What reviewers say

- "If such oscillations are indeed optimal, why are they not universally present?"
- "The approach to establish universality for all biological and physiological systems is **simply wrong**. It cannot be done…"
- "While the notion of universality is well justified in physics, it is perhaps not so useful in biological sciences and medicine. To develop a set of universal principles for biological and physiological systems is mostly likely **a dream that will never be realized**, due to the vast diversity in such systems."
- "…**does not seem to have an understanding or appreciation** of the vast diversity of biological and physiological systems…"
- "…desire to develop rigorous framework is understandable, but usually this can be done only by imposing a high degree of abstraction, which would then **make the model useless** …"
- "… a mathematical scheme **without any real connections to biological or medical problems**…"

Glycolytic Oscillations and Limits on Robust Efficiency

Fiona A. Chandra,[1]* Gentian Buzi,[2] John C. Doyle[2]

Both engineering and evolution are constrained by trade-offs between efficiency and robustness, but theory that formalizes this fact is limited. For a simple two-state model of glycolysis, we explicitly derive analytic equations for hard trade-offs between robustness and efficiency with oscillations as an inevitable side effect. The model describes how the trade-offs arise from individual parameters, including the interplay of feedback control with autocatalysis of network products necessary to power and catalyze intermediate reactions. We then use control theory to prove that the essential features of these hard trade-off "laws" are universal and fundamental, in that they depend minimally on the details of this system and generalize to the robust efficiency of any autocatalytic network. The theory also suggests worst-case conditions that are consistent with initial experiments.

uvate kinase (PK) produces $q + 1$ molecules of y for a net (normalized) production of one unit, which is consumed in a final reaction modeling the cell's use of ATP. In glycolysis, two ATP molecules are consumed upstream and four are produced downstream, which normalizes to $q = 1$ (each y molecule produces two downstream) with kinetic exponent $a = 1$. To highlight essential trade-offs with the simplest possible analysis, we normalize the concentration such that the unperturbed ($\delta = 0$) steady states are $\bar{y} = 1$ and $\bar{x} = 1/k$ [the system can have one additional steady state, which is unstable when $(1, 1/k)$ is stable]. [See the supporting online material (SOM) part I]. The basal rate of the PFK reaction and the consumption rate have been normalized to 1 (the 2 in the numerator and feedback coefficients of the reactions come from these normalizations). Our results hold for more general systems

Chandra, Buzi, and Doyle

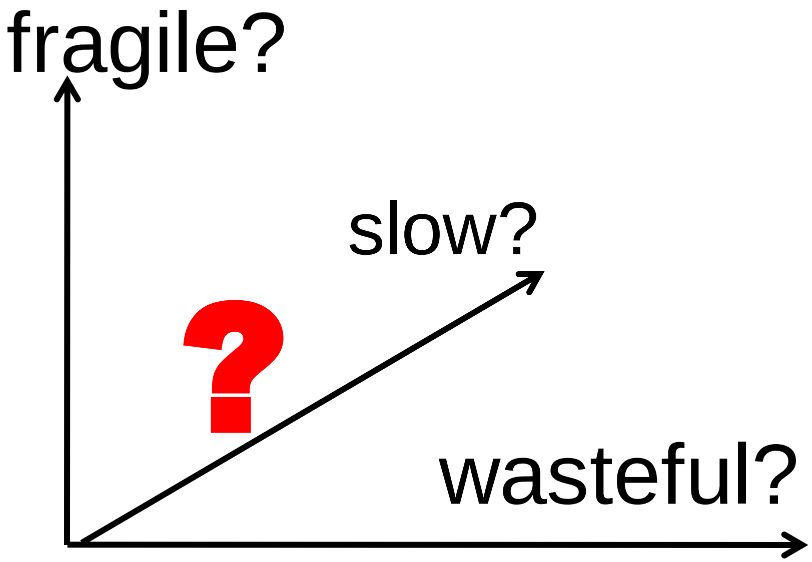
Science

AAAS

Caveats

- Start with paper, give context, brief tutorial
- Won’t repeat what can be read
- Mostly a departure point
- Move quickly to “architecture” (microbial cells)
- Massive topic, lots known, little published
- Fly thru most of the (way too many) slides…
- …all will be posted
- Sorry, if I was smarter this would be better
- Help

From last Monday.



What we want to avoid in ourselves and our technologies

From last Monday.

Architecture, constraints, and behavior

John C. Doyle[a,1] and Marie Csete[b,1]

[a]Control and Dynamical Systems, California Institute of Technology, Pasadena, CA 91125; and [b]Department of Anesthesiology, University of California, San Diego, CA 92103

Edited by Donald W. Pfaff, The Rockefeller University, New York, NY, and approved June 10, 2011 (received for review March 3, 2011)

and zombies

This paper aims to bridge progress in neuroscience involving sophisticated quantitative analysis of behavior, including the use of robust control, with other relevant conceptual and theoretical frameworks from systems engineering, systems biology, and mathematics. Familiar and accessible case studies are used to illustrate concepts of robustness, organization, and architecture (modularity and protocols) that are central to understanding complex networks. These essential organizational features are hidden during normal function of a system but are fundamental for understanding the nature, design, and function of complex biologic and technologic systems.

evolved for sensorimotor control and retain much of that evolved architecture, then the apparent distinctions between perceptual, cognitive, and motor processes may be another form of illusion (9), reinforcing the claim that robust control and adaptive feedback (7, 11) rather than more conventional serial signal processing might be more useful in interpreting neurophysiology data (9). This view also seems broadly consistent with the arguments from grounded cognition that modal simulations, bodily states, and situated action underlie not only motor control but cognition in general (12), including language (13). Furthermore, the myriad constraints involved in the evolution of circuit

Doyle and Csete, *Proc Nat Acad Sci USA, online* JULY 25 2011

IEEE TRANS ON SYSTEMS, MAN, AND CYBERNETICS, JULY 2010, Alderson and Doyle

IEEE TRANSACTIONS ON SYSTEMS, MAN, AND CYBERNETICS—PART A: SYSTEMS AND HUMANS, VOL. 40, NO. 4, JULY 2010 839

Contrasting Views of Complexity and Their Implications For Network-Centric Infrastructures

David L. Alderson, *Member, IEEE*, an[illegible] C. Doyle

Fundamentals?

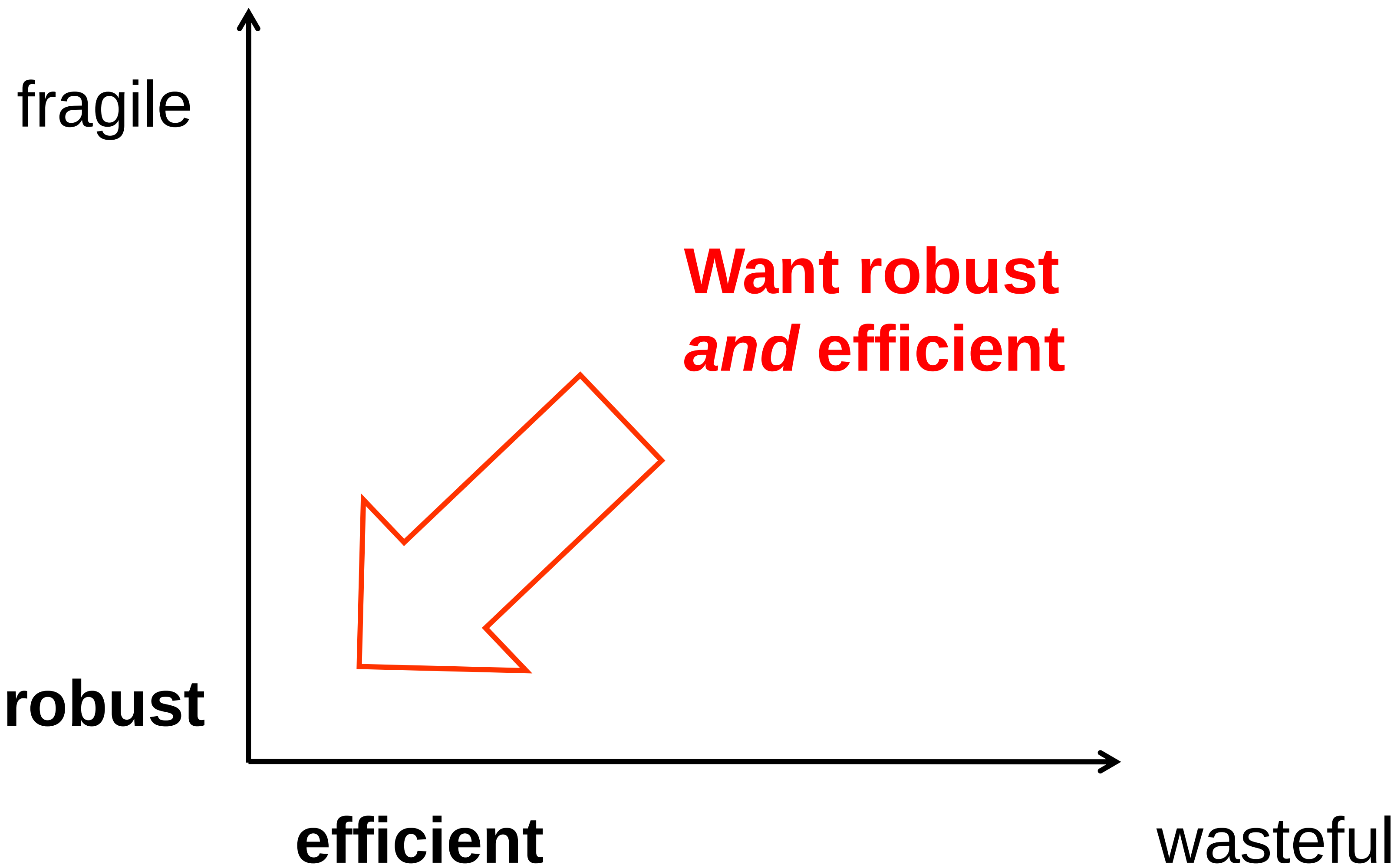
Abstract**—There exists a widely recognized ne[illegible] derstand and manage complex "systems of [illegible] biology, ecology, and medicine to [illegible] This is motivating the search for [illegible] systems and driving demand for [illegible] methods that are consistent, integrative, and [illegible] However, the theoretical frameworks available today [illegible] not merely fragmented but sometimes contradictory and incompatible. We argue that complexity arises in highly evolved biological and technological systems primarily to provide mechanisms to create robustness. However, this complexity itself can be a source of new fragility, leading to "robust yet fragile" tradeoffs in system design. We focus on the role of robustness and architecture in networked infrastructures, and we highlight recent advances in the theory of distributed control driven by network technologies. This view of complexity in highly organized technological and biological systems is fundamentally different from the dominant perspective in the mainstream sciences, which downplays function, constraints, and tradeoffs, and tends to minimize the role of organization and design.**

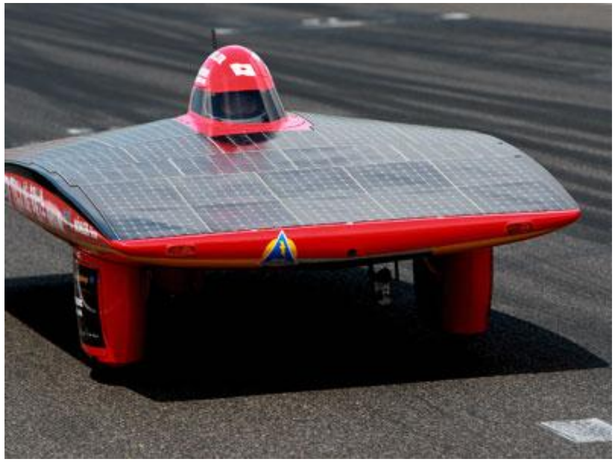
Index Terms**—Architecture, complexity theory, networks, optimal control, optimization methods, protocols.**

[illegible] engineering systems, but much of advanced [illegible]nology has, if anything, made things worse. Computer-based simulation and rapid prototyping tools are now broadly available and powerful enough that it is relatively easy to demonstrate almost anything, provided that conditions are made sufficiently idealized. We are much better at designing, mass-producing, and deploying network-enabled devices than we are at being able to predict or control their collective behavior once deployed in the real world. The result is that, when things fail, they often do so cryptically and catastrophically.

The growing need to understand and manage complex systems of systems, ranging from biology to technology, is creating demand for new mathematics and methods that are consistent and integrative. Yet, there exist fundamental incompatibilities in available theories for addressing this challenge. Various "new sciences" of "complexity" and "networks" dominate the mainstream sciences [3] but are at best disconnected from medicine, mathematics, and engineering. Computing, communication, and control theories and technologies flourish but

Collapsing many dimensions





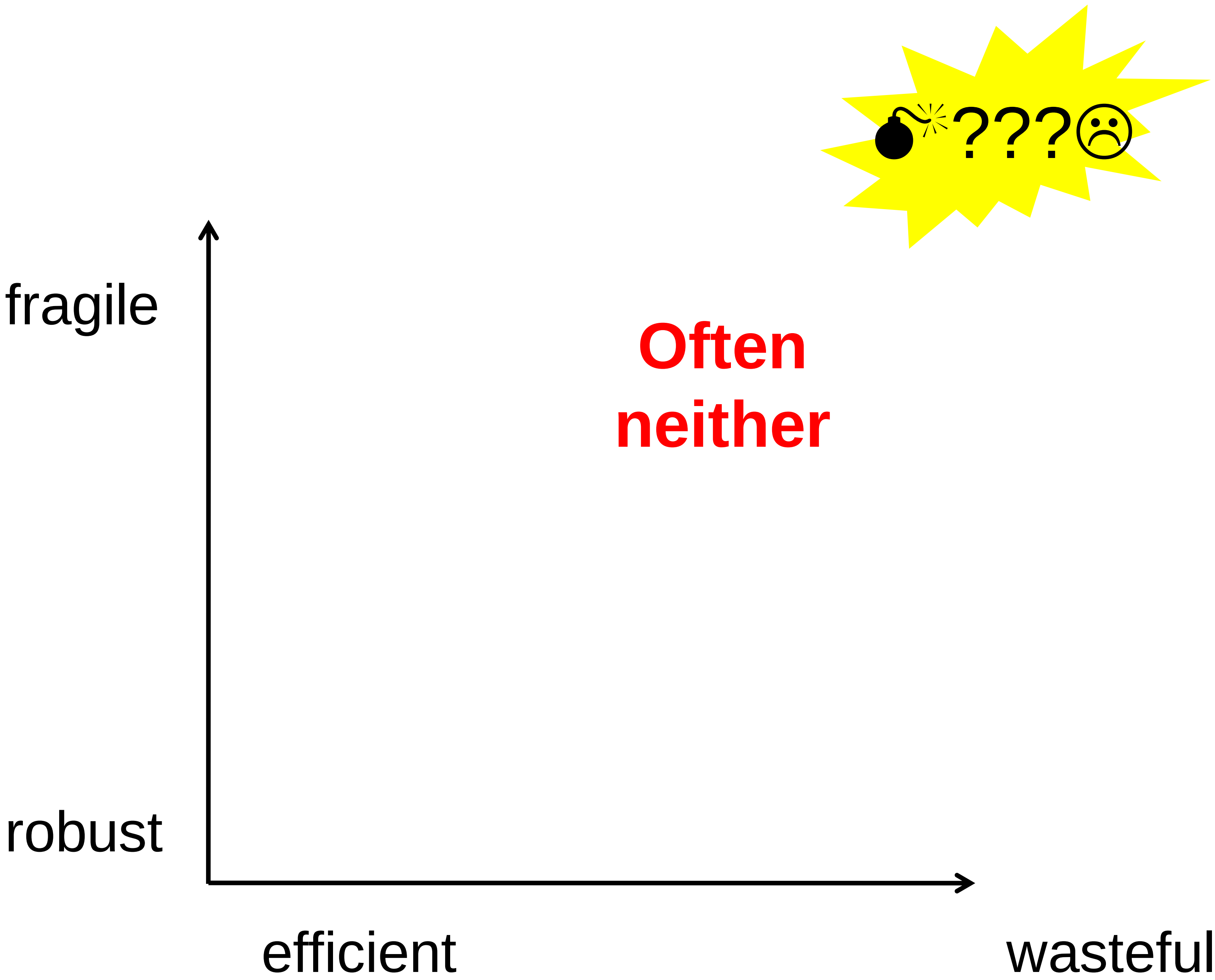
fragile

At best we get one

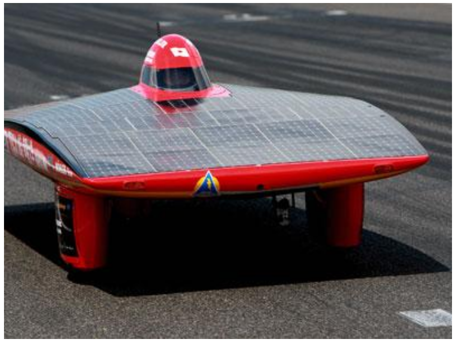
robust

efficient

wasteful



💣*???☹
fragile
Often
neither
robust
efficient
wasteful



💣???☹

Bad architectures?

fragile

?

gap?

Bad theory?

?

robust

efficient

wasteful

Control

Bode

Comms

Shannon

Theory?

Deep, but fragmented, incoherent, incomplete

Carnot

Turing

Boltzmann

Godel

Heisenberg

Compute

Physics

Einstein

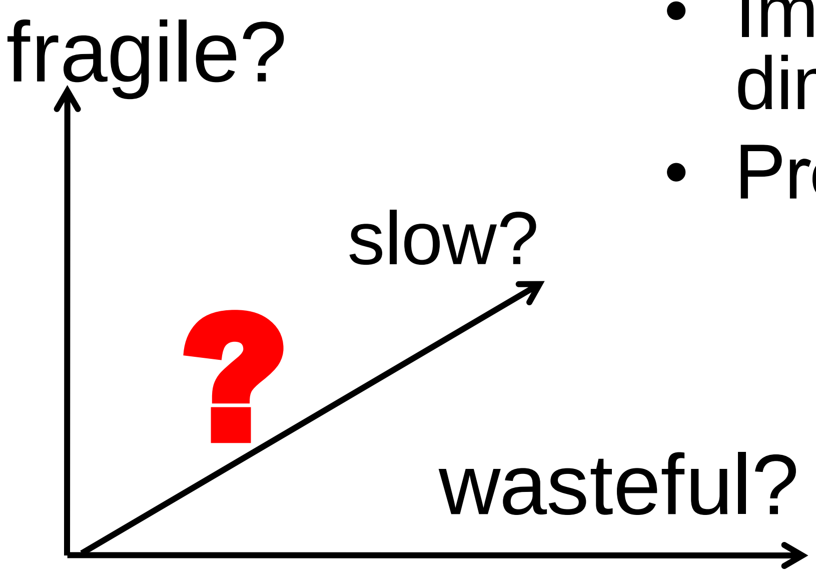
Control

Comms

Bode

Shannon

- Each theory ≈ one dimension
- Important tradeoffs ***across*** dimensions
- Progress is encouraging but…



Carnot

Turing

Boltzmann

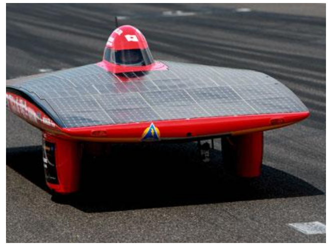
Godel

Heisenberg

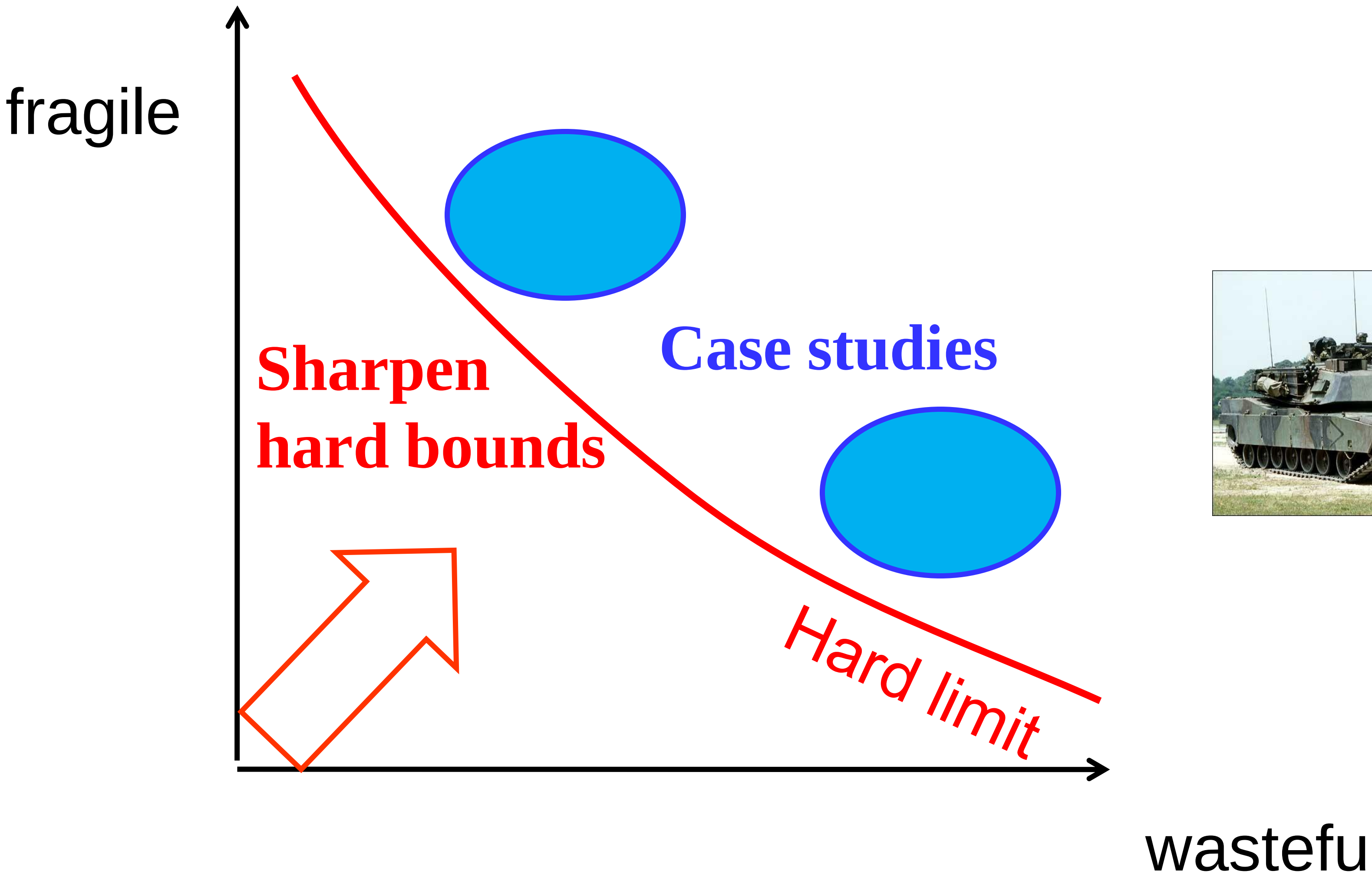
Compute

Physics

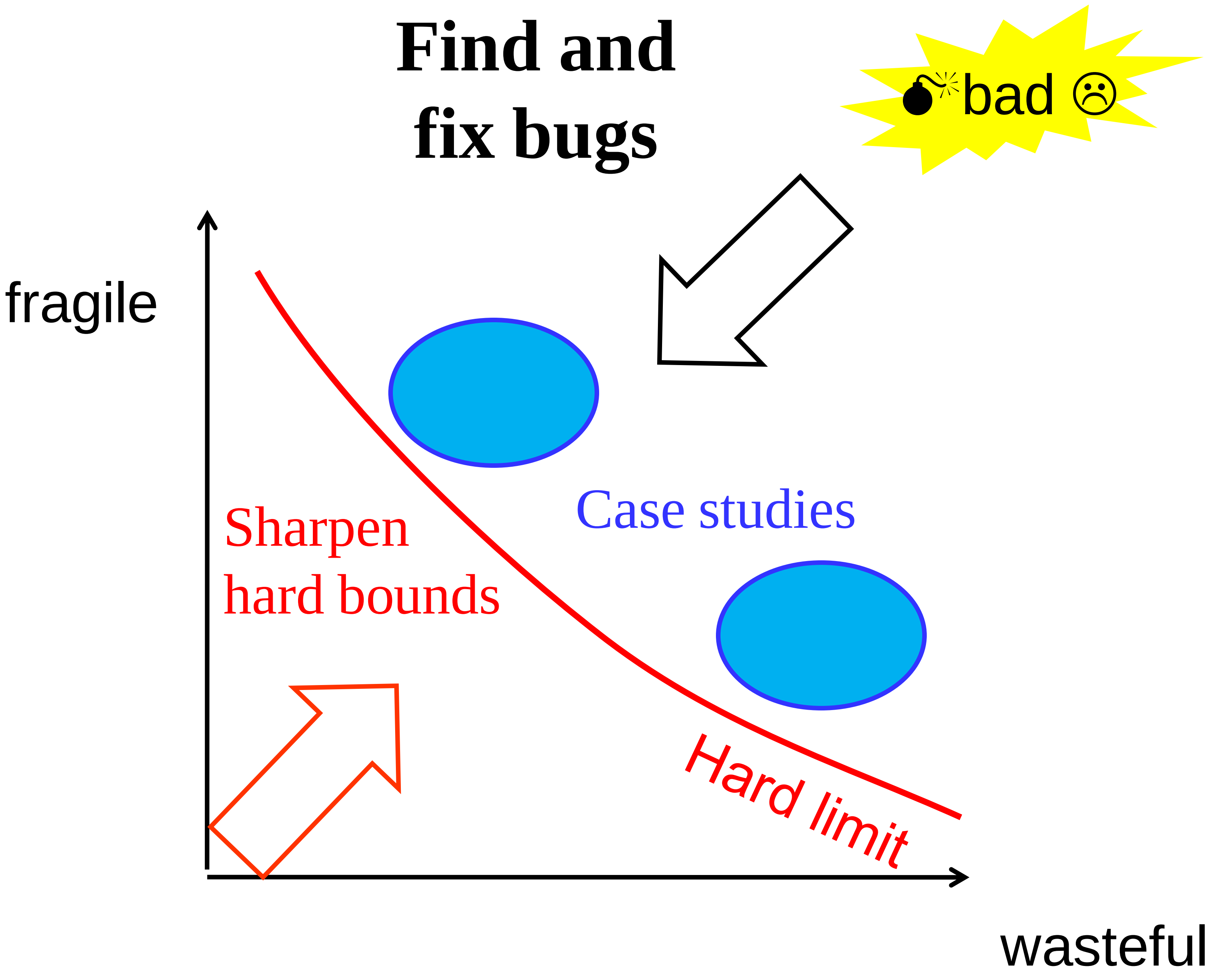
Einstein



Conservation “laws”?



Find and fix bugs



Theory + biology case study

- Longstanding mystery (century? millennia?)
- ~~"Universal"~~ very very very common issues
- Components "well-known"
- Experimentally accessible
- Evolution + physiology + "CDS/CME"
- Broadly relevant

- Extreme responses typical

What reviewers say

- “If such oscillations are indeed optimal, why are they not universally present?”
- “The approach to establish universality for all biological and physiological systems is **simply wrong**. It cannot be done…”
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- “… a mathematical scheme **without any real connections to biological or medical problems**…”

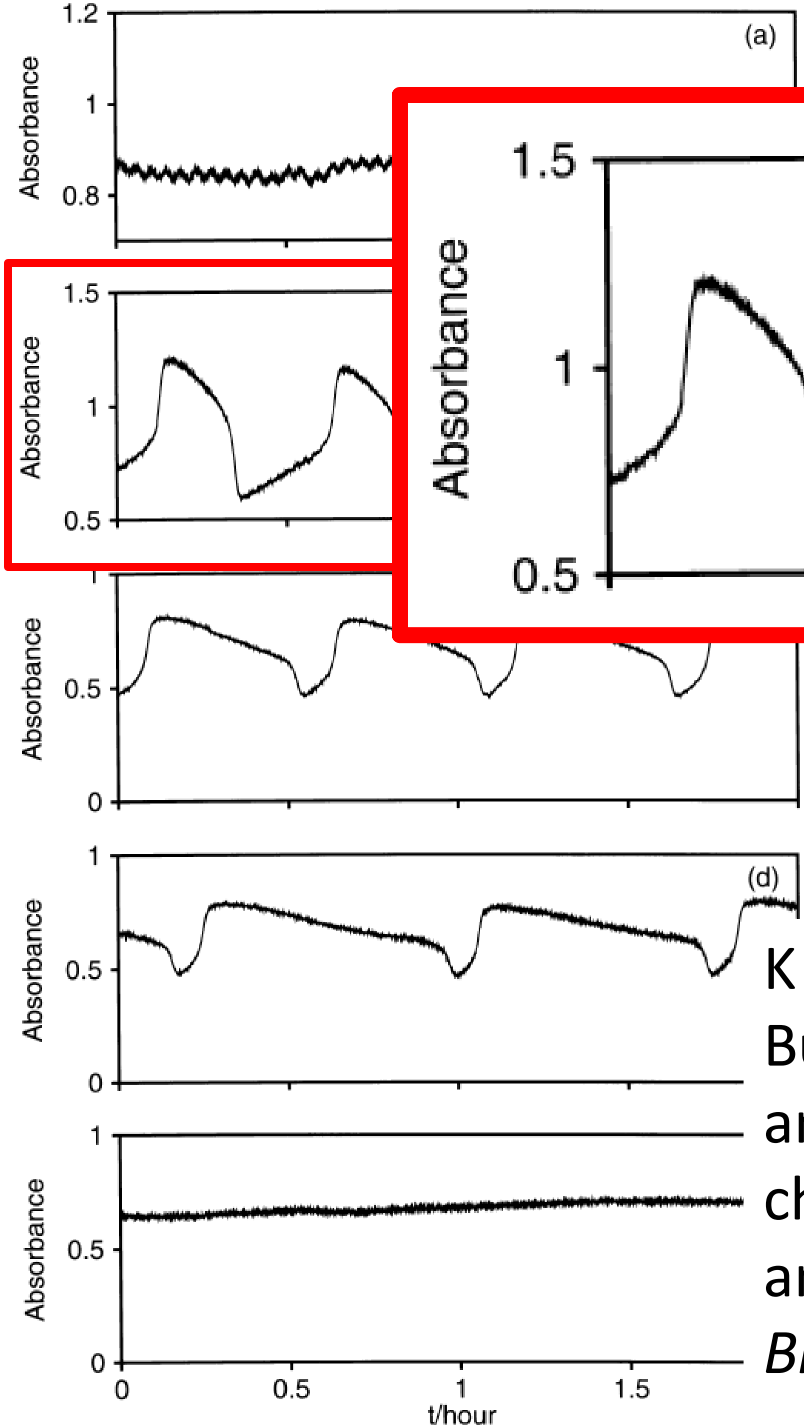
Glycolytic oscillations

Hard tradeoffs between

1. **Fragility** (disturbance rejection)
2. Amount (of enzymes)
3. Complexity (of enzymes)

} **Metabolic overhead** (covers items 2 and 3)

- Most ubiquitous/studied "circuit" in science/engineering
- New insights and experiments



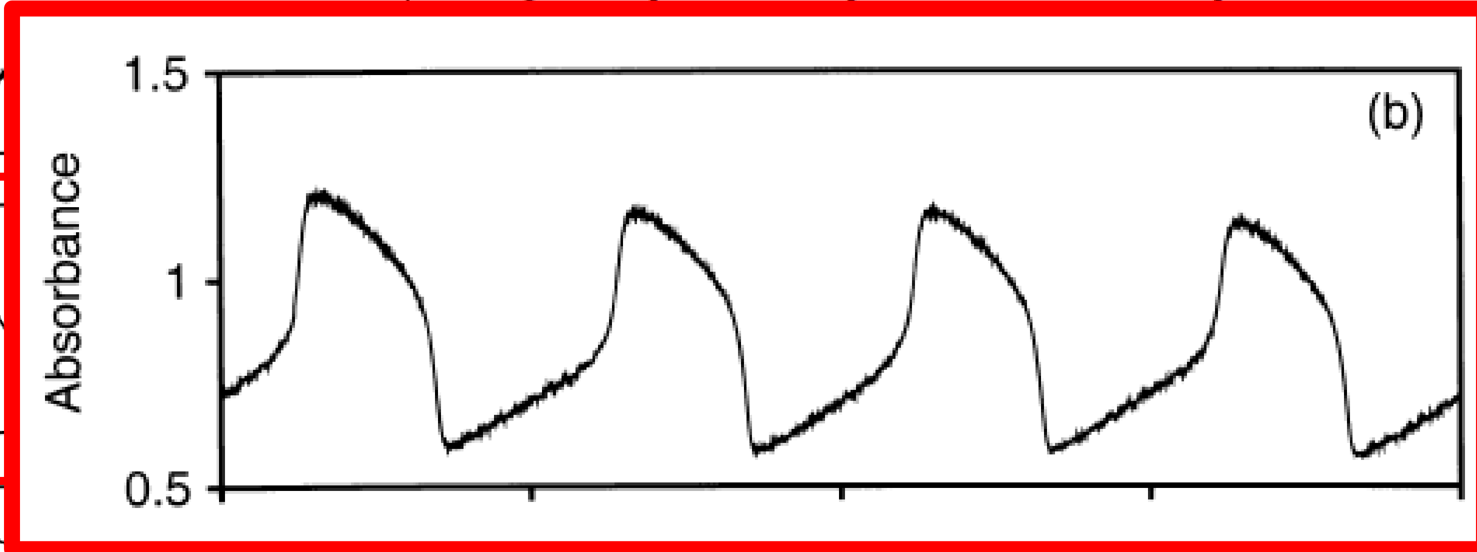


Fig. 2. Dependence of pattern on flow rate. Experimental time

tion becomes longer (b–d), and at the highest flow rate (e), the state is stationary.

Experiments

K Nielsen, PG Sorensen, F Hynne, H-G Busse. **Sustained oscillations in glycolysis**: an experimental and theoretical study of chaotic and complex periodic behavior and of quenching of simple oscillations. *Biophys Chem* 72:49-62 (1998).

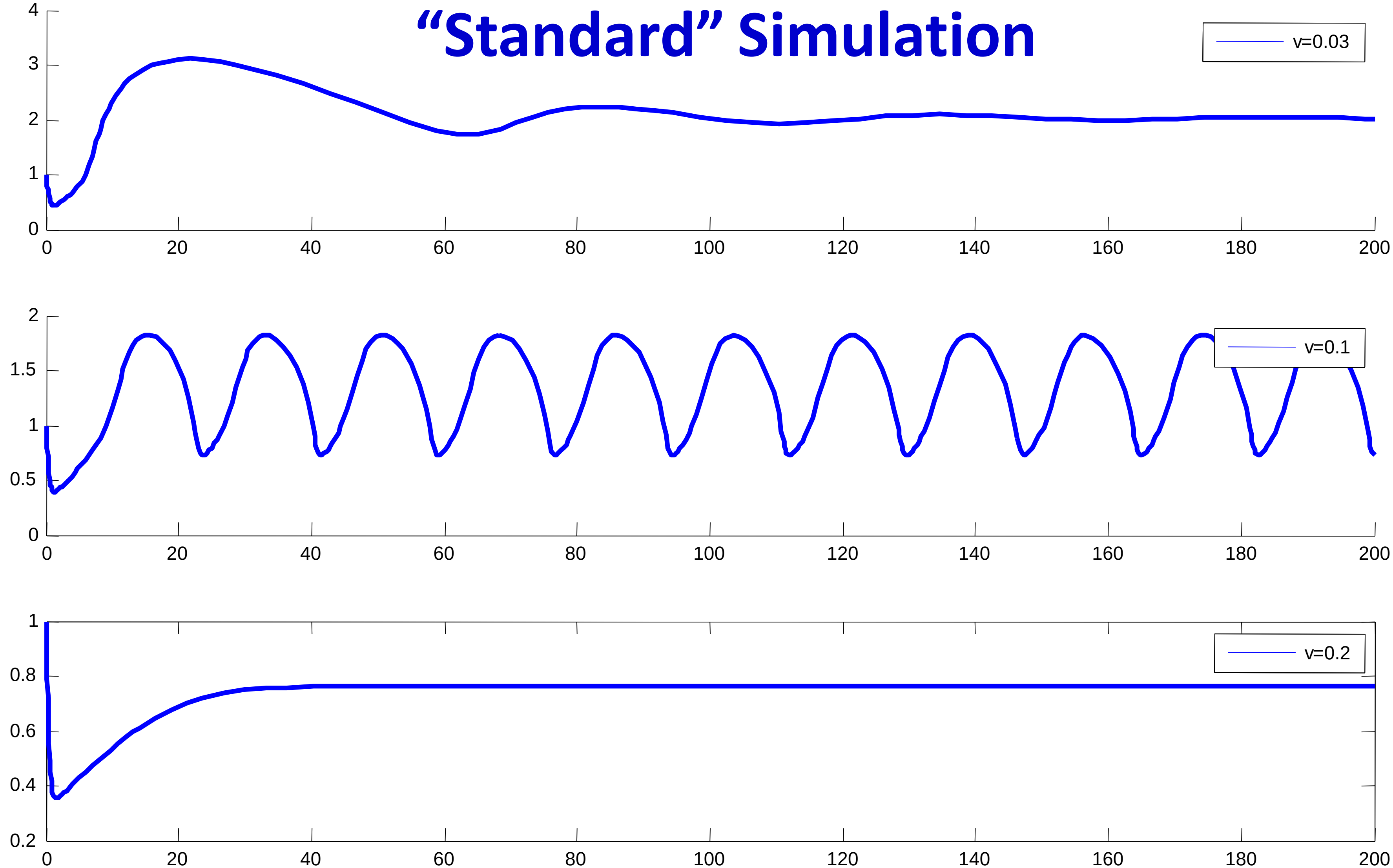
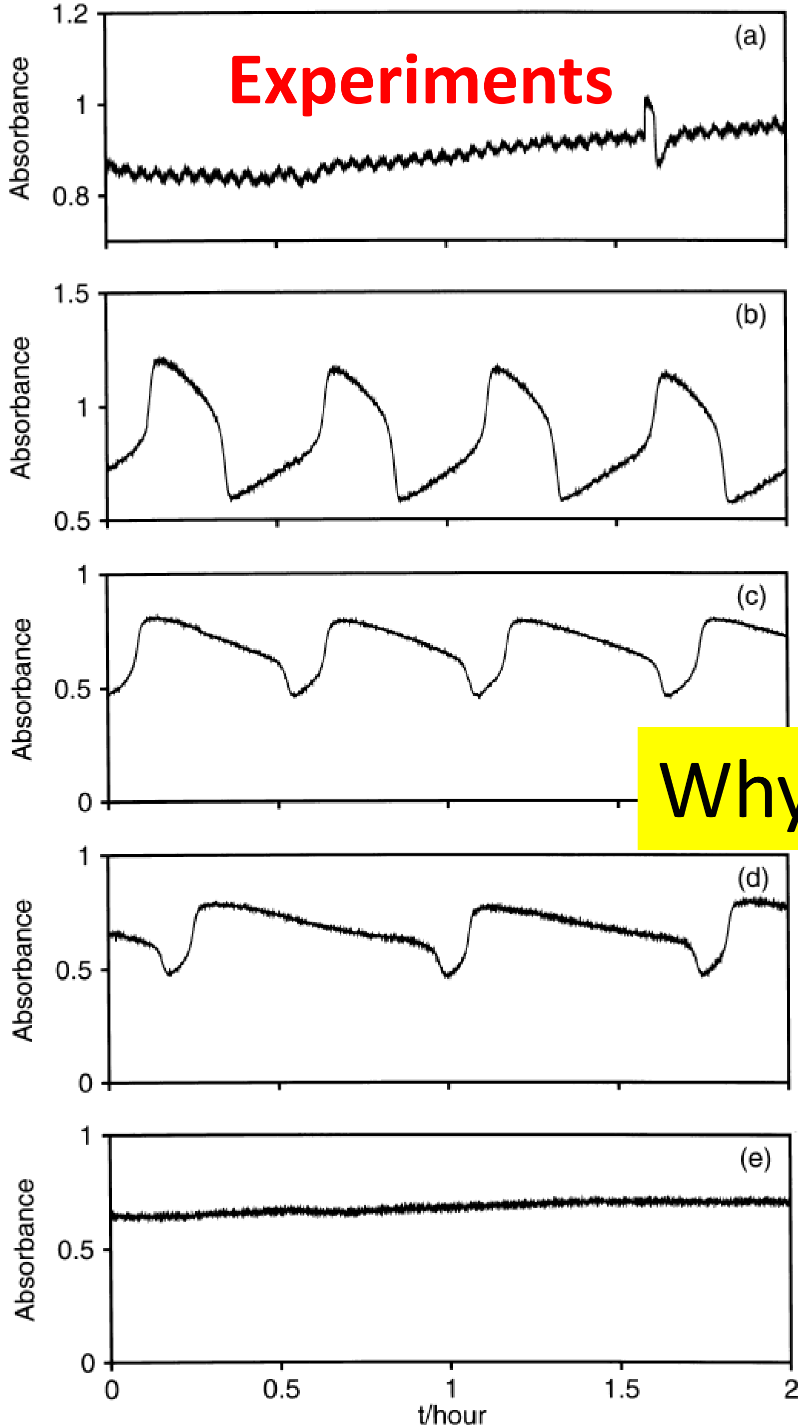
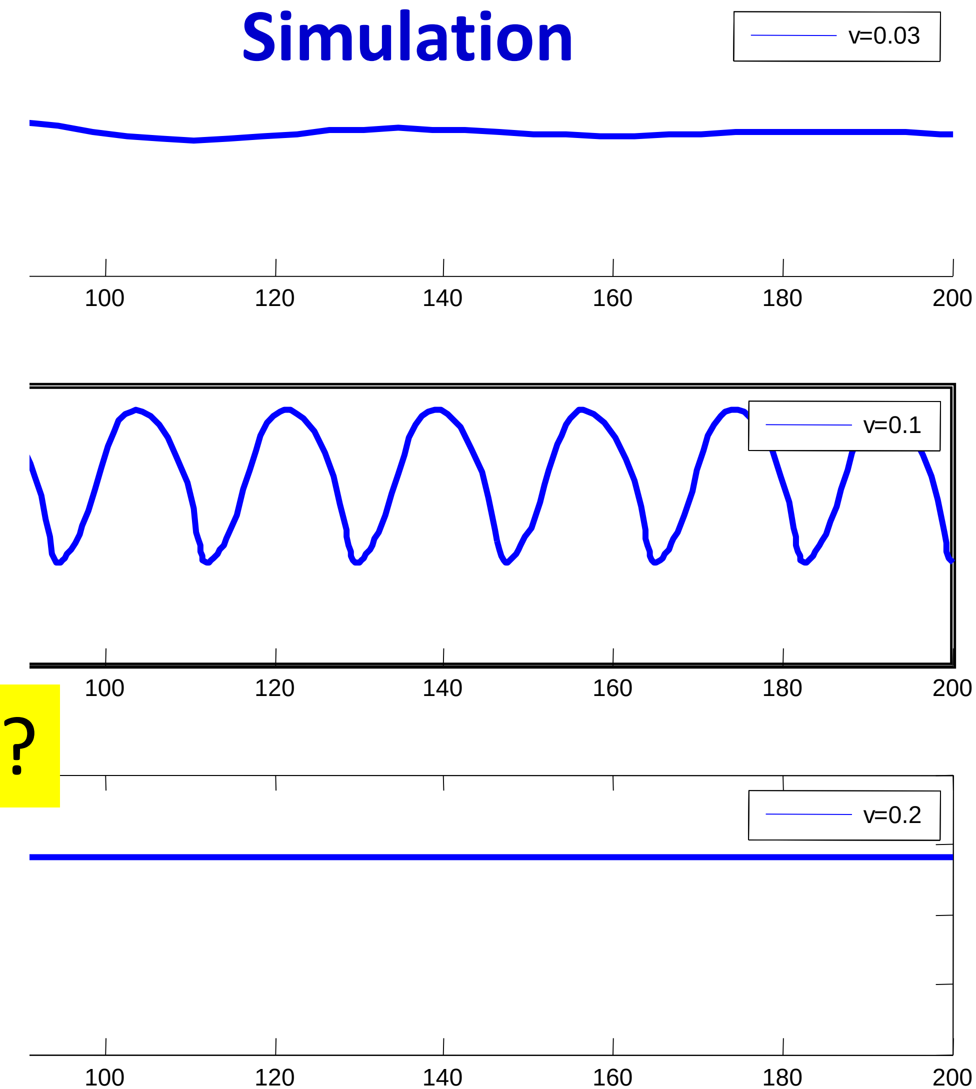


Figure S4. Simulation of two state model (S7.1) qualitatively recapitulates experimental observation from CSTR studies [5] and [12]. As the flow of material in/out of the system is increased, the system enters a limit cycle and then stabilizes again. For this simulation, we take *q=a=Vm=1, k=0.2, g=1, u=0.01, h=2.5.*



Why?



ɔdel (S7.1) qualitatively recapitulates
studies [5] and [12]. As the flow of material
: system enters a limit cycle and then
ve take *q=a=Vm=1, k=0.2, g=1, u=0.01, h=2.5.*

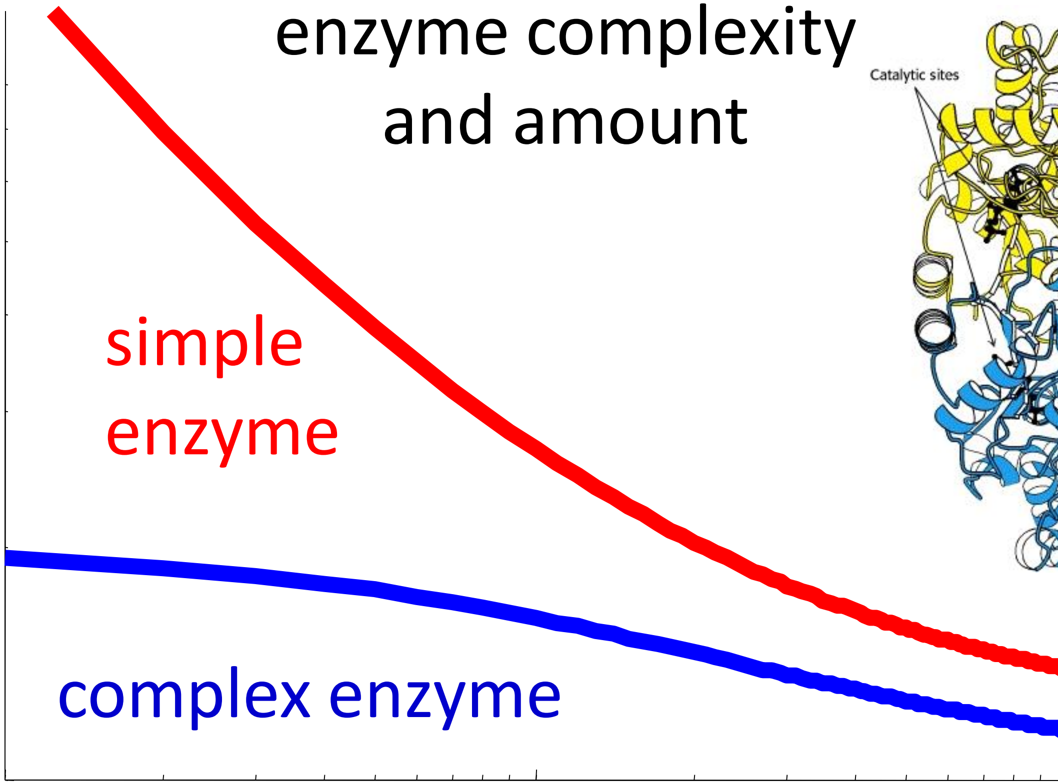
Why?

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

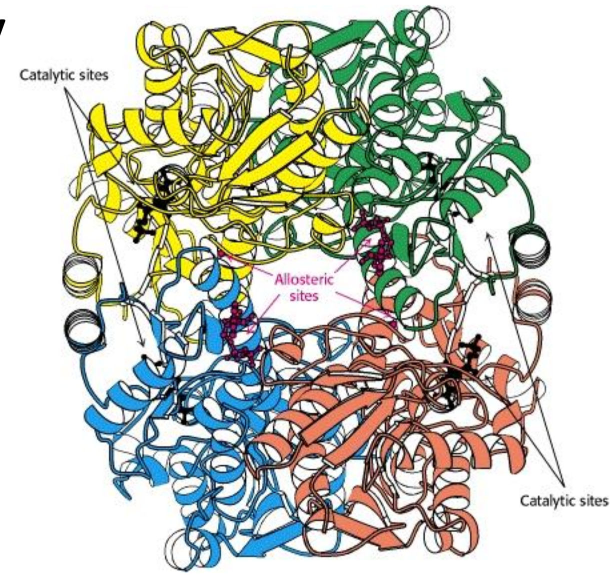
z and p functions of enzyme complexity and amount

Fragility

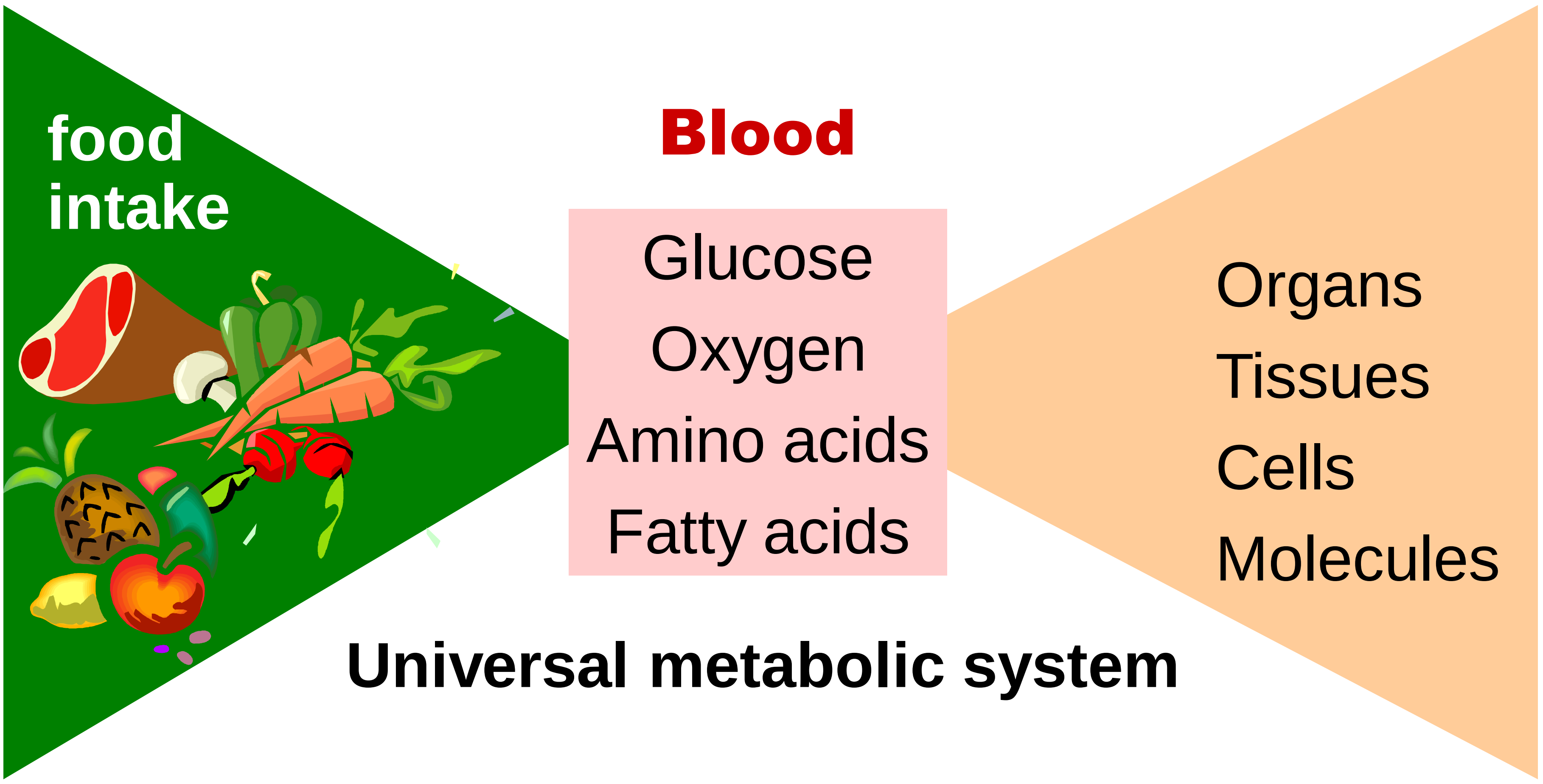
$$\ln\left|\frac{z+p}{z-p}\right|$$

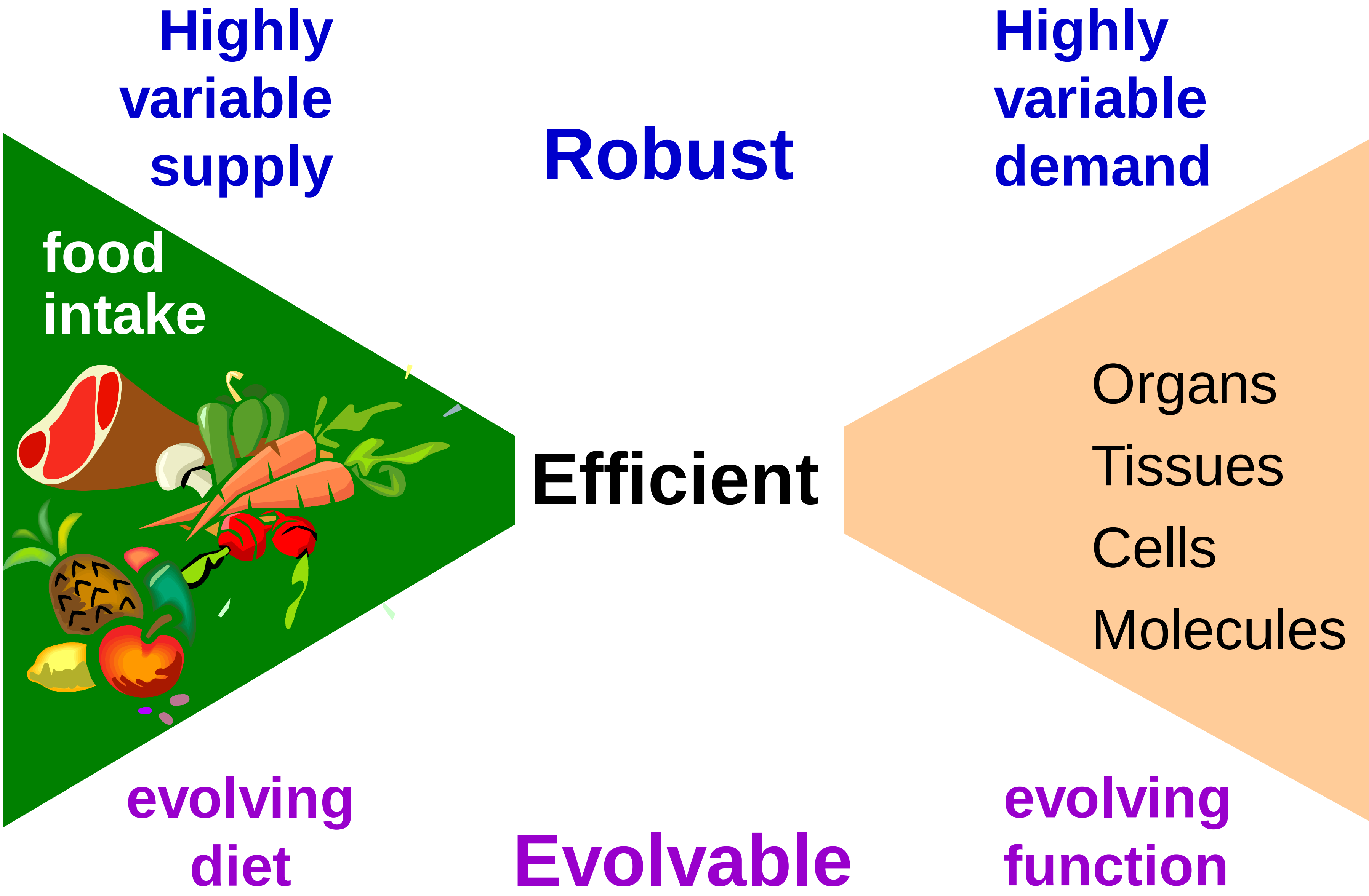


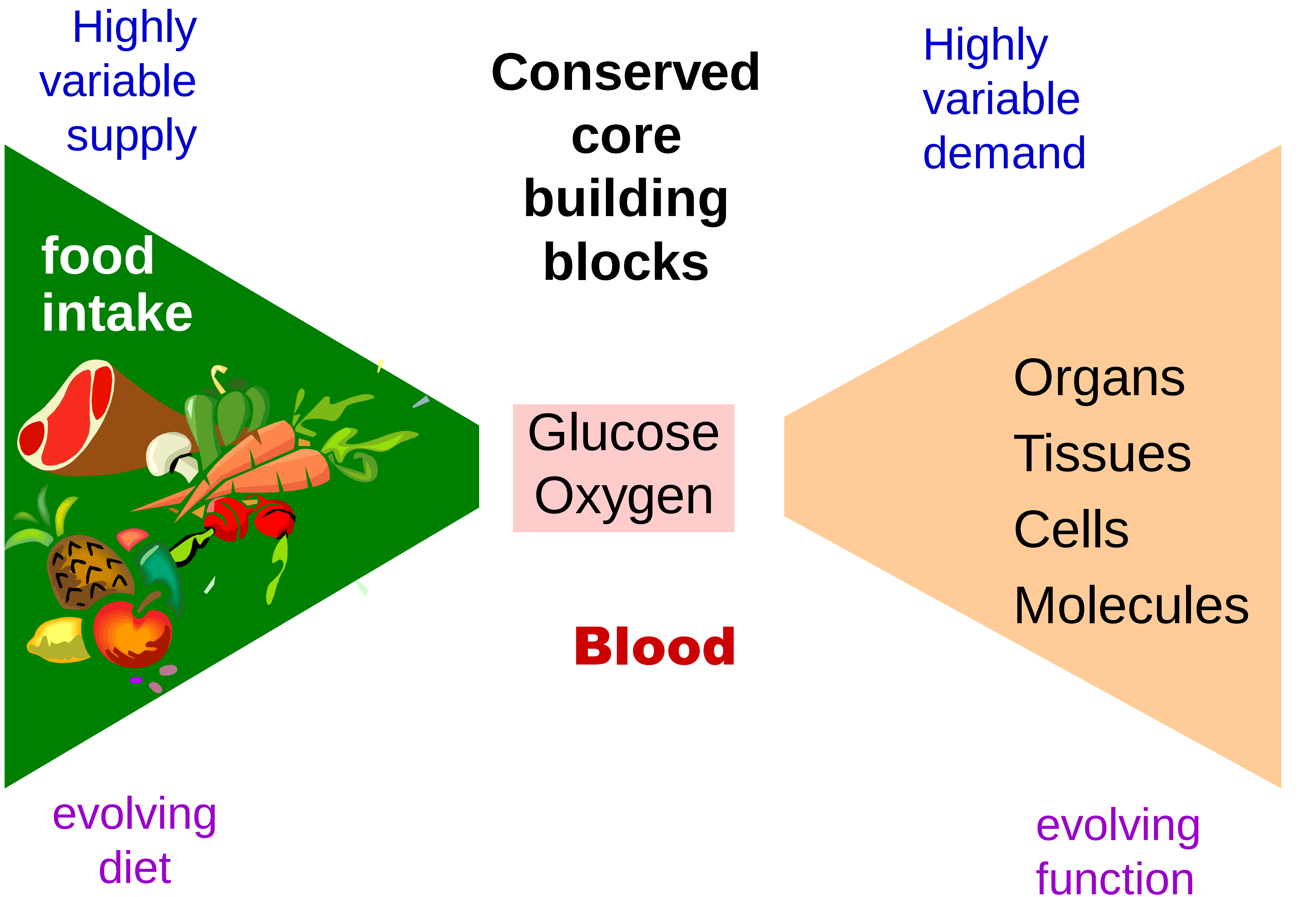
Enzyme amount



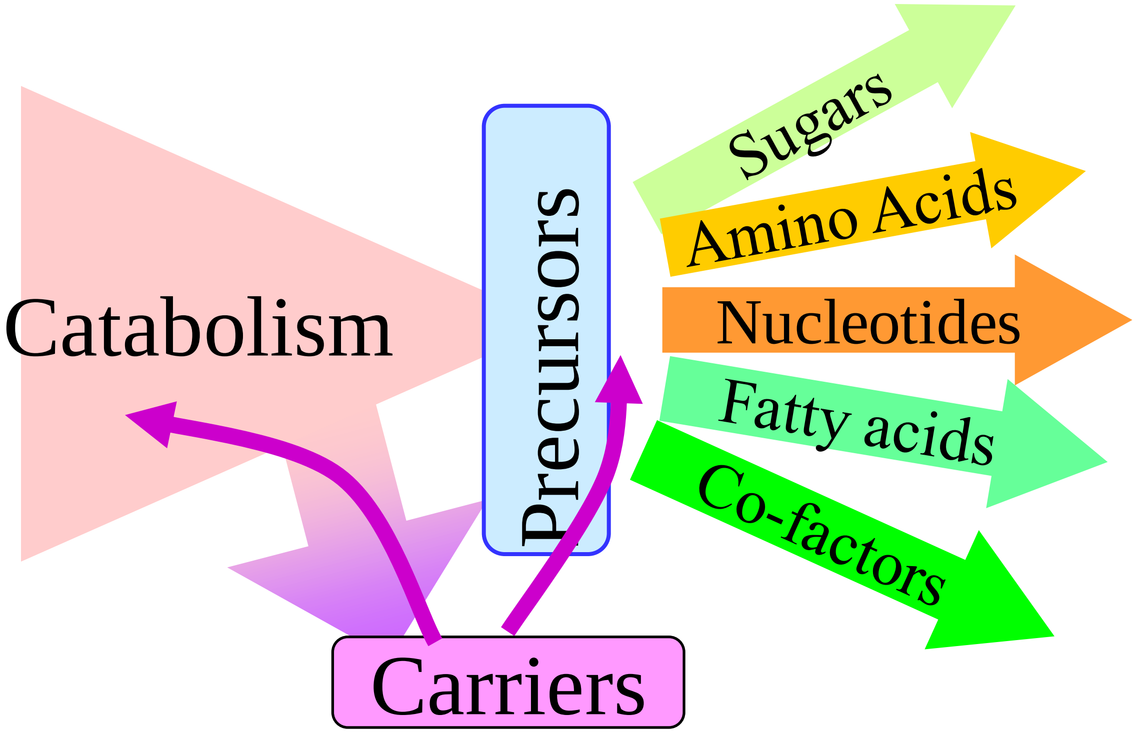
Peter Sterling and Allostasis




Highly variable supply
food intake
Robust
Highly variable demand
Efficient
Organs
Tissues
Cells
Molecules
evolving diet
Evolvable
evolving function

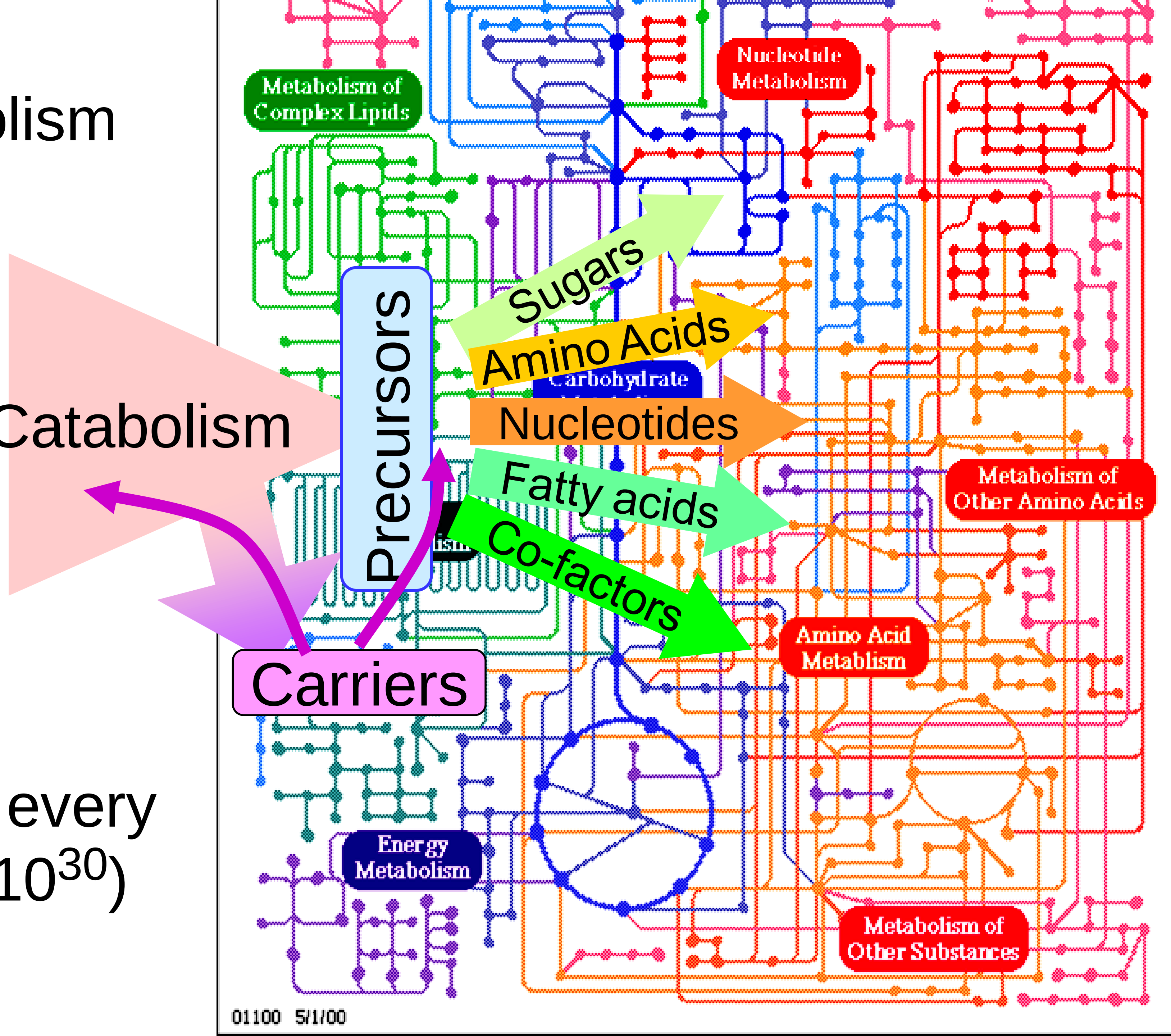

Highly variable supply
Conserved core building blocks
Highly variable demand
food intake
Glucose
Oxygen
Organs
Tissues
Cells
Molecules
Blood
evolving diet
evolving function

Inside every cell

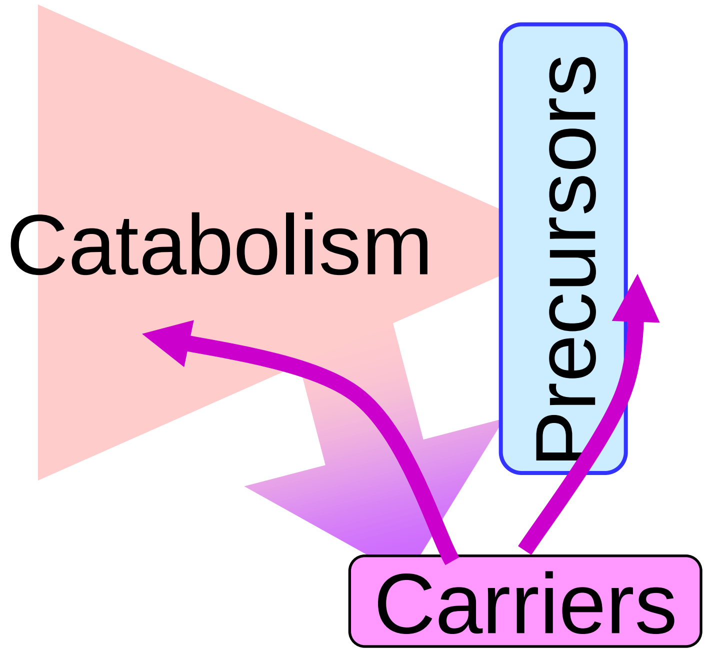


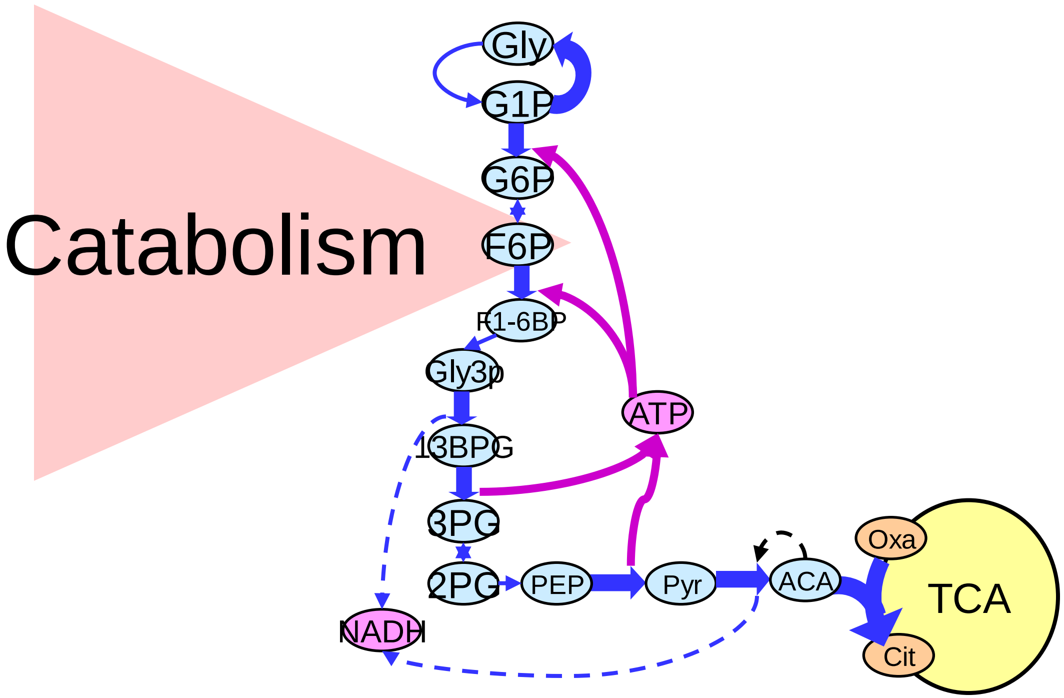
Core metabolic bowtie

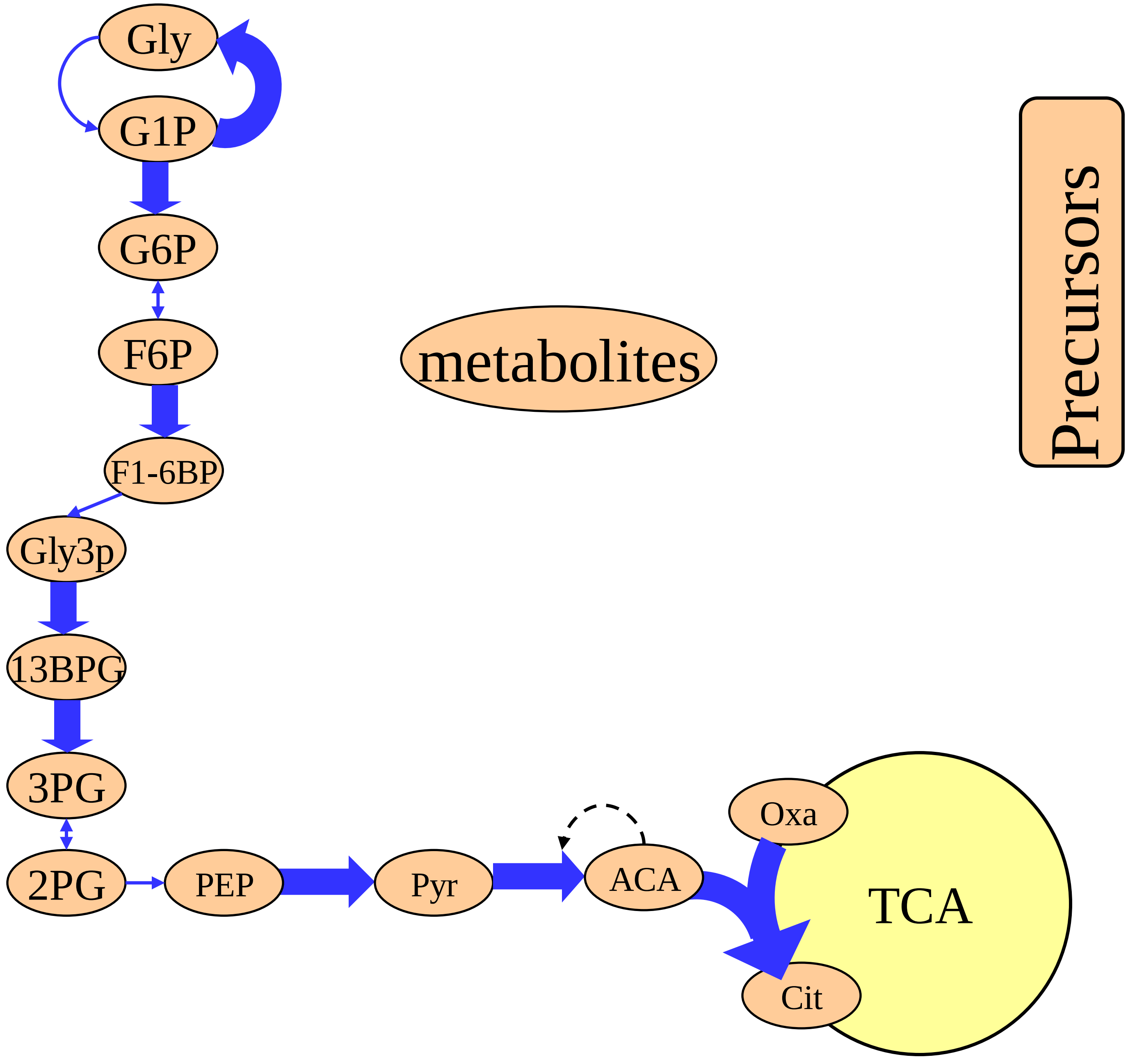
Core metabolism

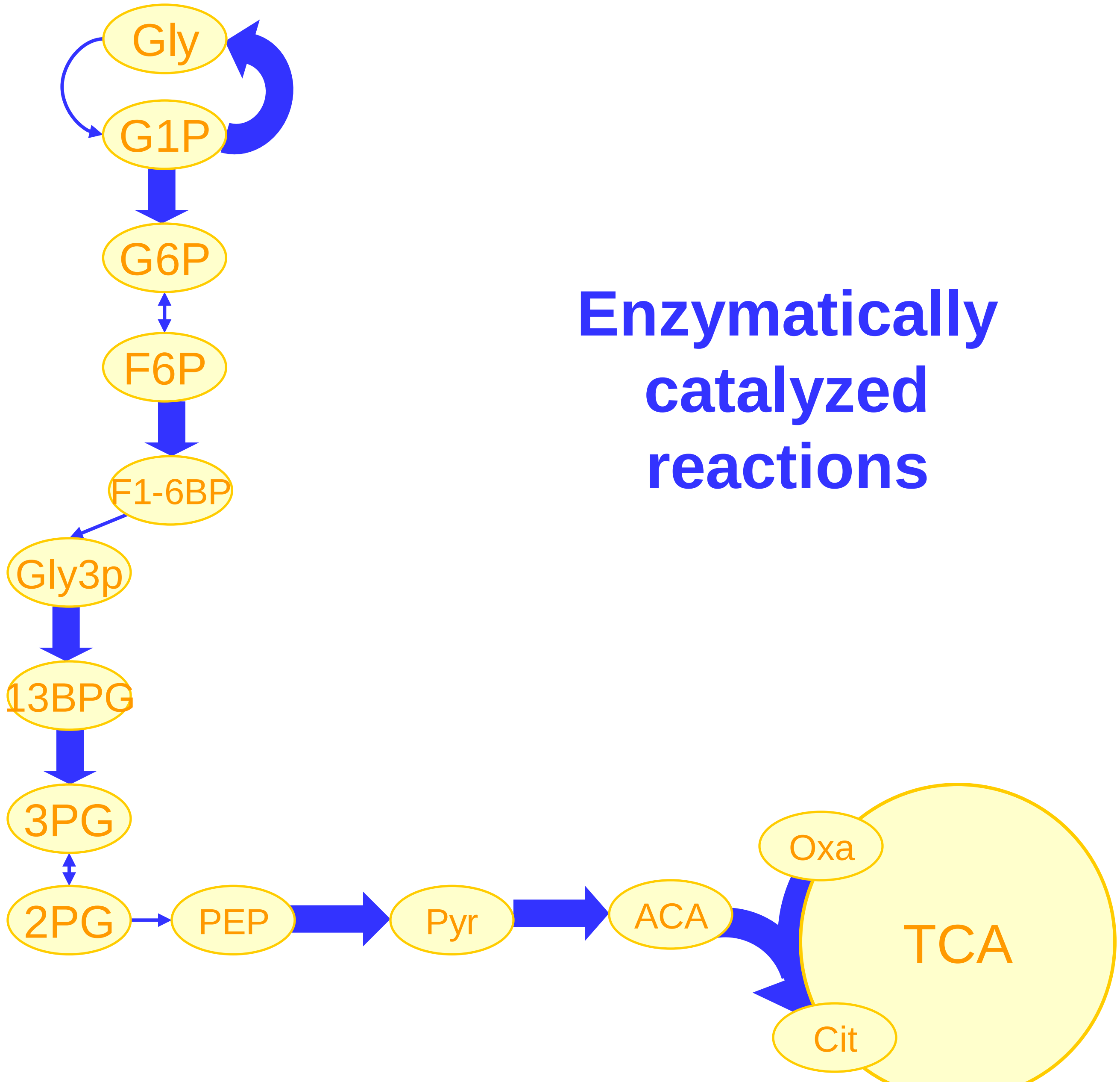


Inside every cell ($\approx 10^{30}$)

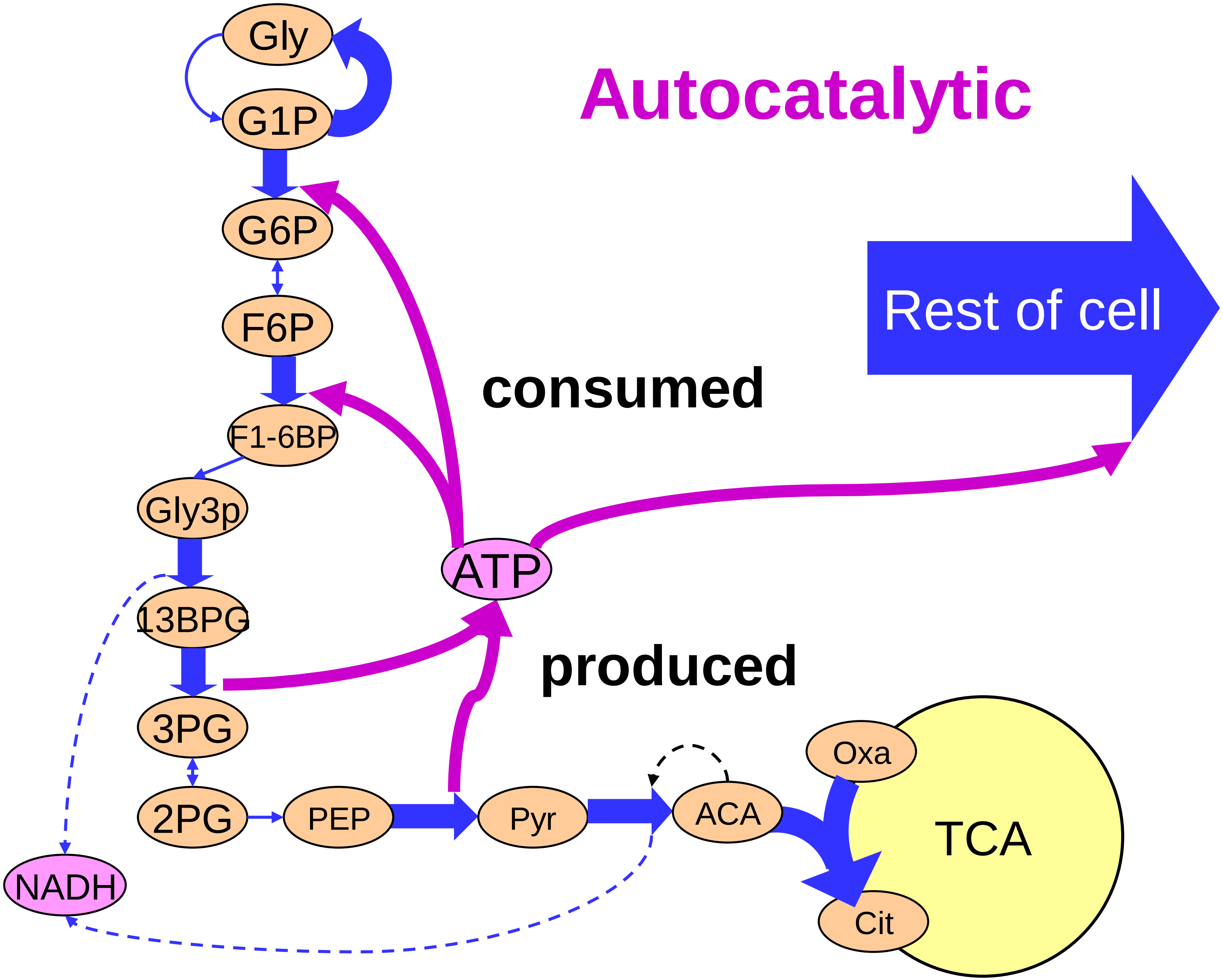

Catabolism
Precursors
Carriers


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

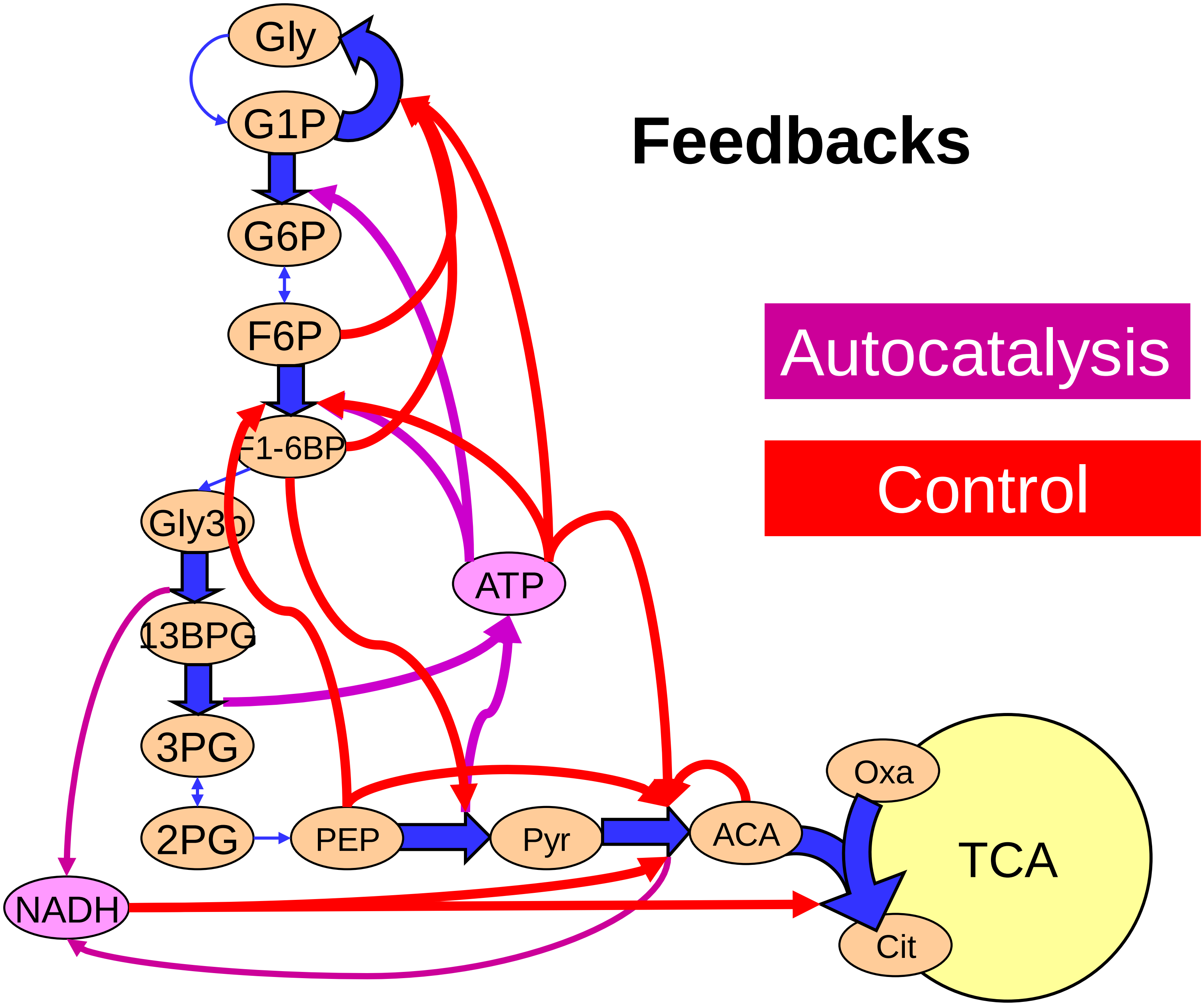

Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
Cit
TCA
metabolites
Precursors

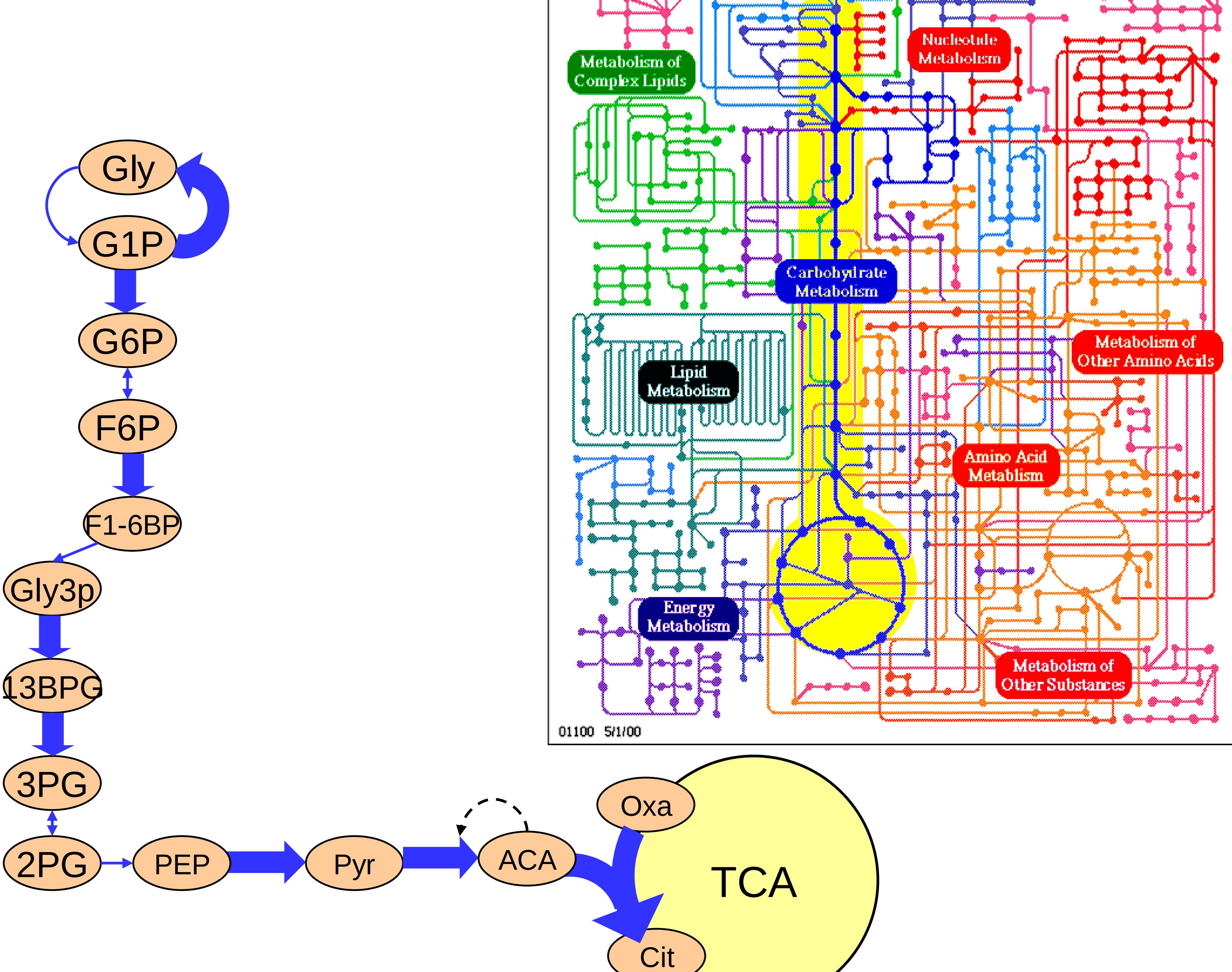


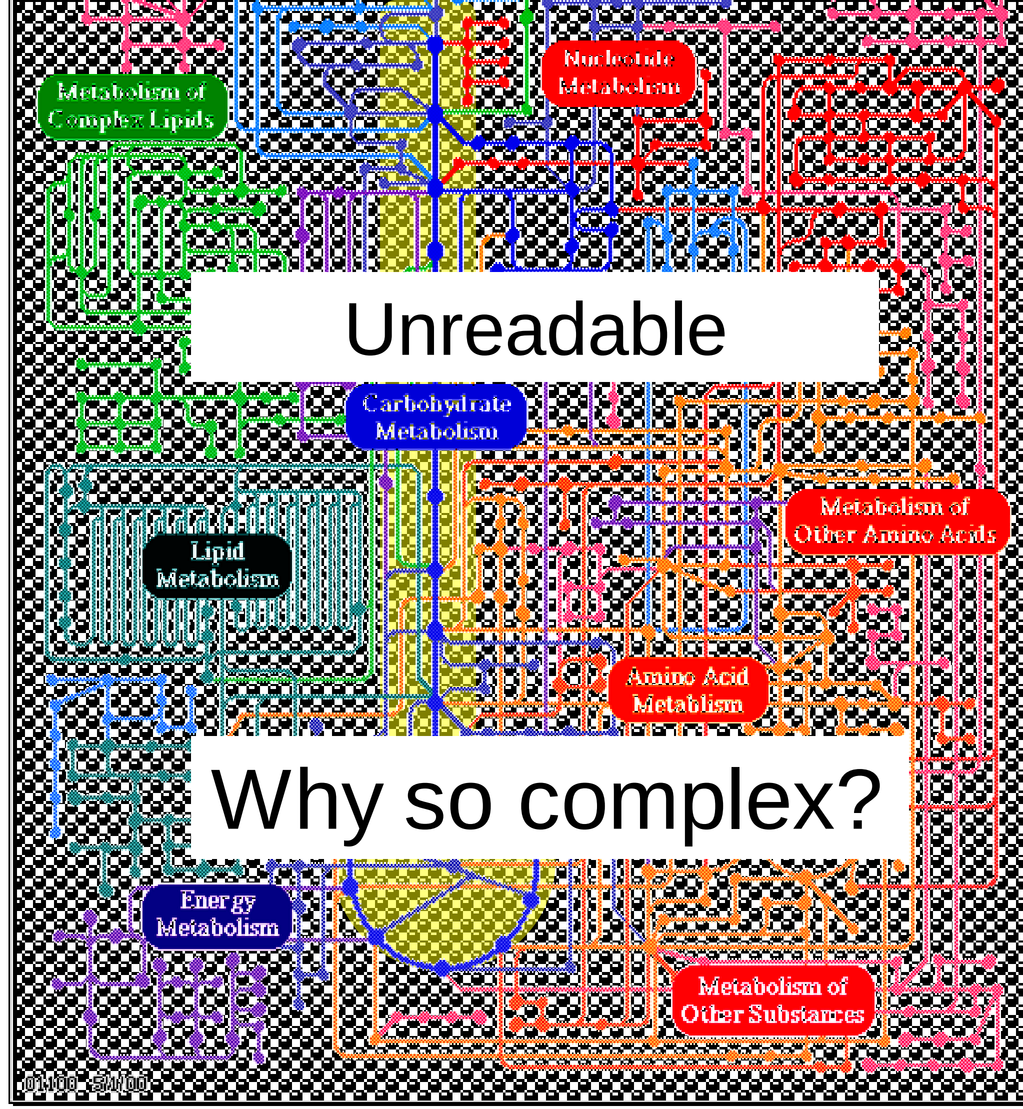
Enzymatically catalyzed reactions

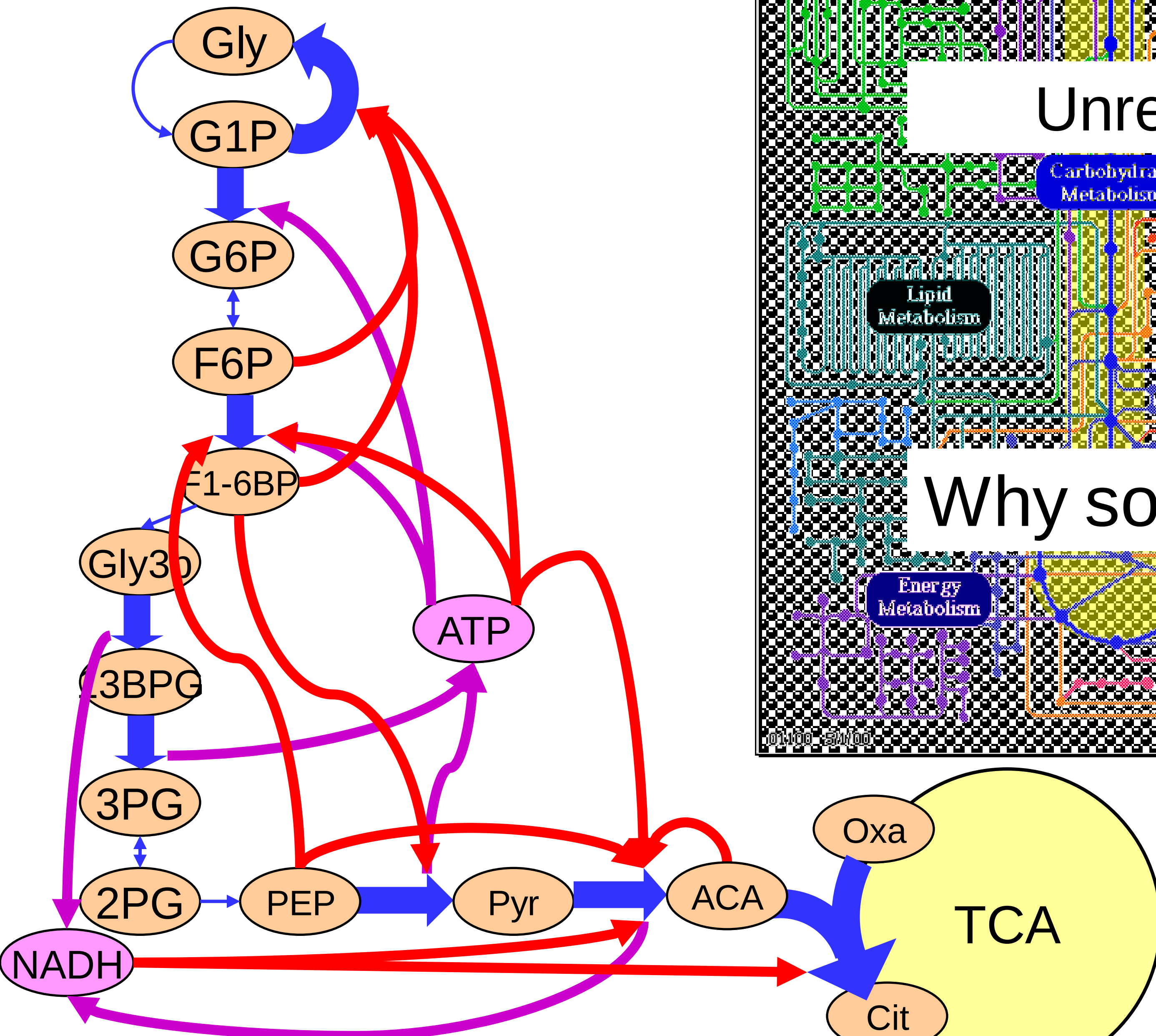

Autocatalytic
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
Oxa
Cit
TCA
NADH
ATP
consumed
produced
Rest of cell

Feedbacks


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


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

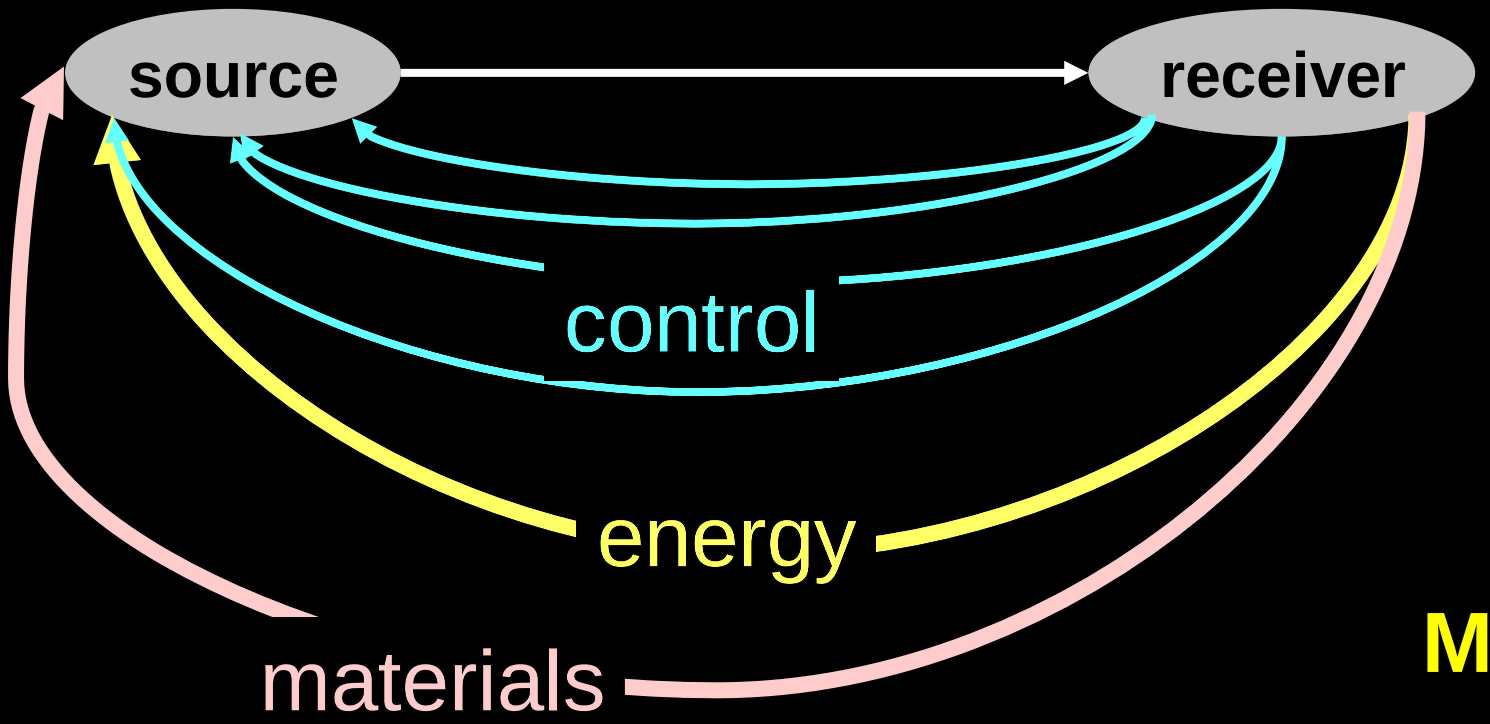

Metabolism of Complex Lipids
Nucleotide Metabolism
Unreadable
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metablism
Why so complex?
Energy Metabolism
Metabolism of Other Substances


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

signaling
gene expression
metabolism
lineage

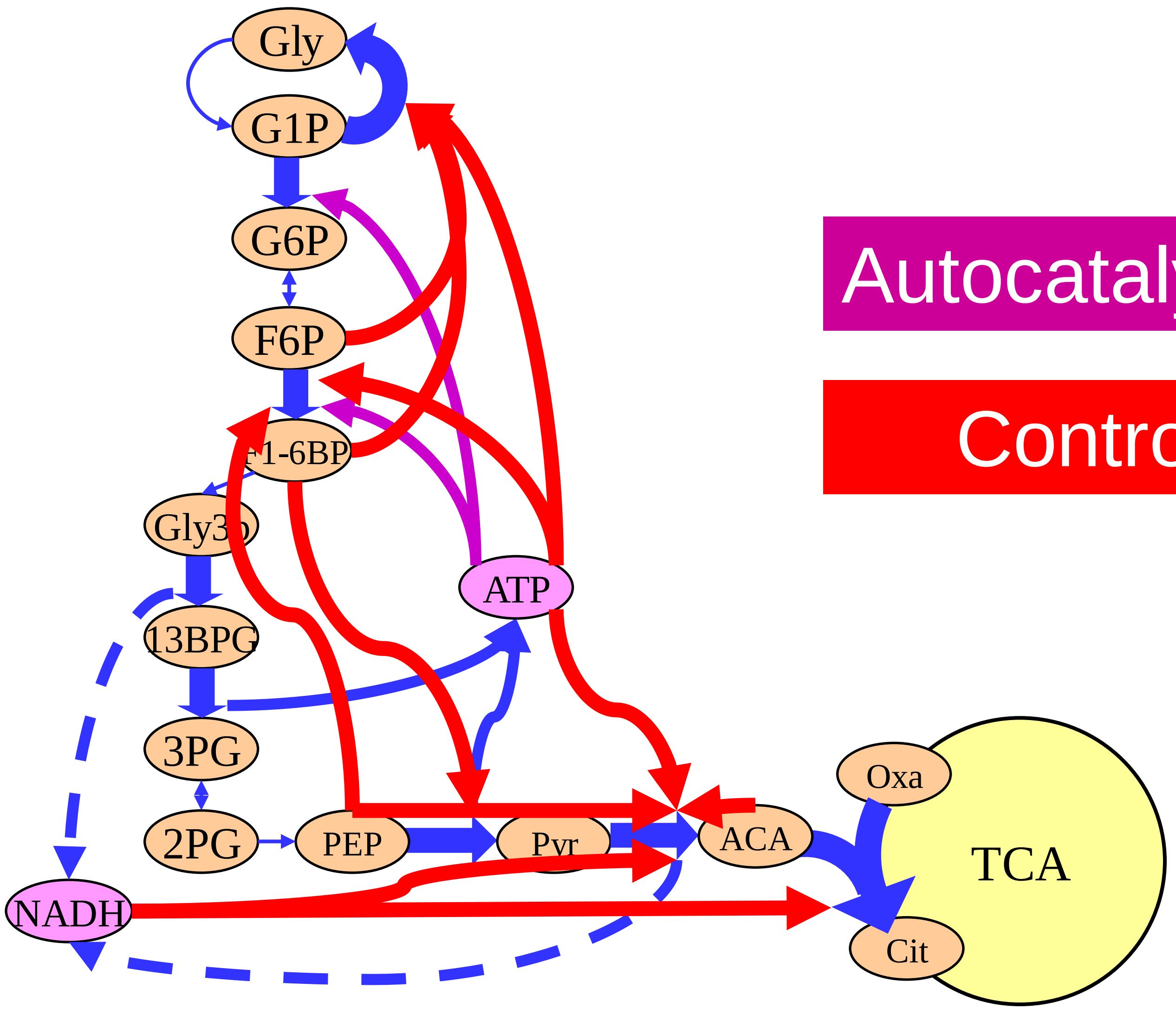
Biological pathways

signaling
gene expression
metabolism
lineage



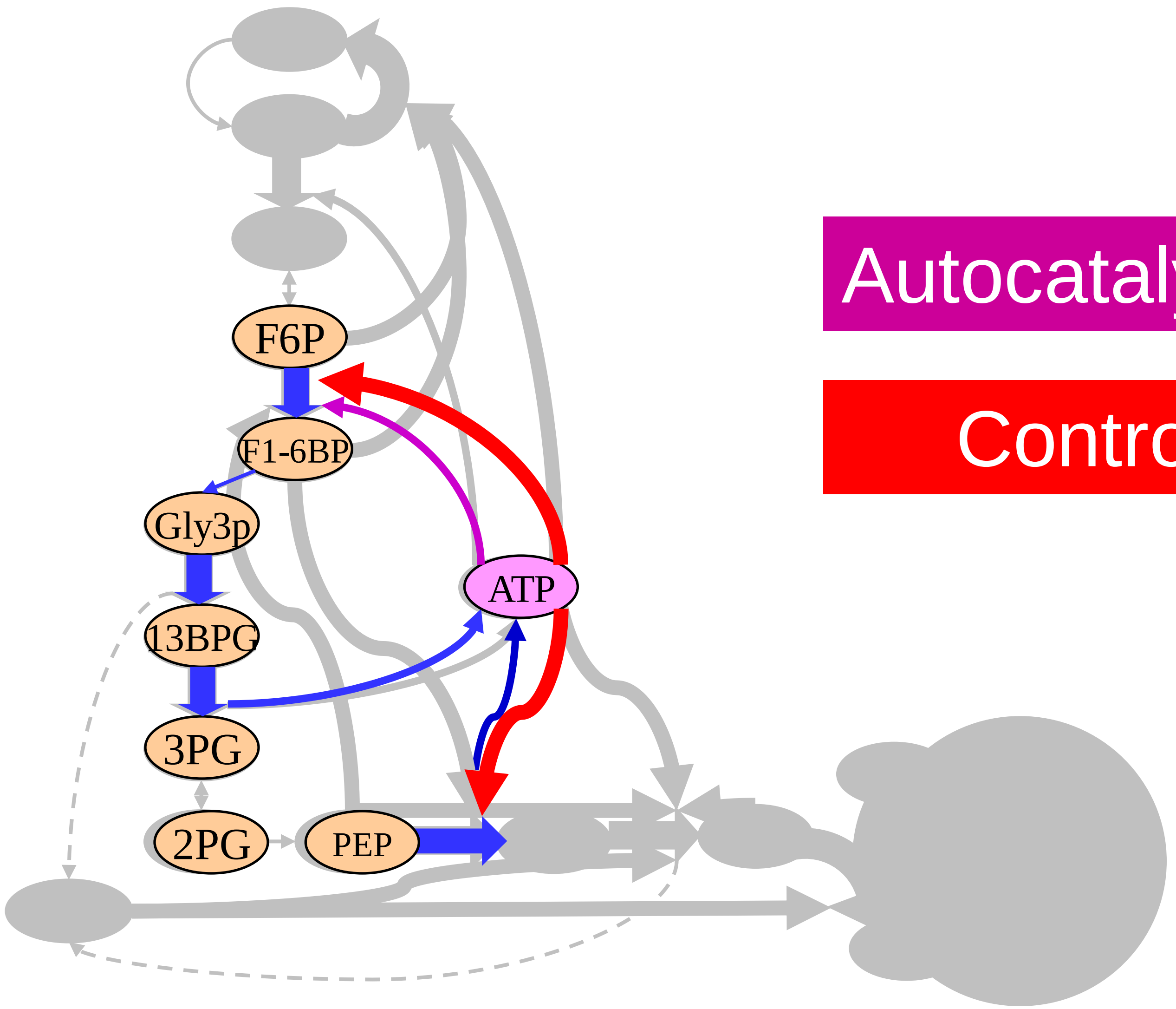
More complex feedback

Feedbacks



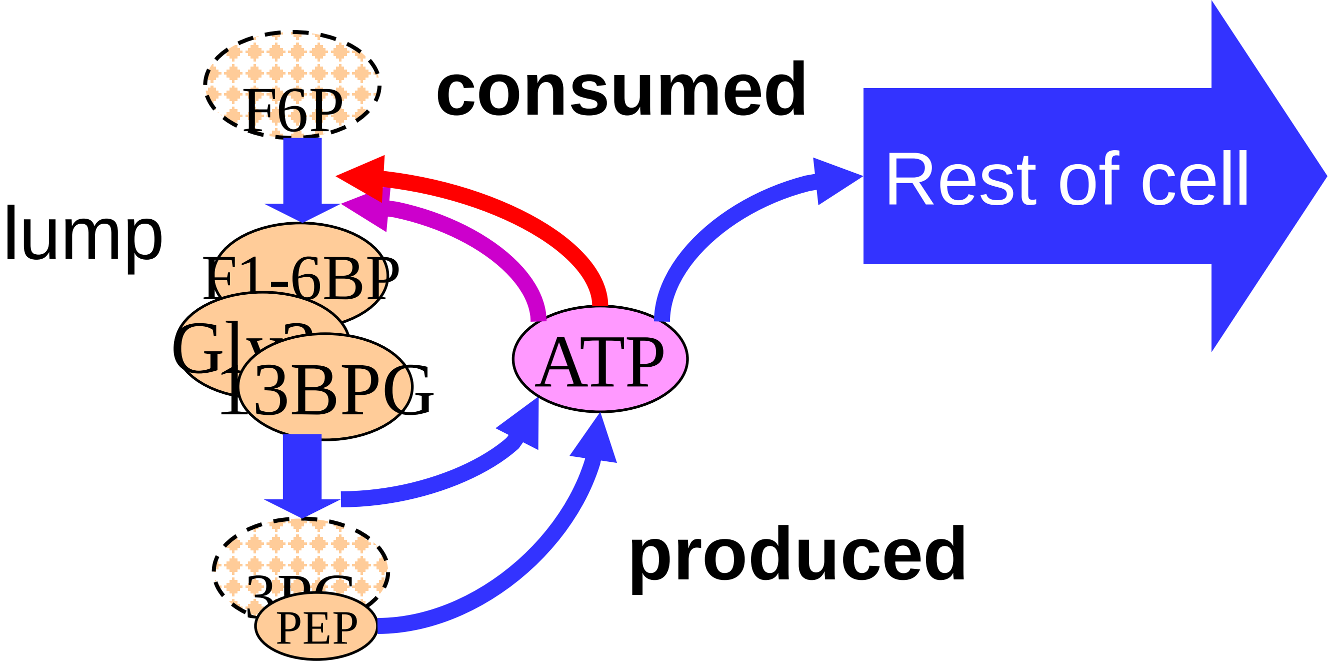
Autocatalysis

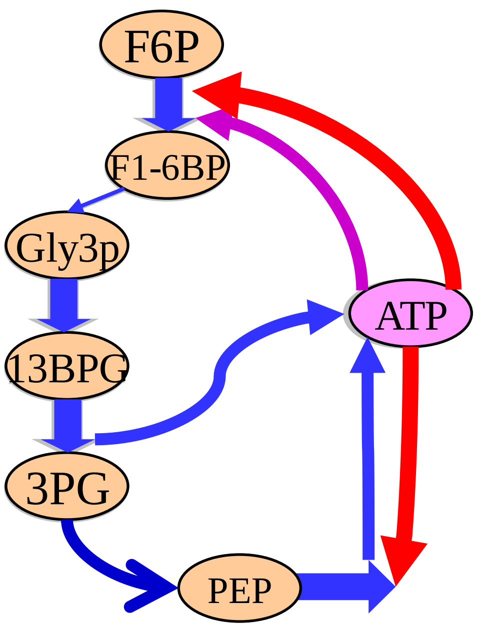
Control



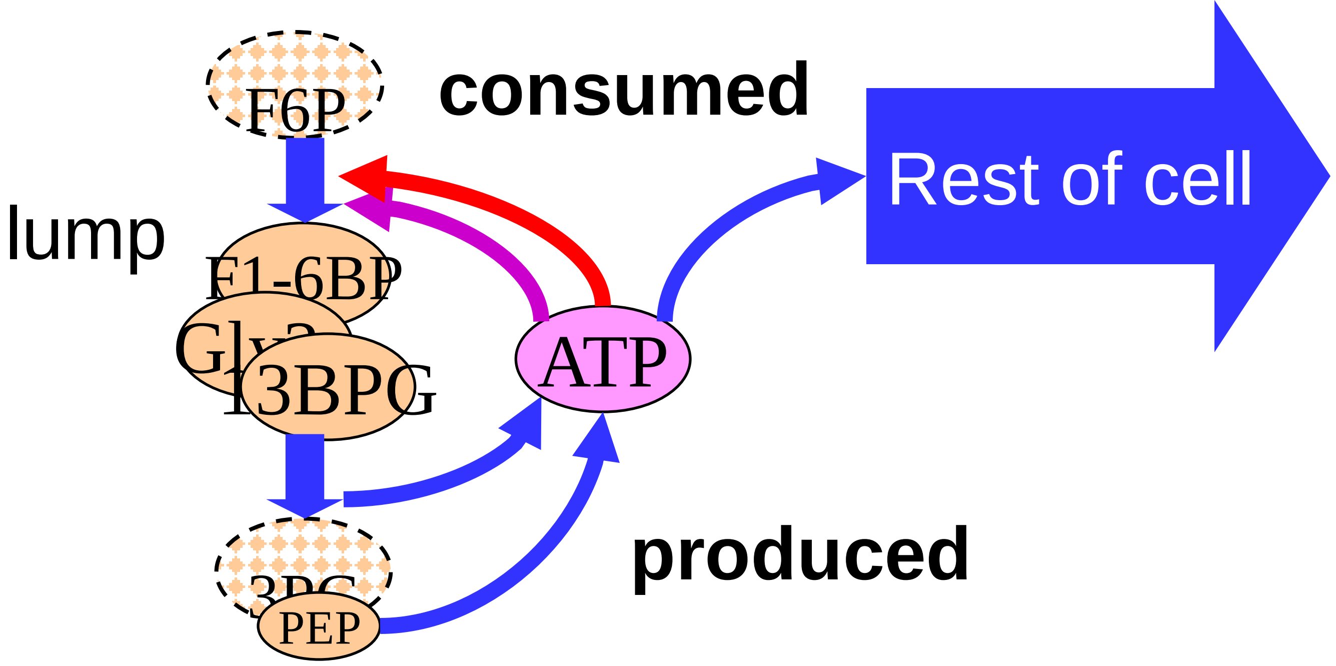
Autocatalysis

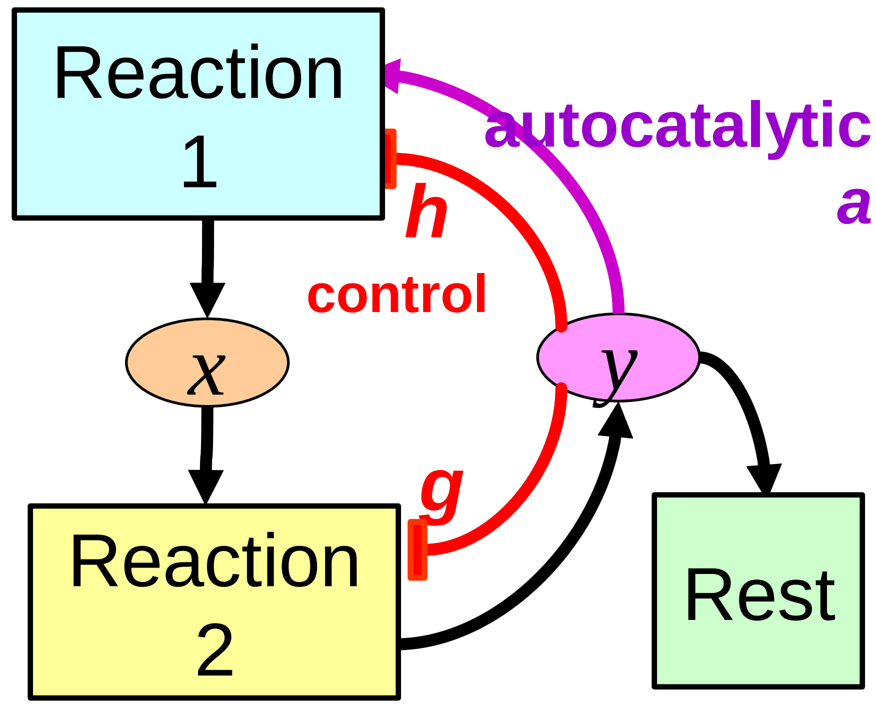
Control





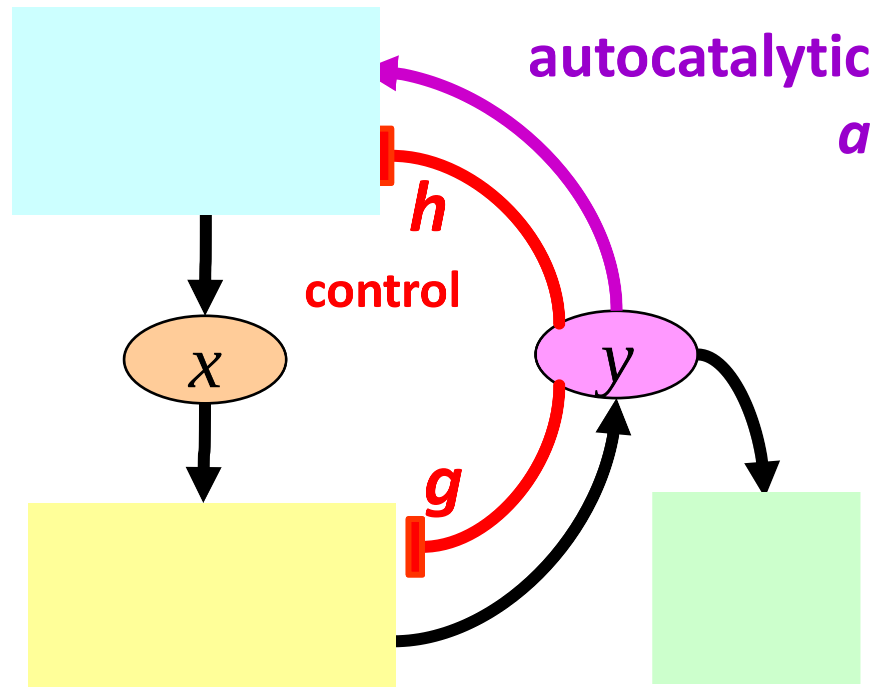
Control
Plus
Autocatalytic
Feedback


F6P
consumed
Rest of cell
lump
F1-6BP
ATP
produced
PEP


Reaction
1
autocatalytic
a
h
control
x
y
g
Reaction
2
Rest

Assume mass action $q=a$ $(=1)$

$$\frac{d}{dt}\begin{bmatrix}x\\y\end{bmatrix} = \begin{bmatrix}1\\-a\end{bmatrix}(a-h)y + \begin{bmatrix}-1\\1+a\end{bmatrix}(kx-gy) + \begin{bmatrix}0\\-1\end{bmatrix}d$$

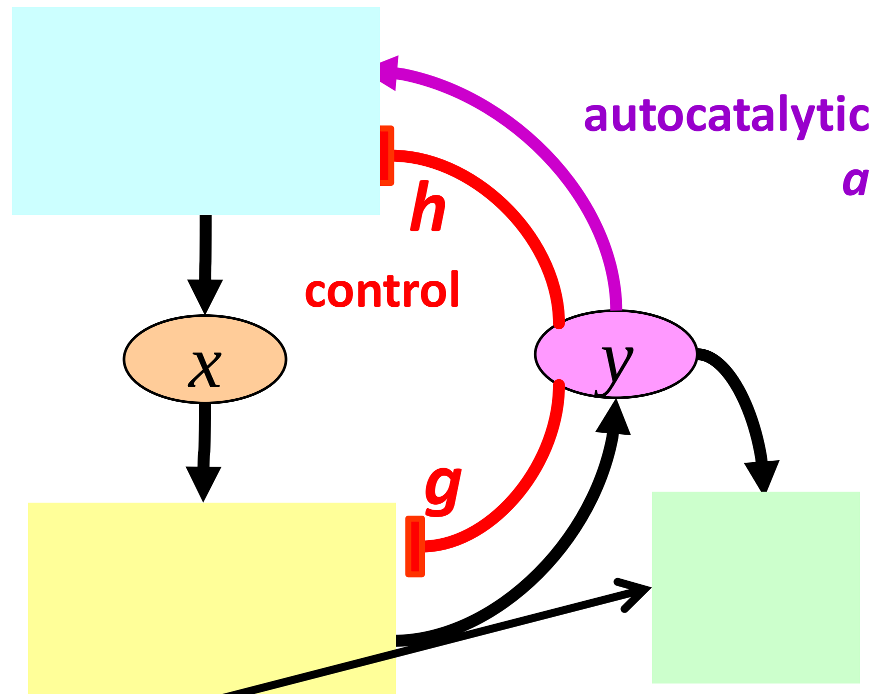


Autocatalysis

$$\frac{d}{dt}\begin{bmatrix}x\\y\end{bmatrix} = \begin{bmatrix}1\\-q\end{bmatrix}(a-h)y + \begin{bmatrix}-1\\1+q\end{bmatrix}(kx-gy) + \begin{bmatrix}0\\-1\end{bmatrix}d$$

Linearization

$$\frac{d}{dt}\begin{bmatrix}x\\ y\end{bmatrix} = \begin{bmatrix}1\\ -a\end{bmatrix}(a-h)\,y + \begin{bmatrix}-1\\ 1+a\end{bmatrix}(kx-gy) + \begin{bmatrix}0\\ -1\end{bmatrix}d$$



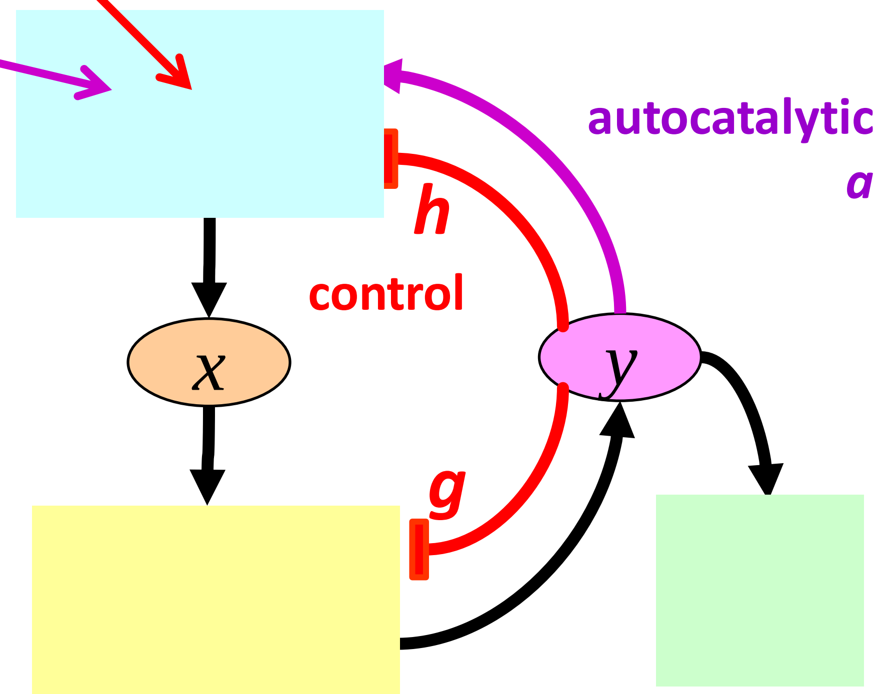
Consumption

$$\begin{bmatrix}\dot{x}\\ \dot{y}\end{bmatrix} = \begin{bmatrix}-k & a+g\\ (a+1)k & -a^2-(a+1)g\end{bmatrix}\begin{bmatrix}x\\ y\end{bmatrix} + \begin{bmatrix}0\\ -1\end{bmatrix}\delta + \begin{bmatrix}-1\\ a\end{bmatrix}hy$$

Autocatalysis

Control

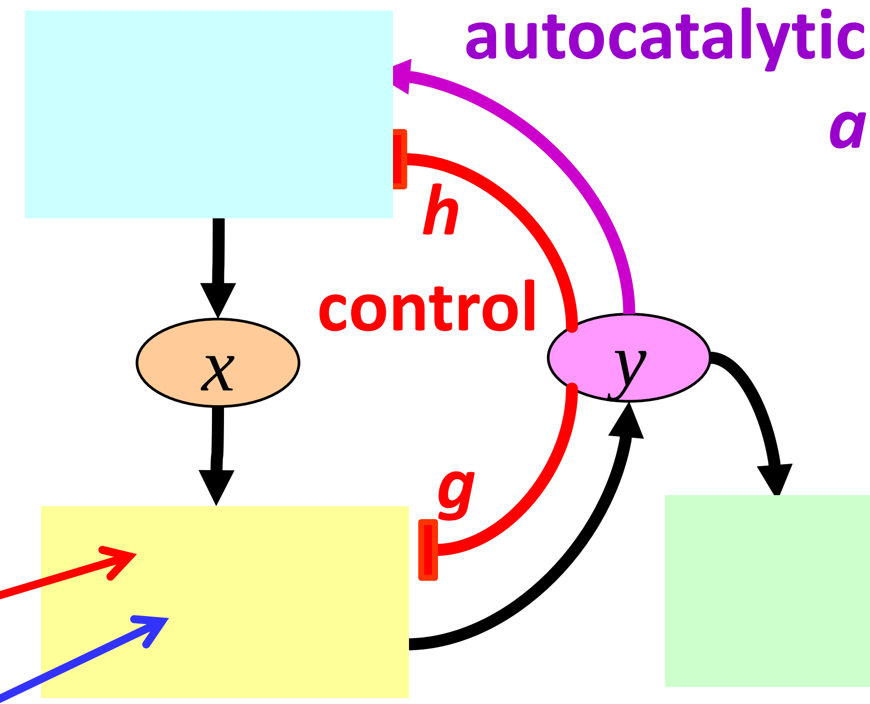
$$\frac{d}{dt}\begin{bmatrix}x\\y\end{bmatrix} = \begin{bmatrix}1\\-a\end{bmatrix}(a-h)\,y + \begin{bmatrix}-1\\1+a\end{bmatrix}(kx-gy) + \begin{bmatrix}0\\-1\end{bmatrix}d$$



$$\begin{bmatrix}\dot{x}\\ \dot{y}\end{bmatrix} = \begin{bmatrix}-k & a+g\\ (a+1)k & -a^2-(a+1)g\end{bmatrix}\begin{bmatrix}x\\y\end{bmatrix} + \begin{bmatrix}0\\-1\end{bmatrix}\delta + \begin{bmatrix}-1\\a\end{bmatrix}hy$$

Autocatalysis

$$\frac{d}{dt}\begin{bmatrix}x\\y\end{bmatrix} = \begin{bmatrix}1\\-a\end{bmatrix}(a-h)\,y + \begin{bmatrix}-1\\1+a\end{bmatrix}(kx-gy) + \begin{bmatrix}0\\-1\end{bmatrix}d$$



Control

enzyme level

$$\begin{bmatrix}\dot{x}\\\dot{y}\end{bmatrix} = \begin{bmatrix}-k & a+g\\(a+1)k & -a^2-(a+1)g\end{bmatrix}\begin{bmatrix}x\\y\end{bmatrix} + \begin{bmatrix}0\\-1\end{bmatrix}\delta + \begin{bmatrix}-1\\a\end{bmatrix}hy$$

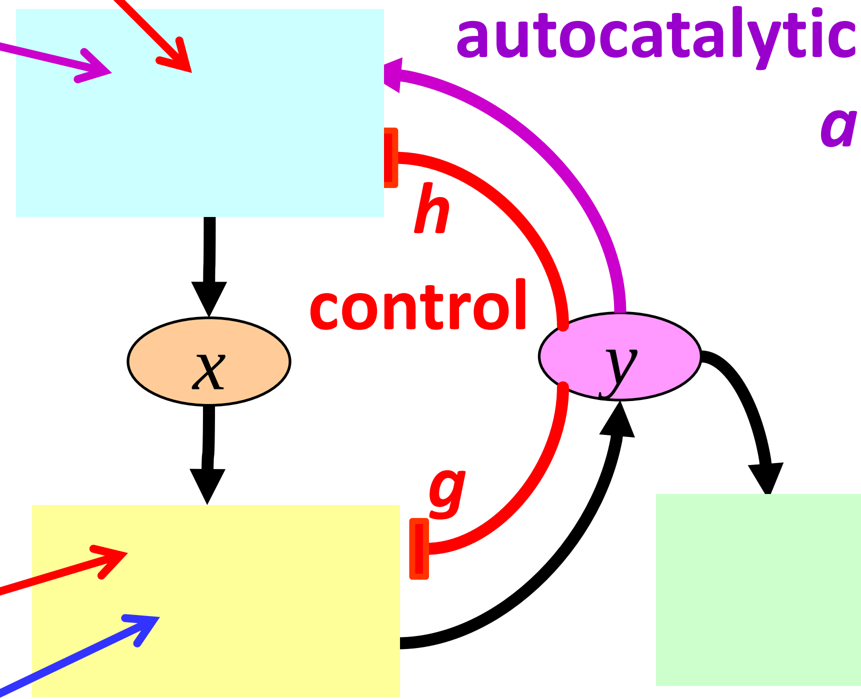
Control

Autocatalysis

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)\,y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

Control

enzyme level



$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -k & a+g \\ (a+1)k & -a^2-(a+1)g \end{bmatrix}\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix}\delta + \begin{bmatrix} -1 \\ a \end{bmatrix} hy$$

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = A\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d \qquad A = \begin{bmatrix} -k & a-h+g \\ (1+q)k & -q(a-h)-(1+q)g \end{bmatrix}$$

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -k & a+g \\ (a+1)k & -a^2-(a+1)g \end{bmatrix}\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix}\delta + \begin{bmatrix} -1 \\ a \end{bmatrix} hy$$

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = A\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d \qquad A = \begin{bmatrix} -k & a-h+g \\ (1+q)k & -q(a-h)-(1+q)g \end{bmatrix}$$

Disturbance response (steady state)

$$\left|\frac{\bar{y}}{\bar{d}}\right| = \left|\frac{1}{h-a}\right|$$

Stability

$$0 < h - a < \frac{k+(1+q)g}{q}$$

Crash

Oscillate

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} -k & a+g \\ (a+1)k & -a^2-(a+1)g \end{bmatrix}\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix}\delta + \begin{bmatrix} -1 \\ a \end{bmatrix} hy$$

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = A\begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d \qquad A = \begin{bmatrix} -k & a-h+g \\ (1+q)k & -q(a-h)-(1+q)g \end{bmatrix}$$

Disturbance response (steady state)

$$\left|\frac{\bar{y}}{\bar{d}}\right| = \left|\frac{1}{h-a}\right|$$

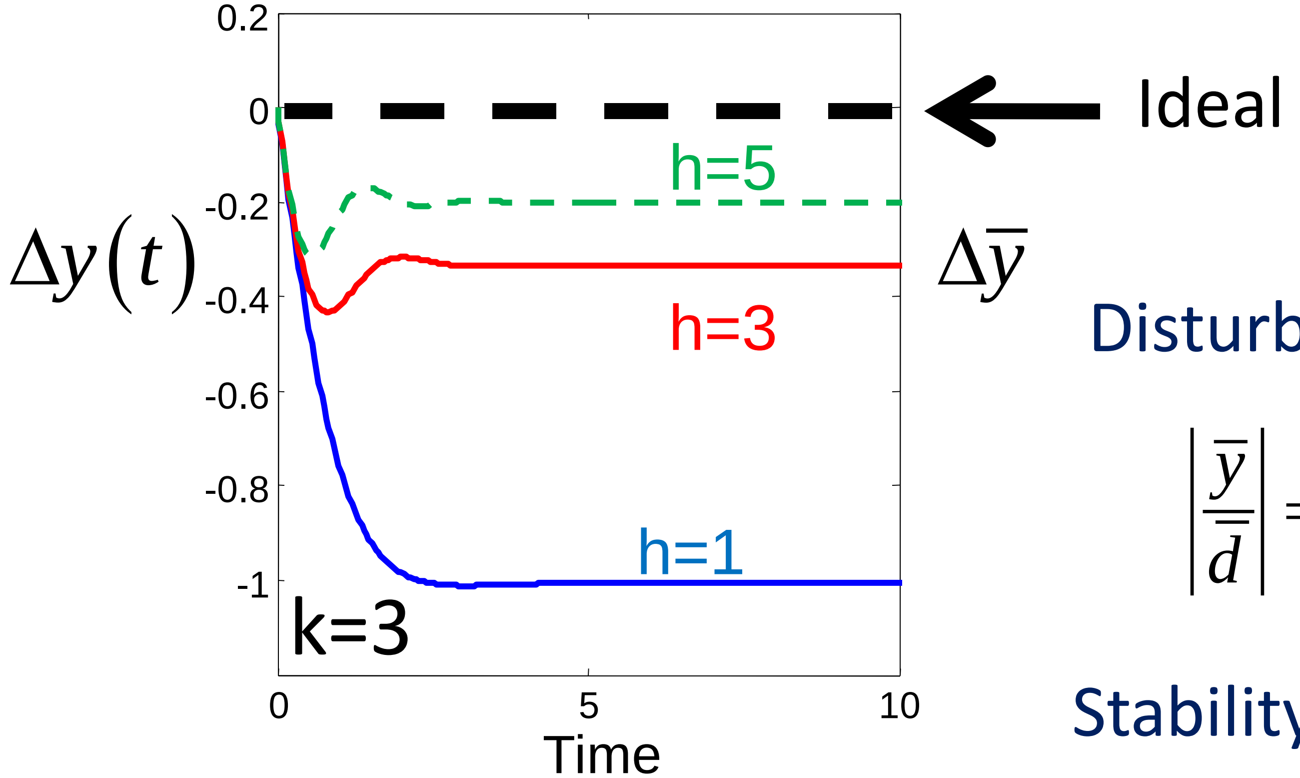
Stability

$$0 < h - a < \frac{k+(1+q)g}{q}$$

Crash

Oscillate

$$\boxed{\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}}$$

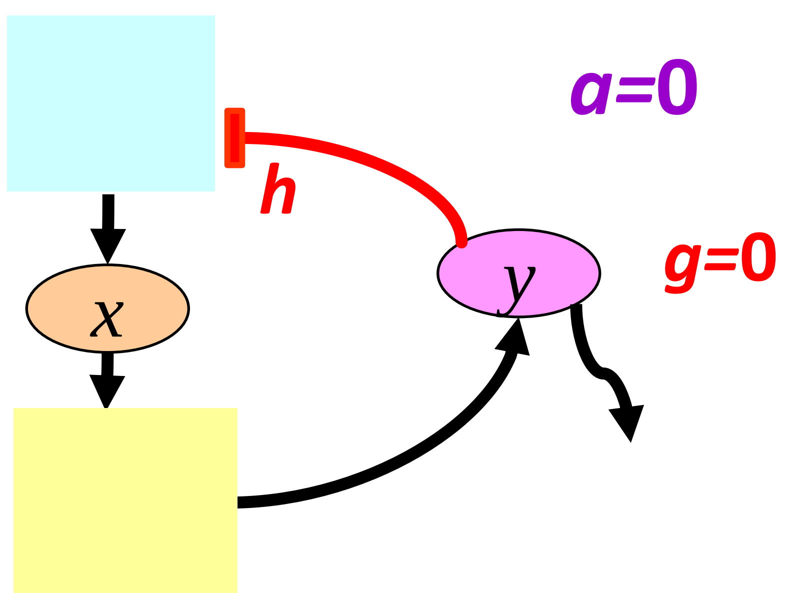


Disturbance response

$$\left|\frac{\bar{y}}{\bar{d}}\right| = \left|\frac{1}{h}\right|$$

Stability

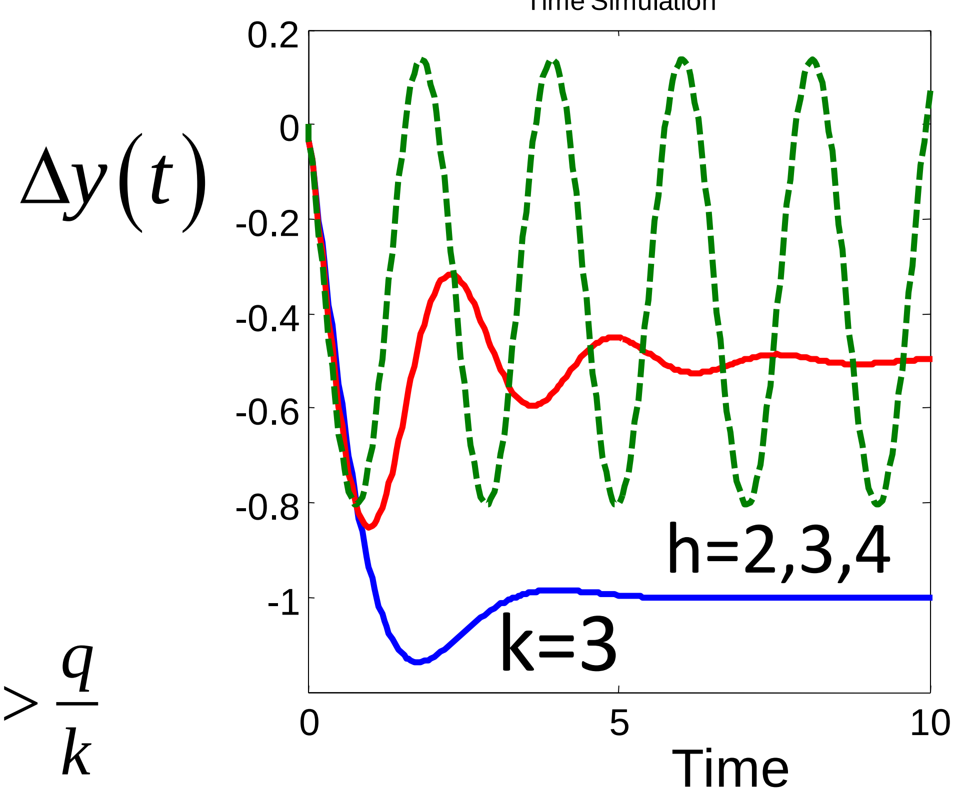
$$0 < h < \infty$$



$$A = \begin{bmatrix} -k & -h \\ k & 0 \end{bmatrix}$$

Disturbance response

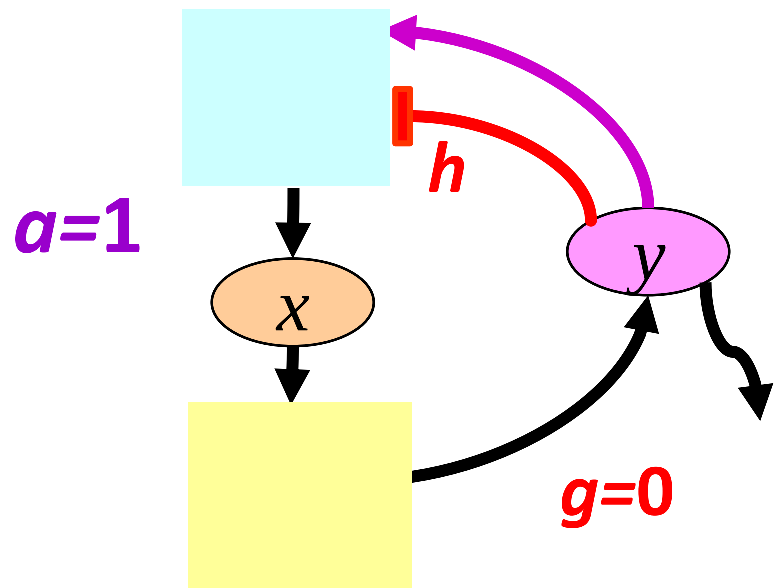
$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| = \left|\frac{1}{h-a}\right|$$

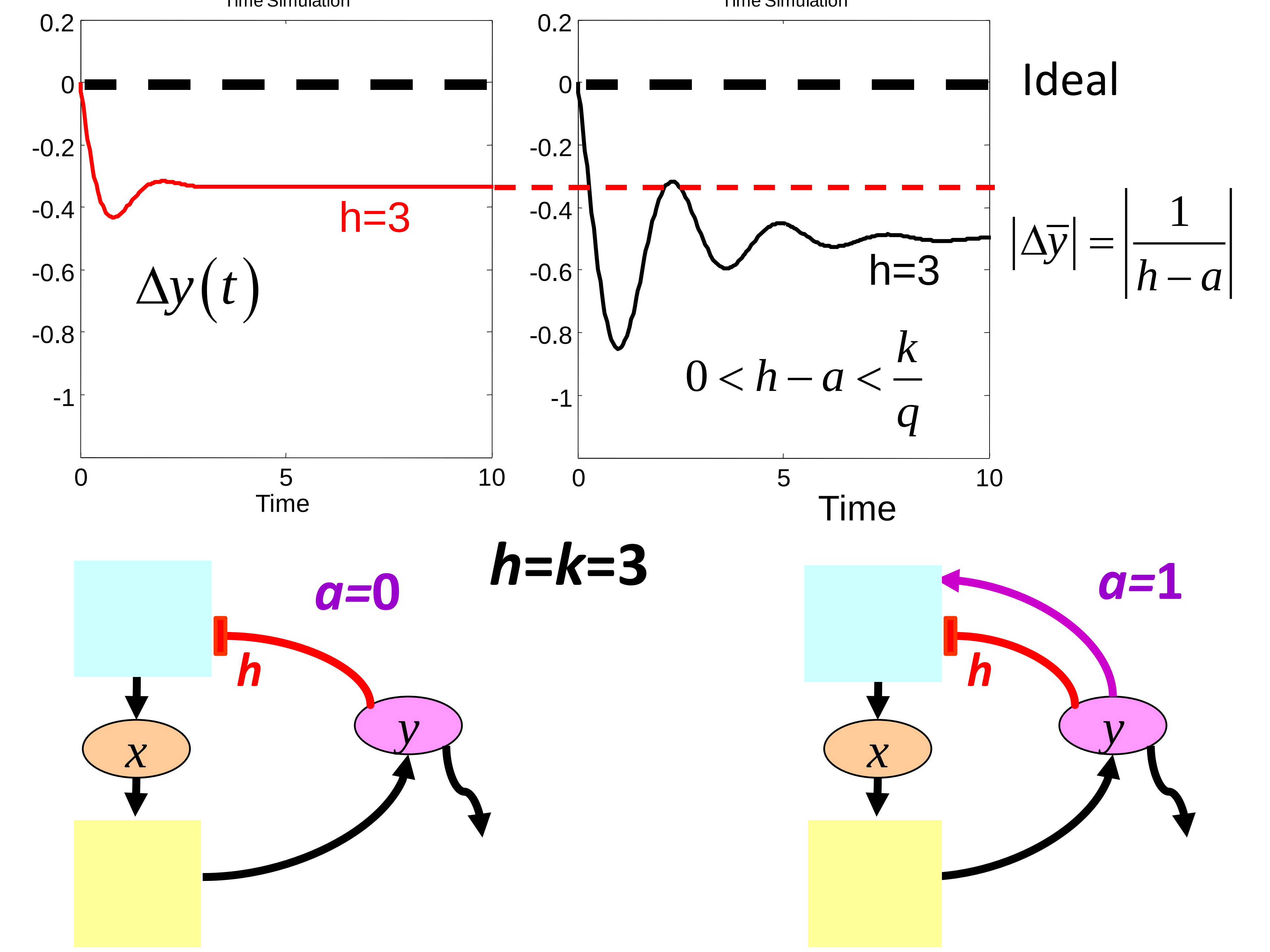


Stability

$$0 < h - a < \frac{k}{q} \quad \Rightarrow \left|\frac{1}{h-a}\right| > \frac{q}{k}$$

$$A = \begin{bmatrix} -k & 1-h \\ 2k & -(1-h) \end{bmatrix}$$




Time Simulation
Time Simulation
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
0
5
10
Time
Time
Ideal
h=3
h=3
$\Delta y(t)$
$|\Delta\bar{y}| = \left|\frac{1}{h-a}\right|$
$0 < h - a < \frac{k}{q}$
h=k=3
a=0
a=1
h
h
x
y
x
y

Control

Autocatalysis

$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}$$

enzyme level

- Hard limit
- Boundary is oscillatory
- g>0 helps

Disturbance

$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}$$

$$0 < h-a < \frac{k+(1+q)g}{q}$$

Stability

Control

Autocatalysis

$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

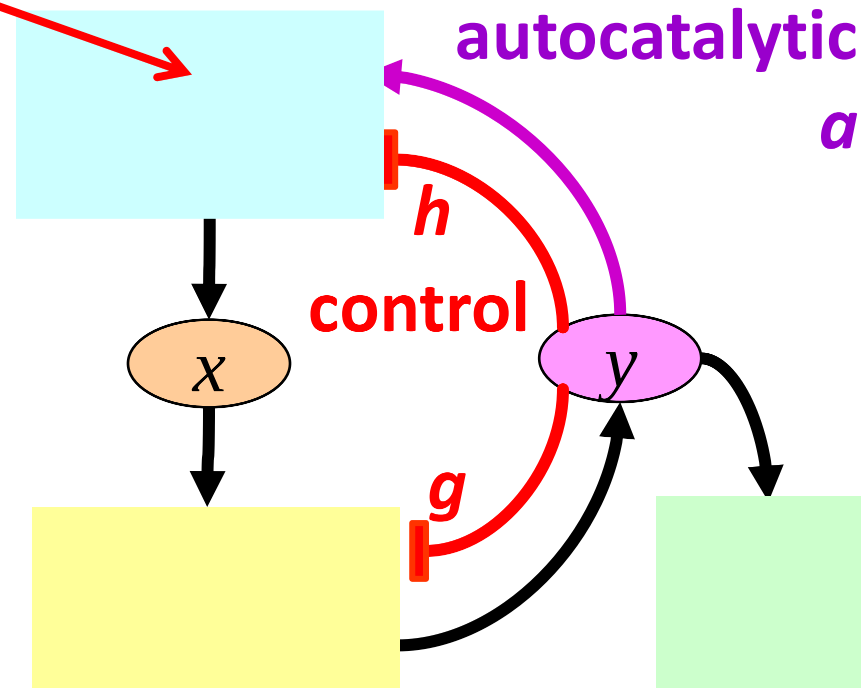
enzyme level

- Hard limit
- Boundary is oscillatory
- g>0 helps

$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

Control

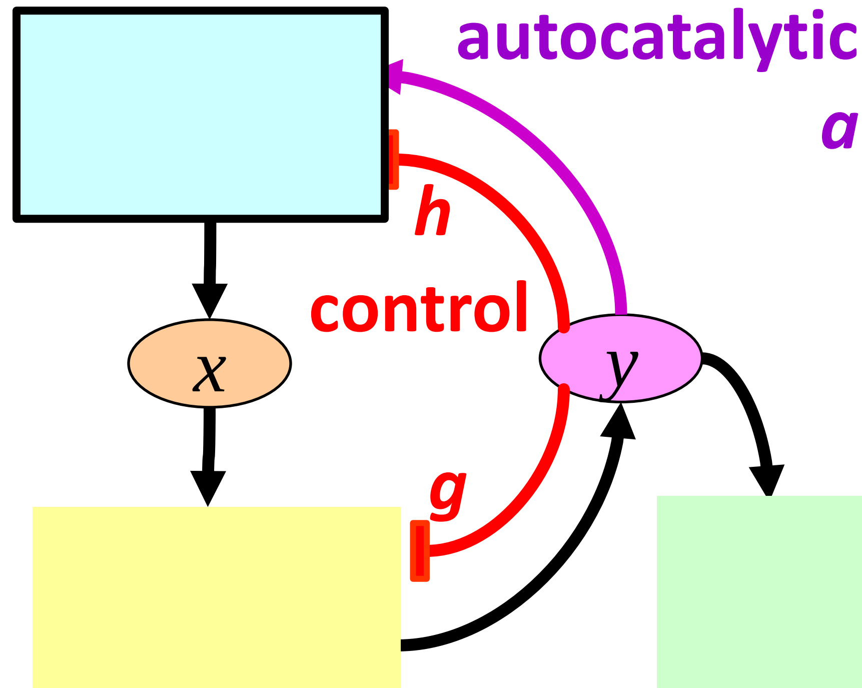
$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix}d$$



$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

Autocatalysis **Control**

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)\,y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

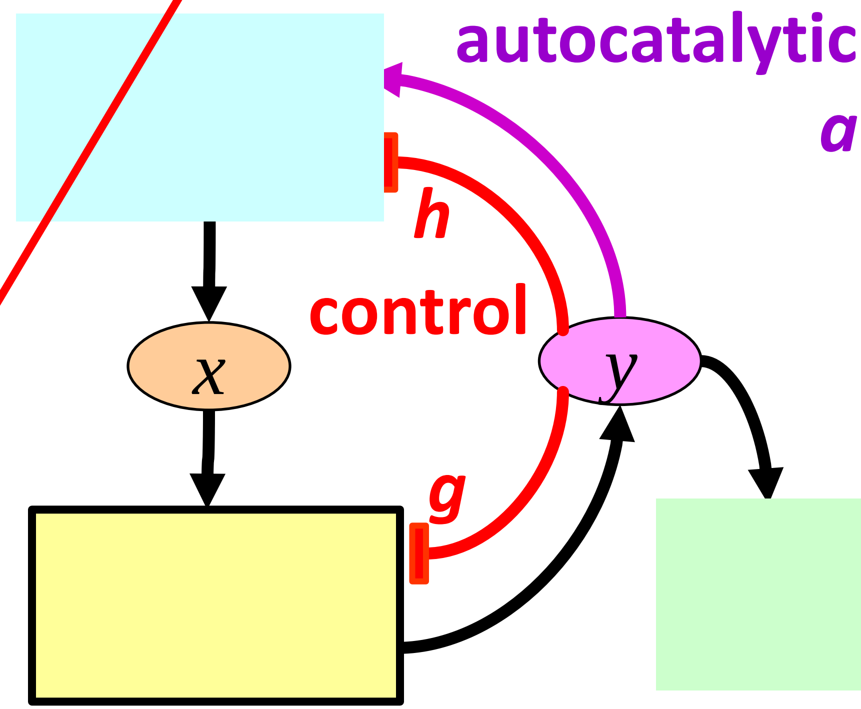


$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

enzyme level

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)\,y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

Control

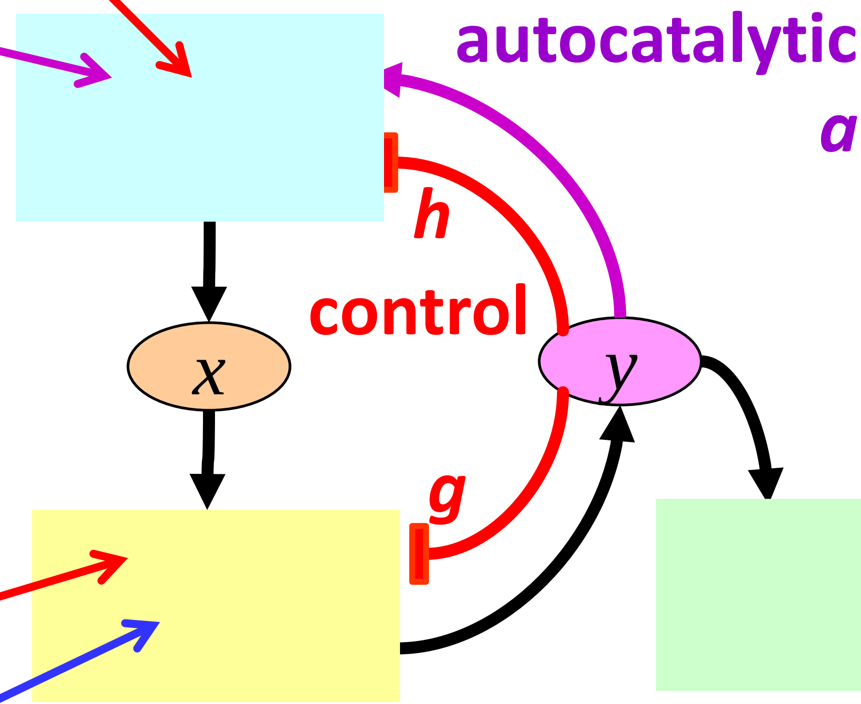


$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

Control

Autocatalysis

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix}d$$



Control

enzyme level

Oscillate

$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

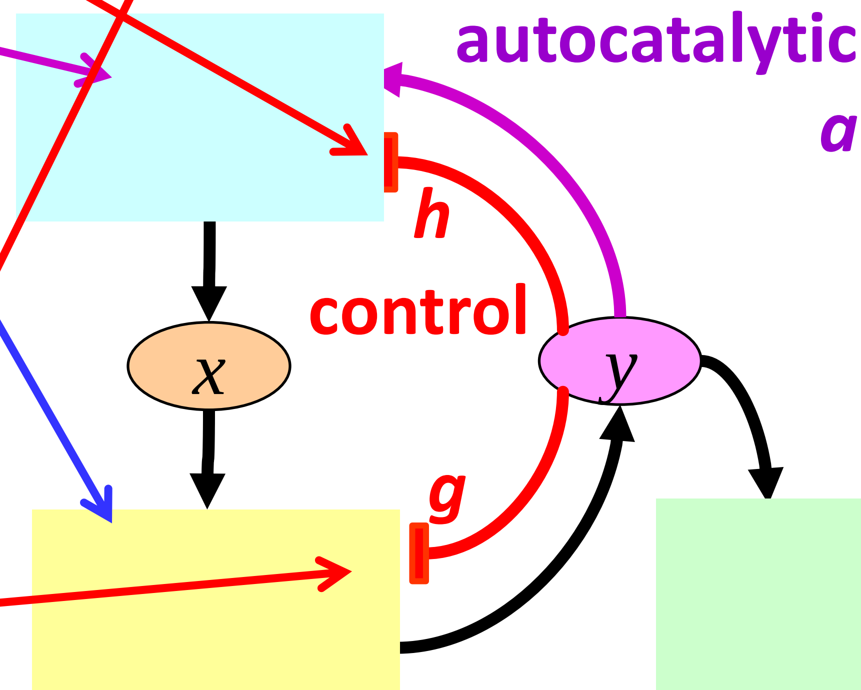
Control

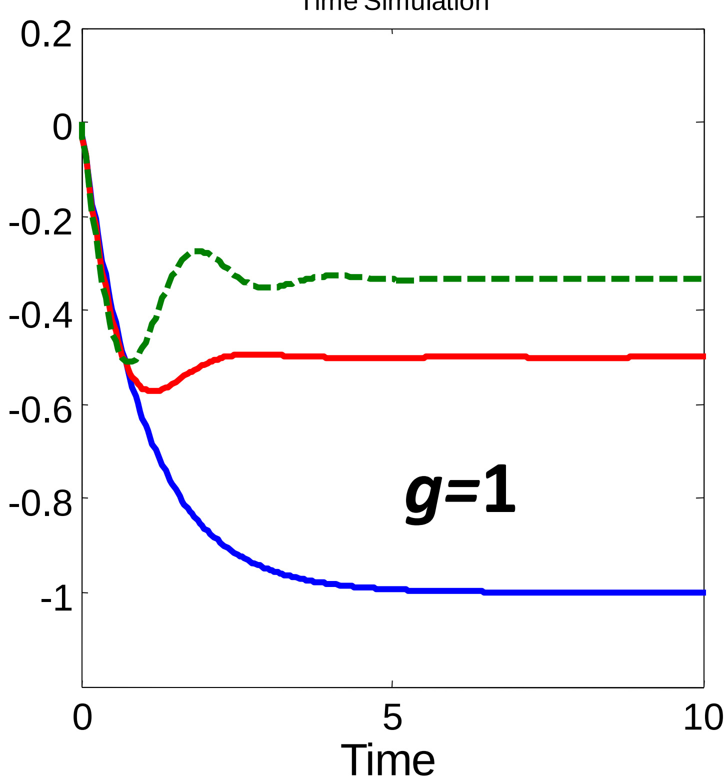
Autocatalysis

enzyme level

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix}d$$

Control

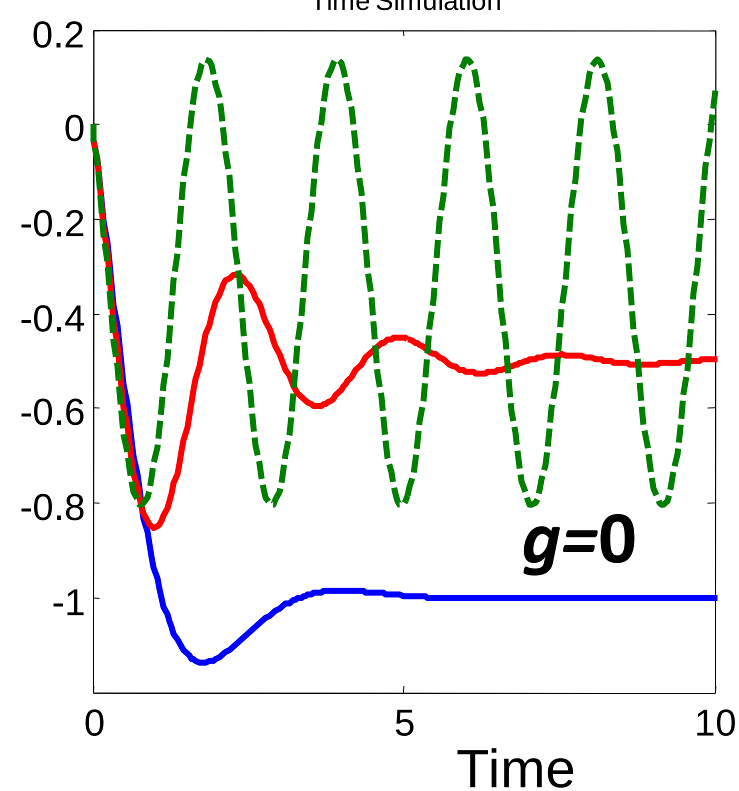


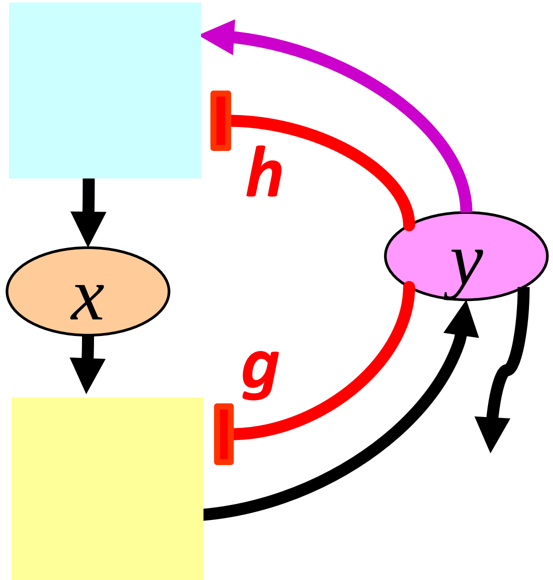


$\Delta y(t)$

h=2,3,4

k=3

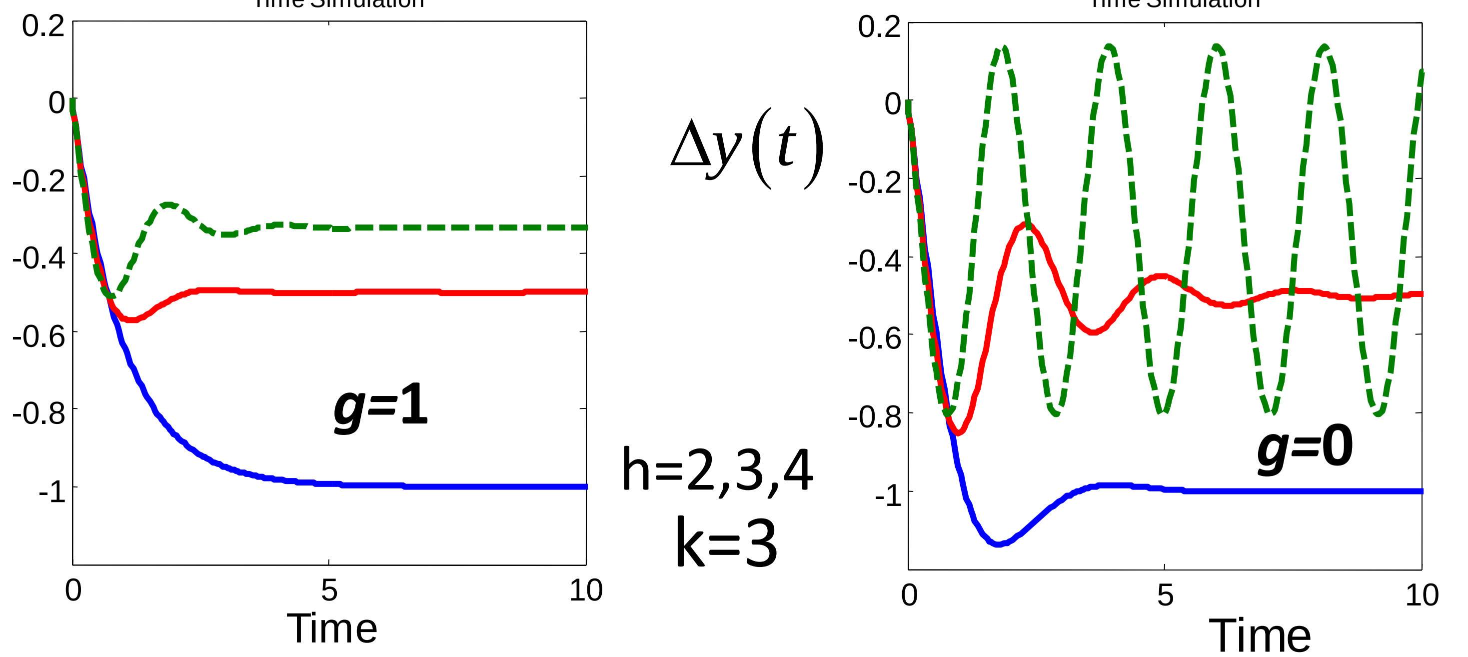


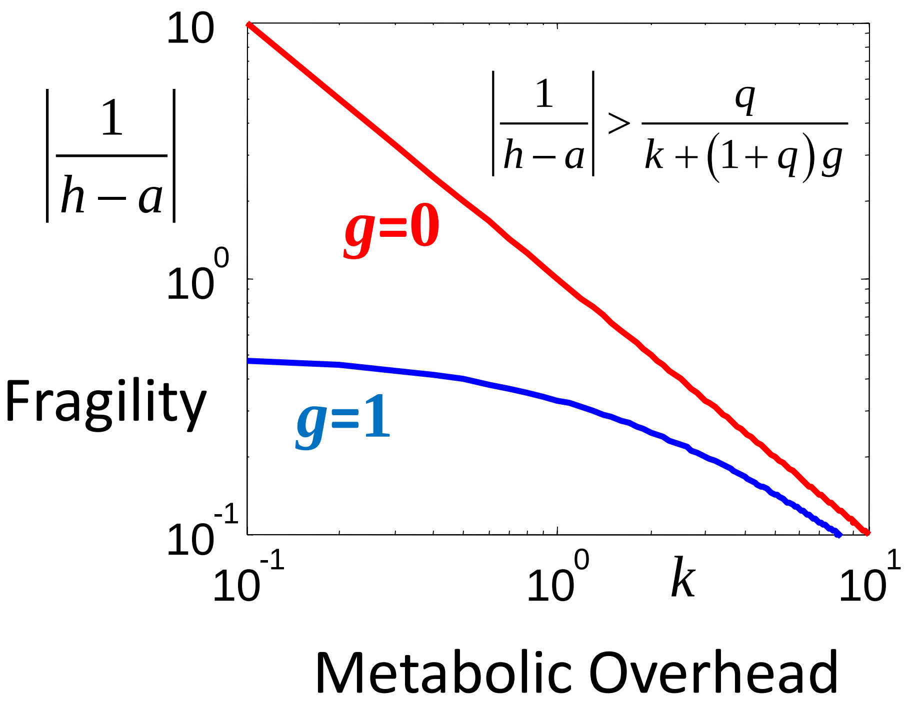


***a*=1**

- Hard limit
- Boundary is oscillatory
- *g*>0 helps

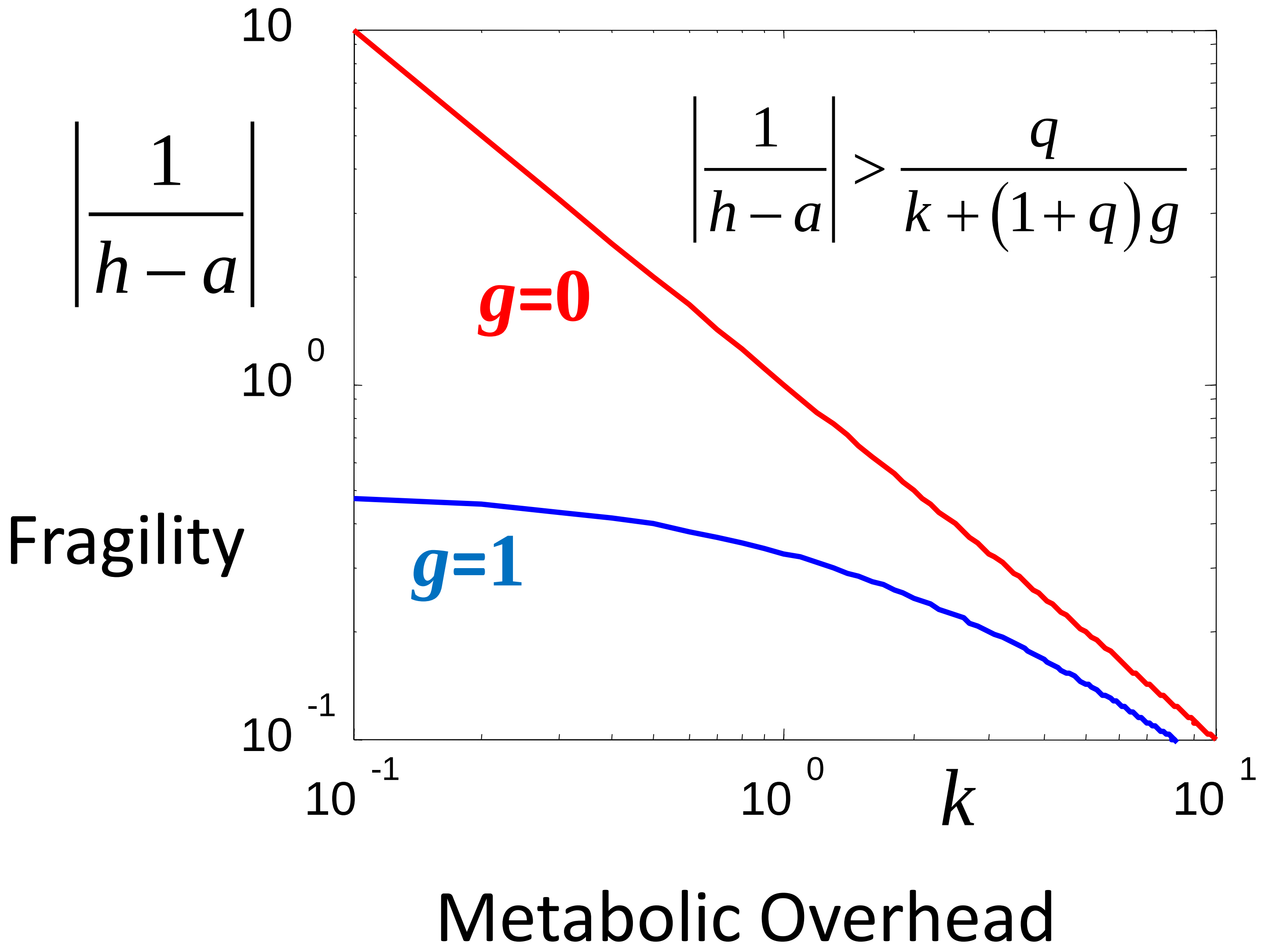
$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}$$

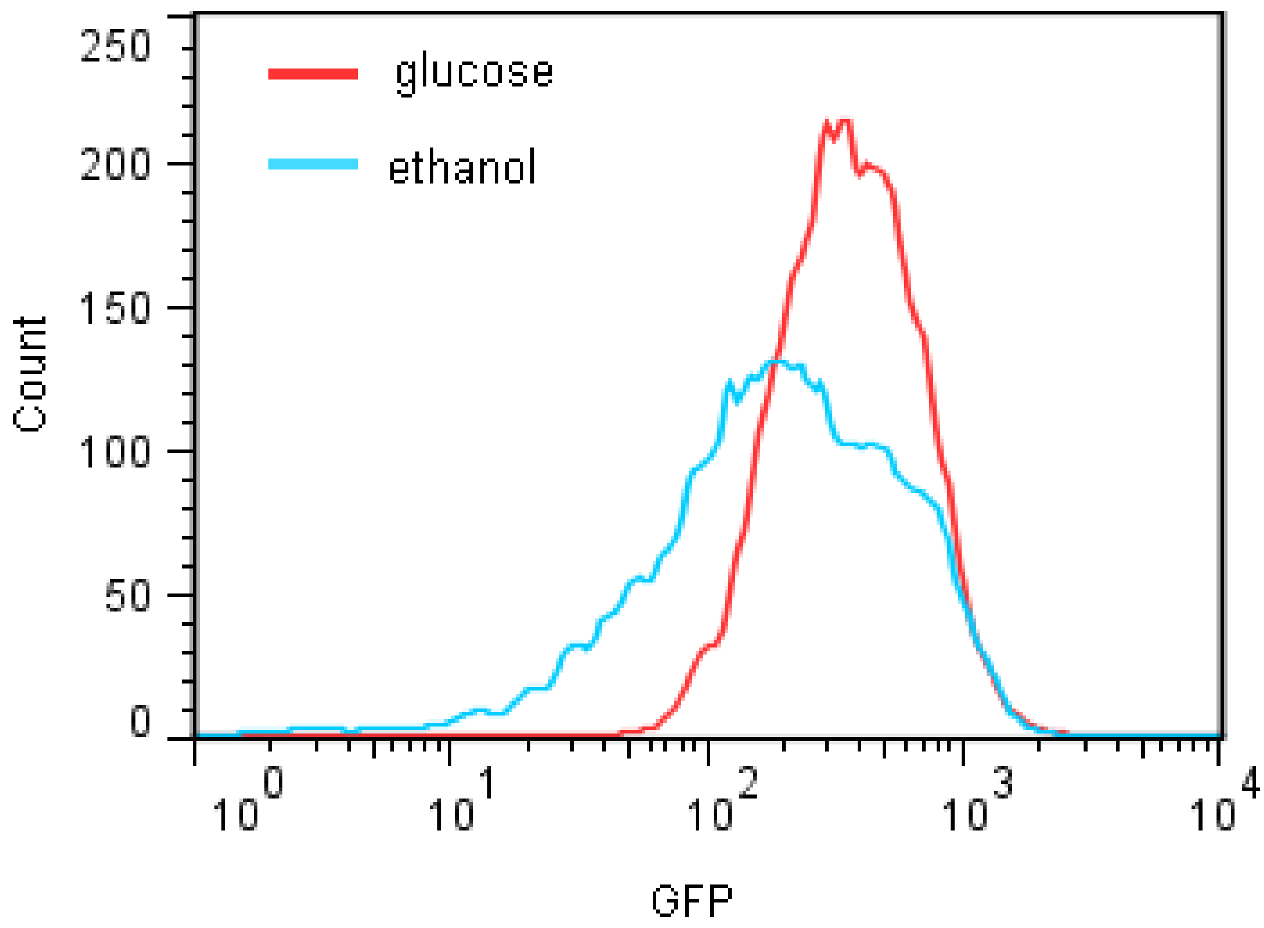




$$\left|\frac{\Delta \bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}$$

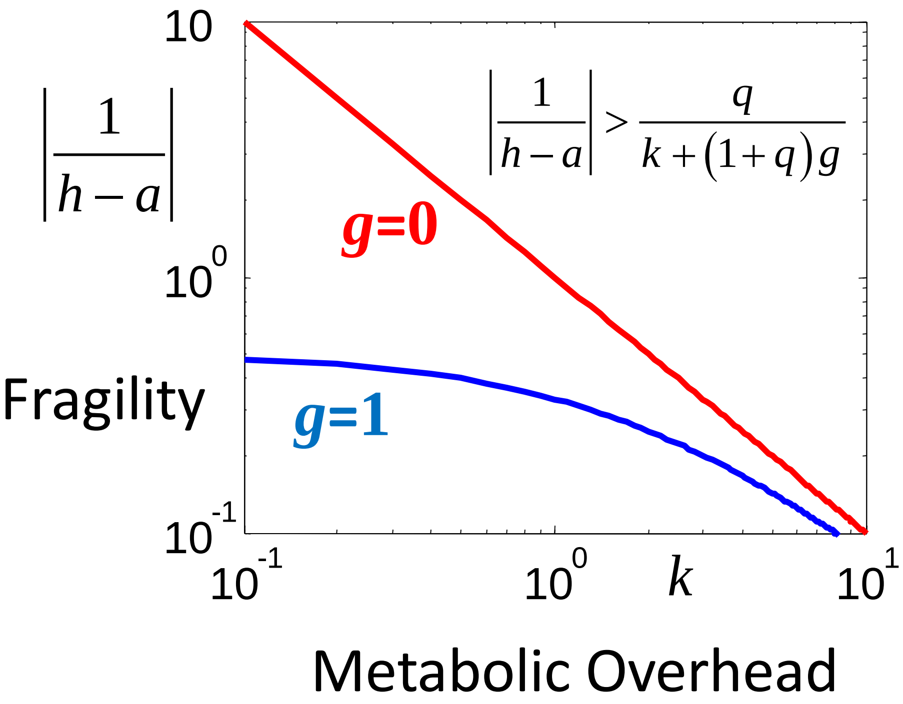
$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{q}{k+(1+q)g}$$

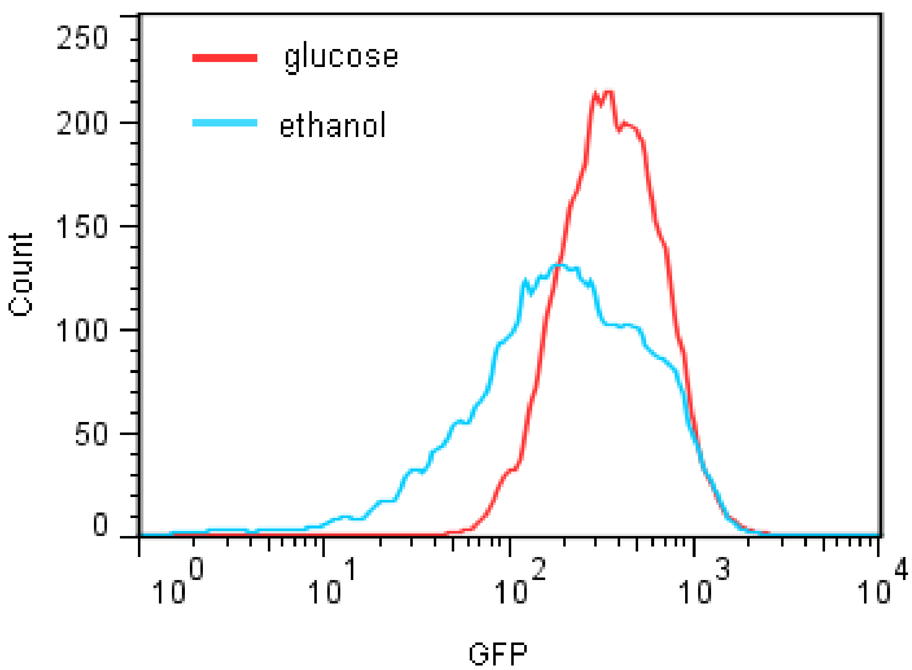




Fluorescence histogram (fluorescence vs. cell count) of GFP-tagged Glyceraldehyde-3-phosphate dehydrogenase (TDH3). Cells grown in ethanol has lower mean and median of fluorescence, and also higher variability.

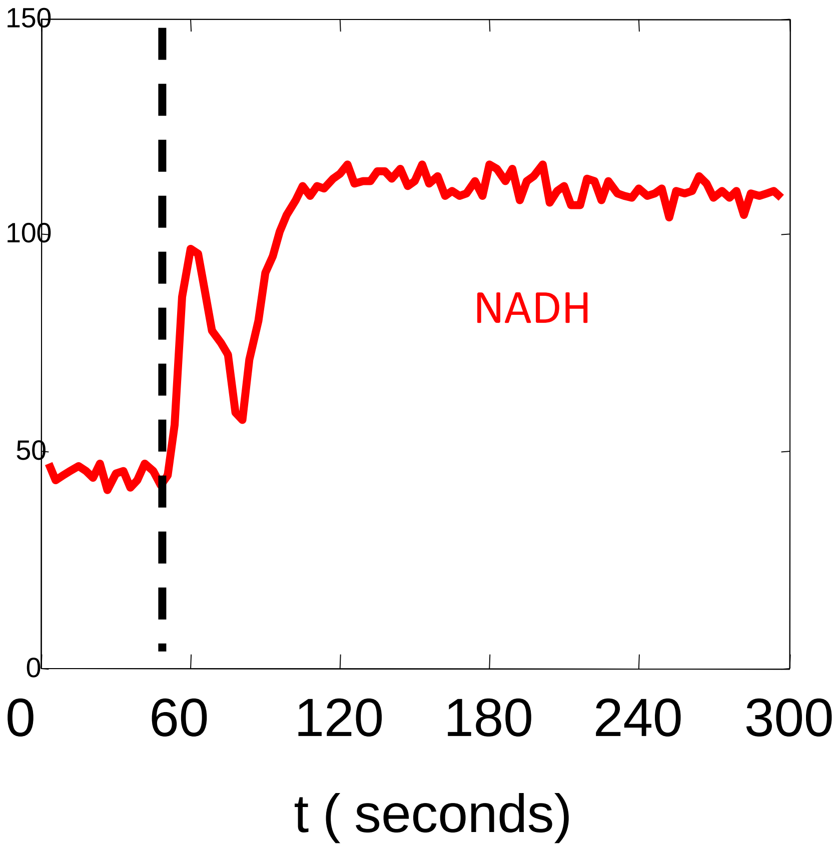
***g*=0 is implausibly fragile**

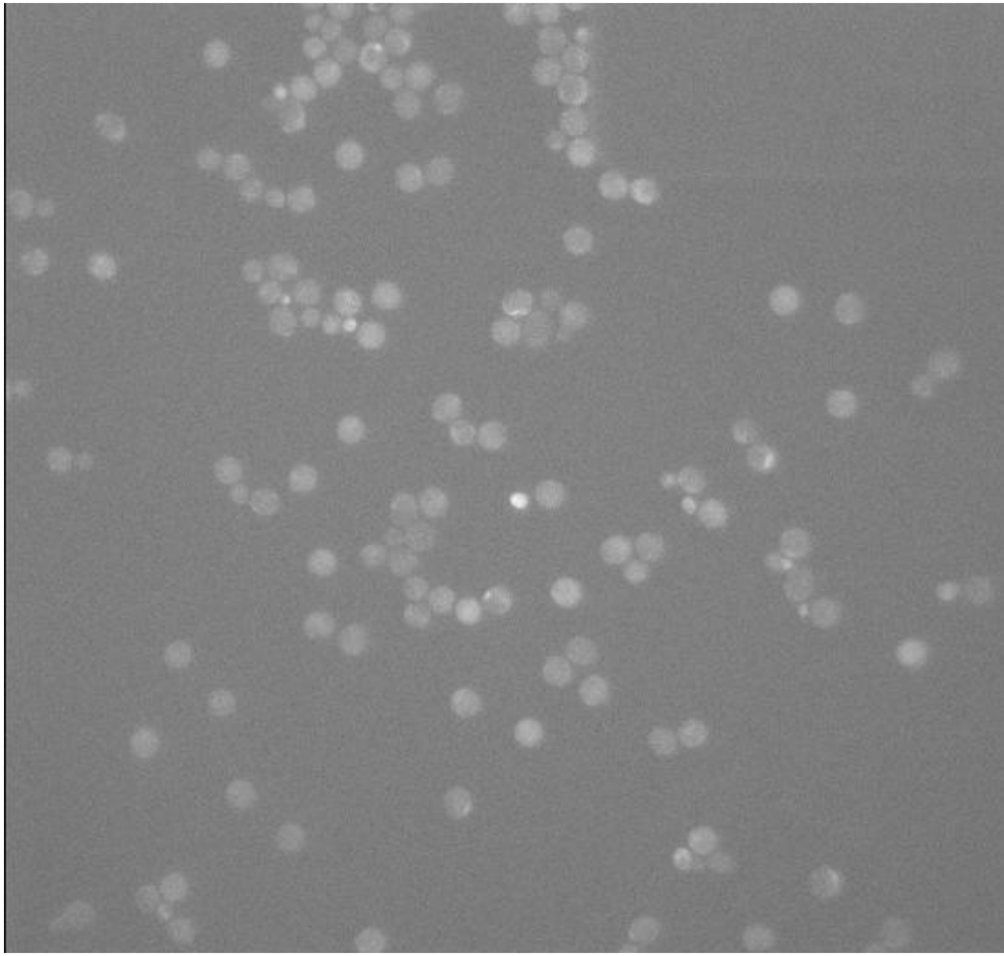


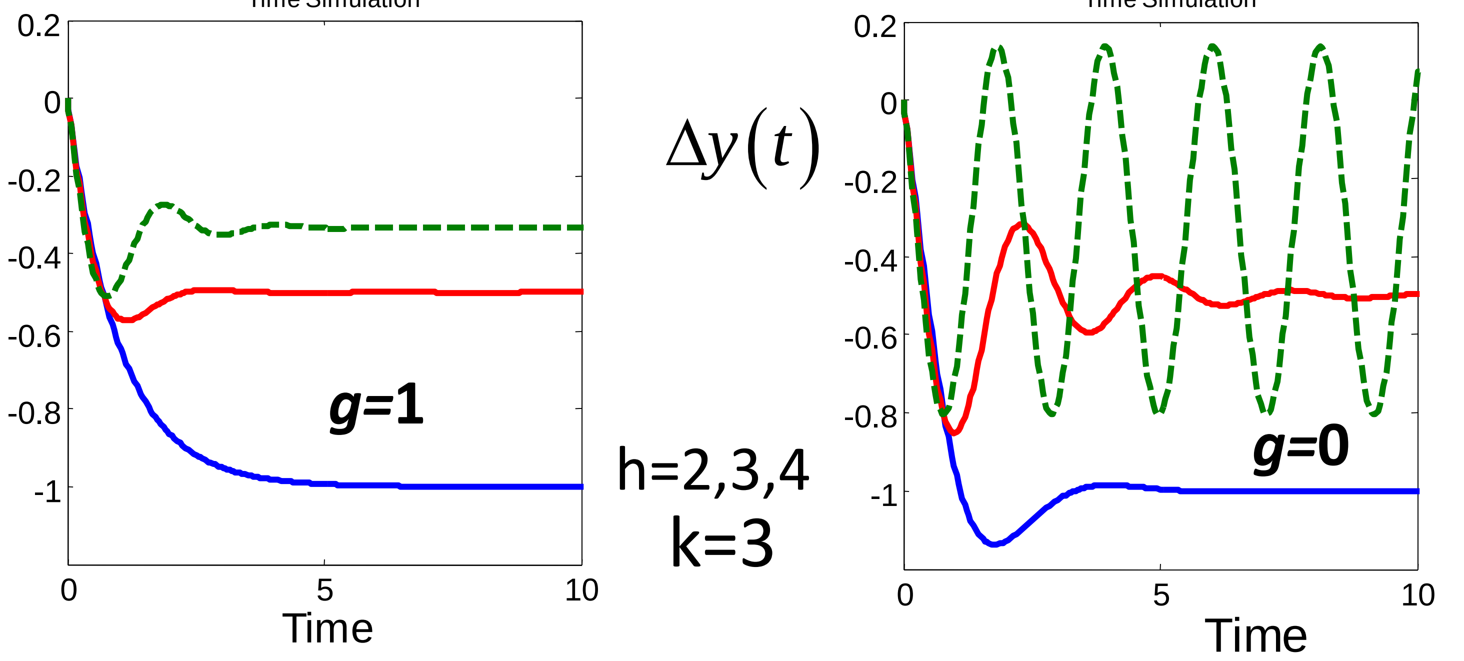


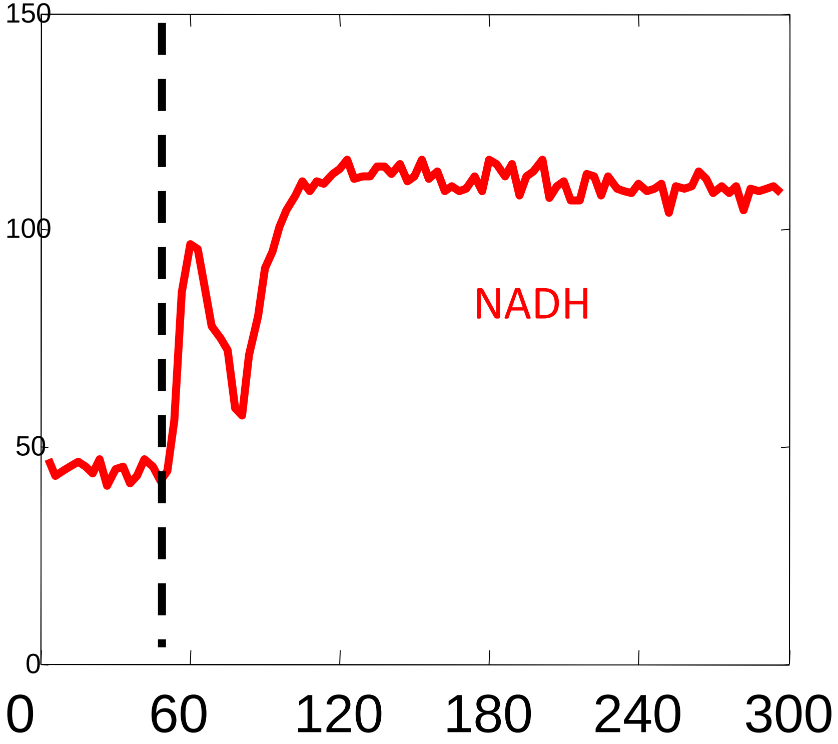
Worst case: Shift from aerobic/ethanol to anaerobic/glucose

- Microfluidic experiments
- Yeast strain W303 grown in Ethanol
- Glucose and KCN added →anaerobic glycolysis
- NADH measured every 3 s





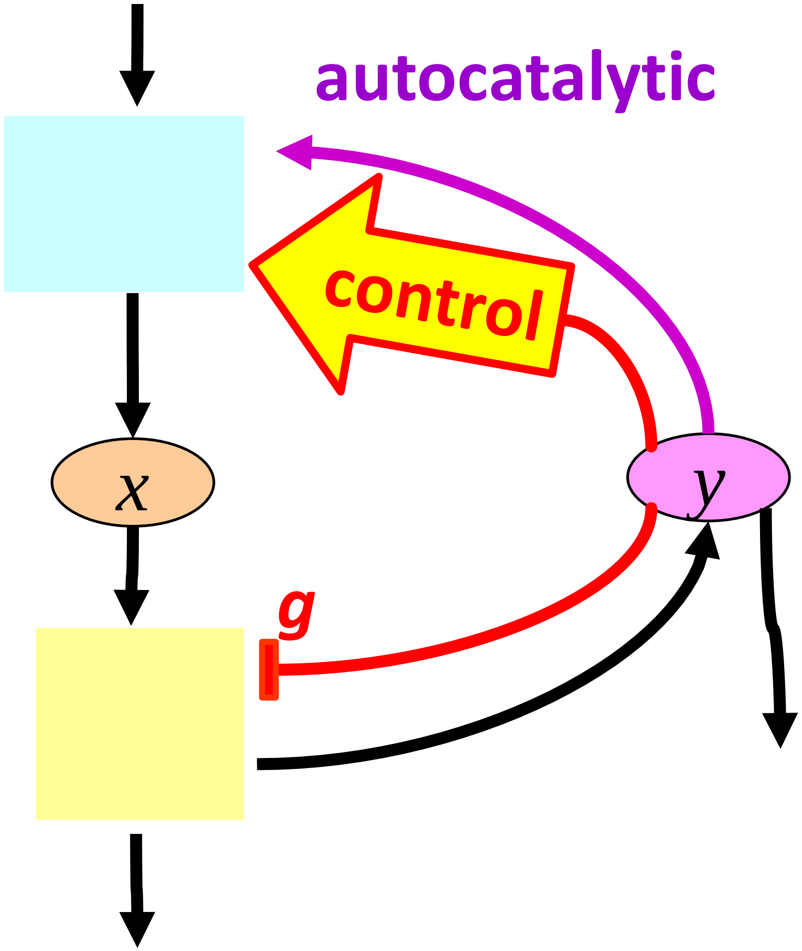




***g*=0 is implausibly fragile**

What about arbitrary

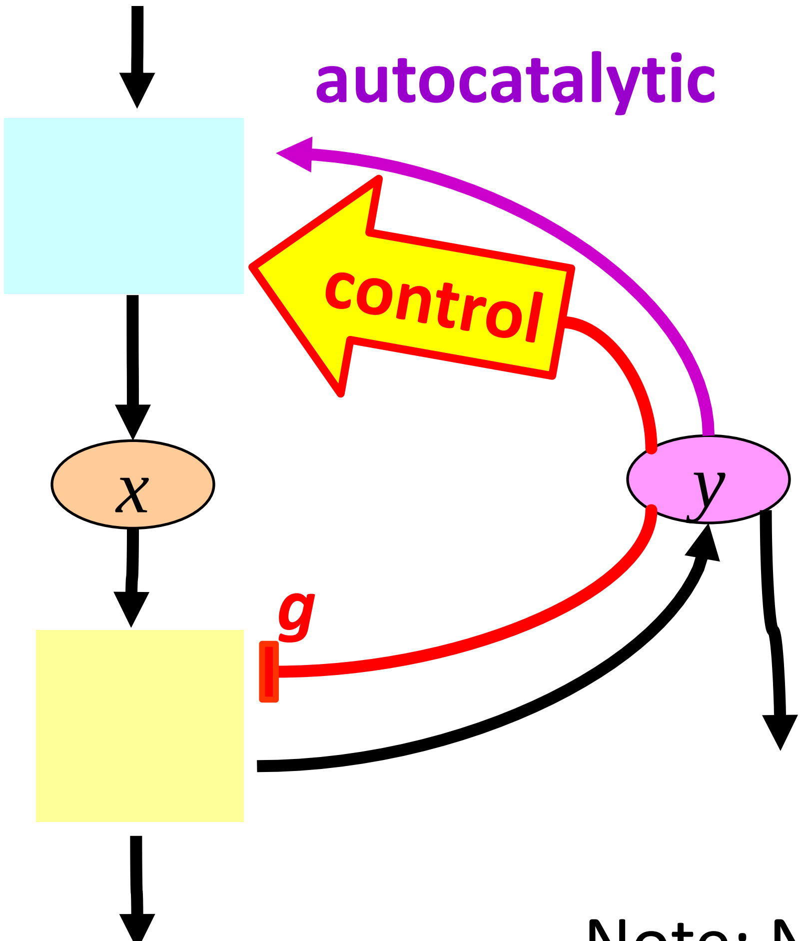
- Nonequilibrium (thermo)dynamics
- Control dynamics
- Realistic models

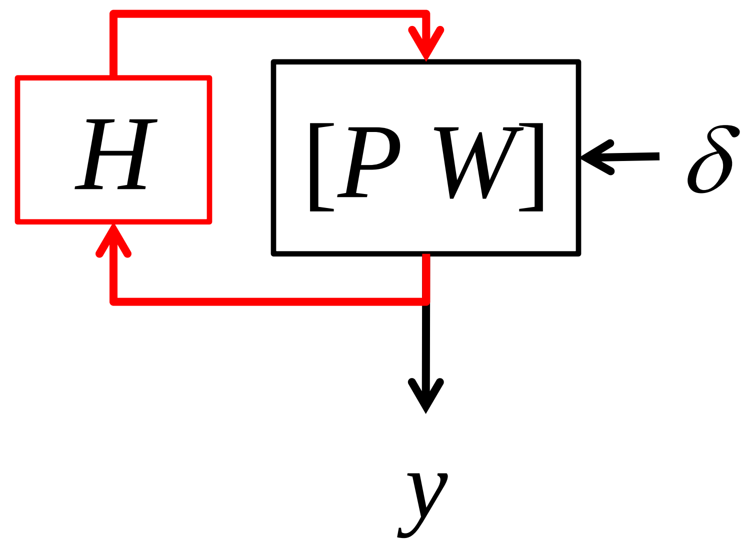


What if the control *implementation* is allowed arbitrarily complex dynamics (states plus nonlinearities)?

$$y = \begin{bmatrix} P & W \end{bmatrix} \begin{bmatrix} Hy \\ \delta \end{bmatrix}$$

$$\Rightarrow y = (1 - PH)^{-1} W\delta$$

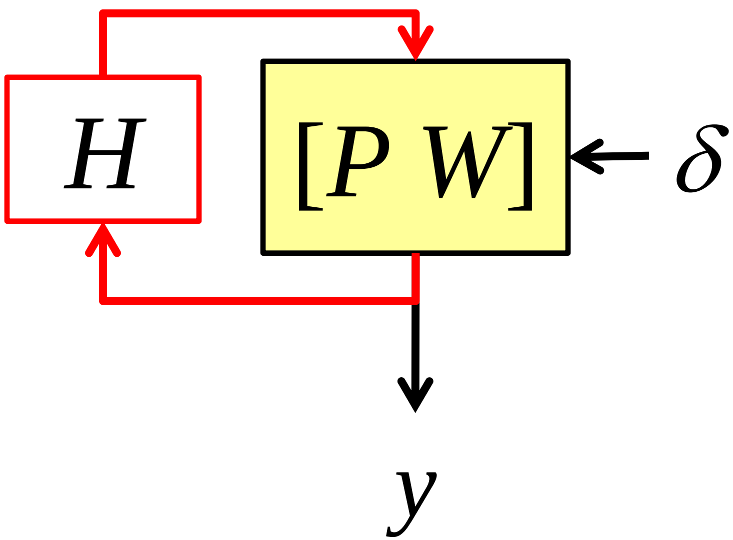




Note: Not ***physical*** interconnections

$$WS(s) \triangleq \frac{\hat{y}(s)}{\hat{\delta}(s)} \qquad \hat{y}(s) \triangleq \int_{-\infty}^{\infty} y(t)e^{-st}dt$$

$$D(s) = s^2 + (k + g + a(a+g))s - ka \qquad P(s) = \frac{-as+k}{D(s)}$$



$$\begin{bmatrix} P & W \end{bmatrix} = \frac{1}{D(s)}\begin{bmatrix} -as+k & s+k \end{bmatrix}$$

$$W(s) = \frac{s+k}{D(s)}$$

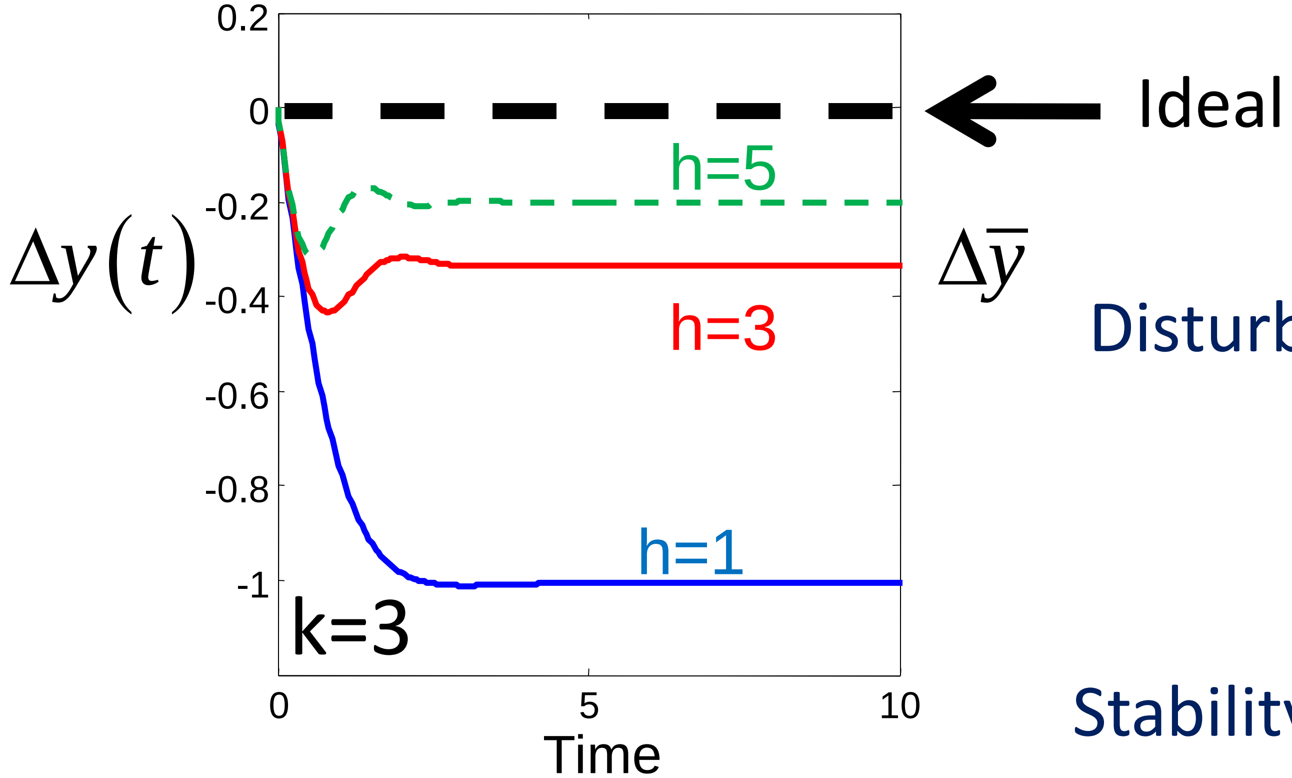
$$W(s) \triangleq -\left(\frac{s+k}{s^2 + (k+g+q(a+g))s - ka} \right) \quad S(s) \triangleq \left(\frac{s^2 + (k+g+q(a+g))s - ka}{s^2 + (k+g+q(a-h+g))s - k(a-h)} \right)$$

Doesn't depend on h

Does depend on h

$$\ln\left|WS(j\omega)\right| = \ln\left|W(j\omega)\right| + \ln\left|S(j\omega)\right|$$

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

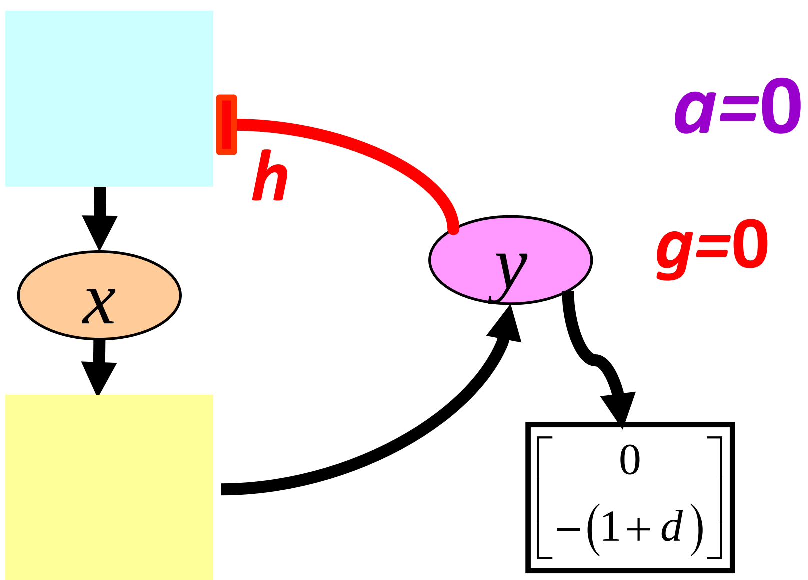


Disturbance response

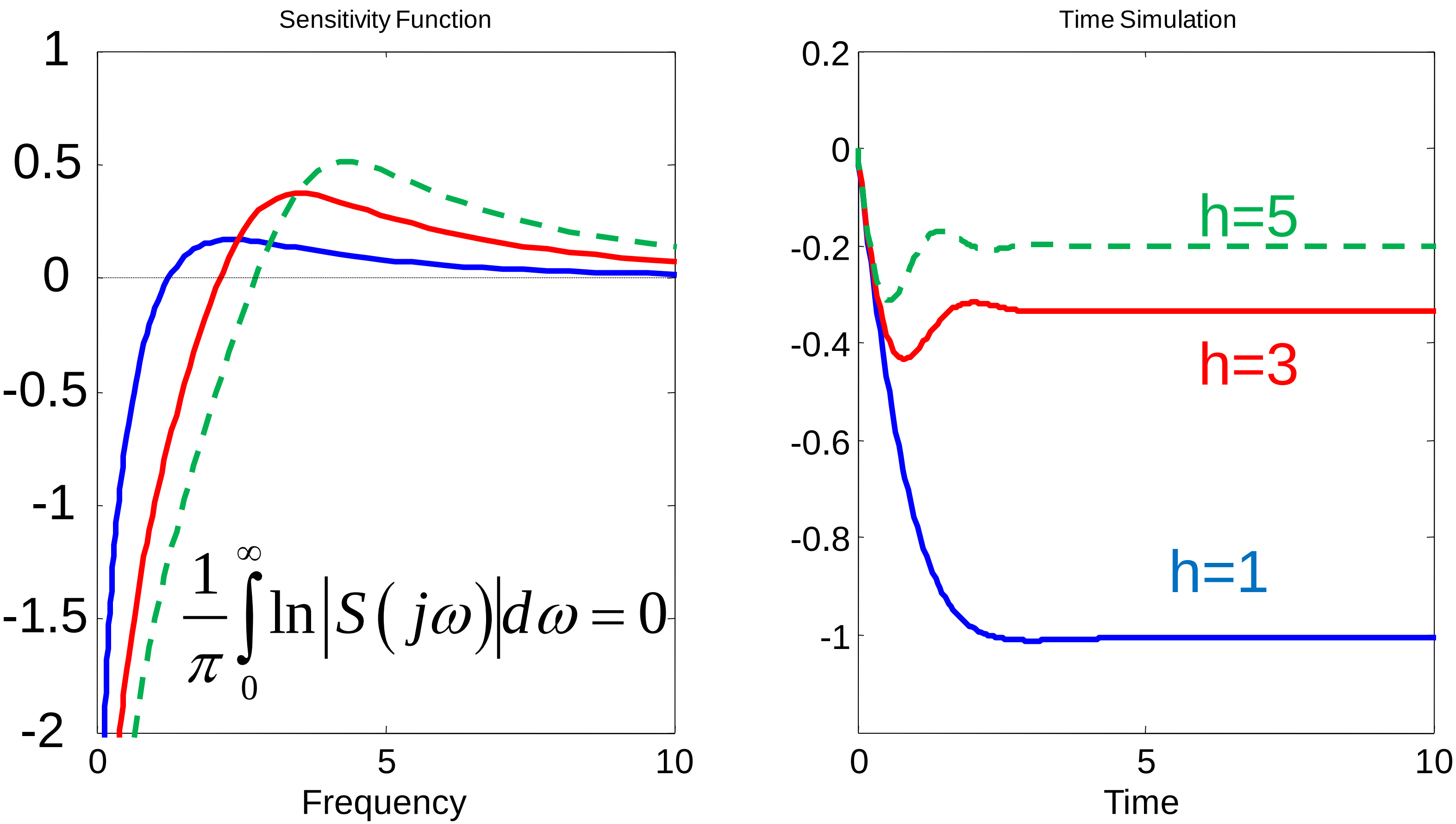
$$\left|\frac{\bar{y}}{\bar{d}}\right| = \left|\frac{1}{h}\right|$$

Stability

$$0 < h < \infty$$



$$A = \begin{bmatrix} -k & -h \\ k & 0 \end{bmatrix}$$

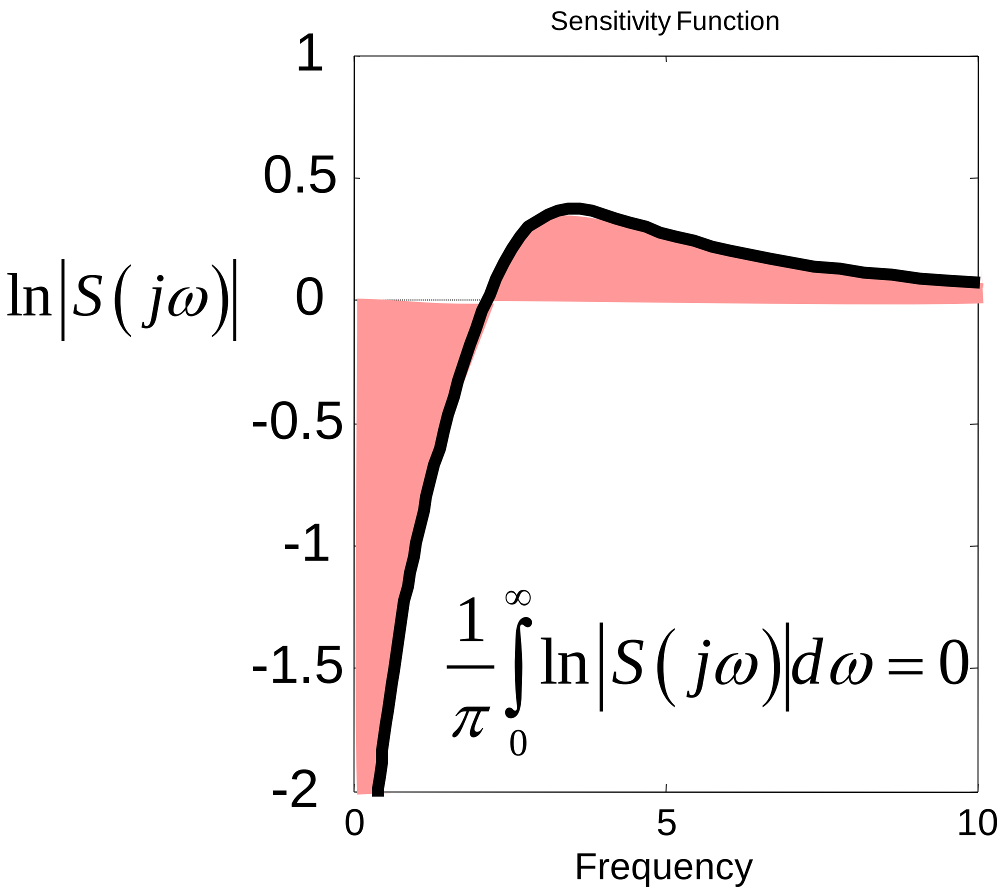


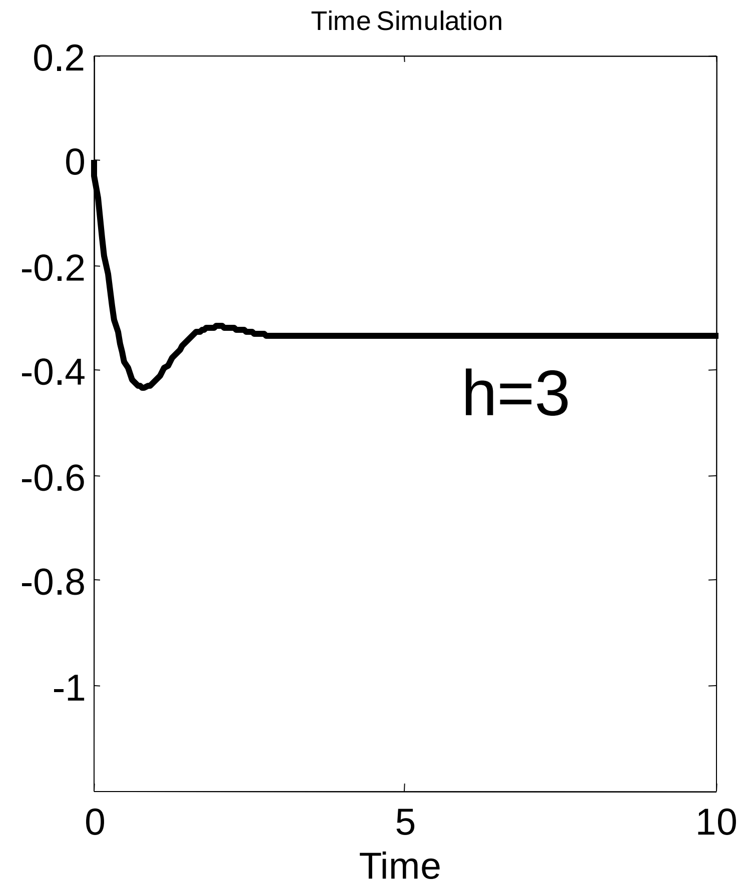
$$\ln|S(j\omega)|$$

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

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

$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$





No matter what!

$$\text{Thm}: \frac{1}{\pi}\int_0^\infty \ln|S(j\omega)|\,d\omega \geq 0$$

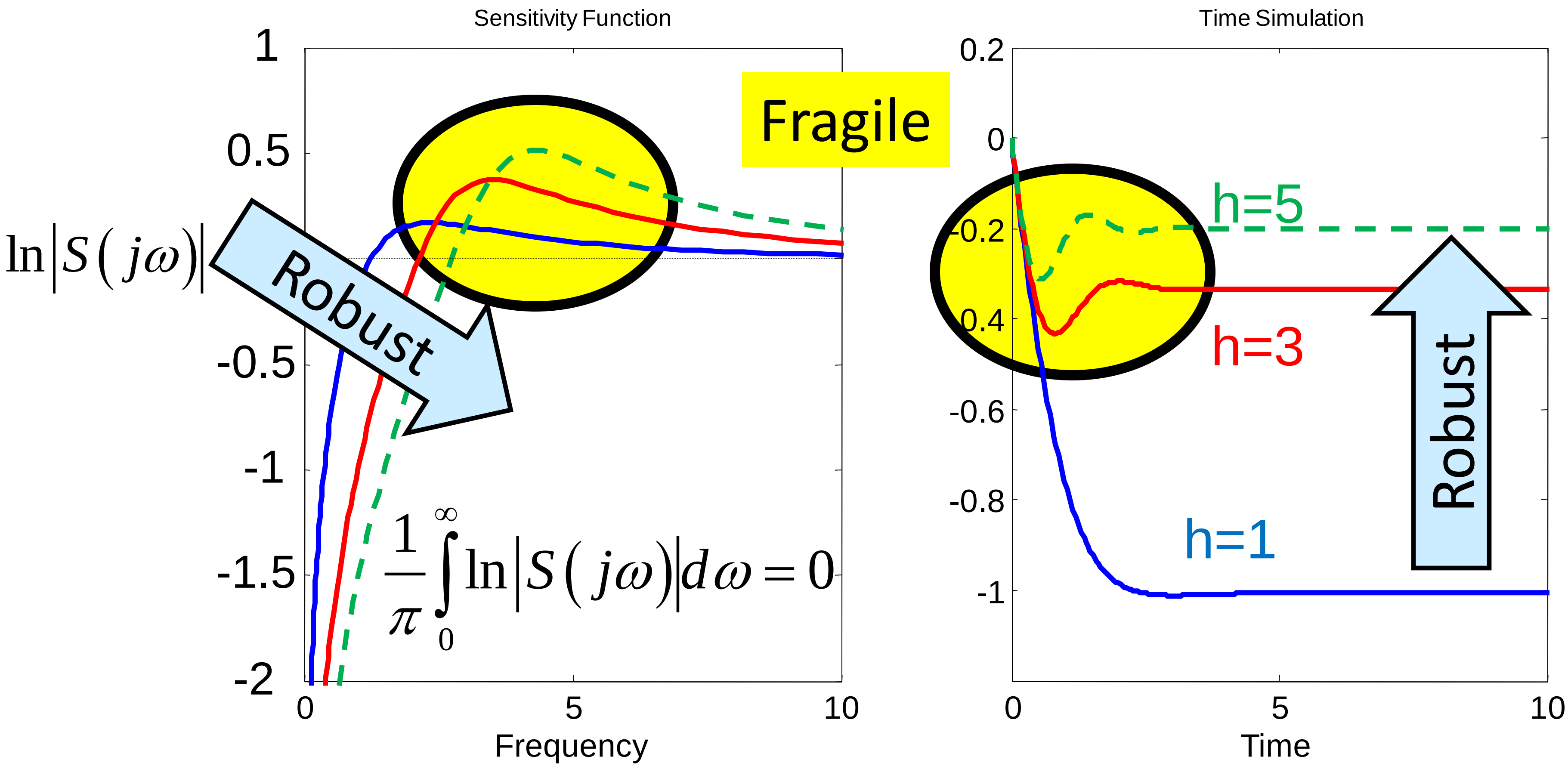
$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$

Gratuitous fragility versus fragile robustness

$$\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq 0$$

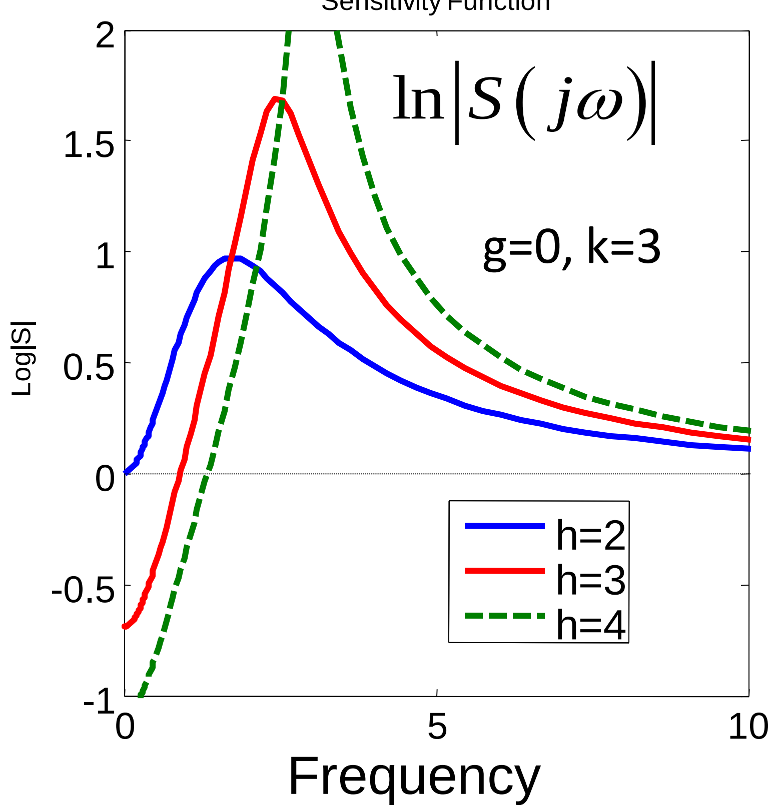
$\gg \quad \Rightarrow \quad$ Gratuitous fragility

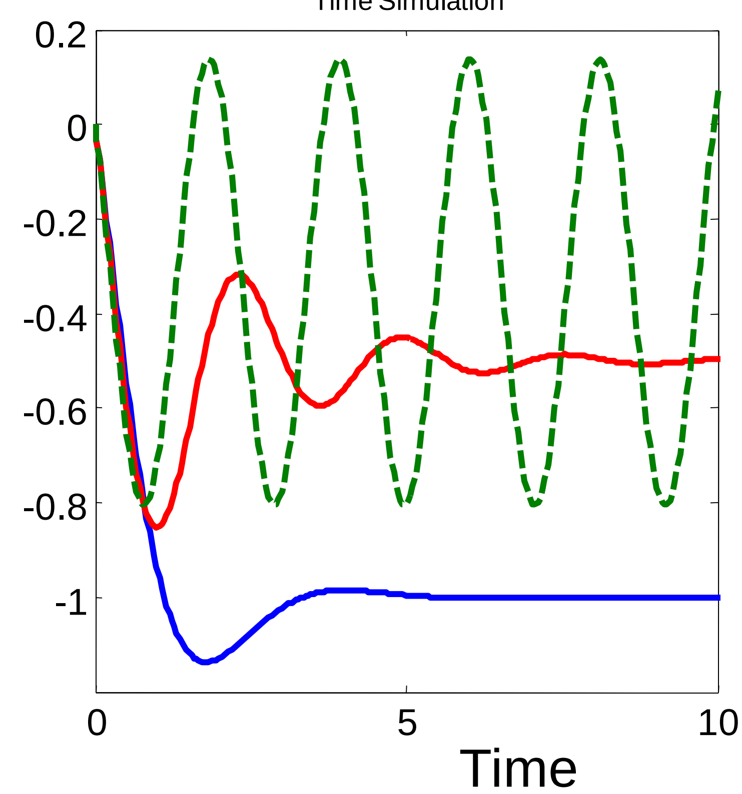
$= \quad \Rightarrow \quad$ Fragile robustness



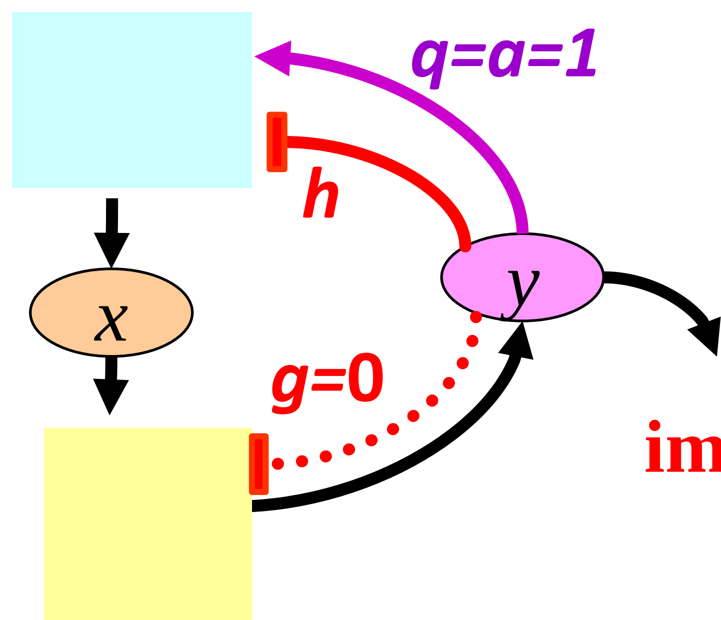
$$\text{Thm}: \frac{1}{\pi}\int_0^\infty \ln|S(j\omega)|d\omega \geq 0$$

$$\ln|WS(j\omega)| = \ln|W(j\omega)| + \ln|S(j\omega)|$$

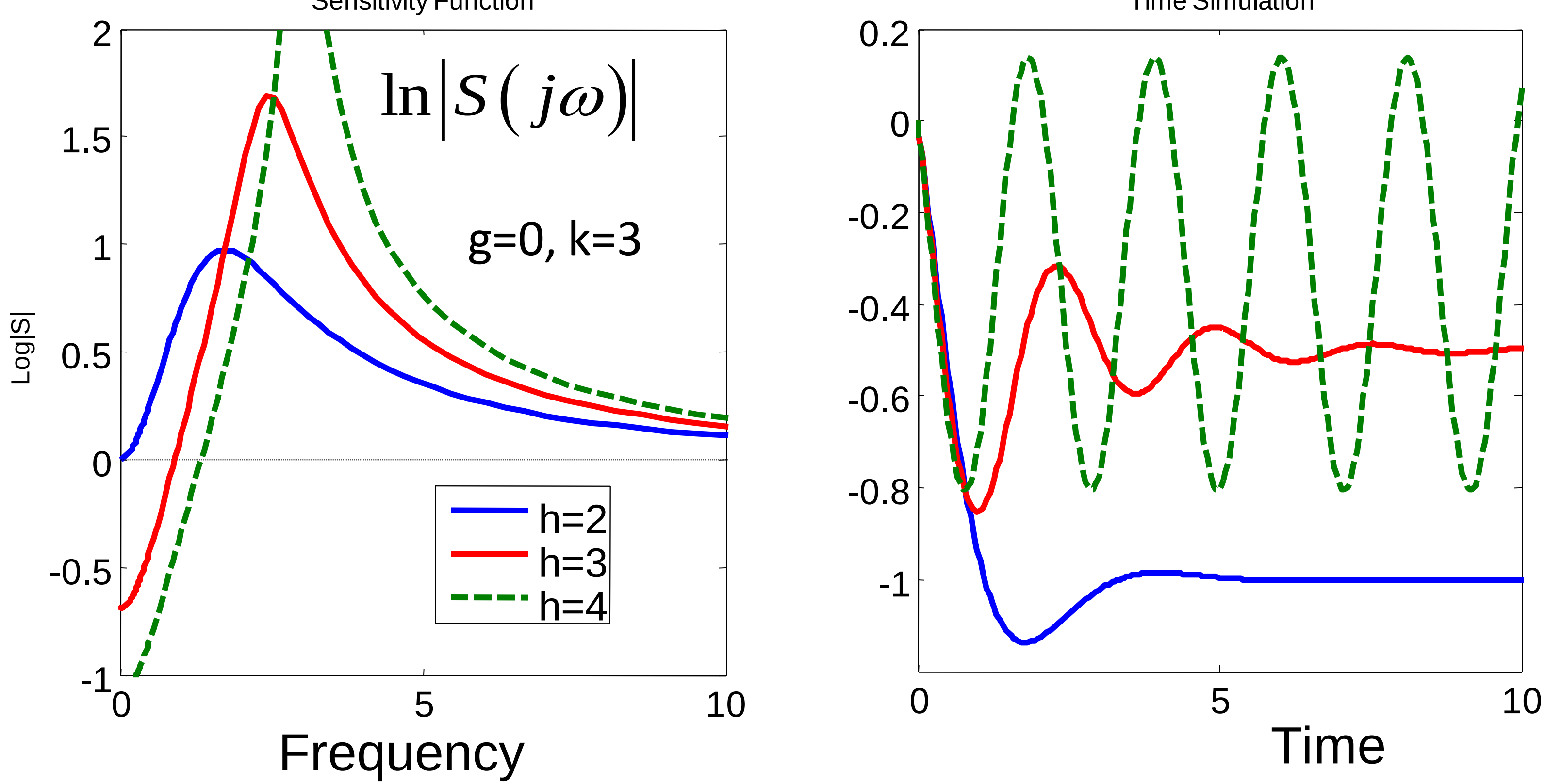




k=3, h=2,3,4



g=0 is implausibly fragile



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

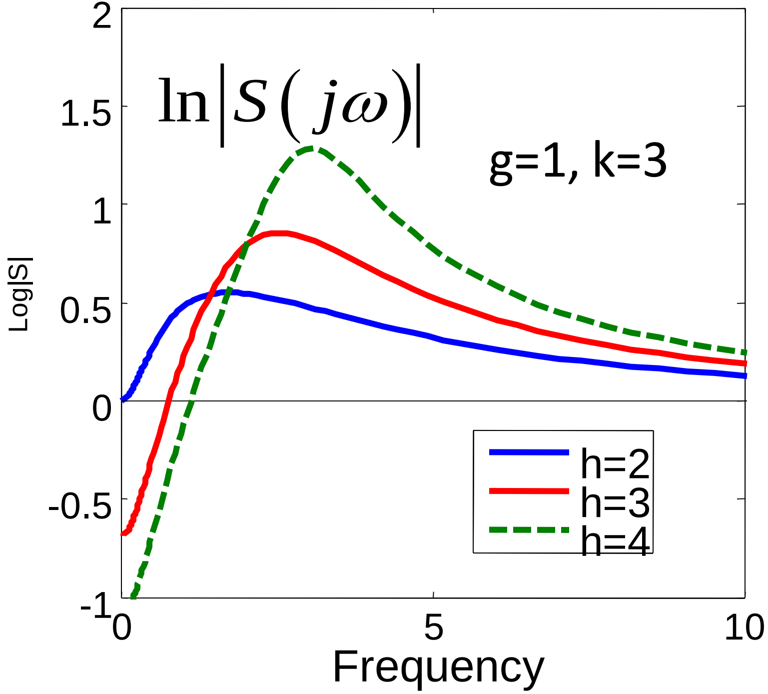
Large *k* good

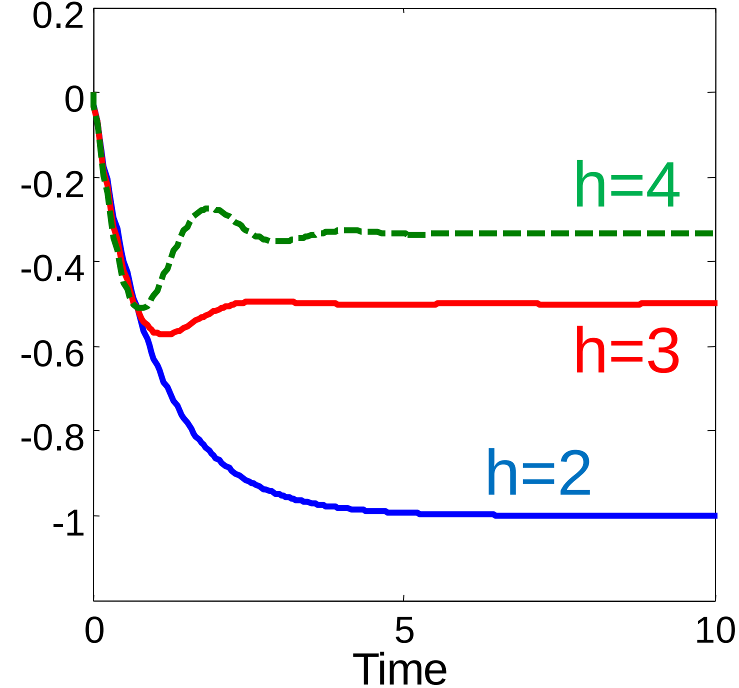
Large *a* bad

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

Small *z* is bad

***g*=0 is implausibly fragile**





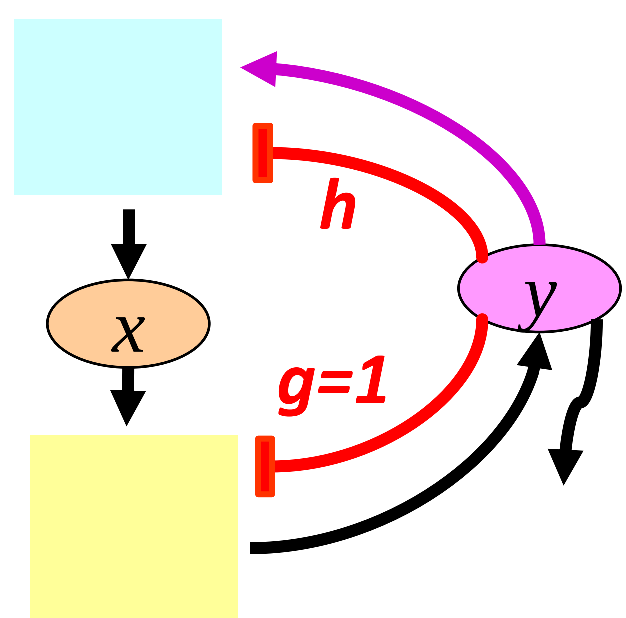
$$\frac{1}{\pi}\int_0^\infty \ln|S(j\omega)|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

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

Small z is bad

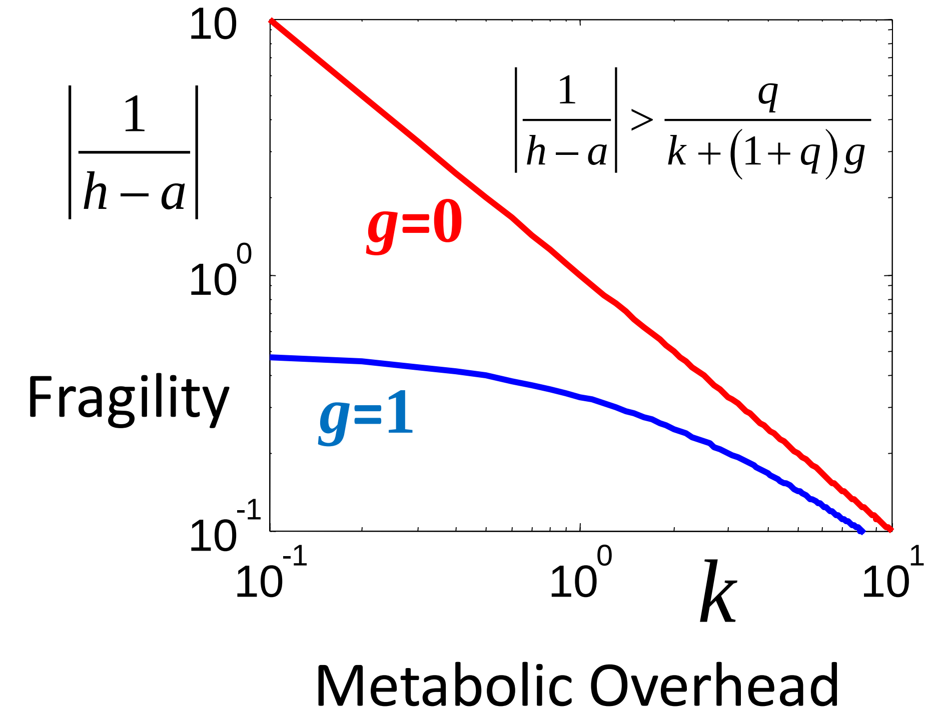
$$p = RHPzero\left(s^2 + (k+g+a(a+g))s - ka\right)$$

Small p is good



$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

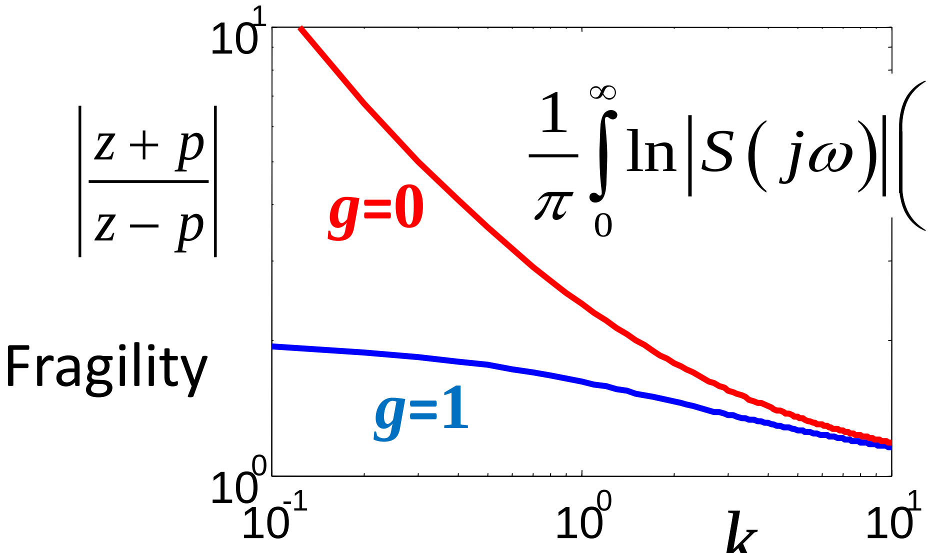
Static + stability + phenomenology

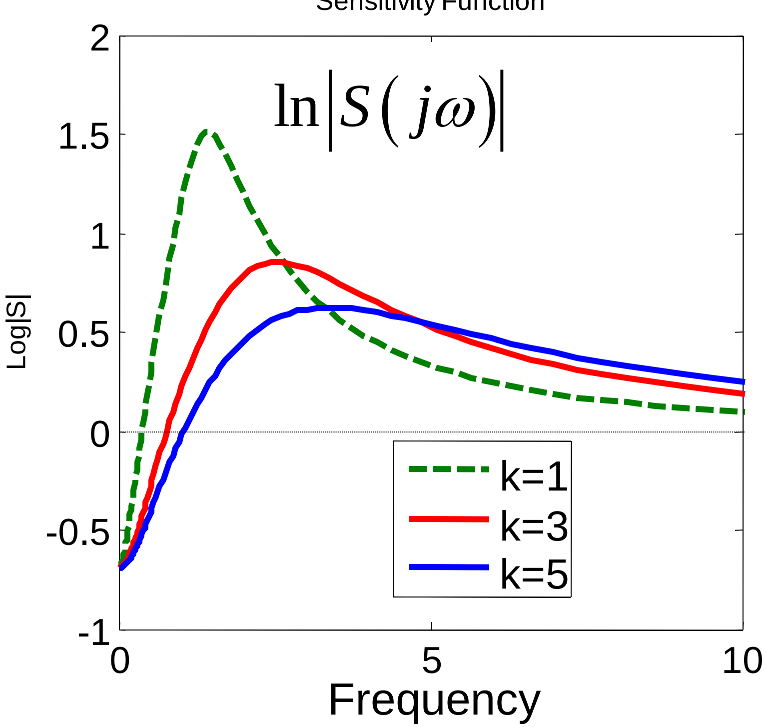


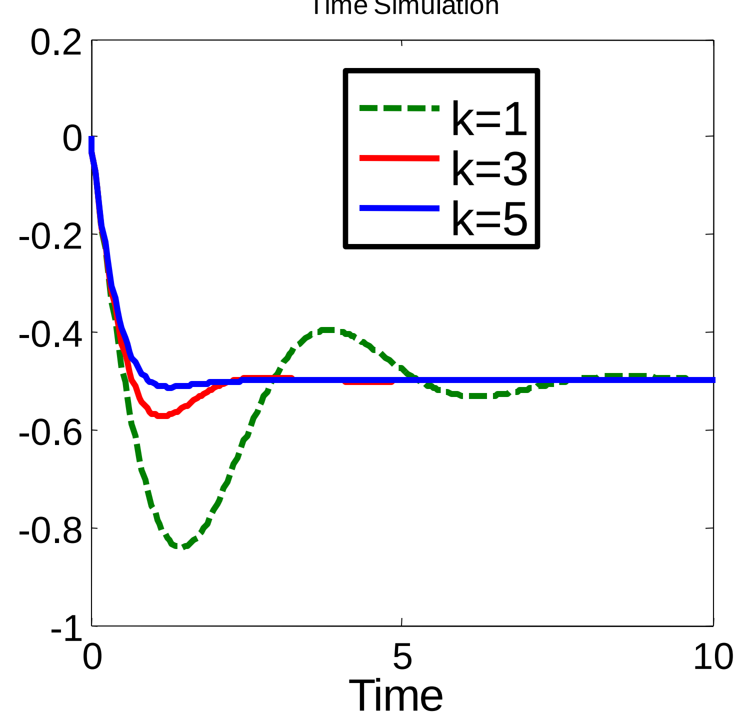
$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega$$

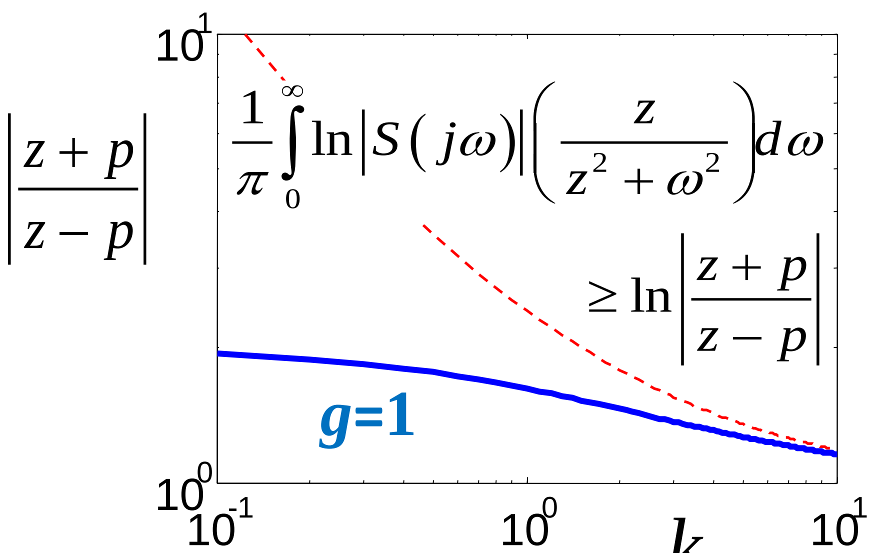
$$\geq \ln\left|\frac{z+p}{z-p}\right|$$

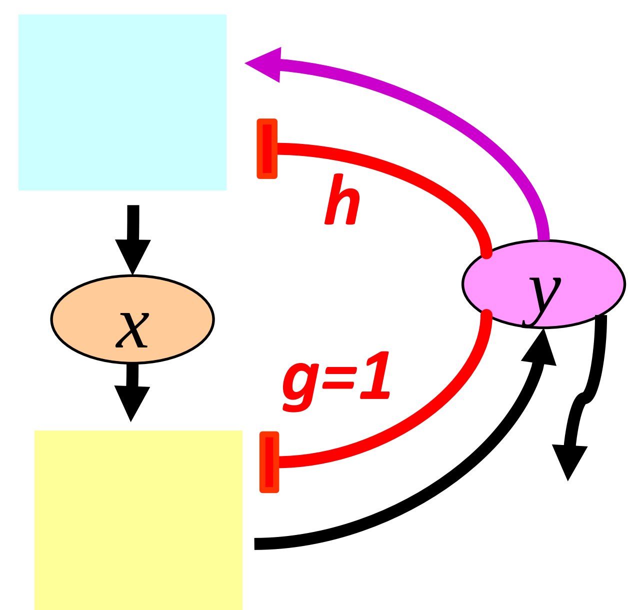
Dynamic + rigor







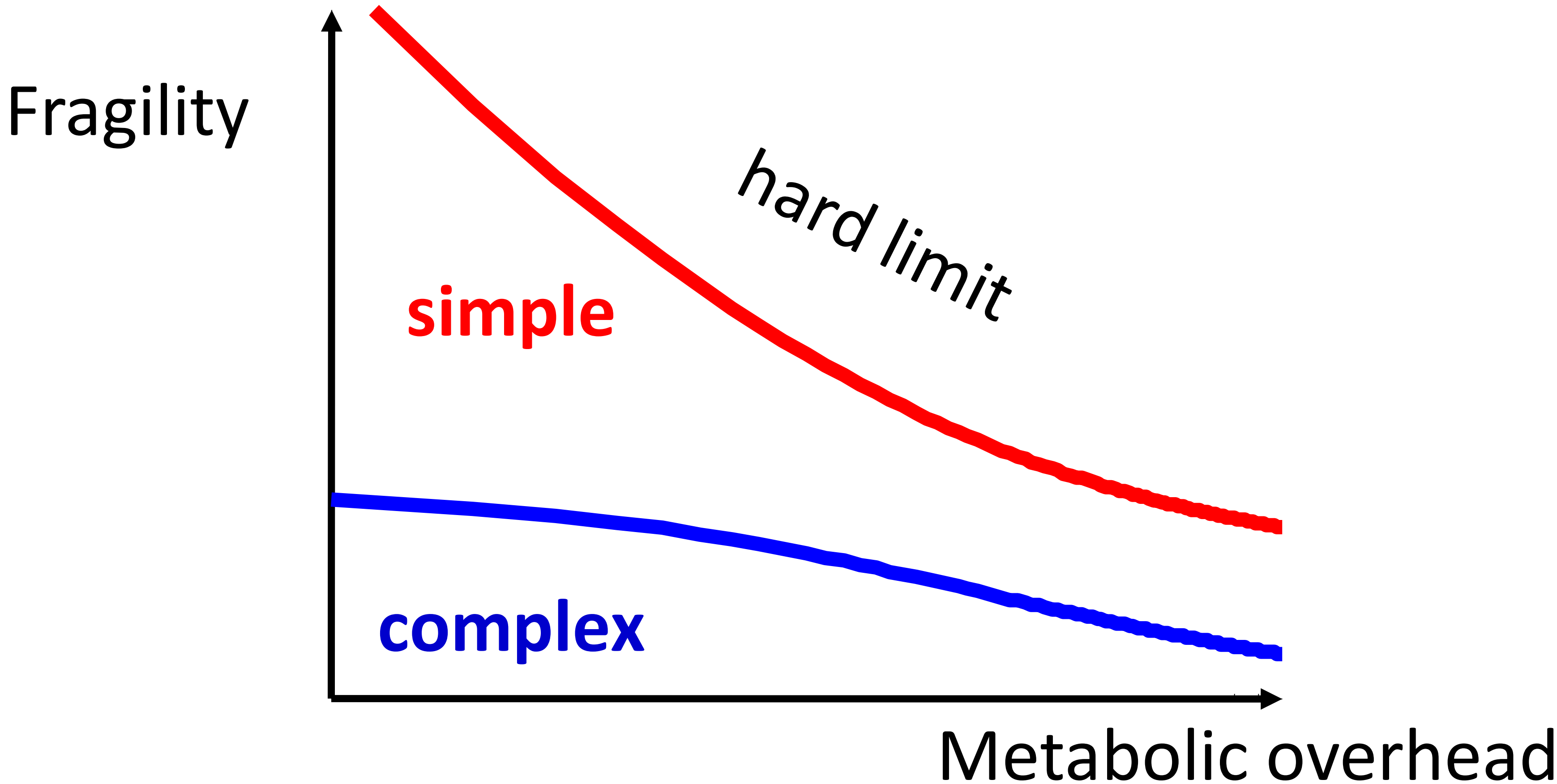




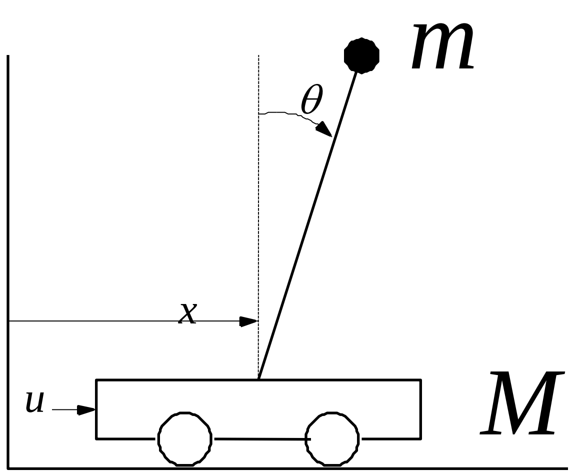
Metabolic overhead

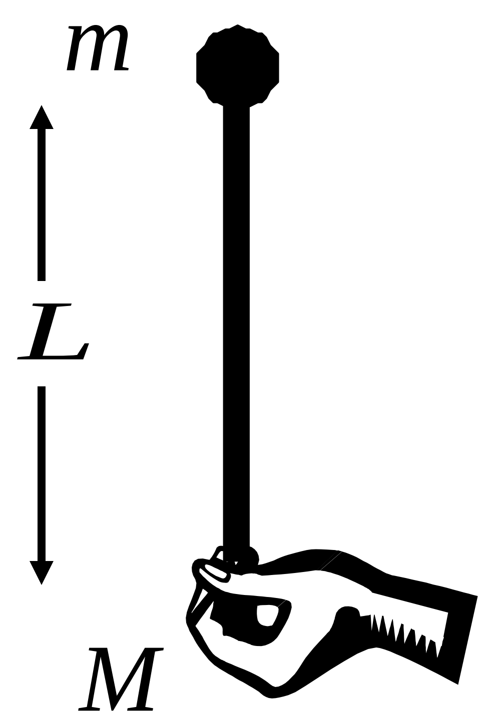
Hard tradeoffs between

1. Fragility (disturbance rejection)
2. Amount (of enzymes)
3. Complexity (of enzymes)



Linearized pendulum on a cart



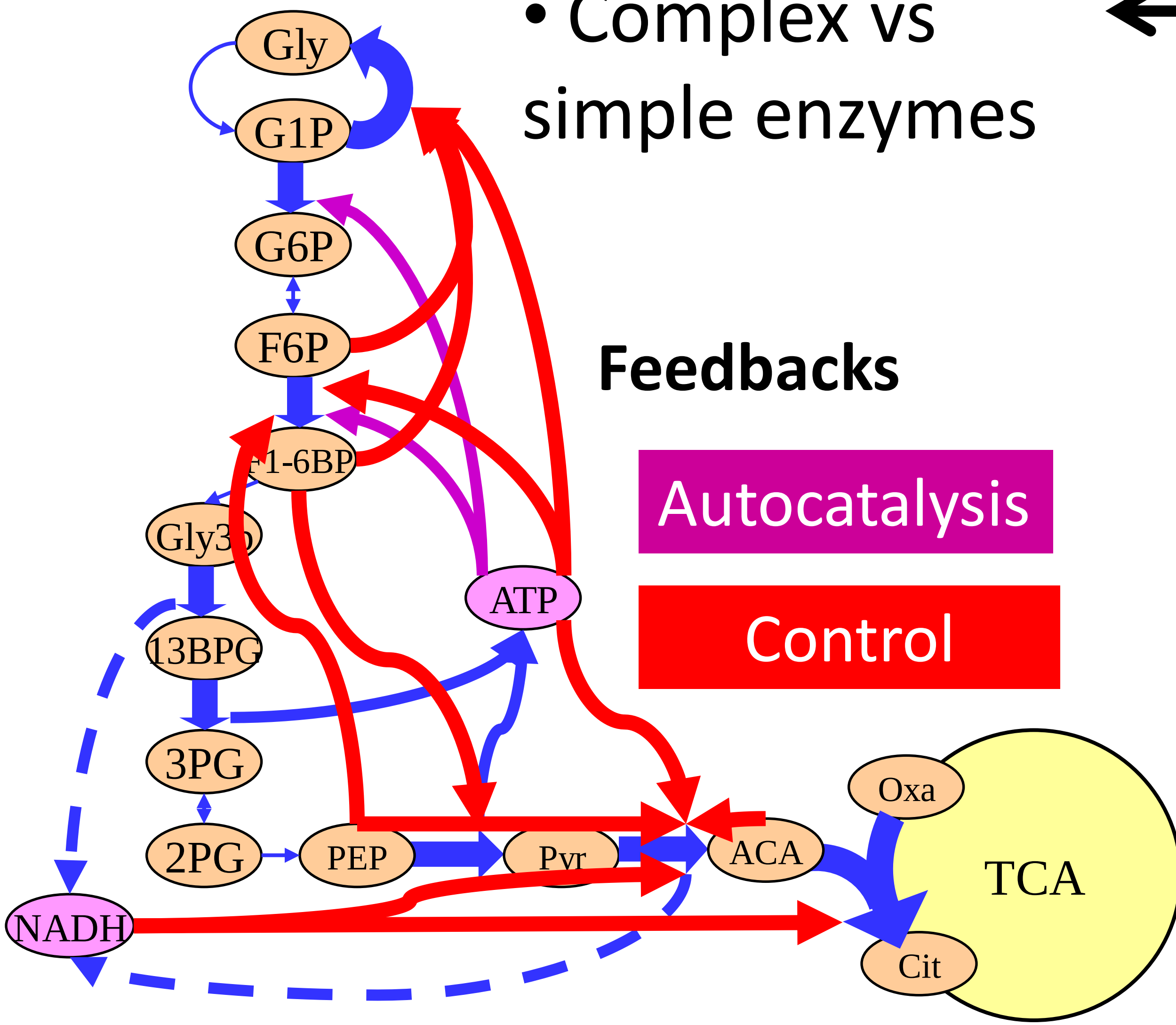


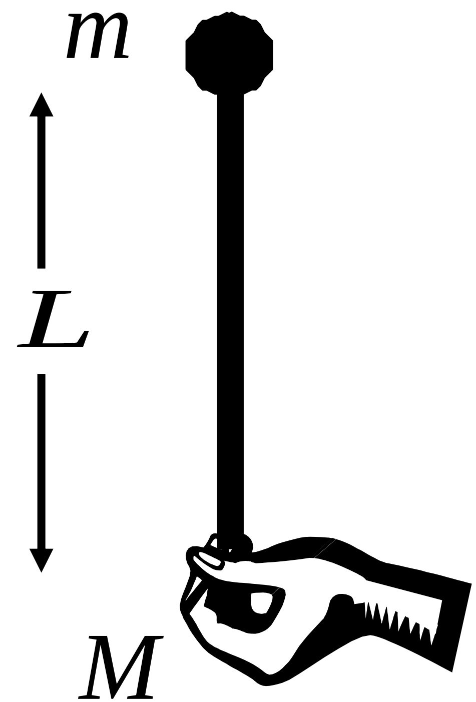
$$\frac{d}{dt}\begin{bmatrix} x \\ \theta \\ \dot{x} \\ \dot{\theta} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & \frac{m^2 g l^2}{q} & \frac{-(J+ml^2)b}{q} & 0 \\ 0 & \frac{mgl(M+m)}{q} & \frac{-mlb}{q} & 0 \end{bmatrix} x + \begin{bmatrix} 0 \\ 0 \\ \frac{J+ml^2}{q} \\ \frac{ml}{q} \end{bmatrix} u$$

$$q = J(M+m) + Mml^2$$

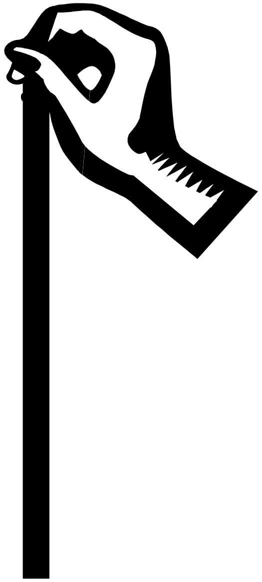
Translation

- Autocatalytic ⟷ • ≈ Up
- Complex vs simple enzymes ⟷ • ≈ eyes vs no eyes





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



Easy, even with eyes closed

No matter what the length

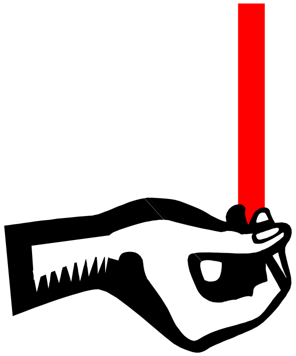
Gratuitous fragility
versus
fragile robustness

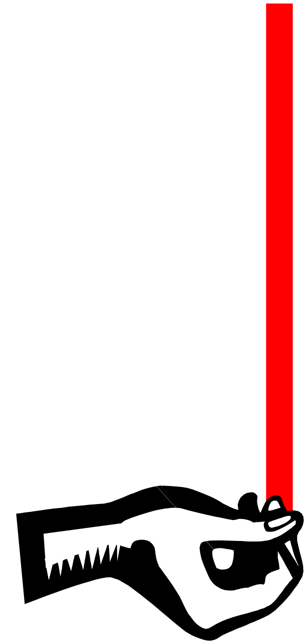
$$\int_0^\infty \ln\left|S(j\omega)\right| d\omega \geq 0$$

$$\gg \quad \Rightarrow \quad \text{Gratuitous fragility}$$

$$= \quad \Rightarrow \quad \text{Fragile robustness}$$

Up is hard for shorter lengths

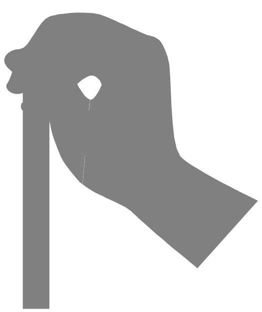


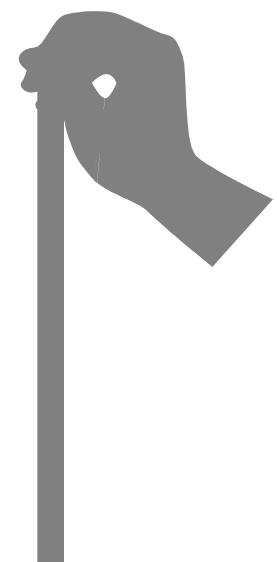


$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| d\omega \geq |p|$$

$$p = z\sqrt{1+r} = \sqrt{\frac{g}{L}(1+r)}$$

$$p \ \text{small} \Rightarrow L \ \text{large}$$





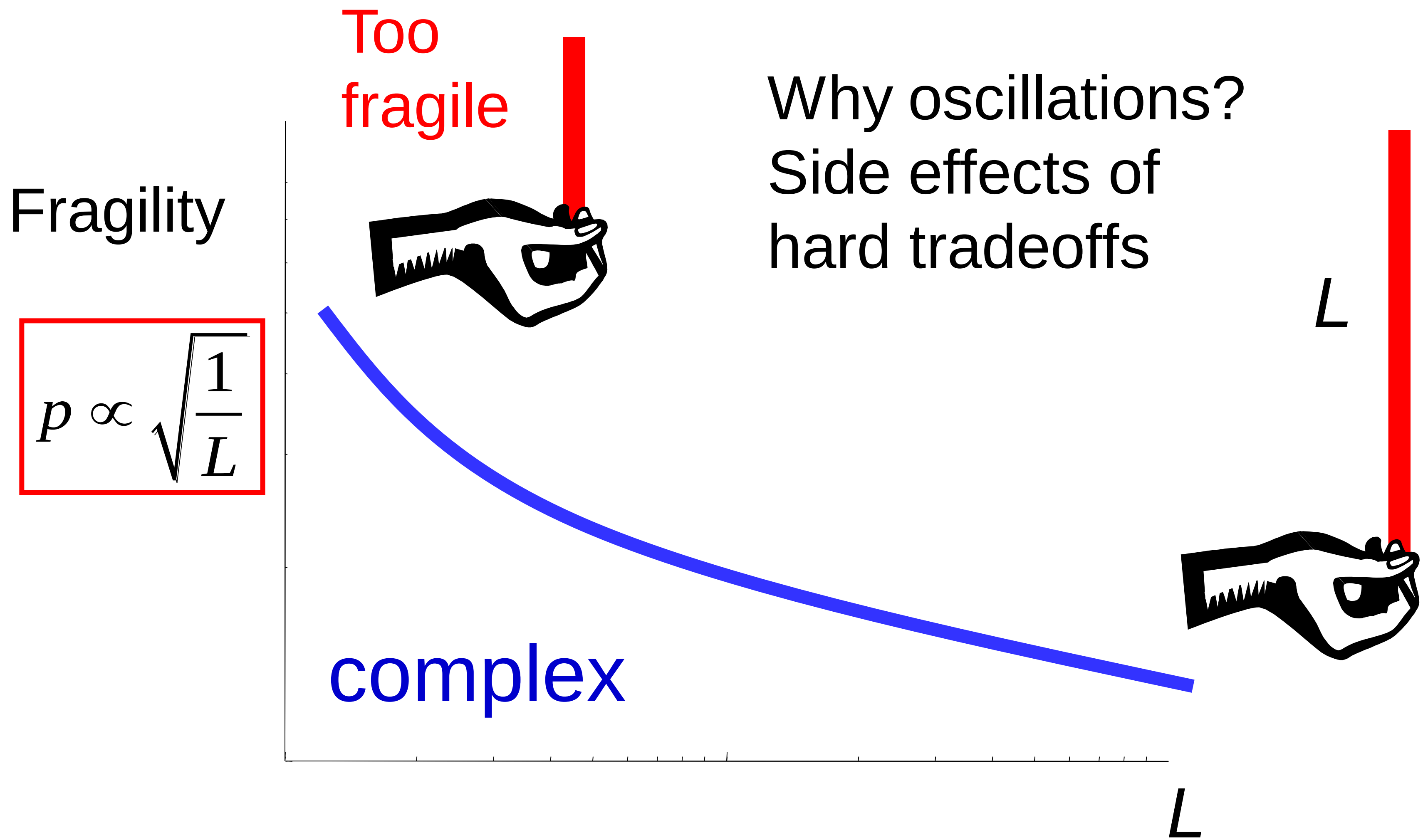
Down easy, even with

- eyes closed
- all lengths

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

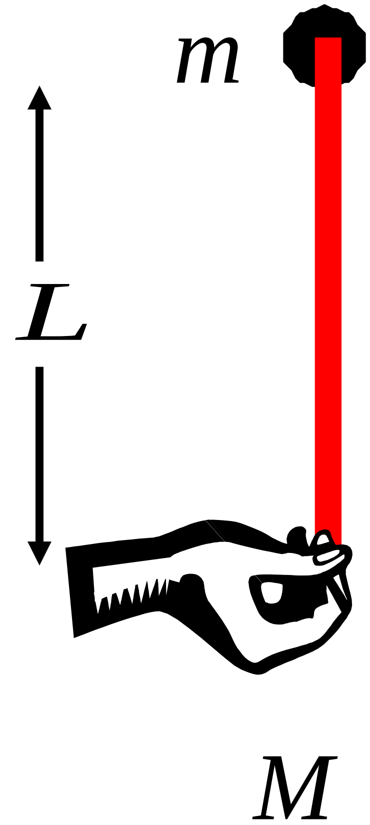
This is a cartoon, but can be made precise.

$$p \propto \sqrt{\frac{1}{L}}$$



Why oscillations?
Side effects of hard tradeoffs

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



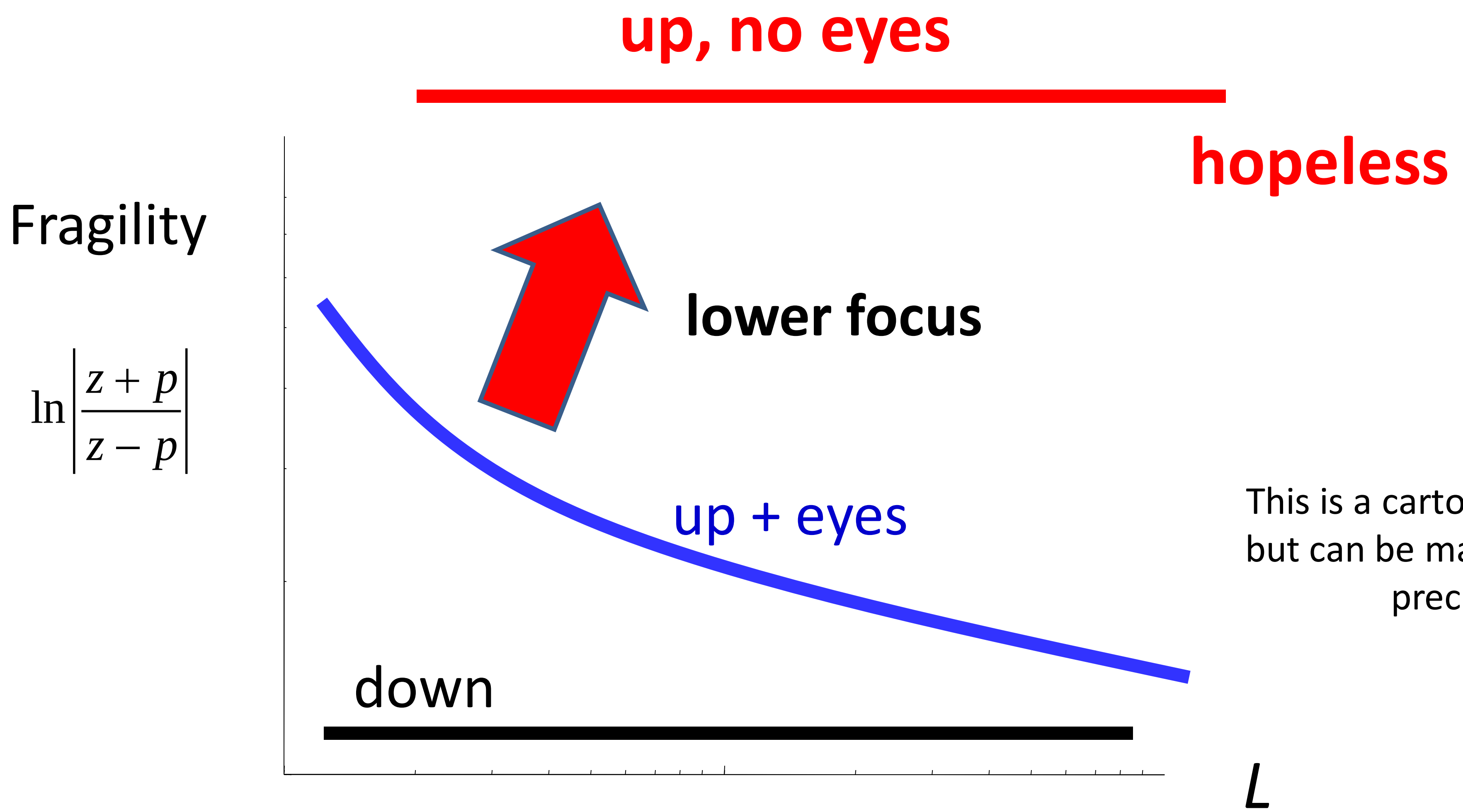
Eyes closed

$$z=\sqrt{\frac{g}{L}} \qquad p = z\sqrt{1+r} \qquad r=\frac{m}{M}$$

$$\frac{p+z}{p-z}=\frac{\sqrt{1+r}+1}{\sqrt{1+r}-1}$$

Want r and z large (but p small).

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

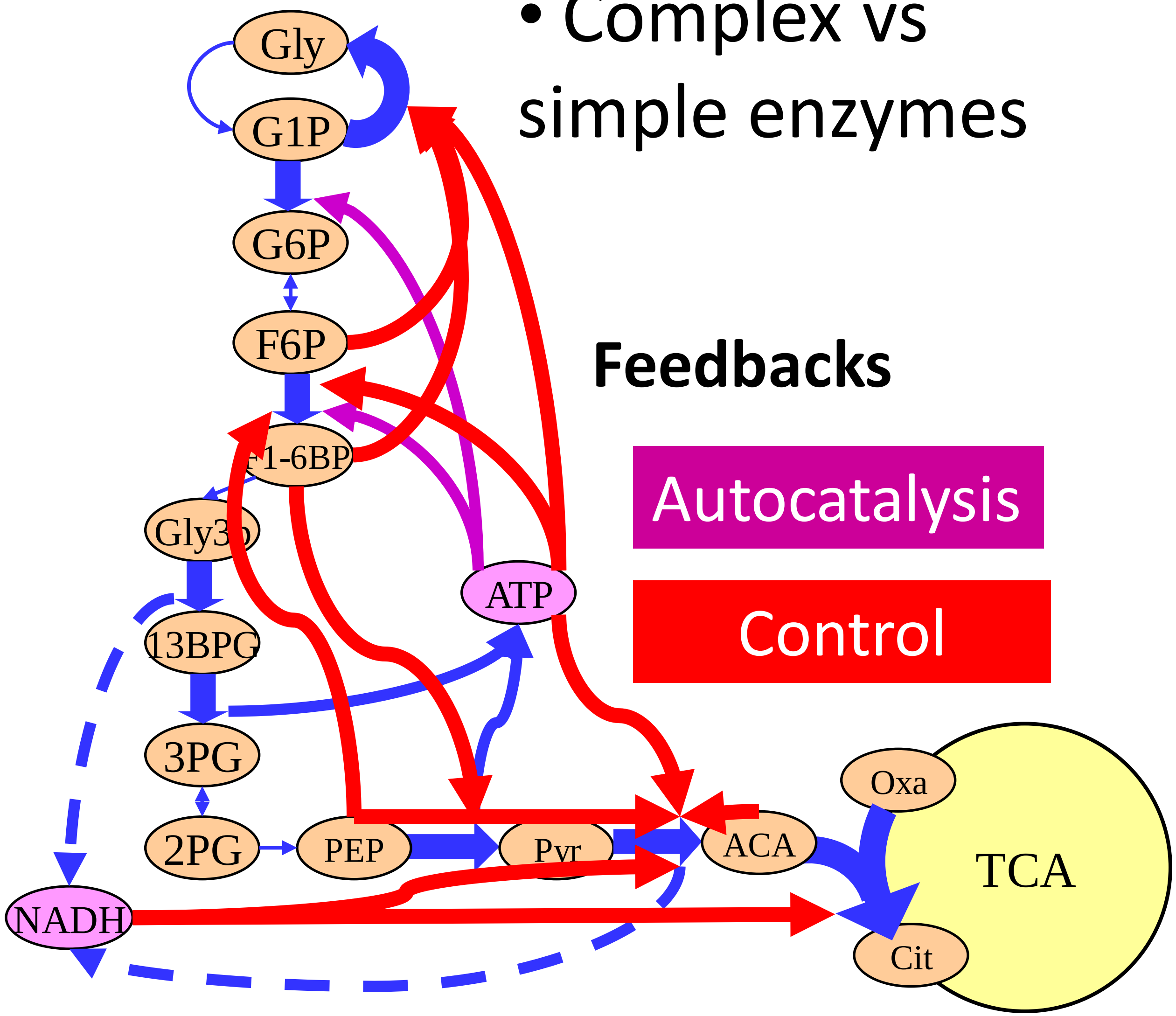


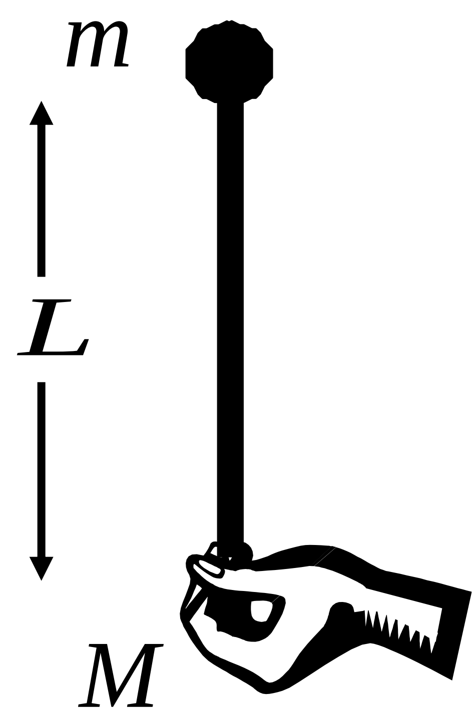
This is a cartoon, but can be made precise.

Translation

- Autocatalytic
- Complex vs simple enzymes

- ≈ Up
- ≈ eyes vs no eyes

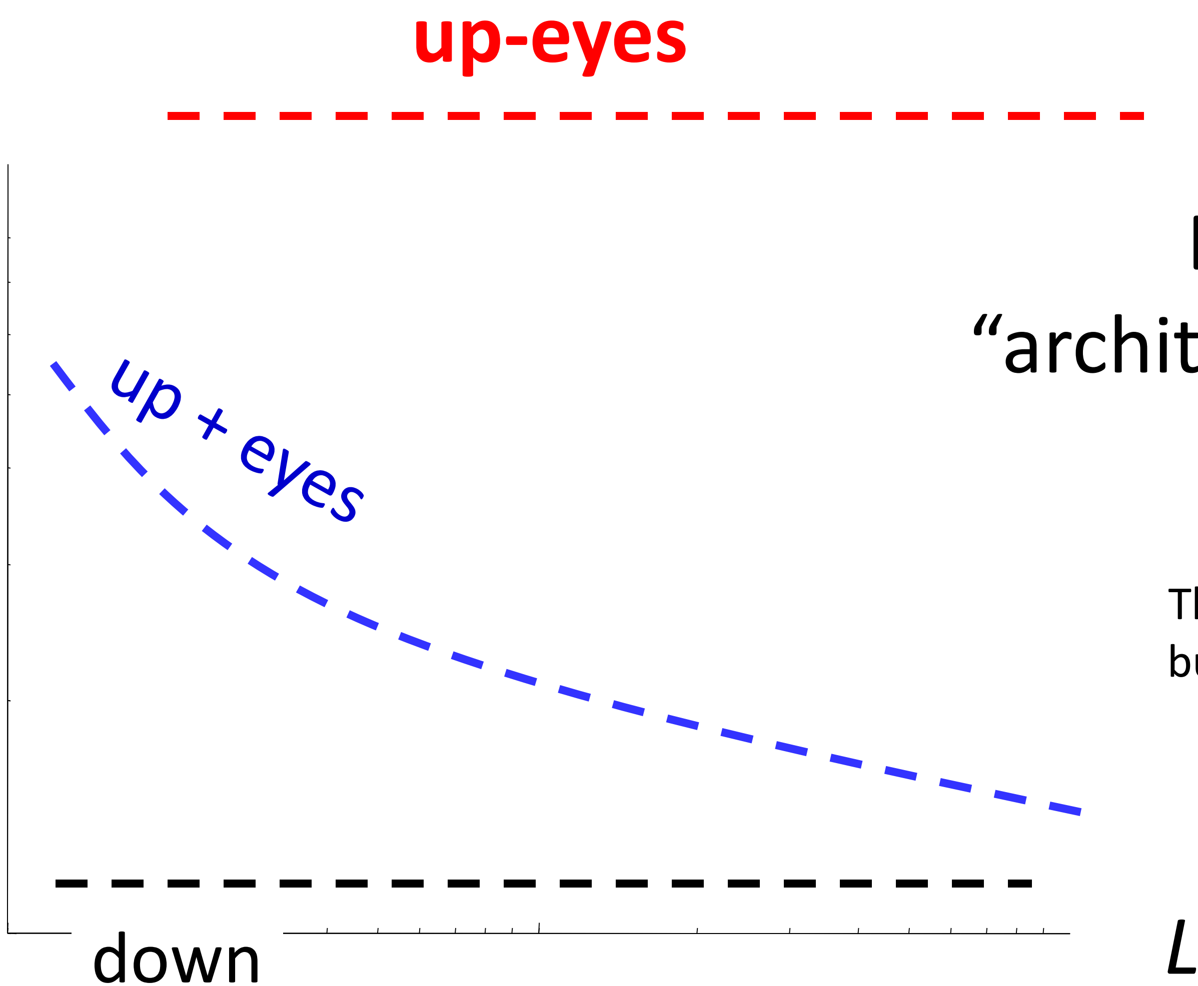




Theorem $$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

Fragility

$$\ln\left|\frac{z+p}{z-p}\right|$$



Different “architectures”

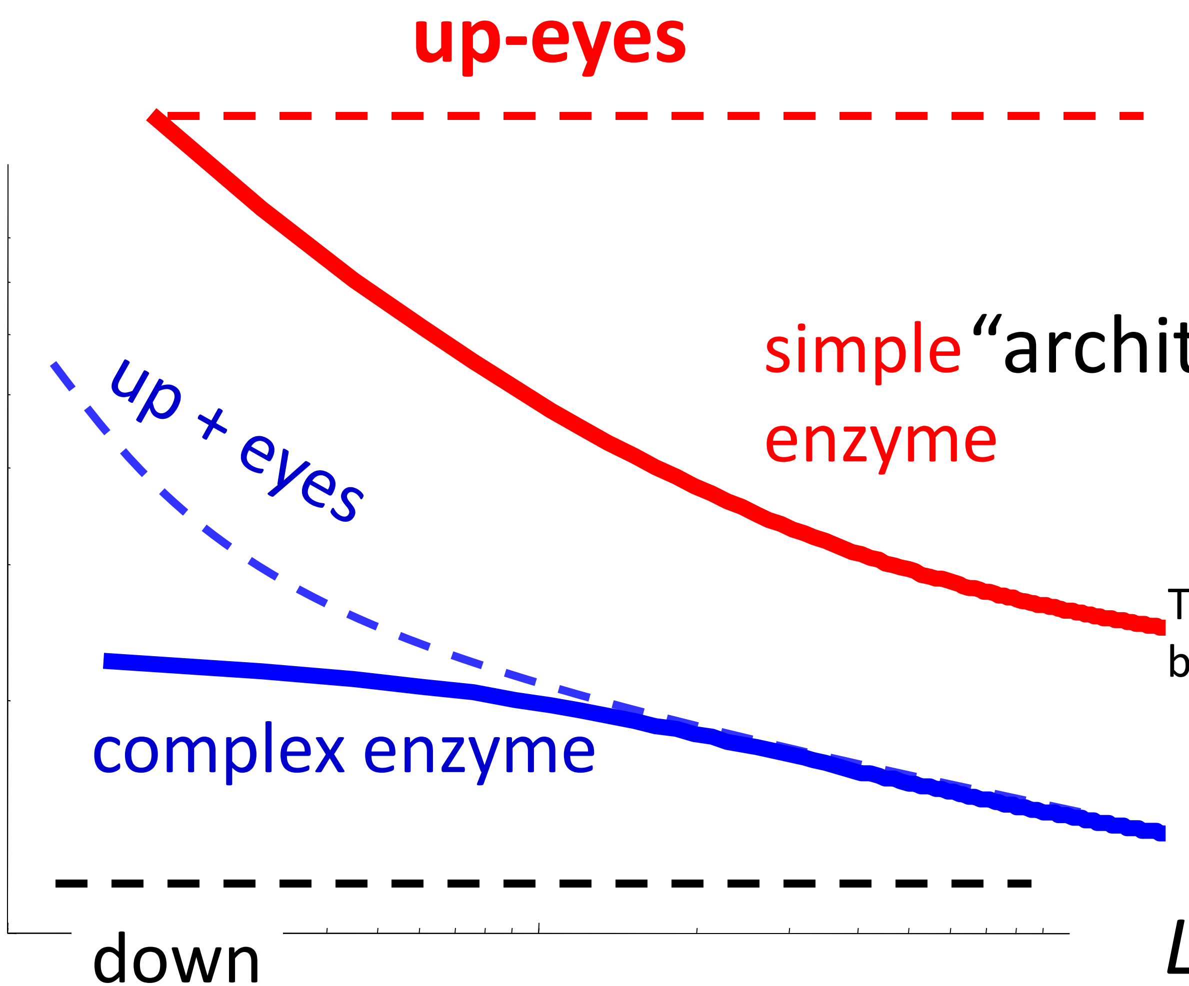
This is a cartoon, but can be made precise.

Theorem

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

Fragility

$$\ln\left|\frac{z+p}{z-p}\right|$$

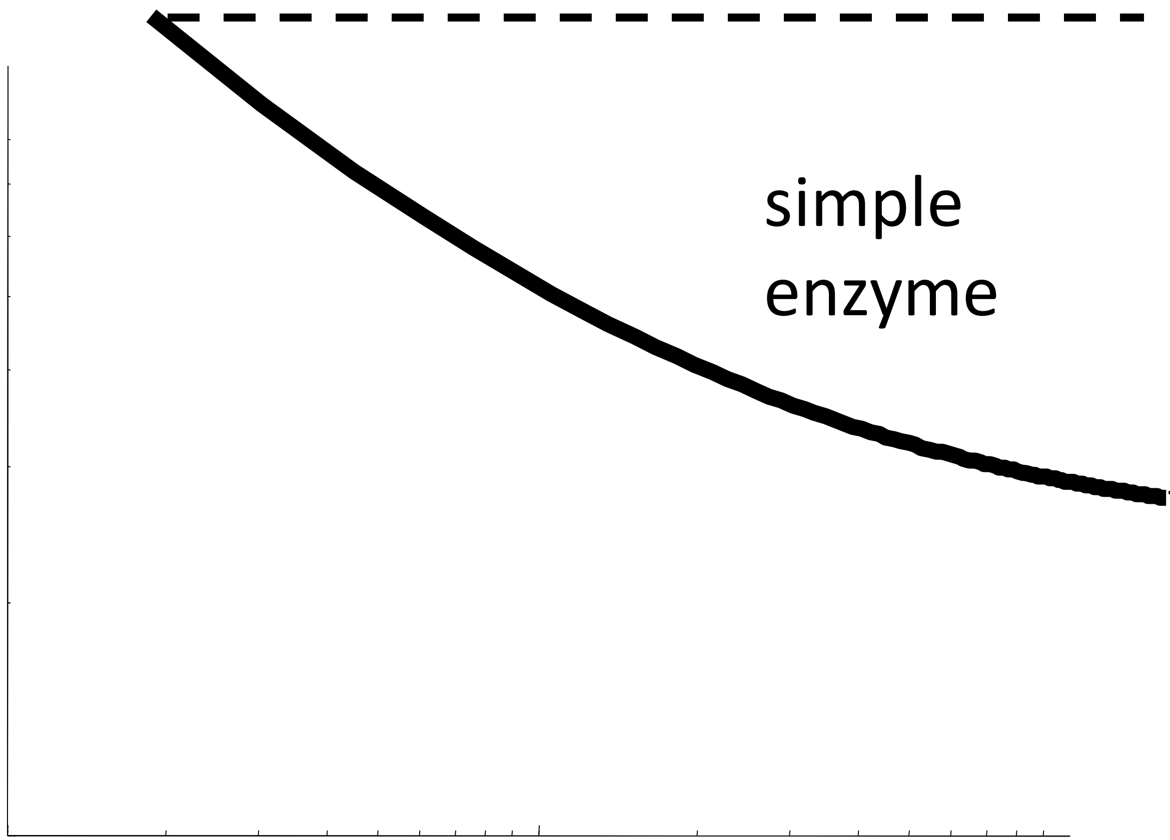


Different
simple “architectures”
enzyme

This is a cartoon, but can be made precise.

Theorem

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

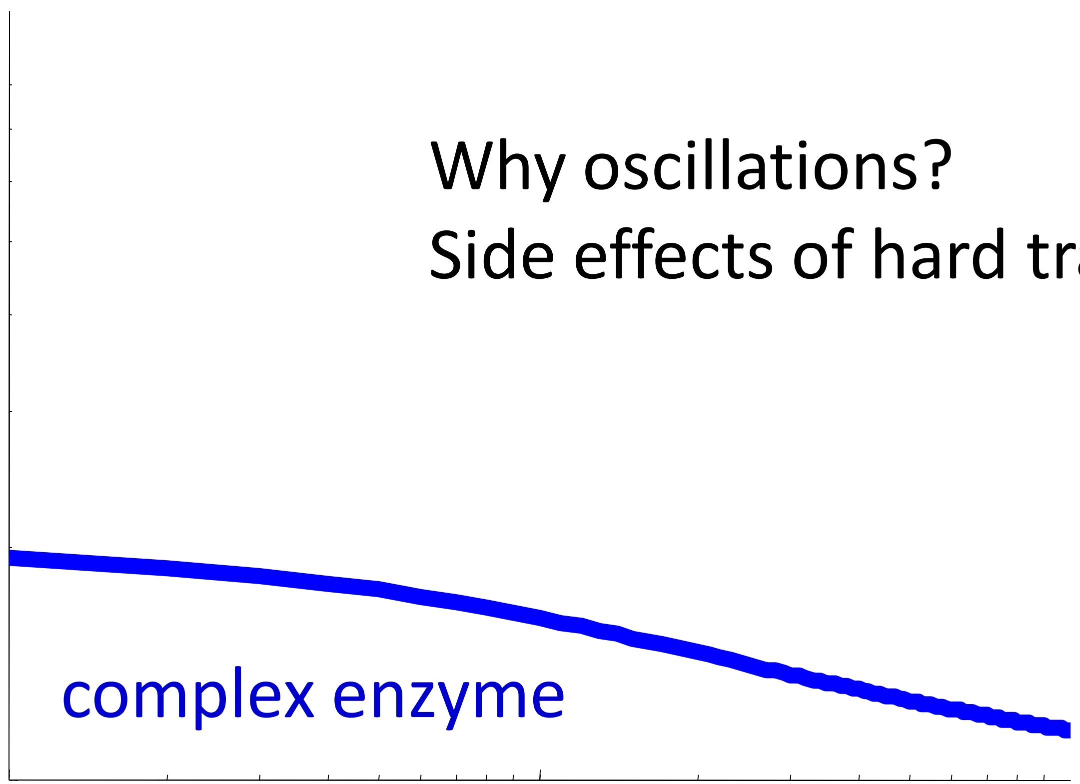


Theorem

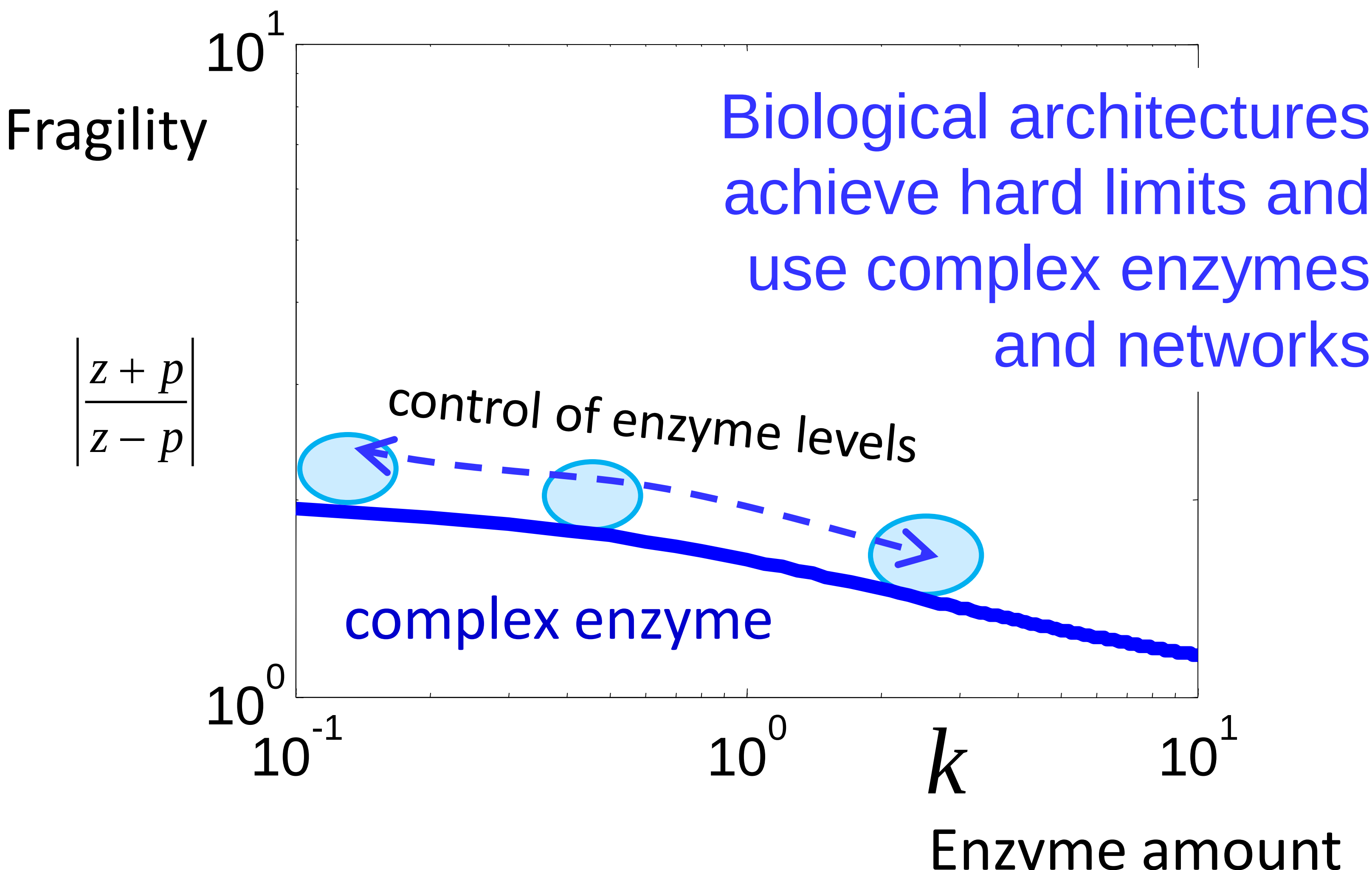
$$\frac{1}{\pi}\int_0^{\infty}\ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

Why oscillations?

Side effects of hard tradeoffs

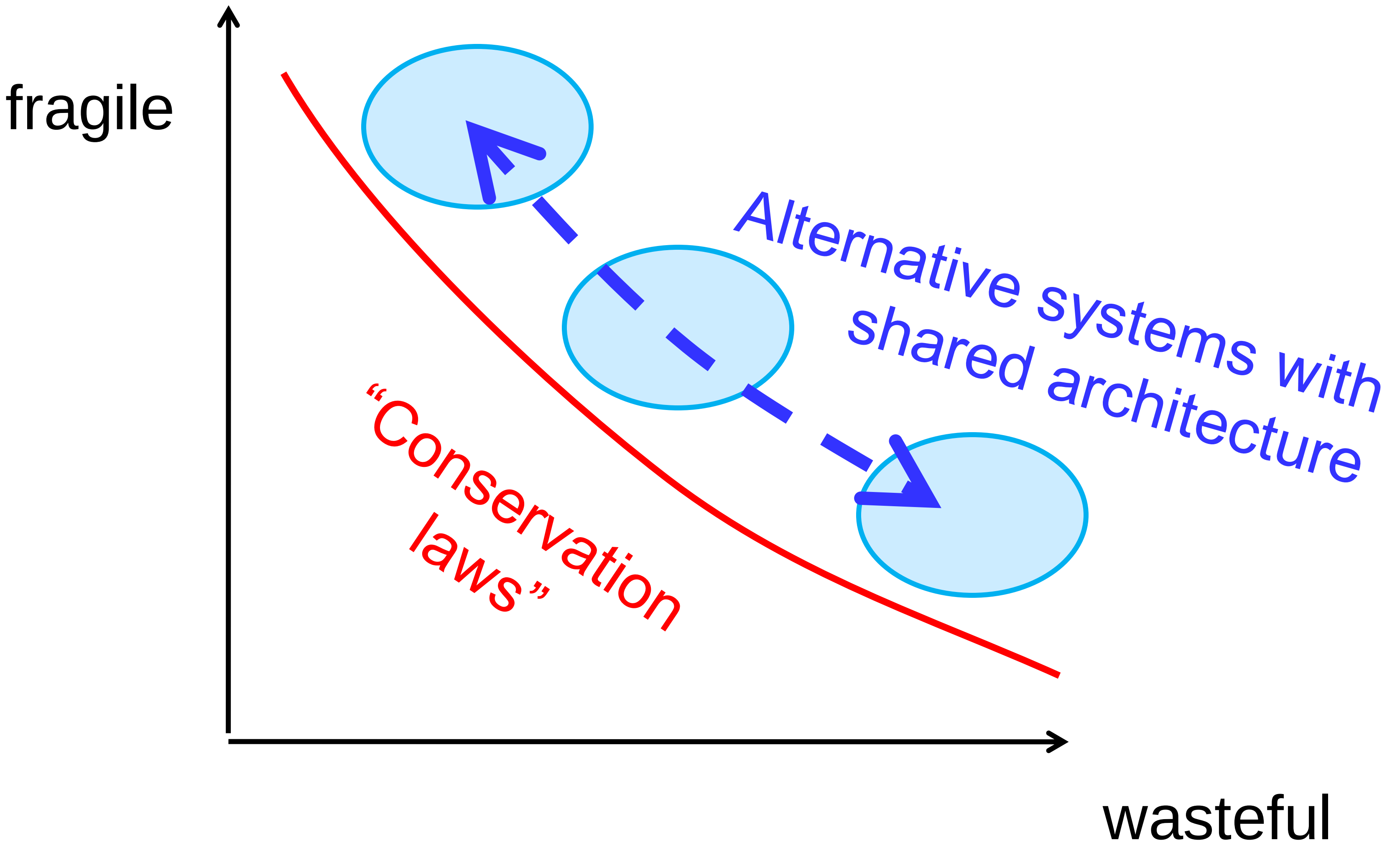


$$\frac{1}{\pi}\int_0^\infty \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$



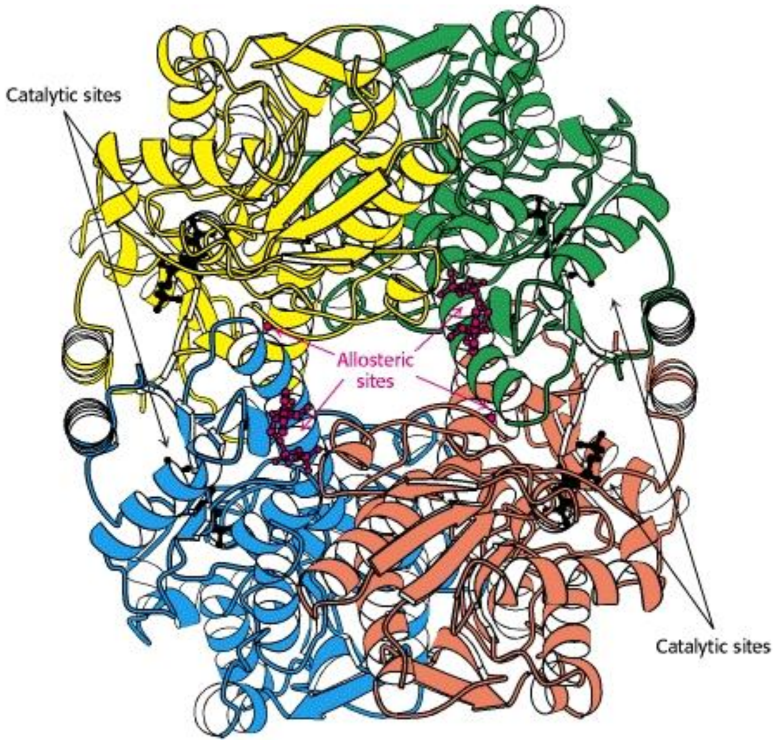
Architecture

Good architectures allow for effective tradeoffs

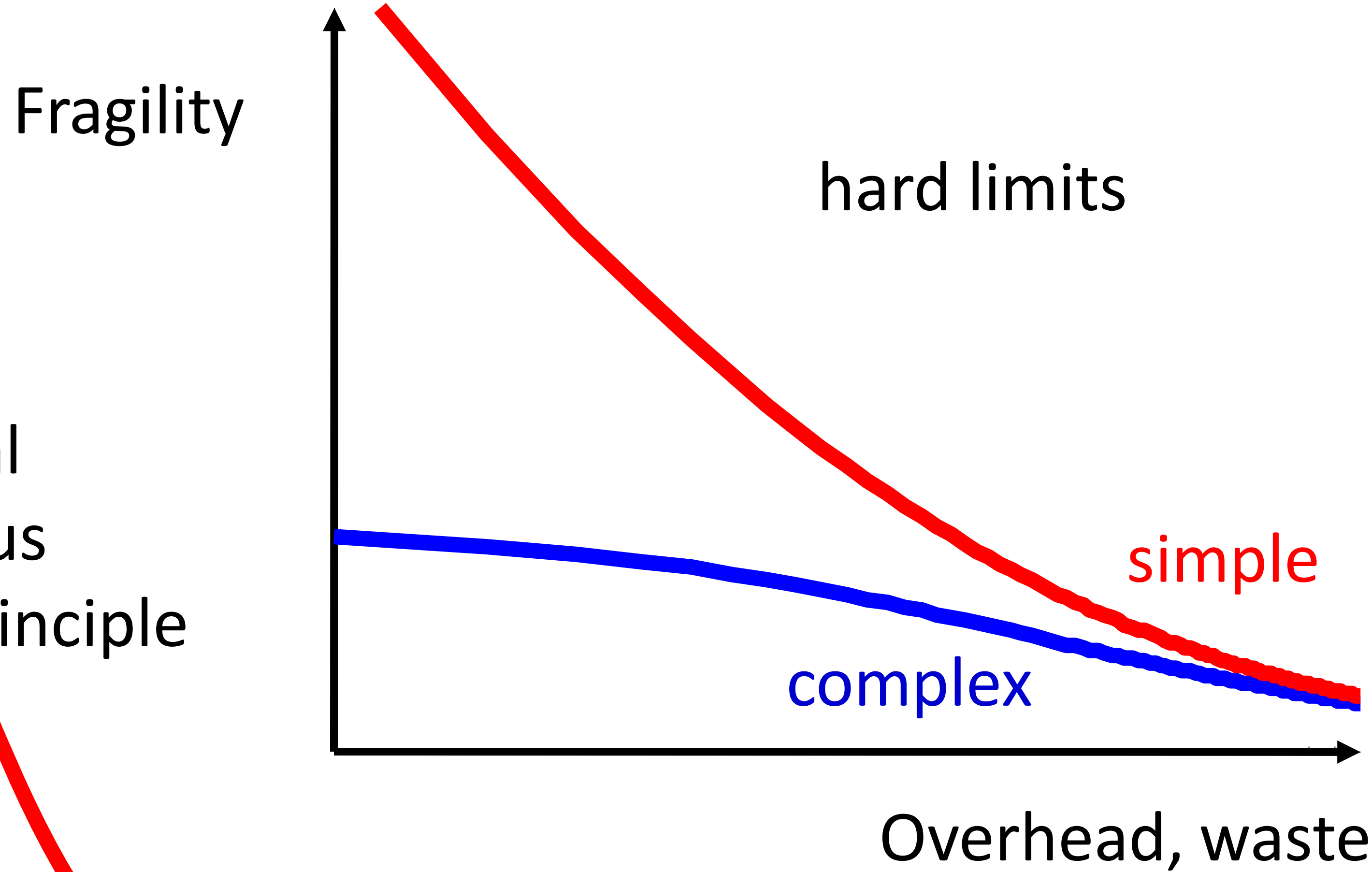


Theorem $$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right|\left(\frac{z}{z^2+\omega^2}\right)d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

- z and p are functions of enzyme complexity and amount
- standard biochemistry models
- **phenomenological**



- **first principles?**



- General
- Rigorous
- First principle

?

Plugging in domain details

- Domain specific
- Ad hoc
- Phenomenological

Control

Wiener

Comms

Bode

robust control

Kalman

- General
- Rigorous
- First principle

- Fundamental multiscale physics
- Foundations, origins of
  - noise
  - dissipation
  - amplification

?

Carnot

Boltzmann

Heisenberg

Physics

IEEE TRANS ON AUTOMATIC CONTROL, FEBRUARY, 2011
Sandberg, Delvenne, and Doyle

http://arxiv.org/abs/1009.2830

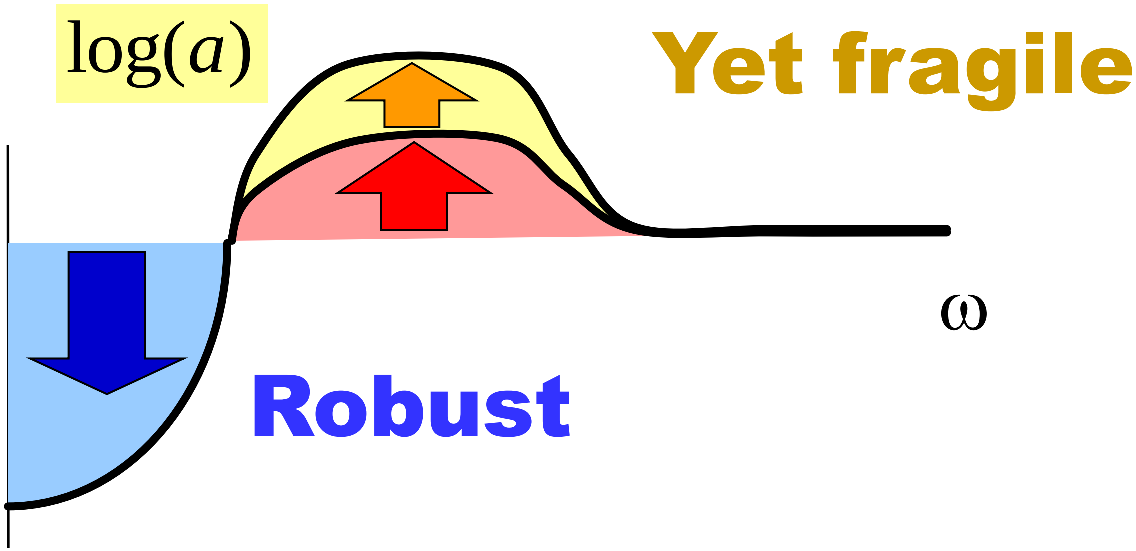
On Lossless Approximations, the Fluctuation-Dissipation Theorem, and Limitations of Measurements

Henrik Sandberg, Jean-Charles Delvenne, and John C. Doyle

***Abstract*—In this paper, we take a control-theoretic approach to answering some standard questions in statistical mechanics, and use the results to derive limitations of classical measurements. A central problem is the relation between systems which appear macroscopically dissipative but are microscopically lossless. We show that a linear system is dissipative if, and only if, it can be approximated by a linear lossless system over arbitrarily long time intervals. Hence lossless systems are in this sense dense in dissipative systems. A linear active system can be approximated by a nonlinear lossless system that is charged with initial energy. As a by-product, we obtain mechanisms explaining the Onsager relations from time-reversible lossless approximations, and the fluctuation-dissipation theorem from uncertainty in the initial state of the lossless system. The results are applied to measurement devices and are used to quantify limits on the so-called observer effect, also called *back action*,**

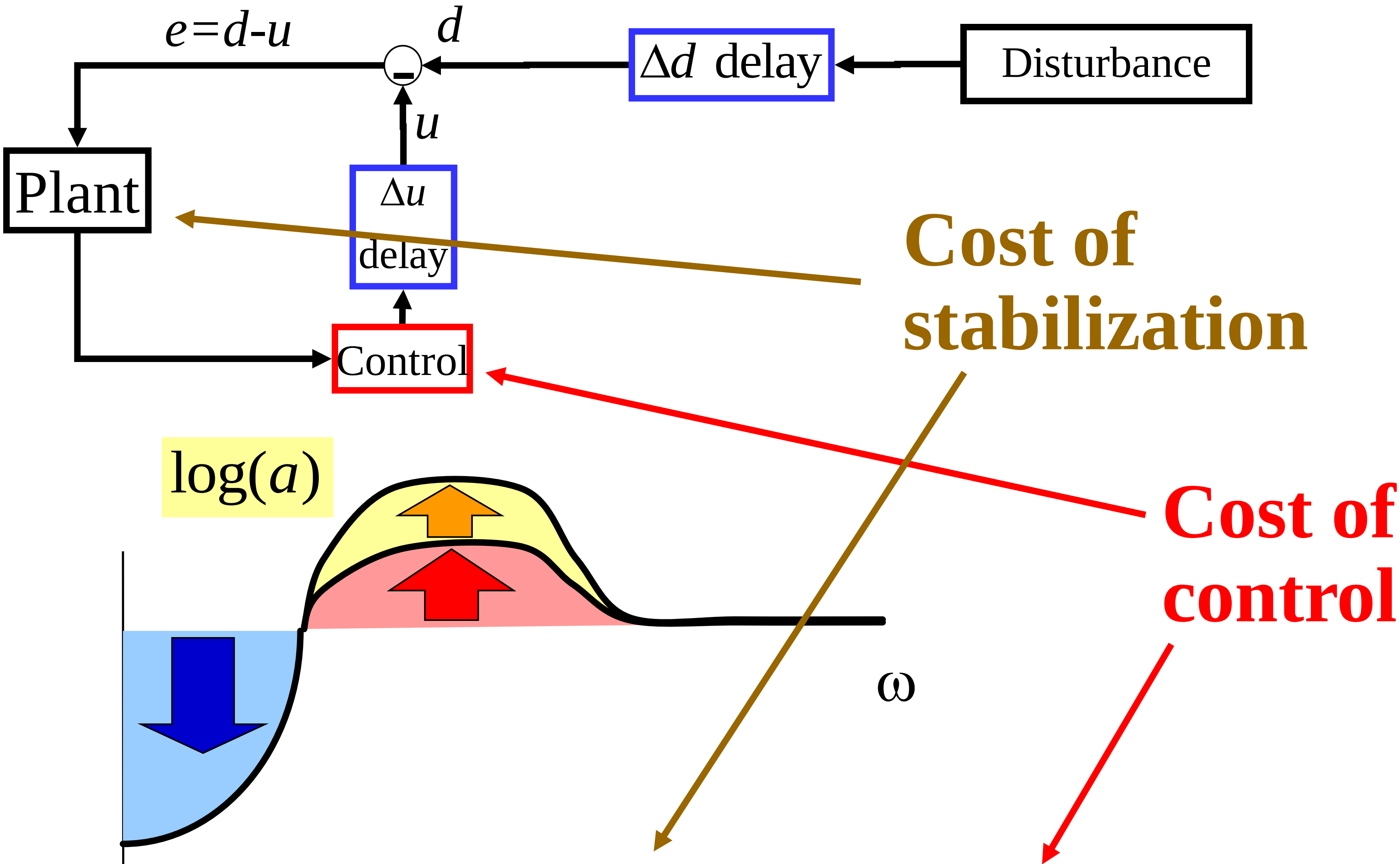
Derivation of limitations is also at the core of physics. Well-known examples are the laws of thermodynamics in classical physics and the uncertainty principle in quantum mechanics [6]–[8]. The exact implications of these physical limitations on the performance of control systems have received little attention, even though all components of a control system, such as actuators, sensors, and computers, are built from physical components which are constrained by physical laws. Control engineers discuss limitations in terms of location of unstable plant poles and zeros, saturation limits of actuators, and more recently channel capacity in feedback loops. But how does the amount of available energy limit the possible bandwidth of a control system? How does the ambient temperature affect the

Bode's integral formula
(Discrete time)



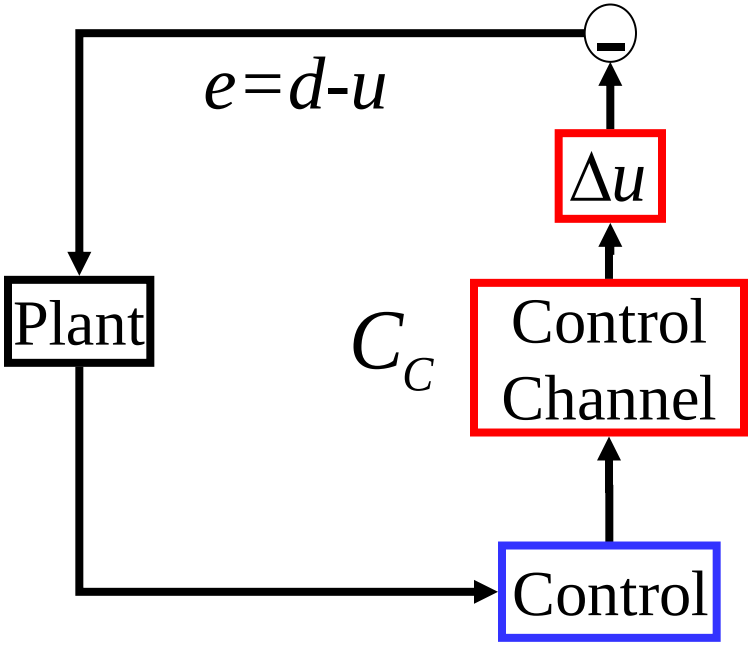
$$\int \left[\log |S| \right]_{-} d\omega - \log(a) \geq - \int \left[\log |S| \right]_{+} d\omega$$

benefits **costs**



$$\int \left[\log|S|\right]_{-} d\omega - \log(a) \geq -\int \left[\log|S|\right]_{+} d\omega$$

benefits **costs**

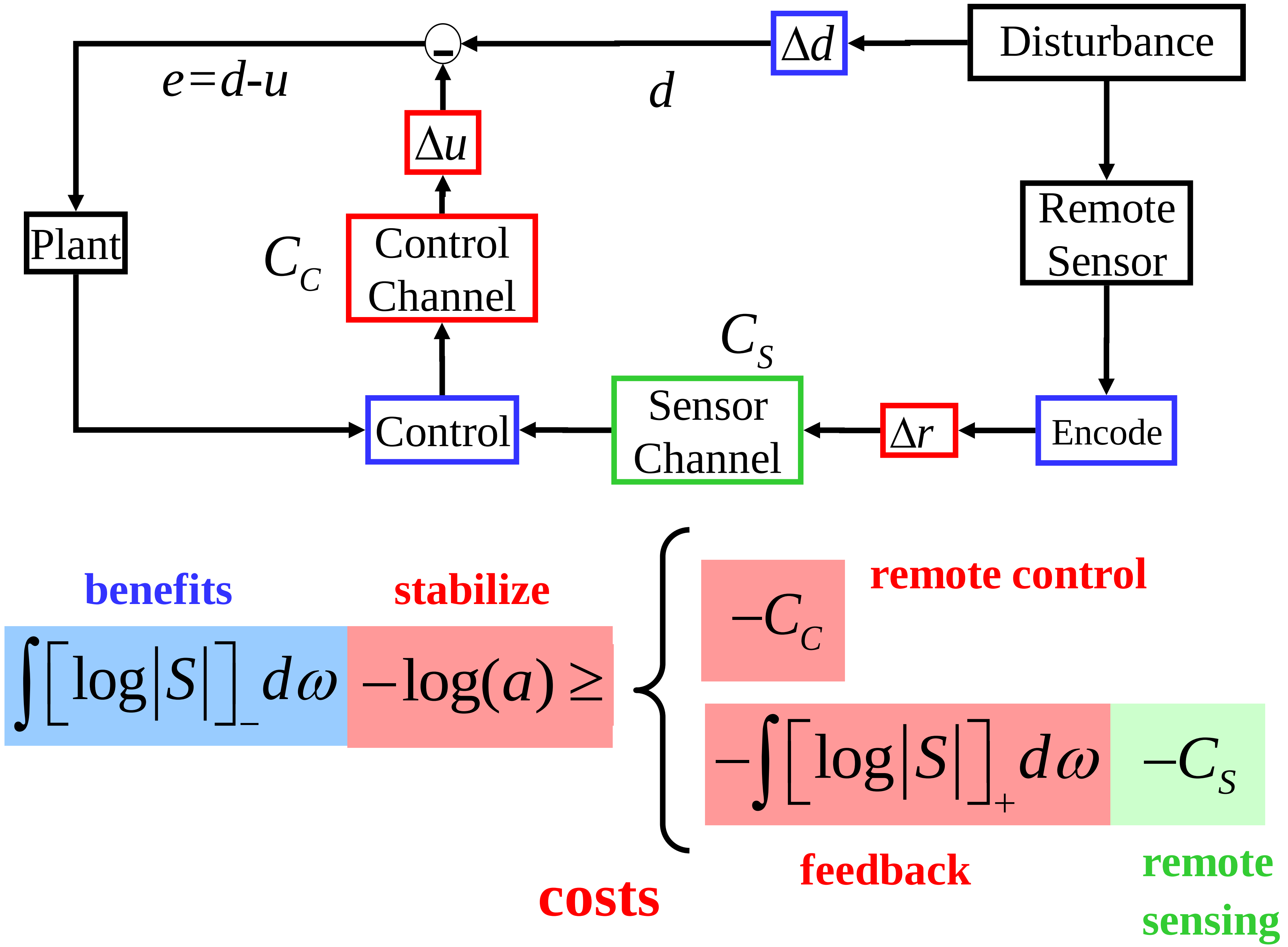


Cost of *remote* control

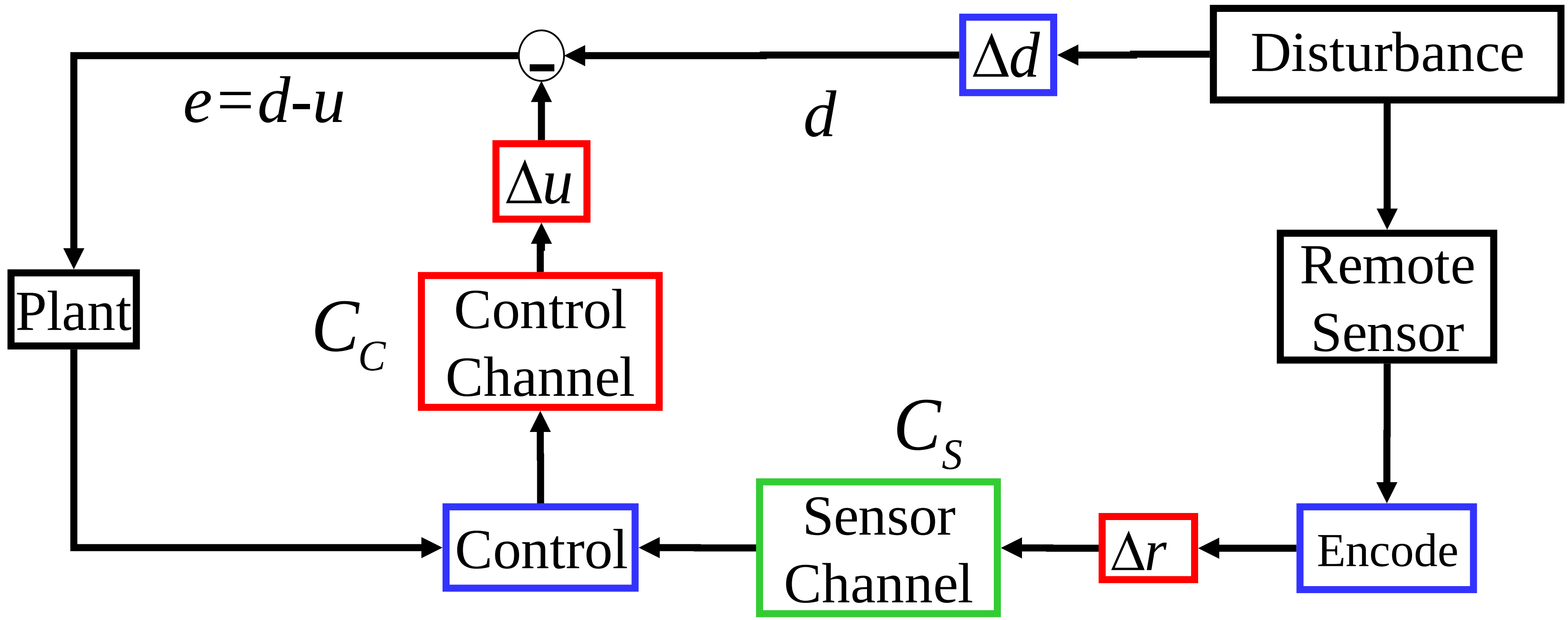
$$\int \left[\log|S|\right]_- d\omega - \log(a) \ge -C_C$$

$$\int \left[\log|S|\right]_- d\omega - \log(a) \ge -\int \left[\log|S|\right]_+ d\omega$$

benefits **costs**



Disturbance
Δd
d
e=d-u
Δu
Plant
C_C
Control Channel
Remote Sensor
C_S
Control
Sensor Channel
Δr
Encode
benefits
stabilize
remote control
$\int [\log|S|]_- d\omega - \log(a) \geq \begin{cases} -C_C \\ -\int [\log|S|]_+ d\omega - C_S \end{cases}$
feedback
remote sensing
costs

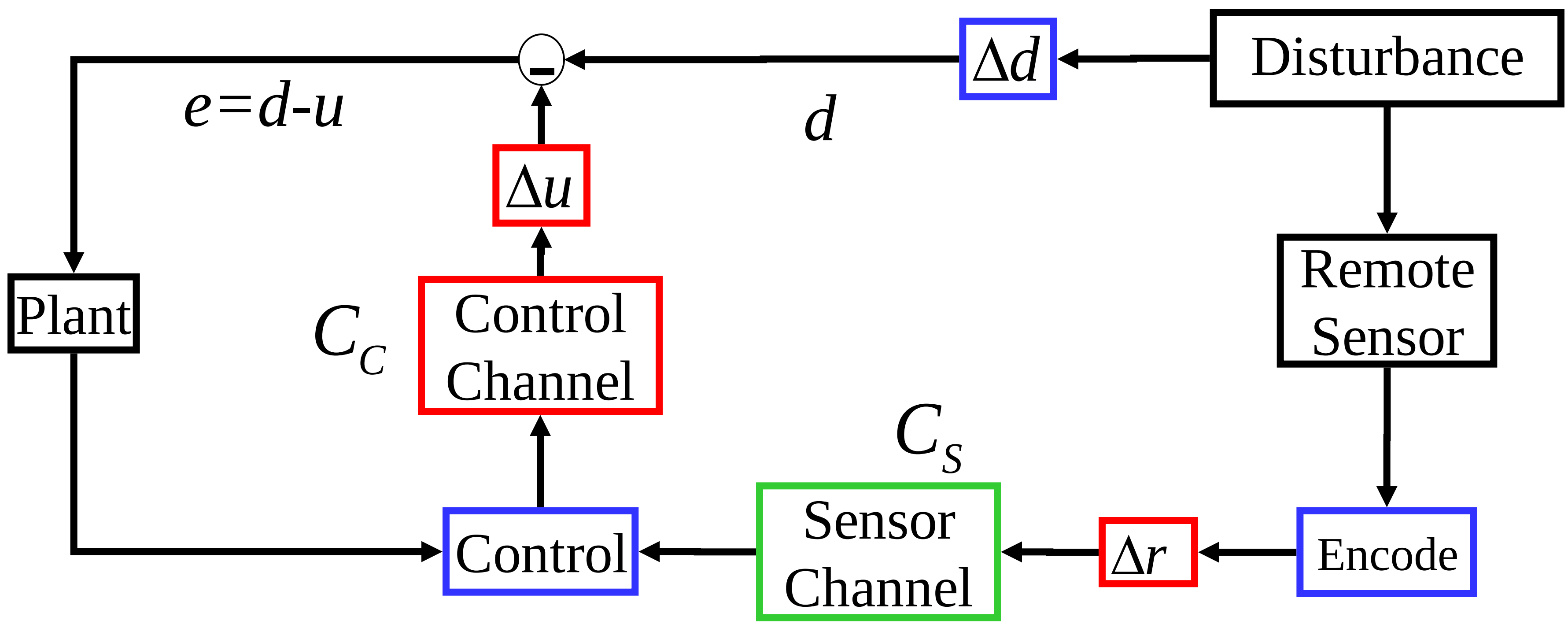


Benefit of remote sensing

$$\int \left[\log|S|\right]_- d\omega - \log(a) \geq -C_C$$

$$\int \left[\log|S|\right]_- d\omega - \log(a) \geq -\int \left[\log|S|\right]_+ d\omega - C$$

benefits **costs**

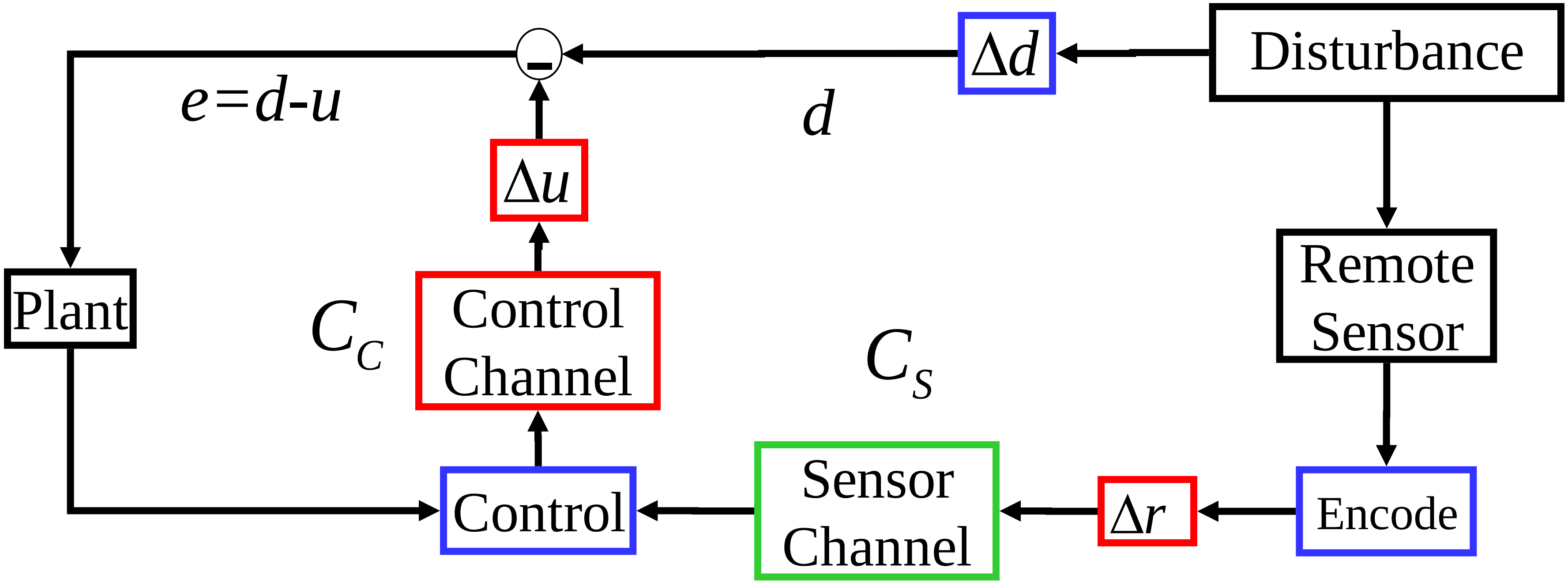


benefits **stabilize**

$$\int \left[\log|S|\right]_- d\omega - \log(a) \geq \begin{cases} -C_C & \text{remote control} \\ -\int \left[\log|S|\right]_+ d\omega - C_S & \text{feedback, remote sensing} \end{cases}$$

feedback **remote sensing**

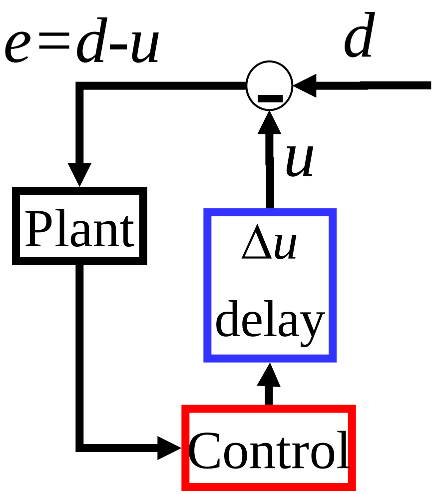
costs



$$\int \left[\log|S|\right]_- d\omega - \log(a) \geq \begin{cases} -C_C \\ -\int \left[\log|S|\right]_+ d\omega - C_S \end{cases}$$

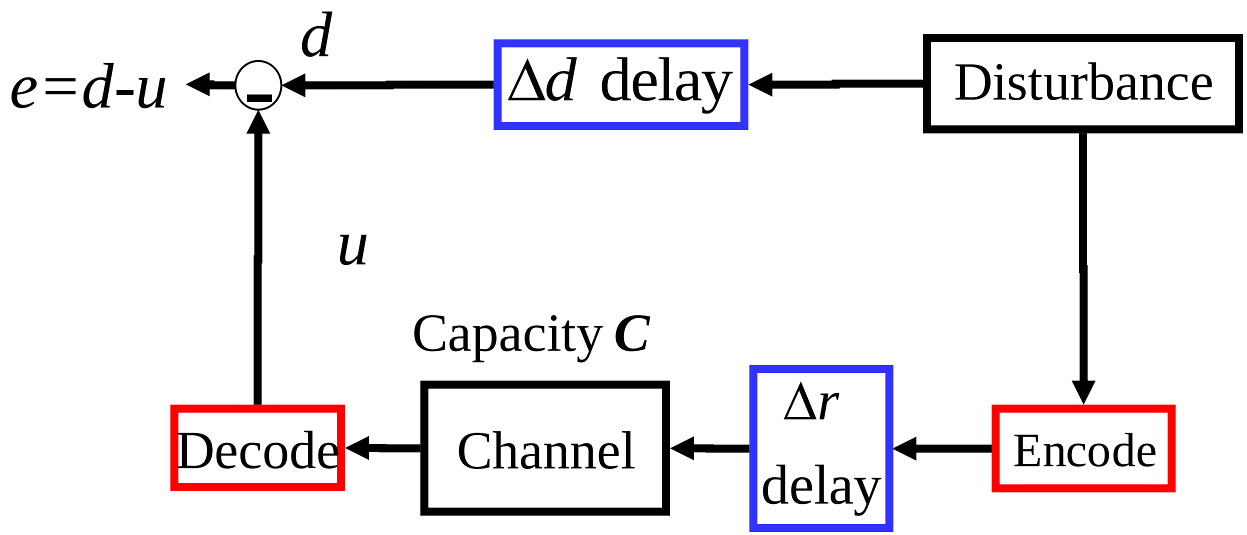
Bode/Shannon is likely a better p-to-p comms theory to serve as a foundation for networks than either Bode or Shannon alone.

Bode



$$\int \log|S|\,d\omega \geq \log(a)$$

Shannon



$$h(E) - h(D) \geq -C$$

$$\text{As } \Delta d \to \infty, \quad \{h(D) < C \Rightarrow e \approx 0\}$$

1. Hard bounds
2. Achievable (⇐assumptions)
3. Solution decomposable (⇐assumptions)

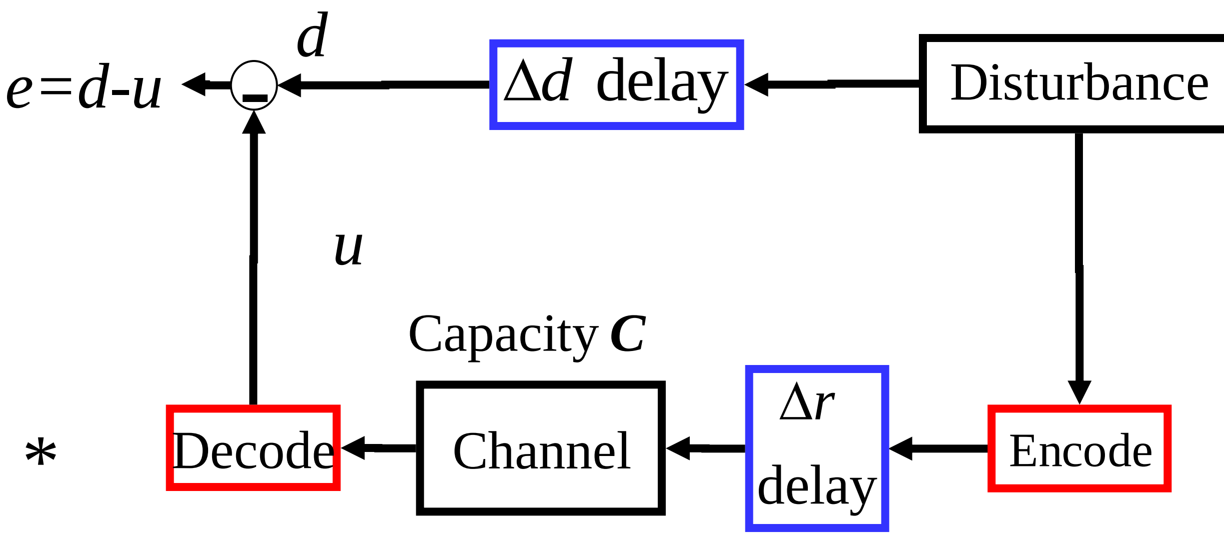
Recall

Shannon

$h(E) - h(D) \geq -C$

As $\Delta d \to \infty$,

$\{h(D) < C \Rightarrow e \approx 0\}$ *



Δr = total delay of encoding, decoding, and channel

Δd =disturbance arrival delay from where it is remotely sensed

Features of the theory:

1. Hard bounds
2. Achievable (⇐assumptions)
3. Solution decomposable (⇐assumptions)

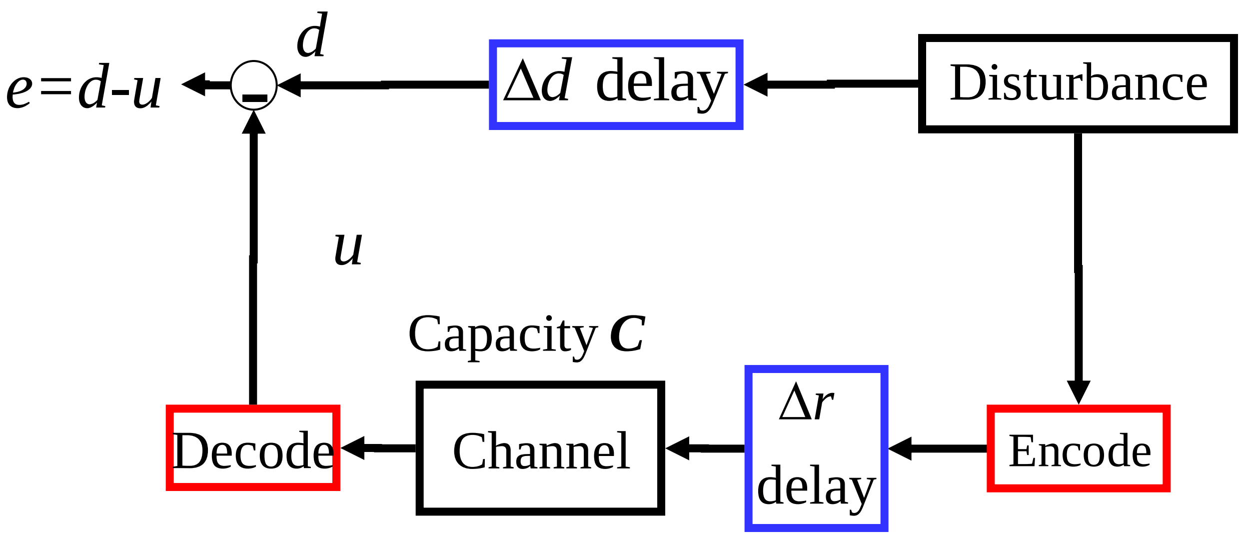
* The interpretation of ≈ depends on the details of the model.

Recall

$$h(E) - h(D) \geq -C$$

$$\text{As } \Delta d \to \infty,$$
$$\{h(D) < C \Rightarrow e \approx 0\}$$

Shannon

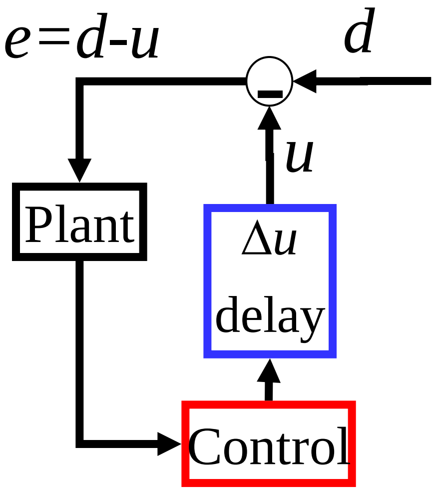


This is a nonstandard way of describing the results but will be convenient later.

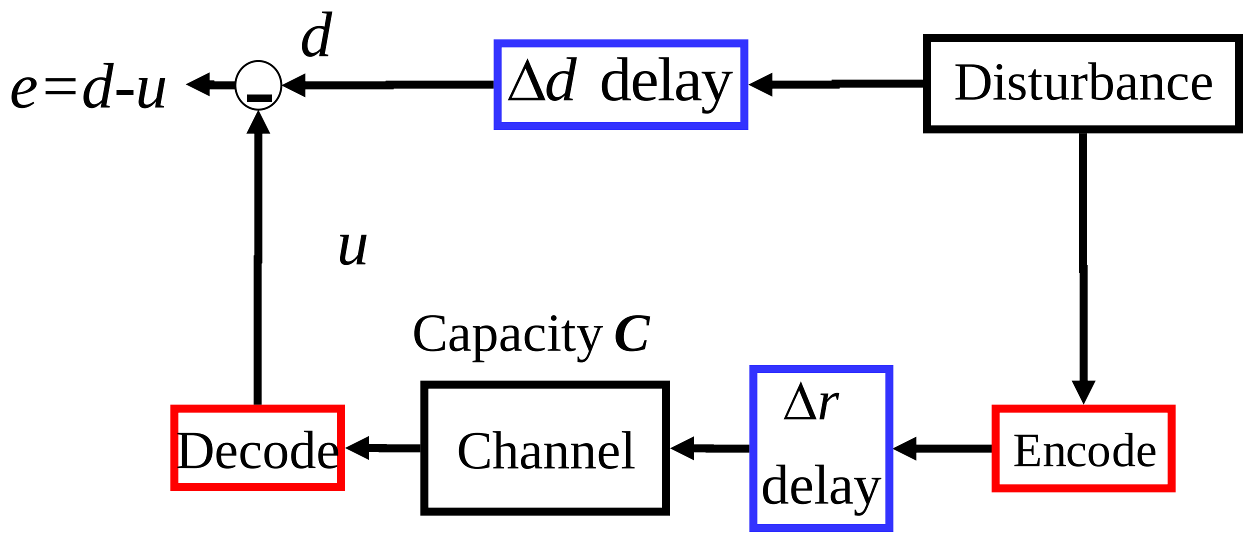
Δr = total delay of encoding, decoding, and channel

Δd =disturbance arrival delay from where it is remotely sensed

Bode



Shannon



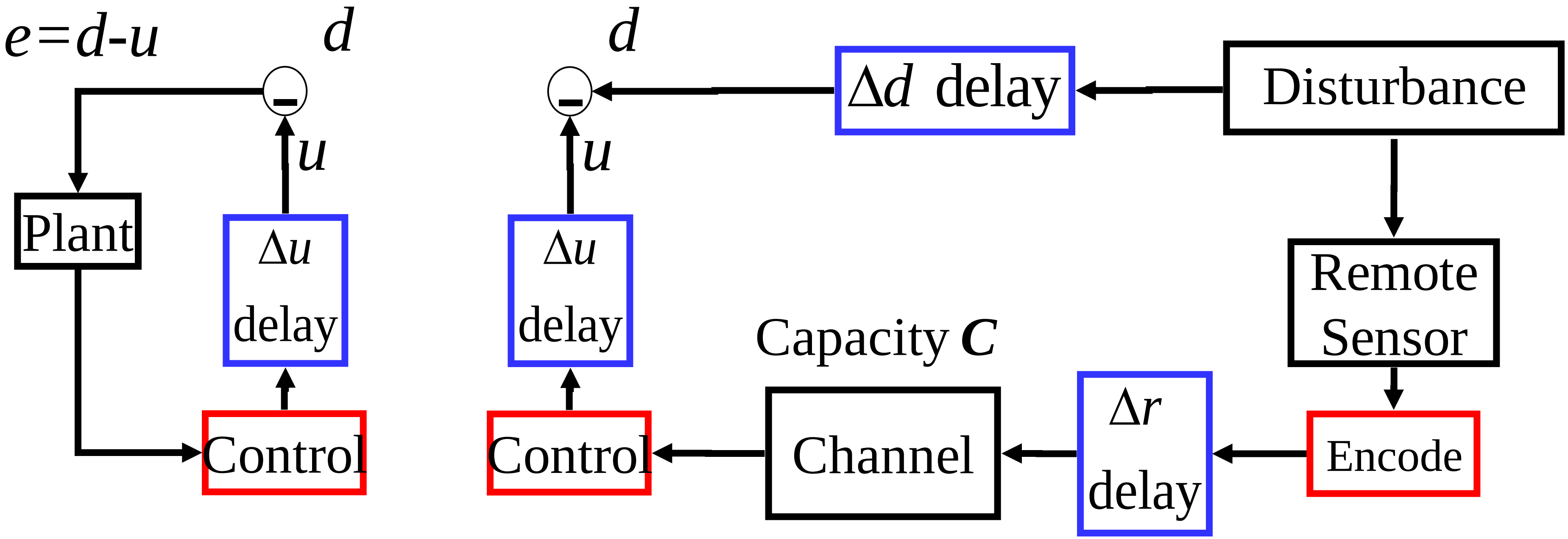
$$\int \log|S| \, d\omega \ge \log(a)$$

$$h(E) - h(D) \ge -C$$

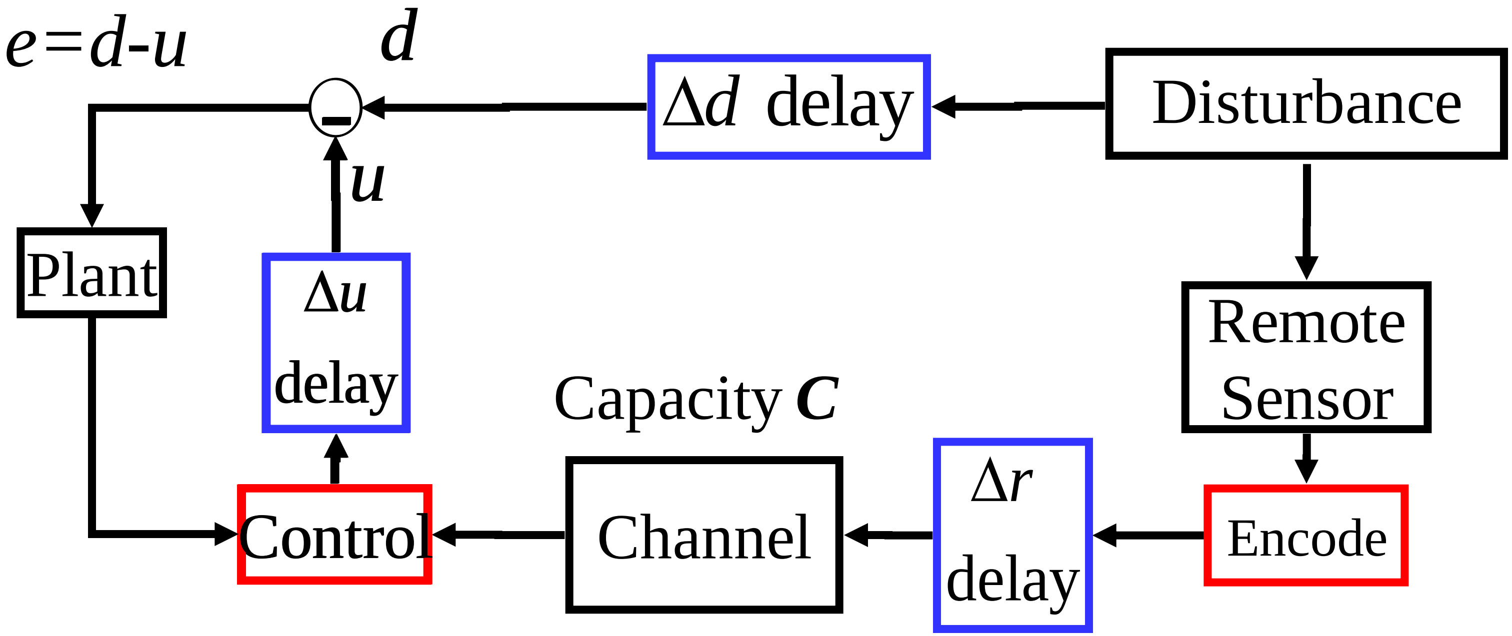
As $\Delta d \to \infty, \quad \{h(D) < C \Rightarrow e \approx 0\}$

1. Hard bounds
2. Achievable (⇐assumptions)
3. Solution decomposable (⇐assumptions)

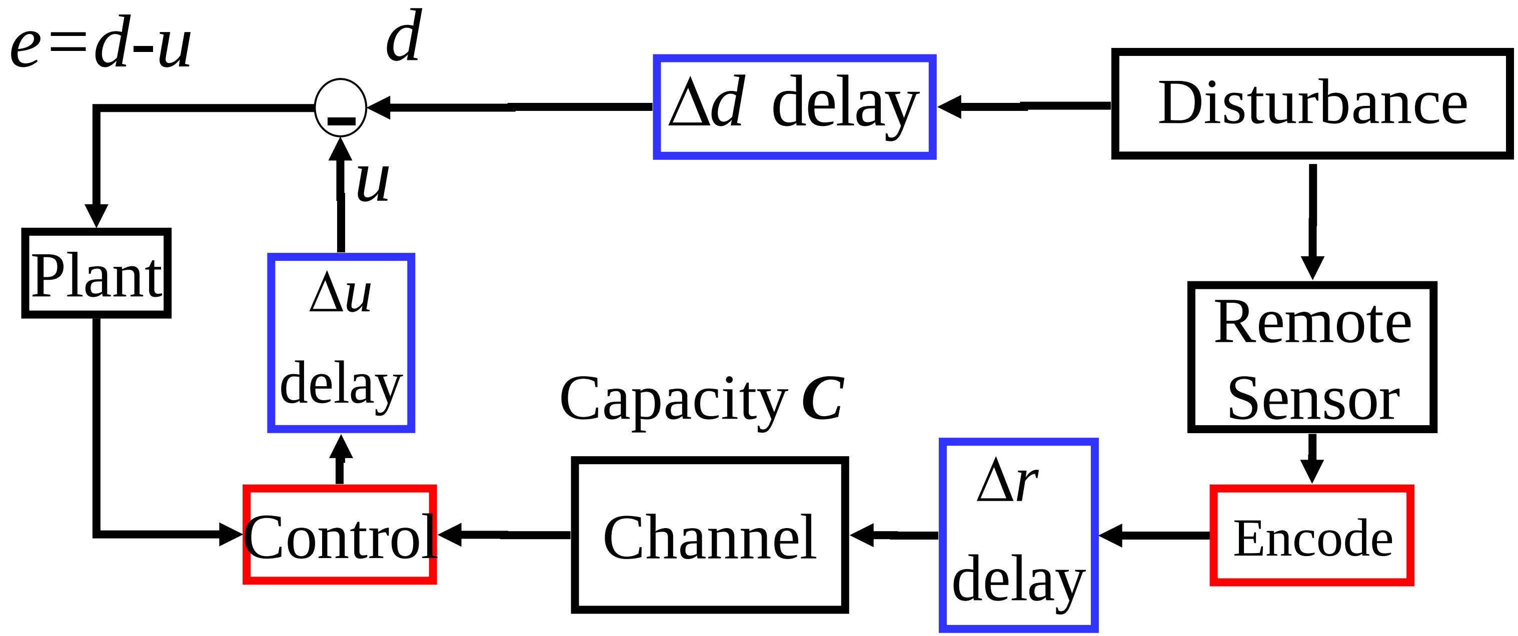
Incompatible assumptions (for 50+ years).



It’s easy to ***pose*** a combined problem.

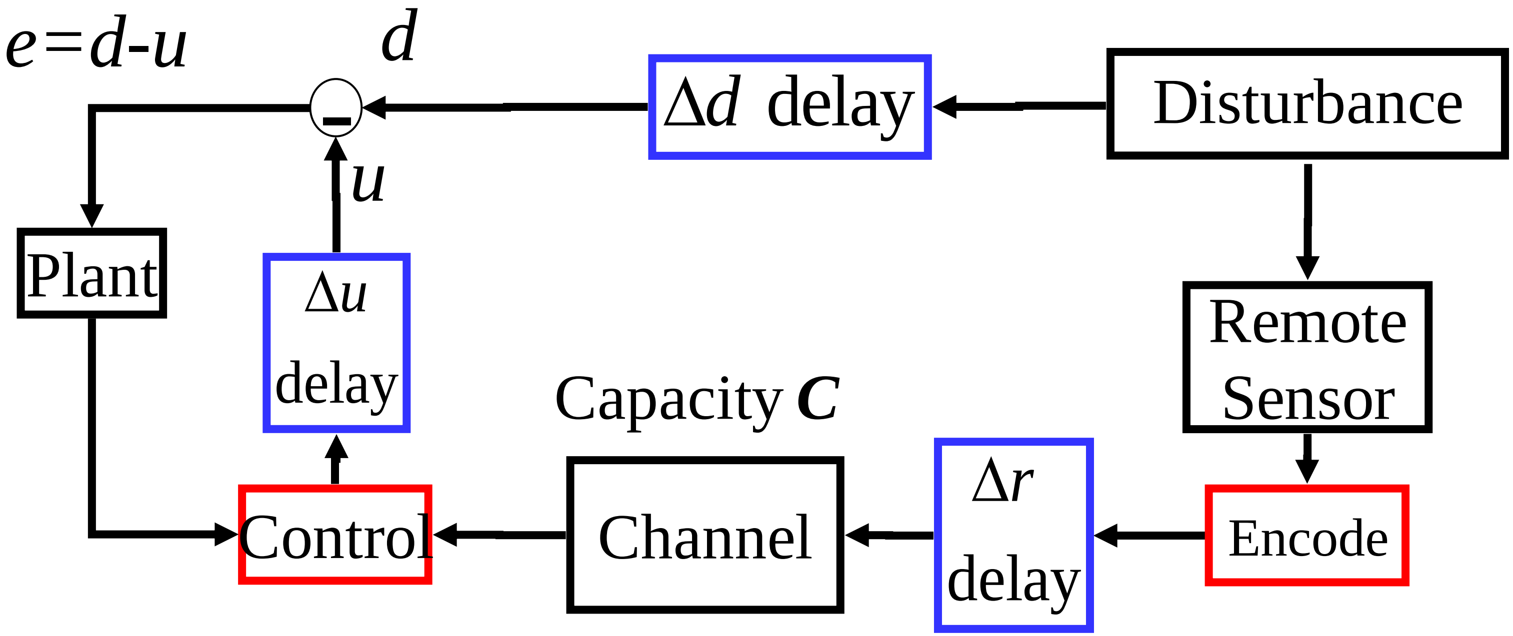


It's easy to ***pose*** a combined problem.



It's easy to ***pose*** a combined problem.

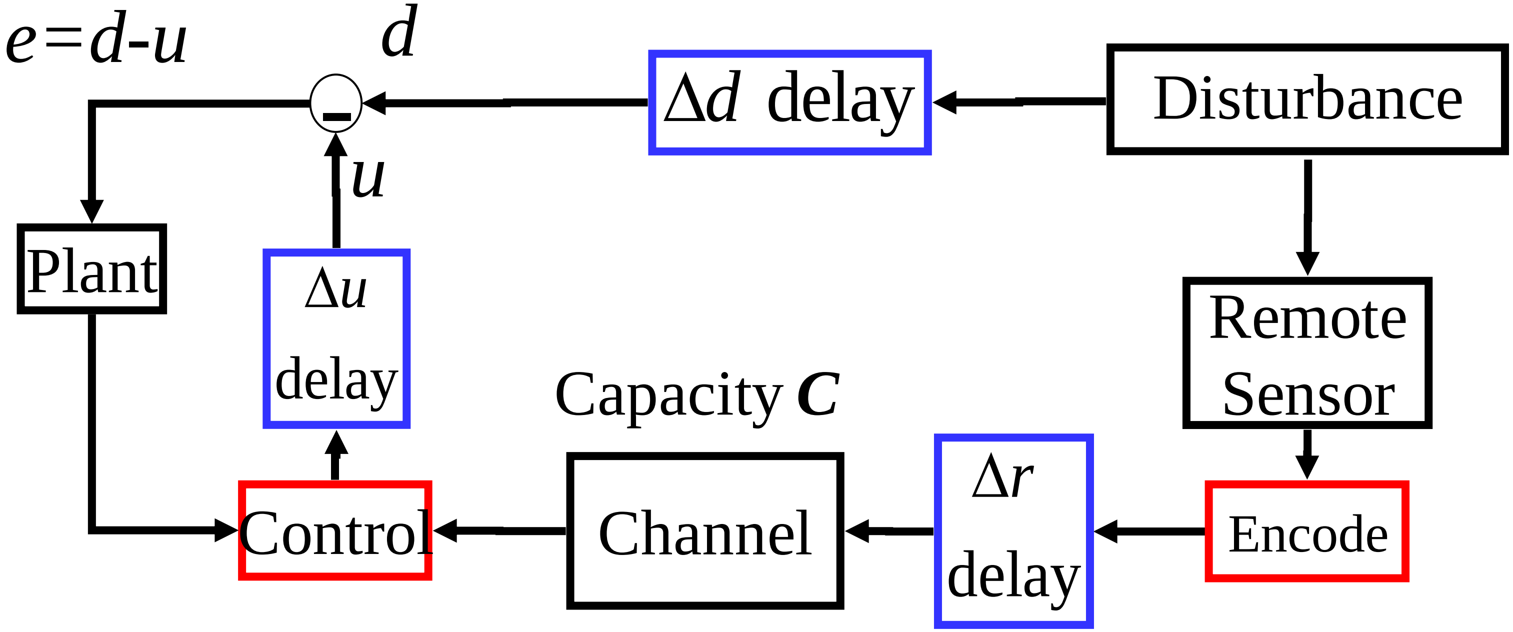
What is the benefit to control of remote sensing?



$$\int \log|S|\,d\omega \geq \log(a) - \begin{cases} 0 & \Delta d < \Delta u + \Delta r \\ C & \Delta d \geq \Delta u + \Delta r \end{cases}$$

This looks too good to be true?

What is the benefit to control of remote sensing?

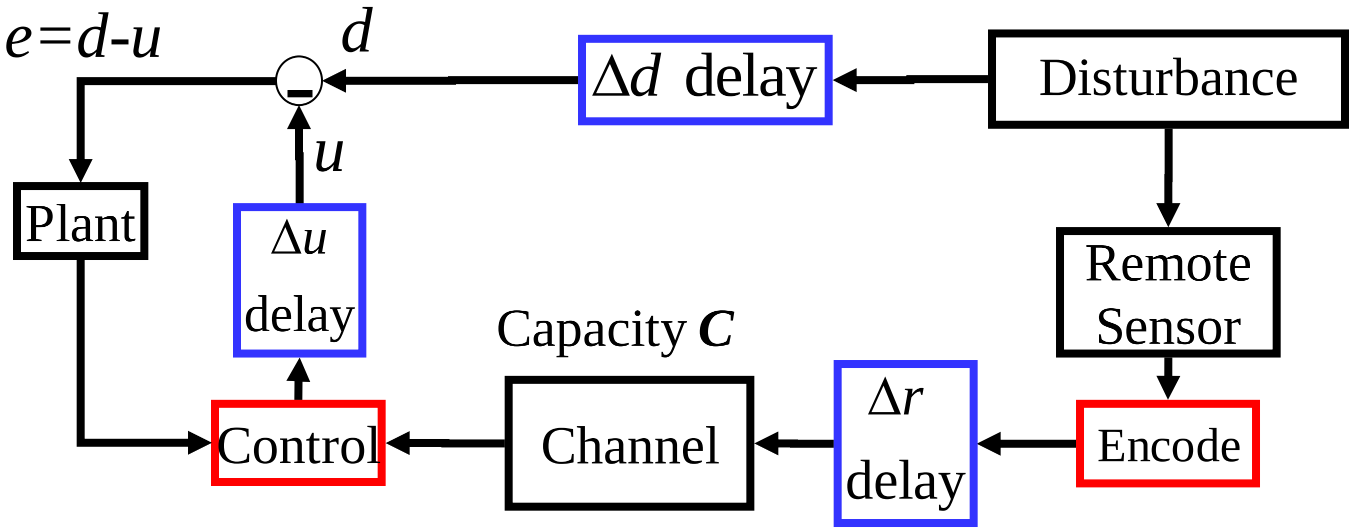


$$\int \log |S| d\omega \geq \log(a) - \begin{cases} 0 & \Delta d < \Delta u + \Delta r \\ C & \Delta d \geq \Delta u + \Delta r \end{cases}$$

Cost of stabilization

Benefits of remote sensing

Need relatively low latency

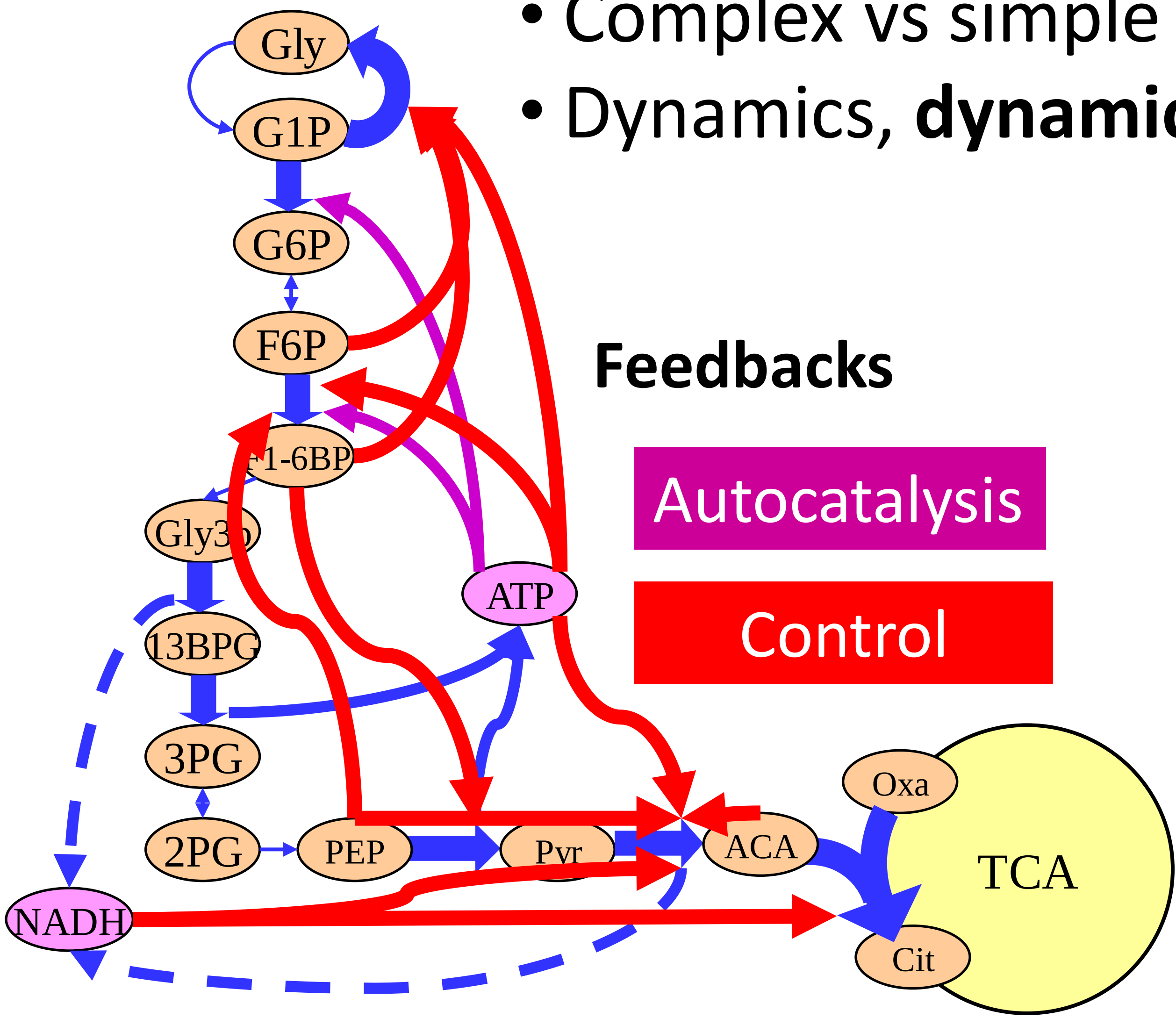


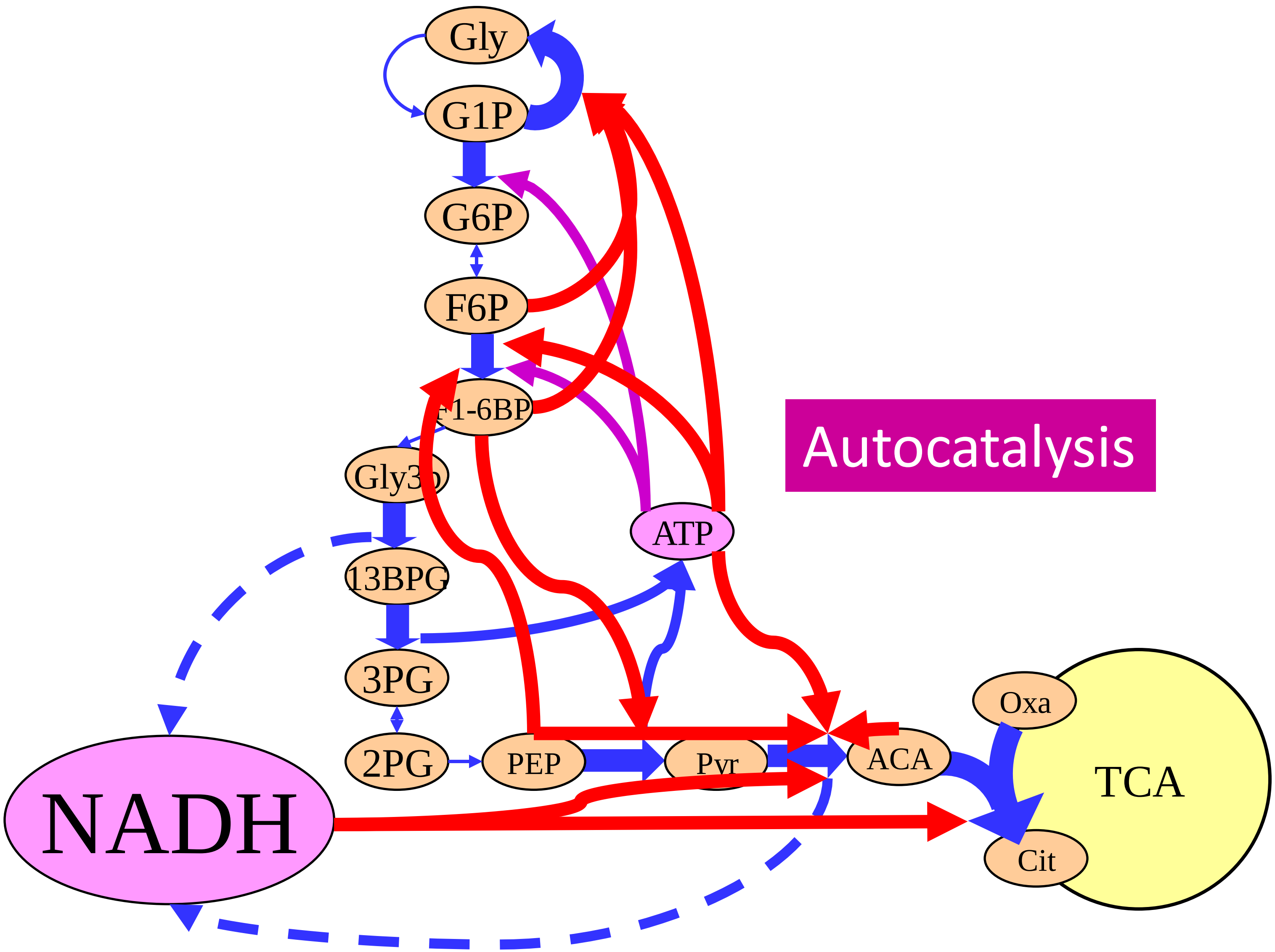
$$\int \log|S| d\omega \geq \log(a) - \begin{cases} 0 & \Delta d < \Delta u + \Delta r \\ C & \Delta d \geq \Delta u + \Delta r \end{cases}$$

1. Hard bounds
2. Achievable (⇐assumptions)
3. Solution decomposable (⇐assumptions)

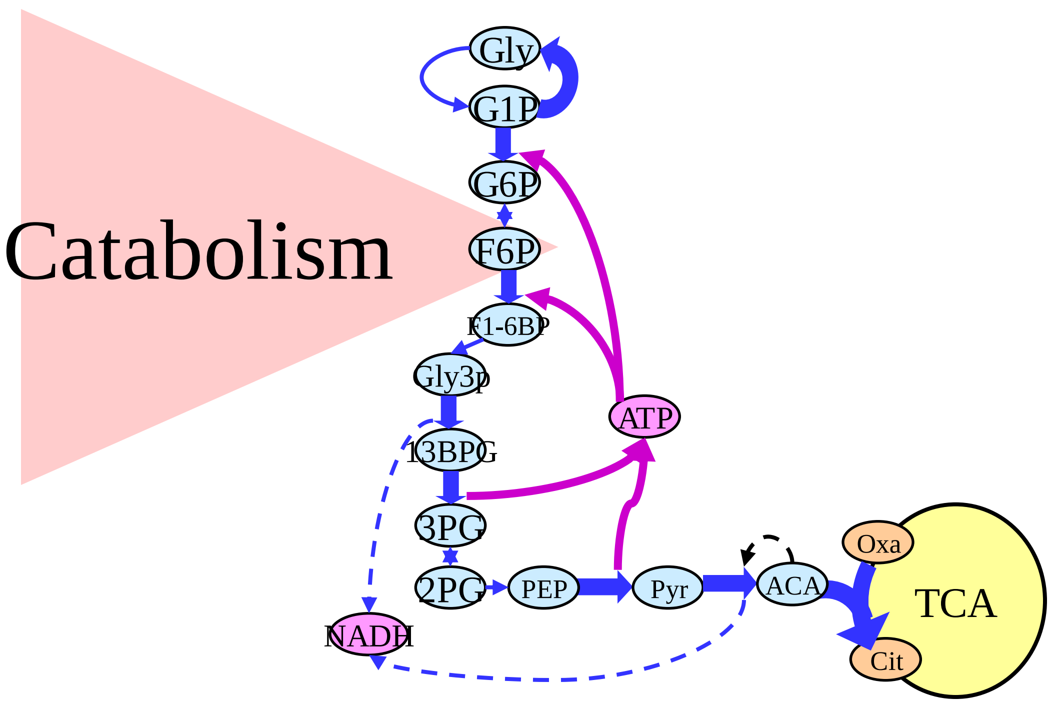
New unified comms, controls, and stat mech.?

- Autocatalytic and control feedback
- Complex vs simple enzymes
- Dynamics, **dynamics**, *dynamics*, …

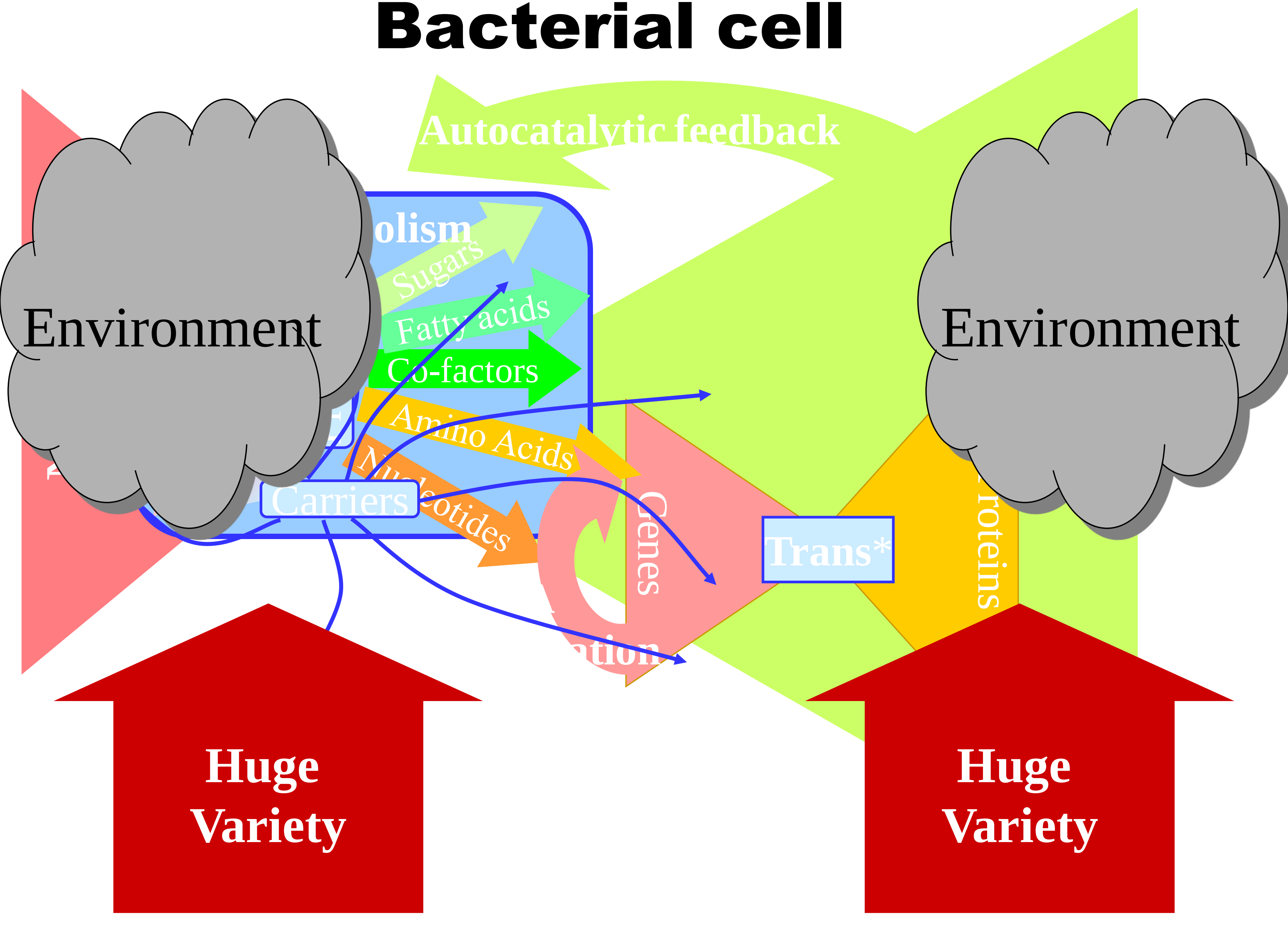


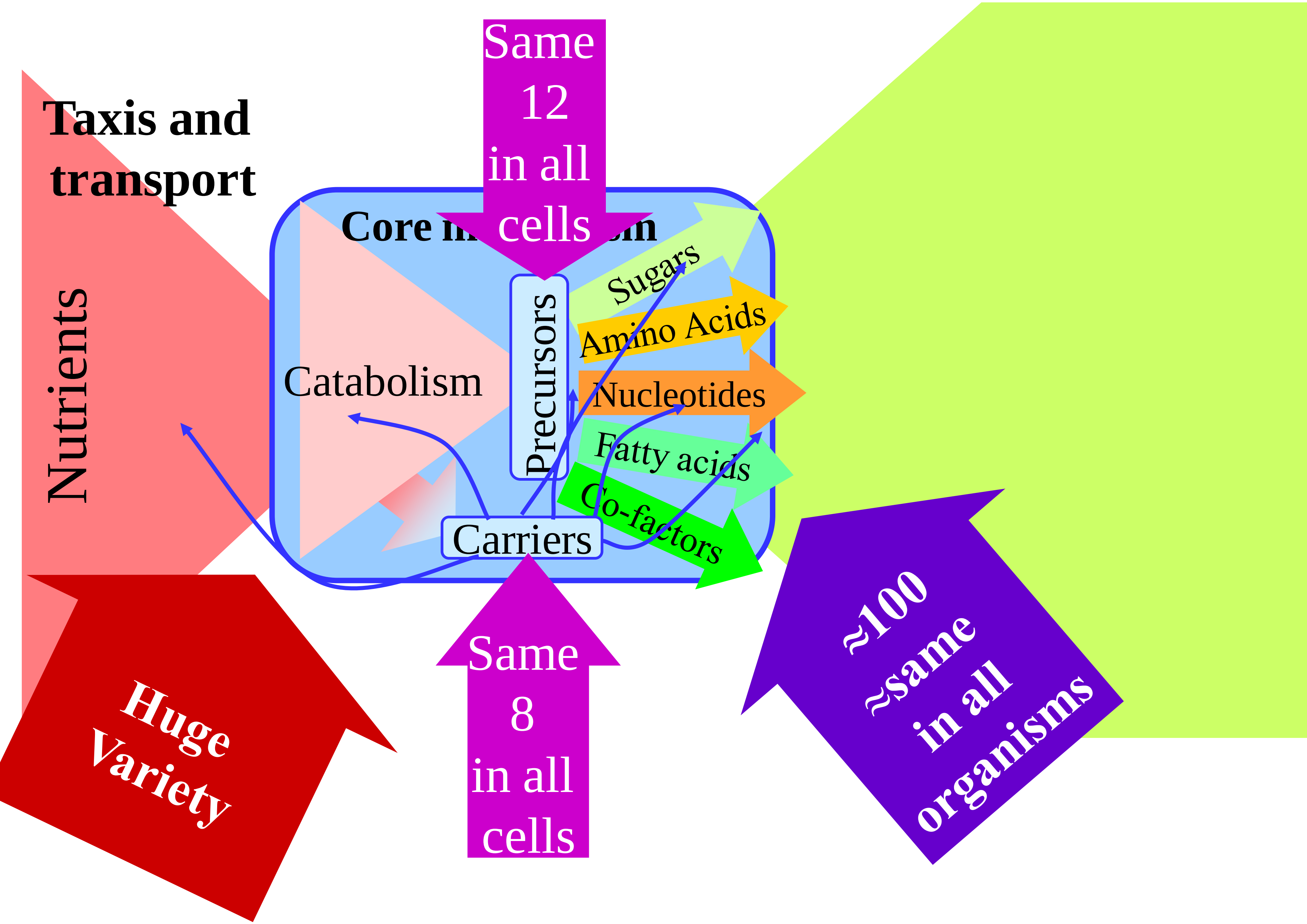


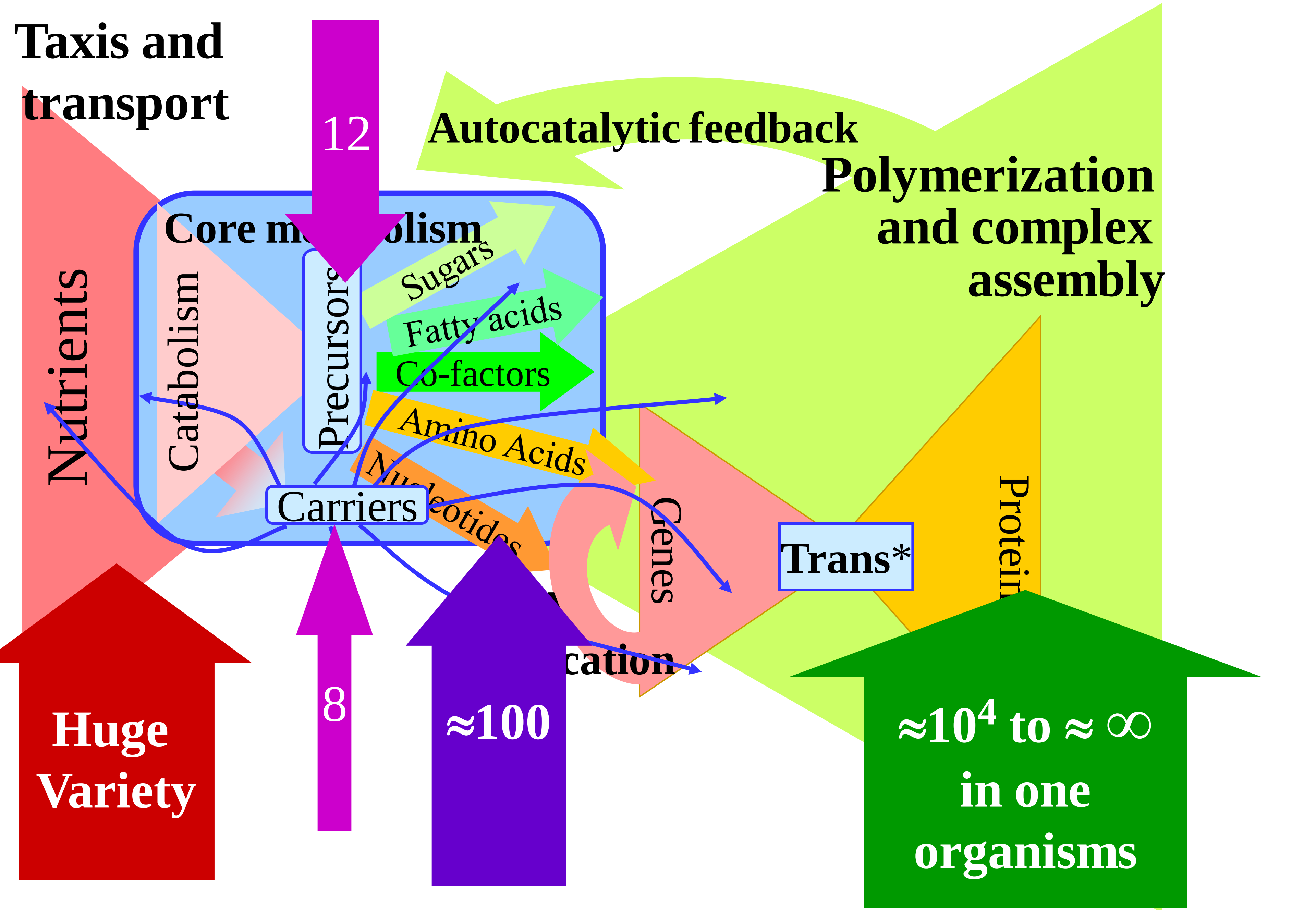
Gly
G1P
G6P
F6P
F1-6BP
Gly3p
13BPG
3PG
2PG
PEP
Pyr
ACA
ATP
NADH
Oxa
Cit
TCA
Autocatalysis


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

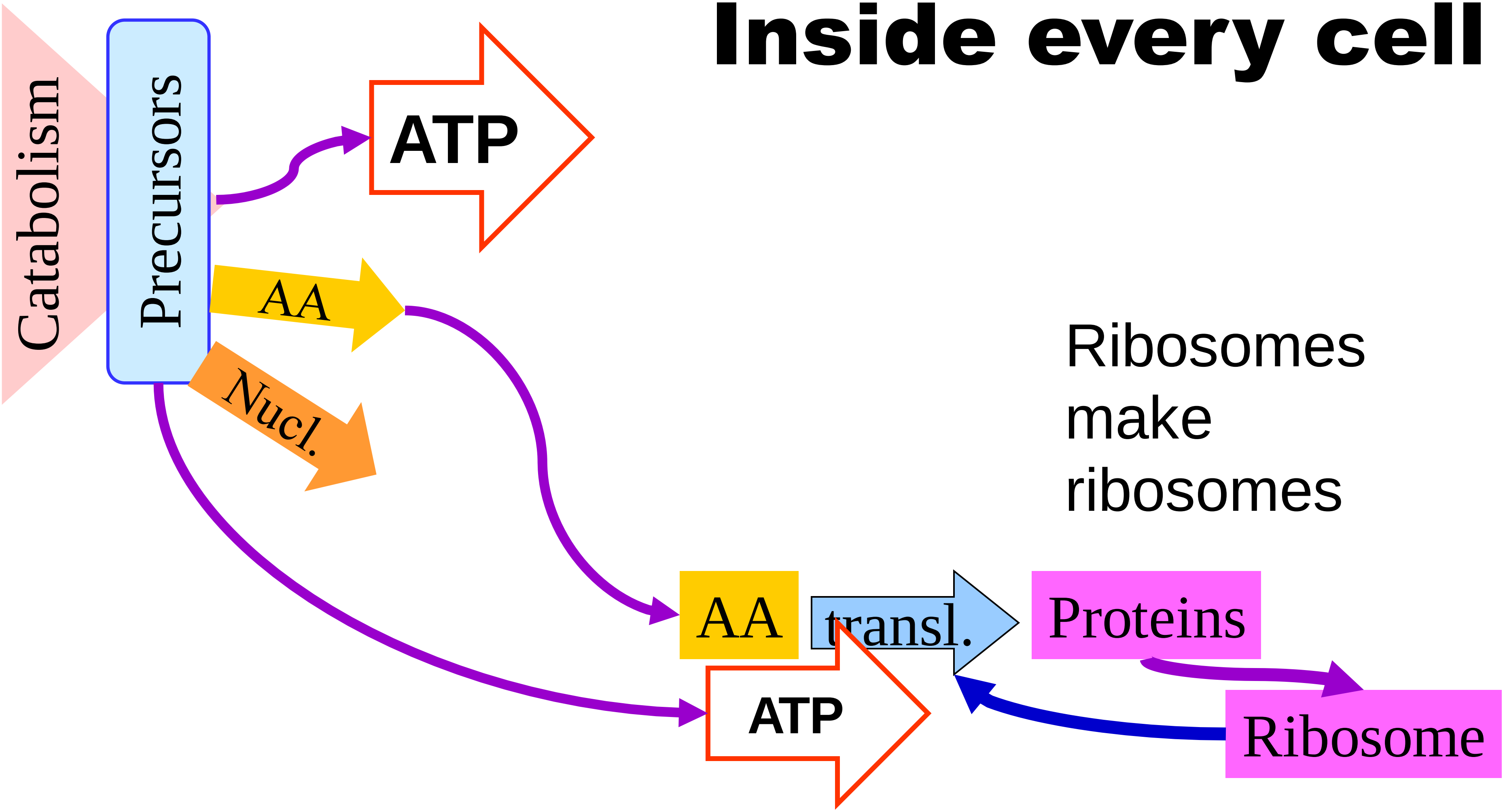
Bacterial cell




Taxis and transport
Nutrients
Huge Variety
Core metabolism
Catabolism
Precursors
Carriers
Sugars
Amino Acids
Nucleotides
Fatty acids
Co-factors
Same 12 in all cells
Same 8 in all cells
≈100 ≈same in all organisms

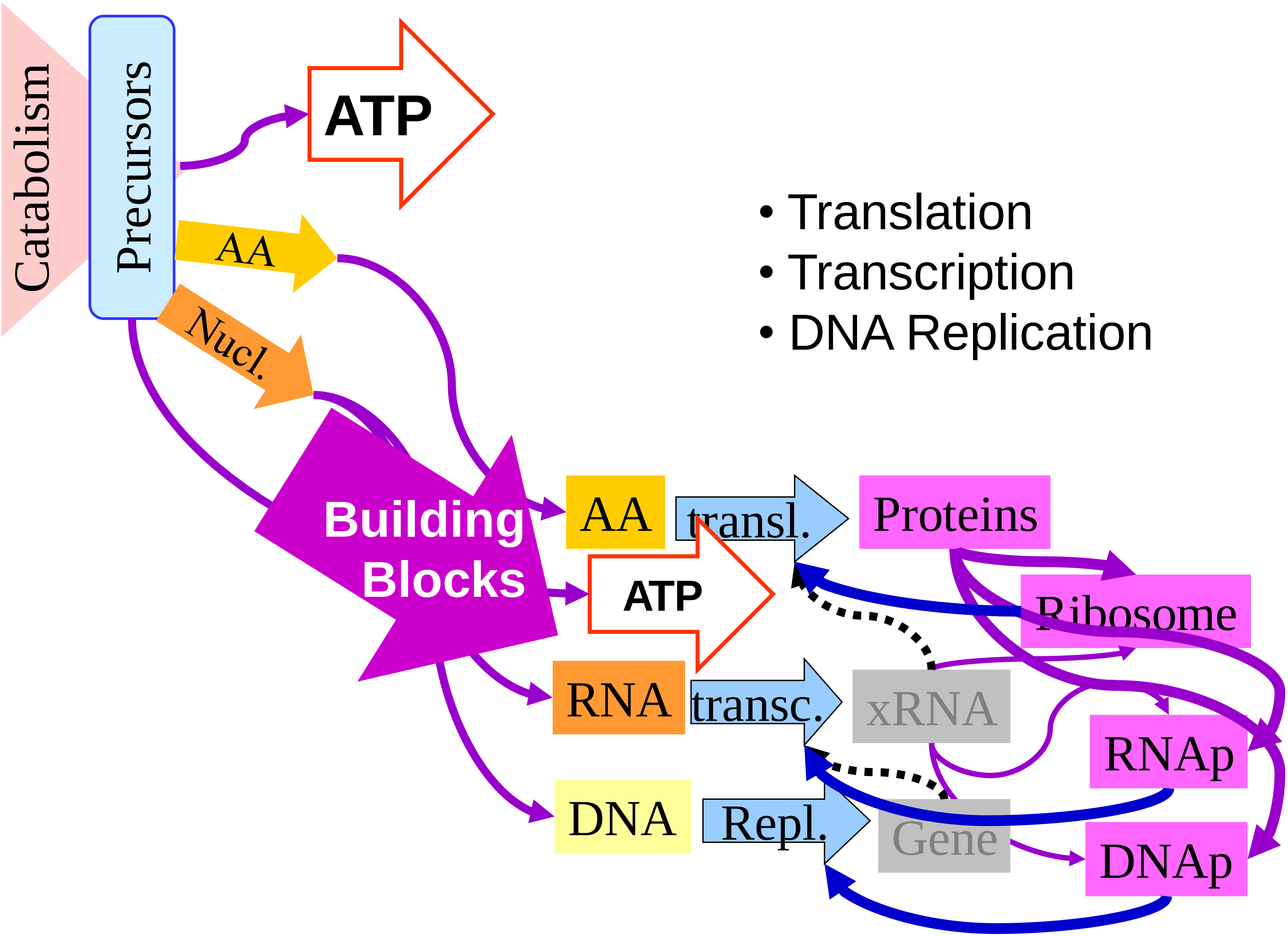

Taxis and transport
12
Autocatalytic feedback
Polymerization and complex assembly
Core metabolism
Nutrients
Catabolism
Precursors
Sugars
Fatty acids
Co-factors
Amino Acids
Nucleotides
Carriers
Genes
Trans*
Protein
cation
Huge Variety
8
≈100
≈10^4 to ≈ ∞ in one organisms

Inside every cell

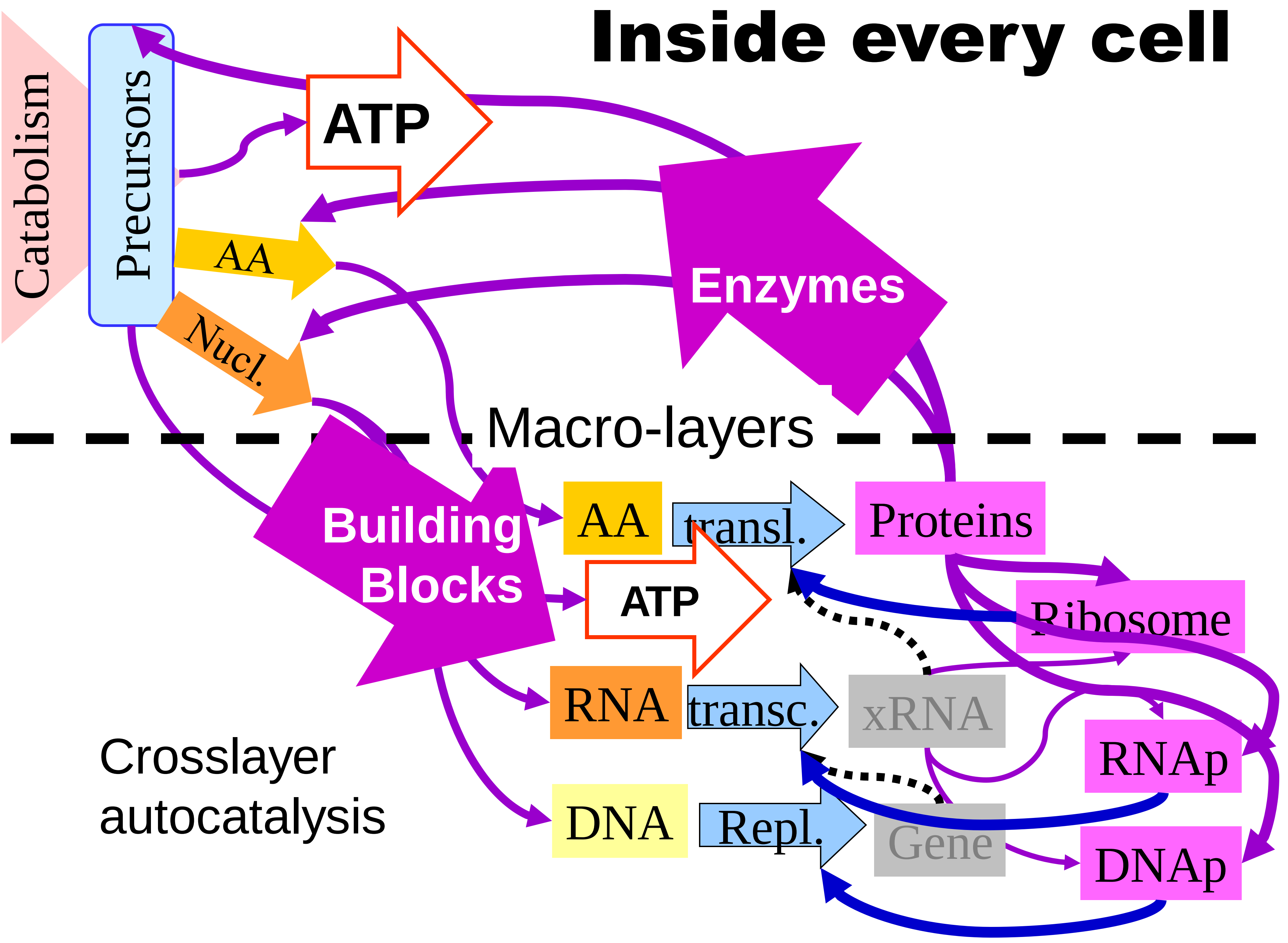


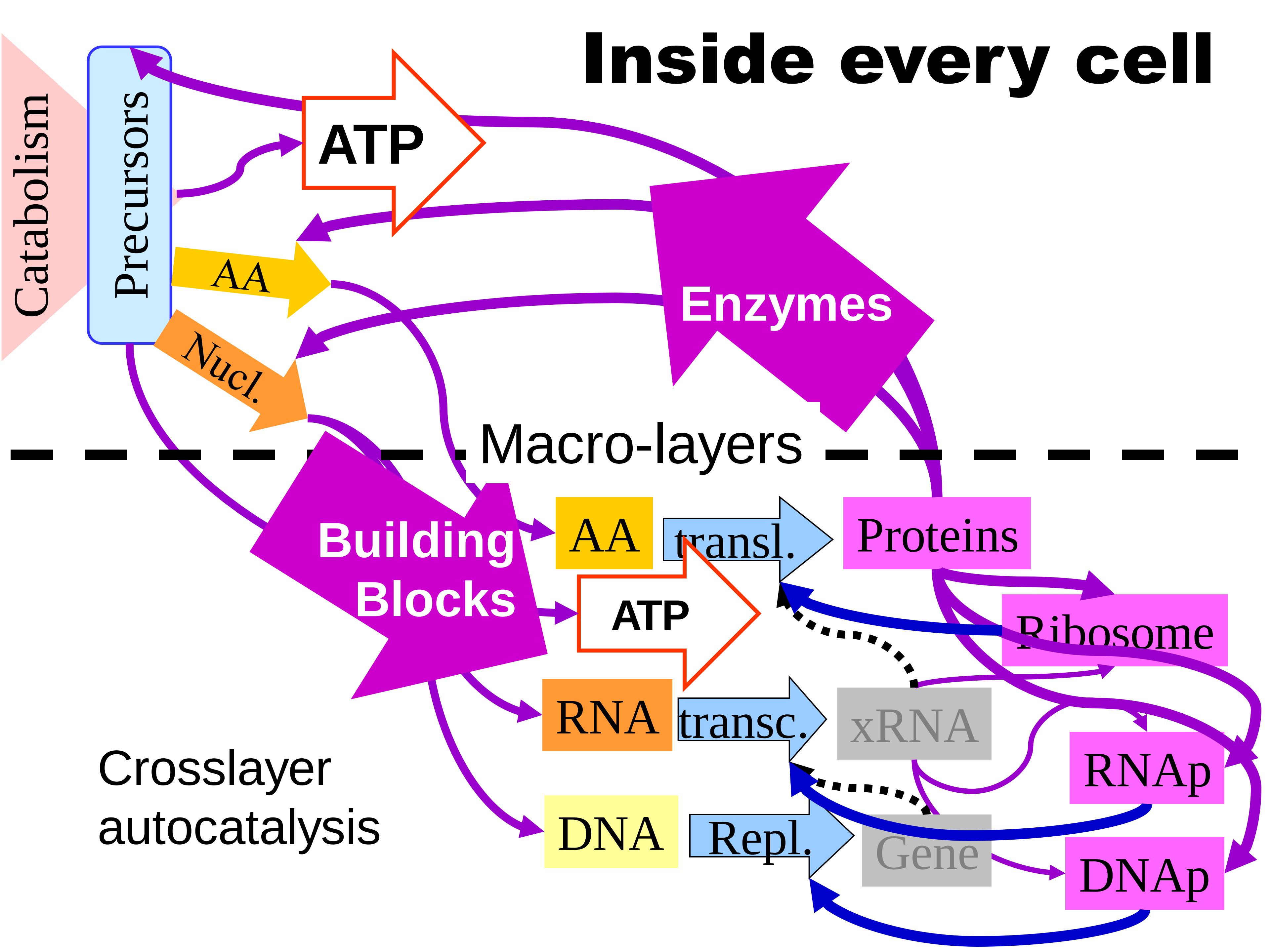
Ribosomes make ribosomes

Translation: Amino acids polymerized into proteins



- Translation
- Transcription
- DNA Replication


Inside every cell
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis



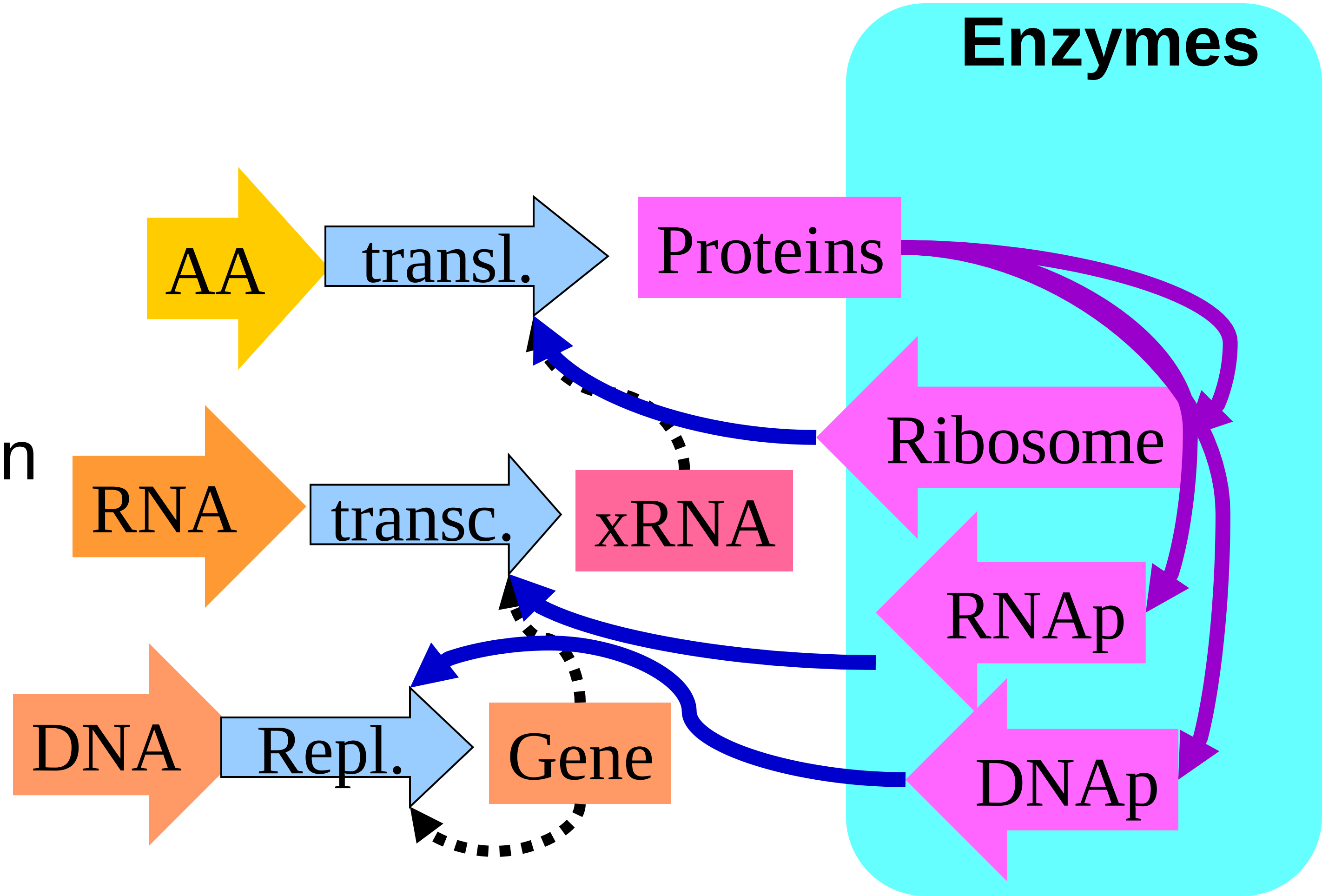
Inside every cell
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis

Lower layer autocatalysis

Macromolecules making …

Three lower layers? Yes:

- Translation
- Transcription
- Replication



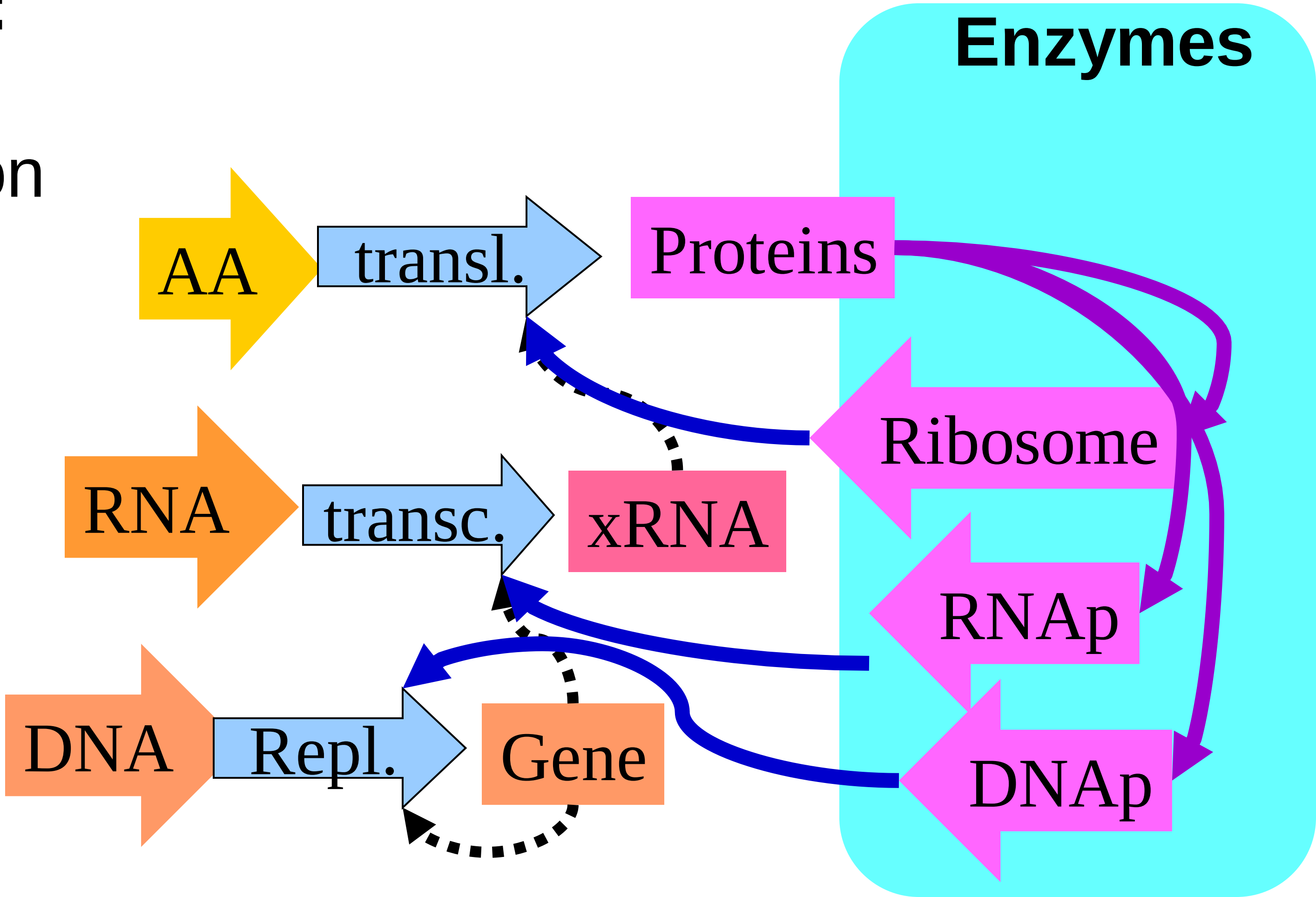
Autocatalytic within lower layers

- Collectively self-replicating
- Ribosomes make ribosomes, etc

Three lower layers? Yes:

- Translation
- Transcription
- Replication

Naturally recursive



Oscillate

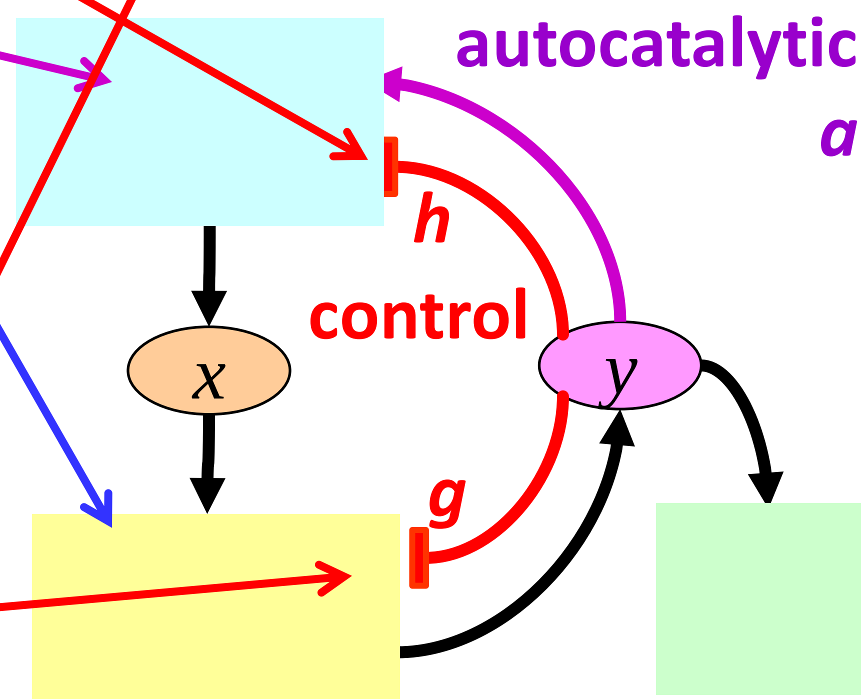
$$\left|\frac{\Delta\bar{y}}{\bar{d}}\right| \triangleq \left|\frac{1}{h-a}\right| > \frac{a}{k+(1+a)g}$$

Control

Autocatalysis

enzyme level

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$



Control

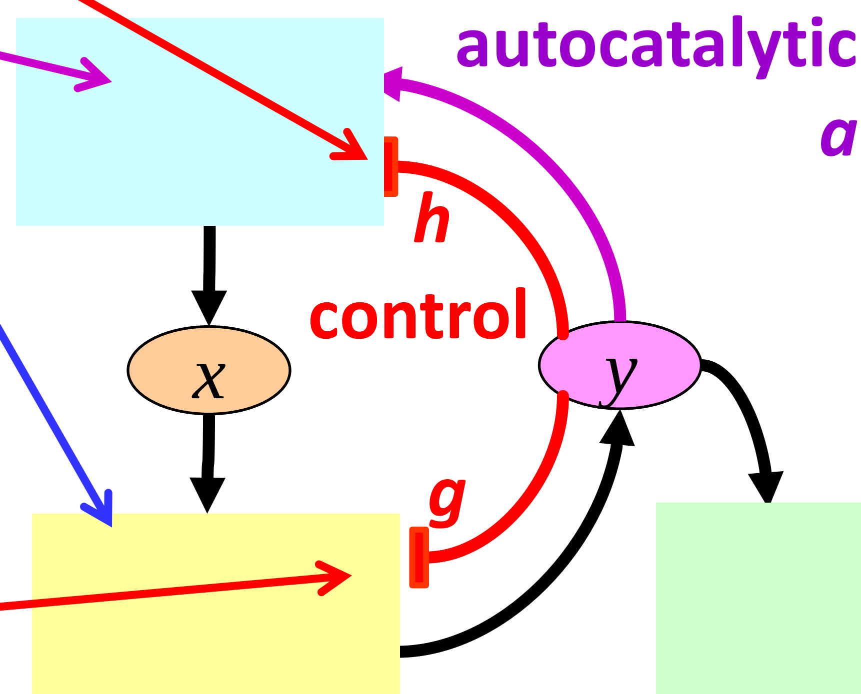
Control

Autocatalysis

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)\,y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix} d$$

enzyme level

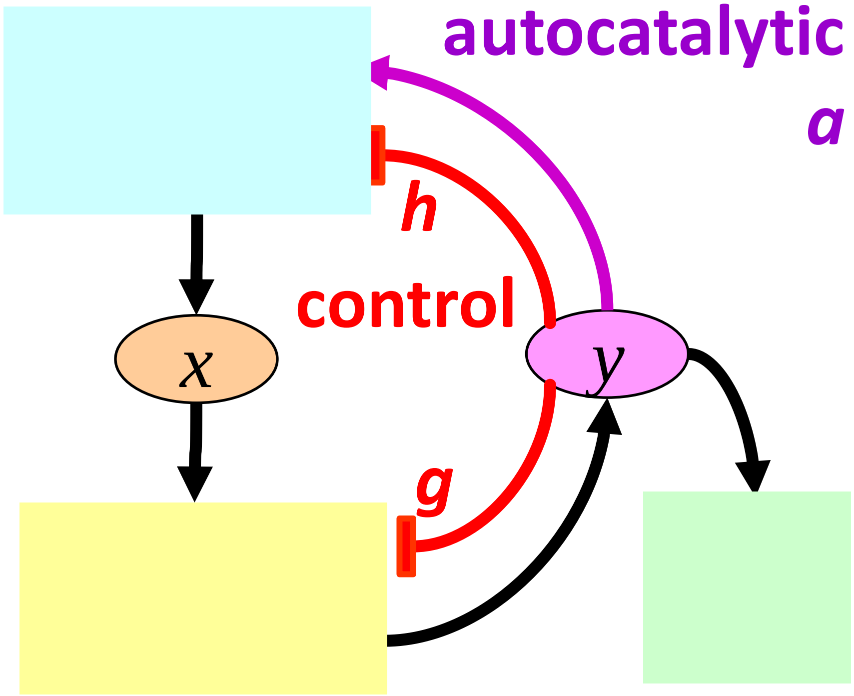
Control



$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \left[\begin{bmatrix} 1 \\ -a \end{bmatrix}\begin{bmatrix} -1 \\ 1+a \end{bmatrix}\begin{bmatrix} 0 \\ -1 \end{bmatrix}\right]\begin{bmatrix} (a-h)y \\ (kx-gy) \\ d \end{bmatrix}$$

$$\frac{d}{dt}\left(\bullet\right) = S\sigma\left(\bullet\right)$$

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix}d$$



Stoichiometry plus regulation

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

$$\frac{d}{dt}\left(\text{Mass\&Energy}\right) = \begin{bmatrix} \text{Mass \&} \\ \text{Energy} \\ \text{Balance} \end{bmatrix} \begin{bmatrix} \text{Reaction} \\ \text{flux} \end{bmatrix}$$

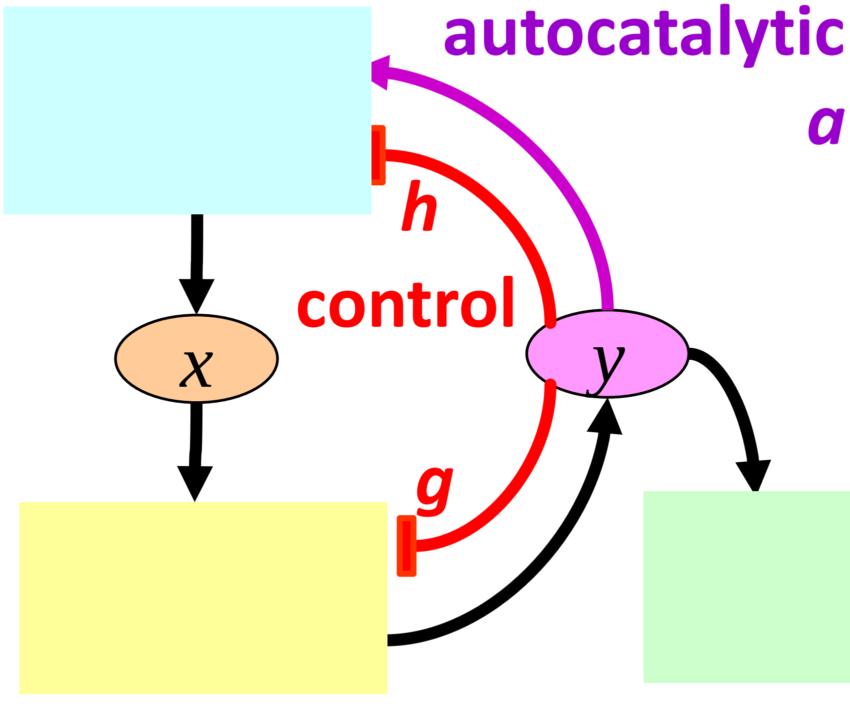
- ☺ Matrix of integers
- ☺ "Simple," can be known exactly
- ☺ Amenable to high throughput assays and manipulation
- ☺ Bowtie architecture

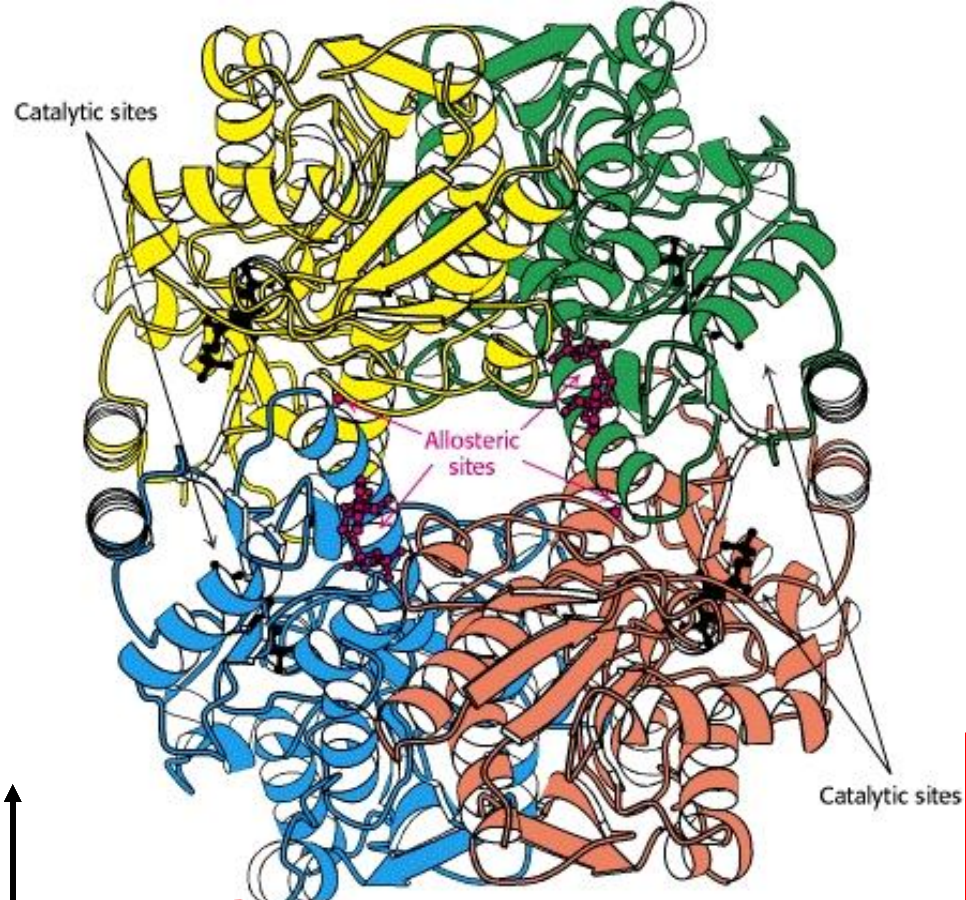
- ☹ Vector of (complex?) functions
- ☹ Difficult to determine and manipulate
- ☹ Effected by stochastics and spatial/mechanical structure
- ☺ Hourglass architecture
- ☺ Can be modeled by optimal controller (?!?)

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \left[\begin{bmatrix} 1 \\ -a \end{bmatrix}\begin{bmatrix} -1 \\ 1+a \end{bmatrix}\begin{bmatrix} 0 \\ -1 \end{bmatrix}\right]\begin{bmatrix} (a-h)y \\ (kx-gy) \\ d \end{bmatrix}$$

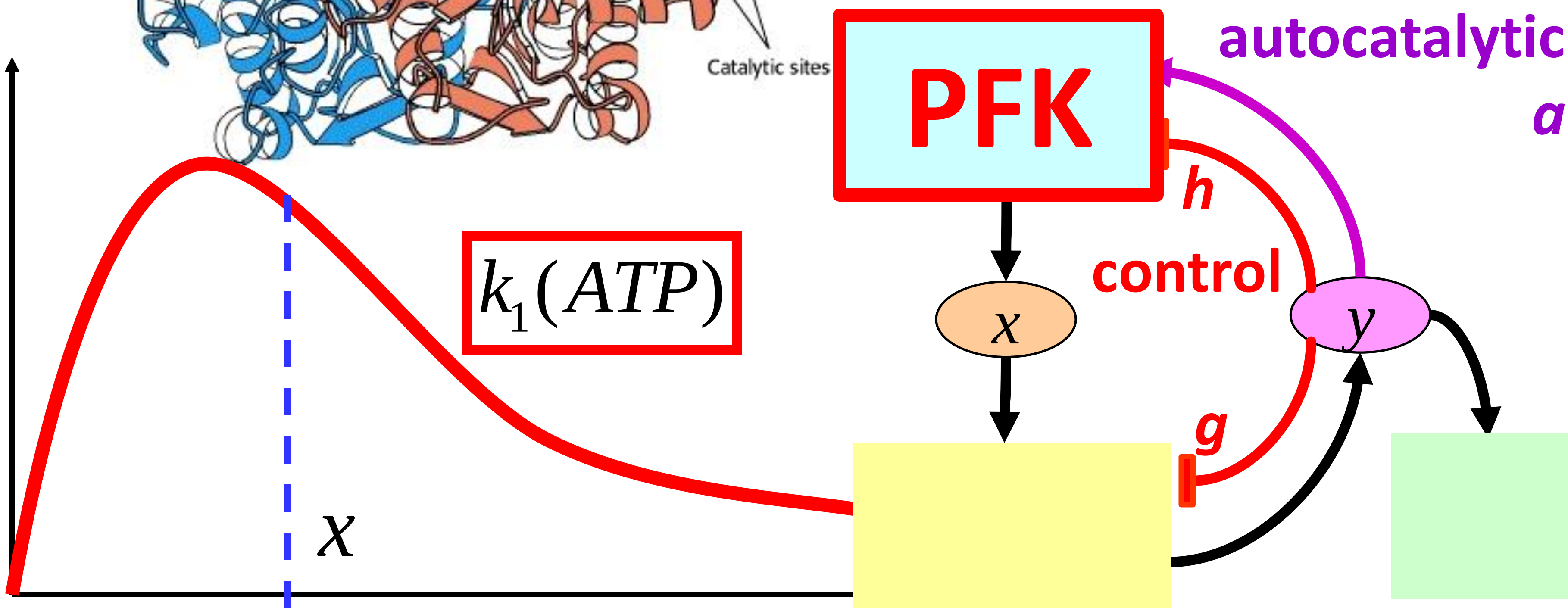
$$\frac{d}{dt}\left(\bullet\right) = S\sigma\left(\bullet\right)$$

$$\frac{d}{dt}\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} 1 \\ -a \end{bmatrix}(a-h)y + \begin{bmatrix} -1 \\ 1+a \end{bmatrix}(kx-gy) + \begin{bmatrix} 0 \\ -1 \end{bmatrix}d$$

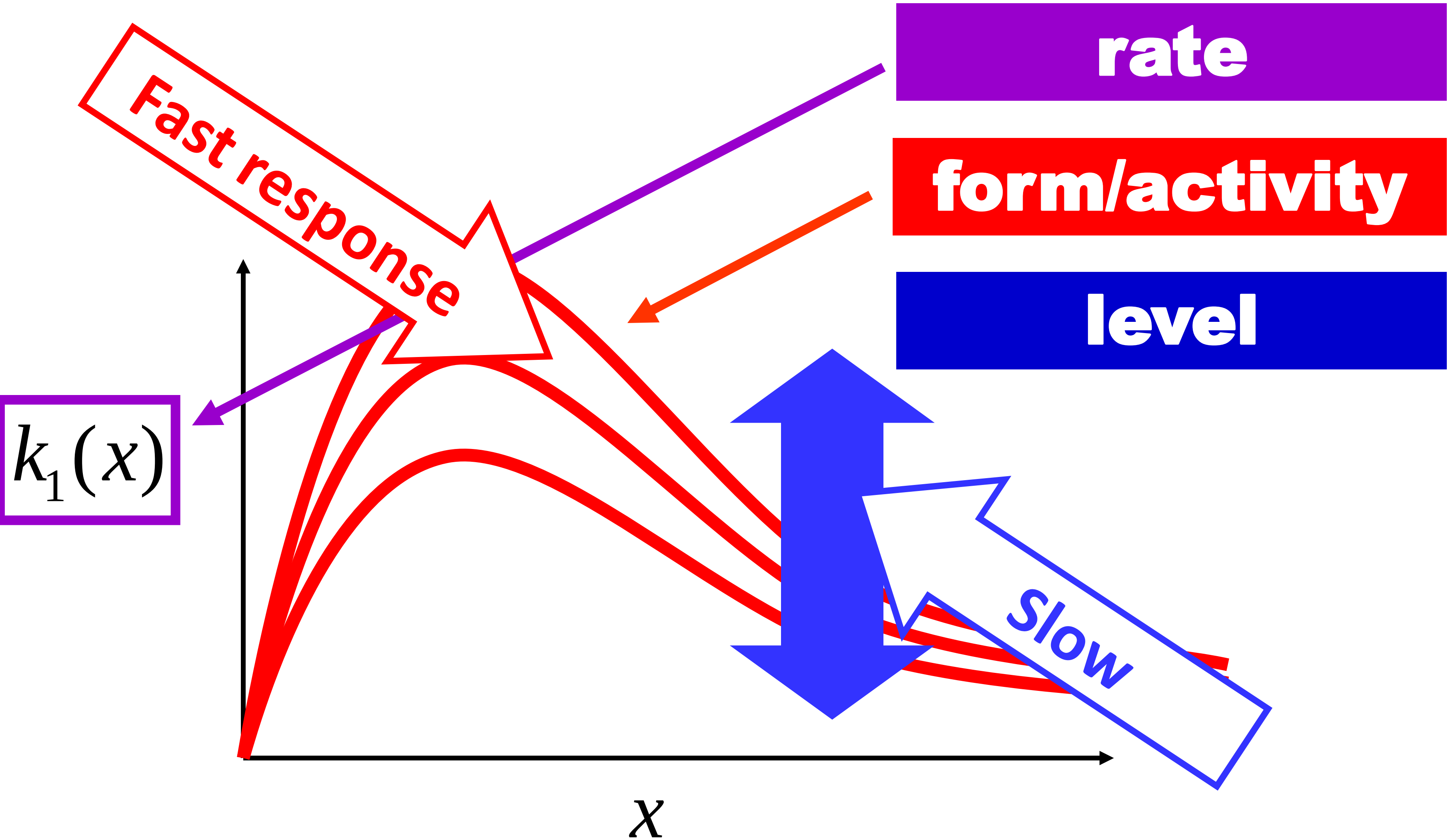




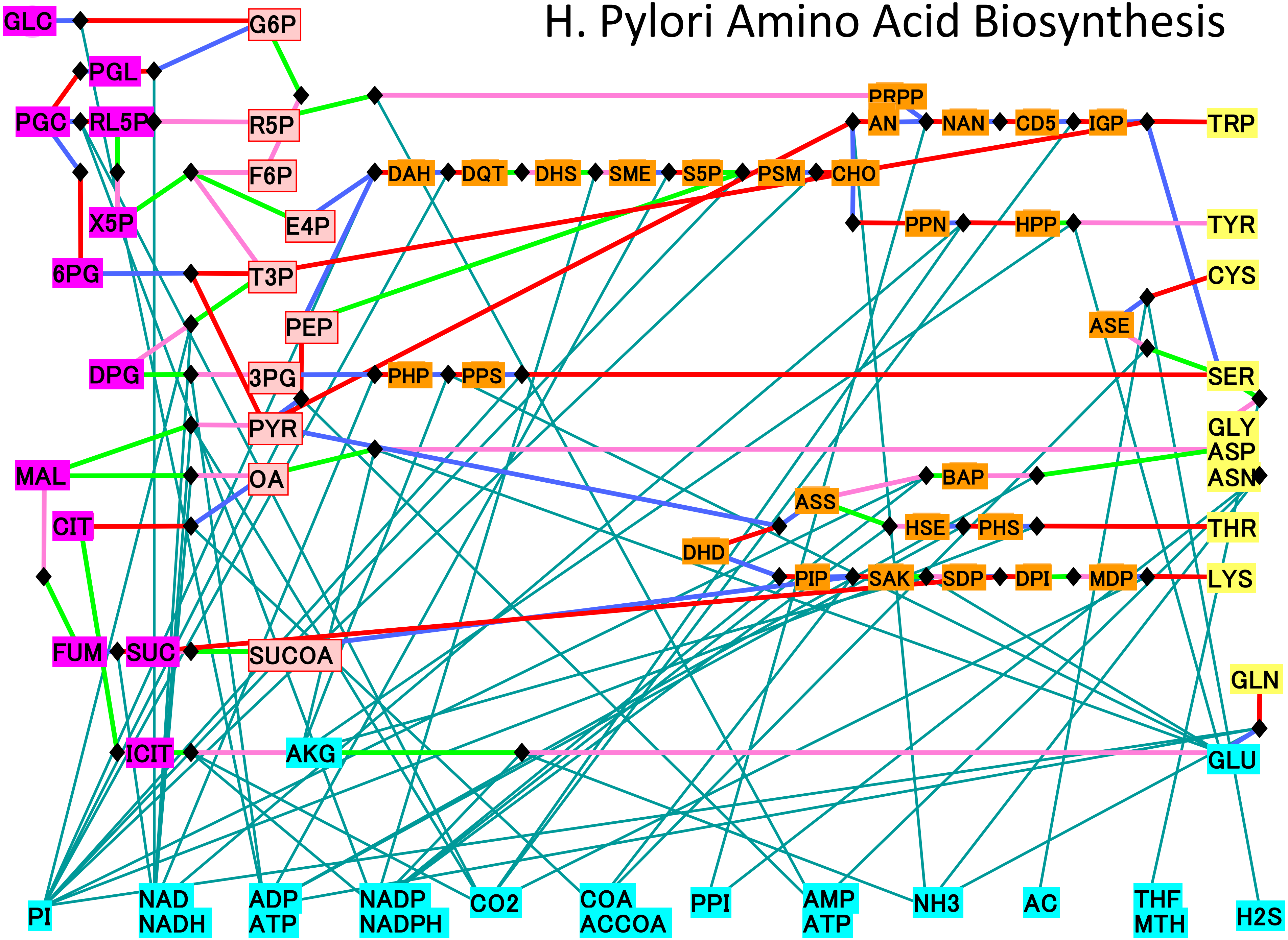
- Fastest allosteric feedback control
- **Complex proteins**
- High metabolic overhead
- **Hard to reprogram**



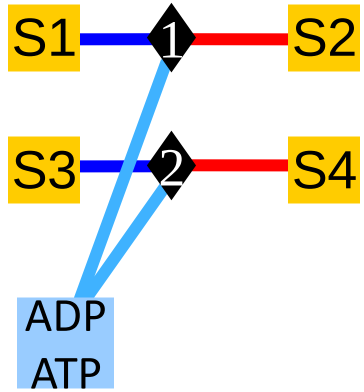
Layered control



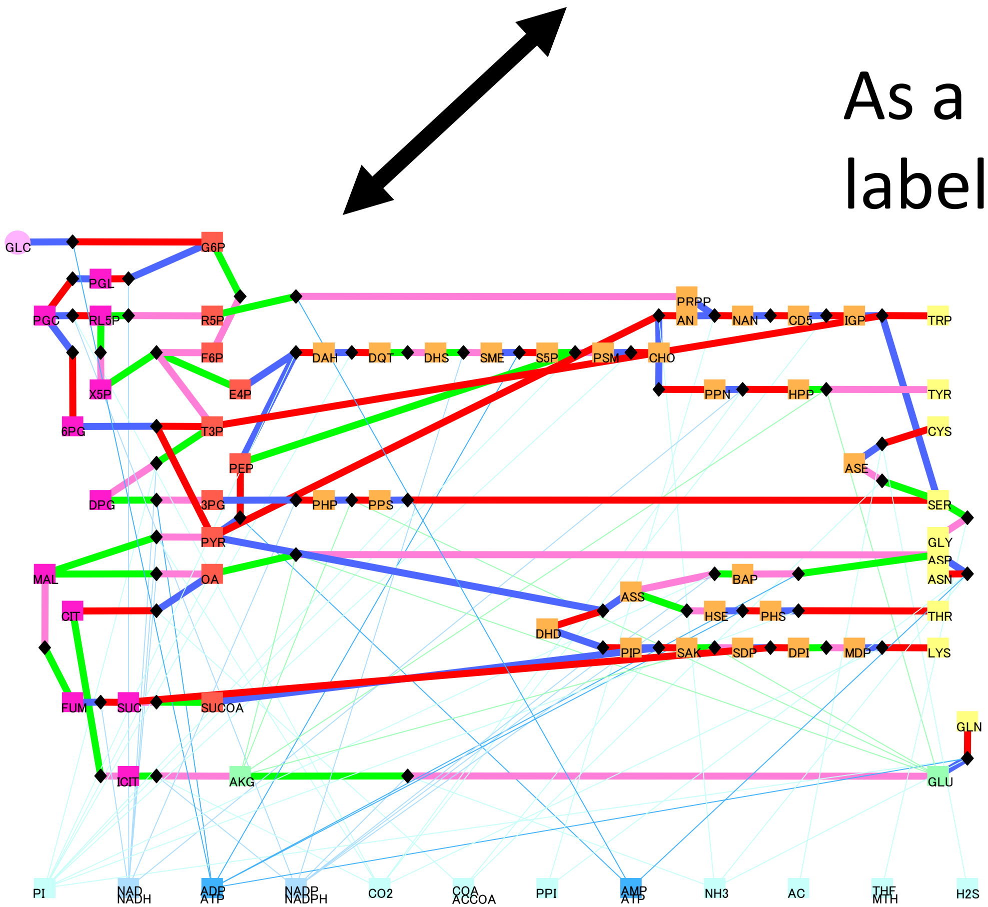
H. Pylori Amino Acid Biosynthesis



H Pylori amino acid biosynthesis



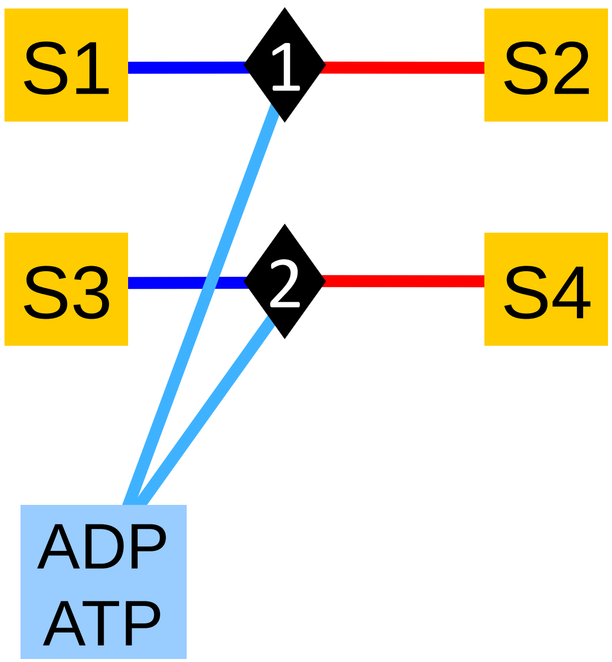
As a bipartite labeled graph.



$$S_1 + ATP \rightarrow S_2 + ADP$$
$$S_3 + ATP \rightarrow S_4 + ADP$$

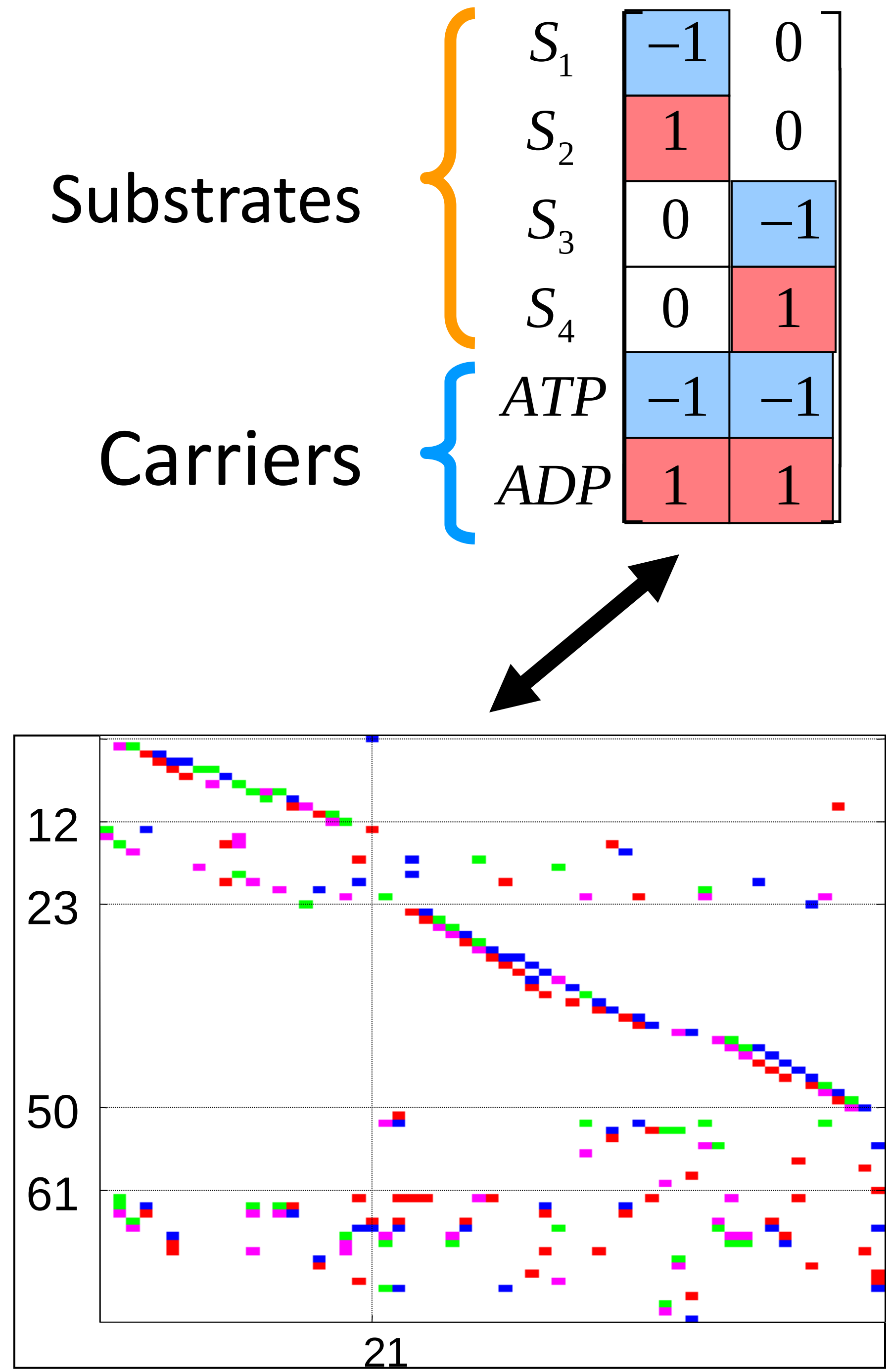
Substrates	S_1	-1	0
	S_2	1	0
	S_3	0	-1
	S_4	0	1
Carriers	ATP	-1	-1
	ADP	1	1

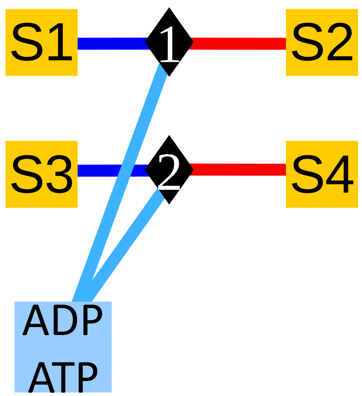
Stoichiometry matrix



H Pylori
amino acid
biosynthesis

As a color coded (for reversibility) stoichiometry matrix.



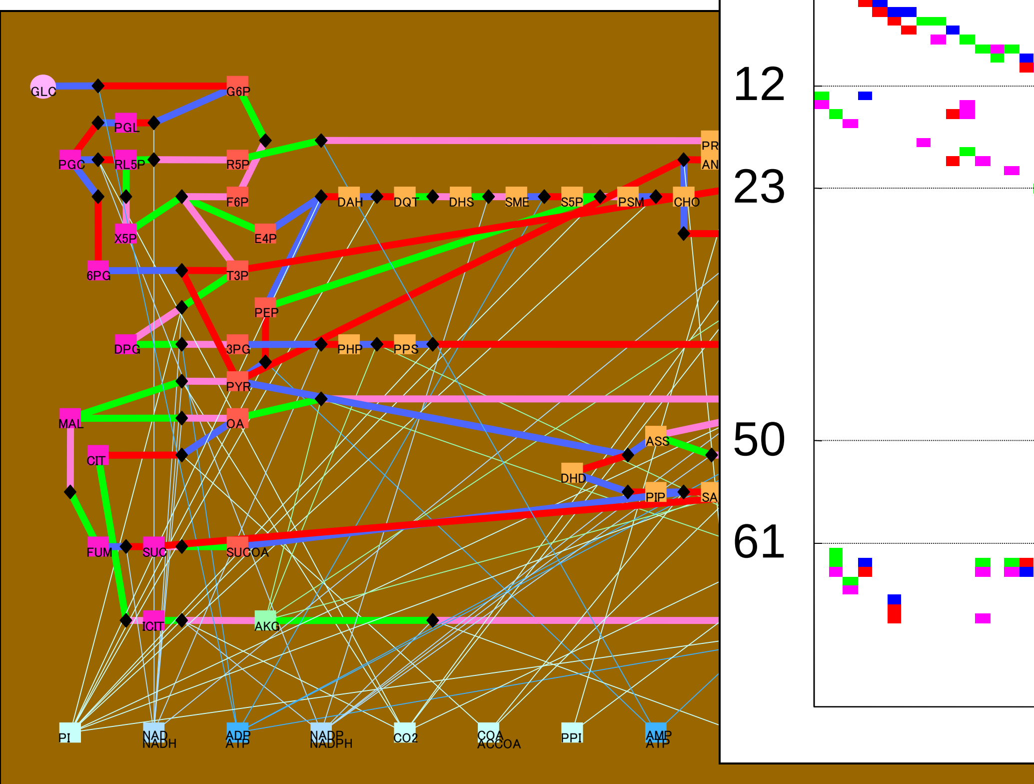


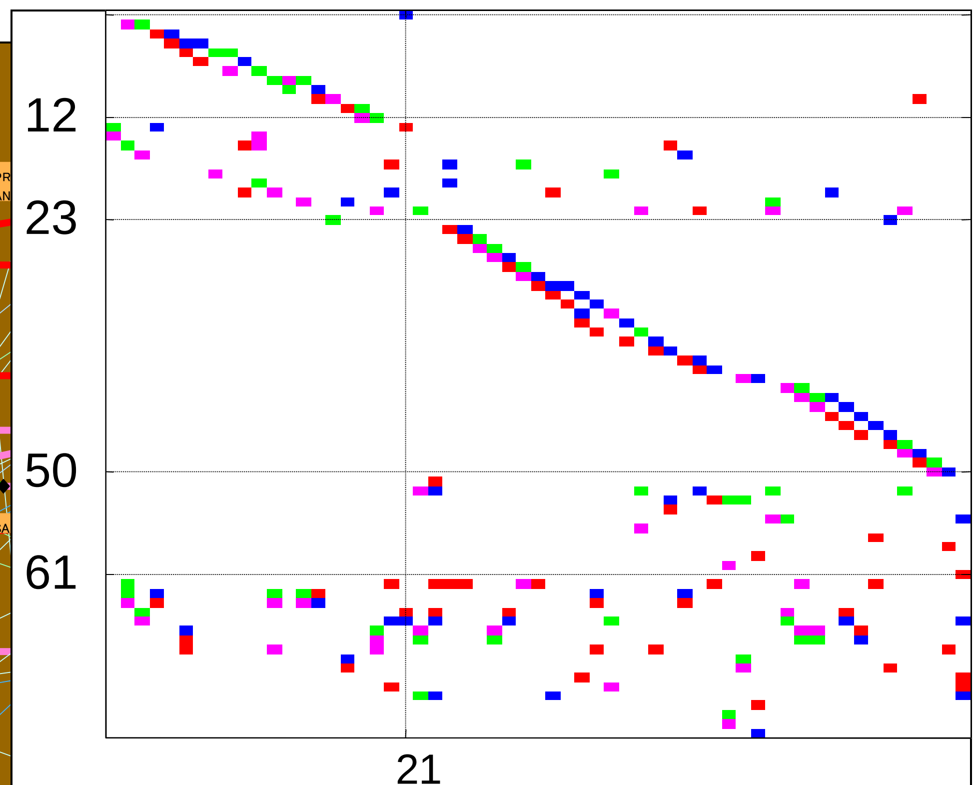
These are equivalent to each other but ***not*** to unipartite graphs.

Substrates

Carriers

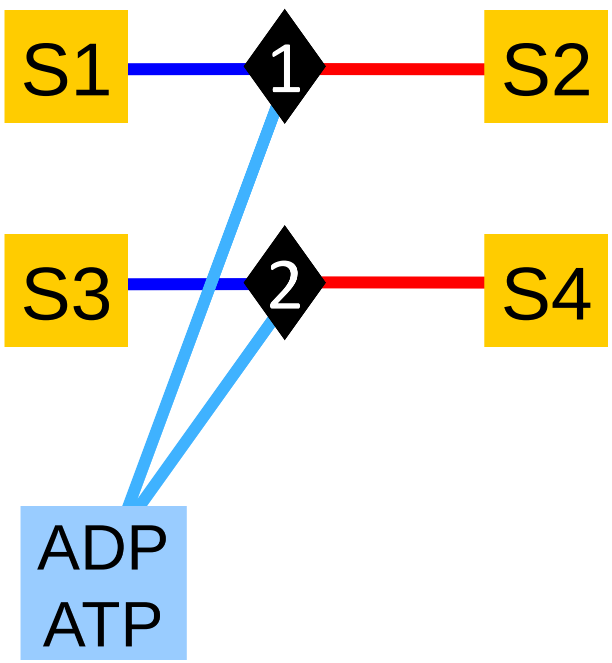
$$\begin{array}{c|cc} S_1 & -1 & 0 \\ S_2 & 1 & 0 \\ S_3 & 0 & -1 \\ S_4 & 0 & 1 \\ ATP & -1 & -1 \\ ADP & 1 & 1 \end{array}$$



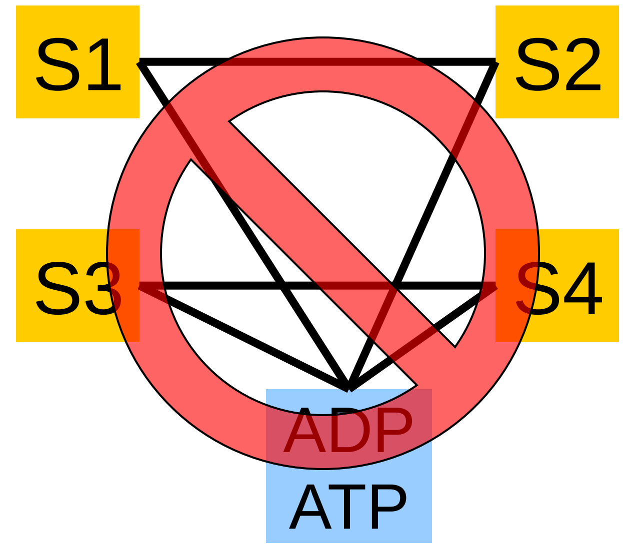


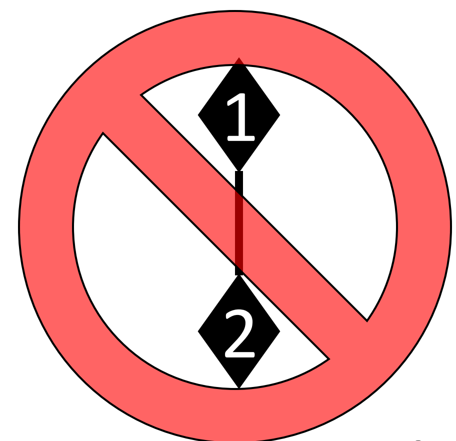
Unipartite projections lose too much.

$$\left.\begin{array}{l} S_1 + ATP \rightarrow S_2 + ADP \\ S_3 + ATP \rightarrow S_4 + ADP \end{array}\right\}$$



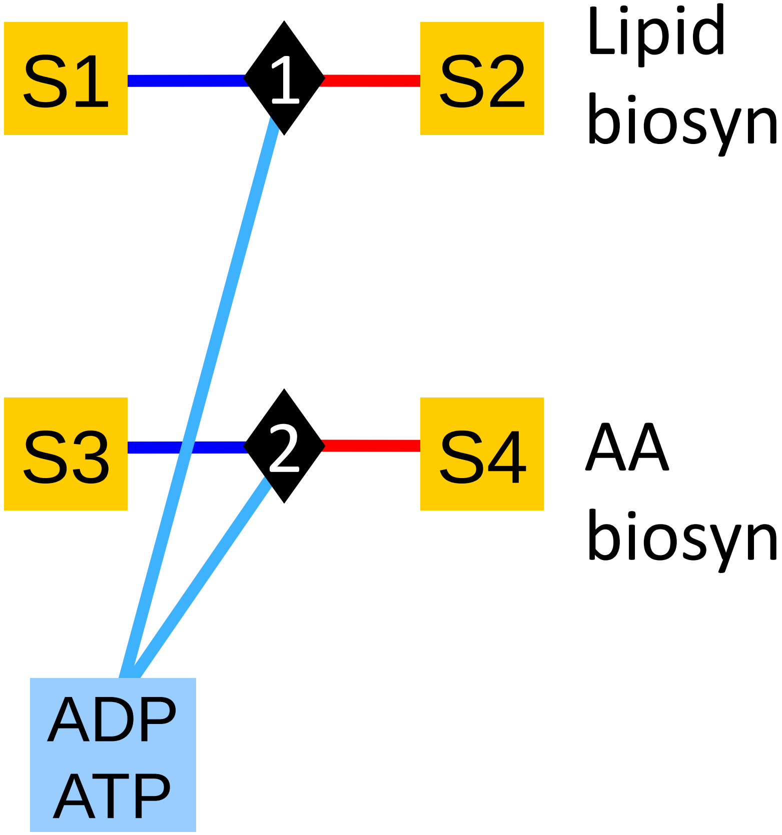
Substrate graph



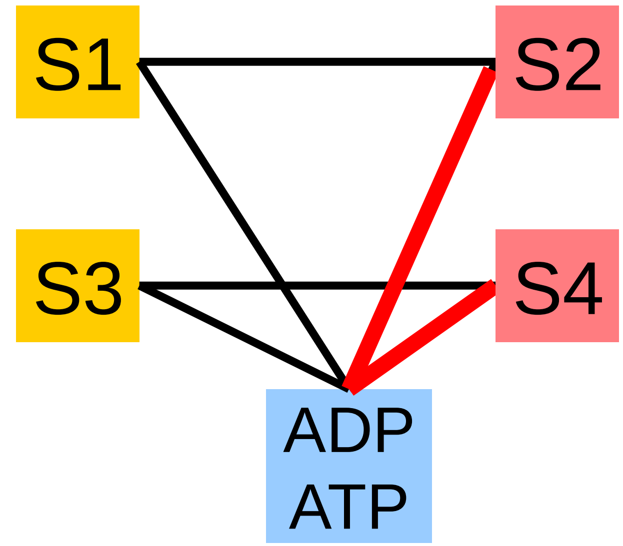


Reaction graph

Suppose these reactions are in different modules, say,



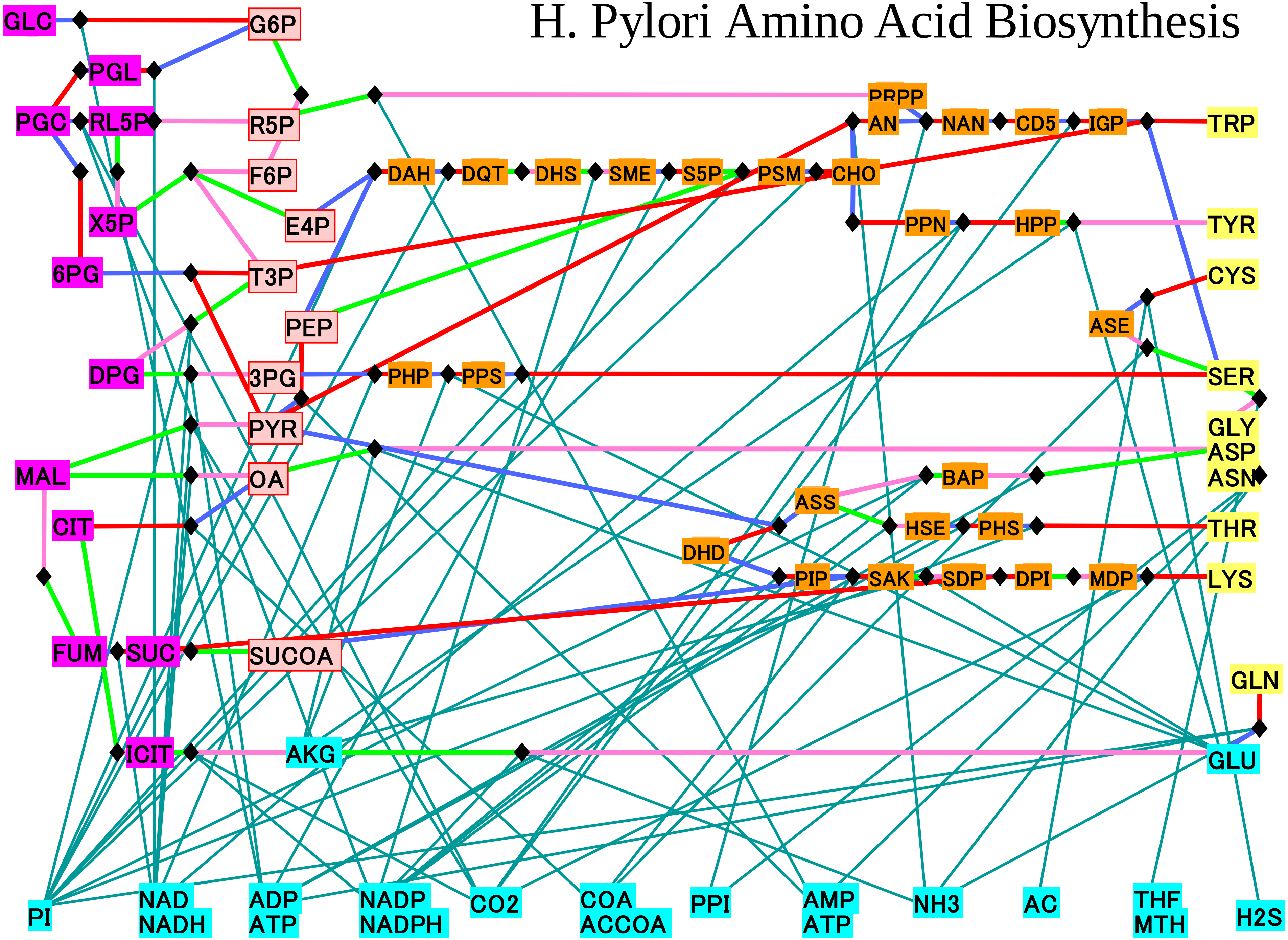
Substrate graph

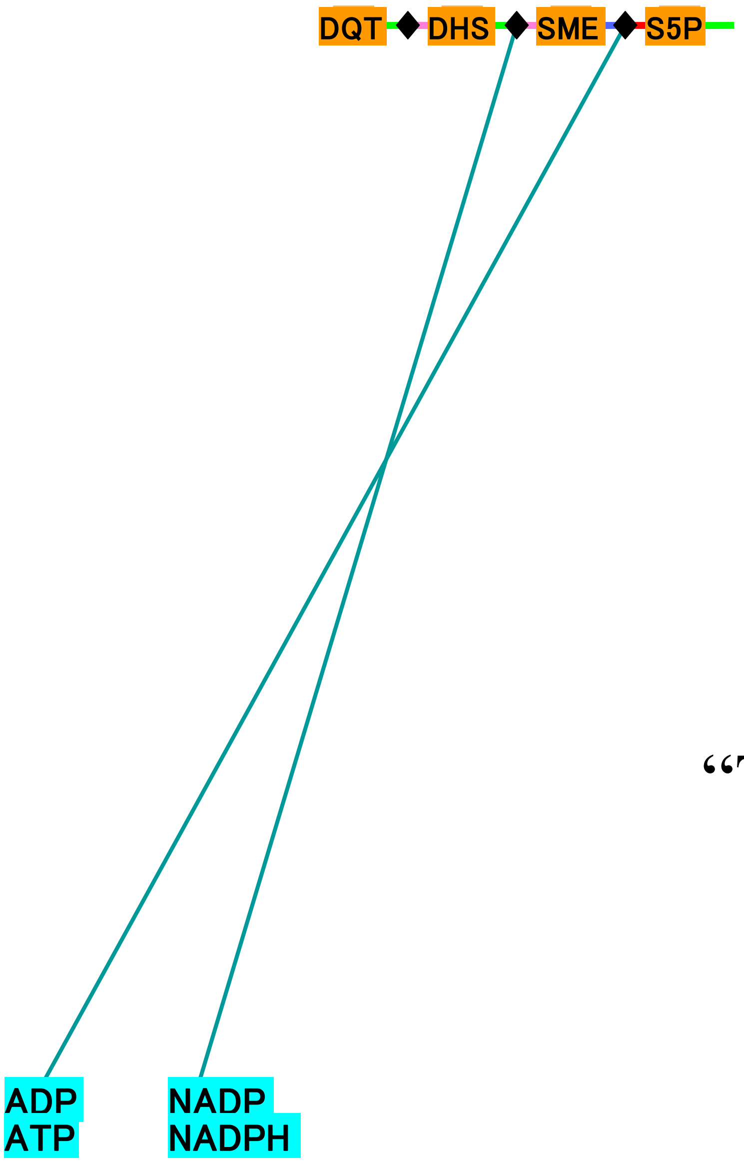


"Small world?"

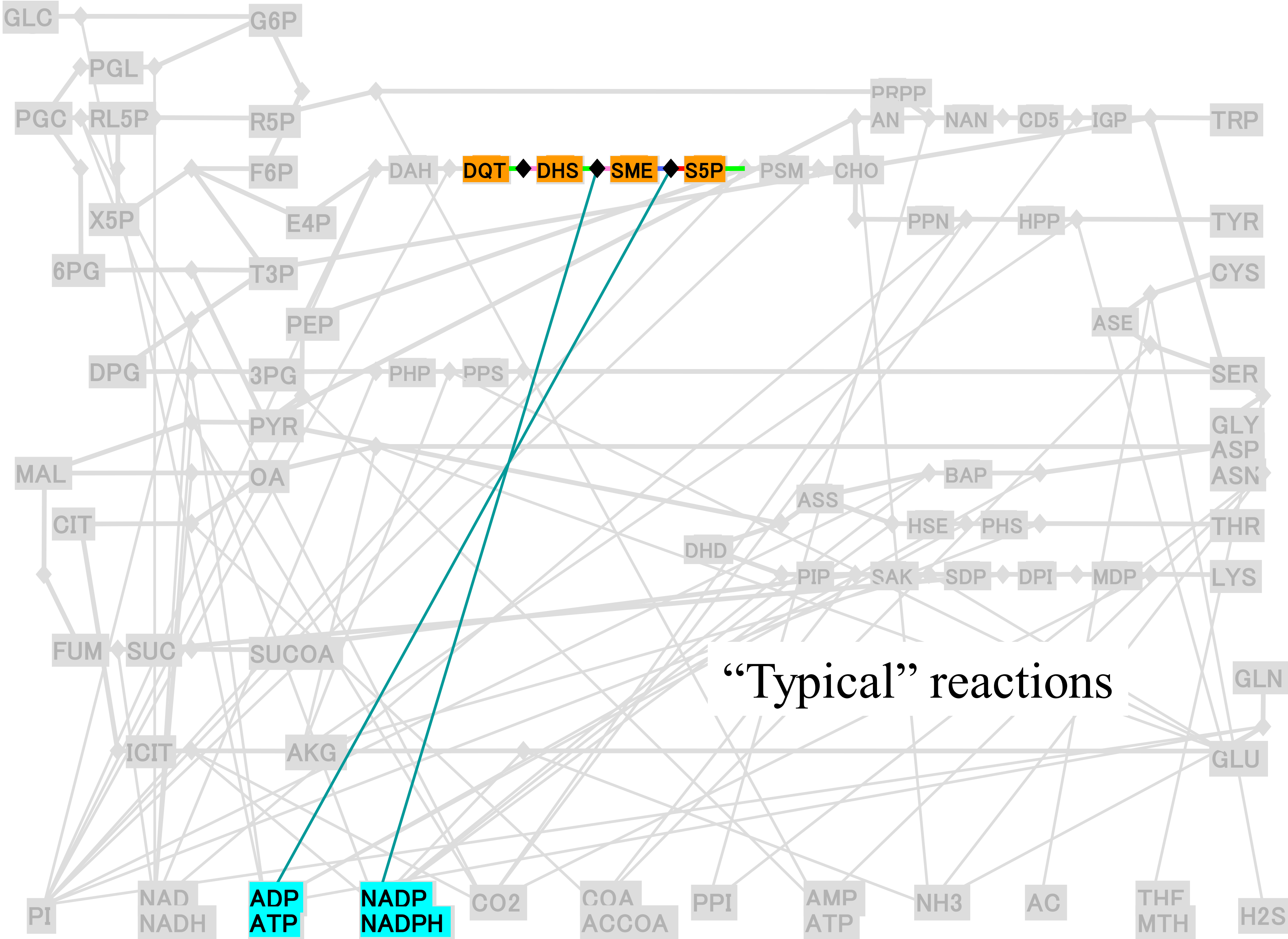
Not really.

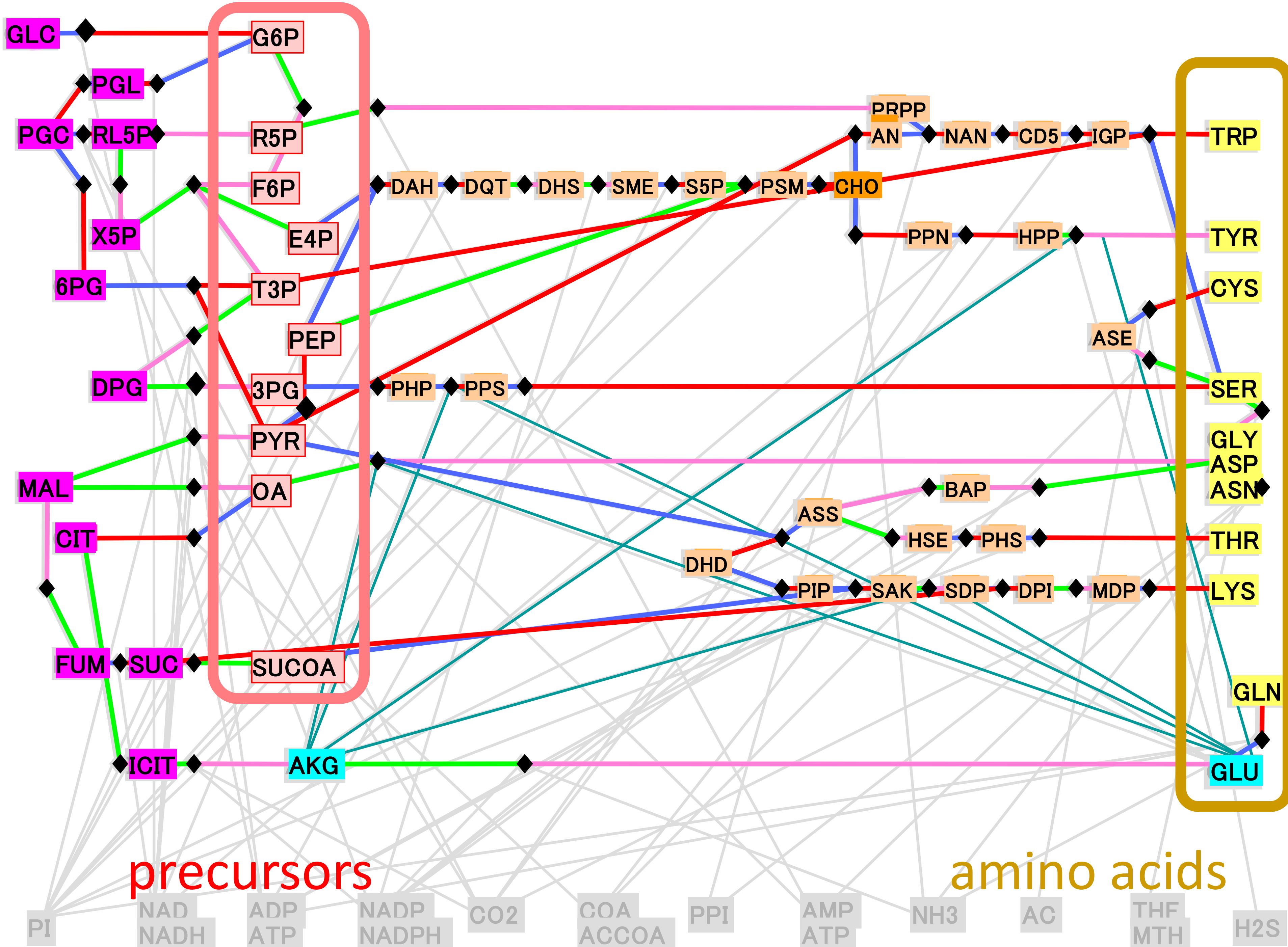
H. Pylori Amino Acid Biosynthesis





“Typical” reactions


GLC
G6P
PGL
PGC
RL5P
R5P
PRPP
AN
NAN
CD5
IGP
TRP
F6P
DAH
DQT
DHS
SME
S5P
PSM
CHO
X5P
E4P
PPN
HPP
TYR
6PG
T3P
CYS
PEP
ASE
DPG
3PG
PHP
PPS
SER
PYR
GLY
ASP
ASN
MAL
OA
BAP
ASS
CIT
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
FUM
SUC
SUCOA
“Typical” reactions
GLN
ICIT
AKG
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S


GLC
G6P
PGL
PGC
RL5P
R5P
F6P
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
PRPP
AN
NAN
CD5
IGP
TRP
DAH
DQT
DHS
SME
S5P
PSM
CHO
PPN
HPP
TYR
CYS
ASE
SER
PHP
PPS
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU
precursors
amino acids
PI
NAD
NADH
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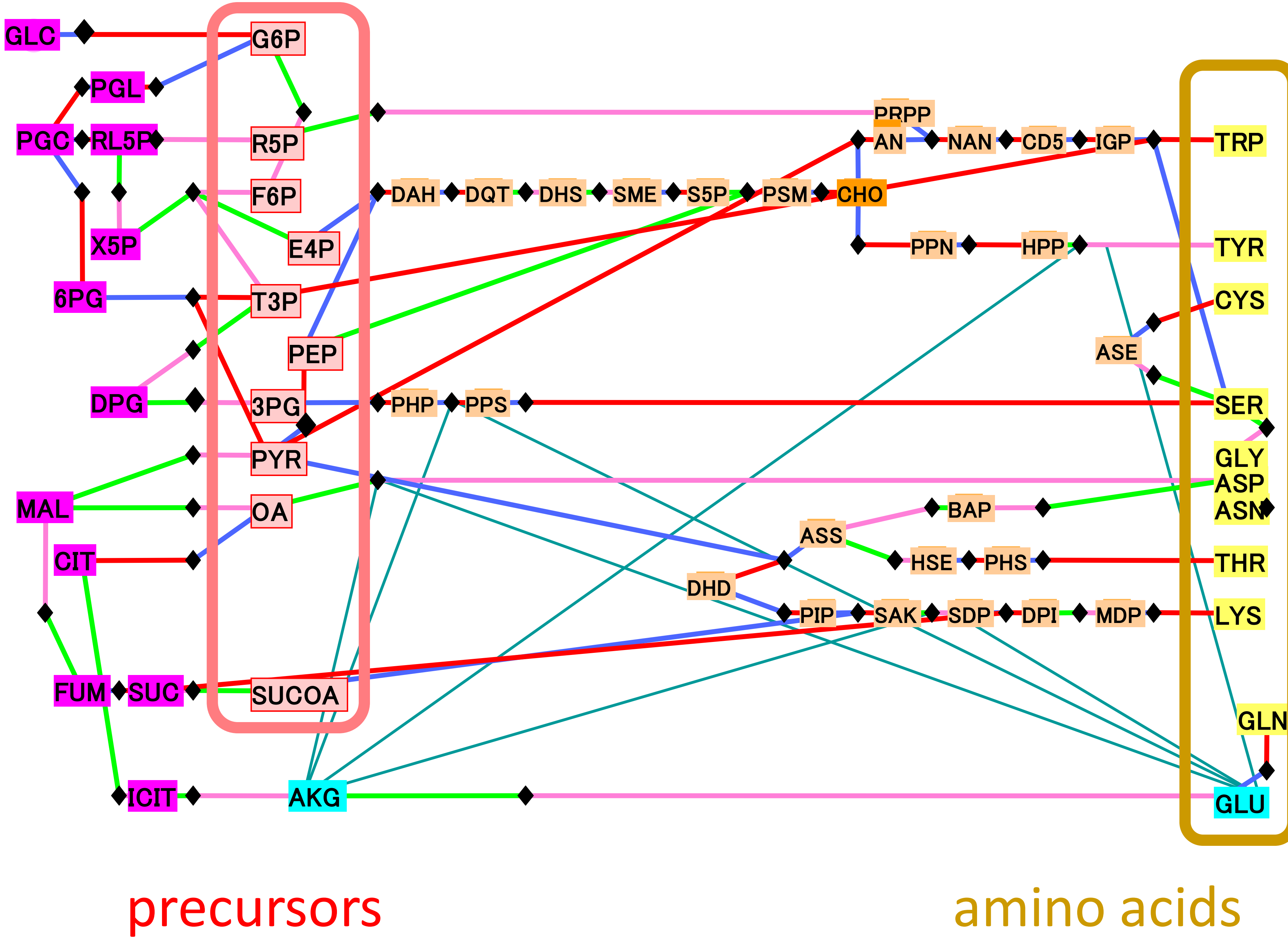
AMP
ATP
NH3
AC
THF
MTH
H2S


GLC
G6P
PGL
PGC
RL5P
R5P
PRPP
AN
NAN
CD5
IGP
TRP
F6P
X5P
E4P
DAH
DQT
DHS
SME
S5P
PSM
CHO
PPN
HPP
TYR
6PG
T3P
CYS
PEP
ASE
DPG
3PG
PHP
PPS
SER
PYR
GLY
ASP
ASN
MAL
OA
BAP
ASS
CIT
HSE
PHS
THR
DHD
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FUM
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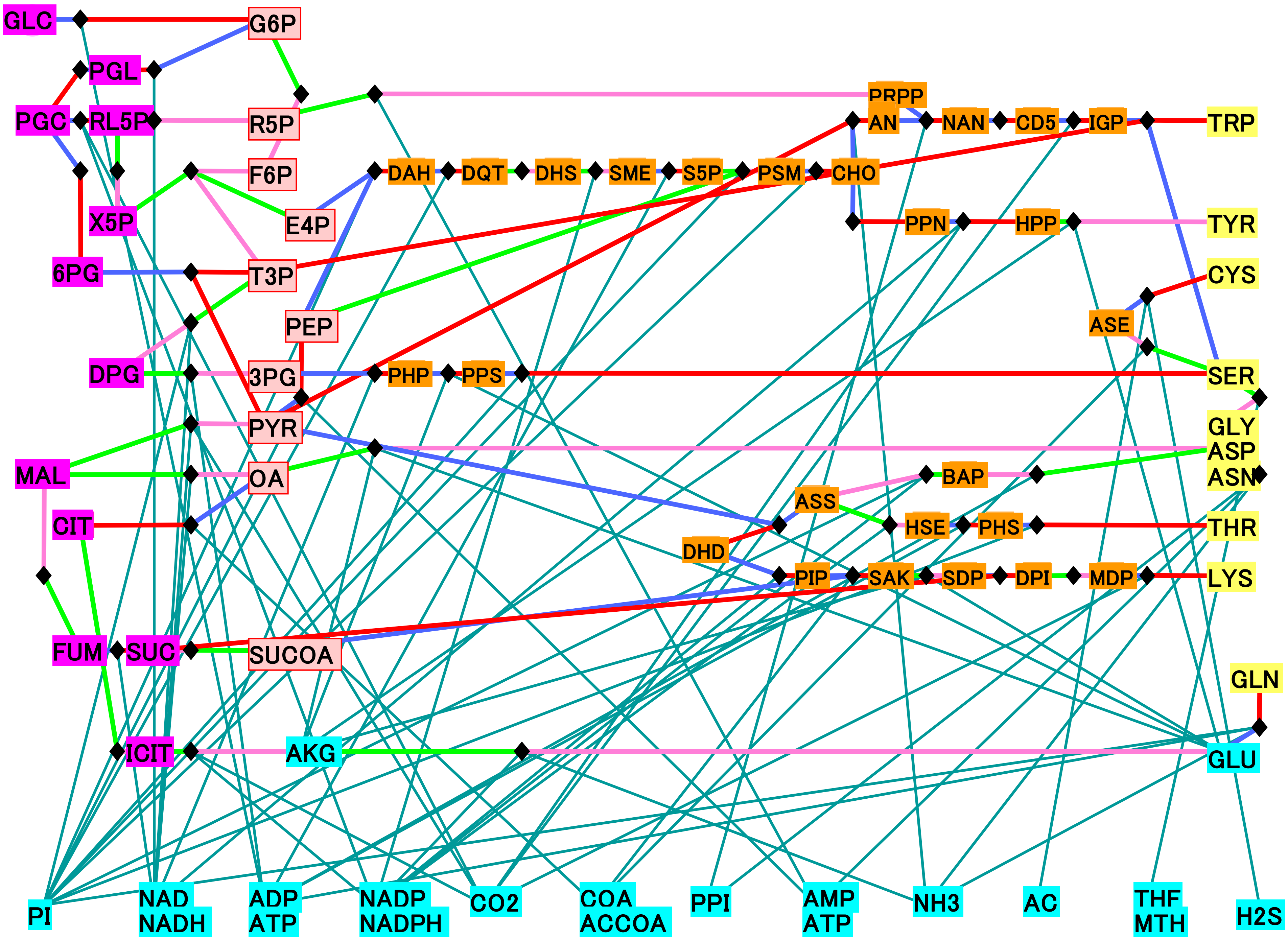
GLN
ICIT
AKG
GLU
precursors
amino acids


GLC
G6P
PGL
PGC
RL5P
R5P
PRPP
AN
NAN
CD5
IGP
TRP
F6P
DAH
DQT
DHS
SME
S5P
PSM
CHO
X5P
E4P
PPN
HPP
TYR
6PG
T3P
CYS
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MAL
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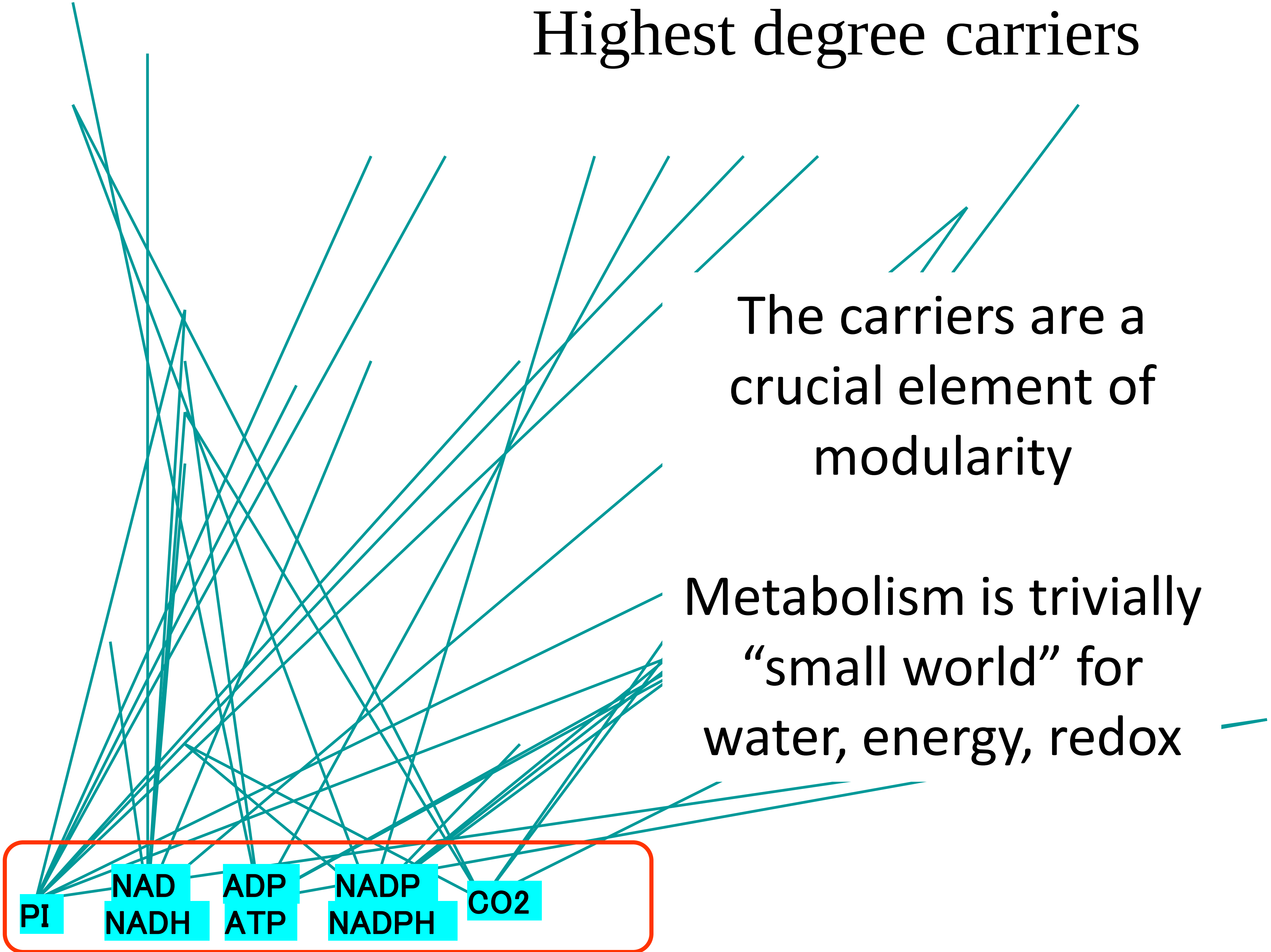
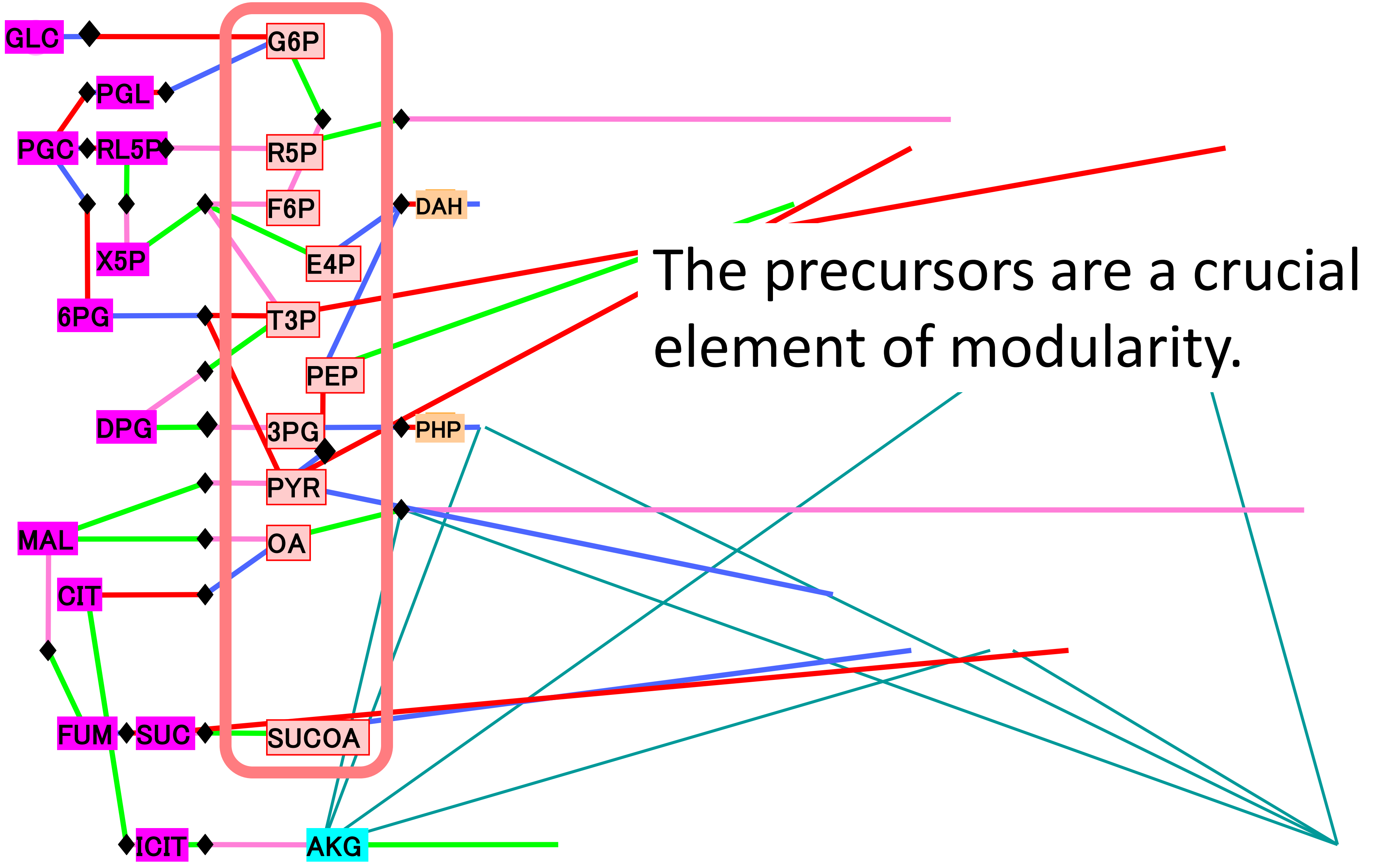
PIP
SAK
SDP
DPI
MDP
LYS
FUM
SUC
SUCOA
GLN
ICIT
AKG
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S

Highest degree carriers



The carriers are a crucial element of modularity

Metabolism is trivially "small world" for water, energy, redox

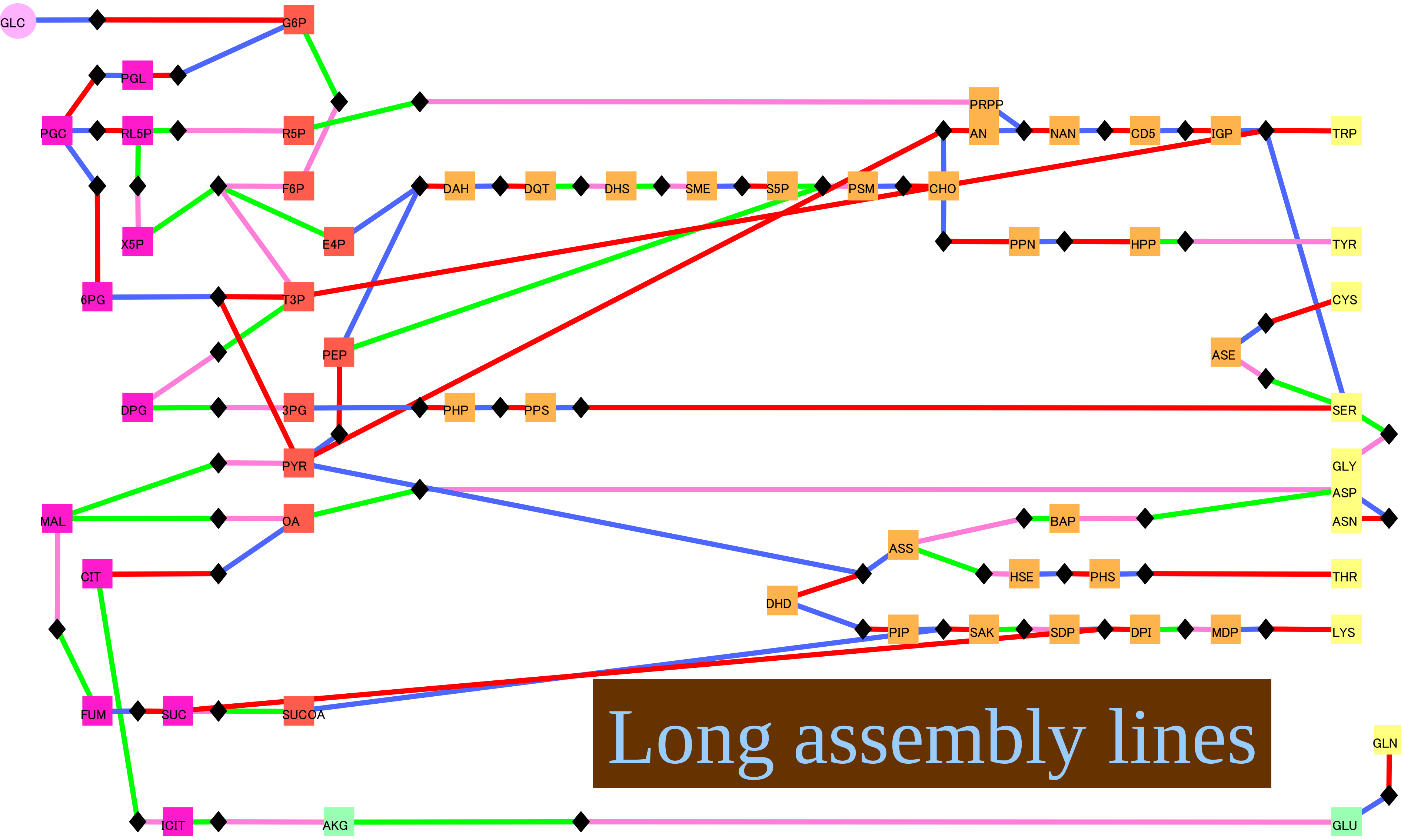


The precursors are a crucial element of modularity.

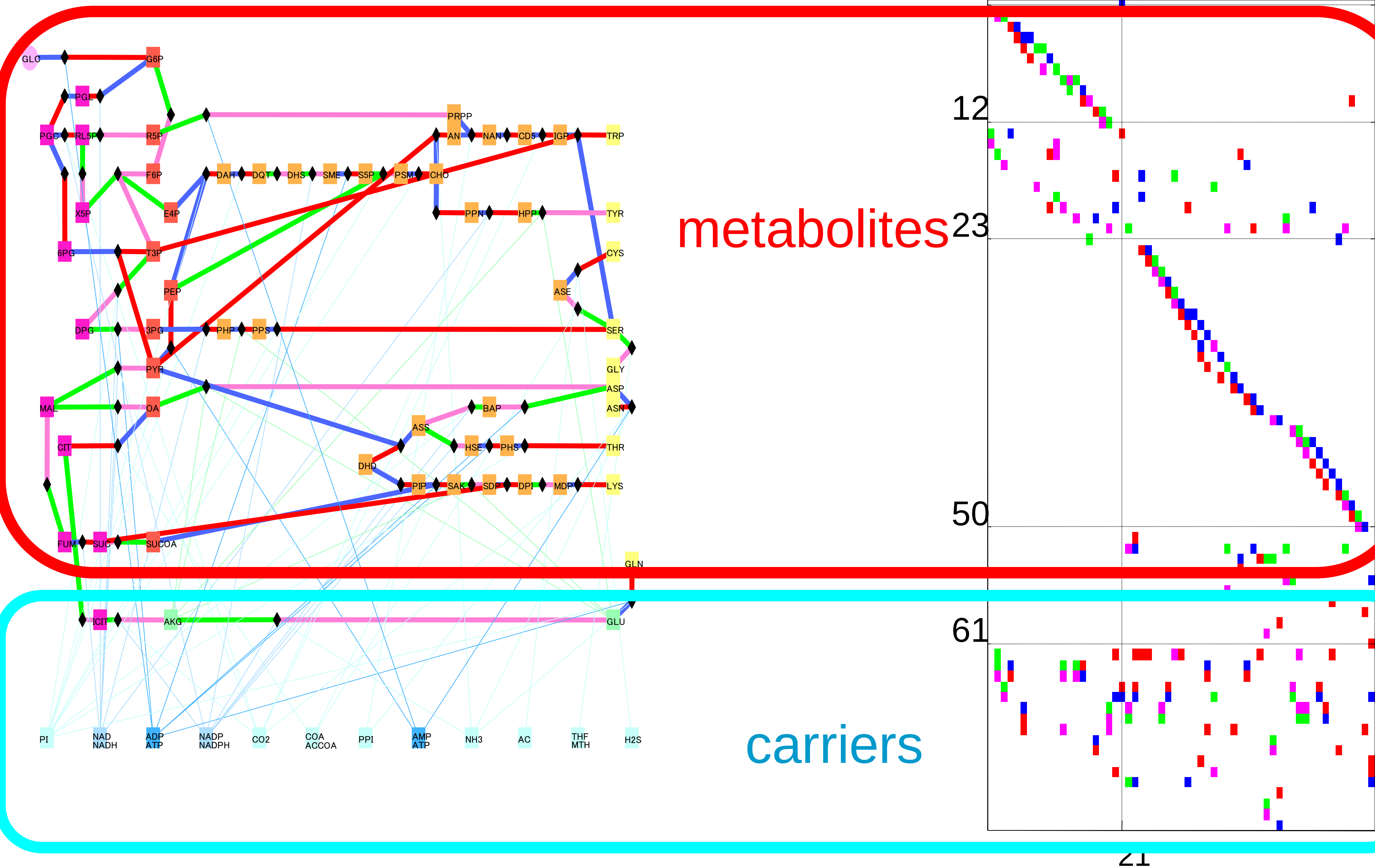
precursors

Without carriers

“long” not “small” worlds

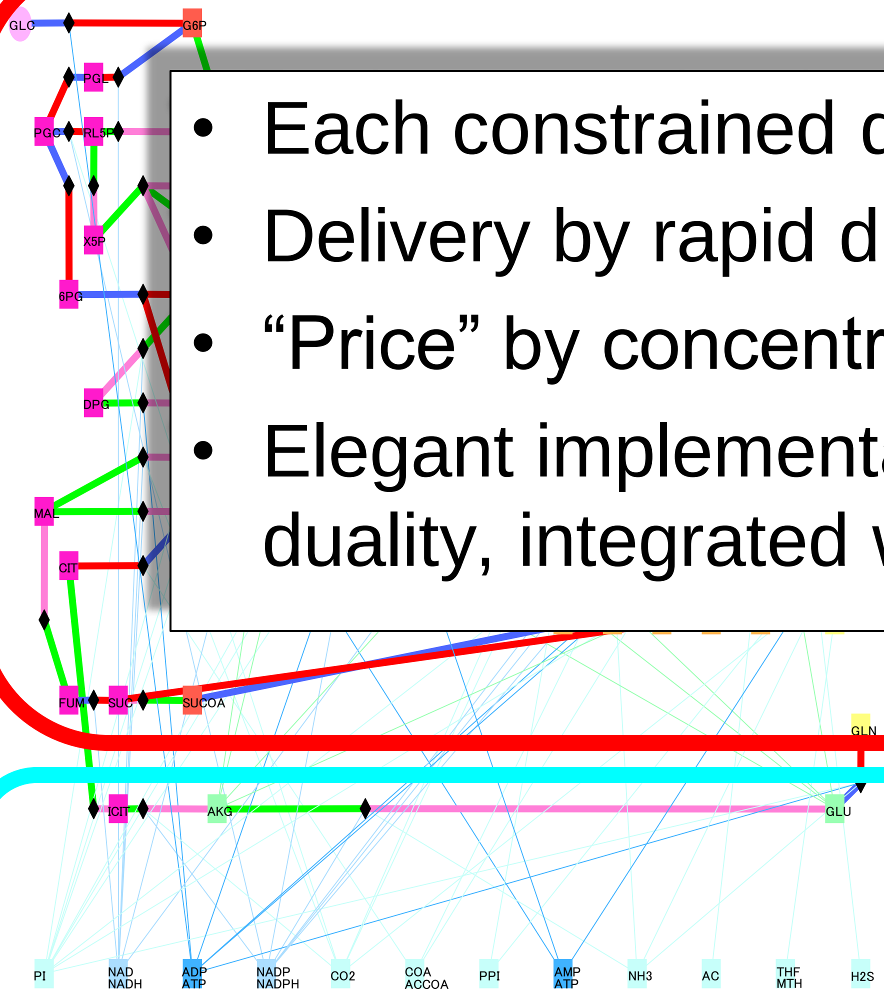


Long assembly lines

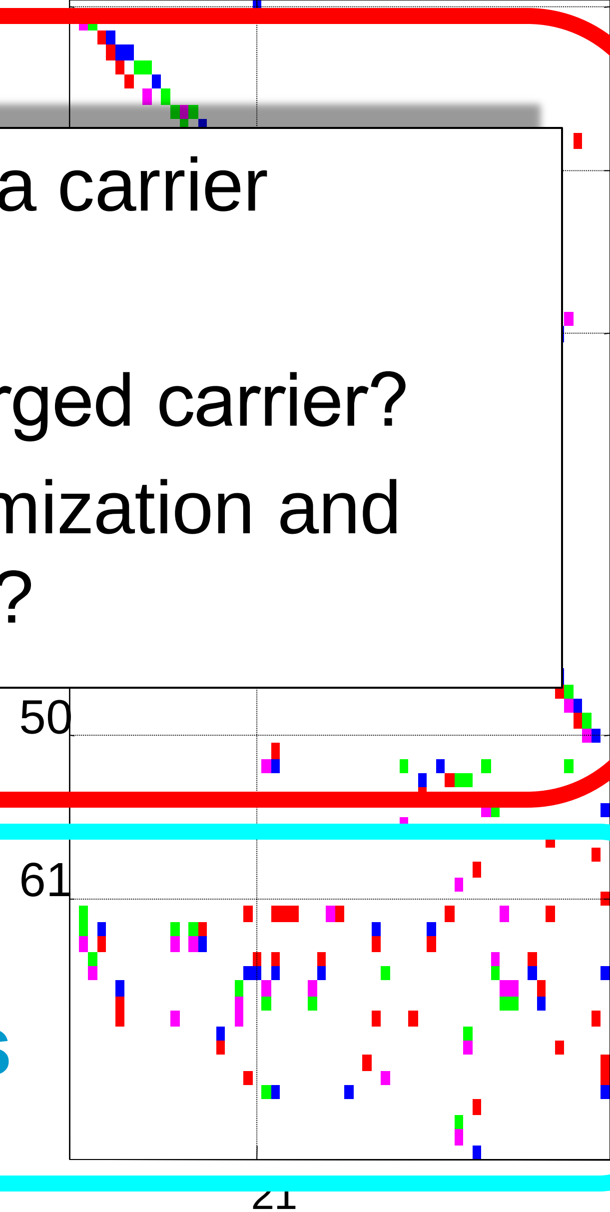


“Vertical” decomposition

reactions

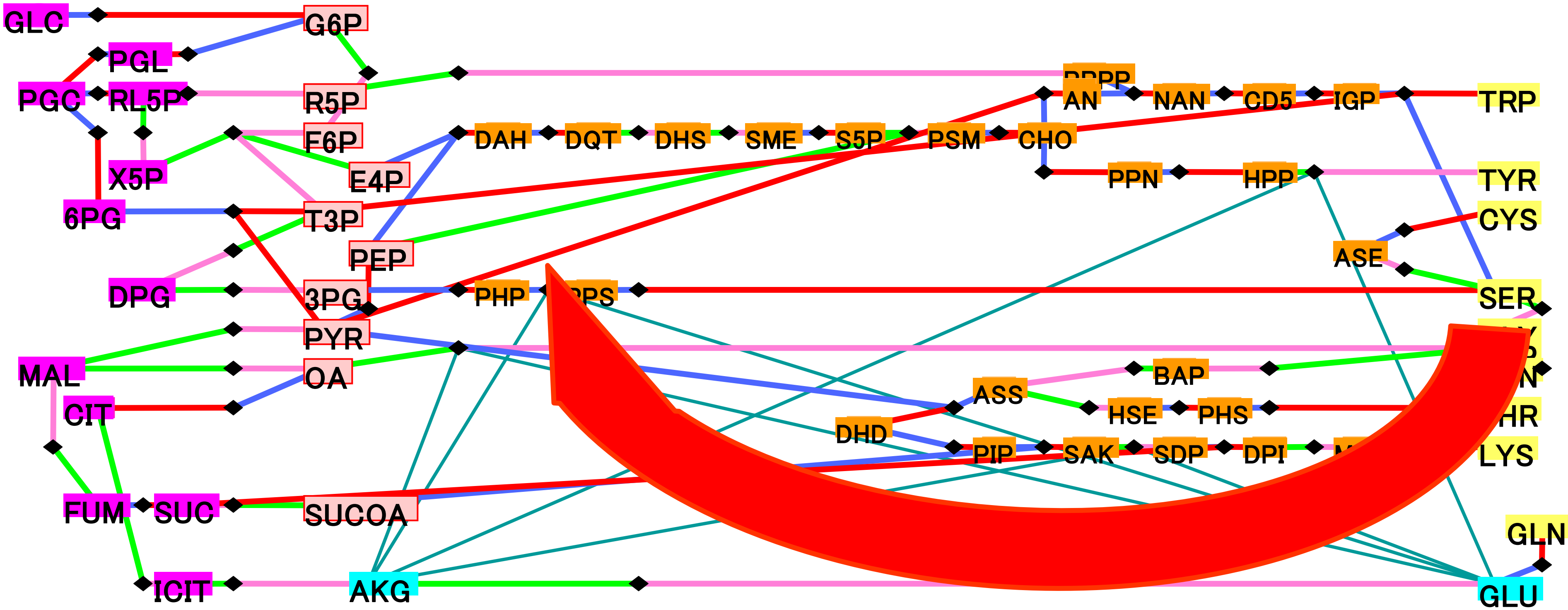


- Each constrained quantity has a carrier
- Delivery by rapid diffusion
- “Price” by concentration of charged carrier?
- Elegant implementation of optimization and duality, integrated with delivery?

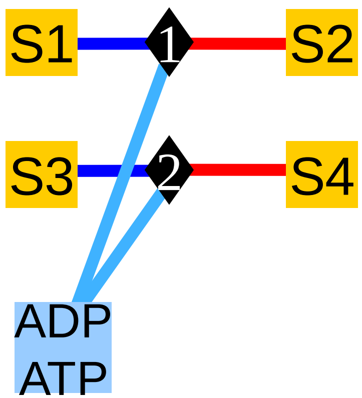


carriers

Prices?

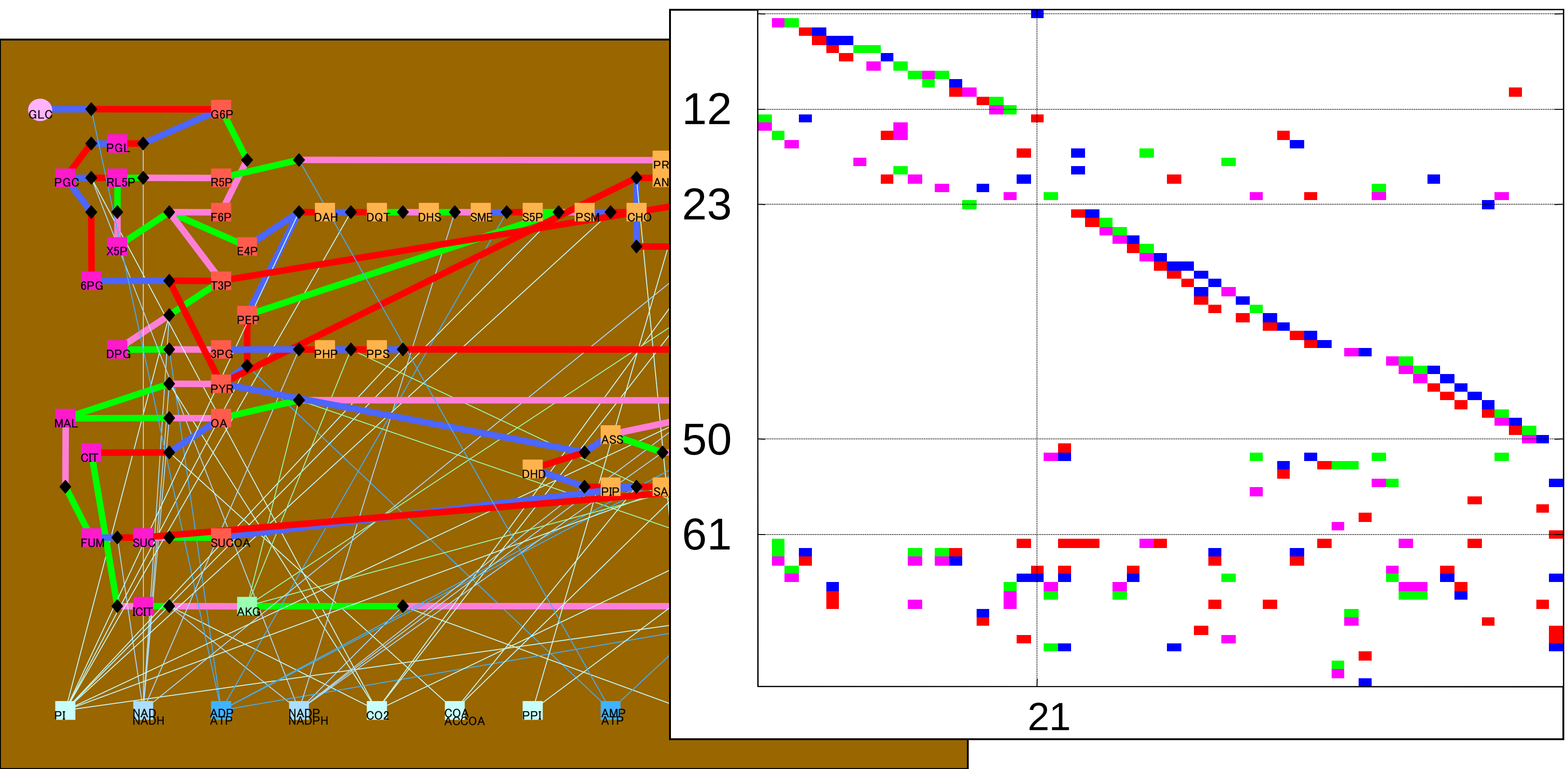


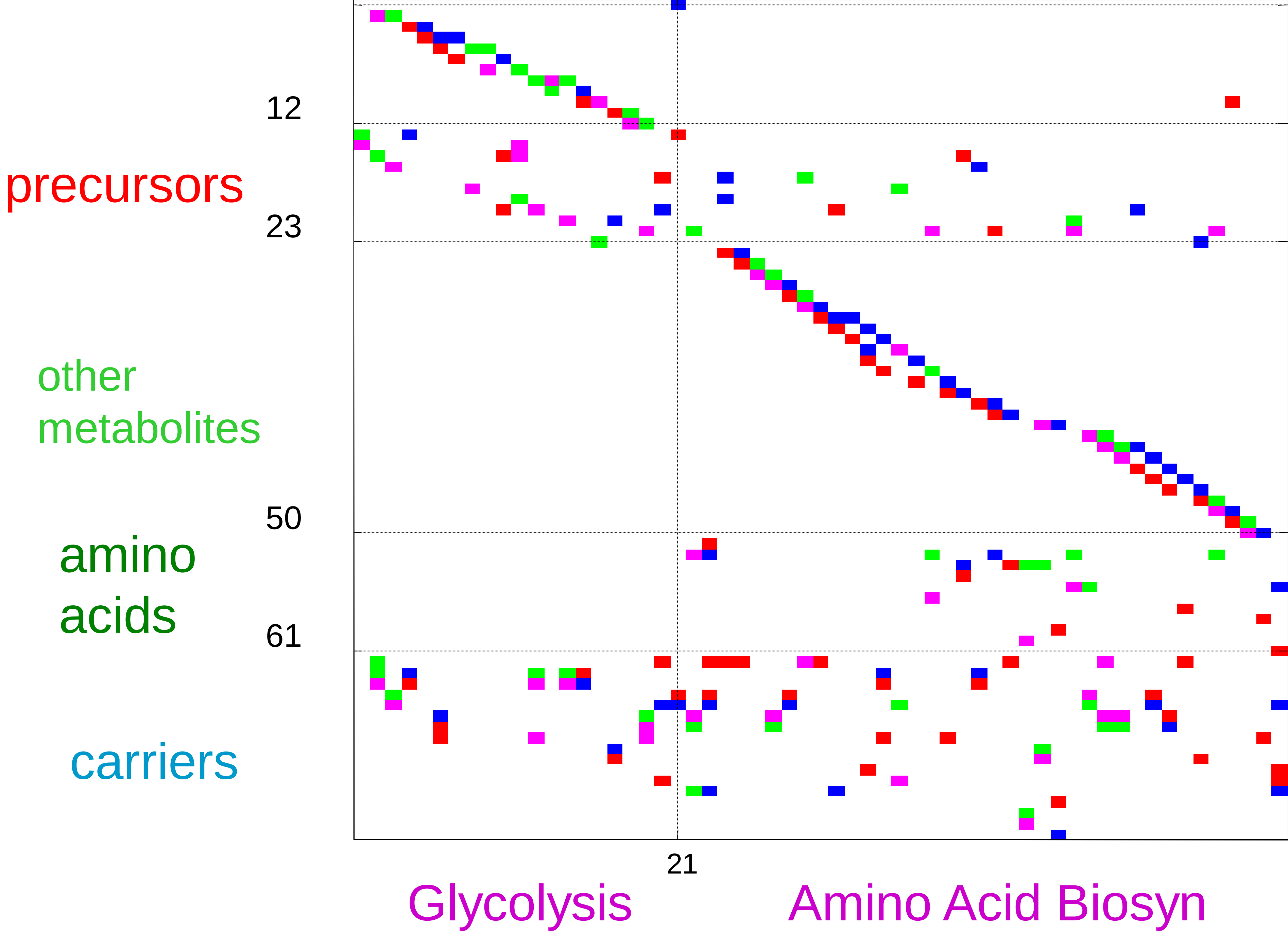
- Fastest allosteric feedback control
- Complex proteins
- High metabolic overhead
- Hard to reprogram



Compare these two visualizations.

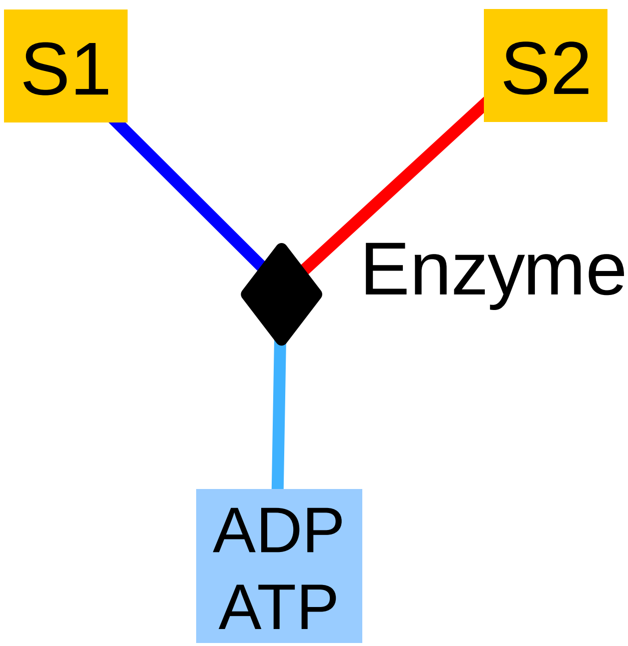
Substrates	S_1	–1	0
	S_2	1	0
	S_3	0	–1
	S_4	0	1
Carriers	ATP	–1	–1
	ADP	1	1




precursors
other metabolites
amino acids
carriers
12
23
50
61
21
Glycolysis
Amino Acid Biosyn

$$S_1 + ATP \rightarrow S_2 + ADP$$

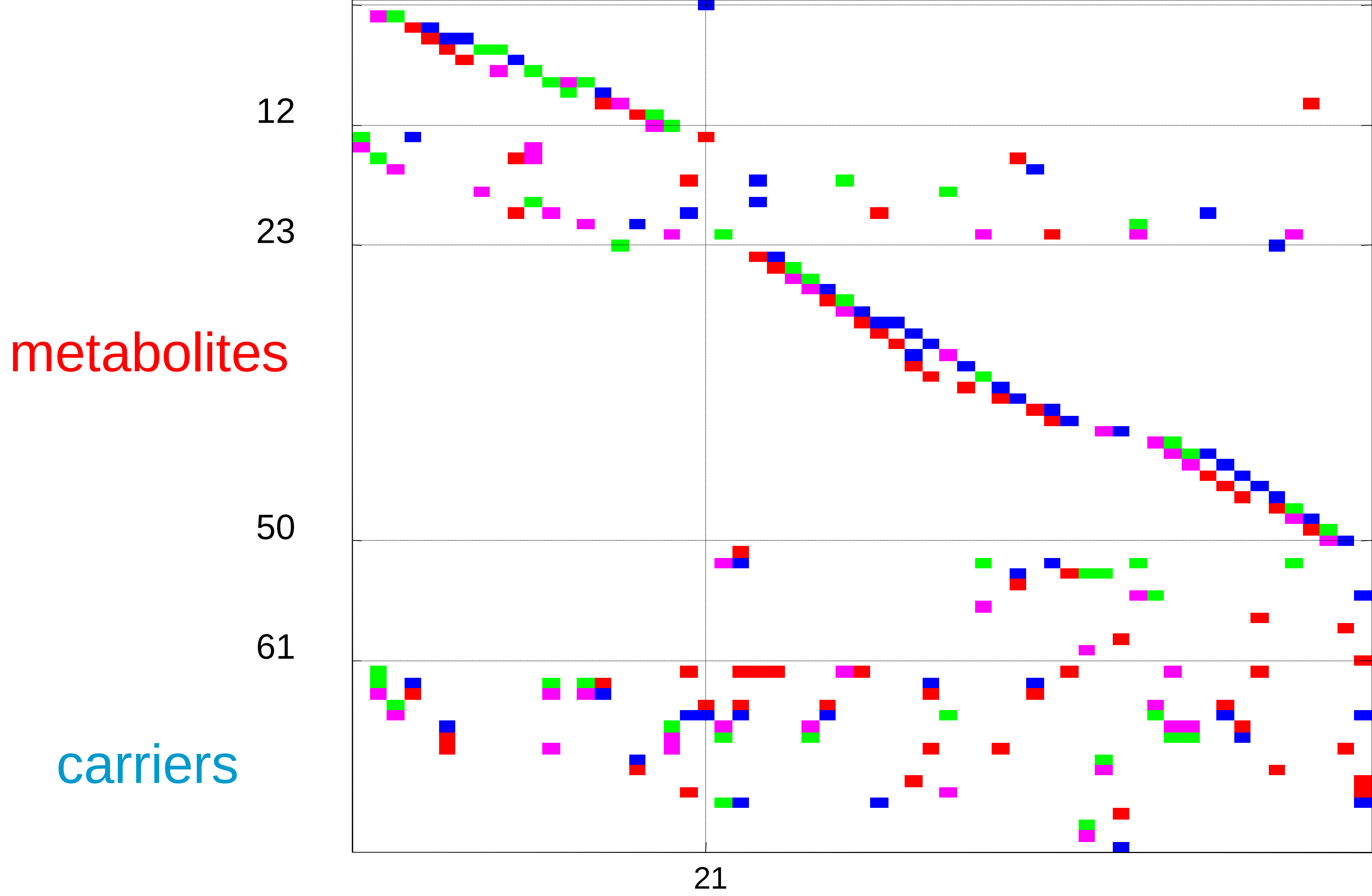
"Vertical" decomposition



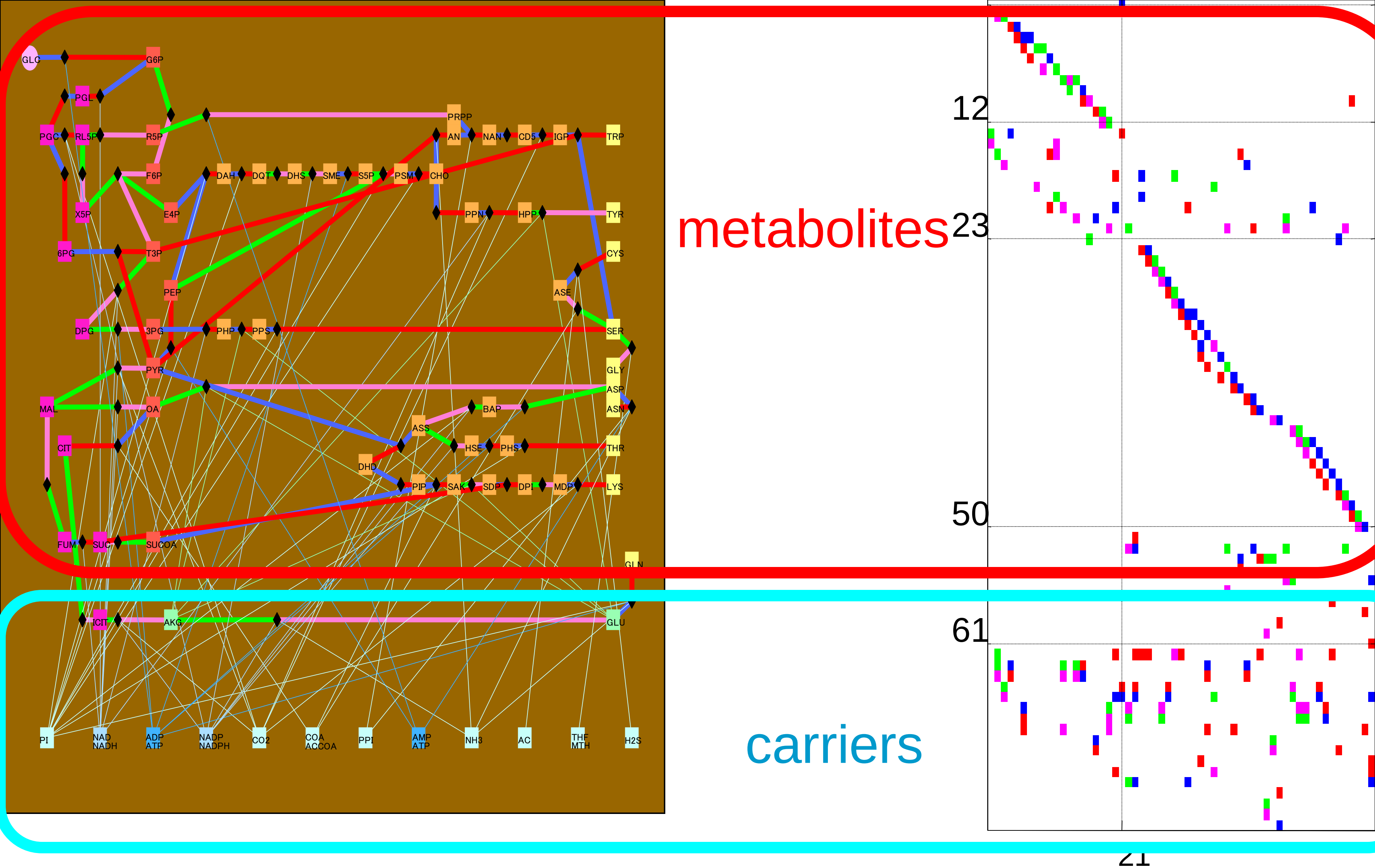
Substrates

Carriers

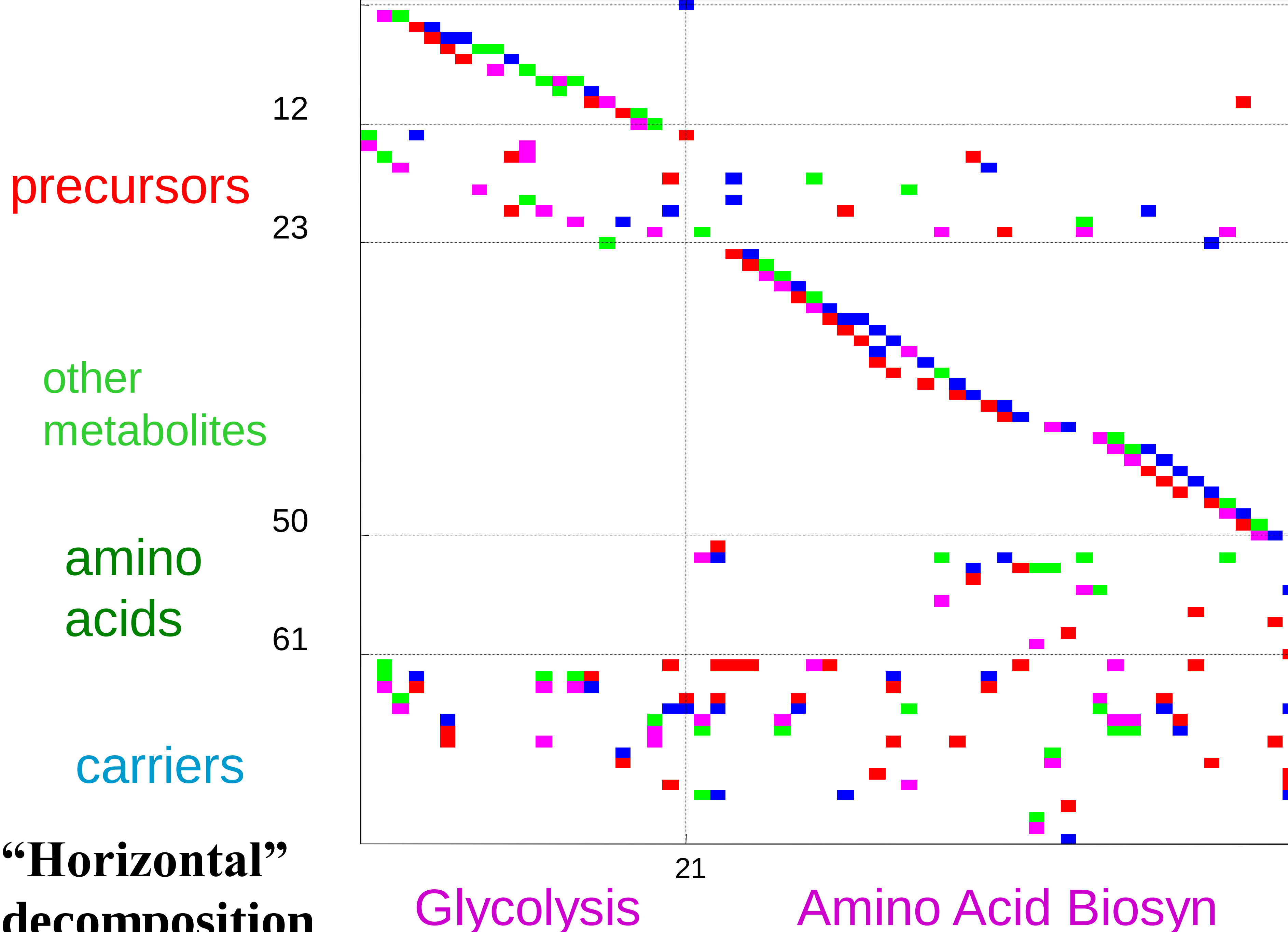
	Reaction
S_1	-1
S_2	1
	0
	0
ATP	-1
ADP	1
	0
	0



“Vertical” decomposition



“Vertical” decomposition



“Horizontal” decomposition

precursors 12

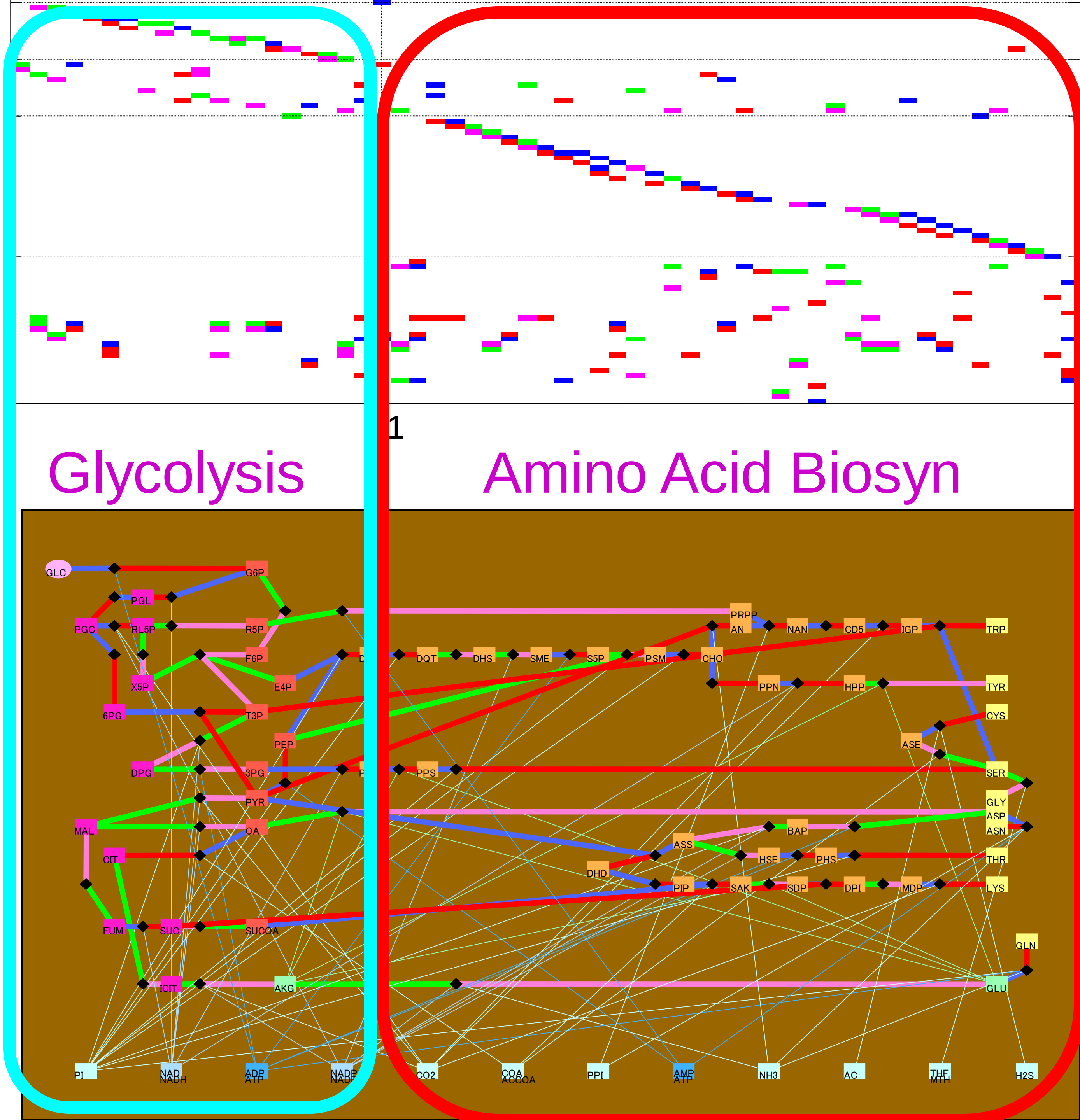
23

other metabolites

amino acids 50

61

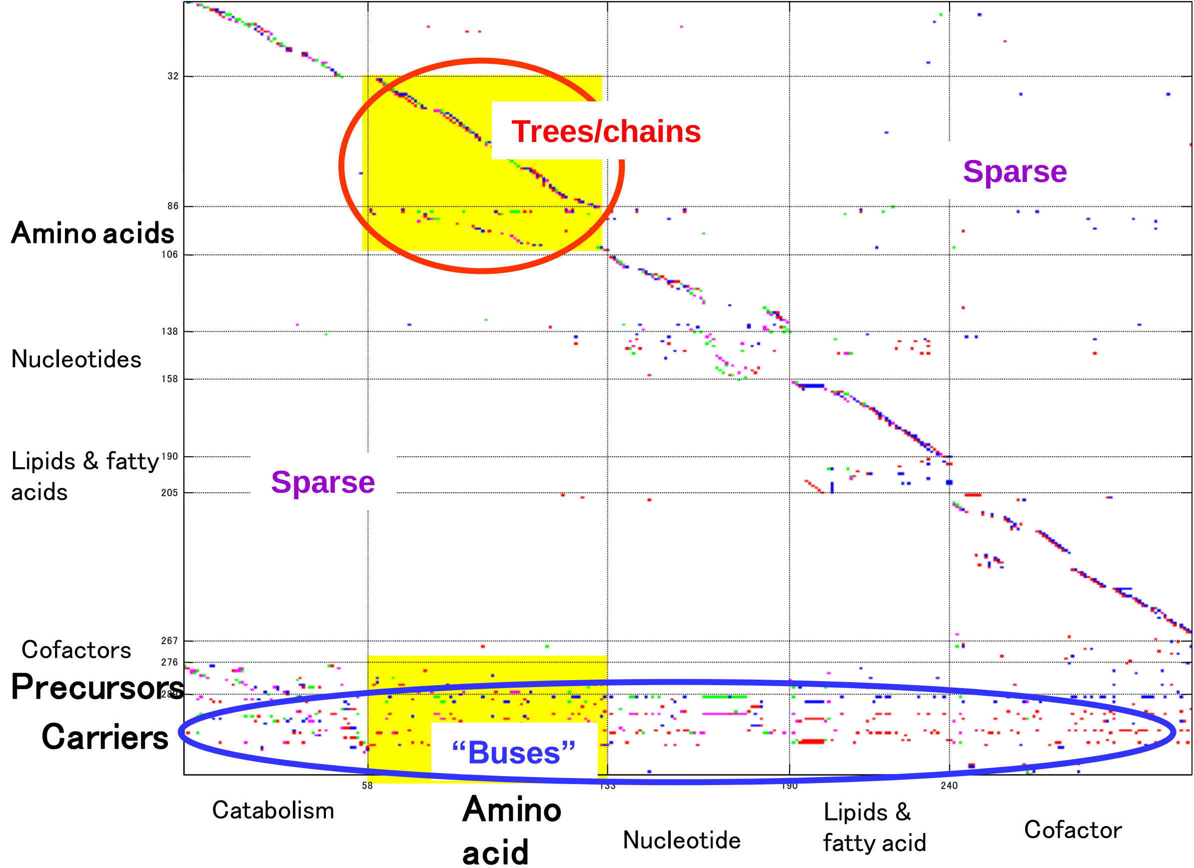
carriers

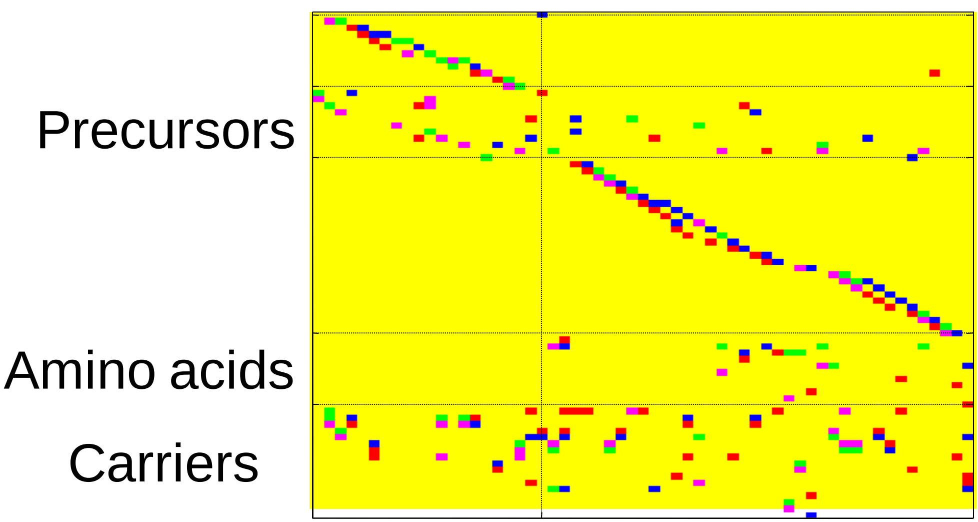


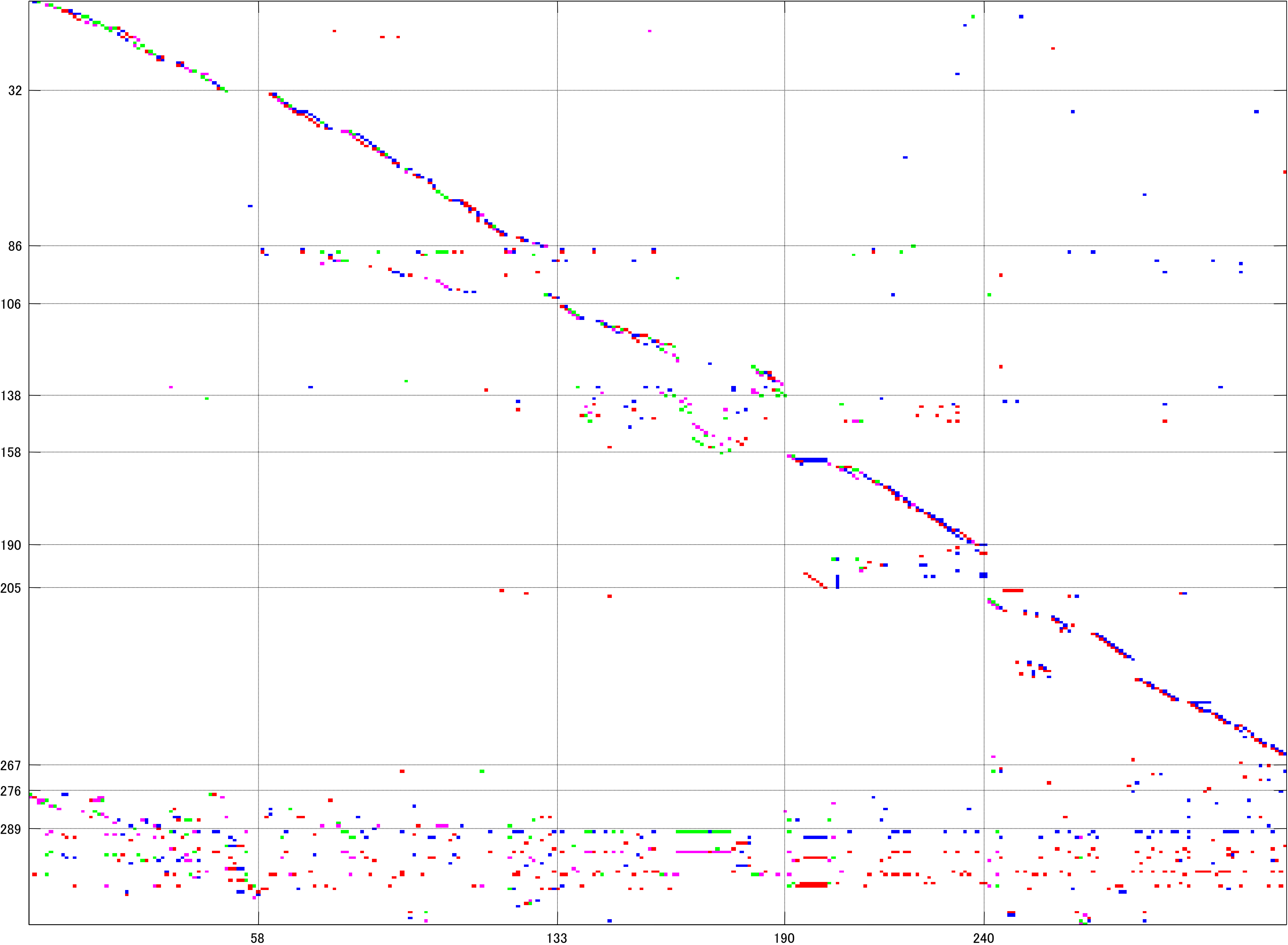
“Horizontal” decomposition

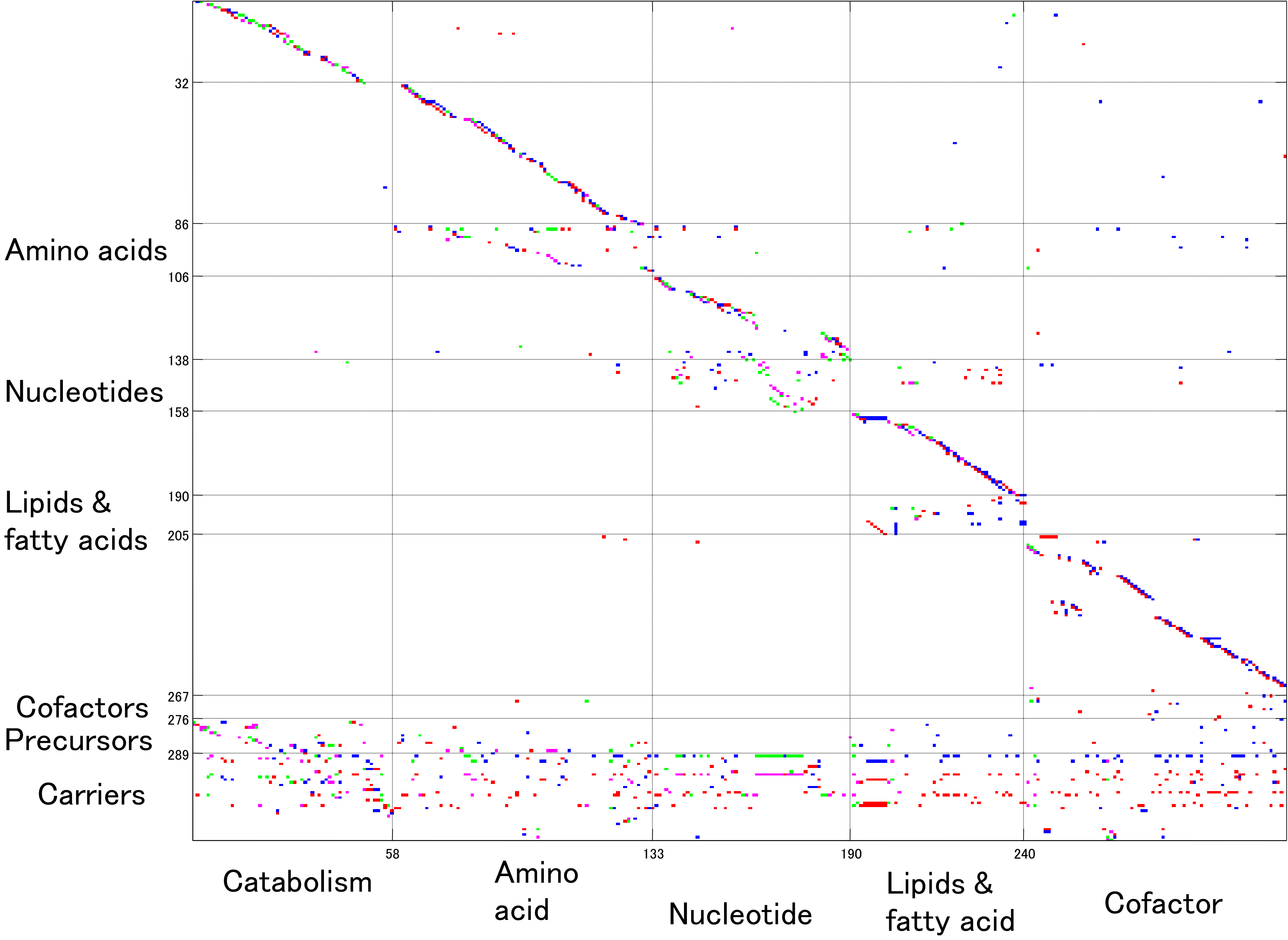
H Pylori core metabolism

Zoom back out to all of metabolism

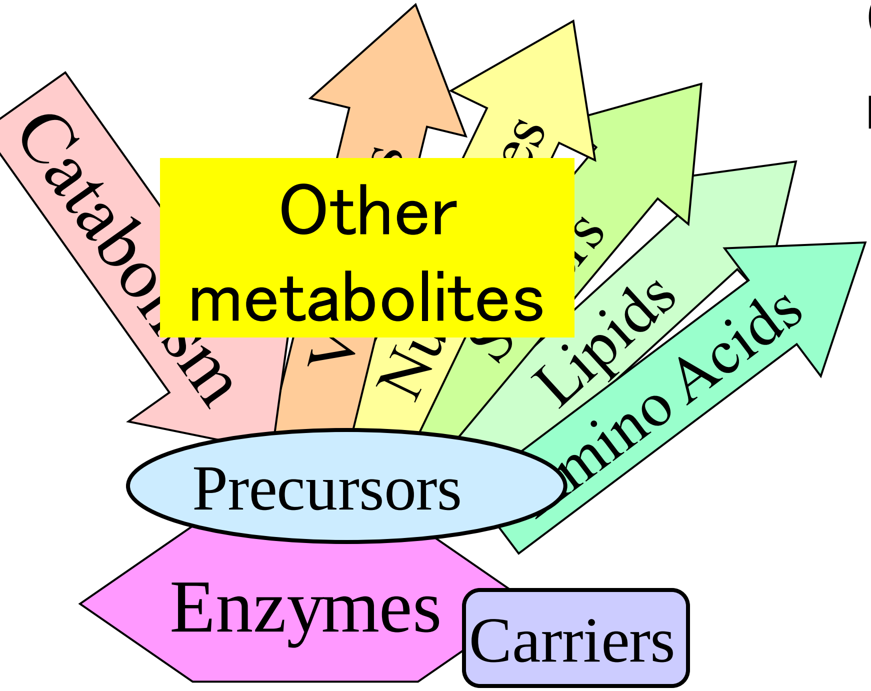


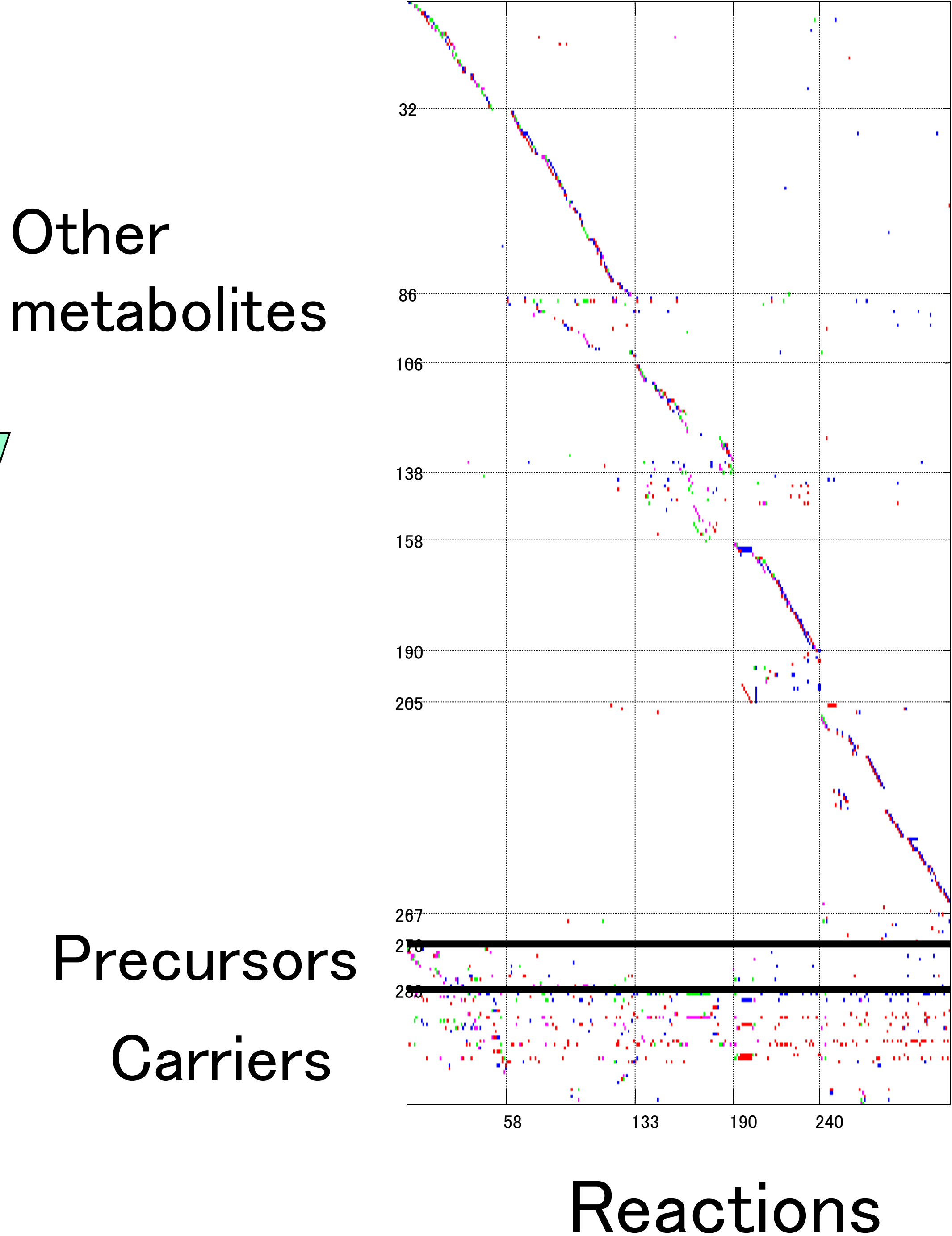



32
86
106
138
158
190
205
267
276
289
58
133
190
240

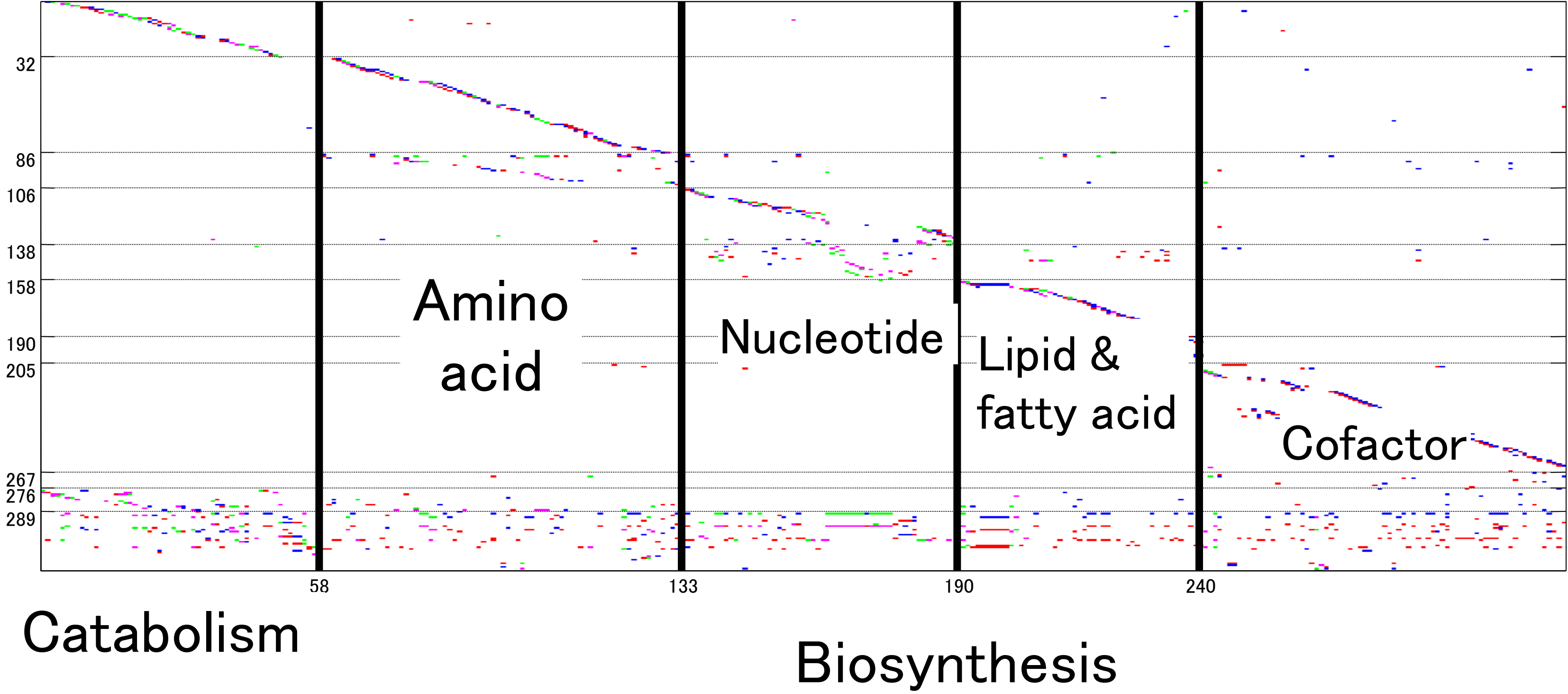


Amino acids
Nucleotides
Lipids &
fatty acids
Cofactors
Precursors
Carriers
32
86
106
138
158
190
205
267
276
289
58
133
190
240
Catabolism
Amino
acid
Nucleotide
Lipids &
fatty acid
Cofactor

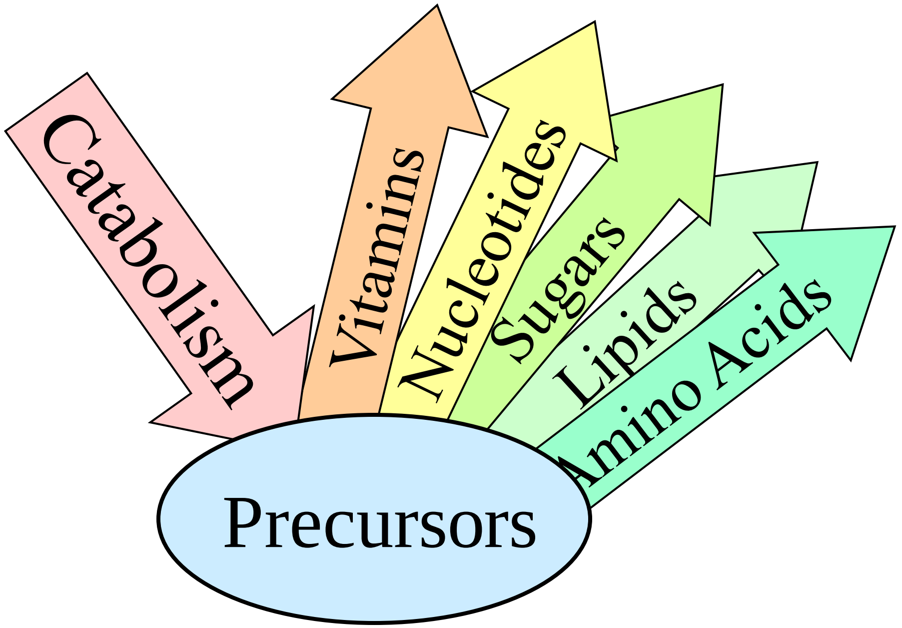


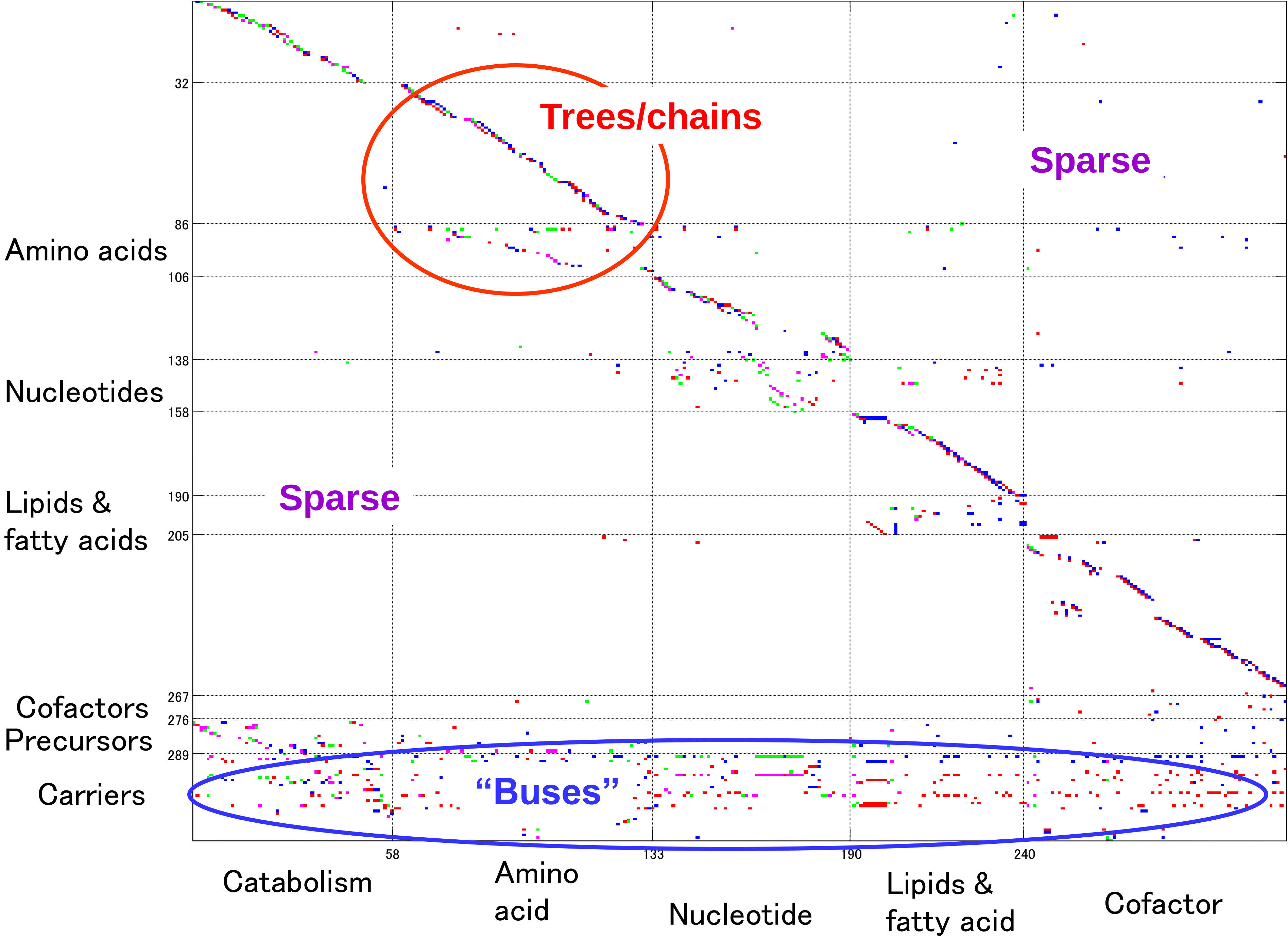


“Vertical” decomposition



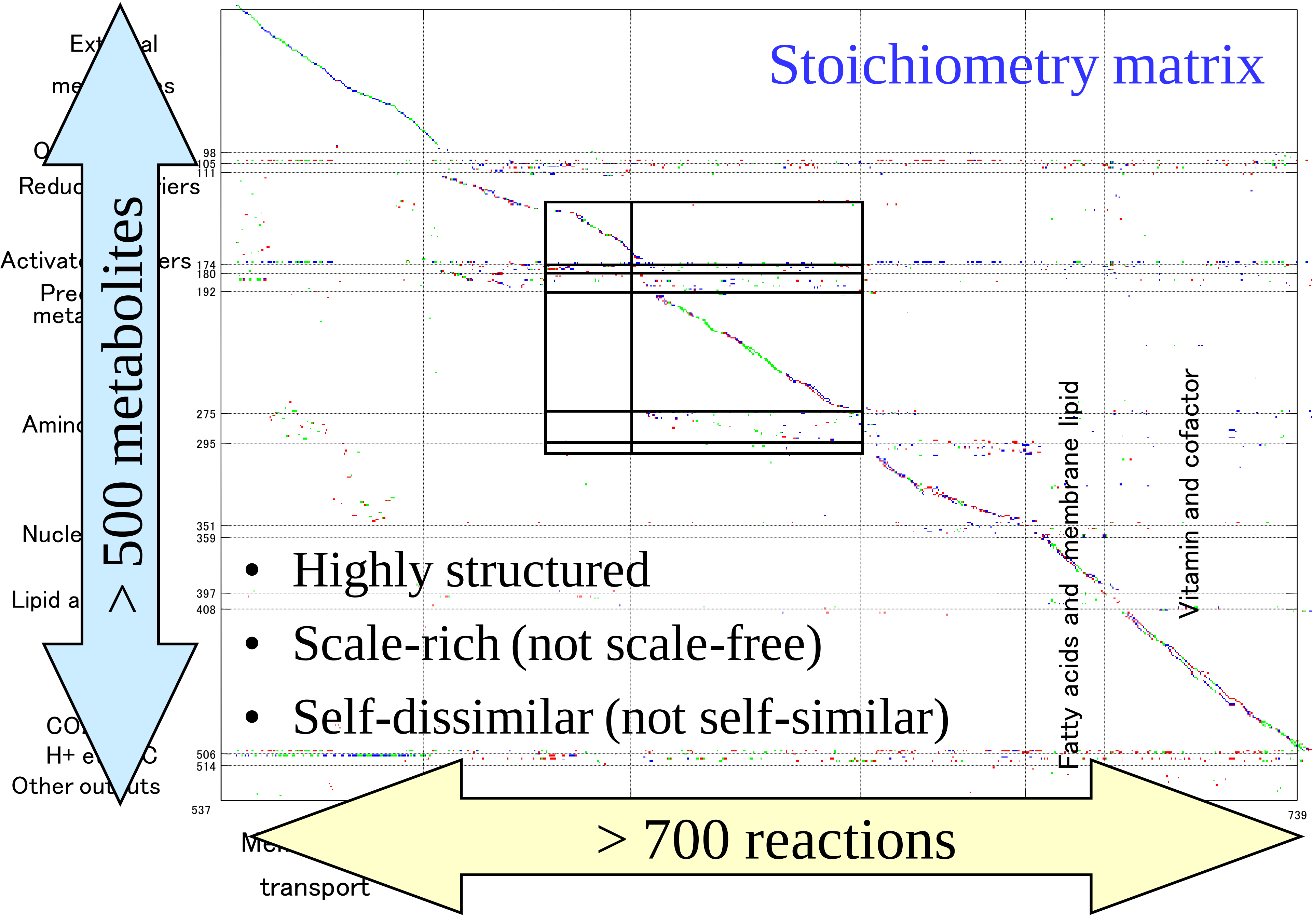
"Horizontal" decomposition



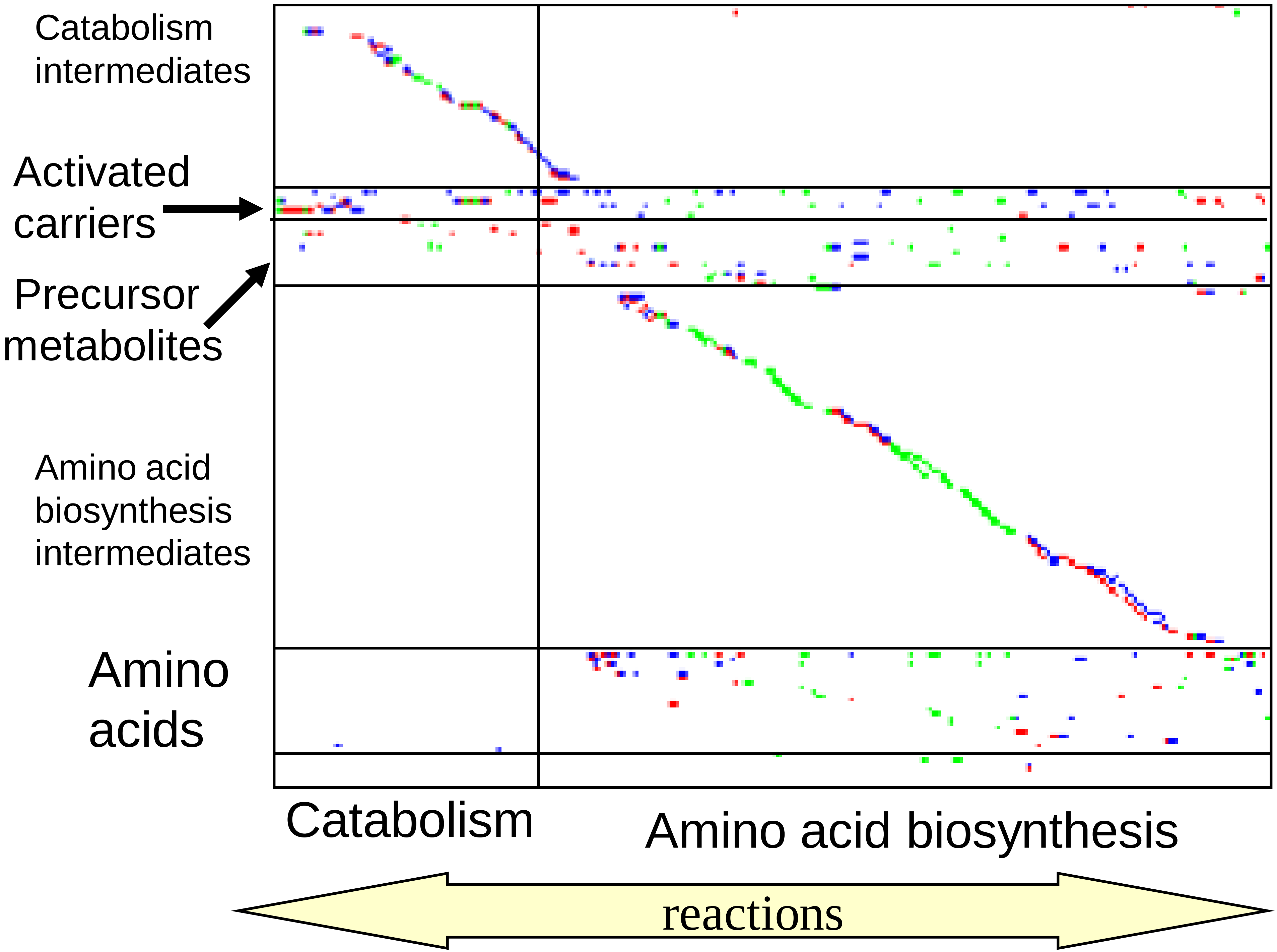


Trees/chains
Sparse
Amino acids
Nucleotides
Lipids &
fatty acids
Sparse
Cofactors
Precursors
Carriers
"Buses"
32
86
106
138
158
190
205
267
276
289
58
133
190
240
Catabolism
Amino
acid
Nucleotide
Lipids &
fatty acid
Cofactor

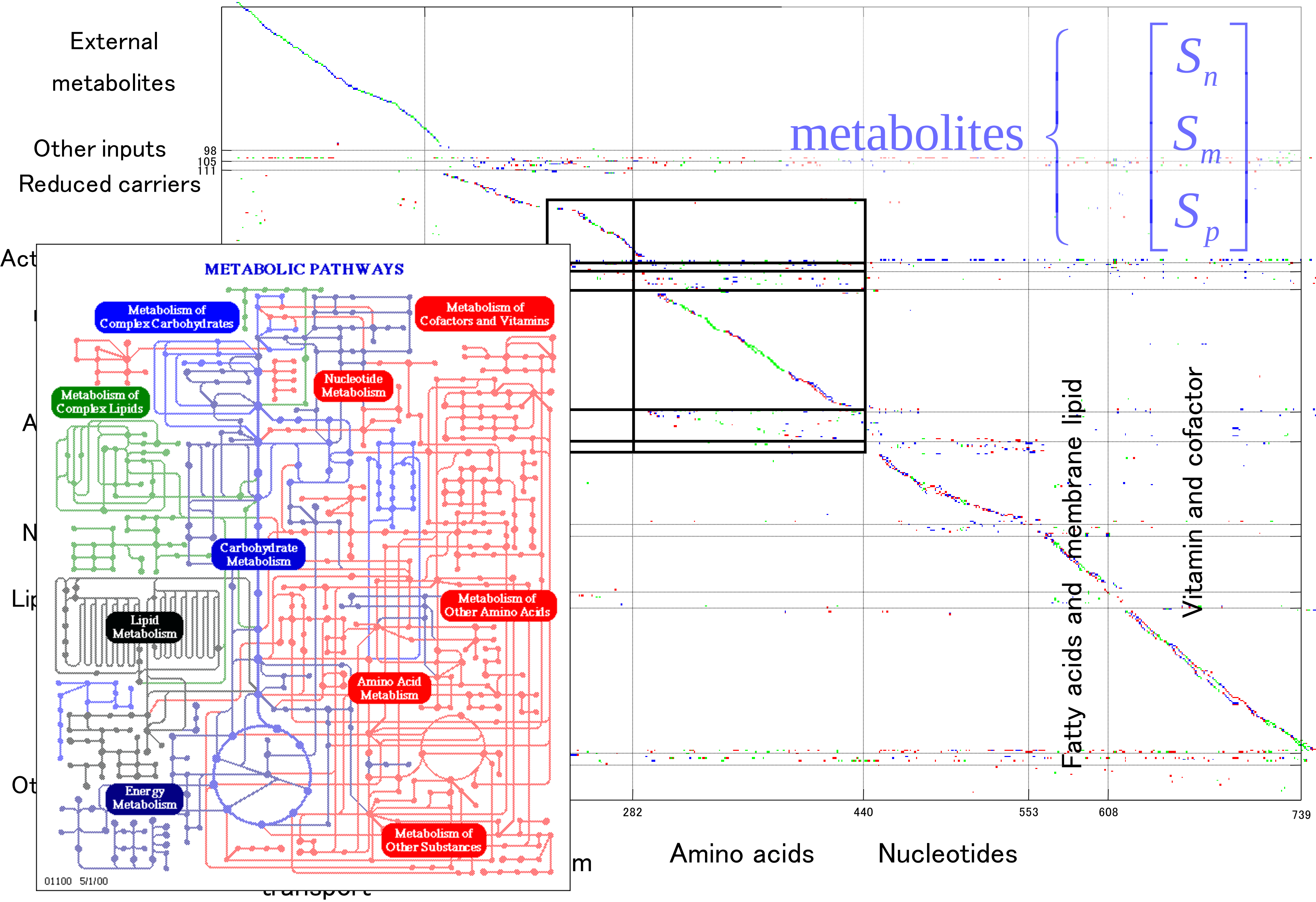
E. Coli: all metabolism



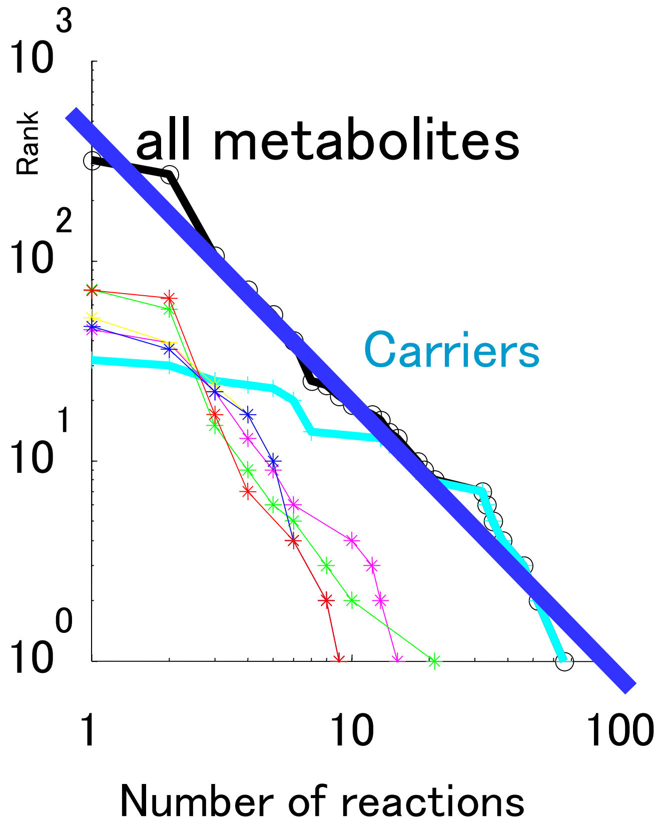
- Highly structured
- Scale-rich (not scale-free)
- Self-dissimilar (not self-similar)

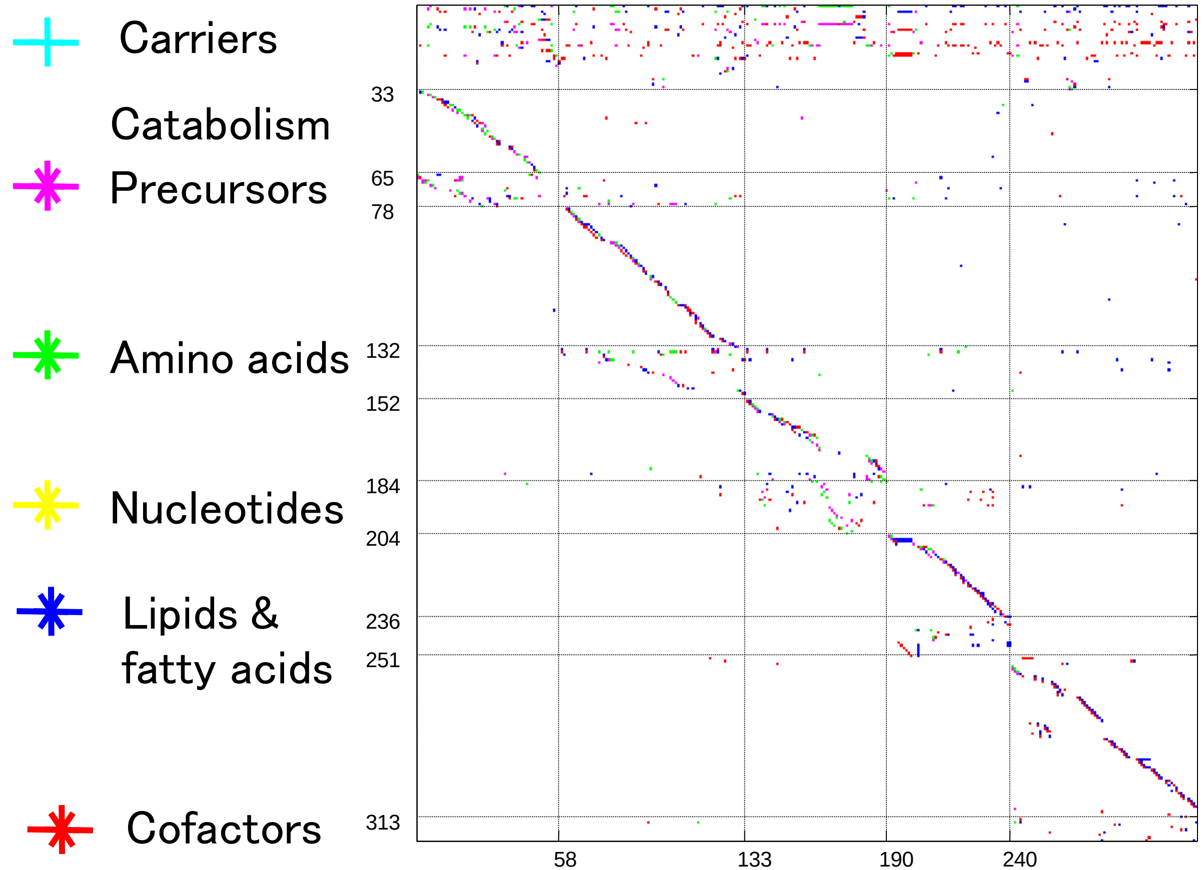

Catabolism intermediates
Activated carriers
Precursor metabolites
Amino acid biosynthesis intermediates
Amino acids
Catabolism
Amino acid biosynthesis
reactions

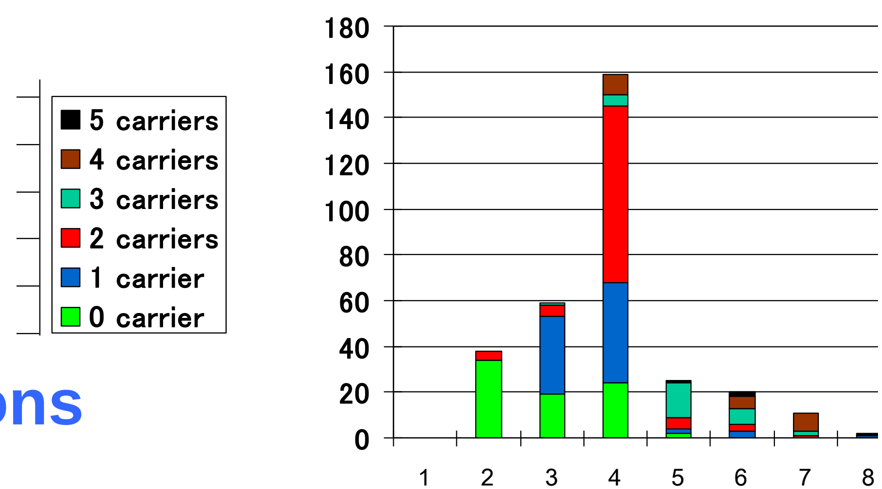
E. Coli: all metabolism



Metabolites

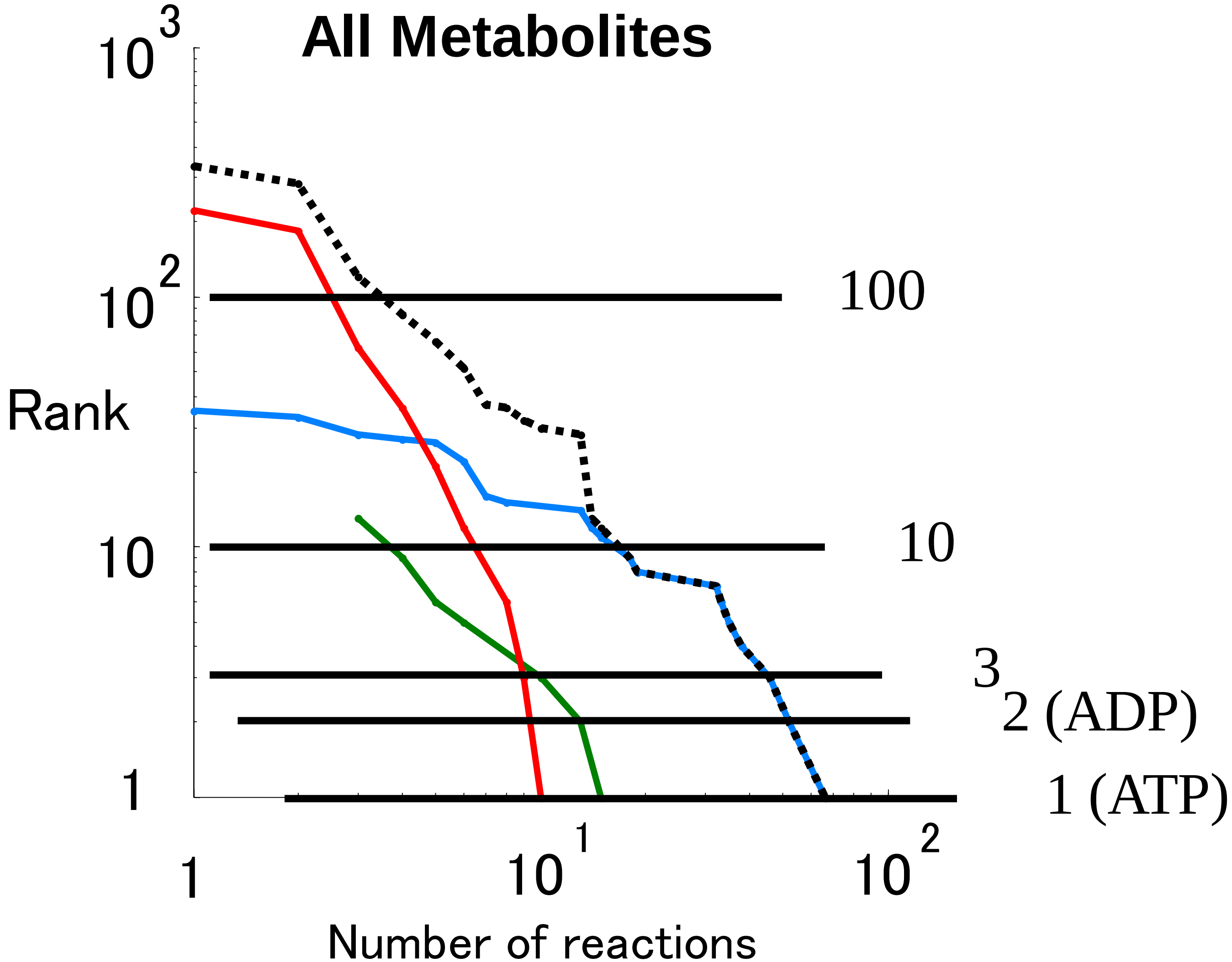




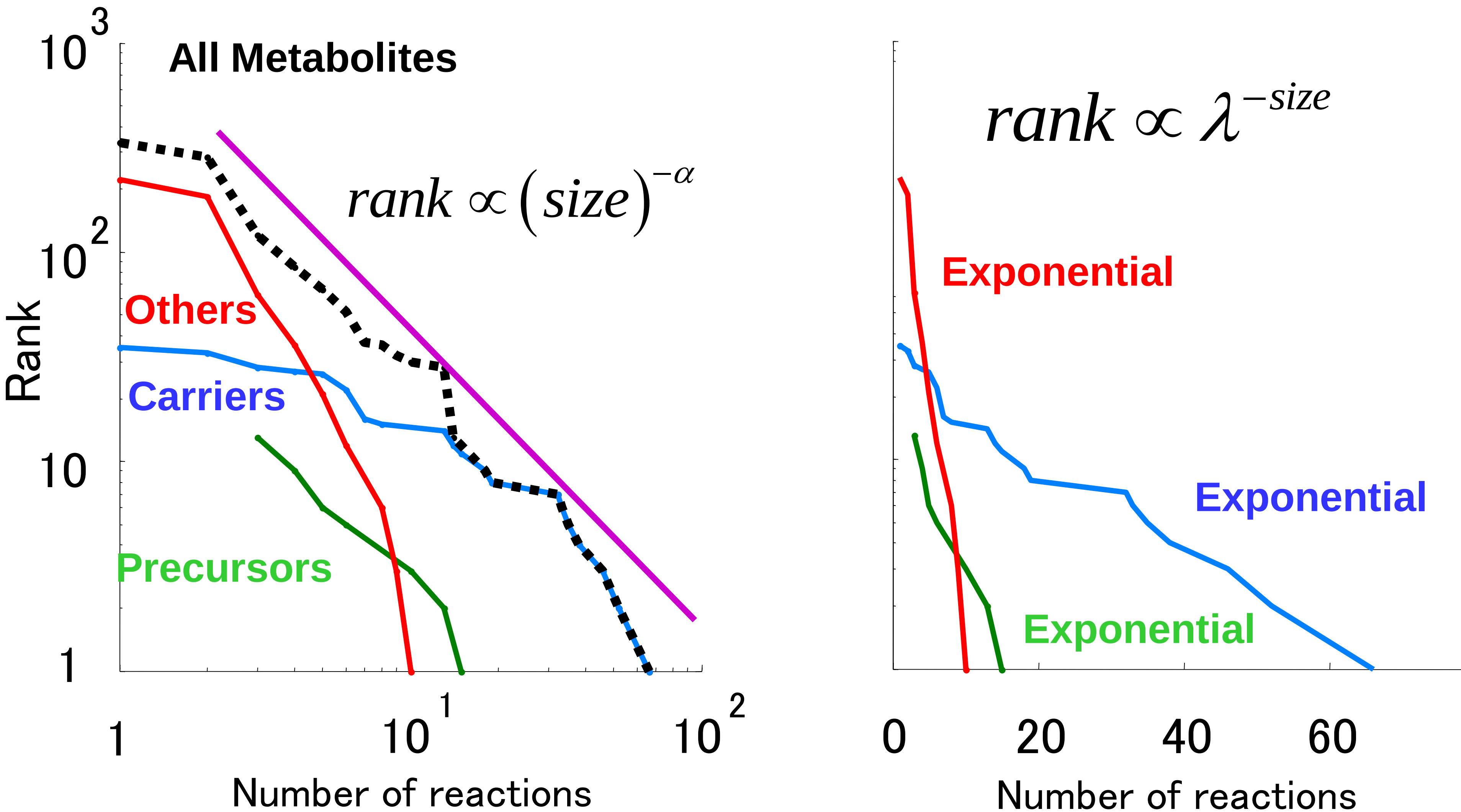


H. Pylori

Reactions



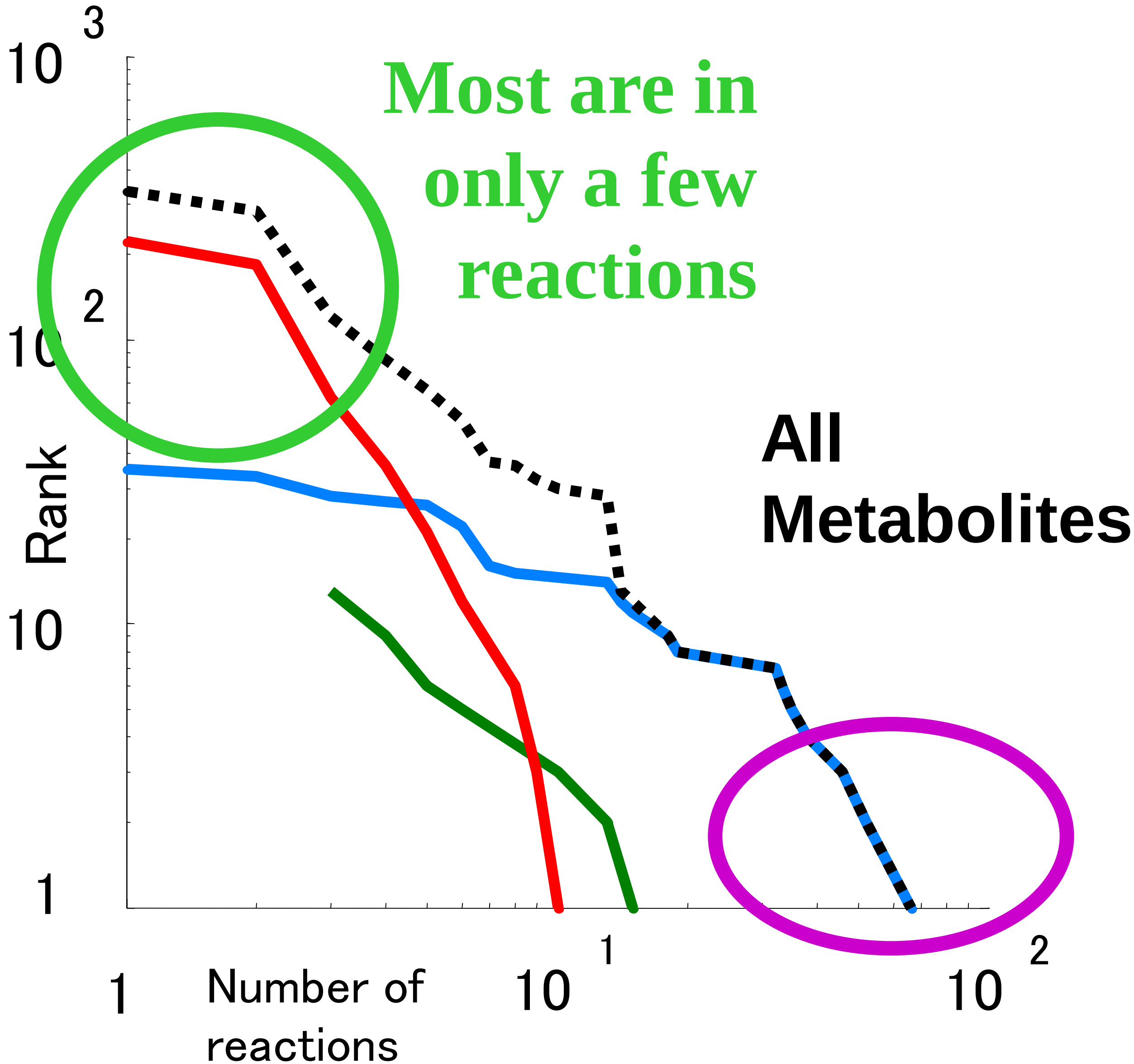
All Metabolites
Rank
Number of reactions
10^3
10^2
10
1
1
10^1
10^2
100
10
3
2 (ADP)
1 (ATP)



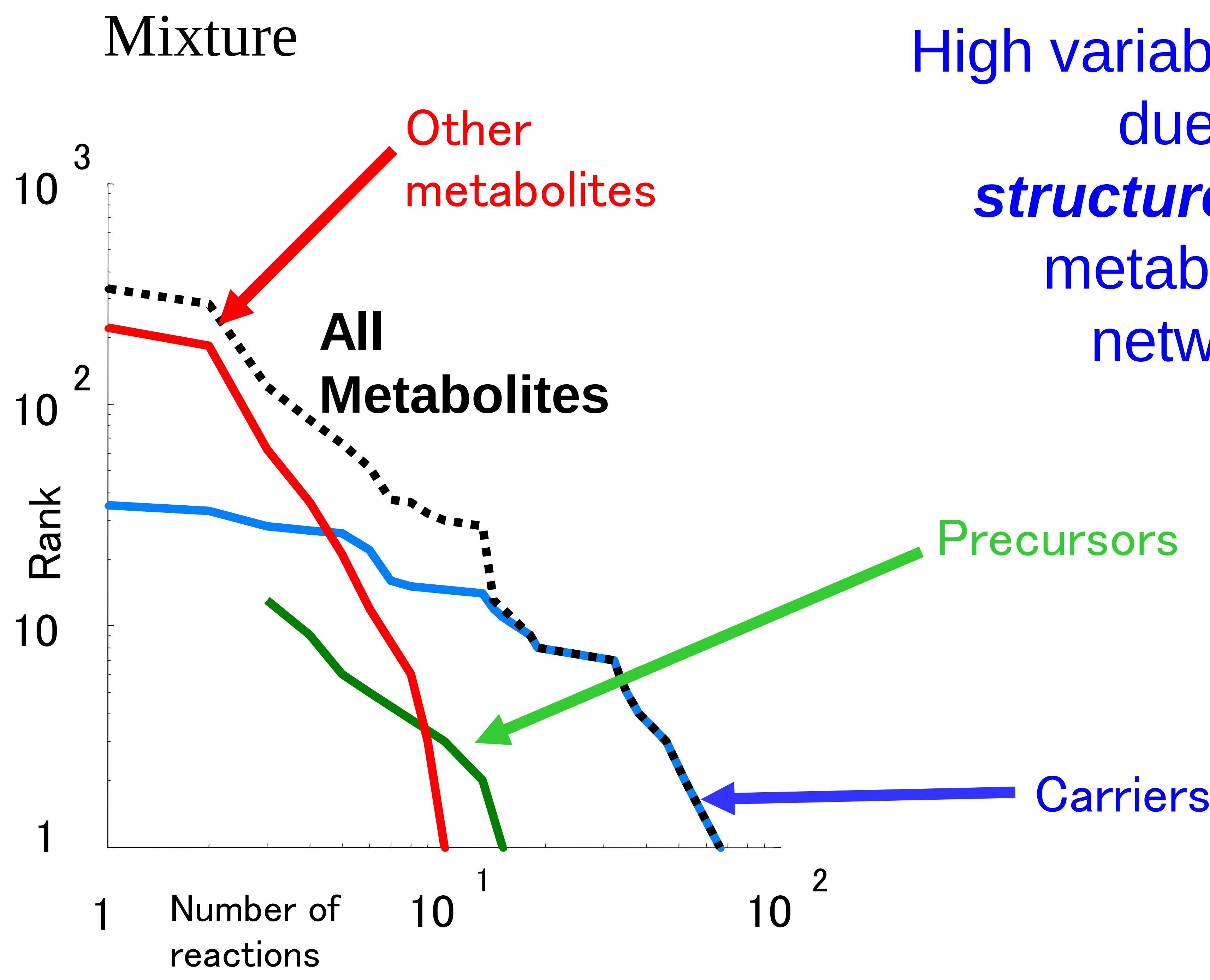
All Metabolites
$rank \propto (size)^{-\alpha}$
Others
Carriers
Precursors
Rank
10^3
10^2
10
1
1
10^1
10^2
Number of reactions
$rank \propto \lambda^{-size}$
Exponential
Exponential
Exponential
0
20
40
60
Number of reactions

Mixture

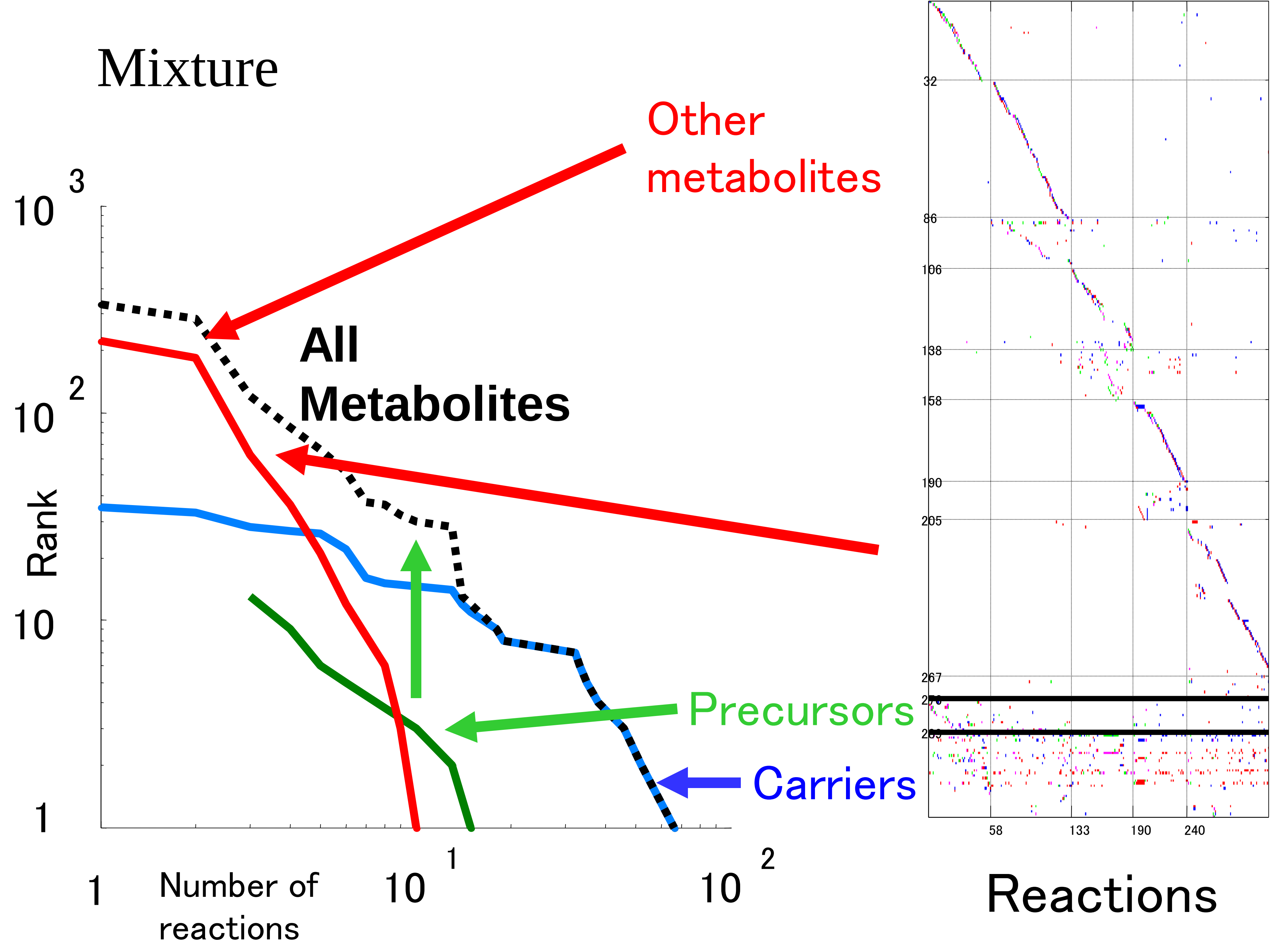
High variability of metabolite degree



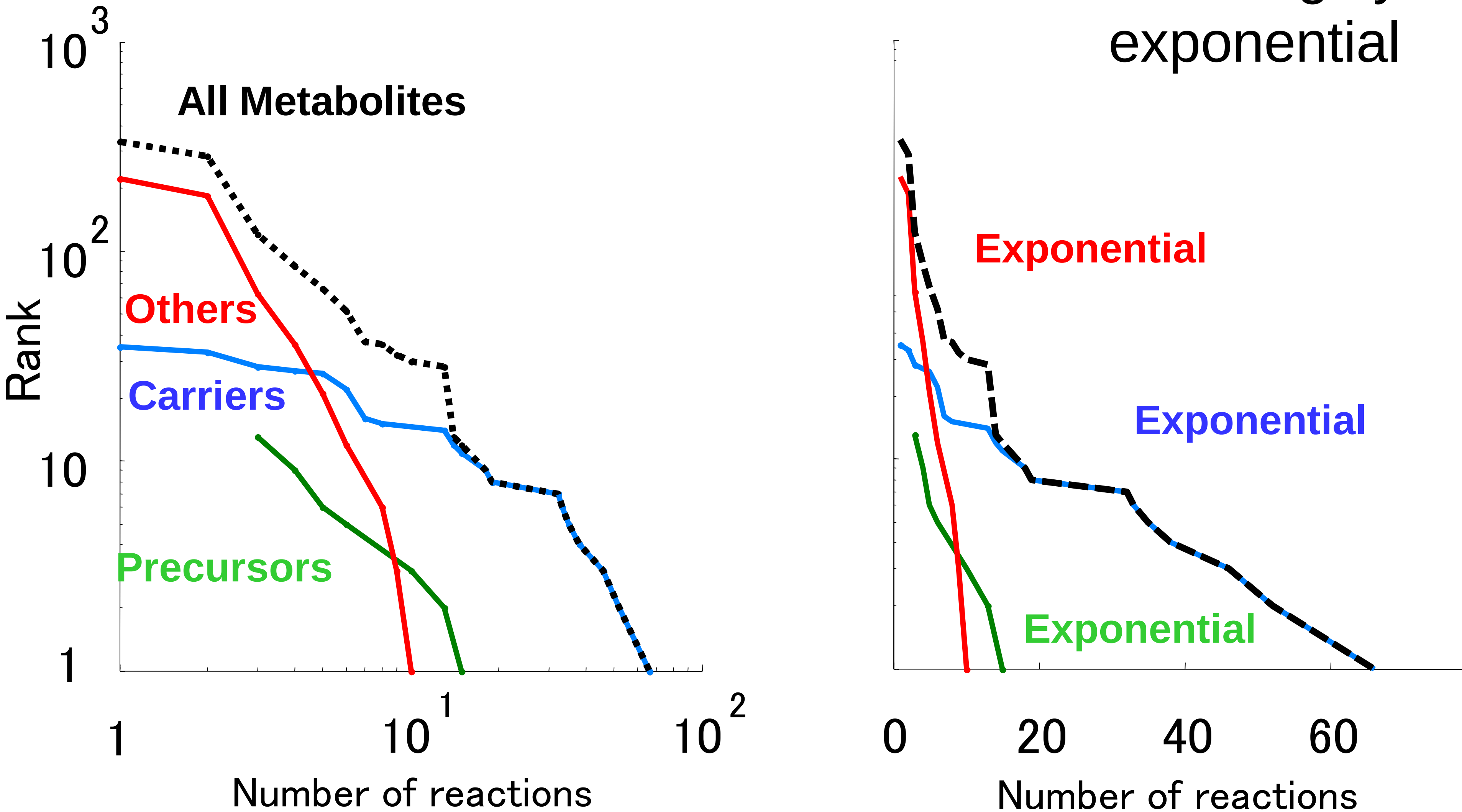
A few metabolites are in *many* reactions

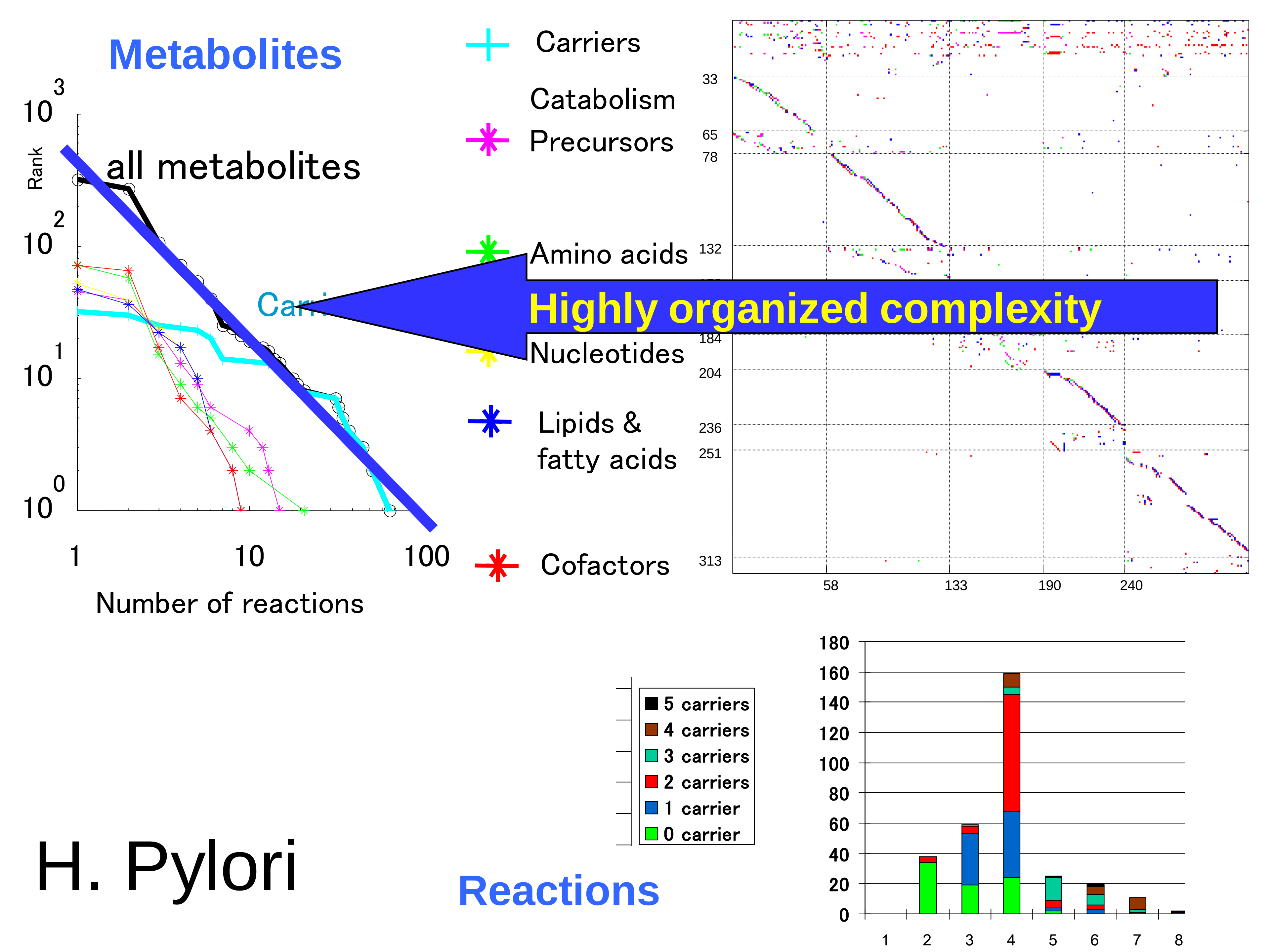


High variability due to ***structure*** of metabolic network


Mixture
Other metabolites
All Metabolites
Precursors
Carriers
Rank
10^3
10^2
10
1
1
Number of reactions
10^1
10^2
32
86
106
138
158
190
205
267
58
133
190
240
Reactions

Component degrees are roughly exponential



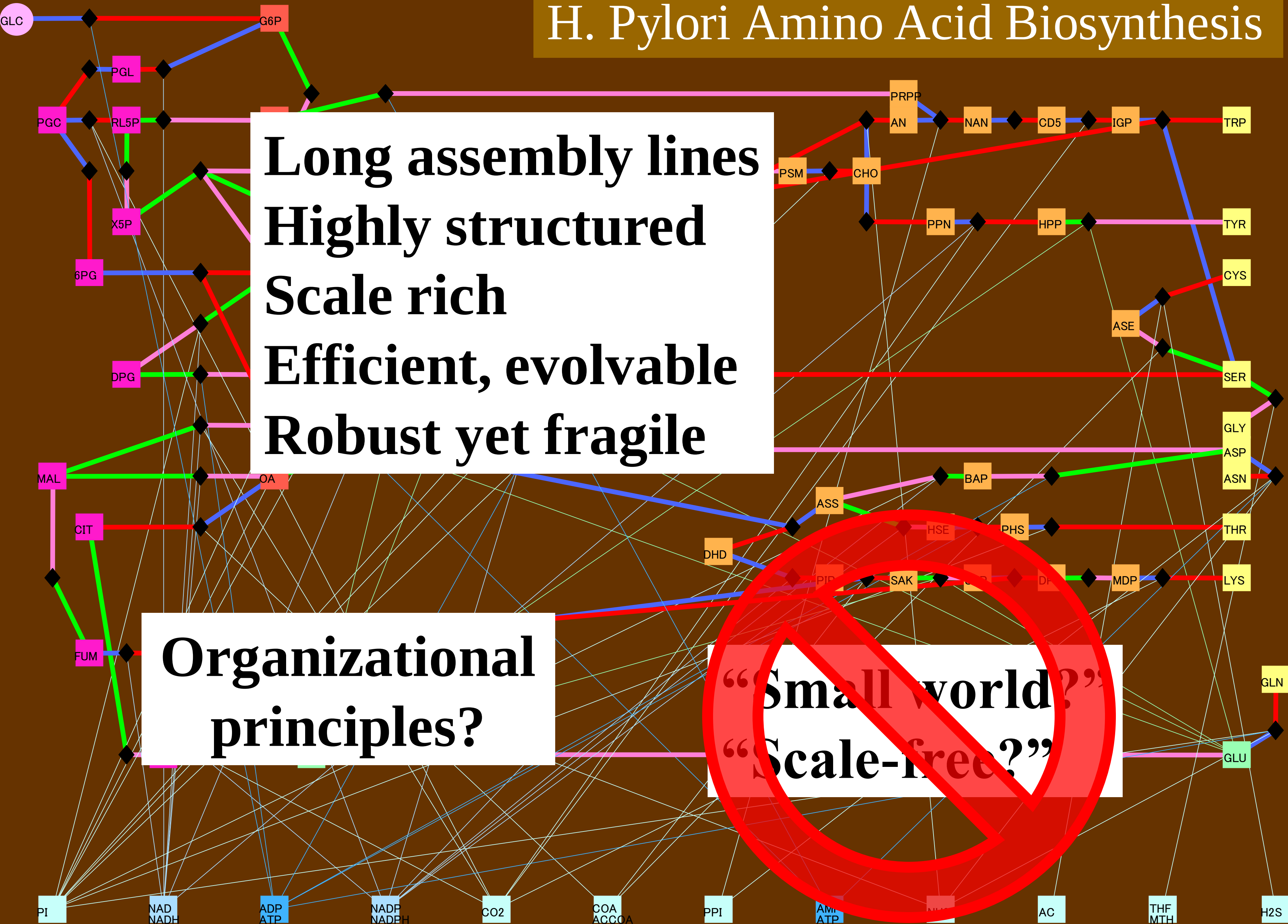

Metabolites
all metabolites
Rank
Number of reactions
Carriers
Catabolism
Precursors
Amino acids
Nucleotides
Lipids &
fatty acids
Cofactors
Highly organized complexity
5 carriers
4 carriers
3 carriers
2 carriers
1 carrier
0 carrier
H. Pylori
Reactions

H. Pylori Amino Acid Biosynthesis

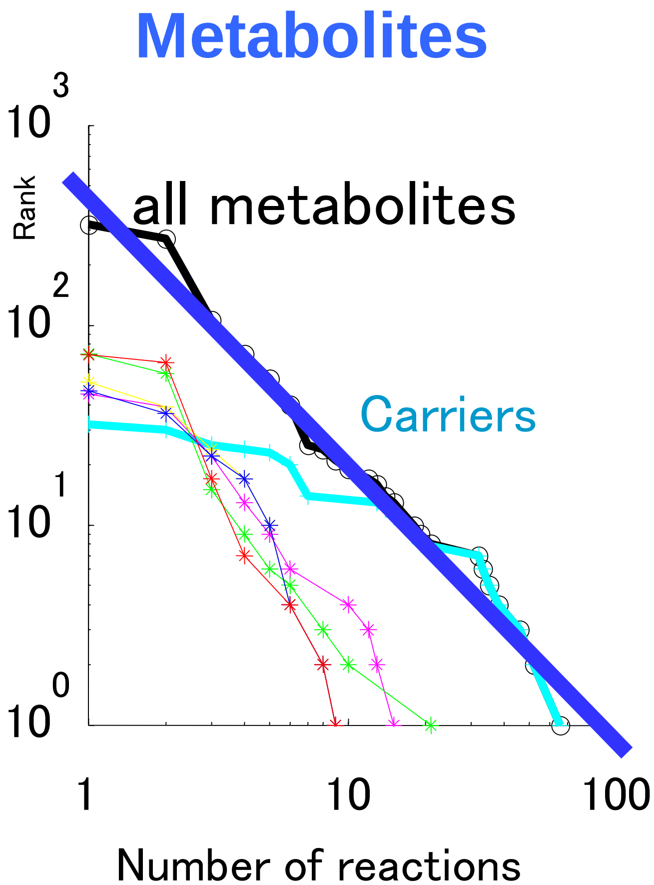
Long assembly lines
Highly structured
Scale rich
Efficient, evolvable
Robust yet fragile

Organizational principles?

"Small world?"
"Scale-free?"



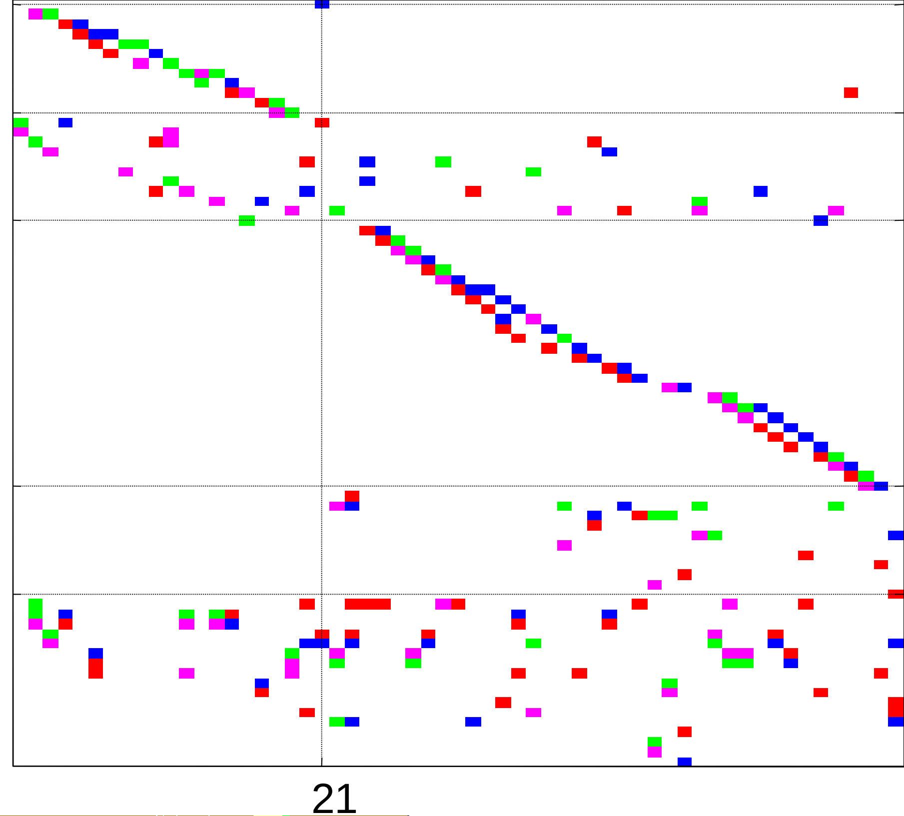
The SF/SOC/EOC approach

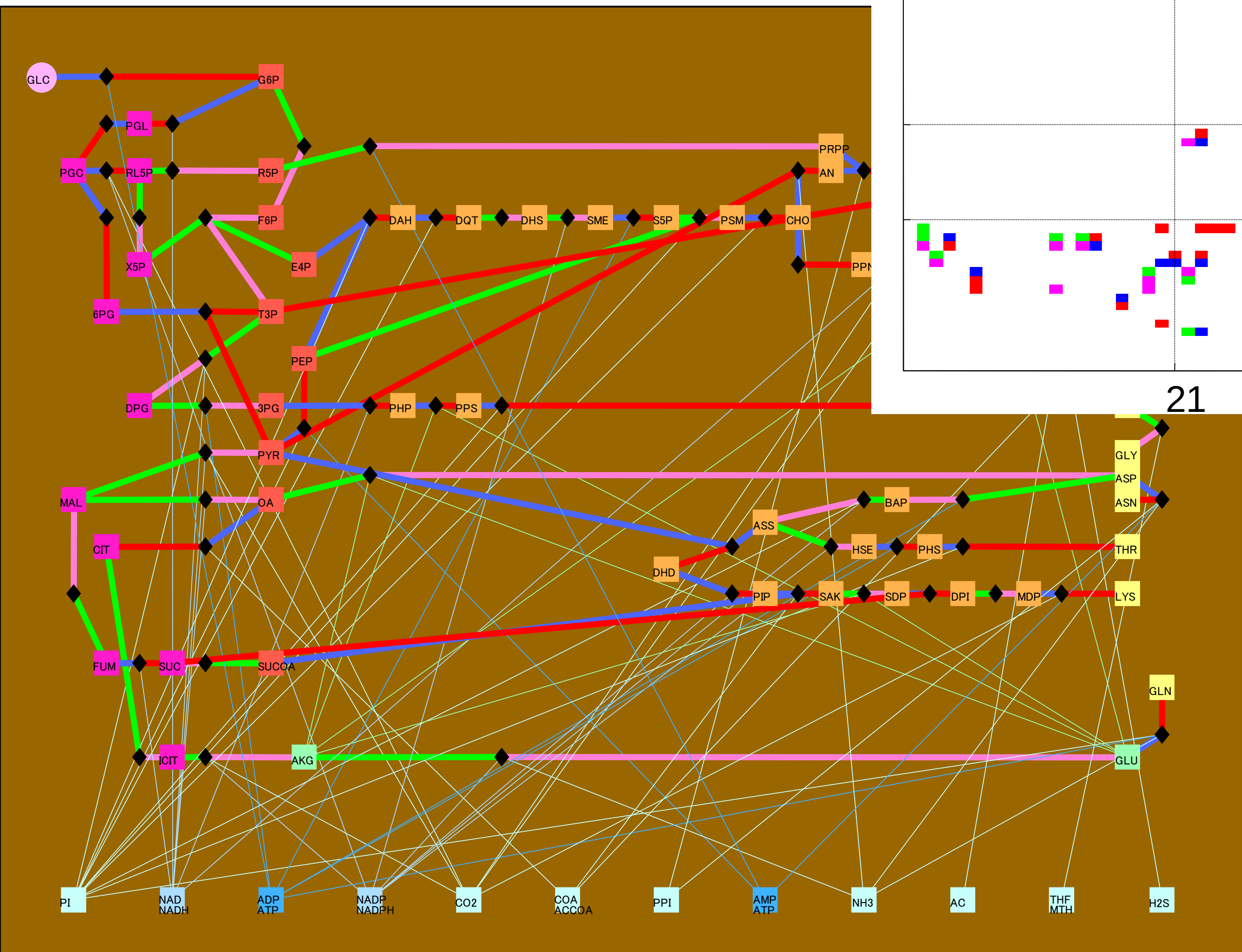


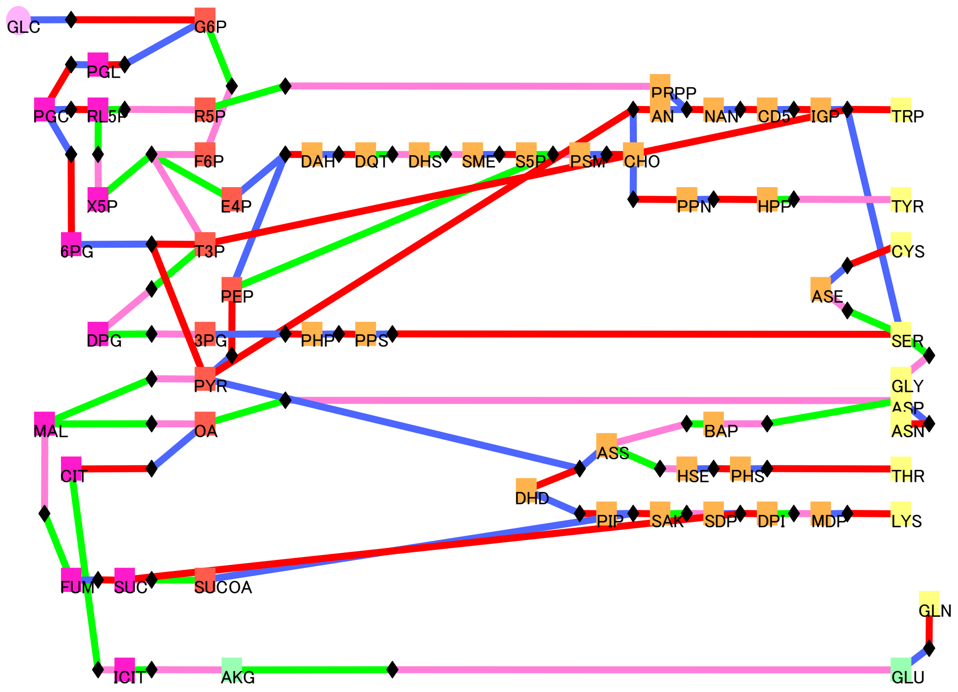
Assume "modules" as given to start with, in this case all metabolites (or find communities)

Try to reproduce statistics as "emergent" phenomena of nearly random ensembles, with minimal tuning.

Random rewiring, even preserving all macroscopic features, destroys functionality



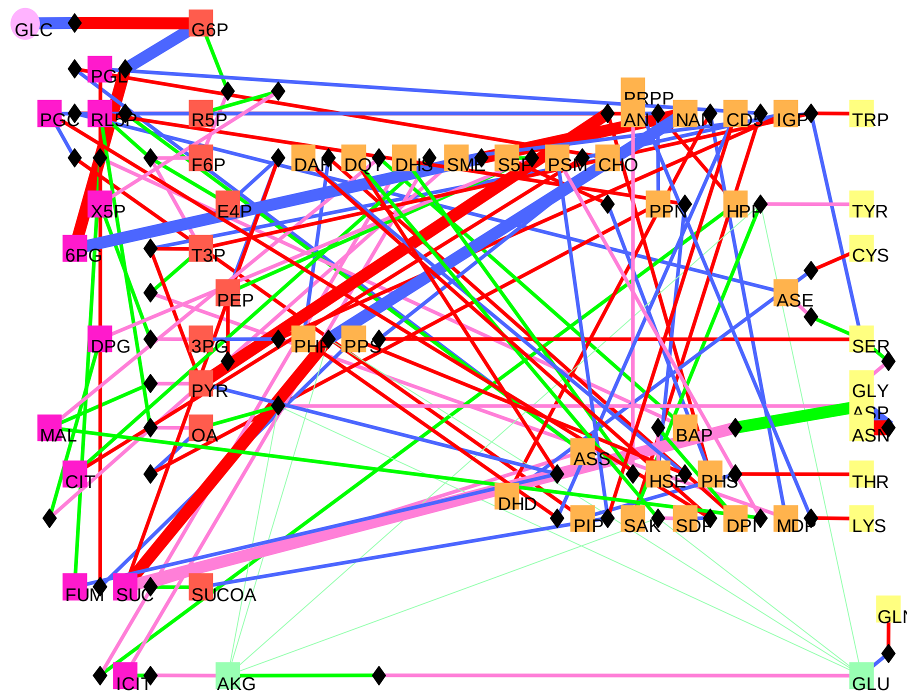




Rewired, but otherwise identical:

- degrees
- role of carriers
- role of precursors
- role of outputs

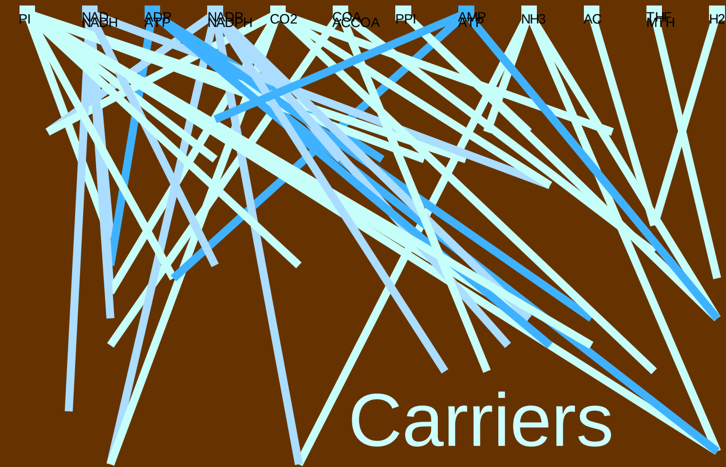
- “Scale-free”
- “Small world”
- Won’t work

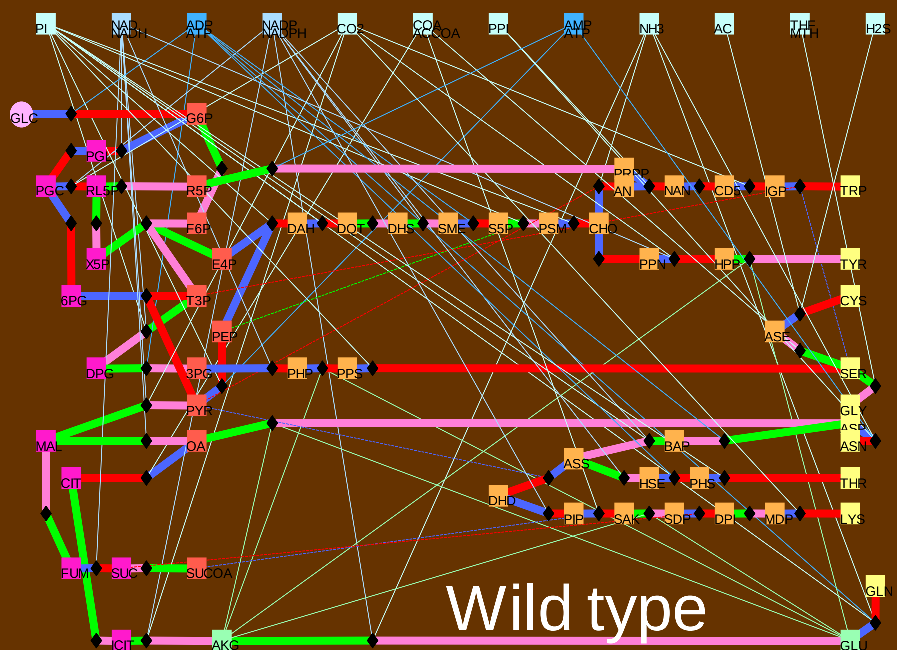


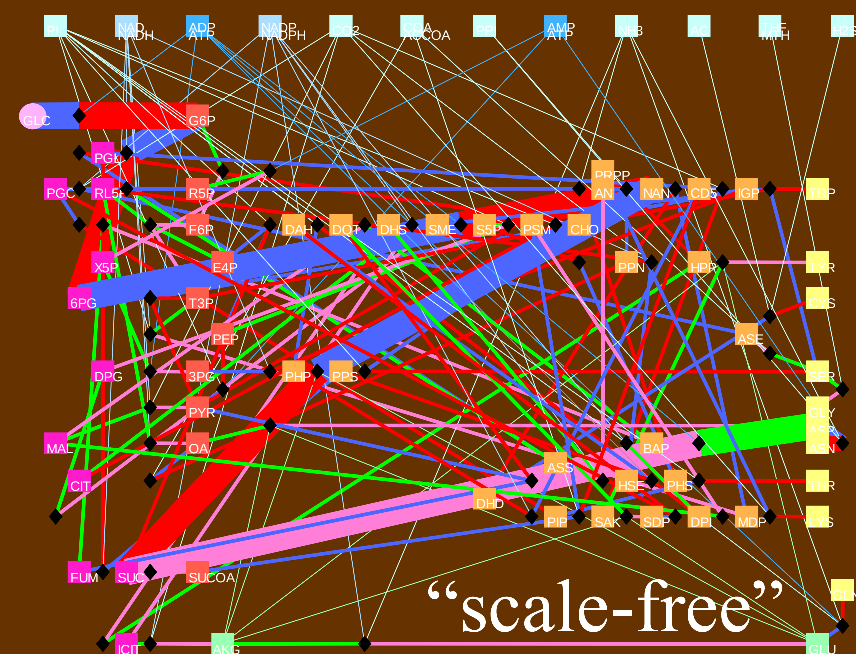
- Preserve
  - degree
  - carrier
  - enzyme

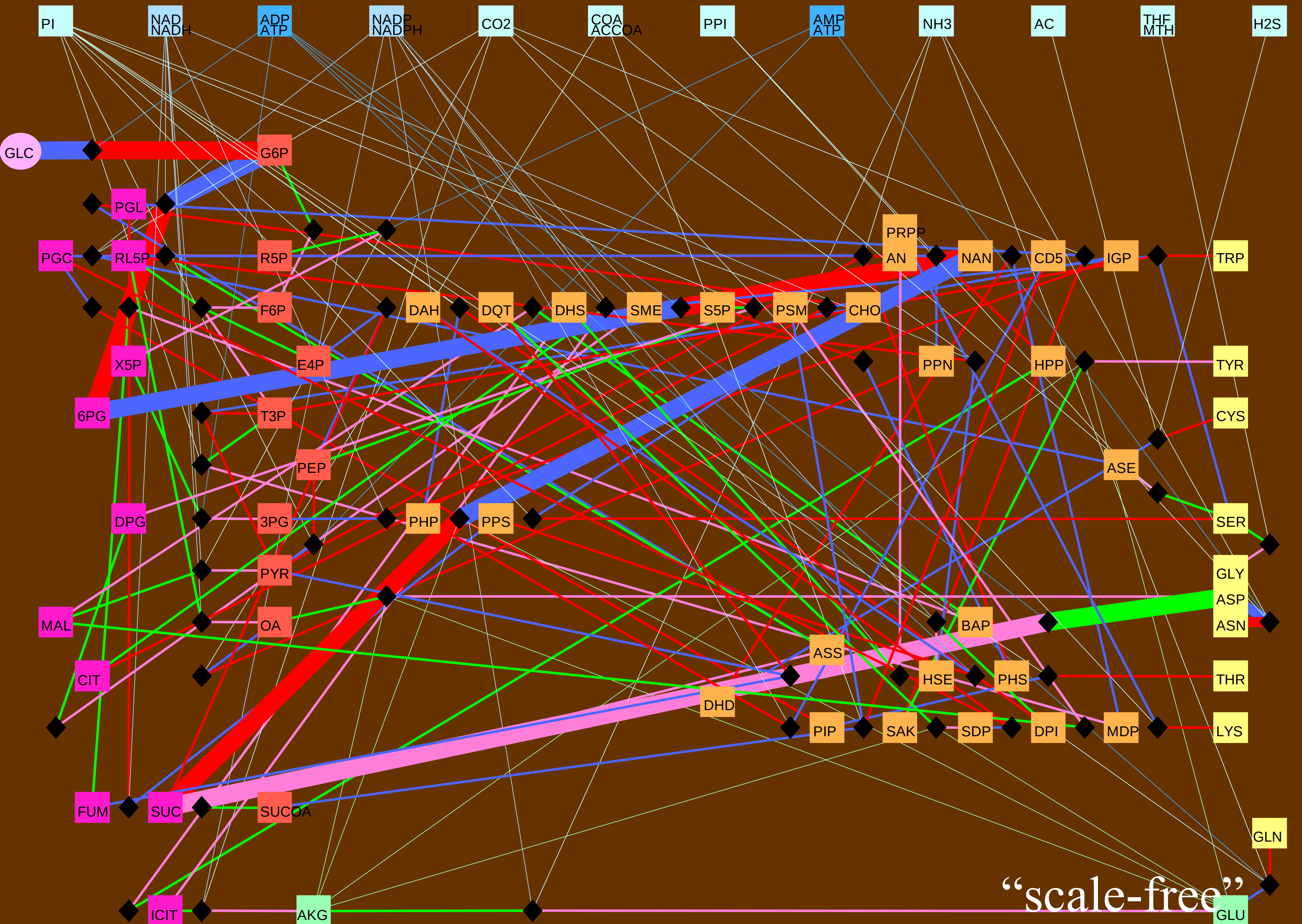
precursors

amino acids





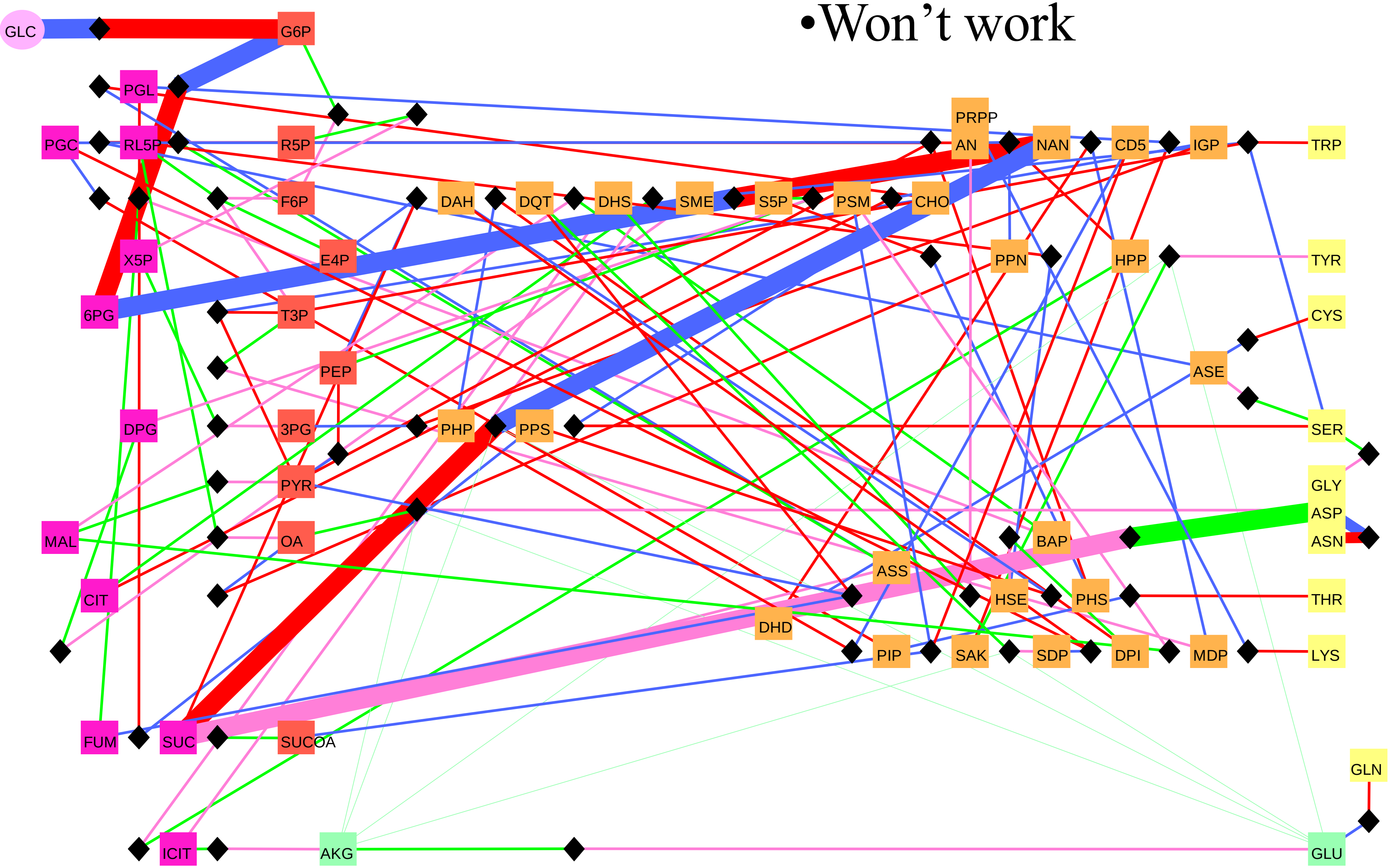



PI
NAD NADH
ADP ATP
NADP NADPH
CO2
COA ACCOA
PPI
AMP ATP
NH3
AC
THF MTH
H2S
GLC
G6P
PGL
PGC
RL5P
R5P
F6P
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
DAH
DQT
DHS
SME
S5P
PSM
CHO
PRPP
AN
NAN
CD5
IGP
TRP
PPN
HPP
TYR
CYS
ASE
PHP
PPS
SER
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU

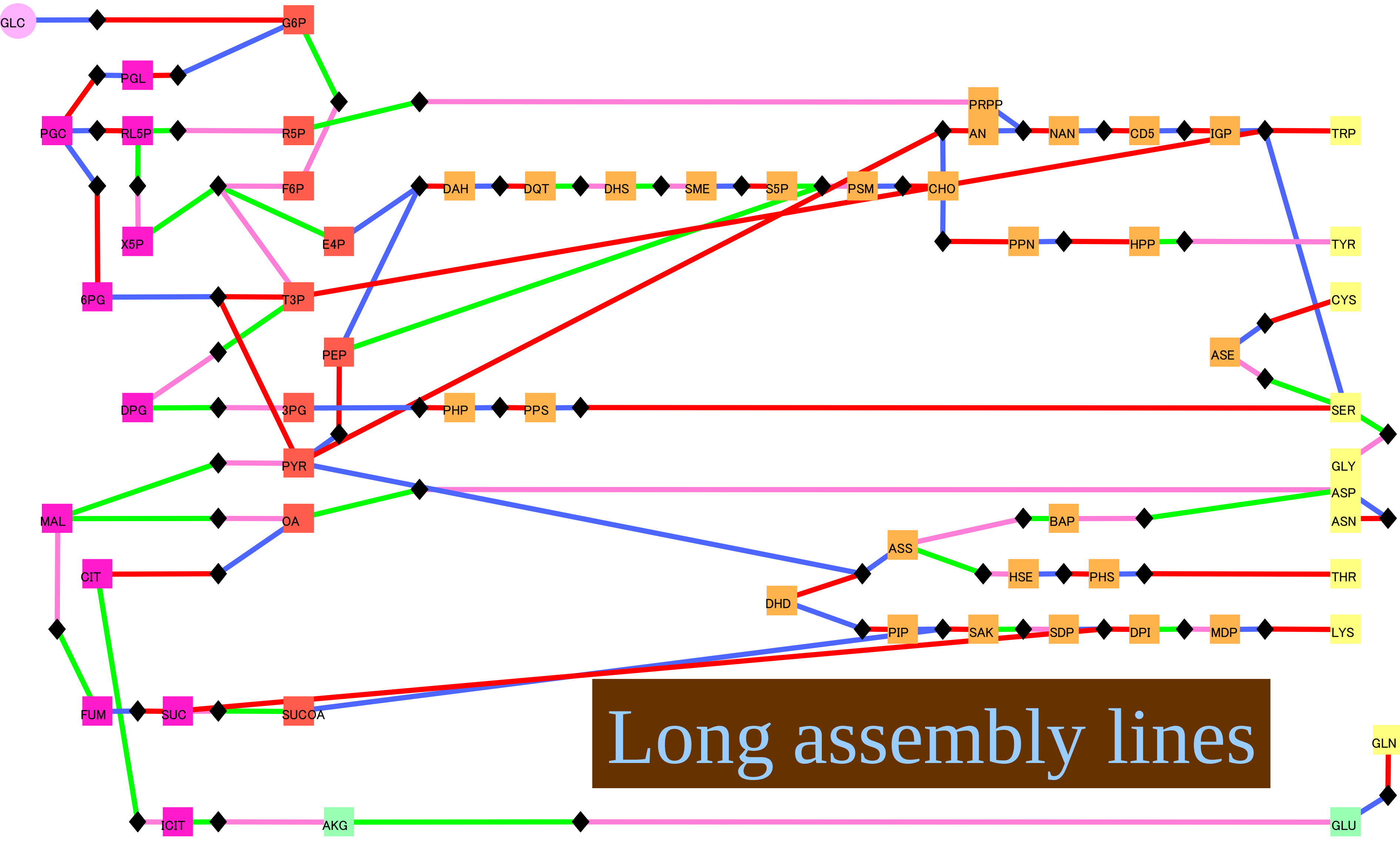
“scale-free”

Without carriers

- “Scale-free”
- “Small world”
- Won’t work

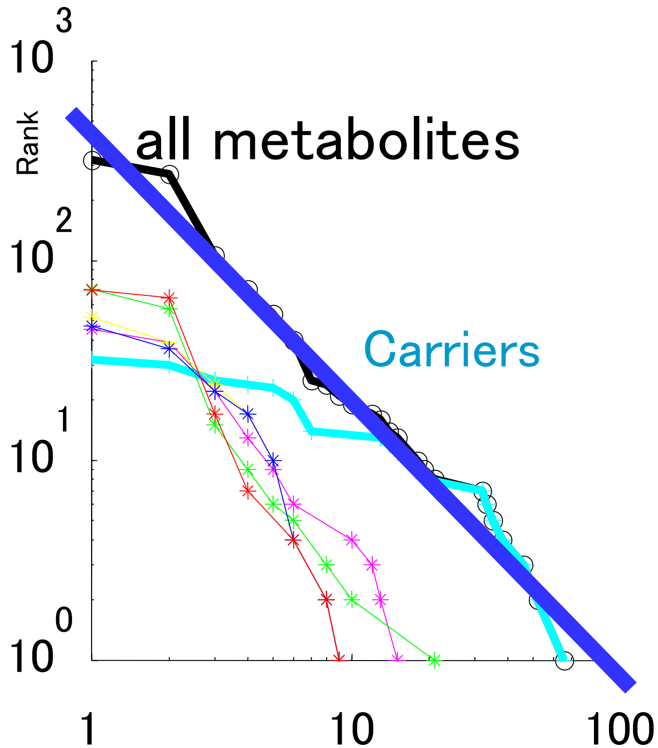


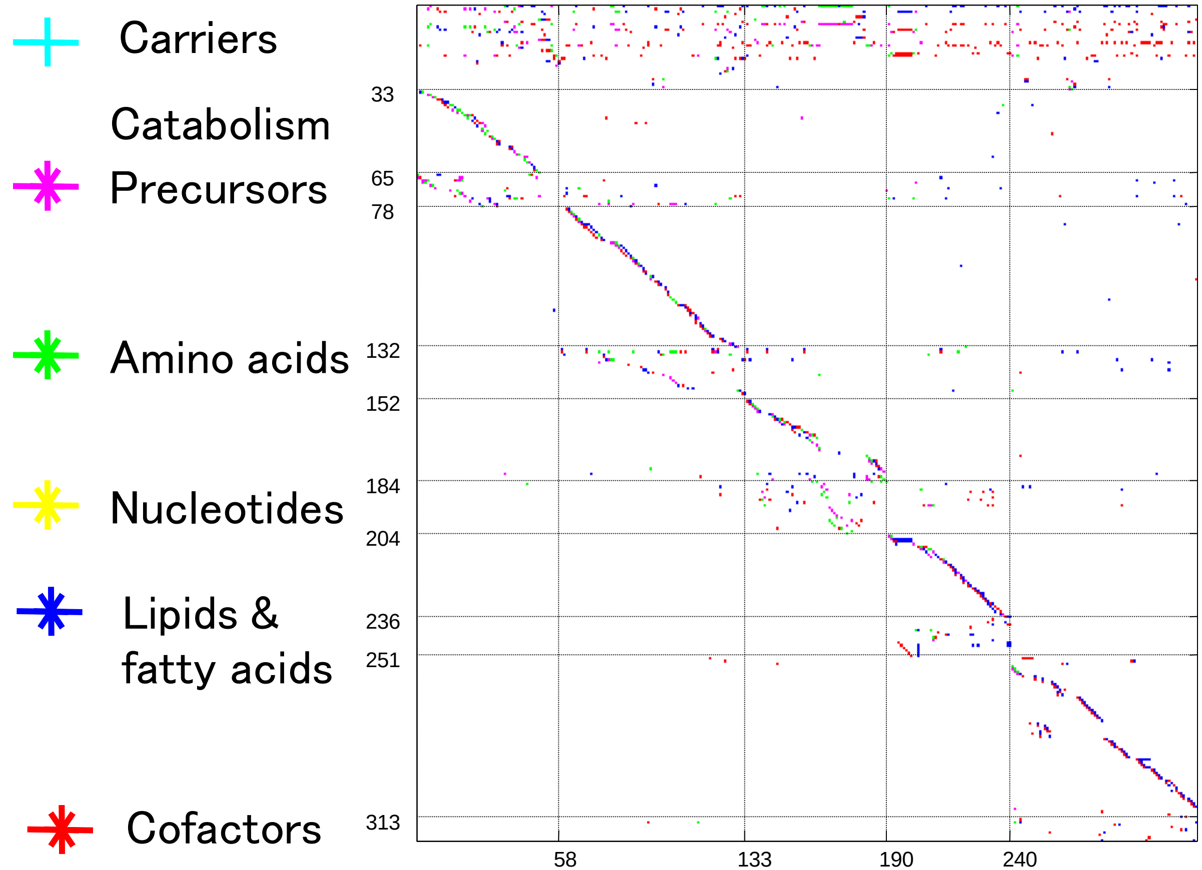
Without carriers



Long assembly lines

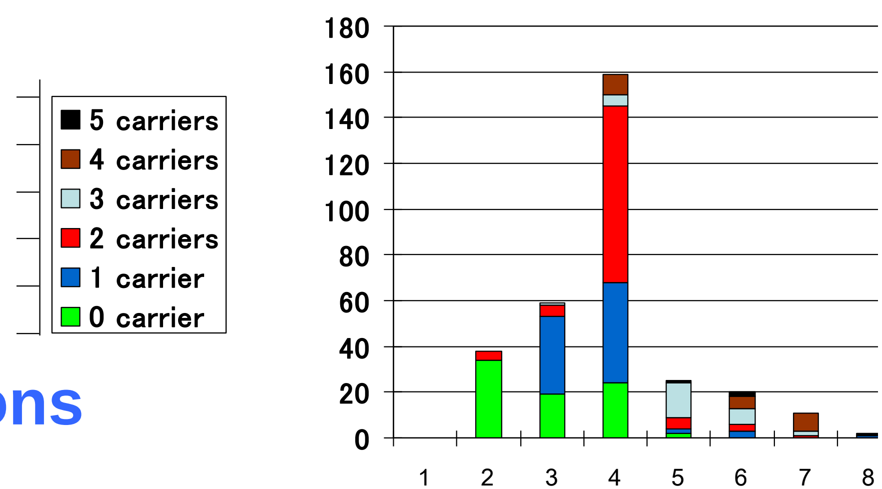
Metabolites



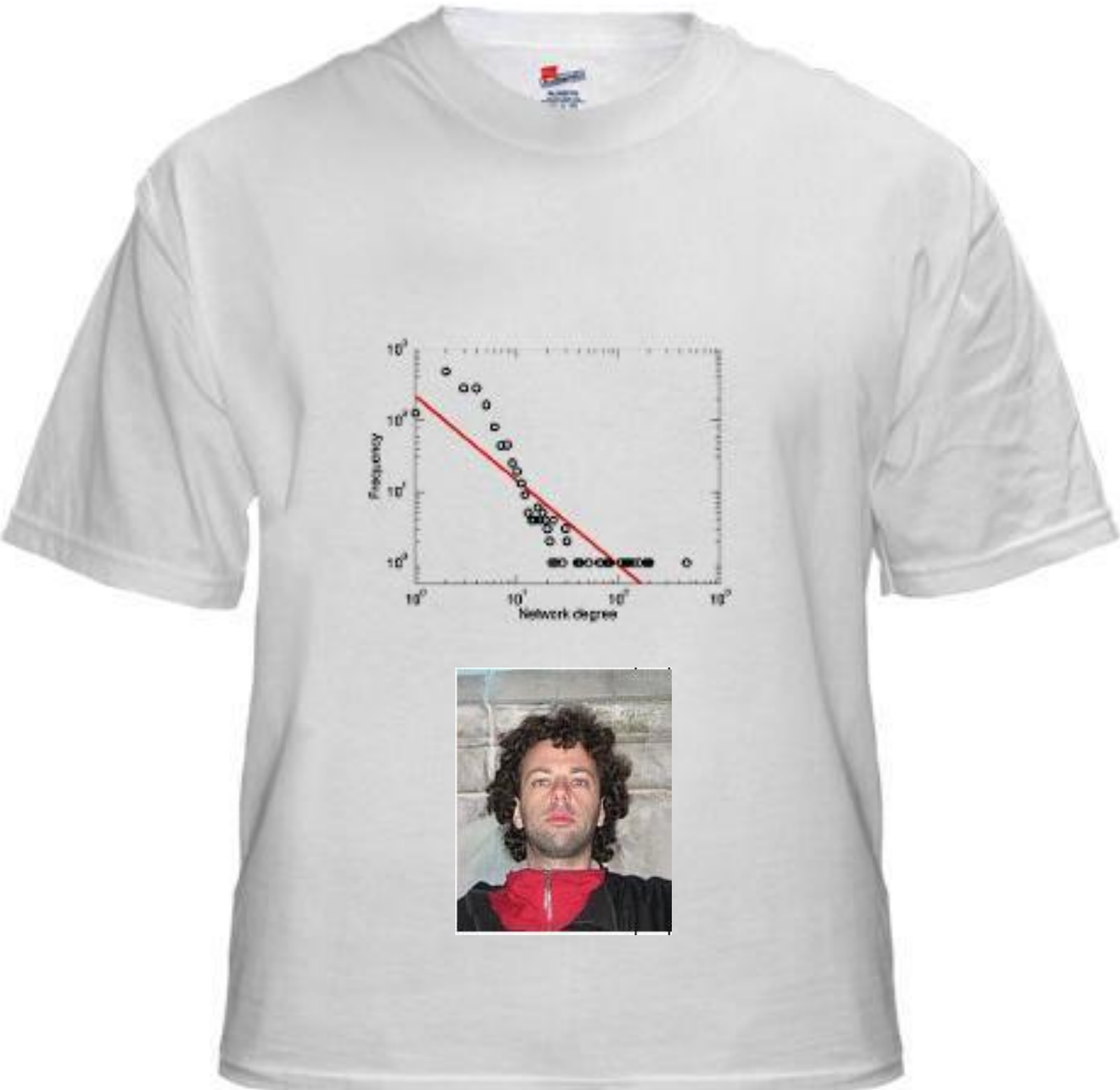


H. Pylori

Reactions



http://www.cafepress.com/ThePowerLawShop

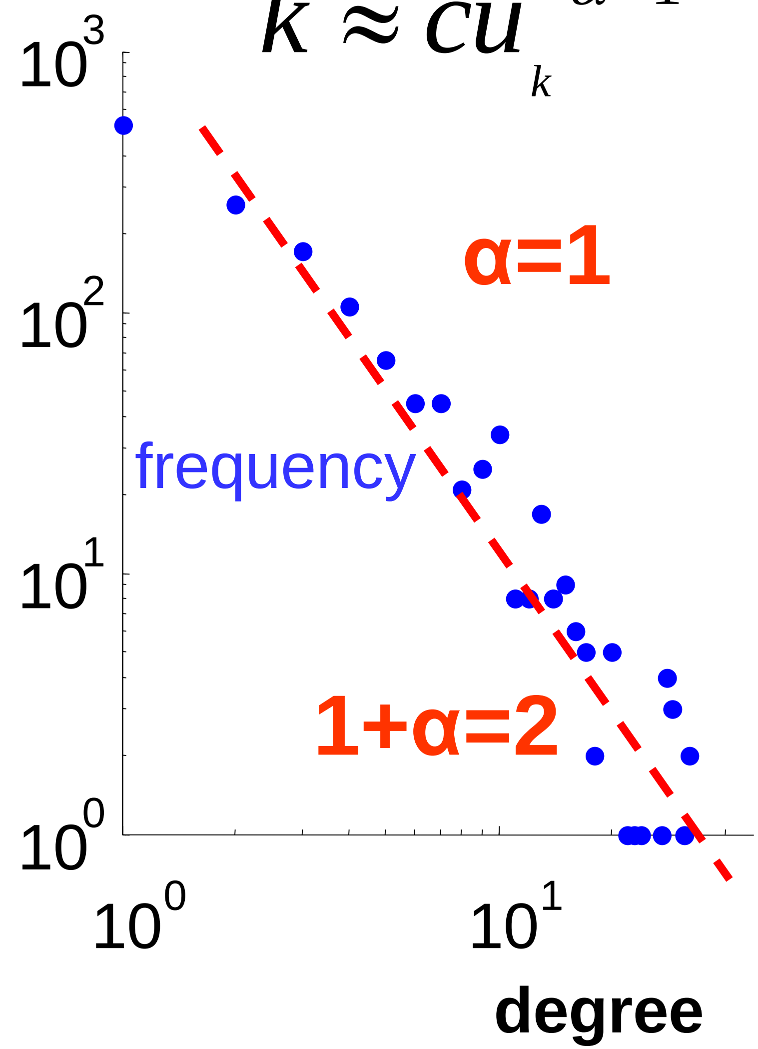


Protein-Protein Interaction (PPI) networks

$$P(X \geq x) = cx^{-\alpha}$$

$$k \approx cu_k^{-\alpha-1}$$

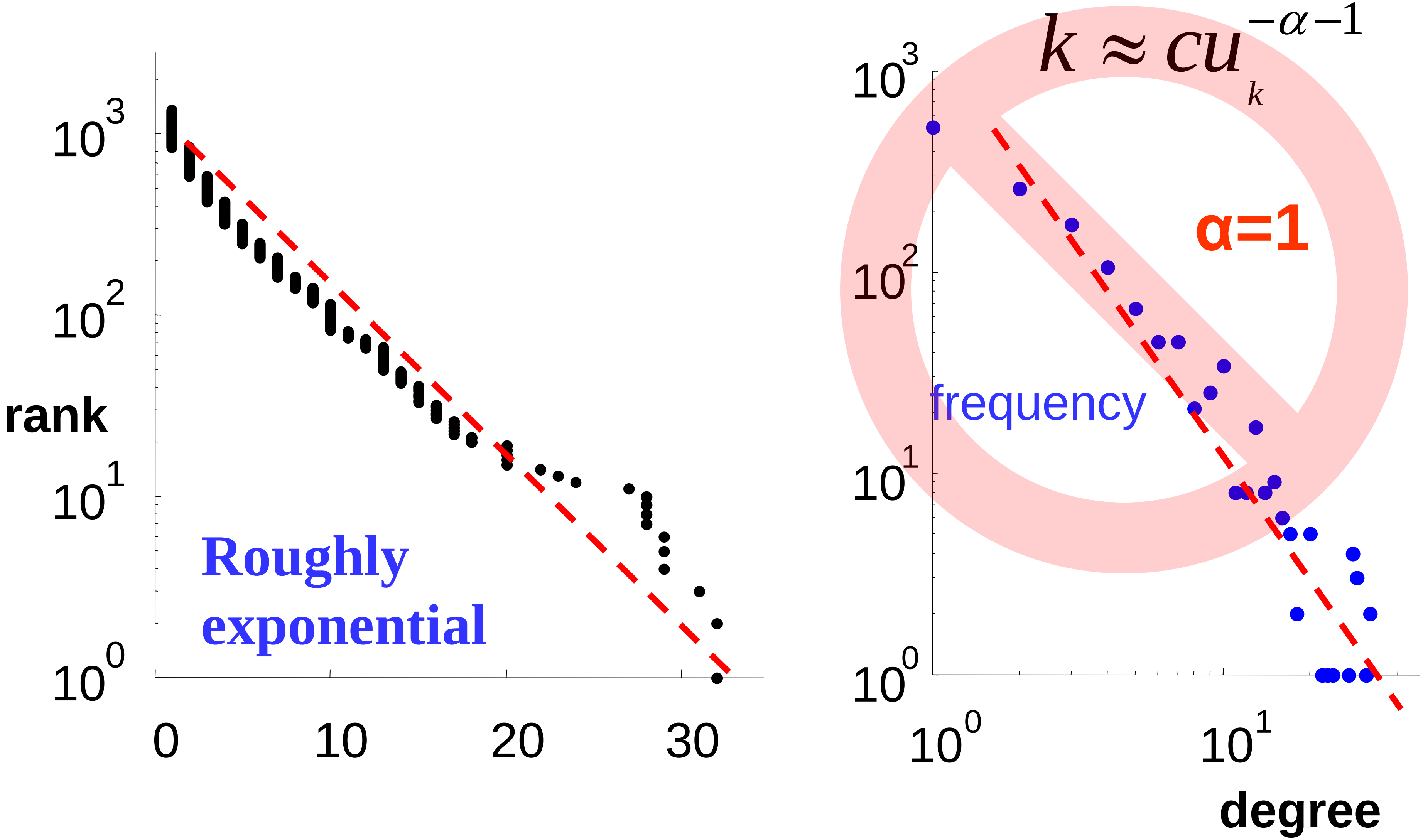
Node degree distribution of all interactions in 'filtered yeast interactome'



Han, J.-D et al (2004). Evidence for dynamically organized modularity in the yeast protein-protein interaction network. ***Nature***, 430, 88-93.

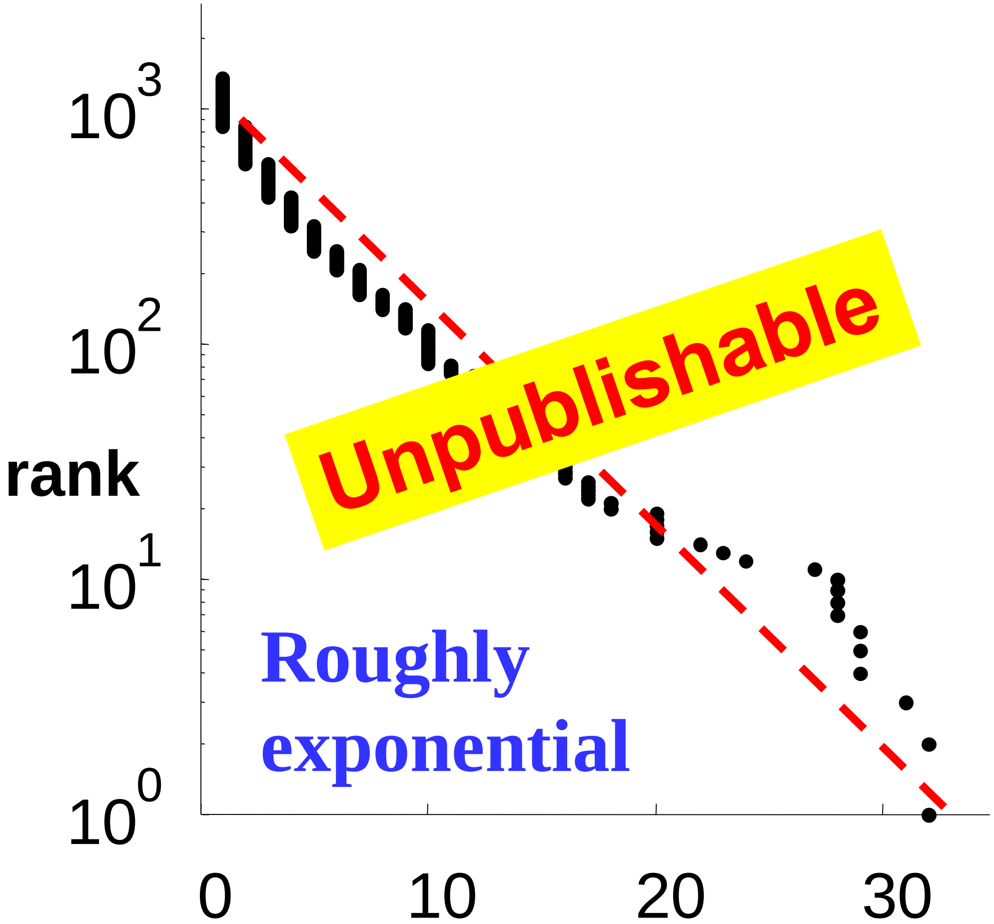
(PPI) networks

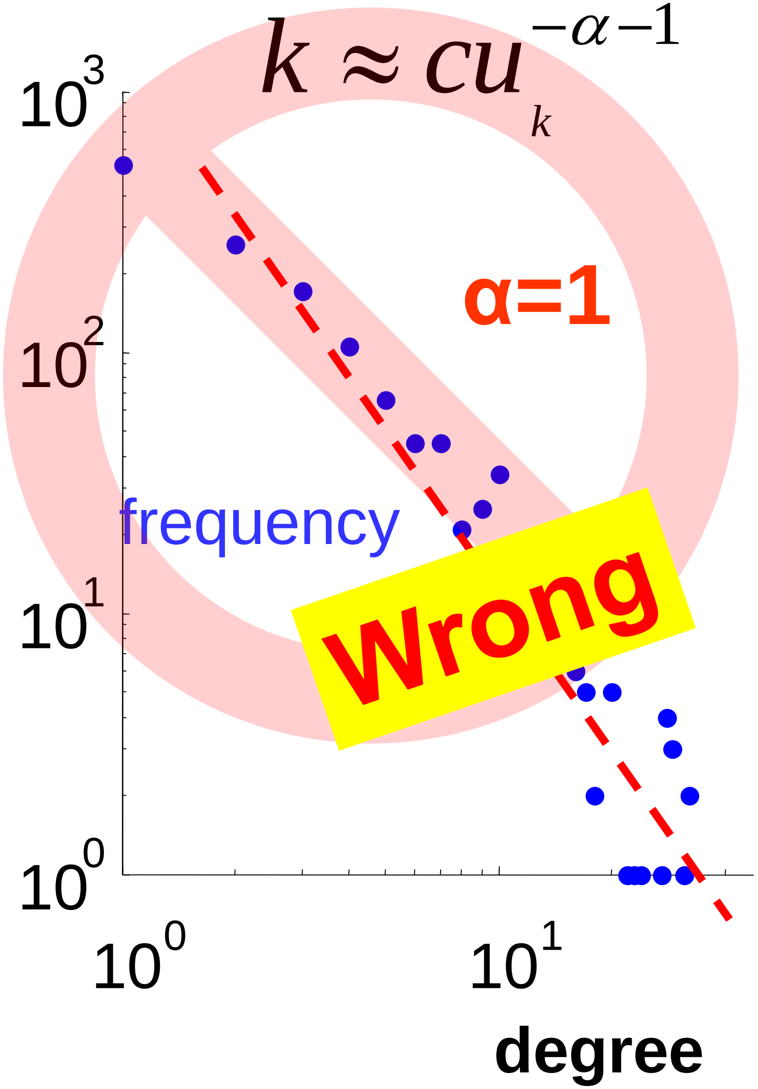
$$P(X \geq x) = cx^{-\alpha}$$



(PPI) networks

$$P(X \geq x) = cx^{-\alpha}$$





(from *Science*)

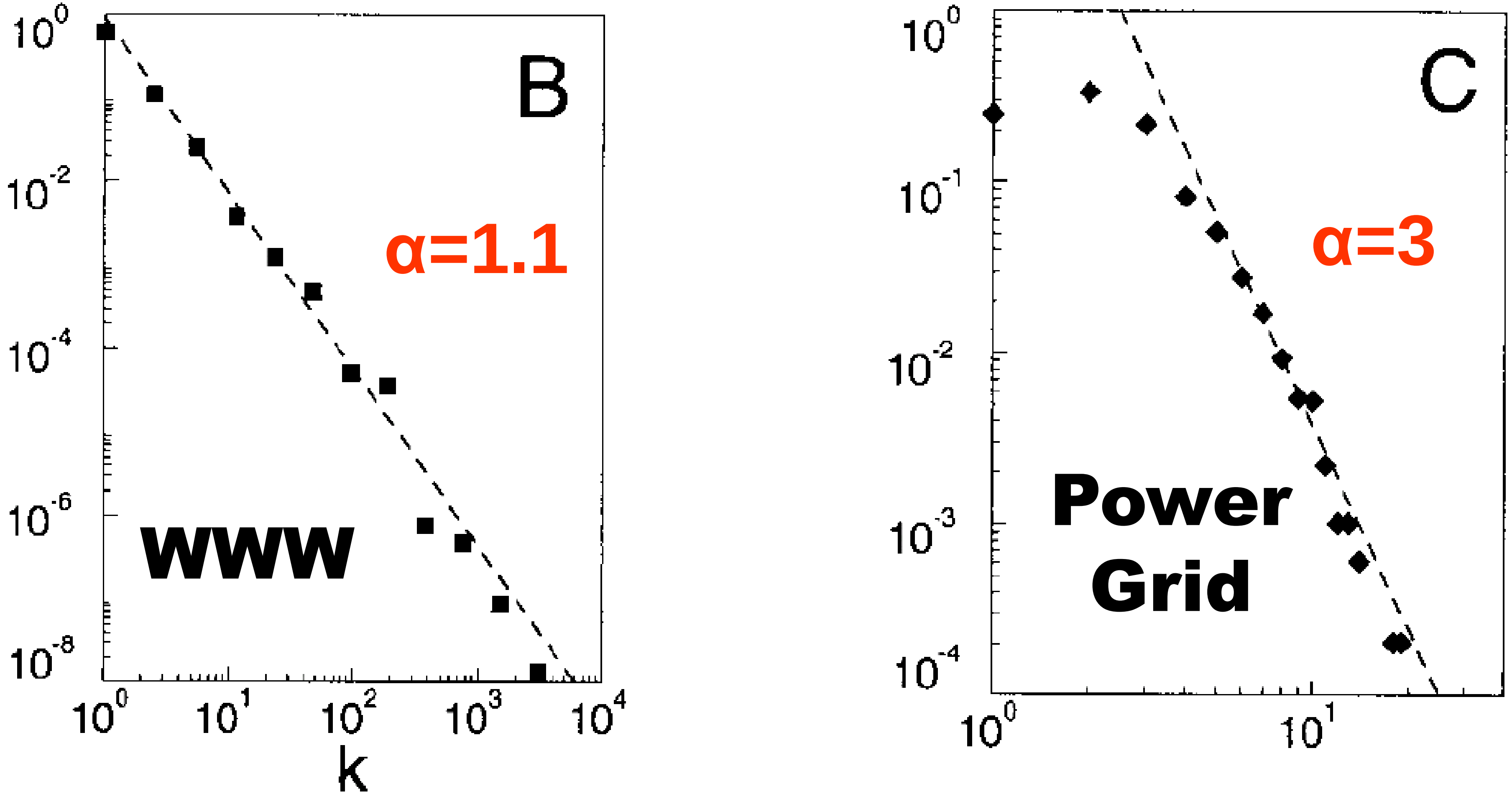
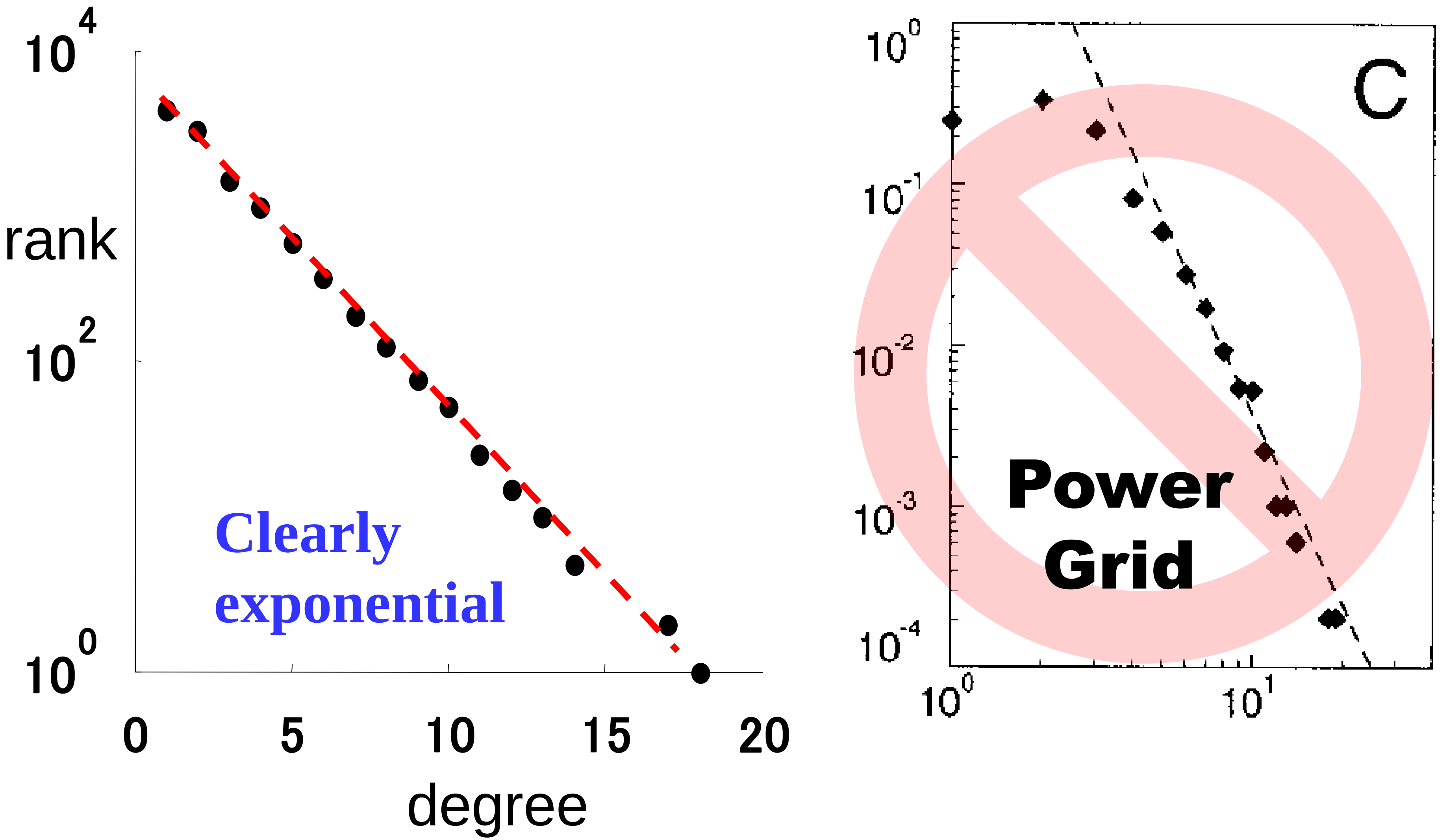
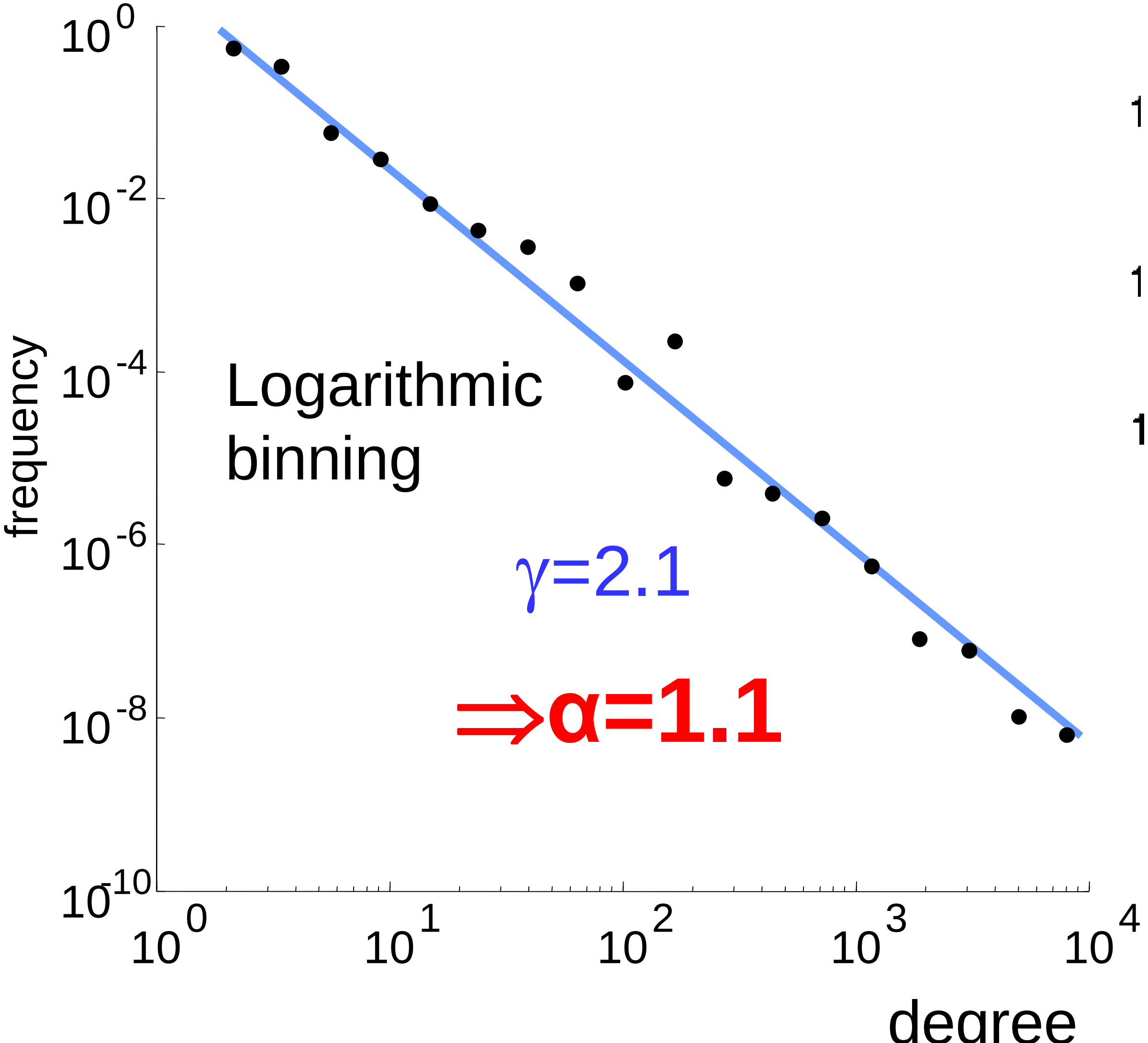


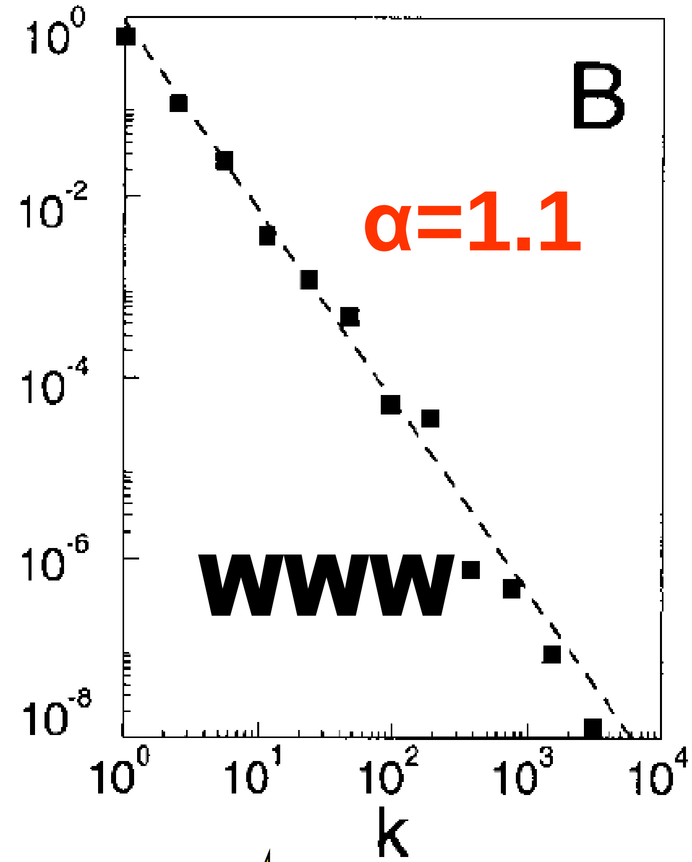
Fig. 1. The distribution function of connectivities for various large networks. (**A**) Actor collaboration graph with $N = 212{,}250$ vertices and average connectivity $\langle k \rangle = 28.78$. (**B**) WWW, $N = 325{,}729$, $\langle k \rangle = 5.46$ (6). (**C**) Power grid data, $N = 4941$, $\langle k \rangle = 2.67$. The dashed lines have slopes (A) $\gamma_{actor} = 2.3$, (B) $\gamma_{www} = 2.1$ and (C) $\gamma_{power} = 4$.

(from *Science*)

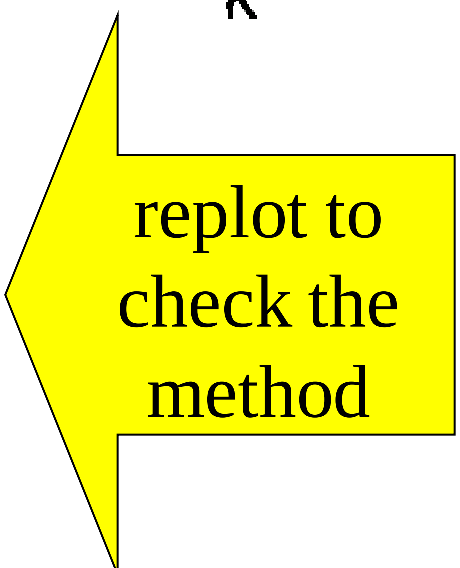




frequency
10^0
10^-2
10^-4
10^-6
10^-8
10^-10
10^0
10^1
10^2
10^3
10^4
degree
Logarithmic
binning
γ=2.1
⇒α=1.1

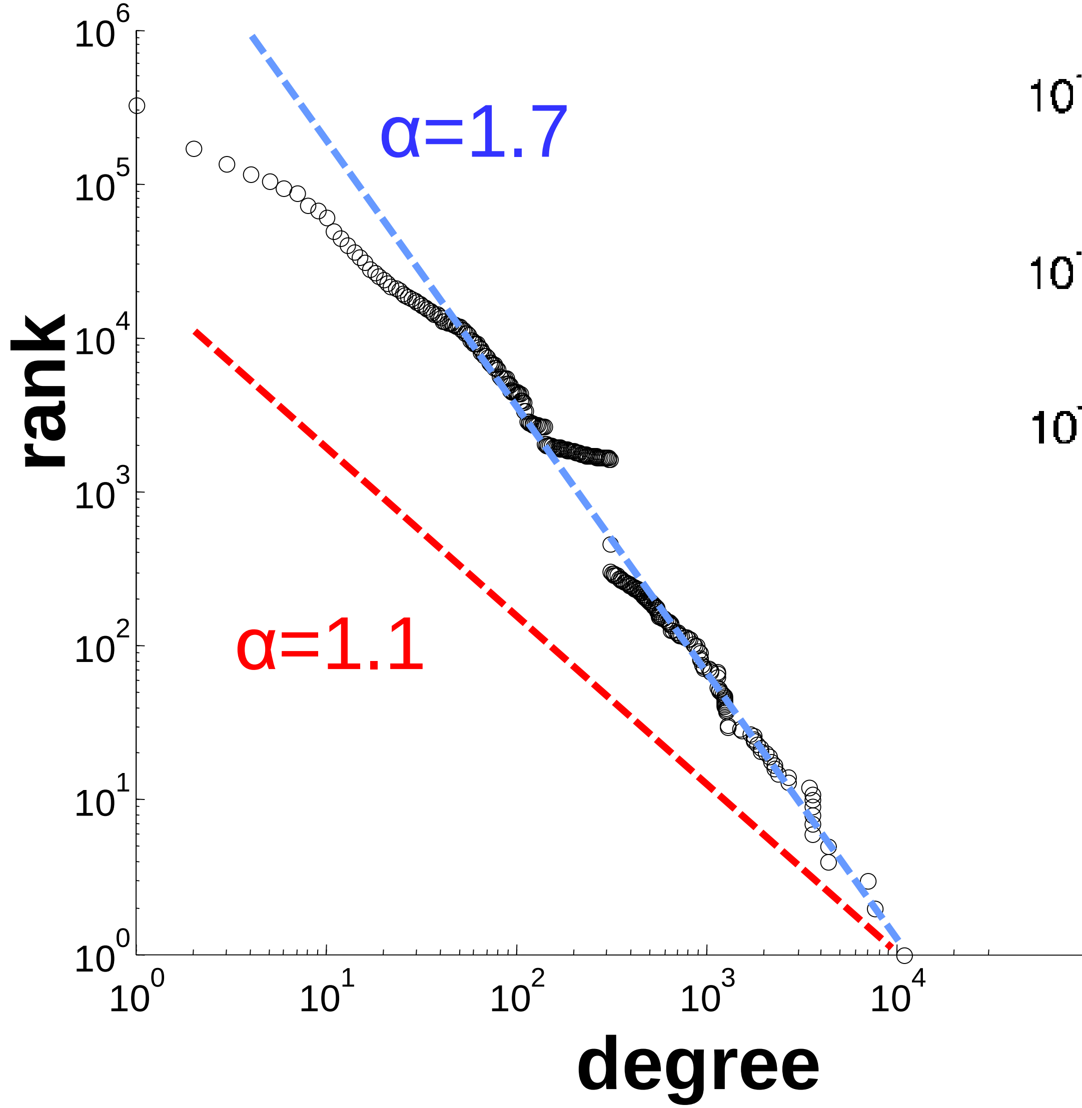


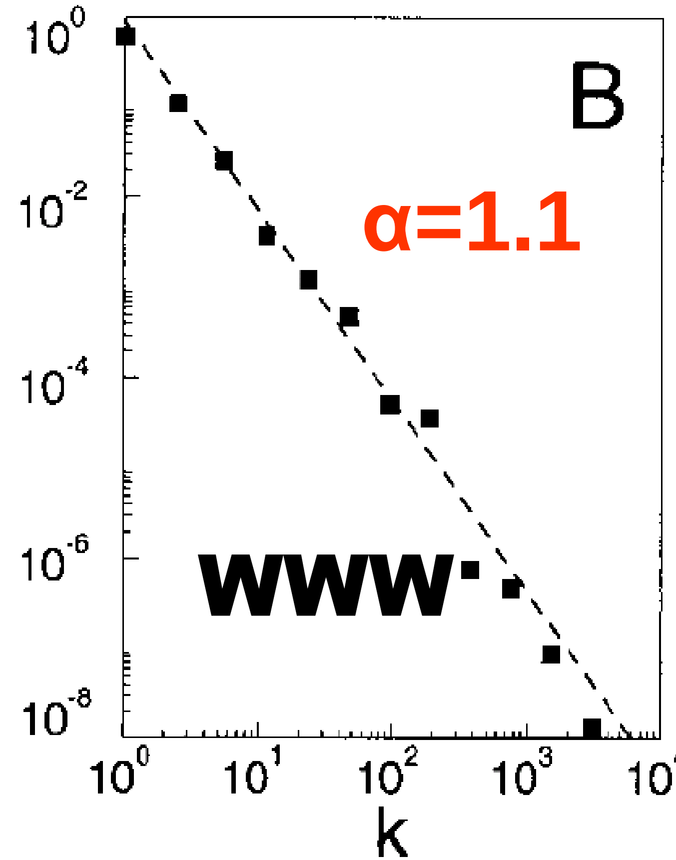
B
α=1.1
www
k



replot to
check the
method

Wrong α


α=1.7
α=1.1
rank
degree
10^0
10^1
10^2
10^3
10^4
10^5
10^6

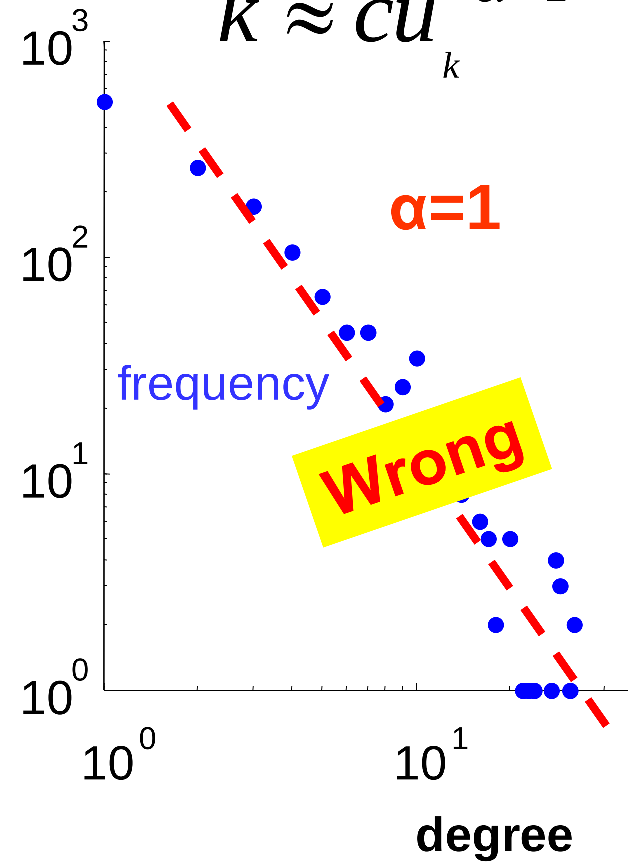

B
α=1.1
WWW
k
10^0
10^{-2}
10^{-4}
10^{-6}
10^{-8}
10^1
10^2
10^3
10^4

This is all well-known:

- Power laws are everywhere
- But most "results" are wrong
- Such errors are ***required*** in all "high impact" physics journals and magazines
- ***All*** well-known results on SOC or scale-free are false
- All papers challenging these errors rejected without review
- *PRL* is (supposedly) trying to reform, others not even trying

$$P(X \geq x) = cx^{-\alpha}$$

$$k \approx cu_k^{-\alpha-1}$$



REVIEW ARTICLES | INSIGHT
PUBLISHED ONLINE: 1 OCTOBER 2010 | DOI: 10.1038/NPHYS1803
nature physics

Emergent complex neural dynamics

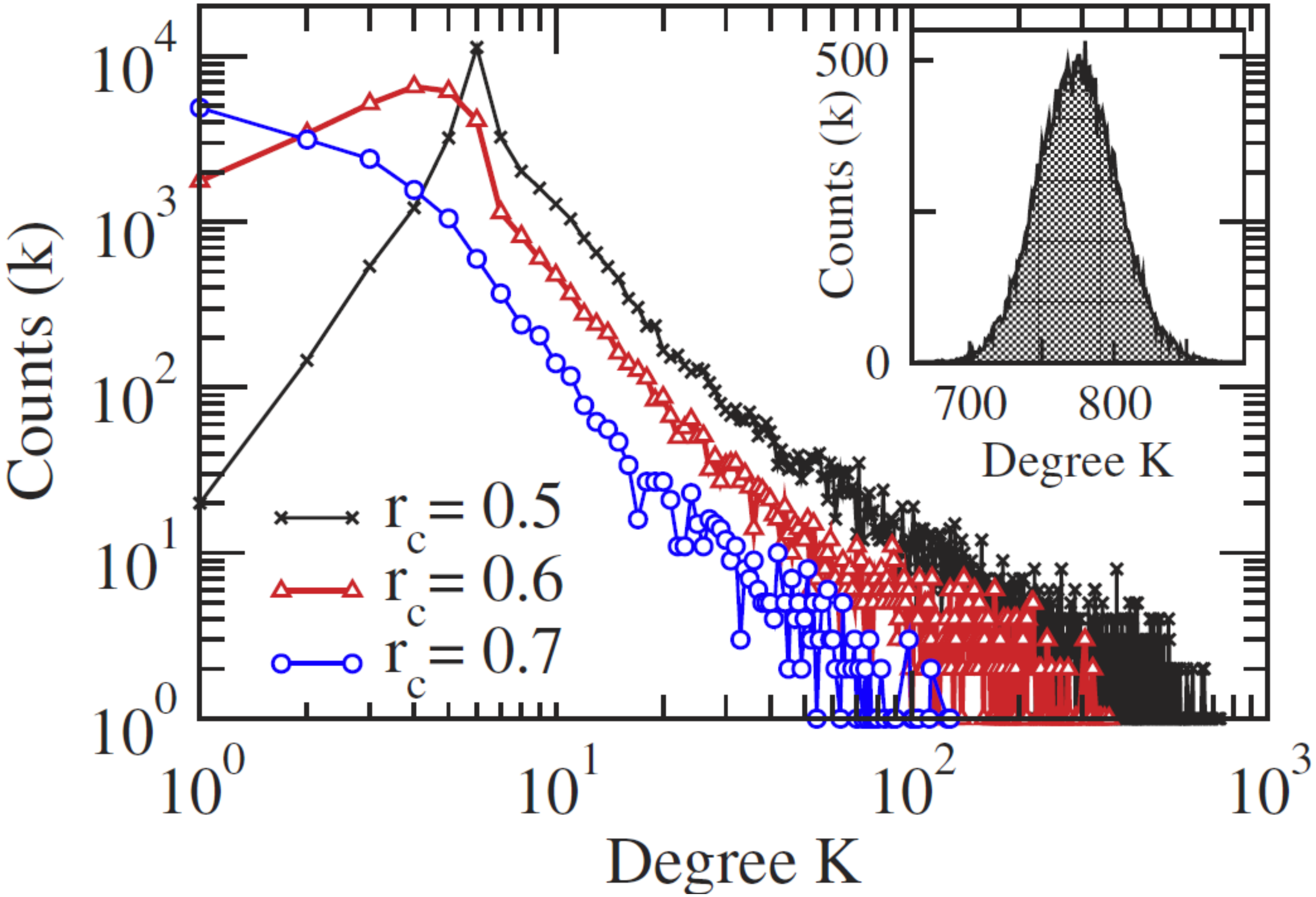
Dante R. Chialvo[1,2]★

A large repertoire of spatiotemporal activity patterns in the brain is the basis for adaptive behaviour. Understanding the mechanism by which the brain's hundred billion neurons and hundred trillion synapses manage to produce such a range of cortical configurations in a flexible manner remains a fundamental problem in neuroscience. One plausible solution is the involvement of universal mechanisms of emergent complex phenomena evident in dynamical systems poised near a critical point of a second-order phase transition. We review recent theoretical and empirical results supporting the notion that the brain is naturally poised near criticality, as well as its implications for better understanding of the brain.

poised near a critical point of a second-order phase transition

Claim:

1. These are power laws
2. Power laws imply scale free (or SOC)
3. The brain is scale free or (SOC)



Are biological systems poised at criticality?

Thierry Mora[1*] and William Bialek[1,2]
[1] *Joseph Henry Laboratories of Physics, Lewis–Sigler Institute for Integrative Genomics,*
nd [2] Princeton Center for Theoretical Science, Princeton University, Princeton, New Jersey 08544 US
(Dated: December 13, 2010)

Many of life's most fascinating phenomena emerge from interactions among many elements—many amino acids determine the structure of a single protein, many genes determine the fate of a cell, many neurons are involved in shaping our thoughts and memories. Physicists have long hoped that these collective behaviors could be described using the ideas and methods of statistical mechanics. In the past few years, new, larger scale experiments have made it possible to construct statistical mechanics models of biological systems directly from real data. We review the surprising successes of this "inverse" approach, using examples form families of proteins, networks of neurons, and flocks of birds. Remarkably, in all these cases the models that emerge from the data are poised at a very special point in their parameter space—a critical point. This suggests there may be some deeper theoretical principle behind the behavior of these diverse systems.

NeuroImage 47 (2009) 1125–1134

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

Generic aspects of complexity in brain imaging data and other biological systems

Ed Bullmore [a,*], Anna Barnes [a], Danielle S. Bassett [a,b,c], Alex Fornito [a,d], Manfred Kitzbichler [a], David Meunier [a], John Suckling [a]

Trends in Cognitive Sciences May 2011, Vol. 15, No. 5

Opinion

Understanding complexity in the human brain

Danielle S. Bassett[1] and Michael S. Gazzaniga[2]

[1] Complex Systems Group, Department of Physics, University of California, Santa Barbara, CA 93106, USA
[2] Sage Center for the Study of the Mind, University of California, Santa Barbara, CA 93106, USA

Look at data from this paper, which is often quoted.

PRL **94,** 018102 (2005) PHYSICAL REVIEW LETTERS week ending 14 JANUARY 2005

Scale-Free Brain Functional Networks

Victor M. Eguíluz,[1] Dante R. Chialvo,[2] Guillermo A. Cecchi,[3] Marwan Baliki,[2] and A. Vania Apkarian[2]

[1]*Instituto Mediterráneo de Estudios Avanzados, IMEDEA (CSIC-UIB), E07122 Palma de Mallorca, Spain*

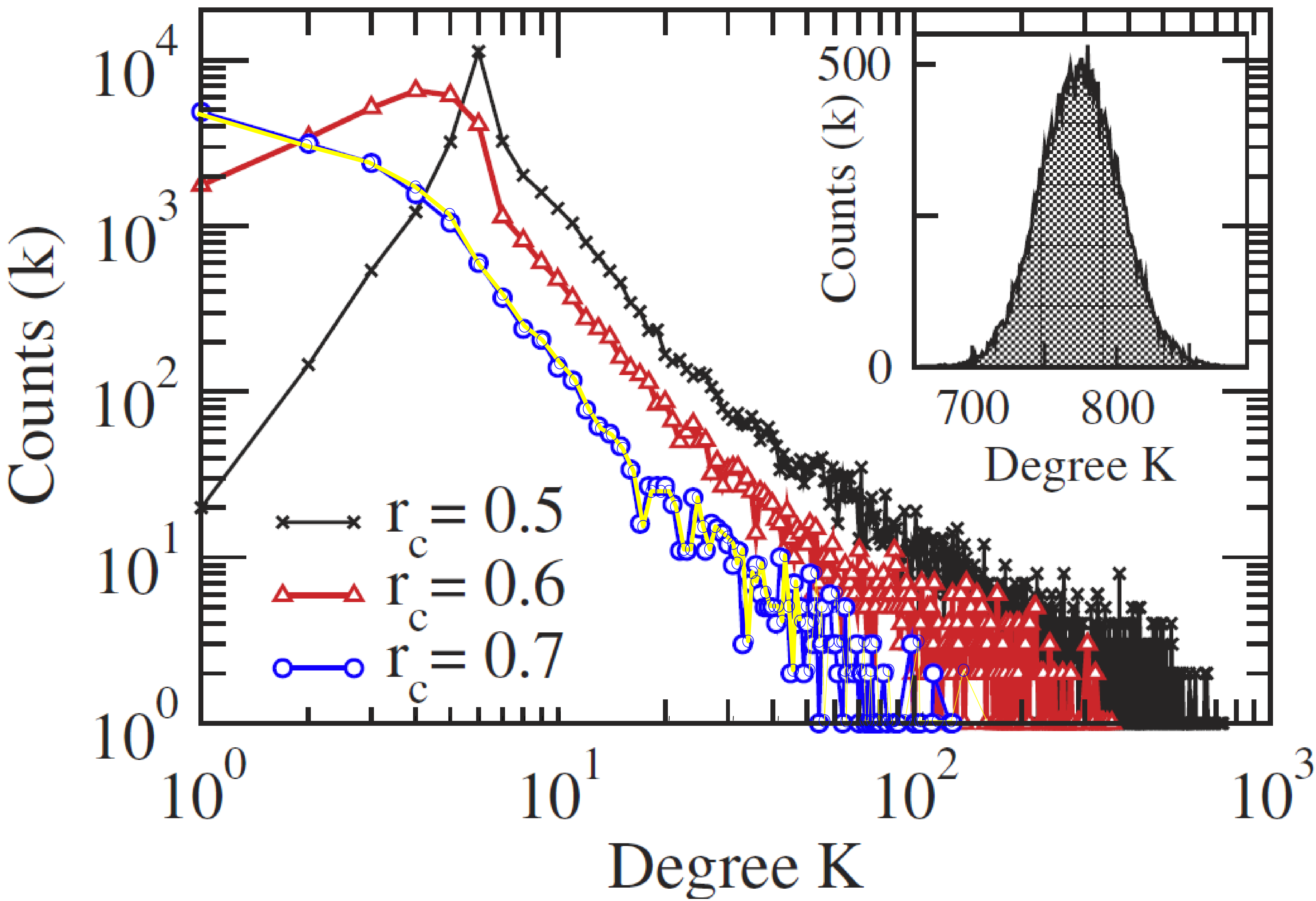
[2]*Department of Physiology, Northwestern University, Chicago, Illinois, 60611, USA*

[3]*IBM T.J. Watson Research Center, 1101 Kitchawan Rd., Yorktown Heights, New York 10598, USA*

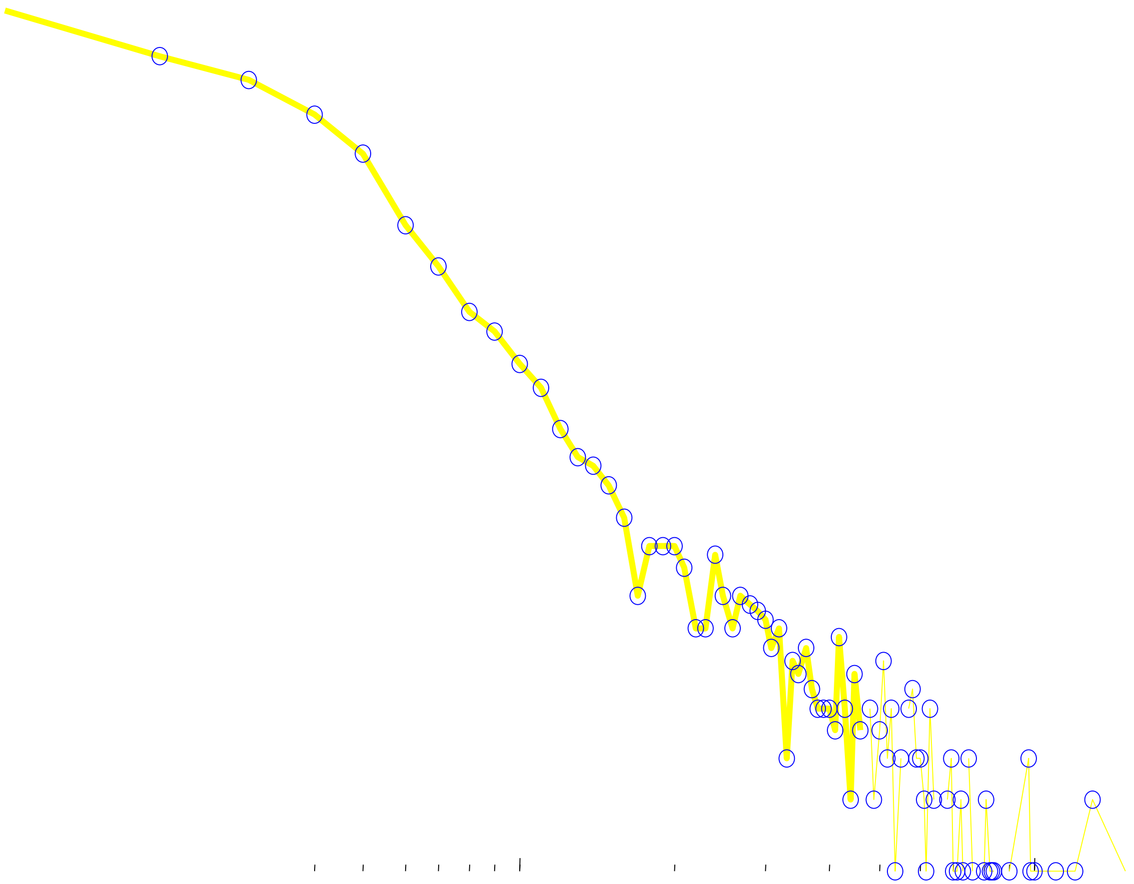
(Received 13 January 2004; published 6 January 2005)

Functional magnetic resonance imaging is used to extract *functional networks* connecting correlated human brain sites. Analysis of the resulting networks in different tasks shows that (a) the distribution of functional connections, and the probability of finding a link versus distance are both scale-free, (b) the characteristic path length is small and comparable with those of equivalent random networks, and (c) the clustering coefficient is orders of magnitude larger than those of equivalent random networks. All these properties, typical of scale-free small-world networks, reflect important functional information about brain states.

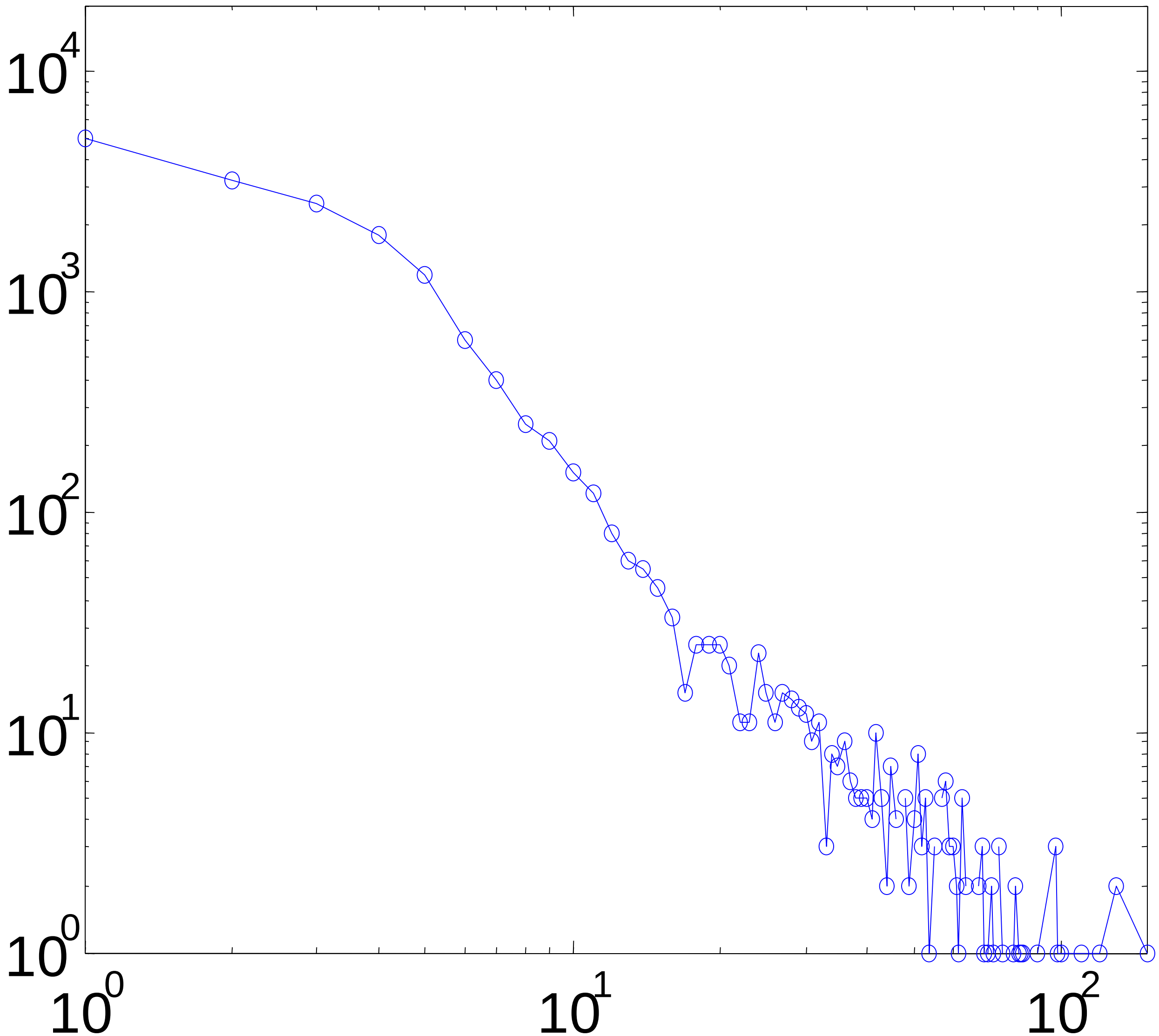
DOI: 10.1103/PhysRevLett.94.018102 PACS numbers: 87.18.Sn, 87.19.La, 89.75.Da, 89.75.Hc



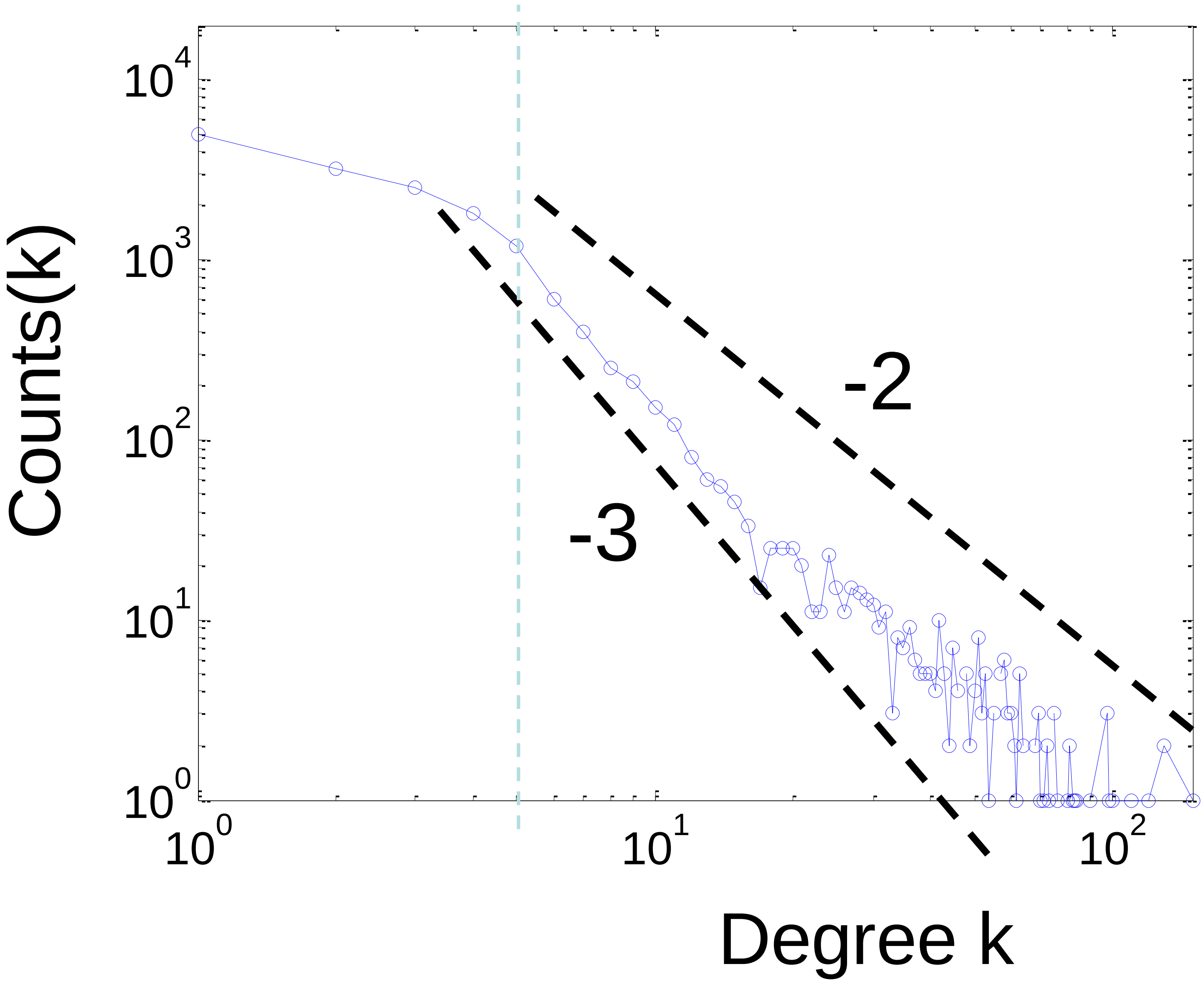
Counts (k)
Degree K
10^0
10^1
10^2
10^3
10^4
$r_c = 0.5$
$r_c = 0.6$
$r_c = 0.7$
500
0
700
800
Counts (k)
Degree K



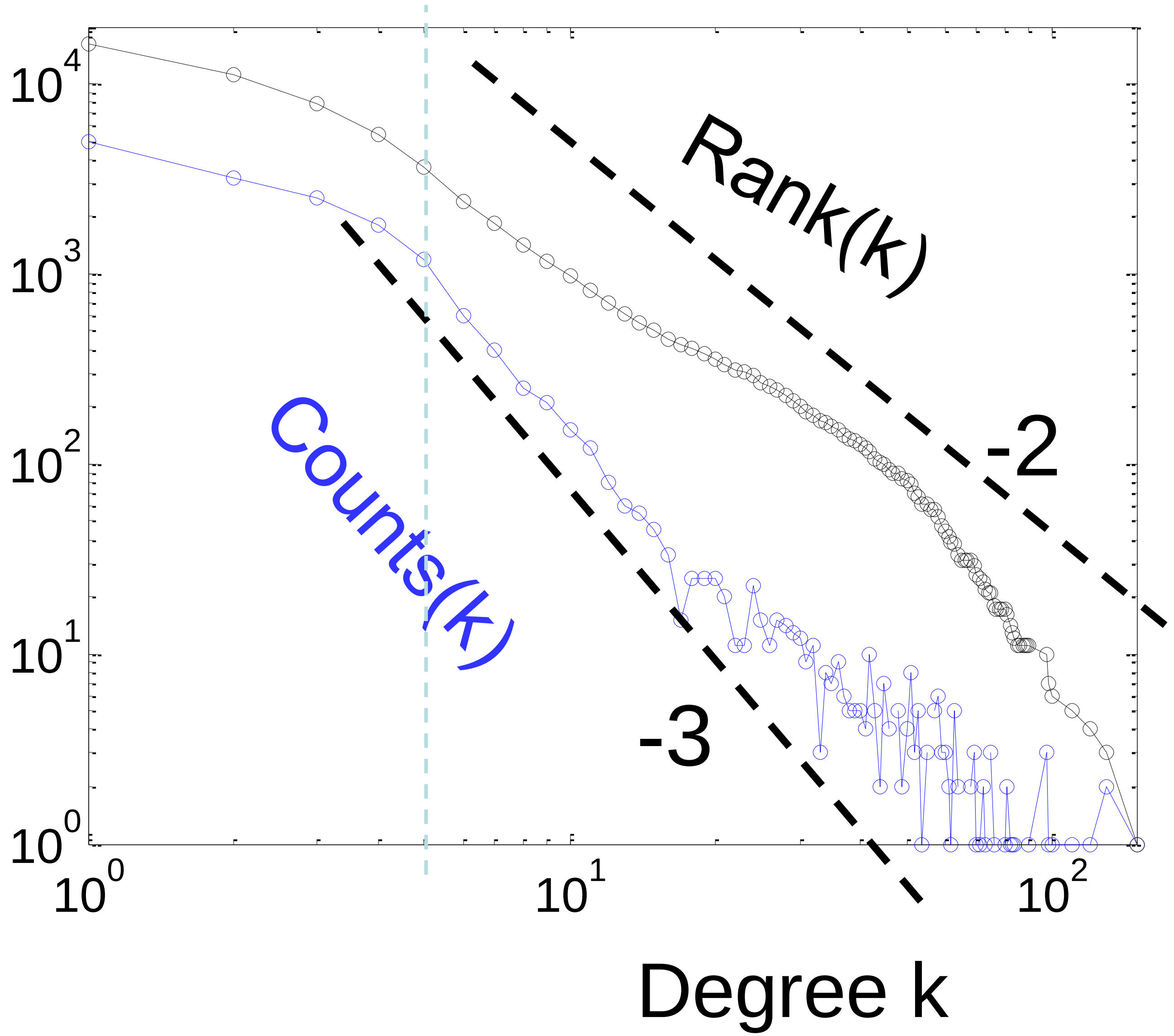
Experimental data



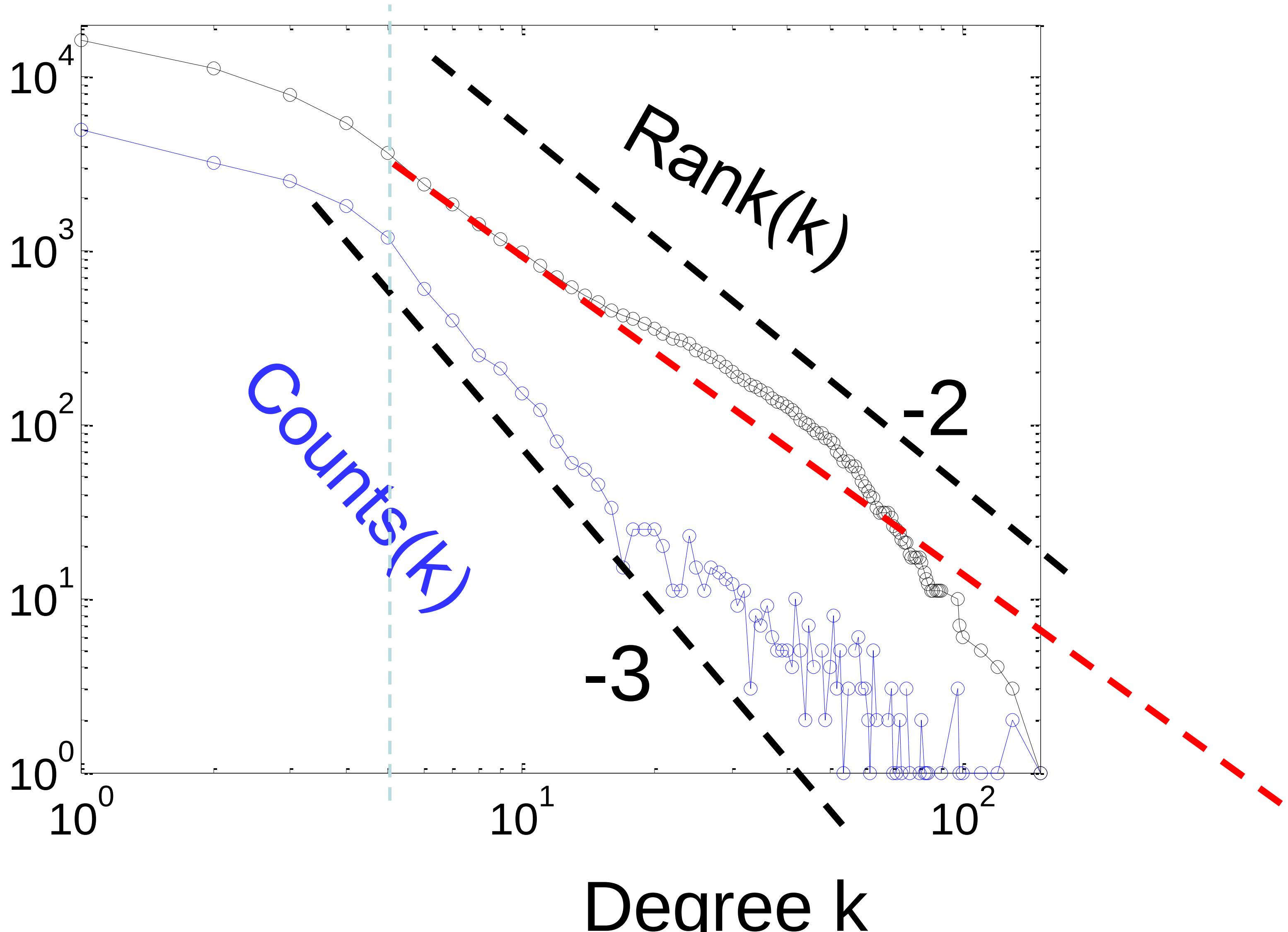
Experimental data



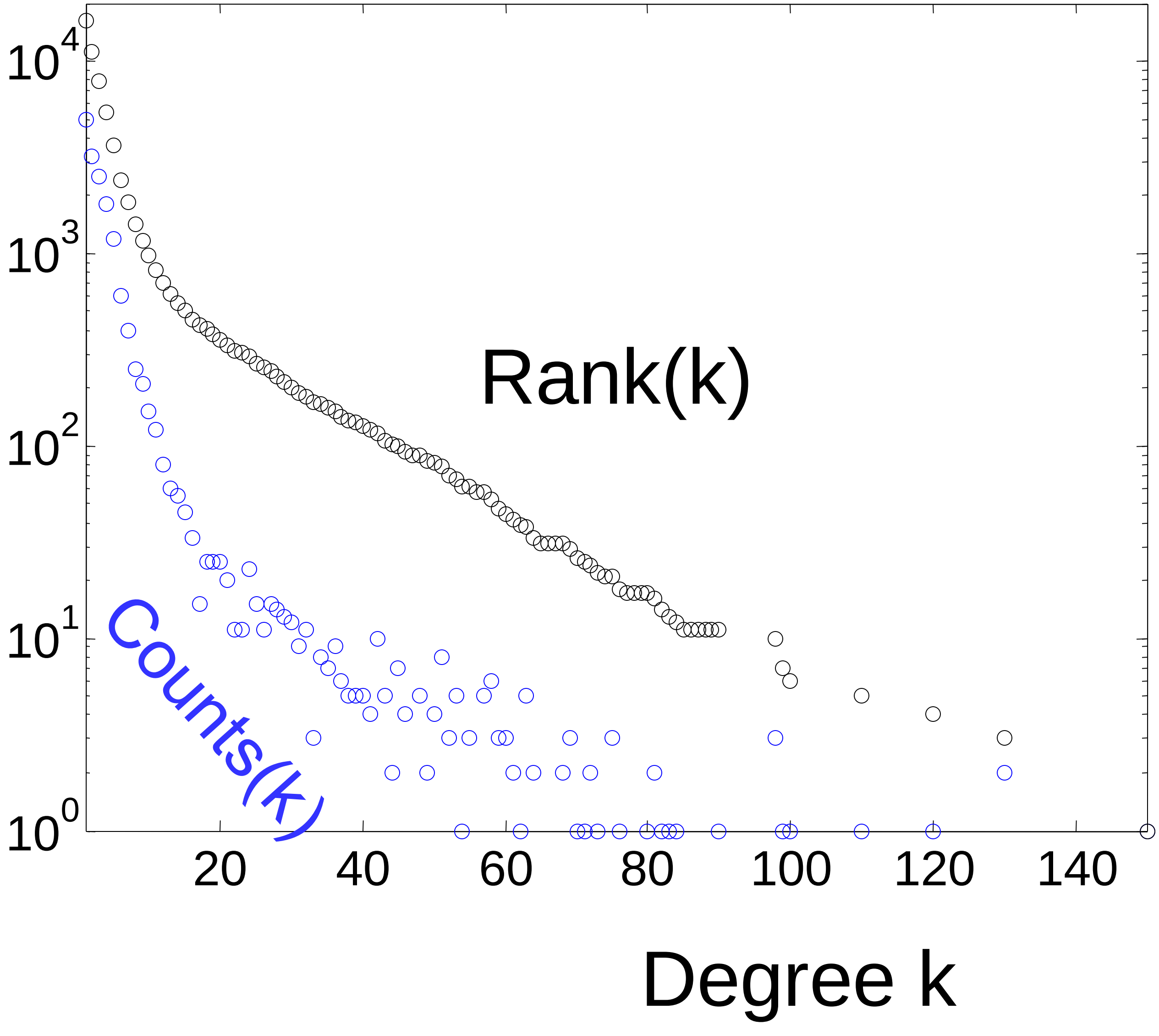
Experimental data

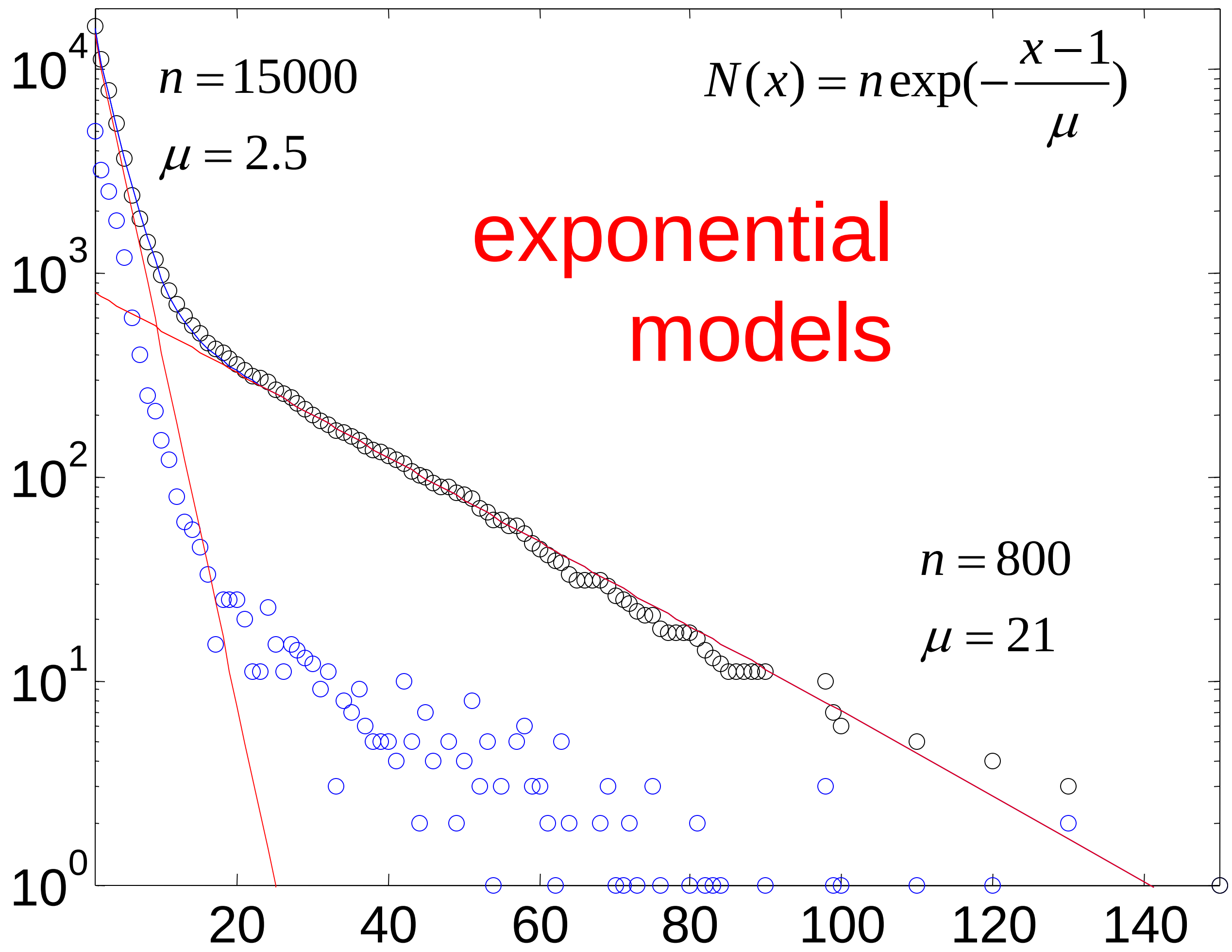


Experimental data



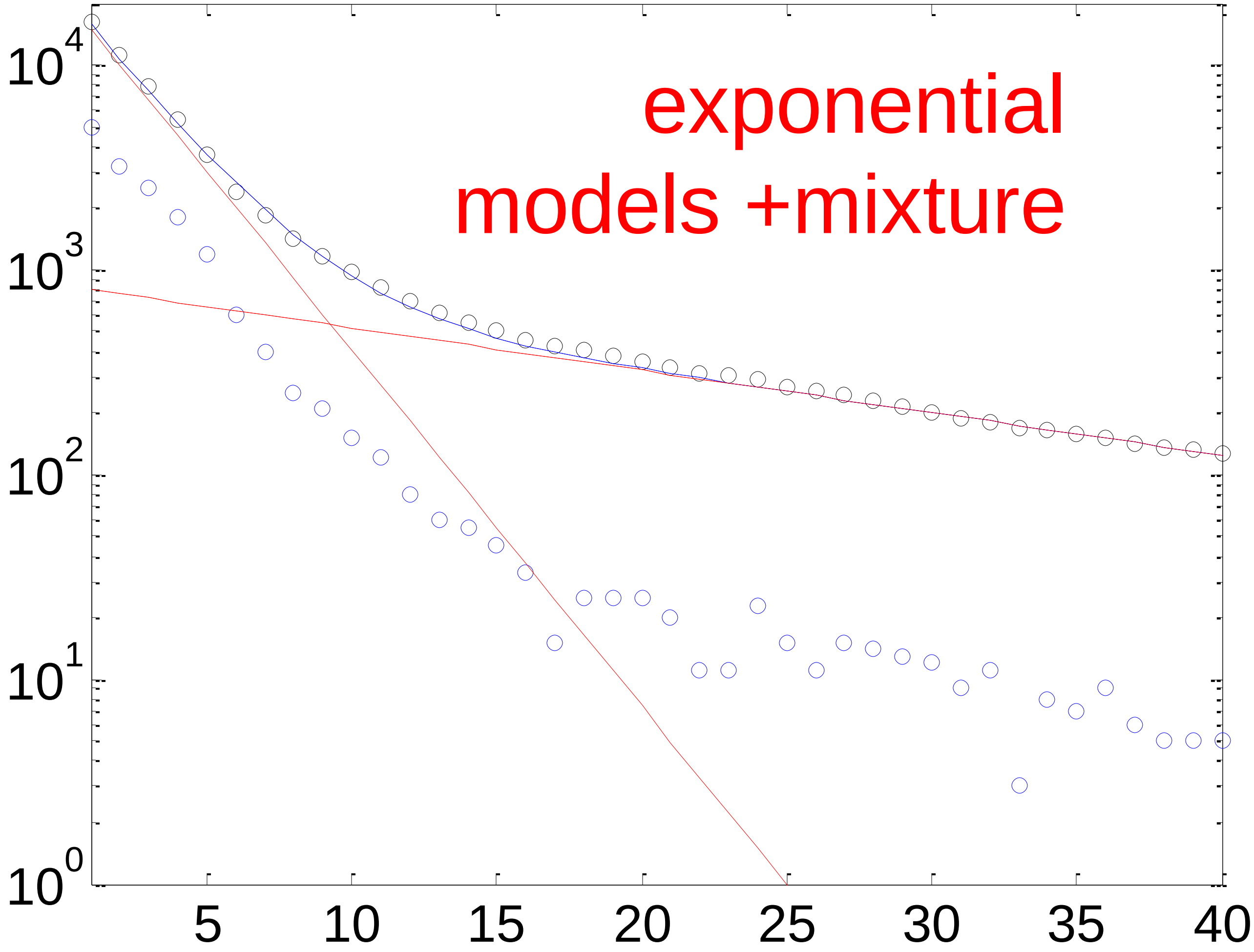
Experimental data





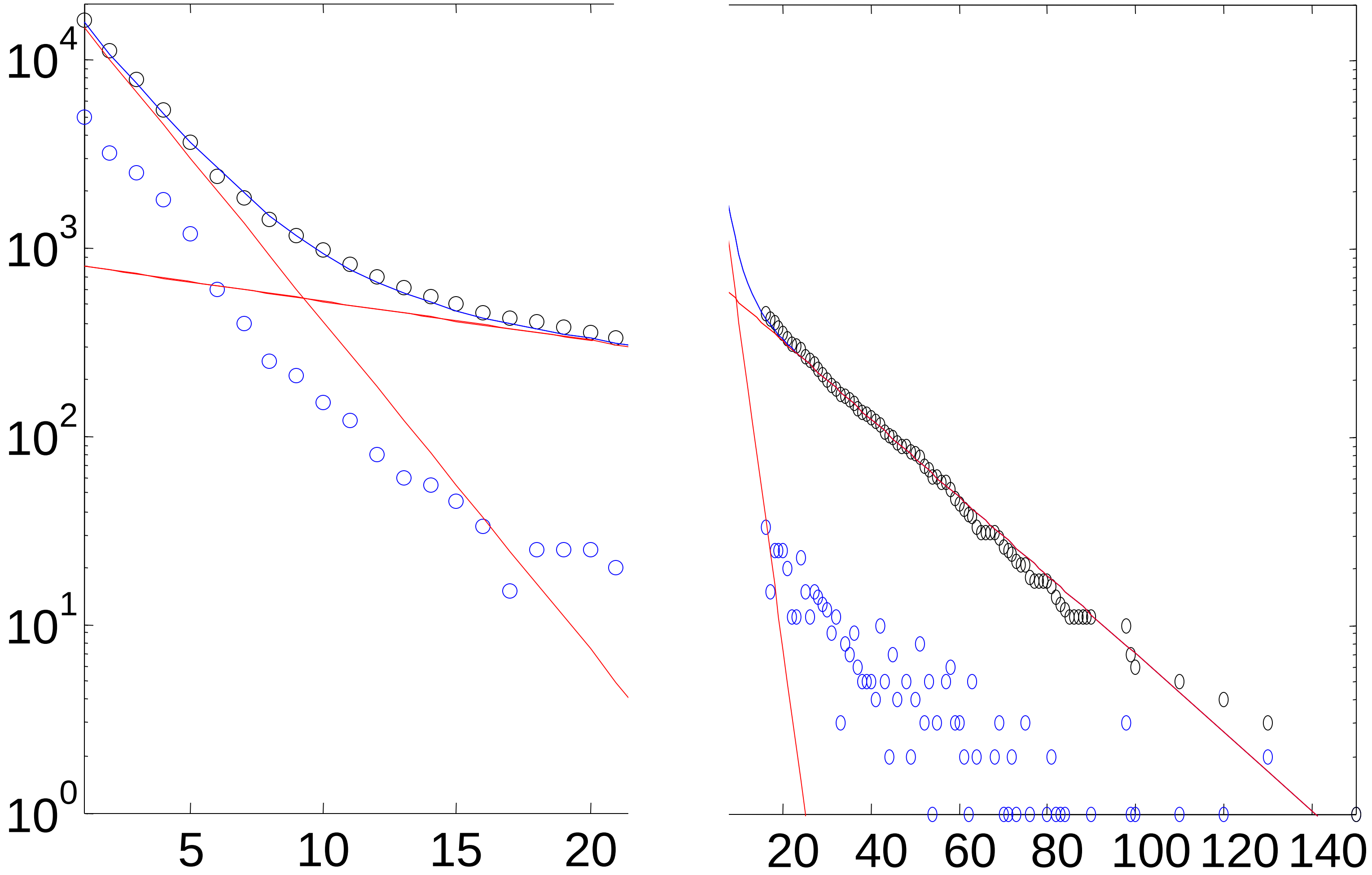
$n = 15000$
$\mu = 2.5$
$N(x) = n\exp(-\frac{x-1}{\mu})$
exponential
models
$n = 800$
$\mu = 21$
10^4
10^3
10^2
10^1
10^0
20
40
60
80
100
120
140

$$N(x) = N_1(x) + N_2(x)$$

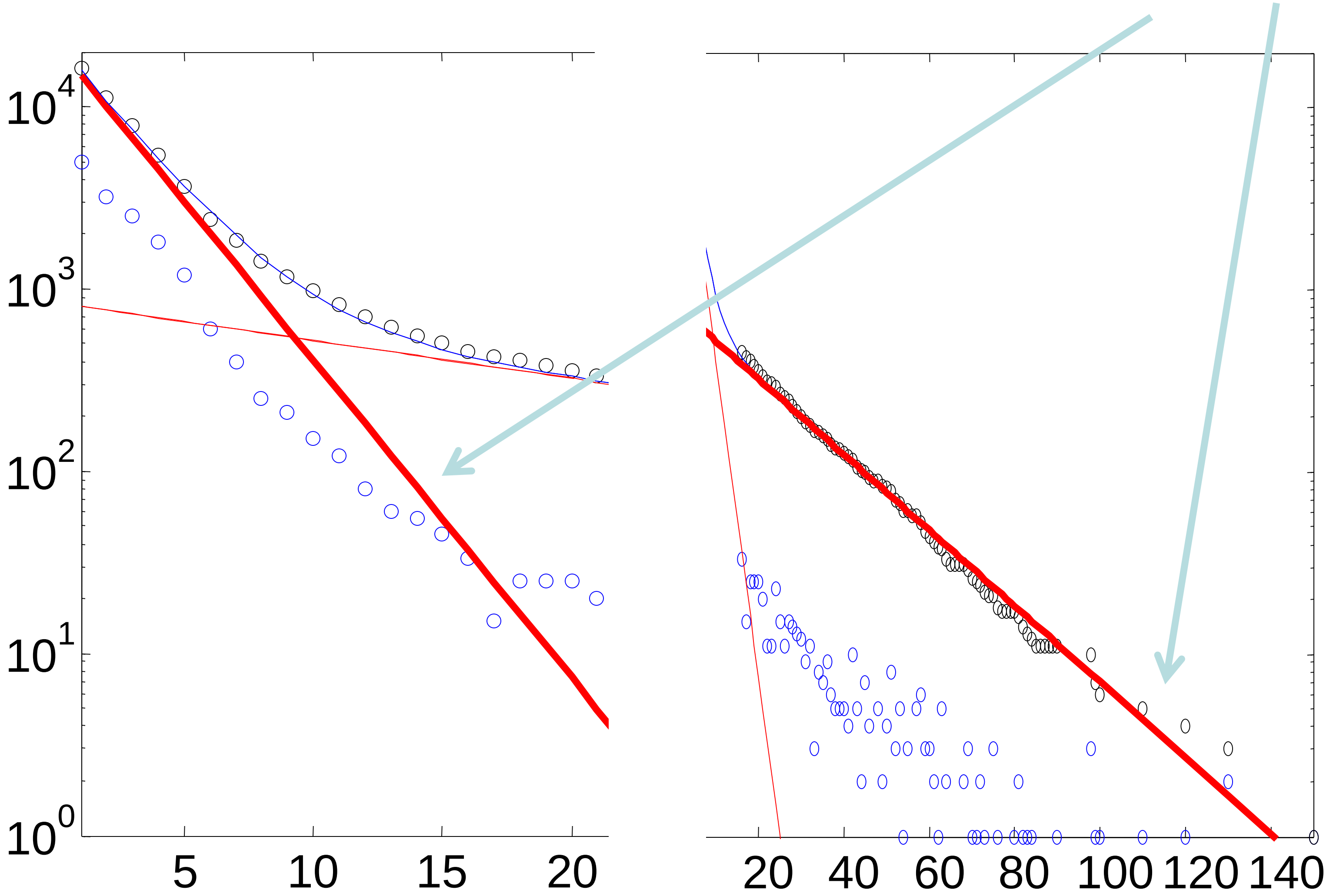


exponential
models +mixture
10^4
10^3
10^2
10^1
10^0
5
10
15
20
25
30
35
40

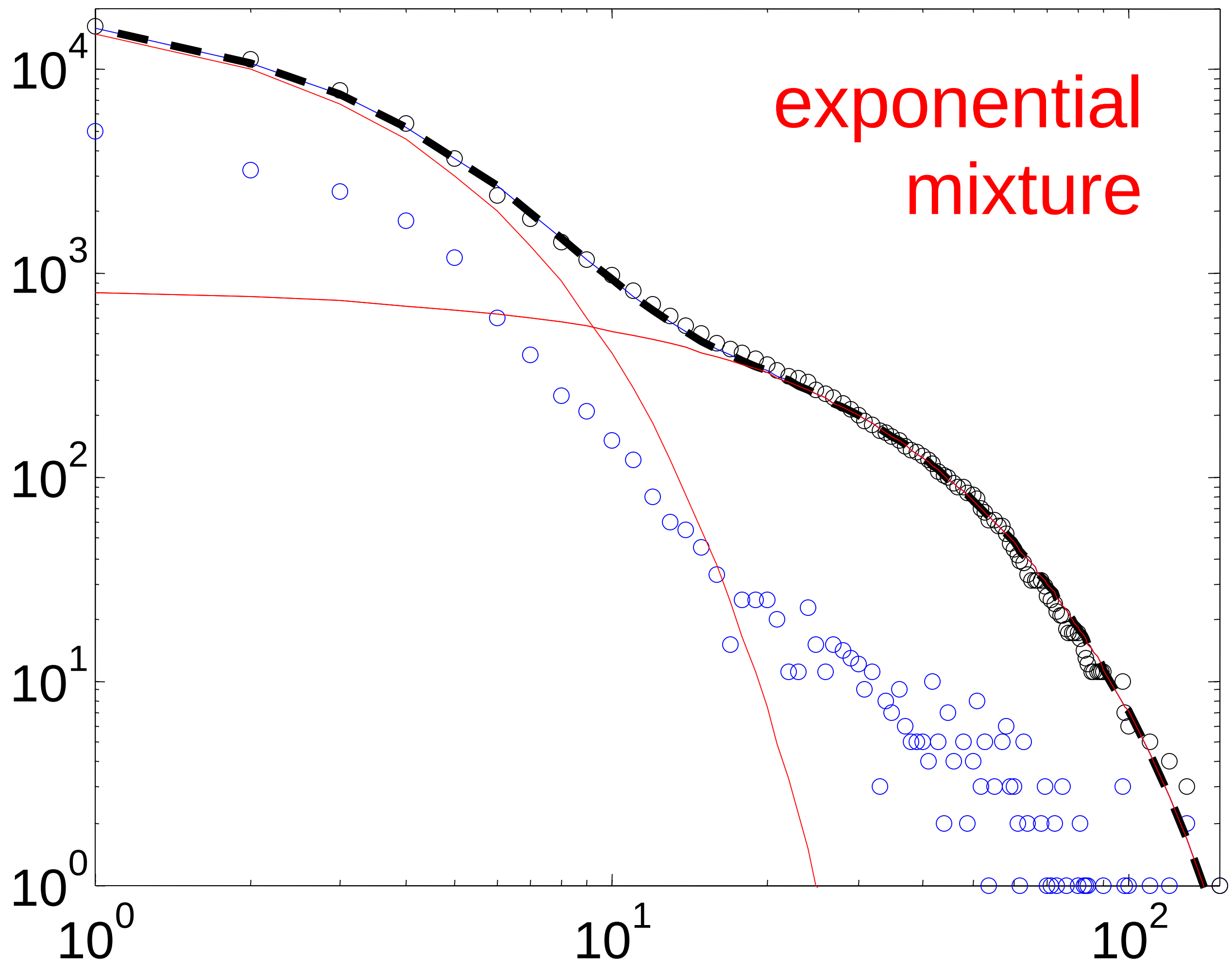
exponential models



The data appear to have two very distinct length scales. What does this correspond to physiologically?

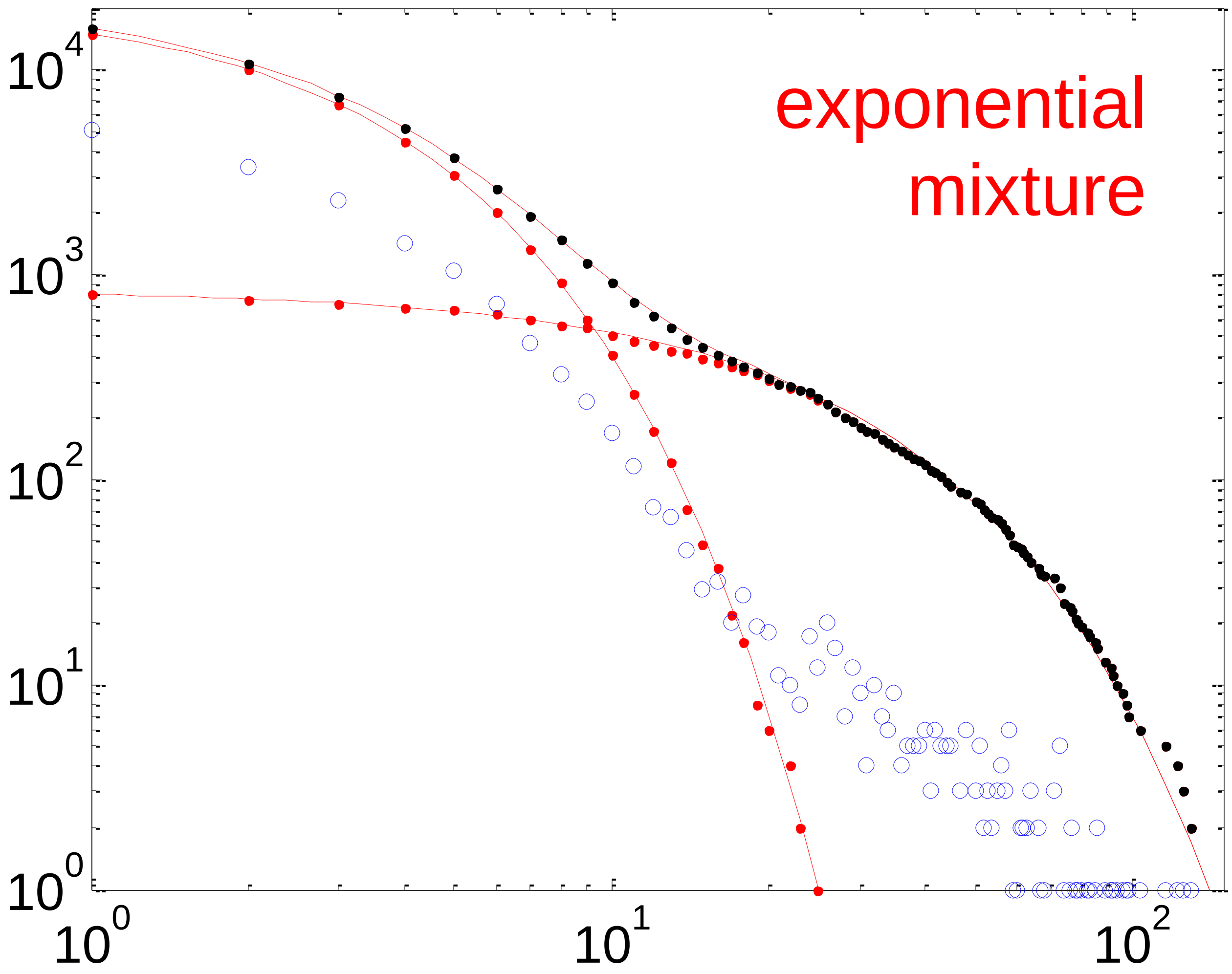


Plotted with different scales to highlight the different lengths.



exponential
mixture
10^4
10^3
10^2
10^1
10^0
10^0
10^1
10^2

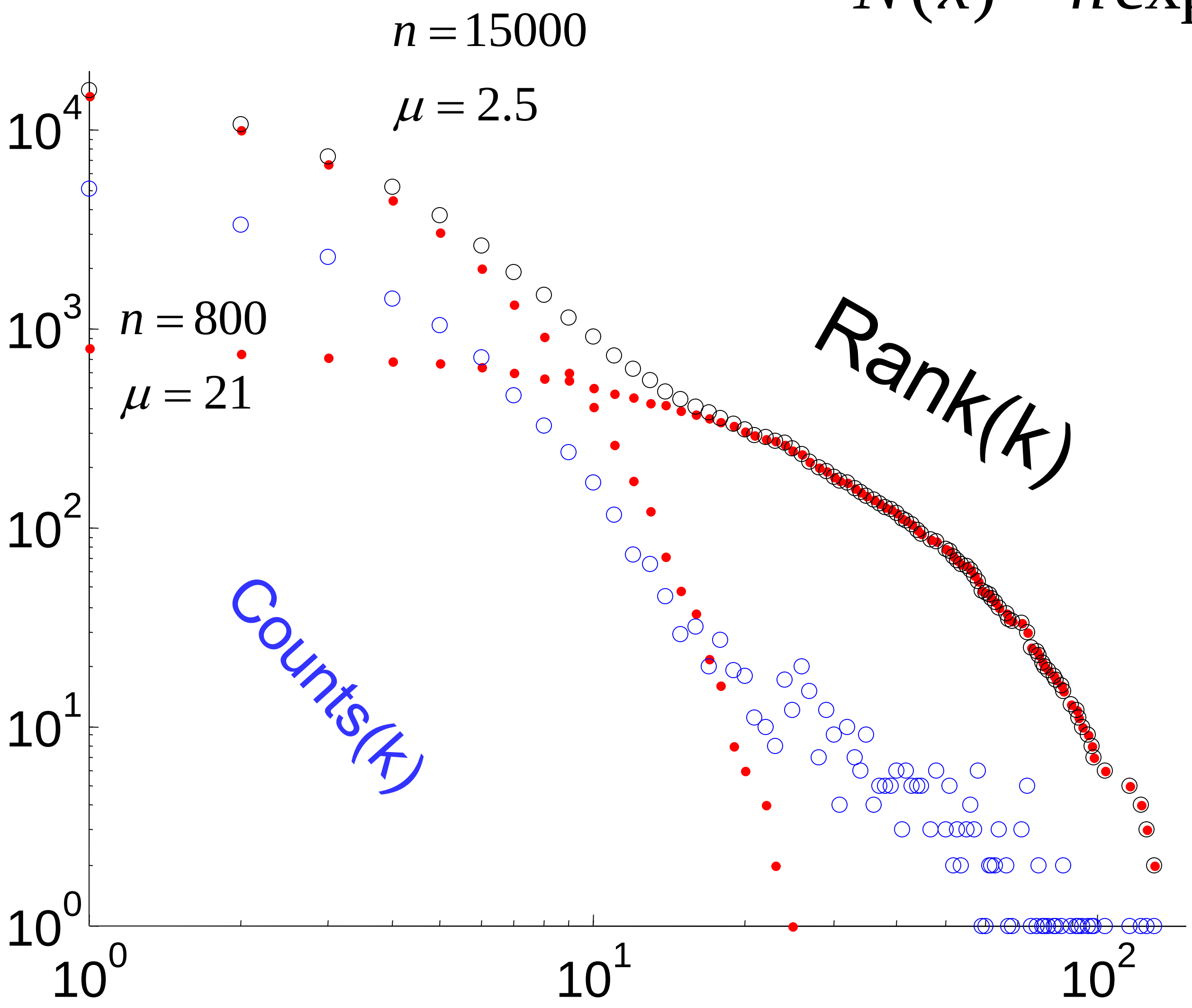
Simulated (pseudorandom) data



Simulated (pseudorandom) data

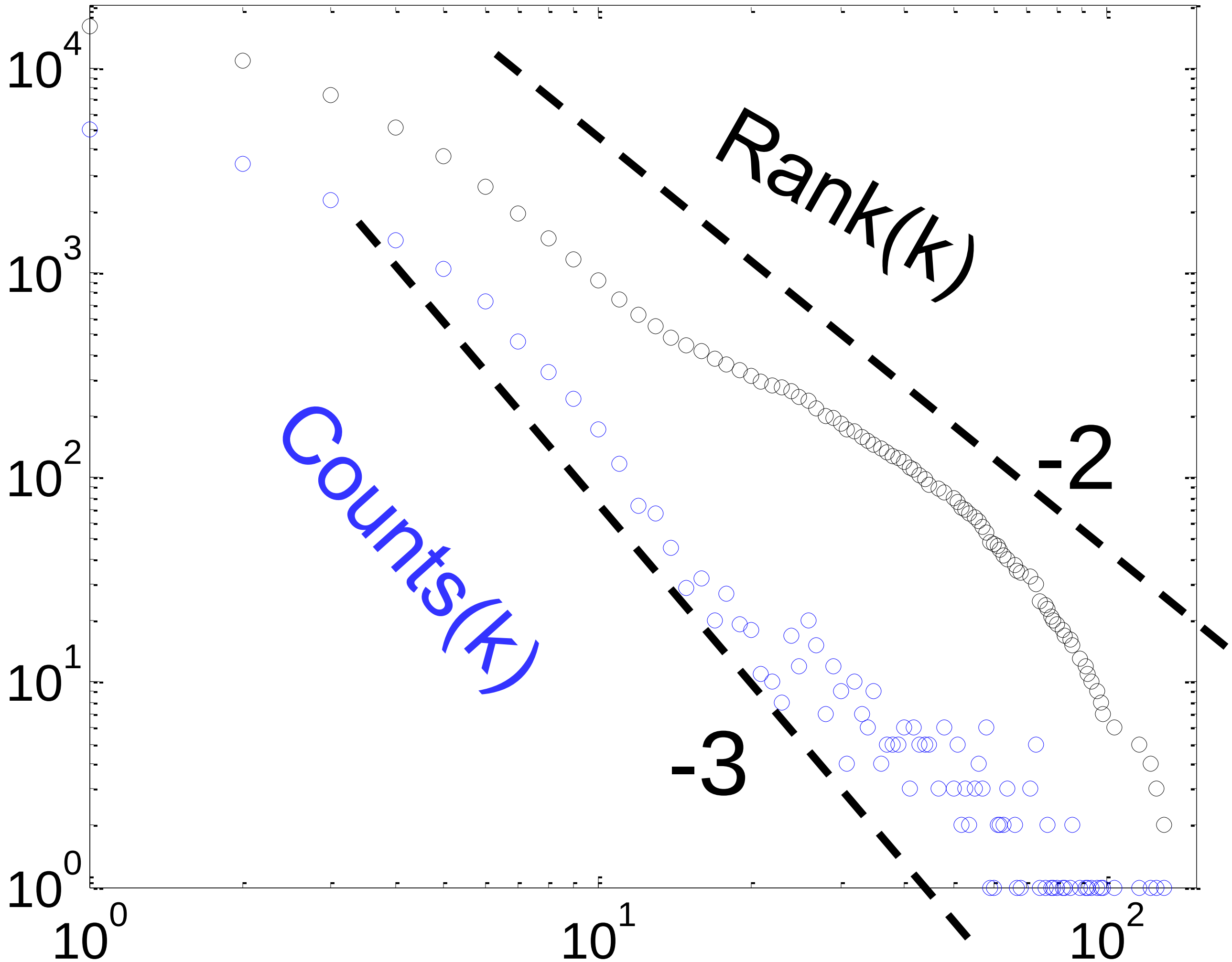
$$N(x) = n \exp(-\frac{x-1}{\mu})$$

exponential mixture



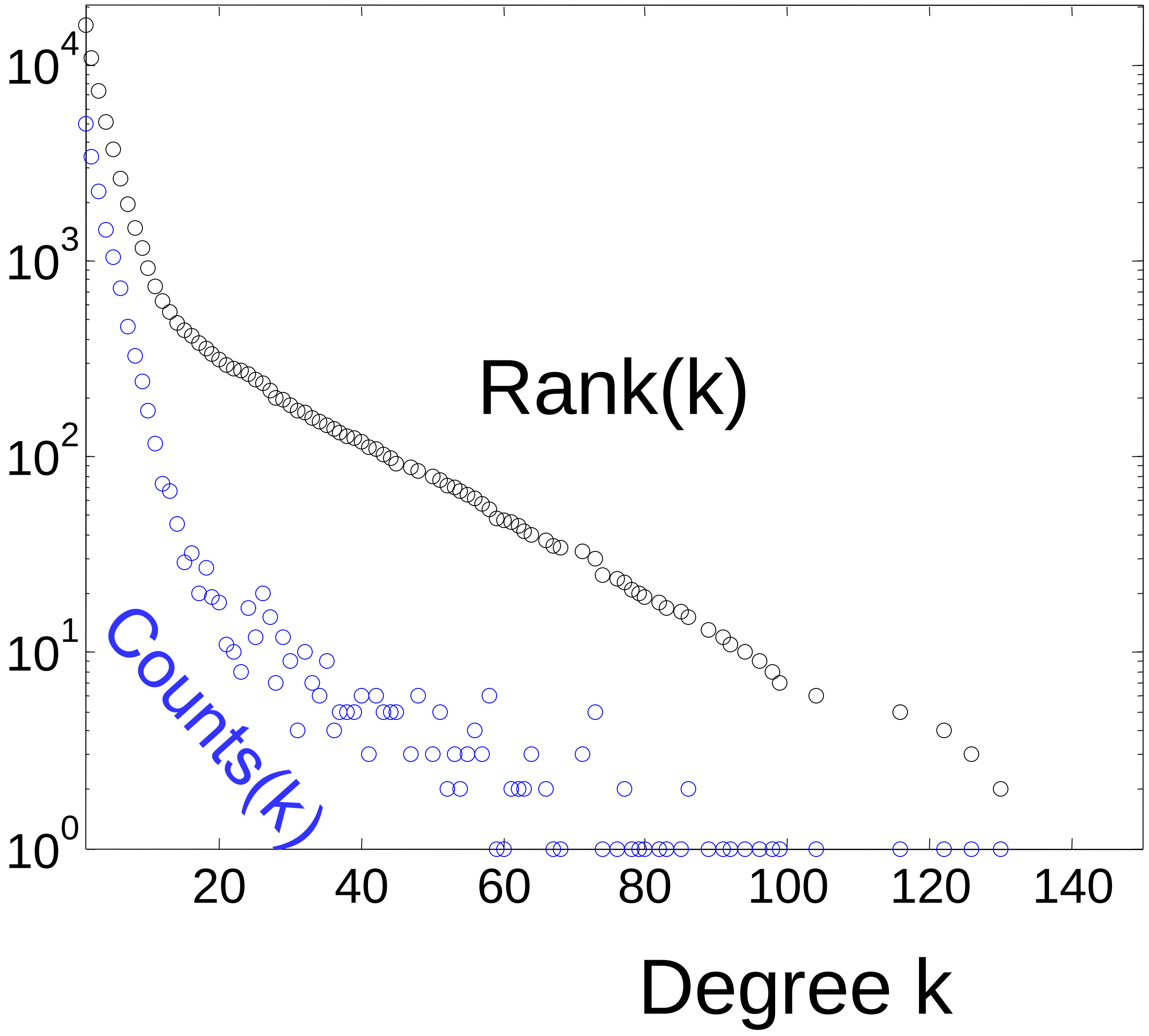
Simulated (pseudorandom) data

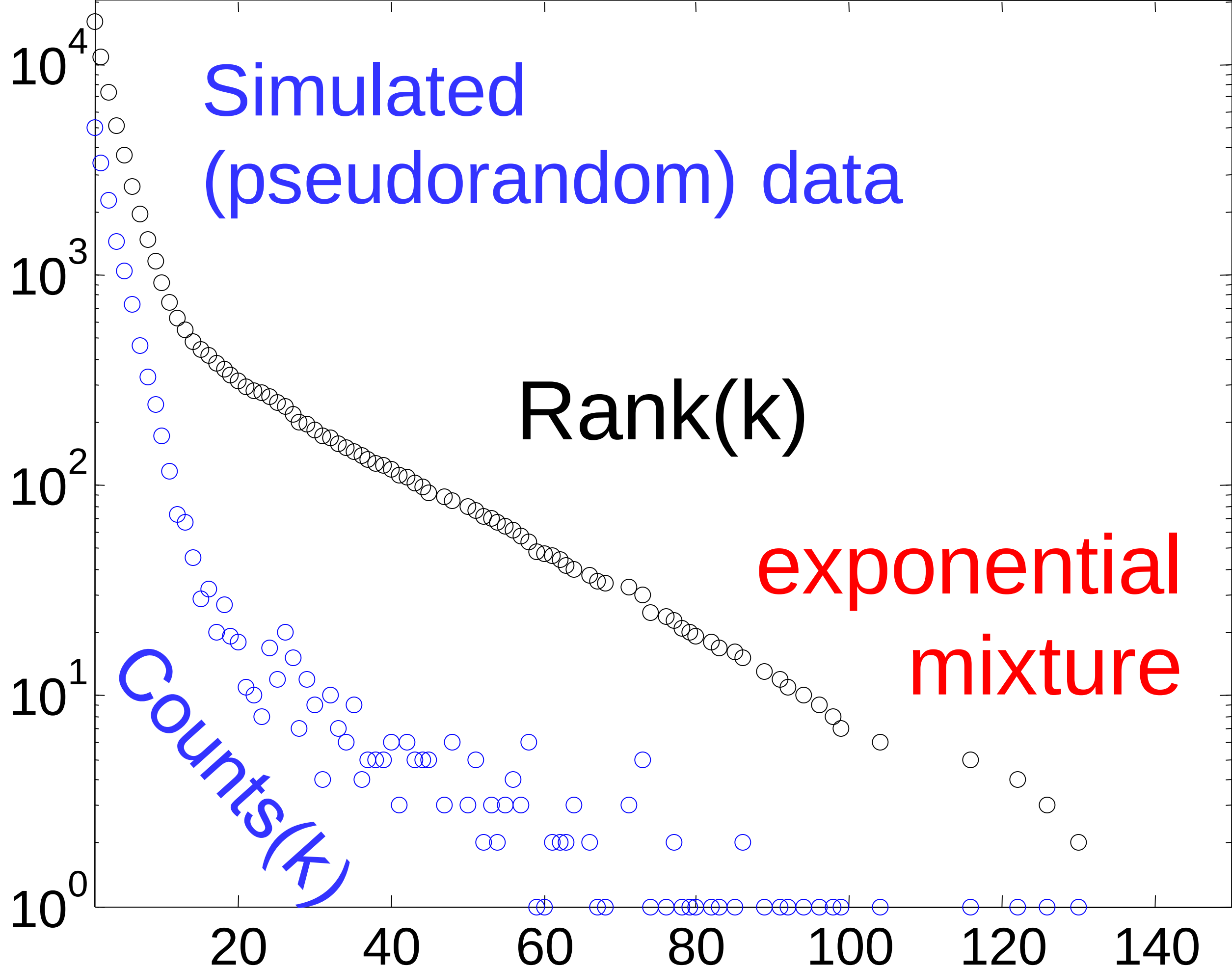
exponential mixture



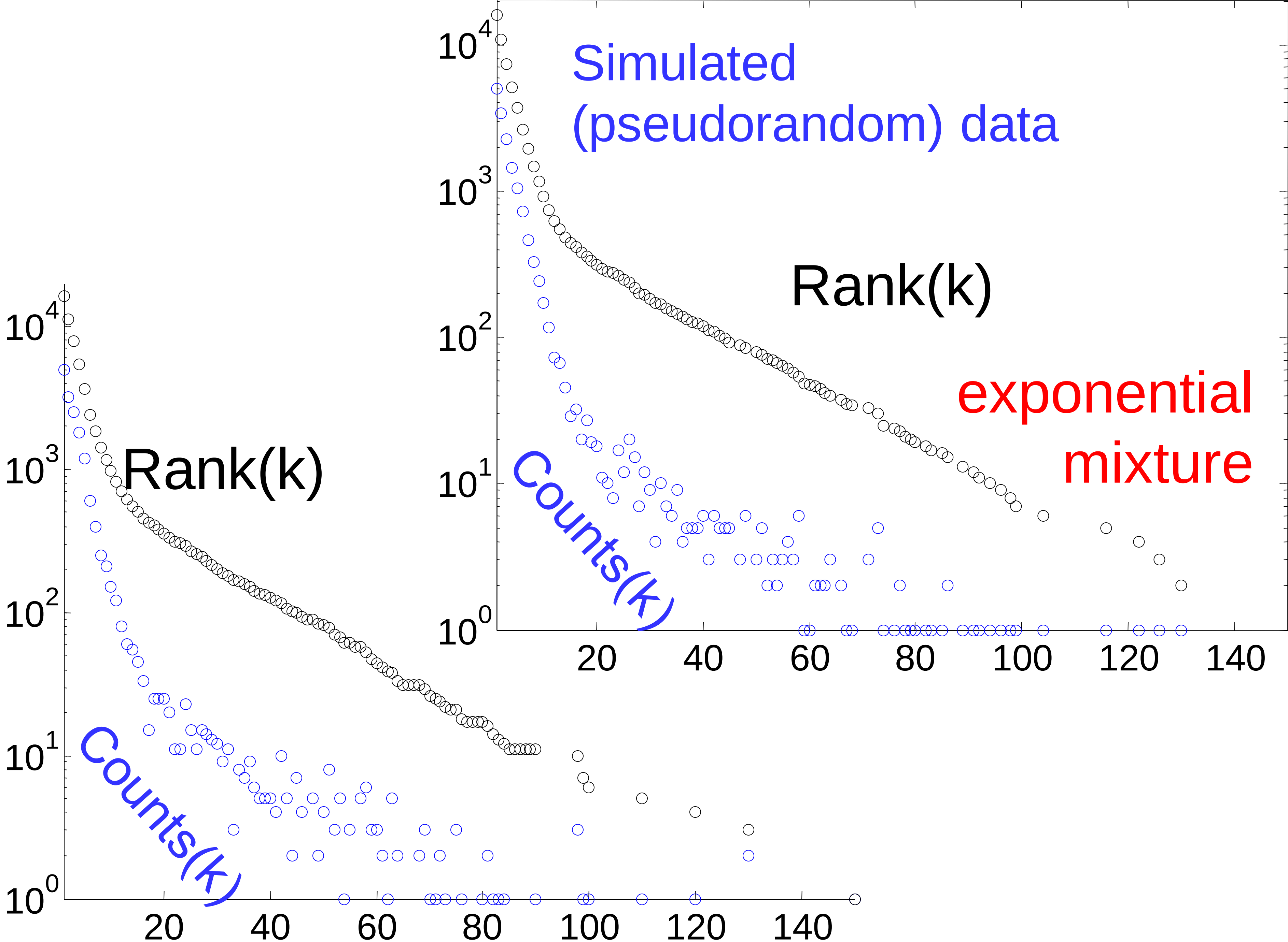
Simulated (pseudorandom) data

exponential mixture

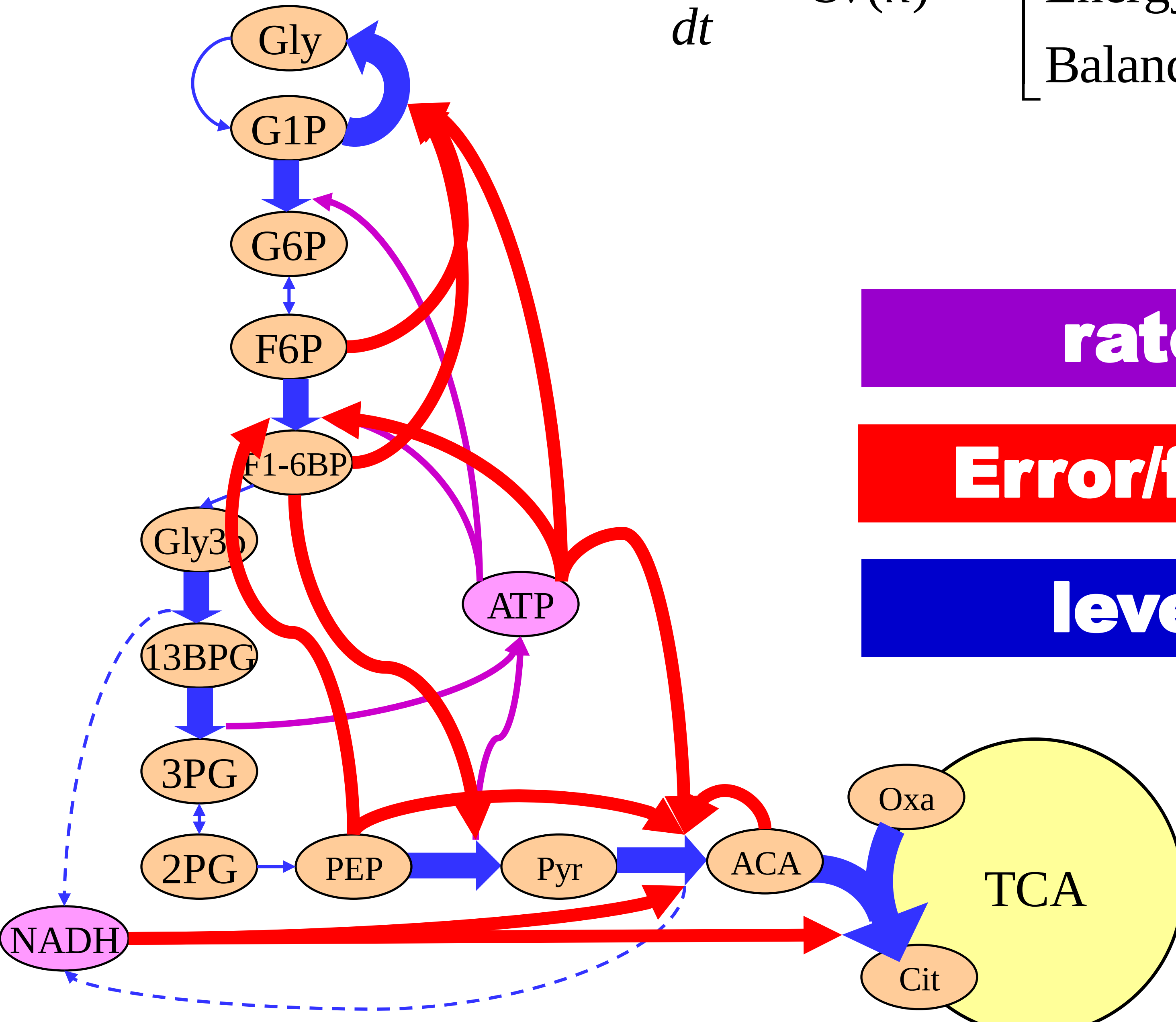




Compare with
Experimental
data


Simulated
(pseudorandom) data
Rank(k)
exponential
mixture
Counts(k)
Rank(k)
Counts(k)
10^4
10^3
10^2
10^1
10^0
20
40
60
80
100
120
140

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



rate

Error/flow

level

$$S \rightarrow P$$

Control/rate

Stoichiometry

$$S + E_2 \underset{1}{\leftrightarrow} SE_2 \underset{2}{\rightarrow} E_2 + P$$

Reaction rate

$$E_1 \underset{3}{\leftrightarrow} E_2$$

Enzyme form/activity

$$AA \underset{4}{\rightarrow} E_1$$

Enzyme level

$$\frac{d}{dt}\begin{bmatrix} S \\ P \\ SE_2 \\ E_2 \\ E_1 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ -1 & 1 & 1 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} \text{1. substrate binds to active enzyme} \\ \text{2. product released by enzyme} \\ \text{3. control enzyme form/activity} \\ \text{4. control enzyme level} \end{bmatrix}$$

$$S \rightarrow P$$

Stoichiometry | **Control/rate**

$$S + E_2 \underset{1}{\leftrightarrow} SE_2 \underset{2}{\rightarrow} E_2 + P$$

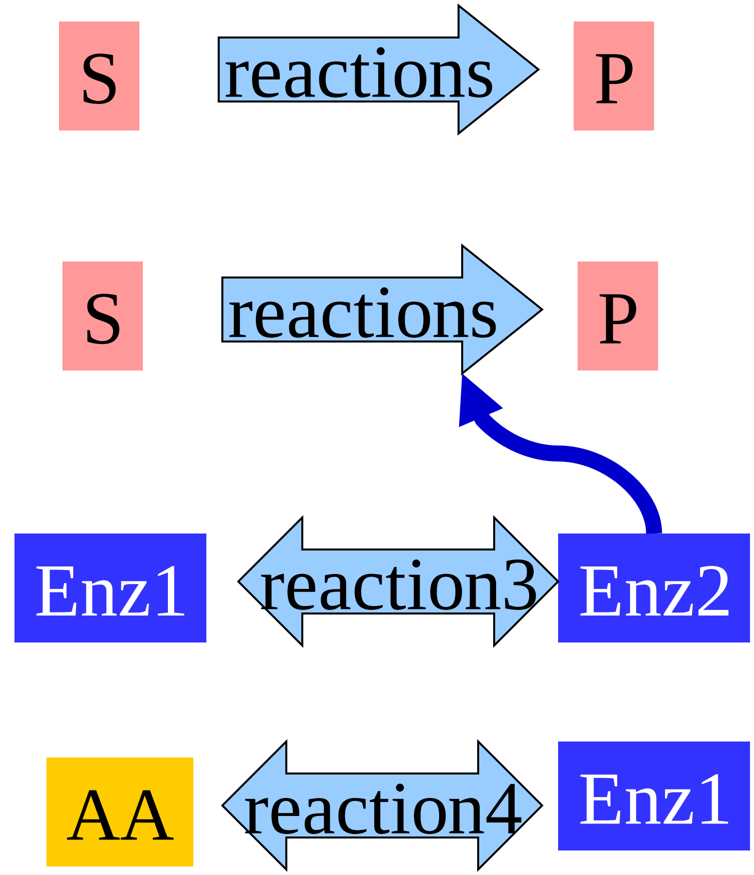
Reaction rate

$$E_1 \underset{3}{\leftrightarrow} E_2$$

Enzyme form/activity

$$AA \underset{4}{\rightarrow} E_1$$

Enzyme level



$$\frac{d}{dt}\begin{bmatrix} S \\ P \\ SE_2 \\ E_2 \\ E_1 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ -1 & 1 & 1 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} \text{1. substrate binds to active enzyme} \\ \text{2. product released by enzyme} \\ \text{3. control enzyme form/activity} \\ \text{4. control enzyme level} \end{bmatrix}$$

$$S \rightarrow P$$

main reaction (fast)

$$S + E_2 \underset{1}{\leftrightarrow} SE_2 \underset{2}{\rightarrow} E_2 + P$$

includes the enzymes (very fast)

$$E_1 \underset{3}{\leftrightarrow} E_2$$

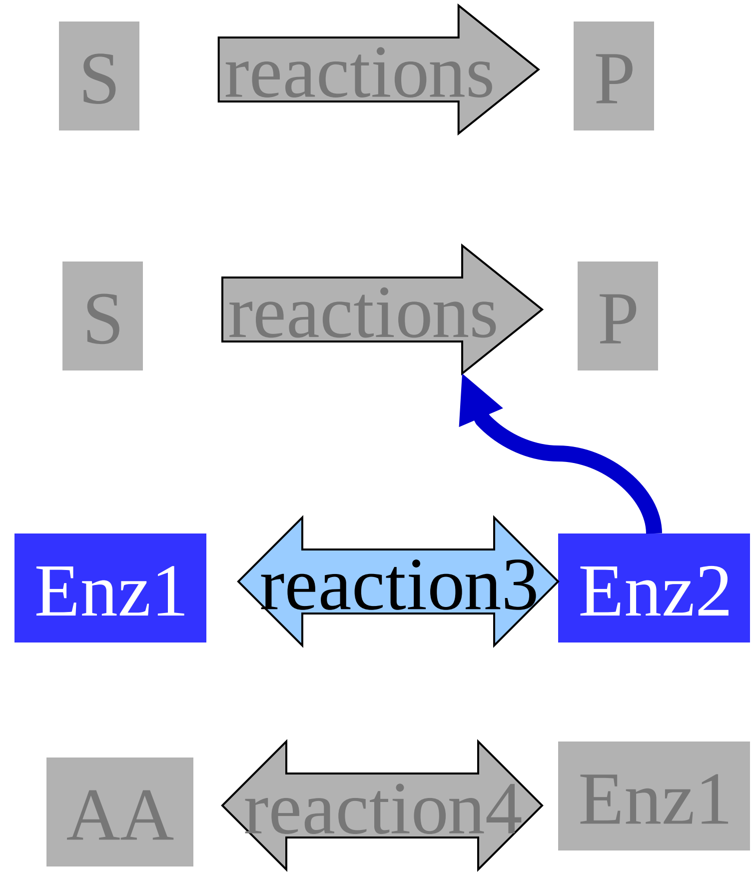
Control of enzyme form/activity (fast)

$$AA \underset{4}{\rightarrow} E_1$$

Control of enzyme level (slow)

$$\frac{d}{dt}\begin{bmatrix} S \\ P \\ SE_2 \\ E_2 \\ E_1 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ -1 & 1 & 1 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} \text{1. substrate binds to active enzyme} \\ \text{2. product released by enzyme} \\ \text{3. control enzyme form/activity} \\ \text{4. control enzyme level (very slow)} \end{bmatrix}$$

The actual complexity of this part dwarfs the complexity of all other parts in this layer.



$$E_1 \underset{3}{\leftrightarrow} E_2$$

Enzyme form/activity

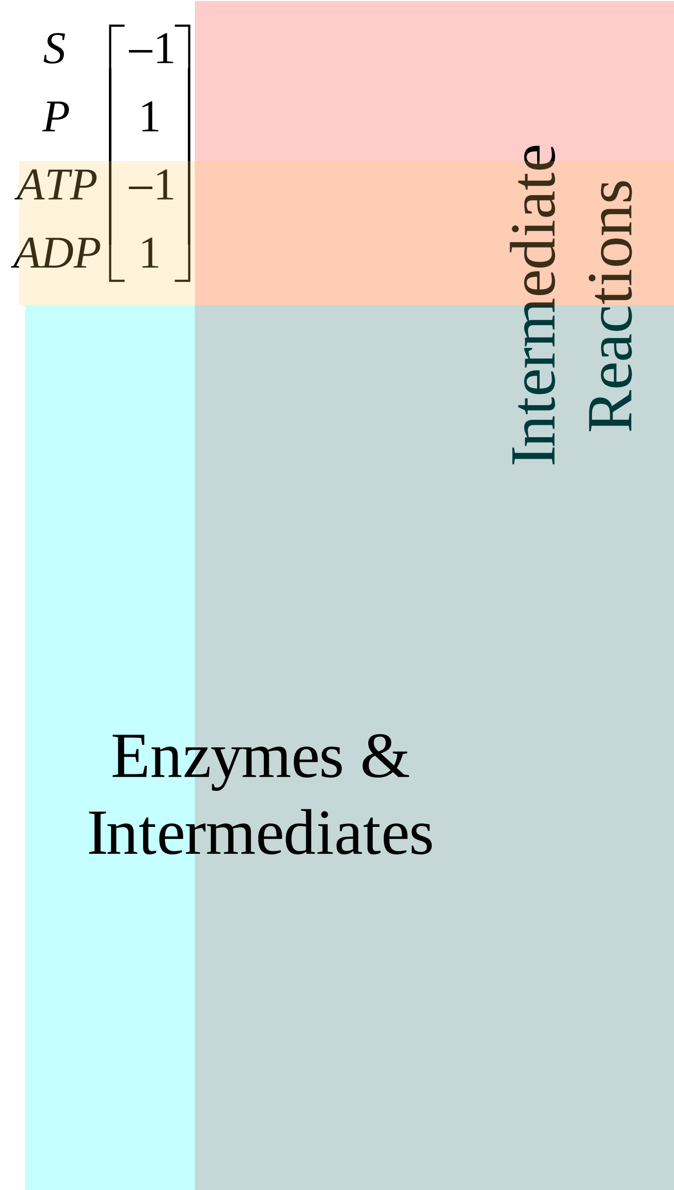
This is too simple, but at least shows the sublayer where enzyme form and activity is controlled.

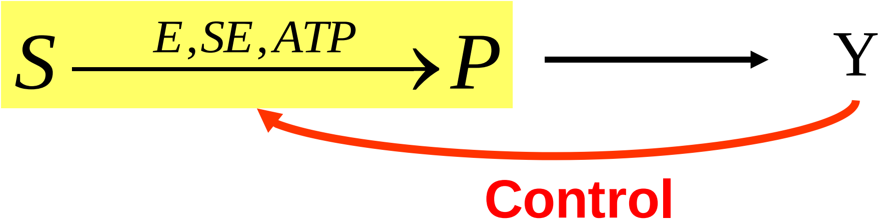
$$\frac{d}{dt}\begin{bmatrix} S \\ P \\ SE_2 \\ E_2 \\ E_1 \end{bmatrix} = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ -1 & 1 & 1 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} \text{1. substrate binds to active enzyme} \\ \text{2. product released by enzyme} \\ \text{3. control enzyme form/activity} \\ \text{4. control enzyme level} \end{bmatrix}$$

$$S \xrightarrow{E,SE,ATP} P$$

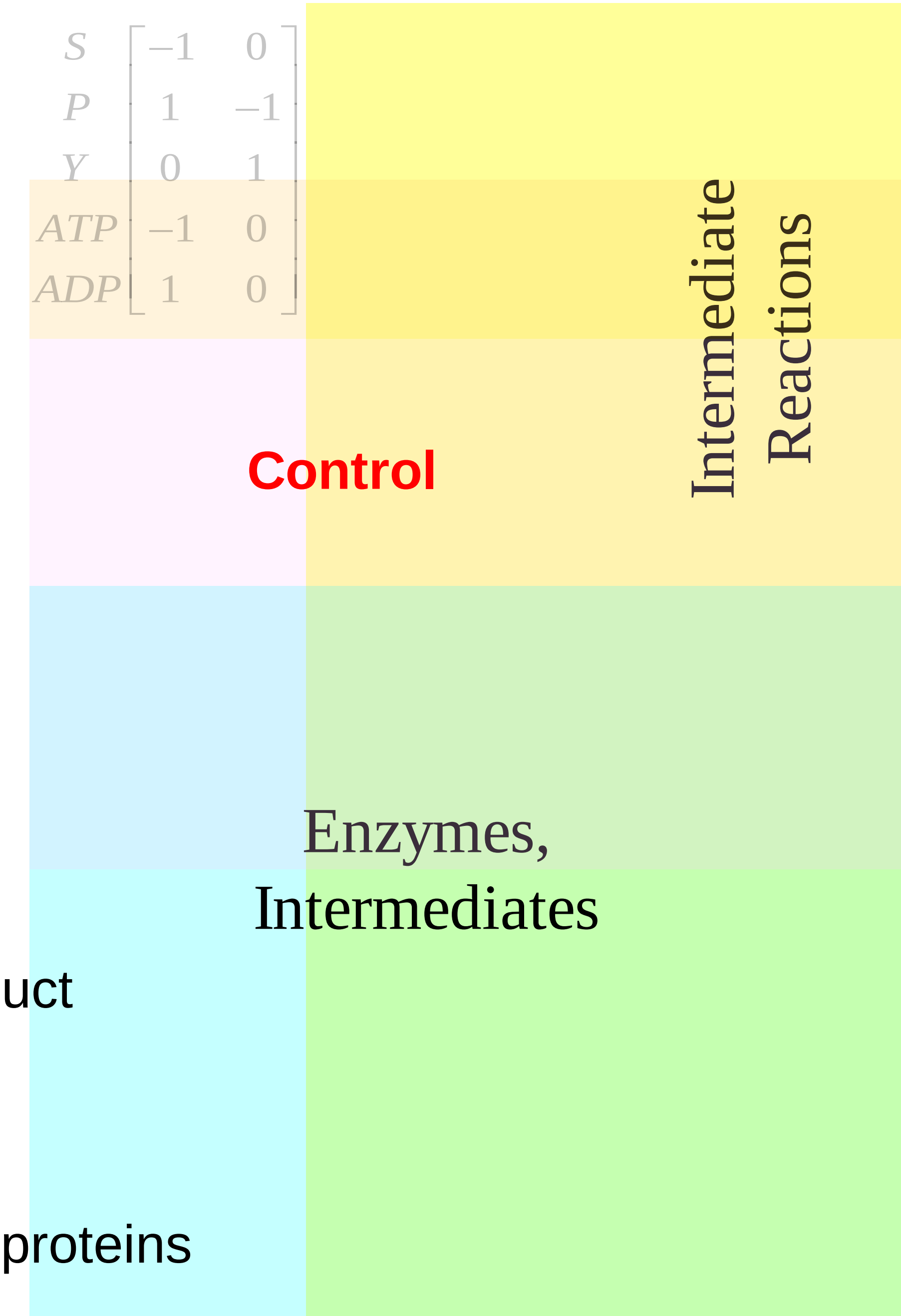
$$S + ATP \xrightarrow{E,ES} P + ADP$$

In general, there is a combinatorial explosion of “intermediates”





Control gives even more combinatorial explosion of “intermediates”



Enzyme form/activity controlled by

- concentration of substrate and product
- concentrations of other metabolites
- interaction with other proteins
- covalent modification
- membership in complexes of many proteins

$$S \xrightarrow{E,SE,ATP} P \longrightarrow Y$$

$$\begin{array}{c} S \\ P \\ Y \\ ATP \\ ADP \end{array} \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \\ -1 & 0 \\ 1 & 0 \end{bmatrix}$$

Any "modularity" and complexity here

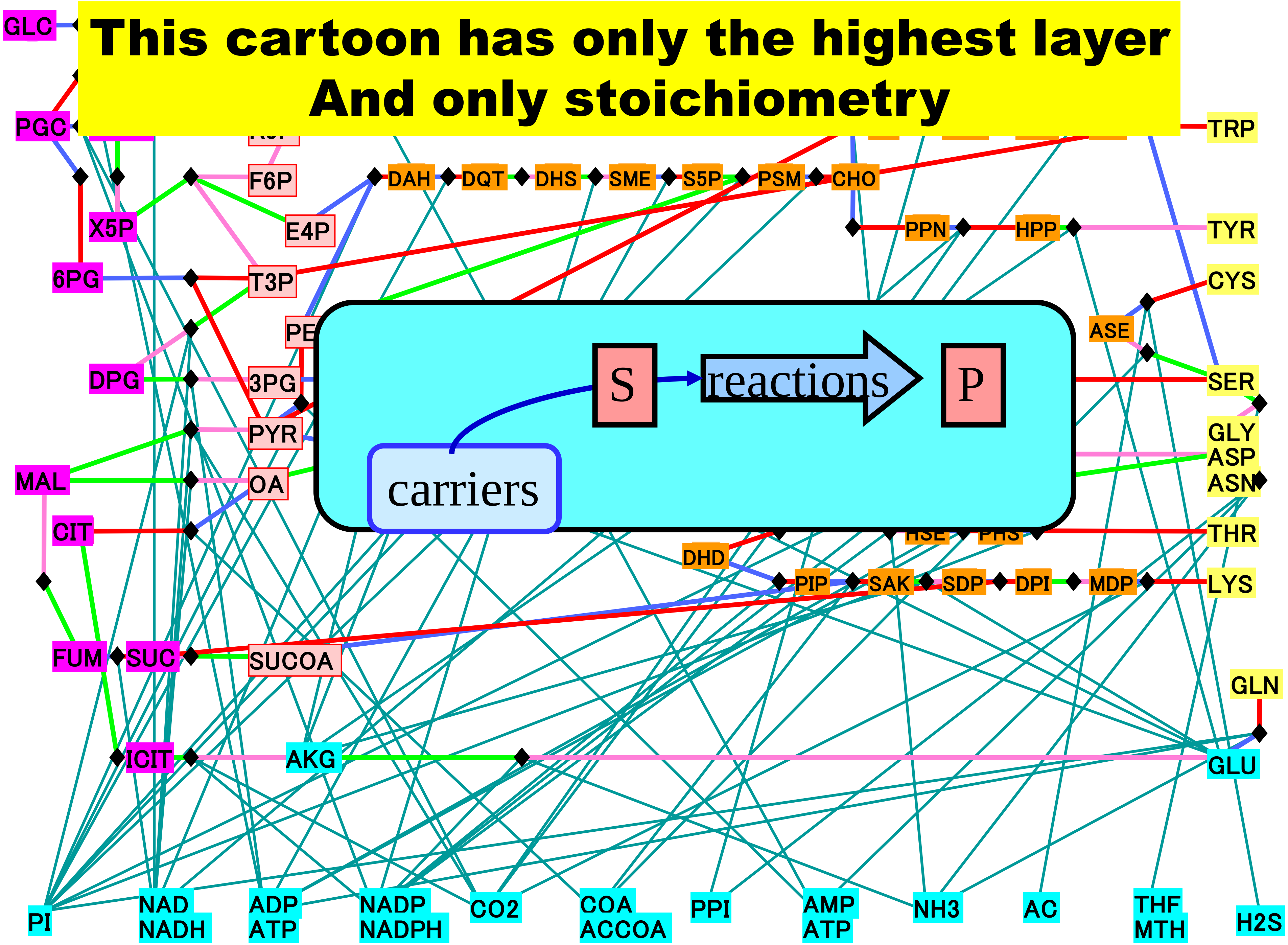
Is almost trivial compared to what exists here.

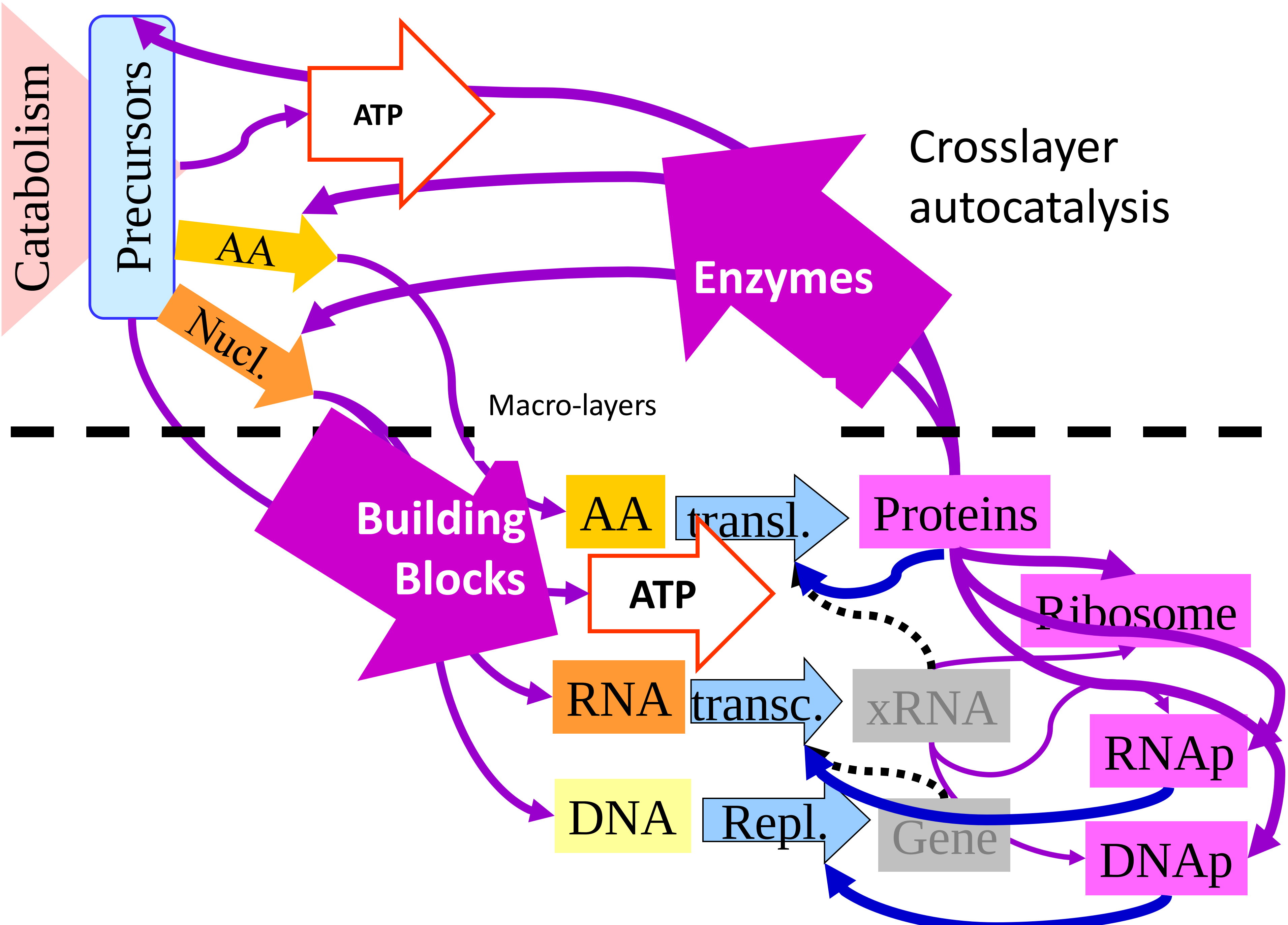
Intermediate Reactions

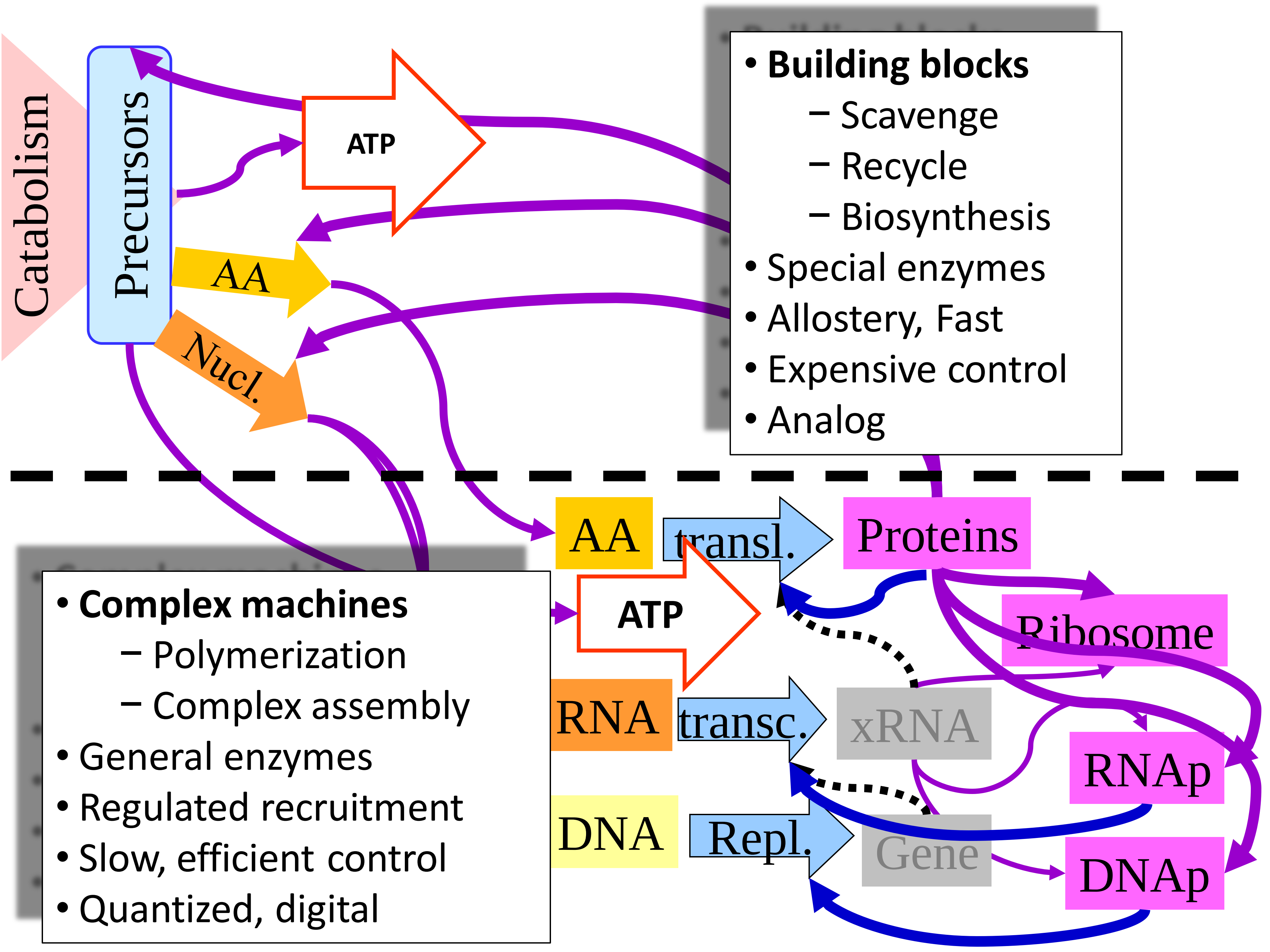
Control

Enzymes, Intermediates

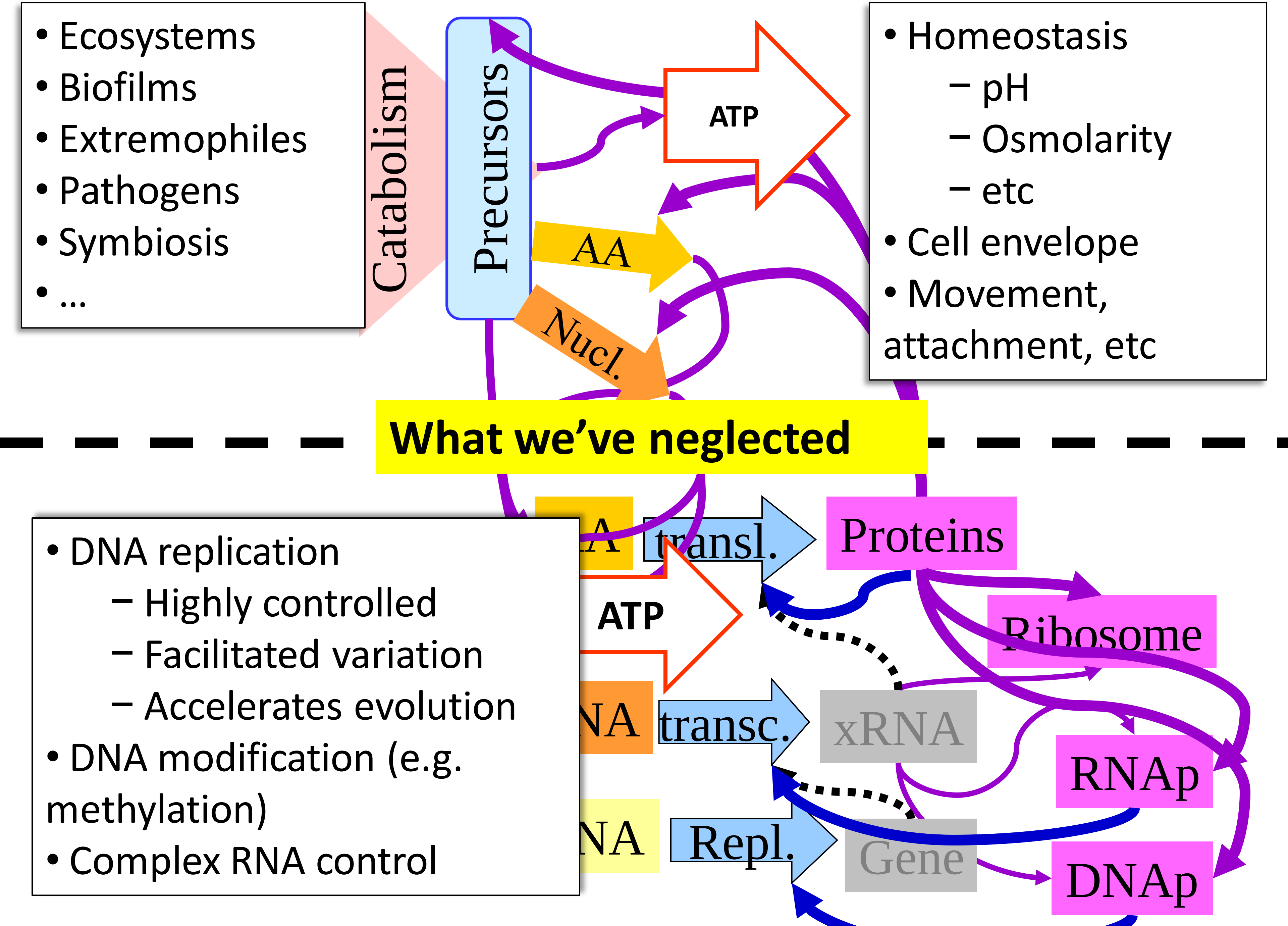
This cartoon has only the highest layer
And only stoichiometry




Catabolism
Precursors
ATP
AA
Nucl.
Crosslayer
autocatalysis
Enzymes
Macro-layers
Building
Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp

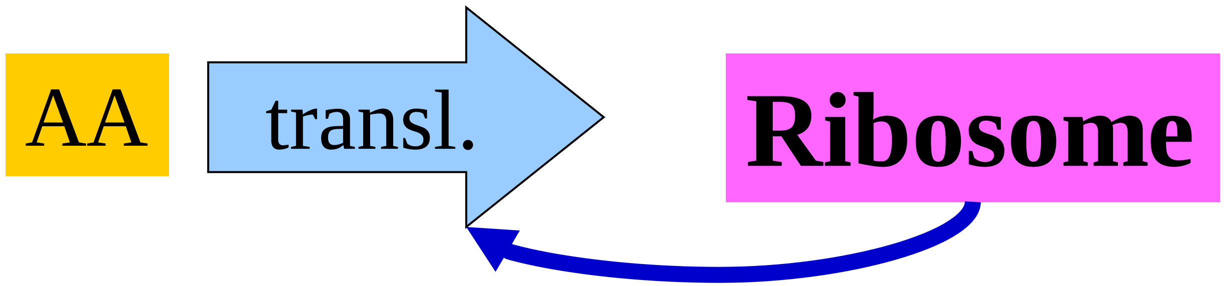


Catabolism
Precursors
ATP
AA
Nucl.
• Building blocks
– Scavenge
– Recycle
– Biosynthesis
• Special enzymes
• Allostery, Fast
• Expensive control
• Analog
• Complex machines
– Polymerization
– Complex assembly
• General enzymes
• Regulated recruitment
• Slow, efficient control
• Quantized, digital
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp


• Ecosystems
• Biofilms
• Extremophiles
• Pathogens
• Symbiosis
• …
Catabolism
Precursors
ATP
AA
Nucl.
• Homeostasis
– pH
– Osmolarity
– etc
• Cell envelope
• Movement, attachment, etc
What we've neglected
• DNA replication
– Highly controlled
– Facilitated variation
– Accelerates evolution
• DNA modification (e.g. methylation)
• Complex RNA control
ATP
transl.
Proteins
Ribosome
transc.
xRNA
RNAp
Repl.
Gene
DNAp

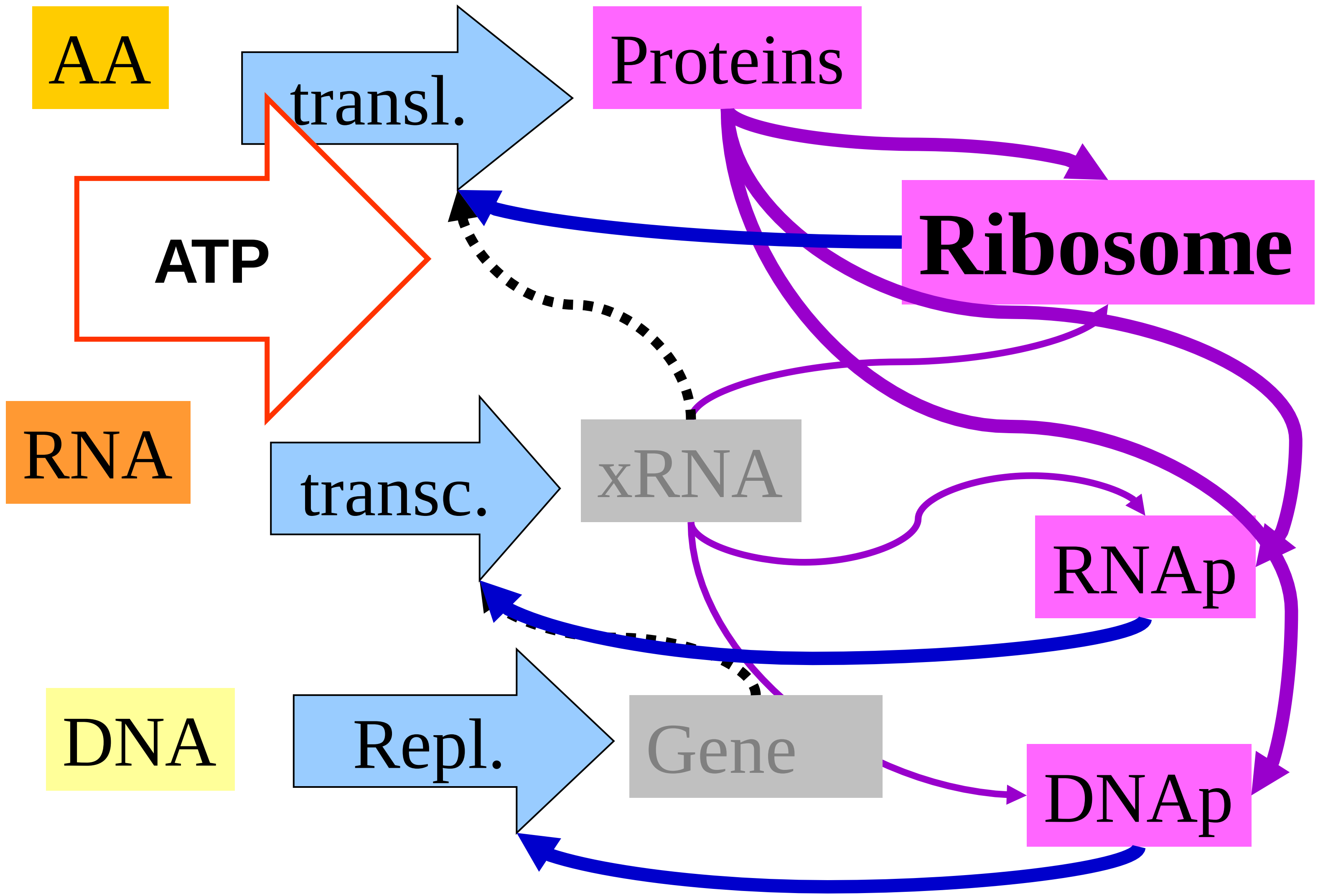
Lower layer autocatalysis

Ribosomes making ribosomes



Lower layer autocatalysis

Macromolecules making …



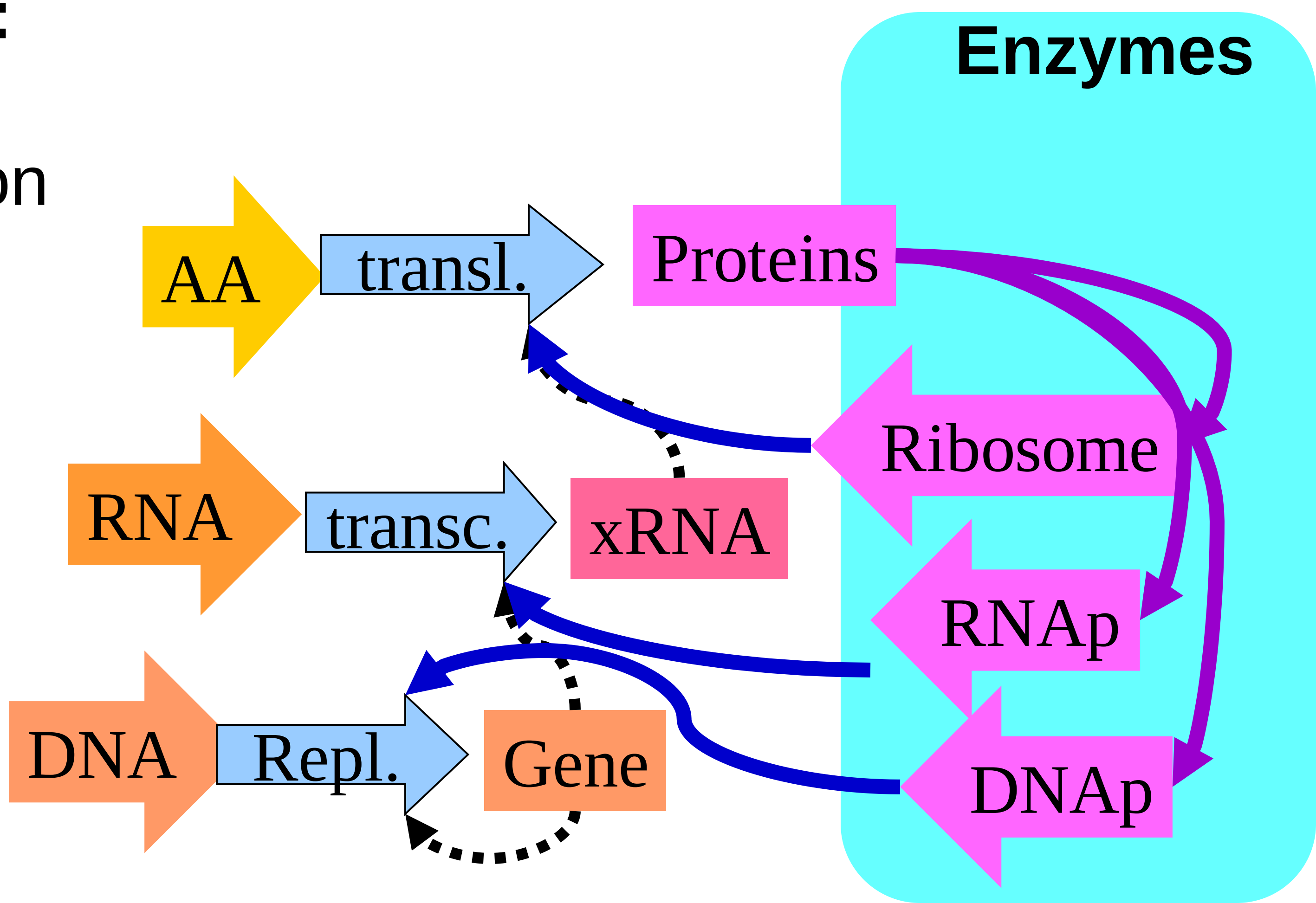
Autocatalytic within lower layers

- Collectively self-replicating
- Ribosomes make ribosomes, etc

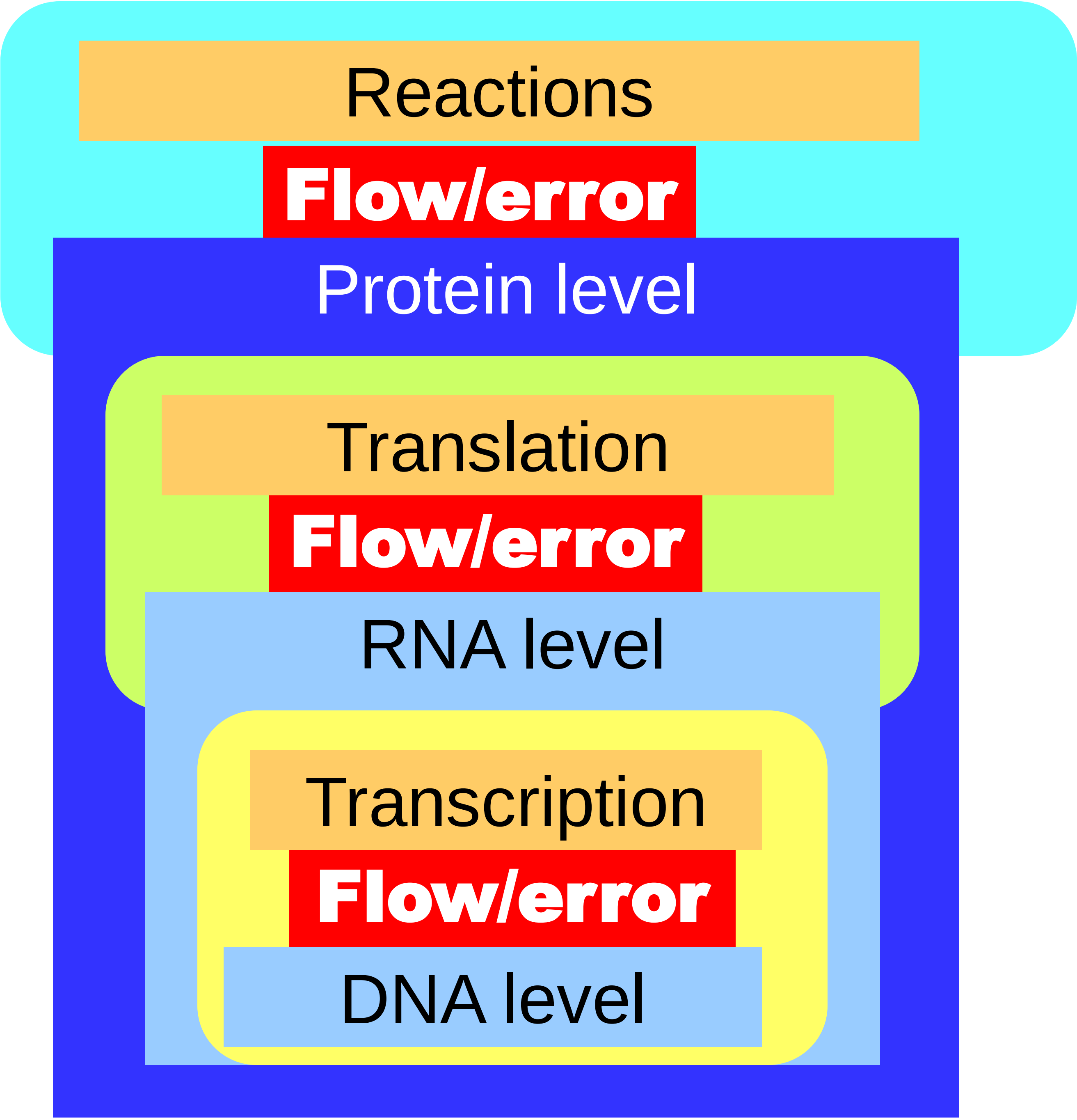
Three lower layers? Yes:

- Translation
- Transcription
- Replication

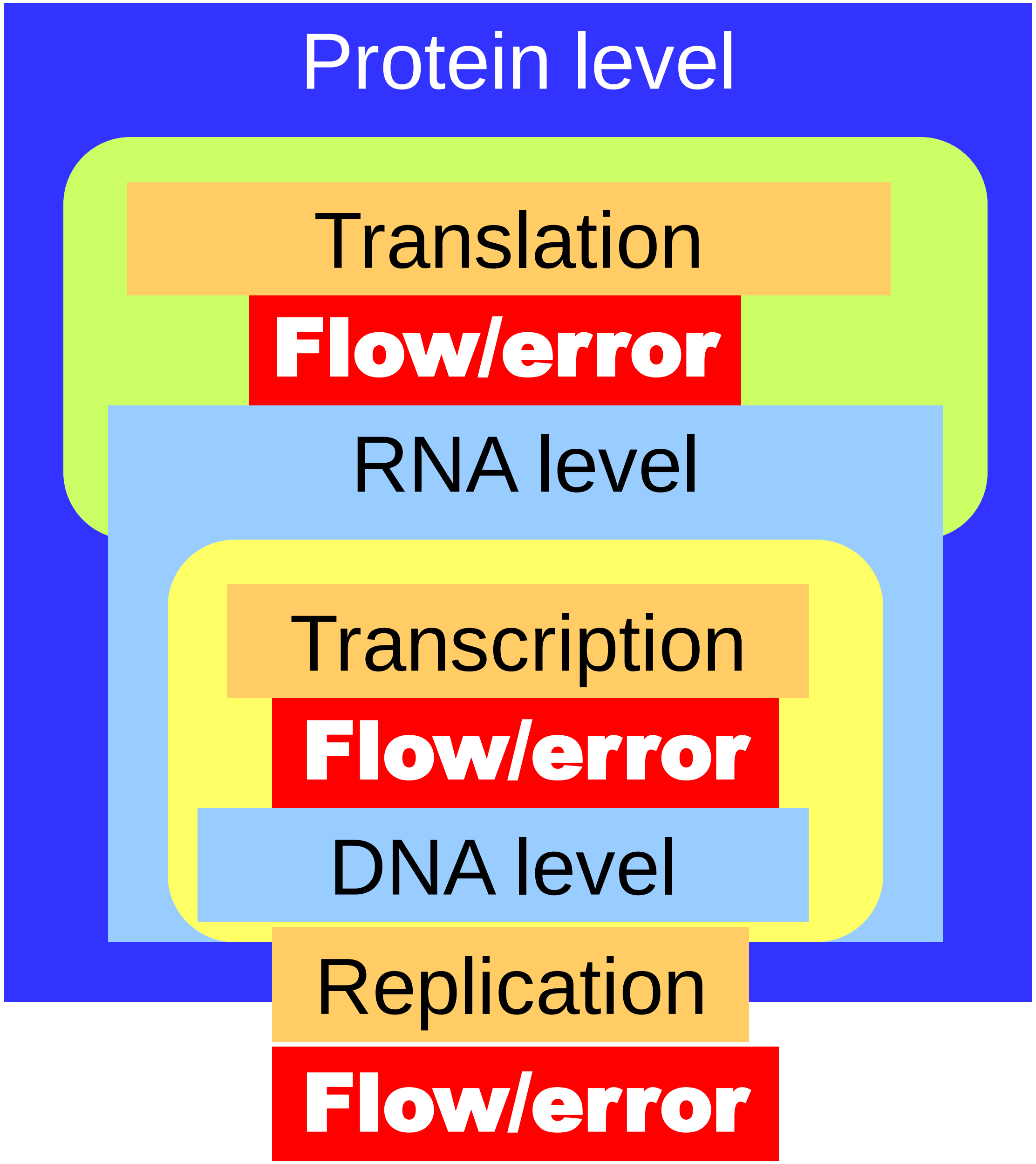
Naturally recursive



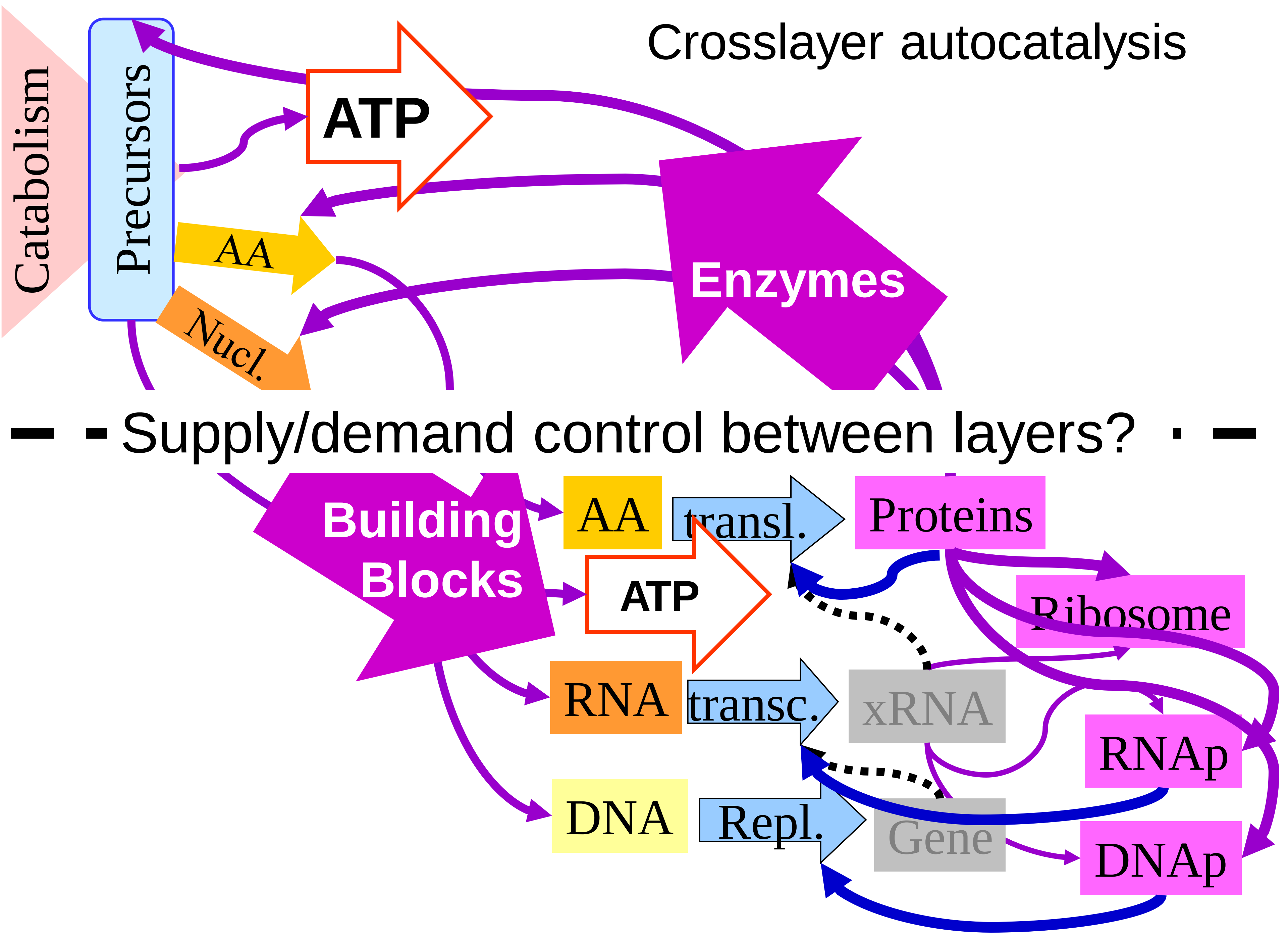
Naturally recursive

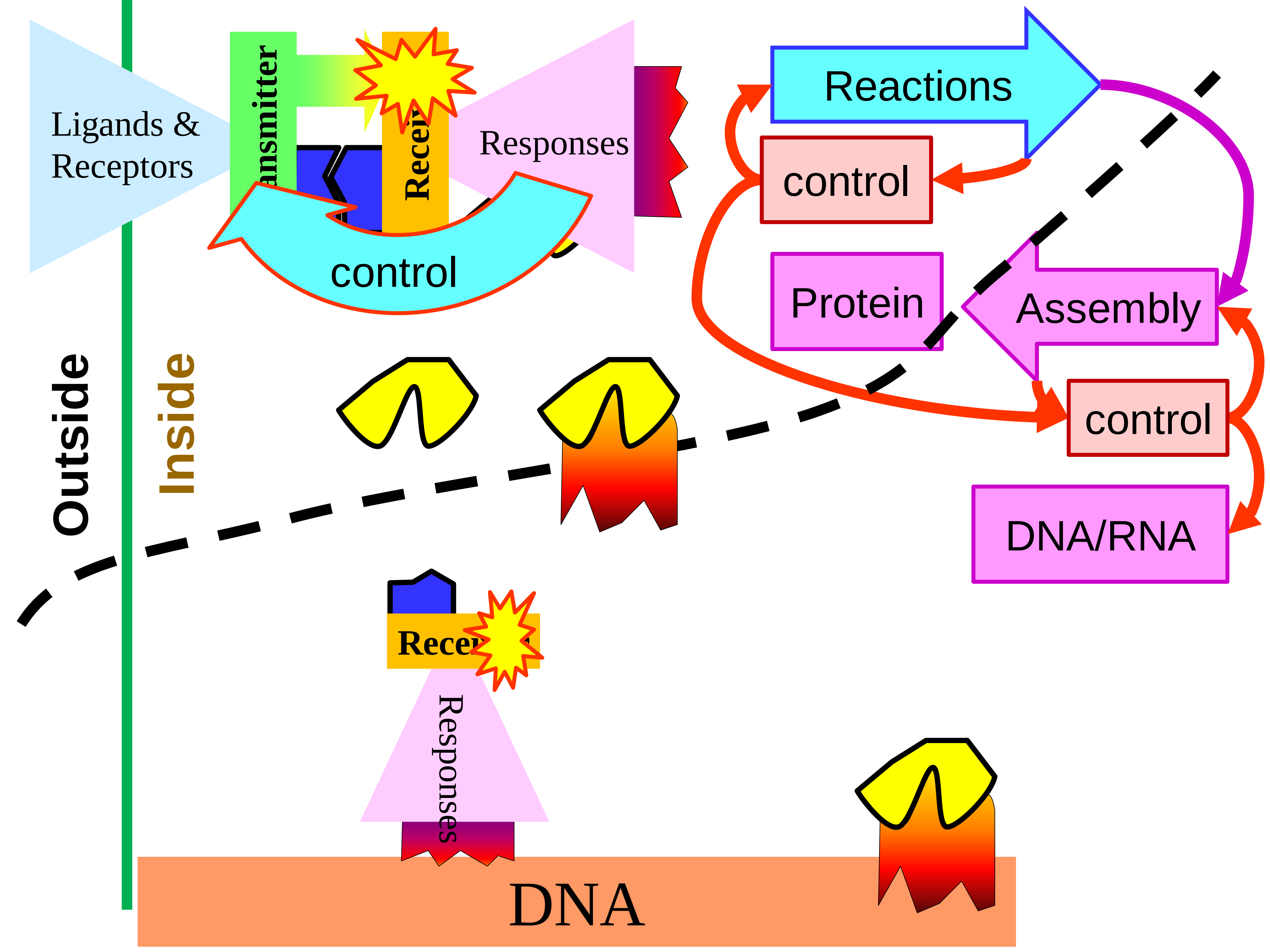


Three lower layers? Yes:
- Translation
- Transcription
- Replication/ rearrangement

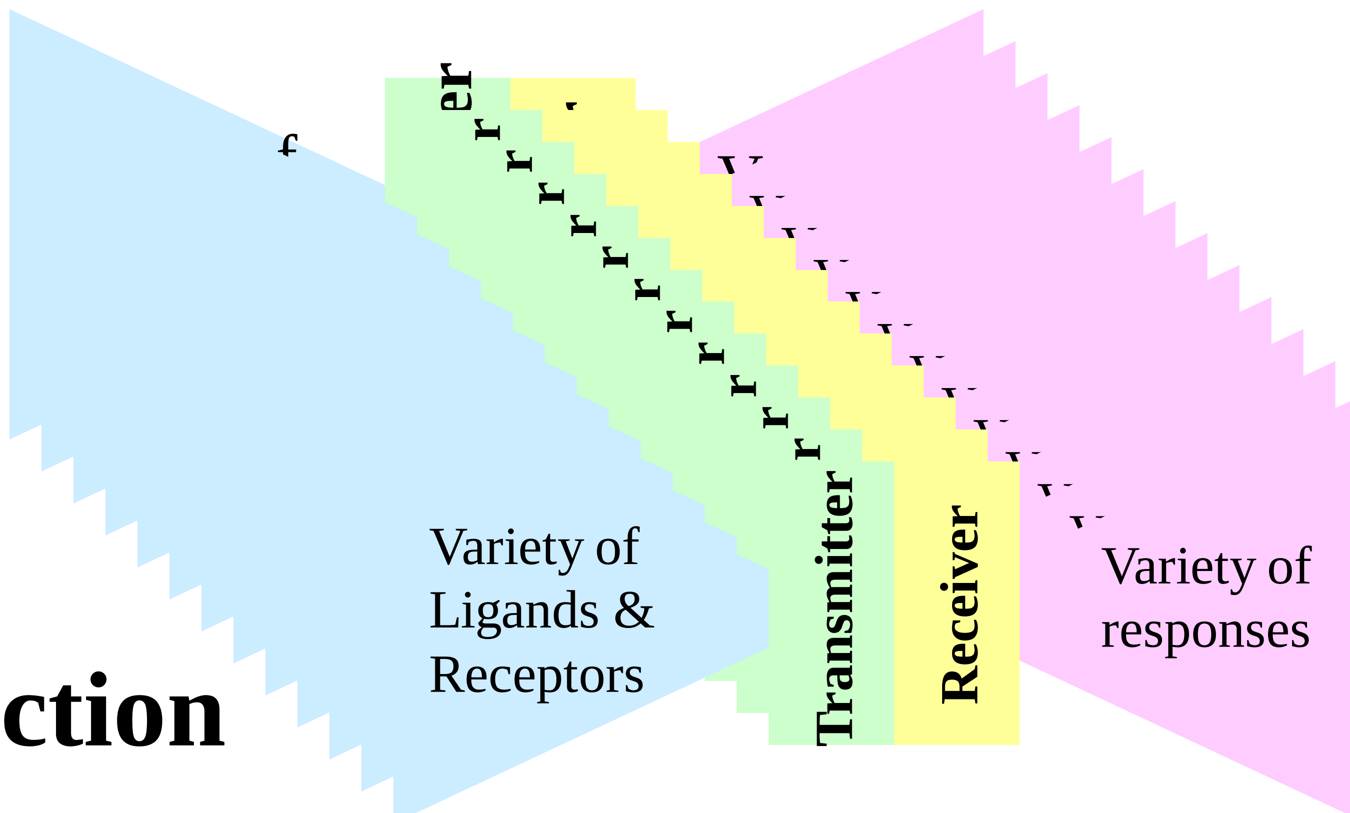


DNA Replication/ Rearrangement is complex and highly controlled

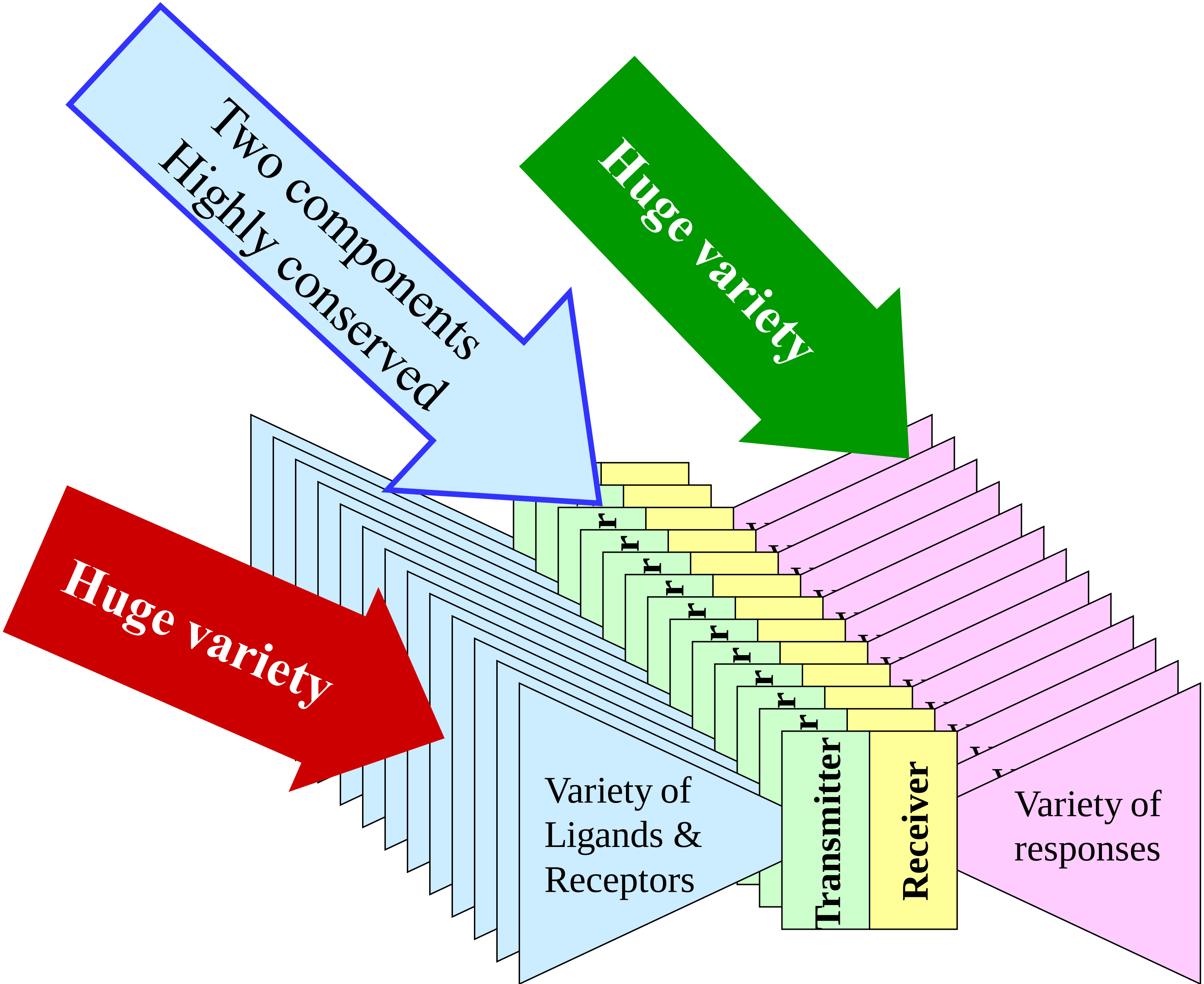

Crosslayer autocatalysis
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Supply/demand control between layers?
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp


Ligands &
Receptors
Responses
control
Reactions
control
Protein
Assembly
control
DNA/RNA
Outside
Inside
Responses
DNA

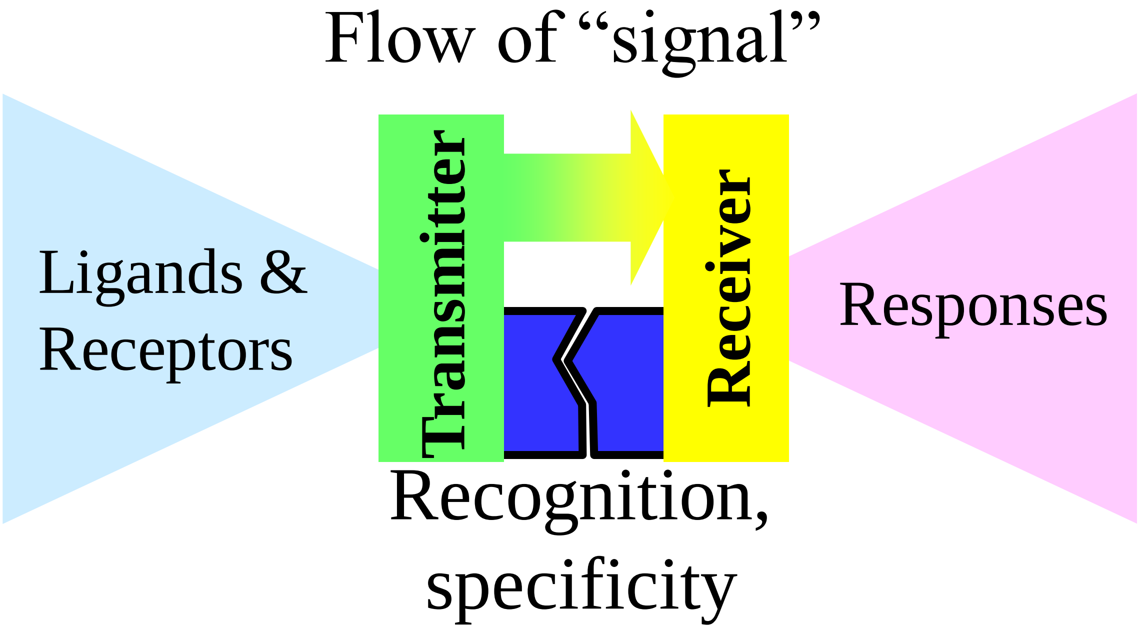
- ≈50 such “two component” systems in *E. Coli*
- All use the same protocol
  - Histidine autokinase transmitter
  - Aspartyl phospho-acceptor receiver
- Huge variety of receptors and responses
- Also multistage (phosphorelay) versions



Signal transduction

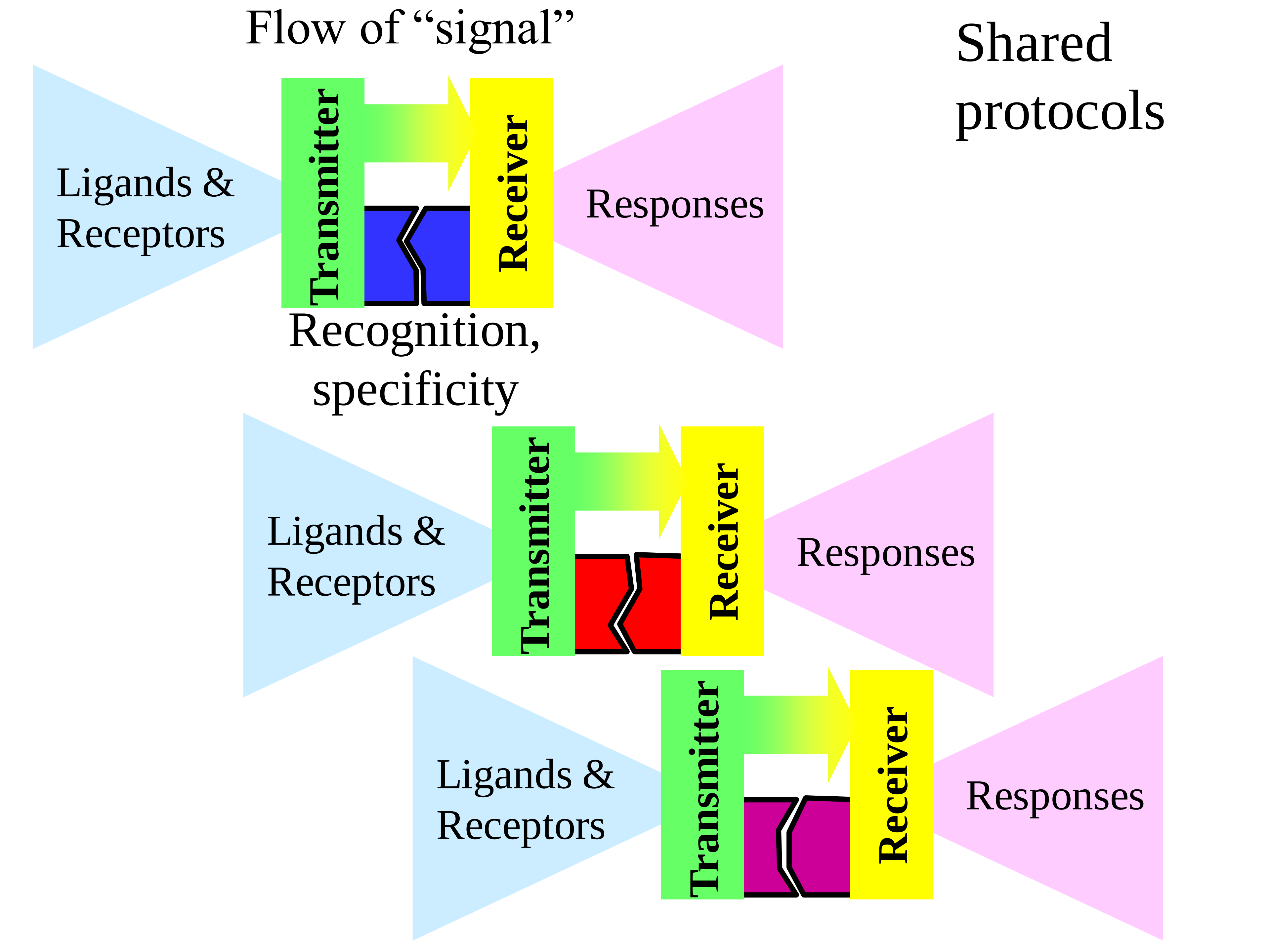


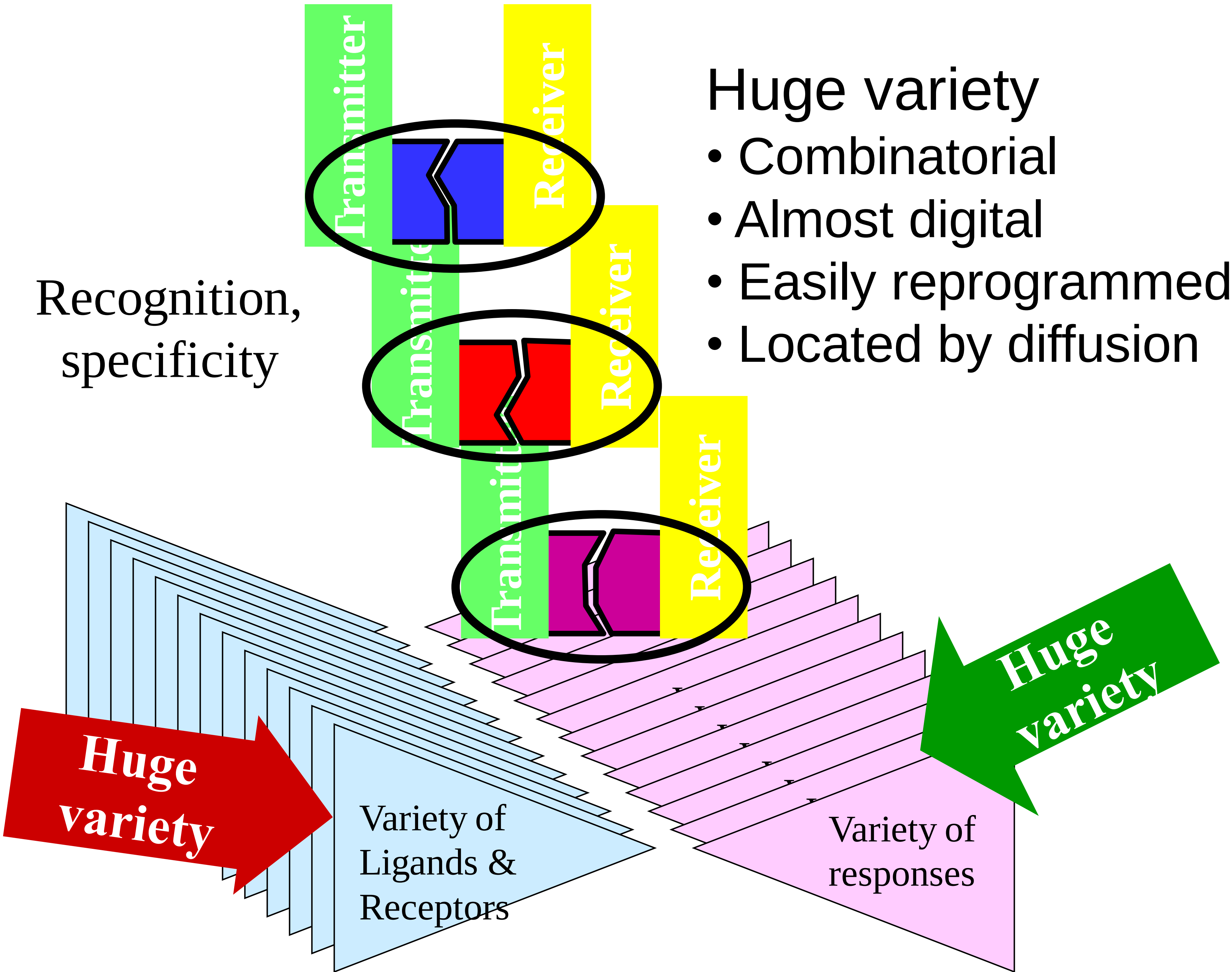
Two components
Highly conserved
Huge variety
Huge variety
Variety of
Ligands &
Receptors
Transmitter
Receiver
Variety of
responses



Shared protocols

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


Flow of "signal"
Shared protocols
Ligands & Receptors
Transmitter
Receiver
Responses
Recognition, specificity
Ligands & Receptors
Transmitter
Receiver
Responses
Ligands & Receptors
Transmitter
Receiver
Responses

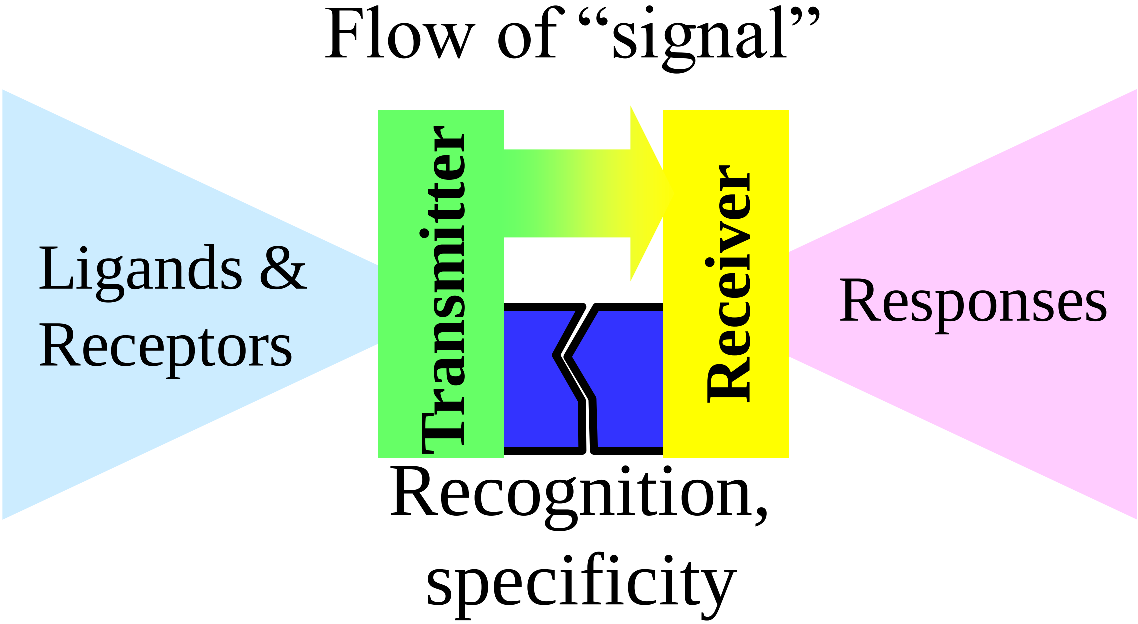

Huge variety
• Combinatorial
• Almost digital
• Easily reprogrammed
• Located by diffusion
Transmitter
Receiver
Transmitter
Receiver
Transmitter
Receiver
Recognition, specificity
Huge variety
Huge variety
Variety of Ligands & Receptors
Variety of responses

Flow of “signal”

Limited variety

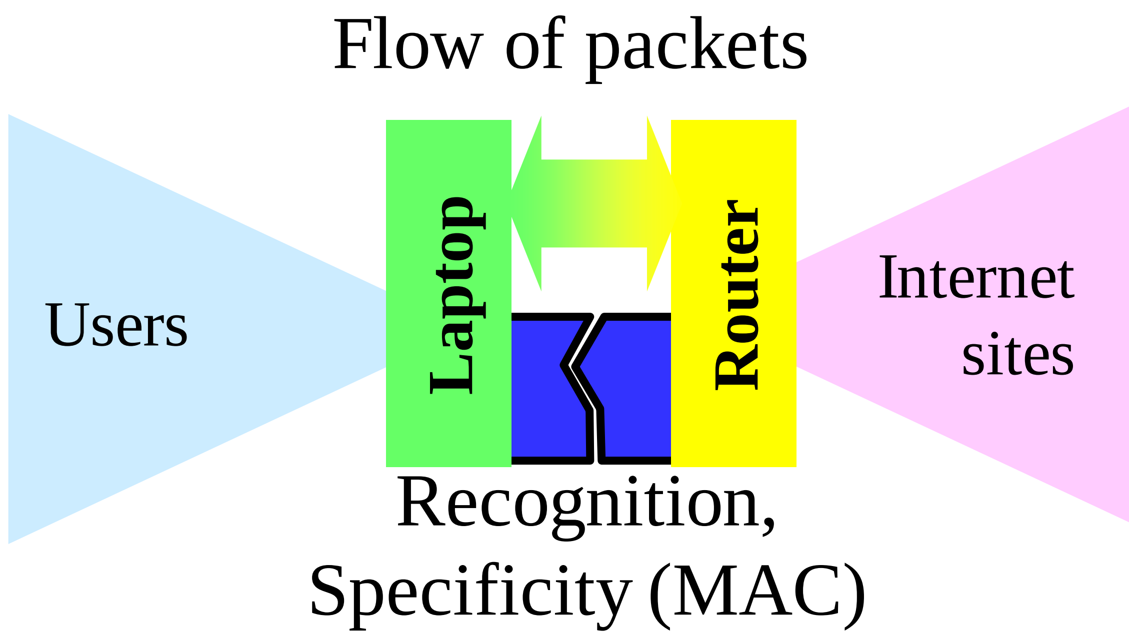
- Fast, analog (via #)
- Hard to change

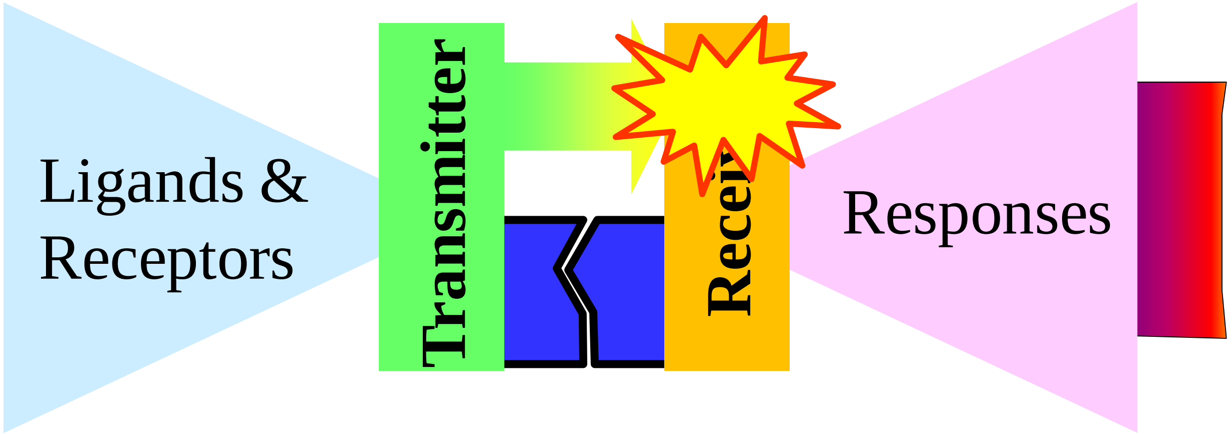
Reusable in
different pathways



Shared protocols

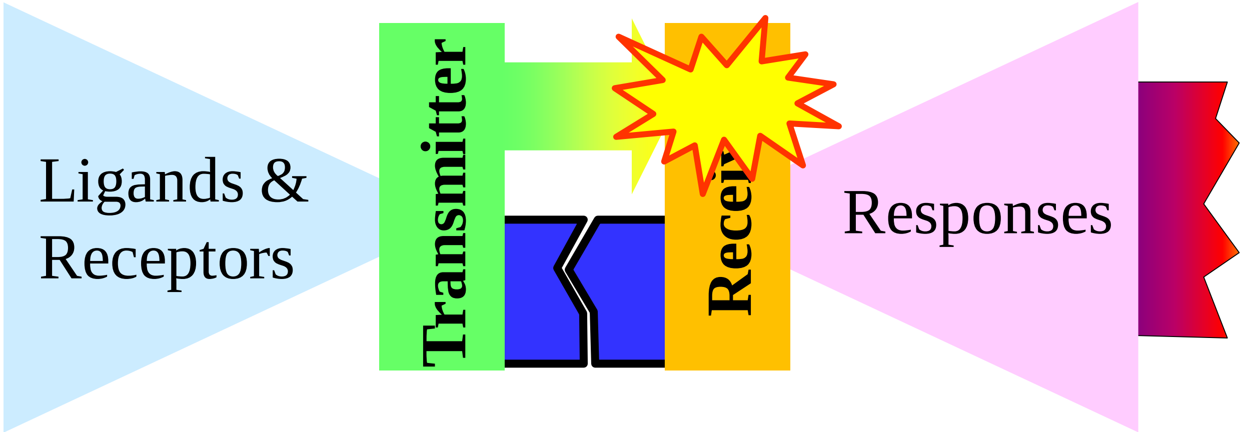
Note: Any wireless system and the Internet to which it is connected work the same way.





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

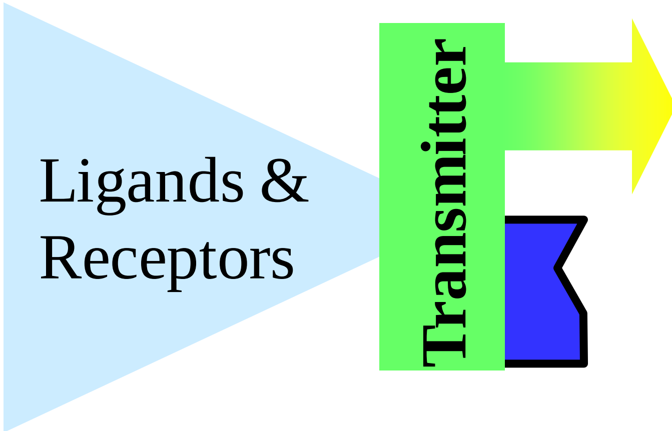
Transcription factors
do “name” to “address”
translation



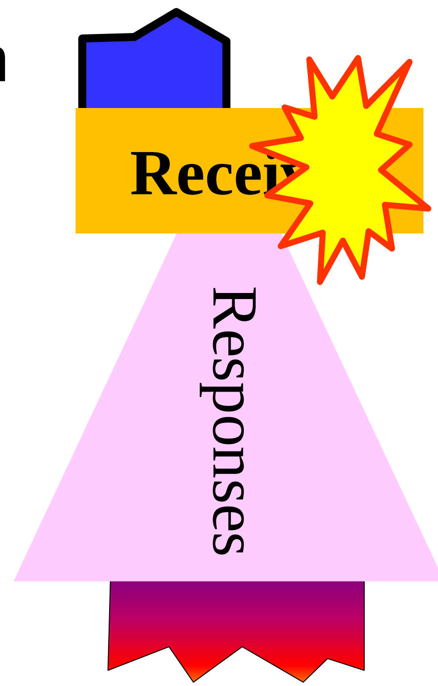
"Name" recognition
= molecular recognition
= localized functionally

Transcription factors
do "name" to "address"
translation

DNA



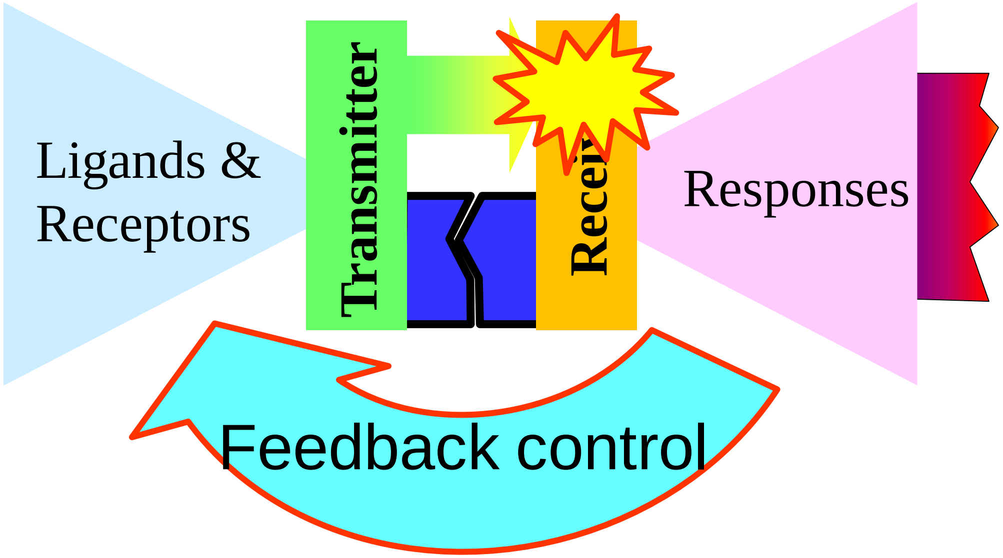
"Name" recognition
= molecular recognition
= localized functionally



Transcription factors do "name" to "address" translation

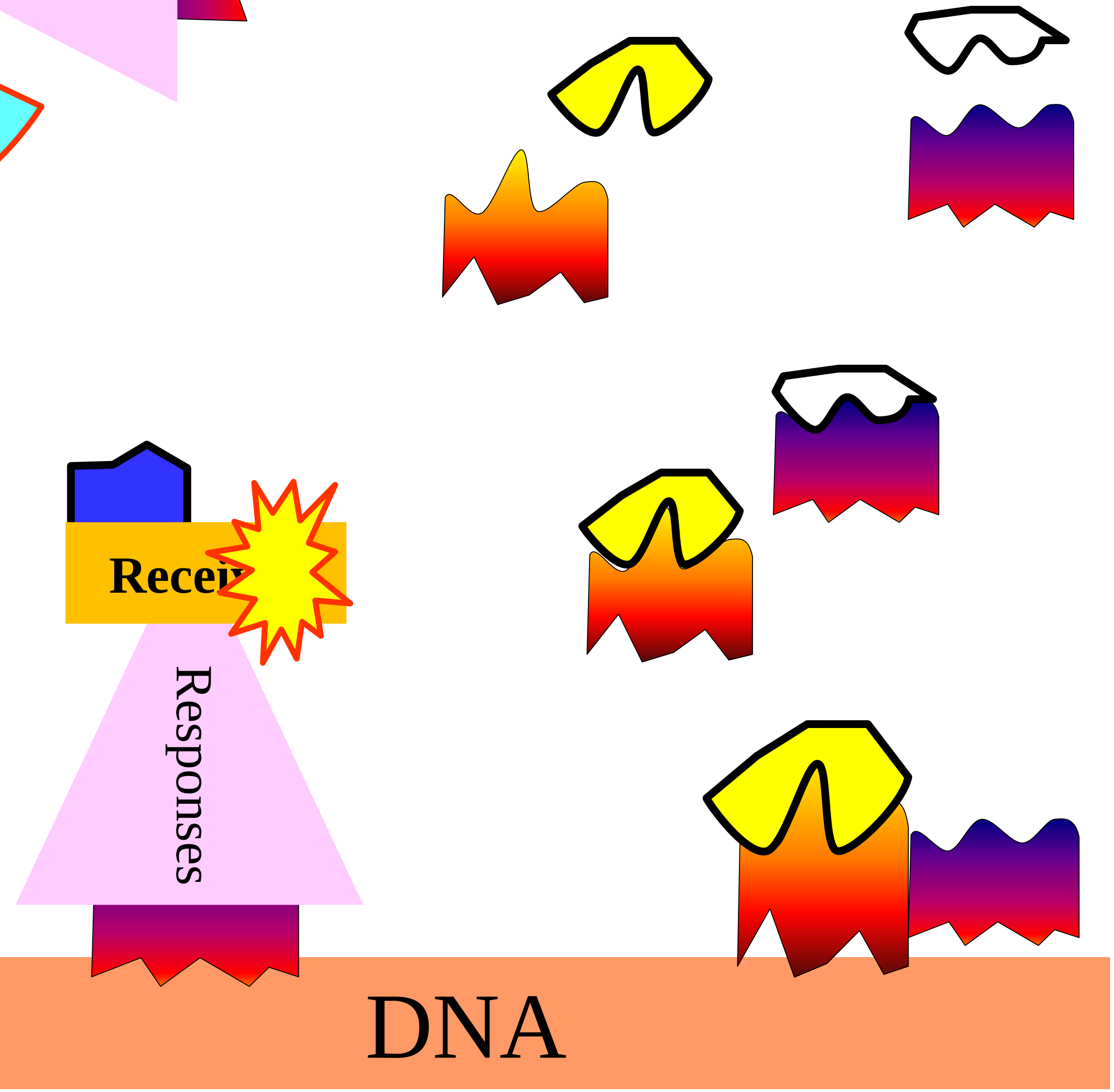
"Addressing"
= molecular recognition
= localized spatially

Both are
- Almost digital
- Highly programmable

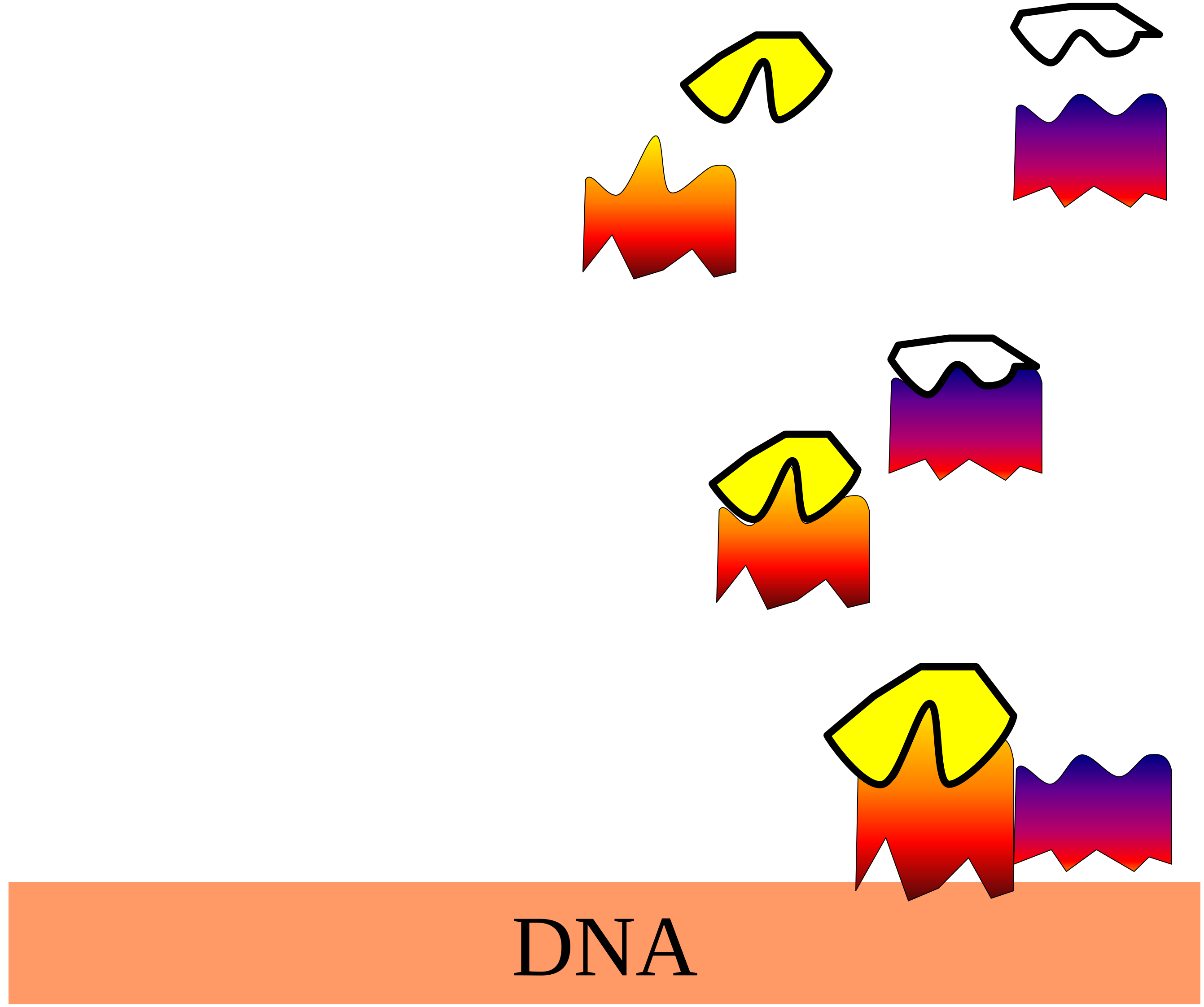


There are simpler transcription factors for sensing internal states

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



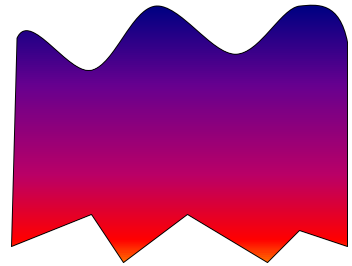
There are simpler transcription factors for sensing internal states



There are simpler transcription factors for sensing internal states

Domains can be evolved independently or coordinated.

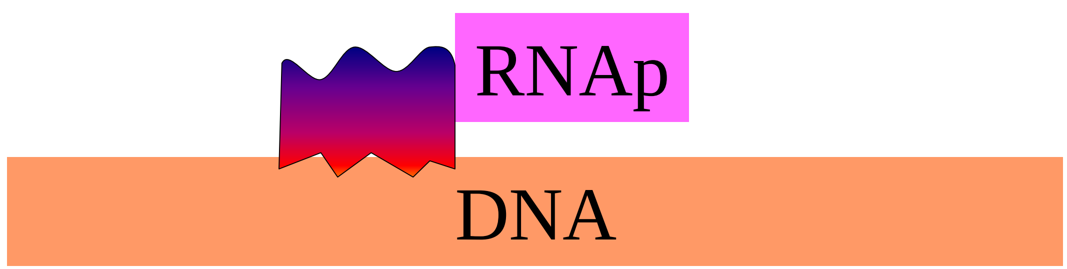
Sensor domains



DNA and RNAp binding domains

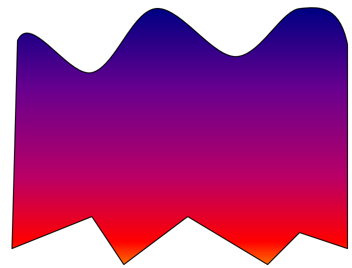
Application layer cannot access DNA directly.

Highly evolvable architecture.



This is like a “name to address” translation.

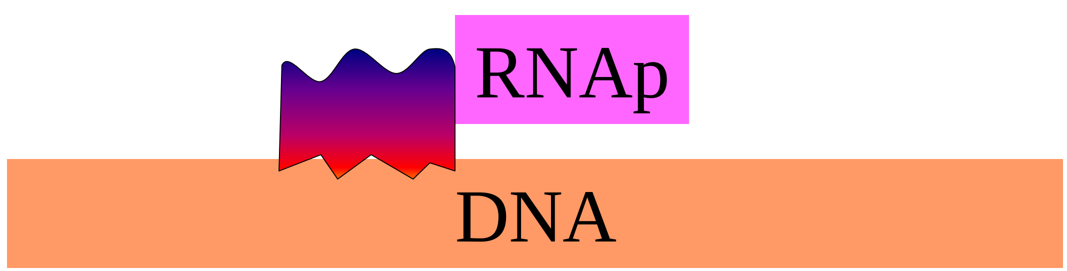
Sensor domains

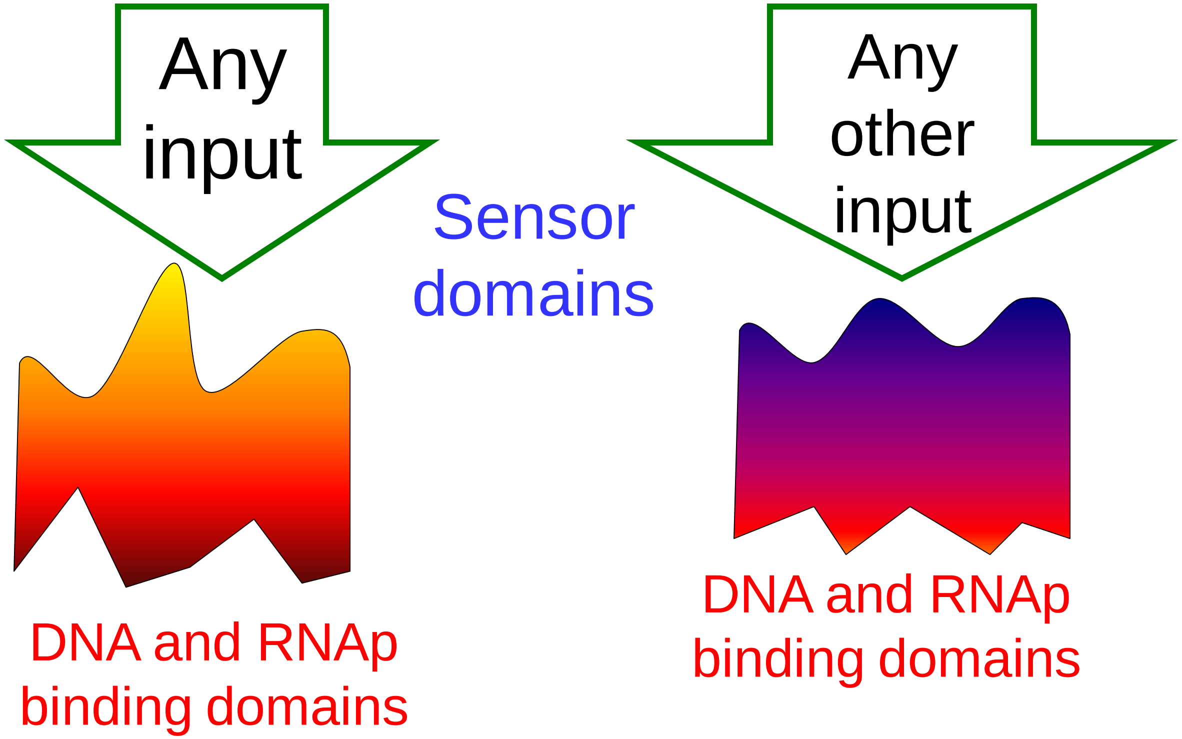


DNA and RNAp binding domains

Sensing the demand of the application layer

Initiating the change in supply

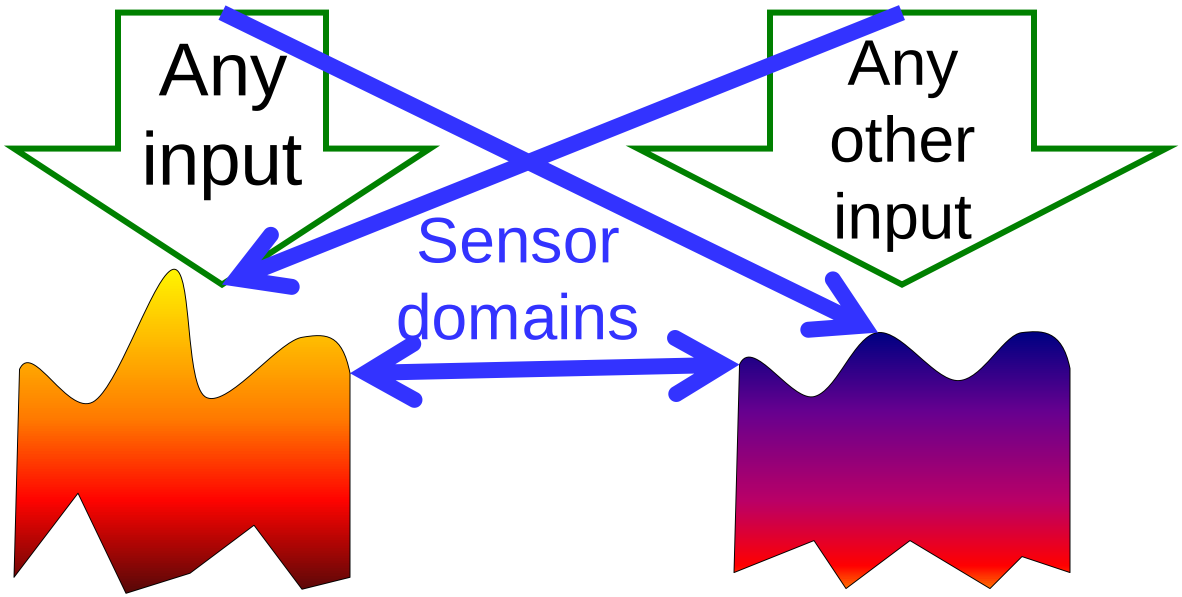




Sensing the demand of the application layer

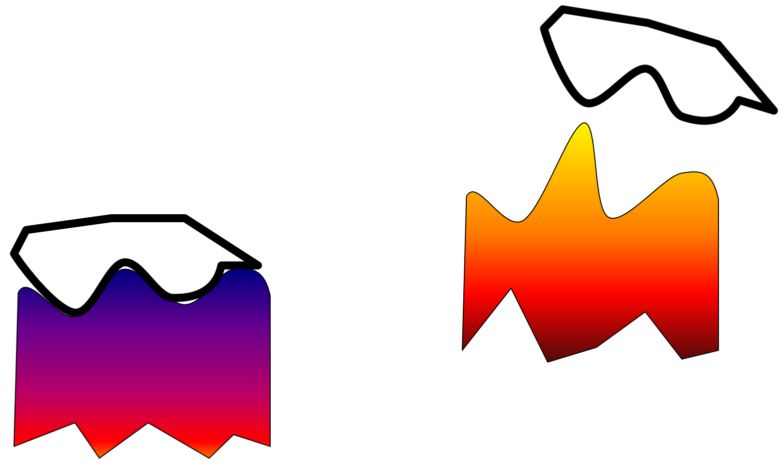
- Sensor sides attach to metabolites or other proteins
- This causes an allosteric (shape) change
- (Sensing is largely analog (# of bound proteins))
- Effecting the DNA/RNAp binding domains
- Protein and DNA/RNAp recognition is more digital
- Extensively discussed in both Ptashne and Alon

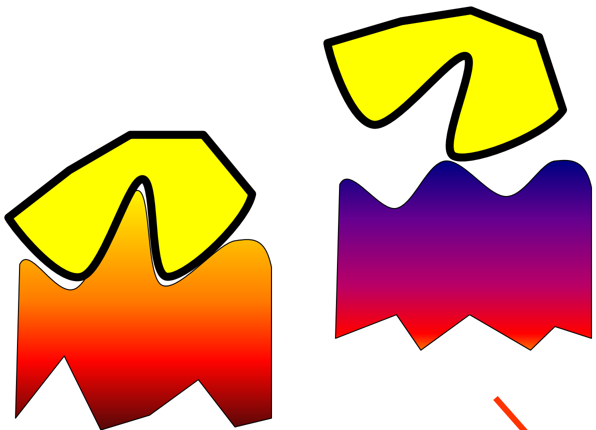
“Cross talk” can be finely controlled



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

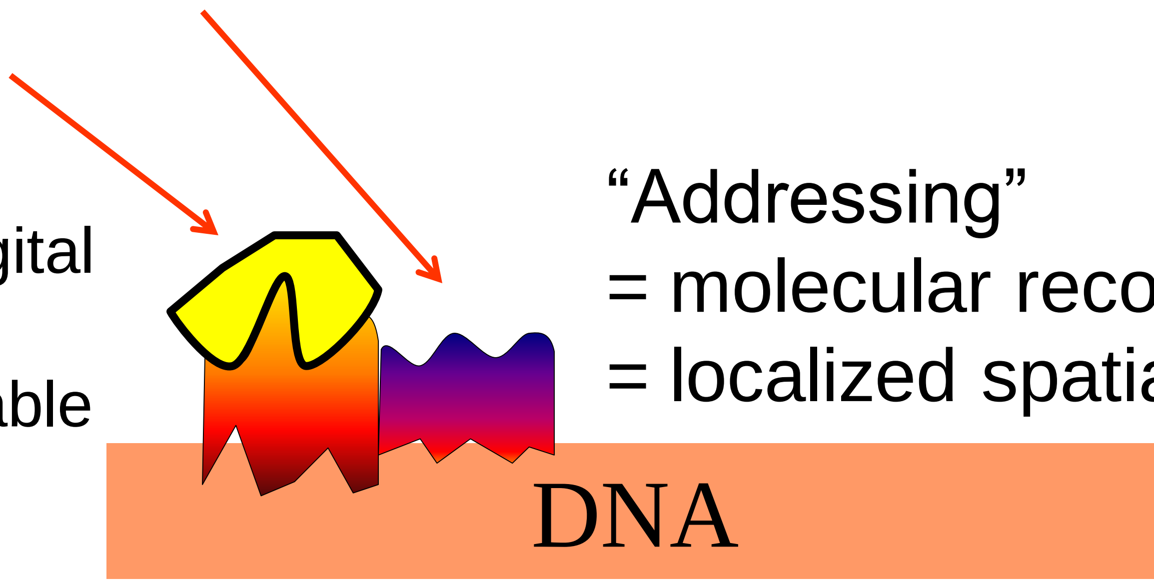
“Name” recognition
= molecular recognition
= localized functionally
= global spatially





Transcription factors do “name” to “address” translation

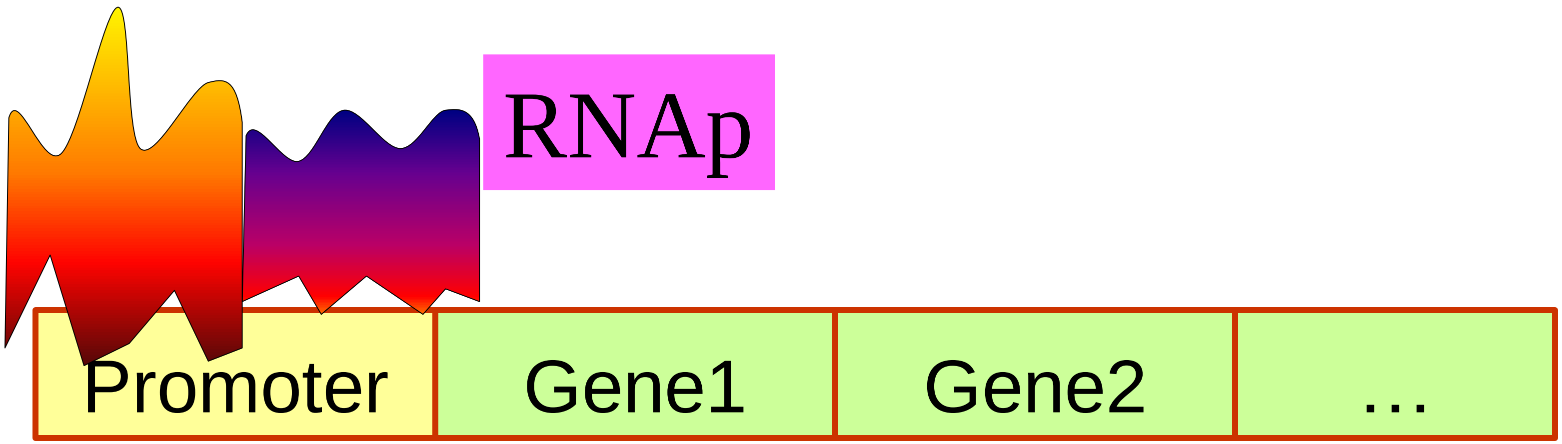
Both are
- Almost digital
- Highly programmable



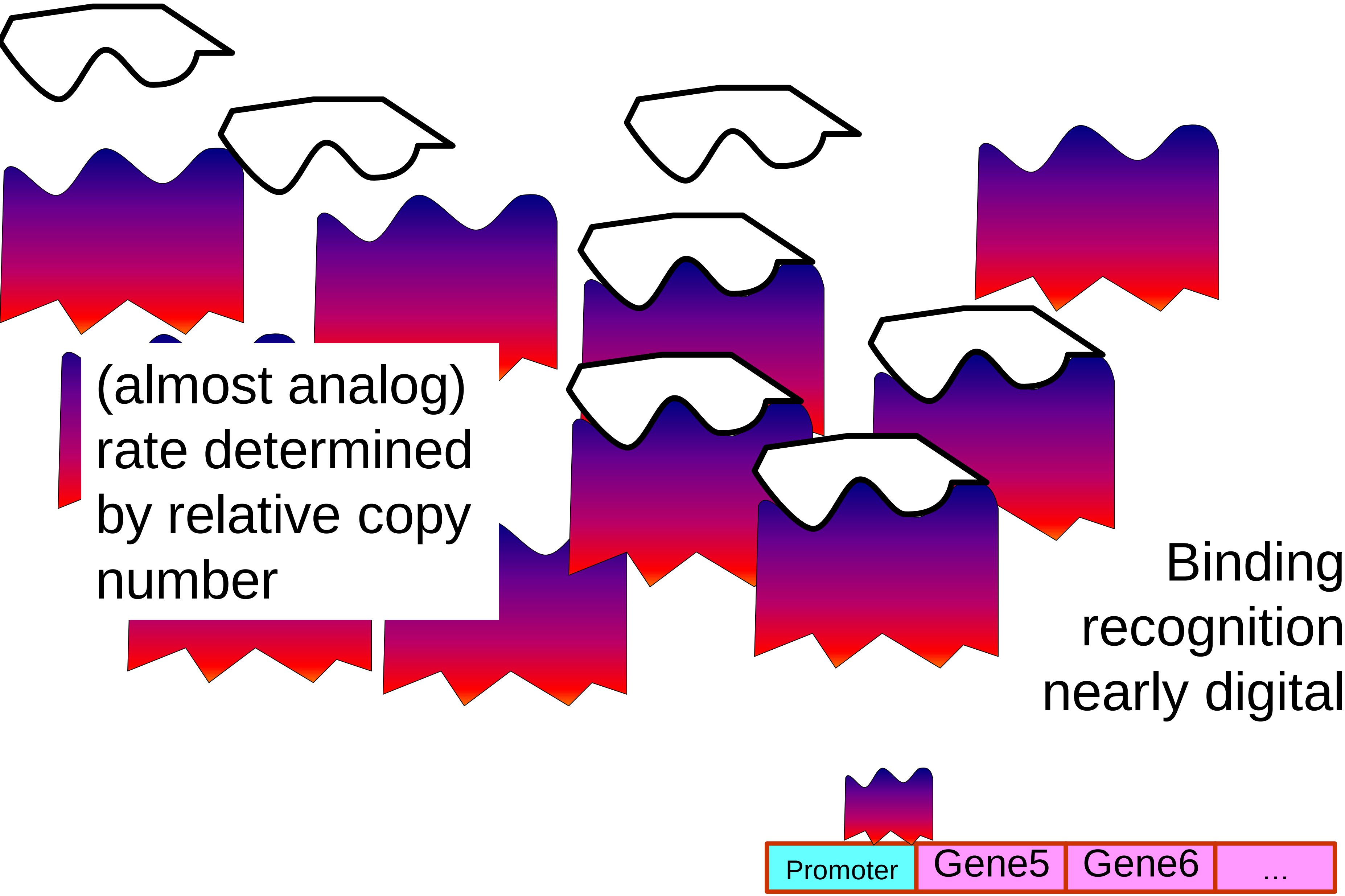
“Addressing”
= molecular recognition
= localized spatially

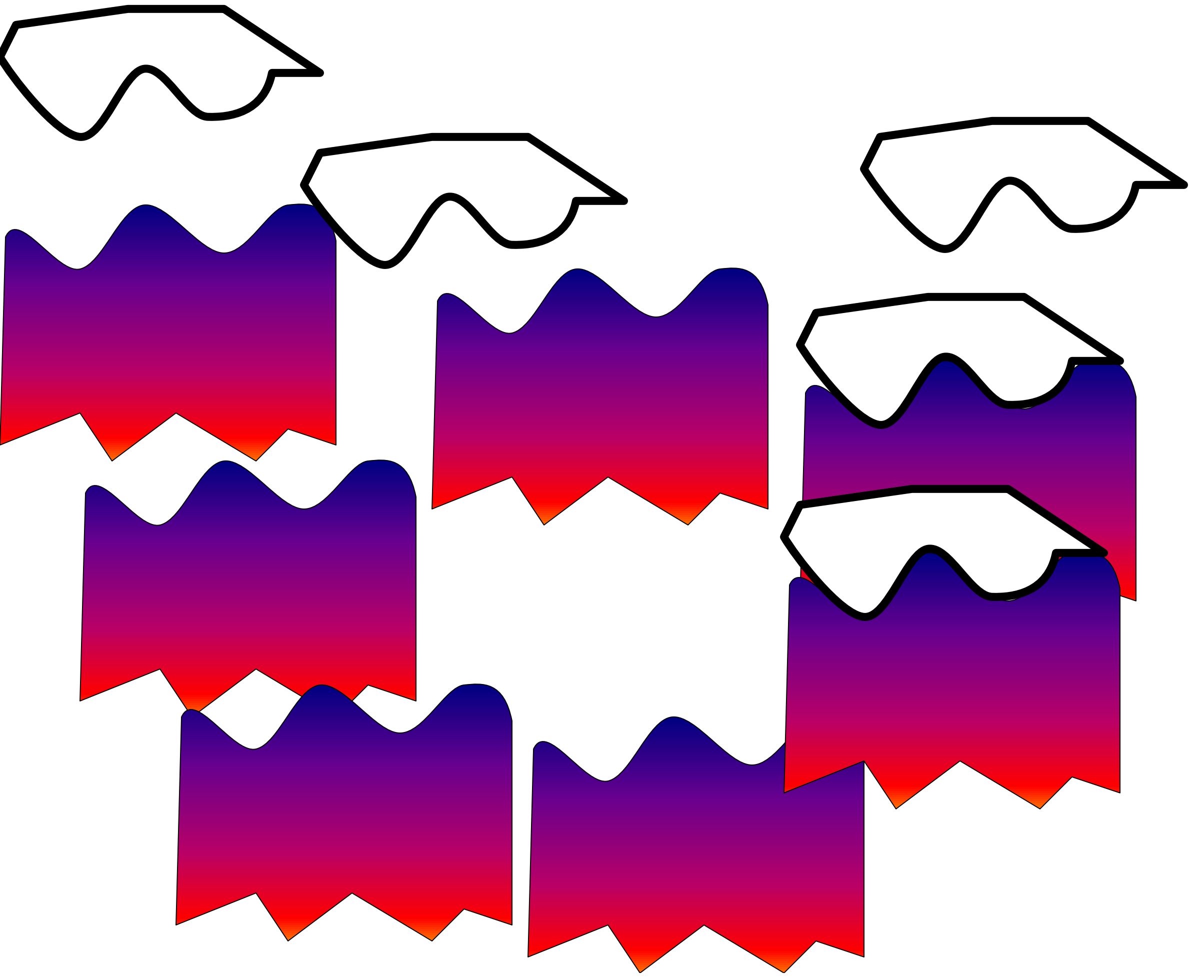
Can activate
or repress

And work in
complex logical
combinations



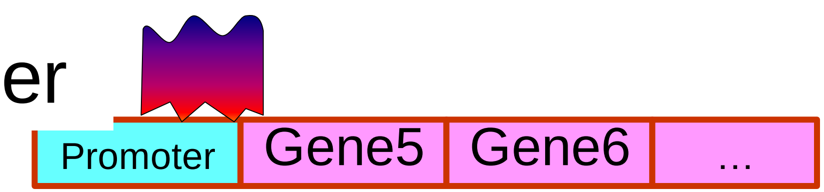
- Both protein and DNA sides have sequence/shape
- Huge combinatorial space of “addresses”
- Modest amount of “logic” can be done at promoter
- Transcription is very noise (but efficient)
- Extremely adaptable architecture


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



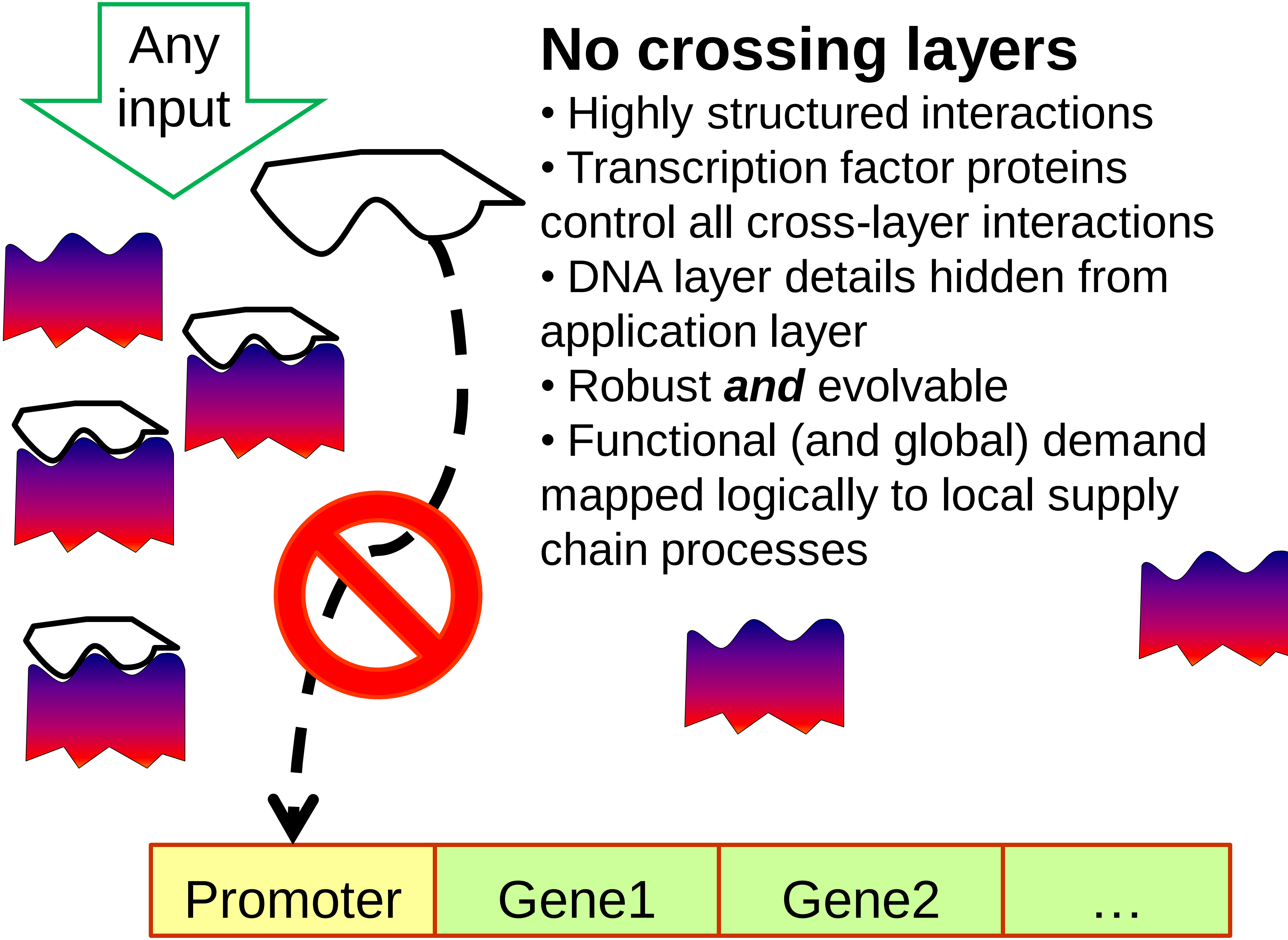
Recall: can work by pulse code modulation so for small copy number does digital to analog conversion

rate (almost analog) determined by copy number

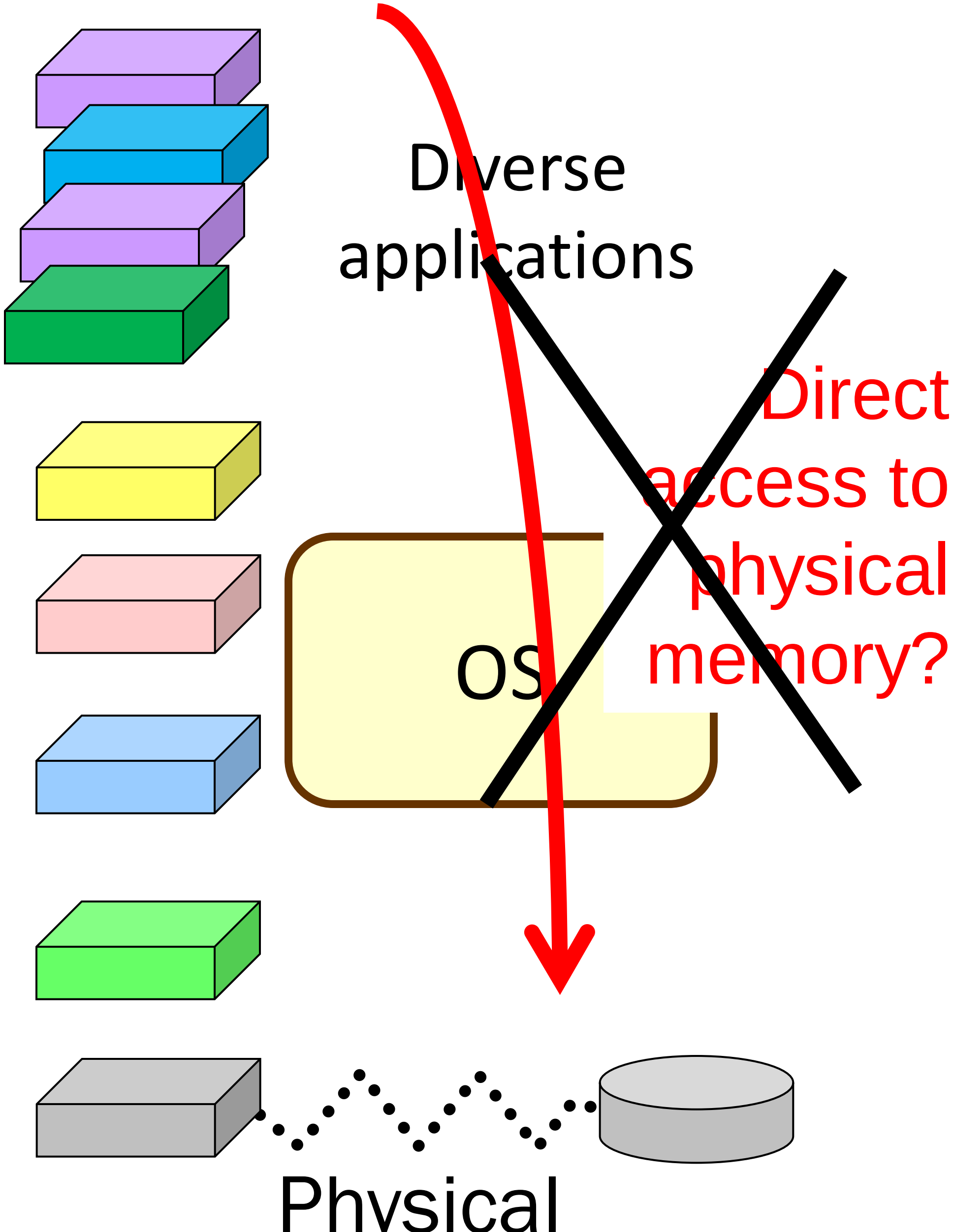


No crossing layers

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



Layered architectures



In programming:
No global variables

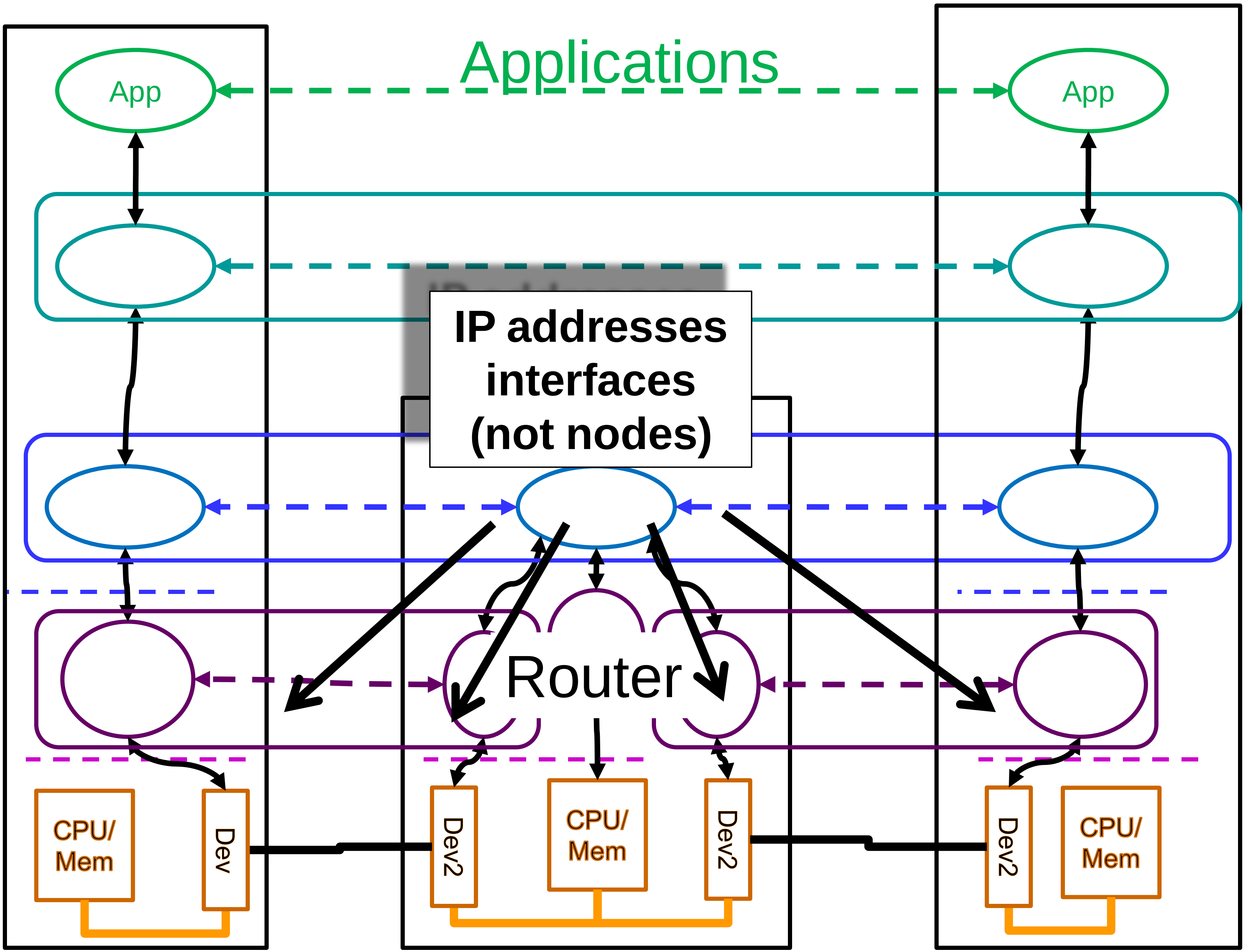
In operating systems:
Don't cross layers (rings)

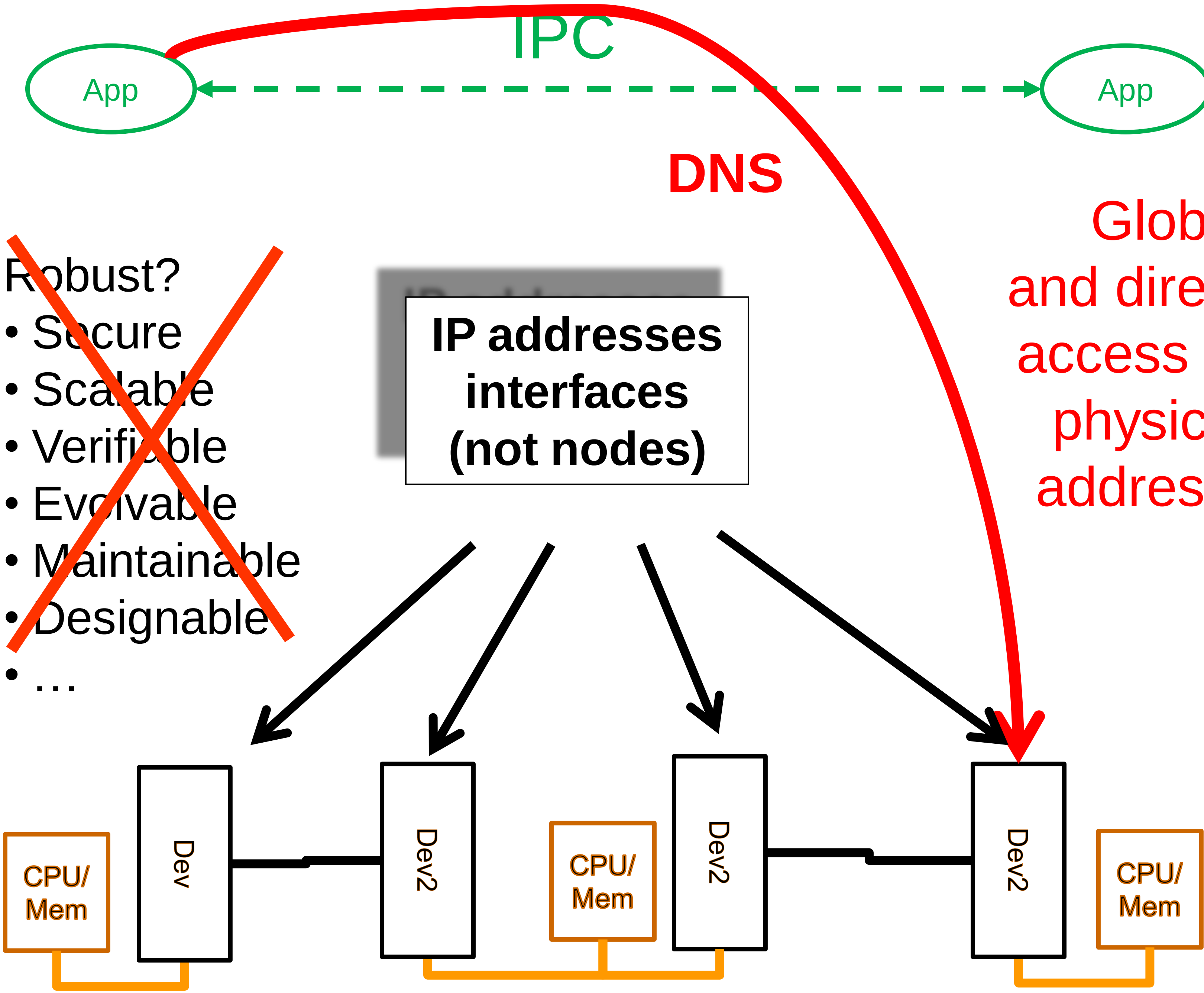
Problems with *leaky* layering

Modularity benefits are lost

- Global variables?   @$%*&!^%@&
- Poor portability of applications
- Insecurity of physical address space
- Fragile to application crashes
- No scalability of virtual/real addressing

- Limits optimization/control by duality?


Applications
App
App
IP addresses
interfaces
(not nodes)
Router
CPU/
Mem
Dev
Dev2
CPU/
Mem
Dev2
Dev2
CPU/
Mem

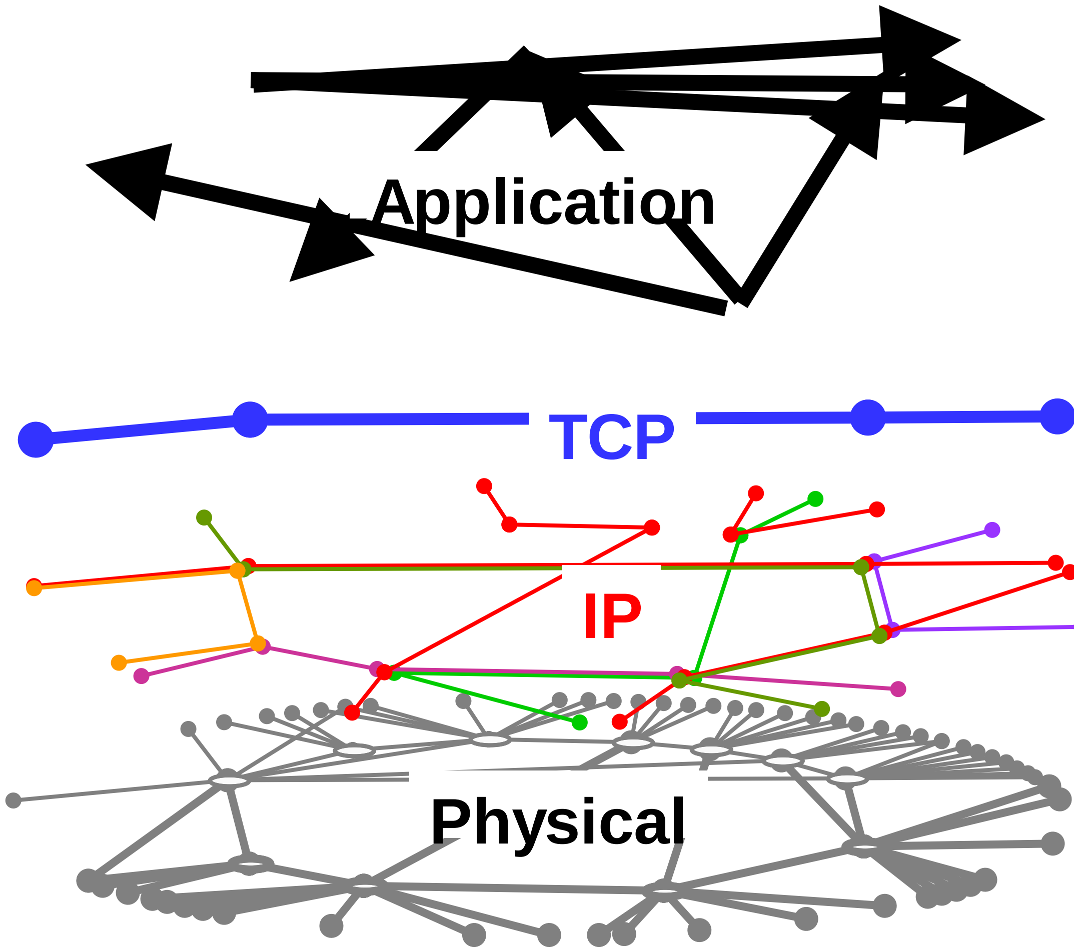

IPC
App
App
DNS
Global
and direct
access to
physical
address!
Robust?
• Secure
• Scalable
• Verifiable
• Evolvable
• Maintainable
• Designable
• …
IP addresses
interfaces
(not nodes)
CPU/
Mem
Dev
Dev2
CPU/
Mem
Dev2
Dev2
CPU/
Mem

Naming and addressing need to be

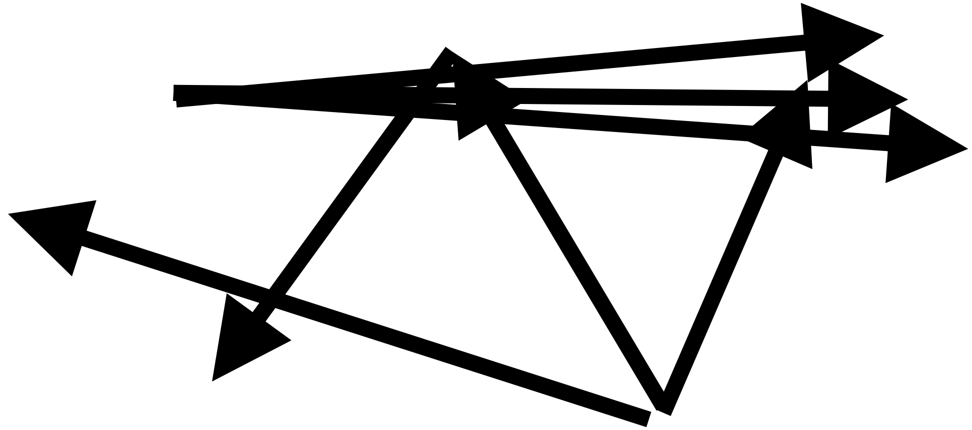
- resolved within layer
- translated between layers
- not exposed outside of layer

Related “issues”

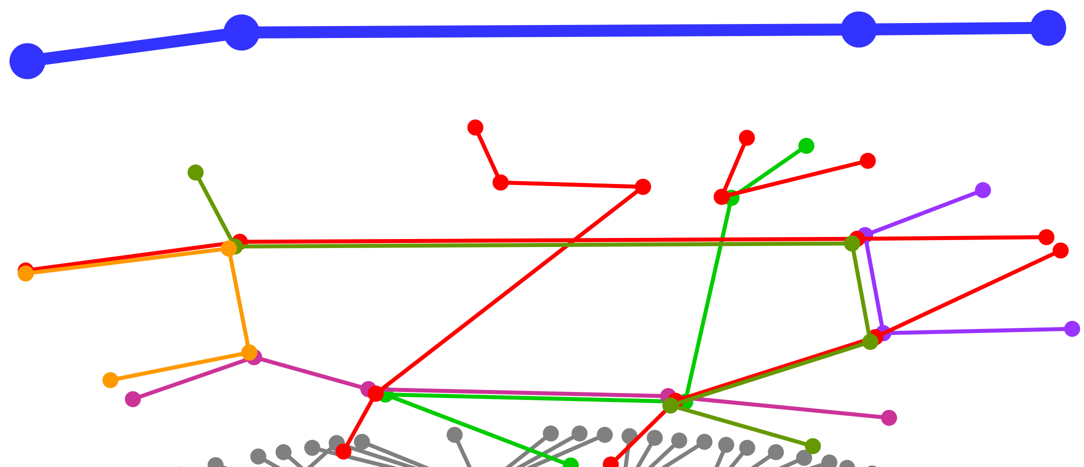
- DNS
- NATS
- Firewalls
- Multihoming
- Mobility
- Routing table size
- Overlays
- …



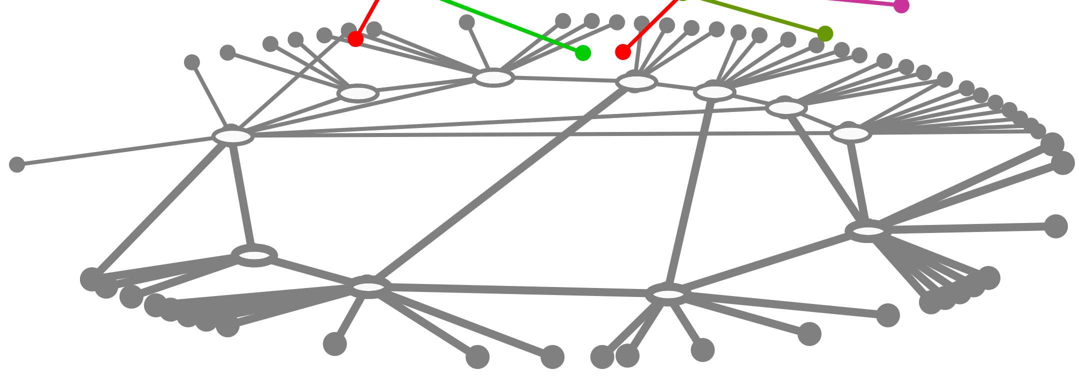
Persistent errors and confusion.



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



Architecture facilitates arbitrary graphs.



The "robust yet fragile" nature of the Internet

John C. Doyle*[†], David L. Alderson*, Lun Li*, Steven Low*, Matthew Roughan[‡], Stanislav Shalunov[§], Reiko Tanaka[¶], and Walter Willinger[‖]

*Engineering and Applied Sciences Division, California Institute of Technology, Pasadena, CA 91125; [‡]Applied Mathematics, University of Adelaide, South Australia 5005, Australia; [§]Internet2, 3025 Boardwalk Drive, Suite 200, Ann Arbor, MI 48108; [¶]Bio-Mimetic Control Research Center, Institute of Physical and Chemical Research, Nagoya 463-0003, Japan; and [‖]AT&T Labs–Research, Florham Park, NJ 07932

Edited by Robert M. May, University of Oxford, Oxford, United Kingdom, and approved August 29, 2005 (received for review February 18, 2005)

The search for unifying properties of complex networks is popular, challenging, and important. For modeling approaches that focus on

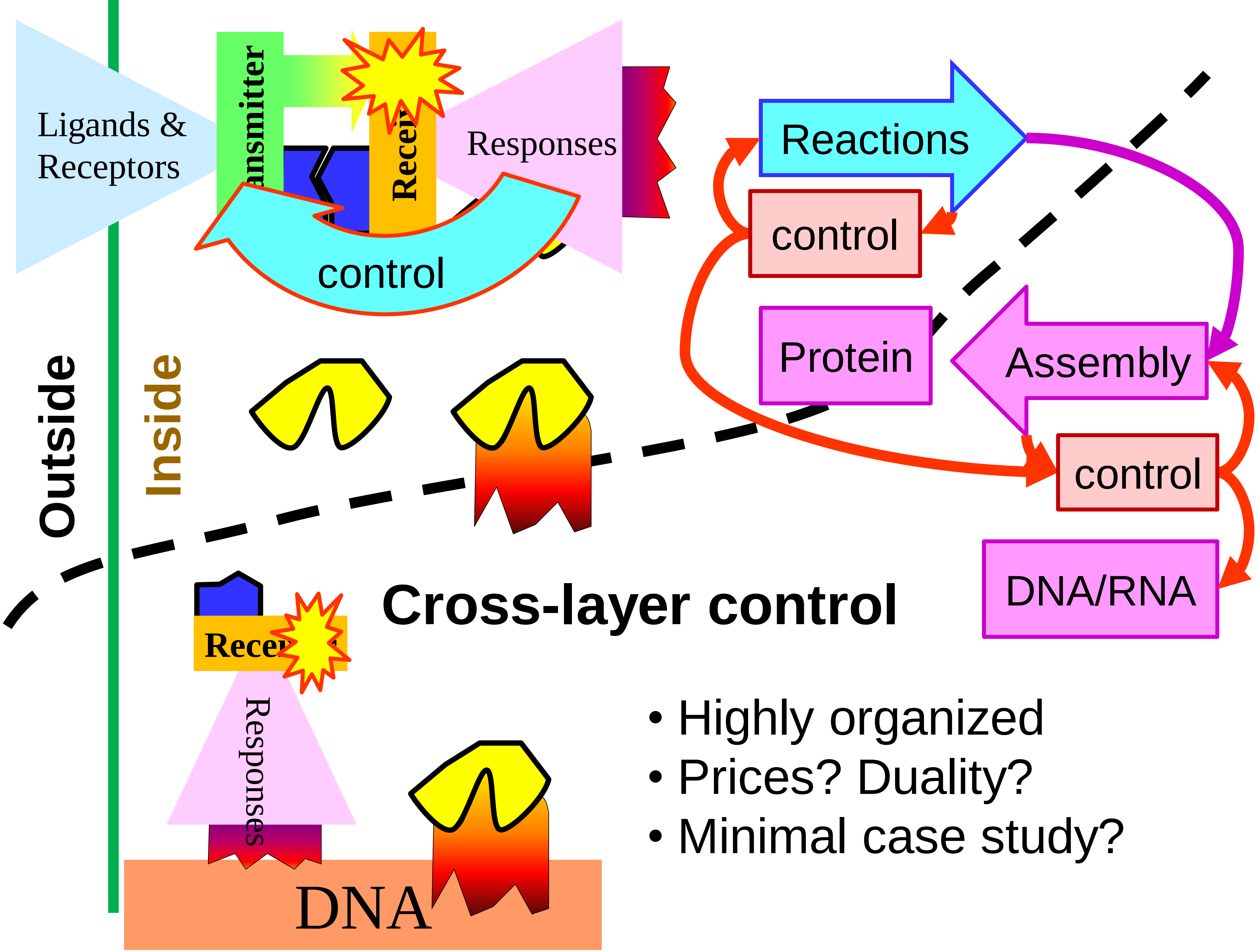
no self-loops or parallel edges) having the same graph degree
We will say that graphs $g \in G(D)$ have scaling-degree sequen

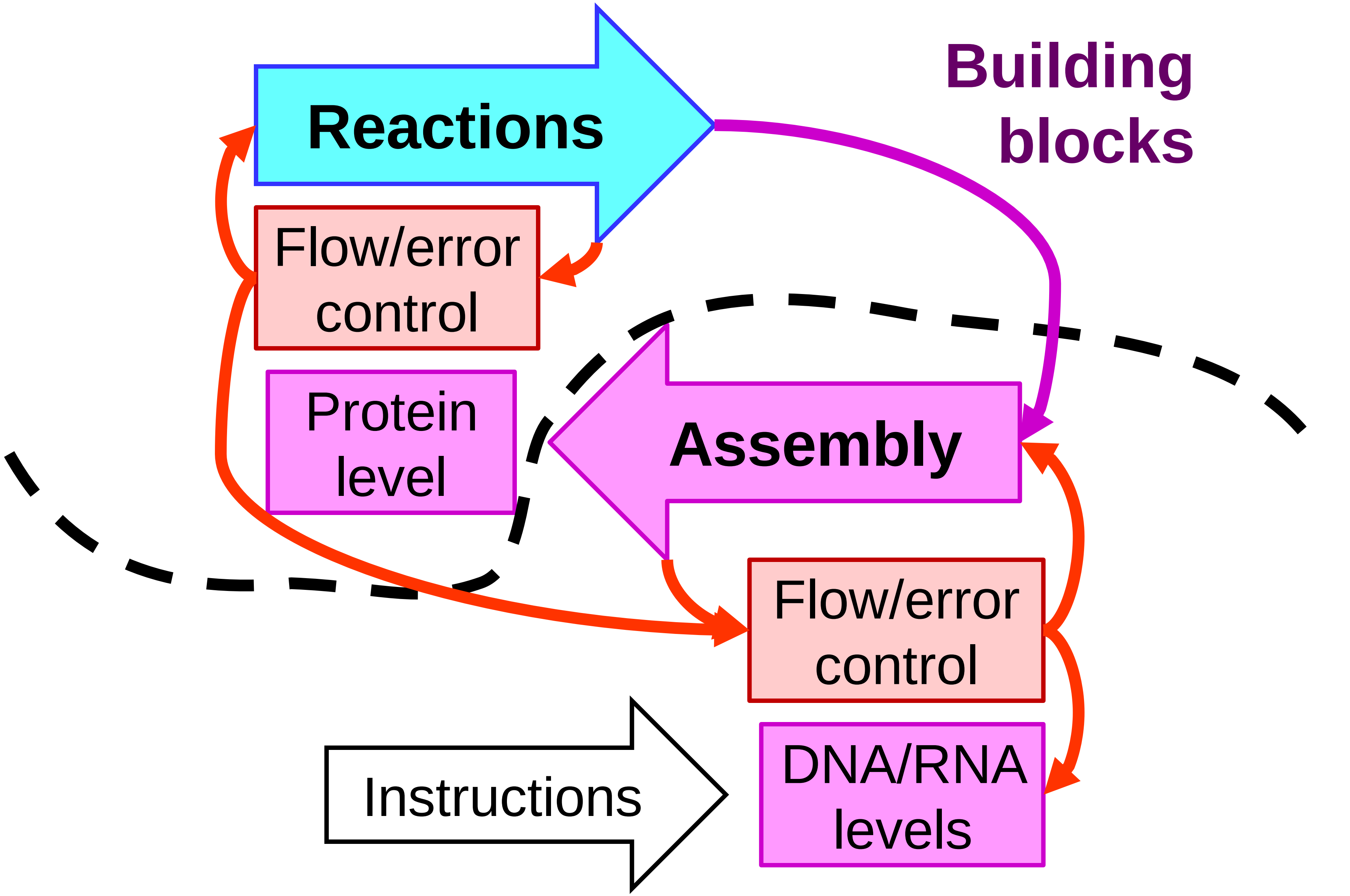
PNAS | October 11, 2005 | vol. 102 | no. 41 | 14497–14502

Notices of the AMS, 2009

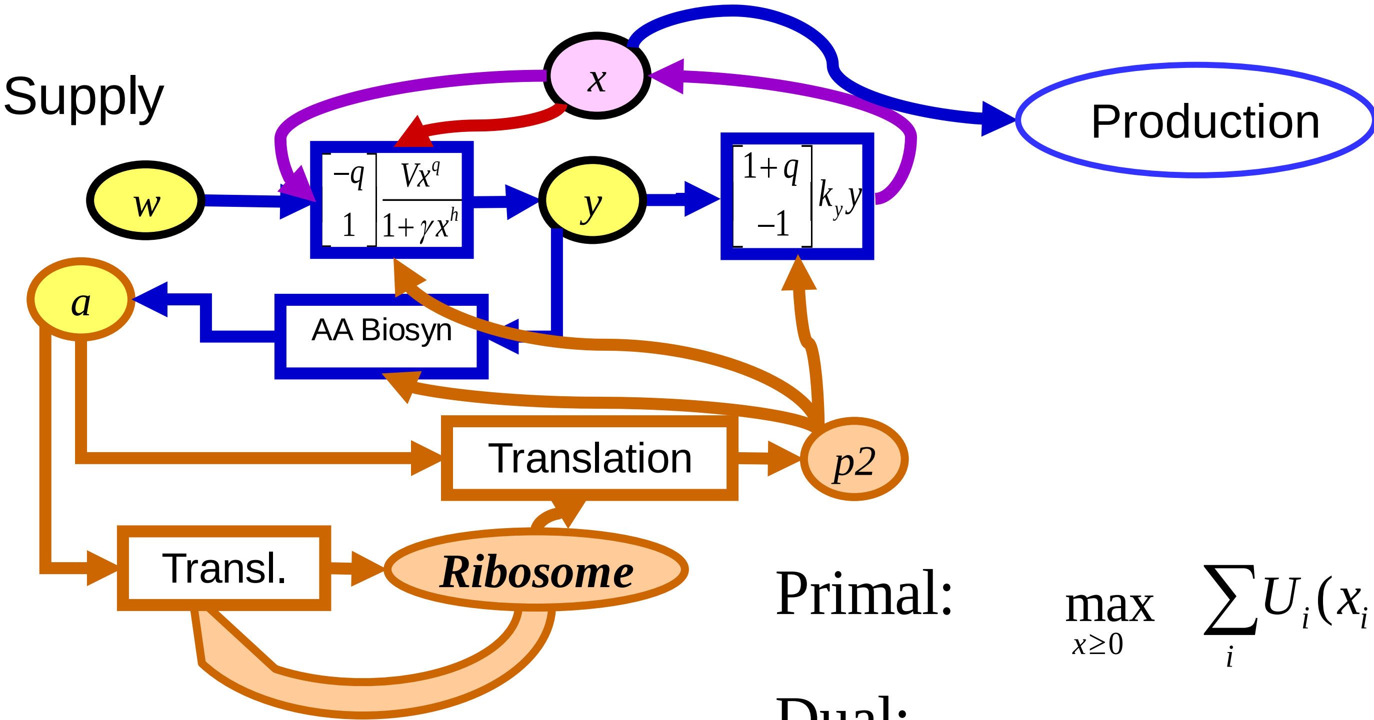
Mathematics and the Internet: A Source of Enormous Confusion and Great Potential

Walter Willinger, David Alderson, and John C. Doyle


Ligands &
Receptors
ansmitter
Recei
Responses
control
Reactions
control
Protein
Assembly
control
DNA/RNA
Outside
Inside
Recep
Responses
DNA
Cross-layer control
• Highly organized
• Prices? Duality?
• Minimal case study?



Reactions
Building blocks
Flow/error control
Protein level
Assembly
Flow/error control
Instructions
DNA/RNA levels



$$\text{Primal:} \quad \max_{x \geq 0} \sum_i U_i(x_i) \quad \text{subject to} \quad Rx \leq c$$

Dual:

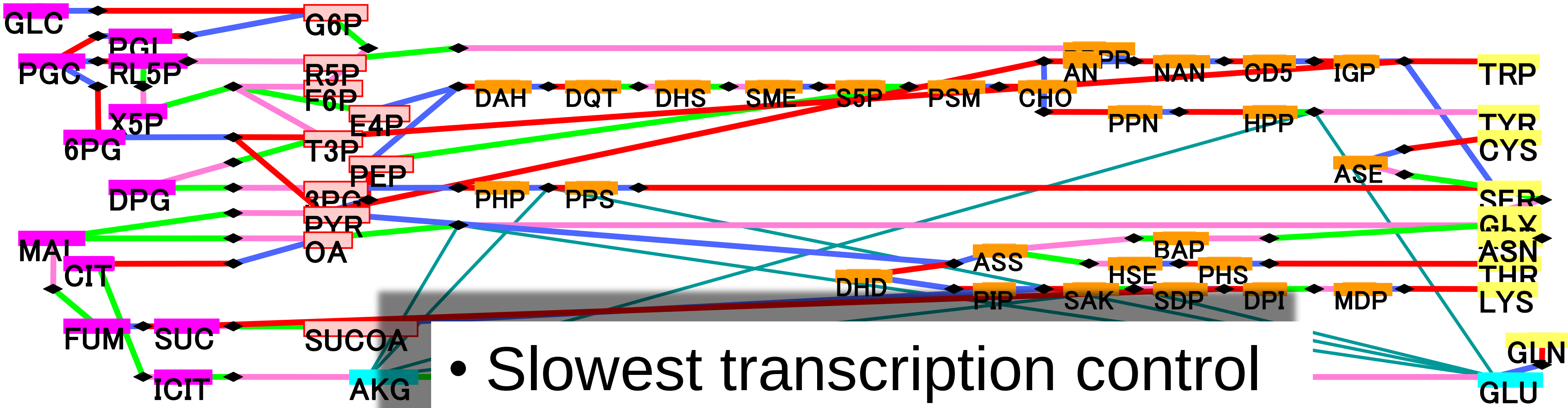
$$\min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - \sum_l p_l \left(R_{li} x_i - c_l \right) \right) \right)$$

$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i \sum_l R_{li} p_l \right) + \sum_l p_l c_l \right)$$

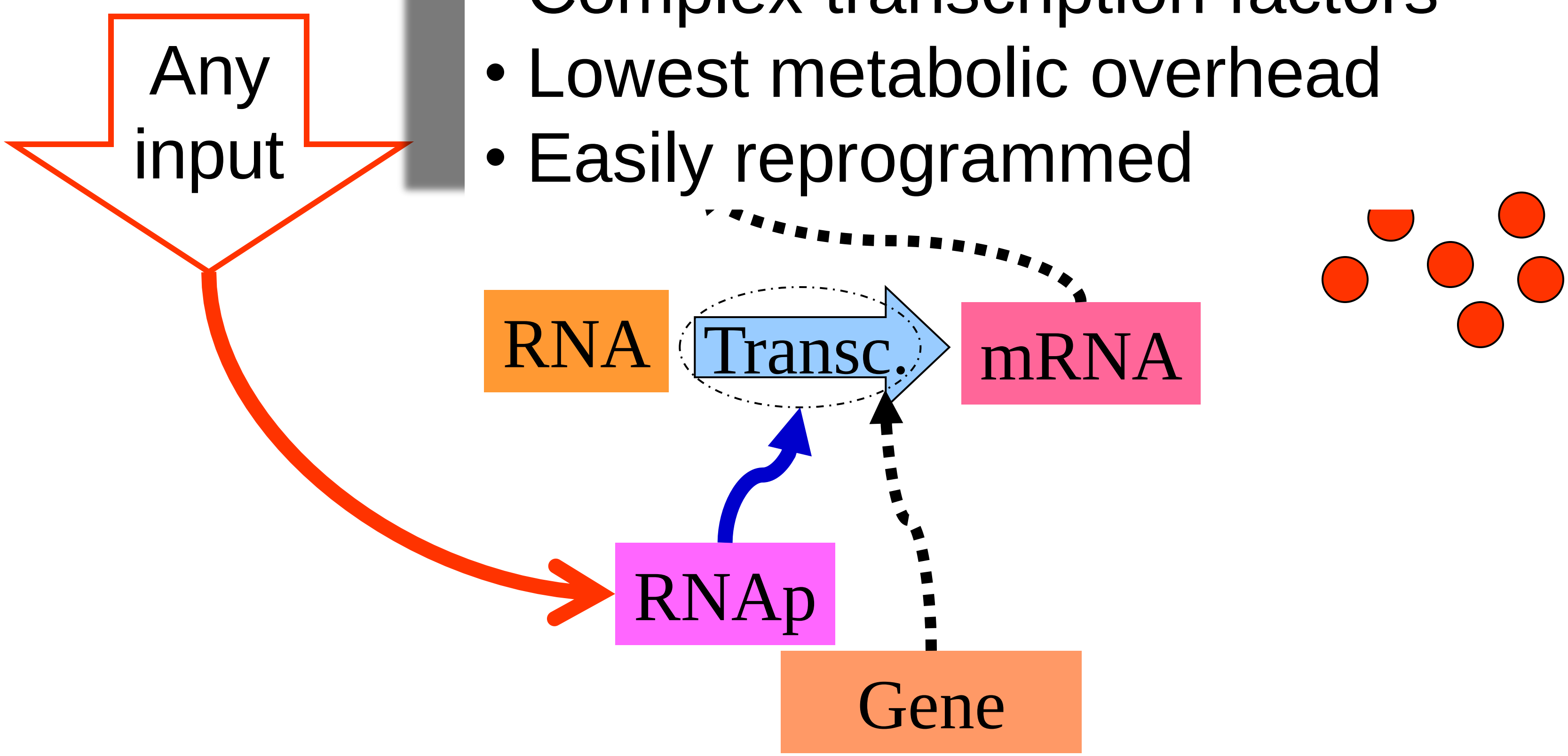
$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i q_i \right) + \sum_l p_l c_l \right)$$

$$\Rightarrow U_i'(x_i) = q_i \Rightarrow x_i = \left(U_i' \right)^{-1} (q_i)$$

No duality gaps?
Multipath routing?
Coherent pricing?



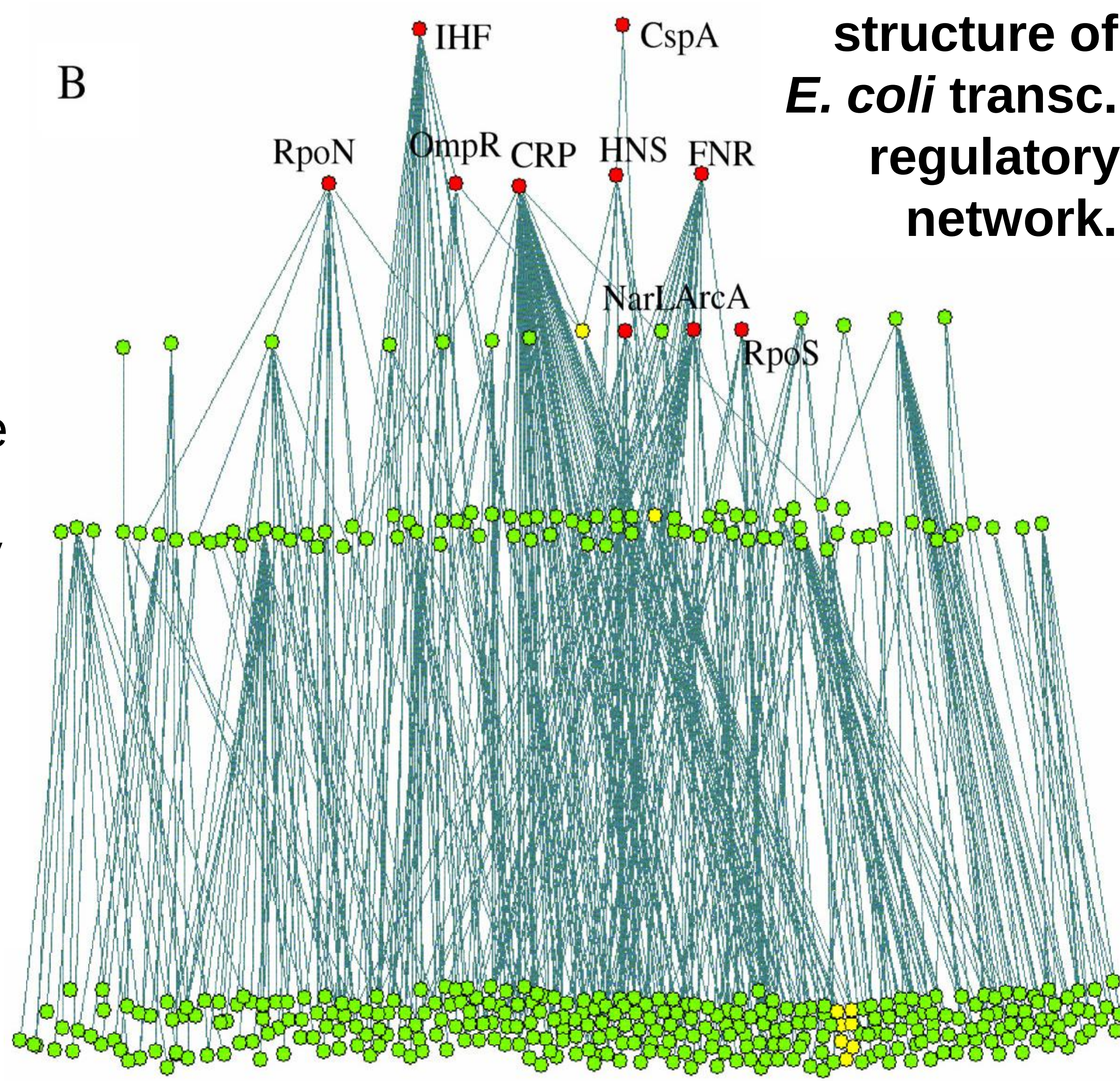
- Slowest transcription control
- Complex transcription factors
- Lowest metabolic overhead
- Easily reprogrammed



Hierarchical structure of *E. coli* transc. regulatory network.

All transcriptional regulatory links are downward. Nodes are operons. Global regulators are red. Yellow marked nodes are operons in the longest regulatory pathway related with flagella motility.

Ma *et al. BMC Bioinformatics* 2004 **5**:199 doi:10.1186/1471-2105-5-199



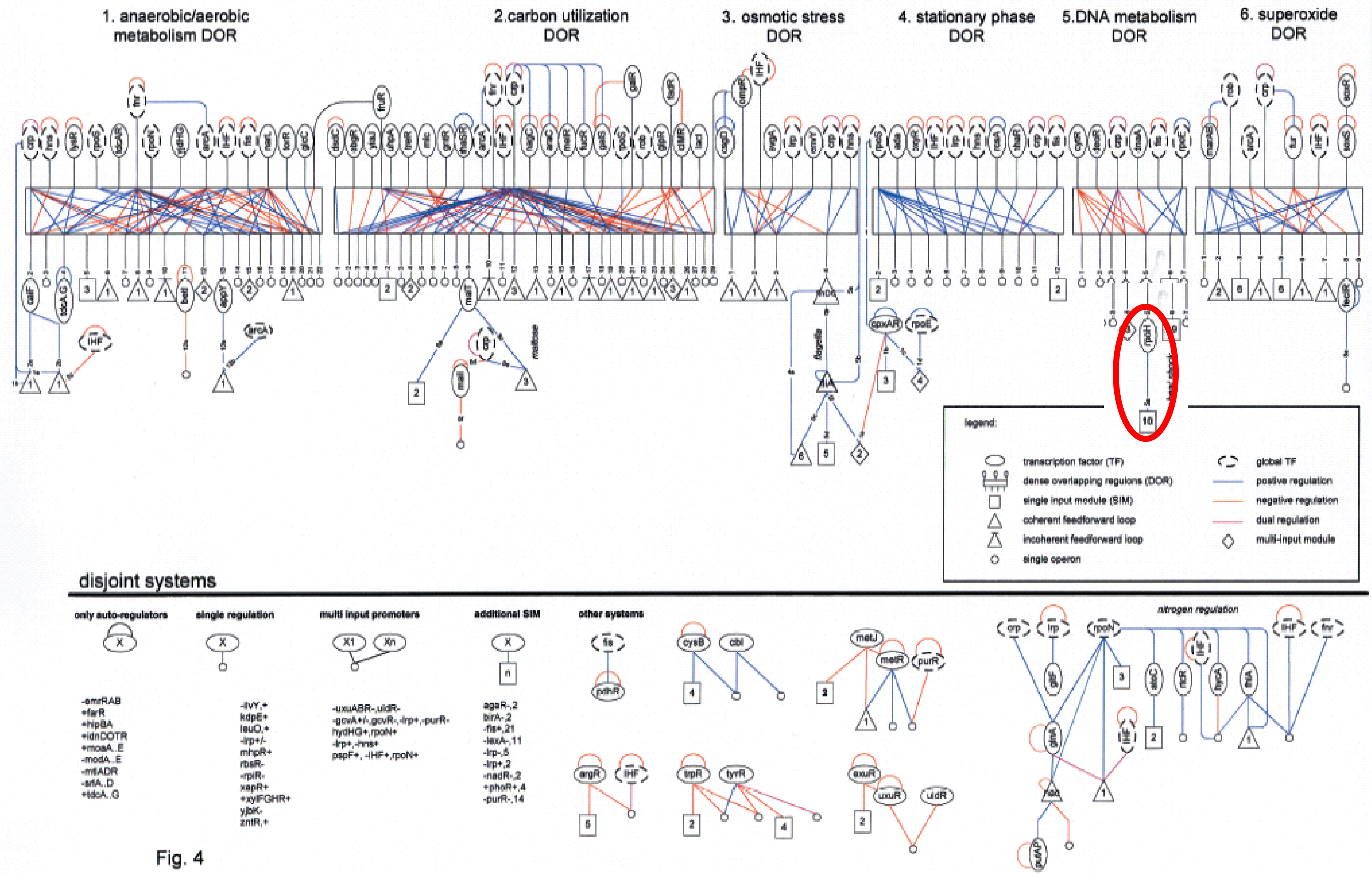
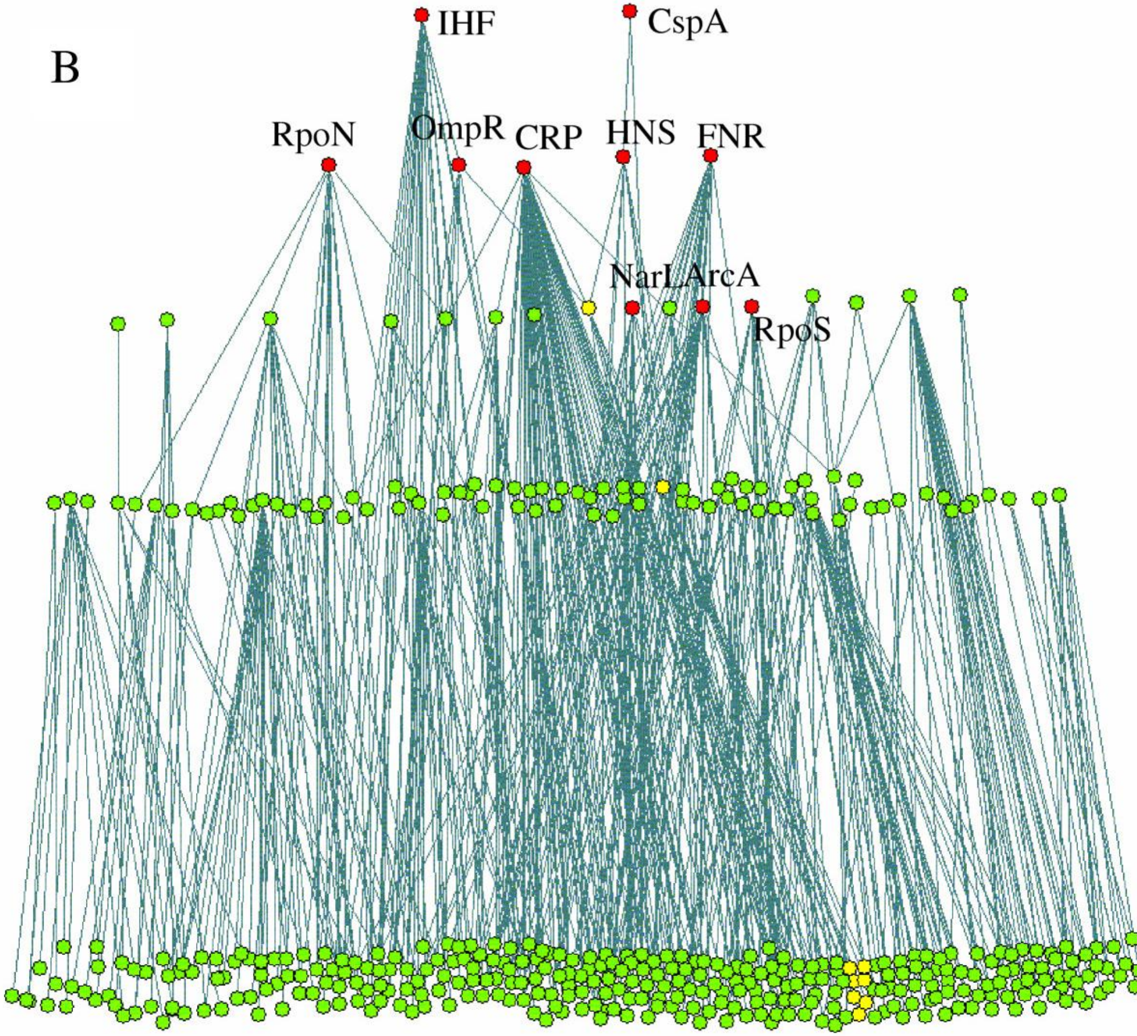

1. anaerobic/aerobic metabolism DOR
2.carbon utilization DOR
3. osmotic stress DOR
4. stationary phase DOR
5.DNA metabolism DOR
6. superoxide DOR
maltose
flagella
heat shock
legend:
transcription factor (TF)
dense overlapping regulons (DOR)
single input module (SIM)
coherent feedforward loop
incoherent feedforward loop
single operon
global TF
positive regulation
negative regulation
dual regulation
multi-input module
disjoint systems
only auto-regulators
single regulation
multi input promoters
additional SIM
other systems
nitrogen regulation

Fig. 4

Note: all feedback in this picture has been removed in two ways:

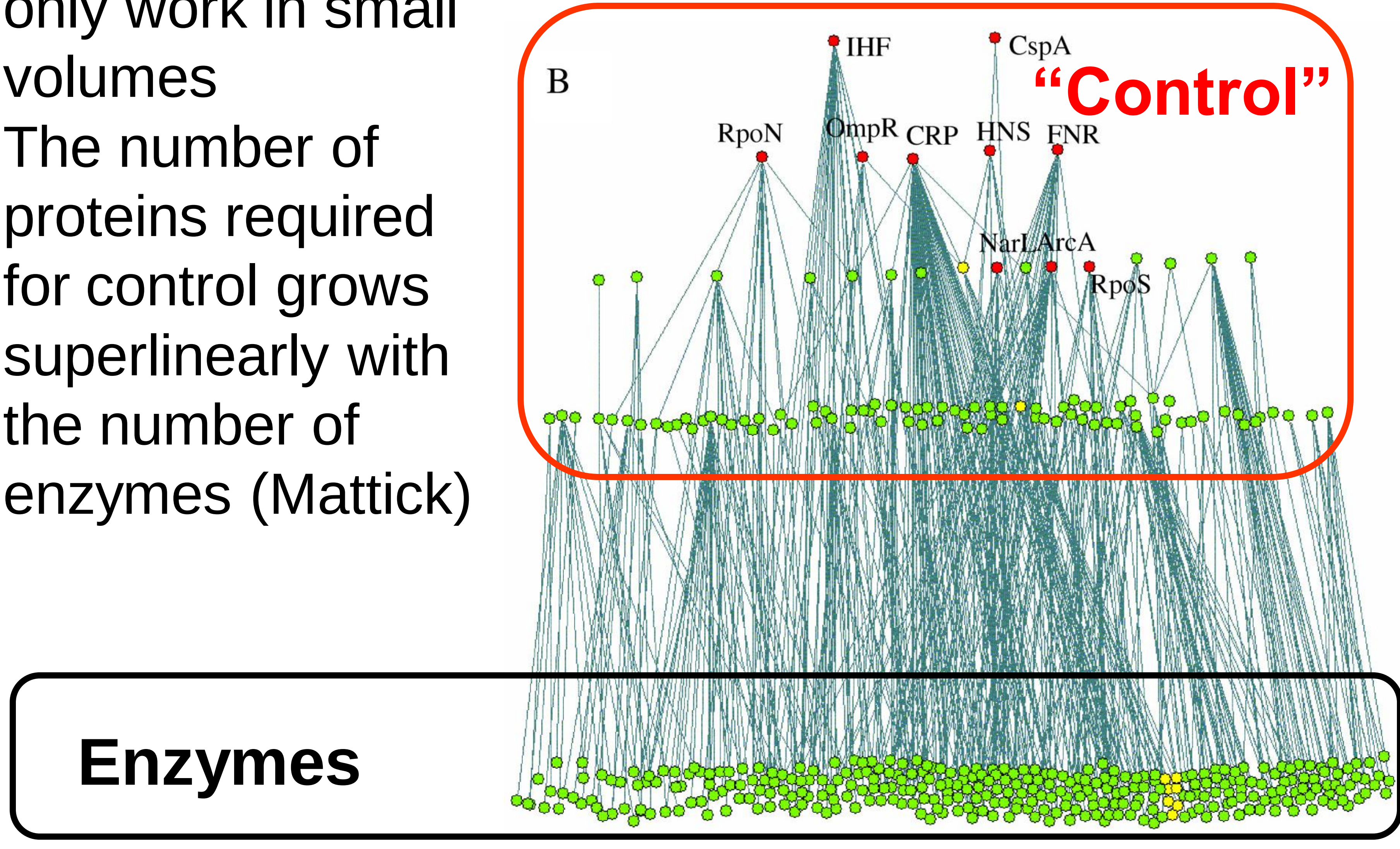
1) There are self-loops where an operon is controlled by one it's own genes
2) All the real complex control is in the protein interactions not shown (e.g. see heat shock details)

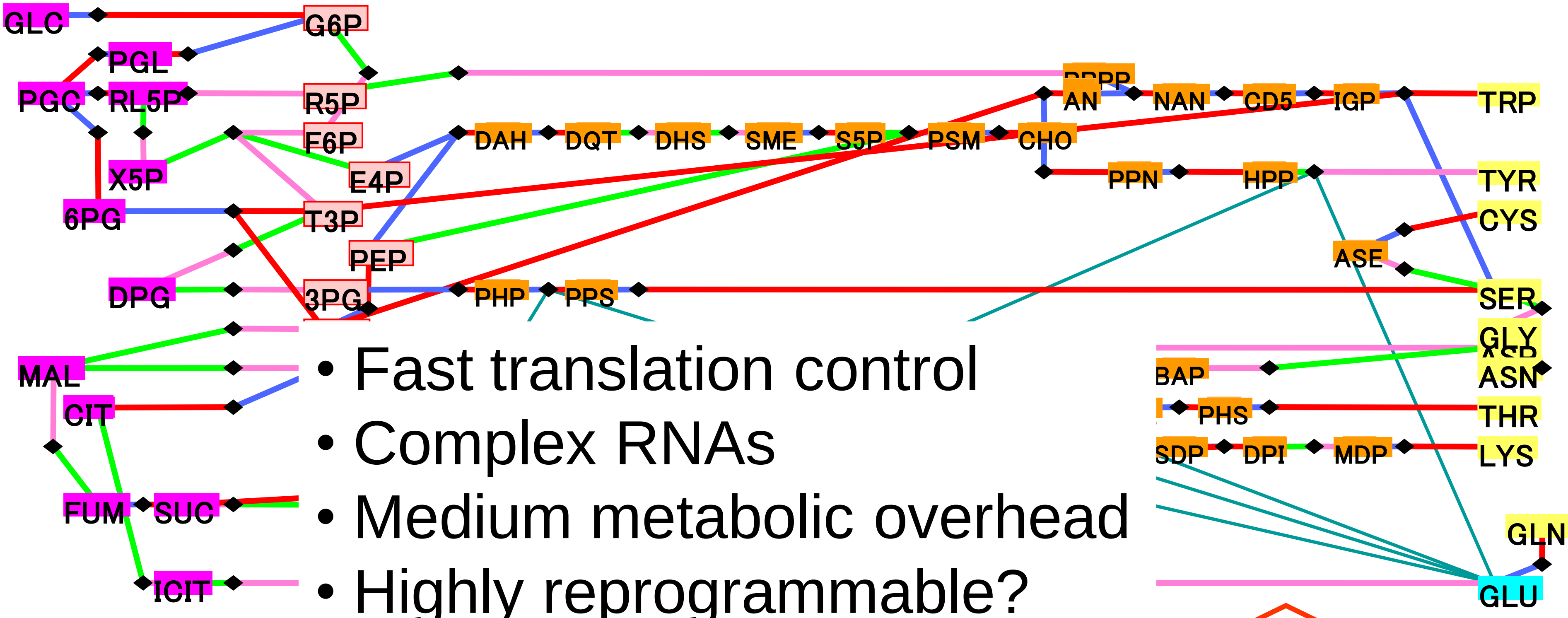
These are not really ***control*** systems, they just initiate manufacturing



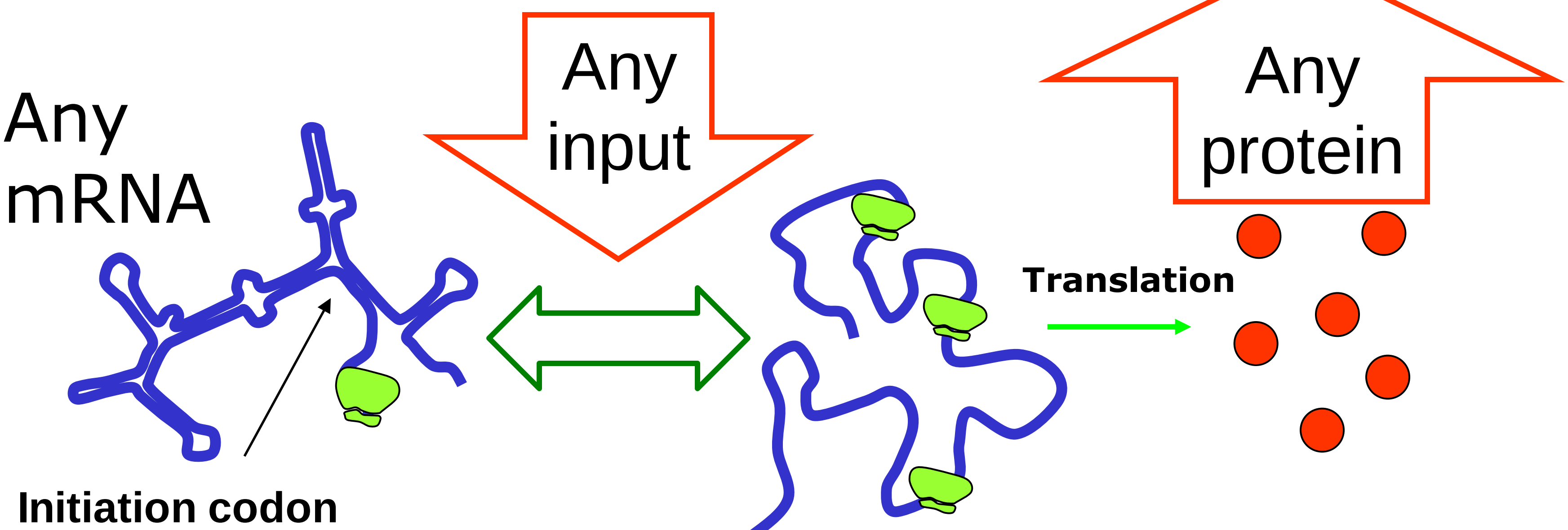
This architecture has limited scalability:

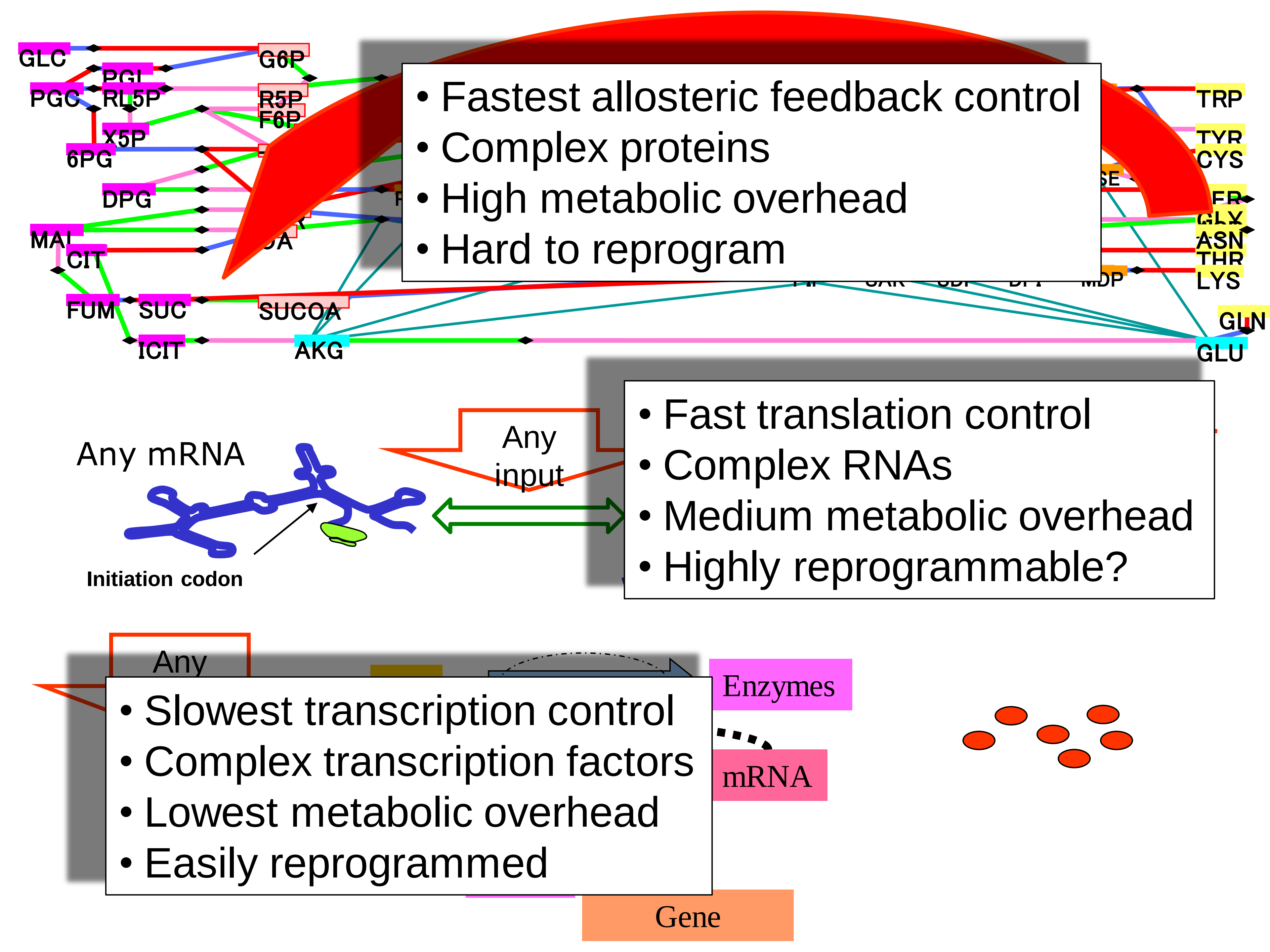
1) Fast diffusion can only work in small volumes
2) The number of proteins required for control grows superlinearly with the number of enzymes (Mattick)





- Fast translation control
- Complex RNAs
- Medium metabolic overhead
- Highly reprogrammable?




GLC
G6P
PGI
PGC
RL5P
R5P
F6P
X5P
6PG
DPG
MAL
CIT
FUM
SUC
SUCOA
ICIT
AKG
TRP
TYR
CYS
LYS
THR
ASN
GLN
GLU
• Fastest allosteric feedback control
• Complex proteins
• High metabolic overhead
• Hard to reprogram
Any mRNA
Initiation codon
Any input
• Fast translation control
• Complex RNAs
• Medium metabolic overhead
• Highly reprogrammable?
Any
• Slowest transcription control
• Complex transcription factors
• Lowest metabolic overhead
• Easily reprogrammed
Enzymes
mRNA
Gene