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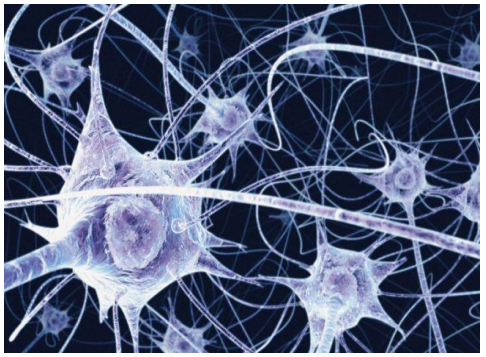
How did chemistry become biology?

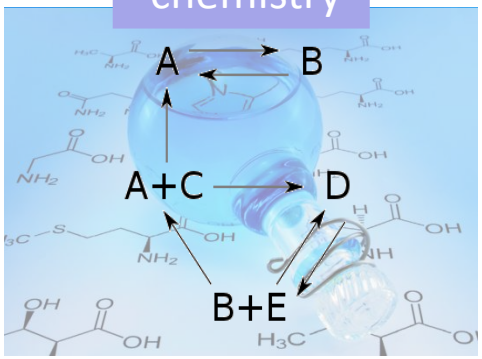
Or: can we make life in the lab?

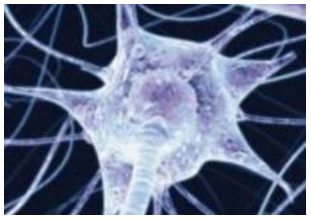
Sijbren Otto

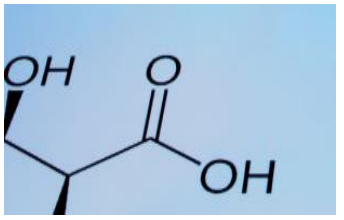
Complexity → Emergent behaviour

Systems chemistry









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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

- Compartmentalised
- Dissipates energy
- Stable yet out of equilibrium

} metabolism

- Ability to reproduce
- Errors in reproduction followed by Darwinian selection
- Ability to adapt

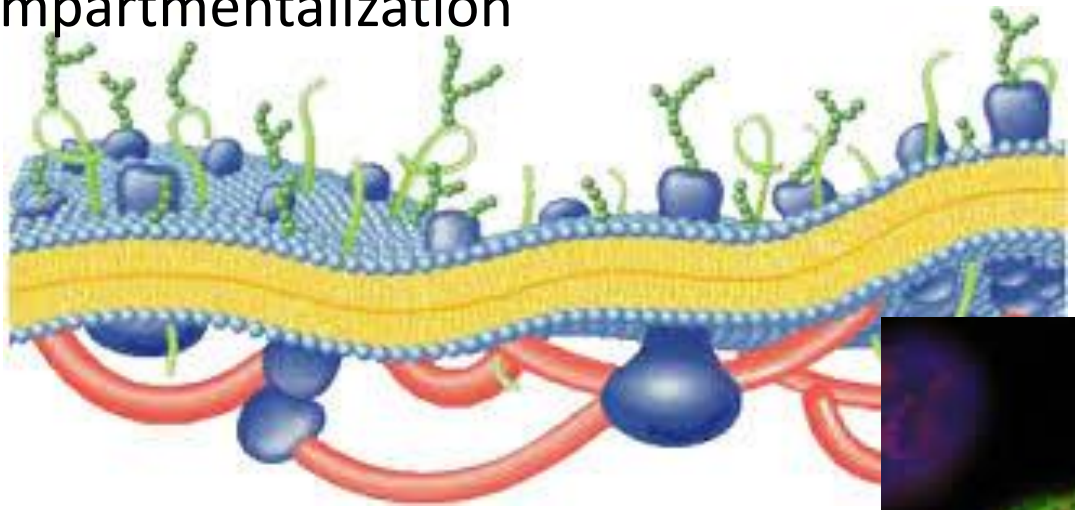
} Darwinian evolution

- In water

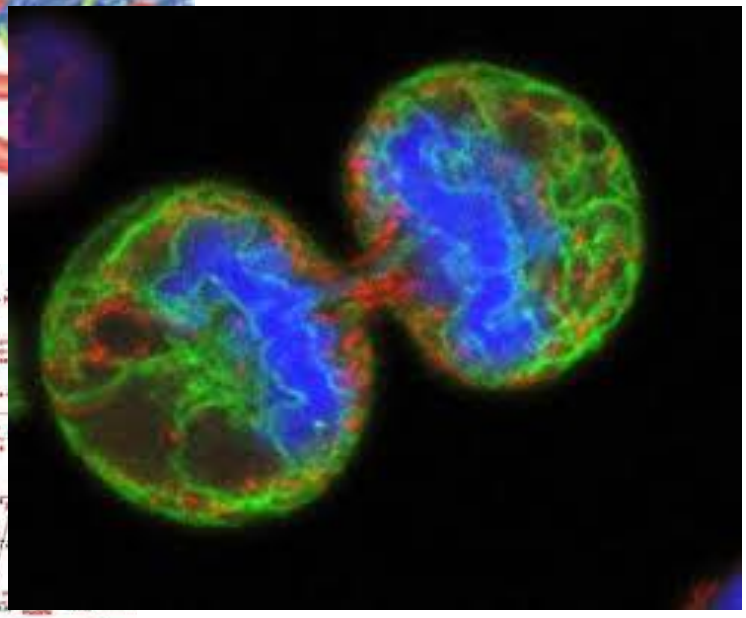
Would we recognise a chemical system that has these characteristics as being alive?

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

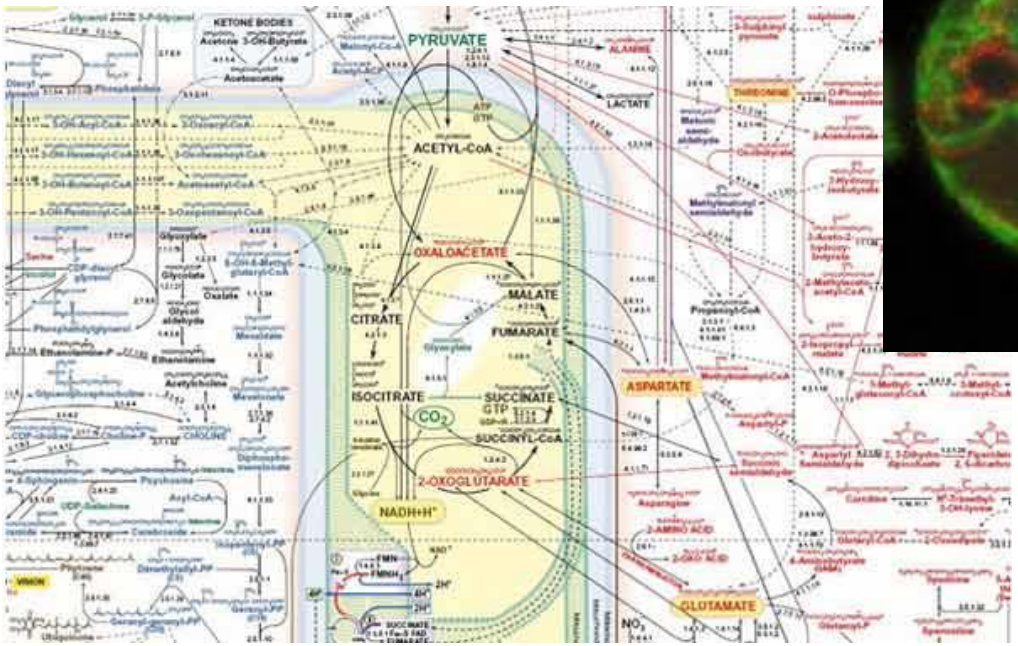
compartmentalization



replication



metabolism



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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 $\xrightarrow{\text{transcription}}$ mRNA $\xrightarrow{\text{translation}}$ proteins

Chicken-and-egg problem

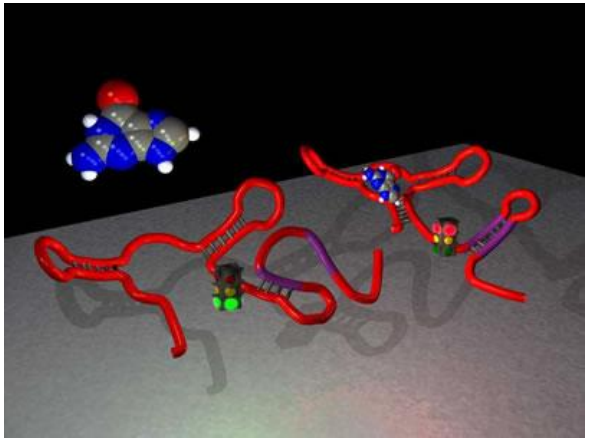
- Proteins are synthesised based on DNA templates
- DNA is synthesised by proteins

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

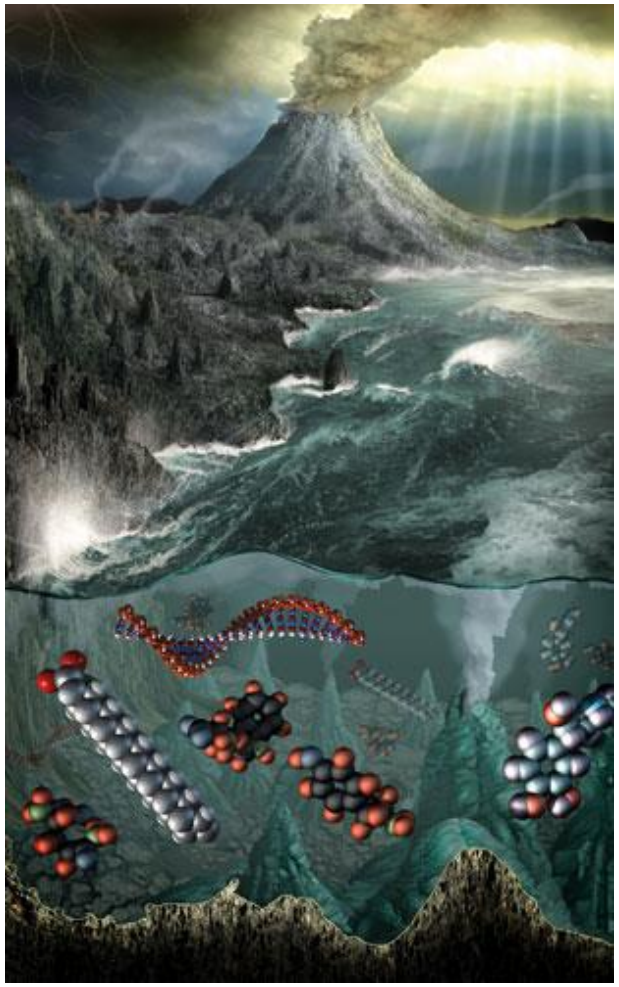
History of the earth

Formation of the earth: 4.6 Ga (= 4.6 x 10^9 years)

Heavy meteorite bombardment until 3.9-3.8 Ga

Earliest fossils: 3.8 Ga

→ Life appeared relatively quickly

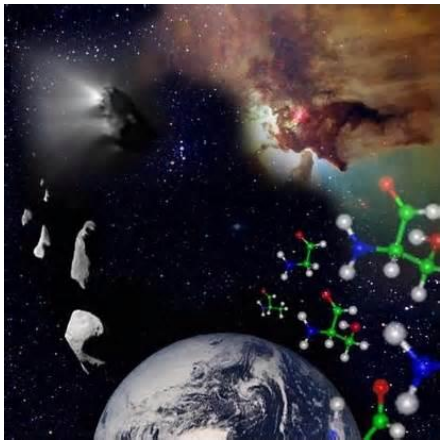


What were the ingredients of the prebiotic soup?

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

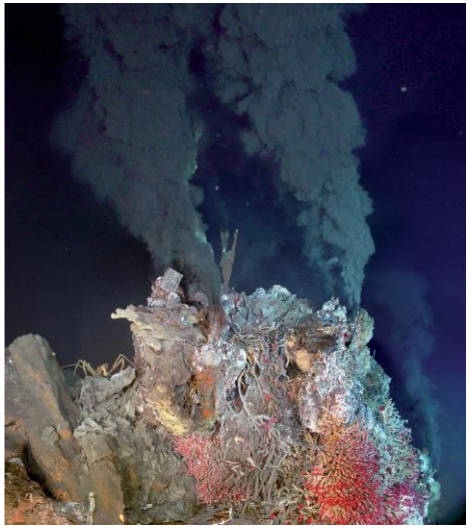


Probable requirement:
concentrated solution of organic molecules

Where is the primordial soup most tasty for life?

- Oceans, but perhaps too dilute (so maybe in coacervates)
- Hot start: hydrothermal vents[1]

  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



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[1] Martin: *Nature Rev. Microbiol*. **2008**, *6*, 805

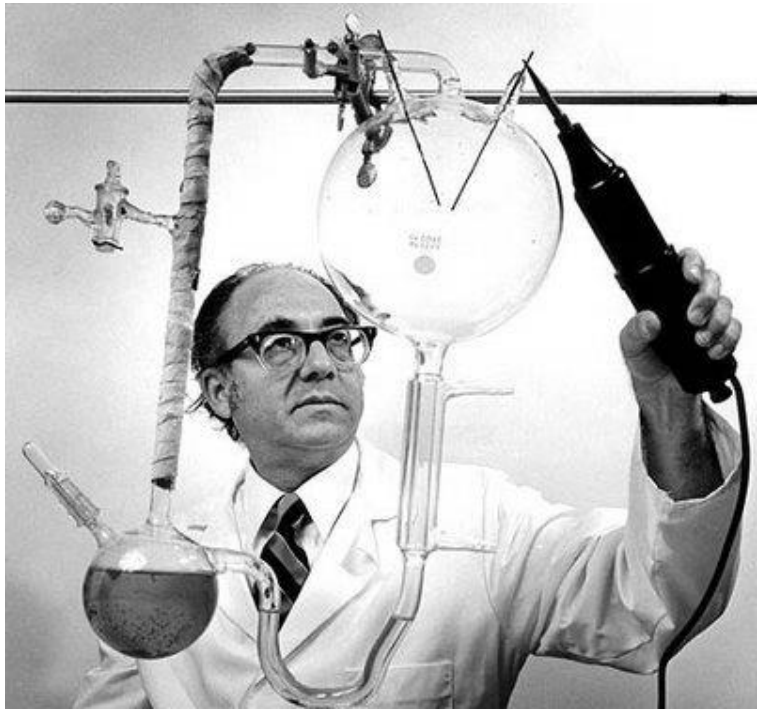
Prebiotic chemistry: Synthesis of α-amino acids

Urey-Miller experiments (1950s)

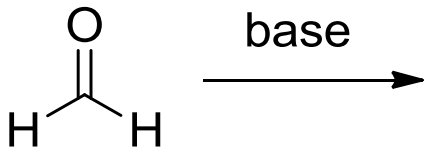
CH_4, NH_3, H_2, H_2O + electric discharge → glycine + alanine + aspartic acid (racemic)

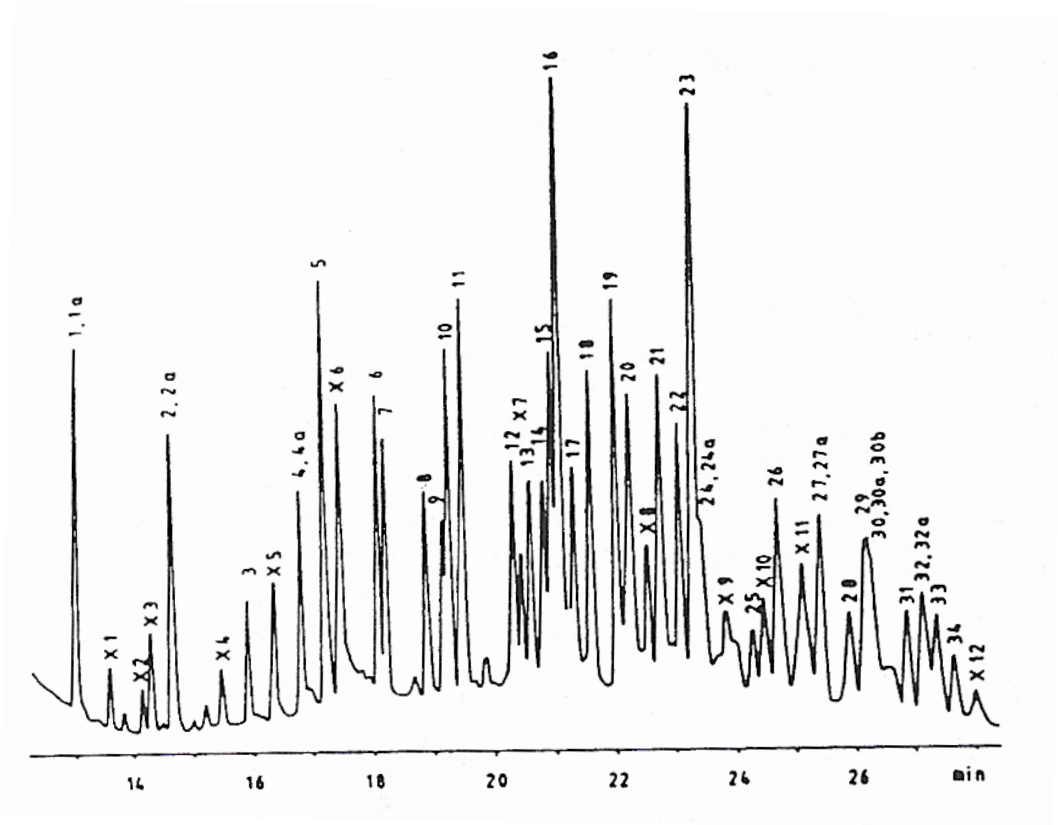
Flow of energy and material

Many, many other products…



Prebiotic synthesis of sugars





GC-MS analysis after derivatisation

J. Chromatogr. **1982**, *244*, 281.

Prebiotic synthesis

Nature's building blocks were around

α-amino acids

nucleobases

sugars

among many many other molecules!!

How were Nature's macromolecules made?

Origin of life – state of the art

Present-day life

RNA world

?

?

Building blocks of life

Pre-biotic soup

Chiral symmetry breaking

Compartmentalisation

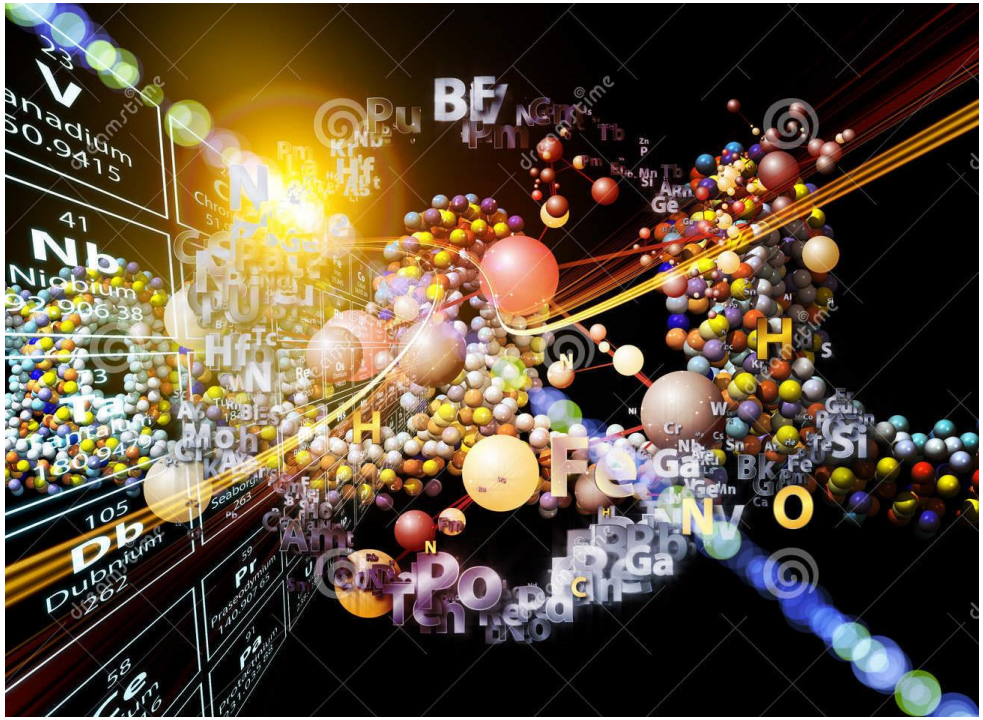
Self-replication/autocatalysis

Metabolism

Chemistry tends to diverge

A + B + C ⟶ A-A + A-B + A-C + B-B + B-C + C-C + A-A-A + A-A-B + A-A-C + A-B-B + A-B-C + A-C-C + B-B-B + ...

combinatorial explosion!

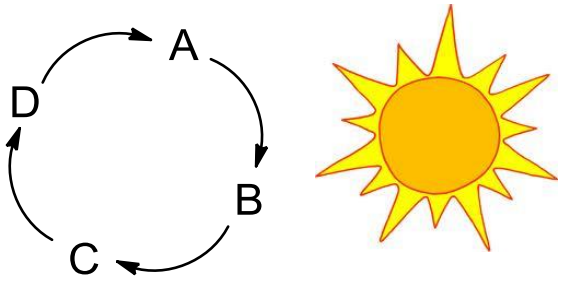


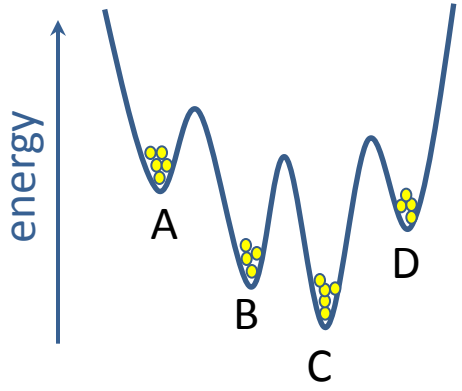
What tamed chemistry?

Earth before life started…

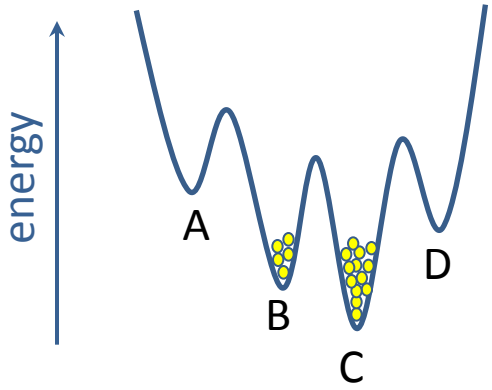
Prebiotic soup

- building blocks of life present
- *far from equilibrium*





far from equilibrium



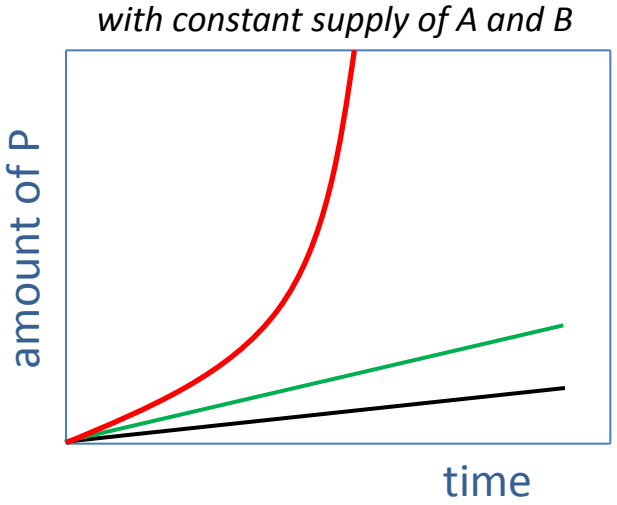
at equilibrium

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: $A + B + P \rightarrow 2P$ (P = autocatalyst)

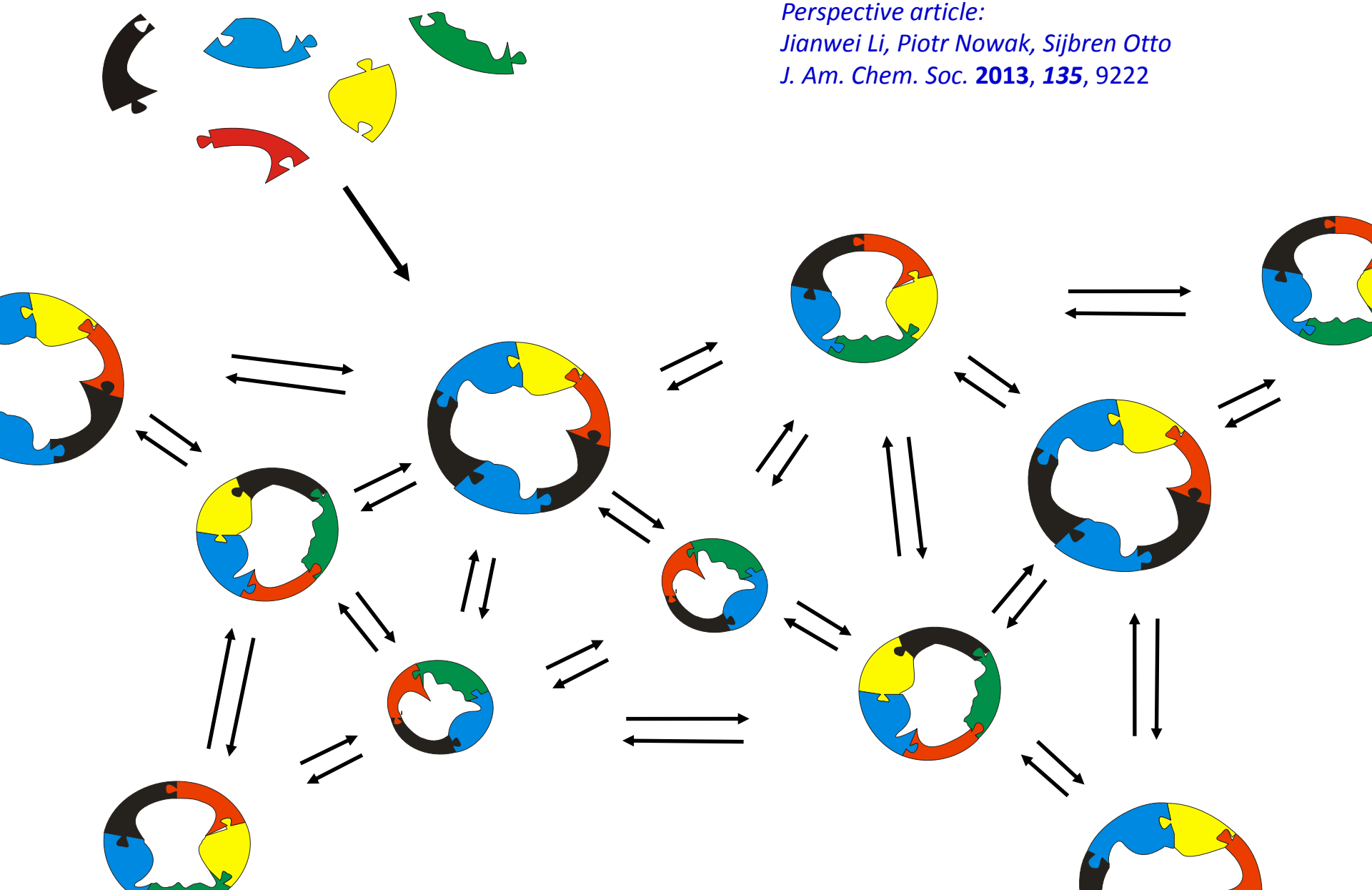


A far-from-equilibrium recycling system is likely to be dominated by products autocatalytic reactions

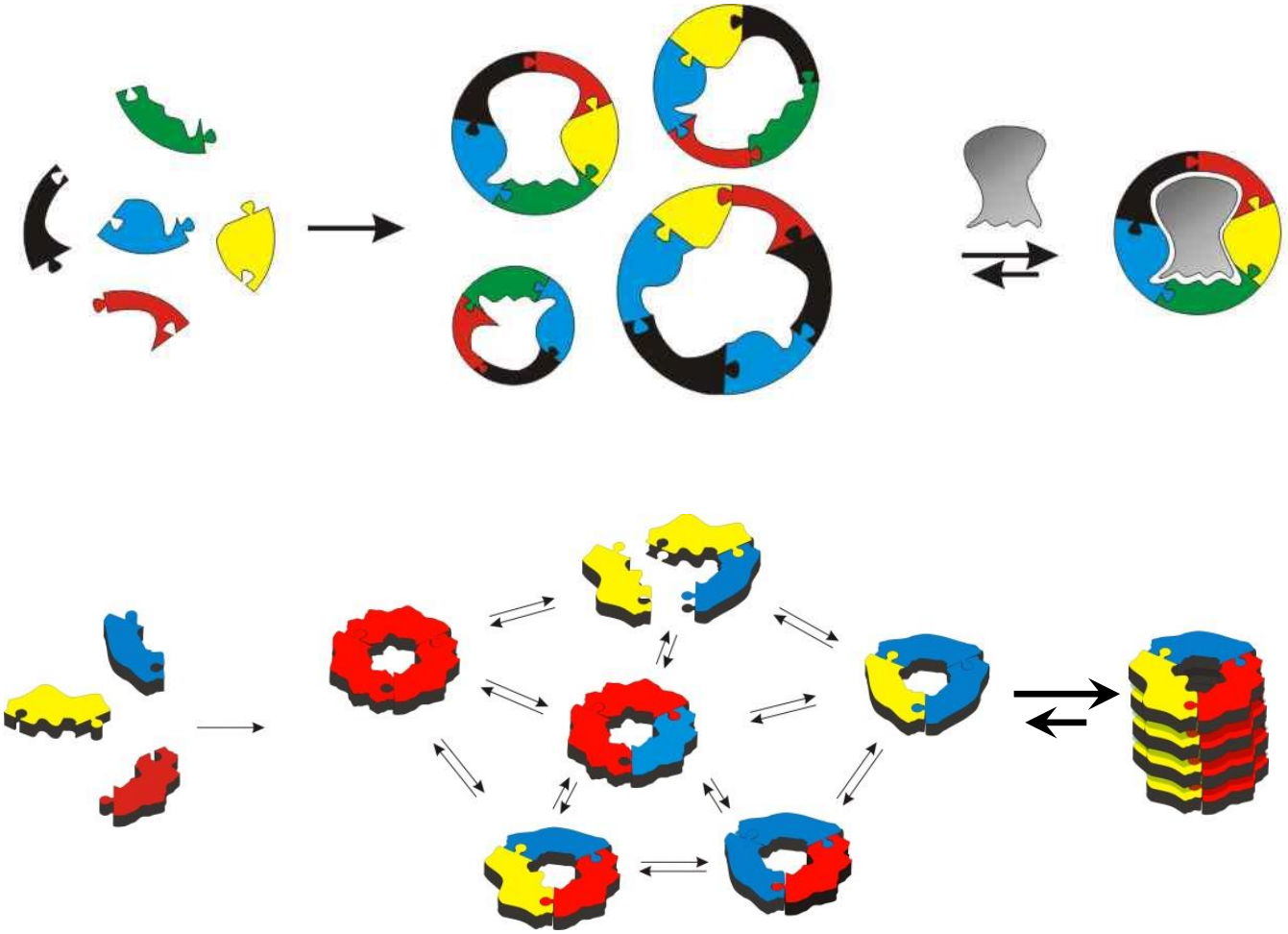
Autocatalytic systems attract matter

Dynamic Molecular Networks

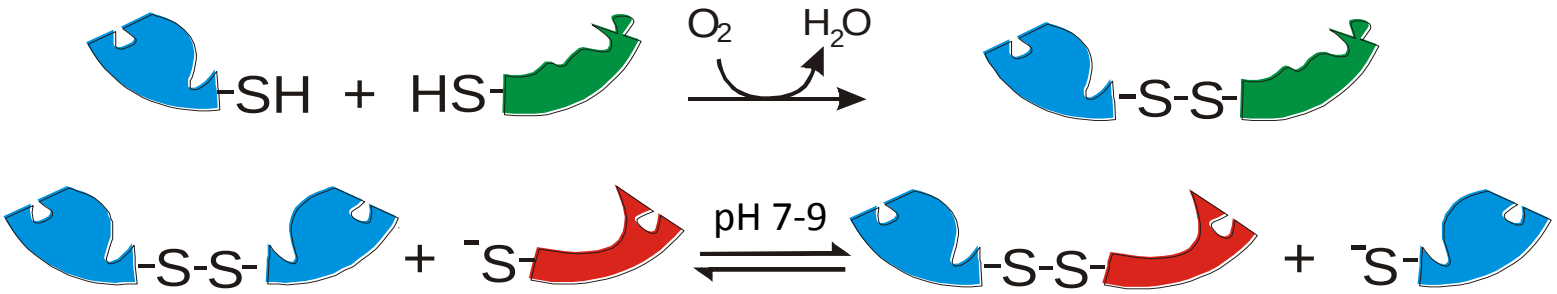
Perspective article:
Jianwei Li, Piotr Nowak, Sijbren Otto
J. Am. Chem. Soc. **2013**, ***135***, 9222



From diversity to specificity through molecular recognition



Disulfide formation and exchange



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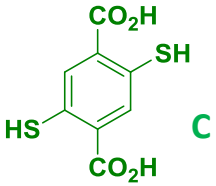
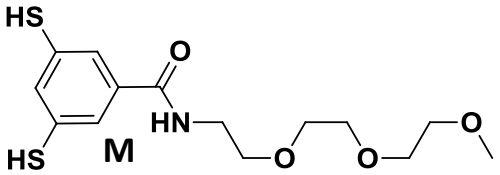
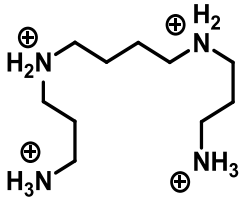
J. Am. Chem. Soc. **2000**, *122*, 12063

What can tame chemistry?

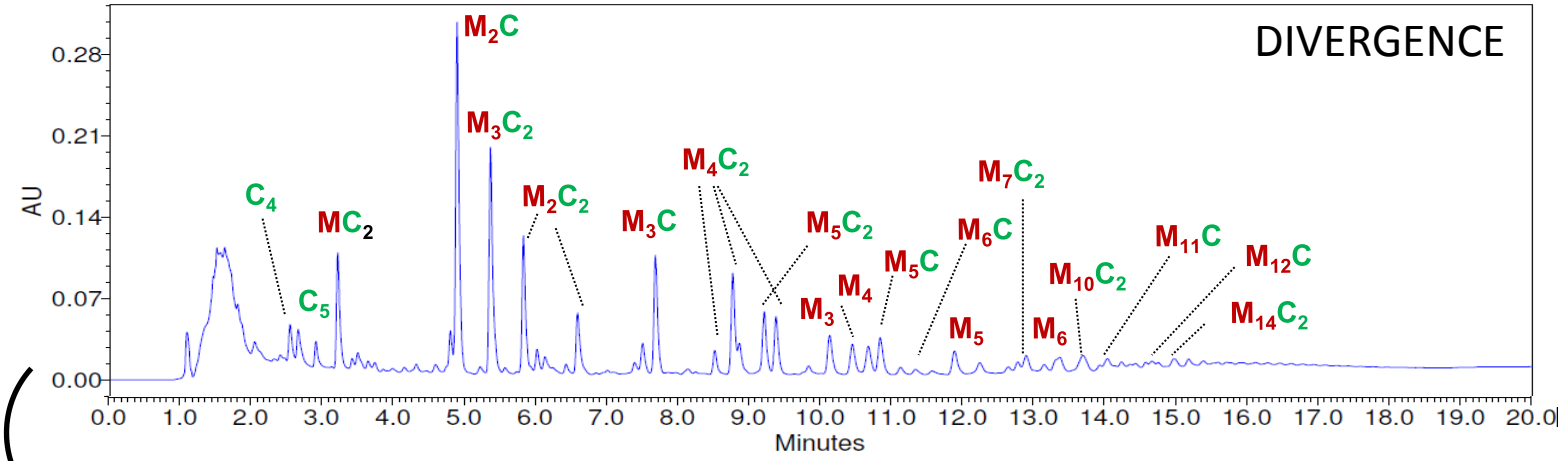


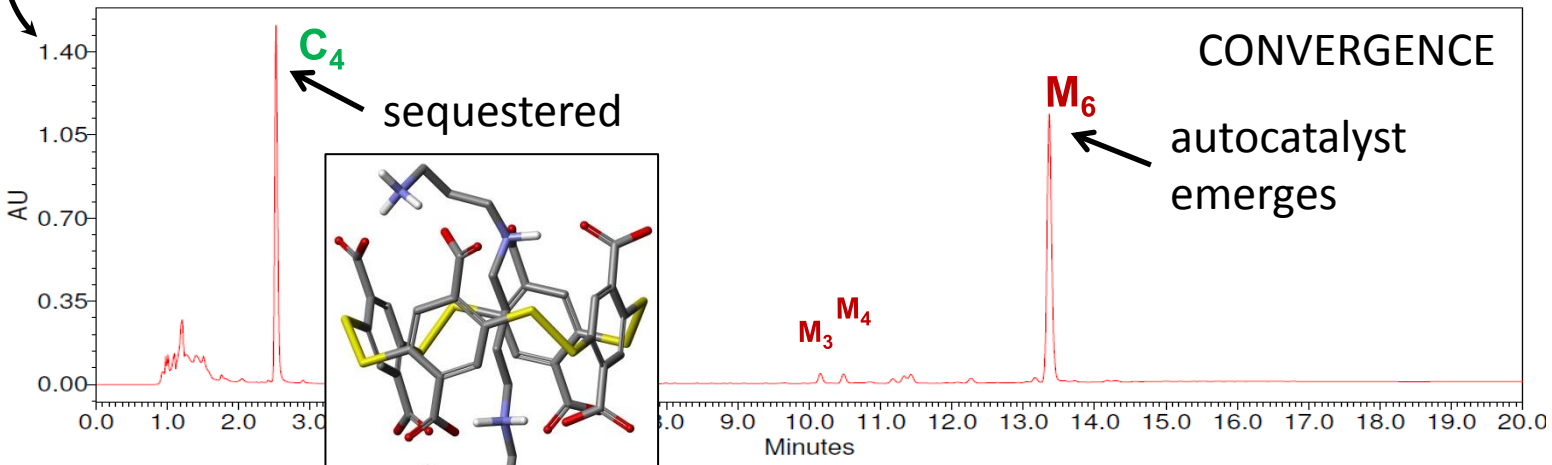
Phase changes
Autocatalysis (rare!)





spermine





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

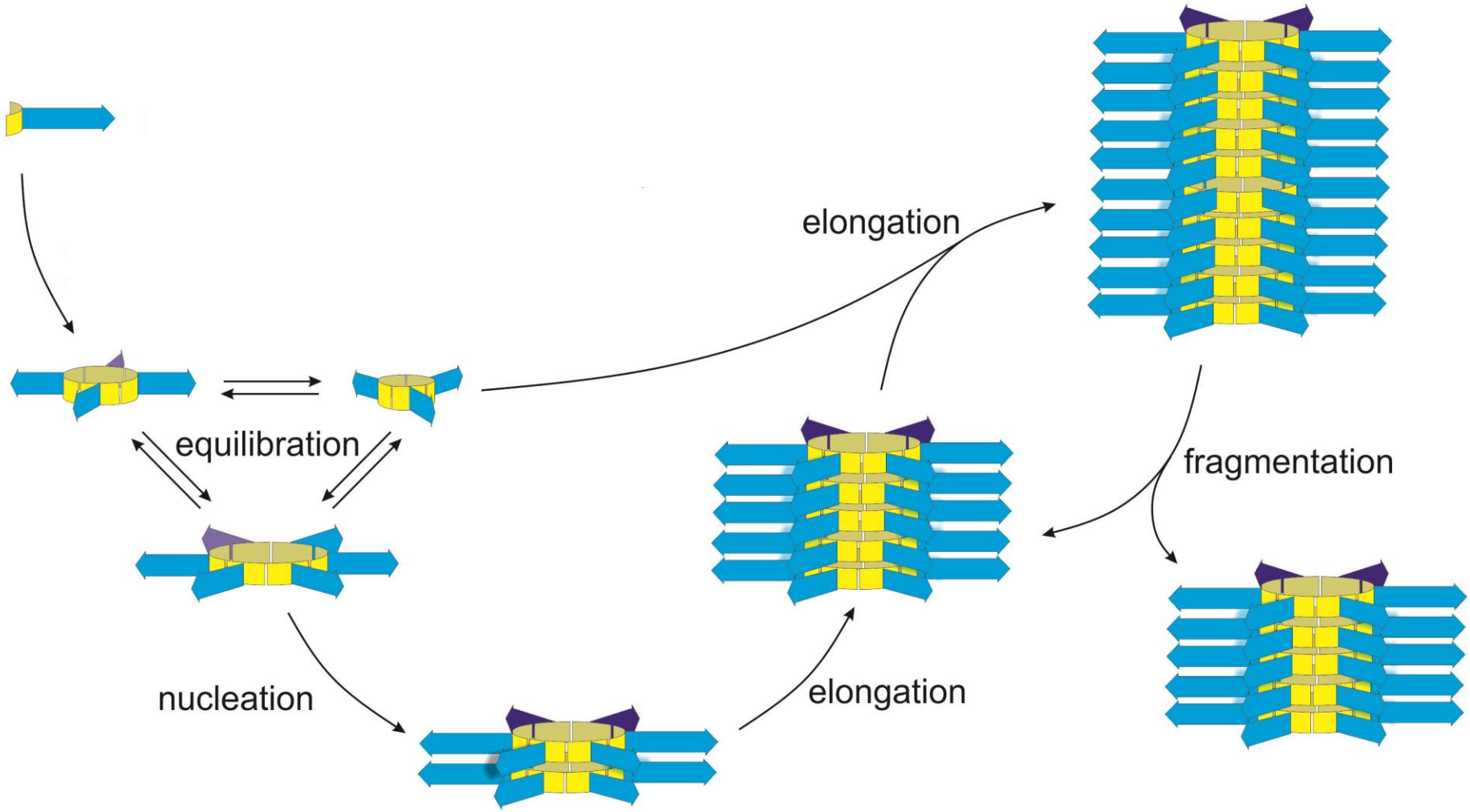
4 – Allow for Darwinian evolution of the replicators

5 – Facilitate invention of new traits (open-ended evolution)

Emergence of an exponential replicator from a soup

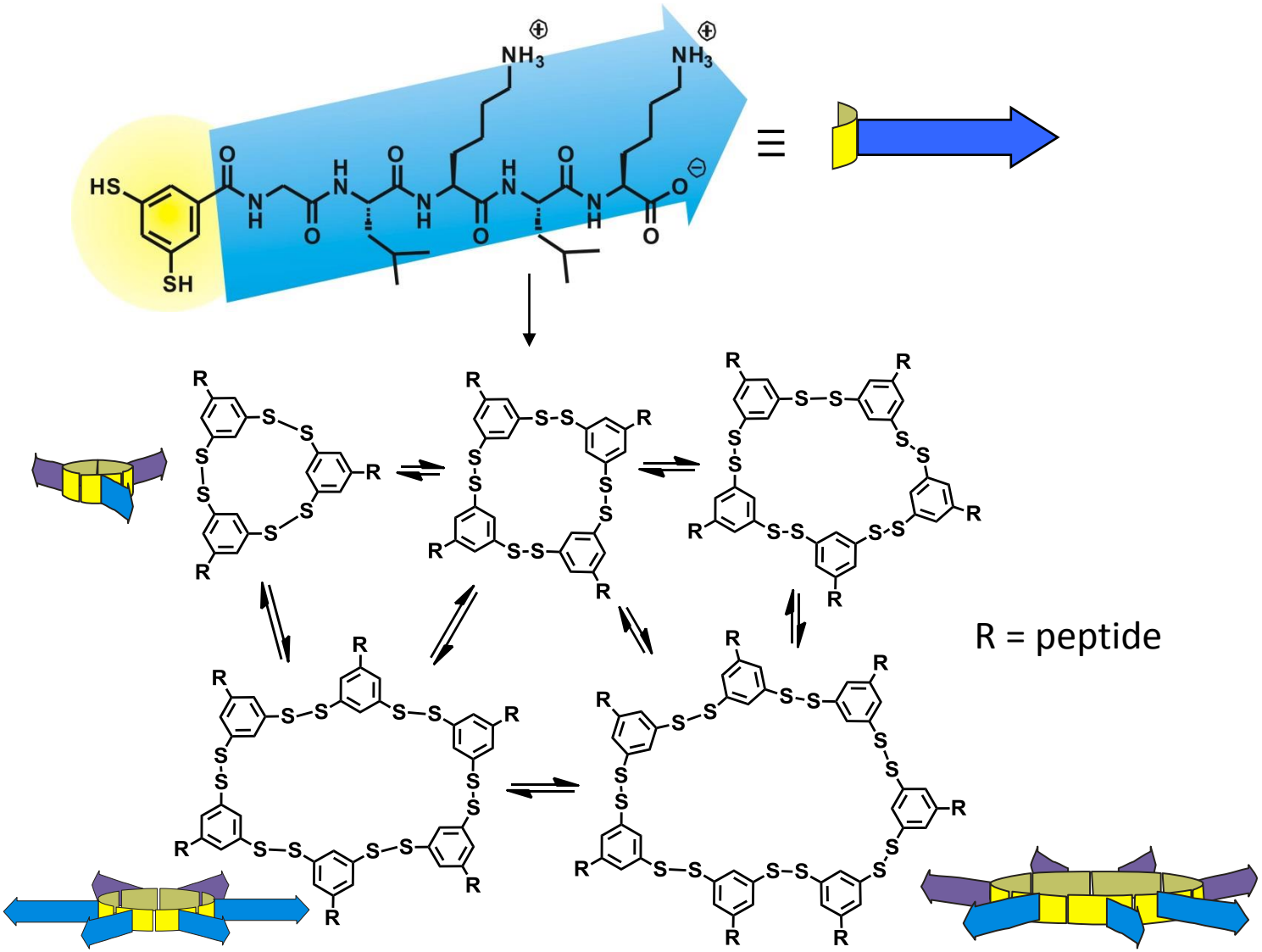
Animation: see www.otto-lab.com

Exponential replication by elongation/fragmentation



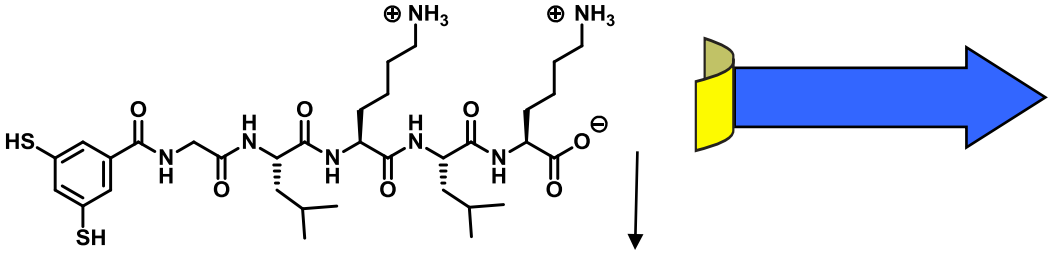
Mathieu Colomb-Delsuc, Elio Mattia, *Nat. Commun*. **2015,** *6*, 7425

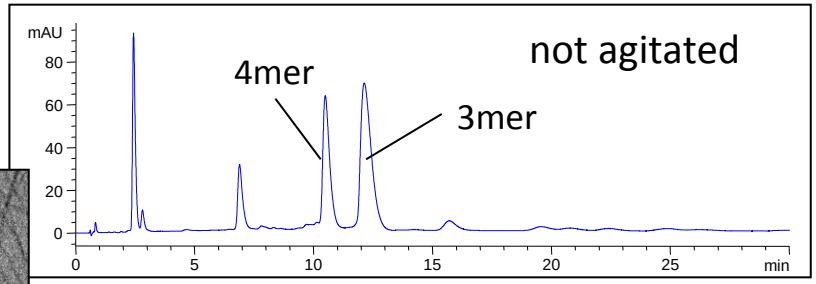
The chemical details

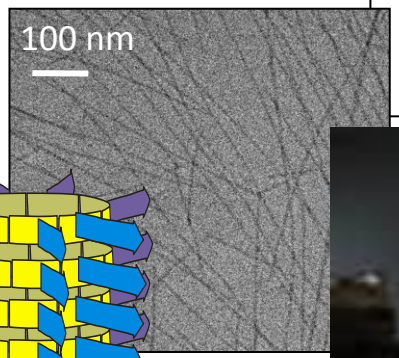


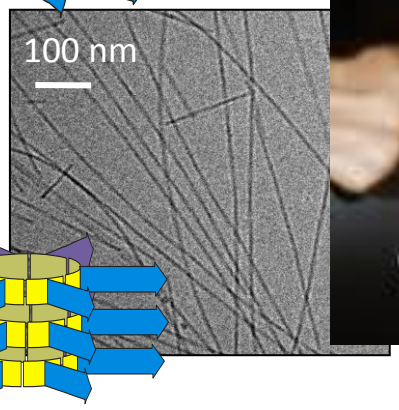
J. M. A. Carnall, C. A. Waudby, A. M. Belenguer, M. C. A. Stuart J. J.-P. Peyralans, S. Otto, *Science* **2010,** *327*, 1502

Mechanical energy determines replicator structure









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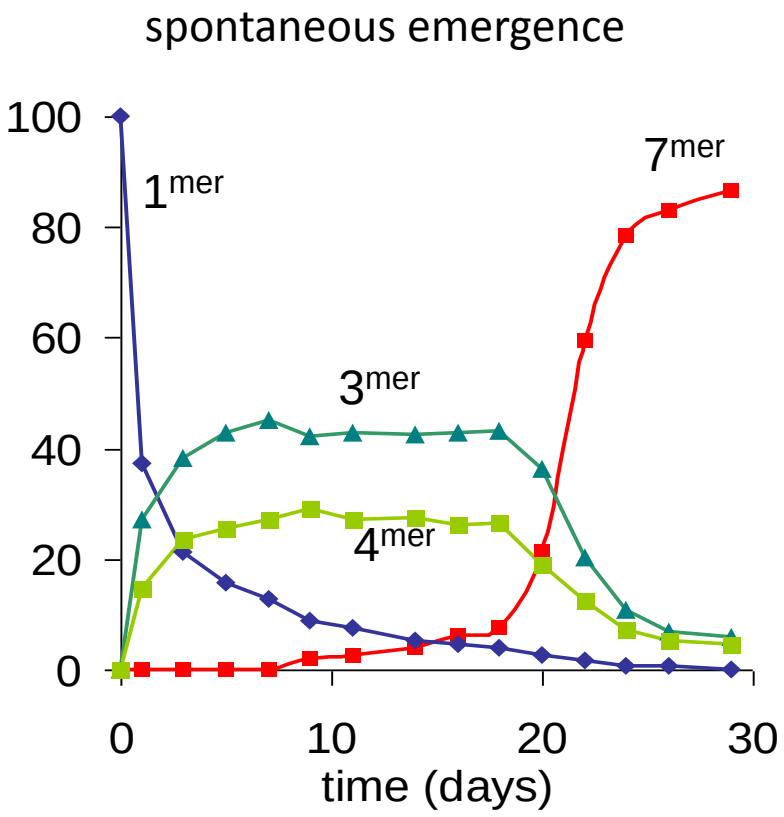
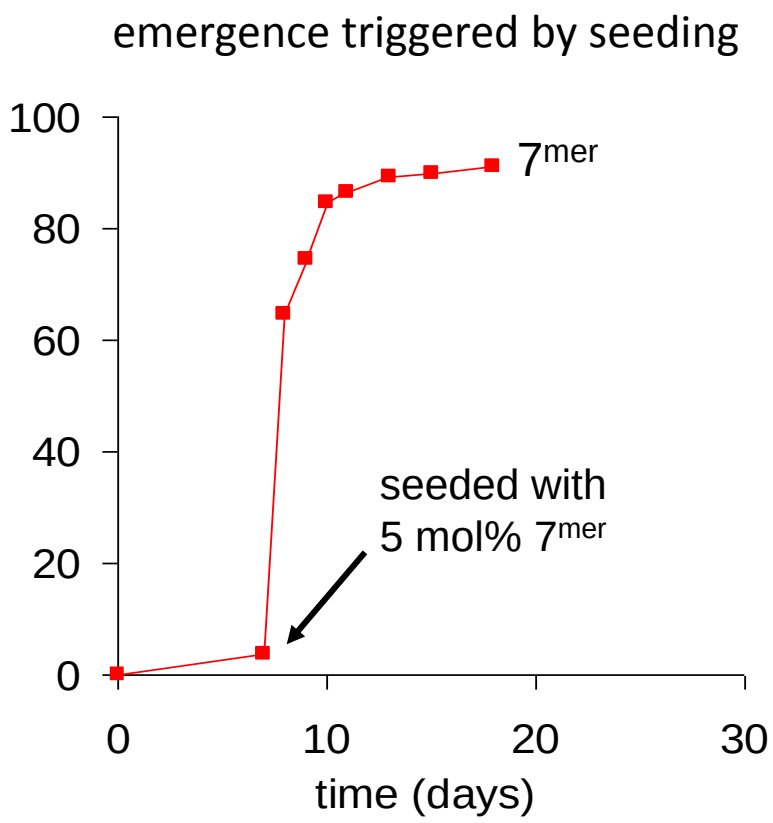
J. M. A. Carnall, C. A. Waudby, A. M. Belenguer, M. C. A. Stuart J. J.-P. Peyralans, S. Otto
Science **2010,** *327*, 1502

Autocatalysis!





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J. M. A. Carnall, C. A. Waudby, A. M. Belenguer, M. C. A. Stuart J. J.-P. Peyralans, S. Otto
Science **2010,** *327*, 1502

Our recipe for life

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2 – Enable mutations

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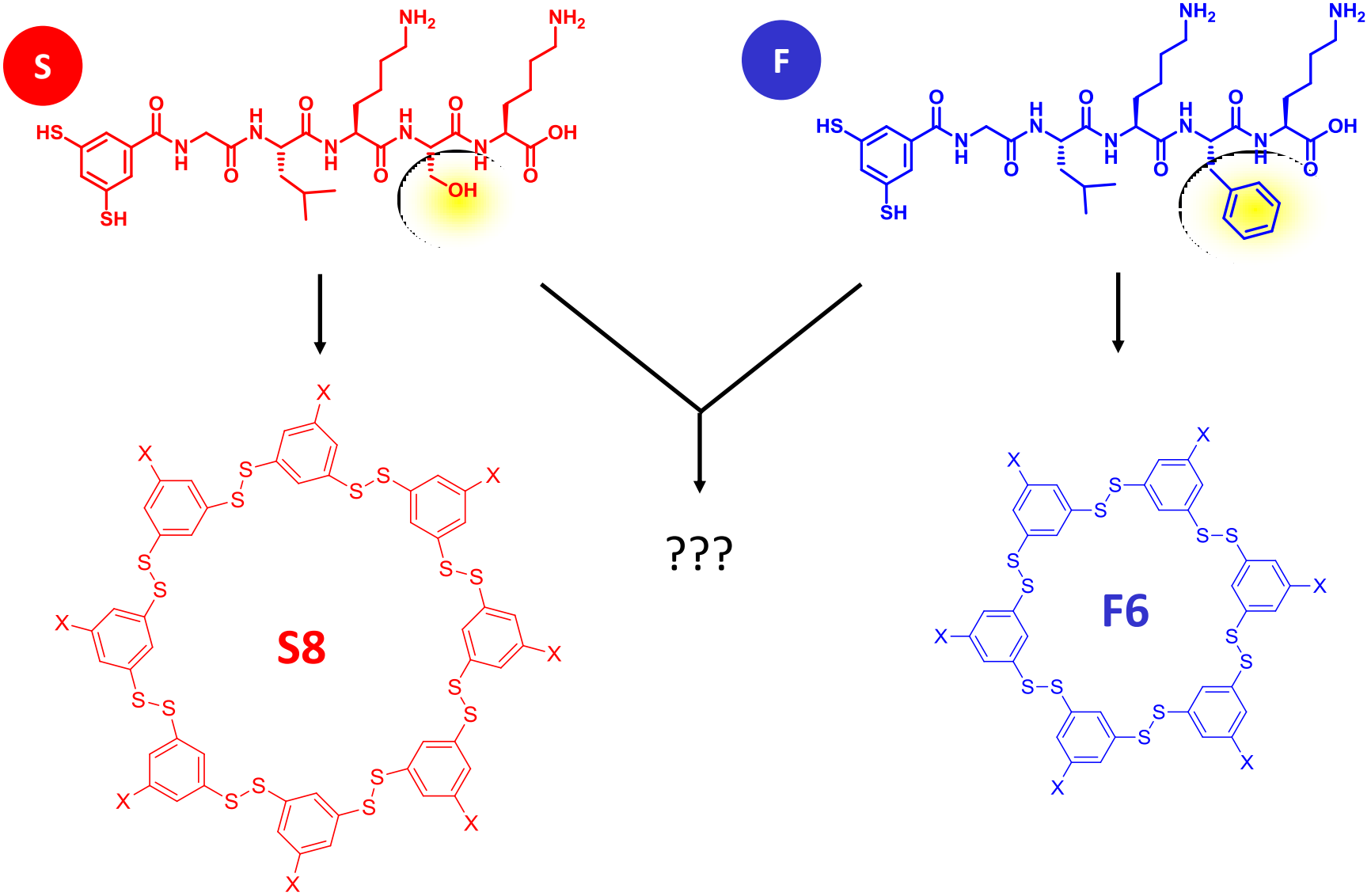
5 – Facilitate invention of new traits (open-ended evolution)

Mixing building blocks: enabling mutations



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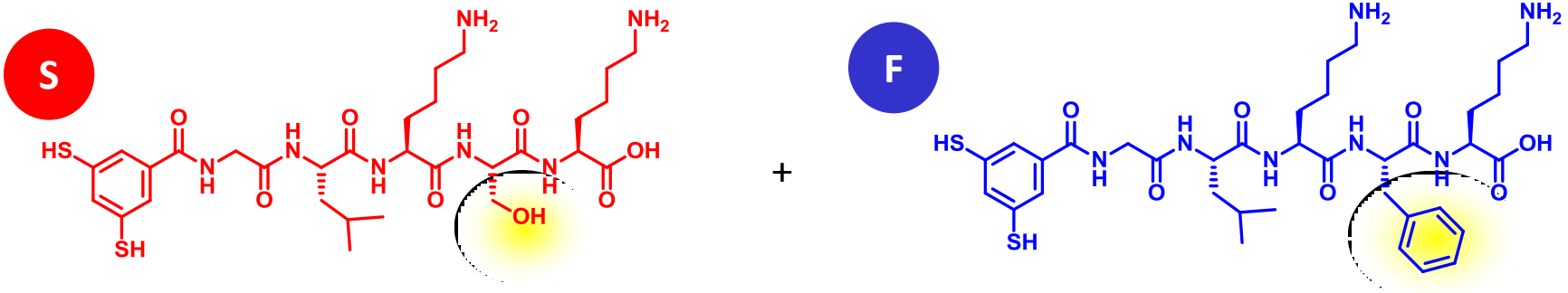
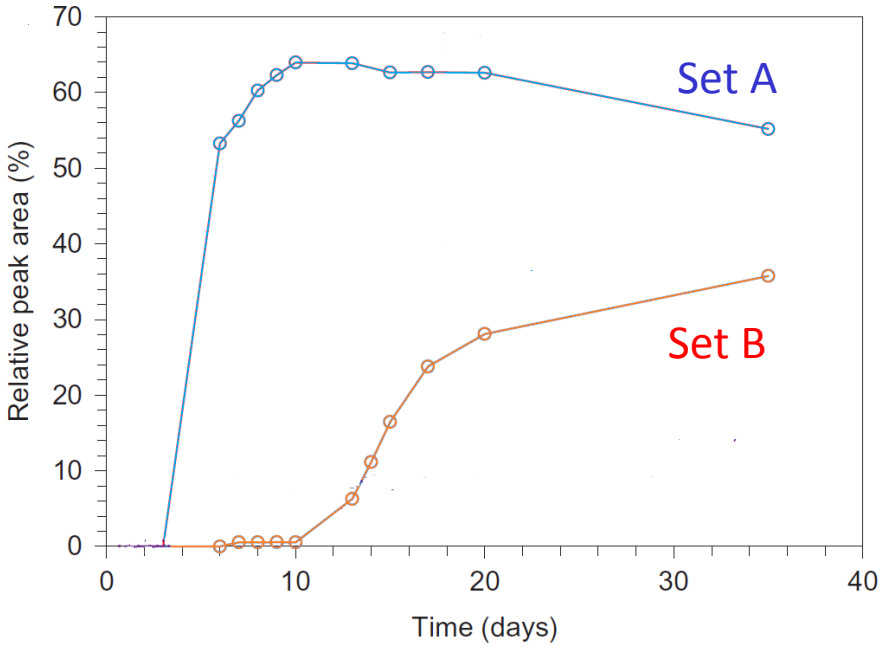
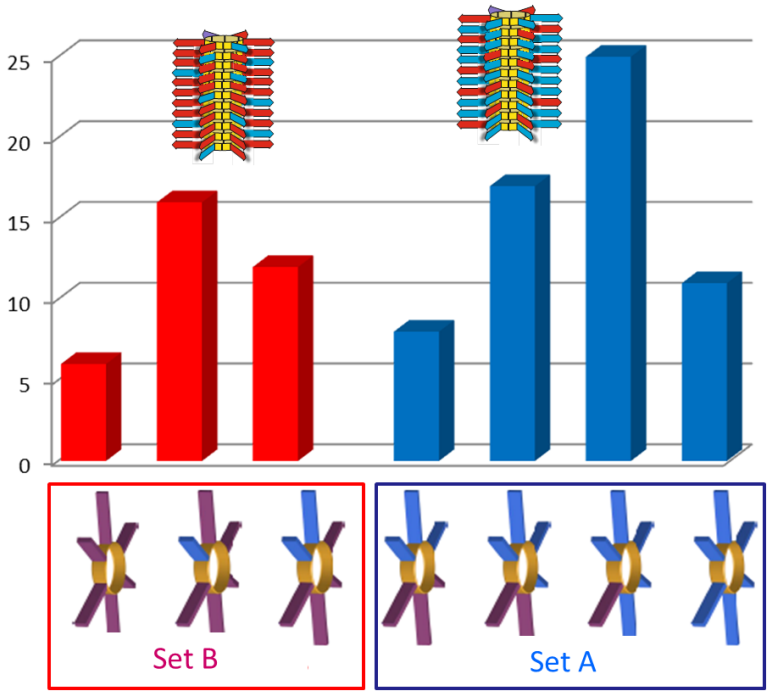
Jan Sadownik, *Nature Chem*. **2016**, *8*, 264

Two sets of 6mer replicators emerge sequentially







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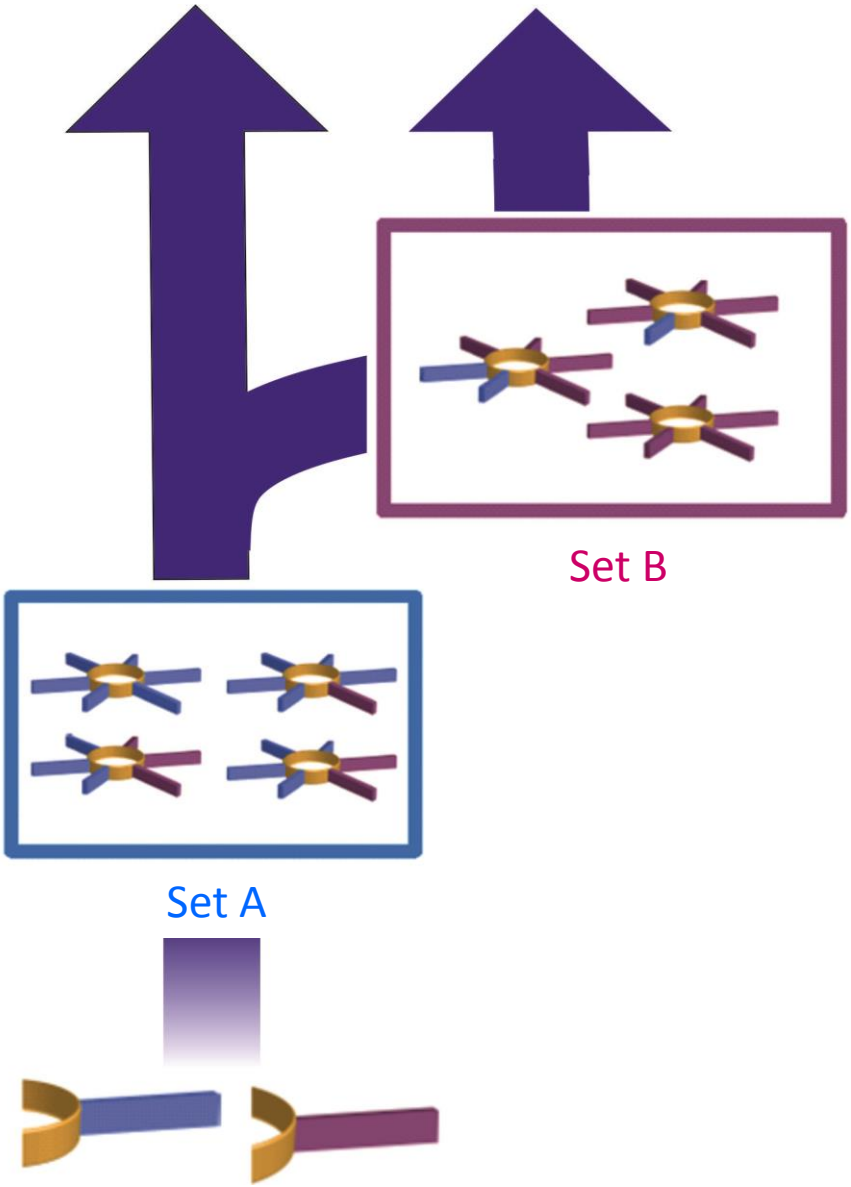
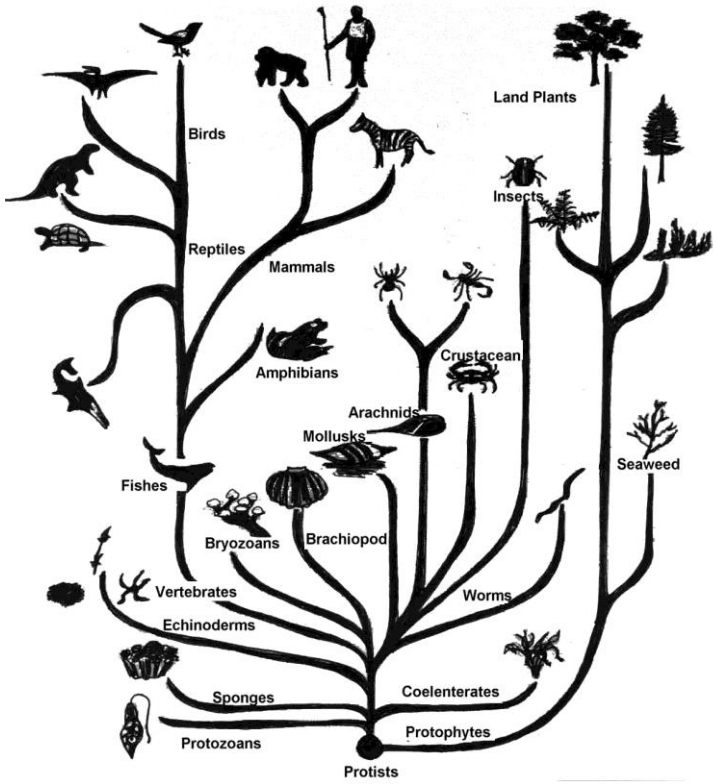
Jan Sadownik, *Nature Chem*. **2016**, *8*, 264

Ancestral relationship!





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Jan Sadownik, *Nature Chem*. **2016**, *8*, 264

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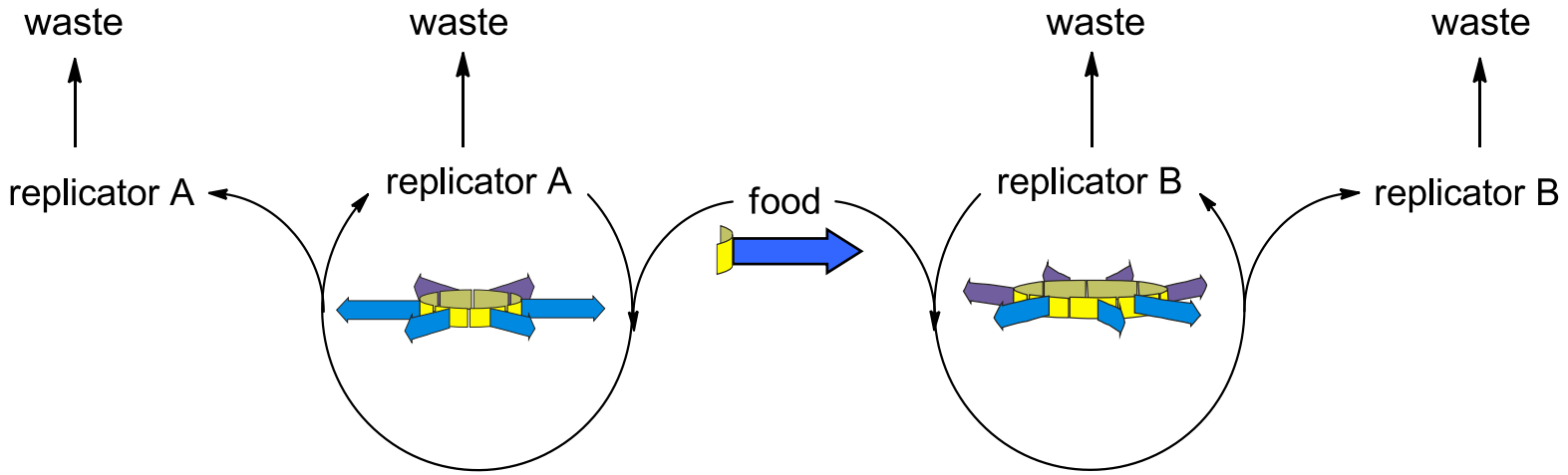
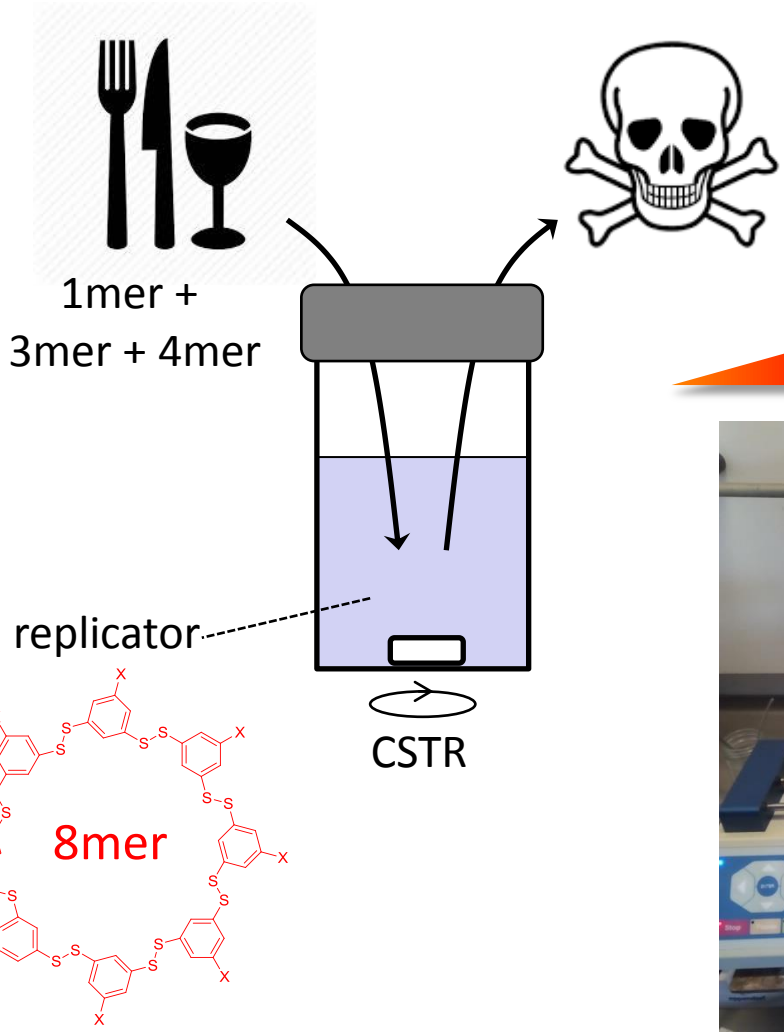
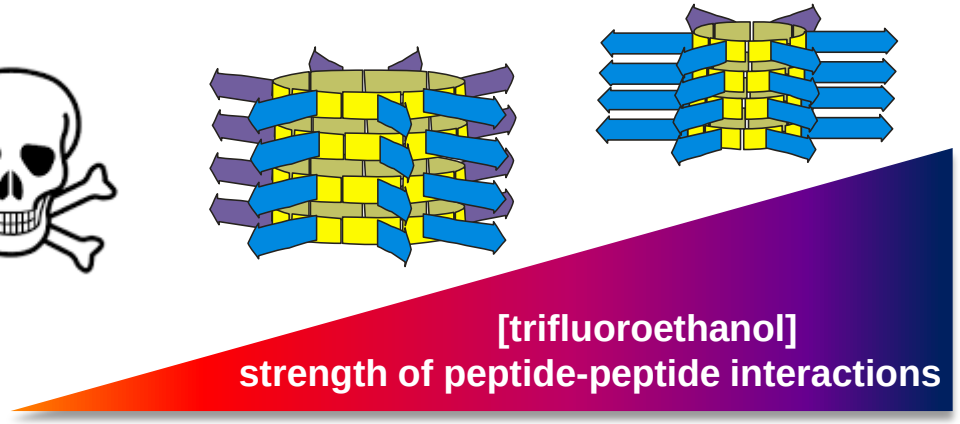
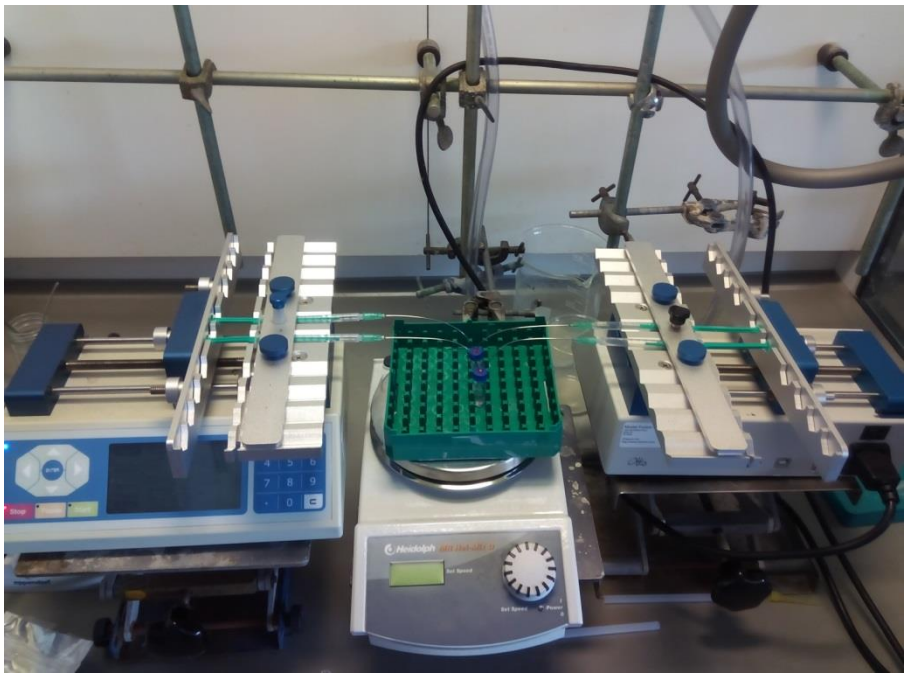


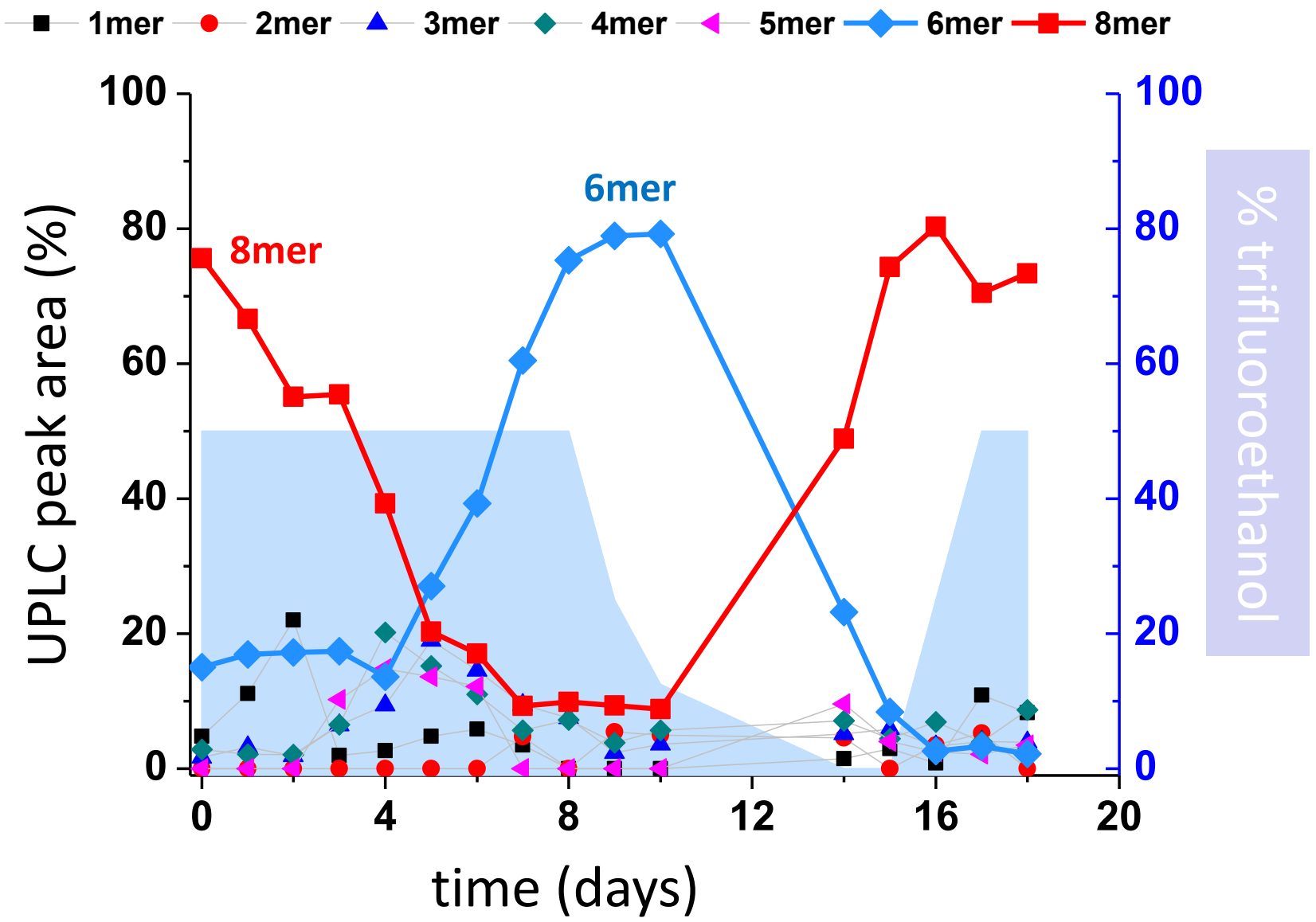
A replication-destruction regime







Adaptation to a changing environment

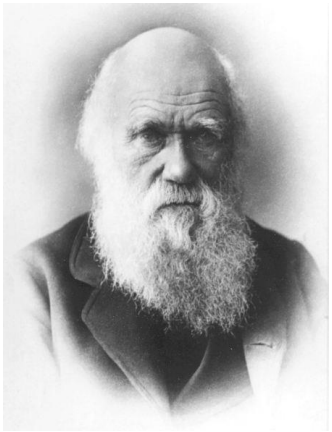


Giulia Leonetti, *manuscript in preparation*

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

MARIE CURIE ACTIONS

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NWO

erc

cost

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Jasper van der Gucht / Duc Nguyen
Siewert-Jan Marrink
Wim Hordijk