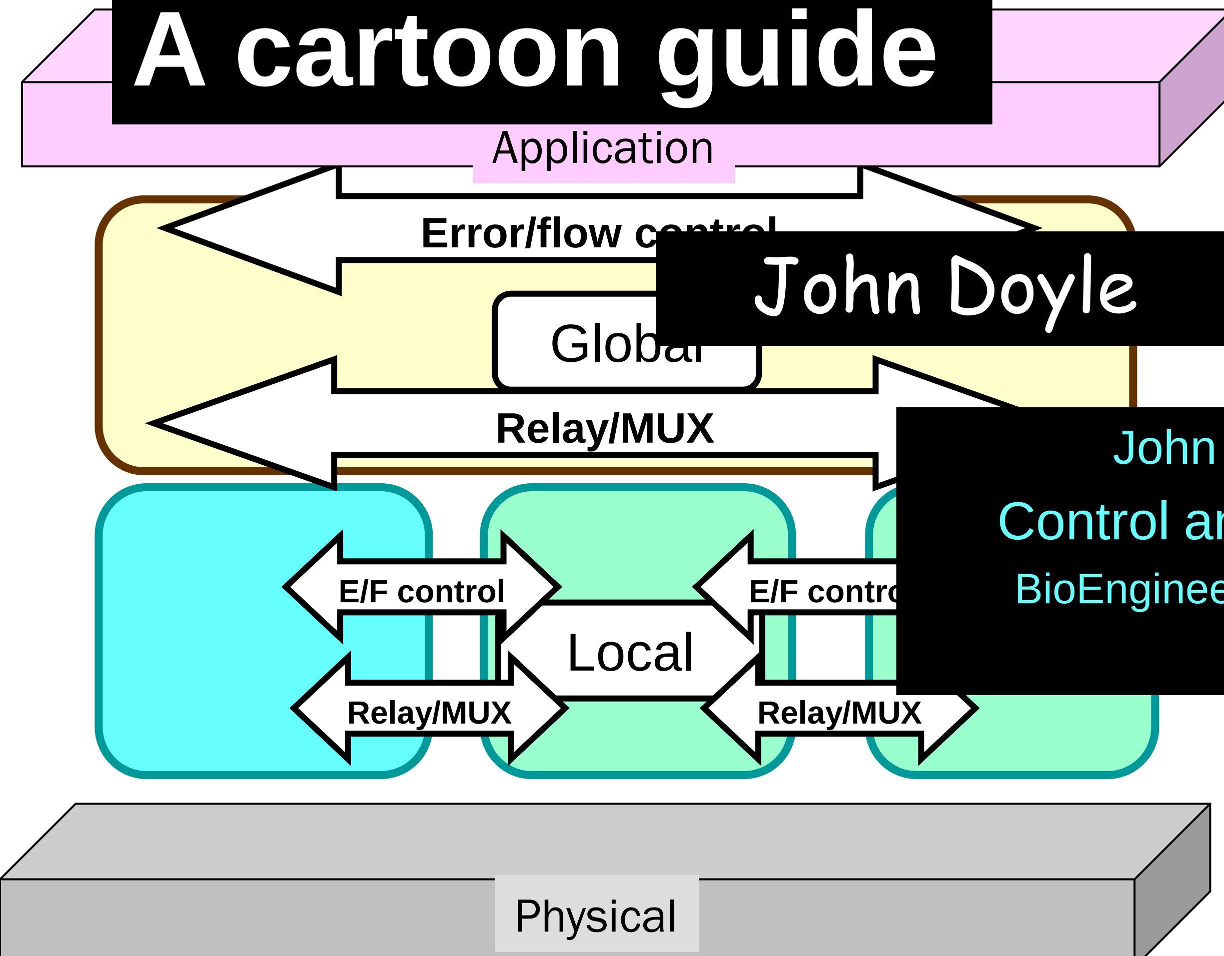
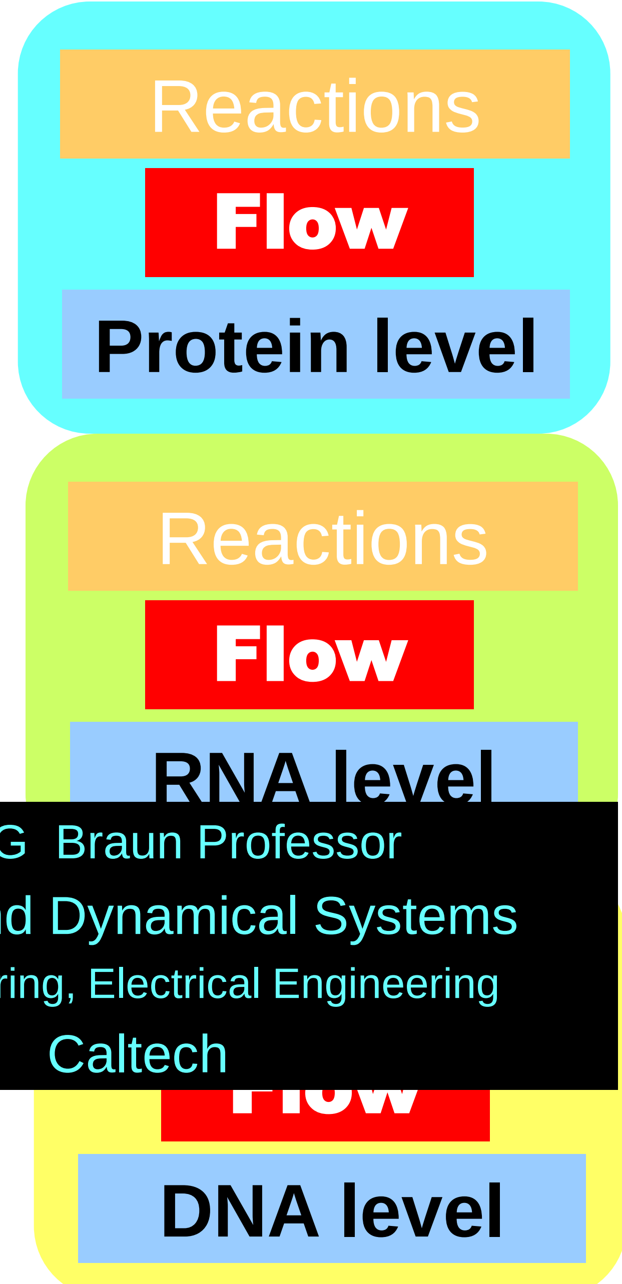
Complex Network Architecture: A cartoon guide



John Doyle

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



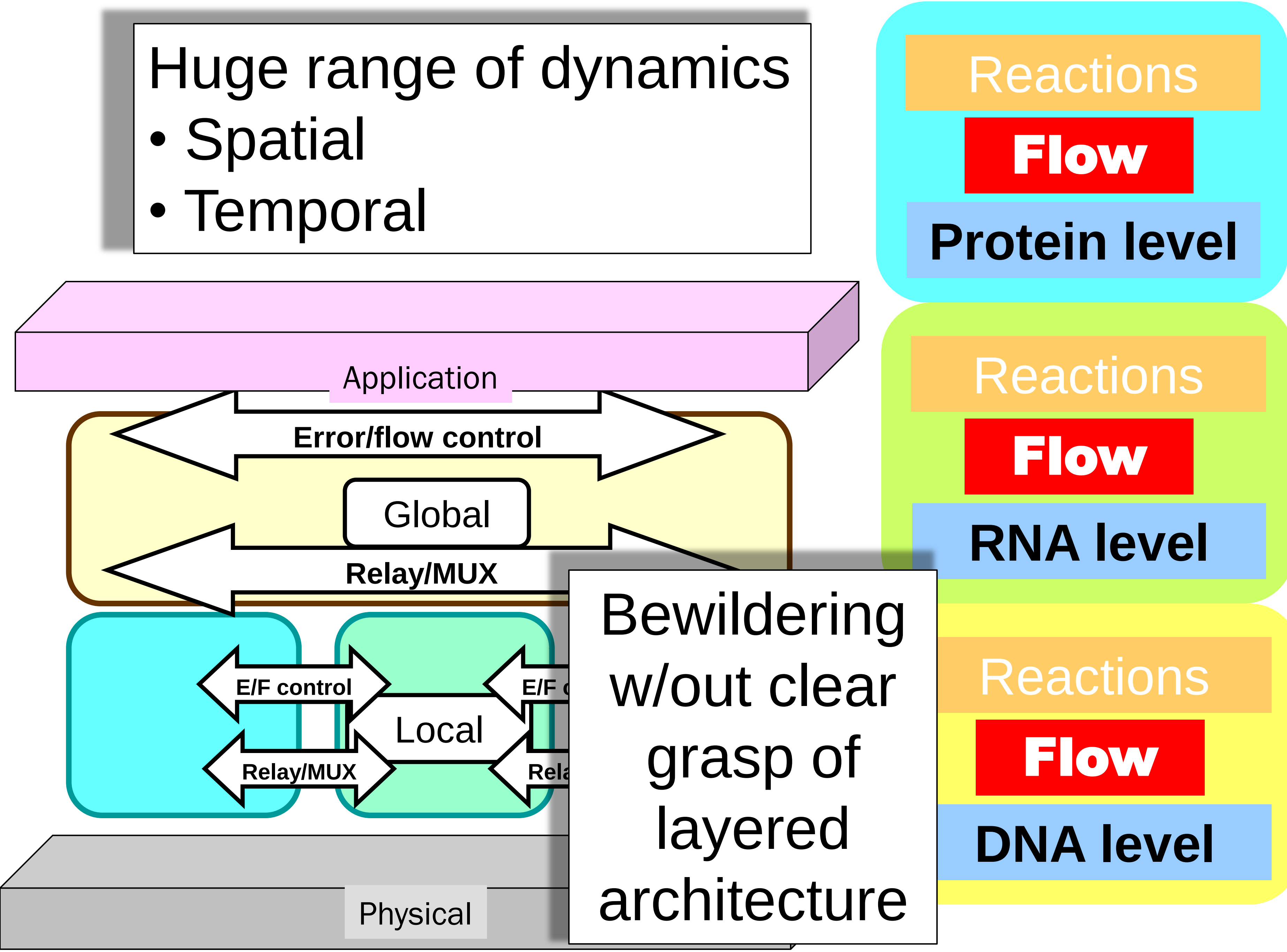
Outline

- Not merely "complexity, networks, abstraction, recursion, modularity,…"
- But very specific forms of these.
- Formal methods have great potential

- Illustrate with case studies and cartoons:

  Internet versus bacterial biosphere

- Implicitly: importance of formal methods, not merely modeling and simulation


Huge range of dynamics
• Spatial
• Temporal
Application
Error/flow control
Global
Relay/MUX
E/F control
Local
Relay/MUX
Physical
Bewildering w/out clear grasp of layered architecture
Reactions
Flow
Protein level
Reactions
Flow
RNA level
Reactions
Flow
DNA level

Network Math and Engineering (NetME) Challenges

- Predictive modeling, simulation, and analysis of complex systems in technology and nature
- Theoretical foundation for design of network architectures
- Balance rigor/relevance, integrative/coherent
- Model/simulate is critical but limited
  - Predicting rare but catastrophic events
  - Design, not merely analysis
  - Managing complexity and uncertainty

“Architecture”

- Most persistent, ubiquitous, and global features of organization
- Constrains what is possible for good or bad
- Platform that enables (or prevents) innovation, sustainability, etc,
- Internet, biology, energy, manufacturing, transportation, water, food, waste, law, etc
- Existing architectures are unsustainable
- Theoretical foundation is fragmented, incoherent, incomplete

Stochastics in Biology

- Arkin, Gillespie, Petzold, Khammash, El-Samad, Munsky, Paulsson, Vinnicombe, many others…
- Noise in the cellular environment
  - Elowitz, van Oudenaarden, Collins, Swain, Xie, Elston, ...
- Stochastic Monte Carlo Simulation
  - Kurtz, Gibson, Bruck, Anderson, Rathinam, Cao, Salis, Kaznessis, ...
- Statistical moment computations
  - Hespanha, Singh, Verghese, Gomez-Uribe, Kimura
- Density function computations
  - McNamara, Sidje, ...
- Stochastic differential equation approximations
  - van Kampen, Kurtz, Elf, Ehrenberg,...
- Spatial stochastic models and tools
  - Elf, Iglesias,…

Very incomplete, idiosyncratic list

Other Influences

- Internet (Kelly/Low, Willinger, Clark, Wroclawski, Day, Chang, etc etc)
- Biology/Medicine (Savageau, G&K, Mattick, Csete, Arkin, Alon, Caporale, de Duve, Exerc Physio, Acute Care, 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, …)

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

- Evolvable architecture
- **Robust yet fragile**
- **Constraints/deconstrain**
- **Layering, modularity**
- **Hourglass with bowties**
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Differences

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

Focus on
bacterial biosphere

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

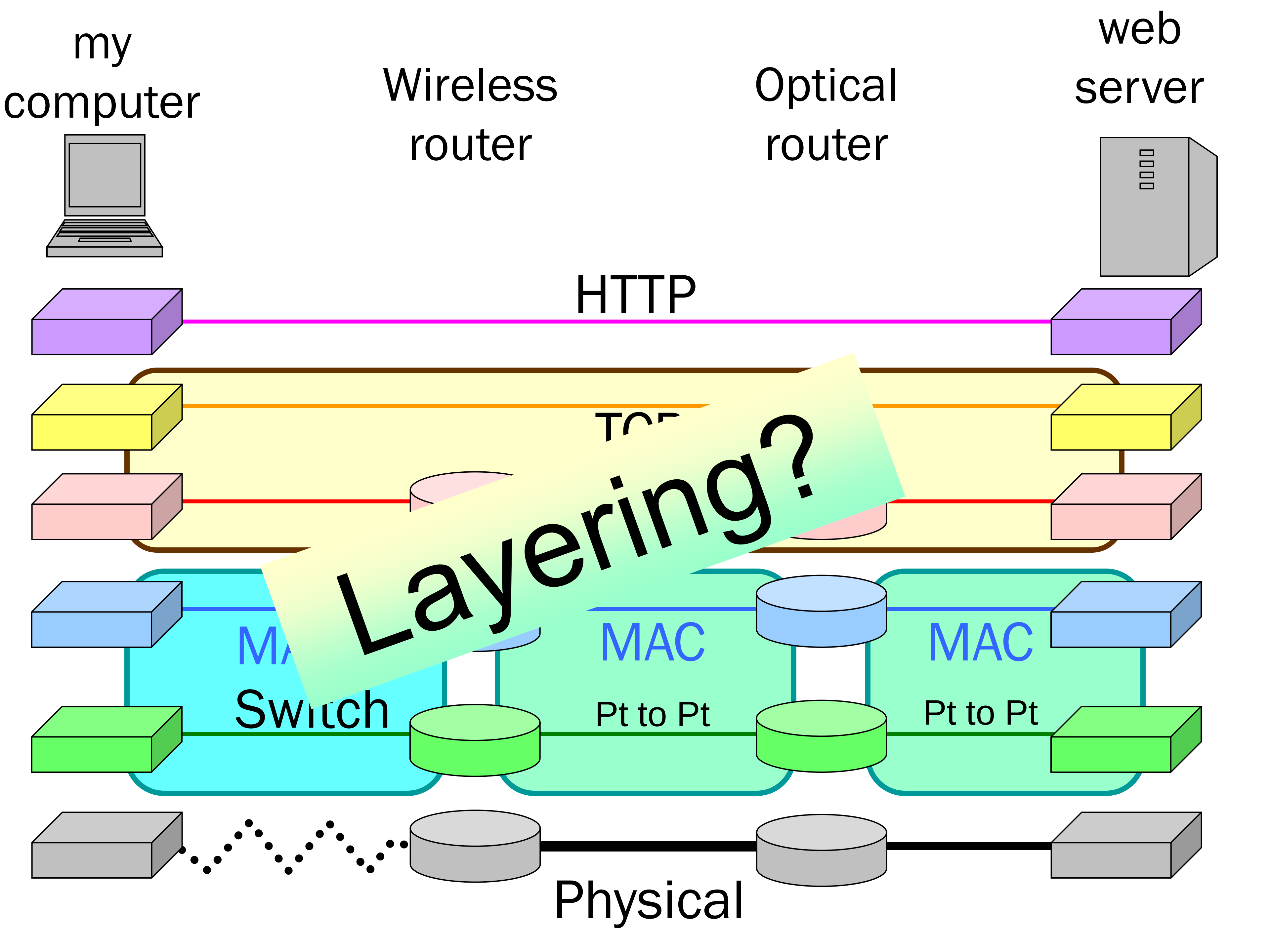
- ☹ Obesity and diabetes
- ☹ Cancer
  - ☹ Fat accumulation
  - ☹ Insulin resistance
  - ☹ Inflammation

Static energy

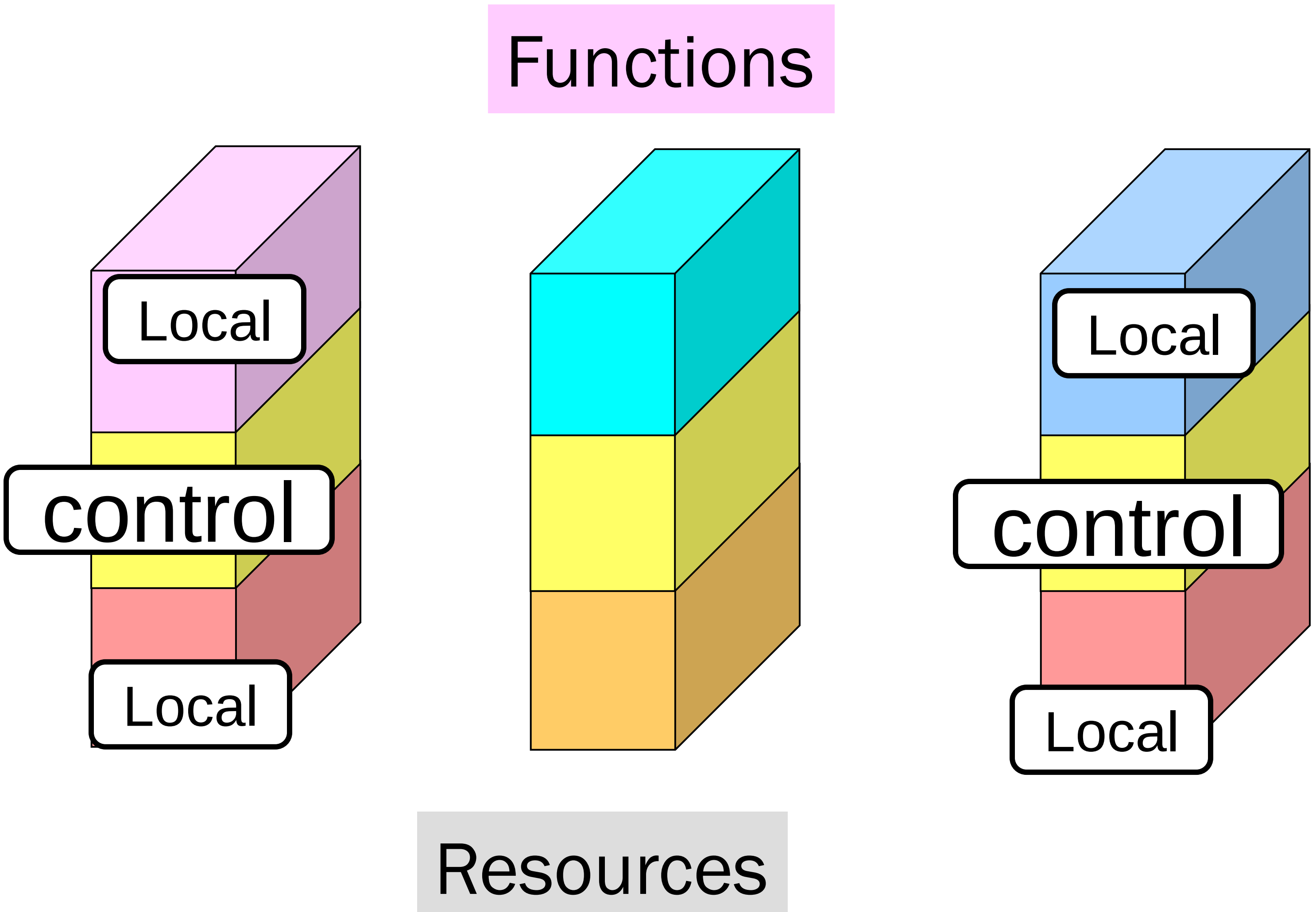
Implications/ Generalizations

Robust		Yet Fragile	
☺	Efficient, flexible metabolism	☹	Obesity and diabetes
☺	Rich microbial symbionts	☹	Parasites, infection
☺	Immune systems	☹	Inflammation, Auto-Im.
☺	Regeneration & renewal	☹	Cancer
	Complex societies	☠	Epidemics, war, …
	Advanced technologies		Catastrophic failures

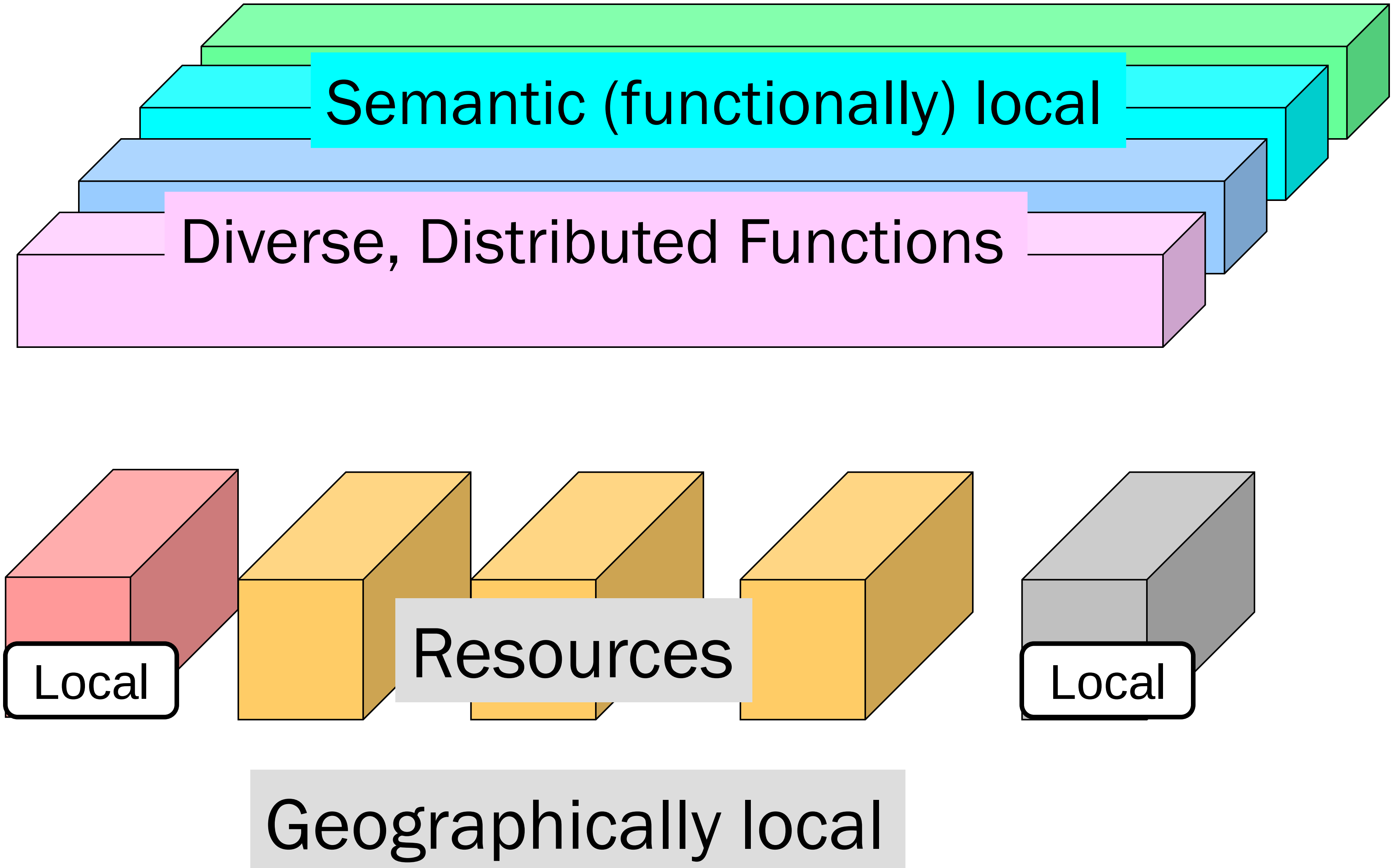
- Fragility = Hijacking, side effects, unintended… of mechanisms evolved for robustness
- Complexity is driven by control, robust/fragile tradeoffs
- Math: New robust/fragile conservation laws


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

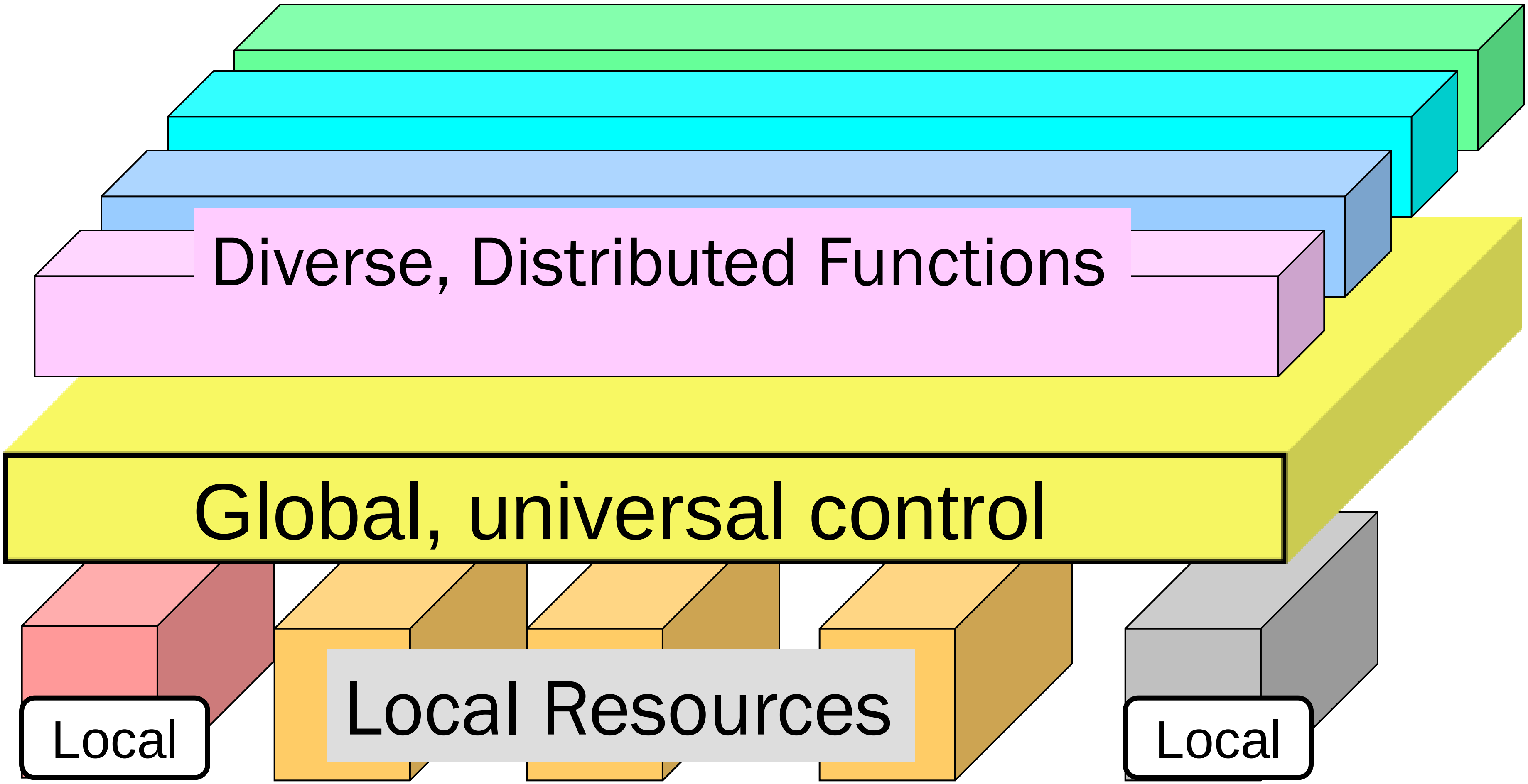
Non-networked Systems



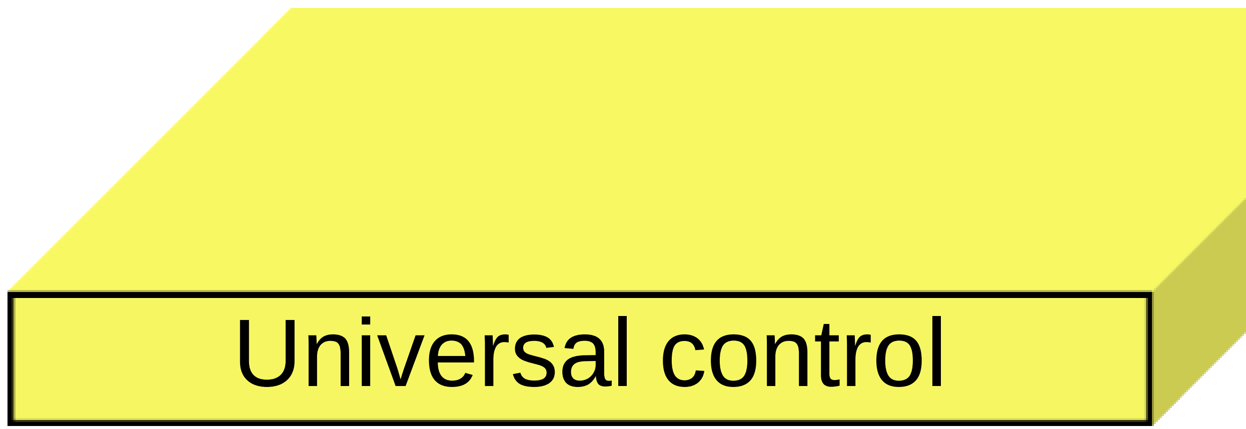
Network requirements



Layered solution

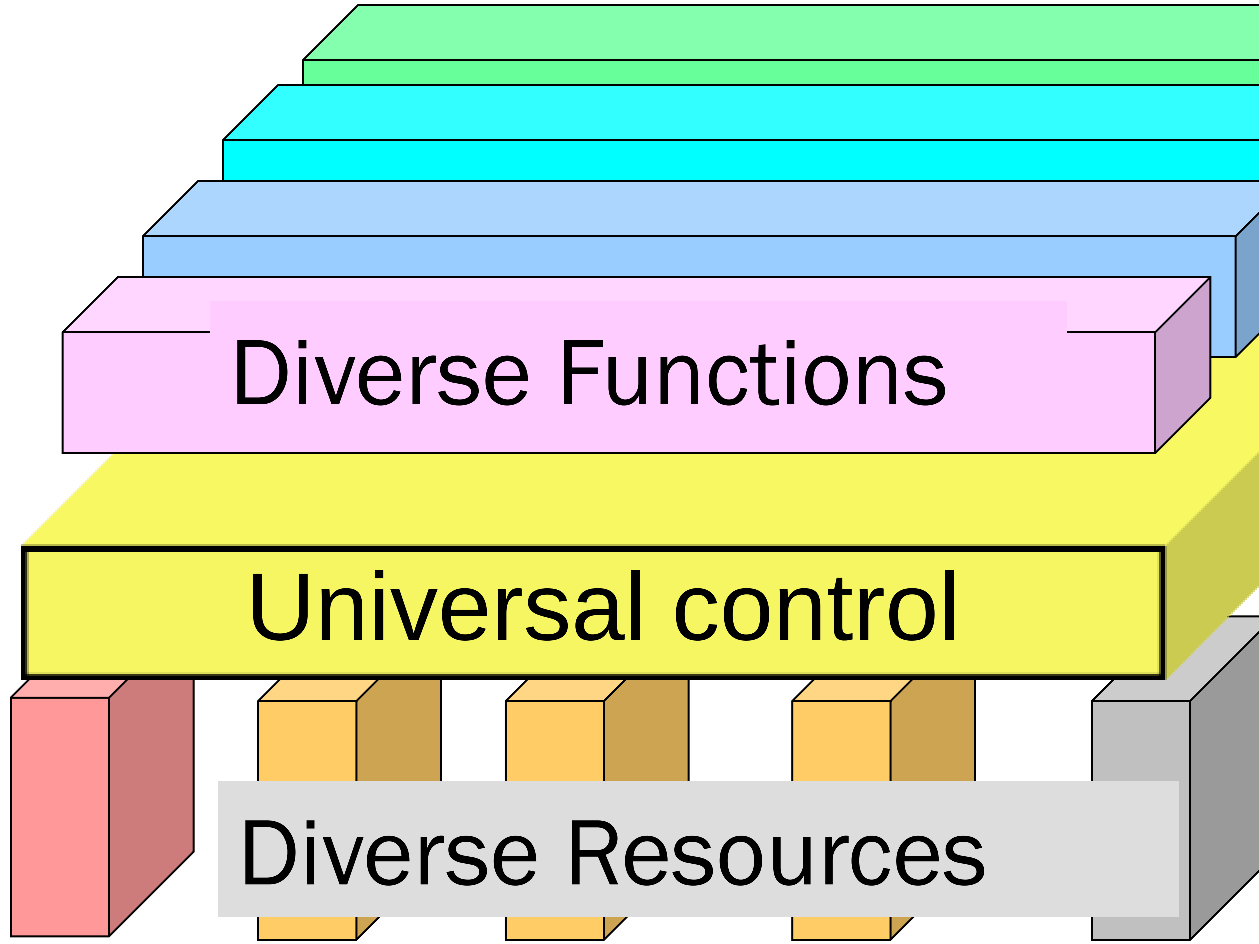


Constraints

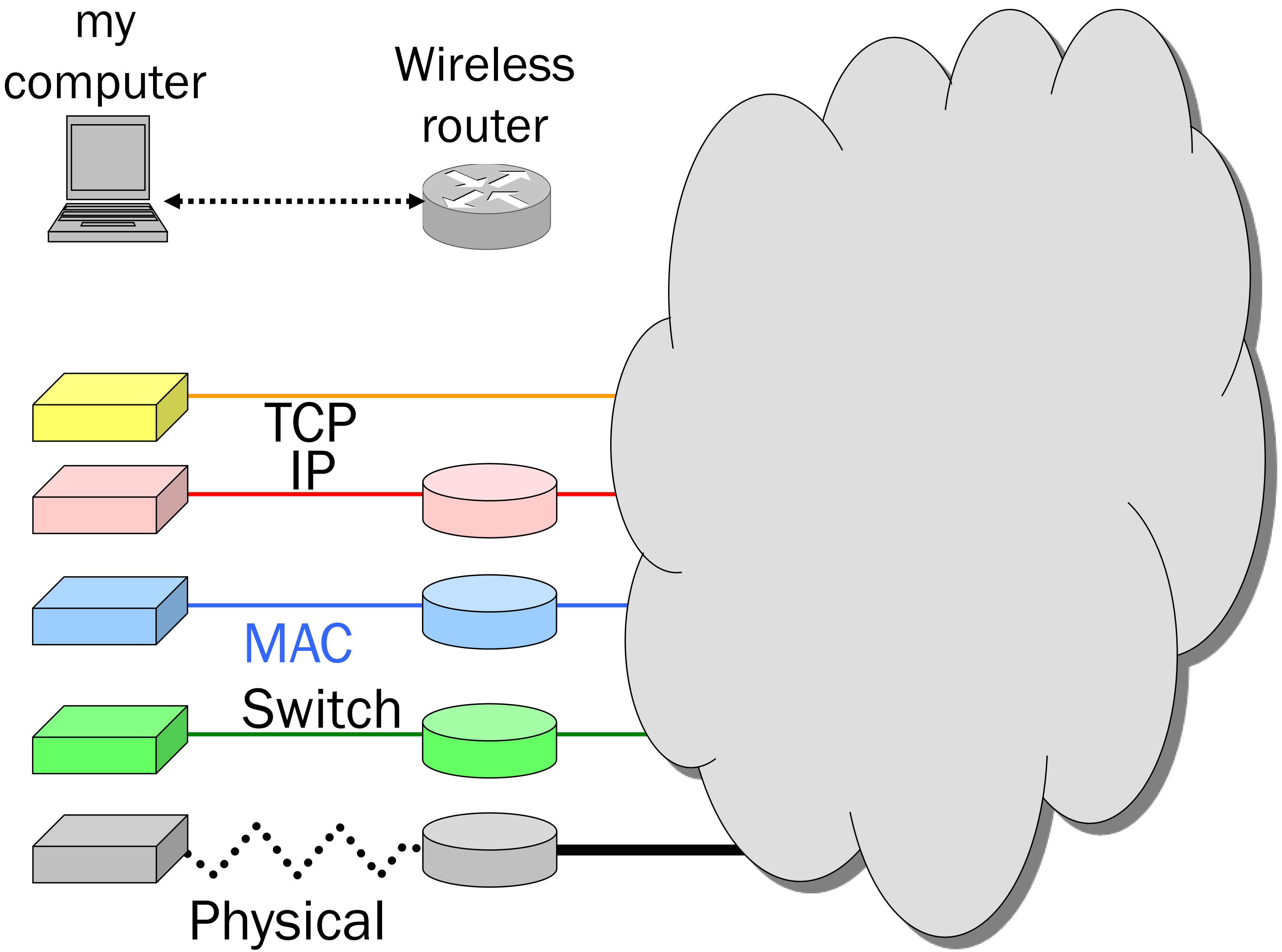


That deconstrain

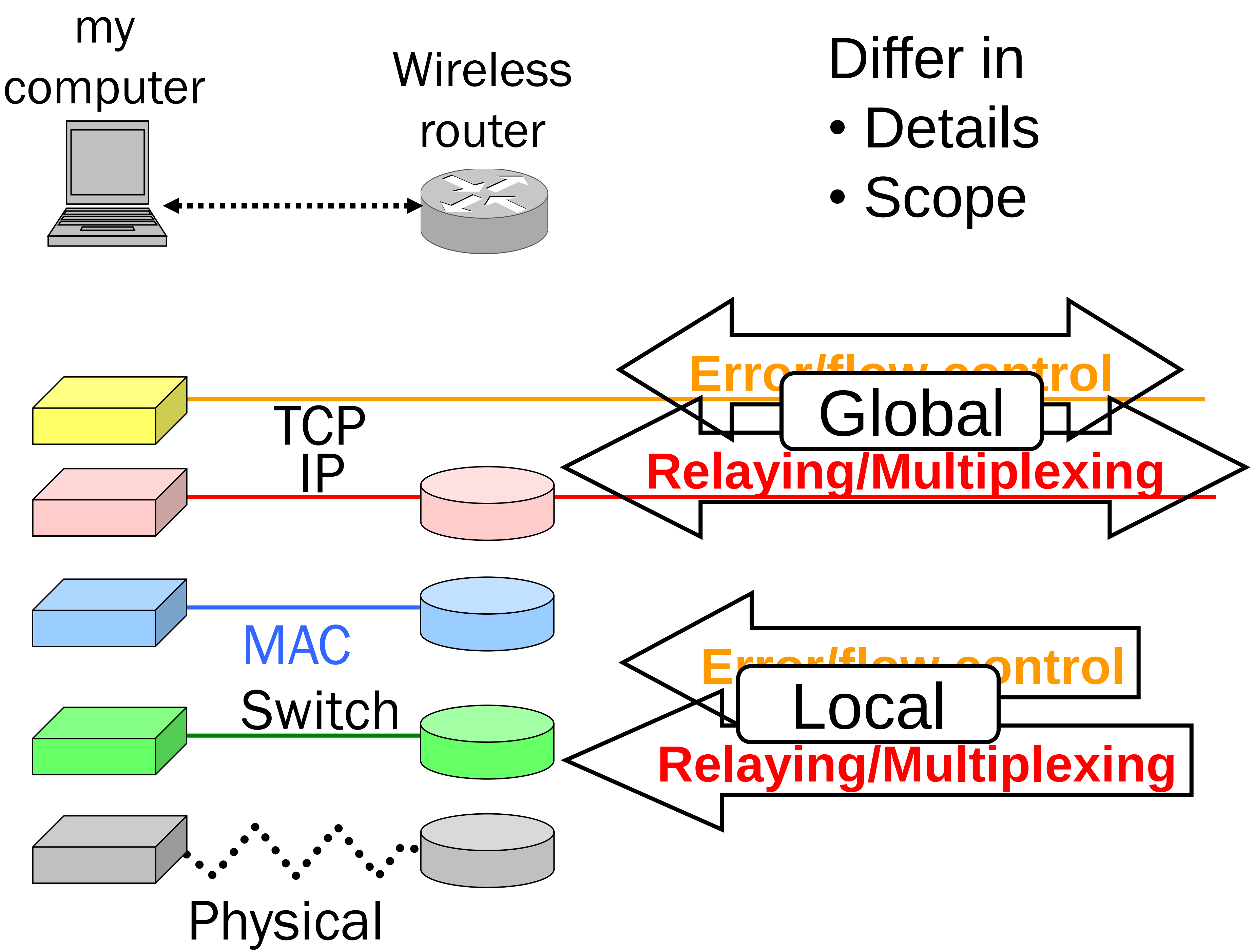
Constraints

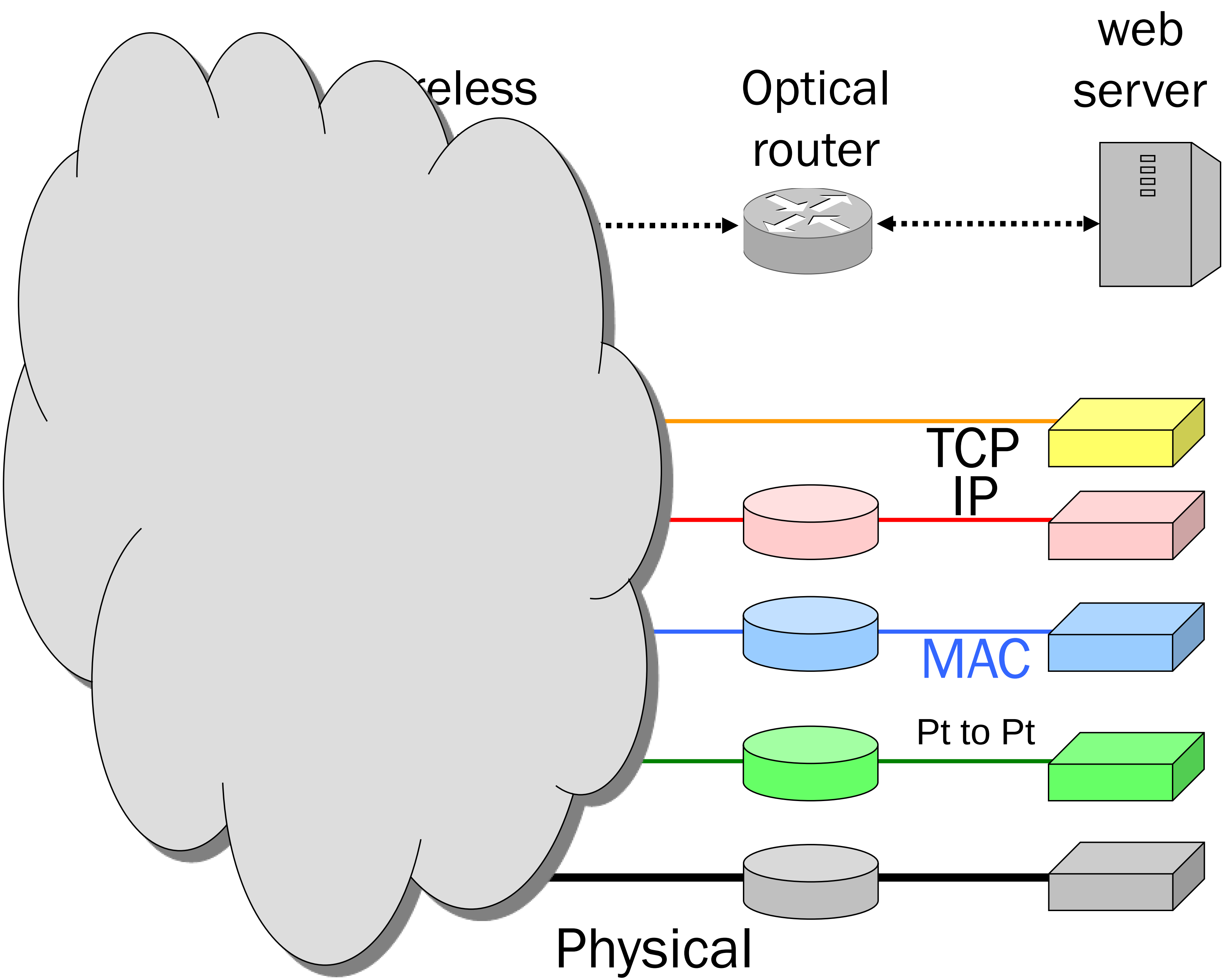


That deconstrain

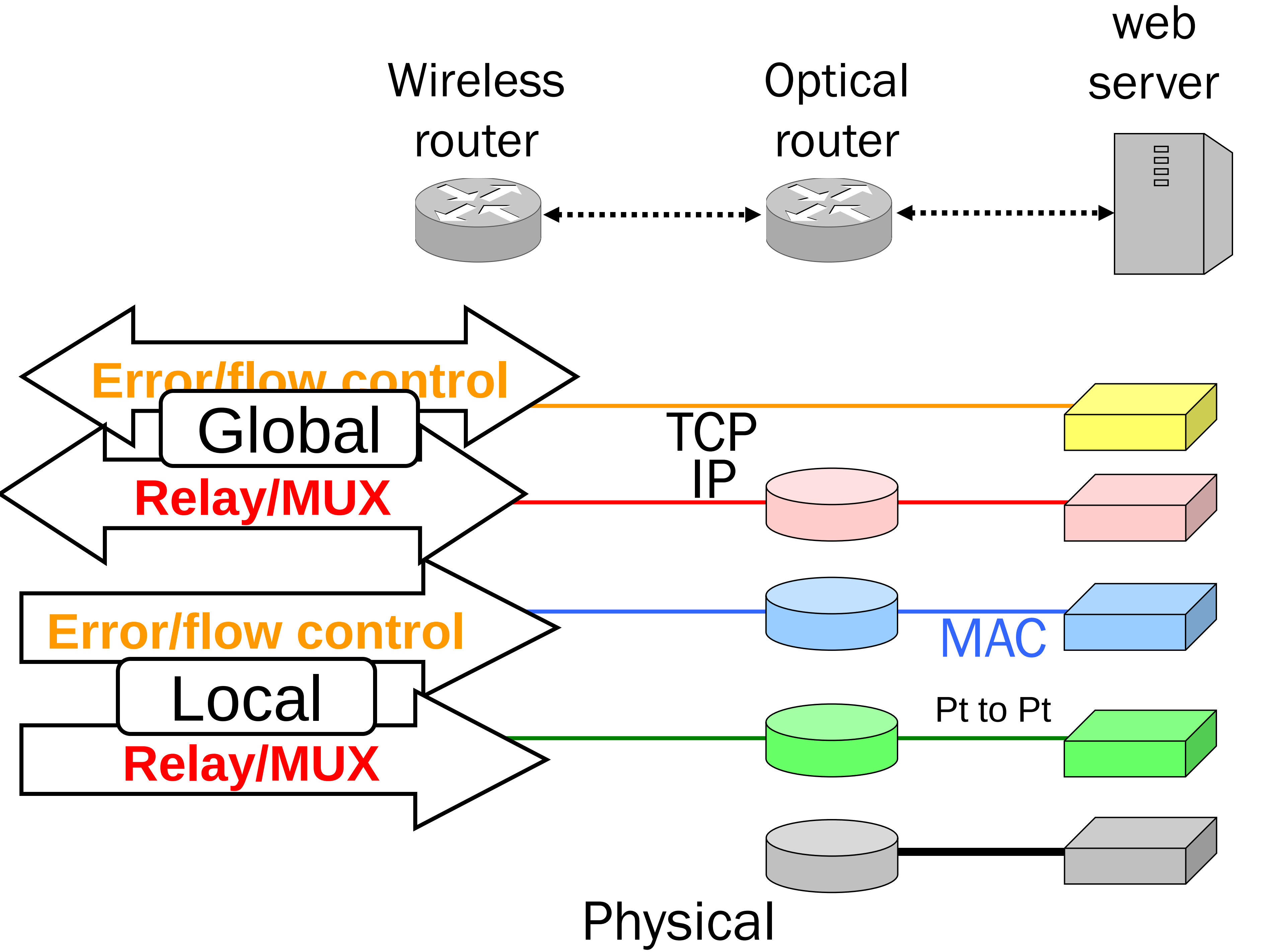

my computer
Wireless router
TCP
IP
MAC
Switch
Physical

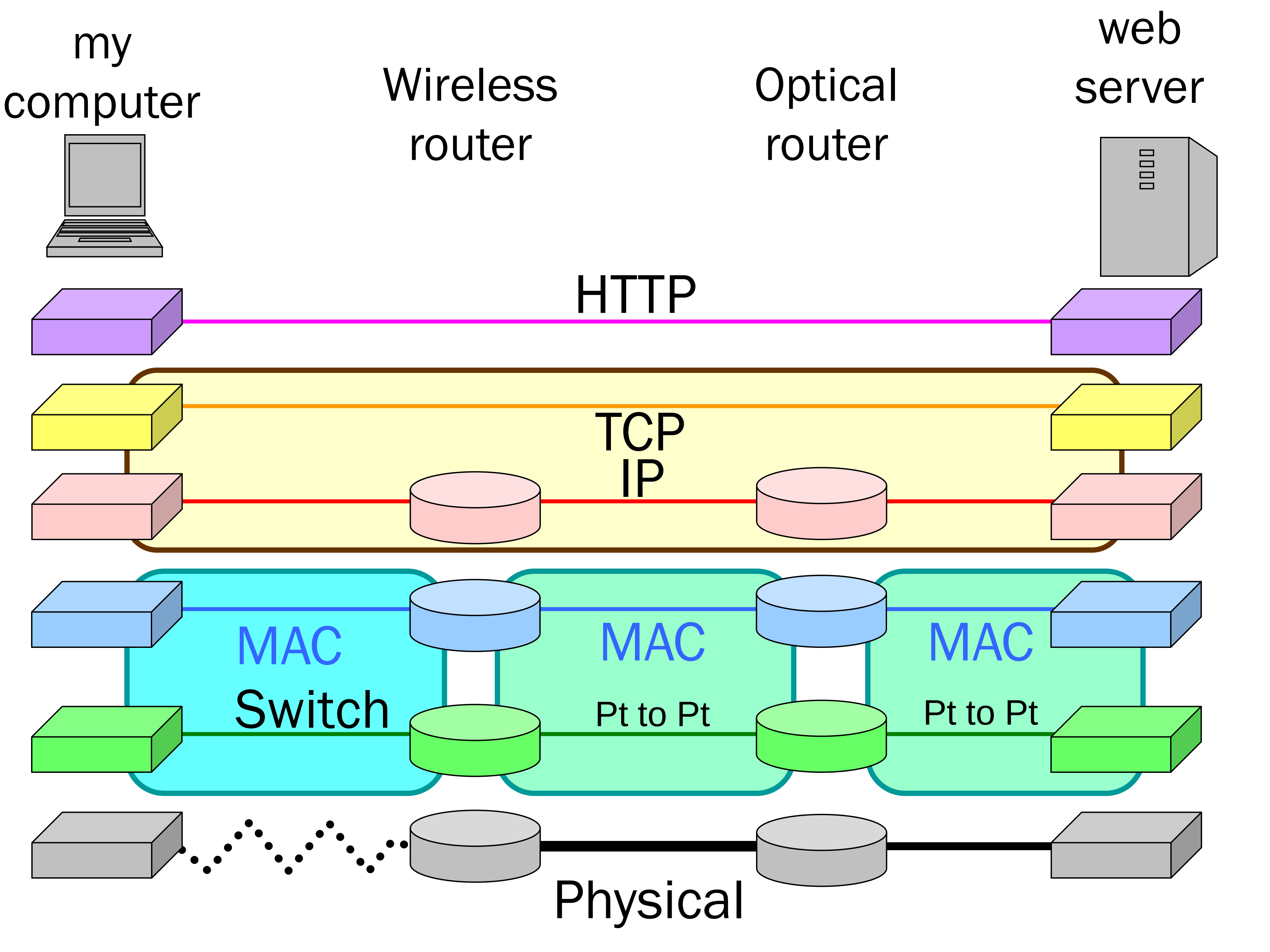
Differ in
- Details
- Scope





reless
Optical
router
web
server
TCP
IP
MAC
Pt to Pt
Physical


Wireless router
Optical router
web server
Error/flow control
Global
Relay/MUX
TCP
IP
MAC
Error/flow control
Local
Relay/MUX
Pt to Pt
Physical


my computer
Wireless router
Optical router
web server
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TCP
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MAC
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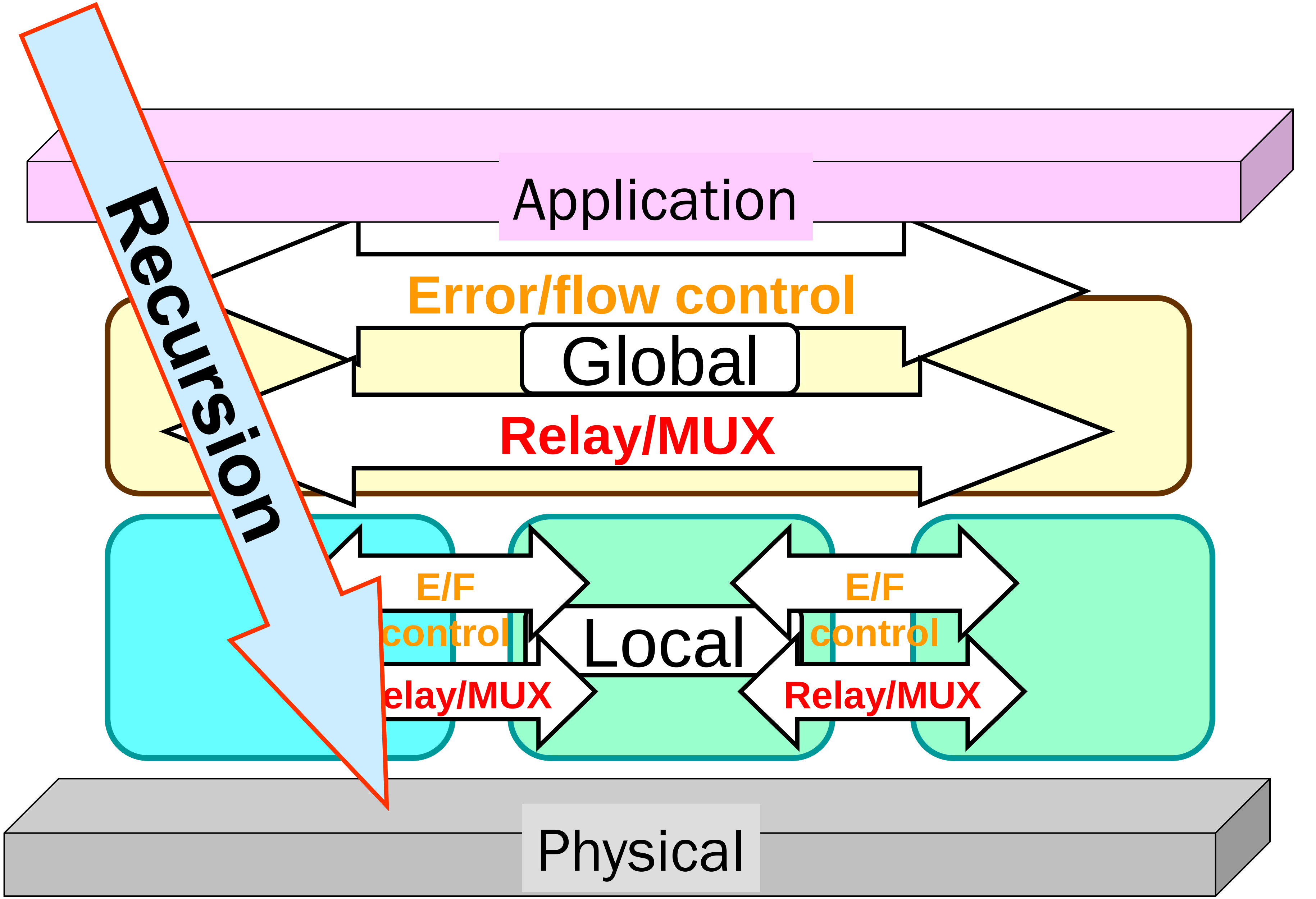
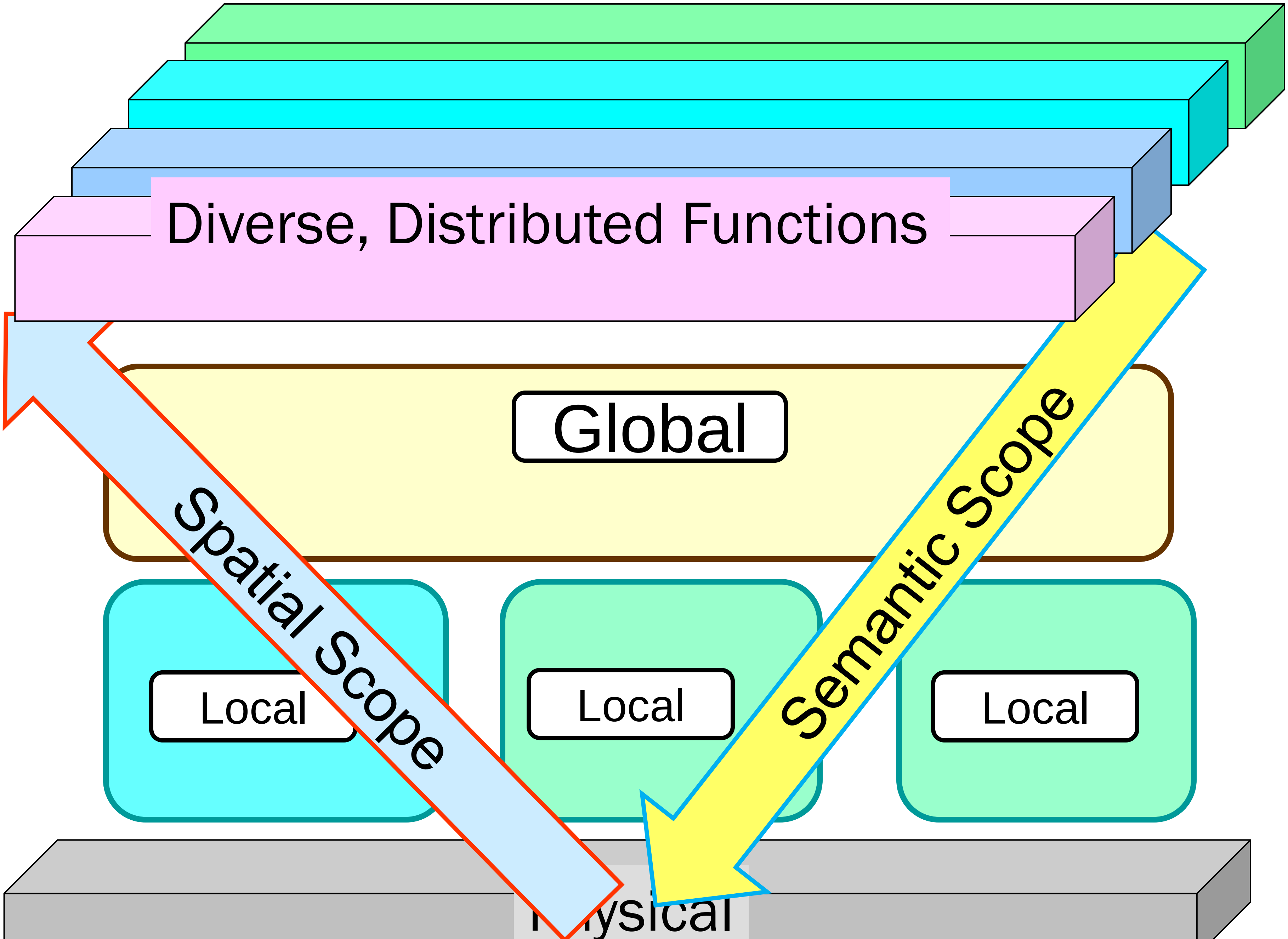
MAC
Pt to Pt
MAC
Pt to Pt
Physical

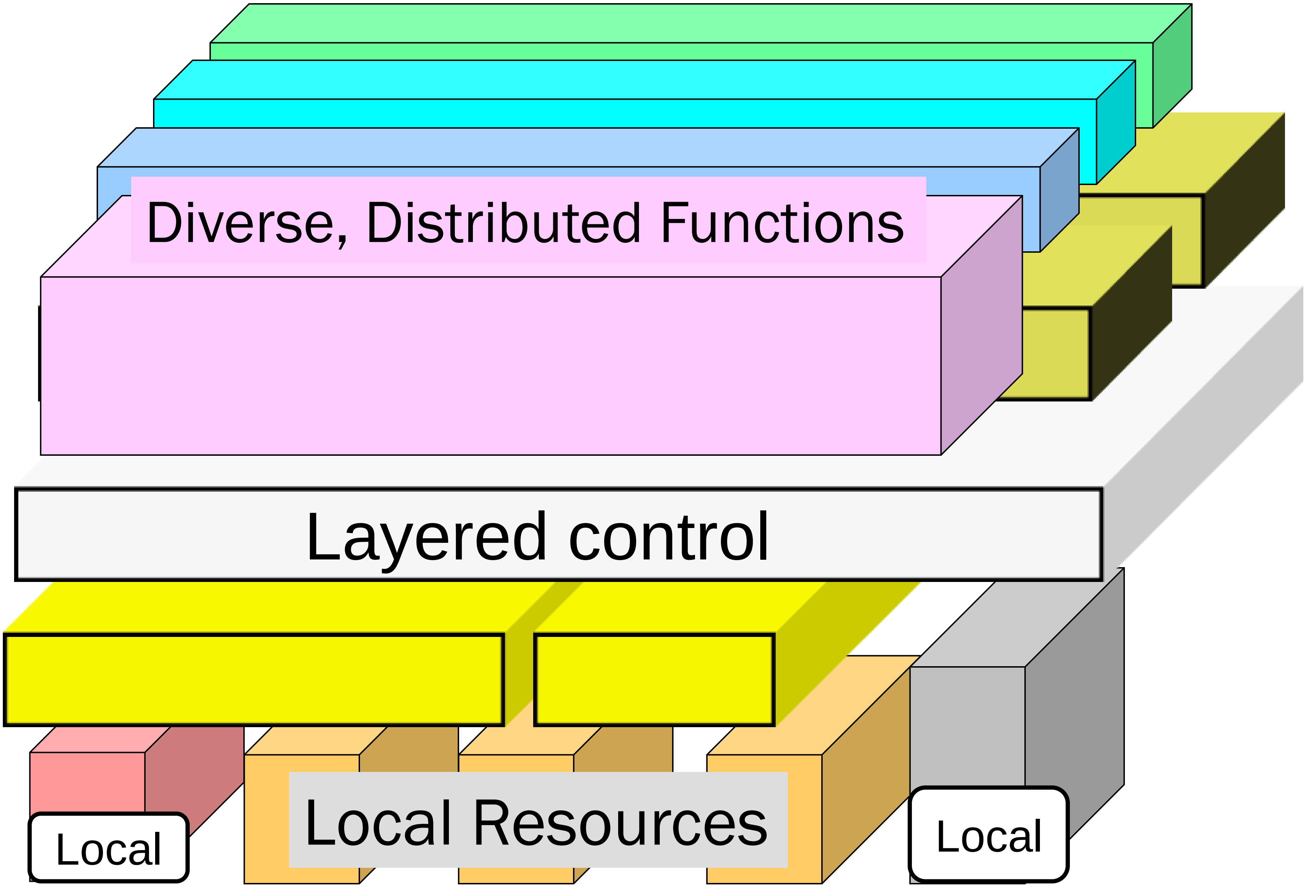
Recursive control structure



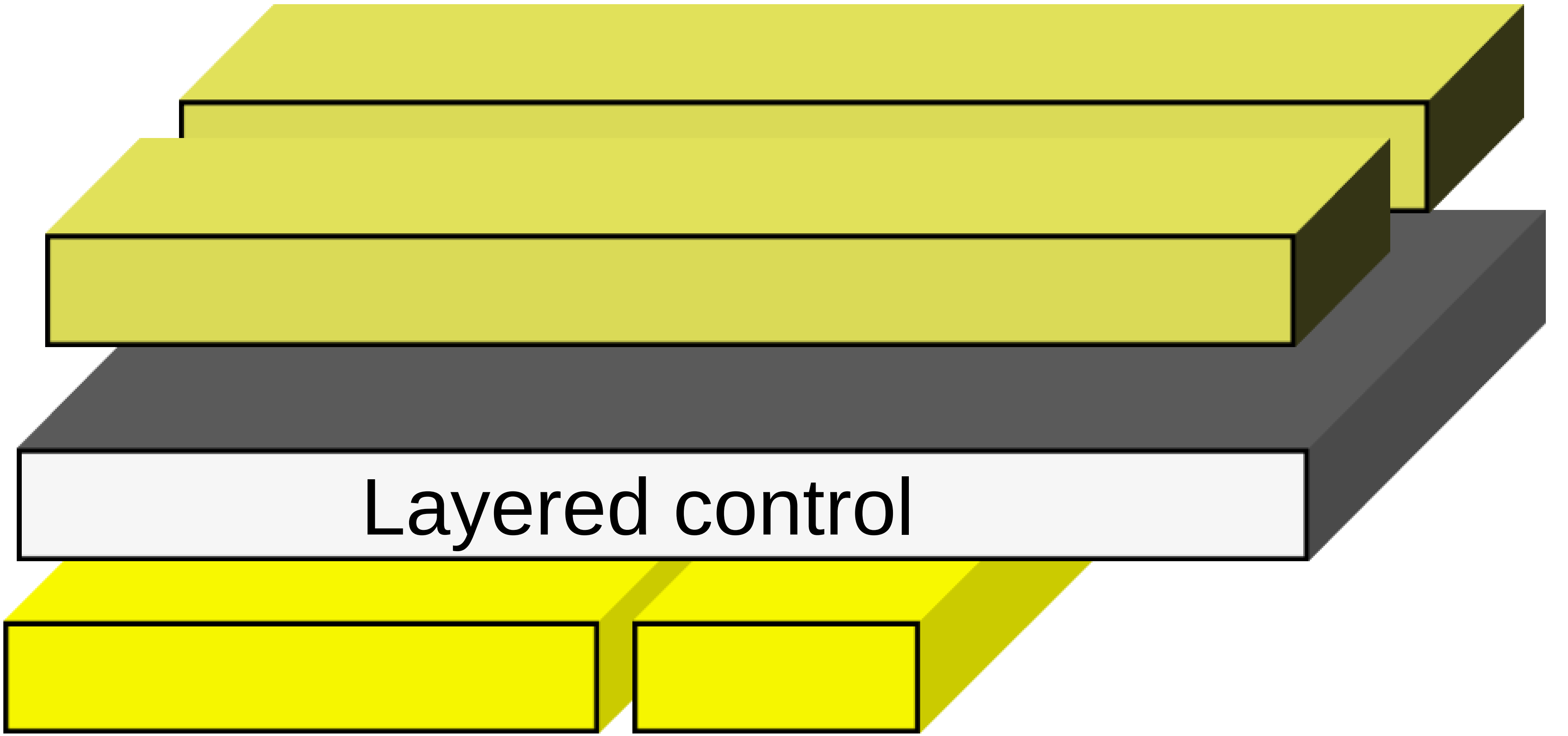


Diverse, Distributed Functions
Global
Local
Local
Local
Physical
Spatial Scope
Semantic Scope

Layered solution

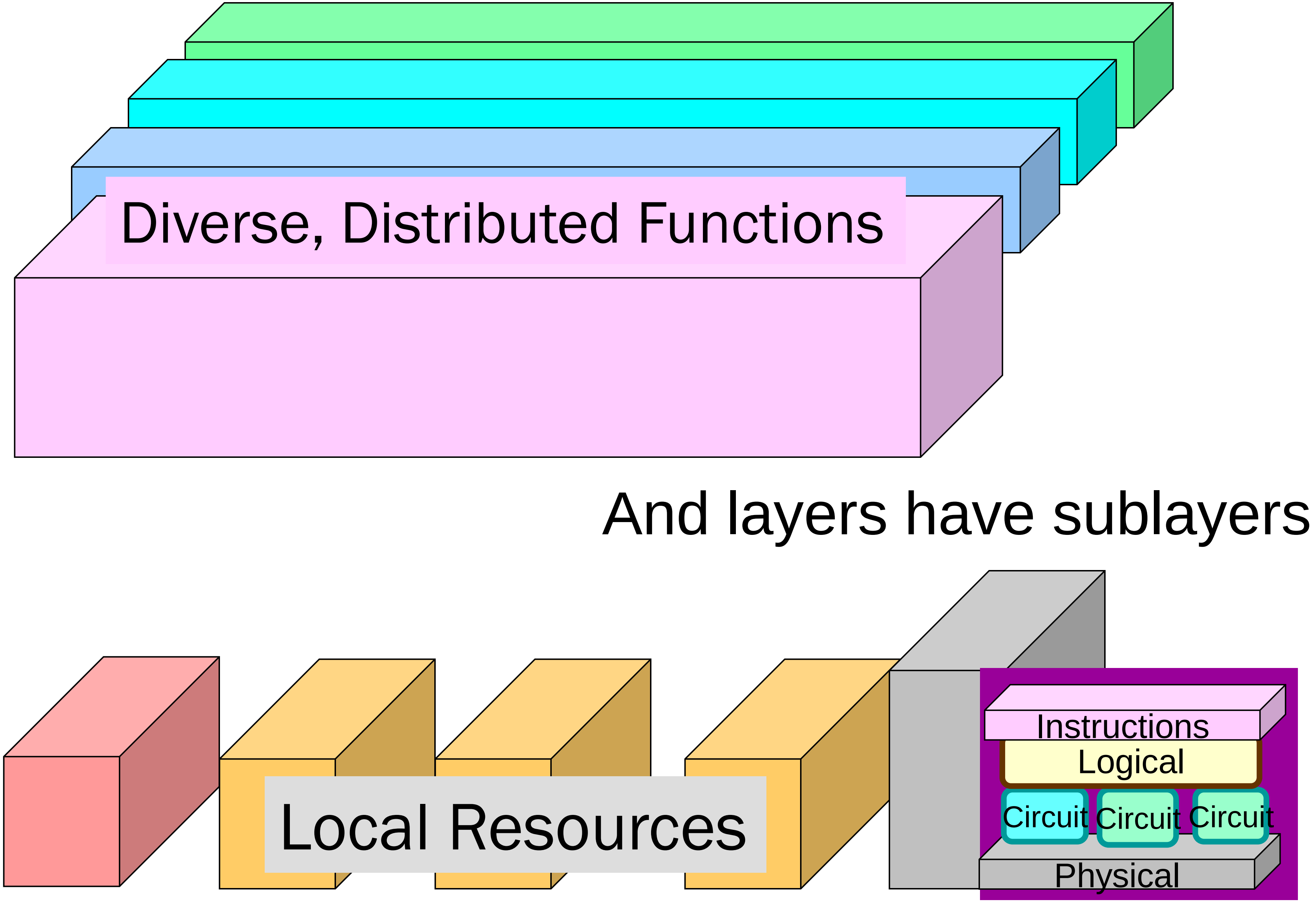


How many layers are there?

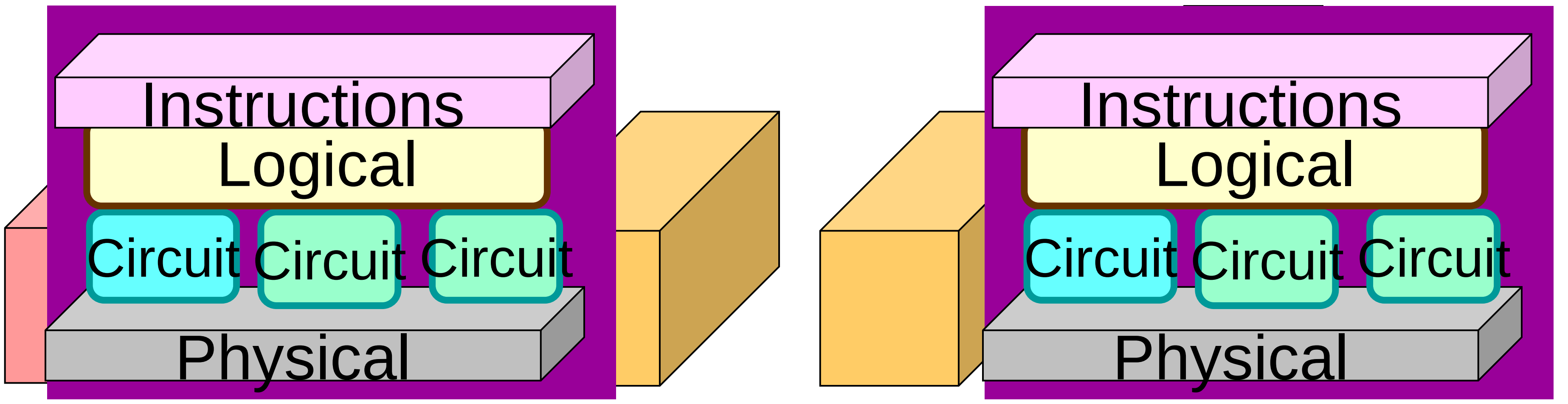


As many as you need.

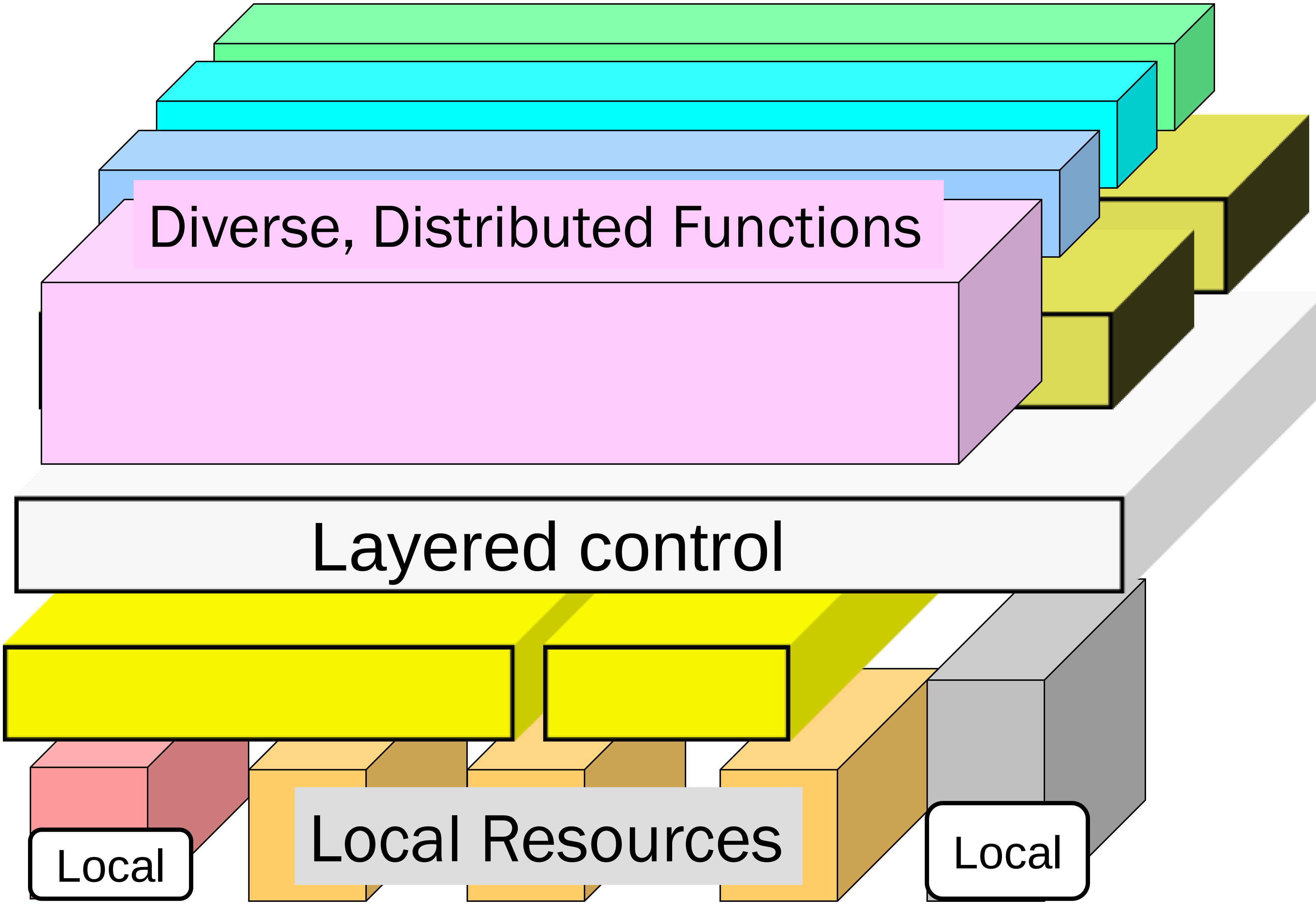
Layered solution

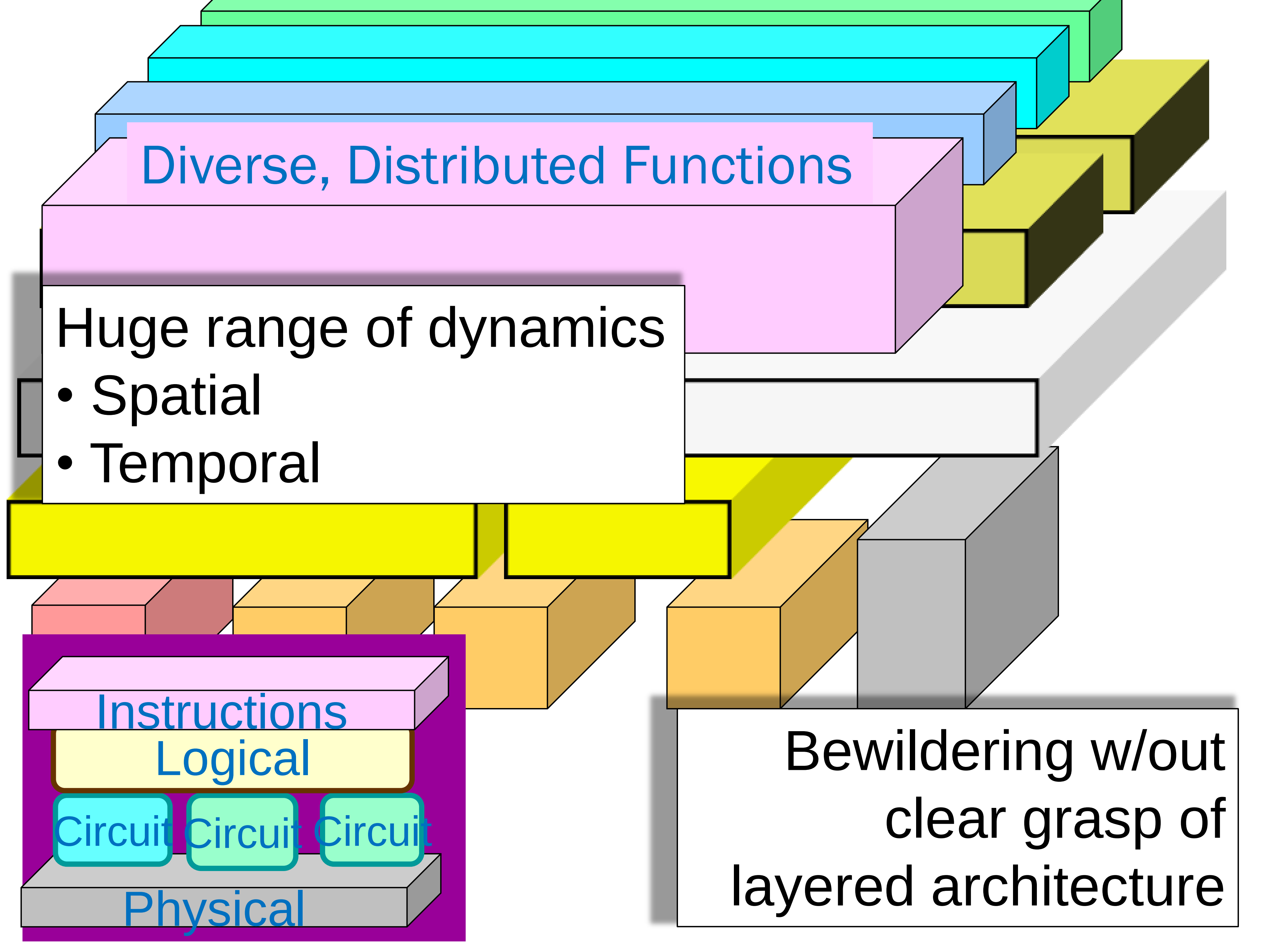


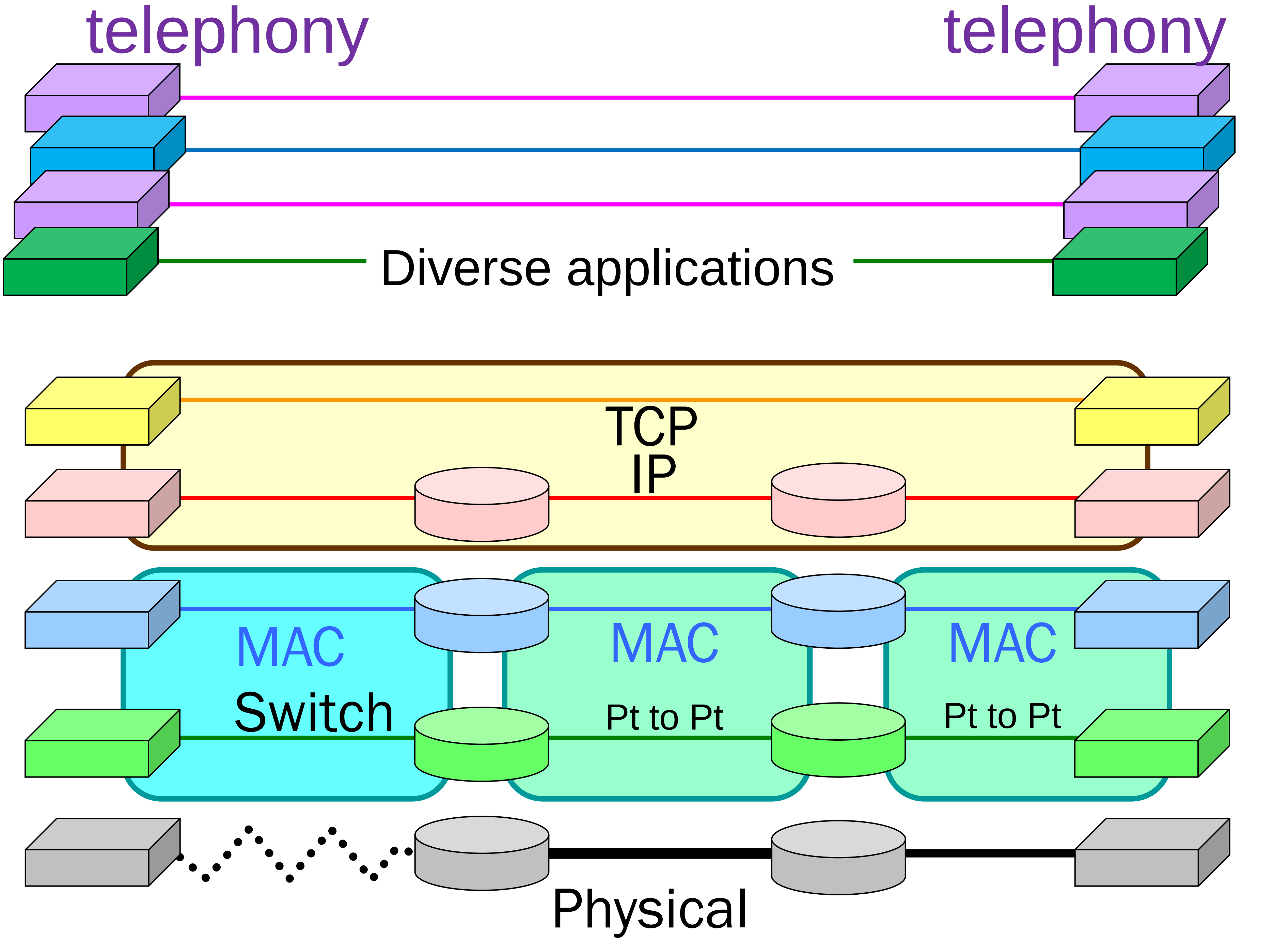
And layers have sublayers



Layered solution



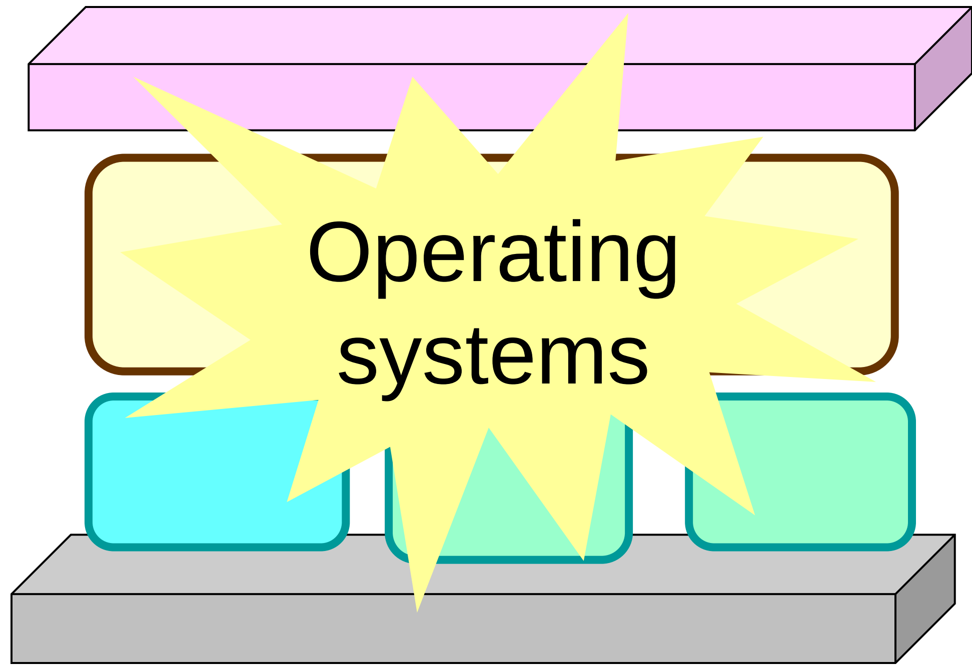

Diverse, Distributed Functions
Huge range of dynamics
• Spatial
• Temporal
Instructions
Logical
Circuit
Circuit
Circuit
Physical
Bewildering w/out
clear grasp of
layered architecture



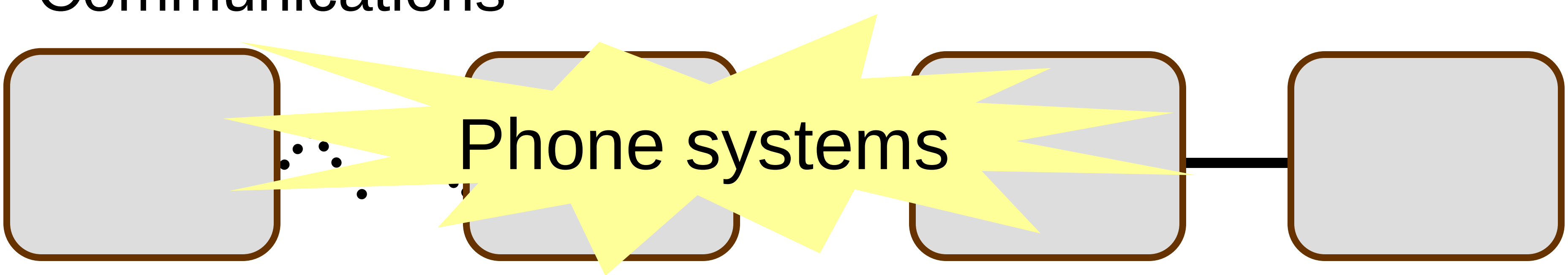
telephony
telephony
Diverse applications
TCP
IP
MAC
Switch
MAC
Pt to Pt
MAC
Pt to Pt
Physical

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

Layers (Net)
Computer



Pathways (Bell)
Communications



Cyber-Physical Theories

- Thermodynamics
- Communications
- Control
- Computation

Cyber	Physical
• Thermodynamics	• Thermodynamics
• Communications	• Communications
• Control	• Control
• Computation	• Computation
Internet	Bacteria

Case studies

Cyber

- Thermodynamics
- Communications
- Control
- Computation

Physical

- Thermodynamics
- Communications
- Control
- Computation

Promising unifications

Theoretical framework:
Constraints that deconstrain

Applications Deconstrained

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

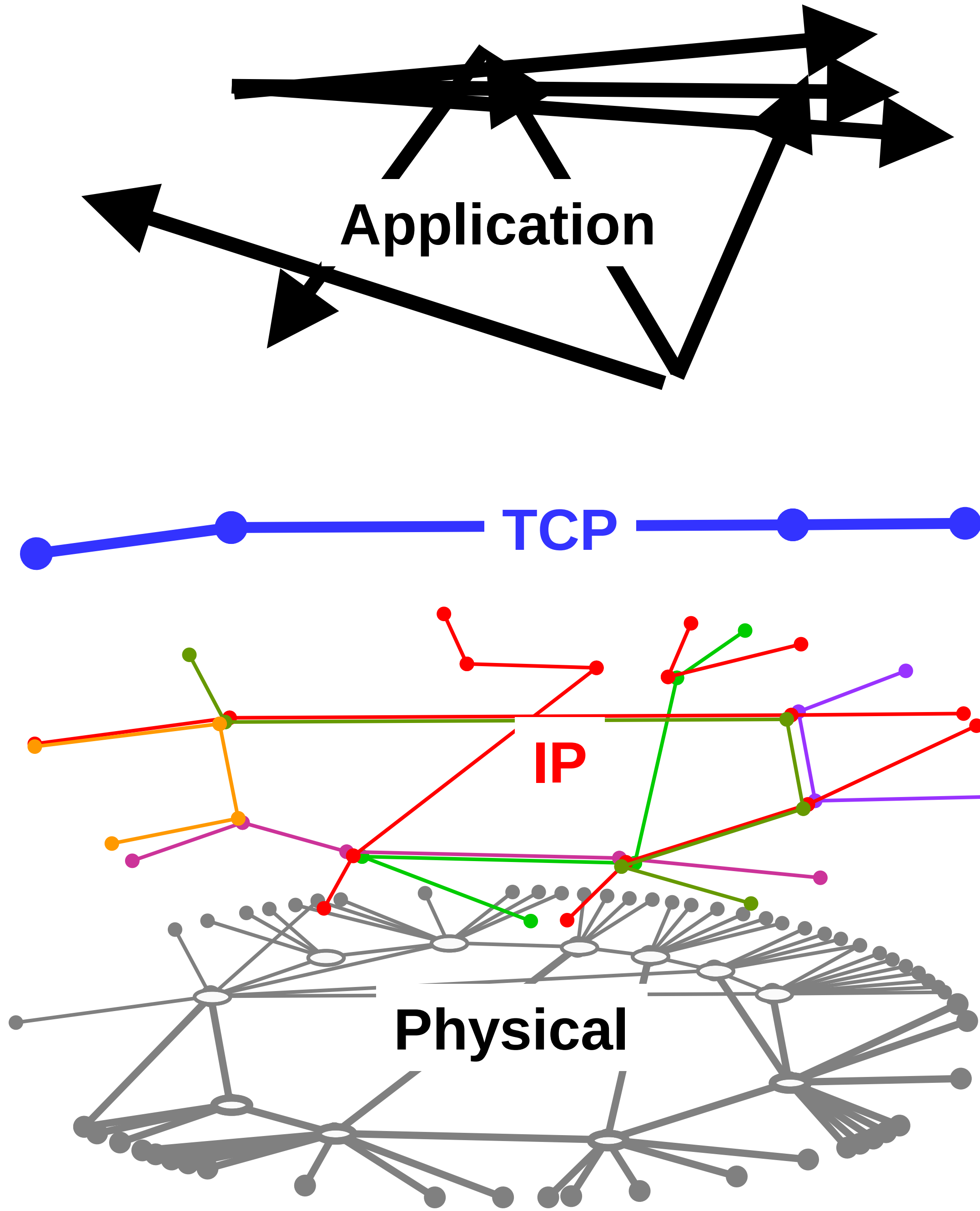
$$\Big| \; \tilde{\mathbf{x}} = \arg\max_{\mathbf{v}} L \;\; \mathbf{v}, \mathbf{p} \;\; , \quad \dot{\mathbf{p}} = R\mathbf{x} - \mathbf{c}$$

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

Resources Deconstrained

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

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



Architecture facilitates arbitrary graphs.

Biology versus the Internet

Similarities

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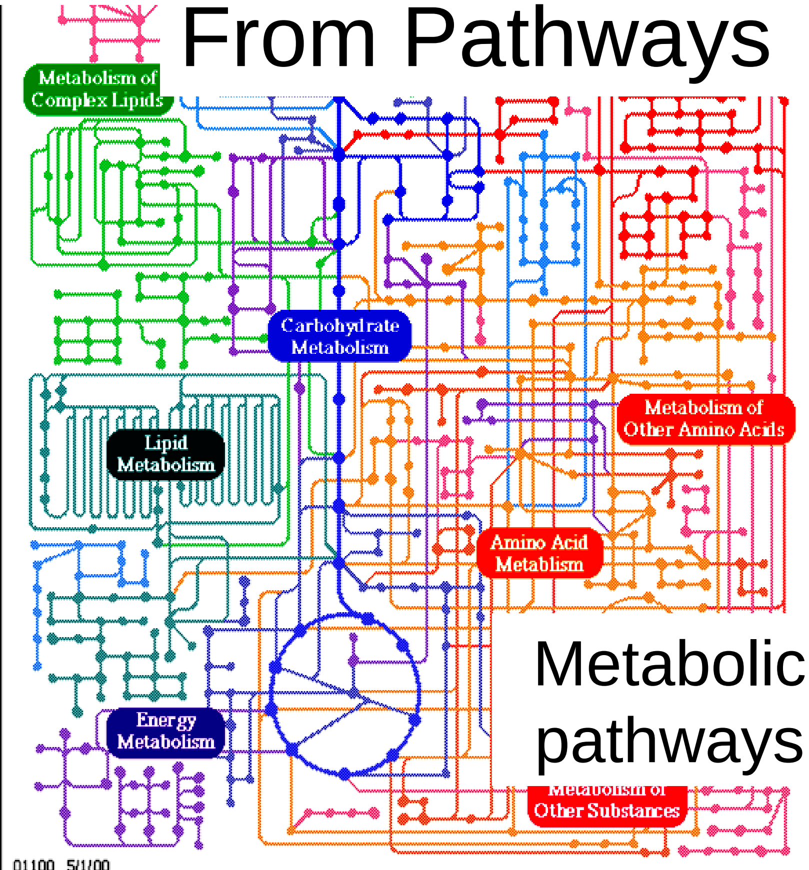
- Hourglass with bowties
- Feedback
- Dynamics
- Distributed/decentralized
- *Not* scale-free, edge-of-chaos, self-organized criticality, etc

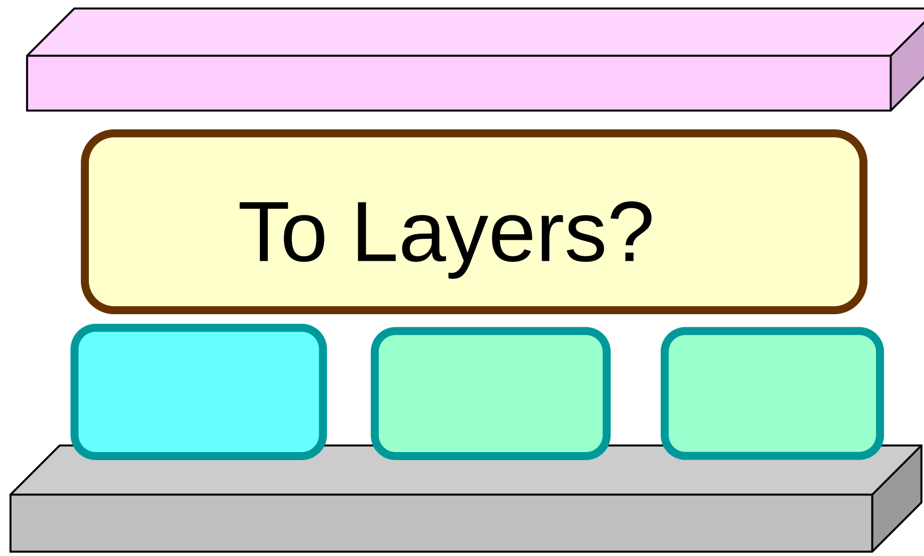
“Central dogma”

Network architecture?

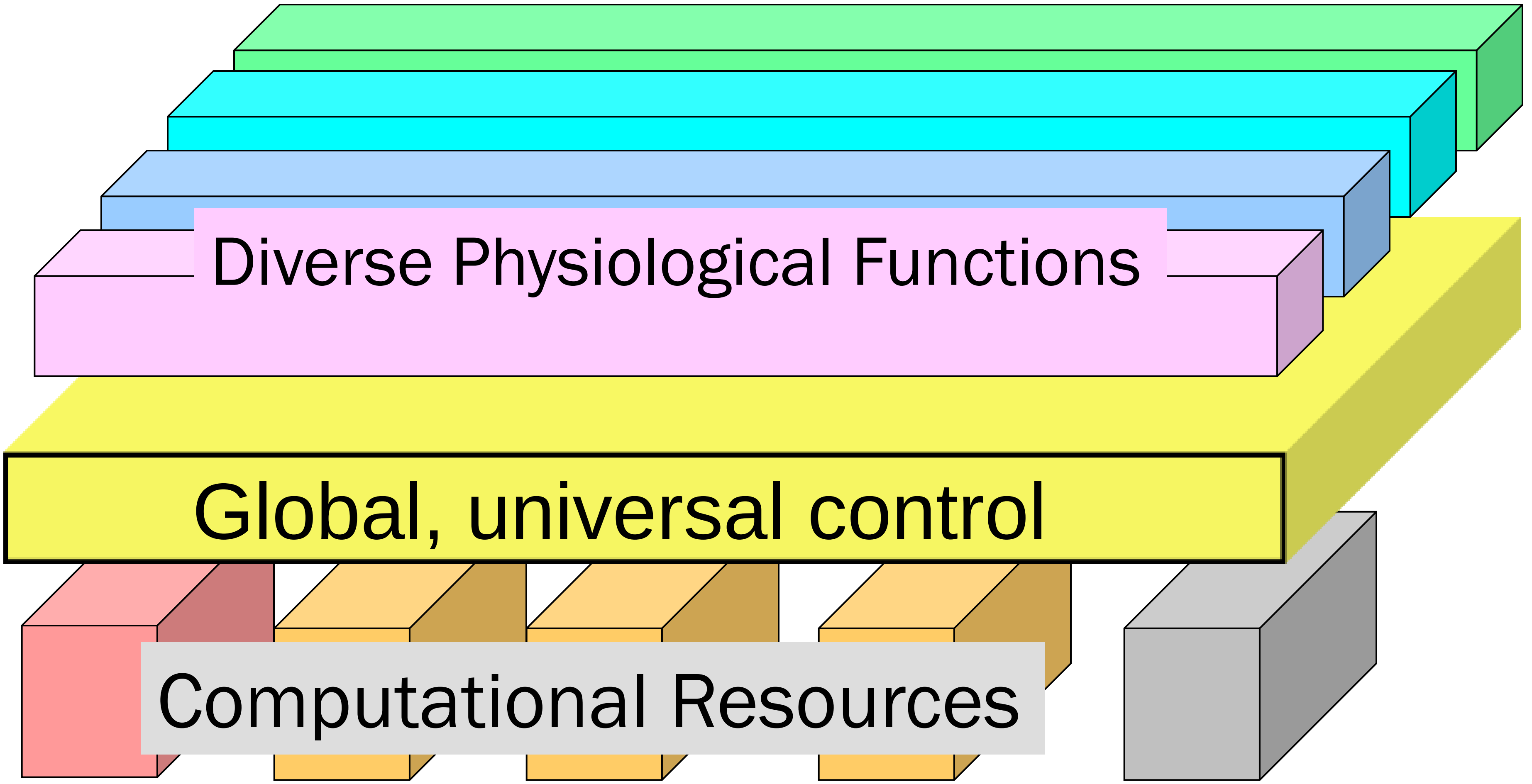
From Pathways

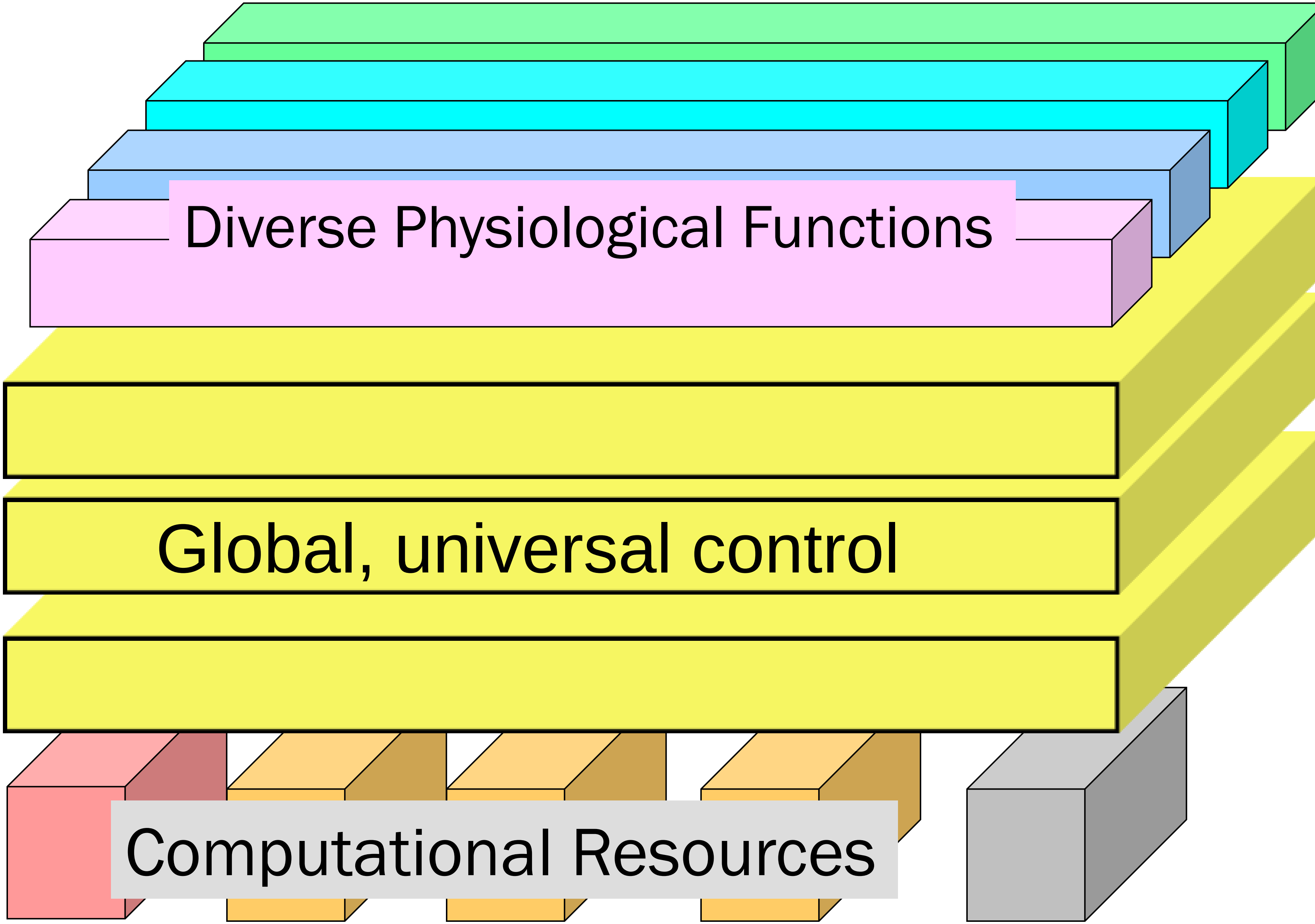


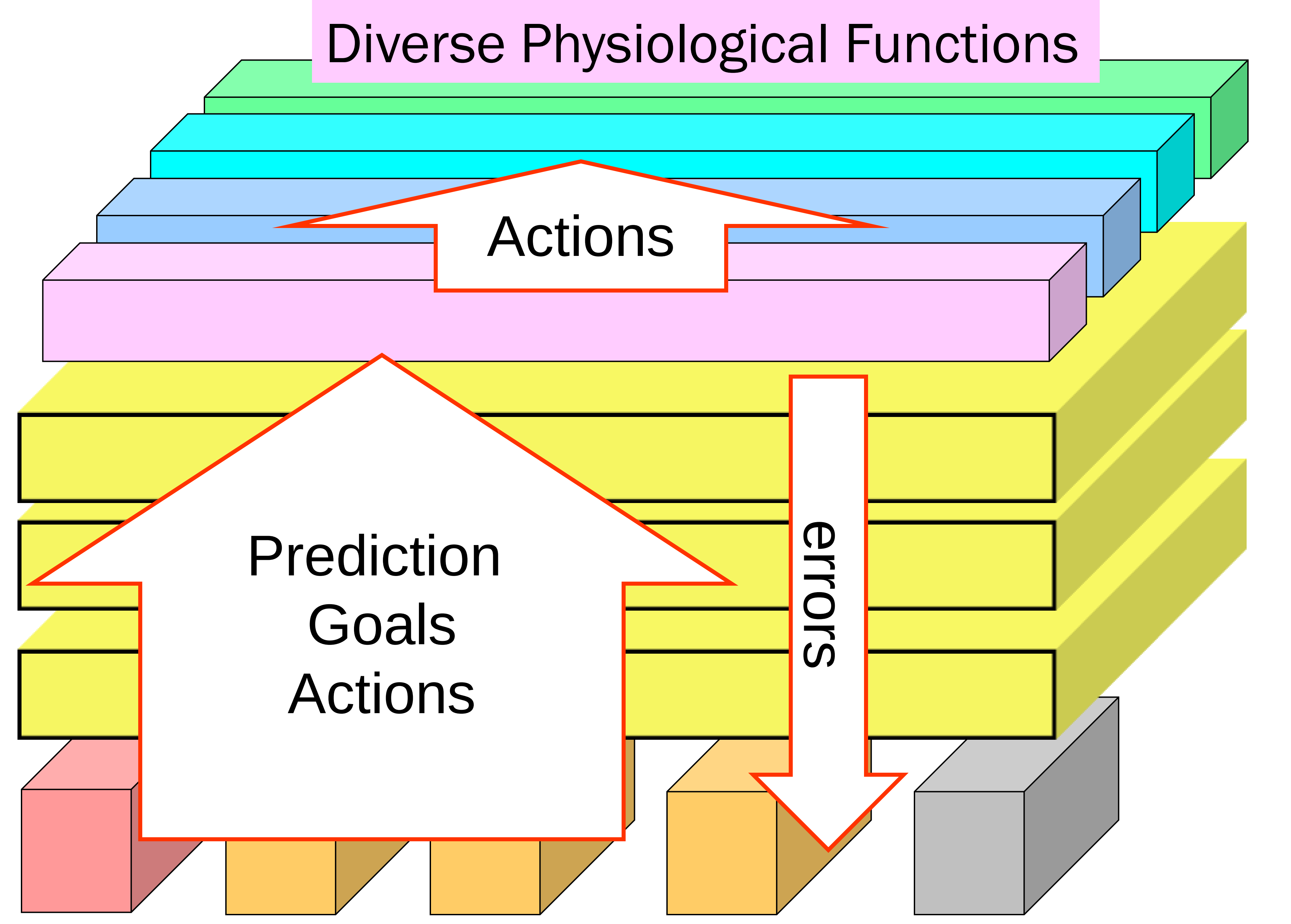
Metabolic pathways



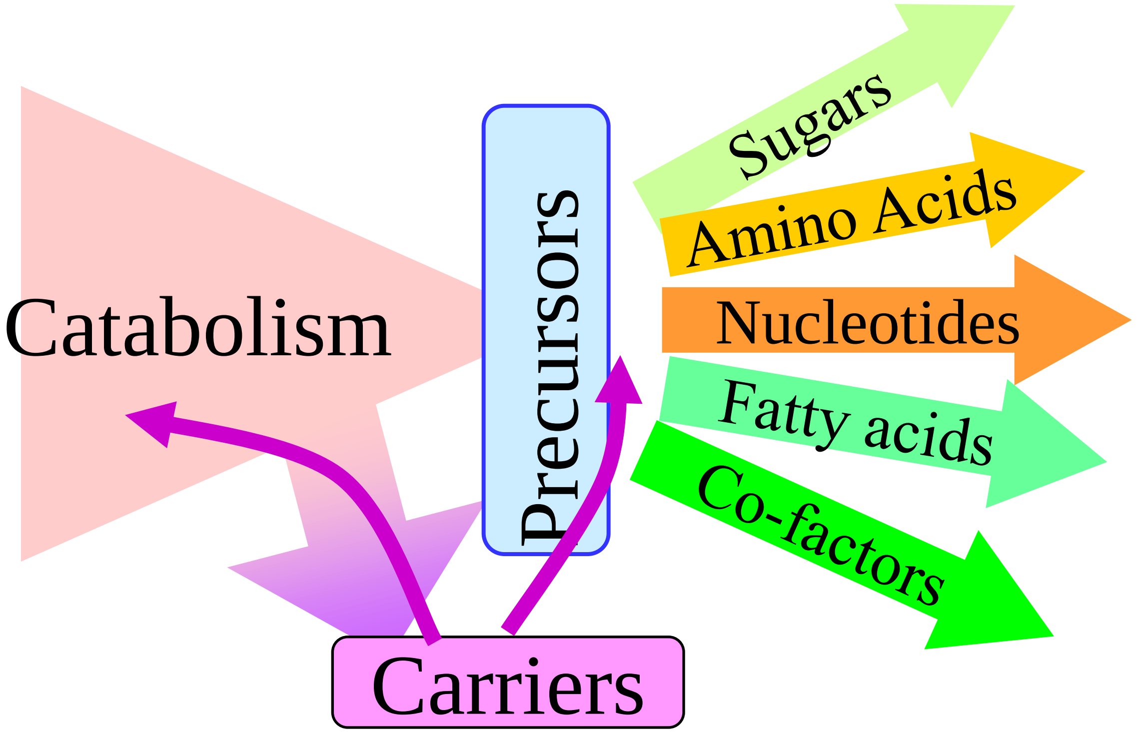
Layered Brain (Hawkins)?




Diverse Physiological Functions
Global, universal control
Computational Resources

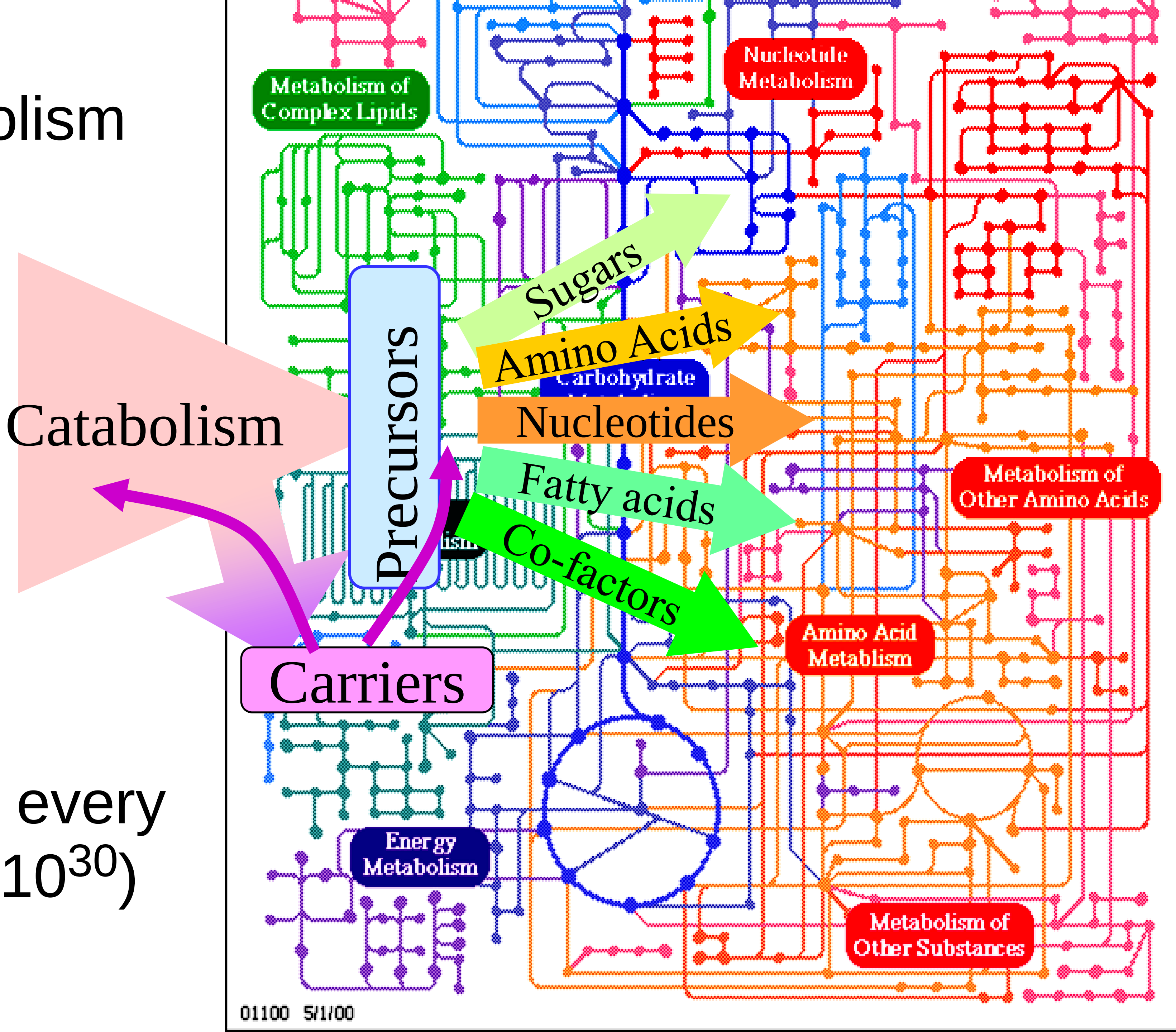

Diverse Physiological Functions
Actions
Prediction
Goals
Actions
errors

Inside every cell

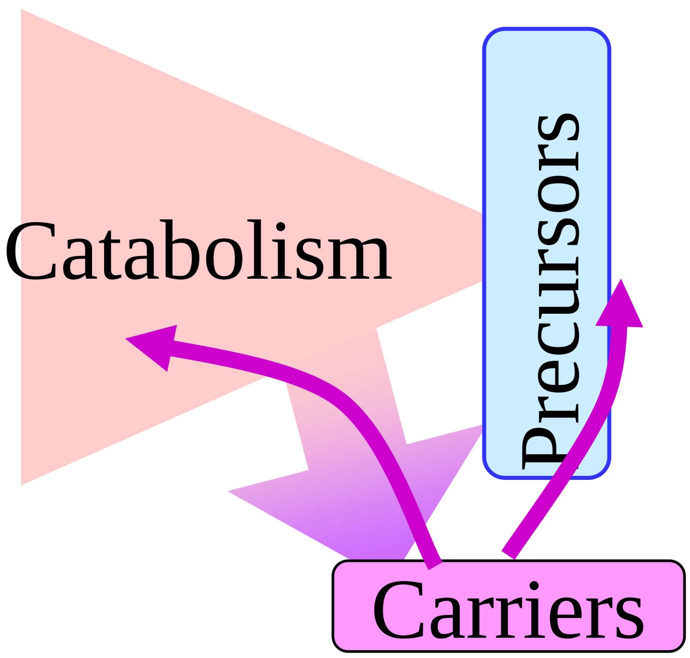


Core metabolic bowtie

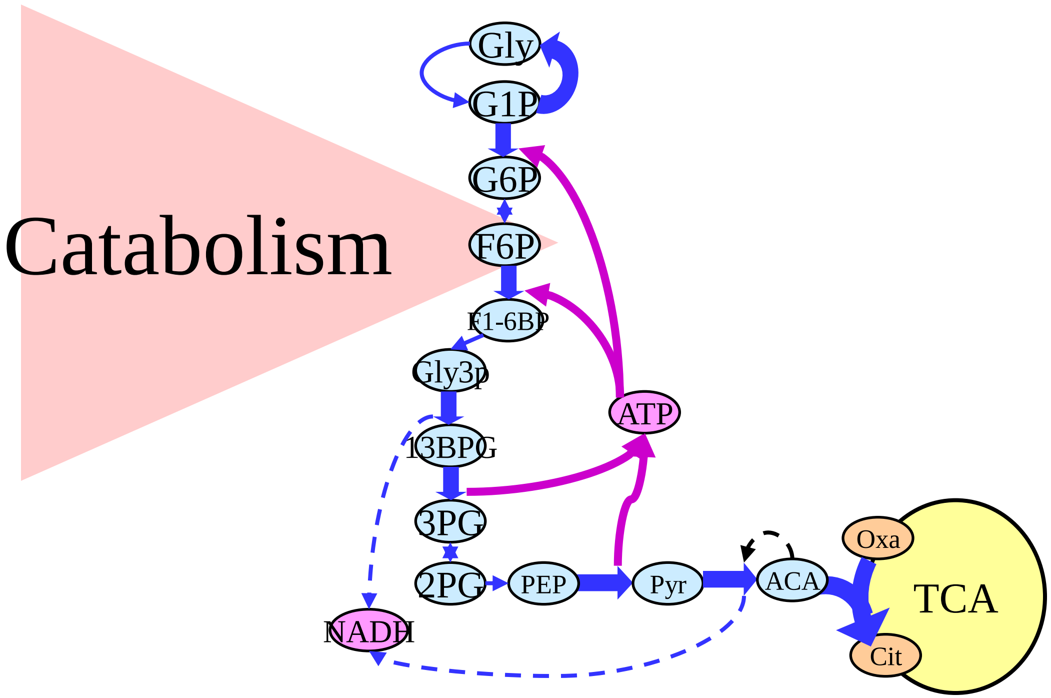
Core metabolism



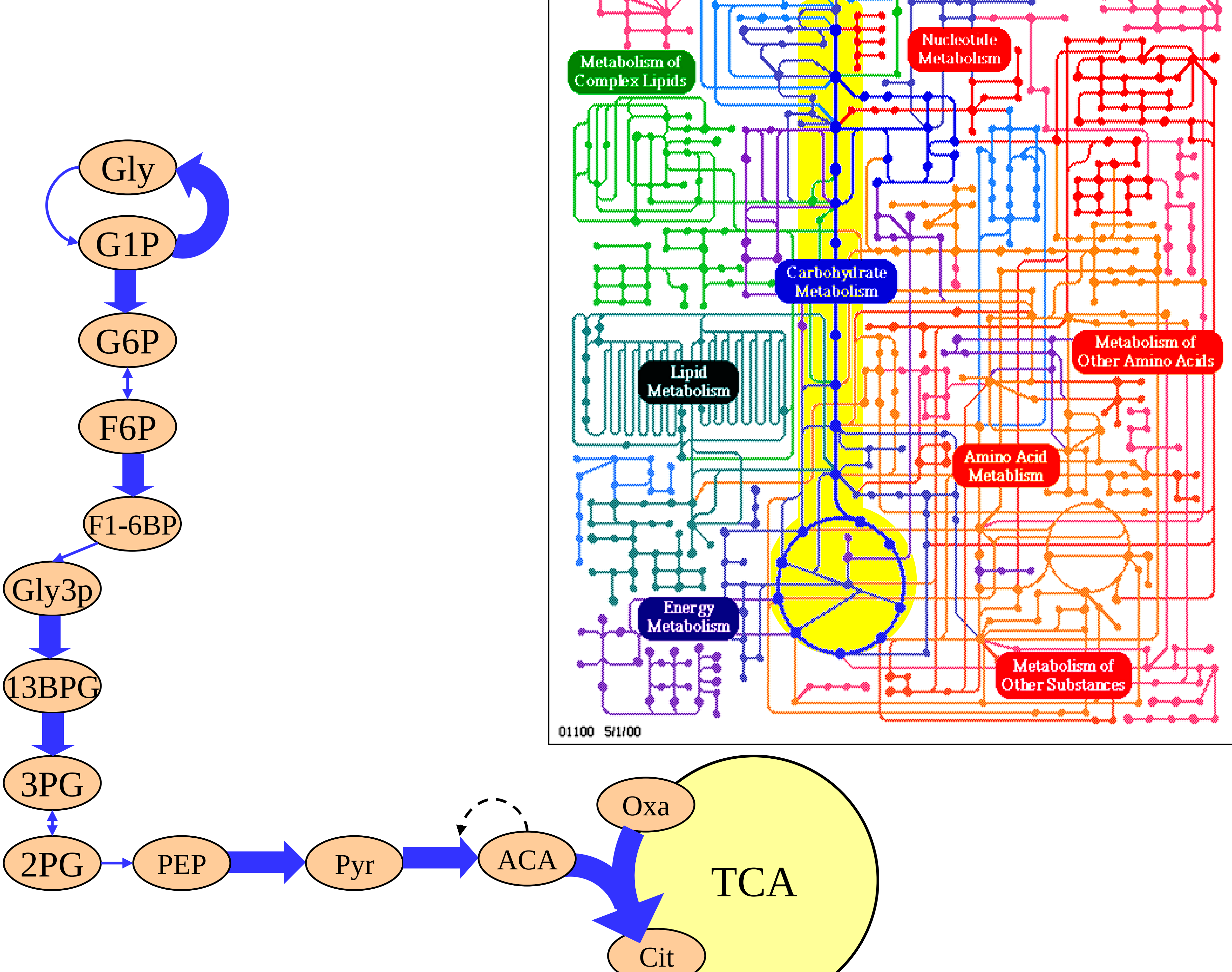
Inside every cell ($\approx 10^{30}$)

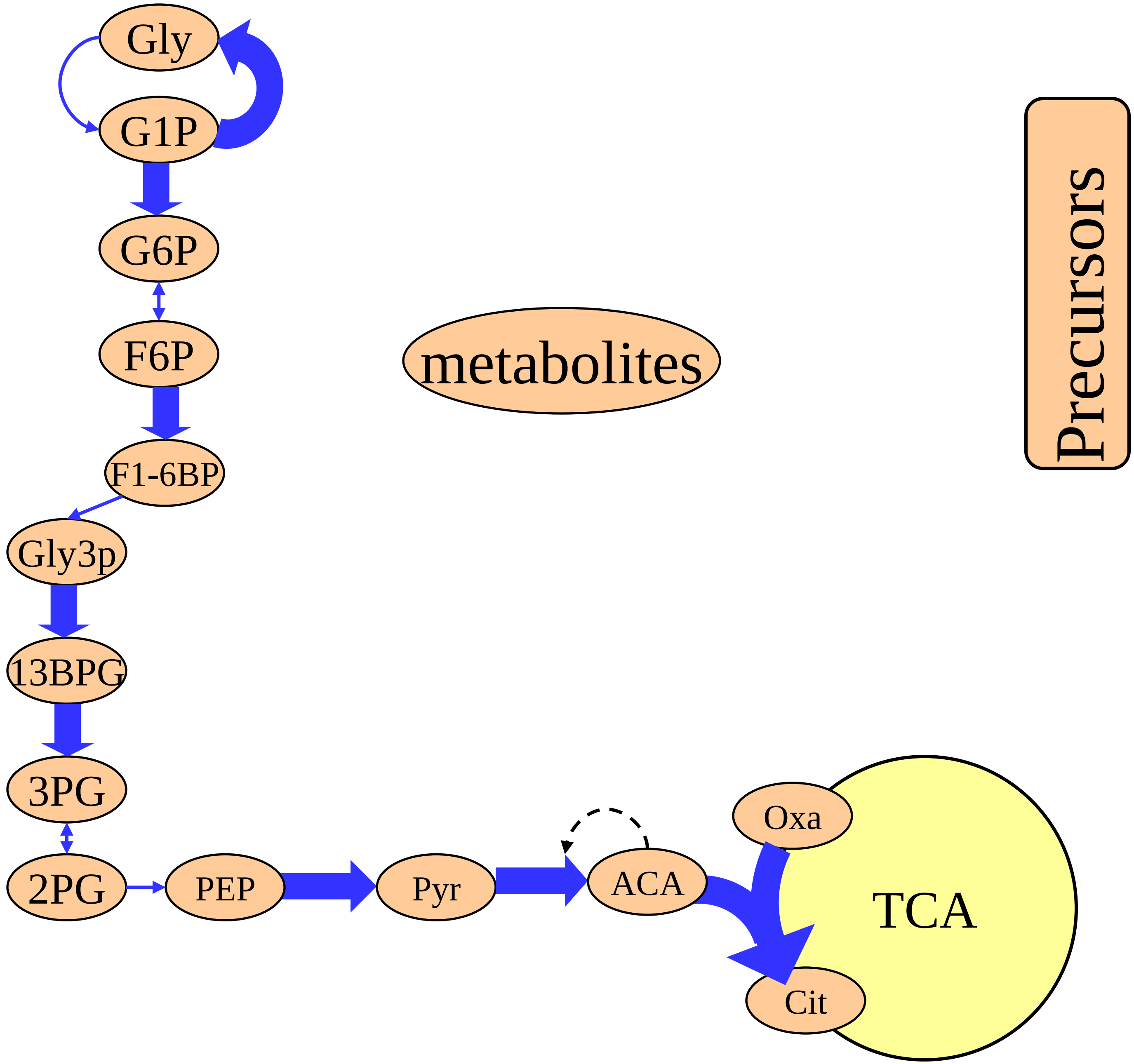


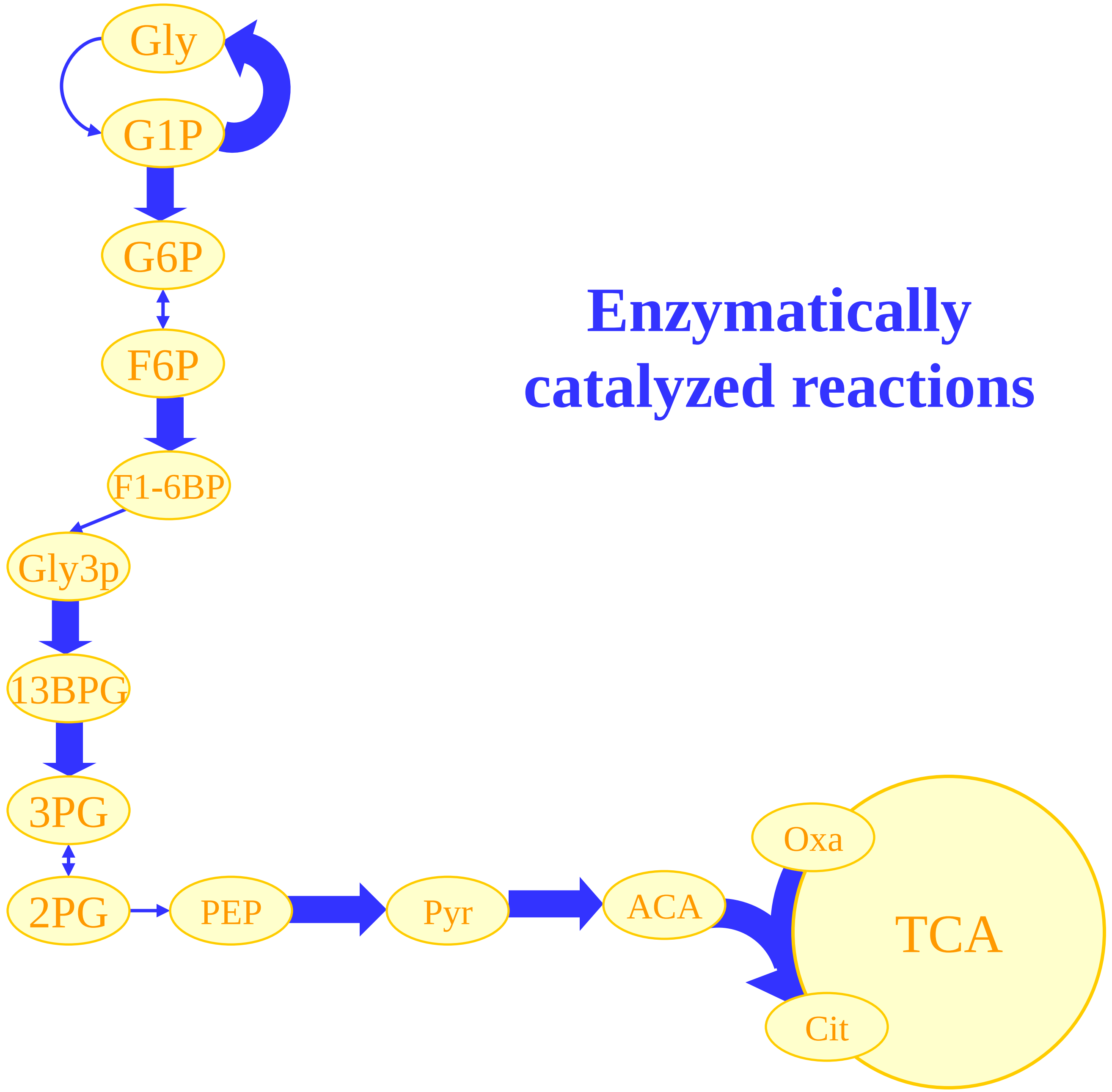
Catabolism
Precursors
Carriers



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

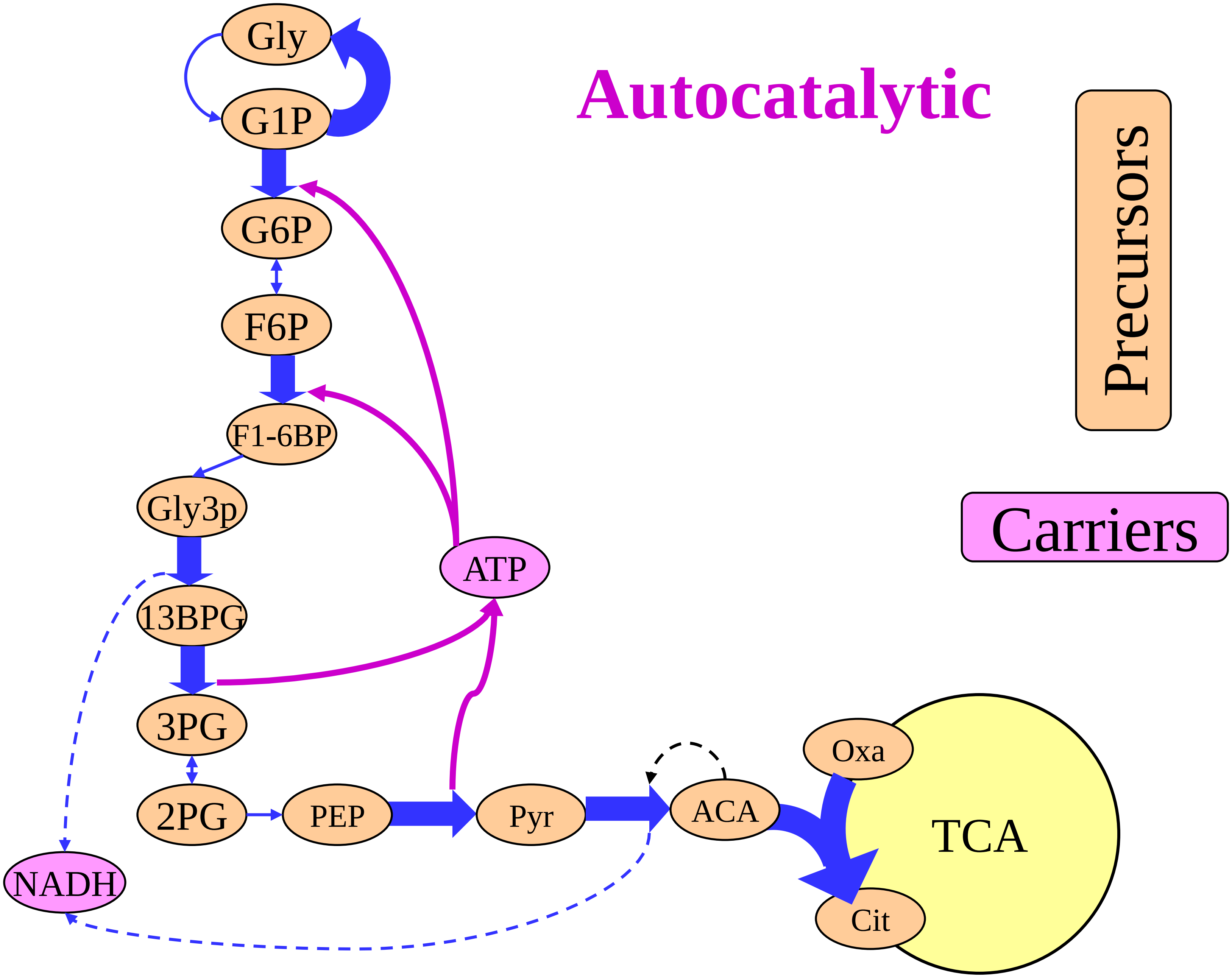

Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
Cit
TCA

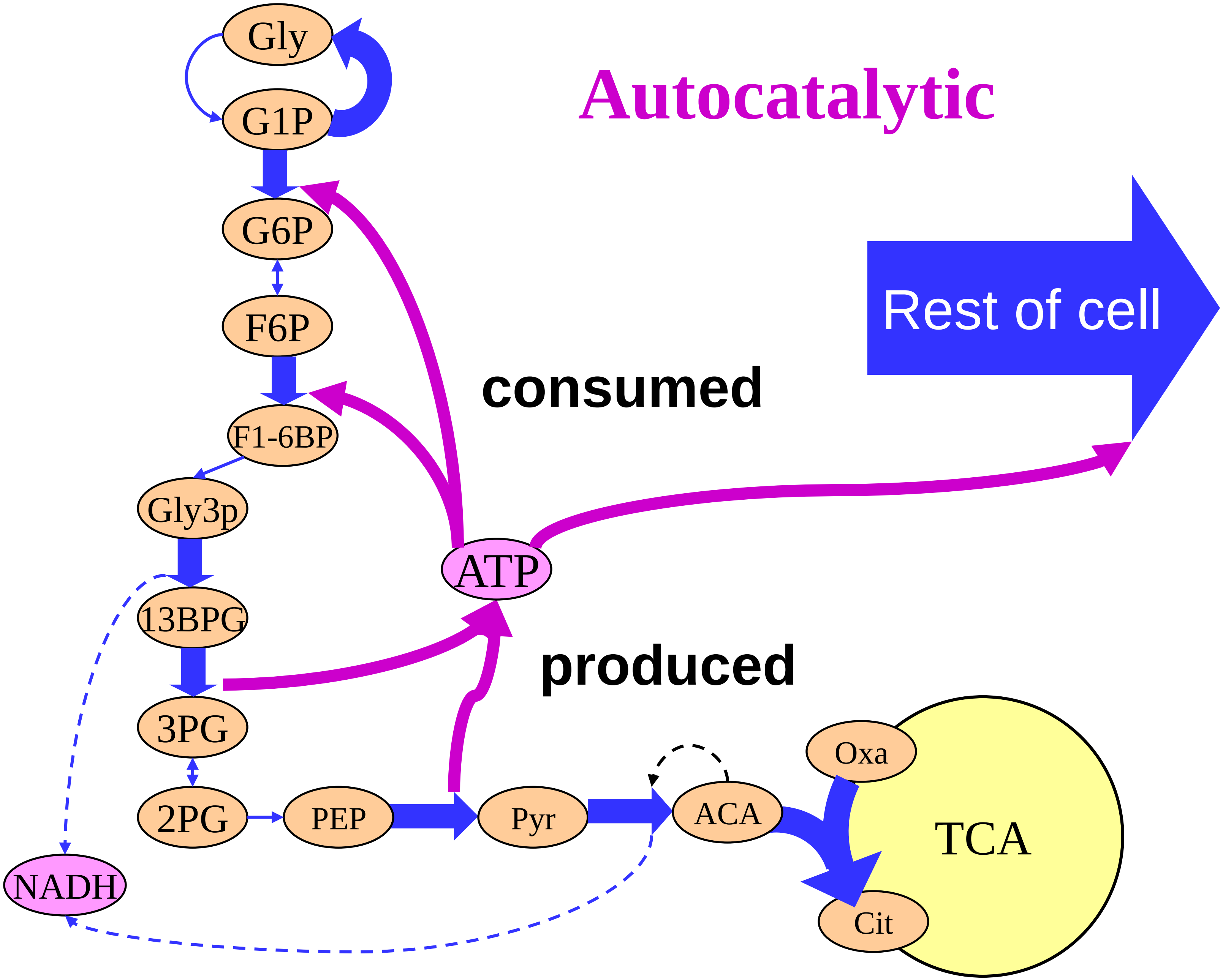

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
Cit
TCA
metabolites
Precursors



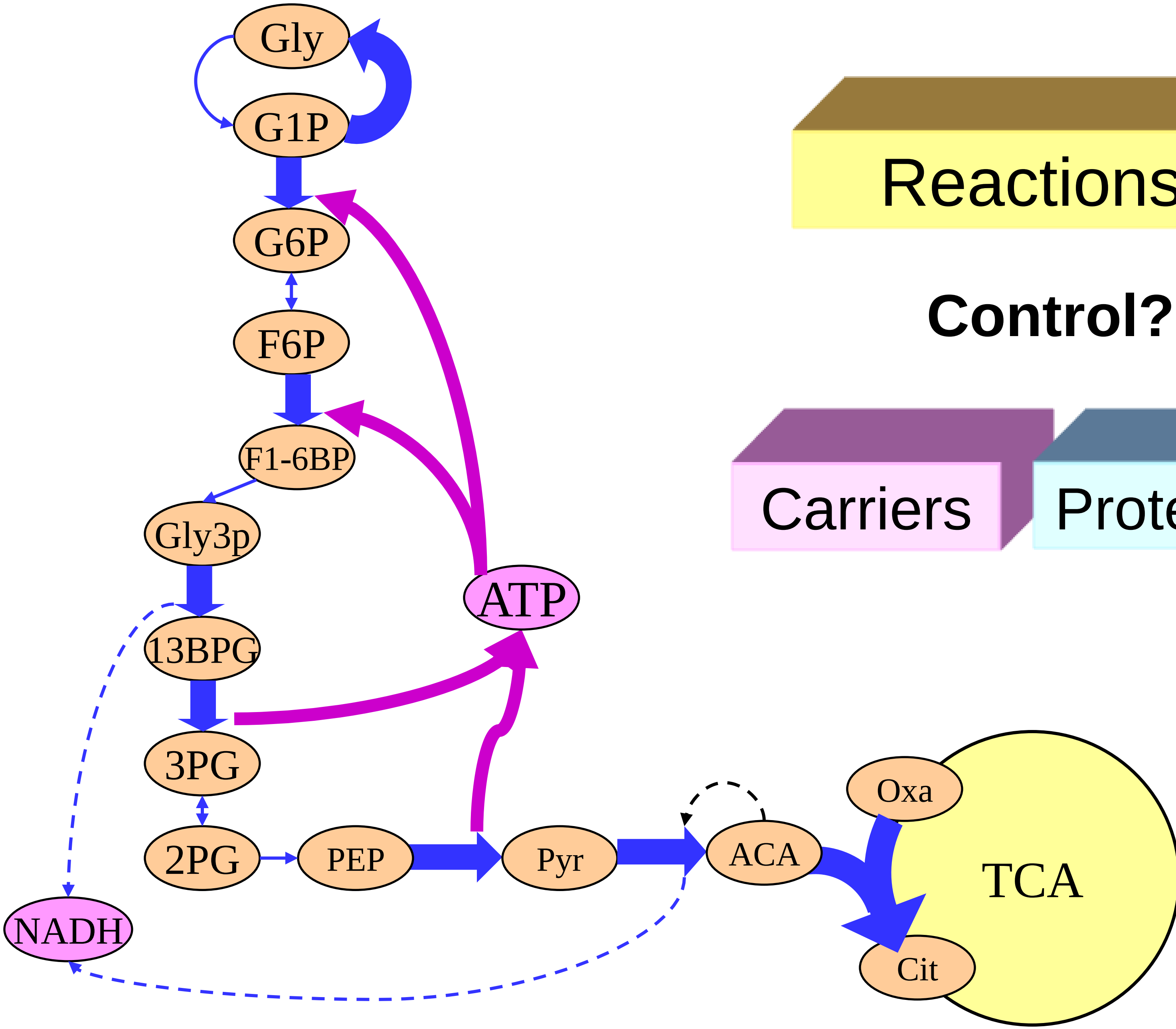
Enzymatically catalyzed reactions

Autocatalytic





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

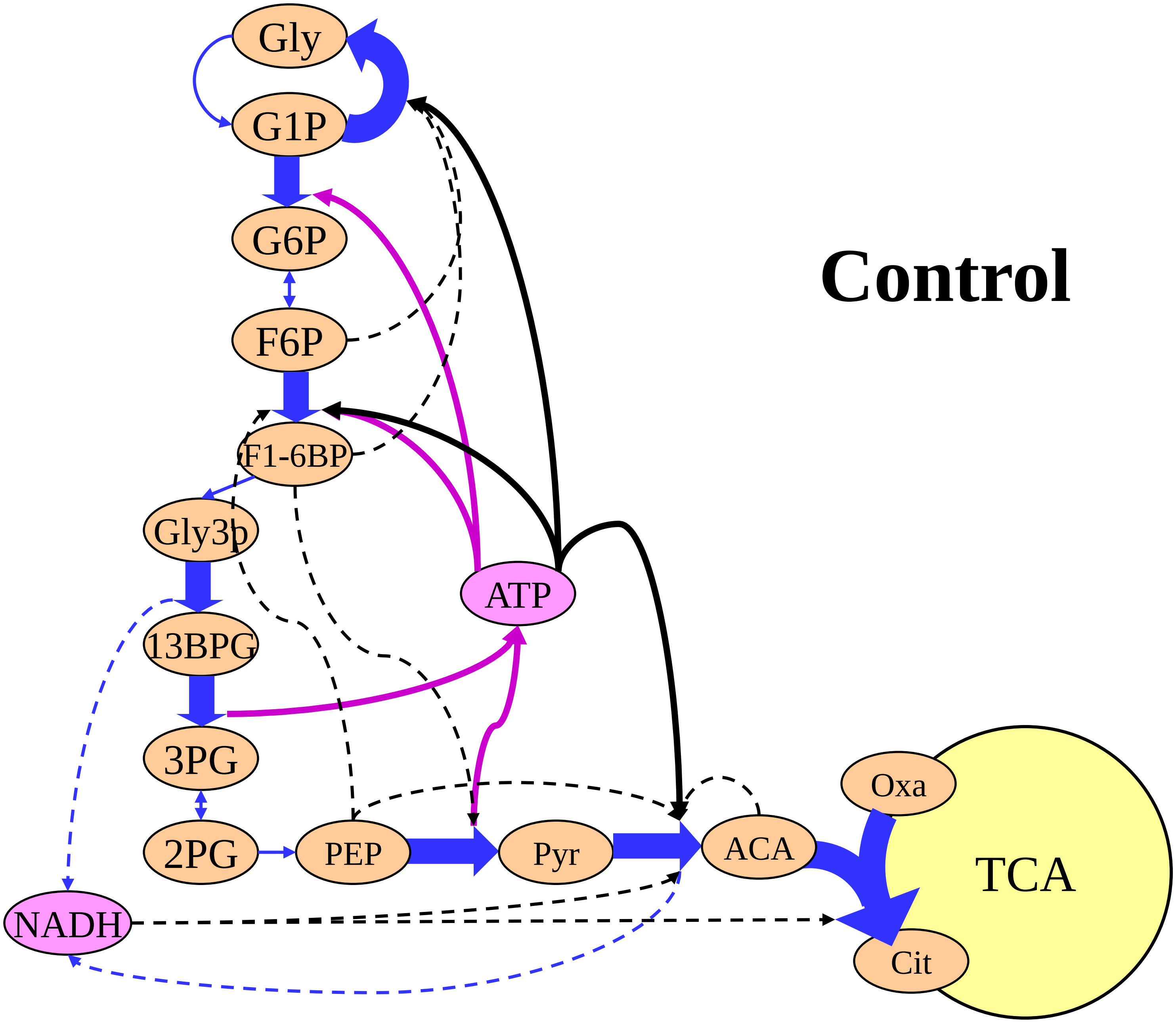


Reactions

Control?

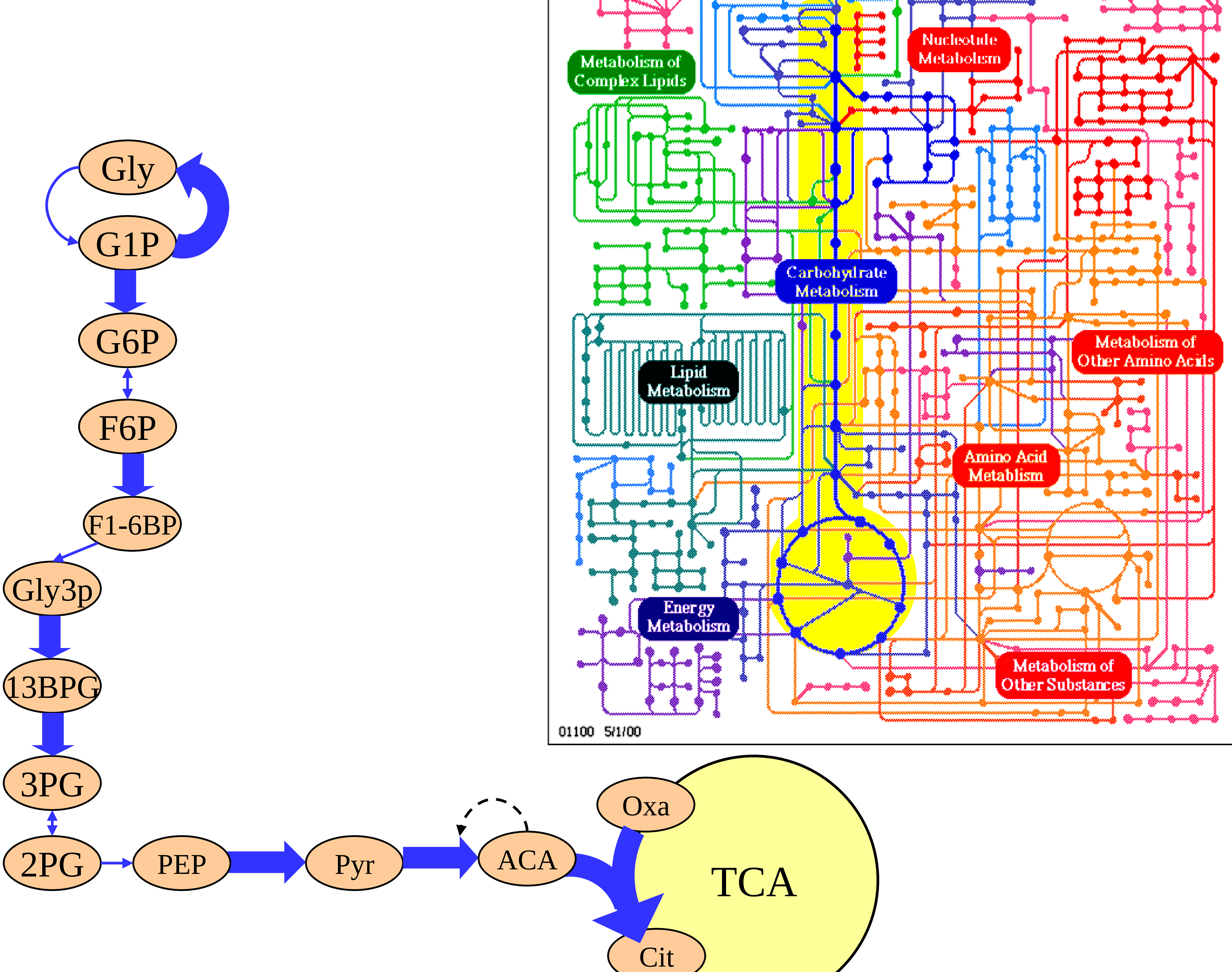
Carriers

Proteins



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

Control


Gly
G1P
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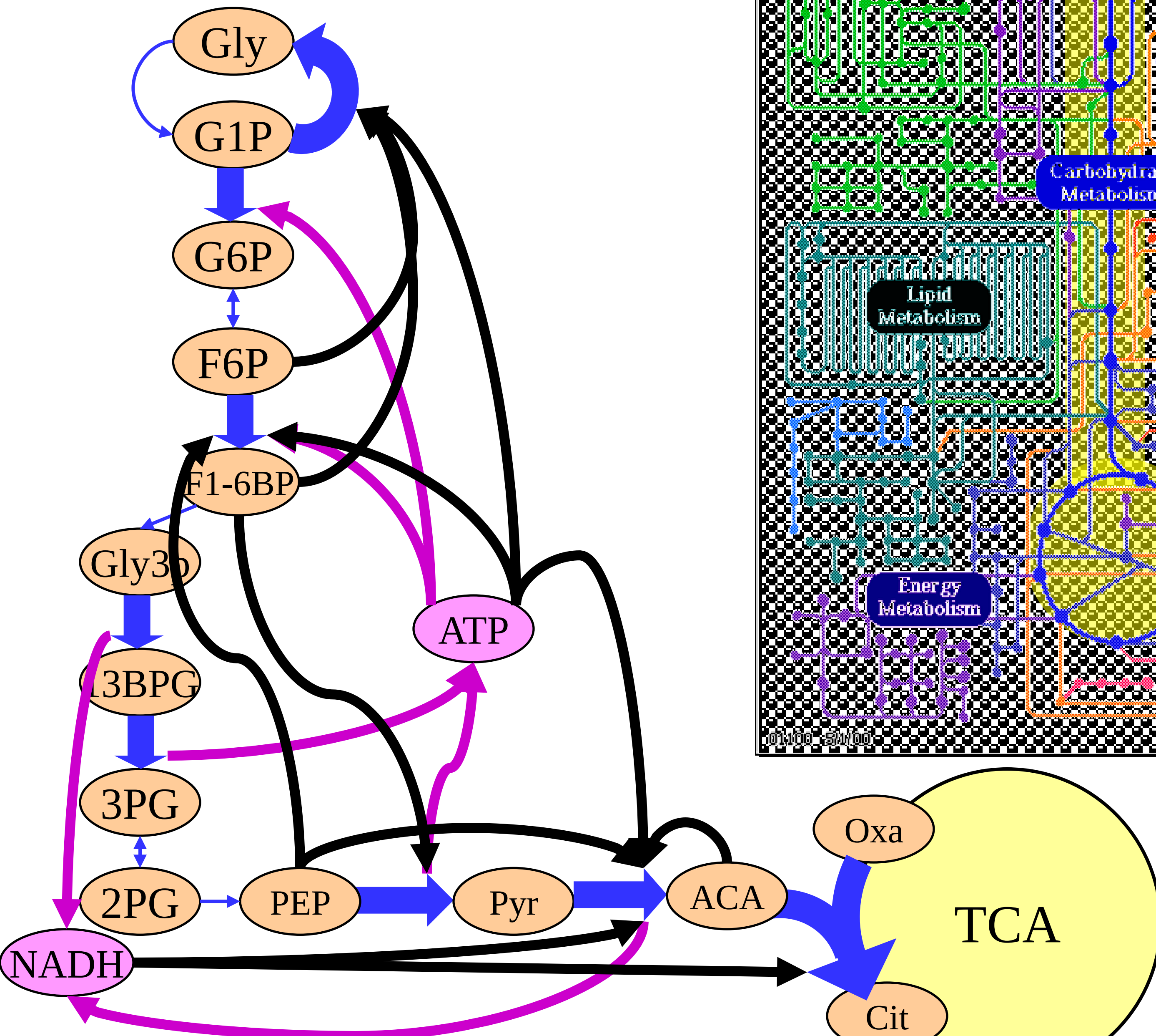
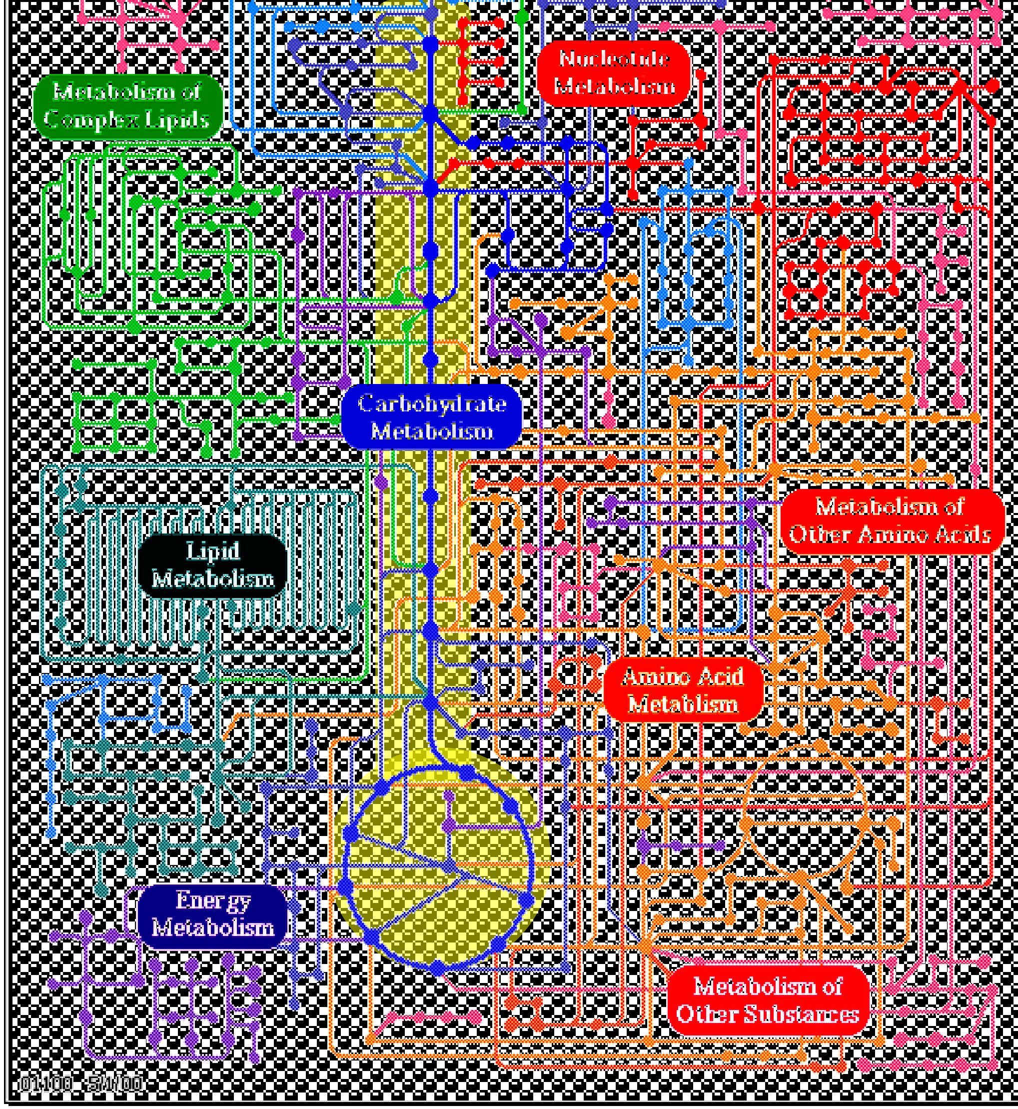
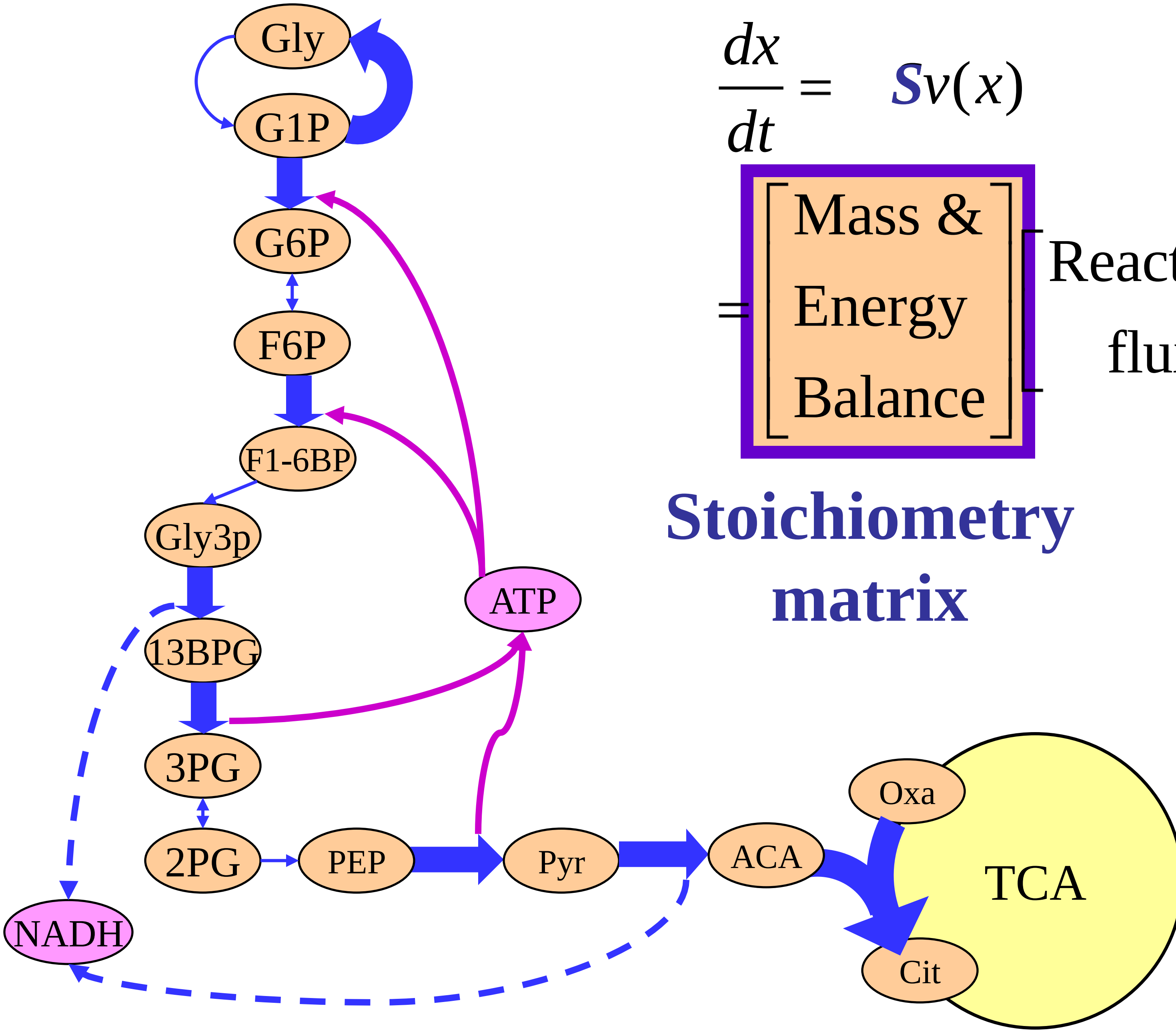
Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00

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





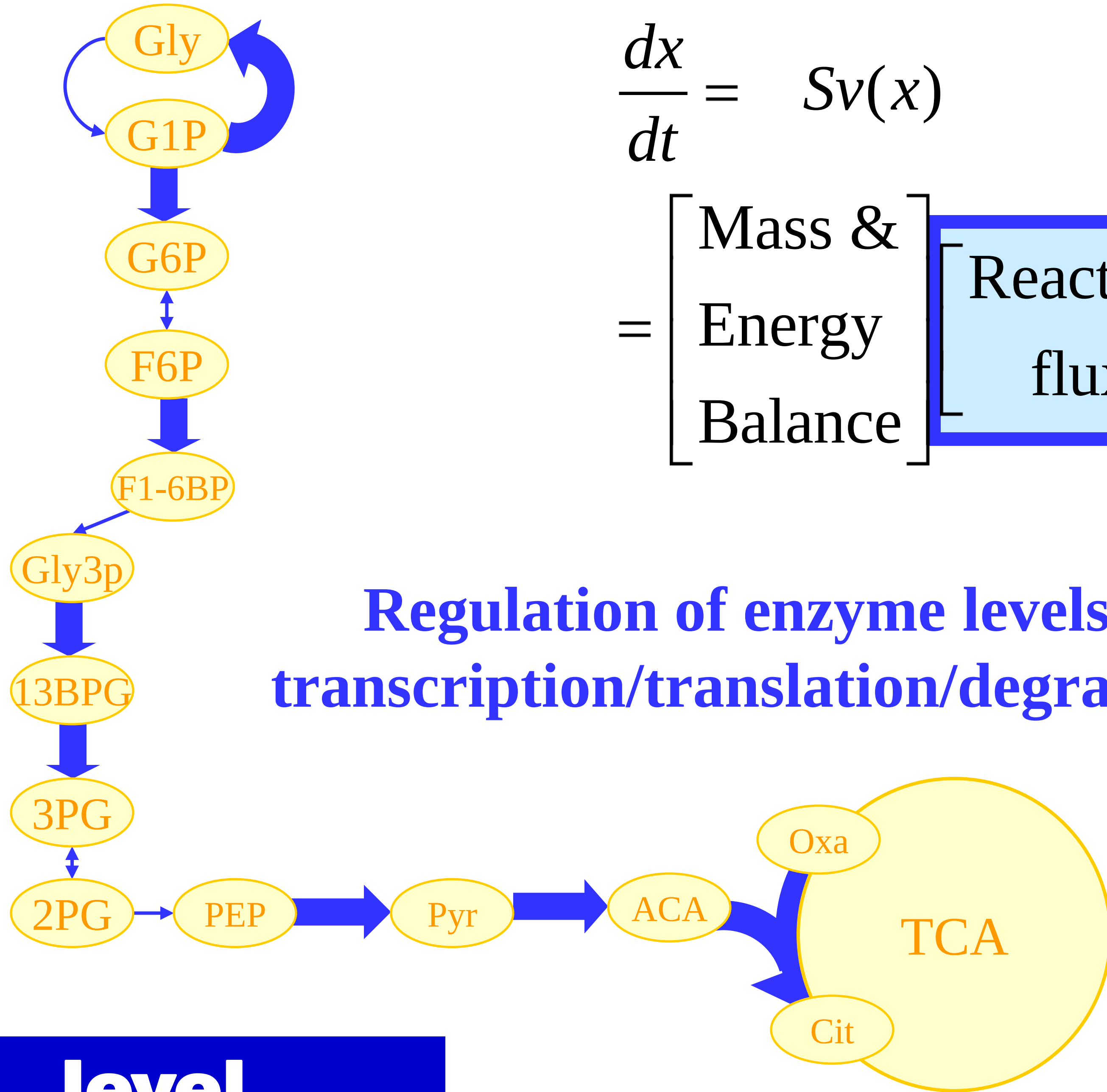


$$\frac{dx}{dt} = \mathbf{S}v(x) = \boxed{\begin{bmatrix}\text{Mass \&} \\ \text{Energy} \\ \text{Balance}\end{bmatrix}} \begin{bmatrix}\text{Reaction} \\ \text{flux}\end{bmatrix}$$

Stoichiometry matrix

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

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

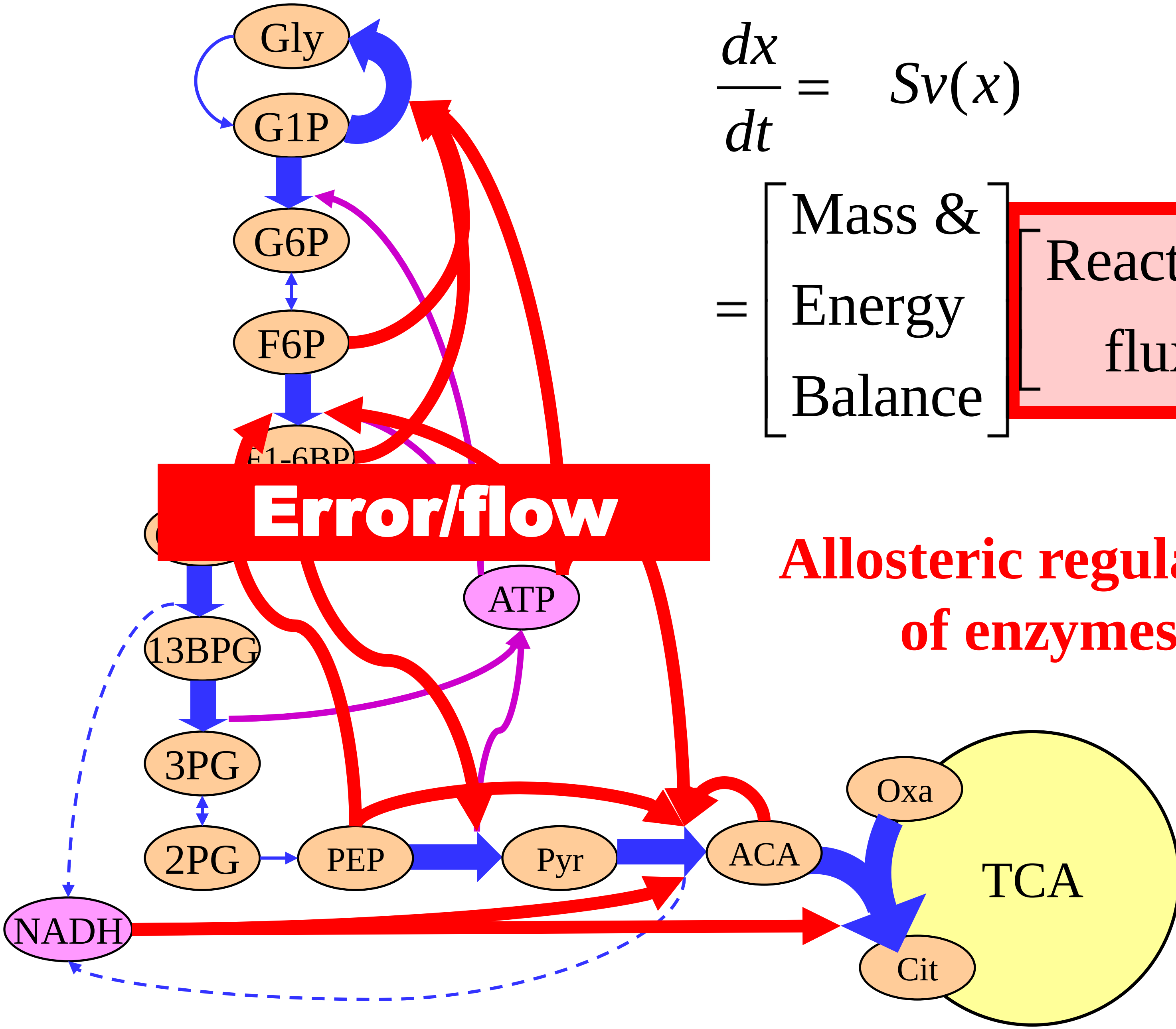


Regulation of enzyme levels by transcription/translation/degradation

level

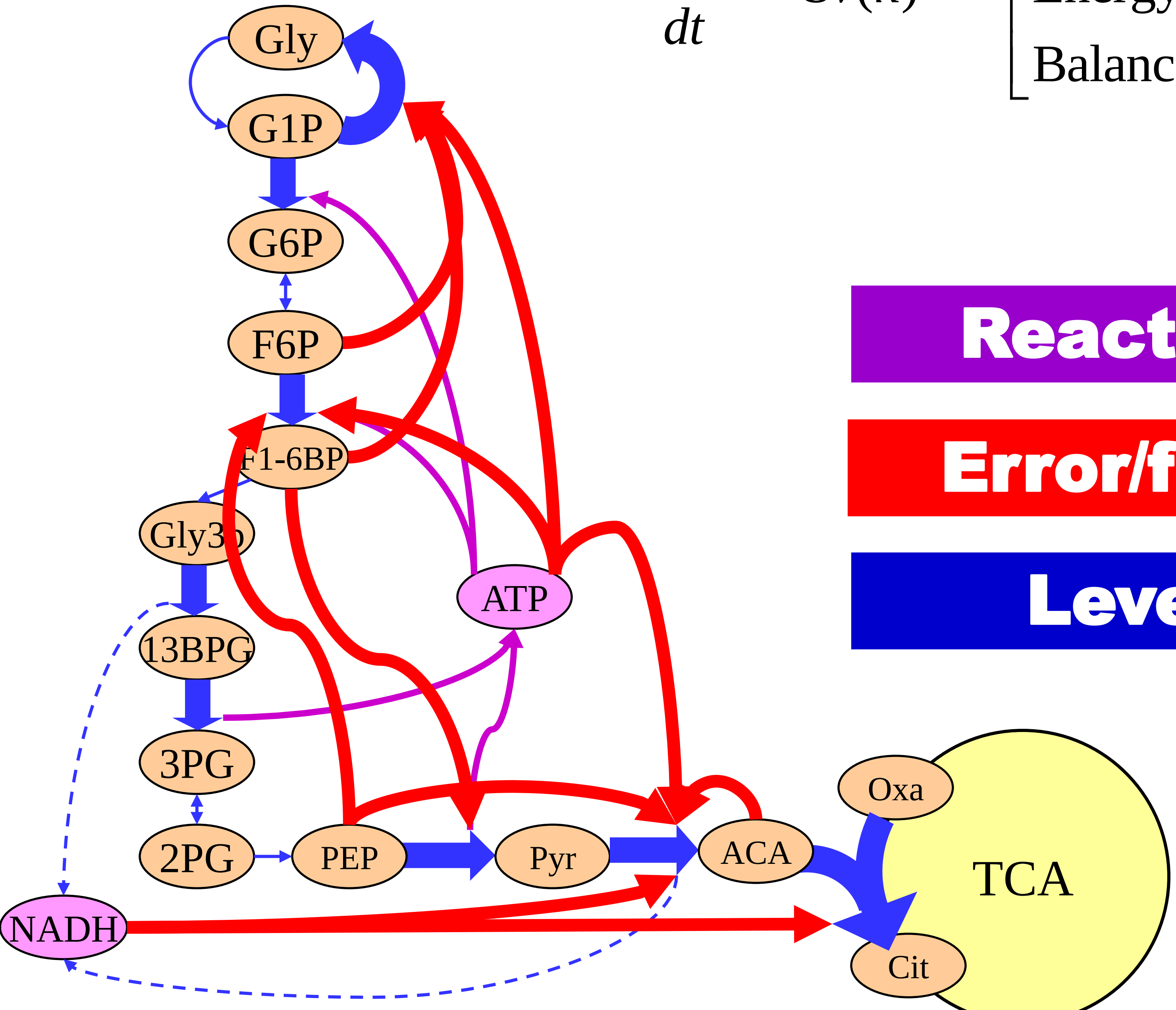
$$\frac{dx}{dt} = Sv(x)$$

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



Allosteric regulation of enzymes

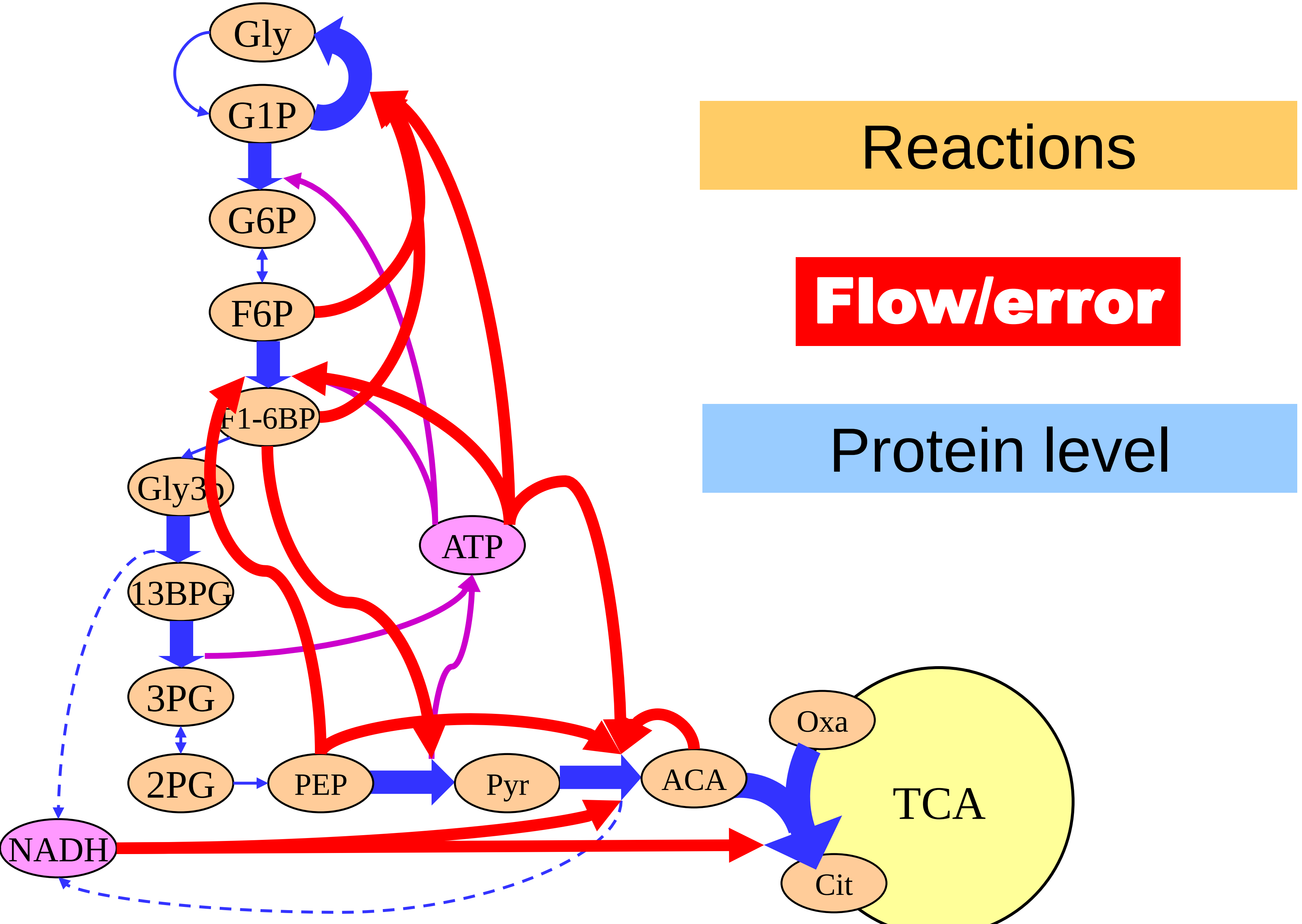
$$\frac{dx}{dt} = Sv(x) = \begin{bmatrix}\text{Mass \&}\\ \text{Energy}\\ \text{Balance}\end{bmatrix}\boxed{\begin{bmatrix}\text{Reaction}\\ \text{flux}\end{bmatrix}}$$



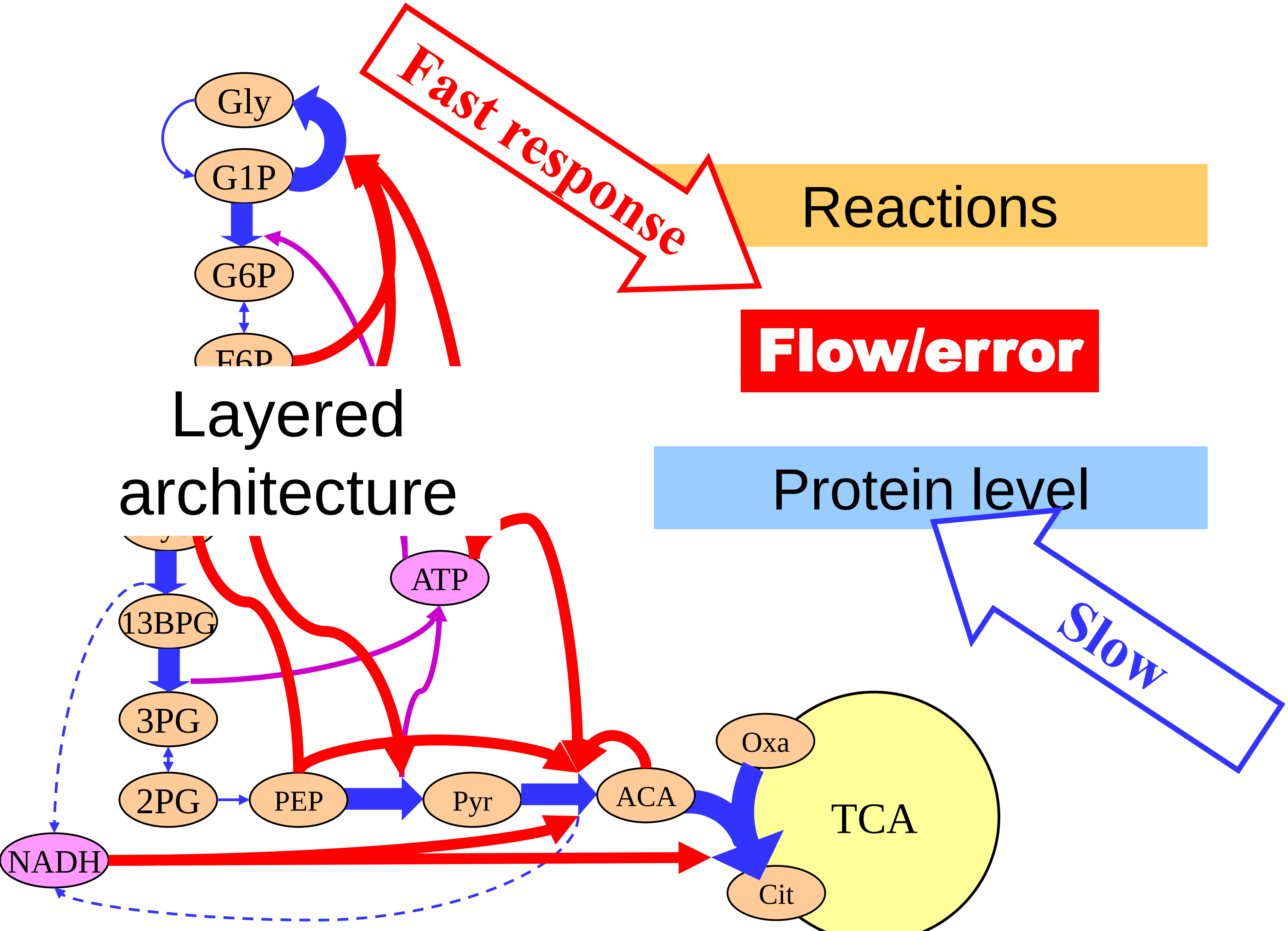
Reaction

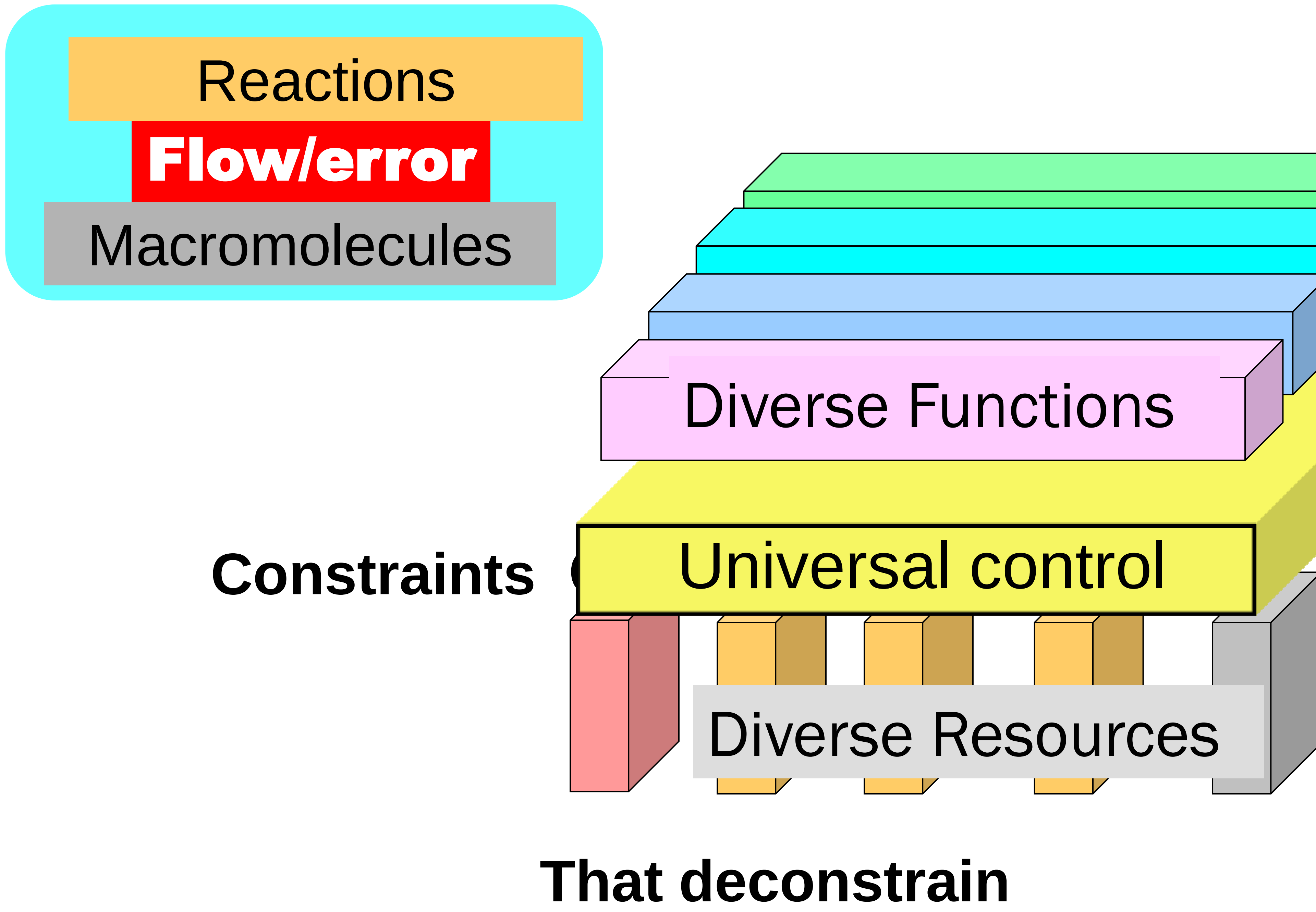
Error/flow

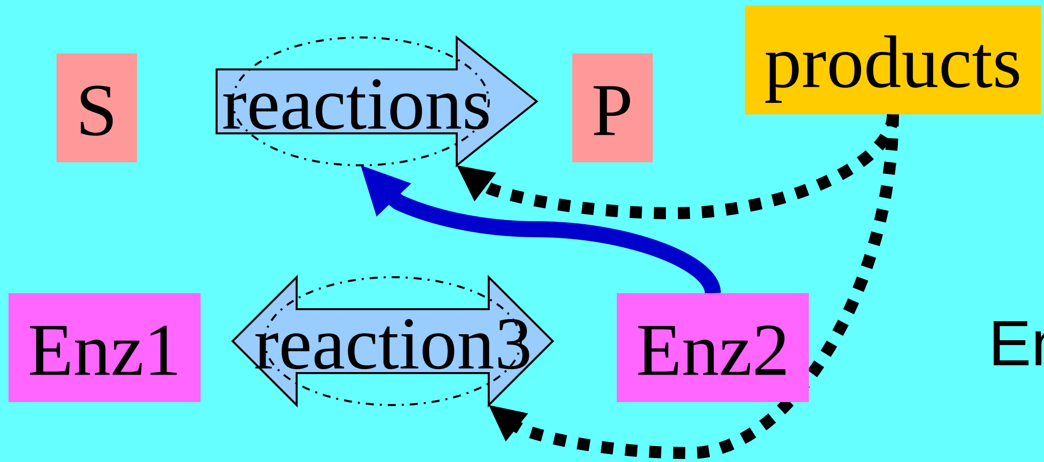
Level



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


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

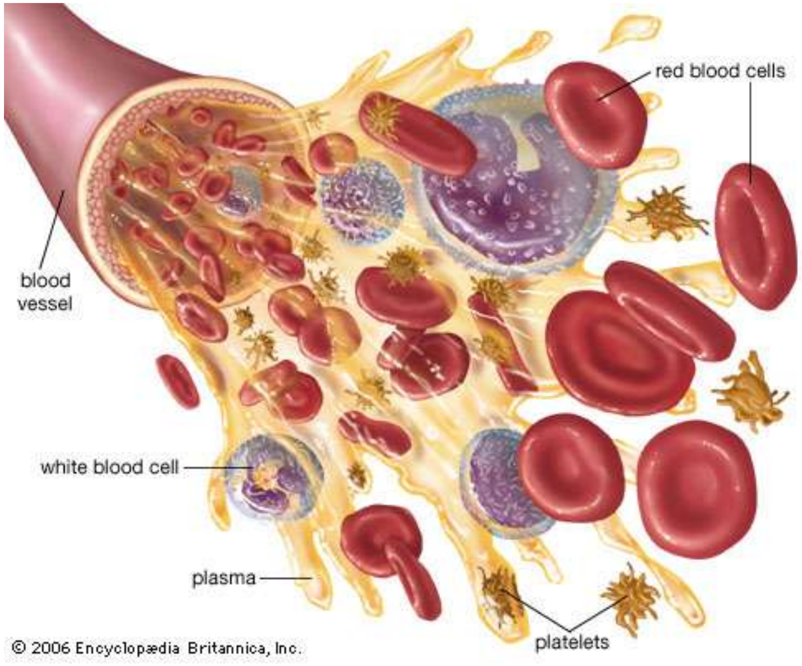

Reactions
Flow/error
Macromolecules
Constraints
Diverse Functions
Universal control
Diverse Resources
That deconstrain



Reaction rate

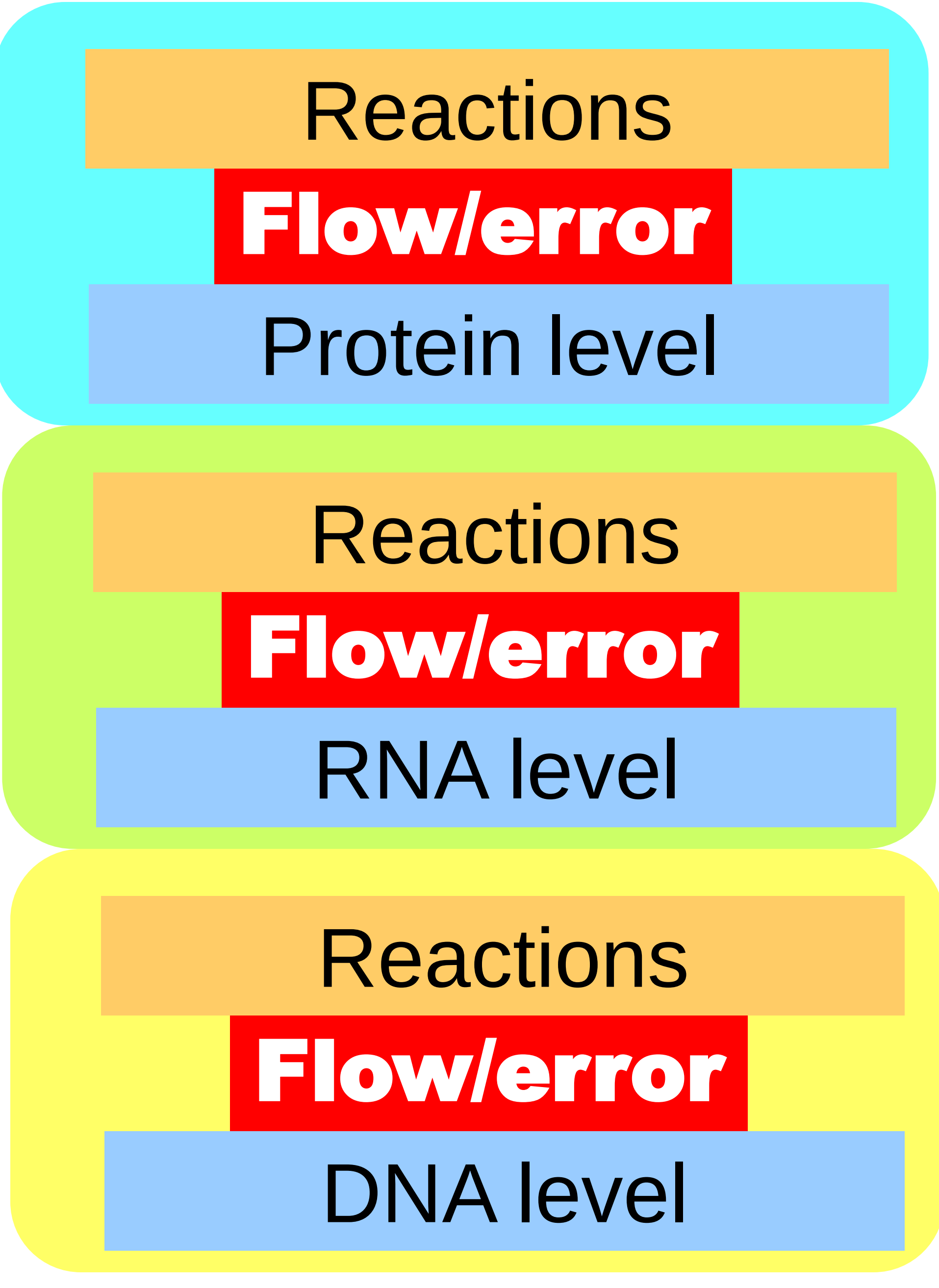
Enzyme form/activity

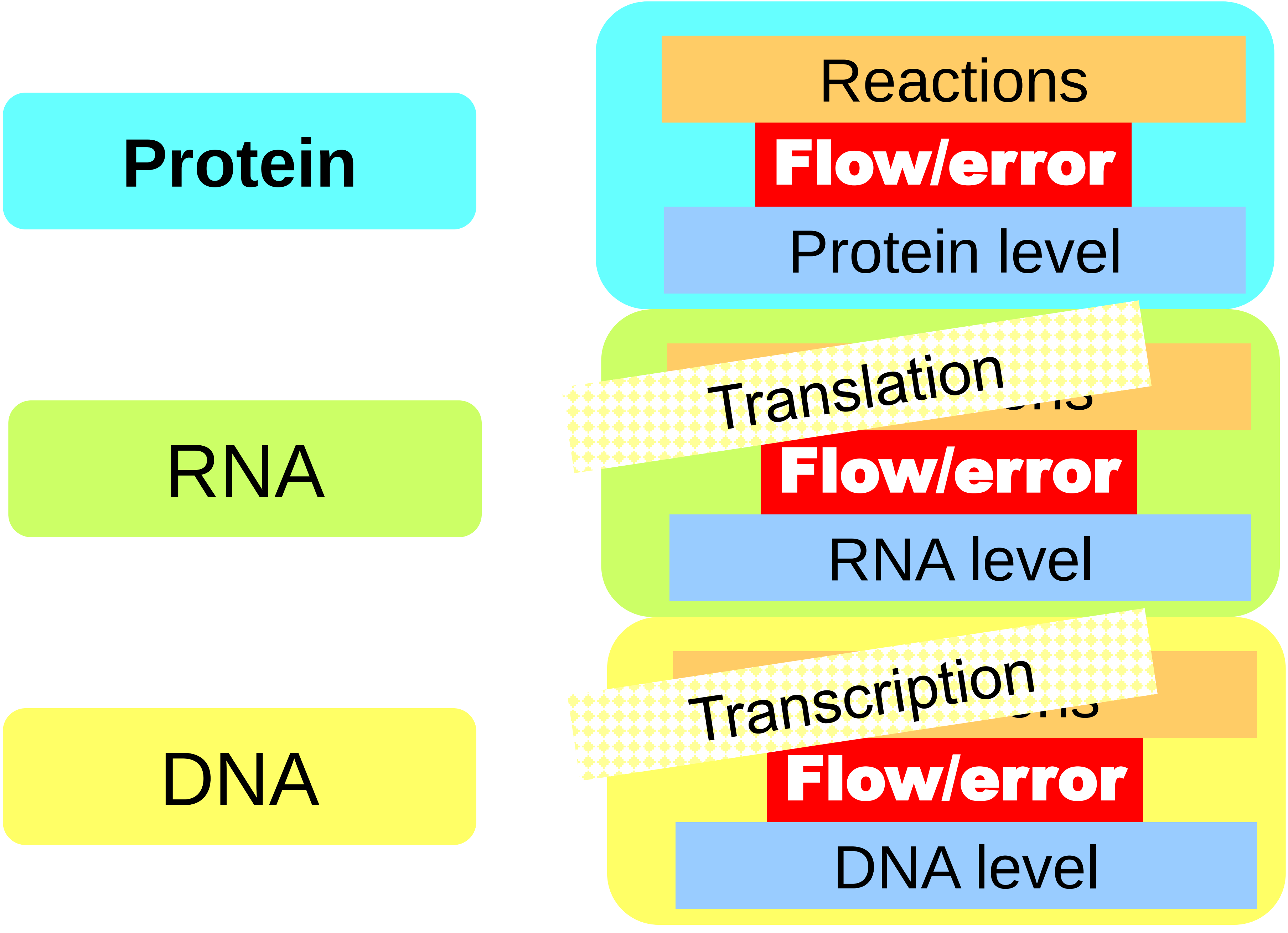
Running only the top layers

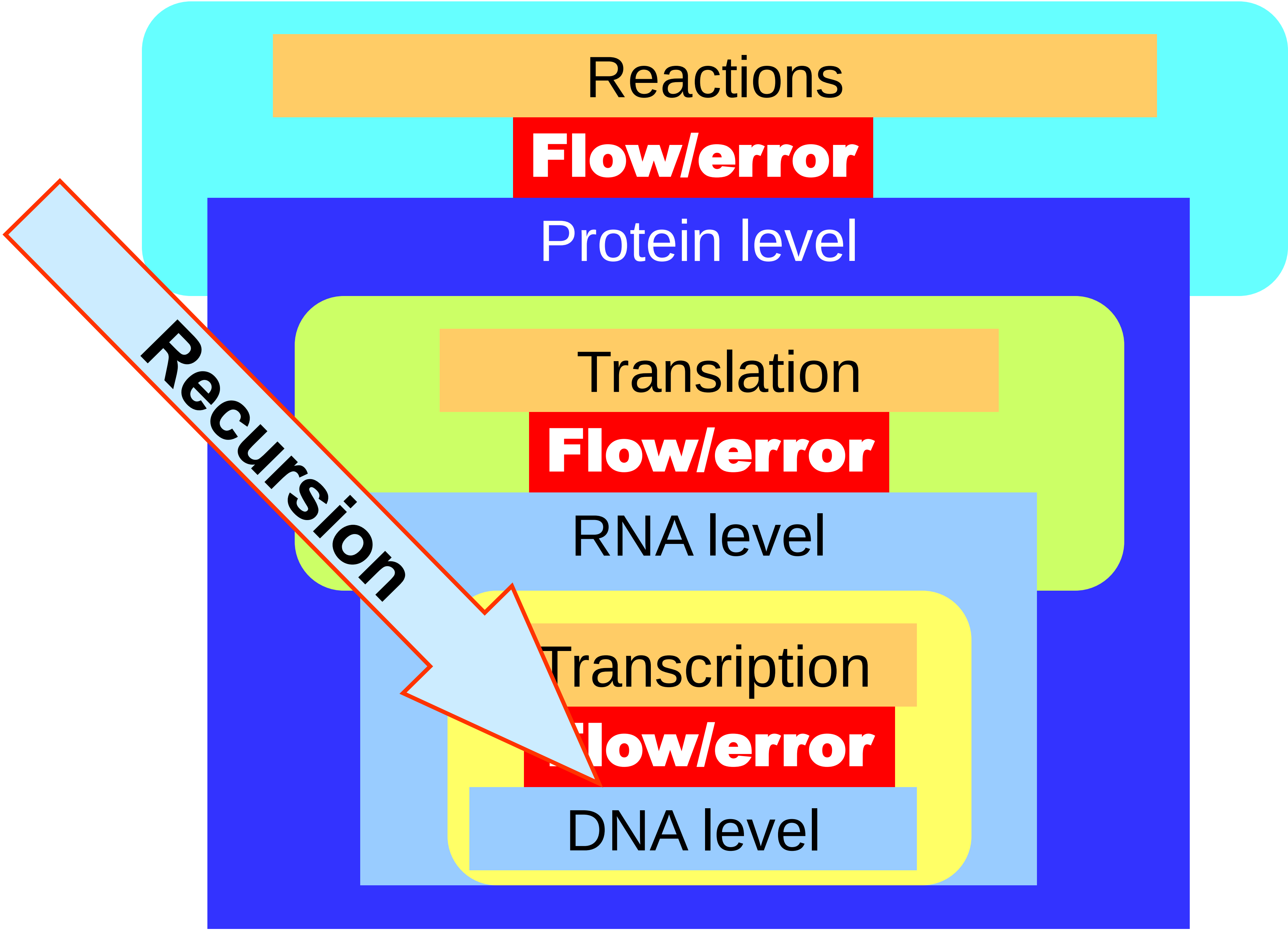


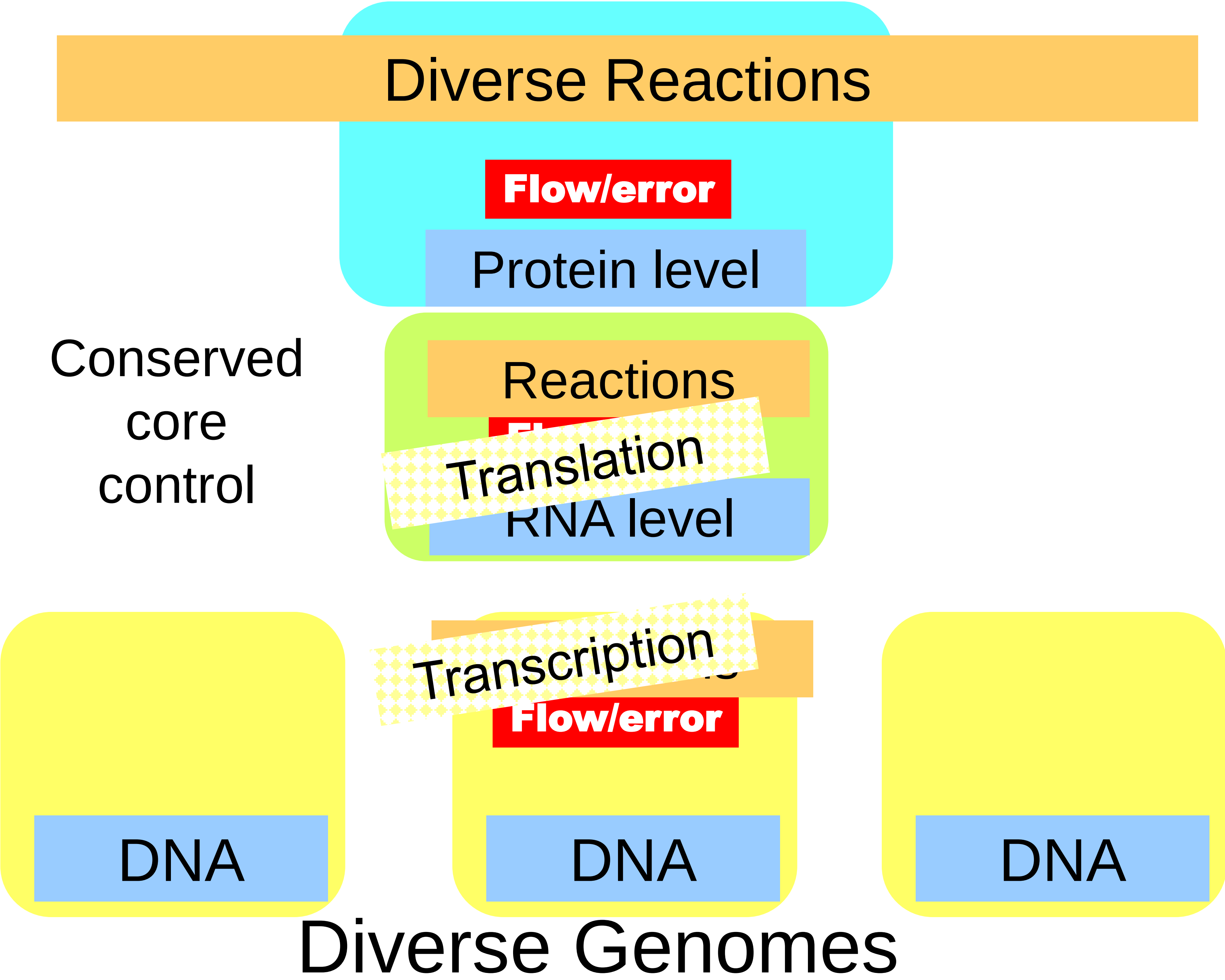
Mature red blood cells live 120 days

“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

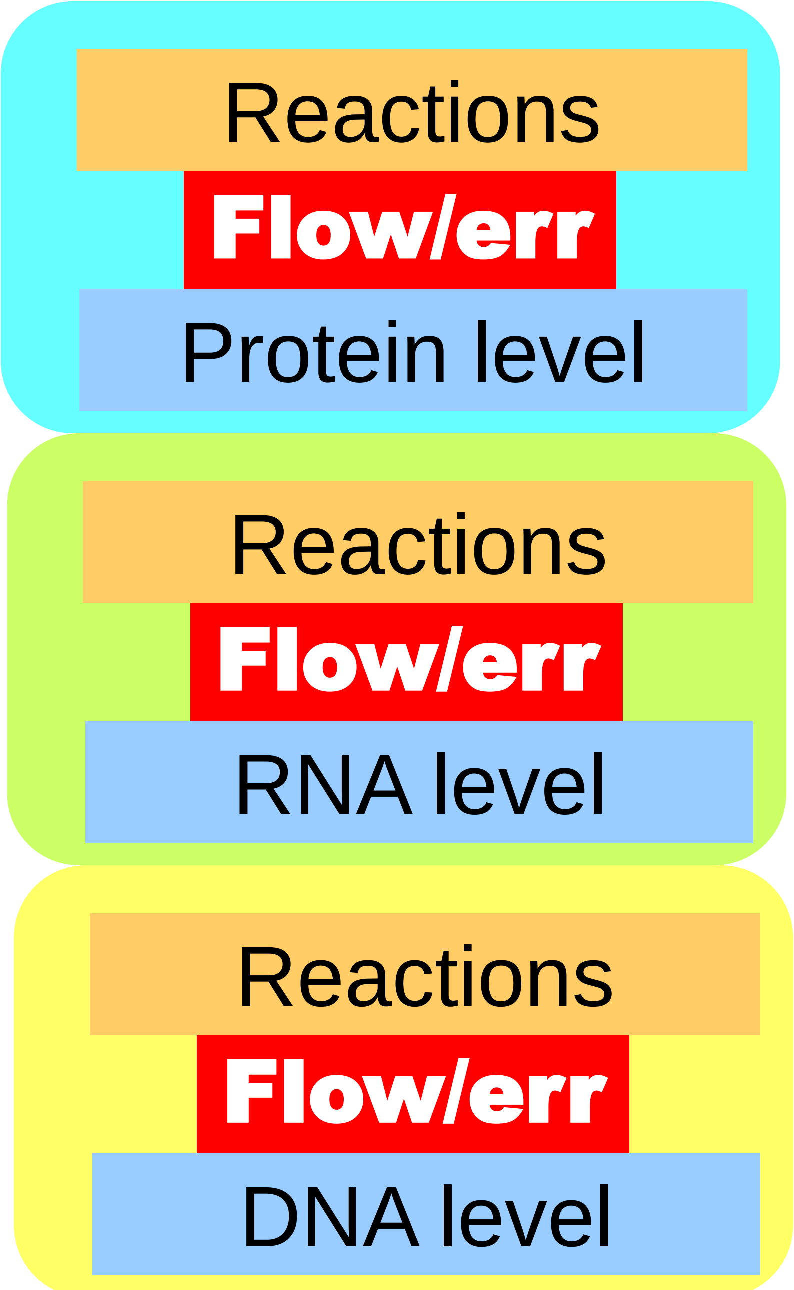


Diverse Reactions
Flow/error
Protein level
Conserved
core
control
Reactions
Translation
RNA level
Transcription
Flow/error
DNA
DNA
DNA
Diverse Genomes

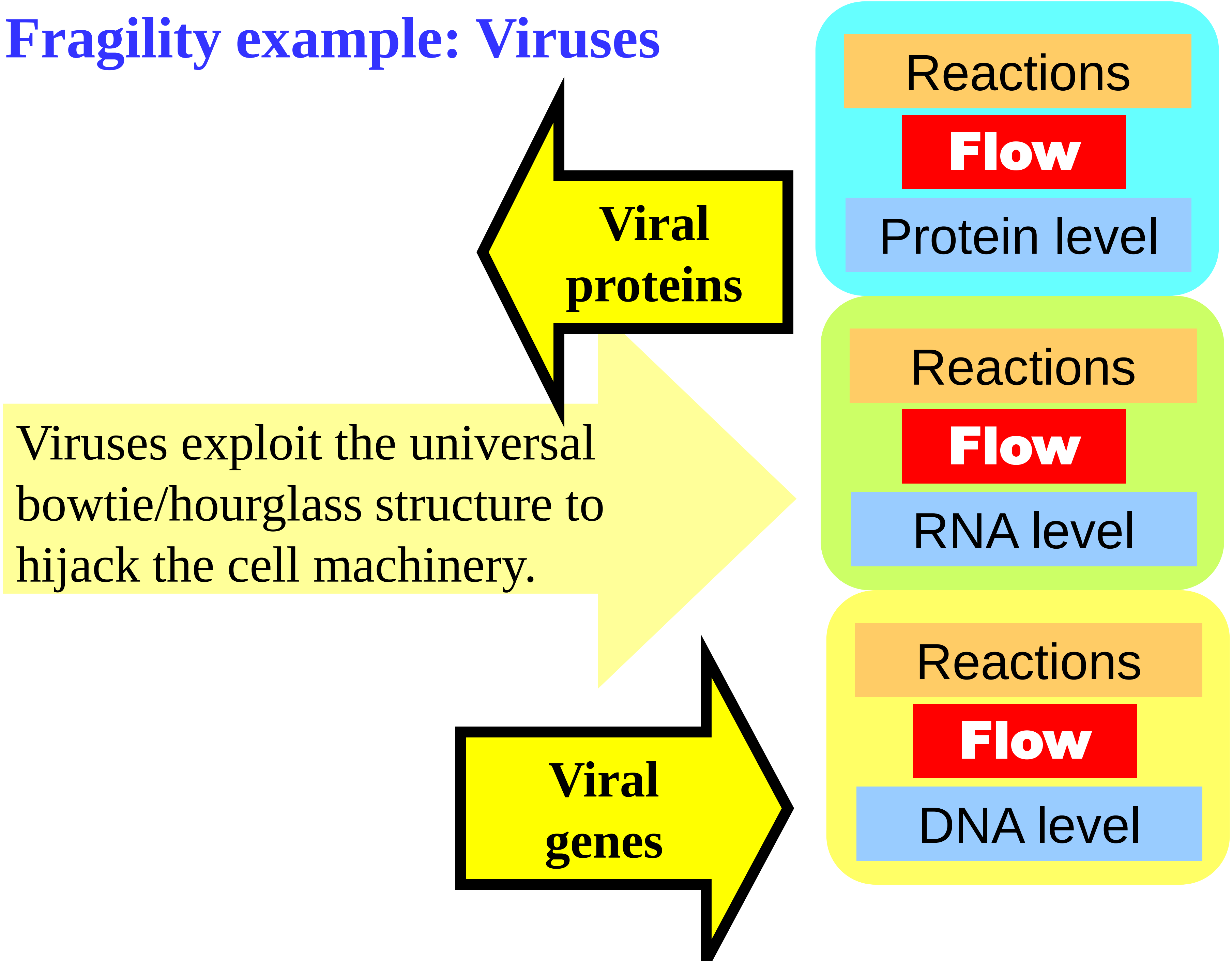
Top to bottom

- 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

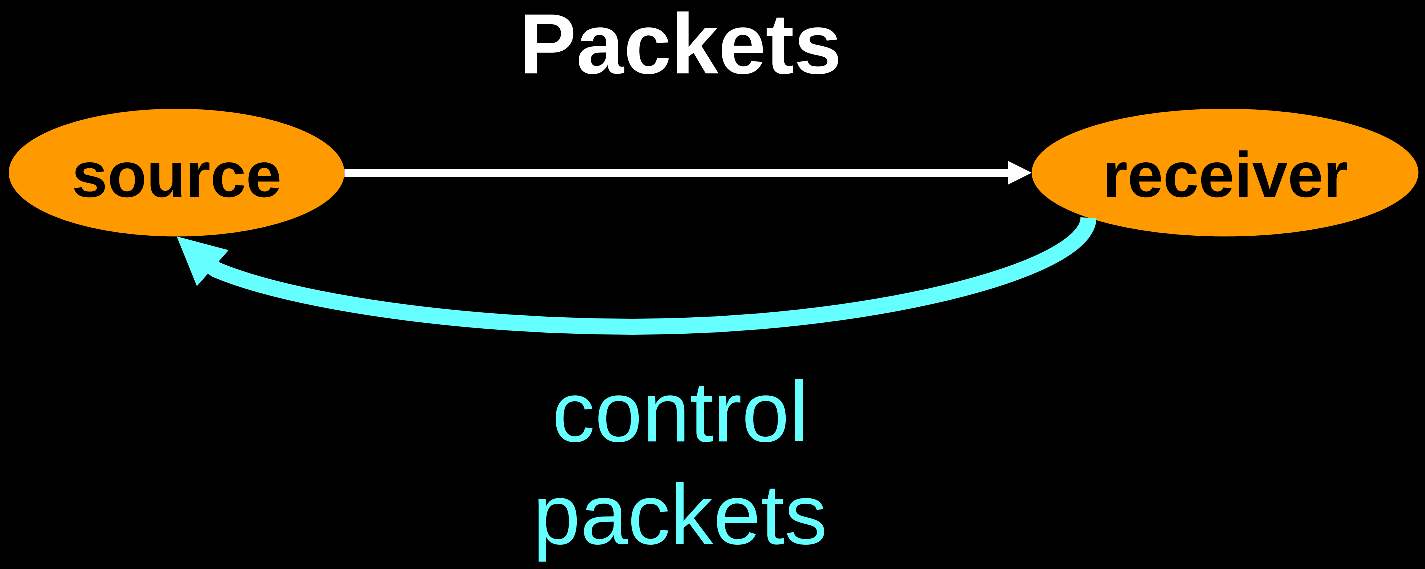
Similarities

- 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

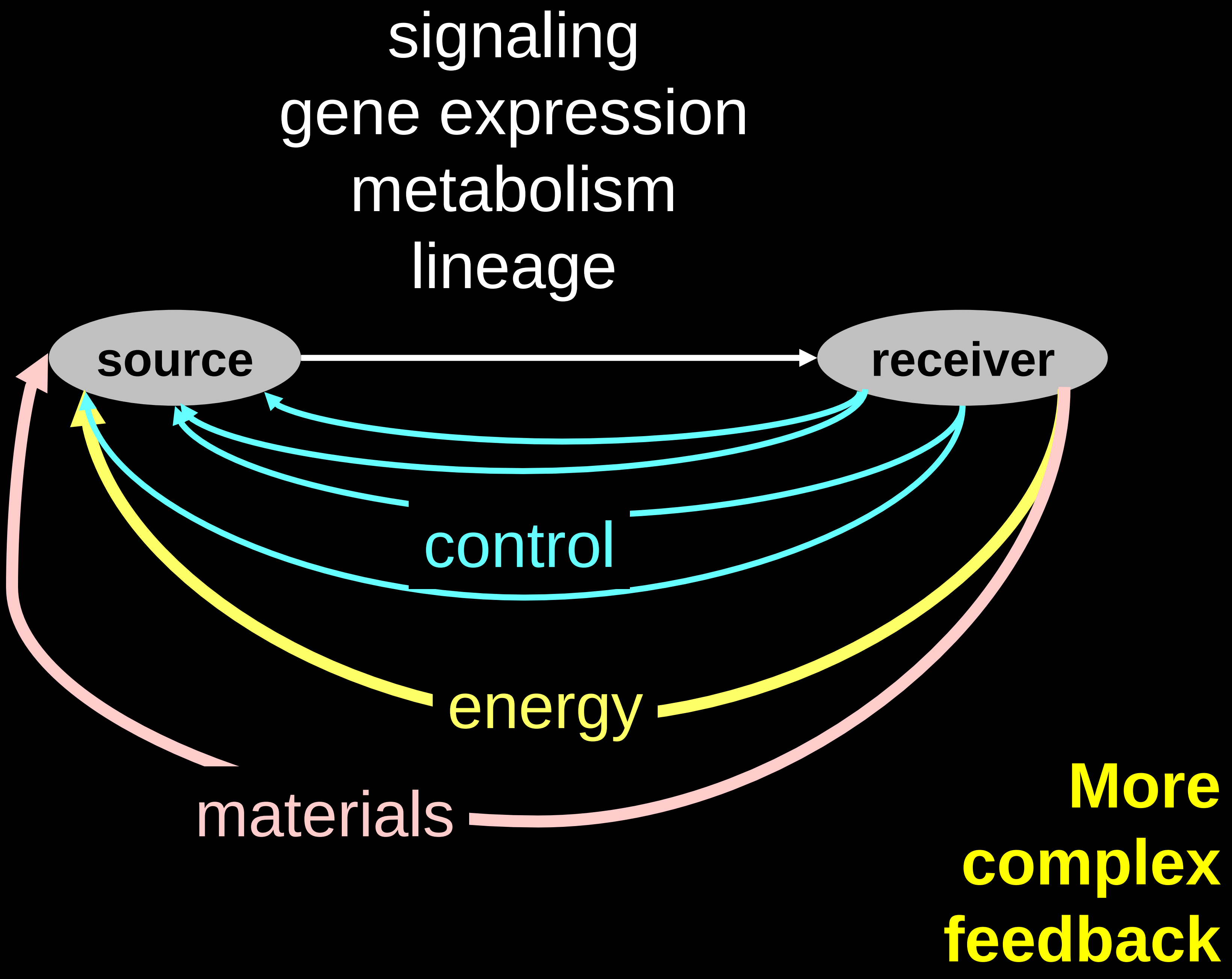
- Metabolism
- Materials and energy
- **Autocatalytic feedback**
- Feedback complexity
- Development and regeneration
- >4B years of evolution

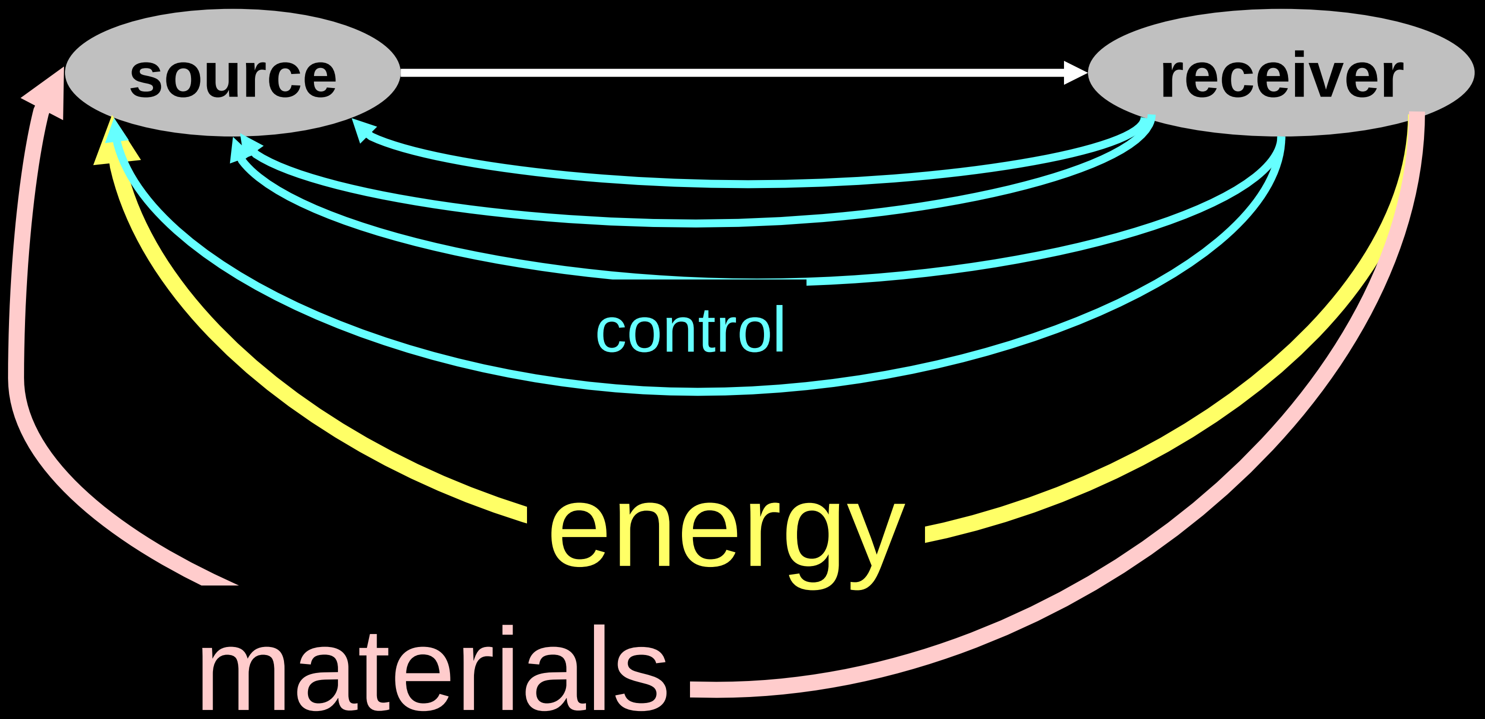
Control of the Internet



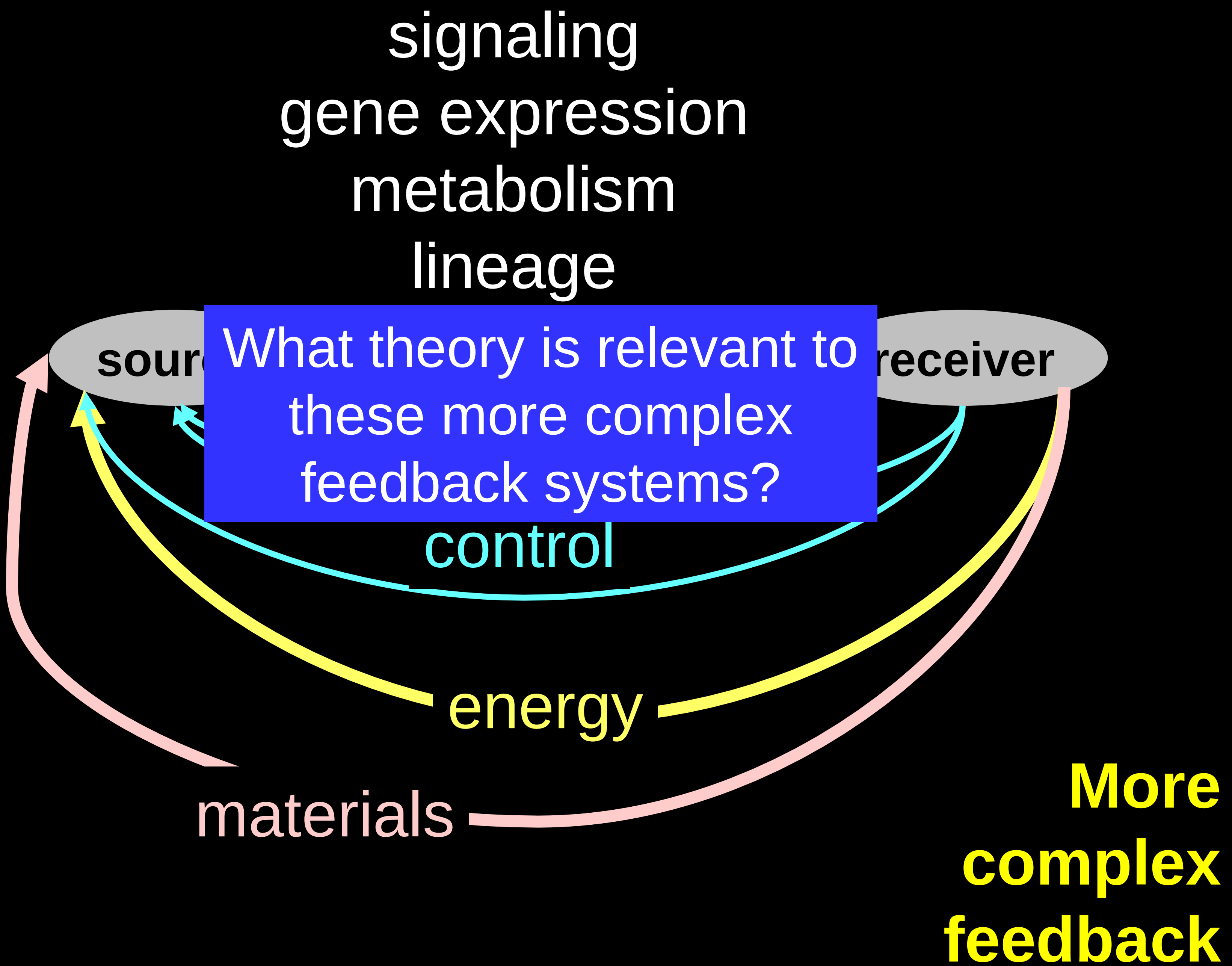
signaling
gene expression
metabolism
lineage

Biological pathways


signaling
gene expression
metabolism
lineage
source
receiver
control
energy
materials
More
complex
feedback



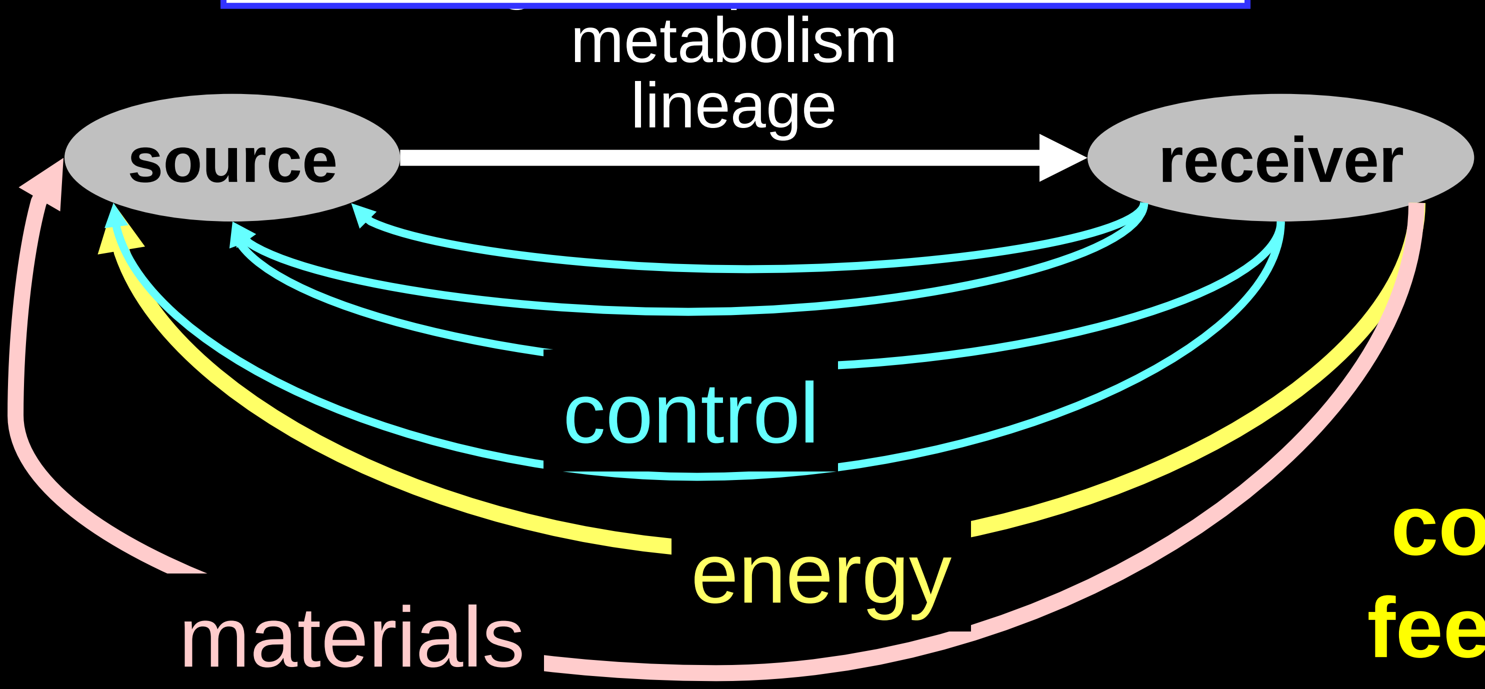
Autocatalytic feedback



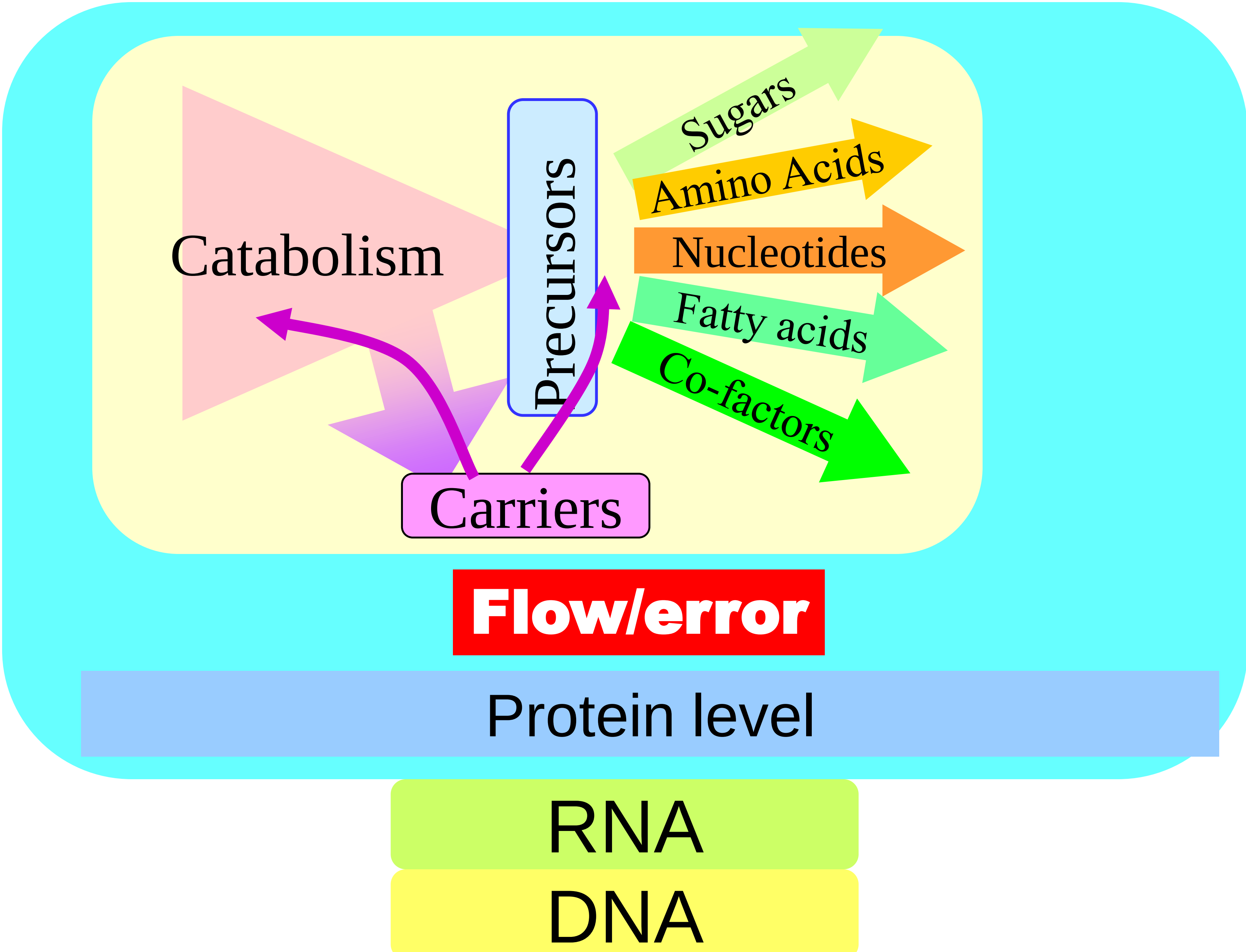
signaling
gene expression
metabolism
lineage
sour
receiver
What theory is relevant to these more complex feedback systems?
control
energy
materials
More complex feedback

What theory is relevant to these more complex feedback systems?

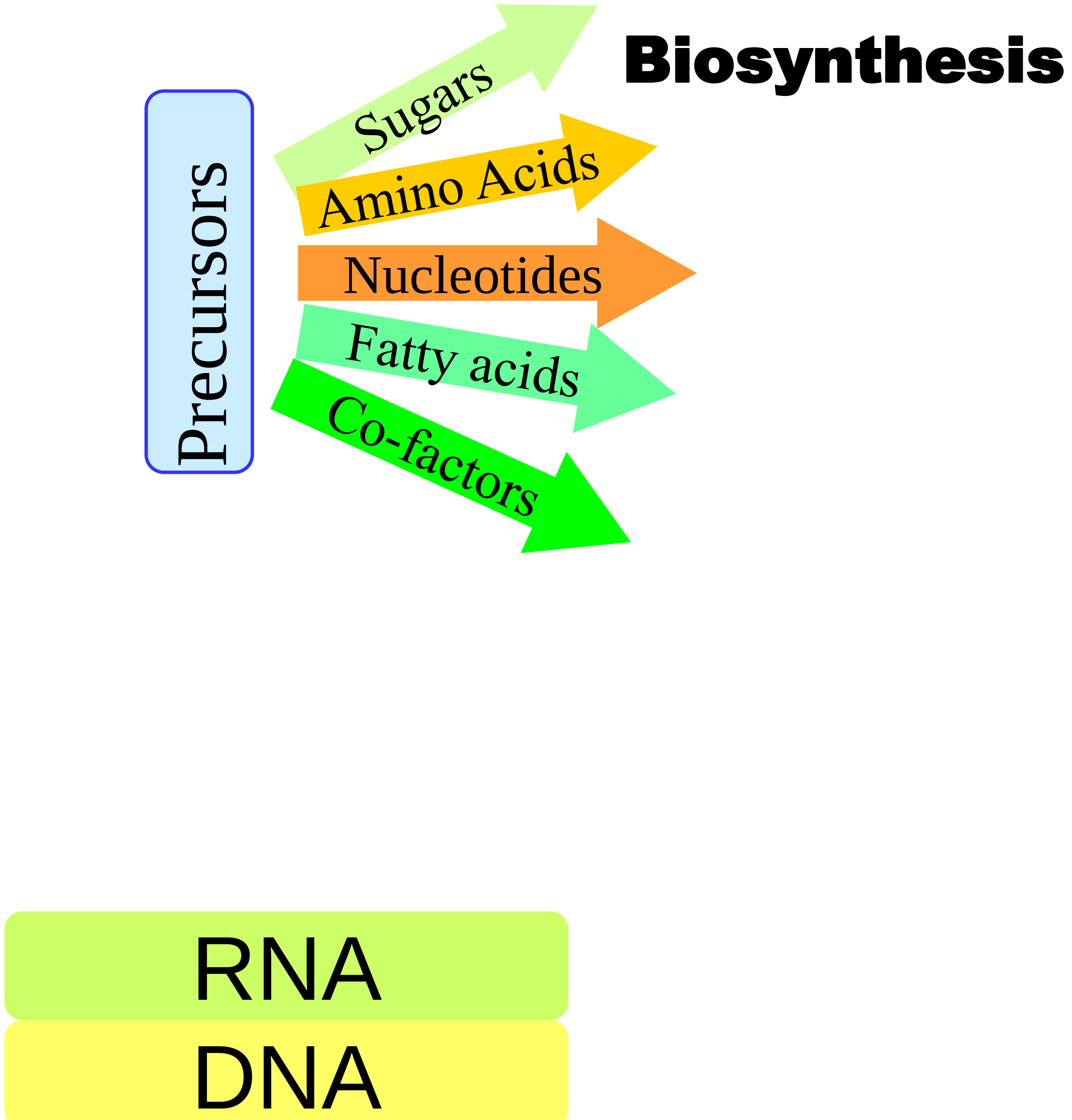
$$\frac{1}{\pi}\int_0^\infty \ln\left|S \quad j\omega \right|\frac{z}{z^2+\omega^2}d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

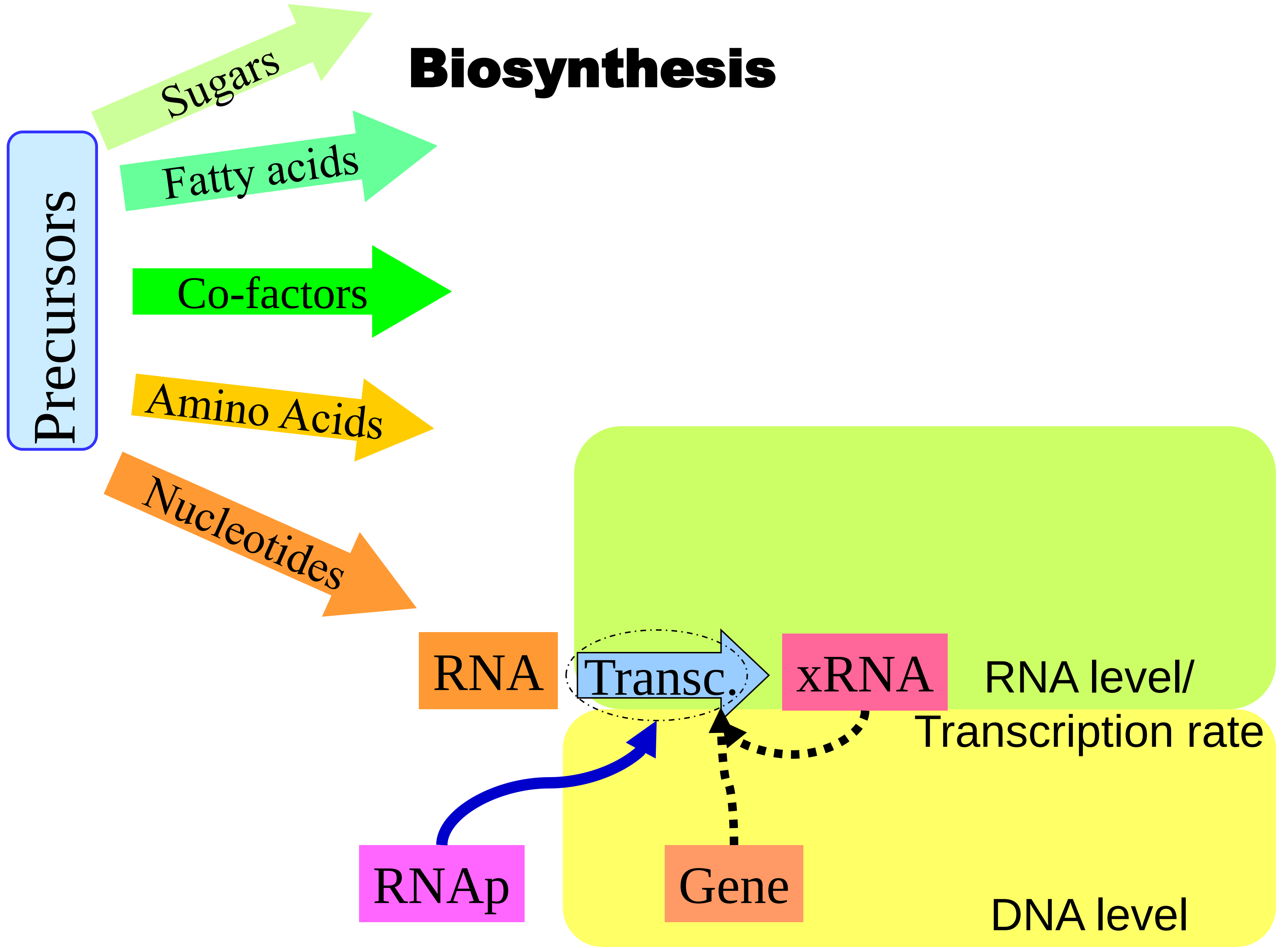


More complex feedback

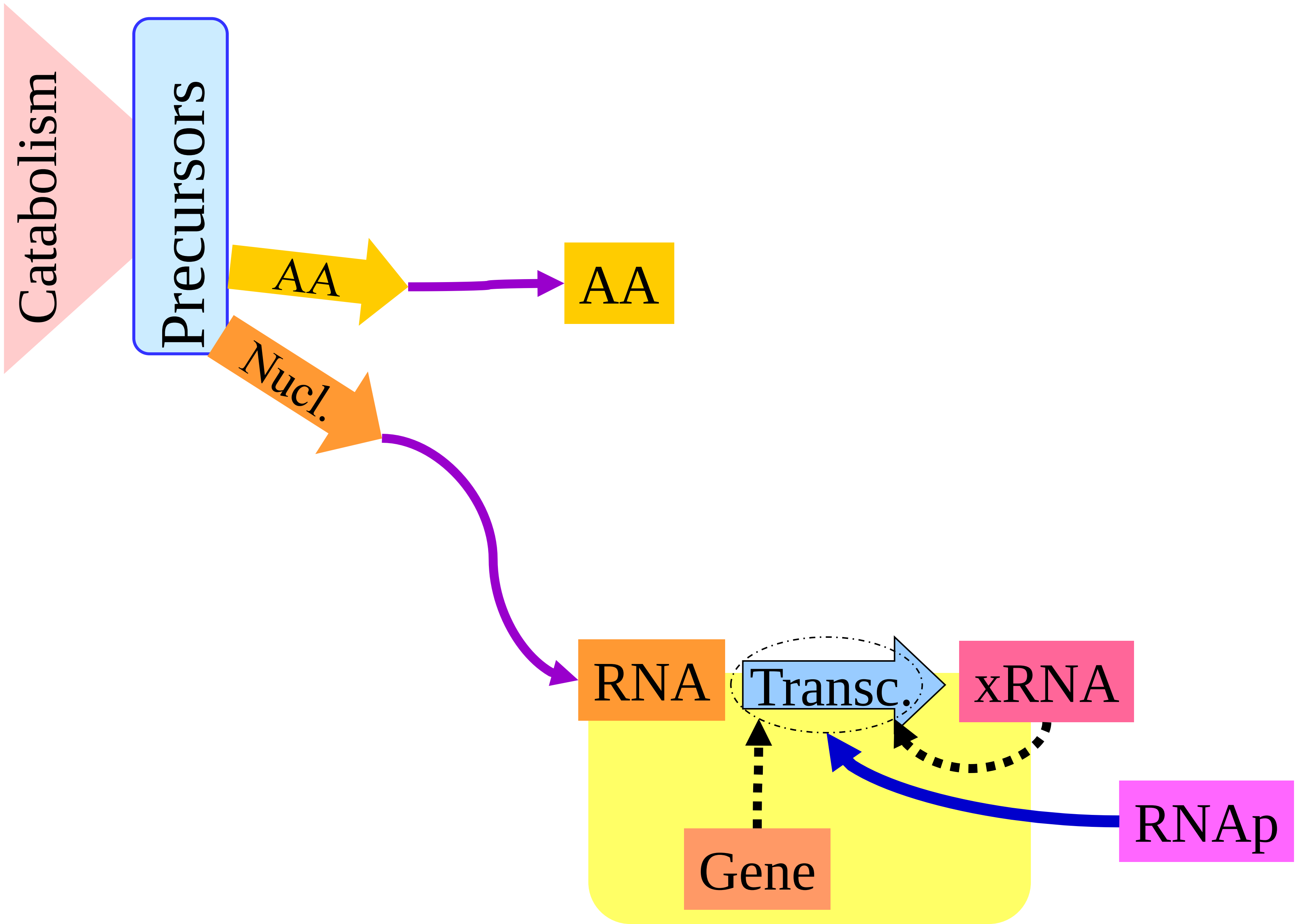


Catabolism
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Carriers
Flow/error
Protein level
RNA
DNA

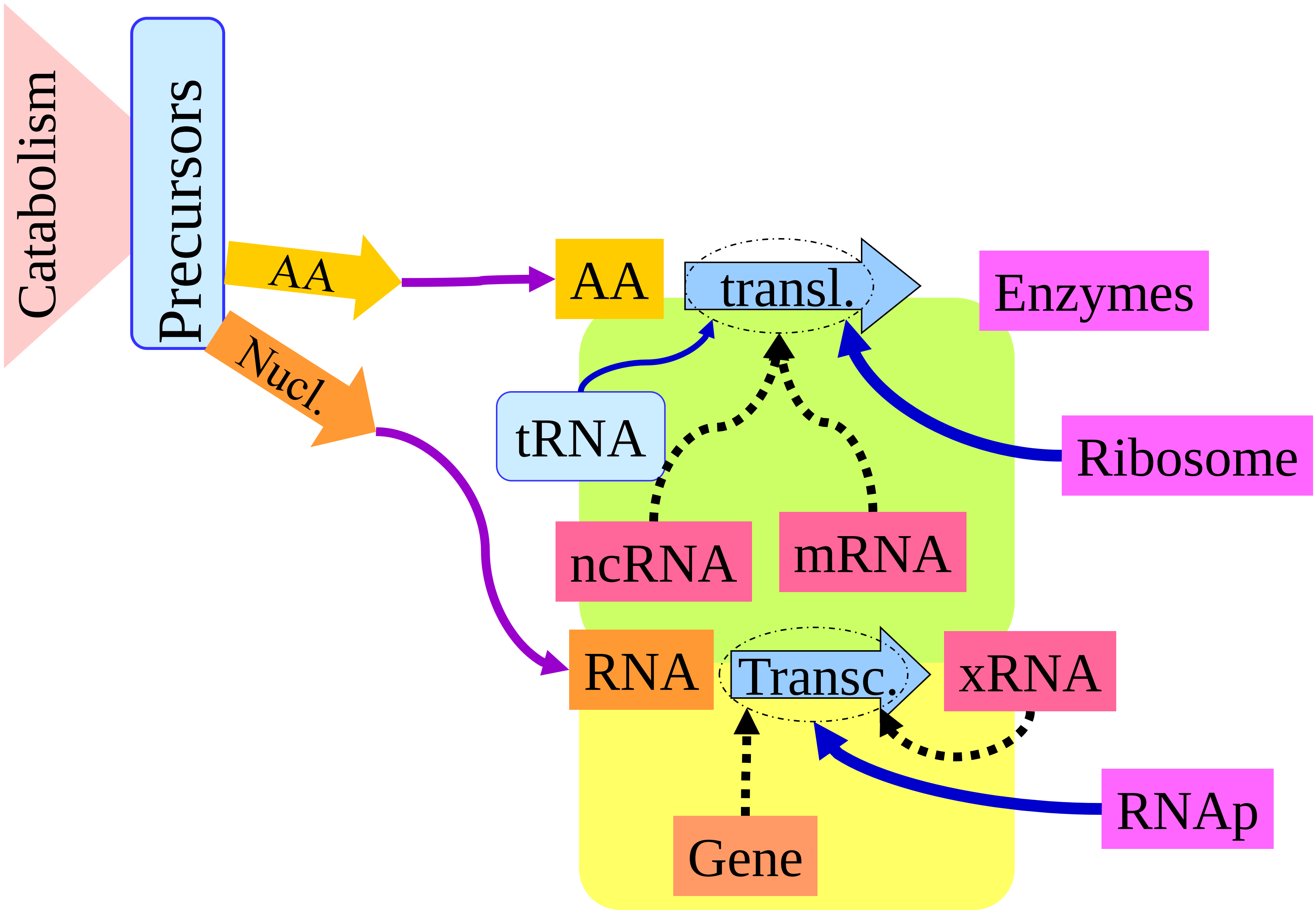

Biosynthesis
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
RNA
DNA



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

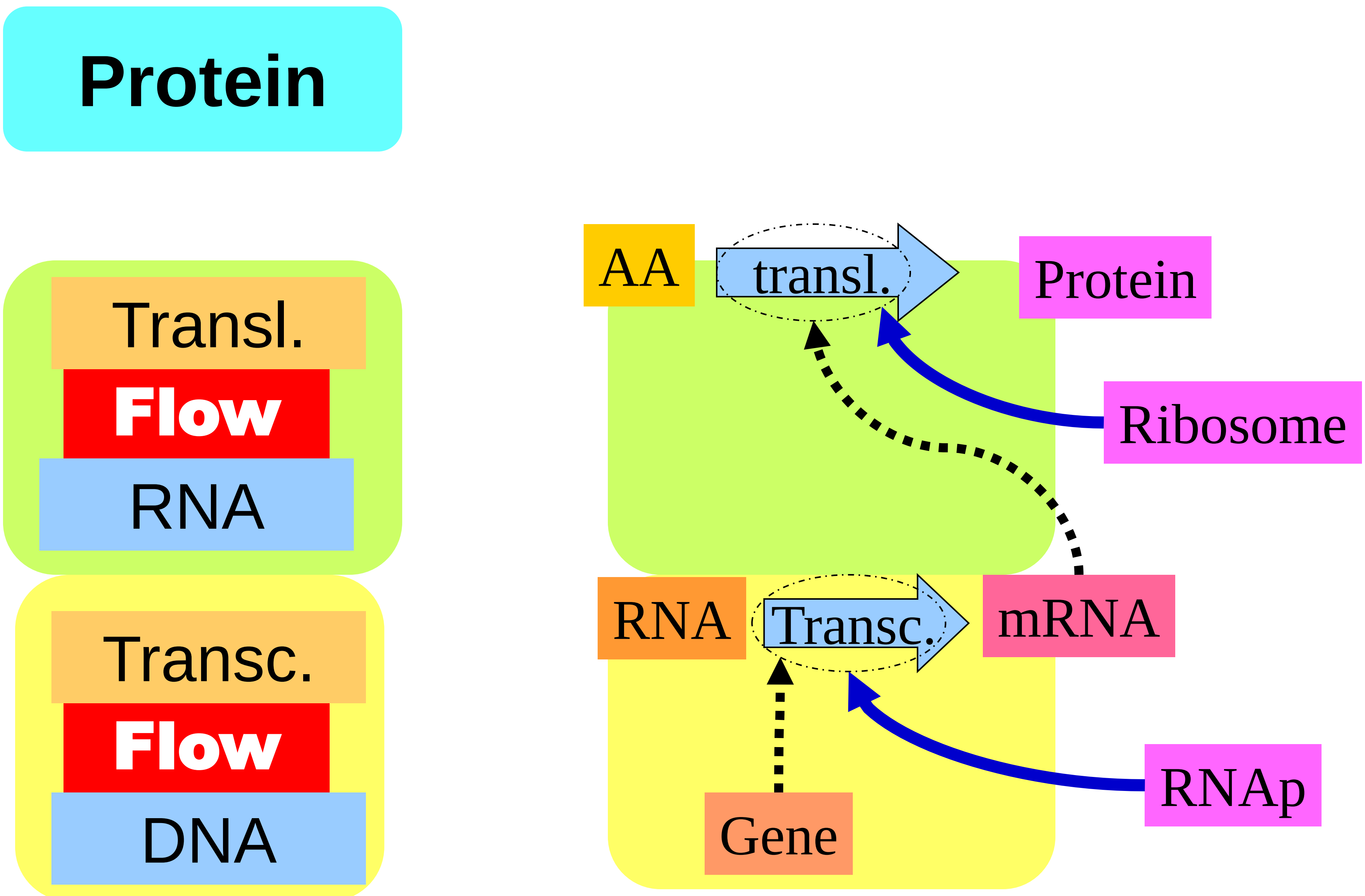


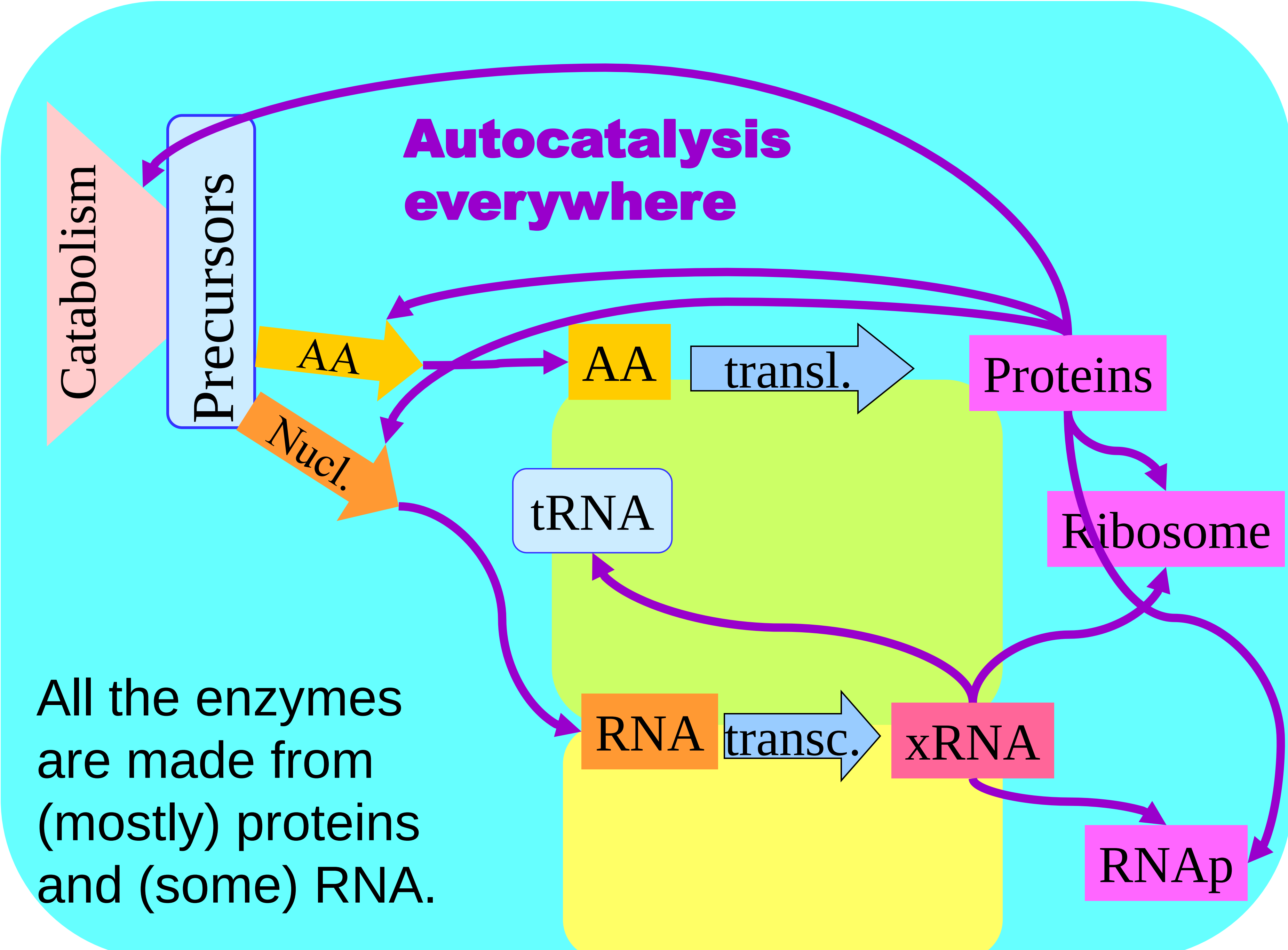
Catabolism
Precursors
AA
AA
Nucl.
RNA
Transc.
xRNA
Gene
RNAp



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

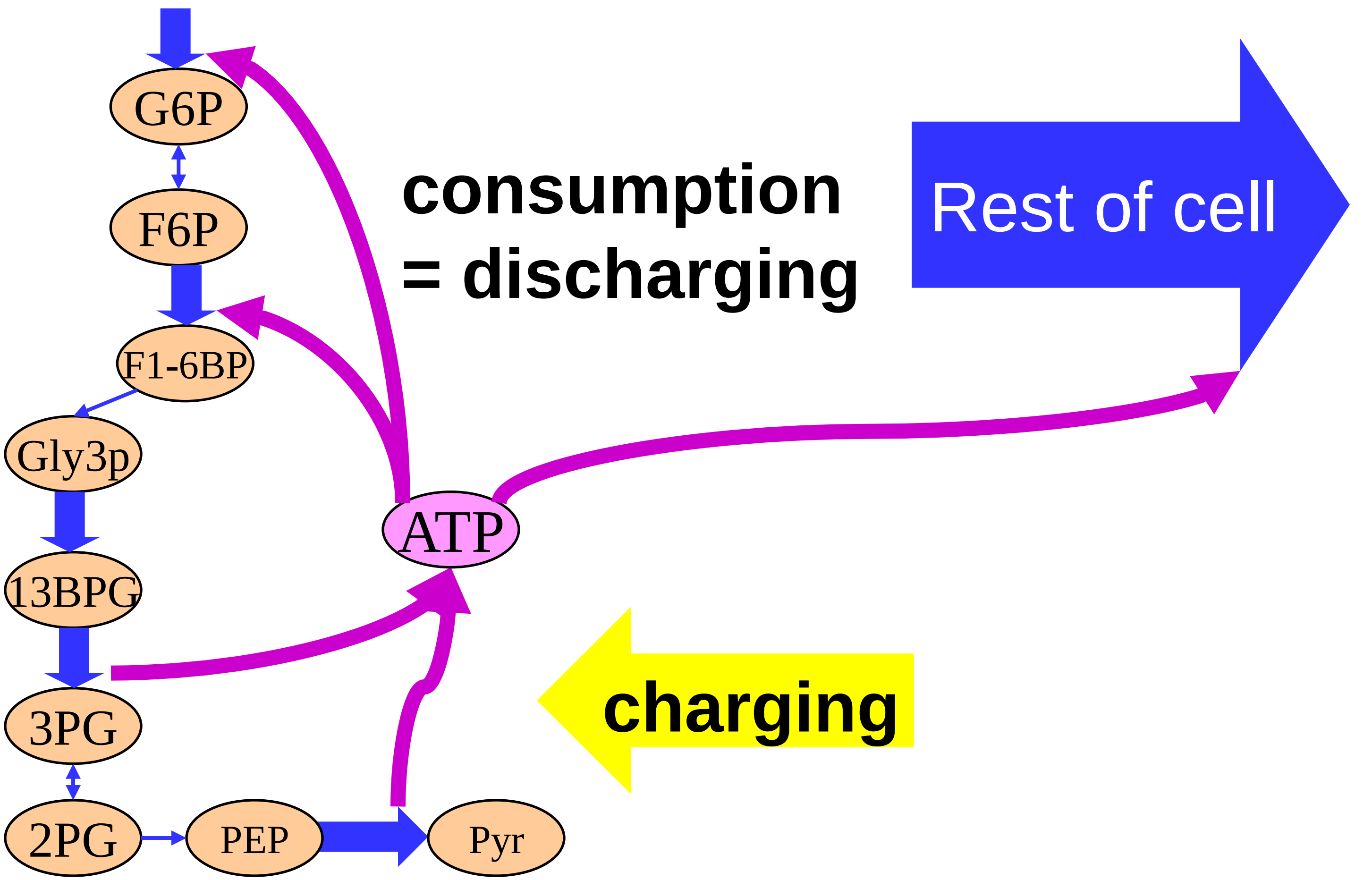
“Central dogma”

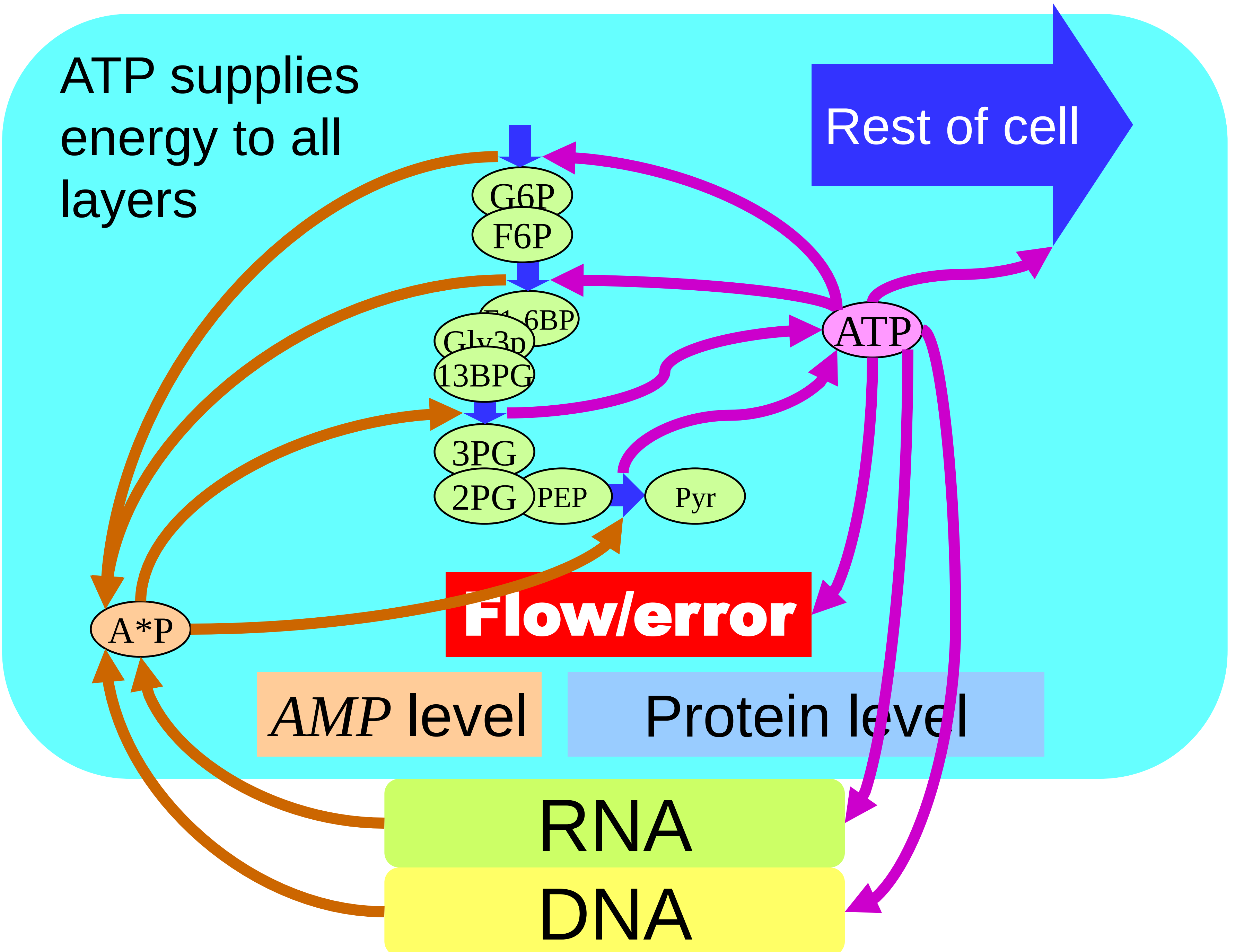




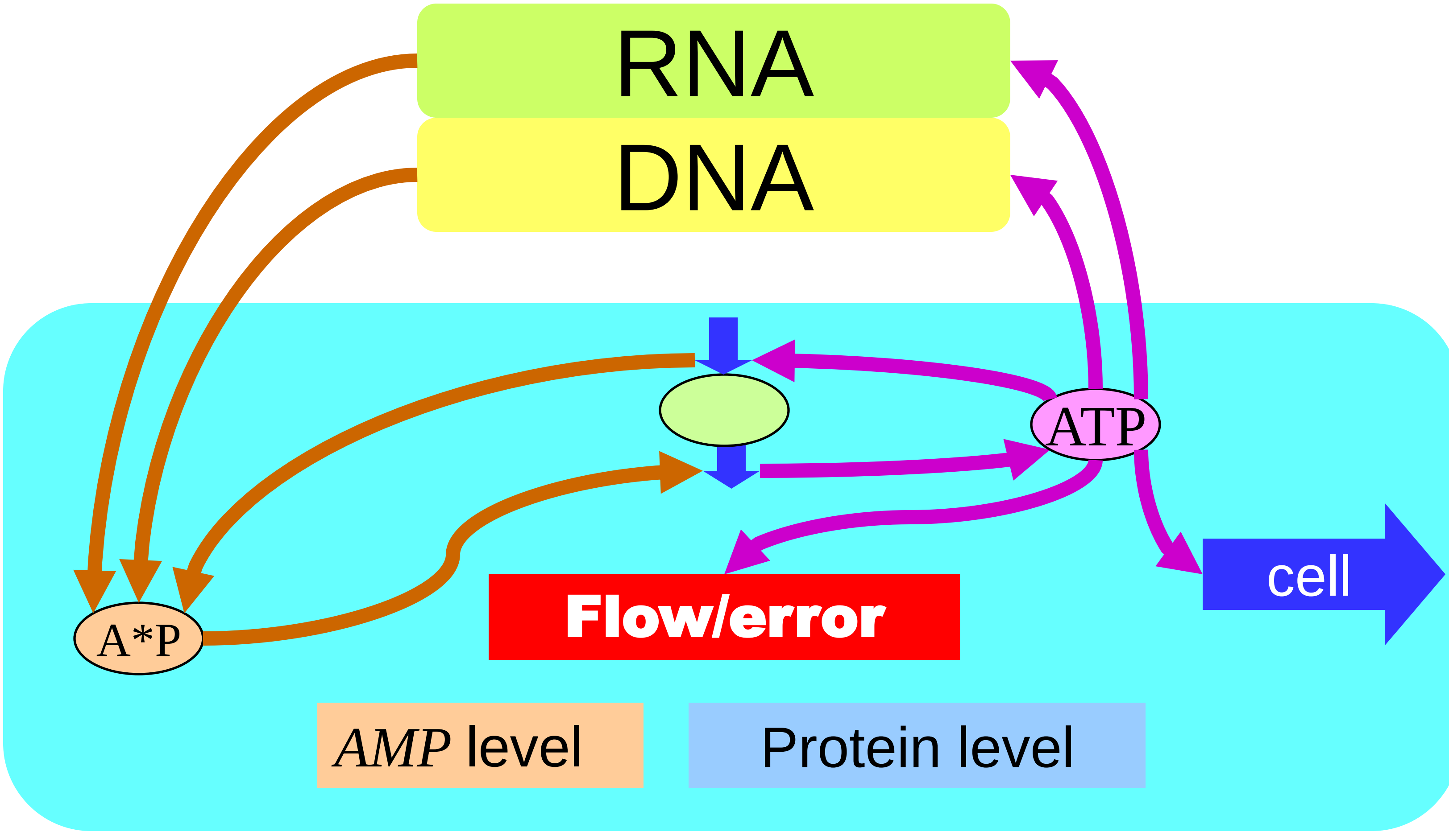
Autocatalysis
everywhere
Catabolism
Precursors
AA
Nucl.
AA
transl.
Proteins
tRNA
Ribosome
RNA
transc.
xRNA
RNAp
All the enzymes
are made from
(mostly) proteins
and (some) RNA.

This is just charging and discharging





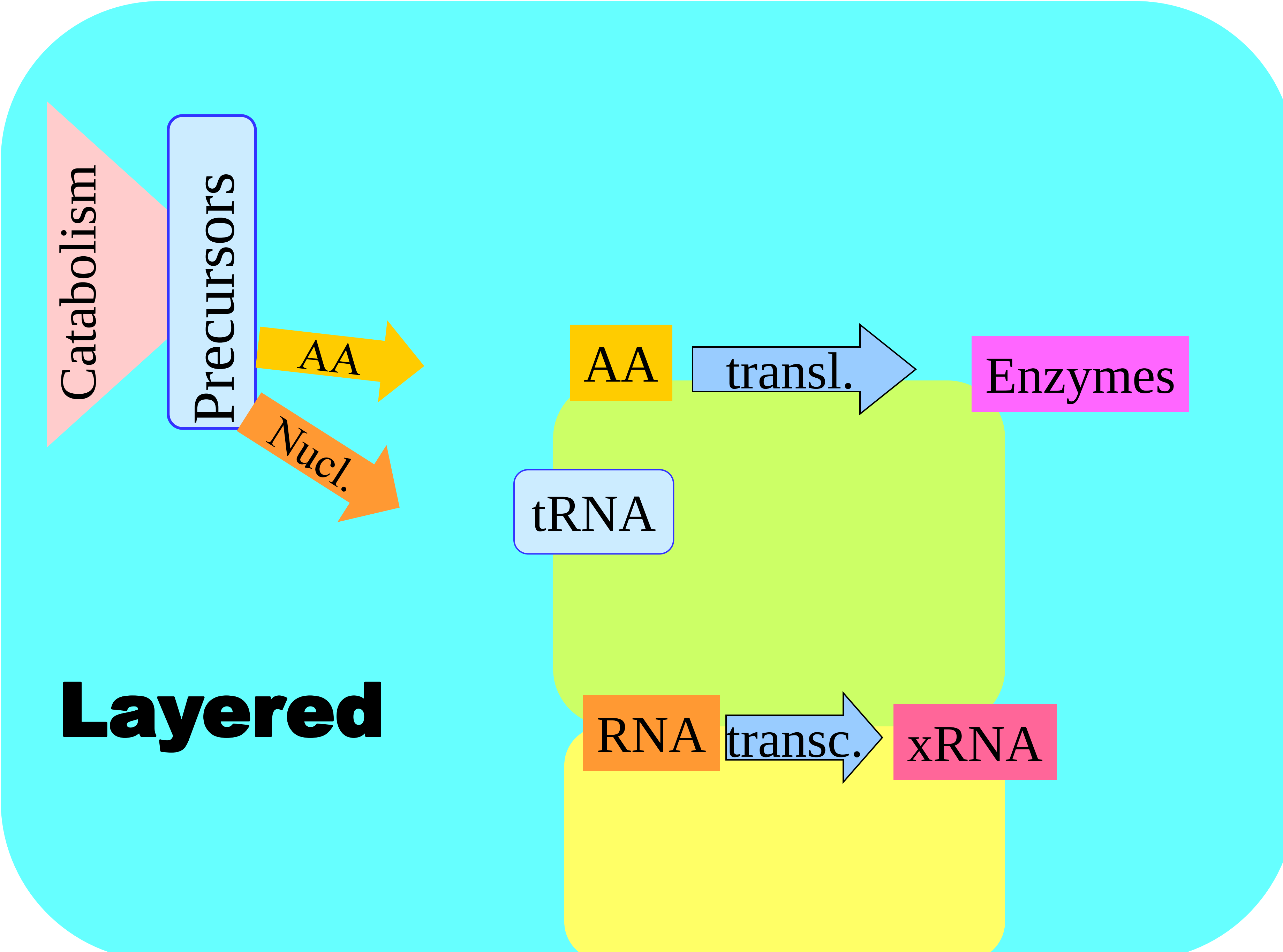
ATP supplies energy to all layers
Rest of cell
G6P
F6P
F1,6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ATP
A*P
Flow/error
AMP level
Protein level
RNA
DNA

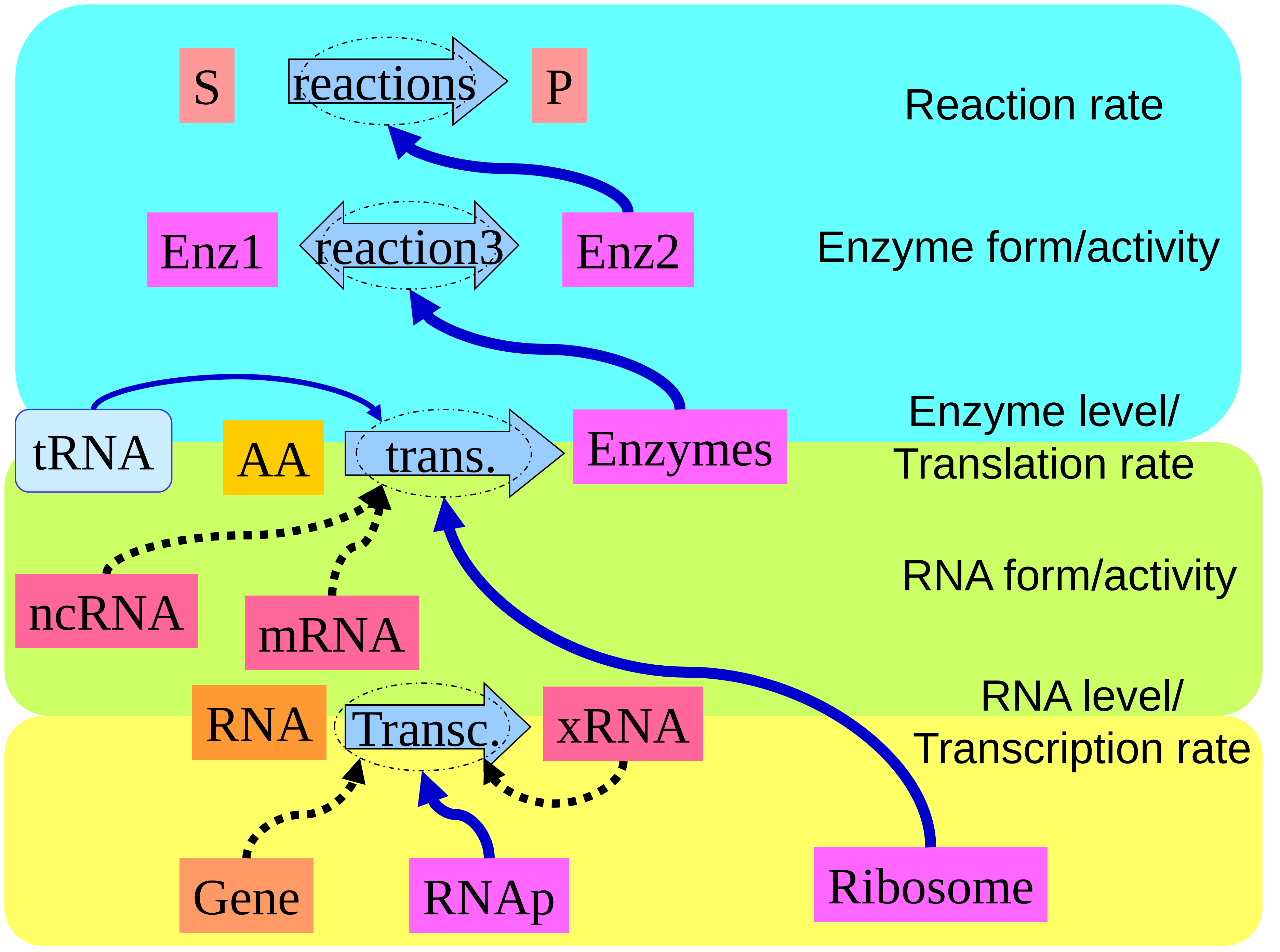


Lots of
ways to
draw this.

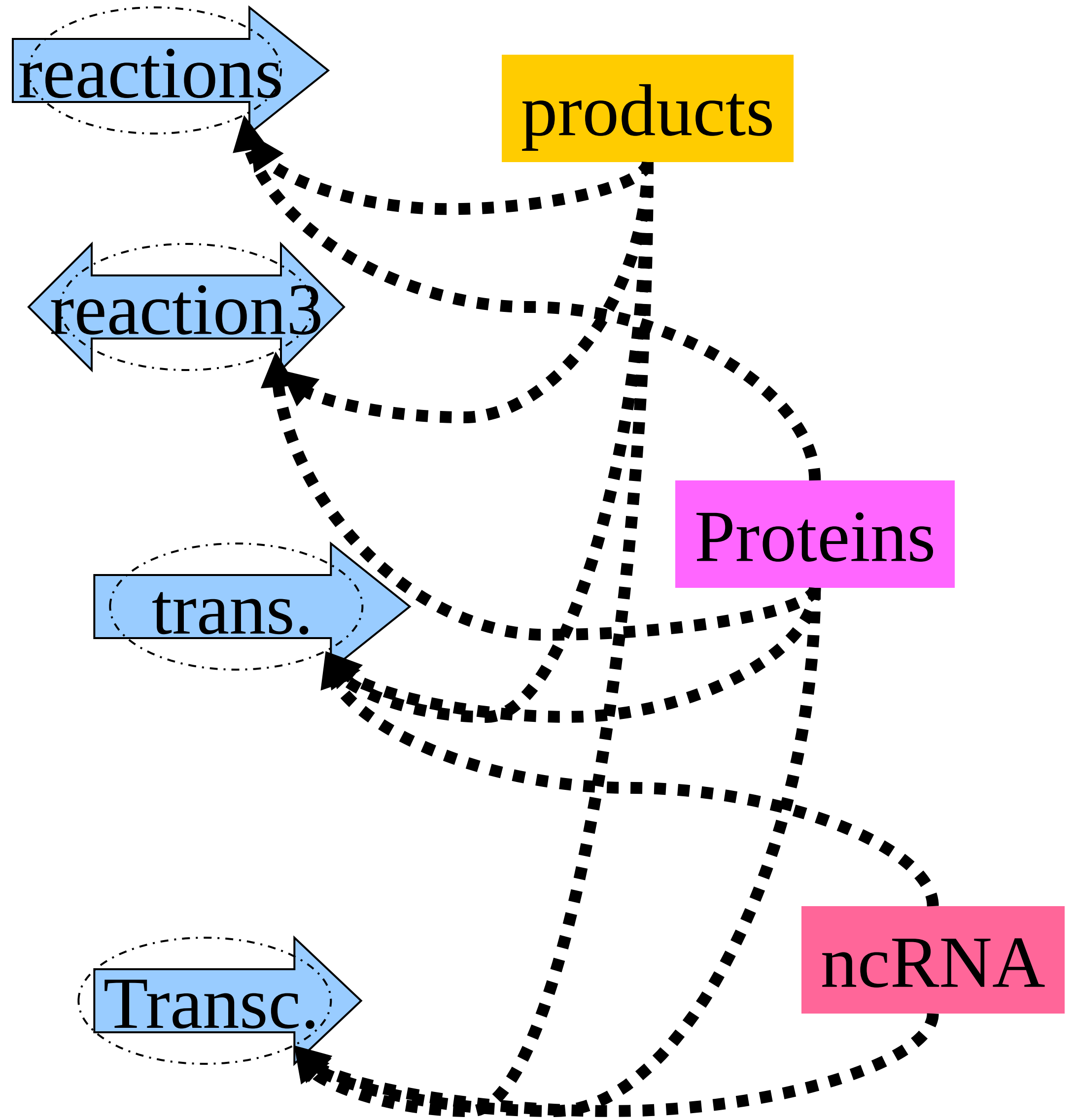
RNA

DNA


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

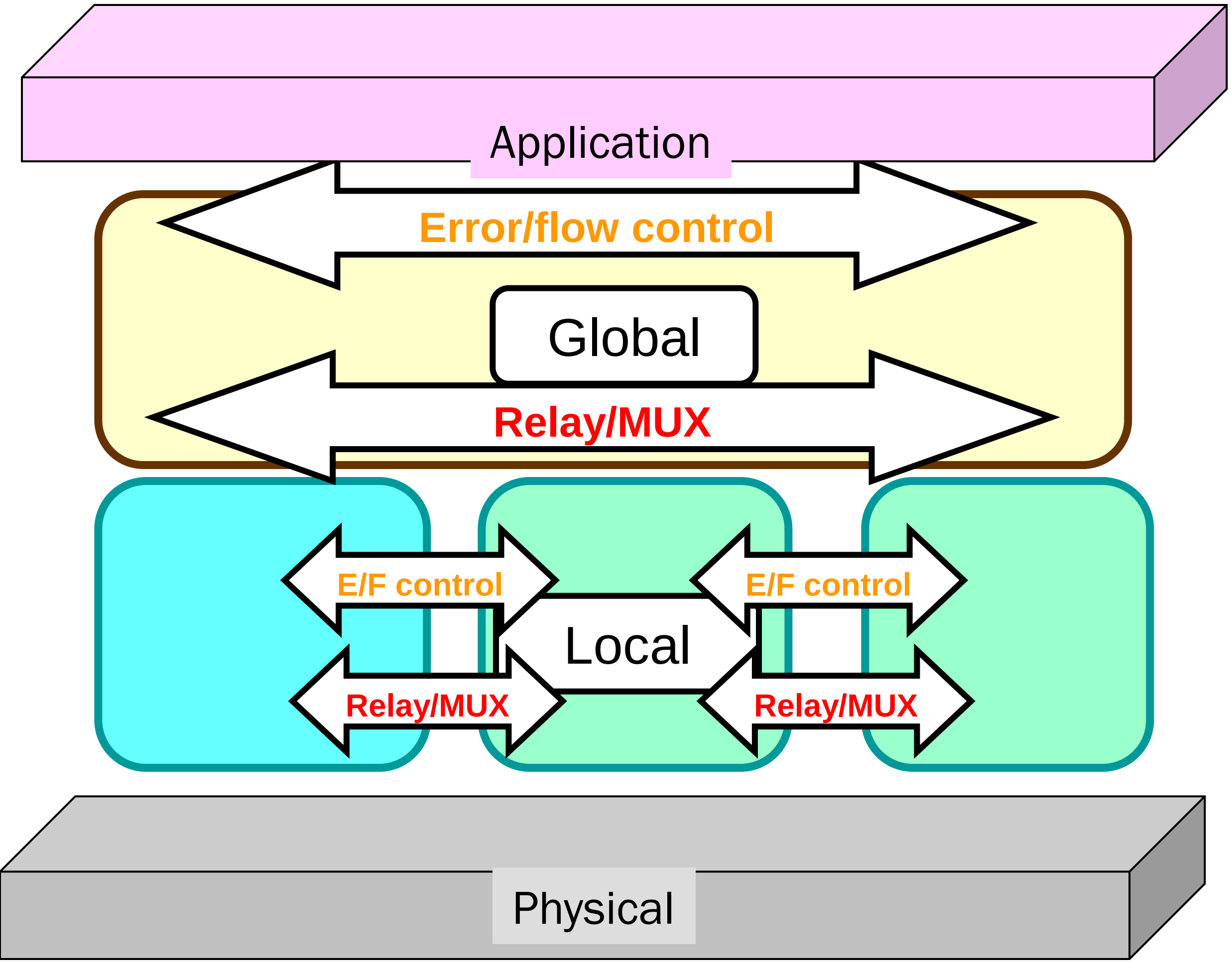

S
reactions
P
Reaction rate
Enz1
reaction3
Enz2
Enzyme form/activity
tRNA
AA
trans.
Enzymes
Enzyme level/
Translation rate
ncRNA
mRNA
RNA form/activity
RNA
Transc.
xRNA
RNA level/
Transcription rate
Gene
RNAp
Ribosome

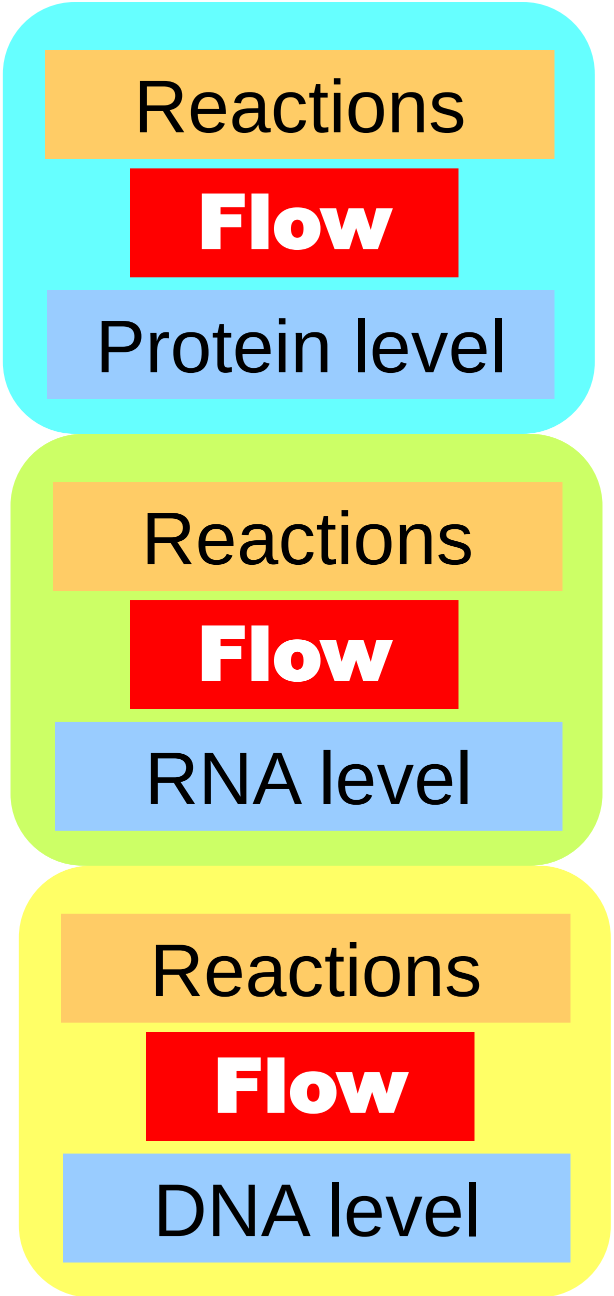
Control?



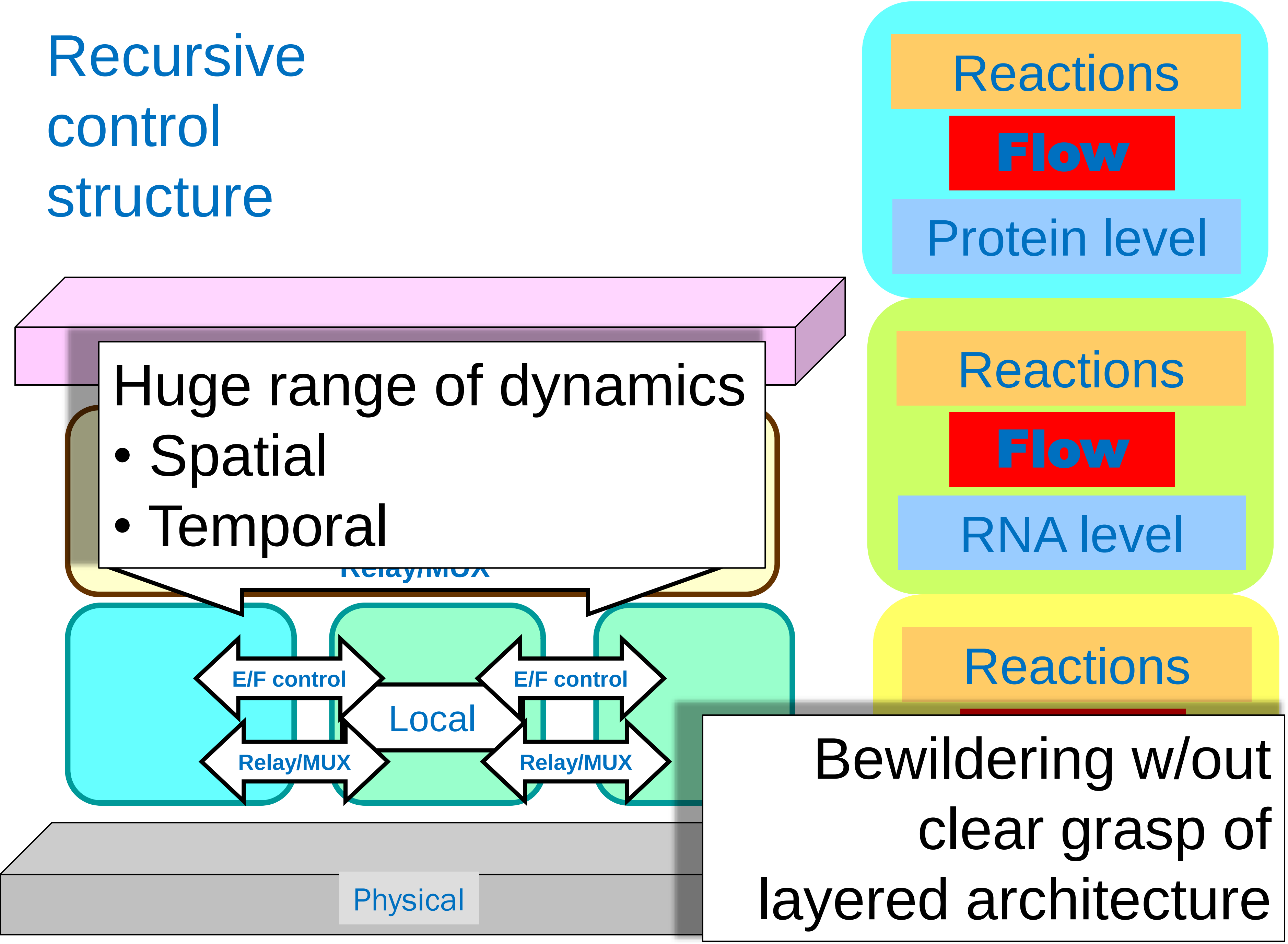
All products
feedback everywhere

Recursive control structure





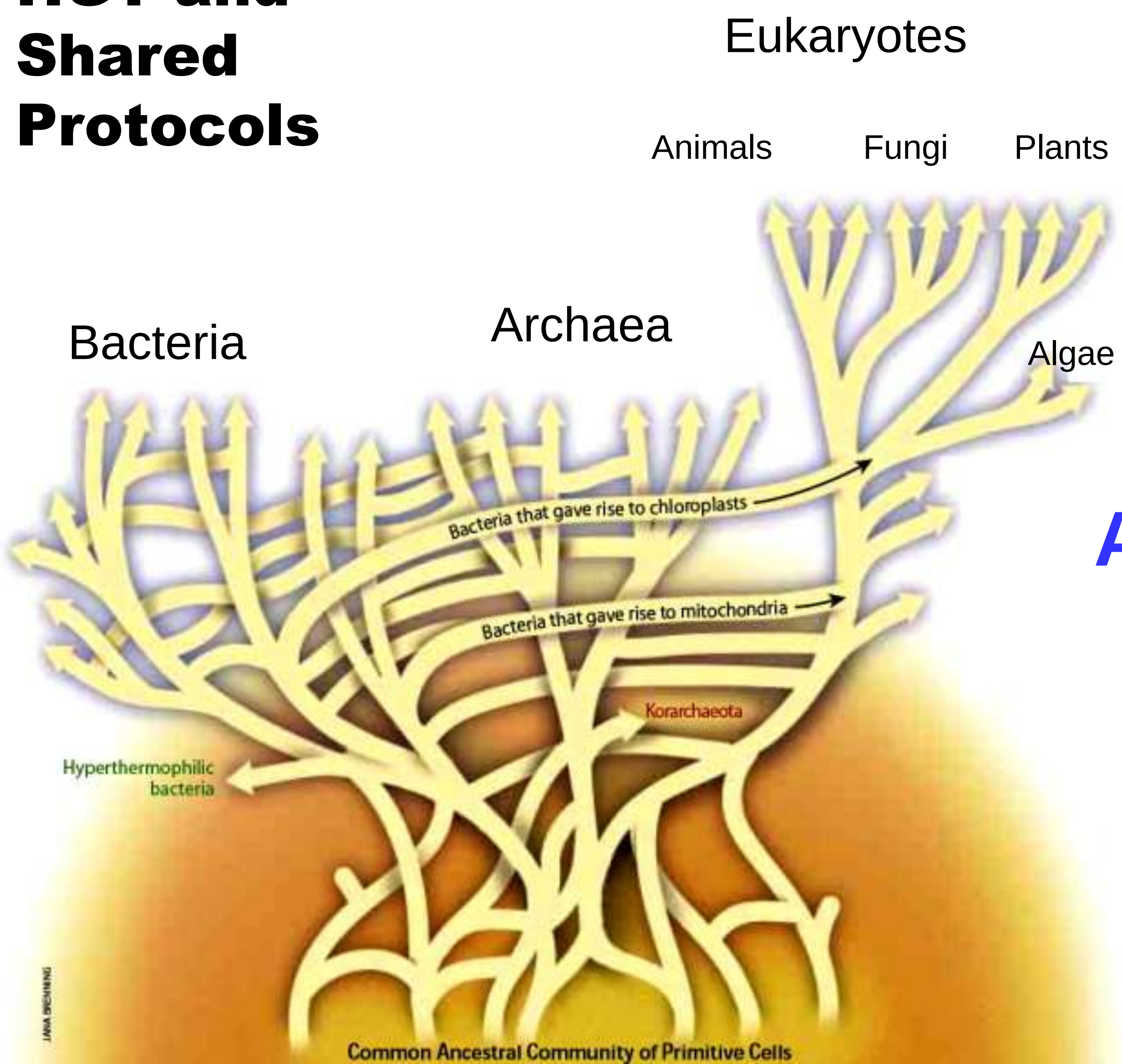
Recursive control structure



Horizontal gene transfer

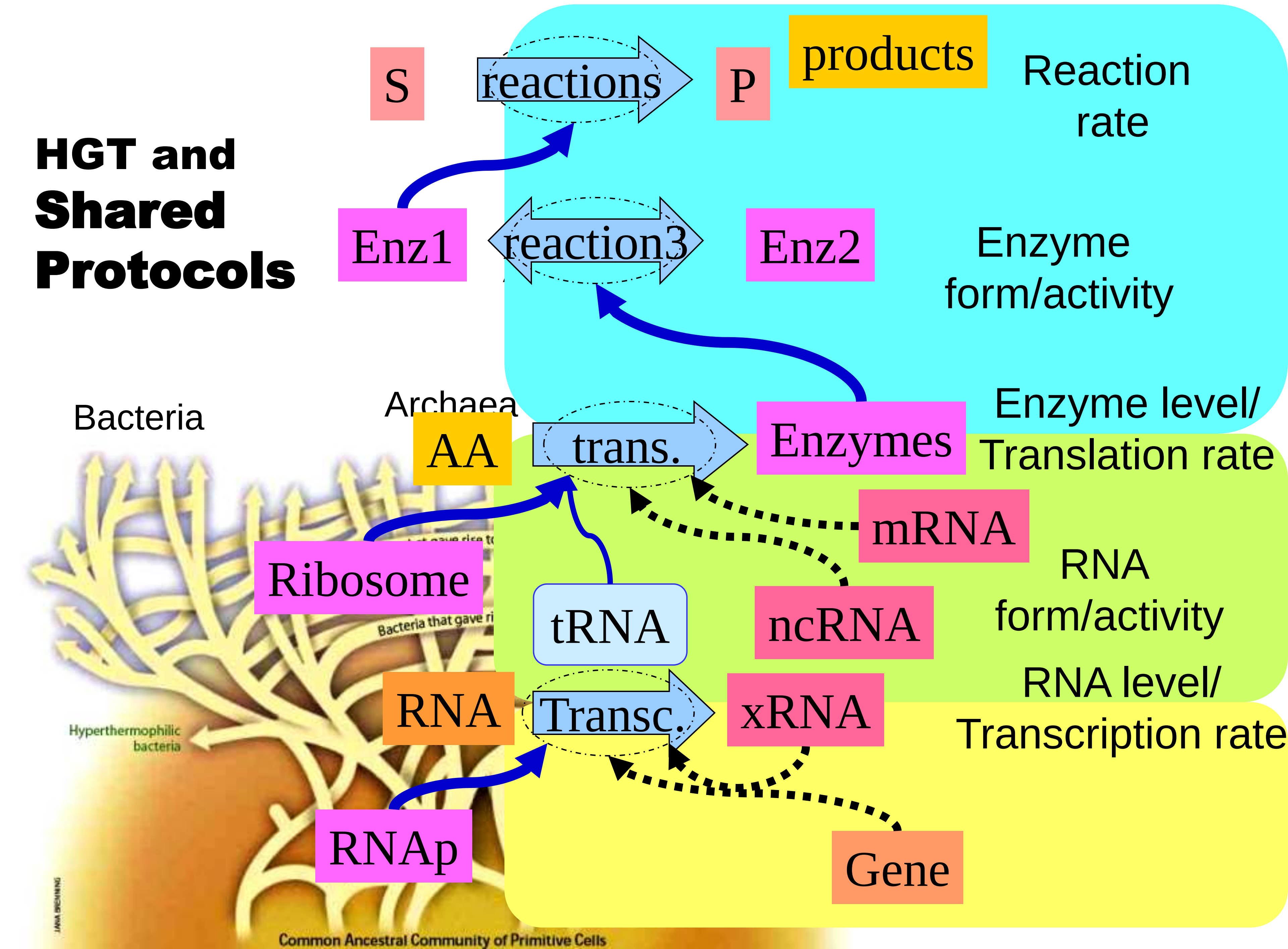
HGT and Shared Protocols

What is locus of early evolution?



Architecture!?!

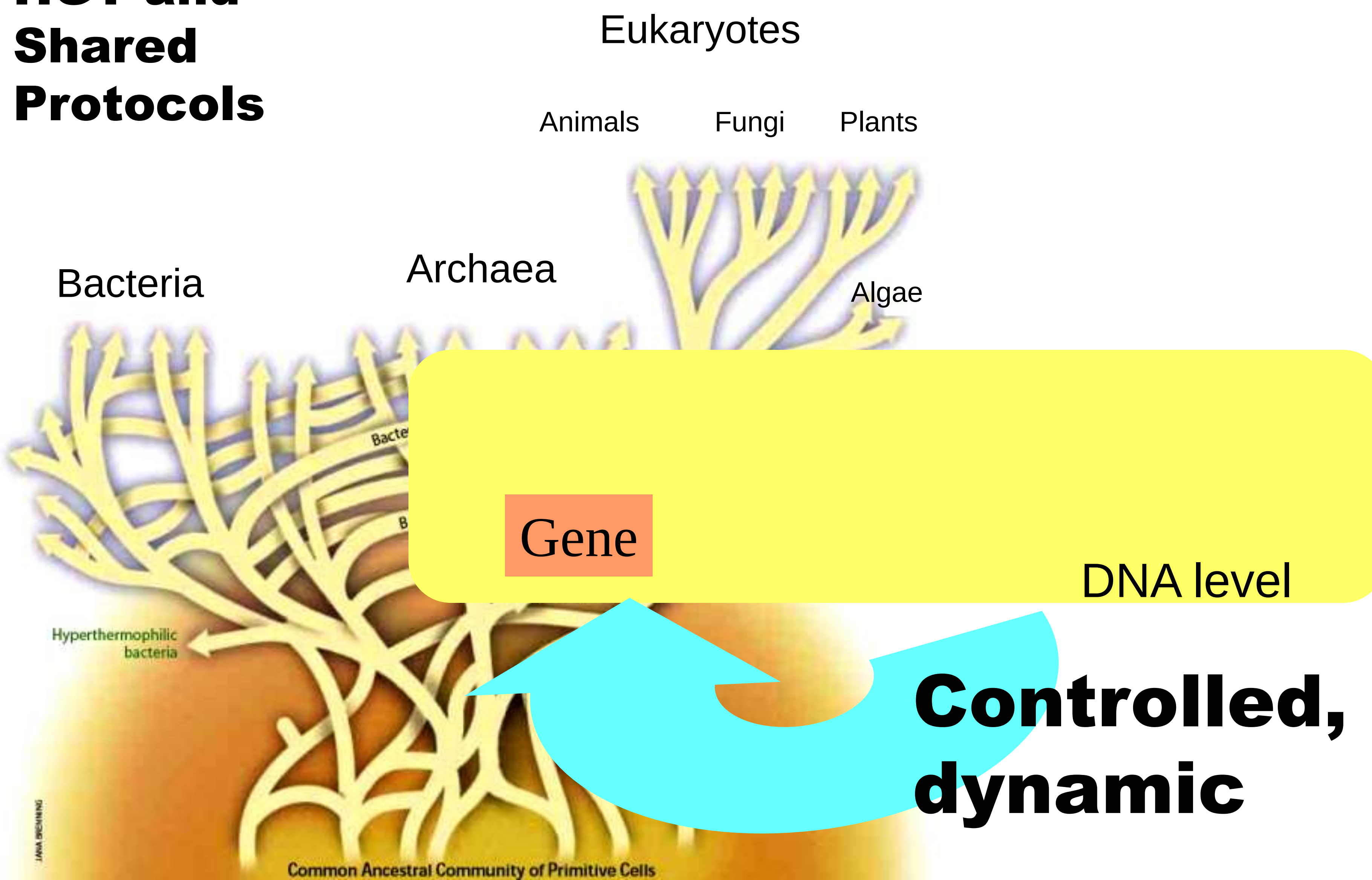
HGT and Shared Protocols

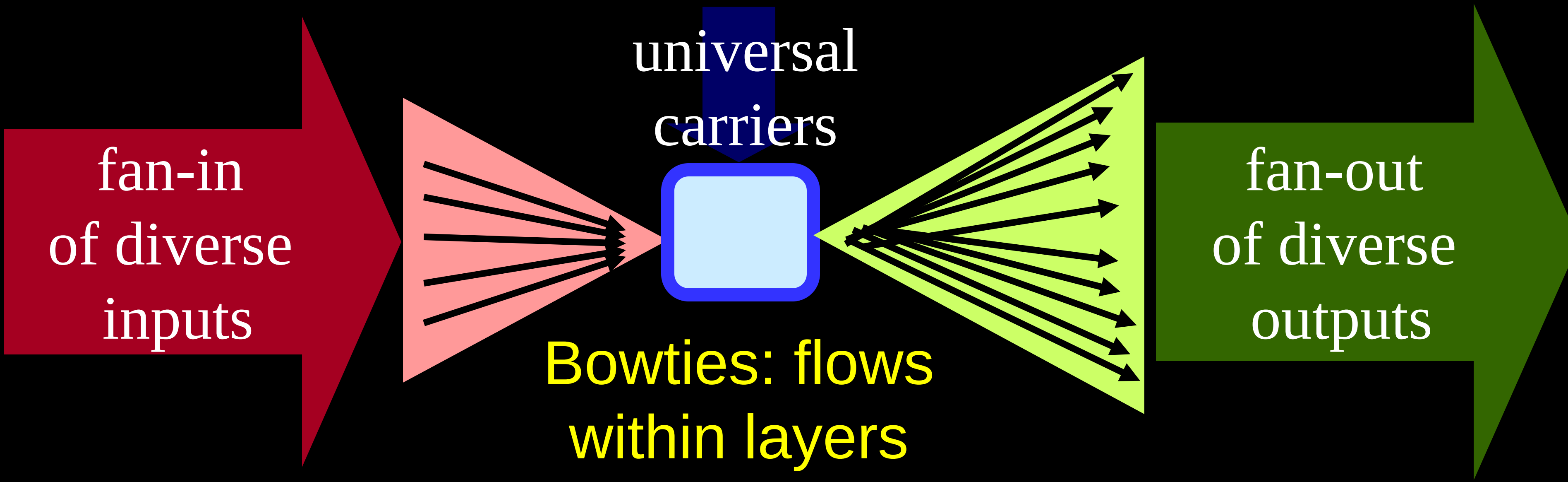


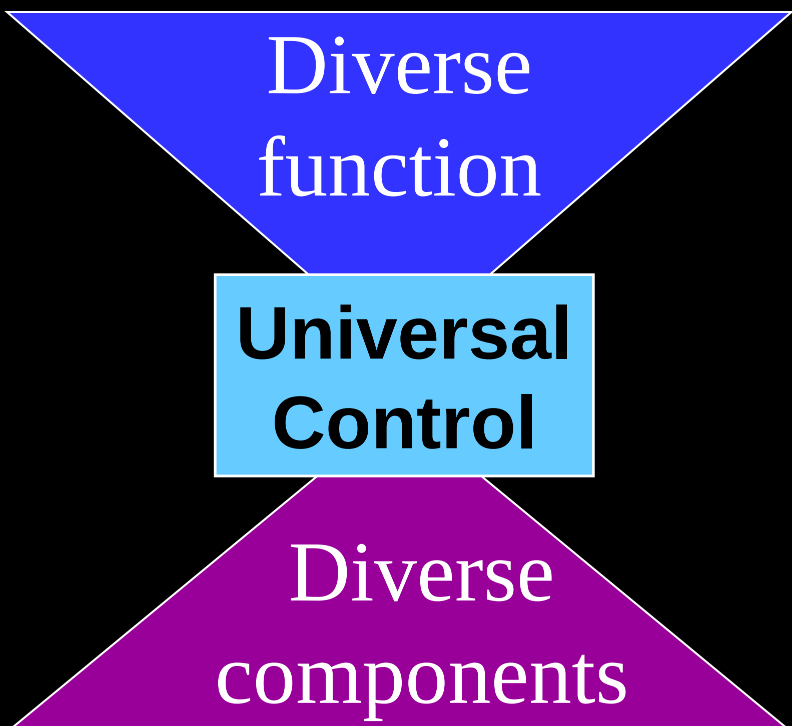
Horizontal gene transfer

- Not a static database
- Not only point mutations

HGT and Shared Protocols



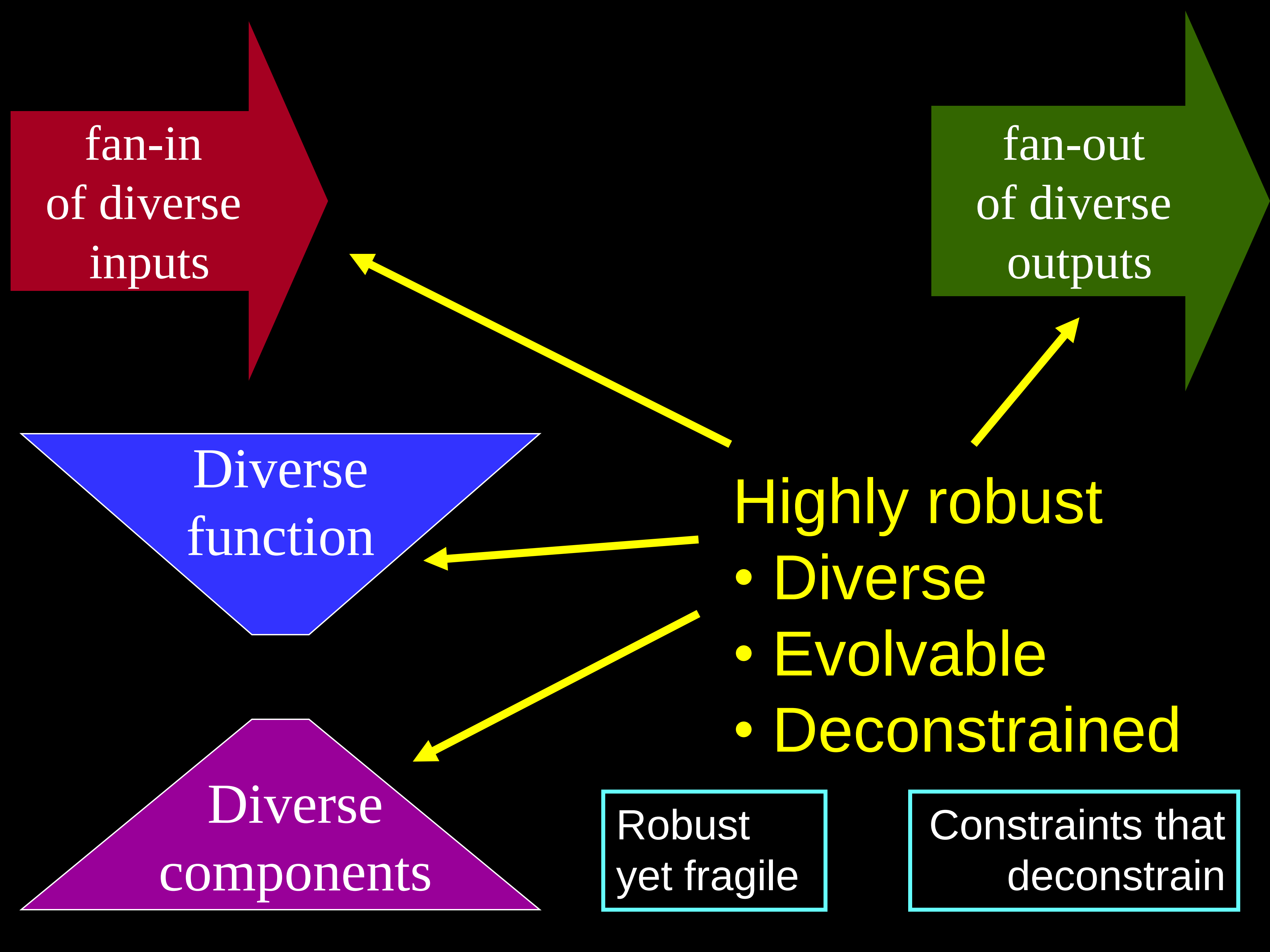


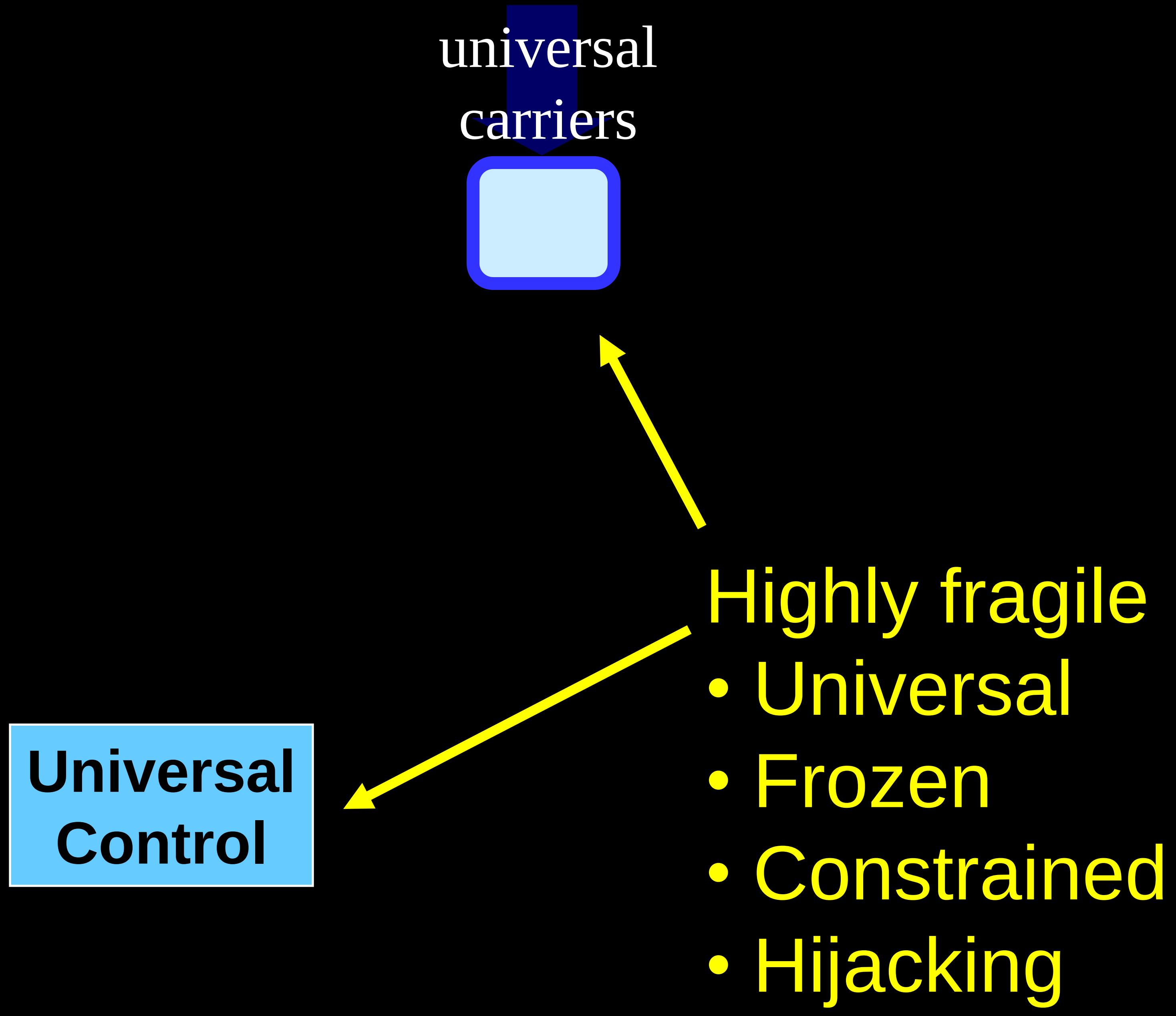


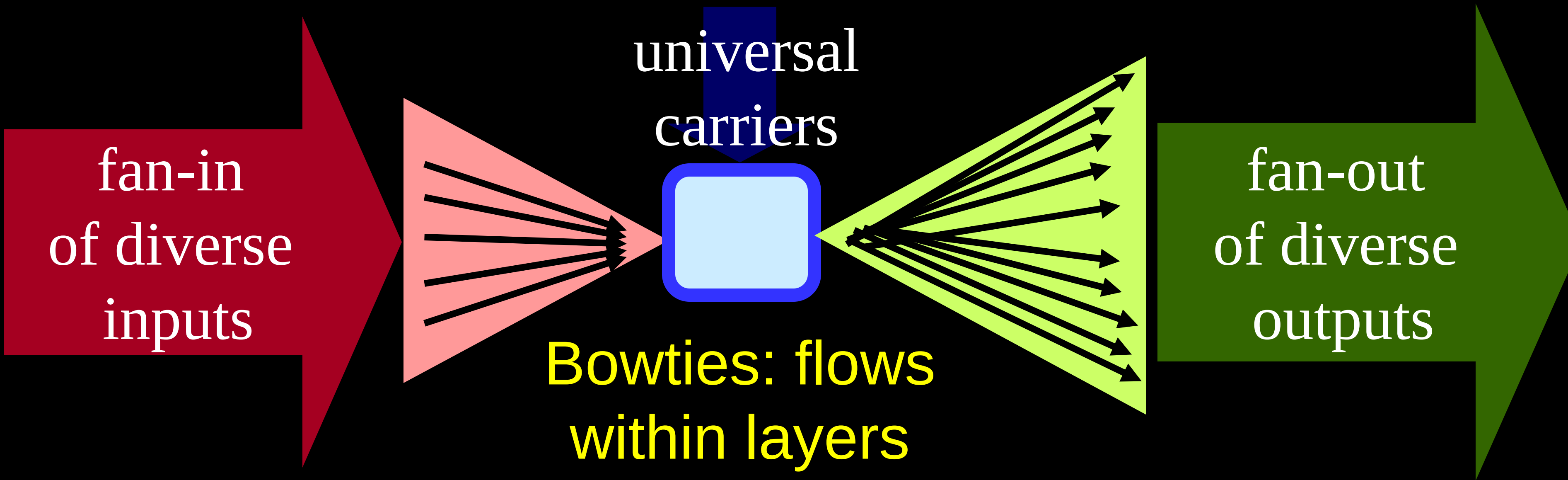
Essential ideas

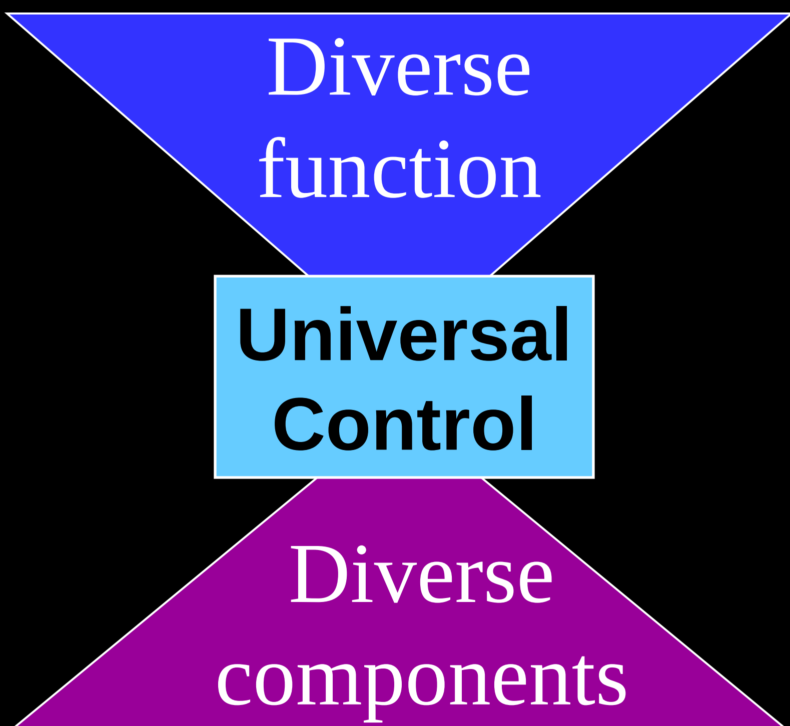
Robust
yet
fragile

Constraints
that
deconstrain


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


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





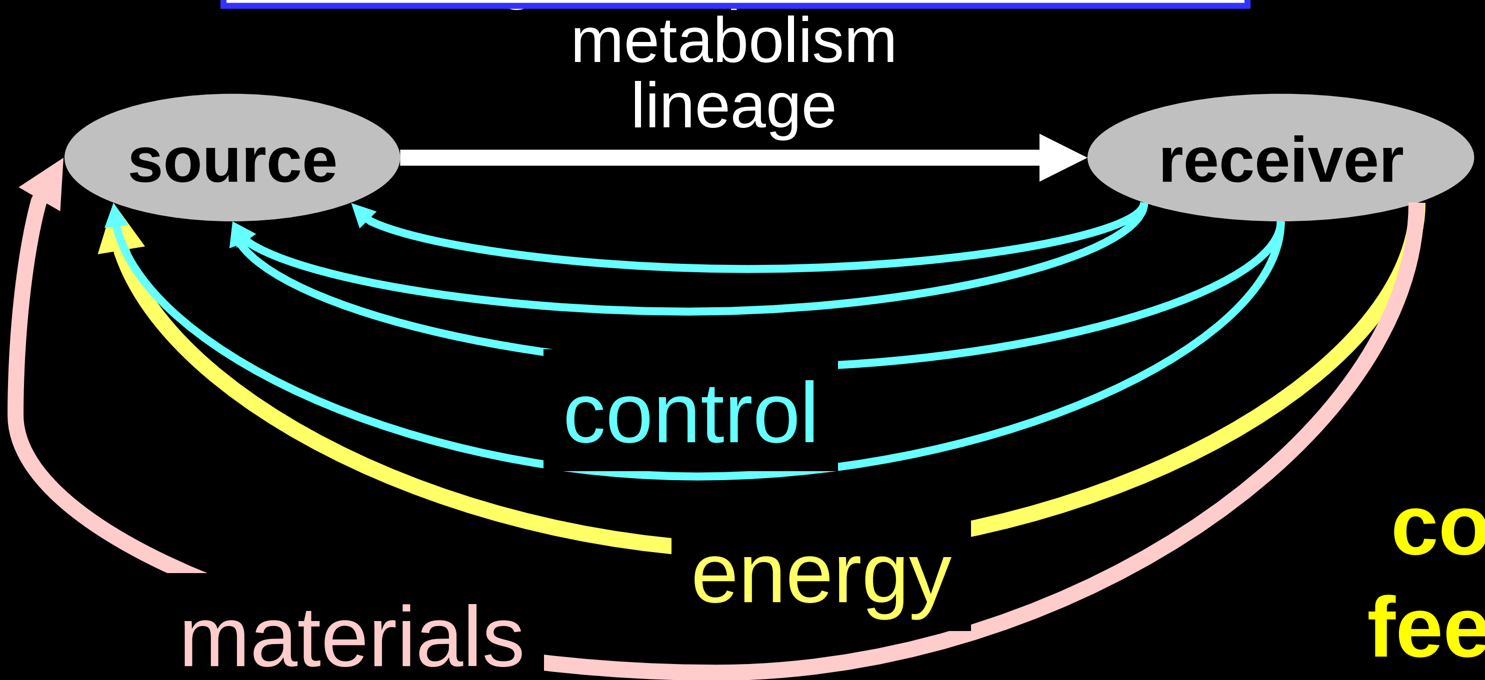
Essential ideas

Robust yet fragile

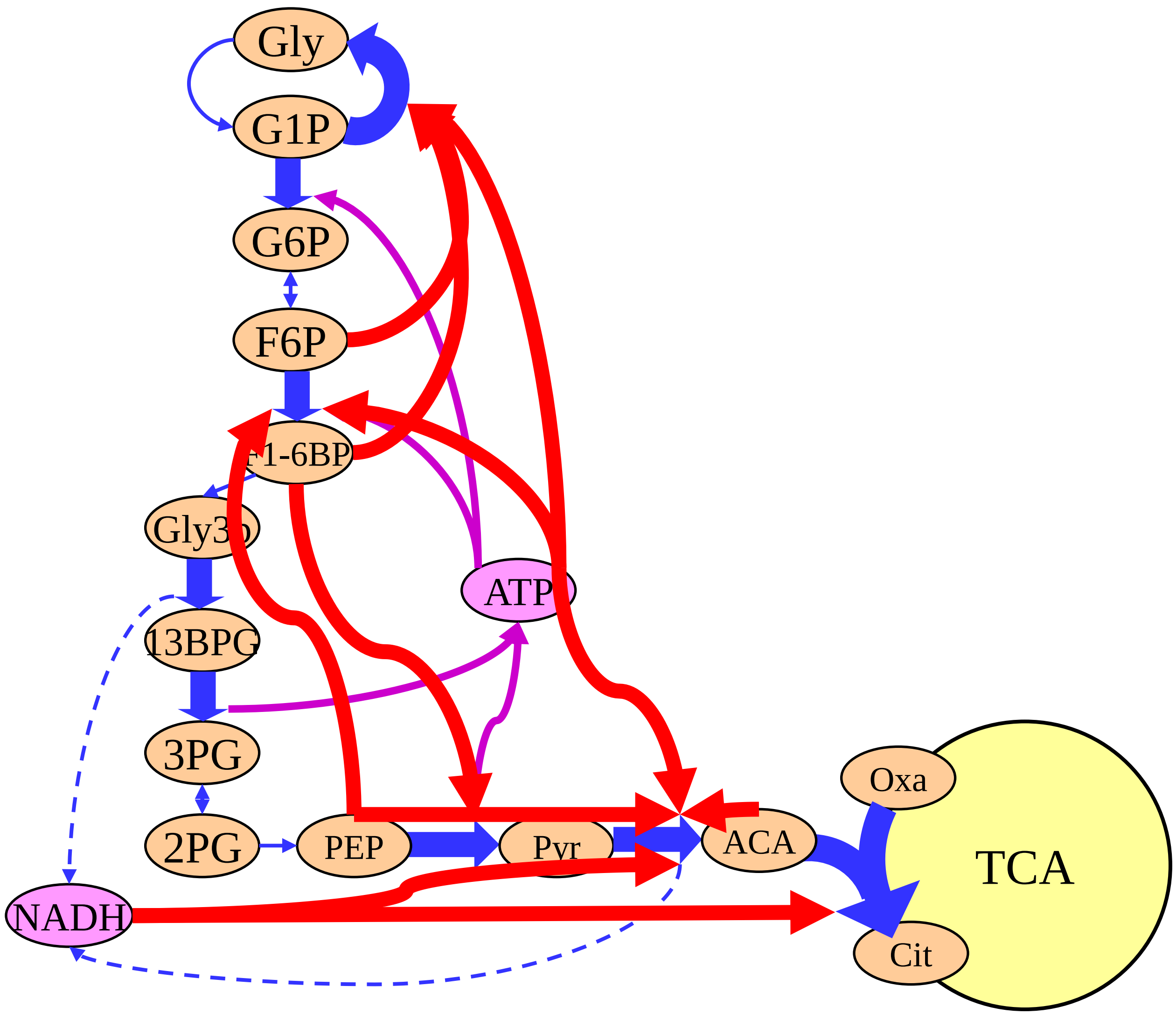
Constraints that deconstrain

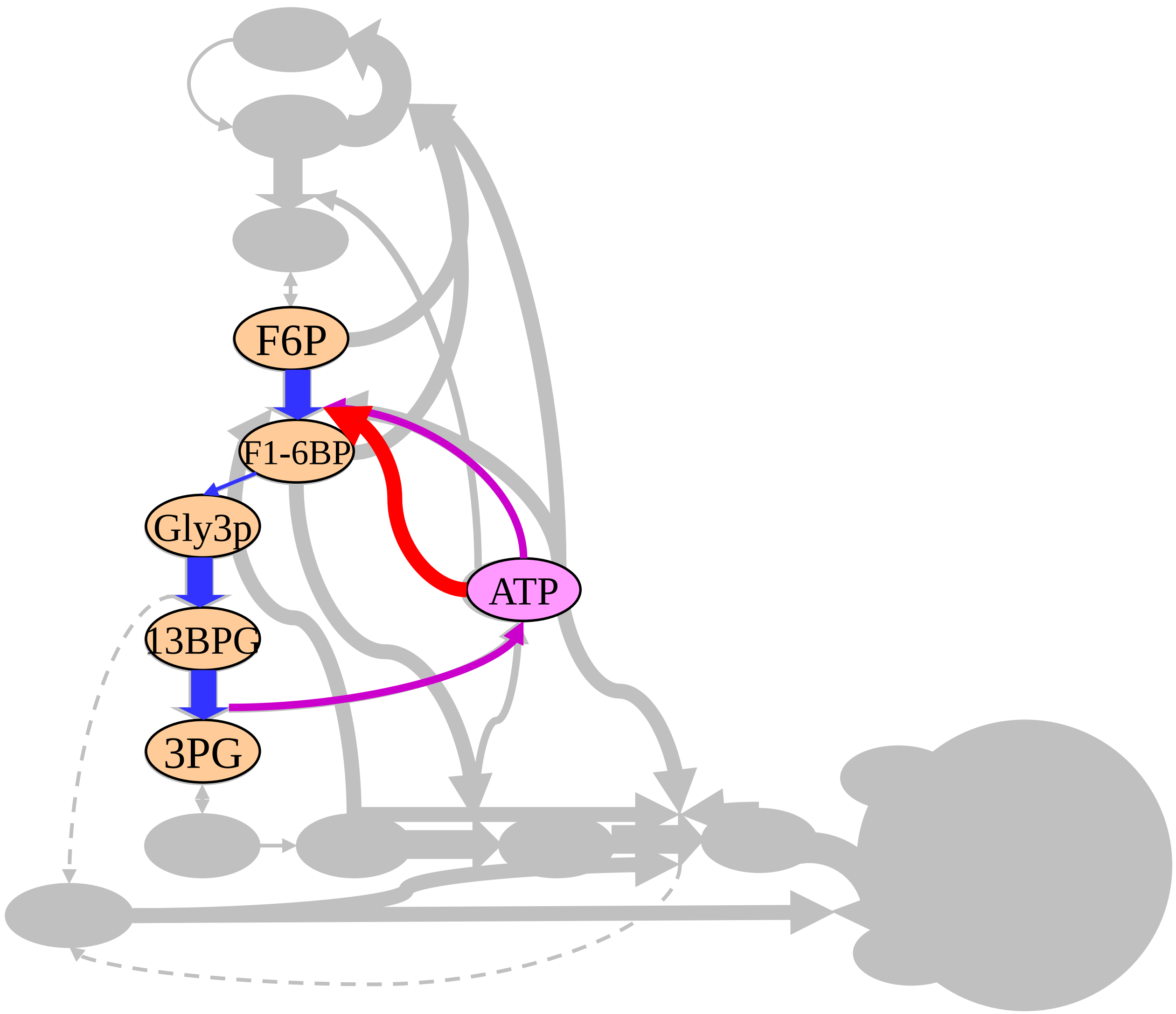
What theory is relevant to these more complex feedback systems?

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

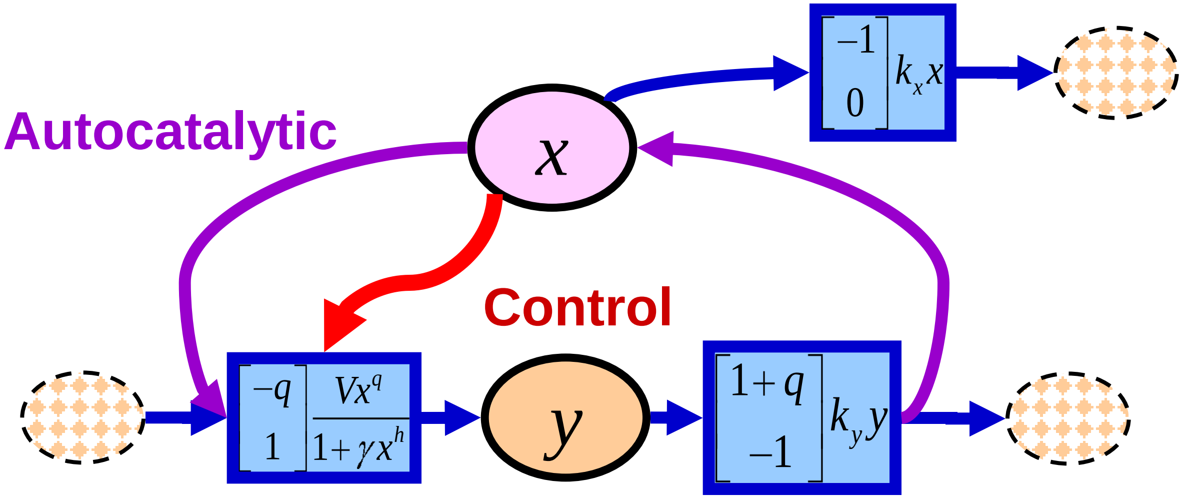


More complex feedback

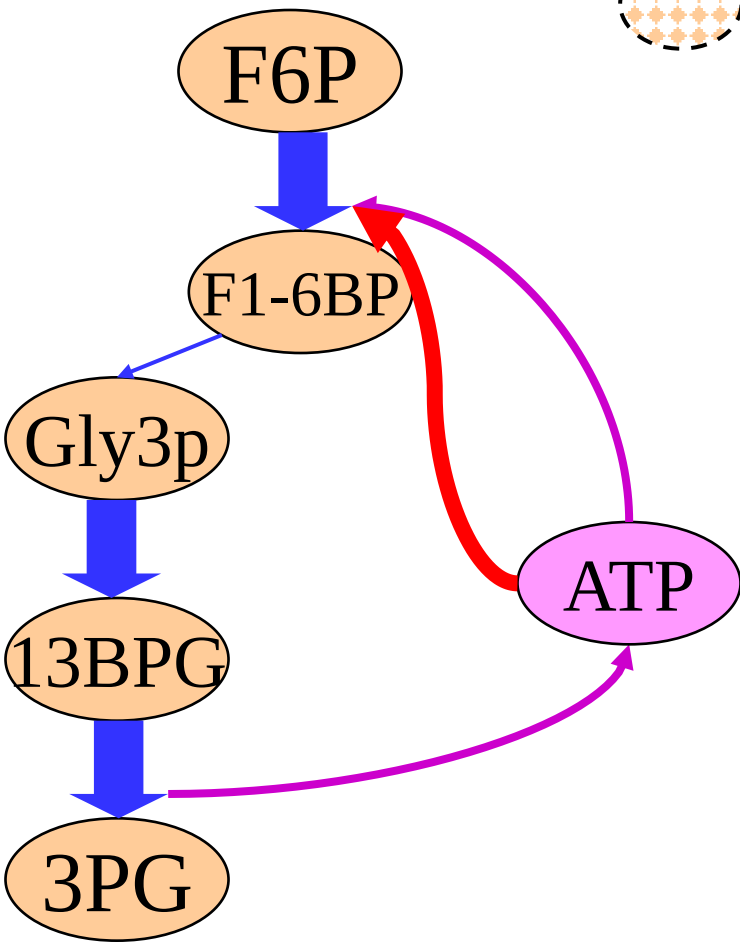

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
ATP
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
TCA
Cit
NADH



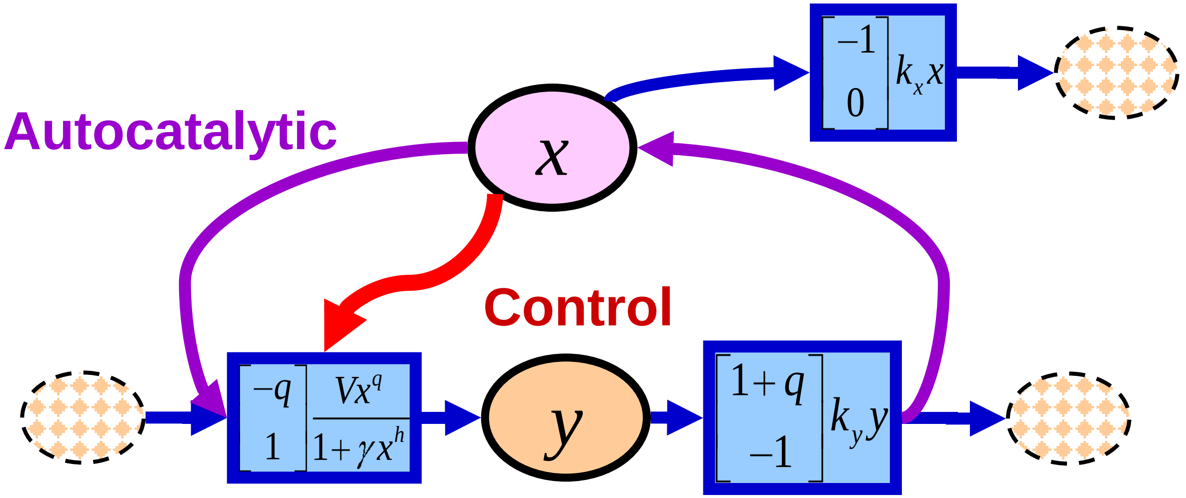
F6P
F1-6BP
Gly3p
ATP
13BPG
3PG



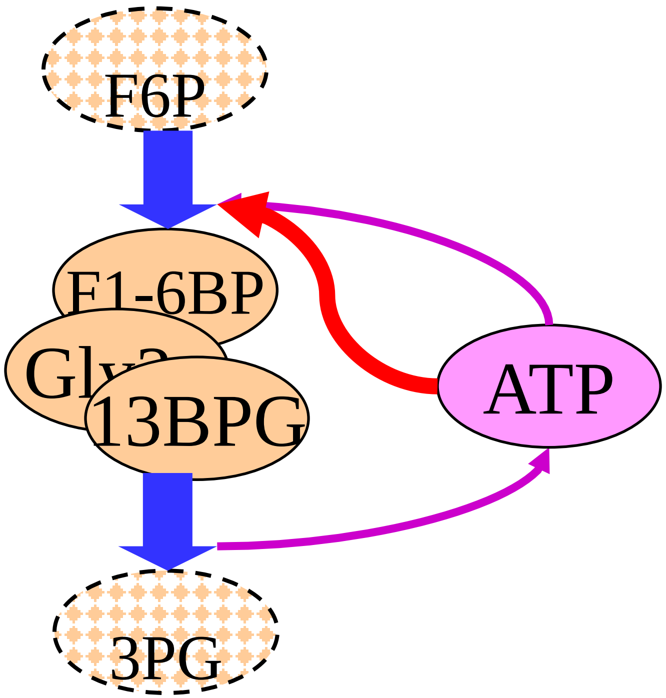
Autocatalytic
x
$\begin{bmatrix} -1 \\ 0 \end{bmatrix} k_x x$
Control
$\begin{bmatrix} -q \\ 1 \end{bmatrix} \frac{Vx^q}{1+\gamma x^h}$
y
$\begin{bmatrix} 1+q \\ -1 \end{bmatrix} k_y y$



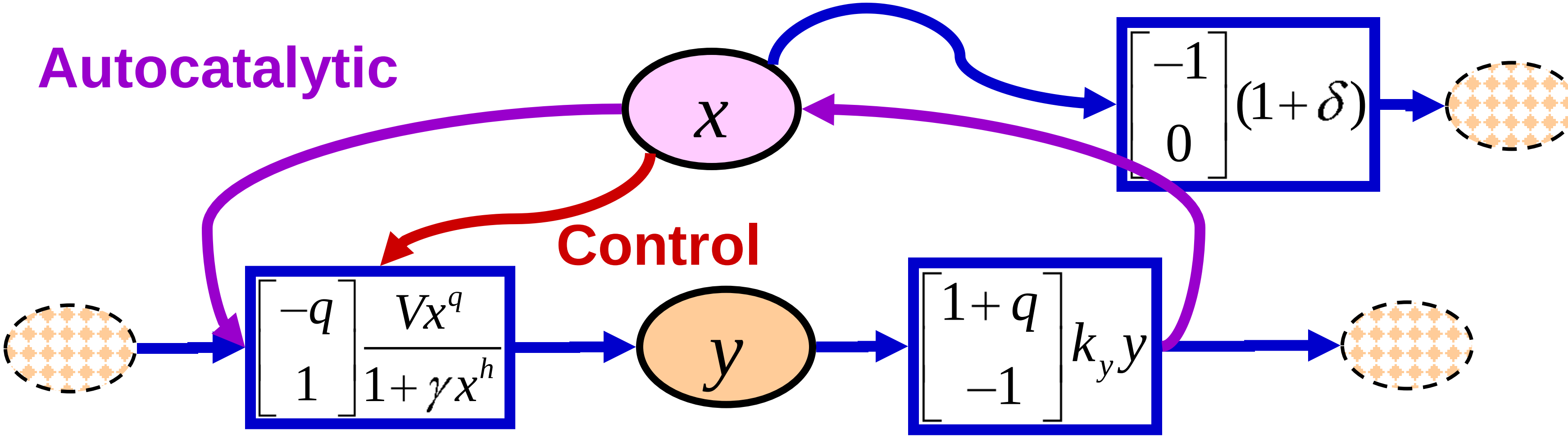
F6P
F1-6BP
Gly3p
13BPG
3PG
ATP



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



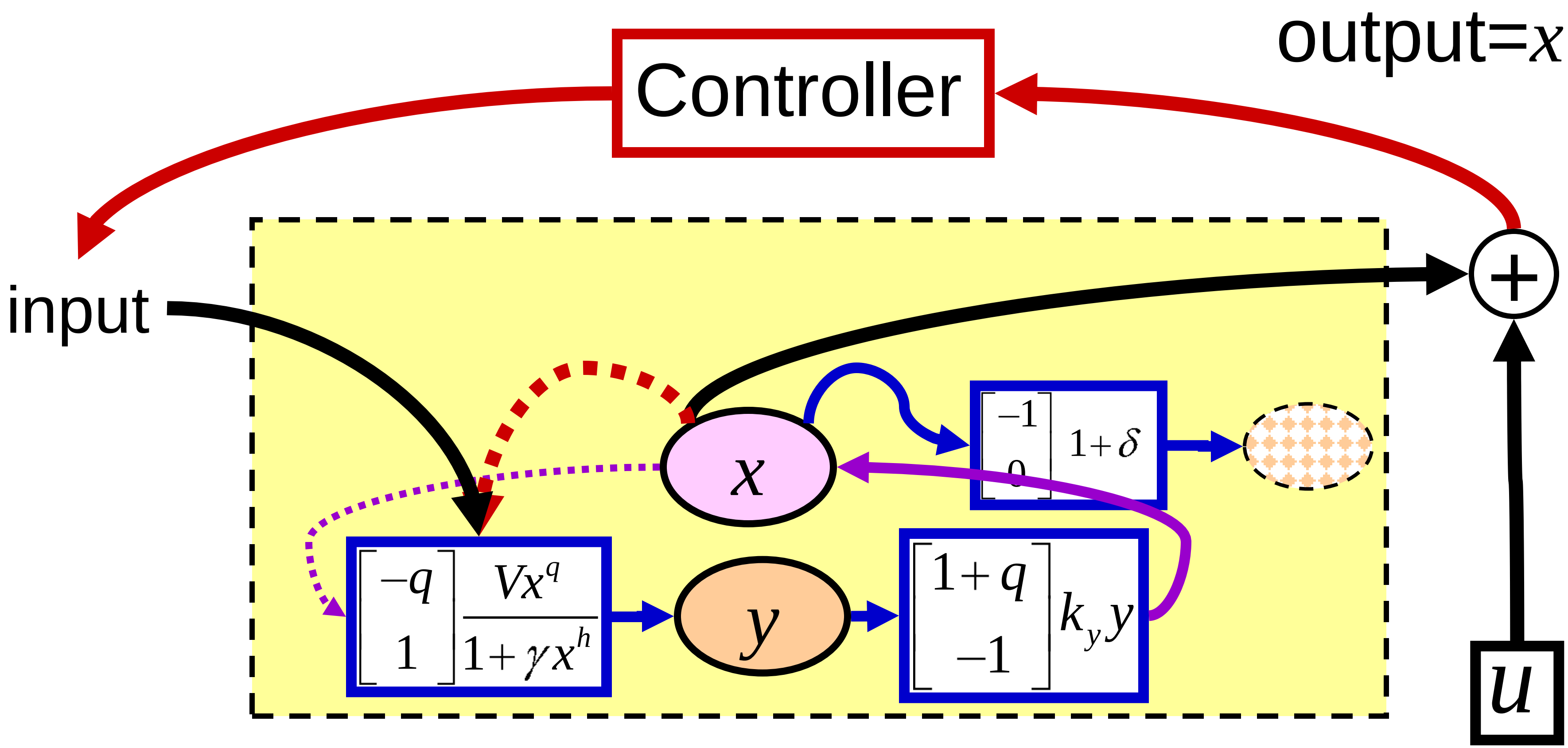
Autocatalytic

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

Control

Control theory cartoon

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



Caution: mixed cartoon

Hard limits

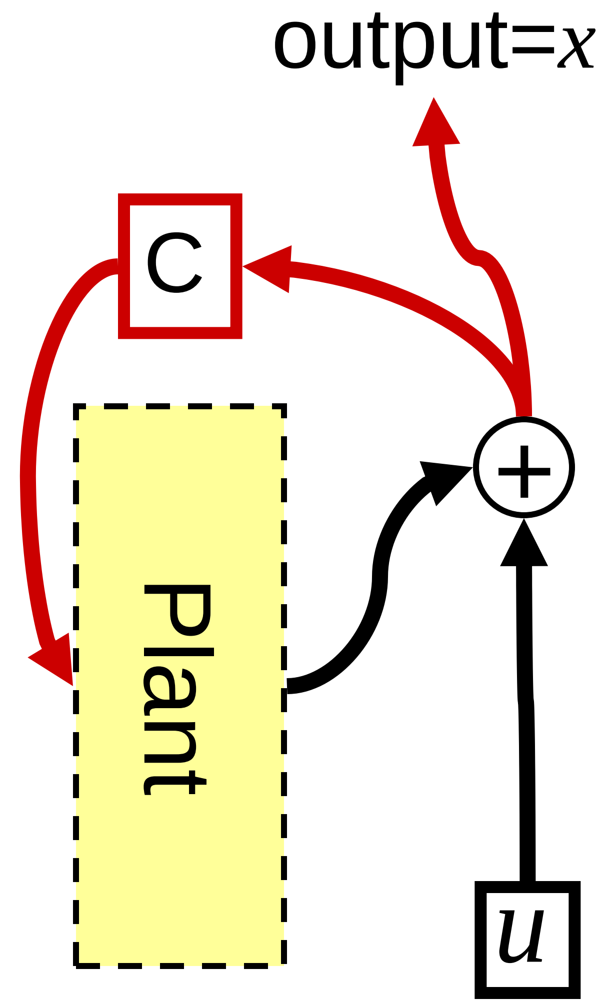
$$\boxed{S(j\omega) = \frac{X(j\omega)}{U(j\omega)}}$$

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

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

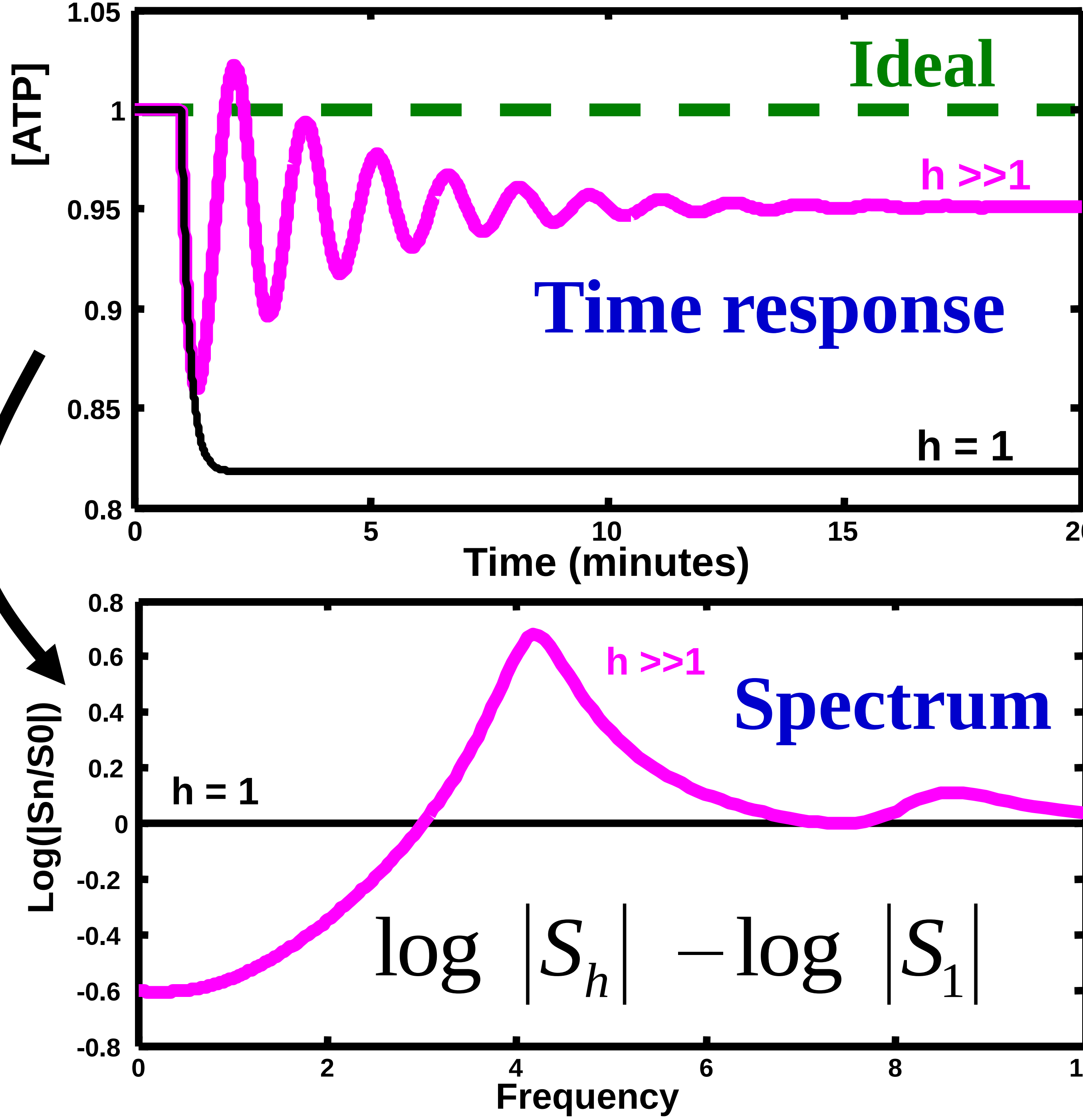
$$= \int_{-\infty}^{\infty} \ln\left|X(j\omega)\right| d\omega - \int_{-\infty}^{\infty} \ln\left|U(j\omega)\right| d\omega$$

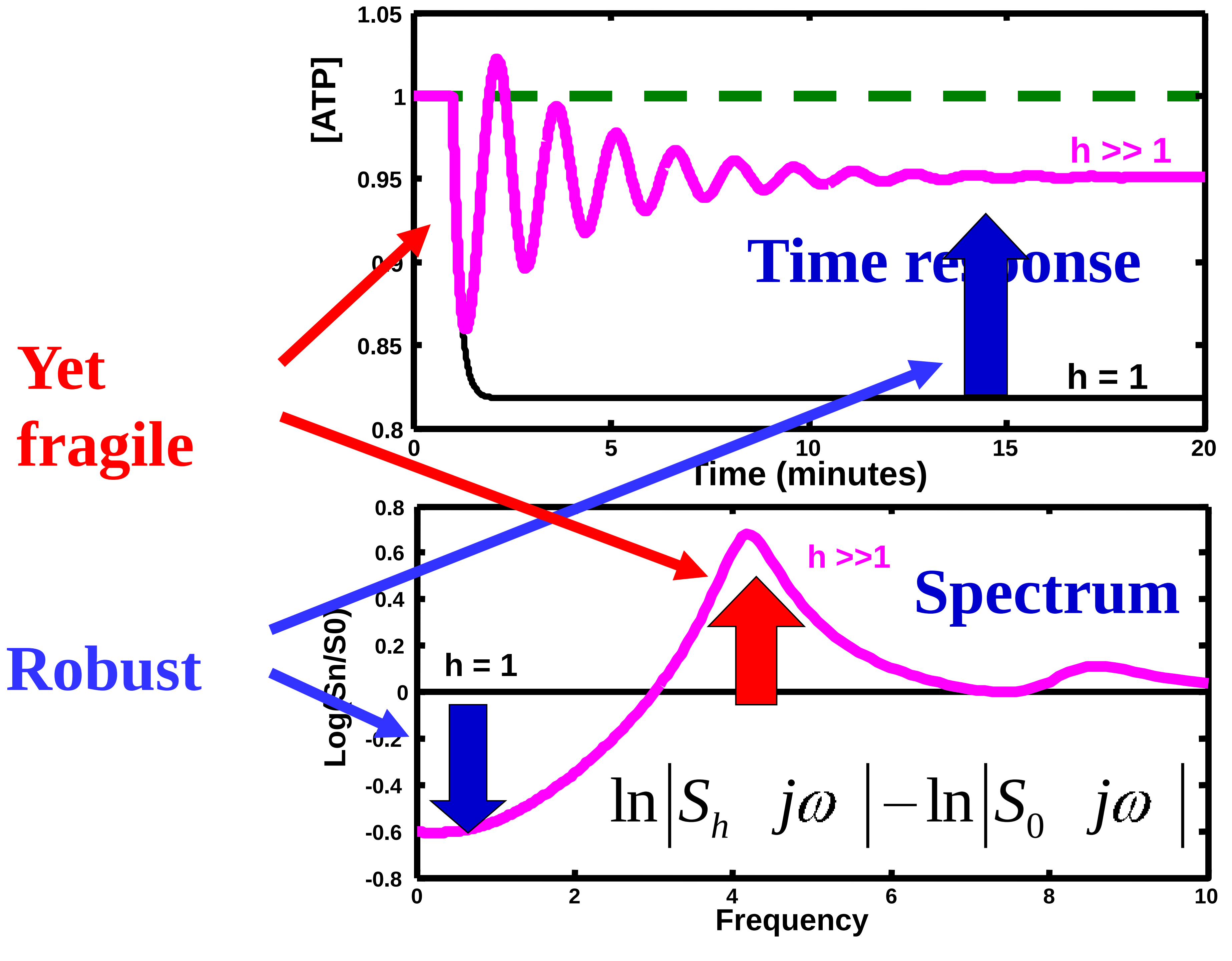
Entropy rates



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

Fourier Transform of error



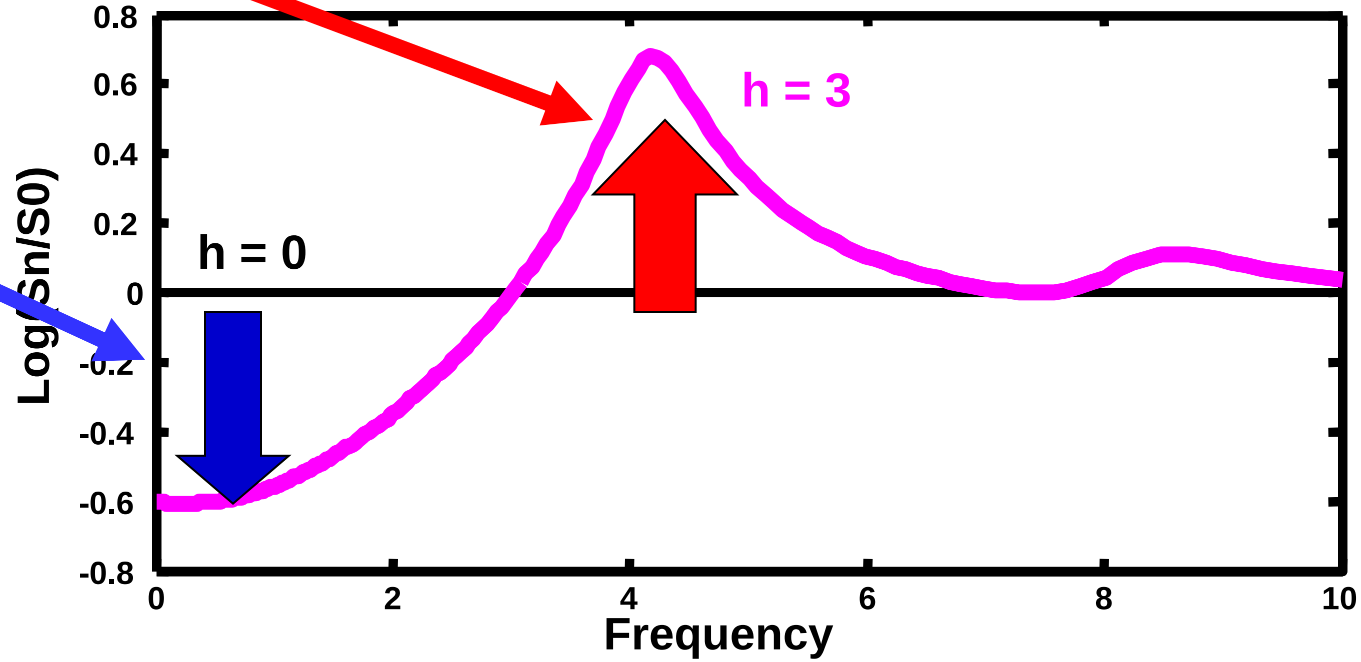


Yet fragile
Robust
Time response
h >> 1
h = 1
[ATP]
Time (minutes)
Spectrum
h >>1
h = 1
Log(Sn/S0)
Frequency
$\ln|S_h(j\omega)| - \ln|S_0(j\omega)|$

$$\int_{0}^{\infty} \Delta \ln \left| S(j\omega) \right| d\omega = 0$$

Yet fragile

Robust

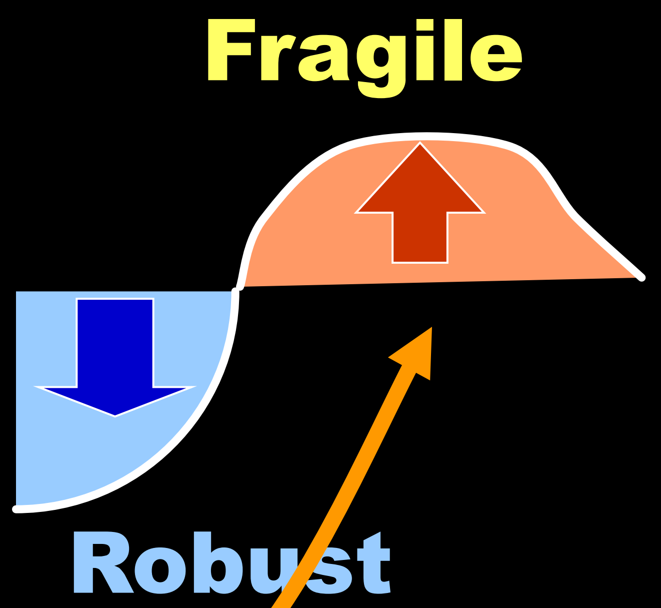


[a system] can have
[a property] ***robust*** for
[a set of perturbations]

Yet be ***fragile for***

[a different property]

Or [a different perturbation]



Robust yet fragile = fragile robustness

Hard limits

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

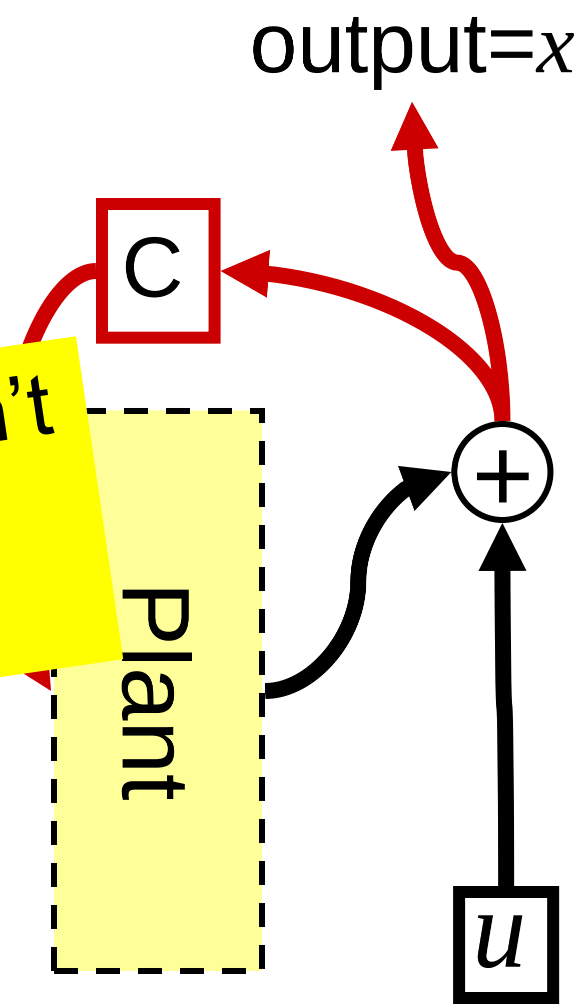
$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq 0$$

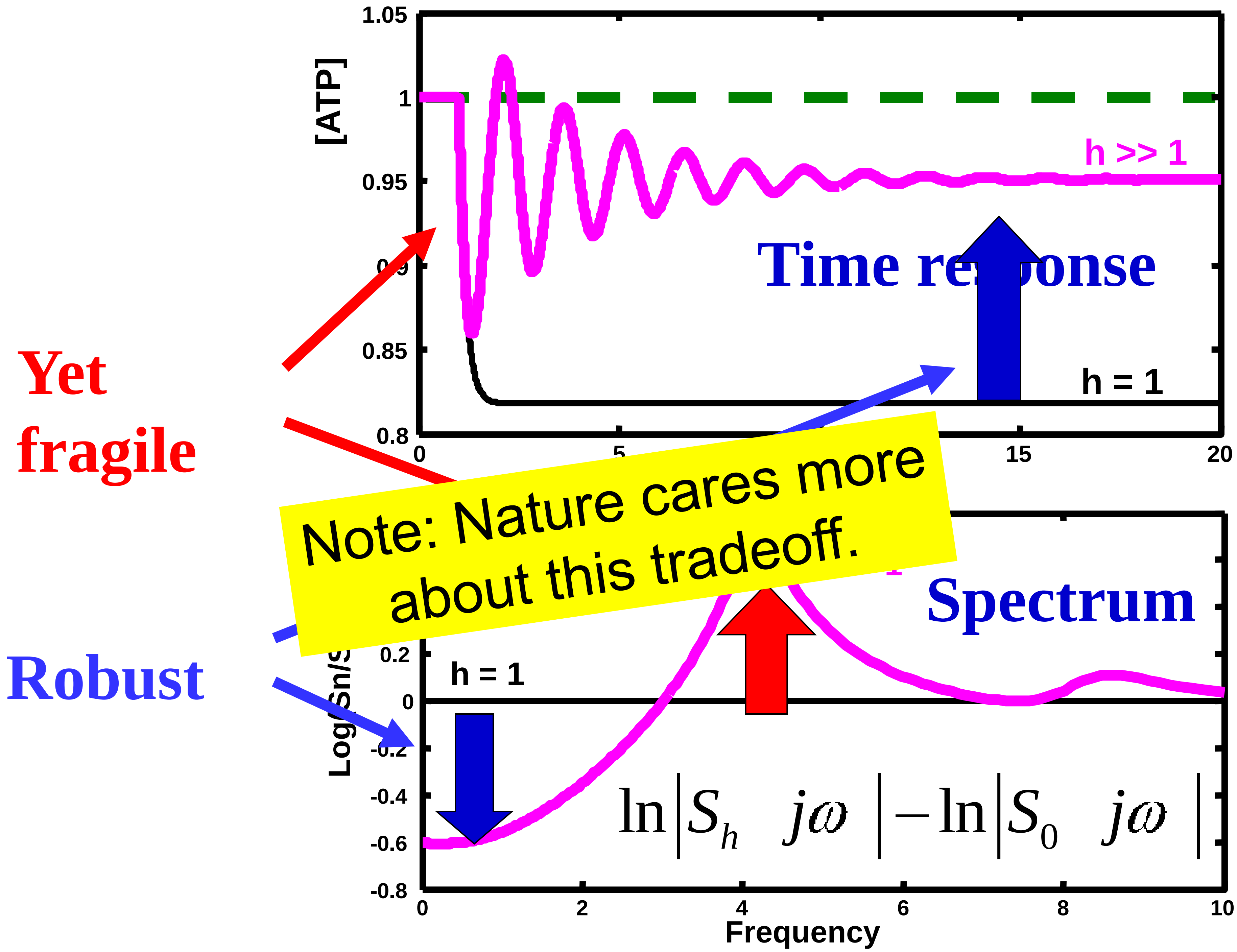
$$\int_{-\infty}^{\infty} \ln\left|S(j\omega)\right| d\omega$$

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

Entropy rates

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



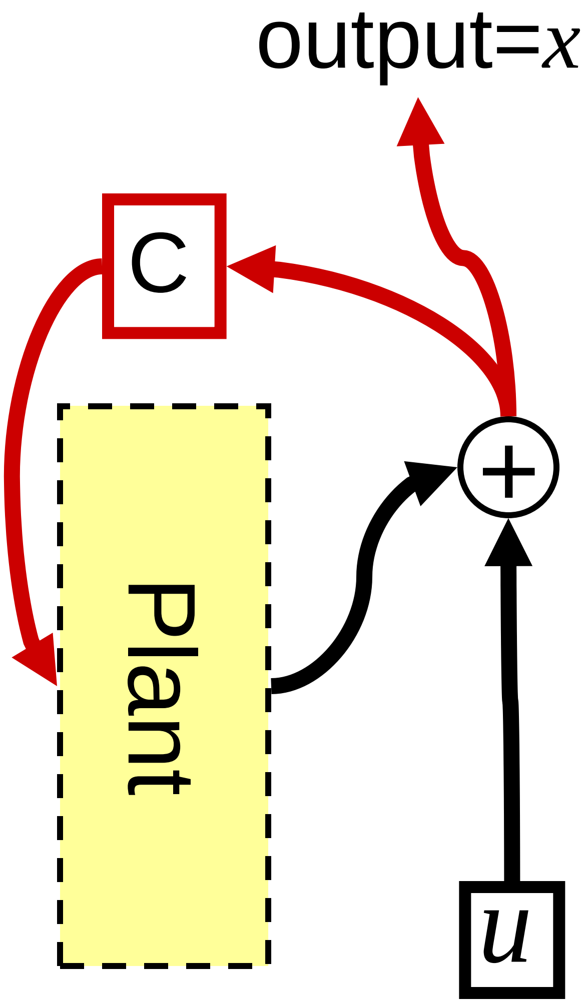


Yet
fragile
Robust
Time response
[ATP]
h >> 1
h = 1
Spectrum
Log(Sn/S
h = 1
Frequency
$\ln\left|S_h\left(j\omega\right)\right| - \ln\left|S_0\left(j\omega\right)\right|$
Note: Nature cares more about this tradeoff.

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

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

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



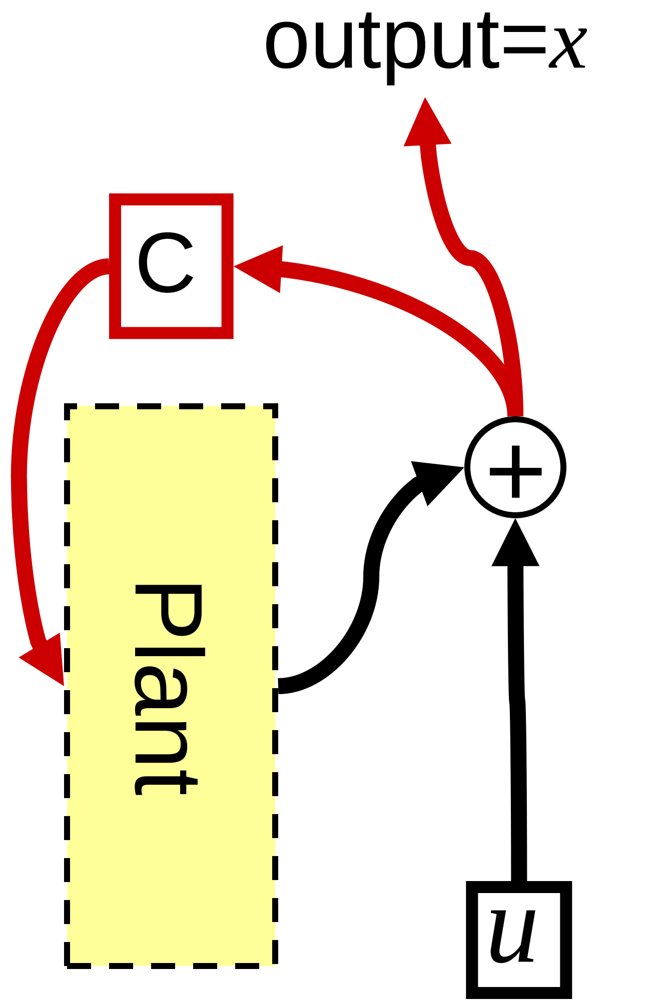
The plant can make this tradeoff worse.

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

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

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

All controllers:	$\geq$
Biological cells:	$=$



$$z = \frac{k}{q} \qquad p = RHPzero\quad s^2 + \quad q\alpha + k \quad s - \alpha k$$

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

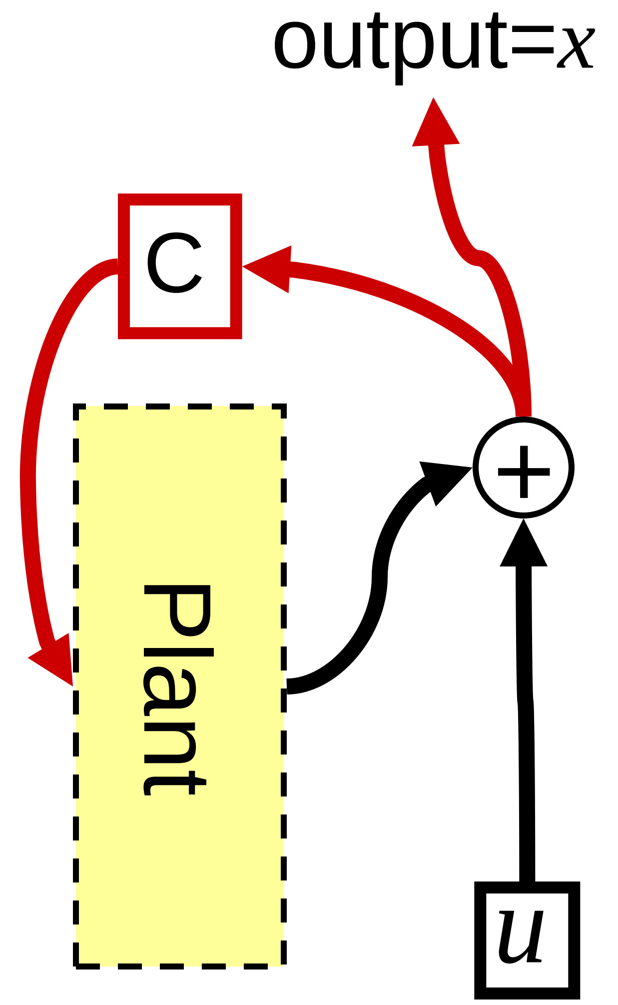
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right| d\omega \ge 0$$

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

Small *z* is *bad*.

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

$$p = RHPzero\left(s^2 + (q\alpha + k)s - \alpha k\right)$$



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***

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

Correctly predicts conditions with “glycolytic oscillations”

Hard limits

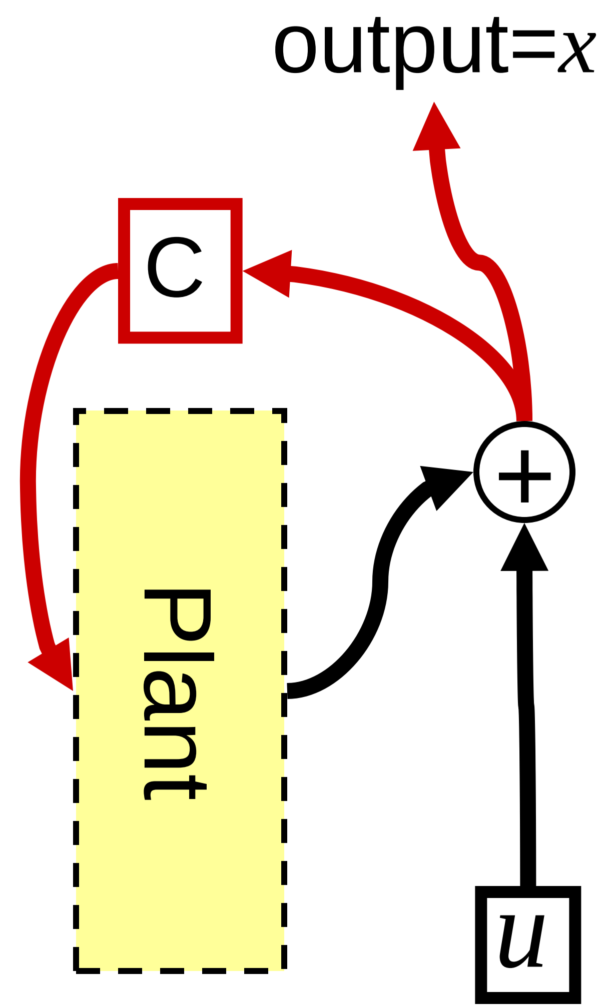
$$\boxed{S\quad j\omega\quad = \frac{X\quad j\omega}{U\quad j\omega}}$$

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

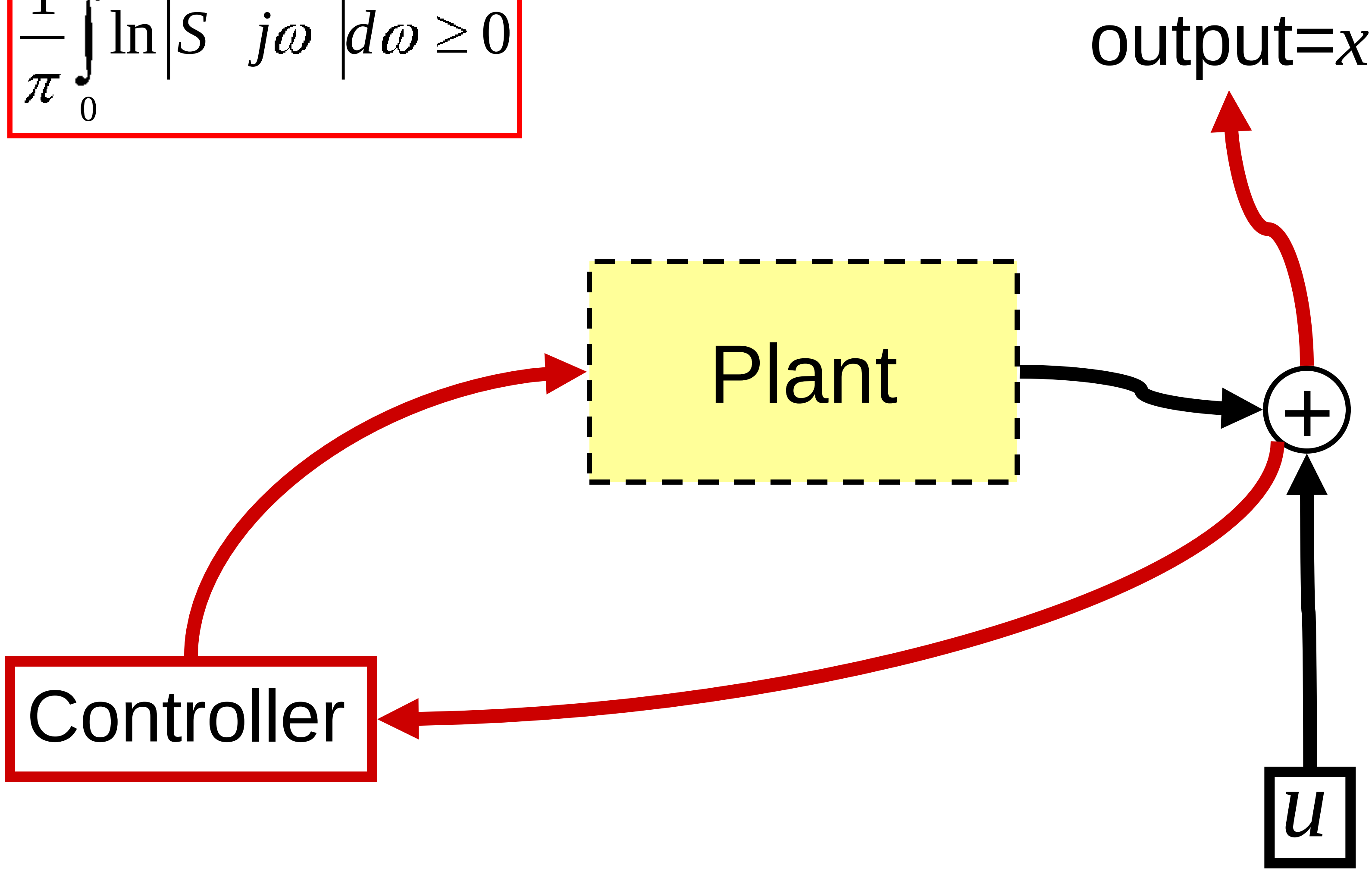
$$\int_{-\infty}^{\infty} \ln\left|S\quad j\omega\quad\right| d\omega = \int_{-\infty}^{\infty} \ln\left|\frac{X\quad j\omega}{U\quad j\omega}\right| d\omega$$

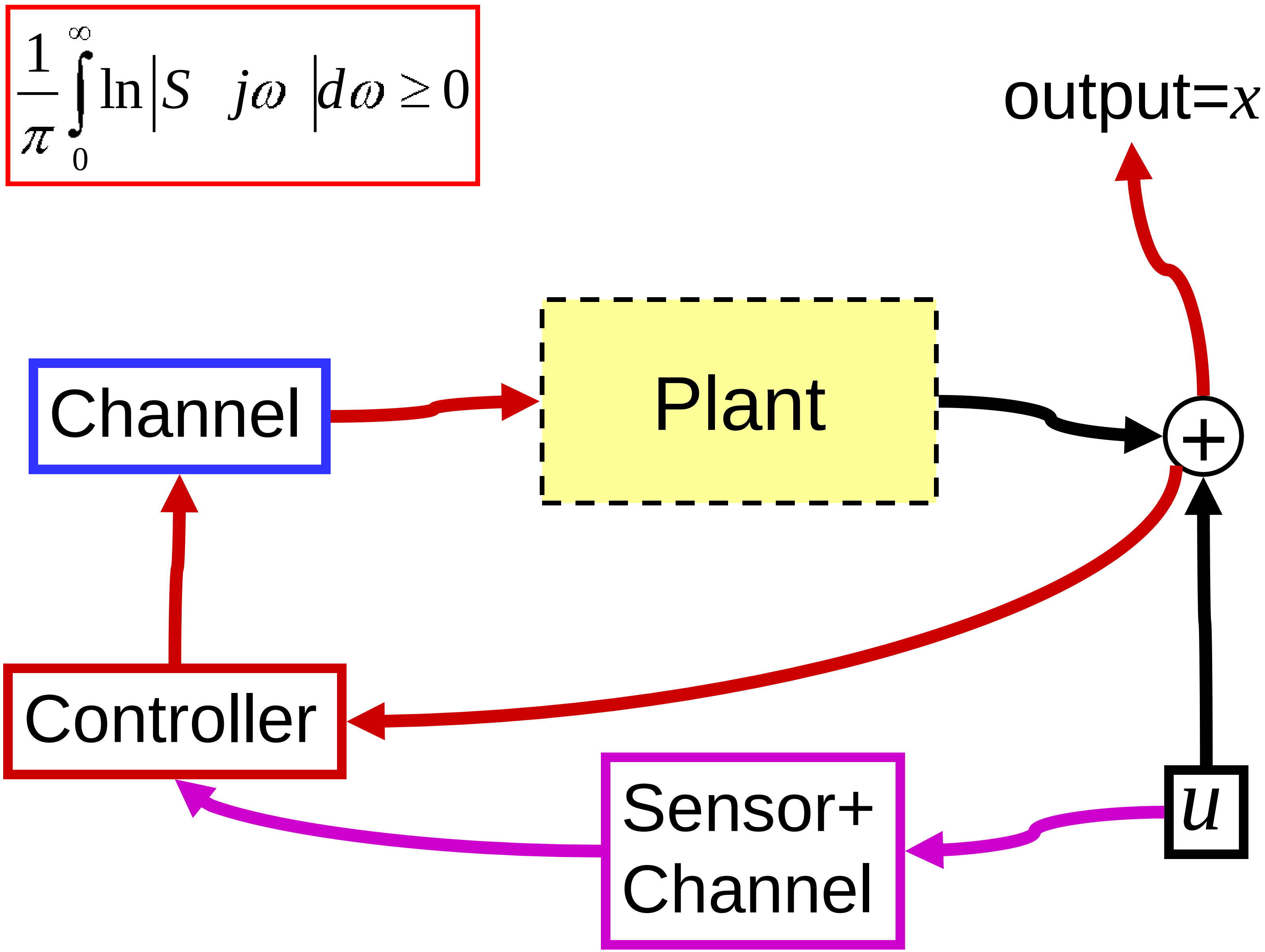
$$= \int_{-\infty}^{\infty} \ln\left|X\quad j\omega\quad\right| d\omega - \int_{-\infty}^{\infty} \ln\left|U\quad j\omega\quad\right| d\omega$$

Entropy rates



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



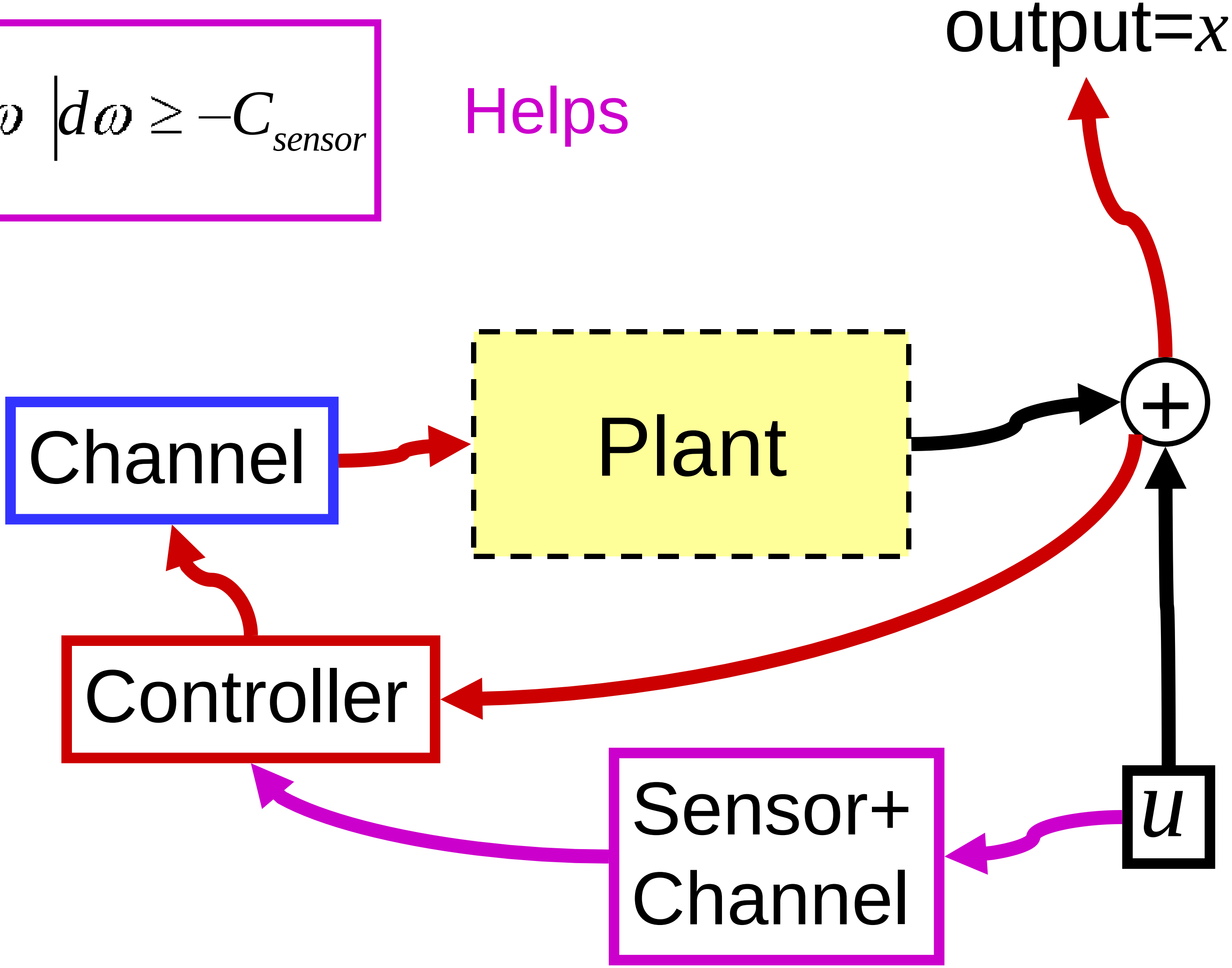

$\frac{1}{\pi}\int_0^\infty \ln|S\ \ j\omega|d\omega \geq 0$
output=x
Channel
Plant
Controller
Sensor+
Channel
u
+

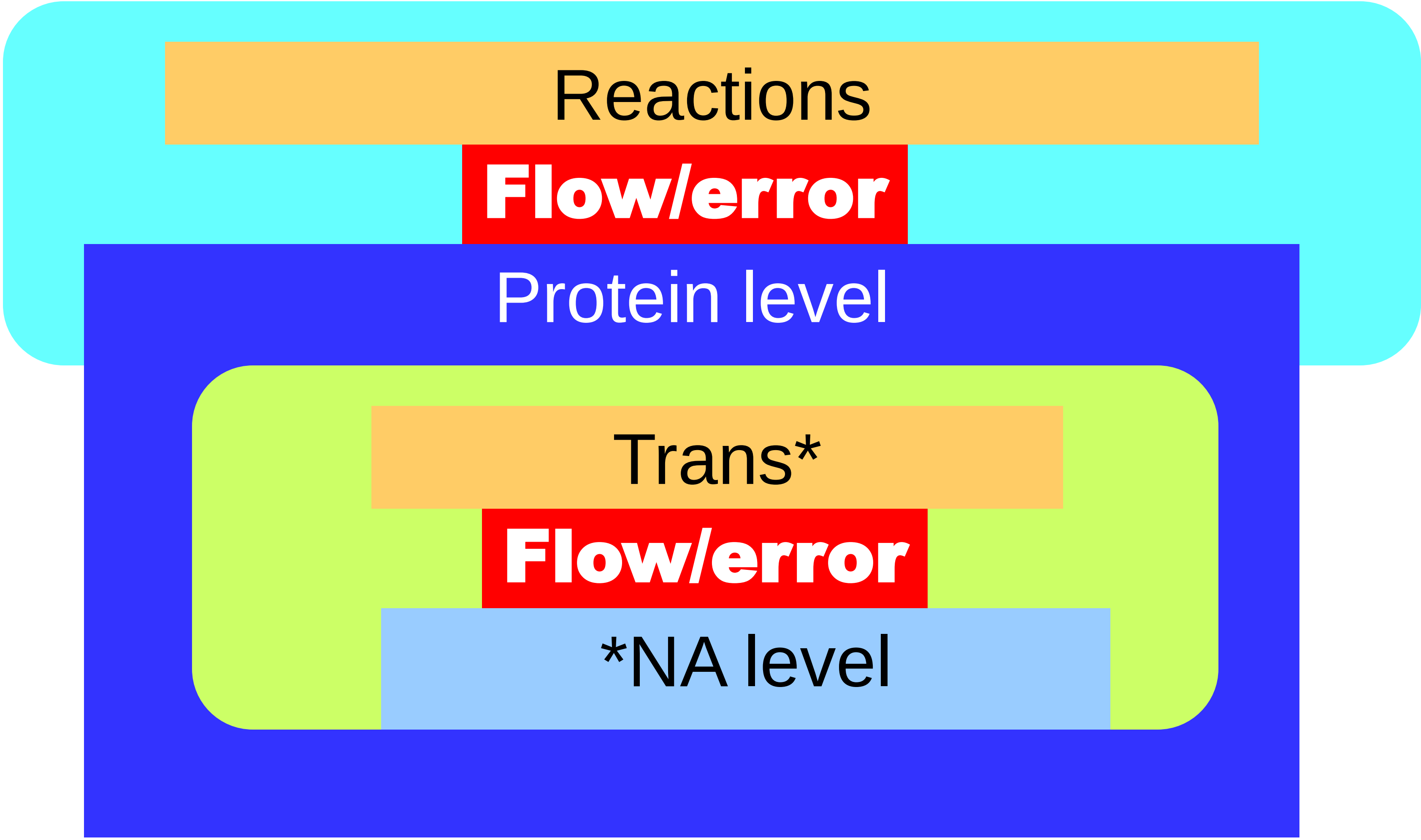
$$\boxed{\frac{1}{\pi}\int_0^\infty \ln\left|S\quad j\omega\quad\right|\_\,d\omega \ge -C_{FB}}$$

Hurts

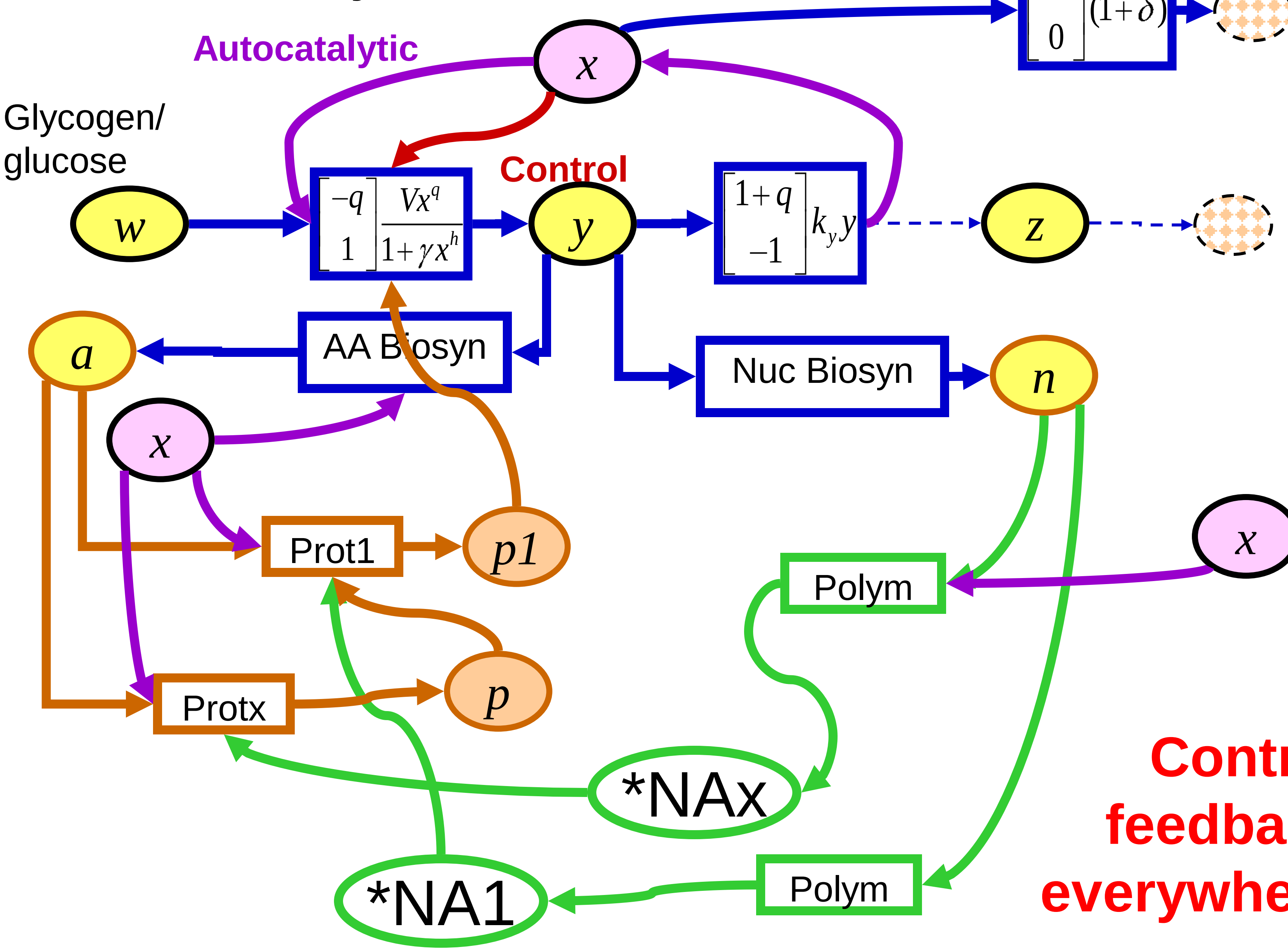
$$\boxed{\frac{1}{\pi}\int_0^\infty \ln\left|S\quad j\omega\quad\right|d\omega \ge -C_{sensor}}$$

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]

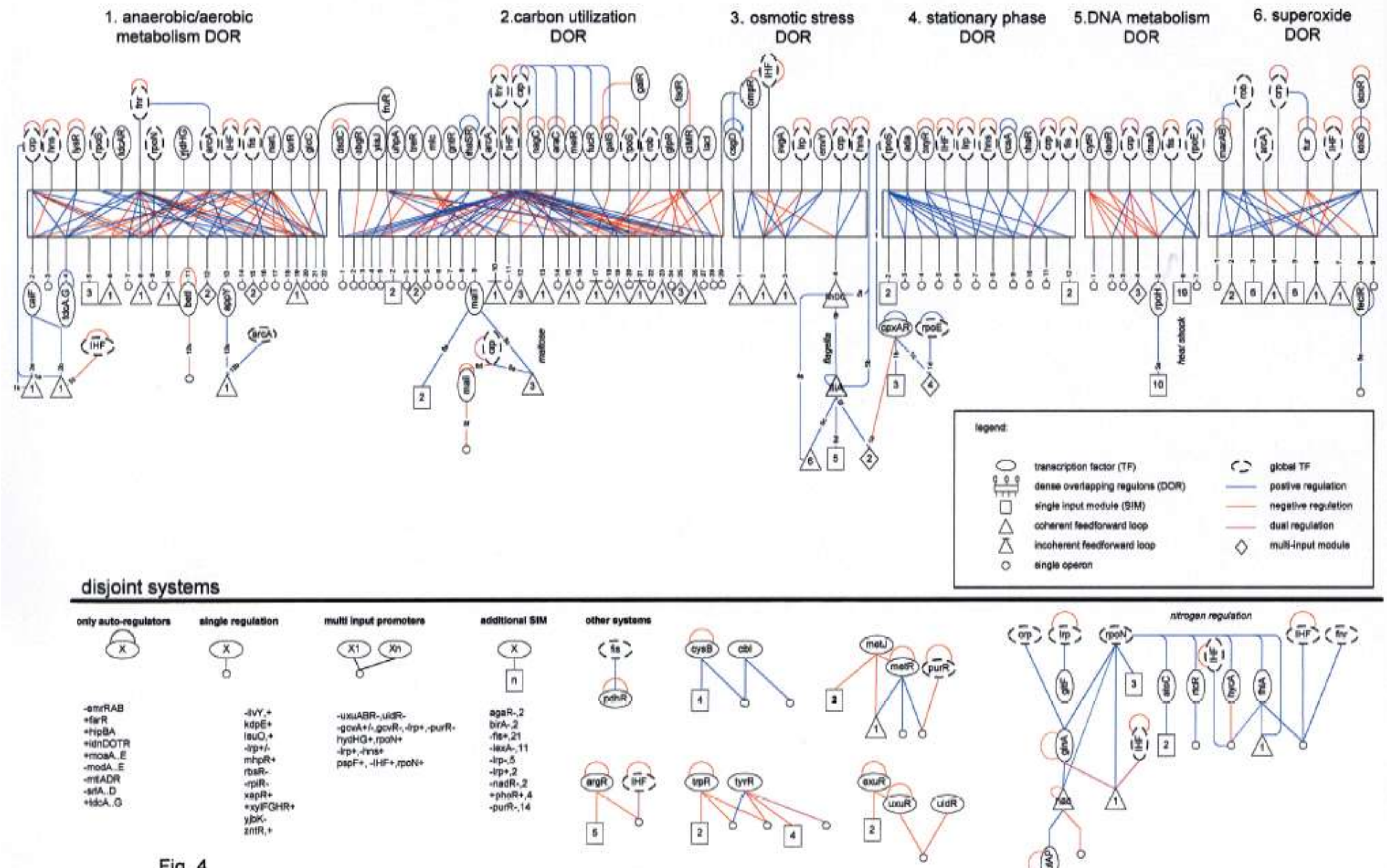


Fig. 4

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

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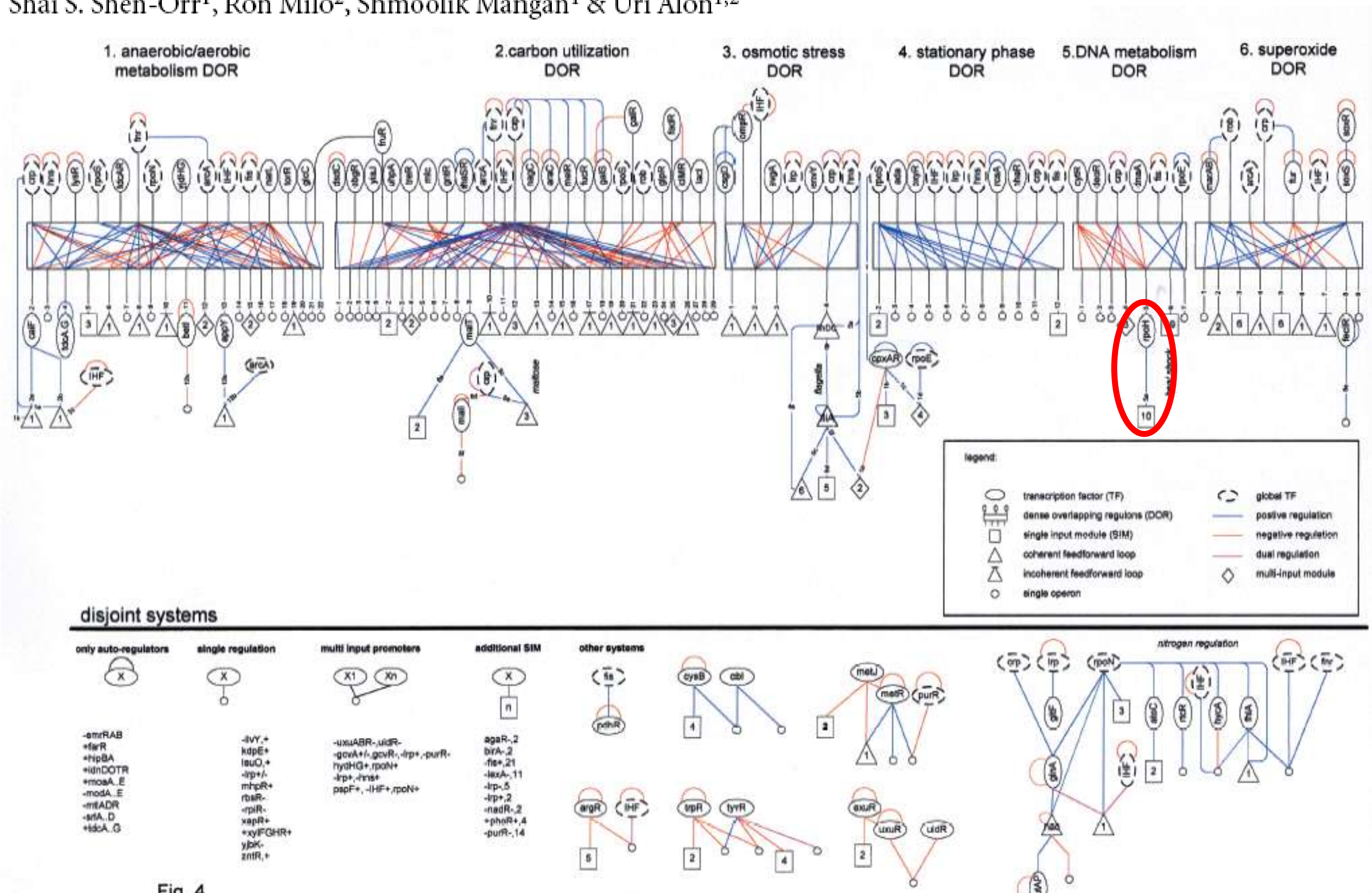
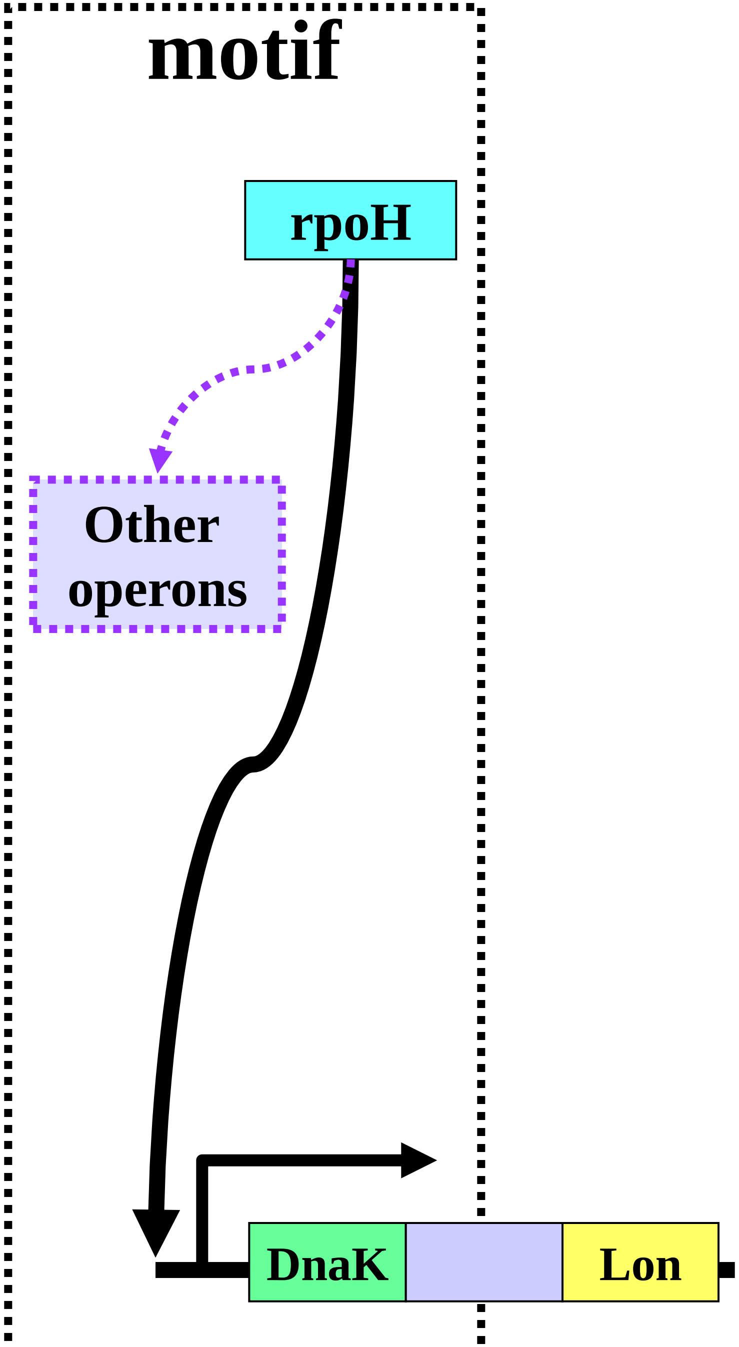
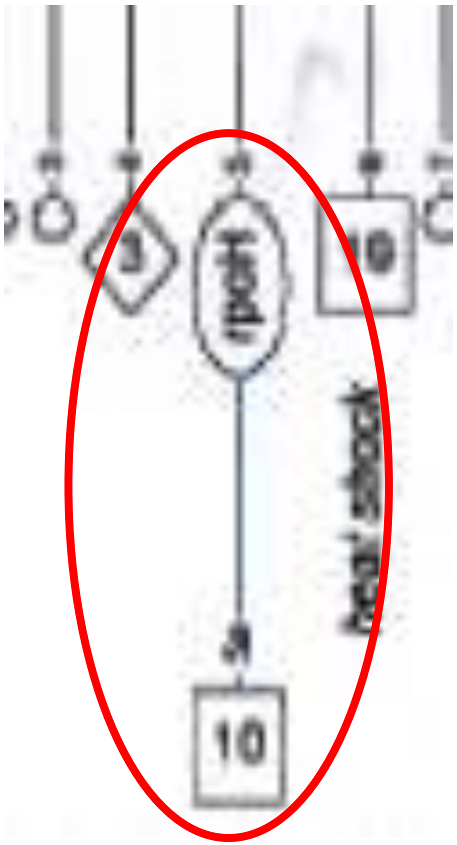
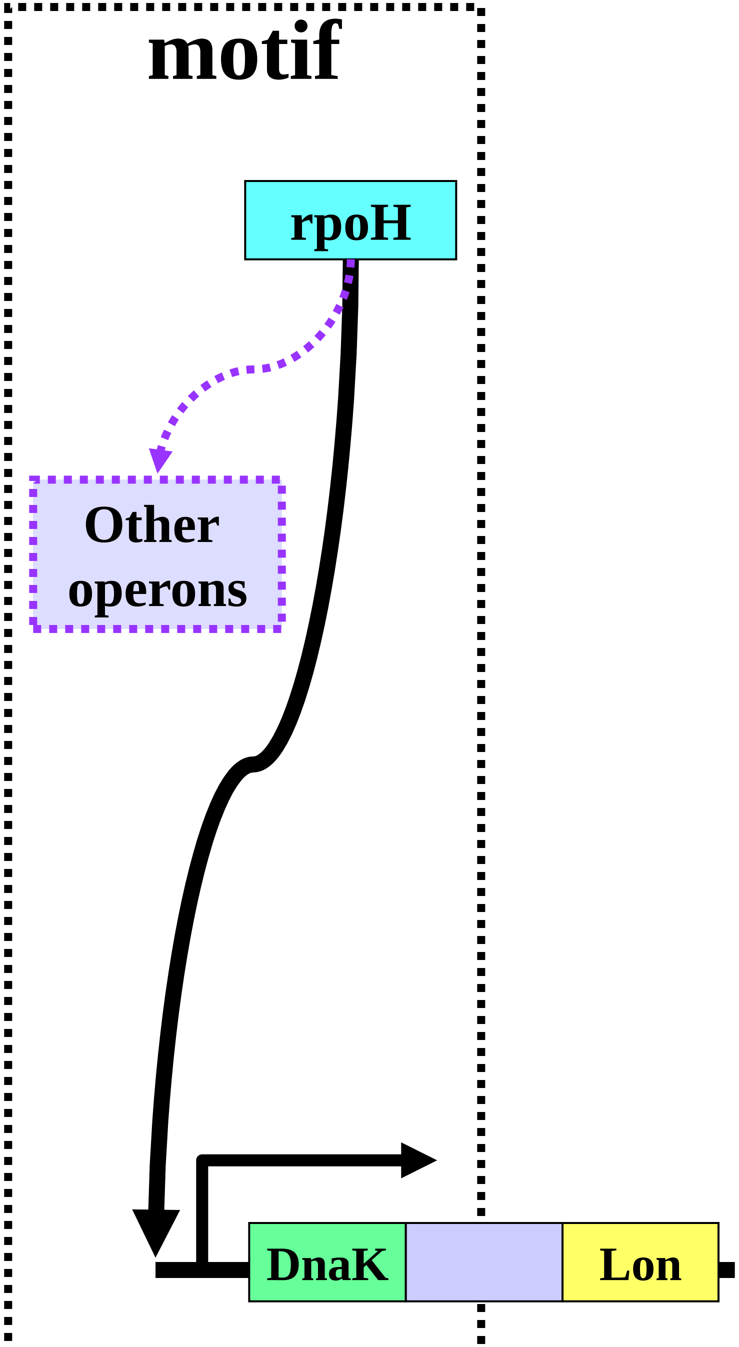


Fig. 4

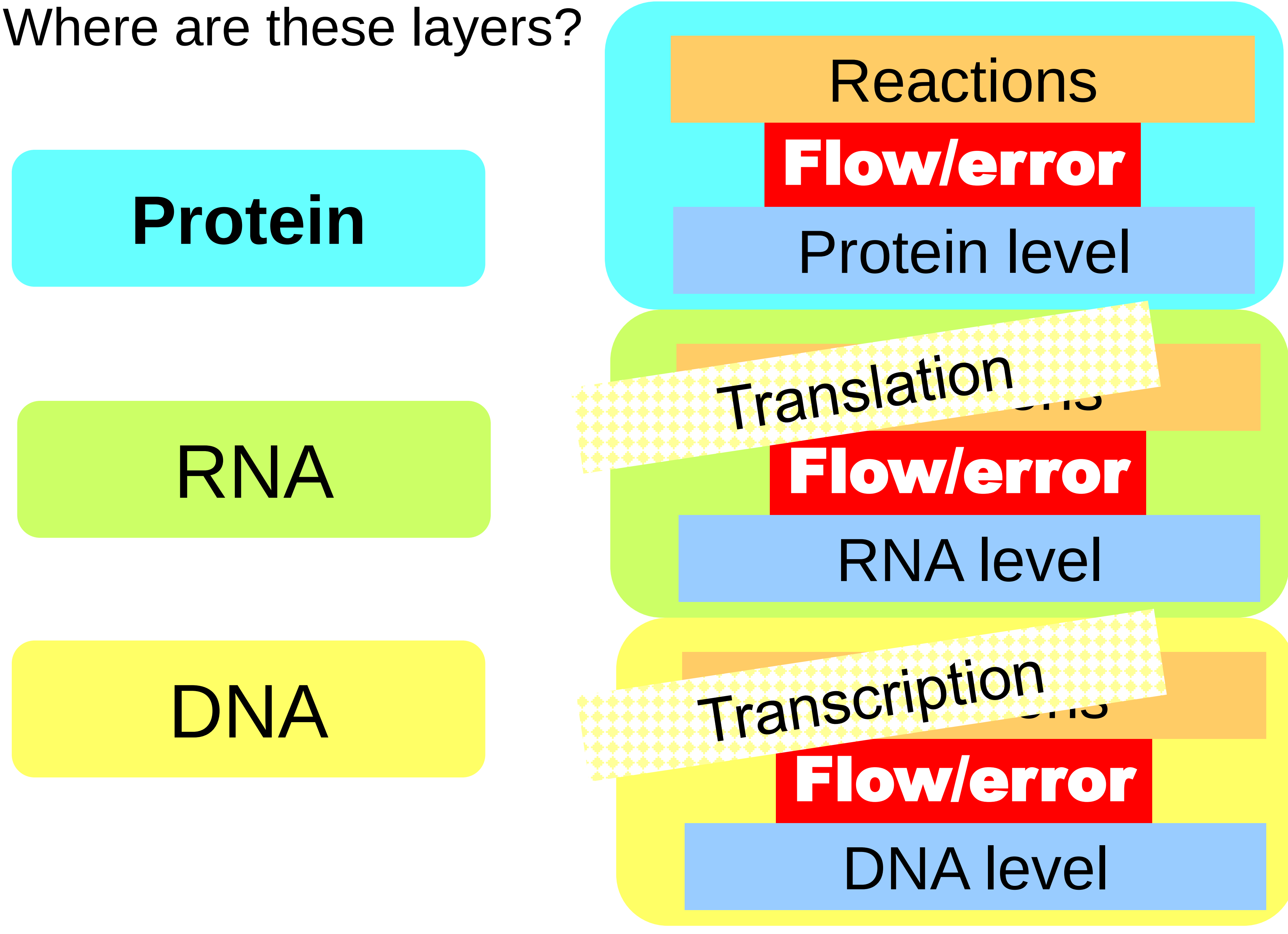


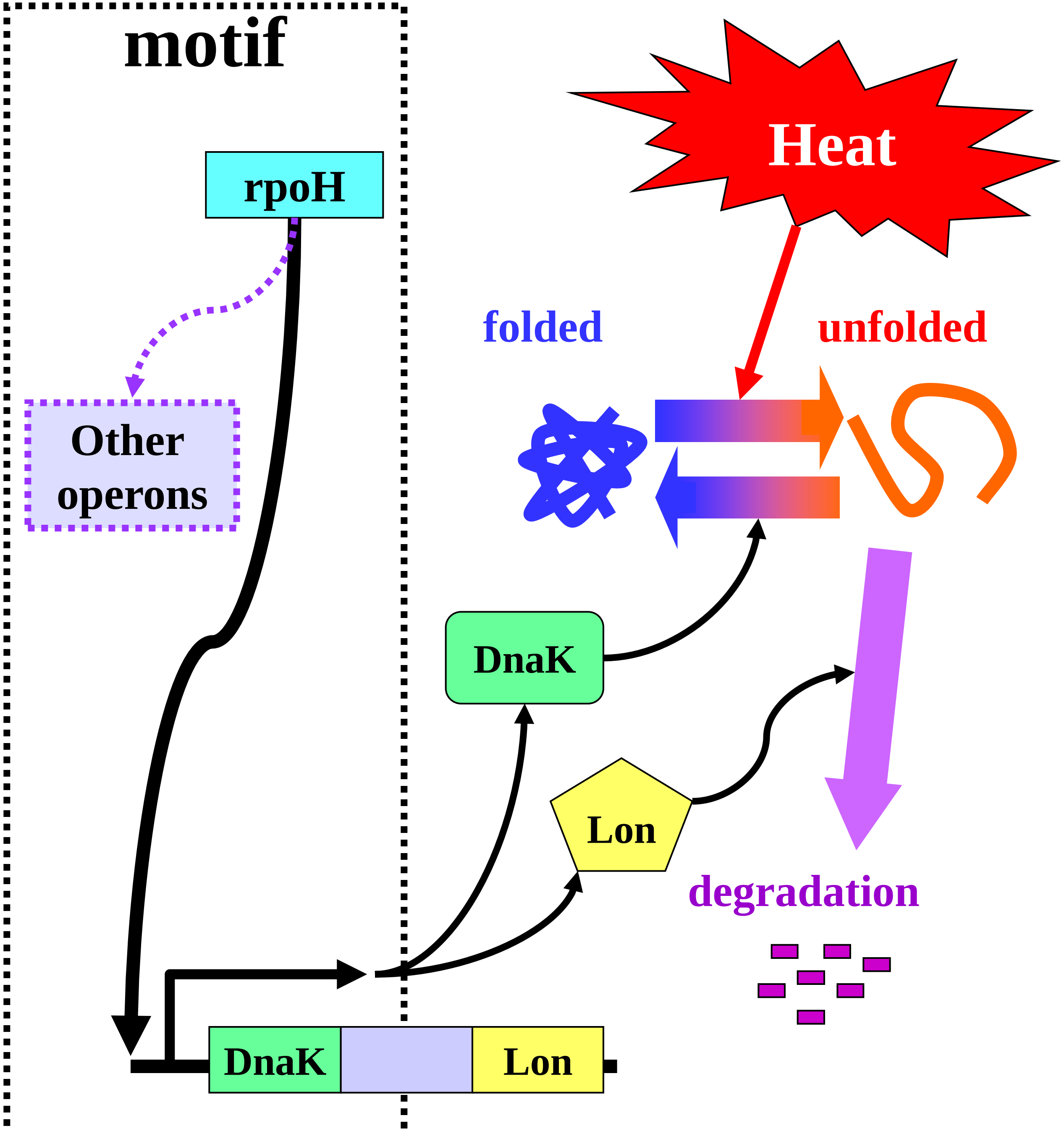


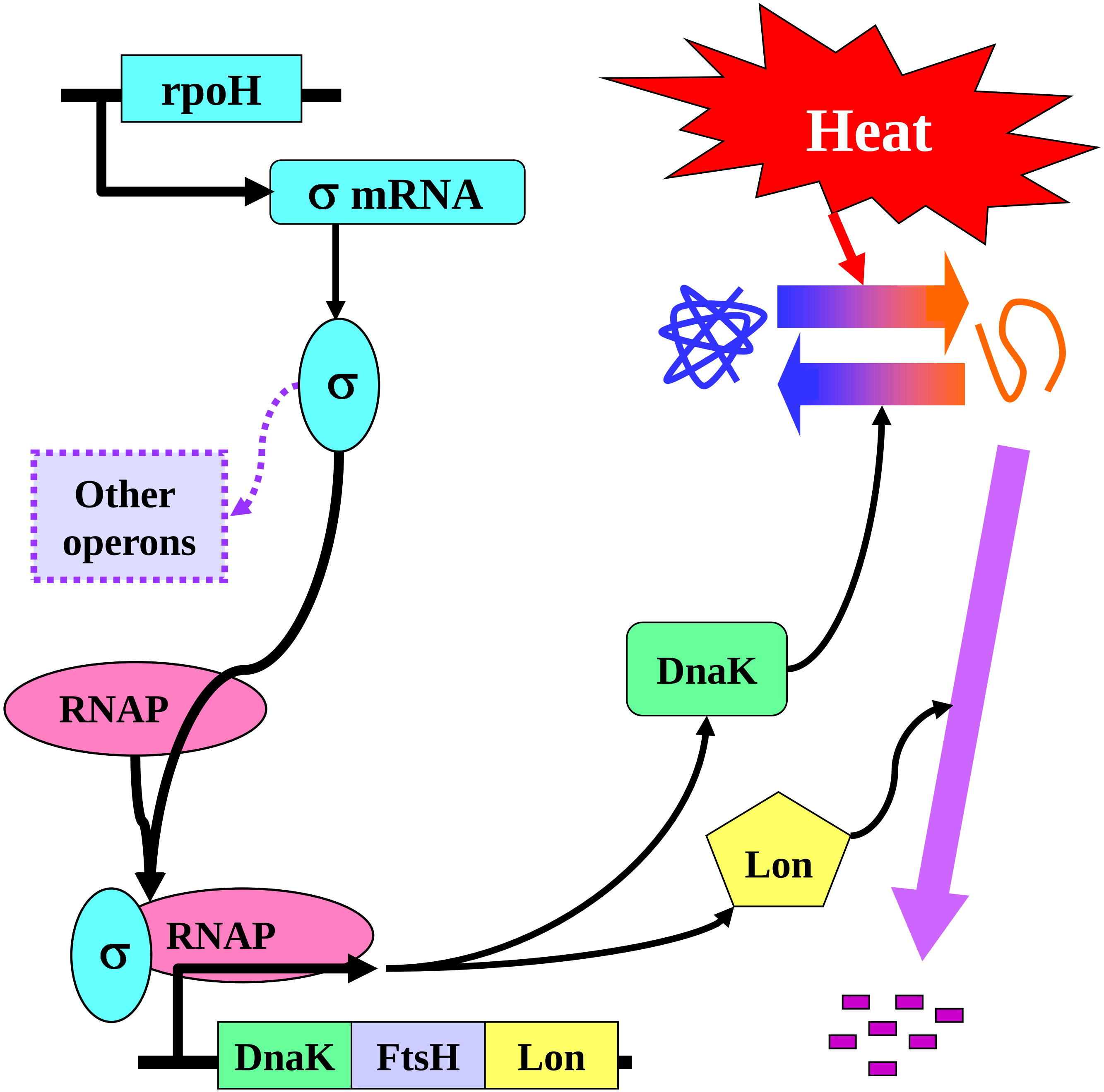
See El-Samad, Kurata, et al…
PNAS, PLOS CompBio

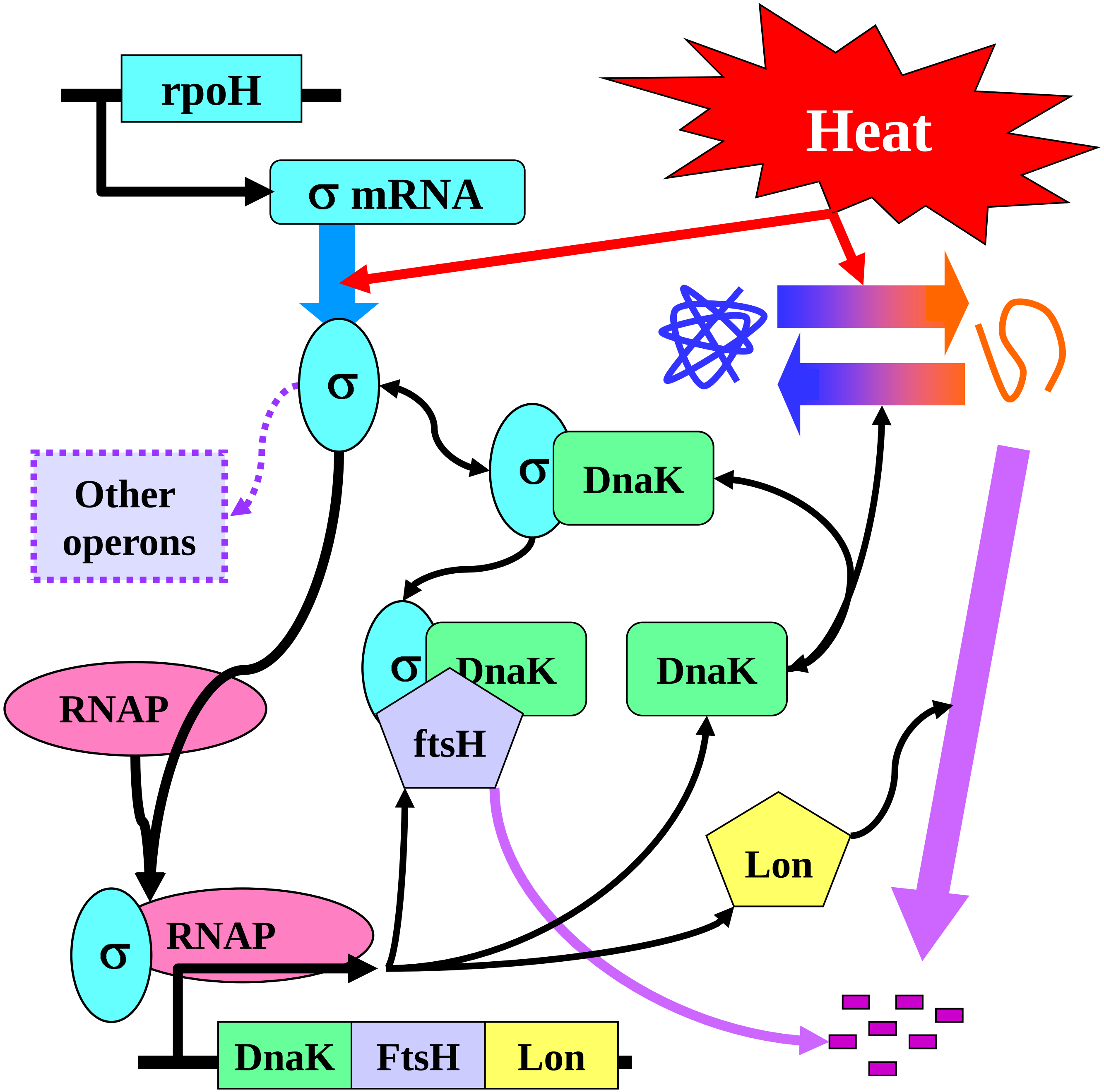

motif
rpoH
Other operons
DnaK
Lon

Where are these layers?



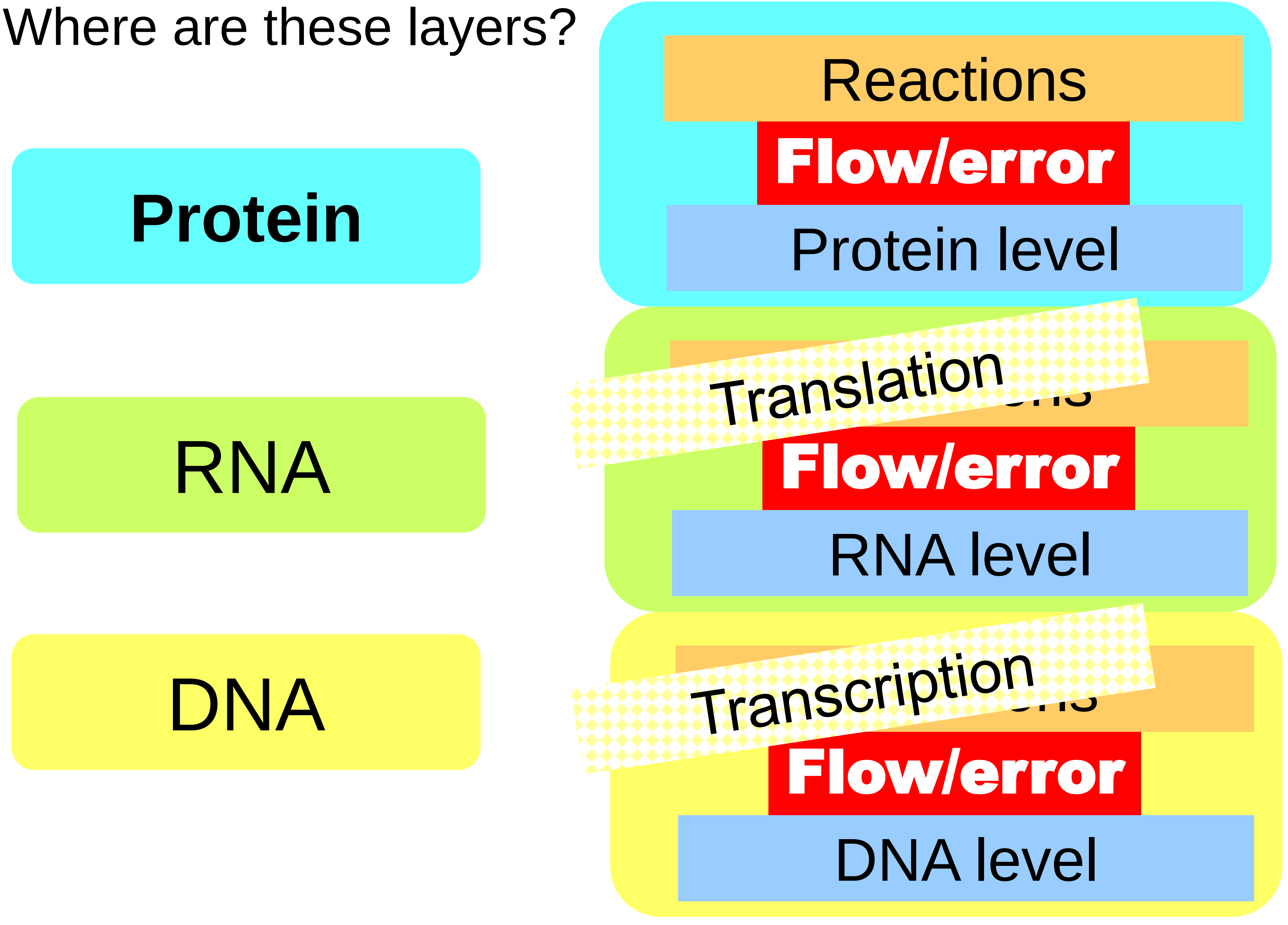

motif
rpoH
Other operons
Heat
folded
unfolded
DnaK
Lon
degradation
DnaK
Lon

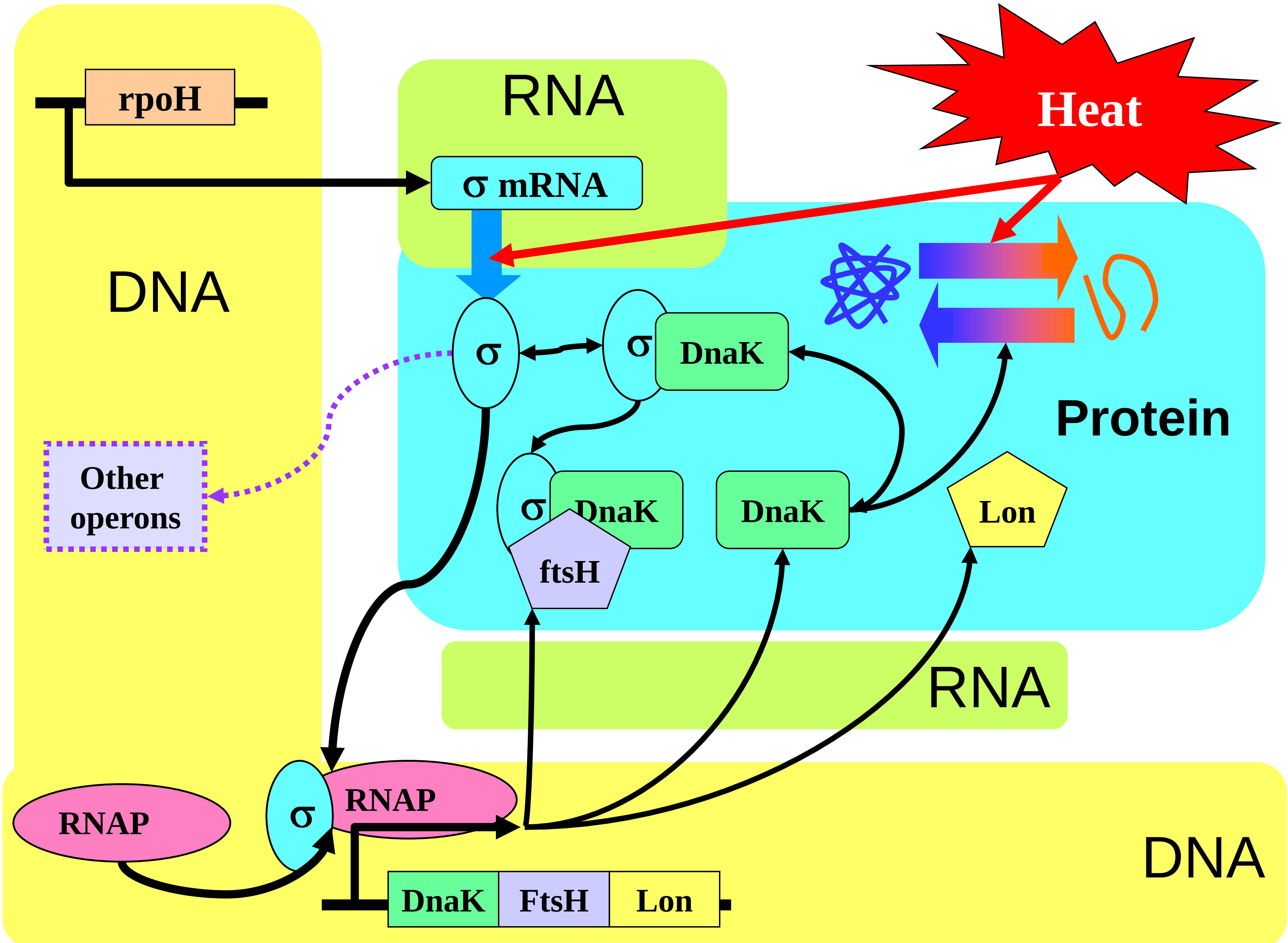

rpoH
σ mRNA
Heat
σ
Other operons
DnaK
RNAP
Lon
σ
RNAP
DnaK
FtsH
Lon

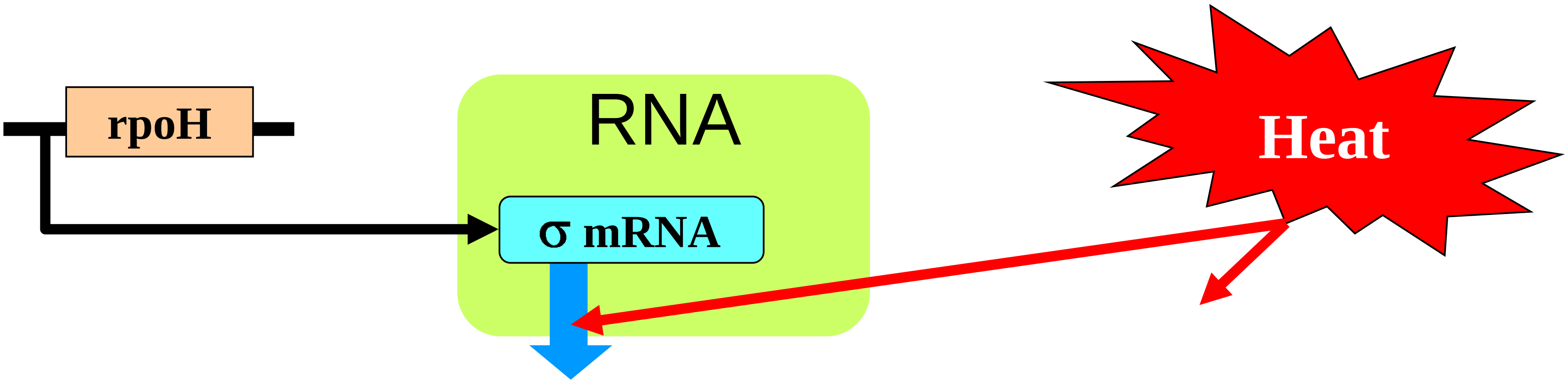


rpoH
σ mRNA
Heat
σ
Other operons
σ
DnaK
σ
DnaK
DnaK
ftsH
RNAP
Lon
σ
RNAP
DnaK
FtsH
Lon

Where are these layers?

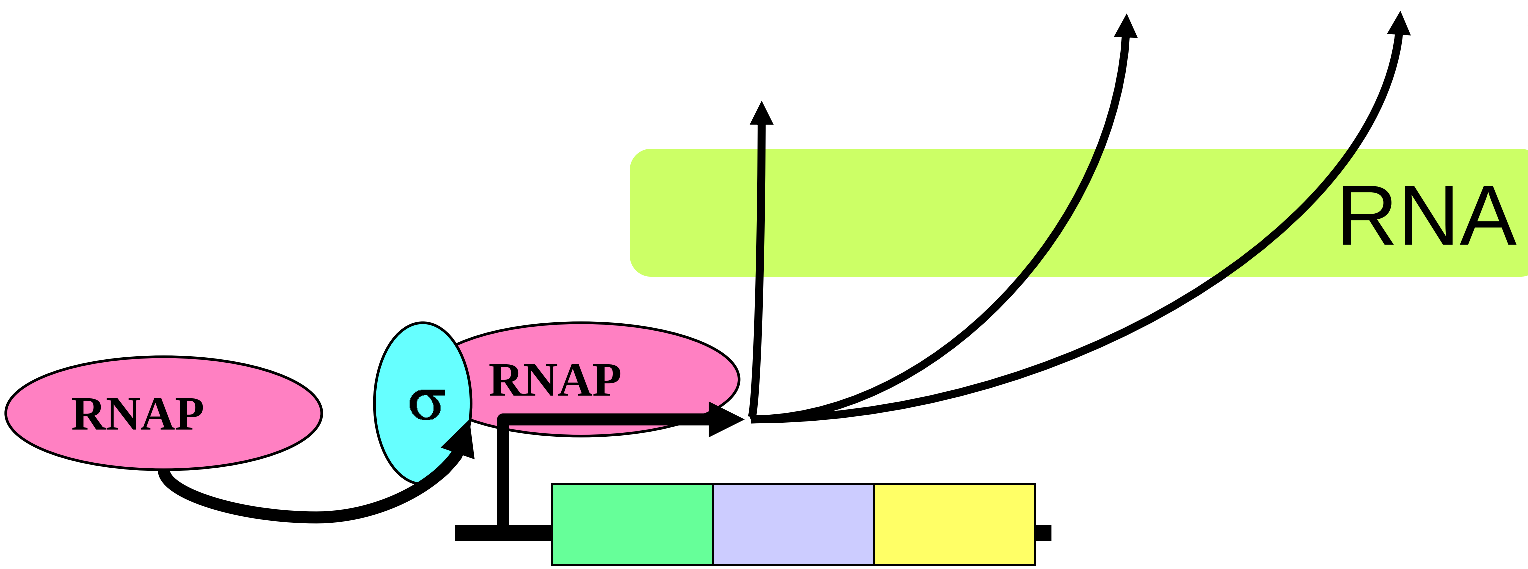


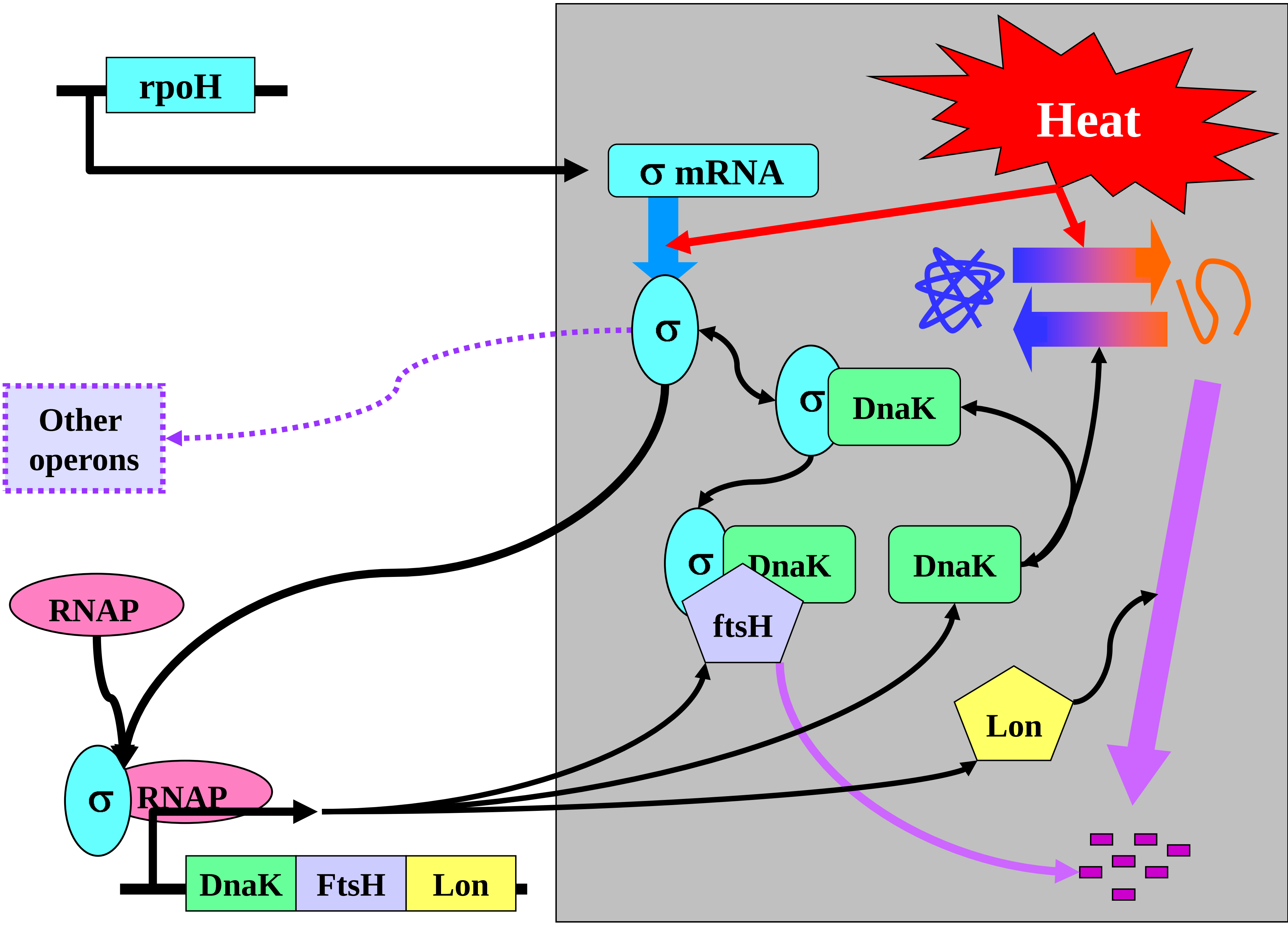

rpoH
RNA
σ mRNA
Heat
DNA
σ
σ
DnaK
Protein
Other
operons
σ
DnaK
ftsH
DnaK
Lon
RNA
RNAP
σ
RNAP
DNA
DnaK
FtsH
Lon

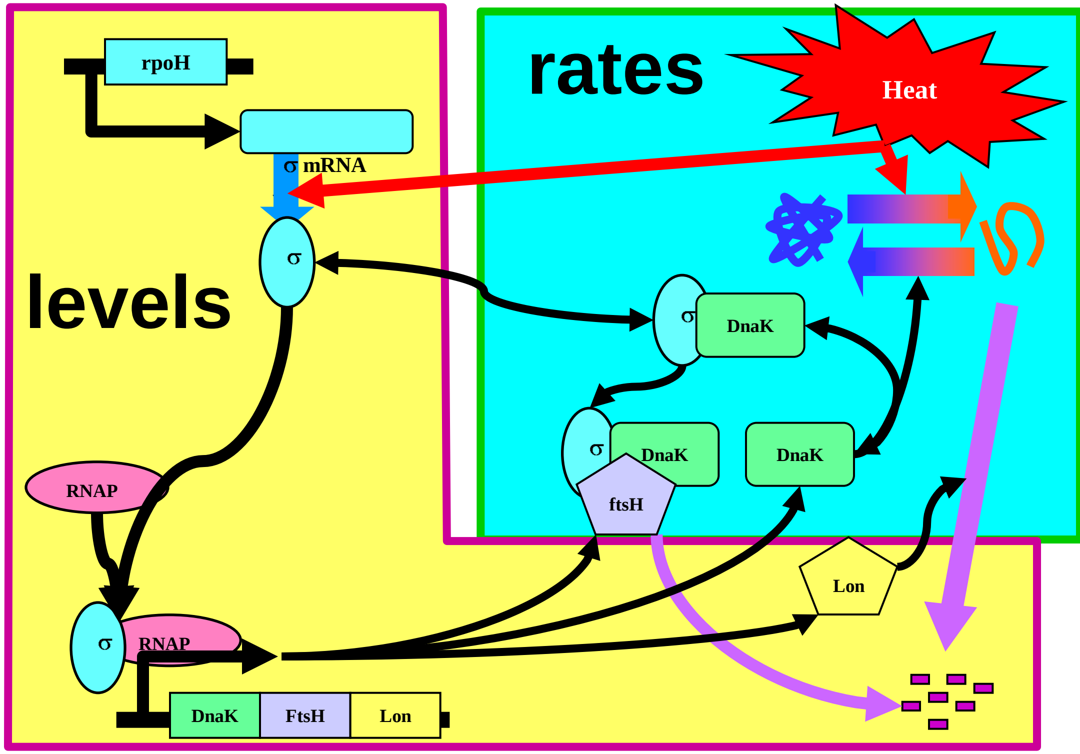


mRNA activity is actively controlled.

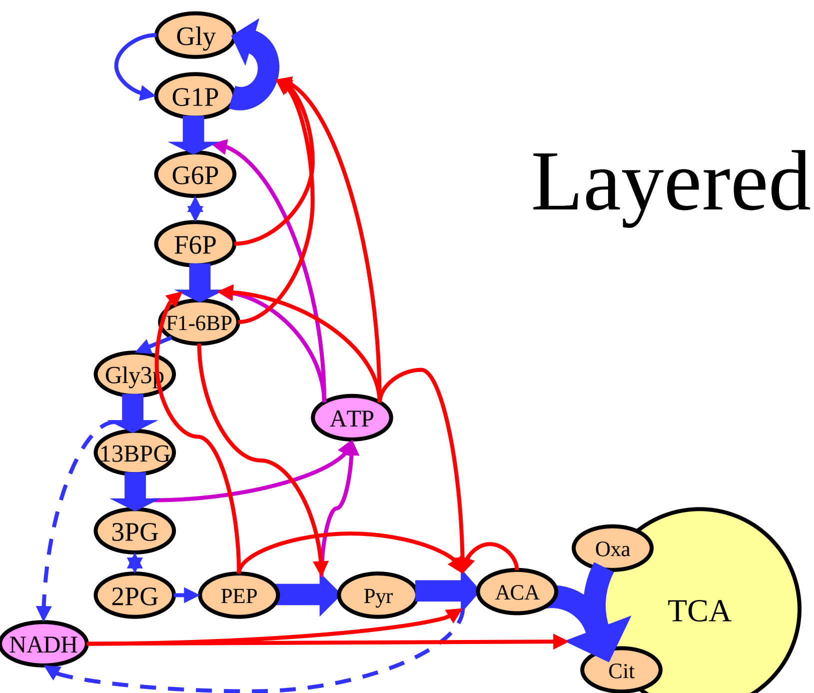
Translation was not shown.




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



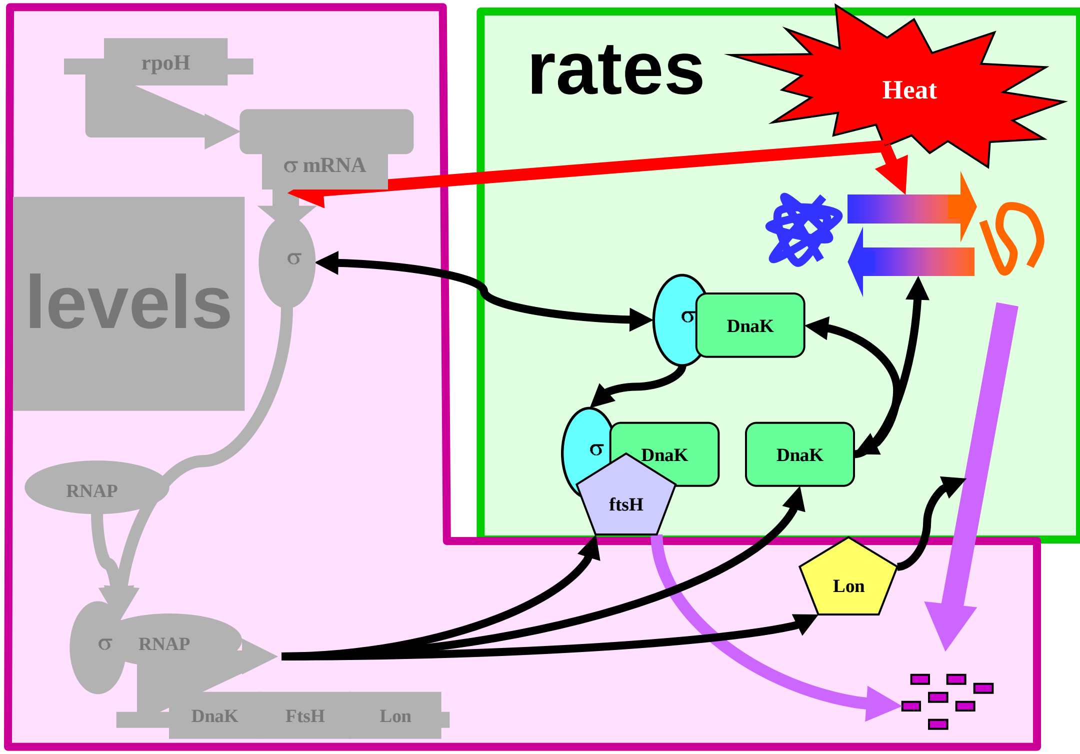
Layered control architectures

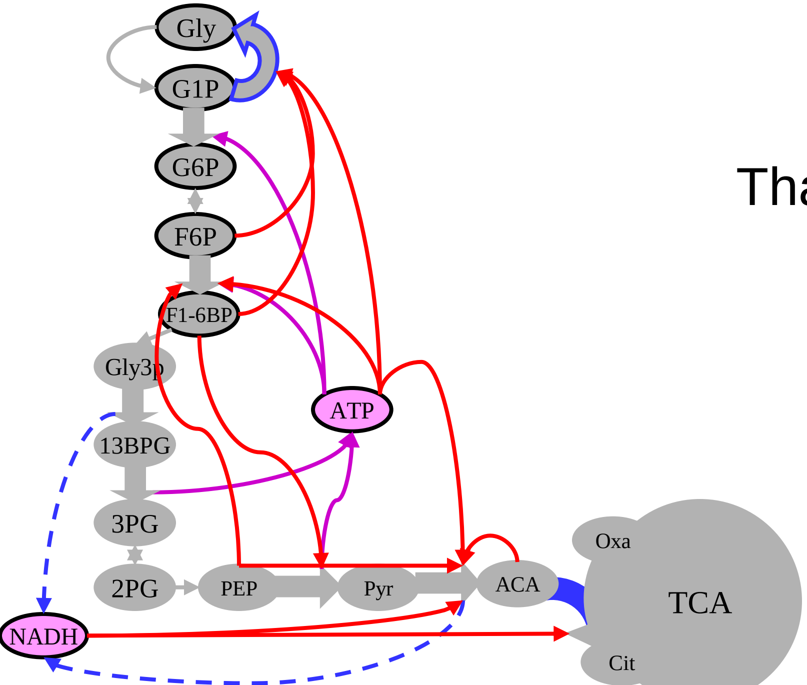


Allosteric

Trans*

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

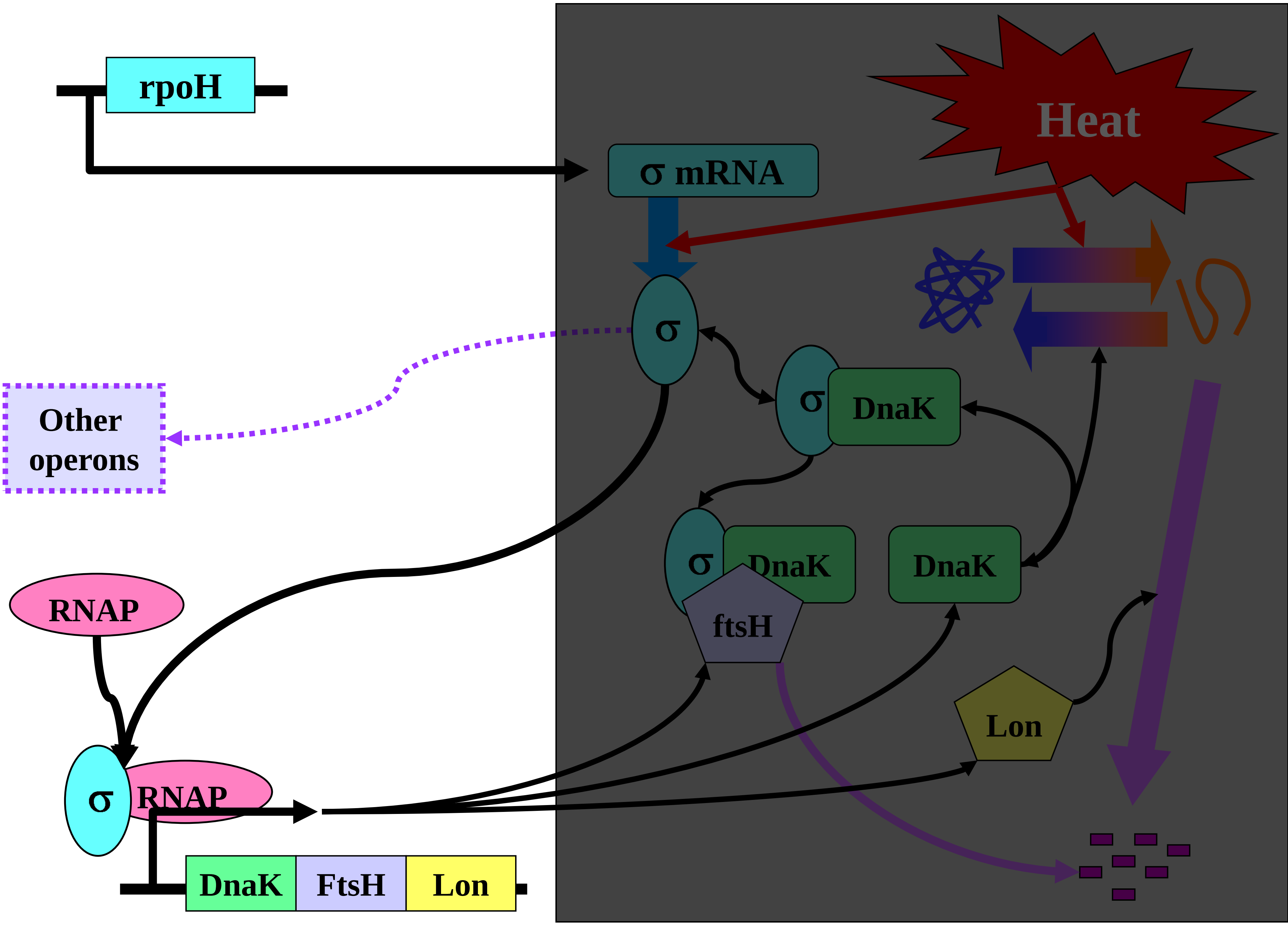


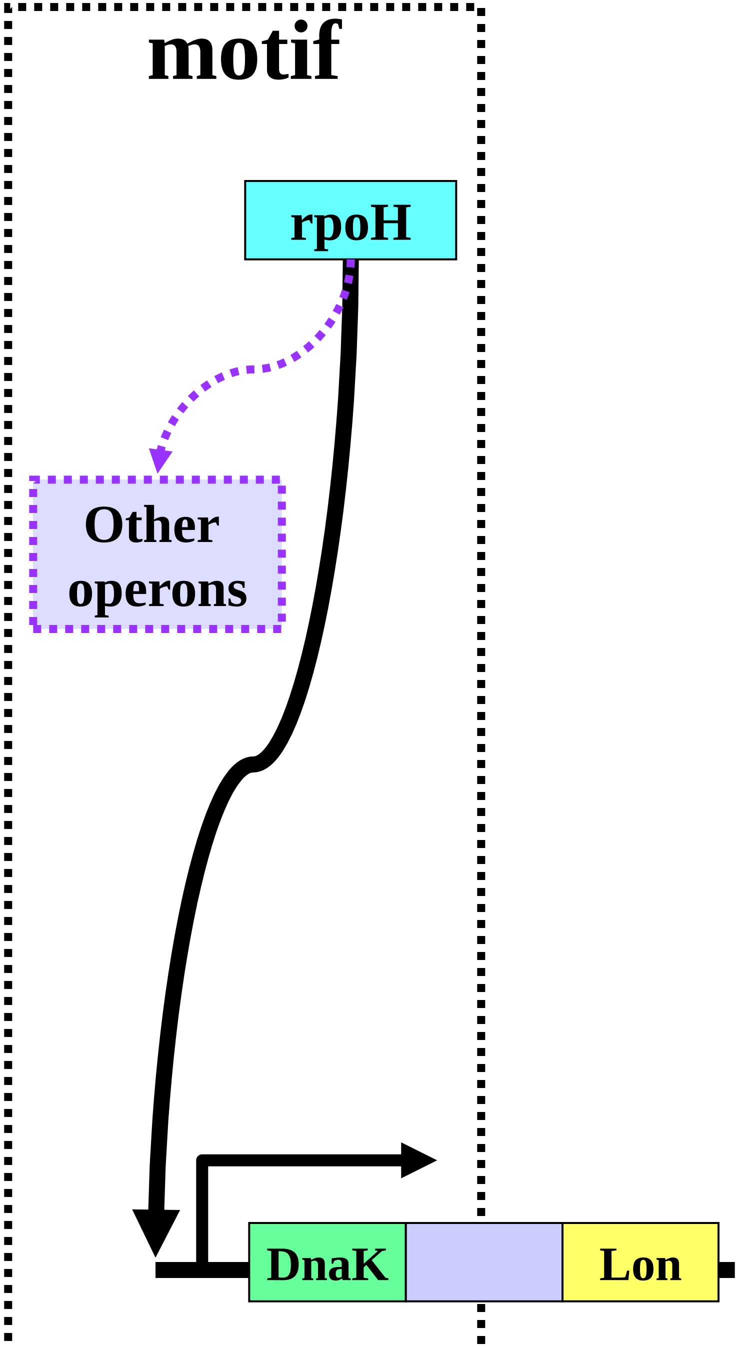


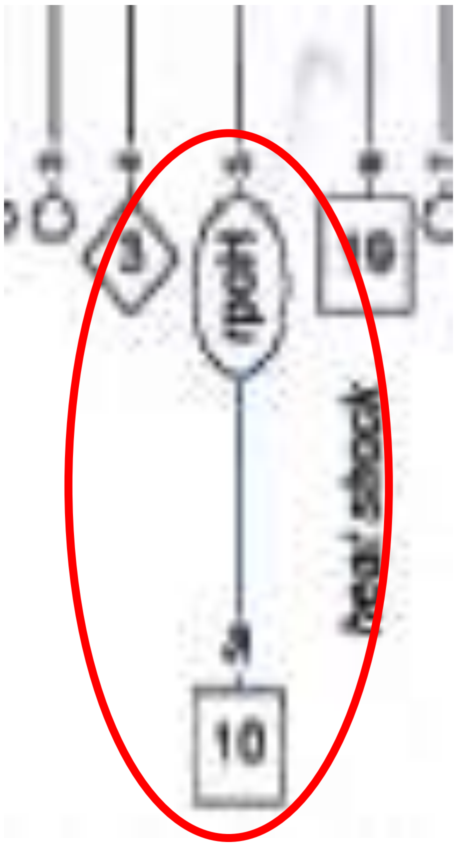
That is not always the case.

Allosteric

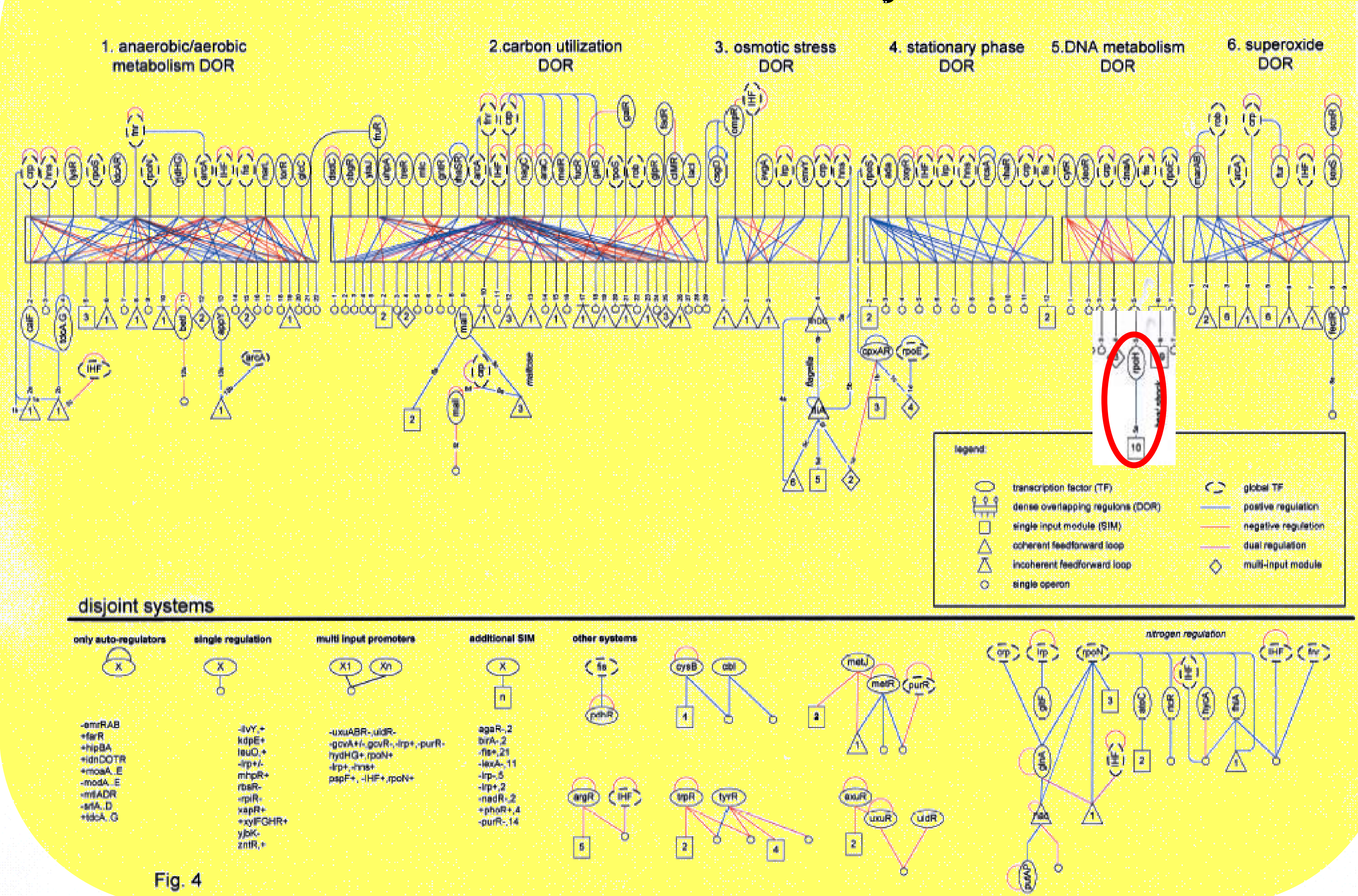
Trans*

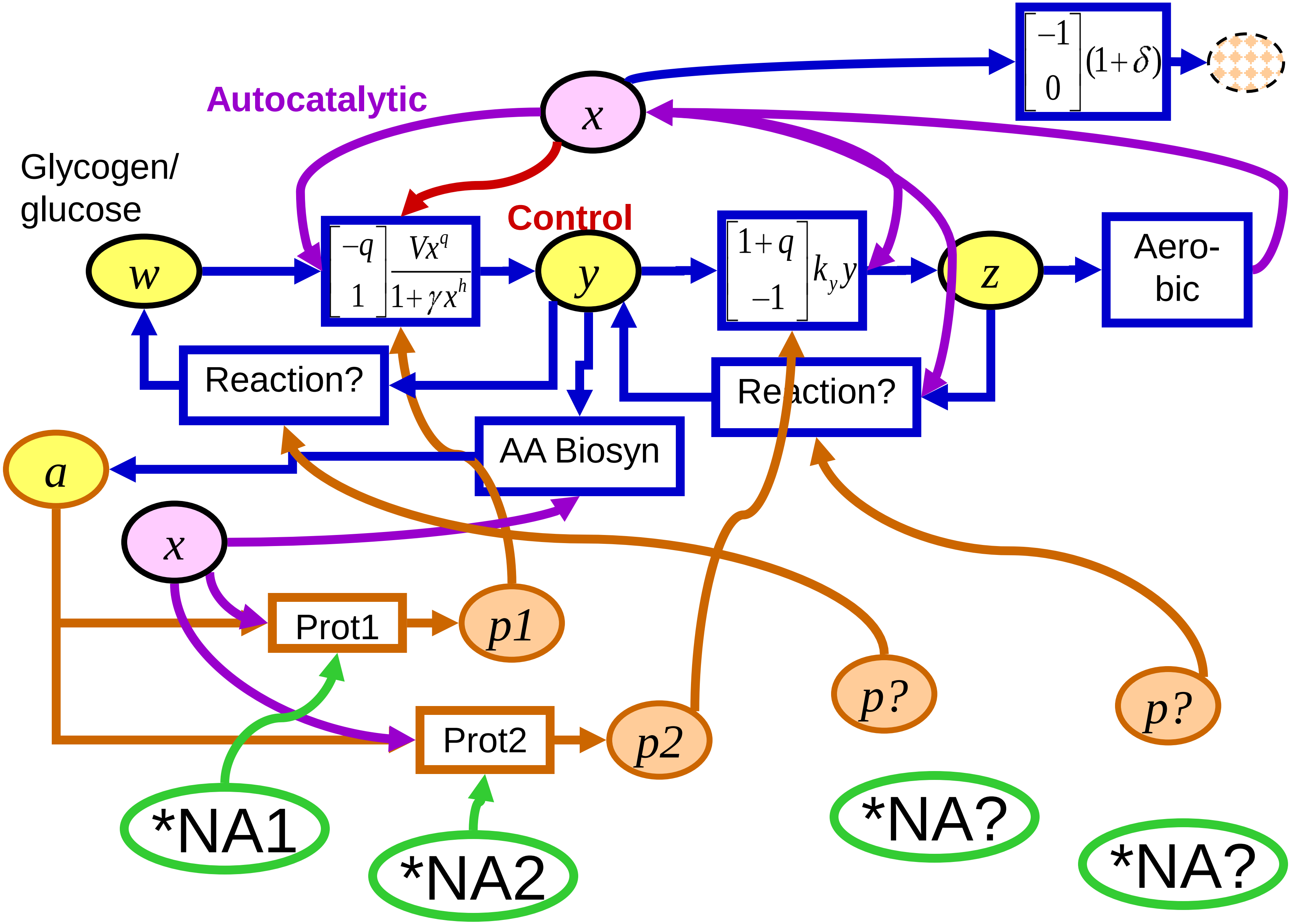

rpoH
σ mRNA
Heat
σ
Other operons
σ
DnaK
σ
DnaK
ftsH
DnaK
Lon
RNAP
σ
RNAP
DnaK
FtsH
Lon


motif
rpoH
Other
operons
DnaK
Lon


3
rpoH
19
10

All at the DNA layer





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

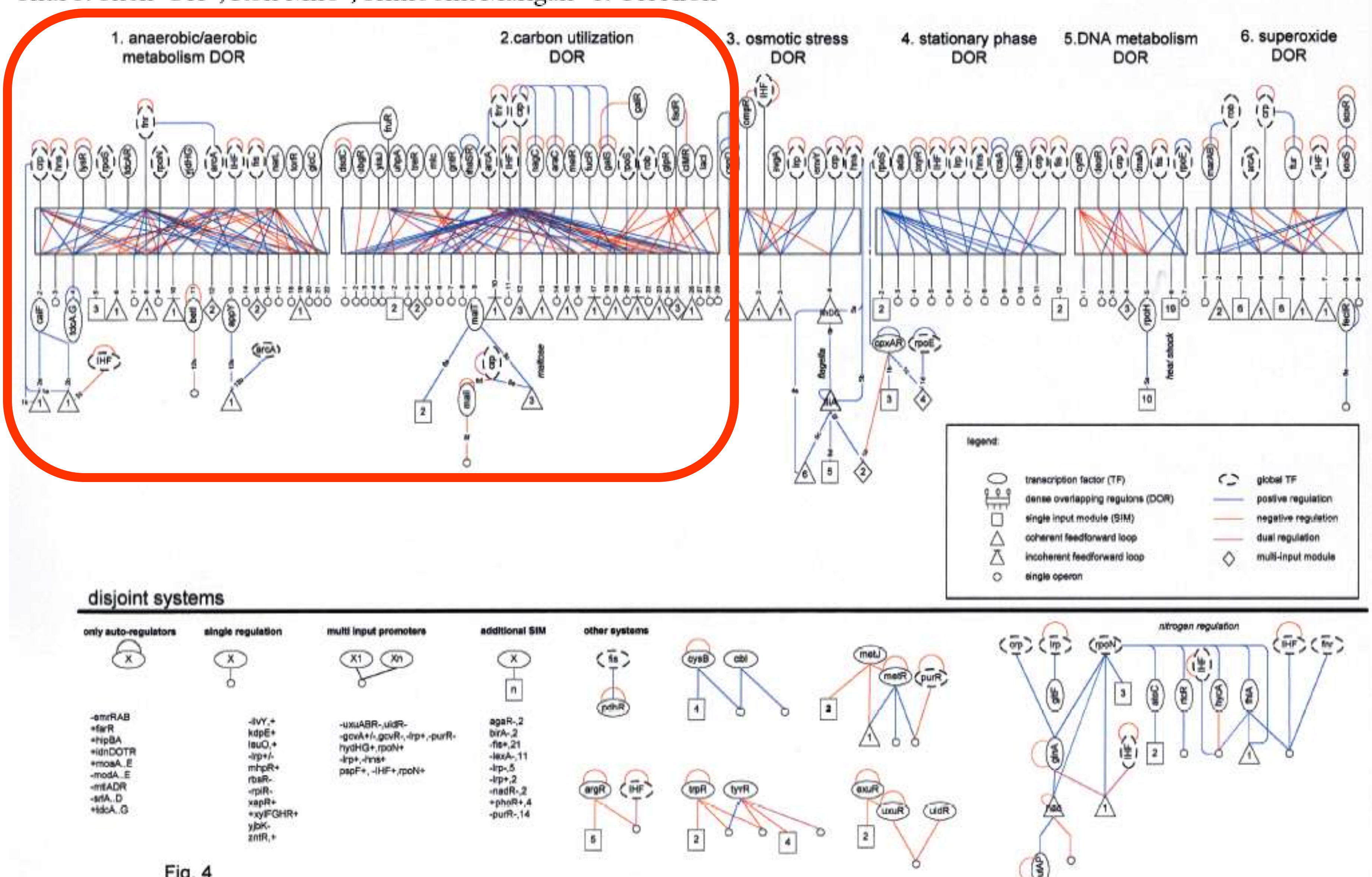
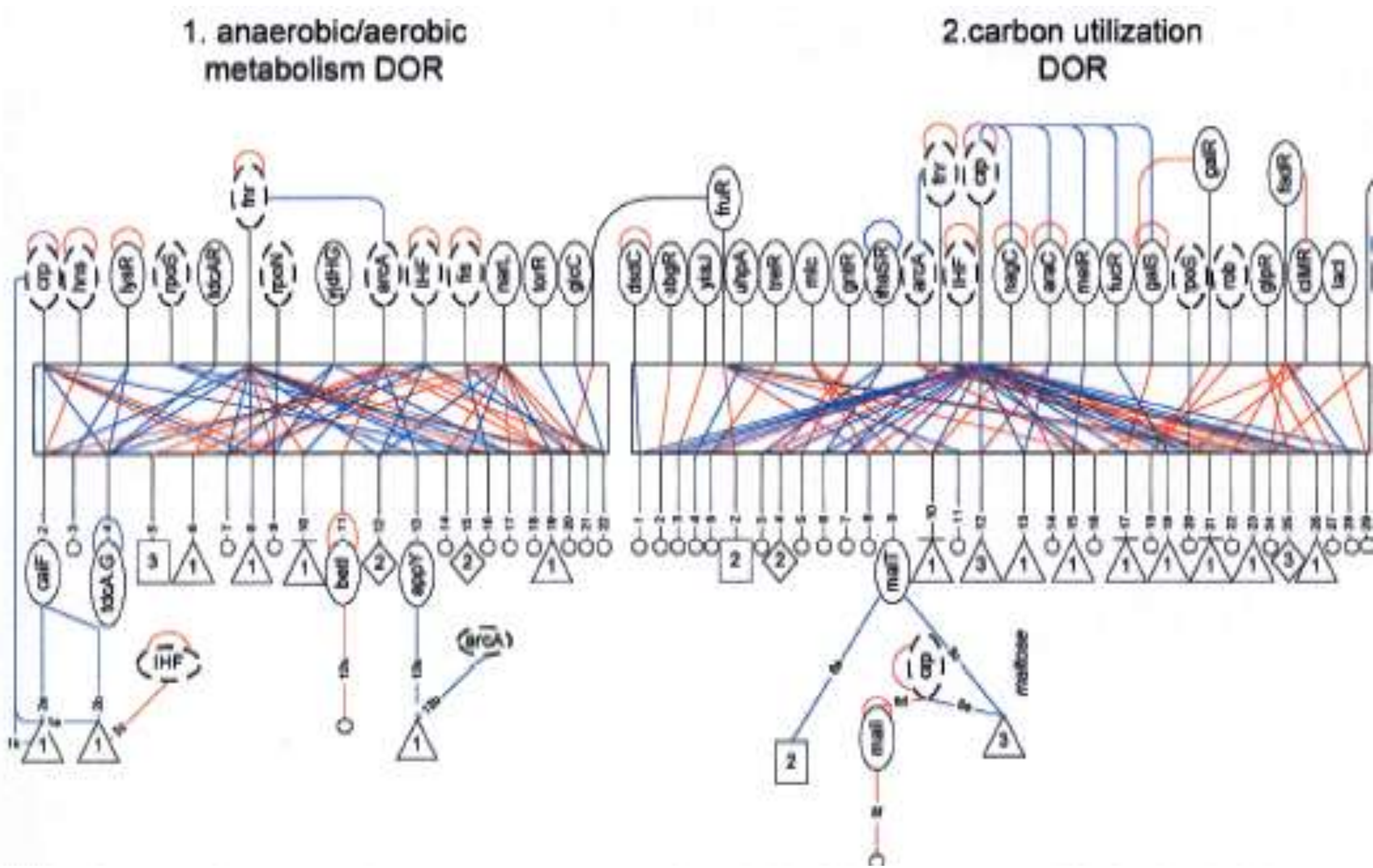
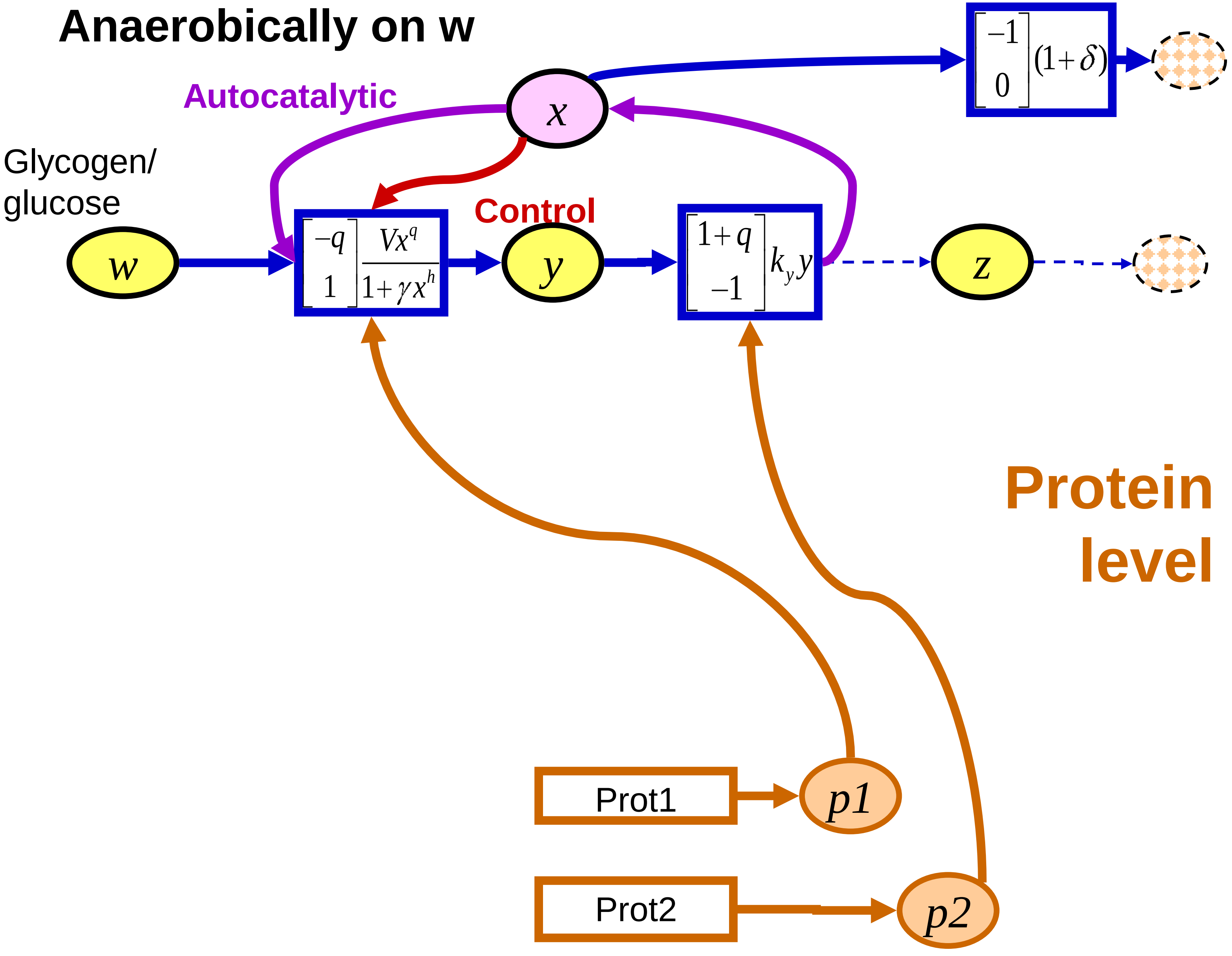


Fig. 4

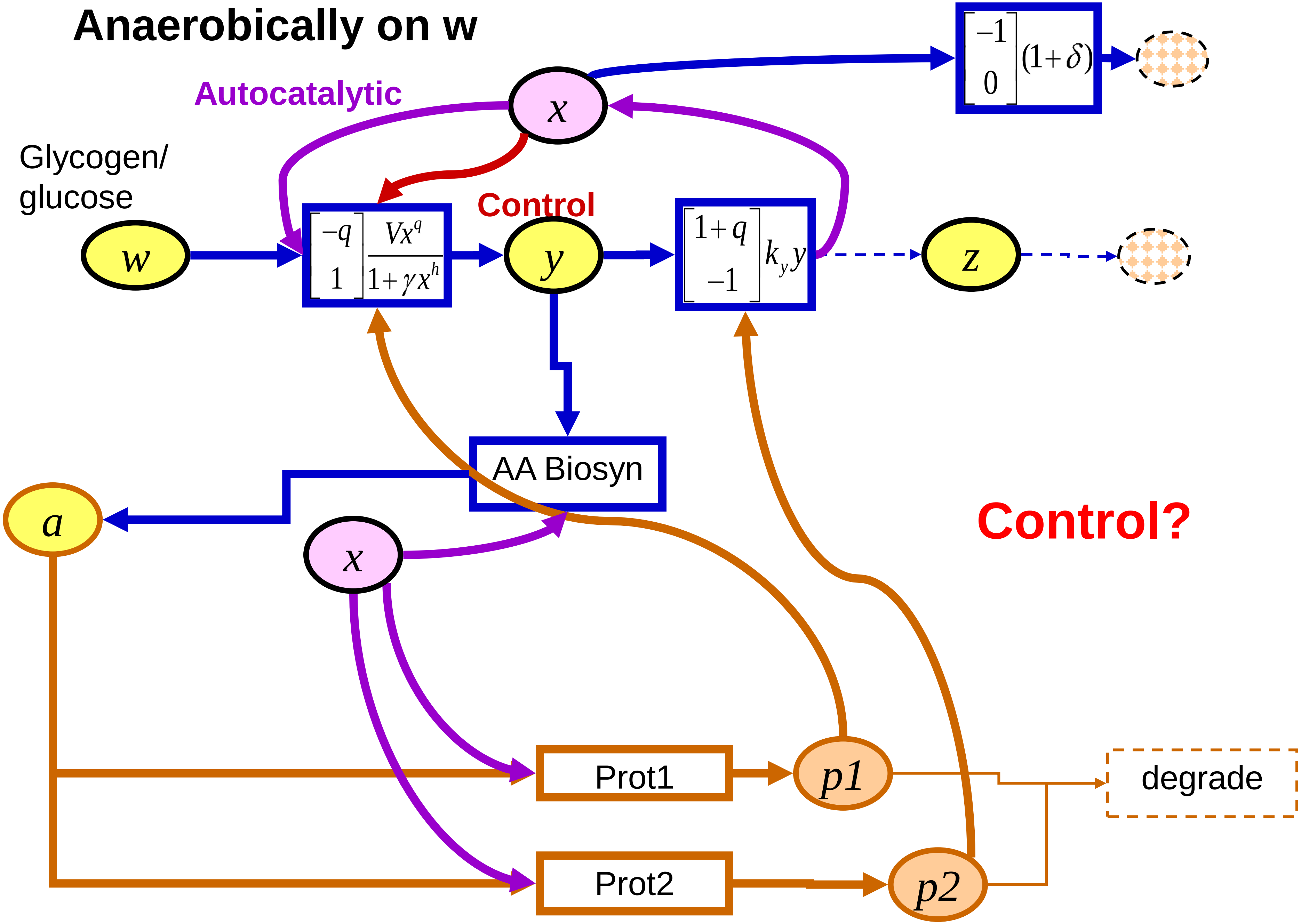


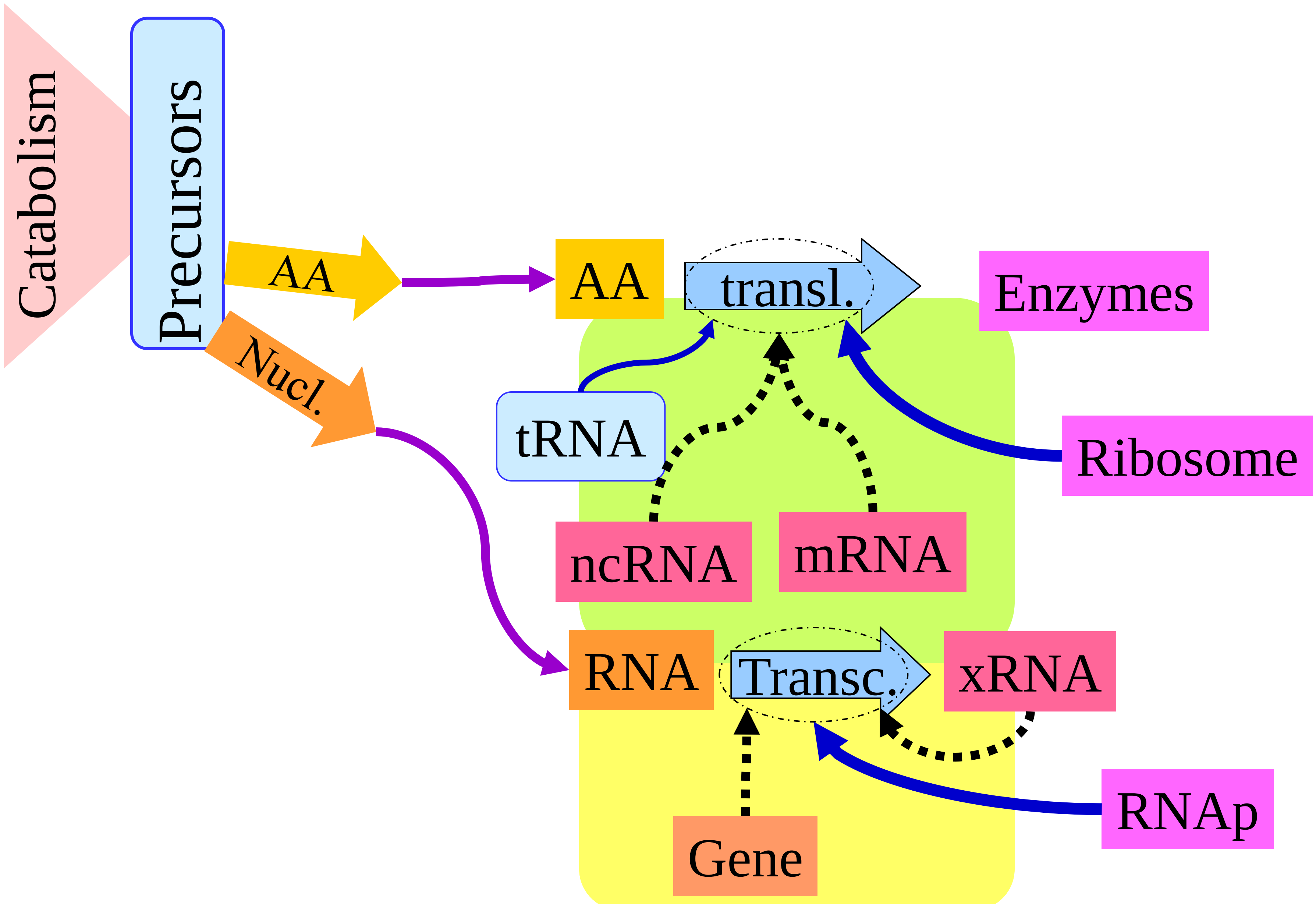
1. anaerobic/aerobic metabolism DOR
2.carbon utilization DOR

Anaerobically on w

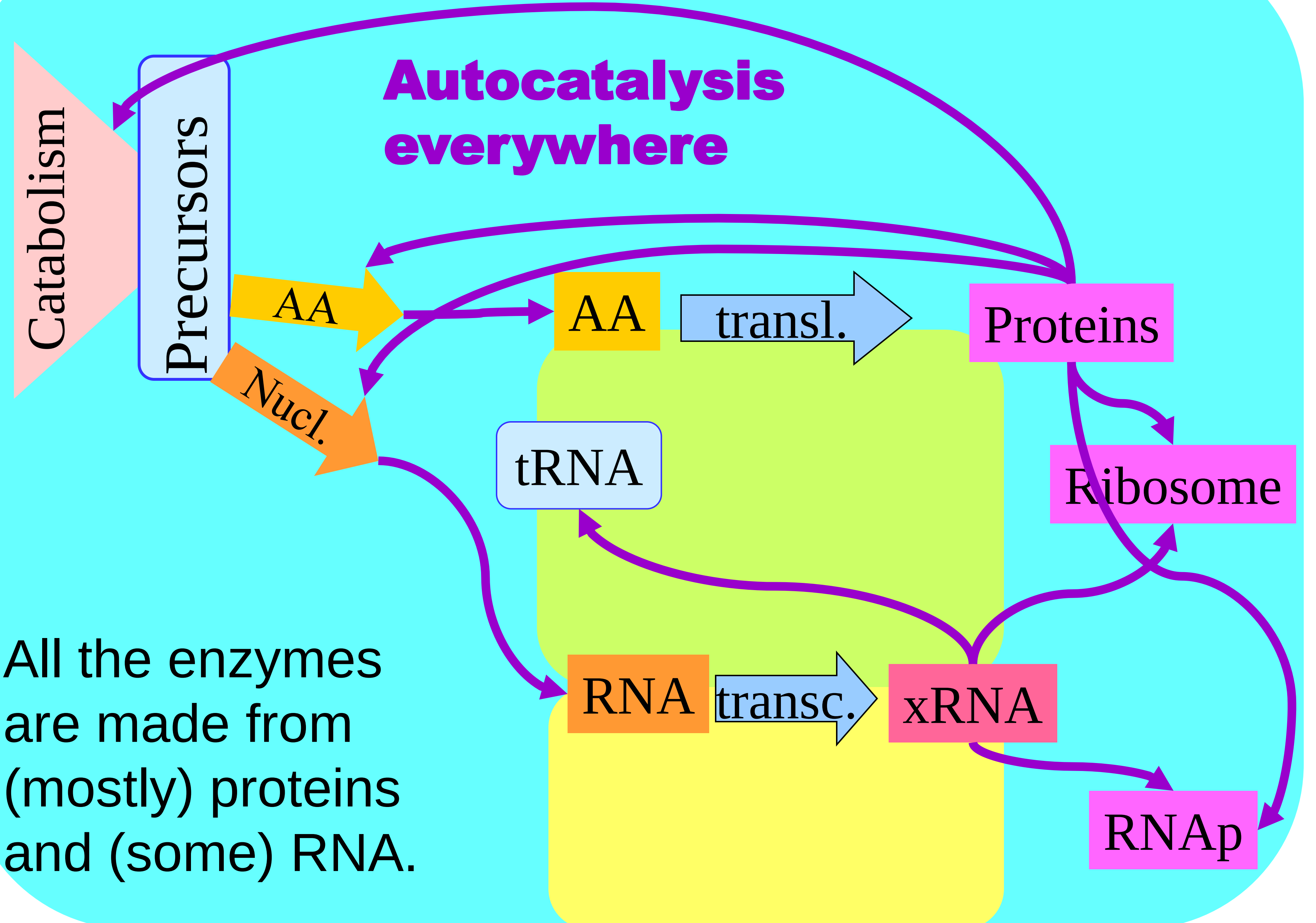


Anaerobically on w



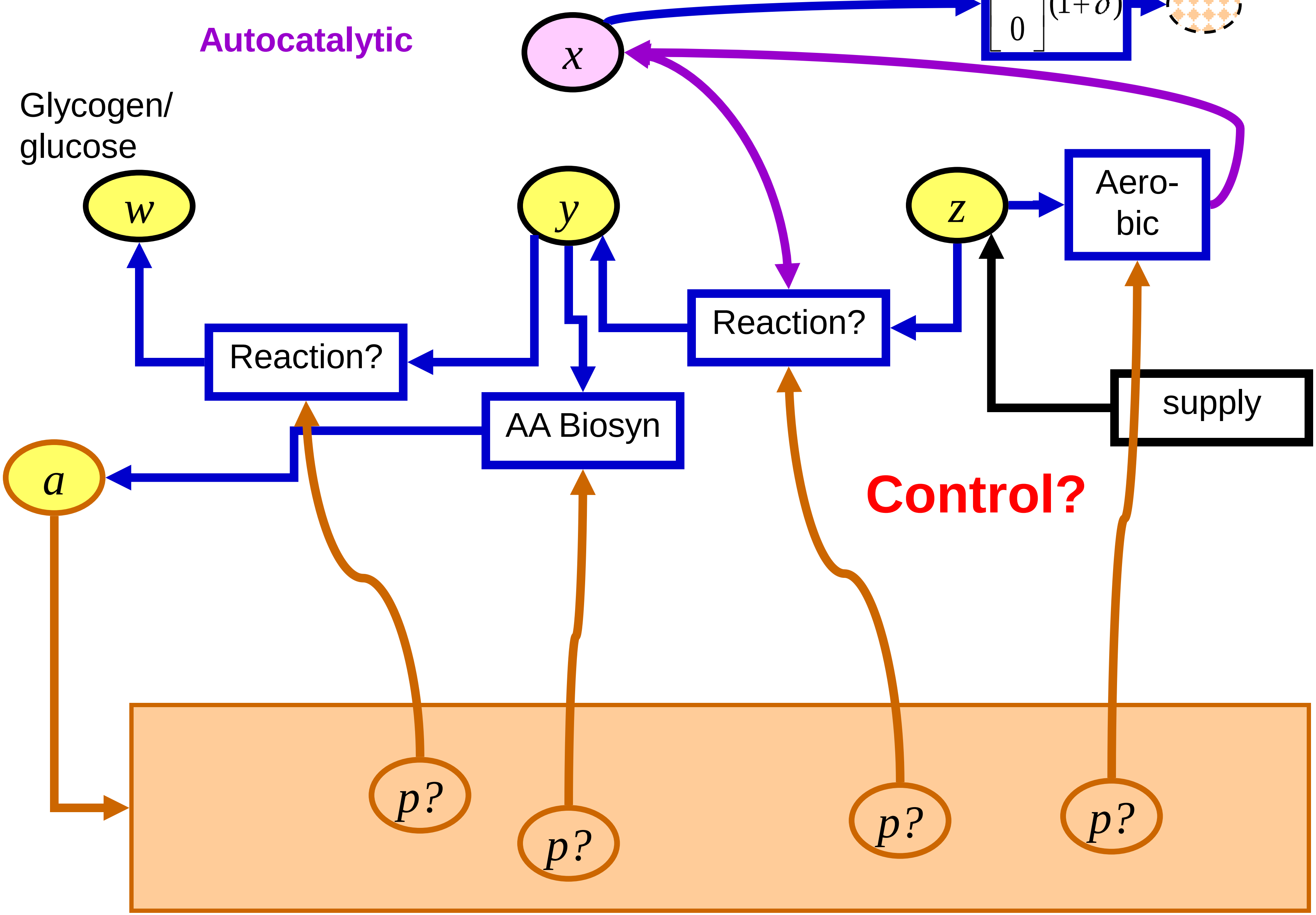

Catabolism
Precursors
AA
Nucl.
AA
transl.
Enzymes
tRNA
Ribosome
ncRNA
mRNA
RNA
Transc.
xRNA
RNAp
Gene

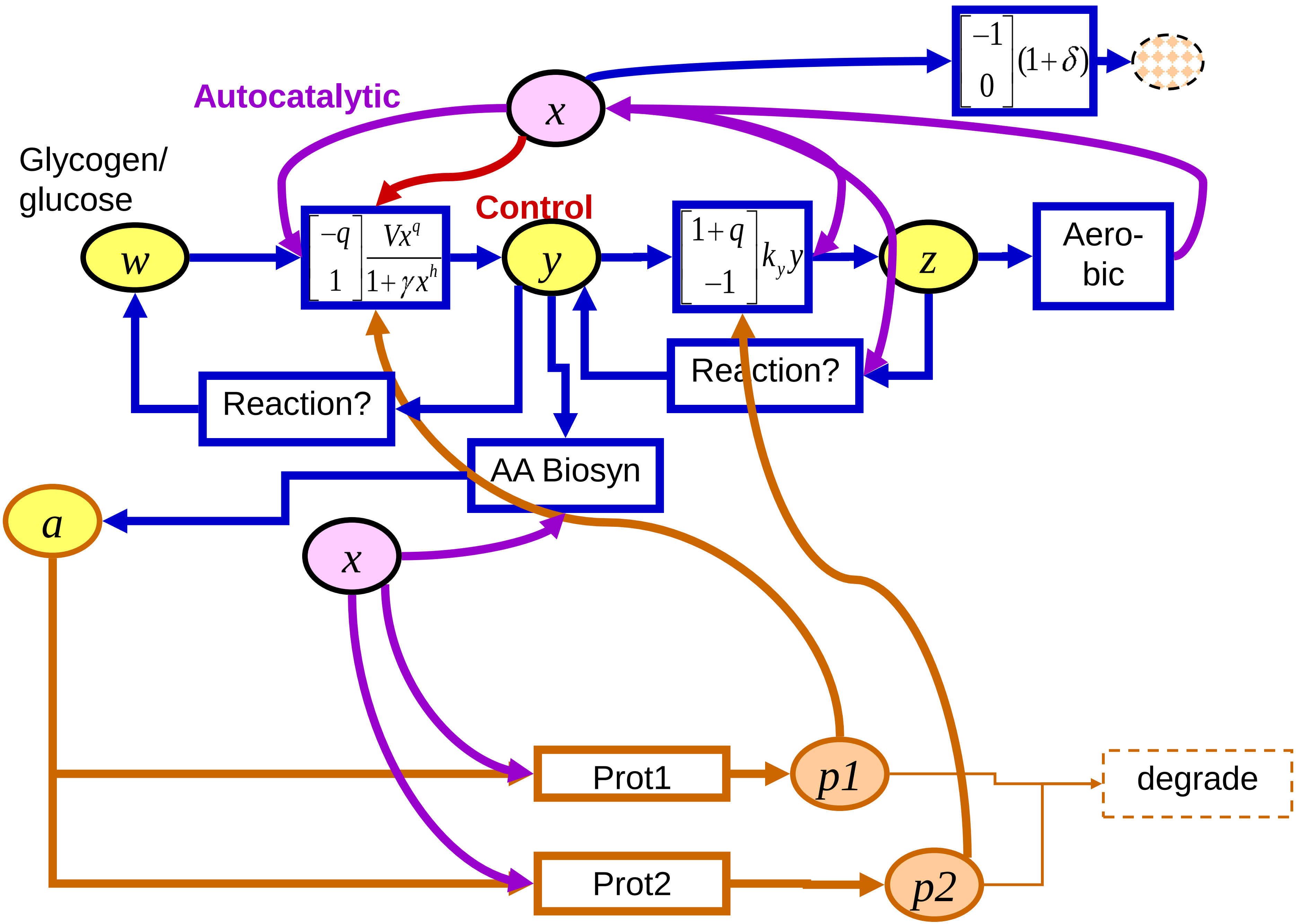
Autocatalysis everywhere



All the enzymes are made from (mostly) proteins and (some) RNA.

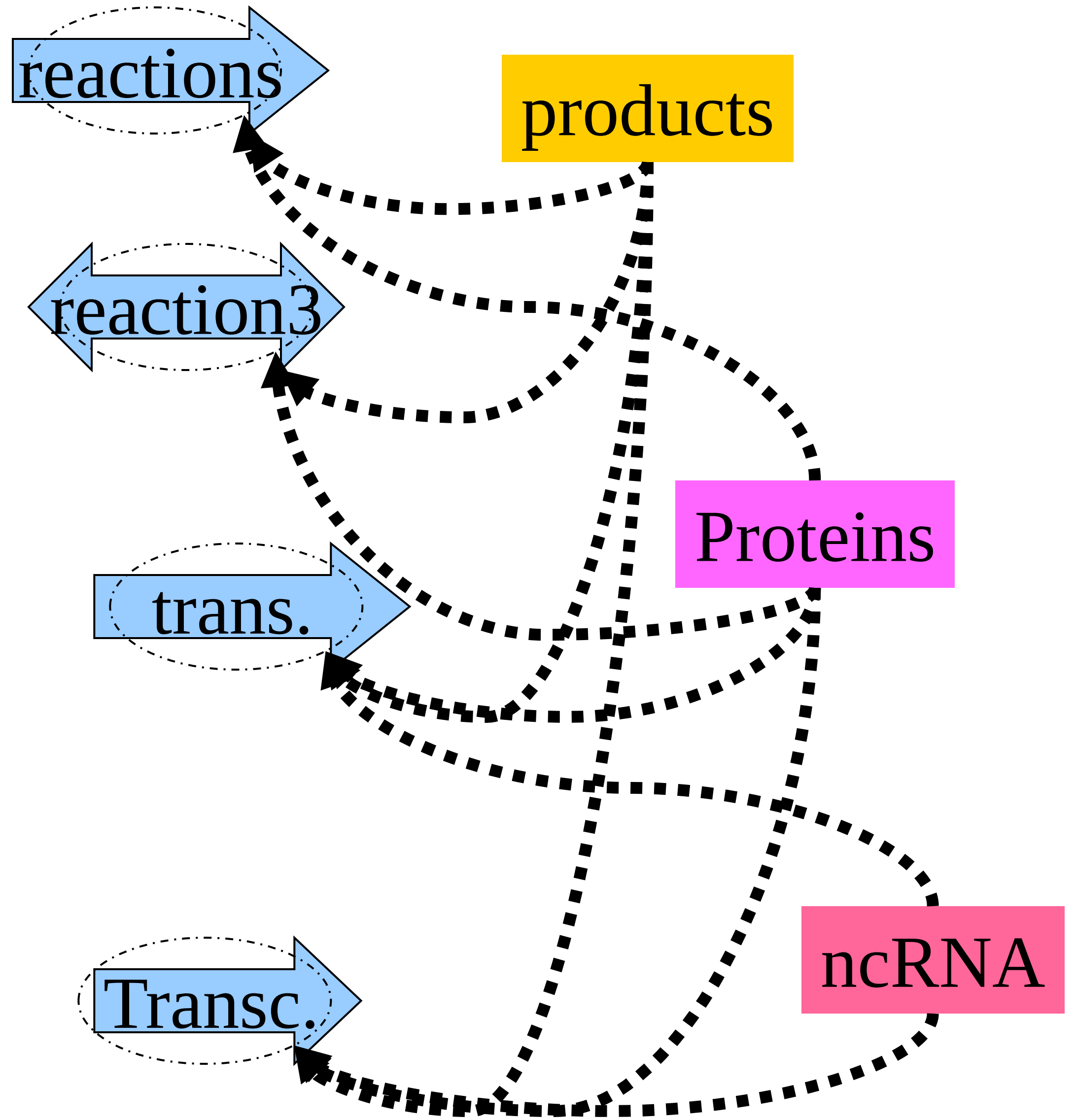
Aerobically on z





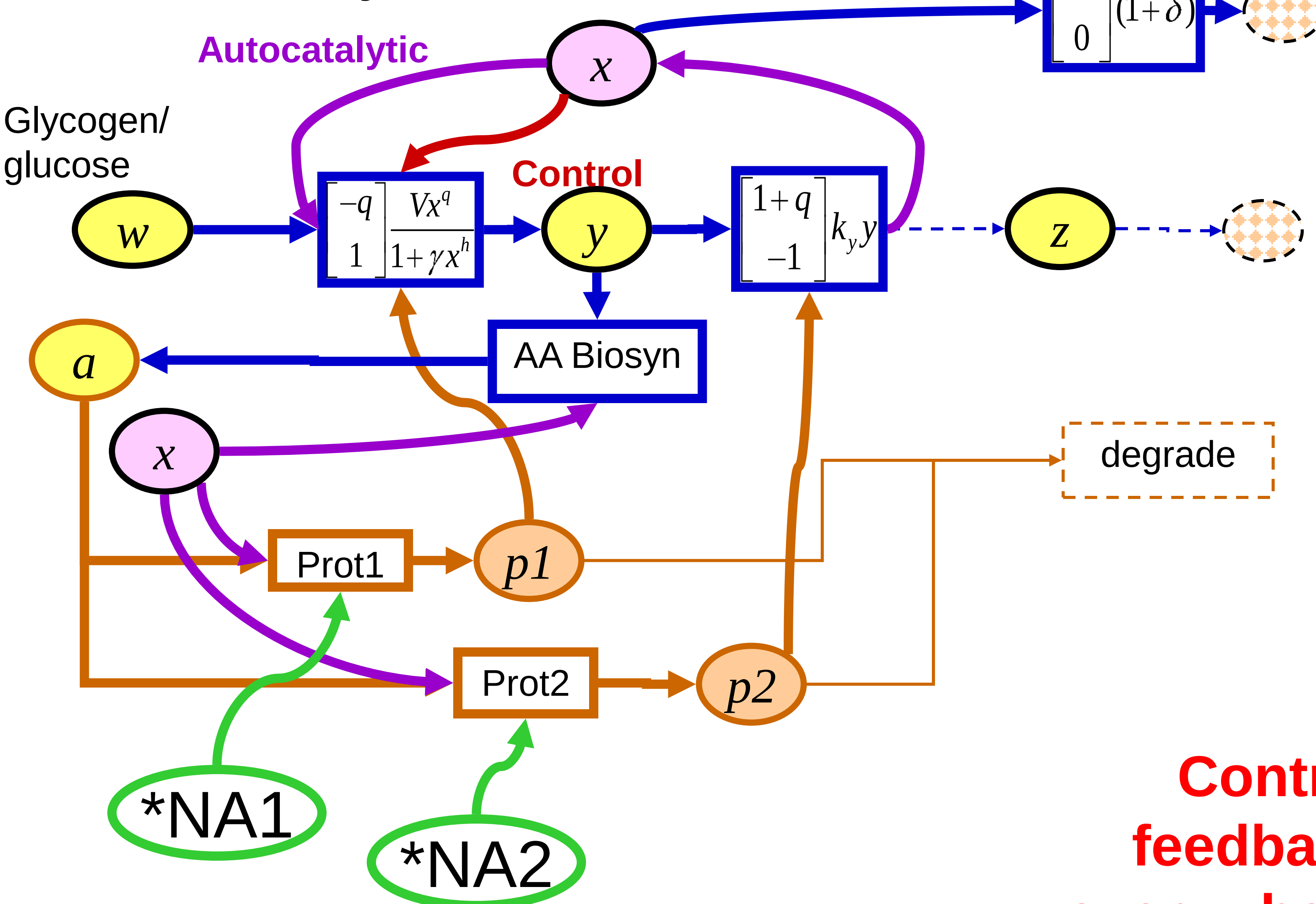
Autocatalytic
Glycogen/
glucose
Control
Reaction?
Reaction?
AA Biosyn
Aero-
bic
Prot1
Prot2
degrade
w
x
y
z
a
x
p1
p2

Control?

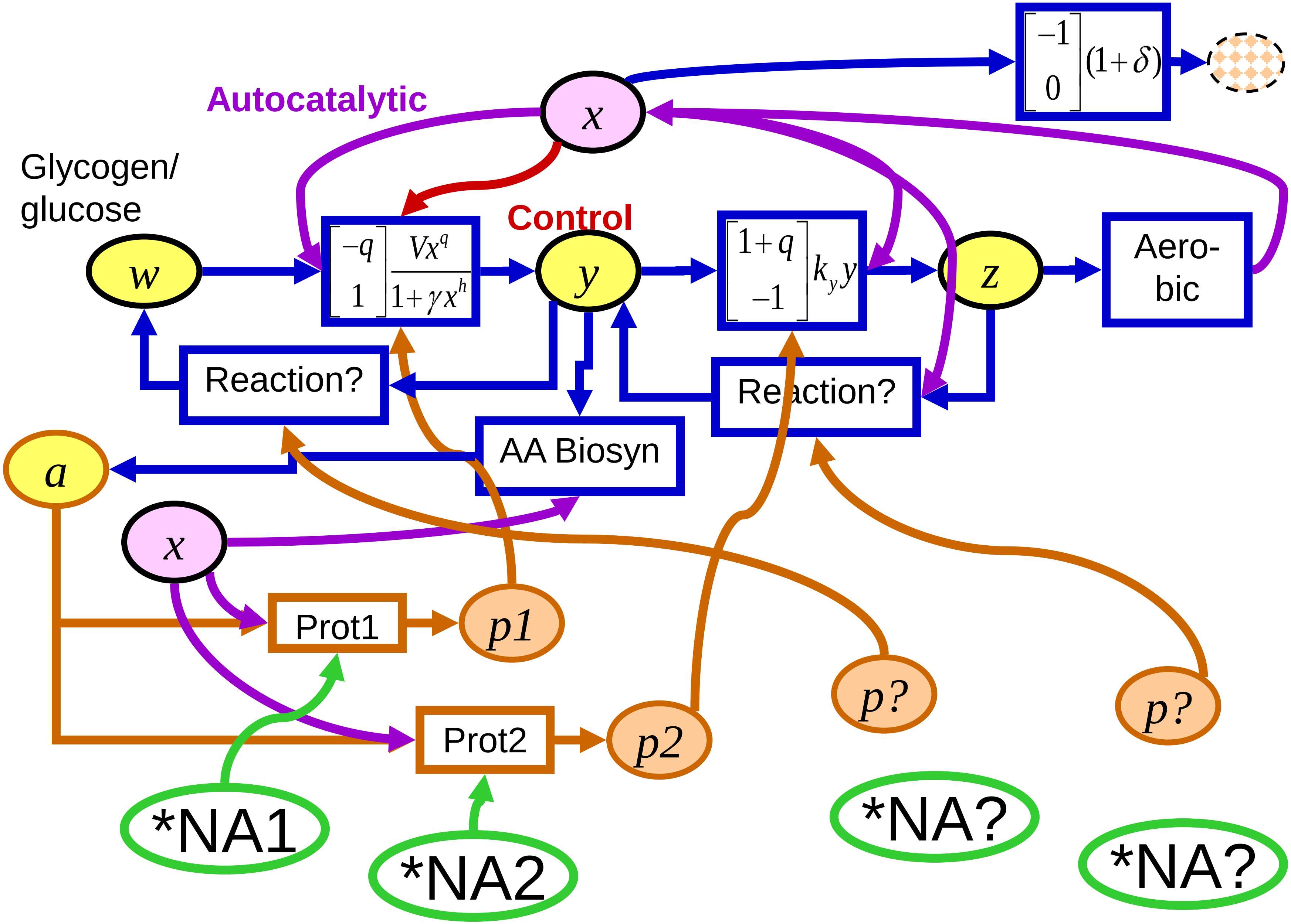


All products
feedback everywhere

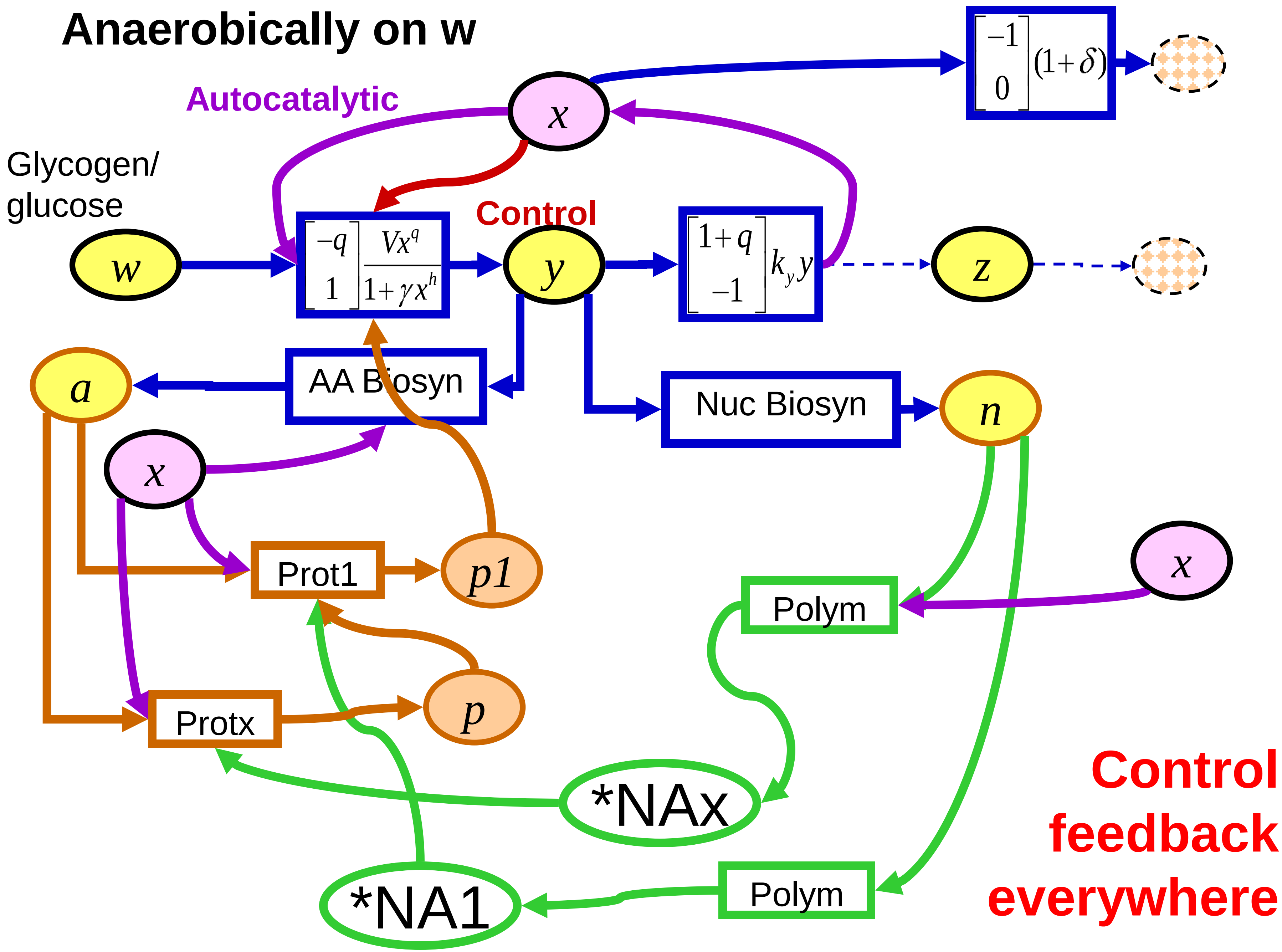
Anaerobically on w



Control feedback everywhere



Autocatalytic
Glycogen/ glucose
Control
x
w
y
z
Aero-bic
Reaction?
Reaction?
AA Biosyn
a
x
Prot1
Prot2
p1
p2
p?
p?
*NA1
*NA2
*NA?
*NA?


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