Understanding the origin and organization of biochemistry

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based on work with

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Complex Systems Summer School 2007, Beijing

3-day outline

- Day I: Introduction to biochemistry and the problem of the origin of life
- Day II: Studying carbon fixation as a self-organized process
- Day III: From metabolism to self-replication and cells

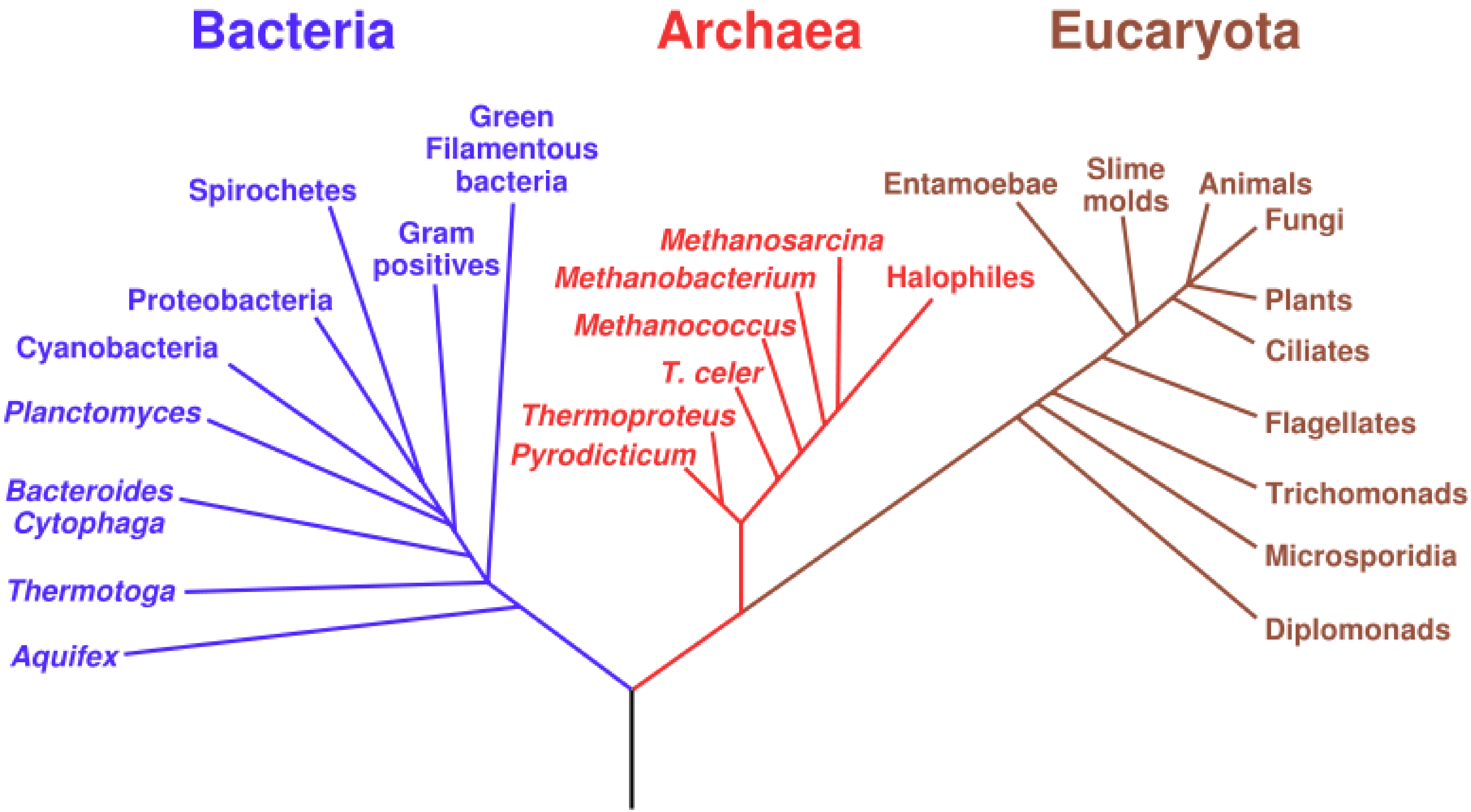
Day 1: general introduction

- How to think about the organization of life
- Life's universal features
- Bioenergetics unifies living processes
- Comparing chemical evolution to species evolution
- Using these observations to think about the origin of life

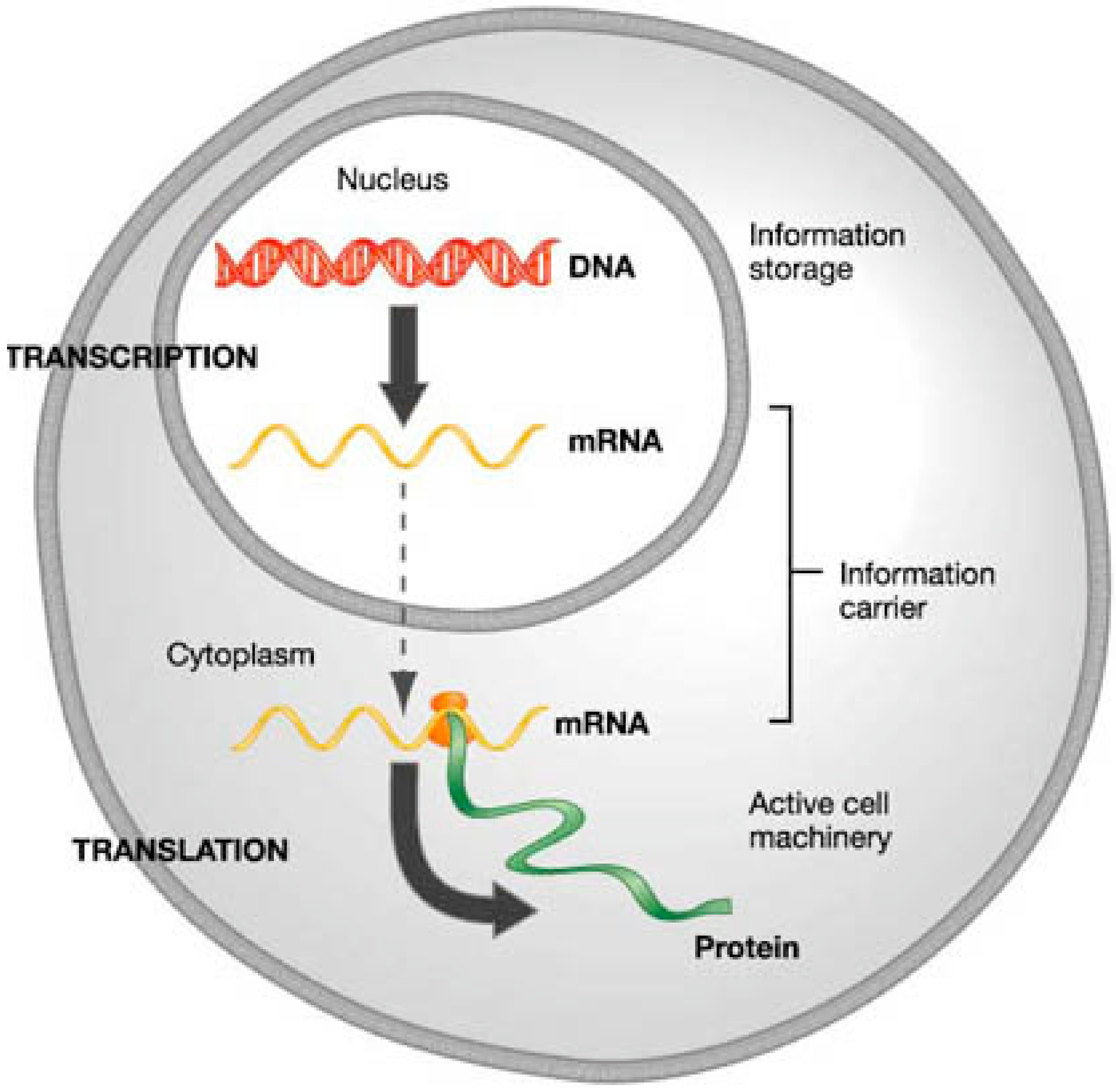
Ways of thinking about organization in the biosphere

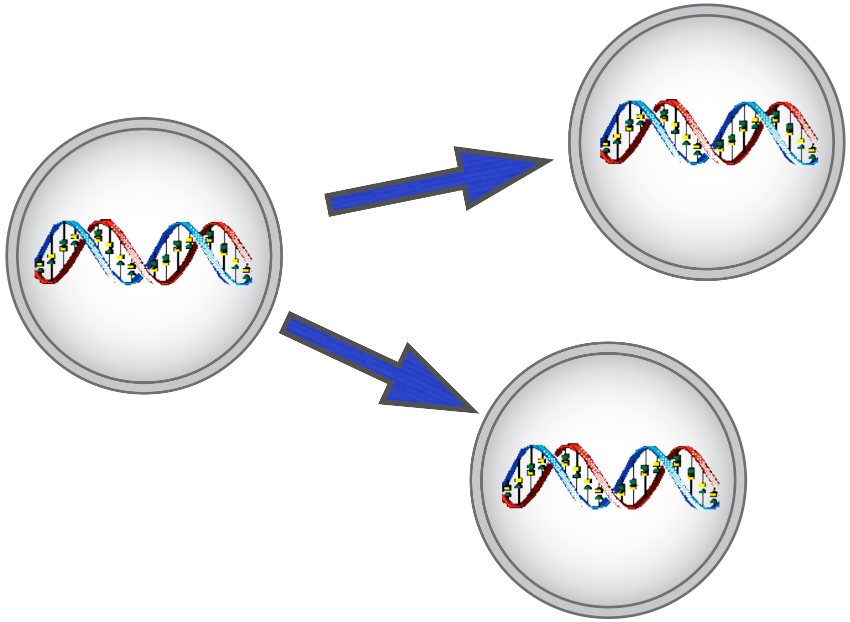
- Chance and necessity
- Control and metabolism
- Biosynthesis and ecology

Phylogenetic organization reflects the history of accidents



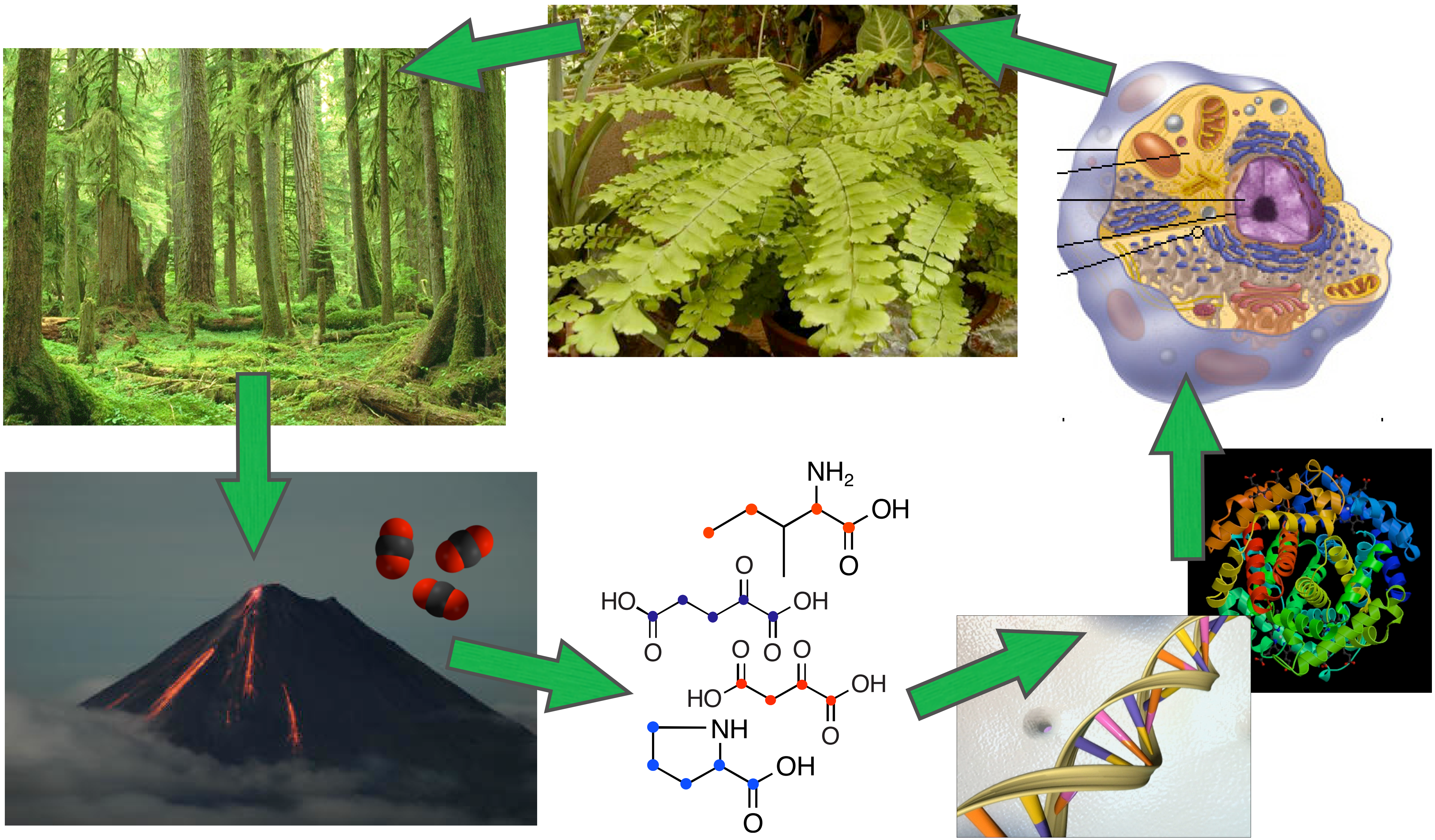
Much of the observed contingency is possible because of top-down control



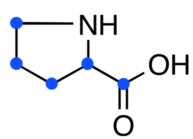


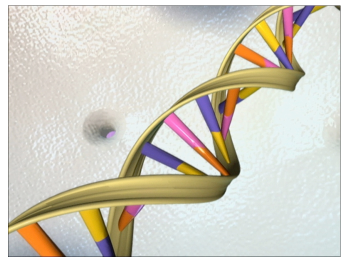
(Genes / enzymes provide “external” control of metabolism)

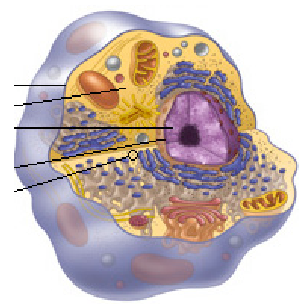
However, different levels of structure involve different problems of organization



Some kinds of organization seem more contingent; some seem more necessary







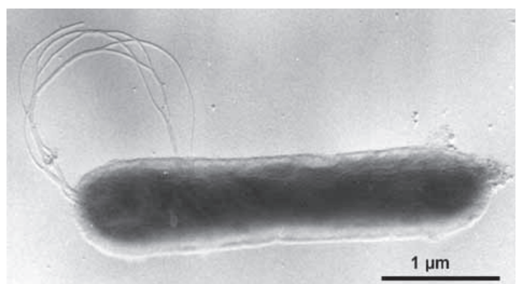
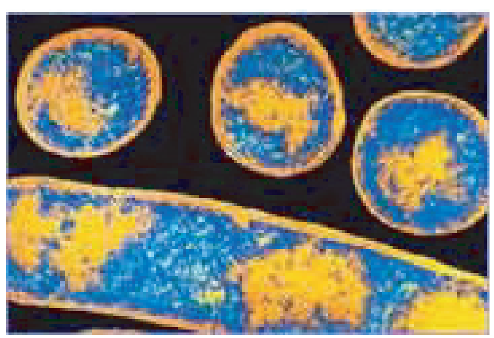
Necessity

Universal
Steady
Predictable

Chance

Variable
Fluctuating
Contingent

Metabolism is organized by different distinctions than phylogeny; more “function” than “control”

	Reductive metabolisms	Oxidative metabolisms	
Autotrophs			(Anabolism)
Heterotrophs			(Anabolism & Catabolism)

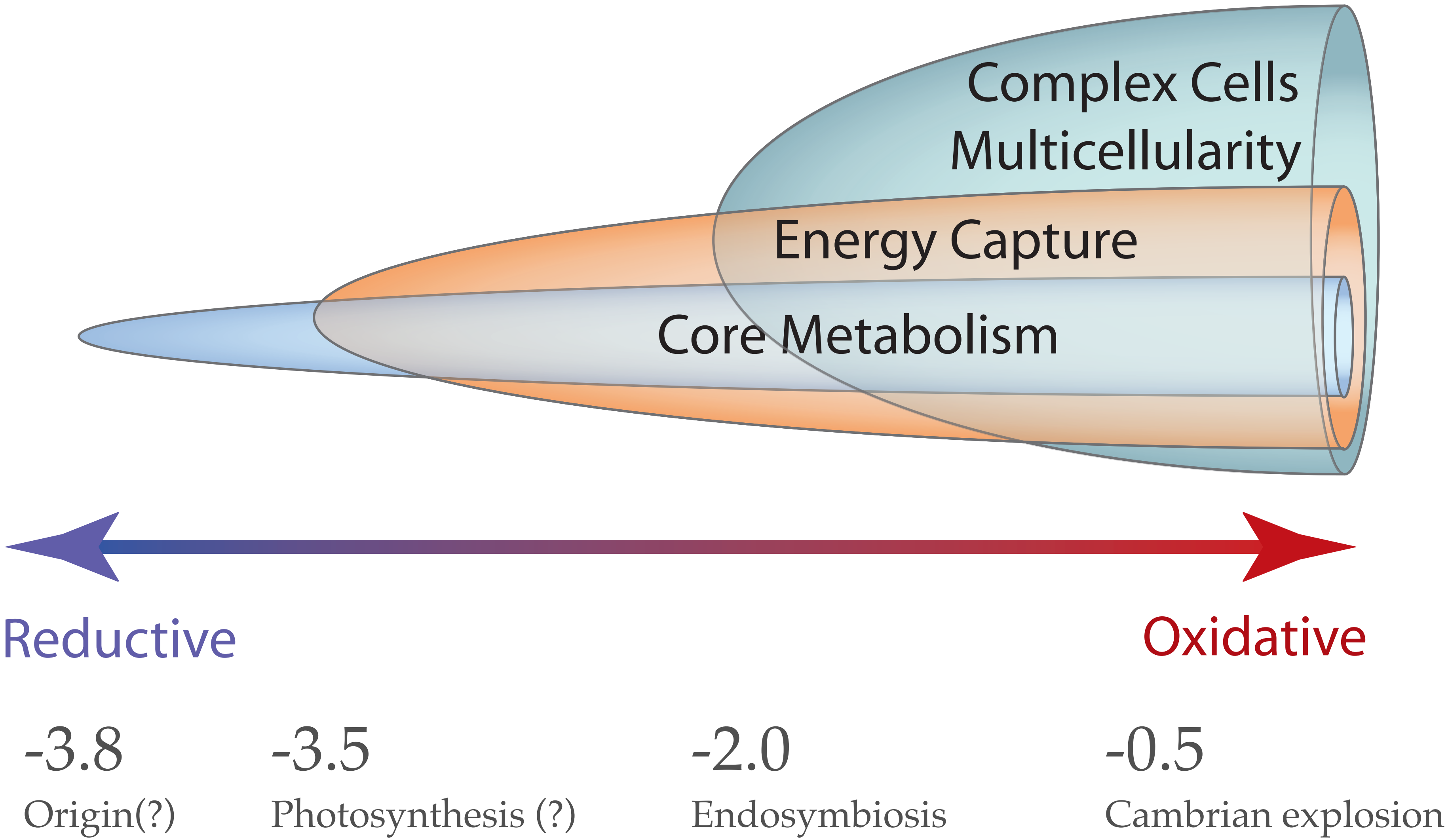
Whole-ecosystem metabolism is simpler and more universal than species metabolism

Reductive ecologies

Oxidative ecologies

(Ecosystems are more fundamental than organisms)

Geological / evolutionary time and complexity



(The major transitions in evolution were chemical)

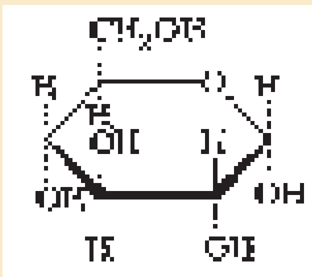
Universal features of life

- Small-molecule metabolic substrate
- Polymer chemistry and cofactors
- Macro-molecular catalysts and genes
- Membranes and compartments

The bulk of life is built from four kinds of small molecules

- Fatty acids (compartments, polar environments)
- Sugars (structure, signaling, energy storage)
- Amino acids (catalysis, structure)
- Nucleic acids (heredity, catalysis)

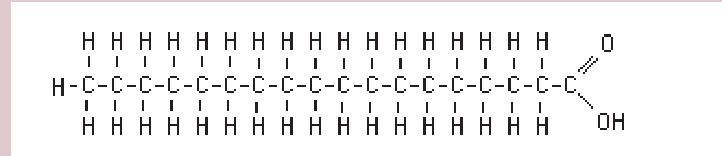
Molecules classes have characteristic chemical form



10s

sugars

Major Energy Carrier
Structure in cell walls

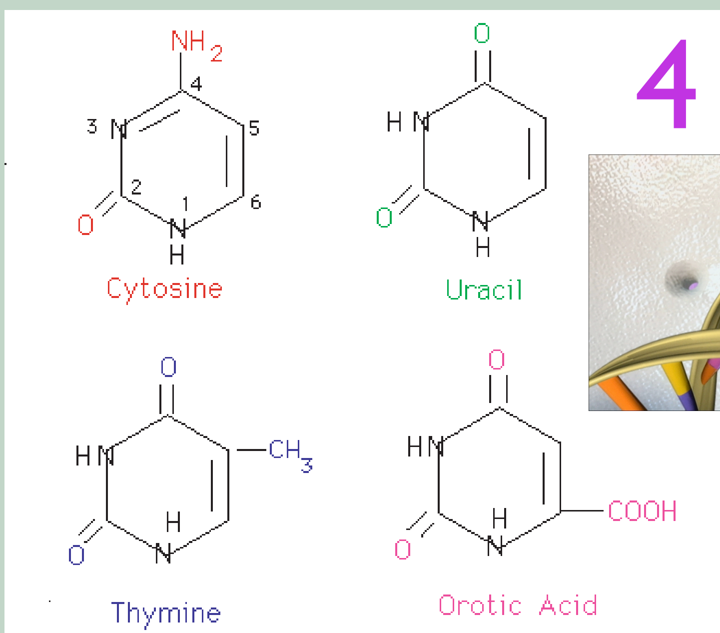


lipids

Compartments, proton semiconductors

10s

Nucleic acids



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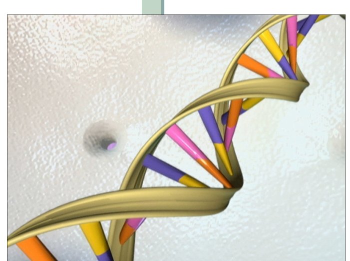
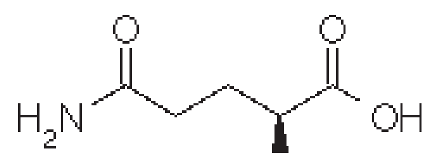


Structure, catalysis, heredity

glutamate



glutamine

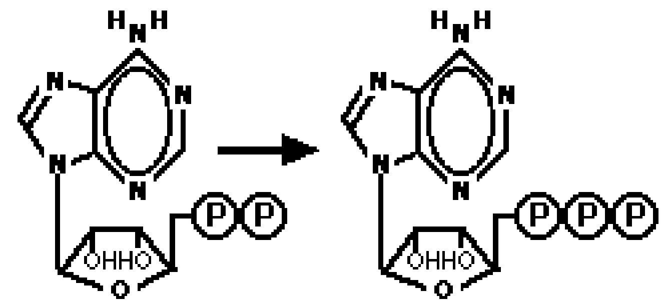
Amino acids

Catalysis/structure/motors

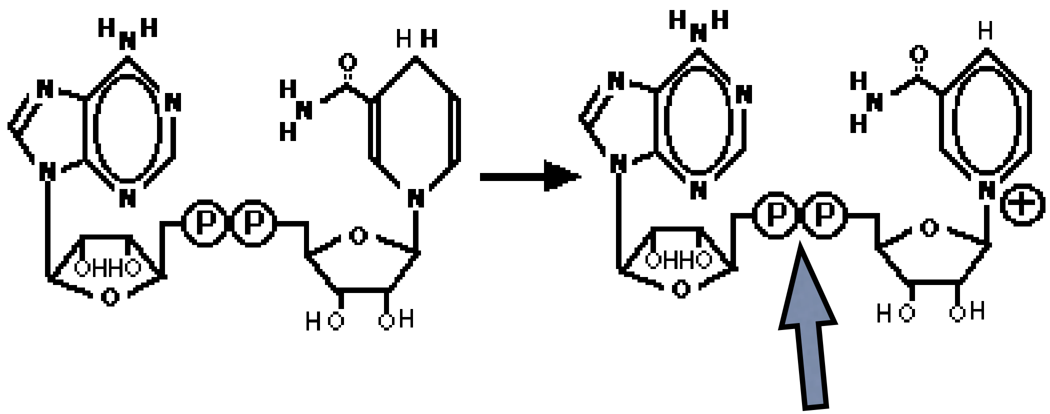
20

Cofactors are a special class of mid-sized molecules

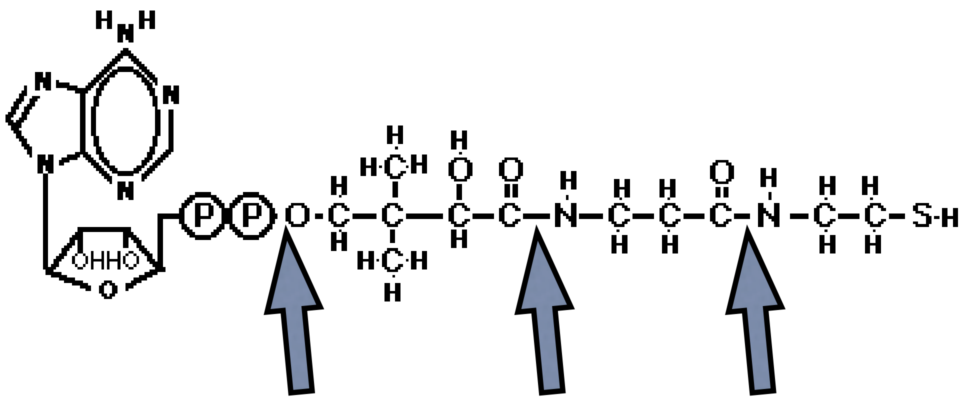
- ATP (gives and takes phosphates)



- NAD (gives and takes electrons)



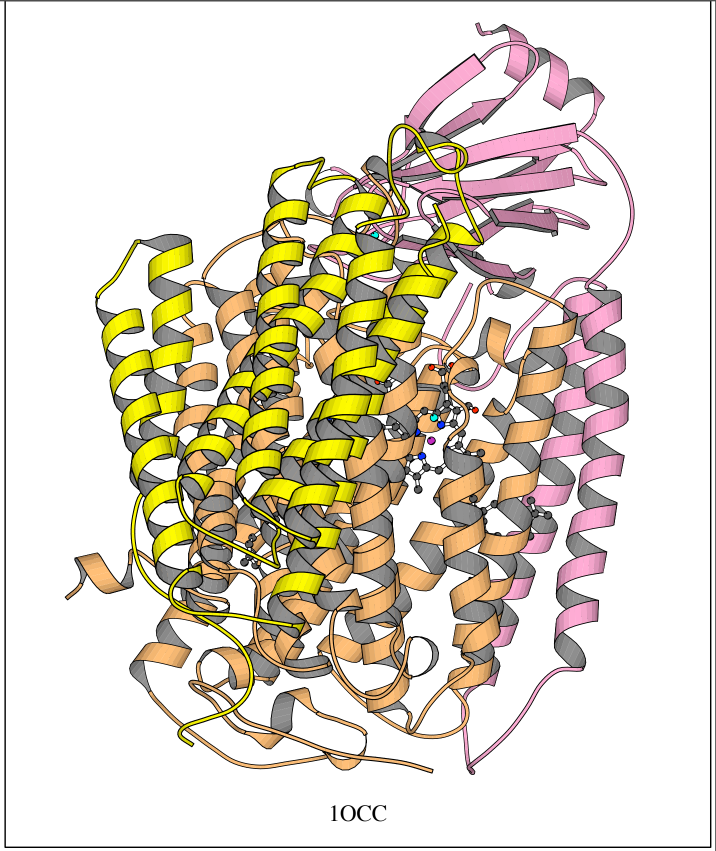
- Coenzyme A (exchanges electrons for phosphates through sulfur intermediate)



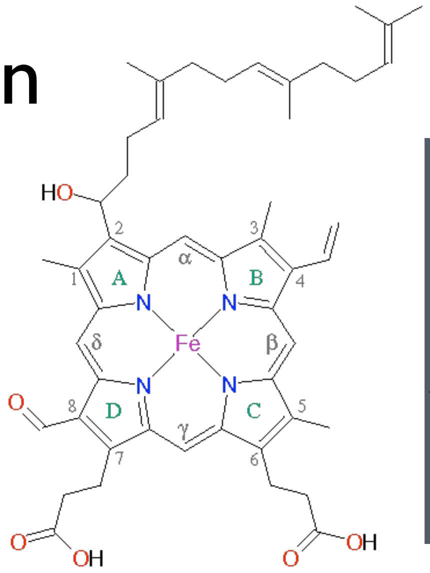
http://www.science-projects.com/MolecStruct.htm

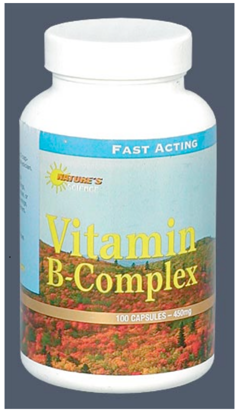
Macro-molecules provide catalysts and genetic templates

- Catalysts enhance reaction rates without being consumed
- Most modern catalysts are proteins, but some important ones are RNA
- Catalysts combine an active site with scaffolds or channels to hold or direct the substrates of the reaction
- Almost half of catalysts still use *cofactors* for the active site



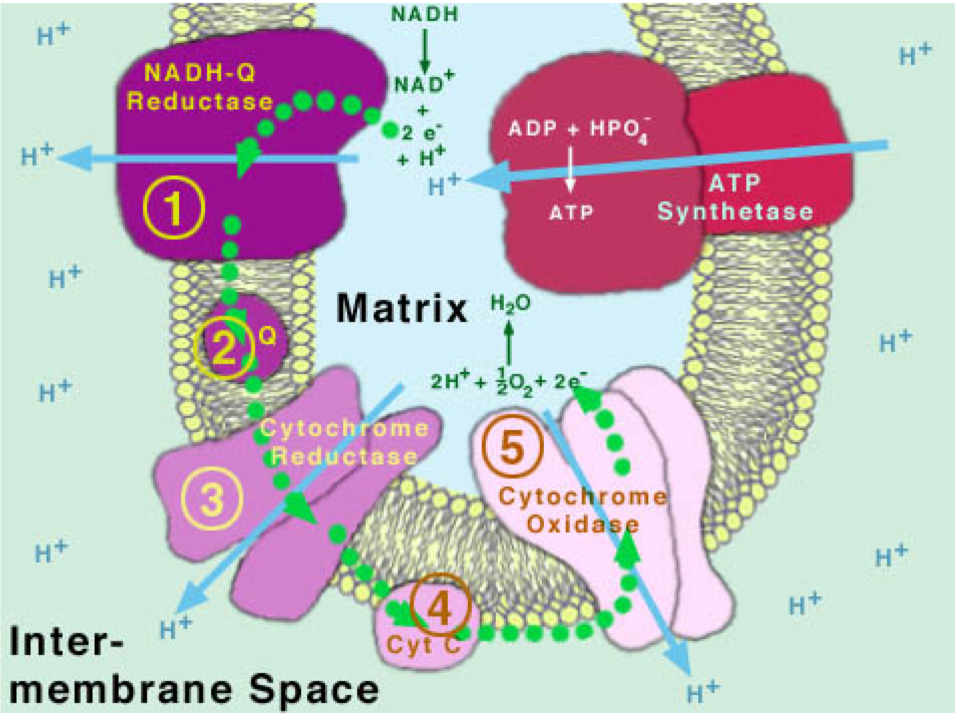
http://metallo.scripps.edu/PROMISE/1OCC.html





Physical structures control reactions and energy flow

- Include membranes, ribosomes, pores, pumps, motors, walls, cytoskeleton
- Topology, geometry, and physical chemistry of membranes are all used
  - Topology concentrates reactants, excludes toxins, and creates pH and voltage differences
  - Geometry creates continuous *energy currency*
  - Oily membranes in a water medium are *proton semiconductors*



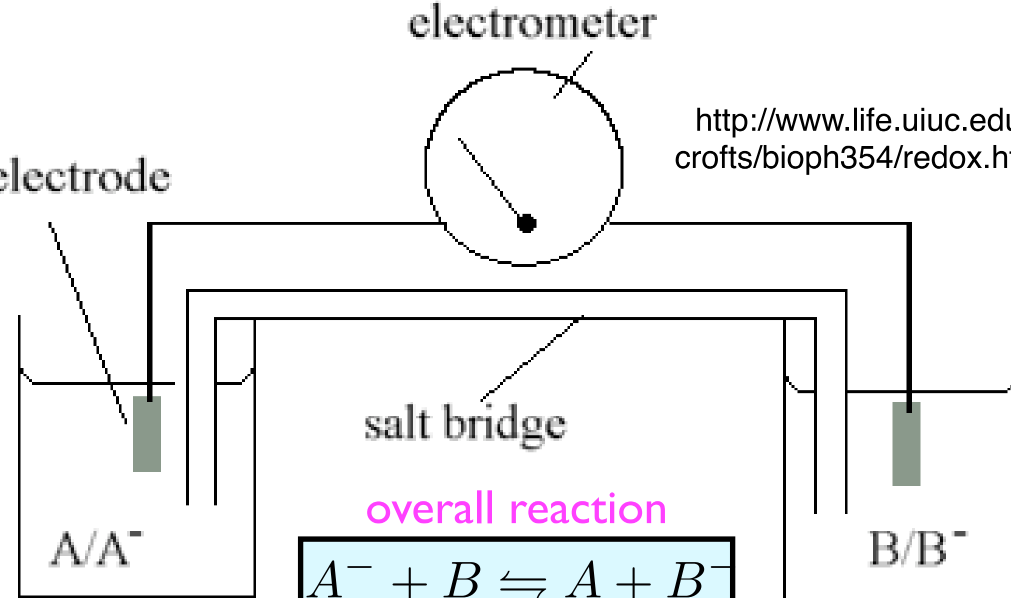
http://www.chemistry.wustl.edu/~edudev/LabTutorials/Cytochromes/cytochromes.html

Bioenergetics unifies living processes

- Electron transfer is the fundamental energy source
- Phosphates power polymerization
- Protons are used to couple electrons and phosphates

Reduction and Oxidation (redox) powers basic organic chemistry

- Transfer of an electron can lower or raise free energy
- The free energy change can be measured as a voltage if electrons move separately from substrates
- A pair like $A^- \leftrightharpoons A + e^-$ is known as a *redox couple*
- Voltage needed to halt a general reaction is proportional to the free energy (with concentration)
- Voltages are expressed relative to a standard couple



http://www.life.uiuc.edu/crofts/biophys354/redox.html

overall reaction

$$A^- + B \leftrightharpoons A + B^-$$

$$A^- \leftrightharpoons A + e^- \qquad B^- \leftrightharpoons B + e^-$$

general reaction schema

$$dn_i = \nu_i d\xi \qquad de = \nu_e F d\xi$$

voltage equivalent

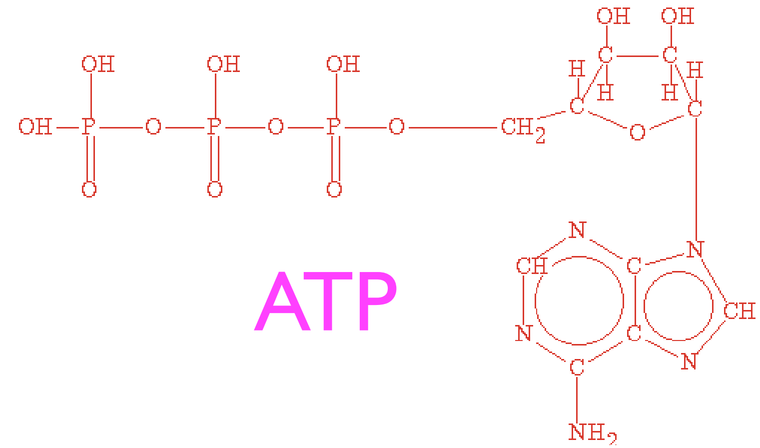
$$\nu_e F E = -\Delta G_0 - RT \sum_i \ln{[C_i]^{\nu_i}}$$

reference couple

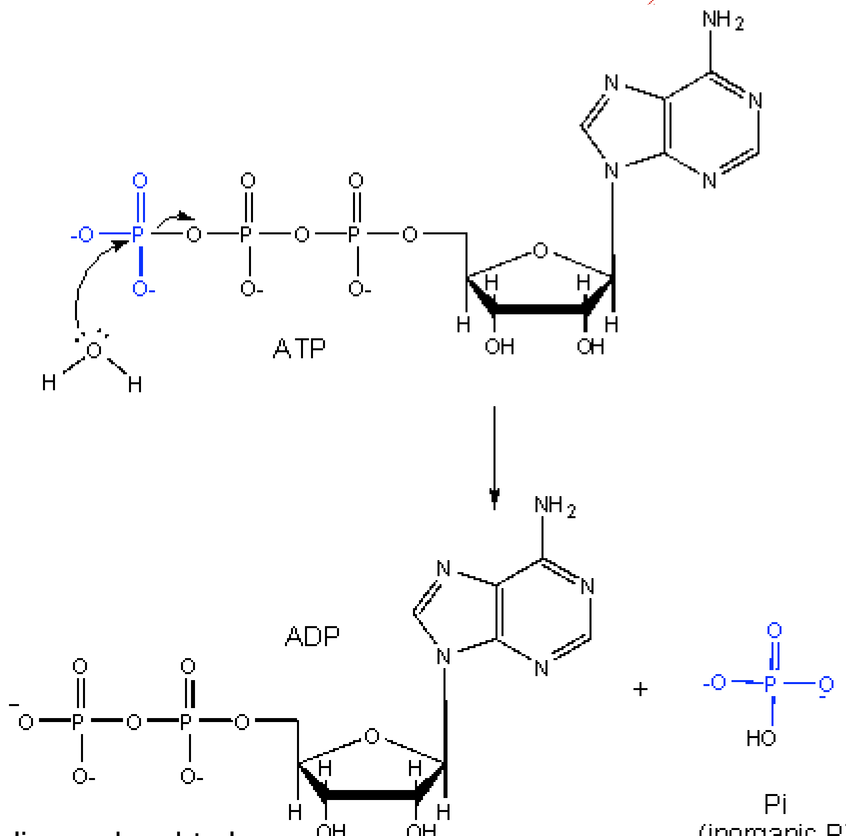
$$H_2(\text{gas}) \leftrightharpoons 2H^+ + 2e^-$$

Phosphate energy is released by hydrolysis

http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBookATP.html



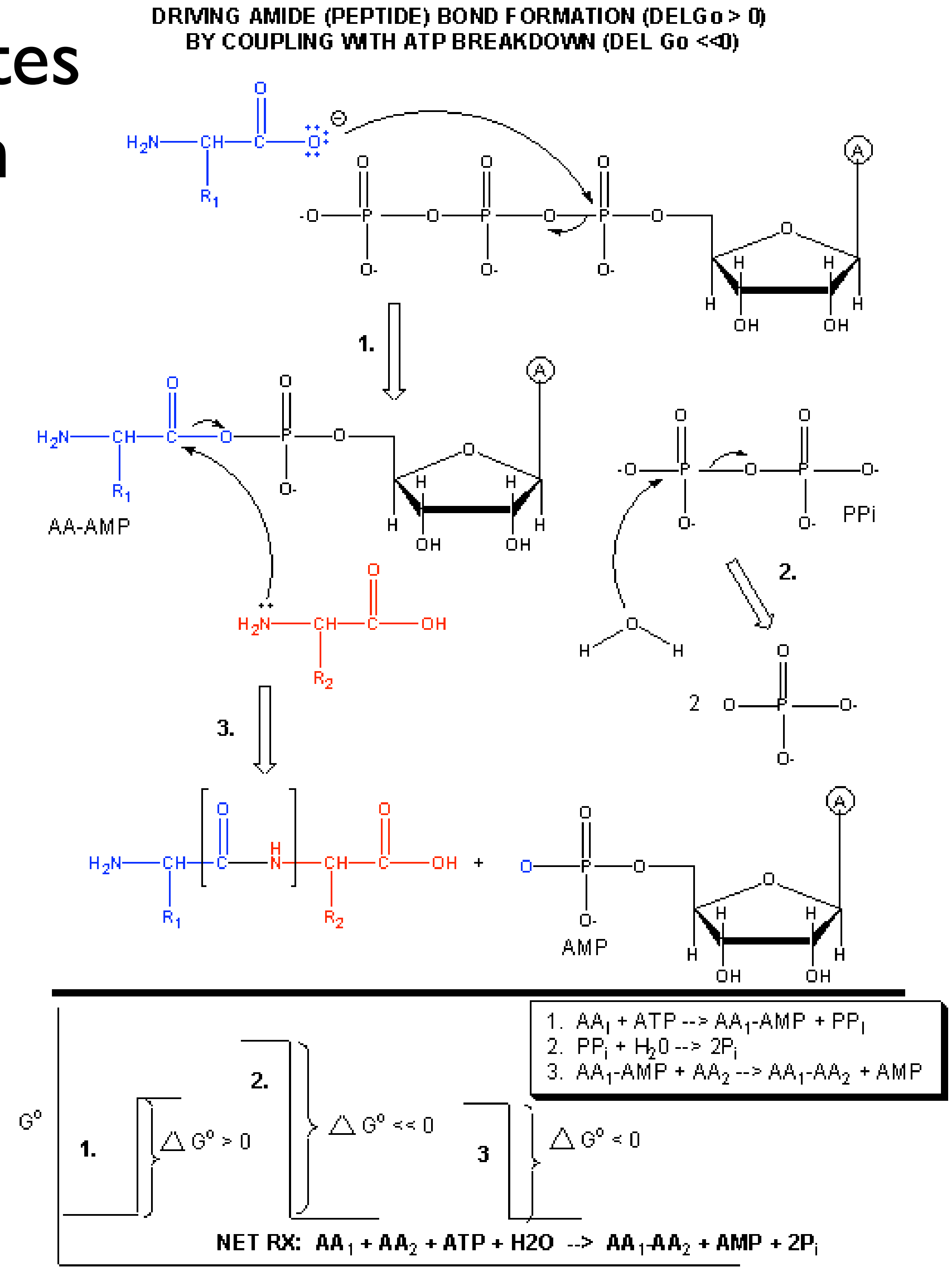
- All biopolymers are formed by *dehydration* reactions *in water solution!*
- Dehydrating agent is ATP, GTP, etc
- ATP has an inorganic analogue, polyphosphate, which has also been found in all organisms searched for it



http://employees.csbsju.edu/hjakubowski/classes/ch331/oxphos/olcouplingoxphos.html

Activation with phosphates enables polymerization

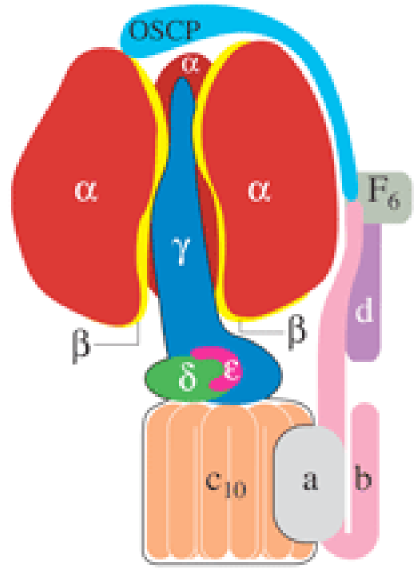
- Using activation of a monomer as an intermediate in ATP hydrolysis dehydrates the monomer to produce a bond



http://employees.csbsju.edu/hjakubowski/classes/ch331/oxphos/olcouplingoxphos.html

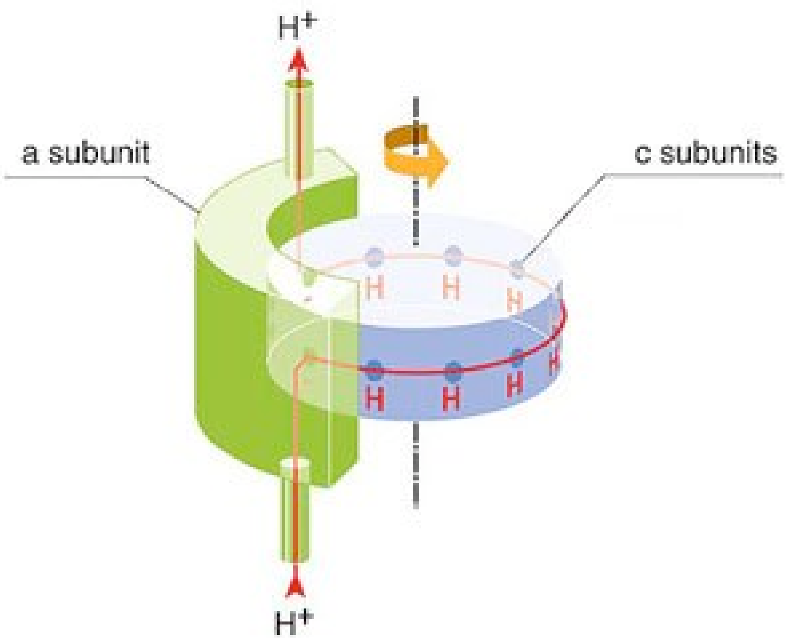
ATP is recycled from proton energy

- ATP synthase (and related flagellar motors) combines a transport pore for H^+ with a rotory shaft



Mitochondrial ATP Synthase

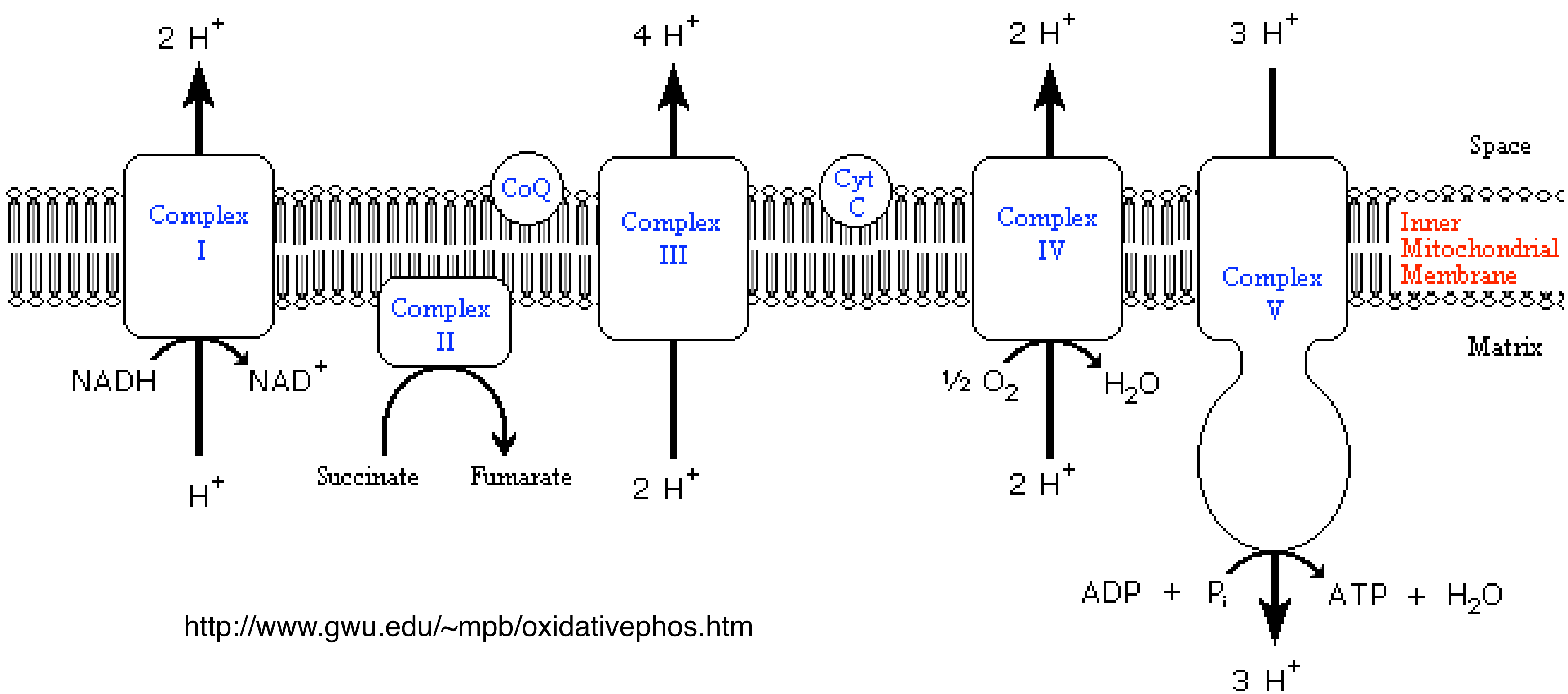
- Proton flux through membranes is only permitted by rotation of the shaft, which deforms enzymes to make ATP



http://www.mrc-dunn.cam.ac.uk/research/atpase.html

Respiration generates protons from reductant to recycle phosphate; both occur at membranes

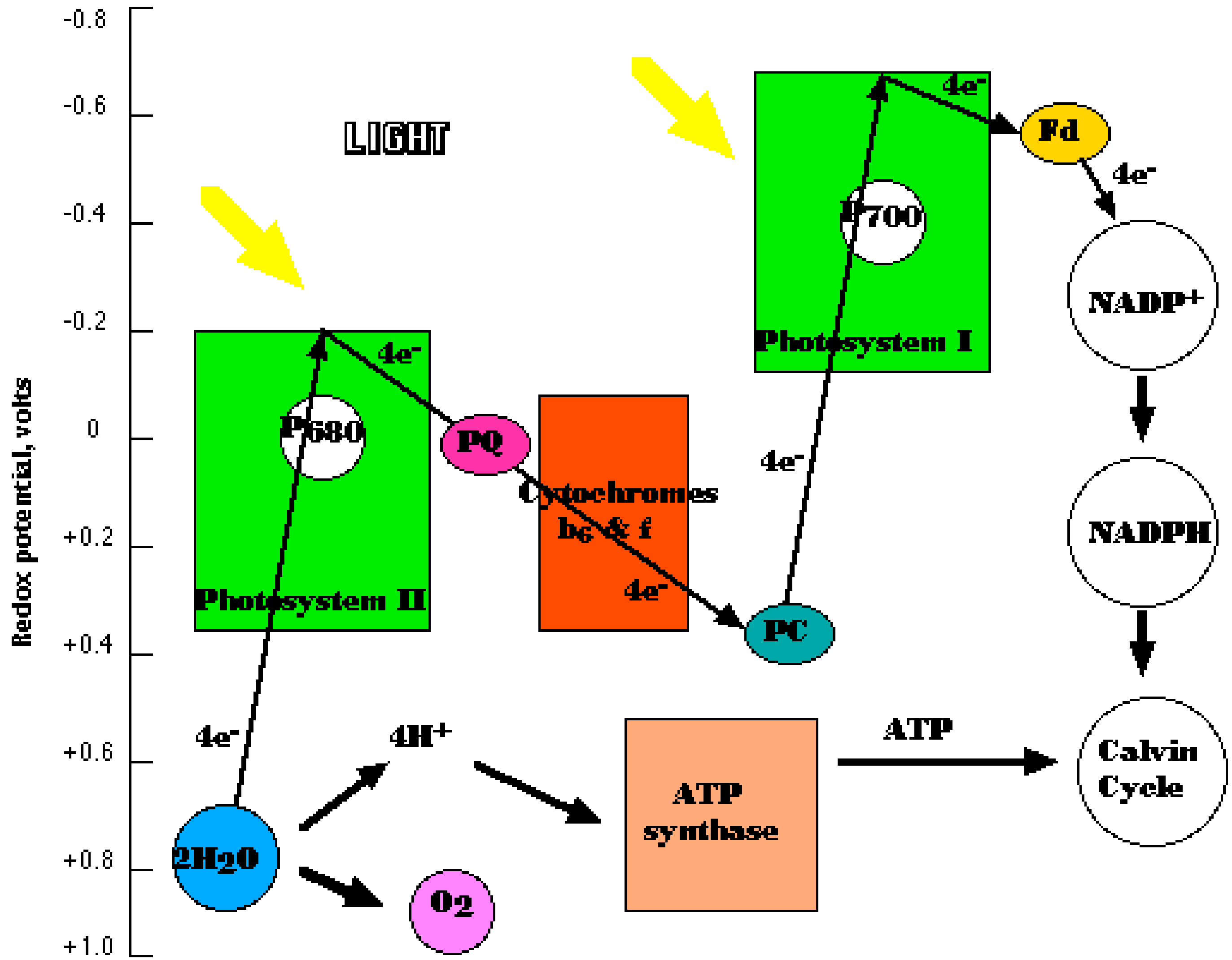
- Lipid-soluble cofactors (quinones) couple electron transfer to proton pumping
- Proton return recycles ATP from ADP and P_i



http://www.gwu.edu/~mpb/oxidativephos.htm

The function of photosynthesis is to produce reductant from light

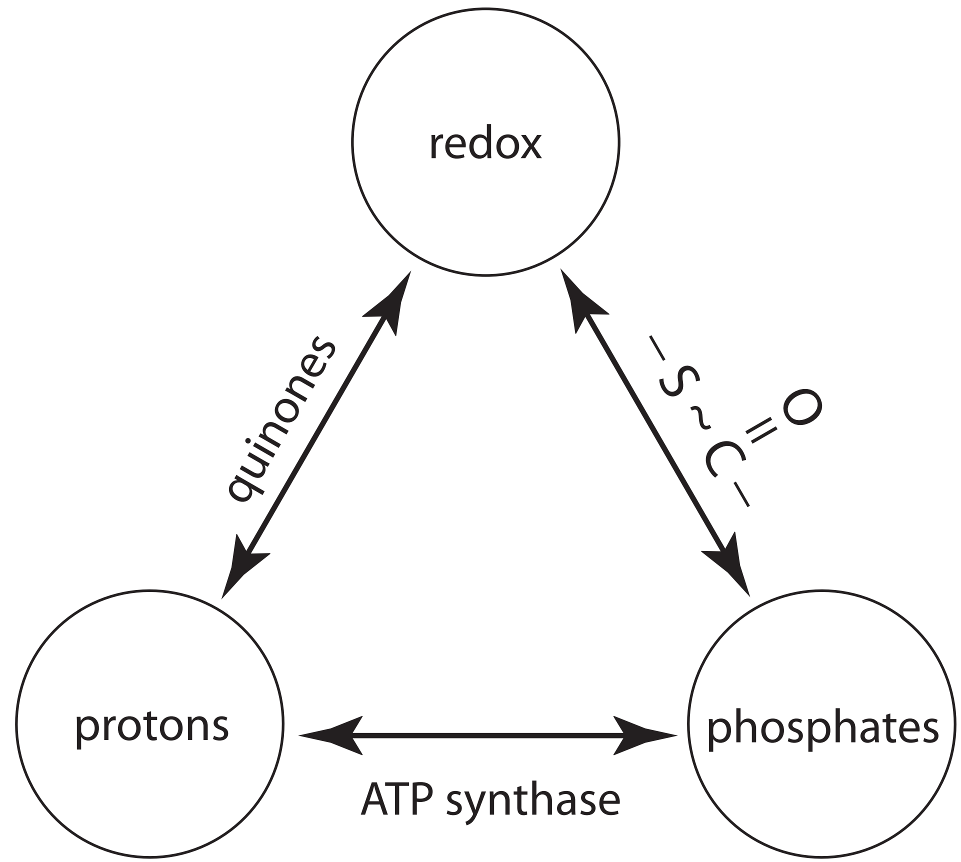
- Electrons are progressively raised in redox potential, then donated to $NADP^+$, to make NADPH, a powerful reductant used in anabolism
- Protons pumped directly can also be used to recycle phosphates



http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/L/LightReactions.html

All biological energy sources are interconvertible

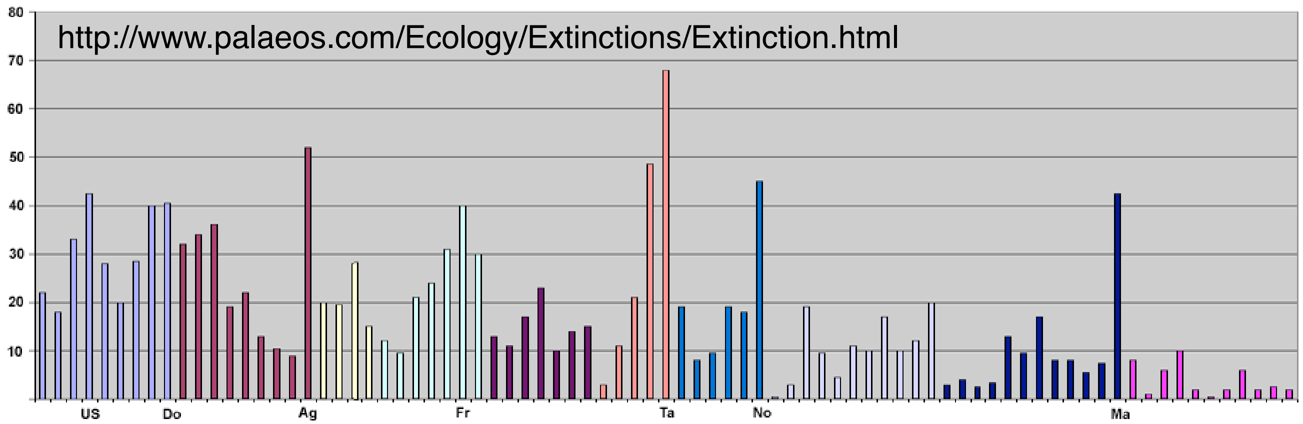
- Permits environmental flexibility and buffers against fluctuations
- Environmental redox couples are widely diverse
- Cellular use of phosphates and protons is much more uniform



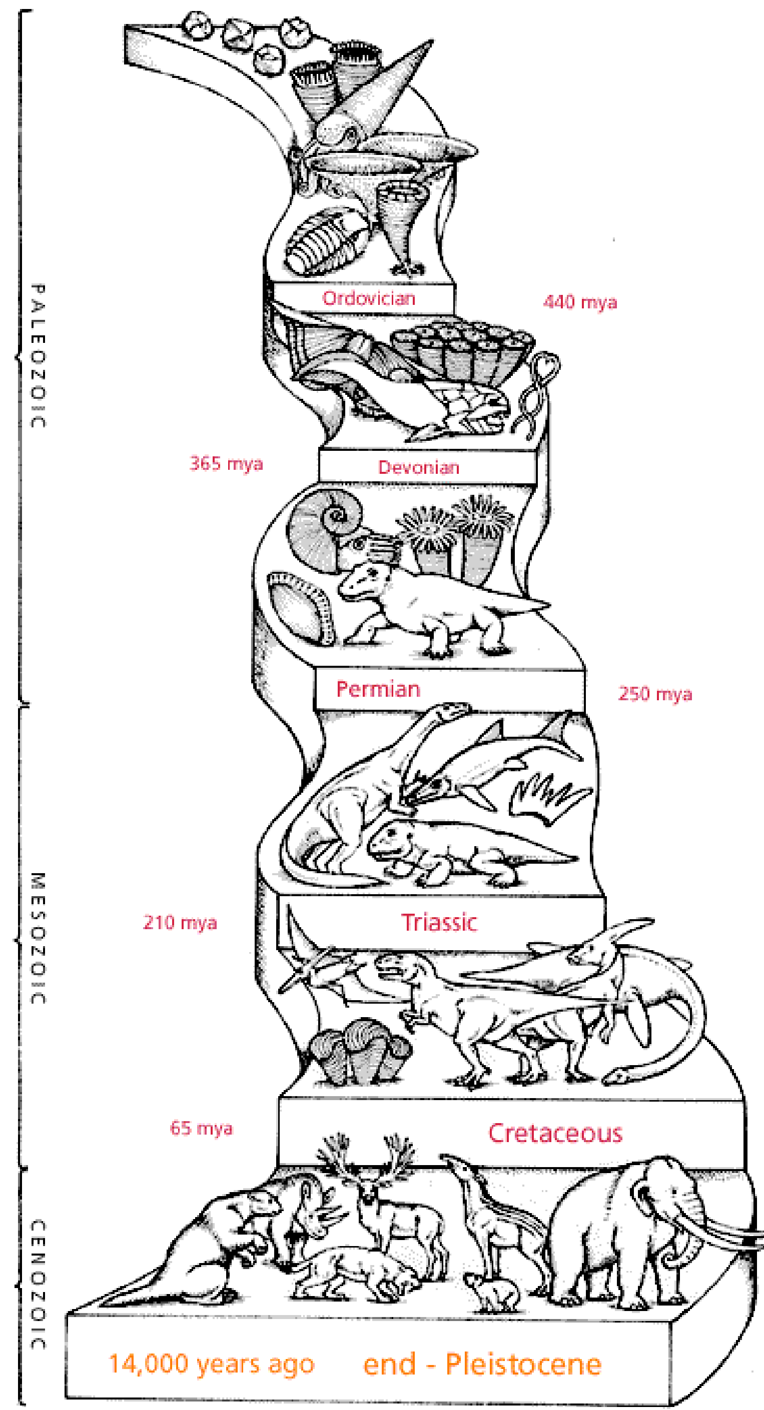
The dynamics of species and ecologies is qualitatively different from the dynamics of chemistry

- Species dynamics is not universal or steady
- Darwinian evolution and ecological structure may reflect the dynamics of partition rather than chemistry

Species go extinct and ecosystems undergo re-arrangements



- Extinctions at many levels have happened constantly
- Yet core biochemistry has persisted with little loss and only occasional innovation

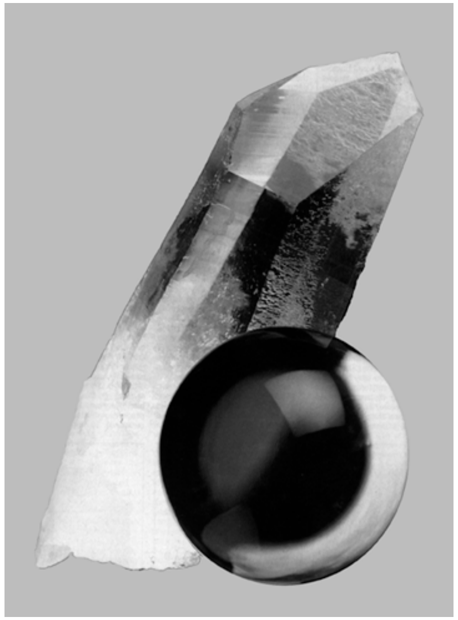


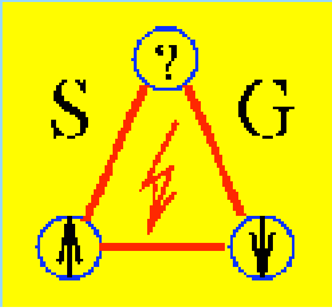
http://www.amnh.org/science/biodiversity/extinction/Intro/OngoingProcess.html

Research Idea

Spin glasses: a mathematical model for ecological organization?

- Glasses: solids without crystal order
- Arise where too many constraints make satisfiability impossible
- Have a huge number of "equally bad" solutions to energy minimization
  - Solutions are ***qualitatively similar***
  - Each solution is stable or metastable
  - Shift between solutions occurs by avalanche dynamics





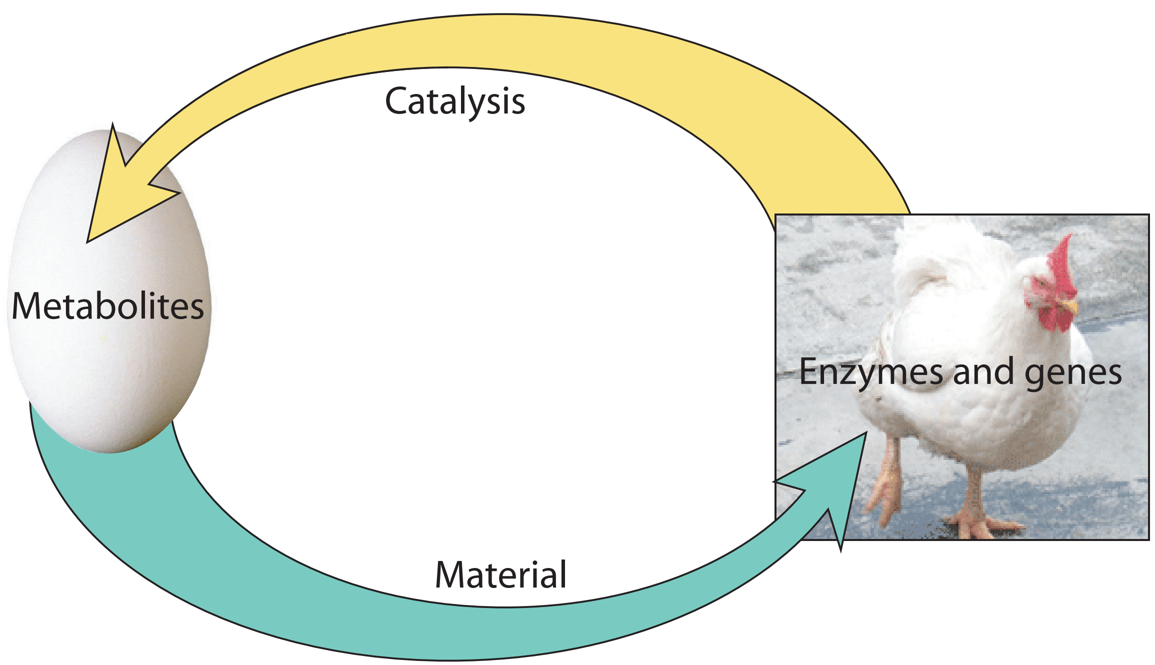
"Frustration"

Clues to thinking about the origin of life

- Chemistry and function are hierarchical
- Biosynthesis has a simple and universal core
- Reducing metabolisms are simpler than oxidizing metabolisms
- The structure of metabolism combines elements of randomness and of constraint

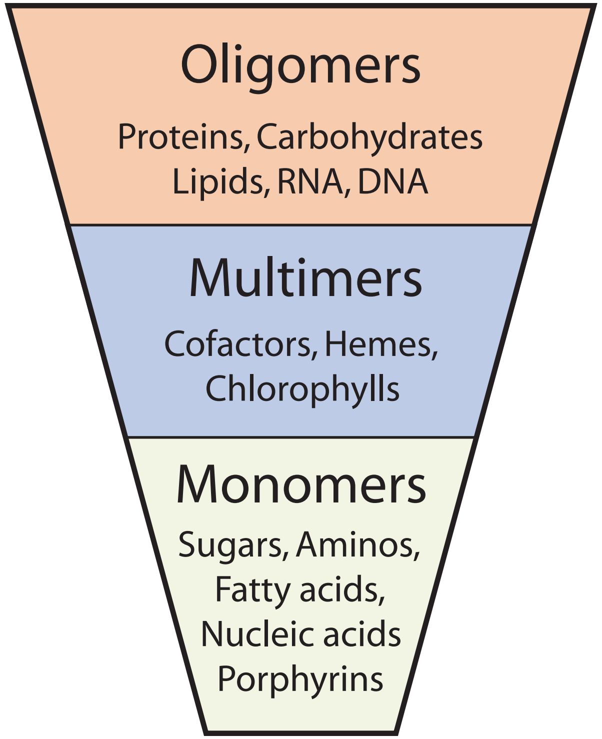
The problem deriving control *and* metabolism

- All enzymes / genes are built from metabolites
- All metabolic reactions are catalyzed by enzymes encoded in genes
- No simple "point of entry" for evolution



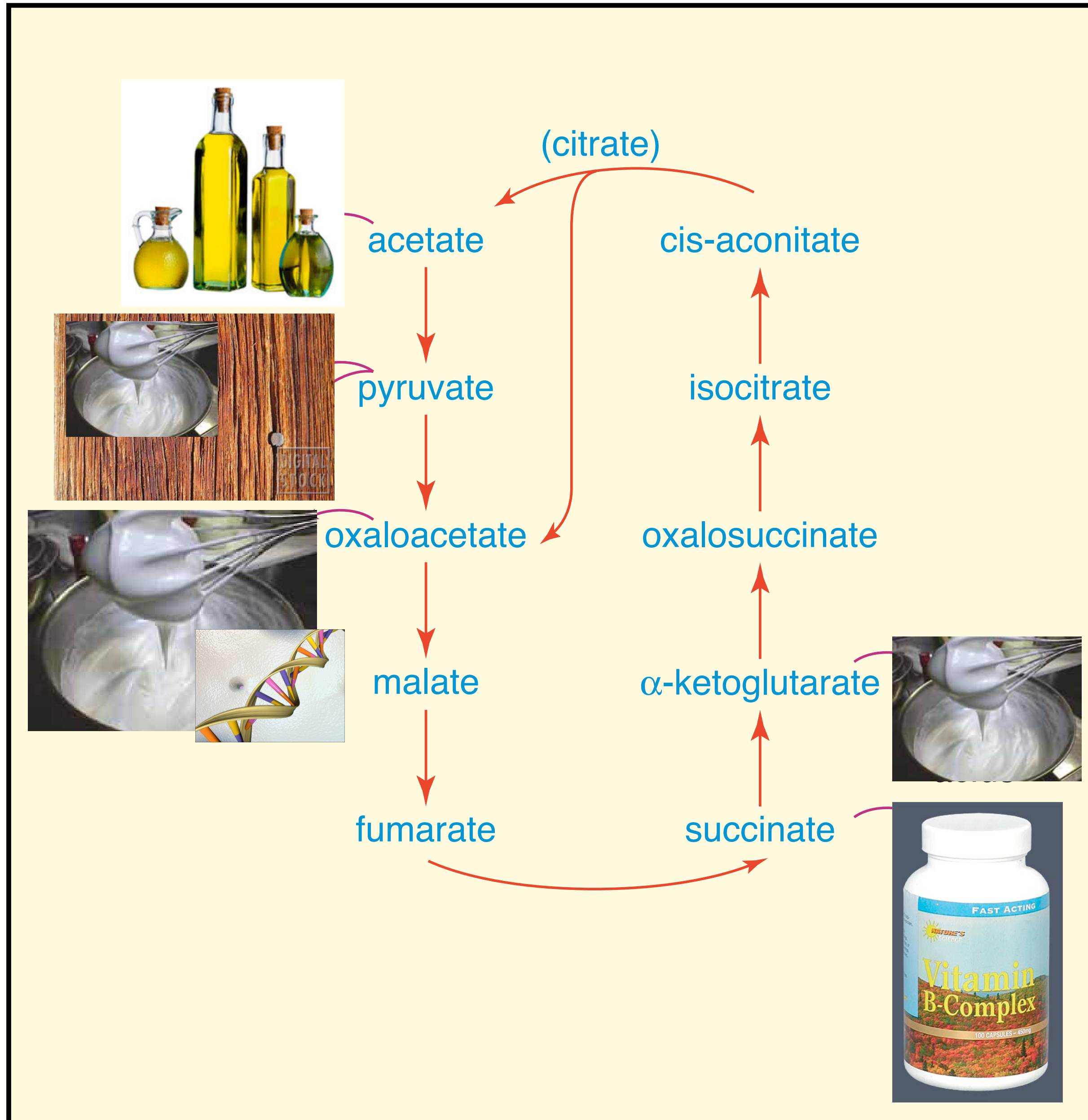
Biochemistry has hierarchical organization

- Organic chemistry mostly concerns monomers
  - Simplest and most universal molecules
- Phosphate-polymer chemistry starts with cofactors
  - Many cofactors are “multimers” of simpler building blocks
- Oligomers become large by introducing secondary structure
  - Uniform molecule type
  - Uniform chirality
  - Retain cofactors as prosthetic groups

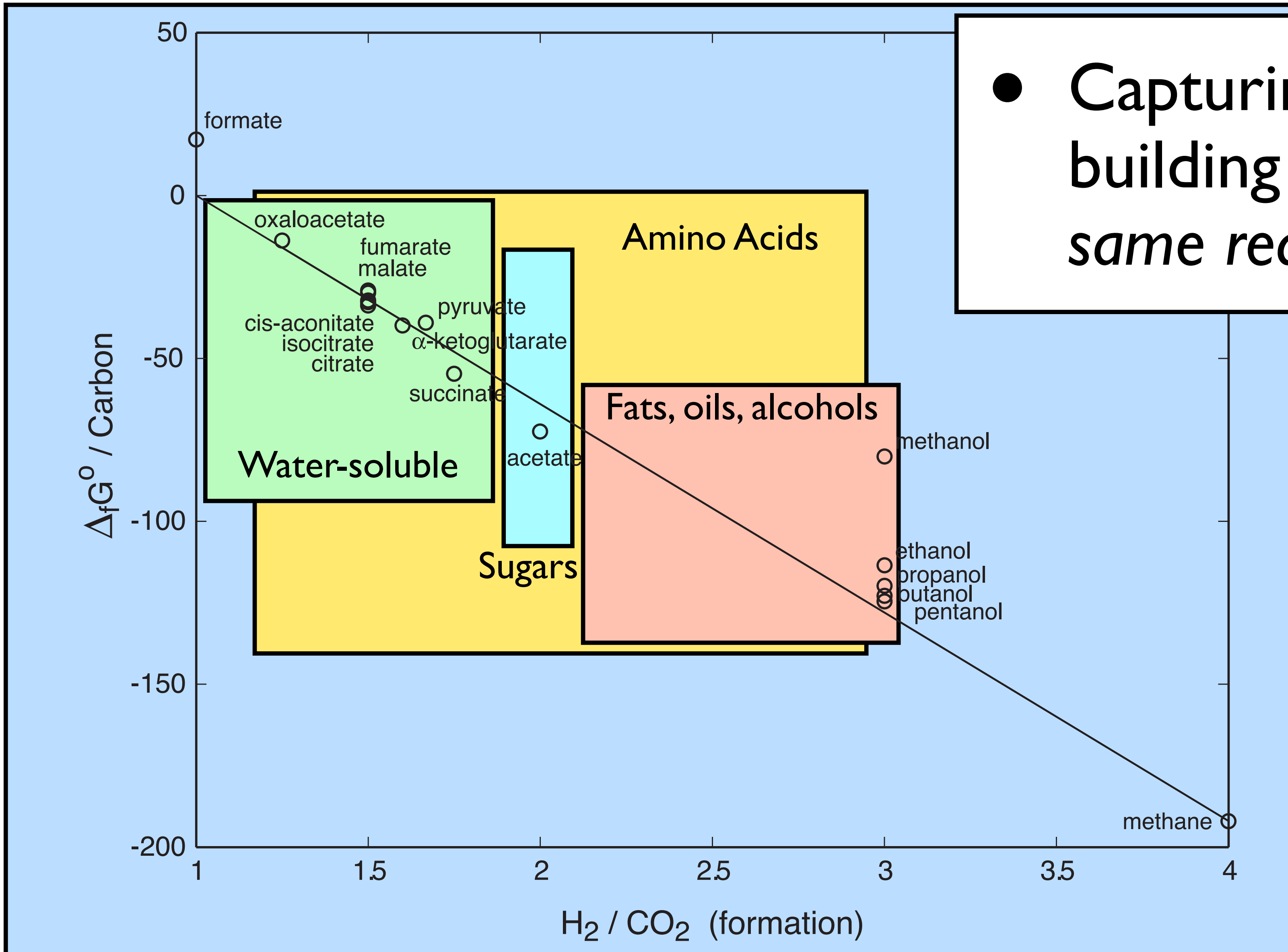


Biosynthesis has a simple core

- Krebs (TCA) cycle makes precursors to all five classes of biomolecules
- Eleven simple acids (<6 Carbon)
- Exists in oxidative and reductive organisms
- Extremely ancient and absolutely conserved



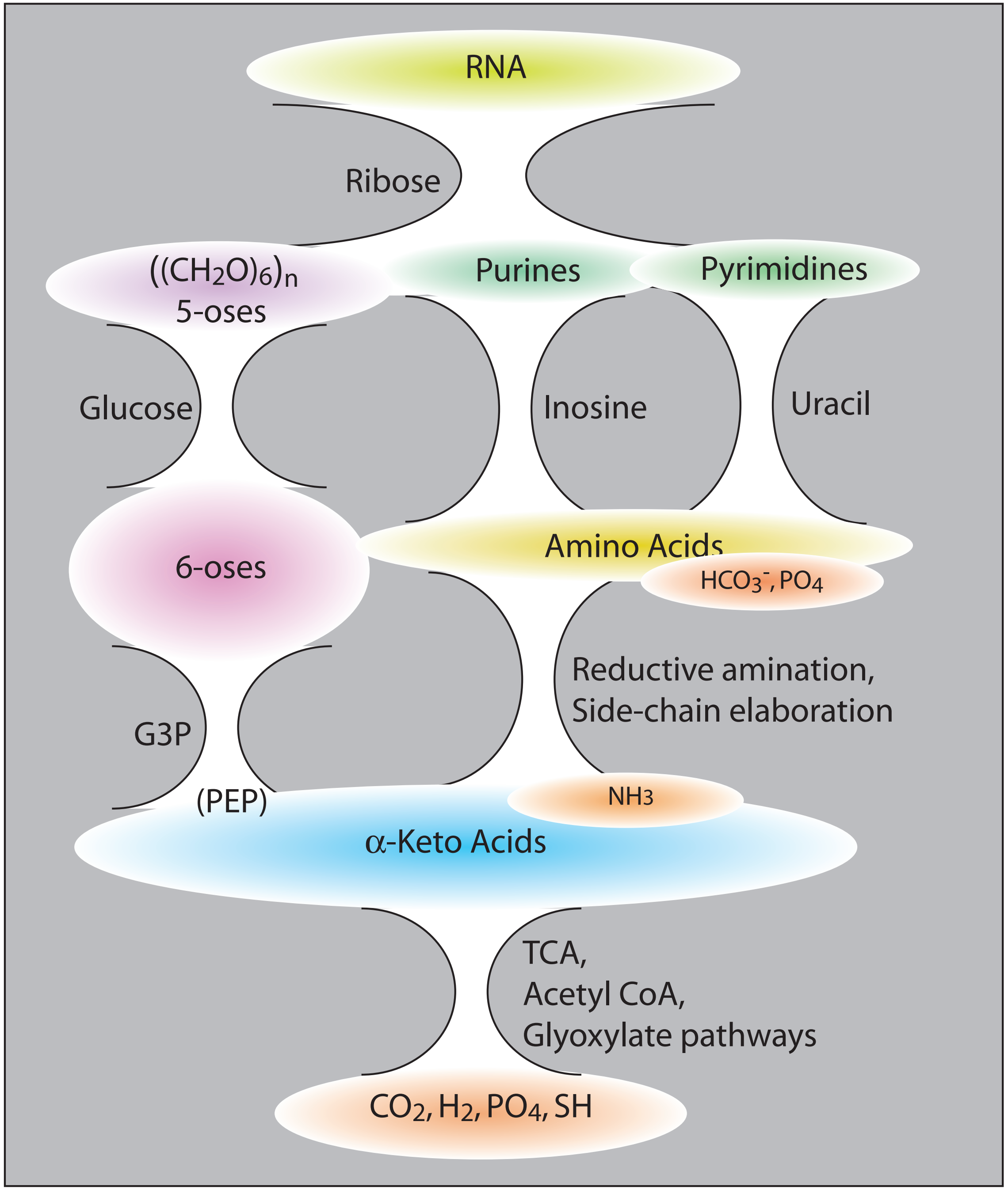
Reductive metabolism: a free lunch you are paid to eat



- Capturing energy, building biomass; *same reactions*

Metabolism combines randomness and order

- Metabolism is a confederacy
- Dependency tree has clouds and gateways
- Clouds look thermodynamic
- Gateways may be molecules or pathways



Summary for Day 1

- Biology combines necessity & contingency; control & metabolism & self-organization
- Biochemistry itself is well-ordered and hierarchical, with many universal properties
- Evolution of chemistry and of species follows different dynamics; chemistry seems more fundamental and more "necessary"
- Understanding the principles of organization should help us understand how life emerged

Further reading

- Schrödinger, Erwin, **What is life? : the physical aspect of the living cell / by Erwin Schrödinger** London : Cambridge University Press, 1955
- Stryer, Lubert **Biochemistry** New York : W.H. Freeman, 1995 4th ed
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- Mezard, Marc, Parisi, Giorgio, and Virasoro, Miguel Angel **Spin glass theory and beyond** Singapore ; Teaneck, NJ, USA : World Scientific, 1987