Understanding the origin and organization of biochemistry

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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
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”

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<th>Autotrophs</th>
<th>Reductive metabolisms</th>
<th>Oxidative metabolisms</th>
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Whole-ecosystem metabolism is simpler and more universal than species metabolism.

Reductive ecologies

Oxidative ecologies

(Ecosystems are more fundamental than organisms)
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

- **Sugars**: Major Energy Carrier, Structure in cell walls
- **Lipids**: Compartments, proton semiconductors
- **Nucleic acids**: Structure, catalysis, heredity
- **Amino acids**: Catalysis/structure/motors

**Examples**
- Cytosine, Thymine, Uracil, Orotic Acid
- Glutamate, Glutamine

**Additional Information**
- 10s
- 20s
- 4s
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)
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 $A^- \rightleftharpoons A + e^-$ 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

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

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

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

Reference couple

Overall reaction schema
Phosphate energy is released by hydrolysis

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

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 $\text{H}^+$ with a rotary shaft.

- 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 $P_i$
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


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
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 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

Water-soluble
- oxaloacetate
- fumarate
- malate
- isocitrate
- citrate

Amino Acids
- pyruvate
- α-ketoglutarate
- succinate
- acetate

Fats, oils, alcohols
- methanol
- ethanol
- propanol
- butanol
- pentanol
- methane

Sugars

formate

\( \Delta G^0 / \text{Carbon} \)

\( H_2 / \text{CO}_2 \) (formation)
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


• 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


• Mezard, Marc, Parisi, Giorgio, and Virasoro, Miguel Angel *Spin glass theory and beyond* Singapore ; Teaneck, NJ, USA : World Scientific, 1987