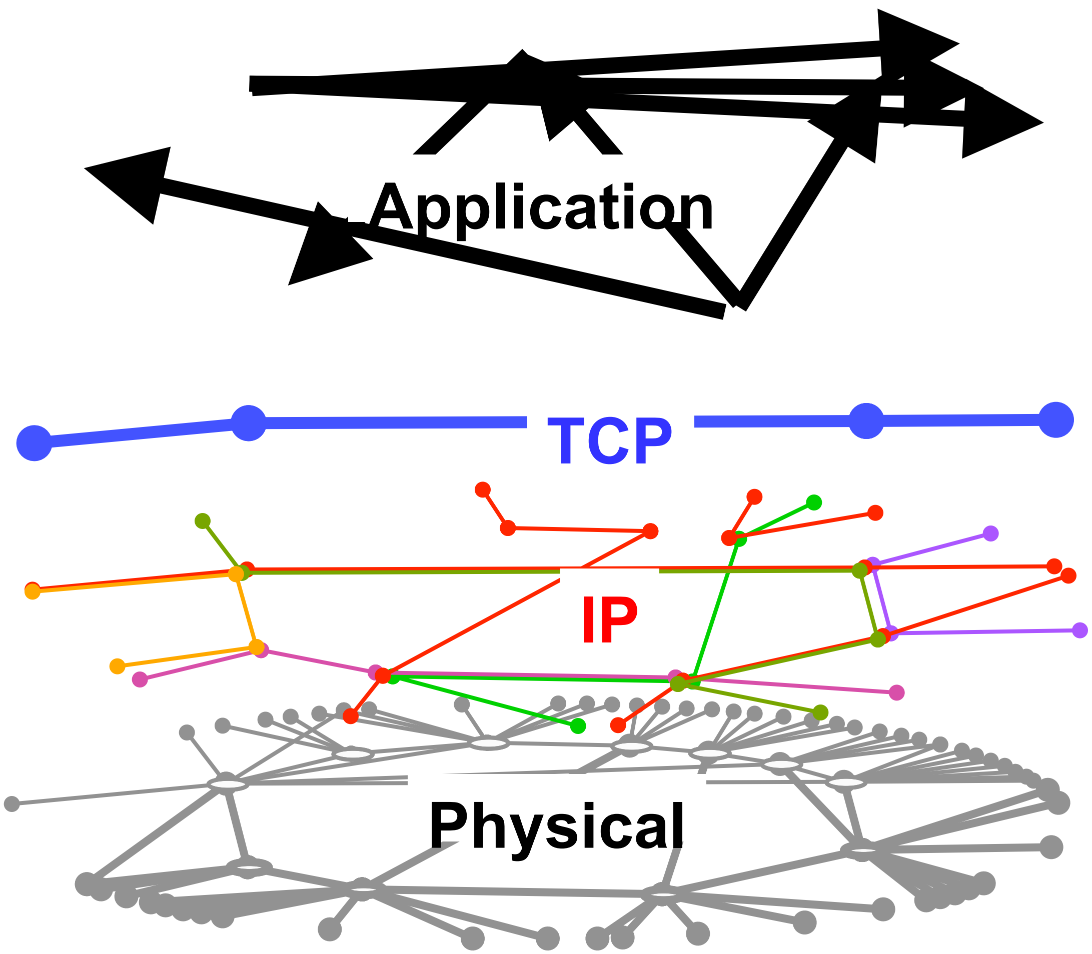
IPC
App
App
DNS
Global
and direct
access to
physical
address!
Robust?
• Secure
• Scalable
• Verifiable
• Evolvable
• Maintainable
• Designable
• …
IP addresses
interfaces
(not nodes)
CPU/
Mem
Dev
Dev2
CPU/
Mem
Dev2
Dev2
CPU/
Mem

"Issues" (hacks)
- VPNs
- NATS
- Firewalls
- Multihoming
- Mobility
- Routing table size
- Overlays
- …

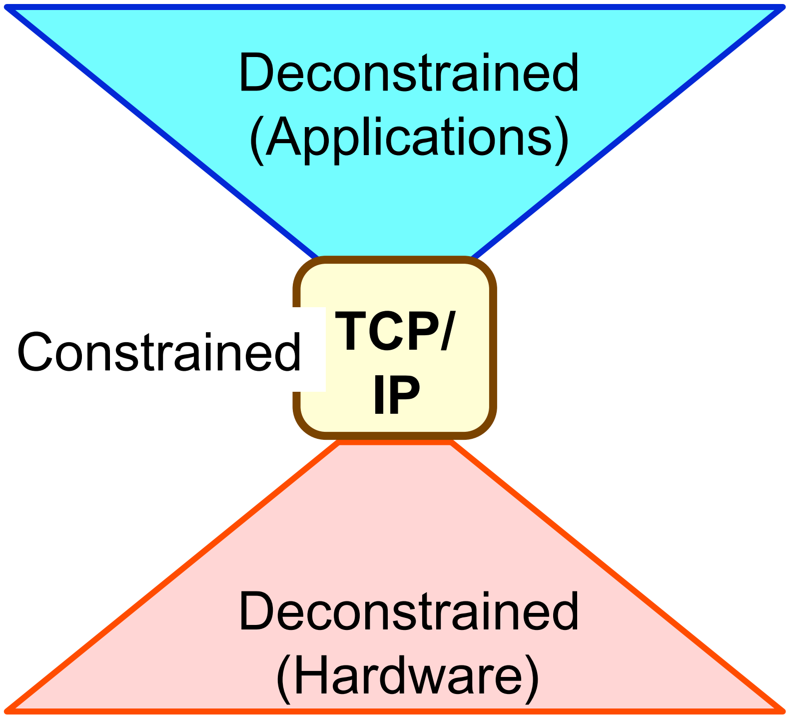


Aside:
Graph topology is ***not architecture***,
but deconstrained by layered architectures.

Internet
graph
topologies?



Original design challenge?



Networked OS

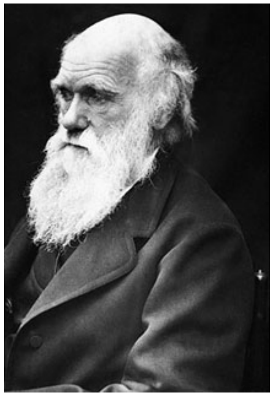
- Expensive mainframes
- Trusted end systems
- Homogeneous
- Sender centric
- Unreliable comms

Facilitated wild evolution

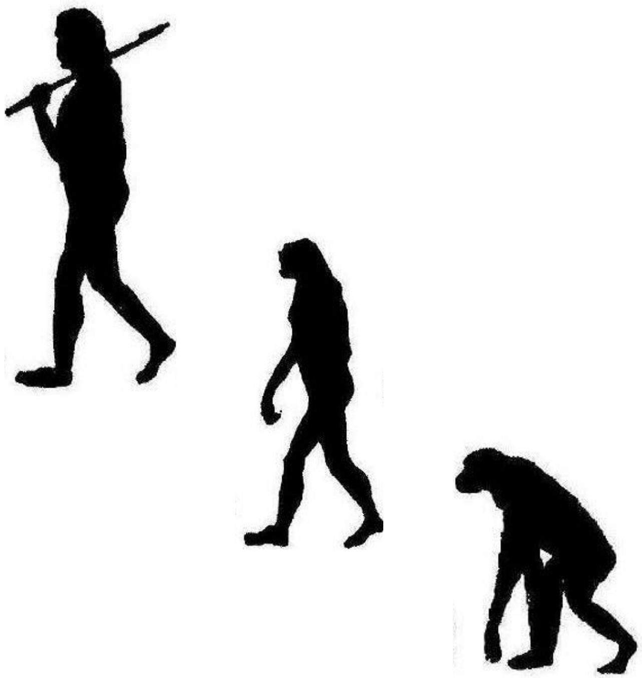
Created

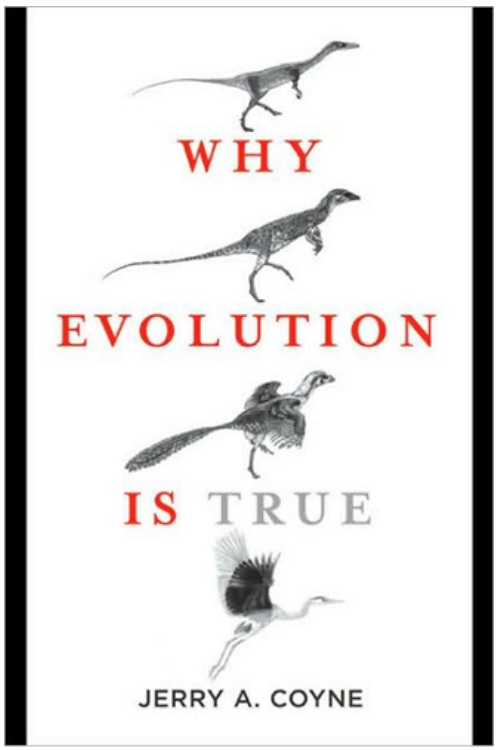
- whole new ecosystem
- completely opposite

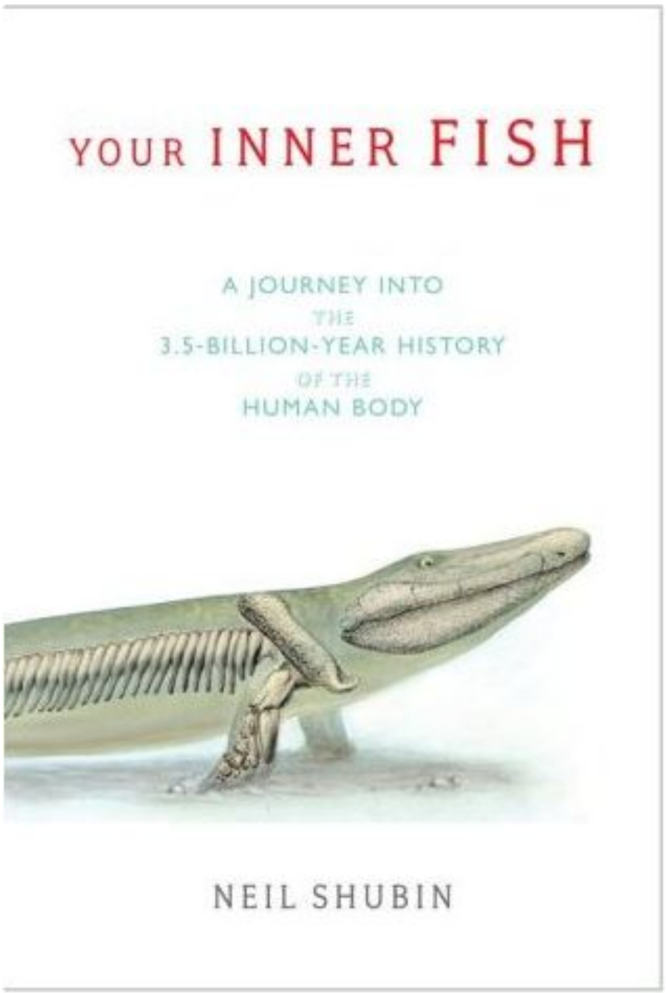
Unfortunately, not intelligent design



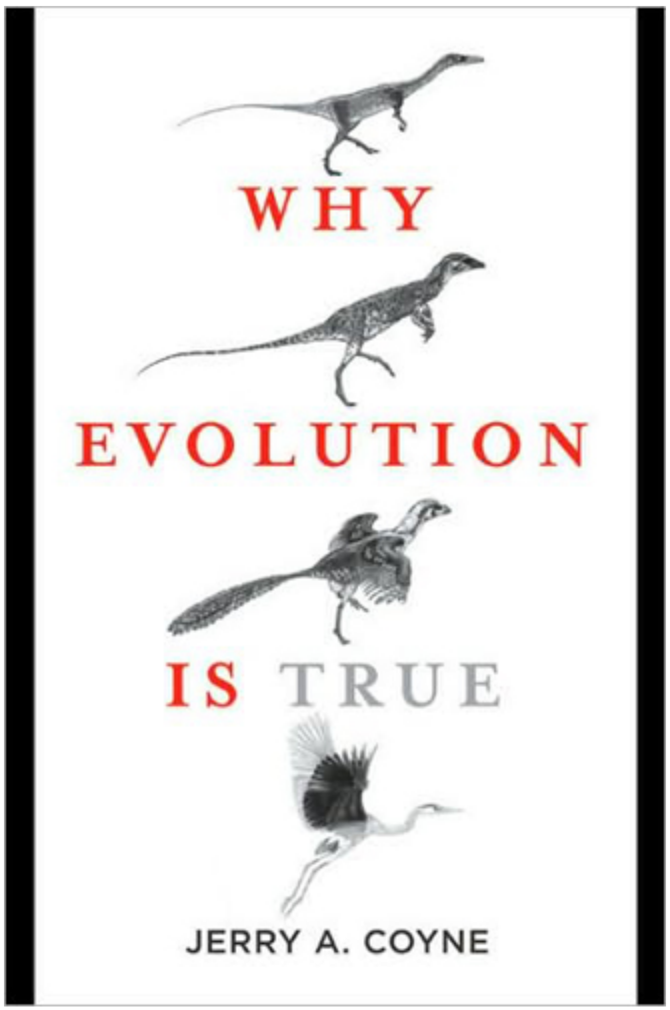
Ouch.

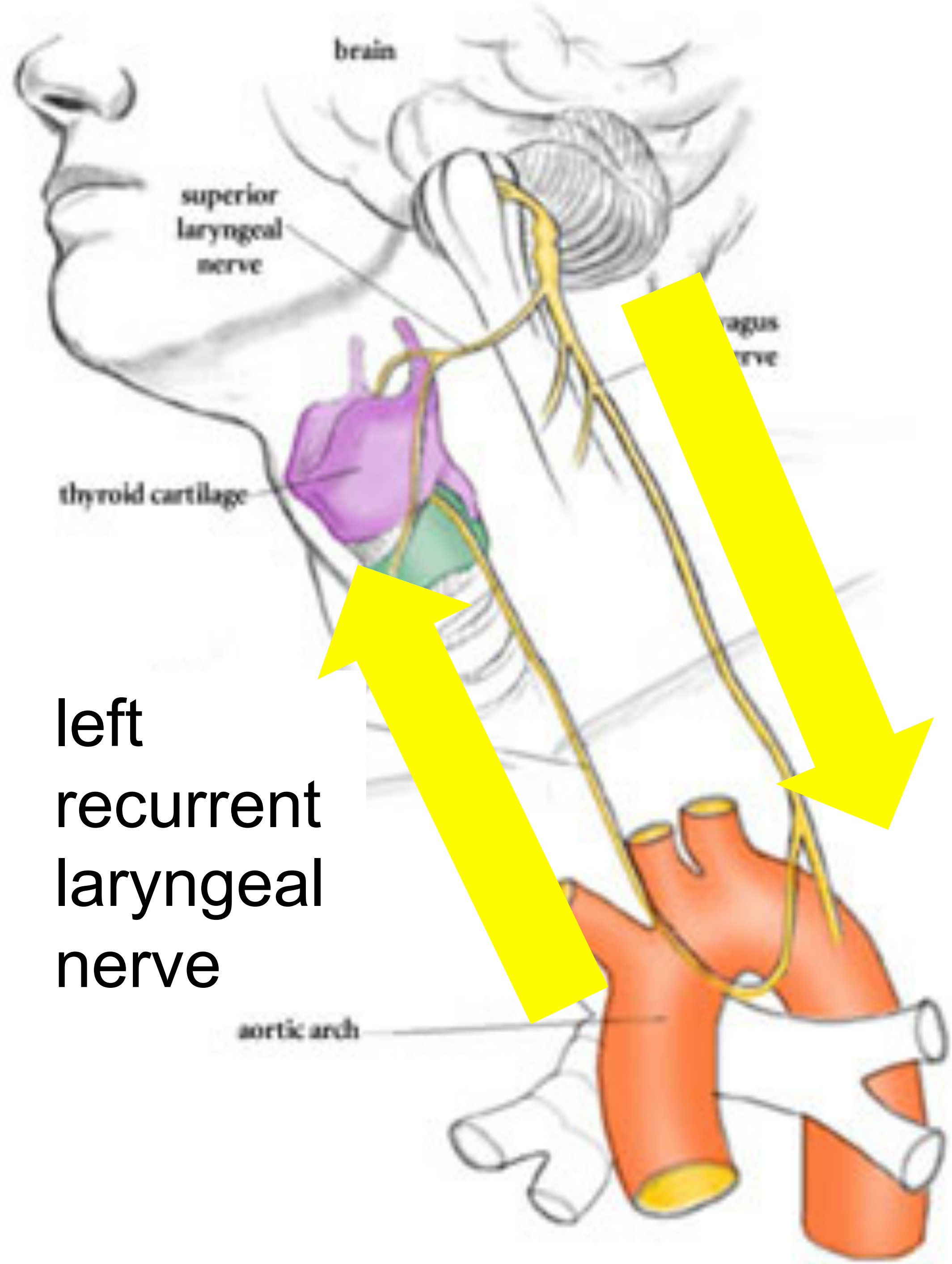






Why?


WHY
EVOLUTION
IS TRUE
JERRY A. COYNE


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

Why? Building humans from fish parts.

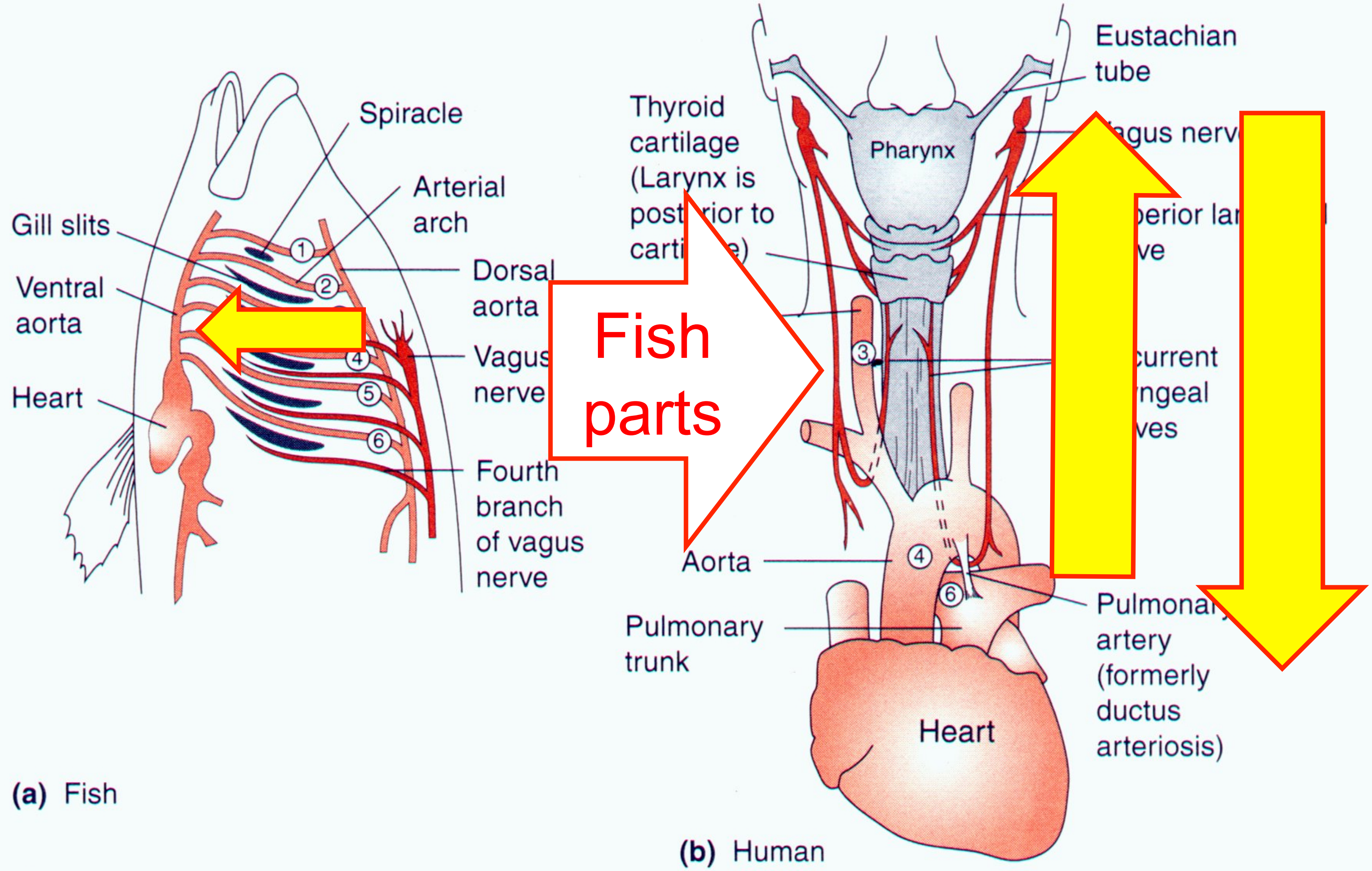
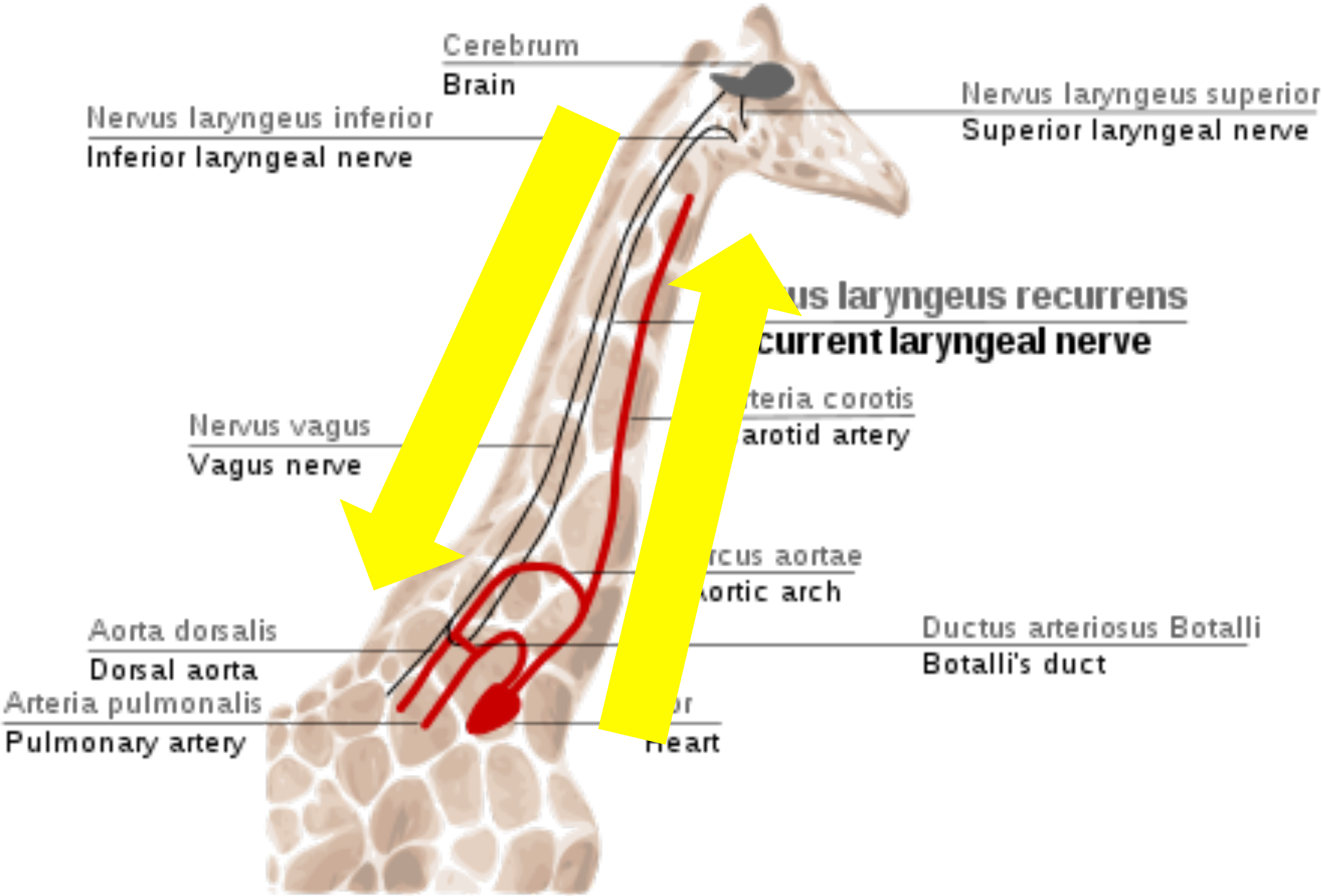
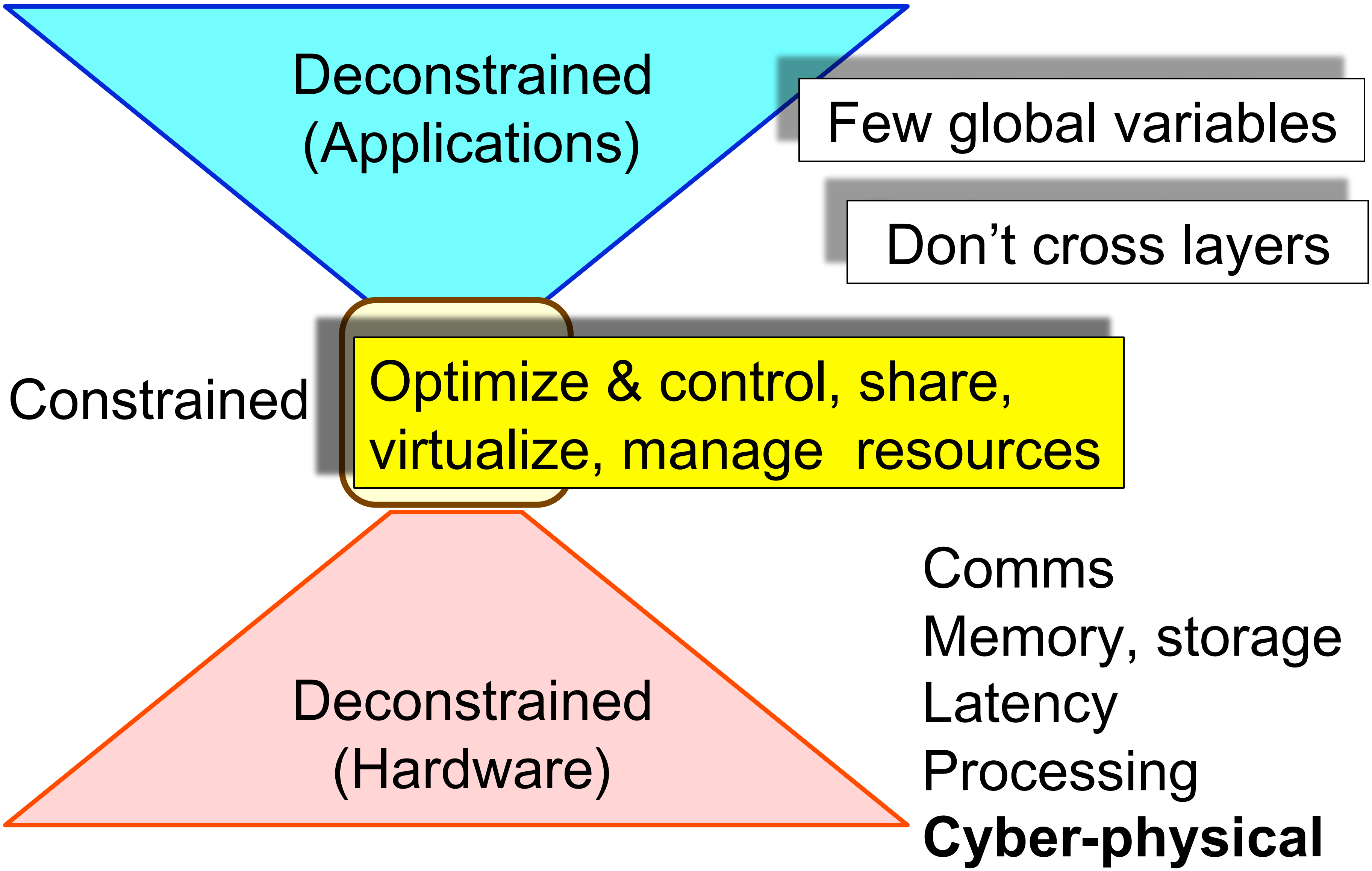


FIGURE 3–11 Schematic diagram showing the relationship between the vagus cranial nerve and the arterial arches in fish (*a*) and human (*b*). Only the third, fourth, and part of the sixth arterial arches remain in placental mammals, the sixth acting only during fetal development to carry blood to the 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.

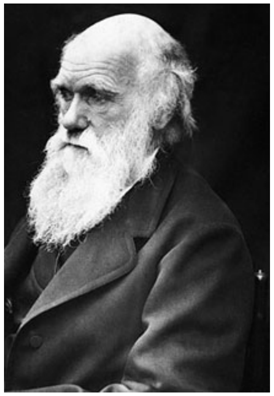


Next layered architectures (SDN)

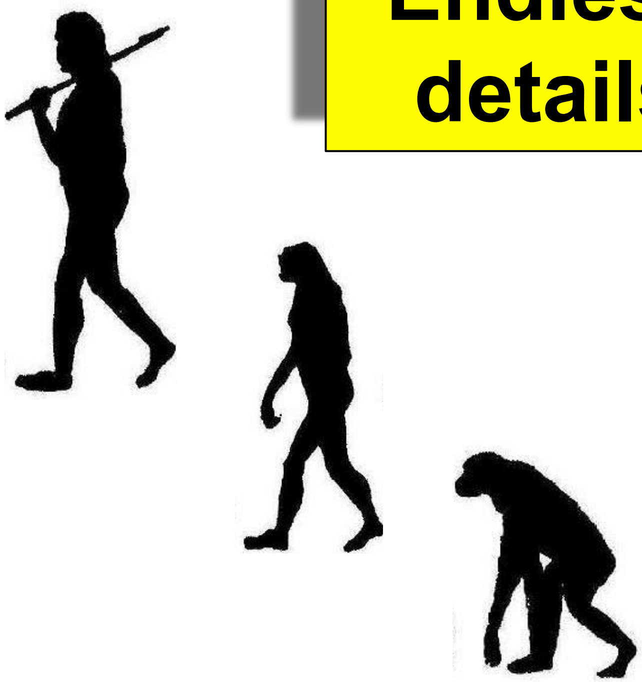


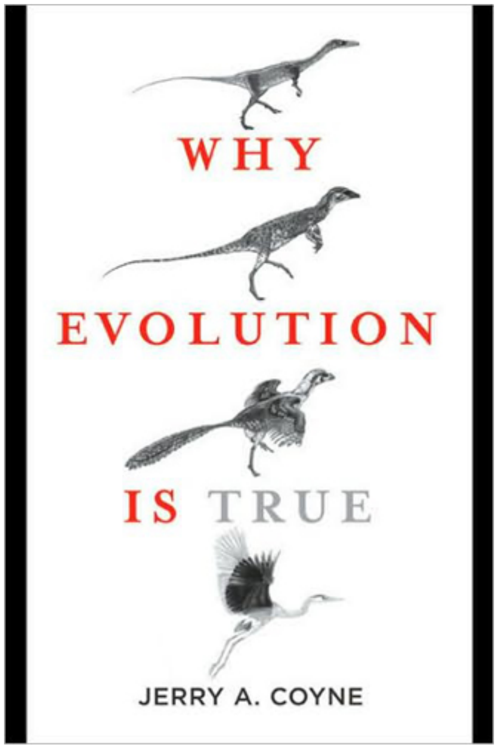
Human physiology

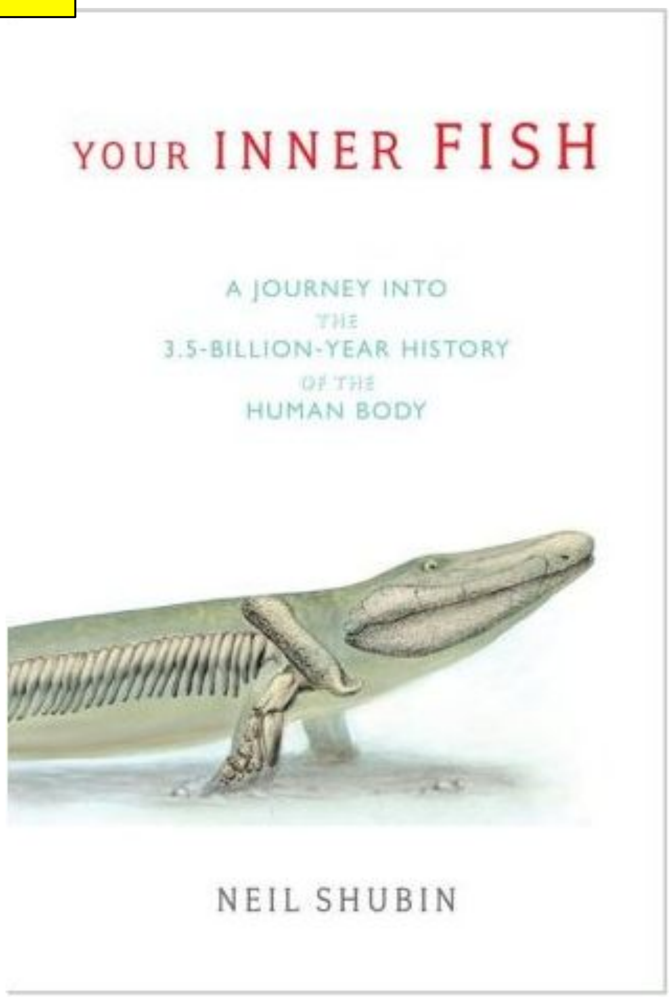
Ouch.



Endless details







Human physiology

Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Healing wound /infect	☹ AutoImmune/Inflame
☺ Efficient cardiovascular	☹ C-V diseases
	☹ Infectious diseases

Lots of triage

Benefits

Robust

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

Efficient

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

Mechanism?

Robust

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

Fragile

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

Mechanism?

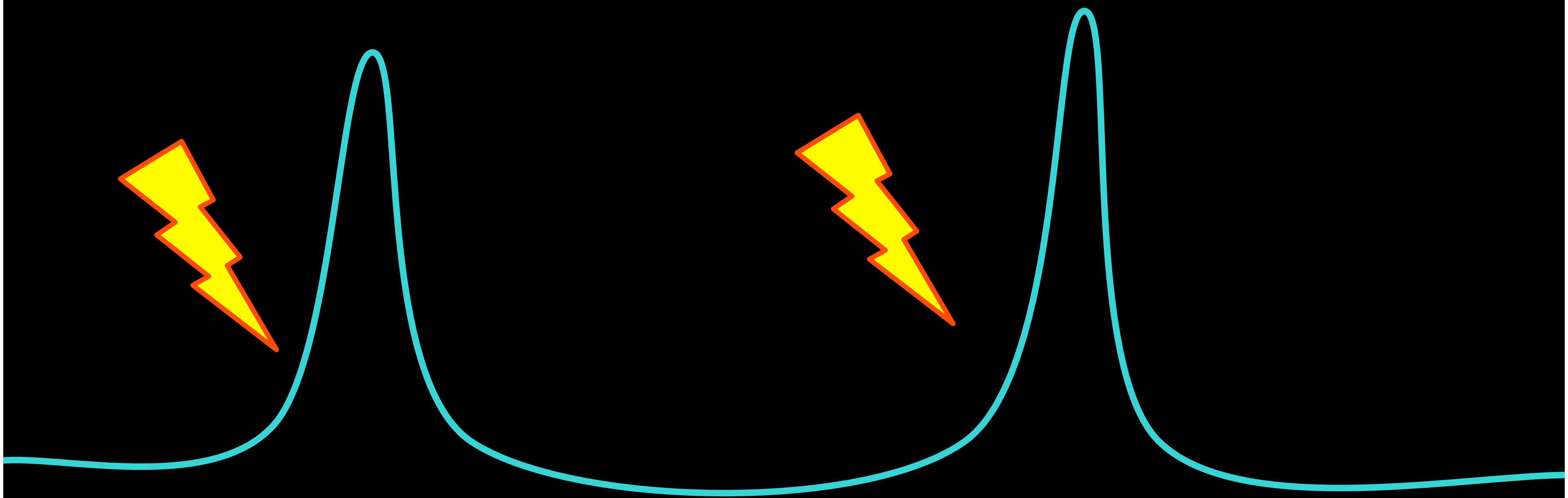
Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Healing wound /infect	☹ AutoImmune/Inflame
☺ Fat accumulation	☹ Fat accumulation
☺ Insulin resistance	☹ Insulin resistance
☺ Proliferation	☹ Proliferation
☺ Inflammation	☹ Inflammation

What's the difference?

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

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

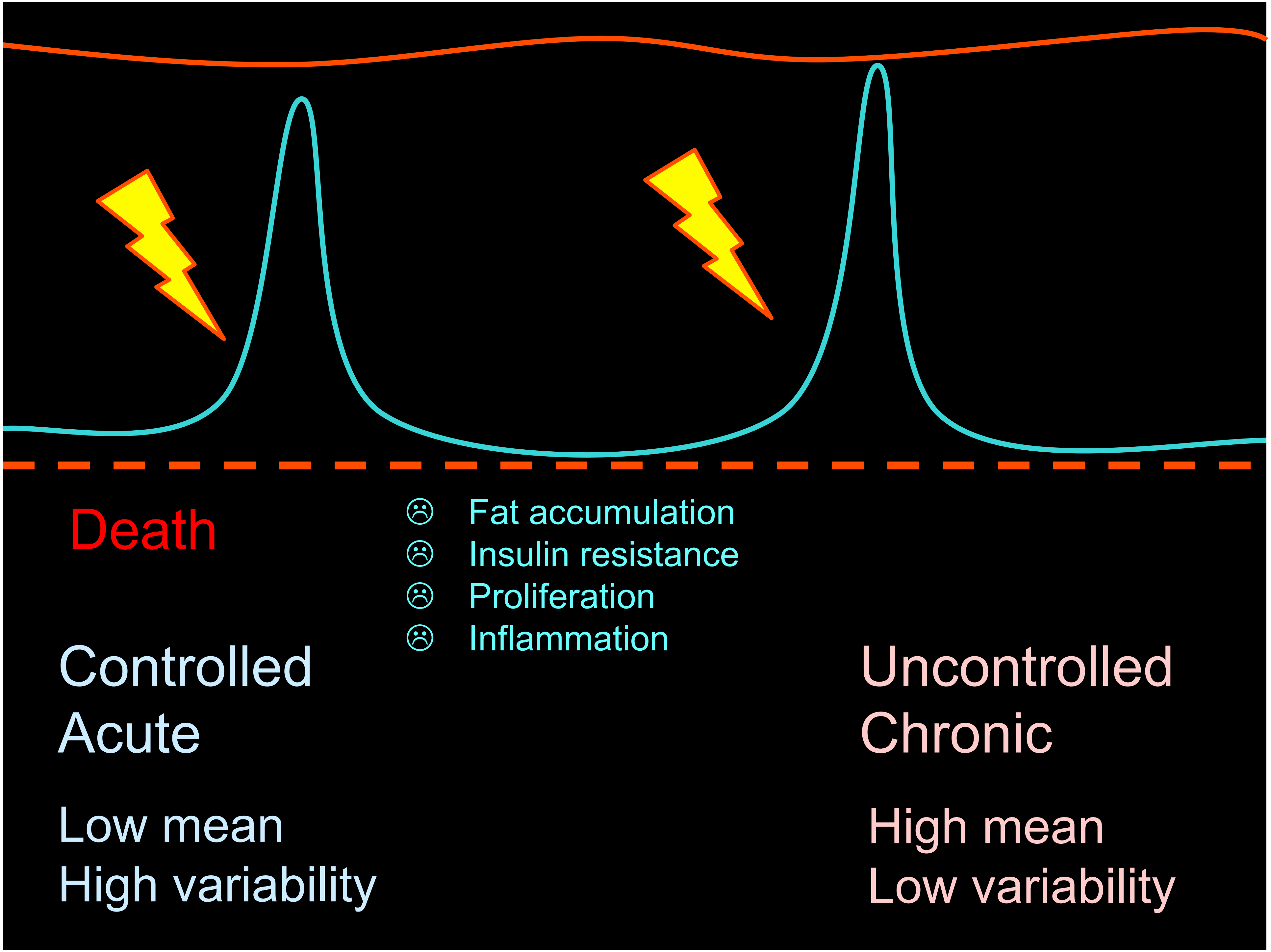
Controlled	Uncontrolled
Acute/responsive	Chronic

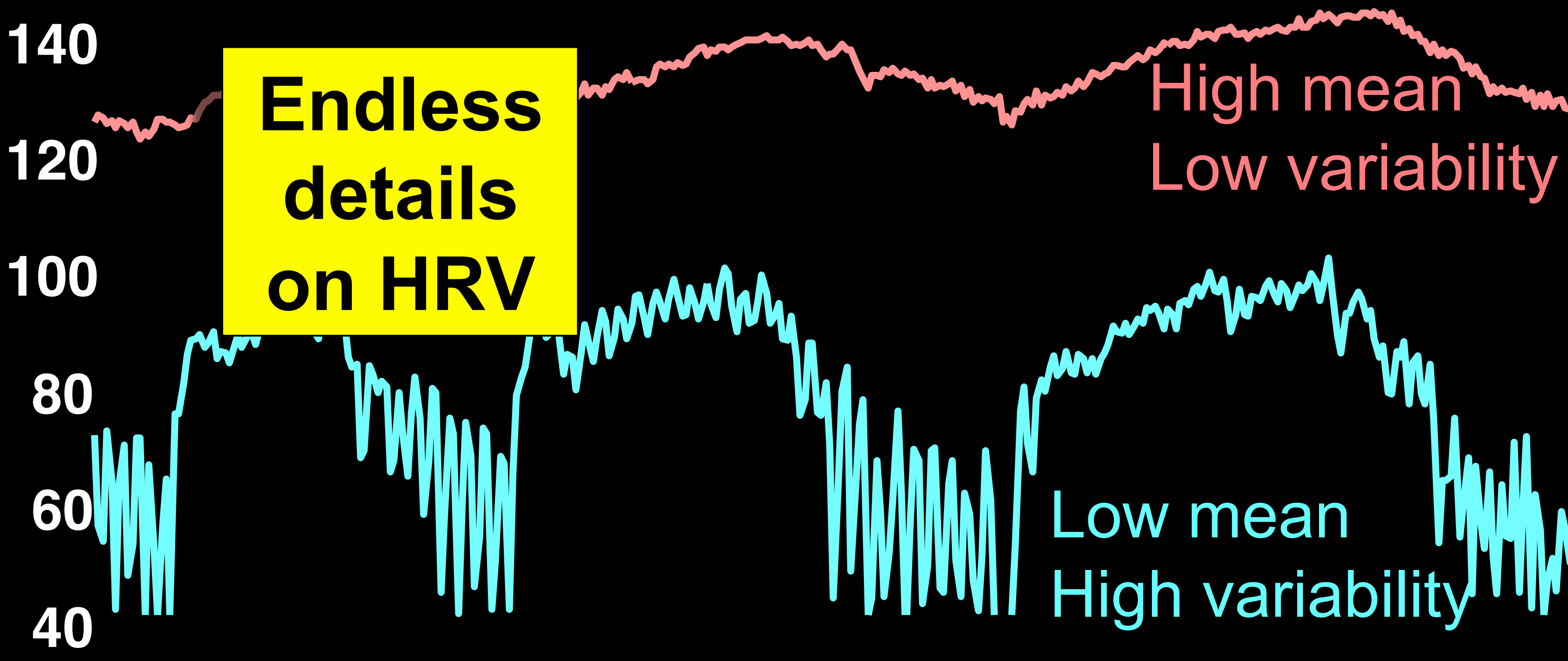


- ☹ Fat accumulation
- ☹ Insulin resistance
- ☹ Proliferation
- ☹ Inflammation

Controlled
Acute/responsive

Low mean
High variability


Death
☹ Fat accumulation
☹ Insulin resistance
☹ Proliferation
☹ Inflammation
Controlled
Acute
Low mean
High variability
Uncontrolled
Chronic
High mean
Low variability



Heart rate variability (HRV)

Healthy =

Low mean
High variability

Not =

High mean
Low variability

Restoring robustness?

Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Healing wound /infect	☹ AutoImmune/Inflame
☺ Fat accumulation	☹ Fat accumulation
☺ Insulin resistance	☹ Insulin resistance
☺ Proliferation	☹ Proliferation
☺ Inflammation	☹ Inflammation

Controlled
Acute

← Heal

Uncontrolled
Chronic

Human complexity

Robust	Yet Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regeneration & repair	☹ Cancer
☺ Immune/inflammation	☹ AutoImmune/Inflame
☺ Microbe symbionts	☹ Parasites, infection
☺ Neuro-endocrine	☹ Addiction, psychosis,…
🗐 Complex societies	☠ Epidemics, war,…
🗐 Advanced technologies	💣 Disasters, global &!%$#
🗐 Risk “management”	💣 Obfuscate, amplify,…

Accident or necessity?

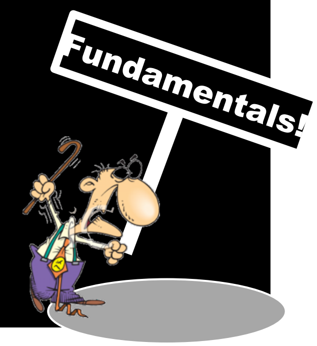
Robust	Fragile
☺ Metabolism	☹ Obesity, diabetes
☺ Regenerati	
☺ Healing wo	une/Inflame

☹ Fat accumulation
☹ Insulin resistance
☹ Proliferation
☹ Inflammation

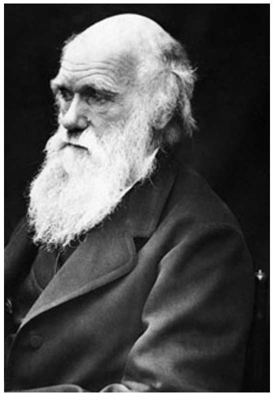
- Fragility ← Hijacking, side effects, unintended…
- Of mechanisms evolved for robustness
- Complexity ← control, robust/fragile tradeoffs
- Math: robust/fragile constraints (“conservation laws”)

Both

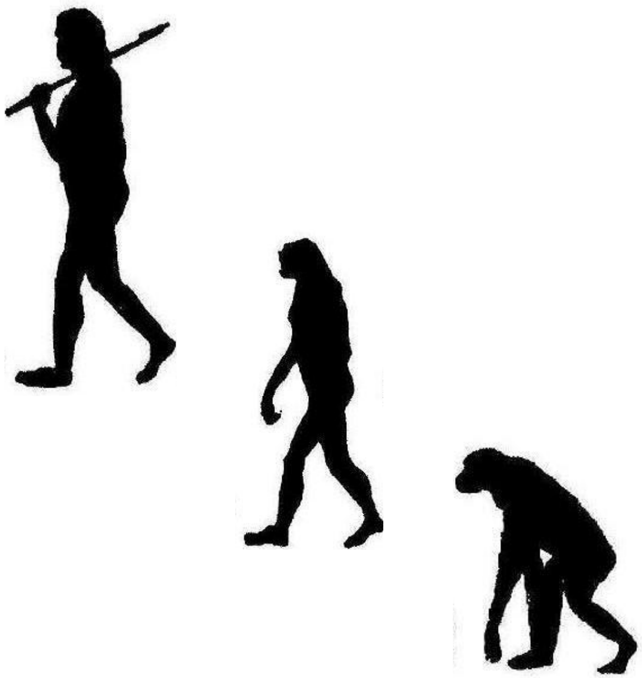
Accident or necessity?

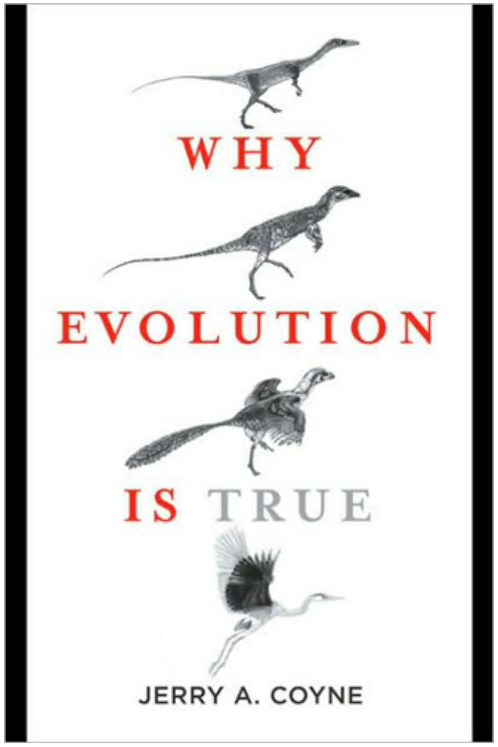


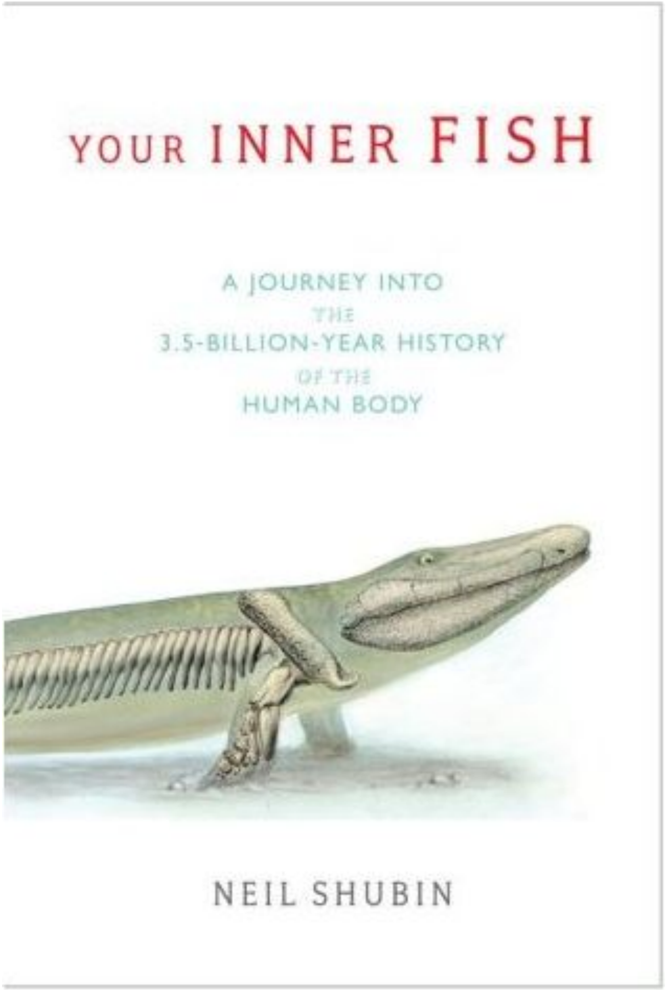
Unfortunately, not intelligent design

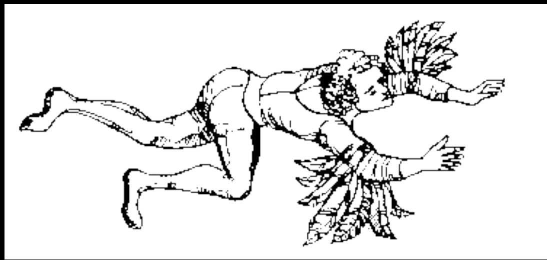


Ouch.

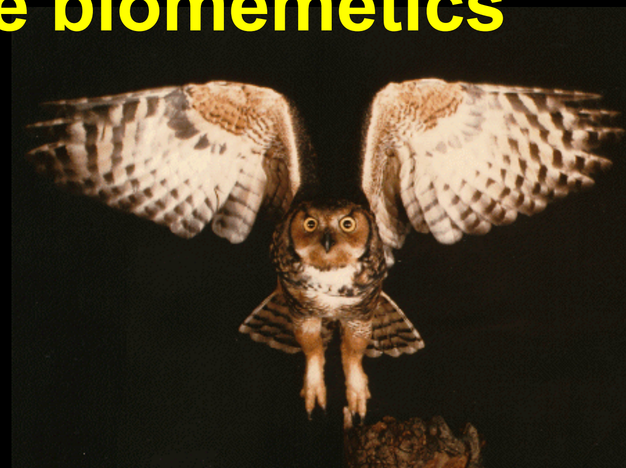






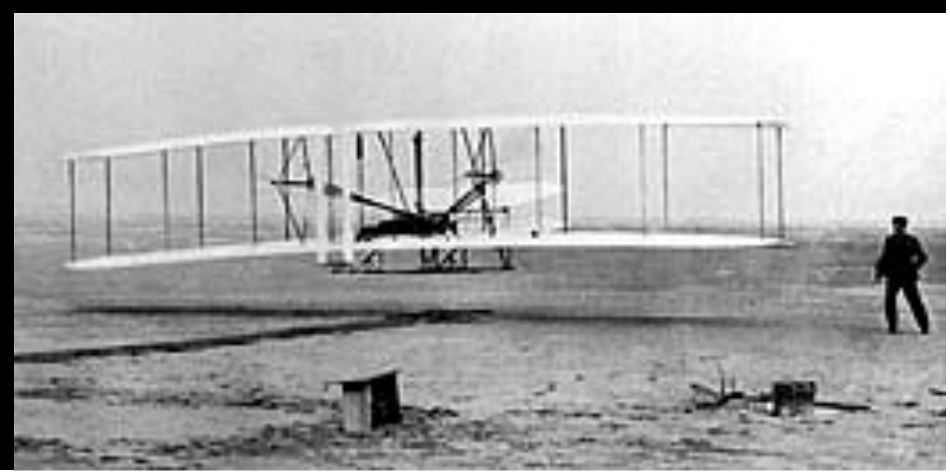


The dangers of naïve biomemetics



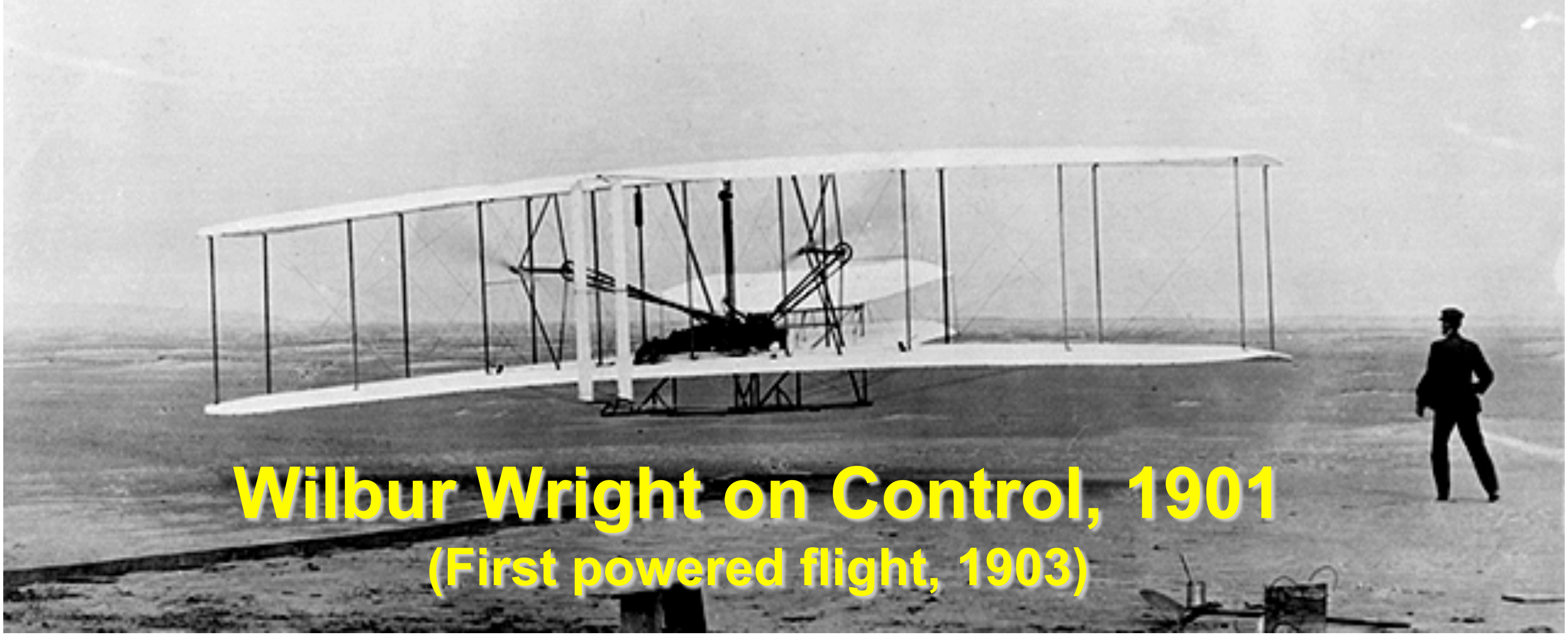
Feathers
and
flapping?

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



Getting it (W)right, 1901

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



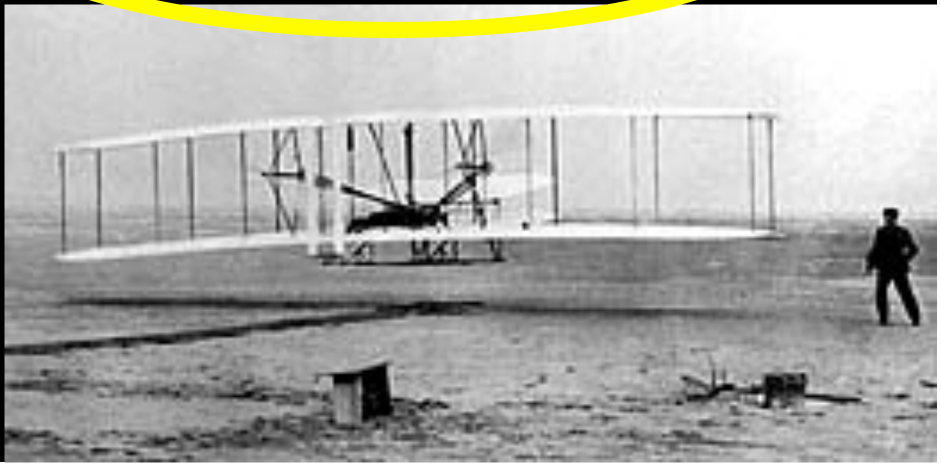
Wilbur Wright on Control, 1901

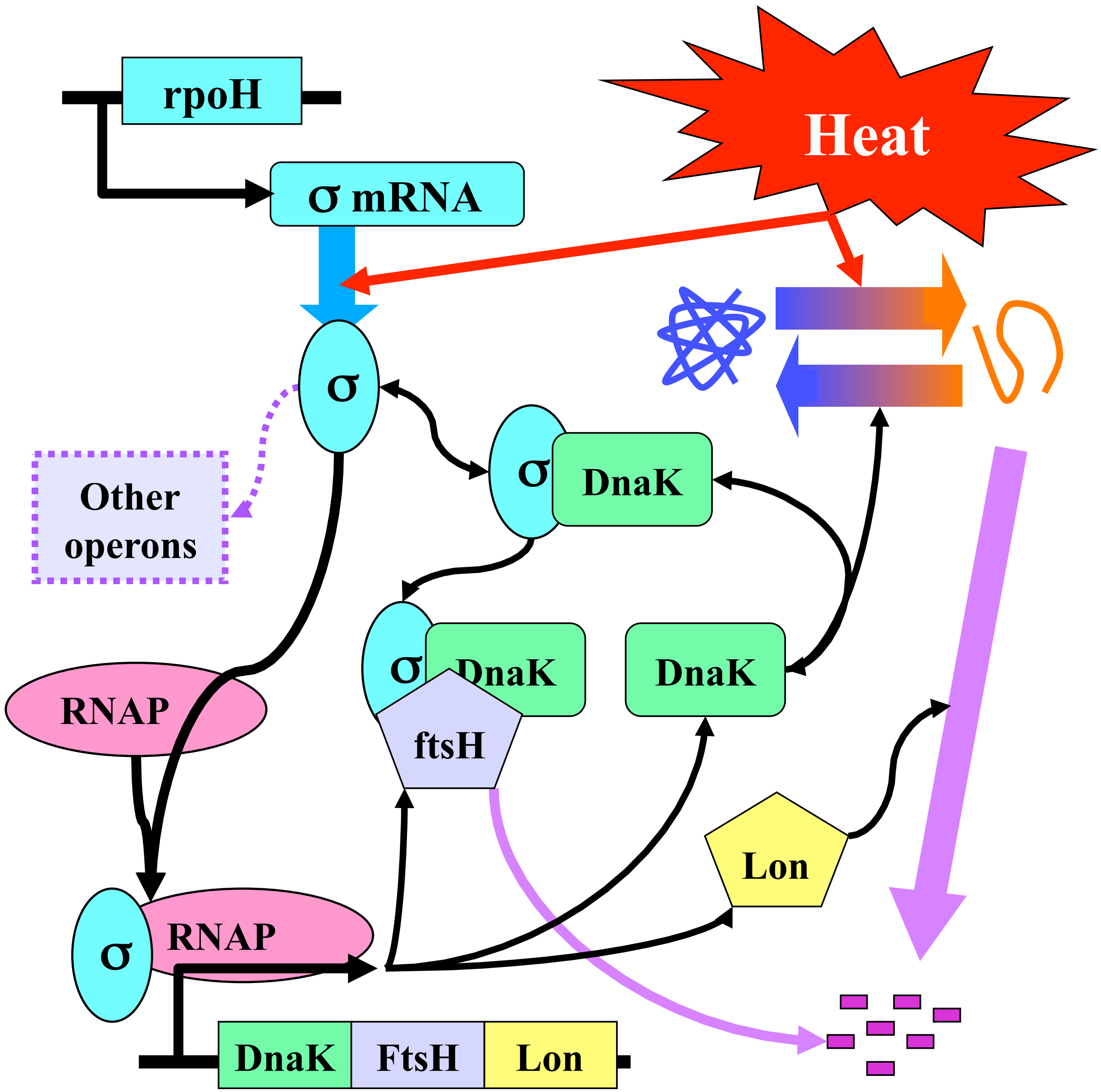
(First powered flight, 1903)

Universals?

Feathers and flapping?

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





Recycle proteins that can't refold