Bi9690en Synthetic Biology – Lecture 1

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Definition of Synthetic Biology

What is life?

Where does life come from?

Why does life exist?

Can we make life?

Synthetic Biology

- "Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems."

  Britisch Royal Society

- Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way."

  High-level Expert Group European Commission

- Fundamental principle of synthetic biology is that biological matter can be predictably designed and utilized as an engineering material.

- Applying rigorous engineering methods to derive economic value from biological matter.

- *De novo* synthesis of life from physical and chemical processes.

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What is life?

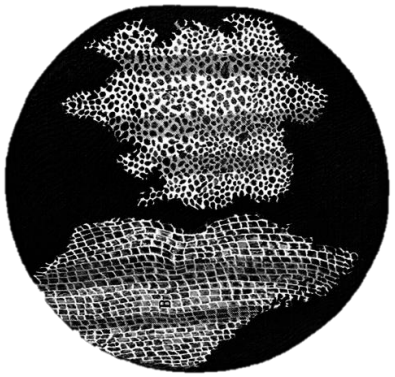
Features of life

- life is cellular
- reproduction/replication
- homeostasis
- metabolism
- selfassembly
- ability to harvest energy
- aging
- life has history: ability to evolve

Grand theories that form the foundation of modern biology

- **Theory of Genetics**
- **Theory of Evolution**
- **Cell Theory**

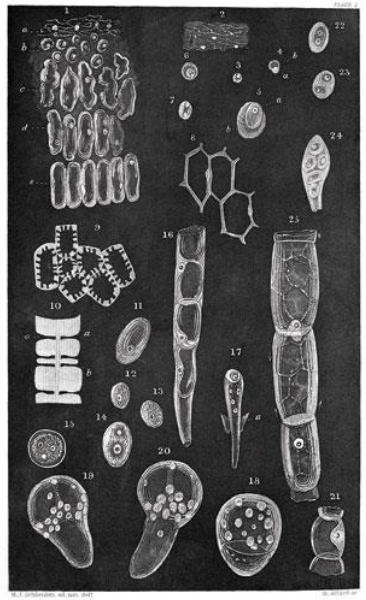
The Cell Theory postulates that cells are the basic units of all living organisms and that cells form from pre-existing cells



- In 1665 Robert **Hook**e discovered in a tine slice of cork a multitude of tiny pores that he named "cells".

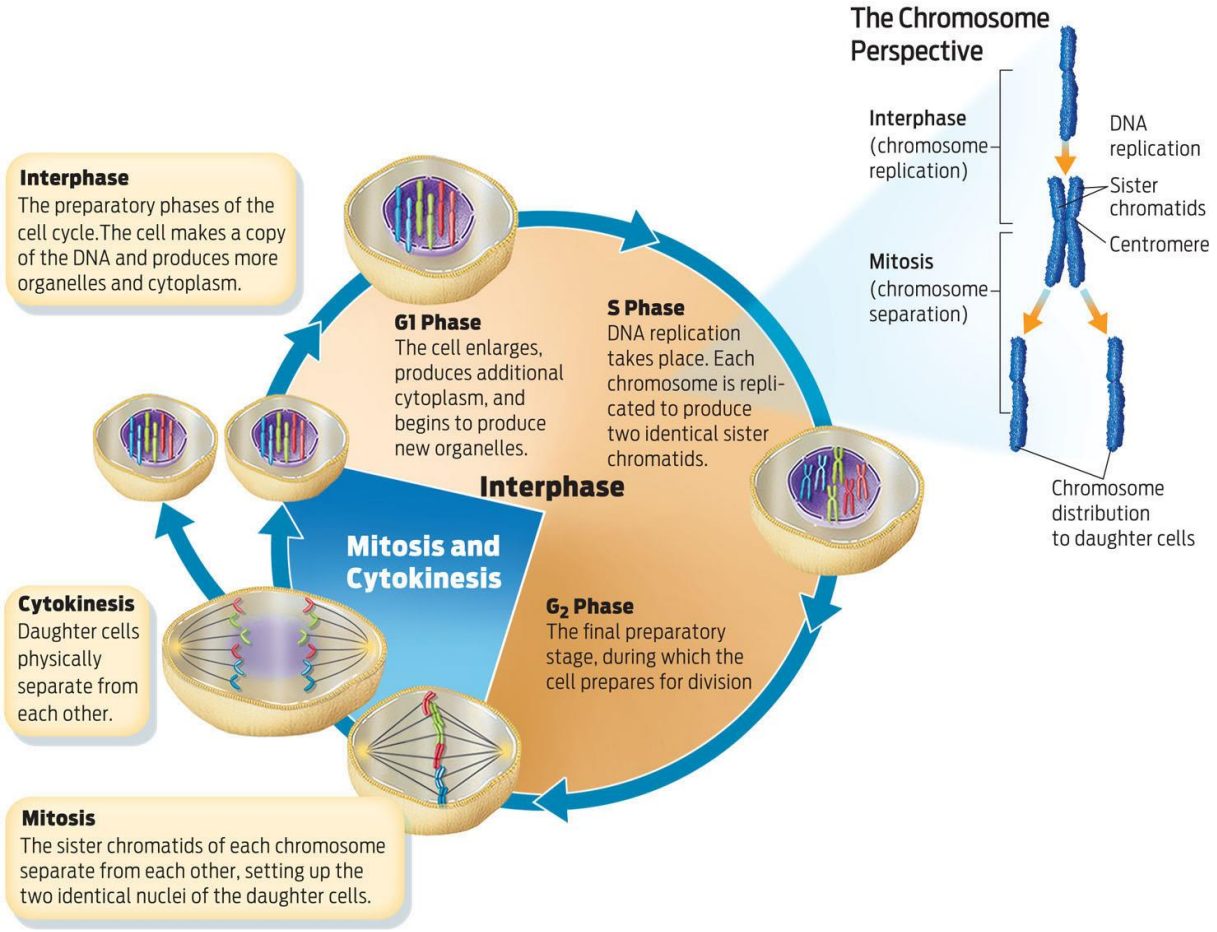
- **Leeuwenhoek** improved magnidication of microscopes (270x) and observed motile objects. He postulated that since motolity is feature of life, these were living organisms. f

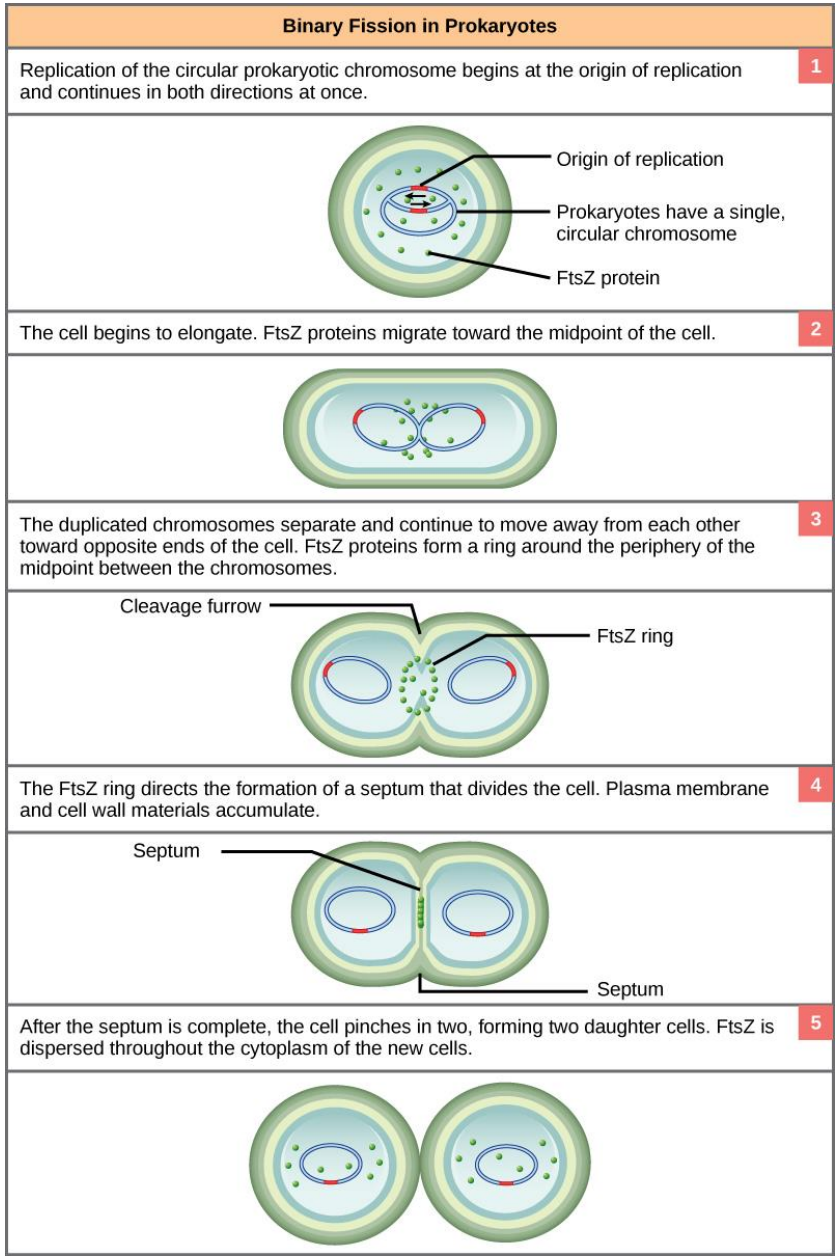
- In 1839, **Schleiden** suggested that every structural part of a plant was made up of cells or the result of cells.
- **Schwann** proposed that all animal tissues are composed of cells, and that the cell was the fundamental structural and functional unit of all living organisms.
- In 1852 **Remak** published evidence that cells are derived from other cells as a result of cell division. This work was popularized by **Virchow** (without giving credit to Remak).
- In 1839 **Purkyne** coined the term protoplasma, the fluid substance of the cell.



Reproduction/replication

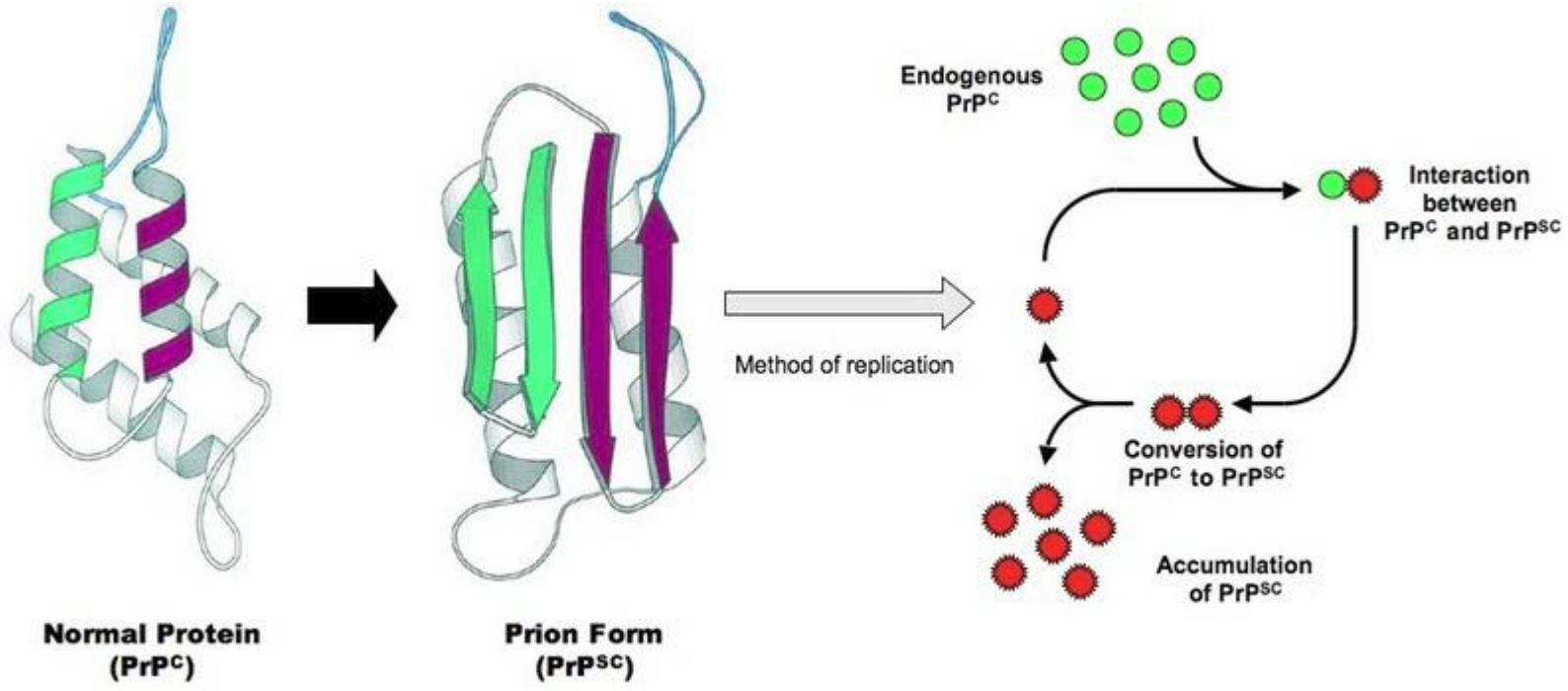
Eukaryotic cell cycle





Is replication and reproduction the defining feature of life?

Prions are misfolded proteins with the ability to transmit their misfolded shape onto normal variants of the same protein.



Life is very good at harvesting energy from its surroundings

In the long run, **nothing escapes the Second Law of Thermodynamics**. The pull of entropy is relentless. Everything decays. Disorder always increases.

How life defies entropy?

"The ultimate purpose of life, mind, and human striving: **to deploy energy** and information to fight back the tide of entropy and carve out refuges of beneficial order." —Steven Pinker

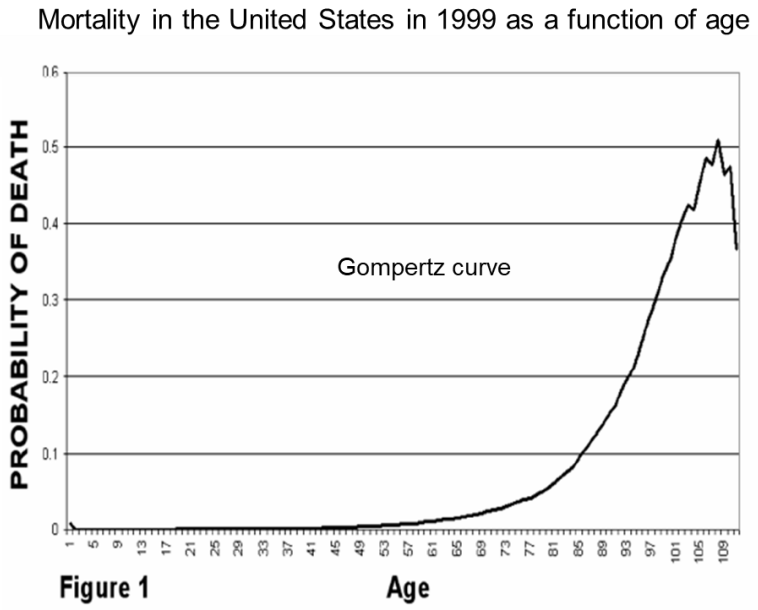
Local clumps of order come at the expense of increasing the disorder around them.

Life a chemical system that drains and dissipates chemical energy.

What is aging?

Aging: the time-sequential deterioration that occurs in most animals including weakness, increased susceptibility to disease and adverse environmental conditions, loss of mobility and agility, and age-related physiological changes. Aging is usually understood to include reductions in reproductive capacity.

Aging: drop in survival probability and fertility with advancing adult age.



PROBABILIY OF DEATH = The chance of dying any given year.

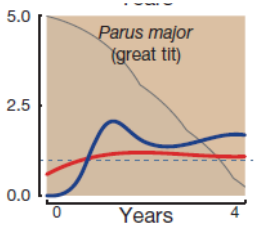
Is aging an inherent feature of life?

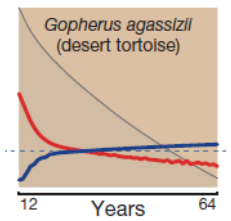
The laws of entropy say that everything goes **from an ordered to a less ordered state** as time passes. Wouldn't aging be an example of entropy?

Isn´t aging in our genes? Isn´t it **genetically programmed characteristic** that conveys a benefit to the species even though it has a negative effect on individual fitness?

Coral reef fish Sign Eviota completes its entire life cycle within 8 weeks.

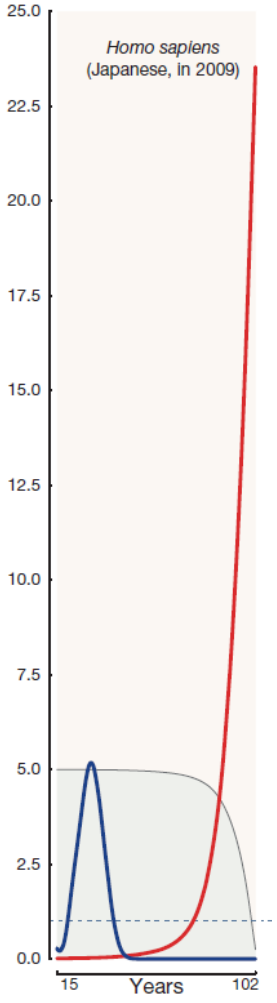
Greenland shark – an individual tha could be up to 512 old

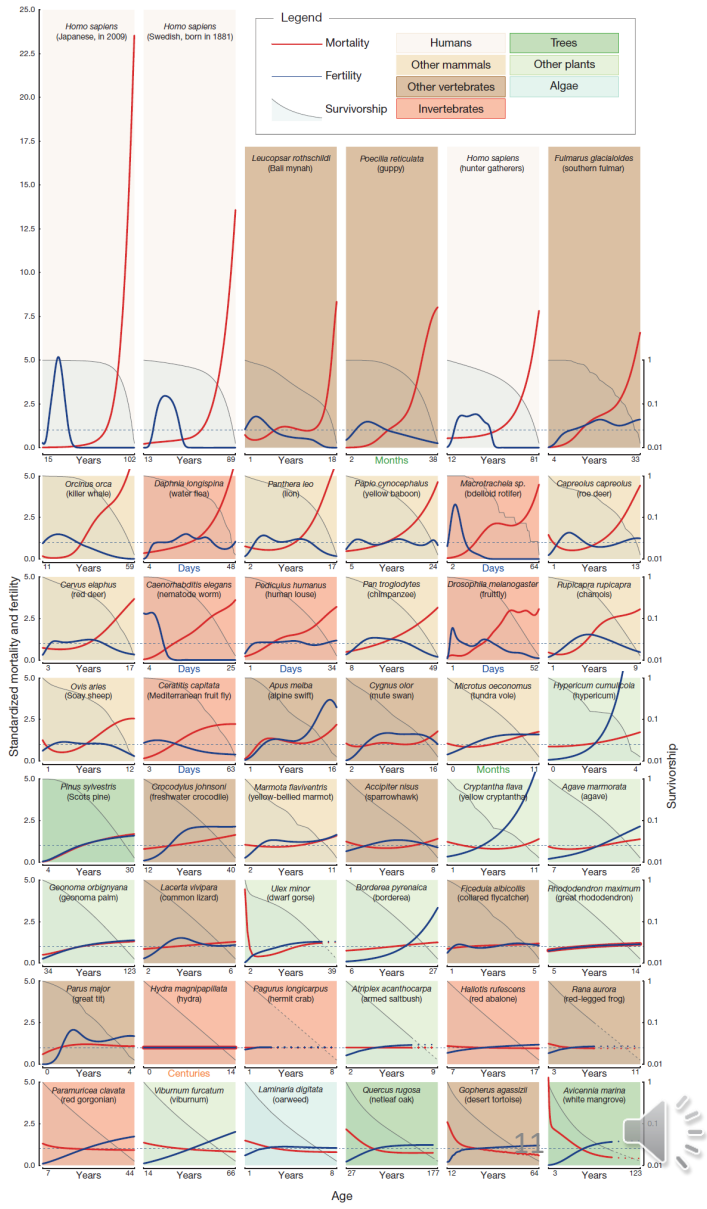




Diversity of ageing across the tree of life

Owen R. Jones[1,2]*, Alexander Scheuerlein[3]*, Roberto Salguero-Gómez[3,4], Carlo Giovanni Camarda[5], Ralf Schaible[3], Brenda B. Casper[6], Johan P. Dahlgren[1,2], Johan Ehrlén[7], María B. García[8], Eric S. Menges[9], Pedro F. Quintana-Ascencio[10], Hal Caswell[2,3,11,12], Annette Baudisch[3] & James W. Vaupel[1,3,13]





Aging is trade off

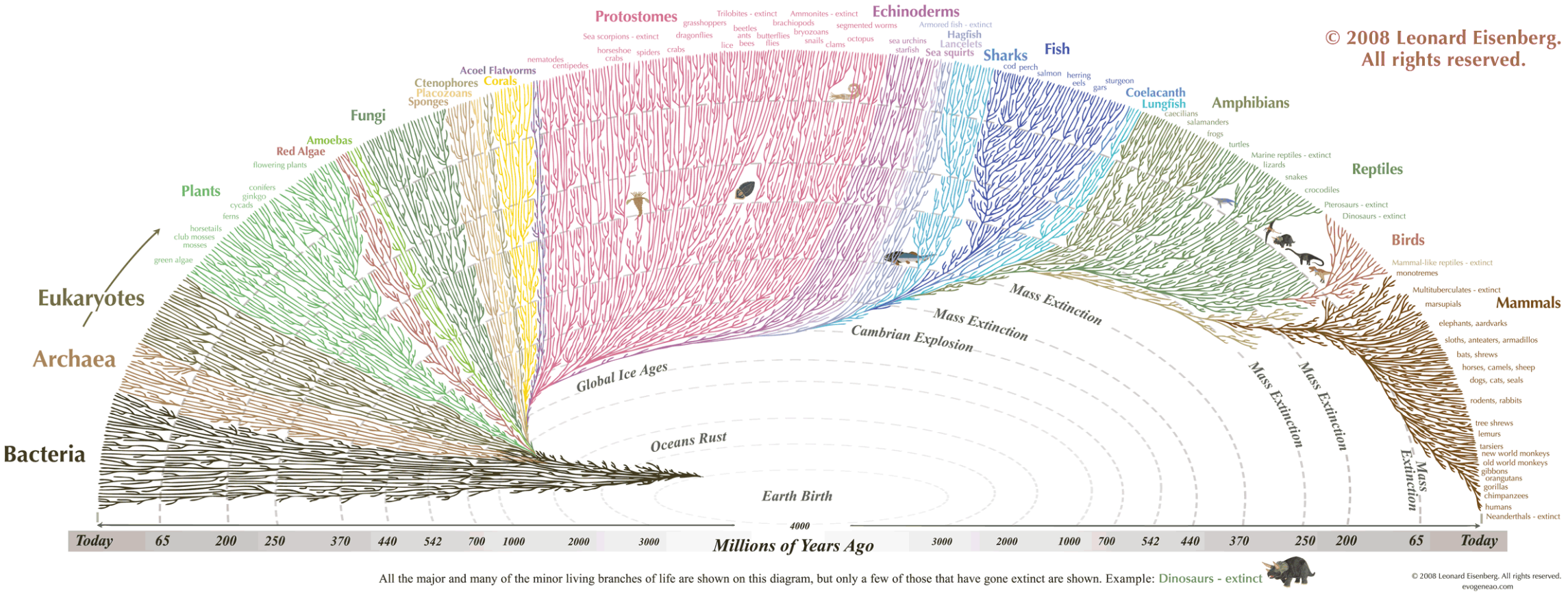
Table 1 | Manifestations of ageing and homeostatic defences

Position in hierarchy	Manifestations of ageing	Homeostatic mechanisms/defence
Molecular changes that lead to cellular dysfunction	Cumulative mutations in nuclear and mitochondrial DNA	DNA repair activities; telomerase activity
	Oxidative damage to cellular constituents	Antioxidant enzymes, cytosolic and membrane free-radical scavengers
	Accumulation and aggregation of abnormal proteins, lipids and other macromolecular constituents	Mechanisms to recognize and degrade abnormal proteins and other macromolecules
Cellular changes that lead to tissue dysfunction	Cell death	Anti-apoptotic pathways
	Oncogenesis	Cell-cycle checkpoints, tumour-suppressor genes, apoptosis pathways
	Senescence	Immune surveillance
Tissue changes that lead to organismal dysfunction	Atrophy from cell loss and diminished regenerative capacity	Stem cells for tissue maintenance and repair
	Extracellular matrix changes	Matrix remodelling activities such as those of metalloproteinases
	Extracellular deposits	Phagocytic activities of resident and circulating cells

Rando, Nature (2006)

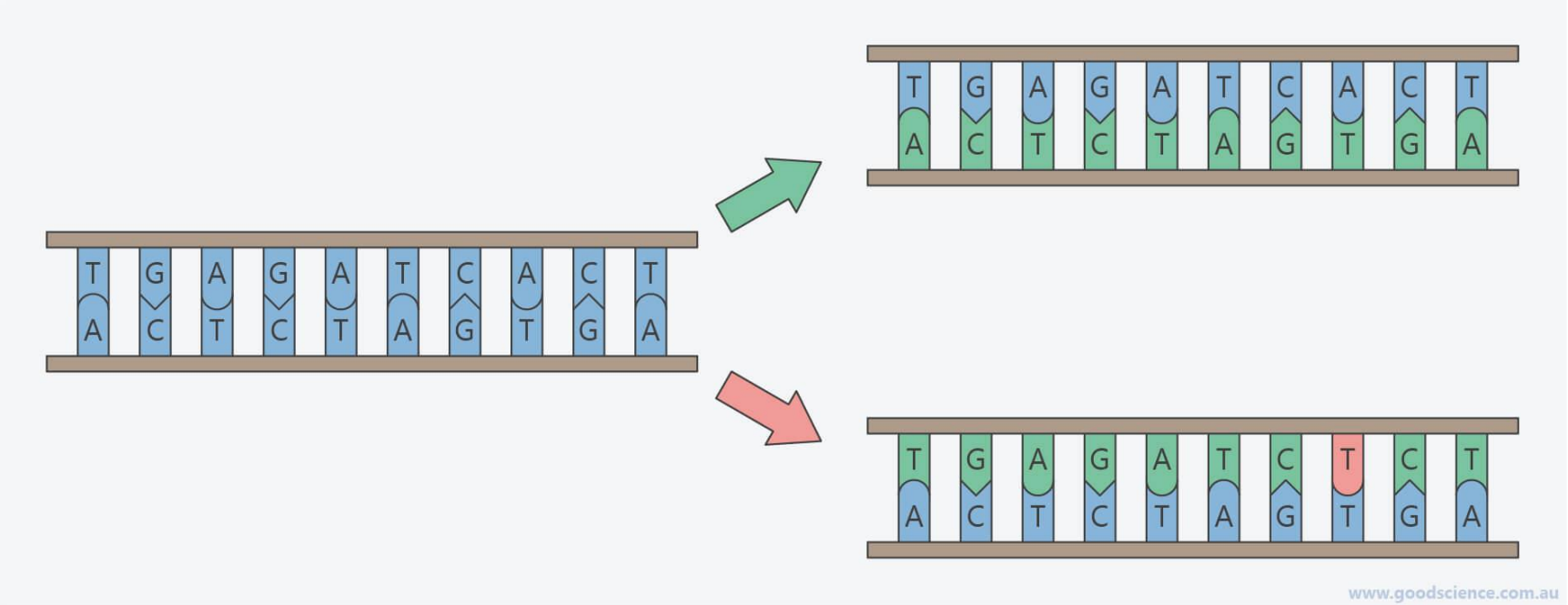
The factors that cause aging are genetically transmitted but not “genetically programmed”.

Life has history: Back to One



LUCA: last universal common ancestor

Generation and propagation of mutations is a key prerequisite of Darwinian evolution

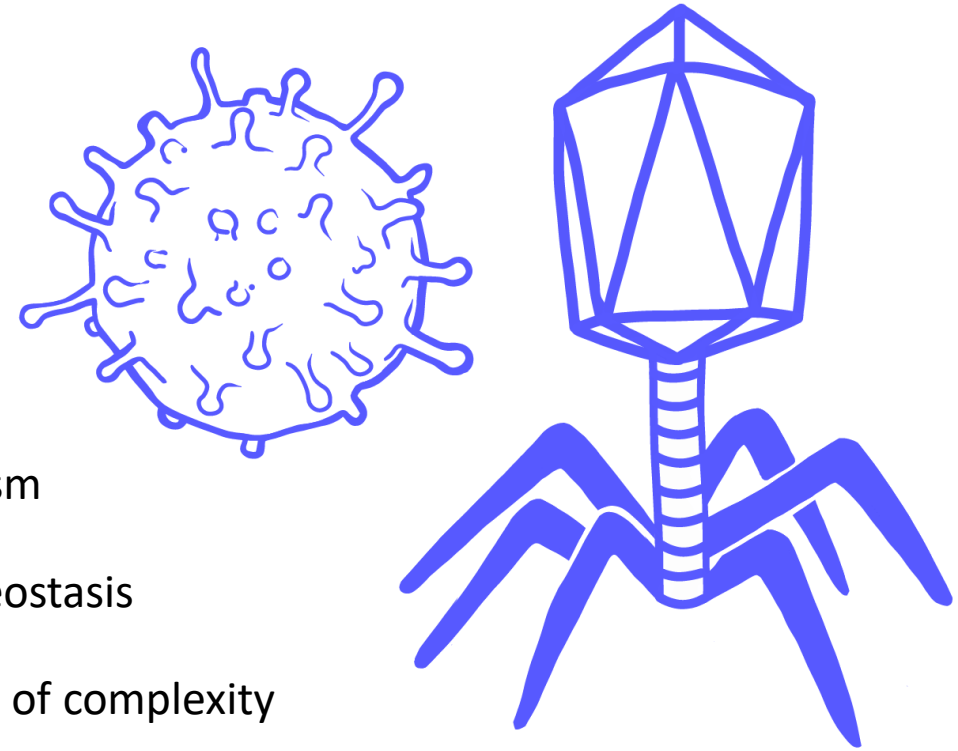


DNA Replication Error

Life could be defined as a self-sustaining chemical system (i.e., one that turns resources into its own building blocks) that is capable of undergoing Darwinian evolution.

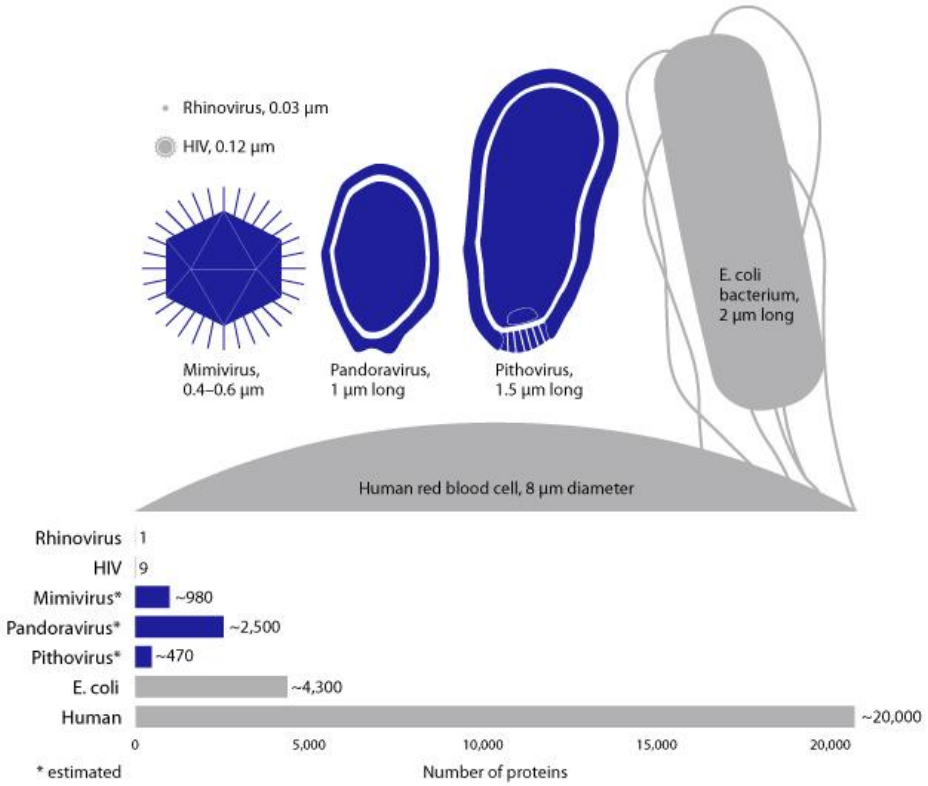
Are viruses alive?

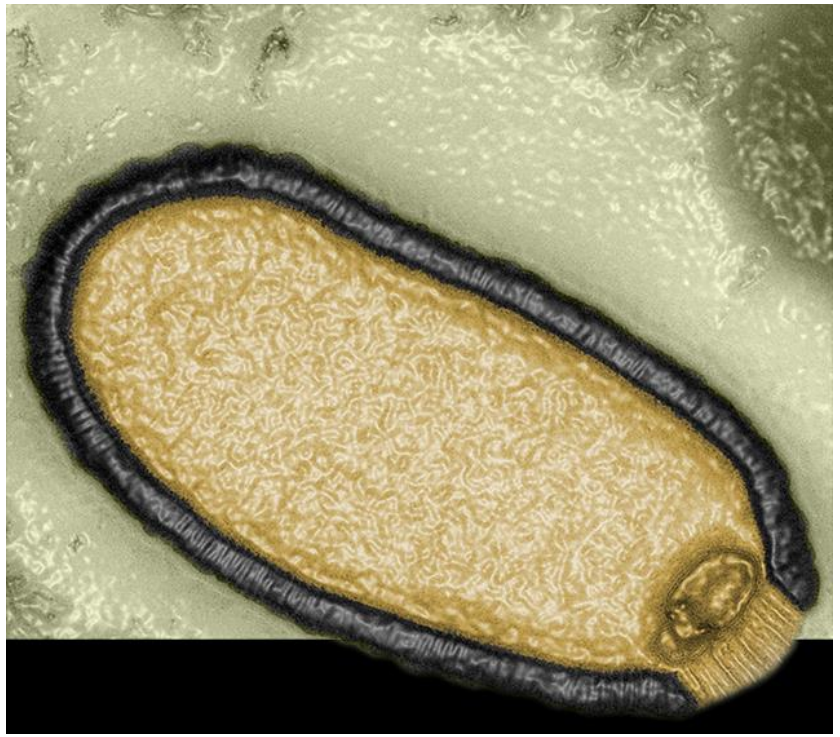
- ✓ they reproduce
- ✓ they eveolve and adapt
- † they do not have cells
- † they do not have metabolism
- † they do not maintain homeostasis
- ✓ selfassembly and high level of complexity



Some scientists argue that viruses don't count as living organisms and are better seen as rogue genetic material that can't reproduce on their own and need to hijack host cells. Others believe viruses evolved from cellular organisms and so count as a fourth domain of life.

Giant viruses further blur the boundary of life

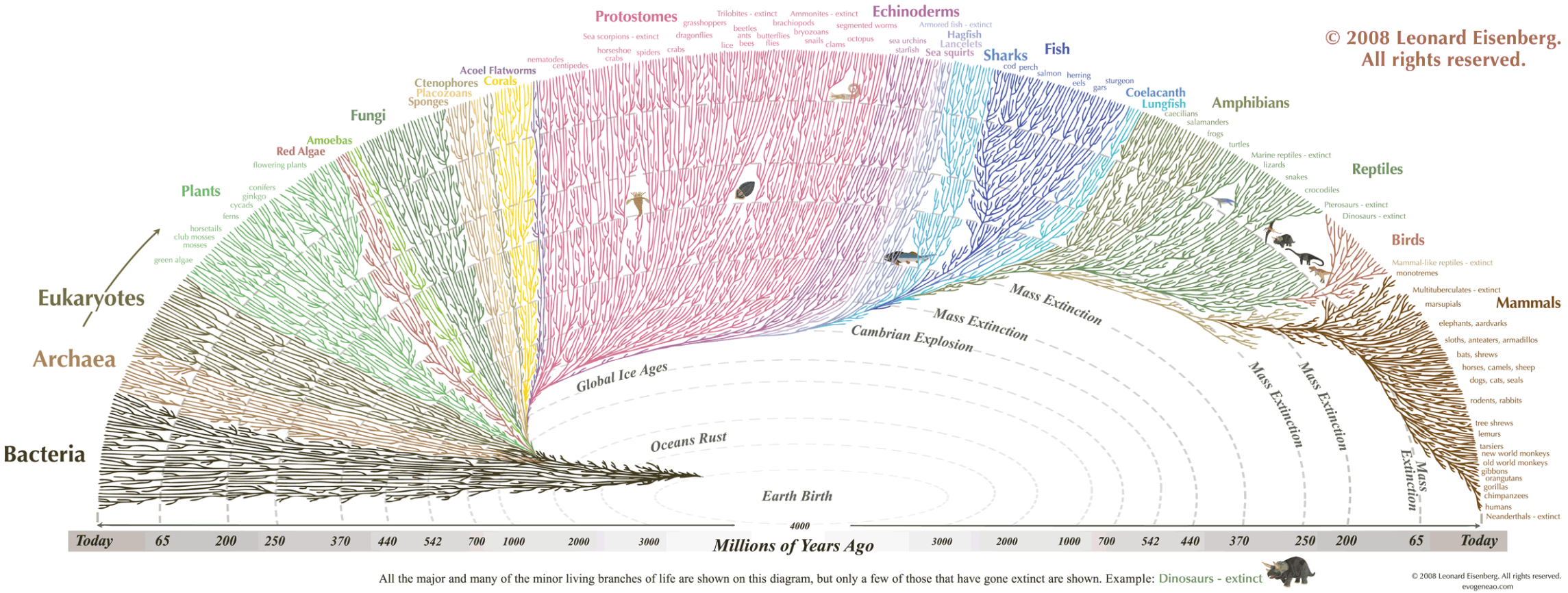




At more than 1.5 micrometers long, pithovirus is the largest virus ever discovered.

There is continuum between non-living and living and it is pointless do draw a strict boundary in between.

Where we come from? - The origin of Life



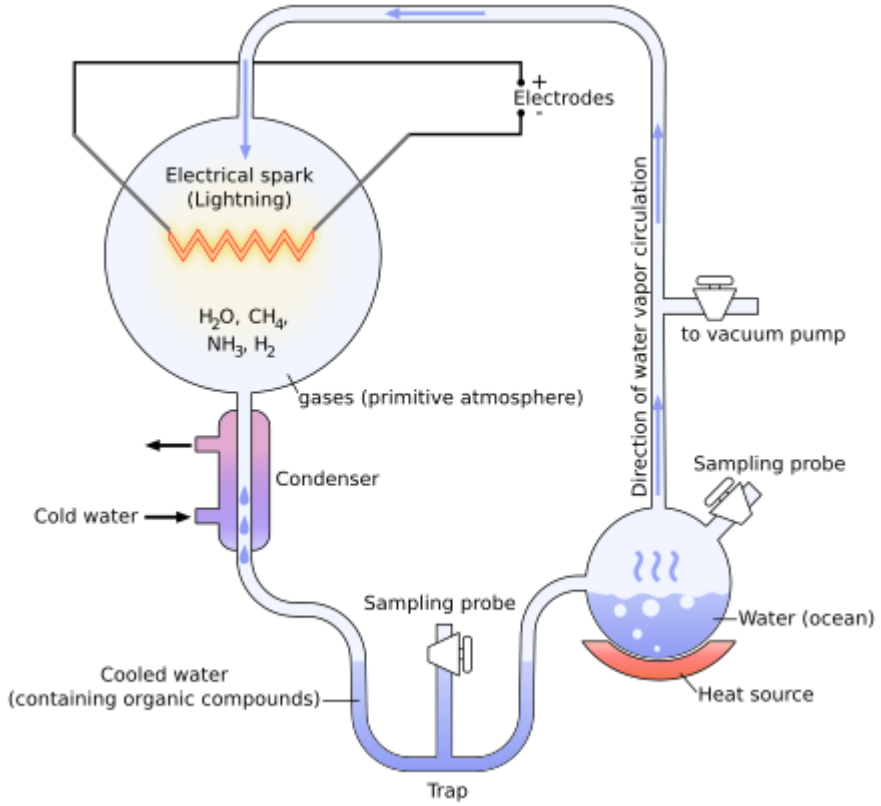
All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct

LUCA: last universal common ancestor

Where we come from? - The origin of life

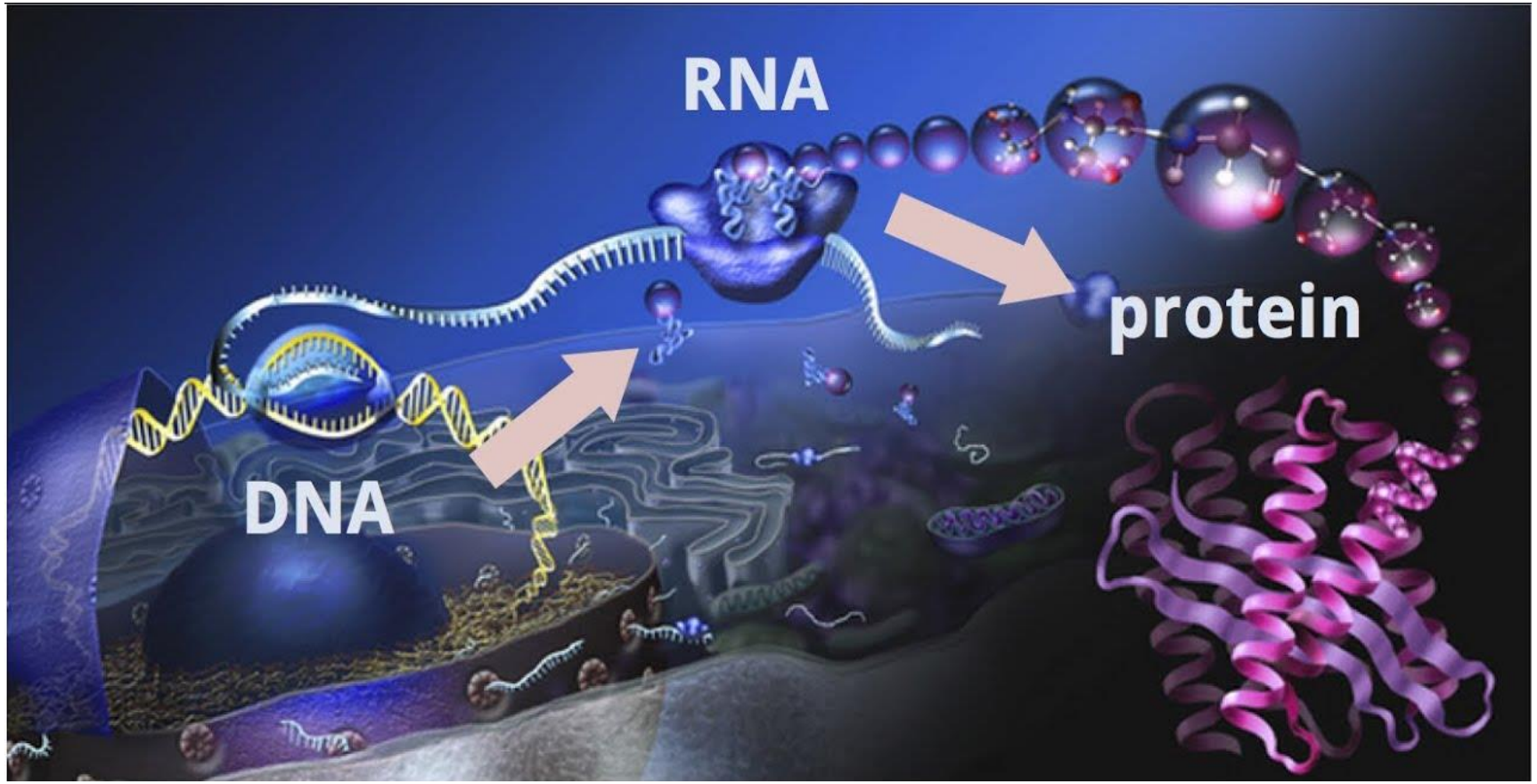
1930´s: Oparin and Haldane proposed that organic material (primordial soup), when subjected to suitable environmental conditions present on early Earth, could begin to increase in complexity, eventually giving rise to living cells.

Miller-Urey experiment (1953)



Modern world:

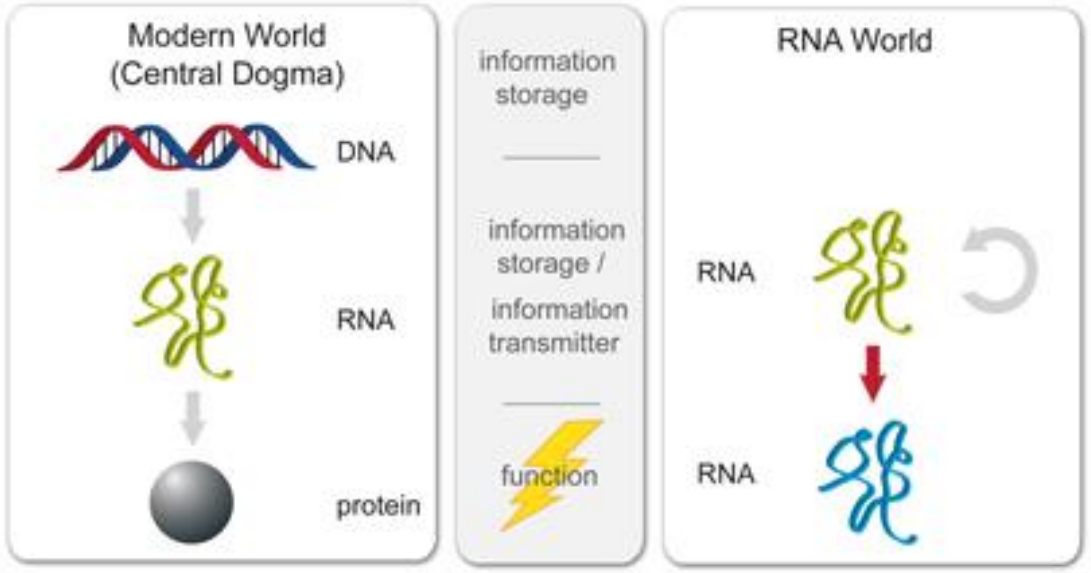
Central dogma:



The RNA world hypothesis

1981: Discovery of self-splicing introns - catalytic RNA - **Rybosymes**

The RNA world hypothesis postulates that selfrepicating RNA molecules were precursors of modern life that is based on DNA, RNA and proteins. It is generally accepted that the current life on Earth descends from an RNA world, although RNA life may not have been the first life to exist.



From RNA ribozymes to protein catalysis

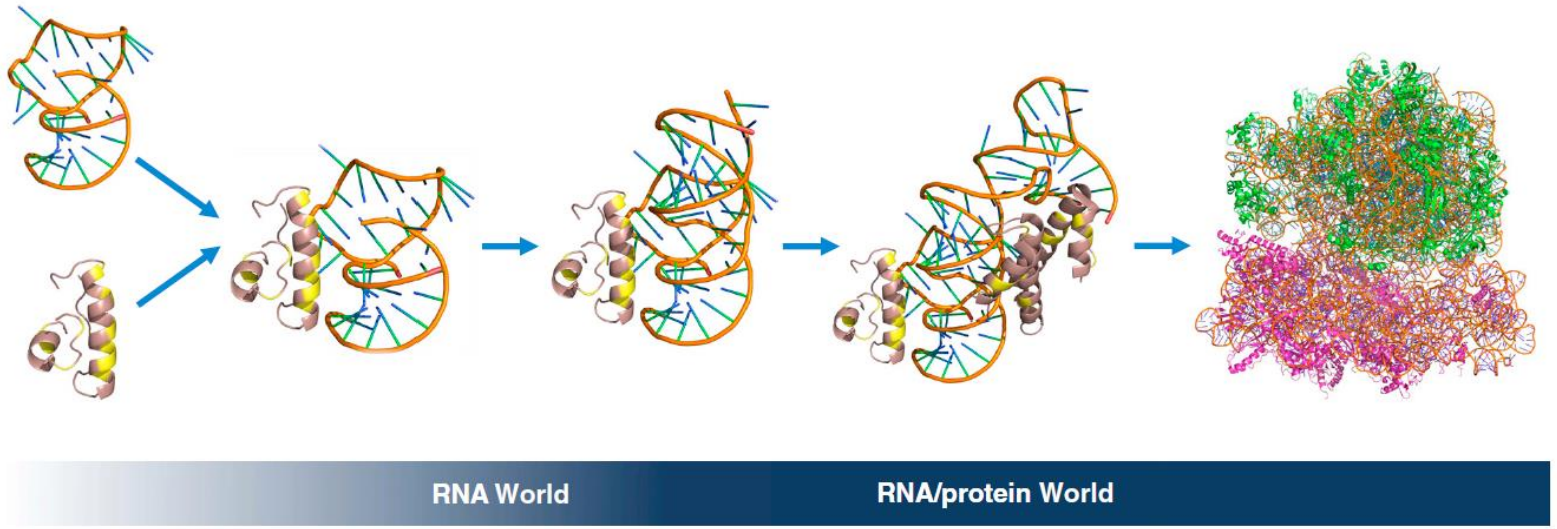


Figure 2. The association between RNA and cationic amino acid-rich oligopeptides.
During primordial times the binding of prebiotic oligopeptides with basic amino acids (in yellow) would stabilize the catalytic and functional conformation of RNAs, leading to the formation of complexes that would coevolve into more complex, efficient ribozymes from which primitive ribosomes are hypothesized to have evolved.

Self-replicating RNA

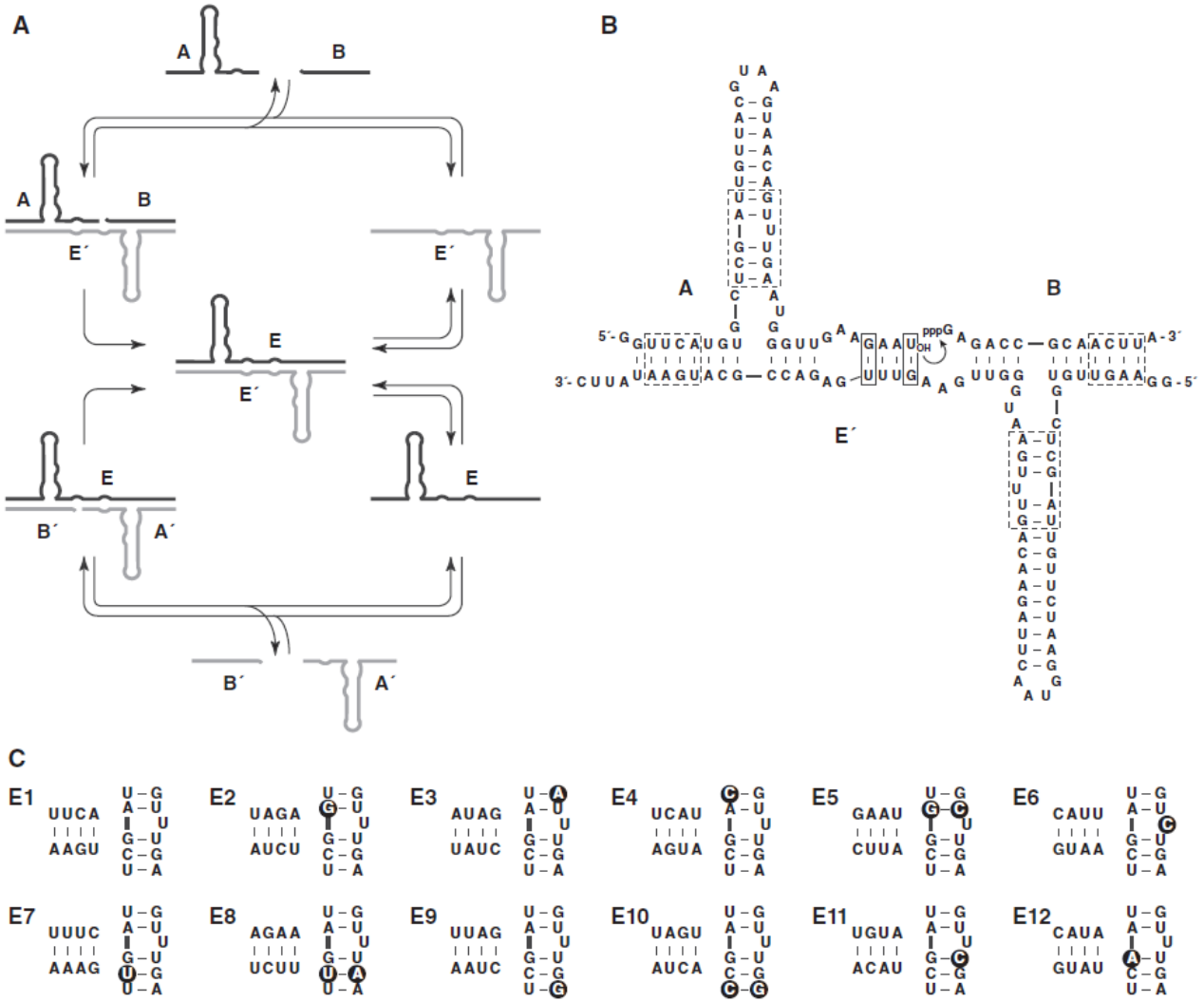


Fig. 1. Cross-replicating RNA enzymes. (**A**) The enzyme E′ (gray) catalyzes ligation of substrates A and B (black) to form the enzyme E, whereas E catalyzes ligation of A′ and B′ to form E′. The two enzymes dissociate to provide copies that can catalyze another reaction. (**B**) Sequence and secondary structure of the complex formed between the enzyme and its two substrates (E′, A, and B are shown; E, A′, and B′ are the reciprocal). The curved arrow indicates the site of ligation. Solid boxes indicate critical wobble pairs that provide enhanced catalytic activity. Dashed boxes indicate paired regions and catalytic nucleotides that were altered to construct various cross replicators. (**C**) Variable portion of 12 different E enzymes. The corresponding E′ enzymes have a complementary sequence in the paired region and the same sequence of catalytic nucleotides (alterations relative to the E1 enzyme are highlighted).

Lincoln and Joyce, Science 2009

Relics of RNA world

Four of the central reactions involved in protein biosynthesis, that is, amino acid activation, aminoacyl-RNA synthesis, peptide-bond formation, and RNA-based coding, are catalyzed by ribozymes, and their complementary nature suggests that they first appeared in an RNA world.

TABLE 4.3. Examples of modern RNA roles

Function	Type of RNA	Role of RNA
Translation	mRNA	Product of DNA transcription
	tRNA	Involved in translation of the genetic code
	rRNA	Serves as part of a ribosomal subunit
DNA replication	RNA primers	Replication of the lagging DNA strand initiates with an RNA primer
	Telomerase RNA	Needed at the ends of linear chromosomes
Splicing and RNA processing	Small nuclear RNA (snRNA)	Involved in splicing
	Small nucleolar RNA (snoRNA)	Required for posttranscriptional processing of rRNA
	RNase P	Essential for tRNA processing
Translation quality control	tmRNA	Targeting aberrant protein products for degradation in bacteria
Protein translocation	Signal recognition particle (srpRNA)	A component of the signal recognition particle (SRP)
RNA interference (RNAi)	Many types	Involved in regulating RNA stability and translation in euykaryotes
Transcription regulation	6S	Regulates the function of bacterial RNA polymerase

Compartmentalization

- essential for more complex functions, such as RNA catalyzed replicative and metabolic reactions

- enables the positive feedback required for Darwinian evolution by keeping useful products close to the catalysts that generated them and by keeping molecules related by descent physically closer, on average, compared with more distantly related molecules.

- essential to prevent system crashes caused by the evolution of parasites. In free solution, parasitic RNAs that are better templates will increase at the expense of functional replicase RNAs, leading to a population crash.

Protocells

Protocells must have been simple enough to self-assemble spontaneously in a chemically rich environment under appropriate physical conditions but sufficiently complex that they were poised to evolve to greater complexity, ultimately giving rise to all of modern biology.

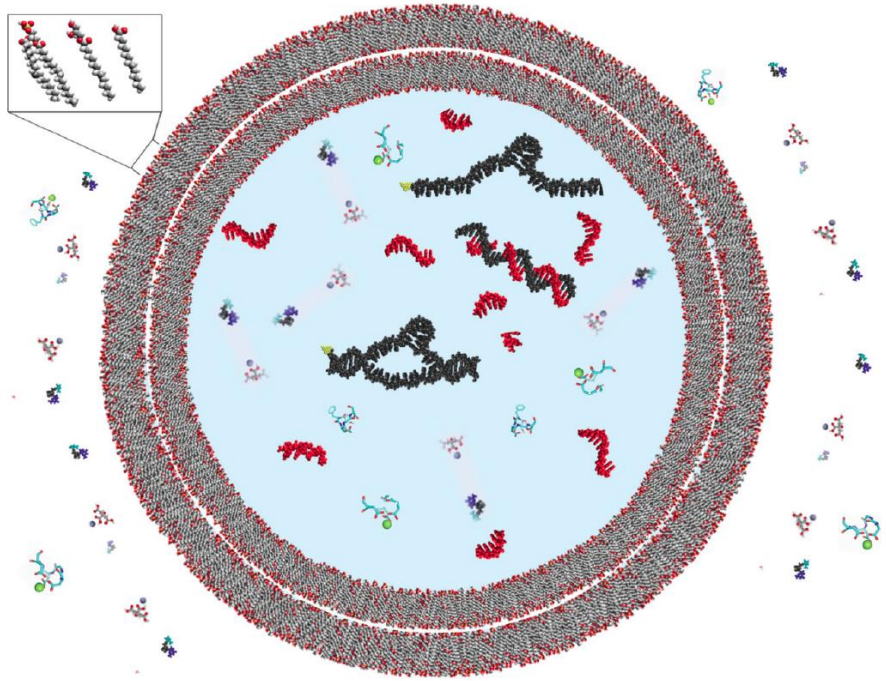


Figure 1. Schematic diagram of a protocell. Protocells bounded by multiple bilayer membranes composed of simple amphiphilic molecules would have been permeable to nucleotides and metal ions complexed with citrate or other ligands. Larger genomic and functional RNA molecules would have been trapped within the protocell interior. Protocell replication would involve growth and division of the membrane boundary as well as replication of the genomic RNA.

Joyce and Szostak, CSH Persp Biol 2018

Hydrothermal vents

- A deep hydrothermal vent is like a hot spring on the sea floor where mineral-rich, hot water flows into the otherwise cold, deep sea.
- The sea water makes its way through the cracks toward magma chamber, which can sit about 1 to 2 km below sea floor. The rock surrounding the magma chamber heats the water, which undergoes chemical reaction with the basaltic or ultramafic rock. Heated water becomes buoyant and is expelled back up like a spring, creating a plume of "**chemical soup**."
- There is strong evidence for the **abiotic production** of methane, hydrocarbons and a simple organic acid in hydrothermal vents
- ideal **incubators for life**, providing a steady supply of hydrogen gas, carbon dioxide, mineral catalysts, and a labyrinth of interconnected micropores

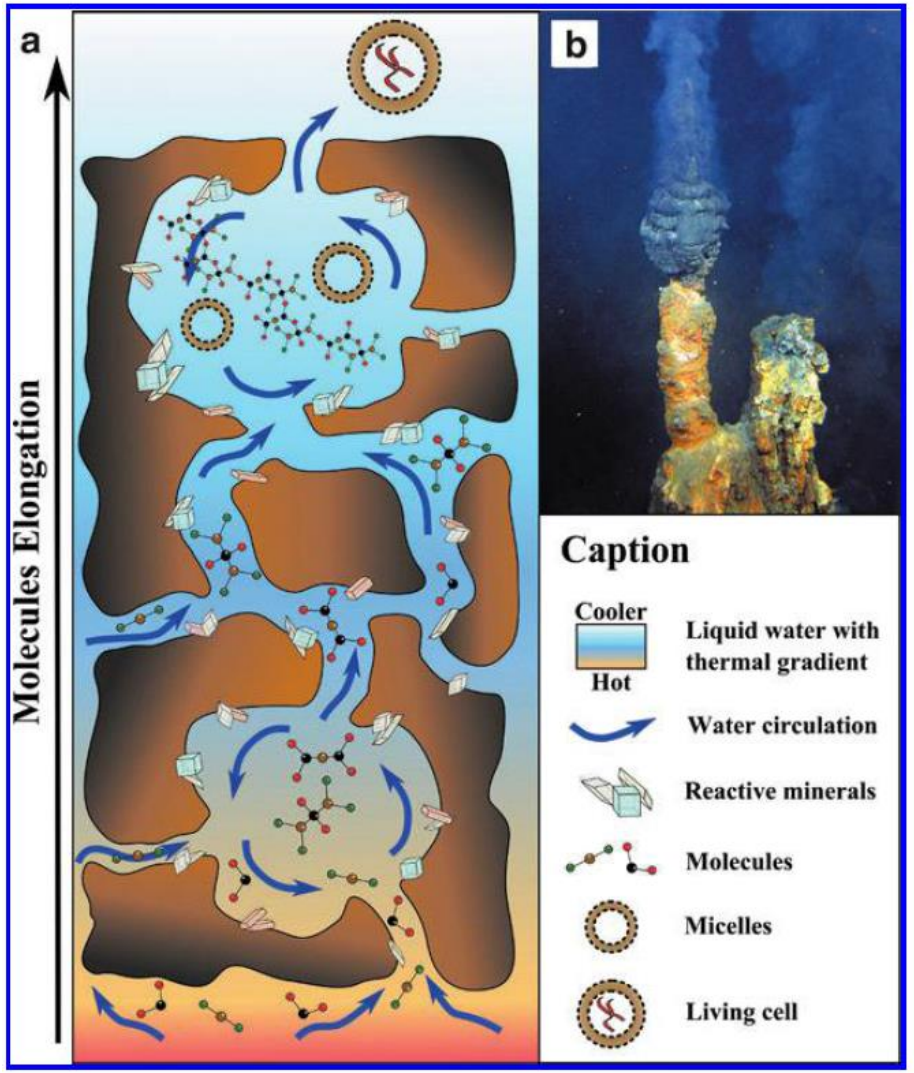
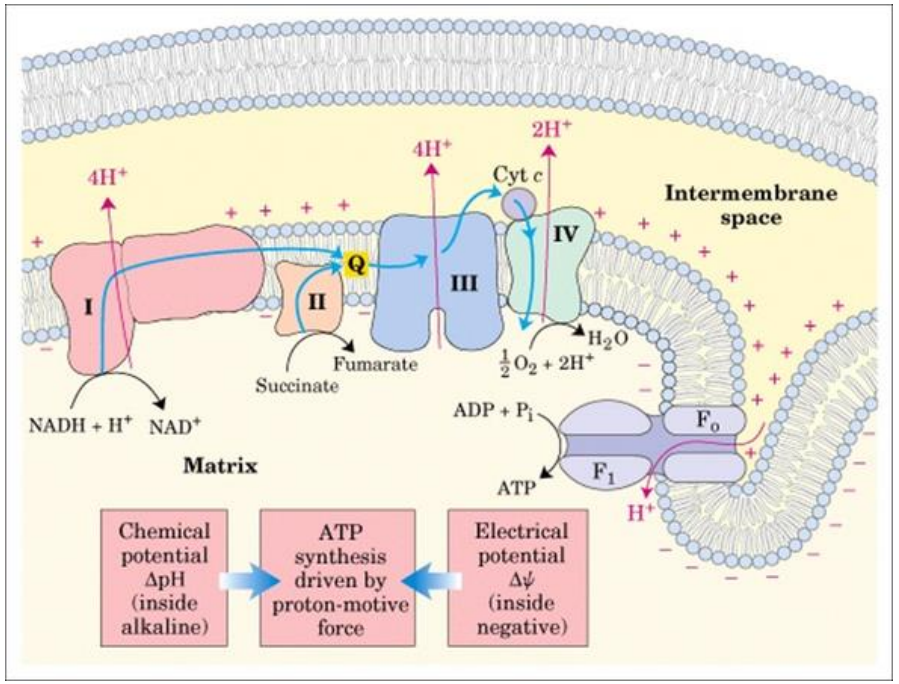


FIG. 1. Possible origin of life in porous (beehive), hydrothermal vents. (a) Sketch showing a porous beehive structure where hydrothermal fluids and seawater can circulate, leading to the accumulation of organic molecules. The reduced mineral surfaces within the vent pores could be favorable locations for the structural organization of macromolecules. We hypothesize the formation of lipid micelles in these environments and the incorporation of information-transferring molecules within the micelles, perhaps due to moderate agitation of the hydrothermal effluent. (b) Image of a modern black smoker (image credit: National Oceanographic and Atmospheric Administration). Color images available online at www.liebertonline.com/ast

Westall et al., Astrobiology 2013

Was an early life fueled by proton gradients in hydrothermal vents?

Living organisms produce energy via chemosmotic coupling



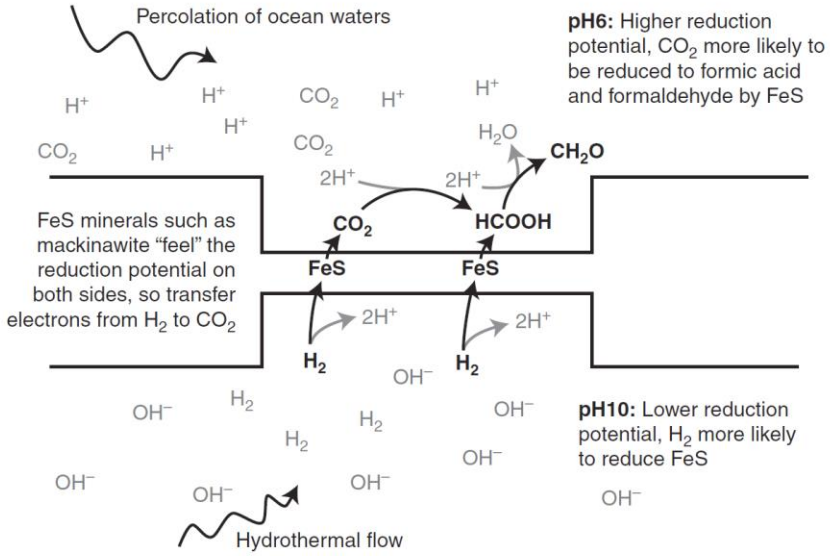


Figure 1. Proposed vectorial reduction of CO_2 by H_2 across a thin FeS barrier. The reduction potential (E_h) of the H^+/H_2 couple is −590 mV at pH 10, whereas the E_h of the CO_2/HCOOH couple at pH 6 is −370 mV, and the E_h of the HCOOH/CH_2O is −520 mV. A semiconducting FeS barrier should "feel" the distinct reduction potentials in both compartments and transfer electrons from H_2 to CO_2, to produce simple organics such as formaldehyde (CH_2O).

Lane, CSH Persp Biol 2014

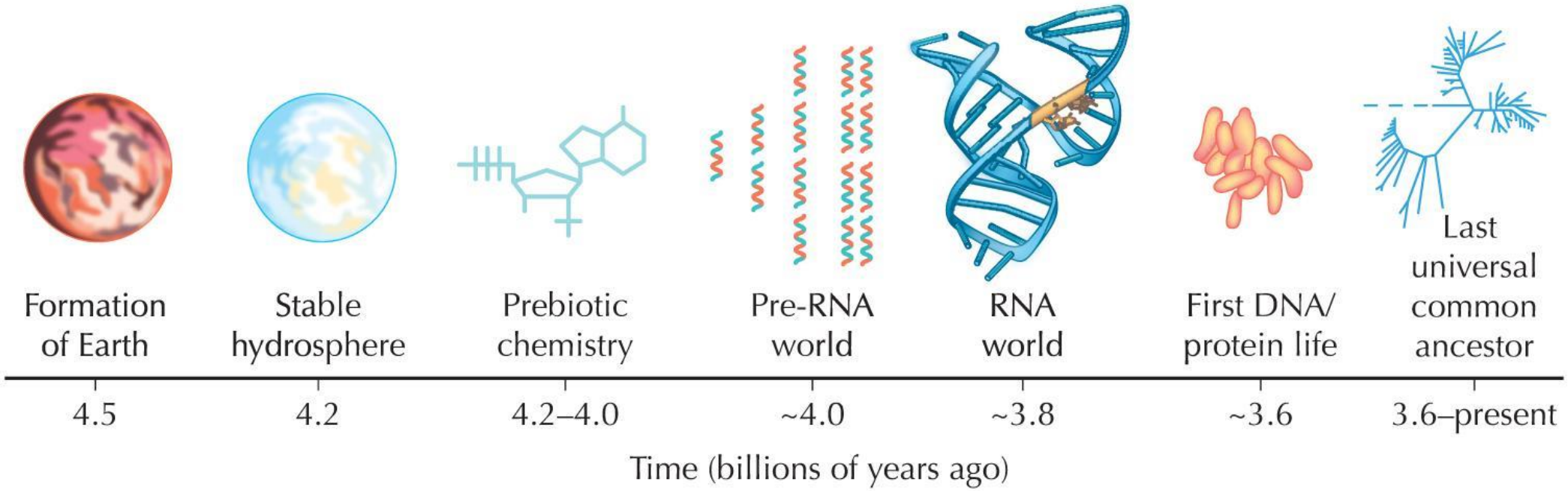
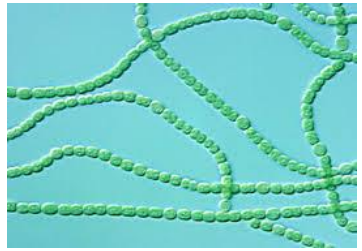


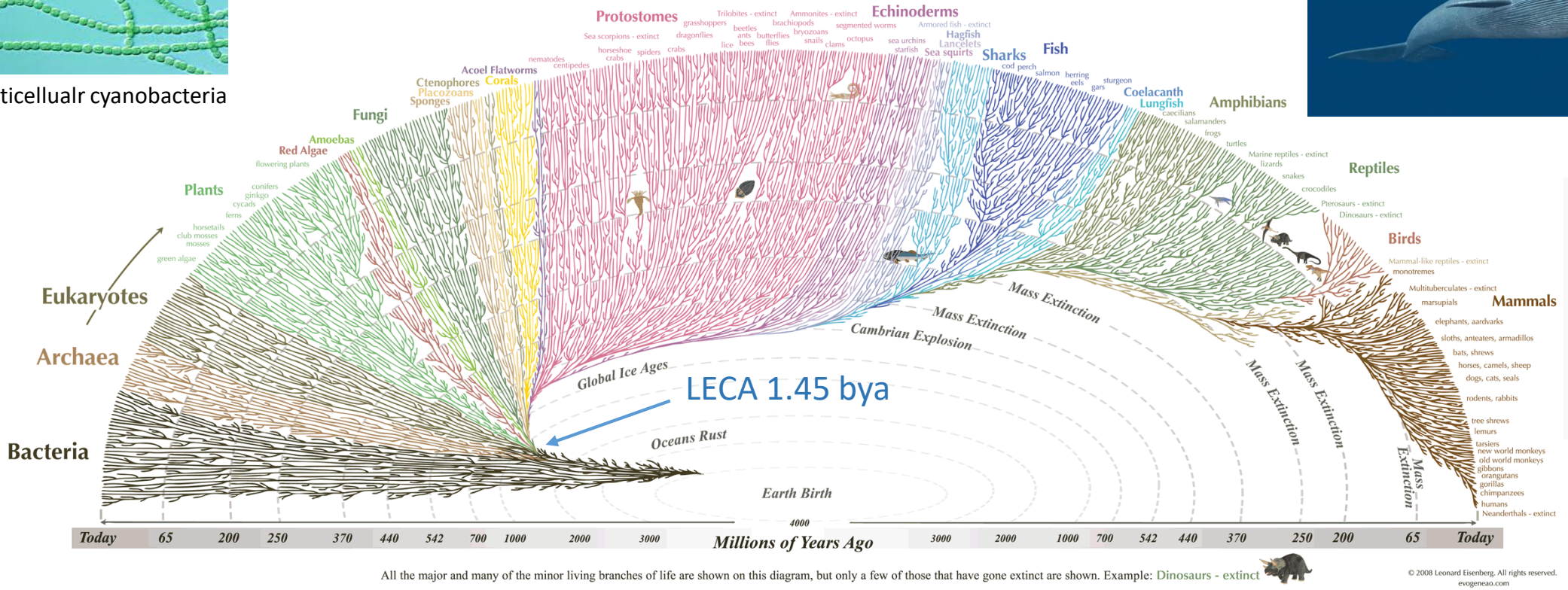
FIGURE 4.4. Steps in the origin of life.

4.4, modified from Joyce G.F., *Nature* **418:** 214–221, © 2002 Macmillan, www.nature.com

Emergence of complex life forms: eukaryotes



multicellualr cyanobacteria



Monophyletic origin of eukaryotes: LECA - last eukaryotic common ancestor

LECA was a typical, fully developed eukaryotic cell

Eukaryotic cell

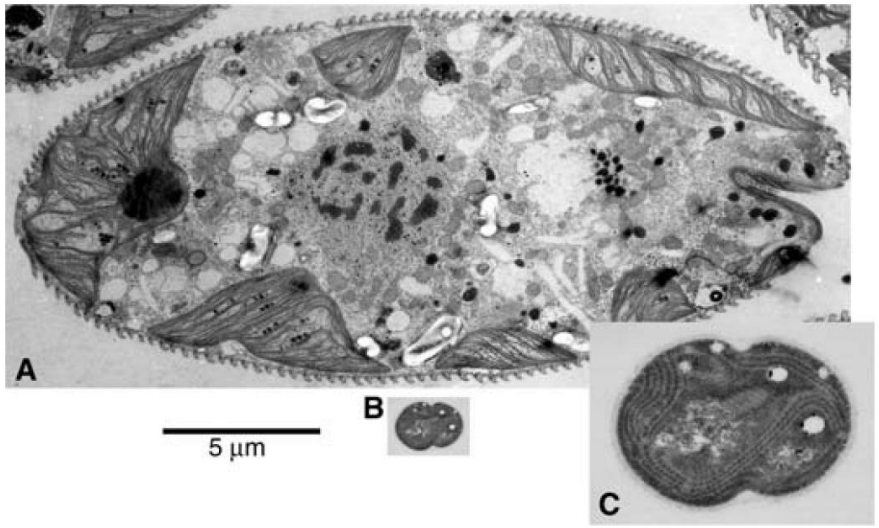


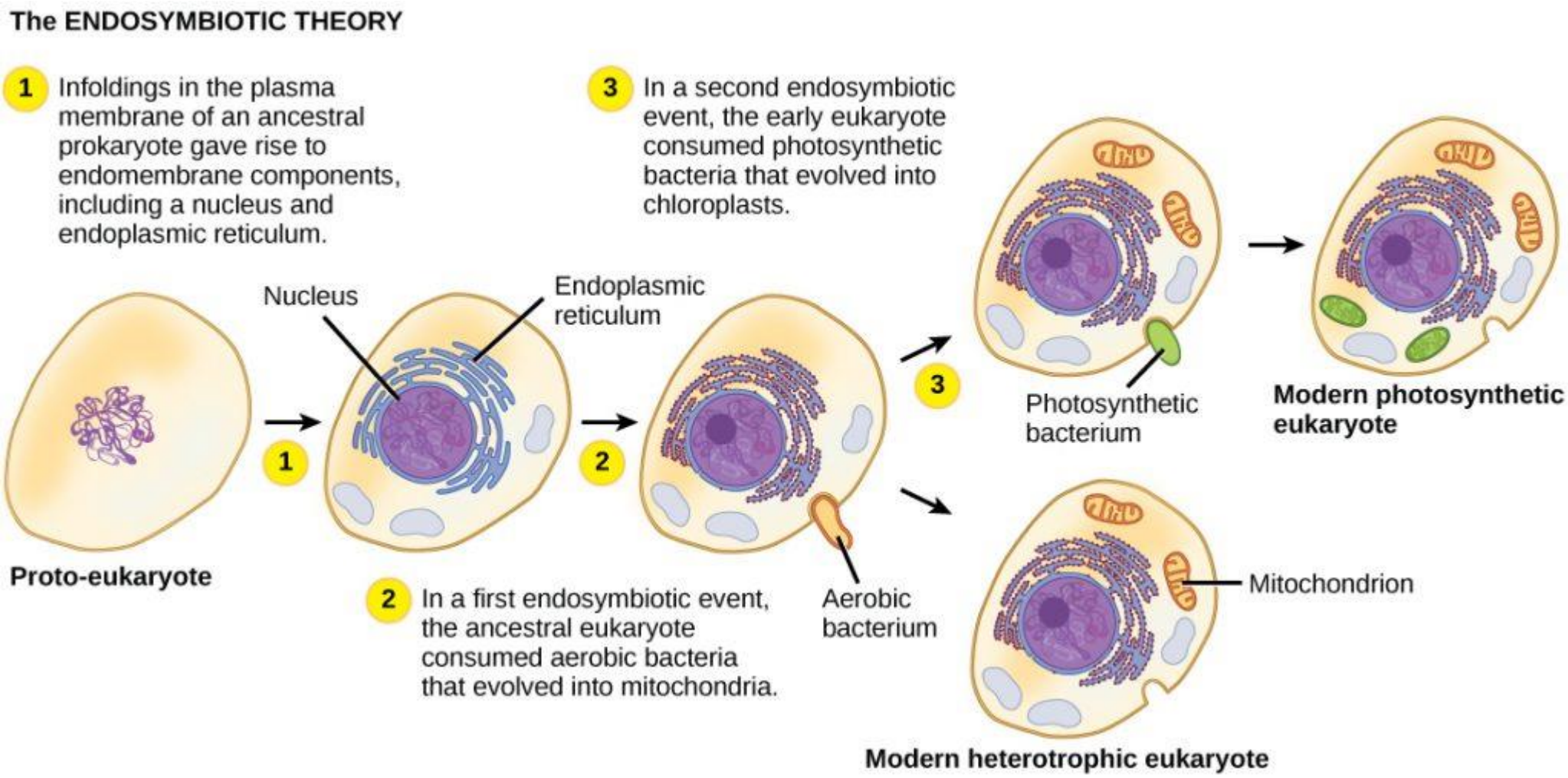
Figure 3. Size and morphological complexity of eukaryotic alga versus cyanobacterium. Approximately scaled comparison of (*A*) the eukaryotic alga *Euglena* with (*B*) the relatively large complex cyanobacterium *Synechocystis*, here approximately to scale. Despite its extensive internal thylakoid membranes (magnified in *C*) and moderate polyploidy (100–200 copies of nucleoid), *Synechocystis* is approximately 1500 times smaller by volume. (Courtesy of Mark Farmer, University of Georgia.)

Lane, CSH Persp Biol 2014

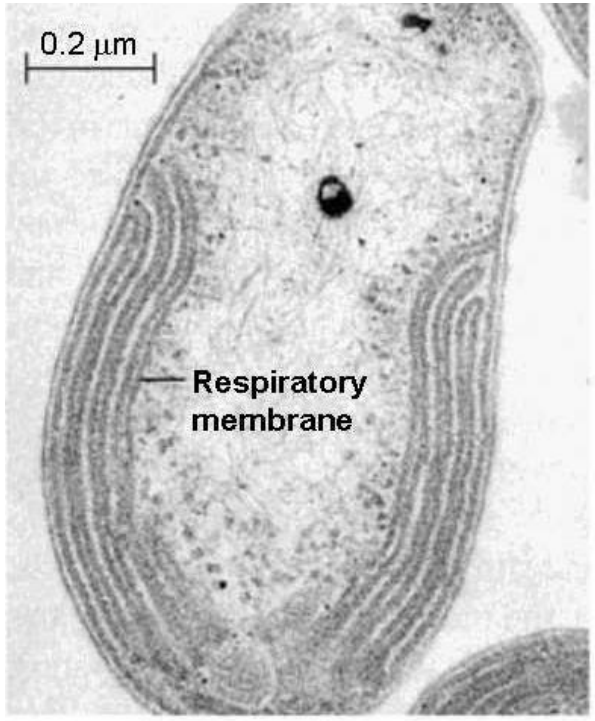
General features of eukaryotic cell

- In average 1000x bigger
- Compartmentalization
- Mitochondria
- Endomembrane system
- Actin-tubulin cytoskeleton
- Linear chromosomes
- Multiple origins of replication
- Meiosis

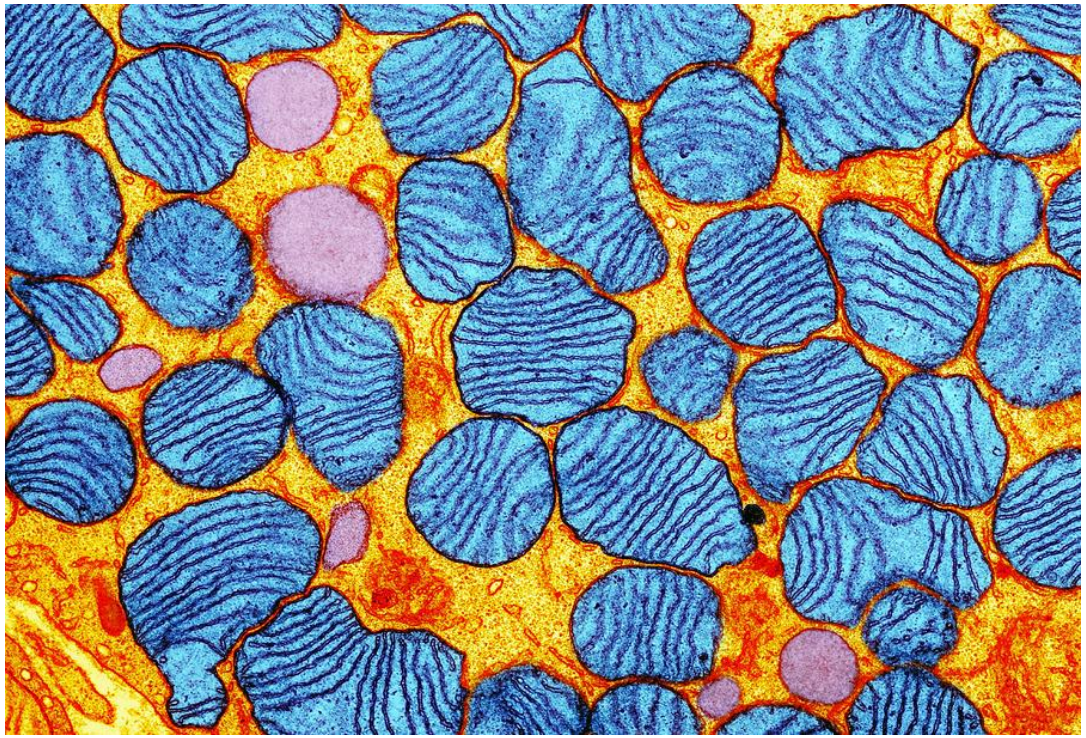
The endosymbiotic theory



Was the acquisition of mitochondria the critical step towards eukatyote genome complexity?



(a) Aerobic prokaryote



Mitochondria in an adipocyte. By enabling oxidative phosphorylation across a wide area of internal membranes, mitochondrial genes enabled a roughly **200,000-fold rise in genome size** compared with bacteria.

Was the acquisition of mitochondria the critical step towards eukatyote genome complexity?

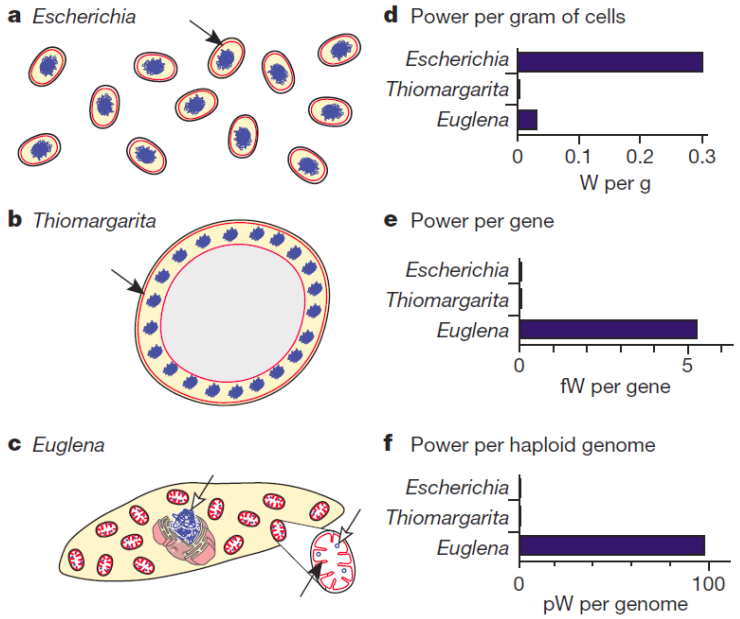


Figure 2 | The cellular power struggle. **a–c**, Schematic representations of a medium sized prokaryote (*Escherichia*), a very large prokaryote (*Thiomargarita*), and a medium-sized eukaryote (*Euglena*). Bioenergetic membranes across which chemiosmotic potential is generated and harnessed are drawn in red and indicated with a black arrow; DNA is indicated in blue. In **c**, the mitochondrion is enlarged in the inset, mitochondrial DNA and nuclear DNA are indicated with open arrows. **d–f**, Power production of the cells shown in relation to fresh weight (**d**), per haploid gene (**e**) and per haploid genome (power per haploid gene times haploid gene number) (**f**). Note that the presence or absence of a nuclear membrane in eukaryotes, although arguably a consequence of mitochondrial origin[70], has no impact on energetics, but that the energy per gene provided by mitochondria underpins the origin of the genomic complexity required to evolve such eukaryote-specific traits (see text).

- Whereas the energetic cost of genom replication in microbial cell is trivial (2%), the cost of expressing them as protein consumes most of the cell's energy budget (75%).
- E. coli cell ha about 13,000 ribosomeos whereas human liver cell has 13,000,000 ribosomes.
- Because ATP synthesis scales with plasma membrane surface area but protein synthesis scales with cell volume, larger prokaryotic cells are energetically less efficient.
- Eukaryotic gene commands some 200,000 times more energy than a prokaryotic gene, or at a similar energy per gene, the eukaryote could in principle support a genome 200,000 times larger.
- The prokaryote-to-eukaryote transition involved the origin of a multiplicity of new complex traits underpinned by some 3,000 new protein families

Lane and Martin, Nature 2010

Why does life exist?

Is emergence of life a fortuitous event or an inevitable process?

According to the inevitable life theory, biological systems spontaneously emerge because they more efficiently disperse, or "dissipate" energy, thereby increasing the entropy of the surroundings. In other words, **life is thermodynamically favorable**.

> When an inanimate system of particles, like a group of atoms, is bombarded with flowing energy (such as concentrated currents of electricity or heat), that system will often self-organize into a more complex configuration—specifically an arrangement that allows the system to more efficiently dissipate the incoming energy, converting it into entropy. A basic example of a dissipative structure is the tiny whirlpool that appears when you remove the stopper from a full sink or bathtub. The emergent vortex is better at dissipating the kinetic energy from the flowing water compared to when the water flows directly.
>
> Jeremy England has outlined a basic evolutionary process he calls "dissipative adaptation." In computational simulations, England's team showed exactly how a simple system of lifeless molecules, like those that existed on Earth before life emerged, may reorganize into a unified structure that behaves like a living organism when hit with a continuous source of energy for long enough. This occurs because the system has to dissipate all that energy, and biological systems, which must metabolize energy to function through chemical reactions, provide a way to do just that.
>
> When a molecular system is undergoing natural fluctuations whereby its collective form is randomly sifting through a number of successive structural states, those arrangements that allow the system to more effectively extract energy from the environment—a requirement for survival—will persist, while those arrangements that do not, go by the wayside. This is presumably how an inanimate network becomes a biochemical network, such as that of a cell.
>
> Another biophysisist, Harold Morowitz theorized that life on Earth first emerged due to inanimate matter being driven by energy currents produced by the planet's geothermal activity, like that which occurs in volcanoes and inside the Earth's core. In their view, life was an inescapable consequence of free energy buildup, presumably in hot areas like the hydrothermal vents at the bottom of the ocean.

The laws of physics and the dynamics of nature not only allow for life, they necessitate it. The **second law of thermodynamics does not just generate disorder; it is also a motor for complexity**, because complex adaptive systems efficiently dissipate free energy, thereby increasing the universe's entropy.

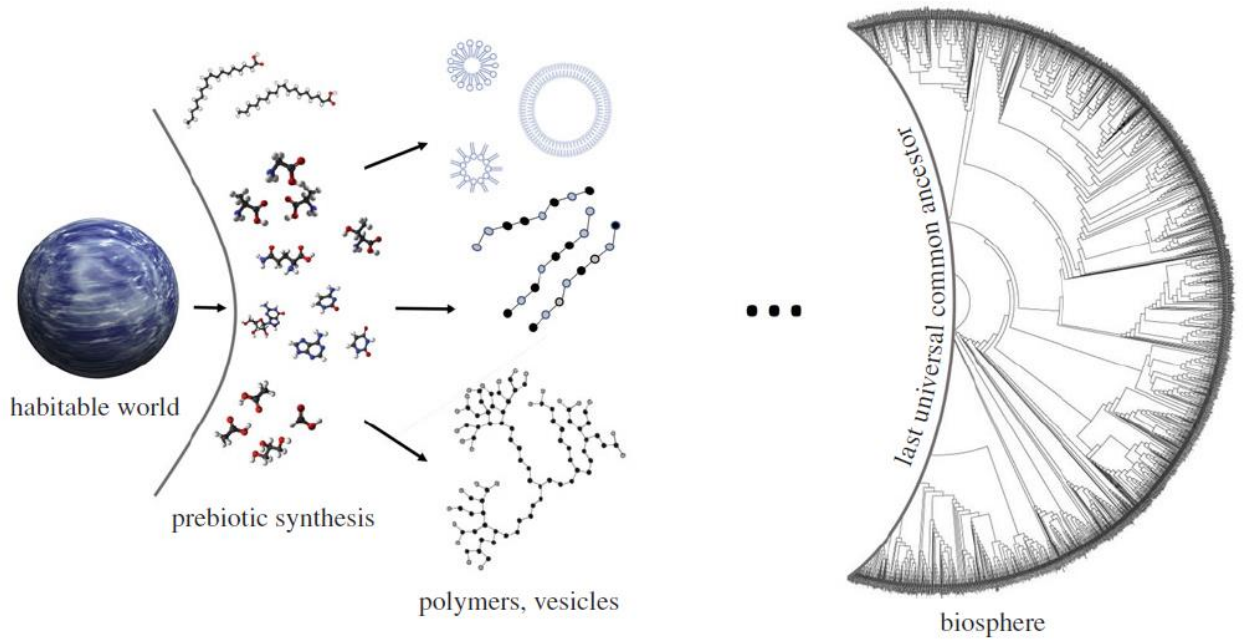
https://qz.com/1539551/is-the-universe-pro-life-the-fermi-paradox-can-help-explain/

Can we make life?

Chasing the origin of life: methodological approaches

bottom-up

prebiotic synthesis



top-down

minimal cell
tracing LUCA from genomic analysis

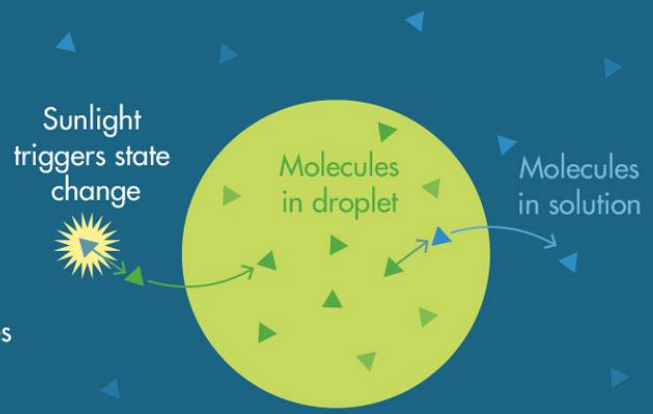
Figure 1. Research on the origins of life approaches the problem from bottom-up, starting from geochemical synthesis of biomolecules, or top-down, uncovering the properties of ancient life: a vast gulf persists in connecting these two approaches, necessitating new conceptual frameworks for addressing life's origins. (Online version in colour.)

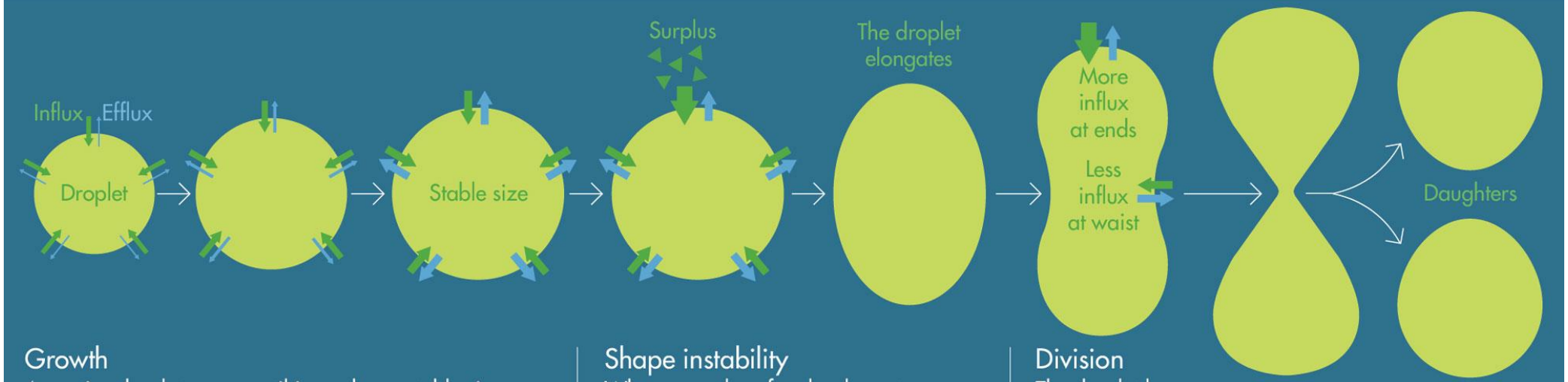
ORIGIN OF DIVISION

Physicists hypothesize that liquid droplets in the primordial soup could have served as the primitive precursors of cells. Unlike familiar oil droplets in water, these "chemically active" droplets proliferate via growth and division, which might have enabled them to evolve into more complex, living cells.

Chemically active droplets

The droplets form from molecules that have two chemical states. Molecules in the green state are insoluble, preferring to aggregate inside a droplet; molecules in the blue state dissolve in the surrounding fluid. Molecules in the green state spontaneously transform to blue, while an energy source can trigger the reverse reaction. Thus, molecules flow in and out of the droplet.





Growth

An active droplet grows until it reaches a stable size, where the amount of influx (proportional to its surface area) balances the efflux (proportional to its volume). Surface tension forces it into a spherical shape.

Shape instability

When a surplus of molecules enters a droplet on one part of its surface, causing it to bulge, the extra surface area from the bulging further accelerates growth as more molecules can diffuse inside.

Division

The droplet keeps elongating and pinches in at the middle, which has low surface area. Eventually, surface tension causes it to split into a pair of droplets, which then grow to the characteristic size, reminiscent of division in living cells.

Back to synthetic biology: what is the future of life?

Biological matter is extremely adaptable

In the past few decades we have come to realize that where there is liquid water on Earth, virtually no matter what the physical conditions, there is life.

Tardigrades are among the most resilient animals known with individual species able to survive extreme conditions—such as exposure to extreme temperatures, extreme pressures (both high and low), air deprivation, radiation, dehydration, and starvation.

Environmental parameter	Type	Definition	Examples
Temperature	Hyperthermophile Thermophile Mesophile Psychrophile	Growth >80 °C Growth 60–80 °C 15–60 °C <15 °C	*Pyrolobus fumarii*, 113 °C *Synechococcus lividis* *Homo sapiens* *Psychrobacter*, some insects
Radiation			*Deinococcus radiodurans*
Pressure	Barophile Piezophile	Weight-loving Pressure-loving	Unknown For microbe, 130 MPa
Gravity	Hypergravity Hypogravity	>1*g* <1*g*	None known None known
Vacuum		Tolerates vacuum (space devoid of matter)	Tardigrades, insects, microbes, seeds
Desiccation	Xerophiles	Anhydrobiotic	*Artemia salina*; nematodes, microbes, fungi, lichens
Salinity	Halophile	Salt-loving (2–5 M NaCl)	Halobacteriaceae, *Dunaliella salina*
pH	Alkaliphile Acidophile	pH > 9 low pH-loving	*Natronobacterium, Bacillus firmus* OF4, *Spirulina* spp. (all pH 10.5) *Cyanidium caldarium*, *Ferroplasma* sp. (both pH 0)
Oxygen tension	Anaerobe Microaerophile Aerobe	Cannot tolerate O_2 Tolerates some O_2 Requires O_2	*Methanococcus jannaschii* *Clostridium* *H. sapiens*
Chemical extremes	Gases Metals	Can tolerate high concentrations of metal (metalotolerant)	*C. caldarium* (pure CO_2) *Ferroplasma acidarmanus* (Cu, As, Cd, Zn); *Ralstonia* sp. CH34 (Zn, Co, Cd, Hg, Pb)

Extremophiles have (commercially) interesting enzymology

Crispin T. S. Little
Scientific American **302**, 78 - 84 (2010)
doi:10.1038/scientificamerican0210-78

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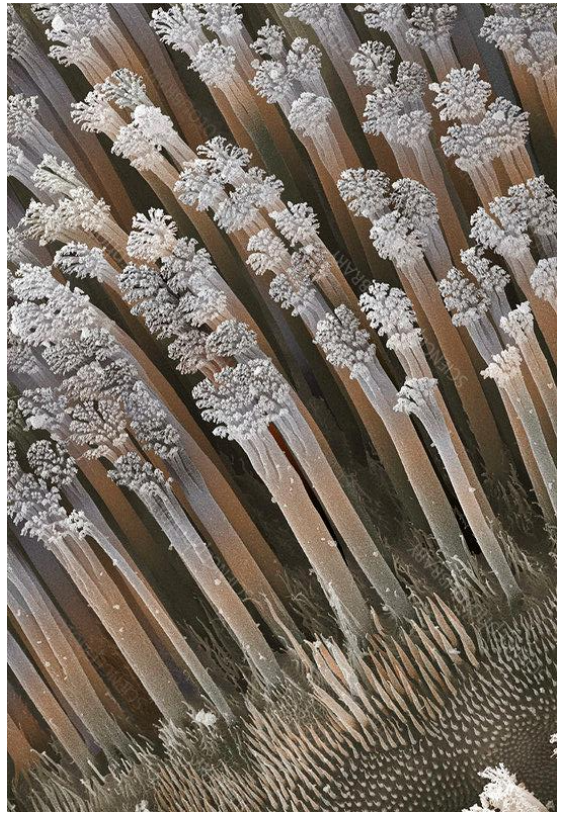
CREDIT: JEN CHRISTIANSEN (*whale-fall illustration*); CATHERINE WILSON (*species inset illustrations*)

The bacterial decomposers on **whale falls** are psychrothrophic and their enzymes, such as lipases, are of particular commercial interest beacuse they sustain high activities at low temperatures (sea bed 2-4°C).

Gecko sticky feet

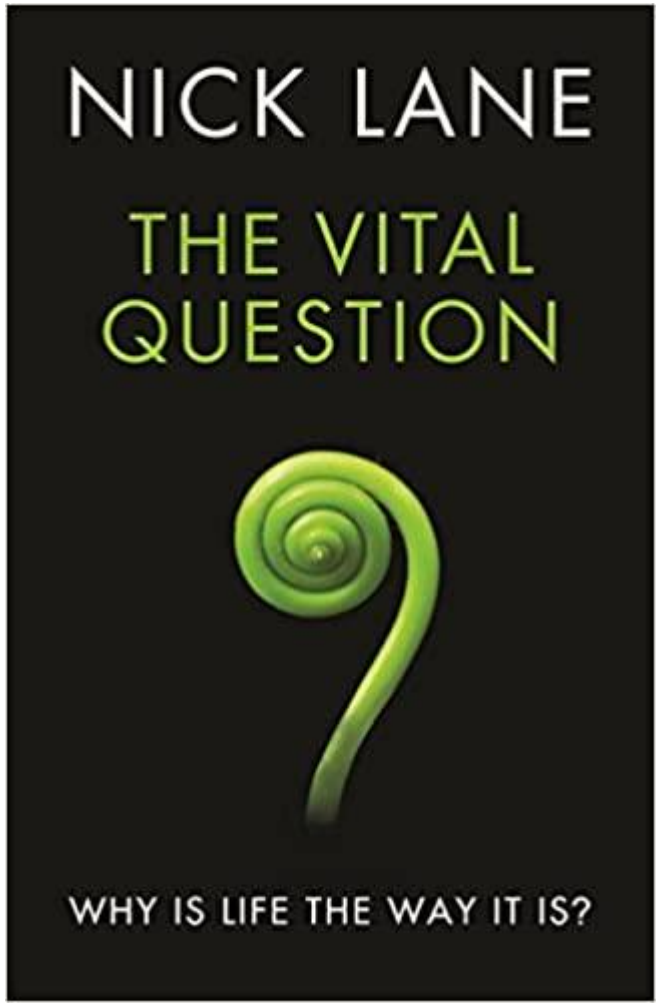


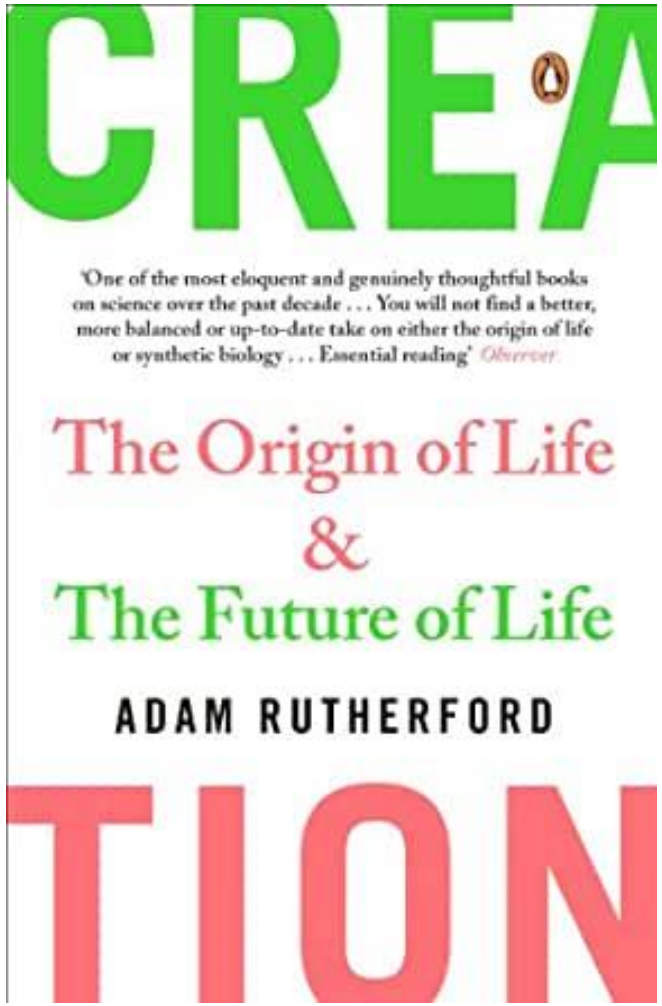
Geckos can stick to surfaces because their toes are covered in hundreds of tiny microscopic hairs called setae. Each seta splits off into hundreds of even smaller bristles called spatulae. The tufts of tiny hairs get so close to the contours in walls and ceilings that the van der Waals force kicks in. This type of physical bond happens when electrons from the gecko hair molecules and electrons from the wall molecules interact with each other and create an electromagnetic attraction.

Biological matter can be easily molded

The silver fox domestication experiment: started in 1959 and it is still running. Started by Dmitri Belyaev to demonstrate power of selective breeding to transform species. Within six generations (6 years in these foxes, as they reproduce annually), selection for tameness, and tameness alone, produced a subset of foxes that licked the hand of experimenters, could be picked up and petted, whined when humans departed, and wagged their tails when humans approached.

Dugatkin, Evolution:Education and Outreach, 2018


NICK LANE
THE VITAL QUESTION
WHY IS LIFE THE WAY IT IS?


CREA
'One of the most eloquent and genuinely thoughtful books on science over the past decade . . . You will not find a better, more balanced or up-to-date take on either the origin of life or synthetic biology . . . Essential reading' Observer
The Origin of Life
&
The Future of Life
ADAM RUTHERFORD
TION

Recommended reading:

Nick Lane and William Martin. The energetics of genome complexity. Nature 467:929-34. doi: 10.1038/nature09486.