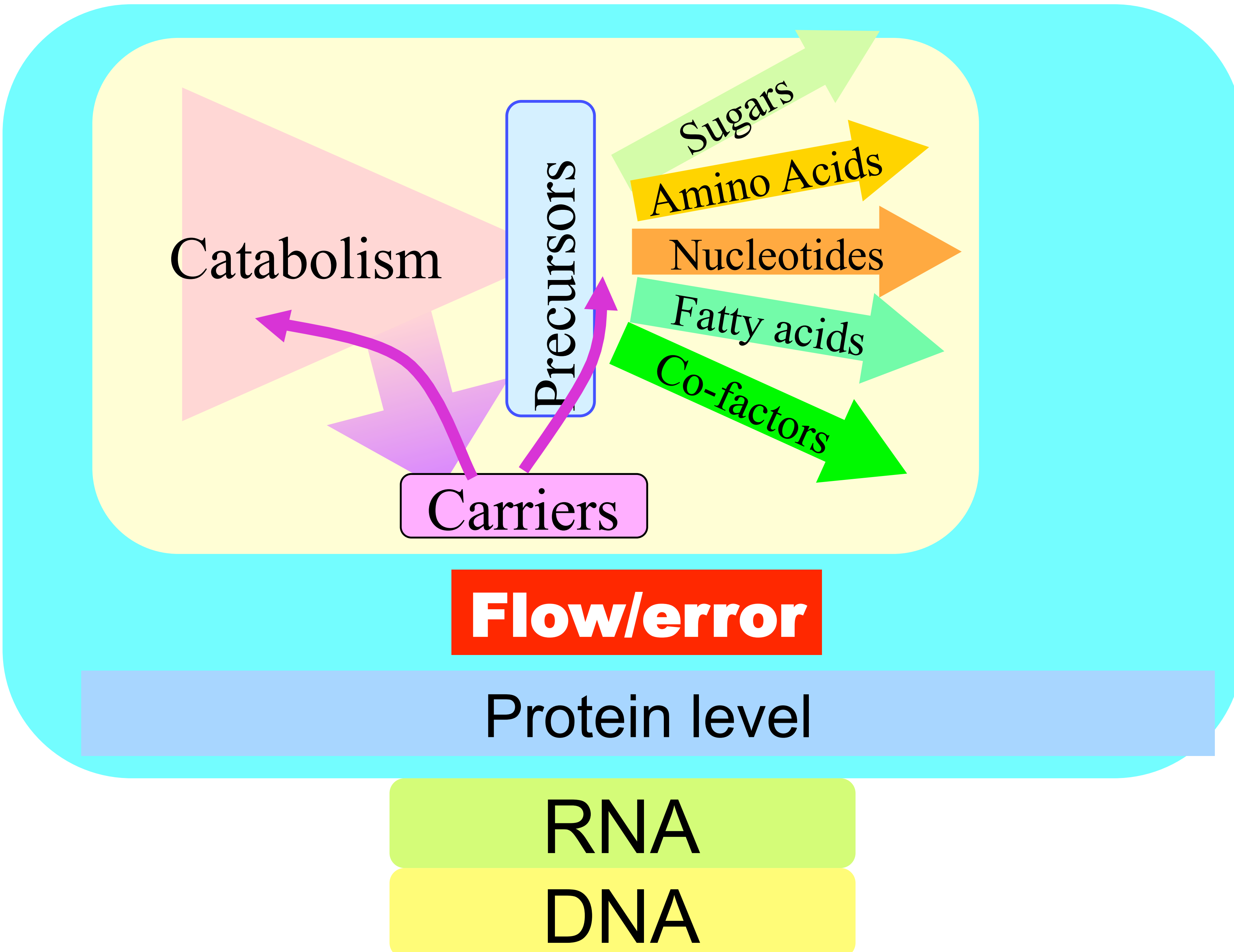
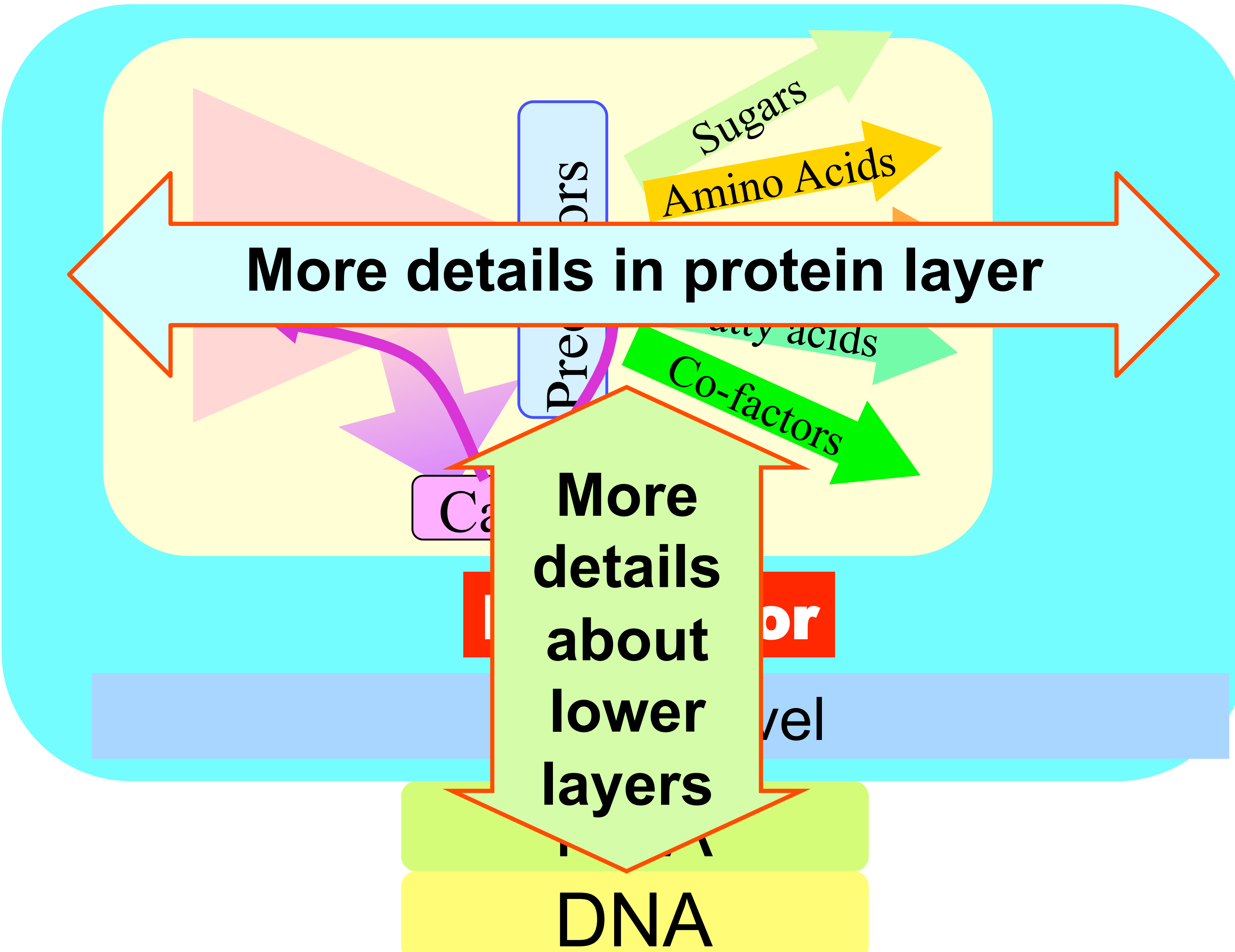


Catabolism
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Carriers
Flow/error
Protein level
RNA
DNA


Sugars
Amino Acids
More details in protein layer
Co-factors
More details about lower layers
DNA

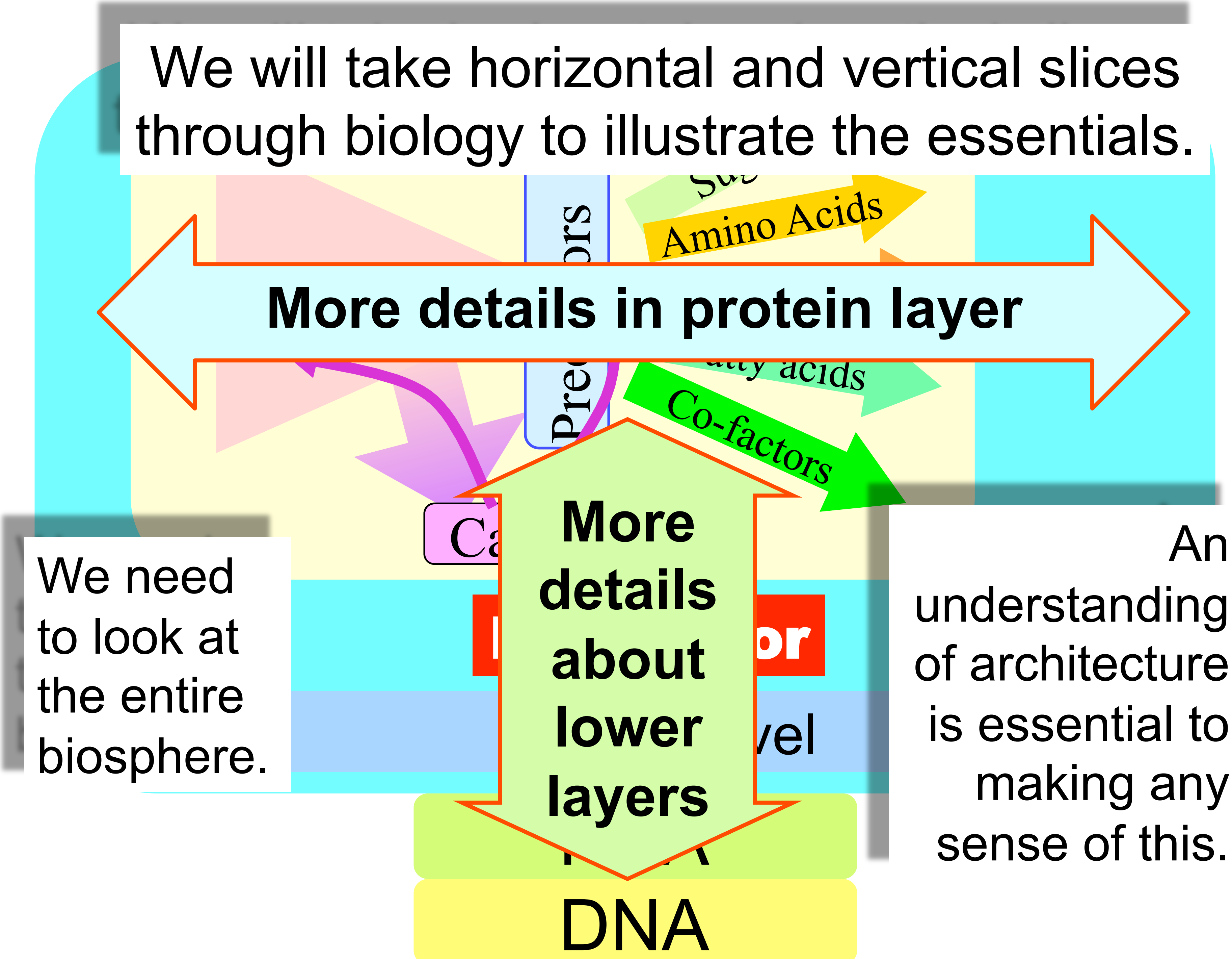
In the much simpler world of the Internet, the details are still bewilderingly complex.

More details in application software

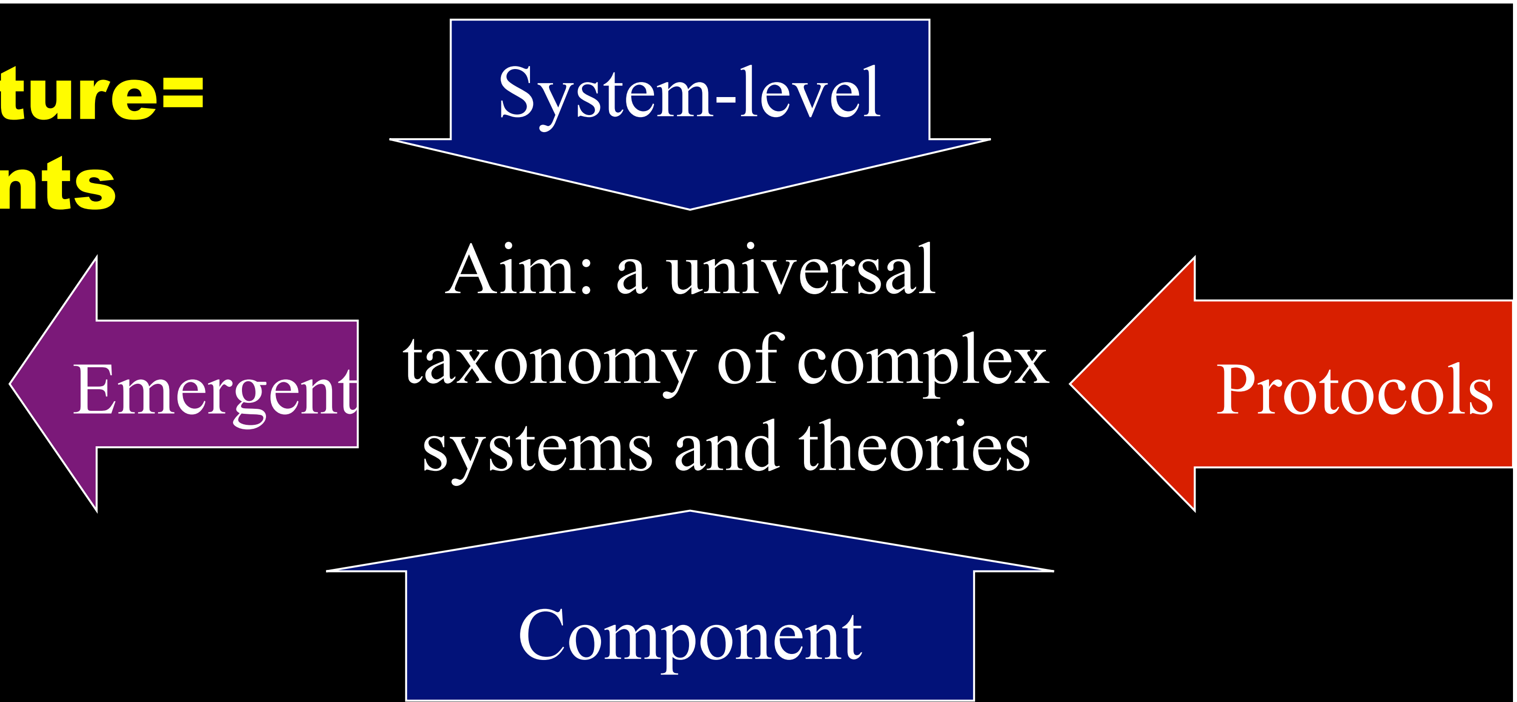
More details about the hardware design and supply chain

We'd need to look at the entire industry.

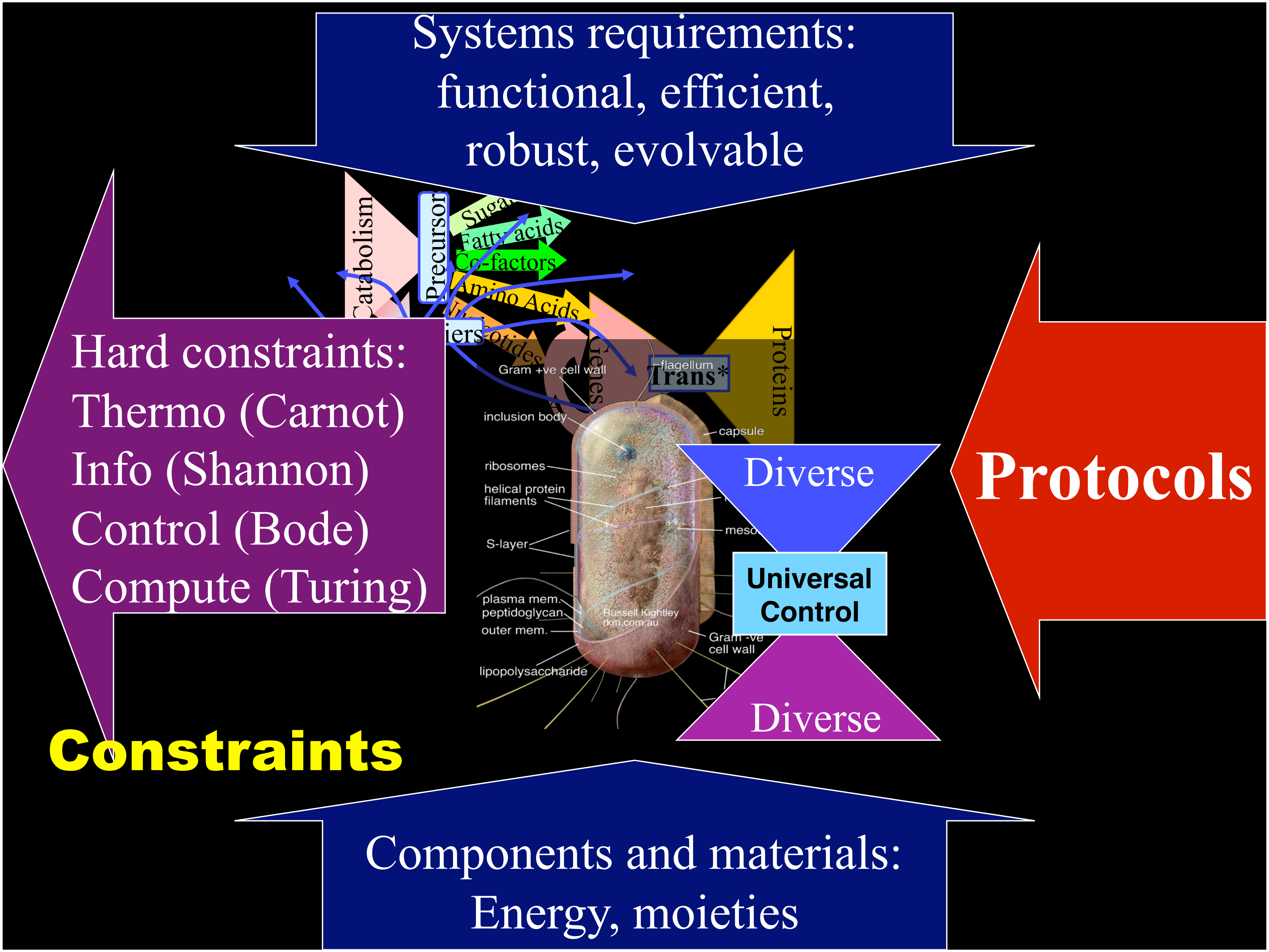
An understanding of architecture is essential to making any sense of this.


We will take horizontal and vertical slices through biology to illustrate the essentials.
Amino Acids
More details in protein layer
Co-factors
More details about lower layers
DNA
We need to look at the entire biosphere.
An understanding of architecture is essential to making any sense of this.

Architecture= Constraints



- Describe systems/components in terms of constraints on what is possible
- Decompose constraints into component, system-level, protocols, and emergent
- Not necessarily unique, but hopefully illuminating nonetheless



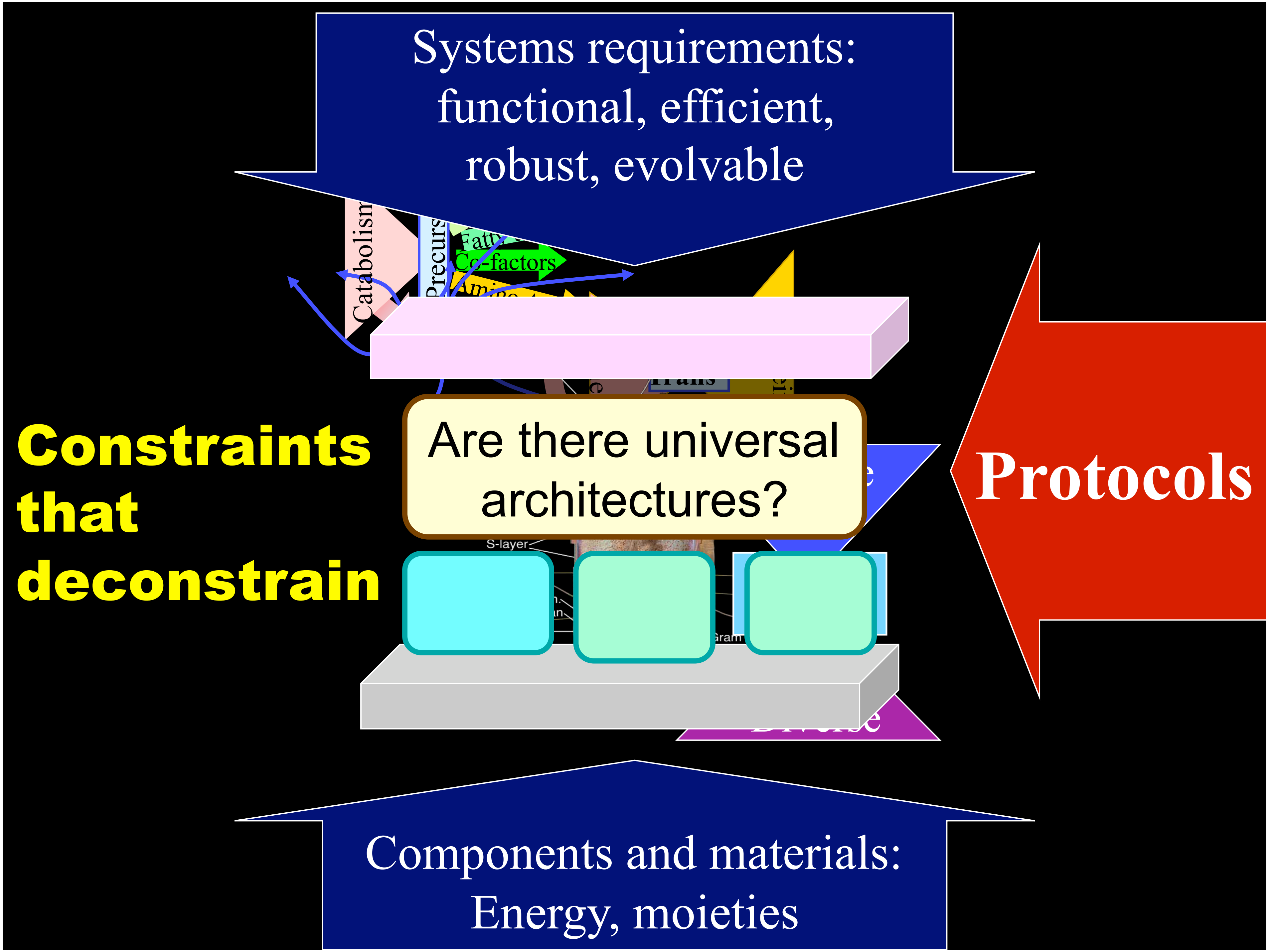
Systems requirements: functional, efficient, robust, evolvable
Hard constraints:
Thermo (Carnot)
Info (Shannon)
Control (Bode)
Compute (Turing)
Constraints
Protocols
Diverse
Universal Control
Diverse
Components and materials: Energy, moieties
Catabolism
Precursor
Fatty acids
Co-factors
Amino Acids
Genes
Proteins
Trans*
flagellum
Gram +ve cell wall
inclusion body
capsule
ribosomes
helical protein filaments
S-layer
plasma mem.
peptidoglycan
outer mem.
lipopolysaccharide
Gram -ve cell wall
Russell Kightley
rkm.com.au

Essential ideas

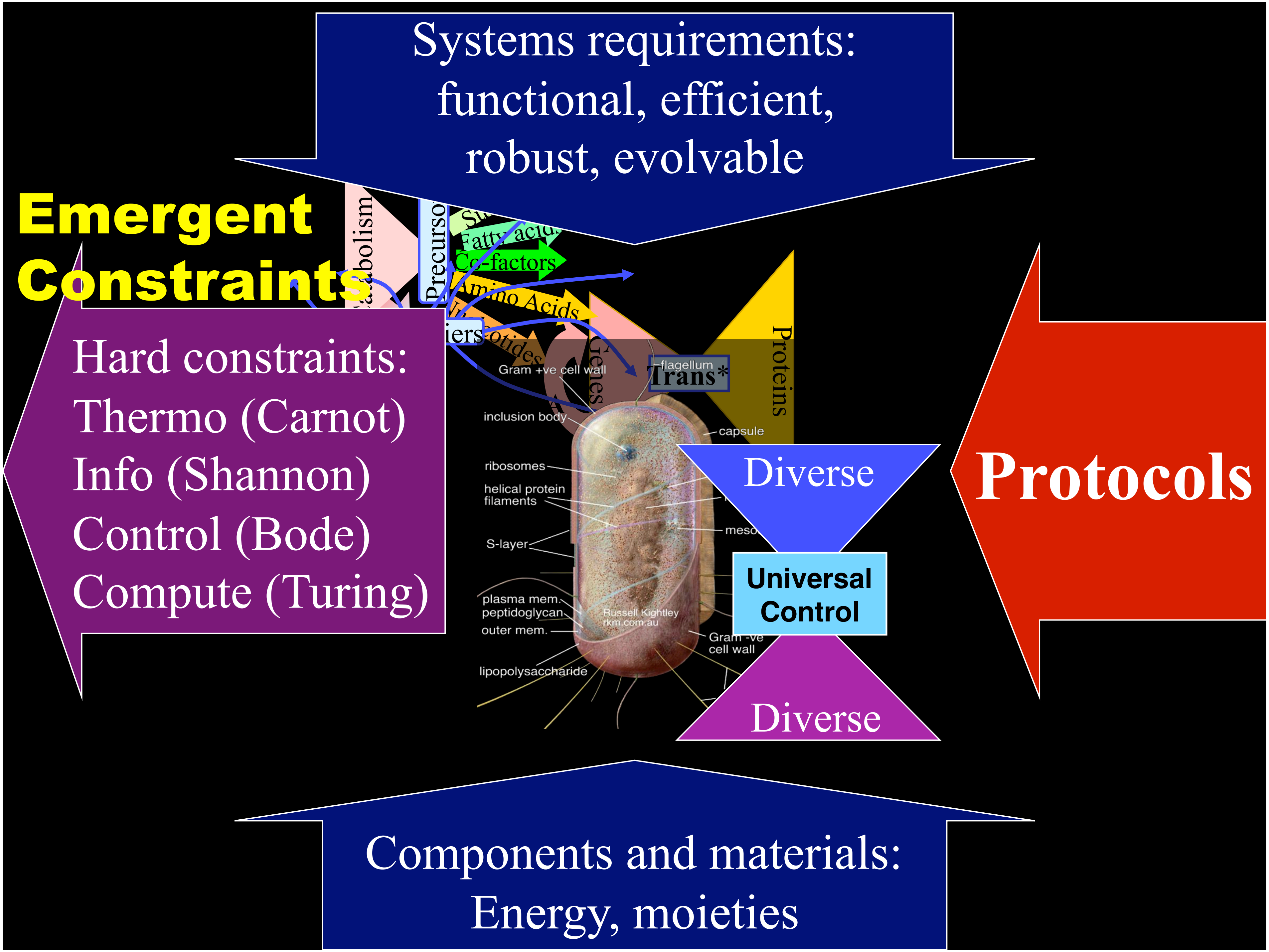
- Listening to engineers and physicians

- Robust yet fragile (RYF)
- “Constraints that deconstrain” (G&K)

- Network architecture
- Layering
- Control and dynamics (C&D)
- Hourglasses and Bowties
- Unity and diversity



Systems requirements: functional, efficient, robust, evolvable
Constraints that deconstrain
Are there universal architectures?
Protocols
Components and materials: Energy, moieties


Systems requirements:
functional, efficient,
robust, evolvable
Emergent
Constraints
Hard constraints:
Thermo (Carnot)
Info (Shannon)
Control (Bode)
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Amino Acids
Genes
Proteins
Trans*
flagellum
Gram +ve cell wall
inclusion body
capsule
ribosomes
helical protein
filaments
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plasma mem.
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outer mem.
lipopolysaccharide
Russell Kightley
rkm.com.au
Gram -ve
cell wall
Diverse
Universal
Control
Diverse
Protocols
Components and materials:
Energy, moieties

Are there universal laws?

Emergent Constraints

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

No networks

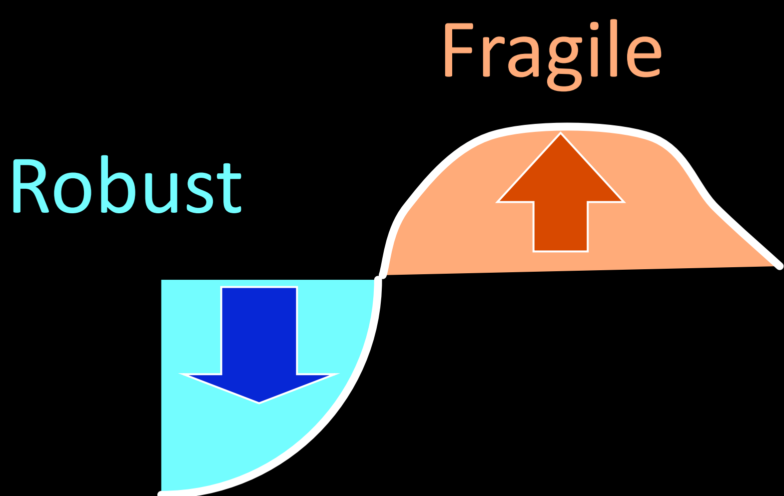
Assume ***different*** architectures a priori.

New unifications are encouraging, but not yet accessible or complete.

Robust Yet Fragile (RYF)

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

Yet be ***fragile*** for
[a different property]
Or [a different perturbation]



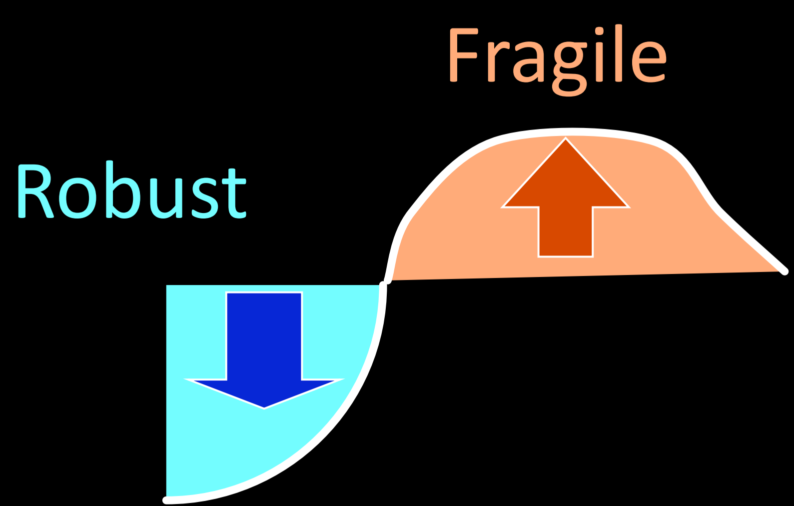
Proposition :
The RYF tradeoff is a ***hard limit***
that cannot be overcome.

Cyber

- Thermodynamics
- Communications
- Control
- Computation

Physical

- Thermodynamics
- Communications
- Control
- Computation



<u>Theorems</u> :
RYF tradeoffs are
hard limits

Robust yet fragile

Biology and advanced tech nets show extremes

- Robust Yet Fragile
- Simplicity and complexity
- Unity and diversity
- Evolvable and frozen

What makes this possible and/ or inevitable?

Architecture (= constraints)

Let’s dig deeper.

More details in applications

We'd need to look at an entire industry.

More details about the hardware design and supply chain

An understanding of architecture is essential to making any sense of this.

Is there a simpler example than Internet?

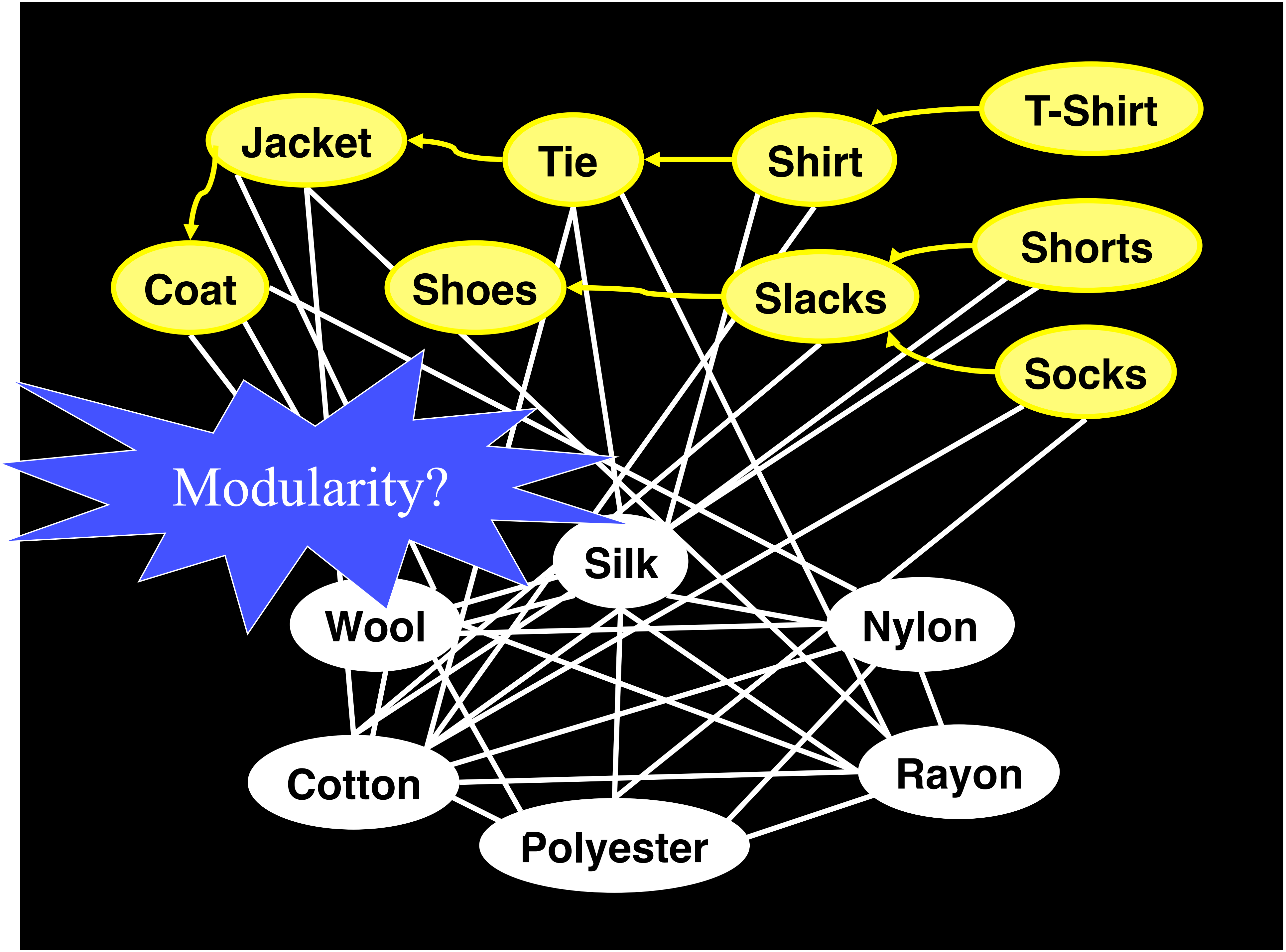
$\exists$ devil $\in$ details

$\Rightarrow$ ☹ architecture

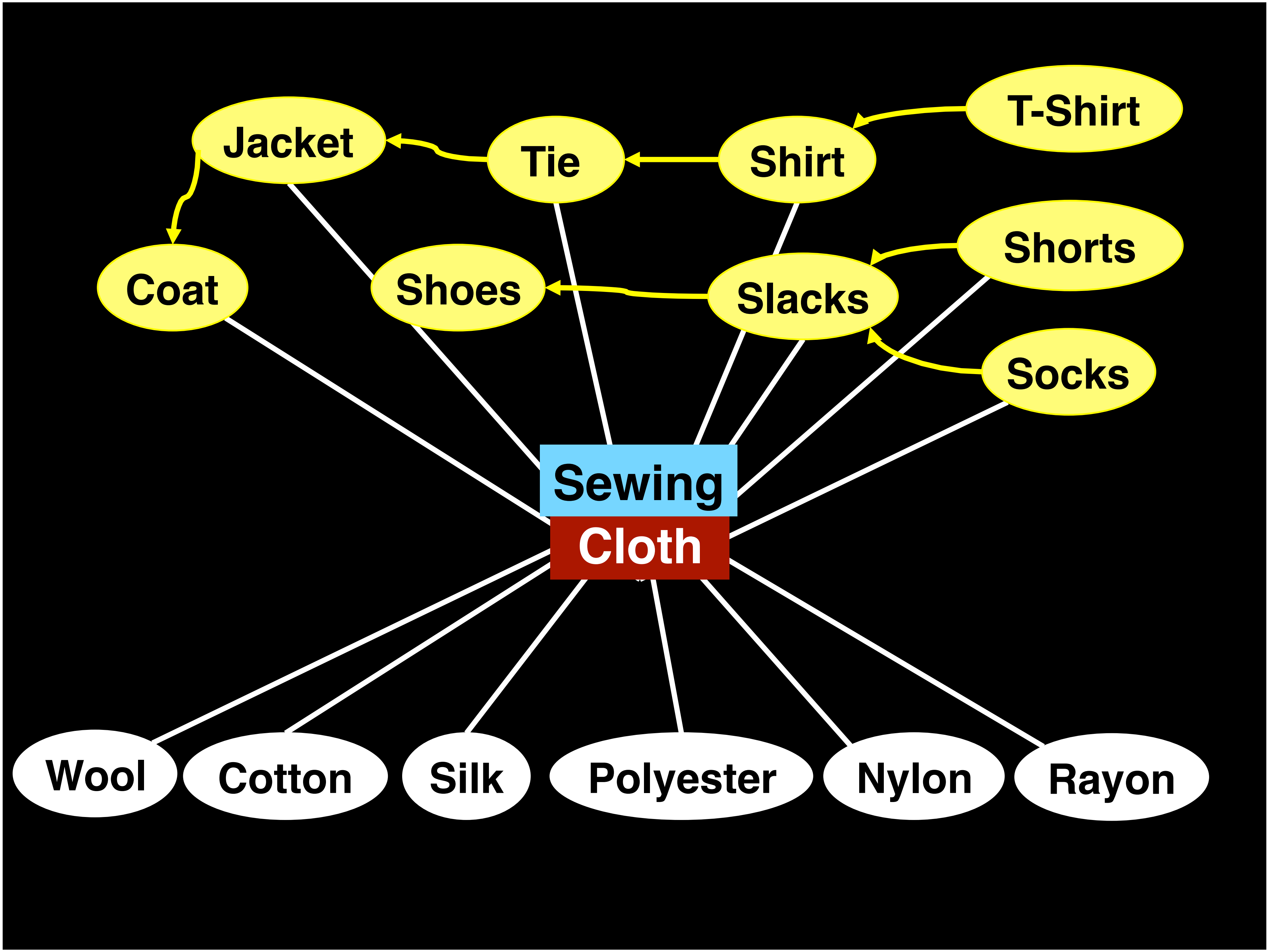
Jean Jour (alias John Day)

Other examples

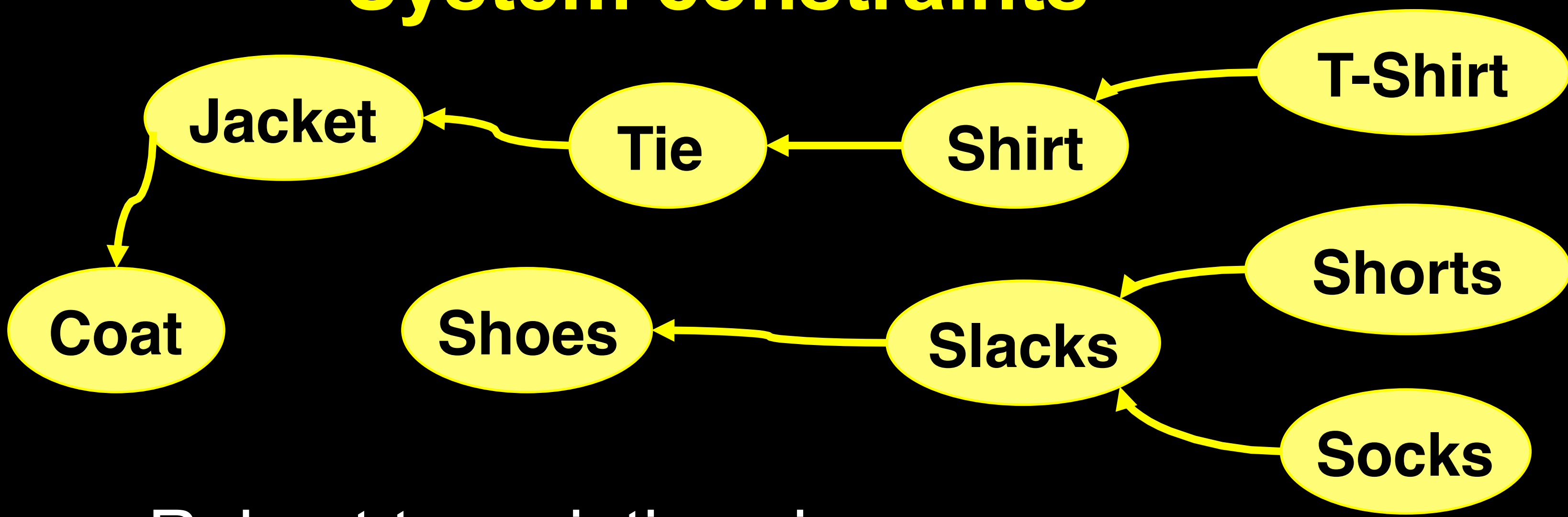
Clothing



T-Shirt
Jacket
Tie
Shirt
Shorts
Coat
Shoes
Slacks
Socks
Modularity?
Silk
Wool
Nylon
Cotton
Rayon
Polyester


T-Shirt
Jacket
Tie
Shirt
Shorts
Coat
Shoes
Slacks
Socks
Sewing
Cloth
Wool
Cotton
Silk
Polyester
Nylon
Rayon

System constraints



Robust to variations in

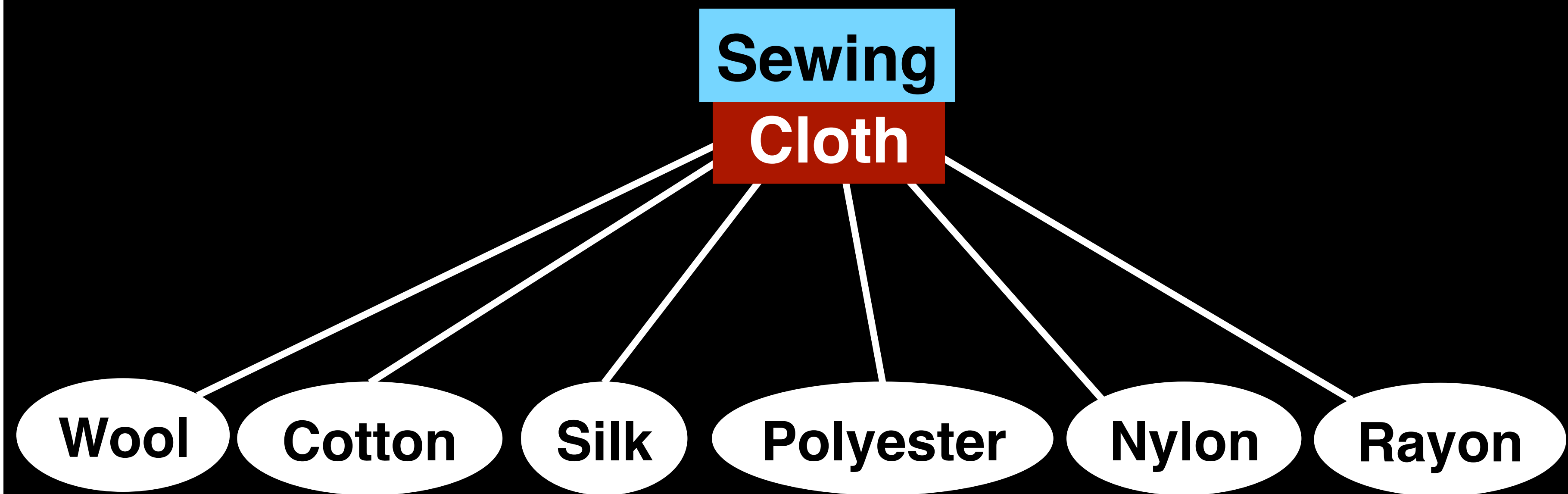
- weather
- activity
- appearance requirements
- wear and tear
- cleaning

Wool Cotton Silk Polyester Nylon Rayon

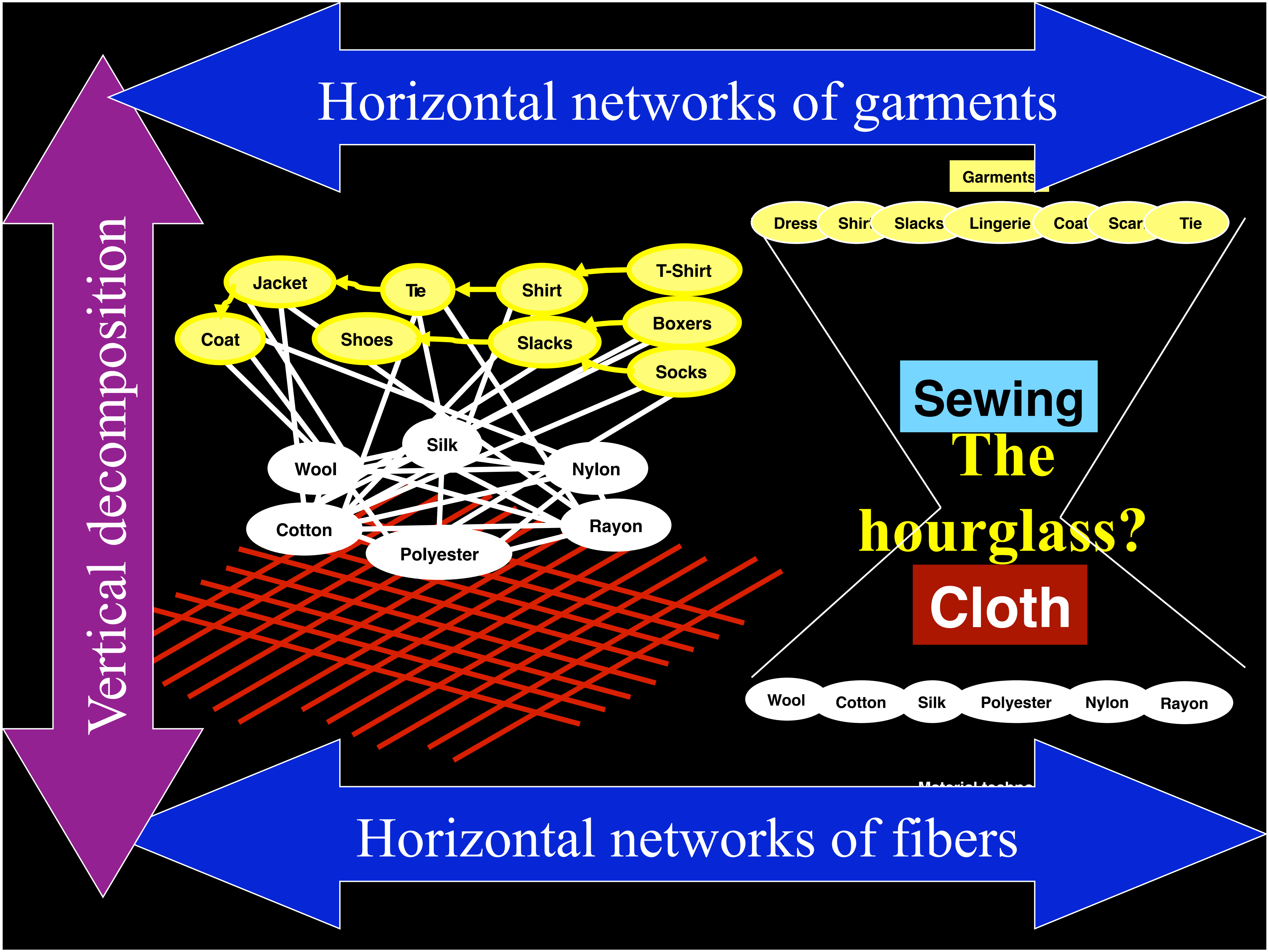
Component constraints

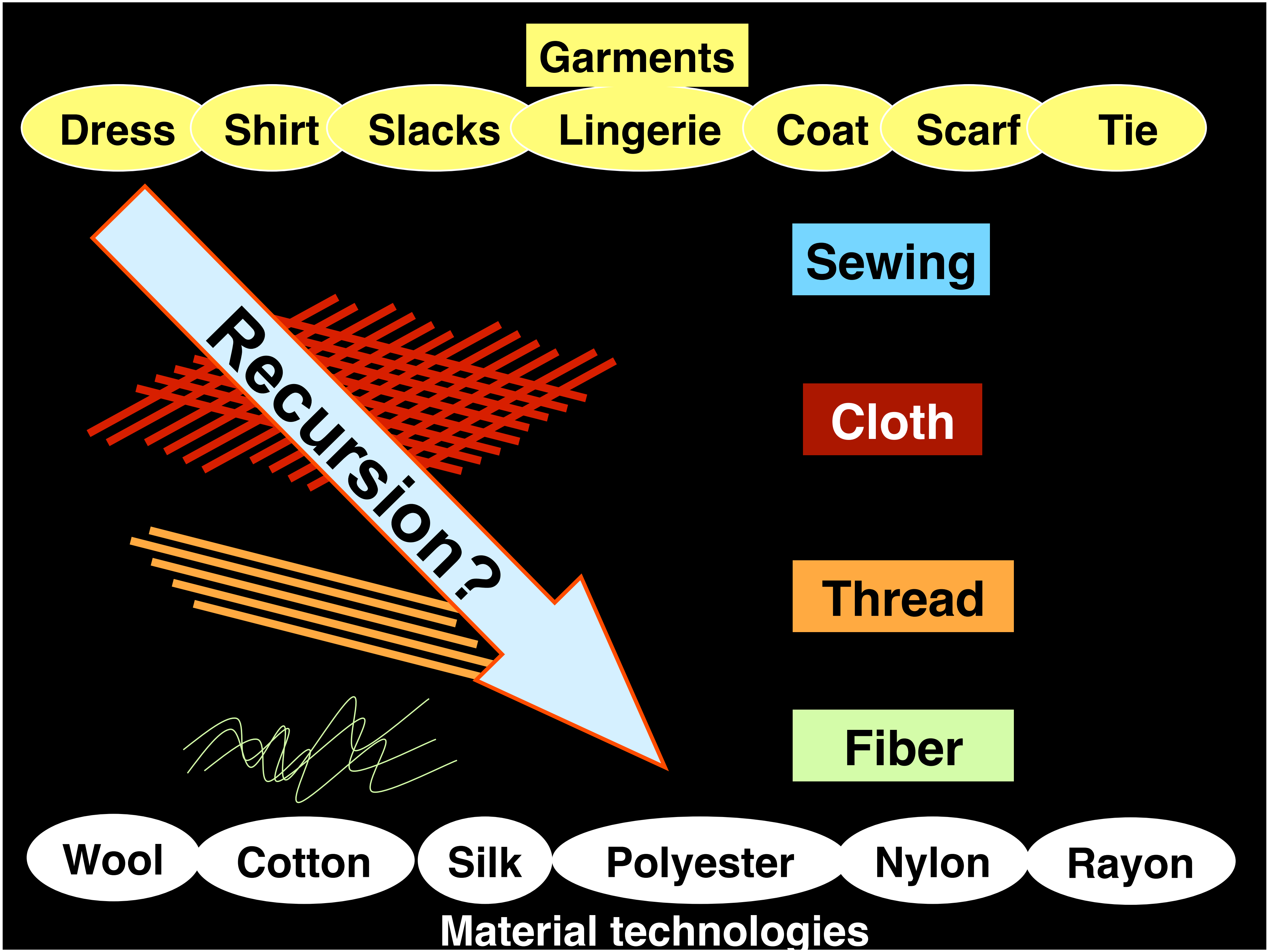
Robust to

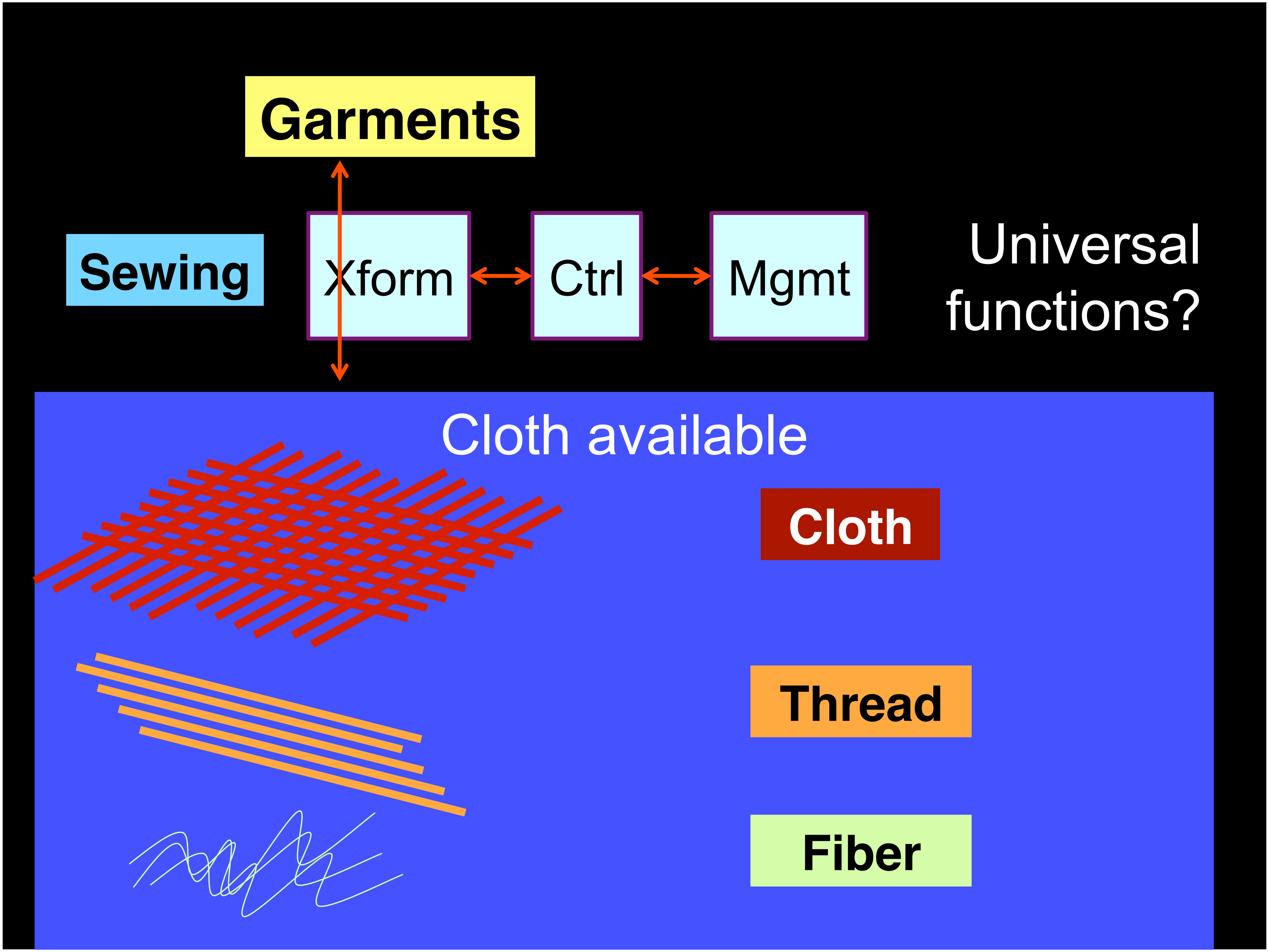
- perturbations to clothing
- variety of raw materials
- ***unraveling***

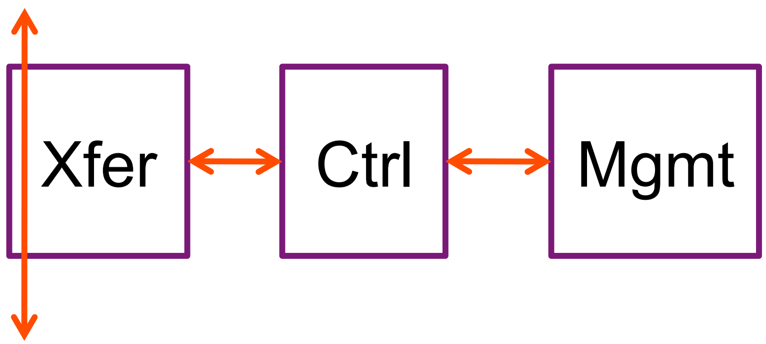


Component constraints


Horizontal networks of garments
Vertical decomposition
Garments
Dress
Shir
Slacks
Lingerie
Coat
Scar
Tie
Jacket
Tie
Shirt
T-Shirt
Coat
Shoes
Slacks
Boxers
Socks
Silk
Wool
Nylon
Cotton
Rayon
Polyester
Sewing
The hourglass?
Cloth
Wool
Cotton
Silk
Polyester
Nylon
Rayon
Horizontal networks of fibers

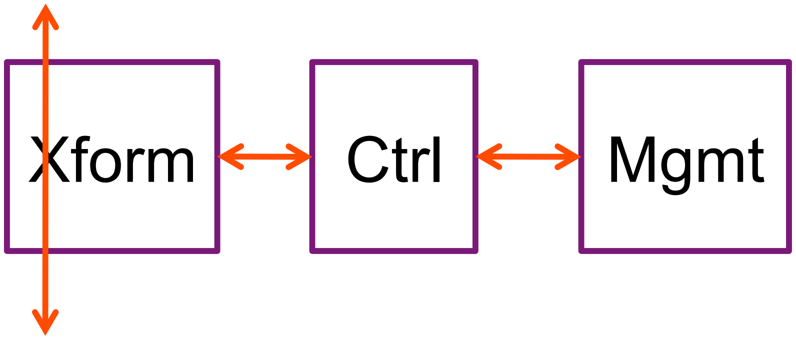

Garments
Dress
Shirt
Slacks
Lingerie
Coat
Scarf
Tie
Recursion?
Sewing
Cloth
Thread
Fiber
Wool
Cotton
Silk
Polyester
Nylon
Rayon
Material technologies


Garments
Sewing
Xform
Ctrl
Mgmt
Universal functions?
Cloth available
Cloth
Thread
Fiber



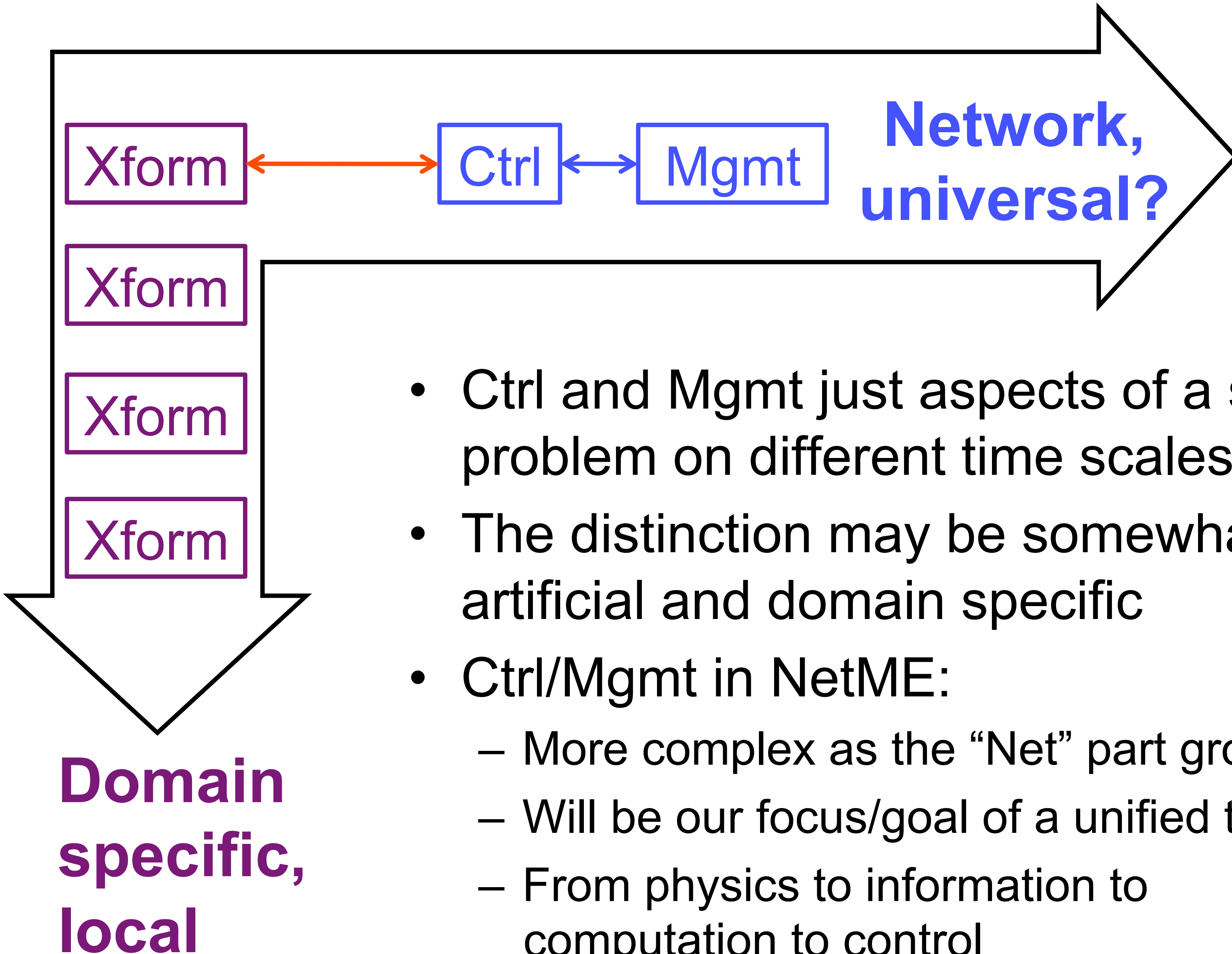
Universal functions?

- Transfer or transform (fastest)
  - **Domain specific (data, power, goods, etc)**
  - Depends on demand and supply
- Control (middle)
  - Schedule/MUX resources in time and space
  - Flow and error control
- Management (slowest)
  - ***What*** resources are available?
  - ***Where*** are they?
  - Cost? Risk? etc

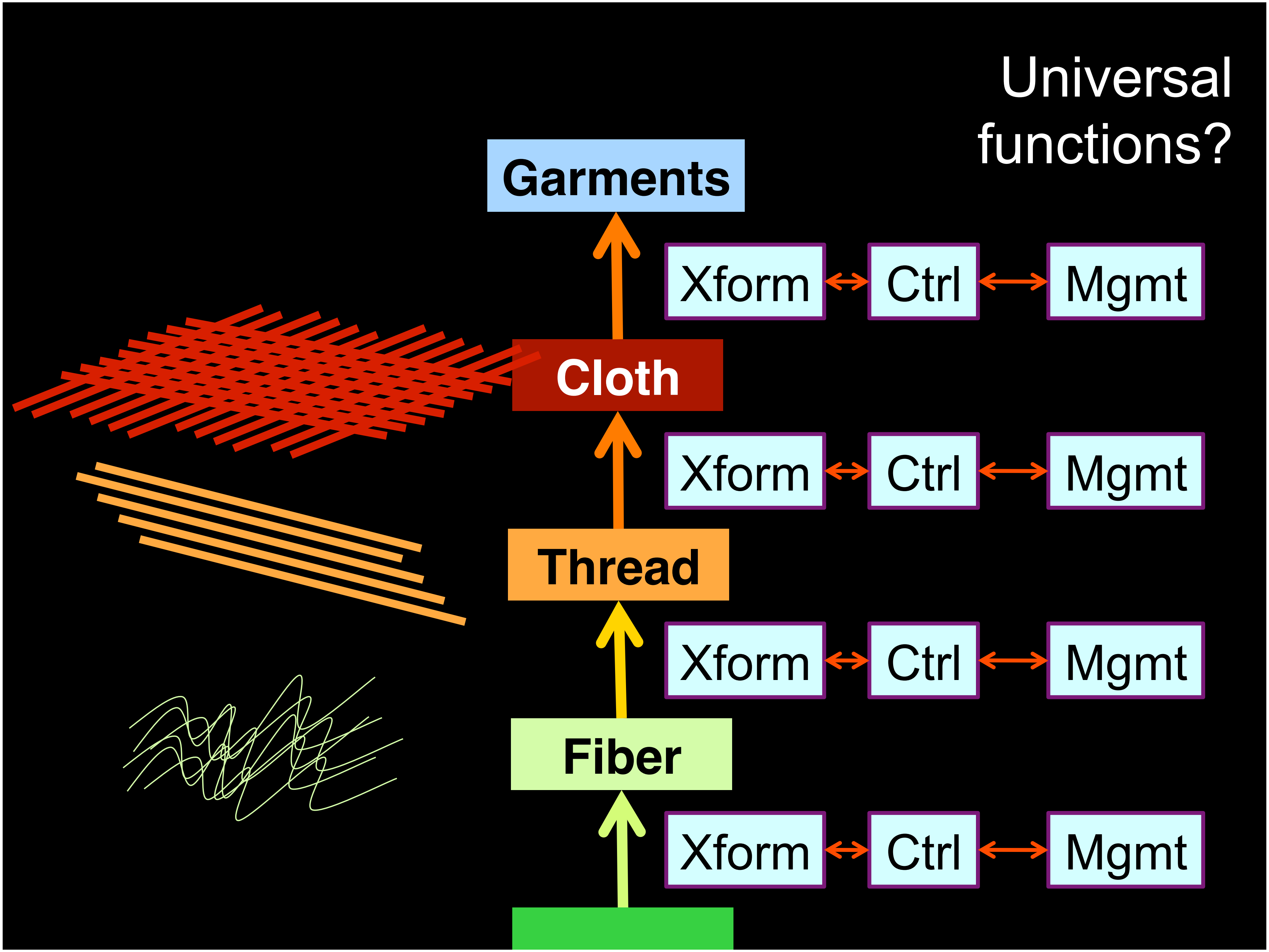


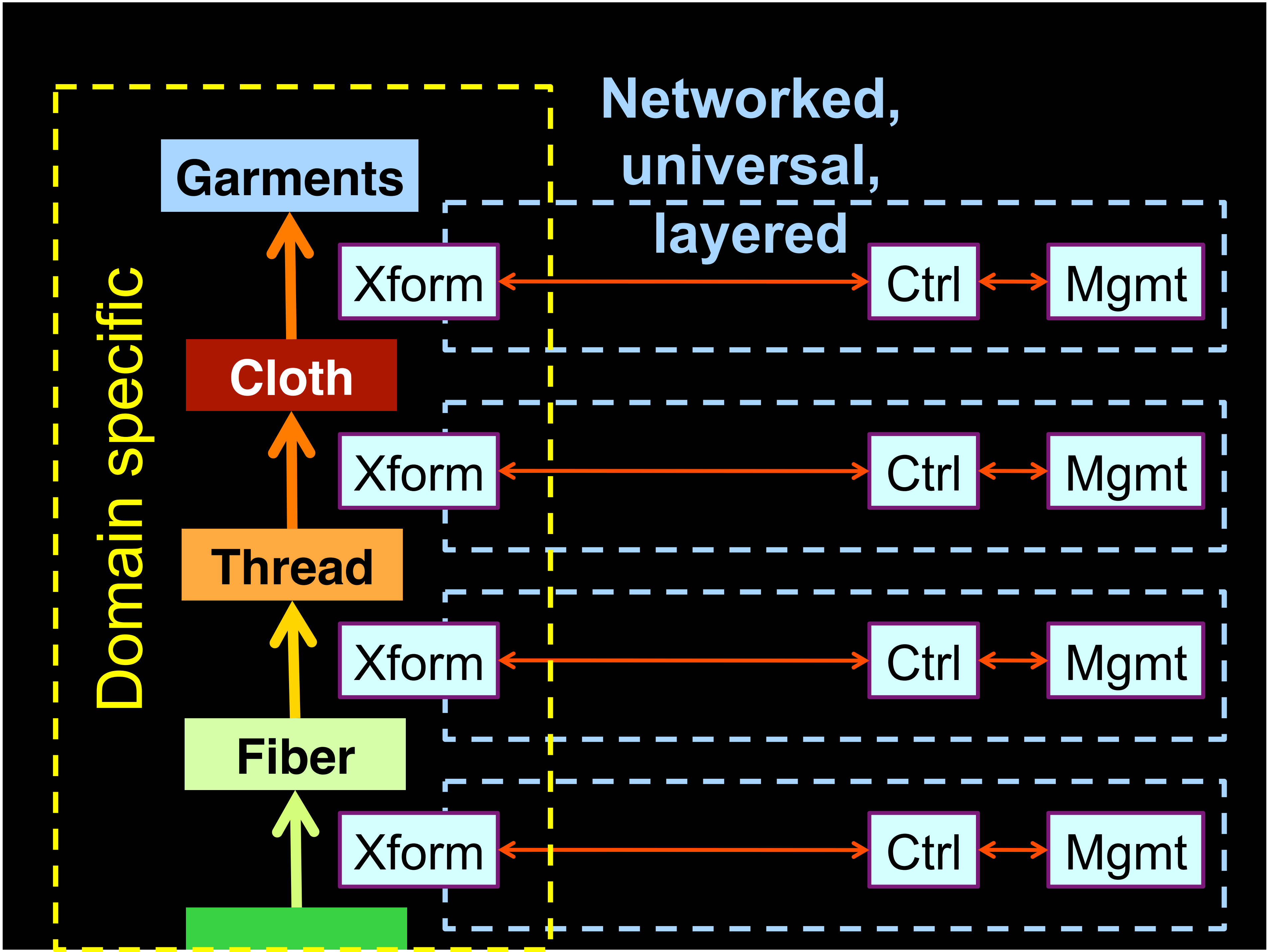
Sewing function?

- Transfer or transform (fastest)
  - **Transform cloth to garments**
  - Depends on demand and supply
- Control (middle)
  - Schedule/MUX resources in time and space
  - Flow and error control
- Management (slowest)
  - ***What*** resources are available?
  - ***Where*** are they?
  - Cost? Risk? etc

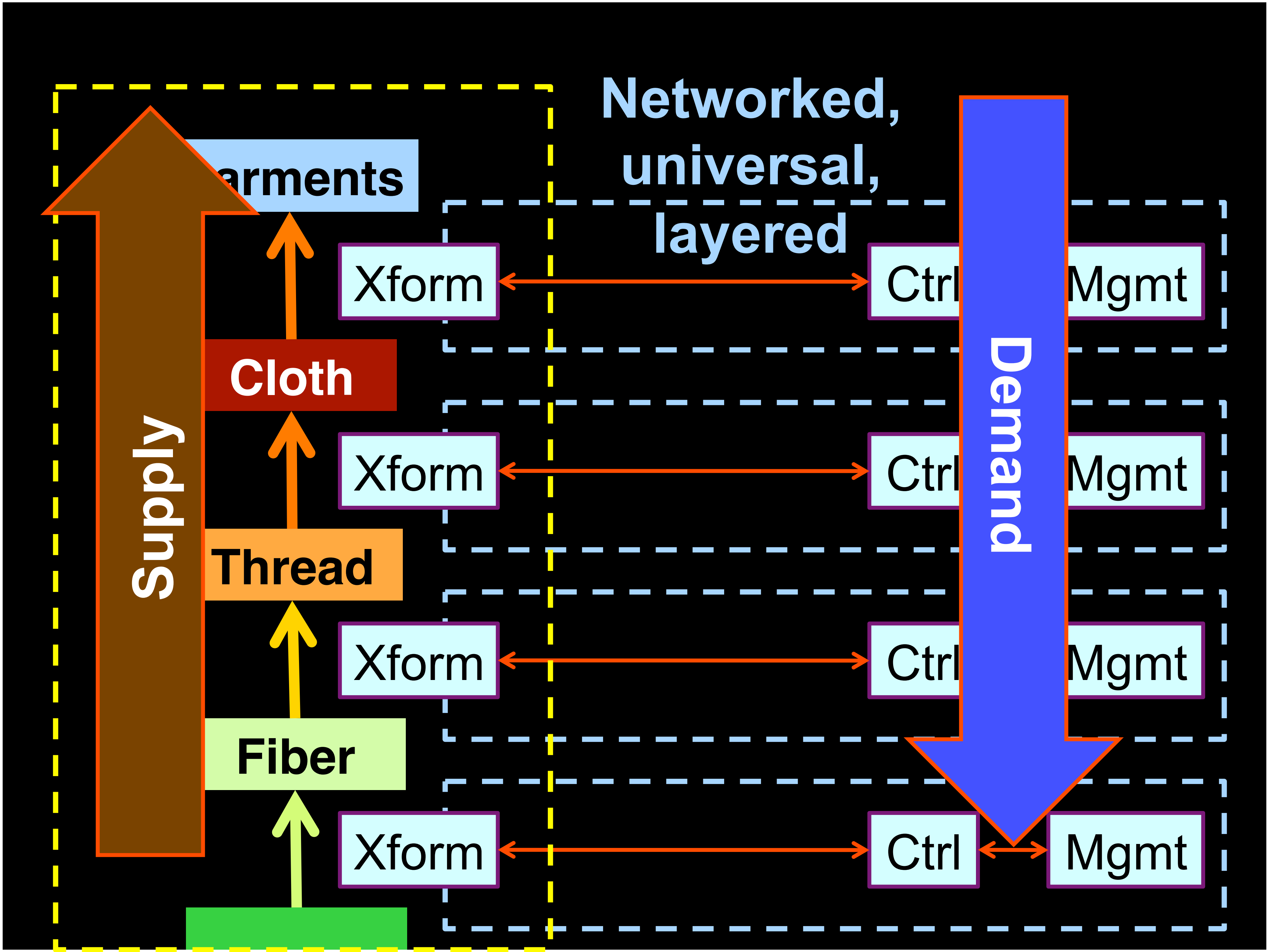


- Ctrl and Mgmt just aspects of a single problem on different time scales
- The distinction may be somewhat artificial and domain specific
- Ctrl/Mgmt in NetME:
  - More complex as the “Net” part grows
  - Will be our focus/goal of a unified theory
  - From physics to information to computation to control


Universal functions?
Garments
Xform
Ctrl
Mgmt
Cloth
Xform
Ctrl
Mgmt
Thread
Xform
Ctrl
Mgmt
Fiber
Xform
Ctrl
Mgmt



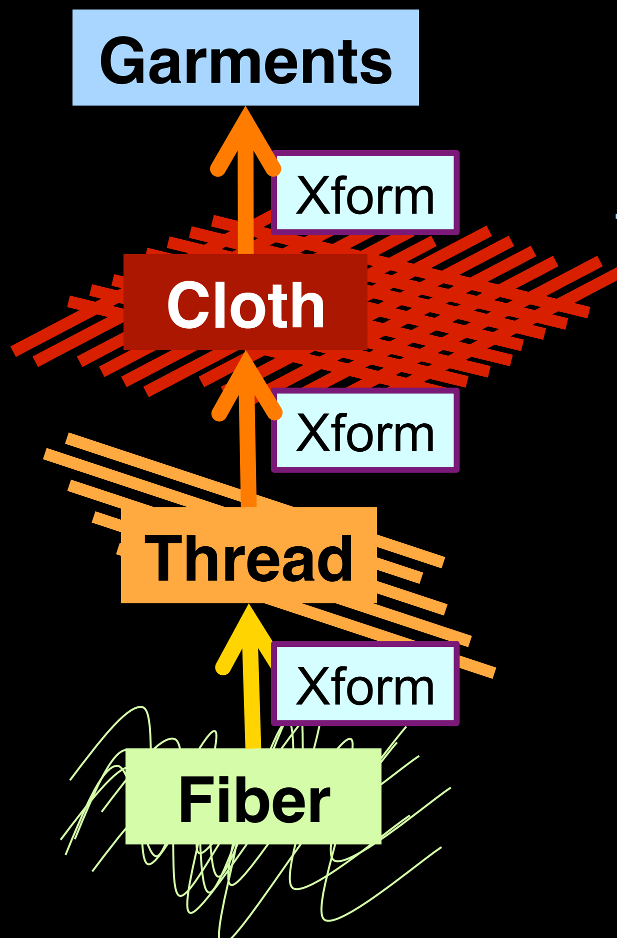
Networked, universal, layered
Domain specific
Garments
Cloth
Thread
Fiber
Xform
Ctrl
Mgmt
Xform
Ctrl
Mgmt
Xform
Ctrl
Mgmt
Xform
Ctrl
Mgmt


Networked,
universal,
layered
Supply
Demand
arments
Cloth
Thread
Fiber
Xform
Xform
Xform
Xform
Ctrl
Ctrl
Ctrl
Ctrl
Mgmt
Mgmt
Mgmt
Mgmt

Universal strategies?

Even though garments seem analog/continuous

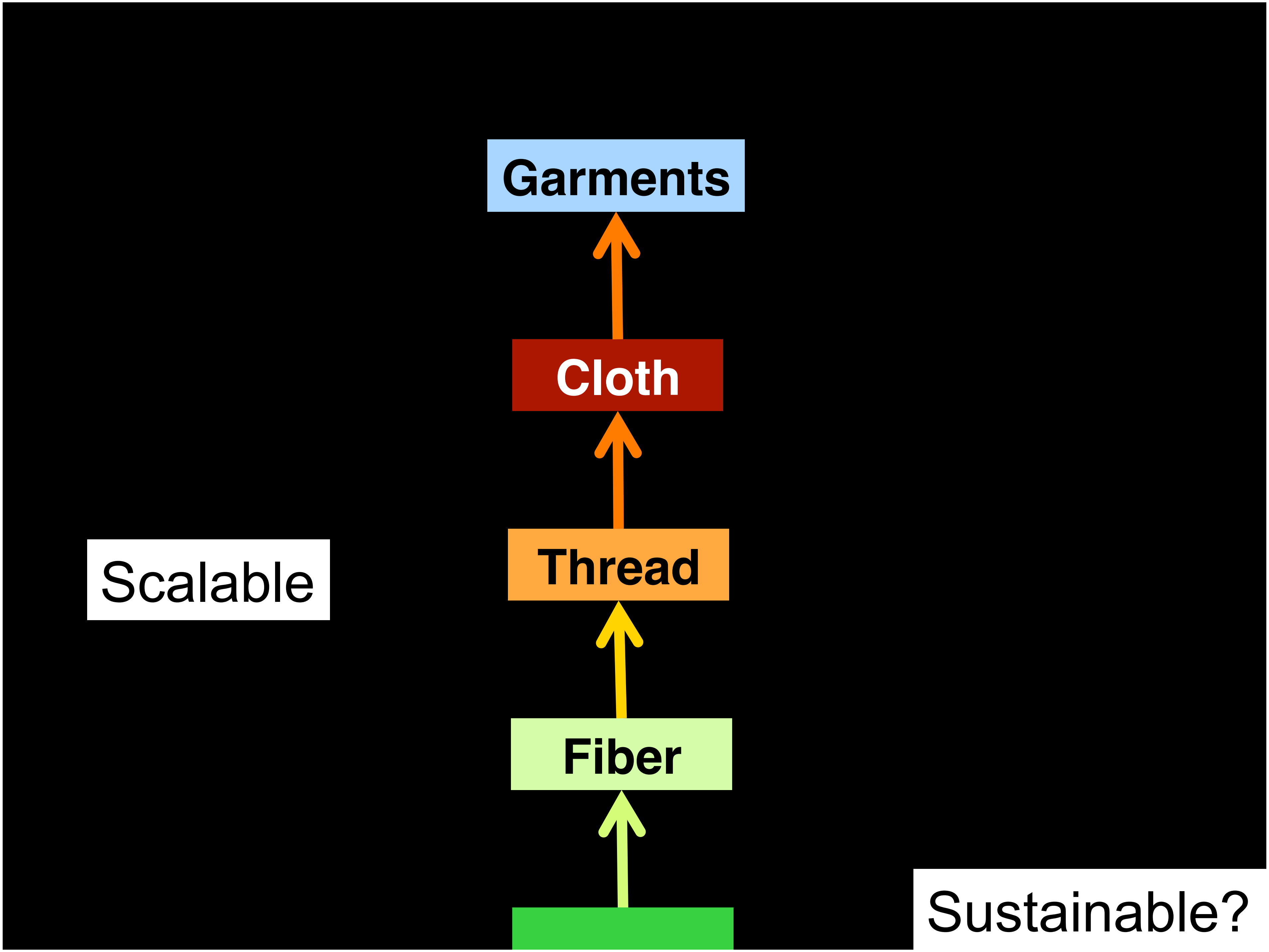
Garments have limited access to threads and fibers

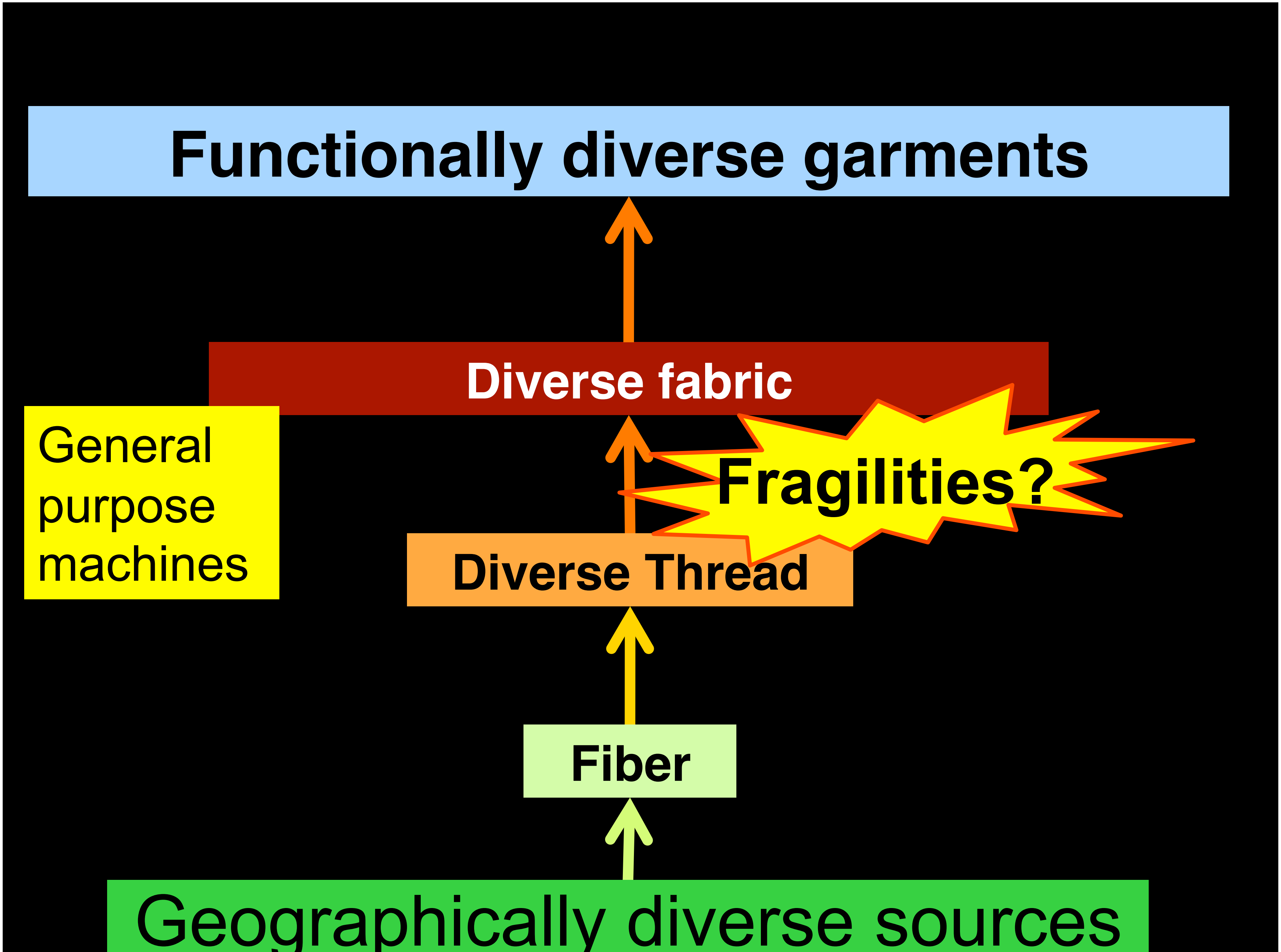


quantization for robustness

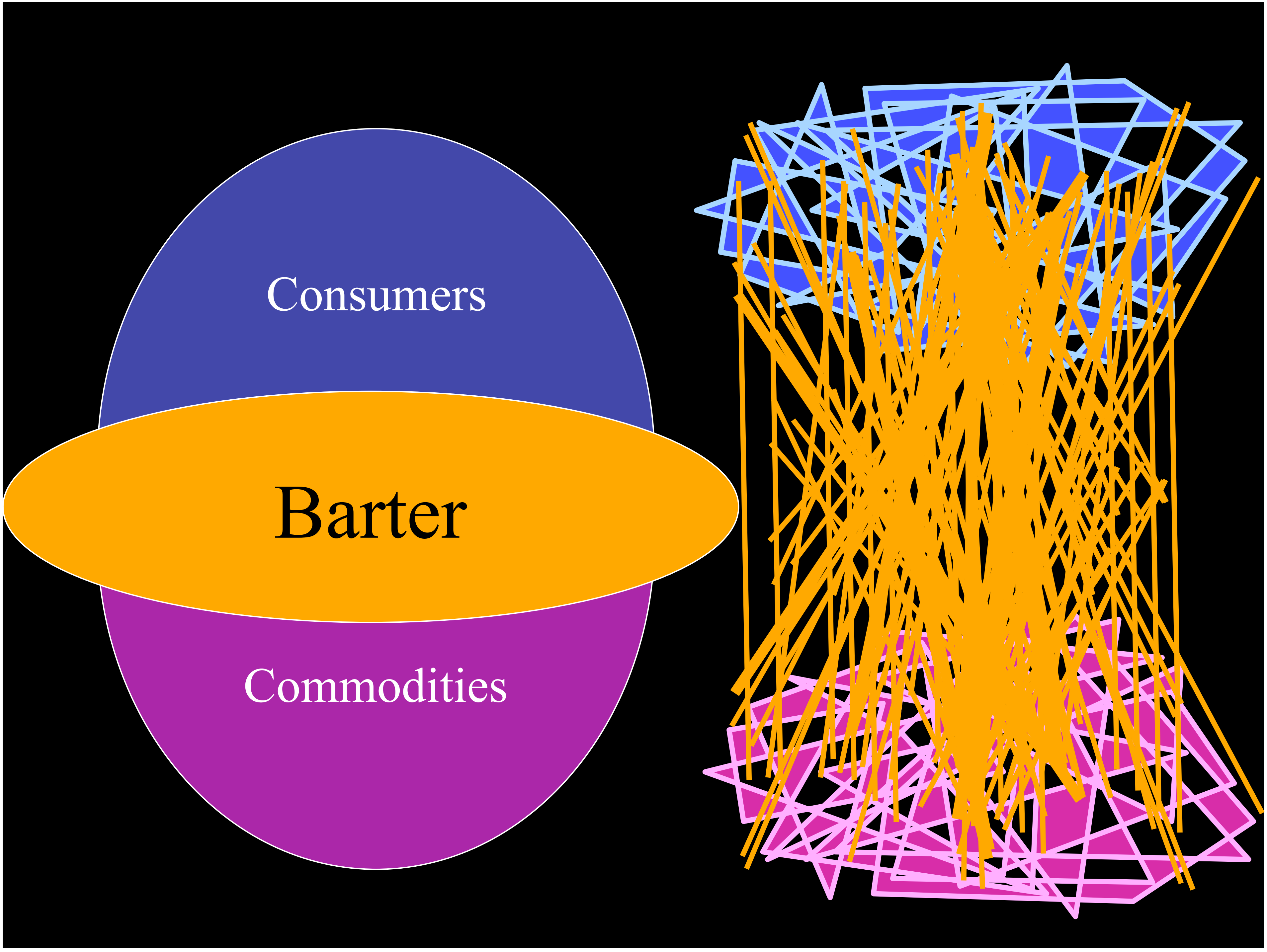
constraints on cross-layer interactions

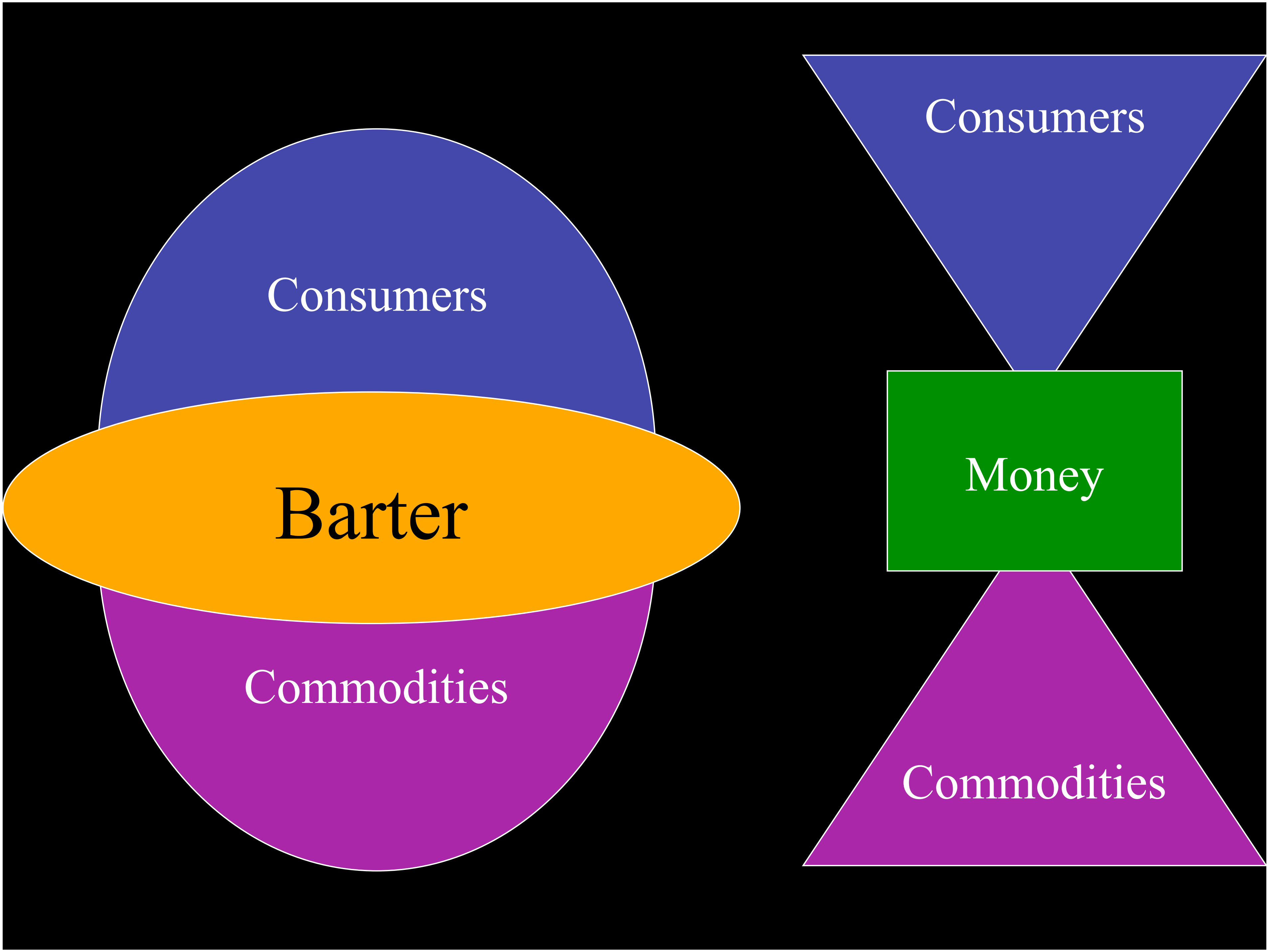
Prevents unraveling of lower layers

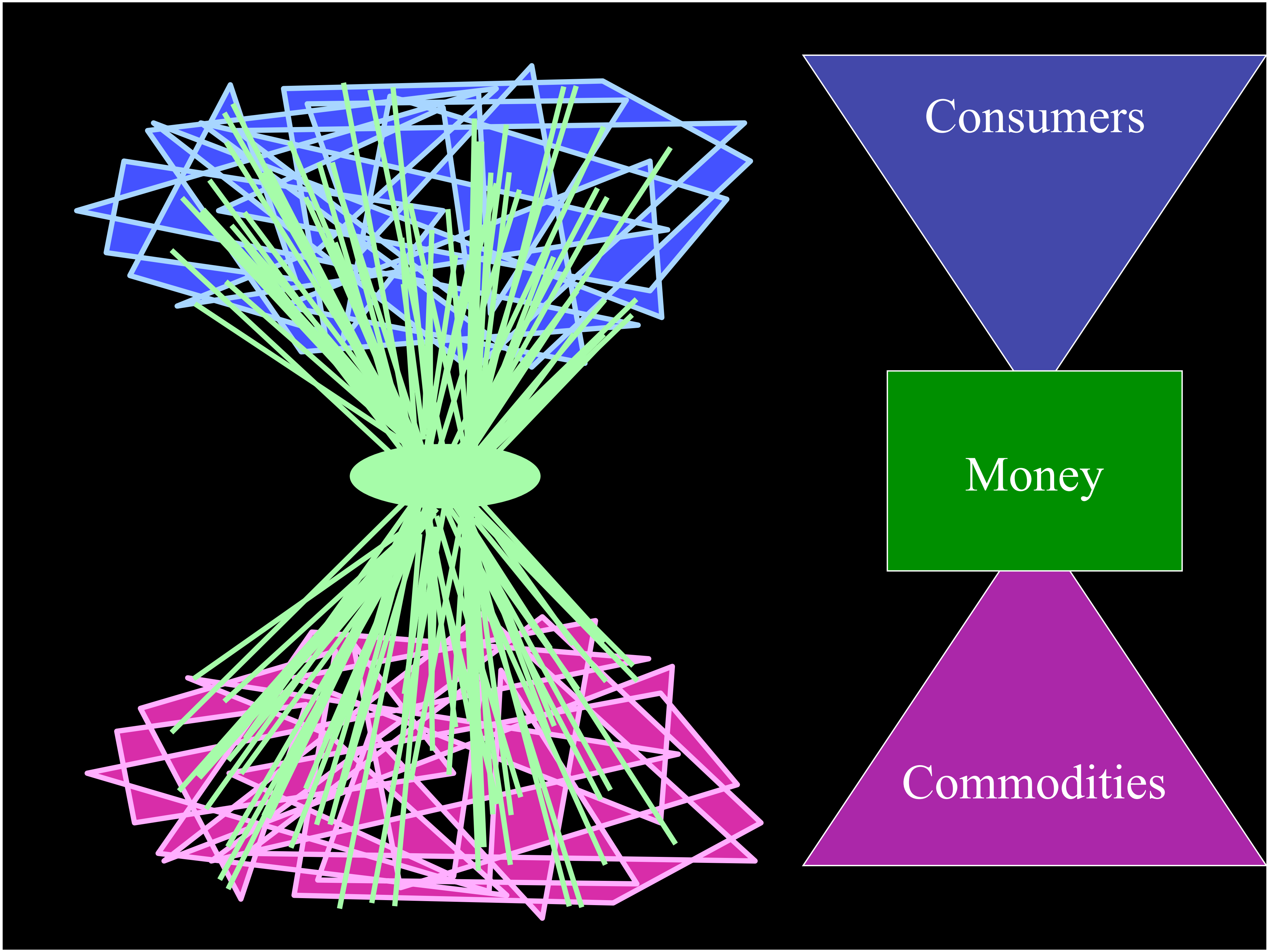

Garments
Cloth
Thread
Scalable
Fiber
Sustainable?


Functionally diverse garments
Diverse fabric
General purpose machines
Fragilities?
Diverse Thread
Fiber
Geographically diverse sources

Money

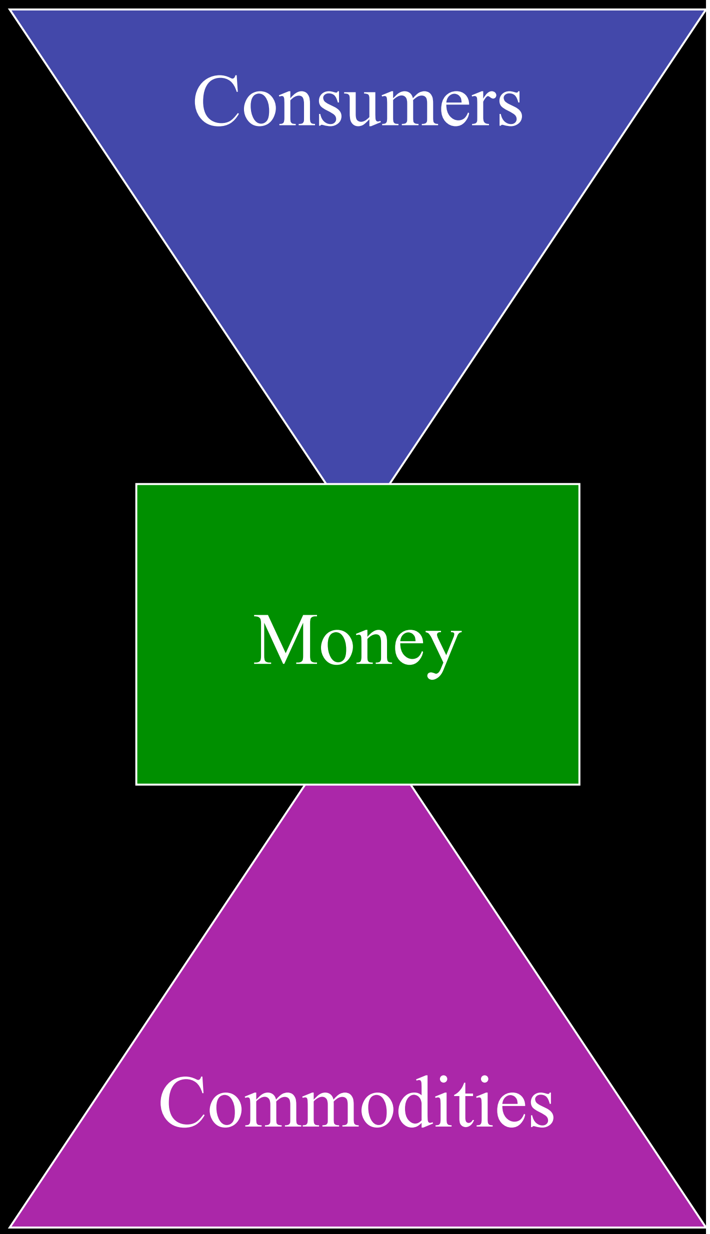

Consumers
Barter
Commodities


Consumers
Barter
Commodities
Consumers
Money
Commodities


Consumers
Money
Commodities

New fragilities

- Theft, counterfeiting, fraud, and “creative accounting” are now possible
- The beginning of a growing complexity-fragility spiral
- Complex legal infrastructure
- Law, banking, finance, Ponzi schemes, derivatives, credit default swaps, …



Lego hourglass

Diverse toys

Universal Control

Diverse instructions

control

assembly

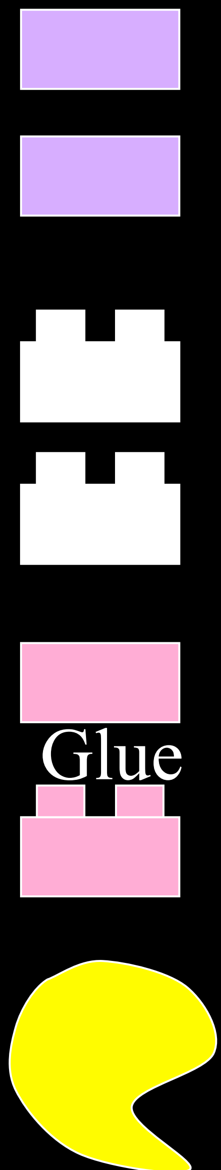
Robust yet fragile

Extremes of
- Robust yet fragile
- Simplicity and complexity
- Constrained and flexible
- Frozen and evolvable
- Digital and analog
- Diverse and conserved

Lego ***system*** requirements

	Alternative designs?			
Performance				
Trauma				
Allowed connections				
Reuse				
Evolvable parts				
Evolvable systems				
Labor cost				
Parts cost				

Alternatives



No interface. Simple blocks.

Standard interface. (Wild type.)

Add glue to hold the parts together.

Injection mold the whole toy from scratch.

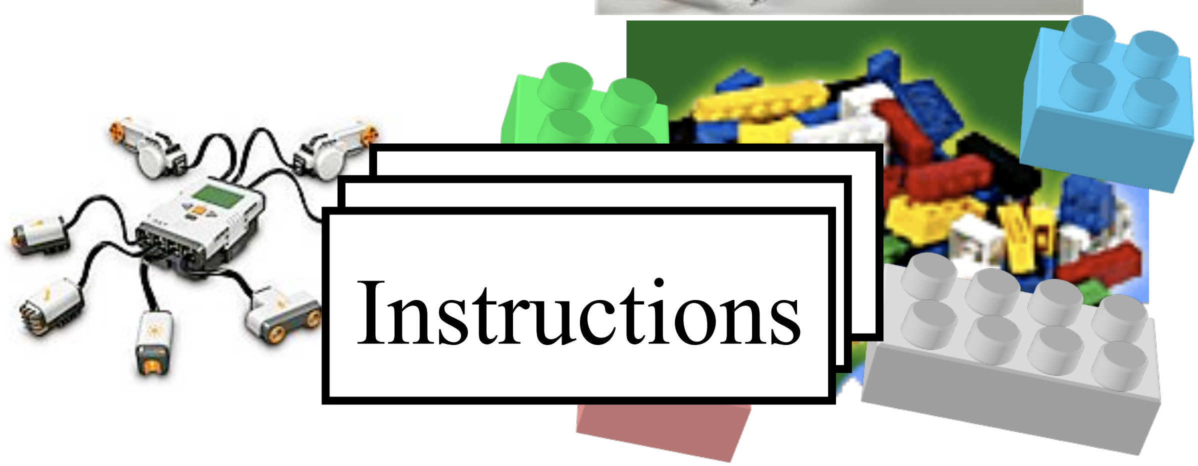
For a single toy

Lego hourglass

Complexity →

control

assembly



Analog behavior
Kinematics
Dynamics

control

Digital description
Control
Assembly

Instructions

Toy *system*

Lego hourglass

Huge variety of toys

Standardized mechanisms
Highly conserved

control

assembly

Huge variety of instructions

Lego hourglass

Huge variety of toys

control

Standardized mechanisms
Highly conserv...

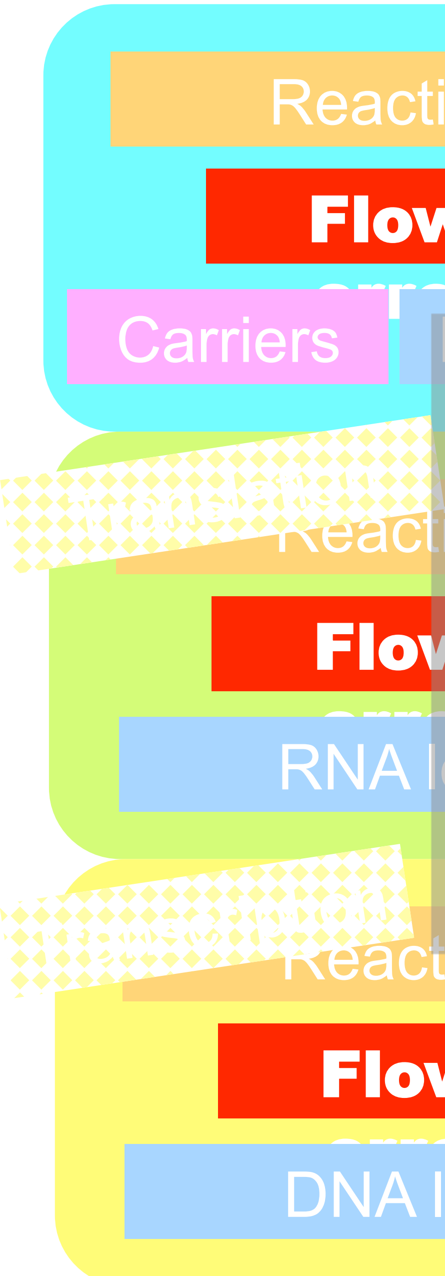
...sembly

Large (<< huge) Variety of parts

Huge variety of instructions

Instructions

Robust yet fragile



Extremes of
- Robust yet fragile
- Unity and diversity
- Simplicity and complexity
- Constrained and flexible
- Frozen and evolvable
- Digital and analog

Diverse

Lessons from Lego:

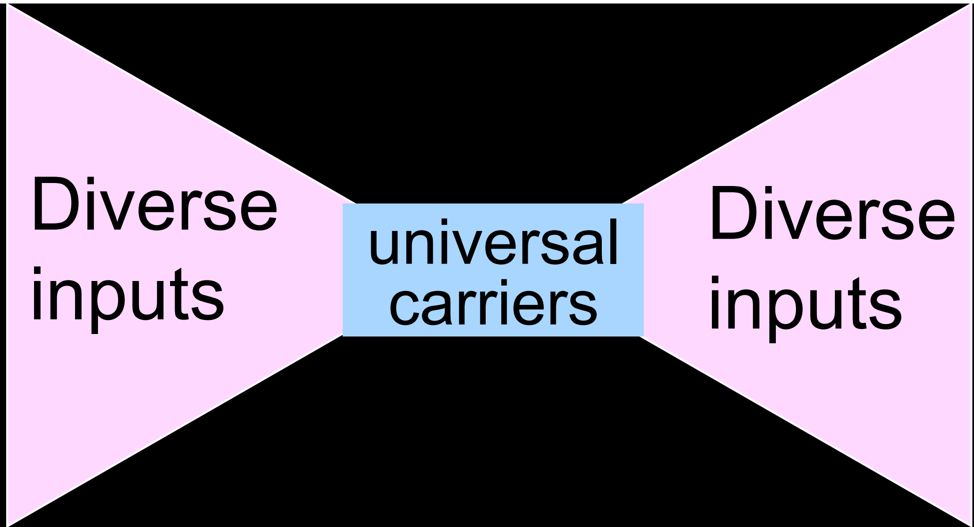
- Infinitely ***diverse*** toys from
- moderately diverse parts
- ***Hourglass*** organization of control
- ***Conserved*** control mechanisms
- ***Bowties*** within layers
- ***Complexity*** is overwhelmingly in conserved control parts, but
- largely hidden in ordinary operation
- Greater internal complexity means more ***robust yet fragile*** external behavior

control

Conserved

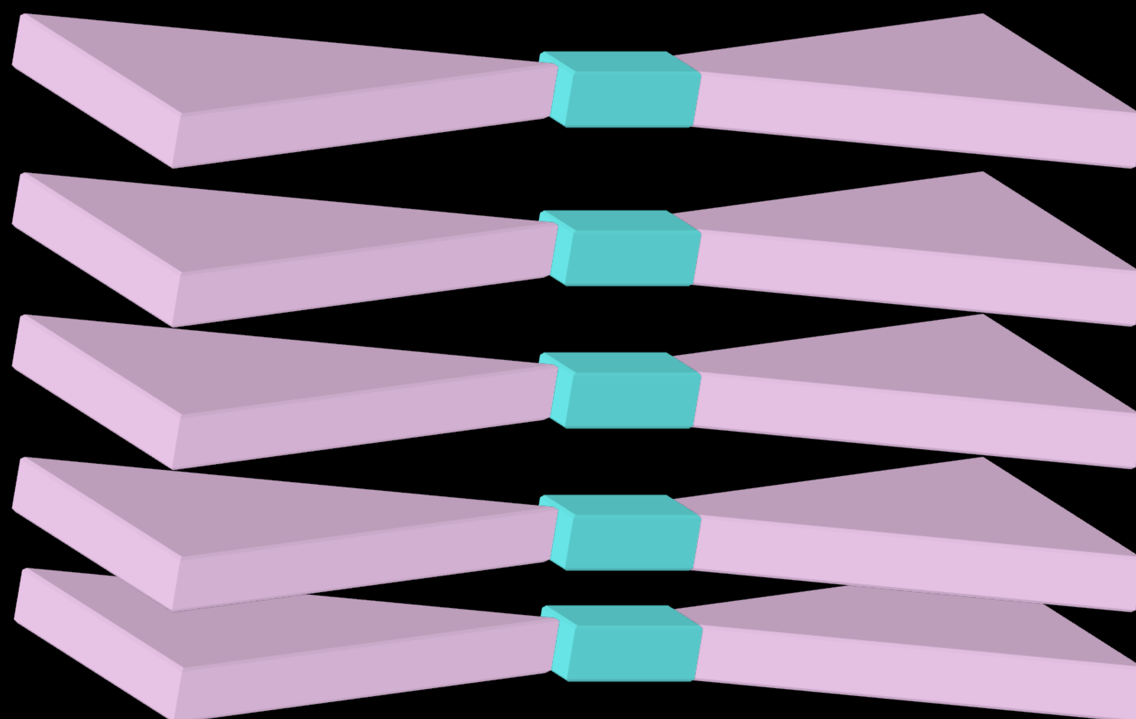
assembly

Diverse



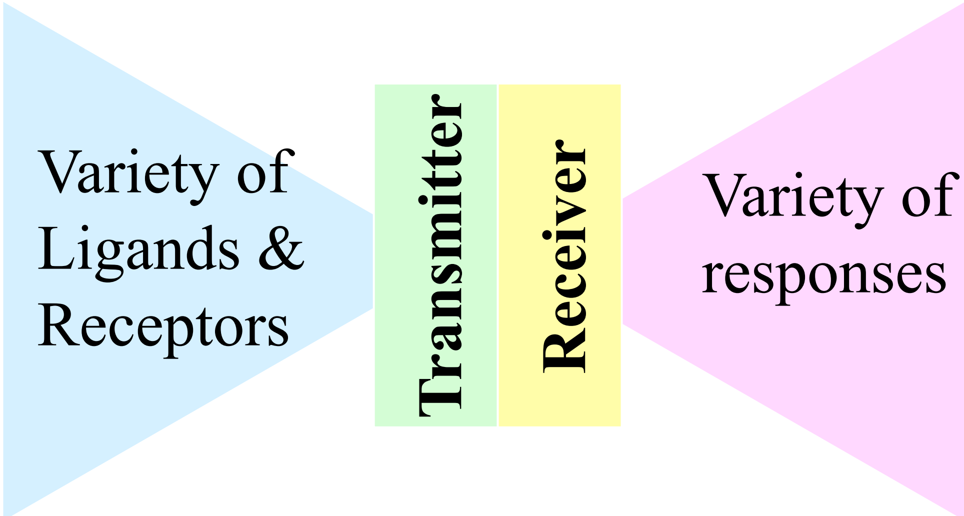
Layers of bowties

We'll come back to this aspect later.



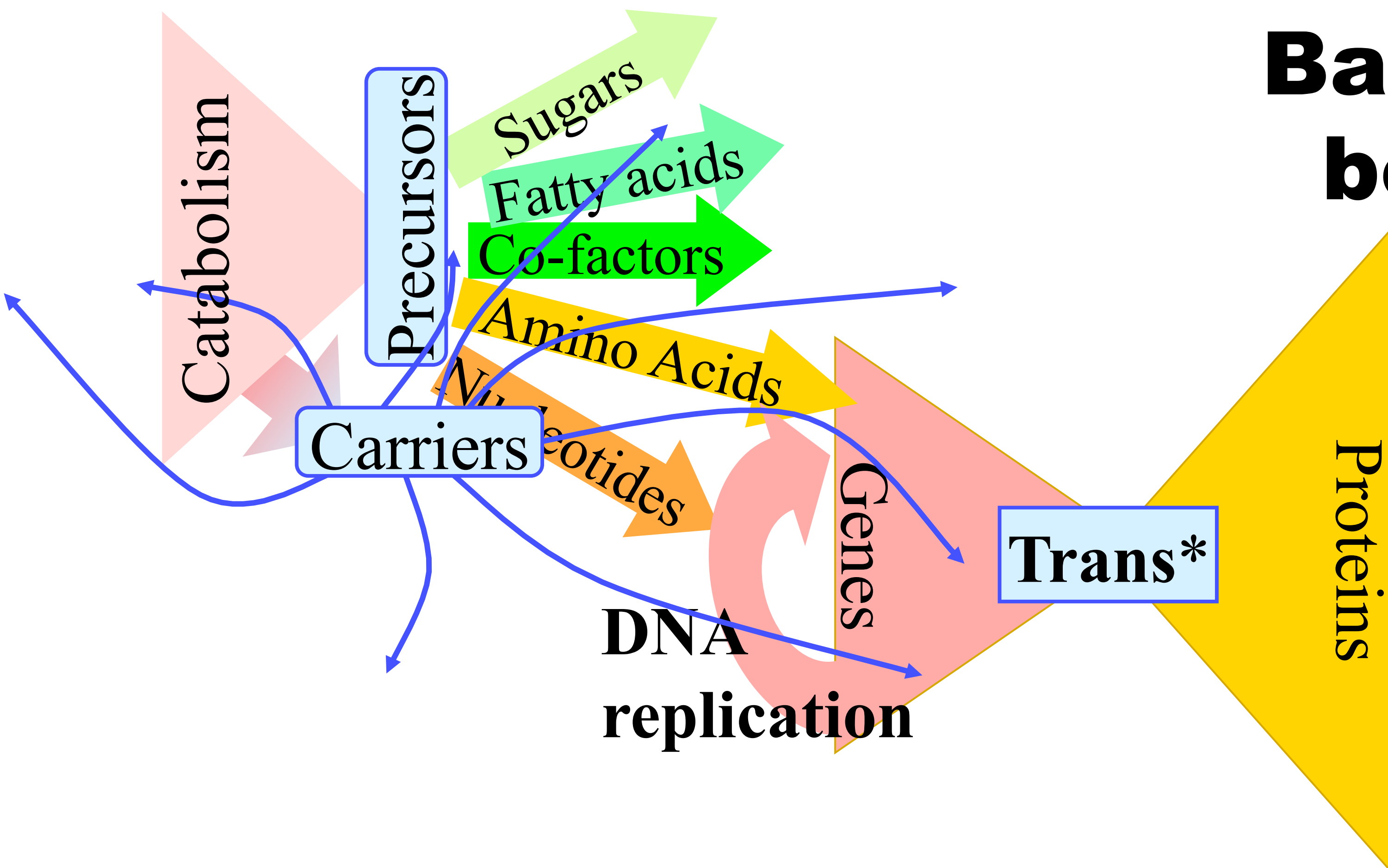
Why bowties?

- Metabolism, biosynthesis, assembly
  1. ***Carriers***: Charging carriers in central metabolism
  2. ***Precursors***: Biosynthesis of precursors and building blocks
  3. ***Trans****: DNA replication, transcription, and translation
- Signal transduction
  4. *2CST*: Two-component signal transduction



1. *Carriers*
2. *Precursors*
3. *Trans**
7. *2CST*

Bacterial bowties



Transmitter

Receiver

1. *Carriers*
2. *Precursors*
3. *Trans**
7. *2CST*

Precursors

Carriers

Trans*

Constraints

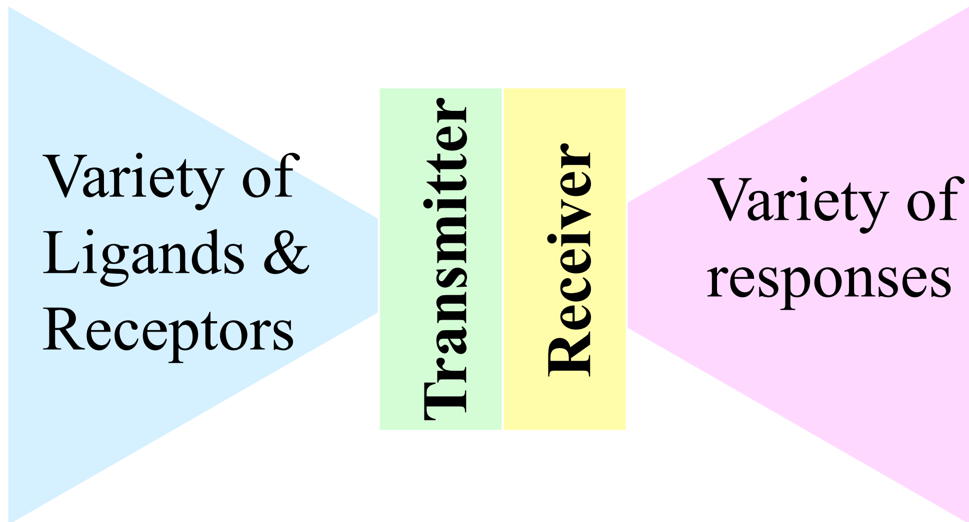
Transmitter

Receiver

Precursors

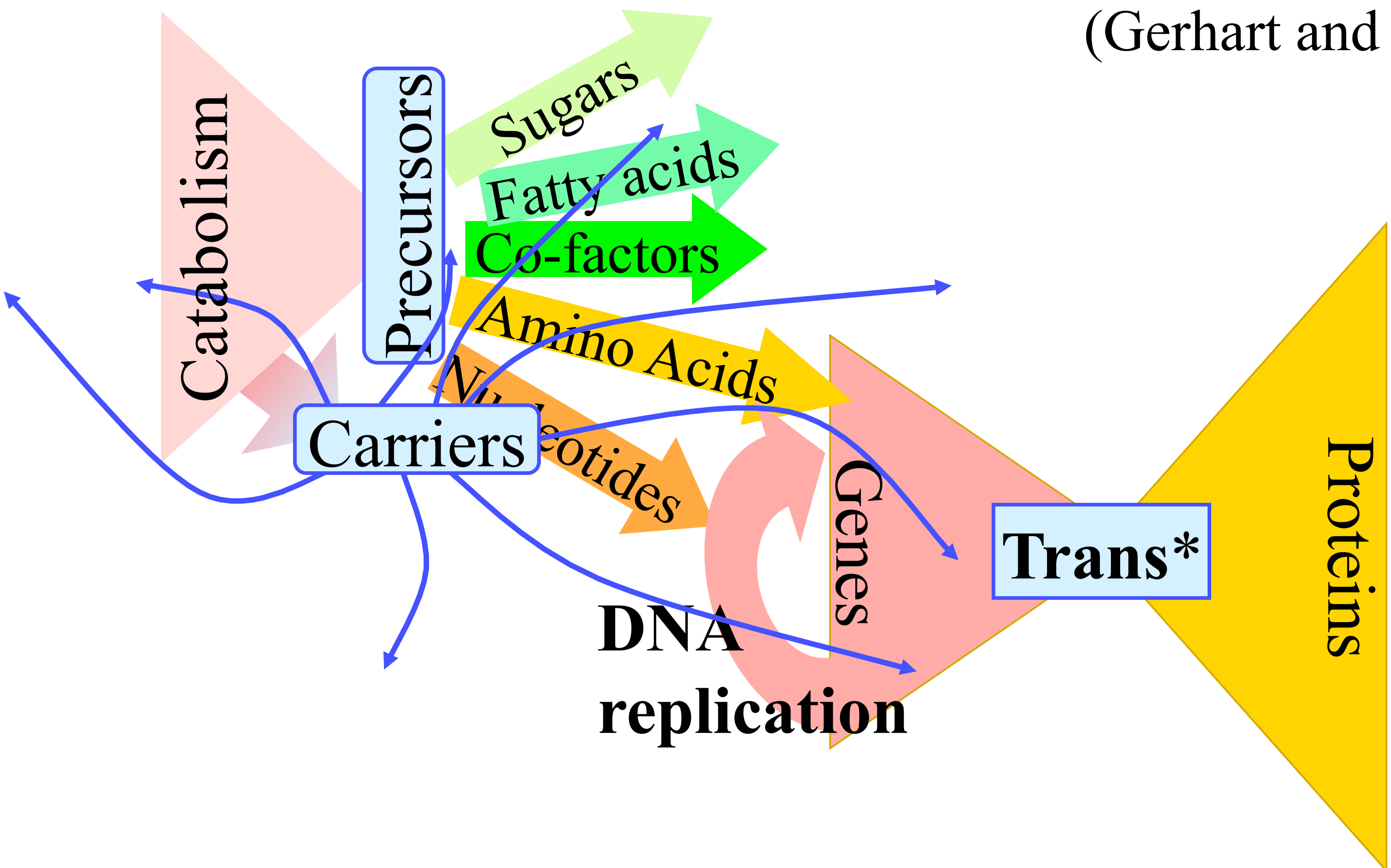
Carriers

Trans*

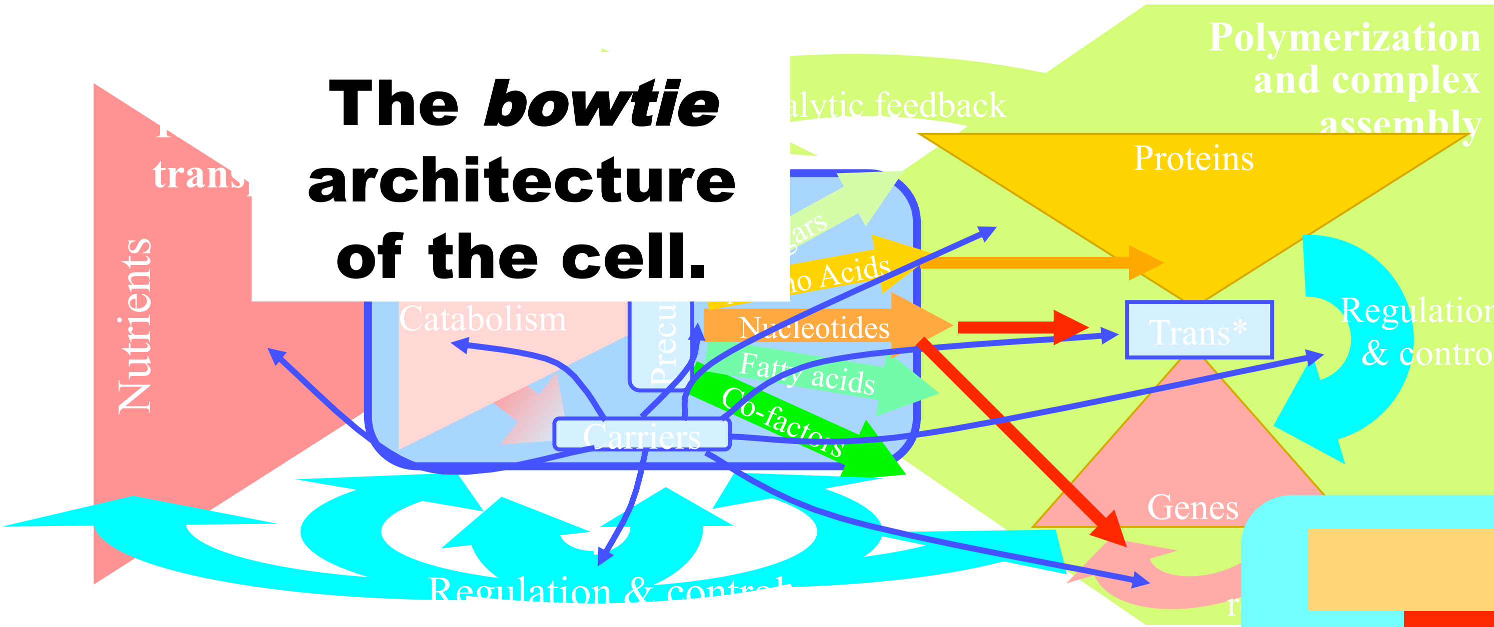


Constraints That Deconstrain

(Gerhart and Kirschner)

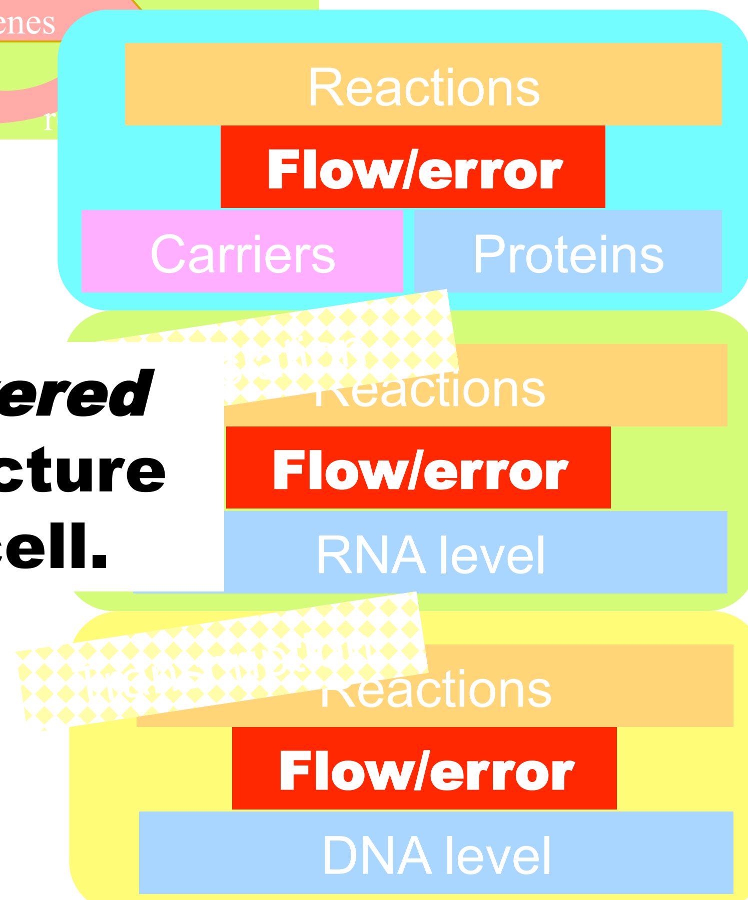


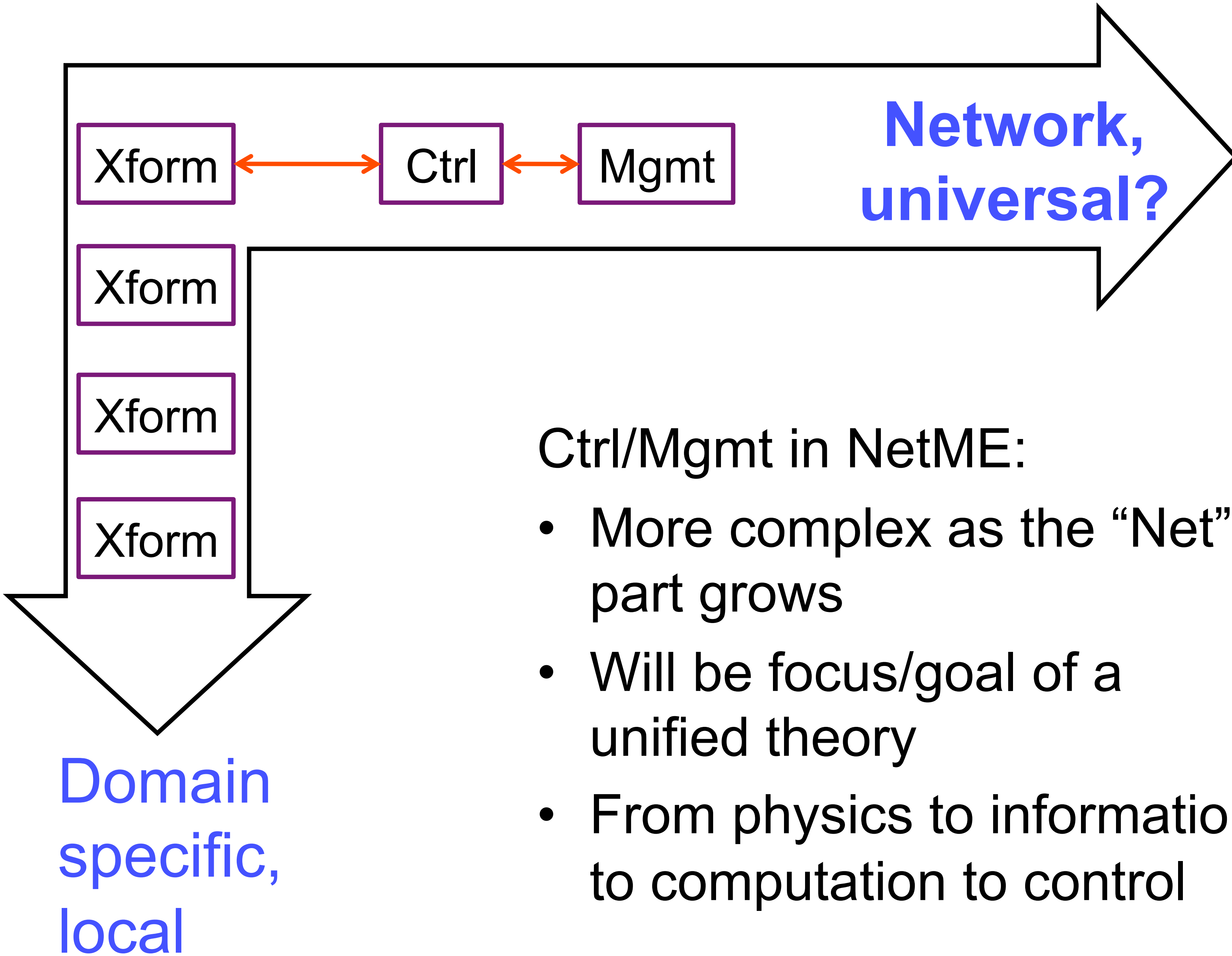
The *bowtie* architecture of the cell.



Need a more coherent cartoon to visualize how these fit together.

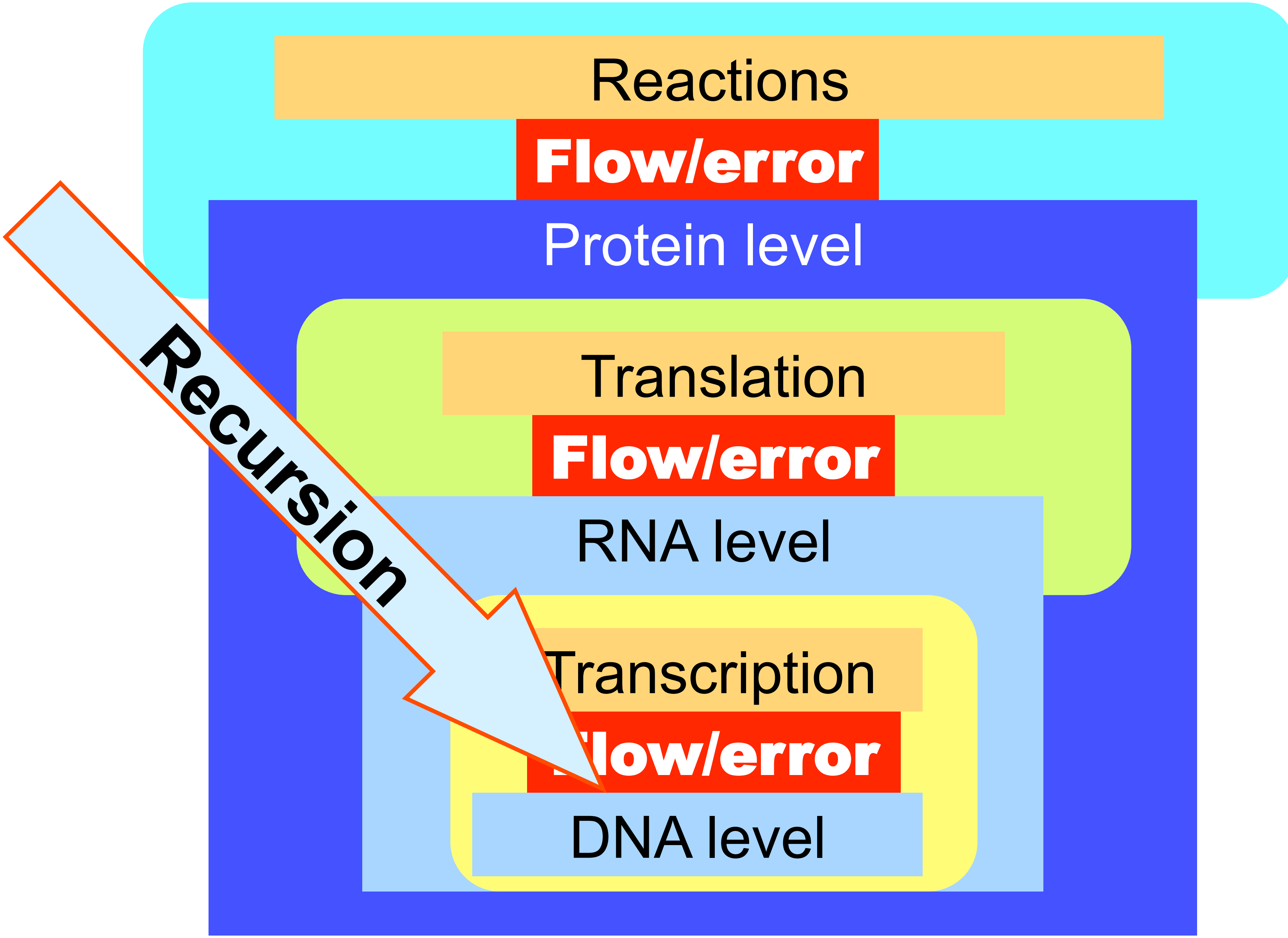
The *layered* architecture of the cell.

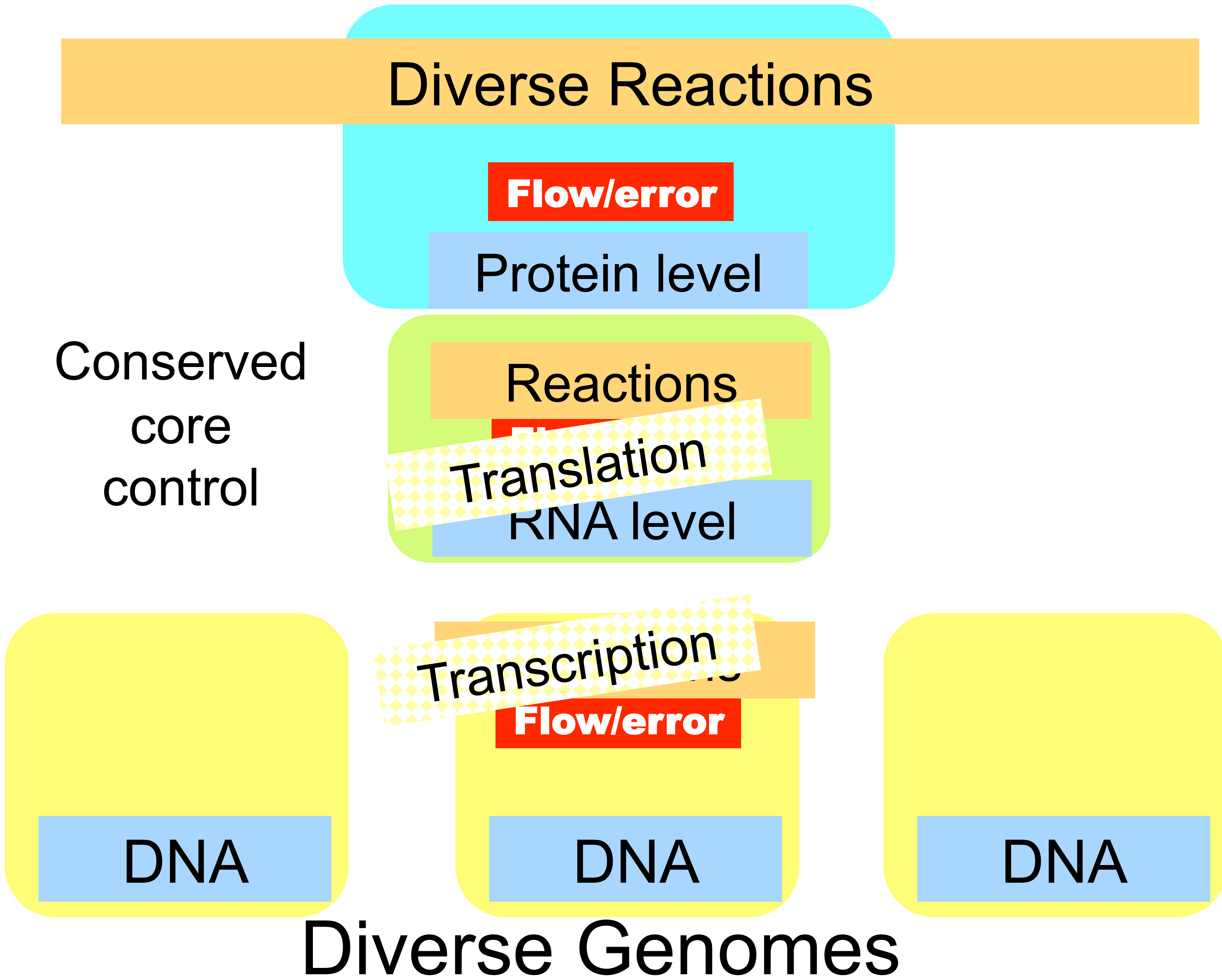




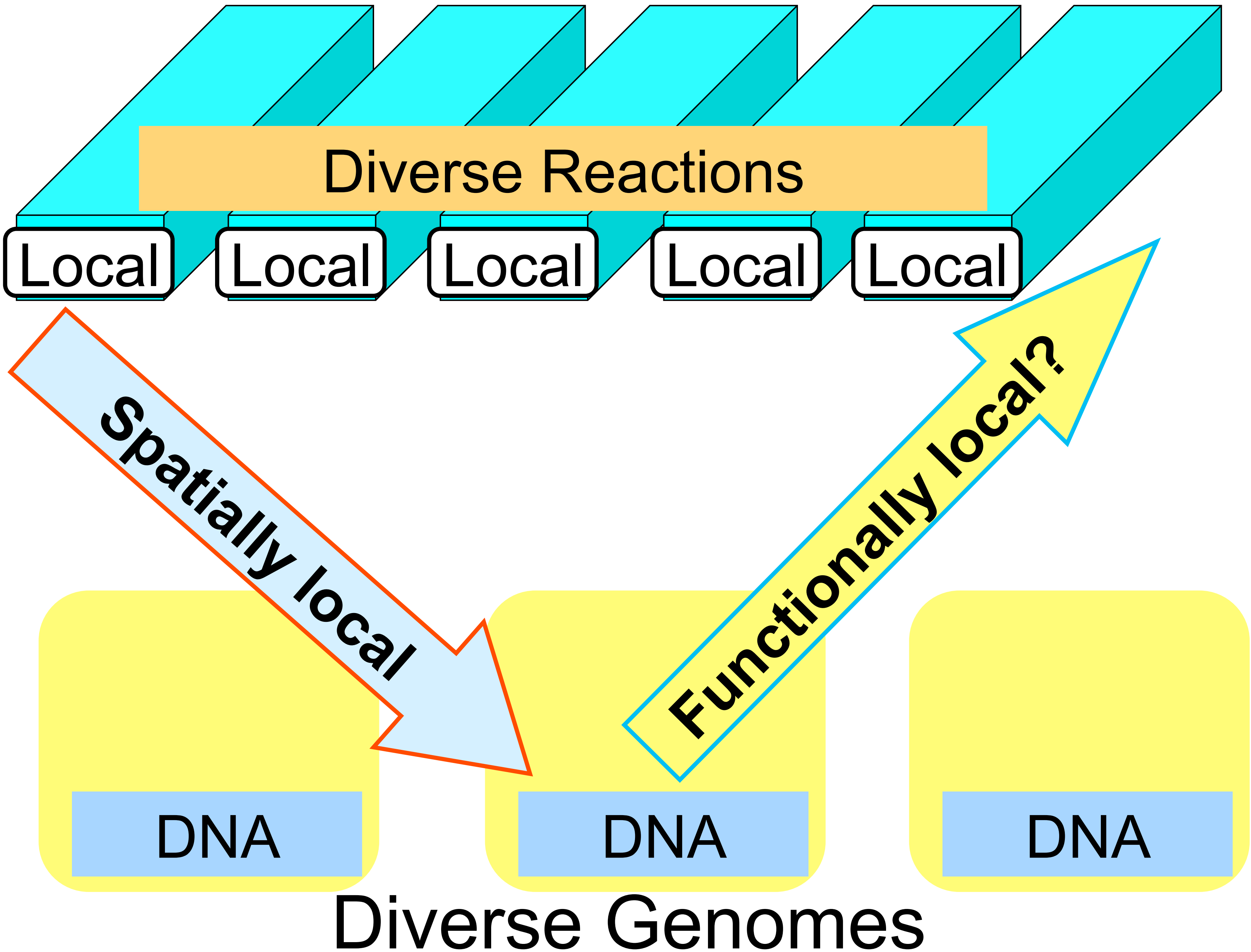
Ctrl/Mgmt in NetME:

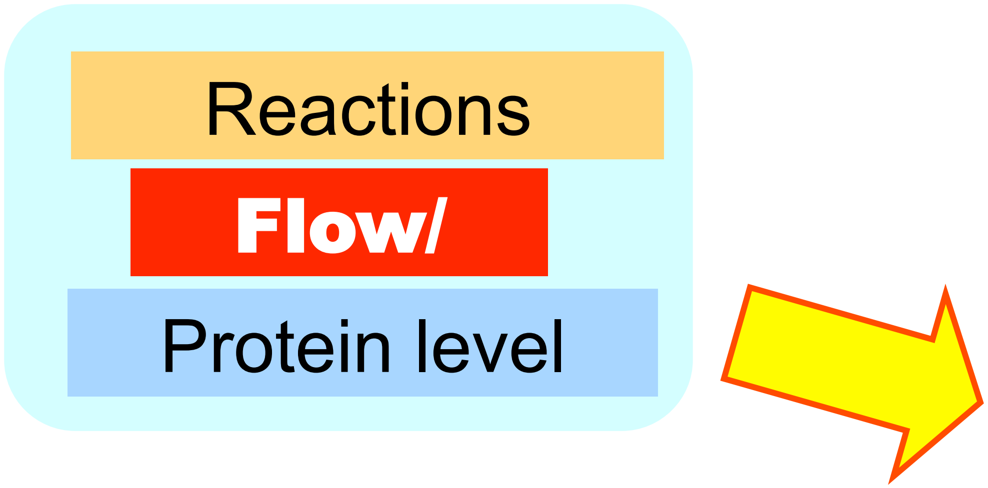
- More complex as the “Net” part grows
- Will be focus/goal of a unified theory
- From physics to information to computation to control

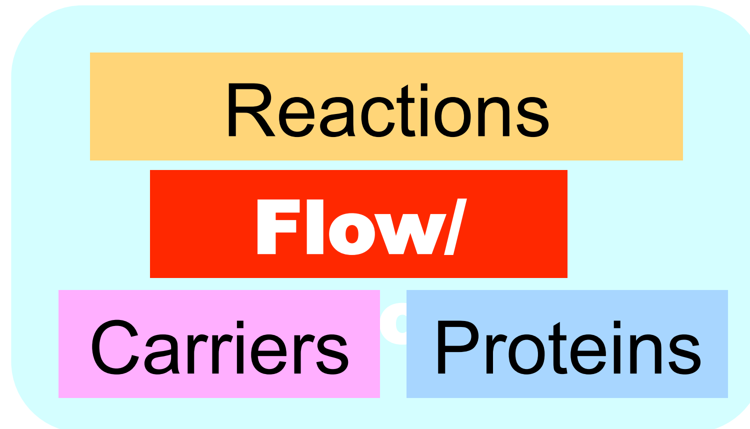

Reactions
Flow/error
Protein level
Translation
Flow/error
RNA level
Transcription
Flow/error
DNA level
Recursion

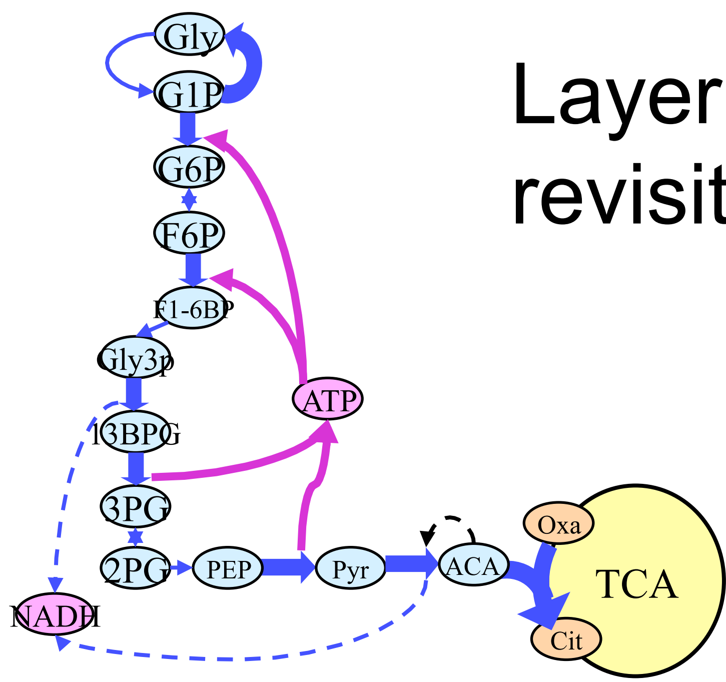


Diverse Reactions
Flow/error
Protein level
Conserved
core
control
Reactions
Translation
RNA level
Transcription
Flow/error
DNA
DNA
DNA
Diverse Genomes


Diverse Reactions
Local
Local
Local
Local
Local
Spatially local
Functionally local?
DNA
DNA
DNA
Diverse Genomes







Layering revisited

More complete picture

Biology versus the Internet

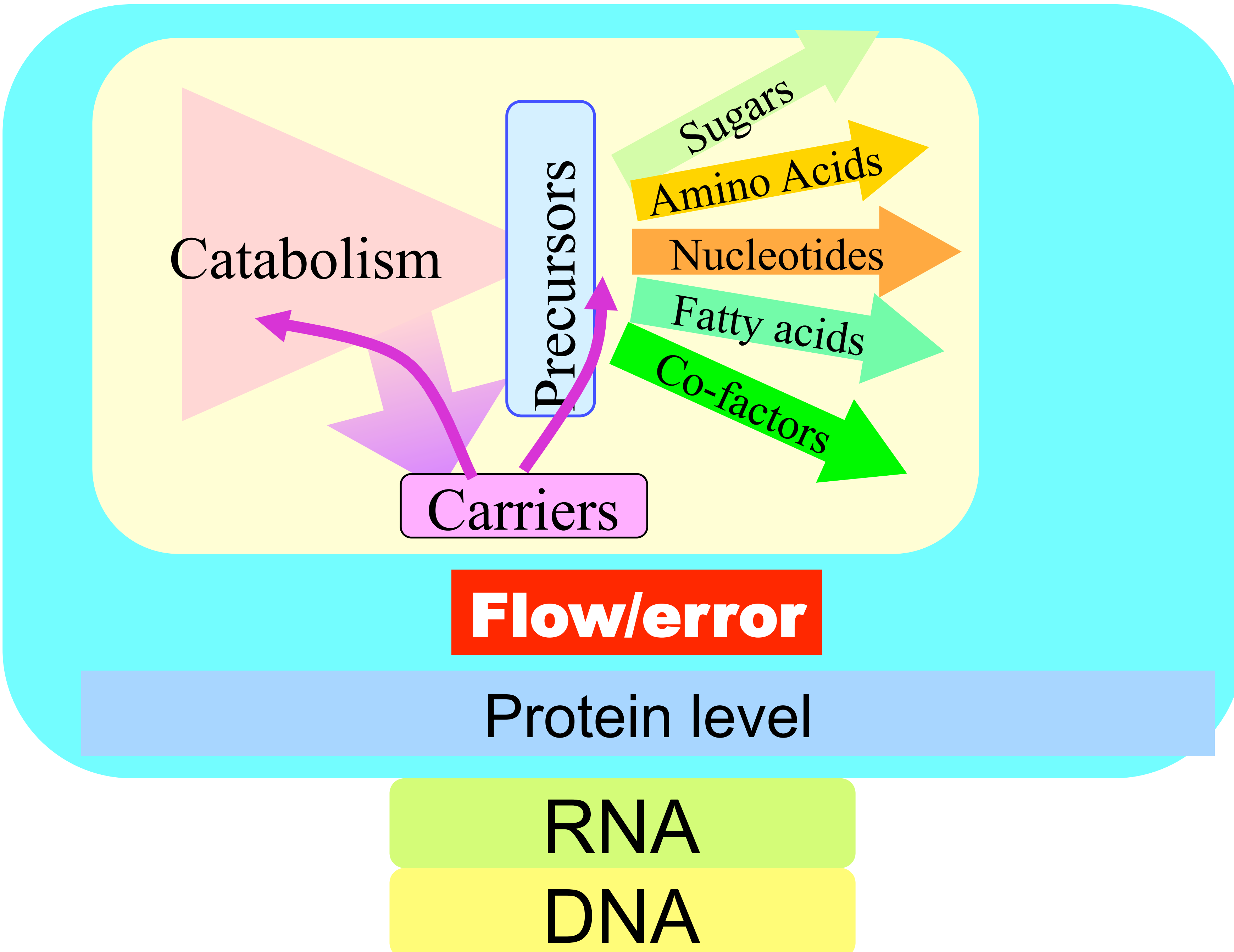
Similarities

- Evolvable architecture
- Robust yet fragile
- **Layering, modularity**
- Hourglass with bowties
- Dynamics
- Feedback
- Distributed/decentralized

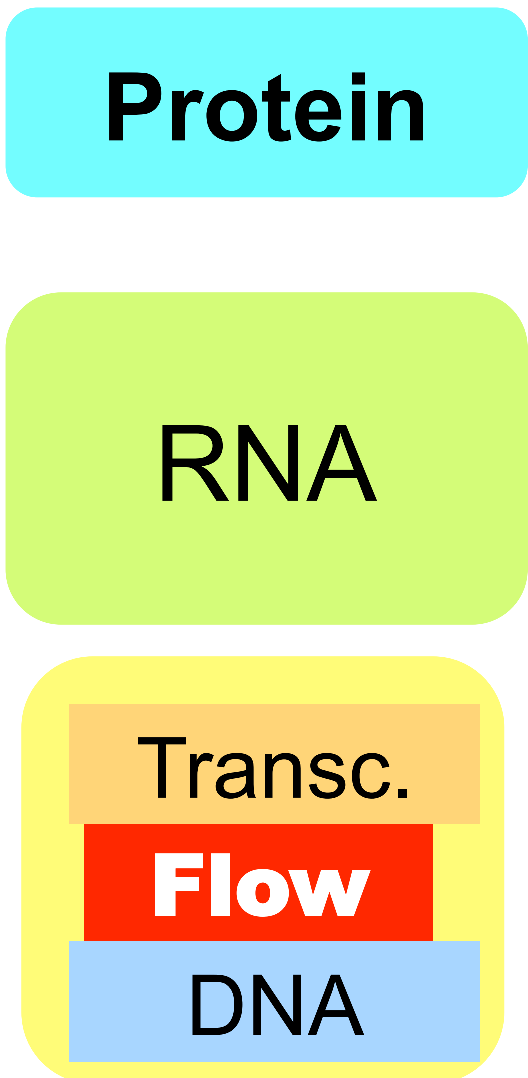
- ***Not*** scale-free, edge-of-chaos, self-organized criticality, etc

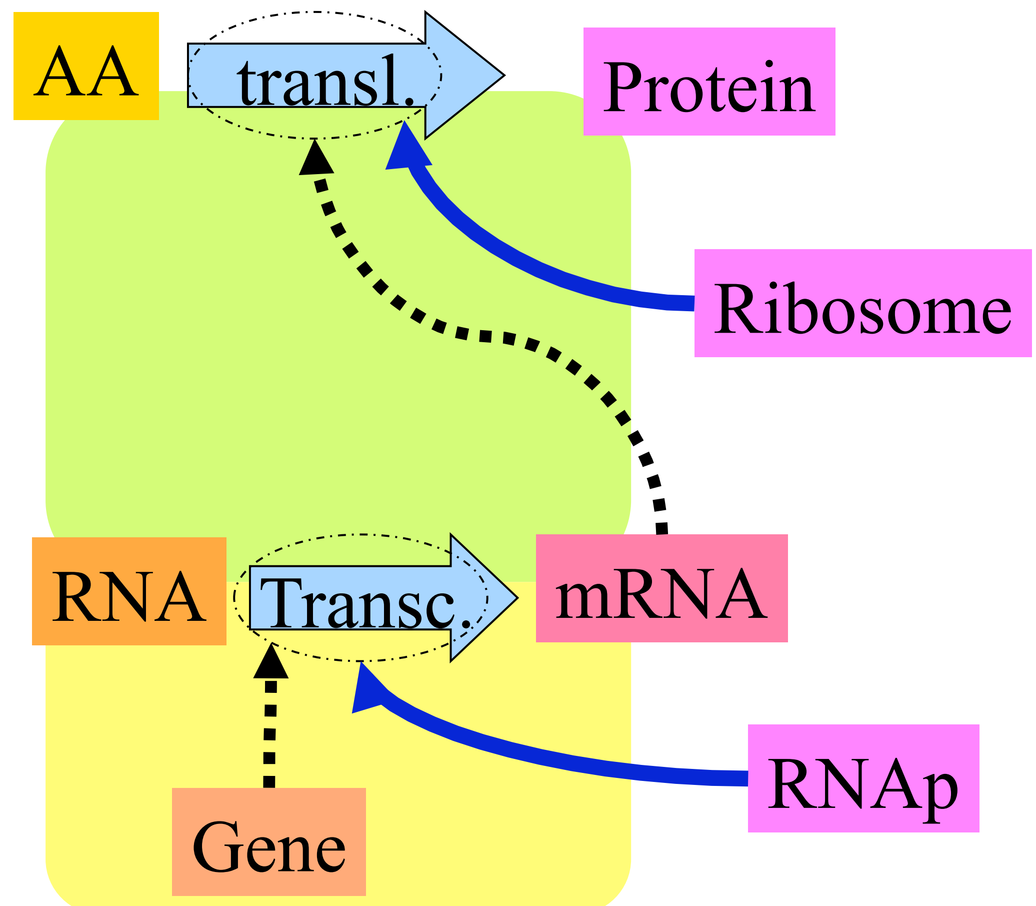
Differences

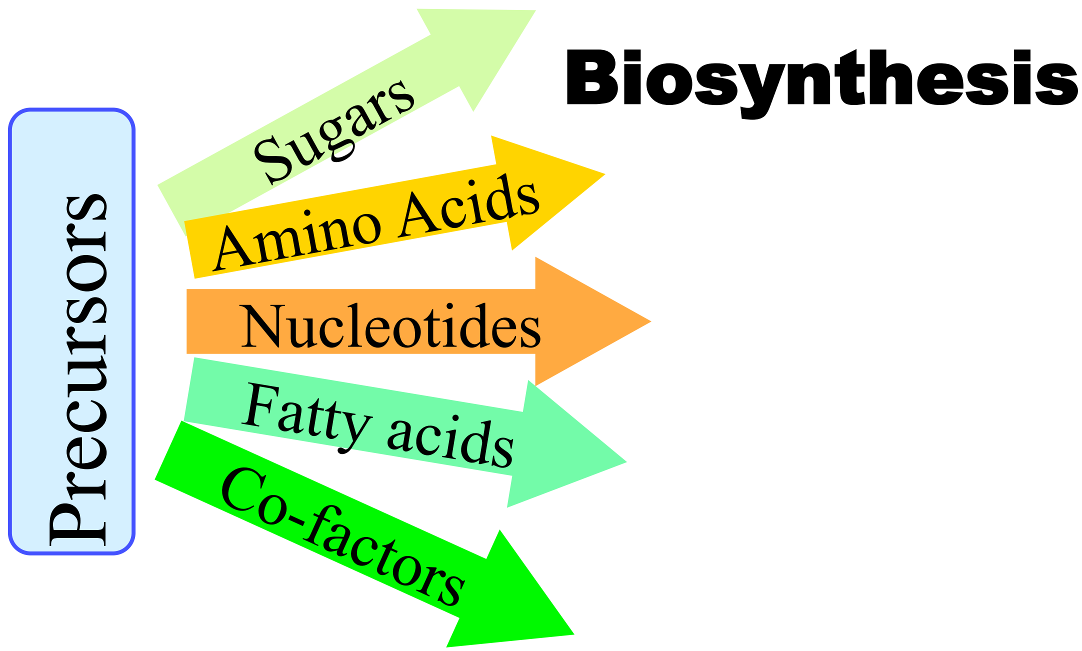
- Metabolism
- Materials and energy
- **Autocatalytic feedback**
- Feedback complexity
- Development and regeneration
- >3B years of evolution


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

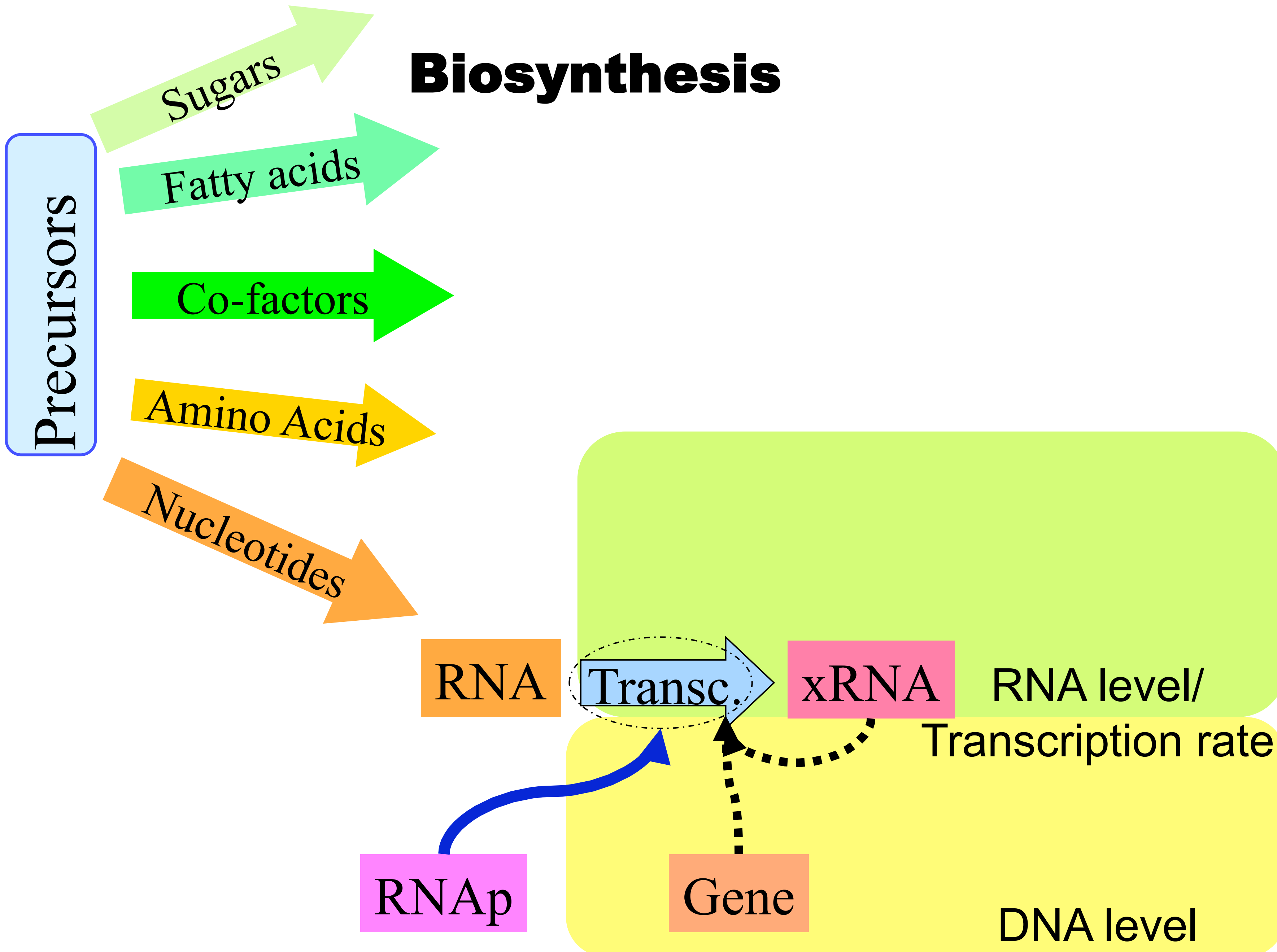
"Central dogma"



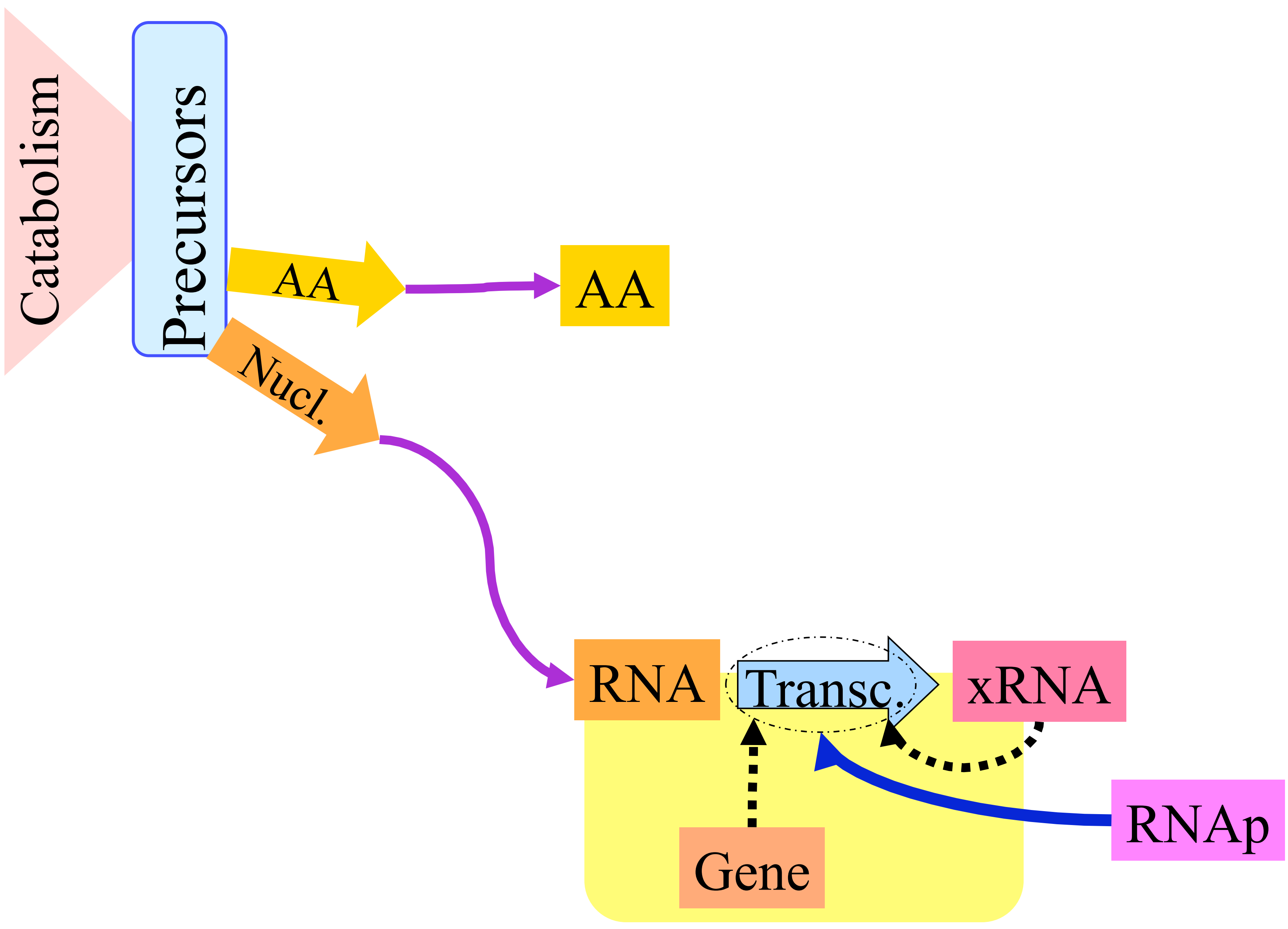



Biosynthesis
Precursors
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors

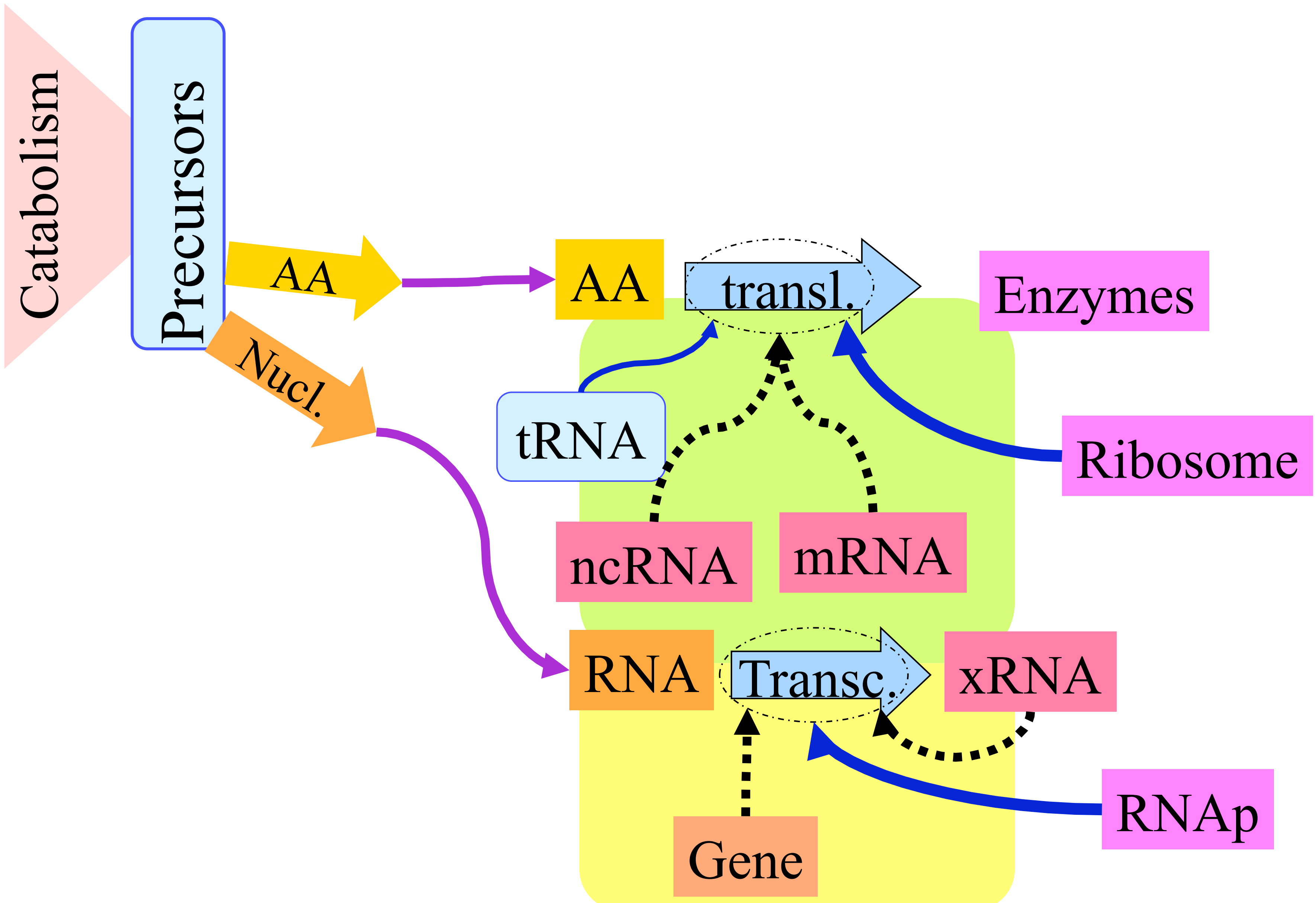

RNA
DNA

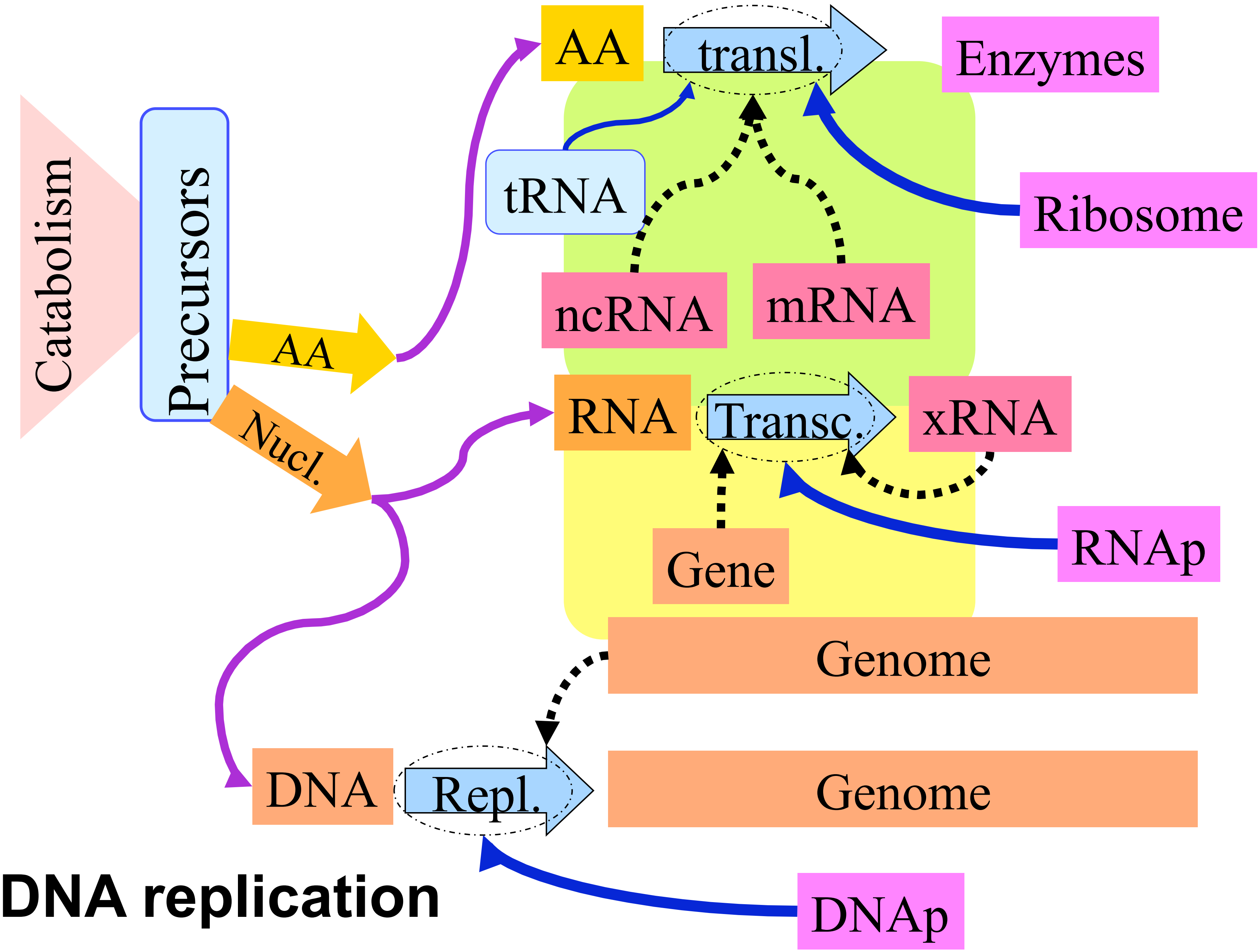


Biosynthesis
Precursors
Sugars
Fatty acids
Co-factors
Amino Acids
Nucleotides
RNA
Transc.
xRNA
RNA level/
Transcription rate
RNAp
Gene
DNA level



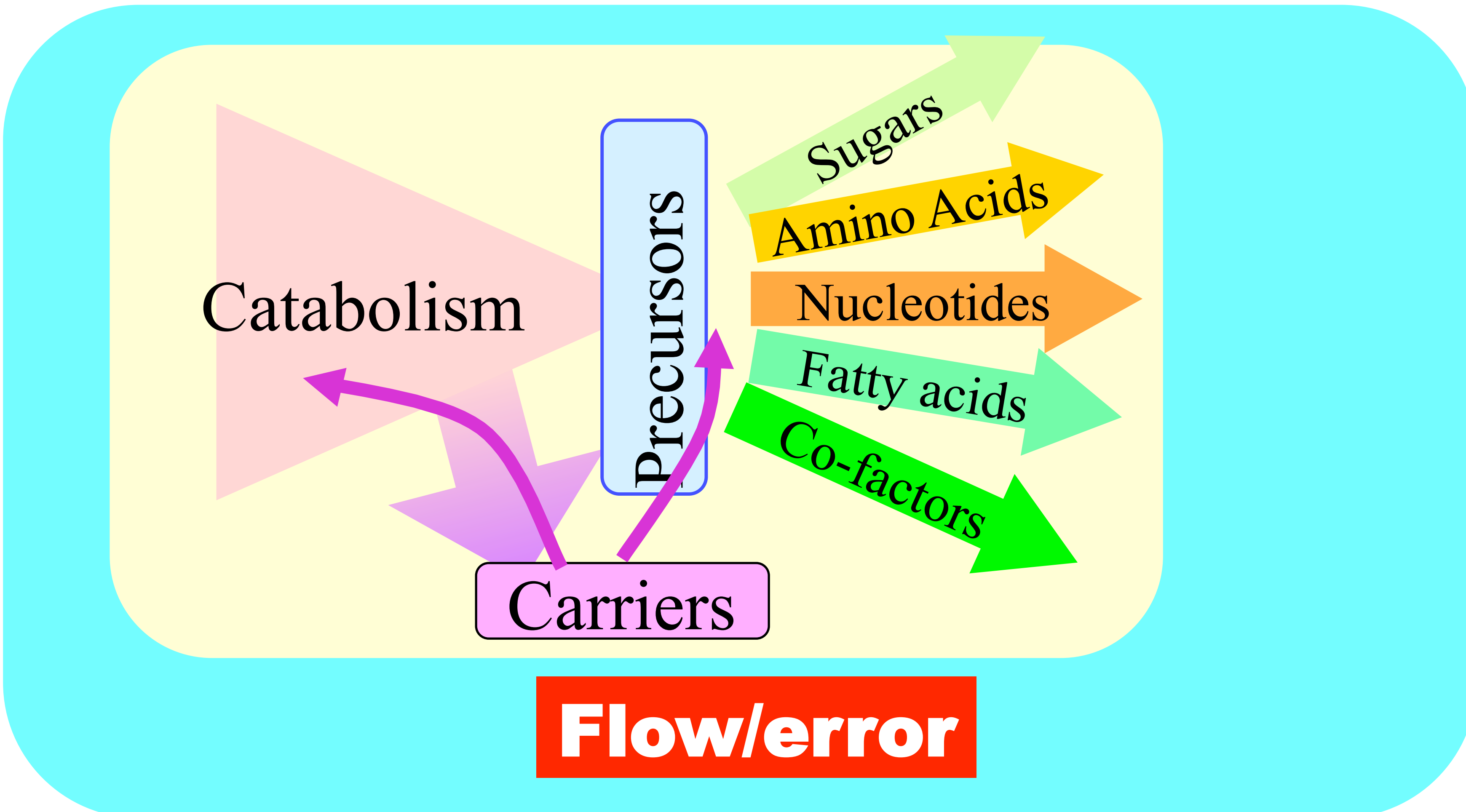
Catabolism
Precursors
AA
AA
Nucl.
RNA
Transc.
xRNA
Gene
RNAp


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

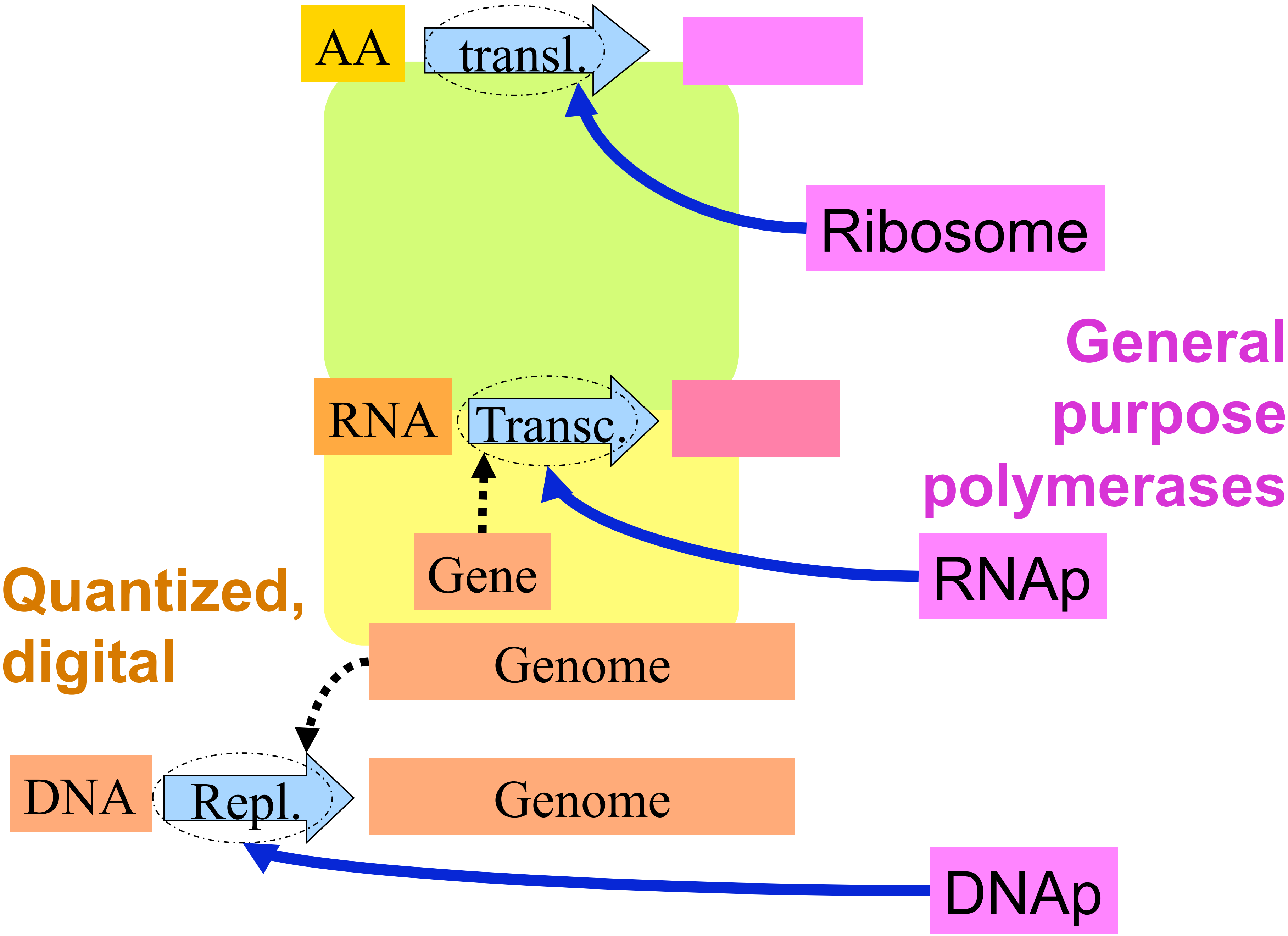


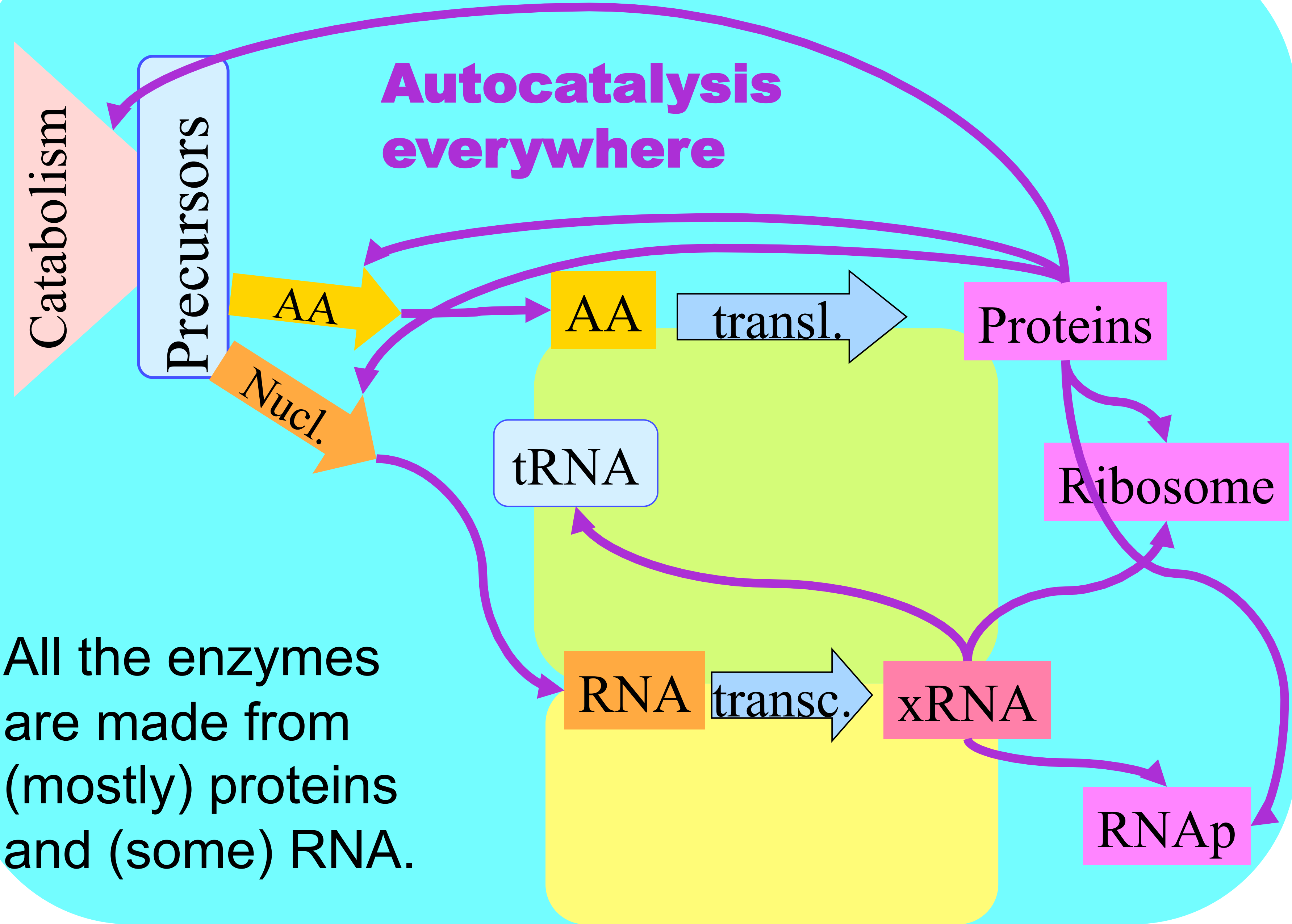
DNA replication

Analog/continuous dynamics



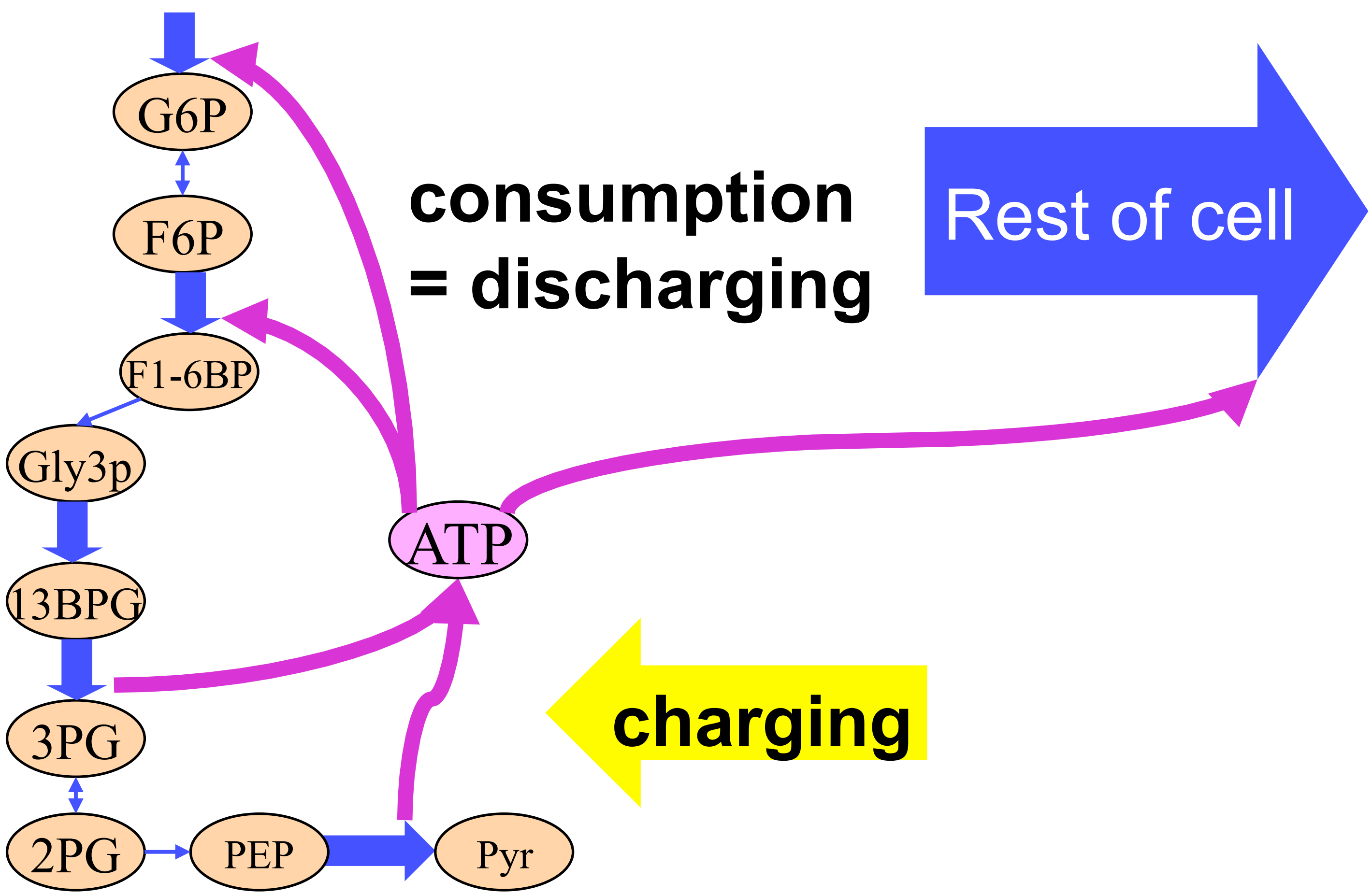
Specialized enzymes
for each reaction

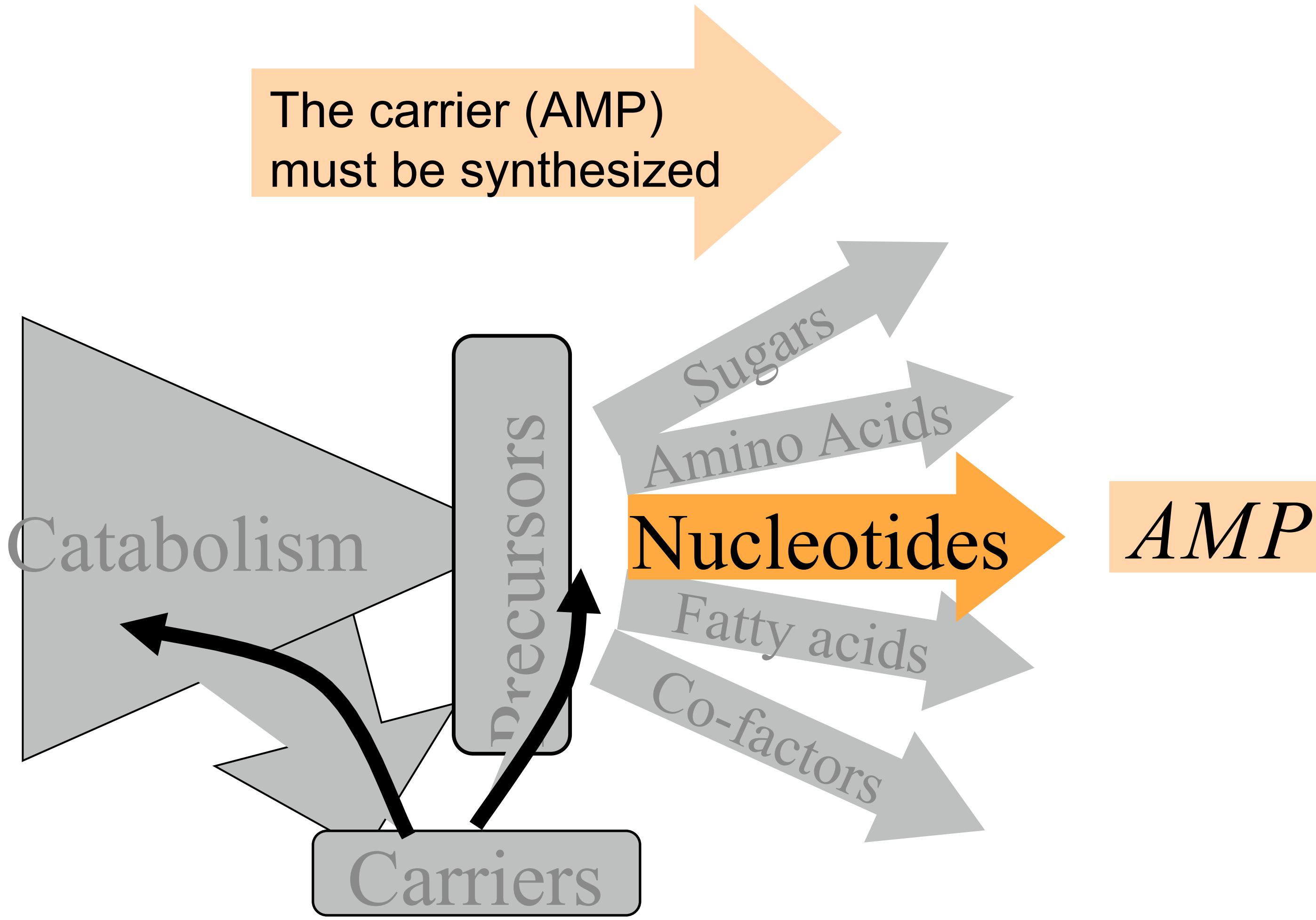

AA
transl.
Ribosome
General
purpose
polymerases
RNA
Transc.
Gene
RNAp
Quantized,
digital
Genome
DNA
Repl.
Genome
DNAp

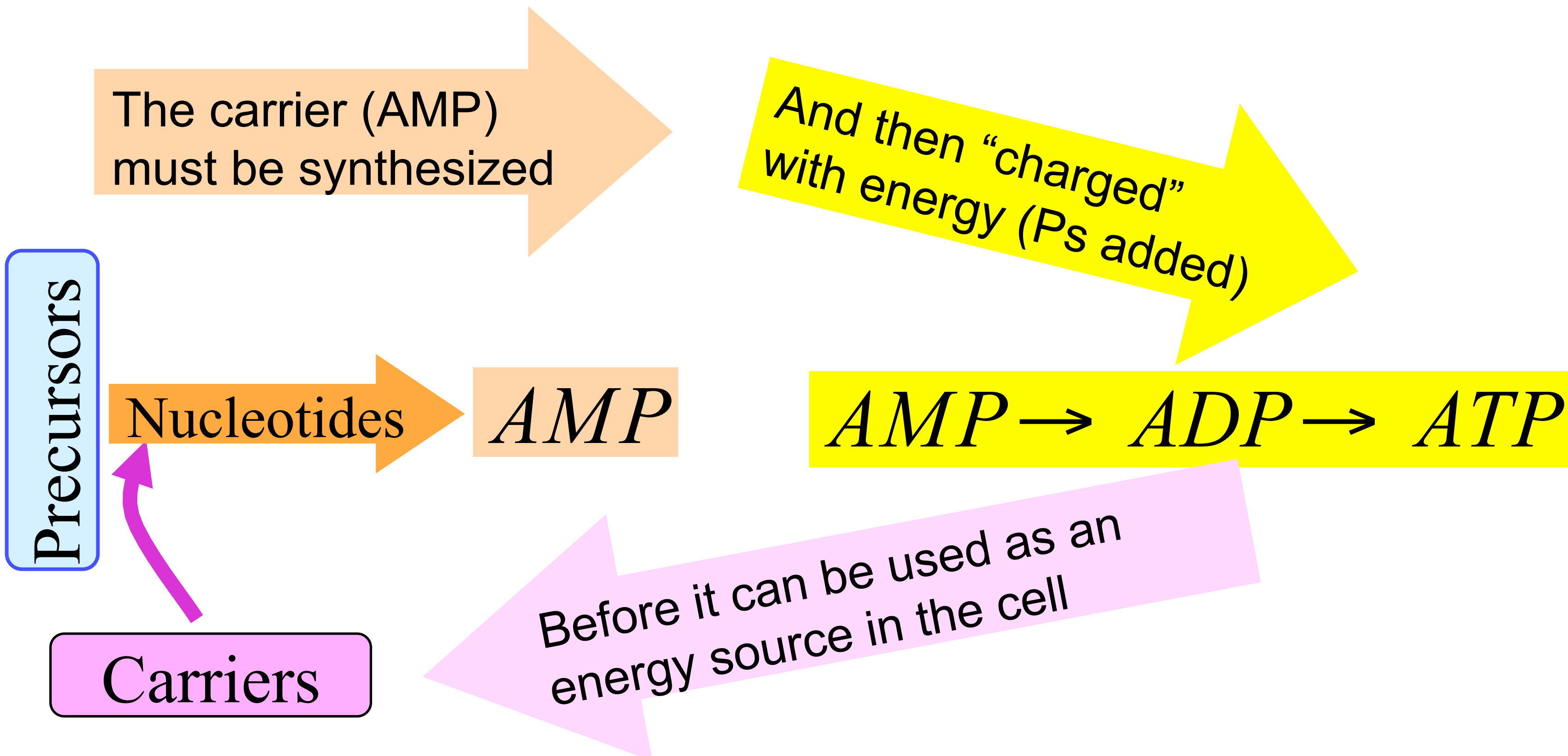


All the enzymes are made from (mostly) proteins and (some) RNA.

This is just charging and discharging

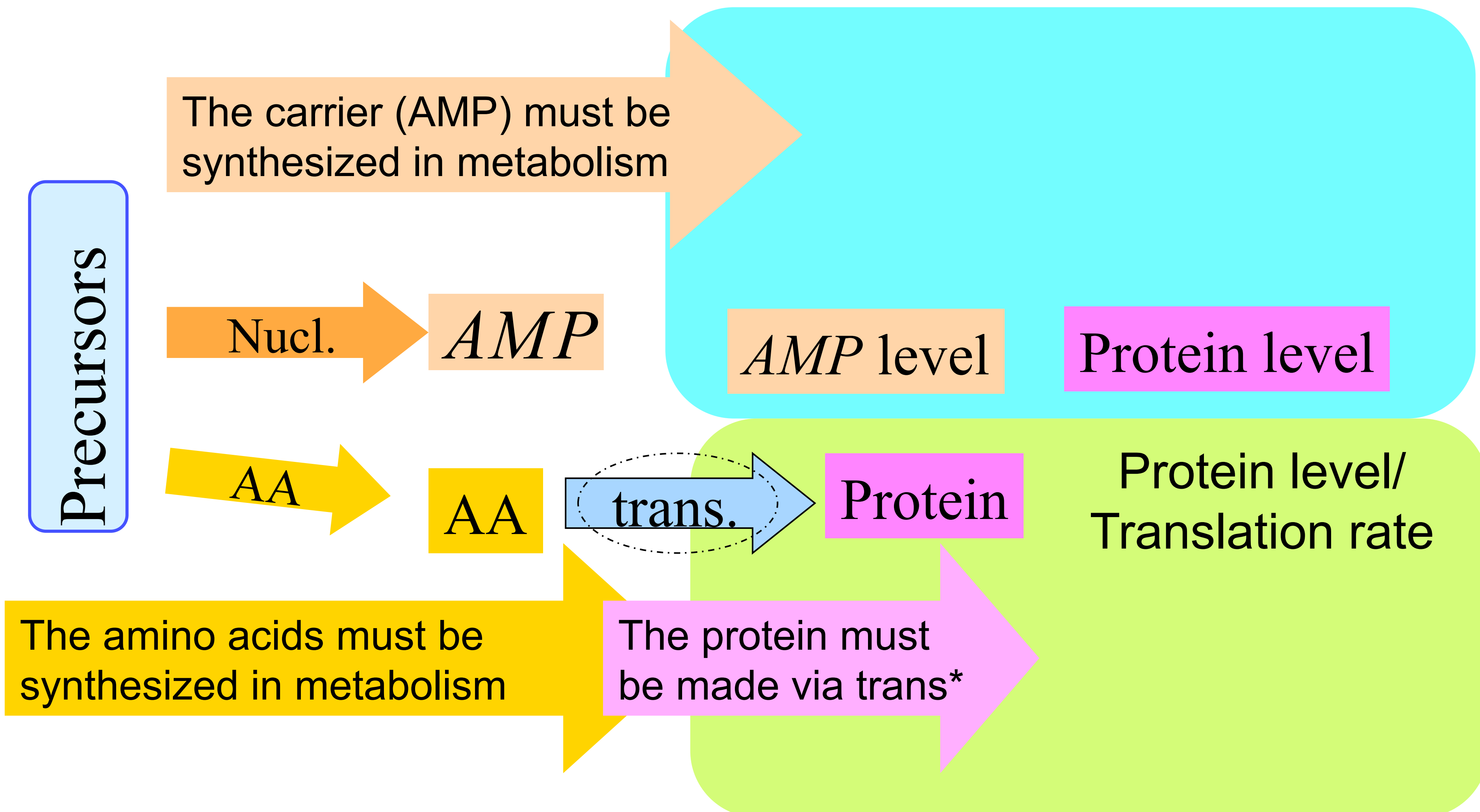



The carrier (AMP)
must be synthesized
Catabolism
Precursors
Carriers
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
AMP



Think of AMP as a battery, and ATP as the charged battery.
There are two autocatalytic processes requiring the feedback of resources:

- manufacturing the "battery" (slower process)
- and then repeatedly charging/using the "battery" (very fast)

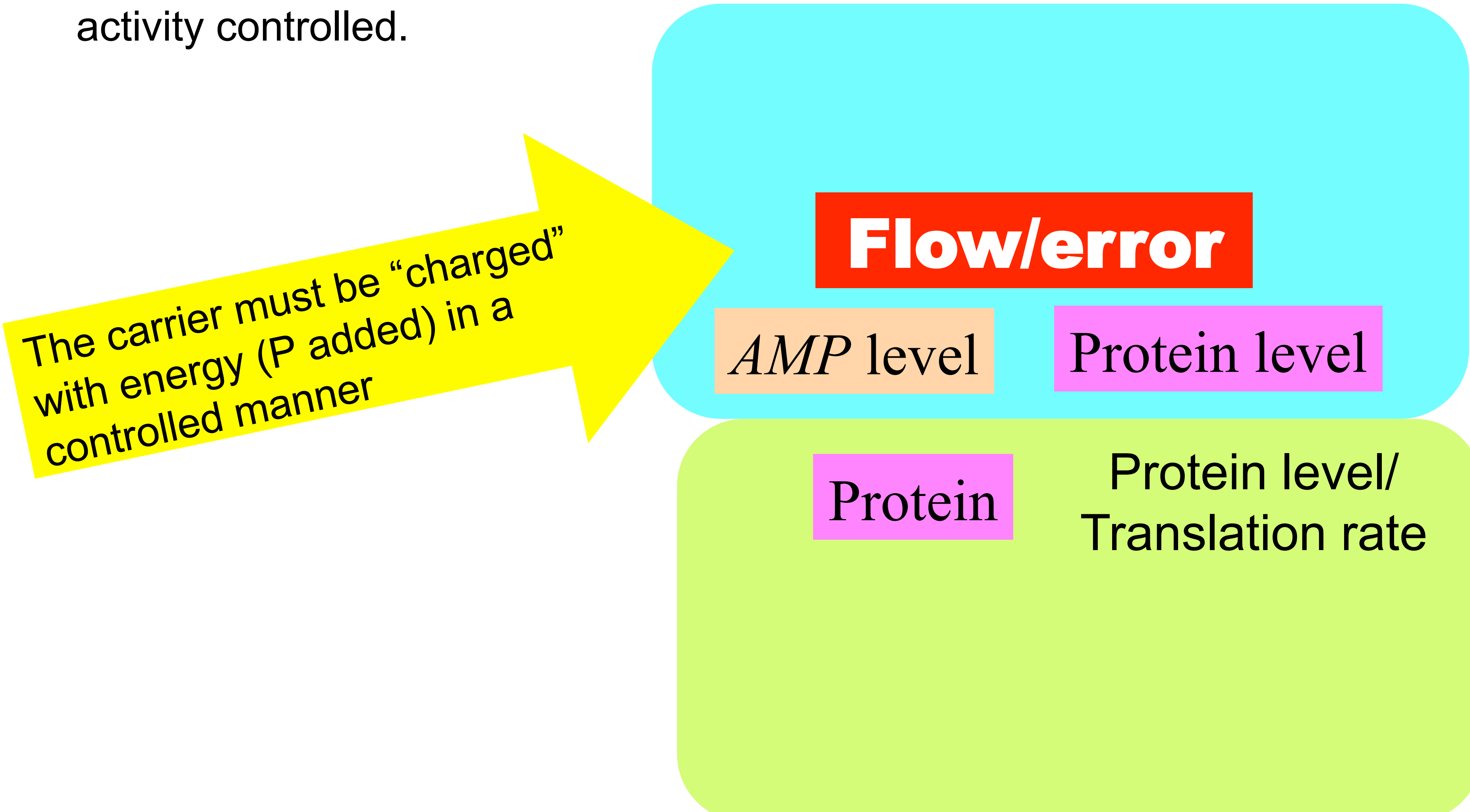


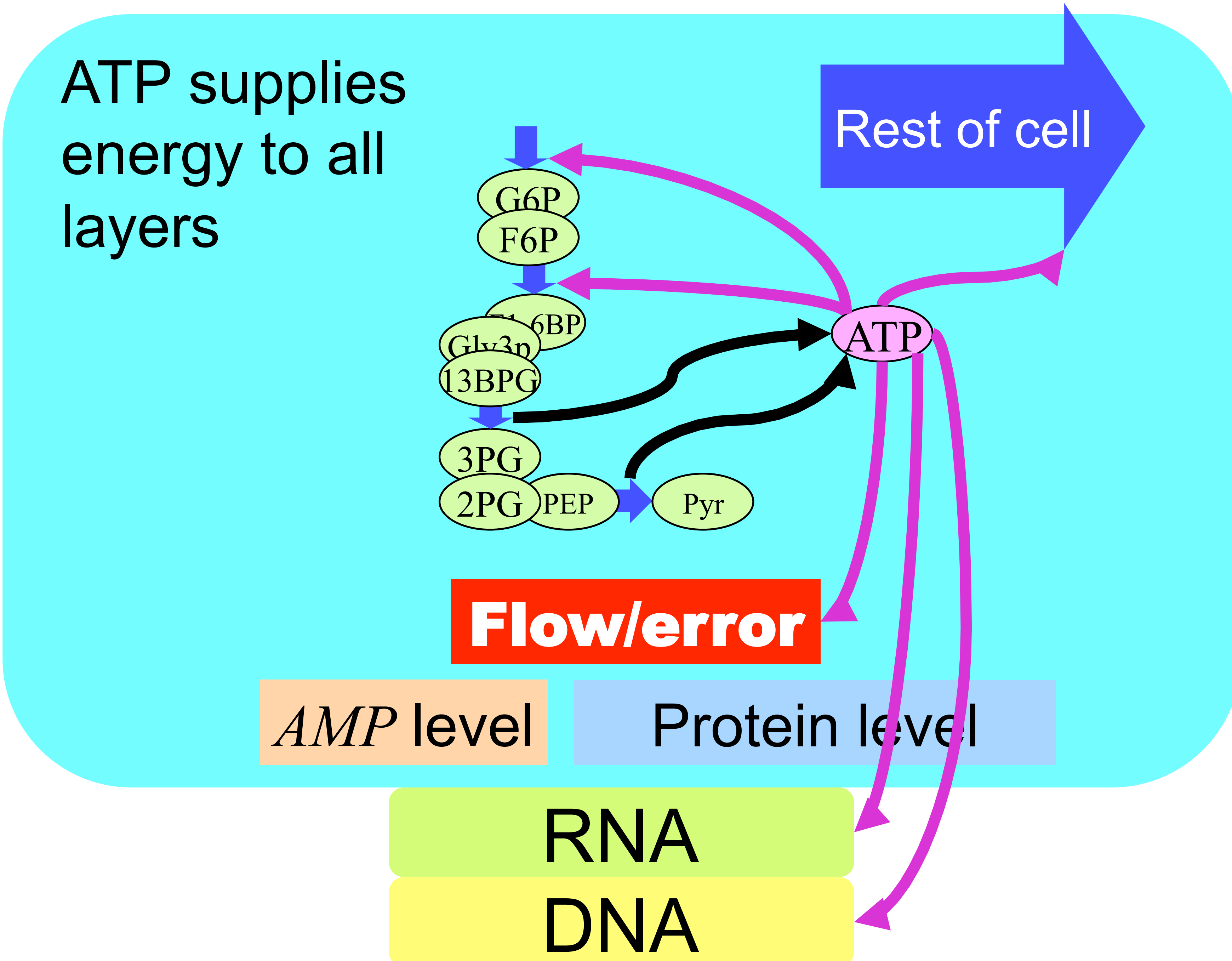
The carrier (AMP) must be synthesized in metabolism
Precursors
Nucl.
AMP
AMP level
Protein level
AA
AA
trans.
Protein
Protein level/ Translation rate
The amino acids must be synthesized in metabolism
The protein must be made via trans*

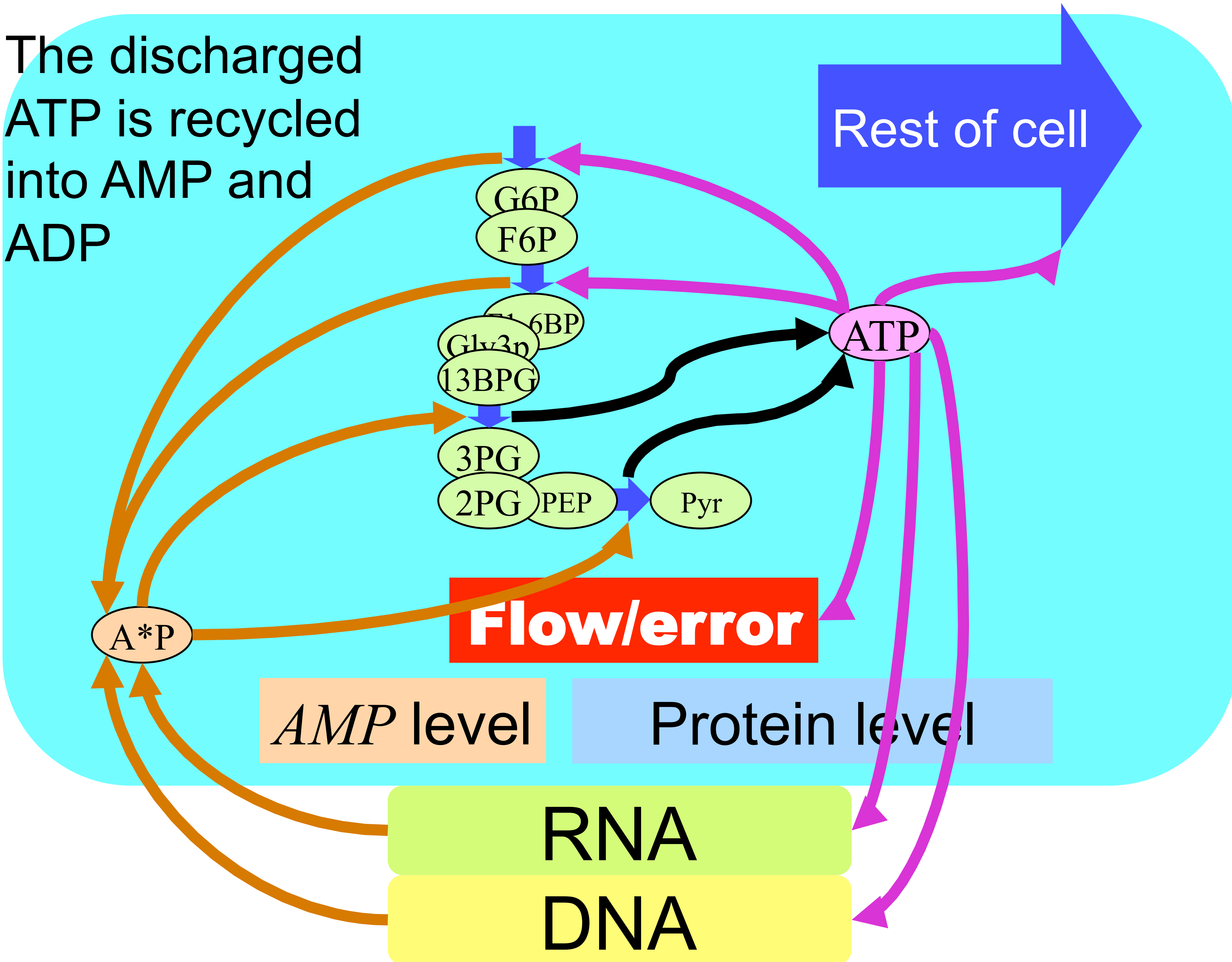
We know what's going on here, but it's hard to draw the layers neatly.

• The carrier (AMP) must be both synthesized (in nucleotide biosynthesis), and then charged in a controlled way.

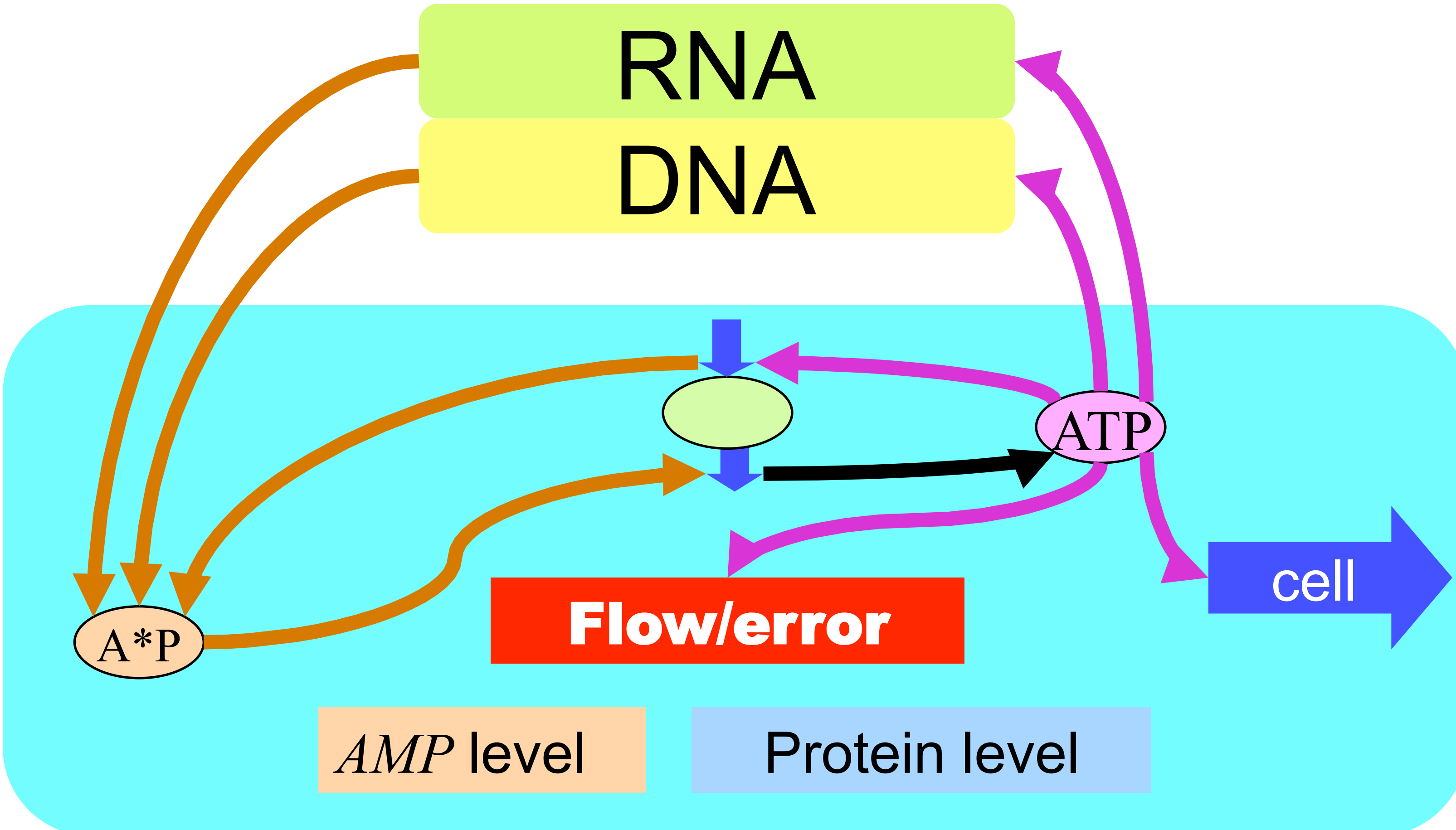
• The protein must be both synthesized and then its form and activity controlled.



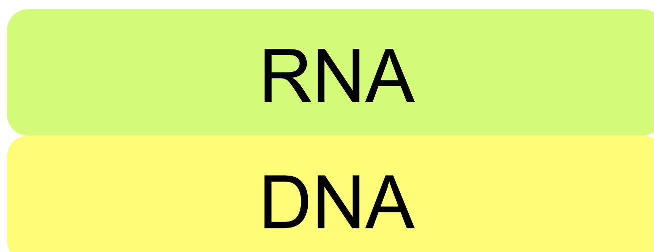

ATP supplies energy to all layers
Rest of cell
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ATP
Flow/error
AMP level
Protein level
RNA
DNA

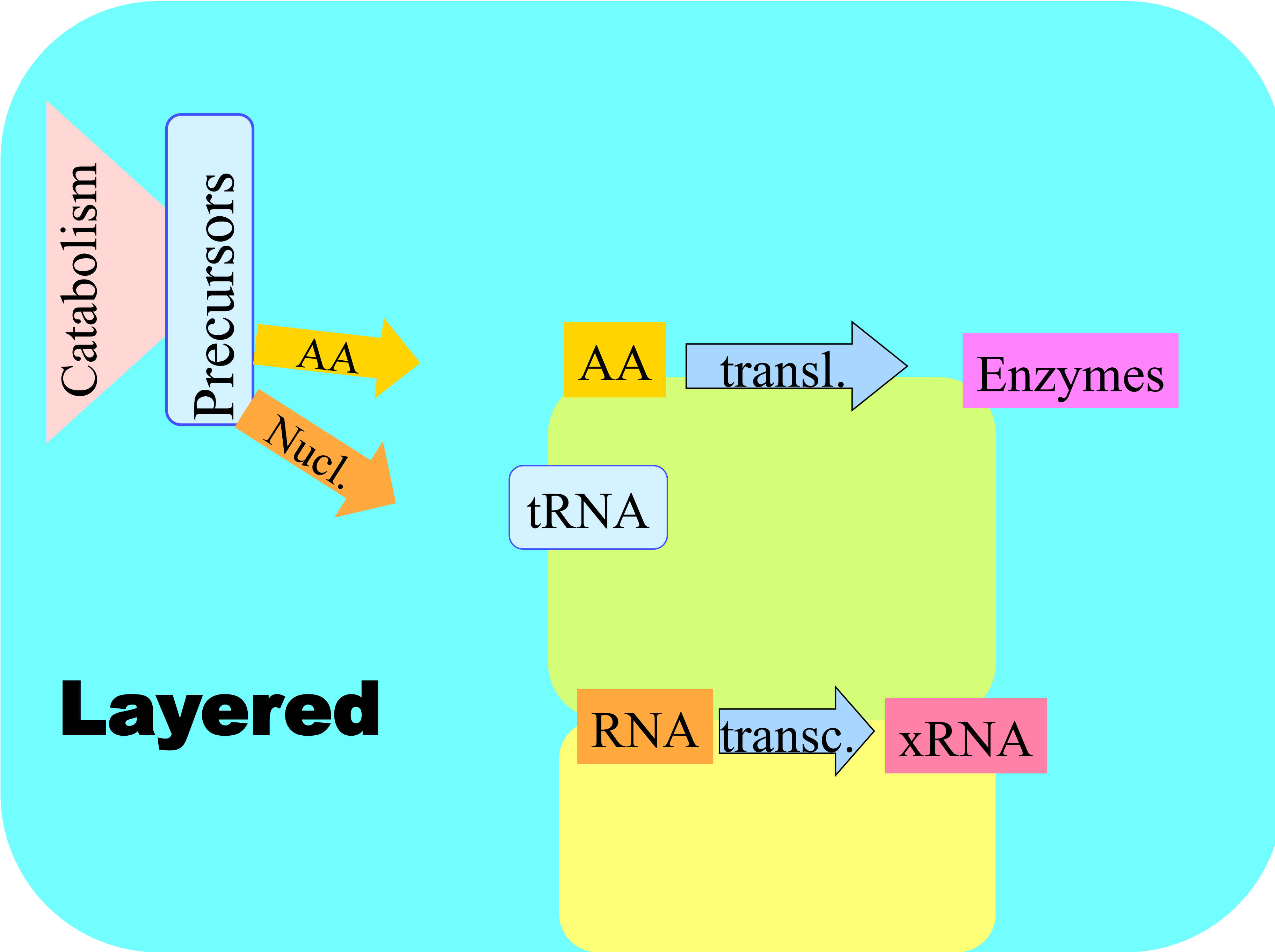


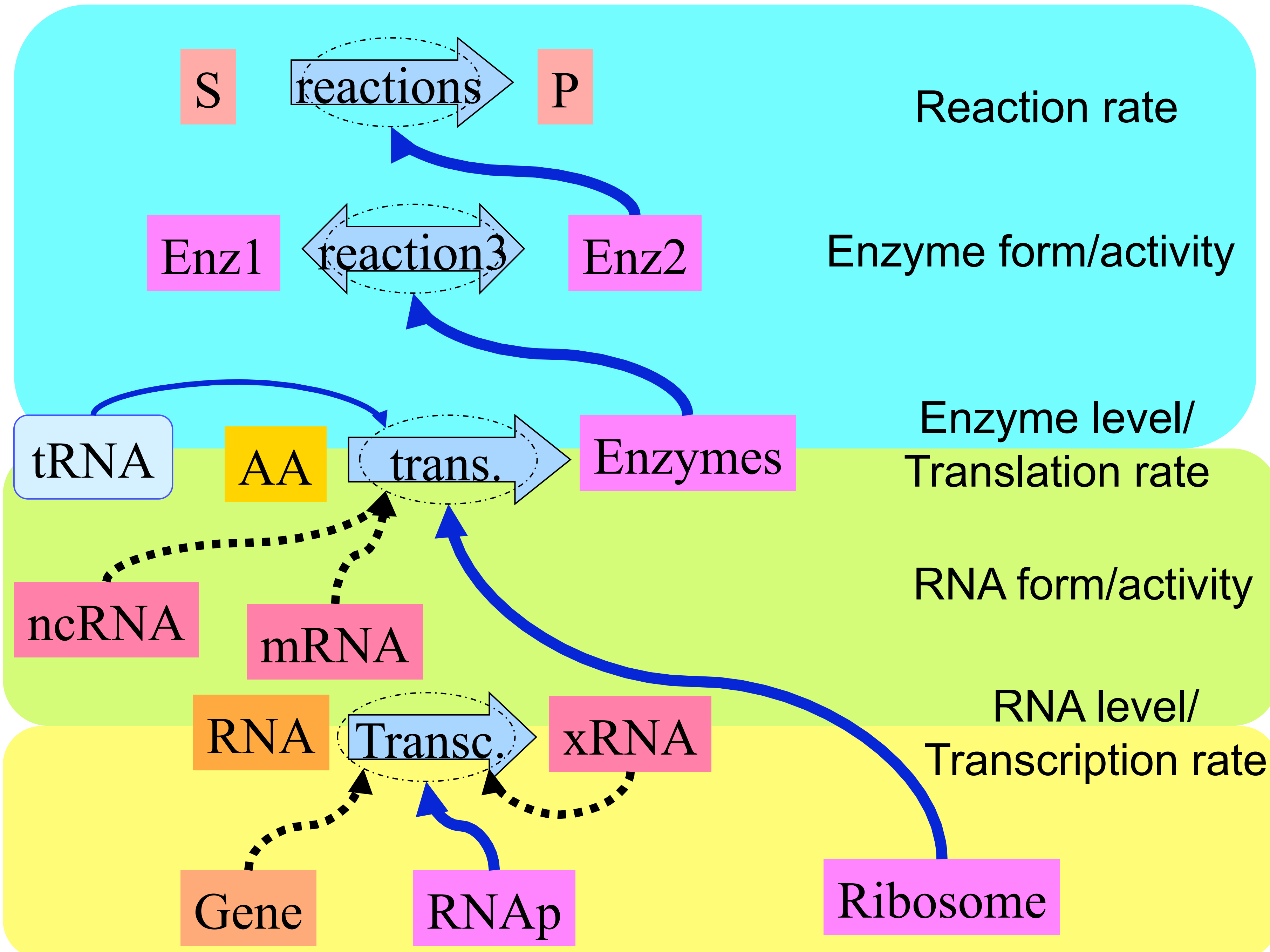
The discharged ATP is recycled into AMP and ADP
Rest of cell
G6P
F6P
6BP
13BPG
3PG
2PG
PEP
Pyr
ATP
A*P
Flow/error
AMP level
Protein level
RNA
DNA



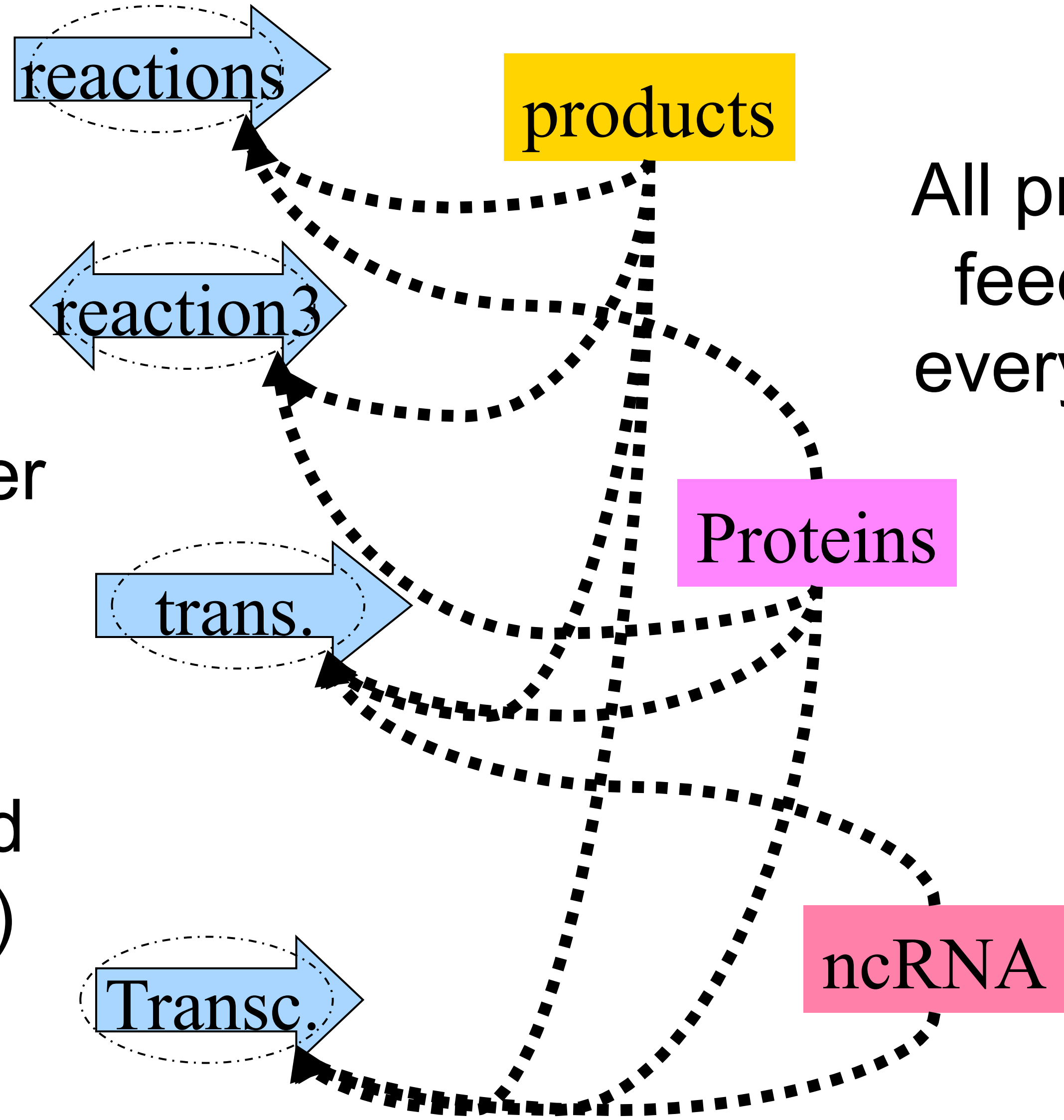
Lots of ways to draw this.




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
ncRNA
mRNA
RNA form/activity
RNA
Transc.
xRNA
RNA level/
Transcription rate
Gene
RNAp
Ribosome

Control?

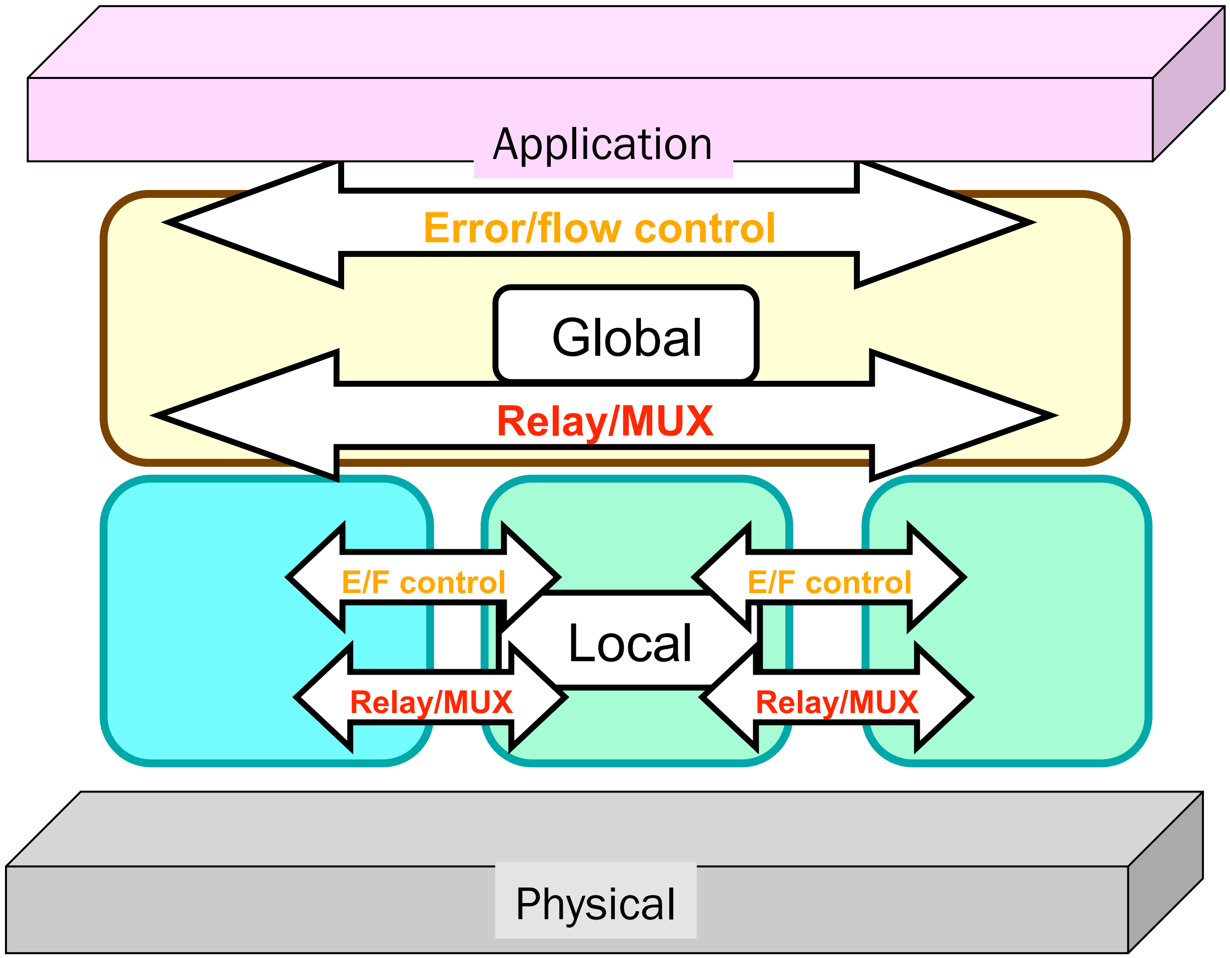


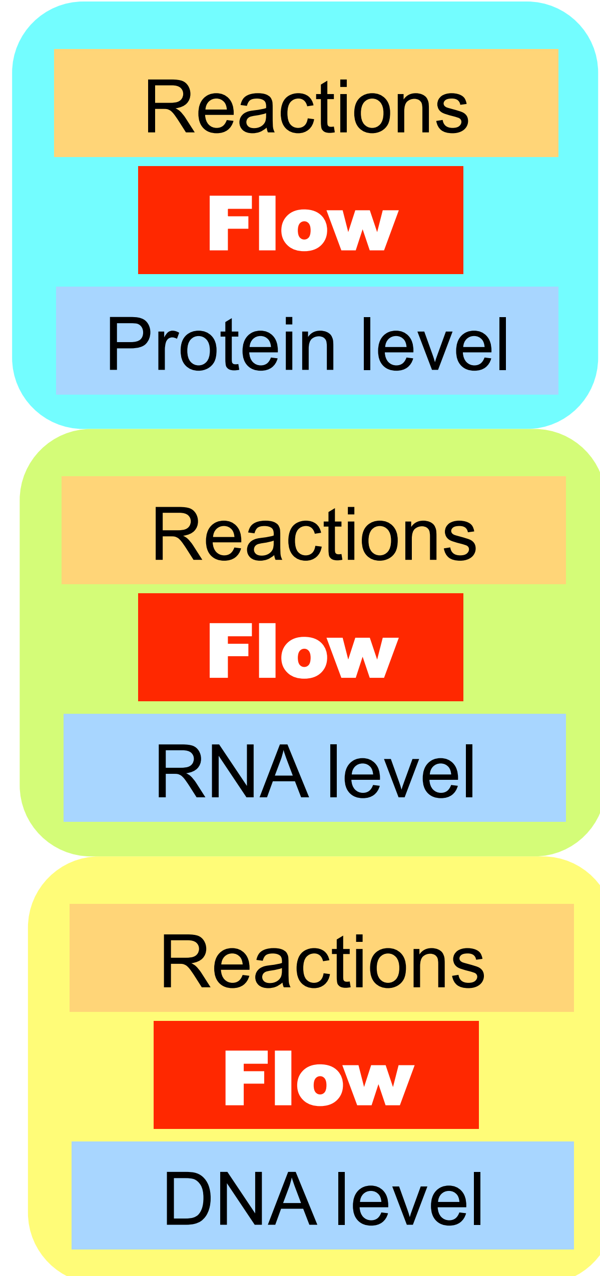
All products feedback everywhere

But each layer has its own controlling molecules (proteins and small RNAs)

So X-layer interactions are highly structured

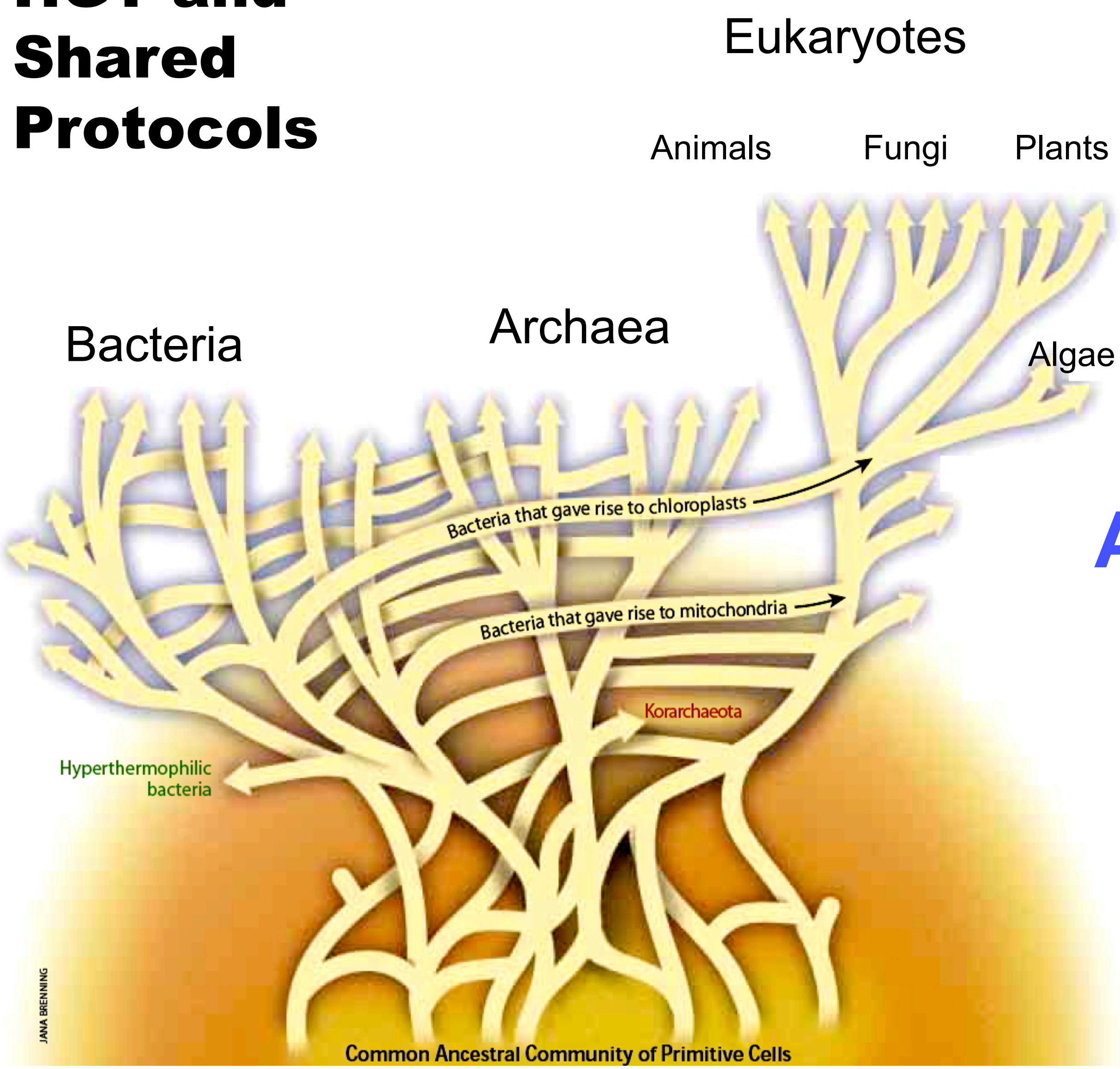
Recursive control structure





Horizontal gene transfer

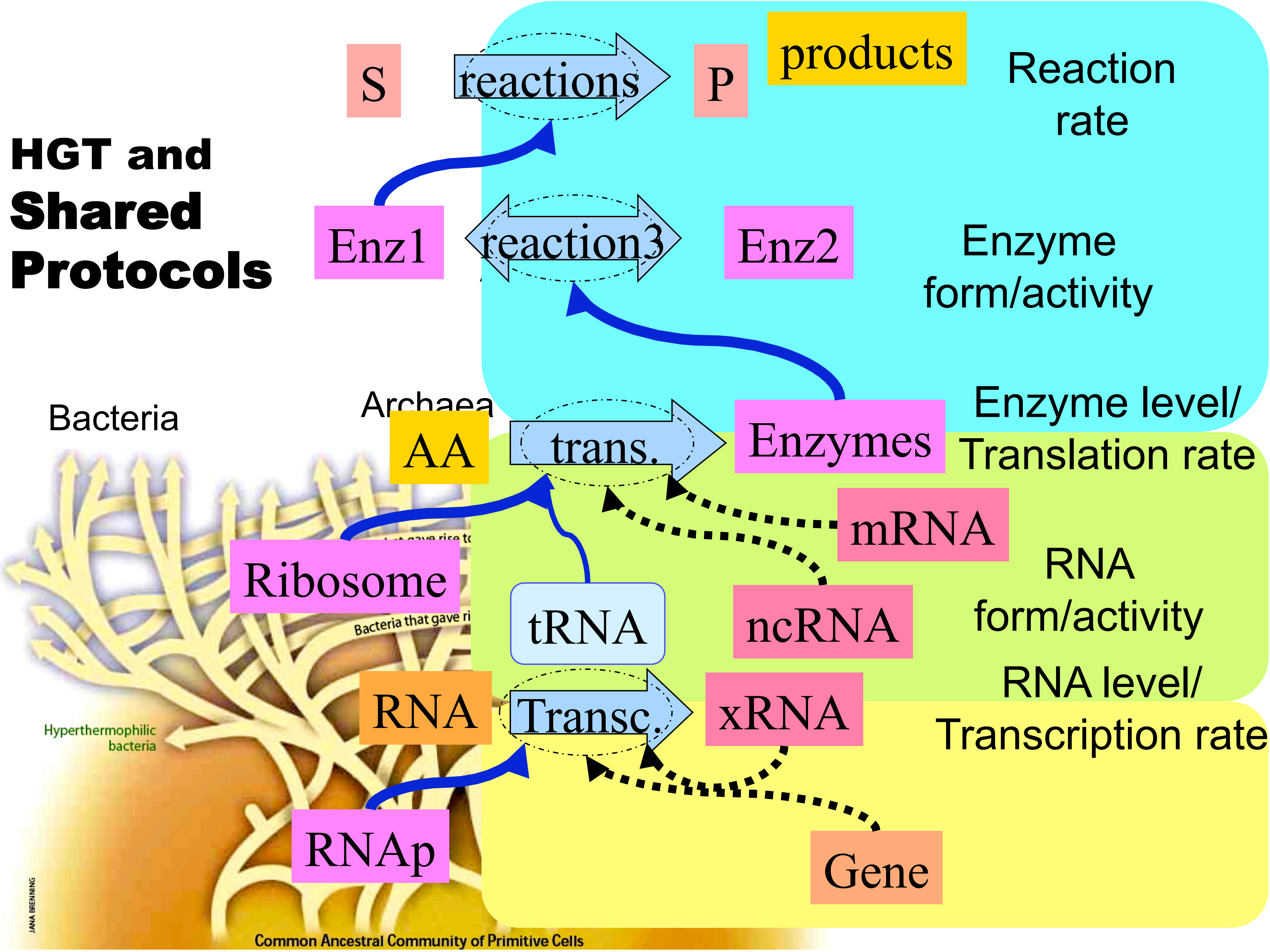
HGT and Shared Protocols



What is locus of early evolution?

Architecture!?!

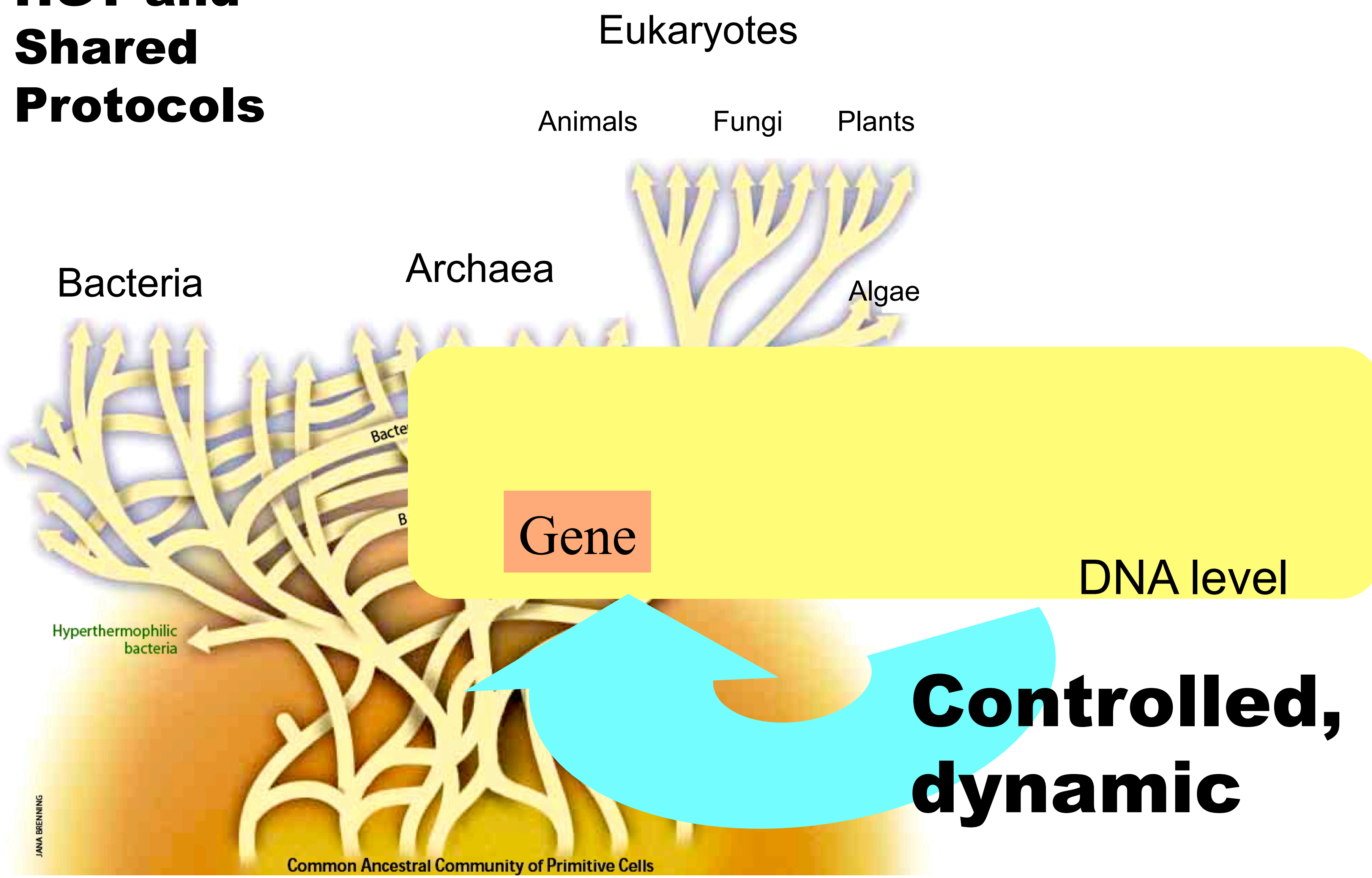
HGT and Shared Protocols



Horizontal gene transfer

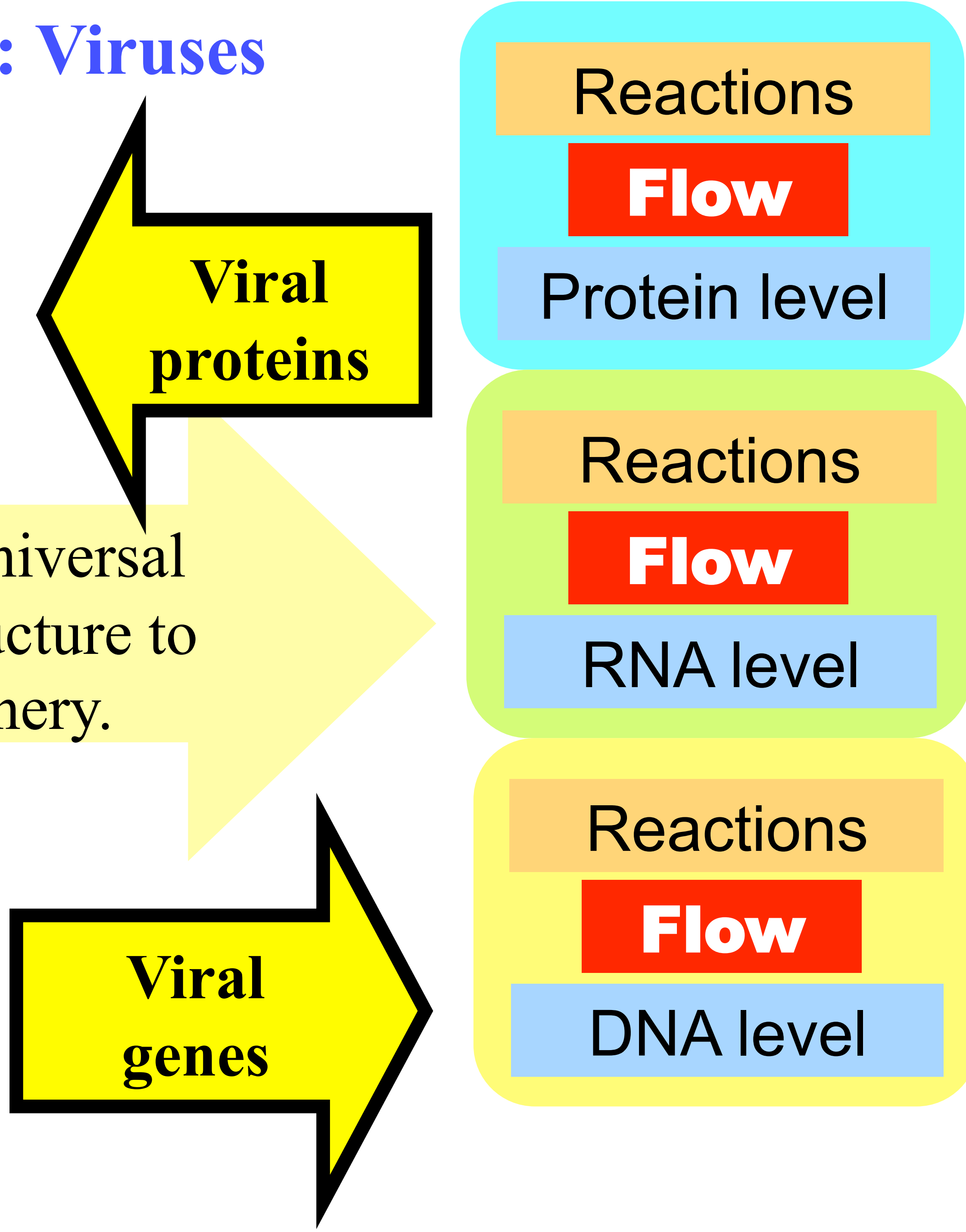
HGT and Shared Protocols

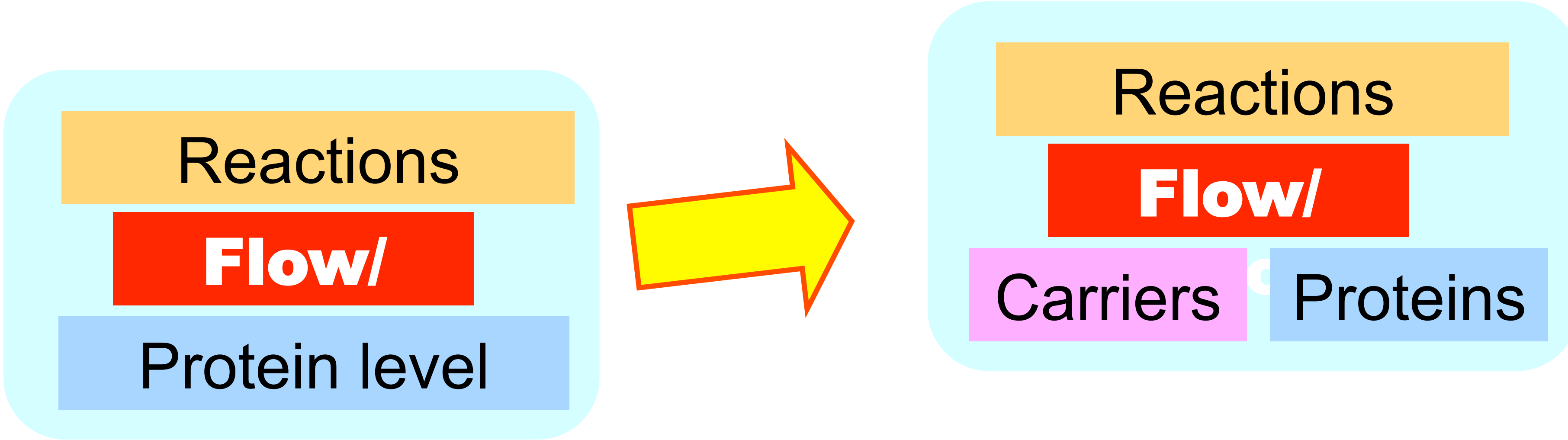
- Not a static database
- Not only point mutations

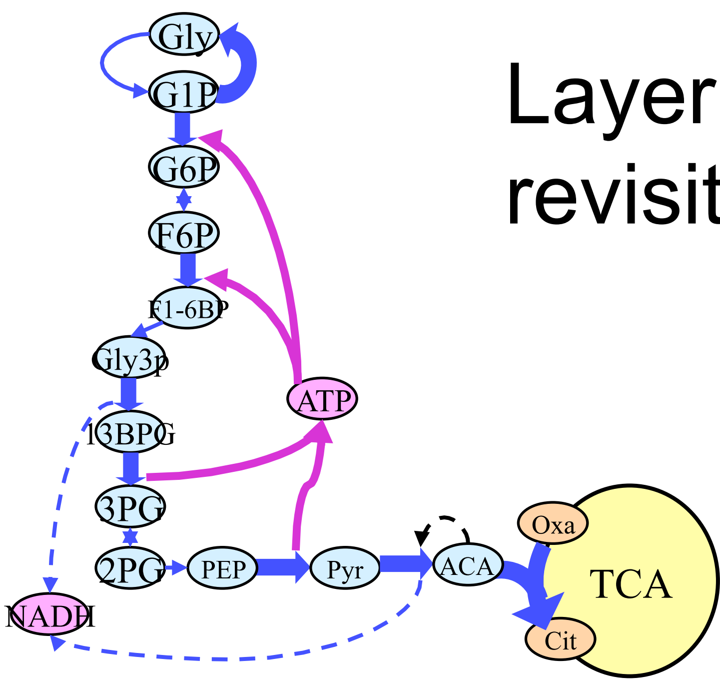


Fragility example: Viruses

Viruses exploit the universal bowtie/hourglass structure to hijack the cell machinery.

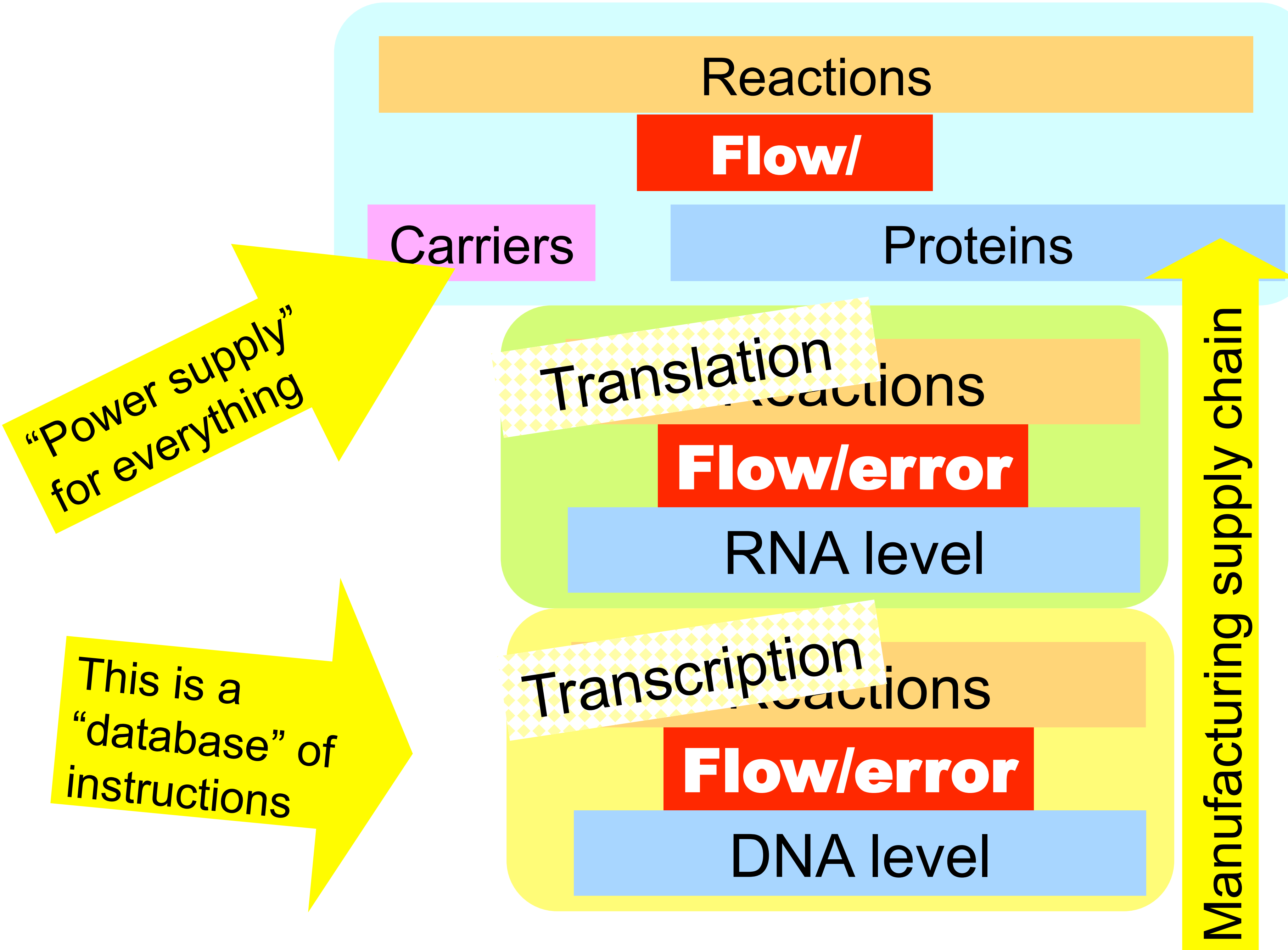


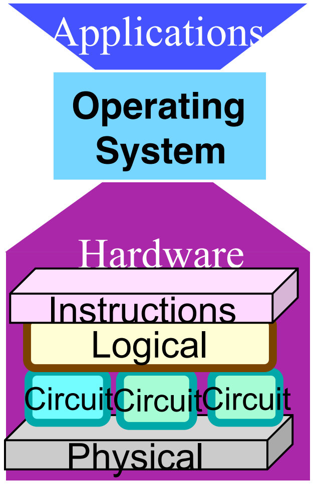


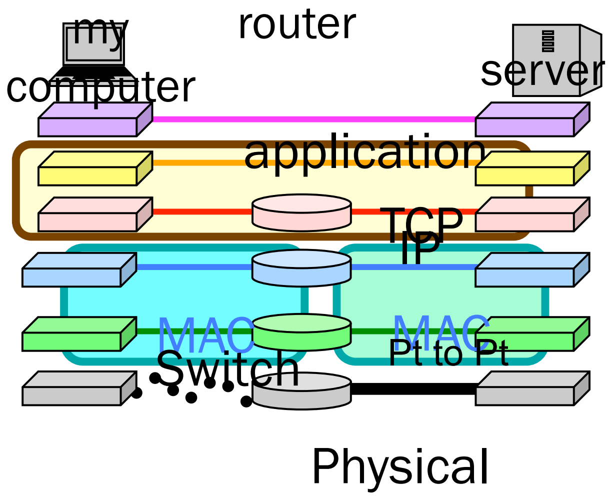


Layering revisited

More complete picture ?


Reactions
Flow/
Carriers
Proteins
Translation
Reactions
Flow/error
RNA level
Transcription
Reactions
Flow/error
DNA level
"Power supply" for everything
This is a "database" of instructions
Manufacturing supply chain



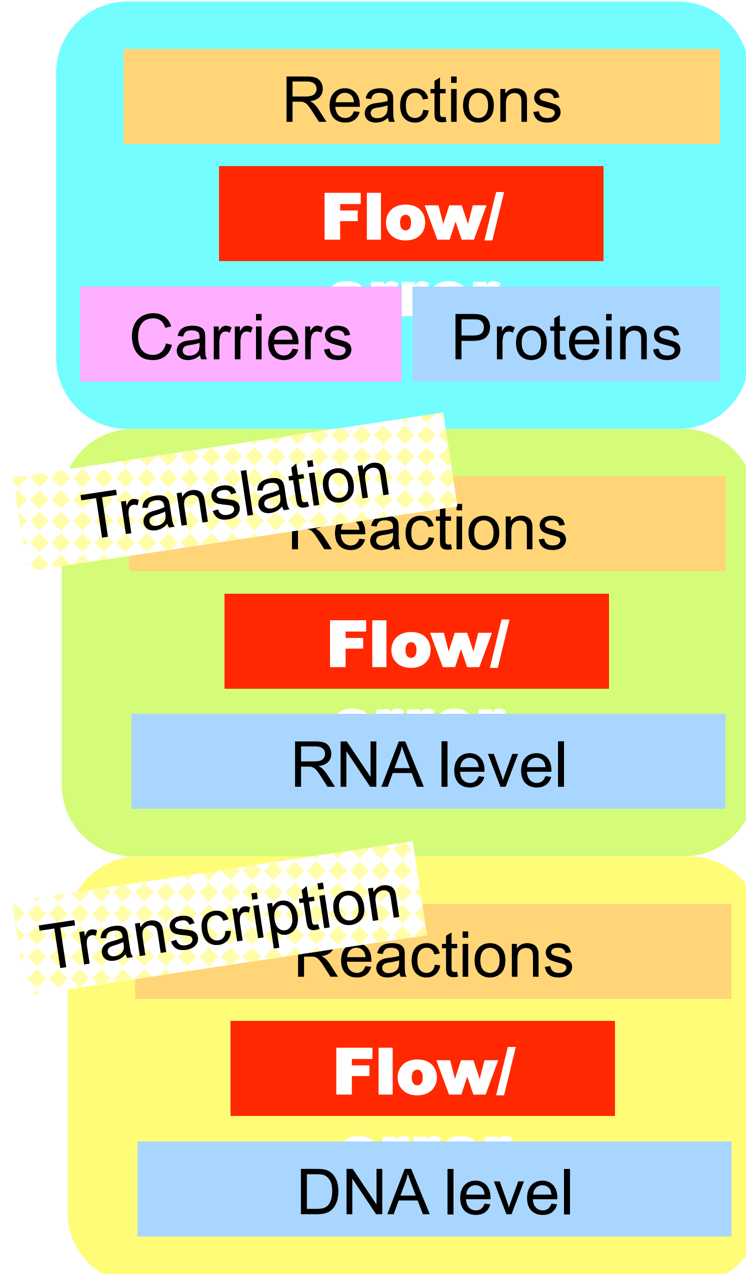


?

What are the additional layers?

?

- Where is the power supply?
- Where are the designs and processes that produce the chips, PCs, routers, etc?



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]

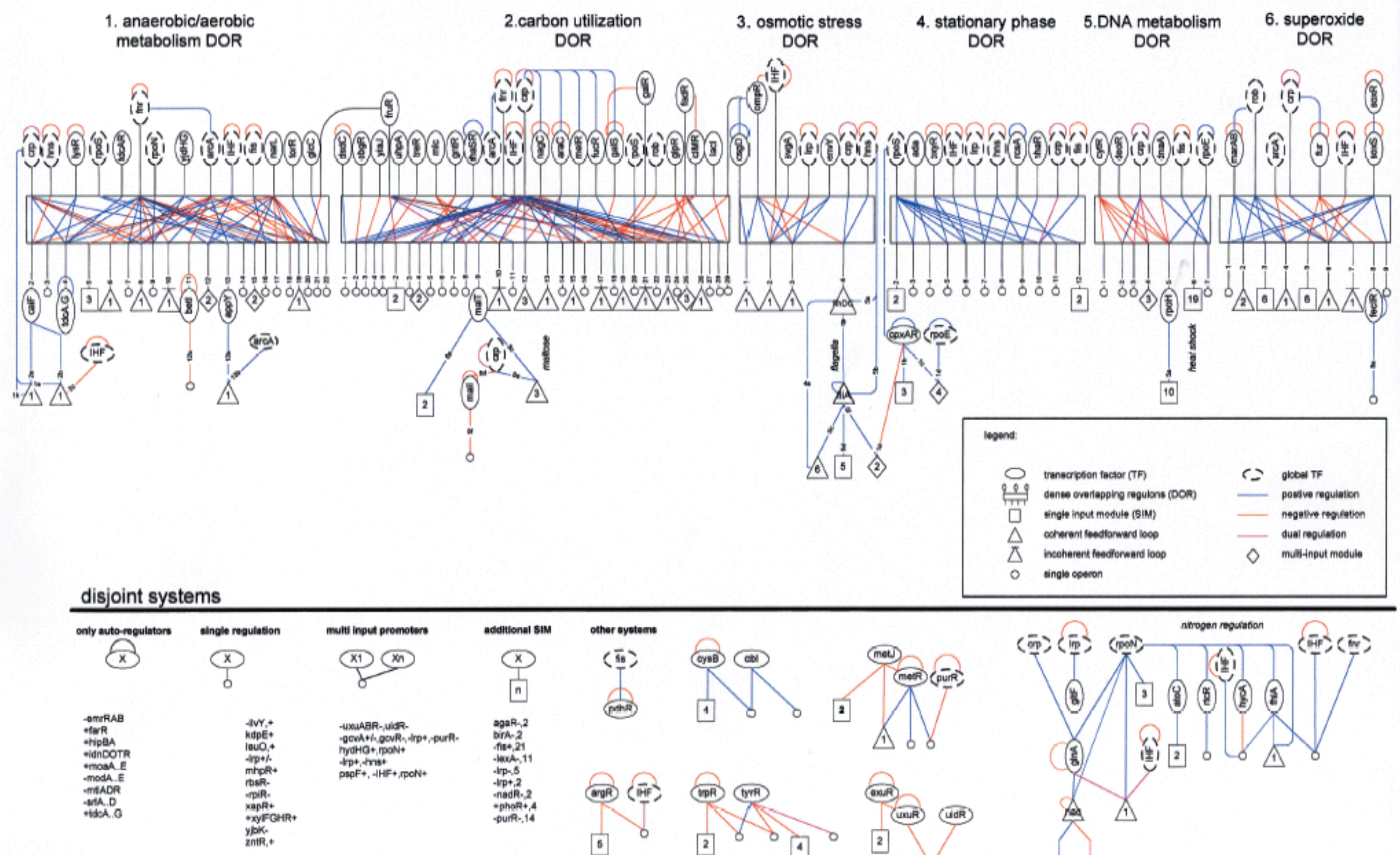


Fig. 4

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]

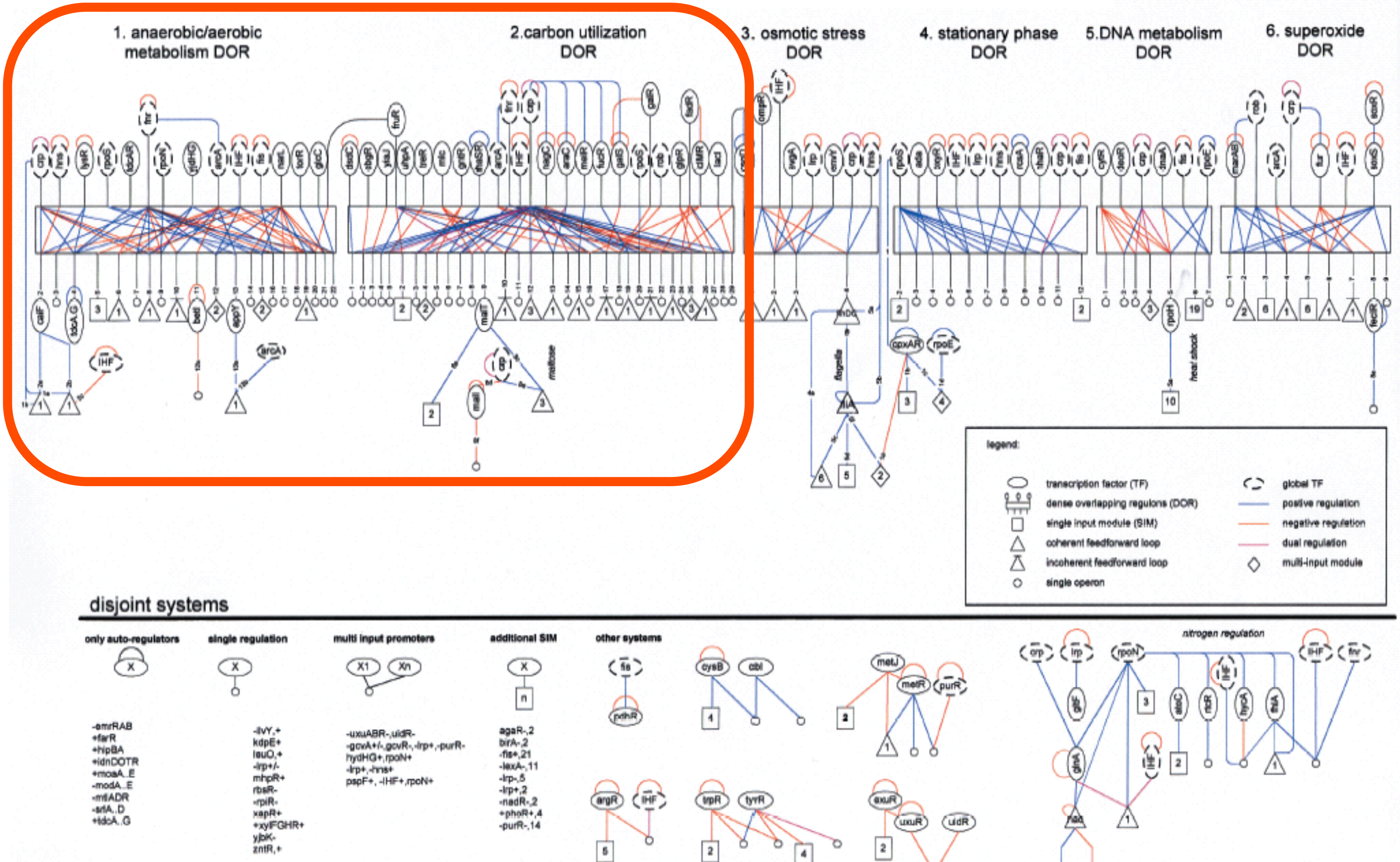
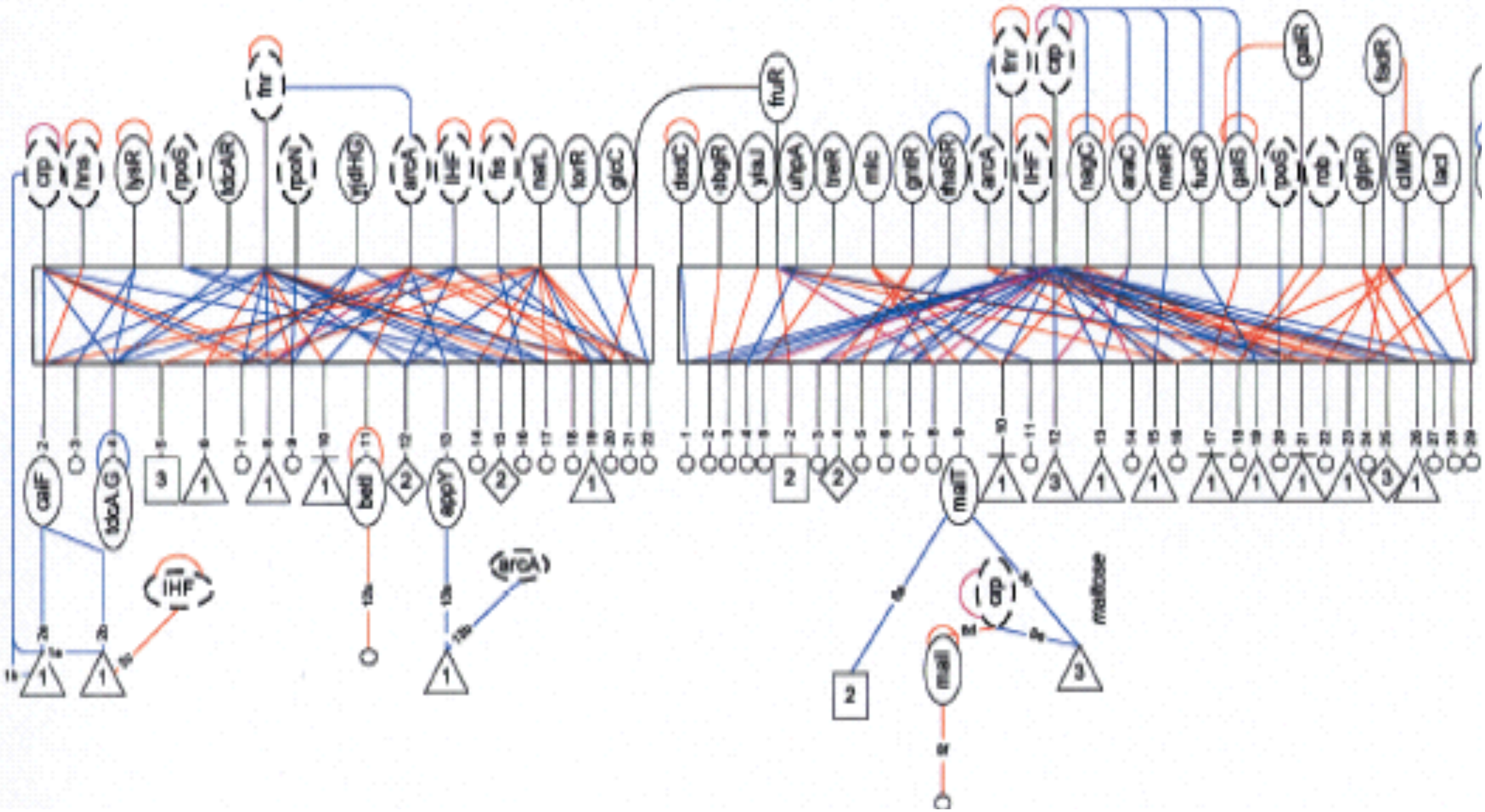


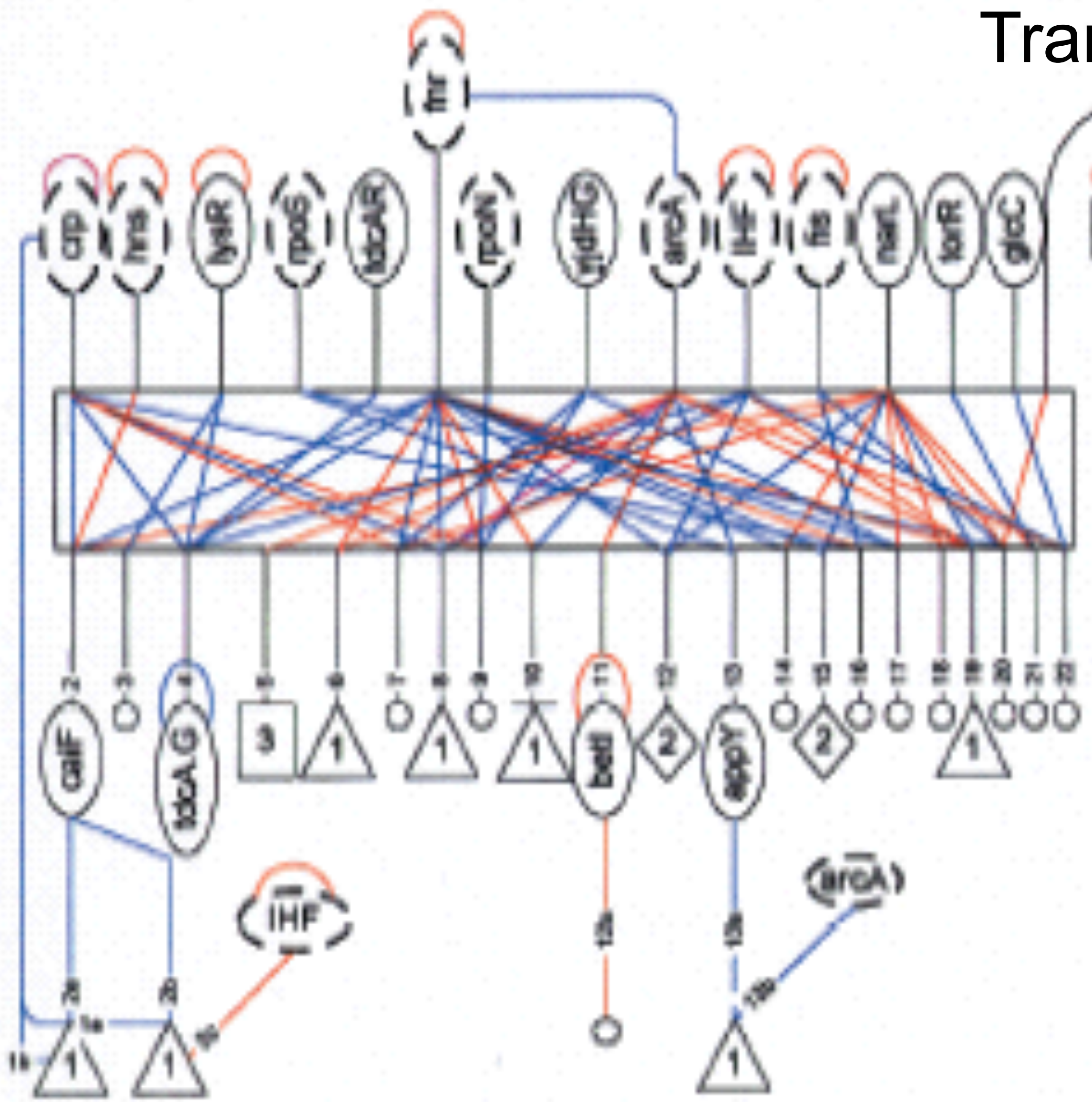
Fig. 4

1. anaerobic/aerobic metabolism DOR

2.carbon utilization DOR



1. anaerobic/aerobic metabolism DOR

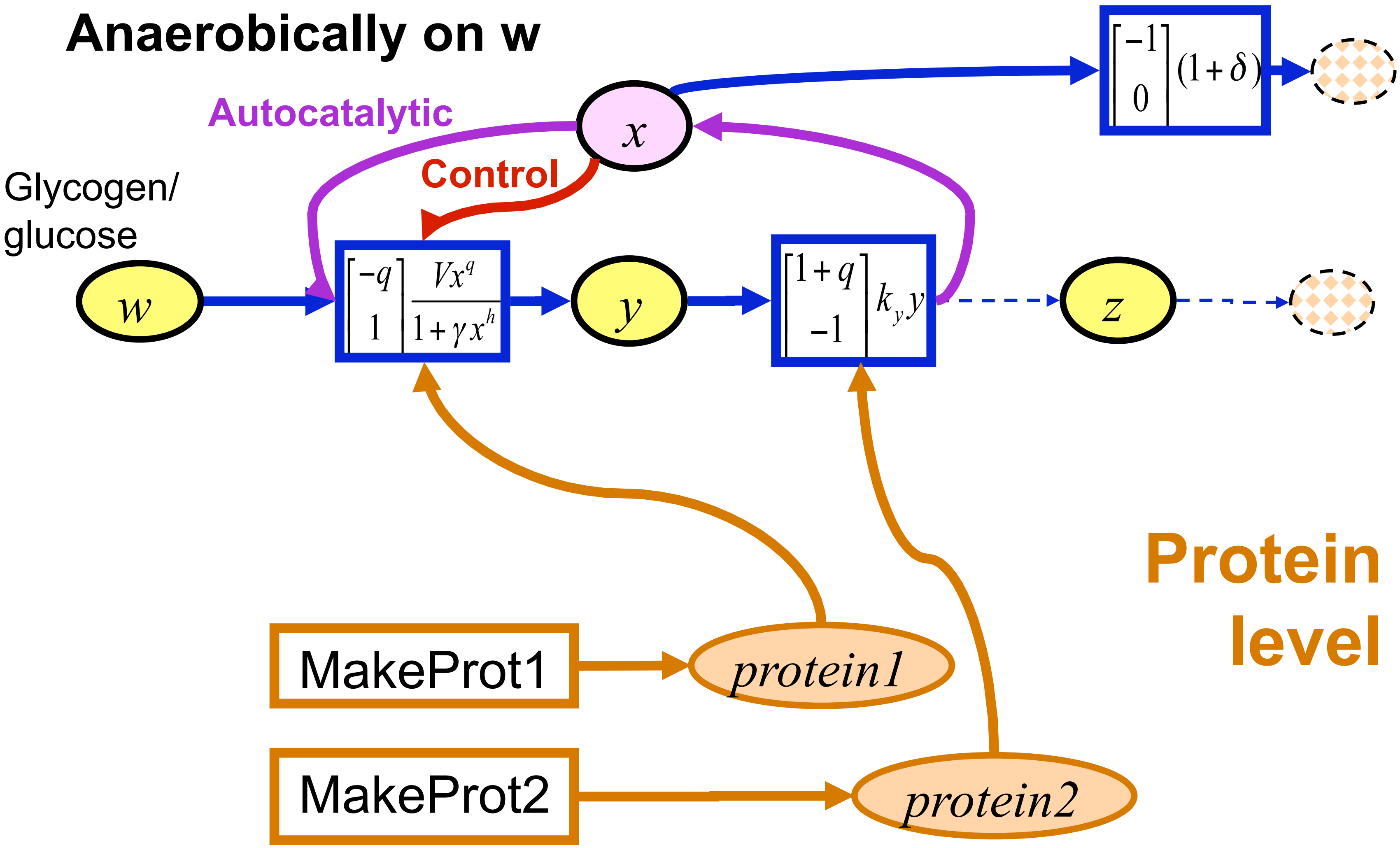


Transcription factors

Special purpose proteins that control gene expression

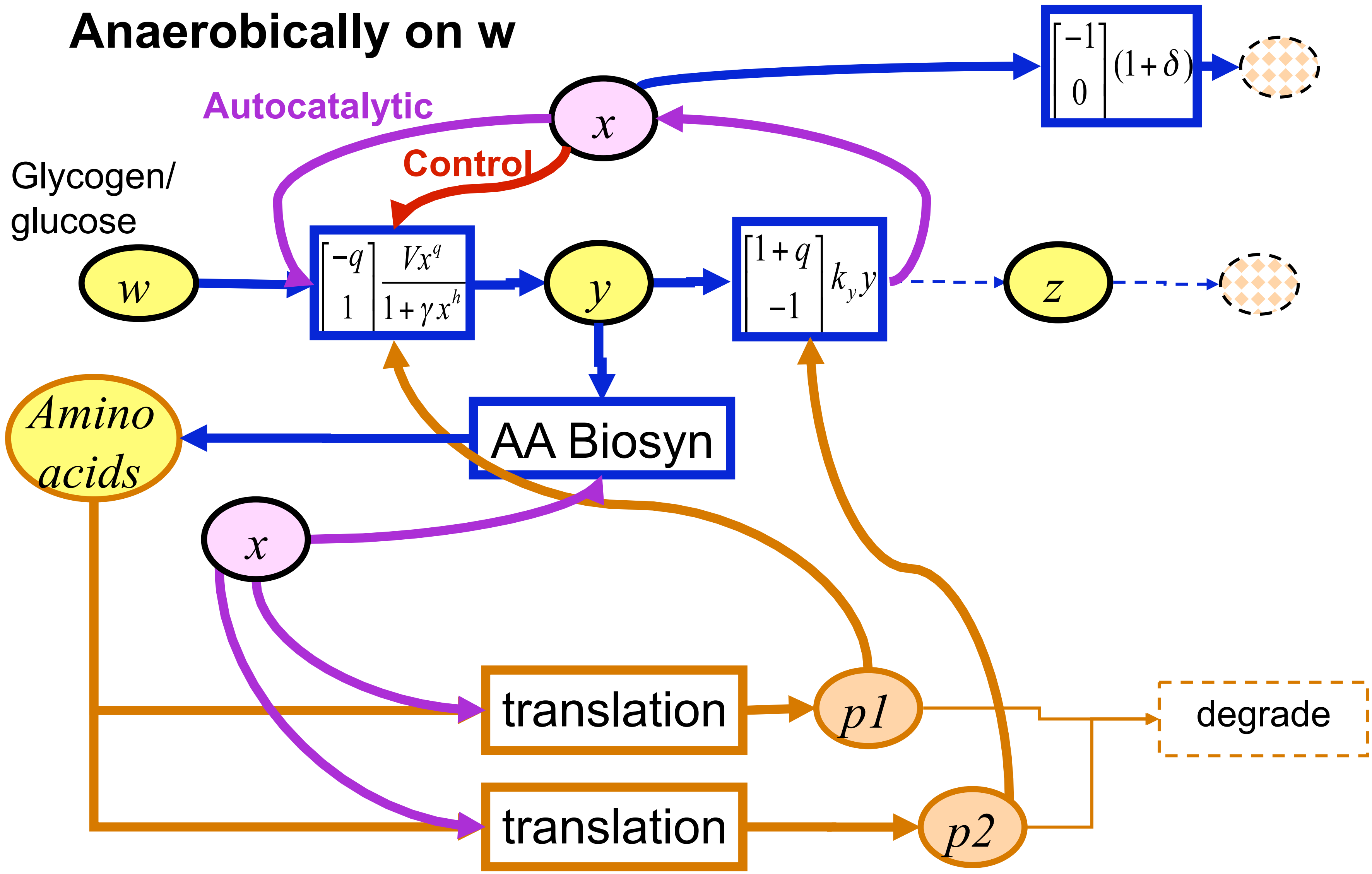
Operons

Small groups of co-regulated genes

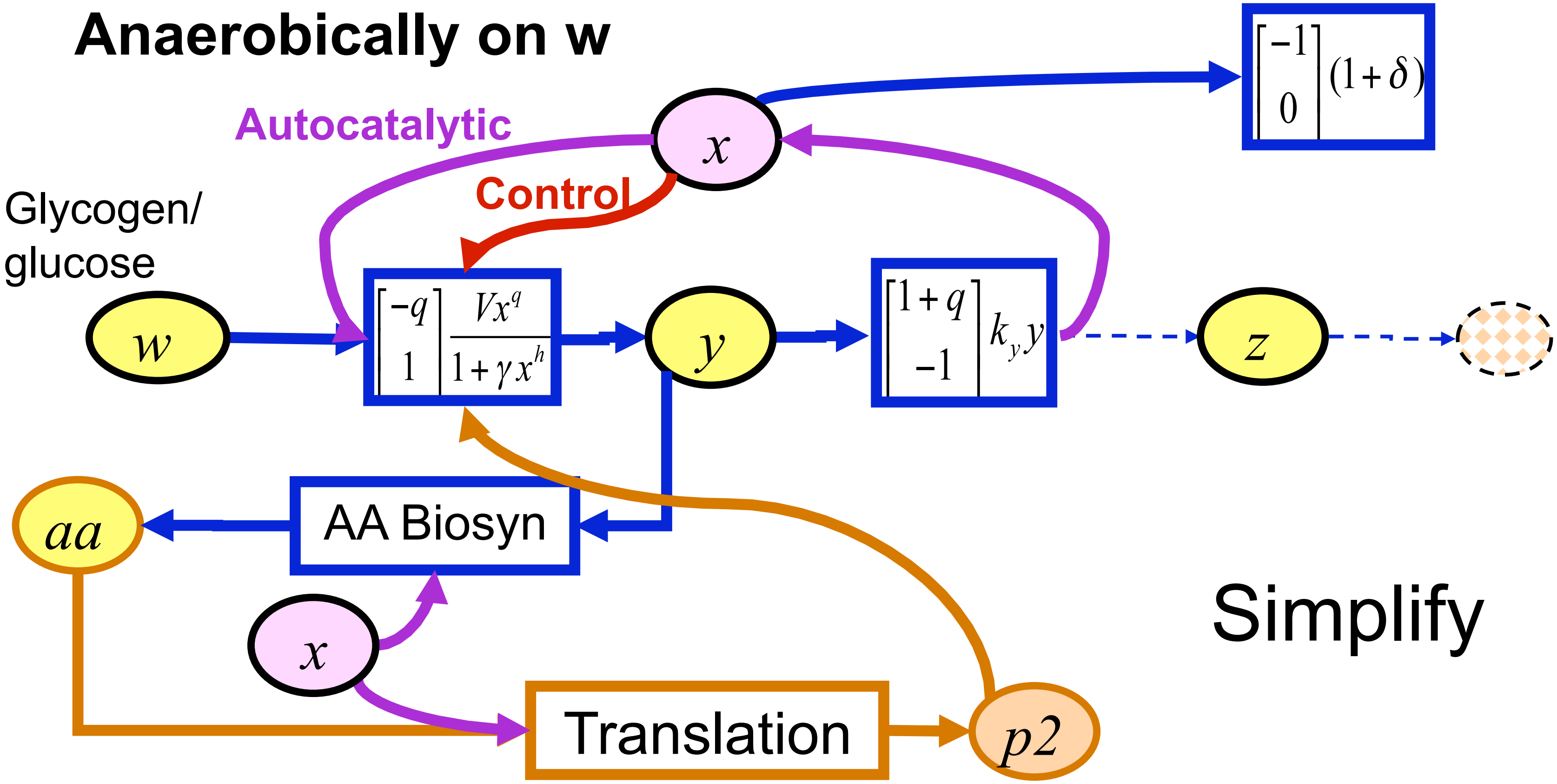


Anaerobically on w
Autocatalytic
Control
Glycogen/
glucose
w
x
y
z
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
MakeProt1
MakeProt2
protein1
protein2
Protein
level

Anaerobically on w

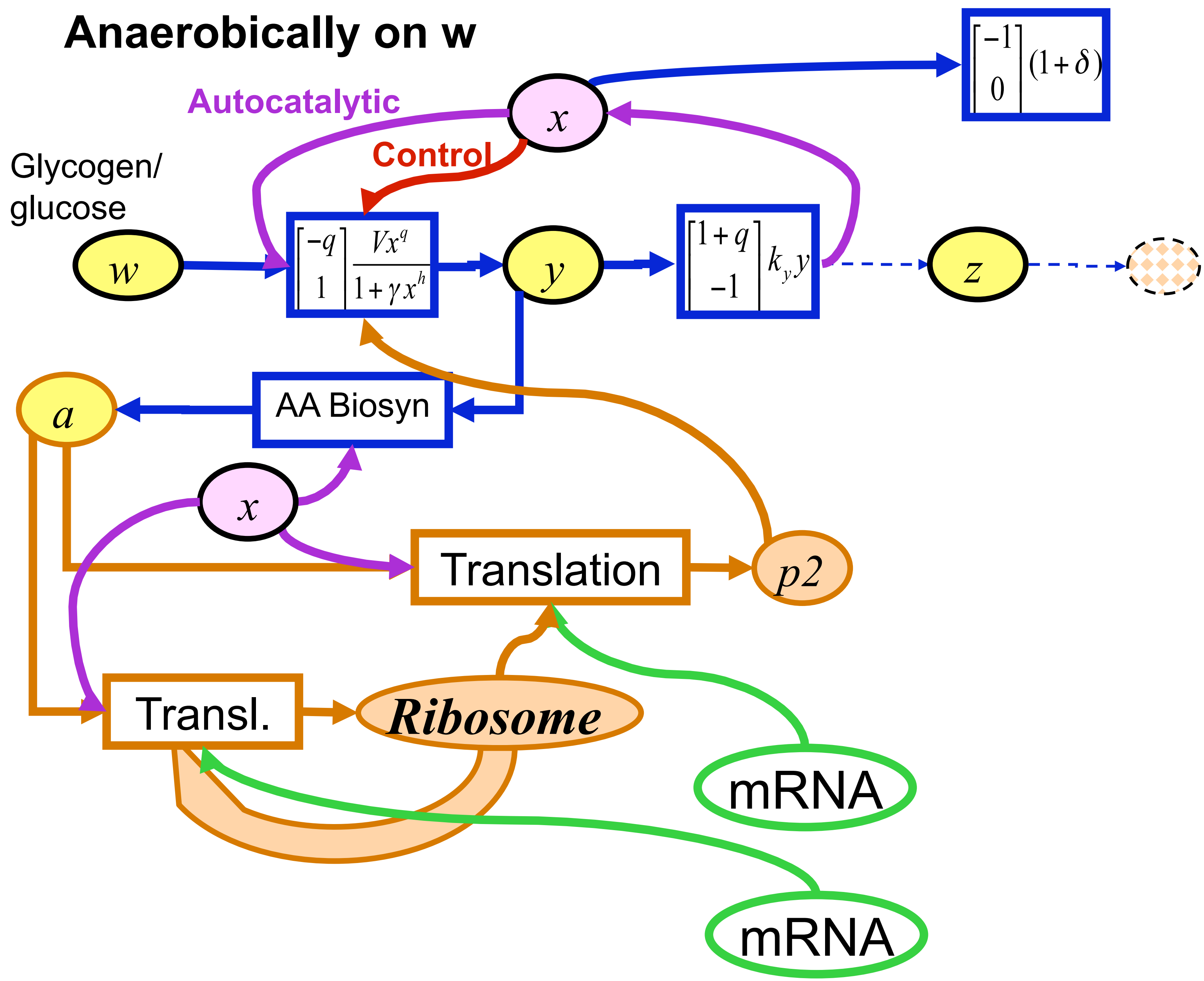


Anaerobically on w

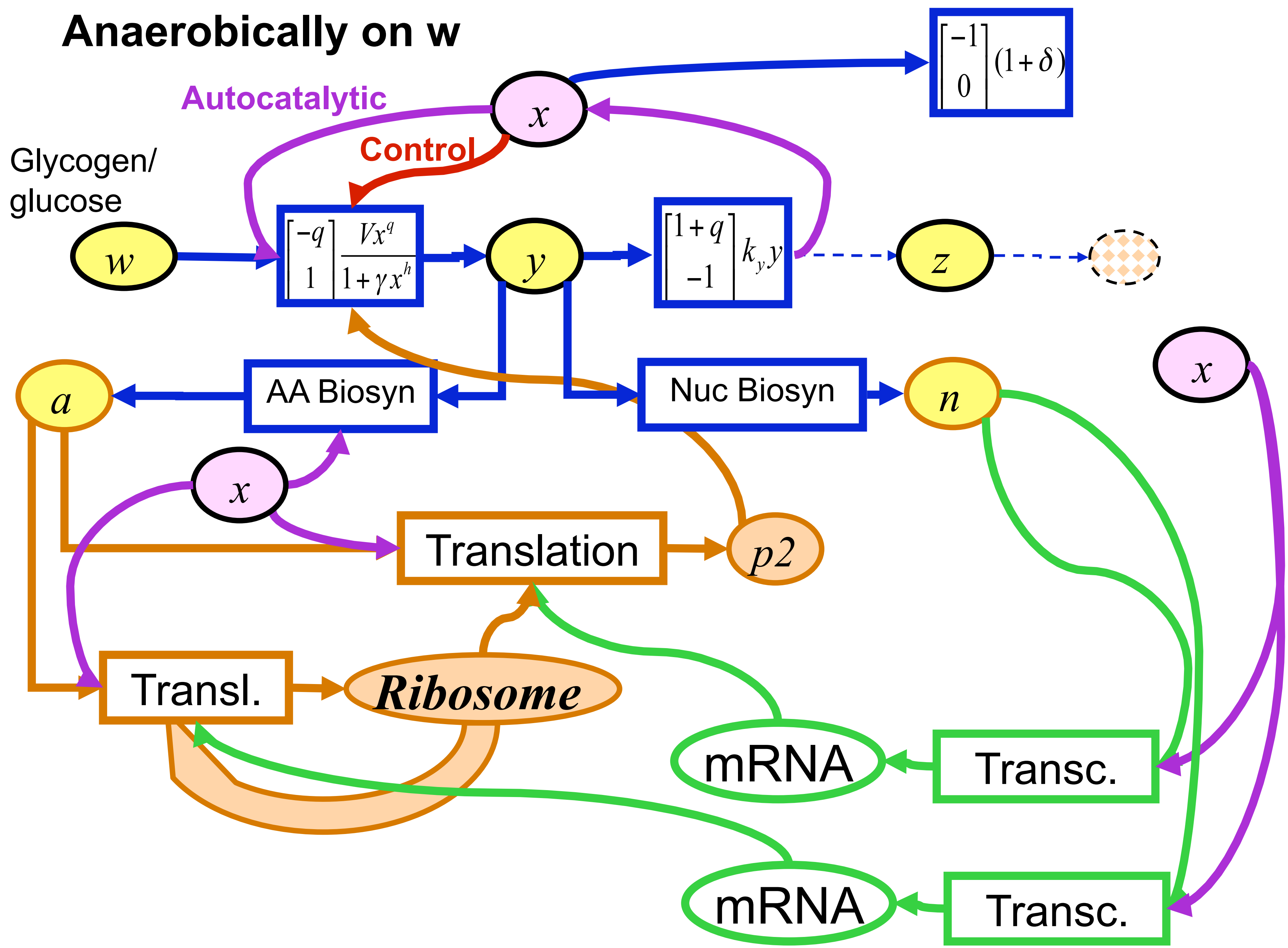


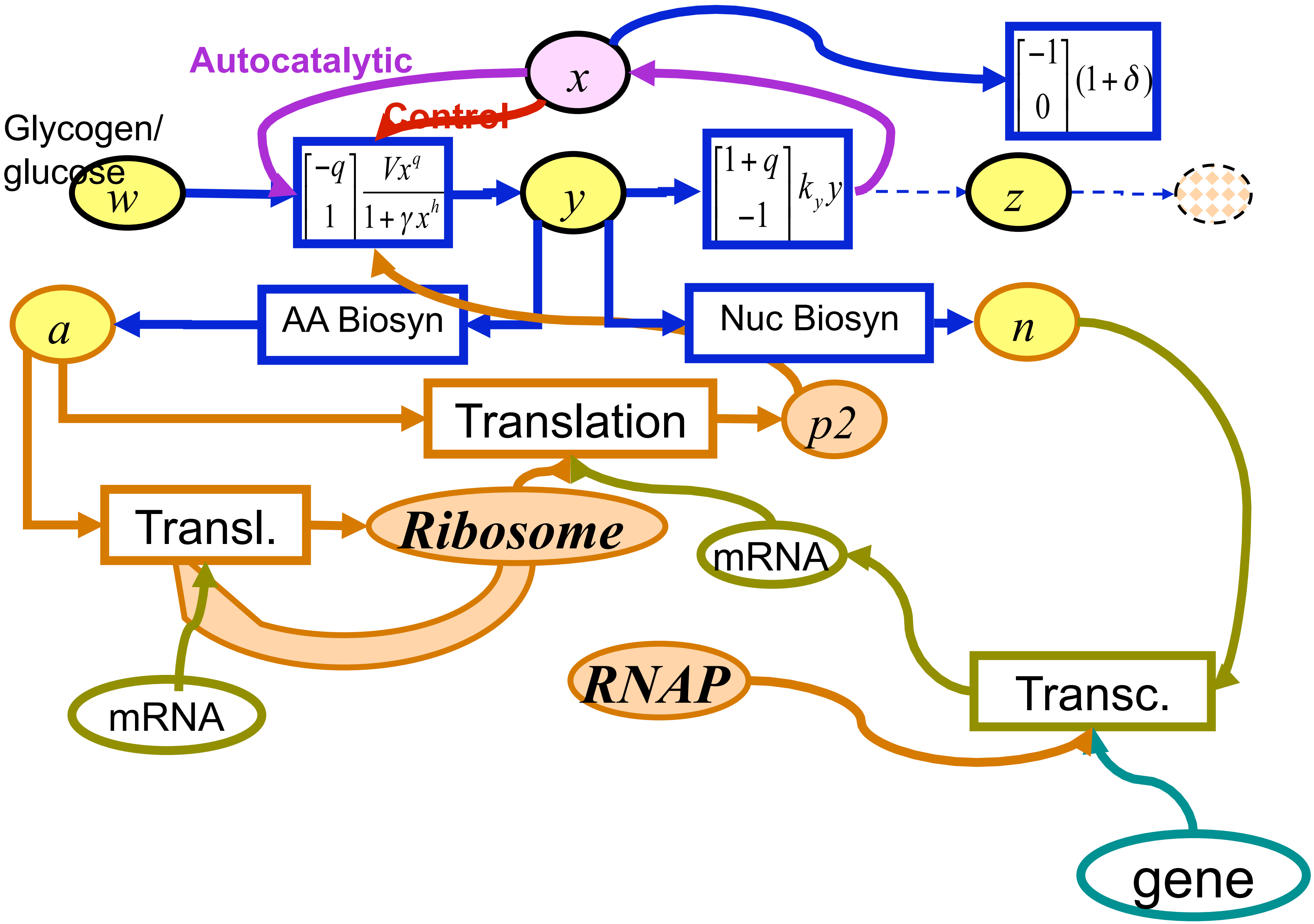
Simplify

Anaerobically on w

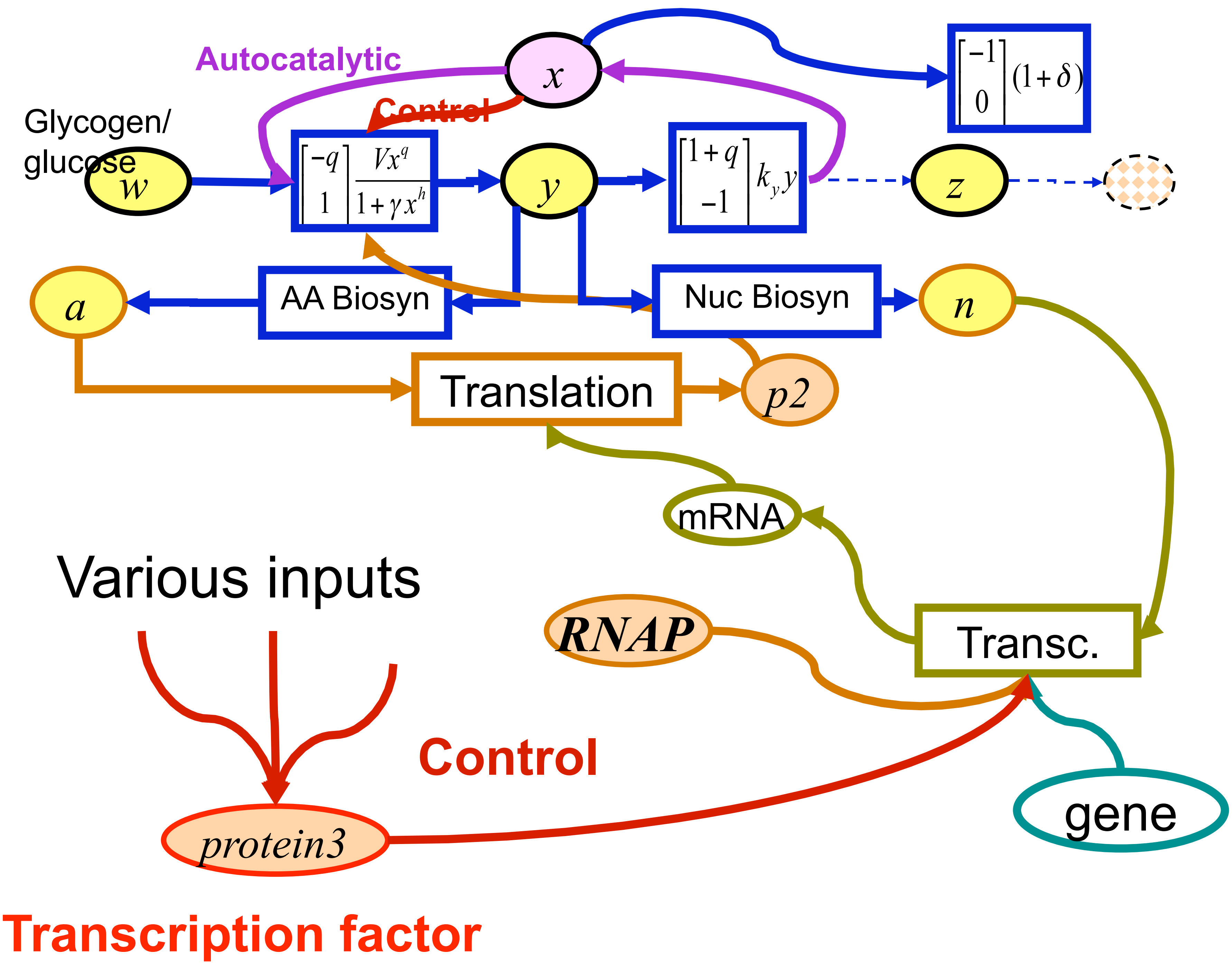


Anaerobically on w

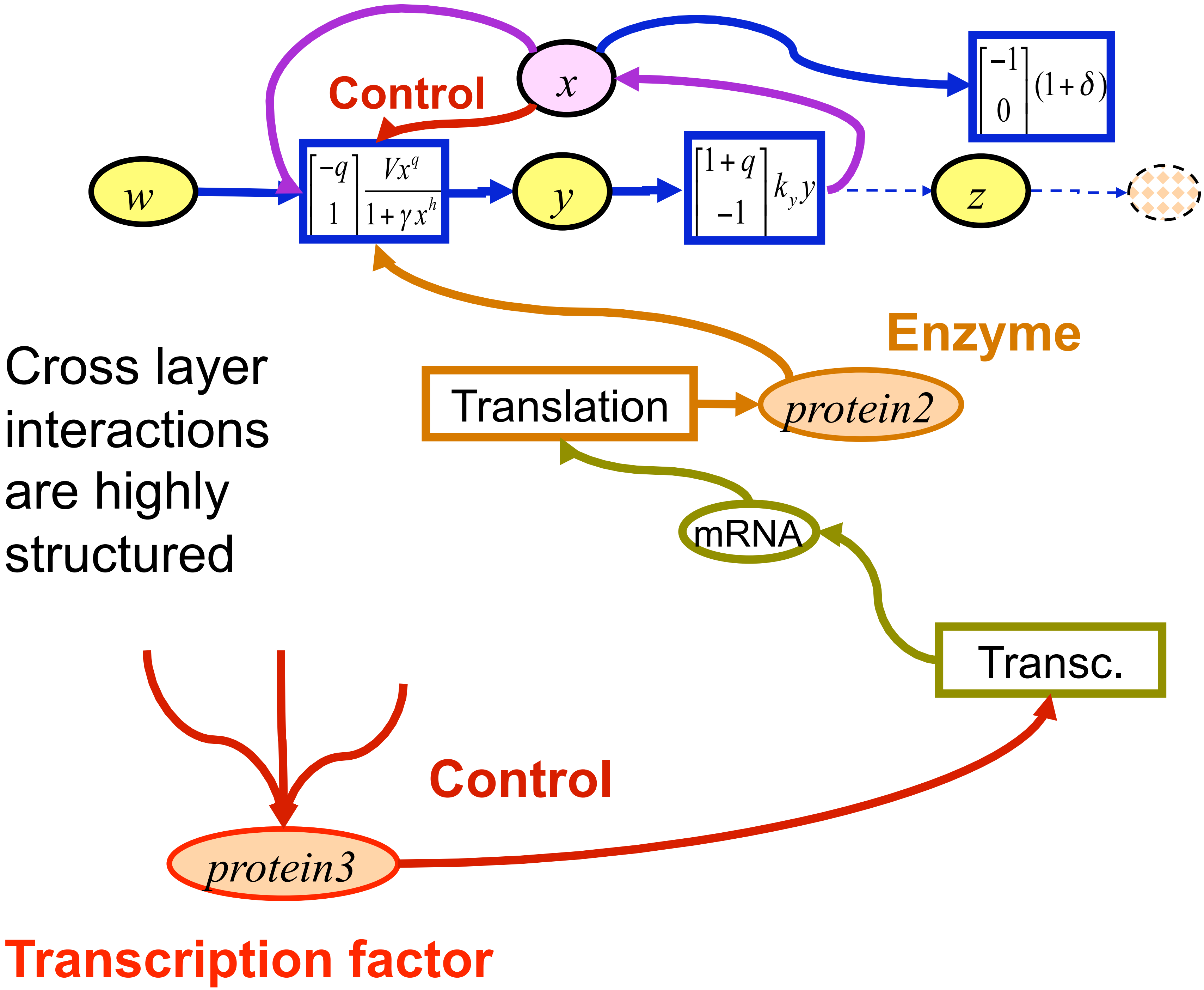


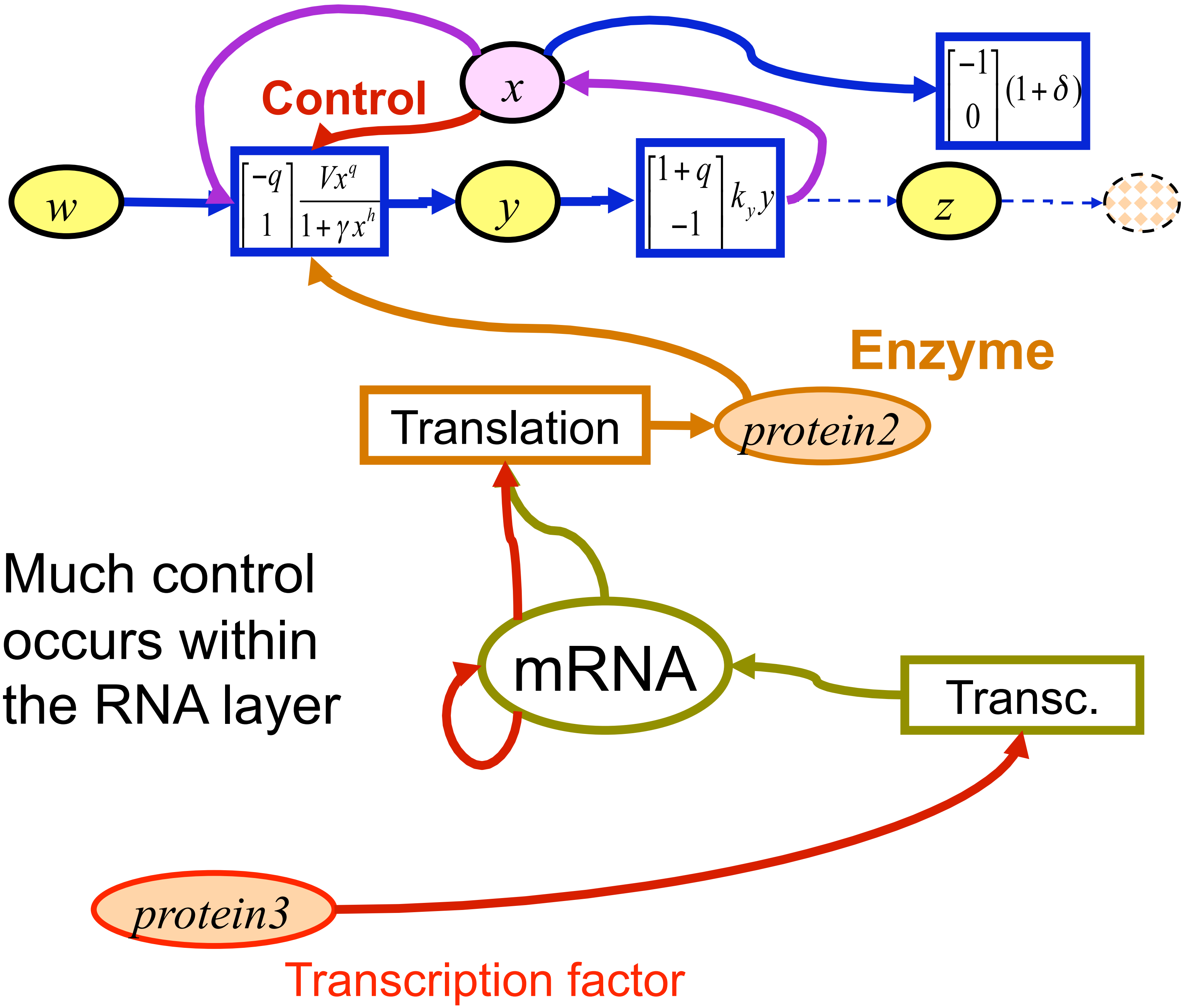


Autocatalytic
Control
Glycogen/
glucose
w
x
y
z
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
a
AA Biosyn
Nuc Biosyn
n
Translation
p2
Transl.
Ribosome
mRNA
mRNA
RNAP
Transc.
gene

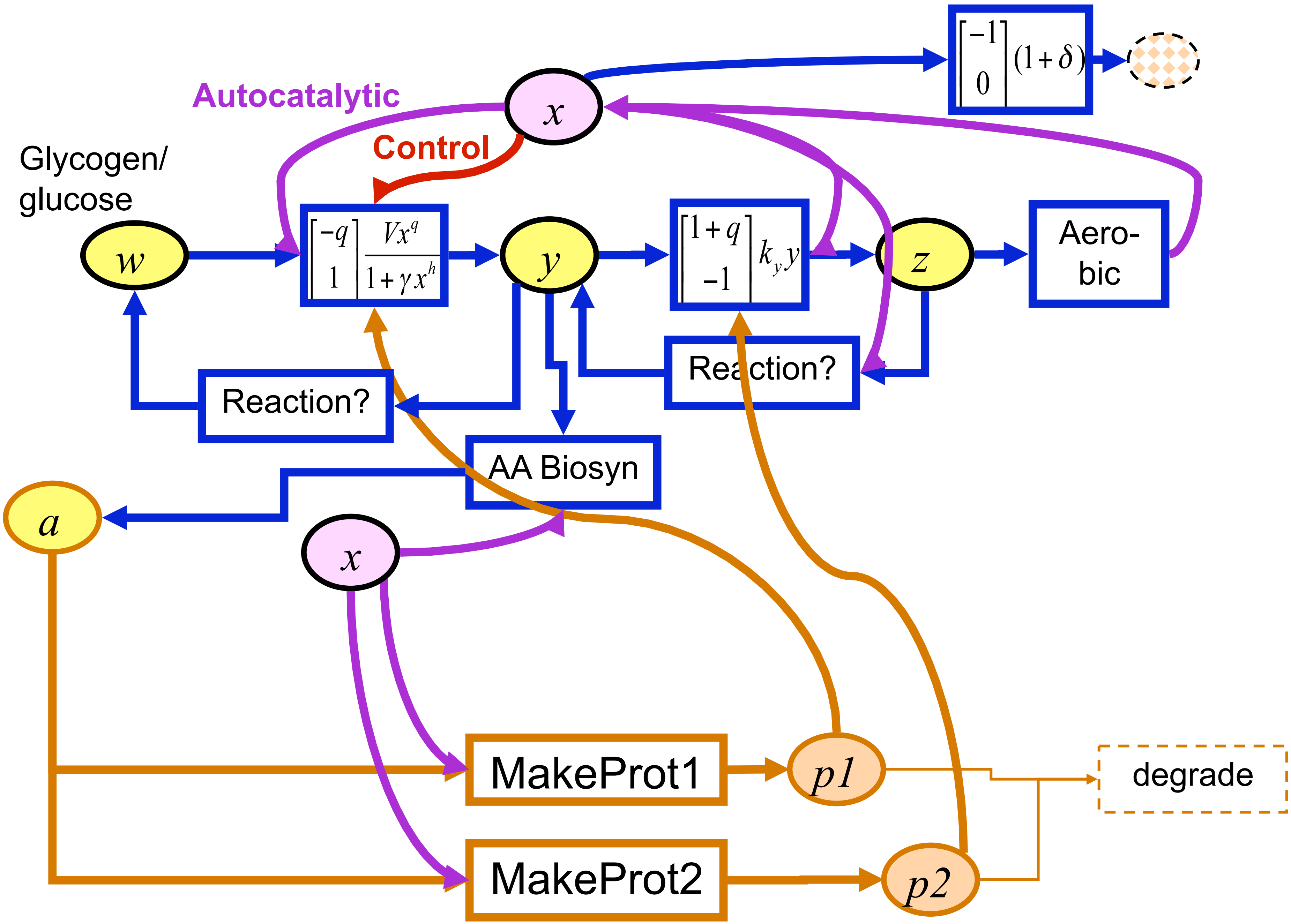


Autocatalytic
Control
Glycogen/ glucose
w
x
y
z
AA Biosyn
Nuc Biosyn
a
n
Translation
p2
mRNA
Transc.
RNAP
gene
Various inputs
Control
protein3
Transcription factor

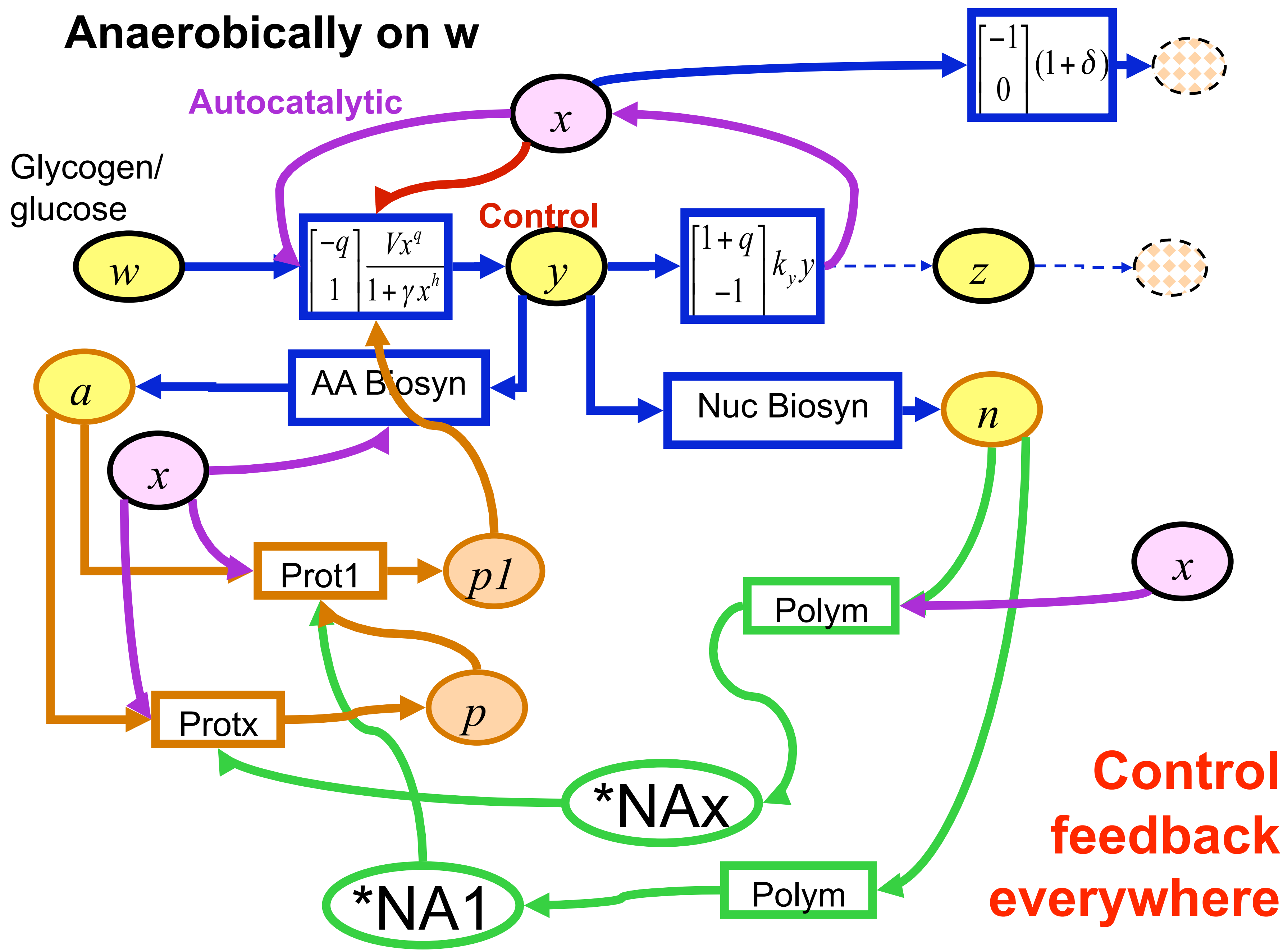

Control
x
w
$\begin{bmatrix} -q \\ 1 \end{bmatrix} \frac{Vx^q}{1+\gamma x^h}$
y
$\begin{bmatrix} 1+q \\ -1 \end{bmatrix} k_y y$
$\begin{bmatrix} -1 \\ 0 \end{bmatrix} (1+\delta)$
z
Enzyme
Cross layer interactions are highly structured
Translation
protein2
mRNA
Transc.
Control
protein3
Transcription factor



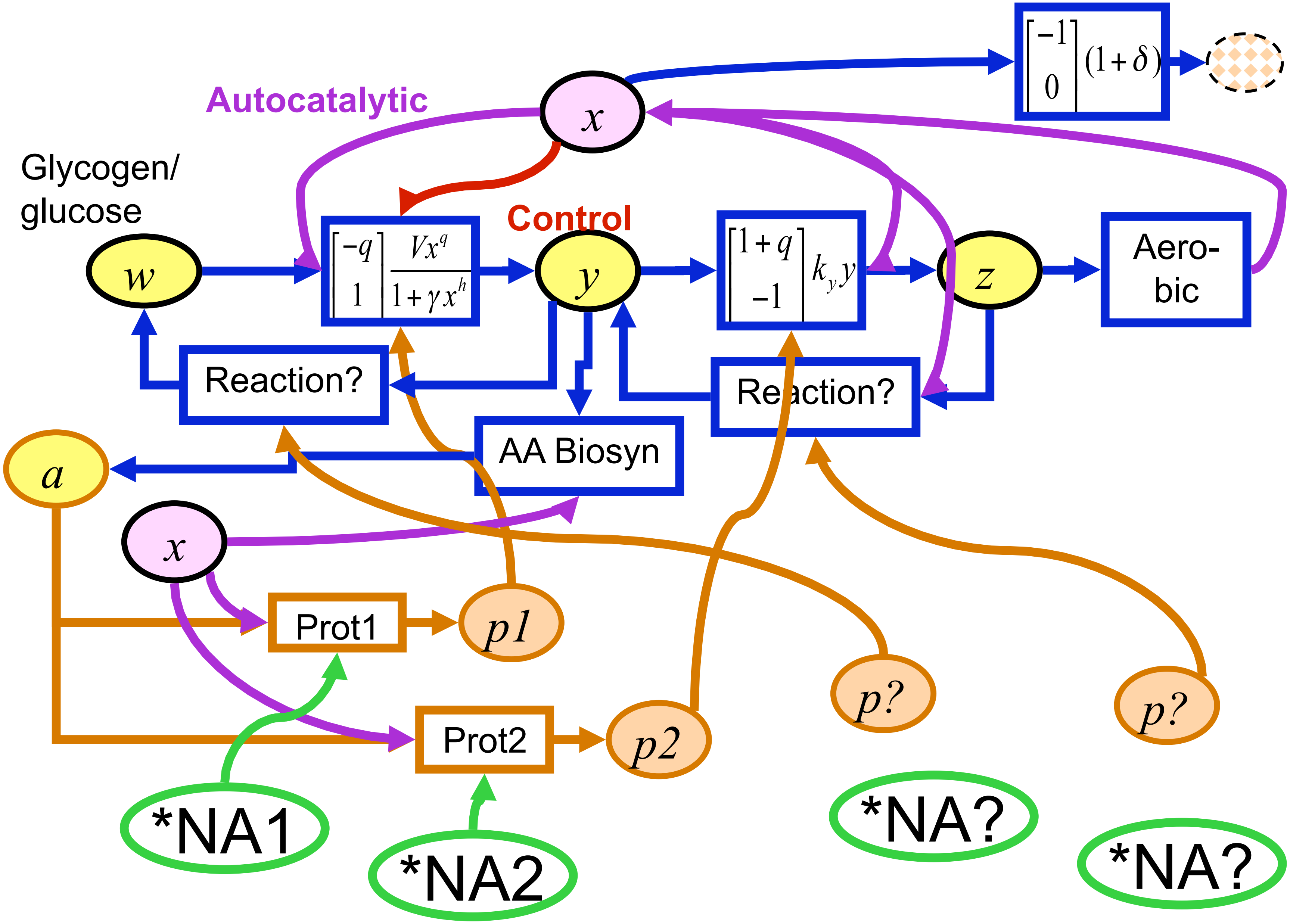
Much control occurs within the RNA layer



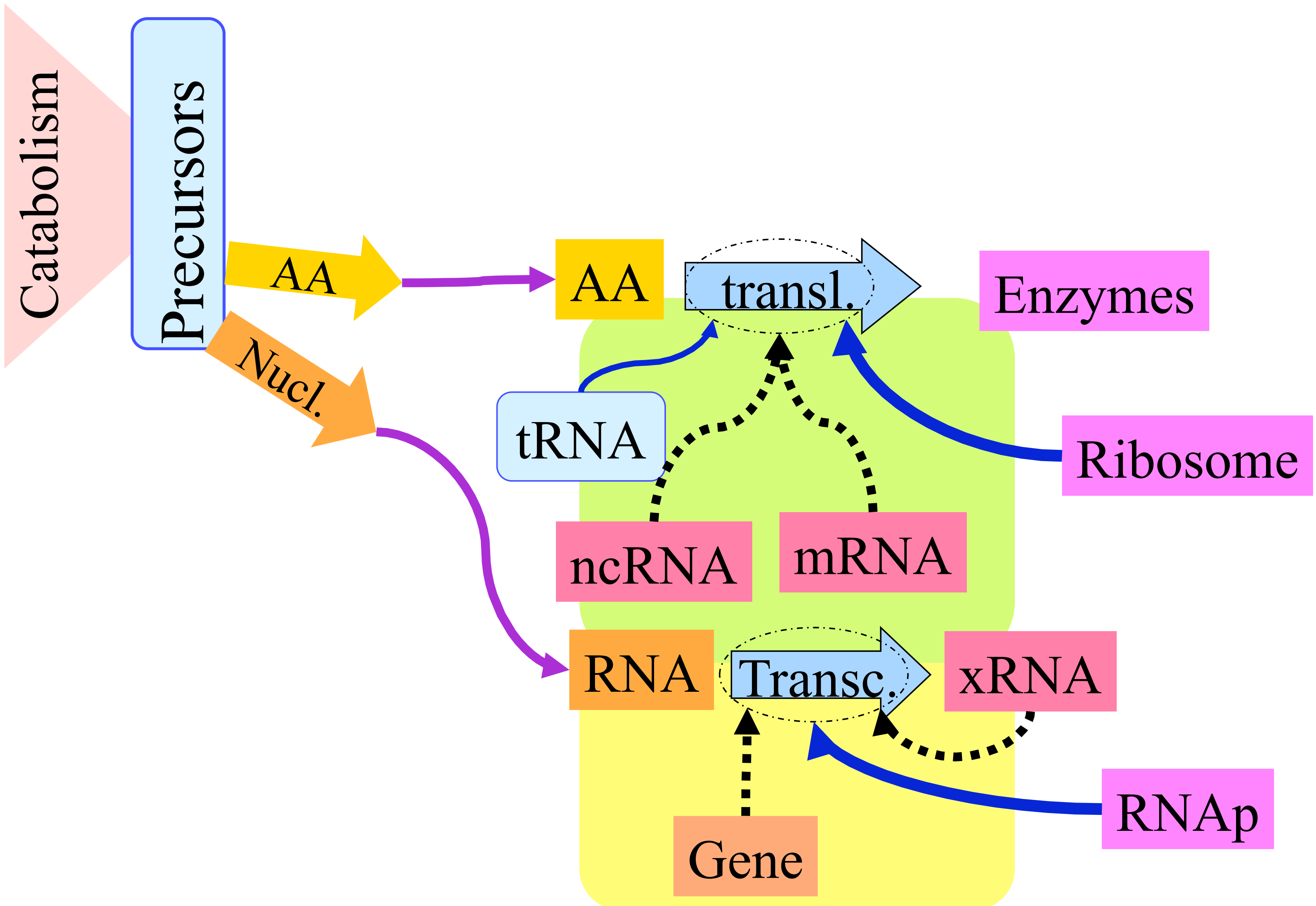
Autocatalytic
Control
Glycogen/
glucose
w
x
$\begin{bmatrix}-q\\1\end{bmatrix}\frac{Vx^q}{1+\gamma x^h}$
y
$\begin{bmatrix}1+q\\-1\end{bmatrix}k_y y$
z
Aero-
bic
$\begin{bmatrix}-1\\0\end{bmatrix}(1+\delta)$
Reaction?
Reaction?
AA Biosyn
a
x
MakeProt1
MakeProt2
p1
p2
degrade

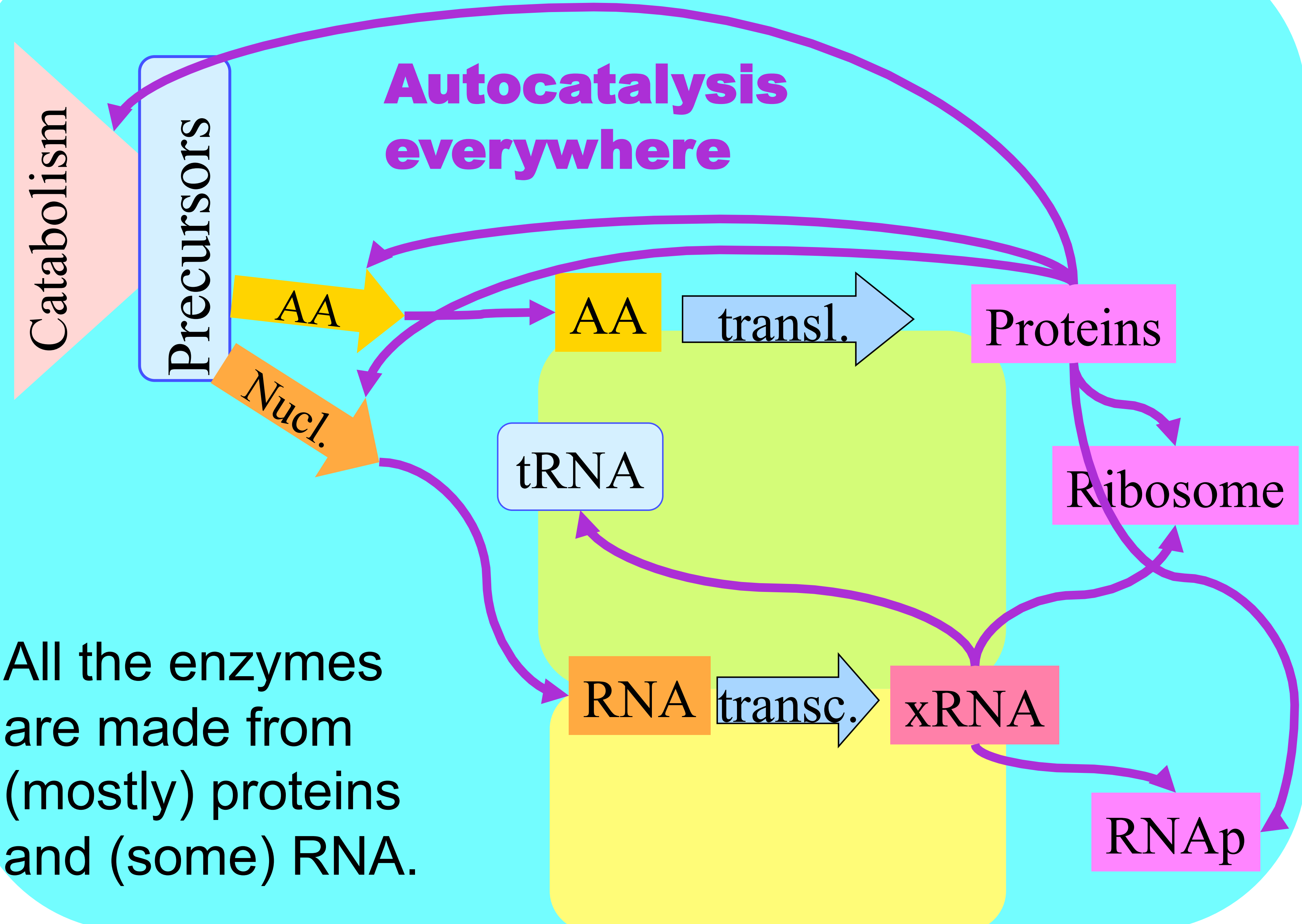


Anaerobically on w
Autocatalytic
Glycogen/
glucose
Control
AA Biosyn
Nuc Biosyn
Prot1
Protx
Polym
Polym
*NAx
*NA1
Control
feedback
everywhere



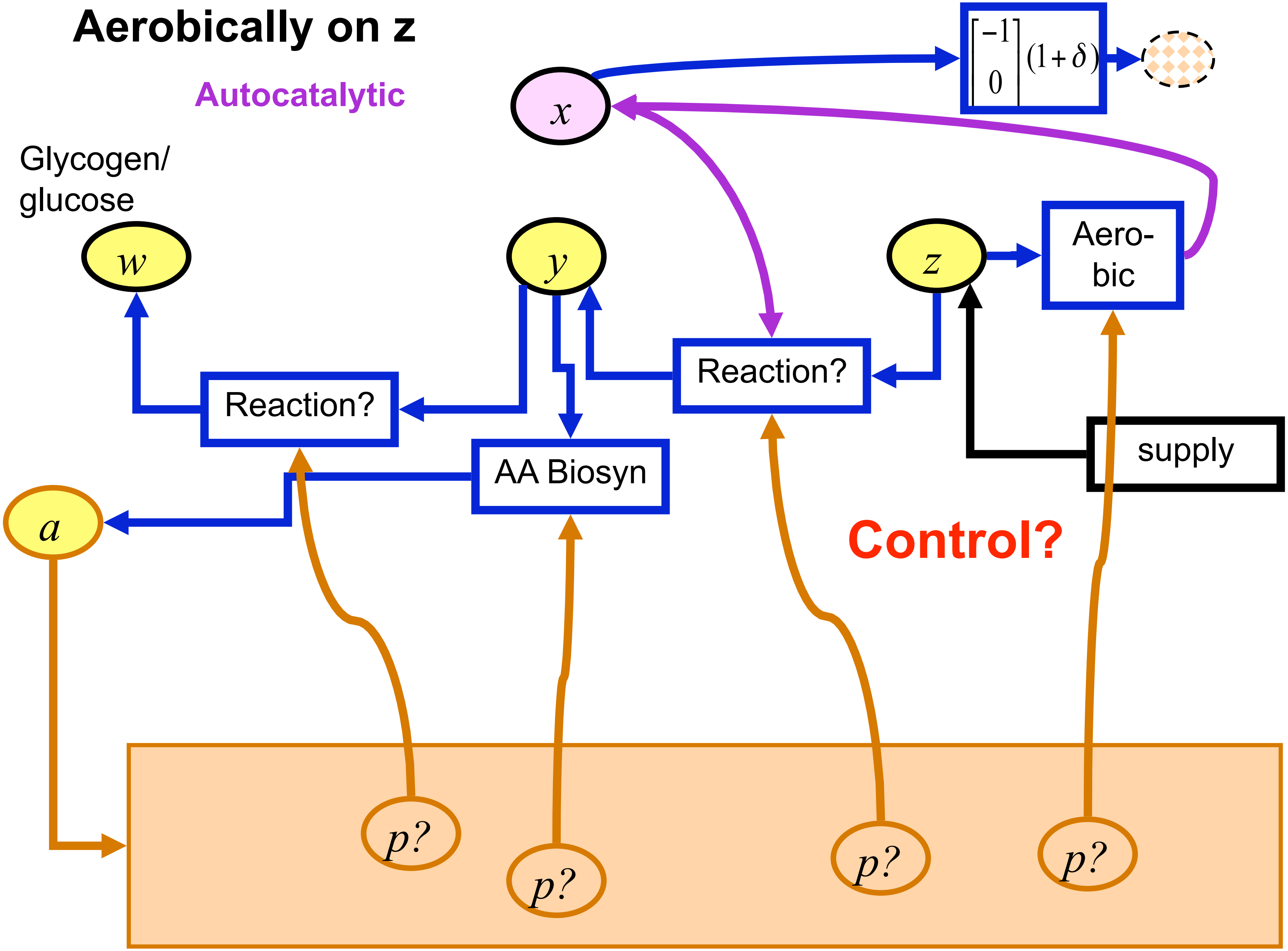
Autocatalytic
Glycogen/
glucose
Control
Aero-
bic
Reaction?
Reaction?
AA Biosyn
Prot1
Prot2
p1
p2
p?
p?
*NA1
*NA2
*NA?
*NA?
w
x
y
z
a
x

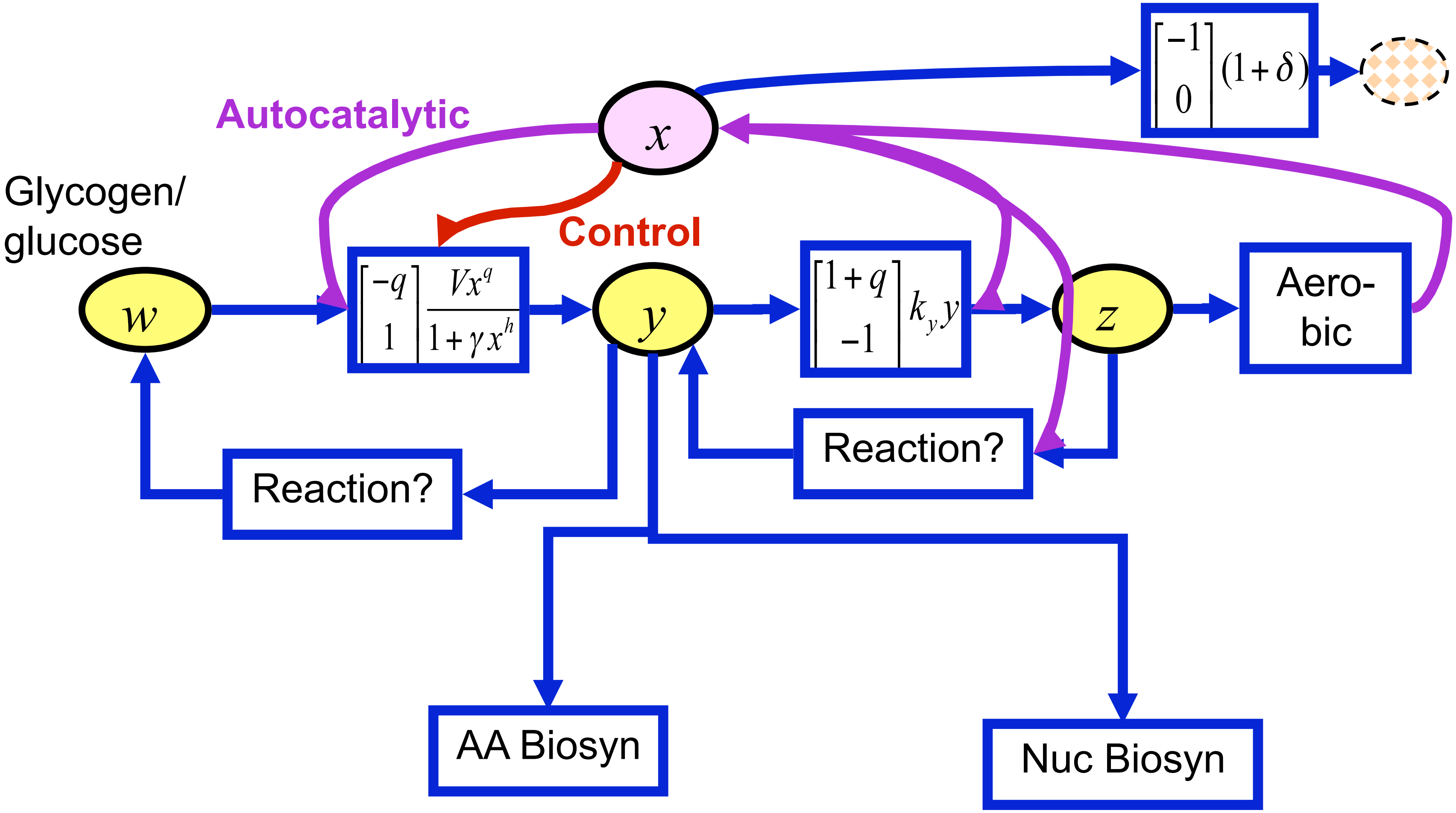

Catabolism
Precursors
AA
Nucl.
AA
transl.
Enzymes
tRNA
Ribosome
ncRNA
mRNA
RNA
Transc.
xRNA
RNAp
Gene



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

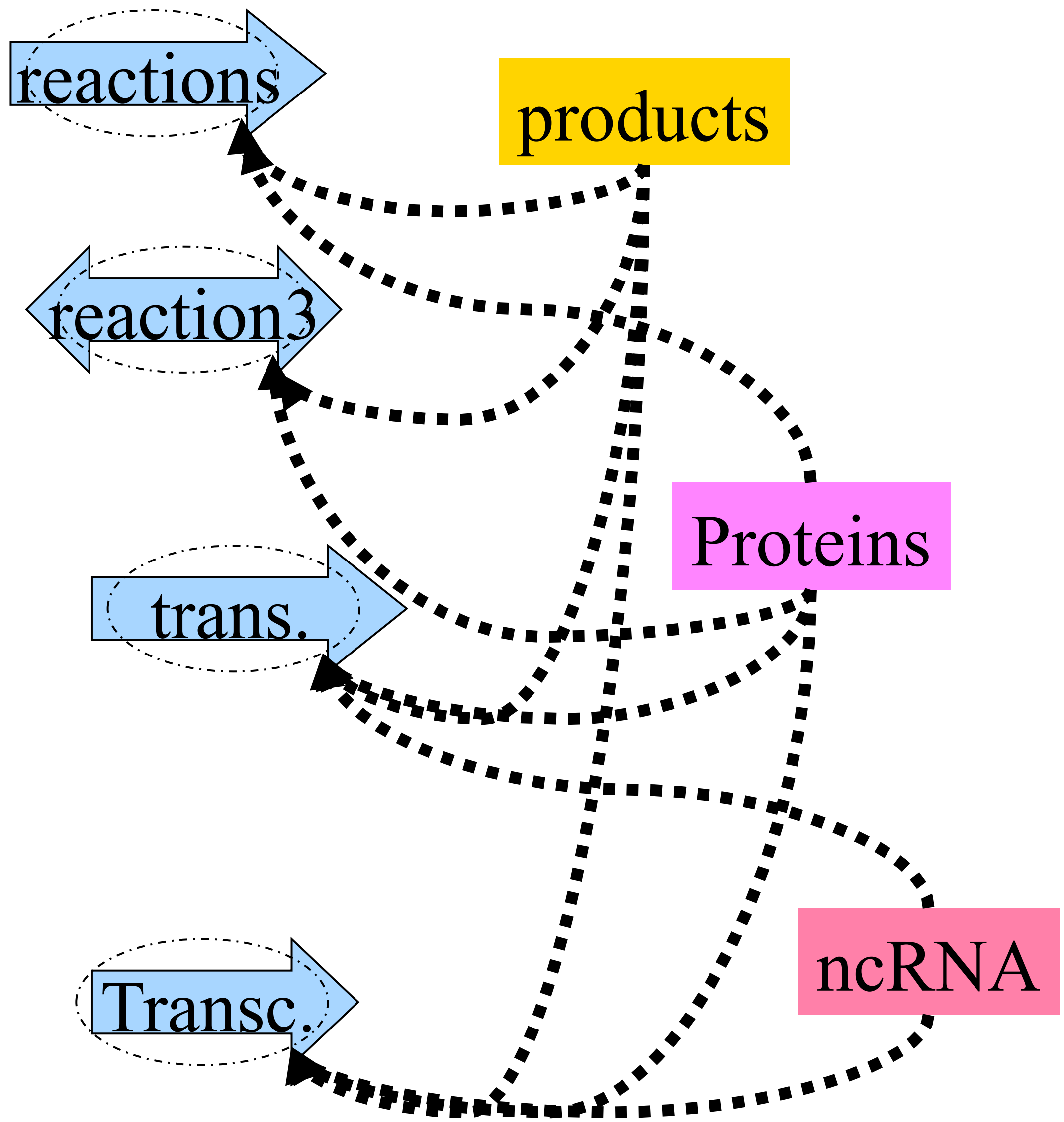
Aerobically on z





Autocatalytic
Glycogen/ glucose
Control
w
x
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
Nuc Biosyn

Control?



All products 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]

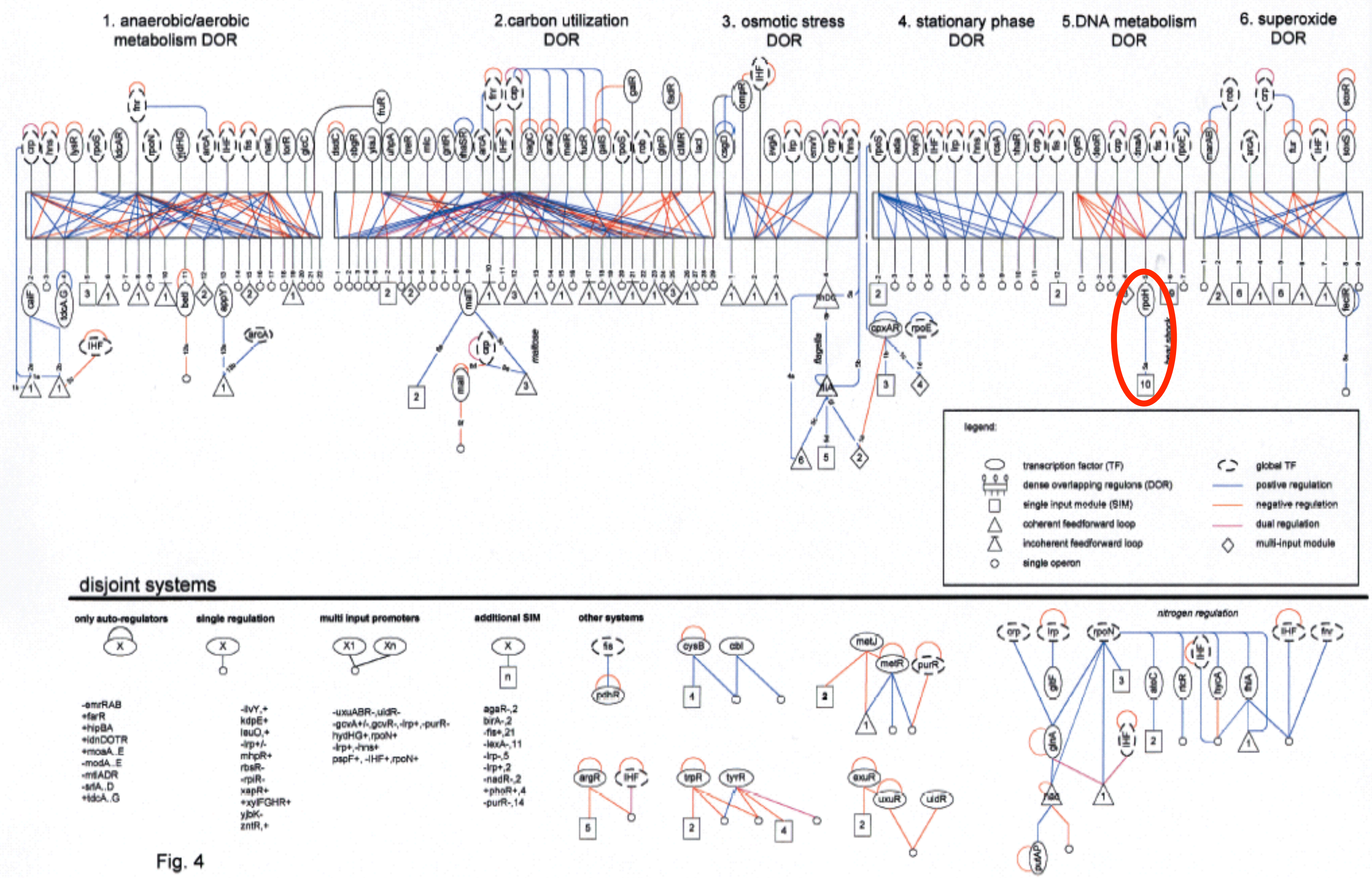
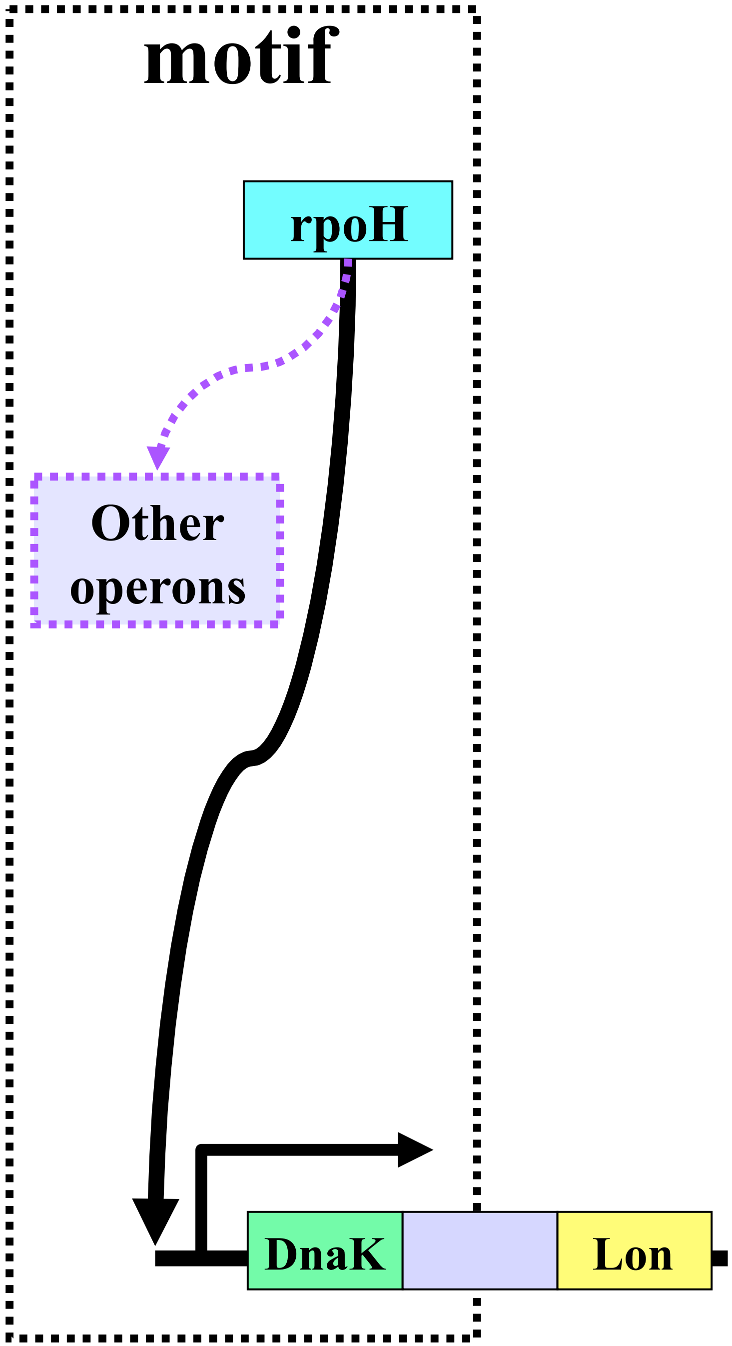
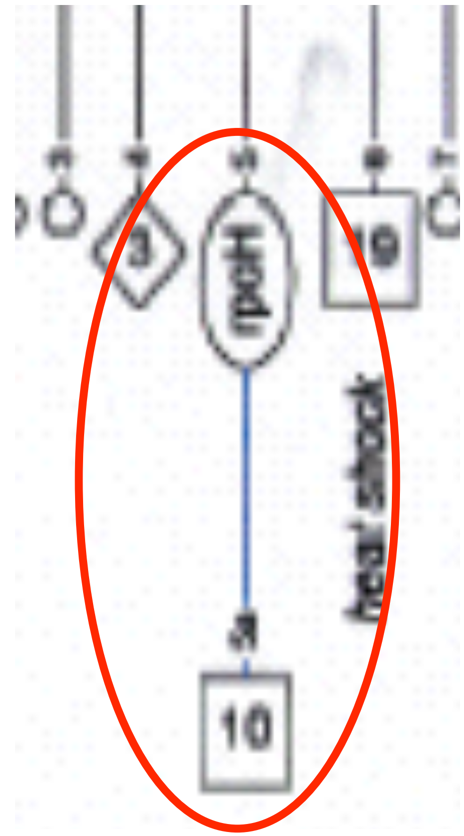
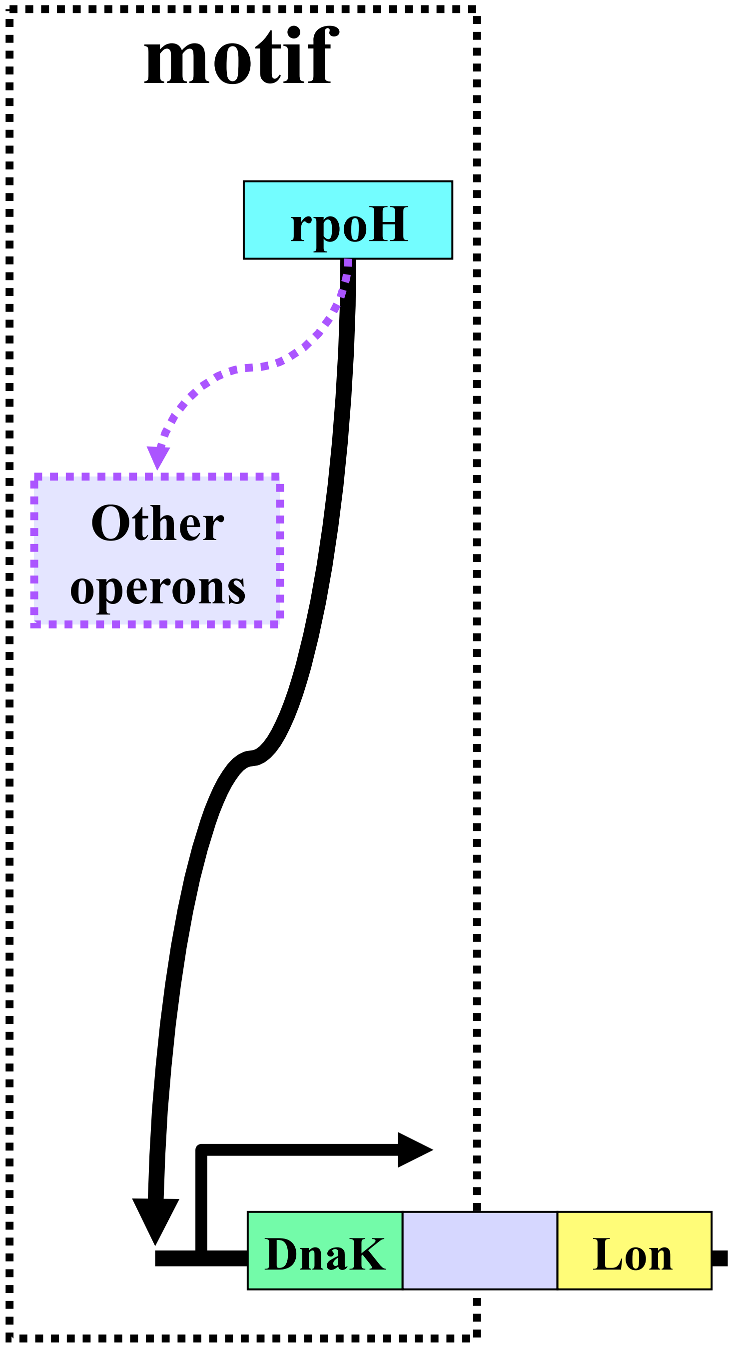


Fig. 4

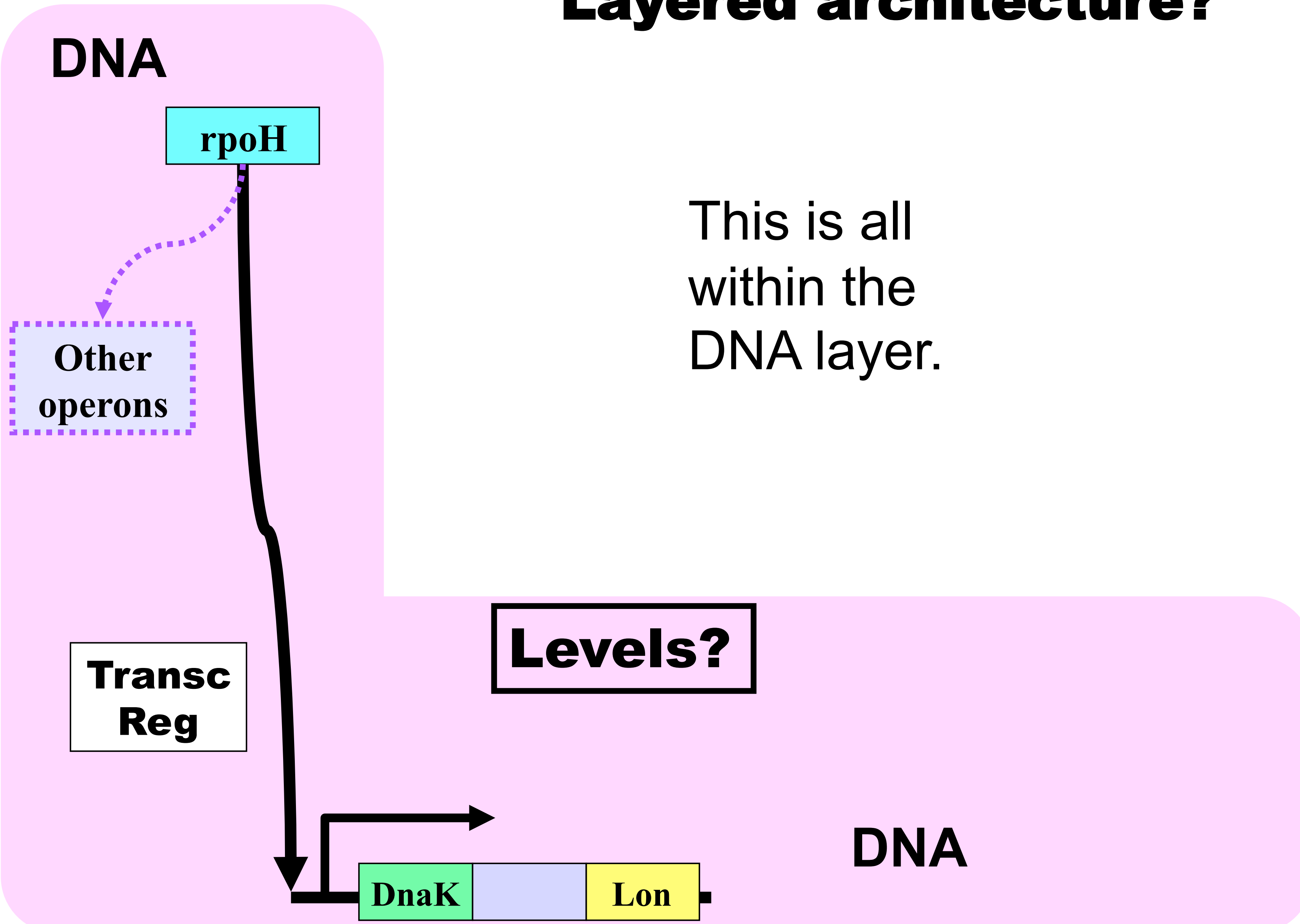




See El-Samad, Kurata, et al…
PNAS, PLOS CompBio

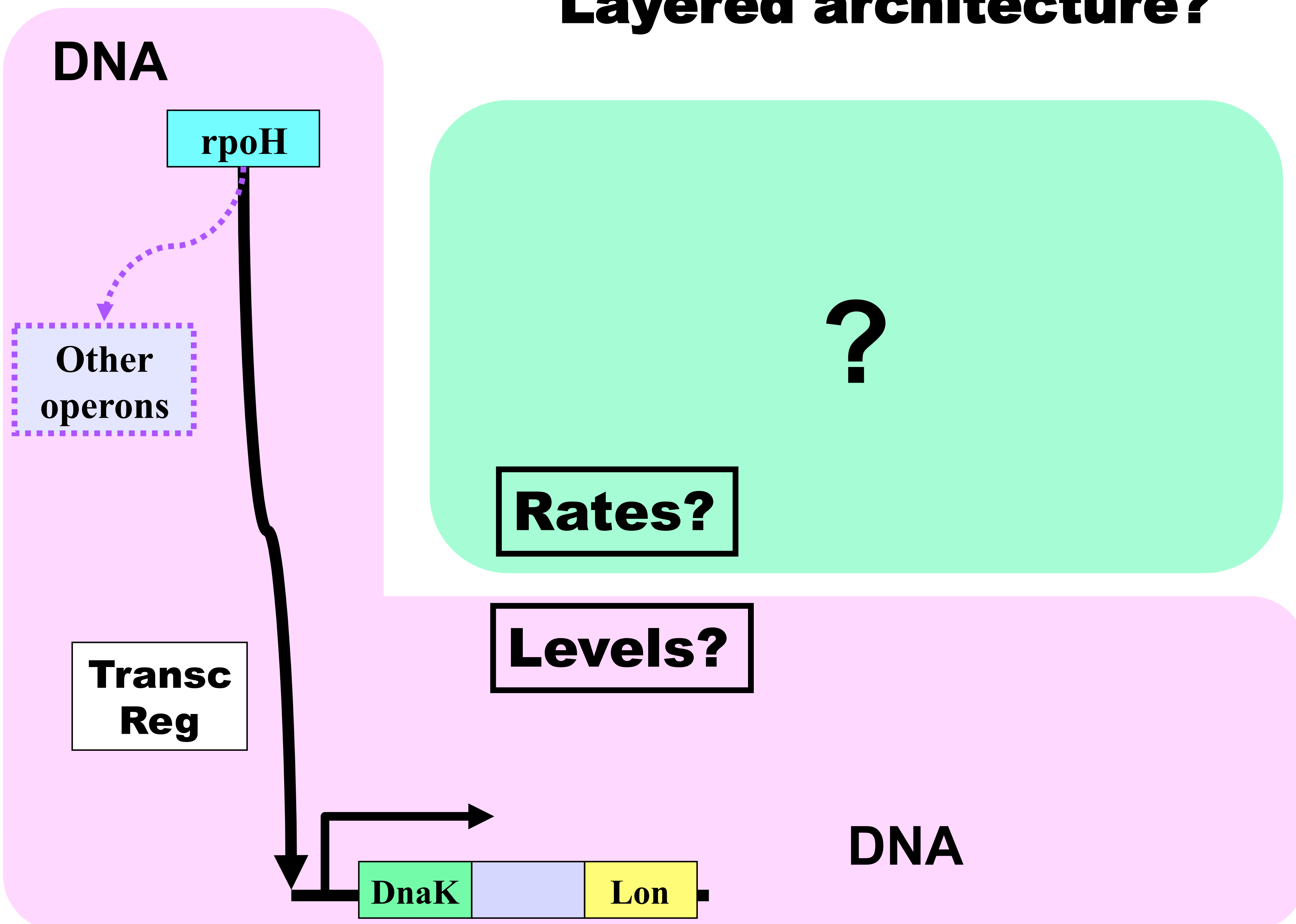

motif
rpoH
Other operons
DnaK
Lon

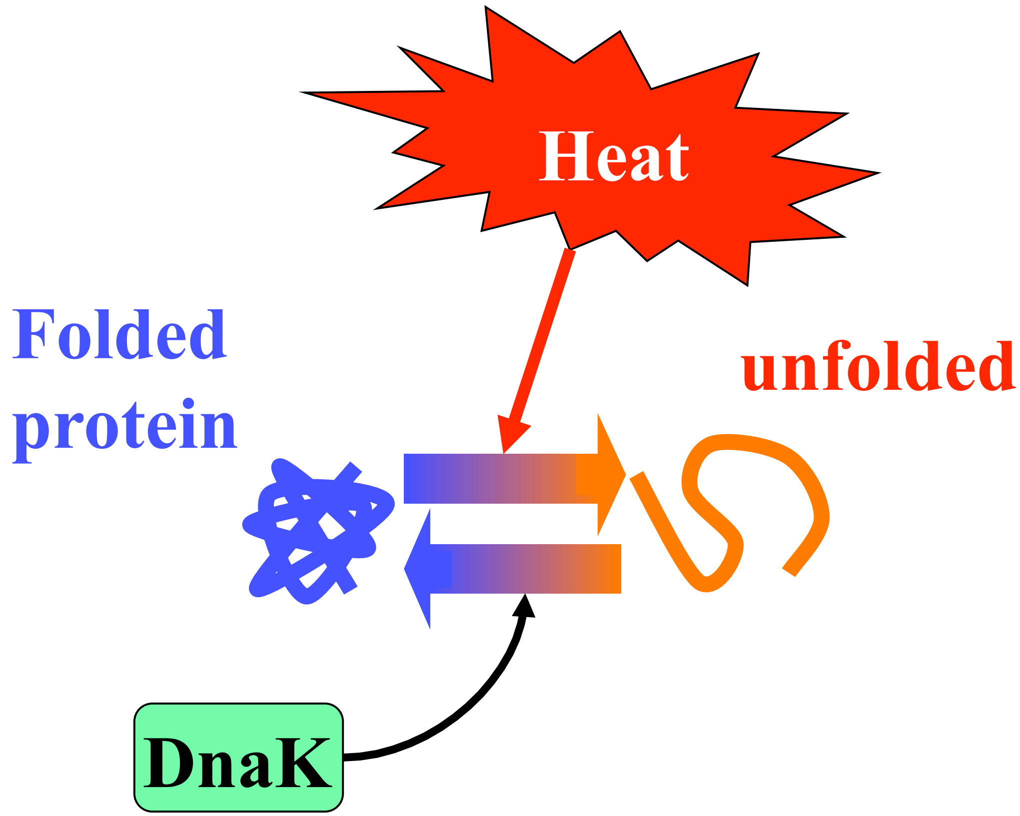
Layered architecture?

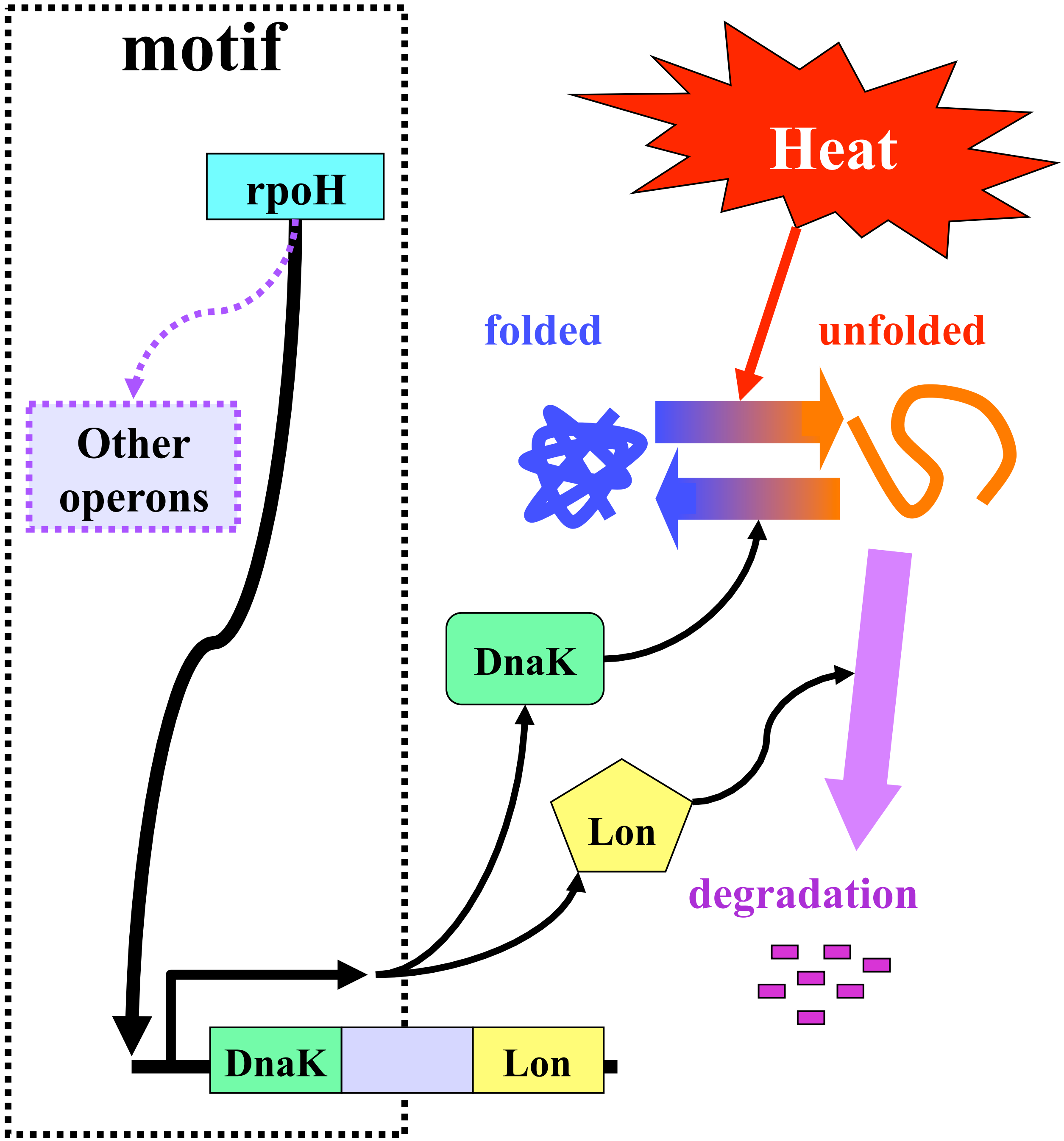


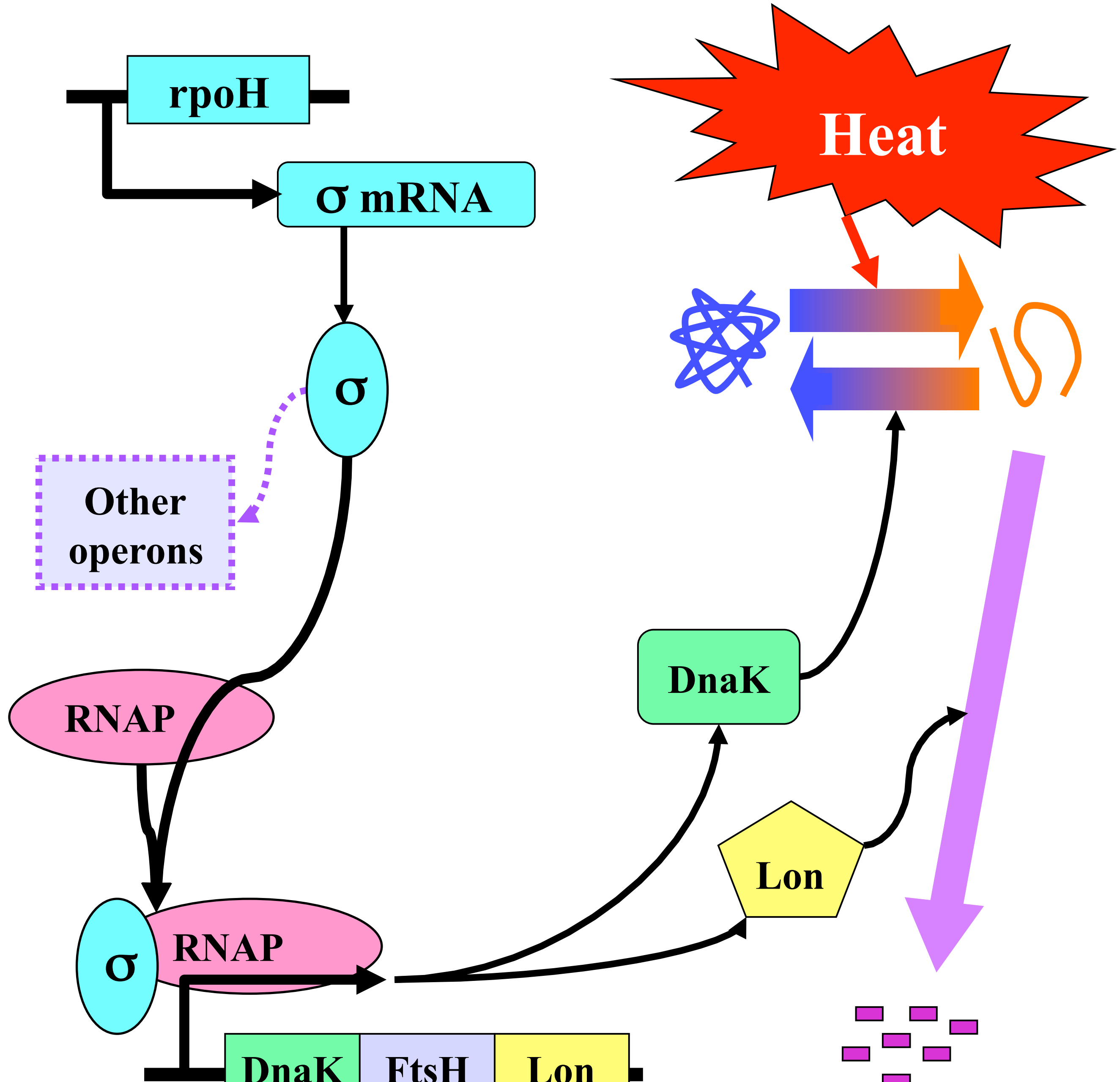
This is all within the DNA layer.

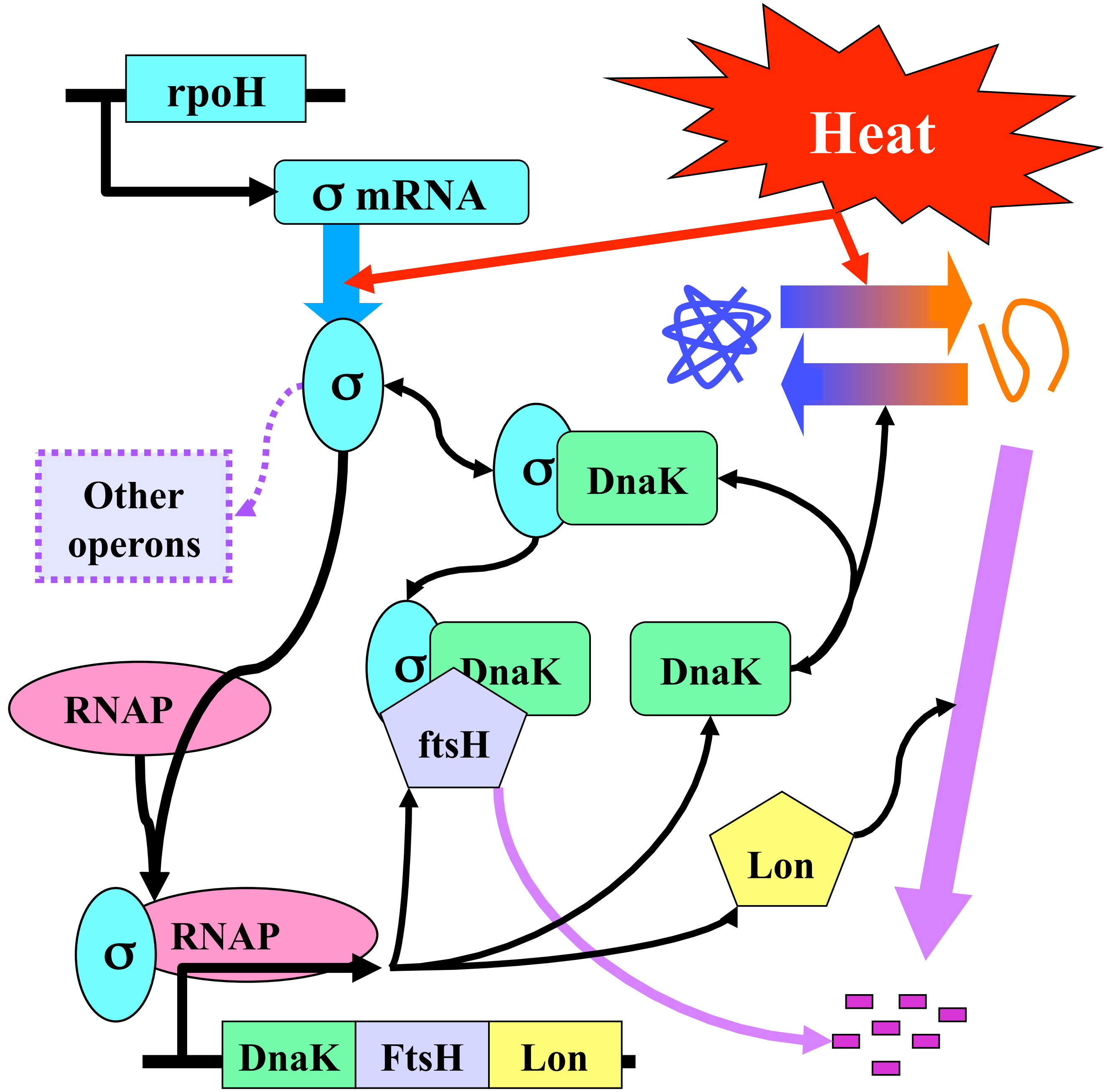
Layered architecture?



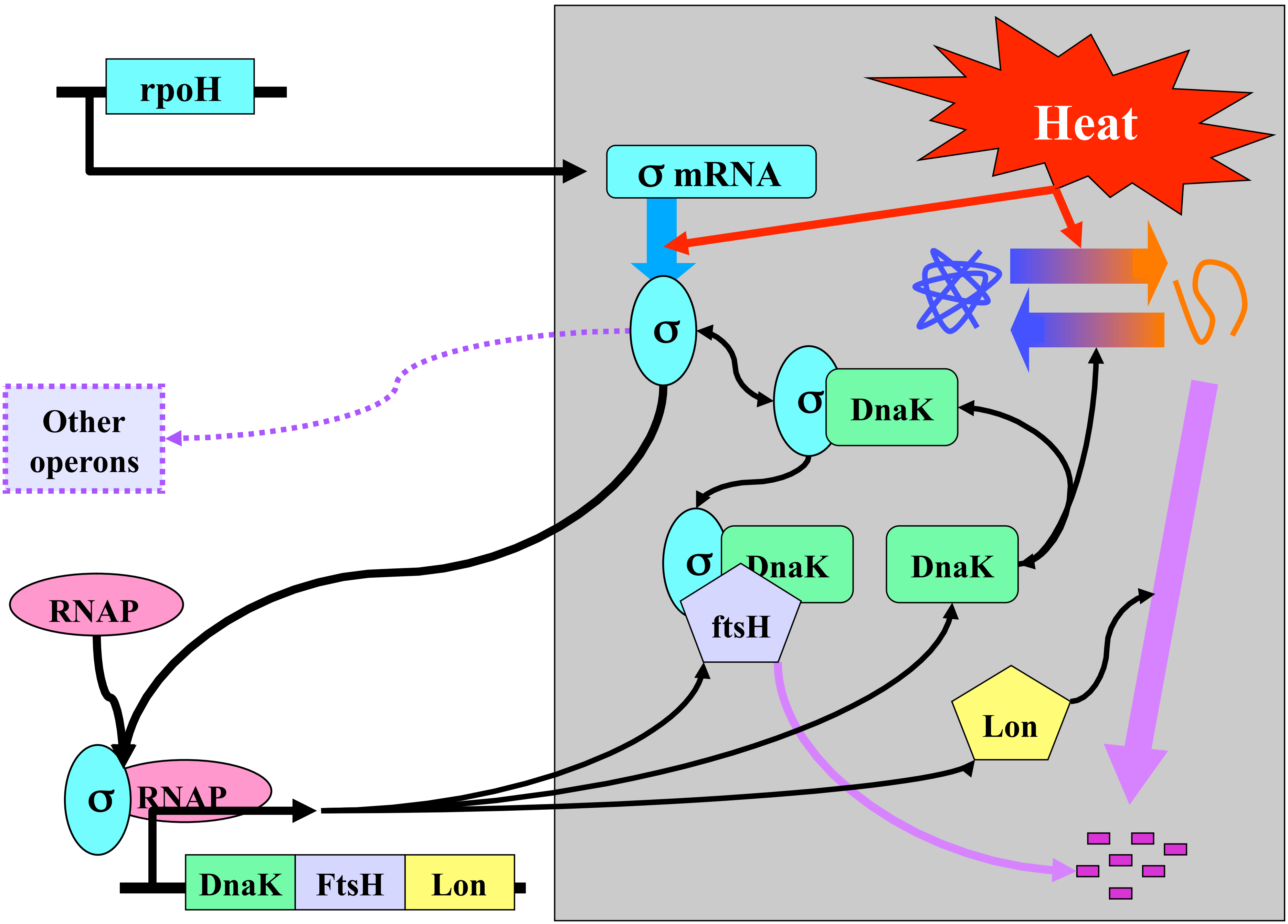

Heat
Folded
protein
unfolded
DnaK


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

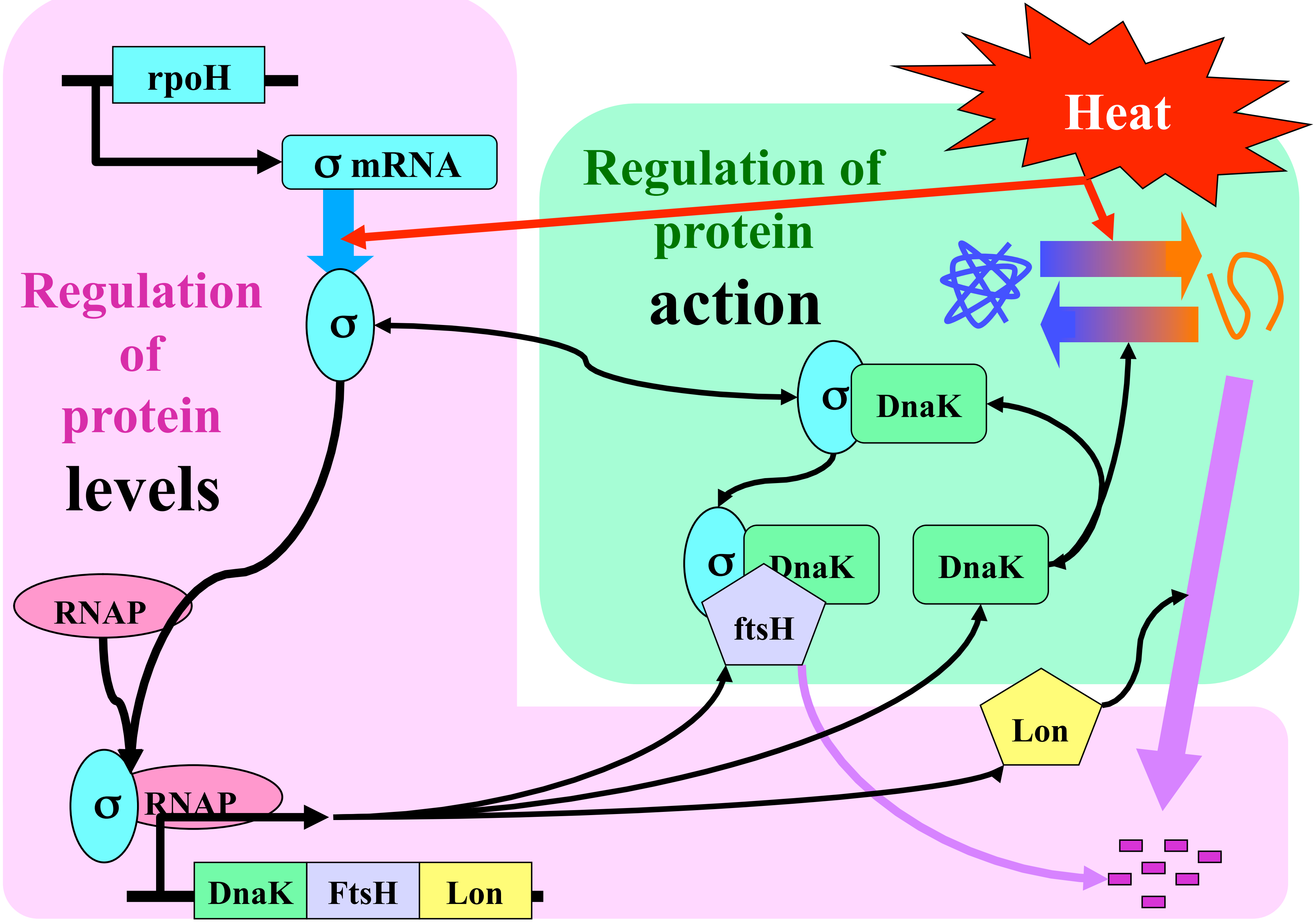

rpoH
σ mRNA
Heat
σ
Other operons
RNAP
DnaK
Lon
σ
RNAP
DnaK
FtsH
Lon



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



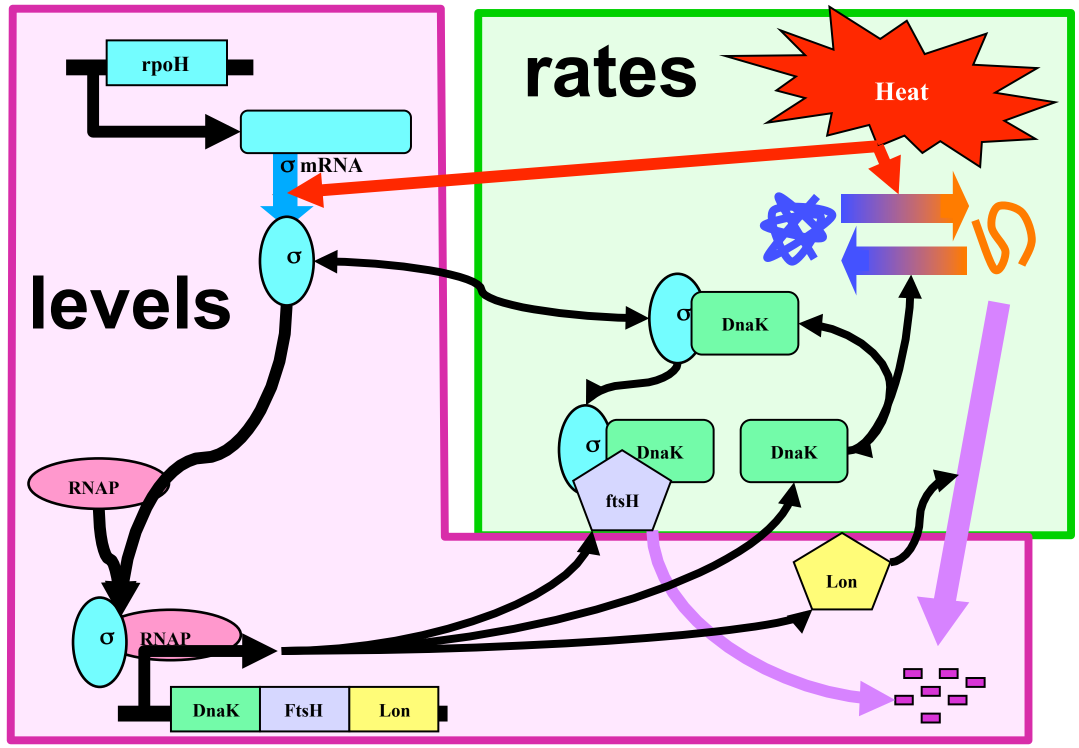
rpoH
σ mRNA
Heat
σ
Other operons
σ DnaK
σ DnaK
ftsH
DnaK
RNAP
Lon
σ RNAP
DnaK FtsH Lon



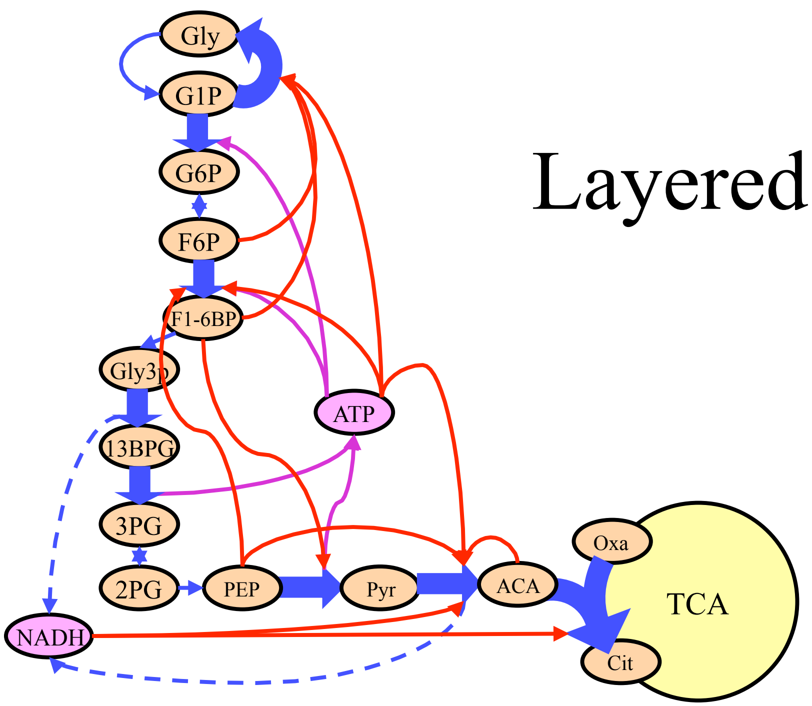
rpoH
σ mRNA
Heat
Regulation of protein action
Regulation of protein levels
σ
σ DnaK
σ DnaK
DnaK
ftsH
Lon
RNAP
σ RNAP
DnaK
FtsH
Lon

Regulation of protein action

Regulation of protein levels



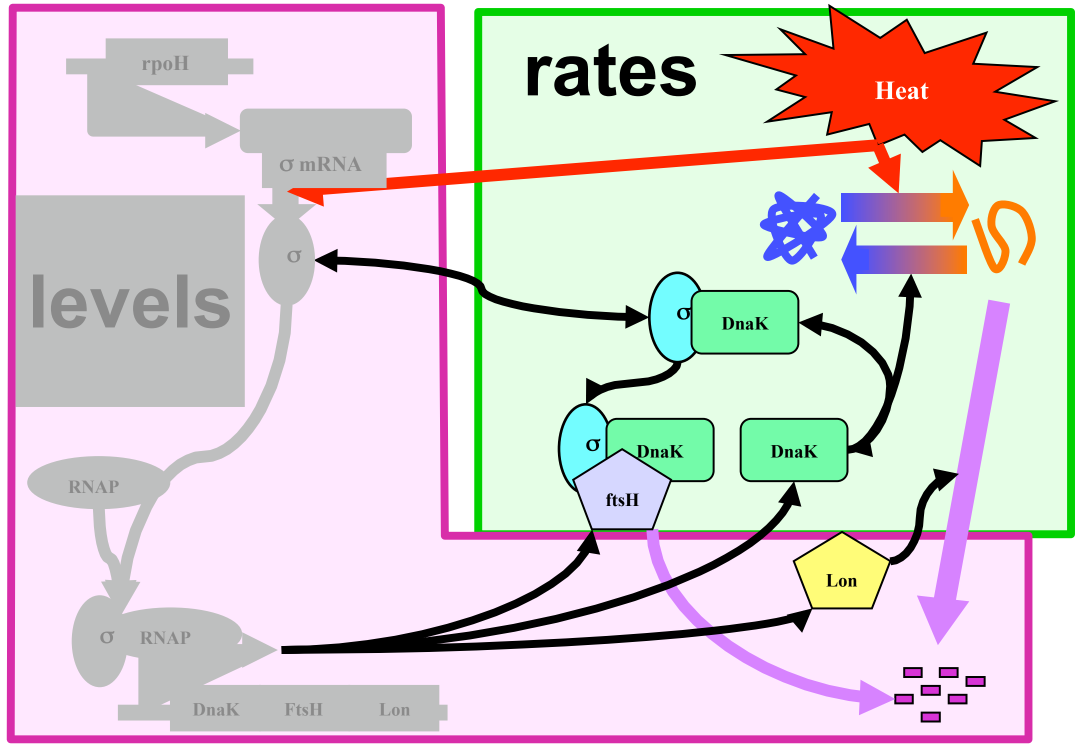
Layered control architectures



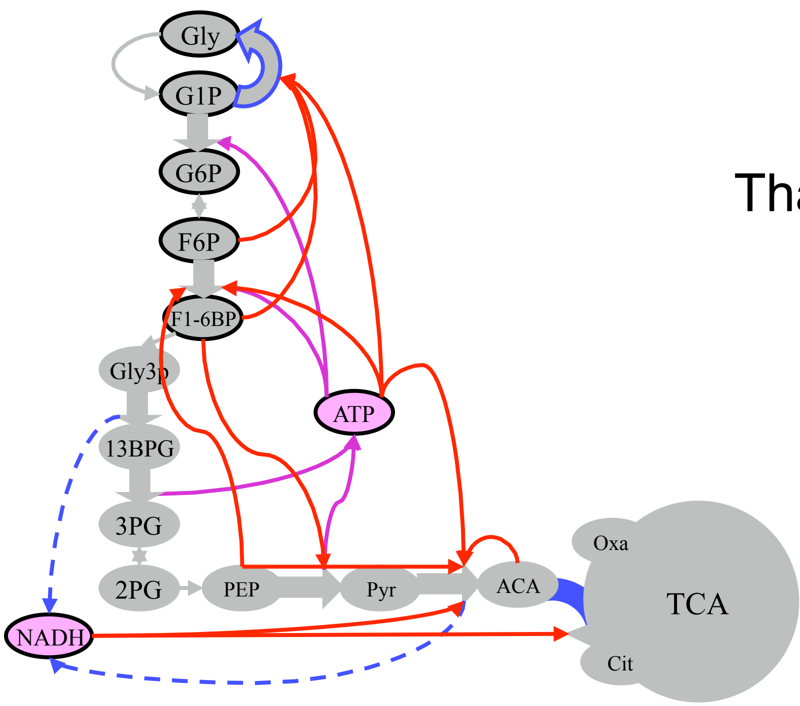
Allosteric

Trans*

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



That is not always the case.



Allosteric

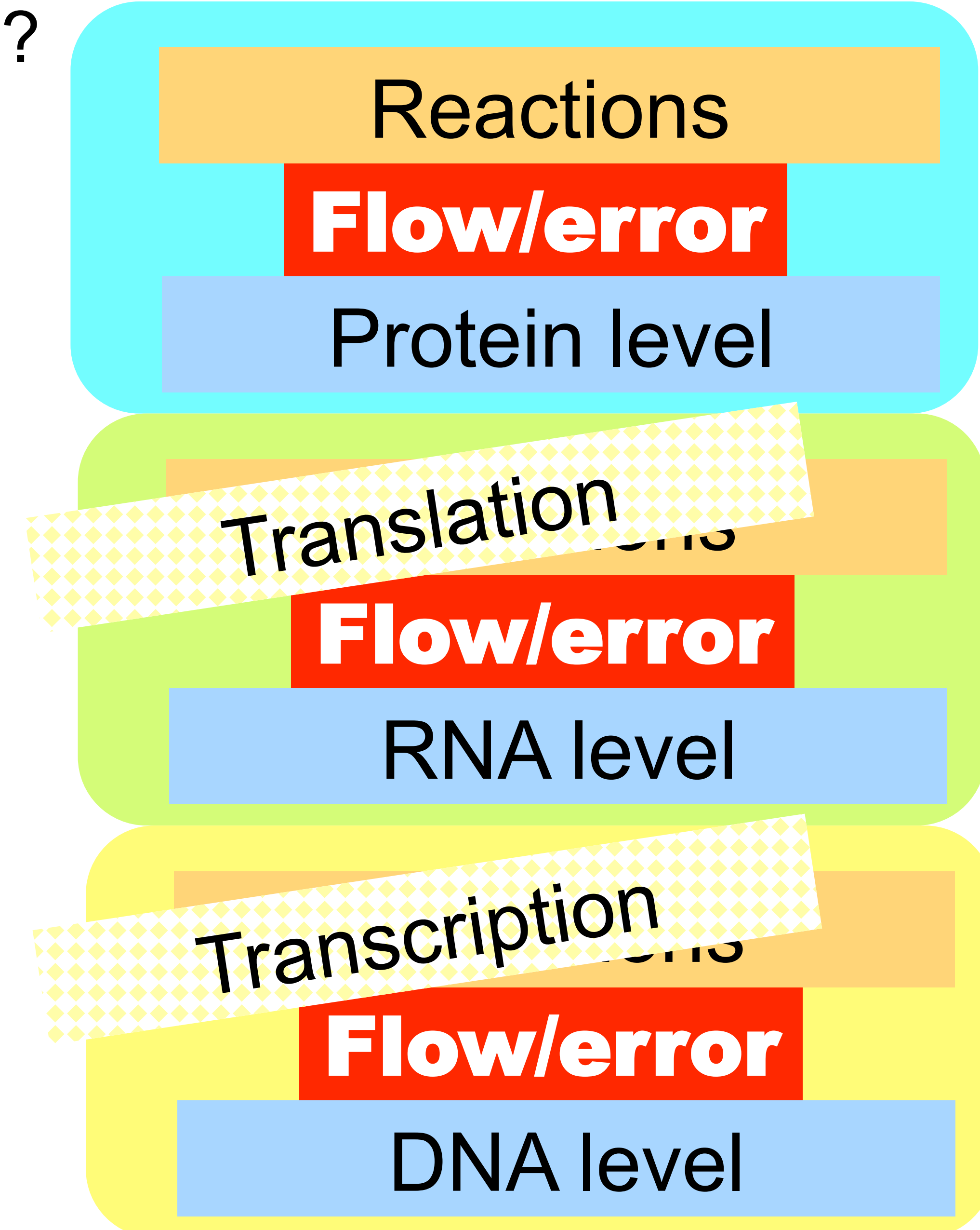
Trans*

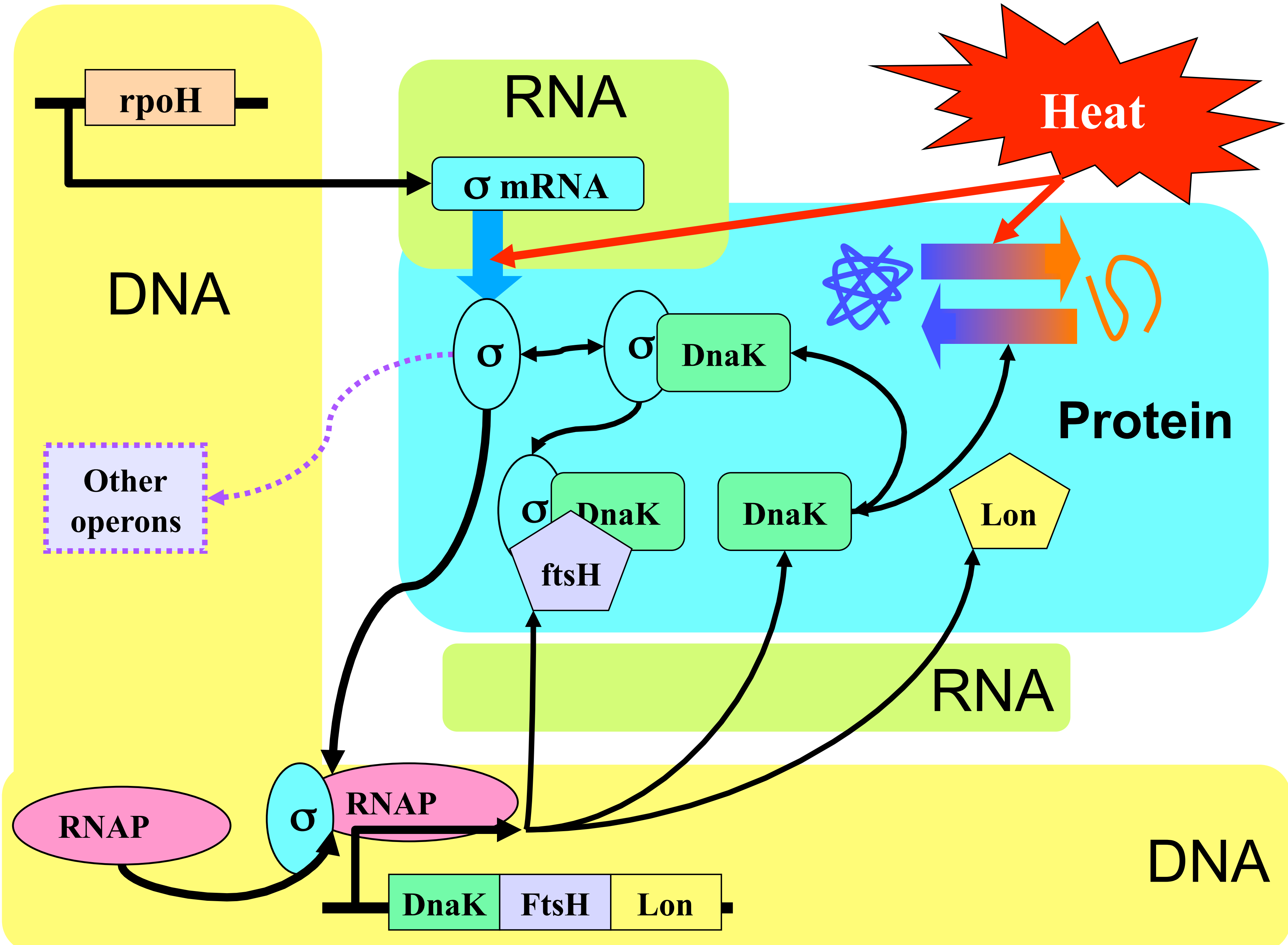
Where are these layers?

Protein

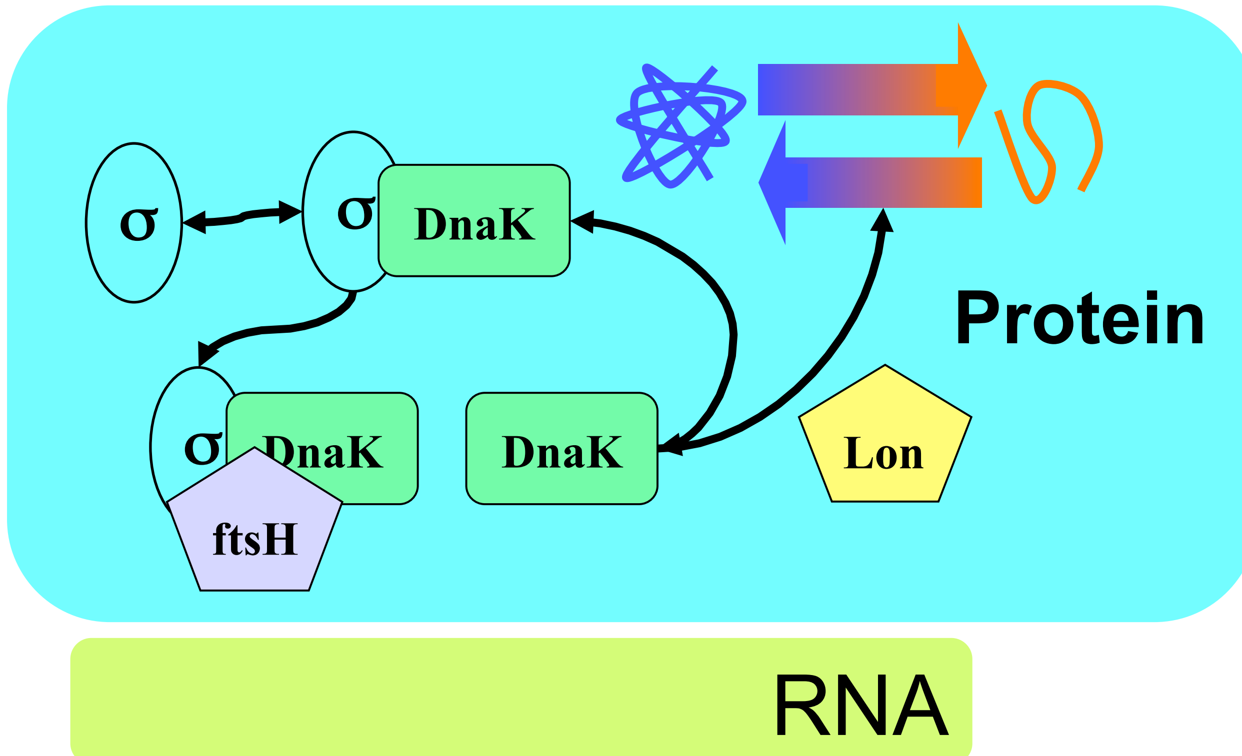
RNA

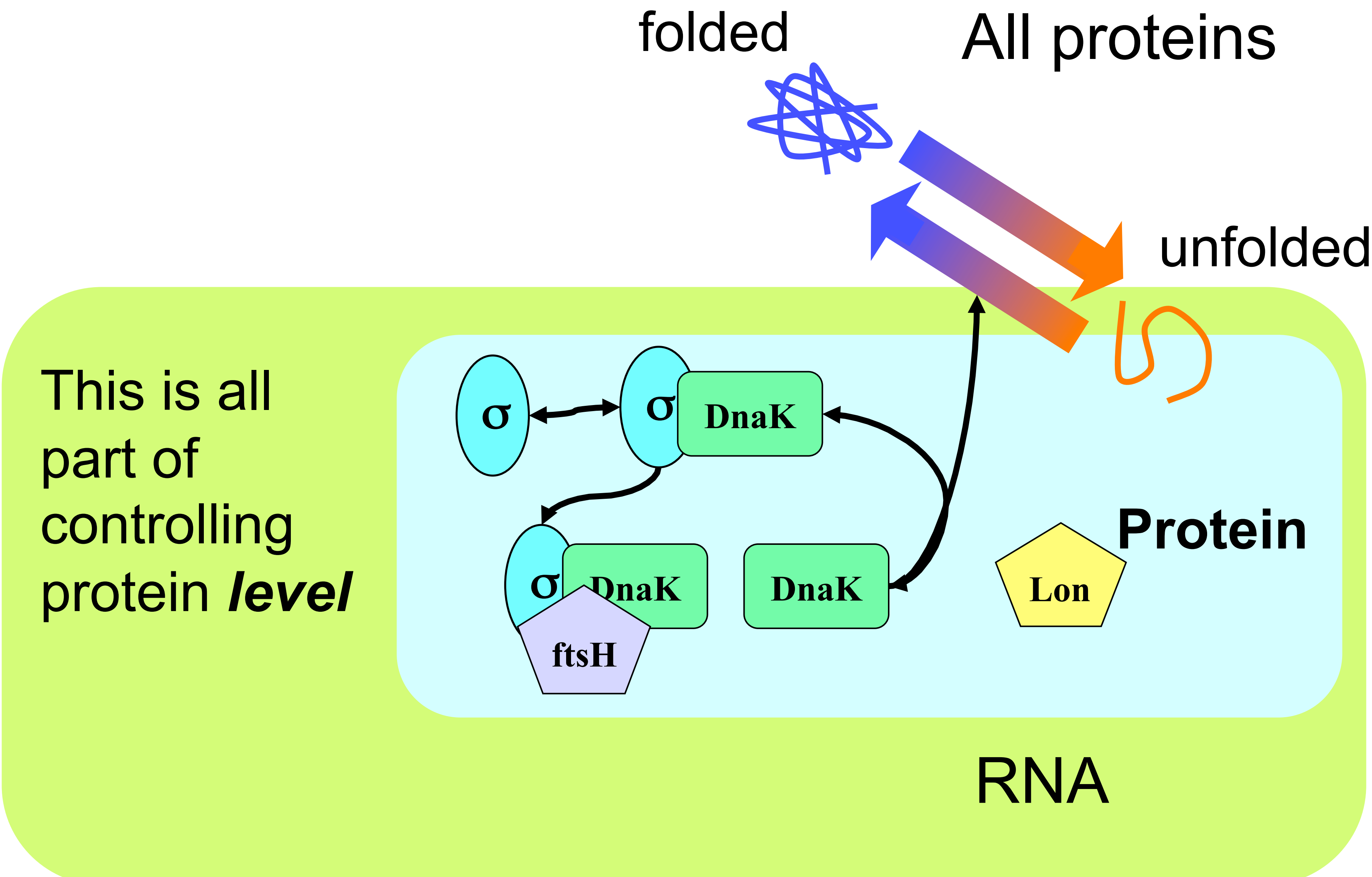
DNA

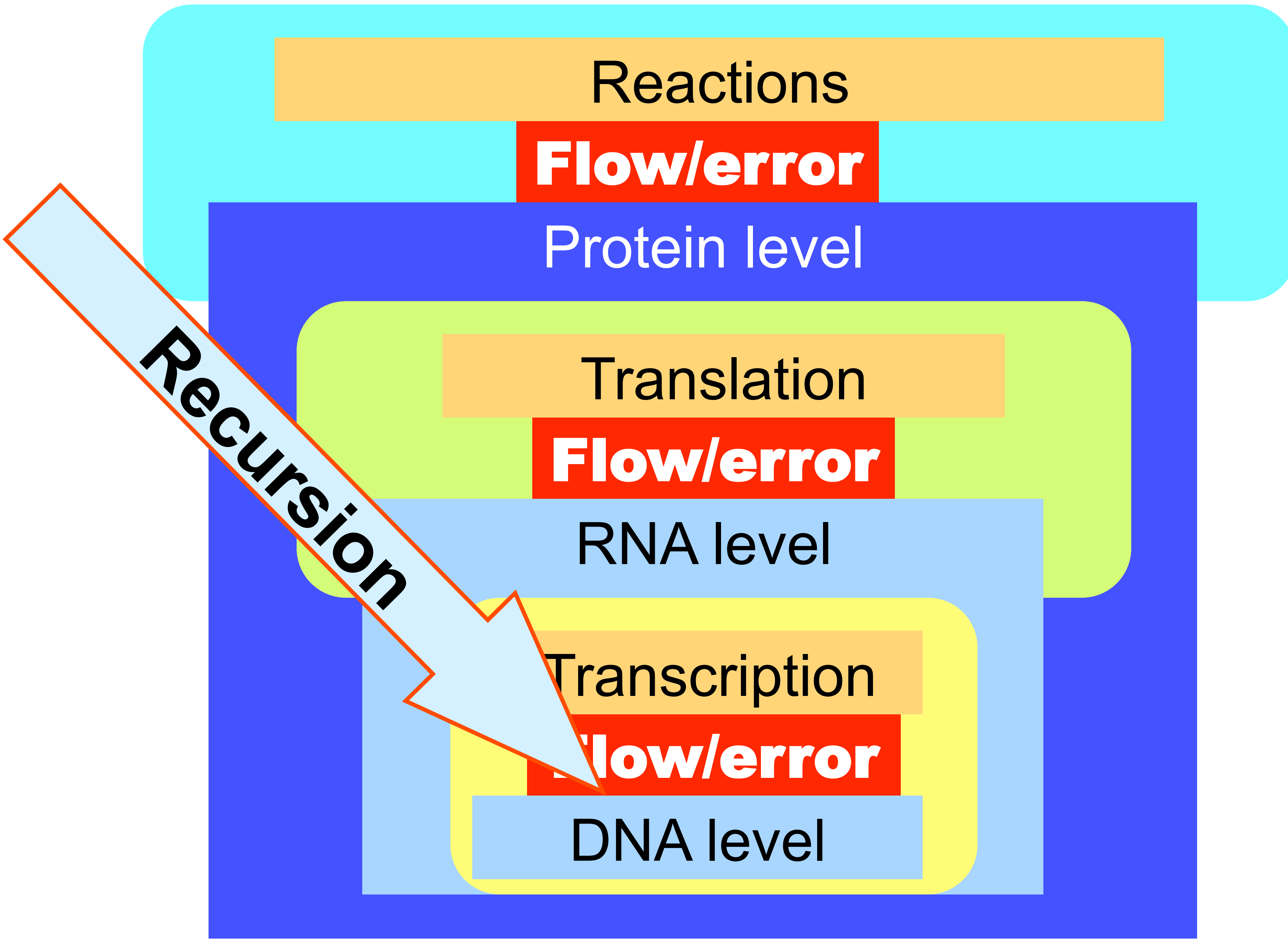


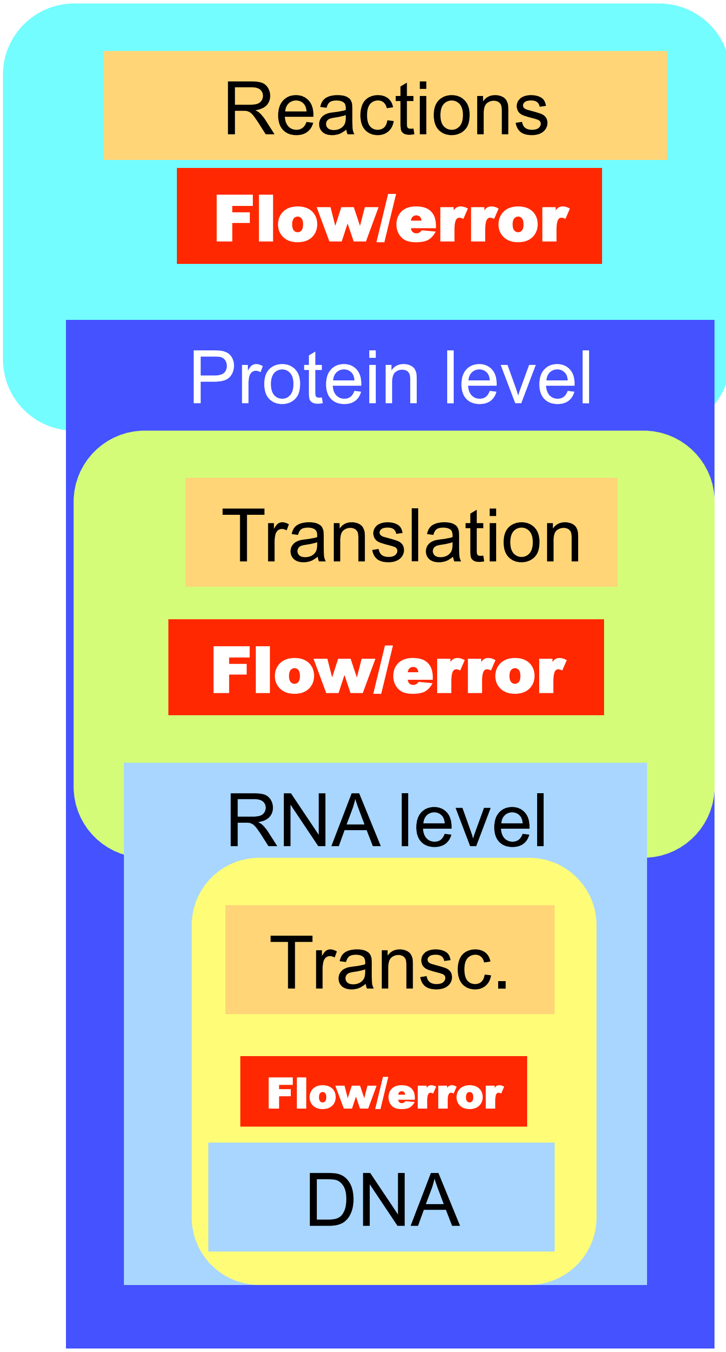


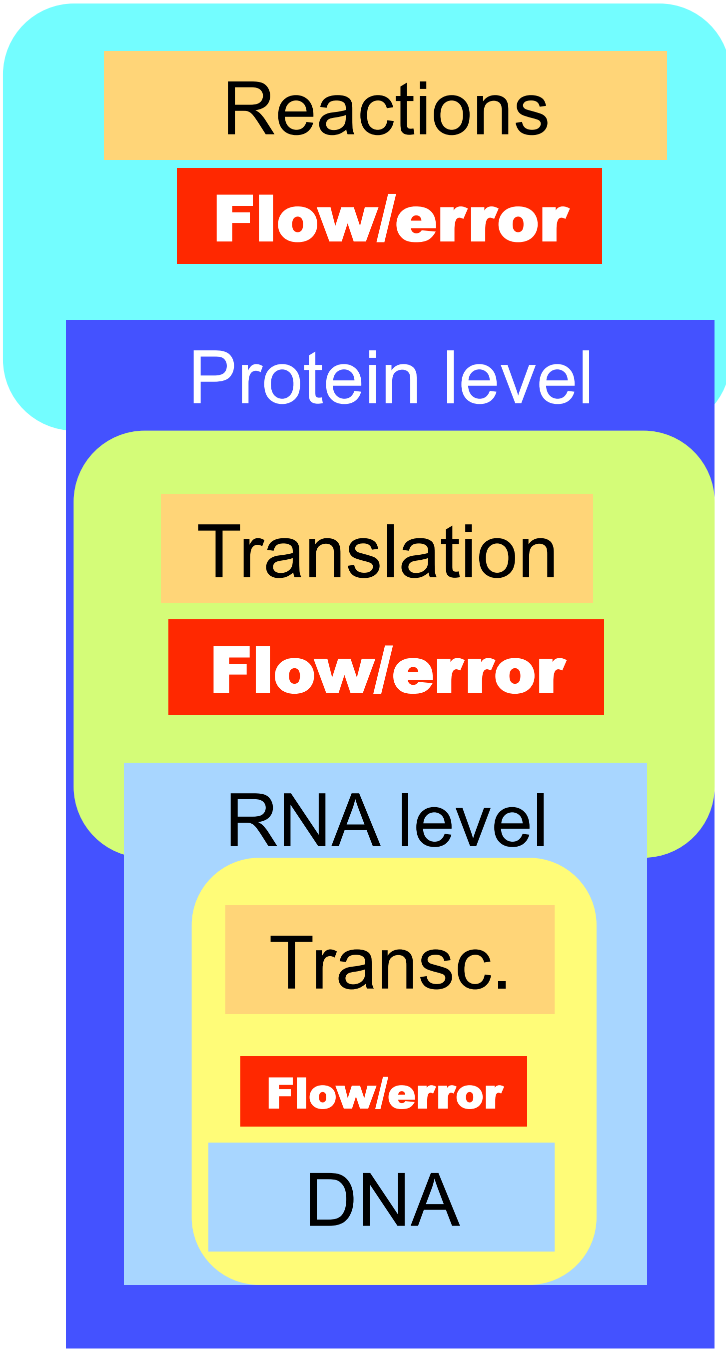
rpoH
RNA
σ mRNA
Heat
DNA
σ
σ
DnaK
Protein
Other operons
σ
DnaK
ftsH
DnaK
Lon
RNA
RNAP
σ
RNAP
DnaK
FtsH
Lon
DNA


σ
σ
DnaK
Protein
σ
DnaK
DnaK
Lon
ftsH
RNA

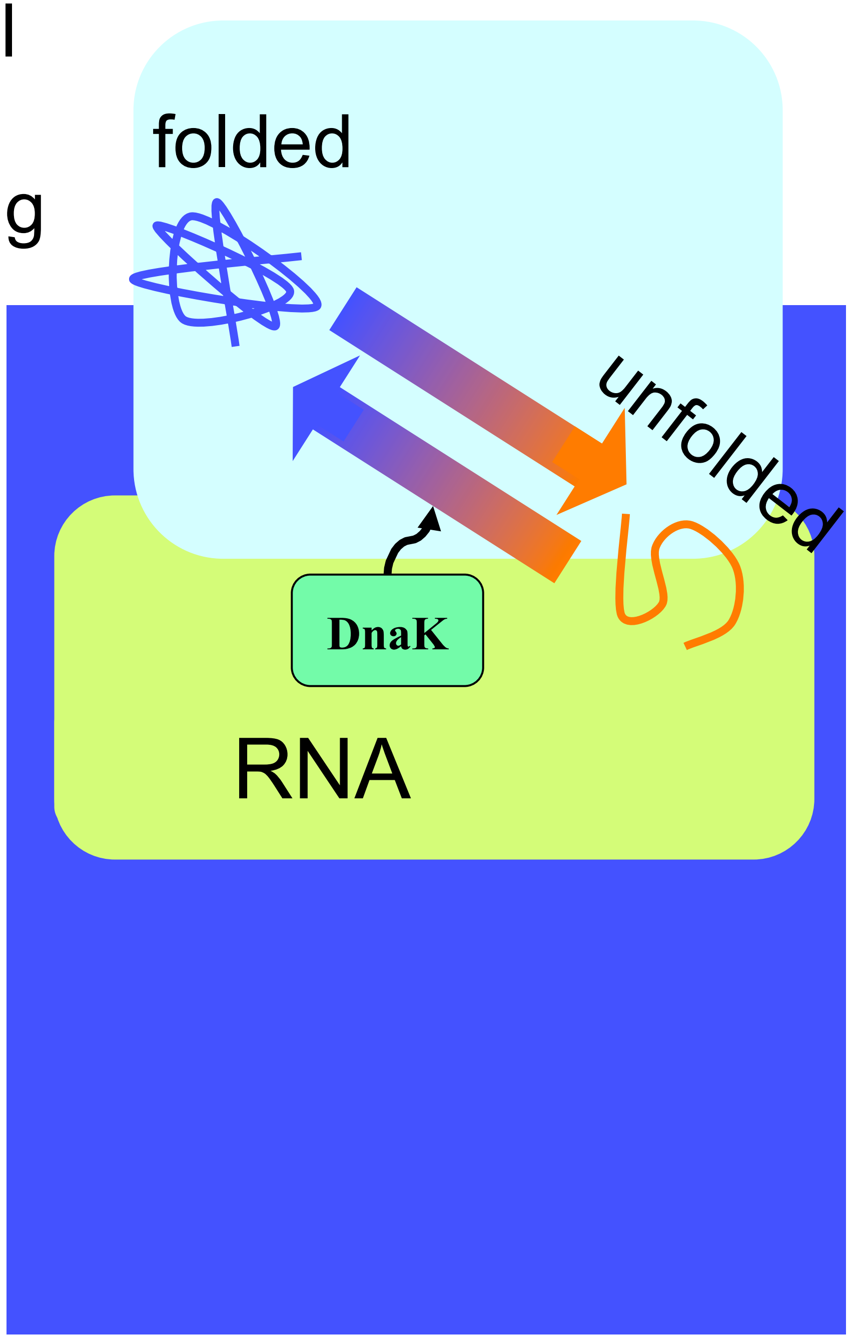

folded
All proteins
unfolded
This is all part of controlling protein *level*
σ
σ
DnaK
σ
DnaK
ftsH
DnaK
Lon
Protein
RNA


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

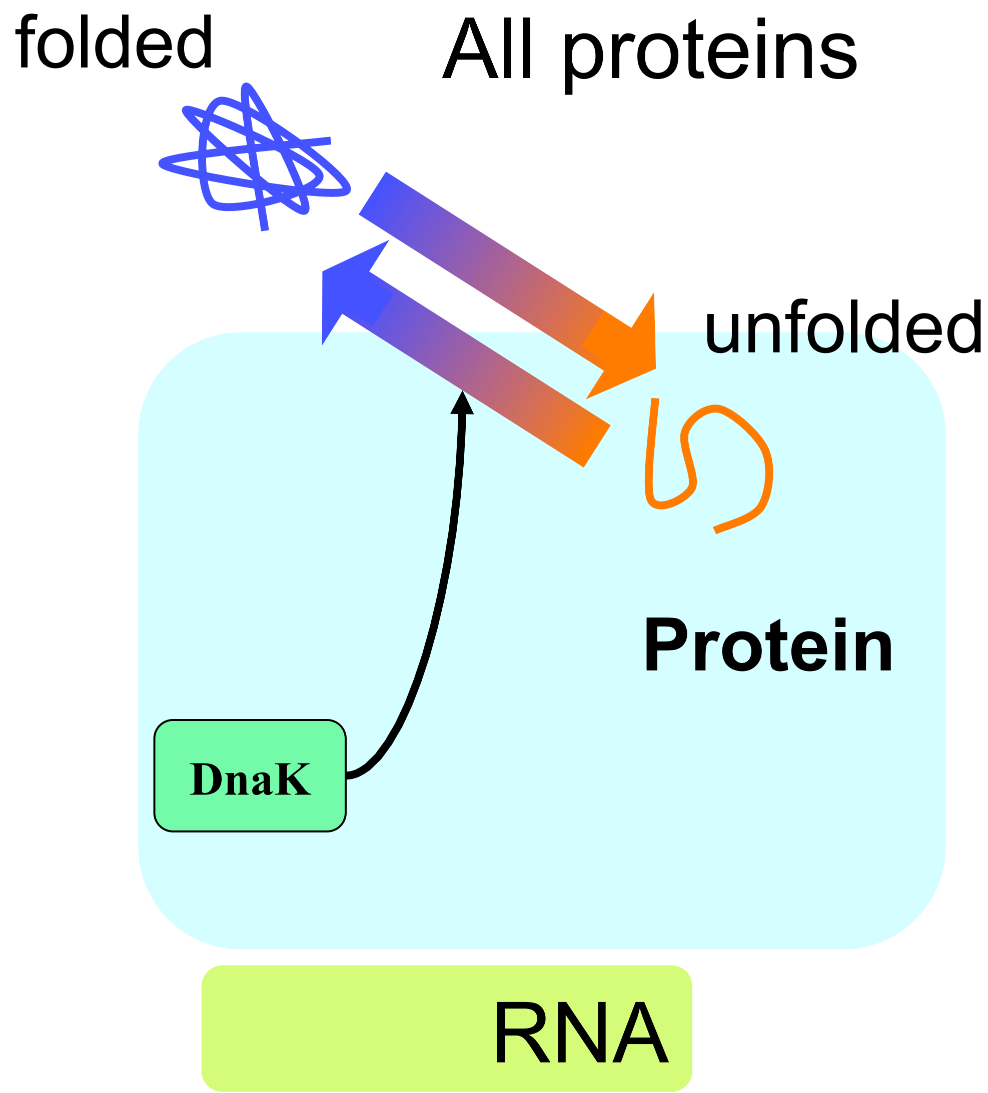

Reactions
Flow/error
Protein level
Translation
Flow/error
RNA level
Transc.
Flow/error
DNA

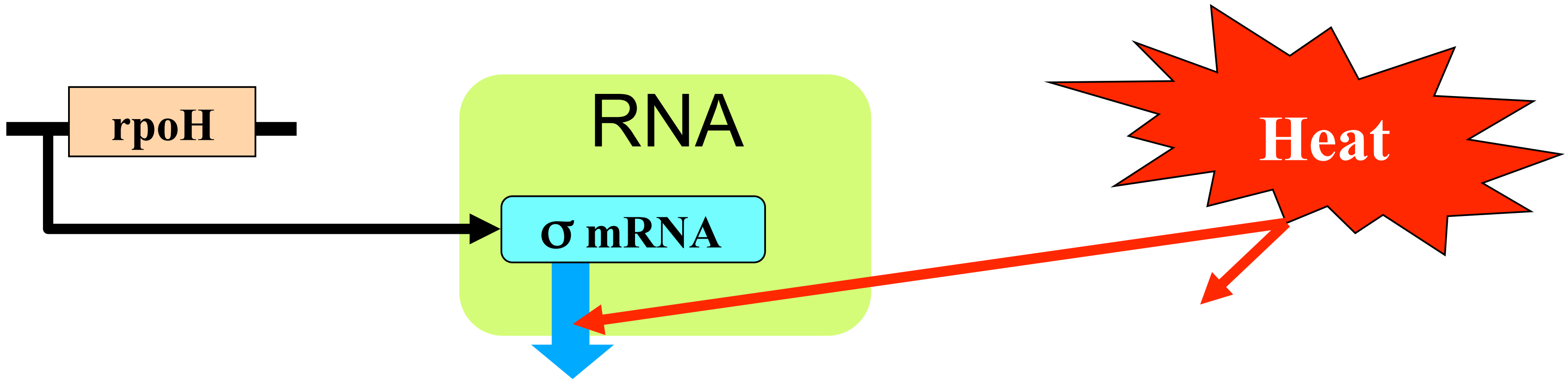


This is all part of controlling protein ***level***



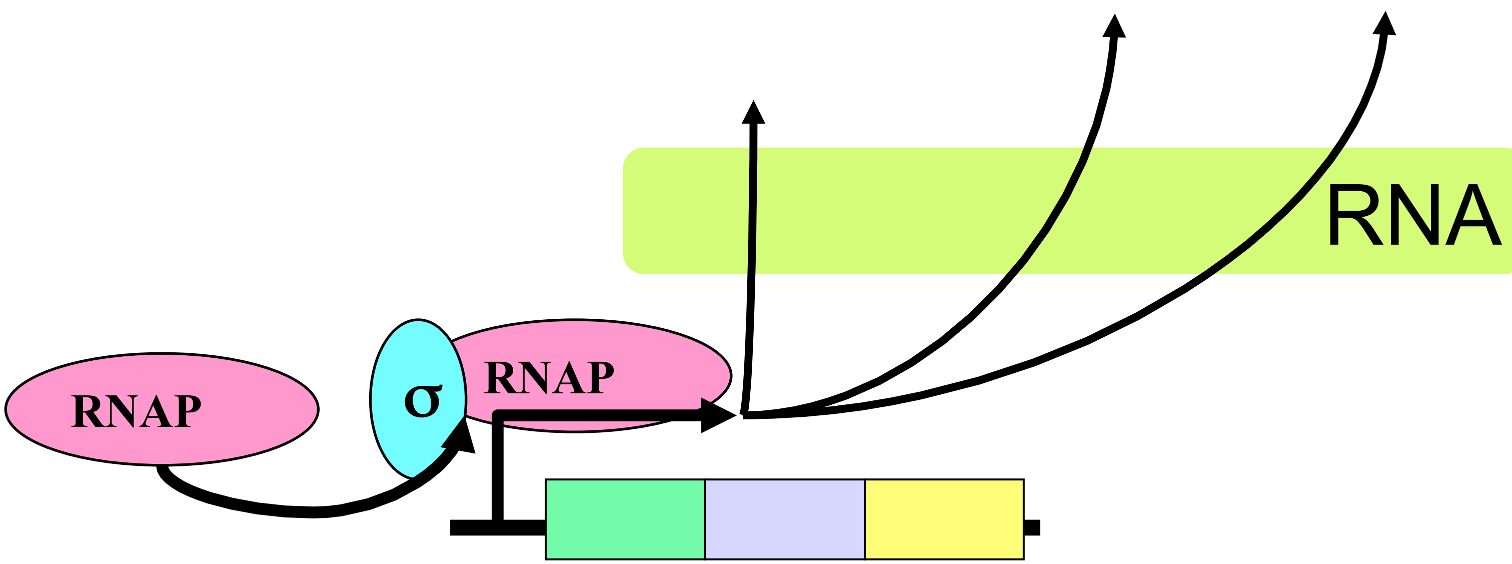
This is all part of controlling protein level

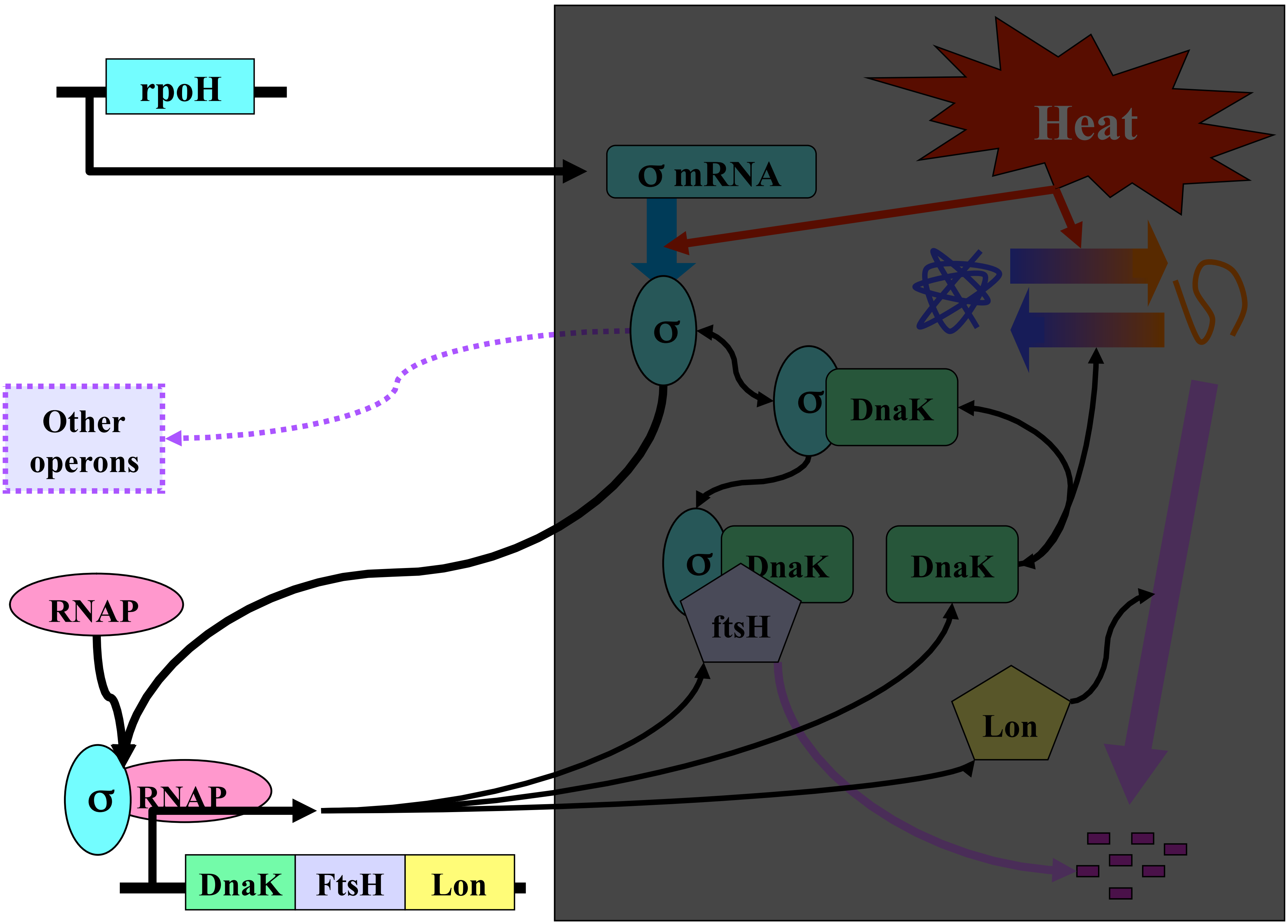


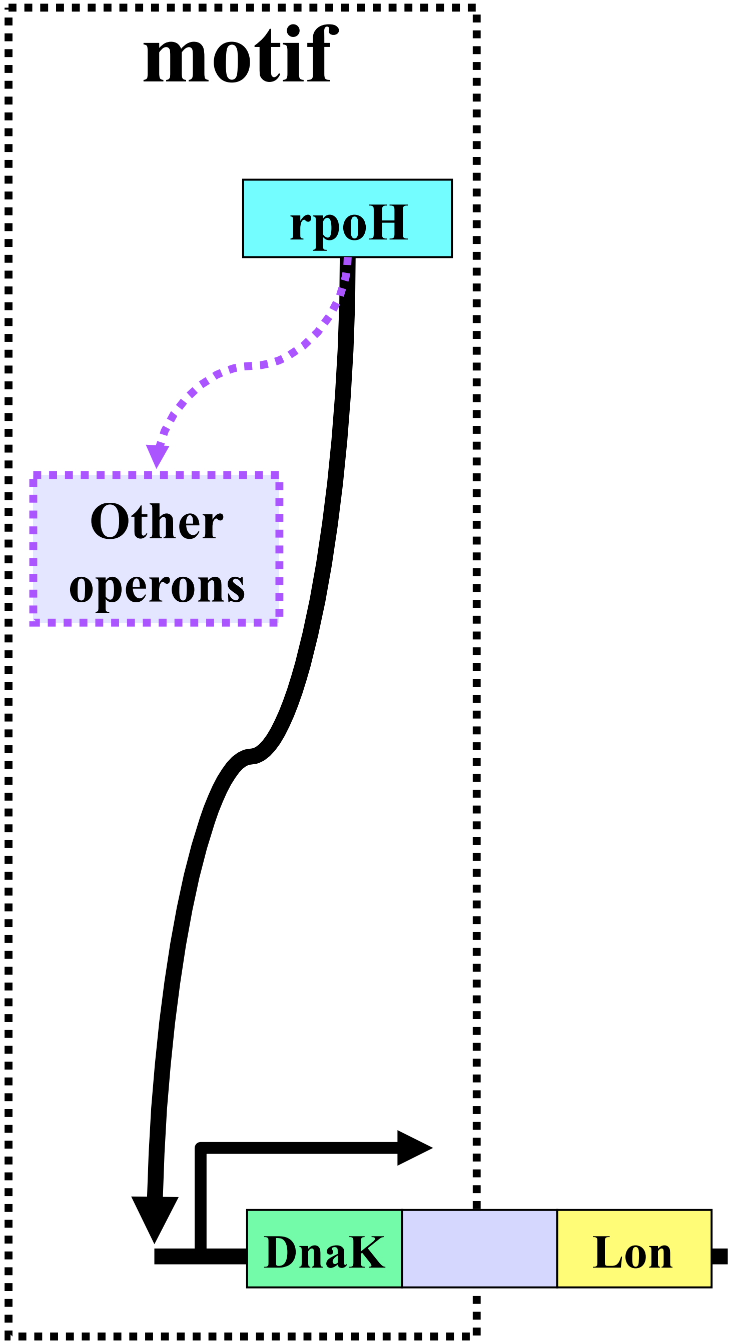


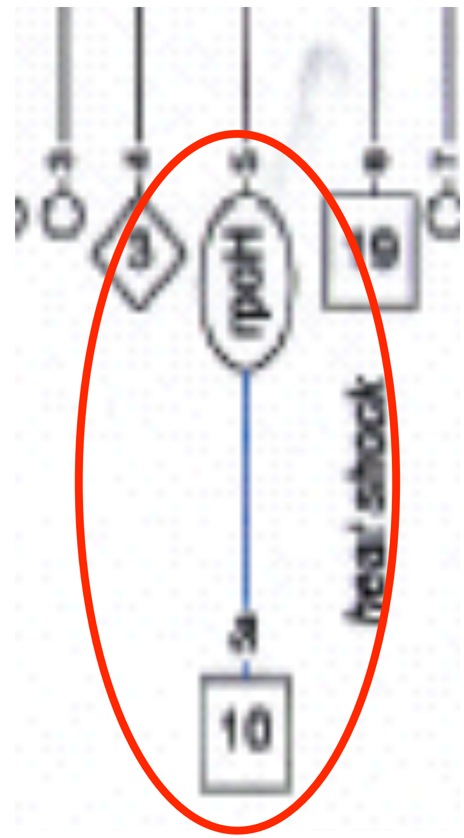
mRNA activity is actively controlled.

Translation was not shown.

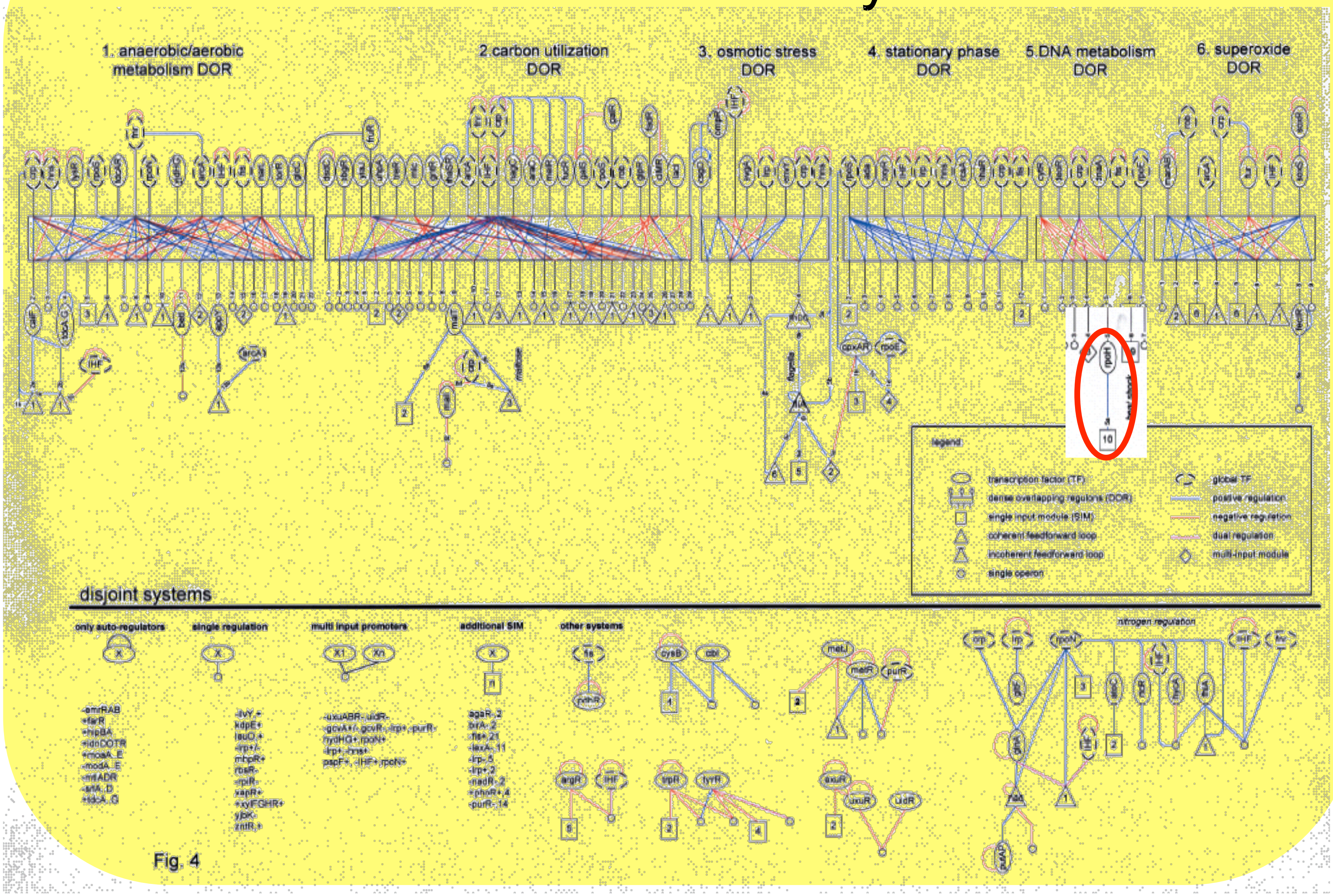


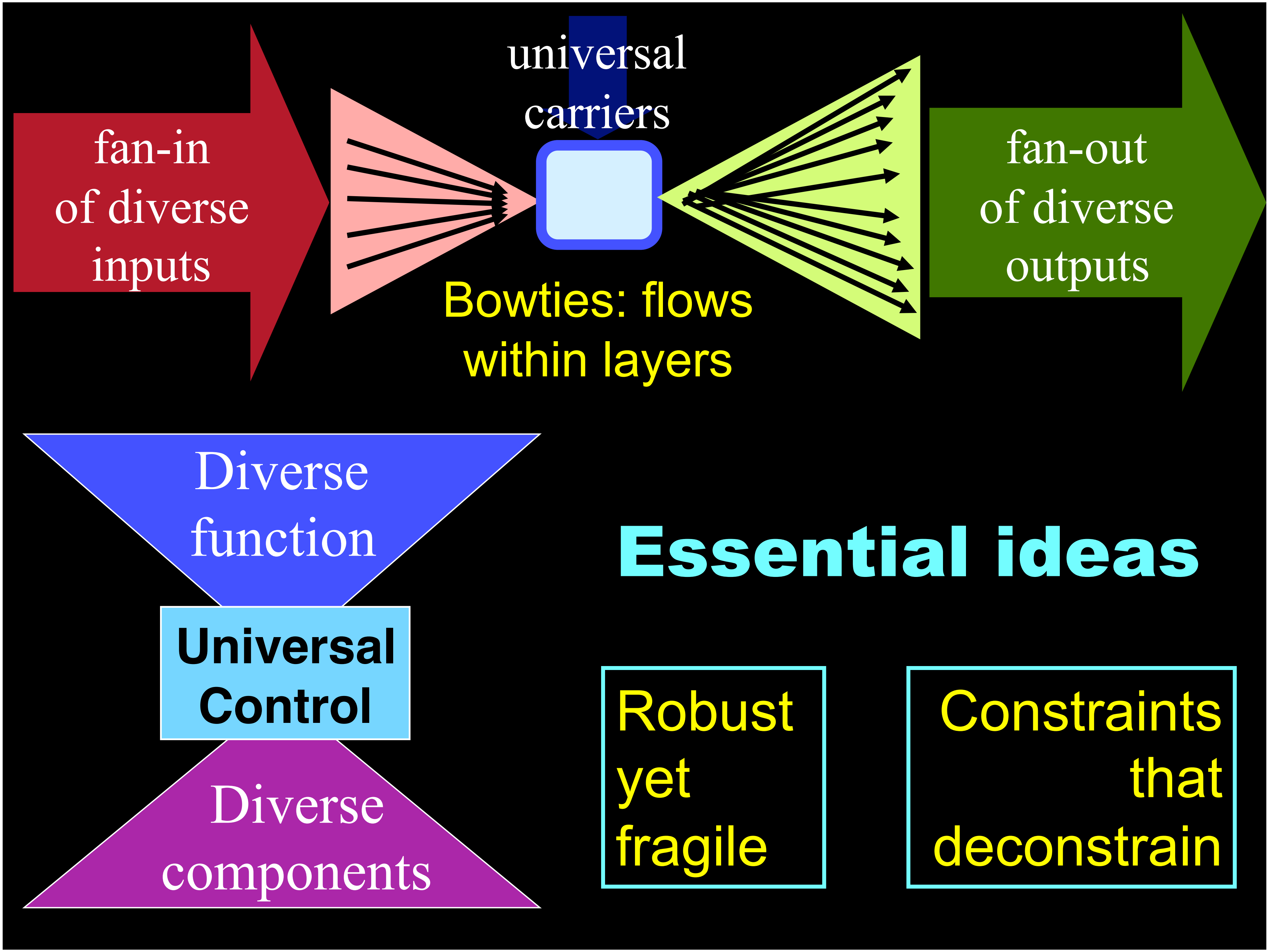

rpoH
σ mRNA
Heat
σ
σ DnaK
Other operons
σ DnaK
DnaK
ftsH
RNAP
Lon
σ RNAP
DnaK
FtsH
Lon

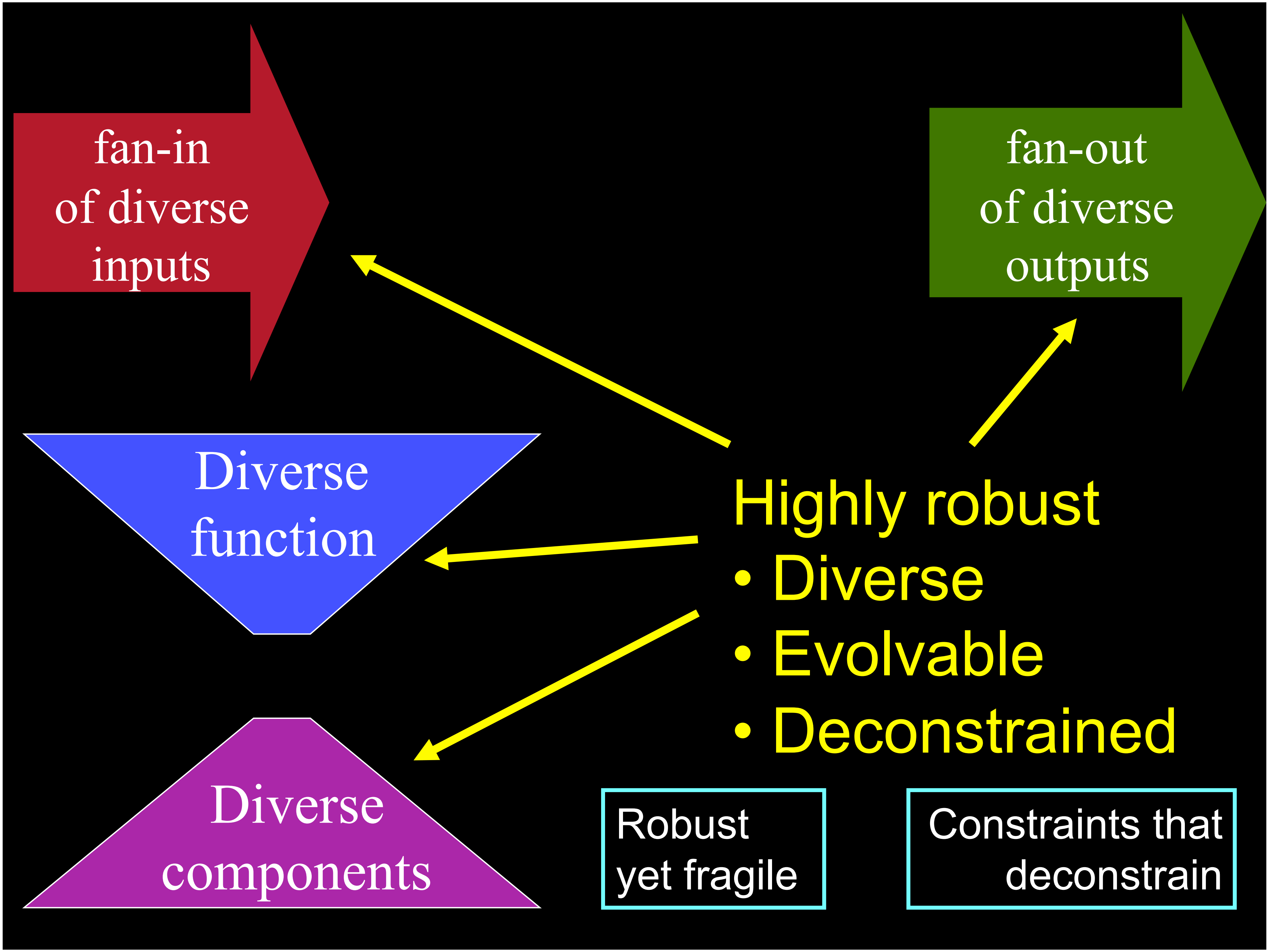

motif
rpoH
Other operons
DnaK
Lon

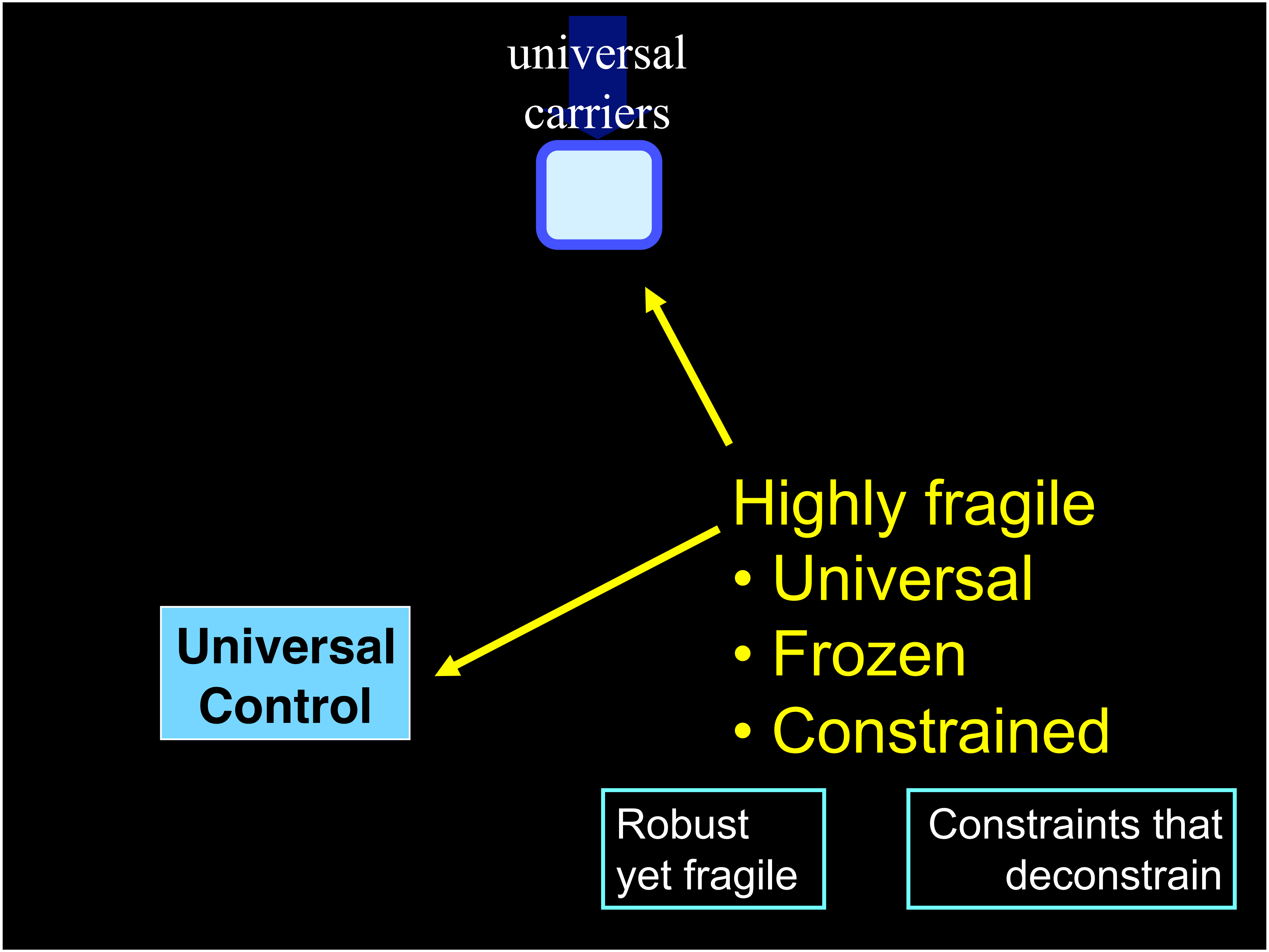

rpoH
heat shock
10

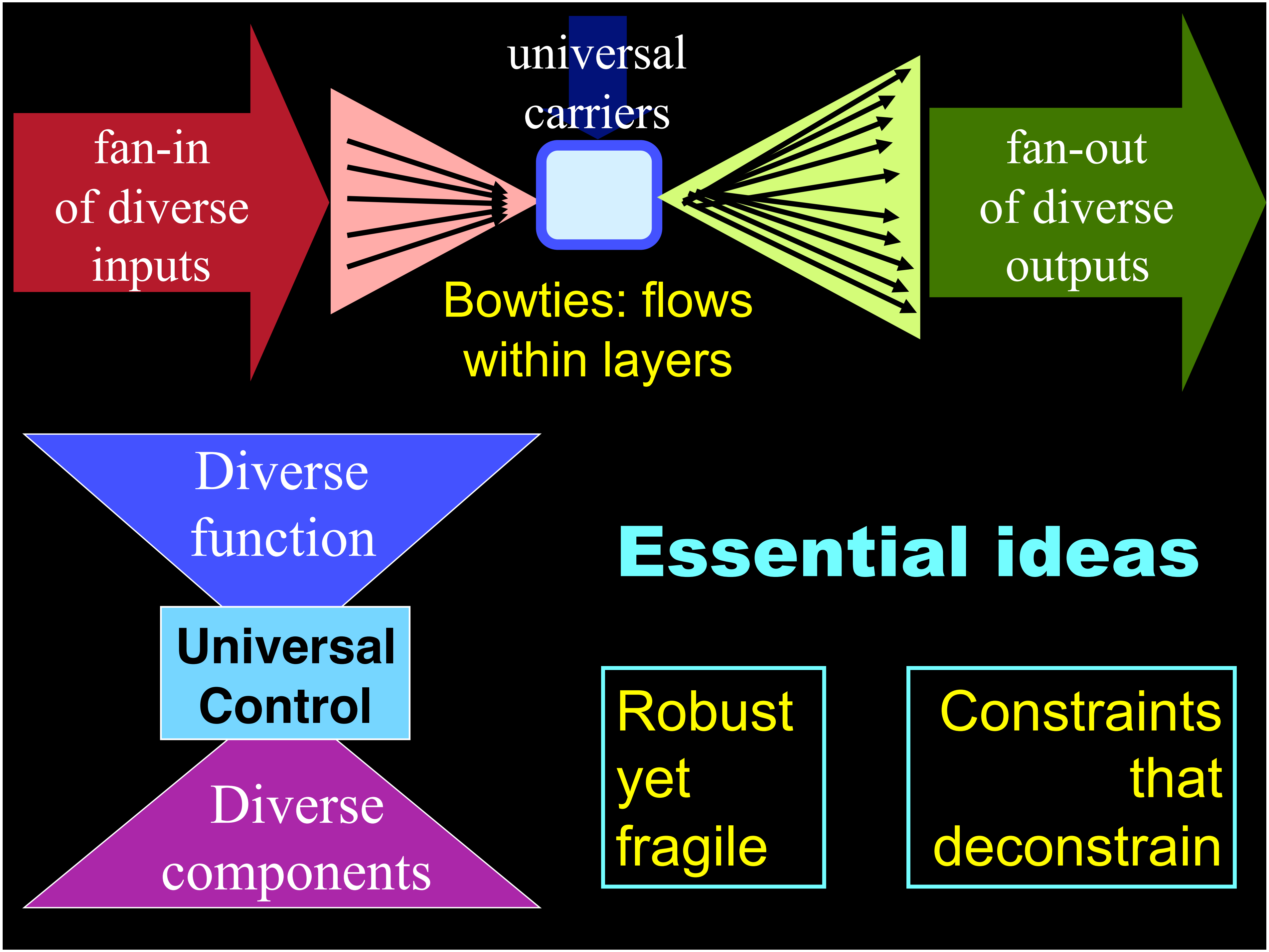
All at the DNA layer




fan-in
of diverse
inputs
universal
carriers
fan-out
of diverse
outputs
Bowties: flows
within layers
Diverse
function
Universal
Control
Diverse
components
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

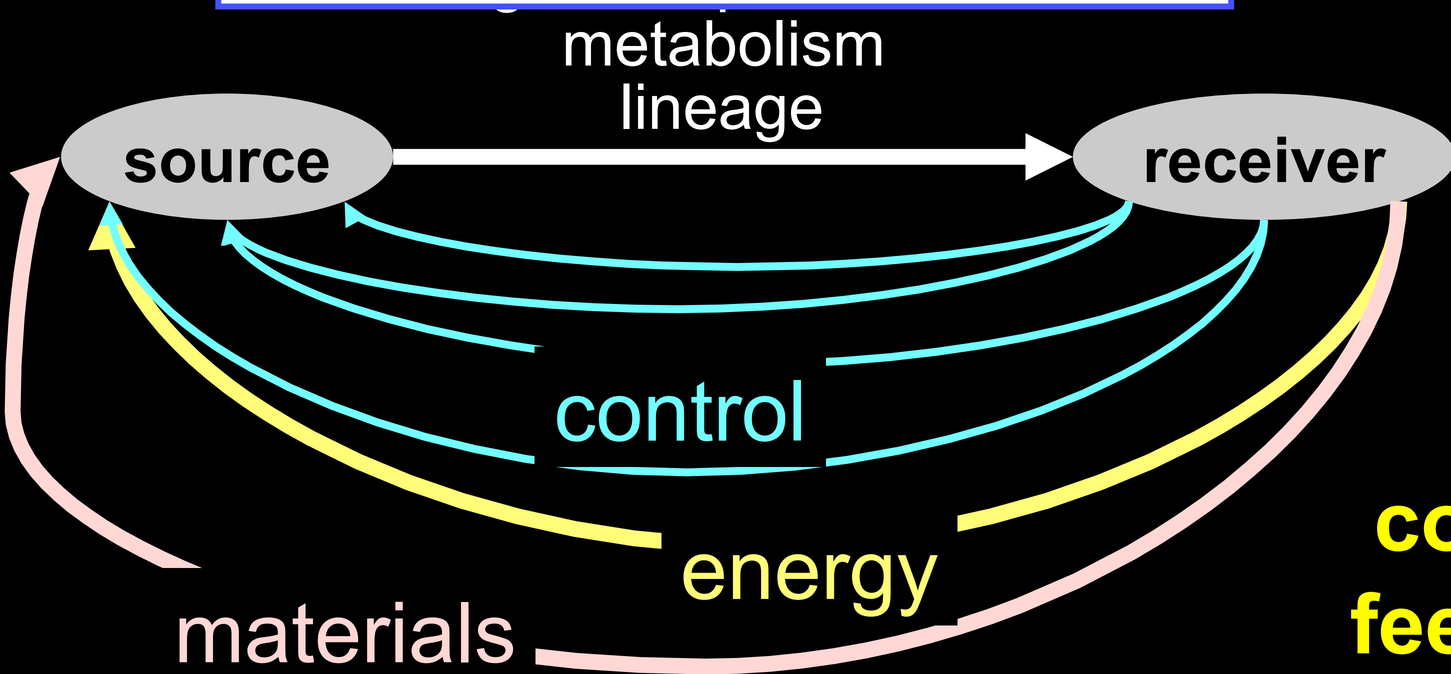

universal
carriers
Highly fragile
• Universal
• Frozen
• Constrained
Universal
Control
Robust
yet fragile
Constraints that
deconstrain



universal carriers
fan-in of diverse inputs
fan-out of diverse outputs
Bowties: flows within layers
Diverse function
Universal Control
Diverse components
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

New fragilities

- Theft, counterfeiting, fraud, and “creative accounting” are now possible
- Need complex legal infrastructure to protect
- The beginning of a growing complexity-fragility spiral