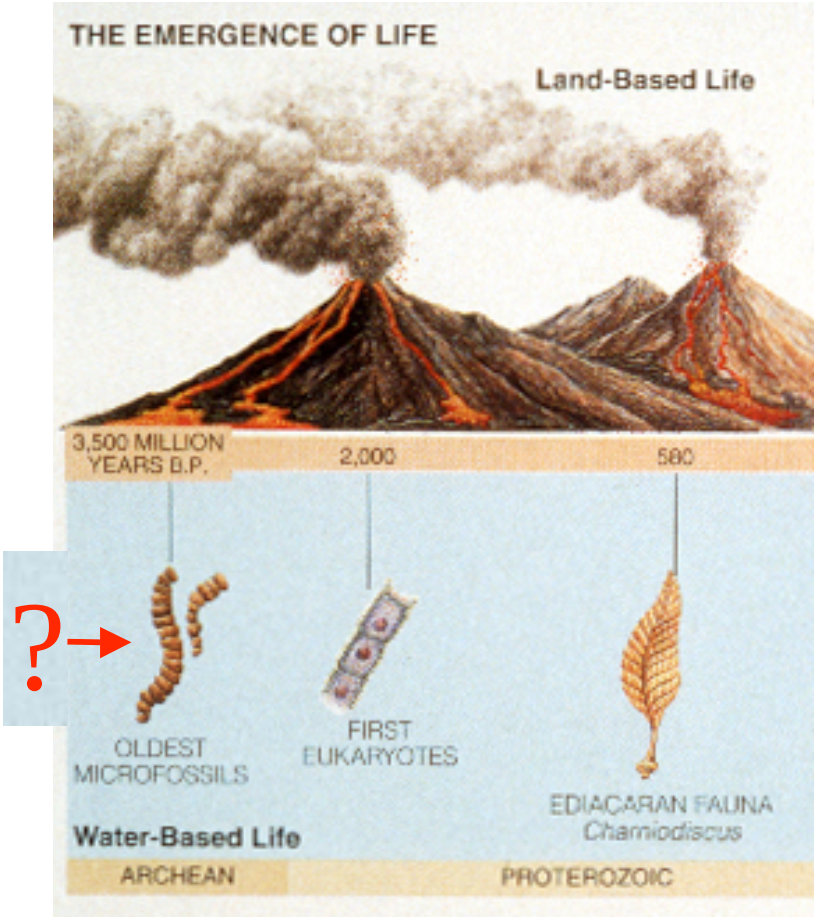
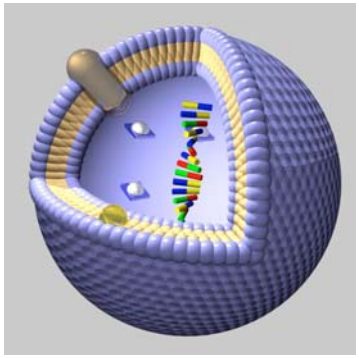
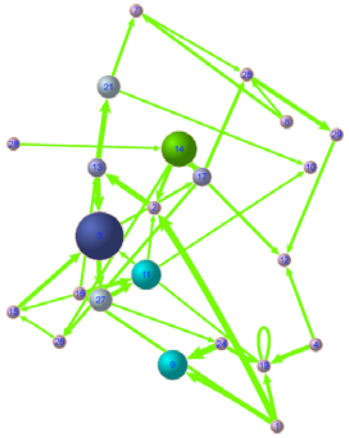
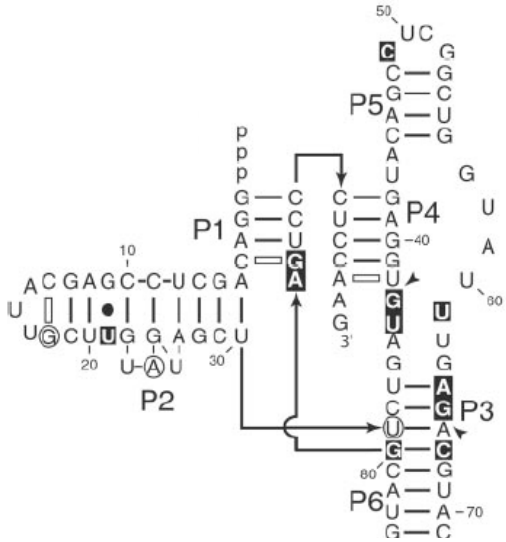
Life's origin: What is the real question?

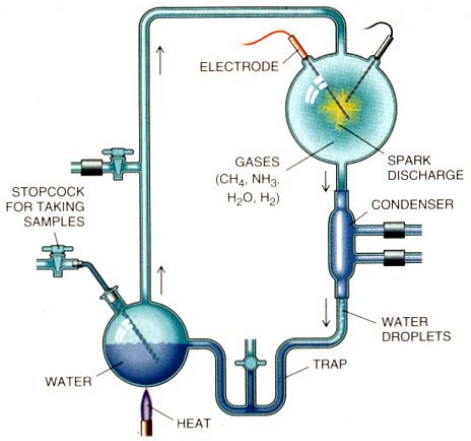
Doron Lancet, Crown Human Genome Center, the Weizmann Institute of Science, Rehovot, Israel; and KITP



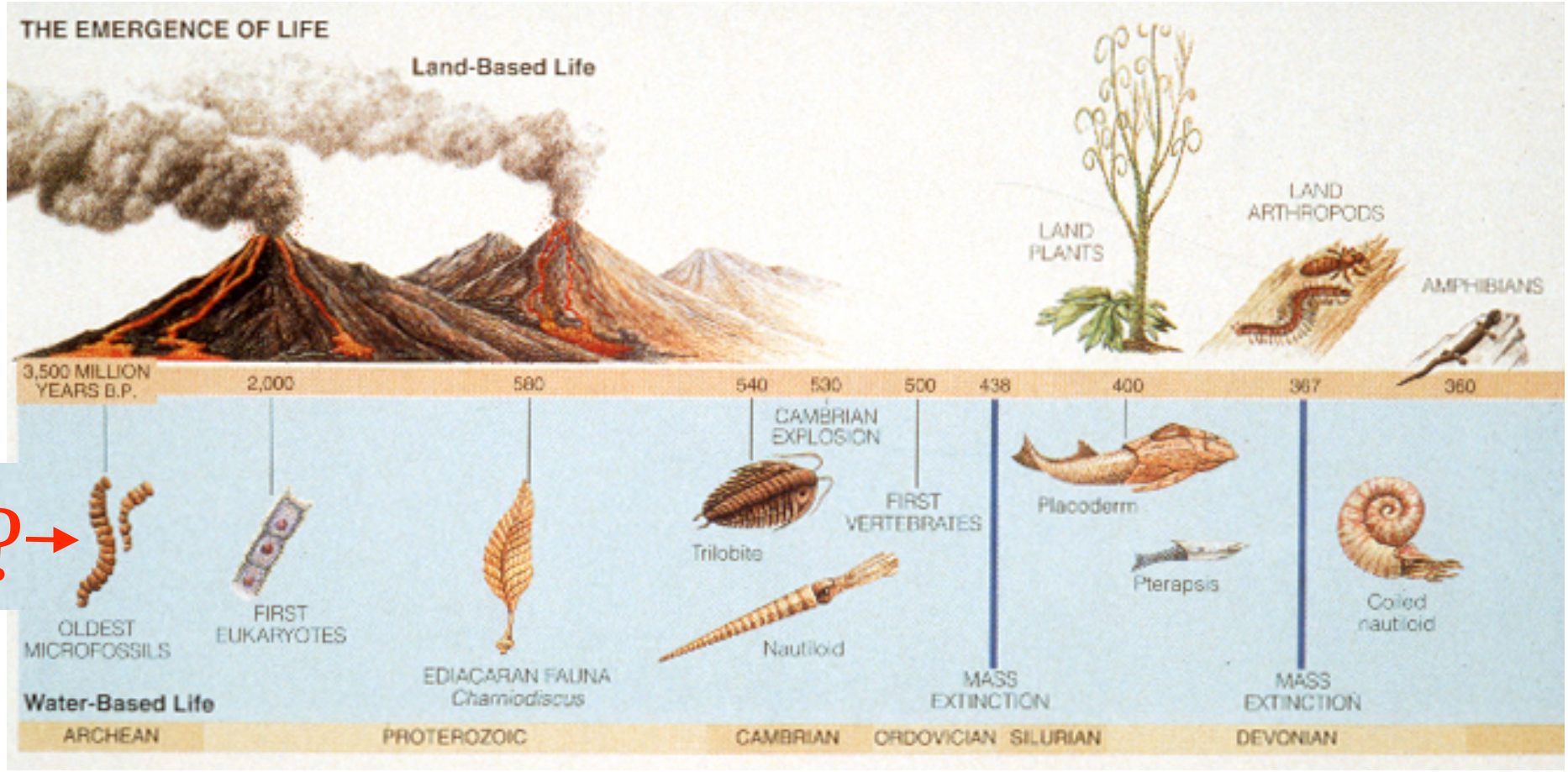




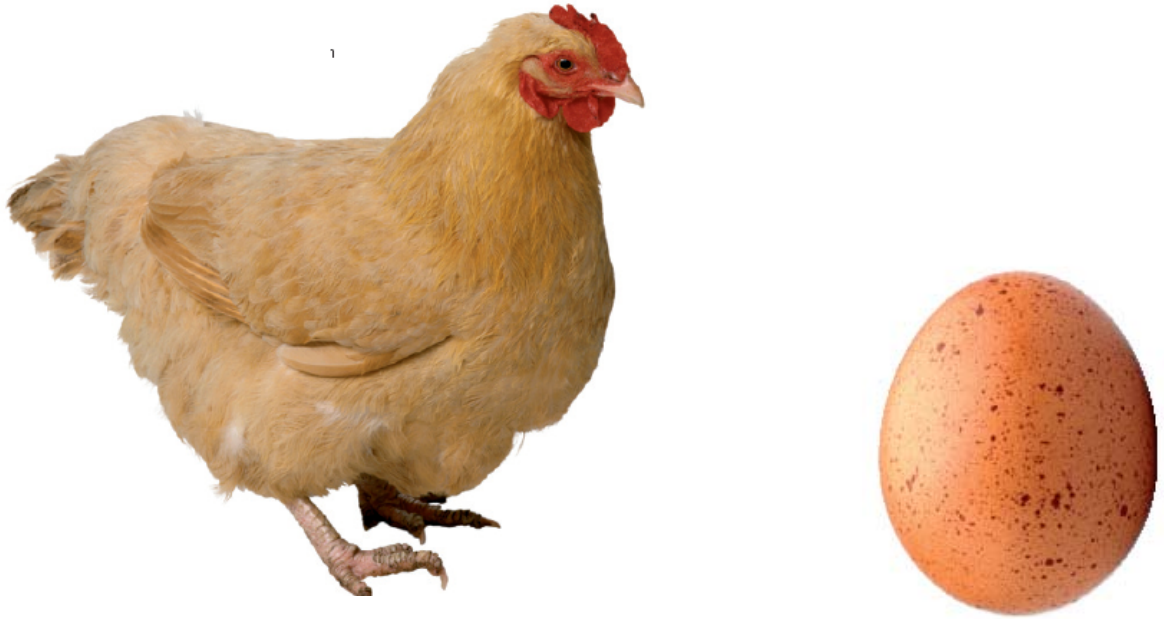




Early evolution and the Origin of Life:
How to reconstruct the events before the fossil record?

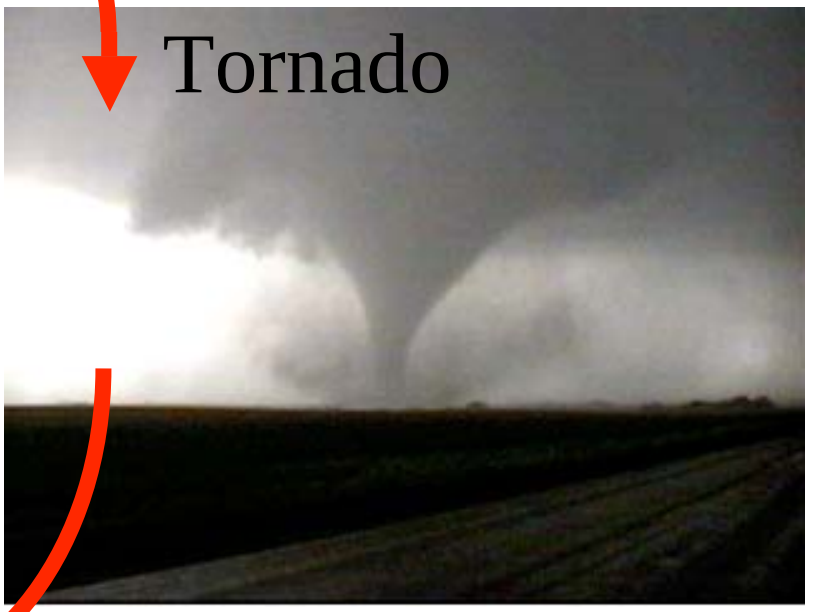


An often stated chicken-and-egg conundrum is that life cannot reach even a most rudimentary level of complexity without self-replication, but that only minimally complex chemical entities can multiply.



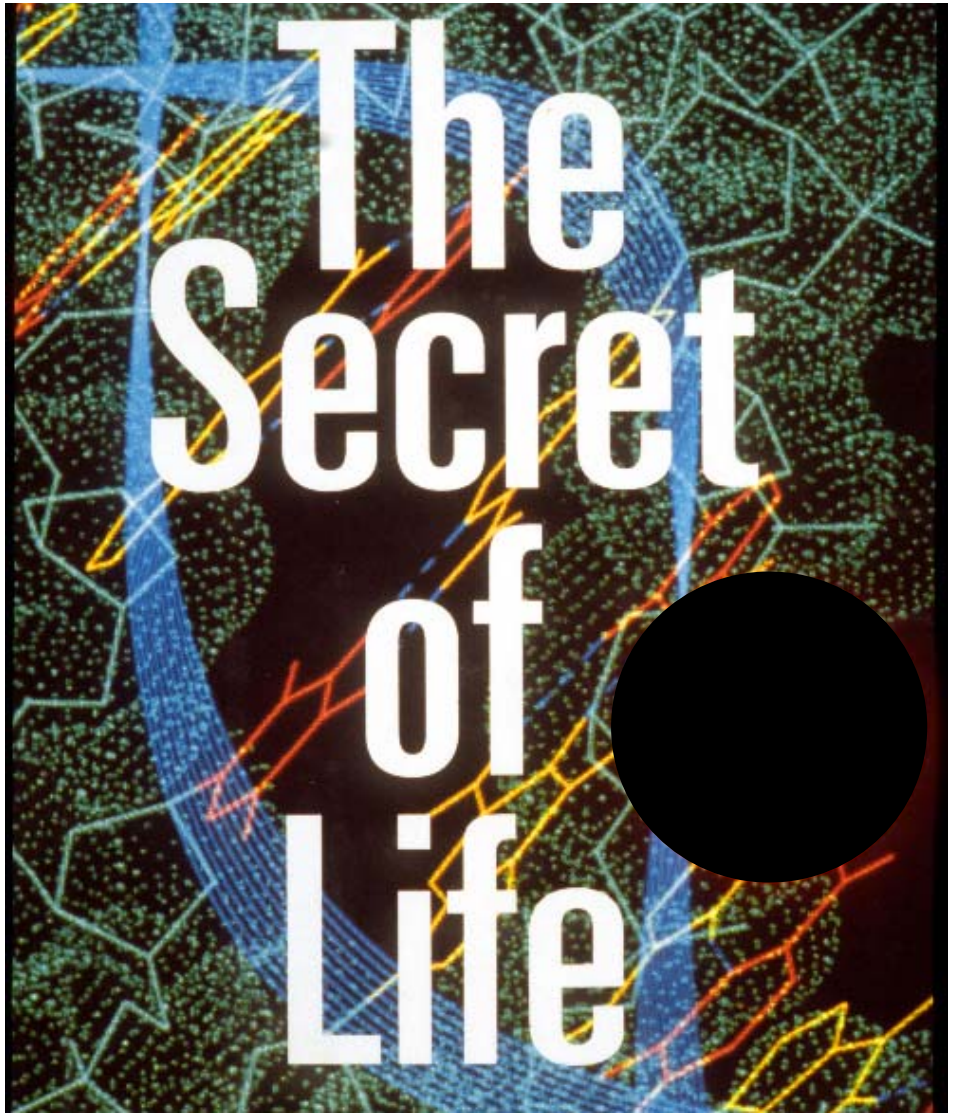
From:Compositional lipid protocells: reproduction without polynucleotides
D Lancet & B Shenhav
In “Protocells: Bridging Nonliving and Living Matter”.
S. Rasmussen, MA Bedau, L Chen, D Deamer, DC Krakauer, NH. Packard & PF Stadler Eds, MIT Press

Can we ever understand the Origin of Life?



A tornado passing through a junkyard would never assemble a 747.
Fred Hoyle1983. “The Intelligent Universe”.

Finding out about the Origin of Life may lead to a much better understanding of present-day life and its more recent evolution!



THE EMERGENCE OF LIFE ON EARTH

A HISTORICAL AND SCIENTIFIC OVERVIEW

Iris Fry

Rutgers University Press

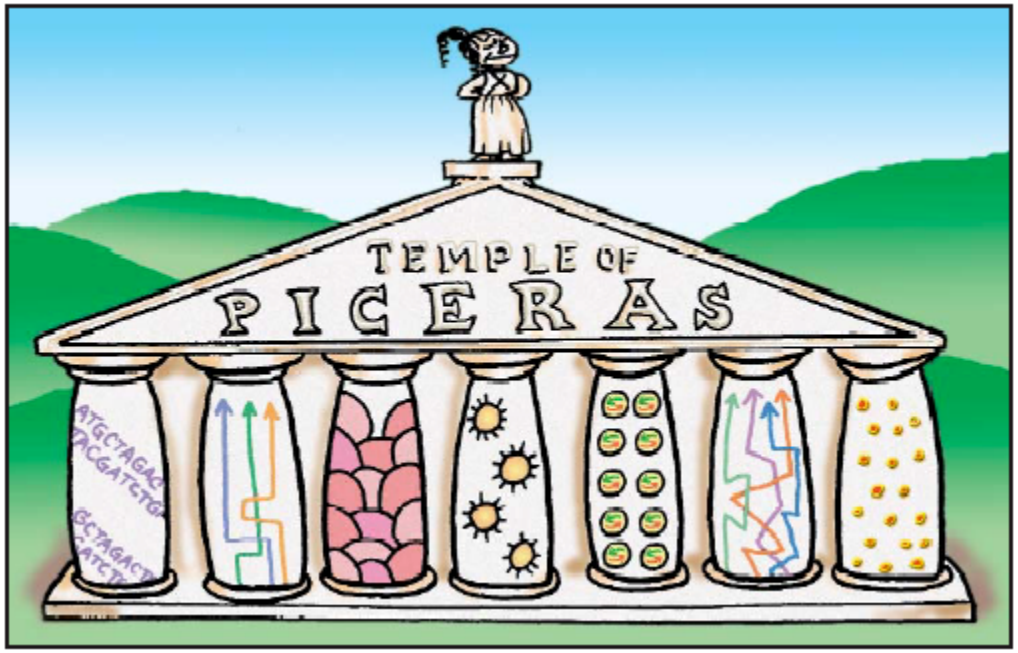
Defining life

SPECIAL ESSAY

The Seven Pillars of Life

Daniel E. Koshland Jr.

Science 295: 2216-7 (2002)

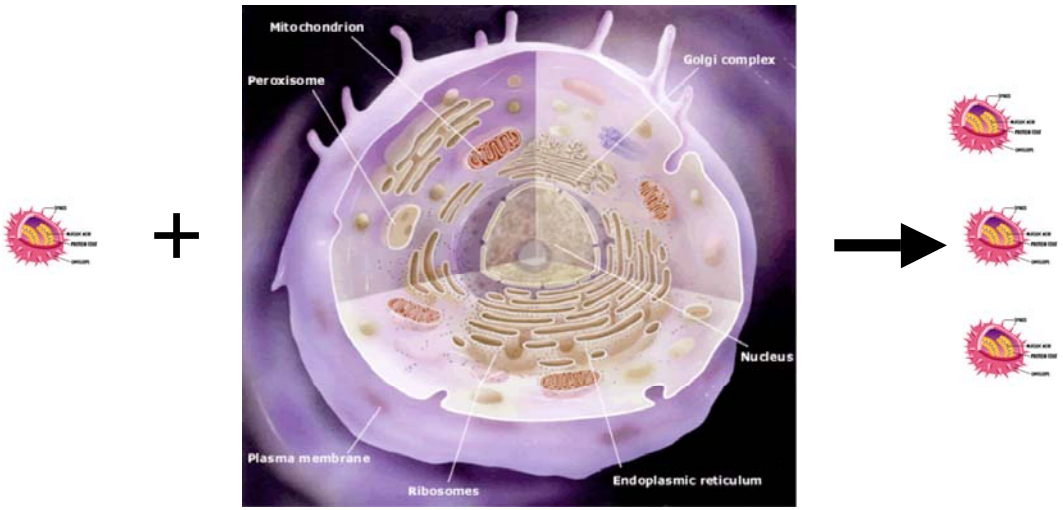


Program (DNA)
Improvisation (mutations)
Compartmentlaization
Energy
Regeneration
Adaptability
Seclusion (specificity)

Is a virus alive?

What is a virus?

- Packaged extracellular nucleic acid which can be transferred from cell to cell
- Requires a host to replicate - obligate intracellular parasite
- Contains information necessary for its own replication



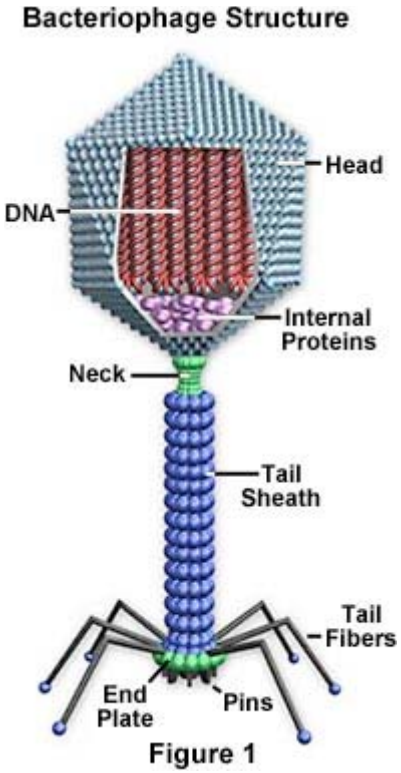
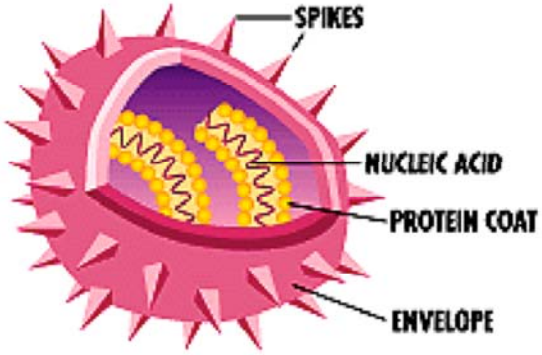
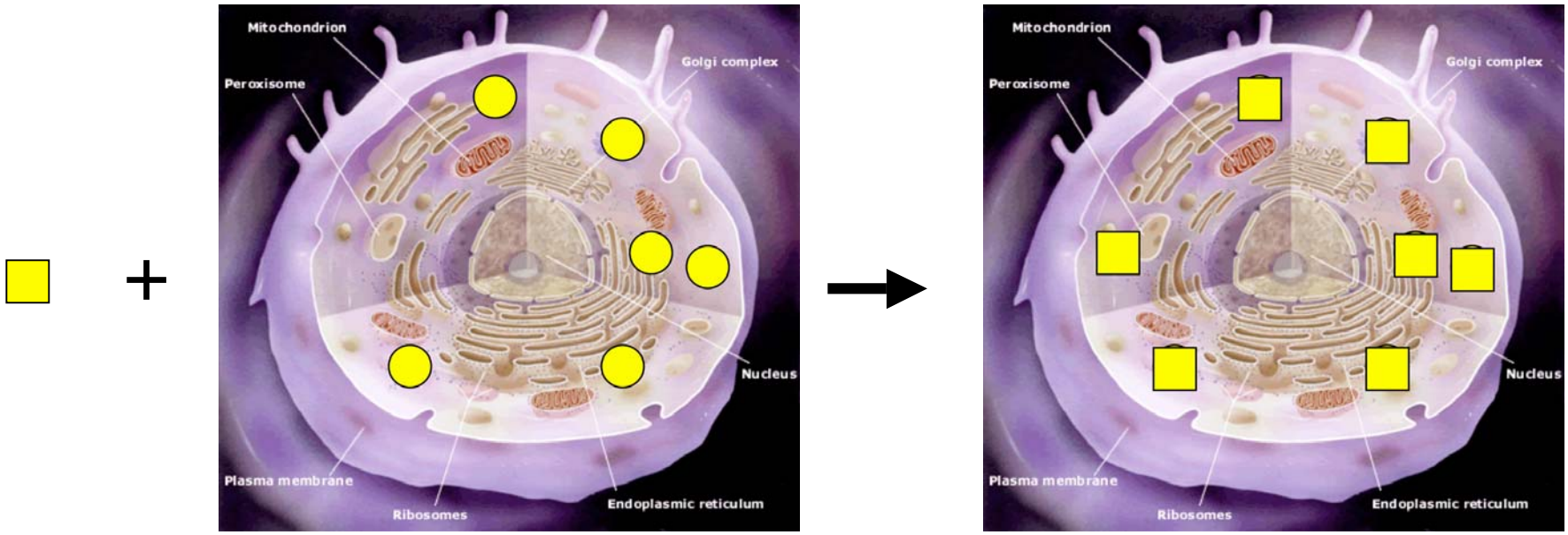


Figure 1



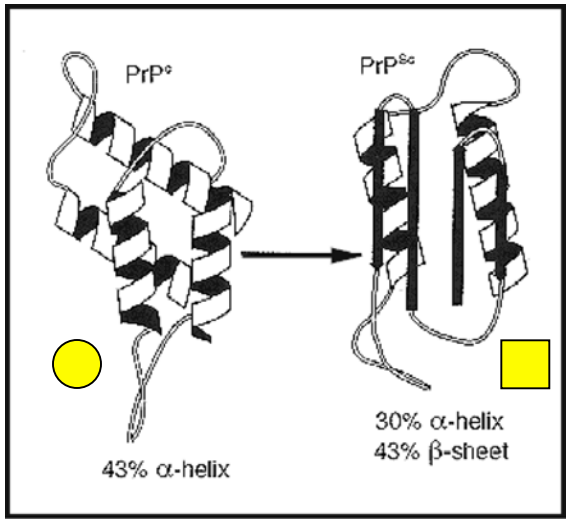
And what about prion proteins?



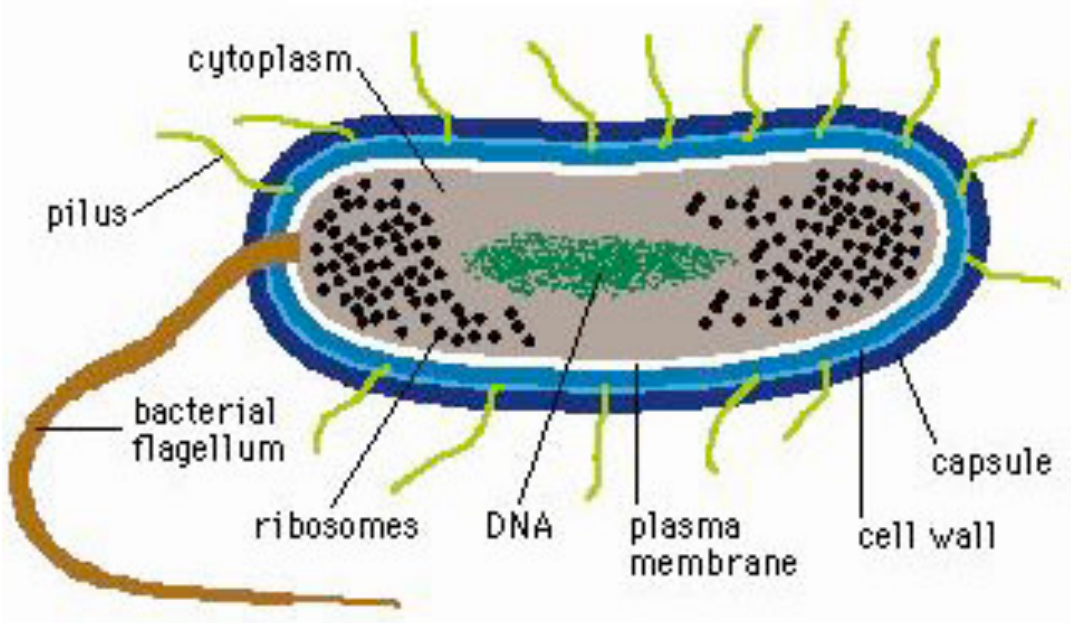
Infecting conformationally modified prion protein

Endogenous normal prion protein coded for by the cell's genome

Autocatalytic conformational modification



Baldwin MA, James TL, Cohen FE, Prusiner SB. The three-dimensional structure of prion protein: implications for prion disease. Biochem Soc Trans. 1998 Aug;26(3):481-6

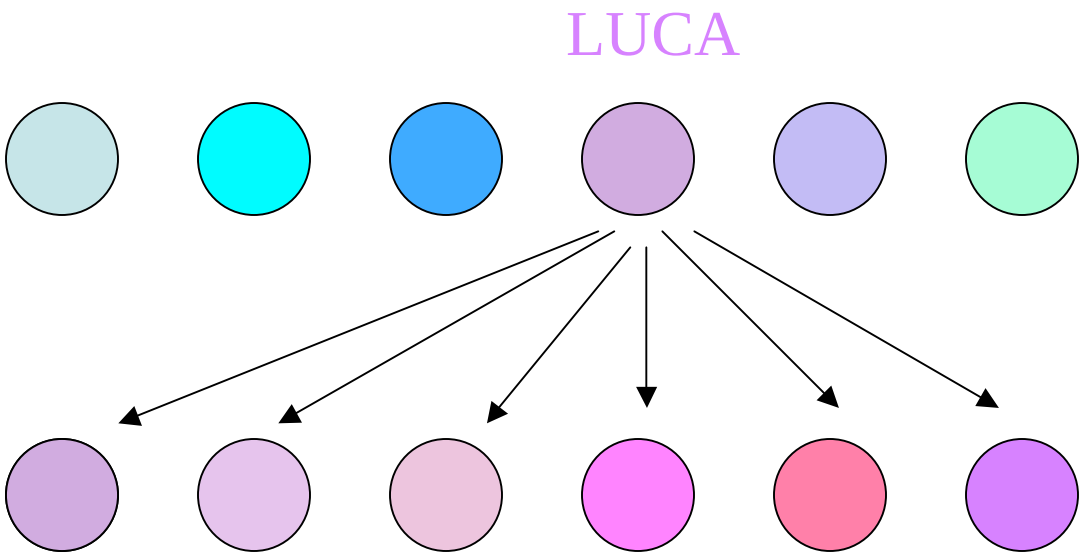


What might be the minimum complexity for a cell that is capable of replicating on its own?

This would give us hints on the Last Universal Common Ancestor (LUCA)

LUCA was not alone

An evolutionary bottleneck!



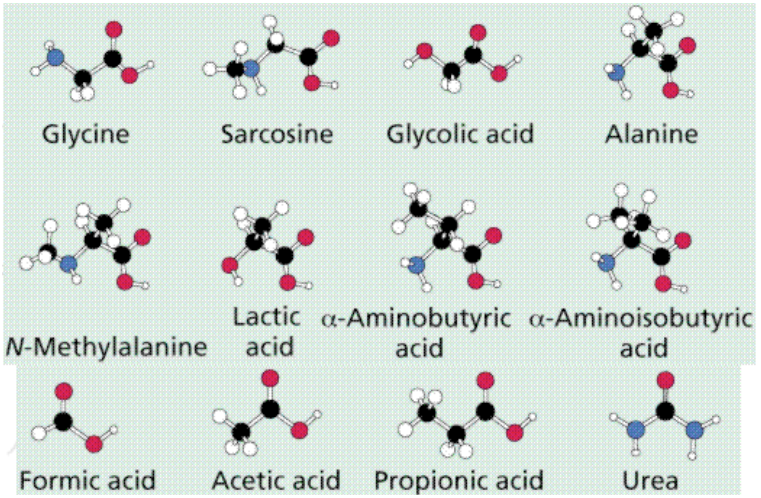
Early life with diverse chemistries

Present-day life

Three stages in the Origin of Life

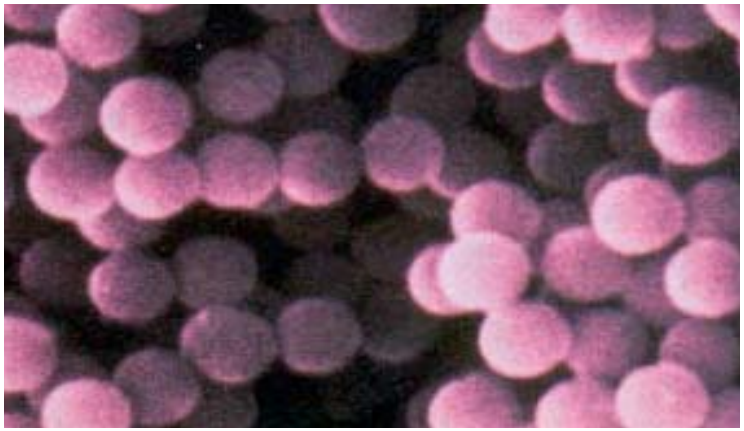
1) Origin of organic compounds

Understood in principle, need more details



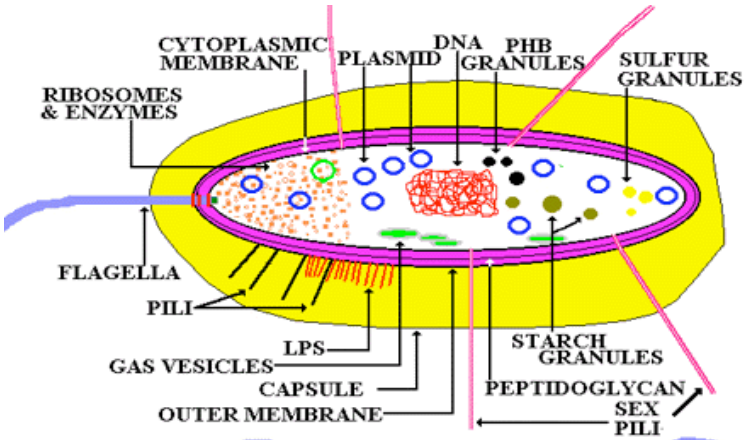
2) Origin of protocells

Possible to model by general physicochemical reasoning



3) Origin of the Last Universal Common Ancestor (LUCA)

Much more difficult, requires detailed historical molecular-evolution scenarios



Minimal genome *Mycoplasma genitalium*

Smallest independently replicating cellular organism 517 genes (480 protein-coding)

Eugene Koonin's suggestion:

Take away all genes related to:

- DNA repair
- Molecular chaparones
- Metabolic pathway for amino acids, nucleotides, sugars, co-factors
- Signal transduction

Leave on all genes that underlie:

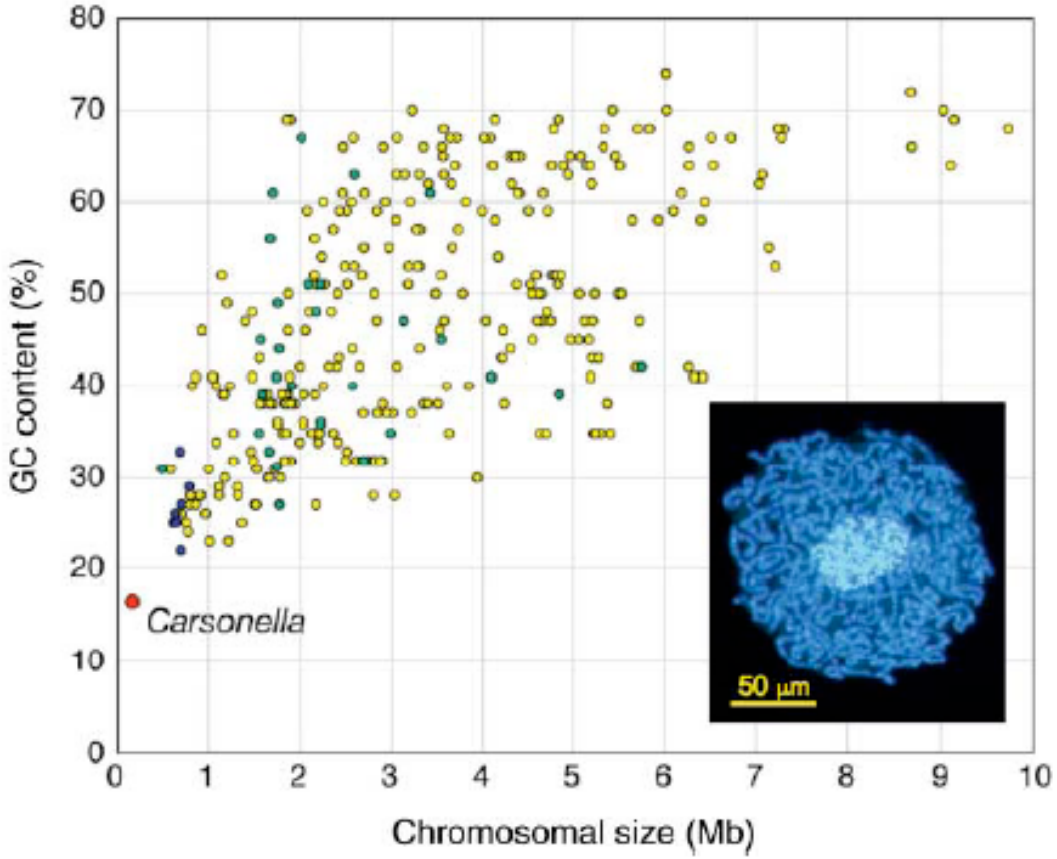
- Translation (including ~50 ribosomal proteins)
- Transcription
- DNA replication
- Membrane and cell envelope synthesis
- Transporters

Estimated remaining gene count: 200-300

The 160-Kilobase Genome of the Bacterial Endosymbiont *Carsonella*

Atsushi Nakabachi,[1,2*] Atsushi Yamashita,[3†] Hidehiro Toh,[3,4†] Hajime Ishikawa,[5] Helen E. Dunbar,[2] Nancy A. Moran,[2] Masahira Hattori[6,7*]

Science. 2006 314(5797):259–60.



Little blue specks are Carsonella inside host

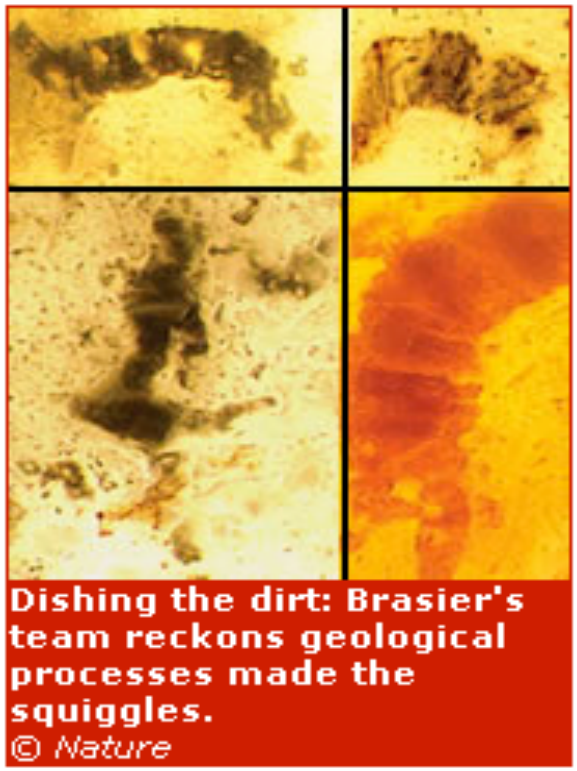
What is the real question?

1) 3.8 or 3.5 billion years ago?
2) Here or elsewhere?
3) Probable or improbable?
4) Organic or inorganic?
5) Organics trivial or not?
6) Today's chemistry or not?
7) Catalysis by proteins only or not?
8) Large molecules or small?
9) Sequential or compositional information?
10) Single molecules or networks?
11) Understandable *in silico* or not?

How old are the oldest bacterial fossils? Schopf vs Brasier

1) 3.8 or 3.5 billion years ago?

Life forms: Schopf thinks these marks are fossils of ancient bacteria.
© Nature



Dishing the dirt: Brasier's team reckons geological processes made the squiggles.
© Nature

Schopf, J. W., et al.
Laser-Raman imagery of Earth's earliest fossils.
Nature, 416, 73 - 76, (2002).

Brasier, D. M. et al.
Questioning the evidence for Earth's oldest fossils.
Nature, 416, 76 - 81, (2002).

Evidence of the oldest living things is being fiercely contested. The argument looks set to run, but it may lead to a better understanding life's origin.

2) Here or elsewhere?

1) Panspermia

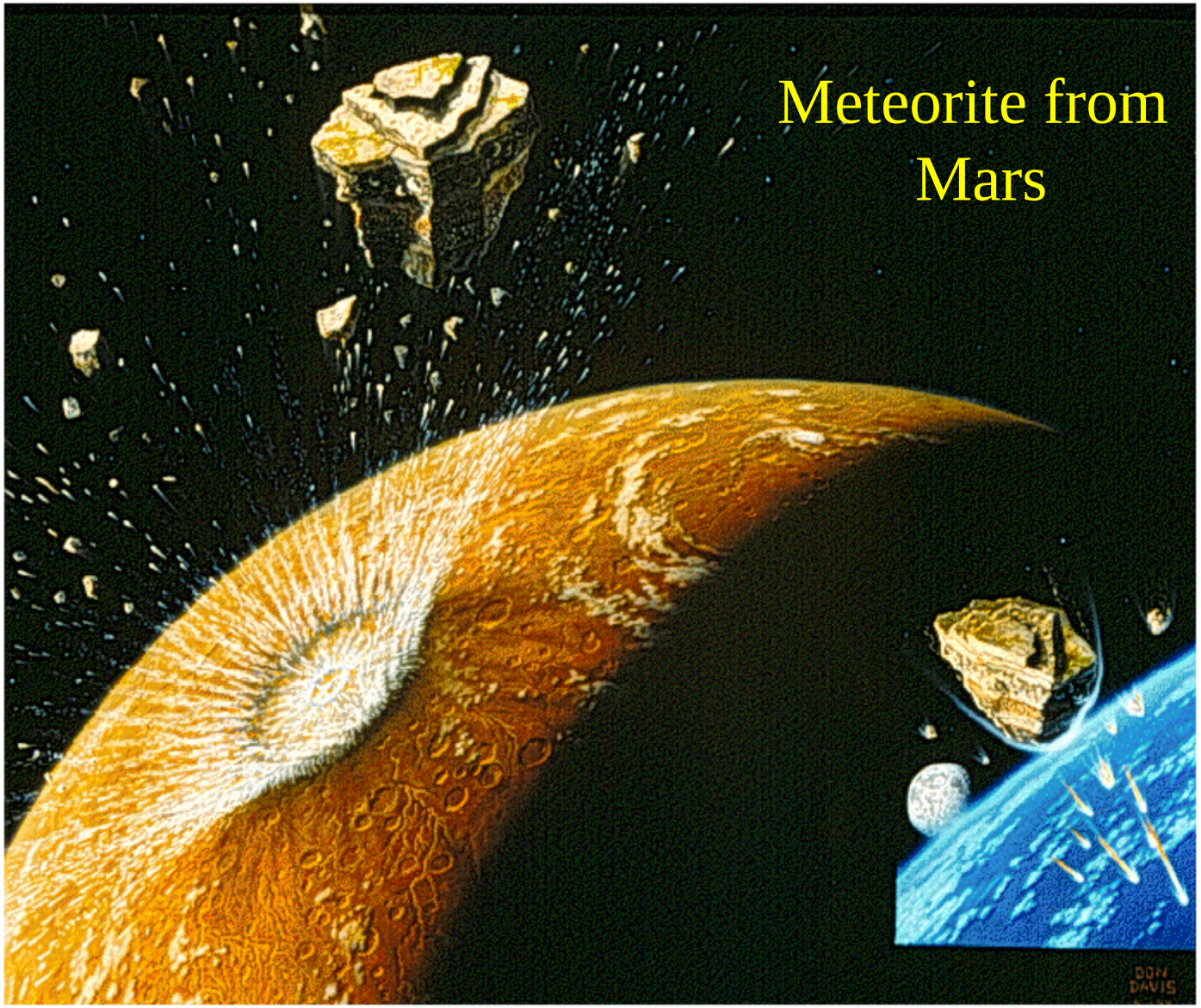
1970

This “explanation” just moves the problem elsewhere!

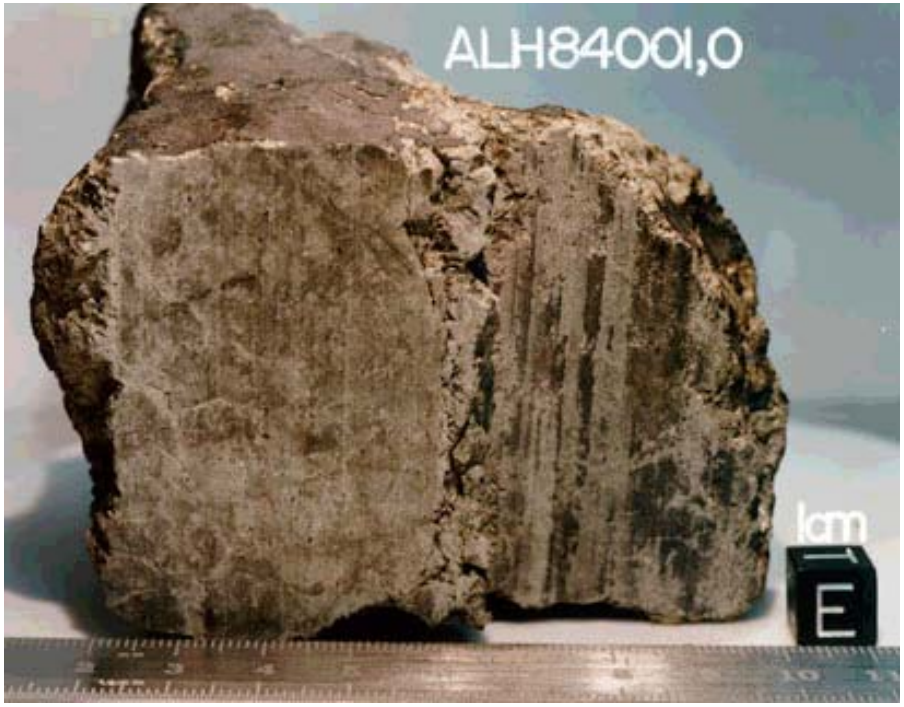
Prebiotic molecules and interstellar grain clumps.
Nature. 1977 17;266(5599):241-3

Chandra Wickramasinghe

Fred Hoyle


Meteorite from
Mars
DON
DAVIS

Meteorite: ALH84001
Location: Allan Hills
Antarctica
Found: December 27, 1984
Type: SNC
(Shergottite, Nakhlite, and
Chassigny classes)
Likely origin: Mars



Fragment with
Exposed surface

Identity confirmed by comparing isotope ratios
To those reported by mars landers

Meteorite dates back to periods when Mars had:

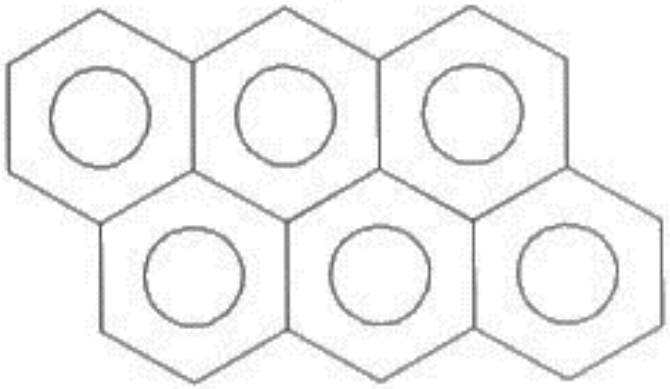
- Thicker atmosphere
- More abundant water

Inside the Martian meteorite ALH84001

Calcium carbonate globules

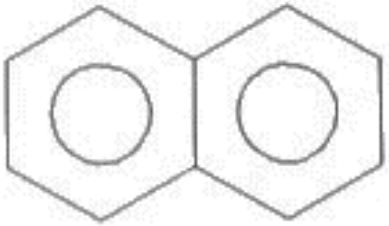
Iron oxides and sulphides

Polycyclic Aromatic Hydrocarbons (PAHs)



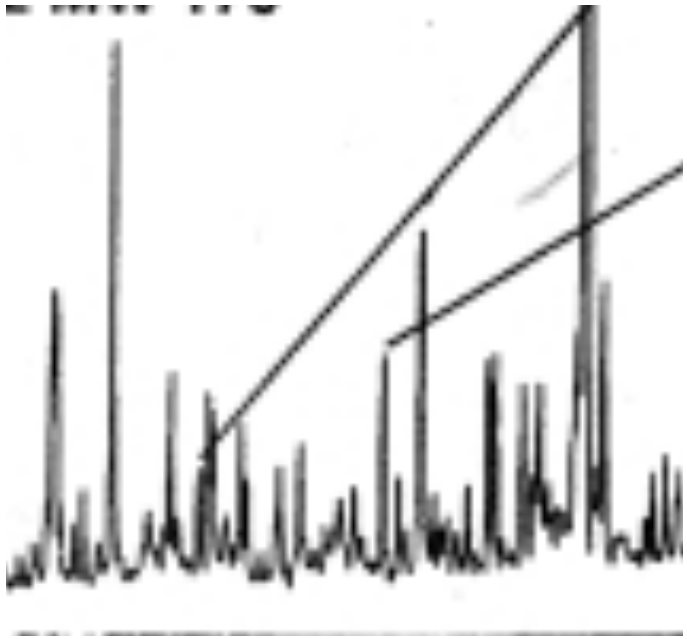
Anthanthrene

$C_{22}H_{12}$

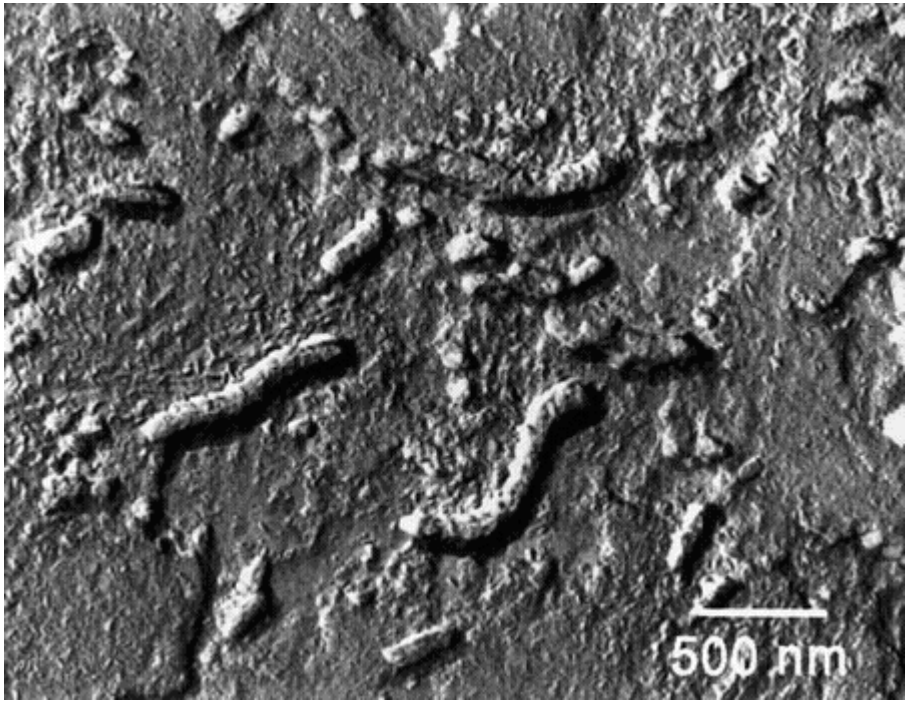


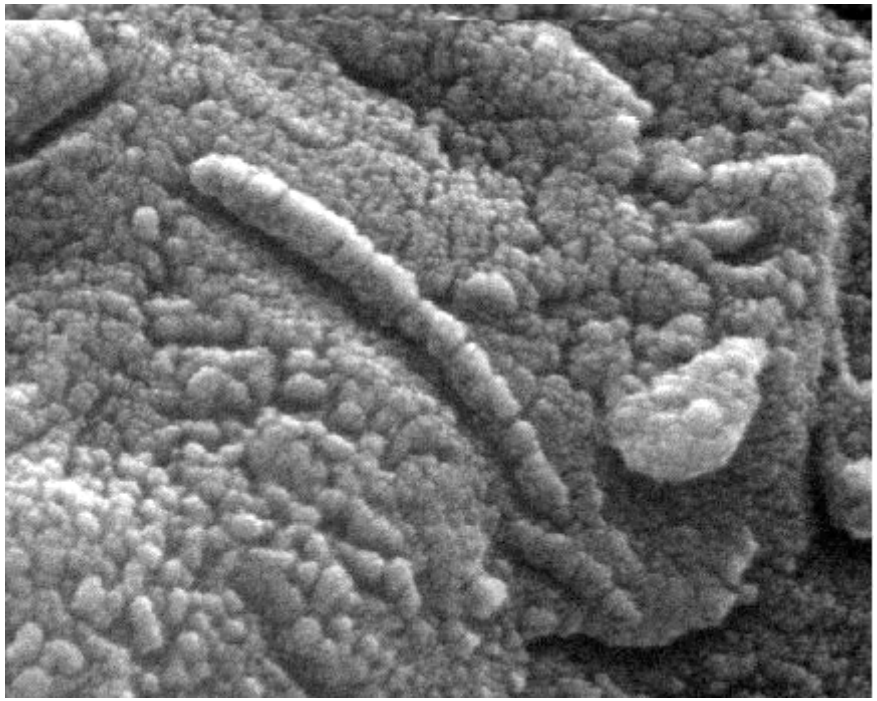
Naphthalene

$C_{10}H_8$



Restricted PAH spectrum in martian meteorite



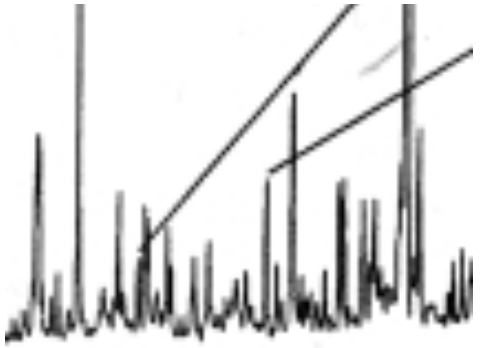


Features resembling fossilized bacteria

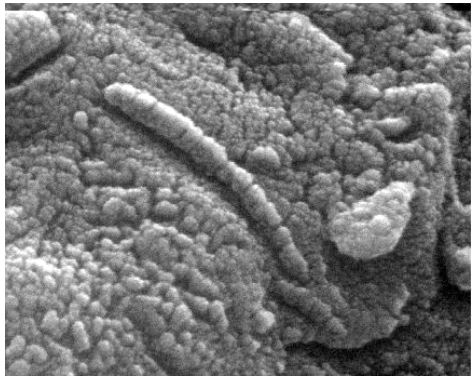
Criticism and dispute on ALH84001 finds

- At what temperature did globules form?
- Is the carbonate organic?
- Did iron compounds form biotically?

- Are the PAHs earthly contaminants?
- Are they not trivial? (present everywhere)



- Are the cell-like features too small?
- Can they be mineral artifacts?



Questions that will NOT be discussed:

Creationism, Intelligent design

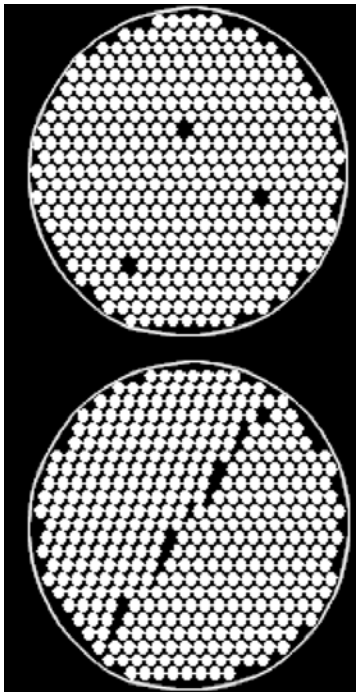
Watchmaker analogy
William Paley, 1802

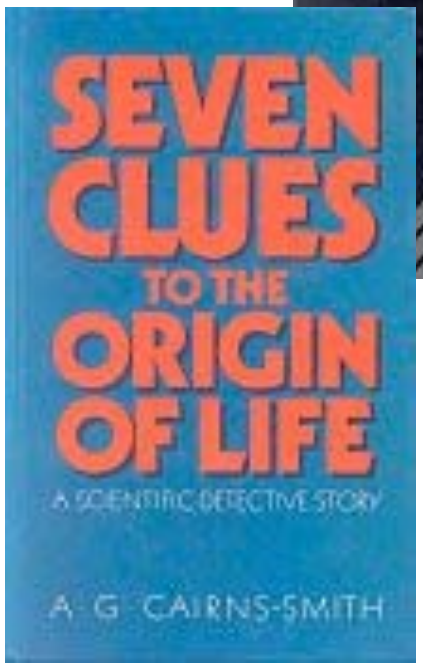
"argument from design“: design implies a designer

4) Organic or inorganic?

Minerals they may have begun life!
(serving as scaffolds for RNA/Protein)

Crystal Imperfections are the information which gets propagated



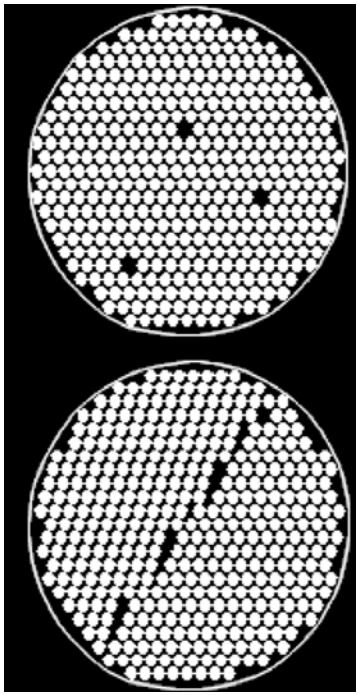


Genetic takeover - and the mineral origins of life,
A. G. Cairns-Smith, Cambridge University Press, 1982;

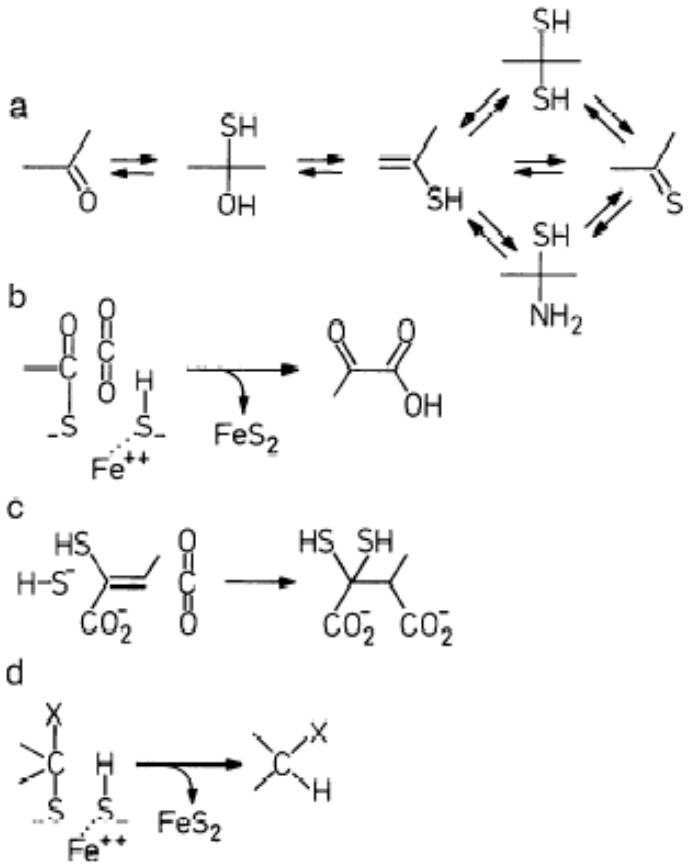
Taking minerals to the extreme:
they may have begun life!
(serving as scaffolds for RNA/Protein)

Counter-argument:
The continuity
principle

Crystal
Imperfections
are the
information
which gets
propagated



Genetic takeover - and the mineral origins of life,
A. G. Cairns-Smith, Cambridge University Press, 1982;



The pyrite connection

Iron disulfide

FeS_2

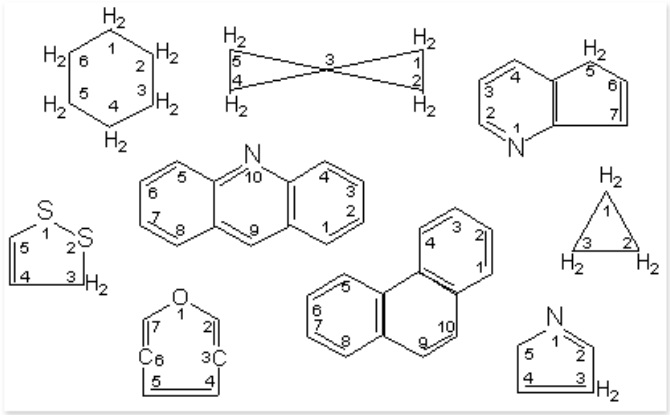
Supply of free energy as well as catalysis

Günther Wächtershäuser

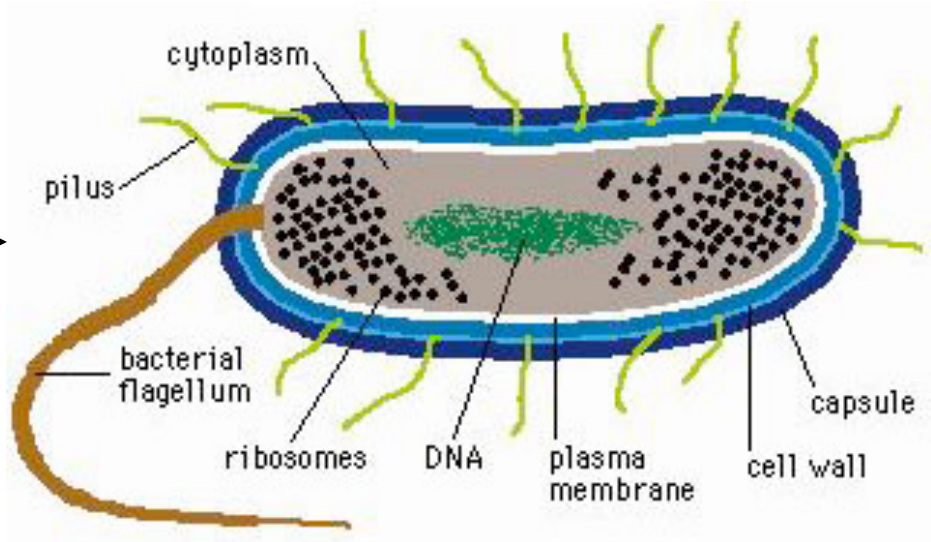
Evolution of the first metabolic cycles.

Proc Natl Acad Sci U S A. 1990 Jan;87(1):200-4.

3) Probable or improbable?



?



To go from a bacterium to people is less of a step than to go from a mixture of amino acids to a bacterium.

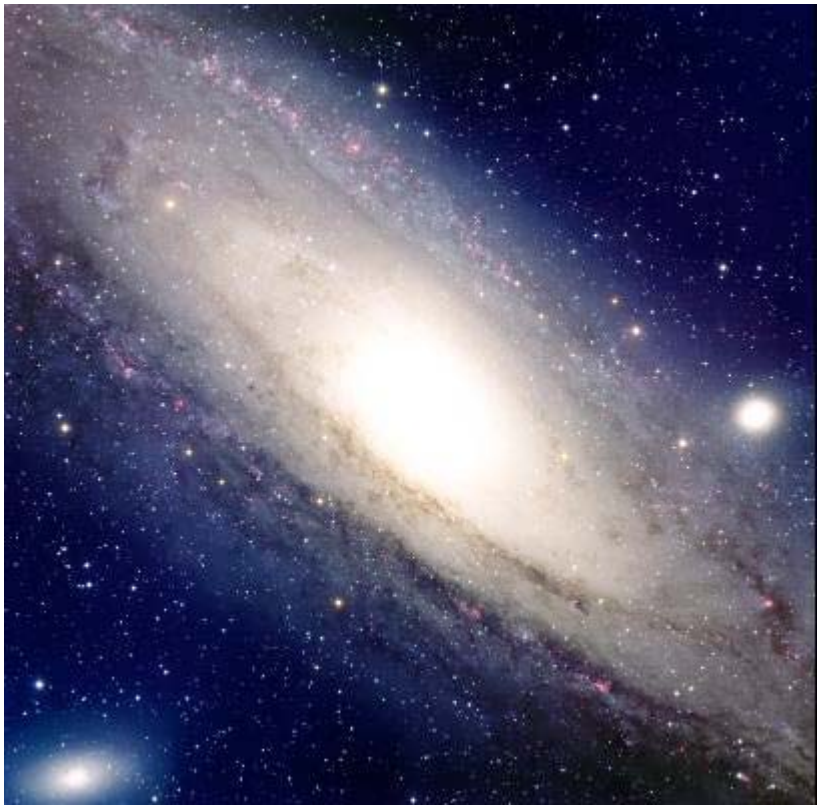
Lynn Margulis interviewed in *The End of Science*, by John Horgan. Addison-Wesley Publishing Company, Inc., 1996. p 140-141

The Drake Equation

The famous Drake Equation gives the number of intelligent civilizations N able to communicate within our own galaxy.

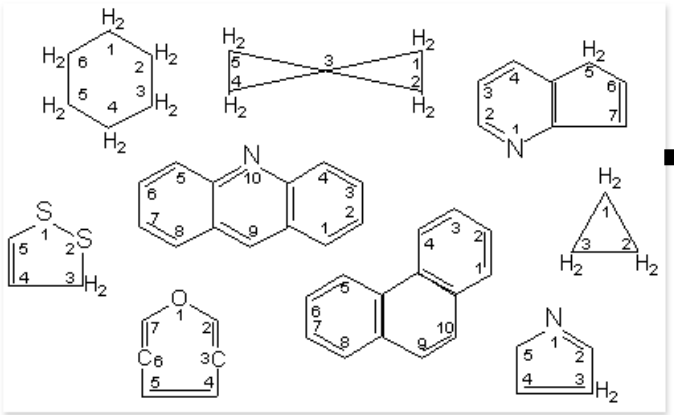
$N=R*f_s*f_p*n_e*f_l*f_i*f_c*L$

100 billion suns

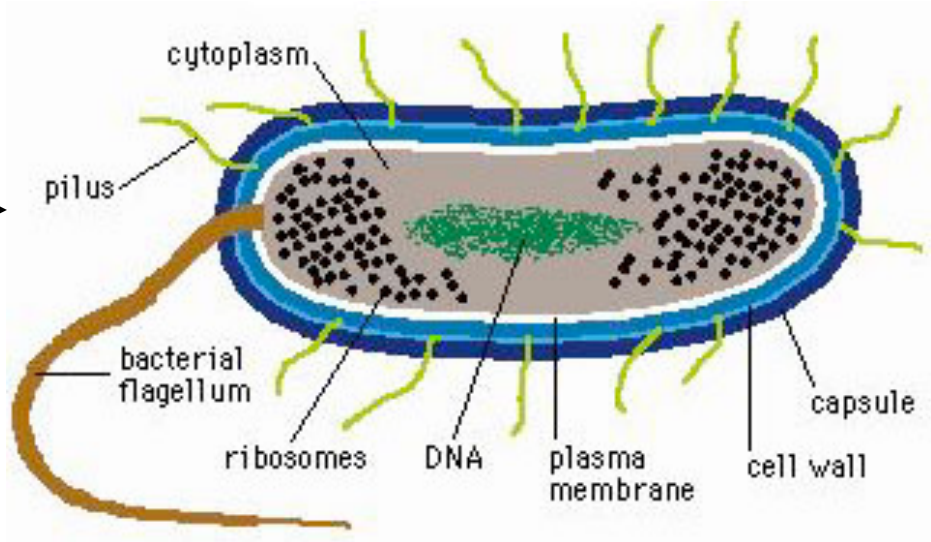


f_l is the fraction of planets on which life actually originates

Nobody knows how to compute its value!



?

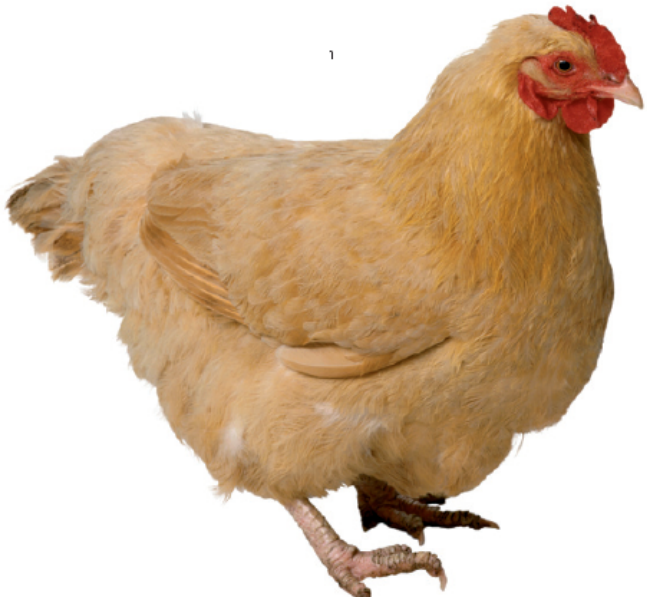


To go from a bacterium to people is less of a step than to go from a mixture of amino acids to a bacterium.

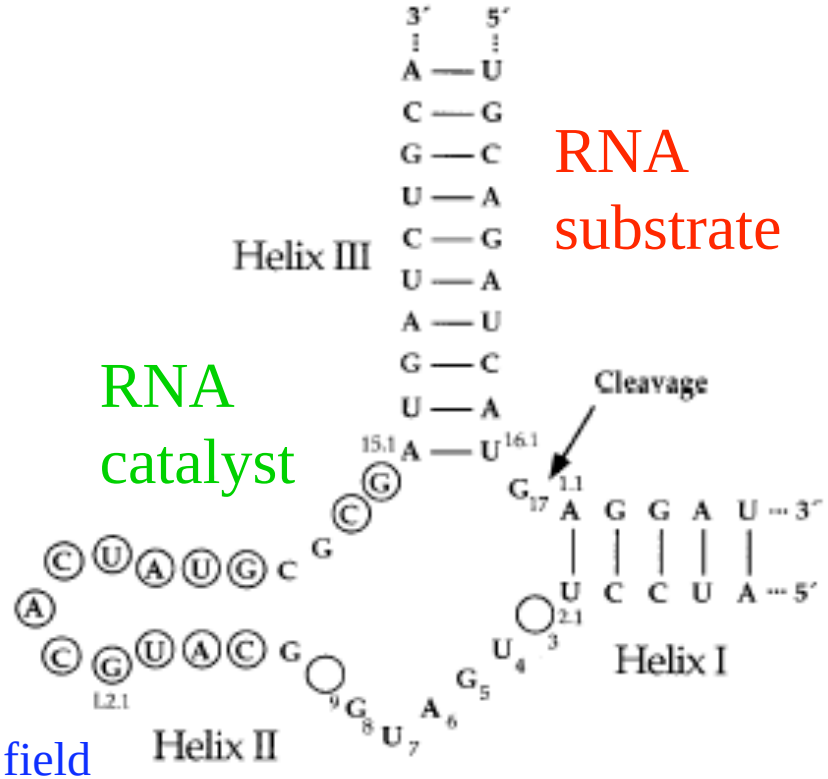
Virtually all biologists now agree that bacterial cells cannot form from nonliving chemicals in one step. If life arises from nonliving chemicals, there must be intermediate forms, "precellular life." Of the various theories of precellular life, the most popular contender today is "the RNA world." http://www.panspermia.org/

7) Catalysis by proteins only or not?

If RNA had the ability to act as both genes and enzymes, this could offer a way around the "chicken-and-egg" problem (Genes require enzymes; enzymes require genes).



RNA catalysis was proven in the 1980s by Nobel Prize-winning researchers Thomas R. Cech and Sidney Altman

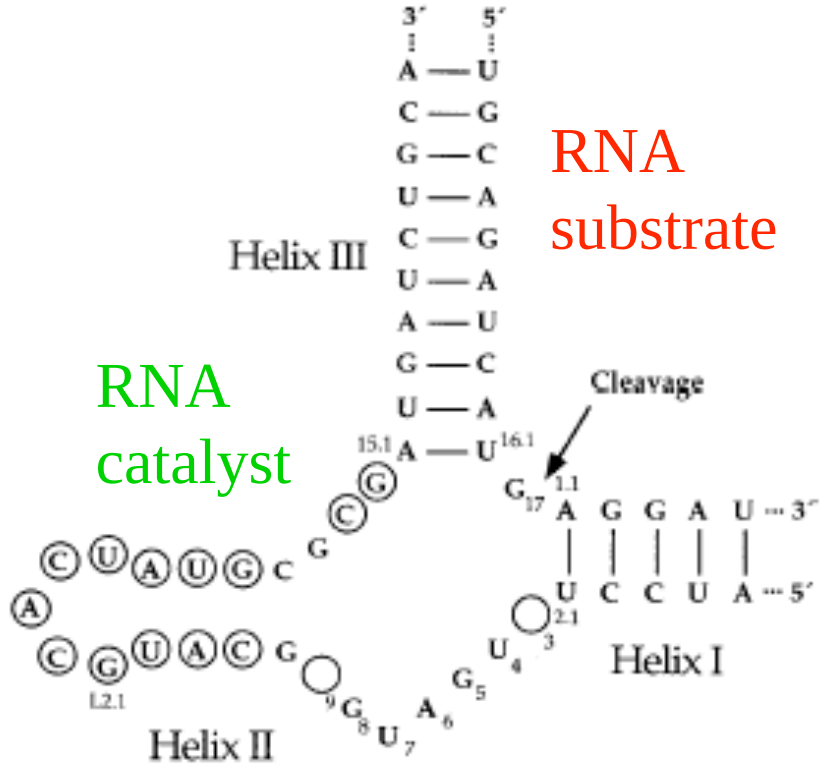


Hammerhead ribozyme

Vaish NK, Kore AR, Eckstein F.
Recent developments in the hammerhead ribozyme field
Nucleic Acids Res. 1998 Dec 1;26(23):5237-42.

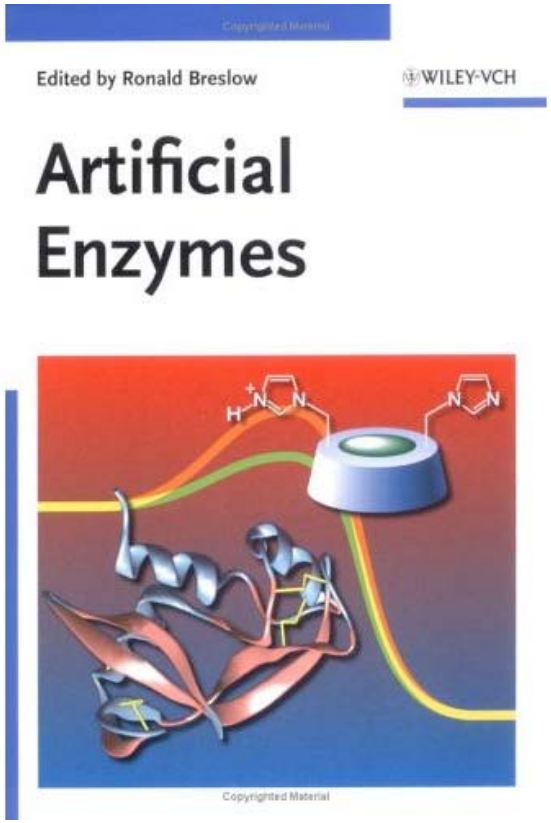
RNA catalysis was proven in the 1980s
by Nobel Prize-winning researchers
Thomas R. Cech and Sidney Altman

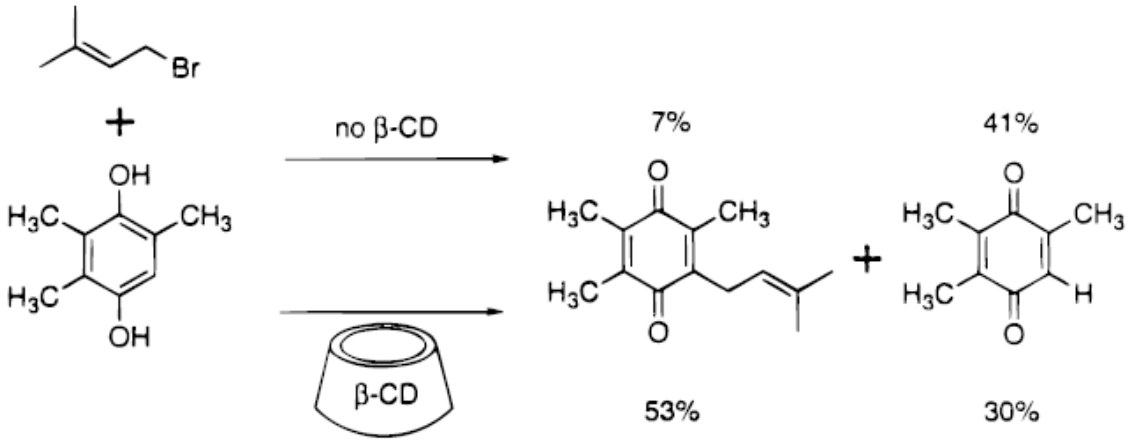
Should we really
be surprised?



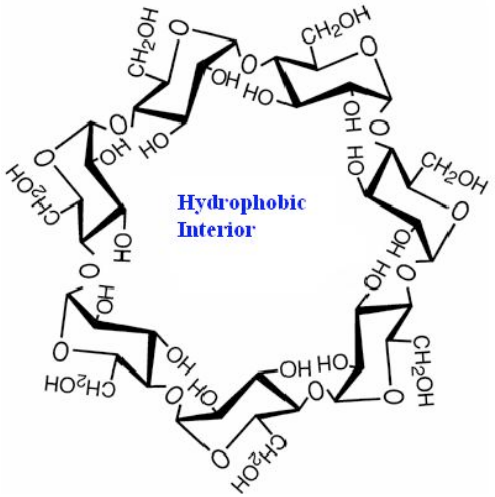
Hammerhead ribozyme

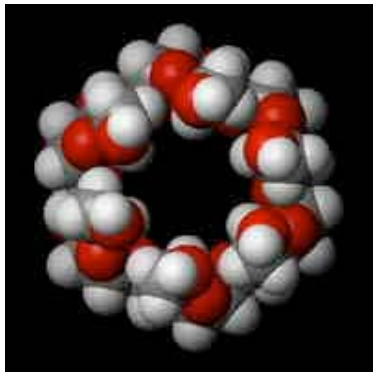
Cyclodextrins act as artificial enzymes





Cyclodextrin: cyclic oligosaccharide

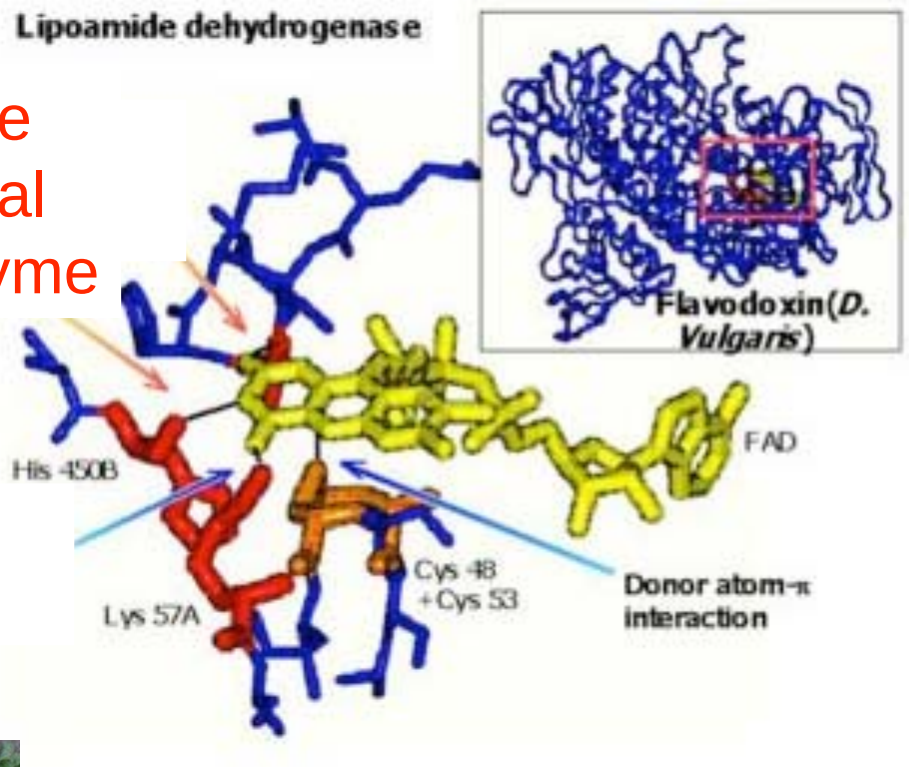




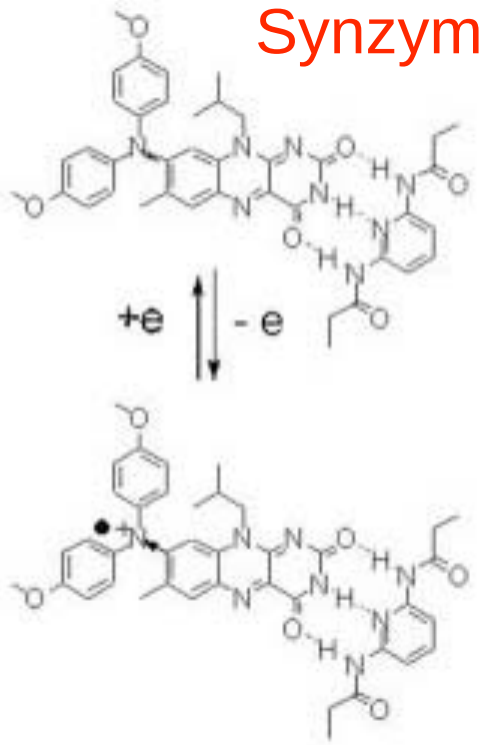
Ronald Breslow
Department of Chemistry
Columbia University

Enzyme mimetics - **Synzymes** : Flavin-functionalized macromolecular and nanoparticle based systems capable of replicating the structural and catalytic properties of natural flavoenzymes.

Active site of a typical flavoenzyme



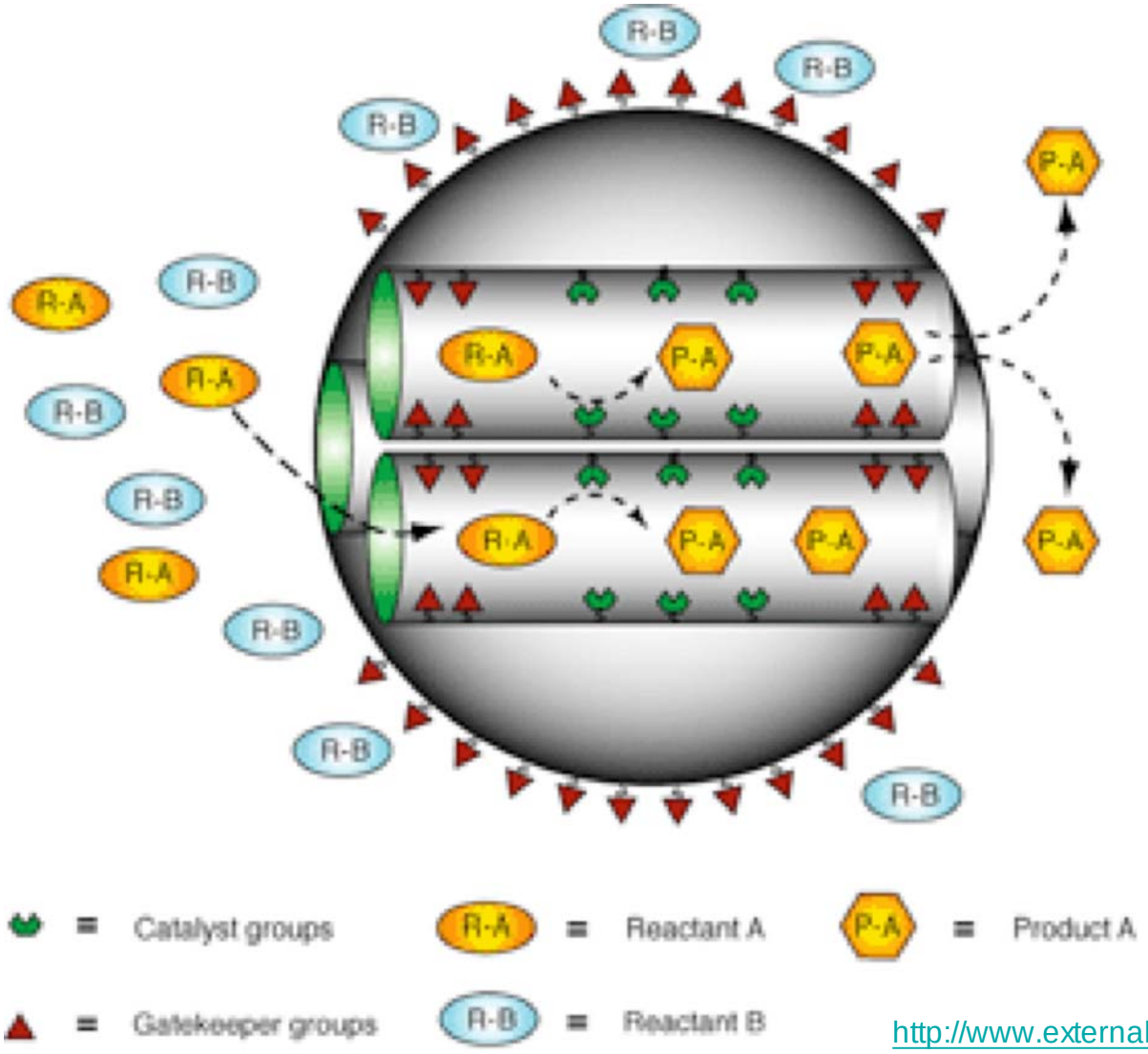
synthetic model – Synzyme



Graeme Cooke
Dept of Chemistry
Univ of Glasgow, Scotland

www.chem.gla.ac.uk/staff/graemec/

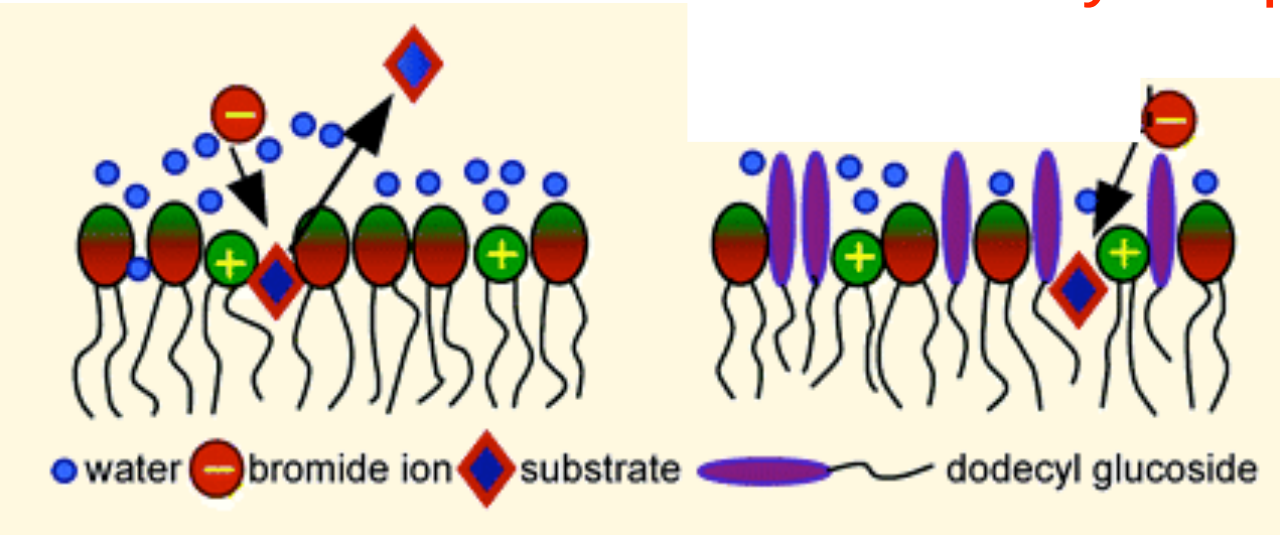
Enzyme mimetics: Multifunctionalized mesoporous silica nanoparticles as 3-D scaffolds that mimic the underlying design principle of enzyme active sites.



Victor Shang-Yi Lin
Ames Laboratory
Iowa State University

http://www.external.ameslab.gov/pbchem/PI%20info/lin.htm

Membrane mimetic chemistry – Lipid catalysis



Vesicular Catalysis of an SN2 Reaction.
Jaap Klijn Jan Engberts
Langmuir; 2005; 21(22) pp 9809 - 9817;

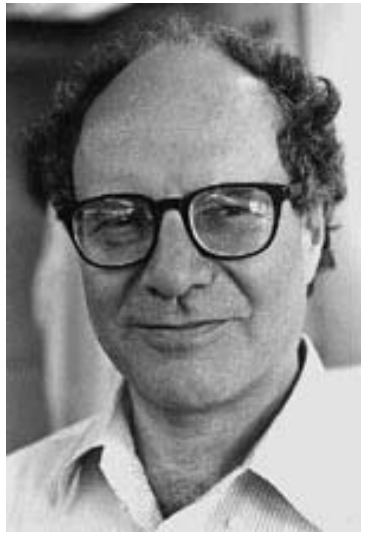
Janos H. Fendler
Dept of Chemistry
Clarkson University,
Potsdam, New York

Catalysis in Micellar and Macromolecular Systems J. H. Fendler and E. J. Fendler, Academic Press, 1975

Zepik, H.H., Maurel, M.-C. & Deamer, D.W. (2004). Lipid catalysis of oligomerization of amino thioacids and thioesters
International Journal of Astrobiology, Supplement 1 (March): 105.

"RNA World" was coined by Walter Gilbert in 1986 in a Nature commentary on the then recent observations of the catalytic properties of various RNAs.

1980 Nobel Laureate in Chemistry for his contributions concerning the determination of base sequences in nucleic acids.

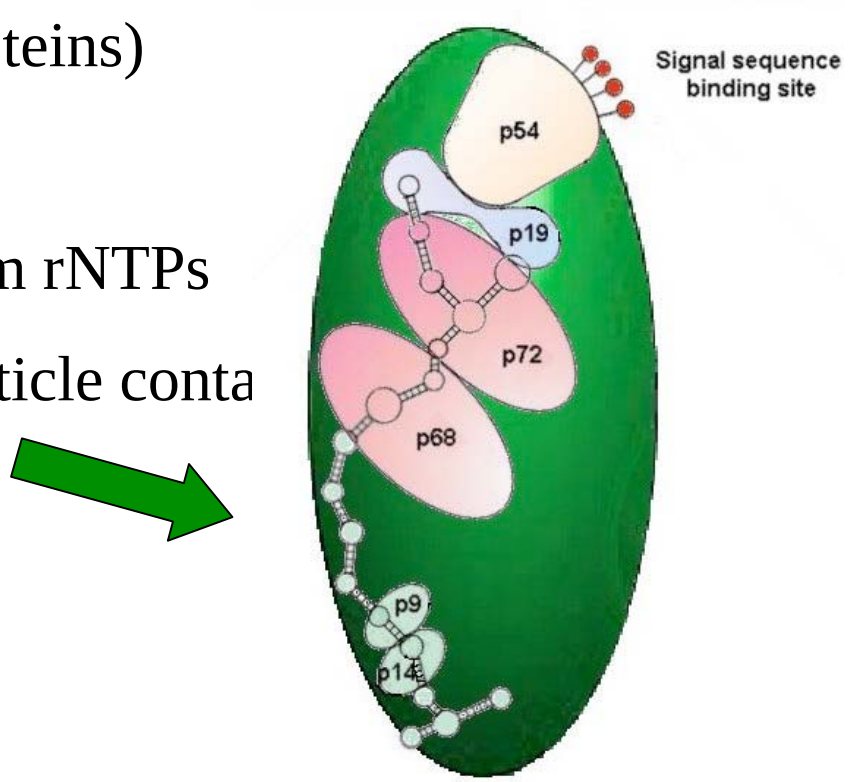


Good review: Michael Yarus, Boundaries for an RNA world
Curr Opin Chem Biol 3:260-267 (1999).

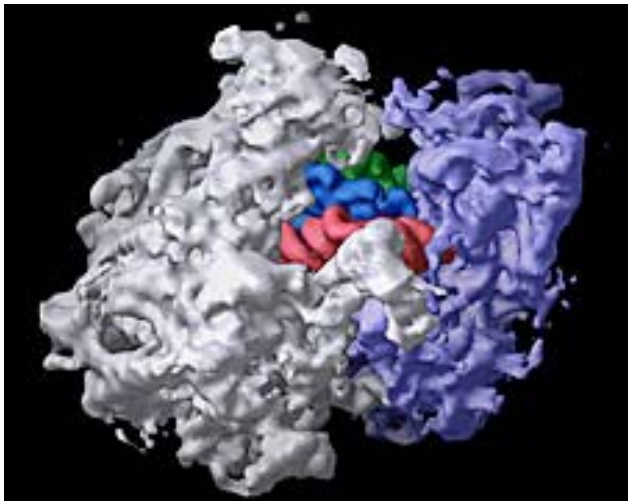
Evidence – key roles of RNA and ribonucleotides

- ATP, NAD(P)H, CoA, nucleotide sugars
- tRNA, rRNA
- Splicing factors are snRNPs

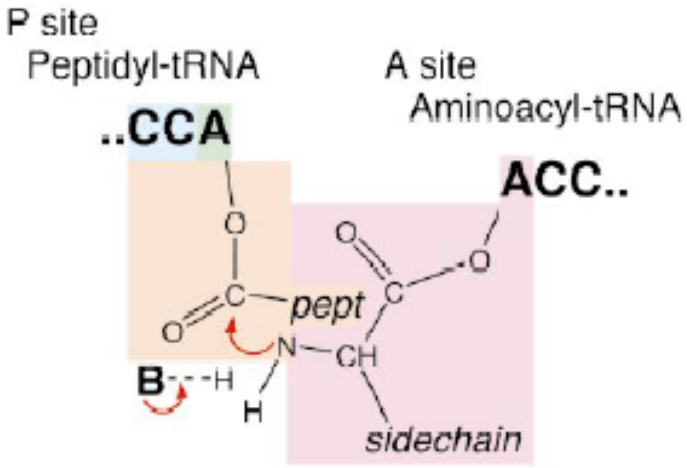
  (small nuclear ribonucleoproteins)
- RNA primer for DNA synthesis
- T made from U, dNTPs made from rNTPs
- telomerase, signal recognition particle conta

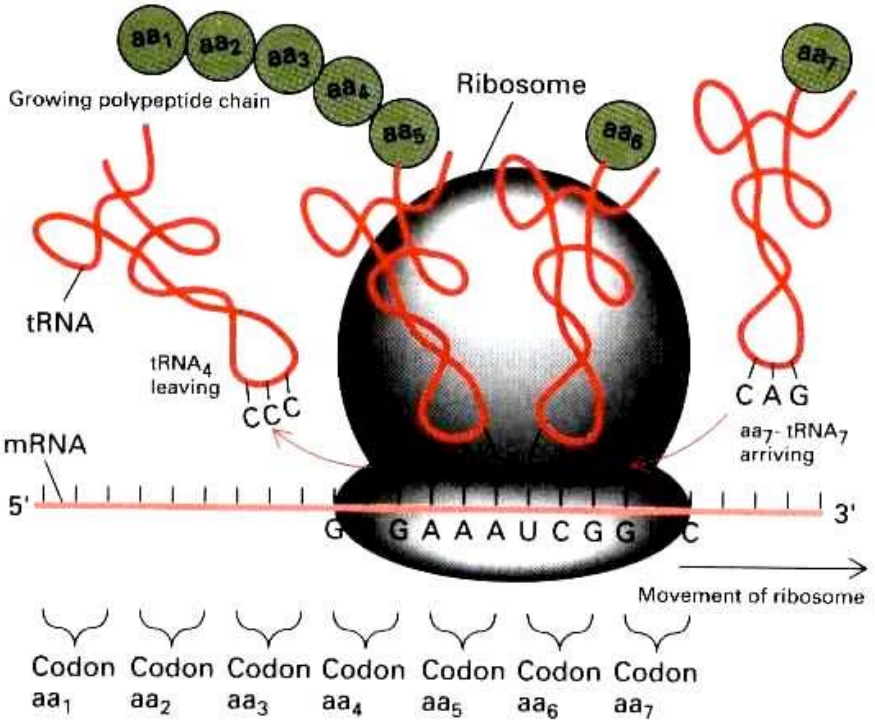


The catalyst for peptide bond formation is RNA



Ribosome



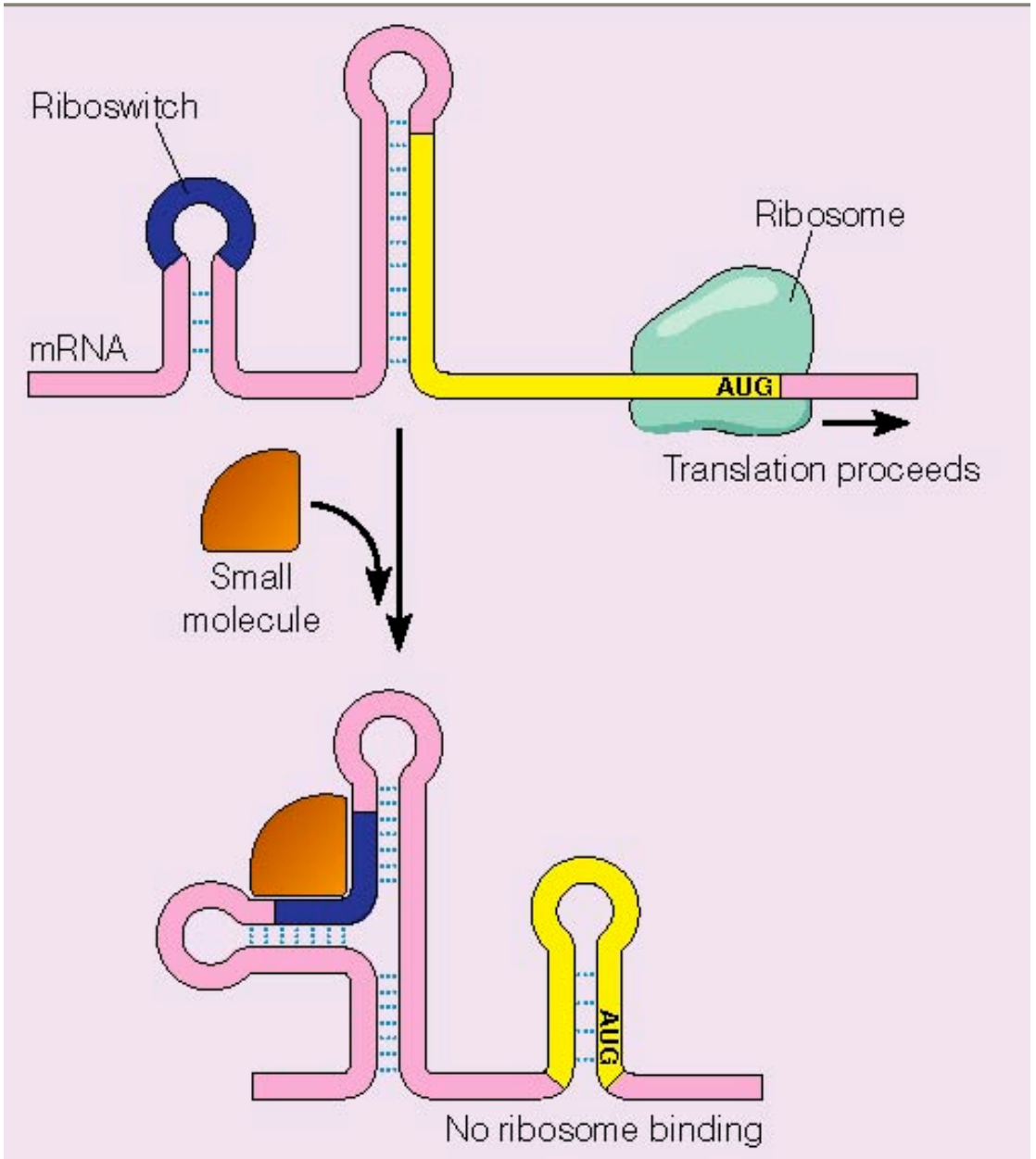


Lilley DM.

The ribosome functions as a ribozyme.

Chembiochem. 2001 Jan 8;2(1):31-5.

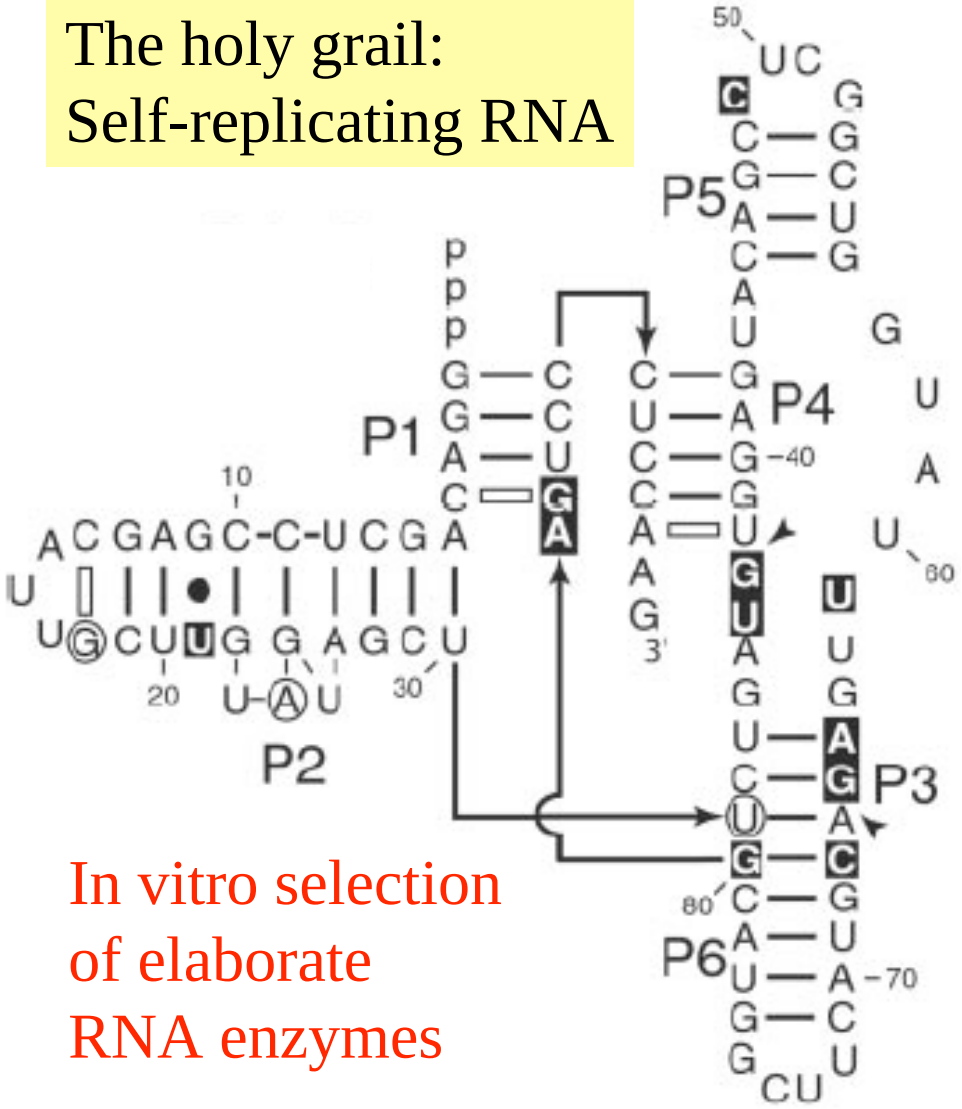
Riboswitches: another instance of present-day RNA world



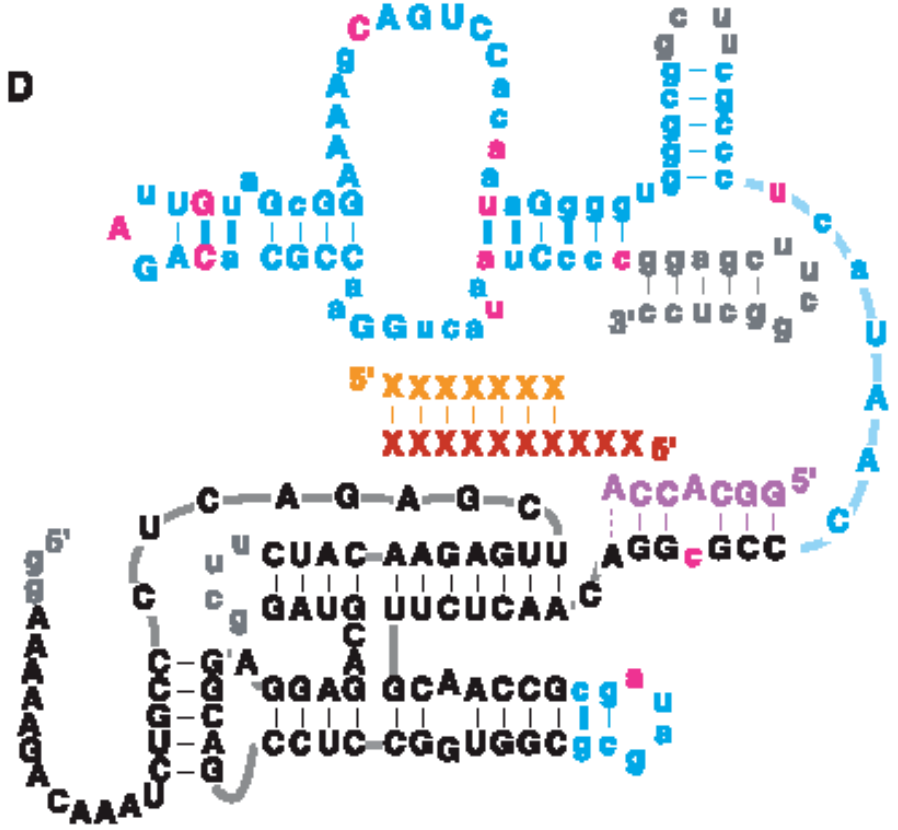
Barrick JE, Breaker RR.
The power of riboswitches.
Sci Am. 2007 Jan;296(1):50-7.

http://www.mun.ca/biology/desmid/brian/BIOL2060/BIOL2060-23/CB23.html

The holy grail: Self-replicating RNA



In vitro selection of elaborate RNA enzymes



Baskerville S, Bartel DP.
A ribozyme that ligates RNA to protein.
Proc Natl Acad Sci U S A. 2002 Jul 9;99(14):9154-9

Johnston WK, Unrau PJ, Lawrence MS
Glasner ME, Bartel DP
RNA-catalyzed RNA polymerization:
accurate and general RNA-templated
primer extension.
Science. 2001 May 18;292(5520):1319-25.

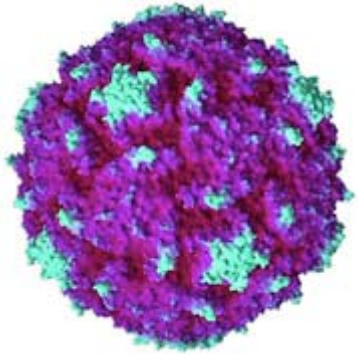
1967 Sol Spiegelman demonstrates the replication and evolution of RNA molecules in the test tube.

- Q-beta is a bacteriophage that reproduces in *E. coli*. Bacteria

- Its RNA genome contains only four genes, coding for three structural proteins and for an enzyme that replicates RNA.

- Sol Spiegelman and colleagues used this RNA replicase to study the evolution of RNA in test tubes.

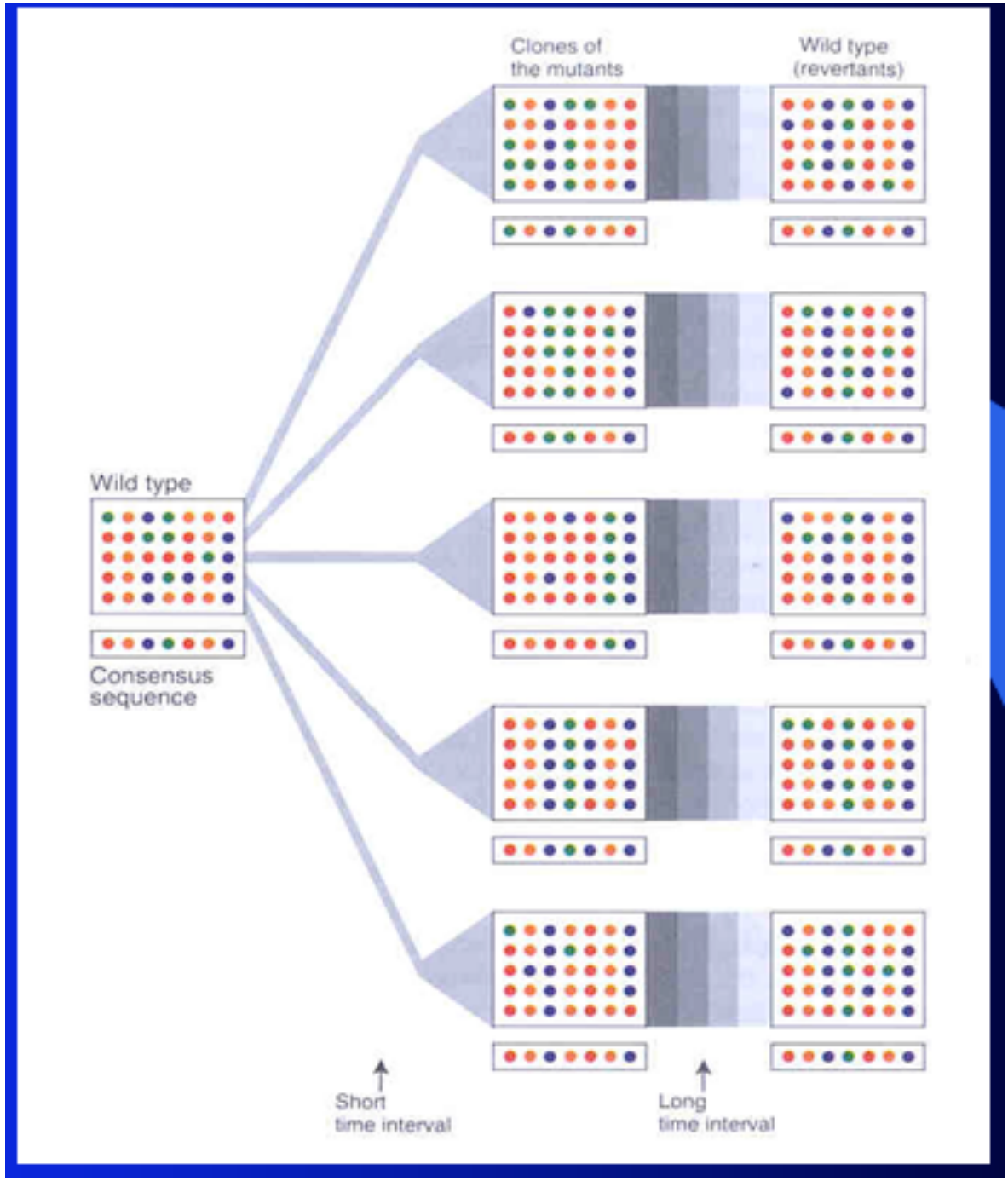
Beware: these experiments do not mimic the origin of life since the replicase is the complex result of evolution!



Pace NR, and Spiegelman S,
In vitro synthesis of an infectious mutant RNA with a normal RNA replicase.
Science. 1966 Jul 1;153(731):64-7.

Manfred Eigen: Quasi-species formed in the test-tube

- Wild type: *average* sequence
- Species is a distribution



Problems with the RNA world scenario

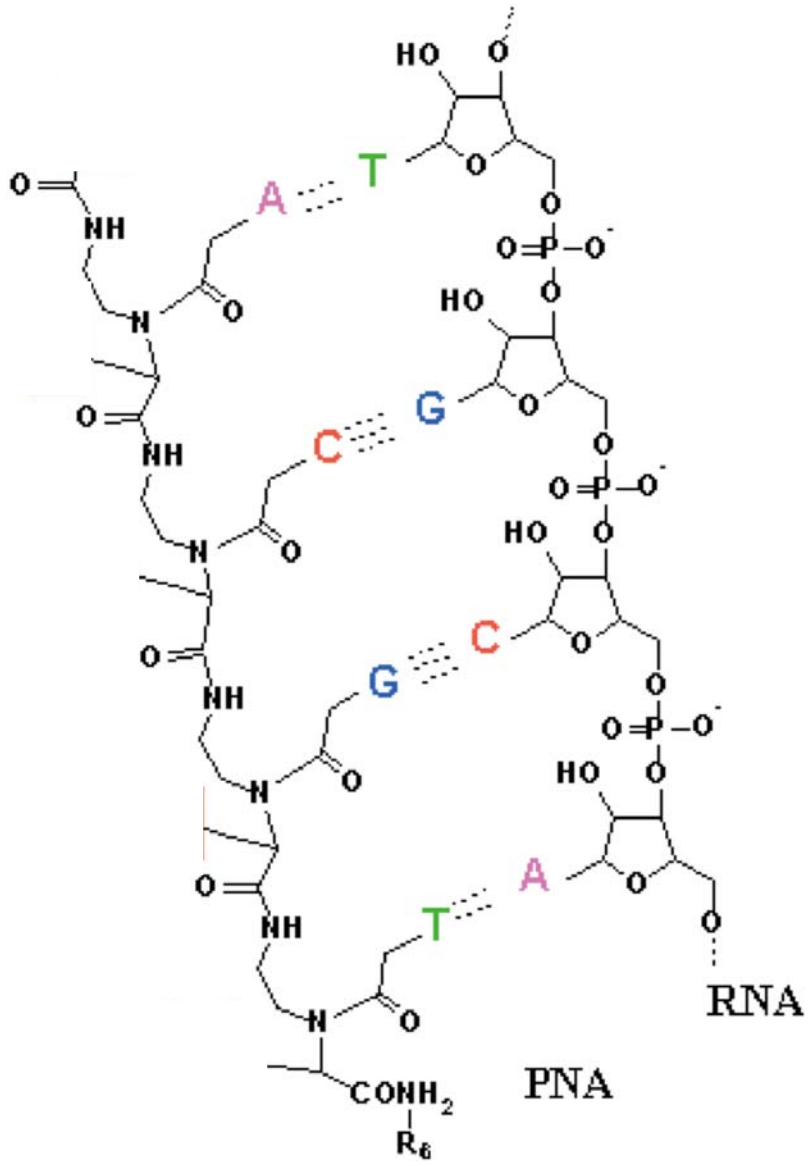
1) No “school chemistry” – the primordial soup was random
2) RNA is hard to make and chemically fragile
3) RNA monomers are difficult to synthesize abiotically
4) RNA (and other polymers) are unfavorable
5) RNA’s range of catalytic activities is narrow
6) Hard to see path from naked RNA to protocells

…chemists are increasingly considering the possibility that RNA was not the first self replicating molecule

Orgel, Leslie E. "The Origin of Life on the Earth"
Scientific American, October 1994: 77-83.

A partial solution: Peptide Nucleic Acid (PNA).

RNA bases with
a more readily forming,
more stable
peptide beckbone.



Nielsen PE.
Peptide nucleic acid (PNA): a m
the primordial genetic material?
Orig Life Evol Biosph. 1993 Dec;23(5-6):323-7.

7) Catalysis by proteins only or not?

Reconsider proteins…

There is no doubt that proteins, which are more easily formed, were first on the scene".

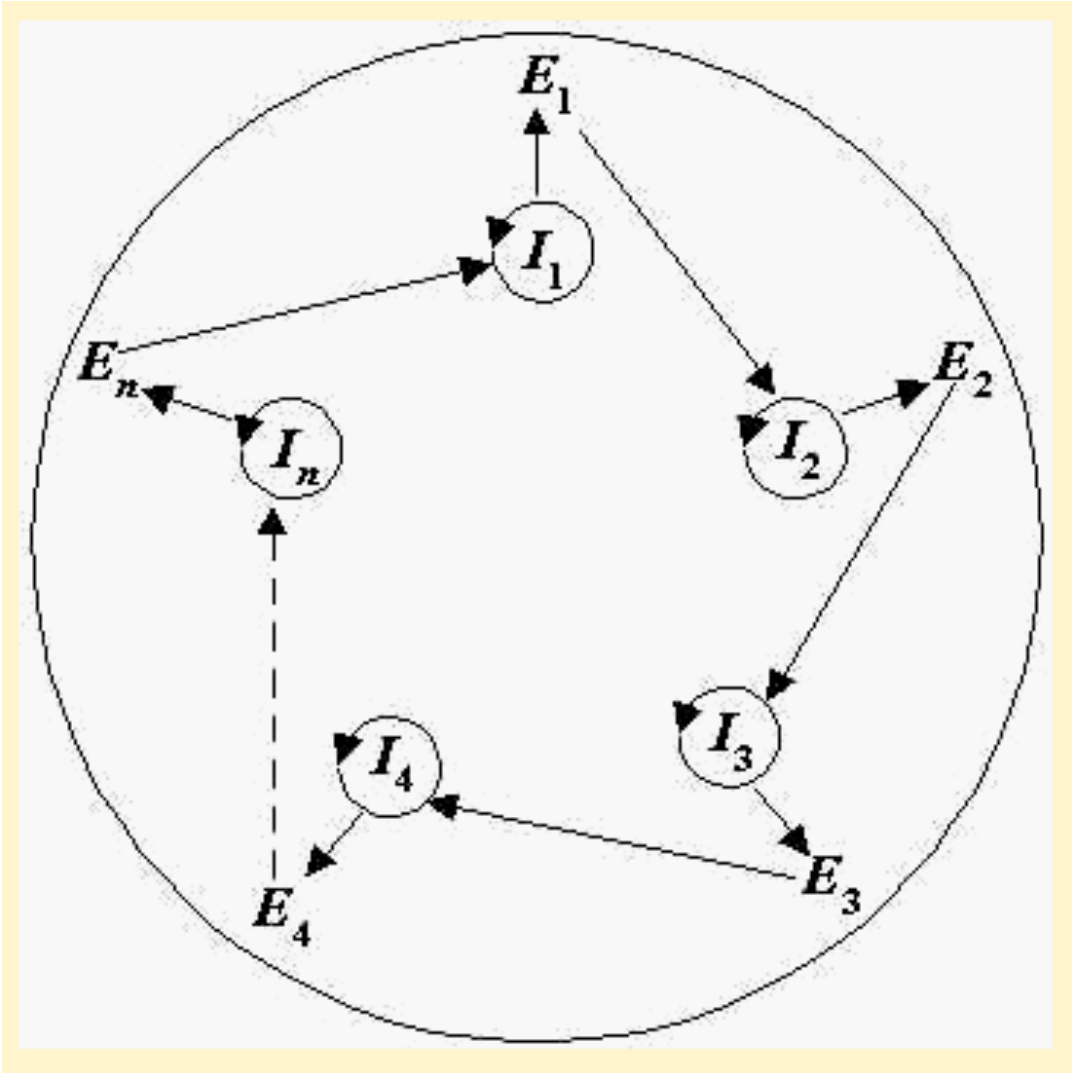
Of course, these first proteins must be much shorter than any used in life today, because of the sheer unlikelihood of forming useful long ones out of a soup of amino acids.
Manfred Eigen*

Solution: a model that includes both RNA and protein –
The Hypercycle

* Steps Towards Life: A Perspective on Evolution,
Oxford University Press, 1992. (German edition, 1987). p 31.

What is a hypercycle?

The answer of Google Image search

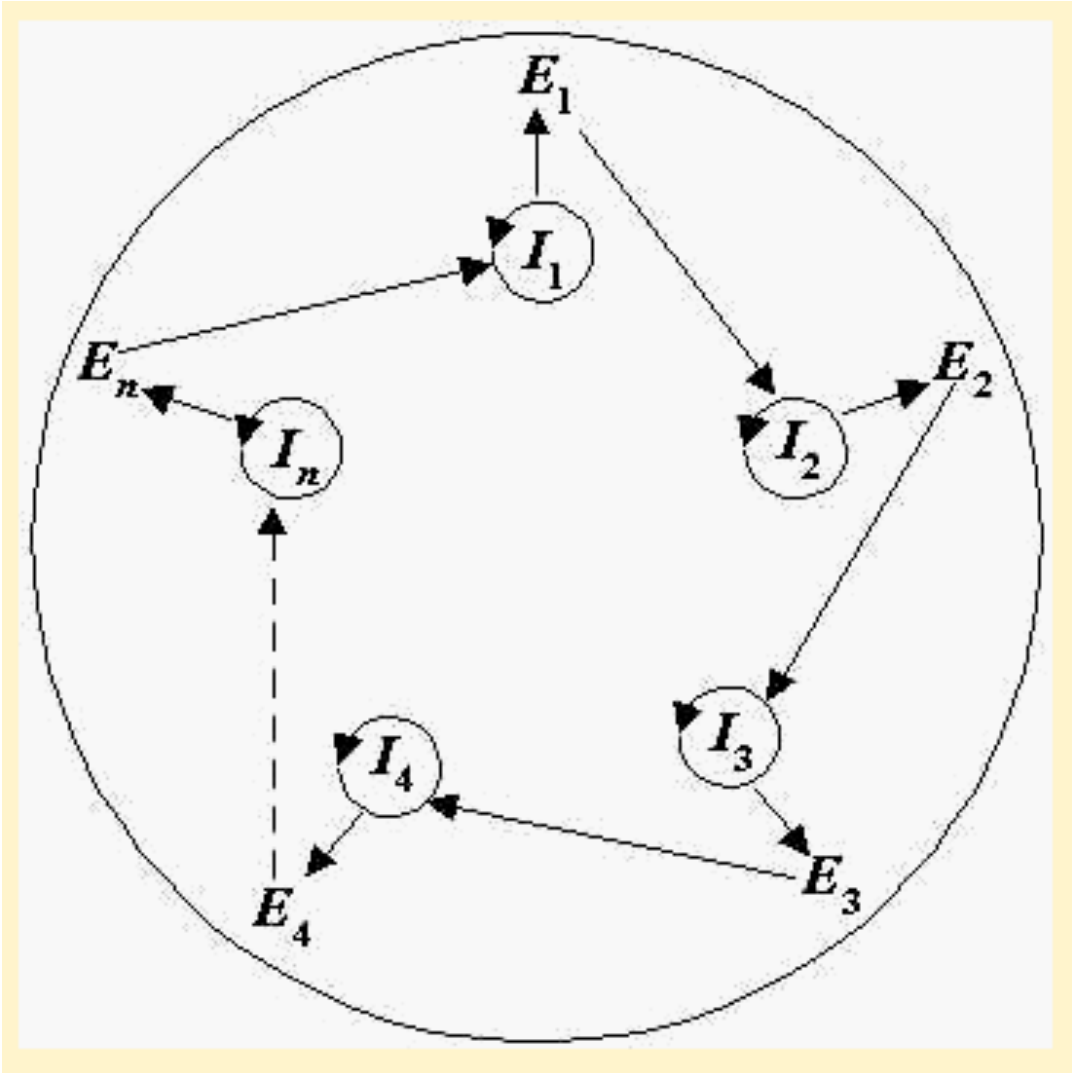


Manfred Eigen's Real Hypercycle

I_x =
Self replicating polynucleotide

E_x =
Coded protein catalyst

Eigen M, Biebricher CK, Gebinoga M, Gardiner WC.
The hypercycle. Coupling of RNA and protein biosynthesis in the infection cycle of an RNA bacteriophage.
Biochemistry. 1991 Nov 19;30(46):11005-18.



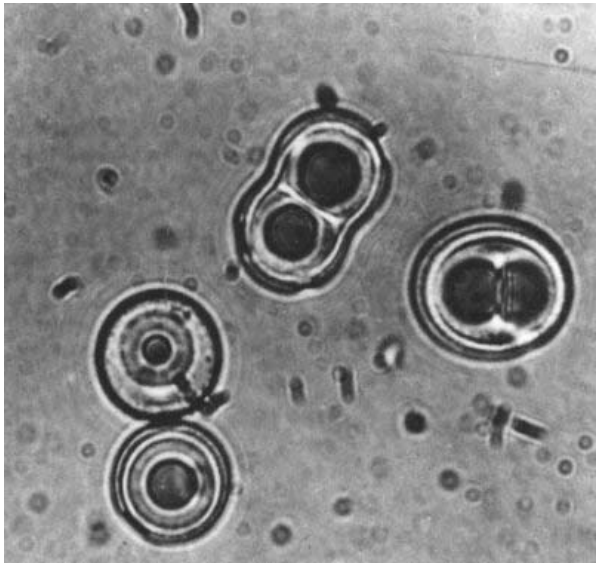
Hypercycle

I_x =
Self replicating polynucleotide

E_x =
Coded protein catalyst

But where would proteins come from?

Experimental “Proteins first" scenario



Proteinoids are protein-like molecules formed inorganically from amino acids at high temperature (180°C) and high pressure.

Proteinoids include branching as well as straight chain polypeptides (problem?).

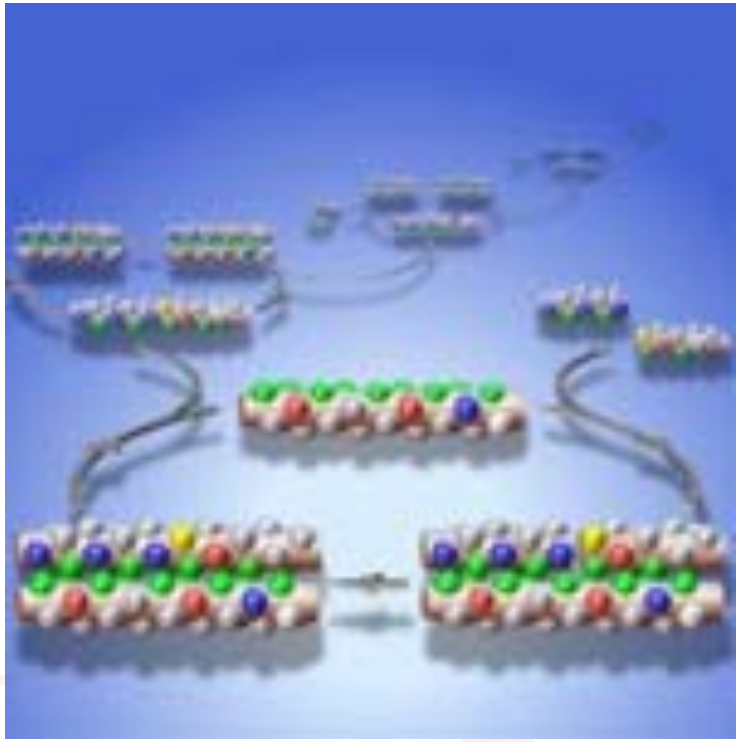
Proteinoids were found in lava and cinders from volcanic vents.

Proteinoids form microspheres, due to the fact that some of the amino acids are more hydrophobic

Proteinoid particles exhibit many of the characteristics of cells - a film-like outer wall, osmotic swelling, budding and fission.

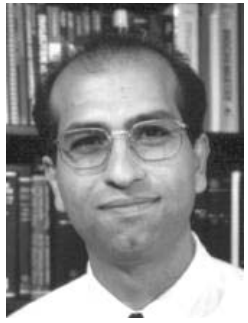
Sidney W. Fox, Synthesis of life in the lab? Defining a protoliving system Q Rev Biol. 1991 Jun;66(2):181-5.

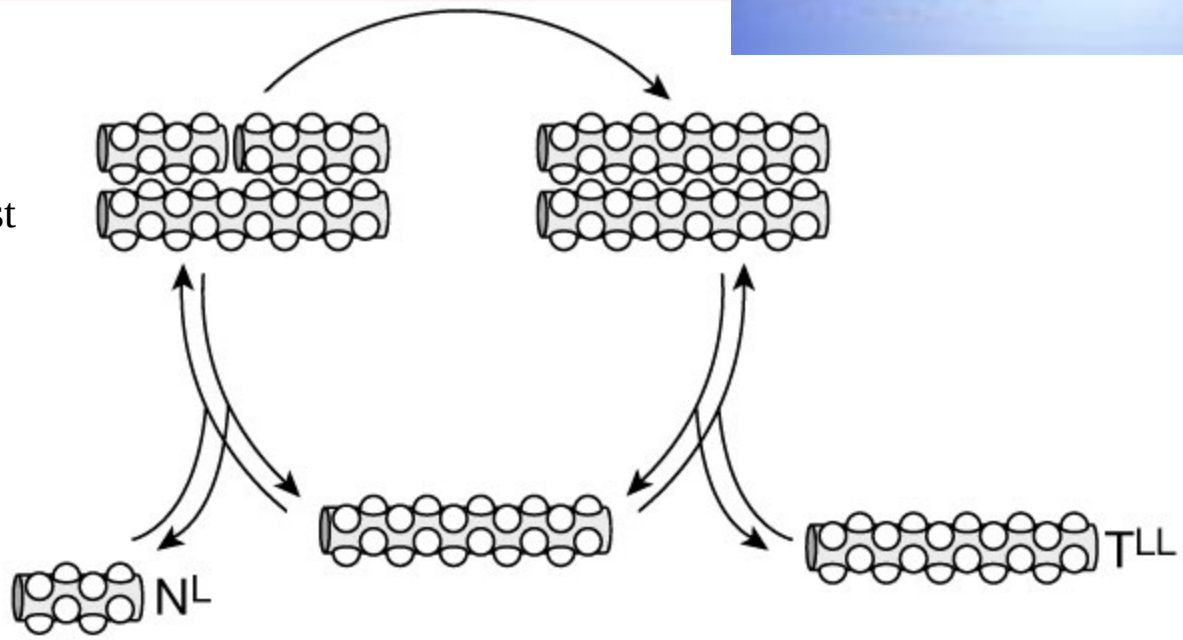
Replicating peptides

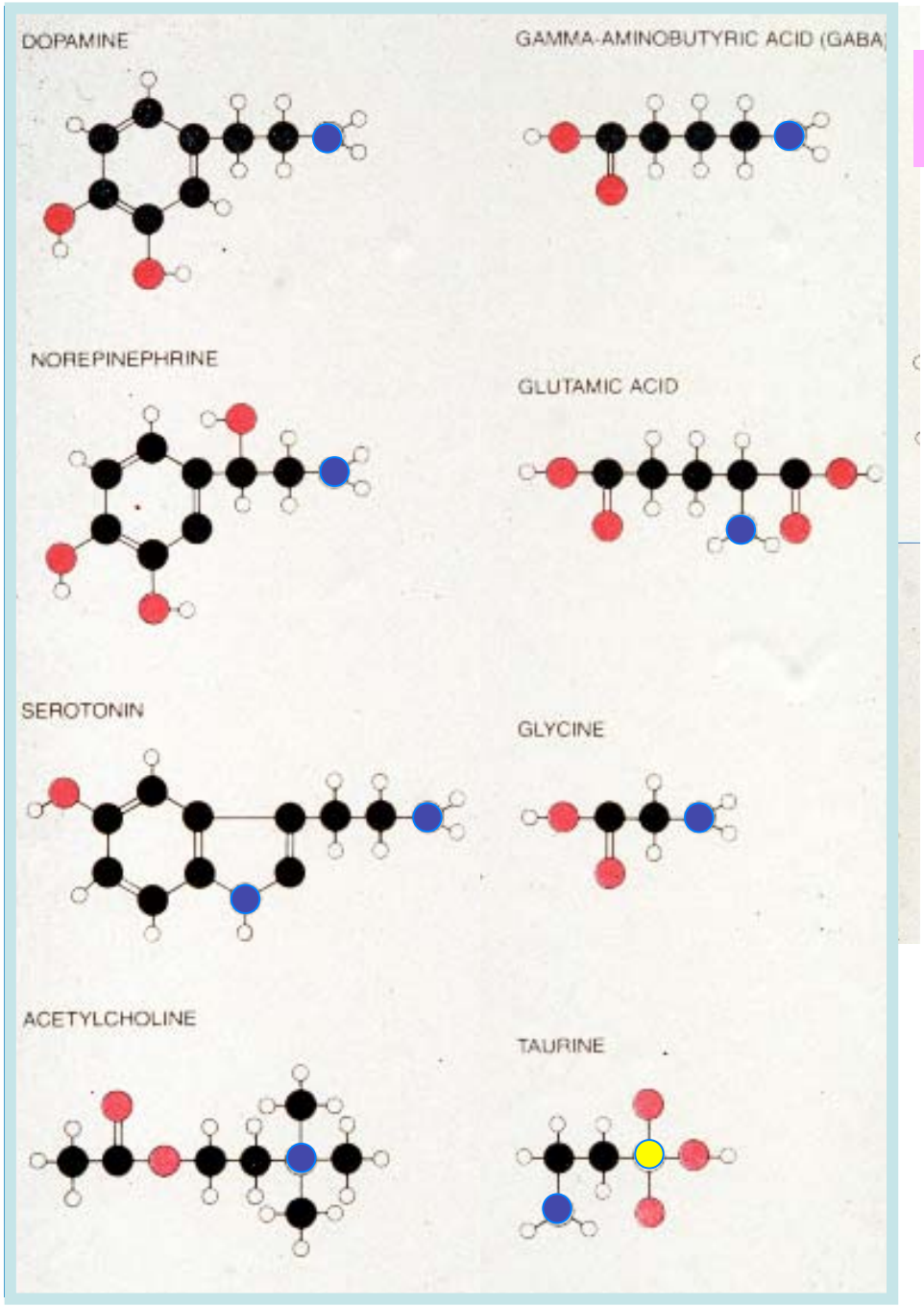


Severin K, Lee DH, Kennan AJ, Ghadiri MR.
A synthetic peptide ligase.
Nature. 16;389:706-9 (1993)

M. Reza Ghadiri
Dept of Chemistry
Scripps Research Inst

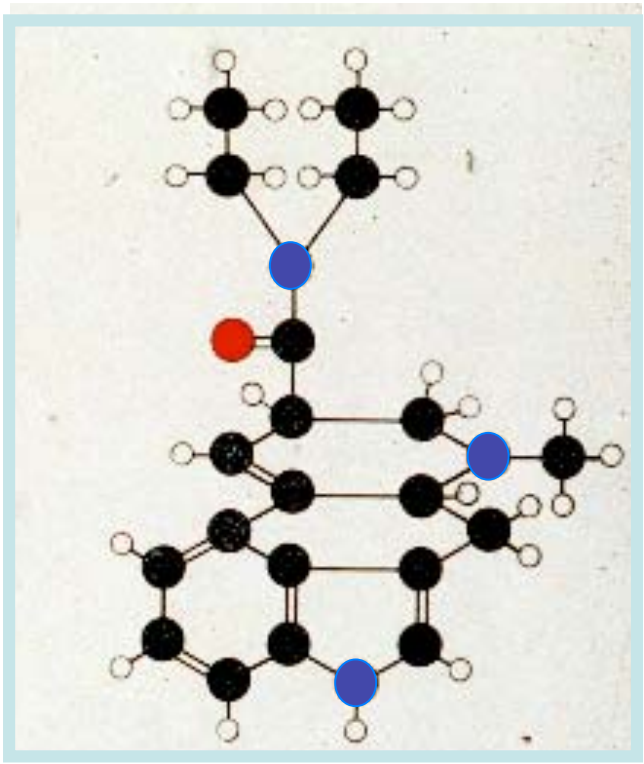






5) Organics trivial or not?

The Origin of Life
is a problem
in organic chemistry!



Darwin on the origin of life

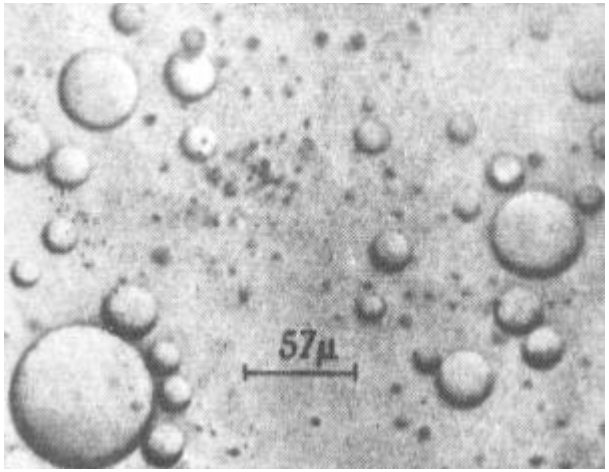
It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh! what a big if!) we would conceive **in some warm little pond**, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured or absorbed, which would not have been the case before living creatures were formed

Alexander Oparin

"Origin of Life" 1924

Prebiotic "Soup"

Colloidal coacervates



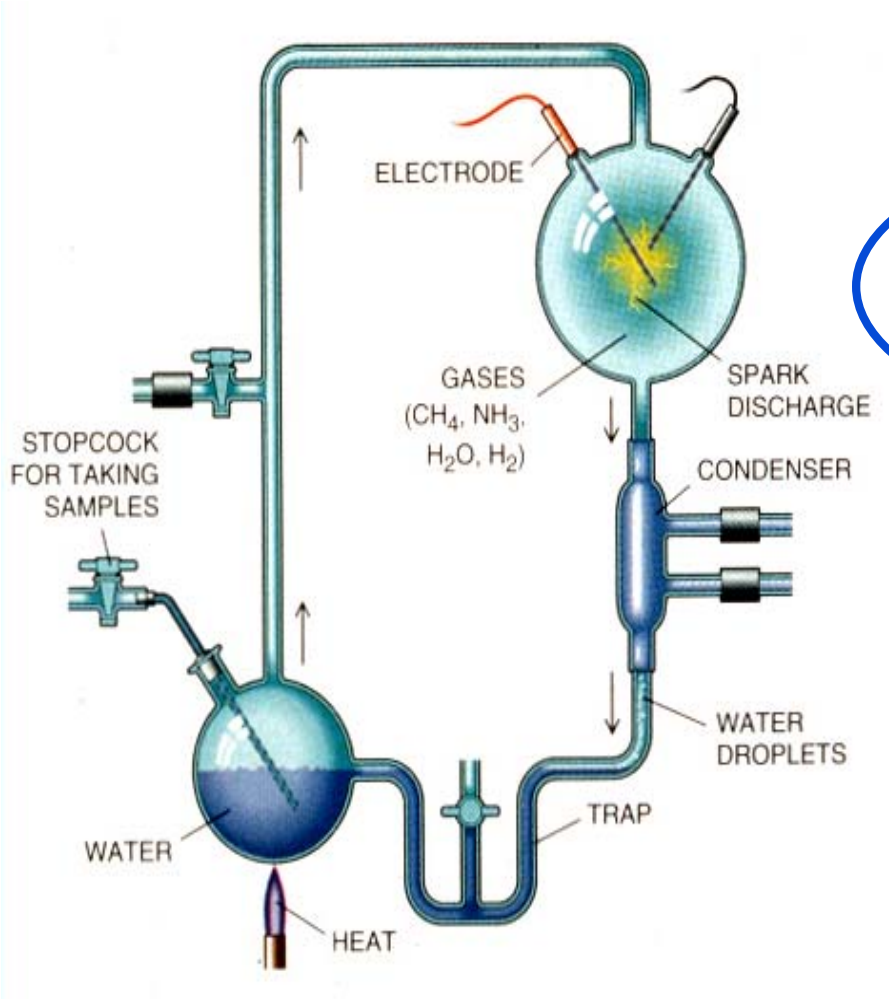
"Metabolism first", not "genome first"

Replication without DNA

Miller SL, Schopf JW, Lazcano A.
Oparin's "Origin of Life": sixty years later.
J Mol Evol. 1997 Apr;44(4):351-3.

Where do organics such as amino acids come from?

The Miller-Urey experiment, 1953



Atmospheric gases

H_2 NH_3 H_2O HCN

H_2CO CH_4 H_2S P_2O_5

Glycine

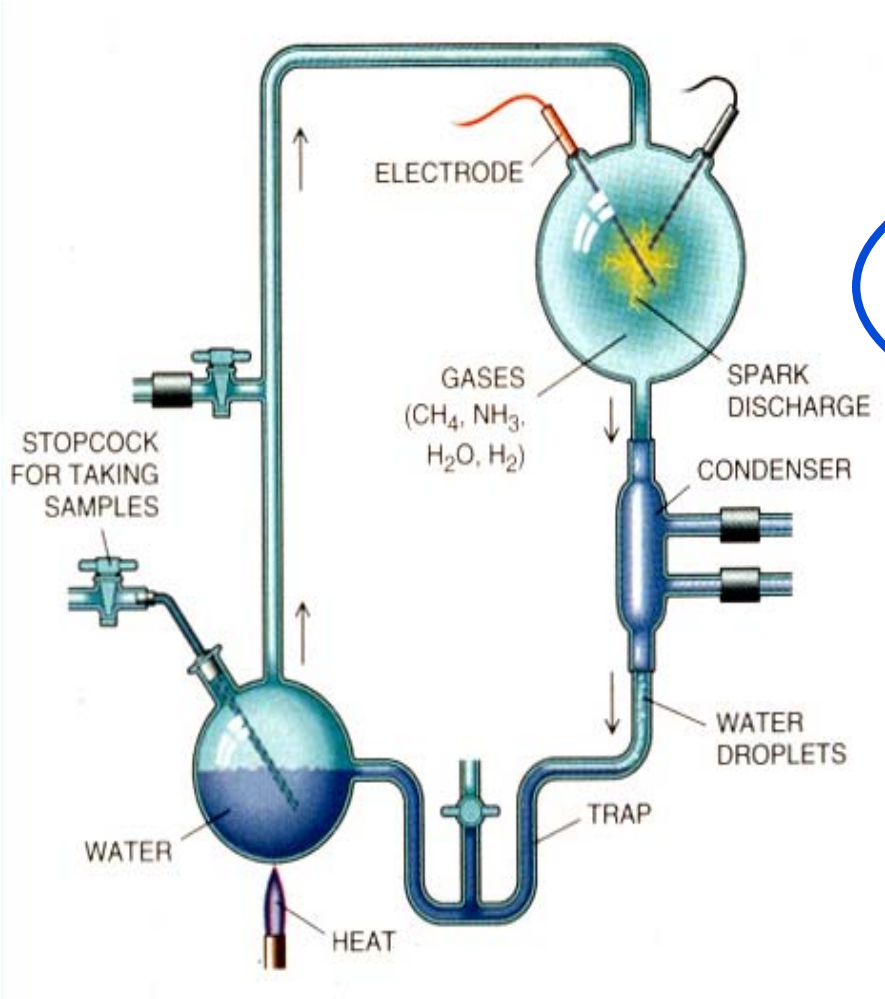
Alanine Serine

Oleic acid?

Guanine?

Ring D, Wolman Y, Friedmann N, Miller SL. Prebiotic synthesis of hydrophobic and protein amino acids Proc Natl Acad Sci U S A. 1972 Mar;69(3):765-8

Where do organics such as amino acids come from?



The Miller-Urey experiment, 1953

Atmospheric gases

H_2 NH_3 H_2O HCN

H_2CO CH_4 H_2S P_2O_5

Glycine

Alanine Serine

Oleic acid?

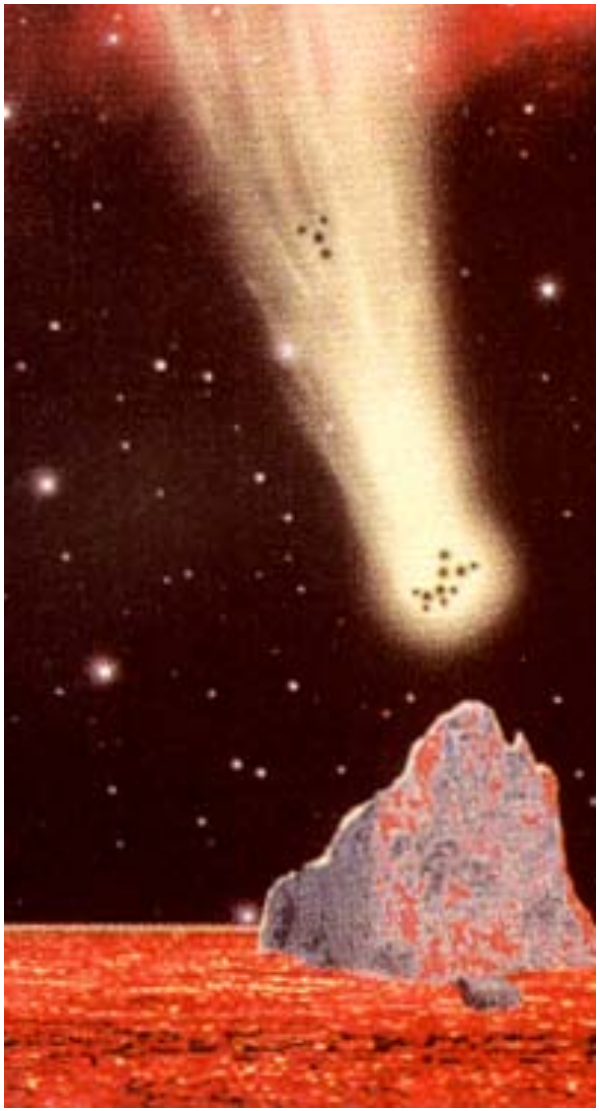
Guanine?

Keyword: “abiogenesis”

But organic compounds
can also come from space
(This is NOT panspermia!)

The Murchison chondritic
(carbonaceous) meteorite

Fragments fell on September 28th 1969
around the small town of **Murchison,**
near Melbourne, Australia



Comets and interstellar
dust particles

The next step:
Understand how monomers connect to form polymers

Ribose

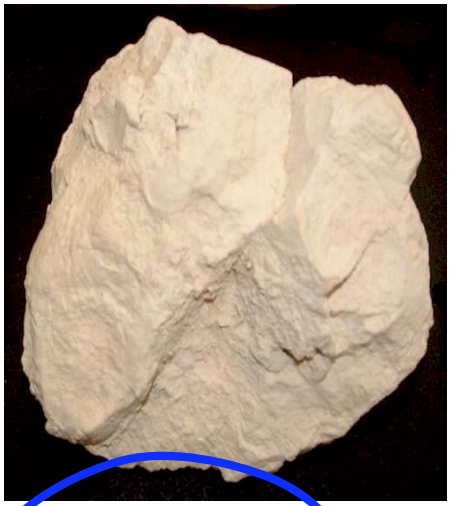
Guanine

Serine

ATP

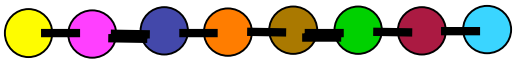
Oleic acid

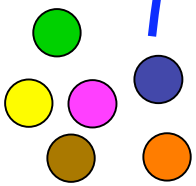
Methionine

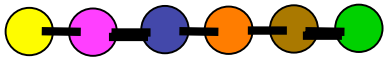


Mineral catalysis

Covalent polymers:
Proteins, RNA, polysaccharides



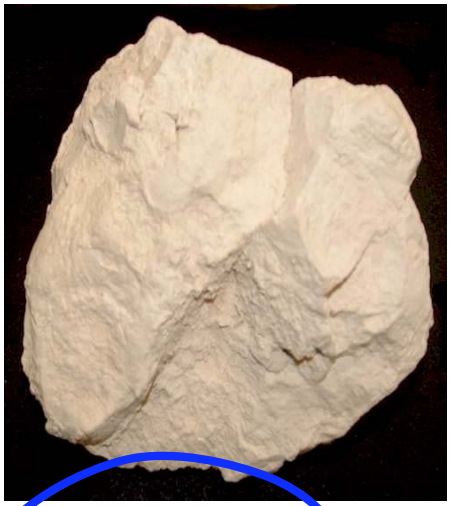




8) Large molecules or small?

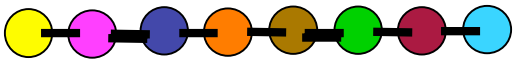
Understand how monomers connect to form polymers

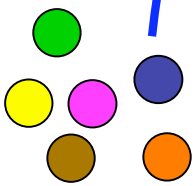
Ribose
Guanine
Serine
ATP
Oleic acid
Methionine

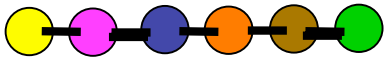


Mineral catalysis

Covalent polymers:
Proteins, RNA, polysaccharides







What is the real question?

1) 3.8 or 3.5 billion years ago?
2) Here or elsewhere?
3) Probable or improbable?
4) Organic or inorganic?
5) Organics trivial or not?
6) Today's chemistry or not?
7) Catalysis by proteins only or not?
8) Large molecules or small?
9) Sequential or compositional information?
10) Single molecules or networks?
11) Understandable *in silico* or not?

Novel experimental approaches to Life's origin

1) Microanalysis of individual entities
   in very large scale/duration experiments
   (cubic kilometers and decades!)

2) Galactic travel

3) Large scale chemistry-realistic
   computer simulations.