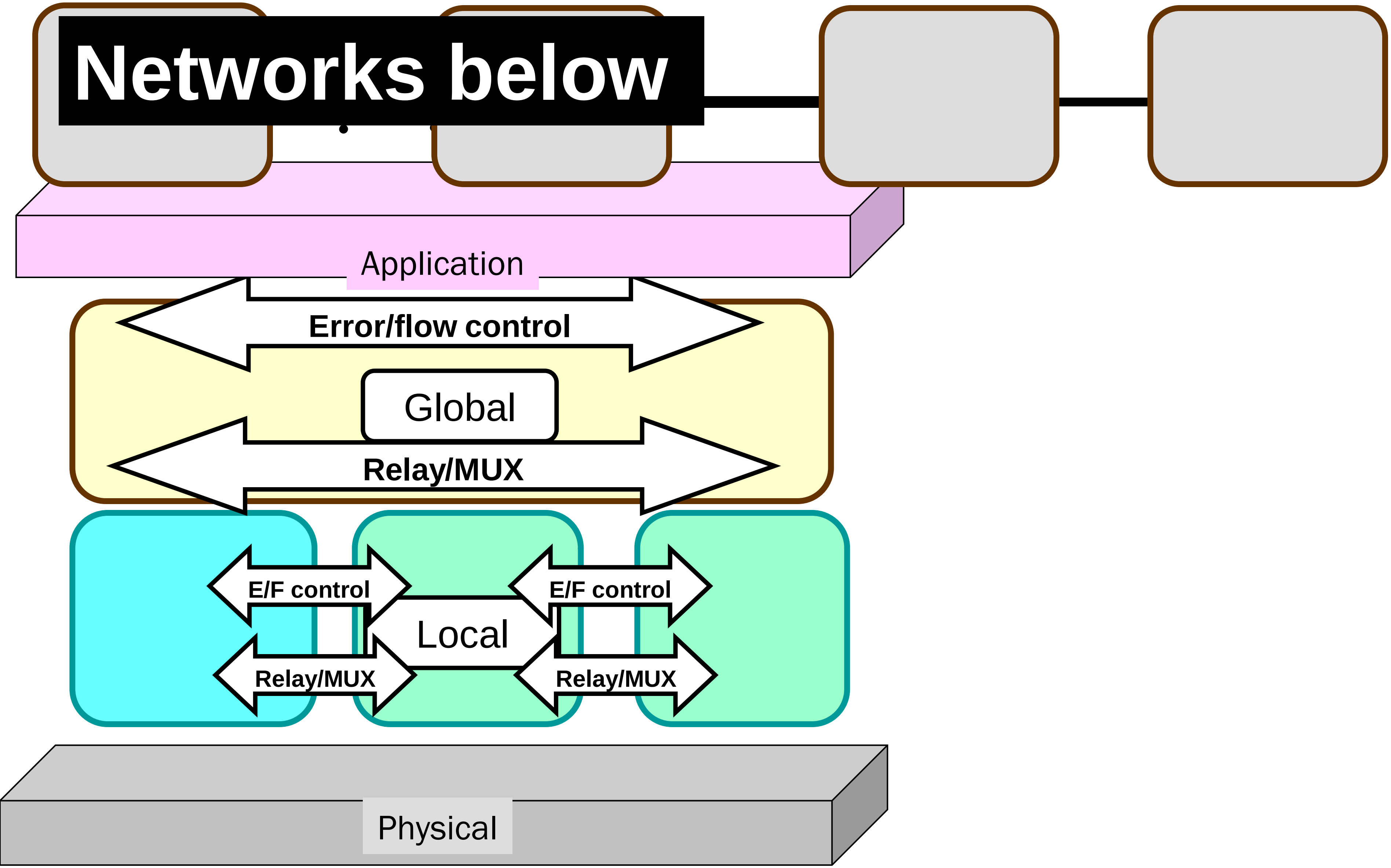
~~Paths ahead~~?

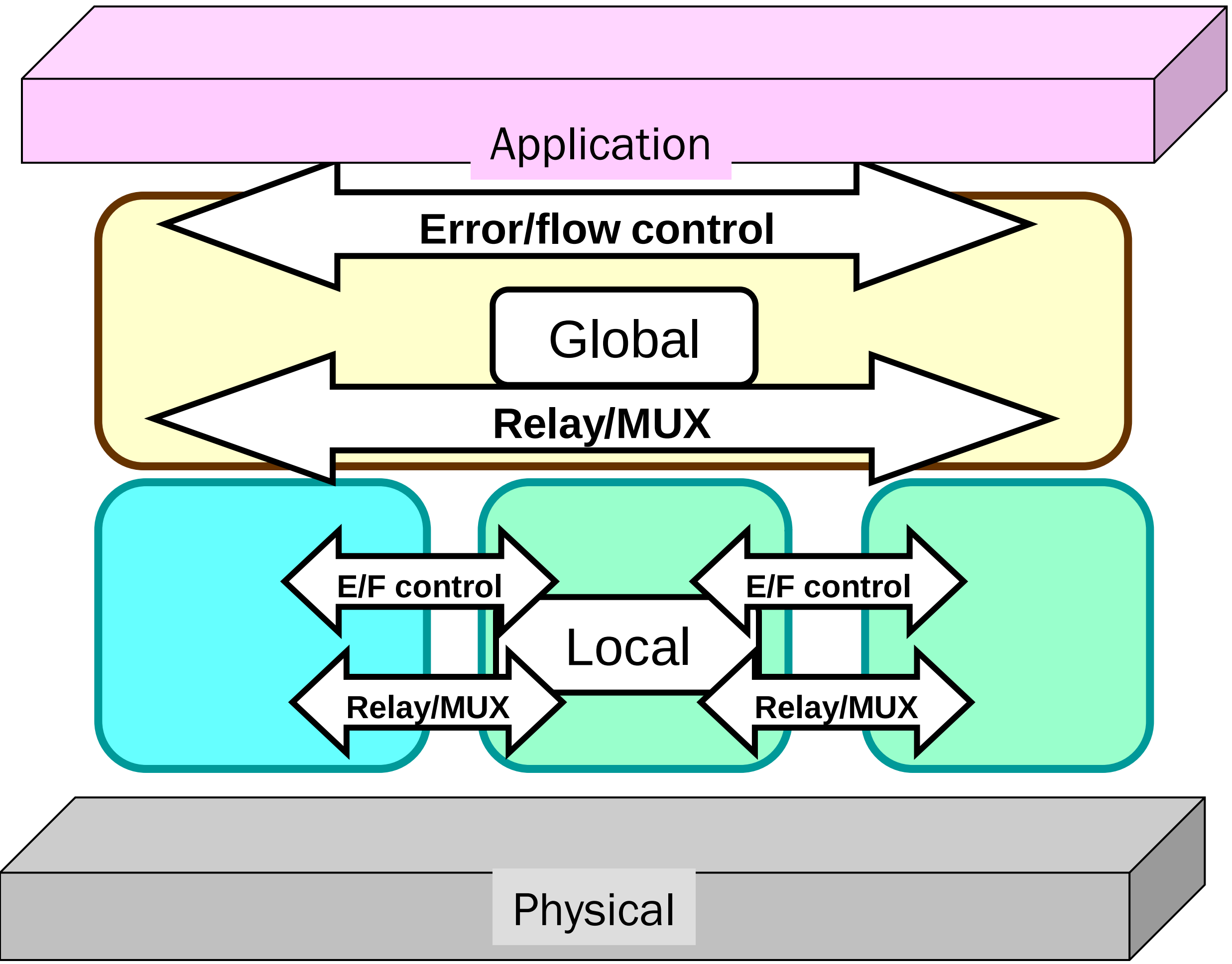
Networks below



Legitimate academic ~~pursuits~~?

wanderings?

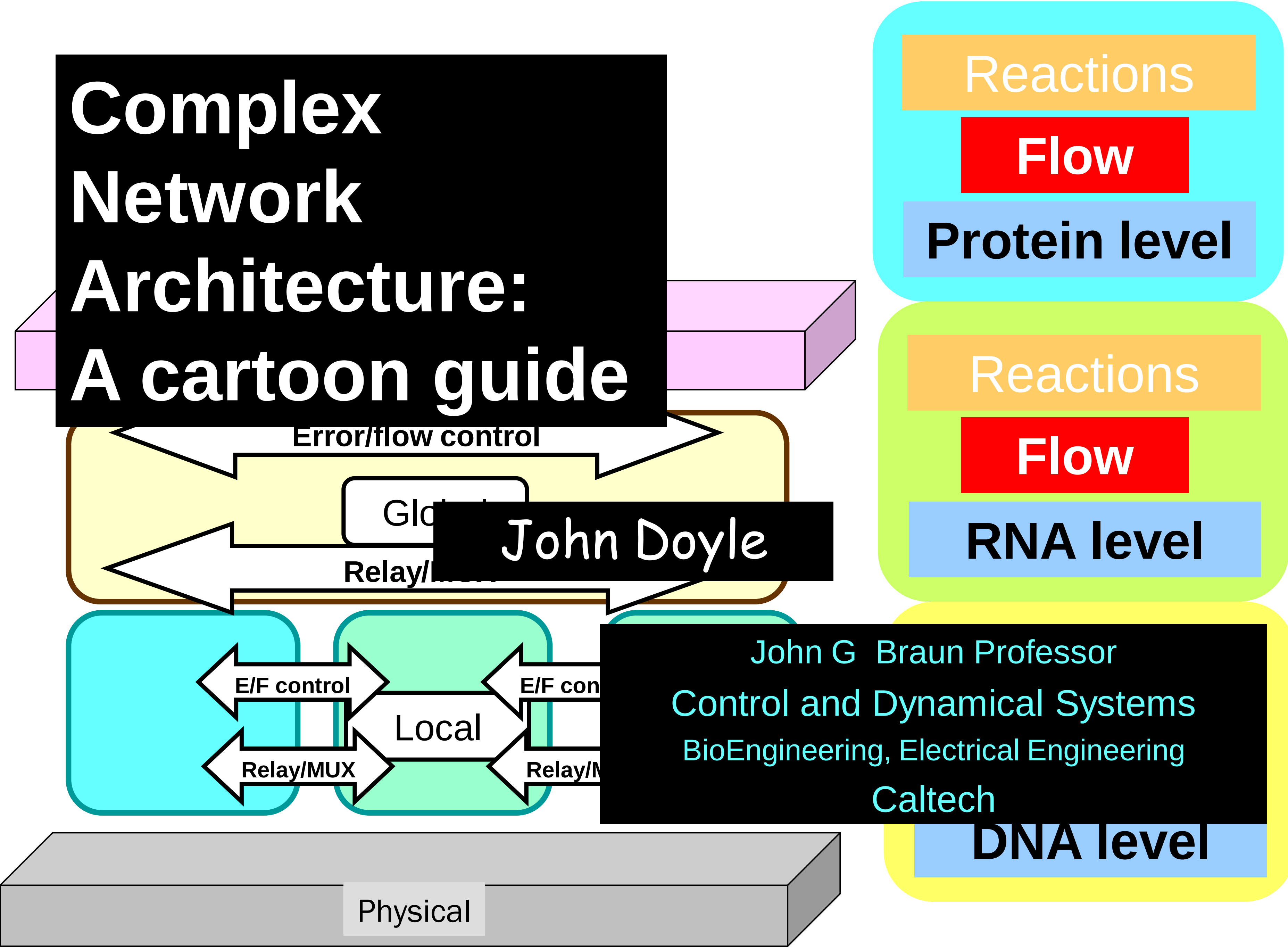
Networks below



Complex Network Architecture: A cartoon guide

John Doyle

John G Braun Professor
Control and Dynamical Systems
BioEngineering, Electrical Engineering
Caltech



Complex Network Architecture

- Is there hope of a theory?
- Are there even informative case studies?
- Is there anything but “hack and ship”?
- Hiding ignorance behind obfuscation?

Other Influences Not Here Today

- Biology/Medicine (Savageau, G&K, Mattick, Csete, Arkin, Alon, Caporale, de Duve, Exerc Physio, Acute Care, etc etc…)
- Internet (Kelly/Low, Willinger, Clark, Wroclawski, Day, Chang, etc etc)
- Architecture (Alexander, Salingeros,…)
- Aerospace (many, Maier is a good book)
- Philosophy/History (Fox Keller, Jablonka&Lamb)
- Physics/ecology (Carlson)
- Management (Baldwin,…)
- Resilience/Safety/Security Engineering/Economics (Wood, Anderson, Leveson, …)

Essential ideas: Architecture

Robust
yet
fragile

Question

Constraints
that
deconstrain

Answer

Question: Human complexity

Robust

- ☺ Efficient, flexible metabolism
- ☺ Regeneration & renewal
- ☺ Rich microbial symbionts
- ☺ Immune systems
- Complex societies
- Advanced technologies

Yet Fragile

- ☹ Obesity and diabetes
- ☹ Cancer
- ☹ Parasites, infection
- ☹ Inflammation, Auto-Im.
- ☠ Epidemics, war, …
- Catastrophic failures

Mechanism?

Robust

- ☺ Efficient, flexible metabolism
- ☺ Regeneration & renewal
  - ☺ Fat accumulation
  - ☺ Insulin resistance
  - ☺ Inflammation

Fluctuating energy

Yet Fragile

- ☹ Obesity and diabetes
- ☹ Cancer
  - ☹ Fat accumulation
  - ☹ Insulin resistance
  - ☹ Inflammation

Static energy

Implications/ Generalizations

Robust

- ☺ Efficient, flexible metabolism
- ☺ Rich microbial symbionts
- ☺ Immune systems
- ☺ Regeneration & renewal
- Complex societies
- Advanced technologies

Yet Fragile

- ☹ Obesity and diabetes
- ☹ Parasites, infection
- ☹ Inflammation, Auto-Im.
- ☹ Cancer
- ☠ Epidemics, war, …
- Catastrophic failures

- Fragility = Hijacking, side effects, unintended… of mechanisms evolved for robustness
- Complexity is driven by control, robust/fragile tradeoffs
- Math: New robust/fragile conservation laws

- Resilience/safety/security Engineering/Economics: “Human error” and “human nature” is often a symptom of bad system architecture

Infrastructure networks?

- Power
- Transportation
- Water
- Waste
- Food
- Healthcare
- Finance

All examples of
“bad” architectures:
- Unsustainable
- Hard to fix

Where do we look for “good” examples?

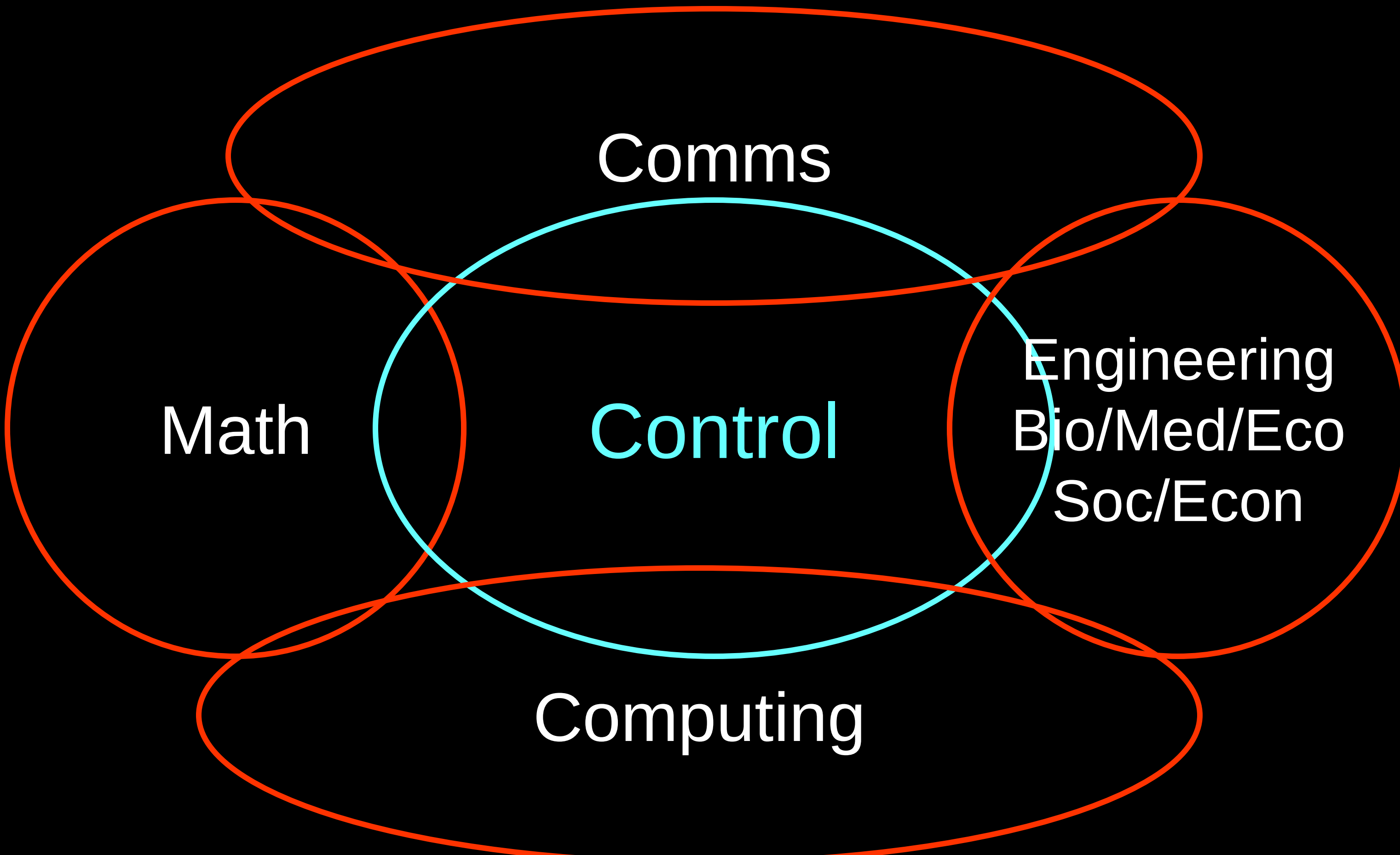
"Architecture" in practice

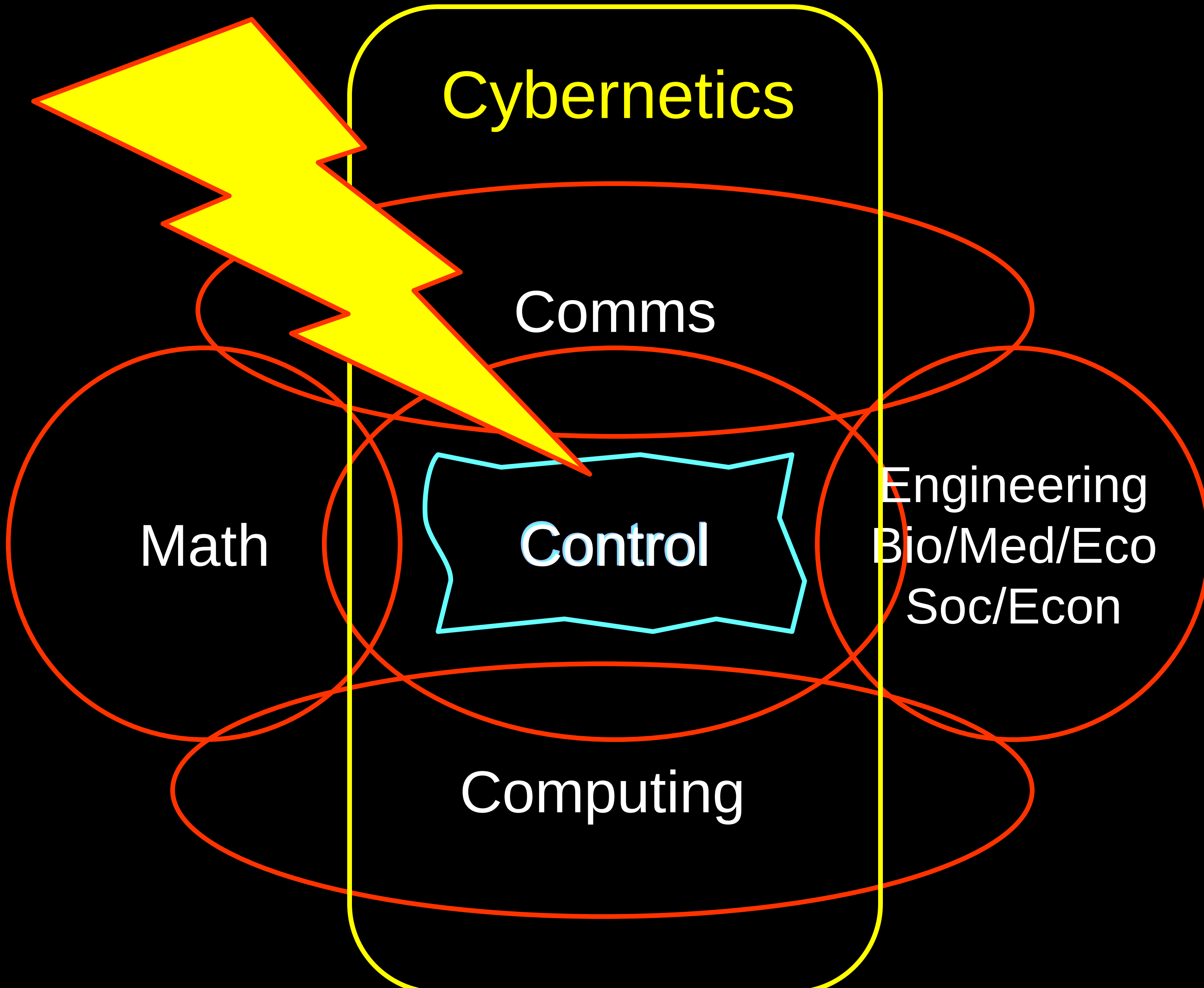
- Internet, biology, energy, manufacturing, transportation, water, food, waste, law, etc
- Many architectures are unsustainable/hard to fix

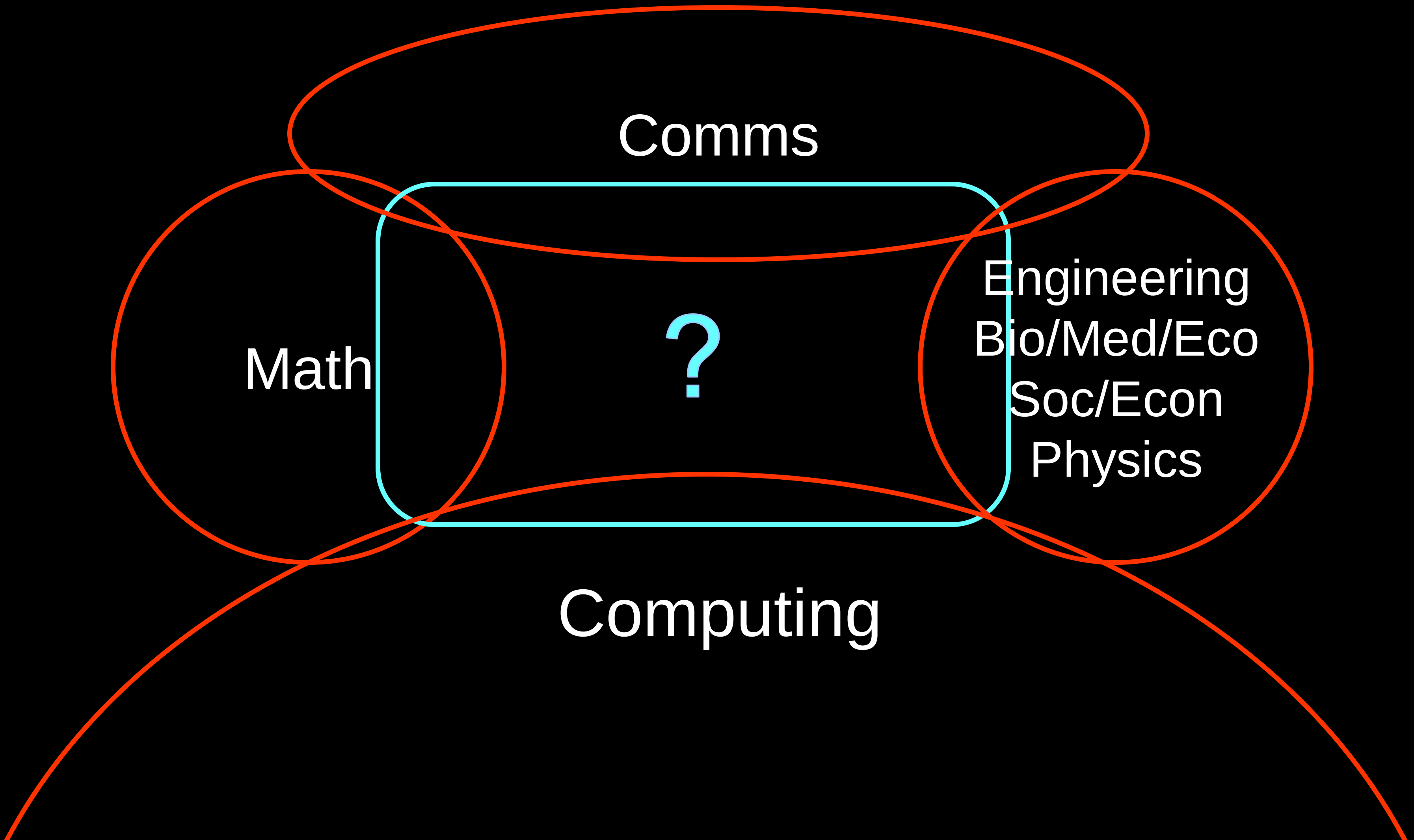
What does "architecture" mean here?

- Persistent, ubiquitous, global features
- Constrains the possible (for good or bad)
- Enables/prevents innovation, sustainability, etc,
- Theory is fragmented, incoherent, incomplete
- Needs rigor and relevance
- "Constraints that deconstrain" and "facilitated variation" (Gerhart and Kirschner)

Astrom bridge




Cybernetics
Comms
Math
Control
Engineering
Bio/Med/Eco
Soc/Econ
Computing


Comms
Math
?
Engineering
Bio/Med/Eco
Soc/Econ
Physics
Computing

Essential ideas: Architecture

Robust yet fragile

Question

Constraints that deconstrain

Answer

Simplest case studies

Internet

Bacteria

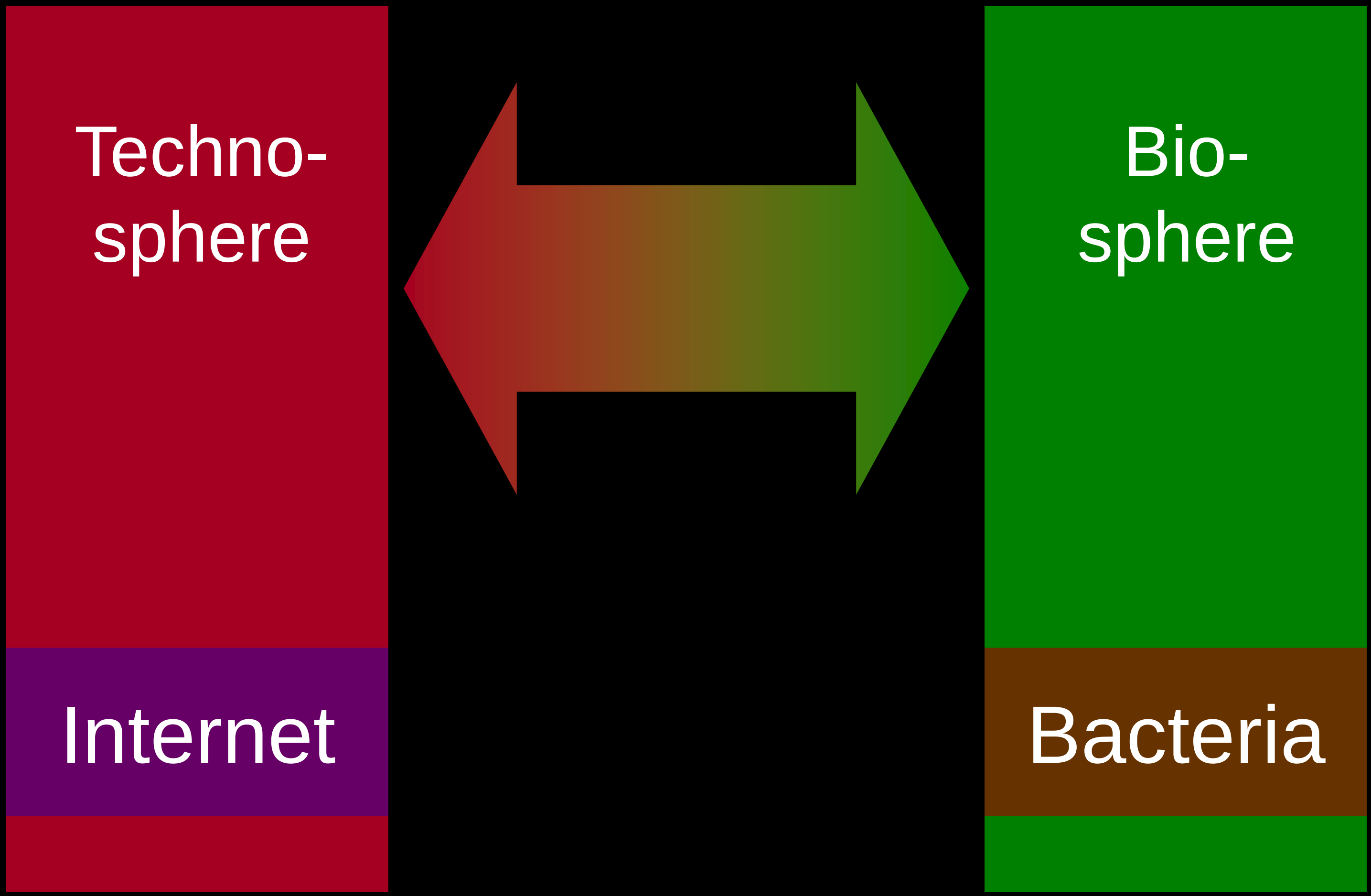
- Successful architectures
- Robust, evolvable
- Universal, foundational
- Accessible, familiar
- Unresolved challenges
- New theoretical frameworks
- Boringly retro?

Simplest case studies

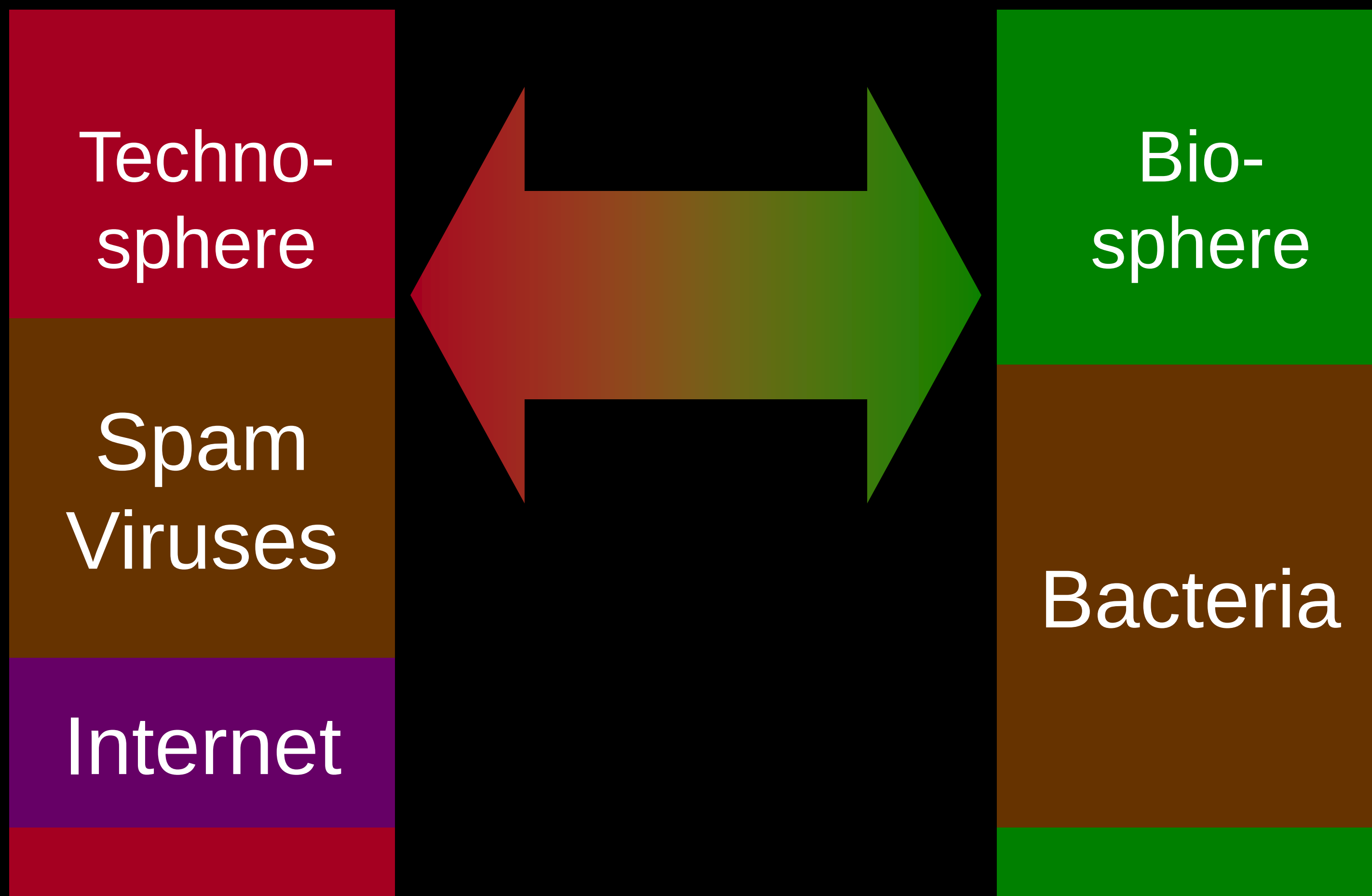
Internet

Bacteria

- Universal, foundational



- Universal, foundational



Two lines of research:

1. Patch the existing Internet architecture so it handles its new roles

- Real time
- Control ***over*** (not just of) networks
- Action in the physical world
- Human collaborators and adversaries
- Net-centric ***everything***

Cyber-Physical Theories

- Thermodynamics
- Communications
- Control
- Computation

Cyber

- Thermodynamics
- Communications
- Control
- Computation

Physical

- Thermodynamics
- Communications
- Control
- Computation

Internet

Bacteria

Case studies

Cyber

- Thermodynamics
- Communications
- Control
- Computation

Physical

- Thermodynamics
- Communications
- Control
- Computation

Promising unifications

Modern theory and the Internet

Levels of understanding

Verbal/cartoon
Data and statistics
Modeling and simulation
Analysis
Synthesis

Topics

Traffic
Topology
Control and dynamics
Layering
Architecture

Recent progress (1995-)

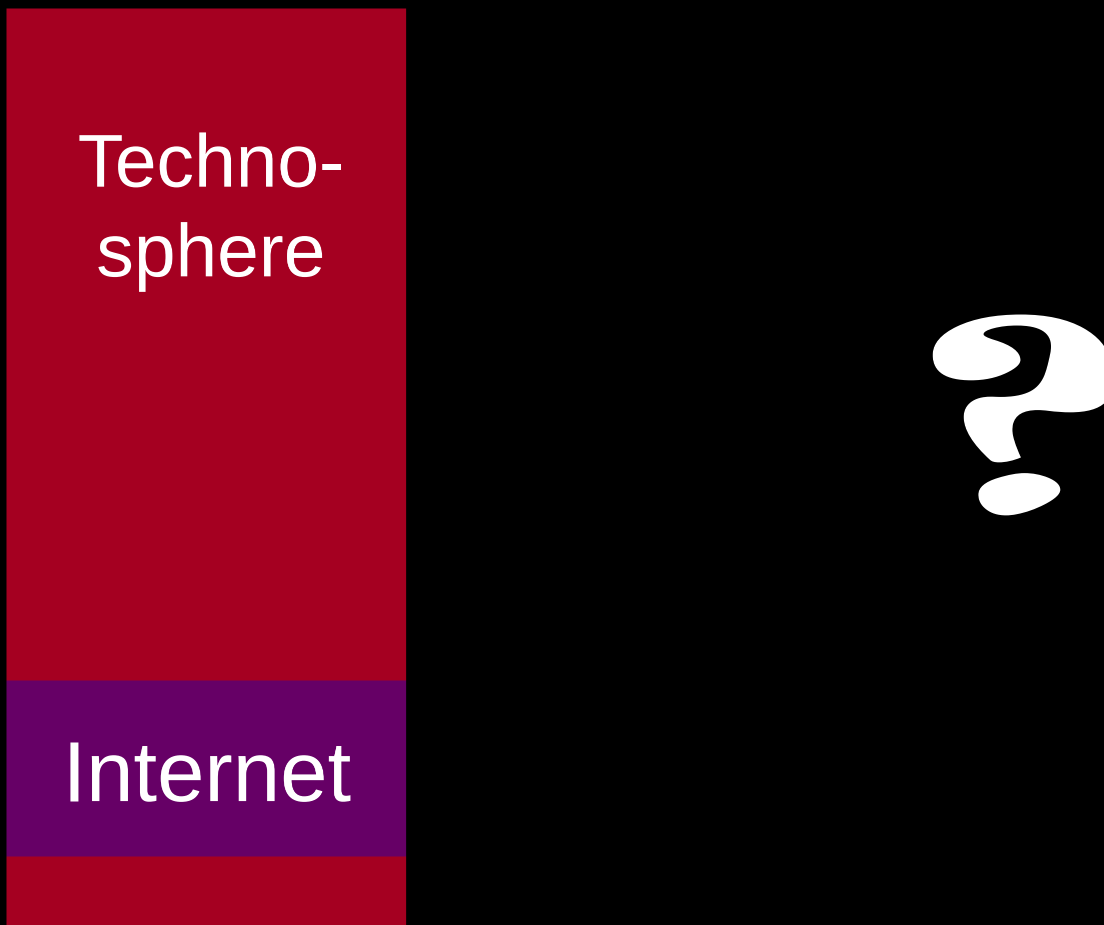
	Traffic	Topology	C&D	Layering	Architect.
Cartoon					
Data/stat					
Mod/sim					
Analysis					
Synthesis					

Recent progress (1995-)

	Traffic	Topology	C&D	Layering	Architect.
Cartoon					
Data/stat					
Mod/sim					
Analysis					
Synthesis					

Two lines of research:

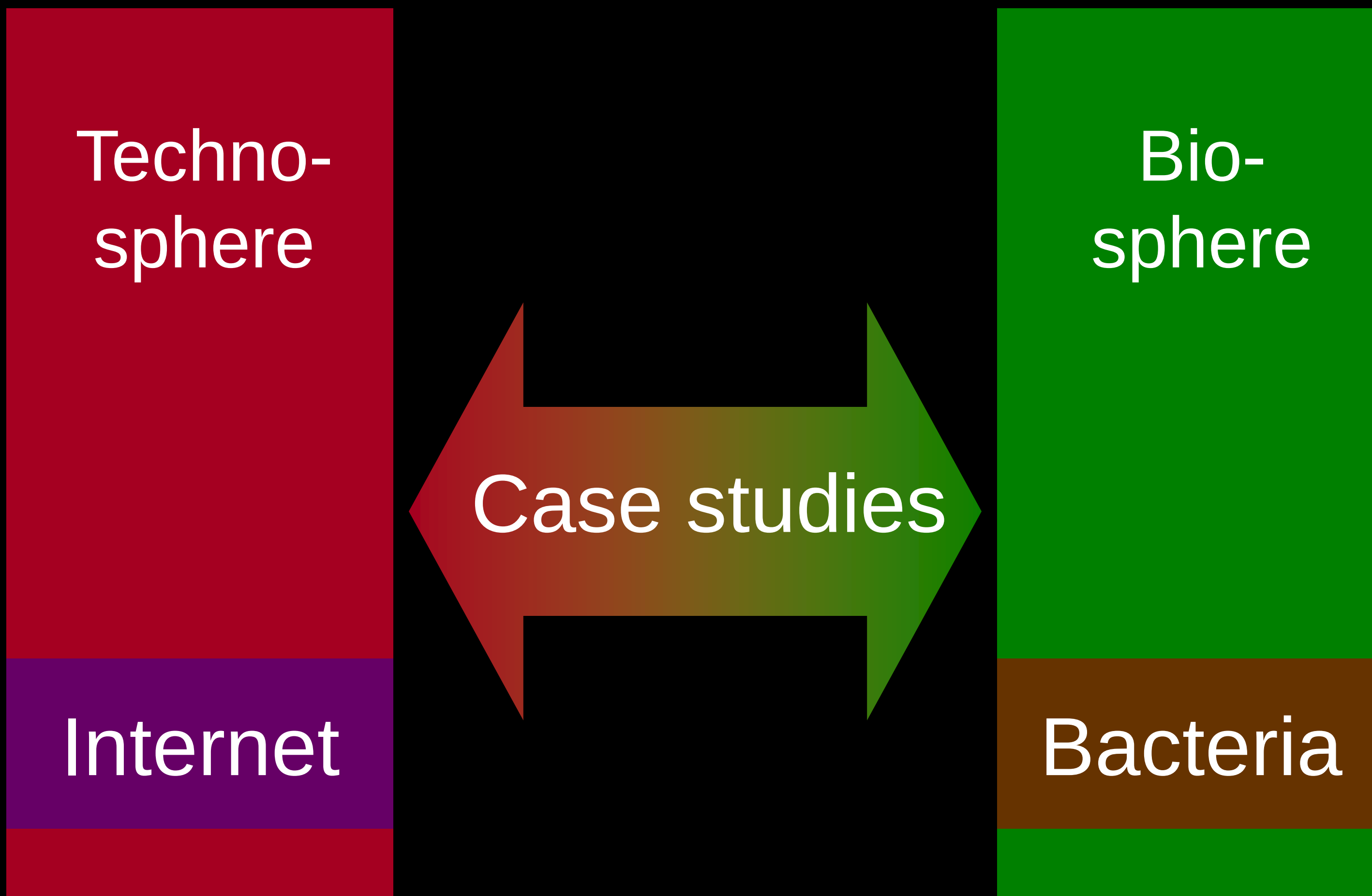
1. Patch the existing Internet architecture
2. Fundamentally rethink network architecture



Focus

	Traffic	Topology	C&D	Layering	Architect.
Cartoon					
Data/stat					?
Mod/sim					?
Analysis					?
Synthesis					?

1.
2. Fundamentally rethink network architecture



Biology versus the Internet

Similarities

- Evolvable architecture
- Robust yet fragile
- Constraints/deconstrain
- Layering, modularity
- Hourglass with bowties
- Feedback
- Dynamic, stochastic
- Distributed/decentralized
- ***Not*** scale-free, edge-of-chaos, self-organized criticality, etc

Differences

- Metabolism
- Materials and energy
- Autocatalytic feedback
- Feedback complexity
- Development and regeneration
- >4B years of evolution
- How the parts work?

Biology versus the Internet

Similarities

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- **Materials and energy**
- Autocatalytic feedback
- Feedback complexity
- Development and regeneration
- >4B years of evolution

Focus on
bacterial biosphere

In the real (vs virtual) world

What matters:

- Action

What doesn't:

- Data
- Information
- Computation
- Learning
- Decision
- …

Biology versus the Internet

Similarities

- Evolvable architecture
- **Robust yet fragile**
- **Constraints/deconstrain**
- **Layering, modularity**
- **Hourglass with bowties**
- Feedback
- Dynamics
- Distributed/decentralized
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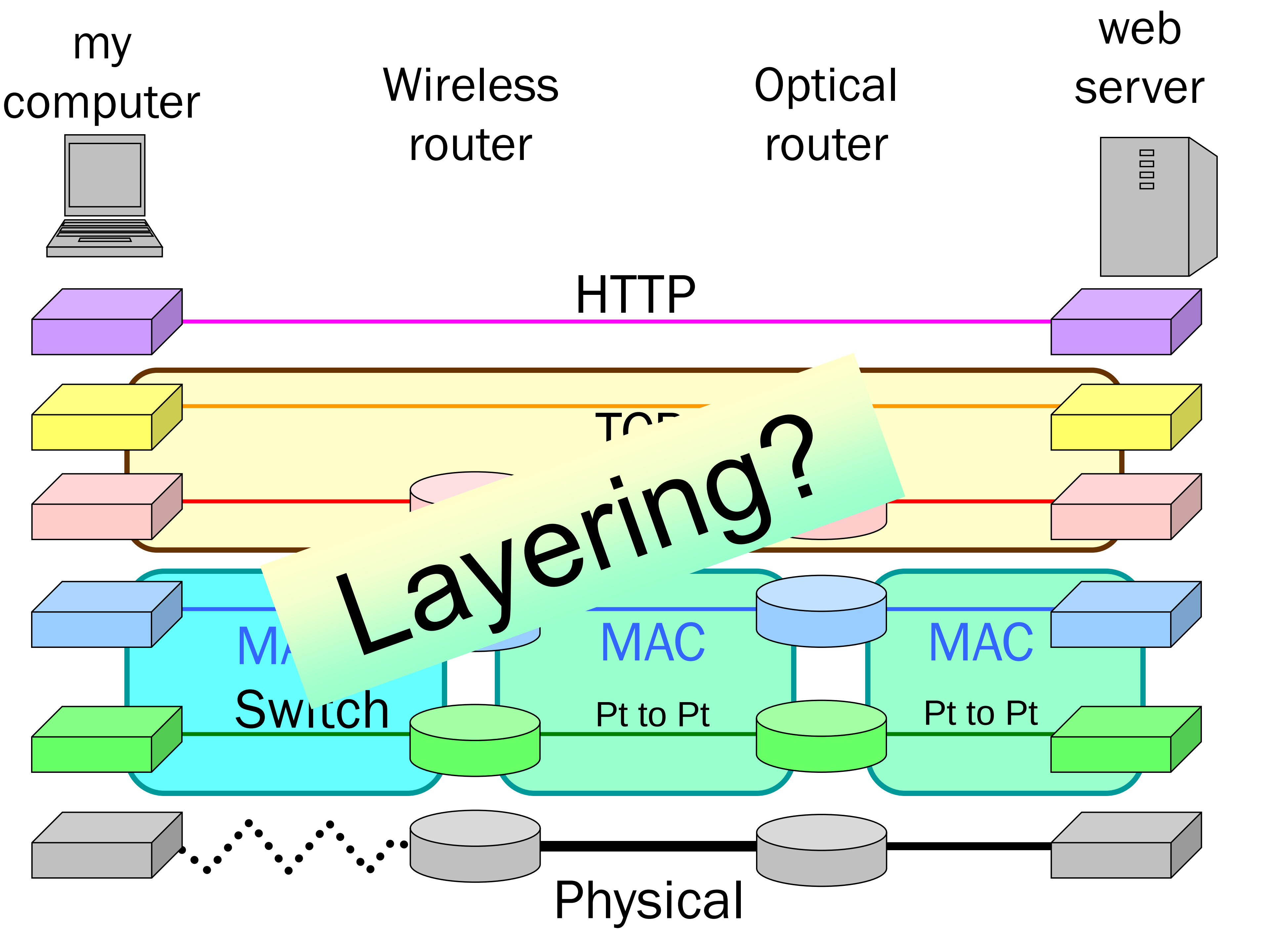
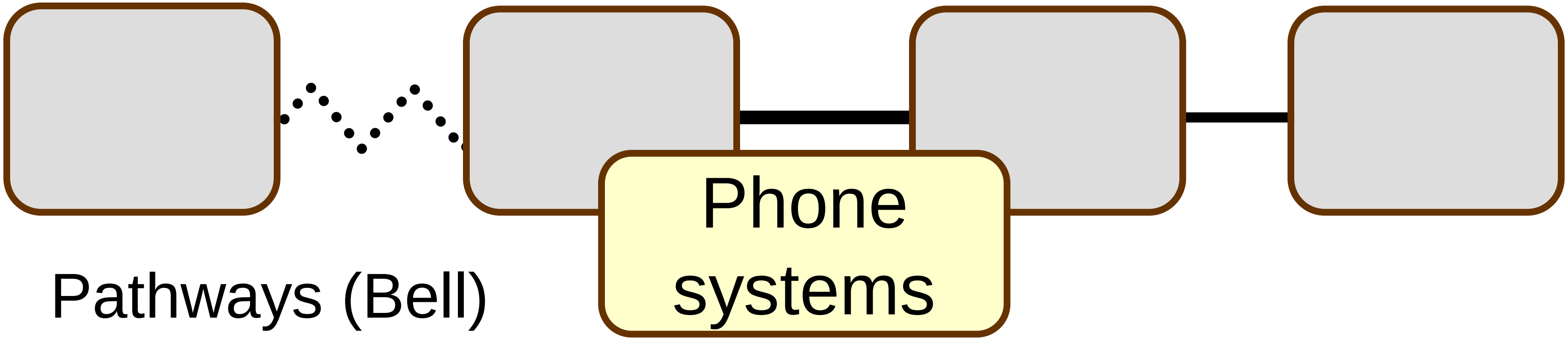
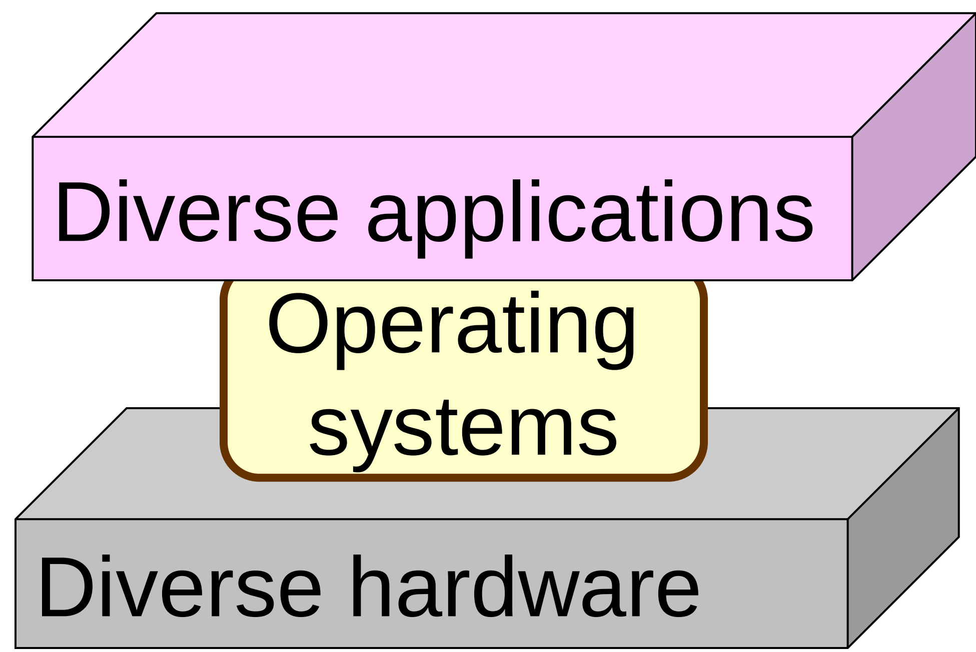
Focus on
bacterial biosphere


my computer
Wireless router
Optical router
web server
HTTP
TCP
MAC
Switch
MAC
Pt to Pt
MAC
Pt to Pt
Physical
Layering?

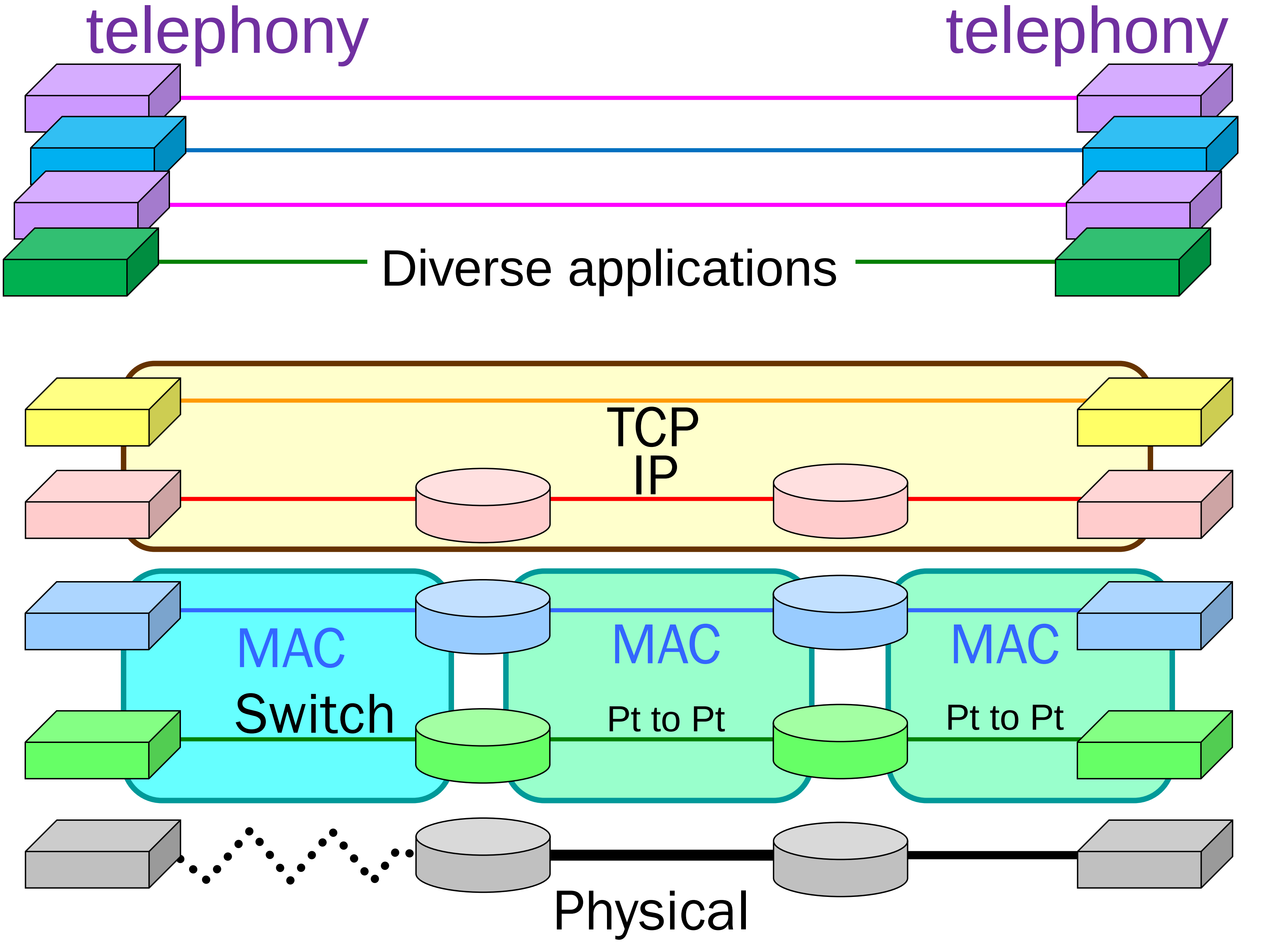


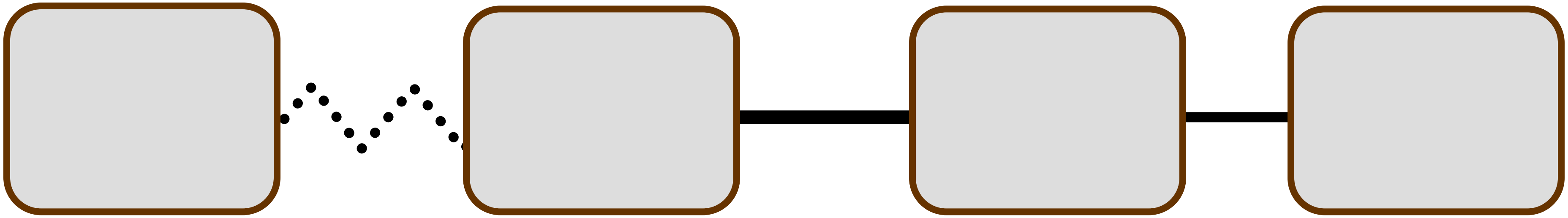
Pathways (Bell)
Communications

Layers (Net)
Computer

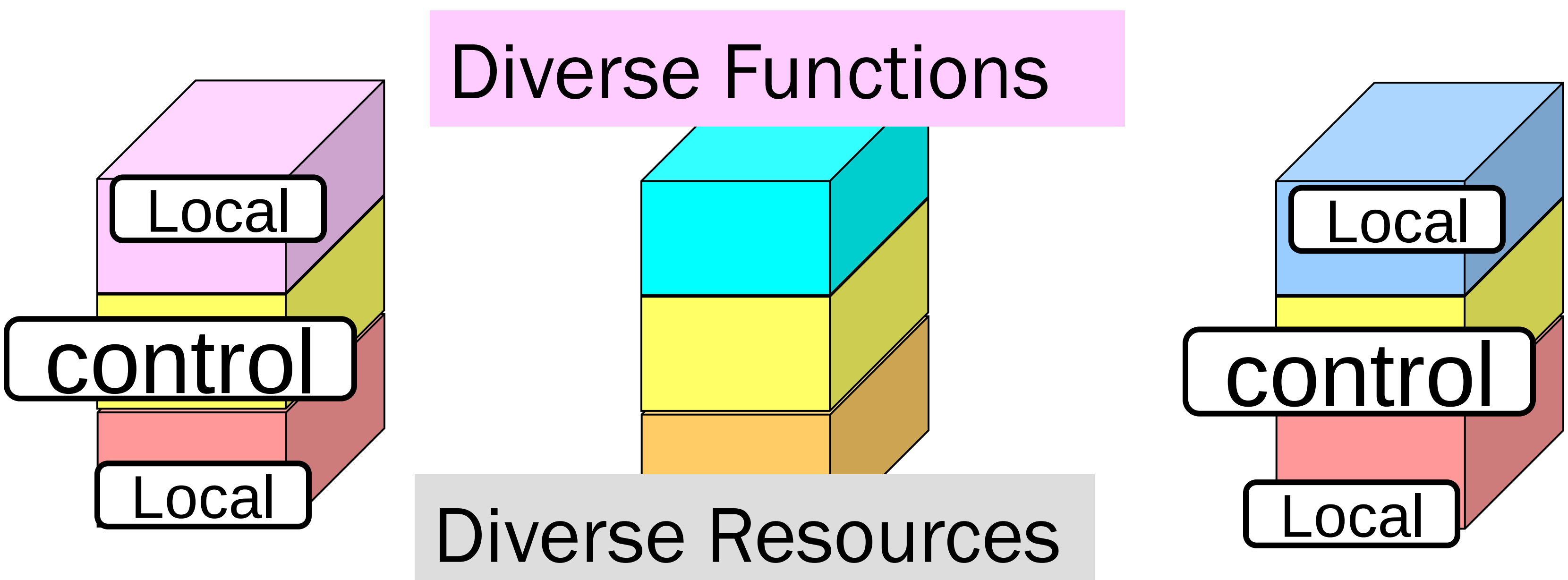


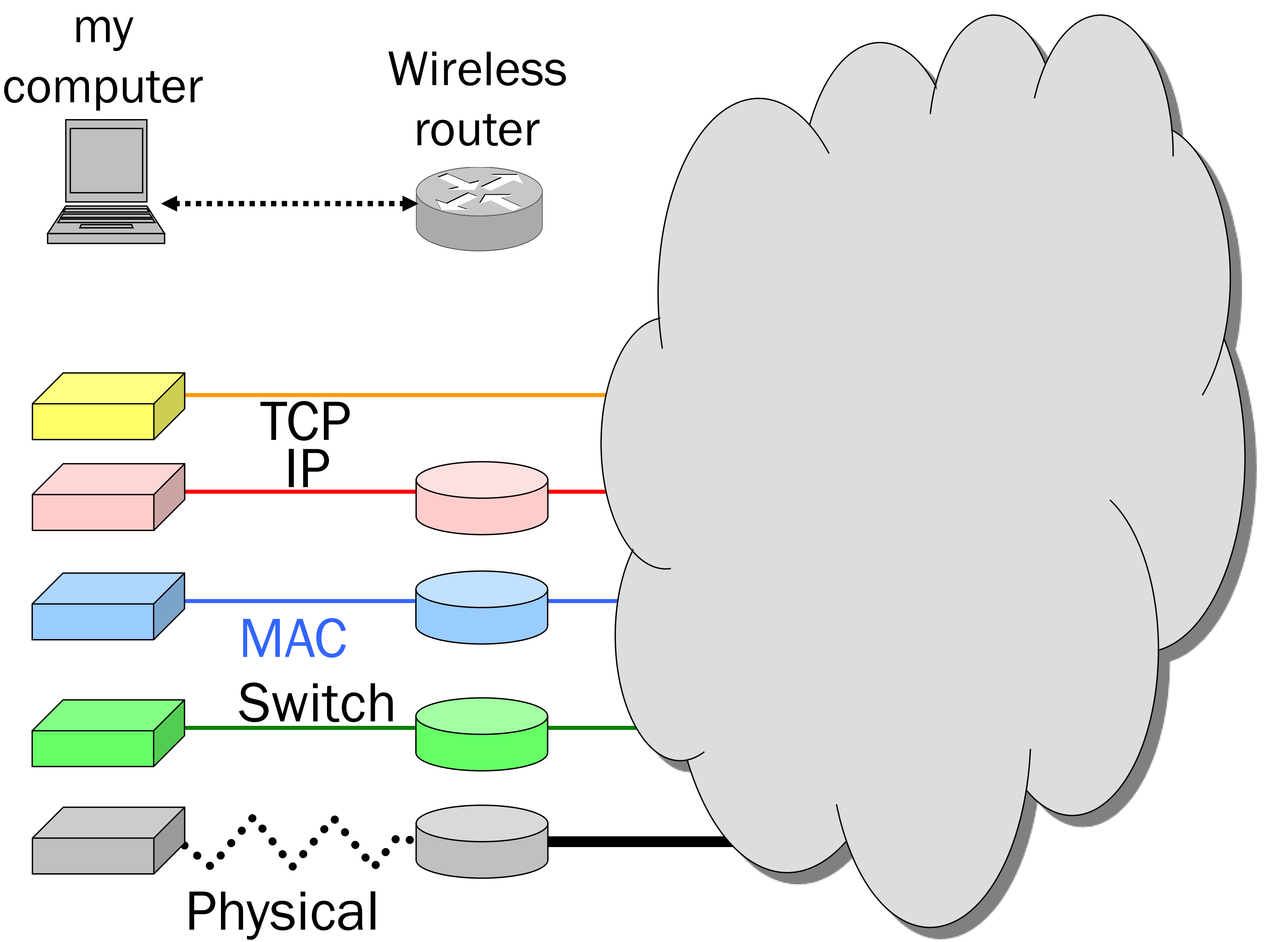
Ancient network architecture:
“Bell-heads versus Net-heads”

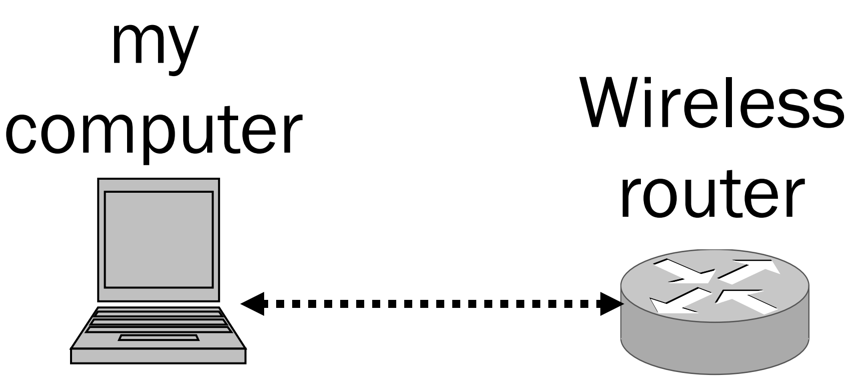

telephony
telephony
Diverse applications
TCP
IP
MAC
Switch
MAC
Pt to Pt
MAC
Pt to Pt
Physical



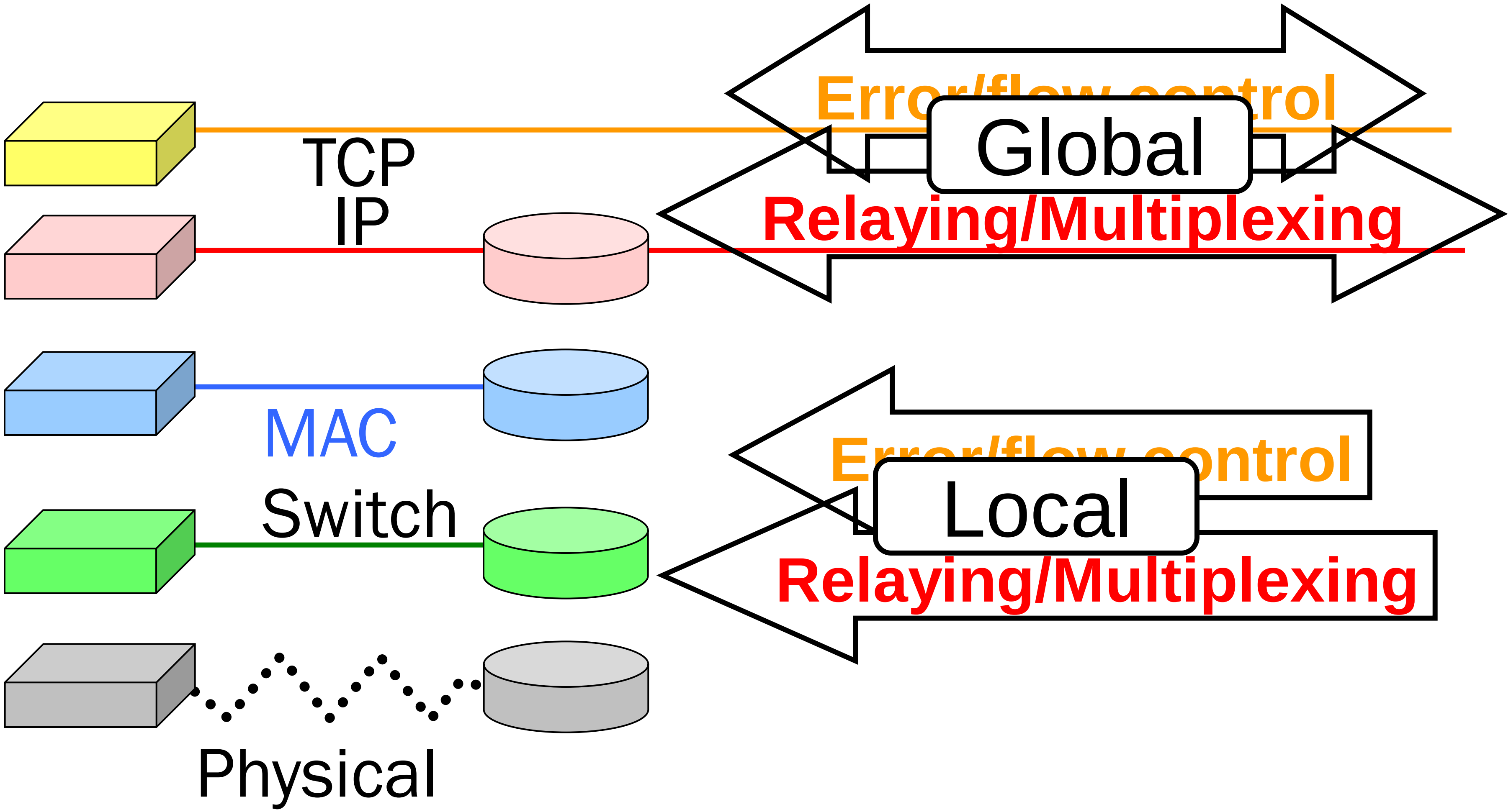
Non-networked Systems



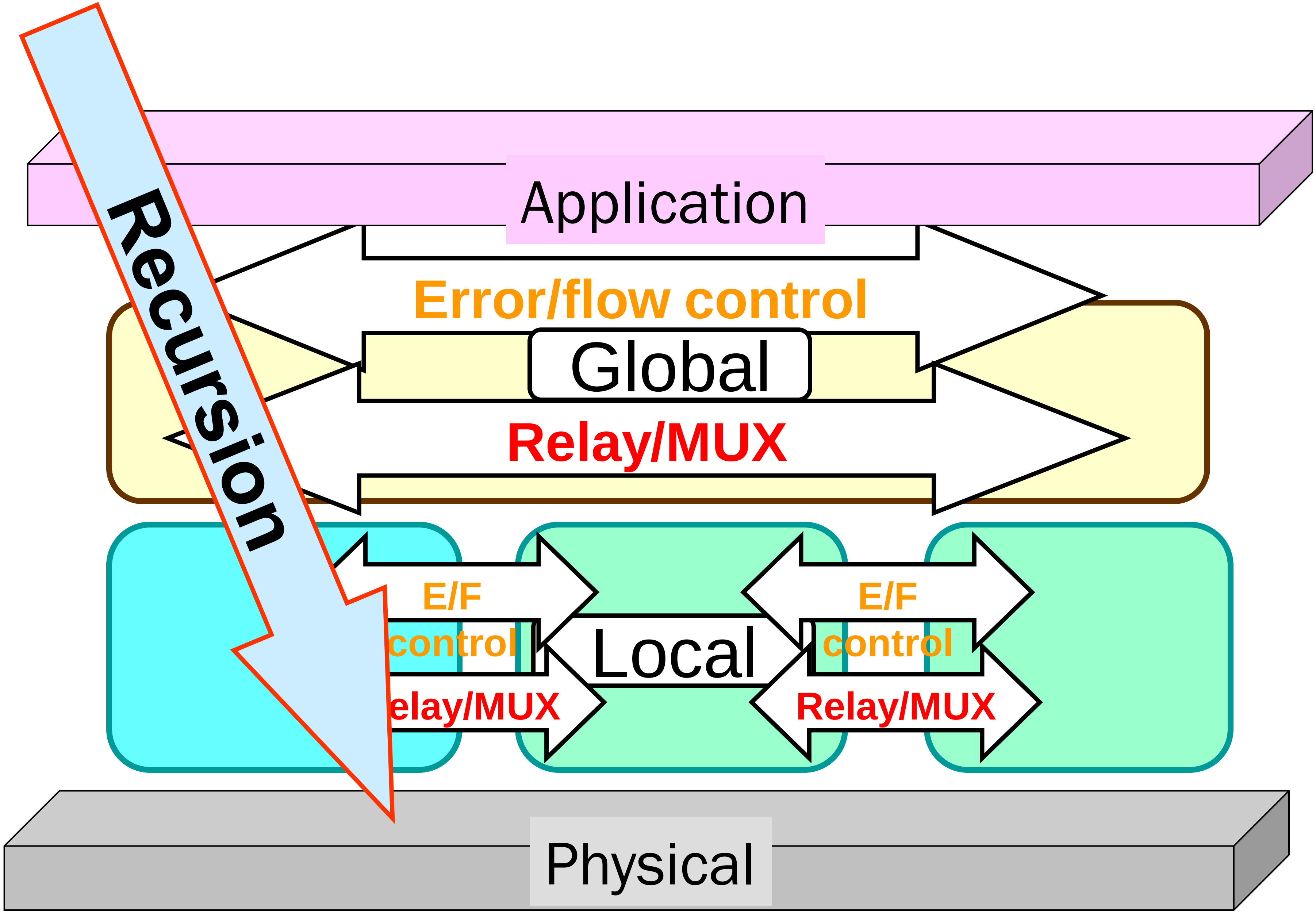

my
computer
Wireless
router
TCP
IP
MAC
Switch
Physical



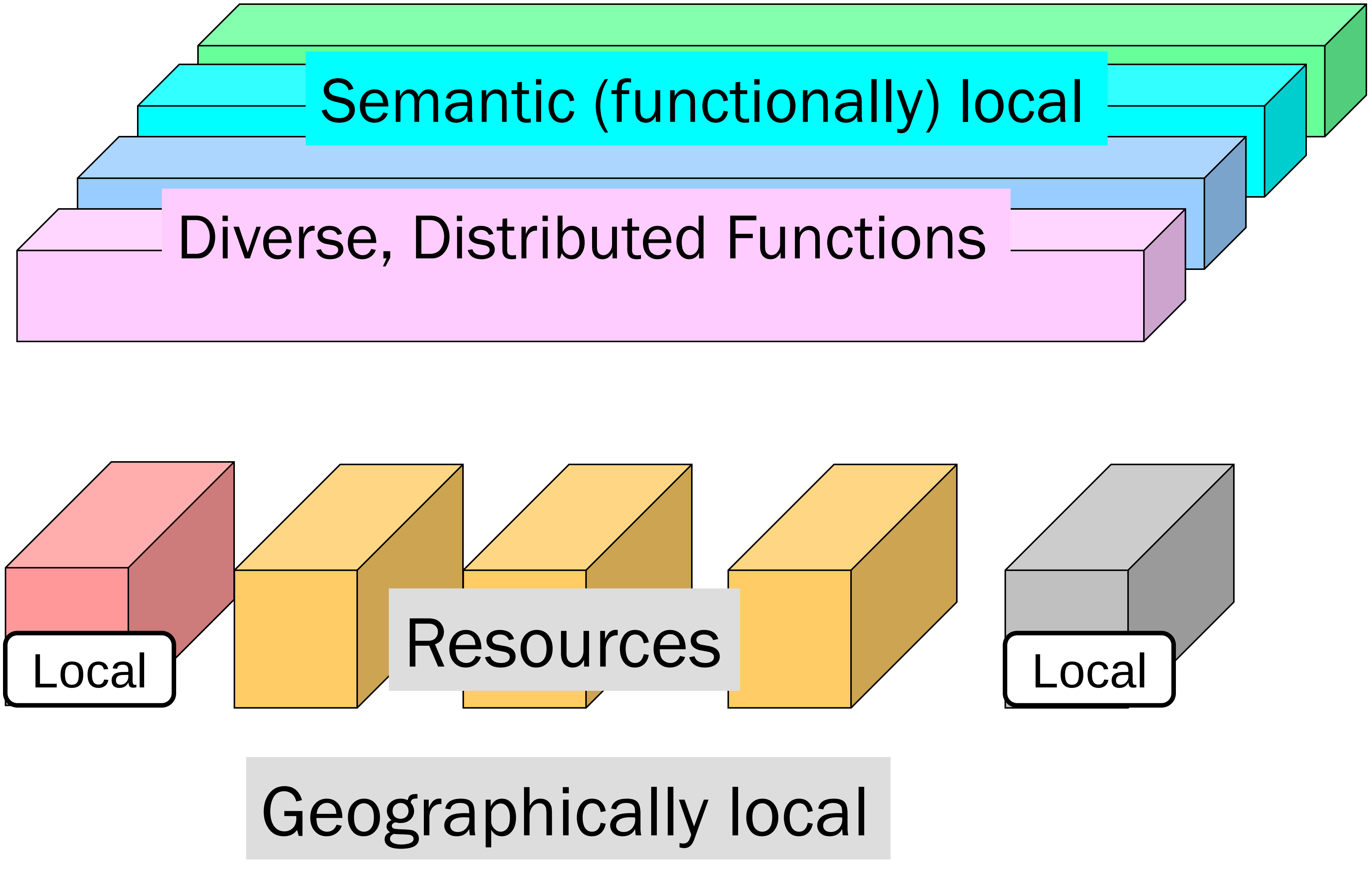
Differ in
- Details
- Scope



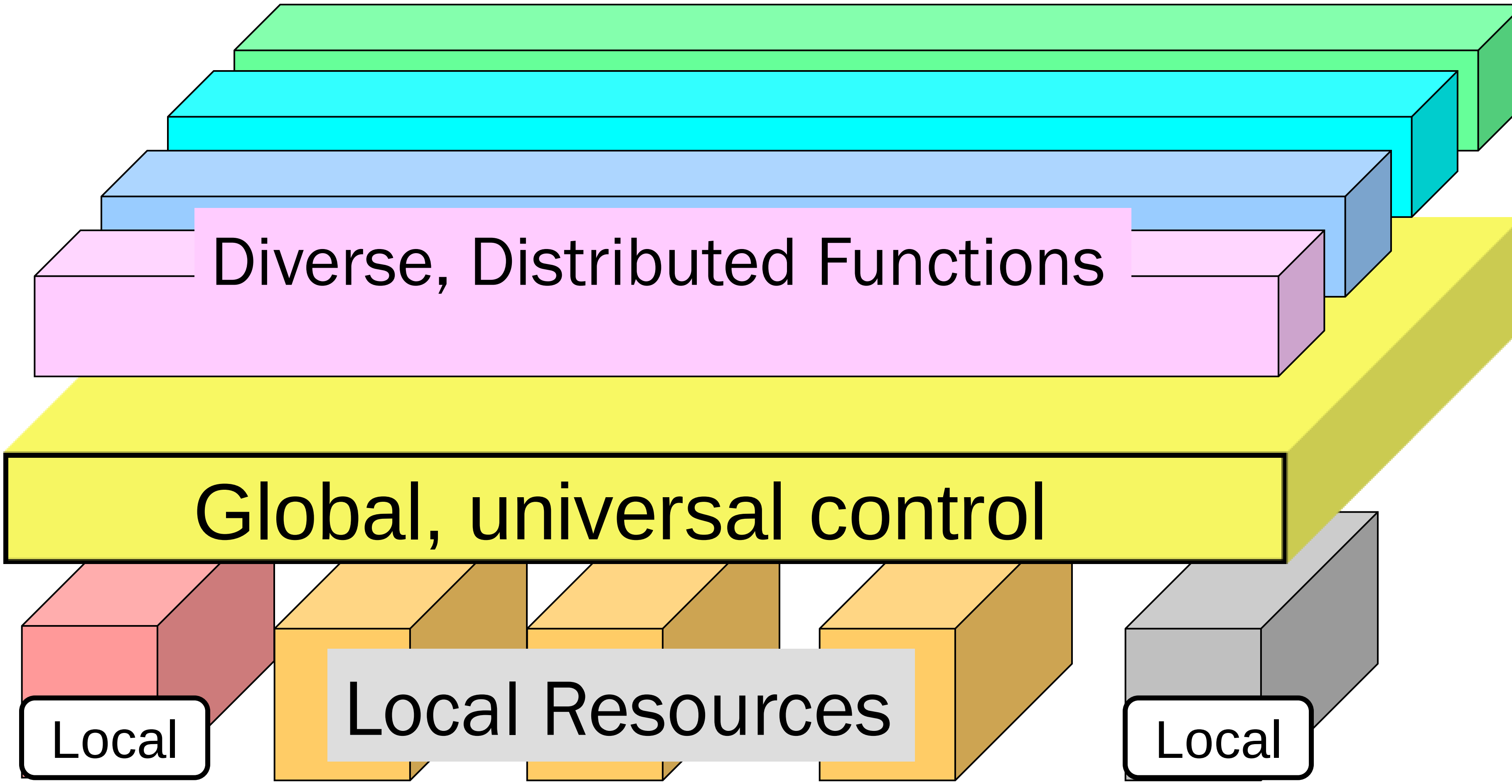
Recursive control structure



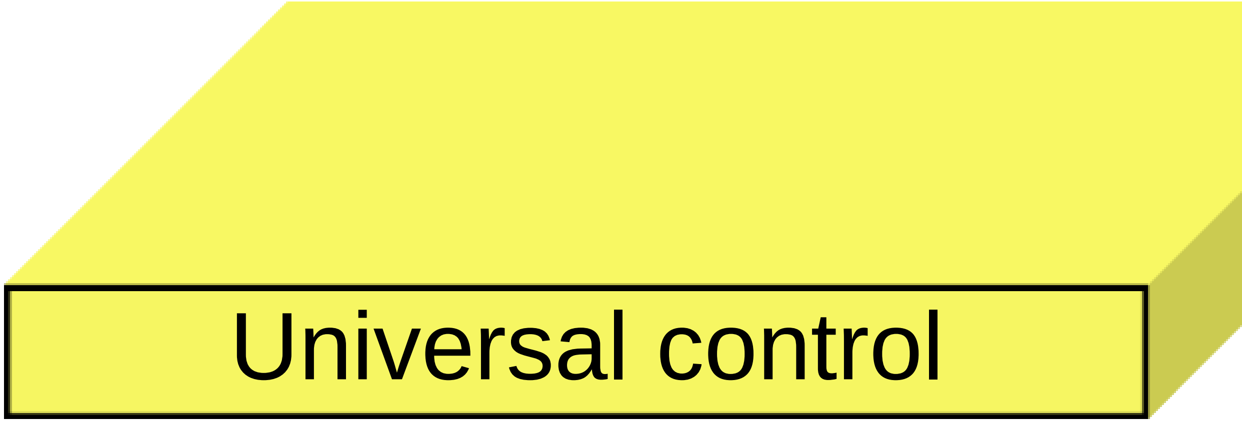
Network requirements



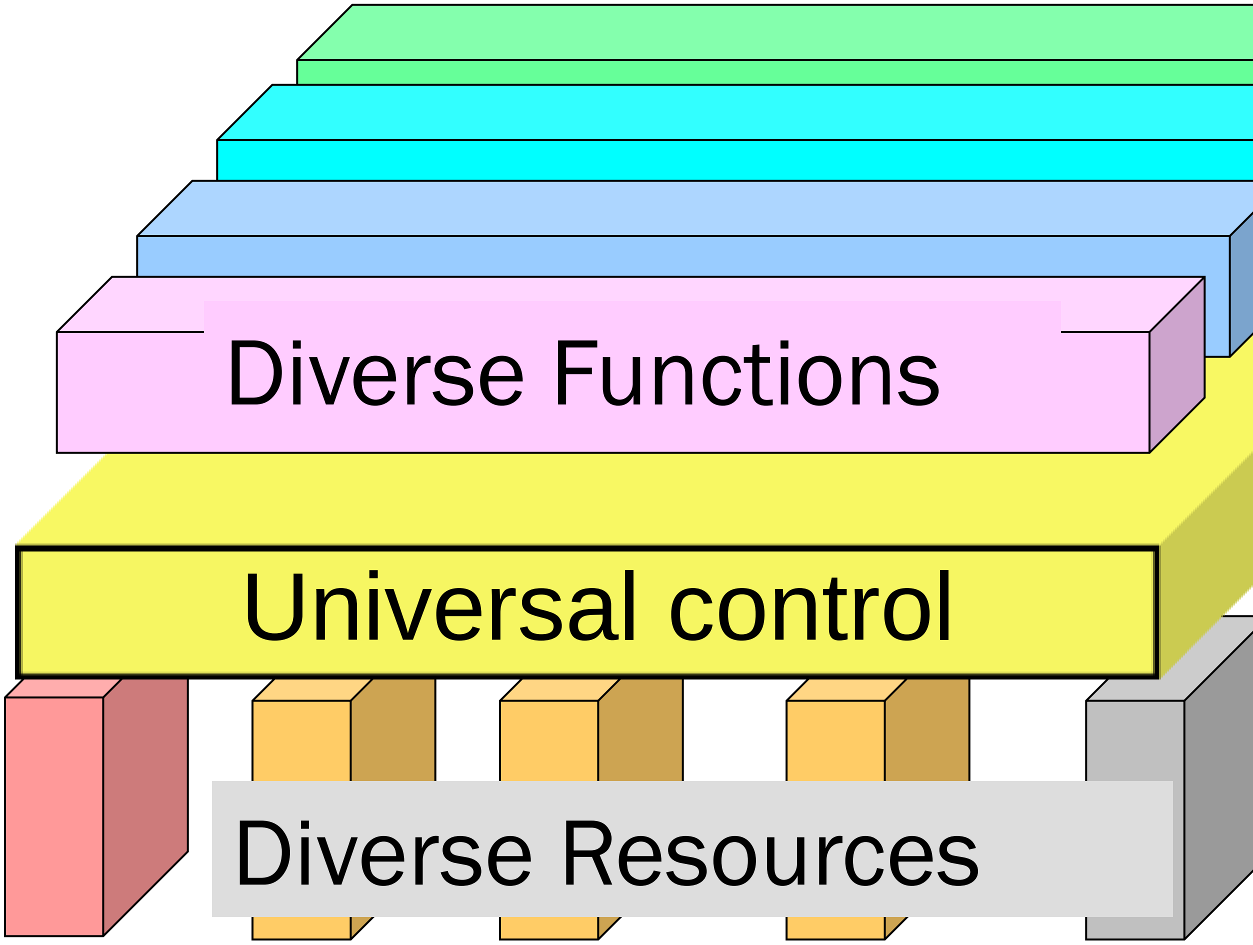
Layered solution



Constraints

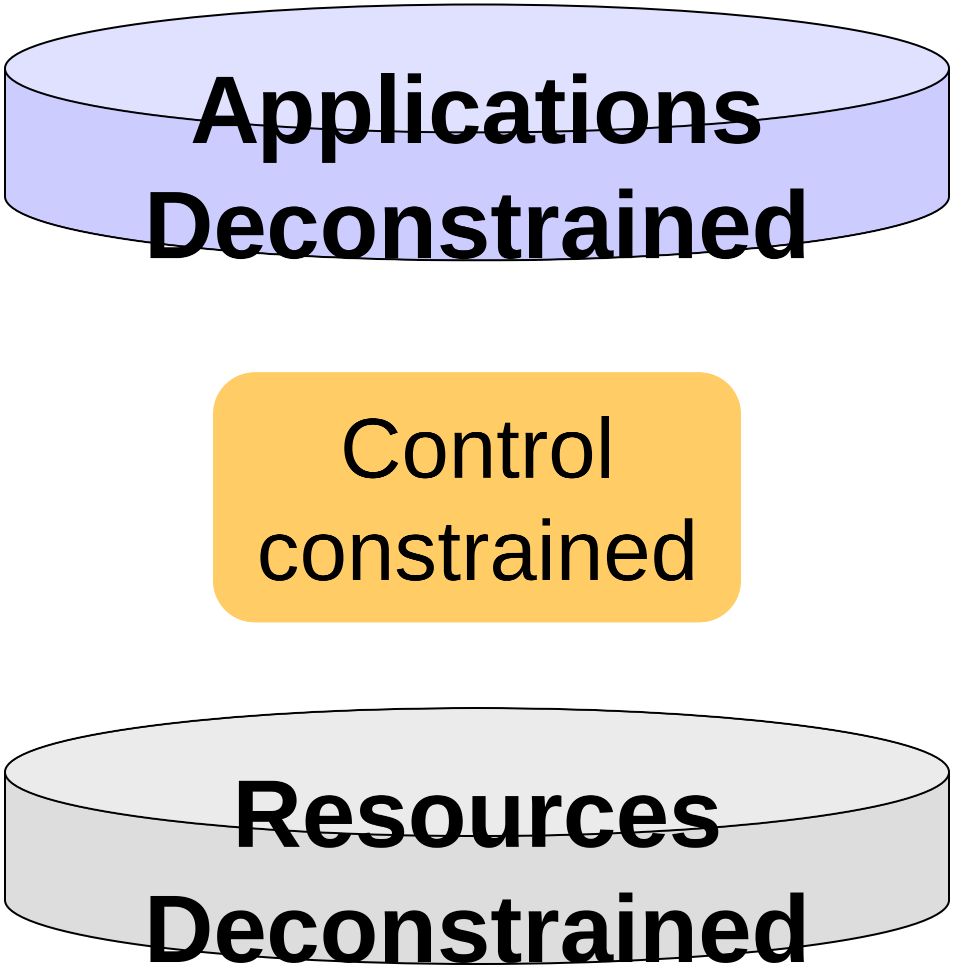


That deconstrain



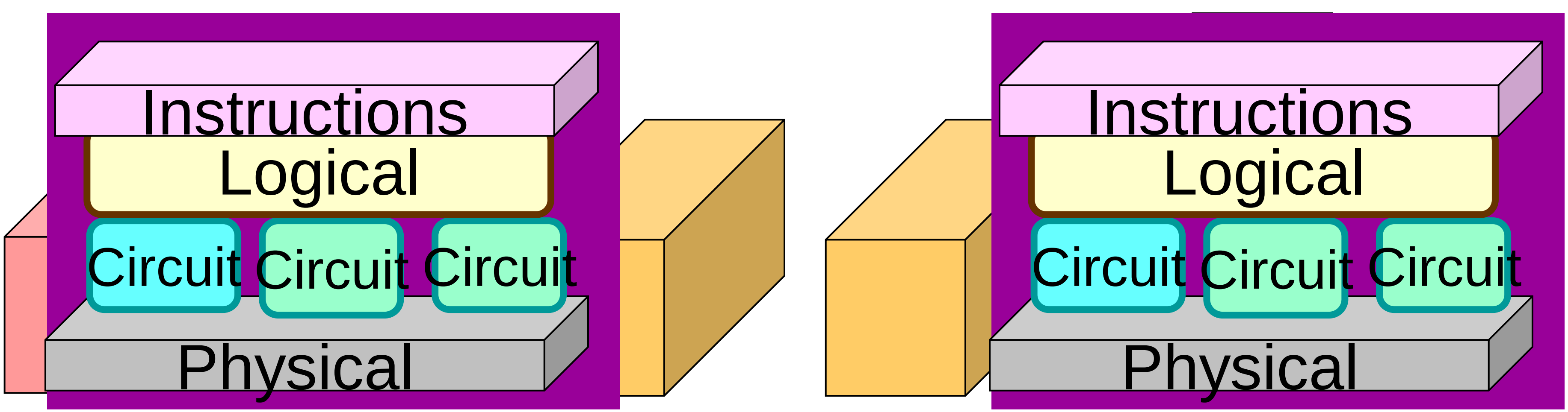
Constraints

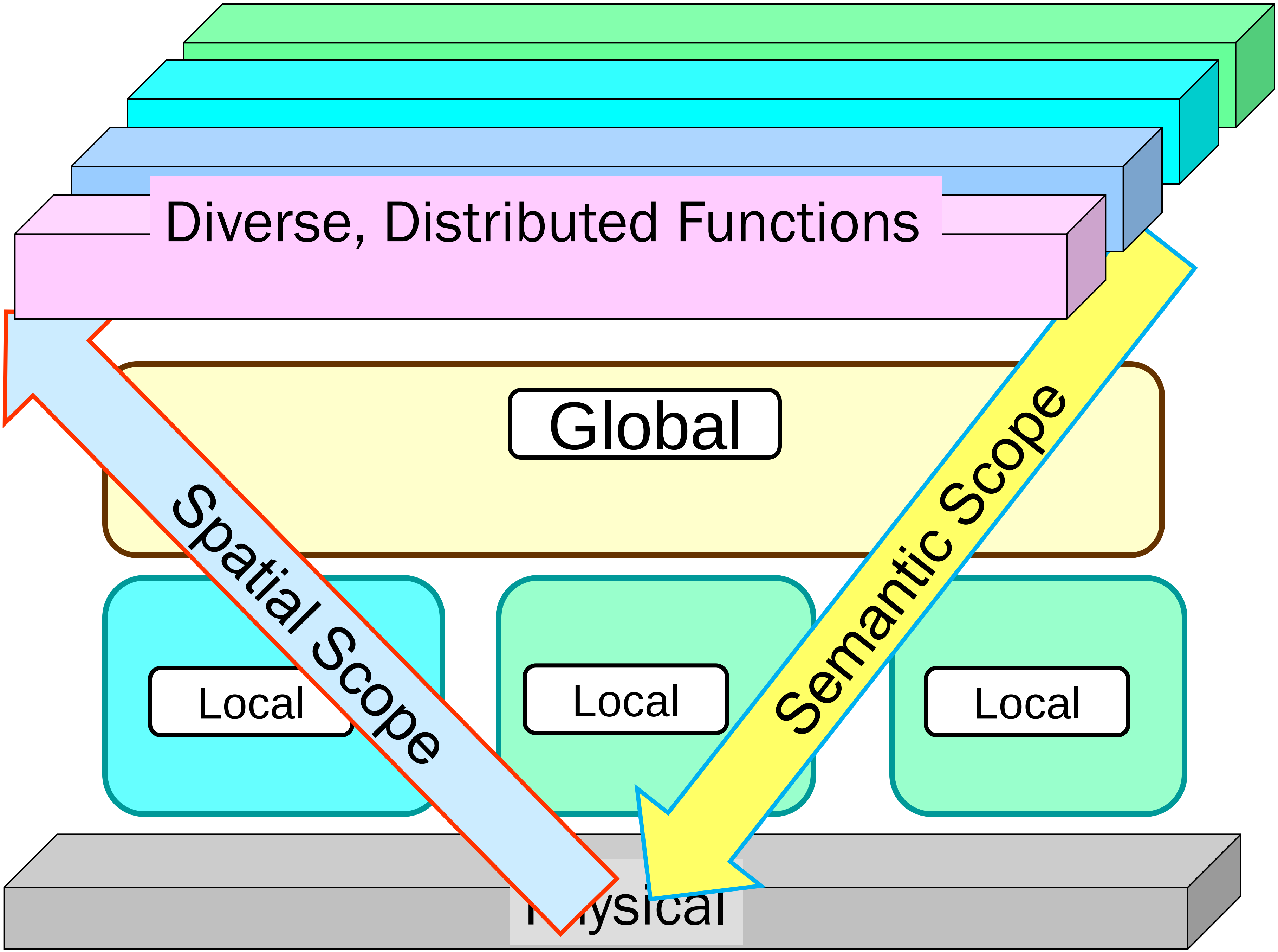
That deconstrain

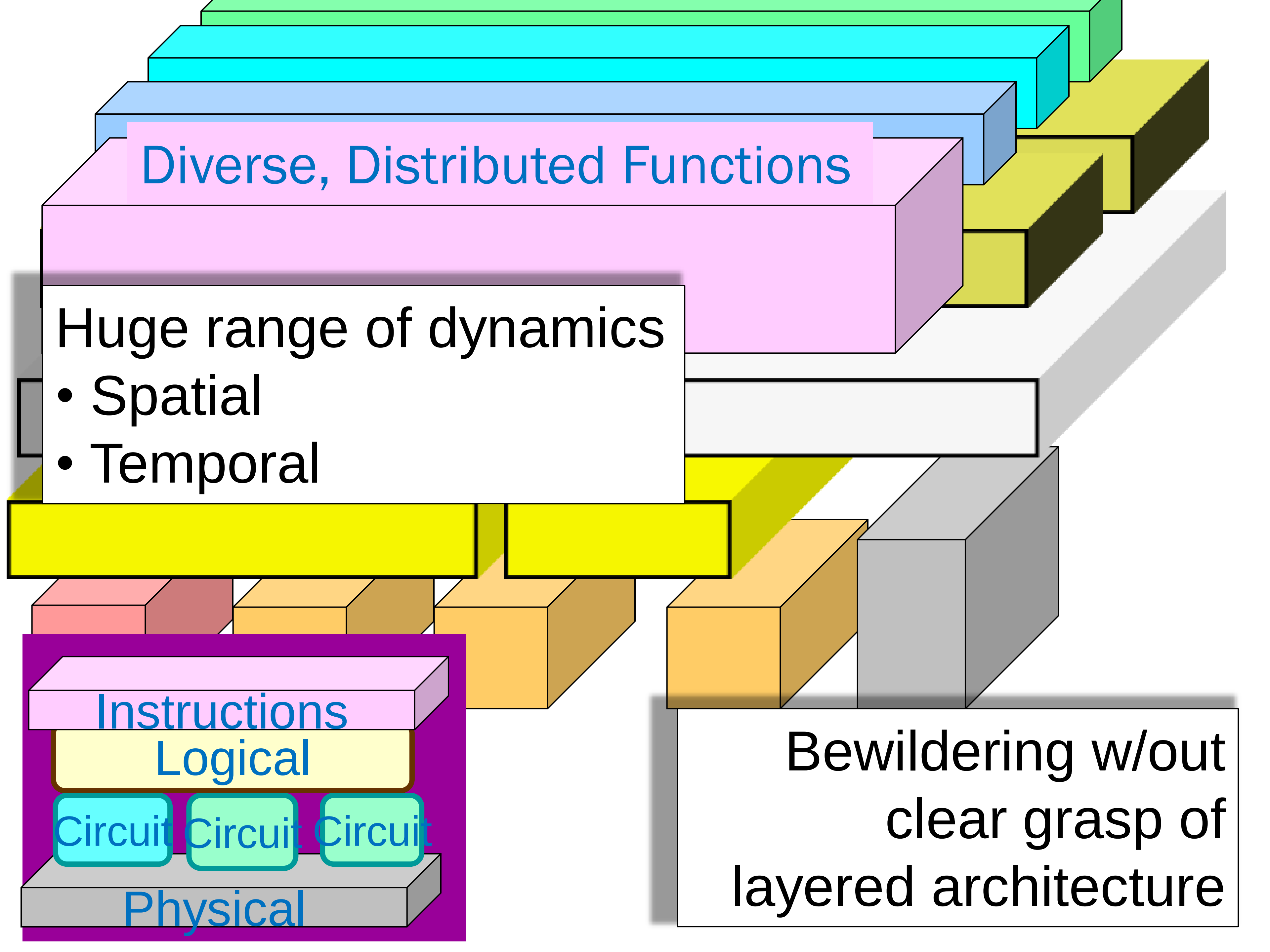


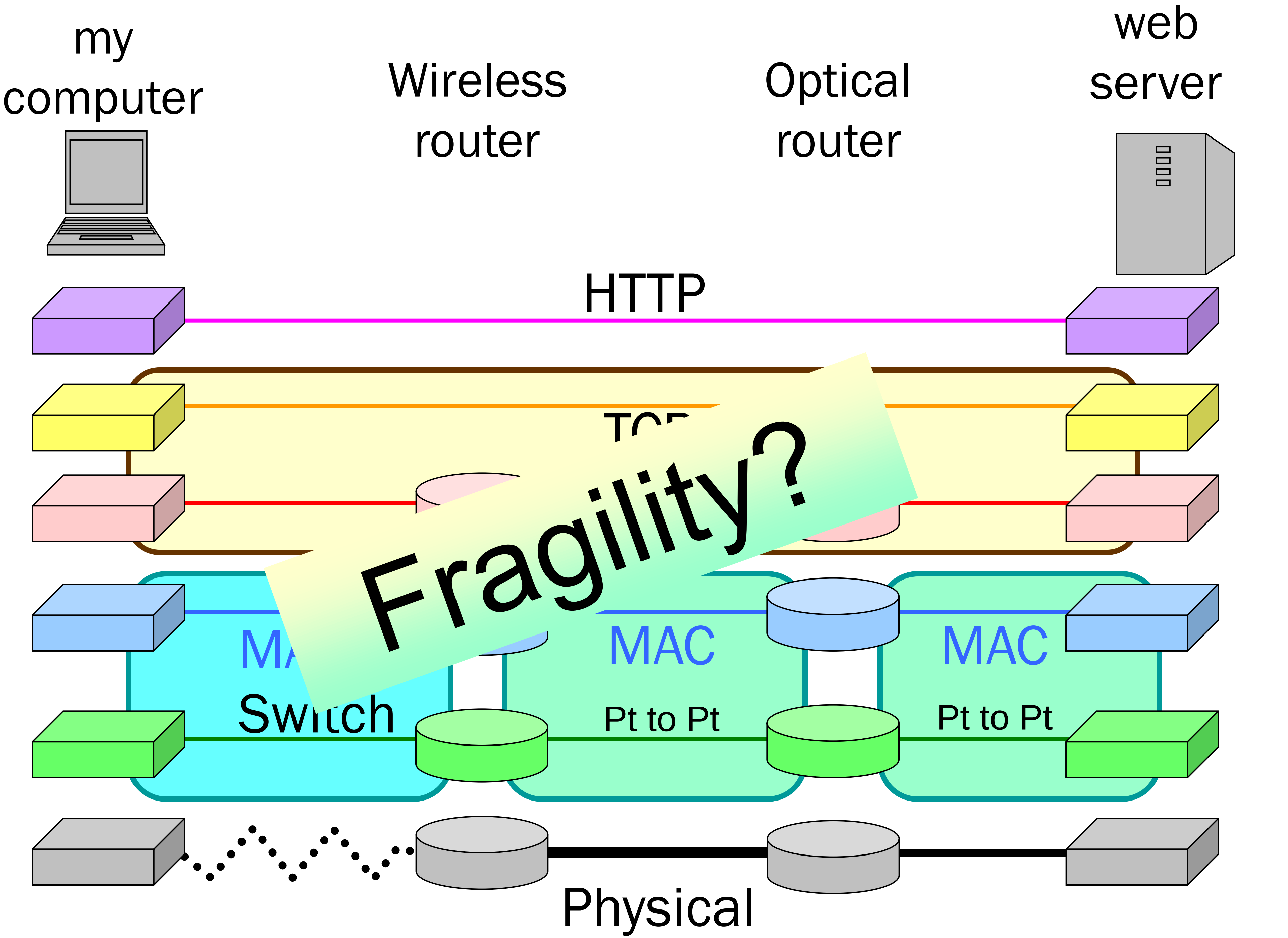
Constraints that deconstrain

And layers have sublayers




Diverse, Distributed Functions
Global
Local
Local
Local
Spatial Scope
Semantic Scope


Diverse, Distributed Functions
Huge range of dynamics
• Spatial
• Temporal
Instructions
Logical
Circuit
Circuit
Circuit
Physical
Bewildering w/out
clear grasp of
layered architecture



my computer
Wireless router
Optical router
web server
HTTP
TCP
MAC
Switch
MAC
Pt to Pt
MAC
Pt to Pt
Physical
Fragility?

Theoretical framework:

Constraints that deconstrain

Applications Deconstrained

$$\min_{\mathbf{x}} \int \left\| R\tilde{\mathbf{x}} - \mathbf{c} \right\|^2 + \left\| R\mathbf{x} - \mathbf{c} \right\|^2 \; dt$$

$$\Big|\; \tilde{\mathbf{x}} = \arg\max_{\mathbf{v}} L \;\; \mathbf{v},\mathbf{p} \;\; , \quad \dot{\mathbf{p}} = R\mathbf{x} - \mathbf{c}$$

$$\Rightarrow x_s = \arg\max_{v} L_s \;\; v,\mathbf{p}$$

Resources Deconstrained

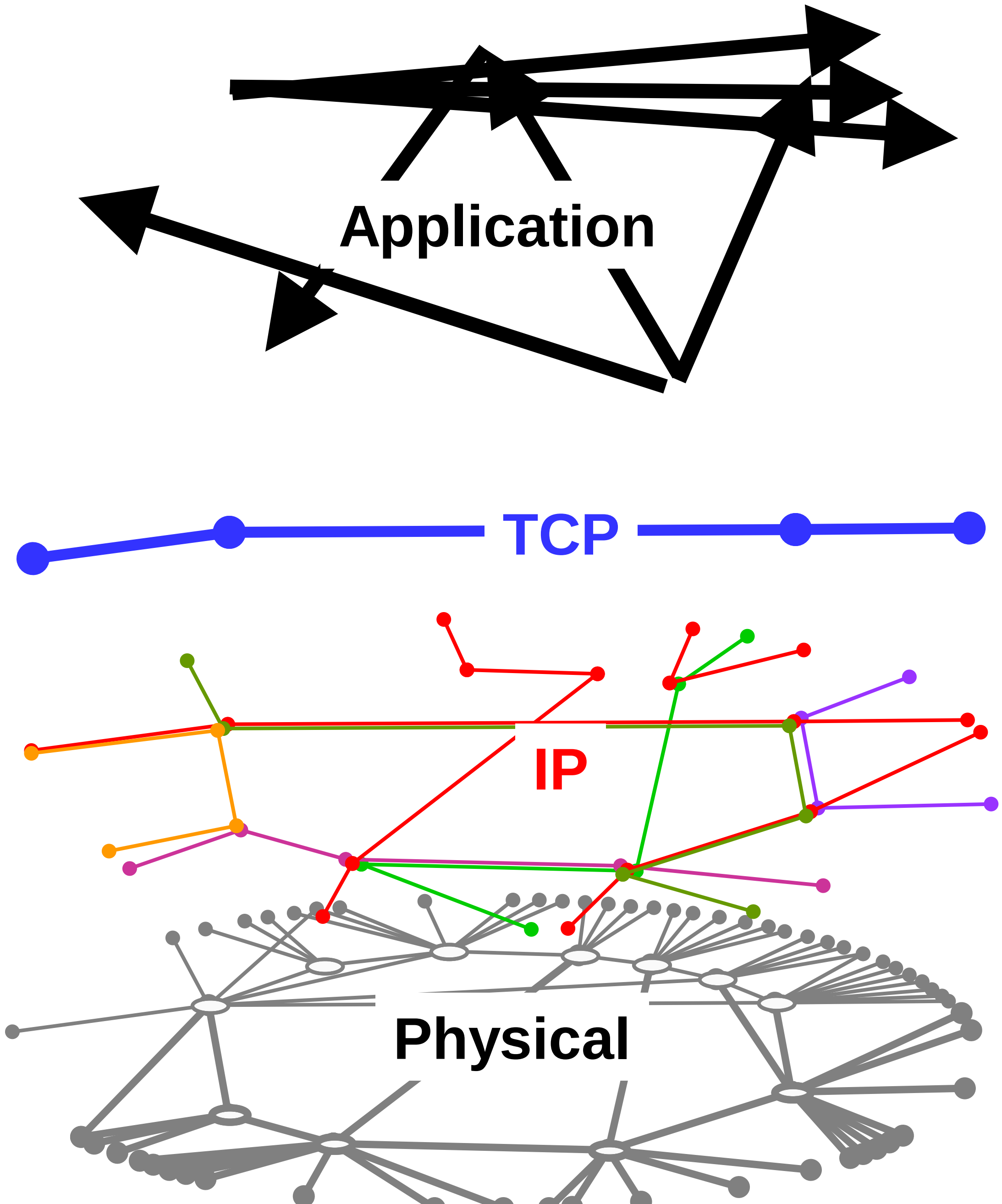
- Optimization
- Optimal control
- Robust control
- Game theory
- Network coding

Cyber-Physical Theories

- Thermodynamics
- Communications
- Control
- Computation

Homework: Reinterpret your favorite separation theorem as "layering"

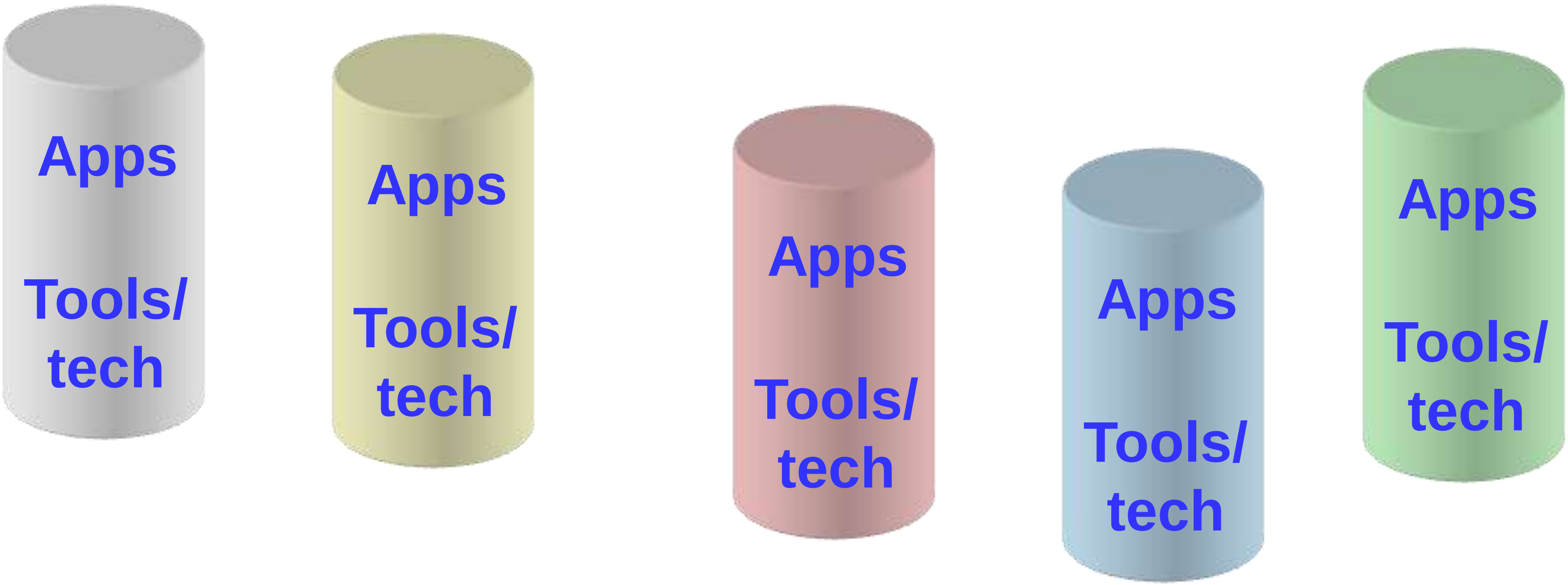
Architecture is ***not*** graph topology.

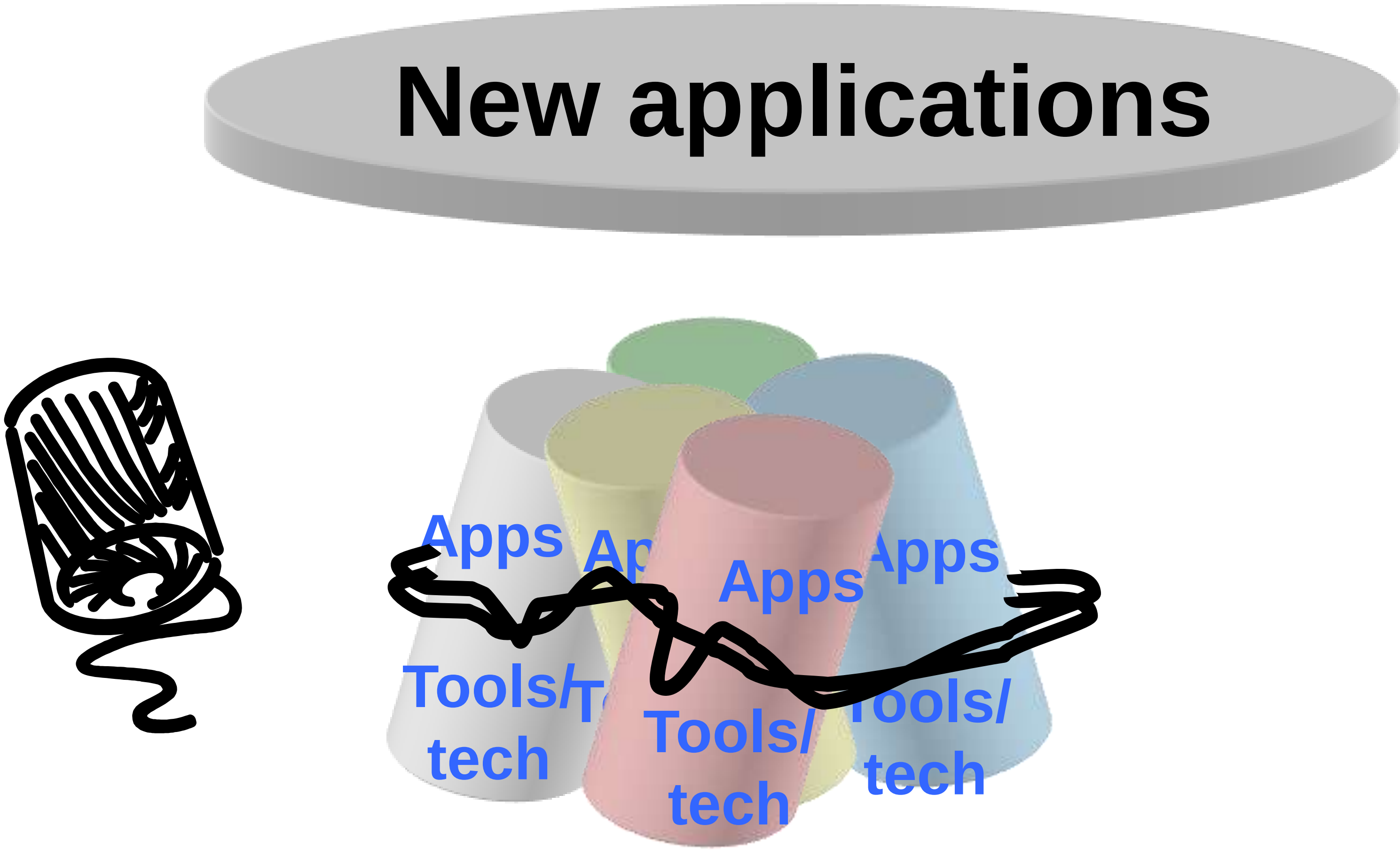


Architecture facilitates arbitrary graphs.

Academic stovepipes

EE, CS, ME, MS, APh, ChE, Bio, Geo, Eco, …

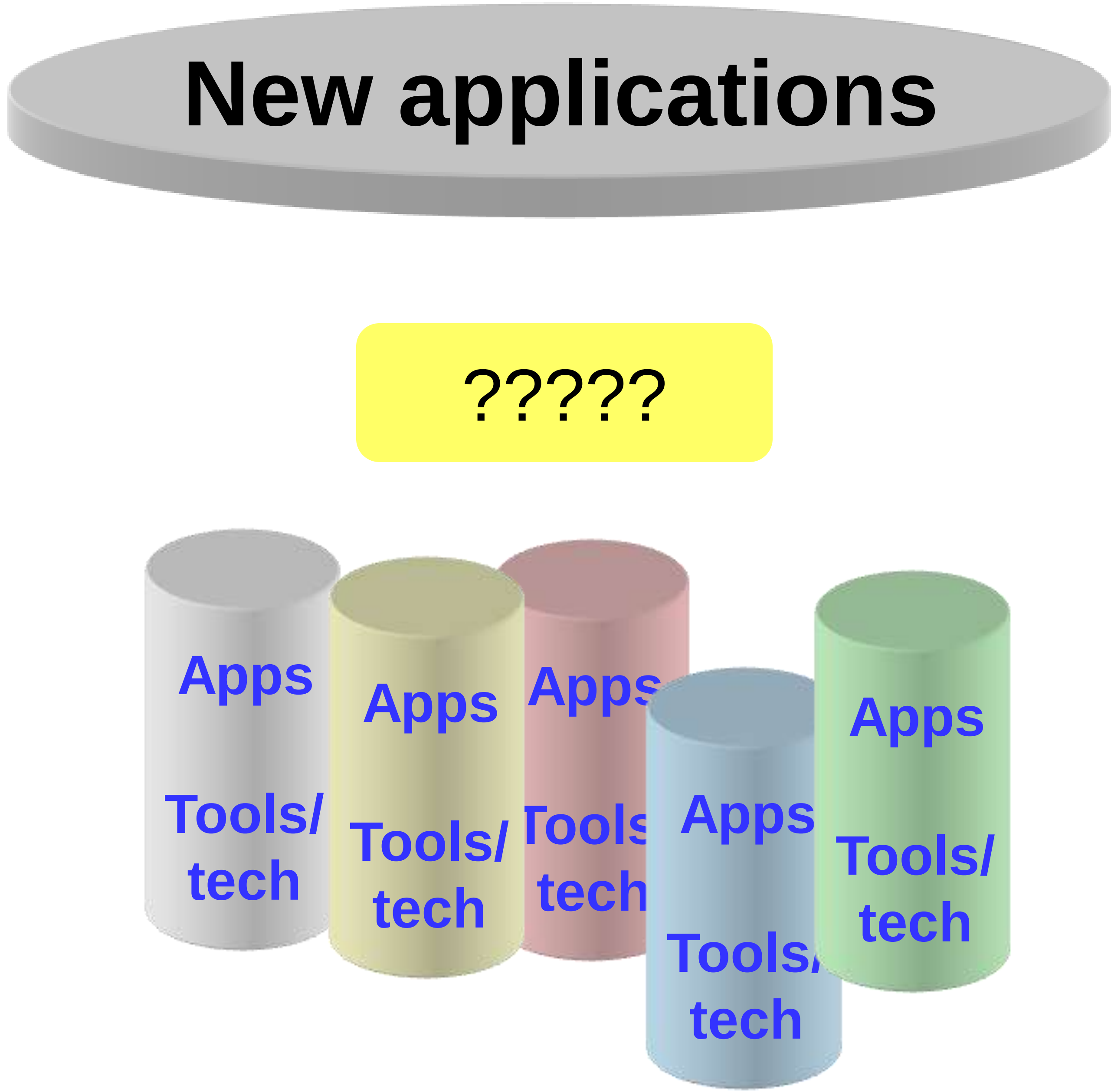




Funding twine

"Multidisciplinary cross-sterilization"

Layering academia?



Biology versus the Internet

Similarities

- Evolvable architecture
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- Constraints/deconstrain
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- Hourglass with bowties
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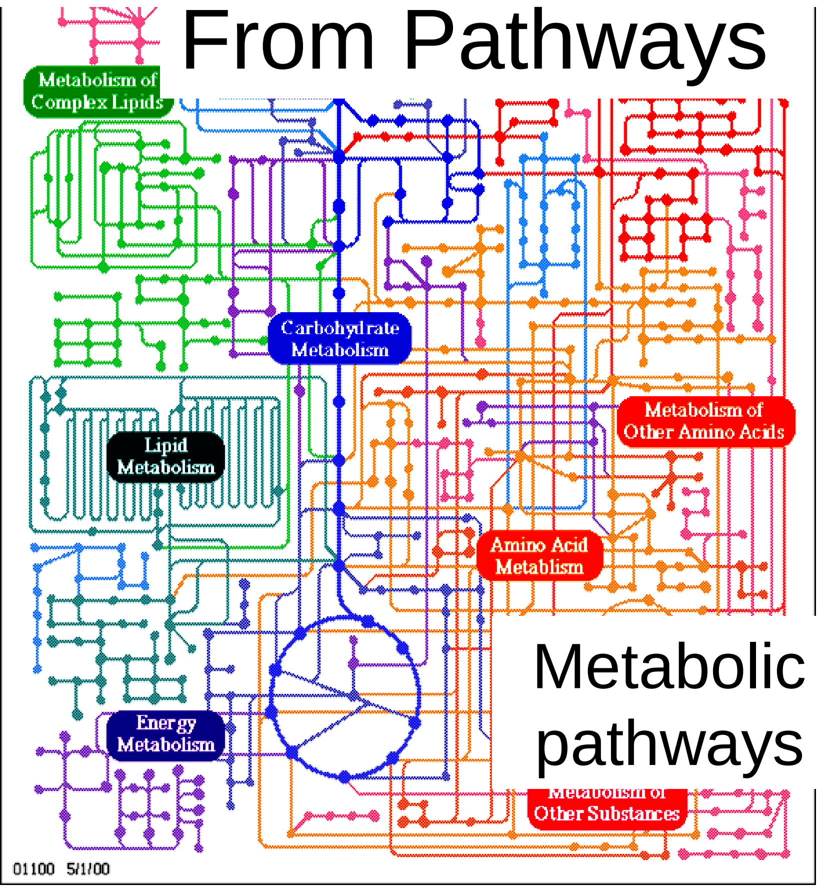
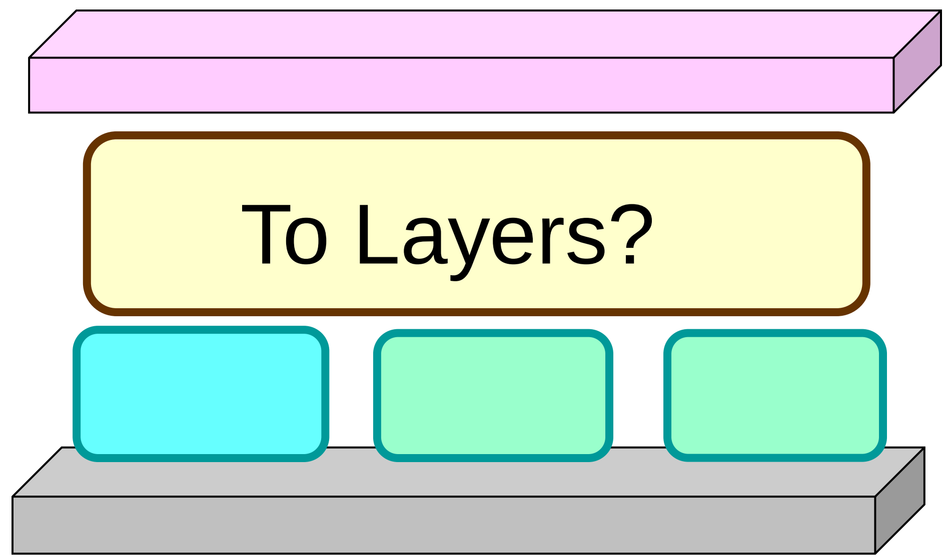
- Dynamics
- Distributed/decentralized
- *Not* scale-free, edge-of-chaos, self-organized criticality, etc

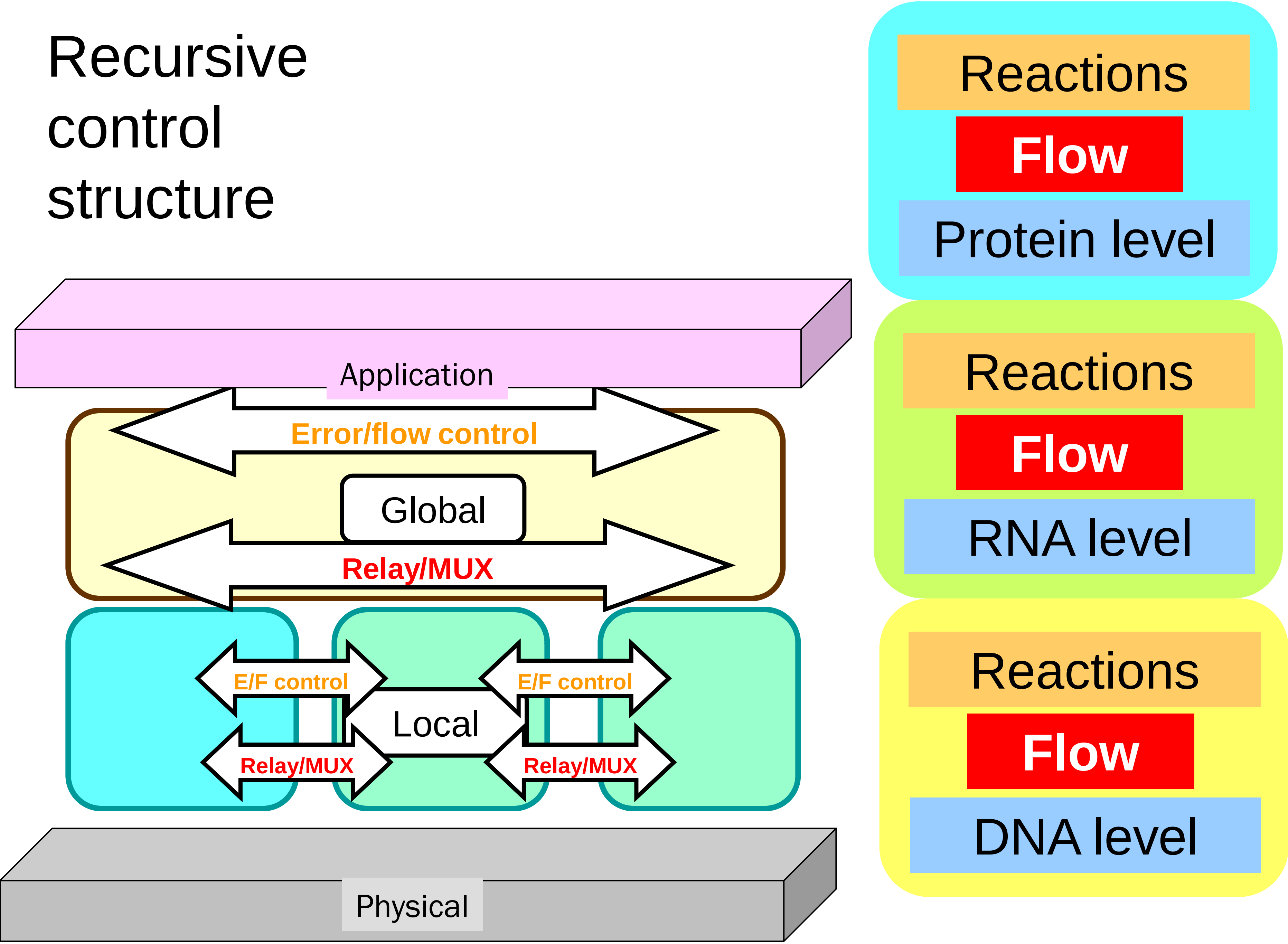
“Central dogma”

Network architecture?





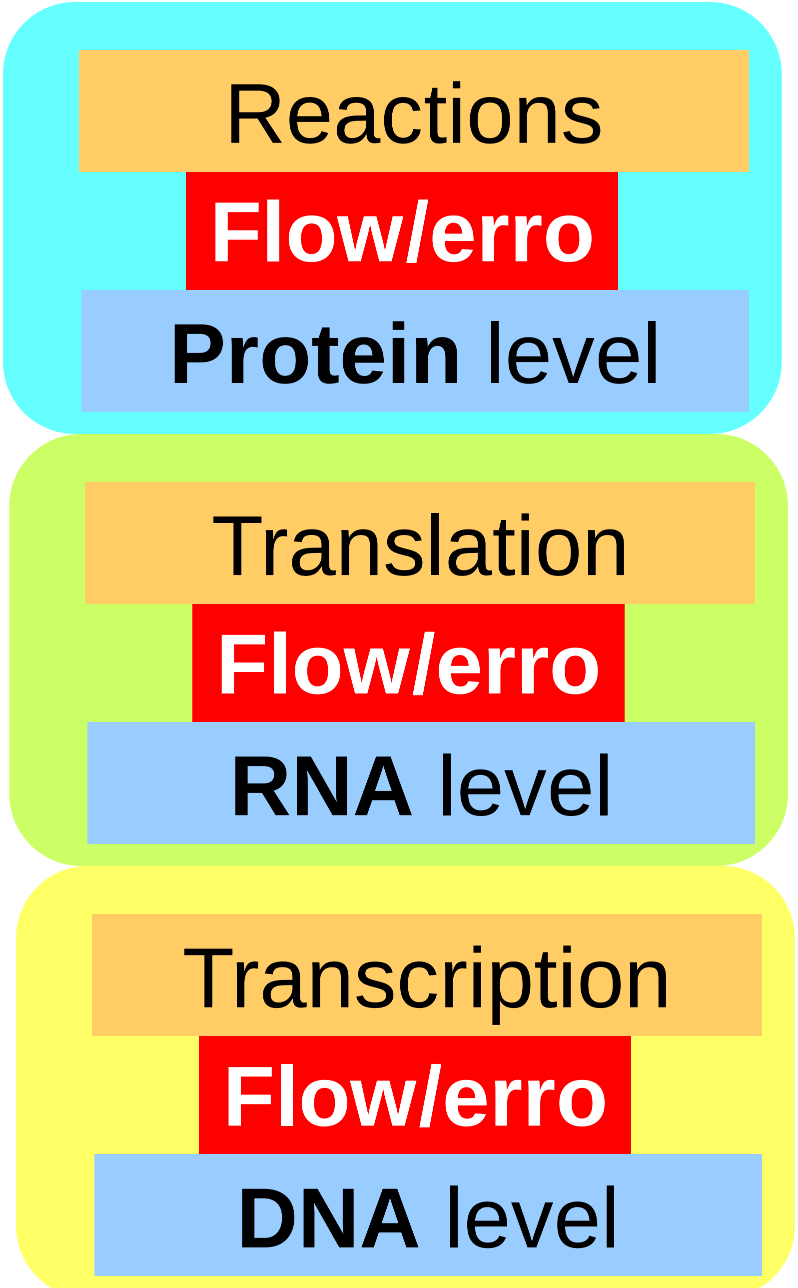
Recursive control structure



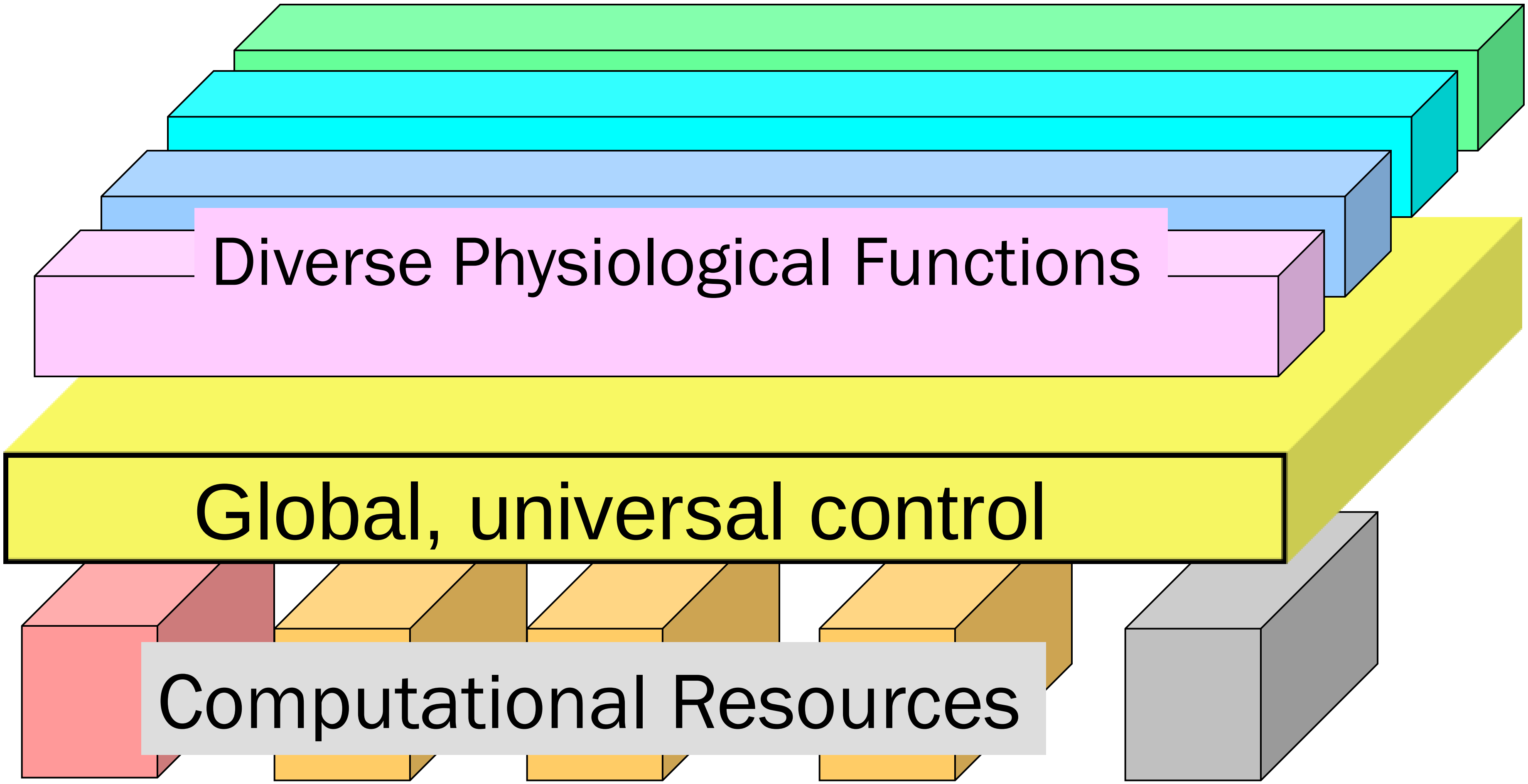
Top to bottom

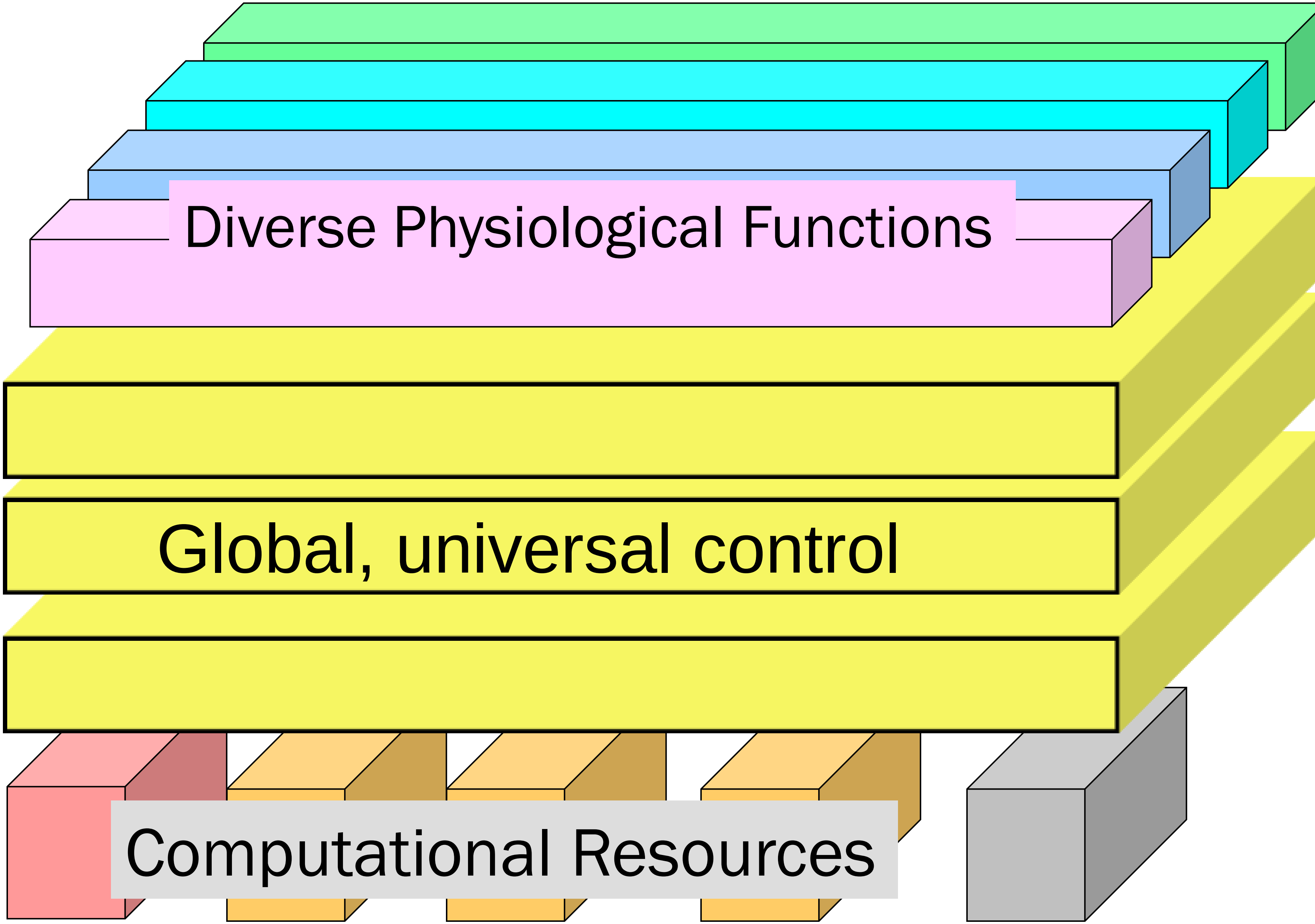
- Metabolically costly but fast to cheap but slow
- Special enzymes to general polymerases
- Allostery to regulated recruitment
- Analog to digital
- High molecule count to low (noise)

Rich Tradeoffs

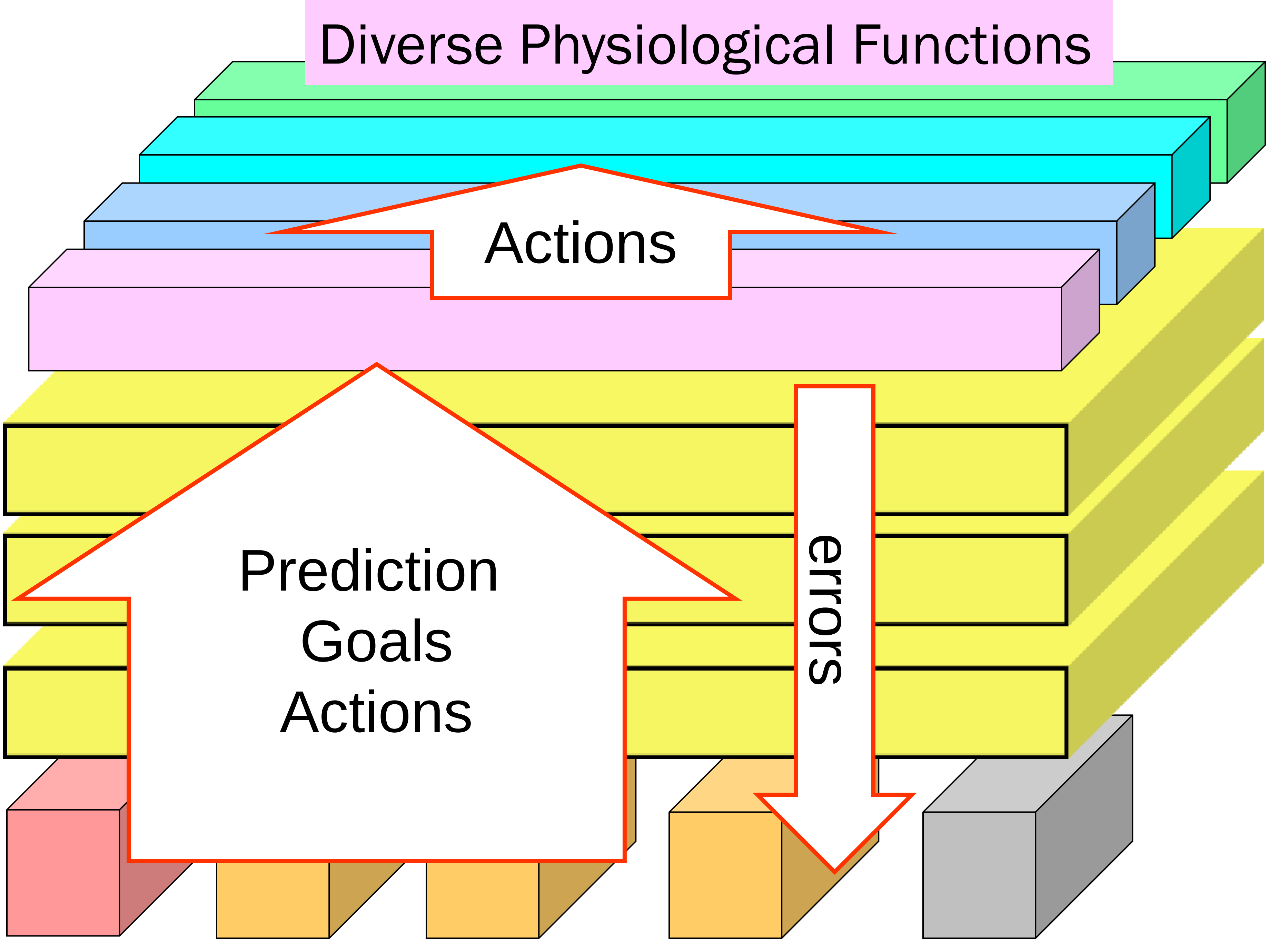


Layered Brain (Hawkins)?





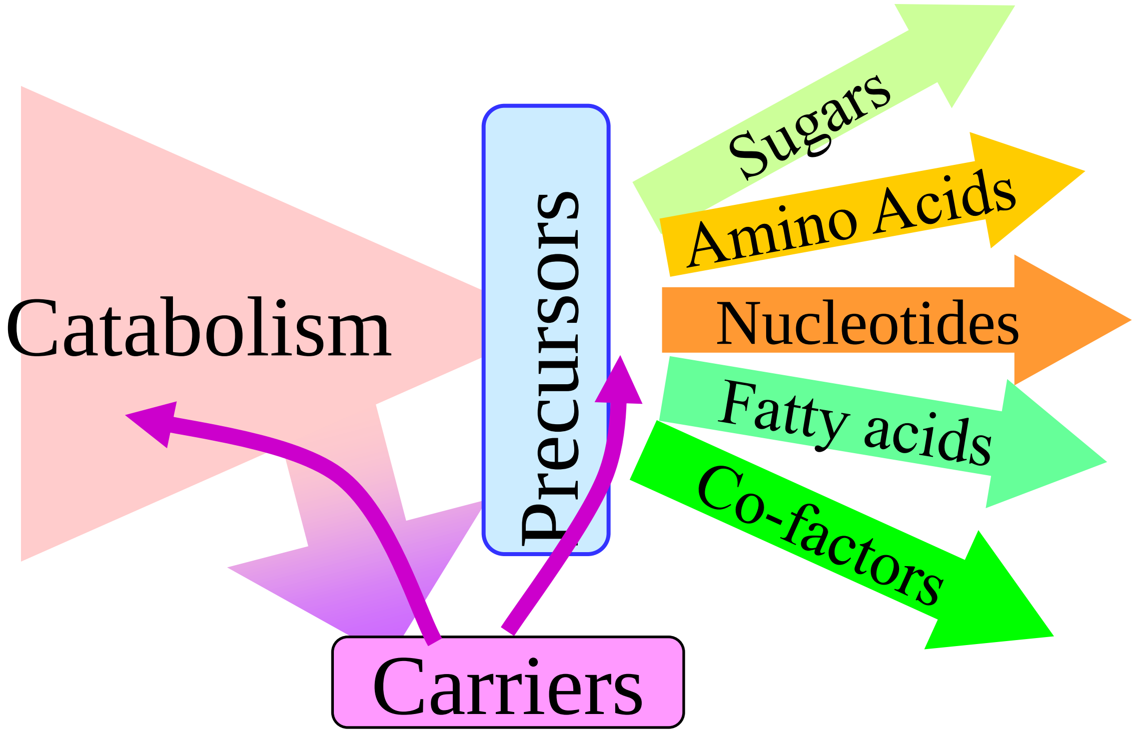
Diverse Physiological Functions
Global, universal control
Computational Resources


Diverse Physiological Functions
Actions
Prediction
Goals
Actions
errors

Why this is all wrong

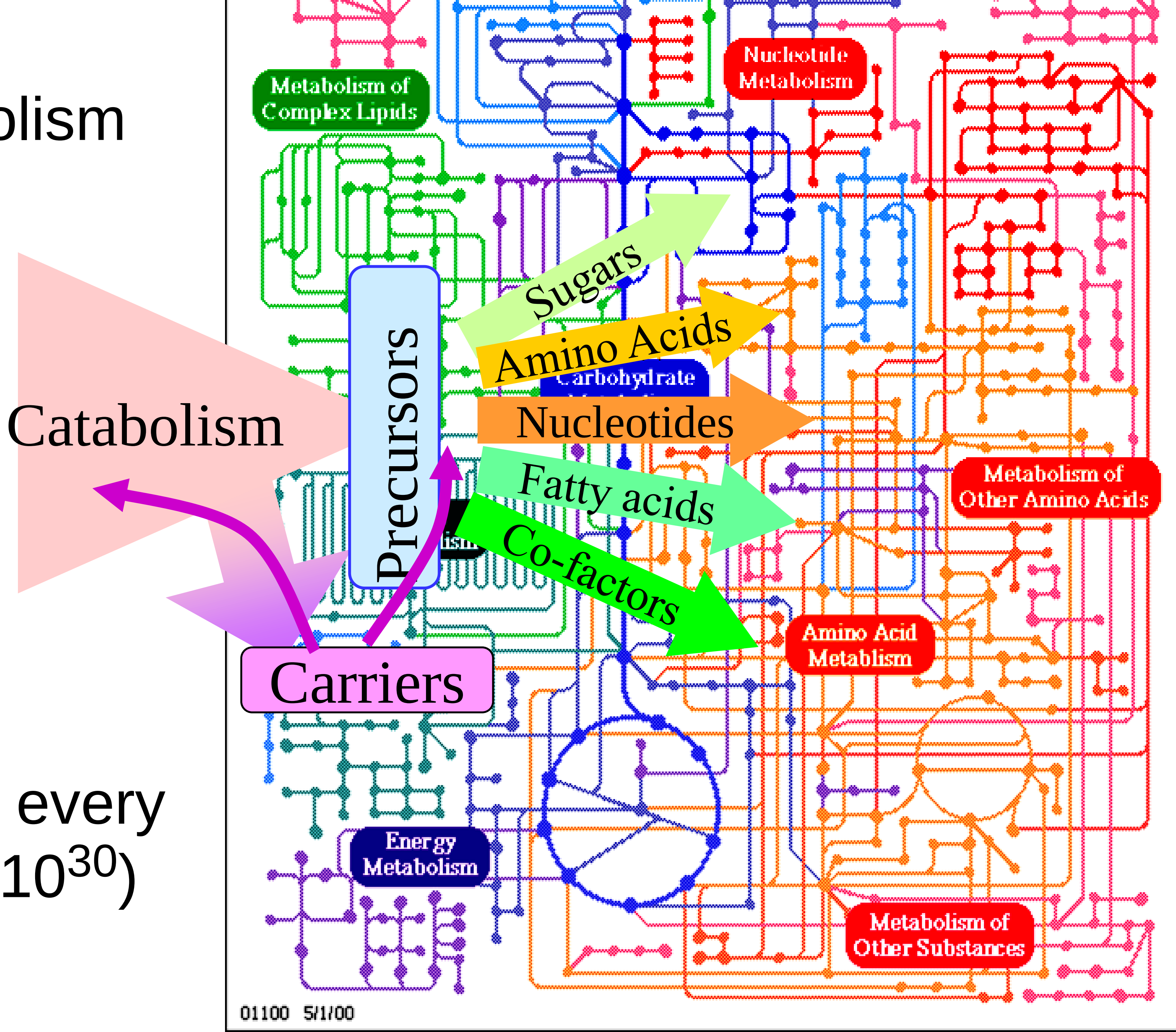
- Network science and emergulent chaocritiplexity
- Peta-phylia, the singularity is near
- Earth is <10K yrs old, evolution a hoax
- The rapture is near
- Global warming and “unsustainability” a hoax
- It’s so stupid it isn’t even wrong

Inside every cell

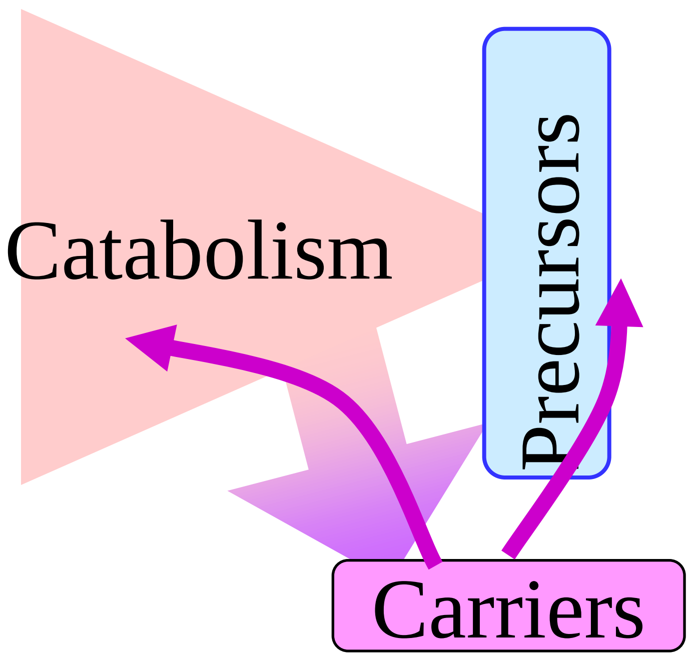


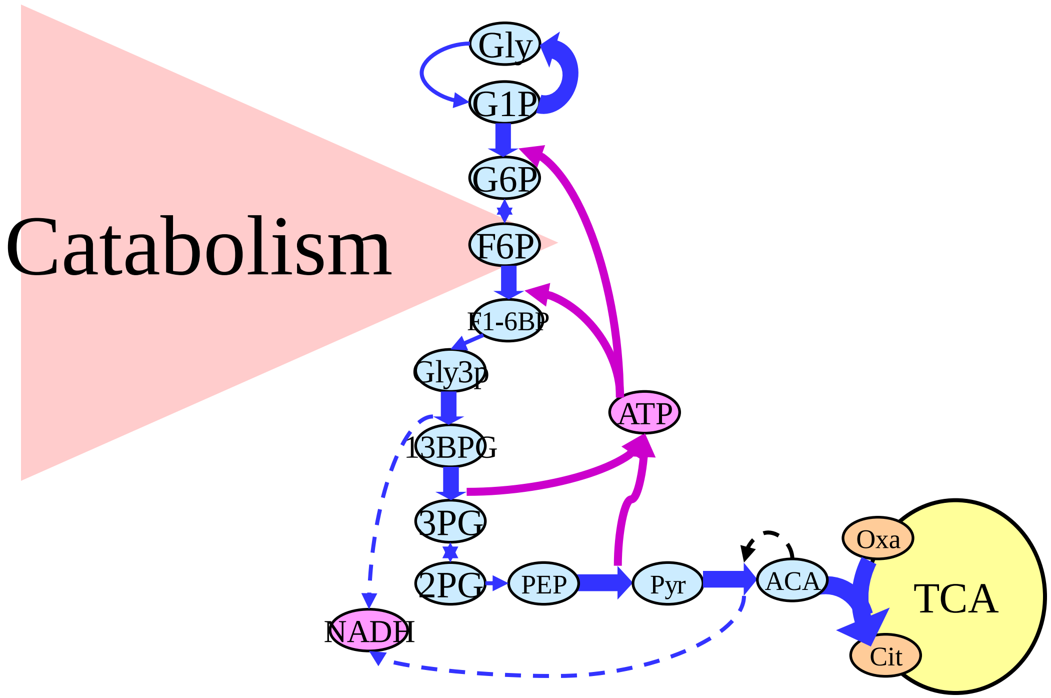
Core metabolic bowtie

Core metabolism

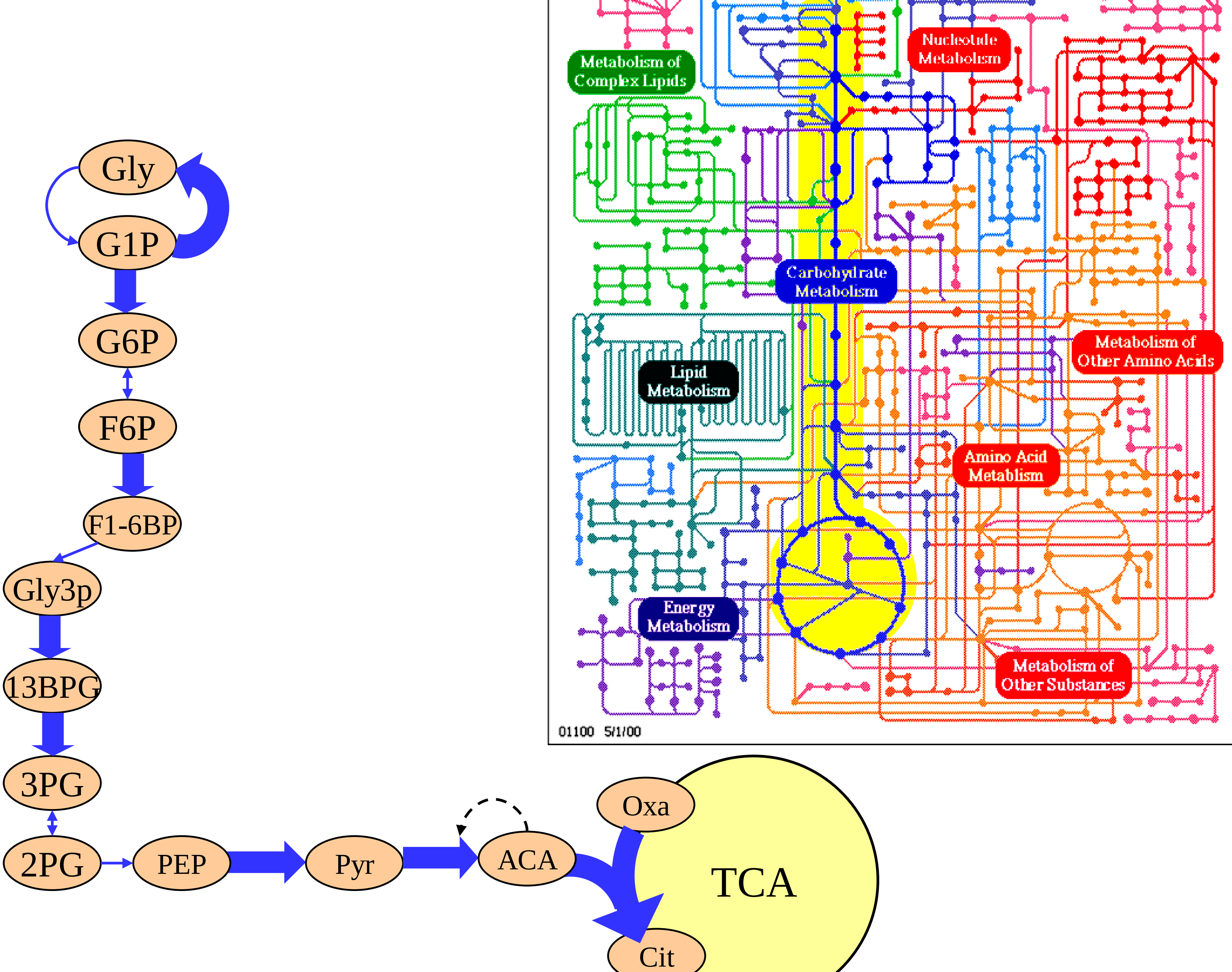


Inside every cell (≈10^{30})

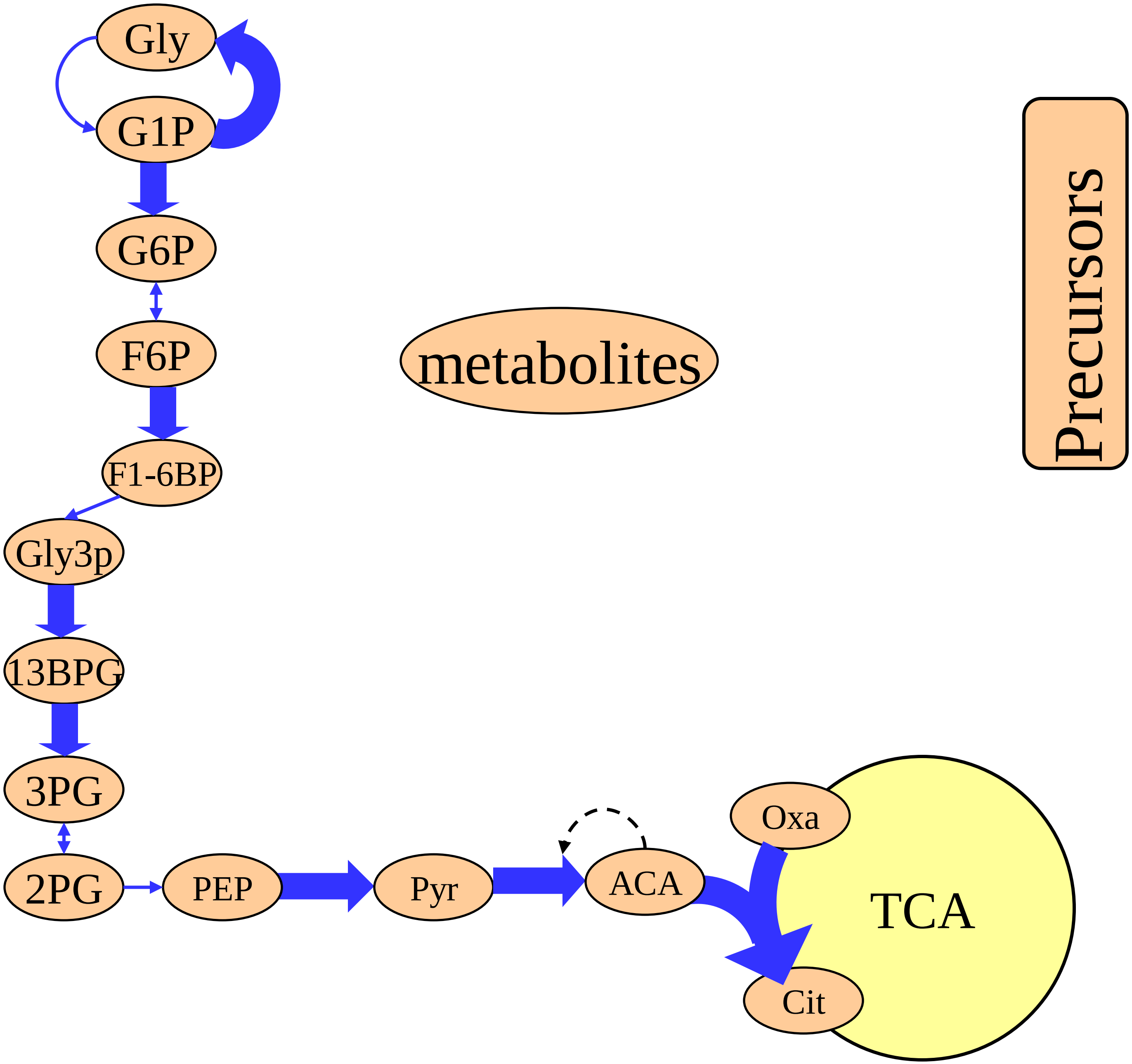

Catabolism
Precursors
Carriers

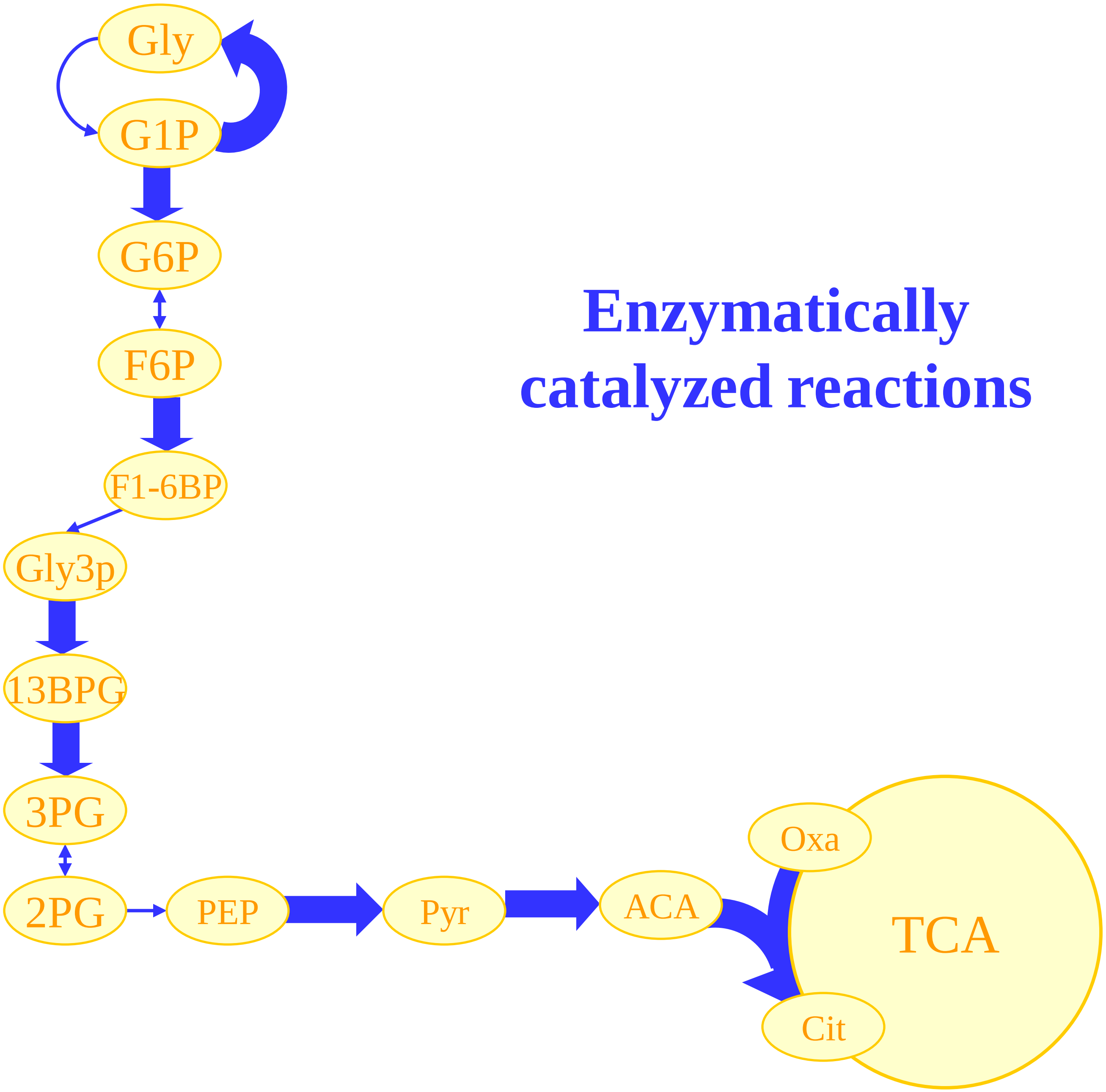


Catabolism
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
Cit
TCA

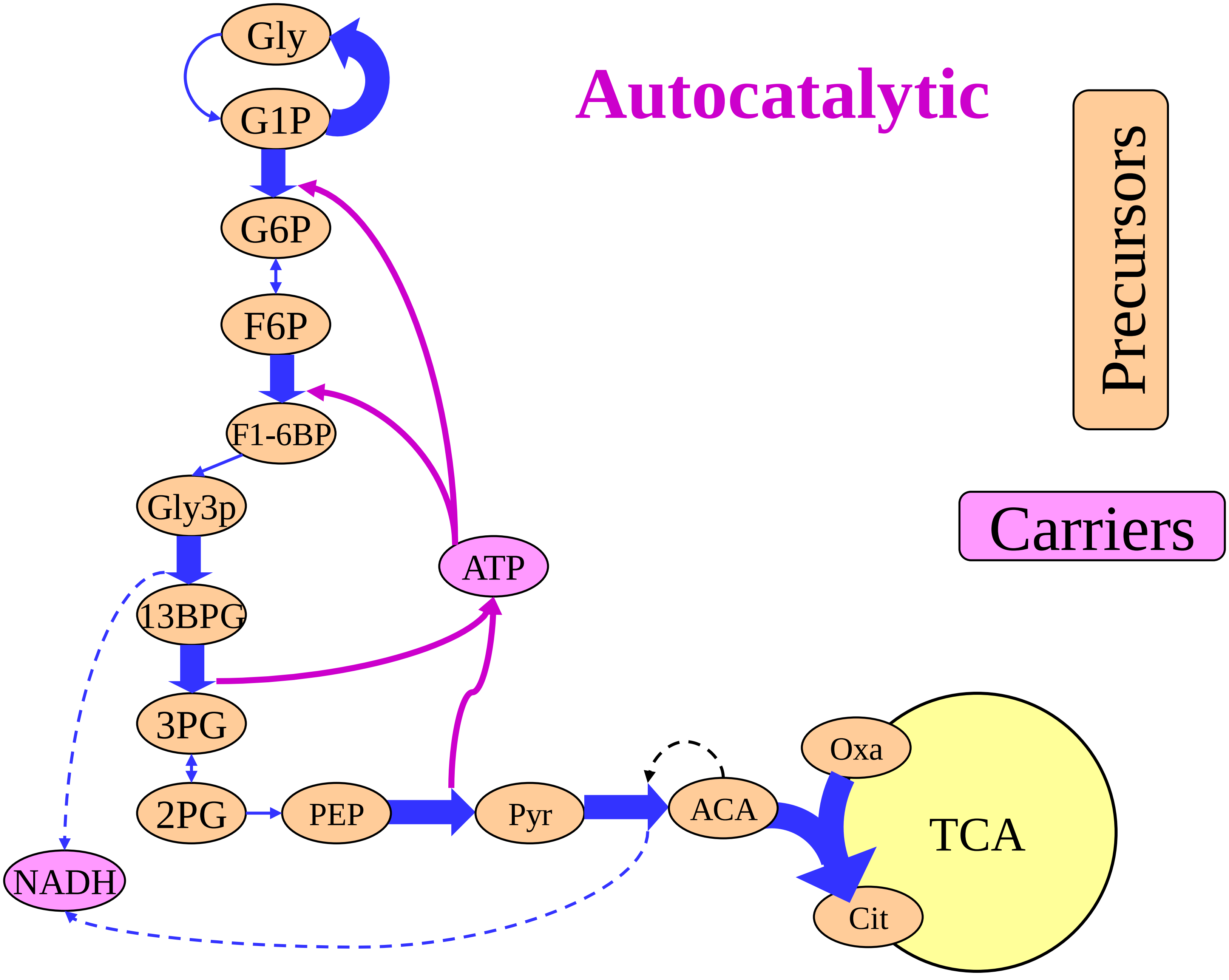


Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00

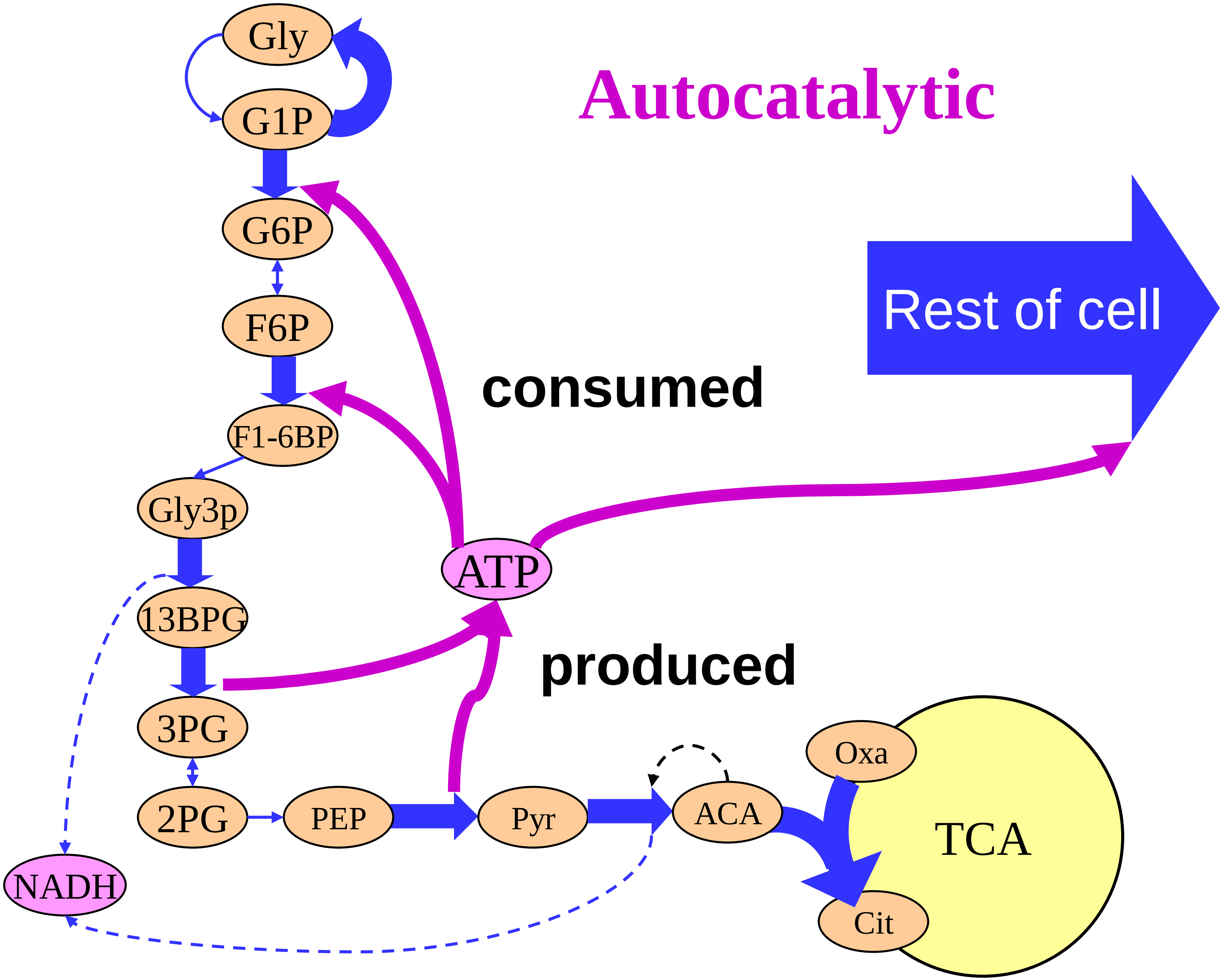

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
Cit
TCA
metabolites
Precursors



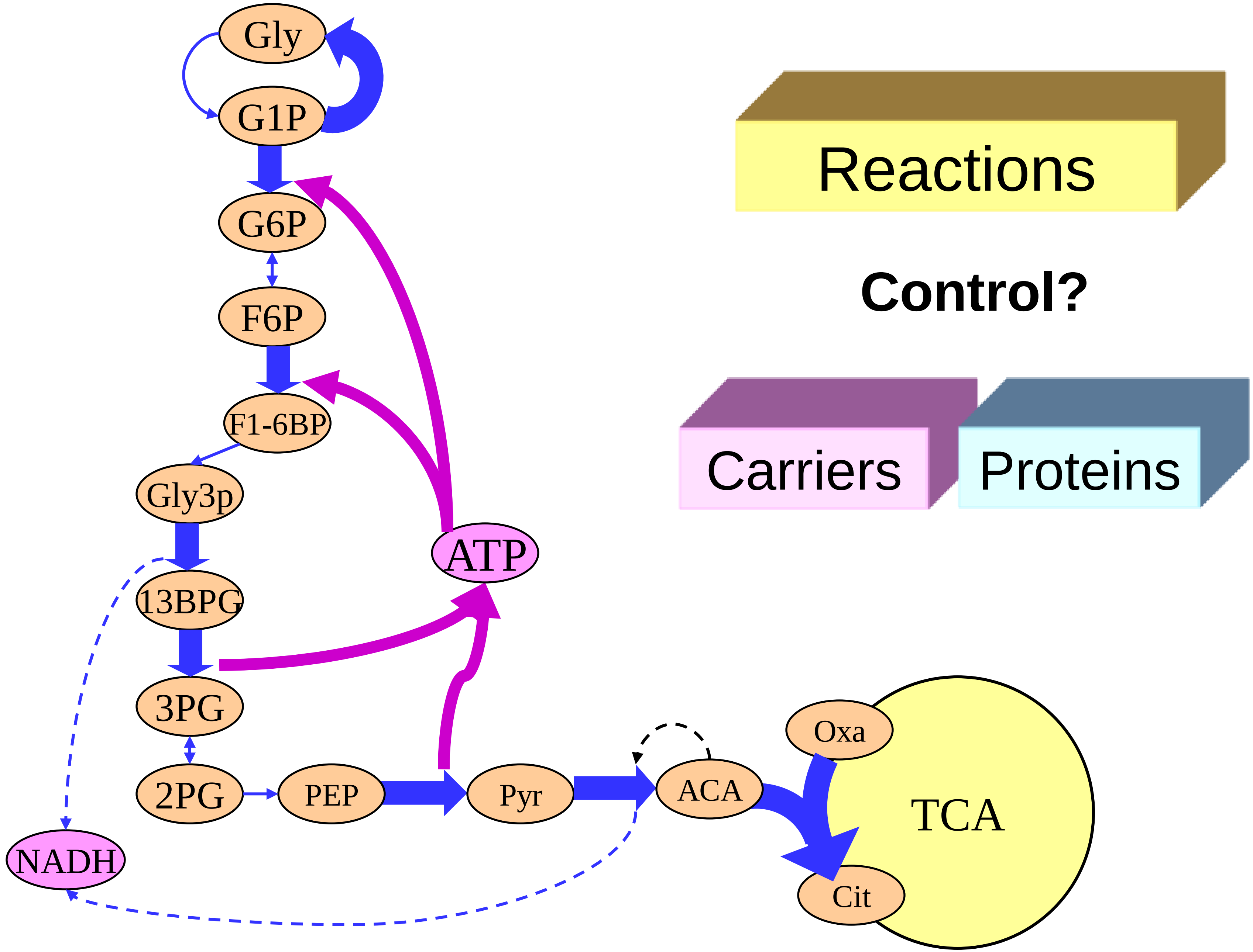
Enzymatically catalyzed reactions



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

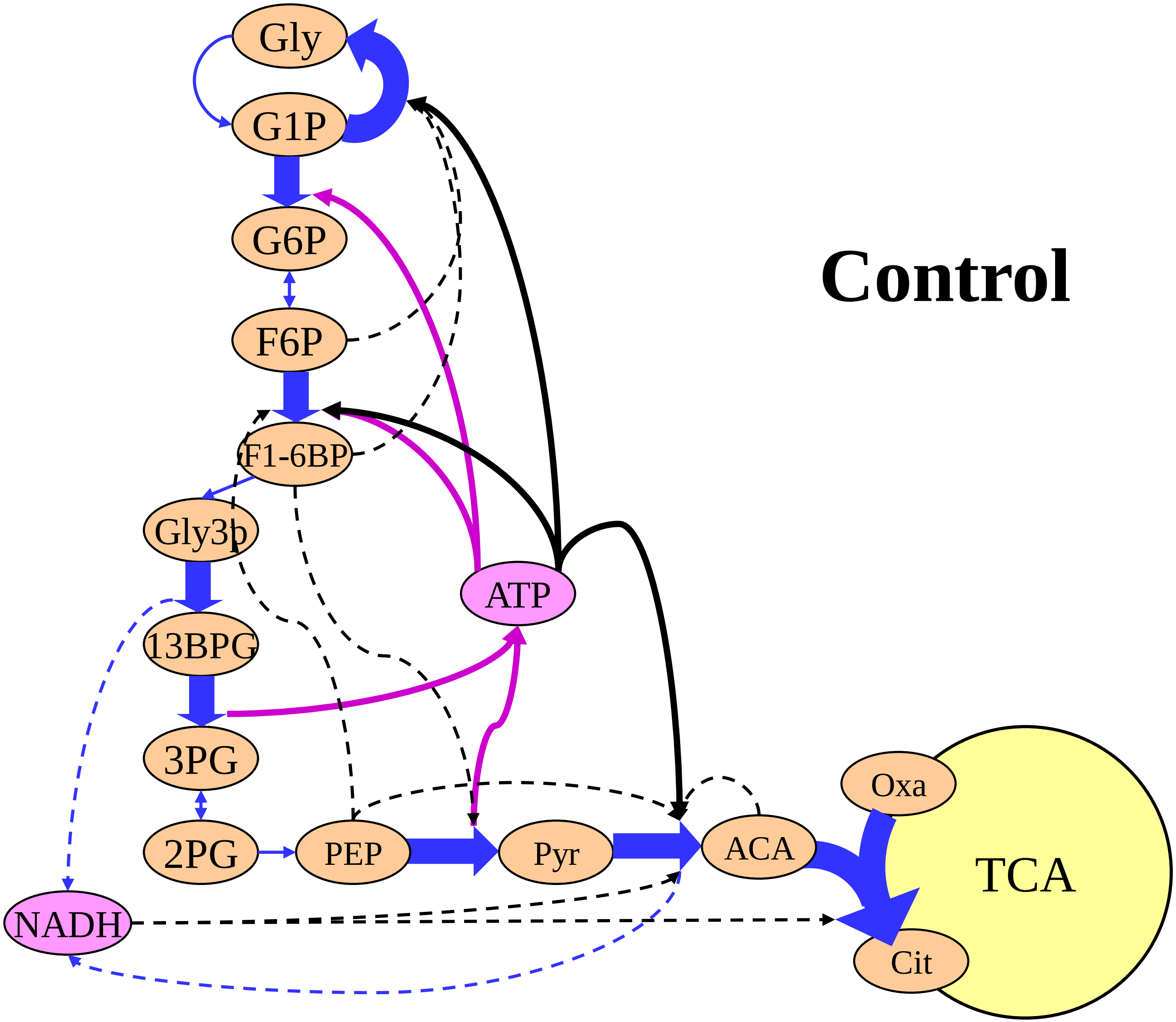


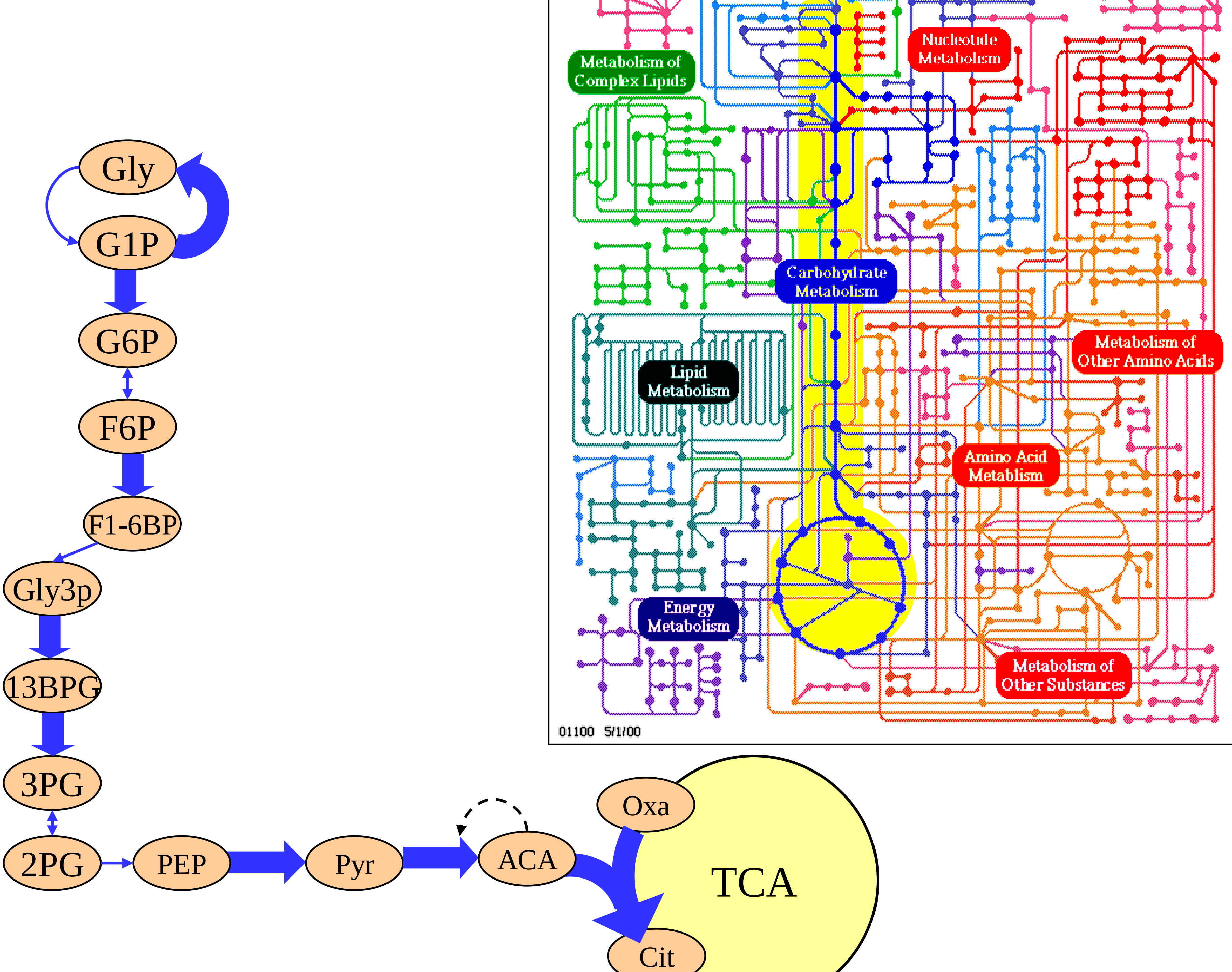
Autocatalytic
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
NADH
ATP
consumed
produced
Rest of cell
Oxa
Cit
TCA



Gly
G1P
G6P
F6P
F1-6BP
Gly3p
ATP
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
NADH
Reactions
Control?
Carriers
Proteins

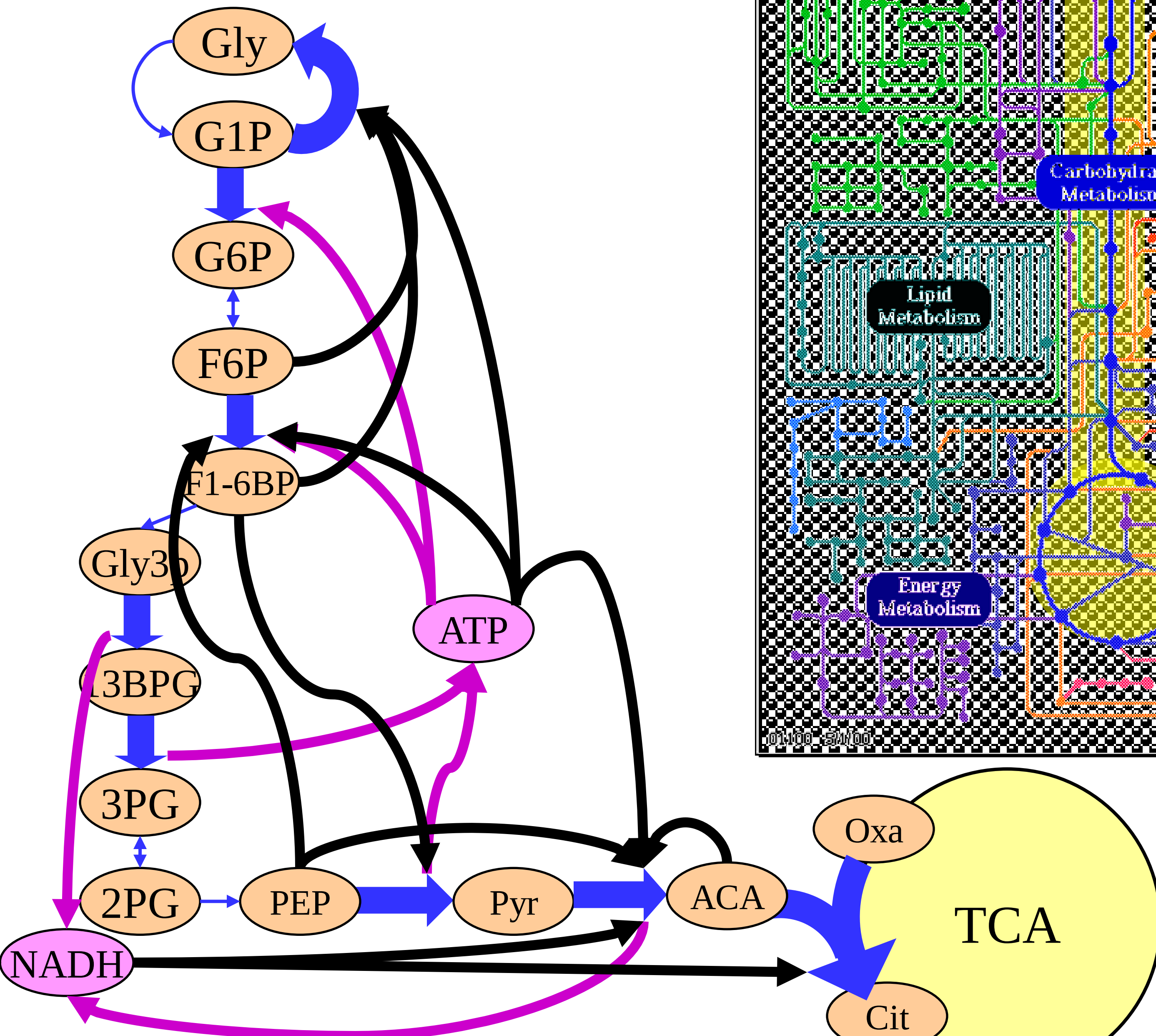
Control

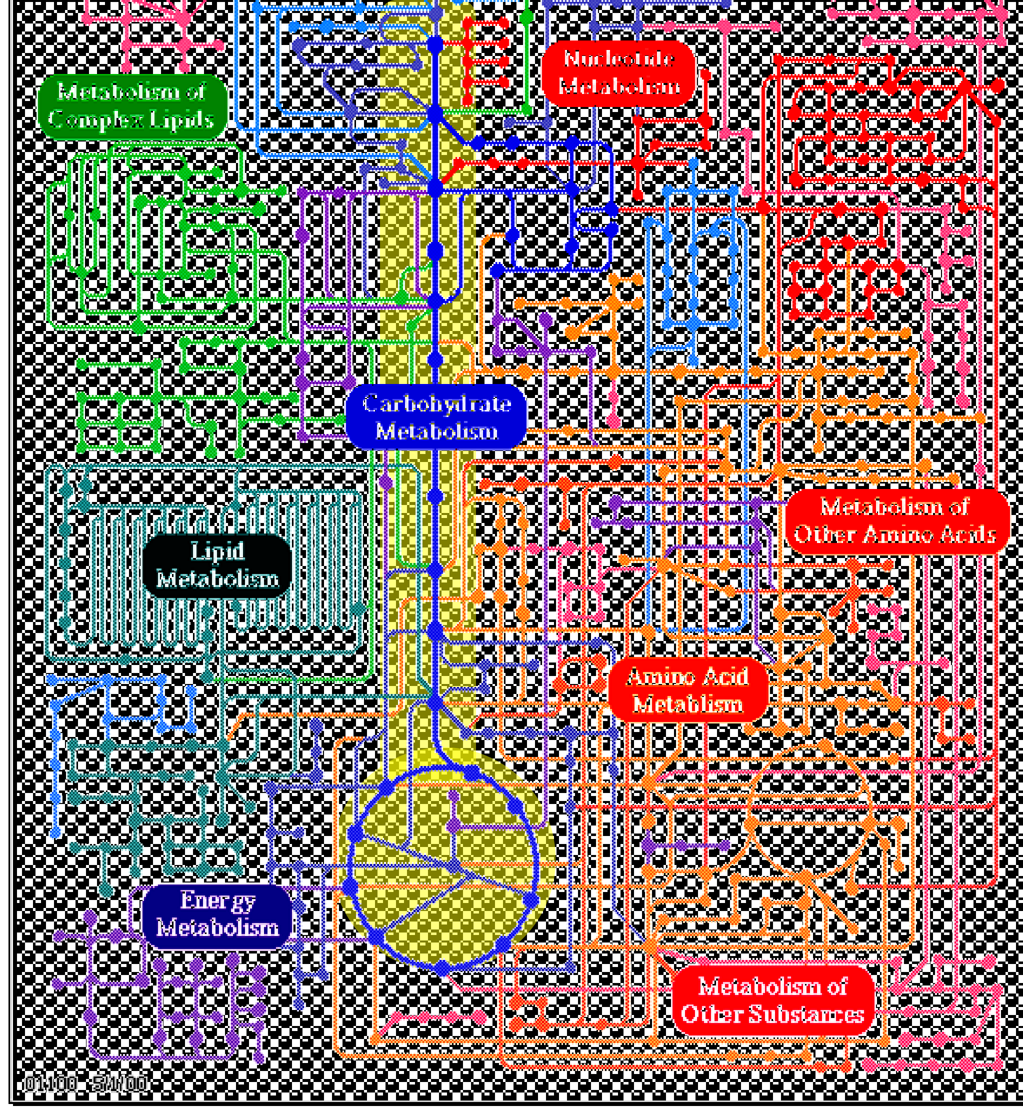

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
Cit
TCA



Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00

If we drew the feedback loops the diagram would be unreadable.

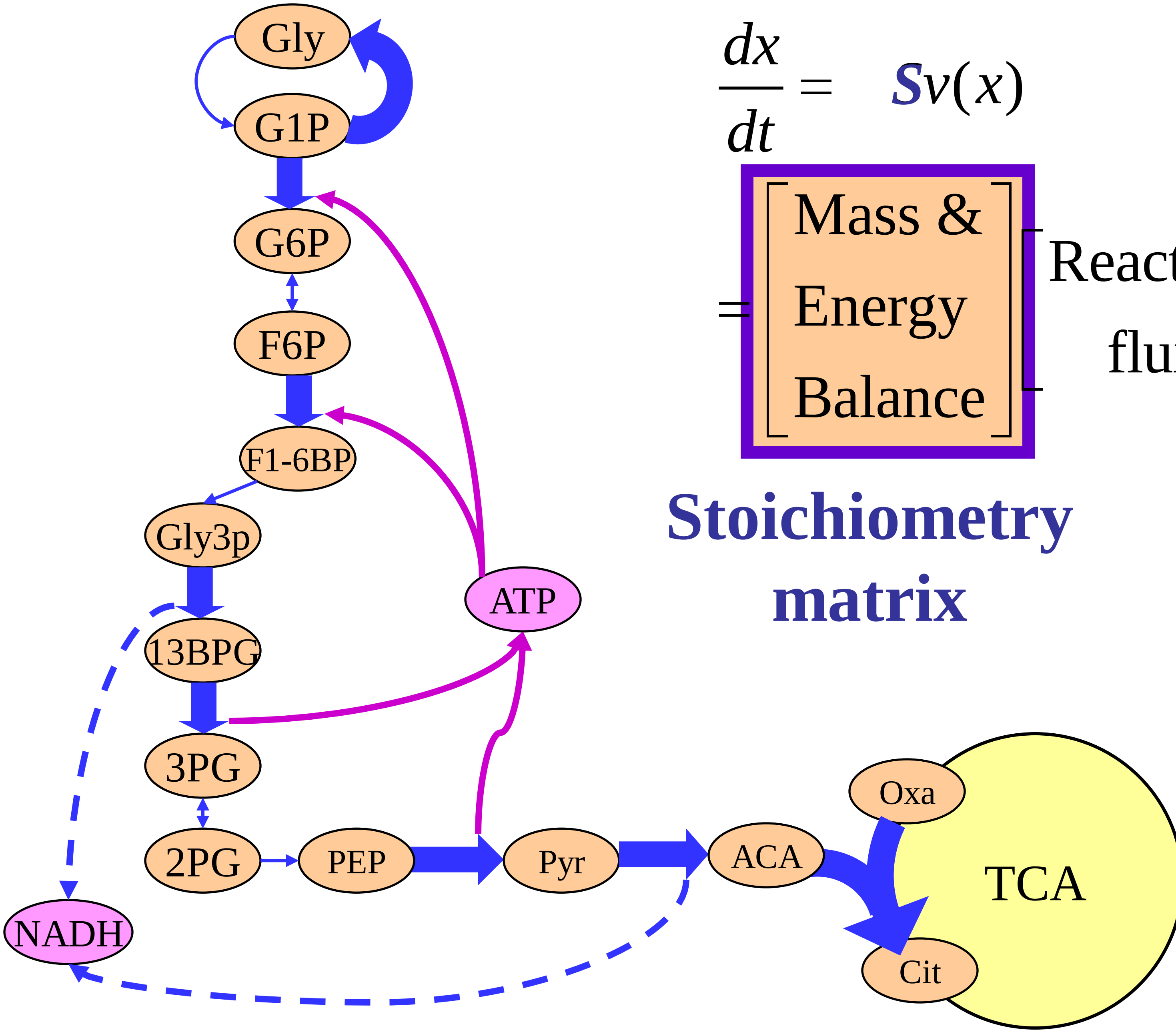


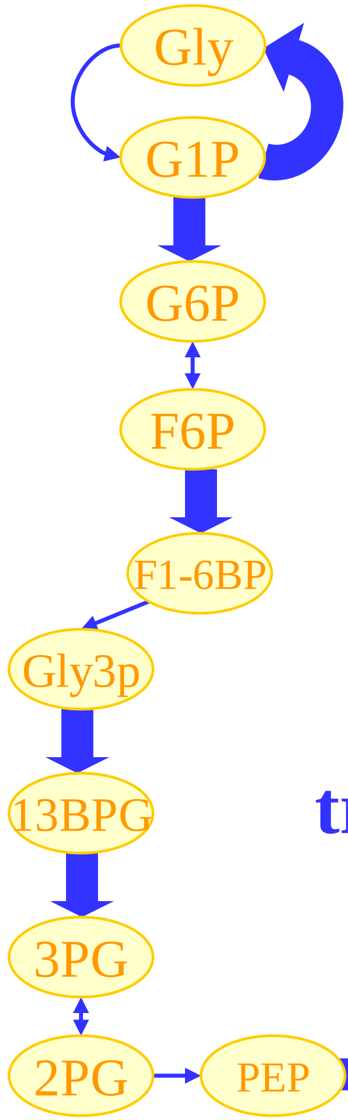


$$\frac{dx}{dt} = \mathbf{S}v(x)$$

$$= \begin{bmatrix} \text{Mass \&} \\ \text{Energy} \\ \text{Balance} \end{bmatrix} \begin{bmatrix} \text{Reaction} \\ \text{flux} \end{bmatrix}$$

Stoichiometry matrix

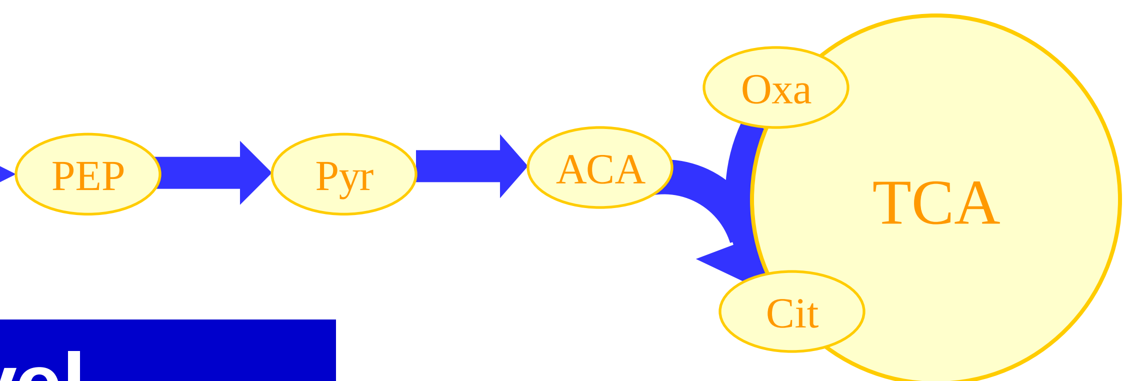




$$\frac{dx}{dt} = Sv(x)$$

$$= \begin{bmatrix} \text{Mass \&} \\ \text{Energy} \\ \text{Balance} \end{bmatrix} \begin{bmatrix} \text{Reaction} \\ \text{flux} \end{bmatrix}$$

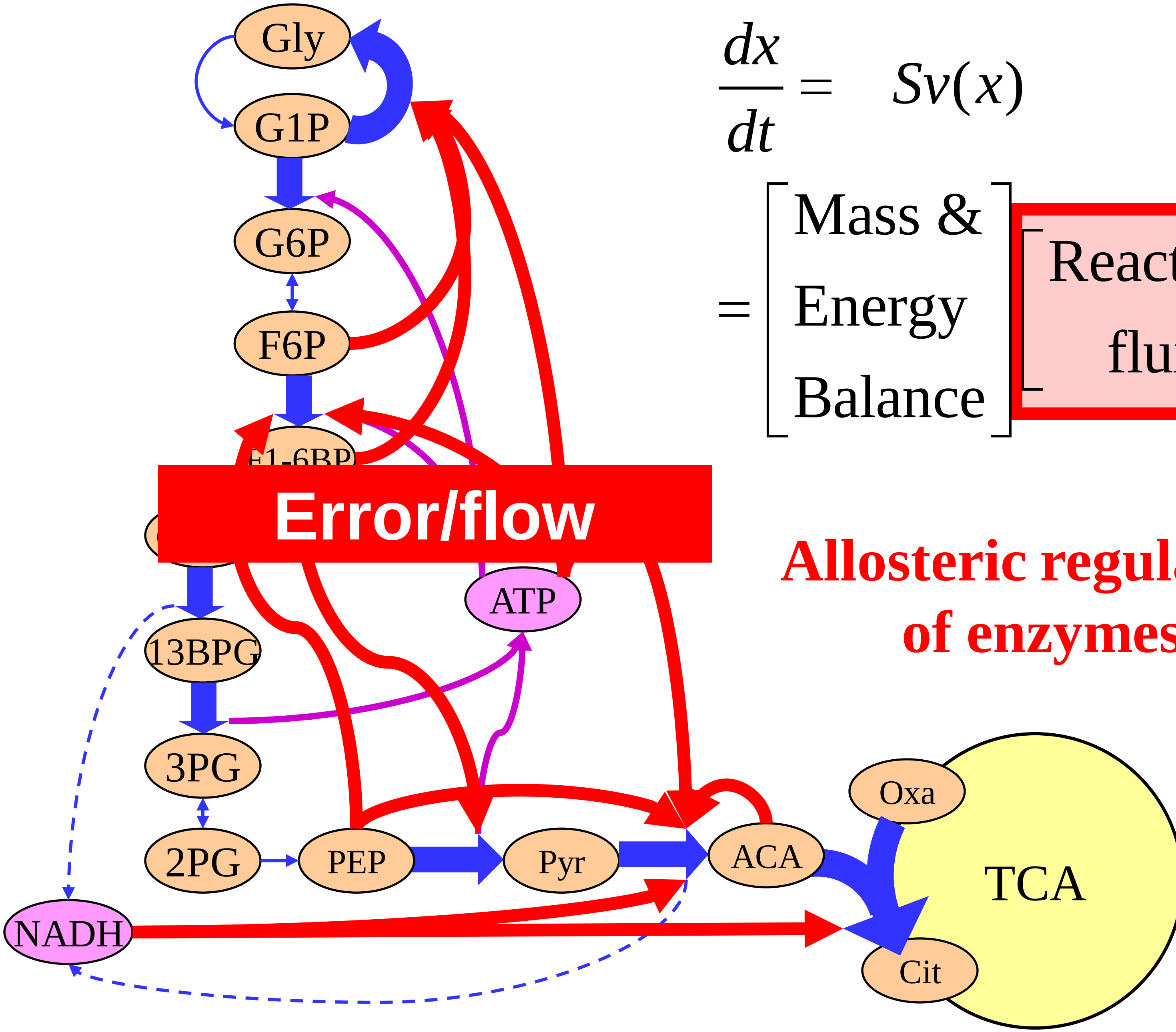
Regulation of enzyme levels by transcription/translation/degradation



level

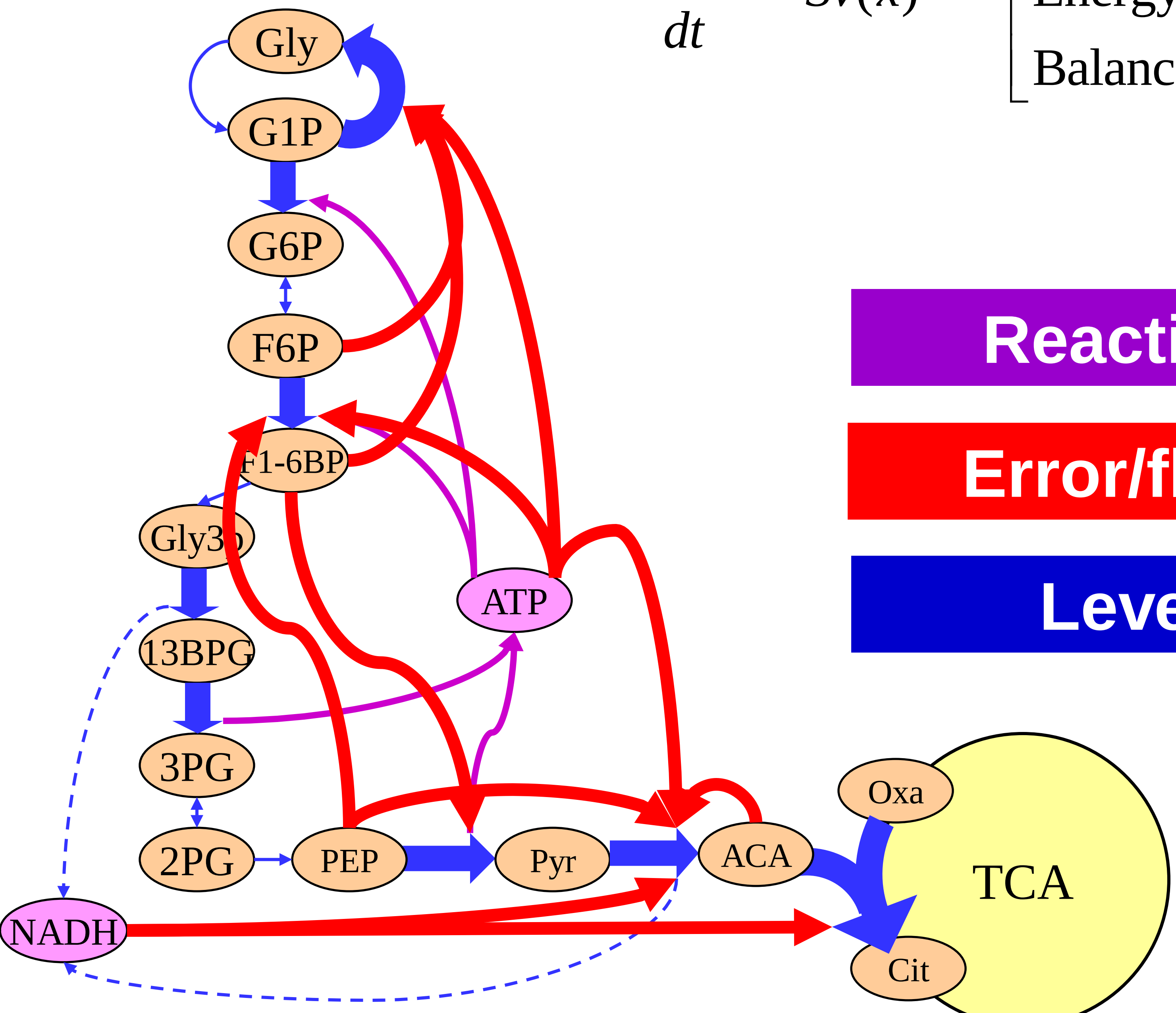
$$\frac{dx}{dt} = Sv(x)$$

$$= \begin{bmatrix} \text{Mass \&} \\ \text{Energy} \\ \text{Balance} \end{bmatrix} \begin{bmatrix} \text{Reaction} \\ \text{flux} \end{bmatrix}$$



Allosteric regulation of enzymes

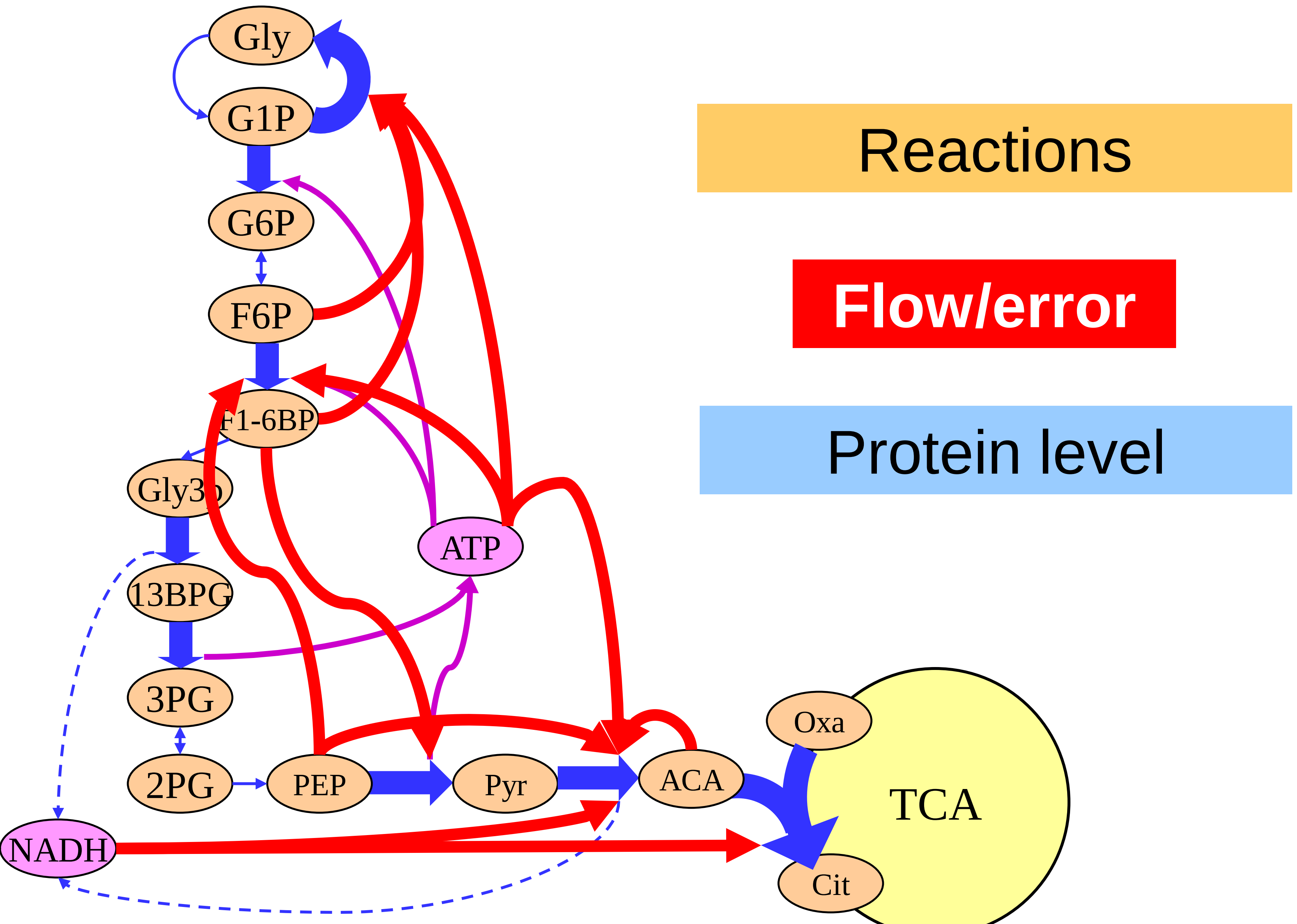
$$\frac{dx}{dt} = Sv(x) = \begin{bmatrix} \text{Mass \&} \\ \text{Energy} \\ \text{Balance} \end{bmatrix} \begin{bmatrix} \text{Reaction} \\ \text{flux} \end{bmatrix}$$

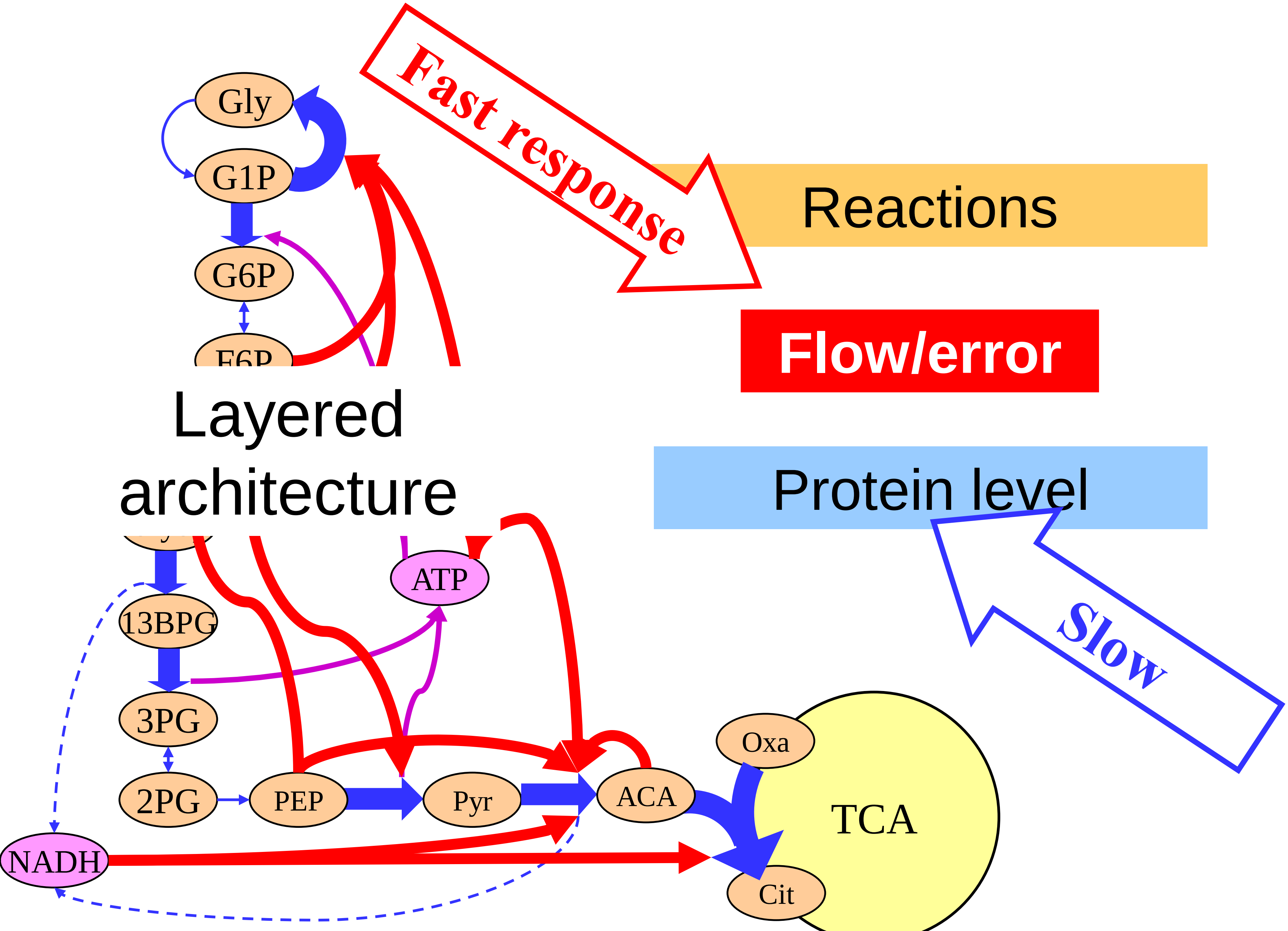


Reaction

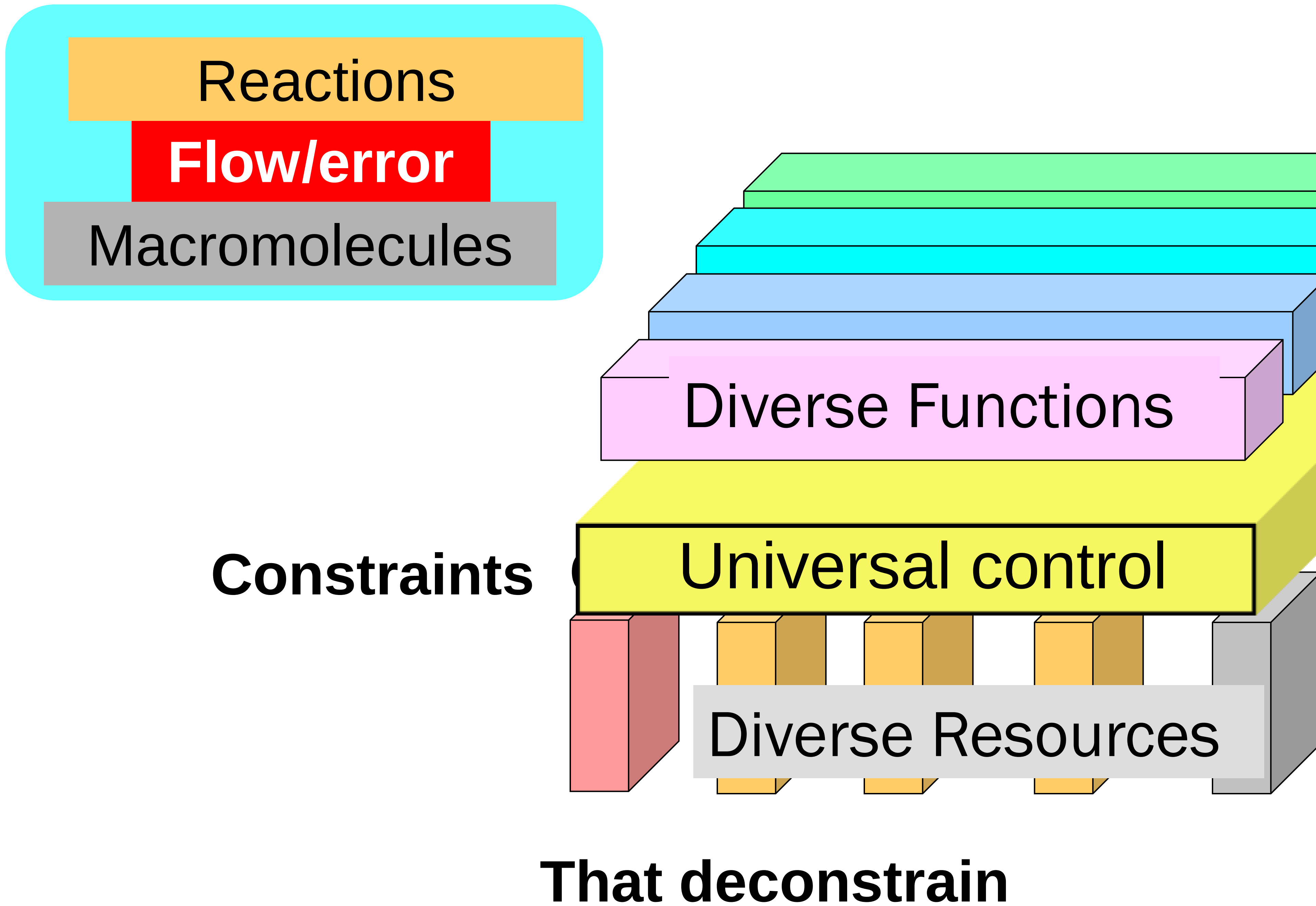
Error/flow

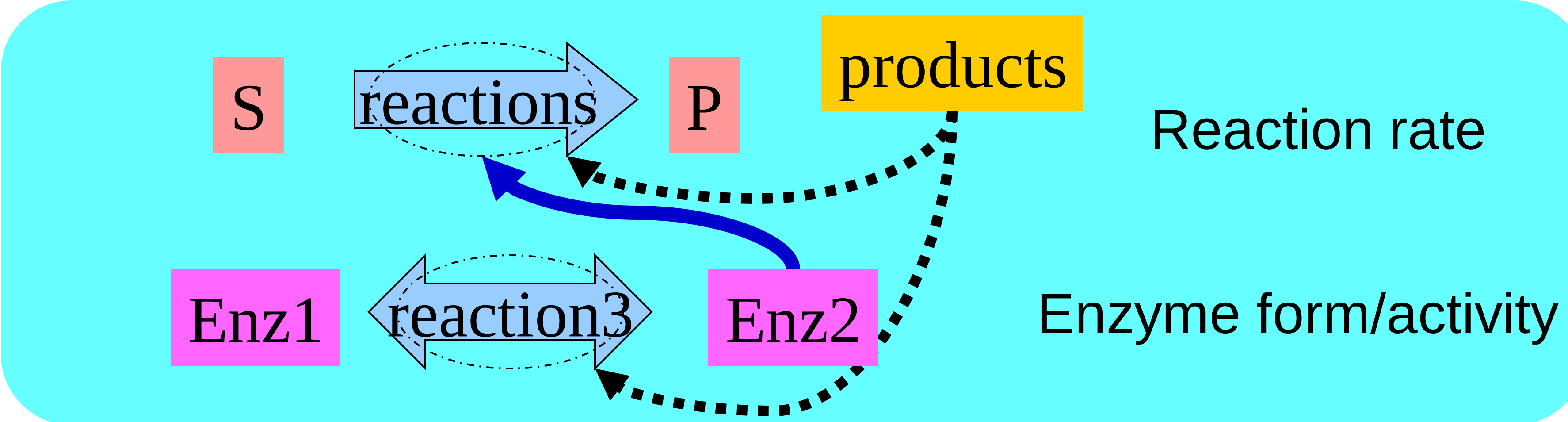
Level


Gly
G1P
G6P
F6P
F1-6BP
Gly3
13BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
Cit
TCA
Reactions
Flow/error
Protein level

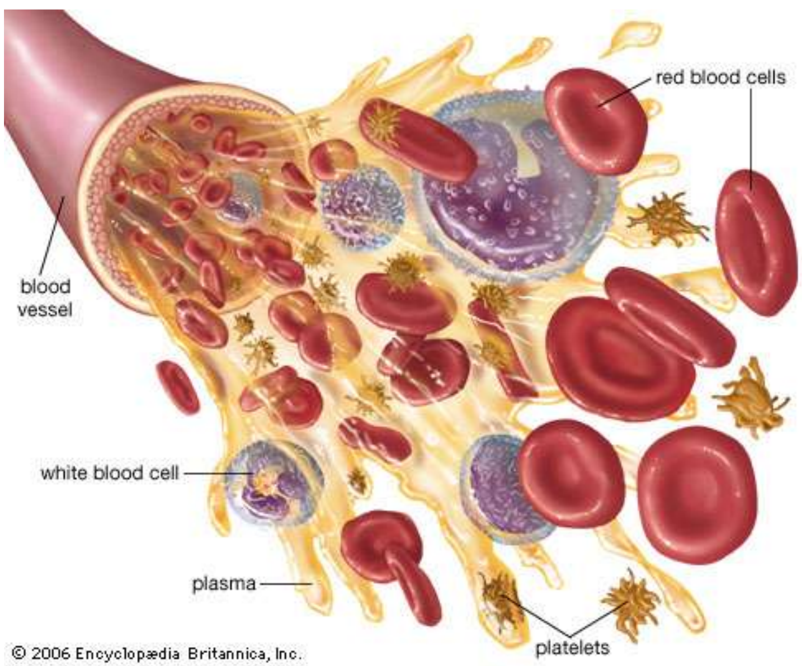


Layered architecture
Fast response
Reactions
Flow/error
Protein level
Slow
Gly
G1P
G6P
F6P
ATP
13BPG
3PG
2PG
PEP
Pyr
ACA
NADH
Oxa
Cit
TCA


Reactions
Flow/error
Macromolecules
Diverse Functions
Constraints
Universal control
Diverse Resources
That deconstrain

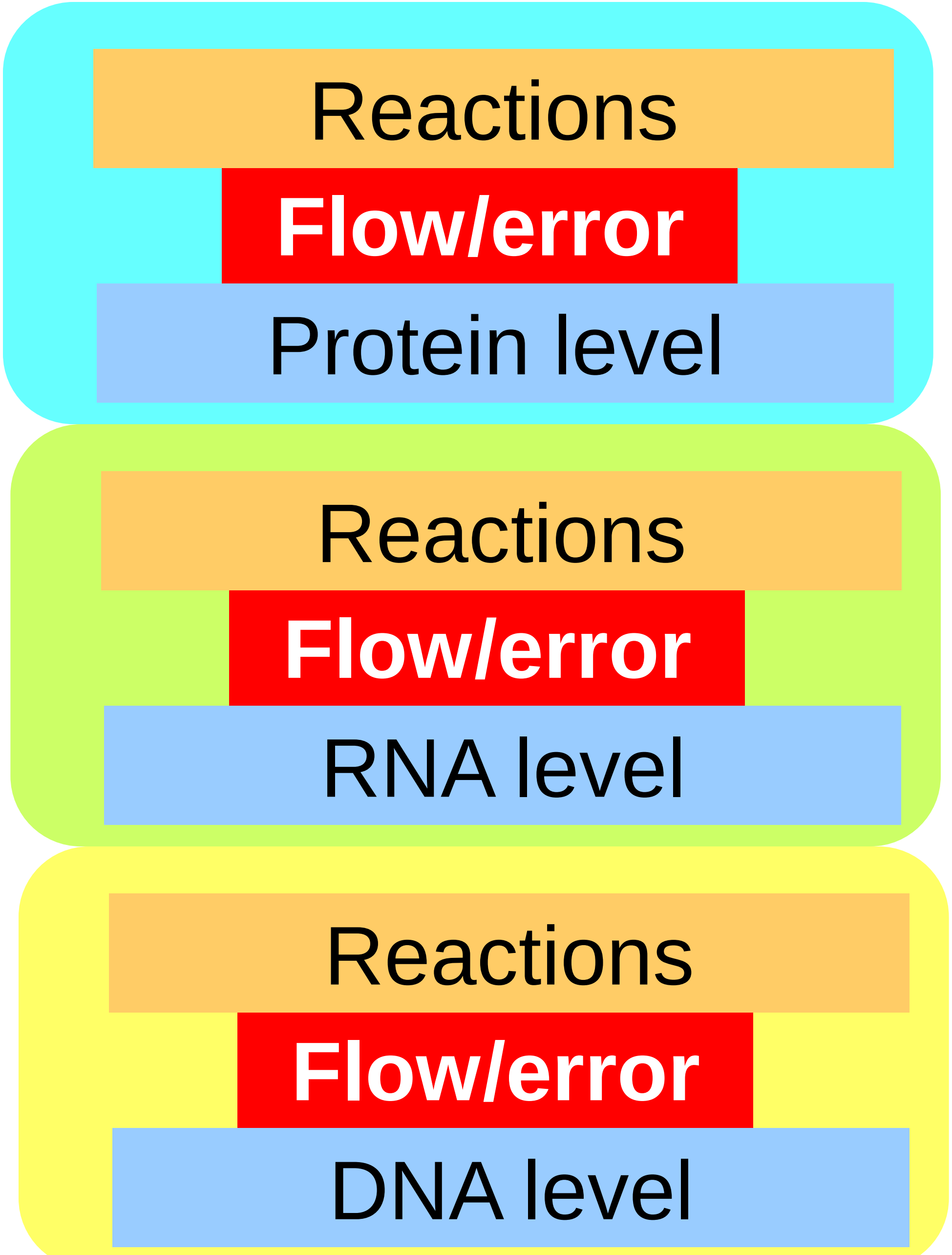


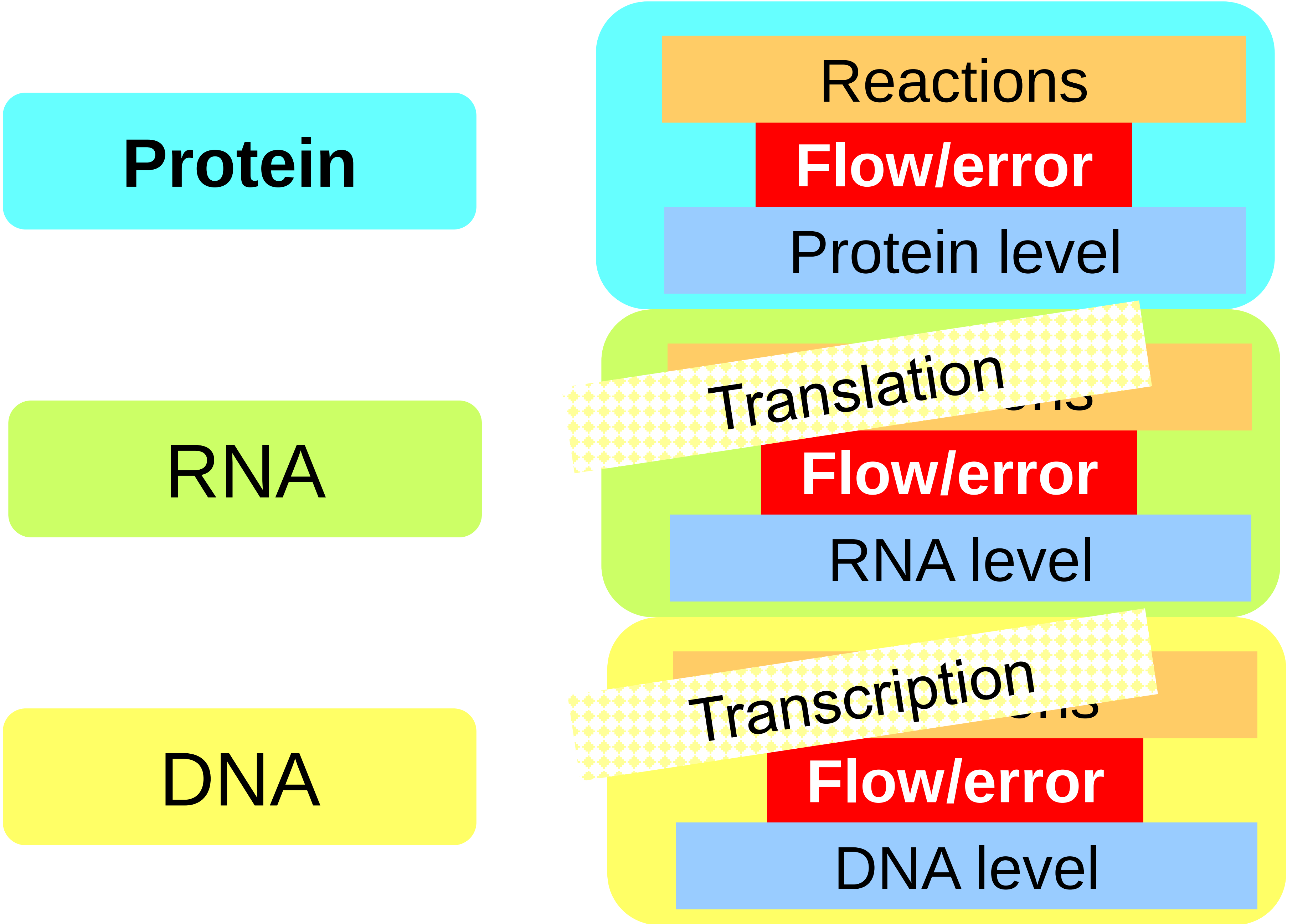
Running only the top layers

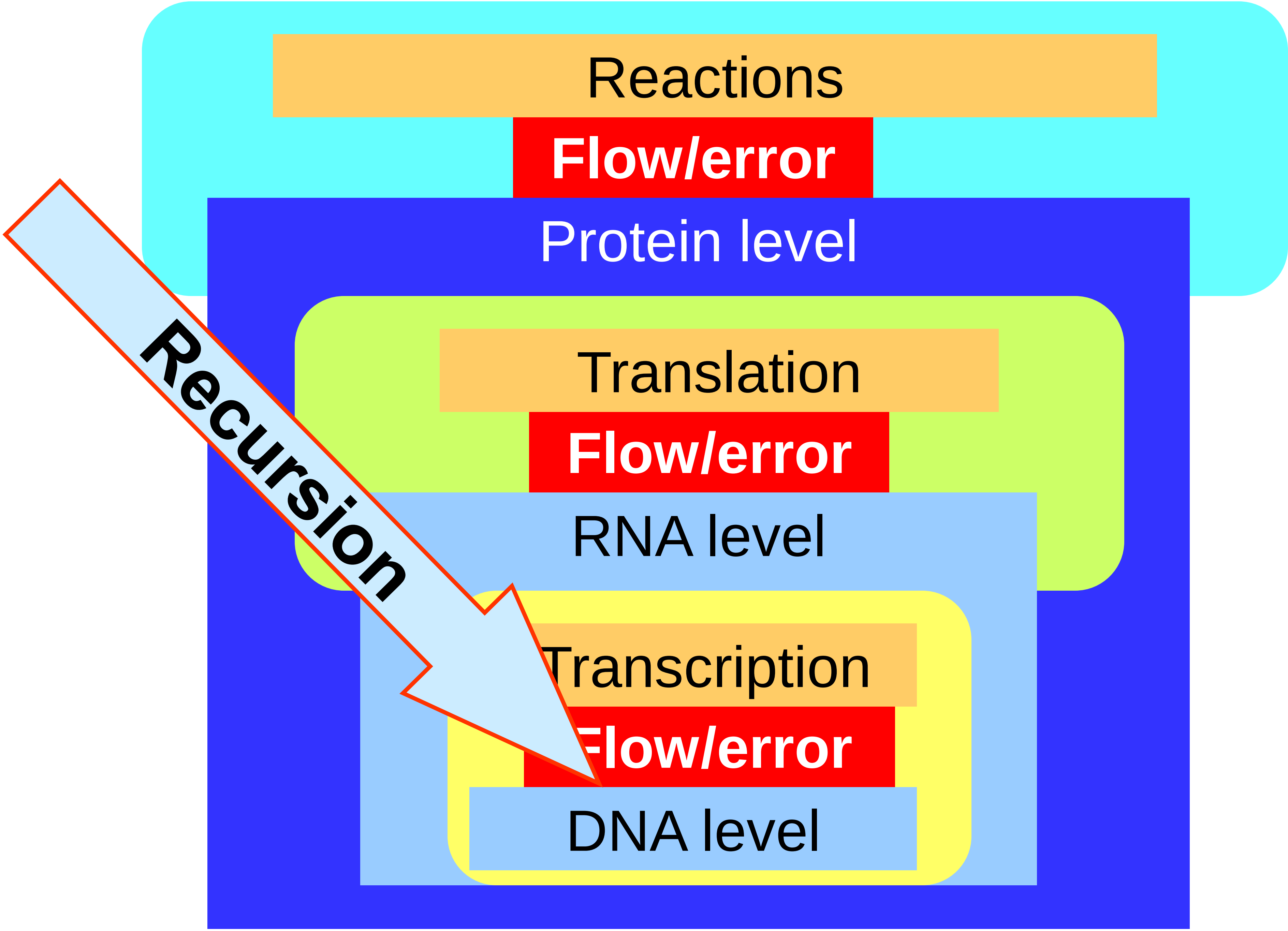


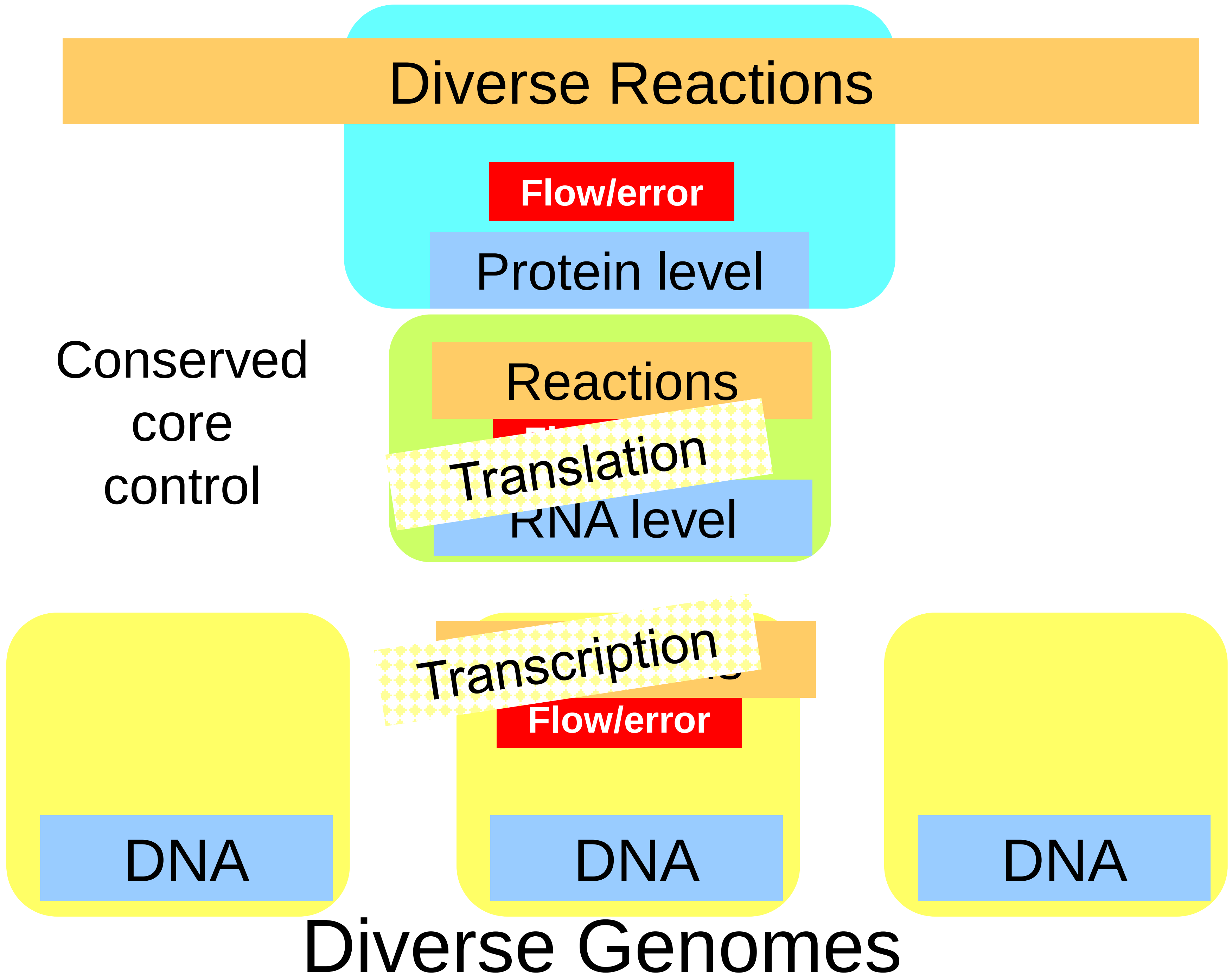
Mature red blood cells live 120 days

“metabolism first” origins of life?


Reactions
Flow/error
Protein level
Reactions
Flow/error
RNA level
Reactions
Flow/error
DNA level


Protein
RNA
DNA
Reactions
Flow/error
Protein level
Translation
Flow/error
RNA level
Transcription
Flow/error
DNA level

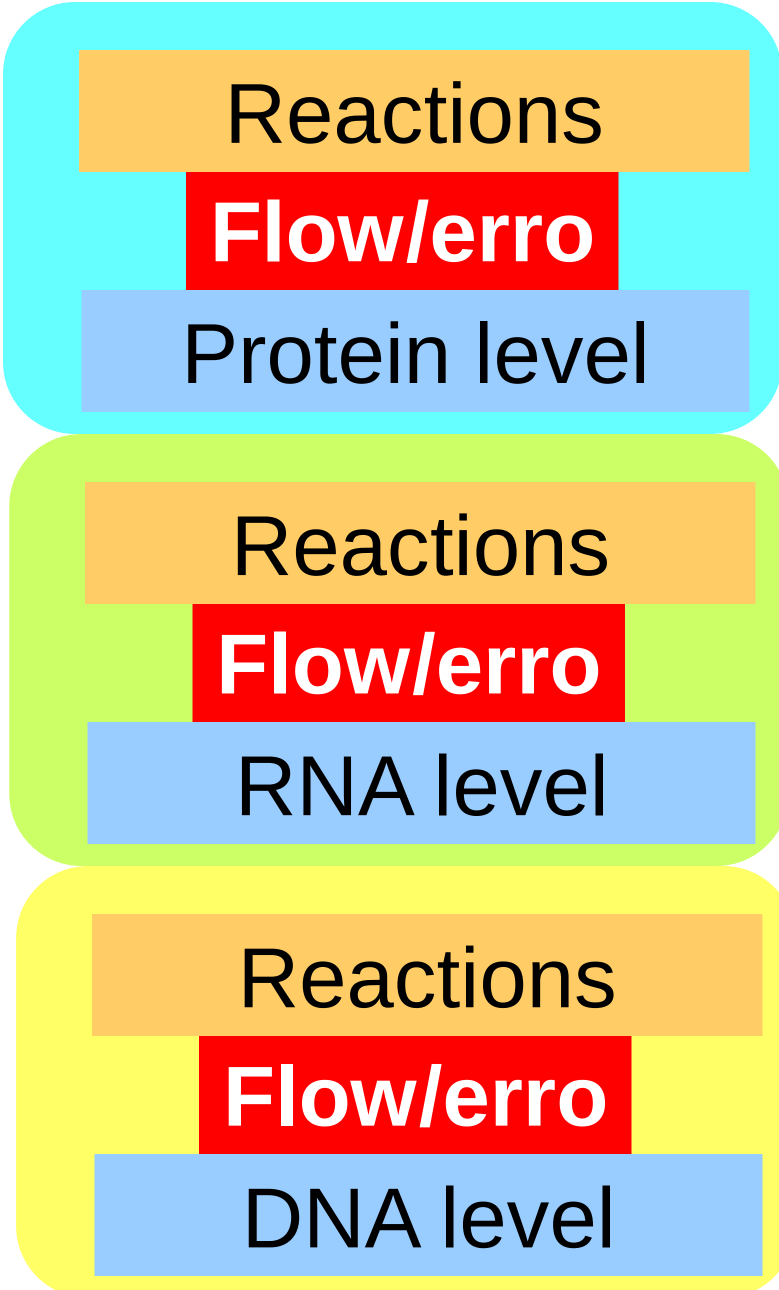

Reactions
Flow/error
Protein level
Translation
Flow/error
RNA level
Transcription
Flow/error
DNA level
Recursion


Diverse Reactions
Flow/error
Protein level
Conserved
core
control
Reactions
Translation
RNA level
Transcription
Flow/error
DNA
DNA
DNA
Diverse Genomes

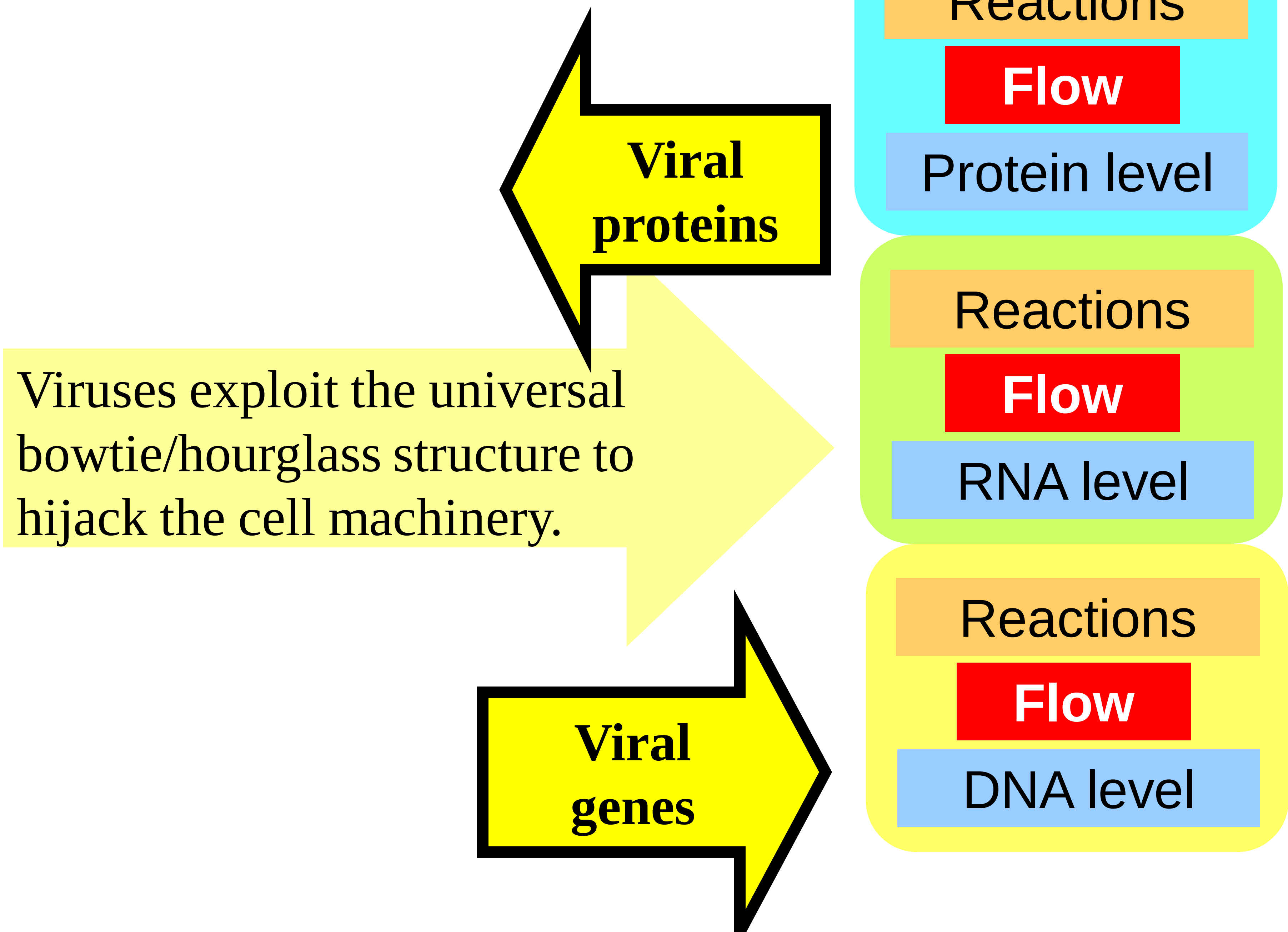
Top to bottom

- Metabolically costly but fast to cheap but slow
- Special enzymes to general polymerases
- Allostery to regulated recruitment
- Analog to digital
- High molecule count to low (noise)

Rich Tradeoffs



Fragility example: Viruses



Biology versus the Internet

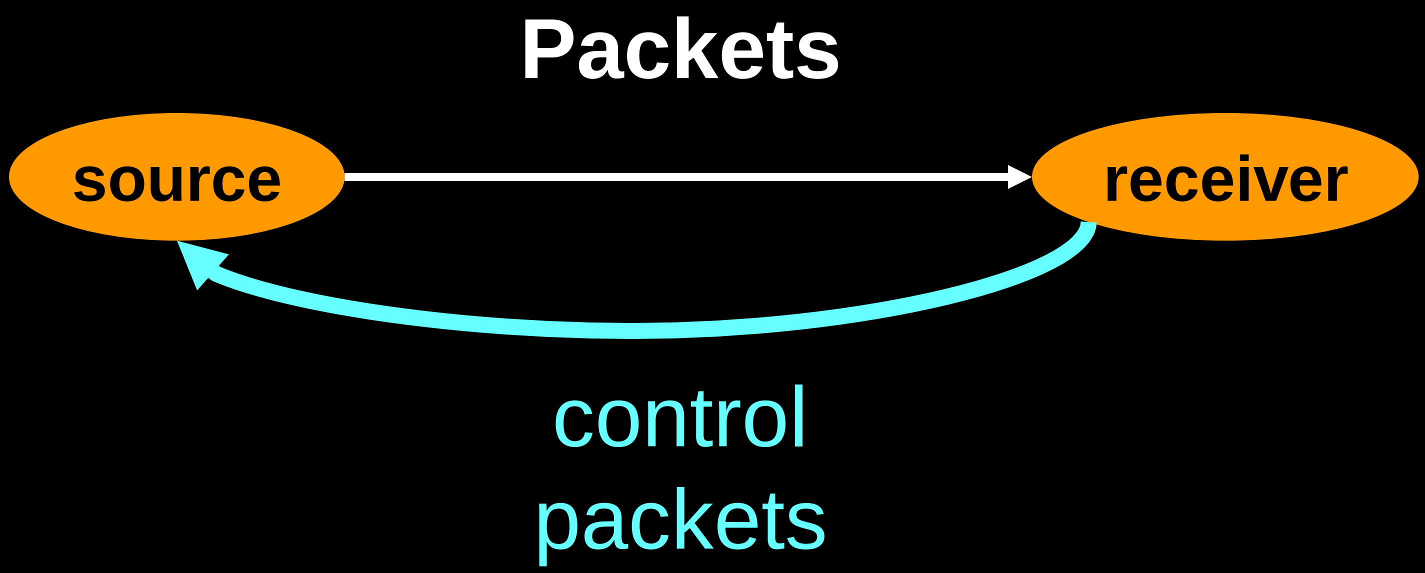
Similarities

- Evolvable architecture
- Robust yet fragile
- **Constraints/deconstrain**
- **Layering, modularity**
- **Hourglass with bowties**
- Feedback
- Dynamics
- Distributed/decentralized
- ***Not*** scale-free, edge-of-chaos, self-organized criticality, etc

Differences

- Metabolism
- Materials and energy
- **Autocatalytic feedback**
- Feedback complexity
- Development and regeneration
- >4B years of evolution

Control of the Internet



signaling

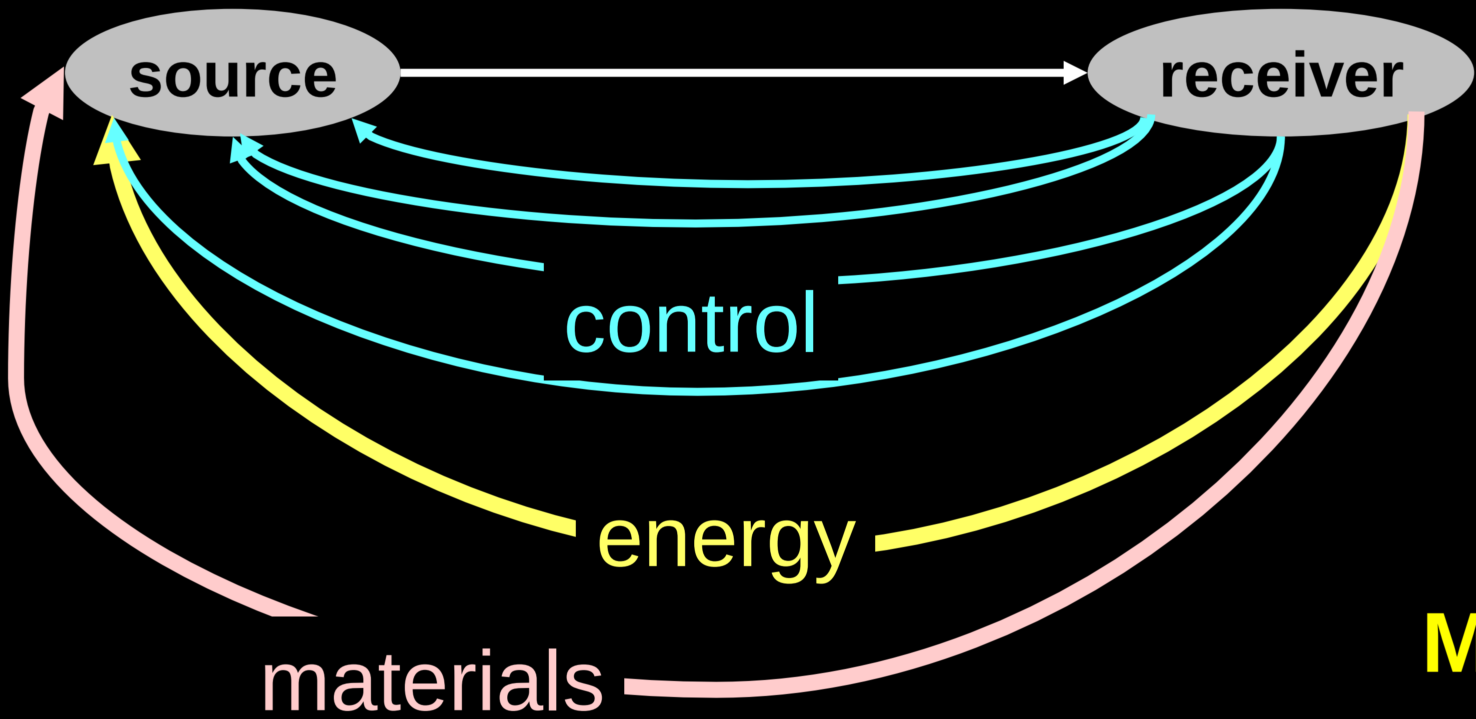
gene expression

metabolism

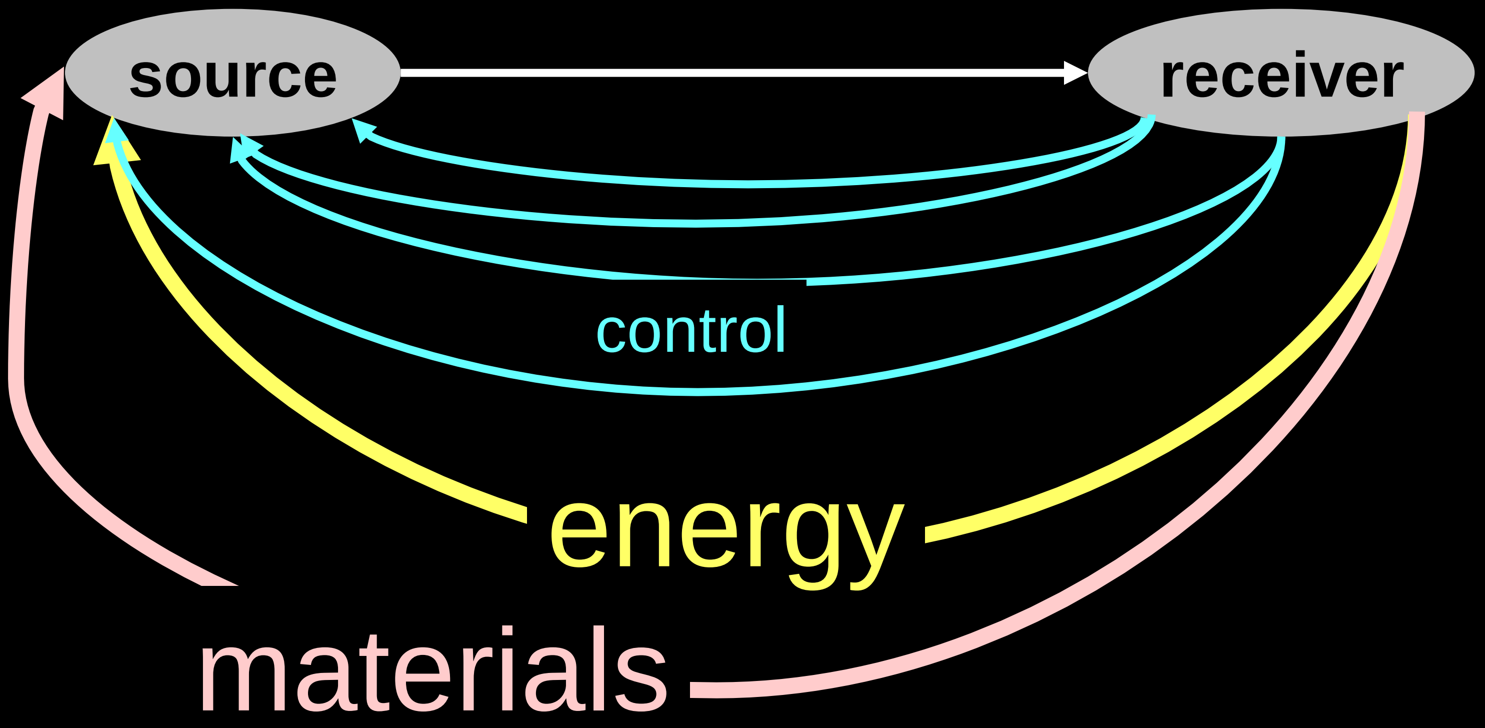
lineage

Biological pathways

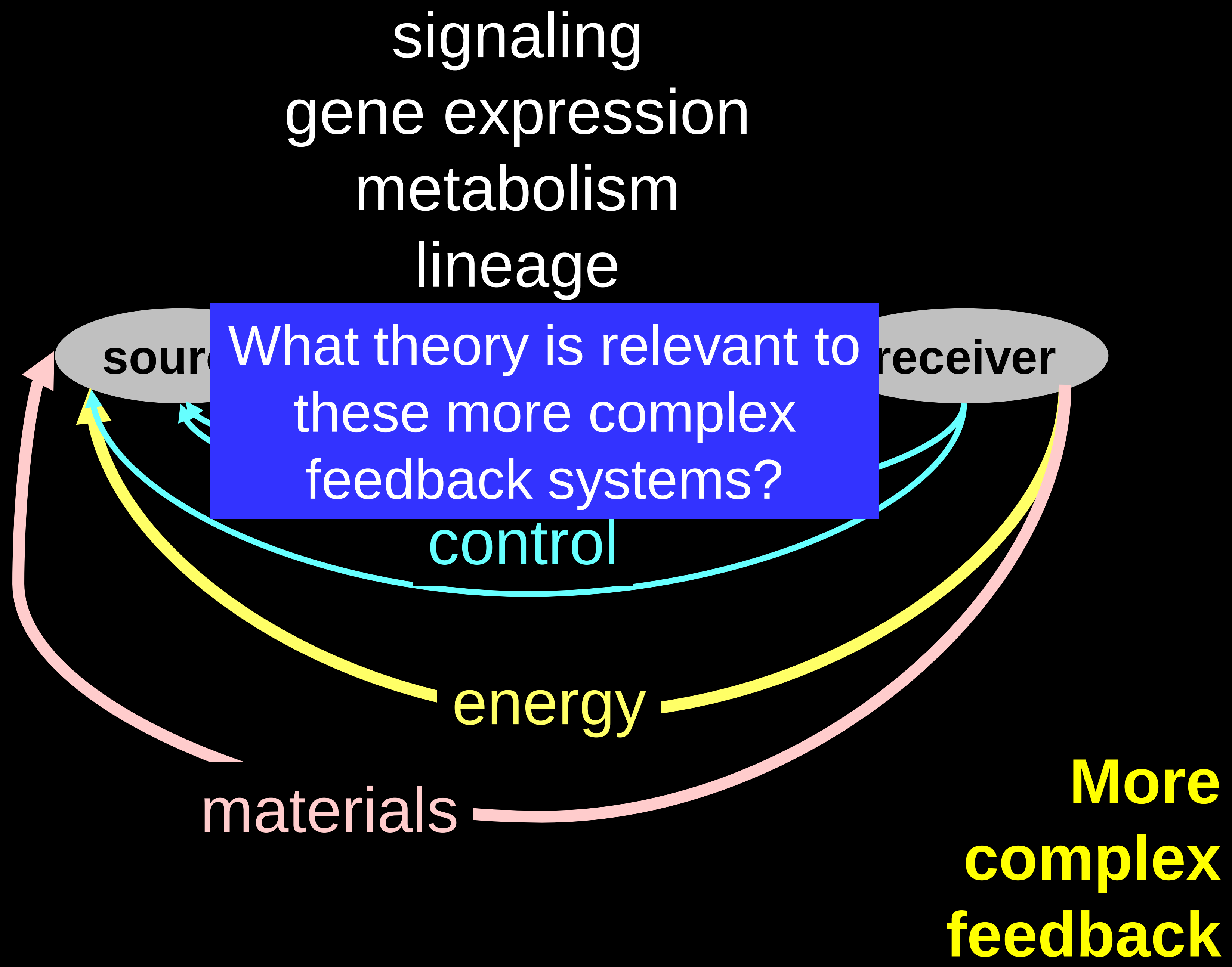
signaling
gene expression
metabolism
lineage



More complex feedback



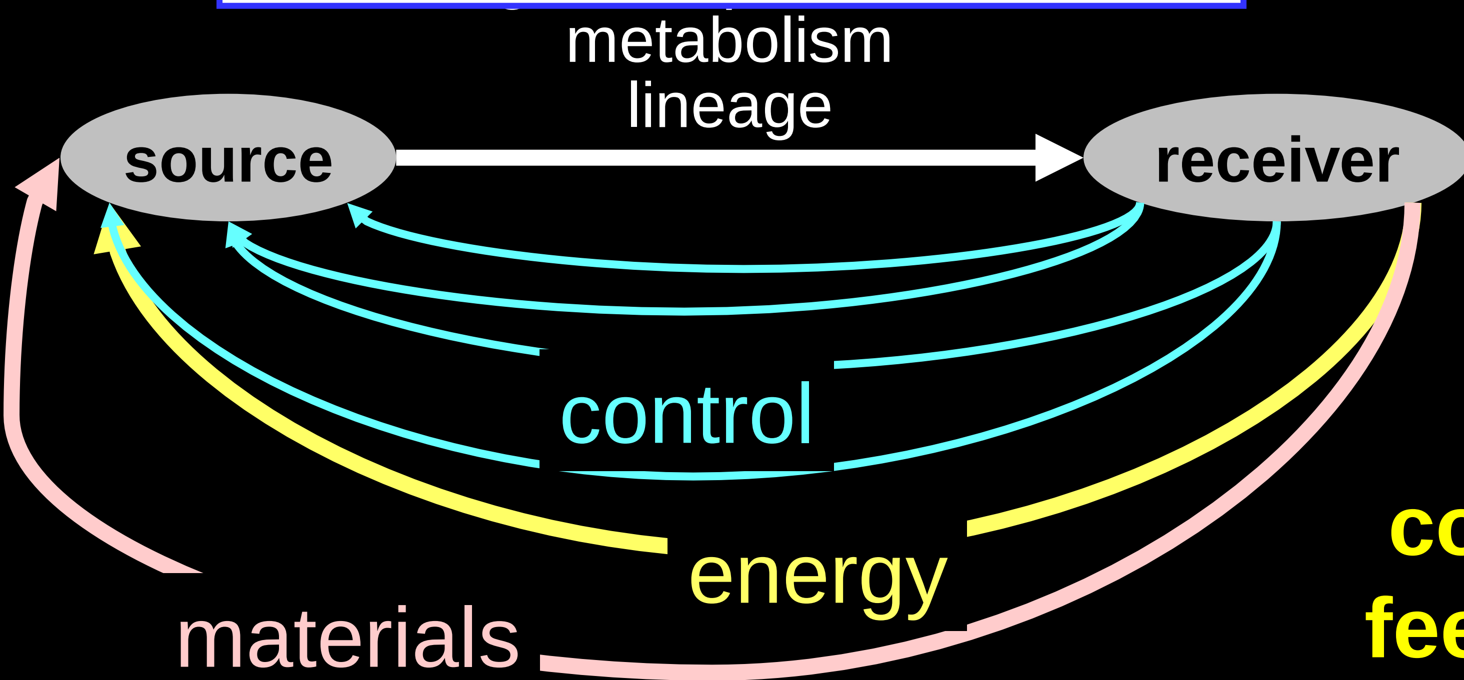
Autocatalytic feedback



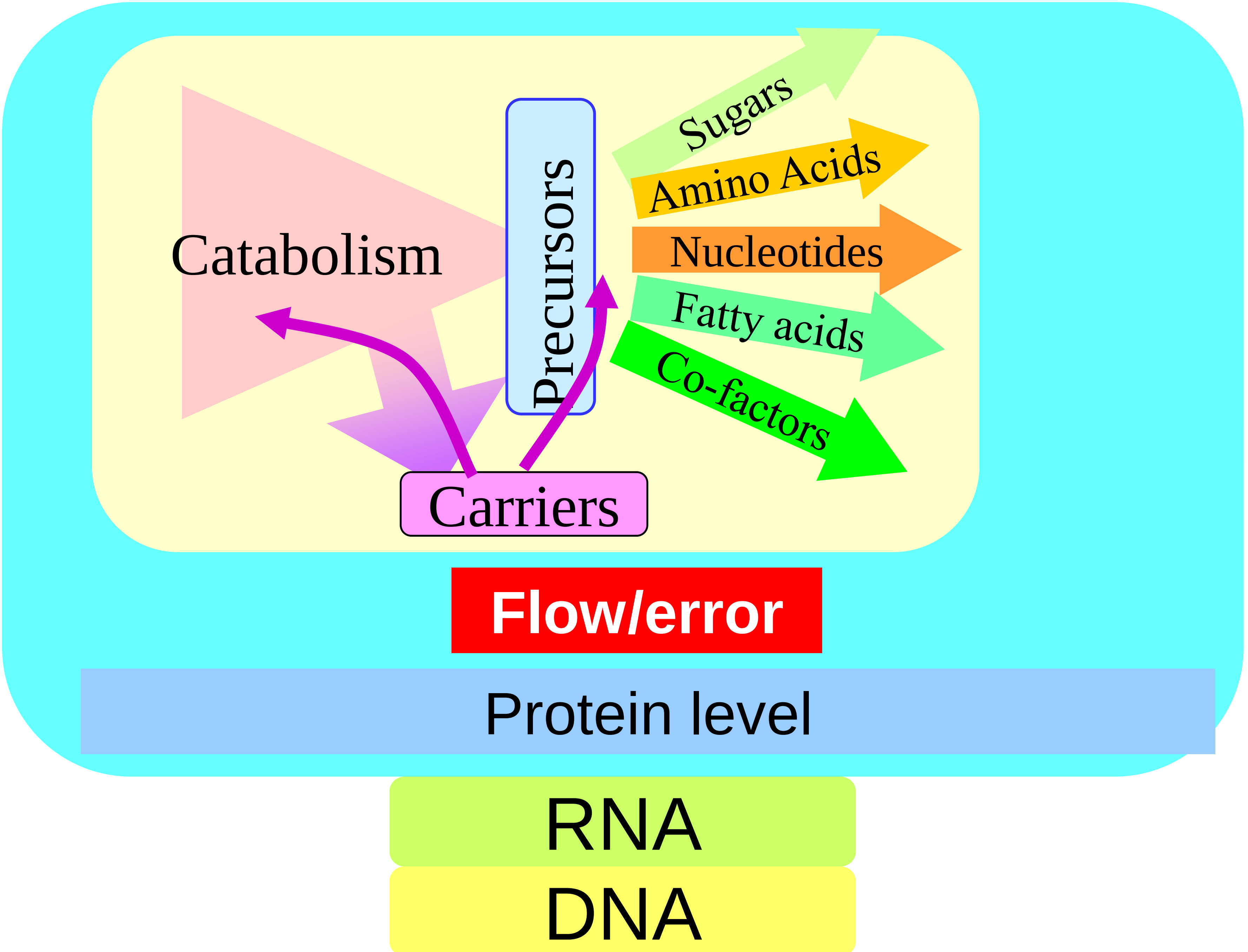
signaling
gene expression
metabolism
lineage
sour
receiver
What theory is relevant to these more complex feedback systems?
control
energy
materials
More complex feedback

What theory is relevant to these more complex feedback systems?

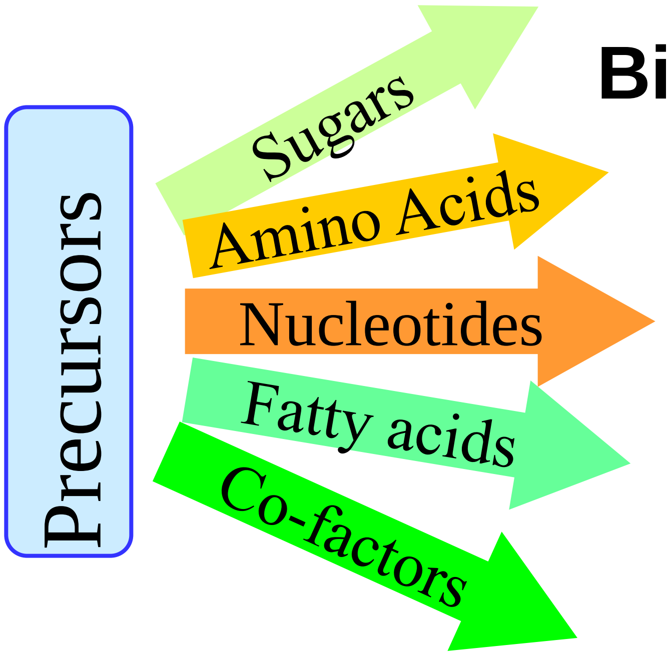
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\frac{z}{z^2+\omega^2}d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$



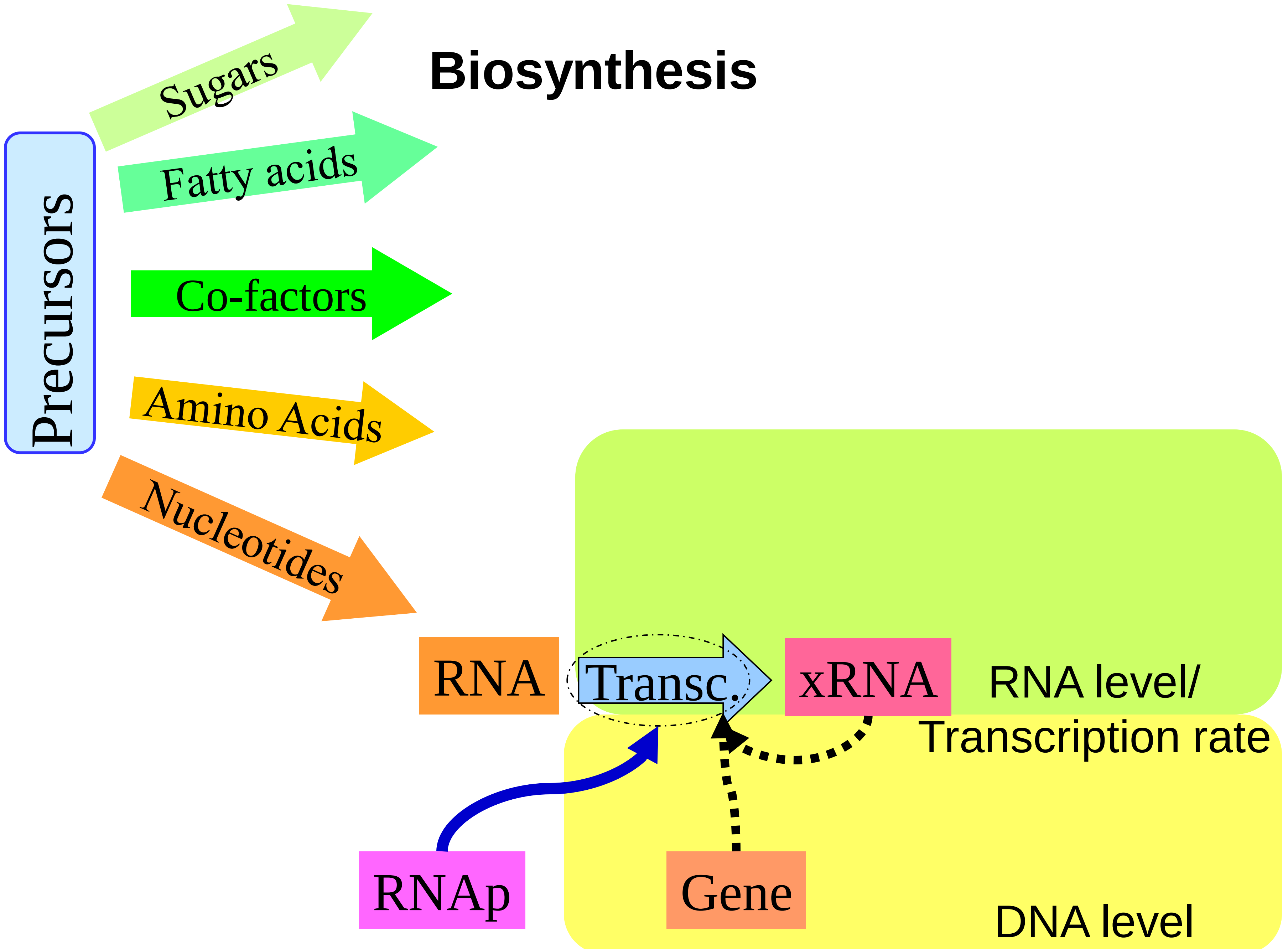
More complex feedback

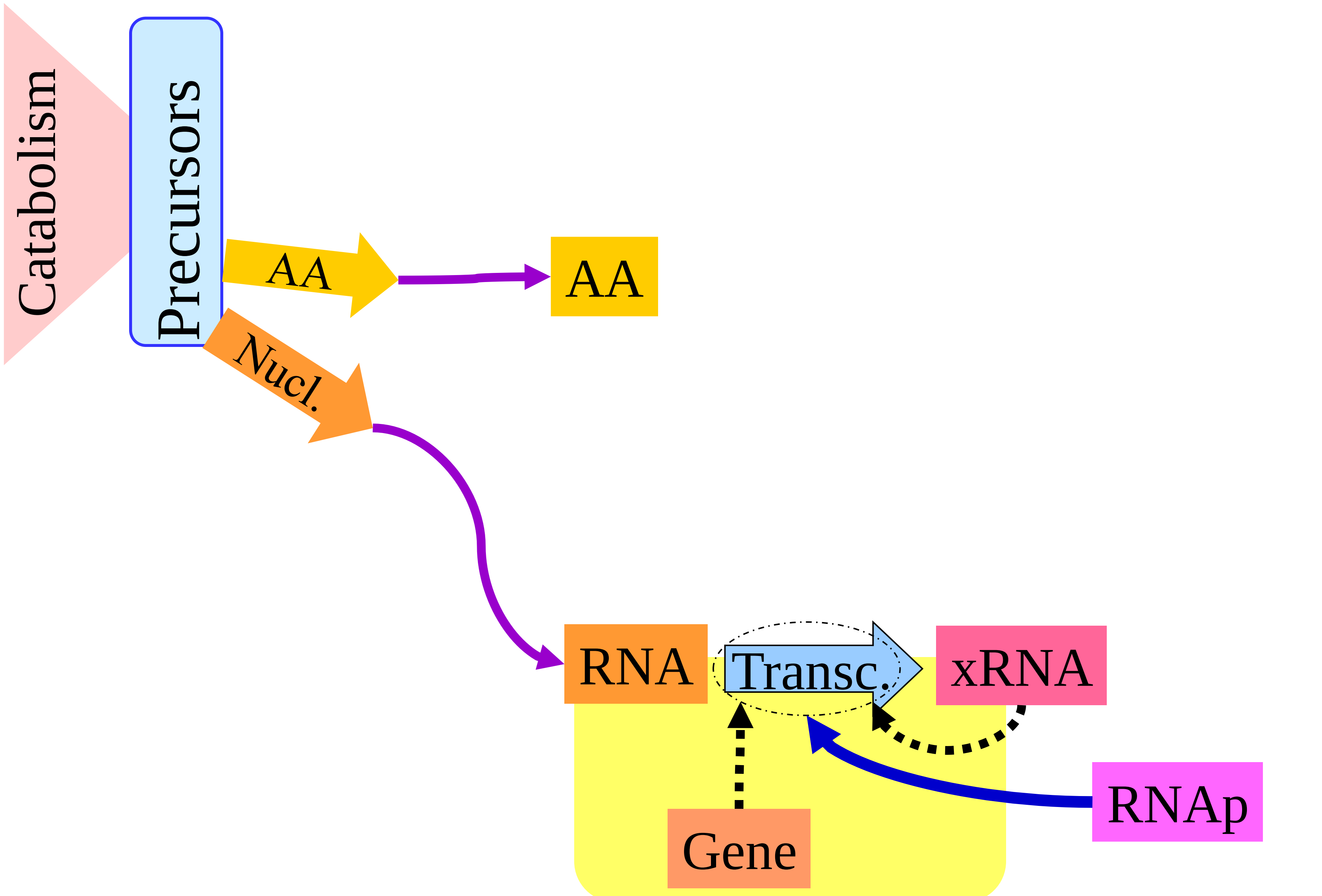


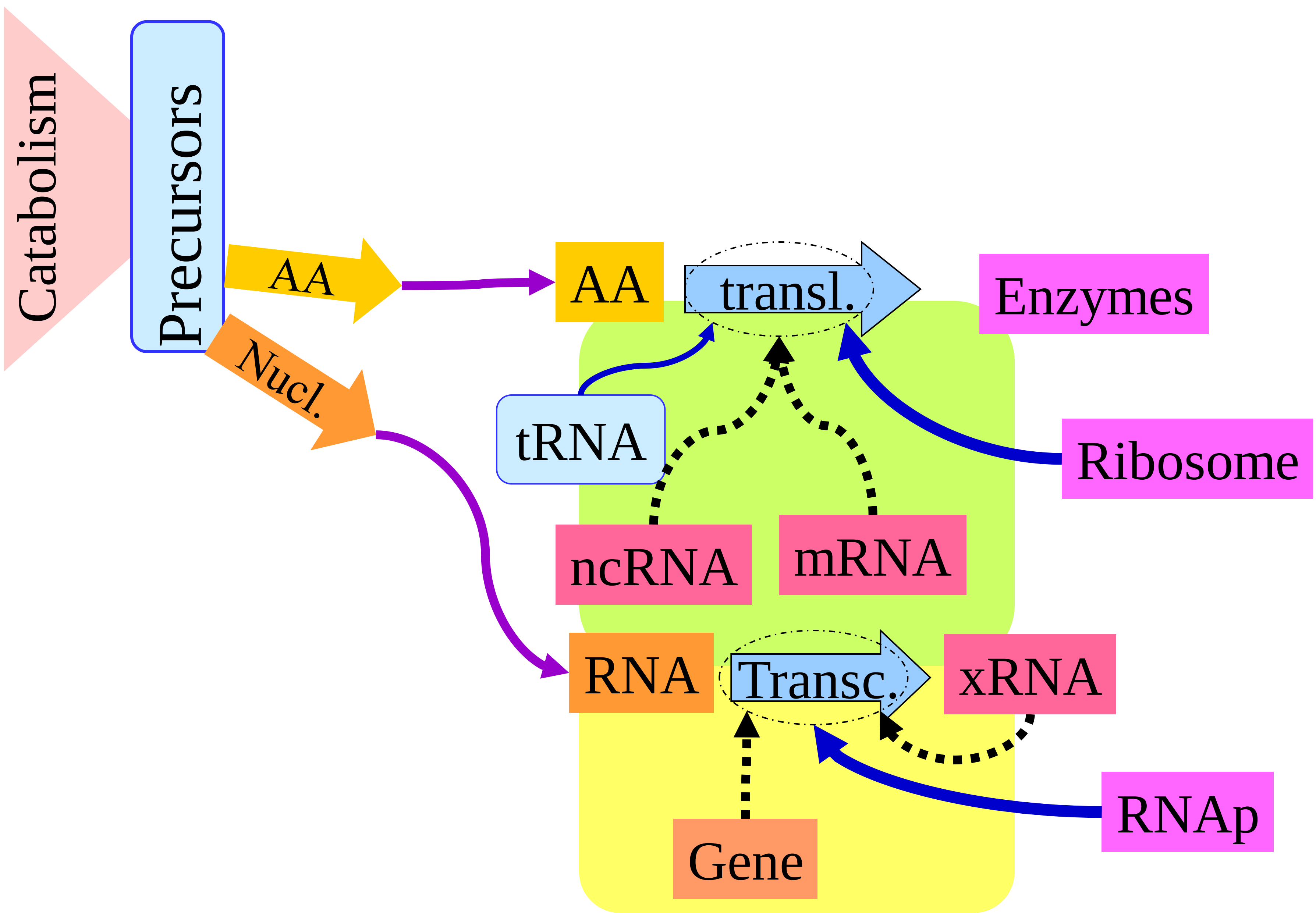
Catabolism
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Carriers
Flow/error
Protein level
RNA
DNA



Biosynthesis

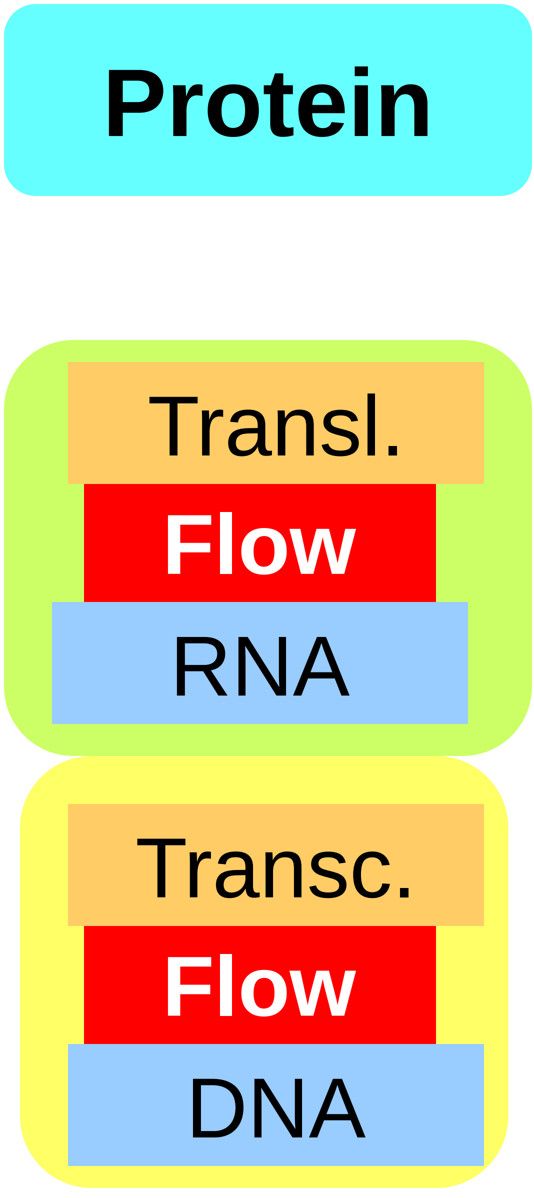

Biosynthesis
Precursors
Sugars
Fatty acids
Co-factors
Amino Acids
Nucleotides
RNA
Transc.
xRNA
RNA level/
Transcription rate
RNAp
Gene
DNA level

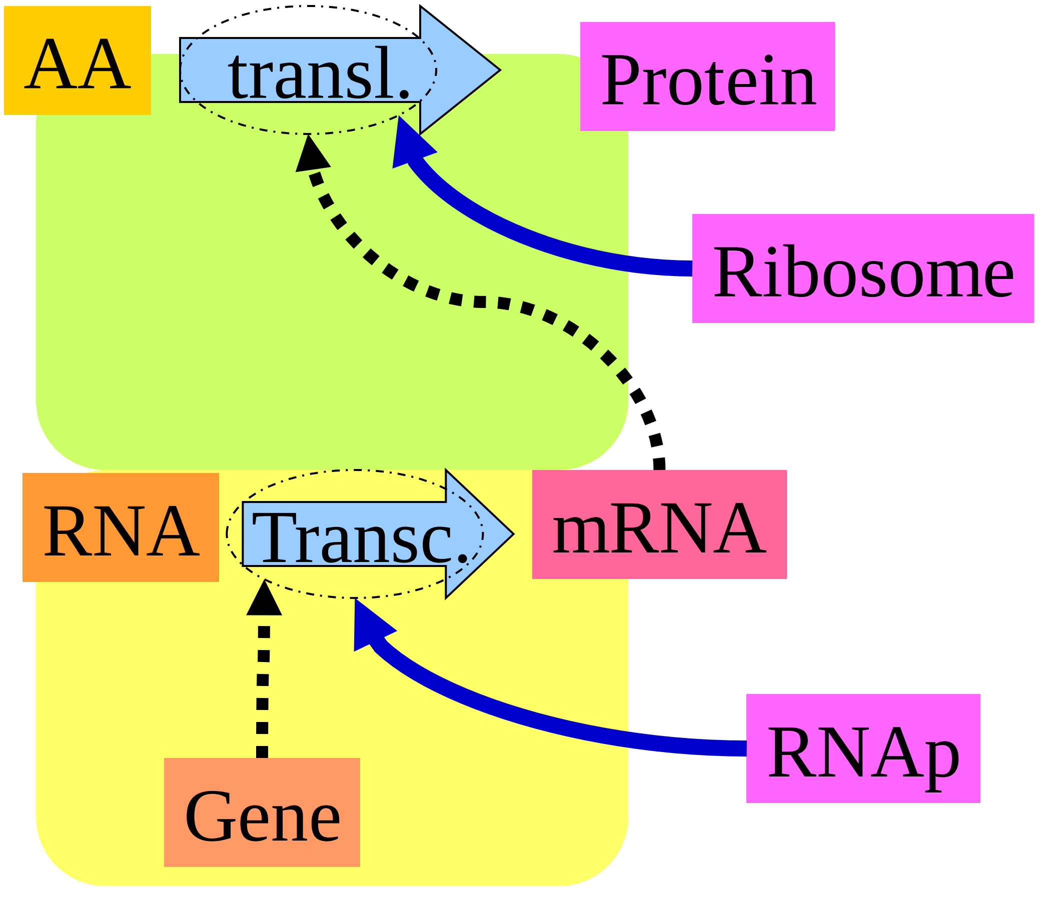

Catabolism
Precursors
AA
AA
Nucl.
RNA
Transc.
xRNA
Gene
RNAp

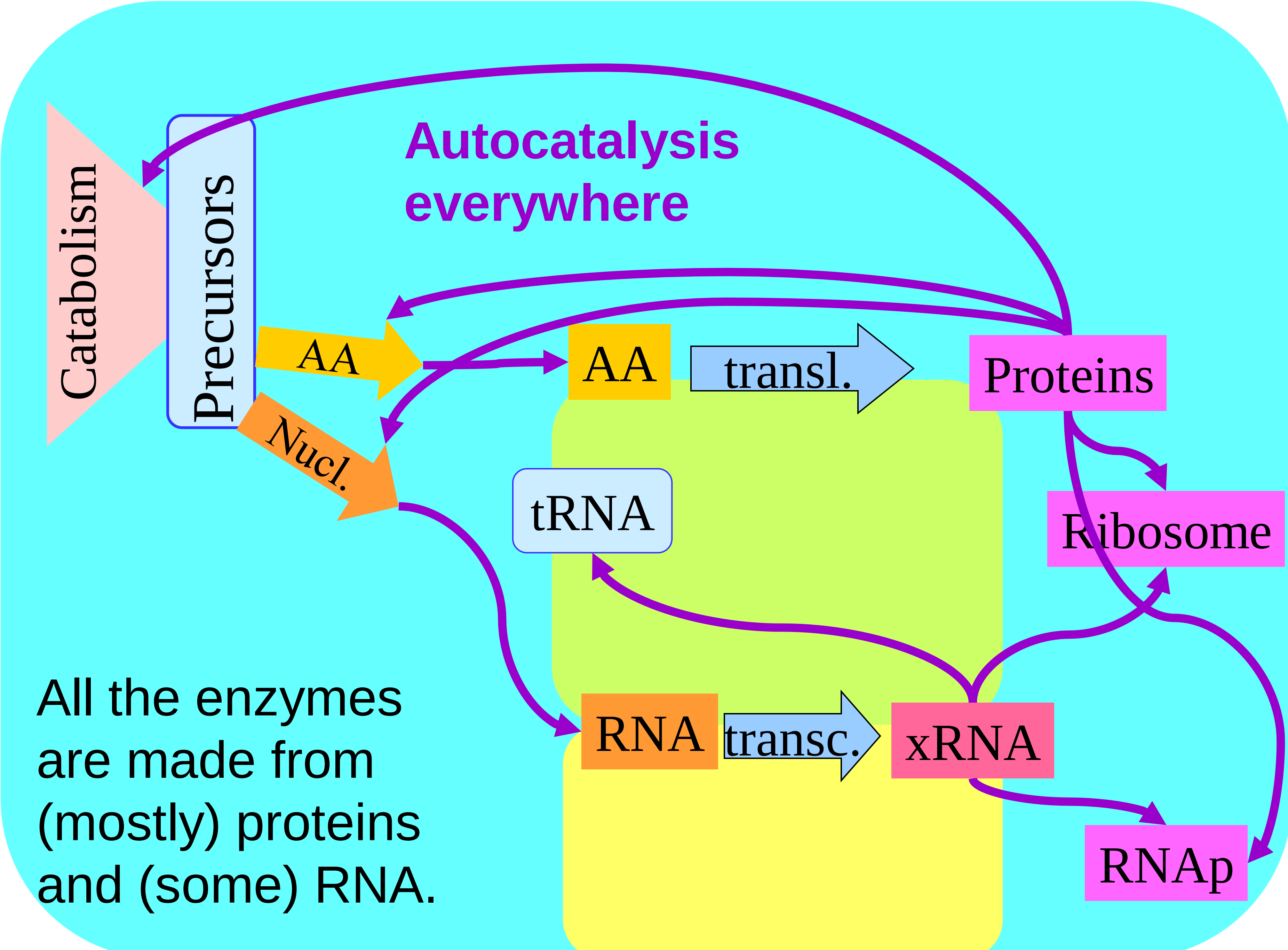


Catabolism
Precursors
AA
Nucl.
AA
transl.
Enzymes
tRNA
Ribosome
ncRNA
mRNA
RNA
Transc.
xRNA
RNAp
Gene

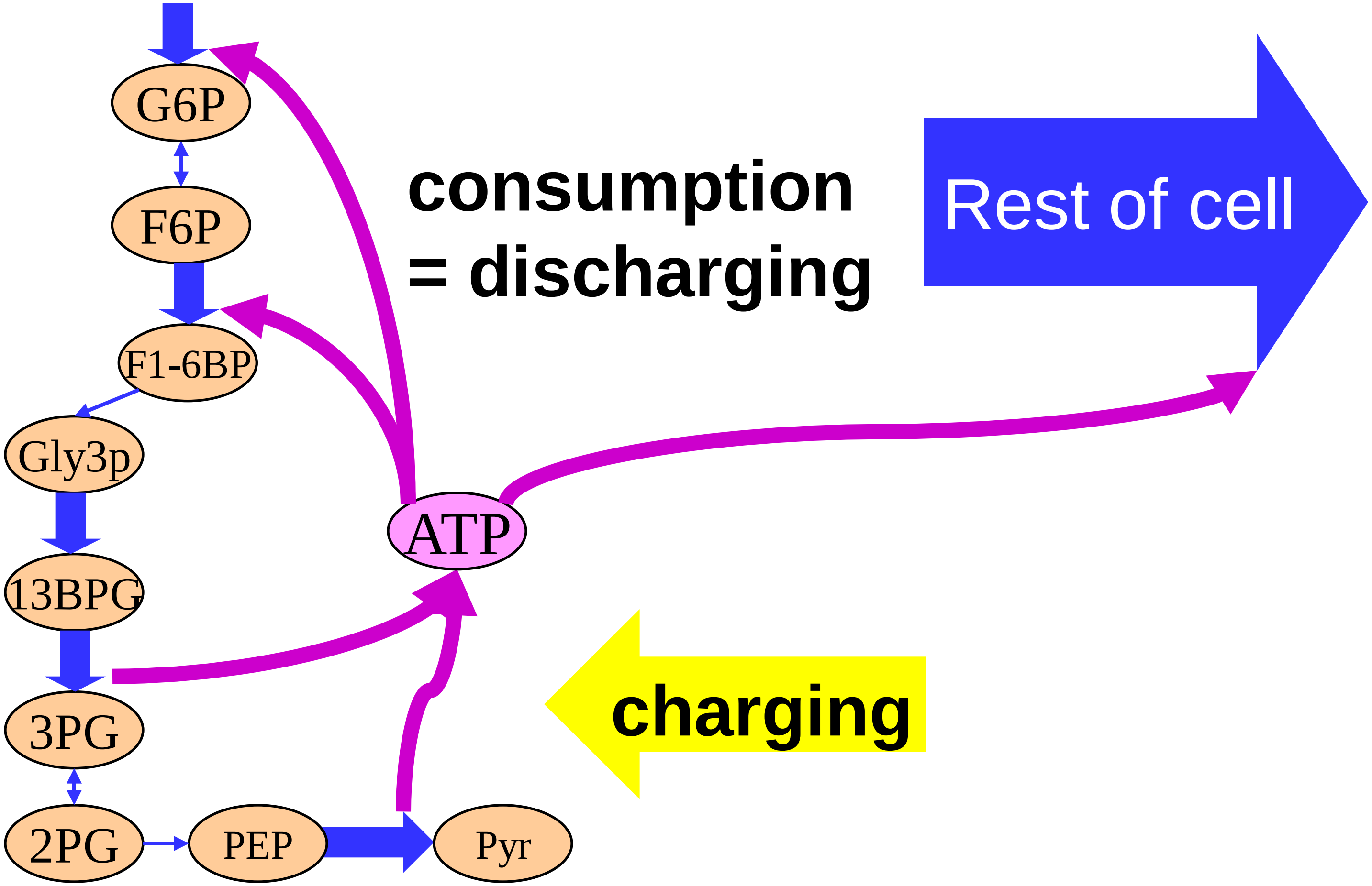
“Central dogma”

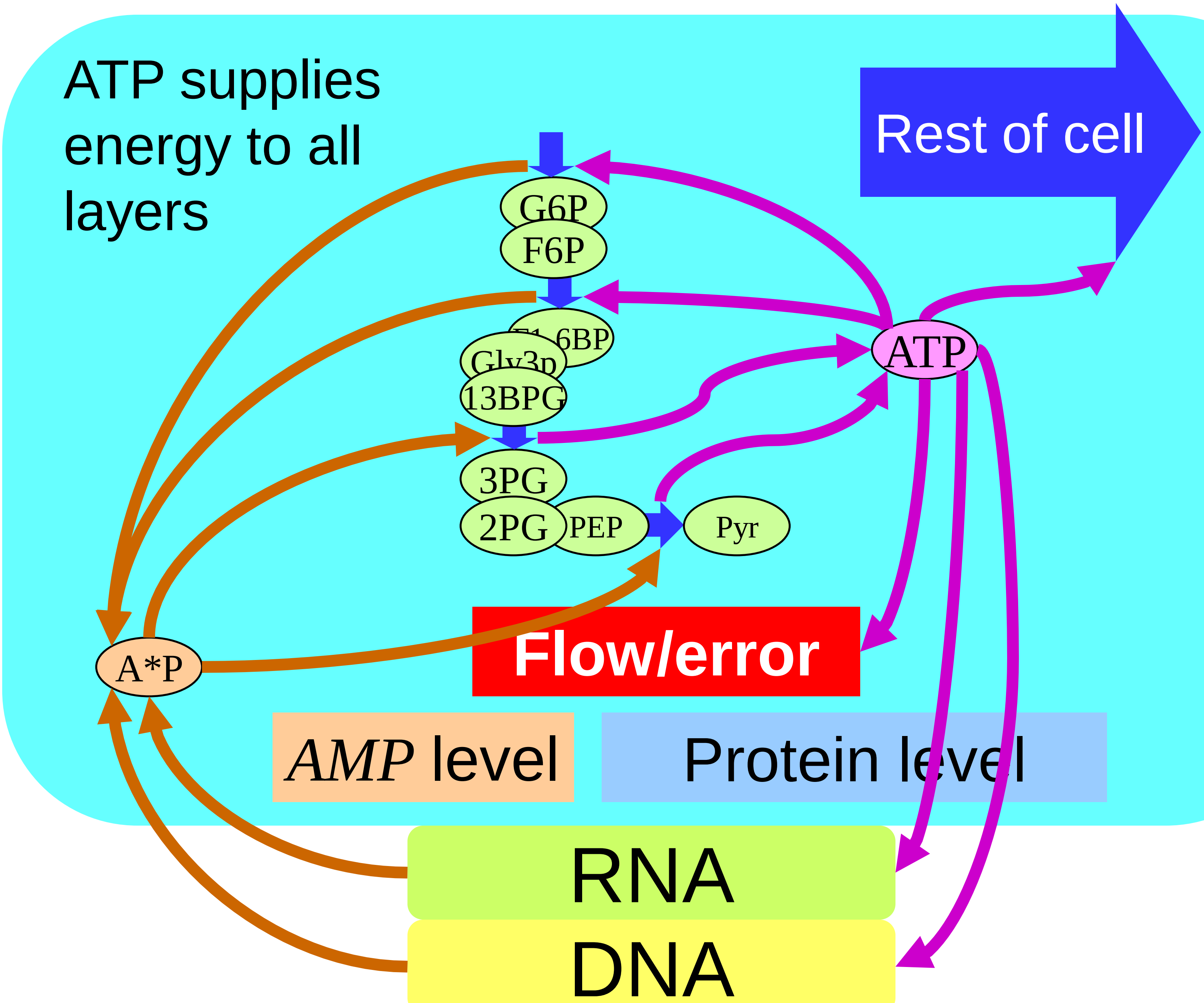


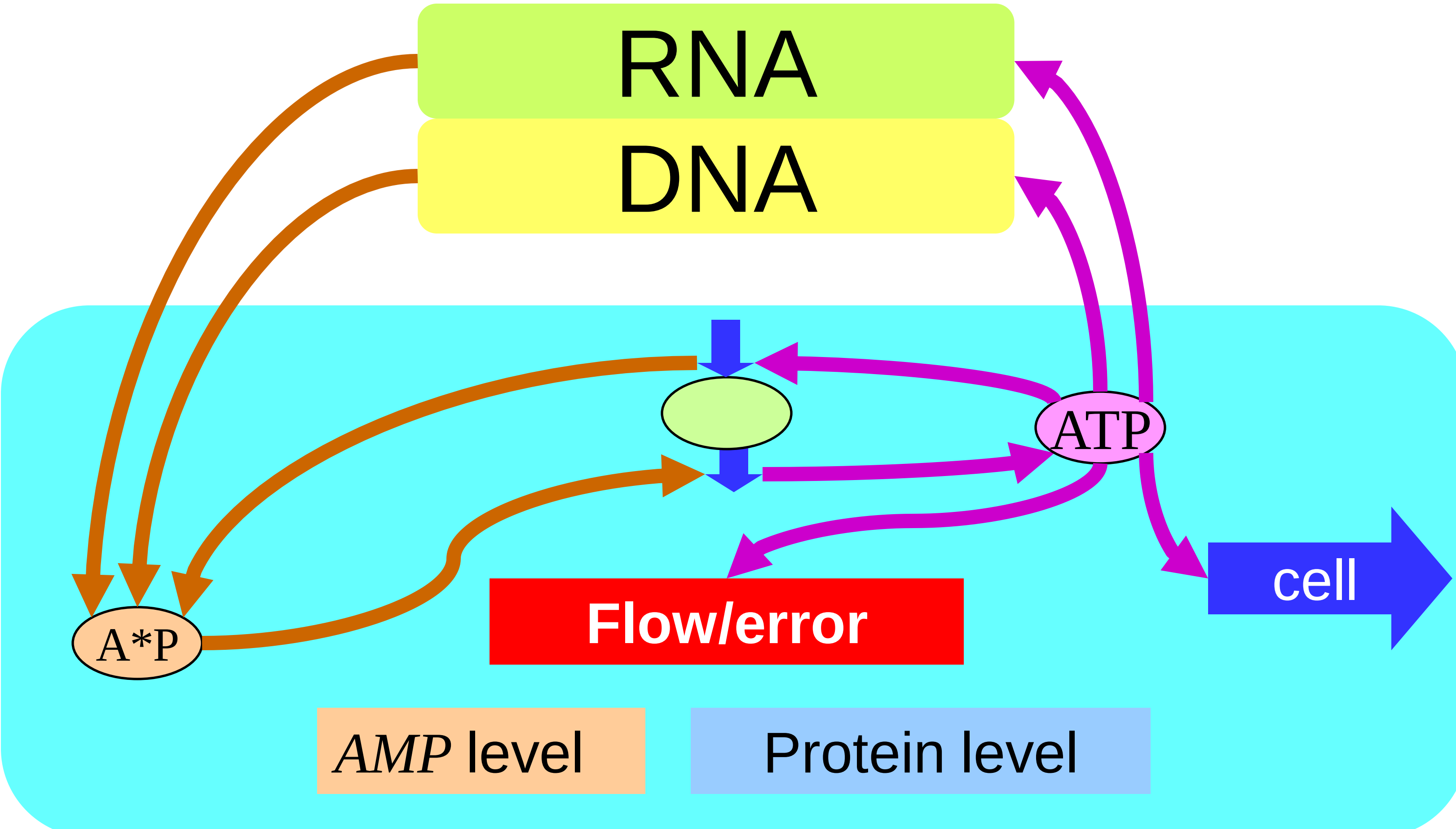



Autocatalysis
everywhere
Catabolism
Precursors
AA
AA
transl.
Proteins
Nucl.
tRNA
Ribosome
RNA
transc.
xRNA
RNAp
All the enzymes
are made from
(mostly) proteins
and (some) RNA.

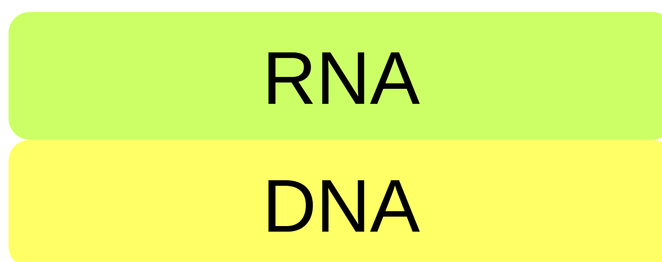
This is just charging and discharging

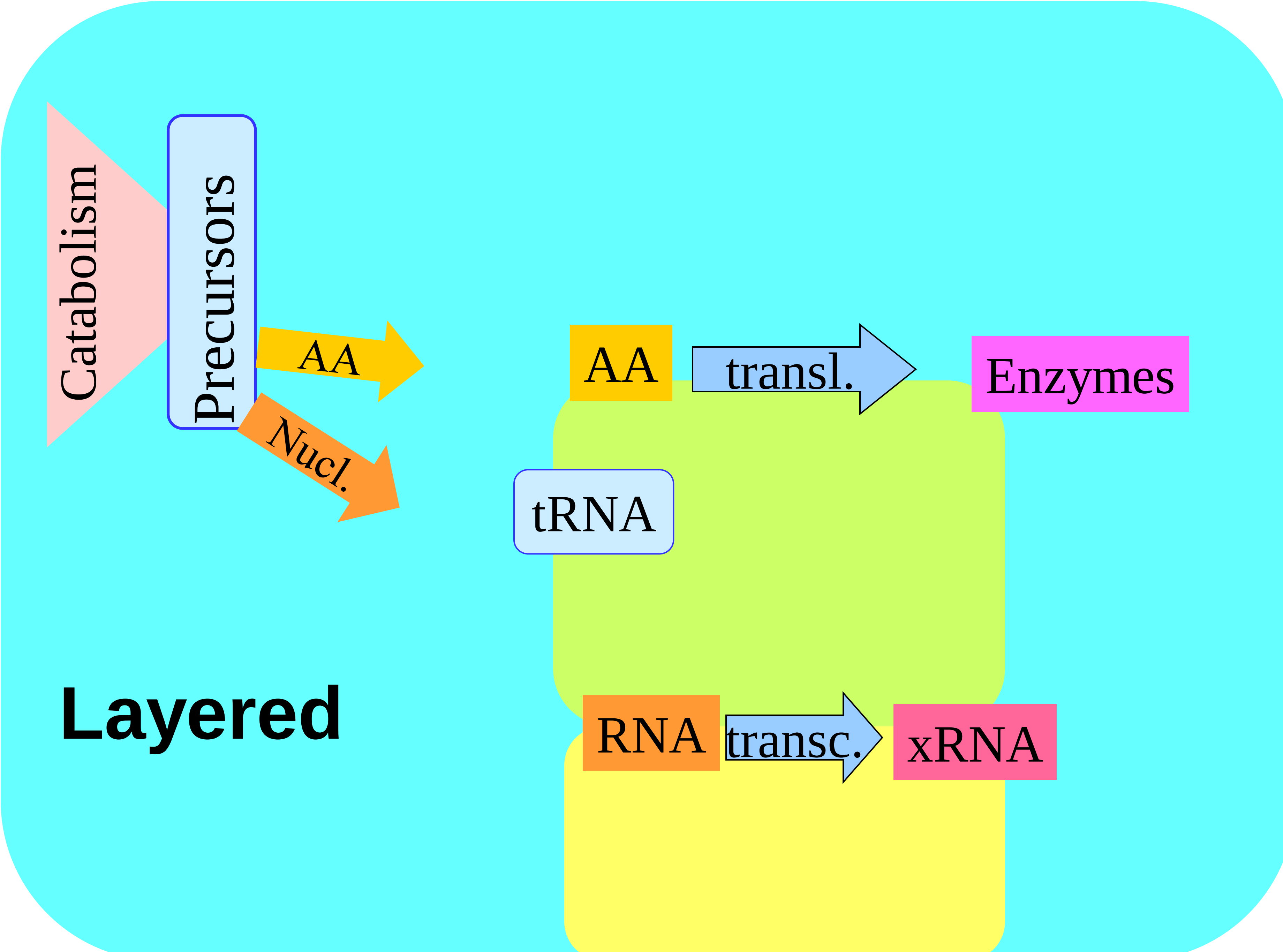


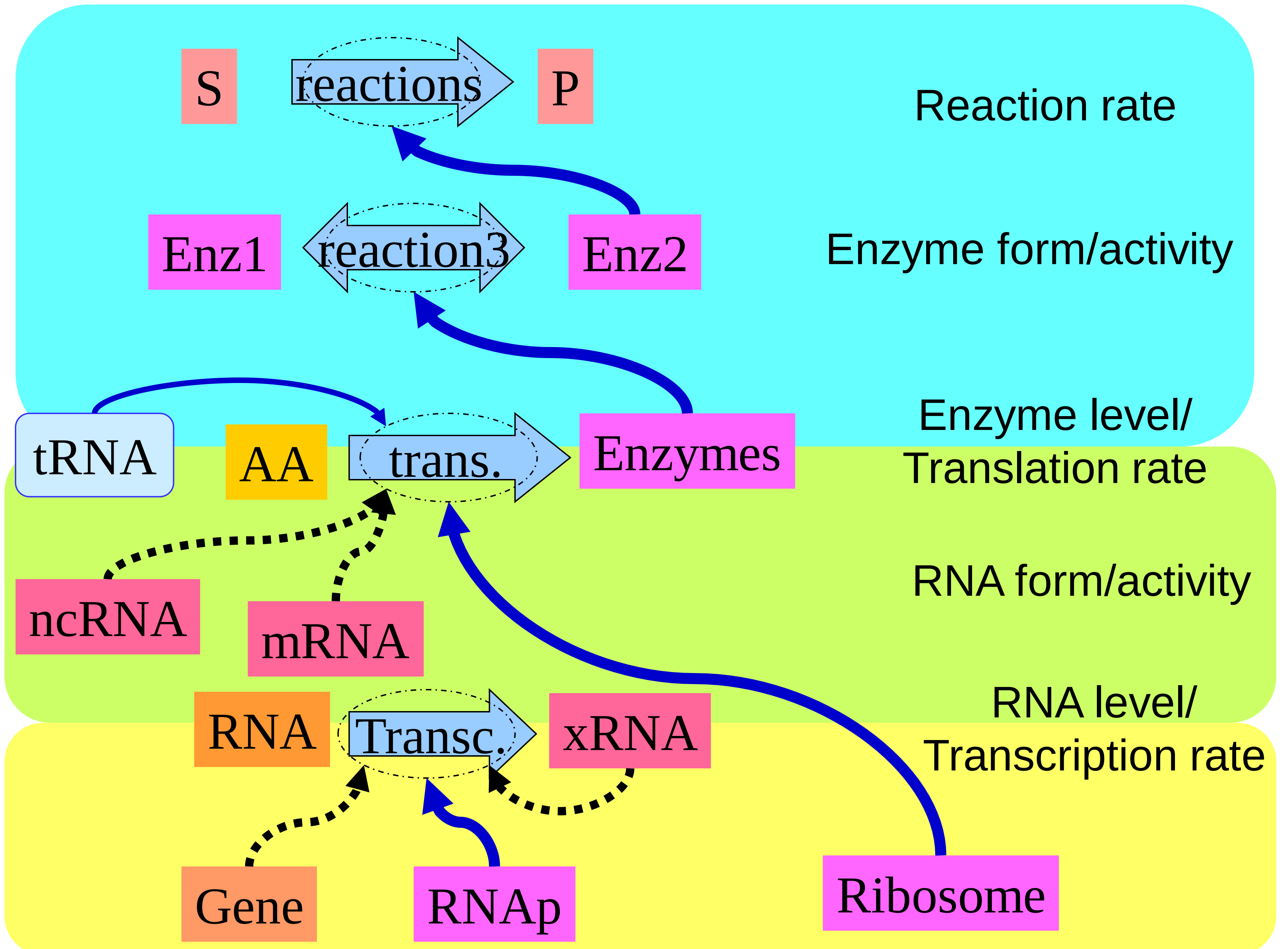

ATP supplies energy to all layers
Rest of cell
G6P
F6P
6BP
13BPG
3PG
2PG
PEP
Pyr
ATP
A*P
Flow/error
AMP level
Protein level
RNA
DNA



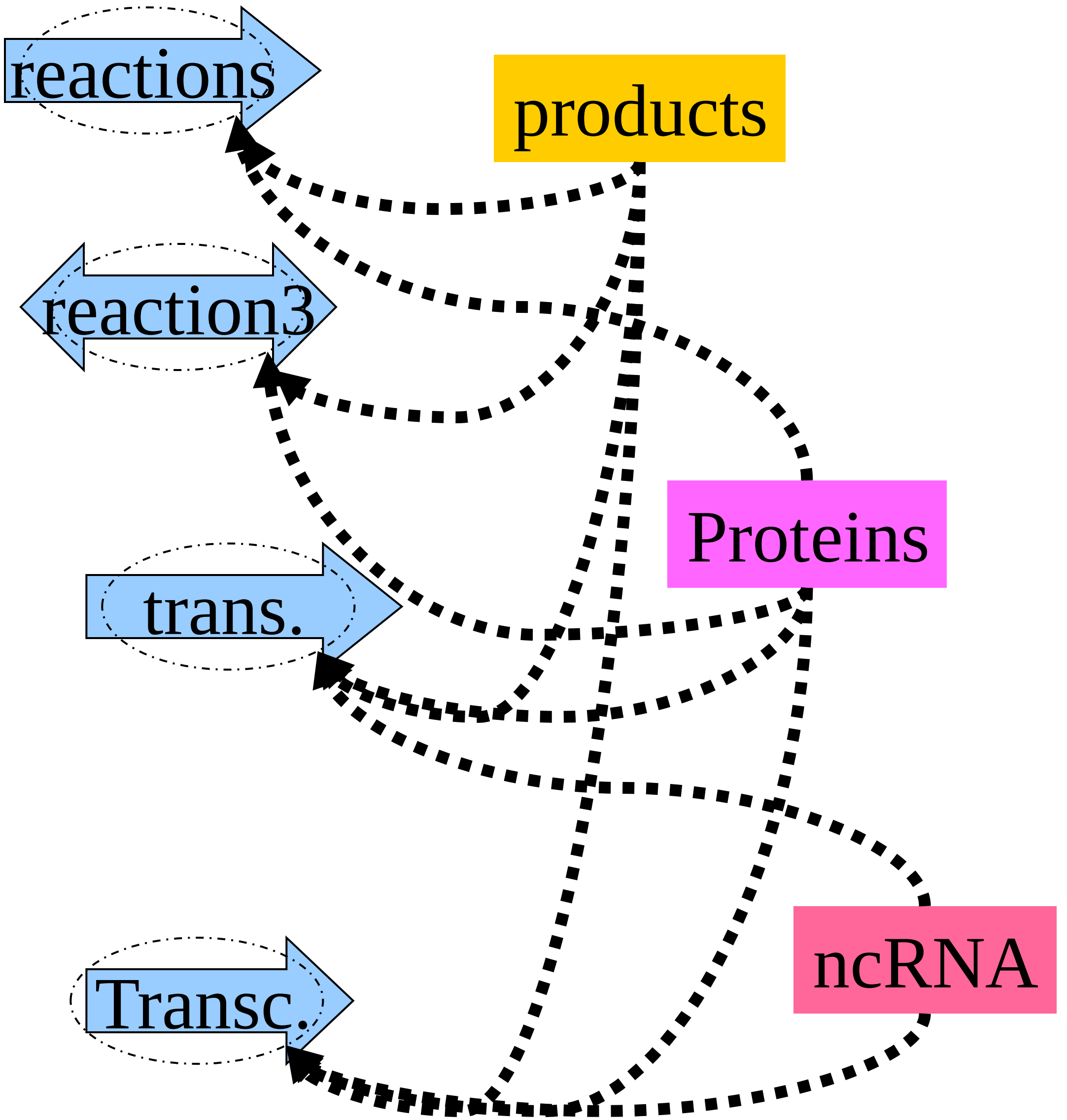
Lots of ways to draw this.




Catabolism
Precursors
AA
Nucl.
AA
transl.
Enzymes
tRNA
RNA
transc.
xRNA
Layered

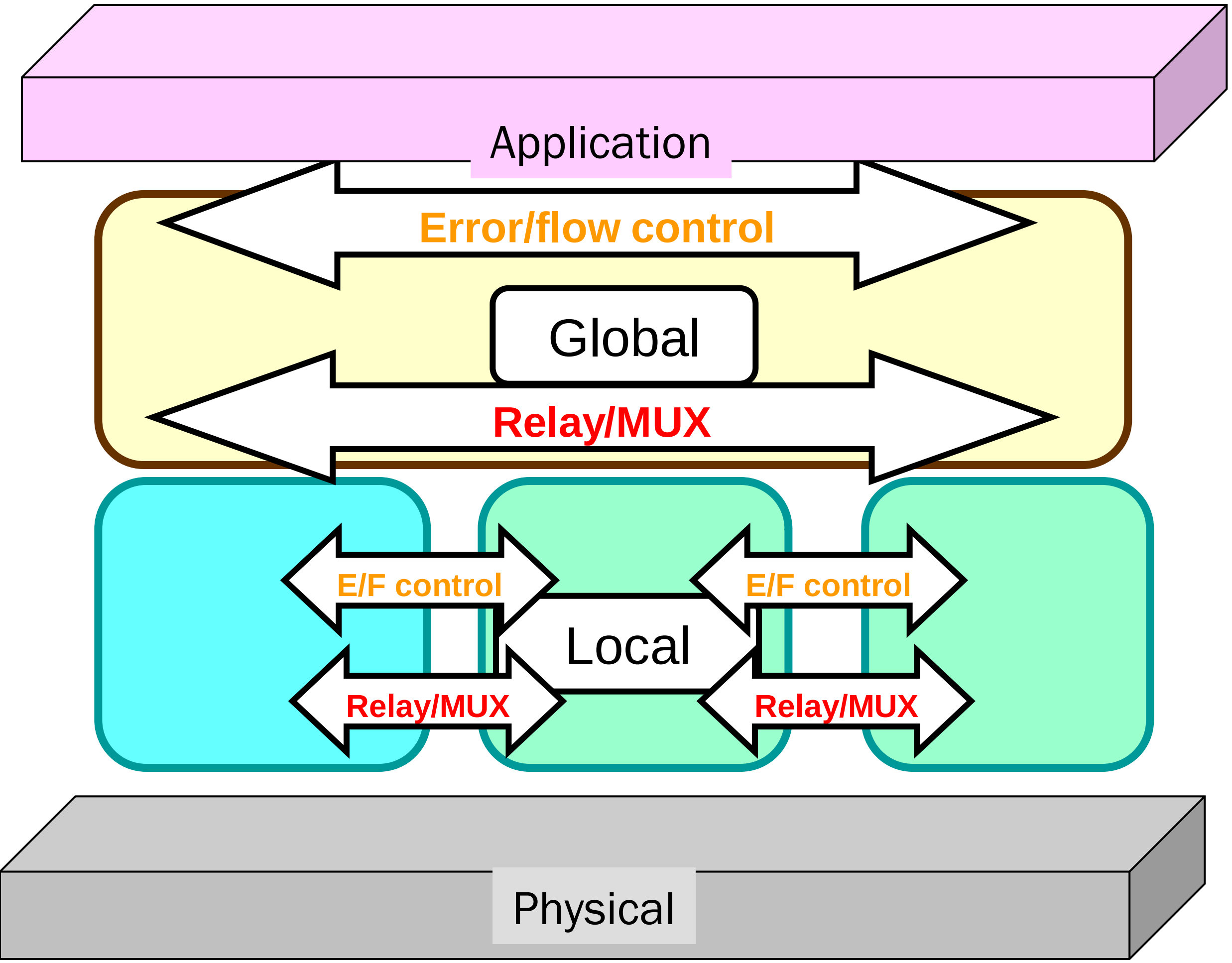

S
reactions
P
Reaction rate
Enz1
reaction3
Enz2
Enzyme form/activity
tRNA
AA
trans.
Enzymes
Enzyme level/
Translation rate
RNA form/activity
ncRNA
mRNA
RNA
Transc.
xRNA
RNA level/
Transcription rate
Gene
RNAp
Ribosome

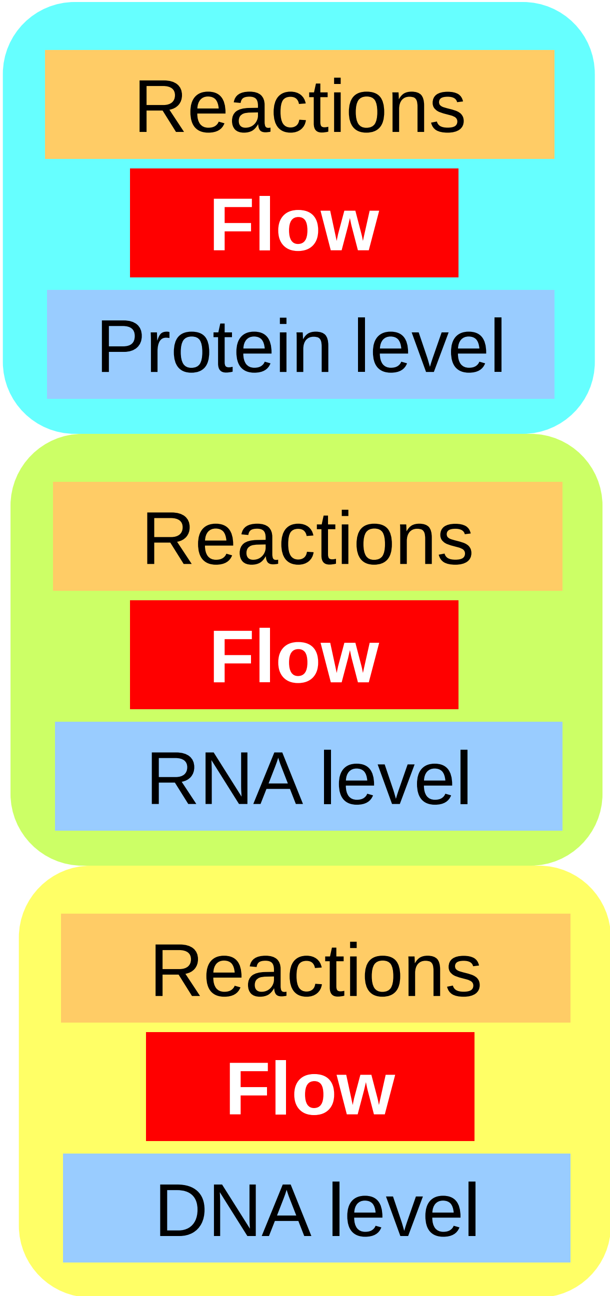
Control?



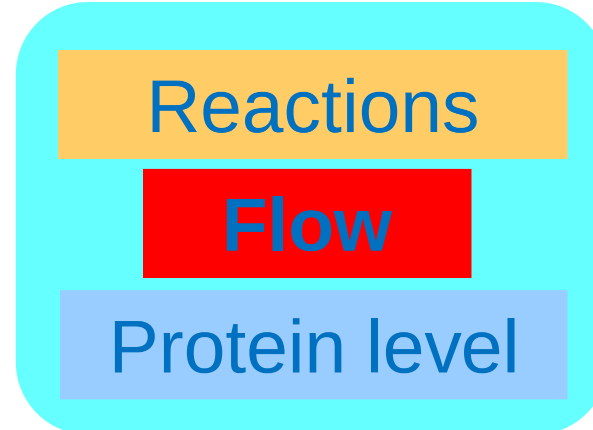
All products
feedback everywhere

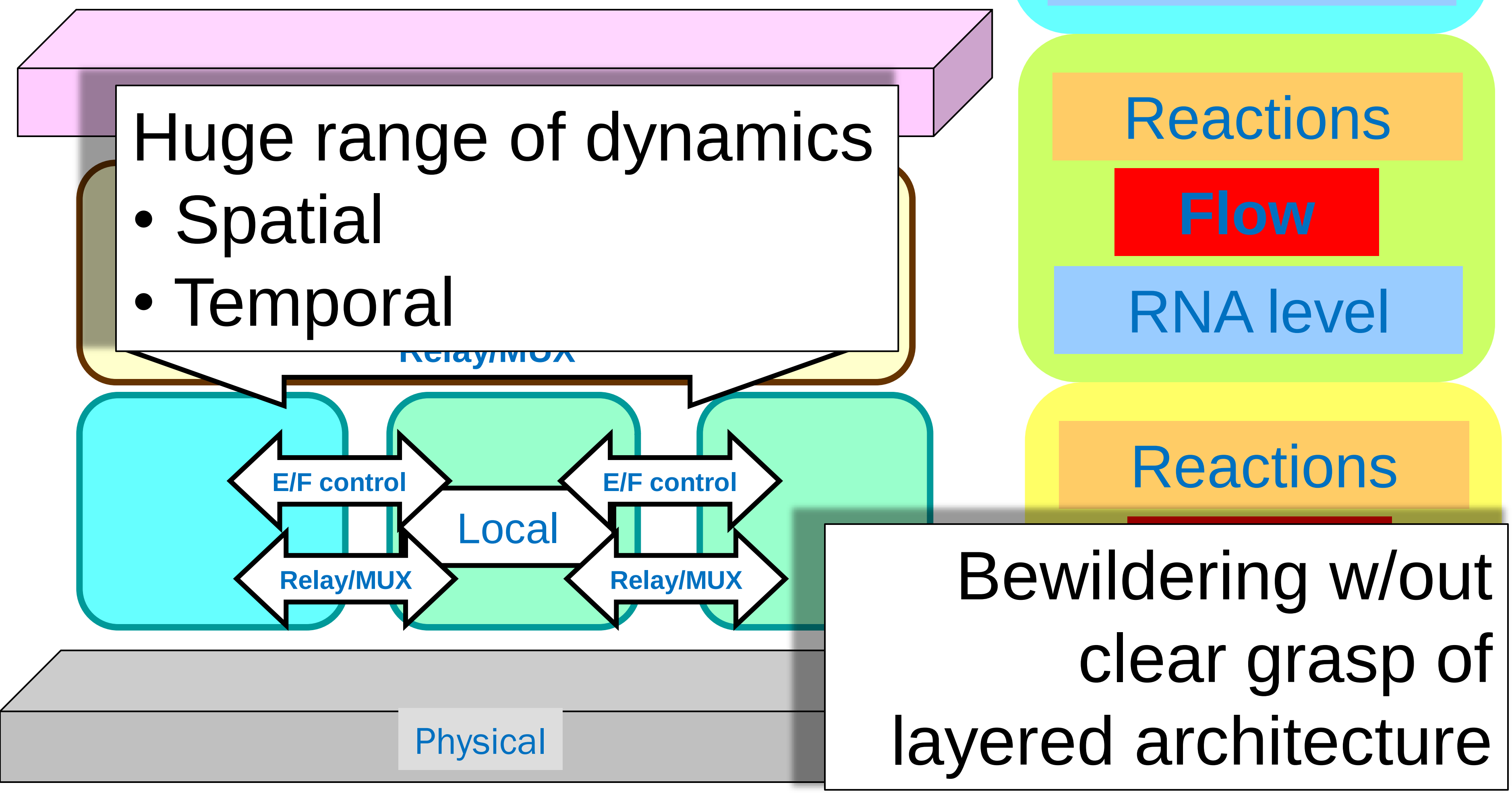
Recursive control structure





Recursive control structure

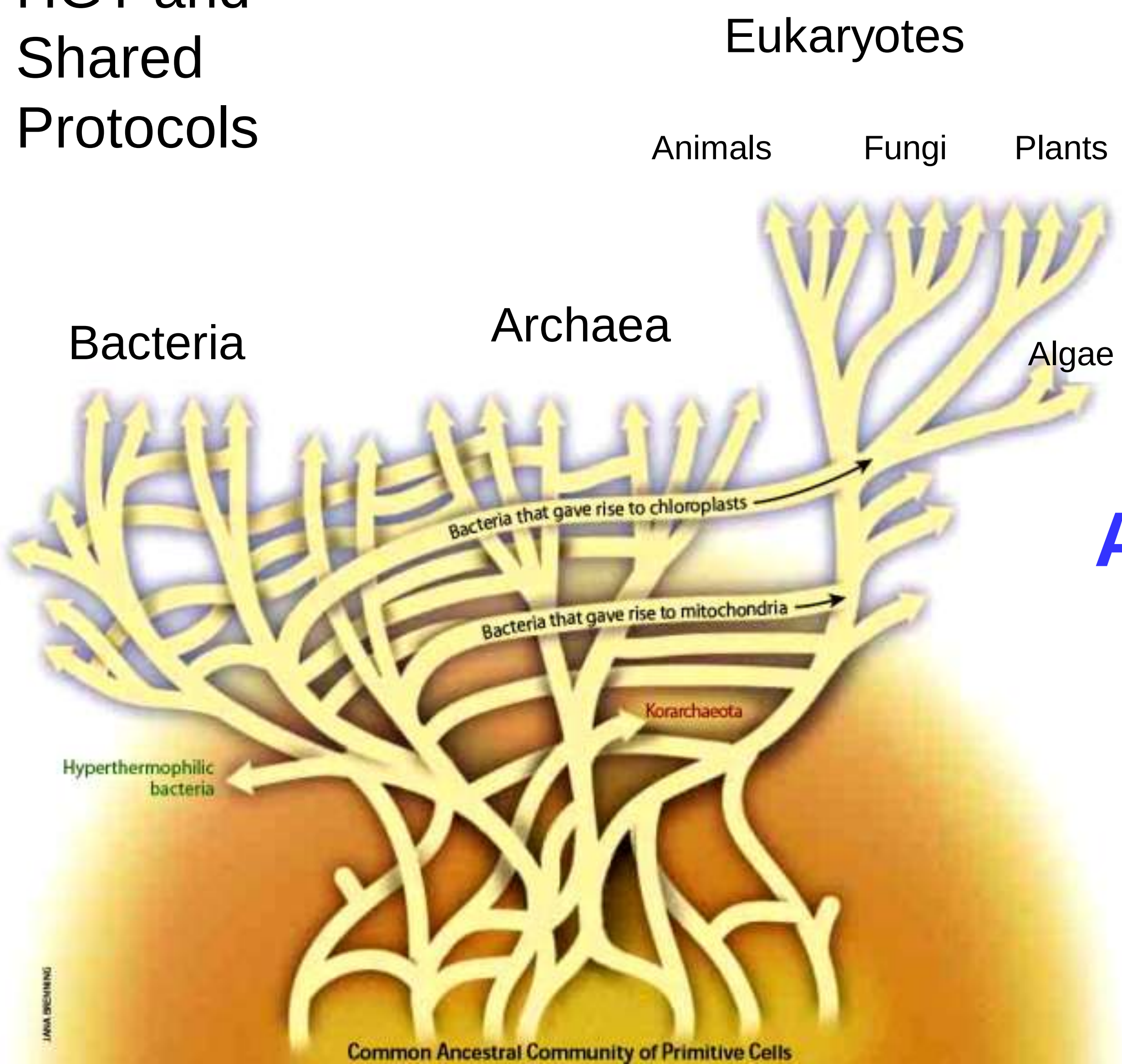




Horizontal gene transfer

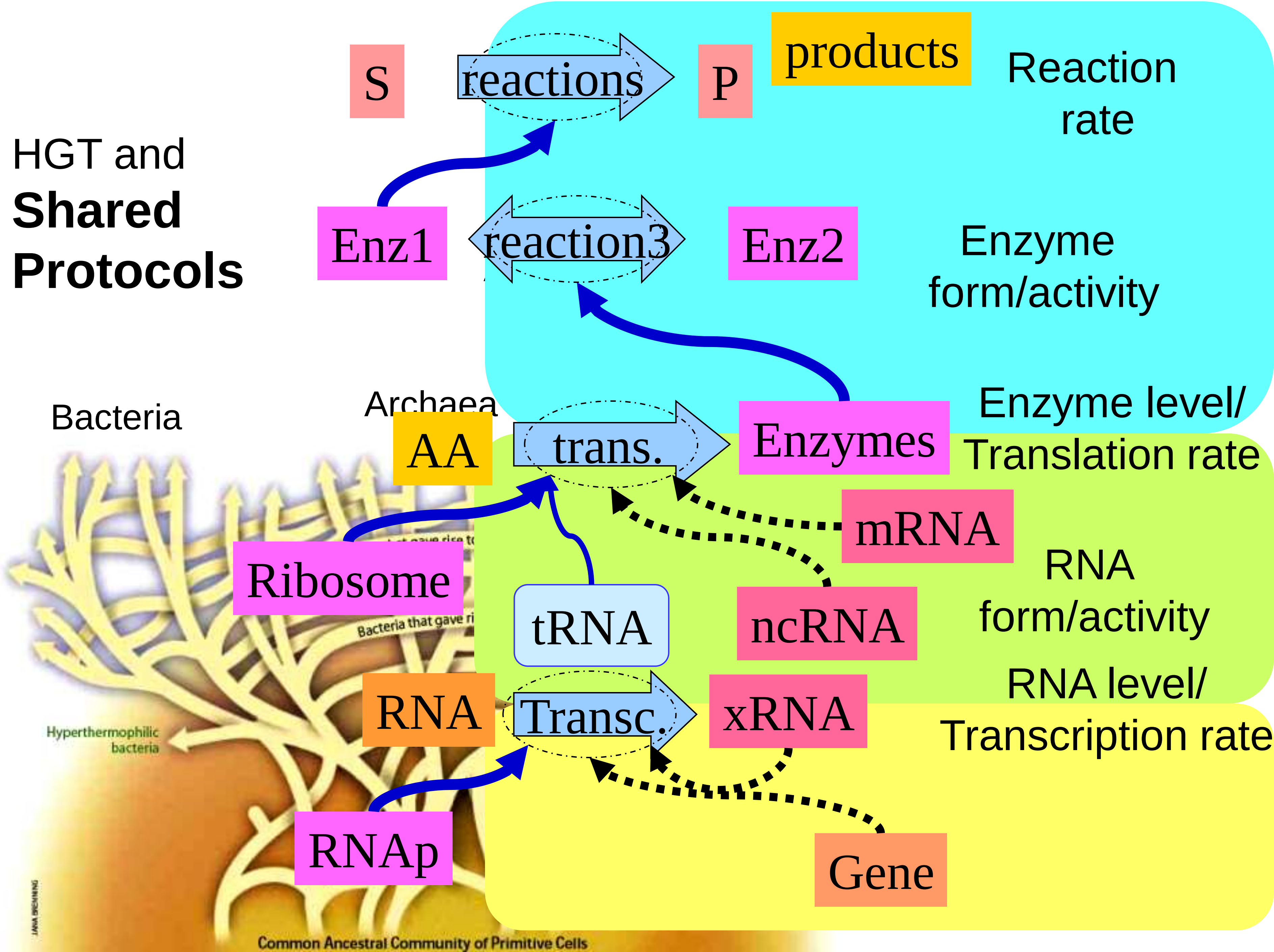
HGT and
Shared
Protocols

What is locus
of early
evolution?



Architecture!?!

HGT and
Shared Protocols



Horizontal gene transfer

- Not a static database
- Not only point mutations

HGT and Shared Protocols

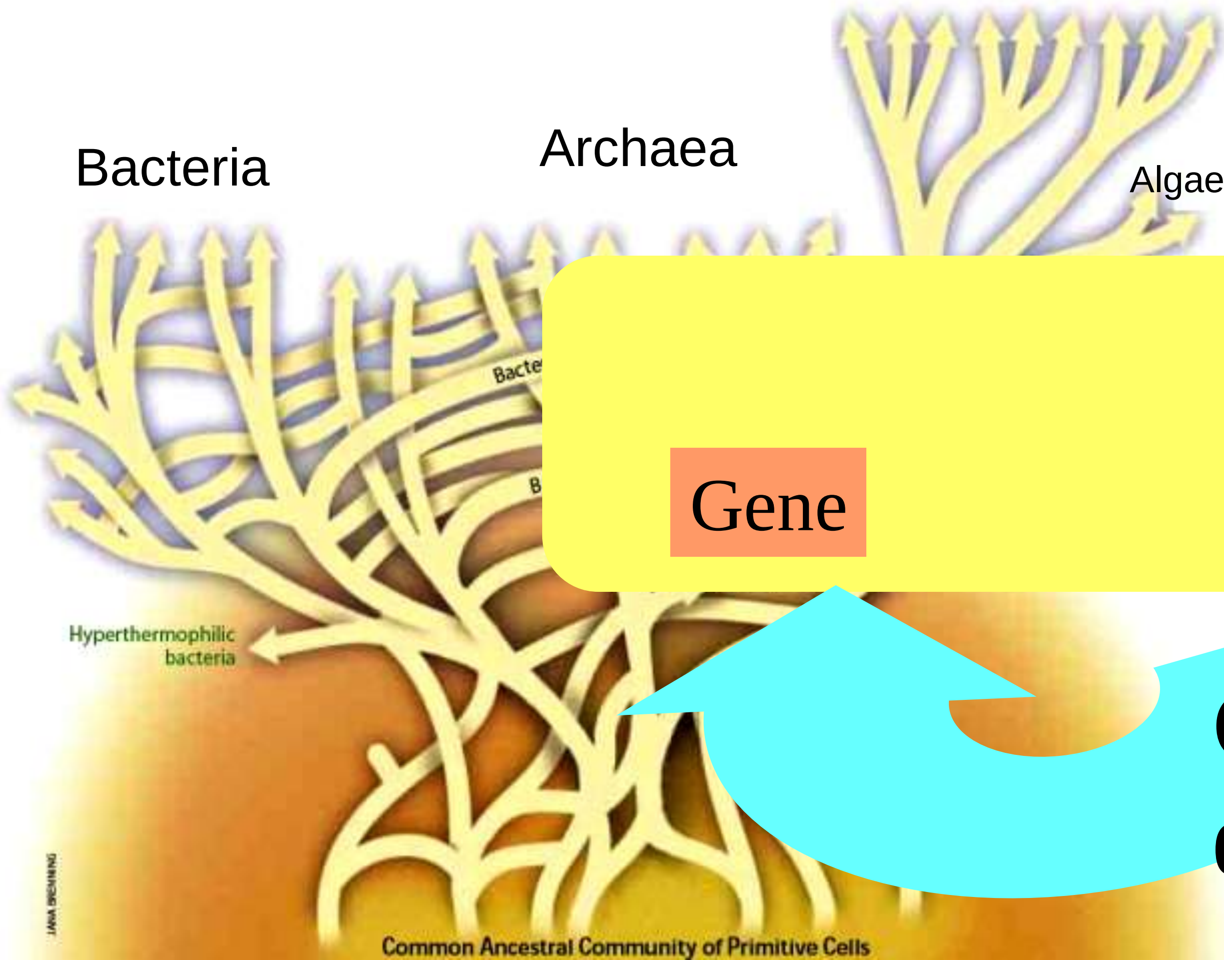
Eukaryotes

Animals Fungi Plants

Bacteria

Archaea

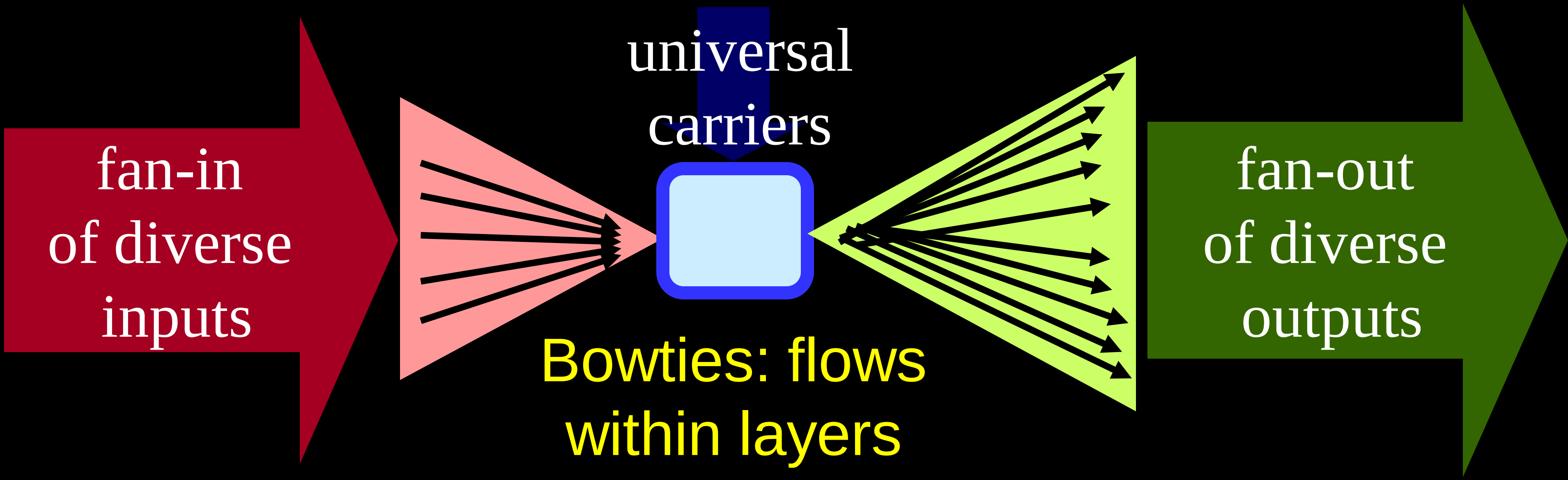
Algae

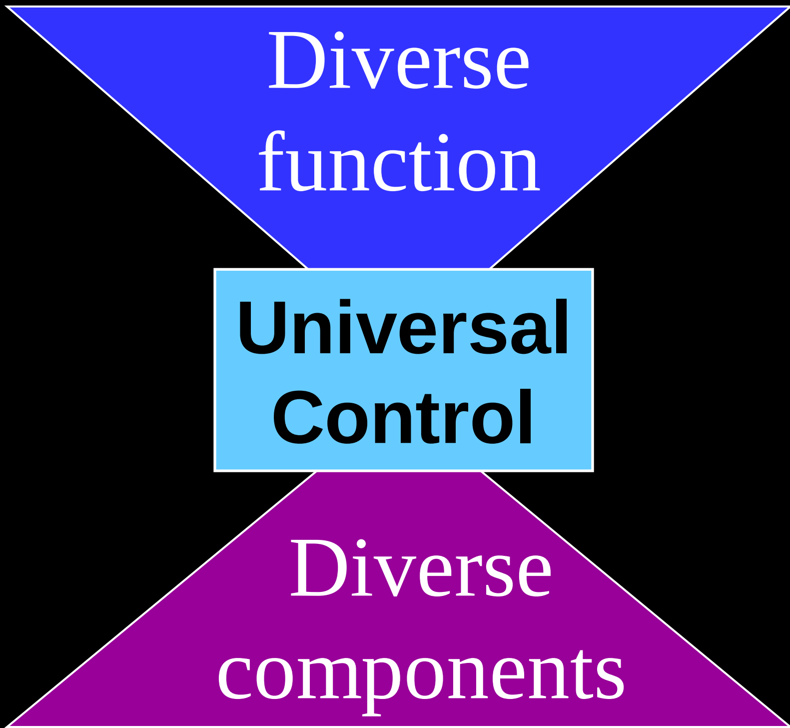


Gene

DNA level

Controlled, dynamic

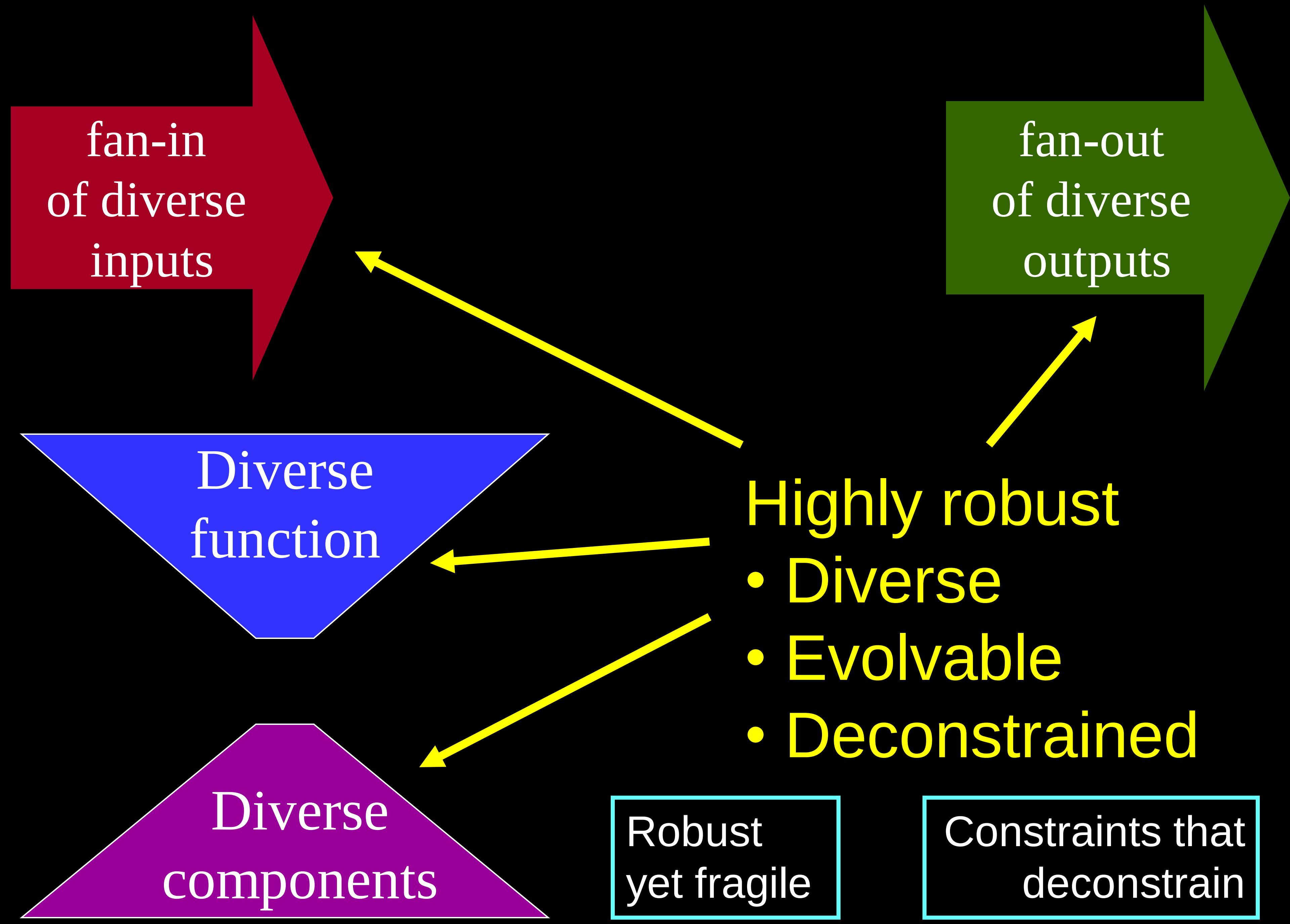


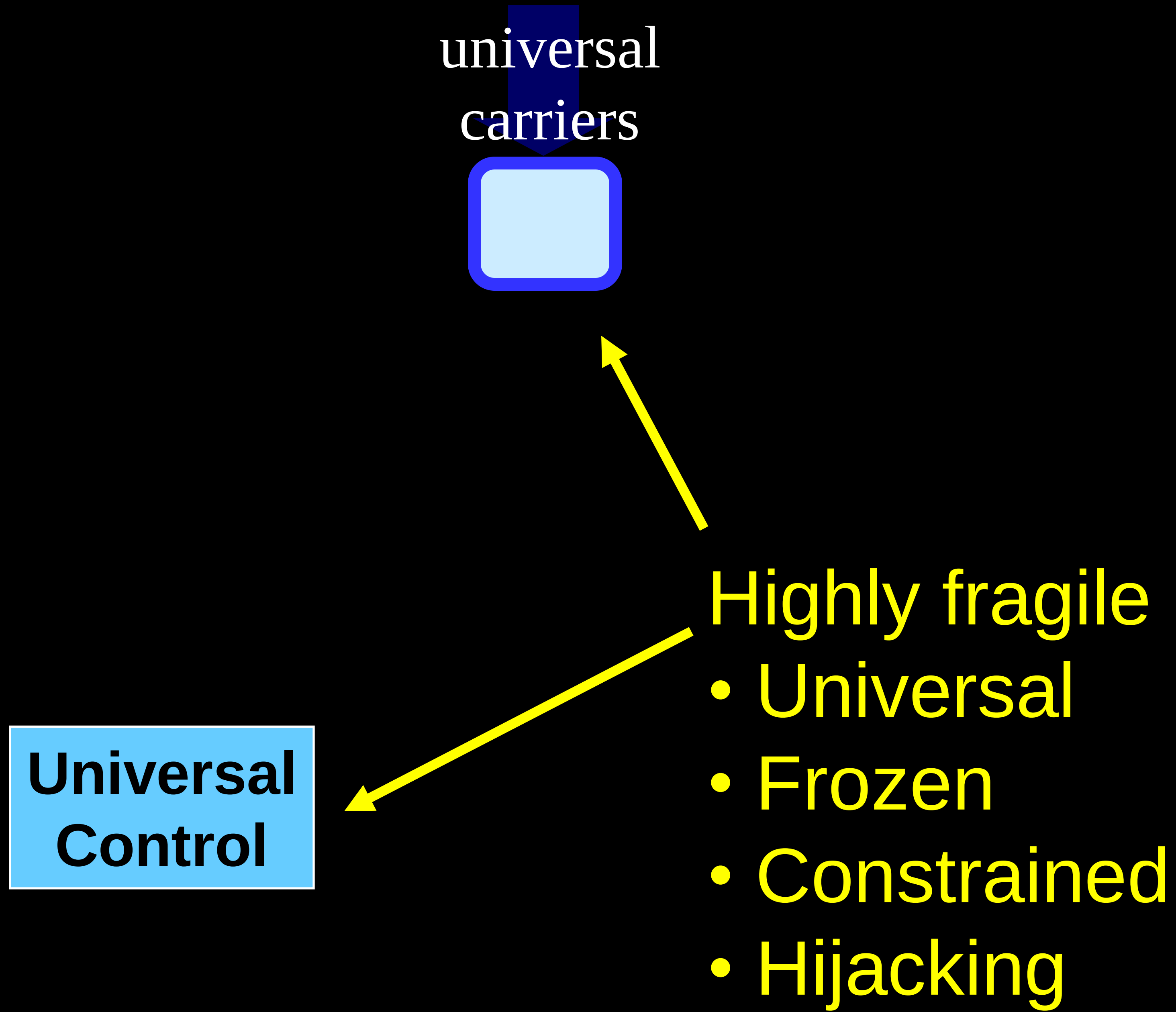


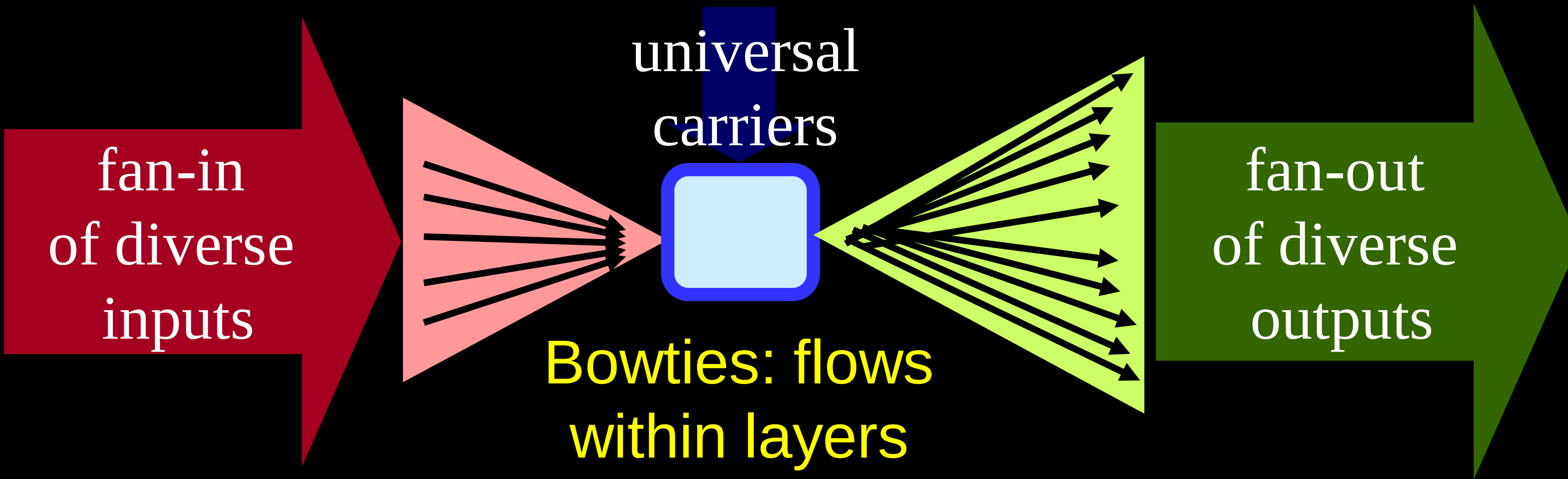
Essential ideas

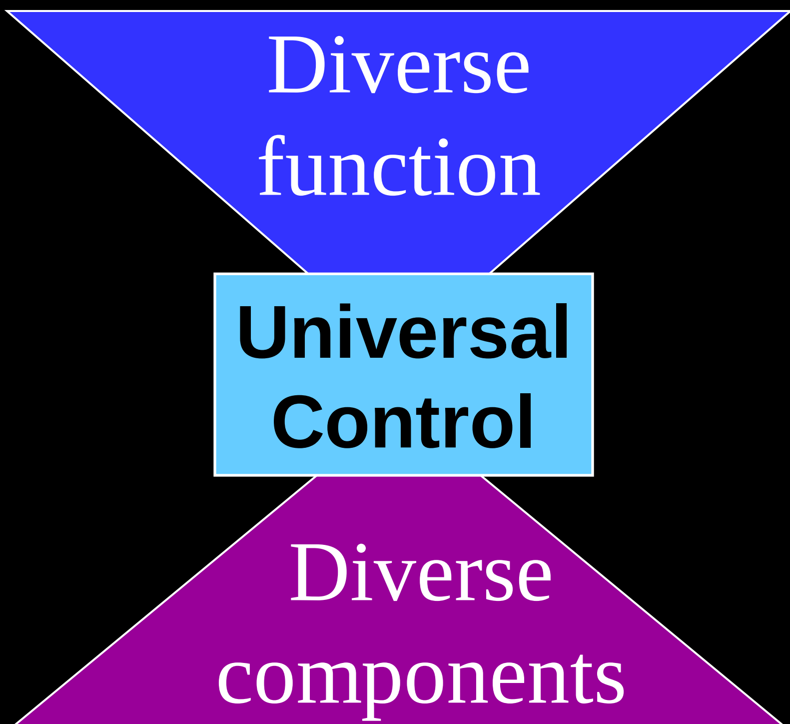
Robust yet fragile

Constraints that deconstrain


fan-in
of diverse
inputs
fan-out
of diverse
outputs
Diverse
function
Highly robust
• Diverse
• Evolvable
• Deconstrained
Diverse
components
Robust
yet fragile
Constraints that
deconstrain


universal carriers
Highly fragile
• Universal
• Frozen
• Constrained
• Hijacking
Universal Control





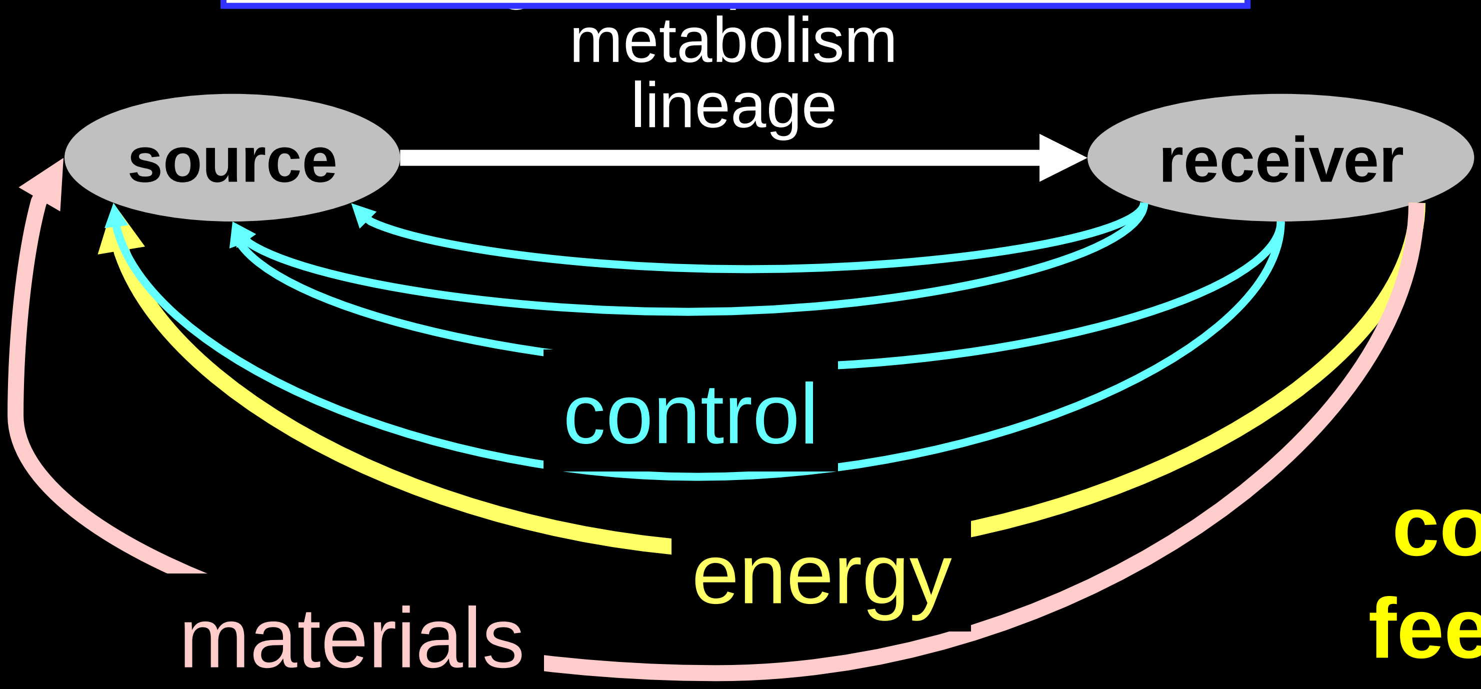
Essential ideas

Robust yet fragile

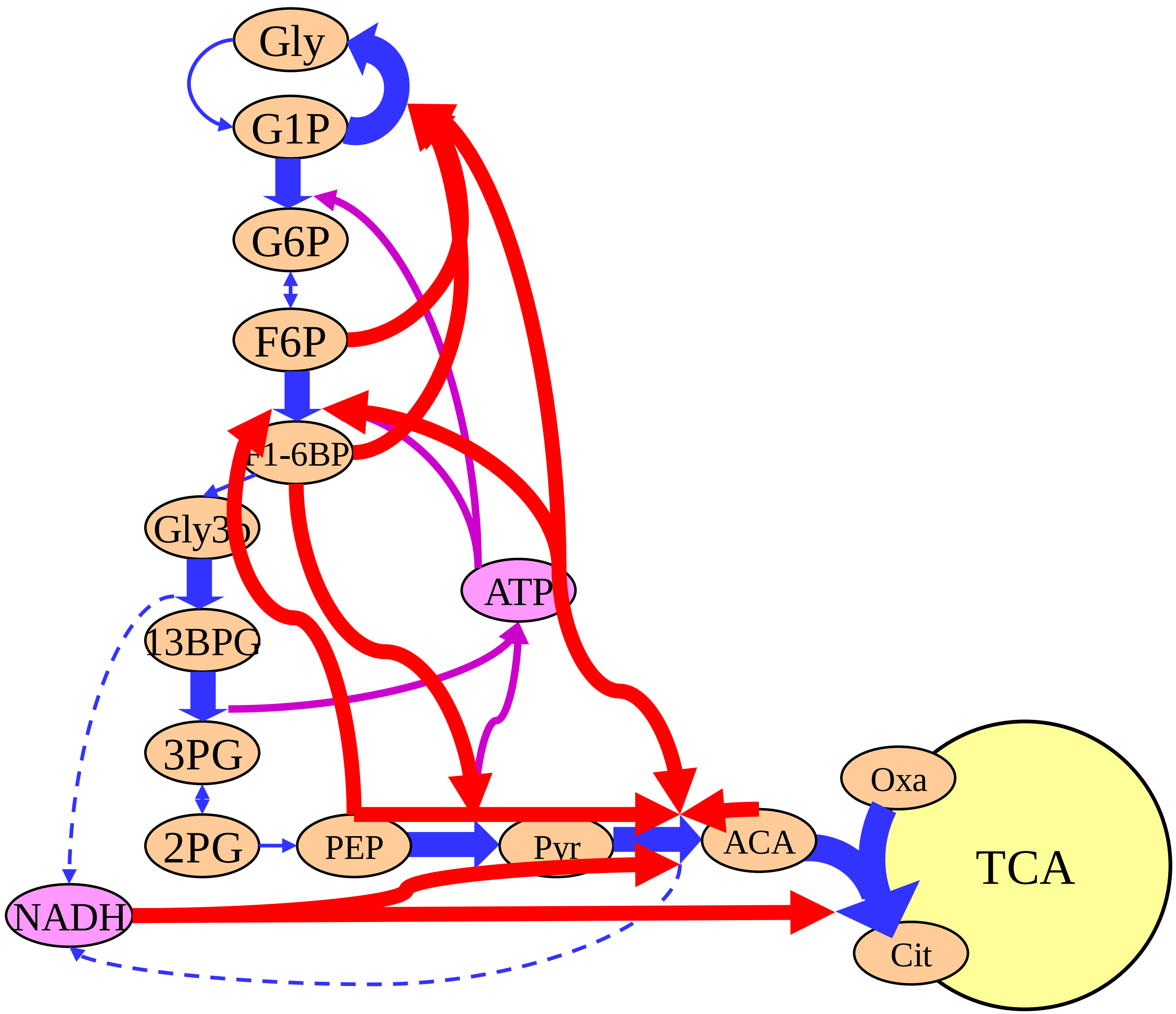
Constraints that deconstrain

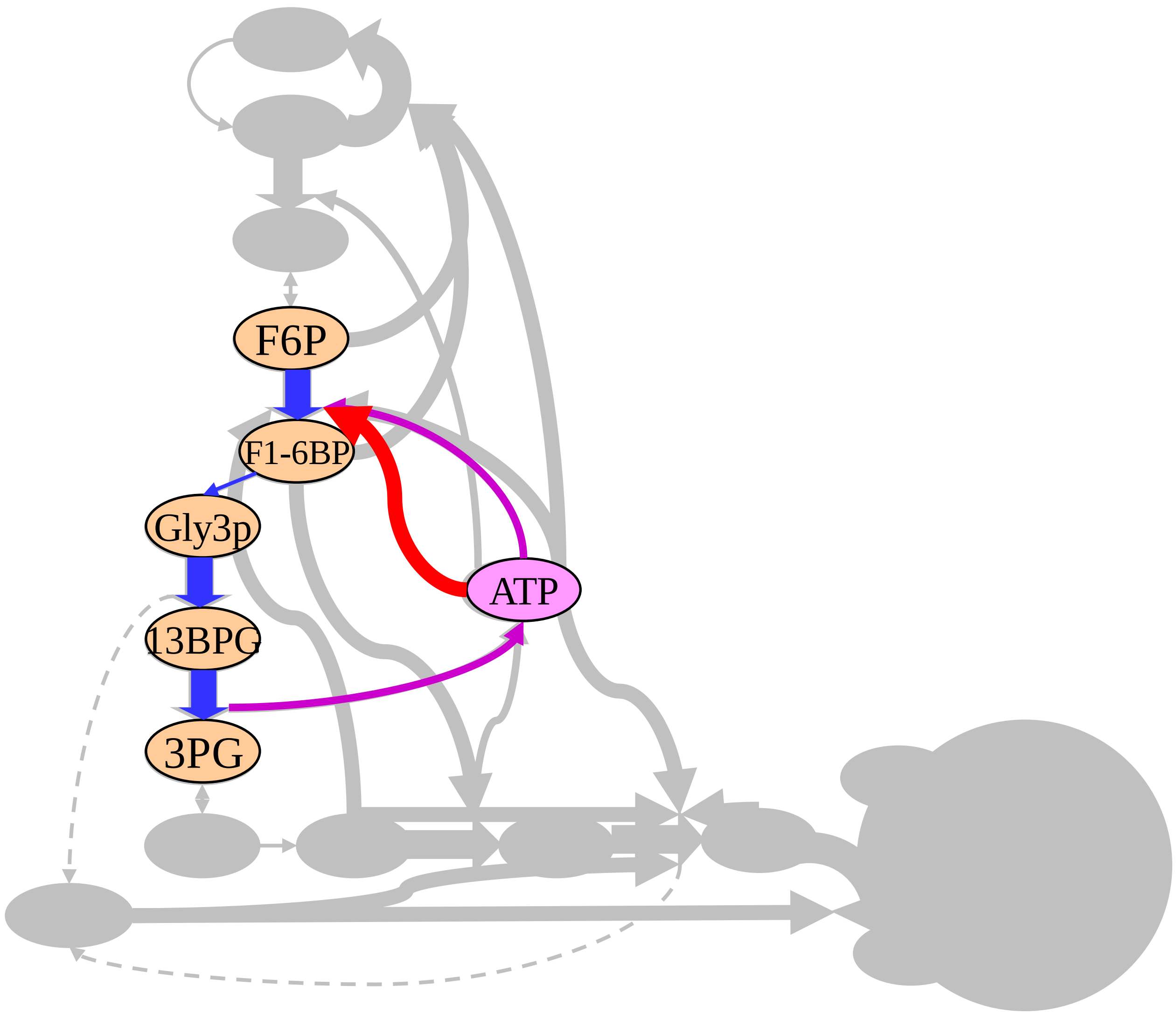
What theory is relevant to these more complex feedback systems?

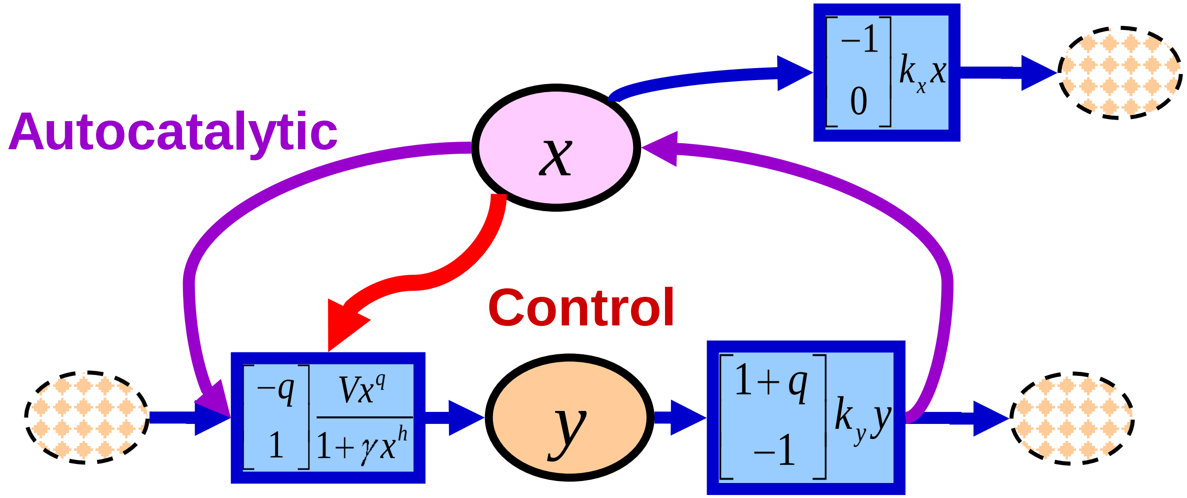
$$\frac{1}{\pi}\int_0^\infty \ln\left|S\ \ j\omega\right| \frac{z}{z^2+\omega^2}\,d\omega \ge \ln\left|\frac{z+p}{z-p}\right|$$



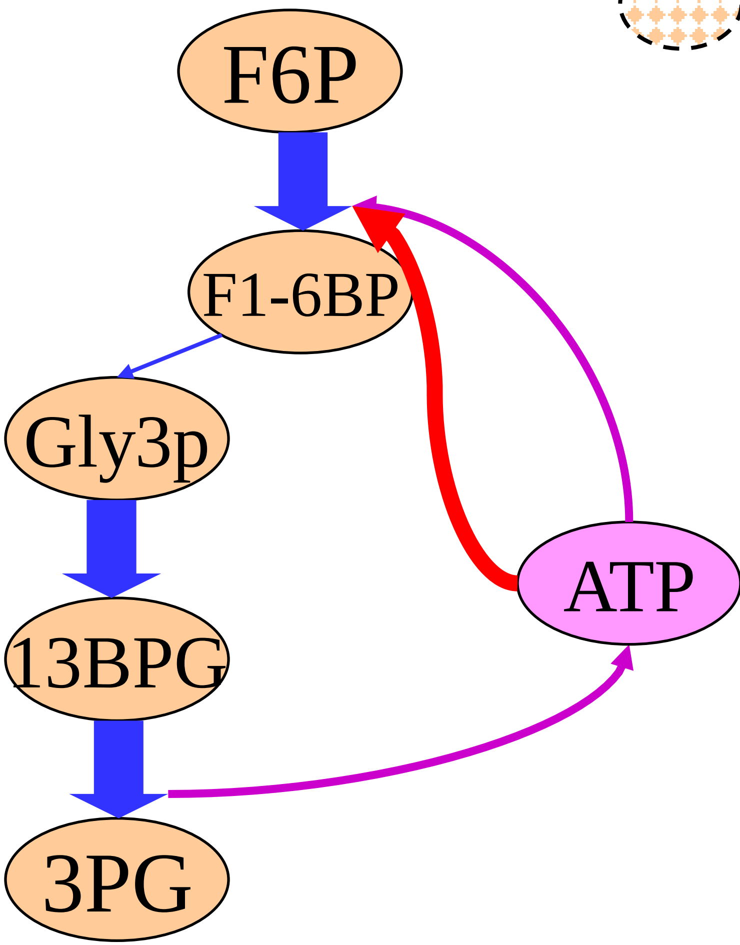
More complex feedback


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

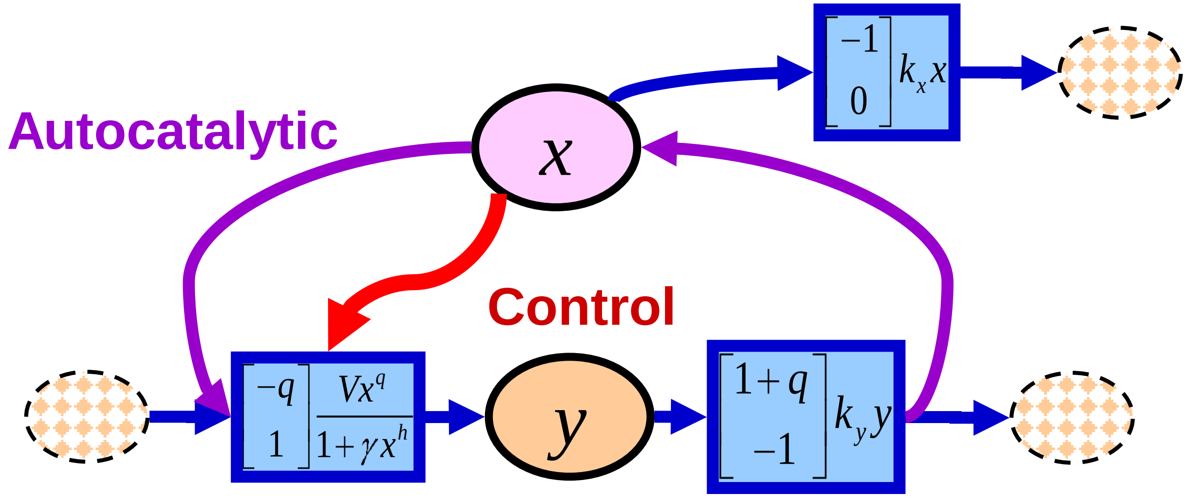

F6P
F1-6BP
Gly3p
ATP
13BPG
3PG

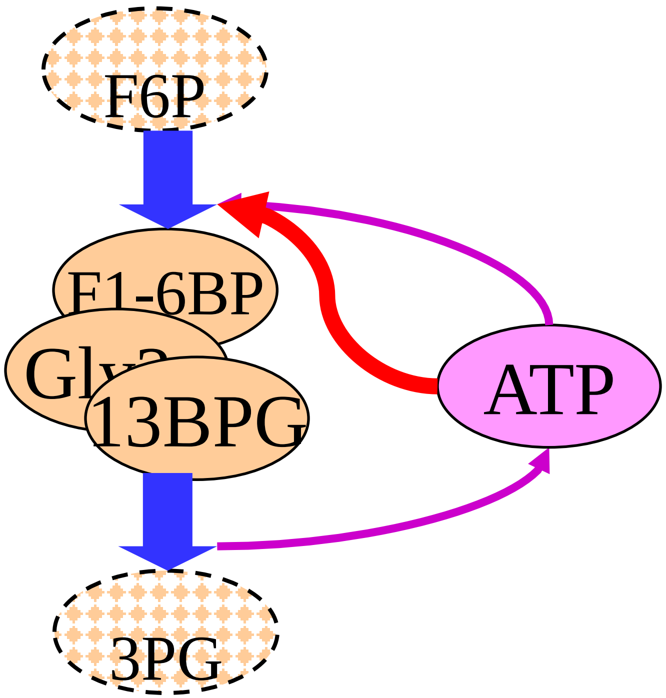


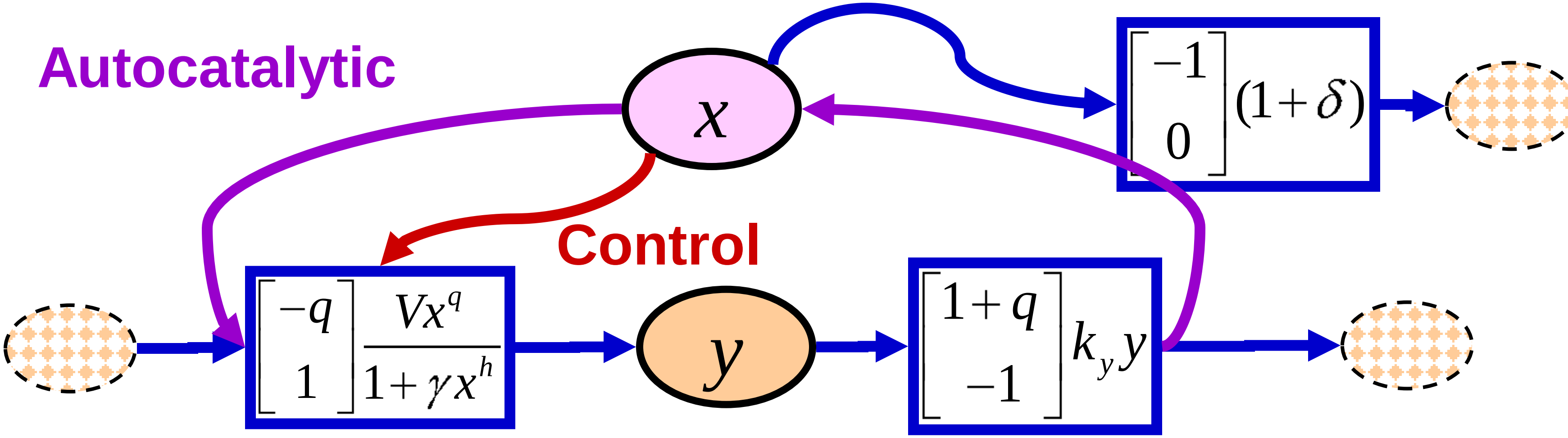
Autocatalytic
x
Control
y
$\begin{bmatrix}-1\\0\end{bmatrix}k_x x$
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$



F6P
F1-6BP
Gly3p
13BPG
3PG
ATP


Autocatalytic
Control
x
y
$\begin{bmatrix}-1\\0\end{bmatrix}k_x x$
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$


F6P
F1-6BP
13BPG
ATP
3PG



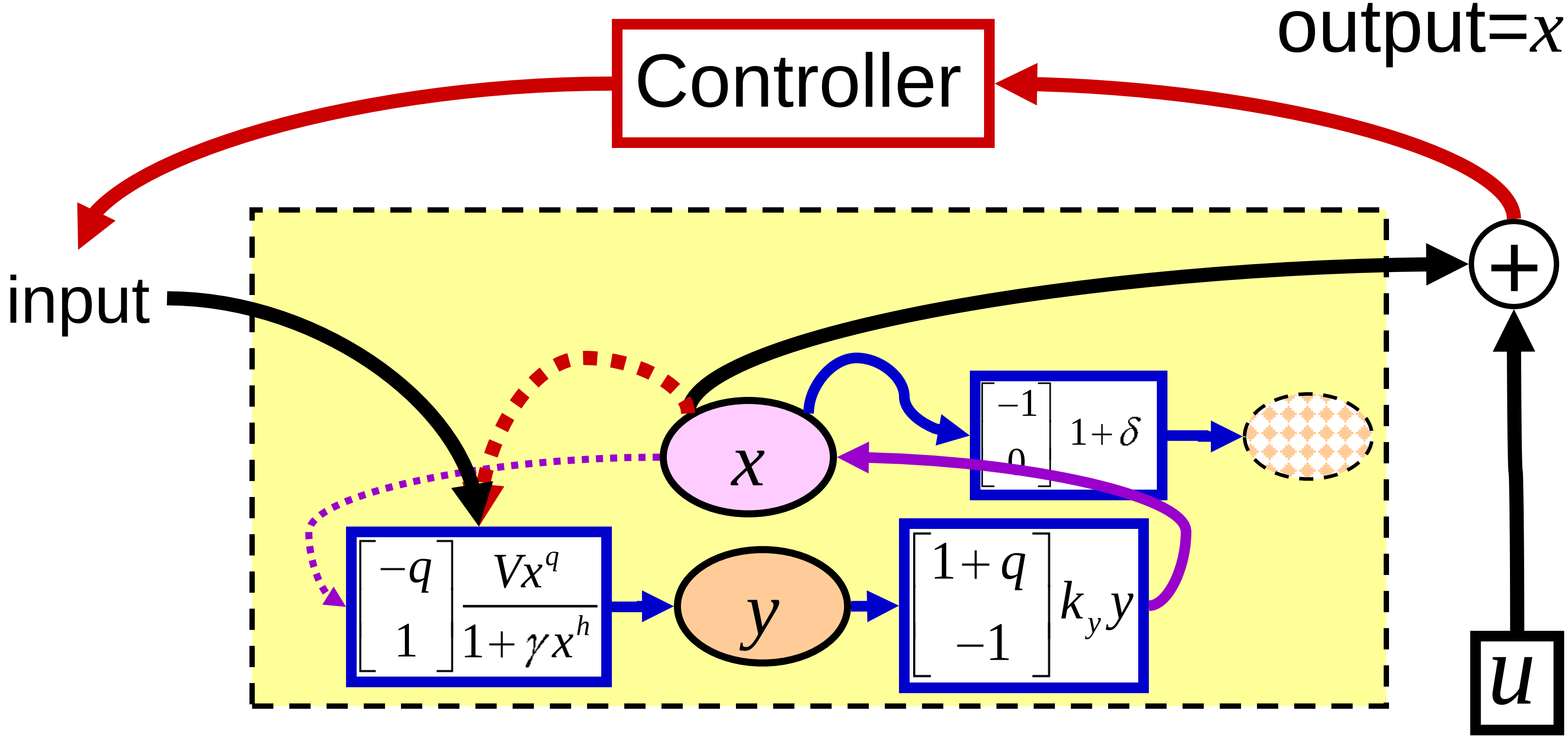
Autocatalytic

$$\begin{bmatrix}\dot{x}\\ \dot{y}\end{bmatrix}=\begin{bmatrix}-q\\ 1\end{bmatrix}\left(\frac{Vx^q}{1+\gamma x^h}\right)+\begin{bmatrix}1+q\\ -1\end{bmatrix}ky+\begin{bmatrix}-1\\ 0\end{bmatrix}(1+\delta)$$

Control

Control theory cartoon

$$S \quad j\omega \quad = \frac{x}{u}$$



Caution: mixed cartoon

Hard limits

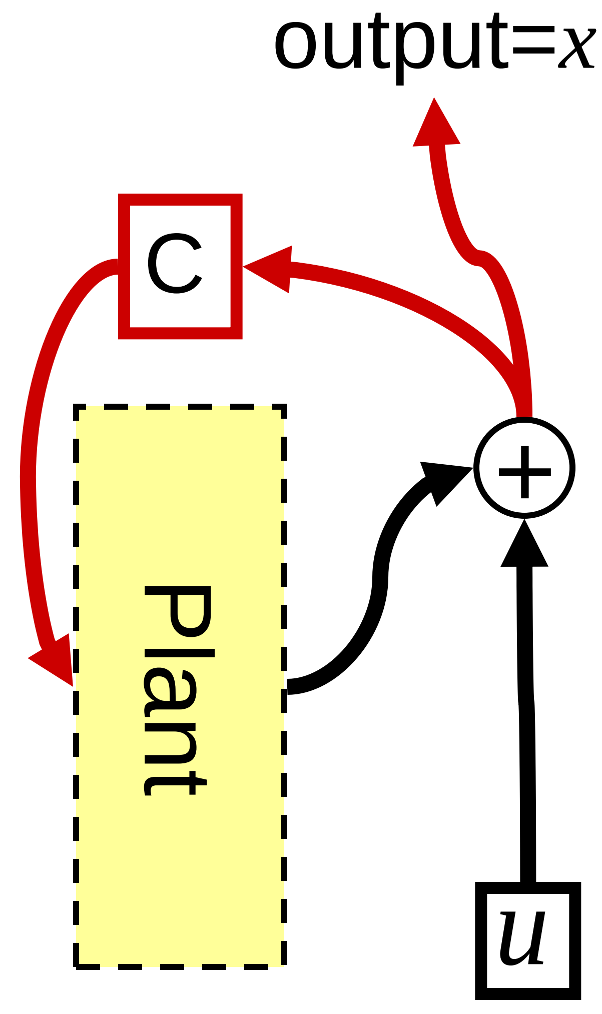
$$S(j\omega) = \frac{X(j\omega)}{U(j\omega)}$$

$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq 0$$

$$\int_{-\infty}^{\infty} \ln\left|S(j\omega)\right| d\omega = \int_{-\infty}^{\infty} \ln\left|\frac{X(j\omega)}{U(j\omega)}\right| d\omega$$

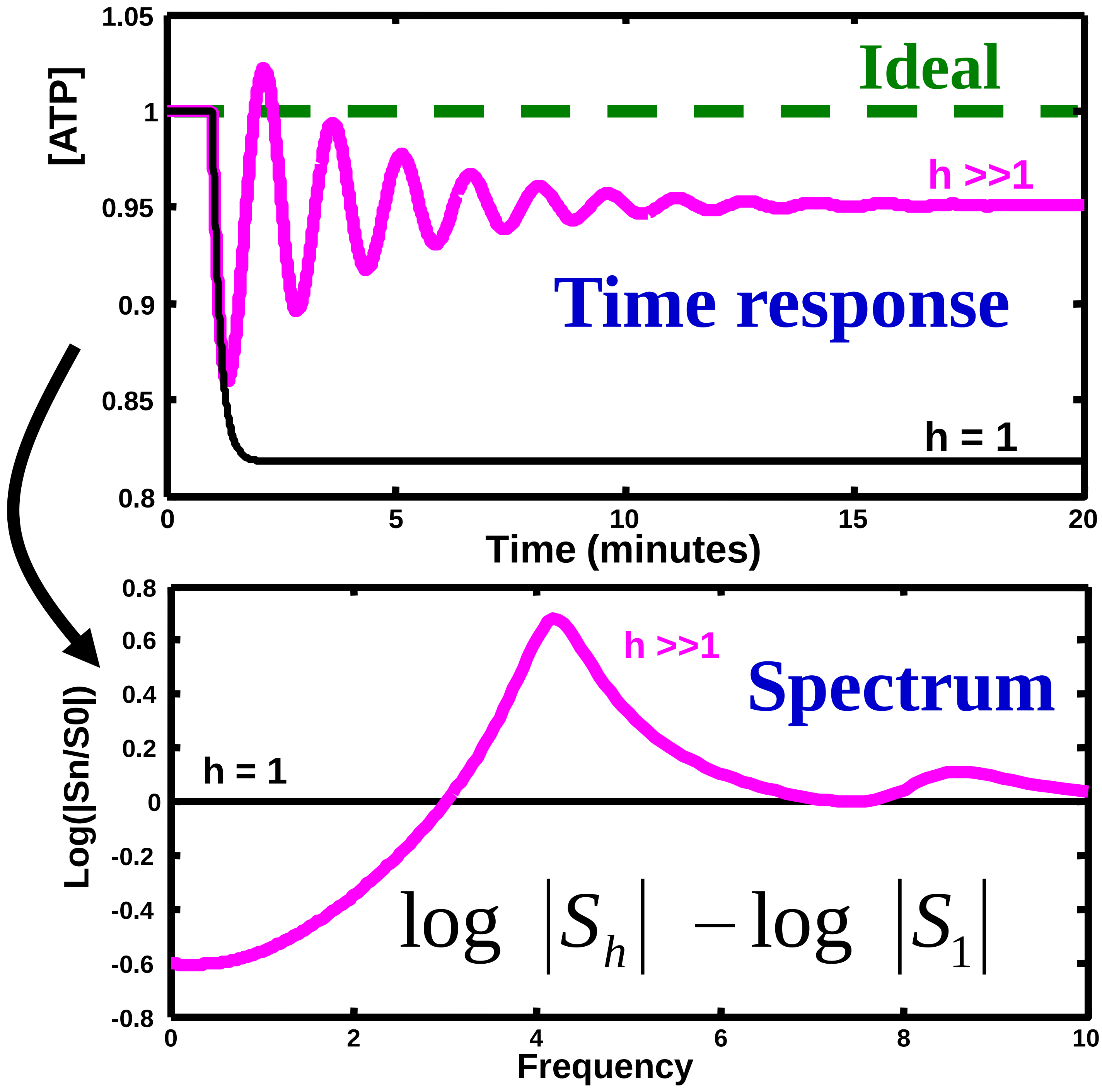
$$= \int_{-\infty}^{\infty} \ln\left|X(j\omega)\right| d\omega - \int_{-\infty}^{\infty} \ln\left|U(j\omega)\right| d\omega$$

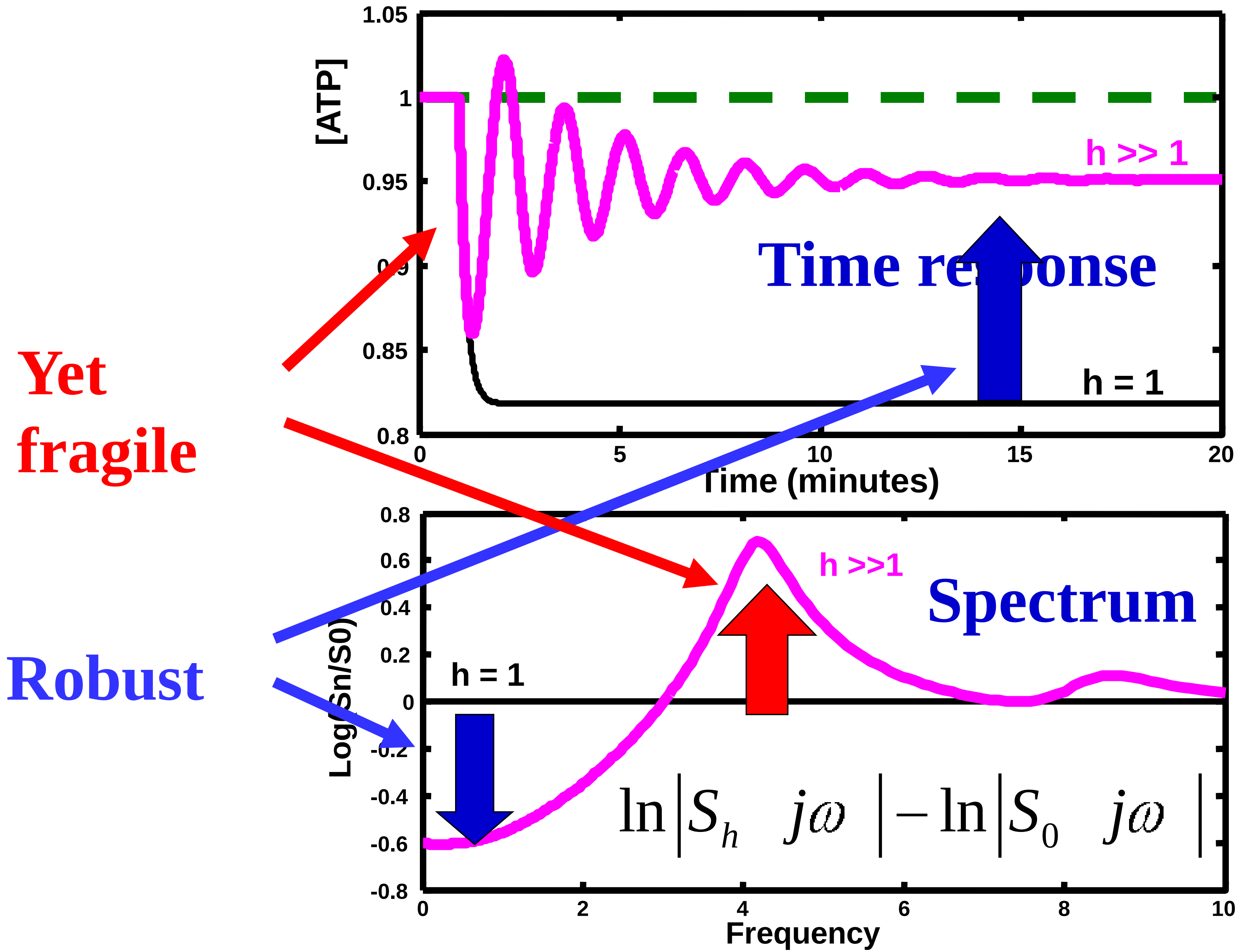
Entropy rates



$$S_h = \mathrm{F}(x)\big|_h$$

Fourier Transform of error



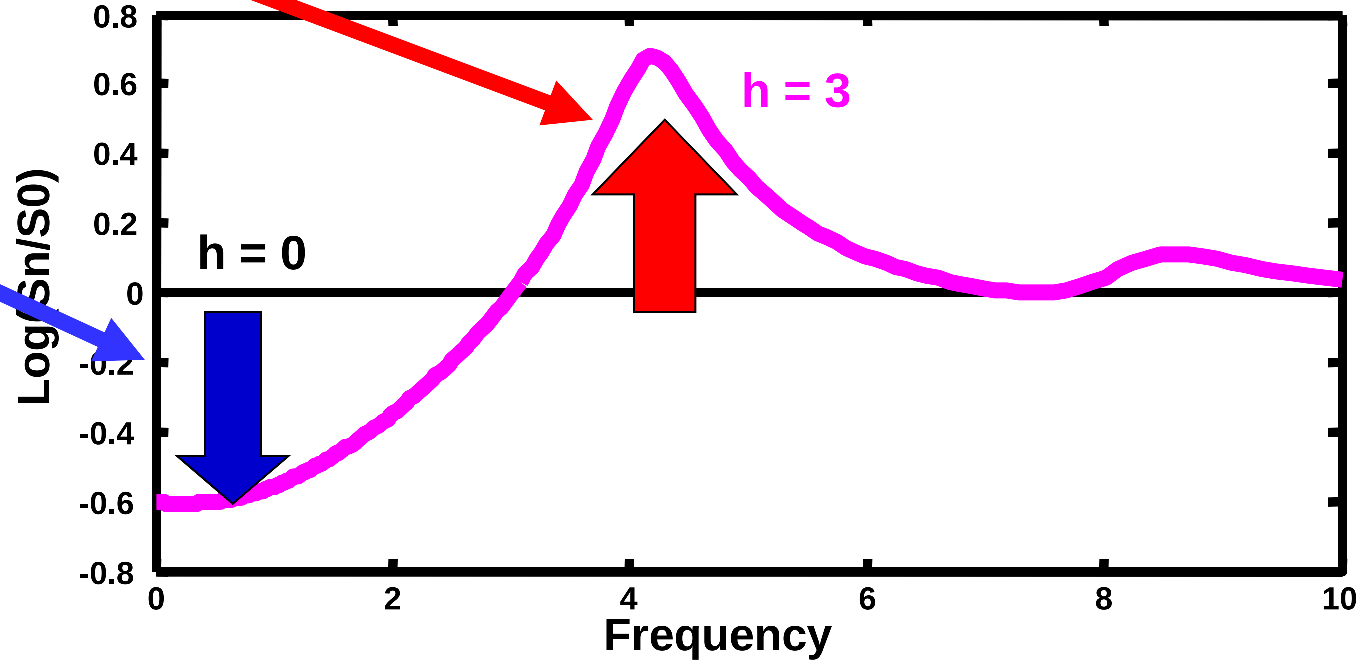


Yet
fragile
Robust
[ATP]
1.05
1
0.95
0.9
0.85
0.8
h >> 1
Time response
h = 1
0
5
10
15
20
Time (minutes)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Log(Sn/S0)
h >>1
Spectrum
h = 1
$\ln|S_h(j\omega)| - \ln|S_0(j\omega)|$
0
2
4
6
8
10
Frequency

$$\int_0^\infty \Delta \ln\left|S \quad j\omega \right| d\omega = 0$$

Yet fragile

Robust

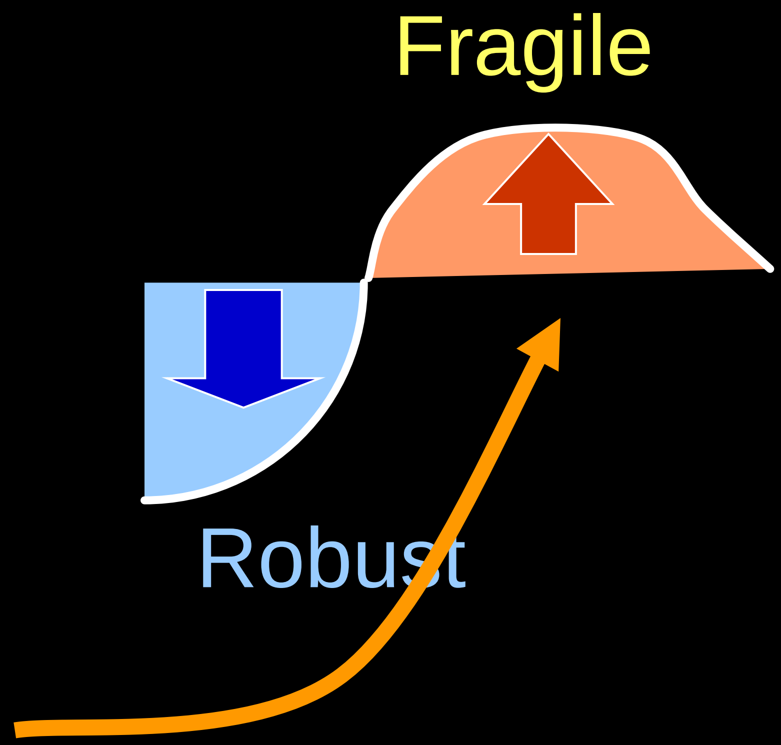


[a system] can have
[a property] ***robust*** for
[a set of perturbations]

Yet be ***fragile for***

[a different property]

Or [a different perturbation]



Robust yet fragile = fragile robustness

Hard limits

$$S(j\omega) = \frac{X(j\omega)}{U(j\omega)}$$

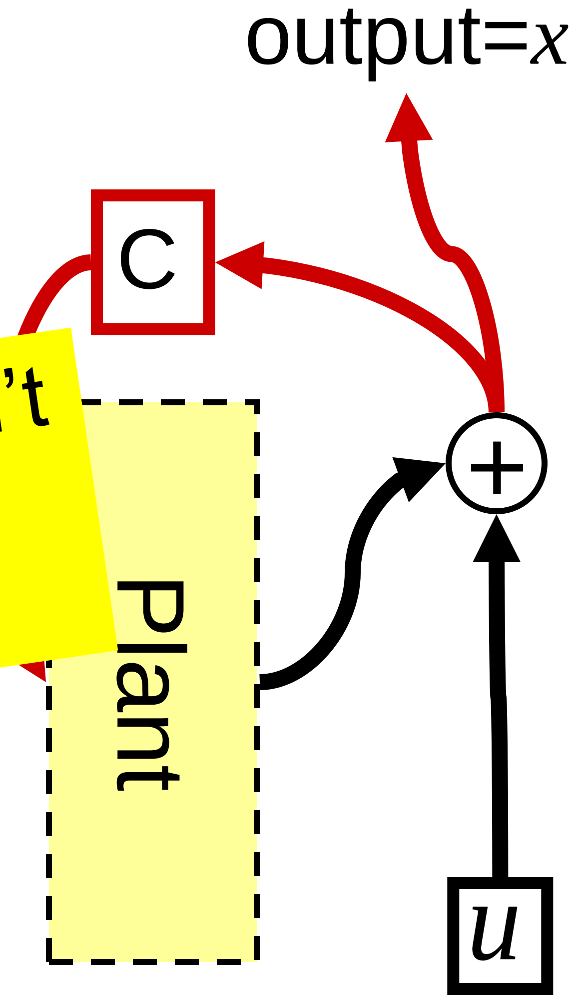
$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq 0$$

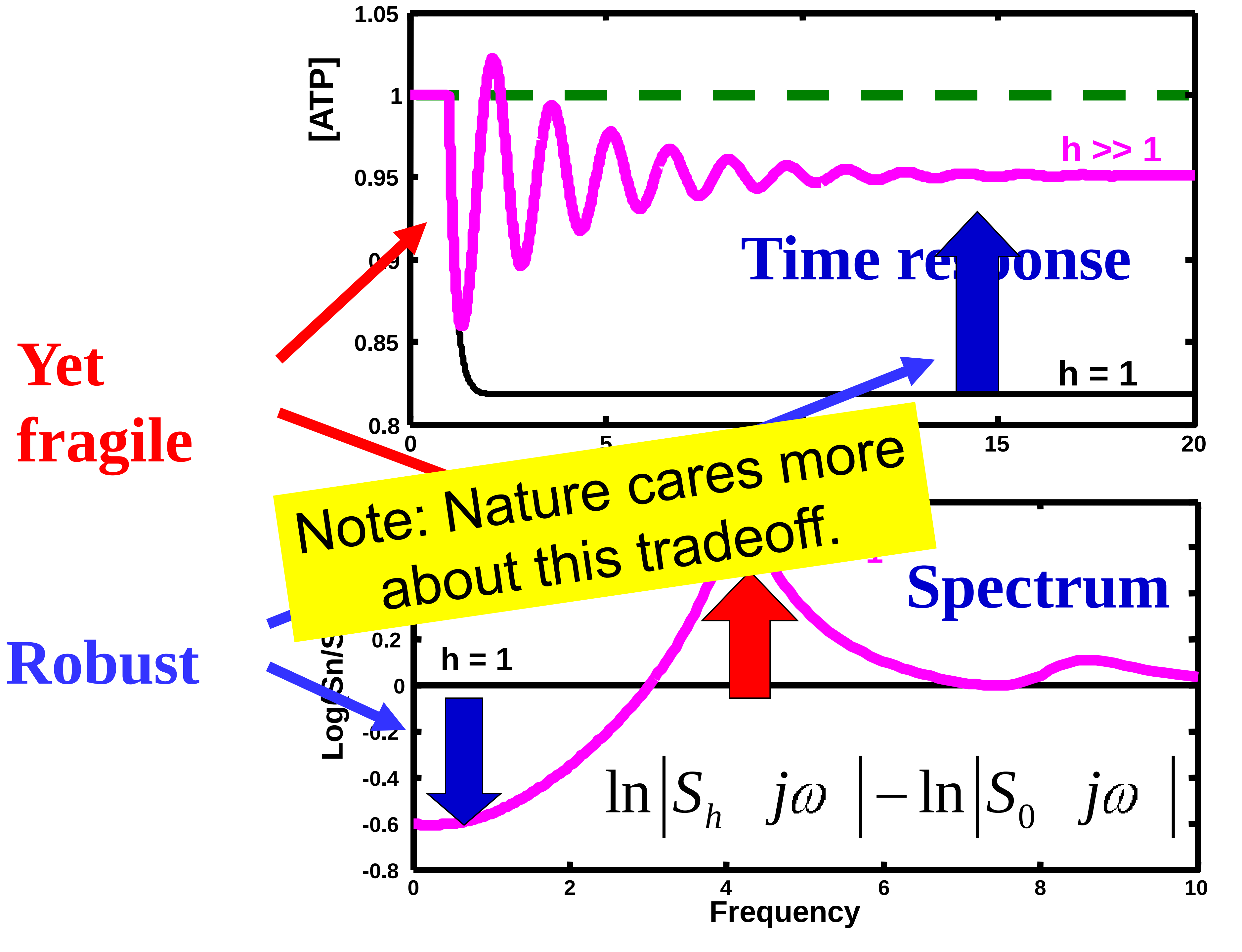
$$\int_{-\infty}^{\infty} \ln\left|S(j\omega)\right| d\omega$$

$$= \int_{-\infty}^{\infty} \ln\left|X(j\omega)\right| d\omega - \int_{-\infty} \ln\left|U(j\omega)\right| d\omega$$

Note: Nature doesn't care much about entropy rates.

Entropy rates



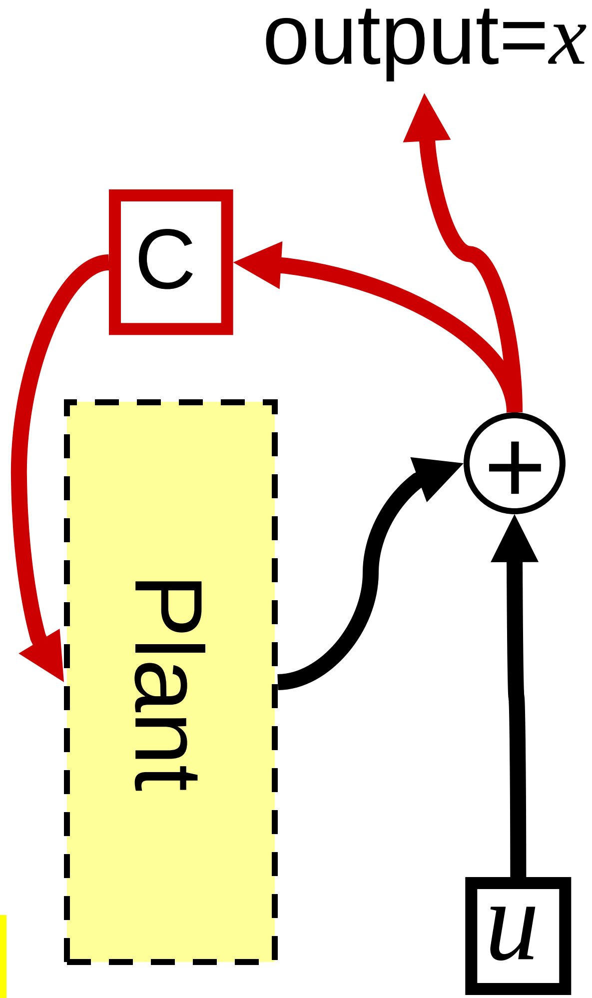


Yet fragile
Robust
Note: Nature cares more about this tradeoff.
Time response
Spectrum
[ATP]
h >> 1
h = 1
h = 1
Log(Sn/S
Frequency
$\ln|S_h(j\omega)| - \ln|S_0(j\omega)|$
1.05
1
0.95
0.9
0.85
0.8
0
5
15
20
0.2
0
-0.2
-0.4
-0.6
-0.8
0
2
4
6
8
10

$$S(j\omega) = \frac{X(j\omega)}{U(j\omega)}$$

$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq 0$$

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



The plant can make this tradeoff worse.

$$S(j\omega) = \frac{X(j\omega)}{U(j\omega)}$$

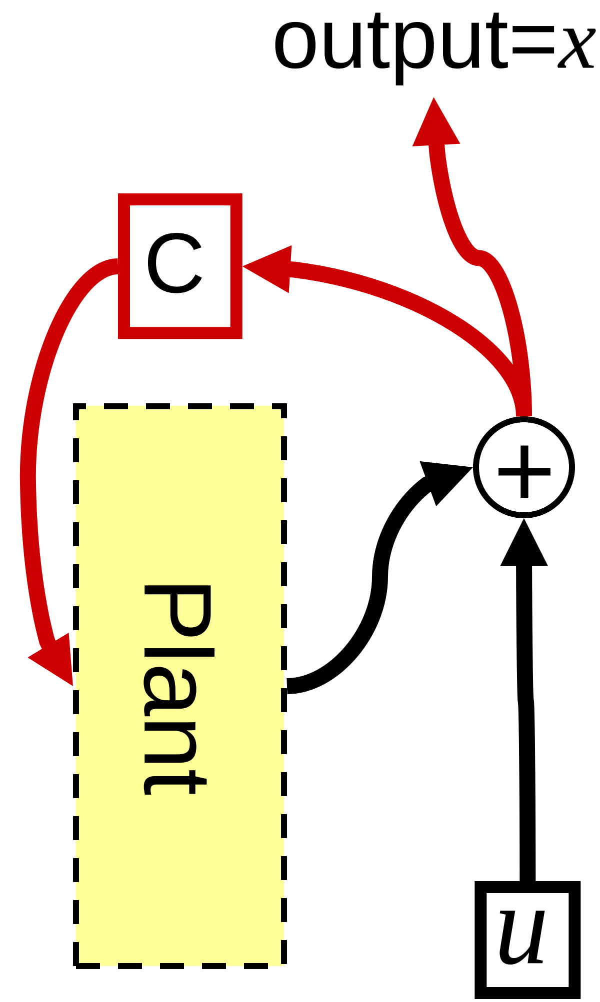
$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq 0$$

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

All controllers: $\geq$

Biological cells: $=$

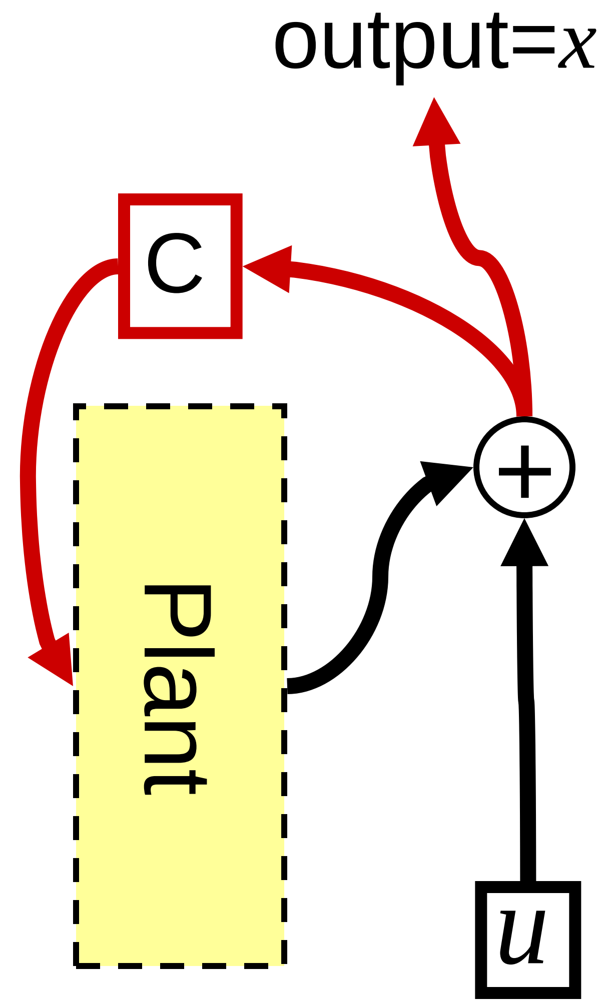
$$z = \frac{k}{q} \qquad p = RHPzero\left(s^2 + (q\alpha + k)s - \alpha k\right)$$



$$S \quad j\omega \quad = \frac{X \quad j\omega}{U \quad j\omega}$$

$$\frac{1}{\pi}\int_0^\infty \ln\left| S \quad j\omega \right| d\omega \geq 0$$

$$\frac{1}{\pi}\int_0^\infty \ln\left| S \quad j\omega \right| \frac{z}{z^2+\omega^2} d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$



Small *z* is *bad*.

$$z = \frac{k}{q}$$

$$p = RHPzero \quad s^2 + \quad q\alpha + k \quad s - \alpha k$$

Small *z* is *bad*
(oscillations and crashes)

$$\frac{1}{\pi}\int_0^\infty \ln\left|S\quad j\omega\;\right|\frac{z}{z^2+\omega^2}d\omega \ge \ln\left|\frac{z+p}{z-p}\right|$$

Small *z* =

- **small *k* and/or**
- **large *q***

Efficiency =

- **small *k* and/or**
- **large *q***

$$z = \frac{k}{q}$$

Correctly predicts conditions with “glycolytic oscillations”

Hard limits

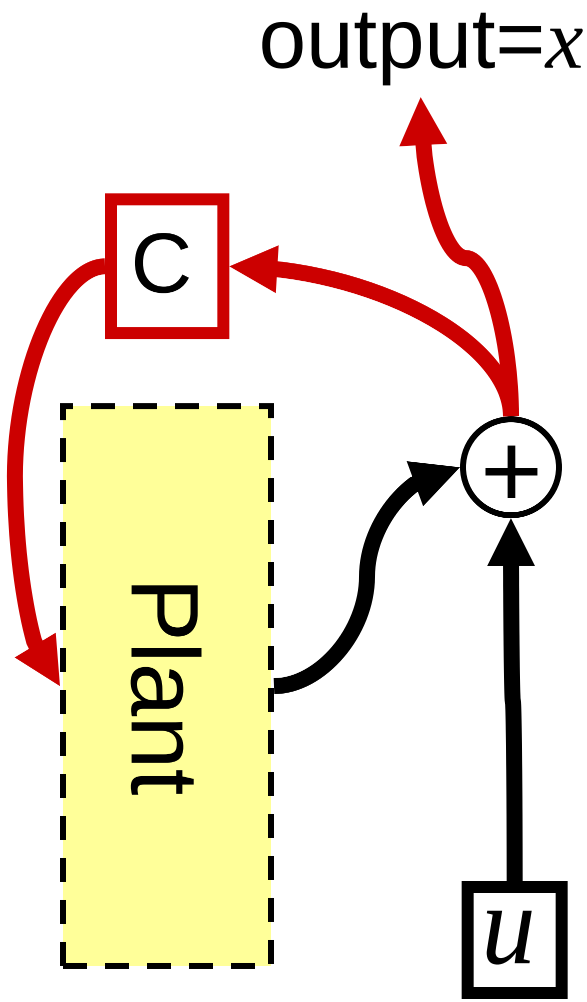
$$\boxed{S(j\omega) = \frac{X(j\omega)}{U(j\omega)}}$$

$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq 0$$

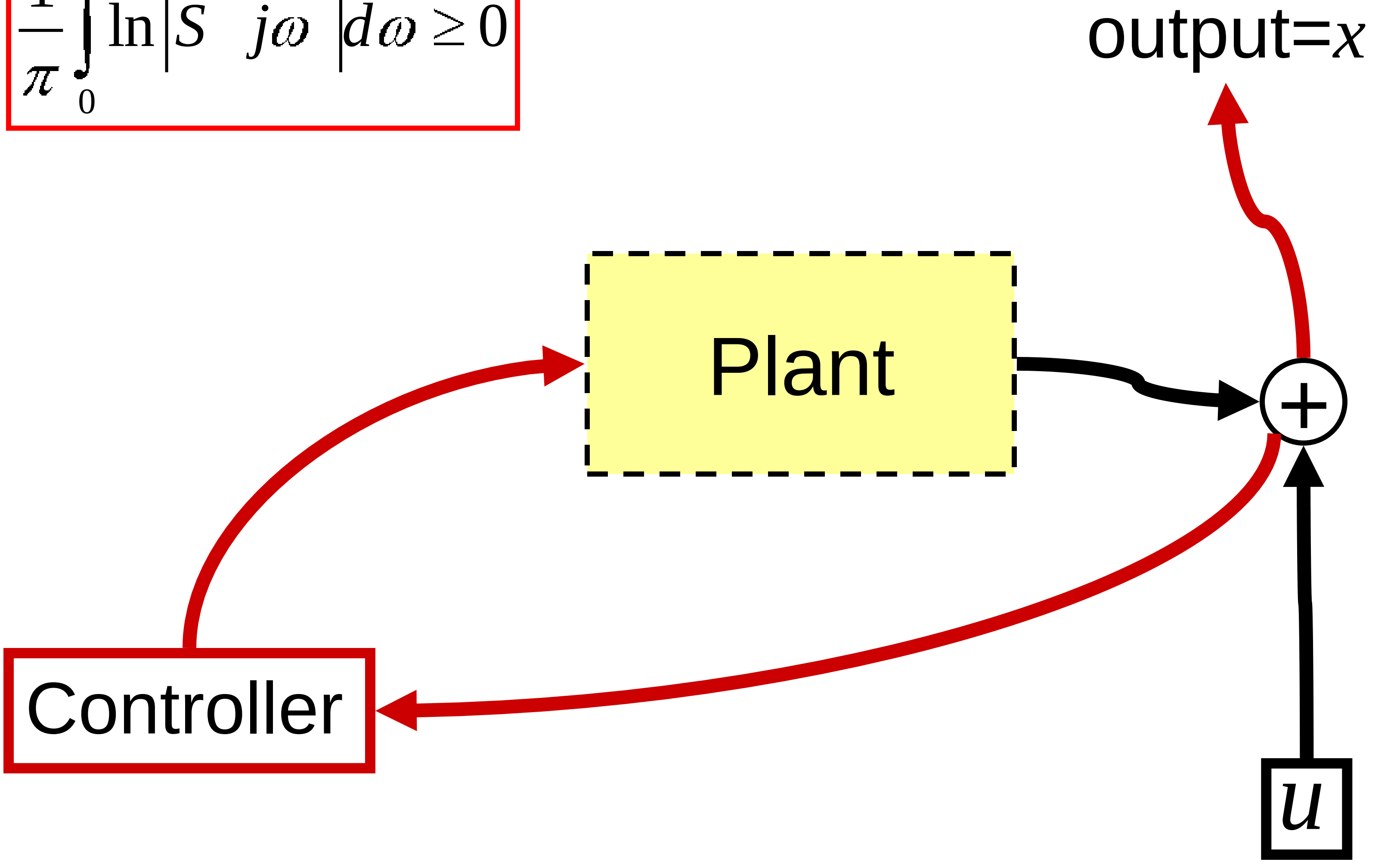
$$\int_{-\infty}^{\infty} \ln\left|S(j\omega)\right| d\omega = \int_{-\infty}^{\infty} \ln\left|\frac{X(j\omega)}{U(j\omega)}\right| d\omega$$

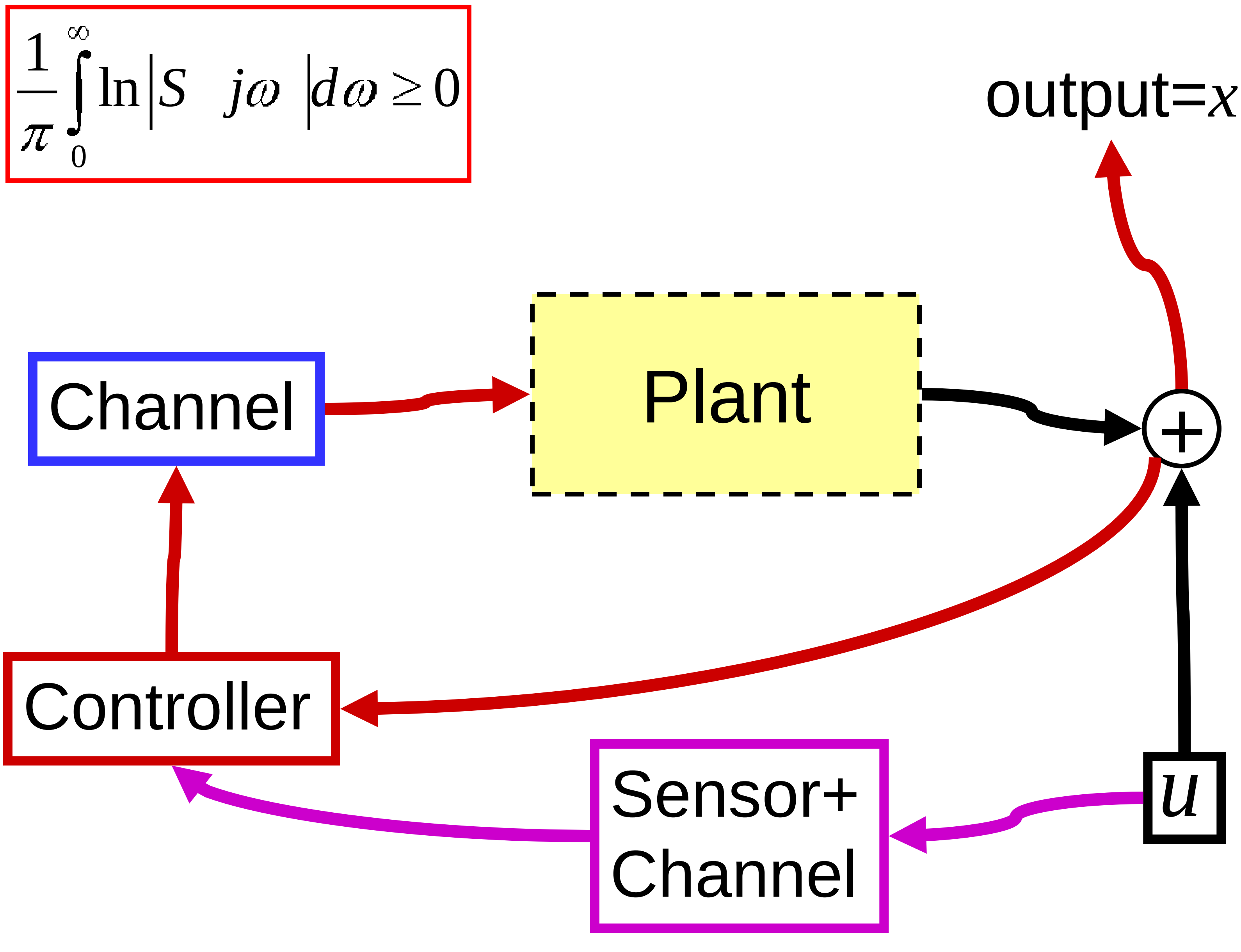
$$= \int_{-\infty}^{\infty} \ln\left|X(j\omega)\right| d\omega - \int_{-\infty}^{\infty} \ln\left|U(j\omega)\right| d\omega$$

Entropy rates



$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq 0$$



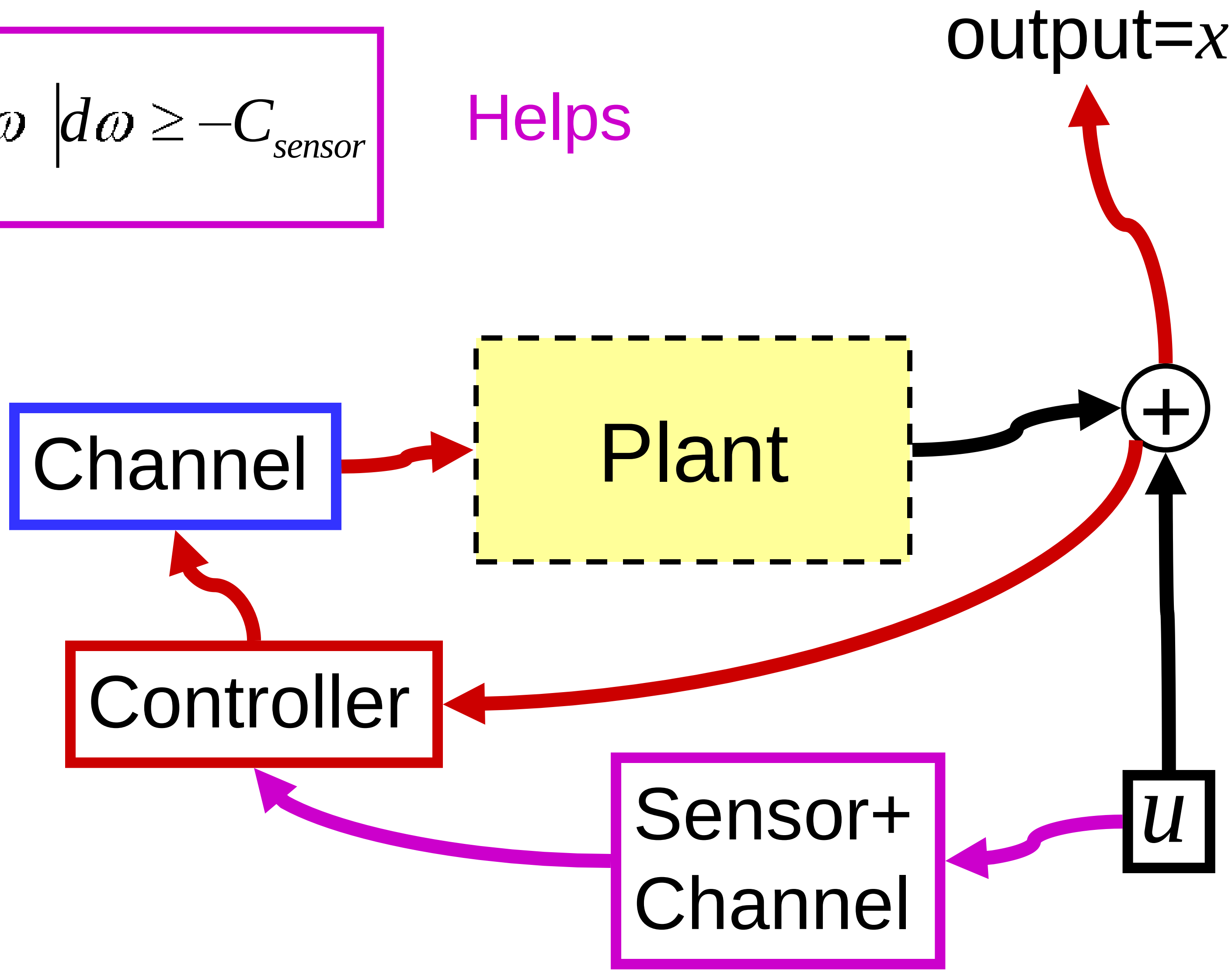

$\frac{1}{\pi}\int_0^\infty \ln|S(j\omega)|d\omega \geq 0$
output=x
Channel
Plant
Controller
Sensor+
Channel
u

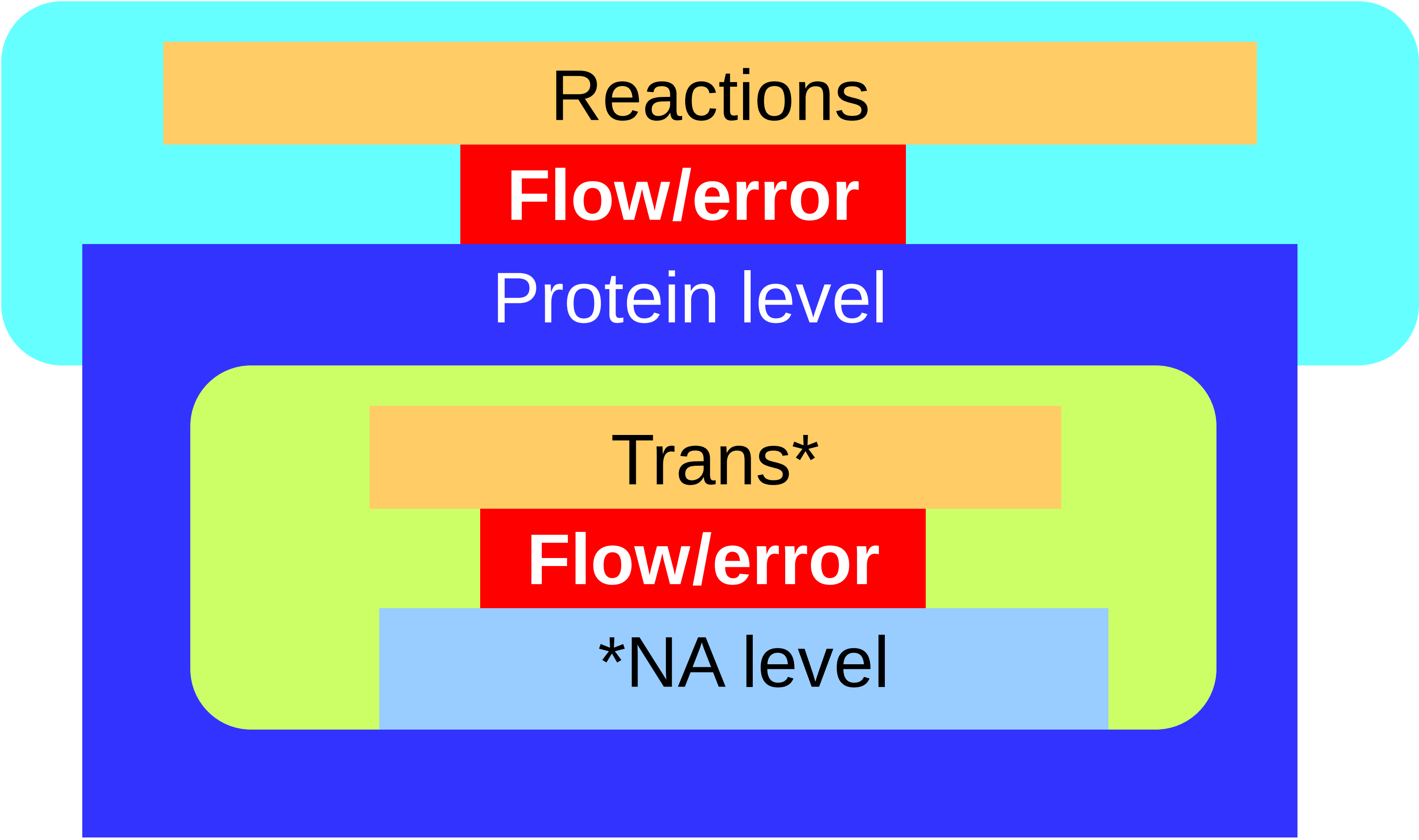
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq -C_{FB}$$

Hurts

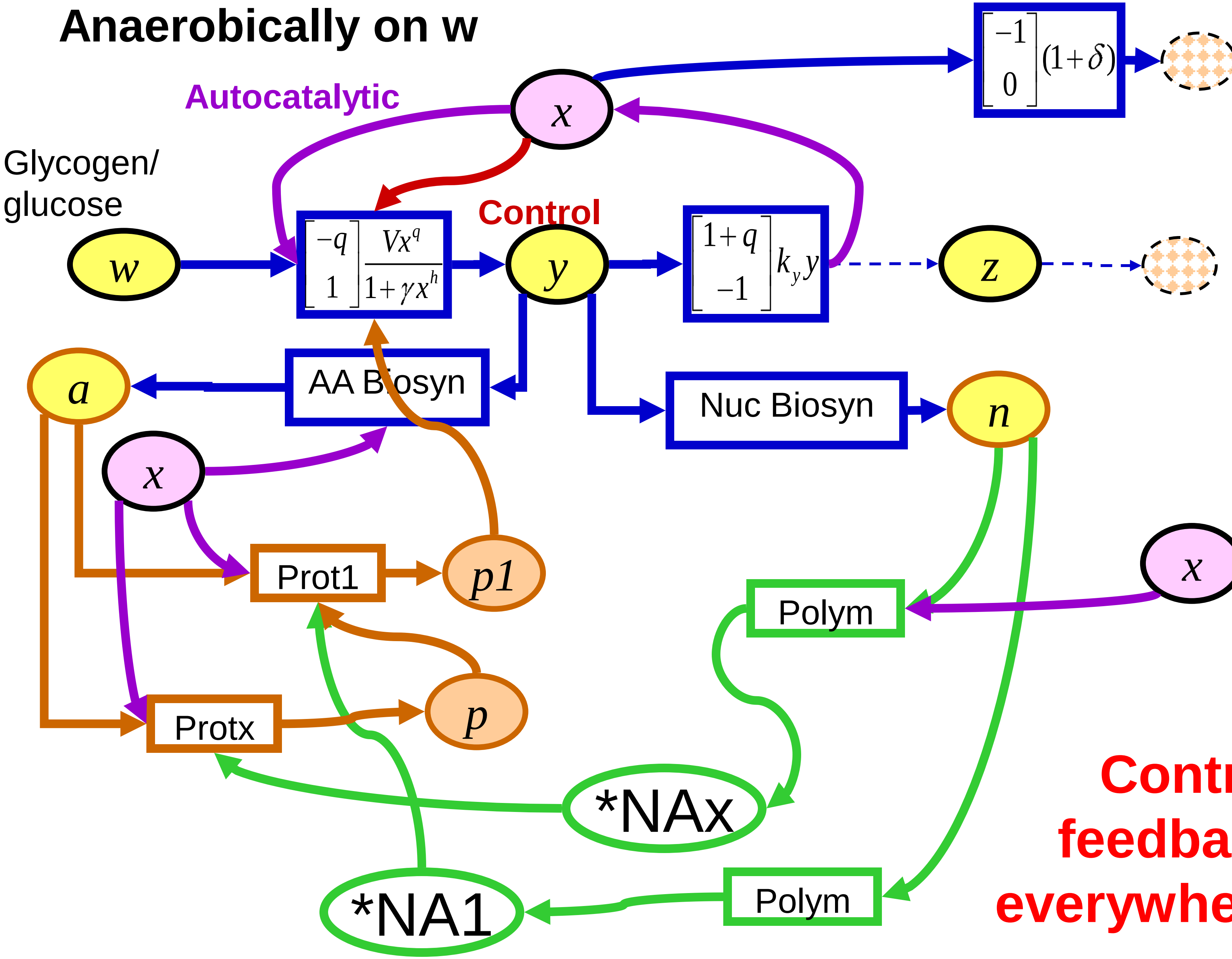
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq -C_{sensor}$$

Helps




Reactions
Flow/error
Protein level
Trans*
Flow/error
*NA level

Anaerobically on w



Control feedback everywhere

Network motifs in the transcriptional regulation network of *Escherichia coli*

Shai S. Shen-Orr[1], Ron Milo[2], Shmoolik Mangan[1] & Uri Alon[1,2]

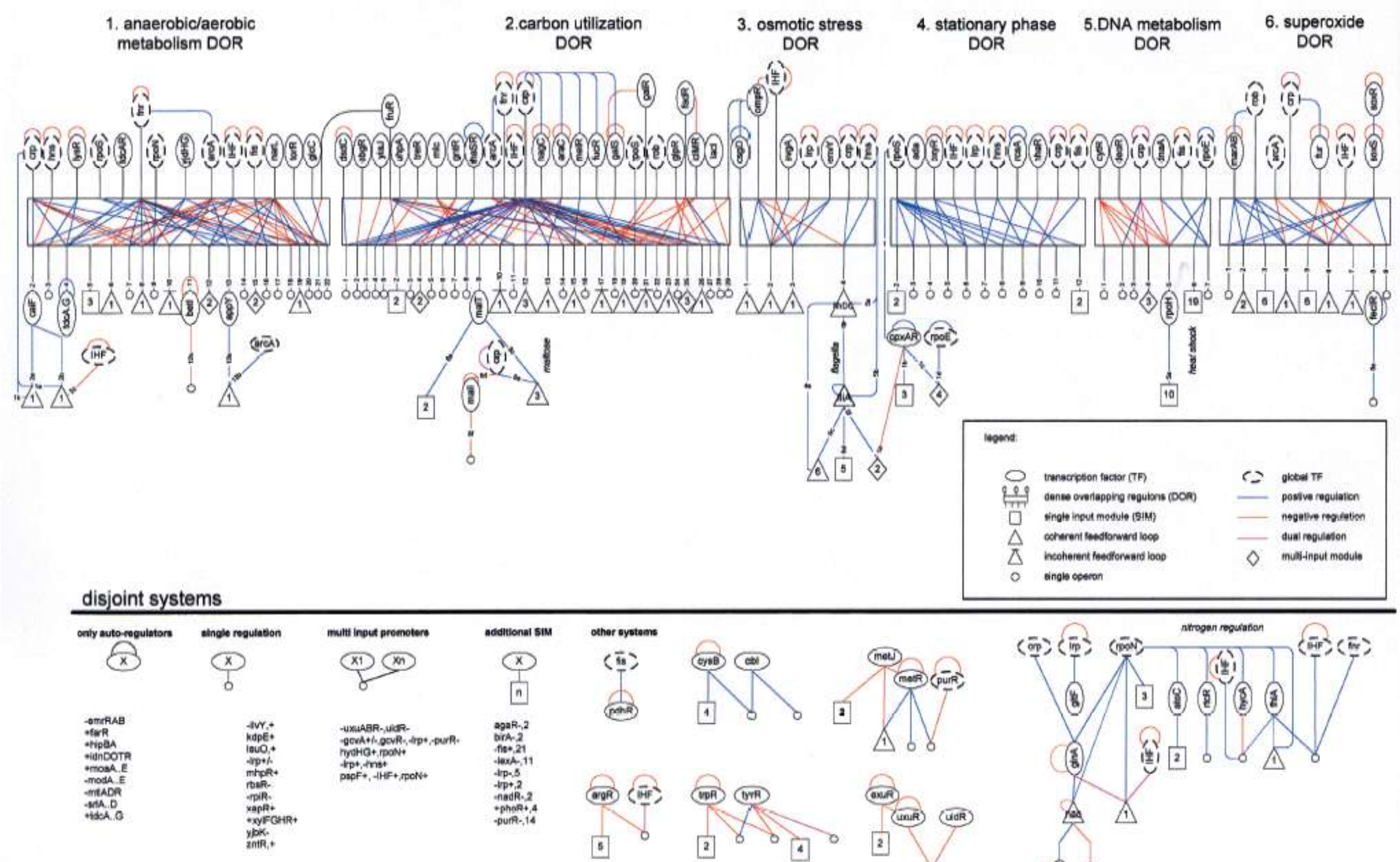


Fig. 4

Network motifs in the transcriptional regulation network of *Escherichia coli*

Shai S. Shen-Orr[1], Ron Milo[2], Shmoolik Mangan[1] & Uri Alon[1,2]

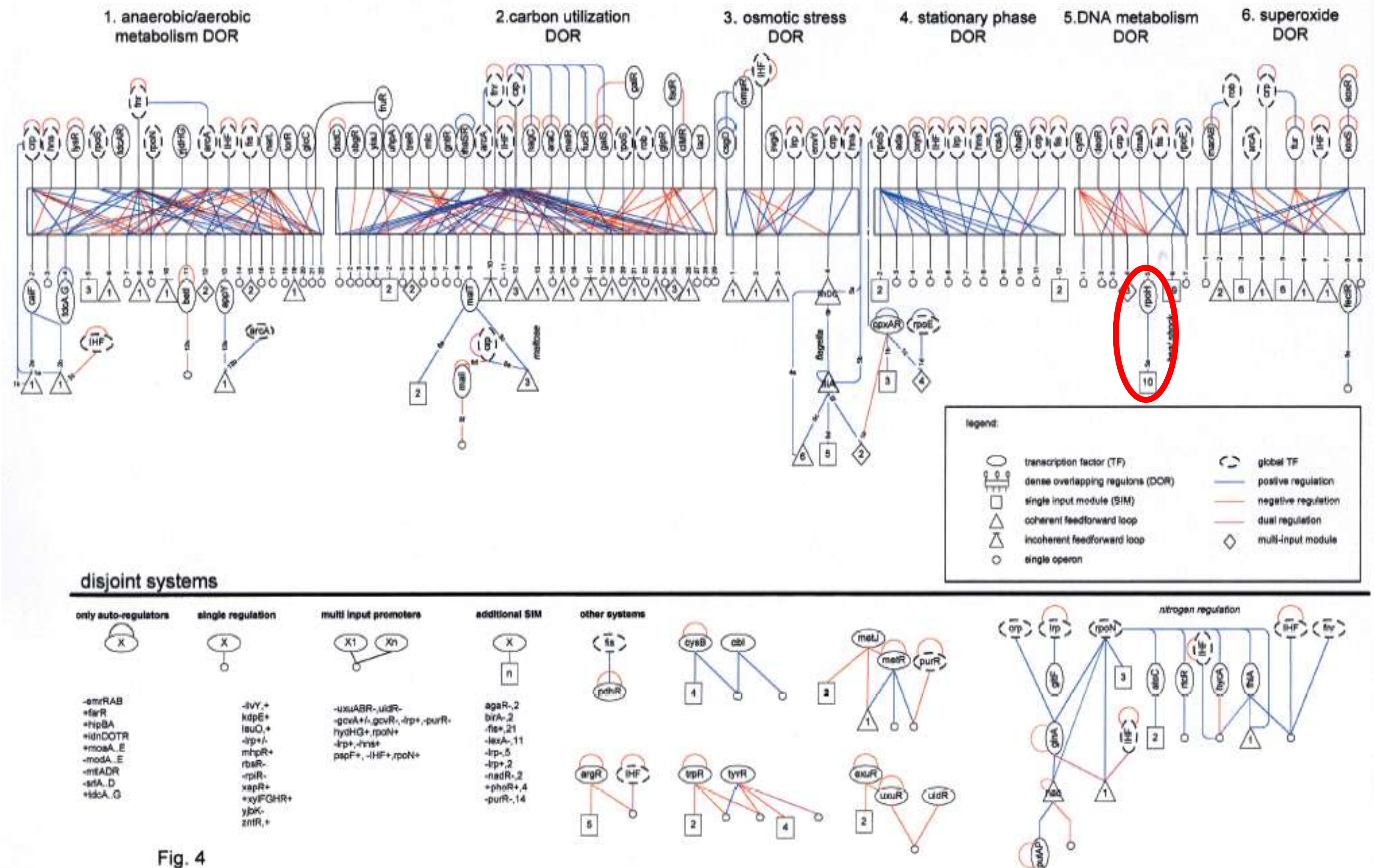
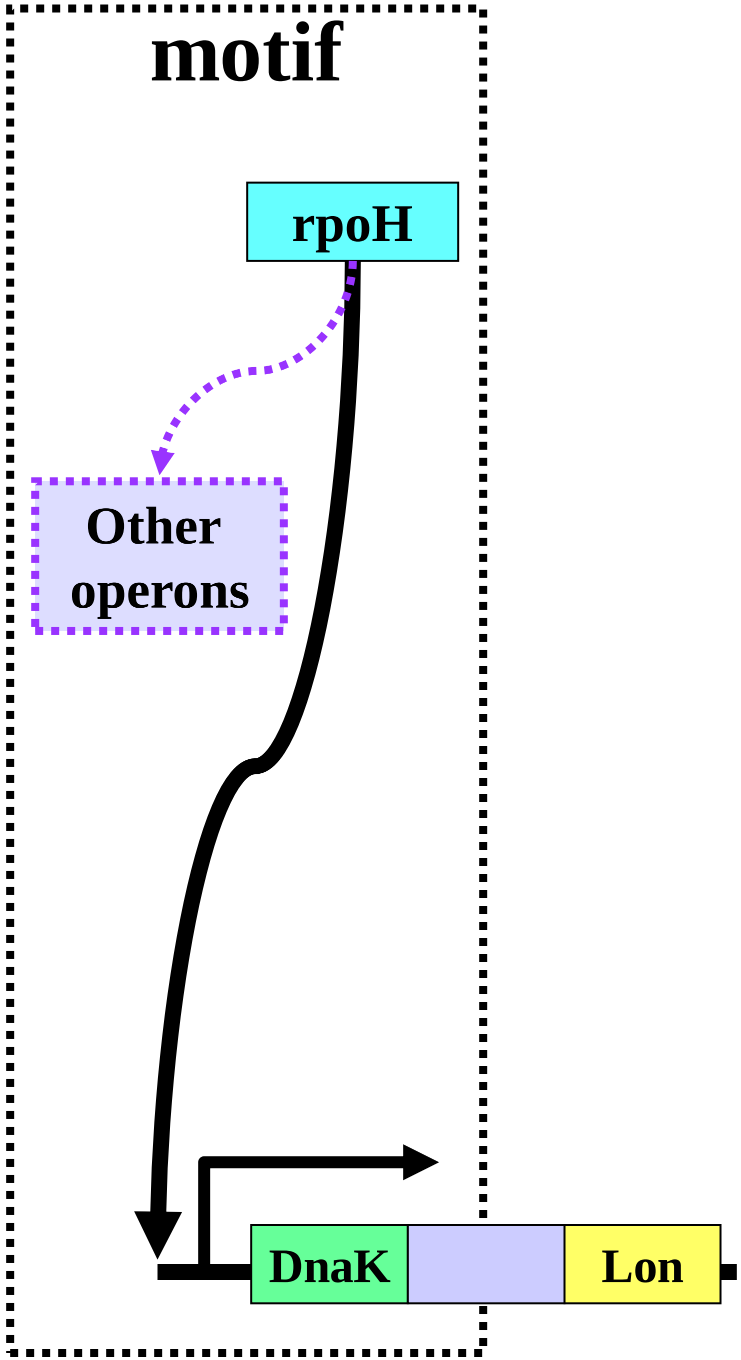
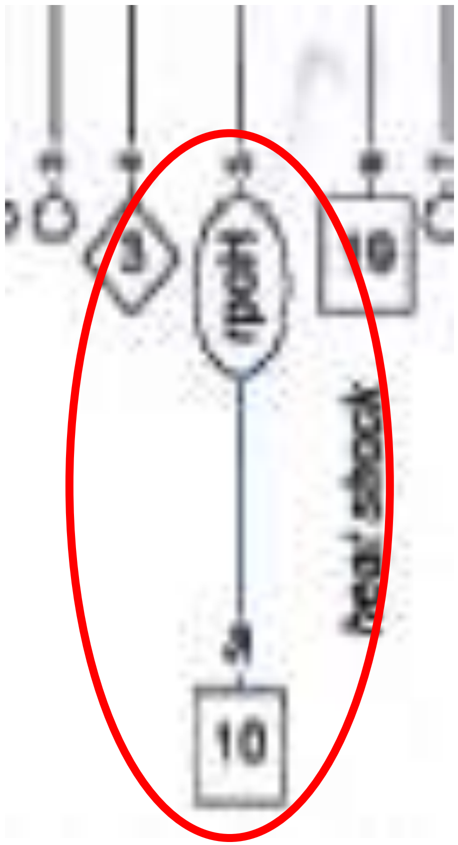
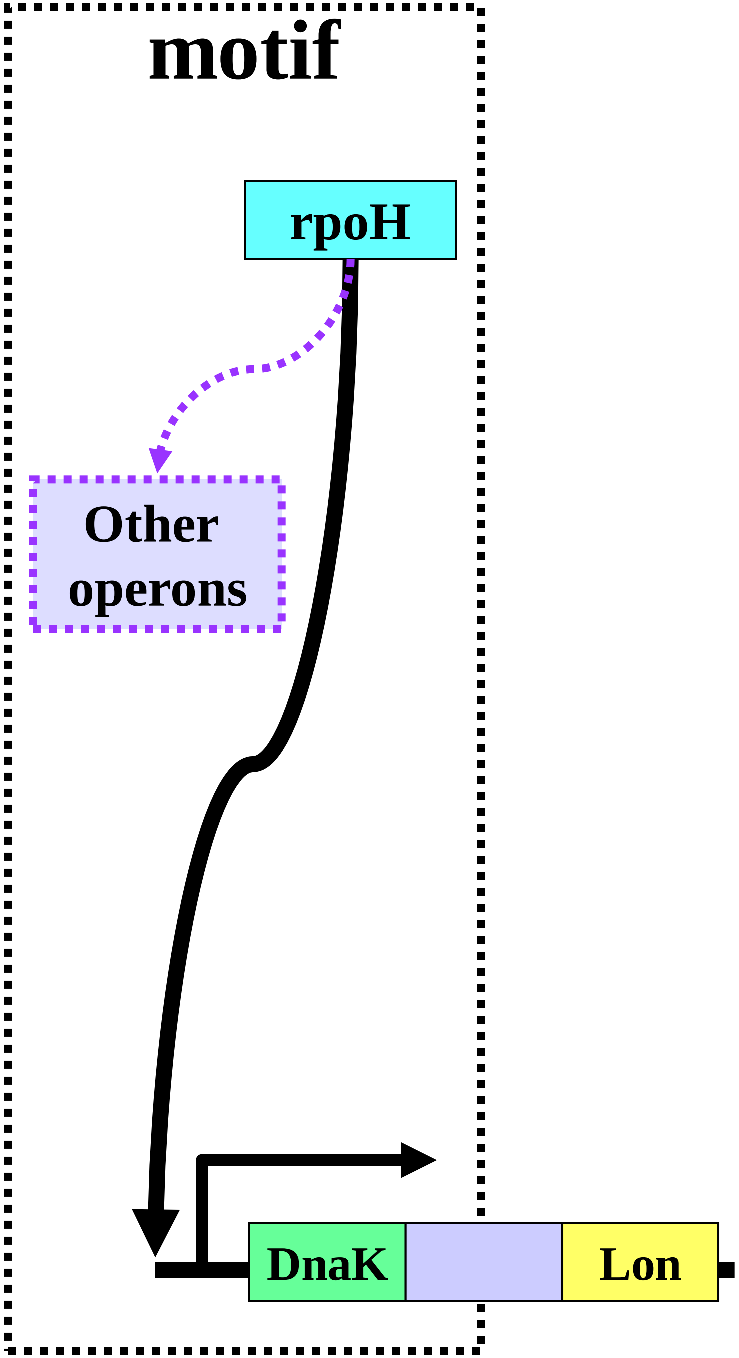


Fig. 4

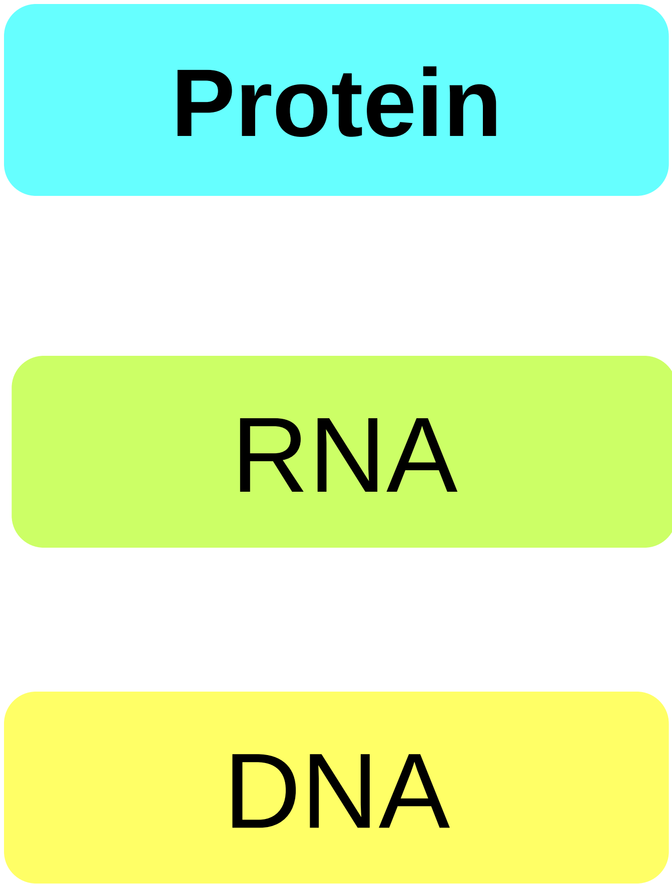


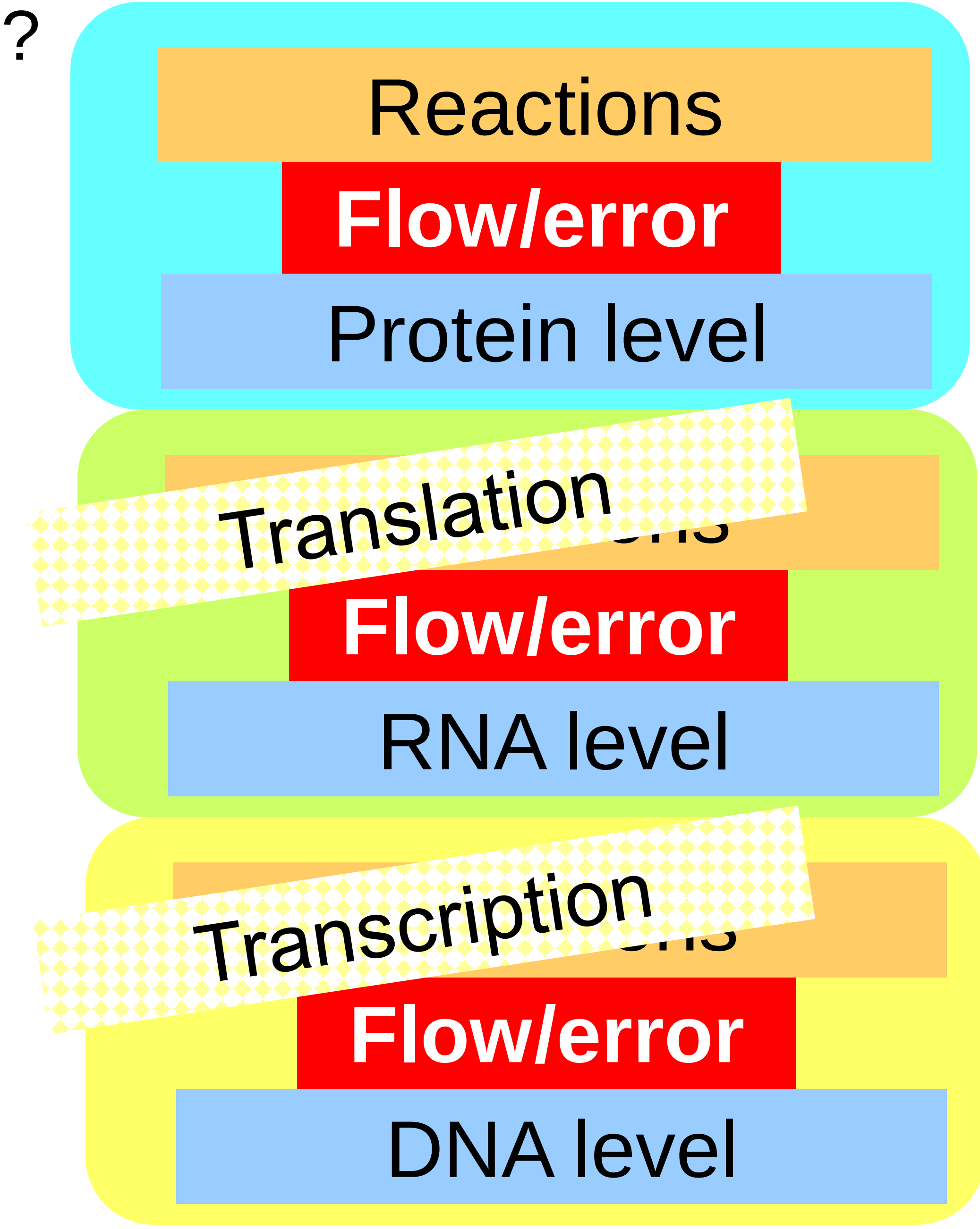


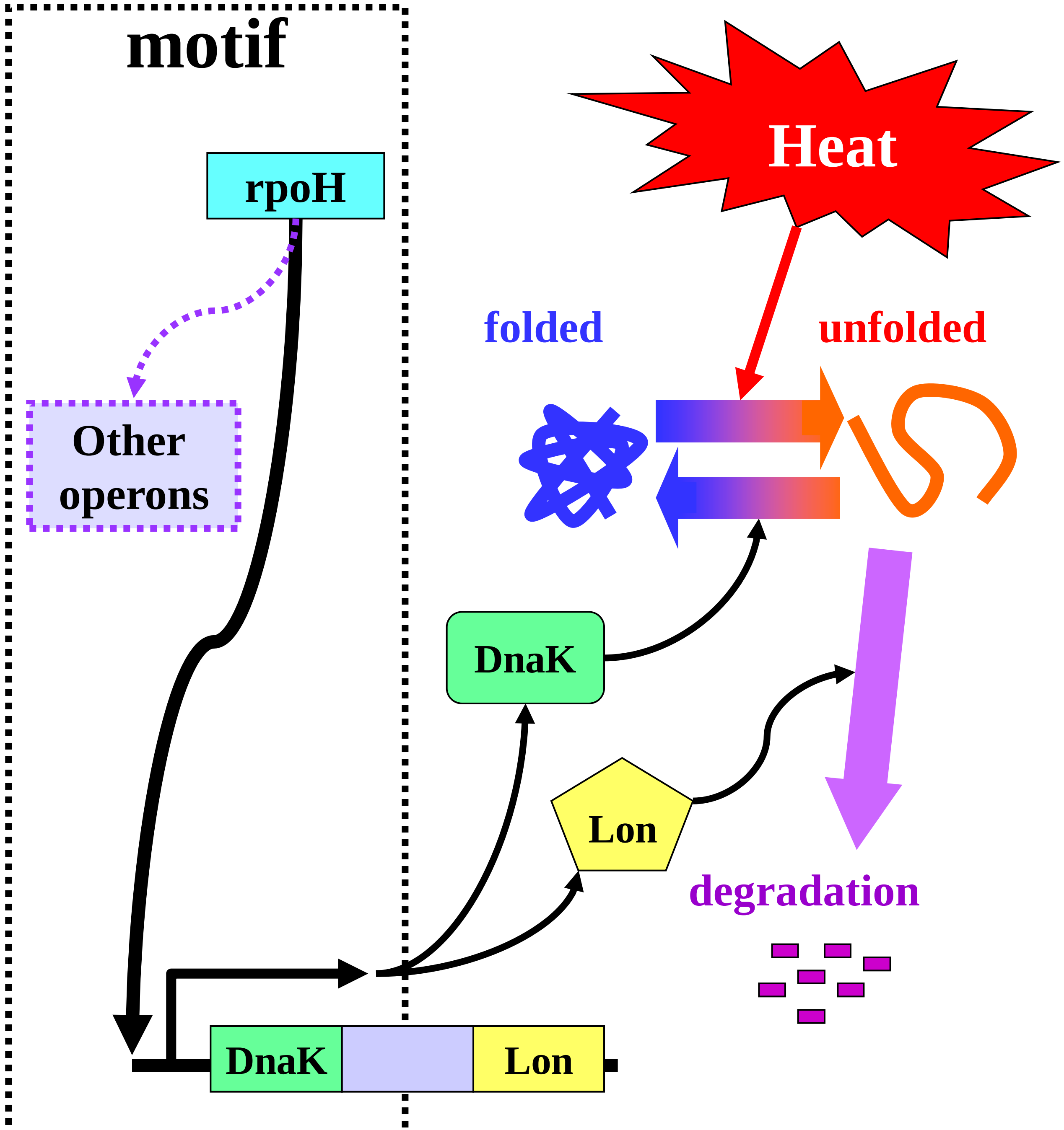
See El-Samad, Kurata, et al…
PNAS, PLOS CompBio

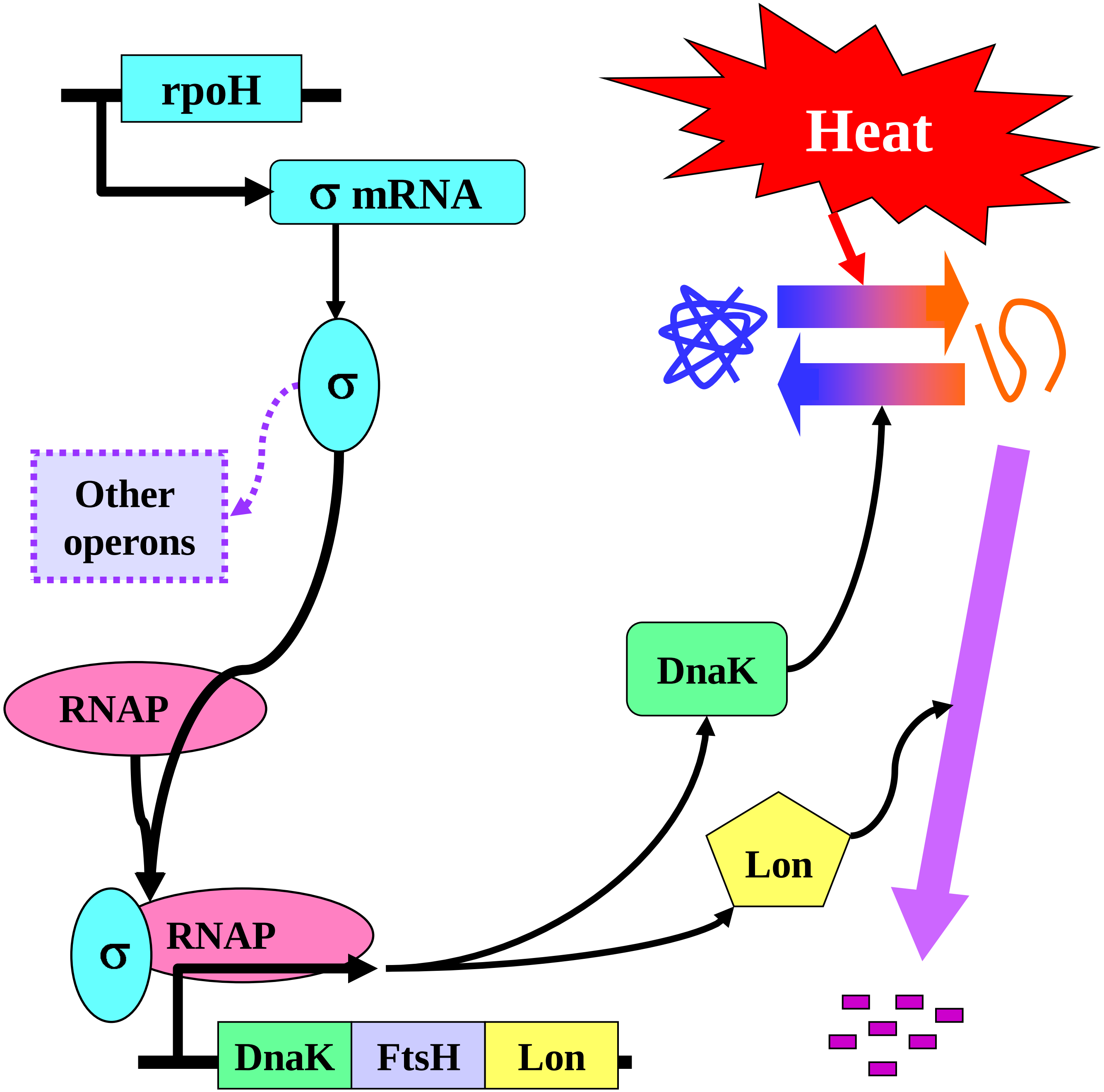

motif
rpoH
Other
operons
DnaK
Lon

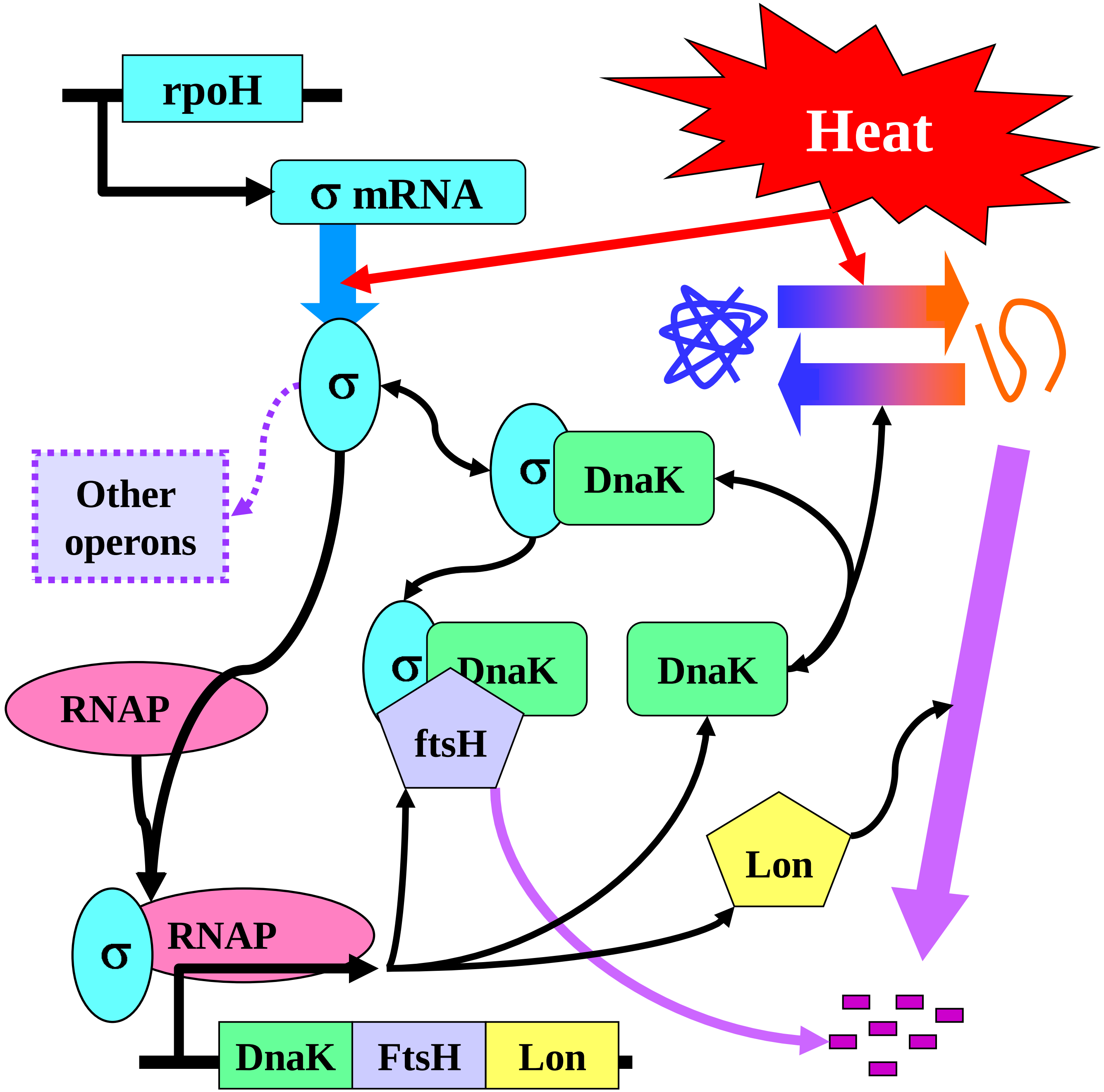
Where are these layers?



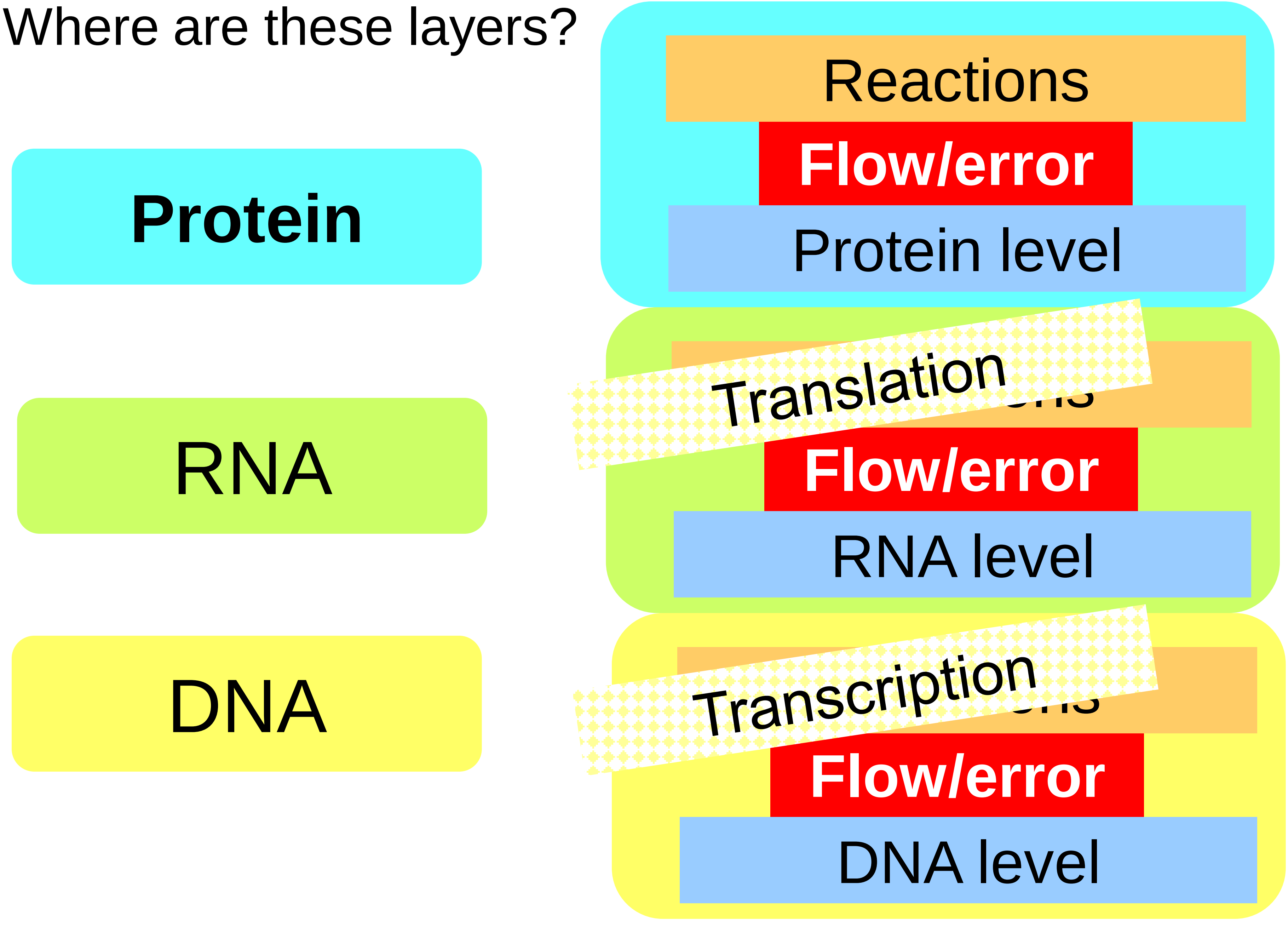


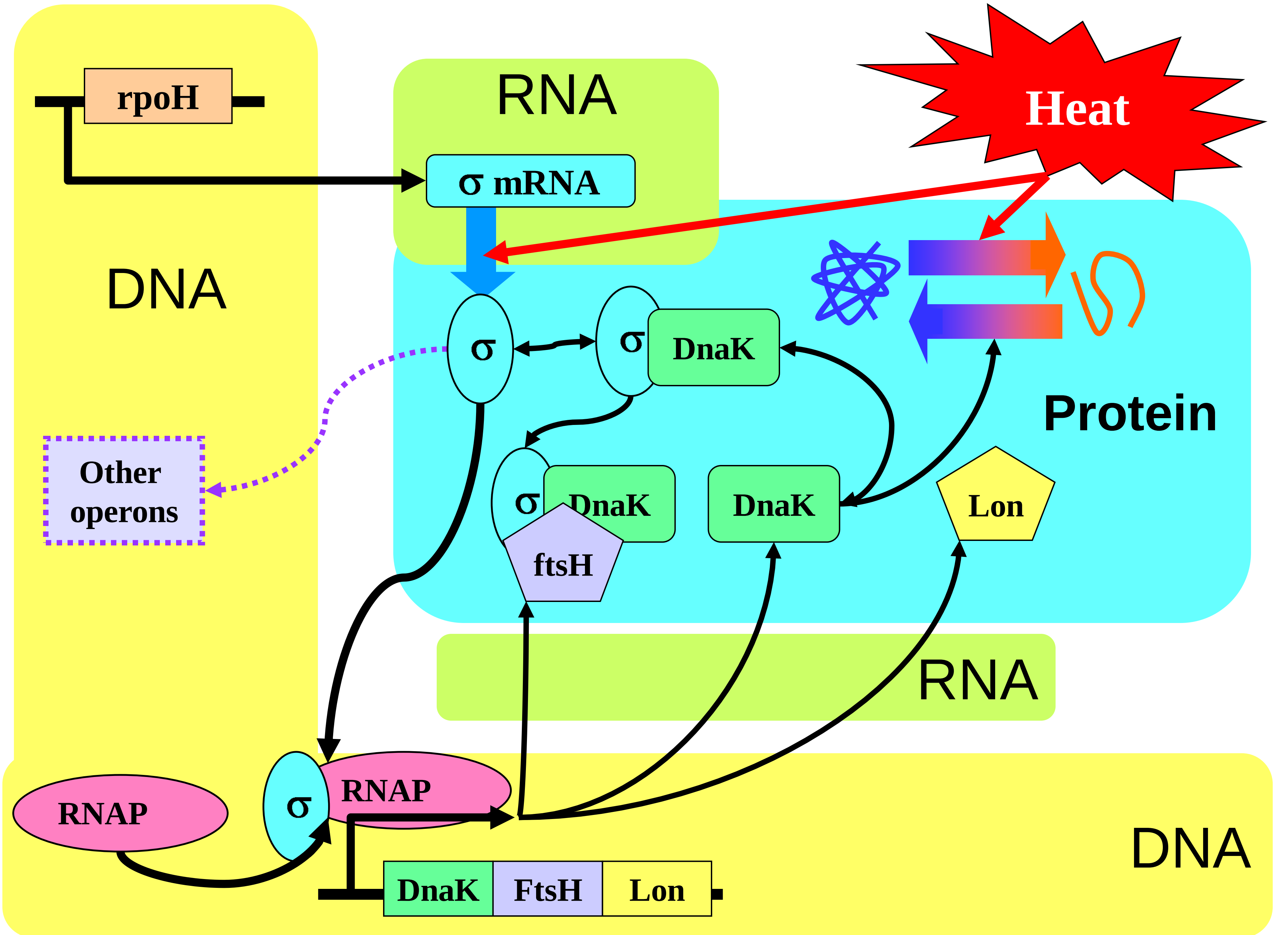

motif
rpoH
Other operons
Heat
folded
unfolded
DnaK
Lon
degradation
DnaK
Lon

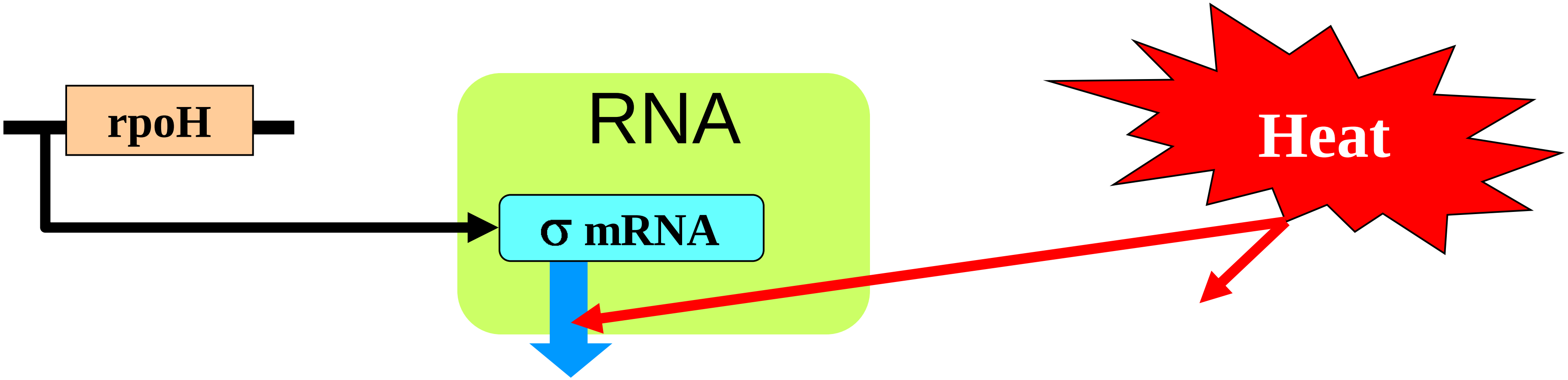

rpoH
σ mRNA
Heat
σ
Other operons
DnaK
RNAP
Lon
σ
RNAP
DnaK
FtsH
Lon


rpoH
σ mRNA
Heat
σ
Other operons
σ
DnaK
σ
DnaK
DnaK
ftsH
RNAP
Lon
σ
RNAP
DnaK
FtsH
Lon

Where are these layers?

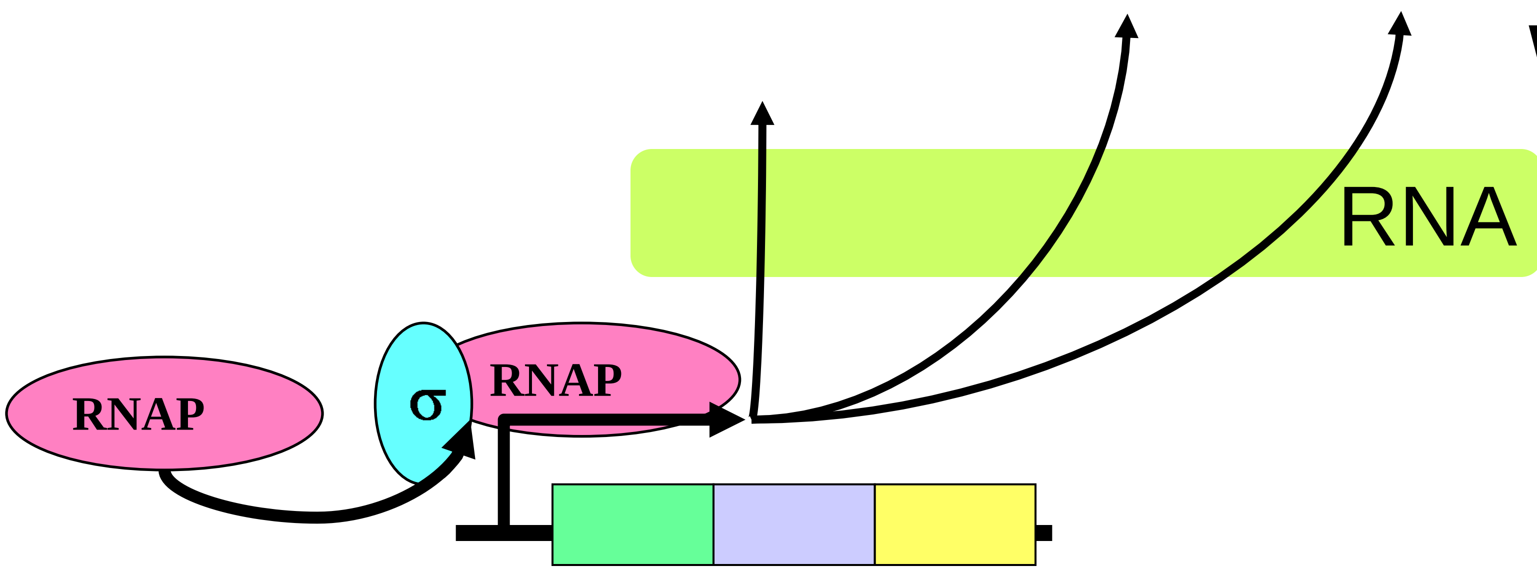


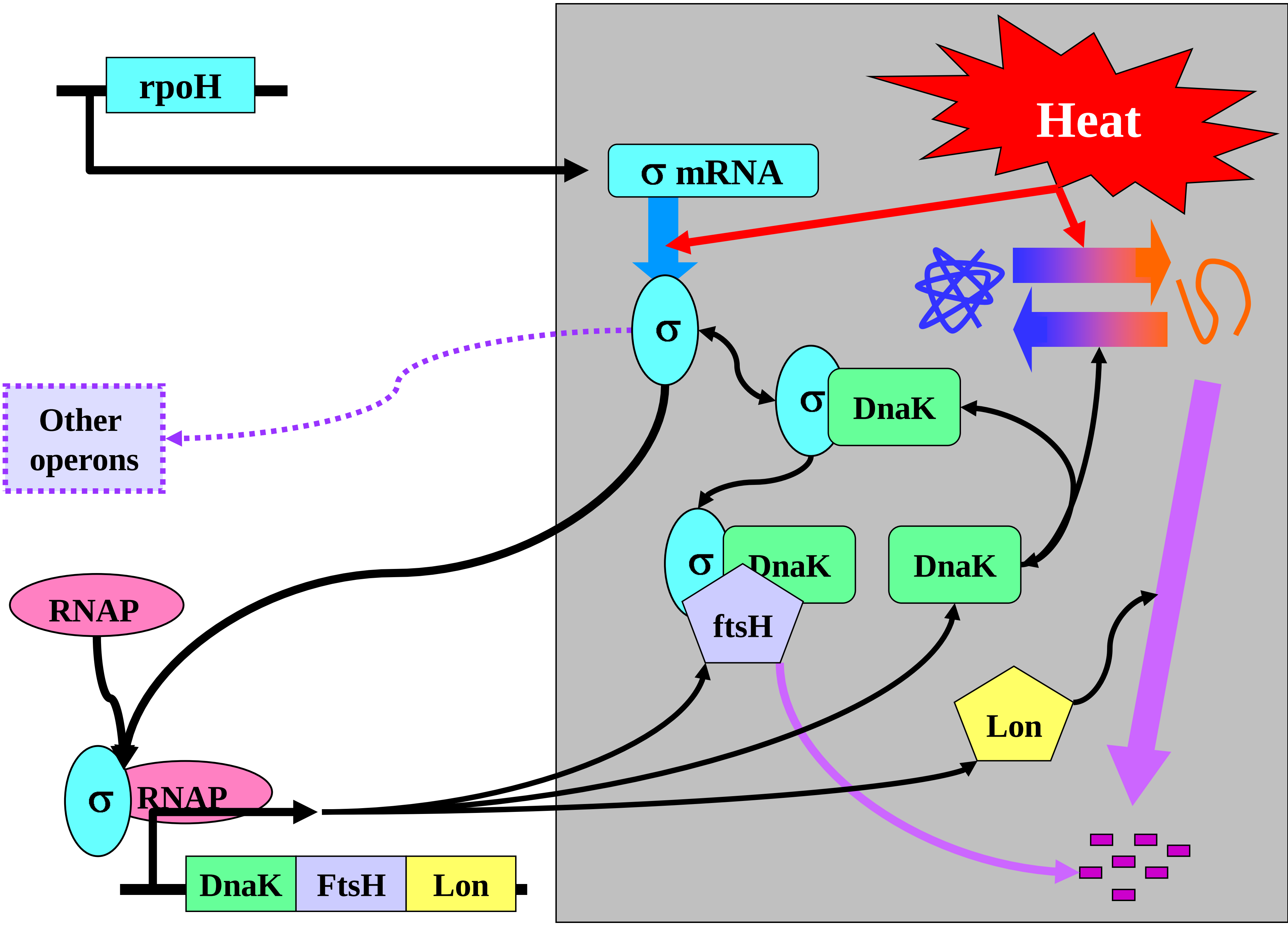

rpoH
RNA
σ mRNA
Heat
DNA
σ
σ
DnaK
Protein
Other
operons
σ
DnaK
ftsH
DnaK
Lon
RNA
RNAP
RNAP
σ
DNA
DnaK
FtsH
Lon



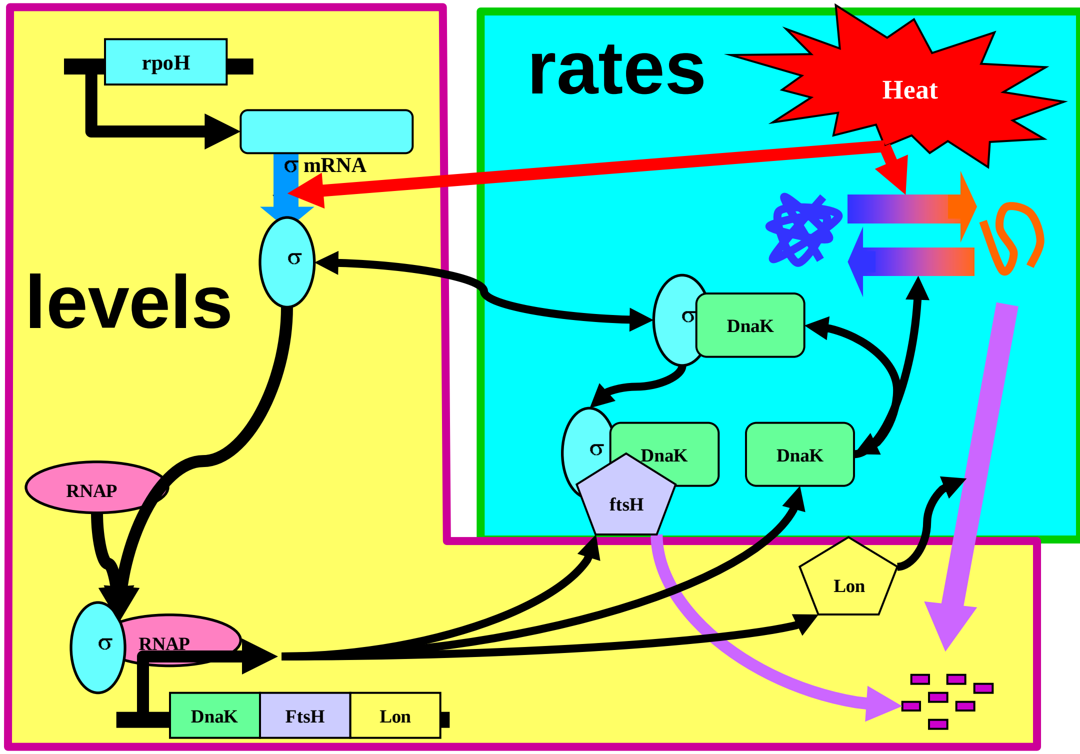
mRNA activity is actively controlled.

Translation was not shown.

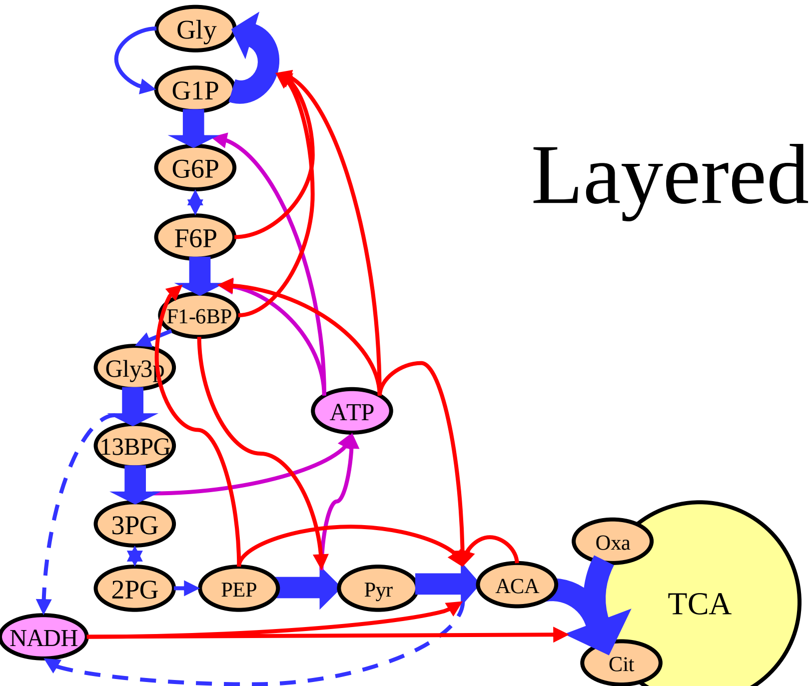




rpoH
σ mRNA
Heat
σ
Other operons
σ
DnaK
σ
DnaK
ftsH
DnaK
Lon
RNAP
σ
RNAP
DnaK
FtsH
Lon



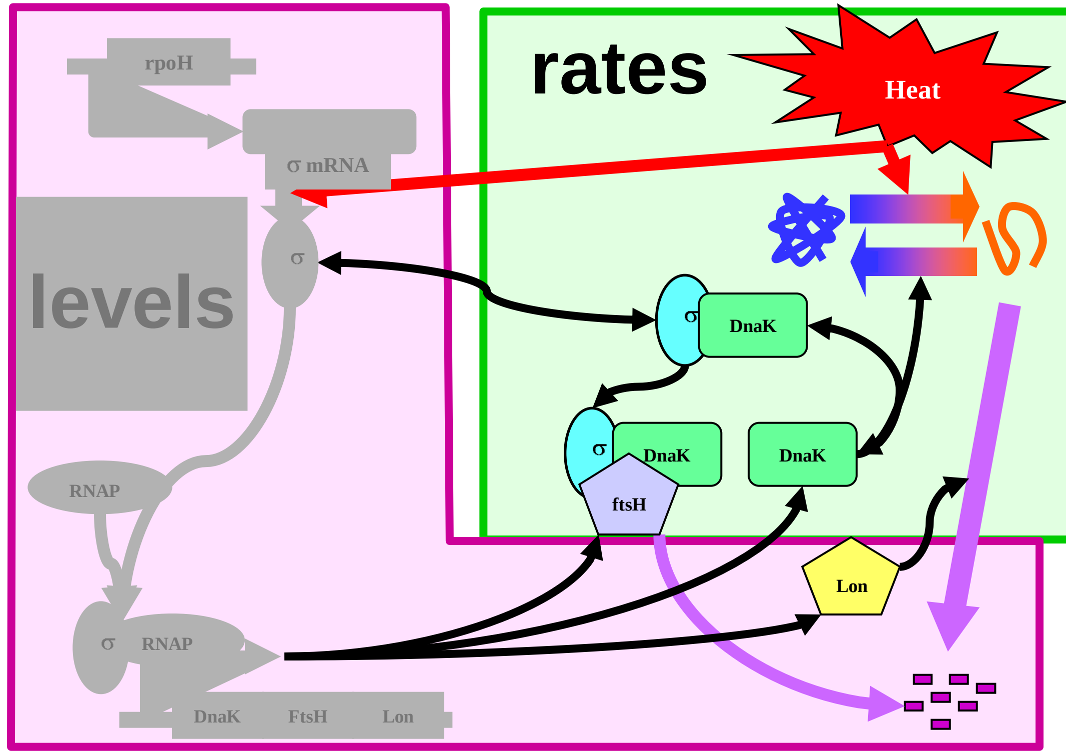
Layered control architectures



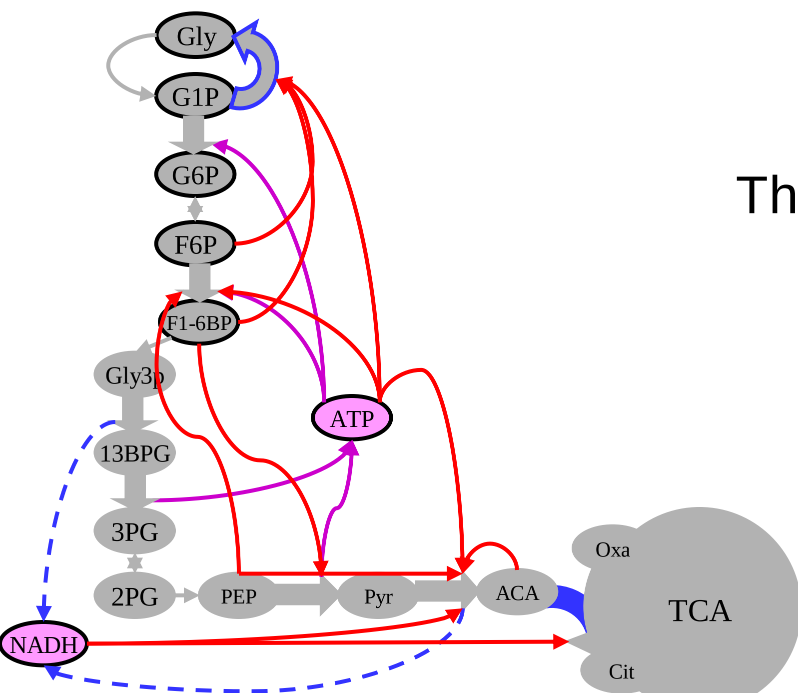
Allosteric

Trans*

The greatest complexity here is primarily in the control of ***rates***

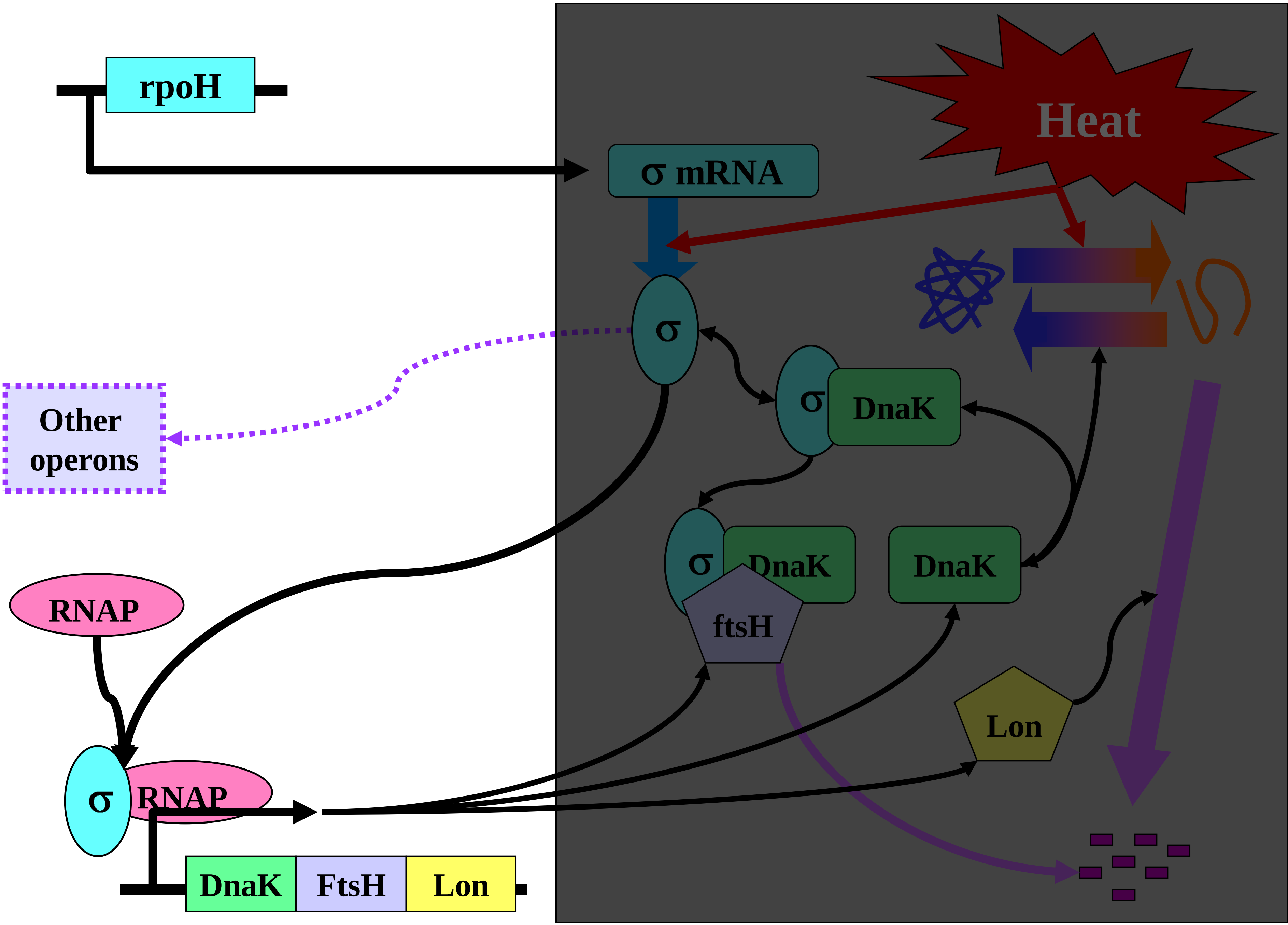


That is not always the case.

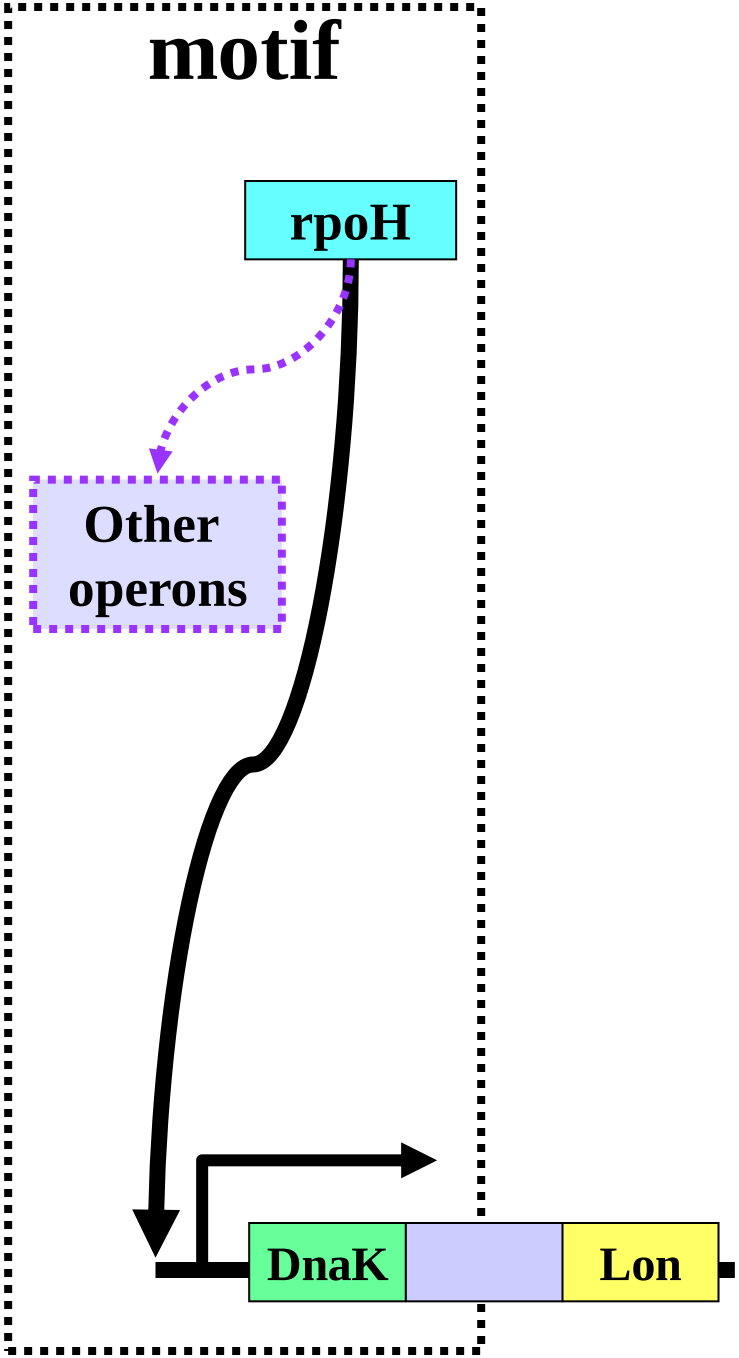


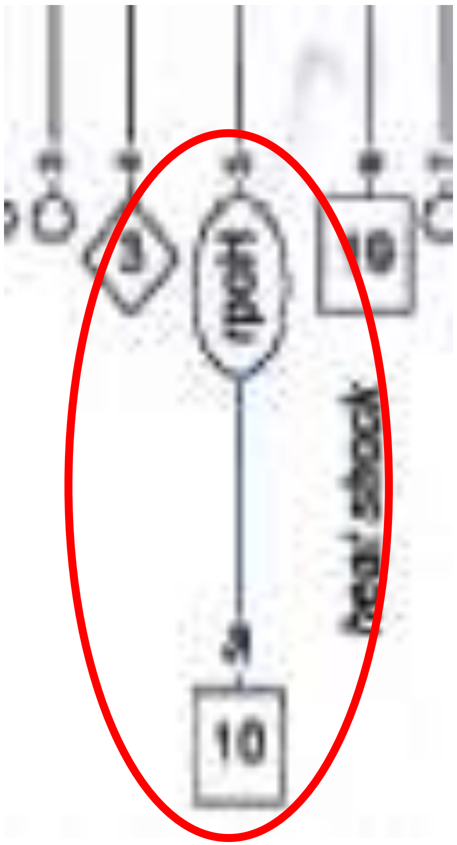
Allosteric

Trans*

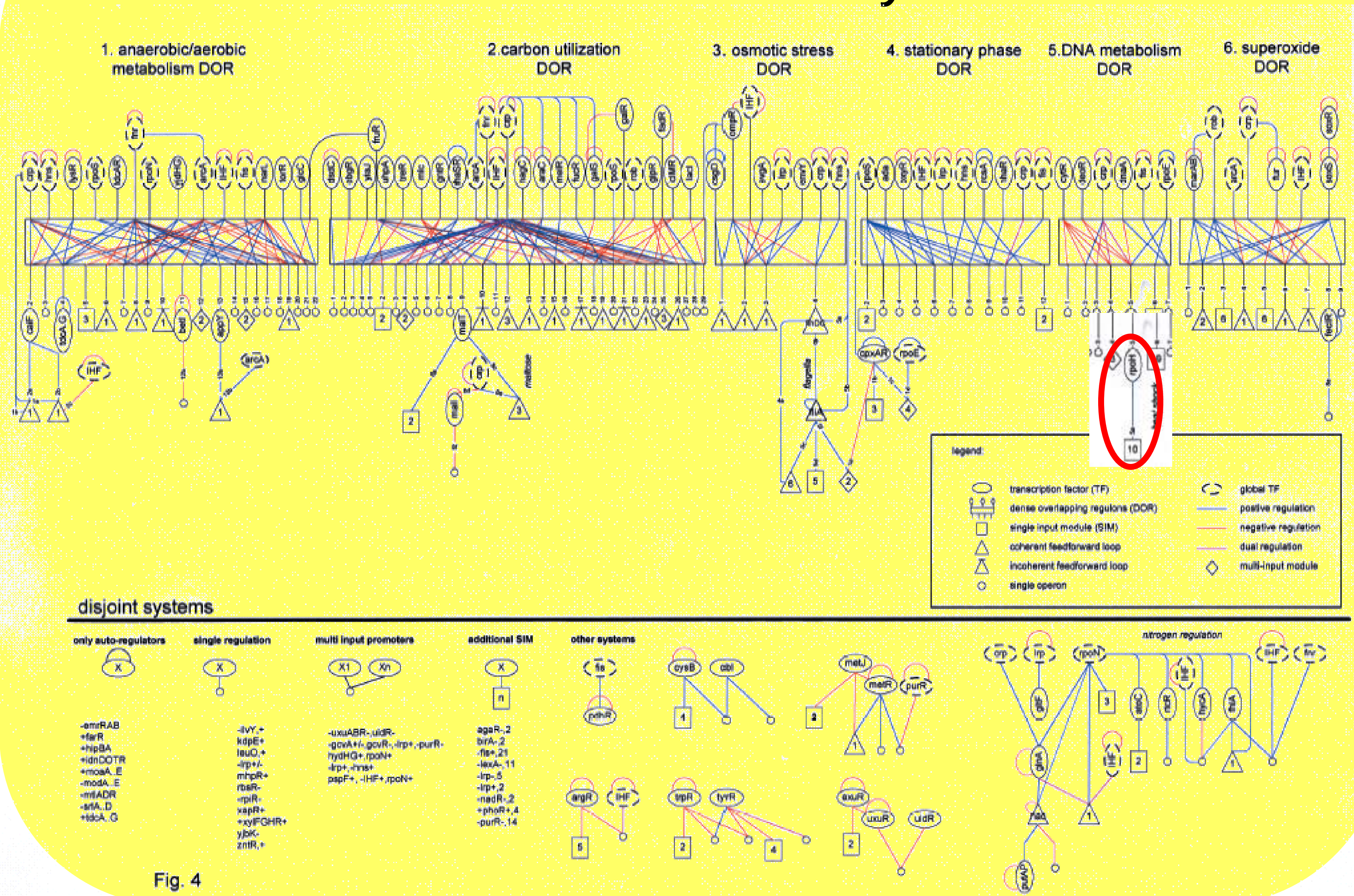


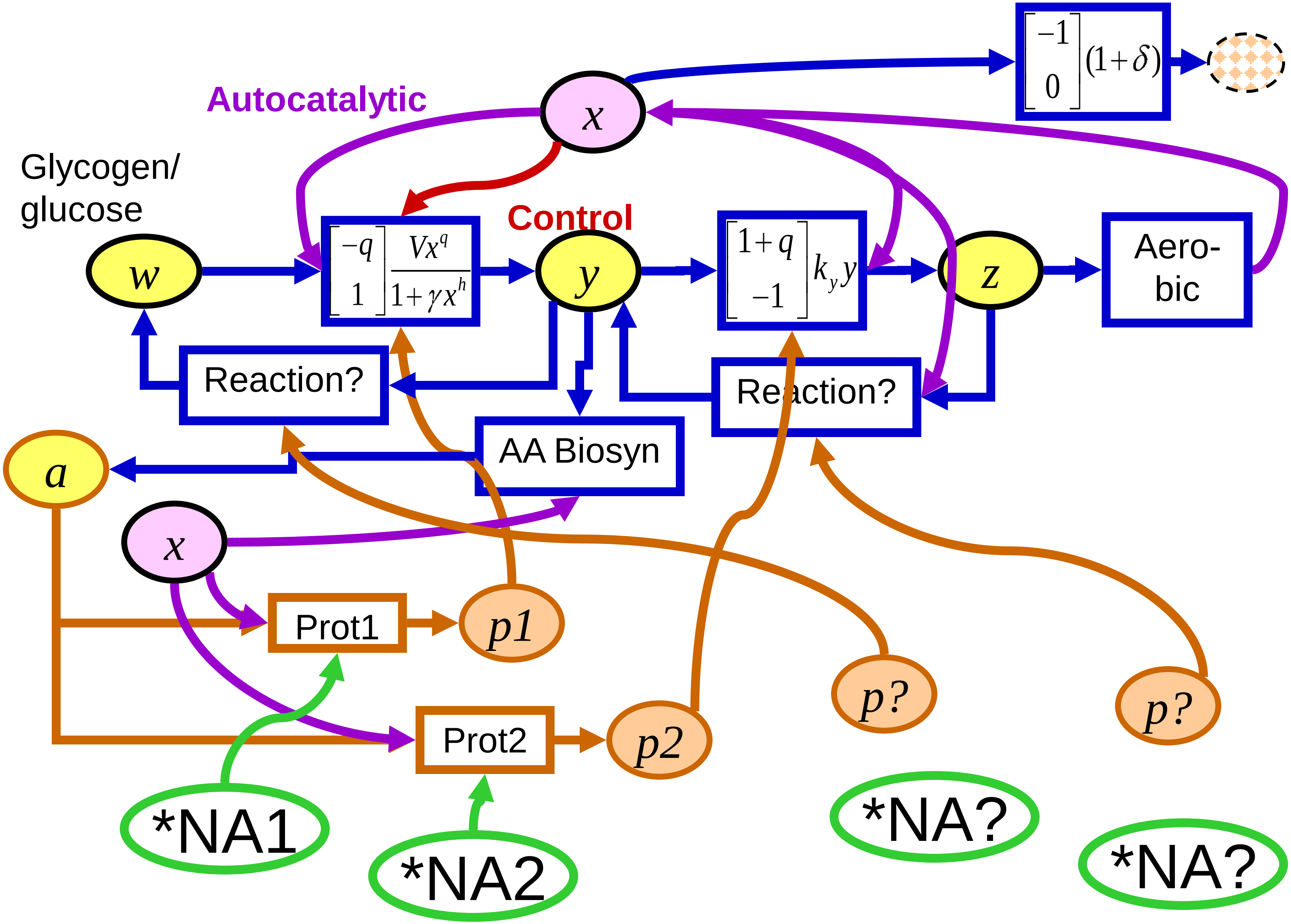
rpoH
σ mRNA
Heat
σ
Other operons
σ DnaK
σ DnaK
DnaK
ftsH
Lon
RNAP
σ RNAP
DnaK
FtsH
Lon


motif
rpoH
Other operons
DnaK
Lon


3
19
rpoH
heat shock
10

All at the DNA layer

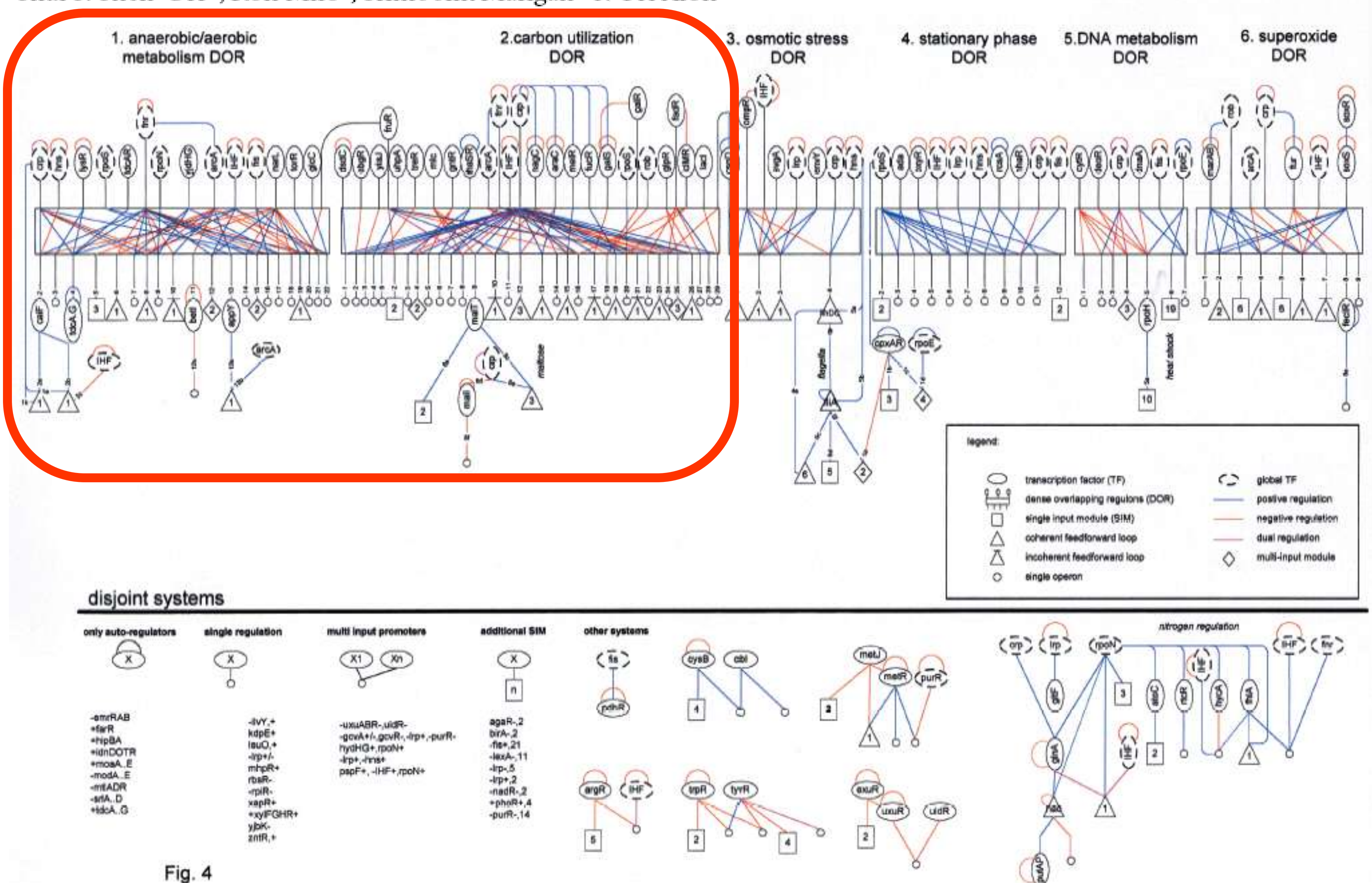


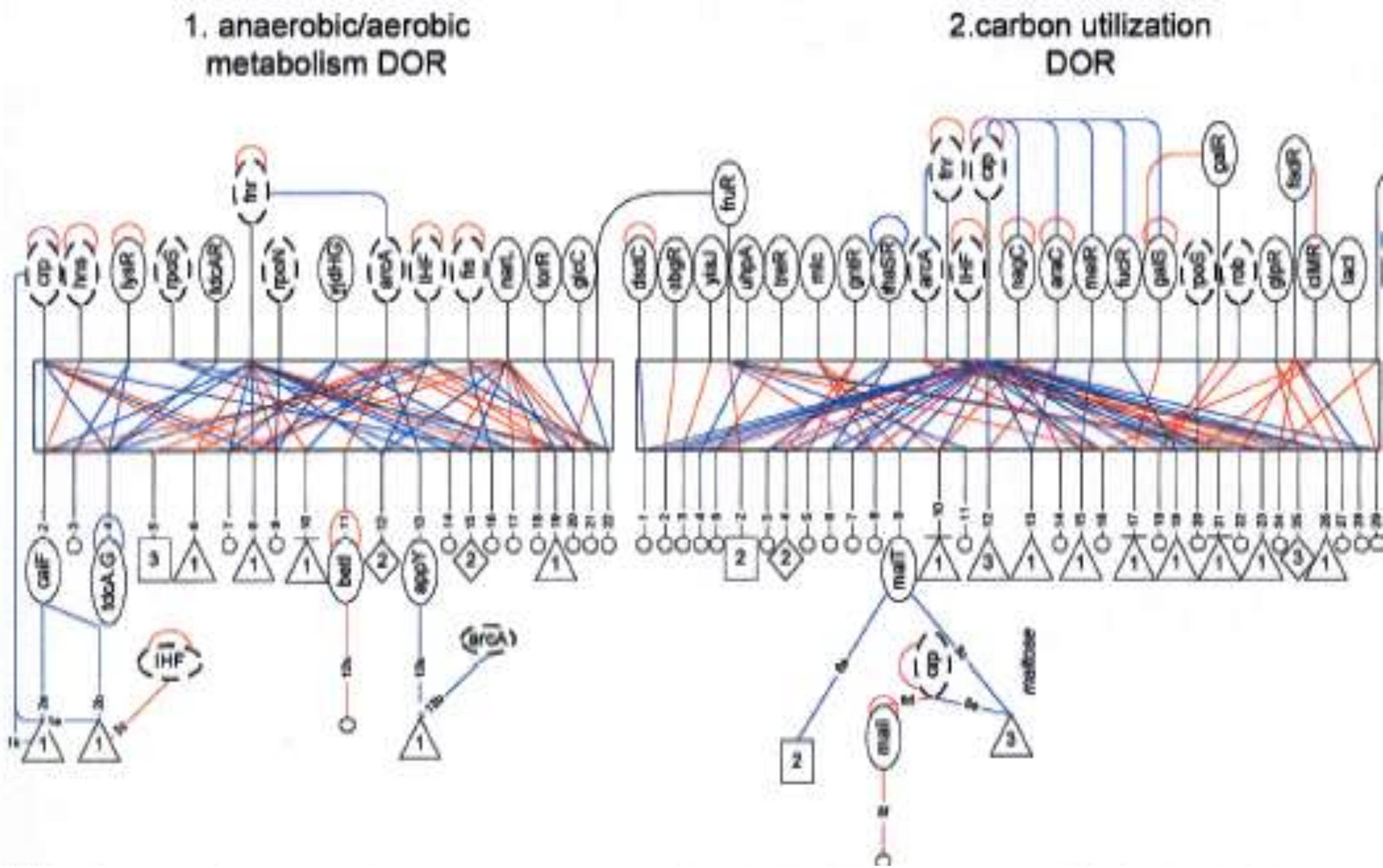


Autocatalytic
Glycogen/
glucose
Control
Aero-
bic
Reaction?
Reaction?
AA Biosyn
Prot1
Prot2
*NA1
*NA2
*NA?
*NA?

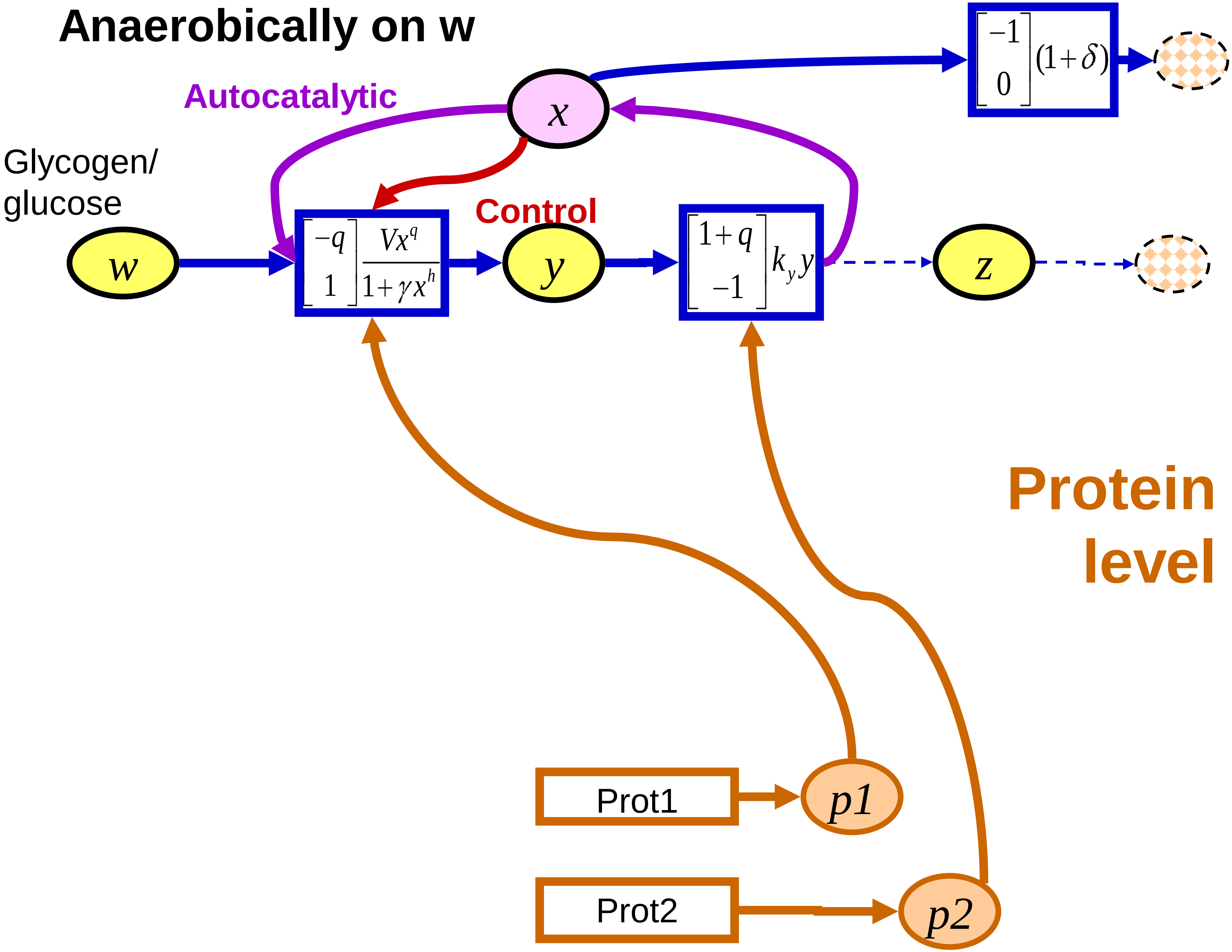
Network motifs in the transcriptional regulation network of *Escherichia coli*

Shai S. Shen-Orr[1], Ron Milo[2], Shmoolik Mangan[1] & Uri Alon[1,2]

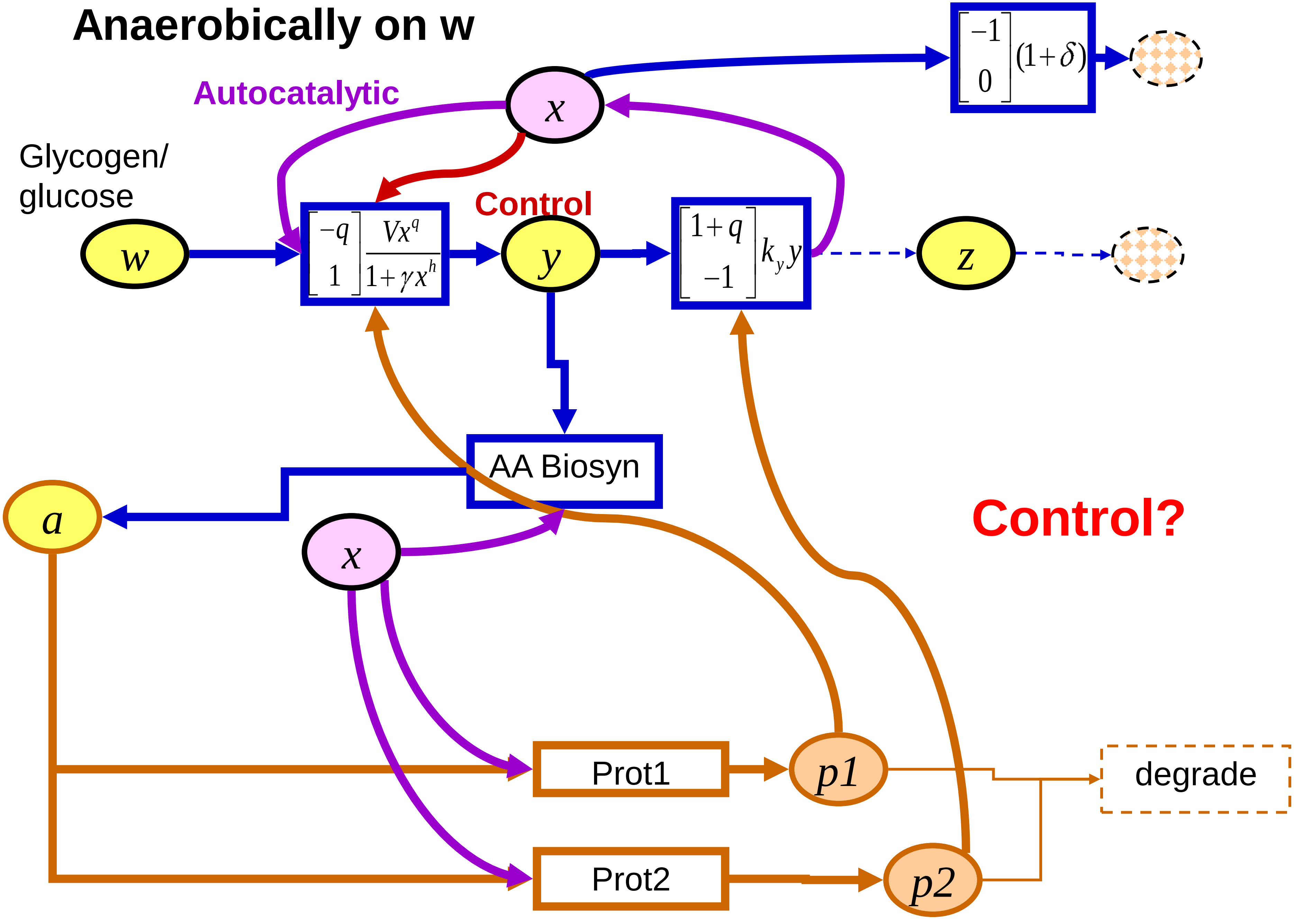


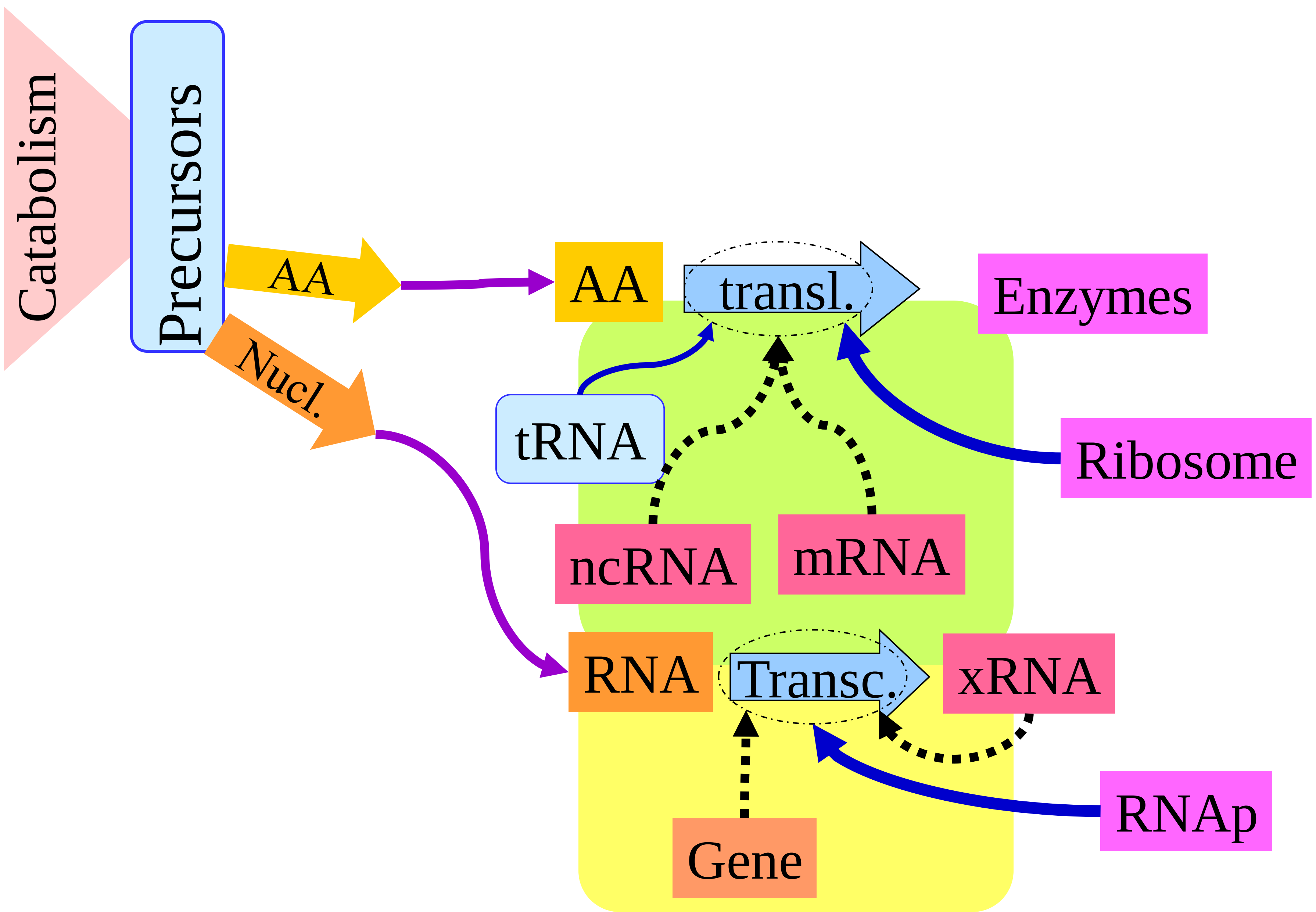

1. anaerobic/aerobic
metabolism DOR
2.carbon utilization
DOR

Anaerobically on w

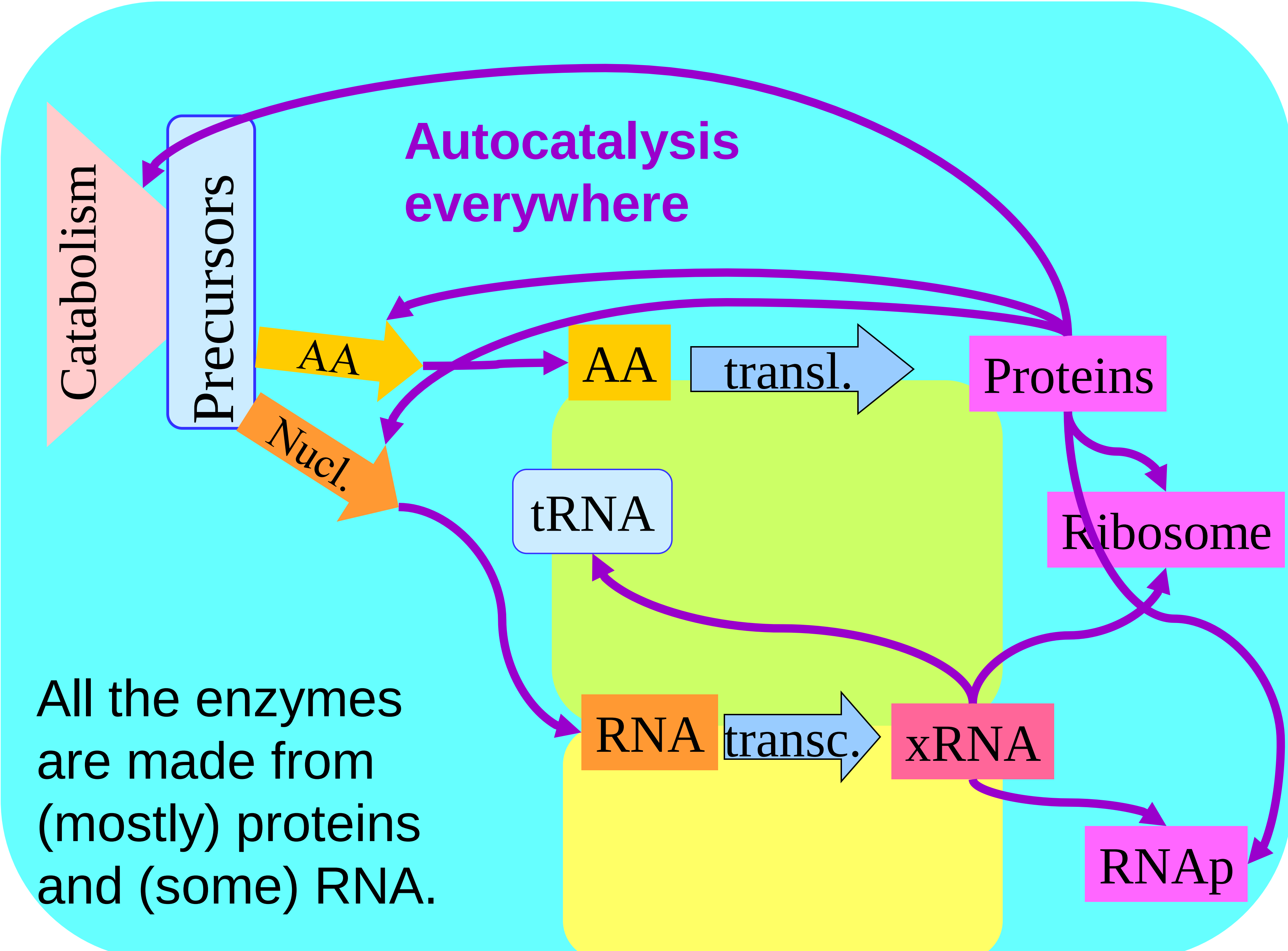


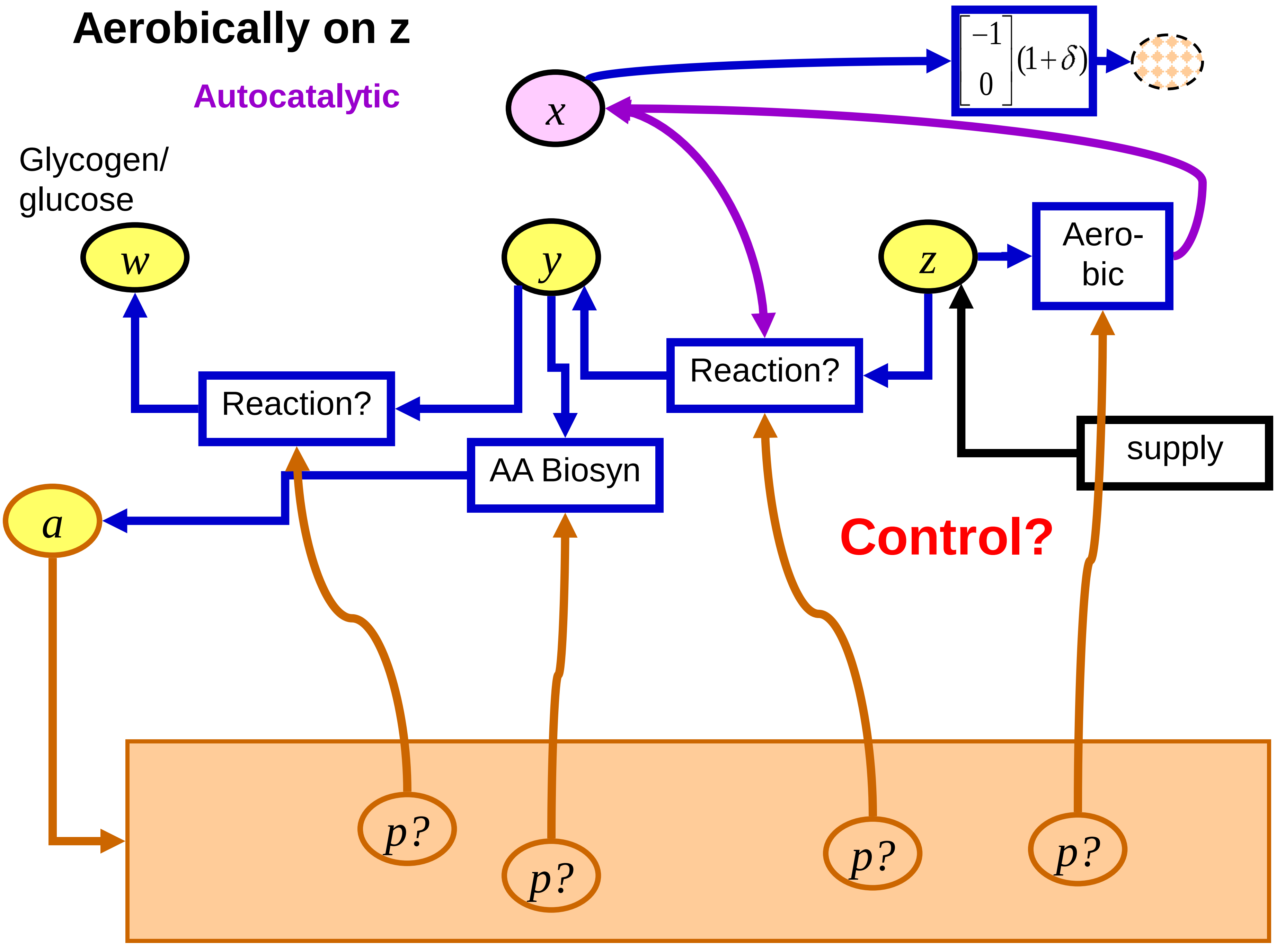
Anaerobically on w



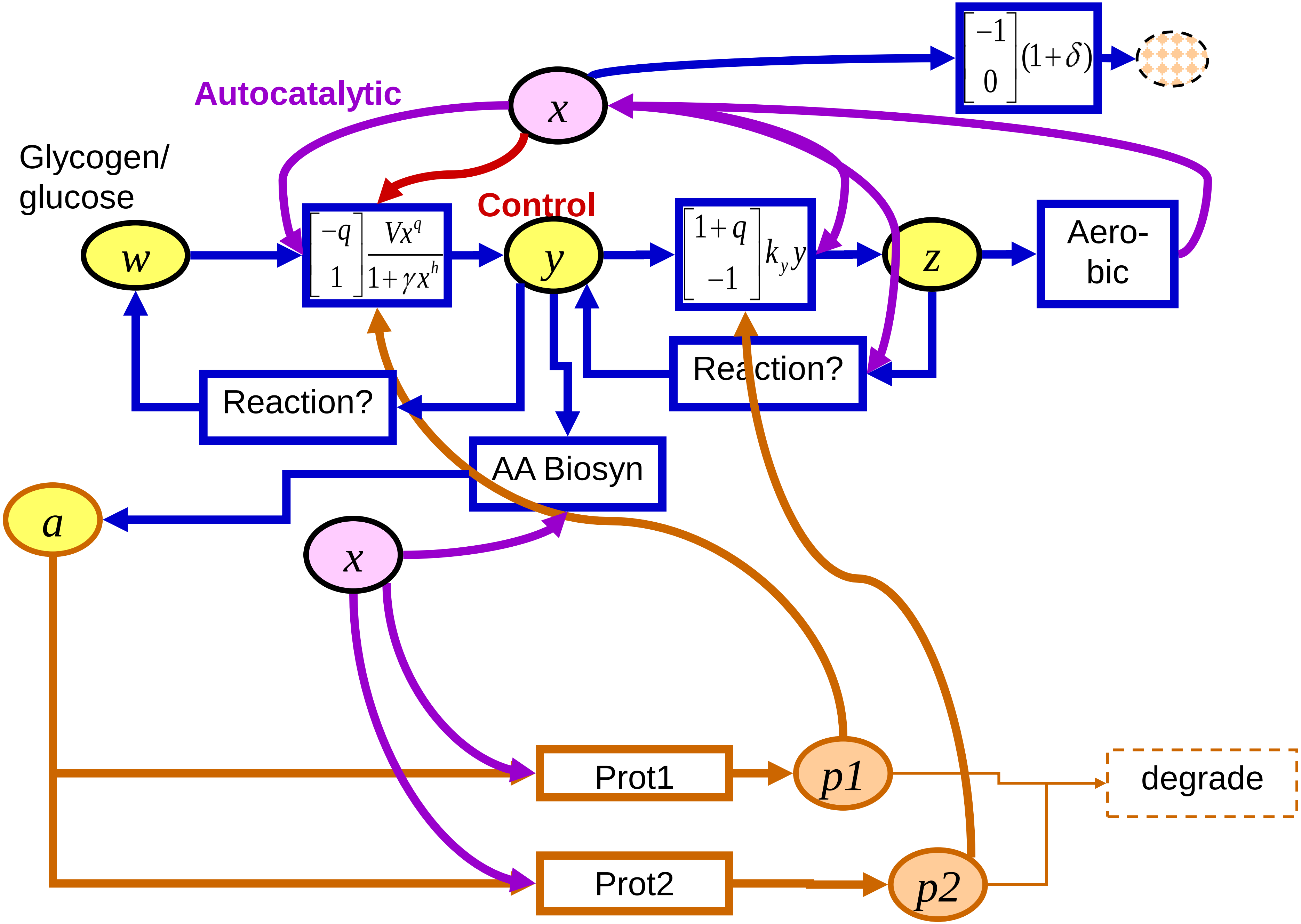


Catabolism
Precursors
AA
Nucl.
AA
transl.
Enzymes
tRNA
Ribosome
ncRNA
mRNA
RNA
Transc.
xRNA
RNAp
Gene


Autocatalysis
everywhere
Catabolism
Precursors
AA
Nucl.
AA
transl.
Proteins
tRNA
Ribosome
RNA
transc.
xRNA
RNAp
All the enzymes
are made from
(mostly) proteins
and (some) RNA.

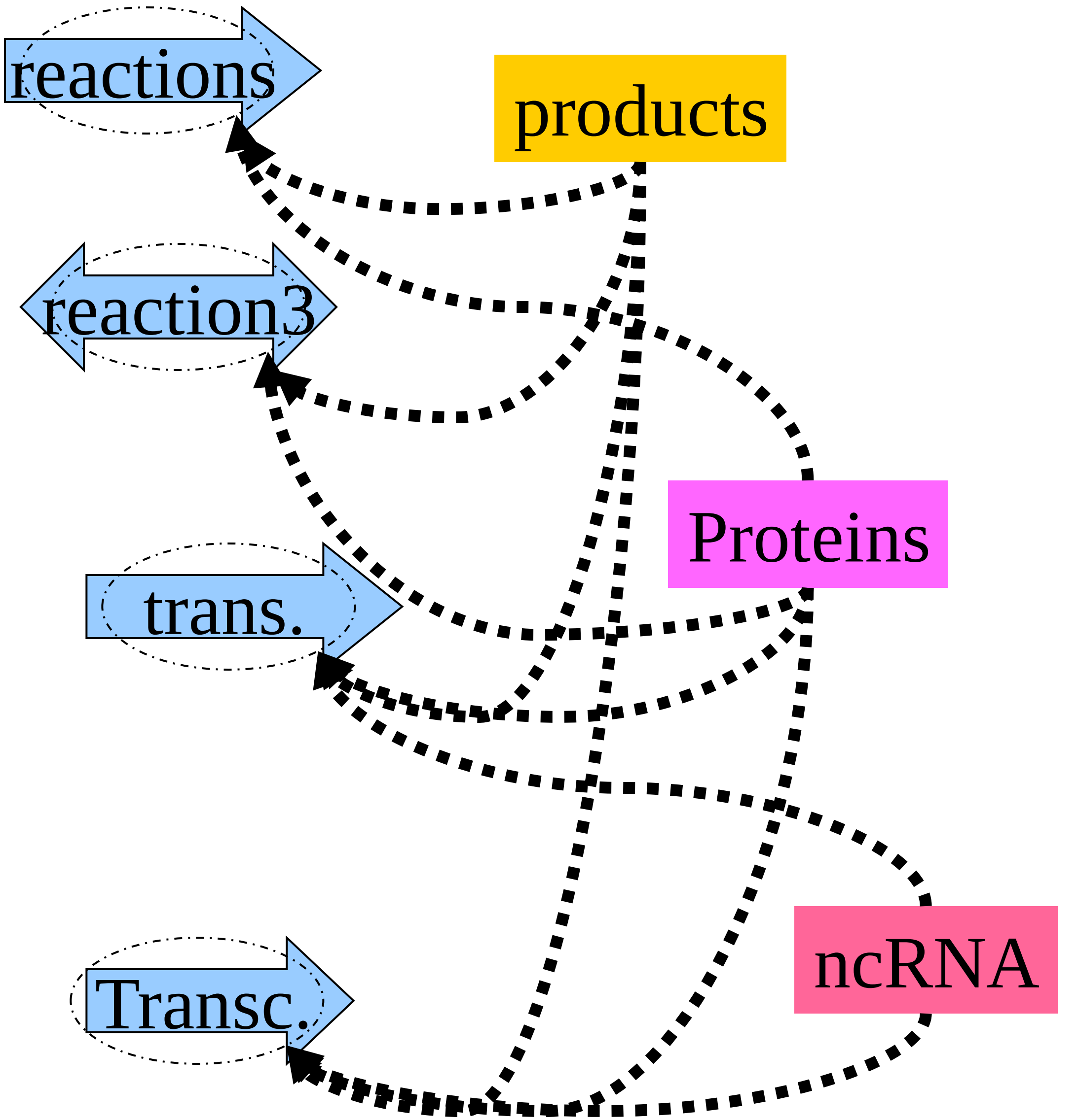


Aerobically on z
Autocatalytic
Glycogen/
glucose
w
y
z
x
a
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
Aero-
bic
Reaction?
Reaction?
AA Biosyn
supply
Control?
p?
p?
p?
p?

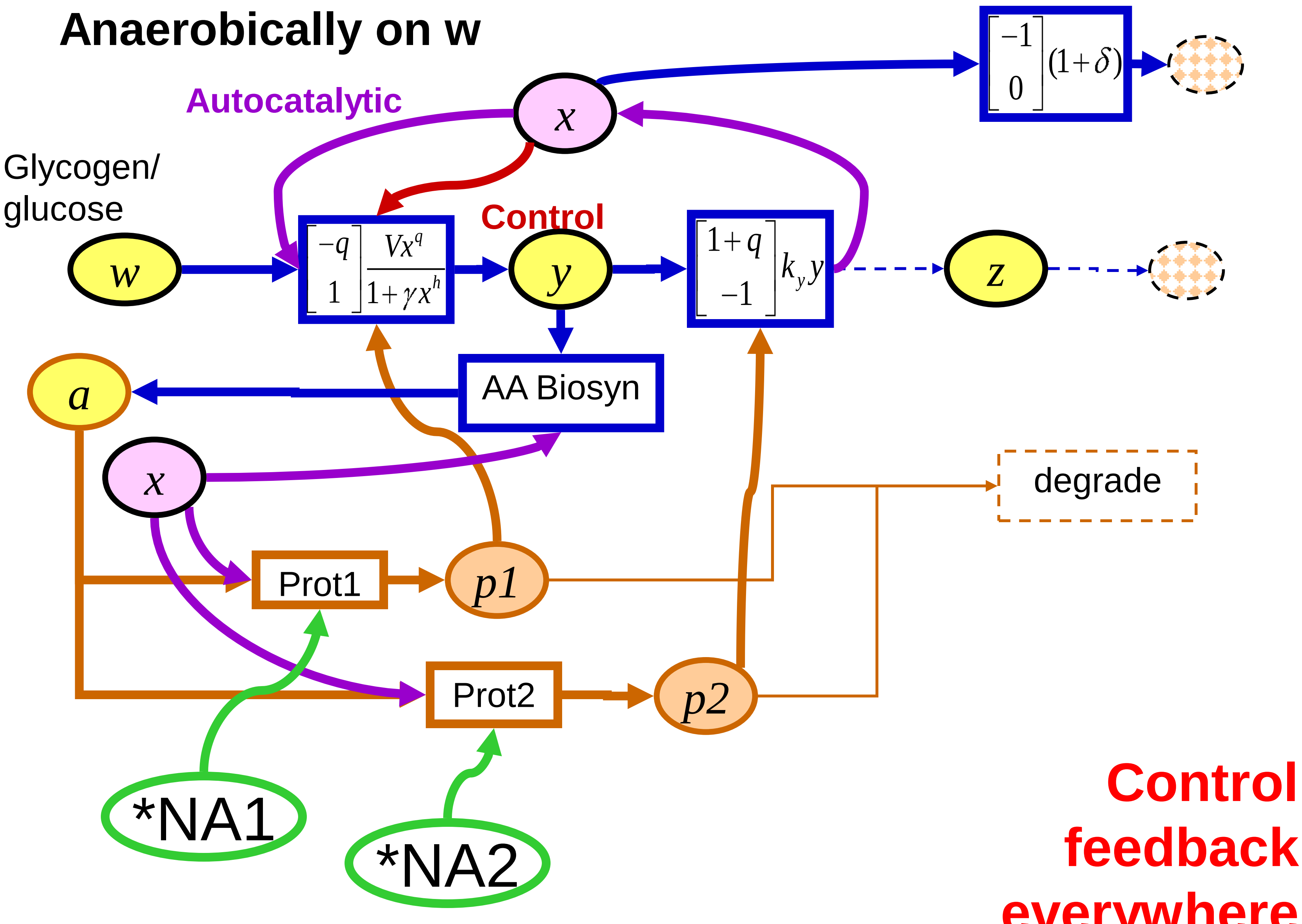


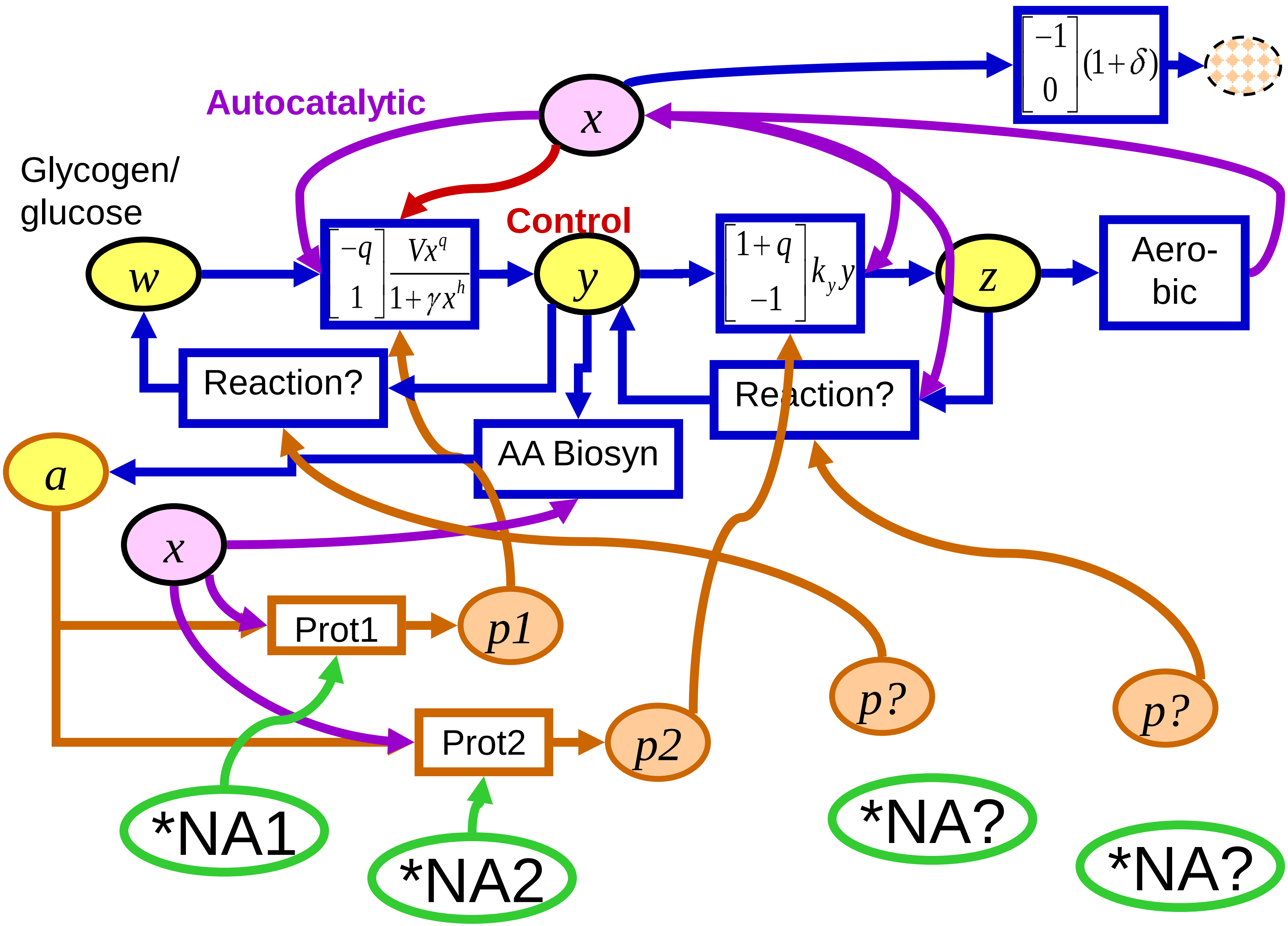
Autocatalytic
x
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
Glycogen/
glucose
w
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
Control
y
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
z
Aero-
bic
Reaction?
Reaction?
AA Biosyn
a
x
Prot1
p1
degrade
Prot2
p2

Control?



All products
feedback everywhere


Anaerobically on w
Autocatalytic
Glycogen/
glucose
w
x
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
Control
y
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
z
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
a
AA Biosyn
x
degrade
Prot1
p1
Prot2
p2
*NA1
*NA2
Control
feedback
everywhere



Autocatalytic
Glycogen/
glucose
Control
x
w
y
z
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
Aero-
bic
Reaction?
Reaction?
AA Biosyn
a
x
Prot1
Prot2
p1
p2
p?
p?
*NA1
*NA2
*NA?
*NA?

Anaerobically on w