# Origin of Life Part 2:
# Core carbon synthesis

# The deep core of carbon biosynthesis is the most important ecological universal to explain

## Outline

- The chemistry, network structure, and energetics of carbon biosynthesis
- Implications for the problem of robust chemical order on earth, and a phase-transition picture for origins?

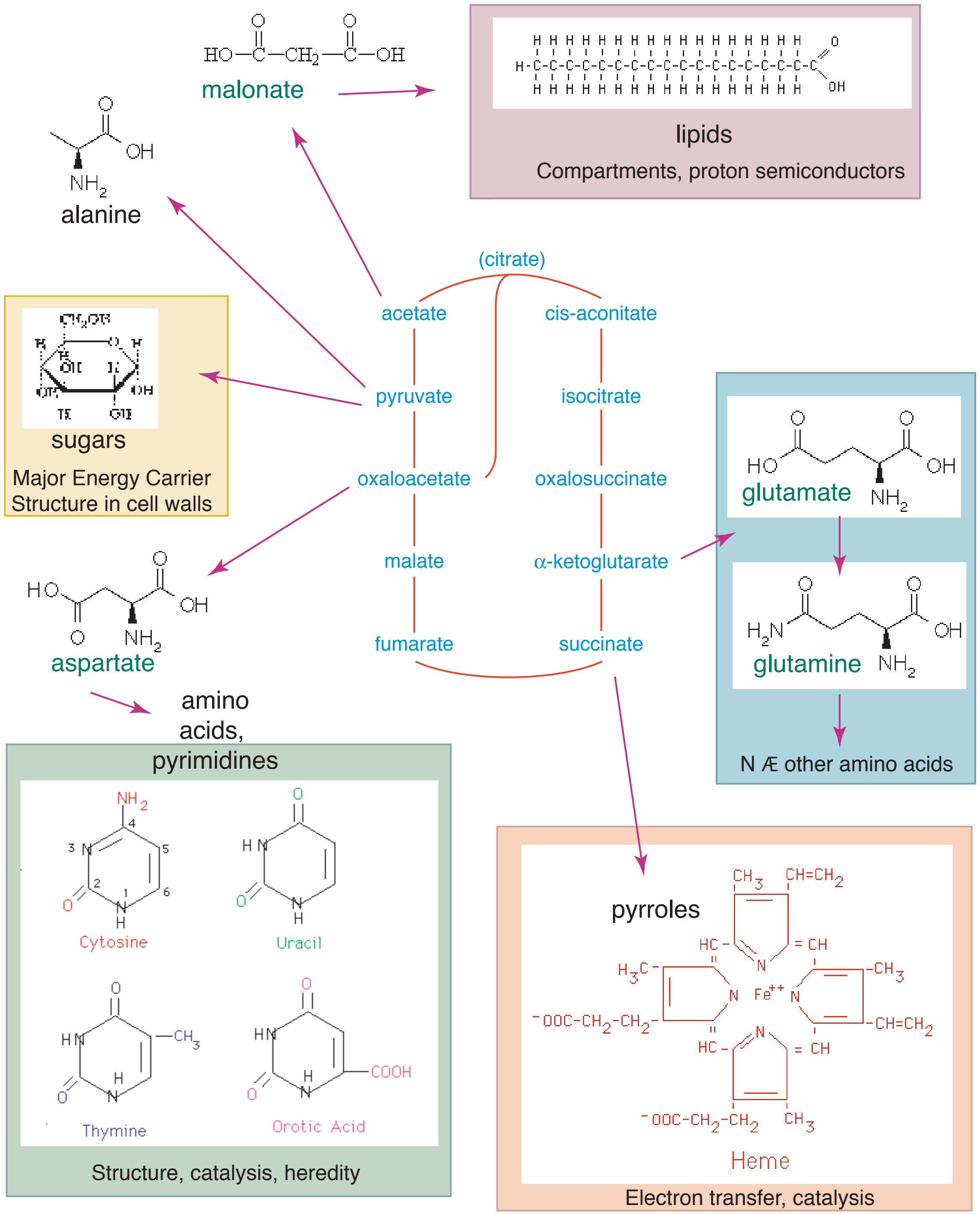
# Chemistry, energetics, and network structure of core carbon biosynthesis

- The TCA cycle and reducing metabolism are the core of biosynthesis
- Chemical and network properties of the reducing version of the TCA cycle
- Network self-amplification and feedback catalysis

# Carbon anabolism today begins within the “Krebs” (or TCA) cycle

(***T**ri-**C**arboxylic **A**cid cycle*)

- TCA intermediates are synthetic precursors of:
  - lipids (Acetate)
  - sugars (Pyruvate)
  - amino acids (several)
  - nucleotides (OAA, AKG)
  - porphyrins (Succinate)



malonate

lipids

Compartments, proton semiconductors

alanine

(citrate)

acetate

cis-aconitate

pyruvate

isocitrate

oxaloacetate

oxalosuccinate

malate

α-ketoglutarate

fumarate

succinate

sugars

Major Energy Carrier
Structure in cell walls

glutamate

glutamine

N Æ other amino acids

aspartate

amino acids, pyrimidines

Cytosine

Uracil

Thymine

Orotic Acid

Structure, catalysis, heredity

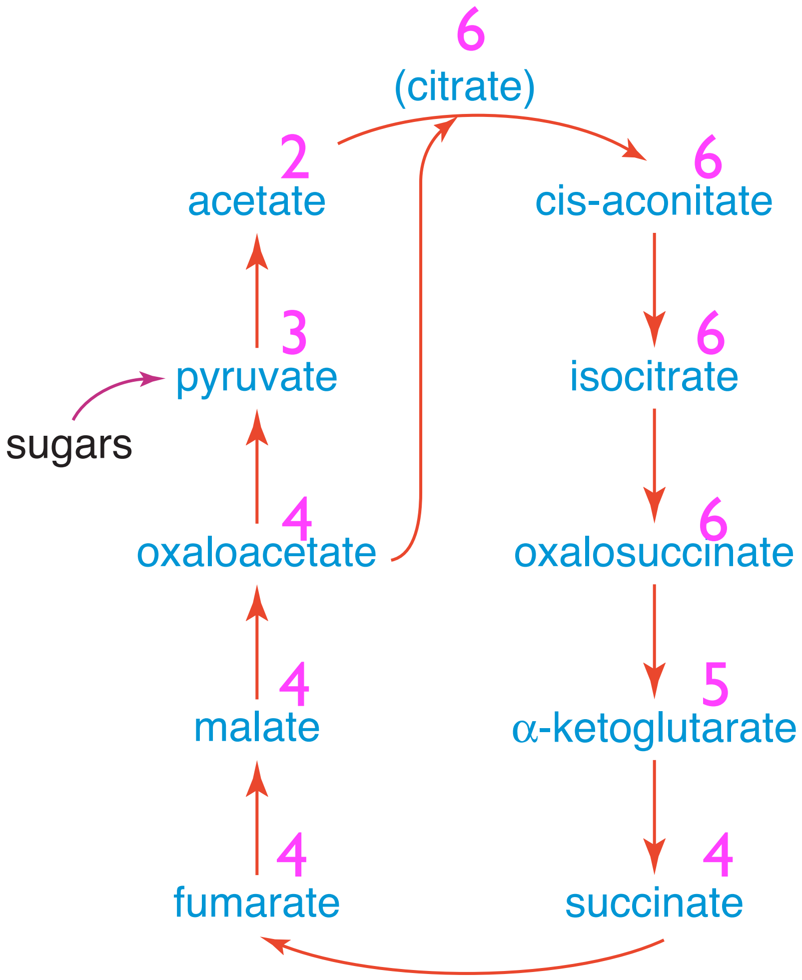
pyrroles

Heme

Electron transfer, catalysis

# In oxidizing metabolism the Krebs cycle extracts energy from sugars

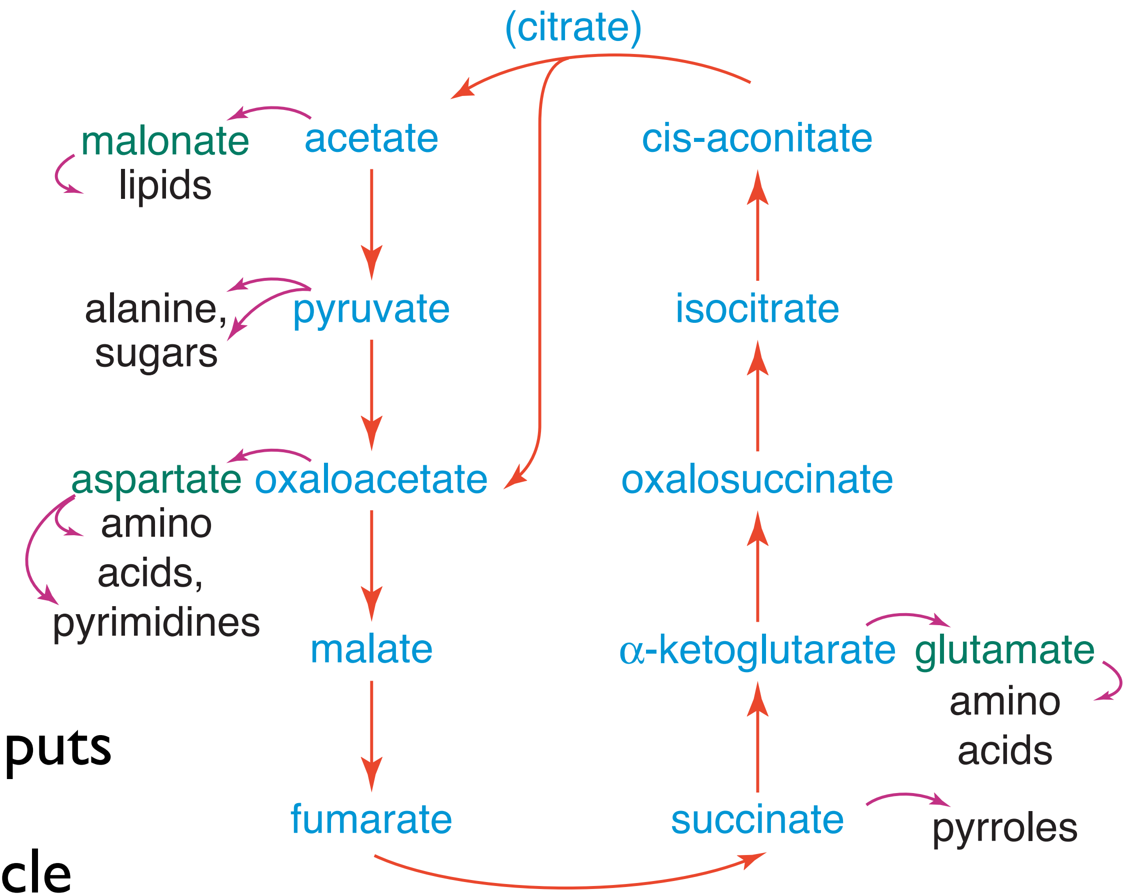
- Sugars fragment to 3-carbon pyruvate, which combines with water to make acetate, CO$_2$, and reductant (NADH)
- Acetate combines with oxaloacetate (network catalyst) to make citrate
- Citrate breaks down with more water to make CO$_2$, reductant, and recover the oxaloacetate
- Net cycle *oxidizes* sugars to CO$_2$, and consumes two complex (pyruvate) molecules to make one (oxaloacetate) complex molecule



6
(citrate)
2
acetate
6
cis-aconitate
3
pyruvate
6
isocitrate
sugars
4
oxaloacetate
6
oxalosuccinate
4
malate
5
α-ketoglutarate
4
fumarate
4
succinate

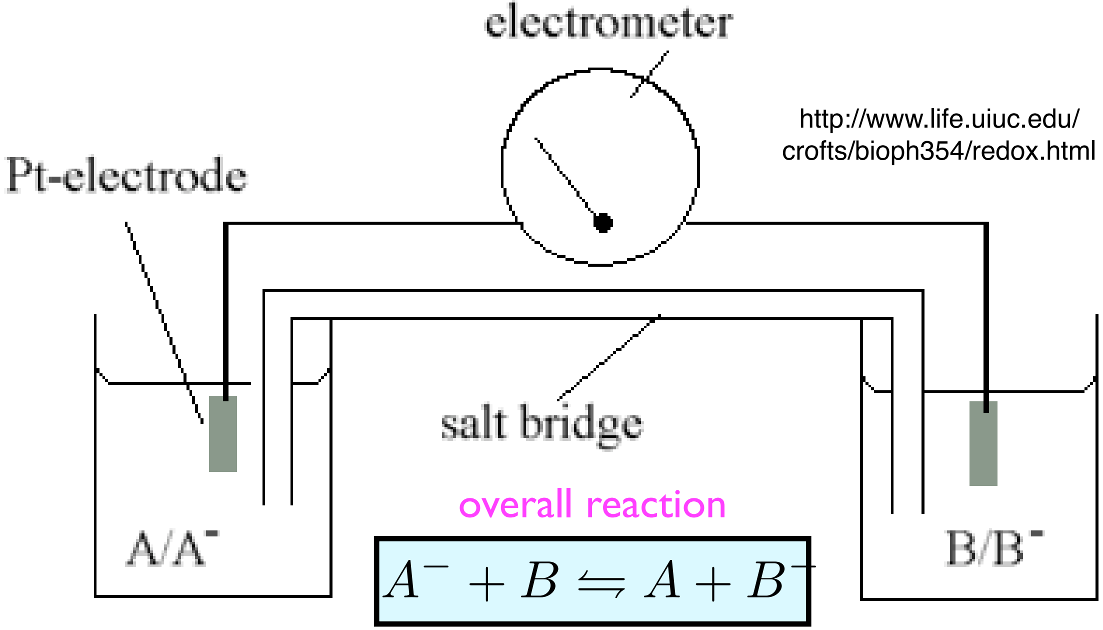
# “Older” reducing organisms use same reactions purely for biosynthesis

- *Reductive* TCA (rTCA) cycle extracts energy and builds biomass at the same time
- All the arrows in the reductive cycle go the same way:
  - Reducing $CO_2$ to acetate
  - Producing complex biomolecules from simple inputs
- Many organisms can use the cycle in either direction (*E.coli* and yeast)


(citrate)
malonate
lipids
acetate
cis-aconitate
alanine,
sugars
pyruvate
isocitrate
aspartate
oxaloacetate
oxalosuccinate
amino
acids,
pyrimidines
malate
α-ketoglutarate
glutamate
amino
acids
fumarate
succinate
pyrroles

# Reduction and Oxidation (redox) powers TCA and other 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 $A^- \leftrightharpoons A + e^-$ 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/bioph354/redox.html

overall reaction

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

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

general reaction schema

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

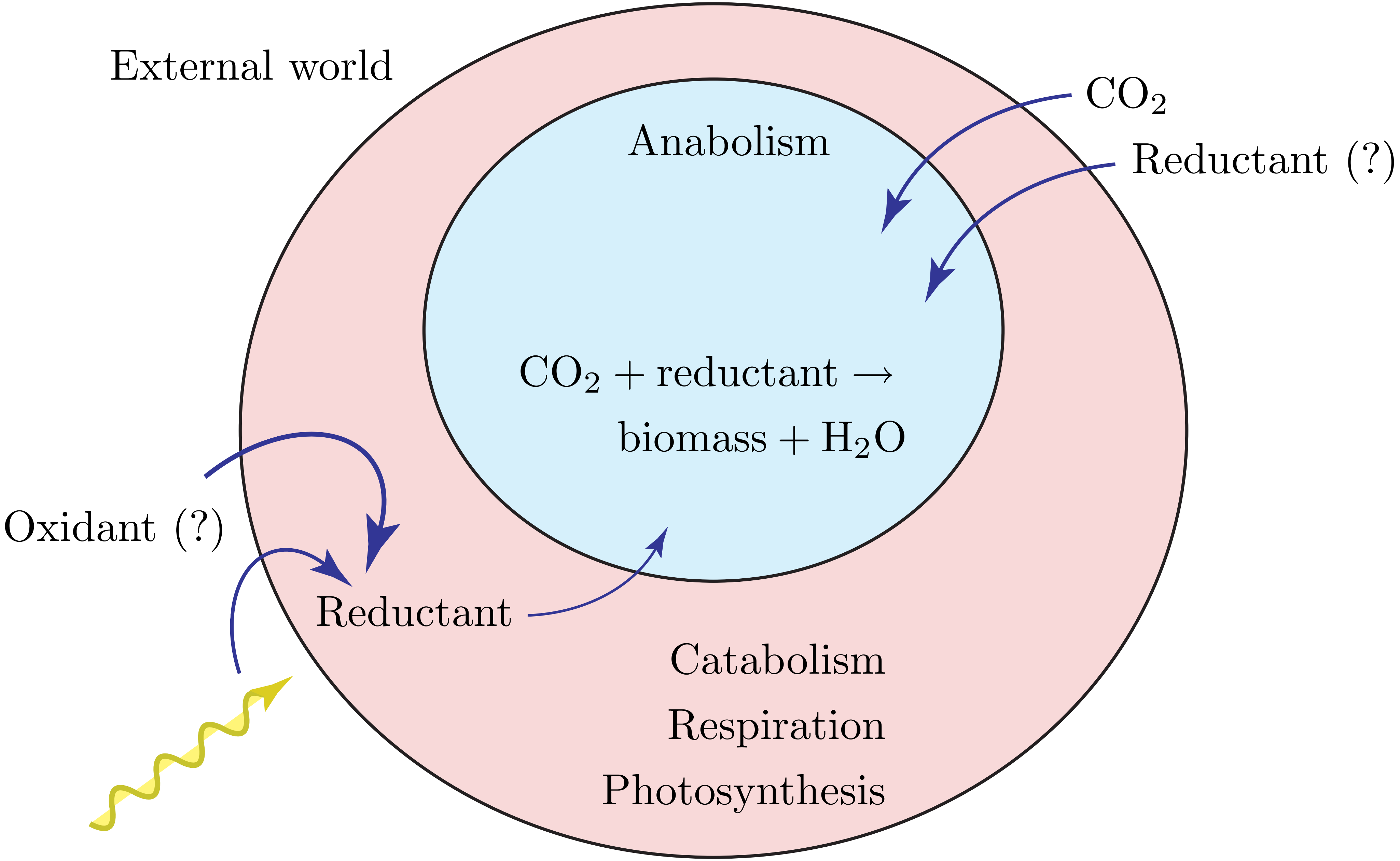
voltage equivalent

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

reference couple

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

# The metabolic and physical structure of cells in relation to electron flow and redox energy



External world

Anabolism

$CO_2$

Reductant (?)

$CO_2$ + reductant →

biomass + $H_2O$

Oxidant (?)

Reductant

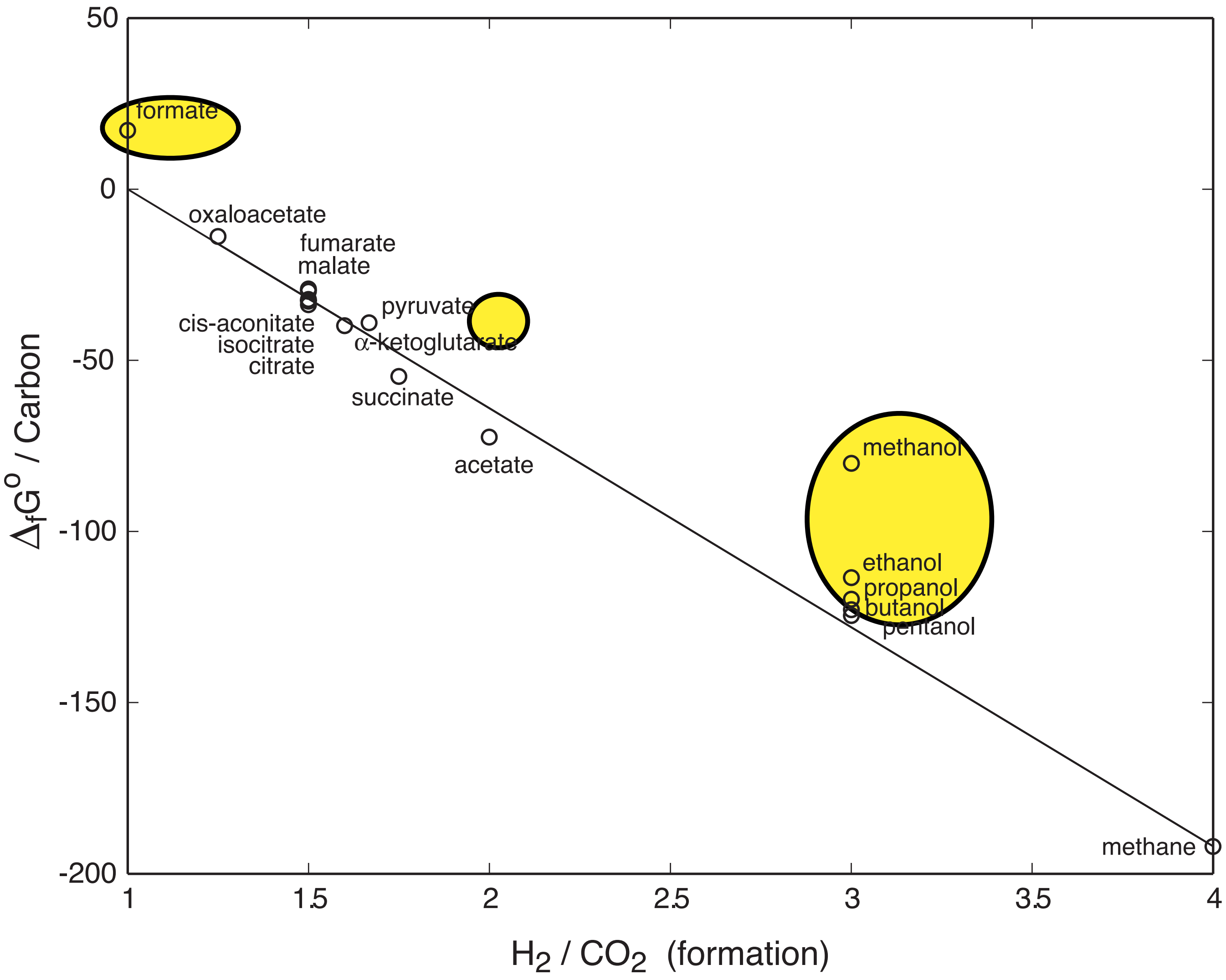
Catabolism

Respiration

Photosynthesis

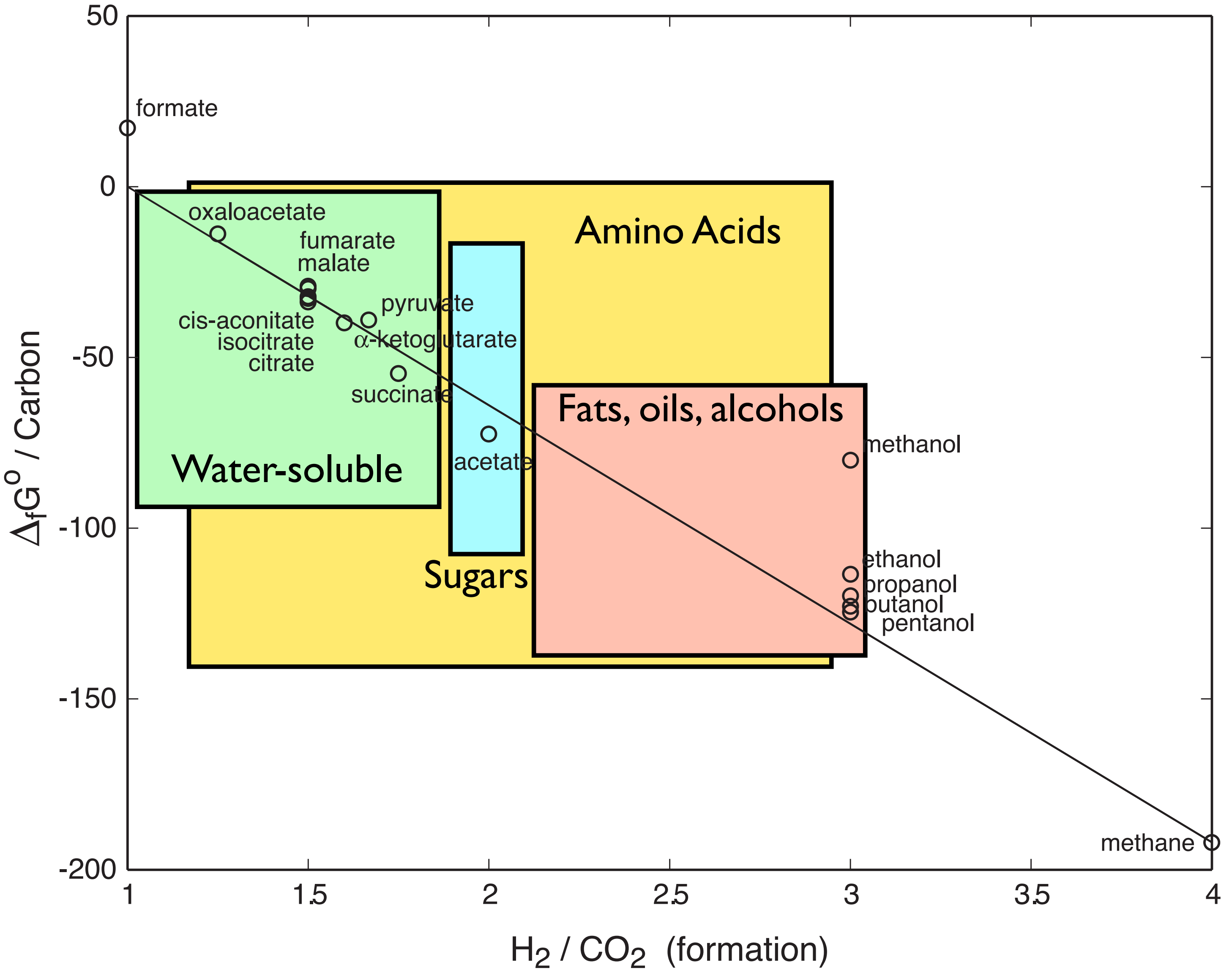
# “Capture of energy” is not separated from formation of biomass in a reducing world

- Number of bonds transferred from HH to CH or HO measures redox energy of formation
- Small molecules of biochemistry sometimes have lowest free energy of formation per carbon

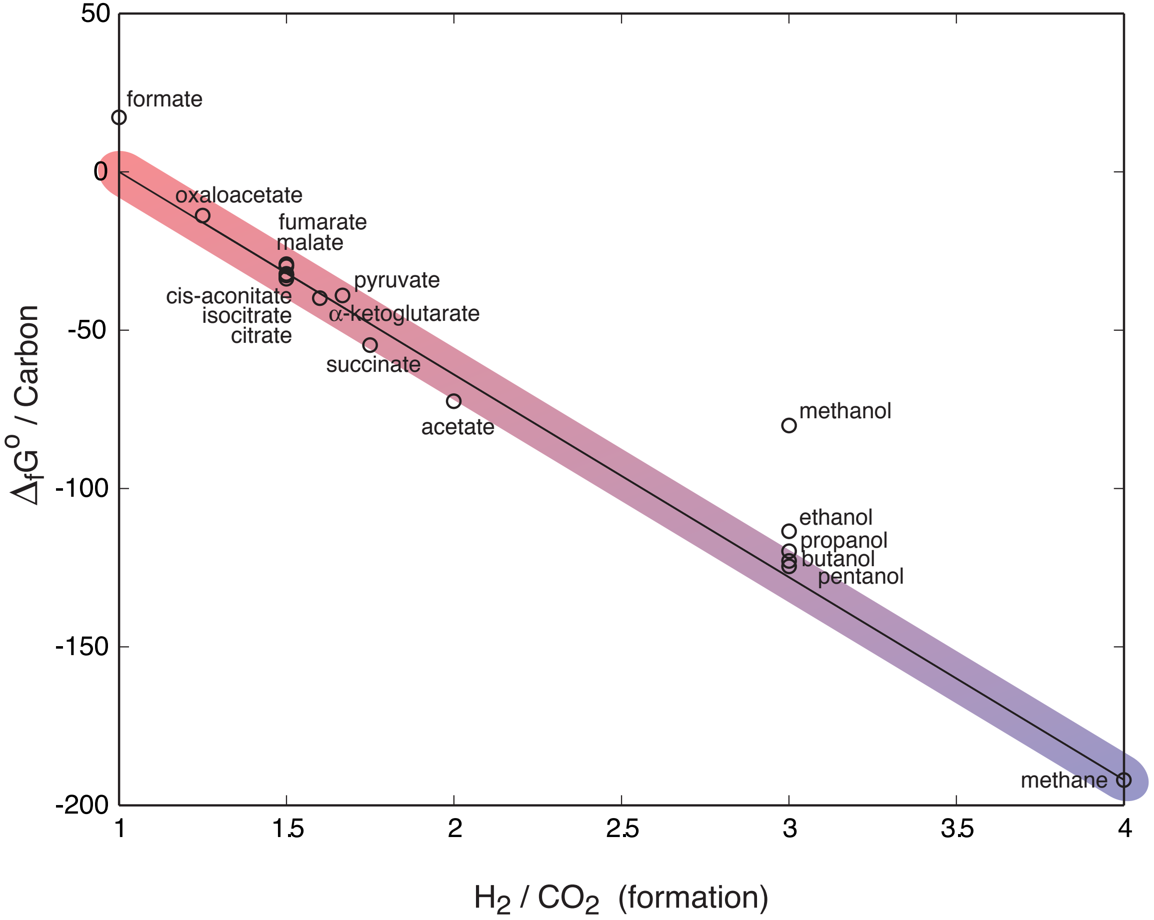


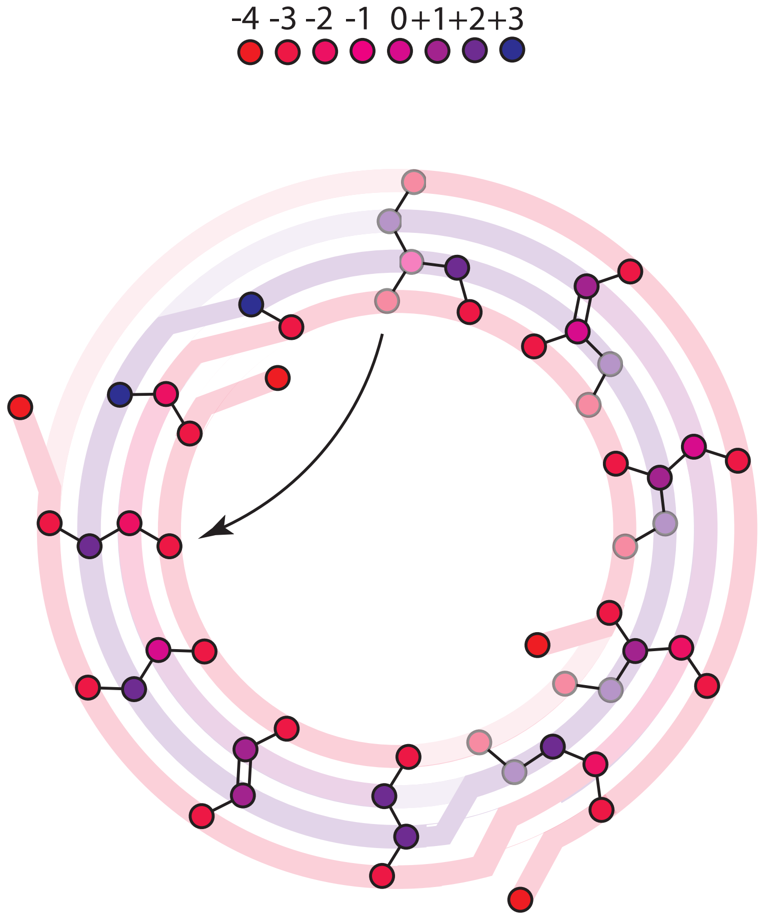
# Electron transfer and formation energy also relate to physical roles of molecules

- rTCA acids ~ water-soluble biomass
- acetate ~ sugars, switch from redox to phosphate energy
- fats and oils phase separate to make compartments
- amino acids couple to all these, so span all their solubilities



# Movement around the cycle reduces individual carbons (on average)

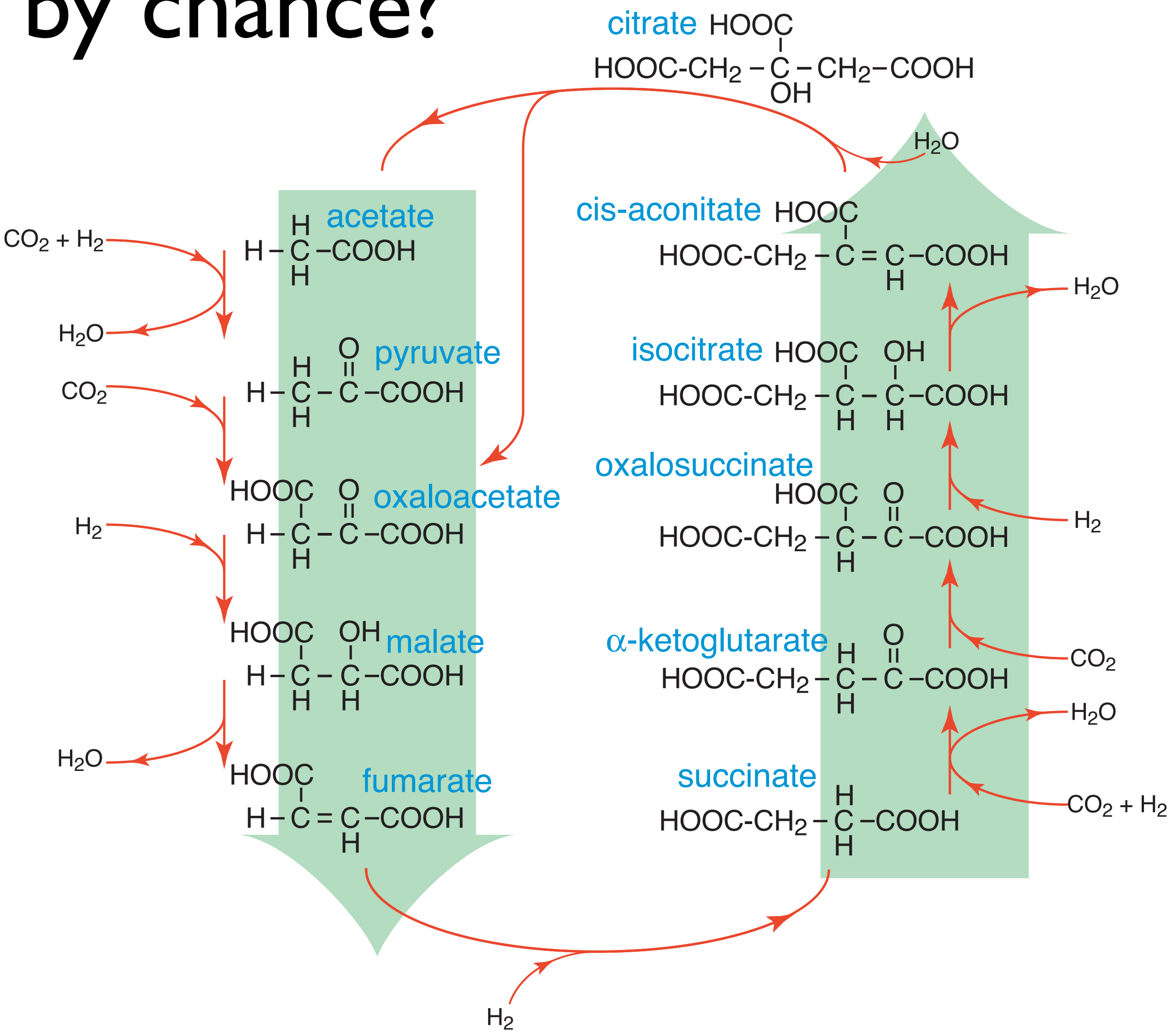




# rTCA is chemically simple and redundant
# So easier to form by chance?

- Only 5 molecular groups and 5 reactions are required

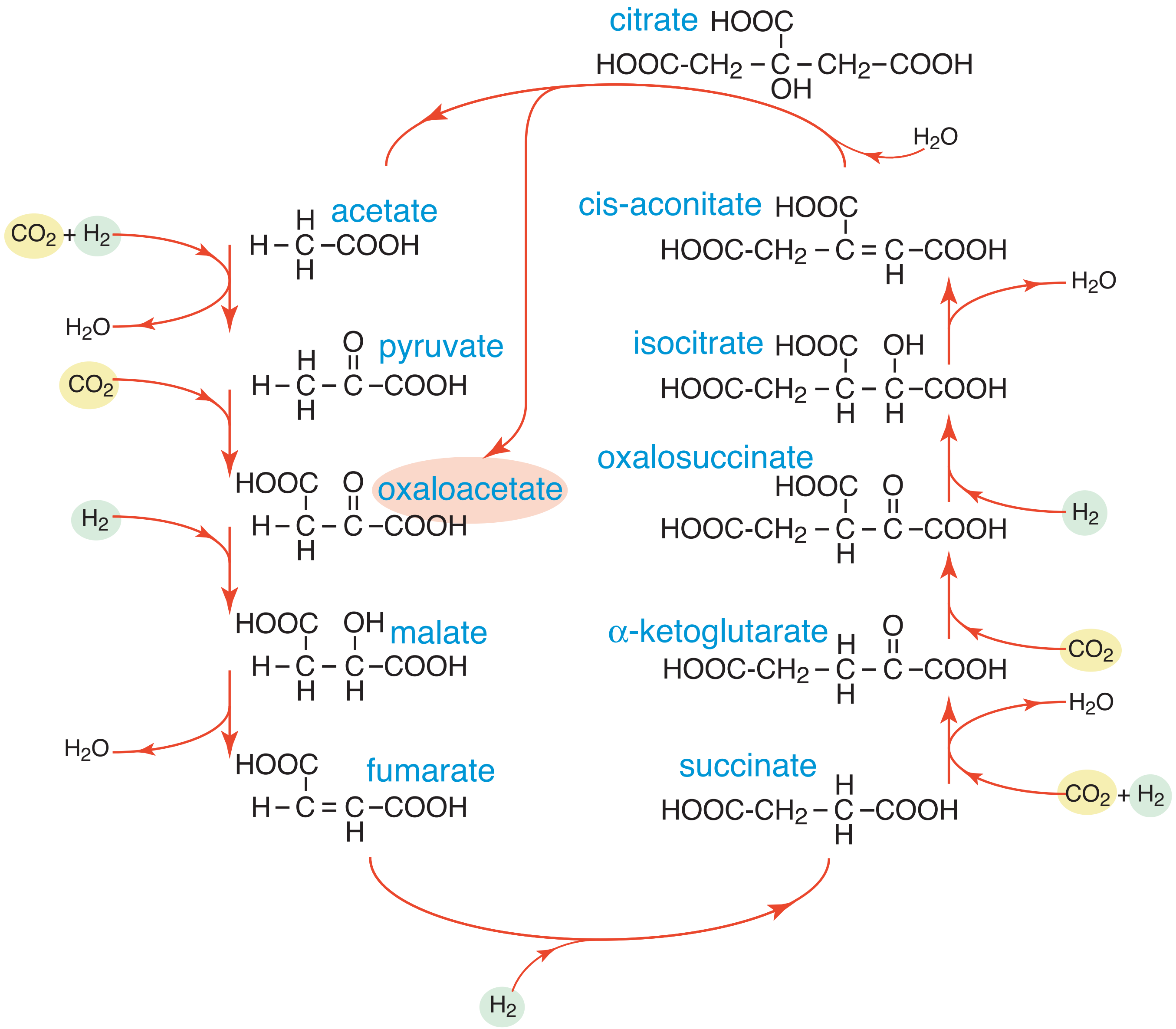
- Enzymes for homologous reactions have often resulted from duplication of a common ancestor



*Simplicity* is the source of *accessibility*

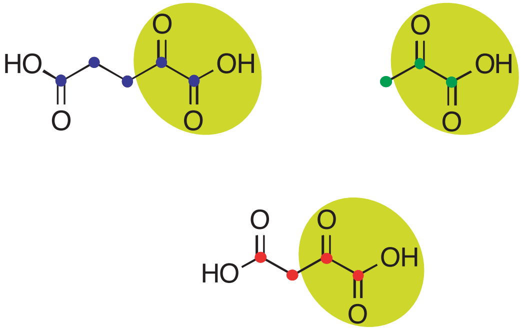
# rTCA reactions are *first order* in complex molecules; may not require compartmentation

- Oxaloacetate converts a 6-body reaction for $CO_2$ reduction to acetate into a sequence of simpler reactions
- No benefit from compartmentation in a pre-enzymatic world
- Suggests the cycle could have been a pre-cellular *bulk-phase* process

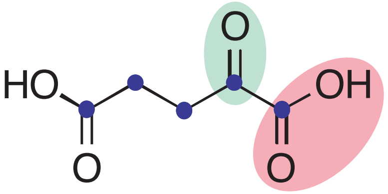


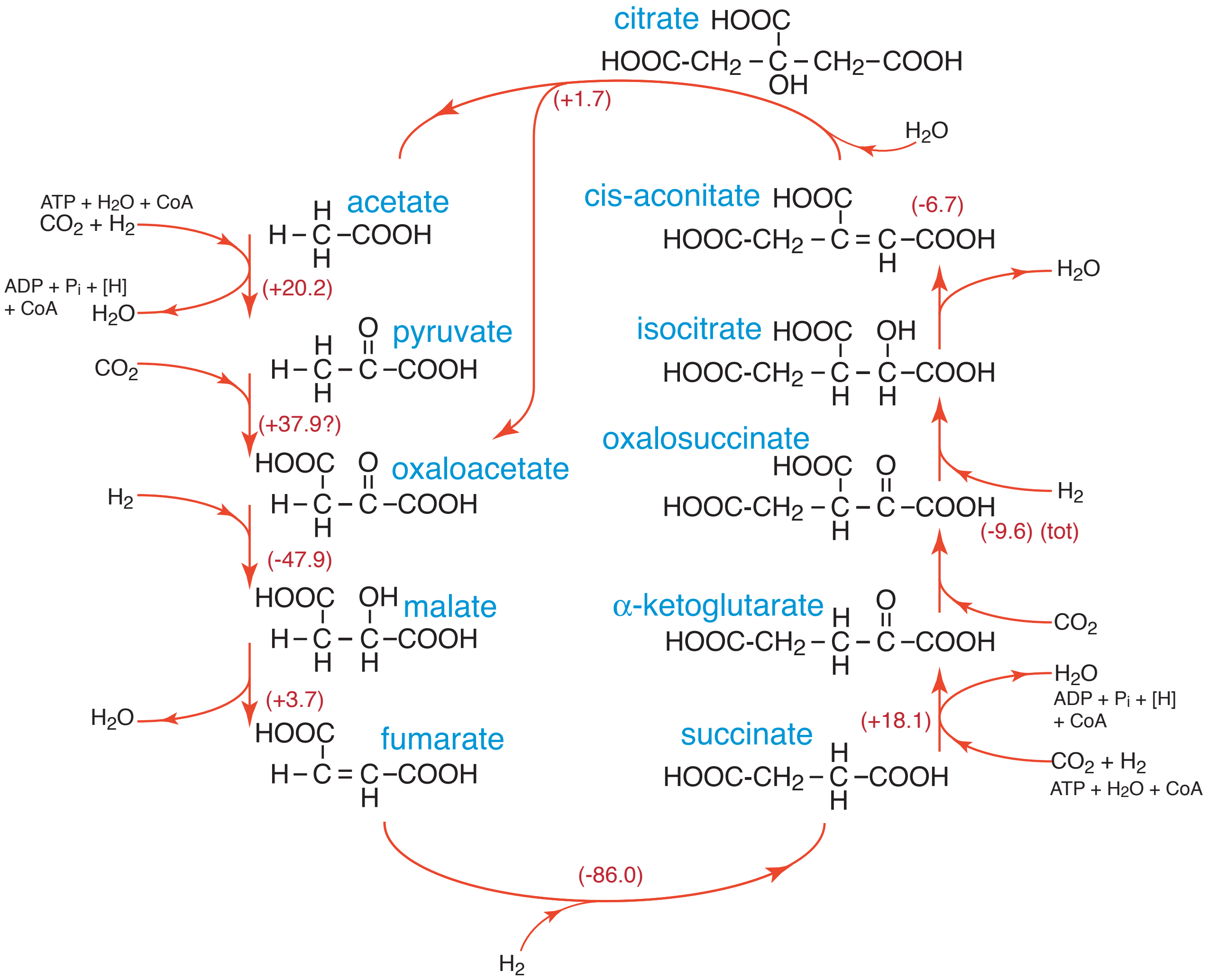
# rTCA molecules made from $CO_2$, form functional groups that capture $CO_2$

Compounds in the cycle are known as "alpha-keto" acids



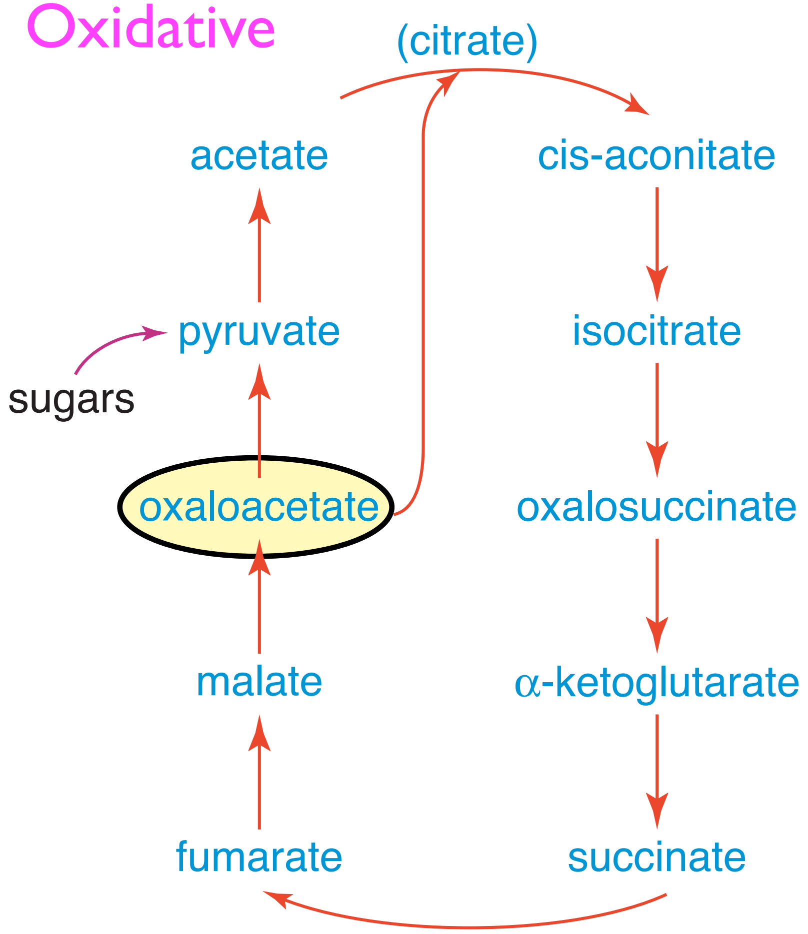
Reactive groups are carboxyl and alpha-ketone





# Oxaloacetate is a *network catalyst* in either TCA direction

Oxidative



(citrate)

acetate

cis-aconitate

pyruvate

isocitrate

sugars

oxaloacetate

oxalosuccinate

malate

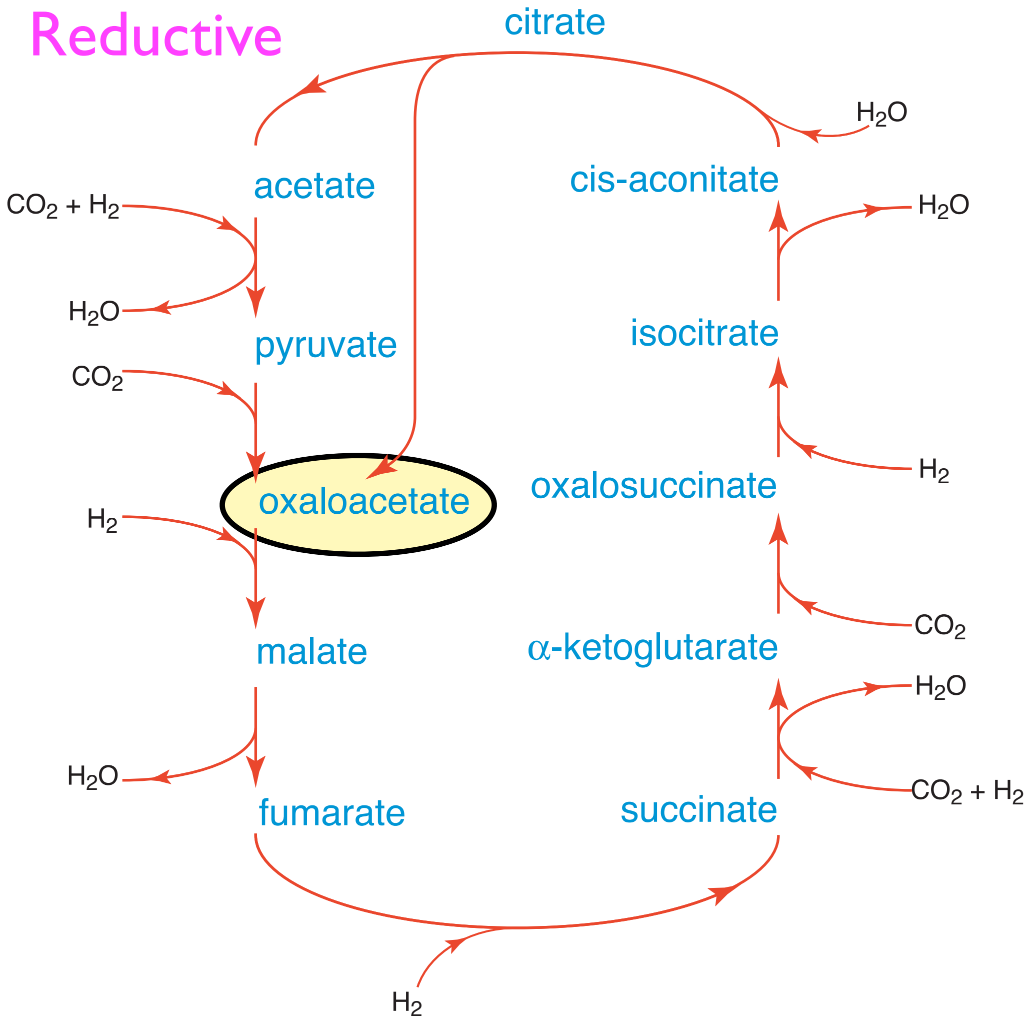
α-ketoglutarate

fumarate

succinate

Condensation of acetate with OXA initiates decarboxylation

Reductive



citrate

$H_2O$

acetate

cis-aconitate

$CO_2 + H_2$

$H_2O$

$H_2O$

isocitrate

pyruvate

$CO_2$

$H_2$

oxaloacetate

oxalosuccinate

$H_2$

$CO_2$

malate

α-ketoglutarate

$H_2O$

$H_2O$

$CO_2 + H_2$

fumarate

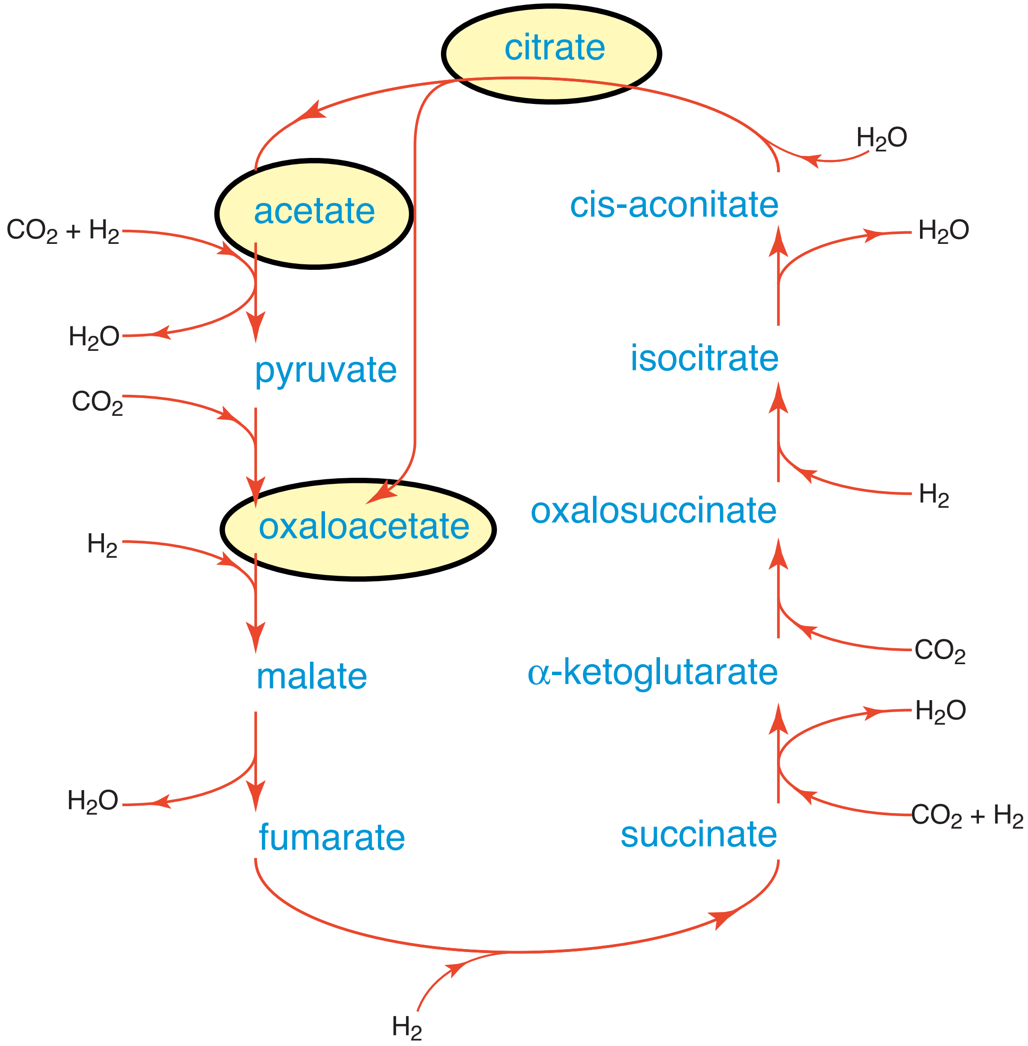
succinate

$H_2$

Reactive OXA favors condensation with $CO_2$ and later reduction

# *Network autocatalysis* (from topology) potentially creates exponential growth from small numbers

- Oxaloacetate ($C_4$) is a network catalyst for C reduction
- Fission of citrate generates *two* cycle intermediates
- Regeneration of Oxa from Ace gives two seeds from one

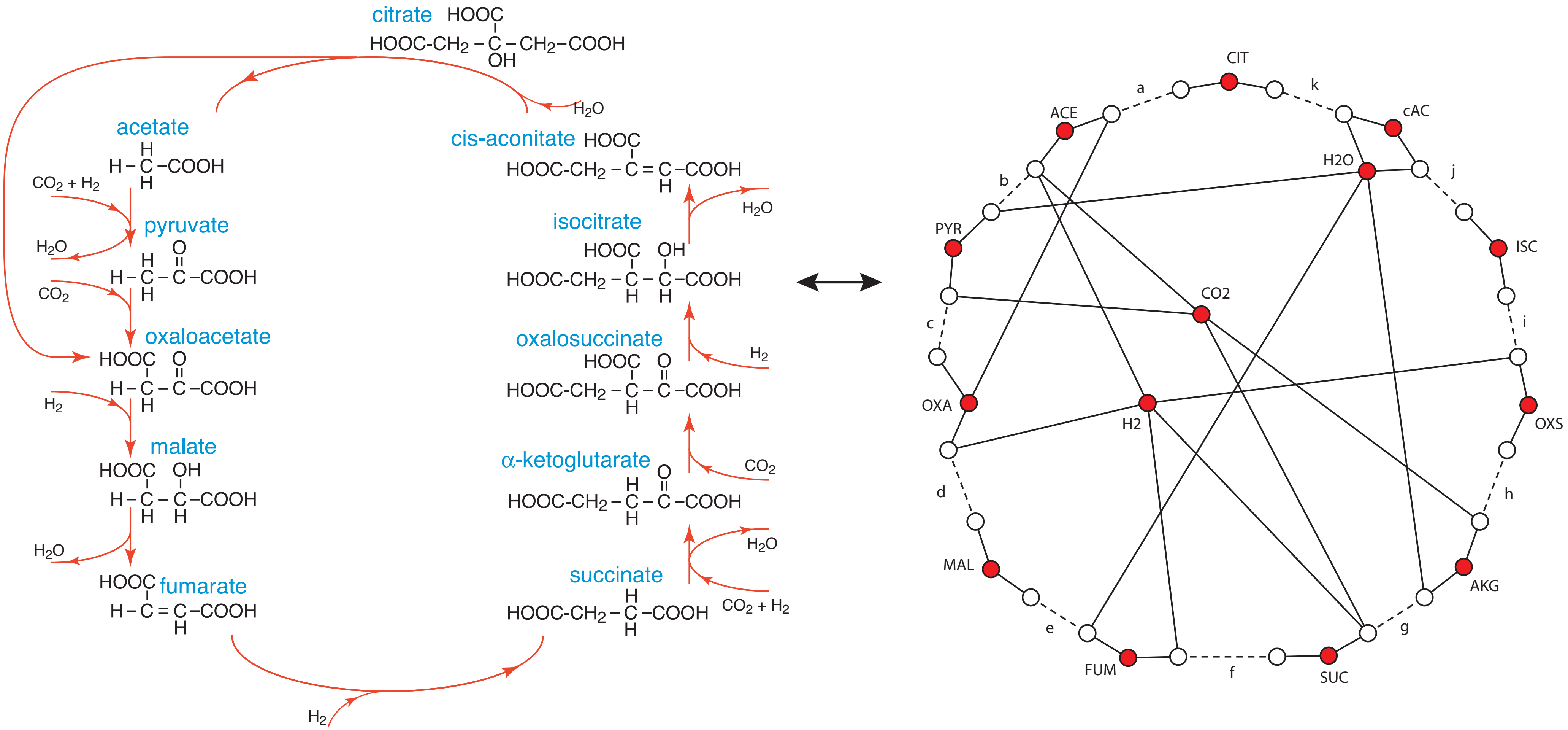


(Think of compound interest or chain reaction)

# Some comments on self-amplification

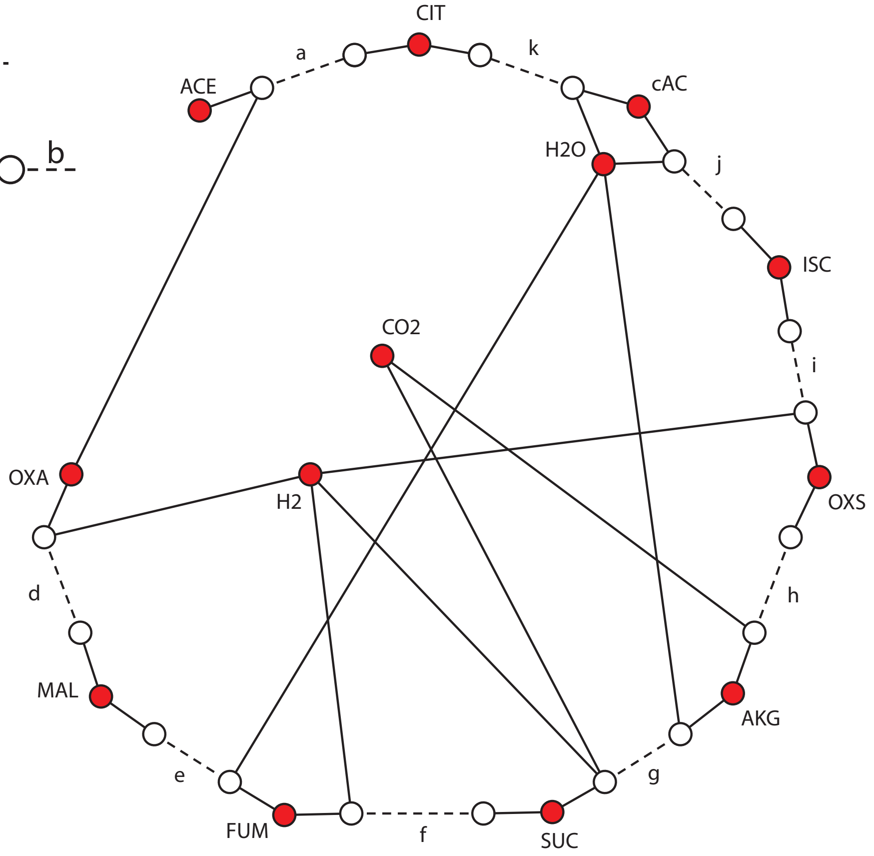
- Any ordered process subject to random events must be self-amplifying -- life as a whole is
- All models for emergence of living order have assumed this property (Eigen hypercycle)
- The surprise is that self-amplification should be contained in such a simple network core
- Only biosynthesis has such a simple core: all networks containing energy systems or self-replication must be huge to be self-contained

# Quantitative analysis of network properties of self-amplifying cycles such as rTCA



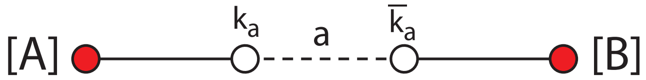
# The graph theory of chemistry is hypergraphs

- Suppose we want to capture the concentration dependence and stoichiometry of a network
    - Each mole of reagent into a reaction is a named line ACE
    - Each reservoir of reagent is a named vertex ACE ●
    - Each reaction (transition state) is a labeled line - - b - - -
    - All inputs and transition states share a vertex Ace $H_2$ $CO_2$ ○ - b - -
- Then the TCA graph as a network producing acetate looks like



# Graph reduction and effective networks

Start with rate equations for a basic reaction



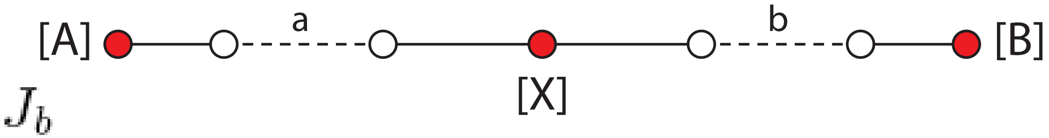
$$[\mathrm{A}]\,k_a - [\mathrm{B}]\,\bar{k}_a = J_a.$$

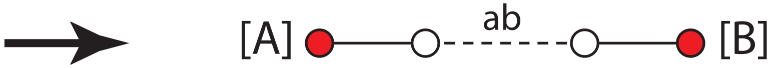
$$\begin{aligned}
[\dot{\mathrm{A}}] &= -J_a\\
[\dot{\mathrm{B}}] &= J_a,
\end{aligned}$$

Two basic reactions with intermediate species X imply a conservation law in steady state

$$\begin{aligned}
[\mathrm{A}]\,k_a - [\mathrm{X}]\,\bar{k}_a &= J_a\\
[\mathrm{X}]\,k_b - [\mathrm{B}]\,\bar{k}_b &= J_b,
\end{aligned}$$

$$\begin{aligned}
[\dot{\mathrm{A}}] &= -J_a\\
[\dot{\mathrm{X}}] &= J_a - J_b\\
[\dot{\mathrm{B}}] &= J_b,
\end{aligned}$$





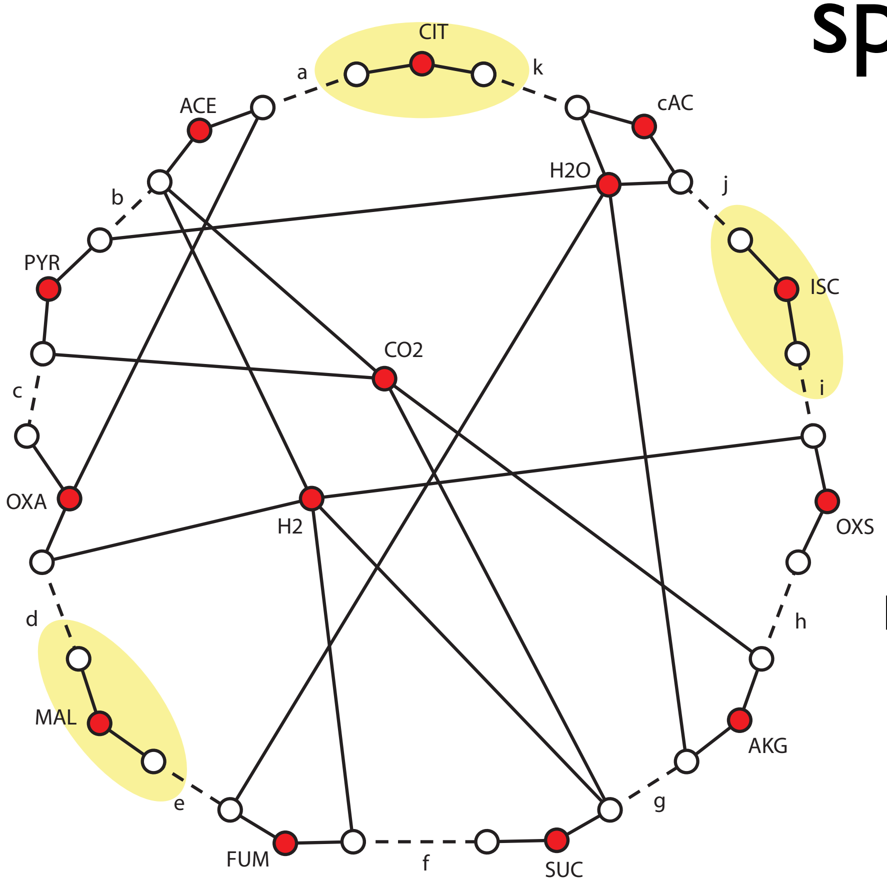
Remove species X and aggregate rate constants in an effective reaction

$$[\mathrm{A}]\,k_{ab} - [\mathrm{B}]\,\bar{k}_{ab} = J_{ab}$$

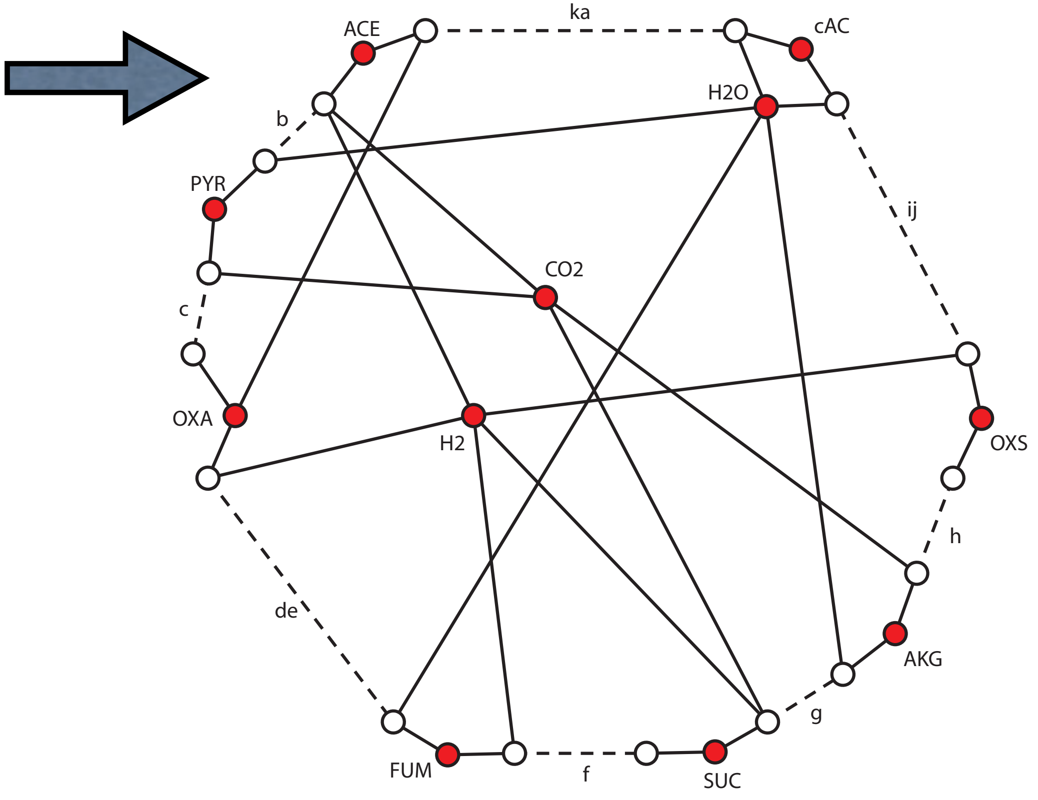
$$(k_a, \bar{k}_a) \circ (k_b, \bar{k}_b) = (k_{ab}, \bar{k}_{ab})$$

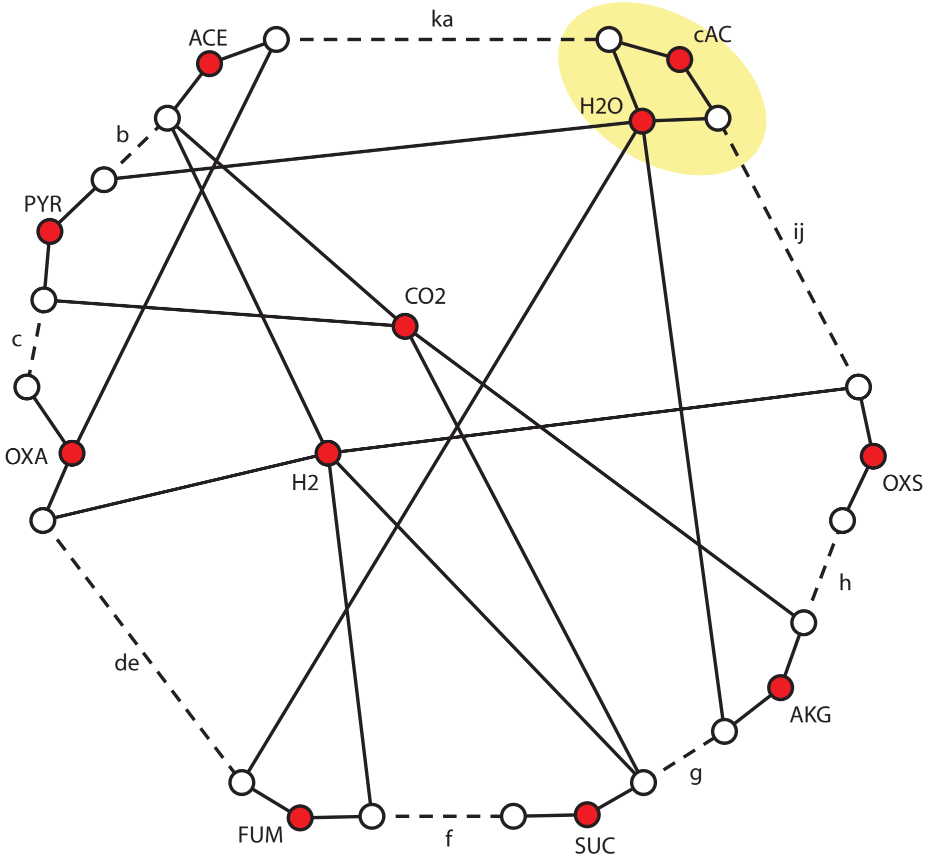
$$\begin{aligned}
k_{ab} &= \frac{k_a k_b}{\bar{k}_a + k_b}\\
\bar{k}_{ab} &= \frac{\bar{k}_a \bar{k}_b}{\bar{k}_a + k_b}
\end{aligned}$$

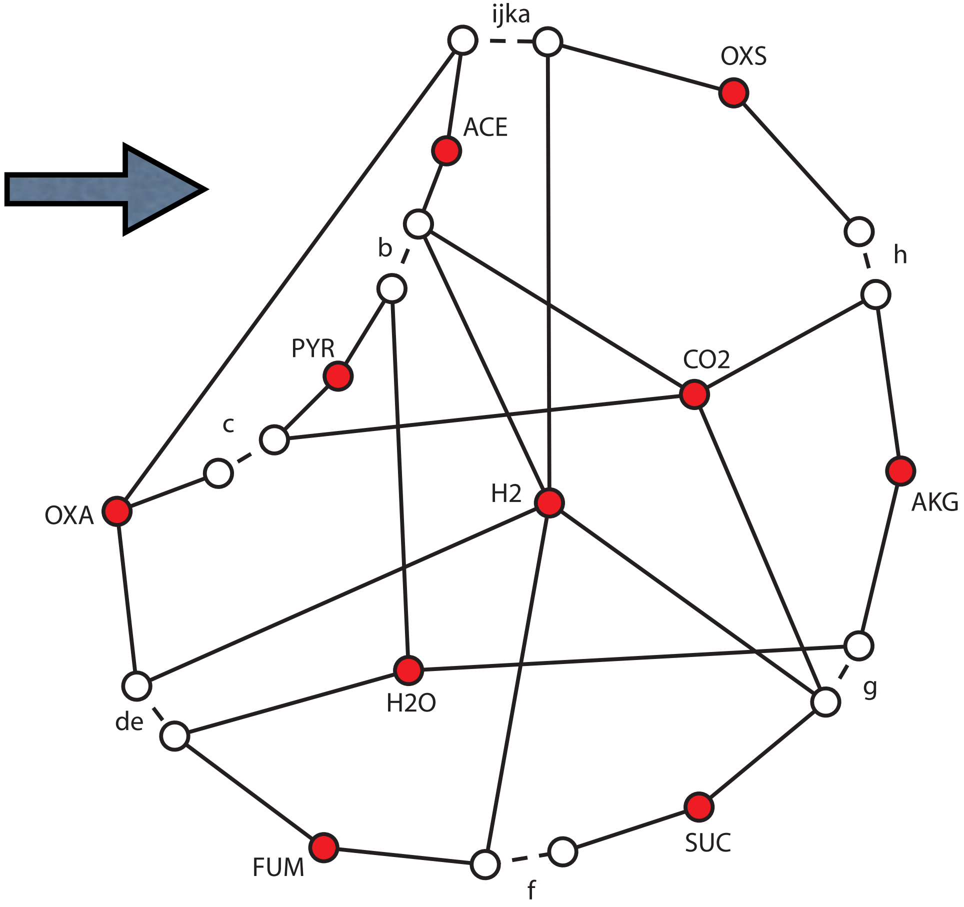
# Example of removal of internal chemical species which preserved total network flows



“Needless” internal nodes

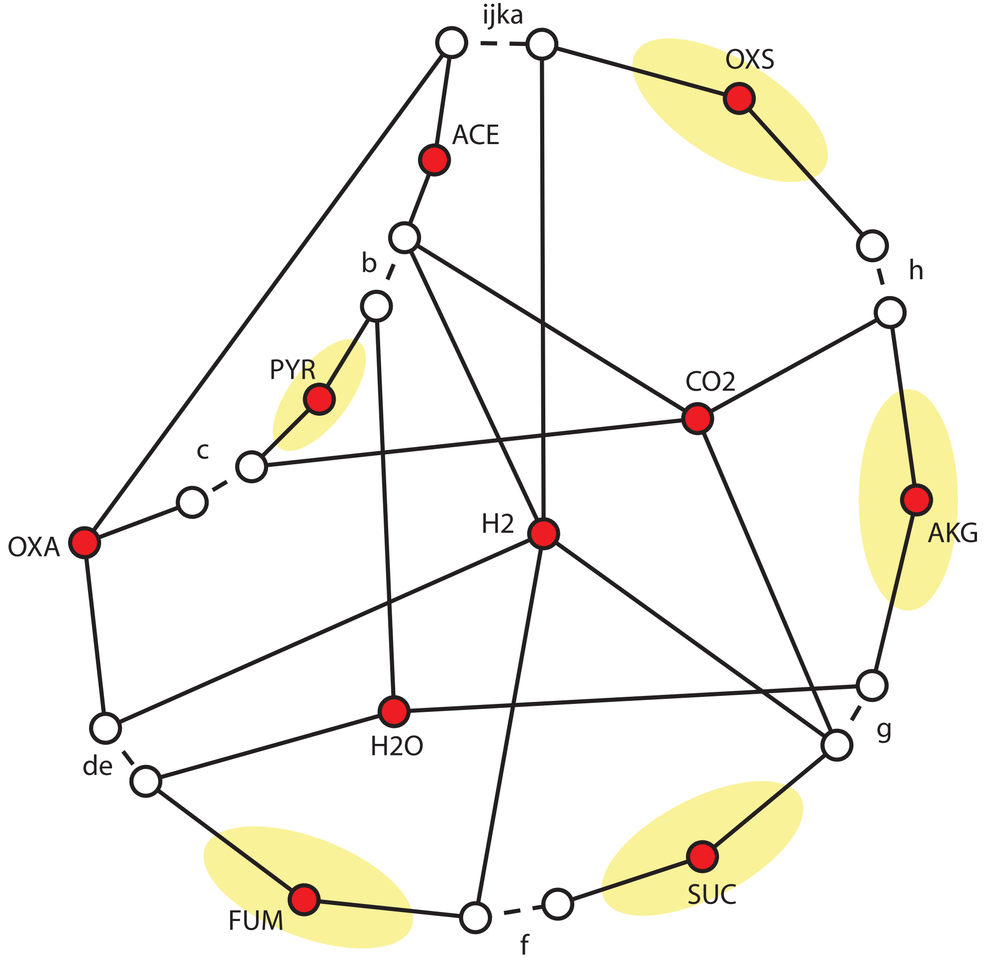


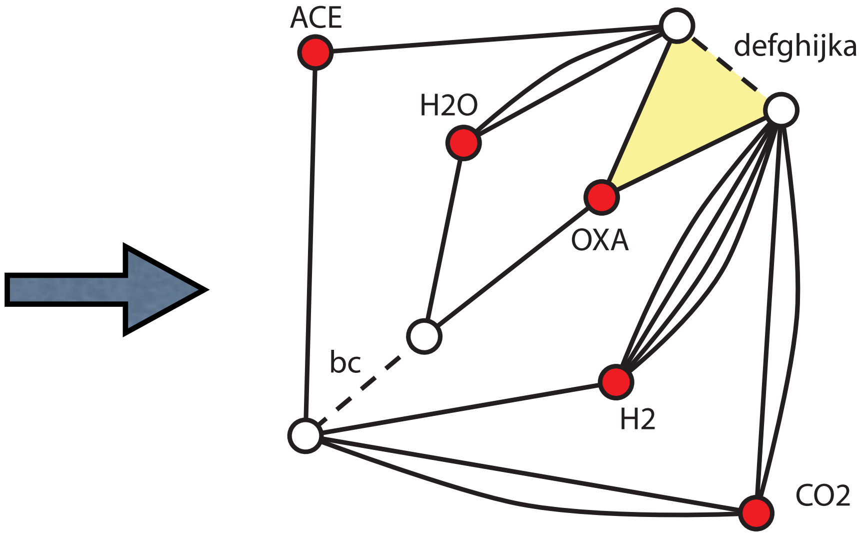




Dehydration/rehydration appears to have internal structure, but it all cancels

# Removal of remaining nodes isolates input/output and network catalysis

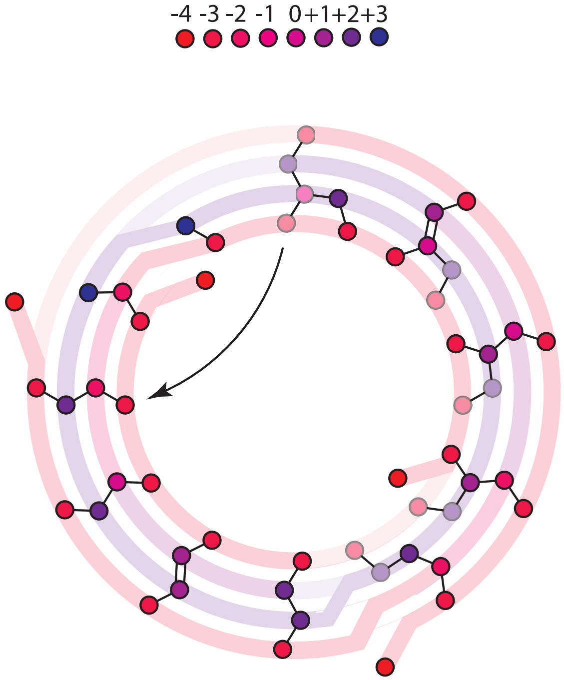


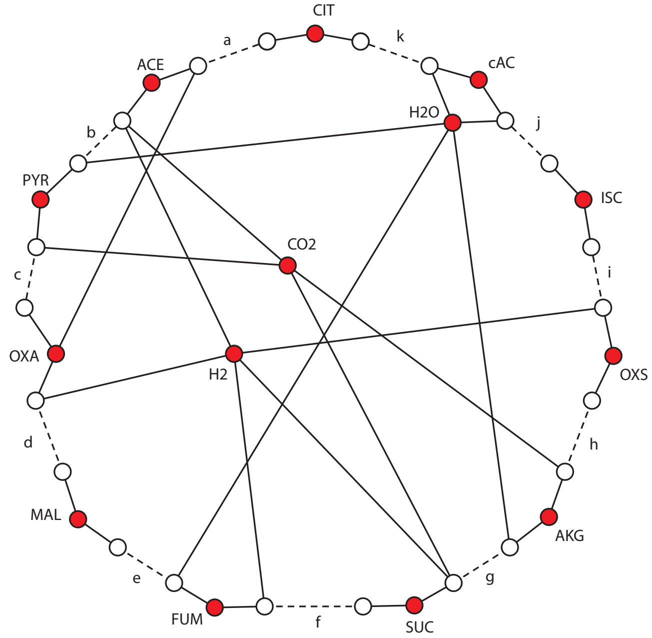


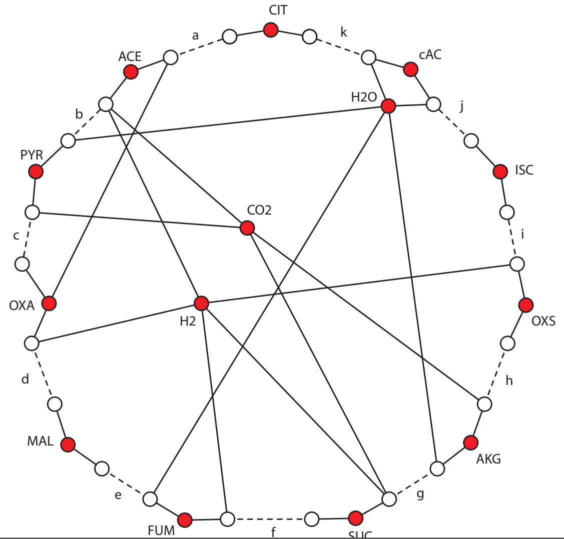
$$J_{bc} = [\mathrm{ACE}]\,[\mathrm{H_2}]\,[\mathrm{CO_2}]^2 k_{bc} - [\mathrm{OXA}]\,[\mathrm{H_2O}]\,\bar{k}_{bc}$$

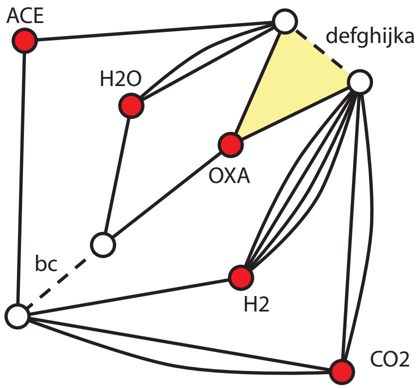
$$J_{defghijka} = [\mathrm{OXA}]\,[\mathrm{H_2}]^4[\mathrm{CO_2}]^2 k_{defghijka} - [\mathrm{OXA}]\,[\mathrm{ACE}]\,[\mathrm{H_2O}]^2\bar{k}_{defghijka}$$

# rTCA cycle is a miniature model of what all of life does: self-catalyzed energy flow

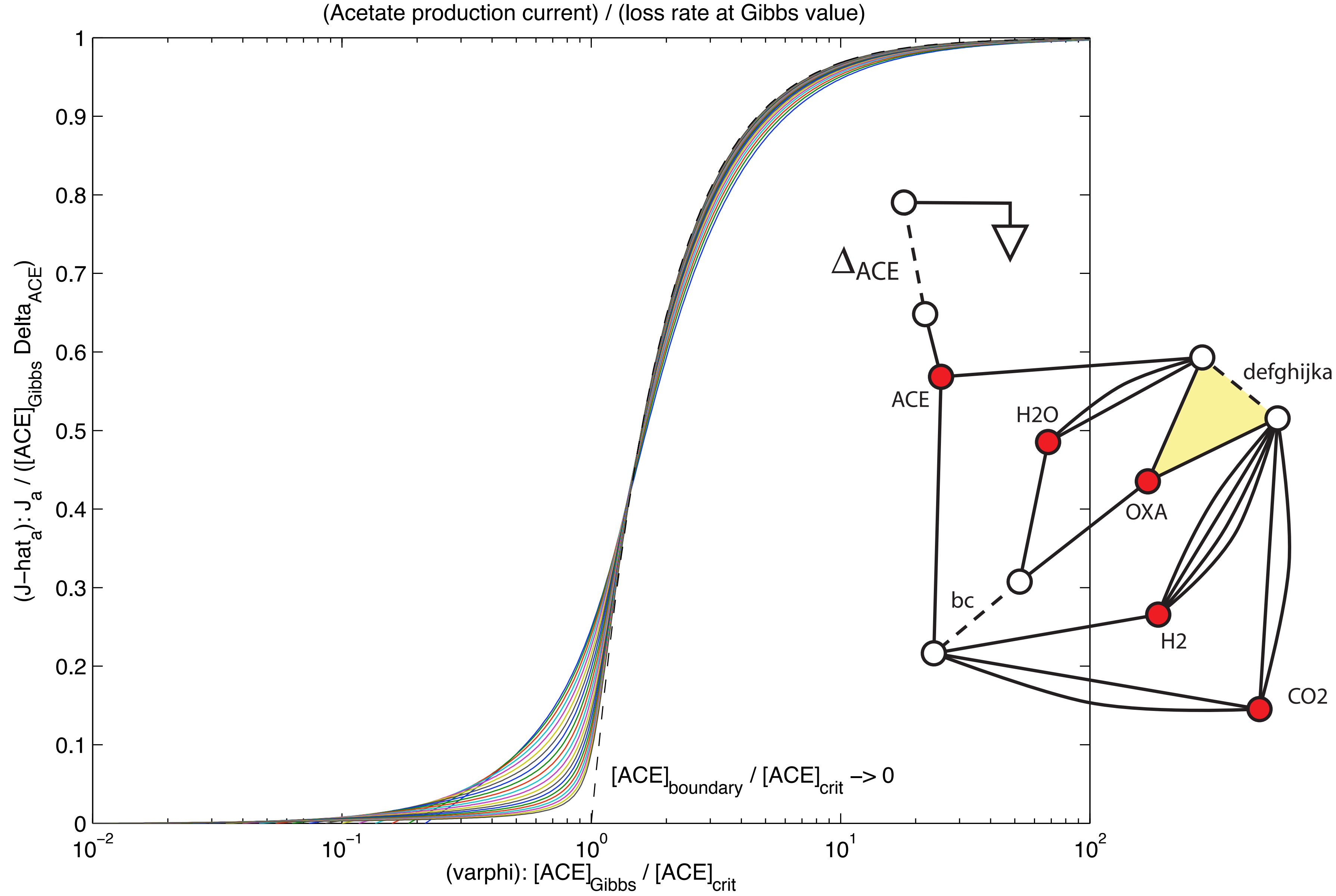








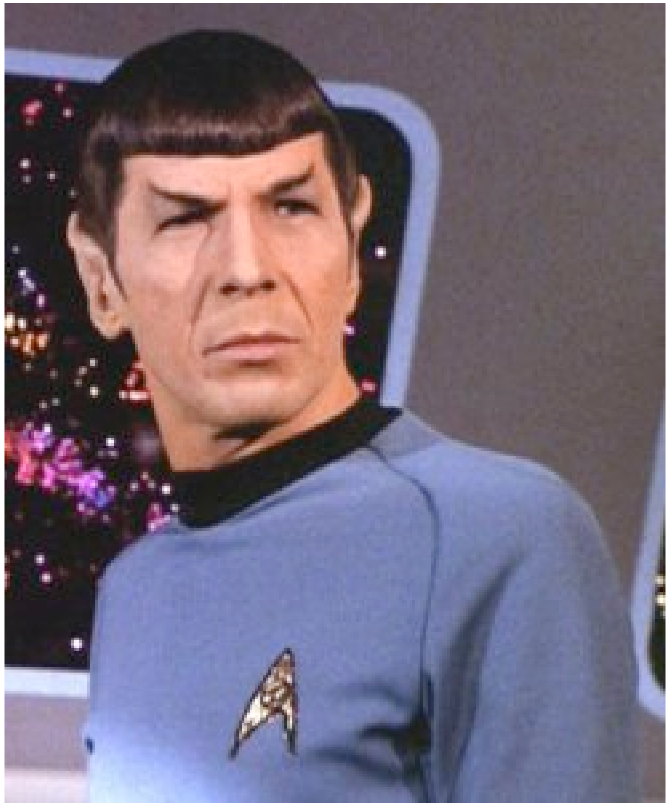
# This can be mathematically modeled, and shows a spontaneous transition to order



# ● Implications for the problem of robust biochemical organization on earth

- The general concept of phase transition as an answer to the problem of robust order
- The interpretation of phase transition in a dynamical setting

# What significance do we assign to such network properties?



- Self-amplification in a small, simple network that could have formed by chance
- Feedback-structure of the amplifier causes thresholds for self-maintenance
- Makes us think of *phase transitions* as the concept explaining robust order

# Why is spontaneous order a problem to explain?

- Energy is related to probability for near-equilibrium systems

$$k_B T \approx 2.6 \times 10^{-2}\mathrm{eV}$$

$$\text{H-bond energy} \approx 0.02 - 0.3 \text{ eV}$$

$$\left\{ \begin{array}{c} \text{C-C} \\ \text{N-N} \\ \text{O-O} \end{array} \right\} \text{bond energy} \approx \left\{ \begin{array}{c} 3.5 \\ 2 \\ 1.5 \end{array} \right\} \text{eV} \qquad P(\text{state}) \sim e^{-\Delta G / k_B T}$$

$$\text{UV photon energy} \approx 3 - 124 \text{ eV}$$

- Morals to the story:

$$e^{-50} \approx 2 \times 10^{-22}$$

  - We might expect one bonded atom per mole by chance
  - A kinetic theory must overcome these probabilities in a *structured way*

# How does phase transition solve the problem of robust order?

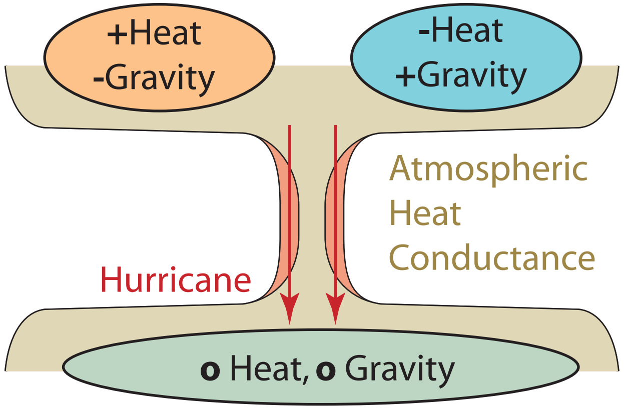
- A frozen system is "as disordered as it can be"
- Even un-complex boundary conditions can drastically reduce disorder within a system
- The boundary conditions that cause life to be more ordered than equilibrium are chemical stresses
- Much of "self-organization" can be understood as dynamical phase transition

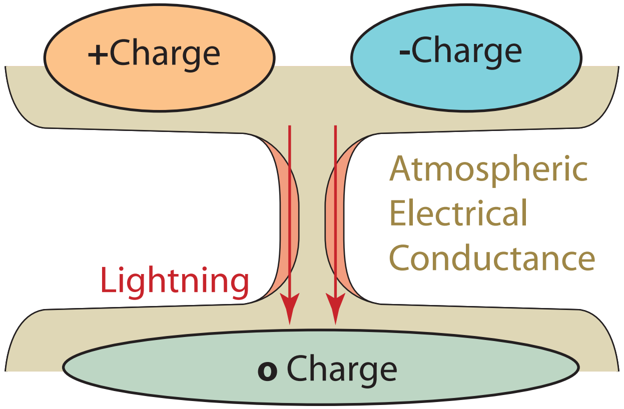
# Self-organization is common when it leads to *channels*

- Common in experience
- Depend on "weakness" under stress, and positive feedback
- Should we understand the origin of metabolic chemistry as a *phase transition* in geochemistry?

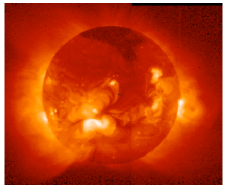
# Stable structures arise at “bottlenecks”

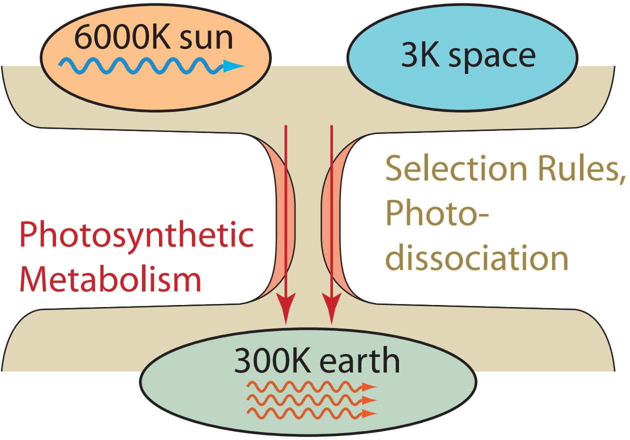
The atmosphere is a poor conductor of heat and electricity

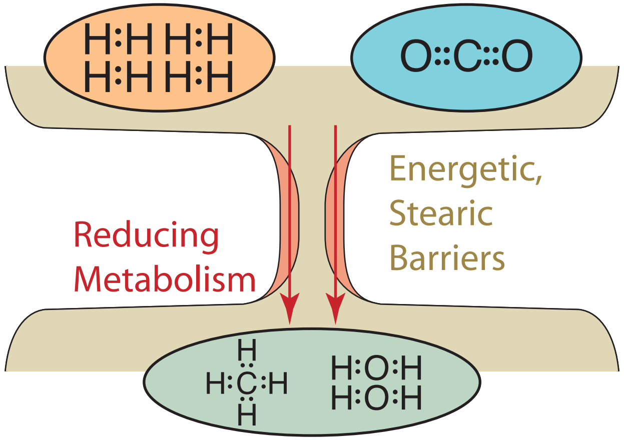


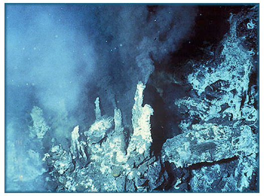


Abiotic matter is a poor “conductor” of light across spectral bands, and electron pairs among bond types



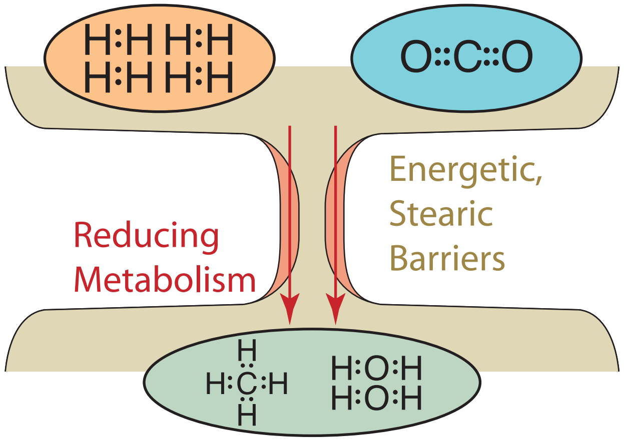




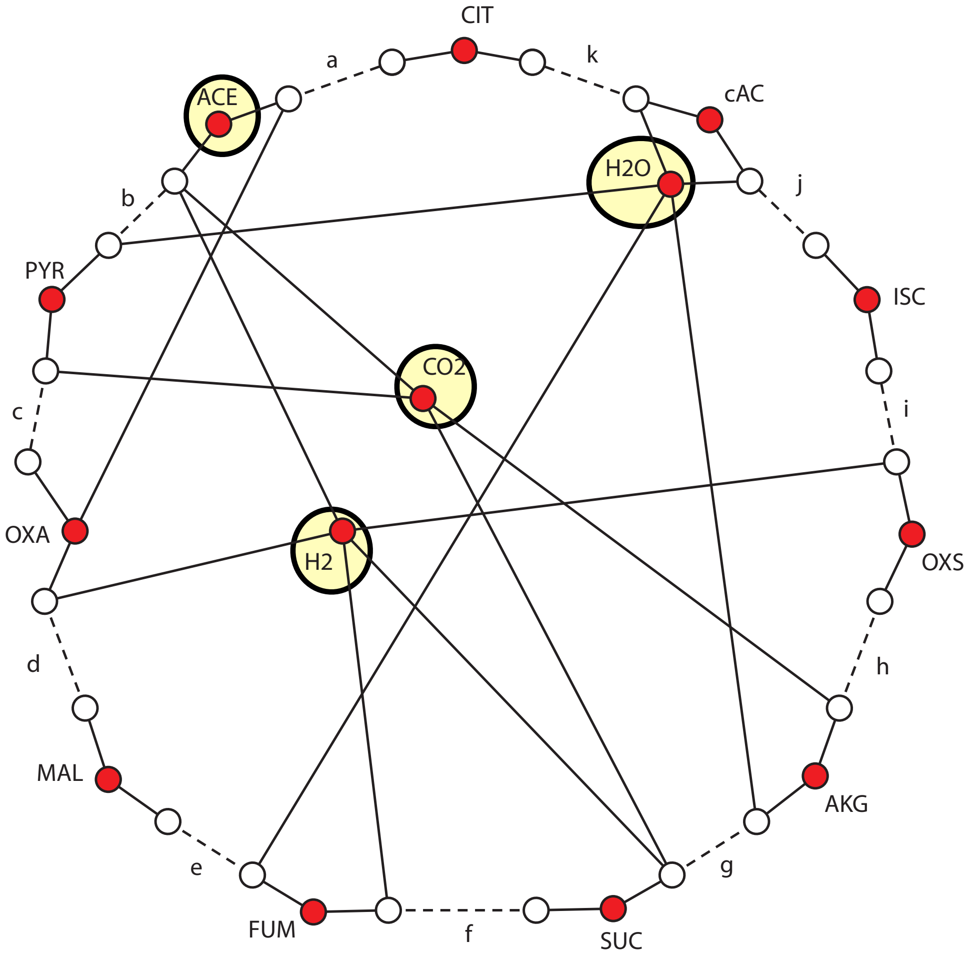


# The channel picture of rTCA (a network point)

- Note: 4 sources; 3 atom types
- Chemical potential drives C and e$^-$ *through* the network

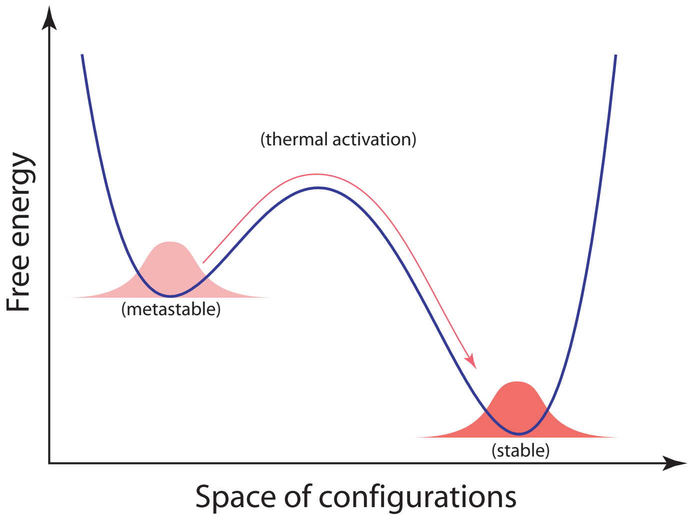


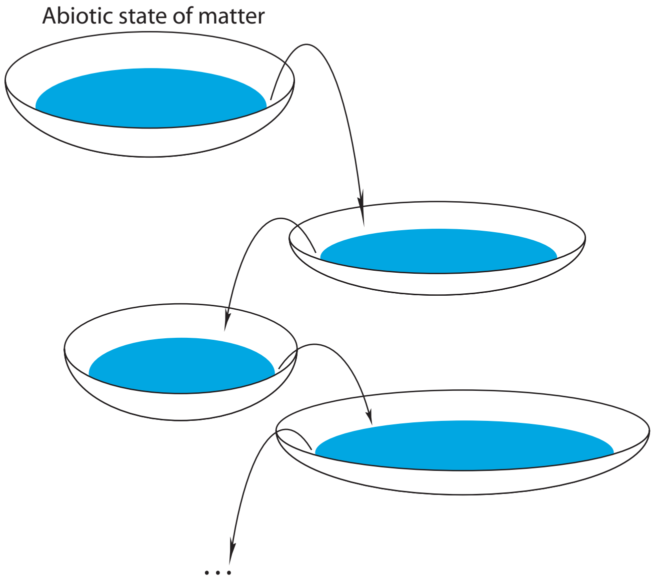
$$\mathrm{CO_2} + \text{reductant} \rightarrow \text{biomass} + \mathrm{H_2O}$$



# A thermodynamic picture of a *necessary* origin of life on earth

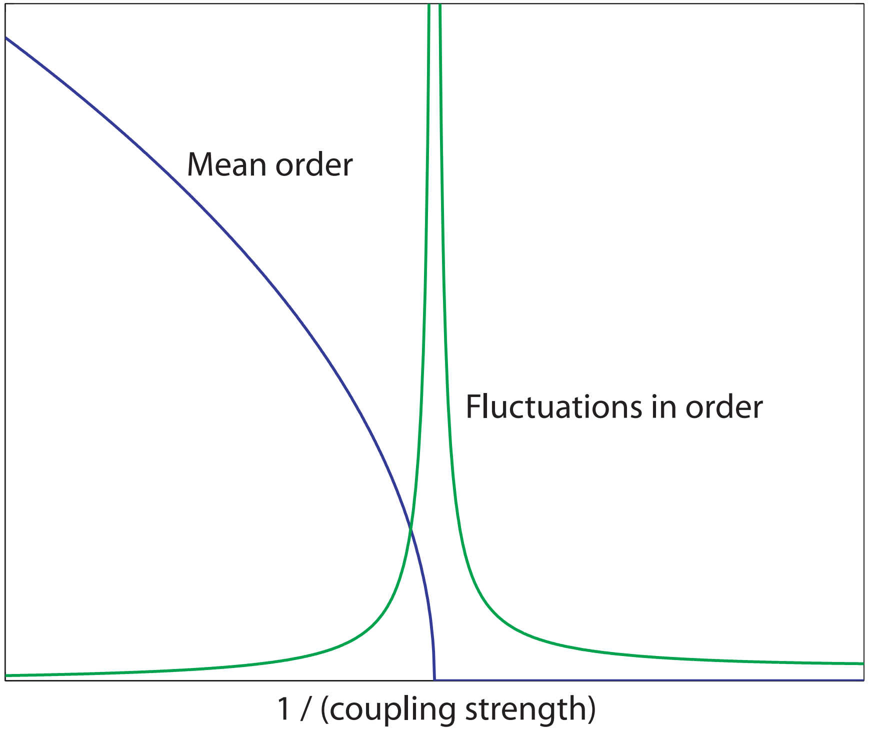
- Lifeless earth, driven by mantle convection, is a *metastable* state
- Life emerged and remained because it creates unique relaxation channels
- Emergence took place in stages





# Lessons from equilibrium phase transitions to apply to dyanamics

- Order can form without “downward causation” of any nontrivial kind
- Order is not easy to form, and cannot be taken for granted scientifically
- The predictable aspects of order determine what kinds of accidents are possible



# Some summary *questions*

- Should we better describe the "origin of life" as the "emergence of a biosphere"?
- Is a phase transition to organic synthesis the correct point of departure?
- Are the order parameters of that phase transition the core biochemical pathways?
- Why then is biochemical order only found in the context of much additional hierarchical control flow and evolutionary dynamics?

# Further reading

- Schrödinger, Erwin, **What is life? : the physical aspect of the living cell / by Erwin Schrödinger** London : Cambridge University Press, 1955
- Morowitz, Harold J **Foundations of bioenergetics** New York : Academic Press, 1978
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- Fenchel, Tom **Origin and early evolution of life** New York : Oxford University Press, 2002
- Fry, Iris **The emergence of life on earth: a historical and scientific overview** New Jersey : Rutgers University Press, 2000
- Smith, Eric **Statistical mechanics of self-driven Carnot cycles** Phys. Rev. E**60**,1999, 3633; **Self-organization from structural refrigeration** Phys. Rev. E**68**,2003, 046114; **The thermodynamic dual structure of linearly dissipative driven systems** Phys. Rev. E**72**, 2005, 36130