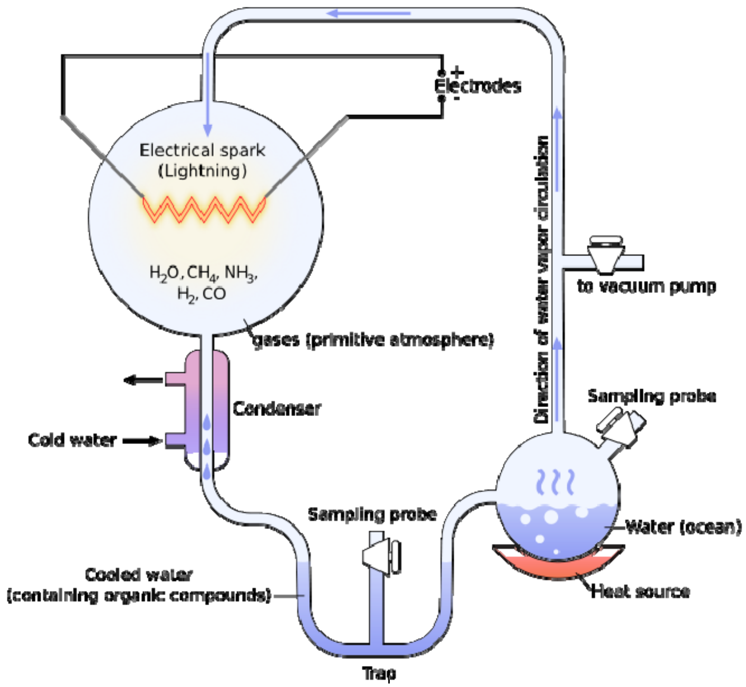
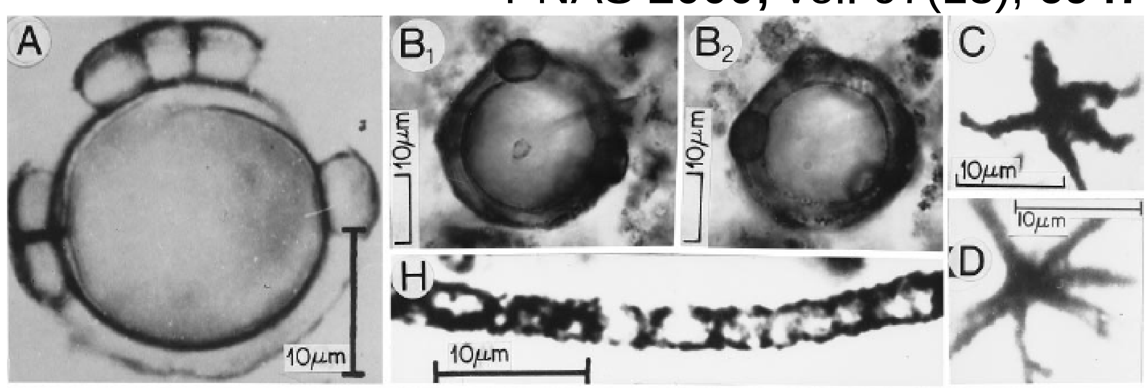
The Origins of Metabolism



PNAS **2000;** vol. 97(13); **6947–6953**



The Origins of Metabolism

- The origins of metabolism, are intimately linked to the origins of life… they will blow your mind…

- Theories on the origins of life can be (roughly) subdivided into:

    - Heredity first

    - Metabolism First

- Obviously, we'll be focusing on the second… which leaves us with two big questions:

    - How did the molecules get there?

    - How did the complexity arise?

Problem 1: The molecules

- Metabolism requires large molecules... unfortunately, the available molecules on the very early earth would have been:

  - Water (H_2O)... handy, but not very big
  - Methane (CH_4)... carbon source, also not very big
  - Ammonia (NH_3)... nitrogen source, also small
  - Nitrogen (N_2)... poor nitrogen source, tiny
  - Hydrogen (H_2)... poor hydrogen source, teeny

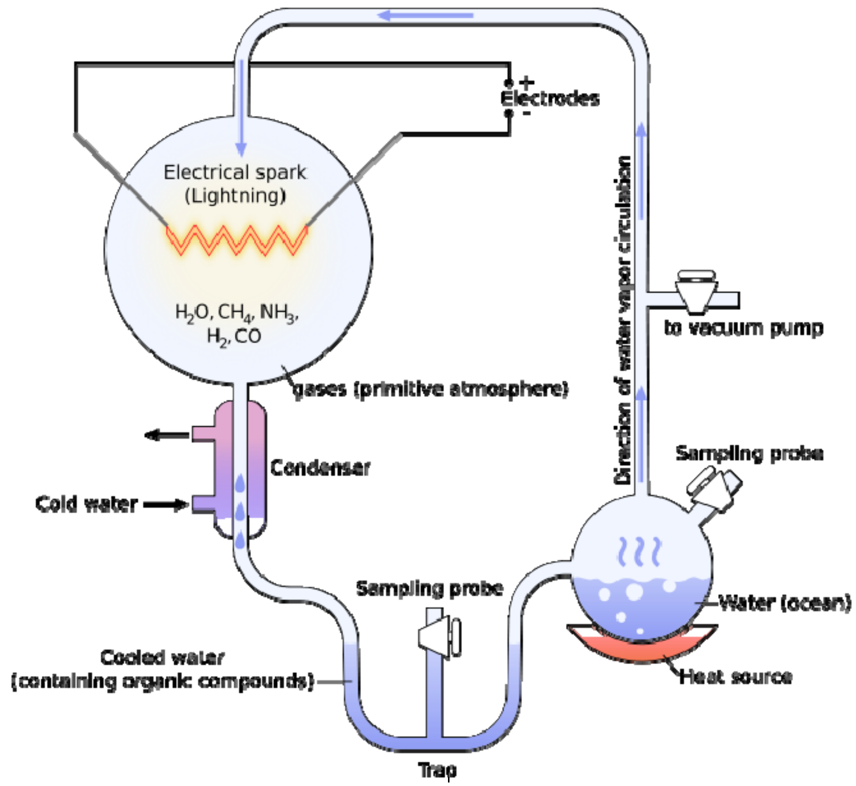
- Remember about large molecules from small molecules? Not terribly exergonic...

- Remember those kinetic barriers? No way to overcome those, really...

Solution 1: Lightning

- The first reasonable solution to this problem came in the form of lightning.

- The first people to test this were Stanley Miller and Harold Urey



- Sagan to Miller: 'What do you expect to make?'. Miller – silently hands him the (equivalent of) the Merck index.

- Originally, in 1952, they found 11 amino acids

- A 'Volcanic' version of the experiment was reexamined in 2008 yielding 22 amino acids.

Solution 1: Lightning

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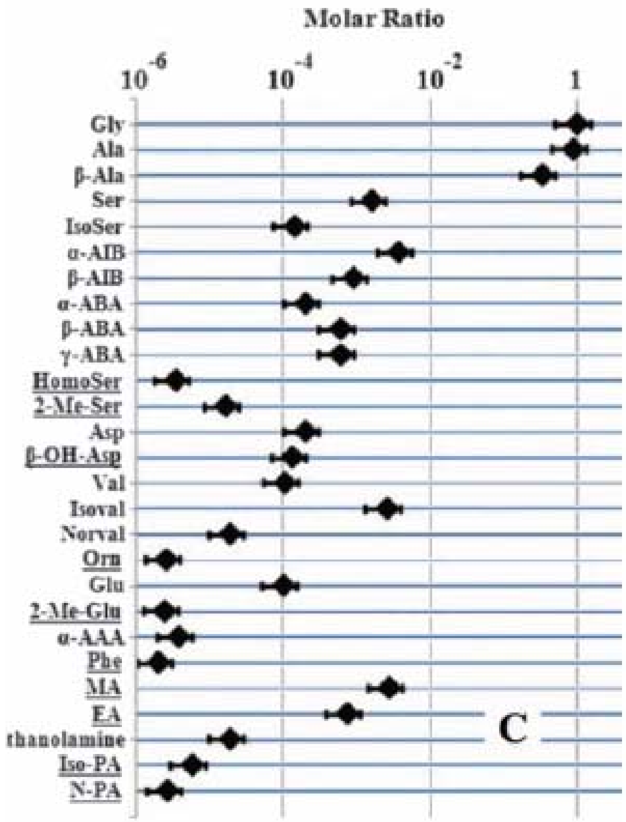
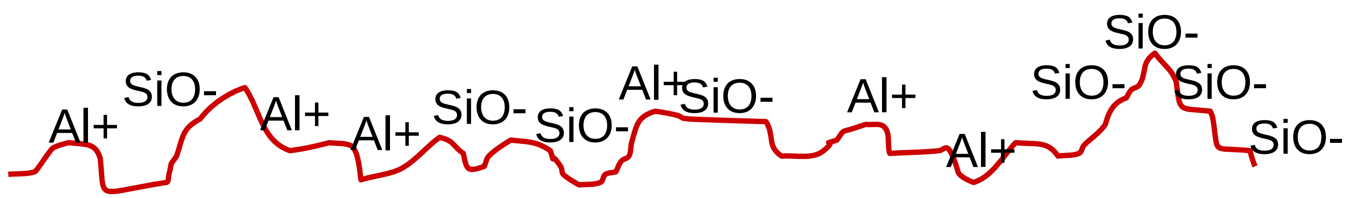


- One thing the Miller-Urey experiments did NOT do was make nucleotides…

Solution 2: Clay

- If we can't get massive amounts of energy from lightining, perhaps we could get some enzymes!!? BUT HOW!!??

- Advanced by Graham Cairns-Smith and a few others. Based on the fact that clay has lots of charged groups in specific positions for catalysis



- Above is my super awesome depiction of Montmorillonite clay, which has Aluminum and Silica (+ve) and their oxidized counterparts Alumina and Silanol (-ve)

- This is not a popular theory at the moment, mainly because there is very little recent experimental evidence to support it

Solution 2: Clay

- Nonetheless, in the 70's...

Table 2. Clay mediated synthesis of aminoacids

Clay or surface	Reactants	Temp.	Products	Analytical methods	References
Kaolinite	$HCHO+NH_3+$ HCN	130-135° C	polyglycine	paper and column chromatography	Akabori (1955)
Kaolinite	polyglycine+ $HCHO+CH_3CHO$		threonine serine	,,	,,
Zeolites	CO, NH_3	250-325° C	amino acids	paper chromatography and IR	Fripiat et al. (1972)
Montmorillonite Kaolinite Chelex 100	paraformaldehyde+hydroxylamine	80° C	amino acids	column chromatography acid hydrolysis, amino acid analysis, determination of primary	Ventilla and Egami (1976, 1977) Hatanaka and Egami (1977a,b)

Table 3. Clay mediated synthesis of nucleotides

Clay or surface	Reactants	Temp.	Products	Analytical methods	References
Zeolites	CO_2+NH_3	250-325° C	cytosine and adenine	IR and UV	Fripiat et al. (1972)
Kaolinite	CO_2+NH_4OH+ H_2O	80° C	cytosine, uracil and cyanuric acid	UV spectrophotometry and chromatography	Harvey et al. (1971)
Montmorillonite	alanine + urea		uracil and thymine	UV adsorption TLC on silica gel and cellulose	Chittenden and Schwartz (1976). Schwartz and Chittenden (1977)

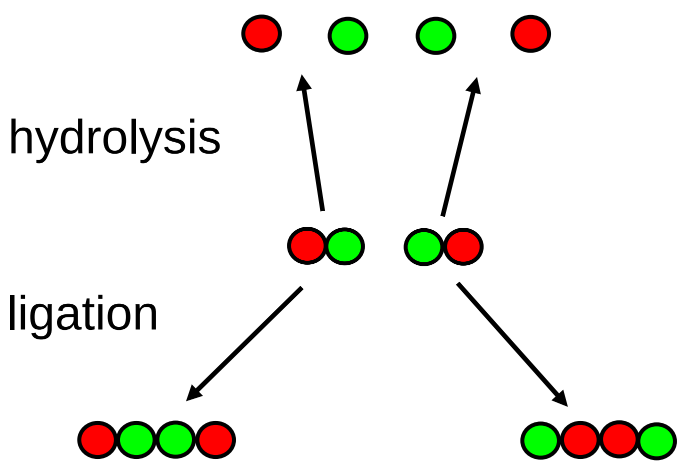
J. Mol. Evol. 15, 317–331 (1980)

Problem 2: Complexity

- Ok, so lets say we happen to get some semi-big molecules via lightning or clay or whatever… but that's not metabolism…

- How do we get the complex, self regulating set of reactions between these molecules? How does complexity arise?

- Enter Stuart Kauffman who point out that complexity arises naturally in autocatalytic sets



- Number of species: 2 (really 2^n)

- Number of reactions: 4 (really 2^{n^2})

- This means the set of reactions grows in complexity relative to the system

Selection in Pre-biotic Chemical Reactions

- Here's the kicker: Members of the set that efficiently catalyze reactions that result in the formation new members that are similar to themselves will have a selective advantage

- This is a primitive form of natural selection…

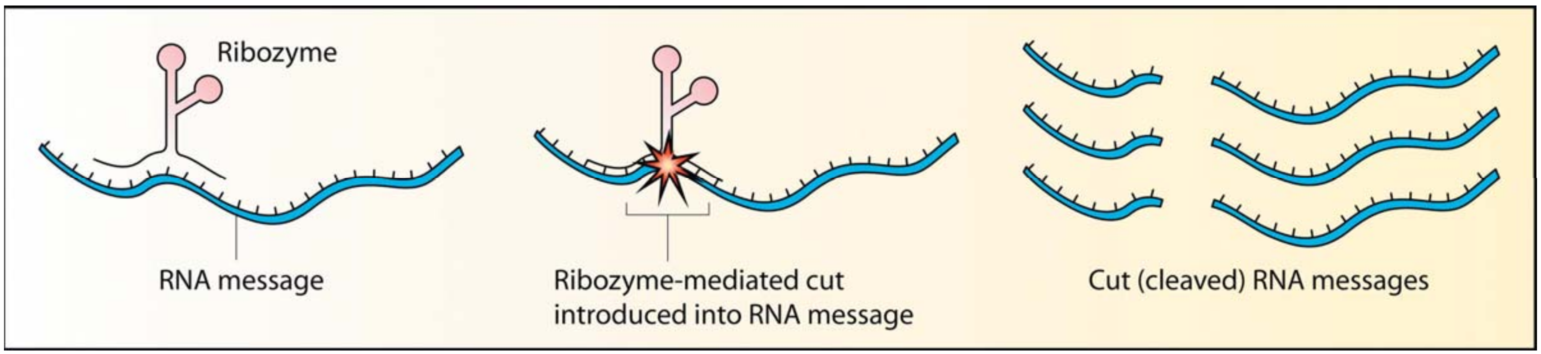
- As the set becomes more complex, subsets of self-replicating reactions (i.e. proto-metabolisms) that are better able to withstand environmental fluctuations will have a selective advantage

- But where oh where can we find an 'autocatalytic set'?

Enter RNA

- So, we need a molecule that:
  - Is a polymer, probably (RNA? DNA? Peptides?)
  - Catalyzes reactions on itself (...anything???)

- In 1980, Thomas Cech identified the first ribozyme, contained in the intron of a tetrahymena gene:

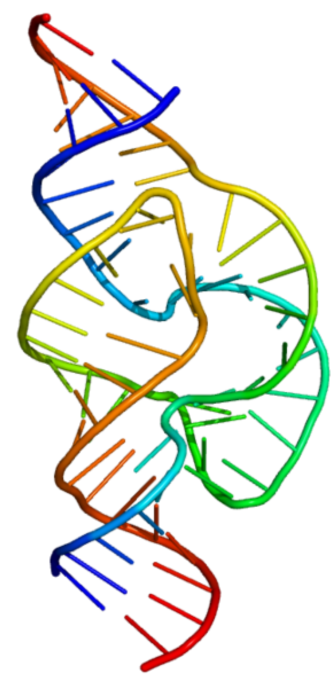


- This amounts to RNA acting on RNA to make more RNA... which is exactly what we're looking for...
- An aside: Cech shared his nobel prize with Sidney Altman...

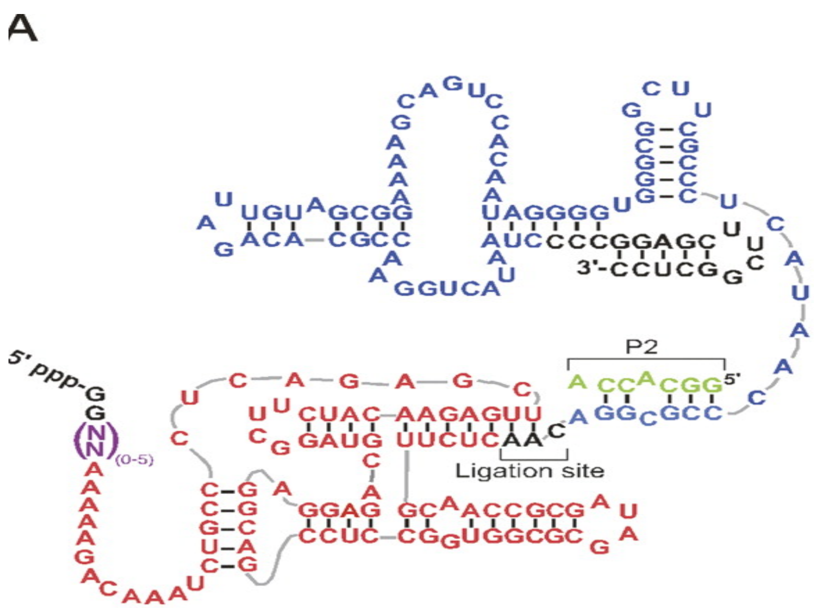
Ribozymes

- Ribozymes are still a 'hot topic' of study today… so far there are about 100 ribozymes identified

- They are able to catalyze a number of different reactions including:
    - hydrolysis (phopshodiester)
    - templated polymerization
    - Aminotransferase



Hammerhead ribozyme



'Round 18' RNA polymerase

RNA (2007), 13:1017–1026

The whole story?

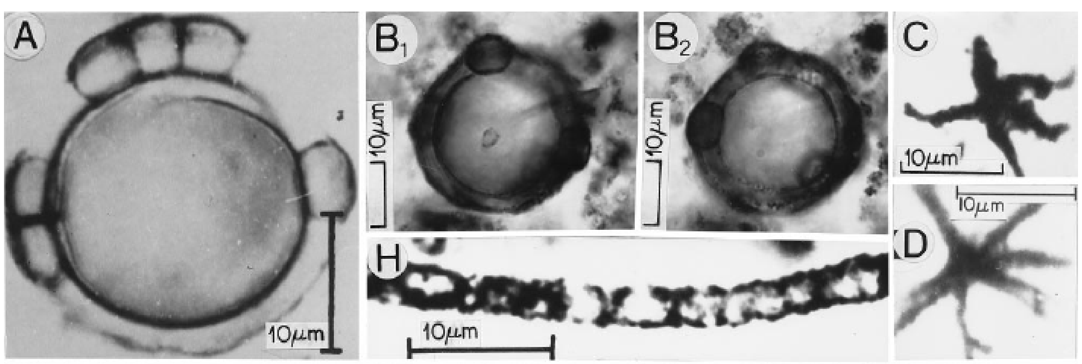
- So there it is... life in two or three easy steps:

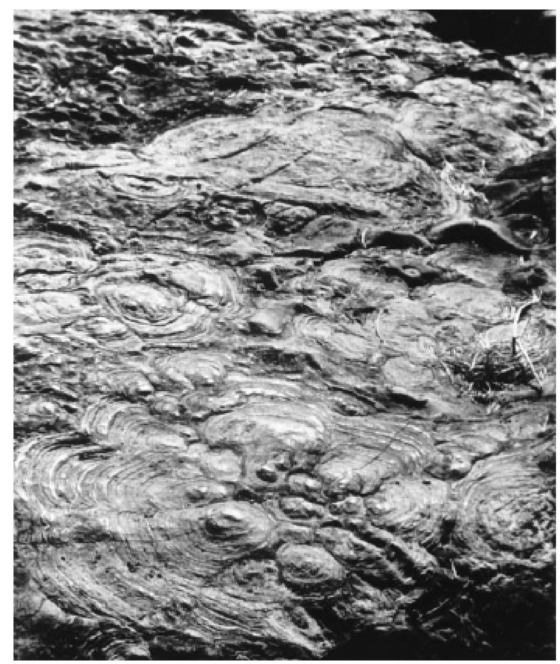
  1) Amino acids from lightning and volcanoes, RNA from clay

  2) Primitive metabolism arises through autocatalytic sets

  3) Highly resistant 'metabolism' hides in a phospholipid 'bubble'?

- And then...





That's all, folks!

- Sometimes, you may have felt like this:

- But now, you're totally like this: