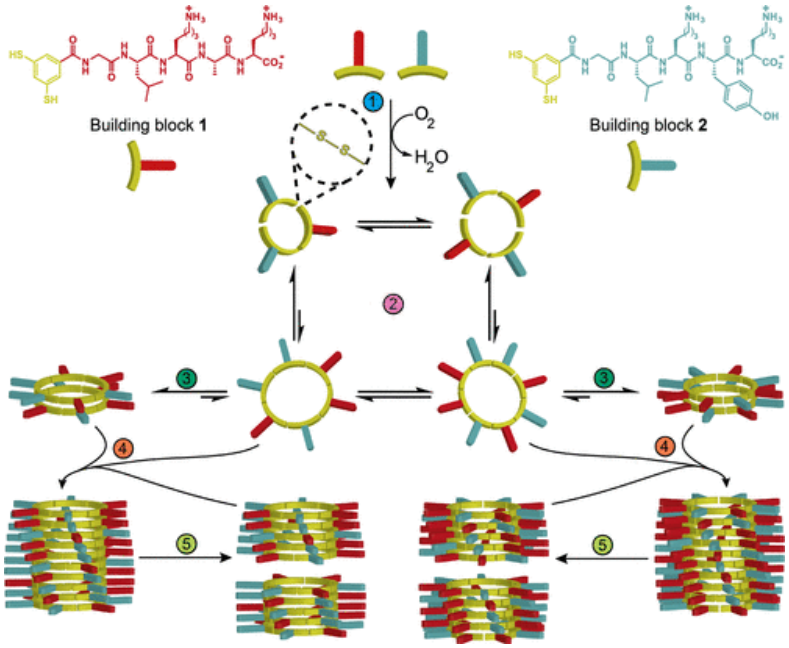
Article 14 - Stochastic Emergence of Two Distinct Self-Replicators from a Dynamic Combinatorial Library

Schaeffer, G.; Eleveld, M. J.; Ottelé, J.; Kroon, P. C.; Pim; Yang, S.; Otto, S. Stochastic Emergence of Two Distinct Self-Replicators from a Dynamic Combinatorial Library. *Journal of the American Chemical Society* **2022**, *144* (14), 6291–6297. https://doi.org/10.1021/jacs.1c12591.

Figure 1:



In this study, researchers explored how two similar building blocks, 1 and 2, form self-replicating molecules. Both building blocks are made of an aromatic core connected to a peptide, but differ in one amino acid: alanine in 1 and tyrosine in 2. When each block is oxidized in a dynamic combinatorial library (DCL), they form macrocycles of different sizes—eight-membered for 1 and three-membered for 2. These macrocycles can interconvert, leading to the formation of fibers that replicate through a process of elongation and fragmentation. When the two blocks are mixed together, the researchers found that the system could produce a variety of self-replicators, with some DCLs dominated by larger macrocycles and others by smaller ones. The outcome of which macrocycle formed was not predictable, showing the role of stochastic (random) processes in the system.

Synopsis:

In the 2022 study Stochastic Emergence of Two Distinct Self-Replicators from a Dynamic Combinatorial Library, researchers Gaël Schaeffer and colleagues explored how two different self-replicating molecules can emerge from a mixture of two synthetic building blocks. This

research offers valuable insights into the fundamental processes that could have led to the origin of life and has potential applications in synthetic biology and materials science.

The researchers focused on two building blocks, 1 and 2, which are composed of an aromatic dithiol core connected to pentapeptides. These building blocks differ in the fourth amino acid in the sequence: alanine in 1 and tyrosine in 2. When these building blocks are mixed in equimolar amounts and oxidized in an aqueous borate buffer, they form a dynamic combinatorial library (DCL) containing a mixture of macrocycles with various ring sizes. This mixture includes predominantly three- and four-membered macrocycles. Under mechanical agitation, larger self-replicating macrocycles can emerge, consuming most of the smaller macrocycles and becoming the main species in the DCL. However, the researchers found that, under the same experimental conditions, two different self-replicators emerge in a stochastic fashion, meaning that the outcome is not deterministic but influenced by random fluctuations. This variation is caused by a stochastic nucleation process and is more pronounced close to a phase boundary.

A key figure in the article illustrates the self-replication mechanism of the two building blocks. The figure shows the oxidation of the building blocks to form a mixture of macrocycles with various ring sizes. These macrocycles interconvert using thiol-disulfide chemistry. Two different nucleation steps can occur, leading to the formation of stacks of macrocycles containing six or eight monomer units. Both nuclei can elongate to form fibers by consuming smaller macrocycles from the solution. Fragmentation of the fibers by mechanical agitation when the stack is sufficiently long leads to an elongation/fragmentation regime, enabling exponential growth.

This study's findings have significant implications for the field of synthetic biology. By demonstrating that two distinct self-replicators can emerge from a mixture of two building blocks in a stochastic manner, the researchers reveal an important mechanism behind the molecular complexification of self-replicating systems. This approach could lead to the development of more complex self-replicating molecules, advancing our understanding of the origins of life and enabling the creation of artificial systems with self-replicating capabilities.

In summary, Schaeffer and colleagues' research provides valuable insights into the mechanisms of self-replication driven by stochastic processes. Their work paves the way for future developments in synthetic biology and materials science, offering potential applications in creating adaptive and responsive systems.