

Today's topic

More on OoL chemistry

- recent updates
- discussion



James Tour's challenge On OoL



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Current status of Origin of Life research

- A. Scientists have made life in the lab from simple chemicals
- B. Great steps of progress have been made recently and the problem of the origin of life from simple chemicals is on the verge of being solved
- C. The origin of life from simple chemicals is virtually impossible and little or no progress has been made

Outline

- A. Review simplest form of life, minimal cell
- B. Tour's challenge and why no one responded
- C. Redefining life – a self sustaining chemical system
Current status, challenges (RNA World, Assembly theory)
- D. Hype, the media, and public perception
- E. Tour's 3 yr challenge to Lee Cronin
- F. Discussion

Review

What is life?

- replicate

- process energy (take energy from environment, transform for growth, metabolism, and reproduction)

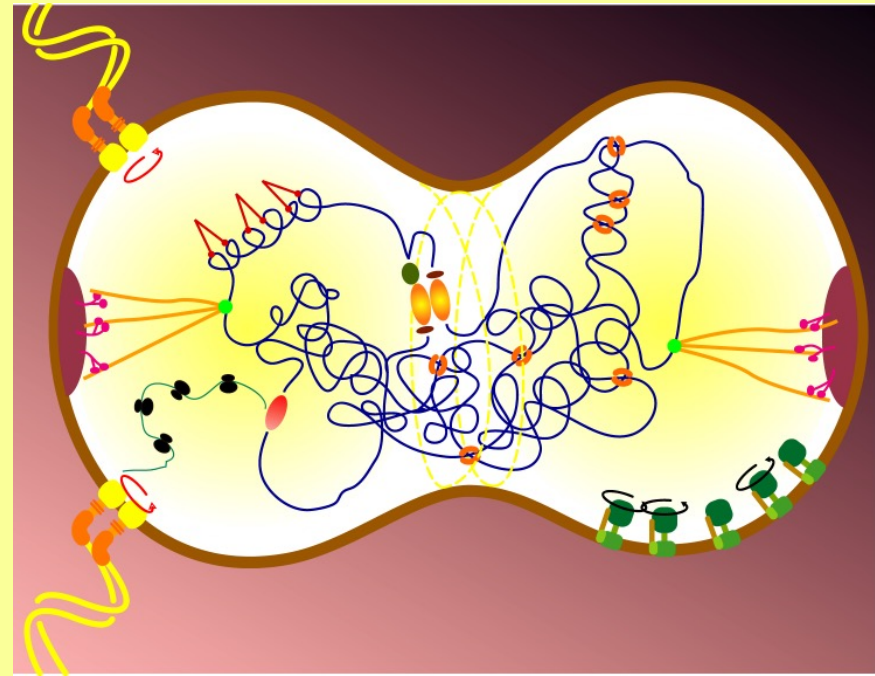
- store and process information

(on its own)

Minimal cells

Lots of Jobs to Do:

- Getting food and fuel
- Eliminating waste
- Converting raw materials to useful stuff
- Building molecular machines
- Repairing damage
- Copying and protecting genetic information
- Dividing the cell
- Controlling and coordinating all these
- Etc.



There is a machine (or system of machines) for every job

There is a system for making machines (central genetic apparatus)

There is a system of coordination among the machines

Minimal cells

RESEARCH ARTICLE

SYNTHETIC BIOLOGY

Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III,^{1,*,†} Ray-Yuan Chuang,^{1,†} Vladimir N. Noskov,¹
Nacyra Assad-Garcia,¹ Thomas J. Deerinck,² Mark H. Ellisman,² John Gill,³
Krishna Kannan,³ Bogumil J. Karas,¹ Li Ma,¹ James F. Pelletier,^{4,§} Zhi-Qing Qi,³
R. Alexander Richter,¹ Elizabeth A. Strychalski,⁴ Lijie Sun,^{1||} Yo Suzuki,¹
Bilyana Tsvetanova,³ Kim S. Wise,¹ Hamilton O. Smith,^{1,3} John I. Glass,¹
Chuck Merryman,¹ Daniel G. Gibson,^{1,3} J. Craig Venter^{1,3*}

Science 351, aad6253 (2016)

Original *Mycoplasma mycoides* genome has **901** genes

M. capricolum with synthesized minimal genome from *M. mycoides* can survive with **473** genes

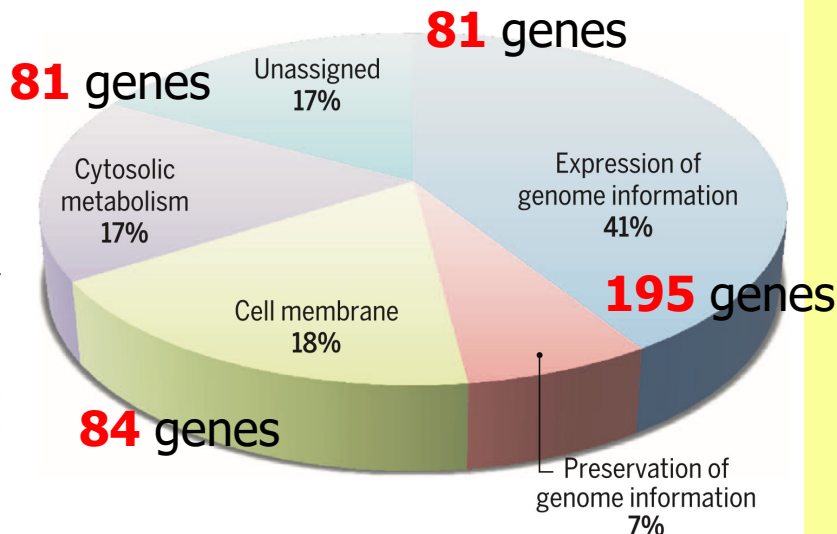
438 protein-coding
35 RNA genes

obligate parasite

Growth in a rich medium

Fig. 6. Partition of genes into four major functional groups.

Syn3.0 has 473 genes. Of these, 79 have no assigned functional category (Table 1). The remainder can be assigned to four major functional groups: (i) expression of genome information (195 genes); (ii) preservation of genome information (34 genes); (iii) cell membrane structure and function (84 genes); and (iv) cytosolic metabolism (81 genes). The percentage of genes in each group is indicated.



Constituents of cells

**(information-
containing
polymers)**



proteins (polymers of amino acids)

DNA, RNA (polymers of nucleic acids)

polysaccharides (polymers of carbohydrates)

Lipids

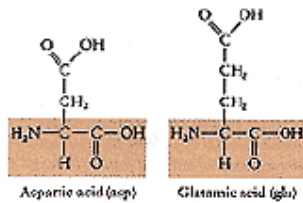
Cofactors: ATP, heme, metal ions, NAD^+ , NADP^+

Proteins

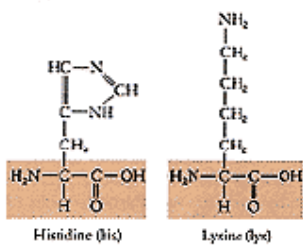
Amino acids

(20 in proteins)

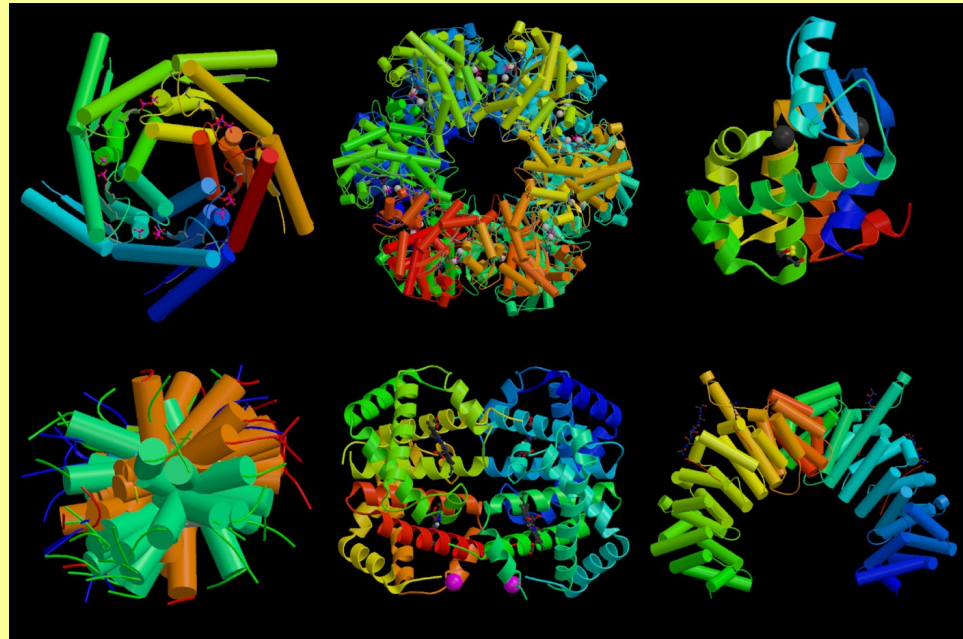
Acidic (negatively charged at pH 7)



Basic (positively charged at pH 7)



chains of amino acids fold into 3D structures



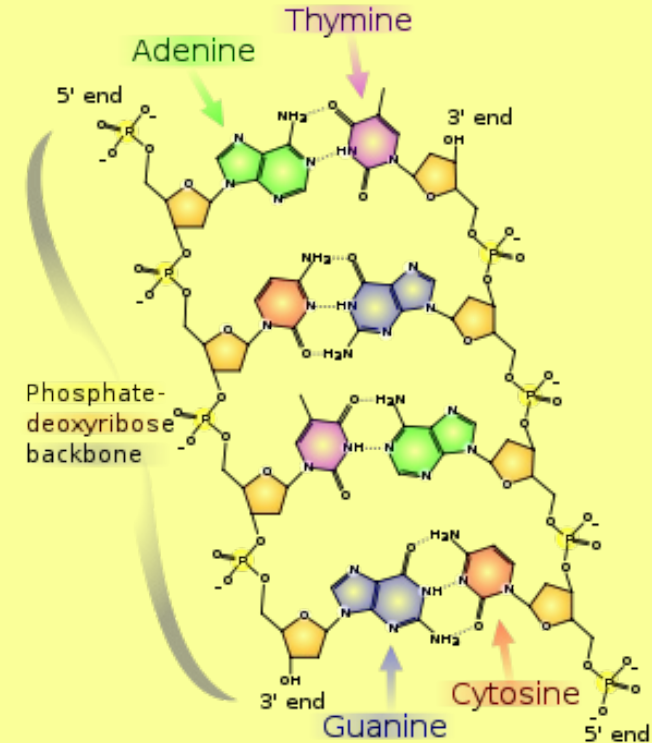
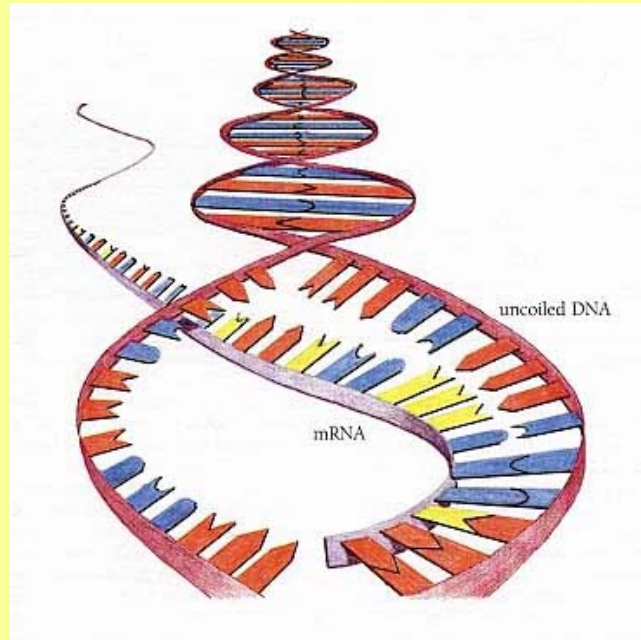
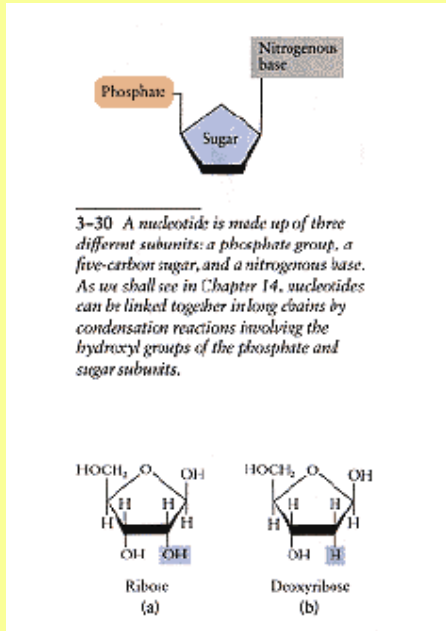
A chain of amino acids:

QYAPQTQSGRTSIVHLFEWRWVDIALECYRLGPKGFGGVQVSPNENVVVTNPSRPWWERYQPVSYKLCTRSGNENEFR
DMVTRCNNVGVRIYVDAVINHMCSGSAAAGTGTTCSYCNPGSREFPAVPYSAWDFNDGKCKTASGGIESYNDPYQVRDC
QLVGLLDLALAKDYVRSMIADYLNKLIDIGVAGFRIDASKHMWPGDIKAVLDKLNHLNTNWFPAWSRPFIFQEVIDLGGE
AIKSSEYFGNGRVTEFKYGAKLGTVVRKWSGEKMSYLNWGEWGFMPDRALVFDNHDNQRGHGAGGSSILTFWDARL
YKVAVGFMLAHPYGFTRVMSSYRWARNFVNGEDVNDWIGPPNNGVIKEVTINADTTGNDWVCEHRWREIRNMVWFRNV
VDGEPFANWWDNGSNQVAFGRGRNGFIVFNDDWQLSSTLQTGLPGGTCDVISGDKVGNSTGVIKVVSSDGTAFQFIS
NSAEDPFIAIHAESKL

DNA and RNA

Nucleotides

4 in DNA



A chain of nucleotides:

ATCGCCTATATAGCGTACAATGGCTACATCGCCTATATAGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGCTAGC
 GCTACATCGCCTATATAGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGCTAGCATCGCCTATATAGCGTACAATGGCTAC
 ATCGCCTATATAGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGCTAGCATCGCCTATATAGCGTACAATGGCTACATCGC
 CTATATAGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGCTAGCATCGCCTATATAGCGTACAATGGCTACATCGCCTATAT
 AGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGCTAGCGCTACATCGCCTATATAGCGTACAATGGCTACGTAGCTACGAT
 GCTAGCTAGCTAGCATCGCCTATATAGCGTACAATGGCTACATCGCCTATATAGCGTACAATGGCTACGTAGCTACGATGCTAG
 CTAGCTAGCATCGCCTATATAGCGTACAATGGCTACATCGCCTATATAGCGTACAATGGCTACGTAGCTACGATGCTAGCTAGC
 TAGC

Molecular machines

Software

Codes: genetic code
polysaccharide code
lipid code

Higher order information:

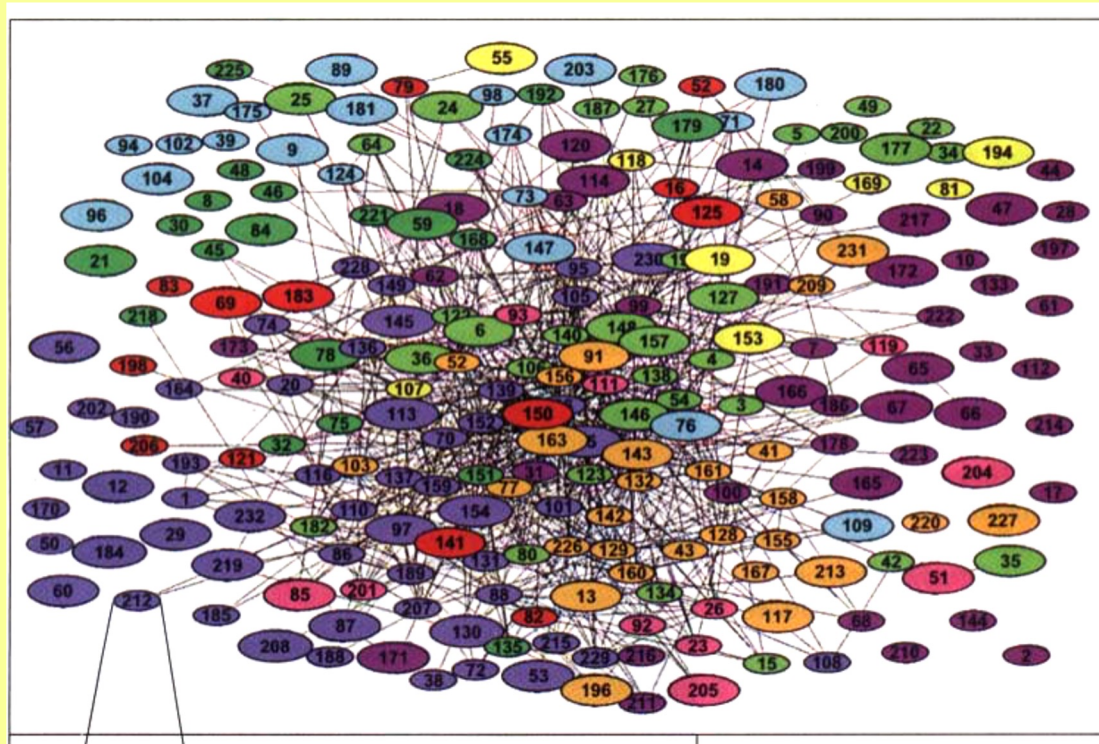
(beyond proteins, nucleic acids, polysaccharides, lipids)

-the interactome-

-the interactome: protein complexes in yeast

“...nearly every major process in a cell is carried out by assemblies of 10 or more protein molecules.”

B. Alberts Cell
1998, 92:291



Protein complexes in yeast. Lines indicate complexes that share at least one protein.

Nature 415,
180, 2002.

most proteins act as components in multiprotein complexes

Budding yeast: avg no. of proteins per complex = 4.9

Mammals: avg no. of proteins per complex ~ 15

Summary:

There is no such thing as a simple form of life!

"We now know not only of the existence of a break between the living and non-living world, but also that it represents the most dramatic and fundamental of all the discontinuities of nature. Between a living cell and the most highly ordered non-biological system, such as a crystal or snowflake, there is **a chasm as vast and absolute as it is possible to conceive.**"

M. Denton, Evolution: A Theory in Crisis, pg 250.

(difference in functional information in enormous)

Steps for making a living cell:

- make the monomers

- make the biopolymers

- biopolymers must have specific sequences to be functional

- assemble the parts into a living cell

Tour's challenge

-make the monomers

very
challenging

-make the polymers **(Tour's challenges 1-3)**

most
challenging
by far!

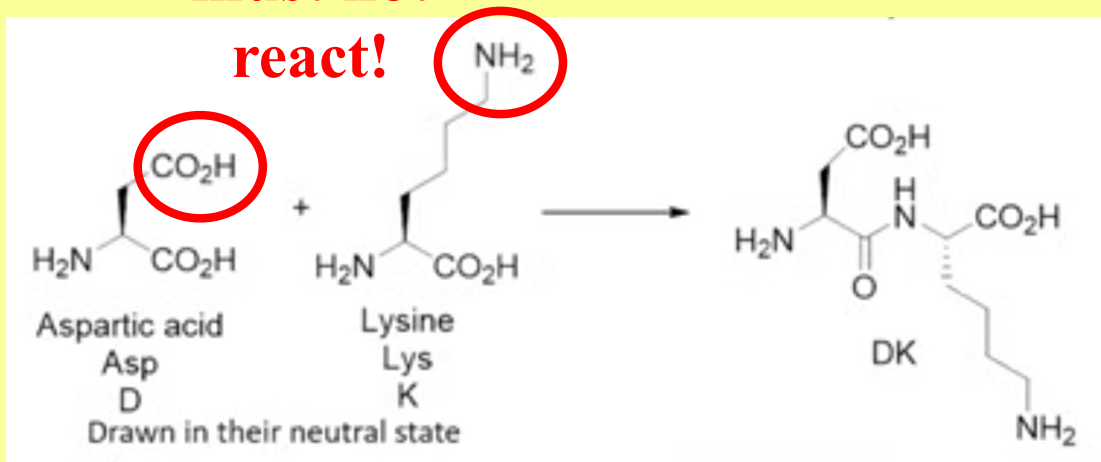
-polymers must have specific sequences to be functional **(Tour's challenge 4)**

-assemble the parts into a living cell
(Tour's challenge 5)

Tour's challenge #1

make **dipeptide** with correct linkages (> 90%)

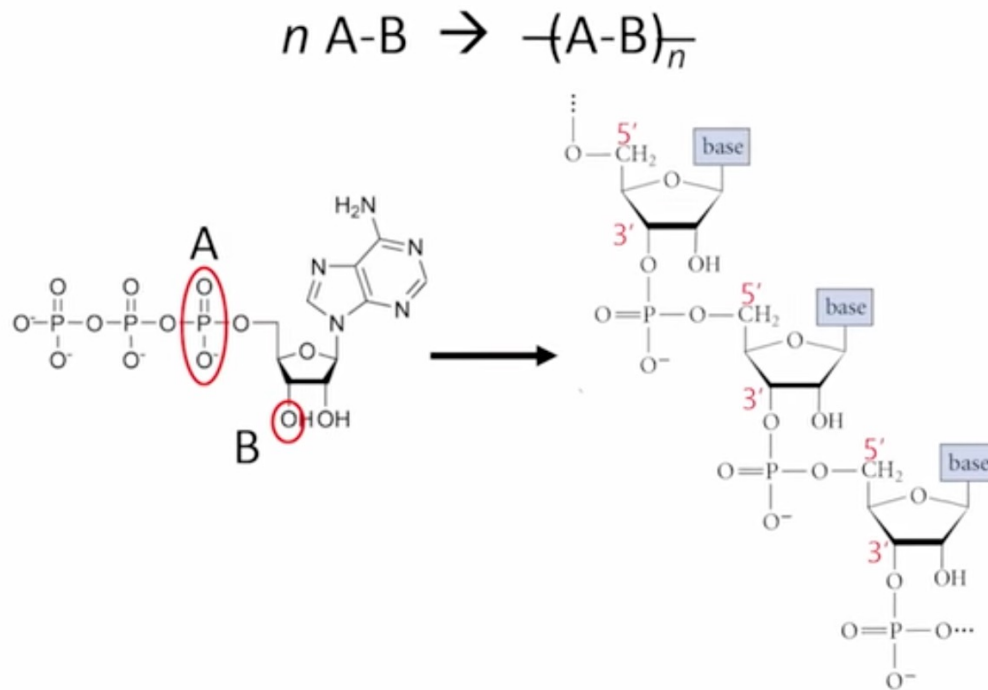
**these
must not
react!**



note
stereochemical
and
regiochemical
control

Tour's challenge #2

make RNA with correct linkages (200 mer, 98% correct)

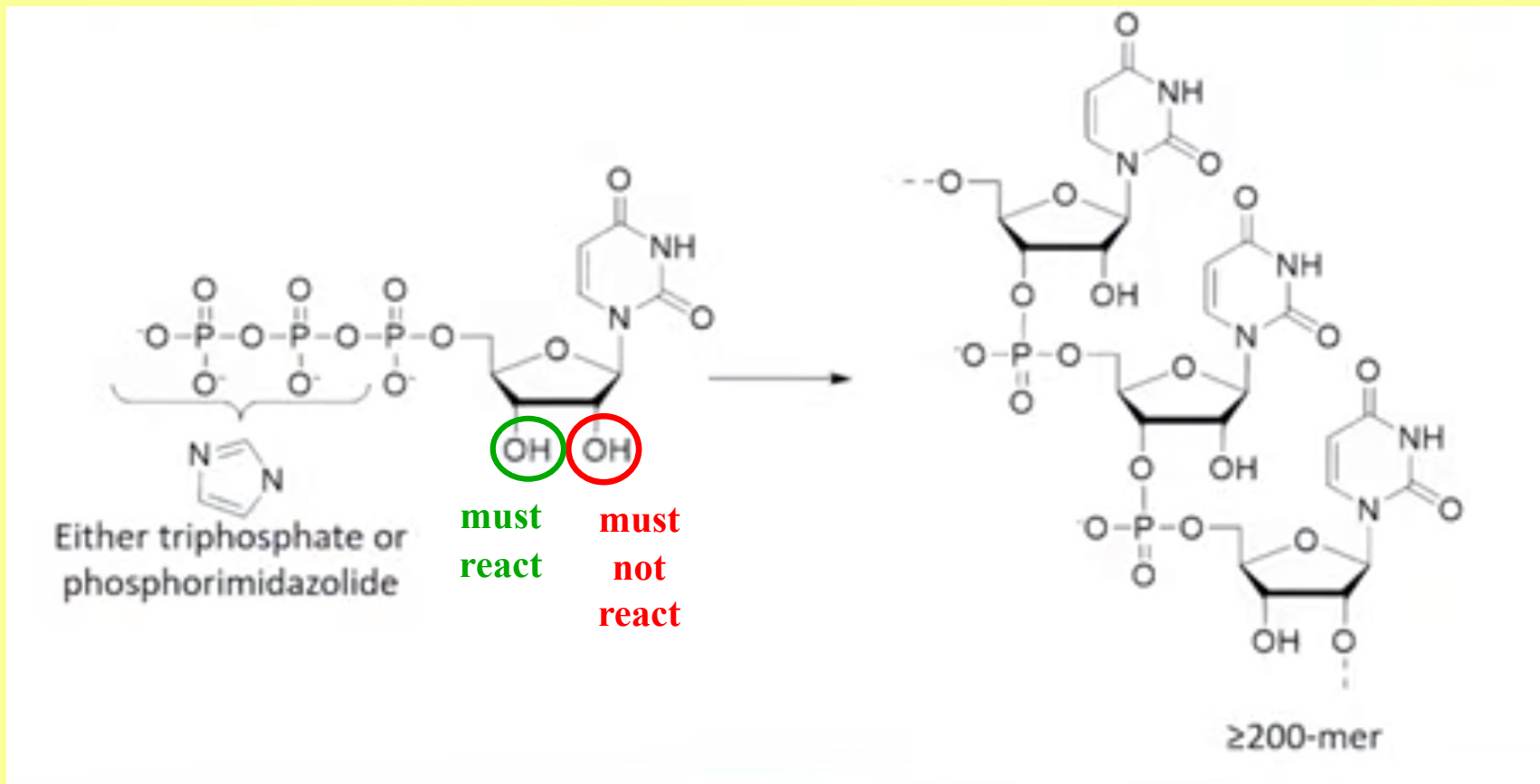


All-3',5'-coupling makes the required RNA

5' triphosphate and 3' hydroxyl

Tour's challenge #2

make RNA with correct linkages (< 200 mer, 98% correct)



Tour's challenge #2

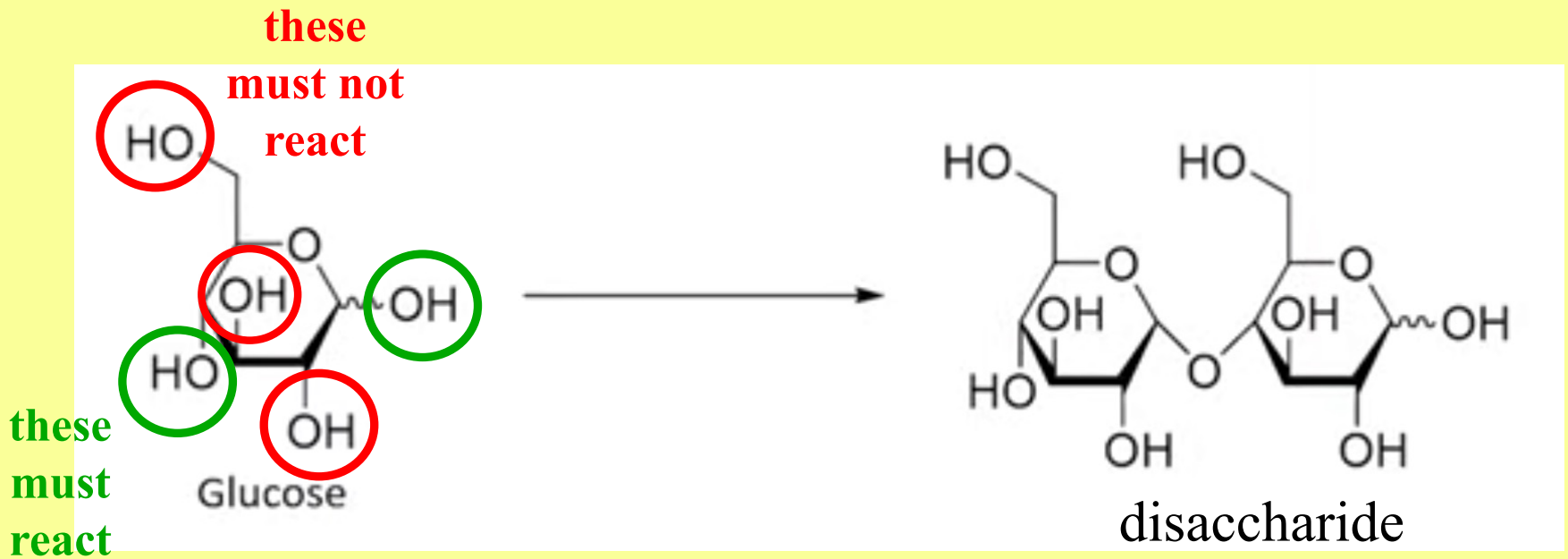
make RNA with correct linkages

From a purely chemical standpoint, it is difficult to imagine how long RNA molecules could be formed initially by purely nonenzymatic means. For one thing, the precursors of RNA, the ribonucleotides, are difficult to form nonenzymatically. **Moreover, the formation of RNA requires that a long series of 3' to 5' phosphodiester linkages form in the face of a set of competing reactions, including hydrolysis, 2' to 5' linkages, 5' to 5' linkages, and so on.**

Molec. Biol of the Cell 4th ed.

Tour's challenge #3

dimerize glucose with correct linkages



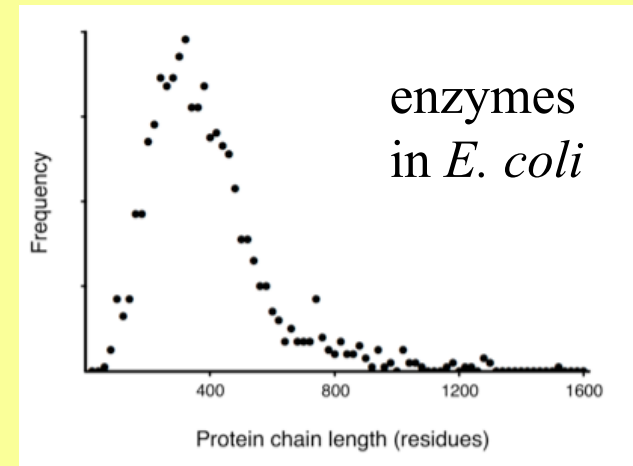
pure enantiomer (D)

Tour's challenge #4

the biopolymers must have specific (very rare) sequences to be functional

- A. Proteins: 20 types of amino acids,
chains of amino acids 150 units long

20^{150} possibilities



**Only a miniscule fraction of
sequence space can be searched!**

- B. Fraction that fold (for 150 residue protein):

1 in 10^{64} (J. Molec. Biol. 2004)

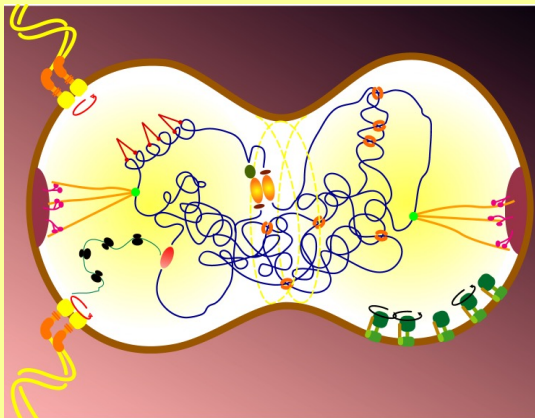
< 1 in 10^{100} (Biophysical J. 2017)

**Only a miniscule fraction of
sequences are functional!**

So where do the functional sequences come from?

Tour's challenge #5

Assemble the parts into a living cell



molecular machines
software algorithms
irreducible complexity
hierarchical coherence
blueprint or design



irreducible complexity
hierarchical coherence
blueprint or design

Tour's challenge

<https://evolutionnews.org/2024/03/james-tour-offers-three-year-challenge-to-lee-cronin-to-demonstrate-legitimacy-of-assembly-theory/>

35:10 – 40:00

Current status

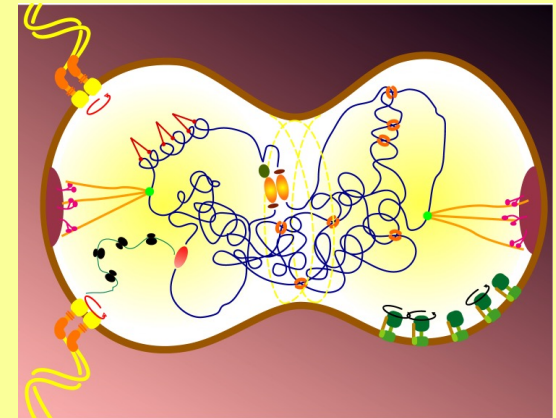
chemistry



**no one is even
trying to do this!**



simplest cell



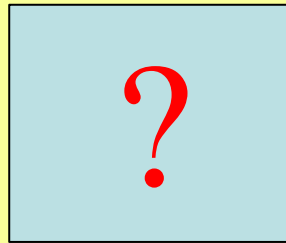
None of the 10 addressed Tour's challenge

Current status

chemistry



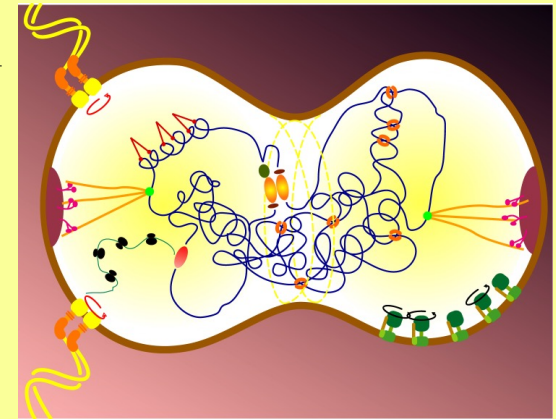
researchers
try to do
this



and believe
that natural
selection will
do this



simplest cell



**chemical
system that
can replicate**



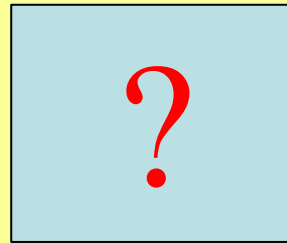
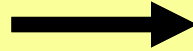
**chemistry
alone
must do
this**

Current status

chemistry

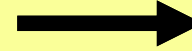


researchers
try to do
this

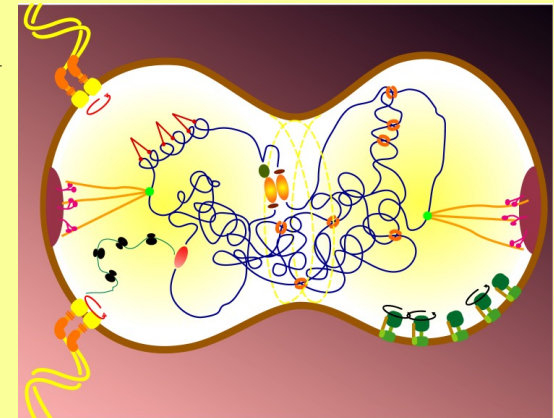


**chemical
system that
can replicate**

and believe
that natural
selection will
do this

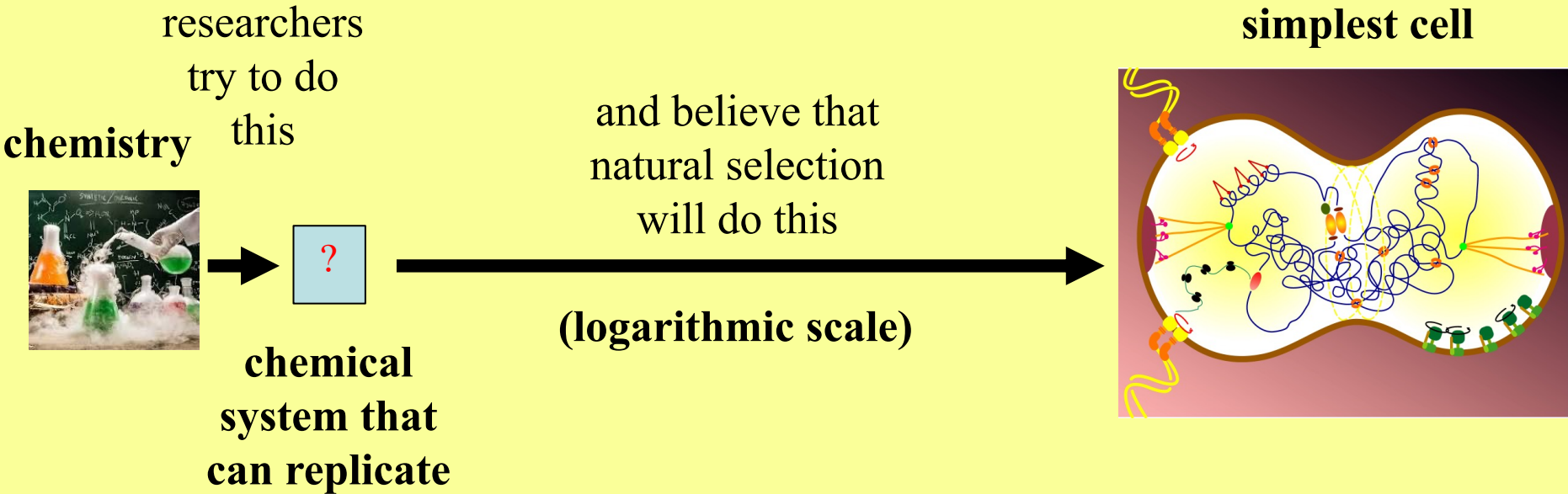


simplest cell



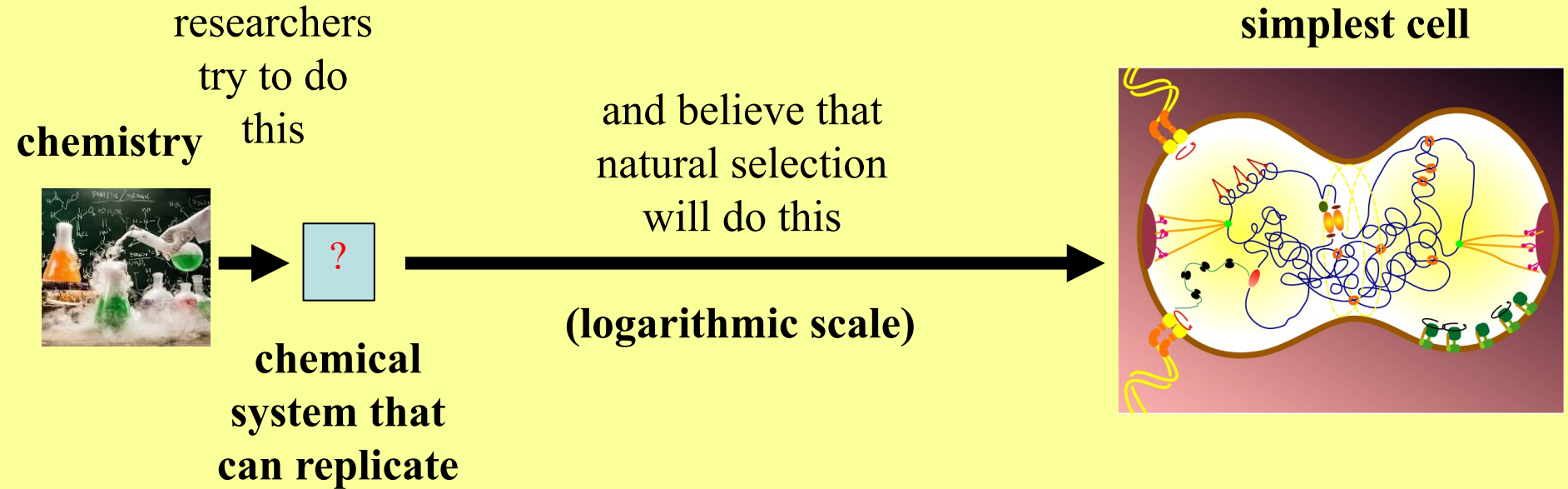
**RNA
polypeptides
lipid vesicles
self sustaining chemistry-metabolism
active droplets**

Current status



**some researchers attribute practically
unlimited creative powers to natural
selection!**

Current status



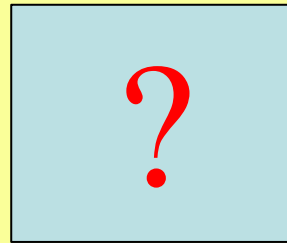
Is that belief warranted by science?

Current status

chemistry

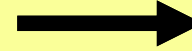


researchers
try to do
this

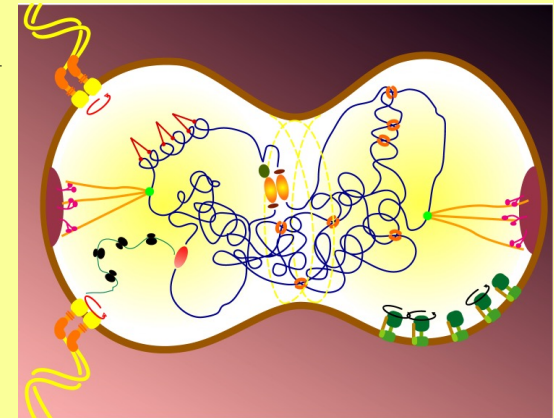


**chemical
system that
can replicate**

and believe
that natural
selection will
do this



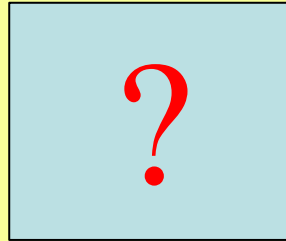
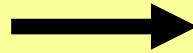
simplest cell



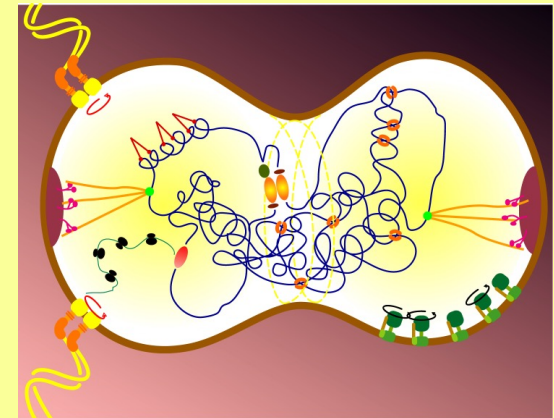
How to judge if any of this is relevant to OoL?

Current status

chemistry



simplest cell



**chemical
system that
can replicate**

Chemistry - chemicals react randomly, make tar or asphalt

Biology – chemistry is constrained by enzymes, etc

How to constrain chemistry outside of biology?

RNA-based Darwinism (RNA World)

RNA contains genetic information and also has some catalytic ability (single stranded, can fold)

hypothesis – life started out as RNA

- history of progress**

- some examples of recent papers**

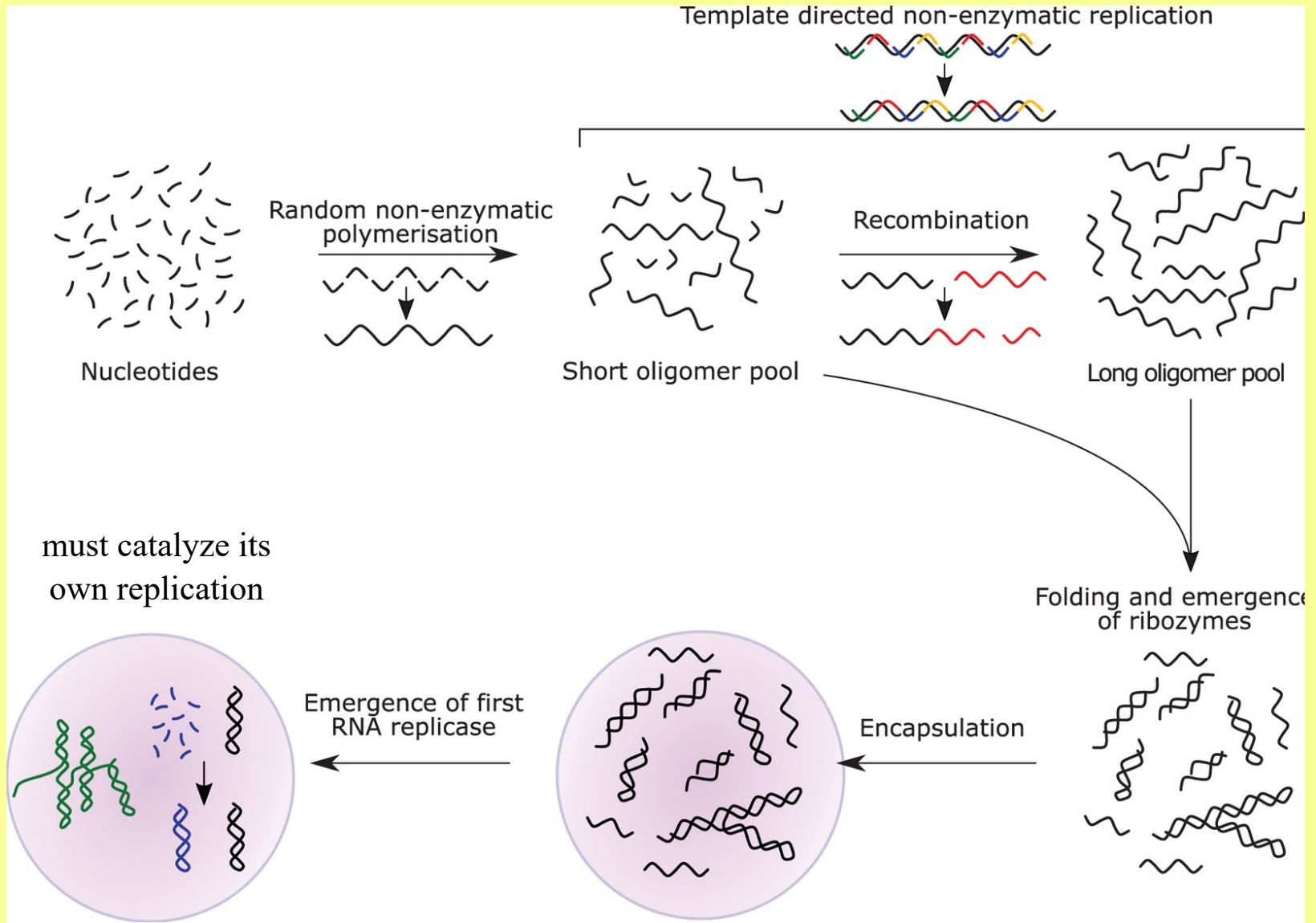
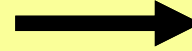
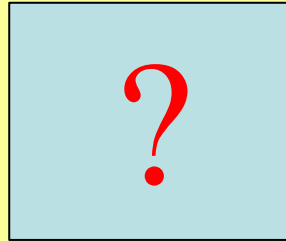
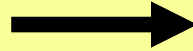


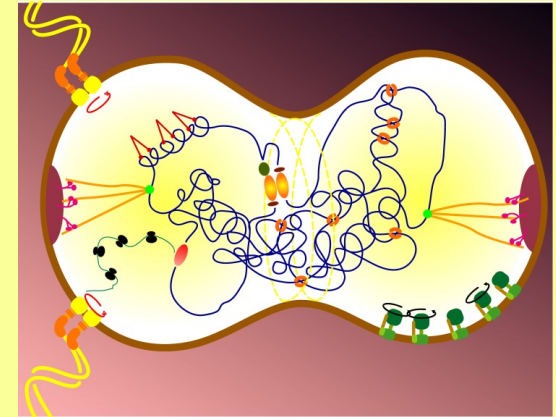
Illustration of RNA World from Wikipedia

Current status

chemistry



simplest cell



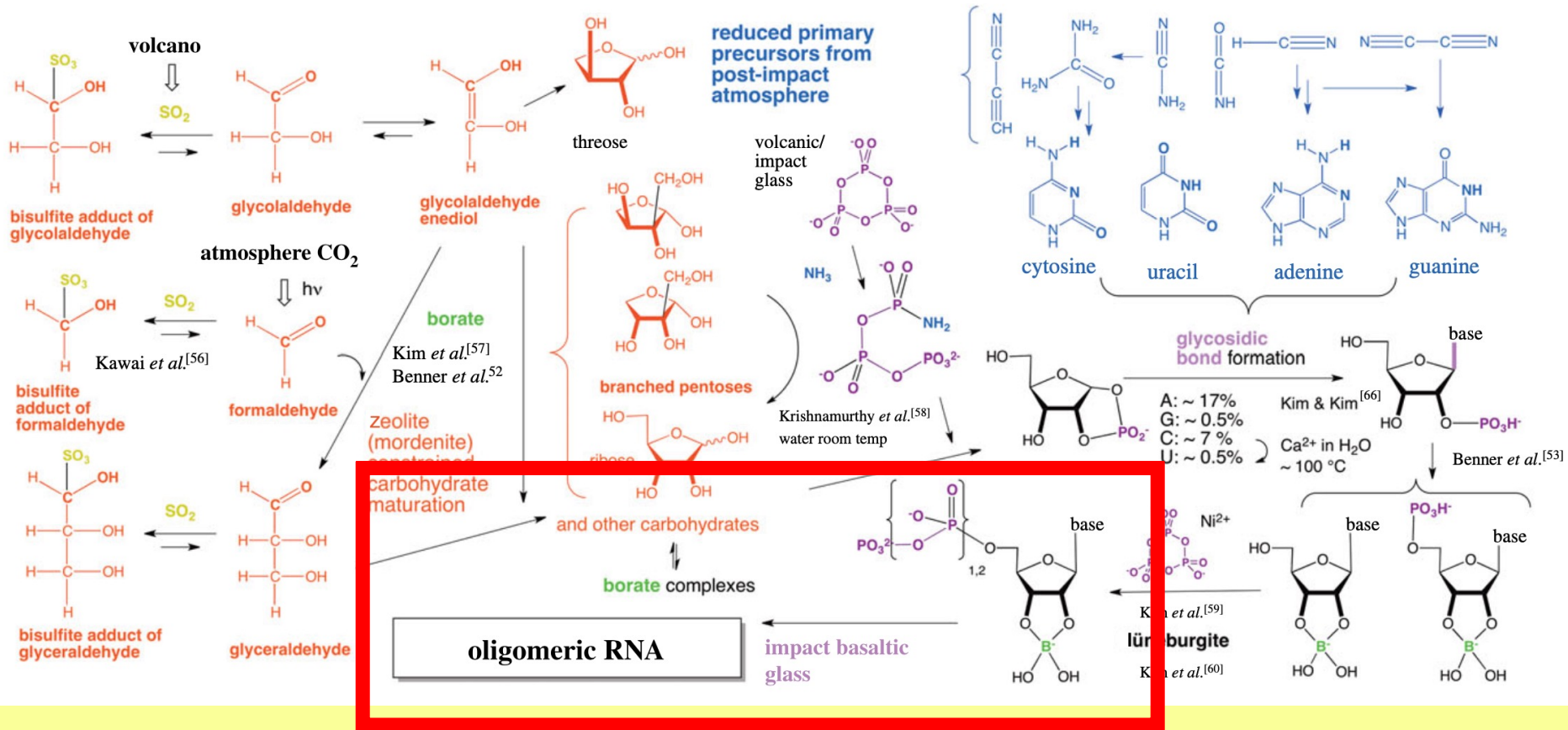
**chemical
system that
can replicate**

In search of an
RNA self replicating system

Challenges for RNA-based Darwinism

1. monomers are highly reactive (react with almost anything)
2. monomers and polymers break down easily in water
3. linkage problem (5'-3' only for life)
4. sequence problem - only certain sequences are functional
5. self-sustained replication

Example 1: RNA synthesis on primitive earth



Benner SA. 2023 Rethinking nucleic acids from their origins to their applications. *Phil. Trans. R. Soc. B* 378: 20220027.

The story remains incomplete, however, because these syntheses still require temporally separated reactions using high concentrations of just the right reactants and would be disrupted by the presence of other closely related compounds. The reactions channel material toward the desired products, but other fractionation processes are required to provide the correct starting materials at the requisite time and place. In addition to the selective crystallization processes described above, it has been proposed that precipitation of ferrocyanide salts could generate a concentrated reservoir of starting materials that can be liberated by

Protocells and RNA Self-Replication

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²Howard Hughes Medical Institute and Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114

Correspondence: gjoyce@salk.edu; szostak@molbio.mgh.harvard.edu

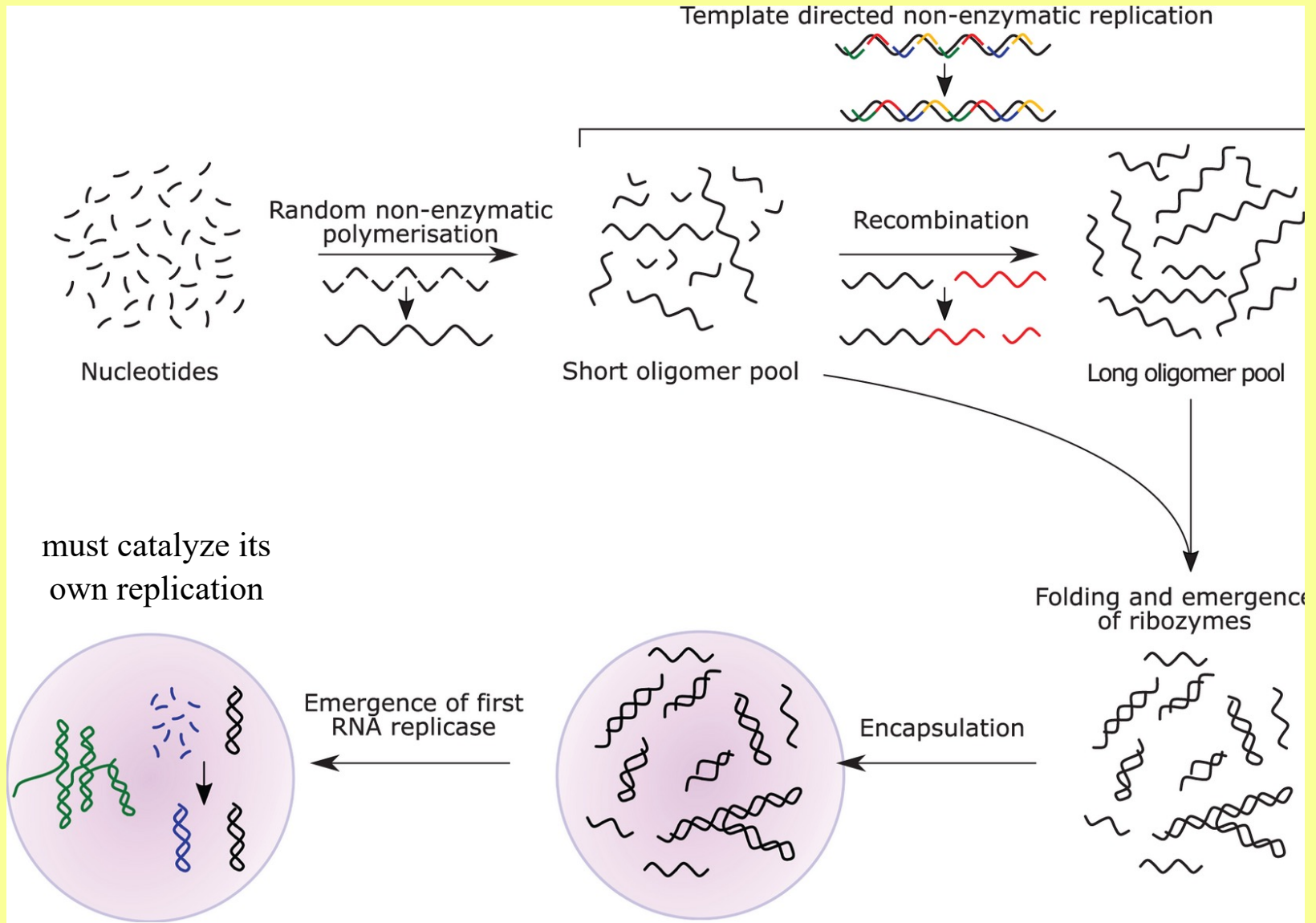


Illustration of RNA World from Wikipedia

Problems:

1. Simple strands that are not folded copy much faster than folded strands
2. Enzymes that cut up strands are much shorter and form easier than enzymes that replicate or copy strands

RNA oligomer synthesis on primitive earth

ASTROBIOLOGY
Volume 22, Number 6, 2022
Mary Ann Liebert, Inc.
DOI: 10.1089/ast.2022.0027

Rapid Communication

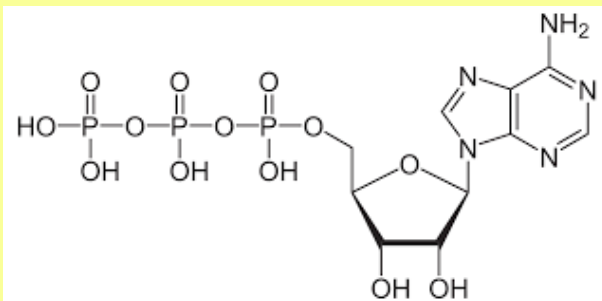
Open camera or QR reader and
scan code to access this article
and other resources online.



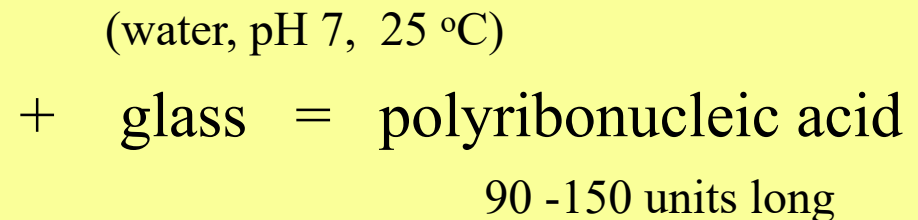
Catalytic Synthesis of Polyribonucleic Acid on Prebiotic Rock Glasses

Craig A. Jerome,^{1,*} Hyo-Joong Kim,² Stephen J. Mojzsis,^{3,4} Steven A. Benner,^{1,2} and Elisa Biondi^{1,2}

used all 4 monomers



purchased pure compounds



RNA oligomer synthesis on primitive earth

ASTROBIOLOGY
Volume 22, Number 6, 2022
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Rapid Communication

Open camera or QR reader and
scan code to access this article
and other resources online.



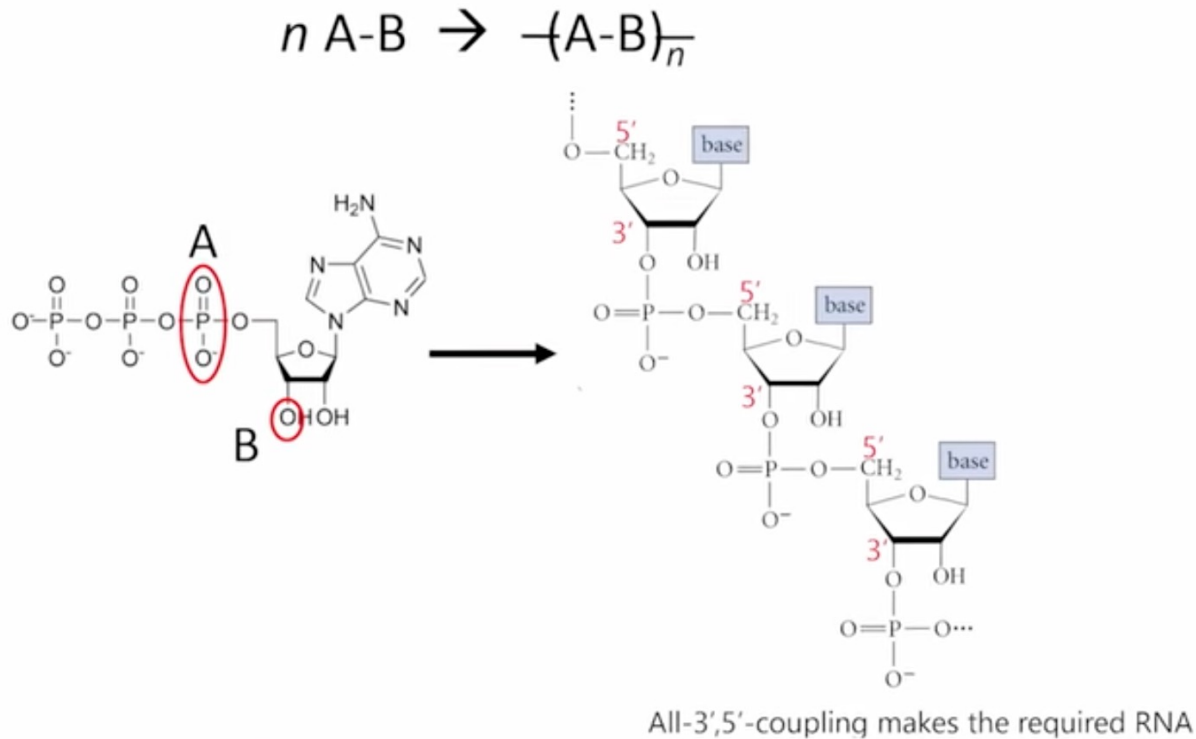
Catalytic Synthesis of Polyribonucleic Acid on Prebiotic Rock Glasses

Craig A. Jerome,^{1,*} Hyo-Joong Kim,² Stephen J. Mojzsis,^{3,4} Steven A. Benner,^{1,2} and Elisa Biondi^{1,2}

The enzymatic digestion experiments prove that a substantial fraction of the linkages in the “prebiotic” polyribonucleic acid are 3',5'. However, these experiments cannot exclude the presence of 2',5' linkages, nor some amount of branching. Most astonishing would be products wherein the linkages were *not* mixed.

Tour's challenge #2

make RNA with **correct linkages** (200 mer, 98% correct)



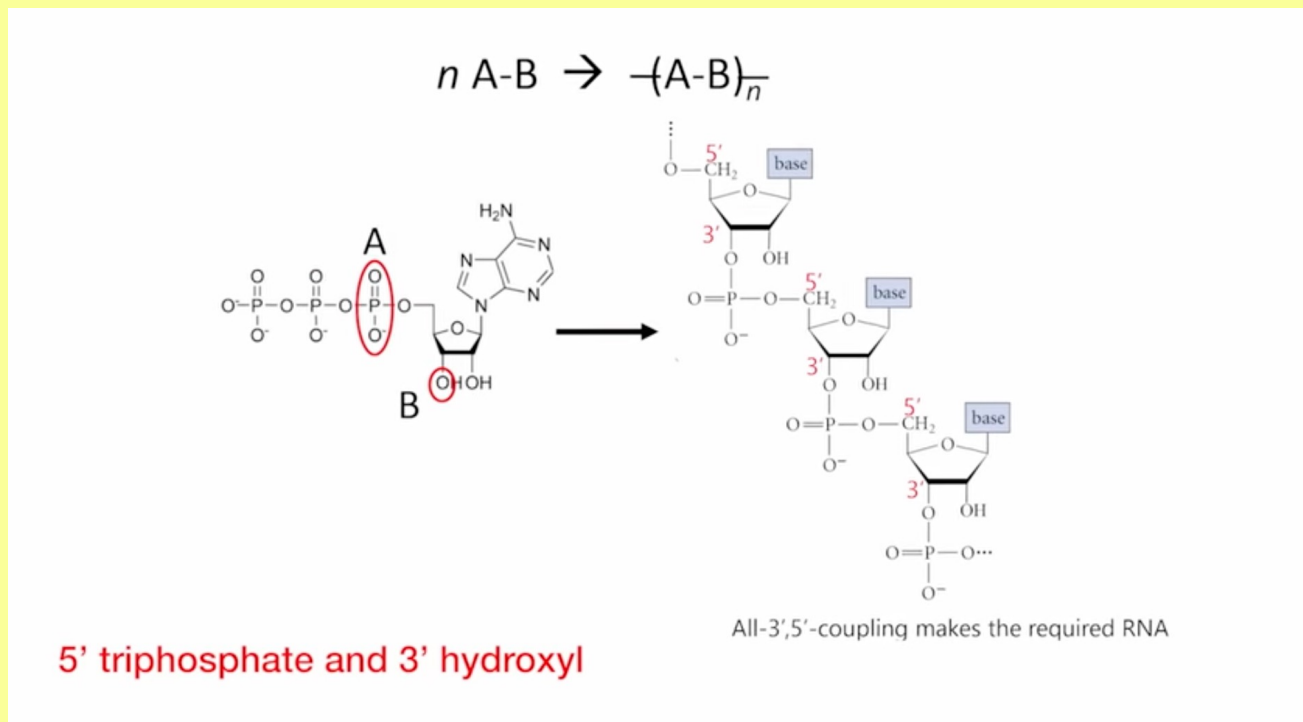
all life uses only 5' – 3' linkage – but is it necessary?

History of RNA polymerizing enzymes

Ribozymes discovered in 1980s (Nobel prize)

no natural polymerases

“... naturally occurring ribozymes carry out phosphoryl transfer, catalyzing the cleavage or ligation of the RNA phosphodiester backbone.” (Res. in Microbiol. 160, 2009, 457)



History of RNA polymerizing enzymes

Ribozymes discovered in 1980s (no natural polymerases)

From ligases, ribozyme polymerases were developed by directed evolution initially:

- only strands lacking secondary structure,
- cannot use both RNA template and its complement

then: able to synthesize from both RNA template and its complement

then: able to amplify short RNA in protein-free PCR

most recent 2024: RNA enzyme that can replicate with high fidelity
a shorter enzyme that cuts strands

PNAS

RESEARCH ARTICLE

BIOCHEMISTRY



RNA-catalyzed evolution of catalytic RNA

Nikolaos Papastavrou^a, David P. Horning^{a,1} , and Gerald F. Joyce^{a,1} 

Edited by Jack Szostak, University of Chicago Department of Chemistry, Chicago, IL; received December 7, 2023; accepted January 25, 2024

‘Monumental’ experiment suggests how life on Earth may have started

Washington Post

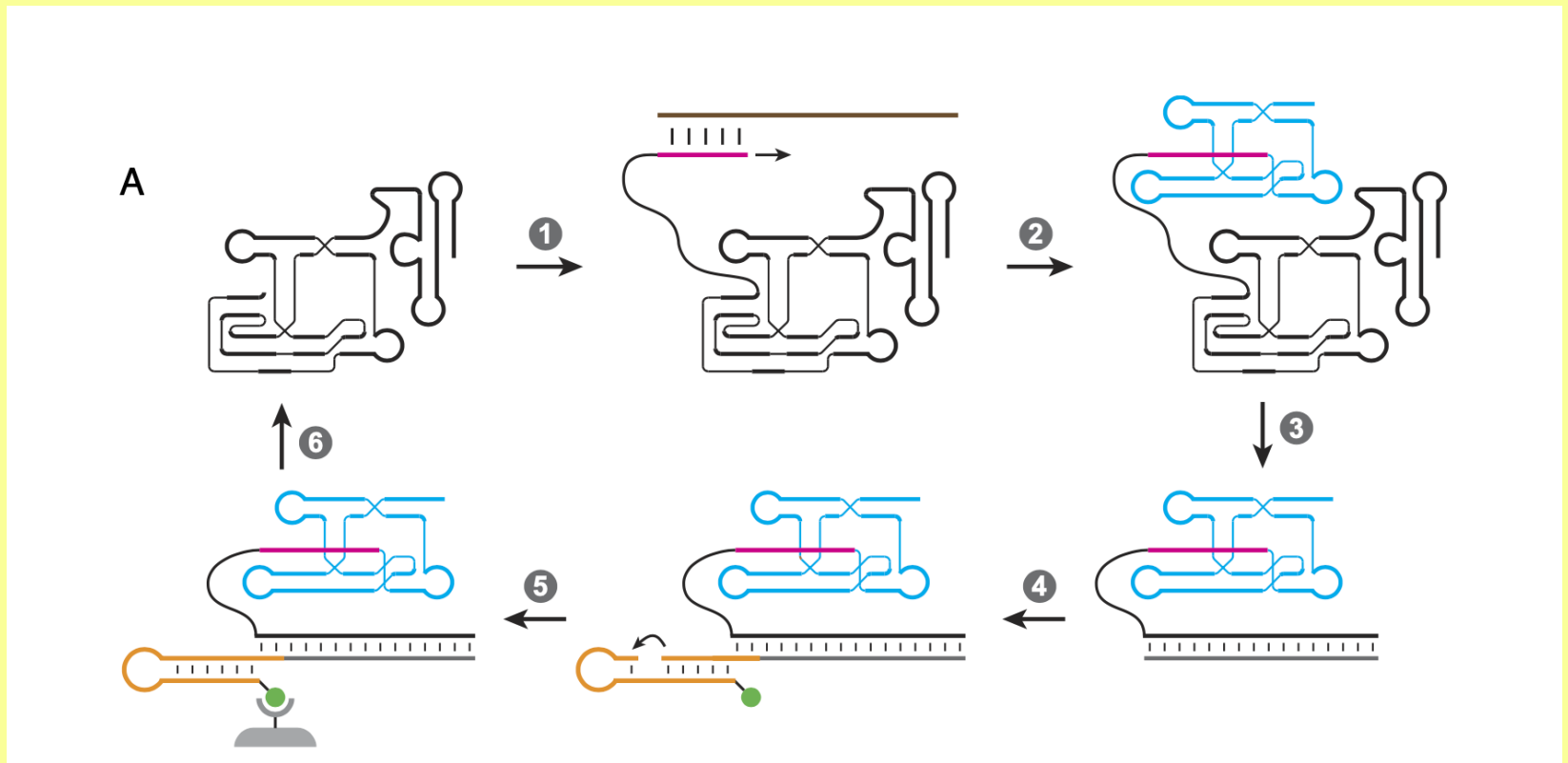
Mar 9, 2024

Replication of RNA enzymes

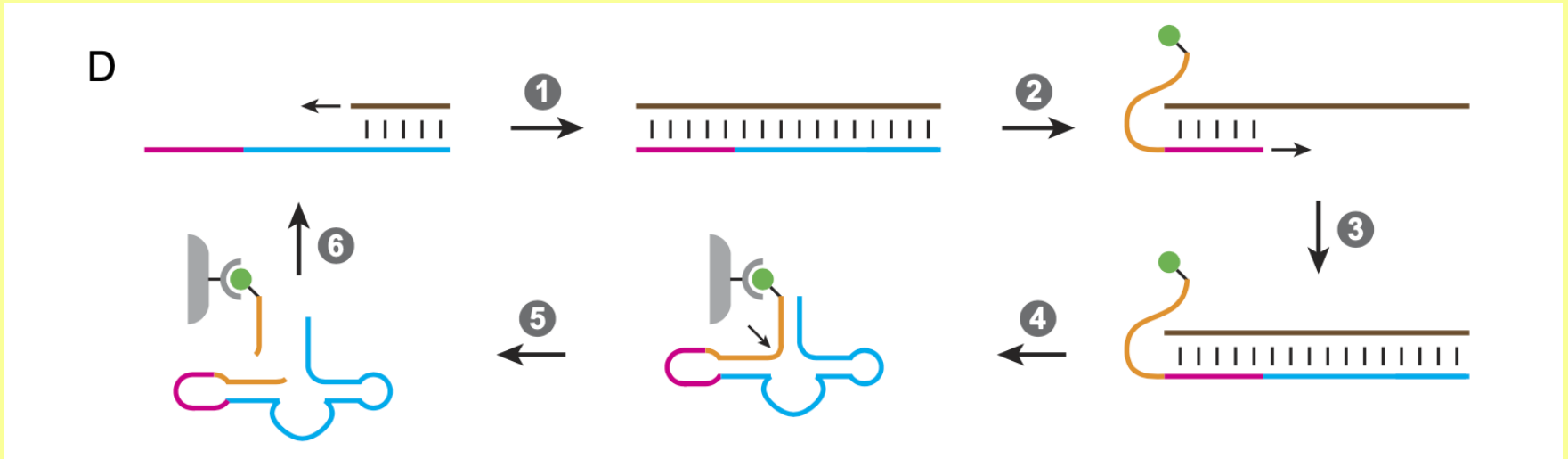
Goal: RNA enzyme that can copy itself

- Large RNA enzymes that are folded are more difficult to copy
- RNA enzymes that **cut** are smaller and easier to copy
- RNA enzymes that **copy** are larger and difficult to copy

Directed evolution of an RNA enzyme that can synthesize an RNA enzyme that **connects** two RNA strands



Directed evolution of an RNA enzyme that
cuts two RNA strands



PNAS 2024, 121, e2321592121

The evolved RNA polymerase was able to replicate this enzyme 8 times without loss of function whereas with the original polymerase function was lost.

They made a better enzyme!

Replication of RNA enzymes

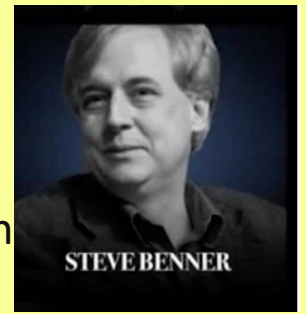
Great work - but is this relevant to OoL?

(See <https://evolutionnews.org/2024/04/fact-check-a-monumental-breakthrough-in-understanding-lifes-origin/>)

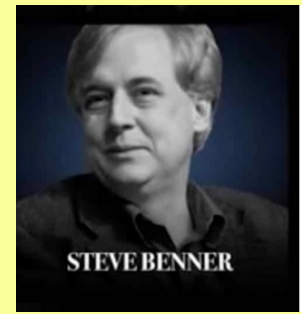
- high conc. of monomers (activated, purified)
- used machinery of modern cells (reverse transcriptase, PCR)
- supplied sequences of templates, primers, substrates
- the team engineered the strands and performed the selection
- carefully controlled reaction conditions and purification steps
- used very high concentrations of RNA enzymes and primers
(essential because RNA enzymes degrade rapidly)
- enzyme that cuts has 34 units (easier to copy) whereas polymerase has > 100 units (enzyme that destroys will be more prevalent)

5 paradoxes in Ool: Benner *Orig Life Evol Biosph* 2014

“pairs of statements, both grounded in theory and observation, that (taken together) suggest that the “origins problem” cannot be solved.”



5 paradoxes in Ool: Benner *Orig Life Evol Biosph* 2014



1. The Asphalt Paradox: an enormous amount of empirical data have established, as a rule, that organic systems, given energy and left to themselves, devolve to give uselessly complex mixtures, “**asphalts**”. it is impossible for any non-living chemical system to escape devolution to enter into the Darwinian world of the “living”.
2. The Water Paradox: RNA requires water to function, but RNA cannot emerge in water, and does not persist in water without repair.
3. The Information-Need Paradox: implausibly high concentrations of building blocks generate biopolymers having inadequate amounts of information
4. The Single Biopolymer Paradox: Even if we can make biopolymers prebiotically, it is hard to imagine making two or three (DNA, RNA, proteins) at the same time. ... genetics versus catalysis place very different demands on the behavior of a biopolymer.
5. The Probability Paradox: Experiments show that RNA molecules that catalyze the destruction of RNA are more likely to arise in a pool of random (with respect to fitness) sequences than RNA molecules that catalyze the replication of RNA, with or without imperfection.



RNA-catalyzed evolution of catalytic RNA

Nikolaos Papastavrou^a, David P. Horning^{a,1} , and Gerald F. Joyce^{a,1} 

Edited by Jack Szostak, University of Chicago Department of Chemistry, Chicago, IL; received December 7, 2023; accepted January 25, 2024

‘Monumental’ experiment suggests how life on Earth may have started

Washington Post

Mar 9, 2024

**This work is great molecular engineering,
but is not relevant to naturalistic Ool!**



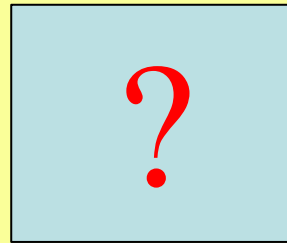
Engineers can make a car but natural processes such as waves lapping up on the beach cannot.

Current status

chemistry

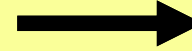


researchers
try to do
this

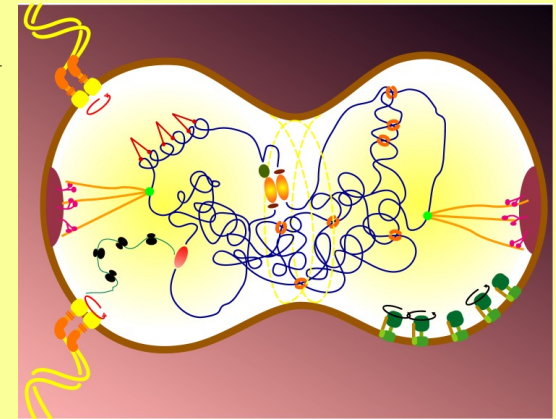


**RNA system
that can
replicate**

and believe
that natural
selection will
do this



simplest cell



Is this life?

Redefinition of “life”

“a self-sustaining chemical system capable of generating replicates, where those replicates are imperfect, and where those imperfections are themselves replicable.”

Cleland and Chyba 2002 cited in Benner 2015 Paradoxes

“life is that which is subject to Darwinian evolution.”

Posted on [January 28, 2024](#) by [Paul M. Sutter](#)

The Improbable Origins of Life on Earth

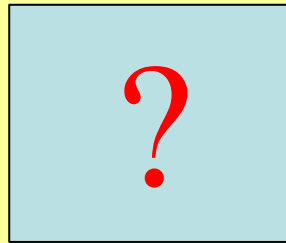
Universe Today – Space and Astronomy News

Current status

chemistry



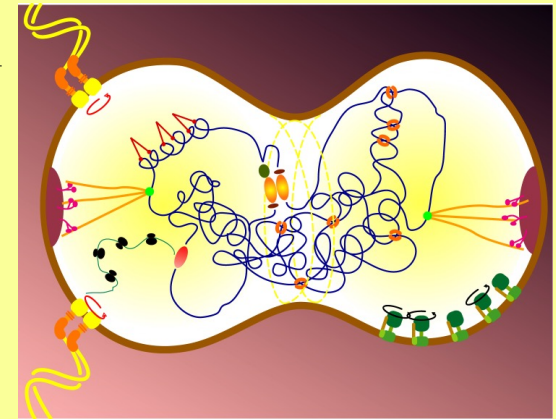
researchers
try to do
this



and believe
that natural
selection will
do this



simplest cell



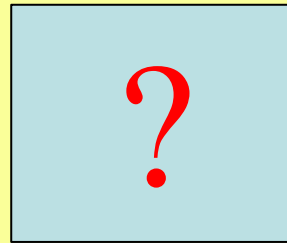
**chemical
system that
can replicate**



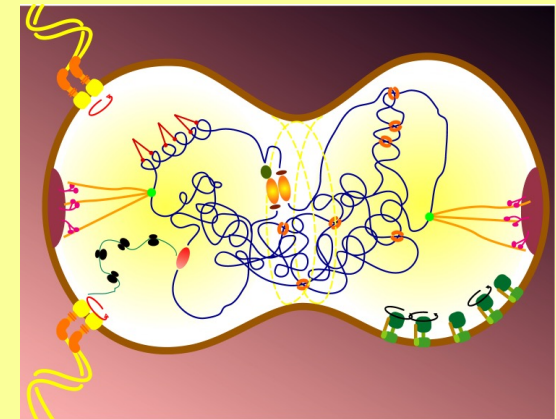
**chemistry
alone
must do
this**

Current status

chemistry



**RNA system
that can
replicate**



simplest cell



**a LOT of
engineering
is needed!**



**this
looks
hopeless
to me**

Hype and misleading the public

<https://evolutionnews.org/2024/03/james-tour-offers-three-year-challenge-to-lee-cronin-to-demonstrate-legitimacy-of-assembly-theory/>

10:58 – 15:47

40:15 – 42:40

Hype and misleading the public

Craig Venter

(CNN) -- Genetics pioneer J. Craig Venter announced Thursday that he and his team have created artificial life for the first time.

Using sequences of genetic code created on a computer, the team assembled a complete DNA of a bacterium, then inserted it in another bacterium and initiated synthesis, or in Venter's words "booted up" the cell.

<http://www.cnn.com/2010/HEALTH/05/21/venter.qa/index.html>

Hype and misleading the public

Craig Ventor



The image shows a screenshot of a news article header from the NIST website. At the top left is the NIST logo. To its right is a search bar with the text "Search NIST" and a magnifying glass icon. Further right is a blue button with a white hamburger menu icon and the text "Menu". Below the navigation bar is a green button with the text "NEWS". The main headline is "Scientists Create Simple Synthetic Cell That Grows and Divides Normally" in a large, bold, black font. Below the headline is a sub-headline in a smaller, bold, black font: "New findings shed light on mechanisms controlling the most basic processes of life." At the bottom left of the article header is the date "March 29, 2021".

NIST Search NIST Menu

NEWS

Scientists Create Simple Synthetic Cell That Grows and Divides Normally

New findings shed light on mechanisms controlling the most basic processes of life.

March 29, 2021

Hype and misleading the public

Craig Ventor

Five years ago, scientists created a single-celled synthetic organism that, with only 473 genes, was the simplest living cell ever known. However, this bacteria-like organism behaved strangely when growing and dividing, producing cells with wildly different shapes and sizes.

the hype



the truth



Scientists at JCVI constructed the first cell with a synthetic genome in 2010. They didn't build that cell completely from scratch. Instead, they started with cells from a very simple type of bacteria called a mycoplasma. They destroyed the DNA in those cells and replaced it with DNA that was designed on a computer and synthesized in a lab. This was the first organism in the history of life on Earth to have an entirely synthetic genome. They called it JCVI-syn1.0.

Minimal cells

RESEARCH ARTICLE

SYNTHETIC BIOLOGY

Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III,^{1,†} Ray-Yuan Chuang,^{1,†} Vladimir N. Noskov,¹
Nacyra Assad-Garcia,¹ Thomas J. Deerinck,² Mark H. Ellisman,² John Gill,³
Krishna Kannan,³ Bogumil J. Karas,¹ Li Ma,¹ James F. Pelletier,^{4,§} Zhi-Qing Qi,³
R. Alexander Richter,¹ Elizabeth A. Strychalski,⁴ Lijie Sun,^{1,||} Yo Suzuki,¹
Bilyana Tsvetanova,³ Kim S. Wise,¹ Hamilton O. Smith,^{1,3} John I. Glass,¹
Chuck Merryman,¹ Daniel G. Gibson,^{1,3} J. Craig Venter^{1,3*}

Science 351, aad6253 (2016)

Original *Mycoplasma mycoides* genome has **901** genes

M. capricolum with synthesized minimal genome from *M. mycoides* can survive with **473** genes

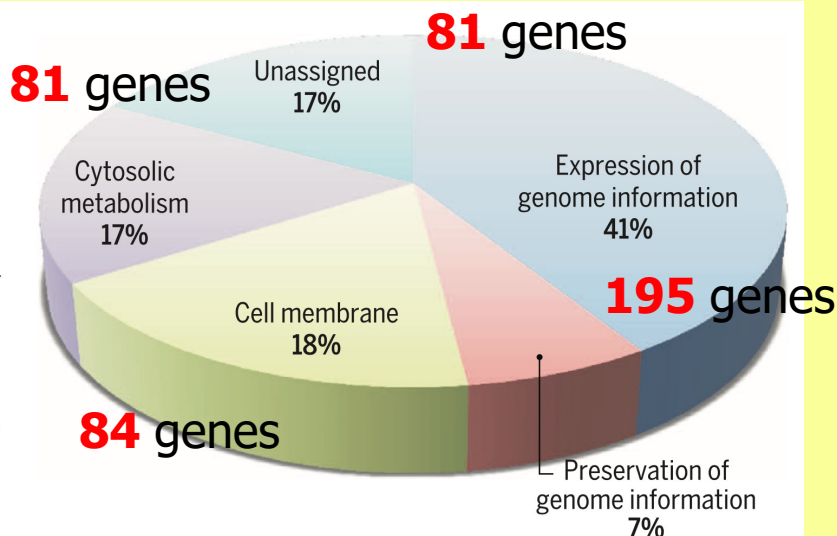
438 protein-coding
35 RNA genes

obligate parasite

Grows in a rich medium

Fig. 6. Partition of genes into four major functional groups.

Syn3.0 has 473 genes. Of these, 79 have no assigned functional category (Table 1). The remainder can be assigned to four major functional groups: (i) expression of genome information (195 genes); (ii) preservation of genome information (34 genes); (iii) cell membrane structure and function (84 genes); and (iv) cytosolic metabolism (81 genes). The percentage of genes in each group is indicated.



Replacing a bacterial genome with a synthetic genome is **not “creating artificial life” or a “synthetic cell”.**

Genes are just one component of a very complicated system

If you get a hip replacement does that make you an artificial life form?

[nature](#) > [book reviews](#) > article

BOOK REVIEW | 05 February 2024

It's time to admit that genes are not the blueprint for life

The view of biology often presented to the public is oversimplified and out of date. Scientists must set the record straight, argues a new book.

By [Denis Noble](#)

- much information in cells resides outside of the genome
- rather than genes controlling an organism, it's the organism that controls the genome
- genome is important but the organism is central

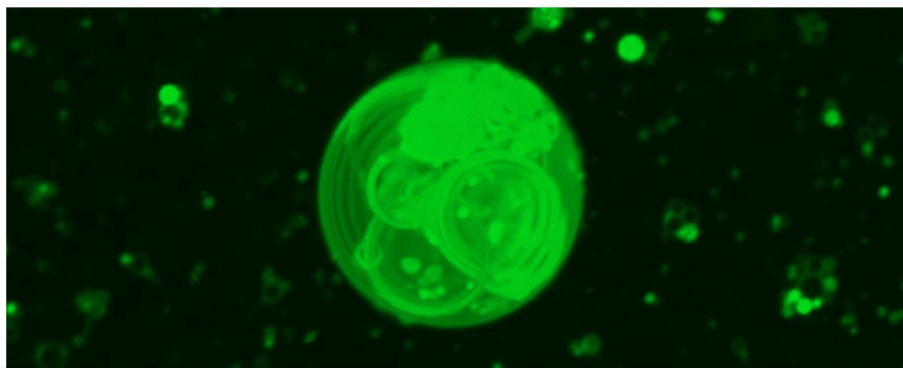
Hype and misleading the public

Typically, a chemical step is achieved that does nothing to address the informational aspect of life, but the chemical step is claimed to be a key to the origin of life.

Hype and misleading the public

We May Finally Know How The First Cells on Earth Formed

NATURE 04 March 2024 By DAVID NIELD



50 Chem



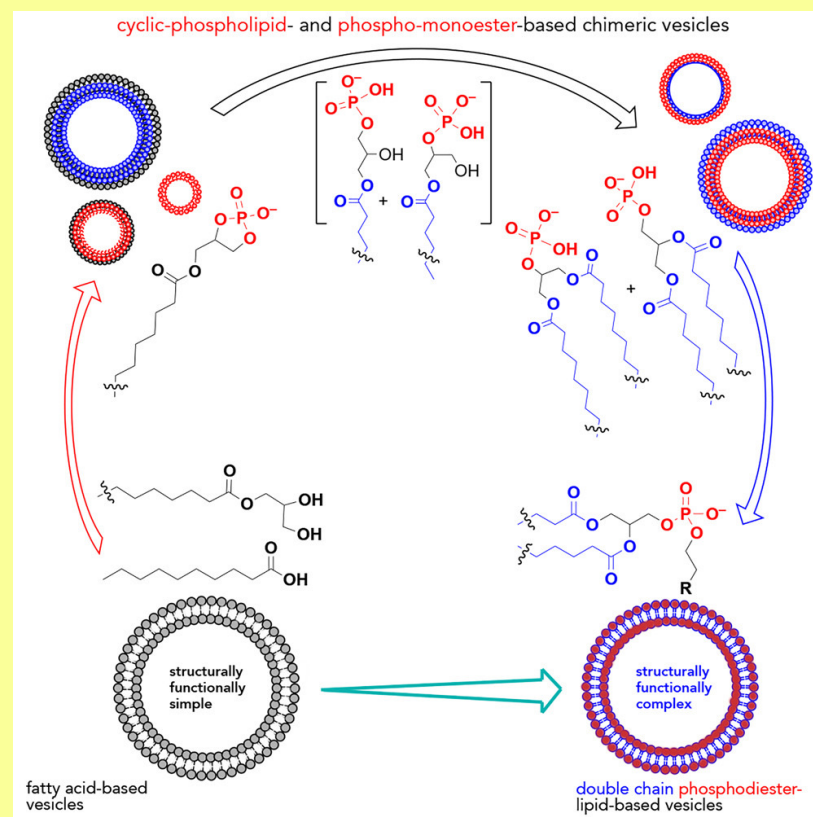
ARTICLE | ONLINE NOW

Experimentally modeling the emergence of prebiotically plausible phospholipid vesicles

Sunil Pulletikurti³ • Kollery S. Veena³ • Mahipal Yadav • Ashok A. Deniz

Ramanarayanan Krishnamurthy ⁴ • Show footnotes

Published: February 29, 2024 • DOI: <https://doi.org/10.1016/j.chempr.2024.02.007>



Hype and misleading the public

Science News

from research organizations

Simple fats, amino acids to explain how life began

Date: January 12, 2017

Source: University of the Basque Country

Summary: A research group has explored how the chemical molecules that could have given rise to life were assembled.

Current Biology
Magazine

Current Biology 26,
R1247, 2016

Feature

How life can arise from chemistry

Rapid progress in several research fields relating to the origin of life bring us closer to the point where it may become feasible to recreate coherent and plausible models of early life in the laboratory. **Michael Gross** reports.

nature
physics

ARTICLES

PUBLISHED ONLINE: 12 DECEMBER 2016 | DOI: 10.1038/NPHYS3984

Growth and division of active droplets provides a model for protocells

David Zwicker^{1,2†}, Rabea Seyboldt^{1†}, Christoph A. Weber¹, Anthony A. Hyman³ and Frank Jülicher^{1*}

exaggerated claims

Hype and misleading the public

New Mexico Museum of Natural History and Science



Gas + energy = DNA \longrightarrow LIFE

Hype and misleading the public

New Mexico Museum of Natural History and Science

**Gas + Energy does not equal DNA, so
why does our museum say that it does?**

Hype and misleading the public

Cronin - Assembly Theory

Article

Assembly theory explains and quantifies selection and evolution

<https://doi.org/10.1038/s41586-023-06600-9>

Received: 1 April 2023

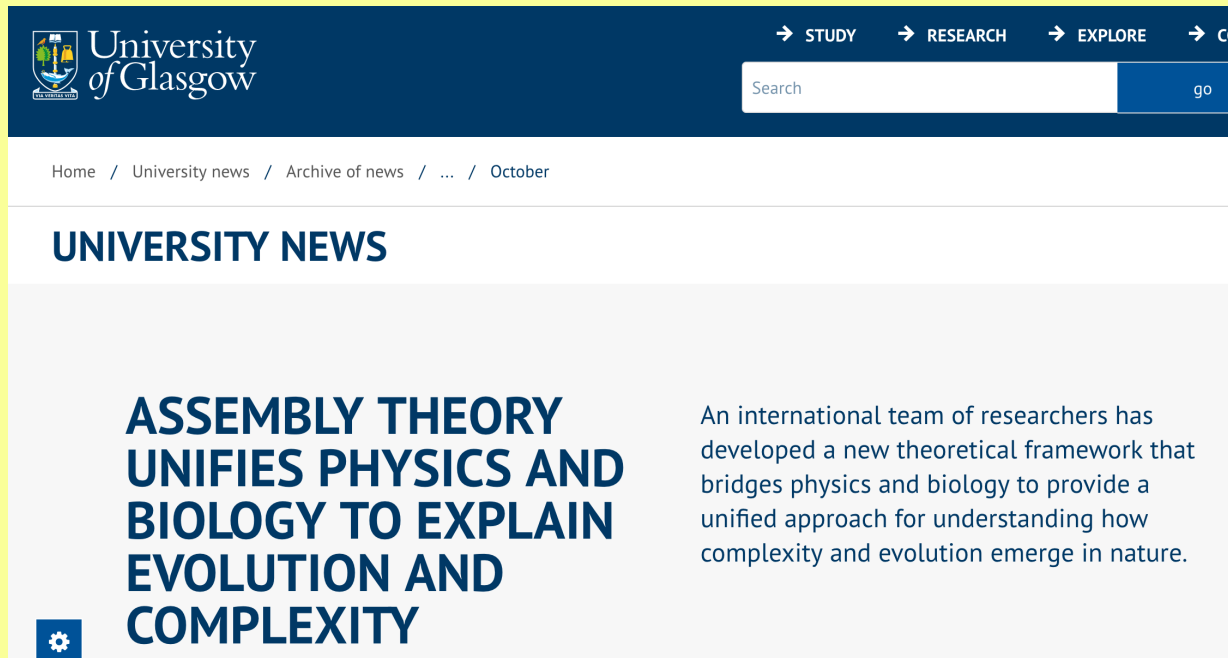
Accepted: 31 August 2023

Abhishek Sharma^{1,6}, Dániel Czégel^{2,3,6}, Michael Lachmann⁴, Christopher P. Kempes⁴, Sara I. Walker^{2,5} & Leroy Cronin¹

Nature **2023**, 622, 321

Hype and misleading the public

Cronin - Assembly Theory



The screenshot shows the top navigation bar of the University of Glasgow website. It includes the university logo and name on the left, and navigation links for 'STUDY', 'RESEARCH', 'EXPLORE', and 'CO' on the right. A search bar with a 'go' button is also present. Below the navigation bar, a breadcrumb trail reads 'Home / University news / Archive of news / ... / October'. The main content area features the heading 'UNIVERSITY NEWS' and a large article title: 'ASSEMBLY THEORY UNIFIES PHYSICS AND BIOLOGY TO EXPLAIN EVOLUTION AND COMPLEXITY'. To the right of the title is a short introductory paragraph: 'An international team of researchers has developed a new theoretical framework that bridges physics and biology to provide a unified approach for understanding how complexity and evolution emerge in nature.'

SCIENCE & TECHNOLOGY NEWS

'Assembly Theory' unites physics and biology to explain the universe

OCTOBER 7, 2023

Assembly Theory: A New Theory of Everything?

Sci&Tech Editor Georgia Brooks explains the exciting new interdisciplinary theory, and its potential to unite discourses and explain unsolved scientific problems.

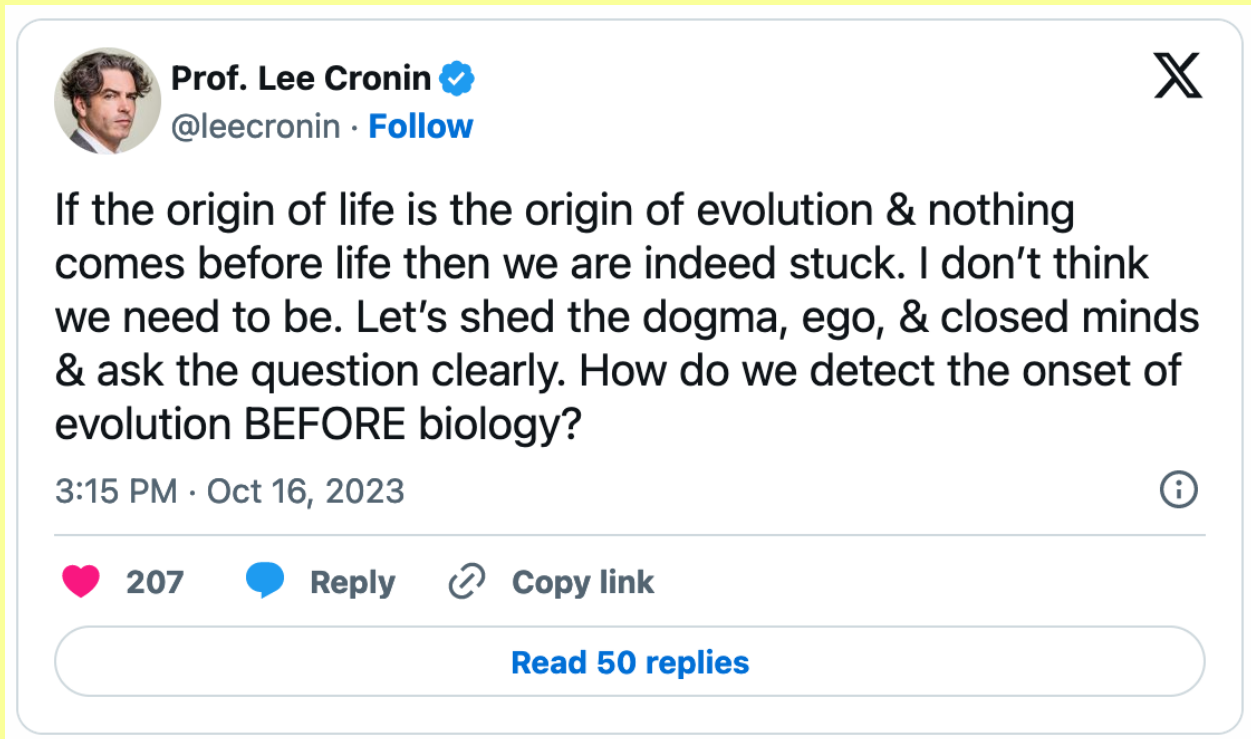
Written by Georgia Brooks

Cronin - Assembly Theory

‘A key feature of the theory is that it is experimentally testable,’ says Cronin. ‘This opens up the exciting possibility of using assembly theory to design new experiments that could solve the origin of life **by creating living systems from scratch in the laboratory.**’

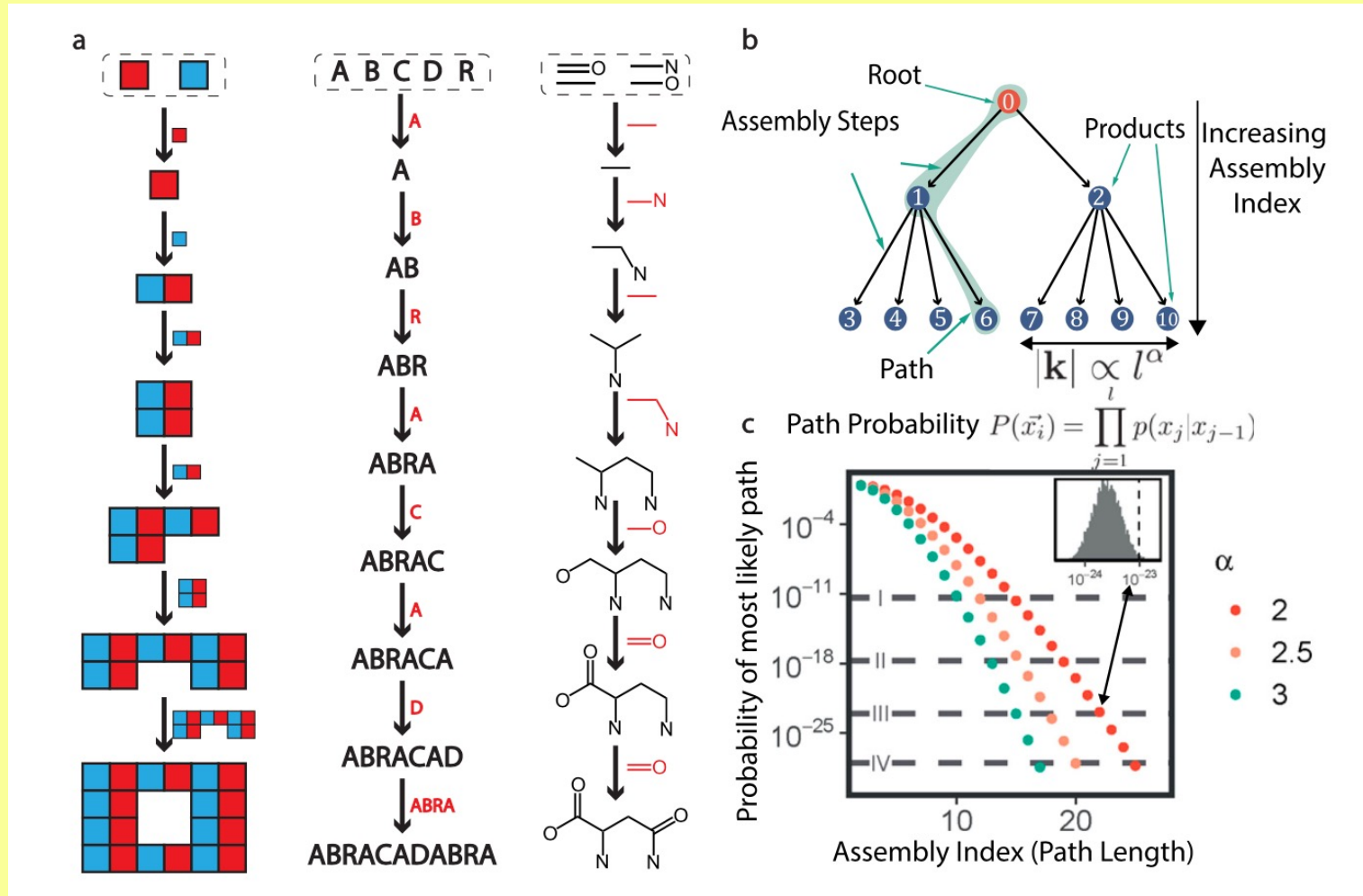
<https://www.chemistryworld.com/news/assembly-theory-puts-chemistry-centre-stage-to-explain-molecular-complexity-and-lifes-origins/4018228.article>

What is Assembly Theory?



“the onset of evolution before biology” What does that mean?

What is Assembly Theory?



The Assembly index of an object is defined as the smallest number of joining operations required to create the object using this model.

Cronin - Assembly Theory

(clips from Tour Cronin debate)

<https://evolutionnews.org/2023/12/watch-it-now-tour-and-cronin-at-harvard/>

Selection and evolution before biology 1:04:30

Combinatorial space in chemistry is immense 1:06:50

Selection is the driving force that produces protoevolution
outside of biology 1:10:50, 1:11:50, 1:13:20

complex chemistry + selection

Tour's 3 yr challenge to assembly theory

<https://evolutionnews.org/2024/03/james-tour-offers-three-year-challenge-to-lee-cronin-to-demonstrate-legitimacy-of-assembly-theory/>

44:25 – 48:43

Cronin - Response

<https://www.youtube.com/watch?v=m4VwgFX1Uv4>

22:30 – 26:10

“...it is a combinatorial gamish, its a terrible mess. it was a mess, but within that mess we saw linear chains in quite high concentrations, detectable concentrations by mass spec”

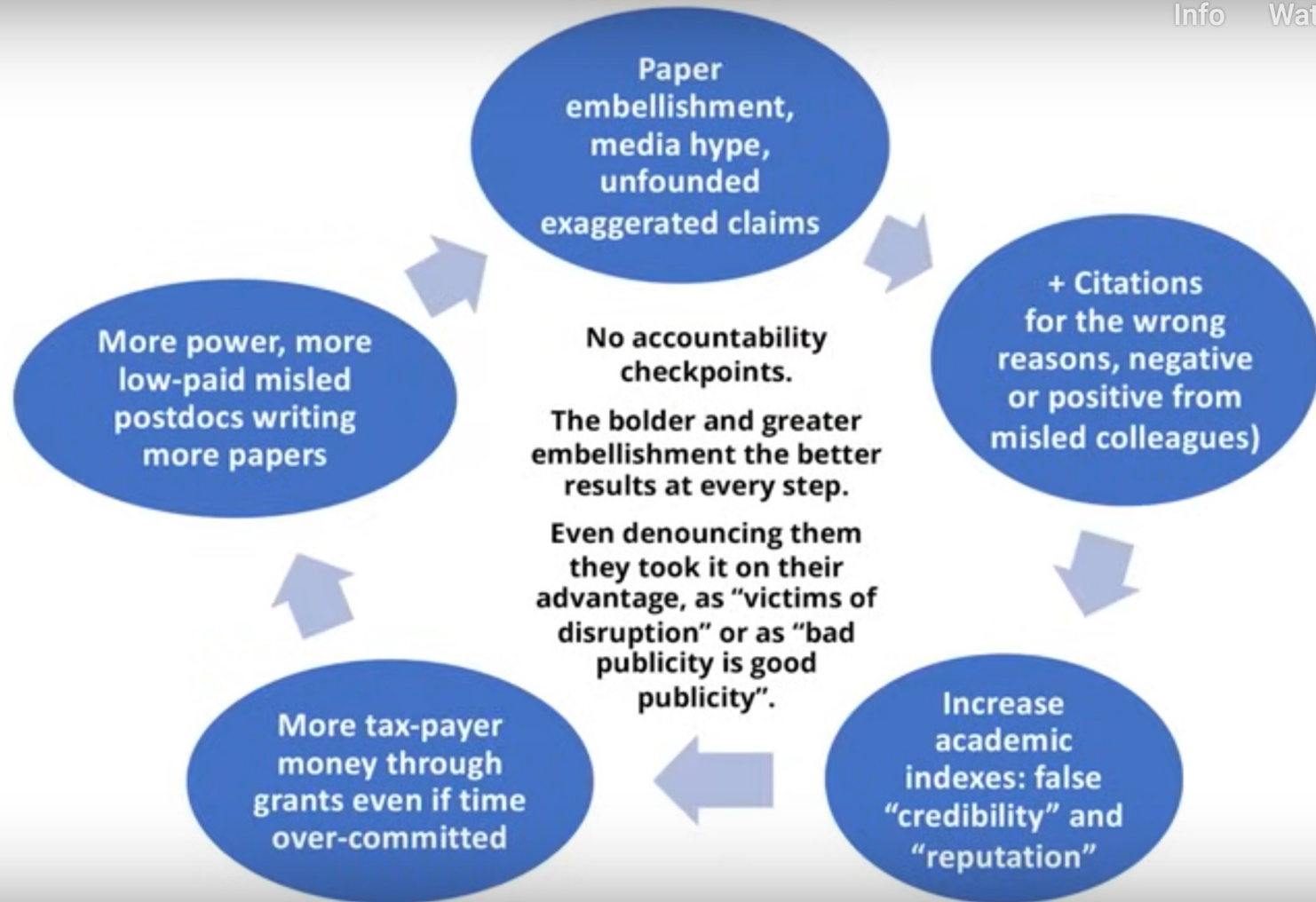
“I had to add in pure amino acids, ... it is evidence that selection has to operate far earlier in a primordial soup which inevitably it has to ...”

“You are going to have all the linkages. In the absence of selection, in a primordial soup, nothing is off limits.... The problem is how deep do you get into the chemical space before you see what you see in cells. But that is because evolution has to kick in.”

Hector Zenil (computational biology)

<https://evolutionnews.org/2024/03/james-tour-offers-three-year-challenge-to-lee-cronin-to-demonstrate-legitimacy-of-assembly-theory/> 56:50 – 57:50

Info Watch later



To unravel the origin of life, treat findings as pieces of a bigger puzzle

Nick Lane & Joana C. Xavier

Explaining isolated steps on the road from simple chemicals to complex living organisms is not enough. Looking at the big picture could help to bridge rifts in this fractured research field.

The origin of life is one of the greatest challenges in science. It transcends conventional disciplinary boundaries, yet has been approached from within those confines for generations. Not surprisingly, these traditions have emphasized different aspects of the question.

Or rather, questions. The origin of life is really an extended continuum from the simplest prebiotic chemistry to the first reproducing cells, with molecular machines encoded by genes – machines such as ribosomes, the protein-building factories found in all cells.

Most scientists agree that these nanomachines are a product of selection – but selection for what, where and how?

There is no consensus about what to look for, or where. Nor is there even agreement on whether all life must be carbon-based – although all known life on Earth is. Did meteorites deliver cells or organic material from outer space? Did life start on Earth in the hot waters of hydrothermal systems on land or in deep seas?

Observations alone cannot constrain these possibilities. The few geological traces that hint at early life are enigmatic. Is a bacterium-like

Improve publishing practices. Researchers should aspire to contextualize their findings in cover letters, papers and press releases, to give a sense of how the work fits into a wider framework. Refraining from hype might seem unrealistic but could work if researchers implemented this practice in their roles as peer reviewers for papers and grants as well as authors.

My view:

-The problem is **NOT** that some people believe that chemistry can make life

-The problem is **NOT** that researchers are exploring ideas to make a self-sustaining chemical systems

The problem is that the public is being misled!

Current status of Origin of Life research

- A. Scientists have made life in the lab from simple chemicals
- B. Great steps of progress have been made recently and the problem of the origin of life from simple chemicals is on the verge of being solved
- C. The origin of life from simple chemicals is virtually impossible and little or no progress has been made

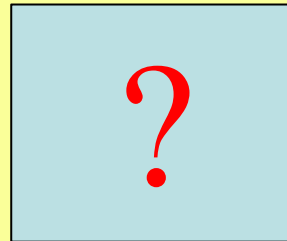
What do you think?

Summary

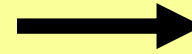
chemistry



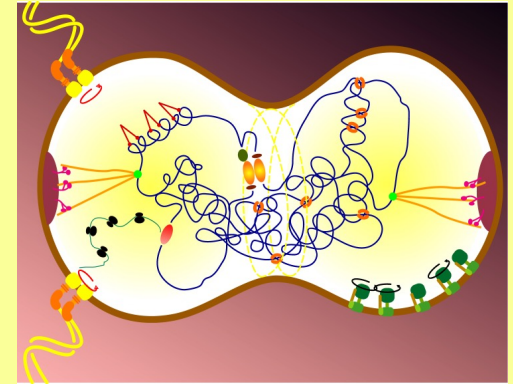
researchers
try to do
this



and believe
that natural
selection will
do this



simplest cell



**chemical system
that can replicate**

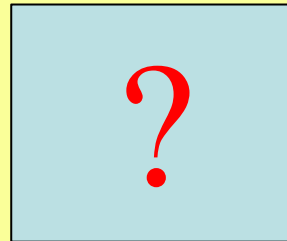
1. Tour's challenge relates to **real** life. (no one responded)
2. OoL research is guided by the idea that life is that which is capable of undergoing Darwinian evolution
3. For OoL, a self-sustaining series of reactions is the target, and it is assumed that the complexity of real life will arise from that.
4. Self-sustained RNA-based Darwinism does not yet exist, researcher-engineered RNA-based Darwinism has improved ribozymes

Summary

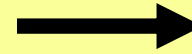
chemistry



researchers
try to do
this

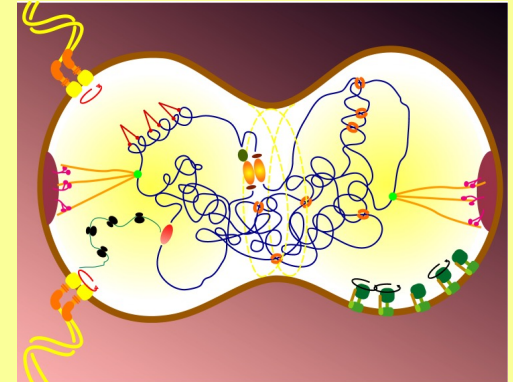


and believe
that natural
selection will
do this



**chemical system
that can replicate**

simplest cell



5. **Lee Cronin proposes that complex combinatorial chemistry can select itself, avoid tar, and lead to life**
6. **Self-sustained evolving chemical systems do not exist because unconstrained chemistry makes asphalt/tar**

Discussion

Does it matter if the public is informed on this topic?

Who is on the side of science? (Tour or the 10 researchers?)

Should we wait until an infinite search is performed to conclude that life did not arise by chemistry alone?

Should the possibility that life did not arise from mindless chemistry and physics be considered? (science, museums, schools, etc)

Extra slides

Cronin - Assembly Theory

Questions I would ask if I were reviewing this work for a grant:

What would one do in the lab that is different from what has been done in the past?

Why should we believe combinatorial chemistry will produce anything other than “asphalt” or ”tar” as has been shown during the past 50 years?

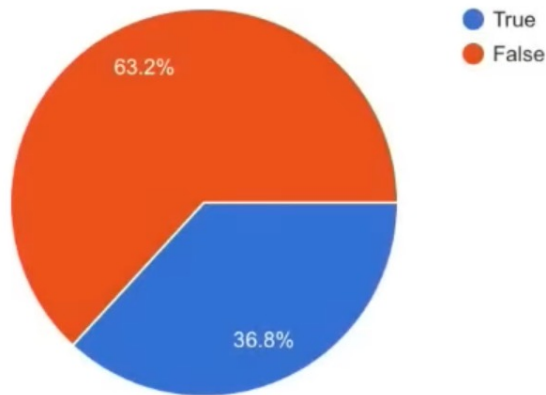
What is selecting among variants before life (or replication) occurs? (Chemistry doesn't select and it doesn't provide constraints – that is why it makes tar)

The public in the US is not well informed on this topic

Has the public been misled on Origin of Life claims?

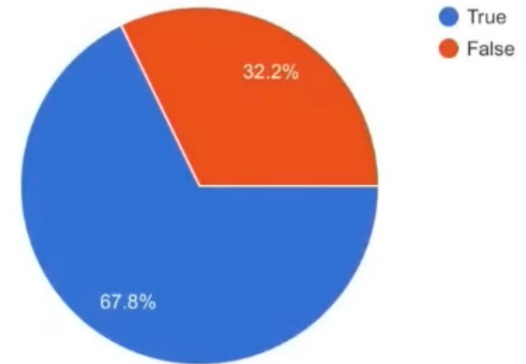
1. Under simulations of Earth's early atmosphere, scientists have mixed molecules together in laboratories to produce complex life forms such as frogs.

152 responses



2. Under simulations of Earth's early atmosphere, scientists have mixed molecules together in laboratories to produce simple single-celled life forms such as bacteria.

152 responses



Current status of Origin of Life research

- A. Scientists have mixed molecules together in laboratories and created simple life forms (True/**False**)
- B. Gas + energy = DNA (True/**False**)
- C. The public is well-informed about the status of OoL (True/**False**)

Information is the key

"Our task is to find an algorithm, a natural law that leads to the origin of **information**."

Manfred Eigen, Steps towards Life: A perspective on Evolution, 1992, pg 12.

"the problem of the origin of life is clearly basically equivalent to the problem of the origin of biological **information**."

Bernd-Olaf Koppers, Information and the Origin of Life, 1990, pg 170-172

"Theories of prebiotic natural selection need **information**, which implies that they have to presuppose what is to be explained in the first place."

Christian de Duve

"Viewed in this way, the problem of the origin of life reduces to one of understanding how **encoded software** emerged spontaneously from hardware."

Paul Davies, The Fifth Miracle, 1999, p 115.

Definitions of information

1. Syntactic: use of symbols, rules
2. Semantic: conveying a meaning or message
3. Shannon:
$$I = -\log_2(p)$$
 (not useful for detecting design)
4. Kolmogorov: algorithmic def - length of the smallest program that can produce a given output, compressibility
5. **CSI, functional information, Shannon – Kolmogorov, number of ways to “break” a system**

Shannon information is not useful for describing life

[C]lassical information theory [i.e., Shannon information] ... does not consider the meaning of a message, defining the information content of a string of symbols as simply that required to specify, store or transmit the string. ... **A new measure of information — functional information — is required to account for all possible sequences that could potentially carry out an equivalent biochemical function**, independent of the structure or mechanism used.”

Nobel prize winner Jack W. Szostak, “Molecular messages,”
Nature, Vol. 423: 689 (June 12, 2003).

Shannon information is not useful for describing life!

“... propose to measure the complexity of a system in terms of **functional information, the information required to encode a specific function.**”

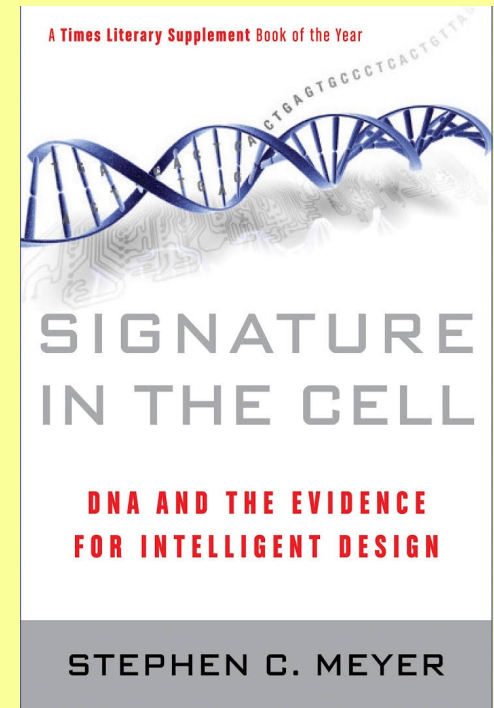
Robert M. Hazen, Patrick L. Griffin, James M. Carothers, and Jack W. Szostak, "Functional information and the emergence of biocomplexity," *Proceedings of the National Academy of Sciences*, 104:8574--8581 (May 15, 2007)

The amount of functional information in the simplest free living cell is inconceivably great!

None of the claims of progress address the origin of information!

"A law of nature of the sort we know and love will not create biological information, or indeed any information at all. ... The secret of life lies, not in its chemical basis, but in the logical and informational rules it exploits. ... Real progress with the mystery of biogenesis will be made, I believe, not through exotic chemistry, but from **something conceptually new.**"

P. Davies, *The Fifth Miracle*, pg 210 – 216, 1998.



2009

Infinite universes?

Biology Direct



Hypothesis

Open Access

The cosmological model of eternal inflation and the transition from chance to biological evolution in the history of life

Eugene V Koonin*

Address: National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD 20894, USA

Email: Eugene V Koonin* - koonin@ncbi.nlm.nih.gov

* Corresponding author

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Accepted: 31 May 2007

This article is available from: <http://www.biology-direct.com/content/2/1/15>

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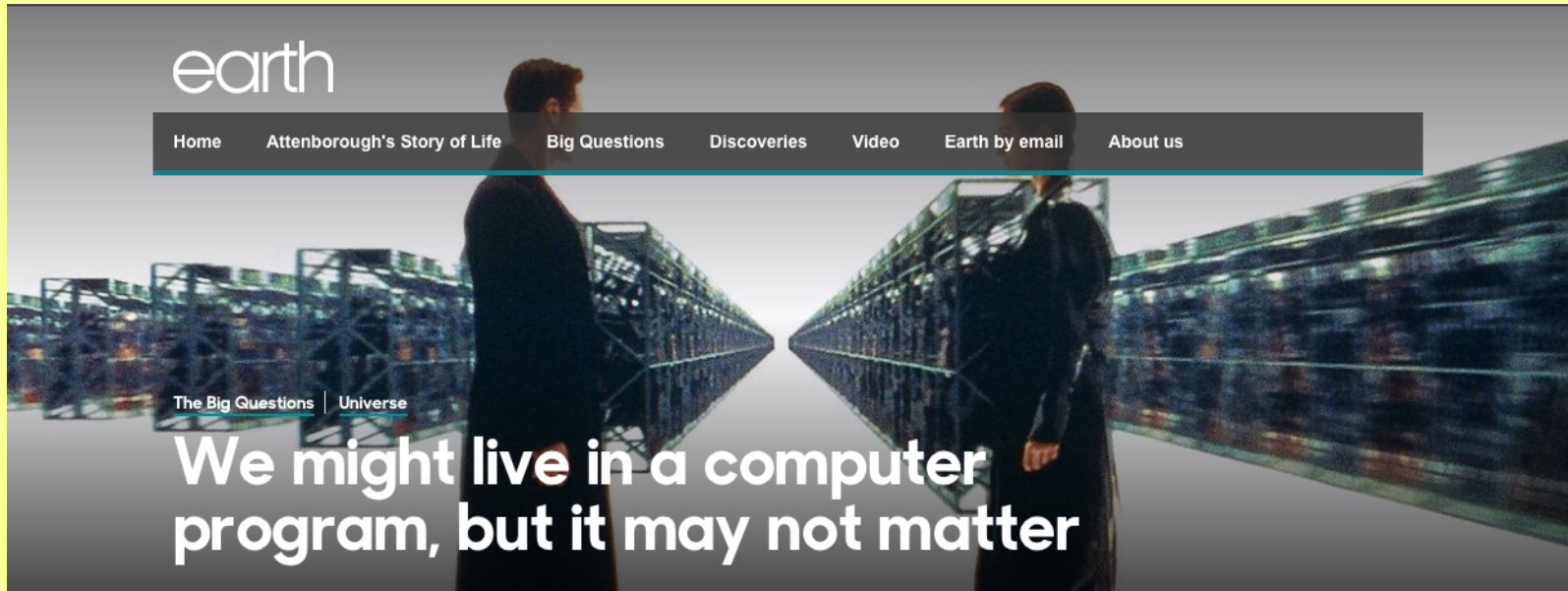
Eugene Koonin
Senior Investigator
NIH

Abstract

Background: Recent developments in cosmology radically change the conception of the universe as well as the very notions of "probable" and "possible". The model of eternal inflation implies that all macroscopic histories permitted by laws of physics are repeated an infinite number of times in the infinite multiverse. In contrast to the traditional cosmological models of a single, finite universe, this worldview provides for the origin of an infinite number of complex systems by chance, even as the probability of complexity emerging in any given region of the multiverse is extremely low. This change in perspective has profound implications for the history of any phenomenon, and life on earth cannot be an exception.

Hypothesis: Origin of life is a chicken and egg problem: for biological evolution that is governed, primarily, by natural selection, to take off, efficient systems for replication and translation are required, but even barebones cores of these systems appear to be products of extensive selection. The currently favored (partial) solution is an RNA world without proteins in which replication is catalyzed by ribozymes and which serves as the cradle for the translation system. However, the RNA world faces its own hard problems as ribozyme-catalyzed RNA replication remains a hypothesis and the selective pressures behind the origin of translation remain mysterious. Eternal inflation offers a viable alternative that is untenable in a finite universe, i.e., that a coupled system of translation and replication emerged by chance, and became the breakthrough stage from which biological evolution, centered around Darwinian selection, took off. A corollary of this hypothesis is that an RNA world, as a diverse population of replicating RNA molecules, might have never existed. In this model, the stage for Darwinian selection is set by anthropic selection of complex systems that rarely but inevitably emerge by chance in the infinite universe (multiverse).

The universe could be a computer program



Several physicists have suggested that our Universe is not real and is instead a giant simulation. Should we care?

By Philip Ball

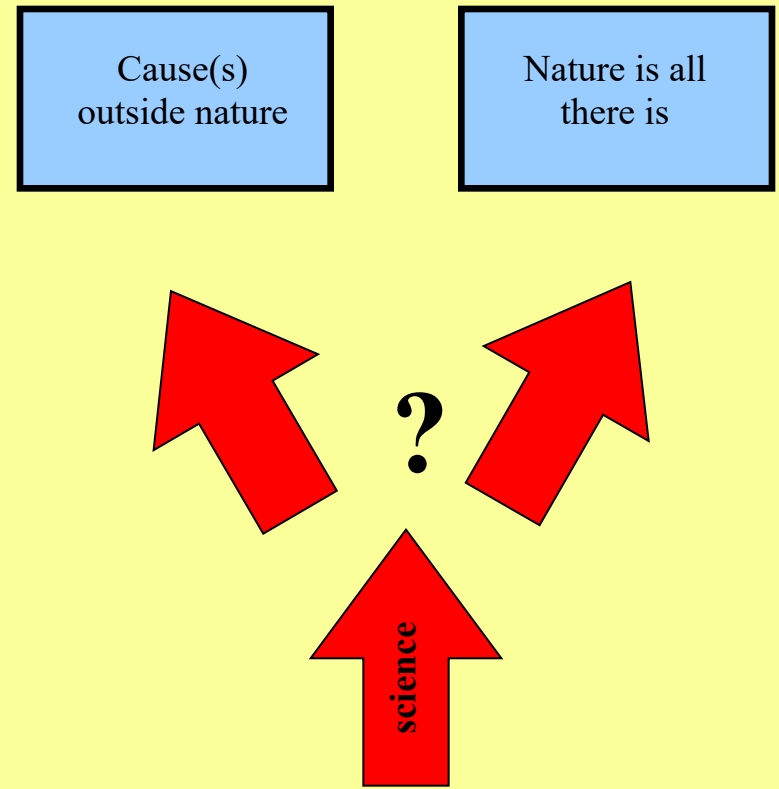
5 September 2016

This story is part of BBC Earth's "Best of 2016" list, our greatest hits of the year. [Browse the full list.](#)

Distinguishing science from naturalistic philosophy

“... we have a prior commitment, a commitment to **materialism**. It is not that the methods and institutions of science somehow compel us to accept a material explanation of the phenomenal world, but, on the contrary, we are forced by our **a priori adherence to material causes** to create an apparatus of investigation and a set of concepts that produce material explanations, no matter how counterintuitive, no matter how mystifying to the uninitiated. **Moreover that materialism is absolute, for we cannot allow a Divine Foot in the door.**”

Richard Lewontin, *New York Review of Books*, Jan. 9, 1997.



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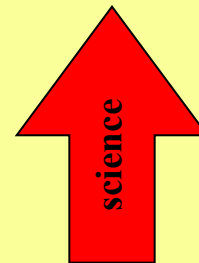
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What’s wrong with a Divine Foot in the door?

Whose job is it to decide that for the rest of society?

What does “cannot allow” mean?

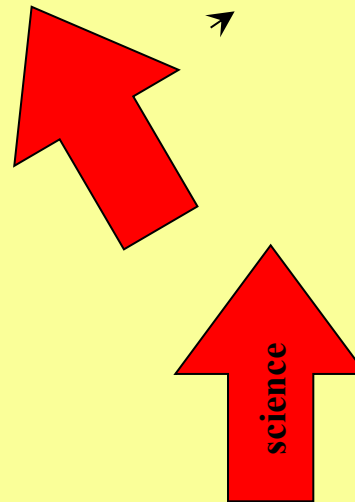
Nature is all
there is



Distinguishing science from naturalistic philosophy

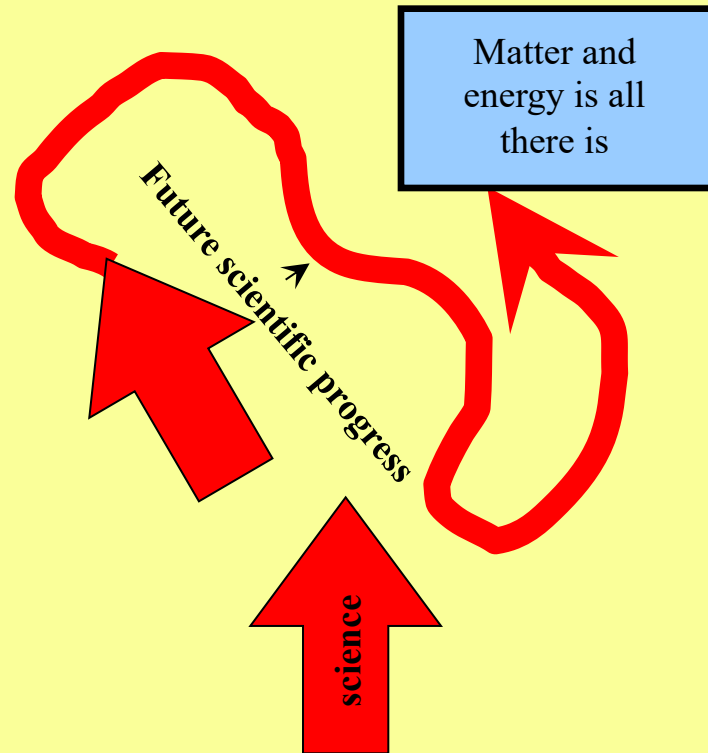
If materialism is not true,
then one must choose between
the **impossible** and the
unthinkable

Matter and
energy is all
there is



Distinguishing science from naturalistic philosophy

Faced with a choice between the **impossible** and the **unthinkable**, a committed naturalist chooses the impossible and hopes (has faith) that naturalistic solutions will eventually be found.



Distinguishing science from naturalistic philosophy

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Theism
Creation
Religion
Irrational
Subjective
Fantasy

Naturalism
Evolution
Science
Rational
Objective
Reality

What’s wrong with a Divine Foot in the door?

Whose job is it to decide that for the rest of society?

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In this view science can
only be on one side!

Redefinitions of life:

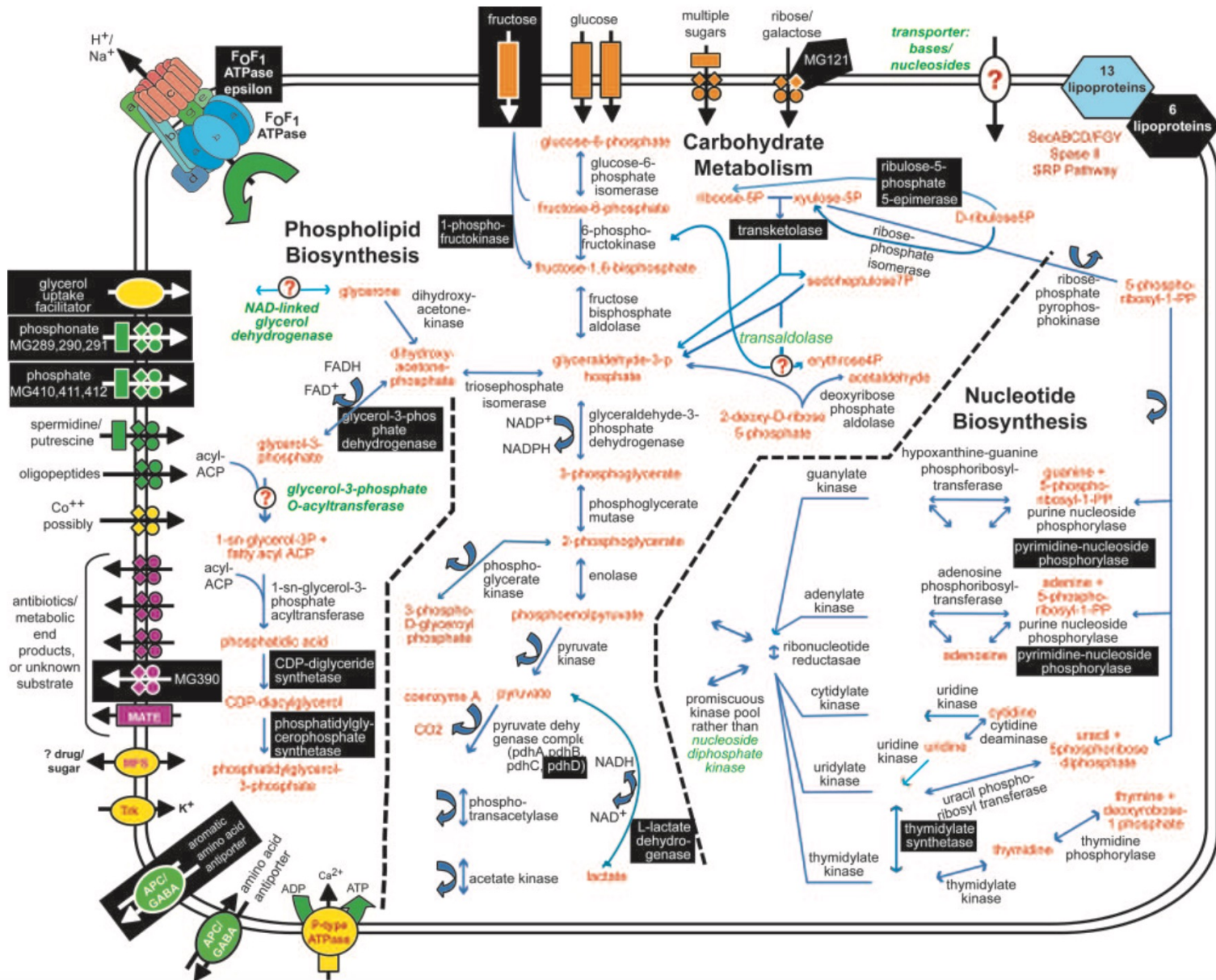
“a self-sustaining chemical system capable of generating replicates, where those replicates are imperfect, and where those imperfections are themselves replicable.”

Cleland and Chyba 2002 cited in Benner 2015 Paradoxes

“life is that which is subject to Darwinian evolution.

The interconnected nature of DNA, RNA, and proteins means that it could not have sprung up *ab initio* from the primordial ooze, because if only one component is missing then the whole system falls apart – a three-legged table with one missing cannot stand.”

The Improbable Origins of Life on Earth, Universe Today – Space and Astronomy News, Posted on [January 28, 2024](#) by [Paul M. Sutter](#).



Essential genes in *M. genitalium*, from PNAS 2006, 103, 425.

<https://trienens-institute.northwestern.edu/news-events/news/2023/unlocking-the-mysteries-of-chirality-induced-spin-selectivity-ciss-in-isolated-molecules.html>

<https://www.science.org/doi/10.1126/science.adj5328>

Non-Enzymatic Assembly of a Minimized RNA Polymerase Ribozyme

Falk Wachowius^[a, b] and Philipp Holliger^{*[a]}

ChemSystemsChem 2019, 1, e1900004 (1–4)

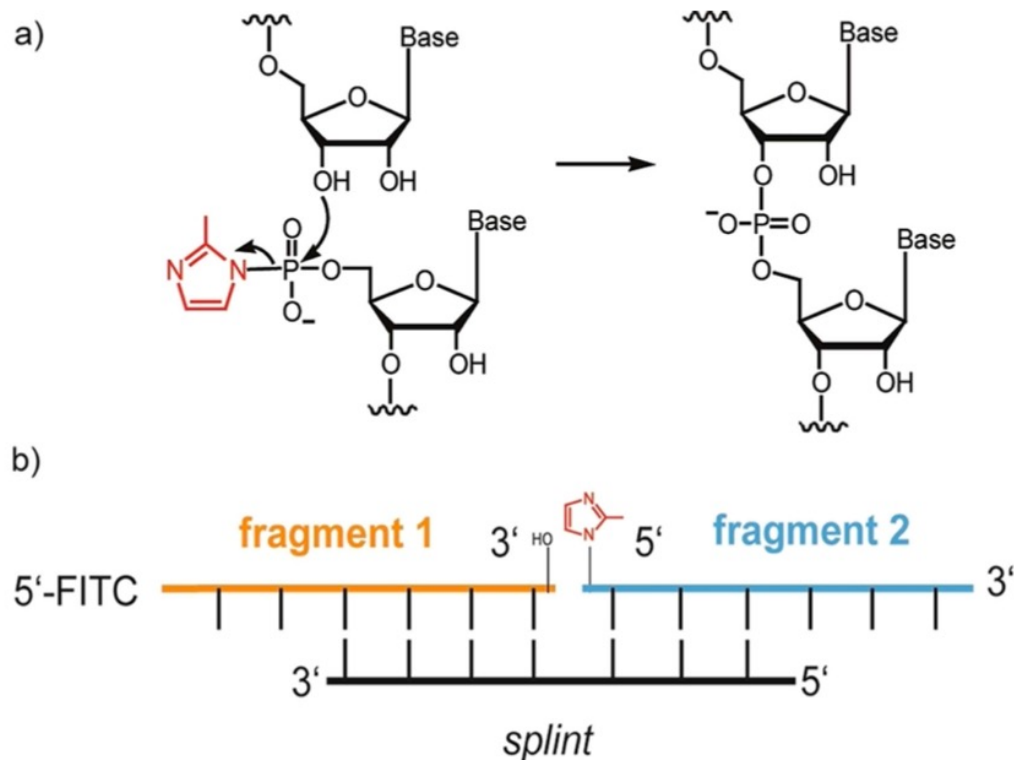


Figure 1. RNA ligation by phosphoimidazolide (Imp) activation chemistry.

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What relevance does this have to OoL?

such Imp-activated RNA fragment pools. Specifically, we show assembly of a newly selected minimal RNA polymerase ribozyme variant (150 nt) by RNA templated ligation of 5'-2-methylimidazole-activated RNA oligomers <30 nucleotides long. Our results provide support for the possibility that complex RNA structures could have emerged from pools of activated RNA oligomers and outlines a path for the transition from non-enzymatic/chemical to enzymatic RNA replication.

Amplification of RNA by an RNA polymerase ribozyme

David P. Horning^{a,b} and Gerald F. Joyce^{a,b,1}

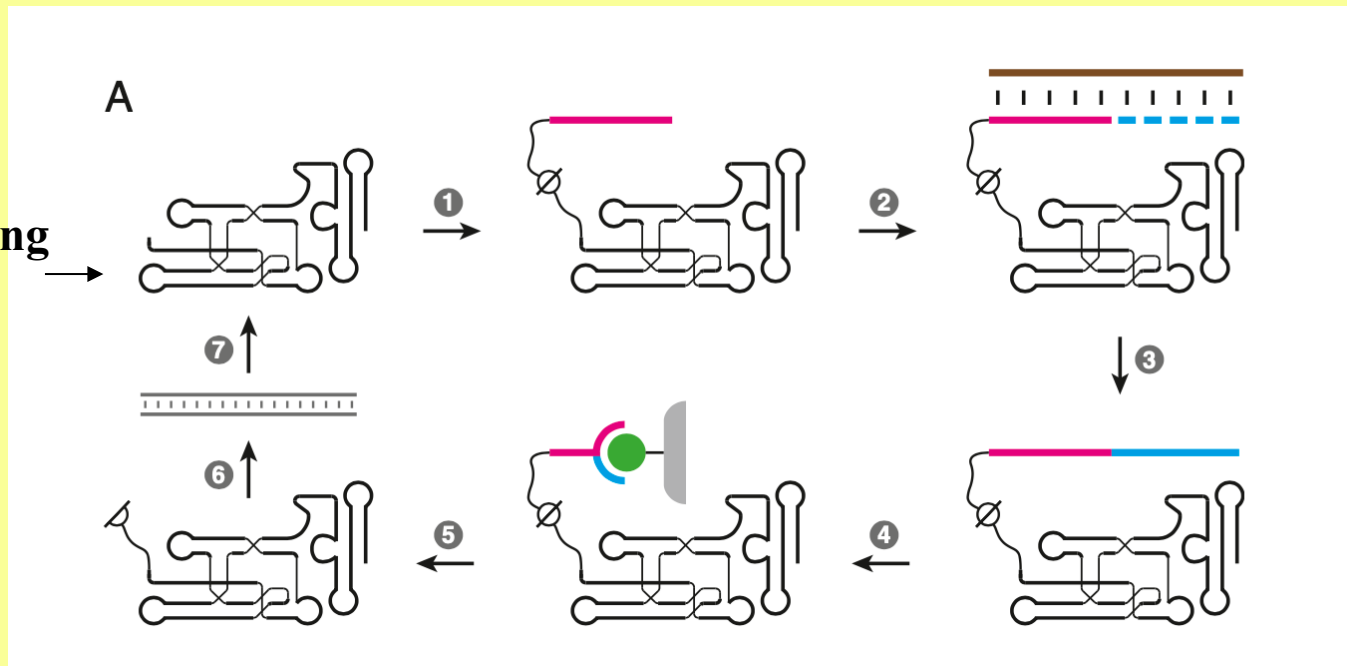
^aDepartment of Chemistry, The Scripps Research Institute, La Jolla, CA 92037; and ^bSkaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037

Contributed by Gerald F. Joyce, June 23, 2016 (sent for review May 17, 2016; reviewed by Ronald R. Breaker and Peter J. Unrau)

In all extant life, genetic information is stored in nucleic acids that are replicated by polymerase proteins. In the hypothesized RNA world, before the evolution of genetically encoded proteins, ancestral organisms contained RNA genes that were replicated by an RNA

polymerization, this approach does not select directly for chemical bond formation, but rather for the efficient and accurate transfer of functional information from template to cRNA. A polymerase variant isolated after 24 rounds of evolution exhibited dramatically

RNA
 polymerizing
 enzyme



RNA-based evolution

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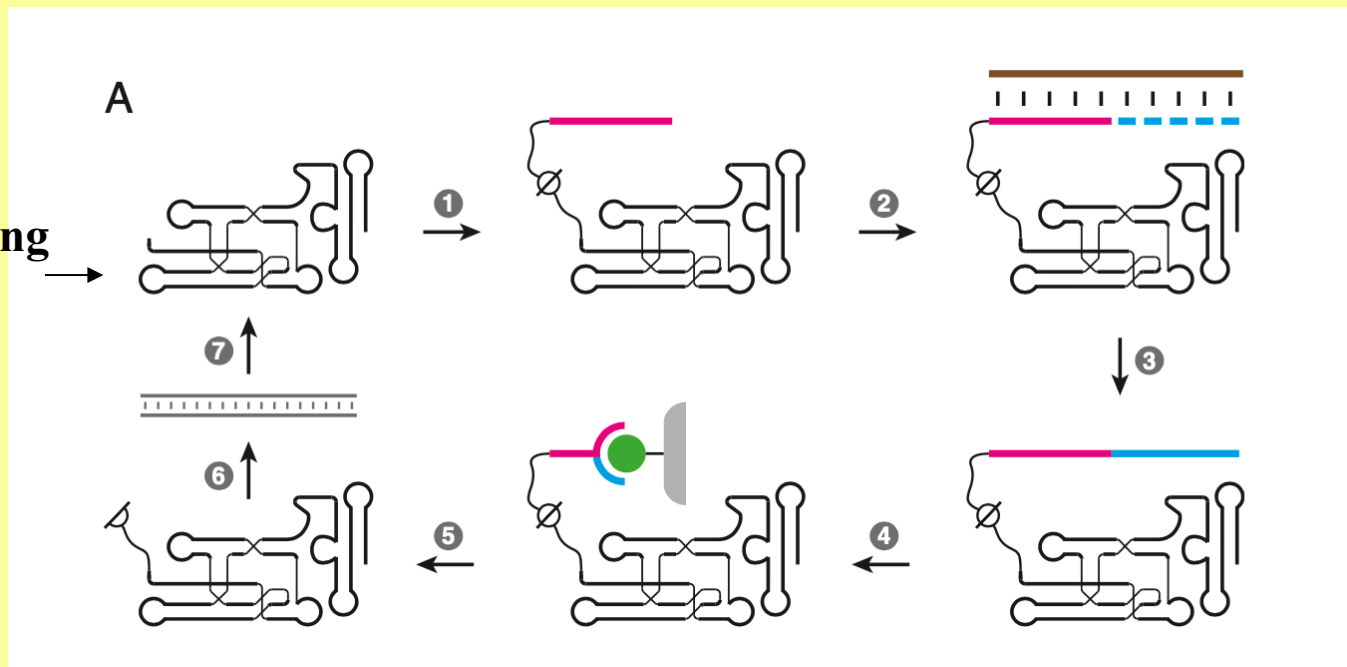
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mutations were incorporated each cycle

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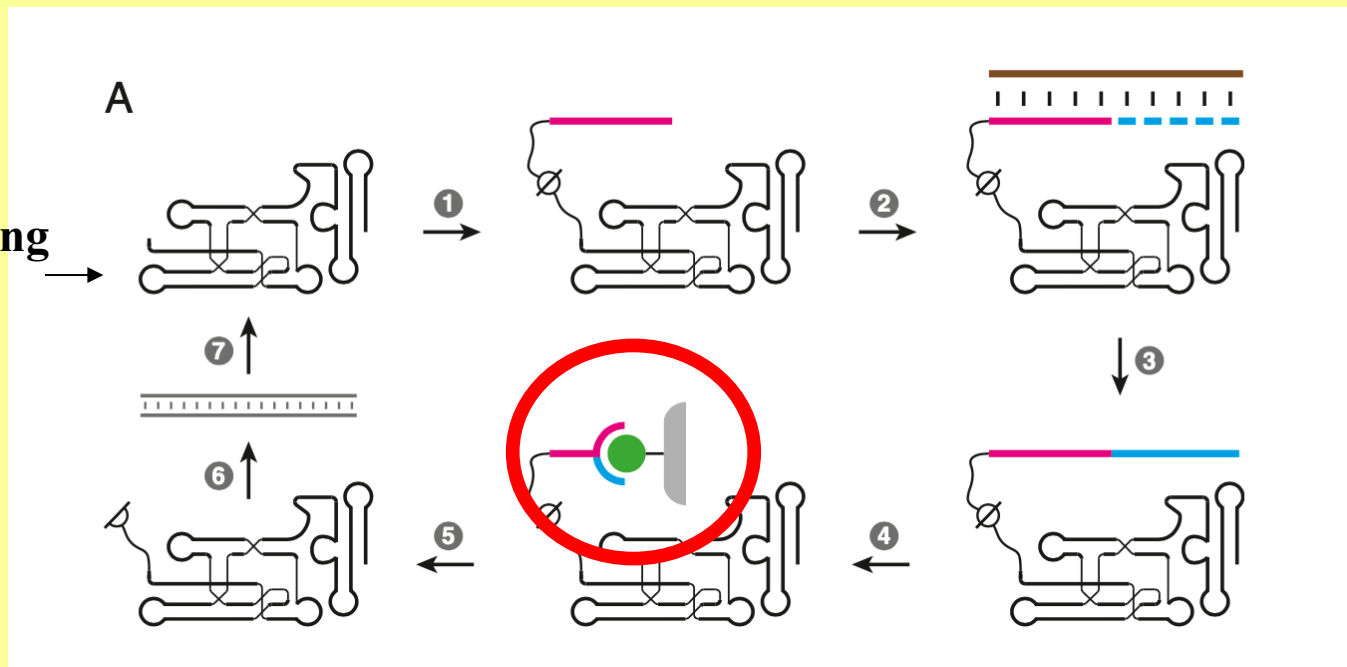
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Selection based on binding, and enzymatic activity

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In vitro evolution:

A pool of synthetic **oligodeoxynucleotides** was prepared, encoding the WT polymerase ribozyme randomizing all nucleotide positions between the two primer regions at a frequency of 10% per position.

The **DNA** was made double-stranded by primer extension using SuperScript II reverse transcriptase

The yield of full-length dsDNA was 165 pmol (55% extension efficiency), corresponding to 10^{14} distinct sequences. The **dsDNA** was amplified by five cycles of **PCR** and then **purified** using the **Qiagen PCR purification kit**.

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In vitro evolution:

- in vitro **transcription** of the population of ribozymes
- tethering of an RNA primer to the 5' end of the ribozymes
- ribozyme-primer conjugates were annealed to a template RNA, and the primer was extended by the ribozyme in the presence of the four NTPs
- the extended materials were captured on streptavidin, the template RNA was removed, and the desired products were selected by either **a gel-shift method** or capture of **a ribozyme-synthesized aptamer**.

Transcription: DNA to RNA

Reverse Transcription: RNA to DNA

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In vitro evolution:

-For **gel-shift selection**, the products were separated by **PAGE** and the fully extended materials were eluted from the gel and **reverse transcribed**. For **aptamer-based selection**, the ribozyme portion of the products was **reverse transcribed** to form an **RNA–cDNA heteroduplex**, and then extended materials that contained a functional aptamer were captured by binding to the corresponding ligand (cyanocobalamin or GTP).

-In both cases, the isolated **cDNA** was **amplified by PCR**, followed by in vitro **transcription** to generate the progeny population of ribozymes.

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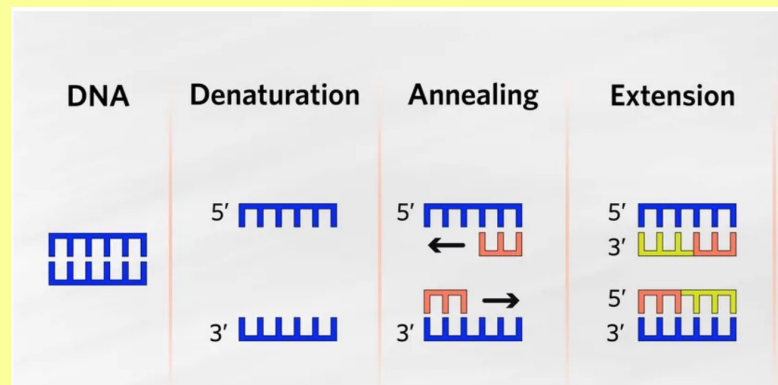
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RNA polymerization: RNA enzyme + RNA template + RNA primer

RNA amplification by riboPCR: 400 nM 24-3 polymerase, 200 nM each primer, and varying amounts of template, + other stuff, **Bio-Rad C1000 thermocycler**



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ABSTRACT:

Thus, the two prerequisites of Darwinian life—the replication of genetic information and its conversion into functional molecules—**can now be accomplished with RNA in the complete absence of proteins.**

CONCLUSION:

To achieve fully autonomous RNA replication, these two activities must be combined and further improved to provide a polymerase ribozyme that can replicate itself and other ribozymes of similar complexity. **Such a system could, under appropriate conditions, be capable of self-sustained Darwinian evolution and would constitute a synthetic form of RNA life.**