

Understanding the origin and organization of biochemistry

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based on work with

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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 I: 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

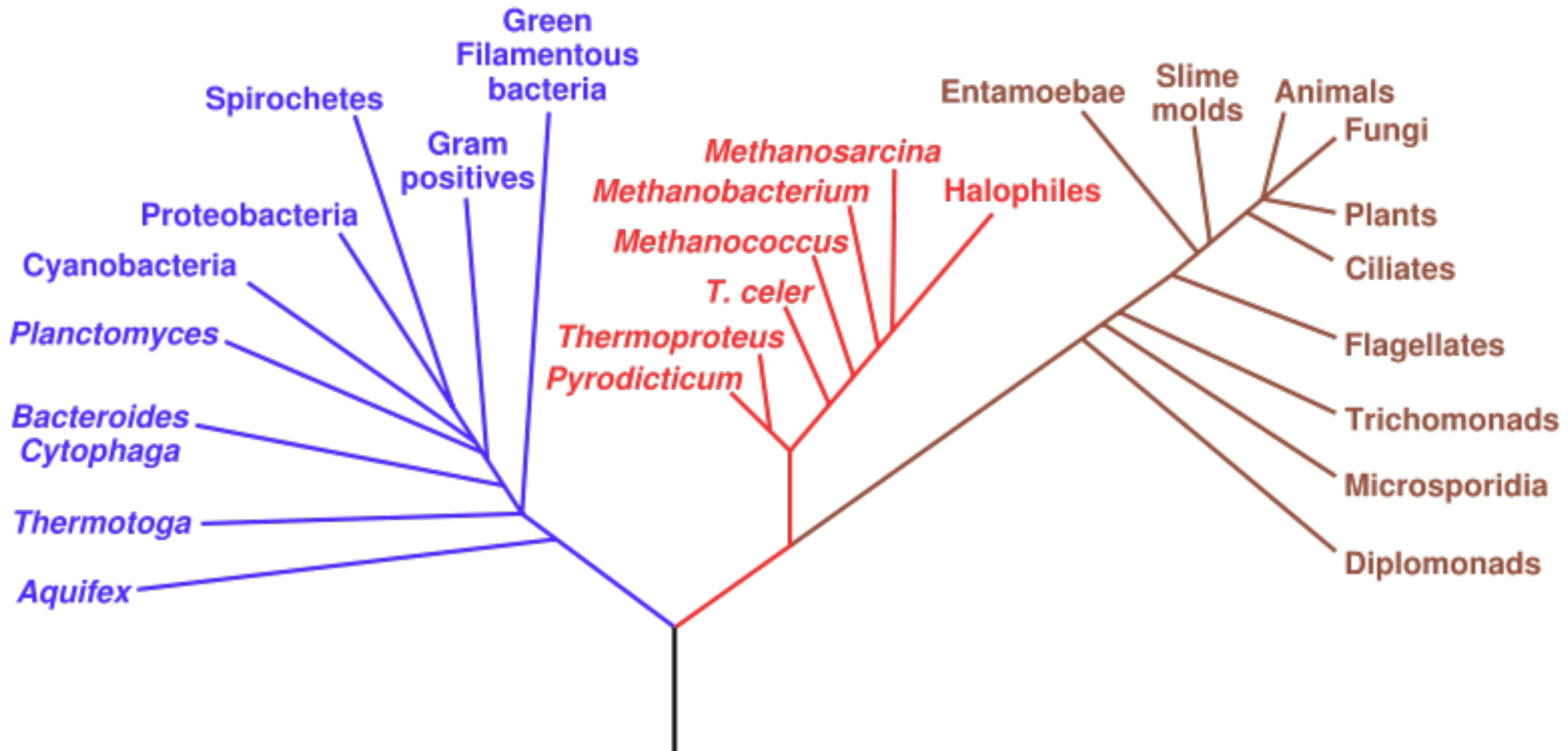
- Chance and necessity
- Control and metabolism
- Biosynthesis and ecology

Phylogenetic organization reflects the history of accidents

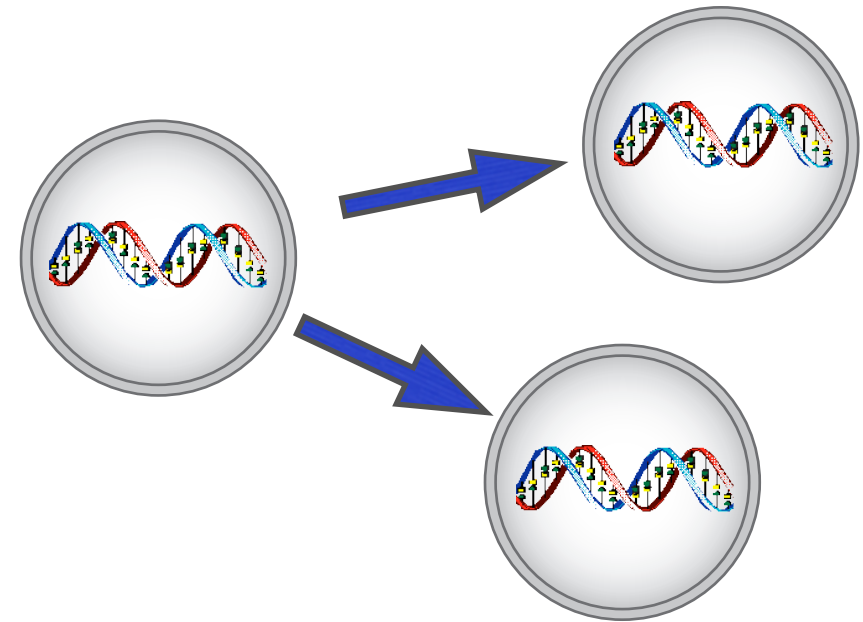
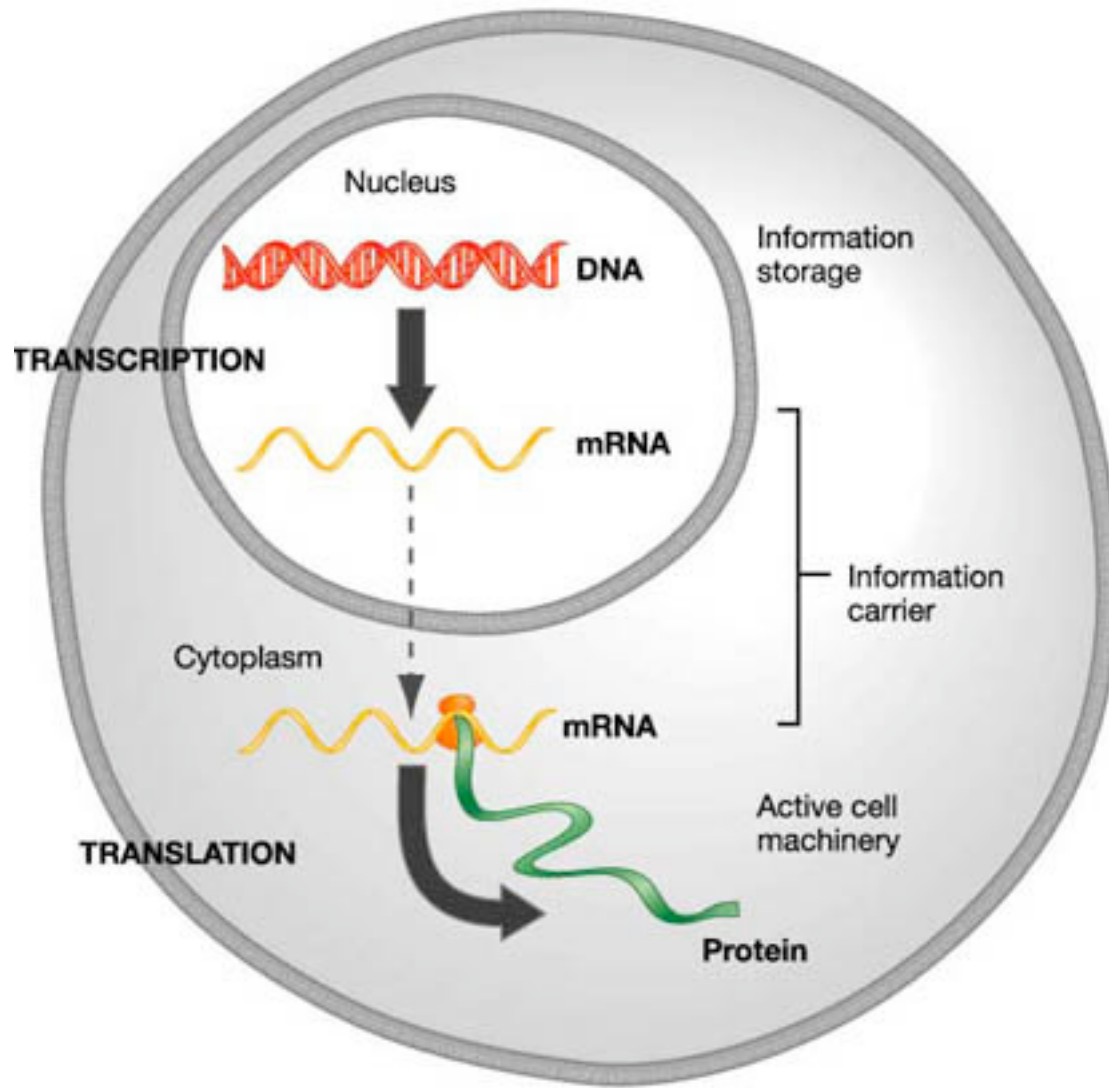
Bacteria

Archaea

Eucaryota

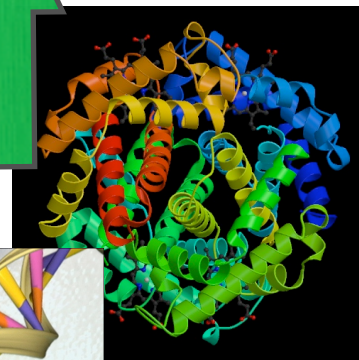
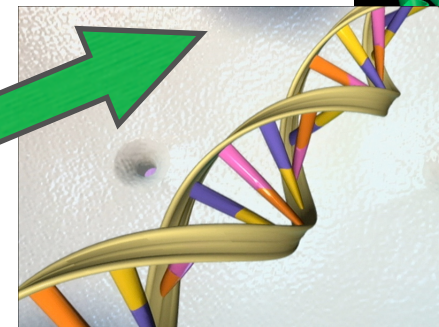
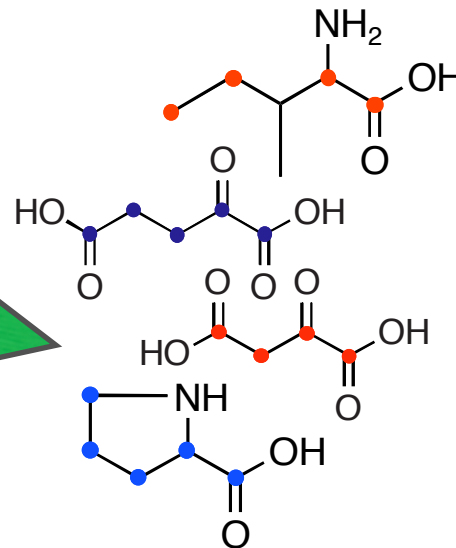
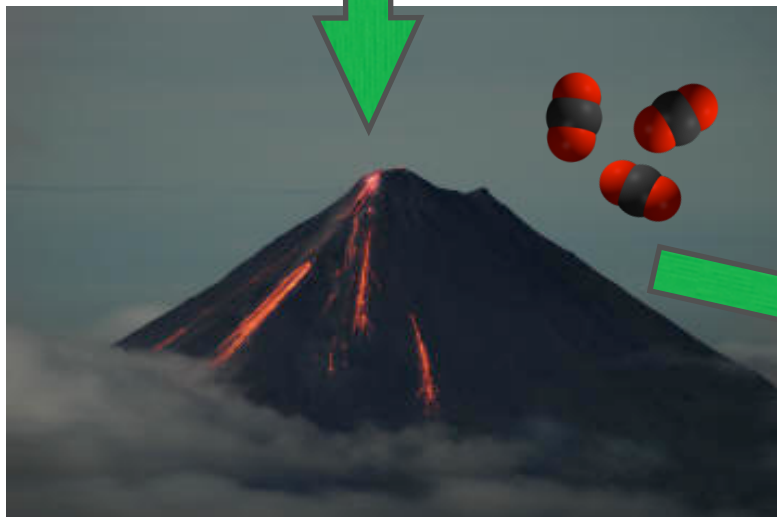
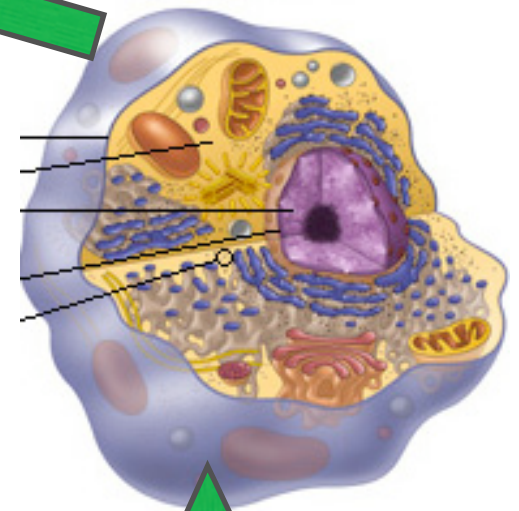


Much of the observed contingency is possible because of top-down control

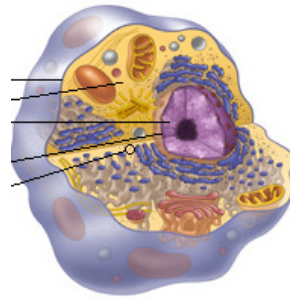
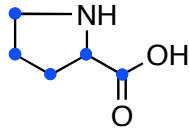
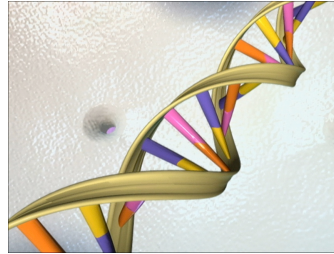


(Genes / enzymes provide “external” control of metabolism)

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

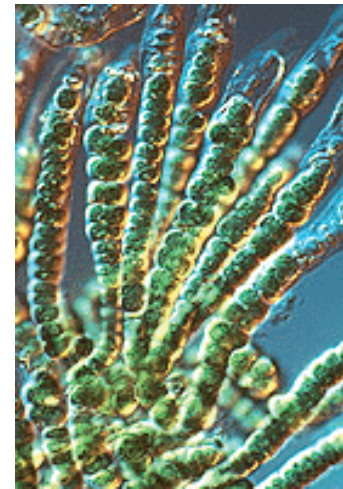
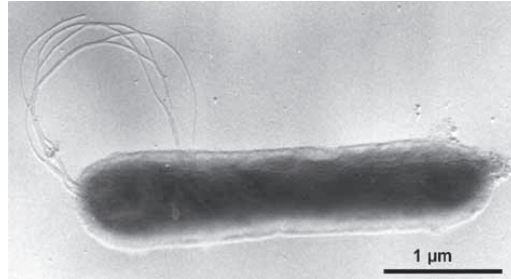
Variable
Fluctuating
Contingent

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

Reductive
metabolisms

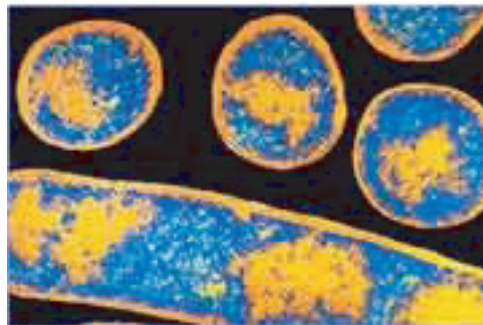
Oxidative
metabolisms

Autotrophs



(Anabolism)

Heterotrophs



(Anabolism
&
Catabolism)

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

Reductive
ecologies

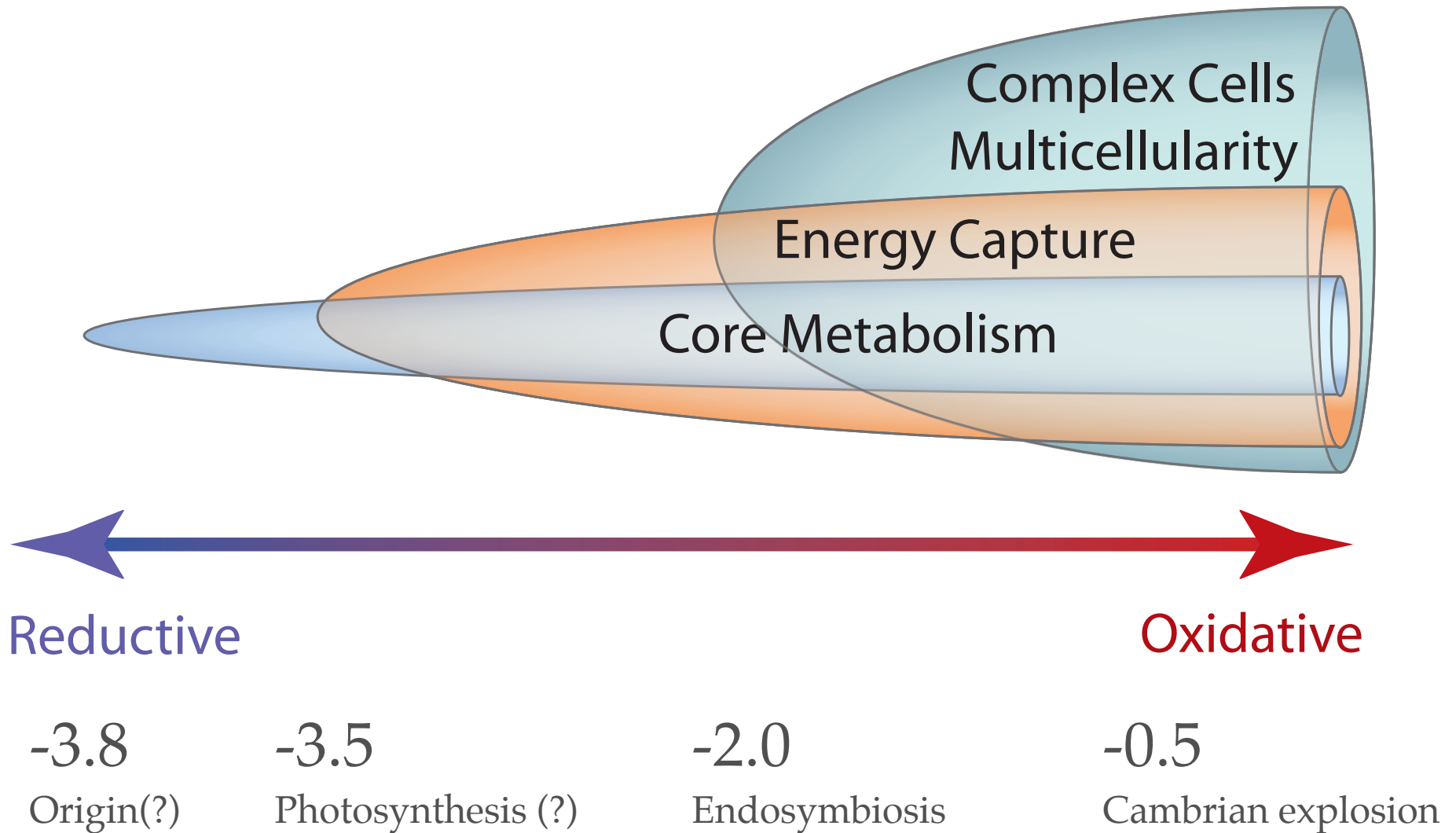


Oxidative
ecologies



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

Isoprenes



Fatty acids



Nucleic acids



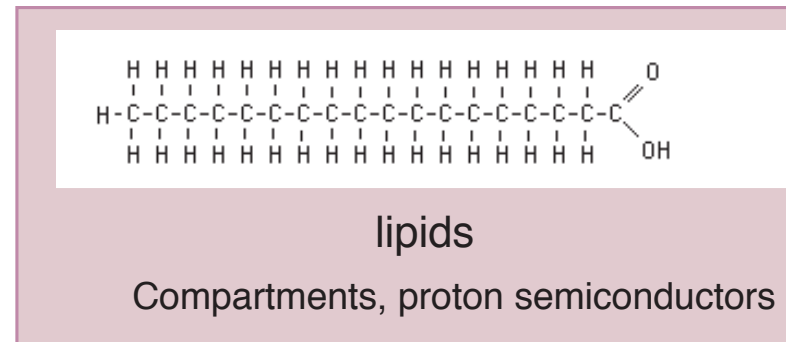
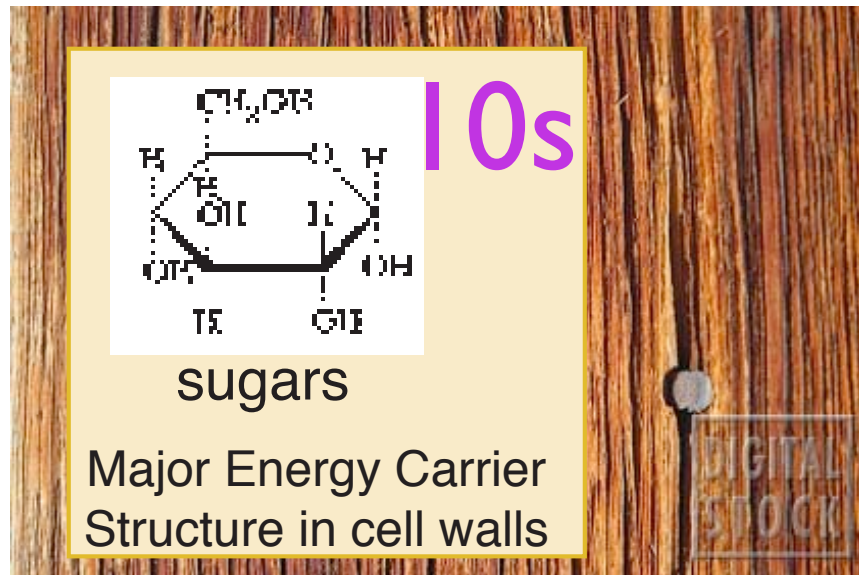
Amino acids



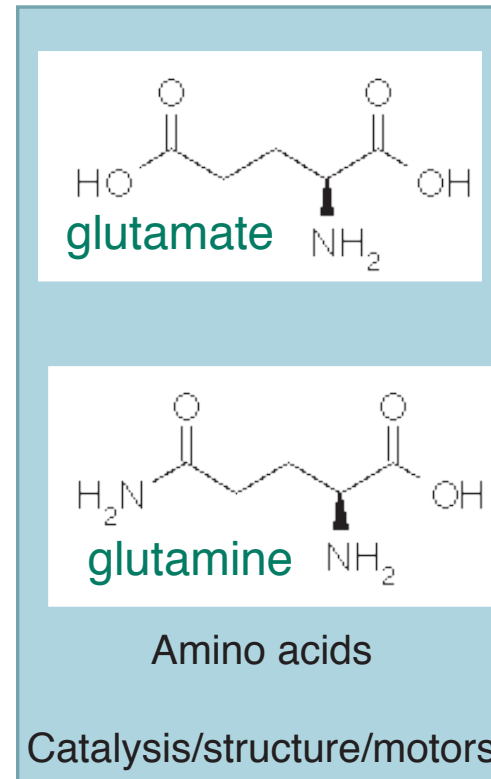
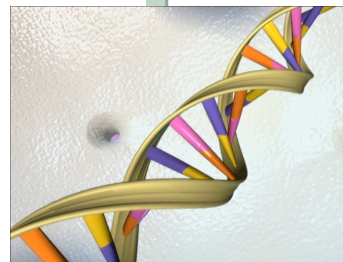
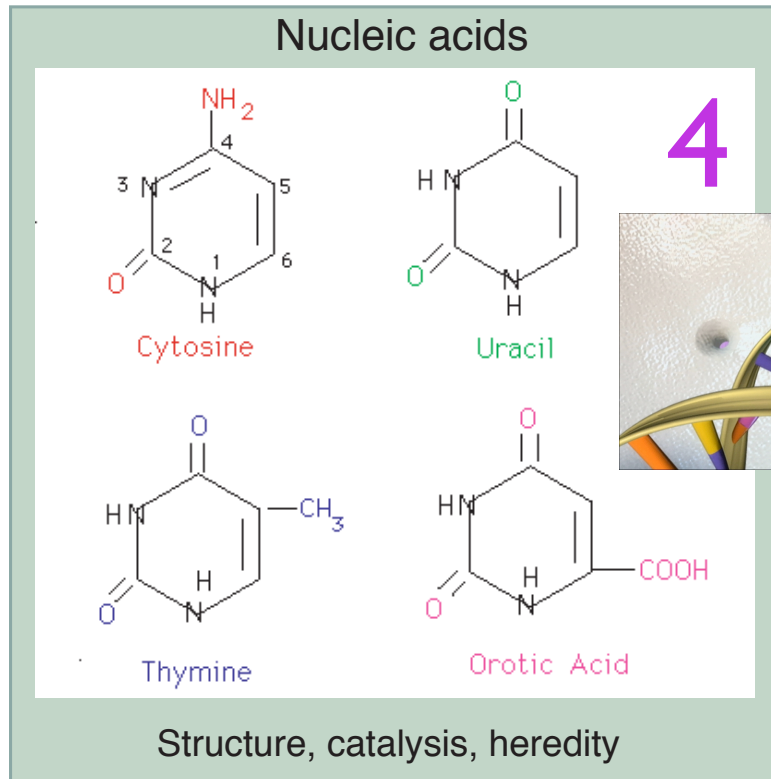
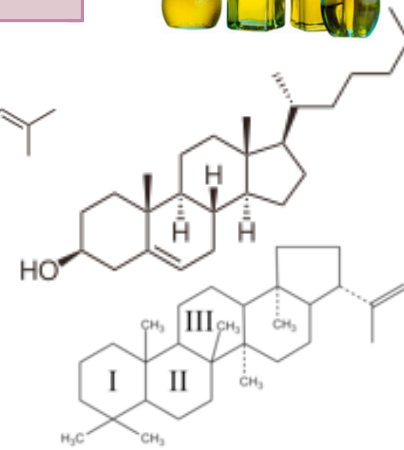
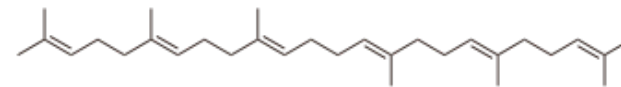
Sugars



Molecules classes have characteristic chemical form



10s

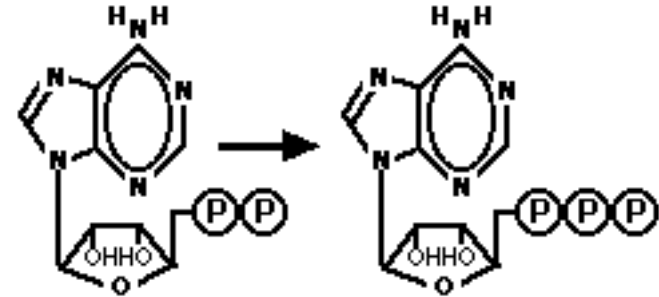


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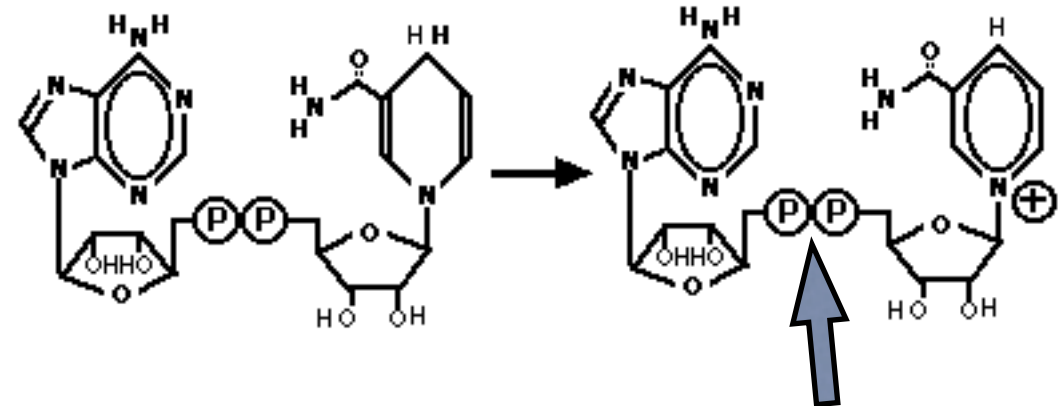


Cofactors are a special class of mid-sized molecules

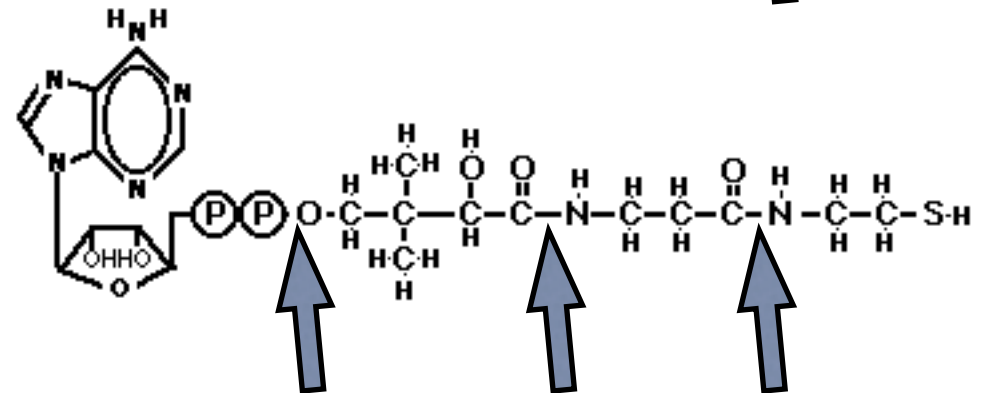
- **ATP** (gives and takes phosphates)



- **NAD** (gives and takes electrons)



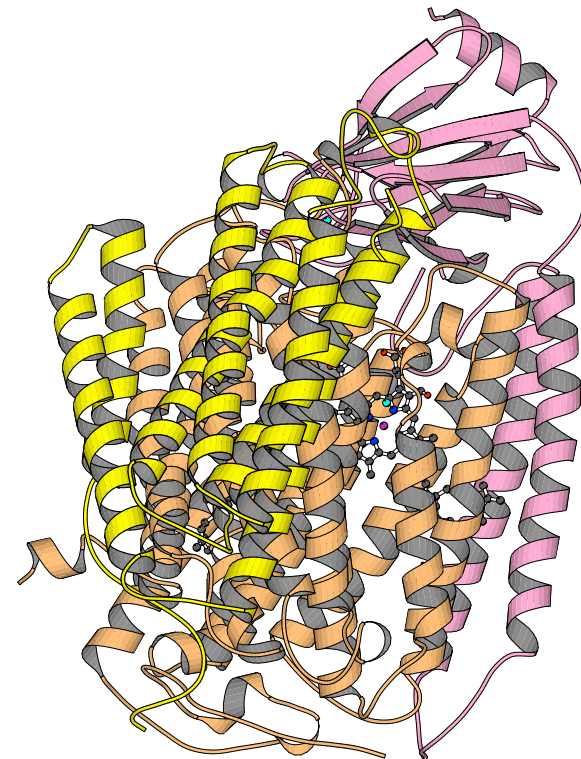
- **Coenzyme A** (exchanges electrons for phosphates through sulfur intermediate)



Strong associations of cofactors with RNA

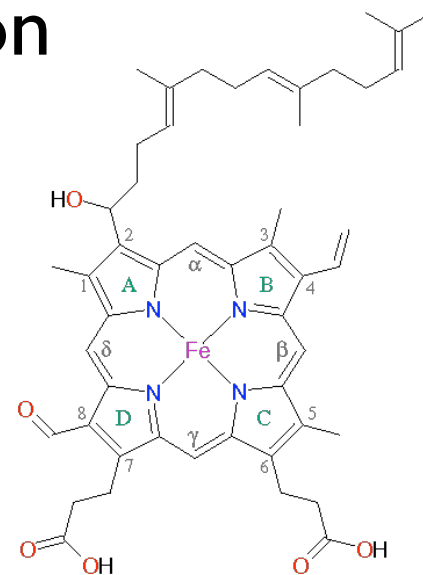
Macro-molecules provide catalysts and genetic templates

- 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
 - more than half if we include metals
 - ~75% if we include histidine, tryptophan, etc.



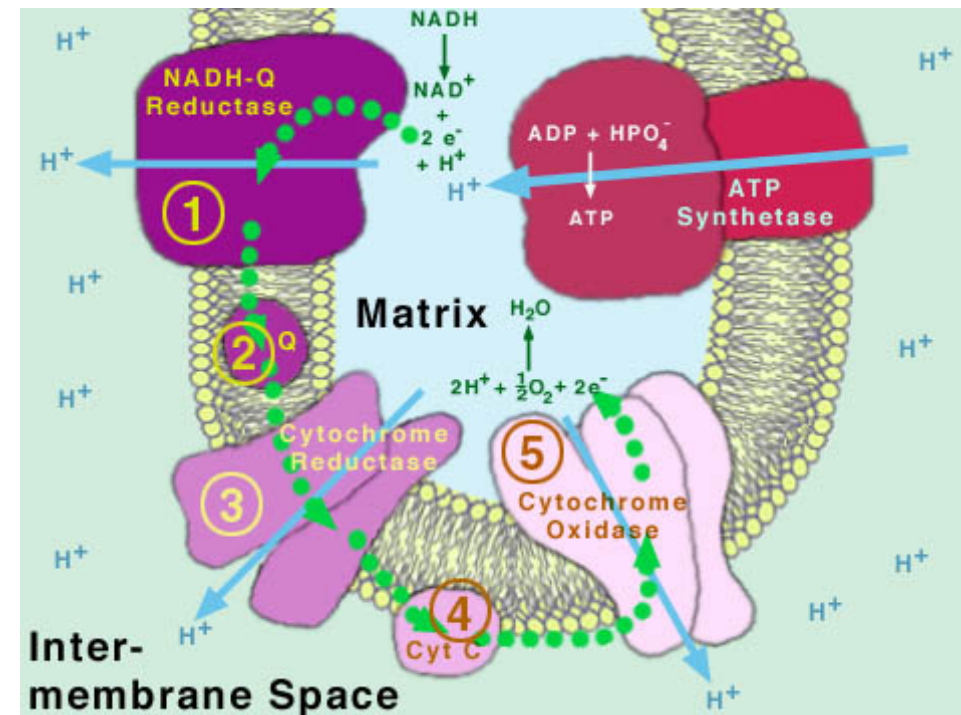
1OCC

<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*

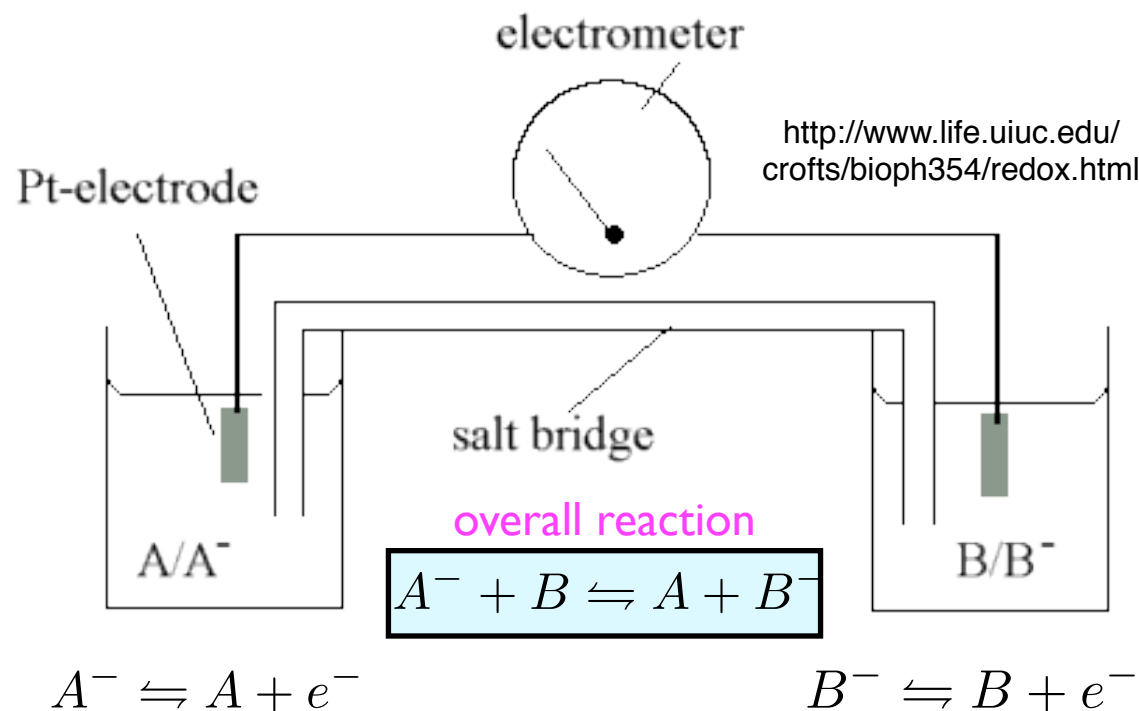


Bioenergetics unifies living processes

- 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 $A^- \rightleftharpoons A + e^-$ 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



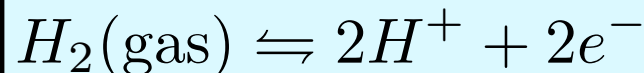
general reaction schema

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

voltage equivalent

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

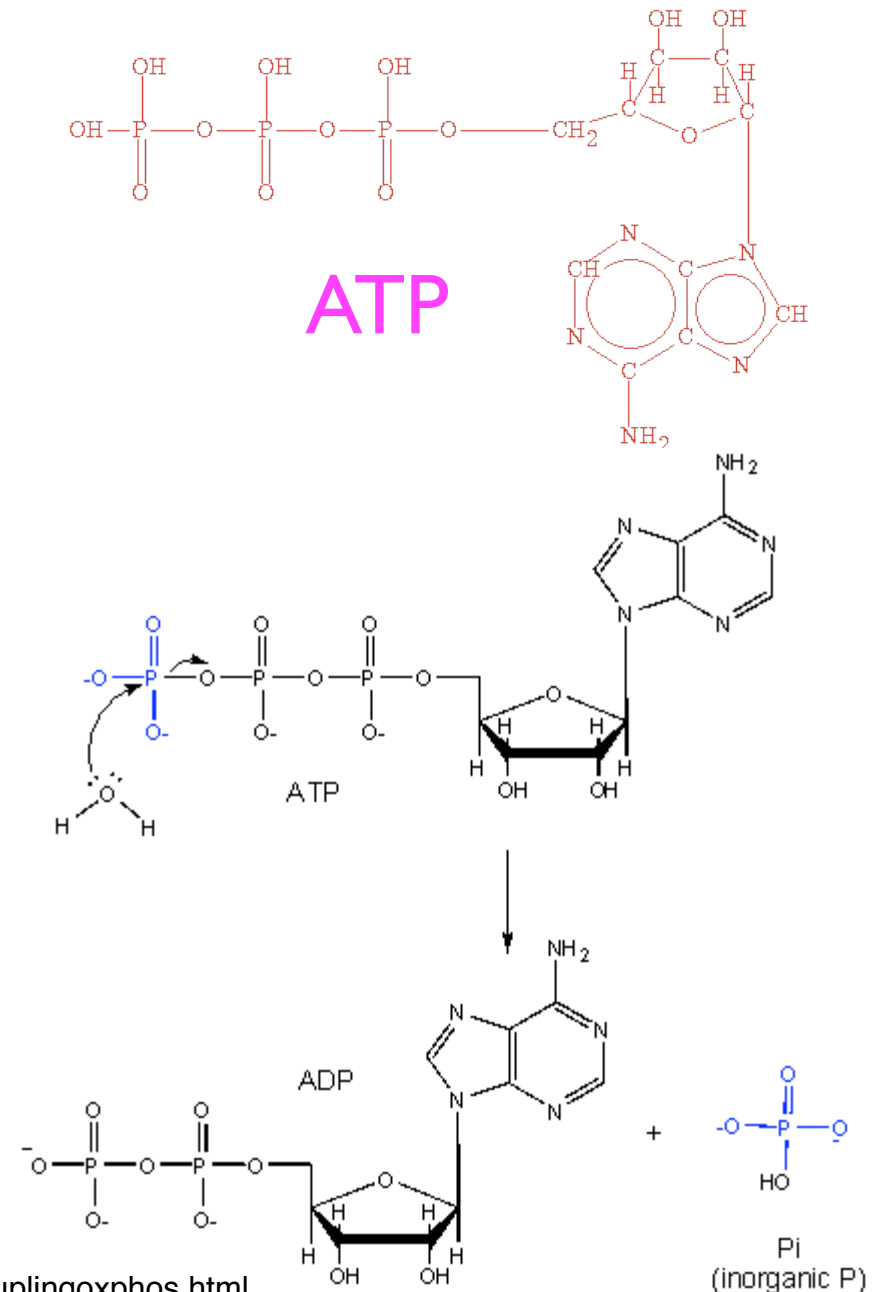
reference couple



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

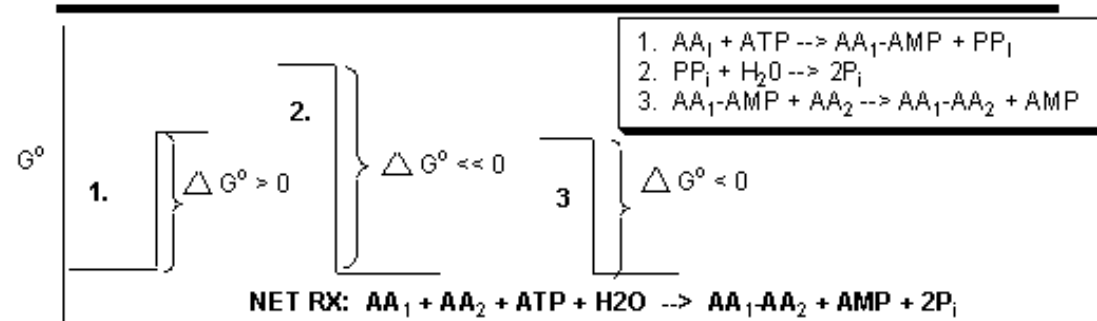
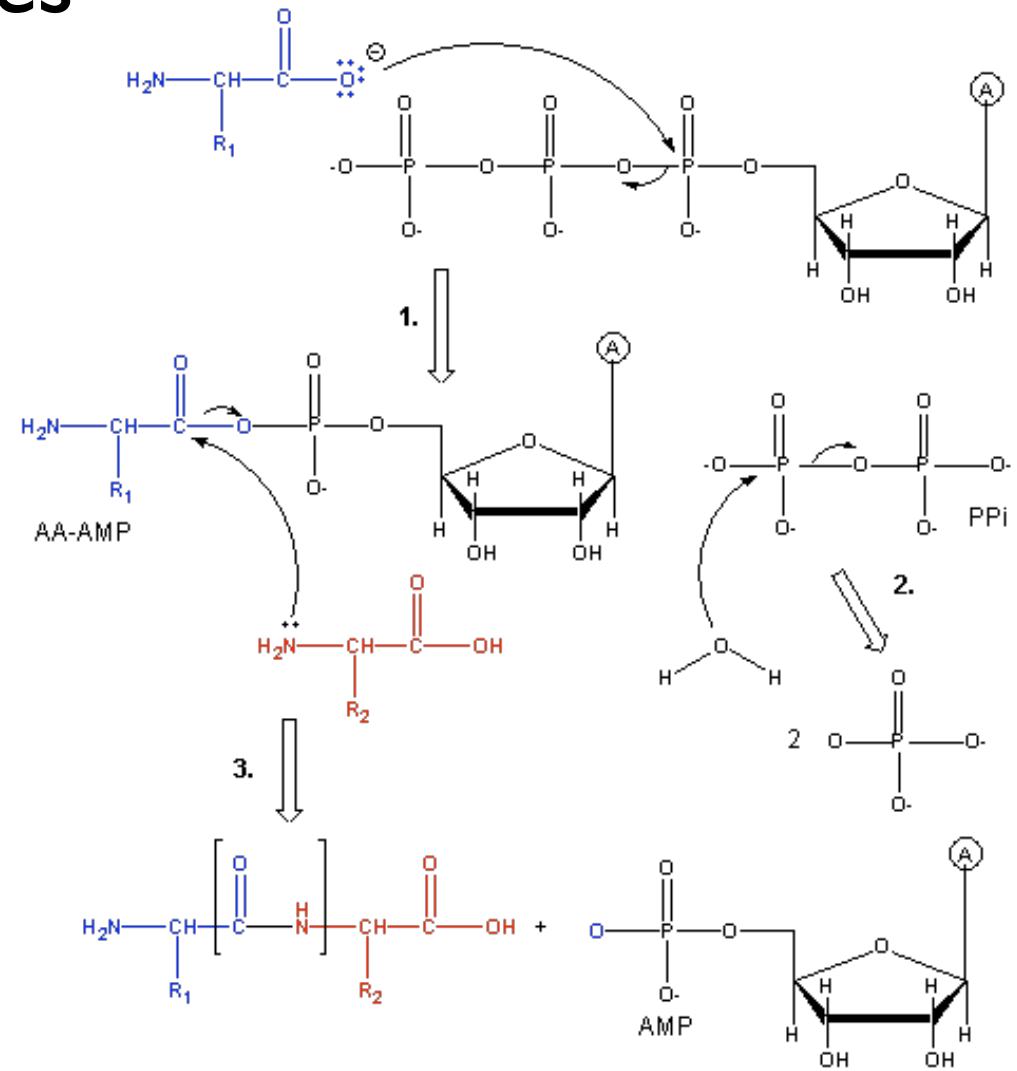


<http://employees.csbsju.edu/hjakubowski/classes/ch331/oxphos/olcouplingoxphos.html>

Activation with phosphates enables polymerization

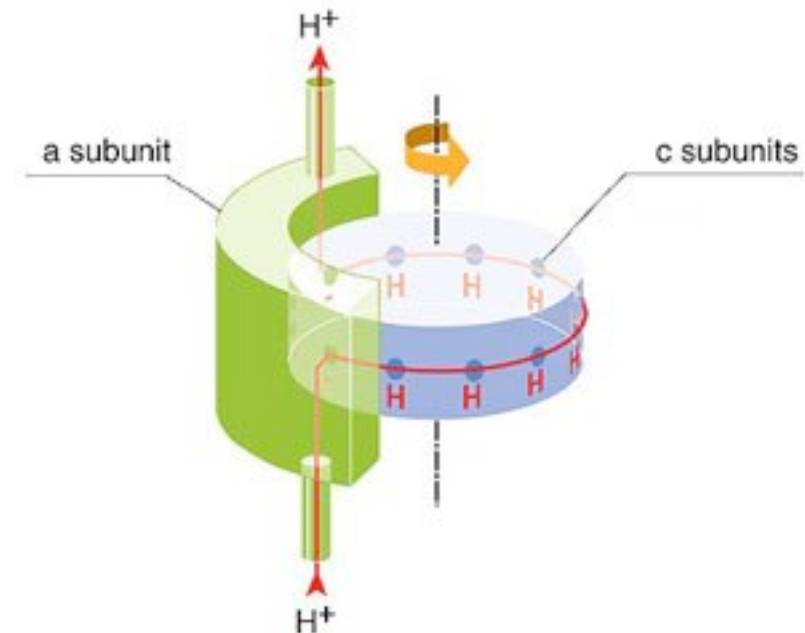
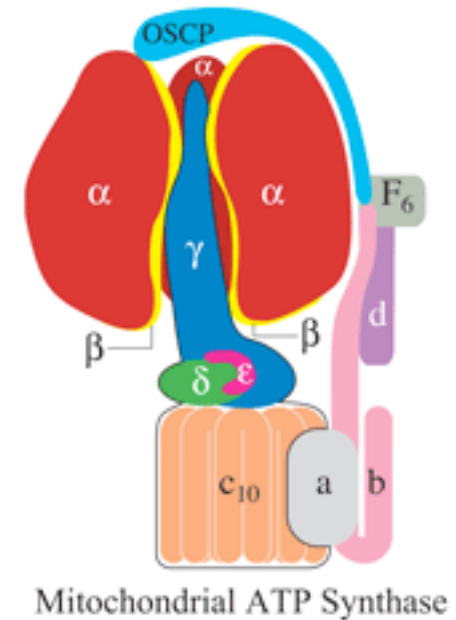
- Using activation of a monomer as an intermediate in ATP hydrolysis dehydrates the monomer to produce a bond

DRIVING AMIDE (PEPTIDE) BOND FORMATION ($\Delta G^\circ > 0$)
BY COUPLING WITH ATP BREAKDOWN ($\Delta G^\circ < 0$)



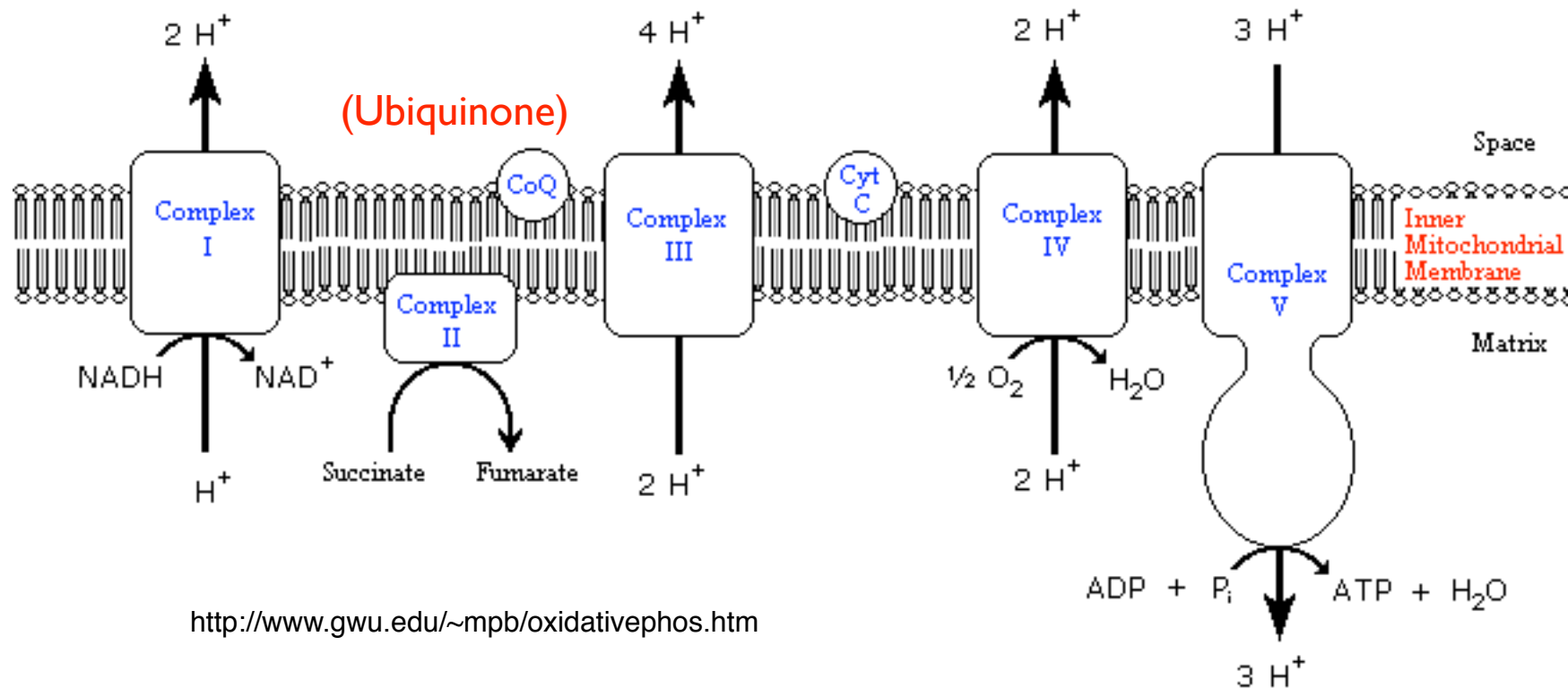
ATP is recycled from proton energy

- ATP synthase (and related flagellar motors) combines a transport pore for H^+ with a rotory shaft
- Proton flux through membranes is only permitted by rotation of the shaft, which deforms enzymes to make ATP



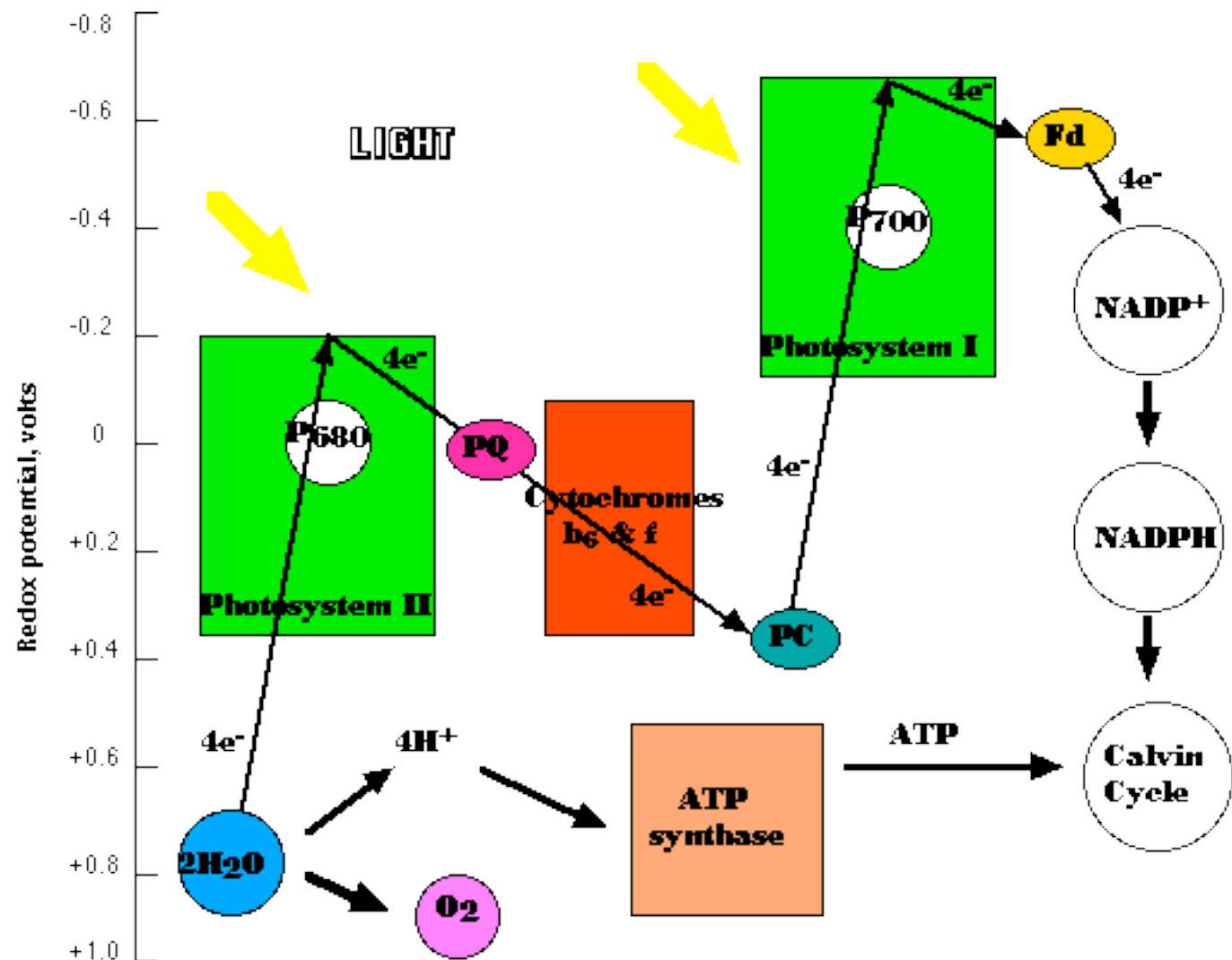
Respiration generates protons from reductant to recycle phosphate; both occur at membranes

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



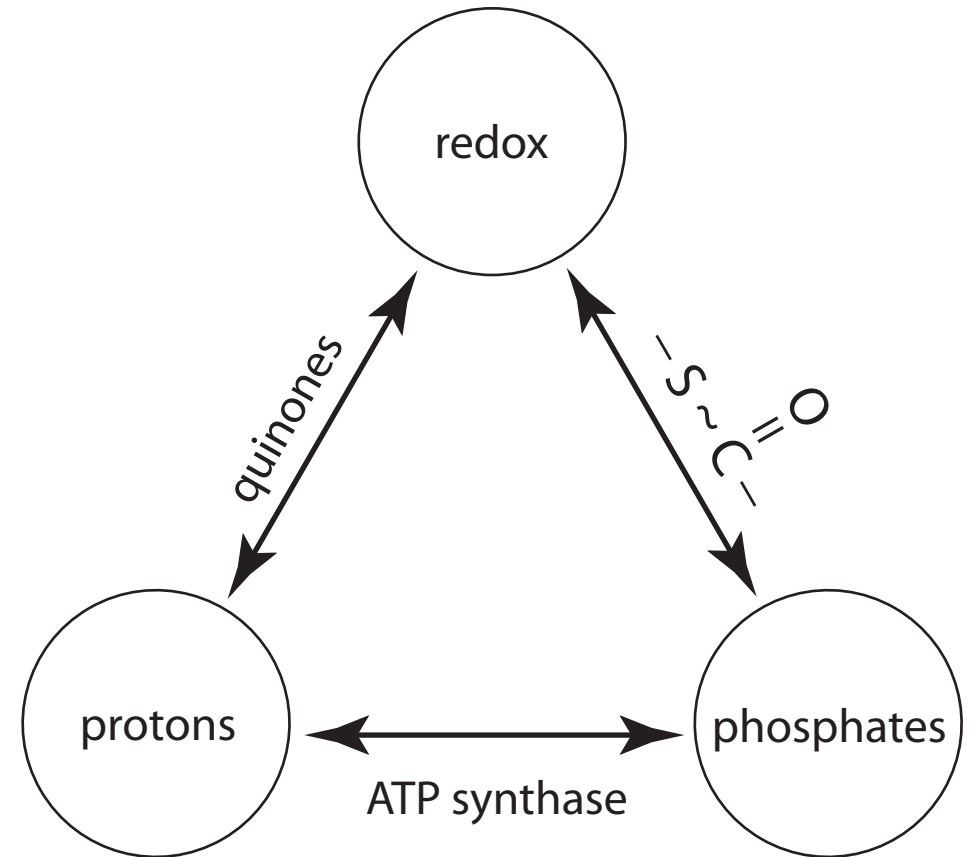
The function of photosynthesis is to produce reductant from light

- 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



All biological energy sources are interconvertible

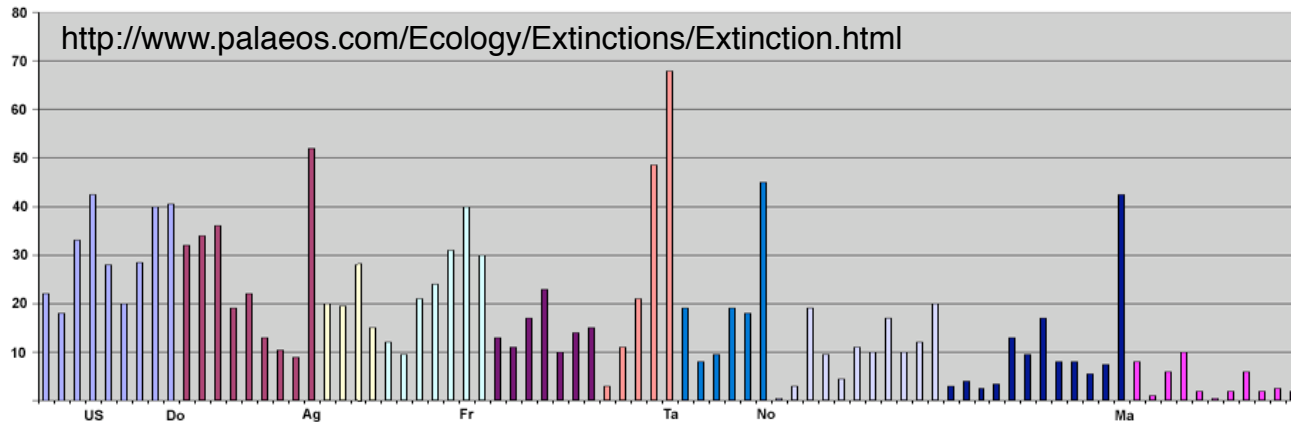
- Permits environmental flexibility and buffers against fluctuations
- Environmental redox couples are widely diverse
- Cellular use of phosphates and protons is much more uniform



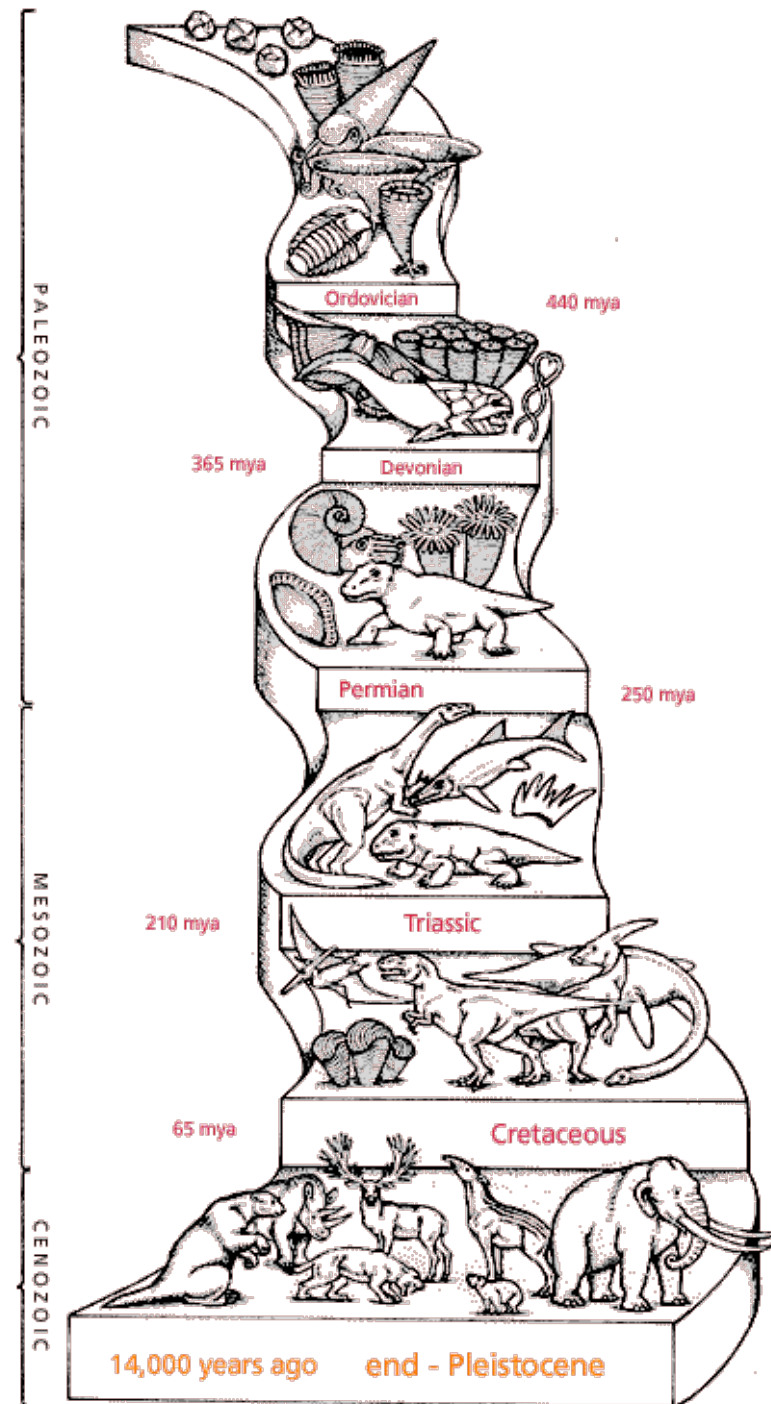
The dynamics of species and ecologies is qualitatively different from the dynamics of chemistry

- 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

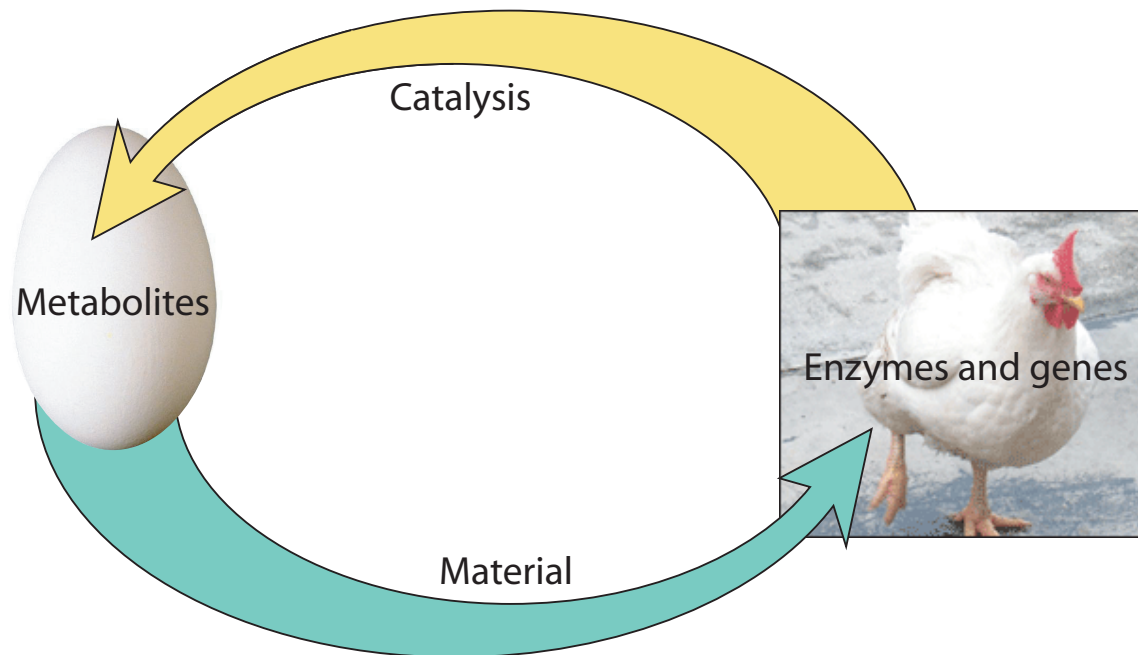


Clues to thinking about the origin of life

- 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

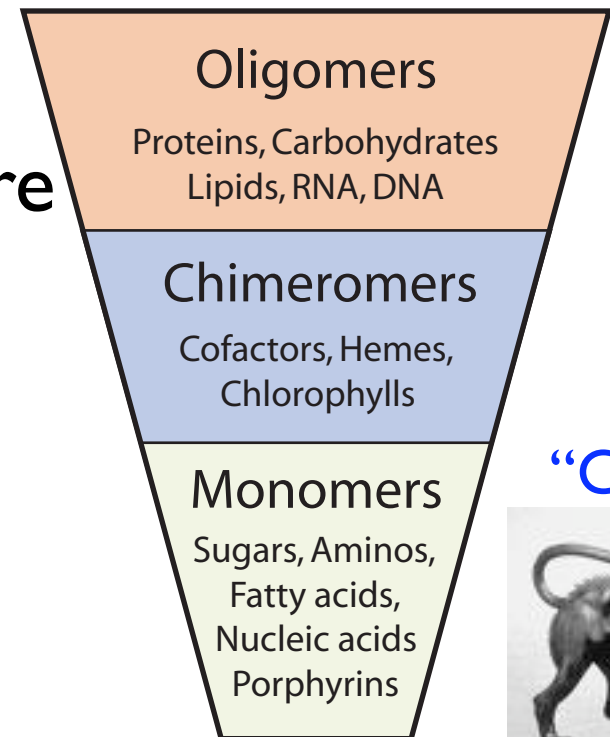
The problem deriving control *and* metabolism

- 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 “chimeromers” of simpler building blocks
- Oligomers become large by introducing secondary structure
 - Uniform molecule type
 - Uniform chirality
 - Retain cofactors as prosthetic groups

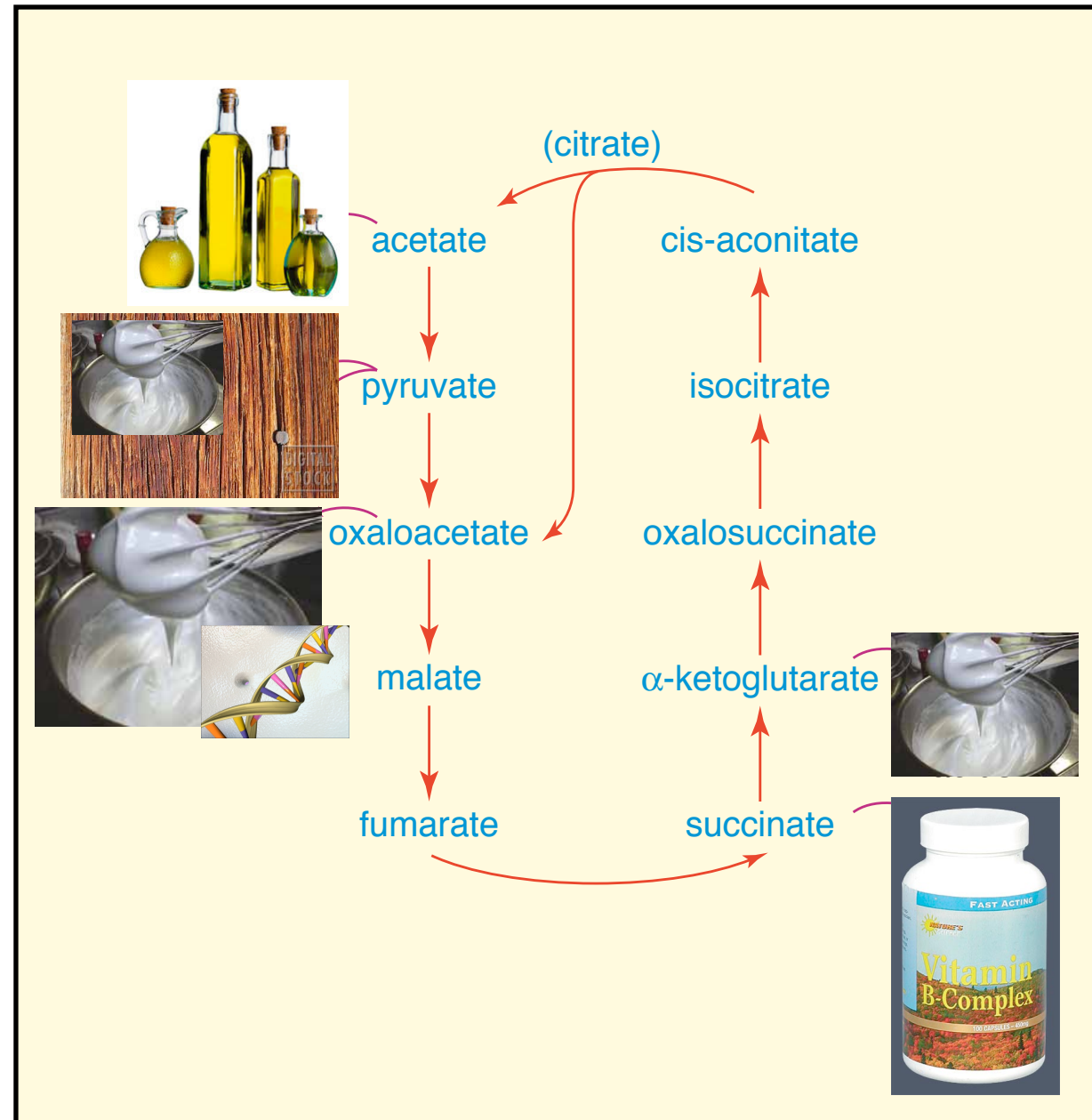


“Chimera”



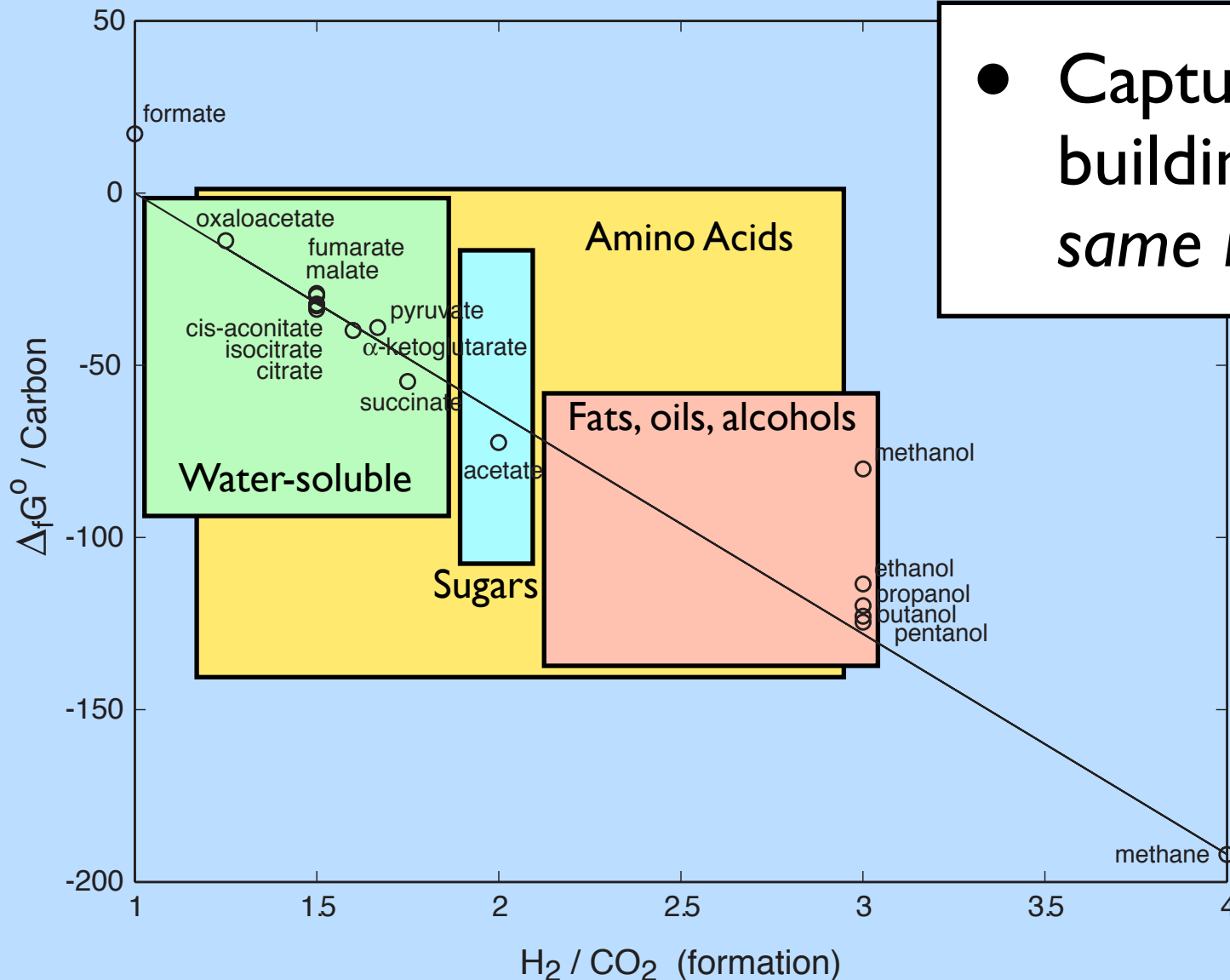
Biosynthesis has a simple core

- 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



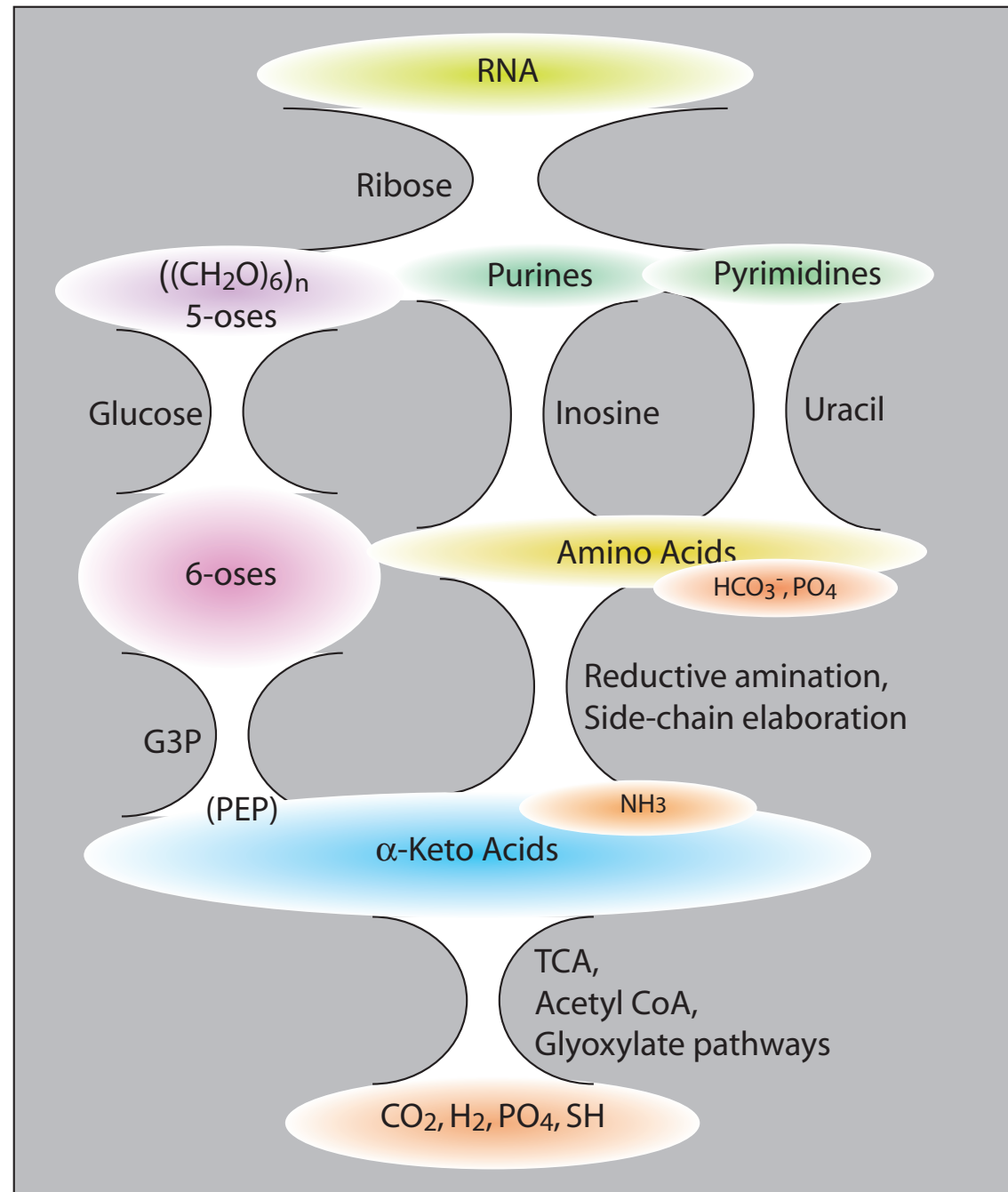
Reductive metabolism: a free lunch you are paid to eat

- 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 I

- 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
- Voet, Donald and Judith G. **Biochemistry** New York : J. Wiley & Sons, 1995 2nd ed
- Metzler, David E **Biochemistry : the chemical reactions of living cells** New York : Academic Press, 1977
- Morowitz, Harold J **Beginnings of cellular life : metabolism recapitulates biogenesis** New Haven : Yale University Press, 1992
- Lowry, Thomas H and Richardson, Kathleen Schueller **Mechanism and theory in organic chemistry** New York, N.Y. : Harper & Row, 1981 2nd ed