How did chemistry become biology?

Or: can we make life in the lab?

Sijbren Otto
Complexity → Emergent behaviour
THE BIG QUESTIONS IN SCIENCE

How did life start?

Can we make life?

*Can we achieve Darwinian evolution in a fully synthetic chemical system?*
What is life?

**NASA definition:**
Life is a self-sustained chemical system capable of undergoing Darwinian evolution.

But...

Lonesome George

Mule
Characteristics of Life

- Compartamentalised
- Dissipates energy
- Stable yet out of equilibrium
- Ability to reproduce
- Errors in reproduction followed by Darwinian selection
- Ability to adapt
- In water

Would we recognise a chemical system that has these characteristics as being alive?

Is there a clear separation between life and non-life or are these extremes on a continuum?
compartmentalization

replication

metabolism
Searching for clues to the origin of life

top-down
what can we learn from current life?

bottom-up
what can we deduce from conditions on early earth?
what can we learn from chemistry?
Top-down: chemical fossils in life

Assumption: current proteins merely speed up reactions that also occur spontaneously

Current life: DNA \xrightarrow{\text{transcription}} \text{mRNA} \xrightarrow{\text{translation}} \text{proteins}

Chicken-and-egg problem
- Proteins are synthesised based on DNA templates
- DNA is synthesised by proteins
Did these systems evolve side-by-side?

The RNA world hypothesis:
- RNA can carry hereditary information
- RNA has a limited ability to replicate itself
- RNA can catalyse reactions

*Problem: RNA is often a lousy catalyst*
**Bottom-up approach: prebiotic chemistry**

**History of the earth**

Formation of the earth: $4.6 \text{ Ga} (= 4.6 \times 10^9 \text{ years})$

Heavy meteorite bombardment until $3.9-3.8 \text{ Ga}$

Earliest fossils: $3.8 \text{ Ga}$

→ Life appeared relatively quickly

**What were the ingredients of the prebiotic soup?**

Geochemistry: what molecules occurred on early earth?

Prebiotic chemistry: aims to establish by experiment the chemical structures, reactions and pathways that may have been involved in producing the last common ancestor.
Searching for clues: Geochemistry

Probable requirement: concentrated solution of organic molecules

Where is the primordial soup most tasty for life?

- Oceans, but perhaps too dilute (so maybe in coacervates)
- Hot start: hydrothermal vents
  The most primitive forms of current life are found in hot water, but...
- Cold start: inclusions in ice
- Muddy start: absorption to clays
  - heterogeneous catalysis by metal ions
  - concentration of reactants by absorption

Prebiotic chemistry: Synthesis of α-amino acids

Urey-Miller experiments (1950s)

\[ \text{CH}_4, \text{NH}_3, \text{H}_2, \text{H}_2\text{O} + \text{electric discharge} \rightarrow \text{glycine} + \text{alanine} + \text{aspartic acid (racemic)} \]

Flow of energy and material

Many, many other products...
Prebiotic synthesis of sugars

J. Chromatogr. 1982, 244, 281.
Prebiotic synthesis

Nature’s building blocks were around

$\alpha$-amino acids

nucleobases

sugars

among many many other molecules!!

How were Nature’s macromolecules made?
Origin of life – state of the art

Building blocks of life

Pre-biotic soup

RNA world

Present-day life

Chiral symmetry breaking

Compartmentalisation

Self-replication/autocatalysis

Metabolism
Chemistry tends to diverge

A + B + C →


What tamed chemistry?
Prebiotic soup
- building blocks of life present
- far from equilibrium

Earth before life started...

Prebiotic soup diagram:
- A: energy
- B: far from equilibrium
- C: energy
- D: at equilibrium

Diagram showing the energy levels and the transition from far from equilibrium to at equilibrium.
What reaction is most efficient at converting molecules?

Spontaneous reaction: $A + B \rightarrow P$

Catalysed reaction: $A + B + \text{catalyst} \rightarrow P + \text{catalyst}$

Autocatalytic reaction: $A + B + P \rightarrow 2P$ \hspace{1cm} (P = autocatalyst)

A far-from-equilibrium recycling system is likely to be dominated by products autocatalytic reactions. Autocatalytic systems attract matter.
Dynamic Molecular Networks

Perspective article:
Jianwei Li, Piotr Nowak, Sijbren Otto
J. Am. Chem. Soc. 2013, 135, 9222
From diversity to specificity through molecular recognition
Disulfide formation and exchange

\[ \text{SH} + \text{HS} \xrightleftharpoons{\text{O}_2, \text{H}_2\text{O}} \text{SS} \]

\[ \text{SS} \xrightleftharpoons{\text{pH 7-9}} \text{S} + \text{S} \]
What can tame chemistry?

Phase changes
Autocatalysis (rare!)

David Komaromy, manuscript in preparation
Can we make life in the lab?
Our recipe for life

1 – Develop an exponential replicator
2 – Enable mutations
3 – Operate system far from equilibrium
4 – Allow for Darwinian evolution of the replicators
5 – Facilitate invention of new traits (open-ended evolution)
Emergence of an exponential replicator from a soup

Animation: see www.otto-lab.com
Exponential replication by elongation/fragmentation

Mathieu Colomb-Delsuc, Elio Mattia, Nat. Commun. 2015, 6, 7425
The chemical details

R = peptide

Mechanical energy determines replicator structure

Science 2010, 327, 1502
Autocatalysis!

spontaneous emergence

emergence triggered by seeding

seeded with 5 mol% 7mer

Science 2010, 327, 1502
Our recipe for life

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Mixing building blocks: enabling mutations

Two sets of 6mer replicators emerge sequentially.

Jan Sadownik, Nature Chem. 2016, 8, 264
Ancestral relationship!

Set B

Set A

Jan Sadownik, Nature Chem. 2016, 8, 264
Our recipe for life

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A replication-destruction regime

1mer + 3mer + 4mer

replicator

CSTR

8mer

[trifluoroethanol]

strength of peptide-peptide interactions
Adaptation to a changing environment

Giulia Leonetti, manuscript in preparation
Current open questions

Open-ended Darwinian evolution requires more than replication, variation, and selection

- Structural space must be larger than sampled space
- How to facilitate emergence of new function / step-changes in efficiency of replication??
Acknowledgements

Collaborators:
Marc Stuart
Jasper van der Gucht / Duc Nguyen
Siewert-Jan Marrink
Wim Hordijk