Getting life started:

Self-organized carbon fixation

CSSS Beijing 2008 (day 2)

Day II outline

- Properties of carbon fixation in modern life
- Concepts of self-organization
- Analyzing carbon fixation as a self-organizing process

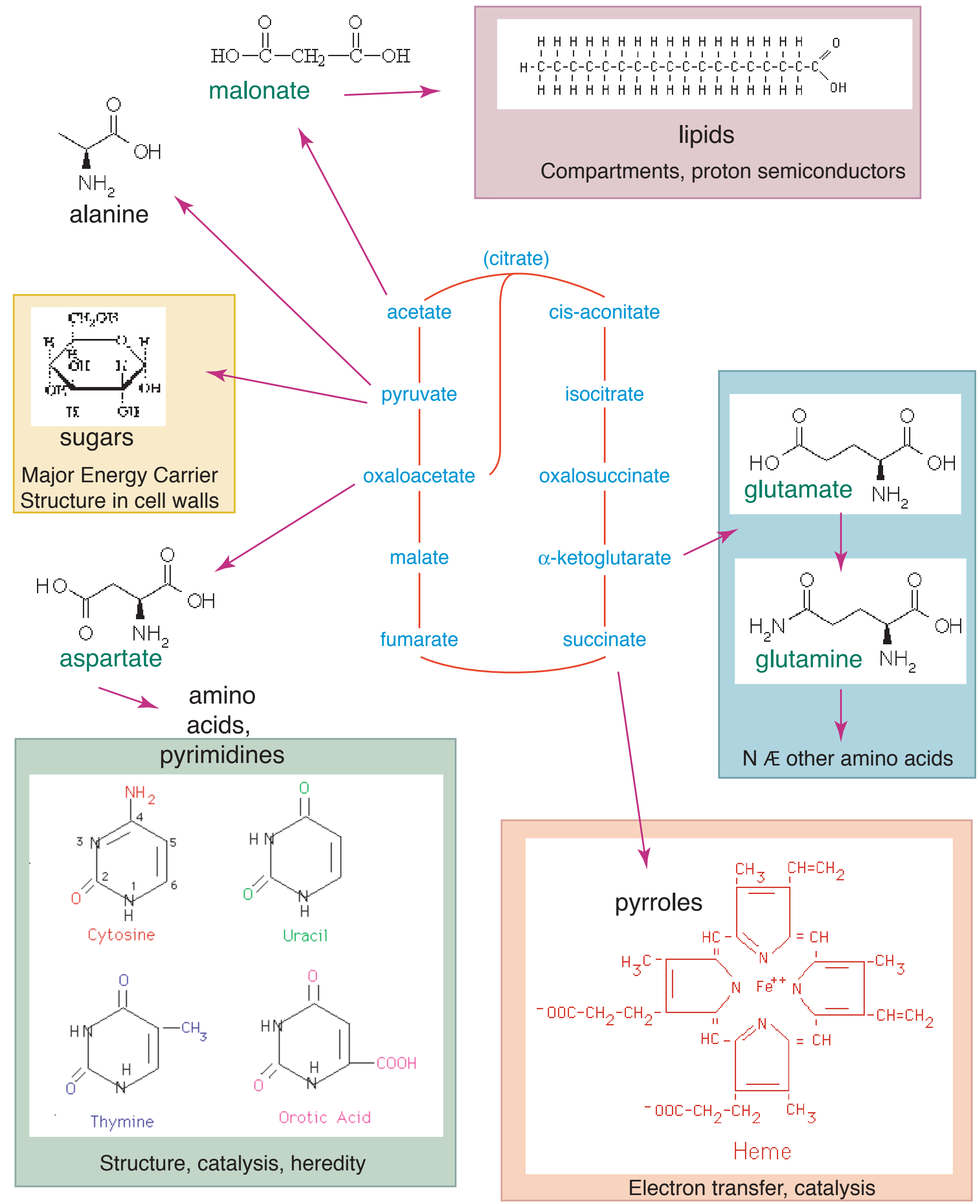
Carbon fixation and its properties in modern life

- Simple universal core
- Creating biomass is a way to release energy
- Core (TCA) cycle has 3 key properties
  - Simple and small
  - Biomass arises naturally
  - Favorable chemistry with carbon and energy sources
  - Possibly does not require containment in cells
  - Topology suggests exponential growth from random initial conditions

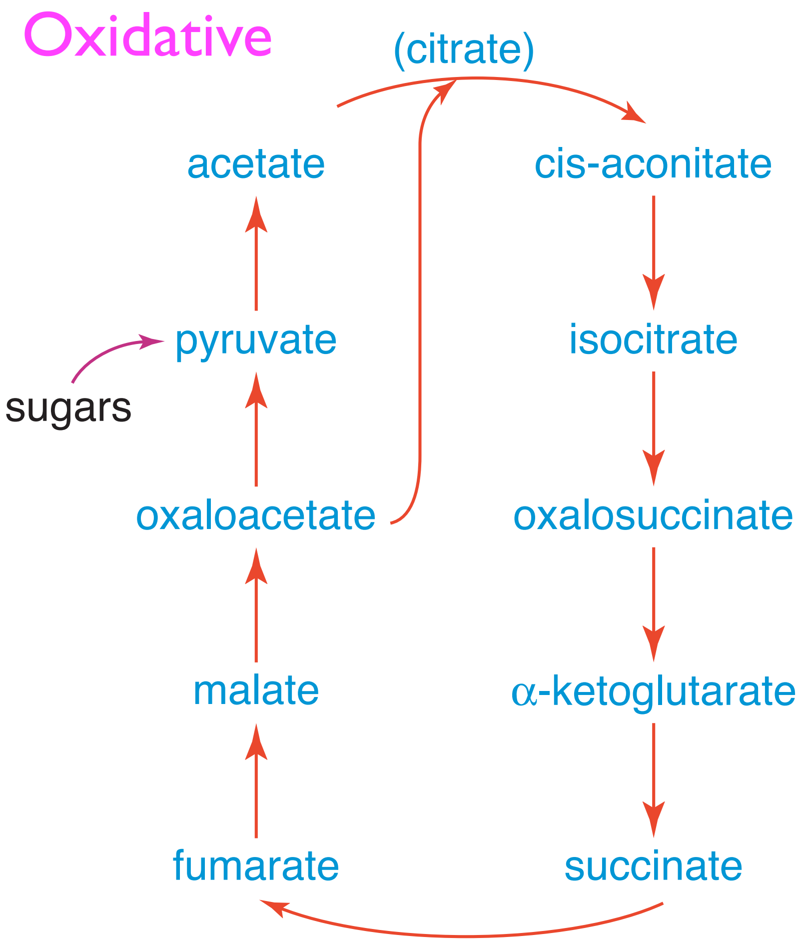
Carbon anabolism today begins within the "Krebs" (or TCA) cycle

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

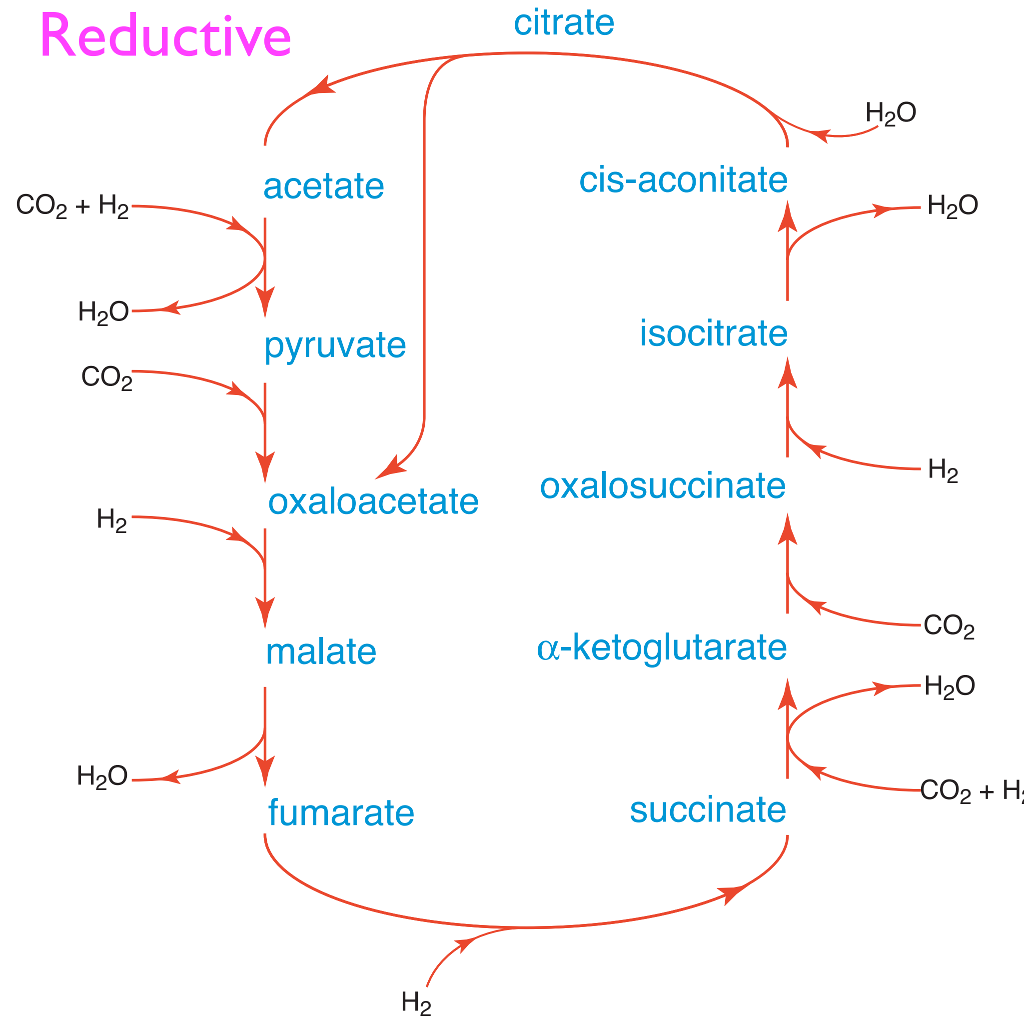
- TCA intermediates are synthetic precursors of:
    - lipids (Acetate)
    - sugars (Pyruvate)
    - amino acids (several)
    - nucleotides (OAA, AKG)
    - porphyrins (Succinate)



The universal reactions can run in either direction



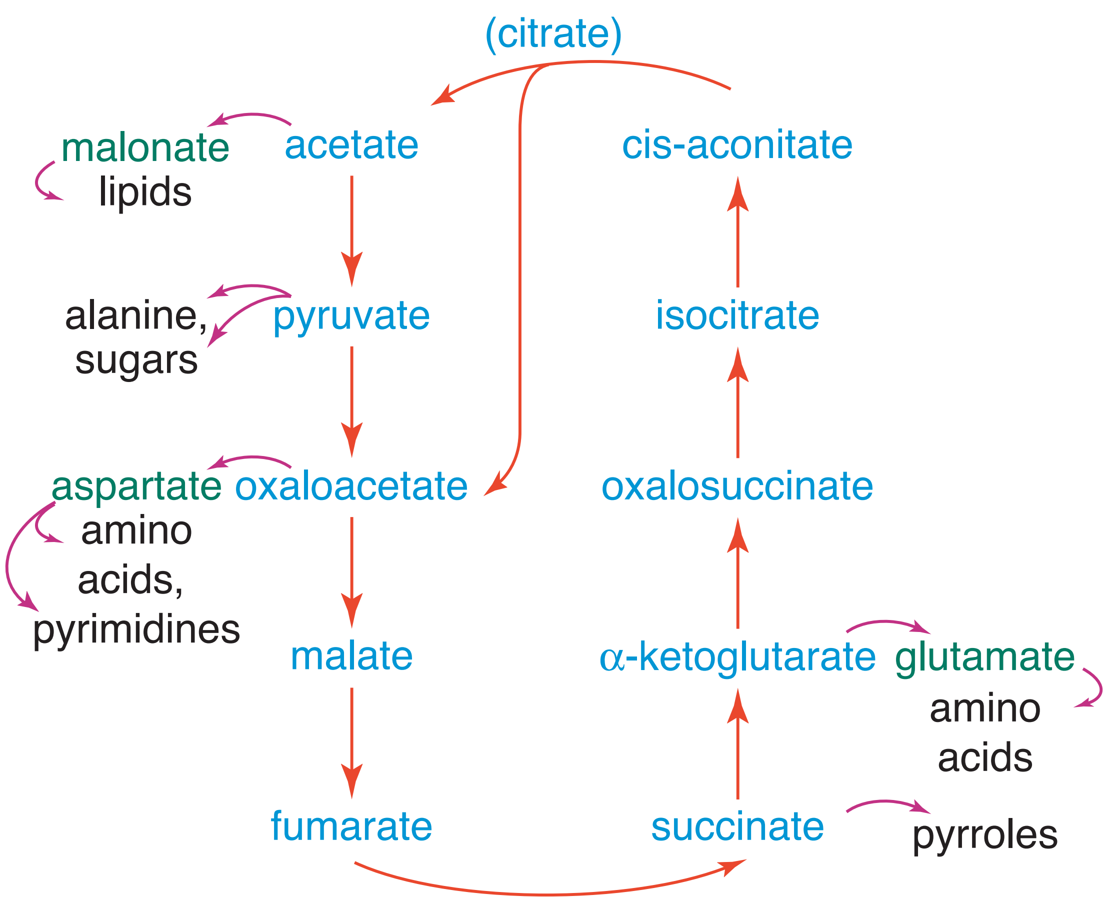
(Takes in sugars or fats & water, to make energetic electrons, CO_2, and precursors)



(Takes in CO_2 and electrons, to make water and precursors)

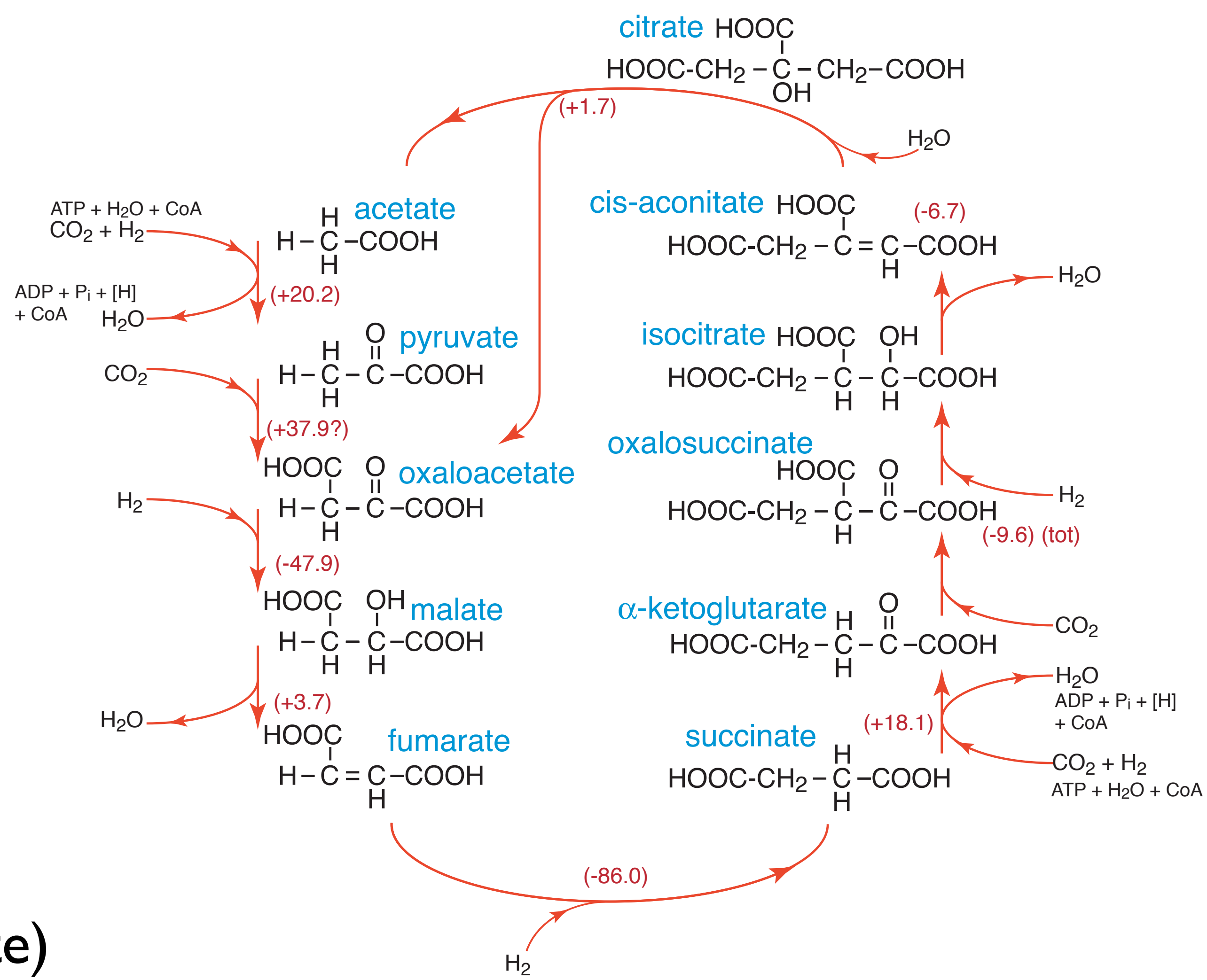
Anabolism is an electron-consuming (reducing) process; therefore possibly older than catabolism

- *Reductive* TCA (rTCA) cycle is a *carbon fixation* pathway that serves as the start for anabolism
- All the arrows in the reductive cycle go the same way:
  - Reducing CO_2 to acetate
  - Producing complex biomolecules from simple inputs



The chemical structures and reactions of the reductive TCA cycle

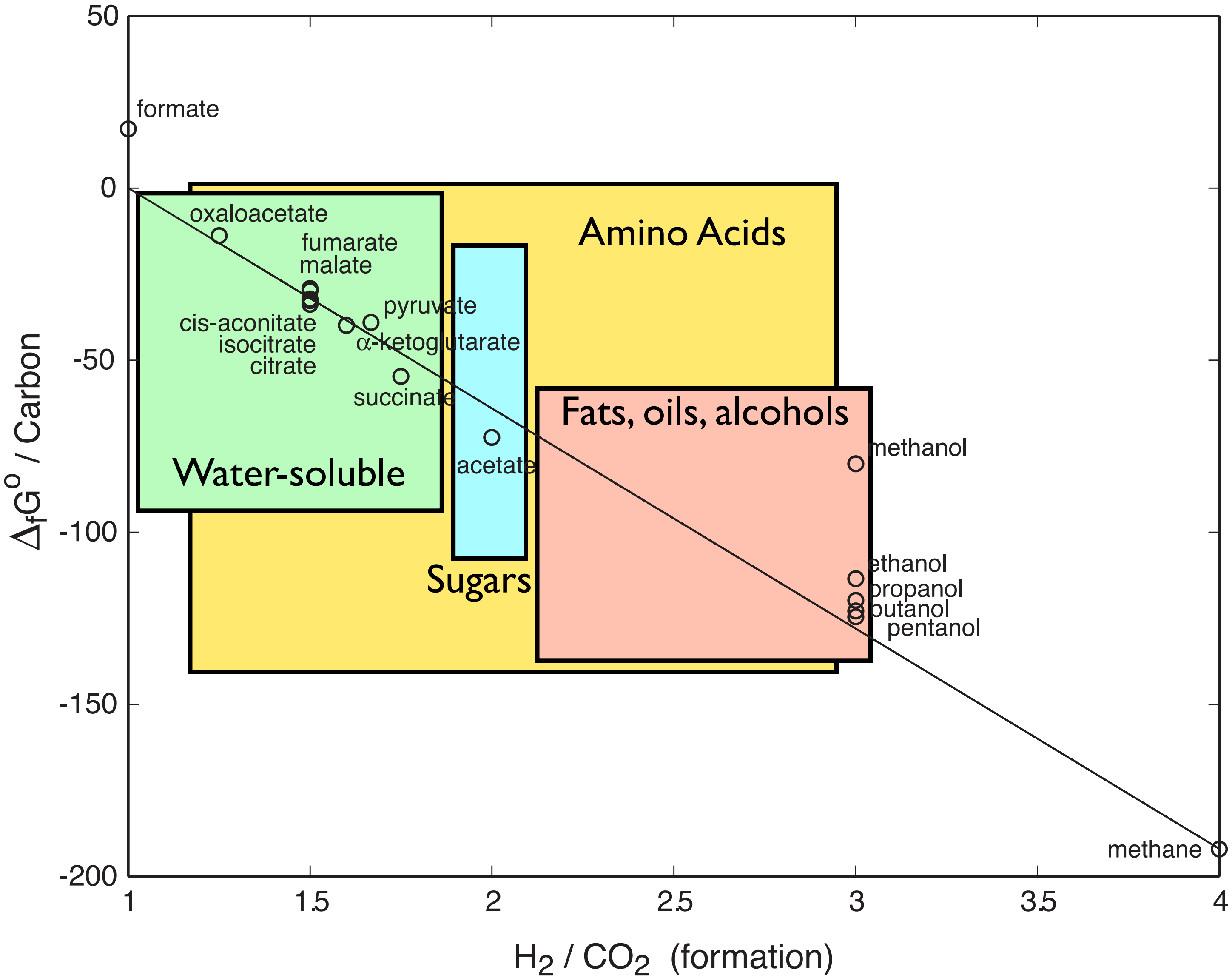
- In each reaction C=O or O-C=O from CO_2 is incorporated into a growing C chain, or else C or O is reduced
- C_4 (oxaloacetate) forms a starting state
- C_6 (citrate) fragments to give C_2 (acetate) and recover C_4 (oxaloacetate)



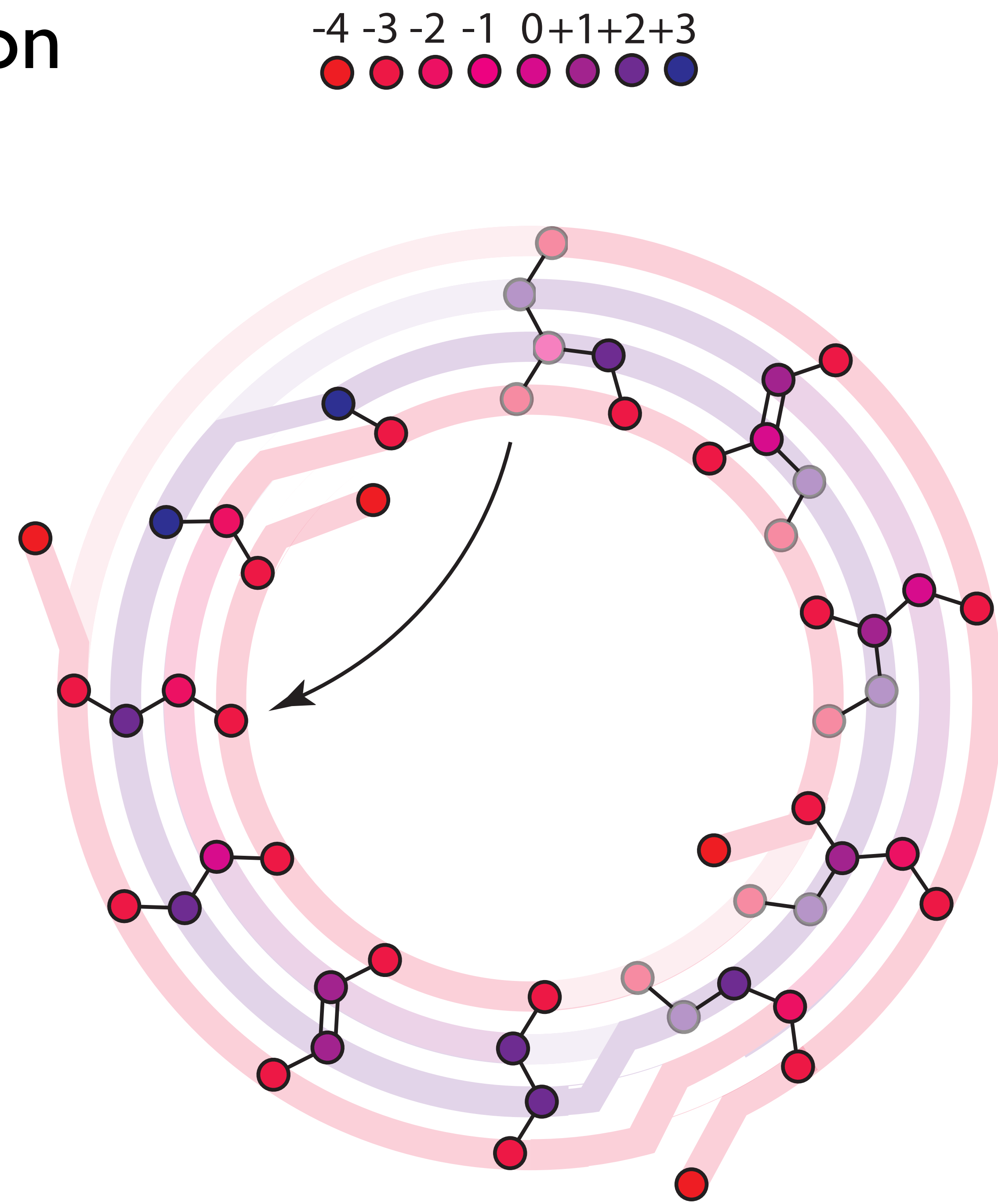
Biosynthesis is energy-yielding in a reducing world

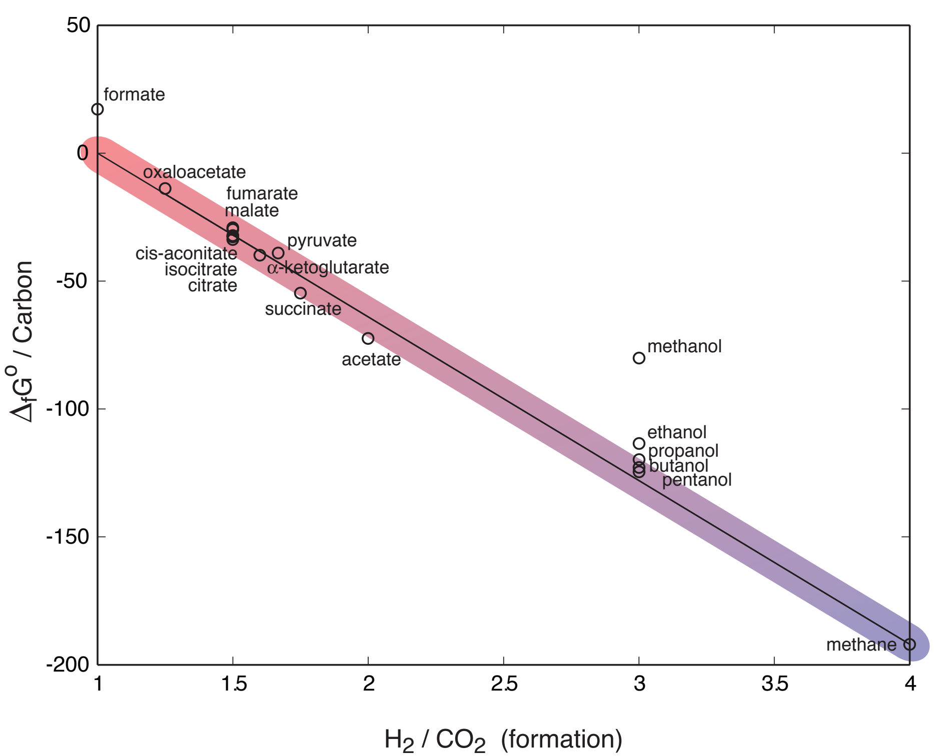
- Extract energy and build biomass *at the same time*

- Biosynthesis only needs to "capture" carbon on the way from CO_2 to CH_4



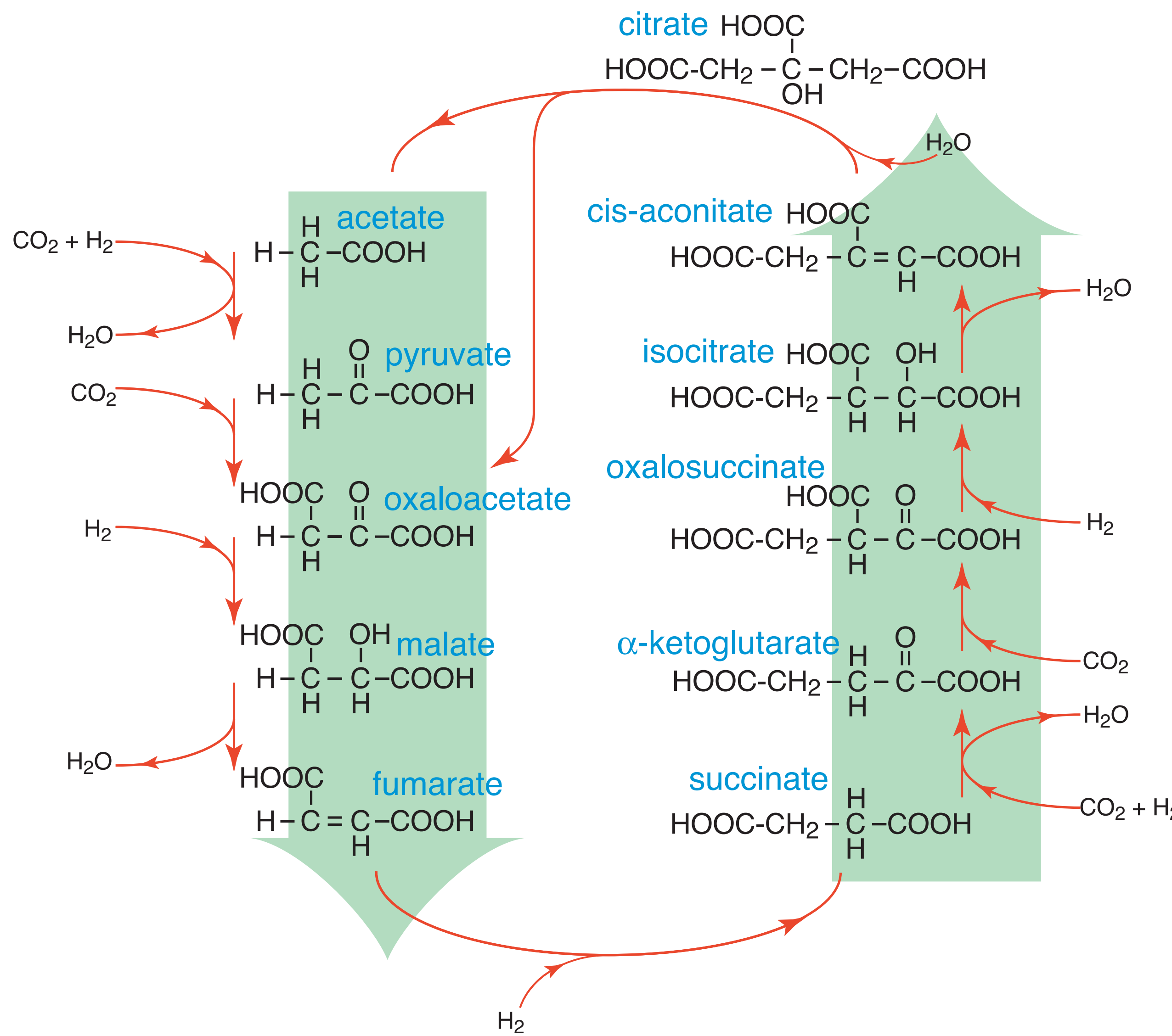
Downhill flow of carbon in reductive TCA





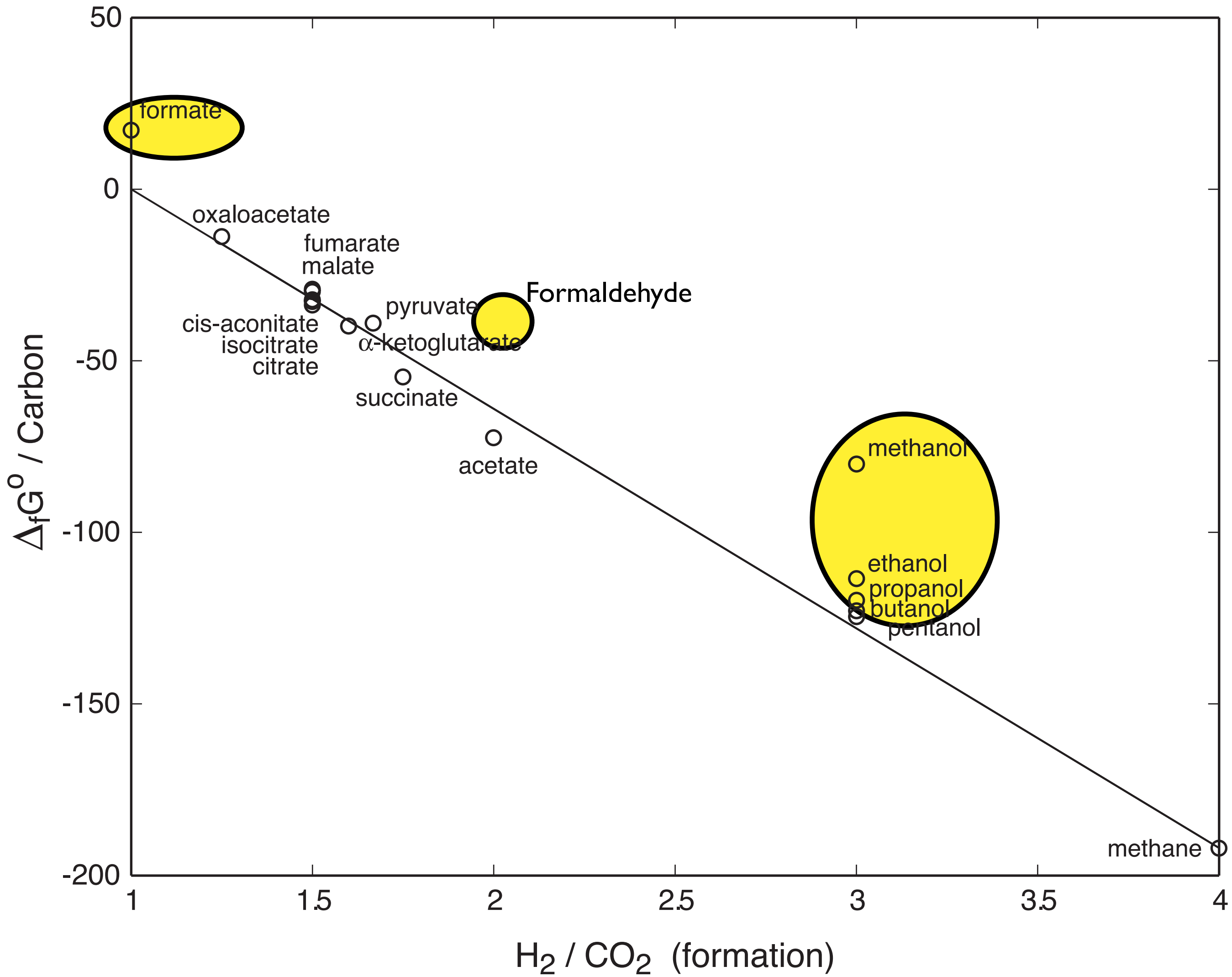
The reductive TCA reactions are few and simple; plausible as primordial "discoveries"

- Only 5 molecular groups and 7 reactions required
- Simplicity may have made the reactions easy to find in a random world



rTCA gets from *simple* CO_2 to *simple* CH_4 through *more complex* intermediate compounds

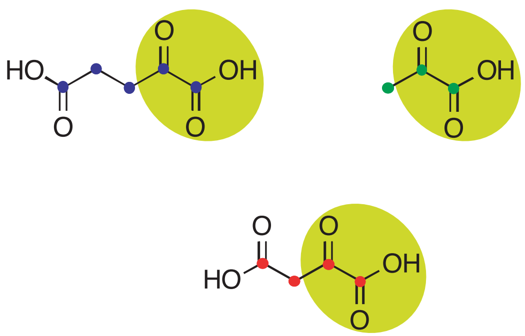
- Inputs and outputs are simple: but *there are no simple, low-energy intermediate compounds*
- Flow into cycle intermediates is thermodynamically favored over flow to smaller molecules at same oxidation states



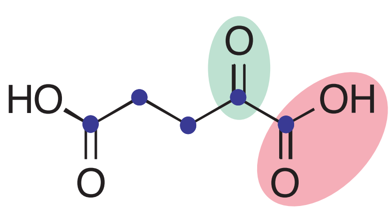
(Explain *why* biomolecules exist before Darwinian selection)

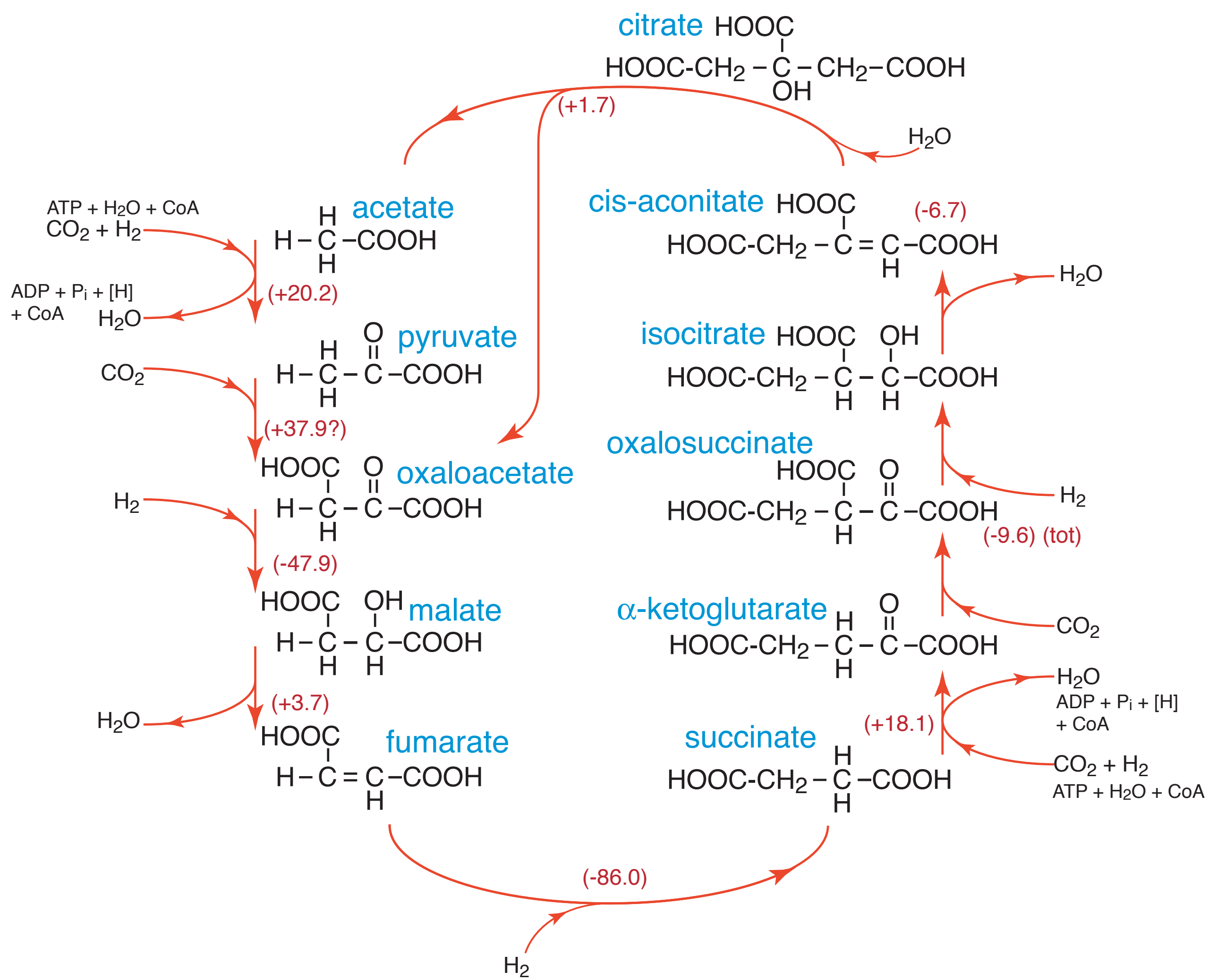
rTCA molecules favor reactions to capture CO_2 as a carbon source (difficult to do)

Compounds in the cycle are known as “alpha-keto” acids



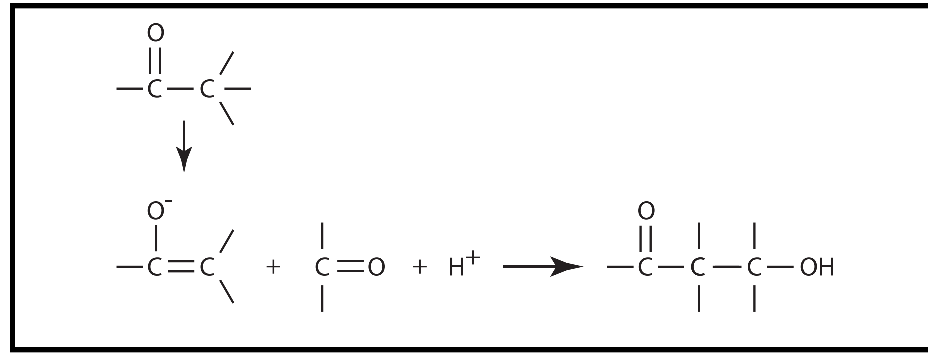
Reactive groups are carboxyl and alpha-ketone

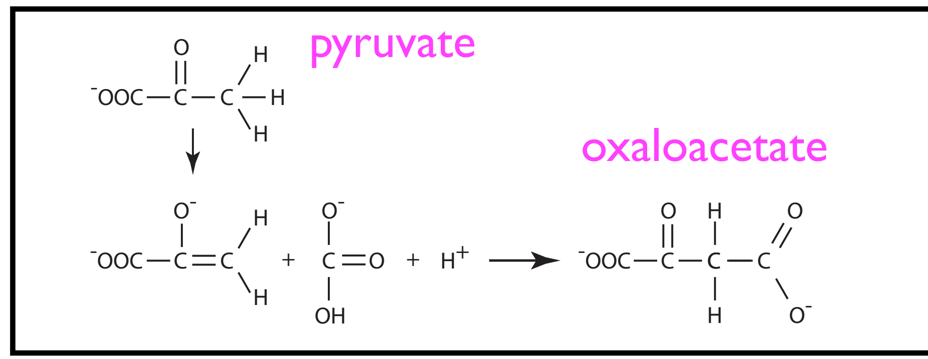


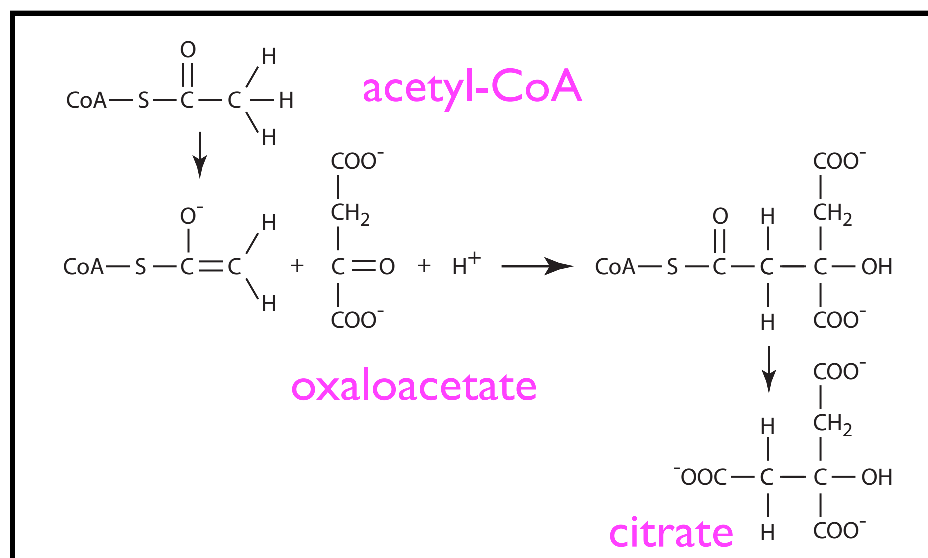


Why alpha (or beta) ketone structure is important for carbon uptake

- How do we put electron density on a carbon to form a C-C bond? (Aldol condensation)
- A related reaction incorporates bicarbonate into pyruvate to form oxaloacetate
- The aldol condensation and its reverse are responsible for citrate formation or cleavage (which solve problems in oxidative and reductive worlds respectively)



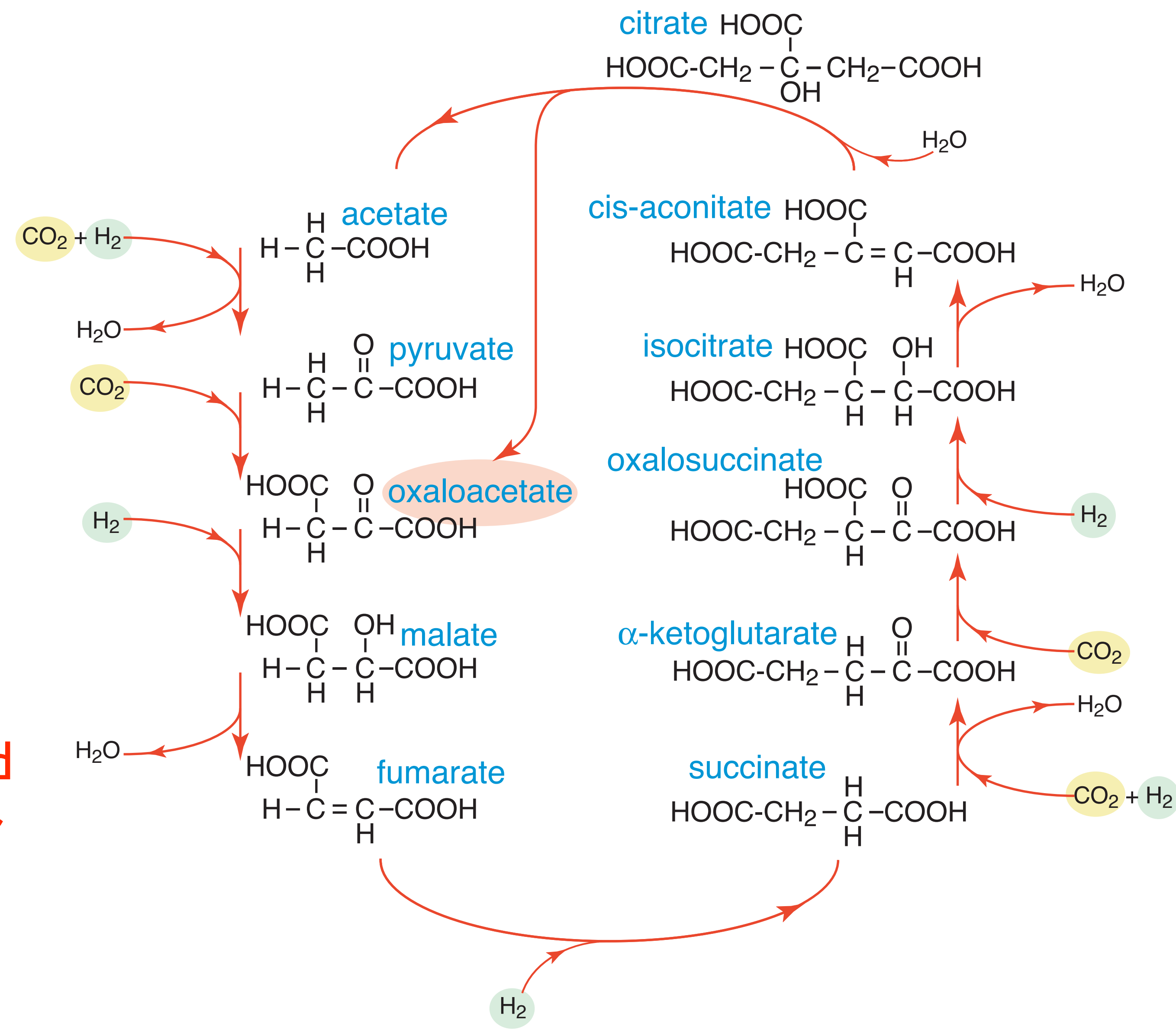




These reactions make rTCA reactions "low-resistance"

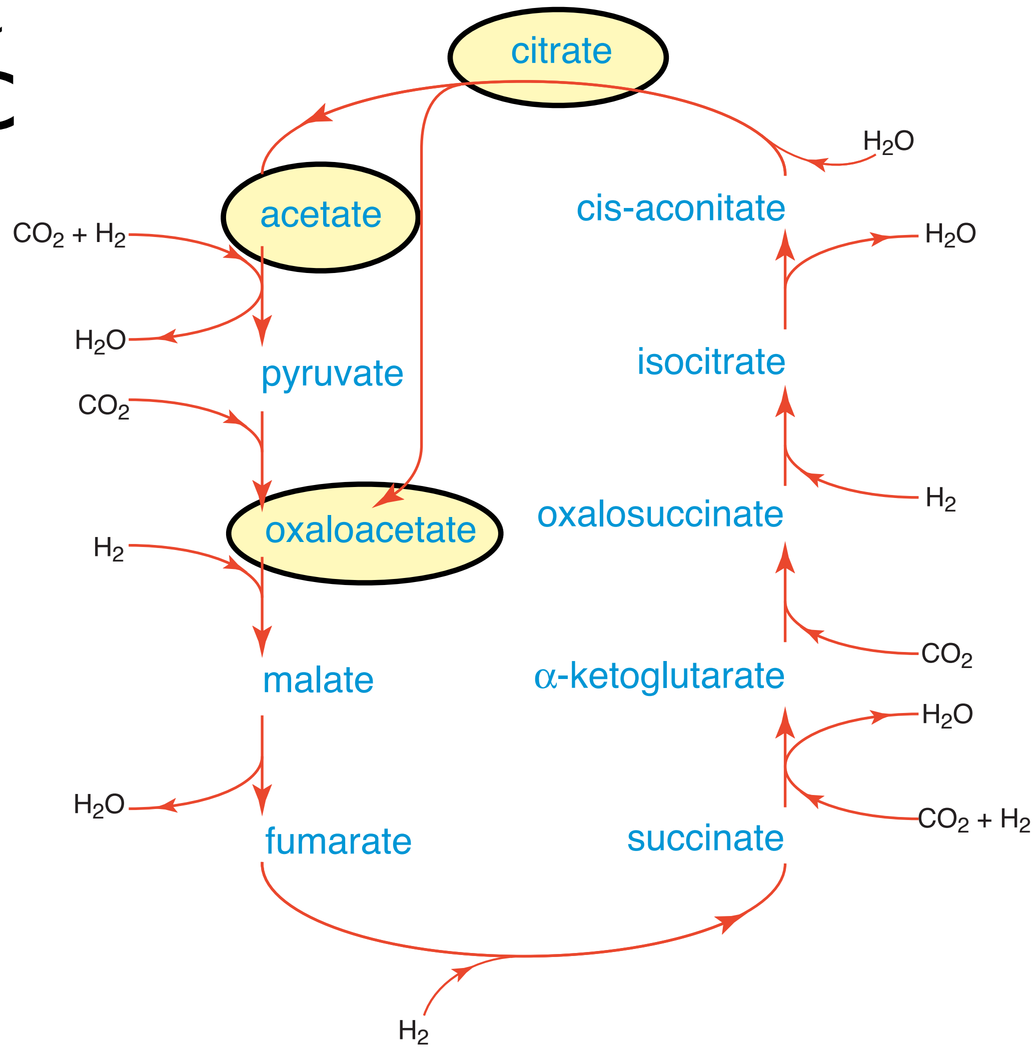
rTCA reactions are *first order* in complex molecules

- 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



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



Interpreting carbon fixation in terms of self-organization

- Energy flow through a system orders that system
- The onset of order can be a phase transition
- Creation of order lowers the impedance to flow (idea of a "bottleneck")

Nonequilibrium states can be stable when they are *energy channels*

- Weather is powered by absorption of sunlight in the oceans
  - Converts visible to microwave photons
  - However, too diffuse to power chemistry
- Lightning (dielectric breakdown of atmosphere) driven by charge separation (created in turn by convective weather)

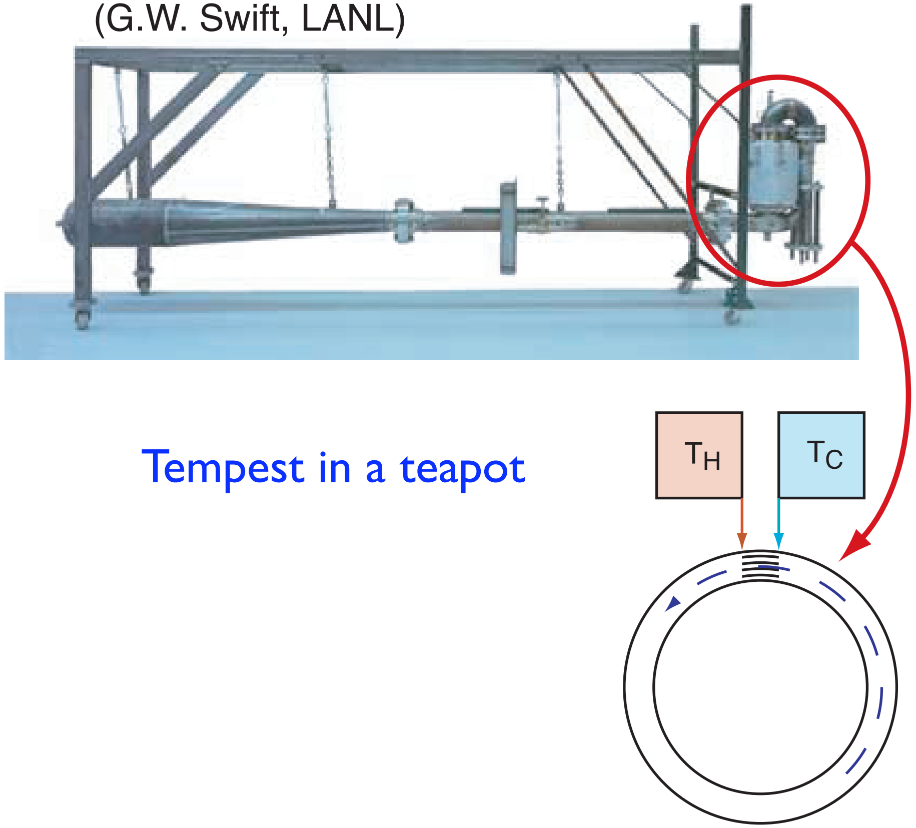
- Both create stable nonequilibrium states

A simple reversible model for self-organizing energy channels

Tempest

- Heat engines with no (mechanical) moving parts
- Self-starting, *self-organizing*
- Form order in the limit of *reversible thermodynamics*
- Order forms by *phase transition*, consistent with maximum uncertainty

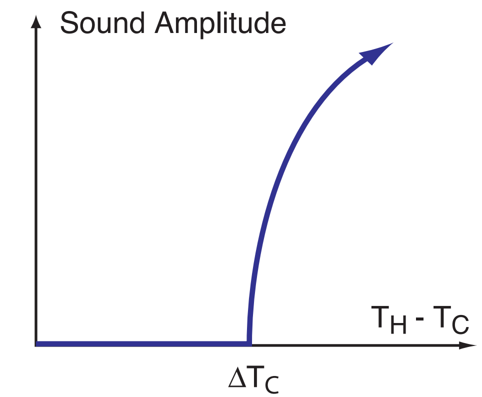
Traveling-Wave Thermoacoustic Engine
(G.W. Swift, LANL)

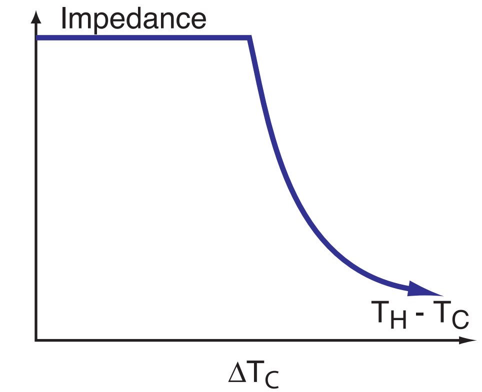


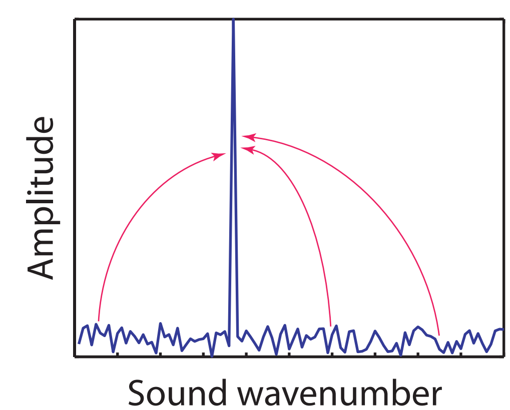
Tempest in a teapot

Emergent order lowers impedance to energy flow by a *phase transition*

- Sound amplitude is the "order parameter"
- Onset of order lowers system resistance to energy transfer:
  - "Off" impedance is high;
  - "On" Impedance decreases as the square of the sound amplitude
- Order forms by a process of "acoustic lasing"



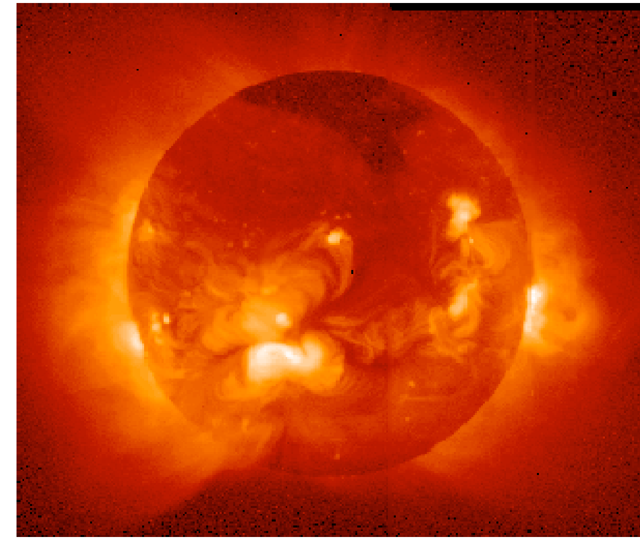




So can we apply the same idea to chemistry?

- What kinds of energy are relevant?
- Did the emergence of life create a low-resistance energy channel?

One energy source comes from stars (fusion)

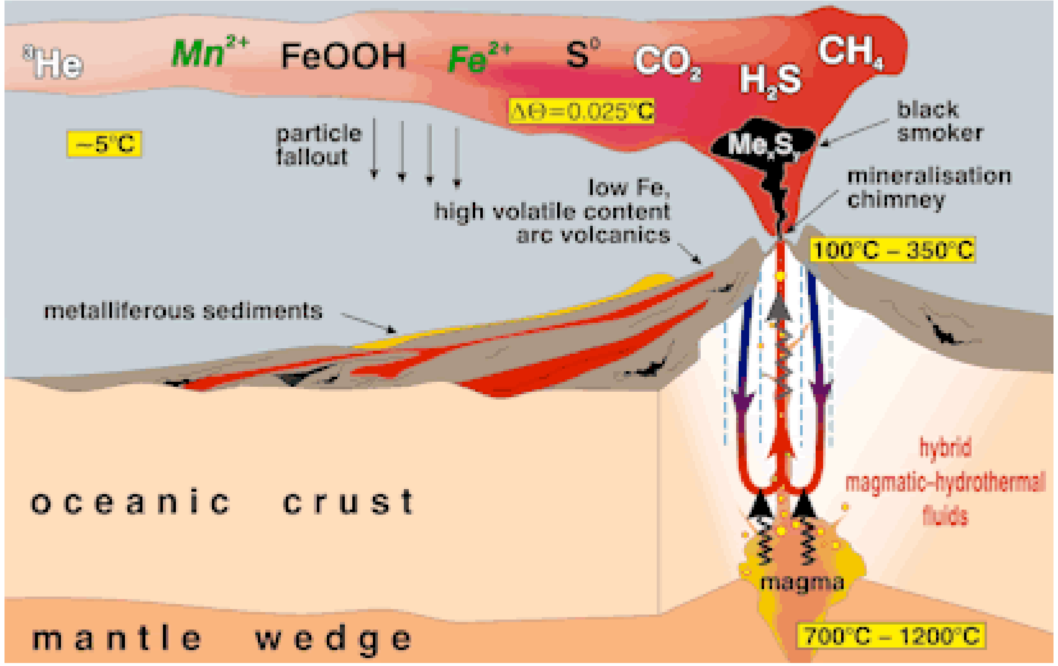


- Stellar radiation can directly excite chemical bonds
  - Very high energy source
  - Difficult to capture, difficult to use

- Secondary reactions in comets, asteroids, and weather creates reactive organic species
- However, bio-molecules are *not special* in the resulting mixtures

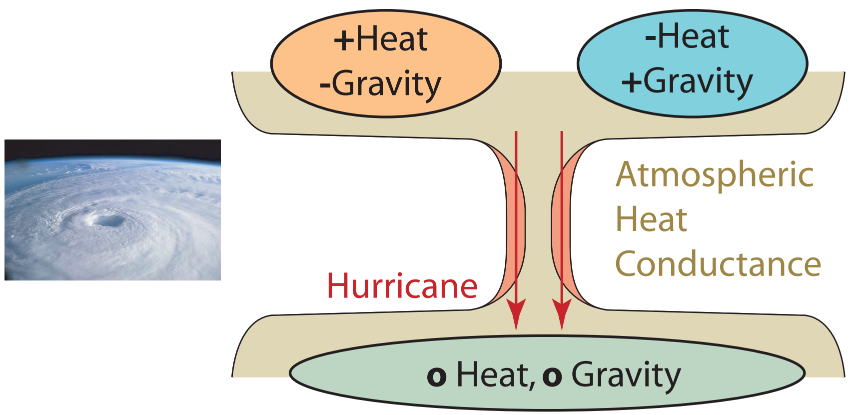
Direct chemical energy comes from earth (fission)

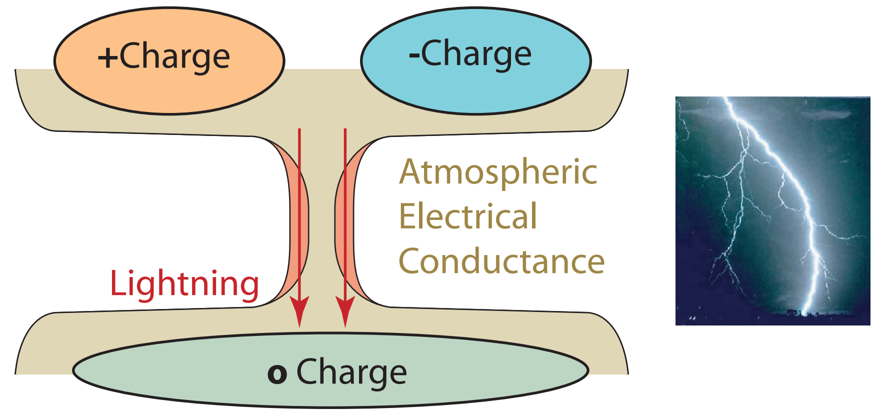
- Mantle convection (powered by heat transfer) trades gravitational for chemical energy
- Reduced metals in contact with seawater generate reductant (H), carbon sources and reduced metals
- Good food for life, but not so reactive that they make many molecules



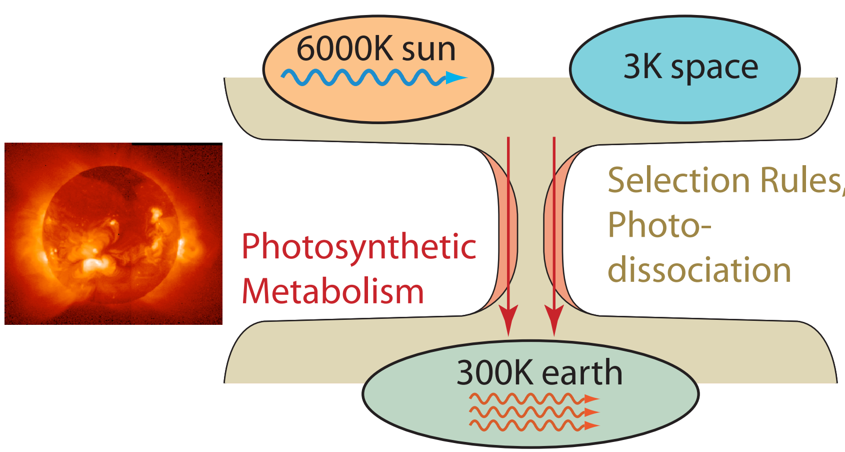
Compare energy channels from weather and life

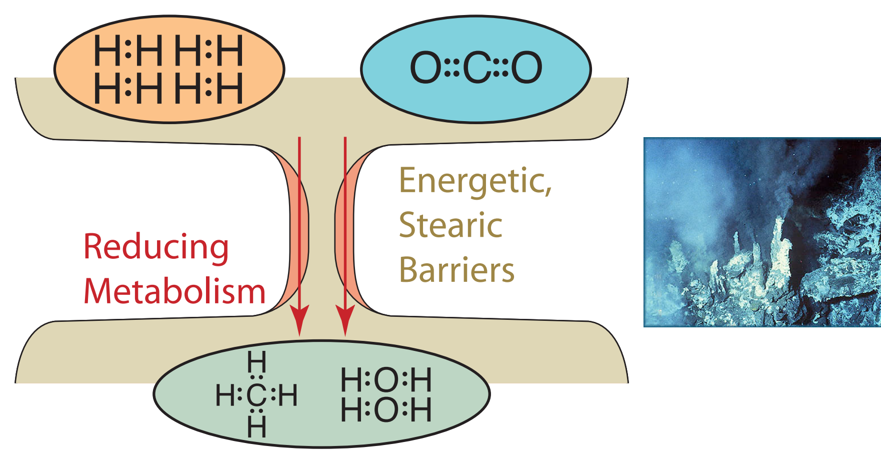
The atmosphere is a poor conductor of heat and electricity





Non-living matter is a poor "conductor" of light across spectral bands, and electron pairs among bond types

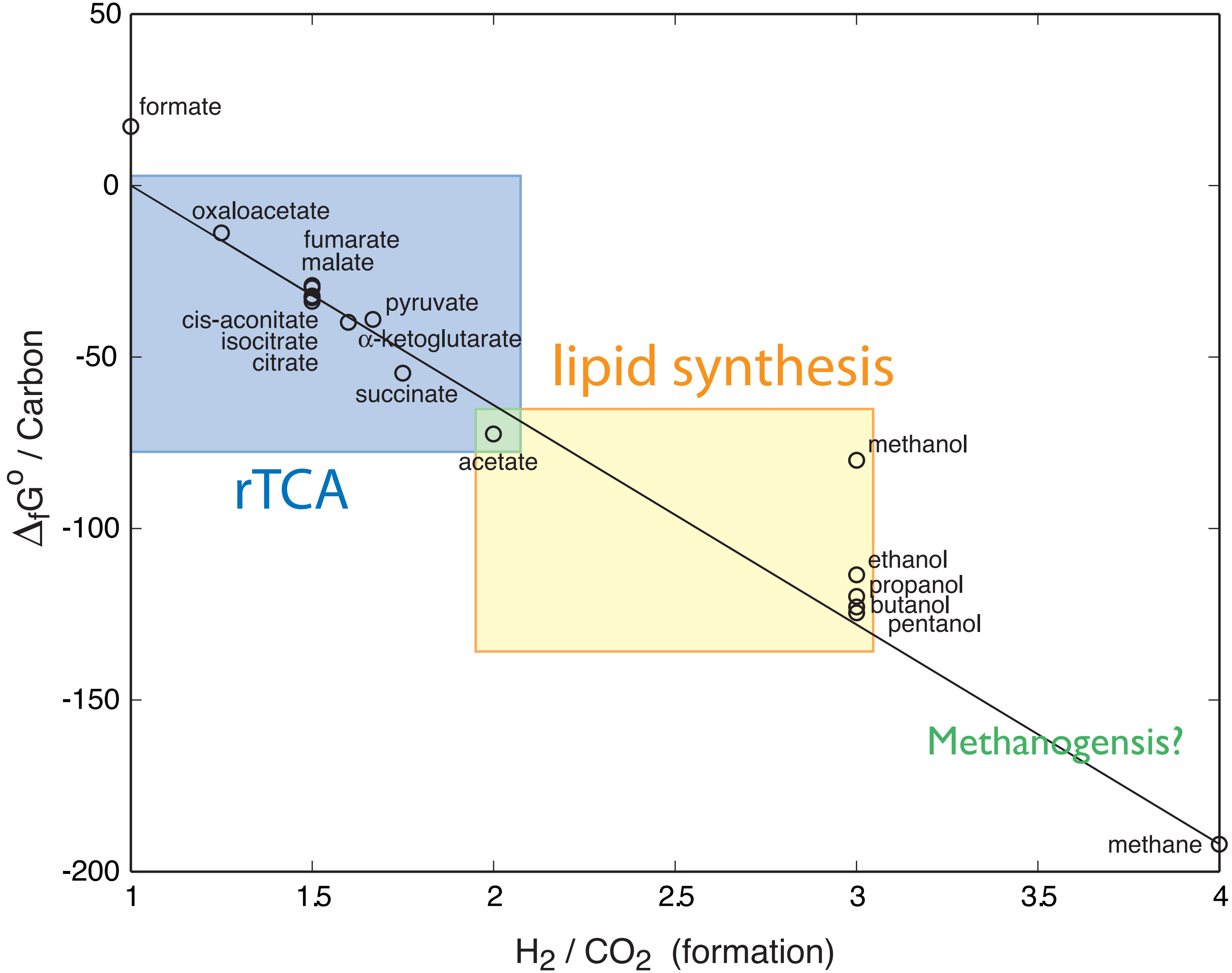




Can we analyze reducing metabolism explicitly as a self-organized channel?

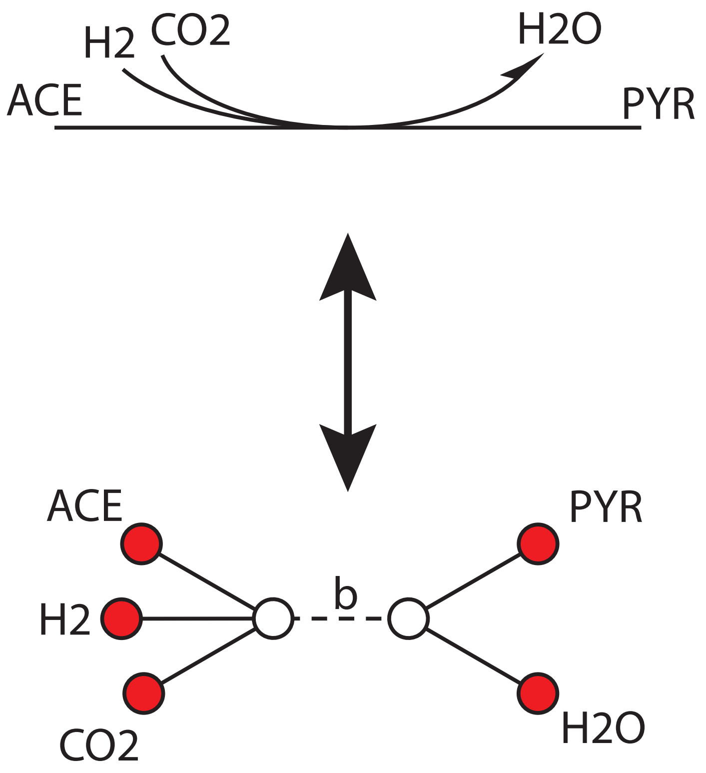
- Break up the problem of CO_2 reduction into stages
- Each stage corresponds to a distinctive class of biomolecules and pathways
- Understand the emergence of the biomolecules as an energetic necessity

Reduction state and free energy of formation



It is convenient to introduce a formal graph theory for chemical reactions

- Convert from chemical "hypergraphs" to formal bi-partite graphs
- Each graphical element corresponds to a mathematical term in a rate equation
- Reduction of graphs corresponds to aggregation of rate equations



Such representations are the basis of Flux Balance Analysis

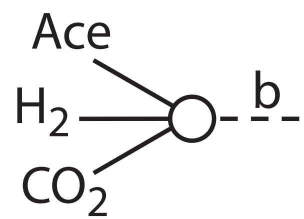
How to construct reaction rate graphs

Graph elements

A concentration: [ACE]

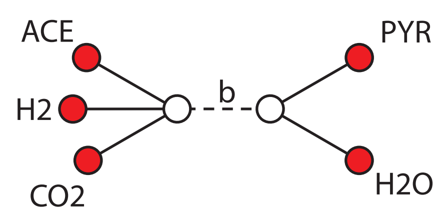
A particular transition state, with current J_b

The forward reaction rate constant k_b



One mole of species ACE

A well-formed graph corresponding to the rate equation



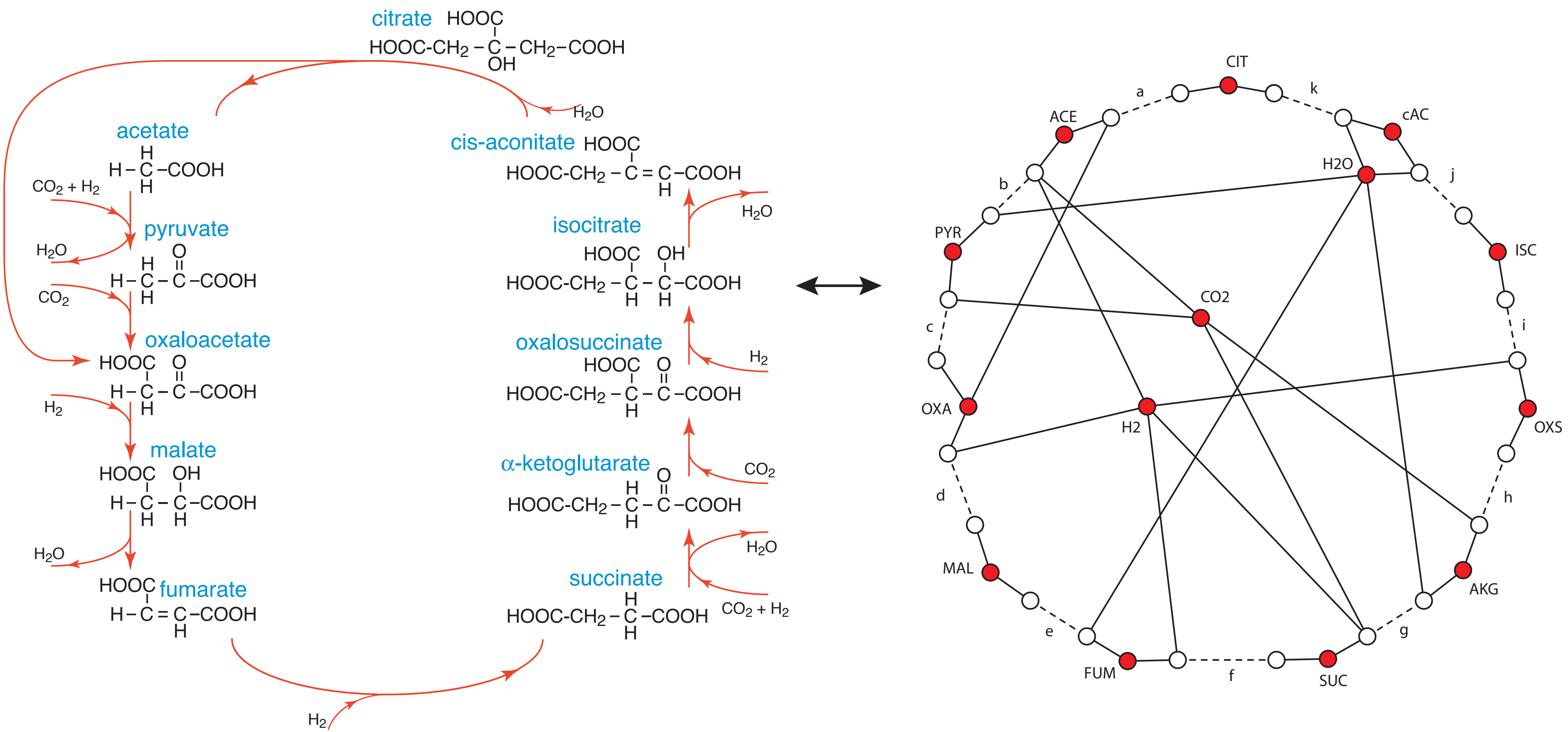
$$[ACE][H2][CO2]\, k_b - [PYR][H2O]\, \overline{k}_b = J_b$$

$$d[ACE] / dt = - J_b \quad \text{etc.}$$

Graph rules

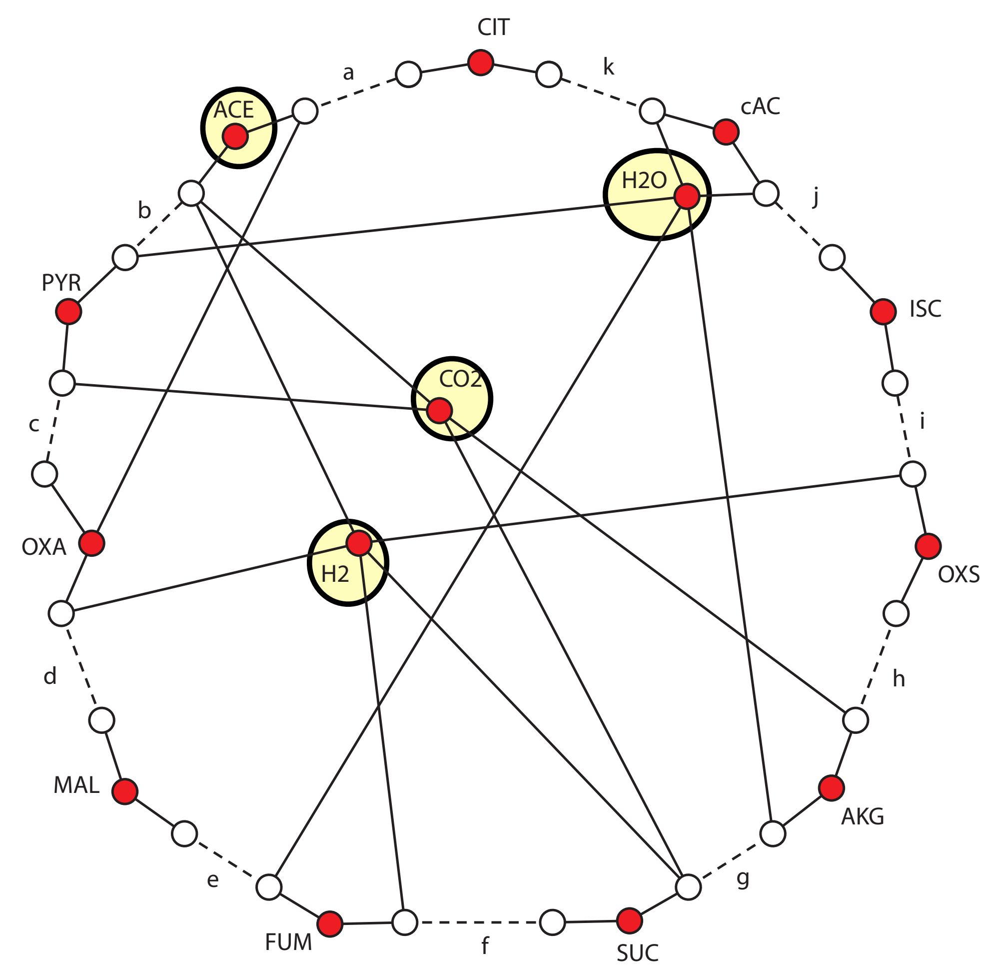
- Connect each species label on an open circle to the appropriate concentration with a solid line: one mole per line
- Connect the input and output circles for a reaction with a dashed line
- Compute transition state current as sum of forward and backward rates from its open circles
- Flows out of concentration dots equal transition currents times numbers of connecting lines

The graph conversion provides a symbolic decomposition of all of the rTCA rate equations



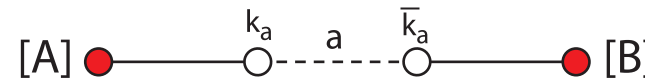
The statistical mechanics problem of network autocatalysis

- The problem of carbon reduction is specified by four molecular chemical potentials (or concentrations)
- CO_2 is the most oxidized form in the network; Acetate is the most reduced
- In Gibbs equilibrium only three (atomic species) concentrations could independently be specified, so this system is overconstrained
- Rate constants convert the excess constraint into a steady-state current



Graph reduction reduces the number of equations while aggregating their coefficients

Start with rate equations for a basic reaction



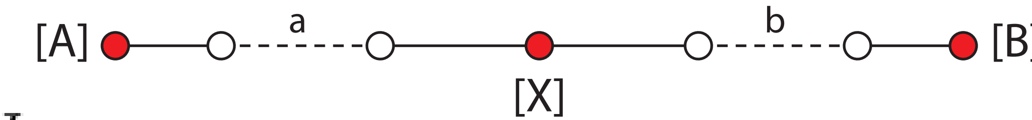
$$[\mathrm{A}]\, k_a - [\mathrm{B}]\, \bar{k}_a = J_a.$$

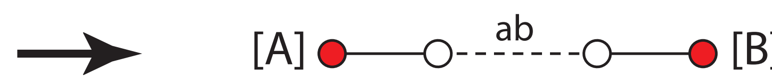
$$\begin{aligned} [\dot{\mathrm{A}}] &= -J_a \\ [\dot{\mathrm{B}}] &= J_a, \end{aligned}$$

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

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

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





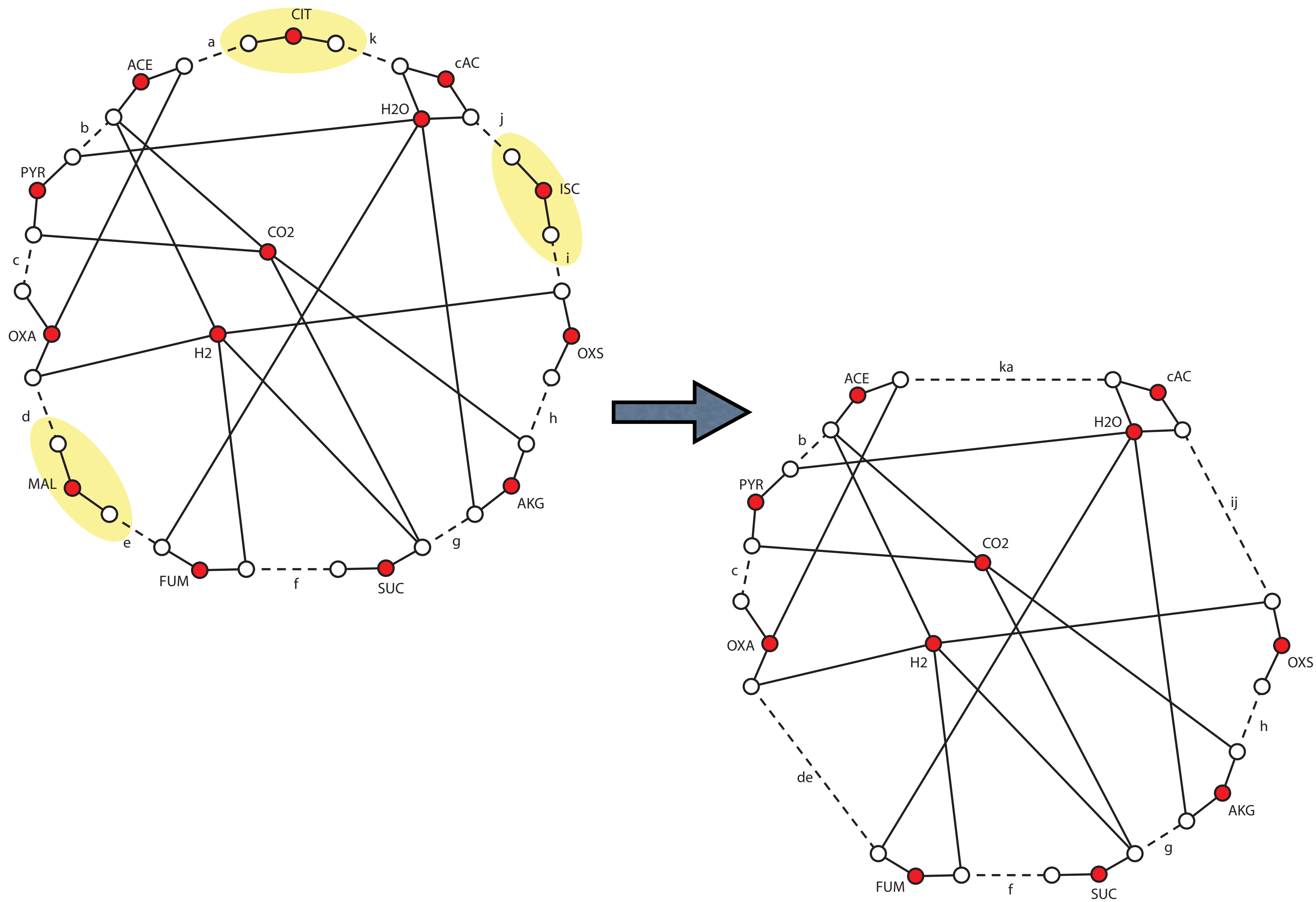
Remove species X and aggregate rate constants in an effective reaction

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

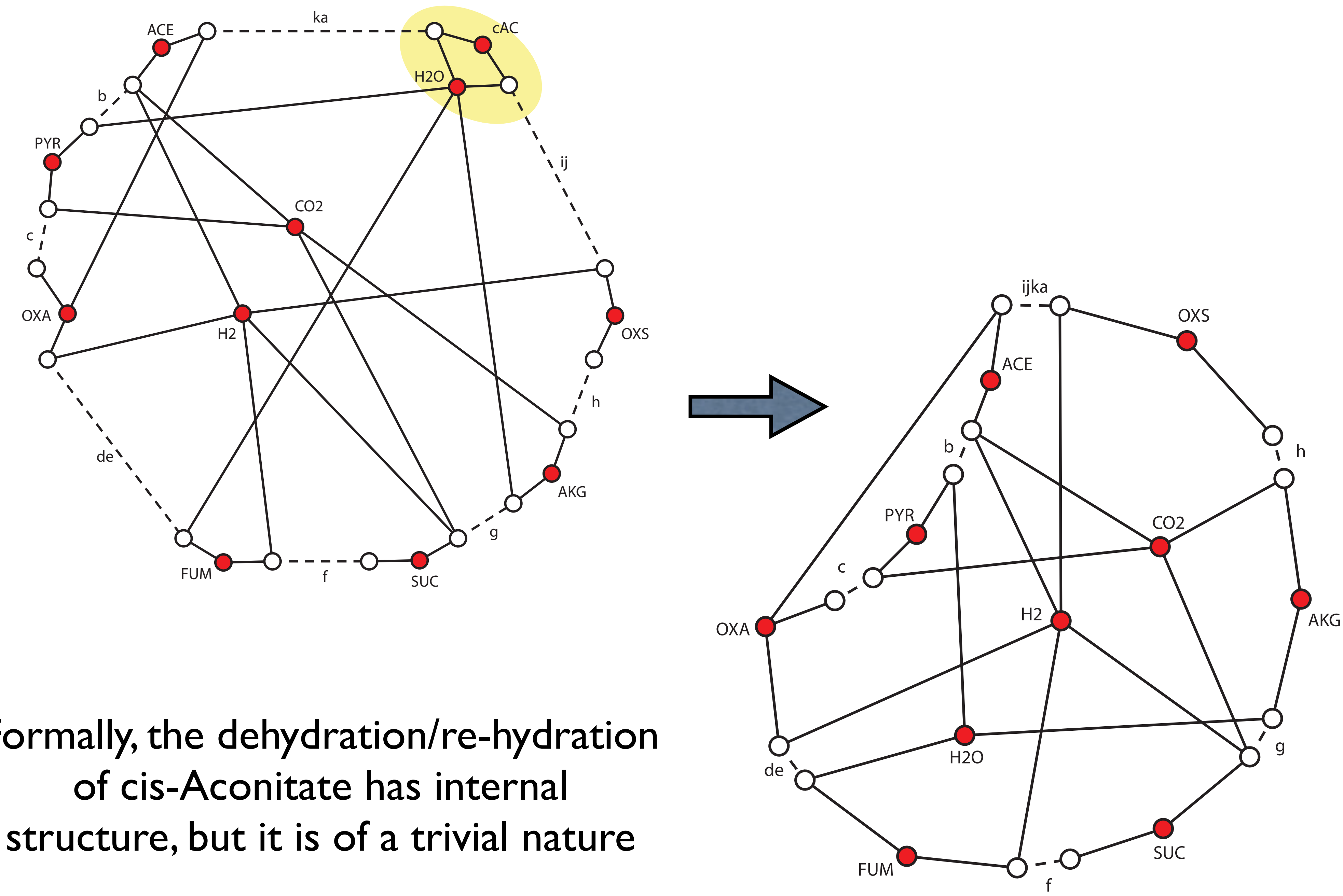
$$(k_a, \bar{k}_a) \circ (k_b, \bar{k}_b) = (k_{ab}, \bar{k}_{ab})$$

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

Begin the analysis of rTCA:
Remove nodes with no internal structure

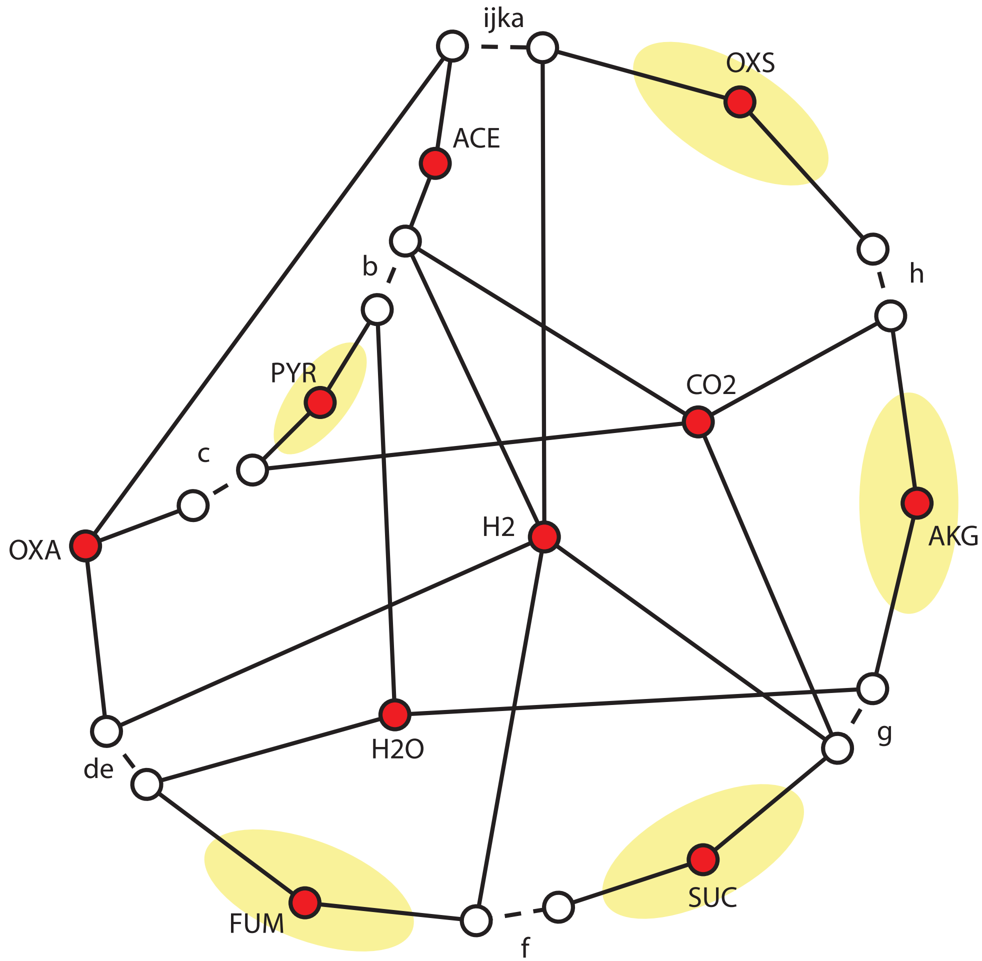


Remove an elementary isomerization

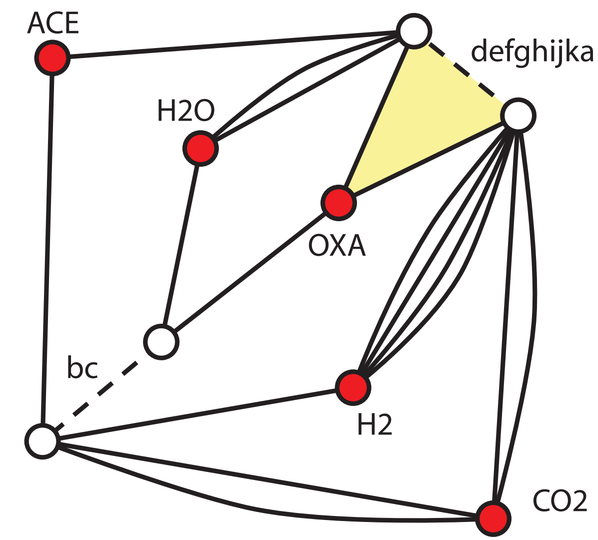


Formally, the dehydration/re-hydration of cis-Aconitate has internal structure, but it is of a trivial nature

Remove all remaining nodes, except boundary conditions and branches



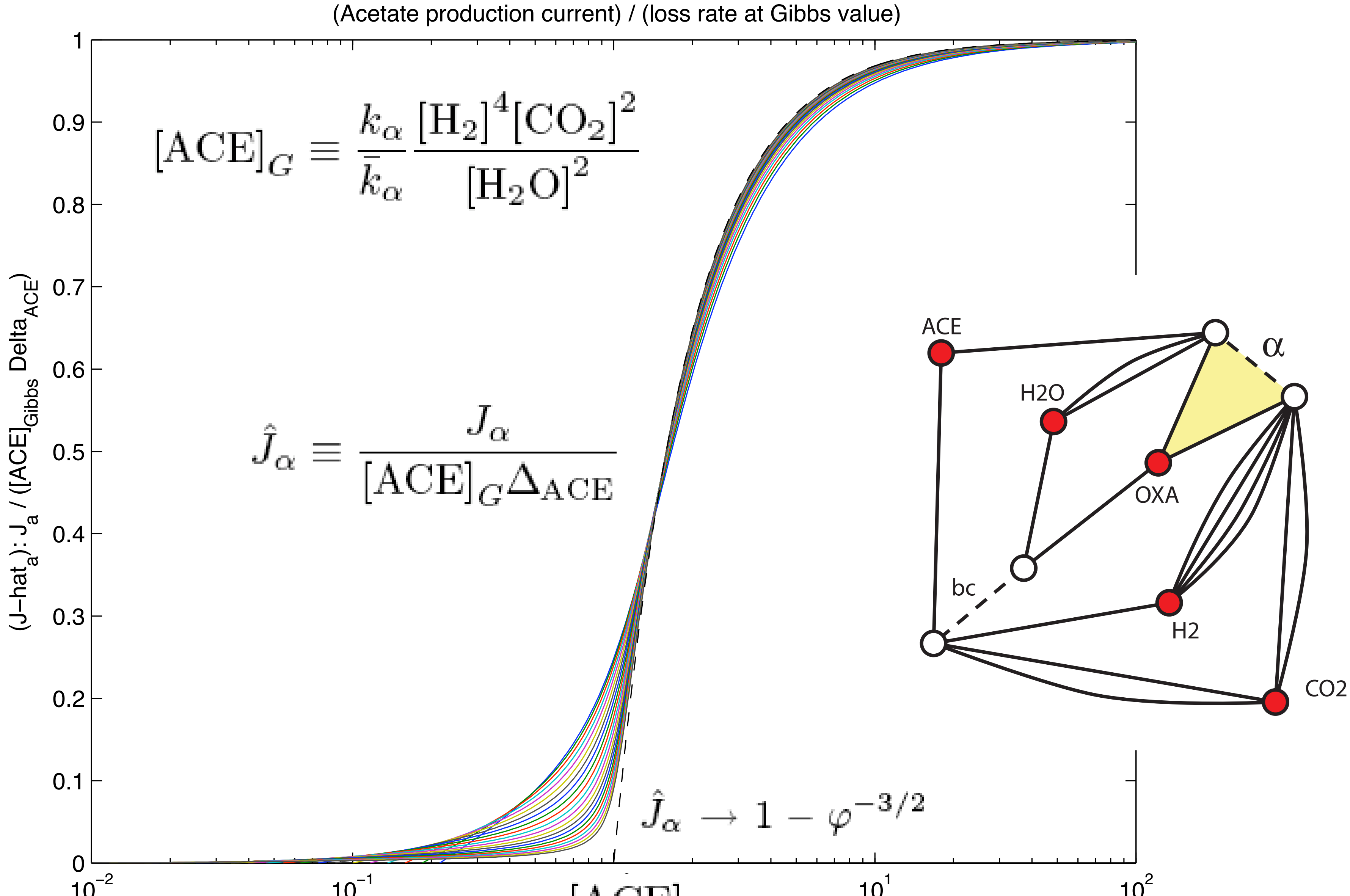
Arrive at the essential description of rTCA network autocatalysis



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

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

The effective equations are easily solved analytically



A phase transition
to carbon fixation !

Summary for Day II

- We can isolate carbon fixation as a core problem on which all the rest of biochemistry depends
- Energetic, chemical, and network properties of the TCA cycle suggest a spontaneous process
- Can understand (some kinds of) self-organization as channel formation by phase transition
- A dynamical model of TCA cycling shows this kind of phase transition

Further reading

- Smith, Eric and Morowitz, Harold J **Universality in intermediary metabolism** Proc. Nat. Acad. USA **101**, 2004, 13168

- Morowitz, Harold J **Foundations of bioenergetics** New York : Academic Press, 1978

- Morowitz, Harold J **Energy flow in biology; biological organization as a problem in thermal physics** New York, Academic Press, 1968

- 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

- Jaynes, E. T. **E.T. Jaynes : papers on probability, statistics, and statistical physics; R.D. Rosenkrantz ed.** Dordrecht, Holland : D. Reidel 1983

- 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

- Sinanoglu, Oktay and Lee, Lih-Syng **Finding the possible mechanisms for a given type of overall reaction. The case of the (A+B to C+D) overall reaction types** Theoretica Chimica Acta **51**, 1979, 1; **On the algebraic construction of chemistry from quantum mechanics. A fundamental valency vector field defined on the euclidean 3-space and its relation to the Hilbert space** Theoretica Chimica Acta **65**, 1984, 249