Evolution Lecture: Initial Remarks

Nice books to start reading:
- Iris Fry: The Emergence of Life on Earth
- Cairns-Smith: Seven Clues to the Origin of Life
- E.G. Nisbet: Living Earth, a short history of life and its home
- Matt Ridley: The Origins of Virtue: Human Instincts and the Evolution of Cooperation
- Michael Yarus: Life from an RNA world.

Good text-books:
- Geoffrey Zubay: Origins of Life on the Earth and in the Cosmos
- Gesteland et.al: The RNA World, 2nd Edition
- Cindy Lee van Dover: The Ecology of Deep-Sea Hydrothermal Vents

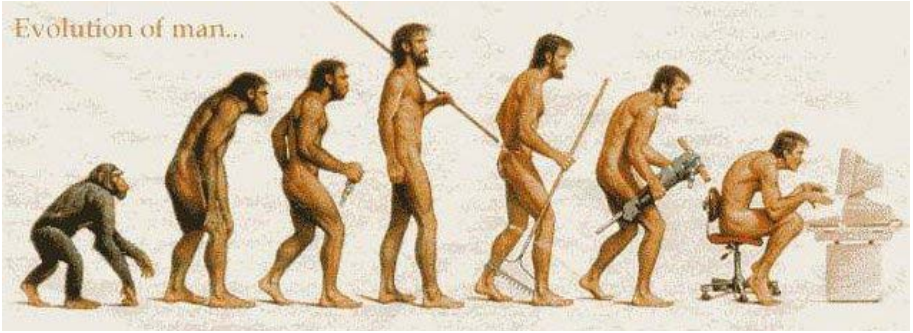
German books:
- Evolution: Carsten Bresch, bei Schattauer
- Ursprung des Lebens, Sven P. Thoms
- Glück gehabt, Olaf Fritsche

eware: many bad books on this area of research are floating around!

However many of them are quite expensive. (You might want to check out the used books database from www.abebooks.de to order them used. This is also a good source for books which are out of print.)

Websites:

Michael Russells Website:
http://www.gla.ac.uk/projects/originoflife/
ISSOL-Website:
http://www.issol.org/



To bring:
Clay, Pyrite, convective PCR cell

Nothing in Biology Makes Sense Except in the Light of Evolution

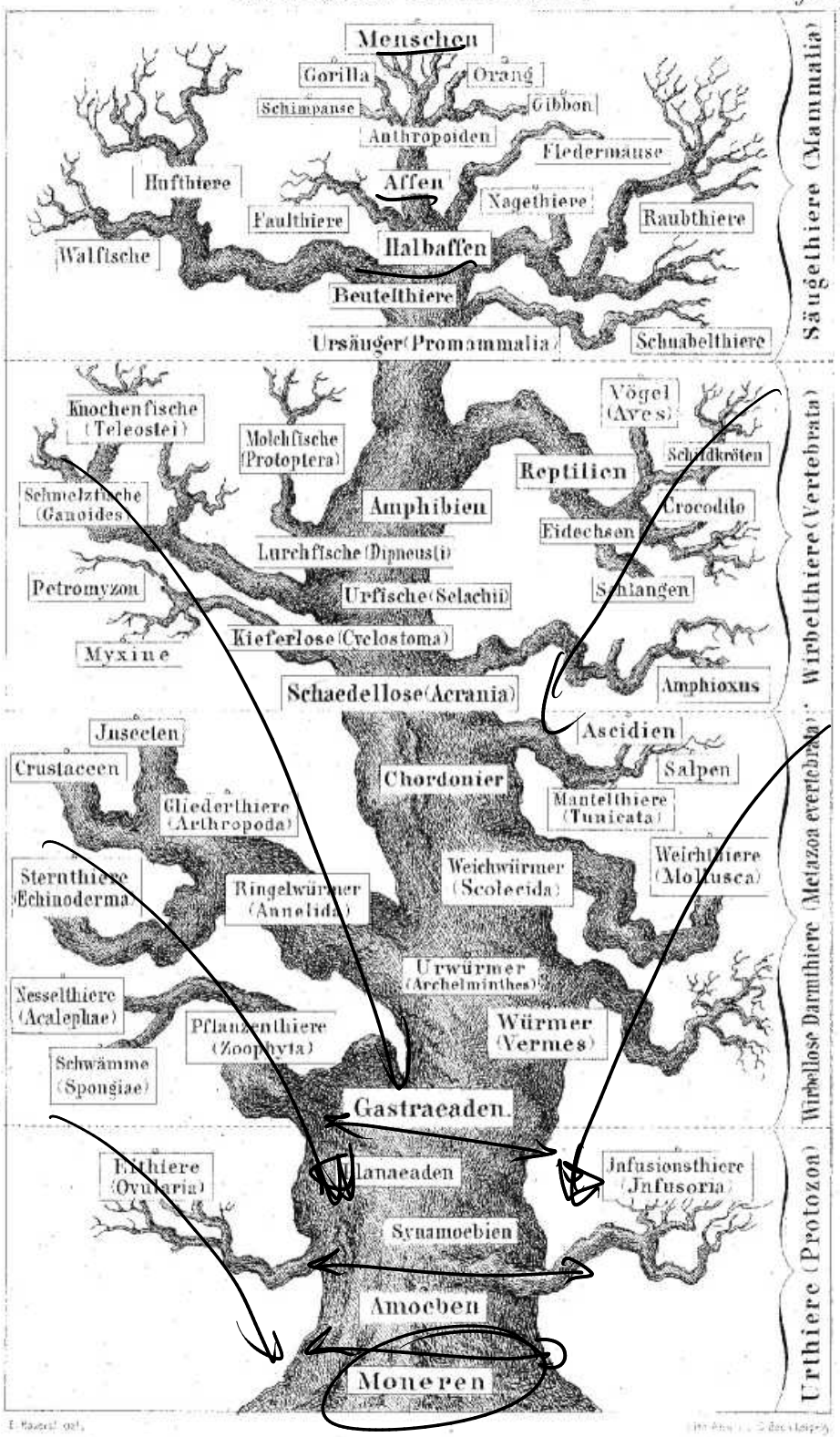
Theodosius Dobzhansky, 1964

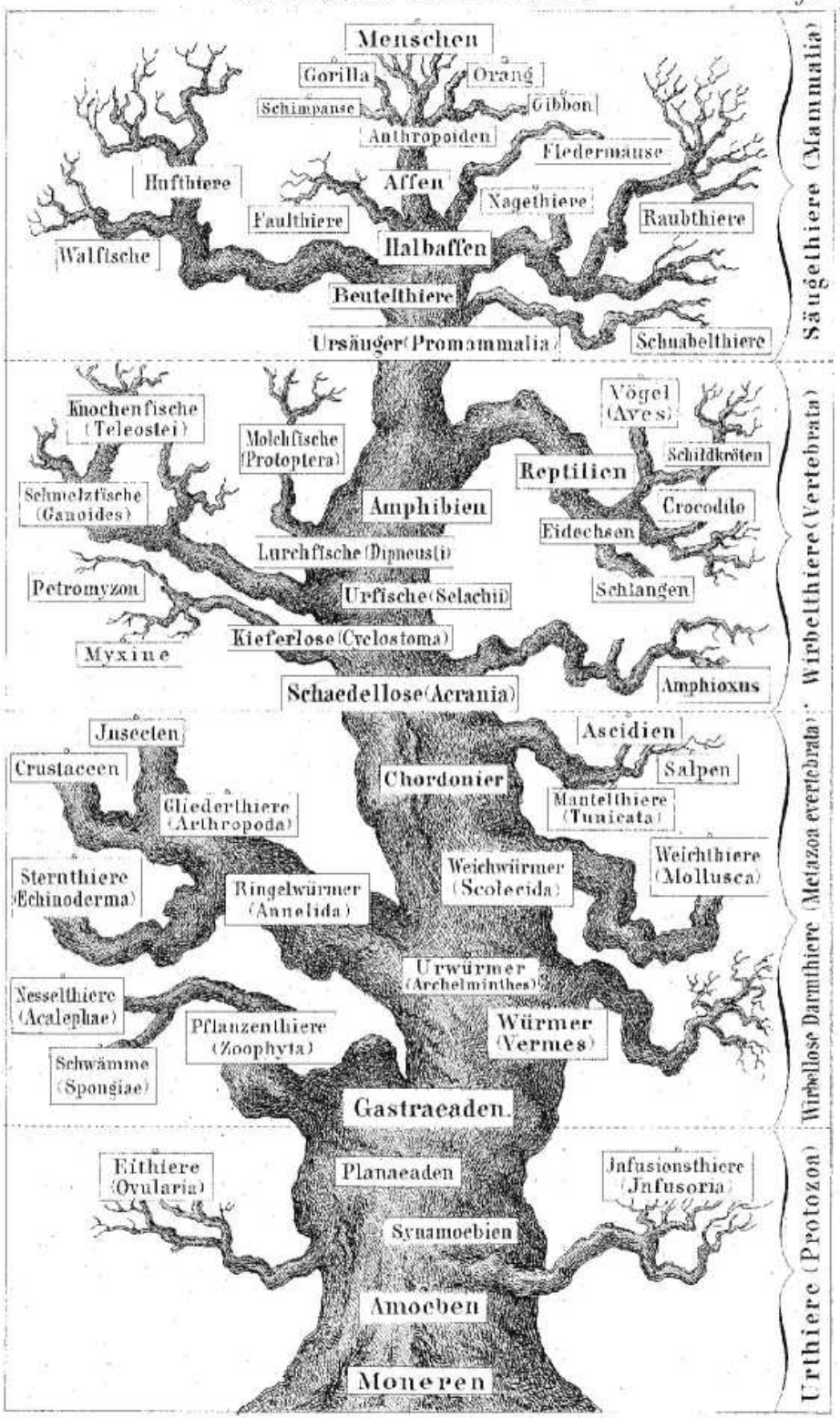
Structure

Part I: Collecting the Evidence
- Darwin and the Phylogenetic Tree
- Common Strategies of Life
- Early Evolution: Problems to Solve
- Time Window
- Chemical Evolution: Building Blocks
- Locations, Locations, Locations
- Hydrothermal: Chemistry + Archaea

Part II:
- Hydrothermal: Microfluidics
- Models of Hydrothermal Evolution
- Models of Chemical Evolution
- Self Replication + RNA World
- Later Problems: Oxygen Crisis
- Towards Grand unifying Theories
- Outlook: Game Theory

Seeing Life as Phylogenetic Tree


Stammbaum des Menschen.
Taf. XII.
Menschen
Gorilla
Orang
Schimpanse
Gibbon
Anthropoiden
Affen
Fledermäuse
Hufthiere
Nagethiere
Faulthiere
Raubthiere
Halbaffen
Walfische
Beutelthiere
Ursäuger (Promammalia)
Schnabelthiere
Säugethiere (Mammalia)
Knochenfische (Teleostei)
Molchfische (Protoptera)
Vögel (Aves)
Schildkröten
Reptilien
Schmelzfische (Ganoides)
Amphibien
Crocodile
Eidechsen
Lurchfische (Dipneusti)
Schlangen
Petromyzon
Urfische (Selachii)
Kieferlose (Cyclostoma)
Myxine
Amphioxus
Schaedellose (Acrania)
Wirbelthiere (Vertebrata)
Insecten
Ascidien
Crustaceen
Salpen
Chordonier
Mantelthiere (Tunicata)
Gliederthiere (Arthropoda)
Weichwürmer (Scolecida)
Weichthiere (Mollusca)
Stachelhäuter (Echinoderma)
Ringelwürmer (Annelida)
Urwürmer (Archelminthes)
Nesselthiere (Acalephae)
Würmer (Vermes)
Pflanzenthiere (Zoophyta)
Schwämme (Spongiae)
Wirbellose Darmthiere (Metazoa evertebrata)
Gastraeaden
Eithiere (Ovularia)
Planaeaden
Infusionsthiere (Infusoria)
Synamoebien
Amoeben
Moneren
Urthiere (Protozoa)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Ascidien
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Sternthiere (Echinoderma)
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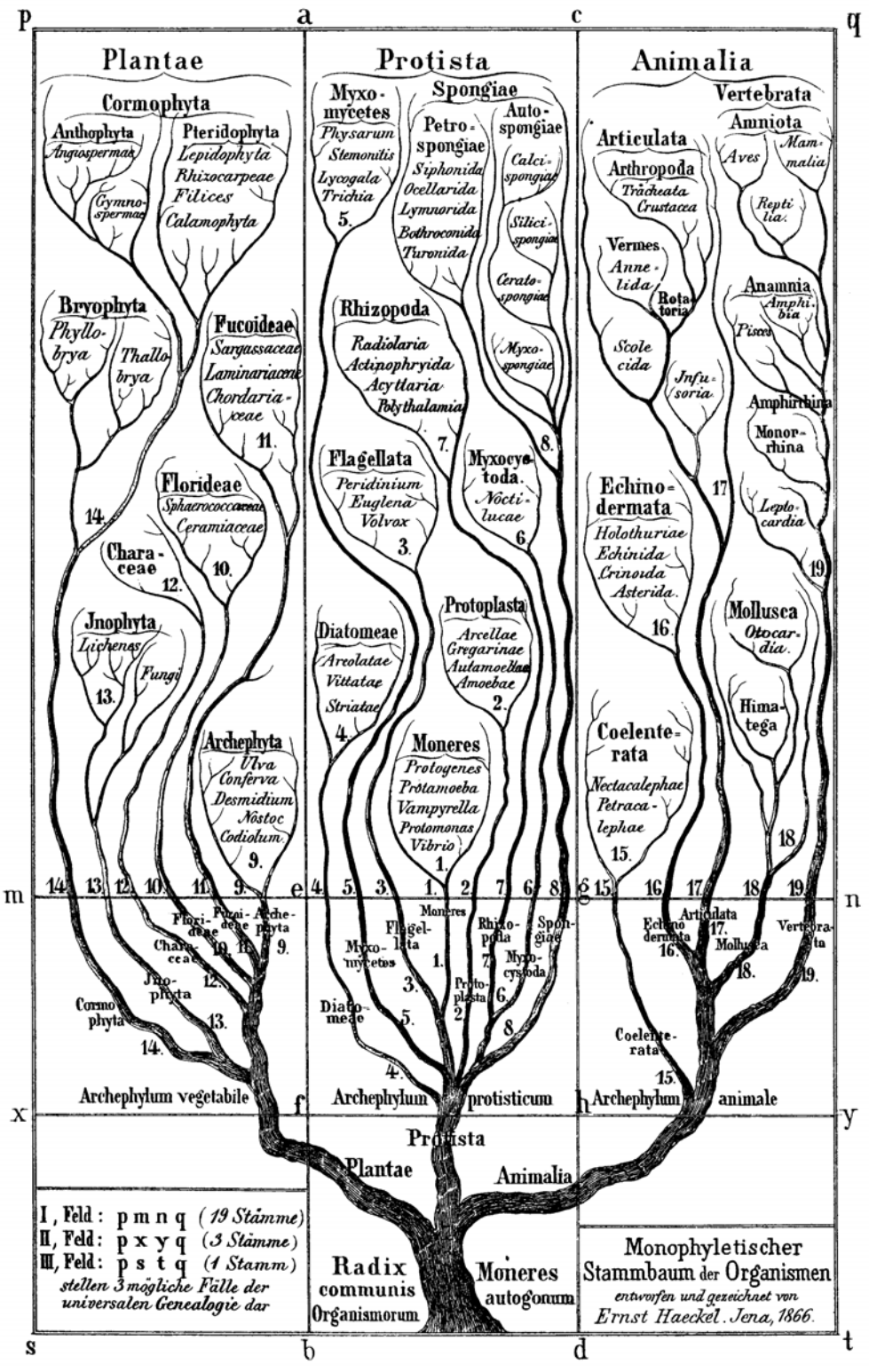
p
a
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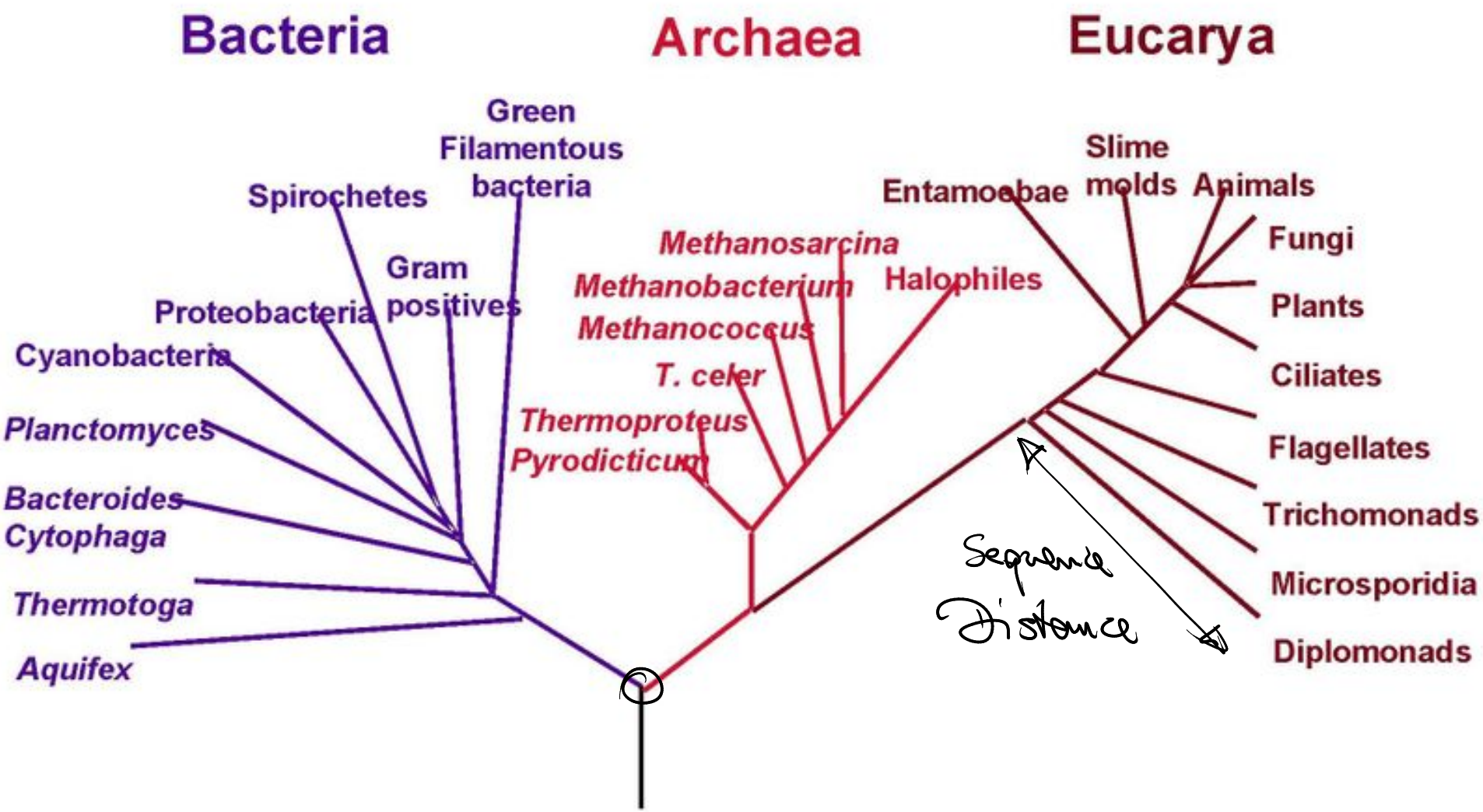
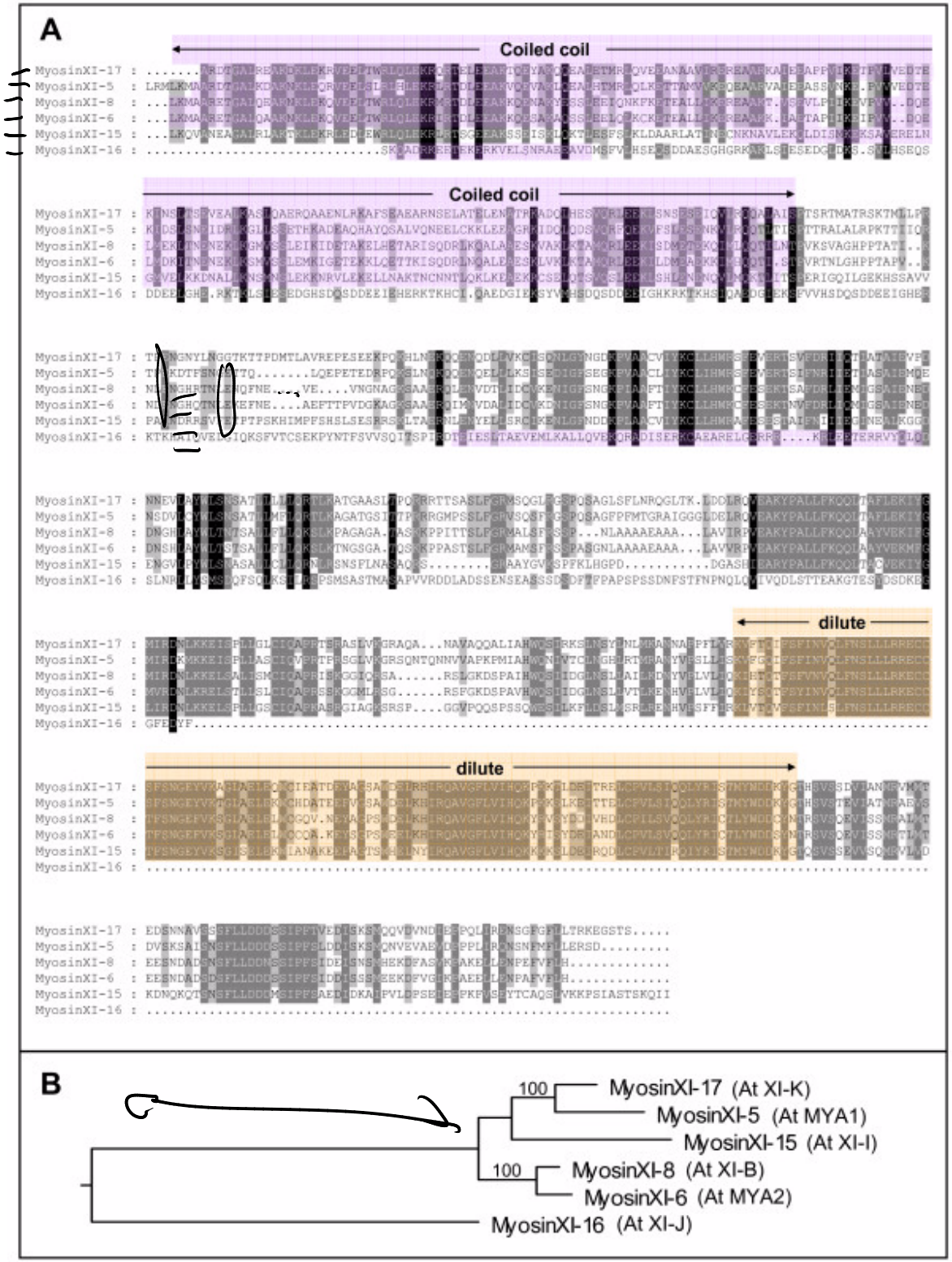
Plantae
Protista
Animalia
Cormophyta
Myxomycetes
Spongiae
Vertebrata
Anthophyta
Angiospermae
Gymnospermae
Pteridophyta
Lepidophyta
Rhizocarpeae
Filices
Calamophyta
Physarum
Stemonitis
Lycogala
Trichia
5.
Petrospongiae
Siphonida
Ocellarida
Lymnorida
Bothroconida
Turonida
Autospongiae
Calcispongiae
Silicispongiae
Cerato-spongiae
Myxospongiae
Articulata
Arthropoda
Tracheata
Crustacea
Amniota
Aves
Mammalia
Reptilia
Vermes
Annelida
Rotatoria
Anamnia
Amphibia
Pisces
Scolecida
Infusoria
Amphirhina
Monorrhina
Bryophyta
Phyllobrya
Thallobrya
Fucoideae
Sargassaceae
Laminariaceae
Chordariaceae
11.
Rhizopoda
Radiolaria
Actinophryida
Acyttaria
Polythalamia
7.
Myxocystoda
Noctilucae
6
8.
Echinodermata
Holothuriae
Echinida
Crinoida
Asterida
16.
17
Leptocardia
19
Florideae
Sphaerococcaceae
Ceramiaceae
10.
Flagellata
Peridinium
Euglena
Volvox
3.
Characeae
12.
14.
Thallophyta
Lichenes
Fungi
13.
Diatomeae
Areolatae
Vittatae
Striatae
4.
Protoplasta
Arcellae
Gregarinae
Autamoebae
Amoebae
2.
Mollusca
Otocardia
Archephyta
Ulva
Conferva
Desmidium
Nostoc
Codiolum
9.
Moneres
Protogenes
Protamoeba
Vampyrella
Protomonas
Vibrio
1.
Coelenterata
Nectacalephae
Petracalephae
15.
Himatega
18
m
n
14 13 12 10 11 9 e
4 5 3 1 2 7 6 8 g
15 16 17 18 19
Archephylum vegetabile
f
Archephylum protisticum
h
Archephylum animale
x
y
s
b
d
t
I, Feld: p m n q (19 Stämme)
II, Feld: p x y q (3 Stämme)
III, Feld: p s t q (1 Stamm)
stellen 3 mögliche Fälle der universalen Genealogie dar
Radix communis Organismorum
Moneres autogonum
Monophyletischer Stammbaum der Organismen
entworfen und gezeichnet von
Ernst Haeckel. Jena, 1866.

Phylogenetic Tree of Life

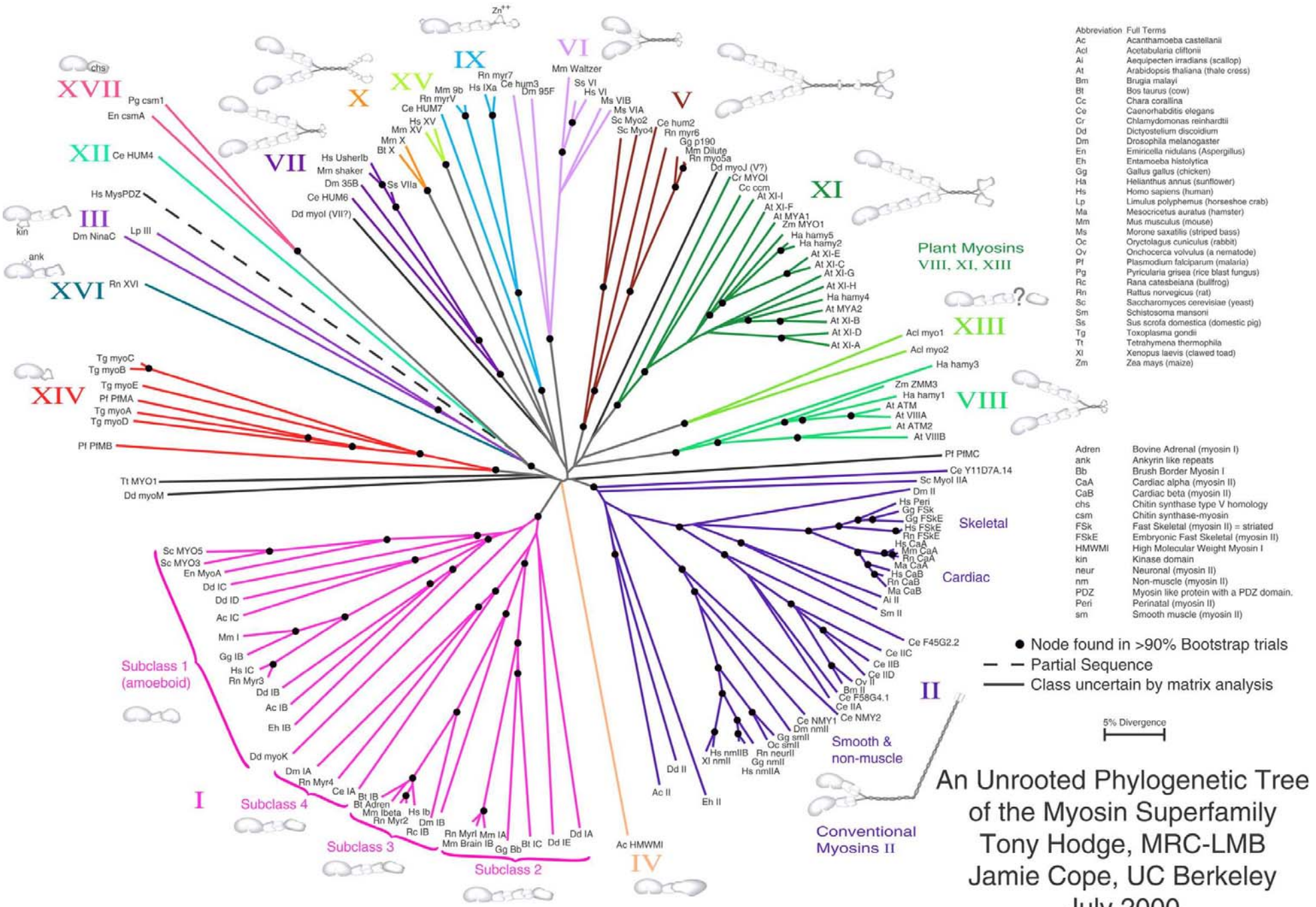


Based on comparing the genetic data of basic proteins, one can construct a phylogenetic tree. However, since genes were most probably exchanged between species with **lateral gene transfer**, it must not be interpreted as **historical record**.



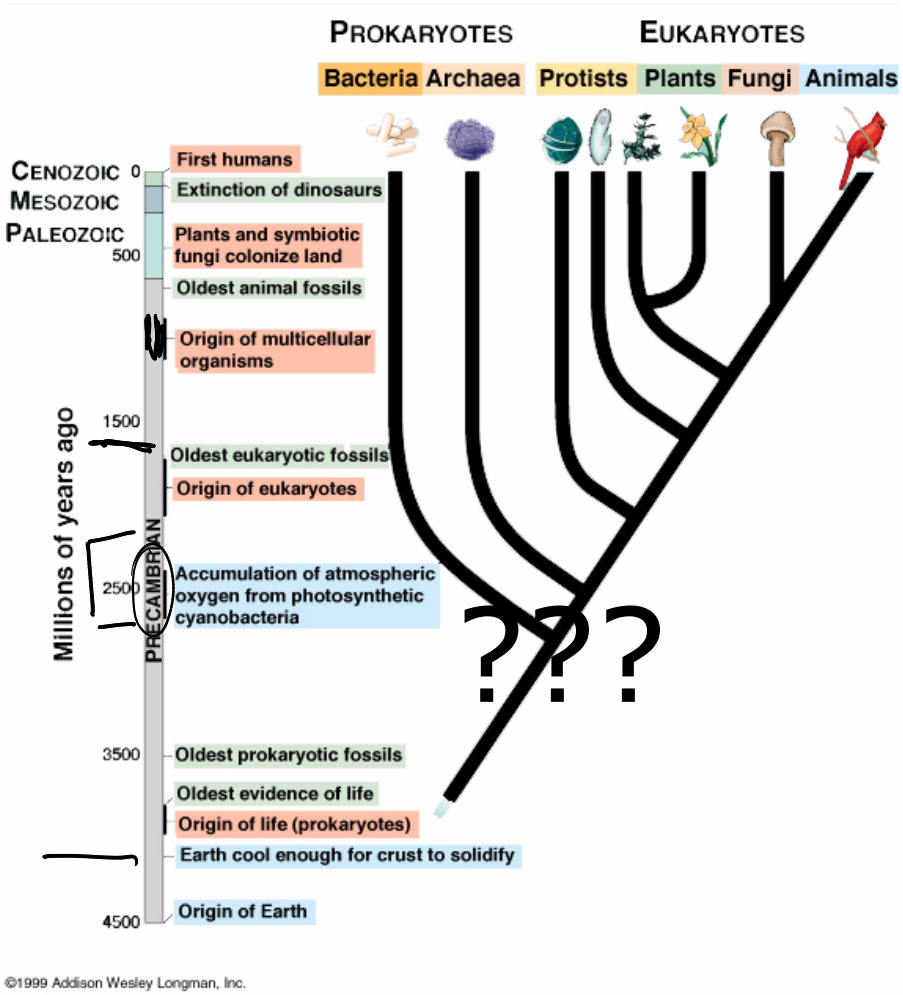
Reisen et al. BMC Plant Biology 2007 7:6
doi:10.1186/1471-2229-7-6

Phylogenetic Tree of Protein Families



Tracing the LUCA
(Last Universal Common Ancestor)

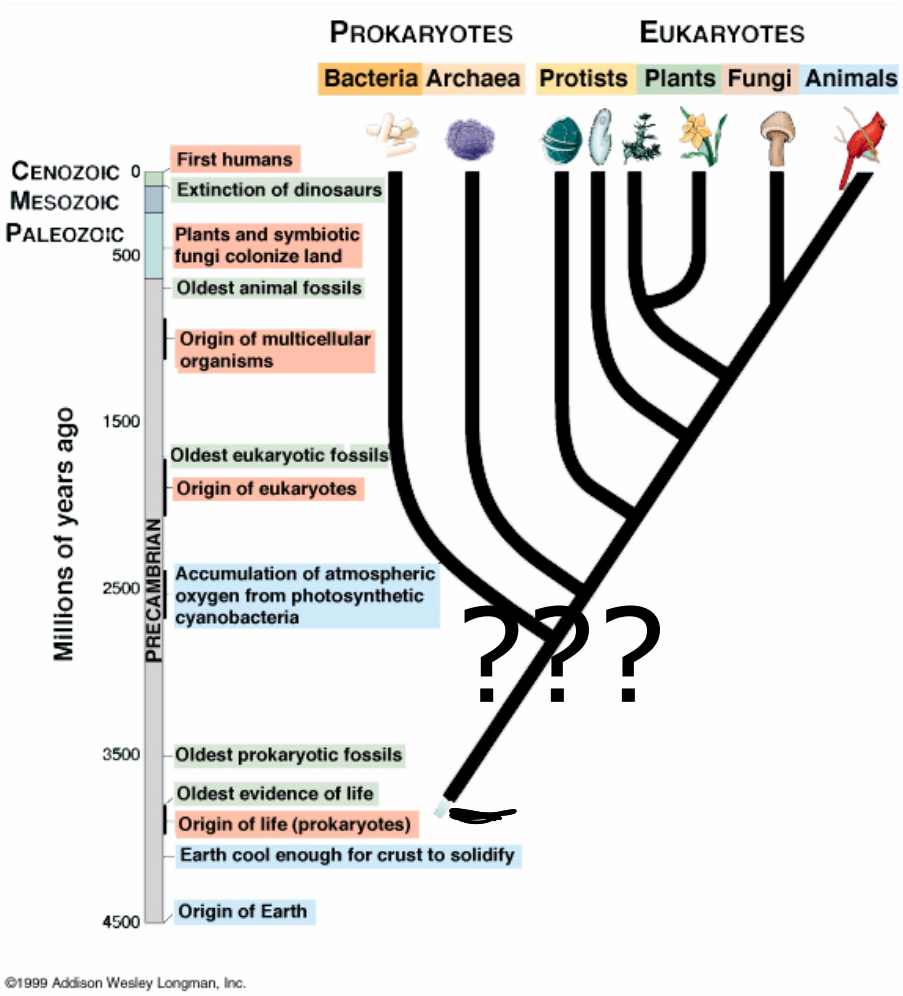
Constructing Phylogenetic Trees



There are three main **methods of constructing phylogenetic trees**: distance-based methods such as neighbor-joining, parsimony-based methods such as maximum parsimony, and character-based methods such as maximum likelihood or Bayesian inference.

Source: en.wikipedia.org

Constructing Phylogenetic Trees



There are three main **methods of constructing phylogenetic trees**:

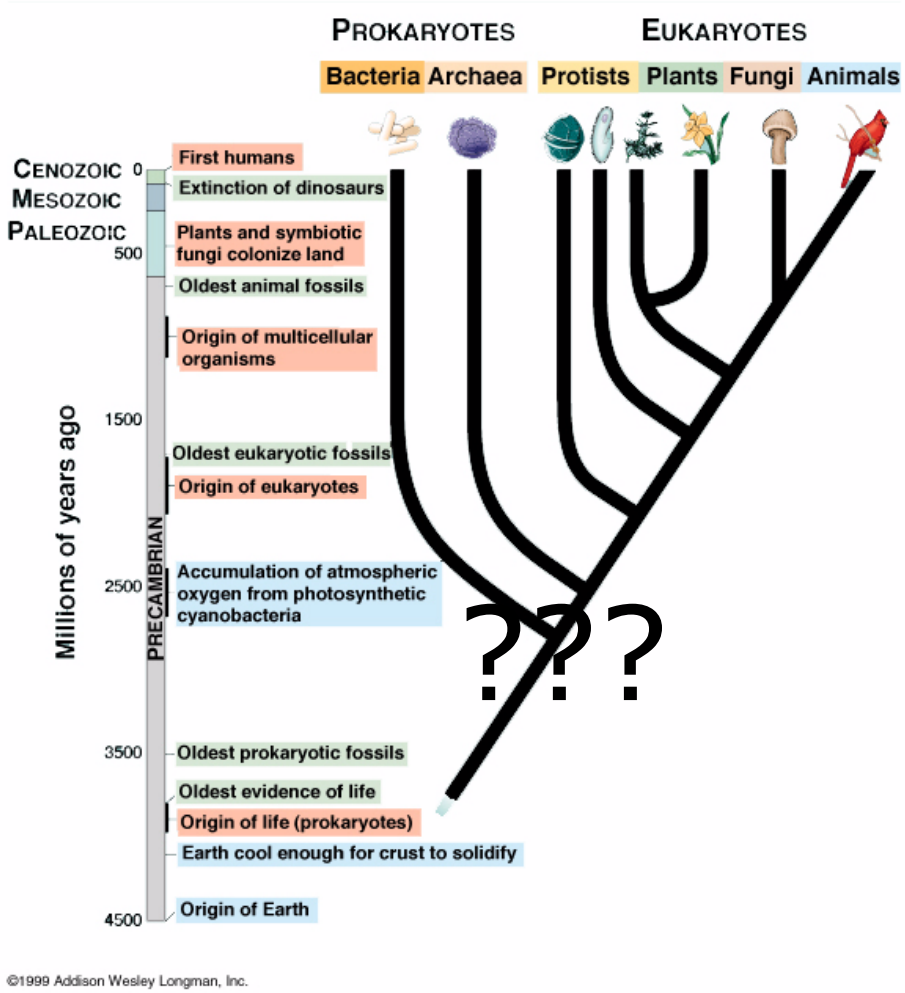
- distance-based methods such as neighbor-joining
- parsimony-based methods (maximum parsimony)
- character-based methods (maximum likelihood or Bayesian inference)

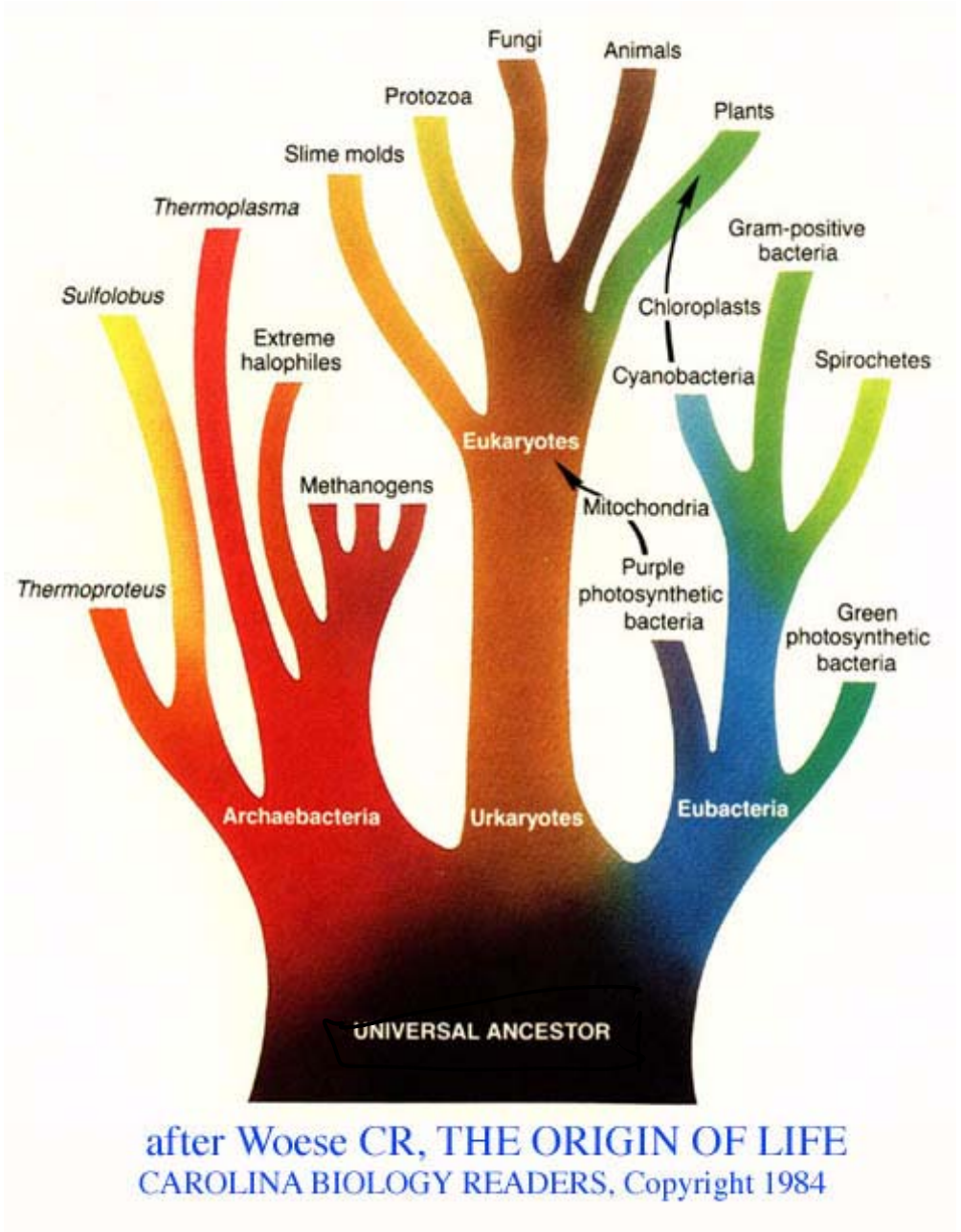
Caveats

- By their very nature, phylogenetic trees cannot represent actual evolutionary patterns and are in fact distorted by, any **lateral gene transfer** or **hybridization between species** that are not nearest neighbors on the tree before.
- The phylogenetic **tree of a single gene or protein** taken from a group of species often **differs** from similar trees **for the same group of species**, and therefore great care is needed in inferring phylogenetic relationships amongst species.

Source: en.wikipedia.org

Searching the Last Universal Common Ancestor



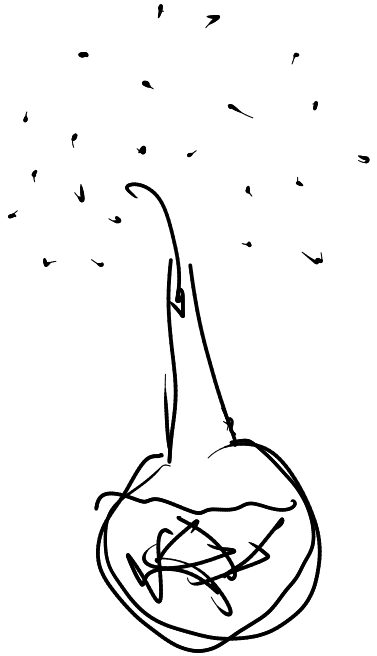


As more sequence data exists from many diverse creatures, there was much optimism to be able to construct back the **last universal common ancestor (LUCA).**

As it turns out, **horizontal gene transfer** between species (as nowadays for example strands of E.coli that exchange plasmids) makes this task virtually impossible. Emerging consensus is that the **LUCA does not exist**, but was a **pool of gene-exchanging organisms**.

The Revolution of Darwin

Before Darwin: Creation and Generation

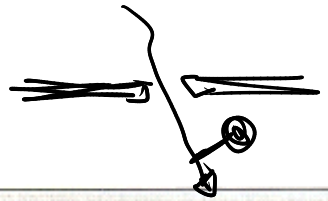


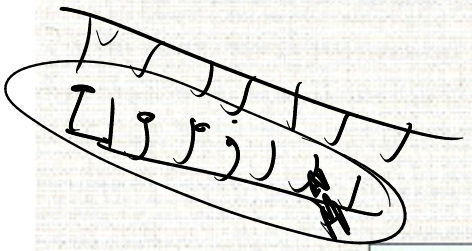
Old ideas dominated by '**spontaneous generation**', i.e. the idea that life transforms itself all the time from non-living matter. Whole animals were supposed to generate themselves out of all kinds of materials. The idea to think of an ancient earth and a long development were utterly foreign. Spontaneous generation died a slow death. Especially the experiments of **Louis Pasteur** gave it a death blow also for microorganisms: "On the Organized Corpuscles That Exist in the Atmosphere" (Annals des sciences naturelles, 1861)

Another group of thought was '**divine creation**', similar to the text found in the bible. All animals were created once and not changed over time.

From: Iris Fry: The Emergence of Life on Earth

Darwin: Historical Context





Wallace (1823–1913)
Mendel (1822–1884) (Genetics)
Darwin (1809–1882) (Replication and Selection)
Lyell (1797–1875)
Cuvier (1769–1832)
Malthus (1766–1834)
Lamarck (1744–1829) (Adaptation is inheritable)
Linnaeus (1707–1778) (Systematics)

1750 1800 1850 1900

1795 Hutton stellt seine Theorie des Gradualismus auf
1798 Malthus veröffentlicht *Eine Abhandlung über das Bevölkerungsgesetz*
1809 Lamarck veröffentlicht seine Evolutionstheorie
1830 Lyell veröffentlicht *Principles of Geology*
1831–1836 Reise der *Beagle*
1837 Darwin beginnt seine Notizbücher über die Entstehung der Arten
1844 Darwin schreibt seine Abhandlung über die Entstehung der Arten
1858 Wallace sendet Darwin seine Theorie zu
1859 *Die Entstehung der Arten* wird veröffentlicht
1865 Mendel veröffentlicht Artikel über die Vererbung

Darwins Insight

It was **Darwin** 1859 which made a very persuasive case based on a vast amount of data, that biological species have **developed one from another in the course of earth's history**.
His main development was the focus on **selection based on random mutations** that can lead to evolution to higher and higher specialization.

Conditions for Natural Selection:

Self-reproduction: Ability to instruct own synthesis (autocatalysis), conservation of information

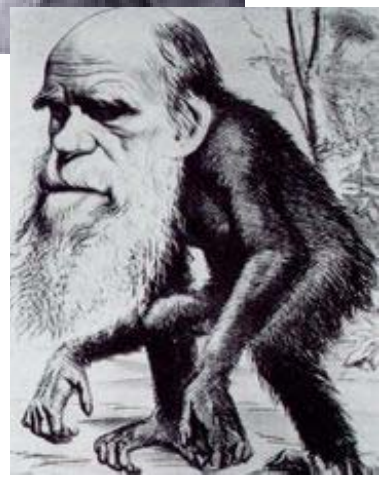
Mutability: Limited fidelity of self-reproductive process

Metabolism: Spontaneous, independent formation and degradation far from equilibrium

From: Iris Fry: The Emergence of Life on Earth

Evolution from Mutation and Selection

Charles Darwin (1809-1882)



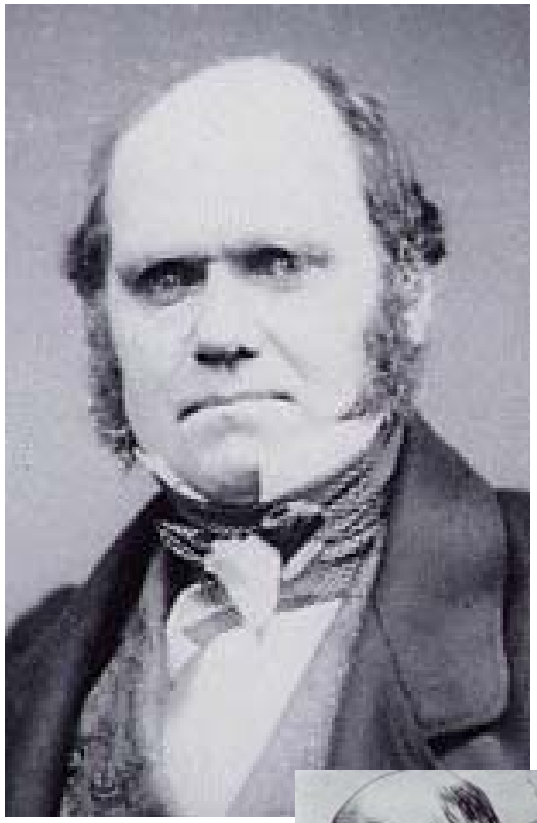
Based on two major findings: (1) Individual variability and (2) Struggle for Life. Charles Darwin proposed in 1859: "*On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*":

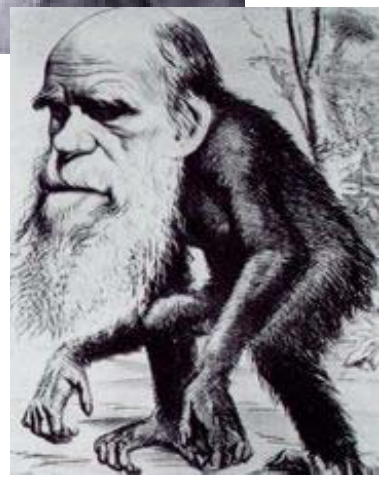
o Differences in Propagation leads to natural selection (survival of the fittest)
o Common Descent of all organisms
o Evolution proceeds in small steps

Source: en.wikipedia.org

Evolution from Mutation and Selection

Charles Darwin (1809-1882)





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- o Common Descent of all organisms
- o Evolution proceeds in small steps

In the 1930s, scientists combined Darwinian **natural selection** with the theory of **Mendelian heredity** to create the modern evolutionary synthesis, also known as **Neo-Darwinism**. The modern synthesis describes evolution as a change in the frequency of alleles within a population from one generation to the next. The mechanisms that produce these changes are the basic mechanisms of **population genetics**: natural selection and genetic drift acting on genetic variation created by mutation, genetic recombination and gene flow. This theory has become the central organizing principle of modern biology.

This theory has become the central organizing principle of modern biology, relating directly to topics such as the origin of antibiotic resistance in bacteria, eusociality in insects, and the staggering biodiversity of the living world.

Source: en.wikipedia.org

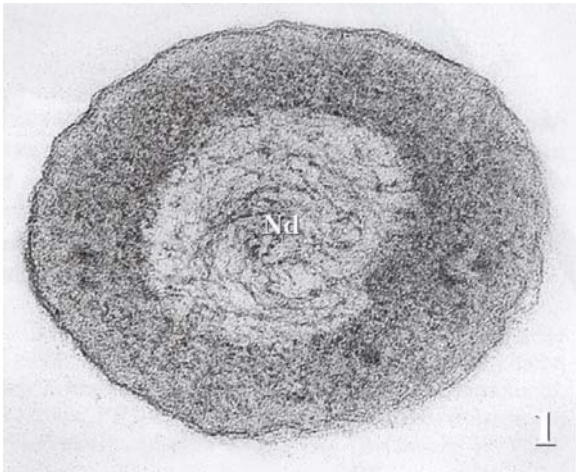
Microbiological Structure: Common Strategies

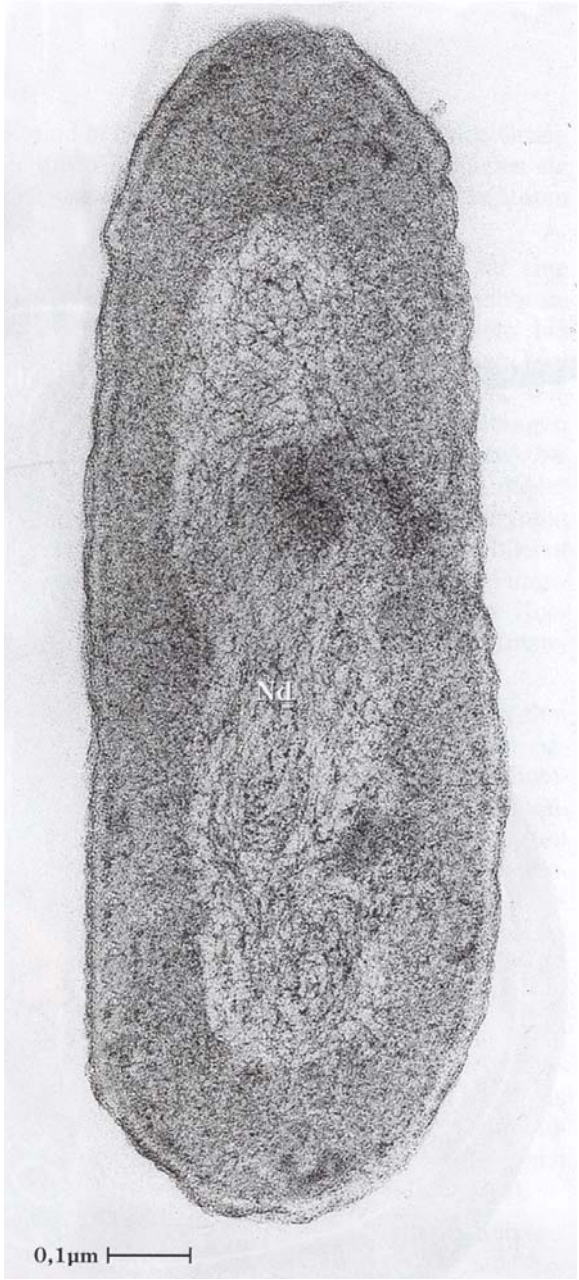
Cell is basic building block of life

Abb. 1

Die DNA der Bakterien besteht aus einem zirkulären Molekül, das im Gegensatz zur eukaryotischen DNA nicht mit Histonen komplexiert ist und als Genophor oder Nucleoid bezeichnet wird. Daneben enthalten Bakterien in der Regel mehrere Plasmide, kleinere zirkuläre DNA-Moleküle, die nur wenige Gene tragen und unter anderem für die Ausbildung von Antibiotika-Resistenzen verantwortlich sind. Das Einsatzbild links oben zeigt die isolierte DNA von *Escherichia coli* nach einer Spezialbehandlung und anschließender Bedampfung. In elektronenmikroskopischen Schnittpräparaten ist sie als fädige Masse in einer relativ transparenten, zentralen Zone zu beobachten.

Dieser als Kernäquivalent bezeichnete Bereich kann bis zu 30 % des Zellvolumens einnehmen. Die vor jeder Teilung einsetzende identische Reduplikation der DNA geht von einer einzigen Stelle aus und erfolgt in engem Kontakt mit der Zellmembran.





From: Ude/Koch: Die Zelle, Atlas der Ultrastruktur

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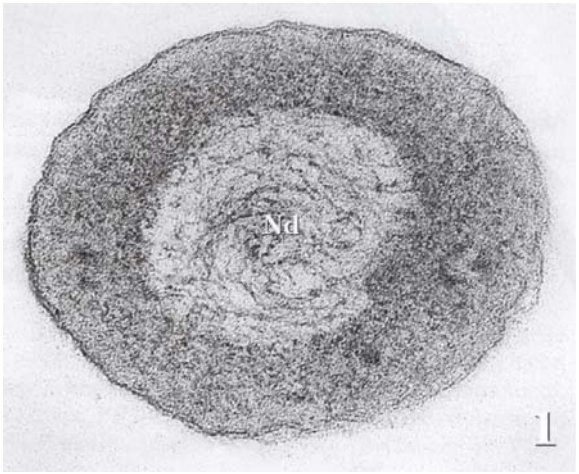


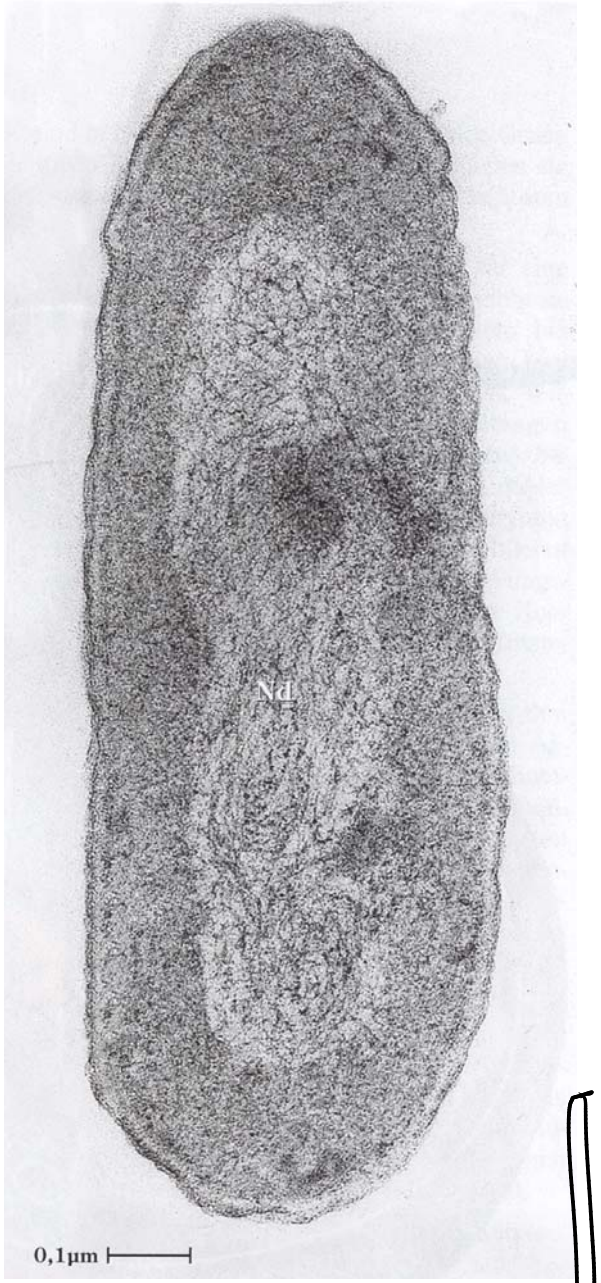
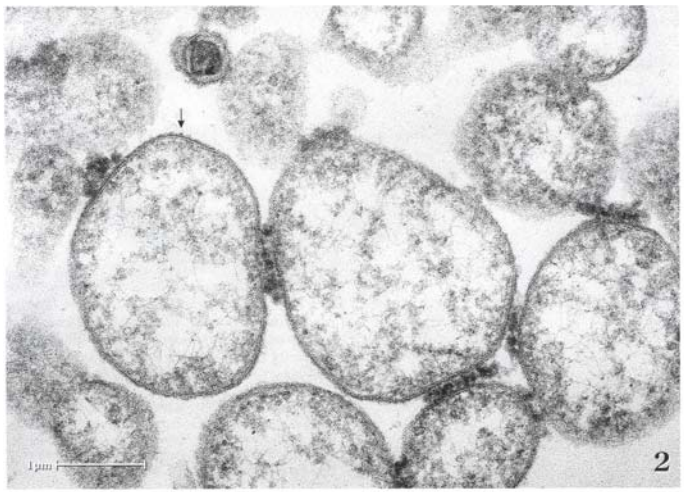


Abb. 2
***Acholeplasma laidlawii.* Eine Minimalzelle**

Mycoplasmen sind die kleinsten autonom existierenden lebenden Systeme. Innerhalb ihres von einer Membran umschlossenen Zytoplasma enthalten sie eine Minimalausstattung an Nucleinsäuren und Proteinen, die ihnen eine eigenständige Existenz an der unteren Grenze des Lebens gestatten. Auf Grund der Masse ihrer DNA, die sich mit $0{,}5 \times 10^{-9}$ Da nur wenig von der der großen DNA-Viren abhebt, wird ihnen eine Codierungskapazität für ca. 700 verschiedene Proteine zugeschrieben, die in einer Menge von insgesamt ca. 60 000 Molekülen sowohl die Reproduktion als auch die gesamten Lebensprozesse steuern.



Mycoplasma laboratorium (Venter et.al): 382 Genes (580000 bases) as minimal genome under lab conditions.

In Nature: Candidatus Hodgkinia cicadi-

From: Ude/Koch: Die Zelle, Atlas der Ultrastruktur

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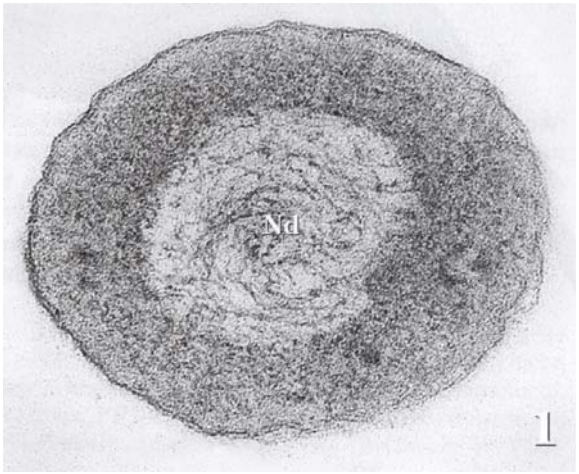
382 Genes (580000 bases) as minimal genome under lab conditions.

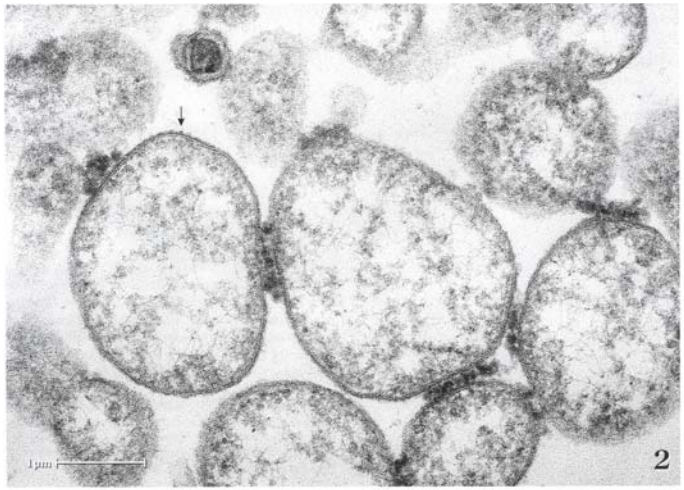
In Nature:
Candidatus Hodgkinia cicadicola Dsem (very hard to culture):



151 Genes
= 38 RNA + 113 proteins
(140000 bases)

Abb. 2
***Acholeplasma laidlawii.* Eine Minimalzelle**

Mycoplasmen sind die kleinsten autonom existierenden lebenden Systeme. Innerhalb ihres von einer Membran umschlossenen Zytoplasma enthalten sie eine Minimalausstattung an Nucleinsäuren und Proteinen, die ihnen eine eigenständige Existenz an der unteren Grenze des Lebens gestatten. Auf Grund der Masse ihrer DNA, die sich mit $0{,}5 \times 10^{-9}$ Da nur wenig von der der großen DNA-Viren abhebt, wird ihnen eine Codierungskapazität für ca. 700 verschiedene Proteine zugeschrieben, die in einer Menge von insgesamt ca. 60 000 Molekülen sowohl die Reproduktion als auch die gesamten Lebensprozesse steuern.

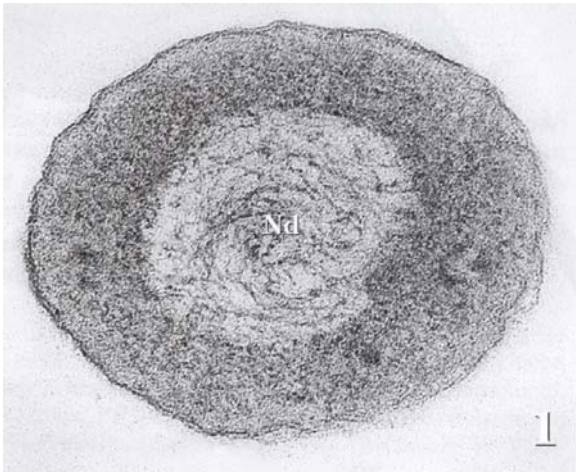


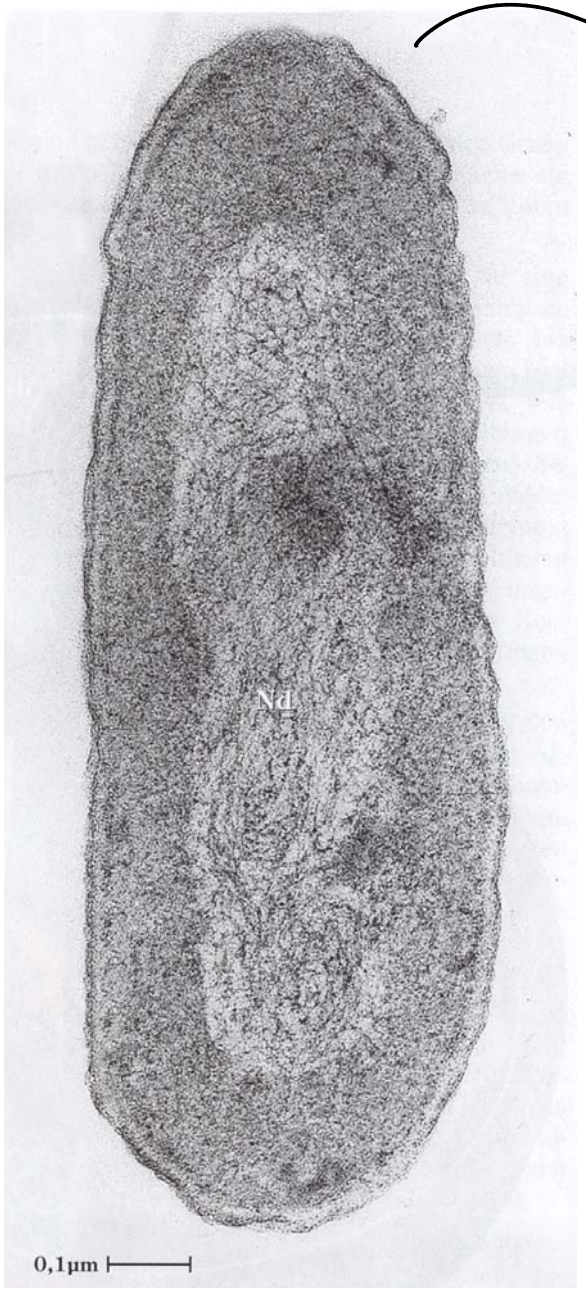
From: Ude/Koch: Die Zelle, Atlas der Ultrastruktur

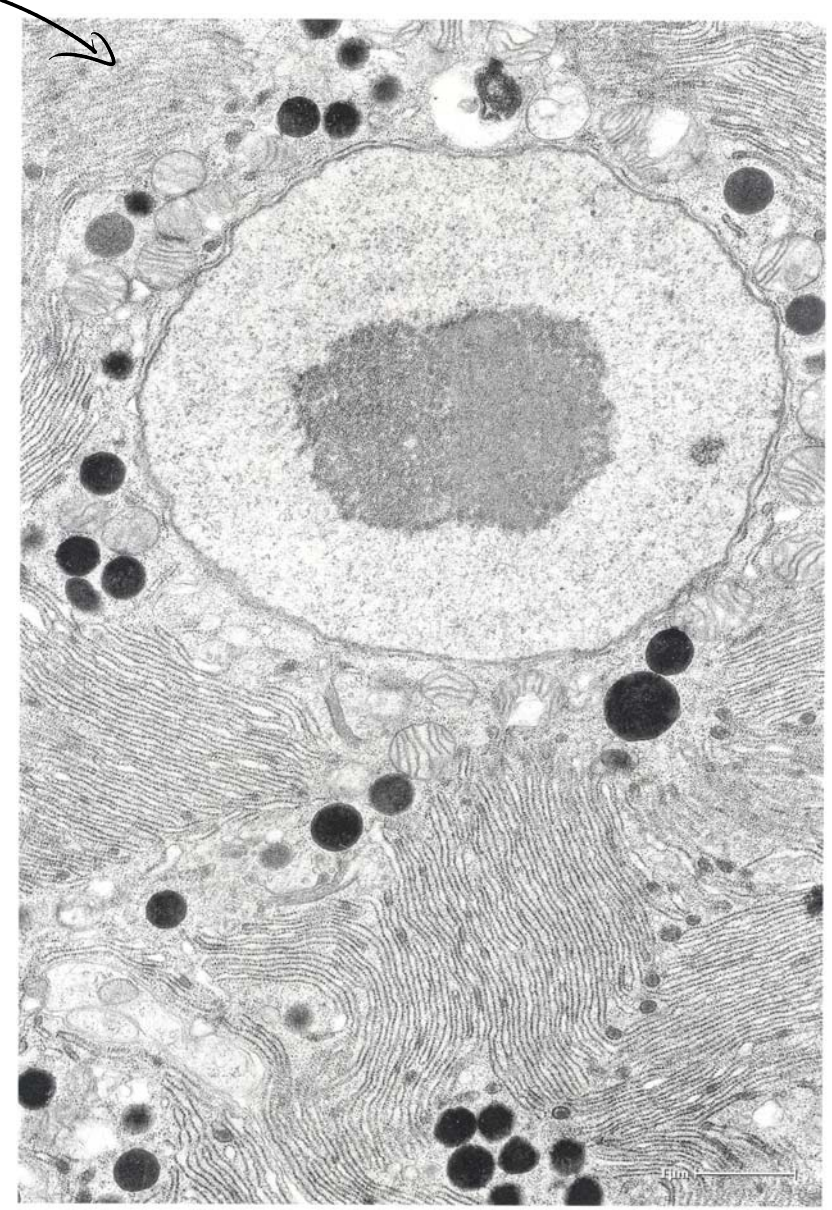
Bacteria vs. Eucaryotic cell

Every autonomously living creature (we thus exclude viruses) are made of cells.

Cells do not come in the same size. Bacteria are about 10-fold smaller than eucaryotic cells (e.g. plant or animal cells). Latter have a more than 1000-fold larger cell volume.

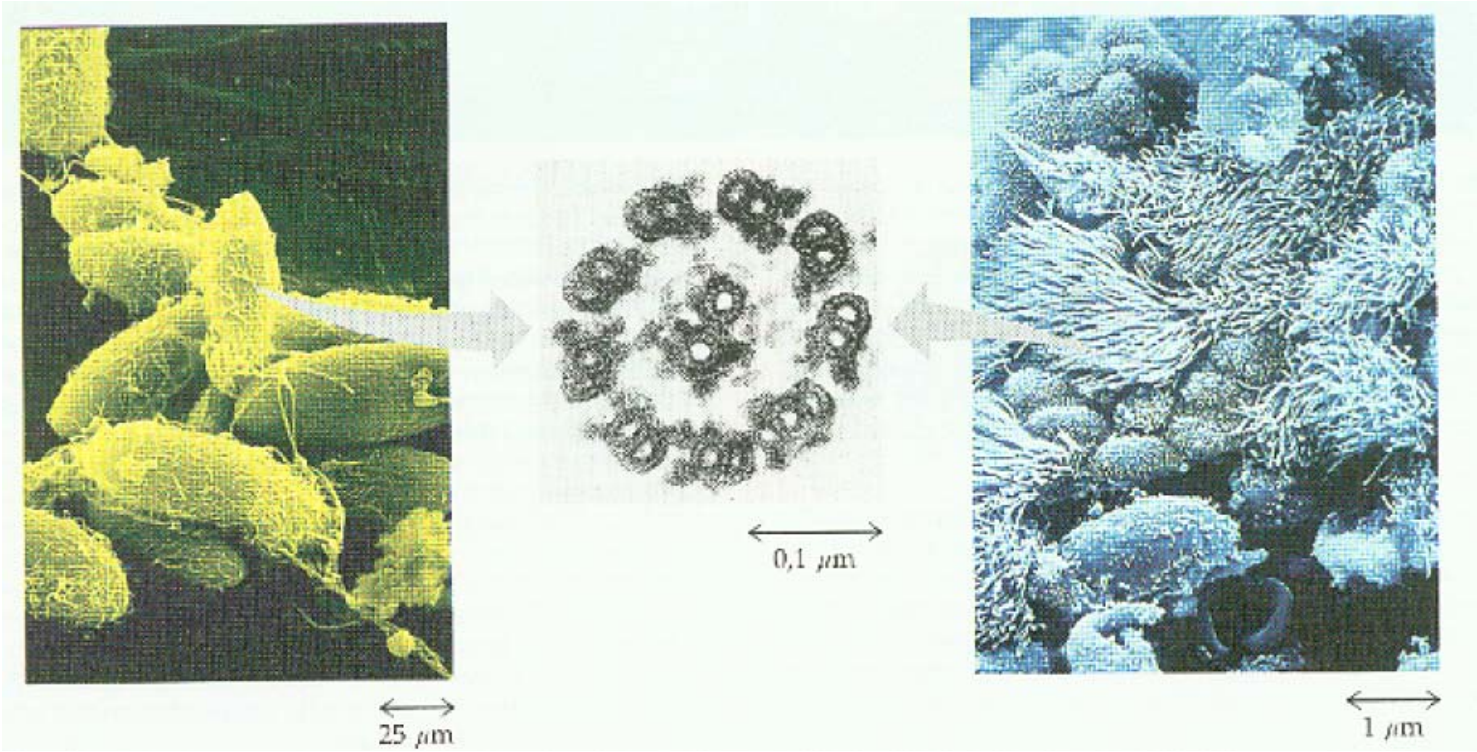






From: Ude/Koch: Die Zelle, Atlas der Ultrastruktur

Common Units in all Life



Besides that every creature consists of cells and are built on its communicative combination, also **small subunits** are used in different organisms.

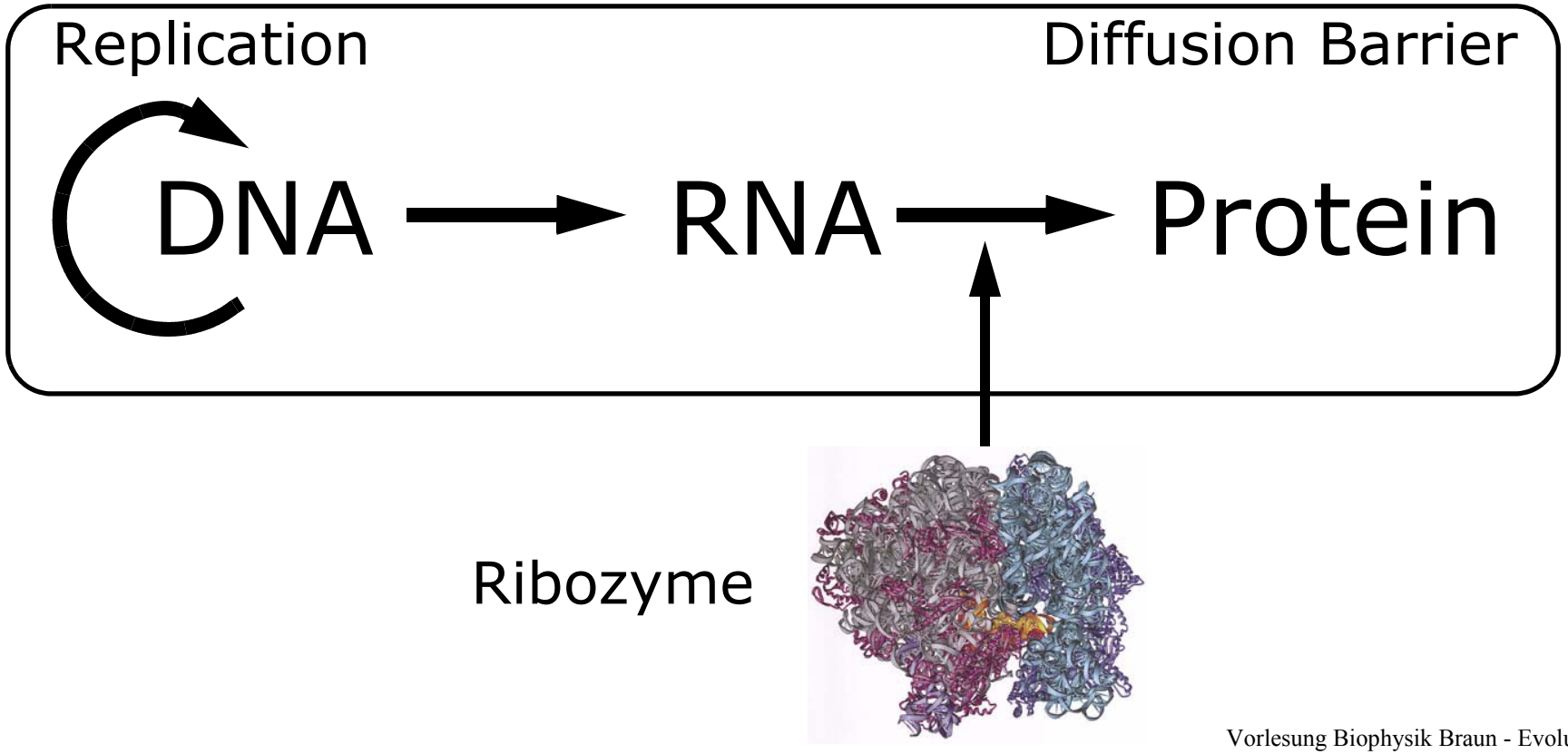
For example, cilia of the (human) lung have the same molecular construction than the Cilia of Paramecium (Pantoffeltierchen).

Moreover, elongated Algae have the same cilia structure, but inside (!) to move its intracellular liquid.

Basic organization: genetic programming

Life is based on Polymers!

The common basis for sharing and exchanging common molecular designs is that in all organisms, the same core functionality is found:
- DNA is replicated
- DNA is transcribed to genetic messenger RNA
- RNA is translated to proteins according a fixed code.



The Roadmap: Problems to Solve in Molecular Evolution

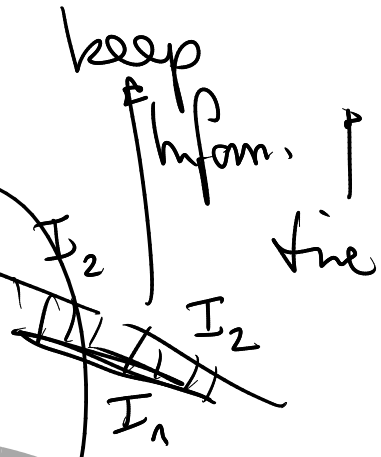
Early Earth

Life

Darwinian Evolution

Protein Coding

Replication



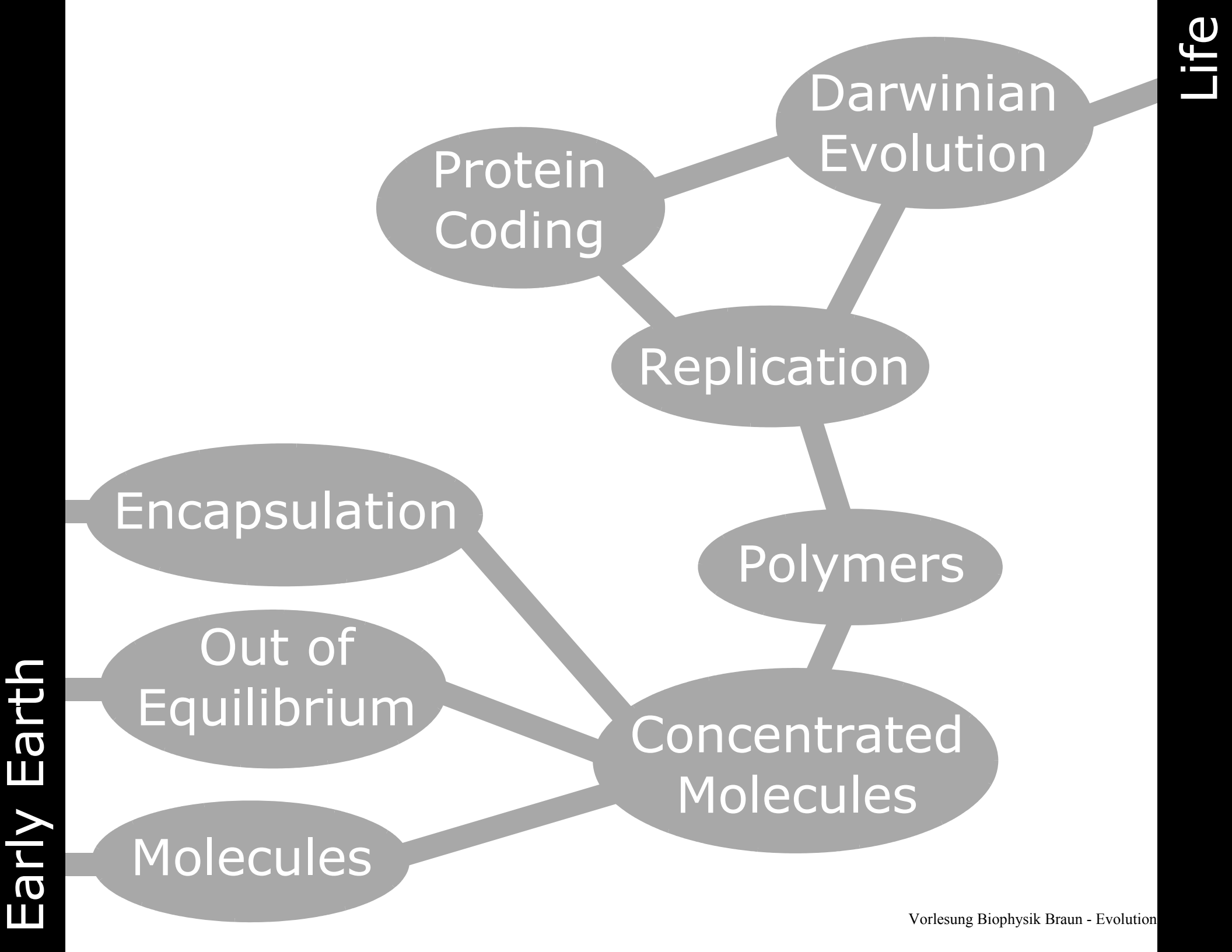
Encapsulation

Polymers

Out of Equilibrium

Concentrated Molecules

Molecules


Early Earth
Life
Darwinian Evolution
Protein Coding
Replication
Encapsulation
Polymers
Out of Equilibrium
Concentrated Molecules
Molecules

From Geochemistry to Life

In Darwin's eyes, life would go back to one **common ancestor**. Darwin, based on his time, considered it futile to **search for the transition from inanimate to animate matter** way back in the earth's history.

Only today the quest for the origin of life has become a serious scientific question. The field started in about 1950 and ever since was an interdisciplinary work between astrophysics, planetary scientists, geologists, physical, organic, and biological chemists, evolutionary biologists and - physics.

From: Iris Fry: The Emergence of Life on Earth

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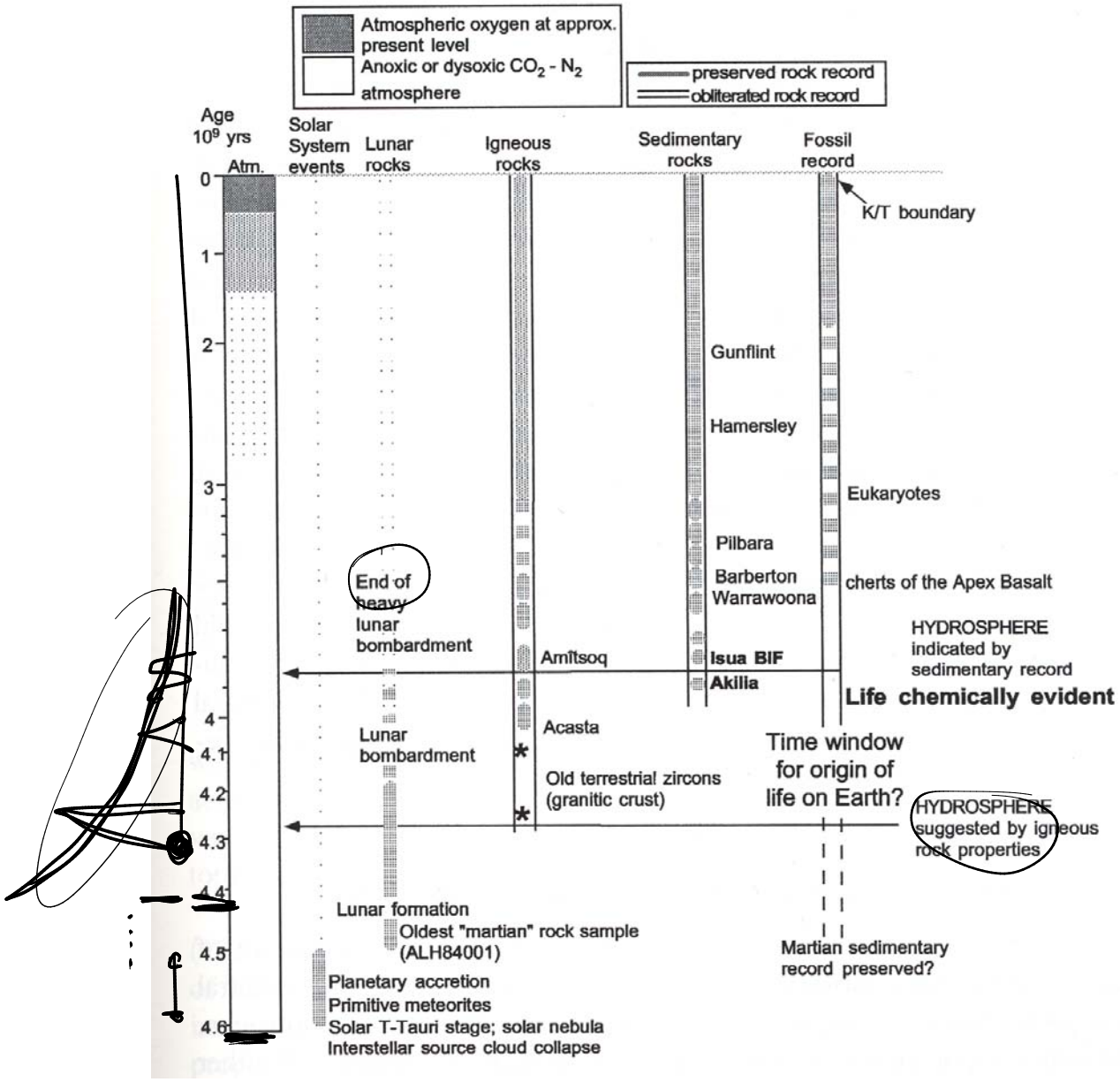
Main questions are:

- **When** in earths history did life emerge?
- **Where** did the process take place?
- **What were the conditions** on Earth during this period?
- Did life emerge on Earth at all, or was it **brought to Earth from outer space**?
- Which was the **first living system** to emerge?
- Was it a primitive cell-like structure, a set of "primitive enzymes" or a primitive replicating molecule (metabolic versus genetic approach)?

From: Iris Fry: The Emergence of Life on Earth

Geology and Time Window

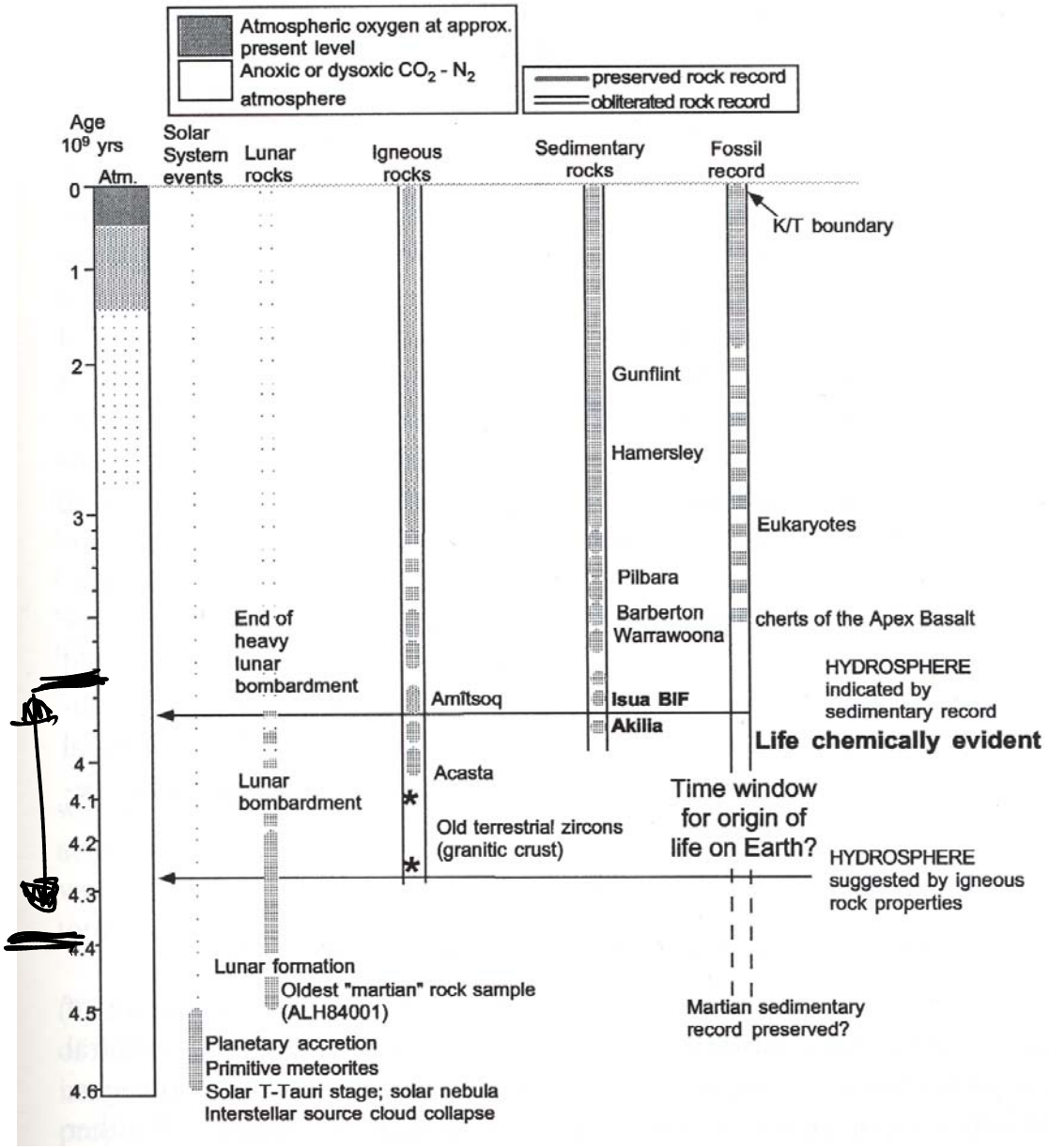


Geology and Time Window

Based on meteorite data, it is a well established fact that the **earth was formed 4.6 billion years ago**. Heavy bombardment from space by **meteorites** lasted a long time, probably until 3.8 billion years, the bigger of them so strong that they evaporated the oceans.

Reliable fossils of life dates back to 2.7 billion years ago: bacteria cells in ancient rocks in Africa. It is not clear at all, whether life needed such a long time to develop first bacteria. Imprints of more early **fossils, dating 3.5 billion years back** with a different C^{12}/C^{13} ratio indicating biological activity have been proposed. But the **evidence is shaky**: geologists suspect nonbiological processes that generate these structures and the measured C^{12}/C^{13} ratios. It is hard to find rock of this age which did not undergo heavy metamorphosis.

However, it is a consensus that first **living organisms probably were evolved around 3.8 billion years ago**. This short time would be a blink of the eye in terms of geological times: life has probably emerged on earth extremely fast.



Chemical Evolution

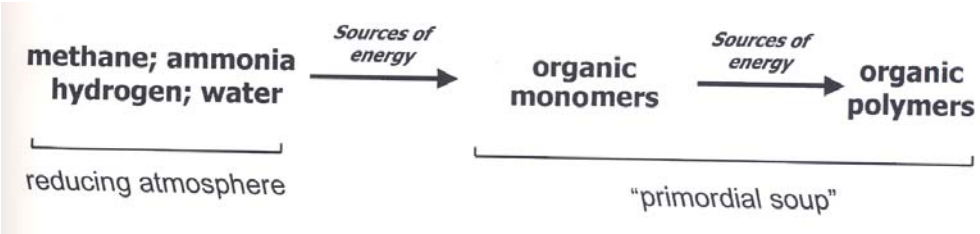
Forerunners: Oparin, Haldane and Troland

Oparin: "Origin of Life", 1926

Biochemical-Metabolic Tradition

Organization of a cell, metabolism, reproduction and response to stimuli have parallel manifestations in the inorganic realm.

Development from organic from inorganic is like **petroleum from minerals** (see spontaneous generation!). Volcanic eruptions created hydrocarbons and ammonia. Organic compounds accumulate in water, yielding a **thick colloidal solution in the primordial ocean**. Coagulation allows absorption of small molecules into droplets. Droplets grow and divide at some size. Some sort of natural selection should set in. "**Protein first**"



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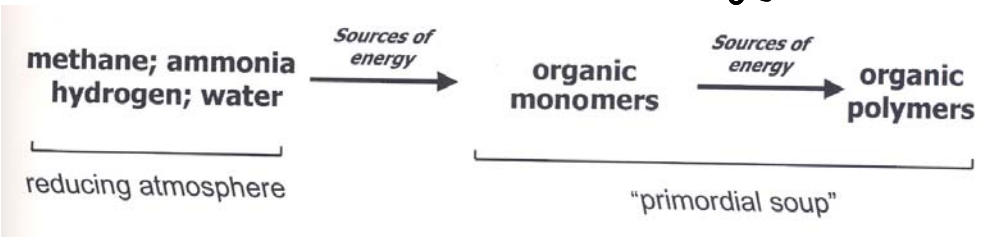


JBS Haldane: "Origin of Life", 1929

Genetic Tradition

Much less oxygen, no ozone layer and intense UV radiation reaches the earth surface uninterrupted (!). This leads to synthesis of organic compounds from CO_2 (Baly 1927), leading to a "hot dilute soup".

He focuses on the capability of reproduction. An oily film was to be produced in the soup and engulfed reproducing molecules, leading to the first cell. Haldane's work was influenced by knowledge about viruses, which he thought was the 'missing link'. "**Genes first**"

Troland:

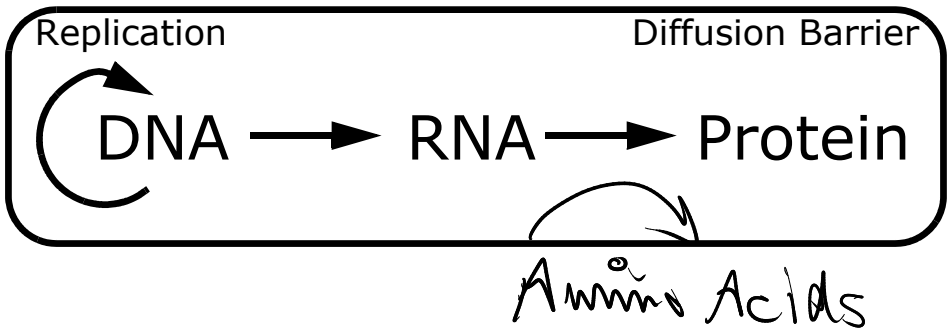
"Physico-Chemical Conception", 1914

In primordial ocean a primitive molecule appeared with catalytic ability to catalyze its own formation - and other chemical reactions. First an enzyme, later a "genetic enzyme". Very near to "RNA world" scenarios.

From: Iris Fry: The Emergence of Life on Earth

Freeman Dyson: Double Origin Hypothesis

Dyson focusses that life consists of two things: **replication and metabolism**. (in an analogy to computers: like a computer consists of software and hardware). He sees a neglect of metabolism in the origin of life research. He makes a distinction between **replication** (of genes) and **reproduction** (of the cell).



The idea: a **metabolism reaction of protoproteins**, comparable to Oparin bubbles, is supposed to reproduce by growth and division. Making use of this metabolism, a **"second beginning"** occurred in which nucleotides were synthesized. (The idea was analog to symbiosis between bacteria that eventually lead to eucaryotes.) **Genes** would first enter as **parasitic disease**, only later to develop the symbiotic advantage of replication and reproduction.

He argues that the **active metabolism** of the beginning is already some carrier of **"genetic" information**. Dyson tries to fill **the gap of replicative models to synthesize their monomers and polymers** in the beginning. However it is not clear whether his idea of metabolism is just another way of constructing a basic genetic system. (Kauffman followed up his ideas with more complex systems.)

Miller-Urey Experiment I

FIGURE 2.5 The glass apparatus used in Miller's experiment. The lower flask was designed to simulate the oceans; the upper flask, the atmosphere. Energy was supplied by sparking between the two wire electrodes. (Scripps Institution of Oceanography)

From: Wills&Bada: The spark of life

Miller-Urey Experiment I

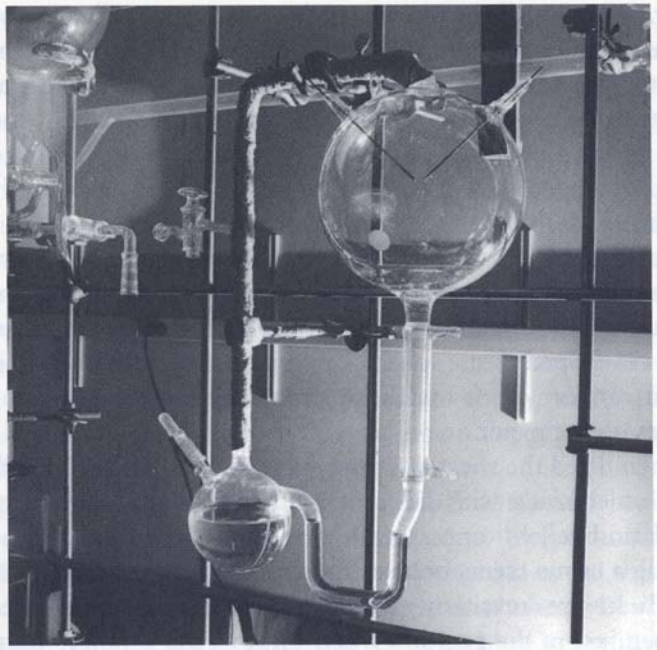


FIGURE 2.5 The glass apparatus used in Miller's experiment. The lower flask was designed to simulate the oceans; the upper flask, the atmosphere. Energy was supplied by sparking between the two wire electrodes. (Scripps Institution of Oceanography)

In 1953, Miller did an experiment proposed by Urey in which the atmosphere of Oparine and Haldane (CH_4, NH_3, H_2O and H_2) was subjected to **electrical sparks** between tungsten electrodes.

The reaction yielded **a wide variety of biologically important molecules** at astonishingly high yield.

However **for a more realistic atmosphere**, i.e. for less CH_4 and more CO or CO_2, **both yields and diversity dropped sharply**. The carbon source appears to be crucial. Also the role of tungsten in the experiment was later-debated. Today it is considered unrealistic.

From: Wills&Bada: The spark of life

Miller-Urey Experiment II

TABLE 2
Yields from Sparking a Mixture of CH_4, NH_3, H_2O, and H_2[a,b]

Compound	Yield (μM)	Yield (%)
Glycine	630	2.1
Glycolic acid	560	1.9
Sarcosine	50	0.25
Alanine	340	1.7
Lactic acid	310	1.6
N-Methylalanine	10	0.07
α-Amino-*n*-butyric acid	50	0.34
α-Aminoisobutyric acid	1	0.007
α-Hydroxybutyric acid	50	0.34
β-Alanine	150	0.76
Succinic acid	40	0.27
Aspartic acid	4	0.024
Glutamic acid	6	0.051
Iminodiacetic acid	55	0.37
Iminoaceticpropionic acid	15	0.13
Formic acid	2330	4.0
Acetic acid	150	0.51
Propionic acid	130	0.66
Urea	20	0.034
N-Methyl urea	15	0.051

[a]Added as CH_4 was 59 mmol (710 mg) of carbon. The percentage yields are based on the carbon.

[b]From Miller, S. L. and Orgel, L. E. *The Origins of Life on Earth*. Englewood Cliffs, NJ: Prentice-Hall, 1974. Reprinted by permission of the author and Prentice-Hall, Inc., Upper Saddle River, NJ.

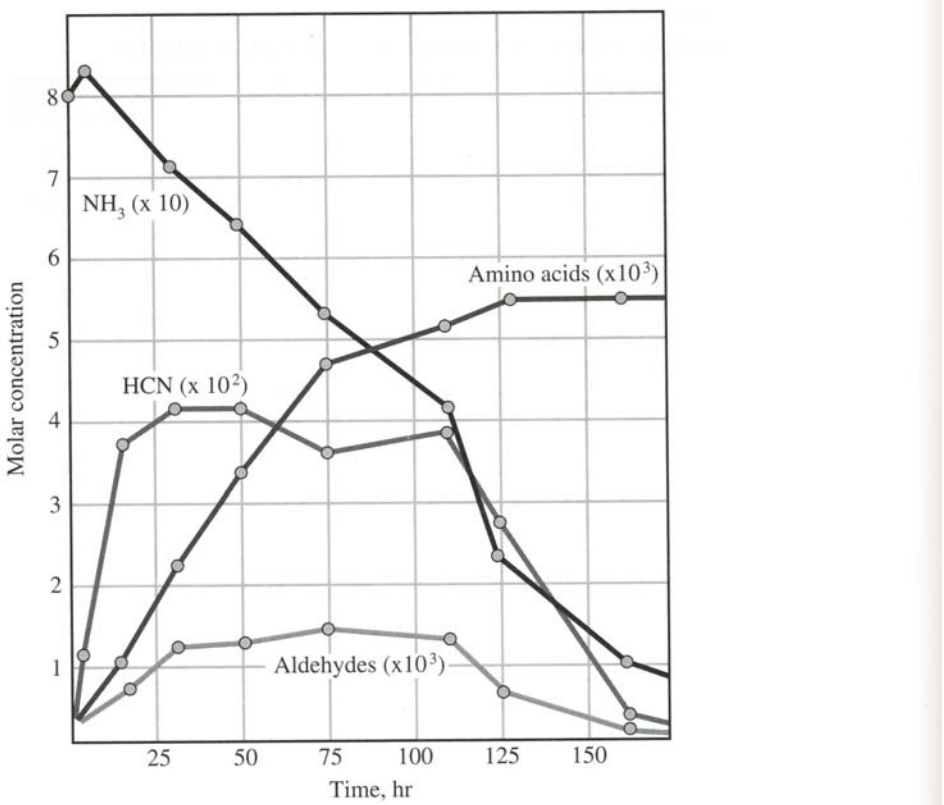
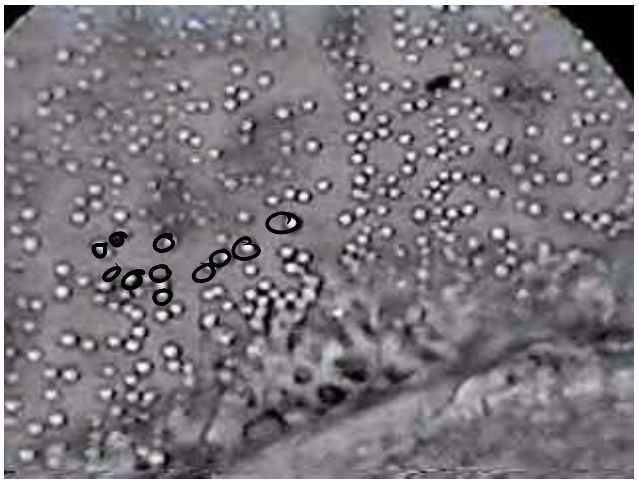
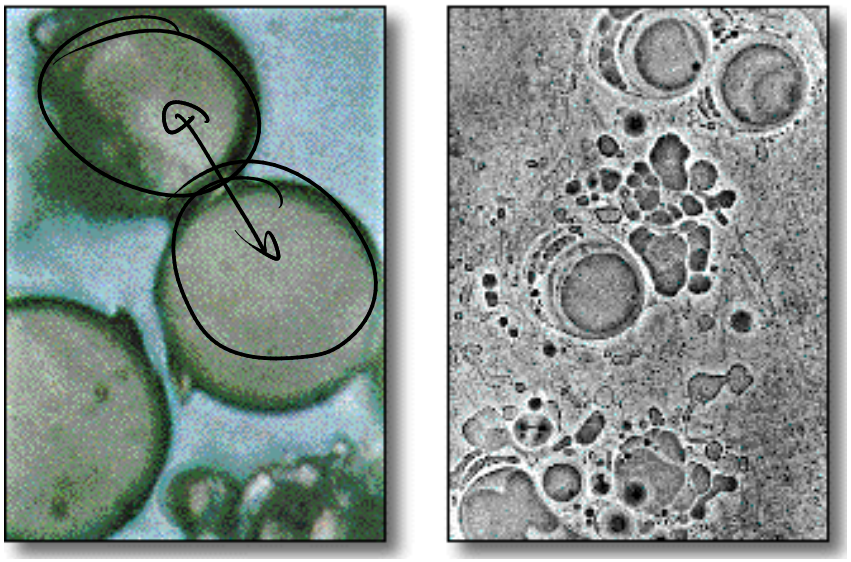


FIGURE 9 The concentrations of ammonia, hydrogen cyanide, and aldehyde in the U-tube; and the concentration of amino acids in the small flask while sparking a mixture of methane, ammonia, water, and hydrogen in the apparatus shown in Fig. 8. (From Miller, S. L. and Orgel, L. E. *The Origins of Life on Earth*. Englewood Cliffs, NJ: Prentice-Hall, 1974. Reprinted by permission of the author and Prentice-Hall, Inc., Upper Saddle River, NJ.)

From: Zubay: Origins of life on the Earth and in the Cosmos

Fox: Dry baking of amino acids



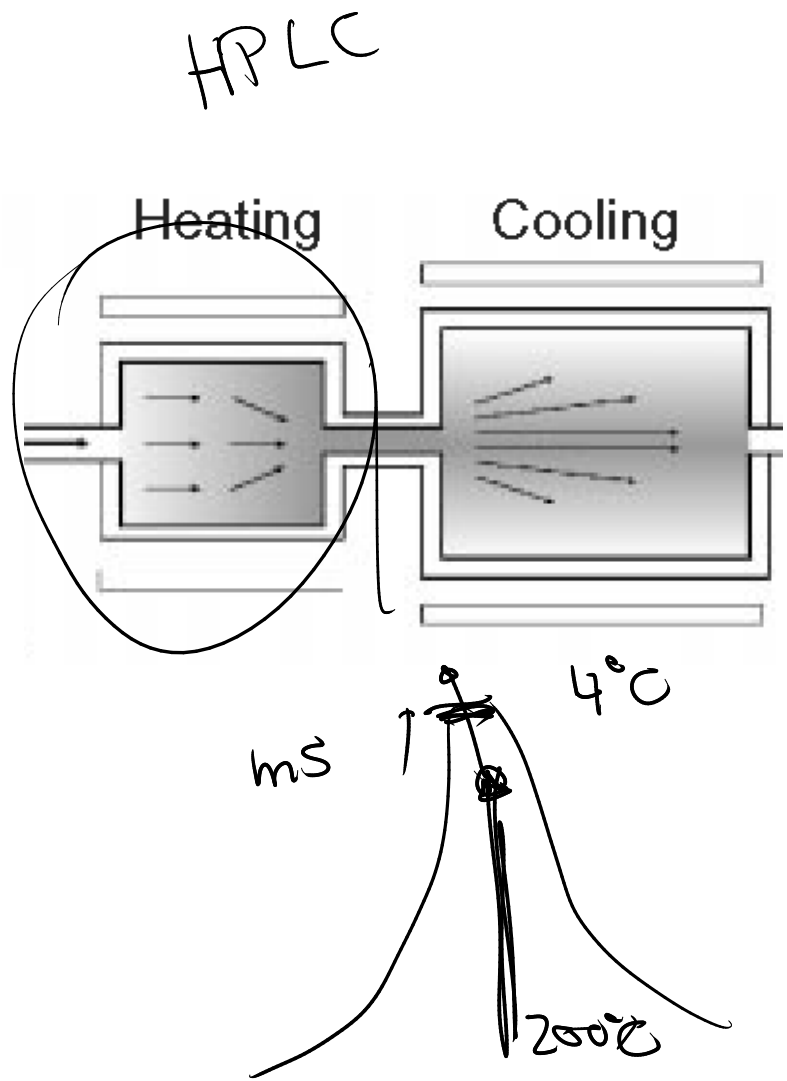


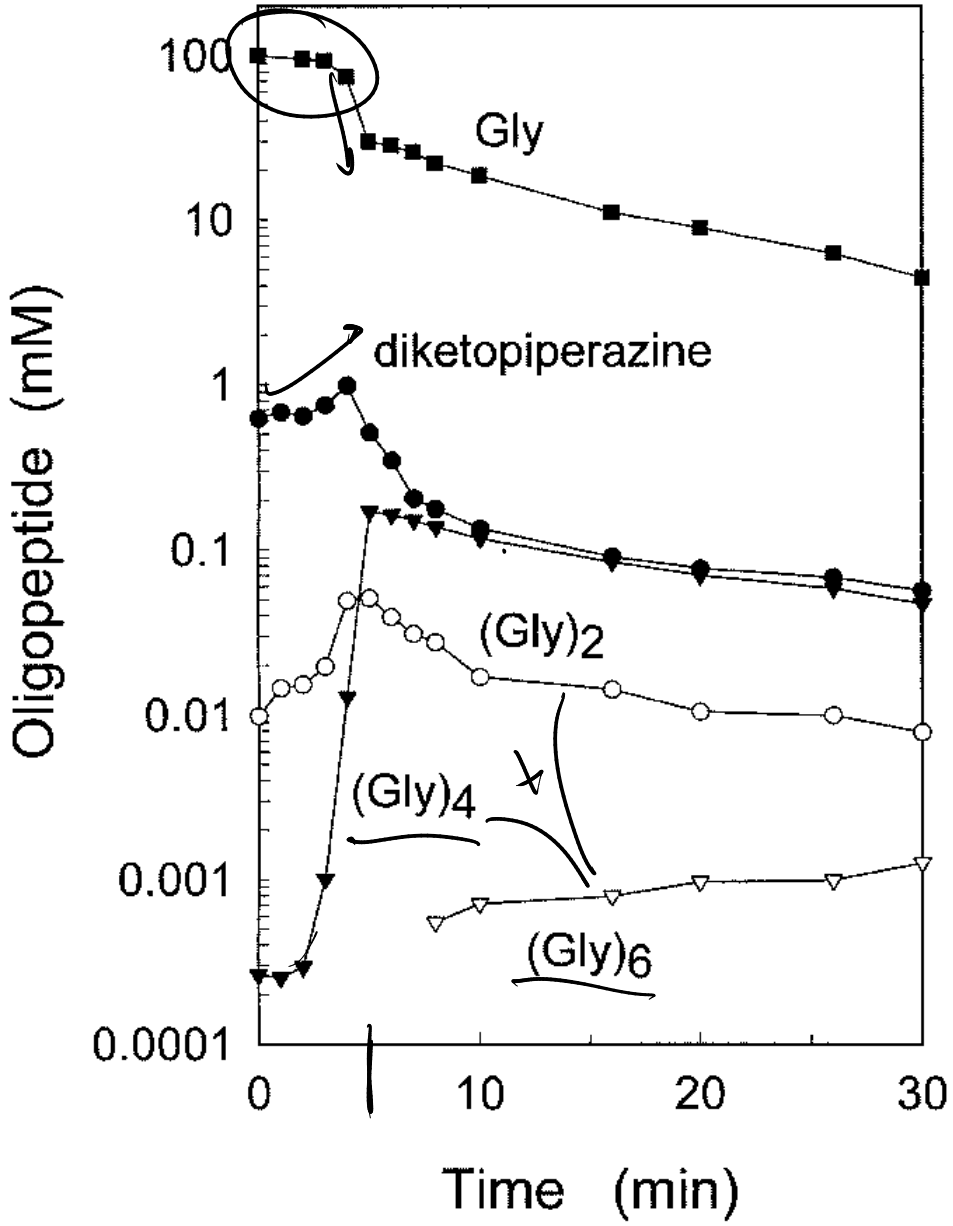
High concentrations of amino acids, dried and baked to 170°C give rise to protein-like molecules that are cross-linked. Being brought in contact with water, they can form bubbles and precipitates with a structure similar to cells.

The molecules have much higher diversity as compared with proteins. Depending on the conditions, more hydrophobic or more hydrophilic amino acids become cross-linked. This was used as evidence, that molecular selection and evolution by self-catalysis was at work.

However no scheme of self-replication could be shown. Also the bubbles have no resemblance to cellular structures and decompose fast. Moreover, the scheme has to start with high concentrations and dry conditions.

Matsuno: Polymerisation by fast cooling





Koichiro Matsuno, Science 283, 831 (1999)

Origin of Genetic Material?

Up-to-date, no good idea is established to make a starting pool of RNA monomers. The chemistry to generate dNTP molecules is not very realistic in typical prebiotic conditions. And secondly, these monomers to not typically attach themselves, especially not in the 3'-5'-direction.

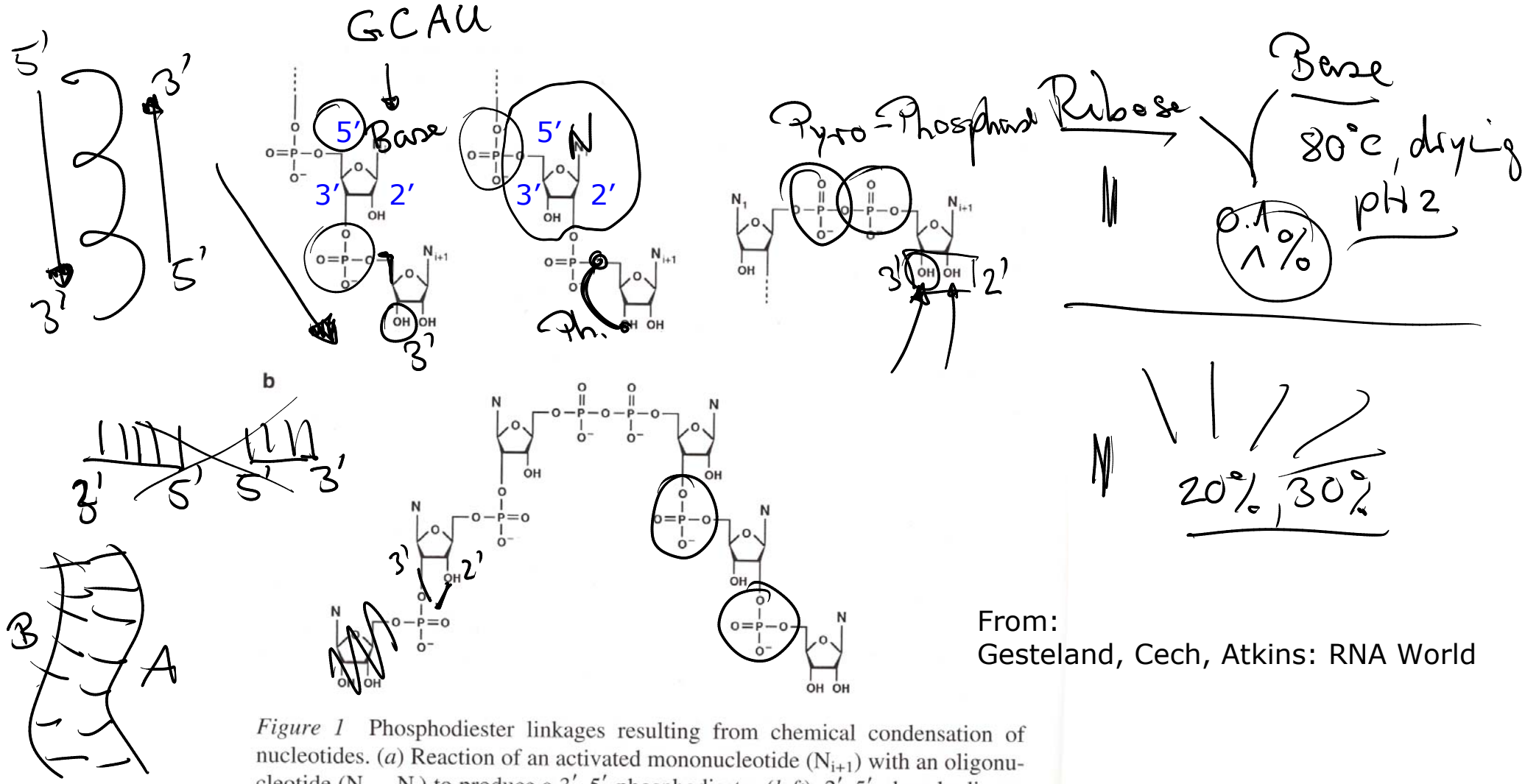
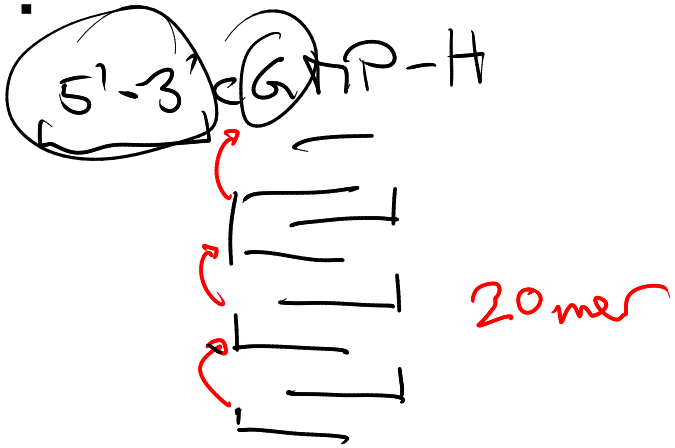
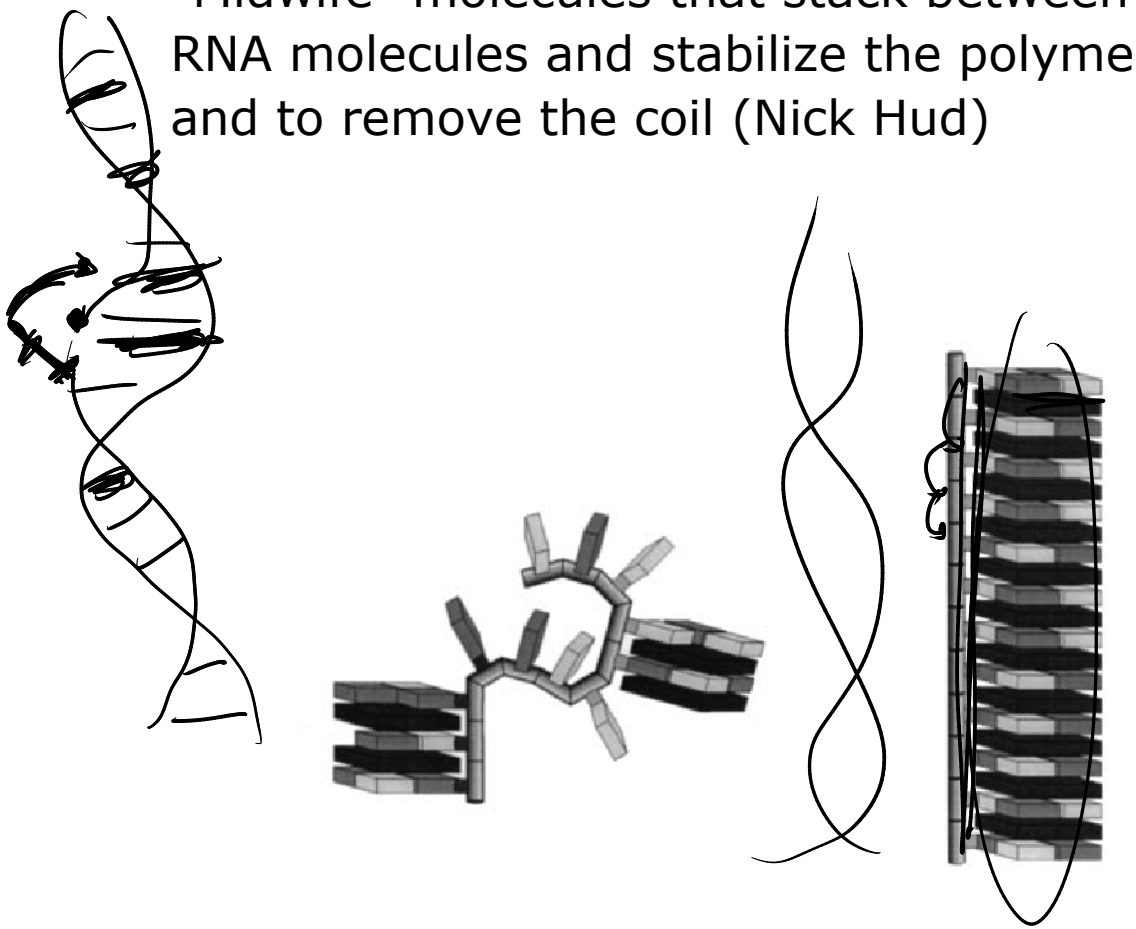


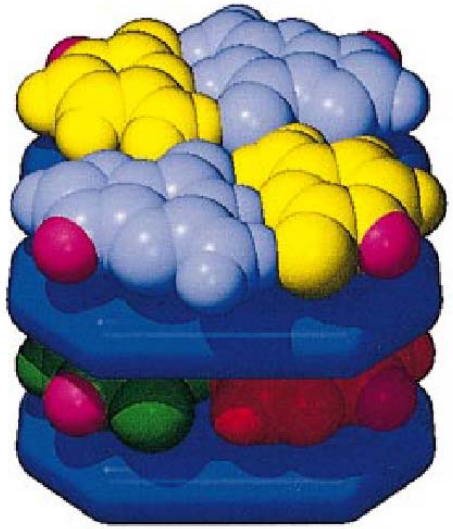
Figure 1 Phosphodiester linkages resulting from chemical condensation of nucleotides. (*a*) Reaction of an activated mononucleotide (N_{i+1}) with an oligonucleotide ($N_1 - N_i$) to produce a 3′, 5′-phosphodiester (*left*), 2′, 5′-phosphodiester (*middle*), or 5′, 5′-pyrophosphate (*right*). (*b*) Typical oligomeric product resulting from chemical condensation of activated mononucleotides.

Polymerization help?

An idea:
"Midwife" molecules that stack between
RNA molecules and stabilize the polymerization
and to remove the coil (Nick Hud)







Ferris: Clay-based polymerisation

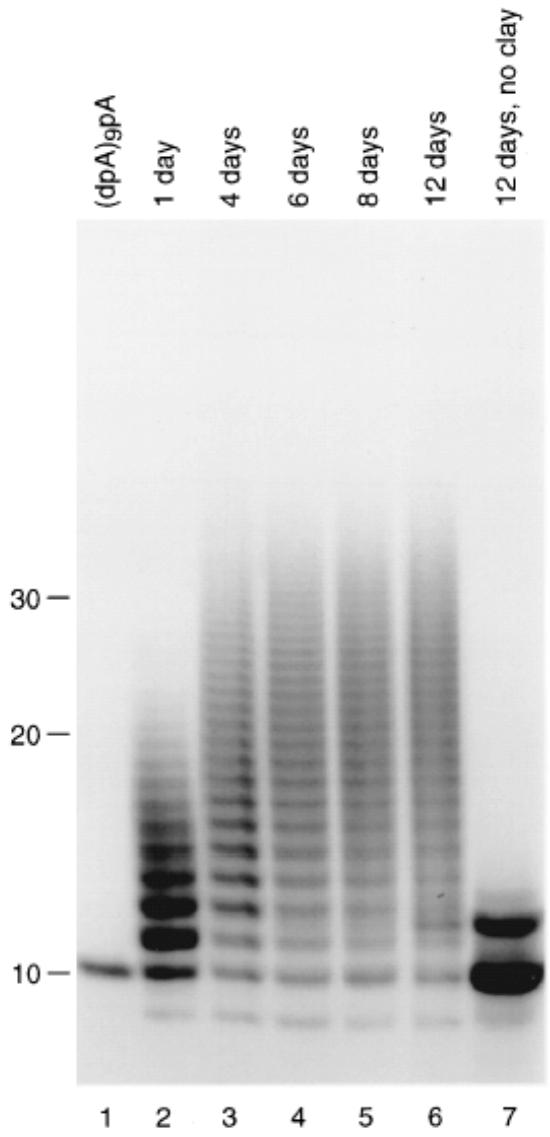
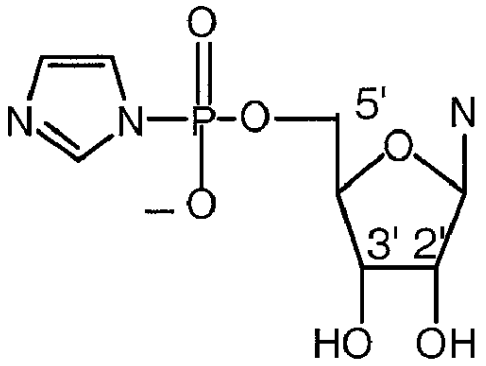


Figure 2. Gel electrophoresis of the elongation of ^{32}pdA(pdA)$_8$pA with ImpA in microcentrifuge tubes. Lane 1, ^{32}pdA(pdA)$_8$pA; lanes 2–6 elongation in the presence of montmorillonite; lane 7, elongation in the absence of montmorillonite.



On the **surface of negative charged montmorillonite** clay, energy rich nucleotide-primers can undergo efficient polymerization. One can reach **30-50-mers within some days**. Surfaces are therefore interesting places for catalysis of prebiotic reactions since they can enhance the concentration of the molecules. Problem is the removal of the polymerized species from the surface and replication priming.

James P. Ferris: Origins of Life and Evolution of the Biosphere **32:** 311–332, 2002.

Wächtershäuser: Life on crystals of “fool’s gold”

Many ideas to the origins of life focus on an **heterotrophic organism**: already quite sophisticated molecules are fed to the organism. **Autotrophs** on the other side synthesize everything from simple carbon sources: such as plants living from H_20 and $C0_2$ by photosynthesis. Wächtershäuser (living in Munich!) conceived a way to for an autotrophic origin of life on a Pyrite (FeS_2) crystal, also called the fool’s gold. This is the most stable ferrous mineral under anaerobic conditions and ubiquitous in ancient rocks, the **chimneys of hydrothermal vents consists largely of FeS_2**.

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The common reaction **to form FeS_2** from Fe and H_2S **releases H_2** which yields important reducing power to form organic molecules from stable carbon sources such as CO_2.

A “**surface metabolist**” consists of the “totality of all surface-bonded organic constituents and of their pyrite base”. Wächtershäuser searches for the **first biochemical pathways**, going back from the most basic pathways of modern organisms. One can imaging polar lipids to be formed on the pyrite, yielding a membrane between pyrite and the other reactions on the pyrite. Further growth of pyrite might lead to **“vesicles” with pyrite grains** in them. One might assume budding of new crystals into new vesicles. Again the **metabolism is first** in this scenario.

Huber and Wächtershäuser showed **synthesis** of interesting intermediates and **polymerization** of activated amino acids both at 100°C and conditions almost comparable to modern hydrothermal vents.

Cairns-Smith's Seven Clues to the Origin of Life

Facts:
- There is life on Earth
- All known living things are at root the same
- All known living things are very complicated

To start, let us:
- not say that the law of nature was broken
- not say it was a freak event
- not say there was a guiding principle
- not say it was an outside job from space

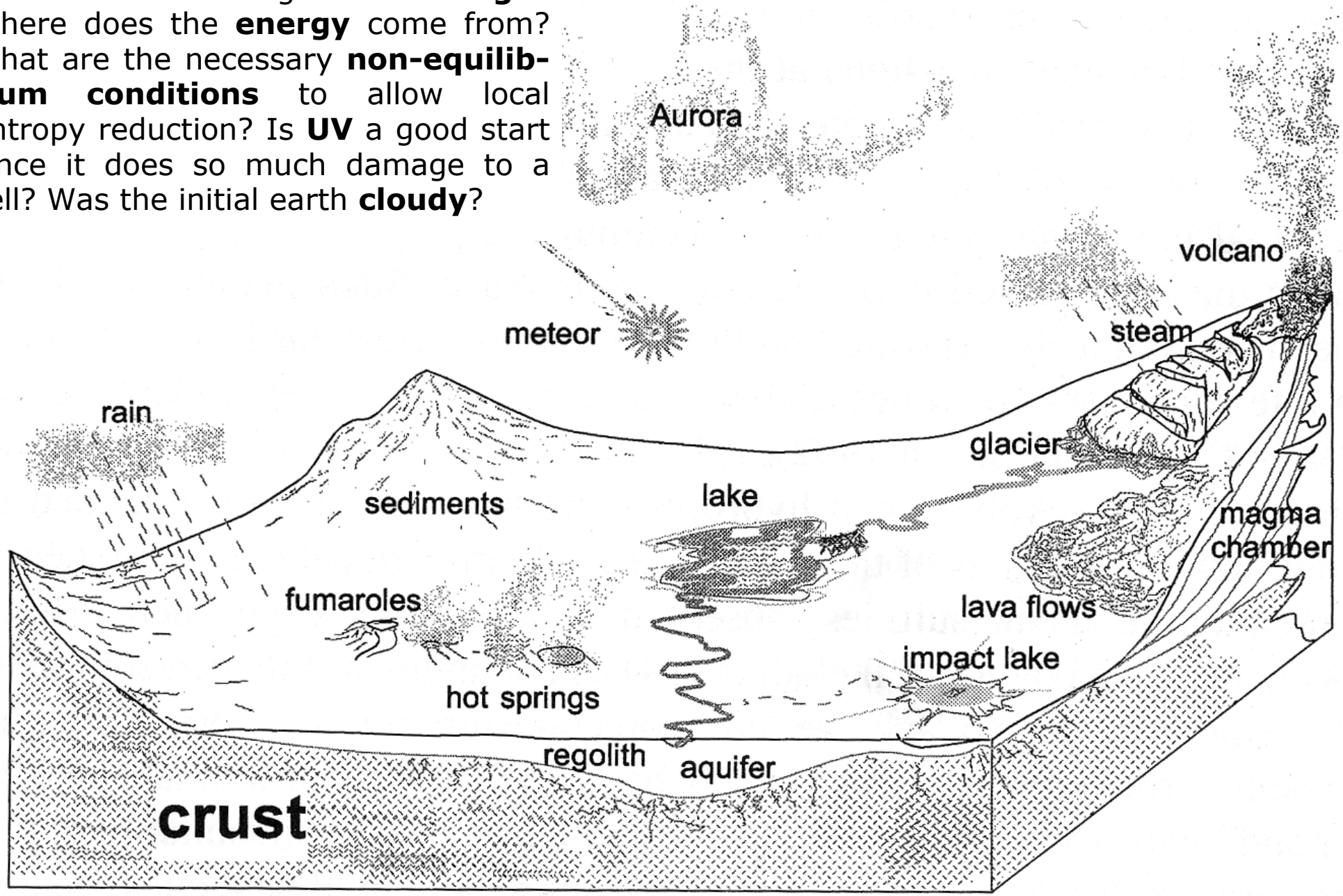
Cairns-Smith's Clues:

1. *From biology*. "Genetic information can evolve through selection since it passes between generations". Therefore, we have to search for some 'naked genes'.
2. *From biochemistry***.** DNA/RNA is difficult to synthesize and 'suburban' as compared to other metabolic pathways. Might there be a late arrival of genetic polymers?
3. *From the building trade.* "To make an arch, you need a scaffold. It is possible that life has evolved on a scaffold totally absent in modern biochemistry".
4. *From the nature of ropes.* "Like fibers in a rope, organisms based on one genetic material could evolve into organisms based on an entirely different genetic material."
5. *From the history of technology*. "The primitive machinery has to be easy to make from immediately available material; and it must work with minimum fuss."
6. *From chemistry*. Crystals put themselves together in a way that might be suitable for 'low-tech' genetic materials.
7. *From geology.* The earth makes clay, tiny crystals, all the time.

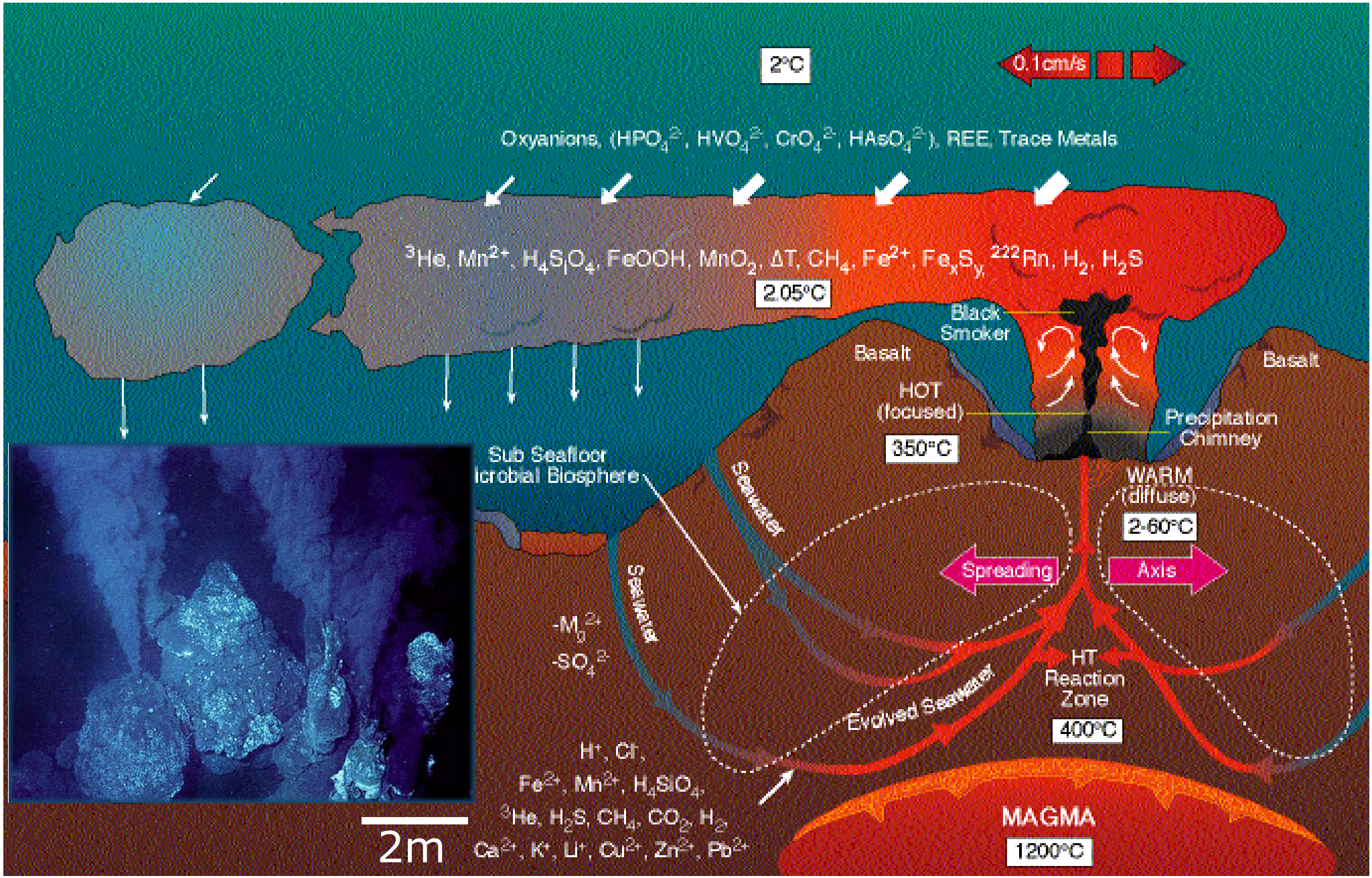
Locations, Locations, Locations...

Locations: Shore, Tide + UV

Where is the **carbon source**? **Where** can the first living creatures **go**? Where does the **energy** come from? What are the necessary **non-equilibrium conditions** to allow local entropy reduction? Is **UV** a good start since it does so much damage to a cell? Was the initial earth **cloudy**?



Locations: Hydrothermal Vents



Locations: Hydrothermal Vents

Figure 2.13. Perspective drawing of the eruptive fissure (axial valley) at 9°N on the East Pacific Rise. The linear fissure defines the ridge axis and the locus of incremental spreading. Note the "bathtub rings" along the margin of the fissure, lava tubes and other drainback features, and the fissure-controlled distribution of high-temperature vents along the one wall. From Fornari and Embley 1995 (artist: P. Oberlander, Woods Hole Oceanographic Institution).

From:
van Dover: The ecology of deep-sea hydrothermal vents

Locations: Hydrothermal Vents

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Advantages of a hydrothermal vents scenario of the origin of life:

- **Methane** is present at high concentrations: useful to form HCN as first important metabolite.
- Discovery of **Archaea** as bacteria-like creatures which can survive at high temperatures (110°C) and within rock. They are at oldest part of the tree of life.
- Earth was initially under **heavy meteorite bombardment** - a deep-sea origin of life would have had stable conditions. Vents existed all the time.
- Strong **gradients of temperature, pH, redox-potential**, chemicals generate a rich far-from-equilibrium system to drive metabolisms and reproduction.

Disadvantage:

- Risk that chemicals become **heat-degraded** at 370°C. Yet even at this temperatures, stabilization by adsorption to surfaces is possible.
- Fast turnover of central vents

From:
van Dover: The ecology of deep-sea hydrothermal vents

Locations: Hydrothermal Vents

Composition of **chemicals in the central, hot hydrothermal vent water** shows high methane concentrations, reduced salts and much sulfur. These concentrations make it interesting for prebiotic synthesis of molecules.

TABLE 3.1.
Chemical composition of typical 350°C black-smoker fluid compared to seawater

Element	*Hydrothermal Fluid*	*Seawater*	*Units*	*Enrichment Factor (minimum)*
H_2S	3–12	0	mM kg^{-1}	∞
H_2	0.05–1	0	mM kg^{-1}	∞
CH_4	25–100	0	μM kg^{-1}	∞
Mn	360–1140	0	μM kg^{-1}	∞
Fe	750–6500	0	μM kg^{-1}	∞
Be	10–40	0	nM kg^{-1}	∞
Zn	40–100	0.01	μM kg^{-1}	4000
Cu	10–40	0.007	μM kg^{-1}	1500
Ag	25–40	0.02	nM kg^{-1}	1250
Pb	10–360	0.01	nM kg^{-1}	1000
Co	20–220	0.03	nM kg^{-1}	650
Si	15–20	0.05	mM kg^{-1}	300
Al	5–20	0.02	μM kg^{-1}	250
Ba	10–40	0.15	μM kg^{-1}	66
Cs	100–200	2	nM kg^{-1}	50
Li	410–1320	25	μM kg^{-1}	16
Rb	10–30	1	μM kg^{-1}	10
CO_2	5–15	2	mM kg^{-1}	2.5
Ca	10–55	10	mM kg^{-1}	1
Sr	90	85	μM kg^{-1}	1
B	450–560	415	μM kg^{-1}	1
As	30–450	30	nM kg^{-1}	1
Se	1–75	2	nM kg^{-1}	0.5
P	0.5	2	μM kg^{-1}	0.25
Mg	0	50	mM kg^{-1}	0
SO_4	0–1	30	mM kg^{-1}	0
Alk	(−0.1)-(−1)	2	mM kg^{-1}	0

From summary data in Elderfield and Schultz (1996), but with numbers rounded and ranked by degree of enrichment above seawater.

Locations: Hydrothermal Vents

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Co	20–220	0.03	nM kg^{-1}	650
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P	0.5	2	μM kg^{-1}	0.25
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Alk	(−0.1)-(−1)	2	mM kg^{-1}	0

From summary data in Elderfield and Schultz (1996), but with numbers rounded and ranked by degree of enrichment above seawater.

Locations of modern life near hydrothermal vents.

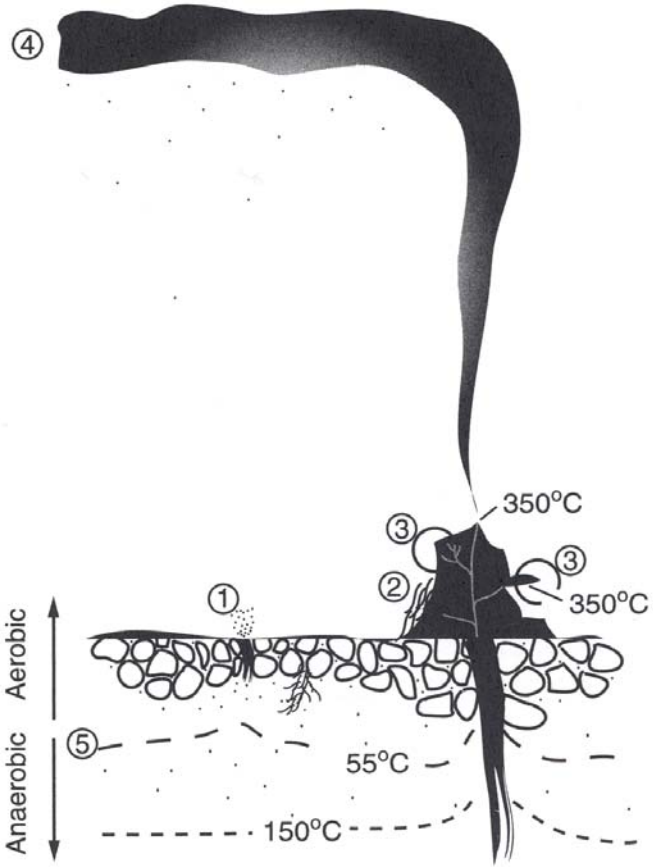


Figure 5.2. Principal habitats of free-living microorganisms as discussed in the text: (1) Suspended microorganisms in outflow of warm-water vents; (2) bacterial mats and colonies (on rock, mineral, and biotic surfaces); (3) hyperthermophiles within a mineral matrix of sulfide structures (including flanges) and near the orifice of black smokers; (4) microbial populations of the neutrally buoyant plume; (5) subsurface microbial populations in porous basalt.

Different Hydrothermal Vents

Table 1 Summary of vent fluid data

Location	Host rock	*T* (°C)	pH	Mg (mmol kg^{-1})	Ca (mmol kg^{-1})	Na (mmol kg^{-1})	Cl (mmol kg^{-1})	SO_4 (mmol kg^{-1})	H_2S (mmol kg^{-1})	CH_4 (mmol kg^{-1})	H_2 (mmol kg^{-1})	Reference
Sea water		7	8.0	54.0	10.4	475	553	28.6	0	4×10^{-7}	4×10^{-4}	
Lost City; 30° N MAR	Peridotite + gabbro	40–75	9–9.8	9–19	21.0–23.3	479–485	546–549	5.9–12.9	0.064	0.13–0.28	0.25–0.43	This work
Rainbow; 36° 14′ N	Peridotite + gabbro	360	2.9–3.1				>750		<2.5	2.2	13.0	19
Broken Spur; 29° N MAR	Basalt	356–360		0	11.8–12.8	419–422	469		9.30	0.06	0.43	38
Lucky Strike;	Basalt	308–324	3.8–6.4	0	32.3–36.7	347–426	417–472		2.1–3.0	0.3–0.7	0.04–0.72	20
37° 17′ N MAR		185–284	3.8–3.9	0	31.3–38.2	363–428	424–514		2.0–3.0	0.4–0.8	0.003–0.27	
Menez Gwen;	Basalt	275–284	4.2–4.8	0	29.7–33.1	312–319	357–381		1.3–1.8	1.5–2.1	0.02–0.05	20
37° 50′ N MAR												
Conical seamount†	Peridotite	3	9.28					30–40	2.1	0.001		11, 12
Endeavour, JdF‡	Basalt	346–370	4.2–4.5	0	13.8–42.9	260–391	350–370	0–2	3.0–8.1	1.8–3.4	0.16–0.42	39–41
21° N EPR	Basalt	273–355	3.3–3.8	0	11.7–20.8	432–510	489–579	0–0.6	6.6–8.4	0.06–0.09	0.23–1.7	40, 41
Oman Ophiolite§	Peridotite	23	11.4–11.6	0.002–0.01	1.5–1.9	11.5–35.9	9.67–26.1	0.05–0.14				42
Experiments‖												
	Harzburgite	300	6.4–11.6	0.002–0.02	0.29–5.24	549–576	512–541	12.1–17.8	0.6–0.8	0.066	0.10–0.33	16
	Lherzolite	200	5.4–8.0	10.7–49.4	7.5–35.7	467–500	534–560	2.04–24.8	ND	ND	ND	16
	Basalt	350	4.8	0.050	18.3	492	581	0.069	7.3	1.0	0.2	43
Theoretical	Peridotite	350	6.5–6.6	0.07–0.1	27.6–35.6	471–543	550–612	≪1.0	3.2–6.3		20.96–164.9	17

From:
An off-axis hydrothermal vent Field near the Mid-Atlantic Ridge at 30°N, NATURE:412:145-149 (2001)

“Lost City”: Off ridge hydrothermal vent

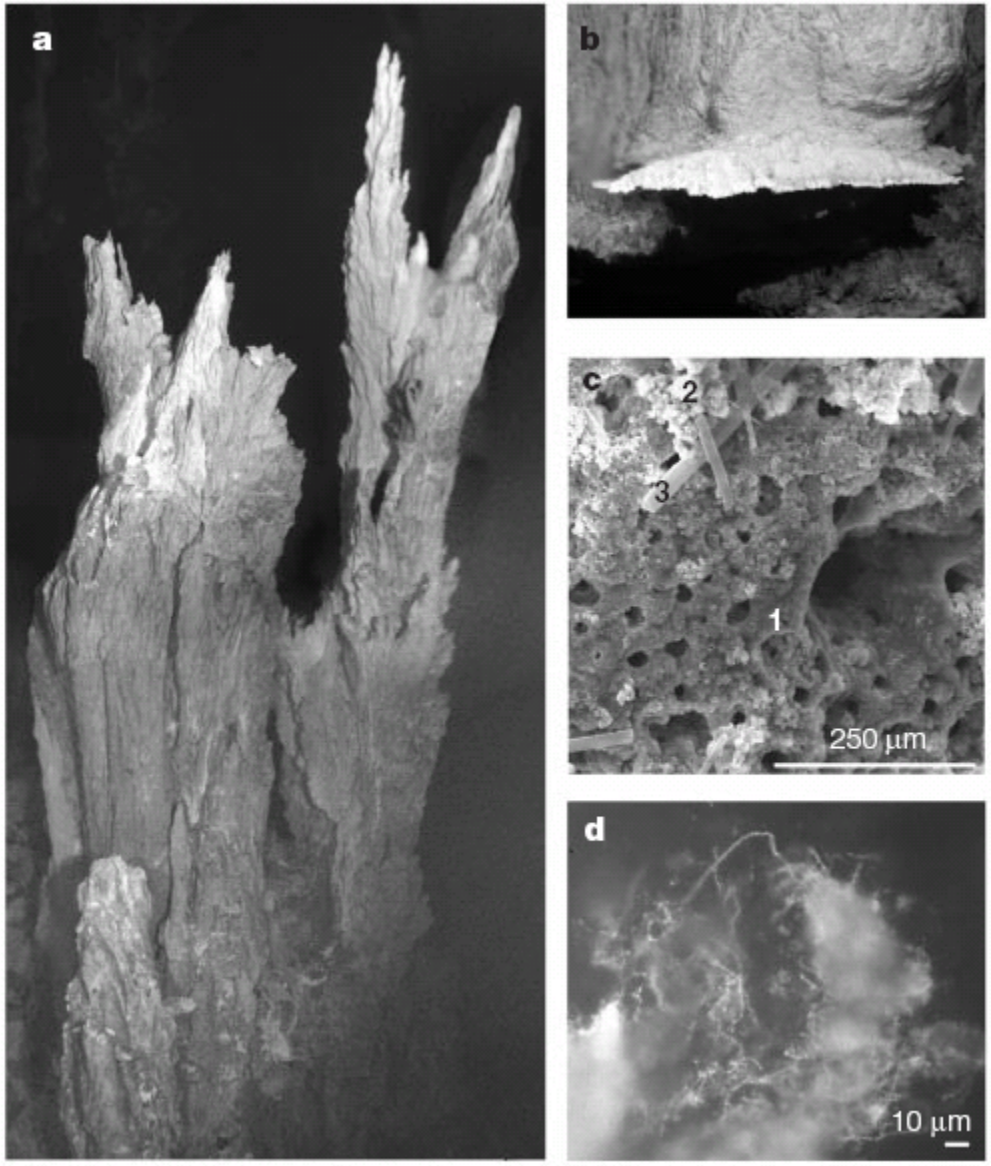
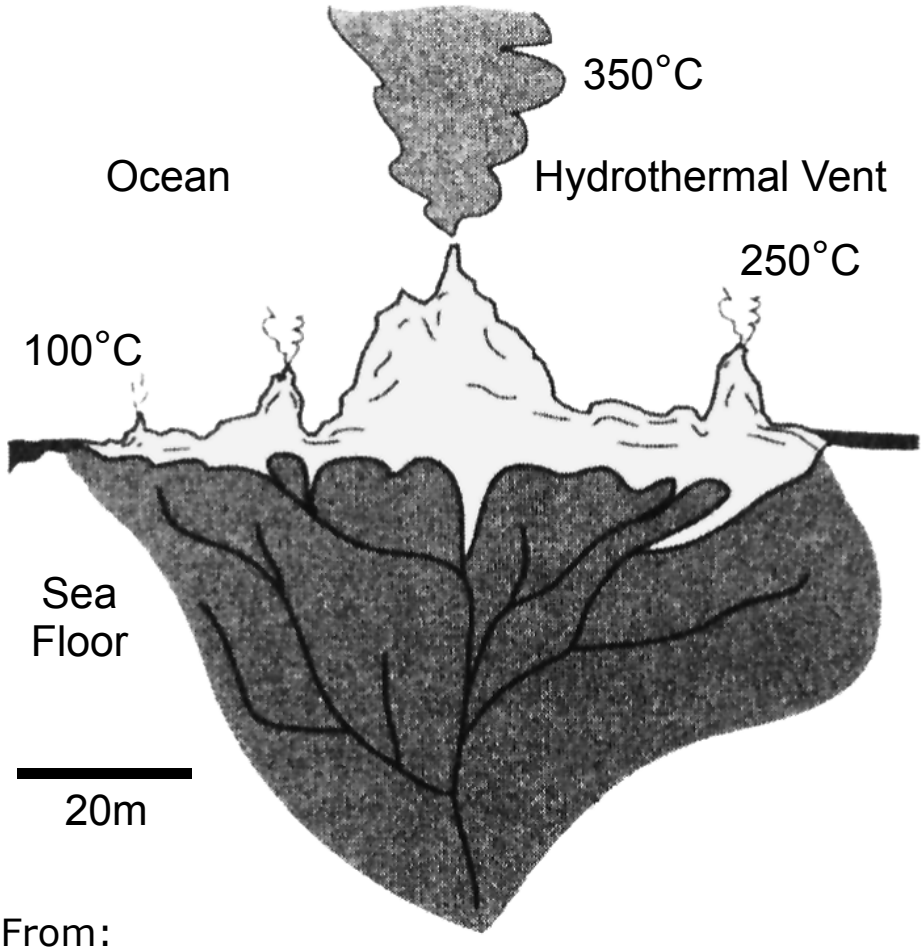


Figure 2 Hydrothermal deposits and microbial communities within the Lost City field. **a**, Photomosaic of an inactive 8-m-tall carbonate chimney in the eastern portion of the Lost City field. This mosaic was produced from digital still camera imagery collected every 15 s by the remotely operated vehicle *Argoll*. The calcite, aragonite and brucite chimneys form delicate to massive pinnacles that reach up to 60 m in height. **b**, Aragonite and brucite flange venting 40 °C fluids (shimmering water in left portion of the image). The carbonate ledges grow horizontally out from the chimney walls and trap buoyant reflecting pools of warm water, which seeps out from the main structure walls. Mixing of sea water and diffusely venting fluids that spill out upward over the lip of the flanges, and up through porous flange tops results in outward growth and thickening of the flanges. The flange shown in this image is about 1 m in width and hosts abundant microbial communities. **c**, Scanning electron image (SEM) of a piece of the flange shown in **b**, collected with *Alvin*. Elemental detection and X-ray diffraction analyses of this sample show that it contains a fine porous matrix of calcium carbonate (aragonite) (point 1), and magnesium hydroxide ($Mg(OH)_2$) minerals (points 2 and 3), which exhibit variable morphologies. The SEM used was an ISI DS-130s with an operating voltage of 18 kV. The images were collected using IXRF Iridium II EDS software. Molecular ratios were determined using ZAF (atomic number, absorption, fluorescence) corrections after deconvolution through the IXRF software. Specimens were sputter coated with palladium before being analysed. **d**, Epifluorescent microphotograph of DAPI (4′,6-diamidino-2-phenylindole)-stained filamentous microbial communities in the flange sample collected from the site shown in **b**. Continuous biofilms composed of several types of microbial cells were observed attached to mineral surfaces within the active vent structures. Microbial cells ranged from 0.5 to 2.0 μm in diameter and included cocci, rods and filaments. Significant biomass is observed within the active samples recovered.

From:
An off-axis hydrothermal vent Field near the Mid-Atlantic Ridge at 30°N, NATURE:412:145-149 (2001)

Locations: Hydrothermal Vents

The precipitation of **silica-sulfate** near the hydrothermal channels and of **porous, massive sulfide** gives rise to - sometimes very - large chimney structures. They have a life-time of some years. Below the surface, there is a large **dendritic flow system.**



From:
van Dover: The ecology of deep-sea hydrothermal vents

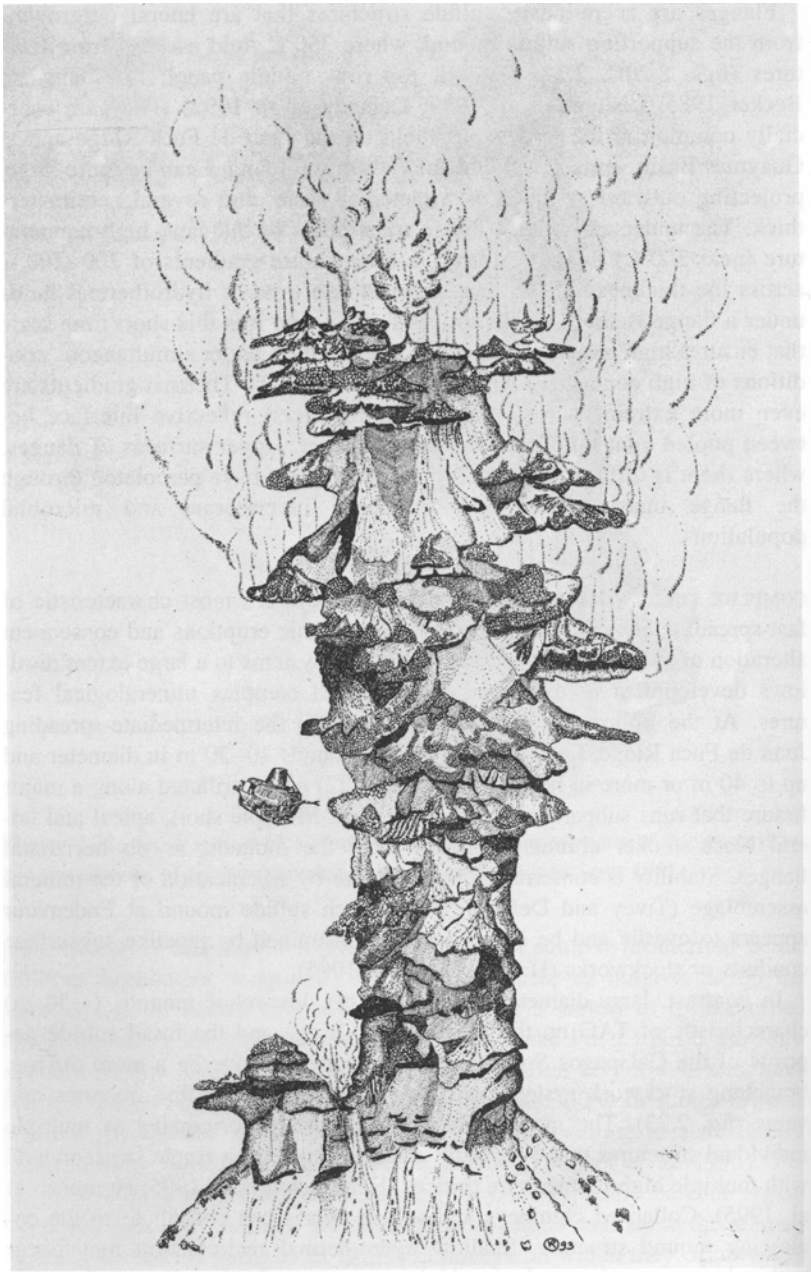
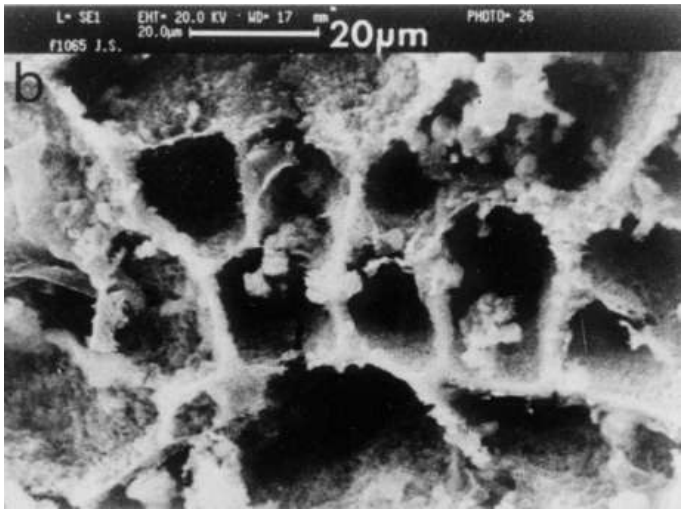


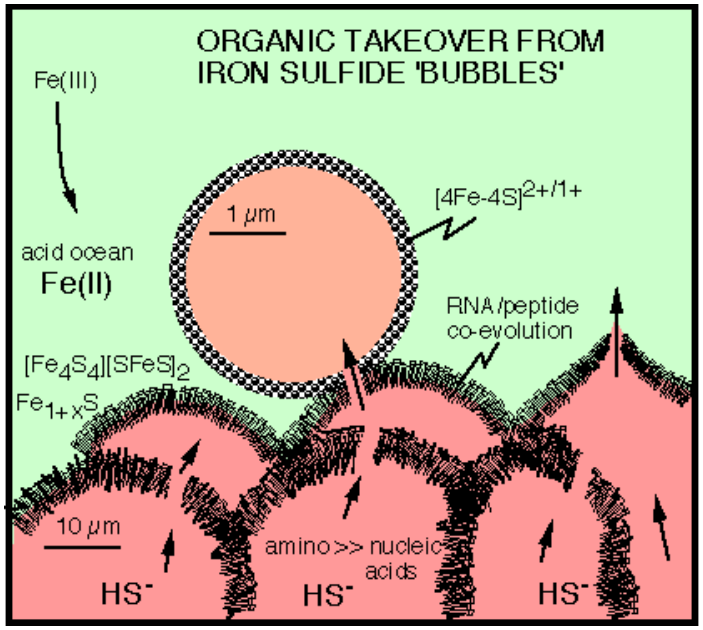
Figure 2.22. "Godzilla," a 45-m-high sulfide mound with flanges on the Juan de Fuca Ridge. The submersible *Alvin* is drawn to scale. From Robigou et al. 1993.

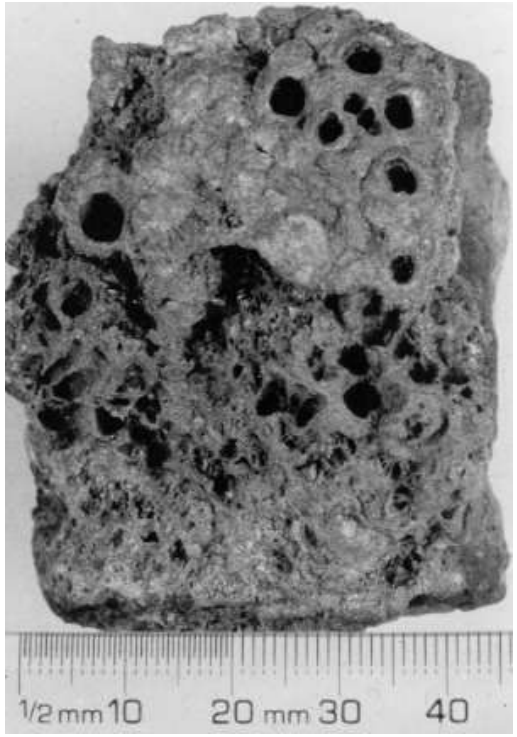
Vesicles as ancestors of modern cells?

Many researches tend to believe that vesicles were **not the place for first replicating molecules**. E.g. Manfred Eigen: "**organization into cells was surely postponed as long as possible**. Anything that interposed spatial limits in a homogeneous system would have introduced **difficult problems** for prebiotic chemistry. Constructing boundaries, transposing things across them and modifying them when necessary are tasks accomplished today by the most refined cellular processes." (Scientific American, 1981: p.91-92).

In many aspects, vesicles are considered too much "equilibrium" than "non-equilibrium" boundary conditions. The exception being **voltage and redox gradients across the membranic boundaries of volcanic rock enclosures**, envisioned by Michael Russell (www.gla.ac.uk/projects/originoflife/).







In Vitro Evolution

Spiegelman: Evolution in the Qβ-virus model

Spiegelman used Qβ-virus that attacks E.coli to demonstrate evolution in the lab. Upon infection, the virus first translates its RNA into a complementary strand which is used to get the original RNA. This replication could be shrunk in a test tube with only three components: the RNA of the virus, the Qβ-Replicase enzyme and activated nucleotides.

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It could be shown:

- Shorter and shorter RNA was created when the selection pressure was on fast replication: sequence information needed to infect E.coli was removed over time.
- Resistance against high temperatures and RNA degrading enzymes could be bred.
- Replication could be even triggered without an initial RNA template (Eigen et.al.).

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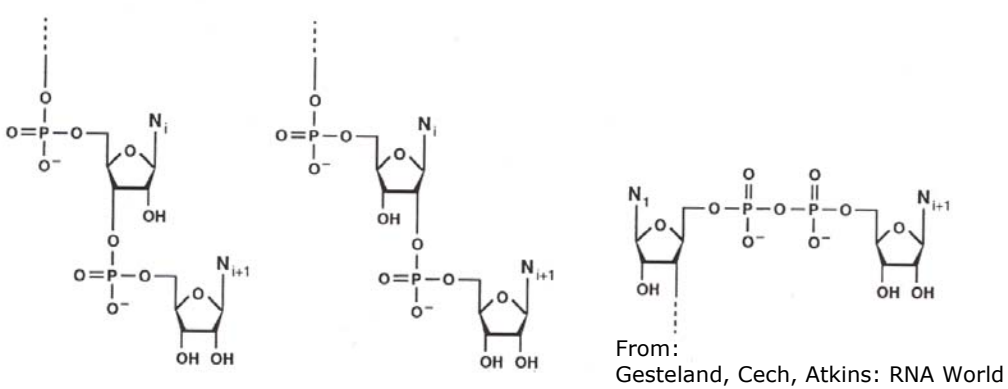
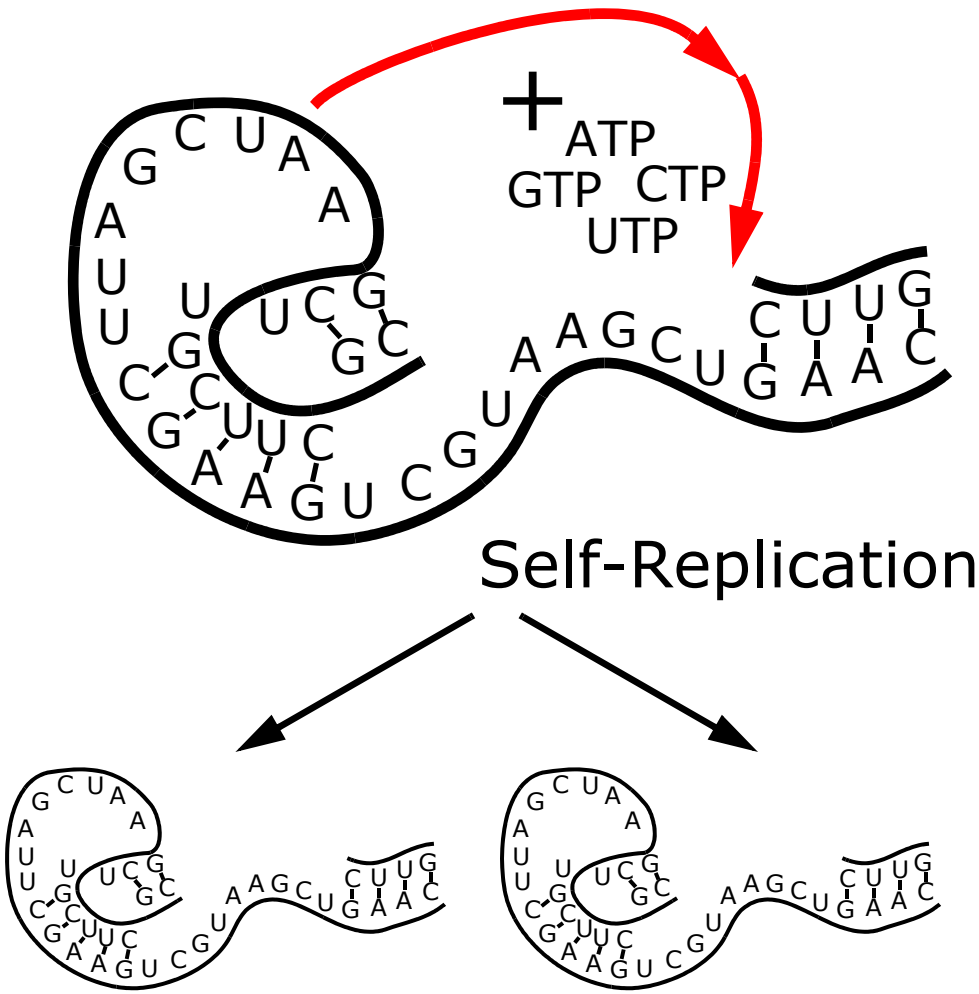
Orgel in the 70s pushed it further by dropping the enzyme. Its existence is anyhow unrealistic for an origin of life scenario. He searched for direct replication on a single stranded RNA. Some short complementary strands could be found in favorable and peculiar environmental conditions, but the polymerization did not produce a correct 3'-5' backbone of the complementary RNA molecule:



From:
Gesteland, Cech, Atkins: RNA World

Eigen established a model for approaches where the RNA itself catalyses the replication

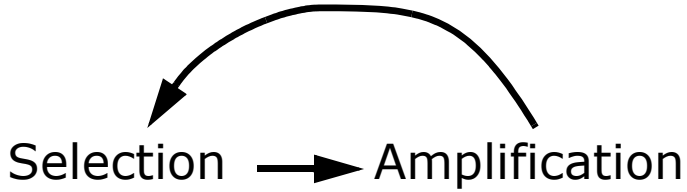
RNA World

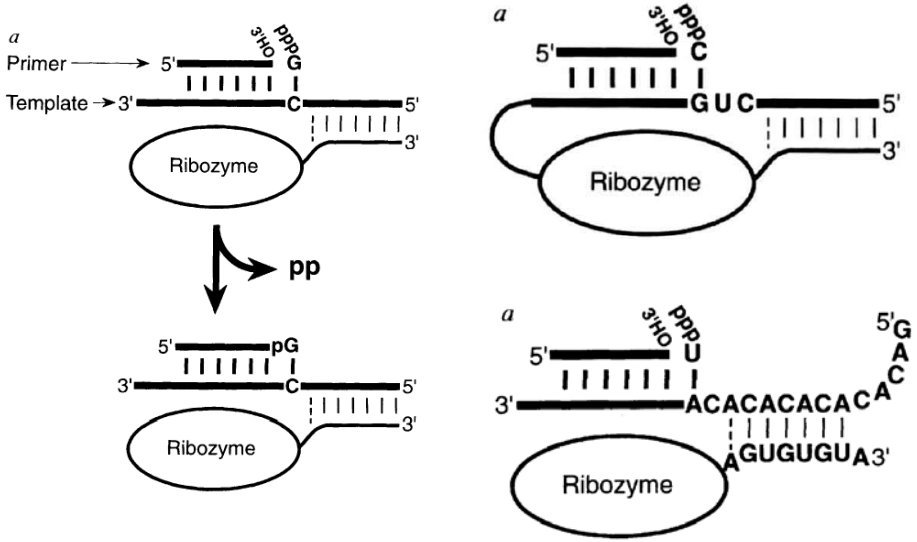


Based on the antiquity of Rybozymes it is argued that RNA might have been the earliest "protein" to replicate, i.e. to replicate itself.

The idea is that dNTPs can be polymerized into a polymerase molecule, allowing for self sustained darwinian evolution within one molecule.

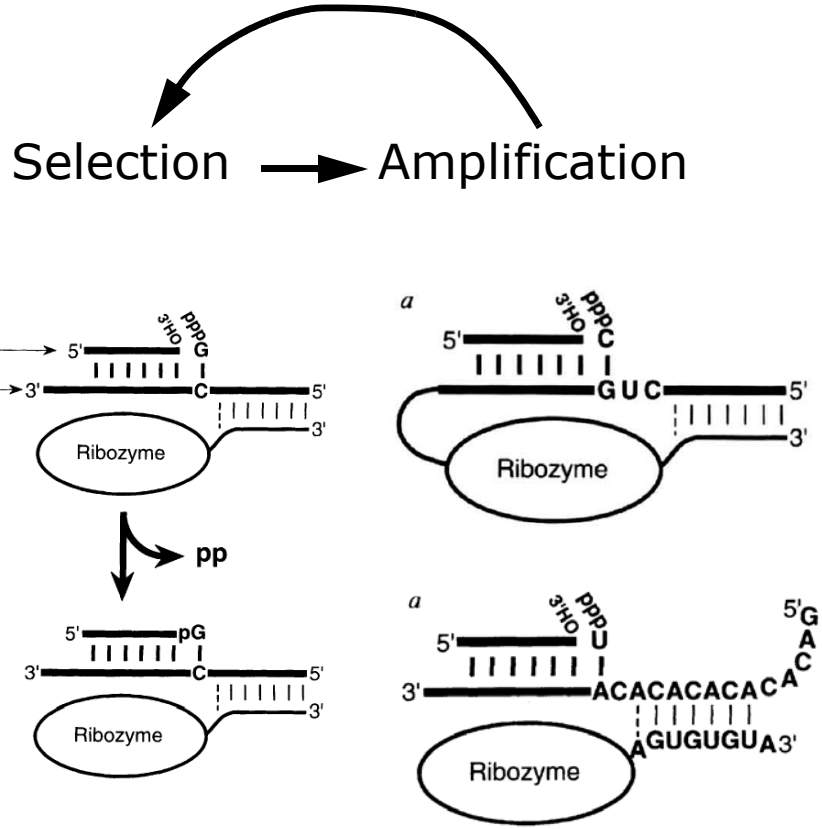
Testing the RNA world: in vitro selection





Replicating for the first base has a fidelity of >95%. However not much more than three bases can be added. The complementary strand shows no catalytic potential.

Testing the RNA world: in vitro selection



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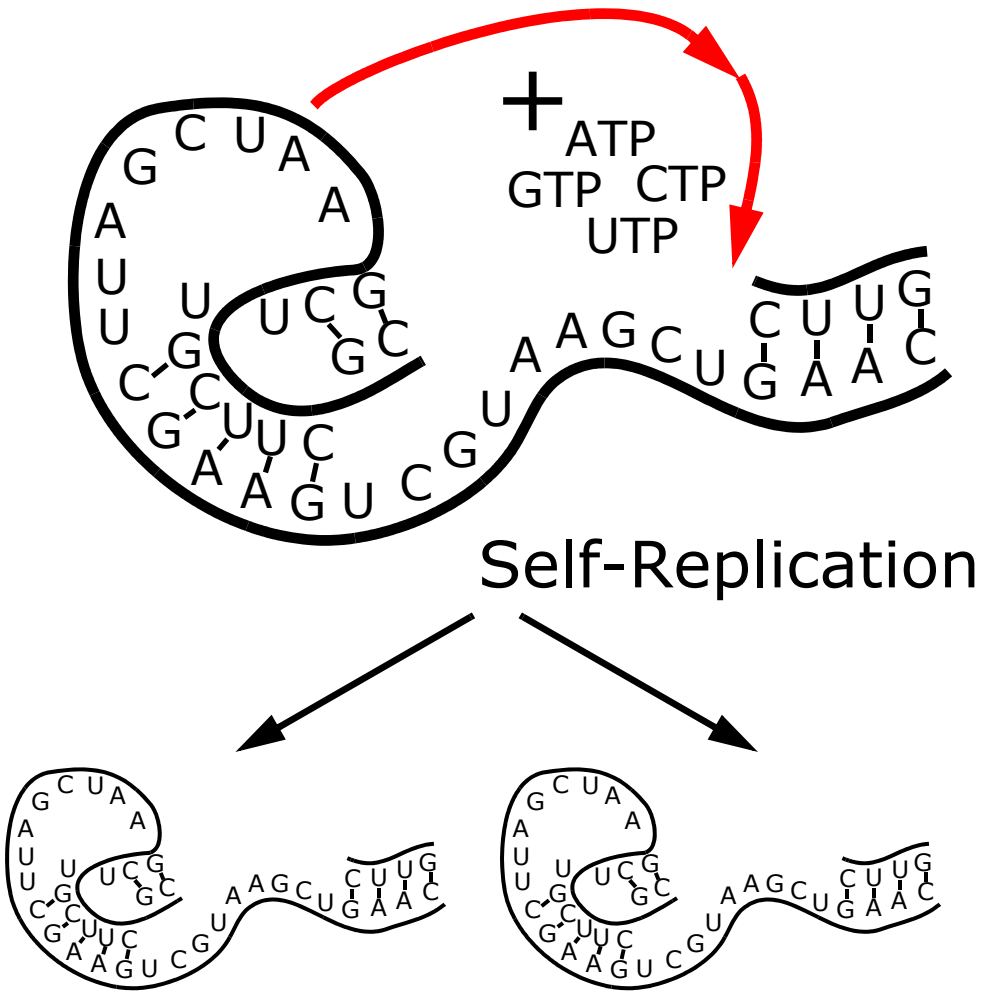
Starting from an already engineered pool of sequences, one can indeed find RNA molecules that can at 1-3 activated base pairs to the end of an already double stranded RNA piece (Ekland&Bartel, 1996) (Szostak&Bartel 1993).

The reaction goes through many cycles of selection and amplification. Note that no high mutation is built into the process. This process can amplify the advantageous molecule exponentially. It needs good balance of selection pressure and amplification strength. This scheme was used in many different areas of biochemistry to 'breed' molecules (note there often is no mutation) like we bred animals. Check

www.pubmed.org for publications

Models of Chemical Evolution

Eigen & Schuster: Selfreplicative Molecules



Eigen and Schuster applied population dynamics to self-replicating molecules, for example to RNA strands.

The idea is that there might exist RNA molecules that can duplicate themselves from activated (and unstable) Tri-Phosphate nucleotides (dNTP). Eigen&Schuster studied these systems in theory.

The equations are easily understood based on standard population dynamics.

Basic Population Dynamics

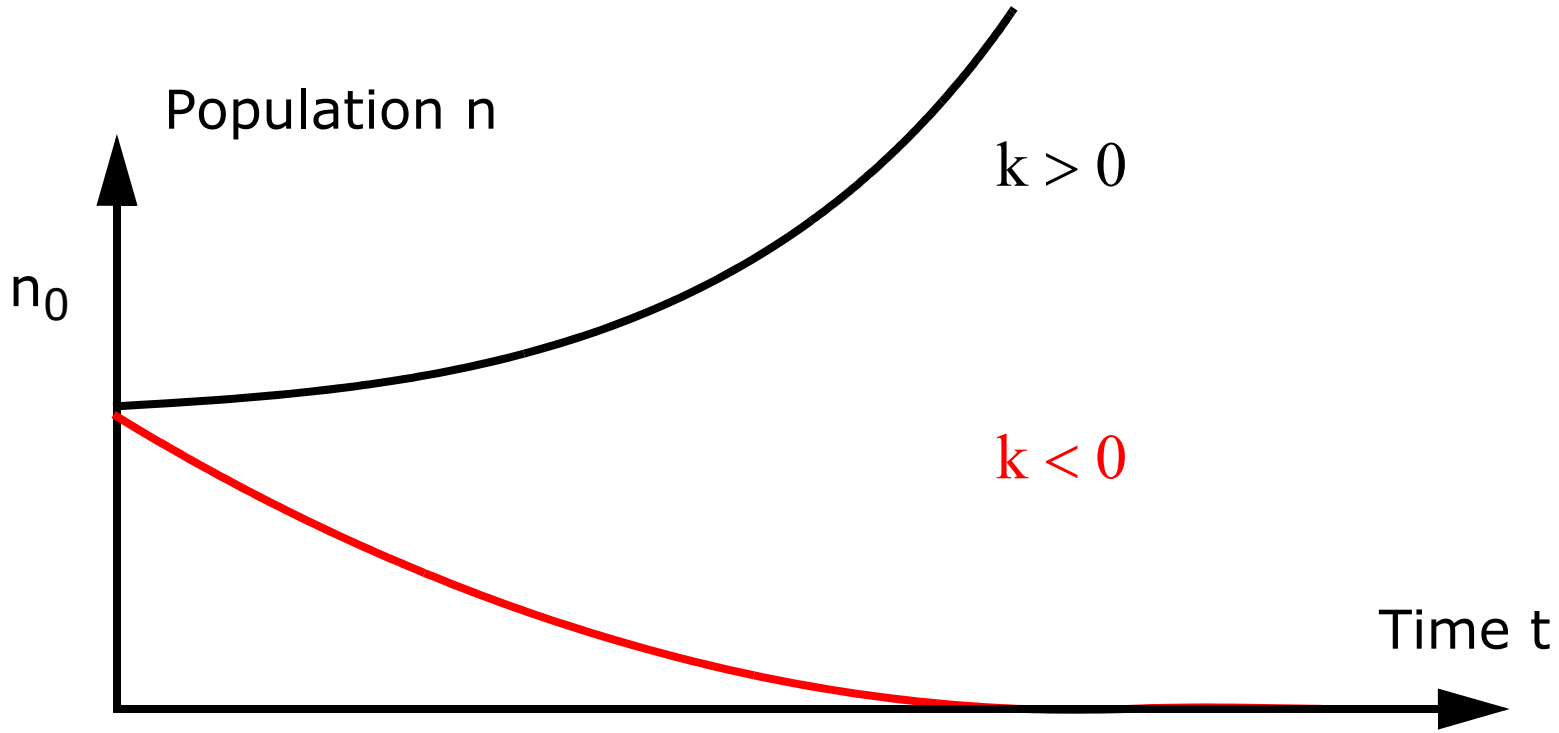
$$\dot{n} = \frac{dn}{dt} = kn$$

$$k = k_p - k_m \qquad \text{Units of k: 1/s}$$

$$n = n_0 e^{kt}$$

Basics:

Most basic is the exponential growth or decay law with a rate k. Based on a propagation rate k_p and a mortality rate k_m the population of a species either grows or shrinks exponentially.

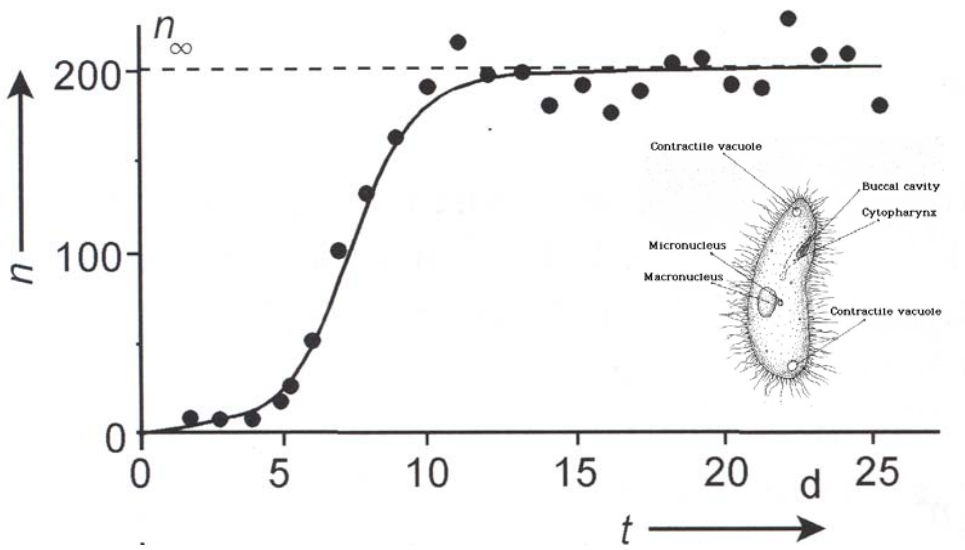


Basic Population Dynamics

$$\dot{n} = (k_p - k_m n)n$$

$$n = \frac{n_0 k_p e^{k_p t}}{k_p + k_m n_0 (e^{k_p t} - 1)}$$

$$n \to \frac{k_p}{k_m}$$



From: Roland Glaser: Biophysics

Basics:

Most simple models of populations start with a first order rate equation of number of entities n with a propagation rate k_p. It leads to exponential growth for positive k_p and to exponential decline for negative k_p.

Most simple way to implement a limitation of the growth, for example by limiting the food available, is to introduce a negative, quadratic term. It implements a mortality term k_m*n which depends on the number of entities.

This most simple approach has the logistic function as solution and can be used for example to model the growth of paramecium, a single cellular organism (Fig. left).

Basic Population Dynamics

Food limited growth

$$\dot{n} = (k_p - k_m n)n$$

Competition for food

$$\dot{n}_1 = (k_{p1} - k_{m1}(n_1 + n_2))n_1$$

$$\dot{n}_2 = (k_{p2} - k_{m2}(n_1 + n_2))n_2$$

Competition Models

Basic competition models involve competing for food or a hunter-prey relationship.

Competition for food is the simple expansion of the previous limited growth model.

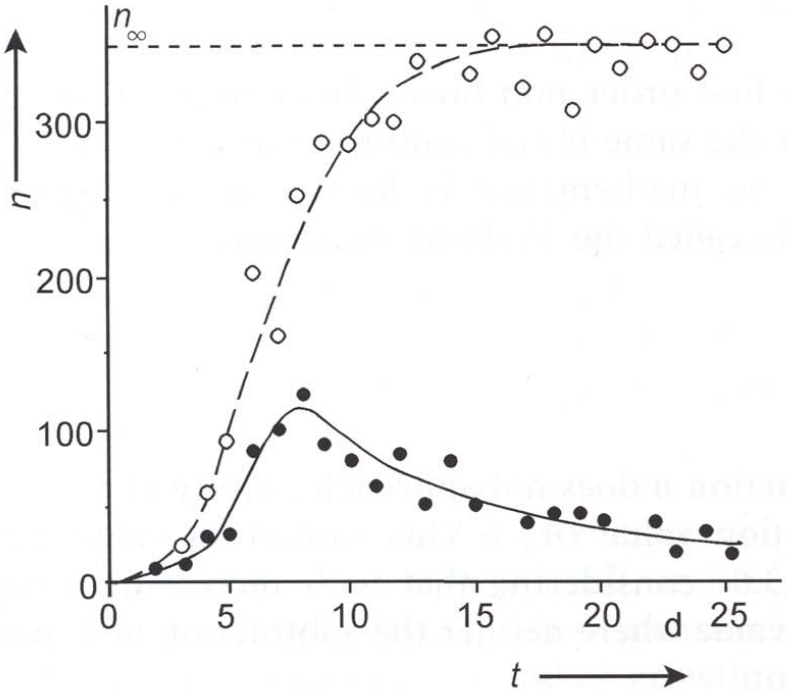
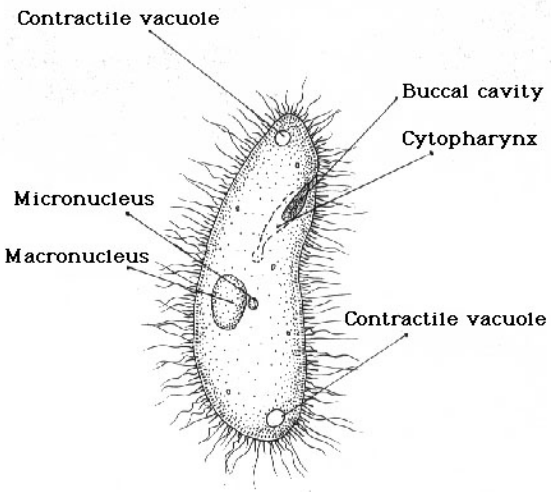


Fig. 5.18. The time dependence of the growth of a pure population of *Paramecium caudatum* (•——• above) and mixed together with a population of *Paramecium aurelia* (○- - -○). The ordinate indicates the number of individuals (n) per 0.5 ml medium. The abscissa gives the time in days (d). (Data from Gause 1935)



From:
Roland Glaser: Biophysics

Basic Population Dynamics

Hunter-Prey relationship (Volterra-Lotka)

$$\dot{n}_P = (k_{pP} - k_{mP} n_H) n_P$$

$$\dot{n}_H = (k_{pH} n_P - k_{mH}) n_H$$

The same logic is applied to hunter-prey relationships, studied in the 1930 by Volterra and Lotka. The mortality rate of the prey depend on the number of hunters and the propagation of hunters depends on the number of prey (see left). These systems can show oscillations in population also recorded in nature (below).

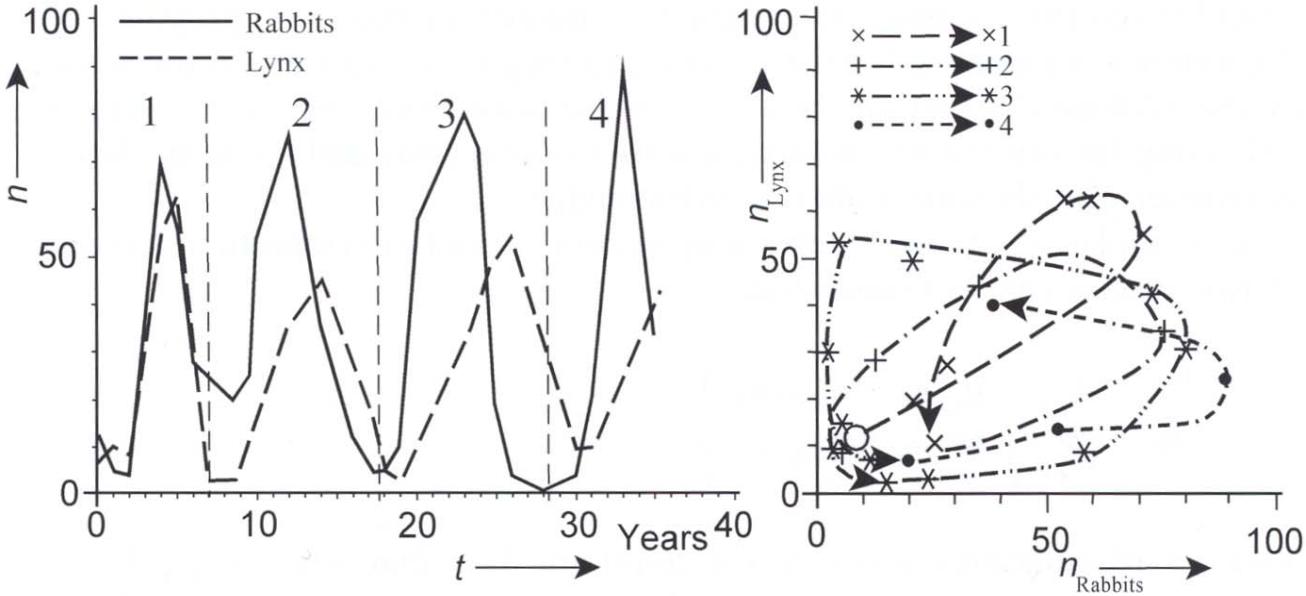


Fig. 5.19. A particular example of population kinetics: the number of pelts, obtained from hunted lynx and snow rabbits in Canada after 1900 (numbers in thousands). On the *left*: time course; on the *right*: the same numbers in a Volterra-plot. The population waves 1–4 of the *left* part of this figure appear as Volterra cycles in the graph on the *right*, starting with the point ○. (Data from Haken 1983)

Simplifications are for example:

- no hunter-hunter interaction
- everything is linearized
- no time delays due to birth/development

From:
Roland Glaser: Biophysics

Eigen & Schuster: Selfreplicative Molecules

$$\dot{n}_i = (k_{pi} q_i - k_{mi}) n_i + \sum_{i \neq j} k_{m,ji} n_j$$

Take molecules the number of molecules n_i of sequence i (also called species) and introduce the following population dynamics:

k_{pi} Propagation rate,
i.e. the ability to self-replicate

k_{mi} Mortality rate and rate to leave the area

$q_i<1$ Replication fidelity

$k_{m,ji}$ Probability to mutate from another species j.

From: Gesteland, Cech, Atkins: RNA World

Eigen & Schuster: Selfreplicative Molecules

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$$\sum_i n_i = \text{const}$$

Note that we enforce additionally a limited total number of molecules.

To make things more realistic, one can group the species into similar and non-competing groups, called quasi-species

From: Gesteland, Cech, Atkins: RNA World

Eigen & Schuster: Error Threshold

Average $\langle x \rangle = \dfrac{\sum_{i \neq j} x n_j}{\sum_{i \neq j} n_j}$

$$\sigma_i = \frac{k_{pi}}{\langle k_p \rangle - \langle k_m \rangle + k_{mi}} > \sigma_j$$

From the Eigen model one can derive the replication fidelity of the best molecule to be able to outgrow all the others. It depends crucially on the length of RNA molecule used.

One can derive that the sequence i is able to outgrow its competitors, if it has a superiority σ_i larger than all others.

From: Gesteland, Cech, Atkins: RNA World

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One can derive that the sequence i is able to outgrow its competitors, if it has a superiority σ_i larger than all others.

$$q_i = q^N > \frac{1}{\sigma_i}$$

This superiority is linked to the replication fidelity of a single base q by the formula to the left.

$$N < \frac{-\ln \sigma_i}{\ln q}$$

This gives a length limitation N depending on the fidelity of replication of the best molecule.

From: Gesteland, Cech, Atkins: RNA World

Eigen & Schuster: Targeting the best

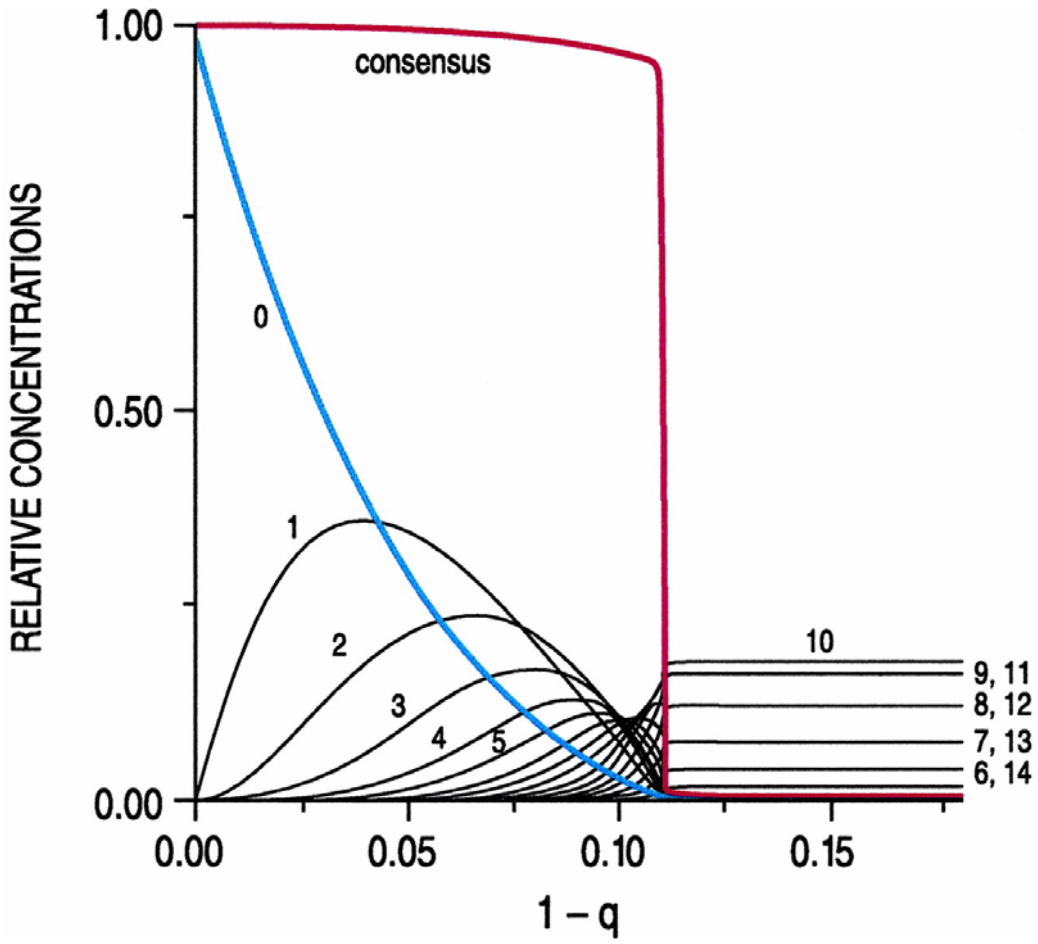


Fig. 1. Relative population numbers of binary sequences S_k (ordinate) as functions of single-digit error rate (1-q) (abscissa). The length of all binary sequences is N = 20. All $2^N=10^6$ sequences are degenerate in their reproductivity except for one "master" sequence S_m, which reproduces 10 times more efficiently than the rest. The resulting quasispecies distribution is centered at the master sequence ("0" errors). The numbers 1, 2, ... 20 refer to the sum of all 1-, 2-, ... 20-error mutants. The red curve refers to the consensus sequence, which shows a sharp first-order phase transition at the error threshold.. From PNAS 99: 13374-13376 (2001).

Replication Fidelity and sequence length

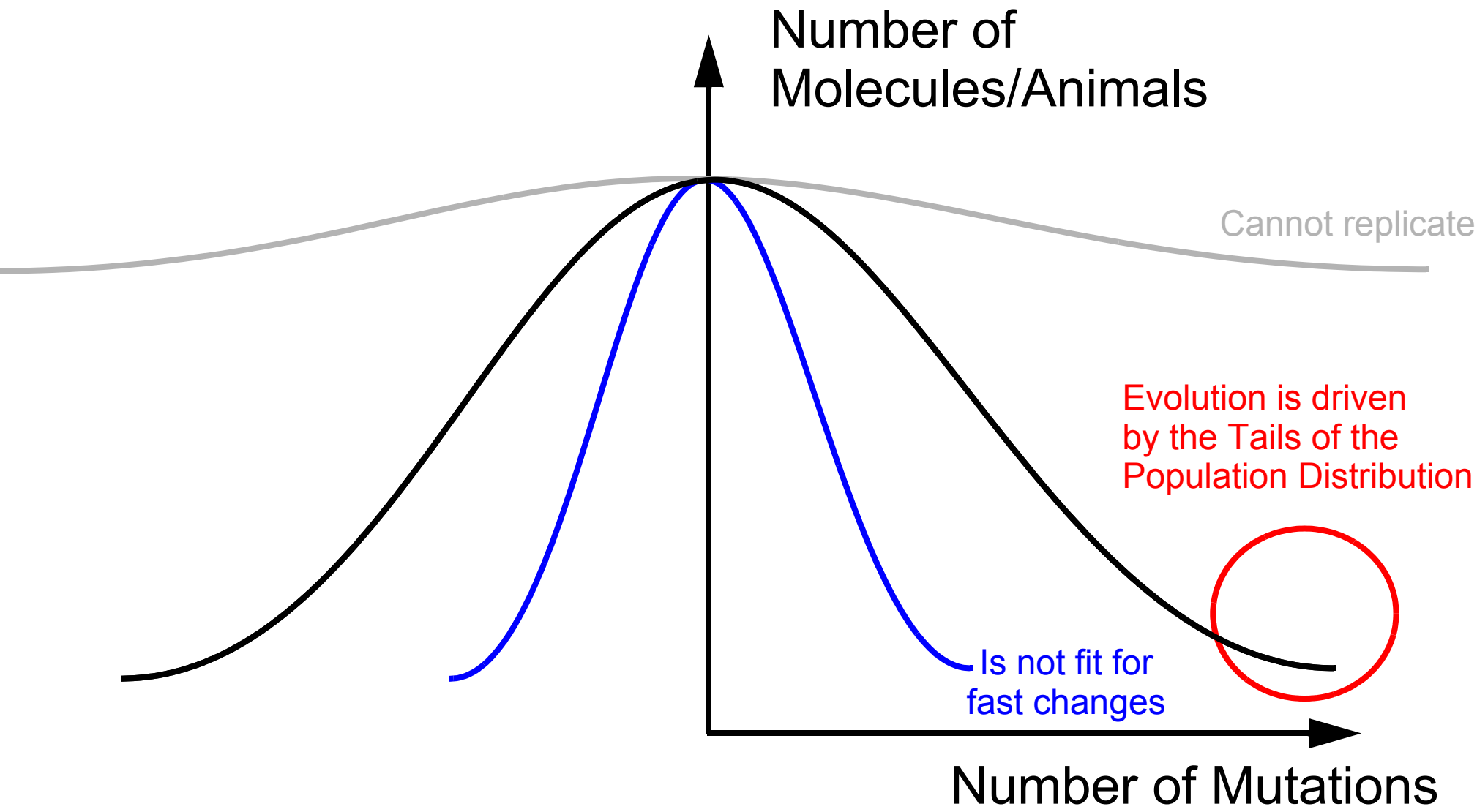
The law that the error of replication depends on the sequence length can be found also for microbes and other animals

Table 4.1 Rates of spontaneous mutation in DNA-based microbes

Organism	Genome size (bp)	Target	Mutation rate: Per bp (μ_{bp})	Mutation rate: Per genome (μ_g)
Bacteriophage M13	6.41×10^3	*lacZα*	7.2×10^{-7}	0.0046
Bacteriophage λ	4.85×10^4	*cI*	7.7×10^{-8}	0.0038
Bacteriophage T2	1.60×10^5	*rII*	2.7×10^{-8}	0.0043
Bacteriophage T4	1.66×10^5	*rII*	2.0×10^{-8}	0.0033
Escherichia coli	4.70×10^6	*lacI*	4.1×10^{-10}	0.0019
			6.9×10^{-10}	0.0033
		his GDCBHAFE	5.1×10^{-10}	0.0024
Saccharomyces cerevisiae	1.38×10^7	*URA3*	2.8×10^{-10}	0.0038
		SUP4	(7.9×10^{-9})	(0.11)
		CANI	1.7×10^{-10}	0.0024
Neurospora crassa	4.19×10^7	*ad-3AB*	4.5×10^{-11}	0.0019
		mtr	(4.6×10^{-10})	(0.019)
			1.0×10^{-10}	0.0042

From: Gesteland, Cech, Atkins: RNA World

Population Genetics



Survival of the Flattest

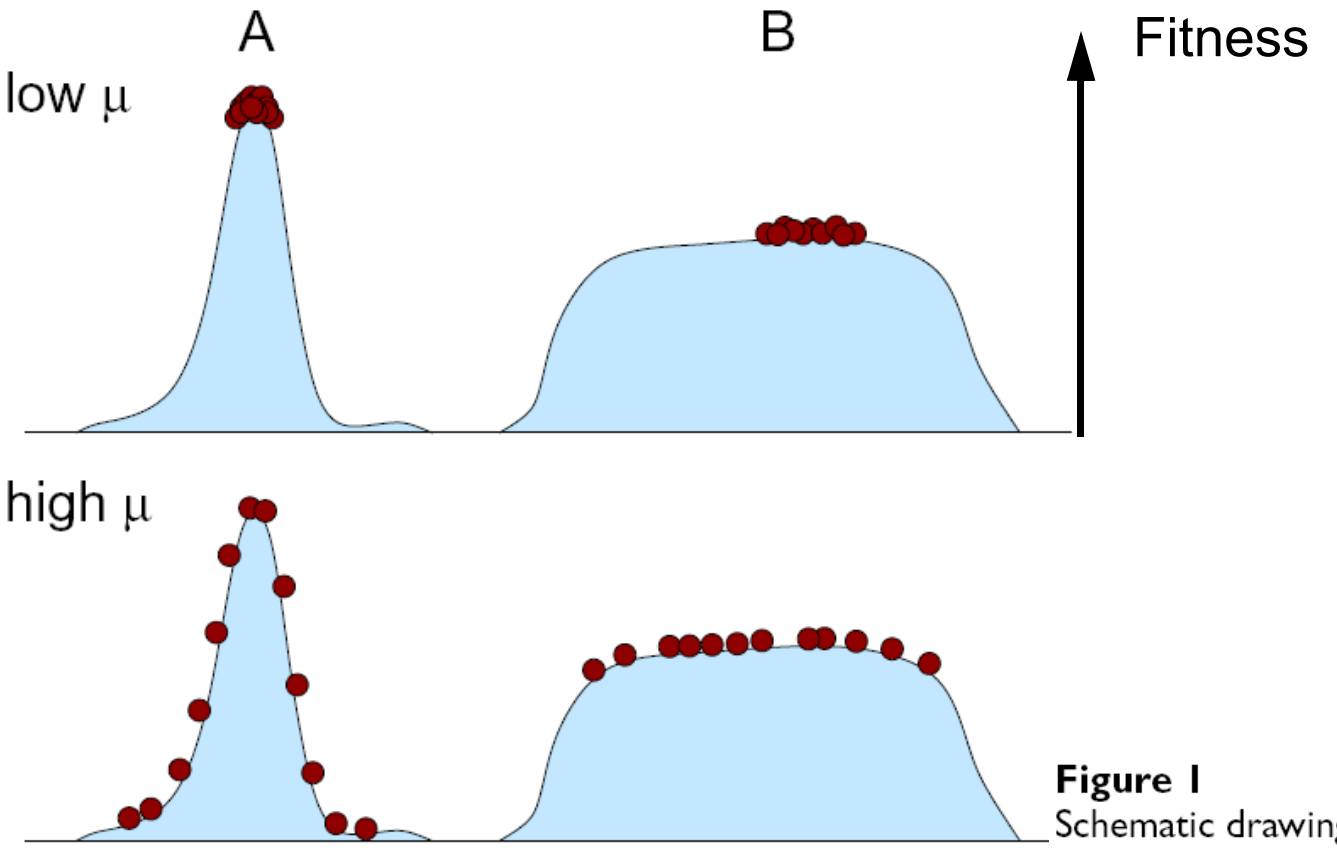


Figure 1
Schematic drawing of the survival-of-the-flattest effect. At low mutation rate μ, all individuals accumulate close to the top of the local fitness peak, and hence the individuals on peak A outcompete the individuals on peak B. At high mutation rate, most individuals on the steep peak A are located at low fitness values, while the individuals on the flat peak B remain close to the local optimum. As a consequence, the mean fitness of the individuals on peak B exceeds that of the individuals on peak A, and thus the former outcompete the latter.

From Wilke, http://www.biomedcentral.com/1471-2148/5/44

Critisism: Combinational Explosion

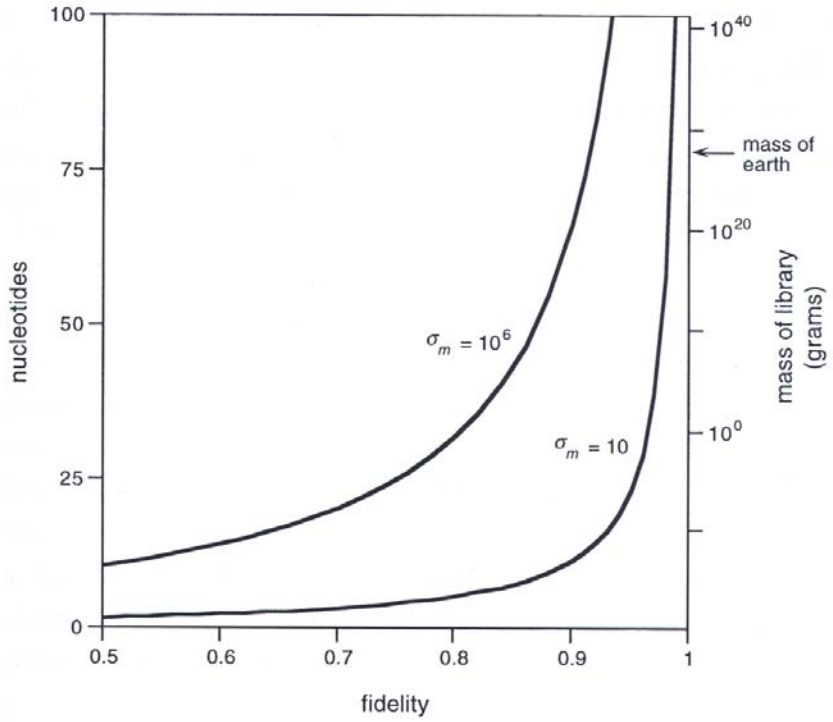


Figure 3 The Eigen error threshold, relating fidelity of replication to the maximum number of nucleotides, for two different values of superiority (σ_m). Fidelity (q) is that of the component condensation reactions in the replication cycle. The number of condensation reactions (ν) is related to the number of nucleotides (n) by: $\nu = 2n - 2$. Scale at right indicates the mass of a combinatorial library containing one copy each of the 4^n possible sequences of length n.

From: Gesteland, Cech, Atkins: RNA World

Let us start with molecules of 500 bases, i.e. with 1000bits of information. The starting pool to have each molecule at least once are $2^{1000}=10^{300}$ molecules. However we have only 10^{32} molecules on the whole hydrosphere of the earth!

So let us be optimistic and assume a 40mer can already do it with a superiority of $\sigma_i=10^3$ and a replication fidelity of q=0.9. The complete library are 1kg. However the complementary part has also to be catalytic and also replicate itself!

This argument leads to the idea of hypercycles.

Eigen & Schuster: Hypercycles

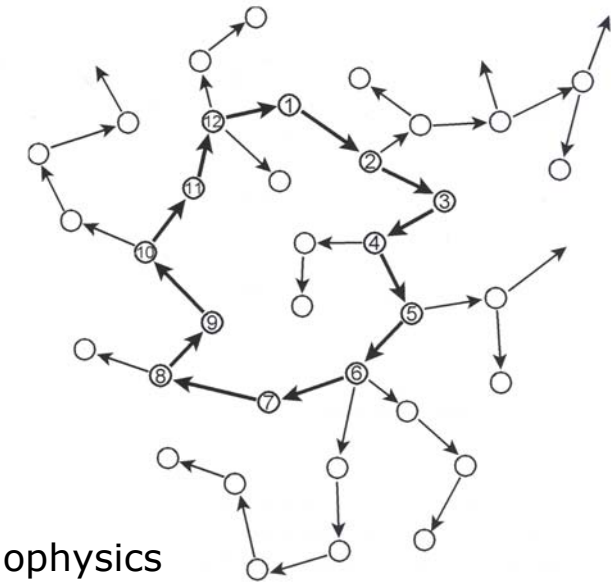
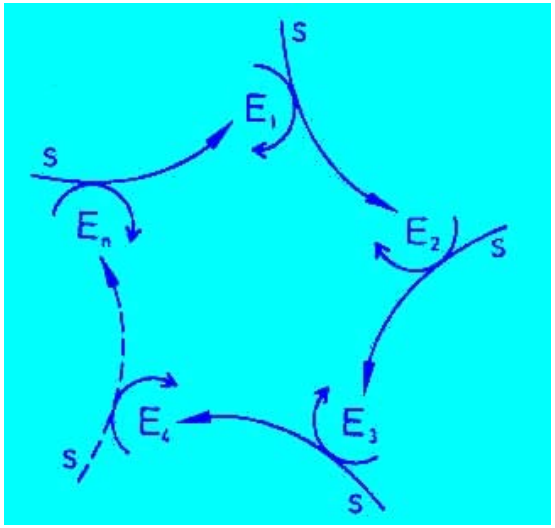
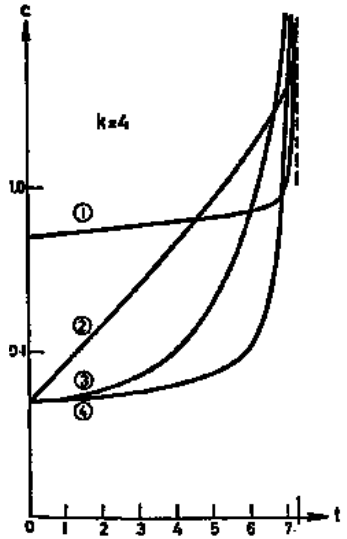


Fig. 5.21. The network of catalytic correlations in a mixture of polymers. The points with numbers connected by *thick arrows* indicate an auto-catalytic cycle

From:
Roland Glaser: Biophysics





Hypercycles are formed from molecules which do not replicate themselves, but other molecules. More specifically, RNA i codes for a protein or Rybozyme to replicate the RNA i+1.

If they **form a loop that eventually also replicate the first molecule**. Comparable to a bee and a flower: each helps replicating the other. It is beneficial to isolate each hypercycle into "chambers".

Depending on the parameters, hypercycles can lead to linear, exponential and hyperexponential growth, yielding 'once-for-all' selection.

However:

- The cycles are unstable for >4 cycles
- Problem of 'selfish' viral mole-

From: Erich Sackmann, Biophysics Script, Ch. 19

Eigen's Paradox: Proteins cannot be reached

Hypercycles show the strong potential of coupled catalysis. Especially heterogeneous cycles (proteins & nucleic acids) appear to have an advantage in the simulations. However we are far away from establishing such heterogeneous hypercycles since the sequence length is much too long. Or formulated as Eigen's paradox:

No enzyme can be produced without a large genome
No large genome can be replicated without the help of enzymes.

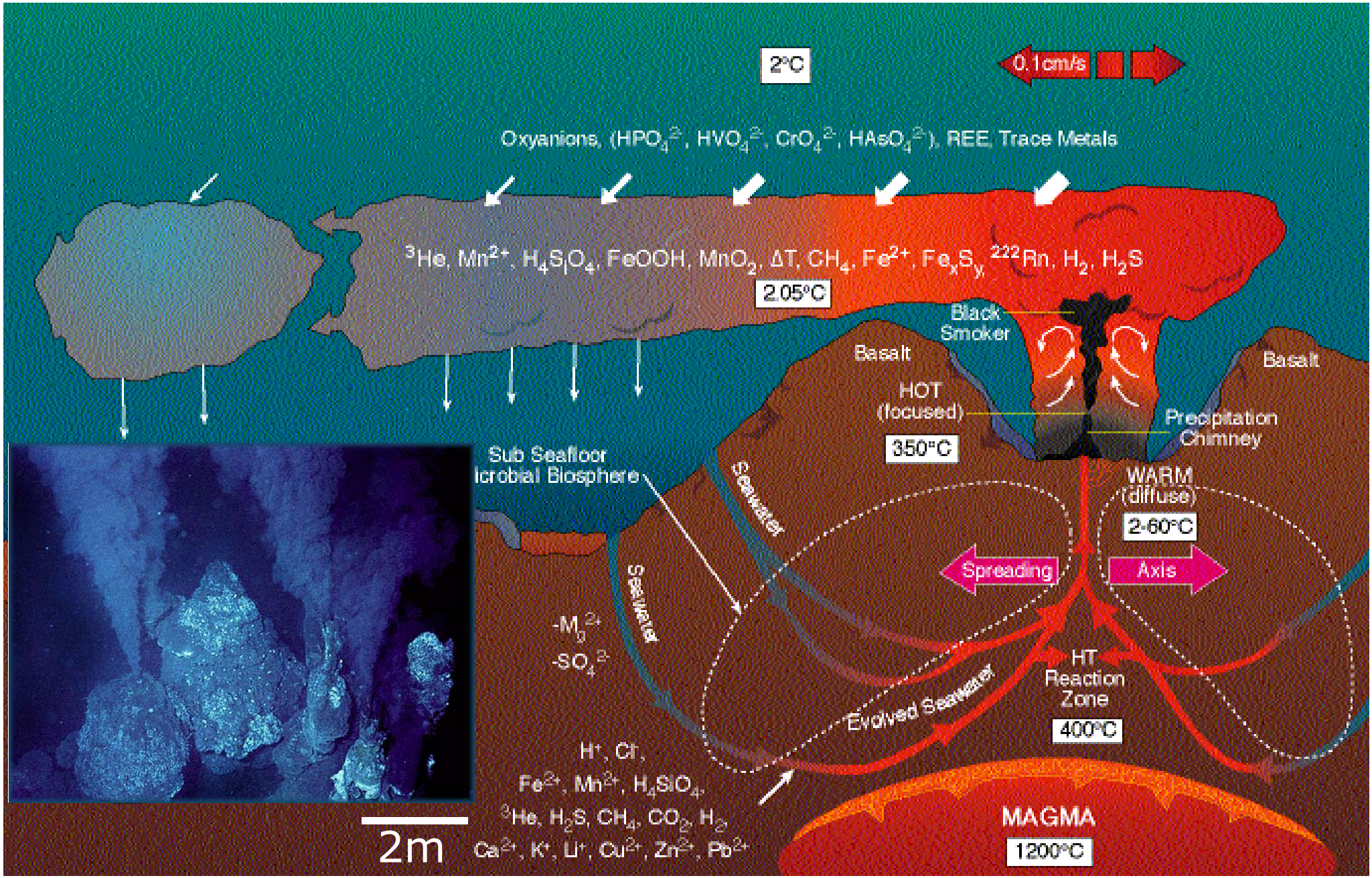
References for Hypercycles:

M. Eigen, P.Schuster, "The Hypercycle", Springer-Verlag, 1979
M. Eigen, "Steps towards life: A Perspective on Evolution", Oxford Univ Press, 1996
J. Hofbauer, K. Sigmund, "The theory of evolution and dynamical system", Cambrige Univ Press, 1988
J. M. Smith, "Hypercycles and the origin of life", Nature 20:445-6, 1979
J. M. Smith, E. Szathmary "The major transitions in evolution", W.H. Freeman, 1995

.... yet still the starting pool gives a lot of headaches.

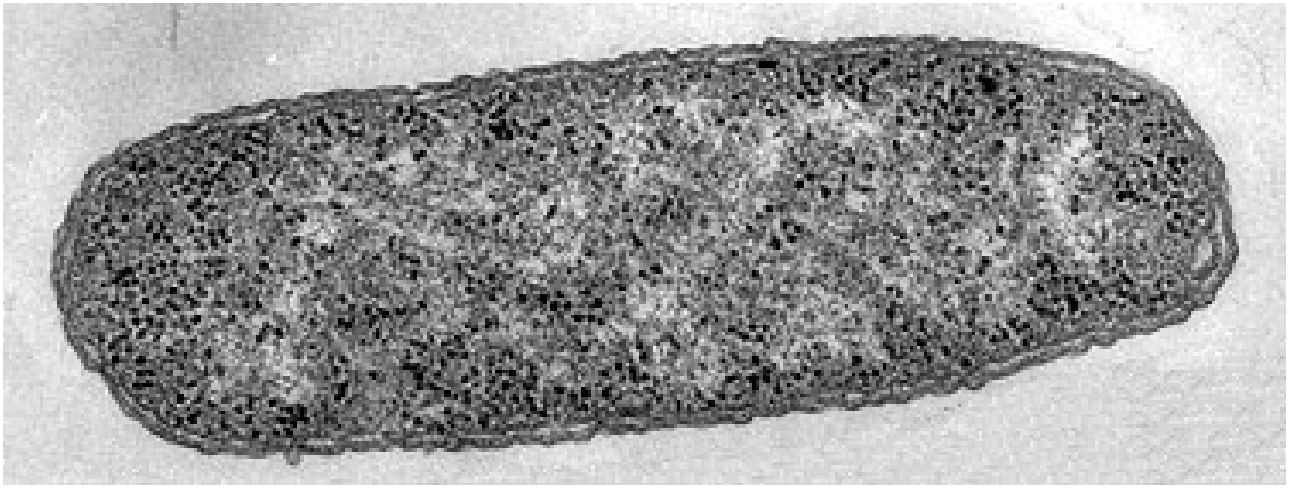
Hydrothermal Microfluidics

Locations: Hydrothermal Vents

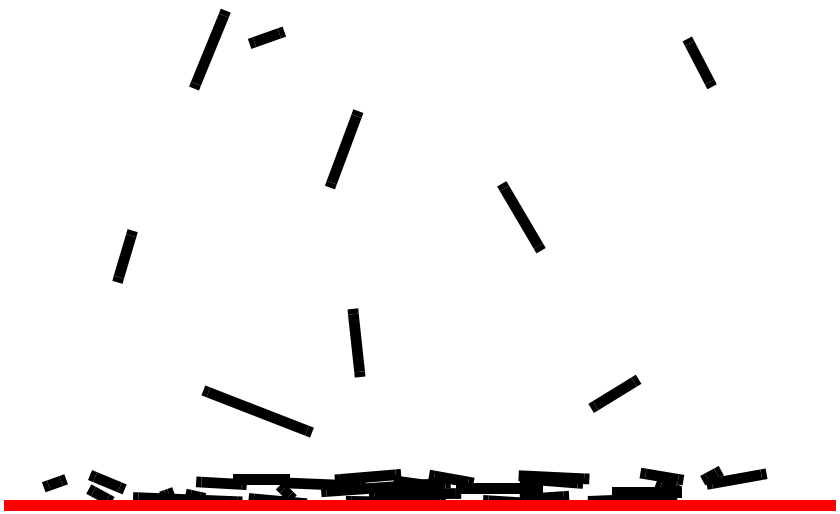


Concentration Problem

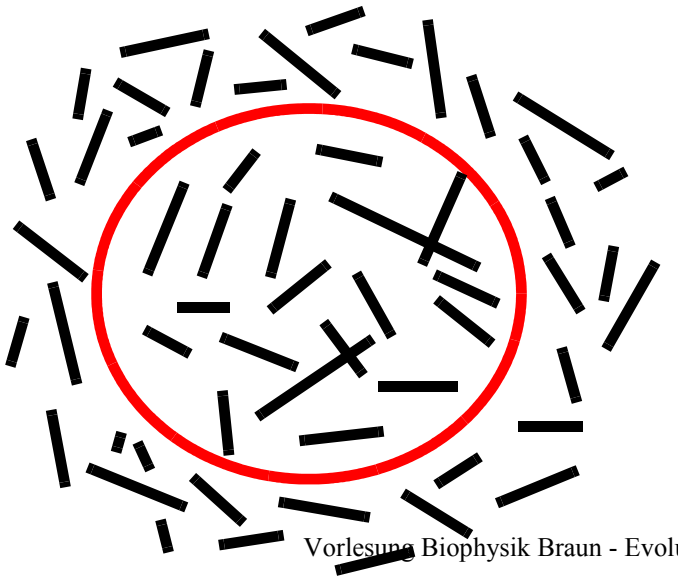
Molecules
in Cells:
- crowded
- diffusive
- nonsticky



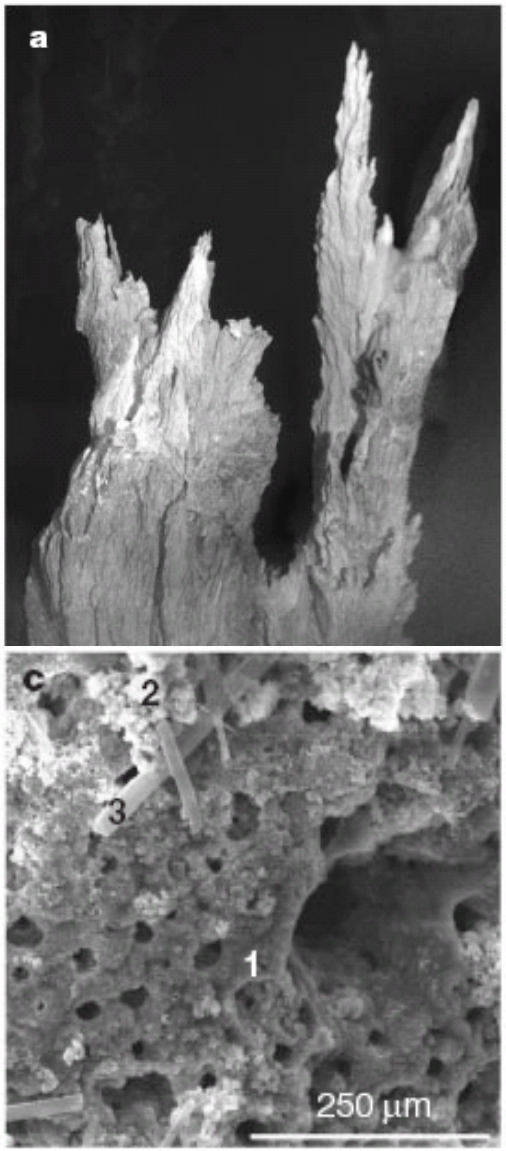
Absorption
of no return



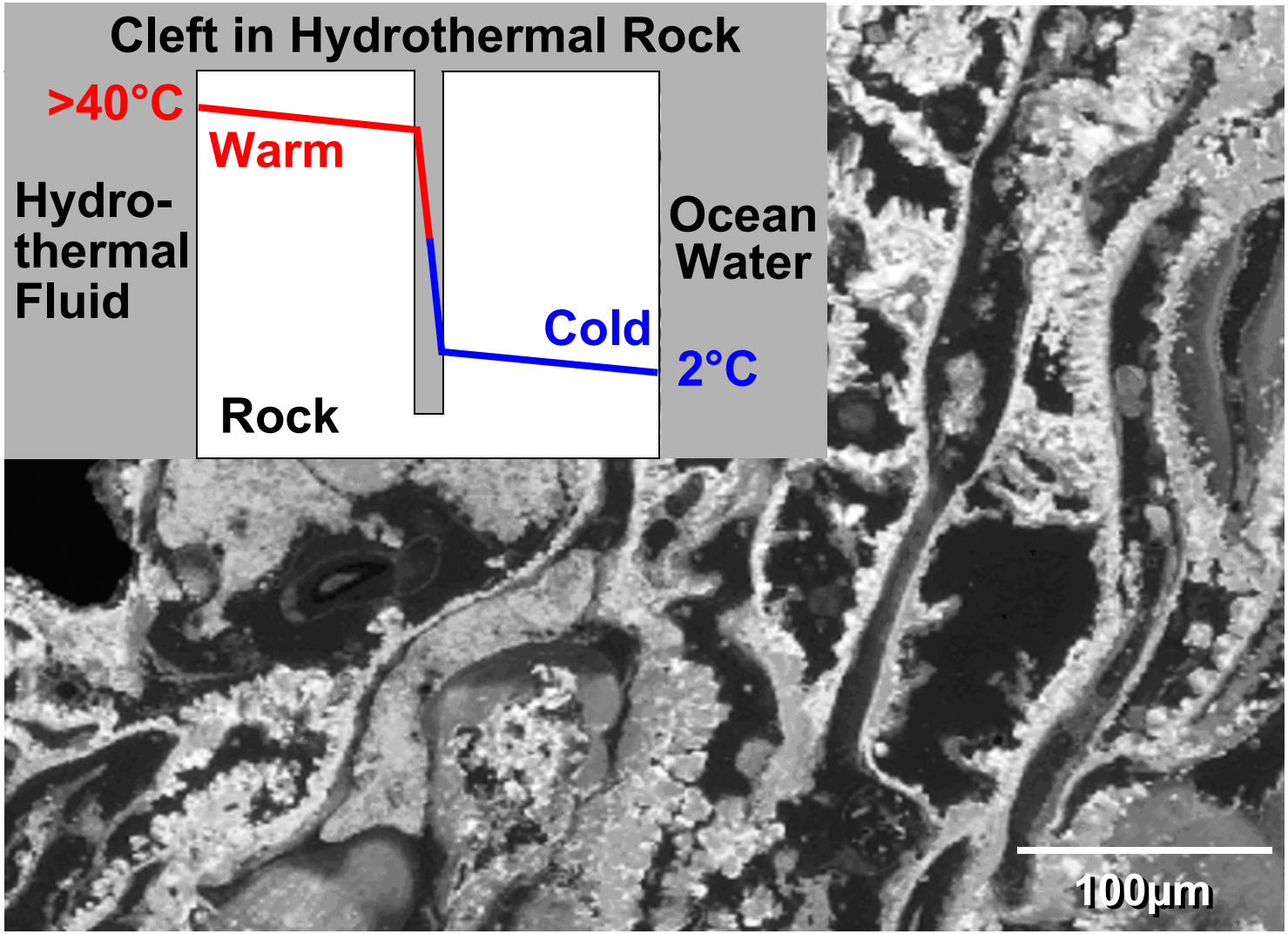
Membrane
isolates



Hydrothermal Vents are Molecule Traps



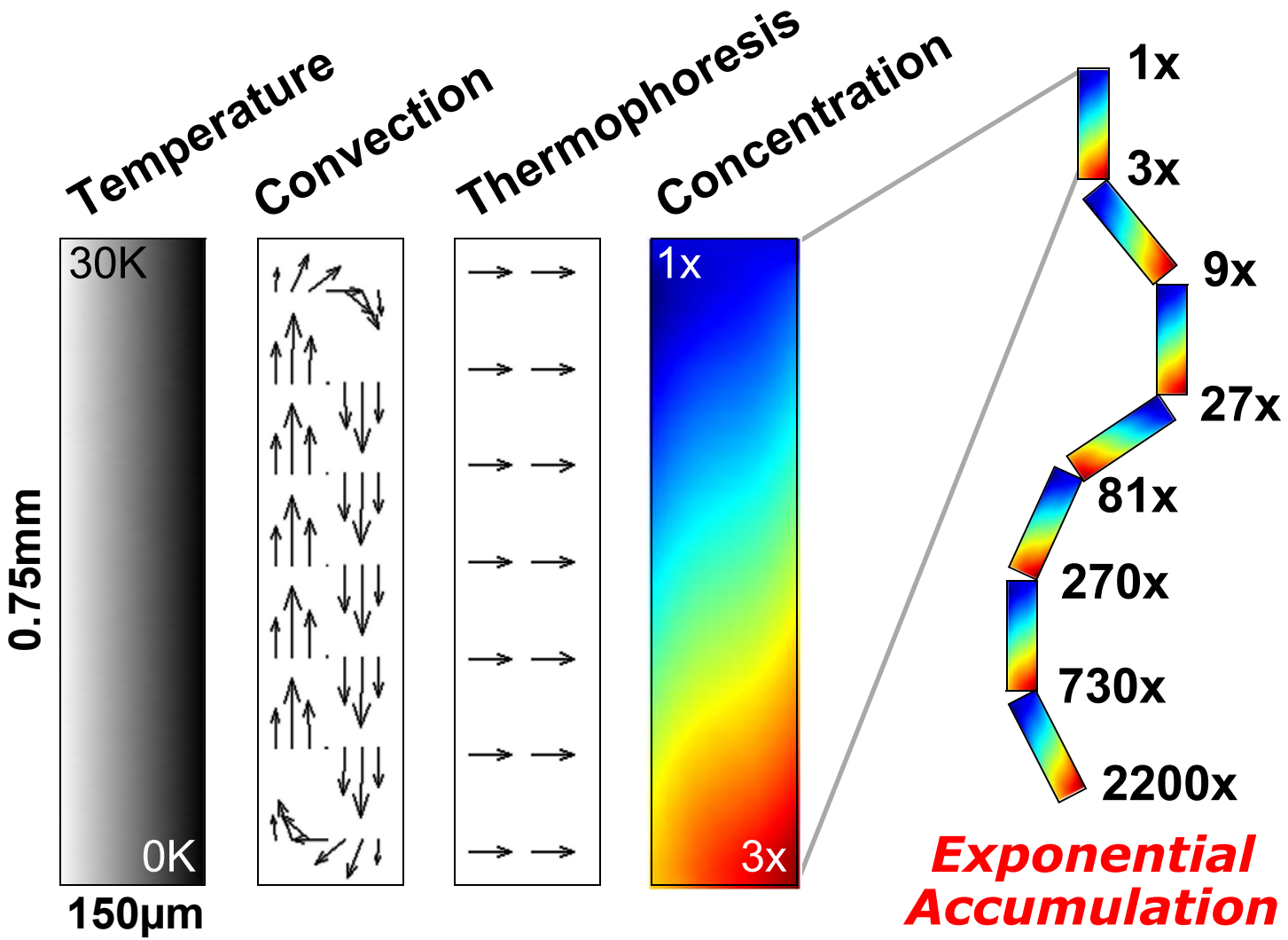
X°C >2°C



Temperature gradients in the pore systems predominantly **drop across water pockets** due to their differential heat conductivity. **Pore structures** 10.300µm wide and several centimeters long give an interesting setting to accumulate molecules by **thermophoresis and convection**.

From: Braun et.al., PNAS 104, 9346–9351 (2007)

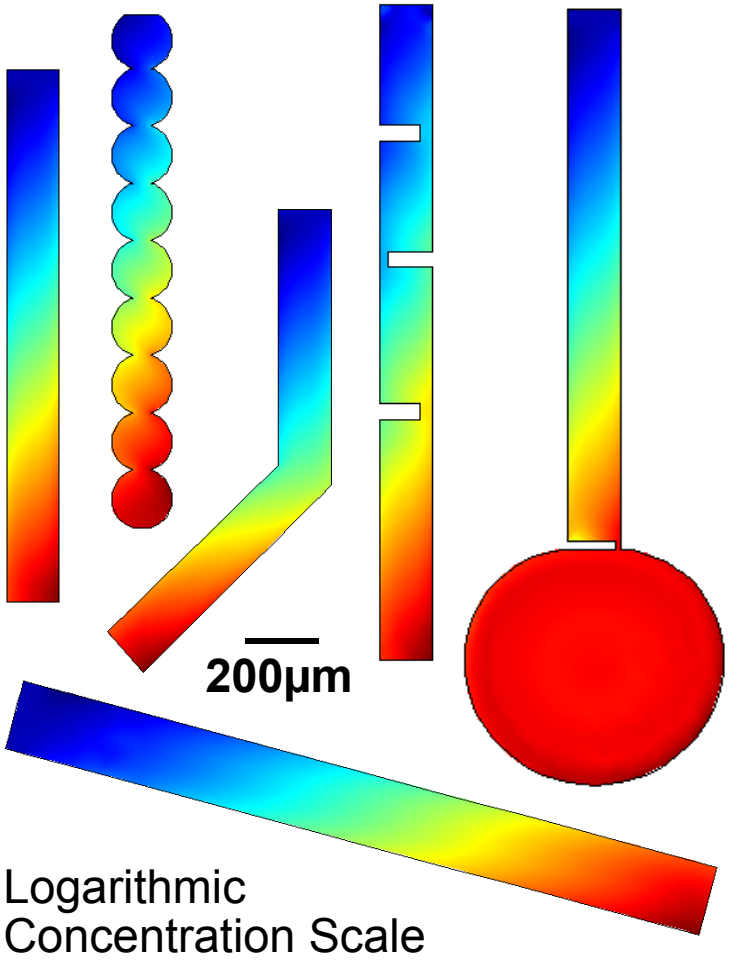
Hydrothermal Vents are Molecule Traps

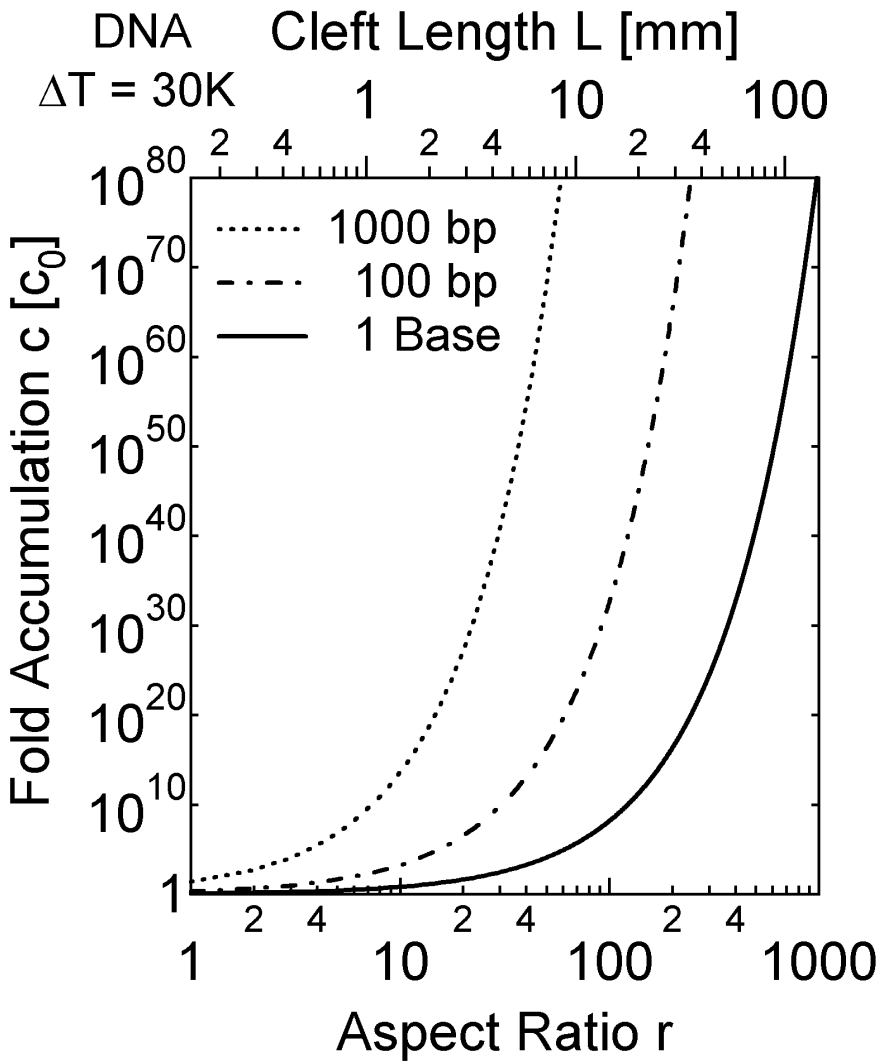


Shown is the **simulation of a cleft**, 150µm wide and 0.75mm long. We assume a 30K vertical temperature gradient which drives both **thermal convection of water** (up-down) and **thermophoresis of molecules** (left to right). We chosen parameters for a **single base pair**, i.e. a very small molecule in salt-poor media. The combination of effects give rise to a **strong 3x concentration** of the molecules from the top **towards the bottom**. Interestingly, these structures can be concatenated by diffusion into a **string of chambers**. This leads to an exponentially rising accumulation.

From: Braun et.al., PNAS 104, 9346–9351 (2007)

Hydrothermal Vents are Molecule Traps



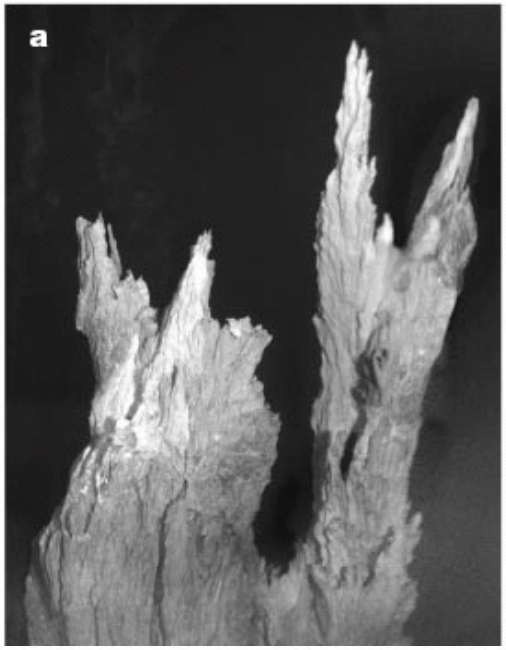


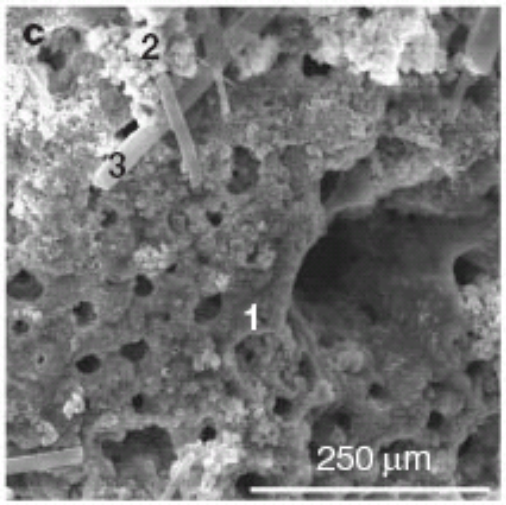
The mechanism is very **robust** and leads to identical concentrations from **top to bottom in a large variety of geometries**. Thus, the found accumulation is very robust.

An analytical solution can be given. It shows that **exponential accumulation** versus **aspect ratio** of the chamber.

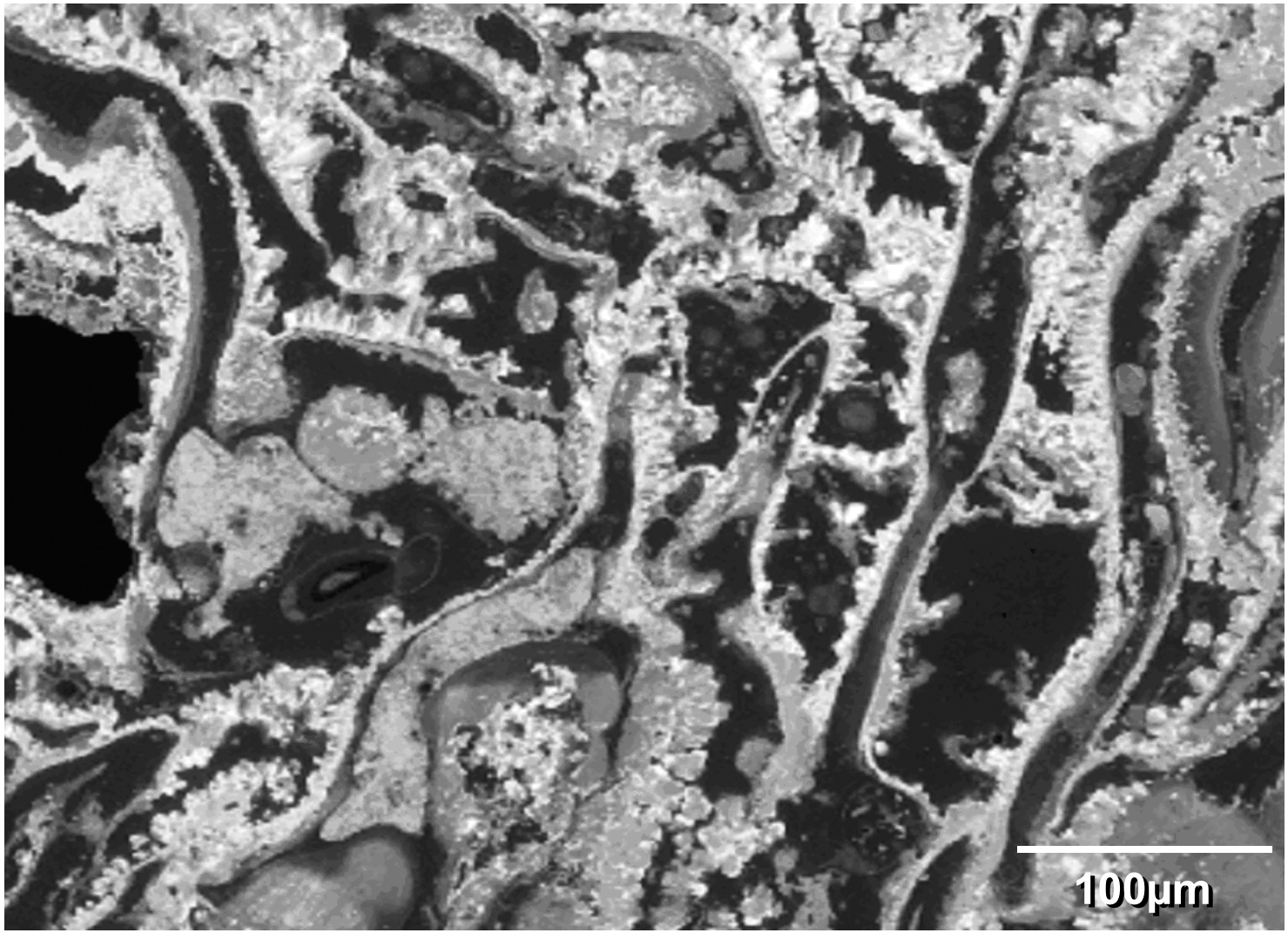
From: Braun et.al., PNAS 104, 9346–9351 (2007)

Adsorption-Desorption Cycles by Thermal Convection



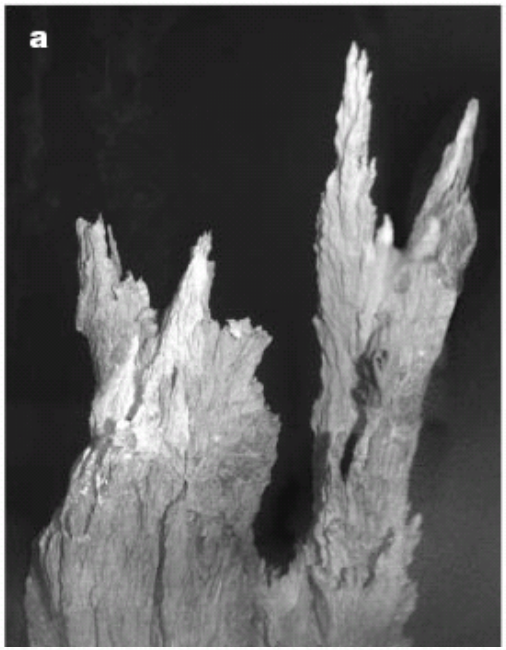


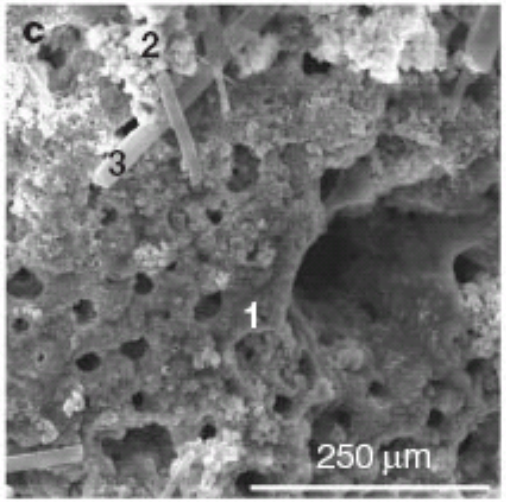
X°C >2°C



We start again from the temperature in the pore systems of hydrothermal vents.

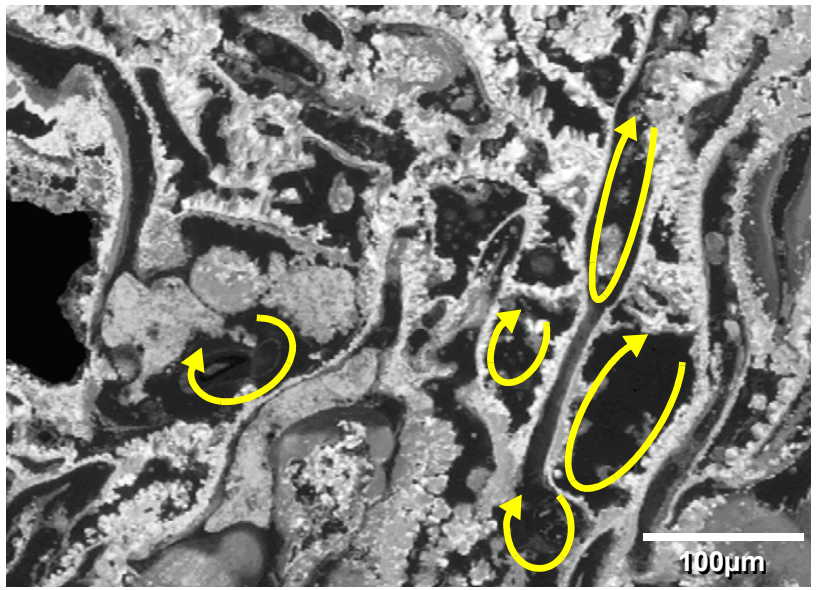
Adsorption-Desorption Cycles by Thermal Convection



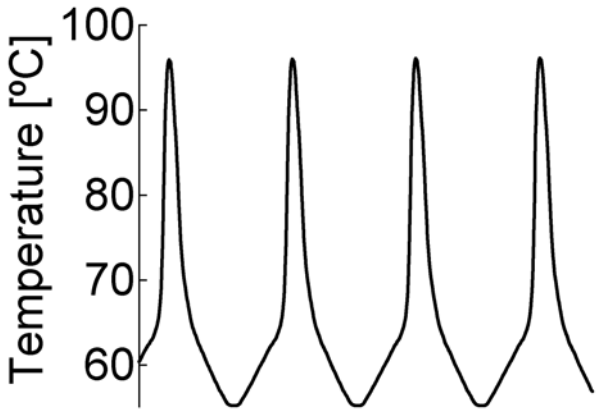


X°C >2°C

Warm
<110°C



Cold
>2°C

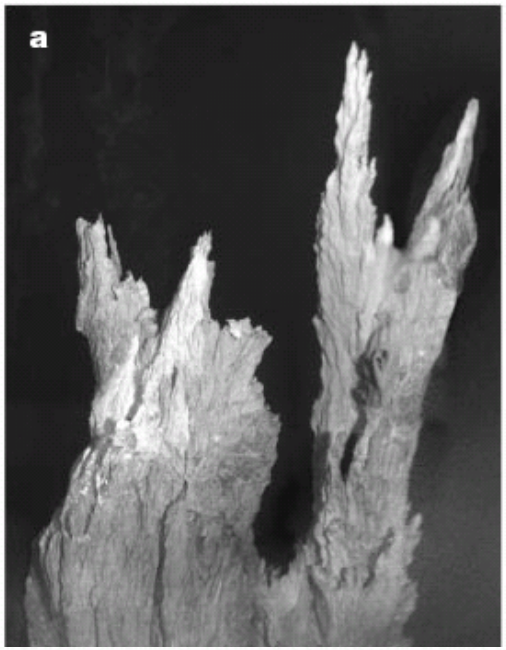


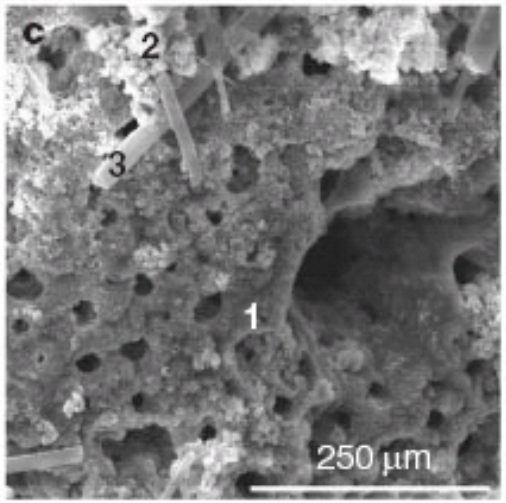
The thermal convection implements a natural temperature oscillation on the 1-100 second time scale.

Braun, Modern Physics Letters B 18:775-784 (2004)

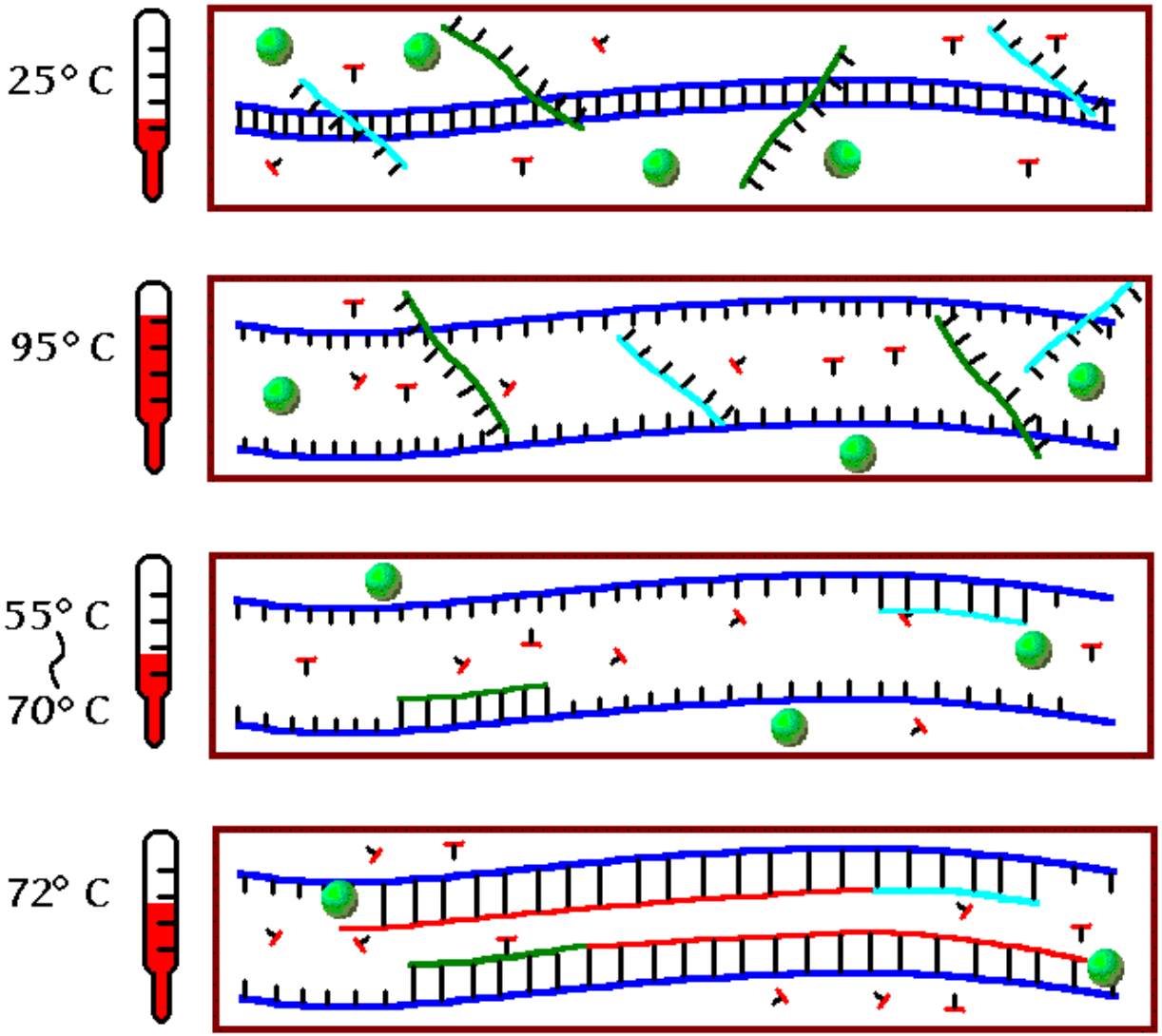
Exponential DNA Replication

Convective Polymerase Chain Reaction (cPCR)





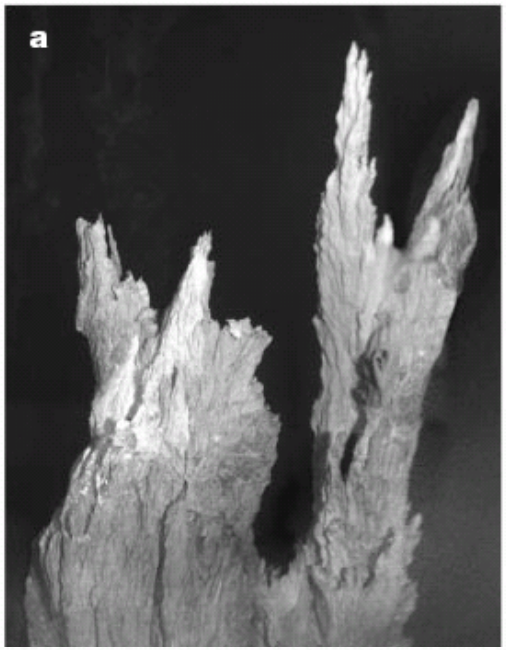
X°C >2°C

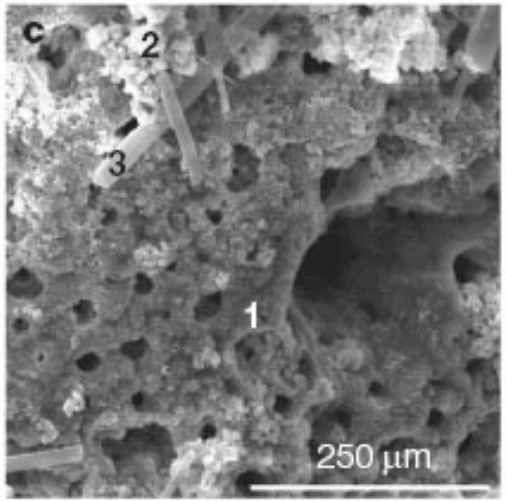


The most important reaction in genetic biochemistry needs a temperature oscillation: PCR.

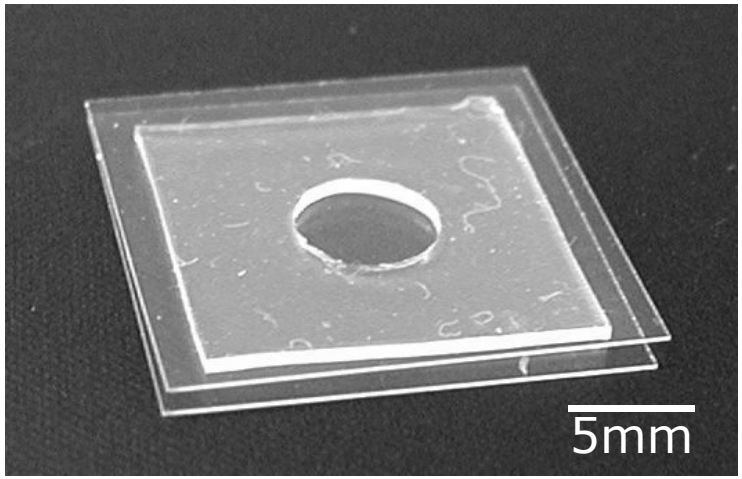
DNA Replication in Convection

Convective Polymerase Chain Reaction (cPCR)

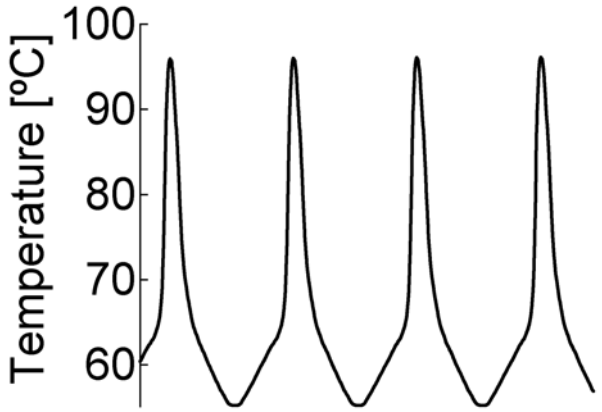


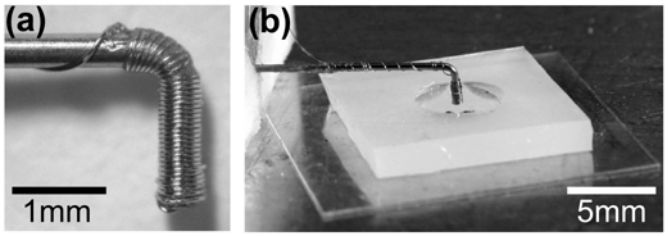


X°C >2°C



Beads Movie





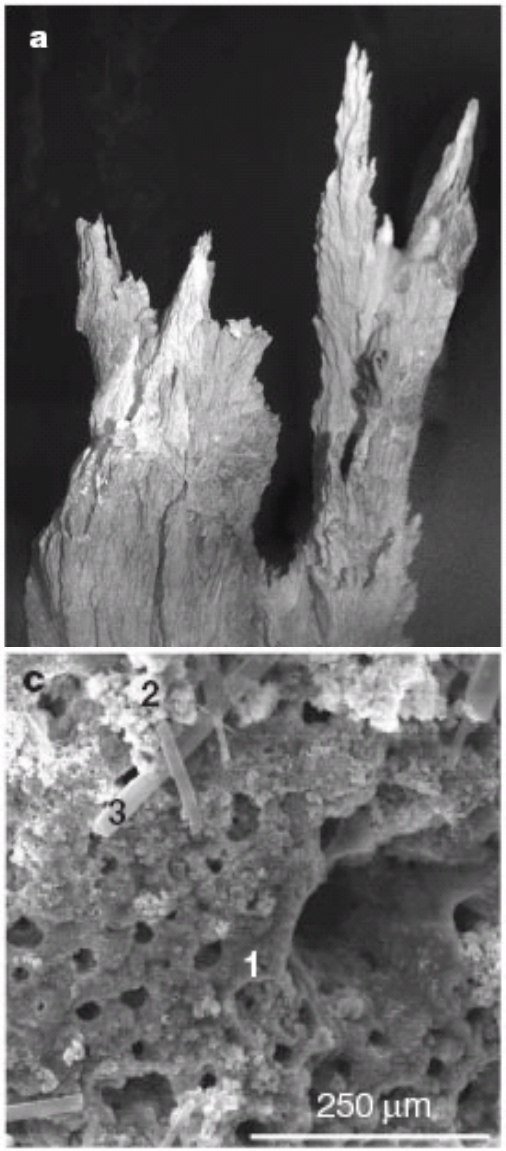
Hennig and Braun,
Applied Physics Letters 87, 183901 (2005)

Thermal convection, either driven by IR-Laser or a hot wire, hosts very efficiently the PCR reaction.

Braun, Goddard and Libchaber
Physical Review Letters 91:158103 (2003)

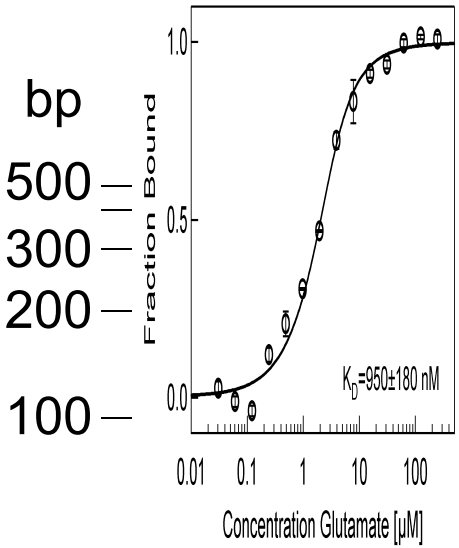
DNA Replication in Convection

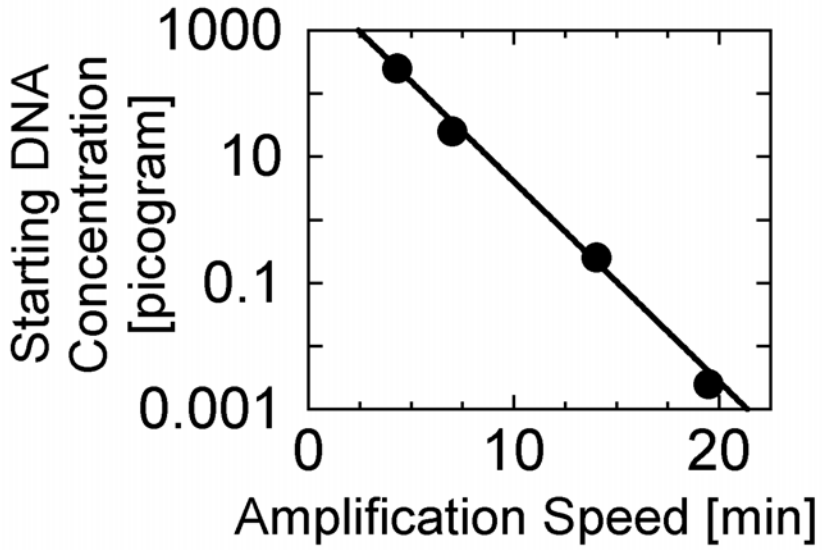
Convective Polymerase Chain Reaction (cPCR)



X°C >2°C

Amplification 100.000x
in 25 Minutes





PCR result is tested in a gel against a standard and was shown to be able to perform real-time PCR: the logarithmic time dependence on initial DNA concentration which was amplified.

Braun, Goddard and Libchaber
Physical Review Letters 91:158103 (2003)

Major Steps in Cellular Evolution

Endosymbiosis: intracellular infection

The **development of the large eucaryotic** cells (1000-times more volume than procaryotes) took a **long time**, approx. 1 billion years.
Its development is believed to be occurred (in parallel to the development of multicellarity) by **intracellular infection**. For example, purple bacteria, being able to do photosynthesis, entered or were 'eaten' by other procaryotes and did not die, but were used in a symbiotic way inside the larger cell.
For example **mitochondria** which specialize in respiration, still have **their own genetic material**, which can be used to track the phylogenetic tree since it has been is replicated in parallel to the genes of the mother cell for a very long time.

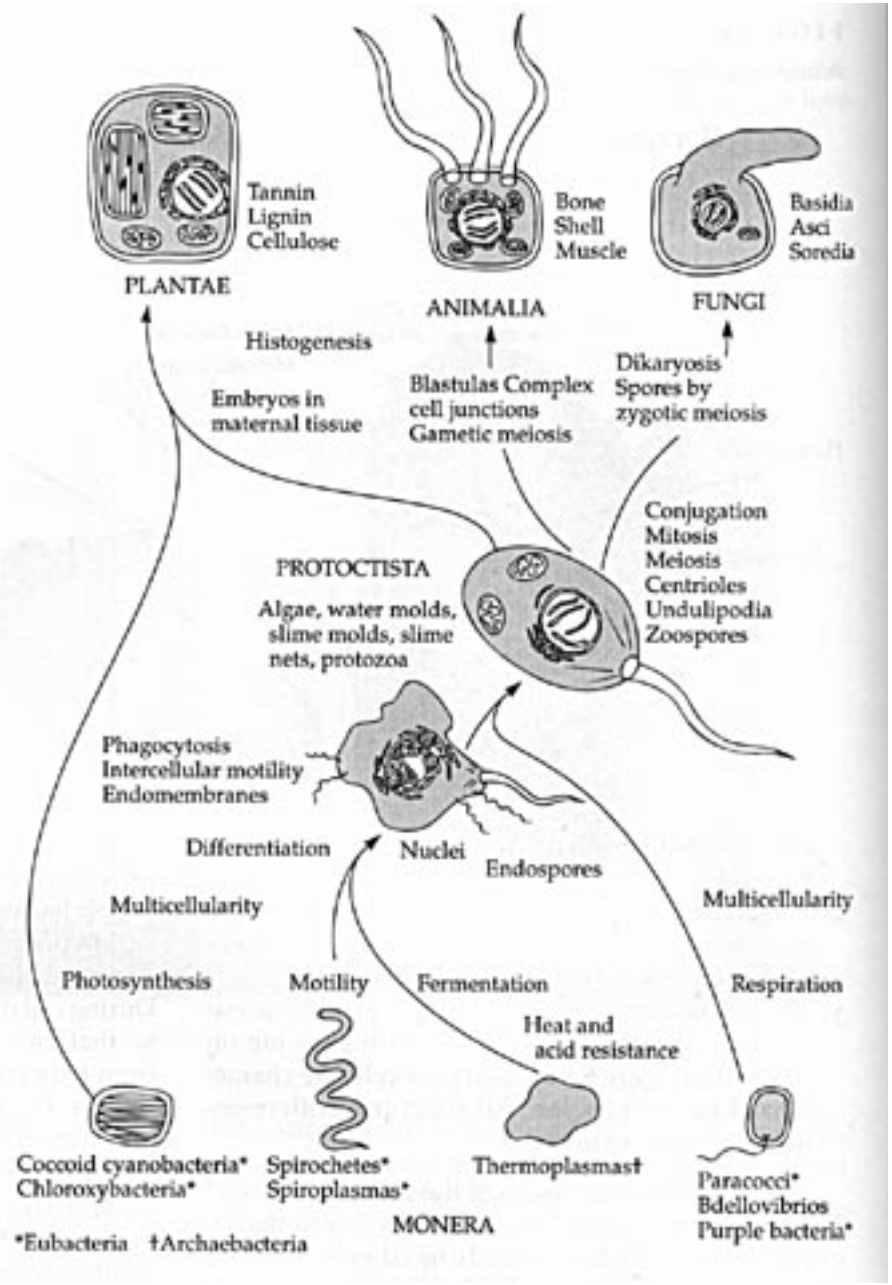


FIGURE 6-10
The stepwise origin of eukaryotic cells by symbiotic mutualism, based on microcosms of tightly integrated prokaryotic organisms. Protoctista is equivalent to Protista. *(From Margulis 1981, 1993)*

Game Theory

Game Theory

History:

First interest in game theory was started by **behavioral sciences** and **economics**. But even in economics, the approach was not very persuasive, mostly because of the lack of experimental foundation.

After a period of **mathematical 'purification'** of the approaches, game theory took of in the beginning of 1970, with the incorporation of **biological and evolutionary approaches**. In Biology, the fitness of the organism gave game theory a serious foundation.

Books:

John Maynard Smith: Evolution and the Theory of Games.

Ulrich Müller: Evolution und Spieltheorie, 1990

Rudolf Schüßler: Kooperation unter Egoisten, 1990

Michael Taylor: The possibility of cooperation, 1987

Richard Dawkins: the selfish gene. 1976, 2nd edition 1989. (dt: das egoistische Gen)

Matt Ridley: The origins of virtue: human instincts and the evolution of cooperation, 1996, pinguin paperback

Summary:

- Motivation: the selfish gene
- Simple games
- Matrix formulation of games
- Single vs. Multiple games: Prisoners dilemma
- Dynamic plotting
- Frequency dependent selection
- Stable bad solutions beat unstable good solutions in memory-less evolution.
- Biological examples

Matrix Games

Payoff Matrix		Player B		
				
Player A		0	-1	1
		1	0	-1
		-1	1	0

$$V = \begin{bmatrix} 0 & -1 & 1 \\ 1 & 0 & -1 \\ -1 & 1 & 0 \end{bmatrix}$$

e.g. Partner Game: $V_{ij} = V_{ji}$

A wide class of games can be described by a **payoff matrix**. They are called matrix games.

Let's look at **Knobeln** (engl: to toss). Each player can show **scissors, paper or stone**. Each of the player has profit matrix depending on what the other is playing.

The matrix has to be **read along the rows**. If I am player A, and play strategy scissors, then I have a payoff of 0 against scissors of player B, loose 1 against player B choosing stone and gain 1 if player B chooses paper.

Games where the payoff is distributed between partners are called **partner games or symmetric games** and yield a symmetric payoff matrix.

Here we also have the case of a **zero-sum game**: what is received is what is given, seen by the zero expectation value.

The Prisoner Dilemma

Another Matrix game is the **Prisoner Dilemma**. The scenario is as follows. **Two agents fight for a resource**. (In the original story, two prisoners are charged for the same criminal act). They first choose their strategy. Either they can be friendly and corporate with the other or they can be fierce and choose a competing strategy.

Payoff Matrix V		Player B	
			
Player A		1	5
		0	3

The interesting structure lays in the pay-offs they obtain depending on the others strategy. If **both compete**, they obtain nothing. If both **cooperate**, they obtain 1. This is the symmetric part.

However, things become asymmetric, if competing meets cooperate: in that case the competing out wins the cooperating: competing gains 2, the cooperating looses 1.

What strategy should be played?

Interestingly, it depends on **the games history, i.e. on how often the game is played**. If the game is played once, the answer is quite clear. Without knowing the other, one will compete. In average, the gain will be (1+5)/2=3. Cooperating is dangerous, the expectation value for this is (3+0)/2=1.5 and in average you will not gain anything. In average it is always better to compete. A boring game?

The Prisoner Dilemma

Payoff Matrix V		Player B	
			
Player A		1	5
		0	3

However the situation changes if the game is played multiple times between the same agents.

Axelrod has asked people to submit **computer programs** to compete in the game of multiple prisoner dilemma. After two tournaments of a wide variety of algorithms, it turned out that the **best strategy** was quite simple. It was called "**TIT for TAT**" ("wie du mir, so ich dir").

serendip.brynmawr.edu/playground/pd.html
www.brembs.net/ipd/ipd.html
Axelrod, R. (1981). Science, 211(4489):1390-6

TIT for TAT is very simple. **The first time** it takes the risk and **cooperates**. For all following games it **copies the strategy of the last move of the other agent**. This means the strategy "TIT for TAT" will cooperate if the other did cooperate last time, it will defect if the other did defect last time.

Axelrod argued that this strategy is "nice", "provokable" and "forgiving". It is "nice" since it starts with a cooperate move, can handle an always-defect strategy of the other well without loosing too much ("provokable"). But most importantly, it becomes immediately nice again if the other player cooperates ("forgiving").

So we see, there are games where it becomes crucial to **memorize both the agent** (did I play against him in the past?) and **what strategy the agent played** (did he compete last time?). A memory is a selection advantage since it allows to implement the optimal strategy.

Stability of Strategies: Frequency dependent Selection

$$(\text{Female}) \div (\text{Male})$$

$$1 \div 1$$

$$20 \div 1$$

Symmetry of the sexes.

We start with a commonly used example. For a farmer to have as many cows as possible, he might choose **one bull per 20 cows**. Why? The reproductive capability of the cow (k_{pi}) is much higher than for the bull ($k_{pi}=0$) and the farmer will yield more animals for equal food resources.

But, how comes that such a solution is not found in nature? Simply: the **strategy is not stable** against random mutations. We start with a cow in average giving birth to 1 bull and 20 cows. **If one cow in the population gives birth with a ratio 1:1**, this phenotype has a large advantage over the others since **its many bulls** can exploit the existence of many cows.

Same is true for the opposite: starting with **1 cow and 20 bulls**, the phenotype with mutation for a 1:1 ratio will propagate better due to its **higher number of cows**.

We see that the frequency of species in the population determines the selection rules, termed **frequency dependent selection**. Technically speaking, the **Nash equilibrium** is not stable (20:1) and the inferior strategy of 1:1 is used.

As a result, nature uses the **inferior, but stable** strategy.

John Maynard Smith and George R. Price (1973).
"The logic of animal conflict." Nature

Evolutionarily Stable Strategy (ESS)

Evolutionary stable strategy (ESS):

"A strategy such that if **all members** of the population adopt it, then **no mutant can invade the population** under the influence of selection."

Assume you have a population which is **dominated by strategy p** of the population and a **mutation strategy m** just developed. With the profit of the game V_{ij} of strategies i and j, **the evolutionary stable strategy is given, if $V_{pp}>V_{mp}$,** i.e. the **majority strategy p** yields more than a single minority m playing against the majority p.

In the case of equality we need a second condition of $V_{mp}>V_{mm}$.

$$V_{pp} > V_{mp}$$

or

$$V_{pp} = V_{mp} \text{ and } V_{pm} > V_{mm}$$

$$V_{pp} < V_{mm}$$

Evolutionarily Stable Strategy (ESS)

As we have seen, such an evolutionary stable strategy does not need to be the best performing. **It is well possible that V_{mm} is much better than V_{pp}, but it is not stable due to $V_{pp}>V_{mp}$.**

We can see this for example in the Prisoner Dilemma. If the **majority population competes** at all times (**V=1**), a **cooperative mutation will loose** against it (**V=0**) and cannot grow. Strategy competition is stable.

A globally better mutation m cannot supplant the worse, but stable strategy p with $V_{pp}>V_{mm}$.

On the other side, if the **cooperative strategy** would be adopted by everyone, it would be **advantageous** (**V=3**). However any **mutation which competes** gains more (**V=5**) and will grow, eventually overtaking the population.

But as we have seen, dynamic, memory based strategies (**TIT for TAT**) can compete against all other strategies and in many situations lead to an **average yield of V=3**.

$$V_{pp} > V_{mp}$$

or

$$V_{pp} = V_{mp} \text{ and } V_{pm} > V_{mm}$$

$$V_{pp} < V_{mm}$$

Example: Prisoner Dilemma

Payoff Matrix V		Player B	
			
Player A		1	5
		0	3

Example: The Hawk-Dove Game
(Chicken Game)

Payoff Matrix V		Player B	
		H 	D 
Player A	H 	(V-C)/2	V
	D 	0	V/2

$$V_{pp} > V_{mp}$$

or

$$V_{pp} = V_{mp} \text{ and } V_{pm} > V_{mm}$$

When **fighting for a resource**, opponents can use **two** typical **strategies**. The

- **Hawk strategy escalates** and continues until injured or until the opponent retreats
- **Dove strategy retreats** if opponent escalates.

We parametrize the payoff. **V for winning the fight** and **C for the cost of an injury**, we find the payoff matrix to the left.

We recall the condition for an evolutionarily stable strategy (ESS) on the left.

If **all were doves**, each gaining V/2, a hawk can always invade with V (V being positive). We again have frequency dependent selection.

All being hawks is evolutionarily stable strategy, if (V-C)/2>0. Otherwise a dove which gains 0 can compete initially. In other words, hawks are ESS if it is worth risking injury (C<V) to get the resource.

The case becomes interesting, when **C>V, i.e. the injury C is not worth taking for the resource V**. To study this we switch to population dynamics.

Davis, Spieltheorie für Nichtmathematiker
en.wikipedia.org/wiki/Hawk-dove_game
Maynard Smith, J. (1982) Evolution and the Theory of Games.

Example: The Hawk-Dove Game
(Chicken Game)

Payoff Matrix V		Player B	
		H 	D 
Player A	H 	(V-C)/2	V
	D 	0	V/2

$$W(H) = W_0 + pV(H,H) + (1-p)V(H,D)$$
$$W(D) = W_0 + pV(D,H) + (1-p)V(D,D)$$

$$p(t+1) = p(t)W(H)/\overline{W}$$
$$\overline{W} = pW(H) + (1-p)W(D)$$

From Game Theory to Population Dynamics

We now allow the **population** to be split into the two strategies with **p the frequency of strategy hawk (H)**.

And we **add a dynamics** to the matrix game by determining the **fitness W** by the **payoff matrix V(i,j)**. W(H) is the fitness of strategy hawk, W(D) the fitness of strategy dove. We linearly **link the fitness to the payoff matrix V(i,j)** and add a constant fitness W_0.

Consider the **fitness of the hawk W(H)**. With probability p it meets another hawk, gaining in fitness by V(H,H), with probability (1-p) the hawk meets a dove, gaining in fitness by V(H,D). The same for the Dove (left).

Additionally, we **add a dynamics** by using the fitness as determinant for the propagation of the strategy. The result is a finite time differential equation. Thus one might want to **reinterpret population dynamics with game theory**.

Stable Strategies in Hawk-Dove Game

Payoff Matrix V		Player B	
		H 	D 
Player A	H 	(V-C)/2	V
	D 	0	V/2

$$V(H, I) = V(D, I)$$

$$pV(H, H) + (1-p)V(H, D) = pV(D, H) + (1-p)V(D, D)$$

$$p(V-C)/2 + (1-p)V = (1-p)V/2$$

$$p = V/C$$

$$V(I, D) = pV + (1-p)V/2 = (p+1)V/2 > V/2 = V(D, D)$$

$$V(I, H) = p(V-C)/2 > (V-C)/2 = V(H, H)$$

Now we can **study the case V<C** (injury is more severe than gain from resource) with **population dynamics**.

As discussed before, **neither all Hawks nor all Doves are an ESS**. Hawks invade Doves with V>V/2 and Doves can invade Hawks with (V-C)/2<0. But now we can analyze **mixtures in the population** with p the probability for playing strategy hawk.

One can incorporate mixtures of populations also by introducing a **genotype I which randomly chooses hawk strategy** with probability p. It can be proved that if I is an ESS, then the following holds: V(H,I)=V(D,I). On the left side it is evaluated leading to the **probability of p=V/C**. If the resource is low in value, less hawks are played, otherwise the mostly hawk is chosen.

We still have to prove the **stability criterion**: V(I,D)>V(D,D) and V(I,H)>V(H,H). As seen on the left, for V<C the mixed strategy is indeed an ESS.

Extensions to Hawk-Dove Game

Payoff Matrix V		Player B	
		H 	D 
Player A	H 	(V-C)/2	V
	D 	0	V/2

We go one step further. Suppose that in a population of frogs, **males fight to the death** over breeding ponds. This would be an ESS if any one **cowardly frog** that does not fight to the death always **fares worse** (in fitness terms, of course). **A more likely scenario** is one where fighting to the death is not an ESS because **a frog might arise that will stop fighting if it realizes that it is going to lose**. This frog would then **reap the benefits of fighting, but not the ultimate cost**. Hence, fighting to the death would easily be invaded by a mutation that causes this sort of "**informed fighting.**"

From: en.wikipedia.org

Hawk-Dove-Retaliator Game

Payoff Matrix V		Player B		
		H	D	R
Player A	H	-1	2	-1
	D	0	1	0.9
	R	-1	1.1	1

R is ESS $$V(R,R) > V(D,R)$$ $$V(R,R) > V(H,R)$$

I is ESS $$I = 0{,}5H + 0{,}5D$$

Another extension to the game of dove and hawks is the **Retaliator strategy**. To keep it simple, we set the game to fixed payoffs: V=2, C=4, therefore the mixed strategy I with P=0.5 is an ESS.

The **Retaliator (R) behaves like a dove** against another dove, but **if the opponent escalates like a hawk**, R escalates also and becomes a hawk.

We assume that escalating properties of **R** allow it to **handle Dove D** a little **better** than does Dove D handle Retaliator R (see 1.1 and 0.9 in the matrix).

All playing **Retaliator R is an ESS** since V(R,R)=1 is greater than either V(D,R)=0.9 or V(H,R)=-1. But can we find stable strategies by using mixed strategies?

Yes, we can. **Mixing I=0.5H+0.5D** leads to V(H,I)=0.5, V(D,I)=0.5, V(R,I)=0.05 and V(I,I)=0.5. We find a **second stable point**!

Hawk-Dove-Retaliator Game

Payoff Matrix V		Player B		
		H	D	R
Player A	H	-1	2	-1
	D	0	1	0.9
	R	-1	1.1	1

The **starting conditions** of the population **will determine, at which ESS** it will land and along which paths.
This **dynamics can be nicely visualized in a pyramid**:

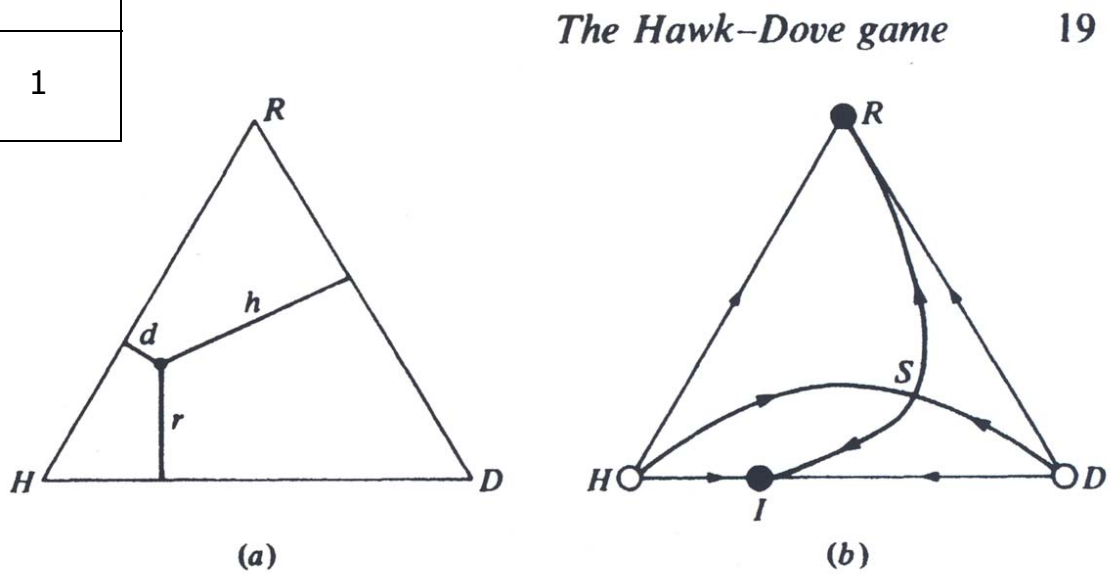


Figure 1. The Hawk–Dove–Retaliator game. (*a*) Representation of the state of a polymorphic population; *h*, *d* and *r* are the frequencies of pure *H*, *D* and *R* respectively. (*b*) Flows for the *H*–*D*–*R* game given in Table 2. There are attractors at *I* and *R* and a saddle point at *S*.

From:
J.M. Smith: Evolution and the theory of Games

Eigen & Schuster: Selfreplicative Molecules

$$\dot{n}_i = (k_{pi} q_i - k_{mi}) n_i + \sum_{i \neq j} k_{m,ji} n_j$$

$$\sum_i n_i = \text{const}$$

Take molecules the number of molecules n_i of sequence i (also called species) and introduce the following population dynamics:

k_{pi} Propagation rate,
i.e. the ability to self-replicate

k_{mi} Mortality rate and rate to leave the area

$q_i<1$ Replication fidelity

$k_{m,ji}$ Probability to mutate from another species j.

In the last slide, we focussed on **how the population** determines the selection pressure and **the profit of an individual**. To recall, in the Eigen model (above): the fitness was determined by k_{pi} and k_{mi}, but not explicitly by the state of the population n_i. However in nature, games with frequency dependent selection are common.

From: Gesteland, Cech, Atkins: RNA World

Game Theory Comments

Stephen Jay Gould:
"One day, at the New York World's Fair in 1964, I entered the Hall of Free Enterprise to escape the rain. Inside, prominently displayed, was an ant colony bearing the sign: '**Twenty million years of evolutionary stagnation. Why? Because the ant colony is a socialist, totalitarian system.**"

A **society with memory** and ways to **punish** its members can very well **enforce an evolutionary unstable strategy with higher profit** for all its participants.

In this sense, **memory-enabled and state-supporting human beings** can be superior to a **state-less fully competing pool of individuals**.

Note that **money** is a very important **memory element** in modern societies.

We probably have to **adjust our meaning of "egoistic"** along the lines of game theory. In such a sense, **really egoistic societies** might **not at all look like egoistic societies** in the popular meaning of the word.

Concerning **molecular evolution**, we are only at the beginning of harvesting the **evolutionary scope of game theory**. It is not improbable that we find imprints if **game theory even down to the molecular level**. Proteins and DNA most probably play a very intricate and complex game. **Life might be indeed the game of selfish genes.**