“Nought may endure but mutability”

P.B. Shelley

Mutability:
key to the nature and origin of life

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• OVERALL
exploring the origin of life
until precision replication started. (clearly biology)

• HERE quick overview.
In 2003 Lynn Margulis visited, and she commented that

“Theories of the origin of life are about chemistry. Where is the theory of the origin of biology?”

Here we assume that the necessary chemicals and environment were available, and show how the natural development would produce a first extremely simple living cell which would be the First Terrestrial Common Ancestor.
What is lifelike?

- Is it alive? So……
- Do I test it for metabolizing?
- Do I check whether it is reproducing?
- Do I check whether it is evolving?

- No. I prod it to see if it will move. I put it in different environments to see what it does.
- I test it for diverse behaviors.
Life is...

An information driven \((it \ has \ diverse \ options)\) survival system \((it \ and \ descendants \ make \ survival \ choices)\) that is implemented in carbon chemical processes. \((implemented \ in \ chemistry \ is \ different \ from \ being \ chemistry.)\)
• It makes logical decisions based on its internal state and its environment.

IF....THEN ....
IF NOT.........
Survival System

• A survival system counters the tendency for disorder to increase by use of environmental energy and matter flows.

These systems are also called DISSIPATIVE
However

The definition also includes crystals with life.

Crystals in saturated solutions operate the logical process:

IF arriving molecule fits the lattice, THEN ADD, IF NOT, REJECT.
Reliance on the environment

• Life relies on the environment for energy and materials.

• Crystals rely on the environment for occasional supply of a saturated solution.
Reproduction

• When a crystal is broken in two, the parts continue to grow separately.

• When a cutting is taken from a plant, the two parts continue to grow separately.

• Life has also developed spontaneous separation into parts.
Life differs from crystals...

- It makes **multiple** IF...THEN decisions.

- Life is able to add or take away IF...THEN decisions. (by evolution or intelligence)

- It is versatile. It can change itself. This is called **MUTABILITY**
How did life make this transition?

• And what gave it the capability to make this transition, this mutability?

• Carbon chemistry!

• But this created problems of production and selection.
Natural Selection

• Decides which of the variant developments of a mutable system will thrive.

• Failure to thrive results in rarity or extinction.

• The information content of life is totally derived from survival selection.

(This is the Principle of Life)
How Natural Selection made Life

Membranes are like crystals, self-forming and adding available membrane molecules.

But when in convecting water, they break.

The rest of the development was a process:
a) Solve the membrane survival problem.
b) Solve the residual problem created by solving the membrane survival problem.
c) Solve the residual problem created by solving the solving of the survival problem - etc.
System Structure - A Template in Time

1. Get needed materials )
   MATTER
2. Make system cohesive)
3. Perform the process core (make itself)]
   ENERGY
4. Extract environmental energy and matter]
5. Develop responses (life) } INFORMATION
6. Select and modify responses (intelligence) }
Talk Sequence *(Uphill all the way!)*

7) Summary

6) A gene/enzyme and the chirality transition


4) Vesicle development.

3) Carbon, water, phosphorus.

2) Systems development.

1) Mutability.
Mutability:
key to the nature and origin of life
Life is organized but how did that happen

- A big enough mess does not self-organize (at least not in my office).
- In general messy things stay messy, so how is life different?
- Organizing takes work (energy).
- Producing order uses energy.
- Energy must come from the environment.
What is Life 1944

*[Life has]* “Organization maintained by extracting order from the environment.”

Later, Prigogine called the process *dissipative* when in the presence of an energy flow, and a matter flow, a process *makes or changes order*. Natural dissipative systems include hurricanes (from solar energy) and plate tectonics (from Earth heat flow).
Zircons maintained by tectonics

4.3 Gy. old core

Growth rings

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50 μm
Zircons are zirconium silicate crystals. Their high melting point lets them survive in magma pools. Old ones grow layers, new ones are born in magma pools when crustal rock is subducted. Re-emerging at the surface, zircons form part of magmatic rock.

They are subducted. Earth processes erode them, break them in two (reproduction), move them, and form them into sedimentary rock. Some are totally destroyed in the process.

Growth = repair = metabolism.
Oparin (1961) recognized three characteristics of life, **metabolism, reproduction and mutability**.

**Mutability** is the capacity to evolve, to modify, but retain essential characteristics. Stabilizing features will be maintained in survival forms.
Non-living processes seen in crystals

- **Metabolism** = growth and repair.
- **Reproduction** = breaking in two, and then both parts metabolize.

BUT *(most)* Crystals are not mutable!

For proto-life, metabolism and reproduction had to be initiated and sustained by the environment as they are for a crystal.
• Membranes played the role of a crystal, selecting molecules to link to them, and when broken in two, both parts grew – reproduction.

• The edge of a membrane selected parts of molecules for their “hydrophobicity”.

• Reactions with phosphates strengthened membranes.
How Origin of Life worked 2

- Stronger membranes needed polymers for transport & structure.
- Triphosphates linked amino acids. These then served for transport and structure.
- In turn the selection of amino acids selected the linkage of triphosphate nucleosides for better performance. In use, the phosphates were reduced to monophosphates.
- Linked monophosphate nucleosides discovered they could replicate.
Metabolism and Reproduction

Life only needed to take over these tasks when:
1) The environment changed.
2) Mutability offered better survival options.

Before that the environment must have offered:
A) Chemical ingredients.
B) Energy.
C) Selection opportunities.
So

• **Metabolism First** is true. It is just that such processes are not unique to life.

• **RNA World** is correct, in that life forms with RNA came before ones with DNA. BUT, a nucleotide (RNA) is a created molecule! Earlier processes drove development of RNA!

• **Mutability makes the difference.** It includes both change of role or function & addition of new roles or functions.

• Mutability distinguishes life from non-life.
Mutability: key to the nature and origin of life
Mutability, metabolism and reproduction.

Part 2
System issues

Complex systems develop from simpler ones
• Mutability is needed to transition from non-life through increasing decision making to a point where there is an organism capable of genetic processes including mutation.
“If a thing is worth doing, it is worth doing badly.”

And Biology adds: modification and evolution MAY fix its problems!
The rate of creating **order** in the crucial part of the process must be greater than the rate of creating **disorder** there.

However a minimal rate of creating disorder and extinction is also needed to have evolution.

So the process cannot be extremely inefficient at the start. **A thing is NOT** worth doing too badly!
Biology 000  Not Alive

Environment

- Supplies Energy
- Supplies Matter
- Environment fluctuates and erodes

Entity

- Accepts or rejects
- Effect on environment
- Continues to exist, or does not (Natural Selection)
Environment

• Supplies Energy
• Supplies Matter

• Environment fluctuates and erodes

Entity

• Accepts or rejects and additional behaviors.
• Mutable

• Effect on environment

• Continues to exist, or does not (Natural Selection)
Mutability: key to the nature and origin of life

Mutability, metabolism and reproduction.
Complex systems develop from simpler ones

Part 3
Why Carbon, Water, Phosphorus?

CARBON, WATER AND PHOSPHORUS, CONDENSATION REACTIONS.
Mutability requires diversity

- Carbon makes more compounds than other atoms, because its covalent bonds can be tetrahedral, pulled into a plane, or pairs or triple bonds pulled together.

- The problem in using this diversity is both in making, and in distinguishing what one has. Functional groups don’t hack this!

- Shape selection and/or manufacture is needed.
Enzymes – a biology, chemistry distinction

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**Enzyme**

1. **Substrate**: Atoms and molecules (e.g., ATP, glucose) that can be acted upon by enzymes.
2. **Active Site**: A region on the surface of an enzyme where substrate molecules are recognized and subsequently acted upon.
3. **Enzyme-Substrate Complex**: Formation of an enzyme-substrate complex, leading to bond weakening and product formation.
4. **Products**: Resultant molecules after reaction with the enzyme.

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**OR right to left**

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(C) E.M. Collins 2001
Selection of shapes

• To select shape requires shape selectors which have themselves been selected by shape!

This needs one of:
A) Life has existed since the Big Bang. **NO**
B) A fantastic accident – e.g. the 707 from a junk yard by way of a tornado. **NO**
C) A bootstrap process, in which diversity and selection led to precision. **YES**
Water - first selector of carbon compounds.

Miller-Urey did not find "Beilstein"
Murchison meteorite

Space performed its own Miller-Urey.
Hydropathy

Carbon compounds ionic bonds,
co-valent bonds
Water distinguishes.

Some compounds have both bond types. Energetics favors an ionic end in water, and a covalent part of the molecule away from it. First separation of such carbon molecules, produces micelles and vesicles – protocells with no interior content.
Both genes and proteins are polymers. The molecules are linked by Condensation Reactions.

• \( \text{ROH} + \text{HR}' \rightarrow \text{RR}' + \text{H}_2\text{O} \)

• In a watery environment this requires energy, which comes from phosphates.

• This is selection by manufacture!
\[ P_2O_5 + 2 H_2O = H_4P_2O_7 \]
The phosphate ionizes to \( 4H^+ + P_2O_7^{4-} \)
This is unstable in water, forming inorganic phosphate:
\[ P_2O_7^{4-} + H_2O \rightarrow 2 HPO_4^{2-} \]
Reactions of simple polyphosphates such as pyrophosphate and ATP normally proceed extremely slowly in all but highly acidic media. However, the two reactions can be combined.
\[ R[OH+H]R' + P_2O_7^{4-} \rightarrow 2 HPO_4^{2-} + RR' \]
How was pyrophosphate energized?

Many Possibilities

a) By volcanoes.
b) Came from space already energized.
c) By solar energy through various processes e.g. lightning.

BUT it seems impossible to have started life without pyrophosphate.

In life forms it is re-energized by using the electric charge across a membrane.
Mutability: key to the nature and origin of life
Mutability, metabolism and reproduction.
Complex systems develop from simpler ones
Carbon and water, condensation reactions

Part 4 Like a cell without an innards
Self-Assembling Amphiphilic Molecules

This is a fuzzy edge.
• For a given molecule, Either:

1) Standard sized micelles.

2) Standard thickness sheet, which can link to itself making a sphere with an inner hole.
Vesicles

Vesicles are bilayers that have folded into a three-dimensional spherical structure, like a micelle with two layers of molecules.

Vesicles form because they get rid of the edges of bilayers, protecting the hydrophobic chains from the water.

Molecules that form vesicles usually have a double chain.

Biological membrane molecules spontaneously form vesicles in solution.
Vesicle strengthening

• “Natural” (meteoritic) membrane molecules tend to have single carbon chains.
• Pyrophosphates and or thioesters can link them to double chains, so strengthening the molecule.
• Further strengthening is by forming phospholipids.
• This path is chosen by Natural Selection
To make connections, sometimes an H or an OH is missing. Therefore there was a benefit from the phosphate being connected to a sugar, which provided multiple H and OHs for bonding.

Ribose – 4 OHs link to 2 phosphates, one base, and have one left over for **condensation reactions**. t-RNA

Deoxyribose -3 OHs are purely used for **reproduction**, and so need one less OH, - DNA
Phospholipids made impermeable membranes
Therefore membrane improvement must have been associated with transport improvement and to keep reproduction, with membrane rigidization, the cytoskeleton (Z-ring pre-cursor).

Transport requires molecules that link across a membrane and provide a path.

Both required polymer production.
Mutability: key to the nature and origin of life

Mutability, metabolism and reproduction.

Complex systems develop from simpler ones

Carbon, water and phosphorus, condensation reactions

Vesicle development

Part 5 structures and the selection of building materials

SIMULTANEOUS DEVELOPMENT OF POLY-AMINOACIDS AND GENETIC CODE.
Amino acids provide distinguishable ends

\[
\text{Amino} \quad \text{Carboxylic Acid}
\]

\[\text{NH}_2R\text{COOH} \quad \text{NH}_2\text{RCO}[\text{OH} \quad + \quad \text{H}\text{NH}R'\text{COOH} \quad \rightarrow \quad \text{NH}_2\text{RCONH}R'\text{COOH} + \text{H}_2\text{O}\]

Further amino acids may be added by pyrophosphate.
Amino acids can be distinguished by their preference for the interior or the exterior of a bilayer. One needs:

a) A linkage of amino acids that can live in the membrane.

b) With ends that live outside the membrane. The first crude alpha-helix like structures. First selection of chirality to protect membrane interior from NH by curling around it.
ATP & RNA

RNA polymer

ATP Molecule

Glue

Selector

Assistant
Nucleobases select still preserved in the genetic code

<table>
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<tr>
<th>2nd base in codon</th>
<th>U</th>
<th>C</th>
<th>A</th>
<th>G</th>
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<td>Phe</td>
<td>Ser</td>
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Also START

Inside membrane

Outside membrane
Whole-Residue Hydrophobicity Scales

Interface Scale

- Adenine
- Guanine
- Cytosine
- Uracil

\( \Delta G \) (water to bilayer, kcal mol\(^{-1}\))

Charged

W. C. Wimley and S. H. White
A and U as middle codon

Charged go with water.
Covalent go in membrane.

Number from the left
A codes 7 amino acids + STOP,
#s 1,2,3,4,5,6 & 8 are ionic
U codes 5 amino acids + START
#s 20,18,17,15,13 are covalent, hydrophobic.

Of course the triphosphate is required to make the linkage.
## Development of the genetic code

### Code Translation

<table>
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<th>Translation</th>
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<tr>
<td>U</td>
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<tr>
<td>A</td>
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### Second letter

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<tr>
<td>C</td>
<td>Leu</td>
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<tr>
<td>A</td>
<td>Start</td>
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<tr>
<td>G</td>
<td>Val</td>
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<td>Ala</td>
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<td>Arg</td>
</tr>
<tr>
<td>A</td>
<td>Asn/Lys</td>
</tr>
<tr>
<td>G</td>
<td>Gly</td>
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</tbody>
</table>

### Version 1

- **U**: hydrophobic
- **A**: hydrophilic

### Version 2

- **U**: hydrophobic
- **A**: Start

### Version 3

Today

Development of the genetic code
Addition of G and C

• U is a poor selector,
• It often links to G instead of A.

• Once G was in the chain, it would have selected C to fit the ladder width.

• GG and CC provided an opportunity to code for Glycine or Proline, needed to fold β sheet proteins.
Linking the linkers

- There are four issues,

1) Code molecules transition from triphosphate to monophosphate for the code molecules. ATP etc. is needed to make the link.

2) Linkage along the chain. Sugar from one nucleotide links to the phosphate of the next.

3) Weak H bonds linking across the ladder.

4) The code selects the amino acid sequence (membrane or water-preferring).

It must have found a way!
Mutability: key to the nature and origin of life

- Mutability, metabolism and reproduction
- Complex systems develop from simpler ones
- Carbon, water and phosphorus, condensation reactions
- Vesicles
- Simultaneous development of poly-amino-acids and genetic code.

Part 6 How to make precision copies

THE FIRST GENE/ENZYME AND THE TRANSITION TO CHIRALITY
The RNA was used in short chains, and the selection of the next amino acid was just by its position (water sensitivity).

The amino acids were of all kinds (including non-biological and both chiralities).

Both chiralities of ribose were used.

An RNA chain could not yet reproduce itself.
However

• Linking of RNA randomly continued, and so short chains developed.
• One specific 5 nucleotide RNA chain can replicate, at least when it is monochiral.
• The probability of the ribose being monochiral is $\sim 1/16$.
• The probability of the right base sequence is $1/1024$.
• Overall probability of production $1/16,384$. 
Once this happened

- The protocell that could replicate had a huge advantage and would take over.
- Since the ribose had selected the chirality, this selection would also apply to the amino acids, since the ribose links to them to start the linking process.

So the entire protocell operation would abruptly become chiral.
What has not happened

• These developments belong to a world of RNA plus membranes plus simple proteins.

As of yet.

• No ATPase.
• No Krebs cycle.
• No Ribosome
• No DNA
• No protein enzymes
Mutability: key to the nature and origin of life
Mutability, metabolism and reproduction.
Complex systems develop from simpler ones
Carbon, water and phosphorus, condensation reactions
Vesicles
Simultaneous development of poly-amino-acids and genetic code.
The first gene/enzyme and the transition to chirality
How Natural Selection made Life

• First selection was a membrane acting like a crystal.
• Second selection was membrane survival improvement.
• Third selection was membrane edge dividing the parts of molecules by their hydrophobicity.
• Fourth selection was for gene shape, setting up the first gene.
First Selection

• Organic material and energized phosphate were provided by the environment.
• In water, lipid molecules formed vesicles.
• These were disrupted by convection and heat.
Second selection

- Phosphates and sugars made stronger membrane materials.
- Protocells could then break in two.
Third selection

- The sugar and phosphate could link amino acids together, but protocells where the selection was base-aided, ATP and UTP developed more useful structures.

- ATP and UTP paired and coded START and STOP and linked amino acids across the membrane boundary.
Fourth selection

- RNA linked to itself, and by a 1/16,384 chance, formed a molecule that could reproduce itself.
- It was the first gene-enzyme.
- The system abruptly became chiral.
- This was the First Terrestrial Ancestor.

- Further evolution developed capability for environmental deficiencies and other environments.
Why CHONP?

- Carbon – mutability
- Hydrogen – naturally with C, N, O.
- Water, H-OH – divides by hydrophobicity
- Nitrogen, NH – alternate to OH in polymers
- Phosphorus – polymer creation.

- Metals ….. Catalysts
- Sulfur ……. Energy pathways
END
How we got into this mess

• **Metabolism, Reproduction** and **Evolution** were seen as the characteristics of life.
• But since evolution could not be seen as an observed characteristic, it was ignored.
• However, the **option to evolve** is THE key characteristic of life. It explains the nature and origin of life.

Focus on metabolism and reproduction was misplaced.
Passive System

Environment ➔ Structure

Destruction
Dissipative non-living system

Environment

Energy

Matter

Structure & Behavior

Destruction
Dissipative Living System
e.g. a microbe

Environment

Energy

Destruction

Matter

Mutable Reproduction

Survival

Changes

Structure & Behavior
Dissipative Intelligent System
e.g. animal life

Environment

- Energy
- Matter
- Destruction

Structure & Behavior

- Mutable Reproduction
- Survival
- Changes

S.C.M.
Intelligence

- Survival
How can we look for life without knowing what we are looking for?

It is a recipe for failure.
What is different about this talk? 1

1) Origin of Life operates by Natural Selection all the way. (Natural Selection requires production, but not precision reproduction).

2) Metabolism and reproduction occur in crystals, NON-LIVING objects.
Issues

• How to break out of the paradigm that life requires life to create it?

• How did the genetic code and proteins and genes co-develop?
Equilibrium abundance $A$:

Subscripts $f =$ formation, $d =$ destruction

$$A \frac{dN}{dt}_d = \frac{dA}{dt}_f$$

Equilibration time $\sim A/ \frac{dA}{dt}_f$

All else being equal, the abundance $A$ is proportional to $1/ \left( \frac{dN}{dt} \right)_d$.

If ingredients are added, the “fitter” becomes proportionately more abundant.
What is different about this talk? 2

Includes *(can’t avoid)*:

- Production of first *membranes*.
- Energizing of *polymer* formation.
- Origin of *nucleotides* and tri-phosphates.
- Origin of the *genetic code*.
- First crude *protein*-like molecules.
- Production/reproduction of first *gene-enzyme*.
- How life became *chiral*. 