Synthesis of life

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Catalyst optimization through synthetic Darwinian evolution

Héctor Soria-Carrera & Job Boekhoven

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A study demonstrates that fully synthetic molecules can undergo self-replication, mutation and selection — hallmarks of Darwinian evolution — without relying on DNA or proteins.

Darwinian evolution has shaped all life around us in one way or another. It operates based on three critical pillars: replication, mutation and selection. Replication with mutation ensures diversity among an ecosystem of organisms, while selection pressure guarantees competition and the success of the fittest. From a molecular point of view, Darwinian evolution operates by encoding an organism's genetic information in DNA, which is replicated and passed to offspring. Mutations in this genetic code occur through recombination and errors, ensuring the offspring are not exact copies of their ancestors. Through genotype–phenotype coupling, mutants with variations in their DNA have differing physical traits because DNA encodes for RNA, which is translated into proteins — the central dogma of molecular biology. In an ever-changing environment, some traits are more suited than others, further spreading the genotype.

Long before Darwin, humans used evolution to their advantage, for example, in artificial selection in farming to selectively breed crops and livestock. The discovery of DNA, its role in the central dogma, and the biotechnology revolution that followed have enabled scientists to use evolution outside the context of classical biology, such as in the evolution of enzymes for non-natural chemical reactions (directed evolution)[1] or RNA to bind non-natural targets (SELEX)[2]. Yet Darwinian evolution has remained tied to DNA, RNA and proteins. What if we could use Darwinian evolution outside of biomolecules? Darwinian evolution in non-biological, chemical systems would be pioneering and have important implications for catalyst discovery or materials science, for example[3]. In their work in *Nature Catalysis*, Otto and colleagues now report a set of molecules that self-replicate, mutate and are selected based on catalytic activity — put differently, Darwinian evolution in a synthetic system[4].

For the first pillar of Darwinian evolution, replication, the team of researchers used a known replicator[5], which consists of a stack of ring-shaped molecules that catalyses the production of more rings, which themselves assemble onto the stack. In a stirred solution, the stacks frequently break, leading to a replication event — one stack becomes two, and each continues growing (Fig. 1a).

The rings are cyclic disulfides formed by oxidation of their dithiol precursors in a dynamic mixture. These rings exchange building blocks, allowing different ring sizes — trimers, tetramers, pentamers and so on — to form. However, each stack accommodates only its own ring size, leading to replication through templation. For example, hexamer stacks can only fit hexamers, while trimer stacks only fit trimers. Moreover, once a ring is incorporated in a stack, it is frozen in the stack out of the dynamic equilibrium. Thus, replicator stacks compete for the limited dithiol precursors and oxidizing agents.

For evolution, genotype must affect phenotype. Thus, the researchers ensured the replicator stack could affect its own behaviour. They designed the stacks to affect the chemical production of the ring building block through photocatalysis — a primitive mimic of metabolism. Indeed, the replicator stacks can bind Thioflavin-T. This dye can convert triplet oxygen into its singlet form, thus accelerating the oxidation of thiols to disulfides, forming the macrocycles that can stack. Importantly, this oxidation only occurs near the fibres, so the replicators locally produce more of their building blocks for themselves but not for others. Finally, some stacks (for example, hexamer stacks) take up Thioflavin-T better than others, making them catalytically better photocatalysts (Fig. 1b).

To introduce diversity, the authors designed dithiol precursors with varying peptides. These variations led to mixtures of stacks — some made mostly from one type of building block and others from combinations. Although these mixed stacks replicate less efficiently, they can still catalyse their own growth and that of closely related structures. Notably, one dithiol precursor could bind Thioflavin-T well and preferred to form hexamers, while another variant was less able to bind it and formed trimers. In this way, the population contains mutants — stacks with similar but distinct compositions — and some are better photocatalysts than others.

Evolution cannot occur in equilibrium. Thus, the authors employed a continuously stirred tank reactor (CSTR) to which the replicator building blocks were continuously added, while a portion of the reactor contents was constantly removed. This efflux acts as a selection mechanism that randomly removes replicator stacks, dithiol precursors, and oxidizing agents, introducing pressure to replicate quickly or be lost (Fig. 1c).

When the experiment started with a mix of hexamers and trimers, the population shifted toward hexamers — those that photocatalyse building-block production most effectively and replicate fastest. However, when the researchers used a non-selective oxidant, $Ru(bpy)_3$ (which oxidizes thiol homogeneously through the solution), the reactor selected for trimers non-selectively, which inherently replicates faster — trimers are easier to form compared to hexamers. This contrast highlights how catalytic activity, not just replication rate, can drive selection (Fig. 1d).

This work elegantly combines replication, mutation and natural selection to find an optimal catalyst without using biomolecules. To date, catalyst optimization based on the principles of Darwinian evolution has been primarily applied to biomolecules, including proteins, RNA and DNA. Replication without biomolecules has been demonstrated to be possible[6–9], but limited to systems without mutations or natural selection.

Given the system's synthetic nature, perhaps synthetic selection, countering natural selection, would be a more appropriate term for the findings. While this work is highly designed compared to evolution, it opens a door to more complex mixtures. For example, given the group's

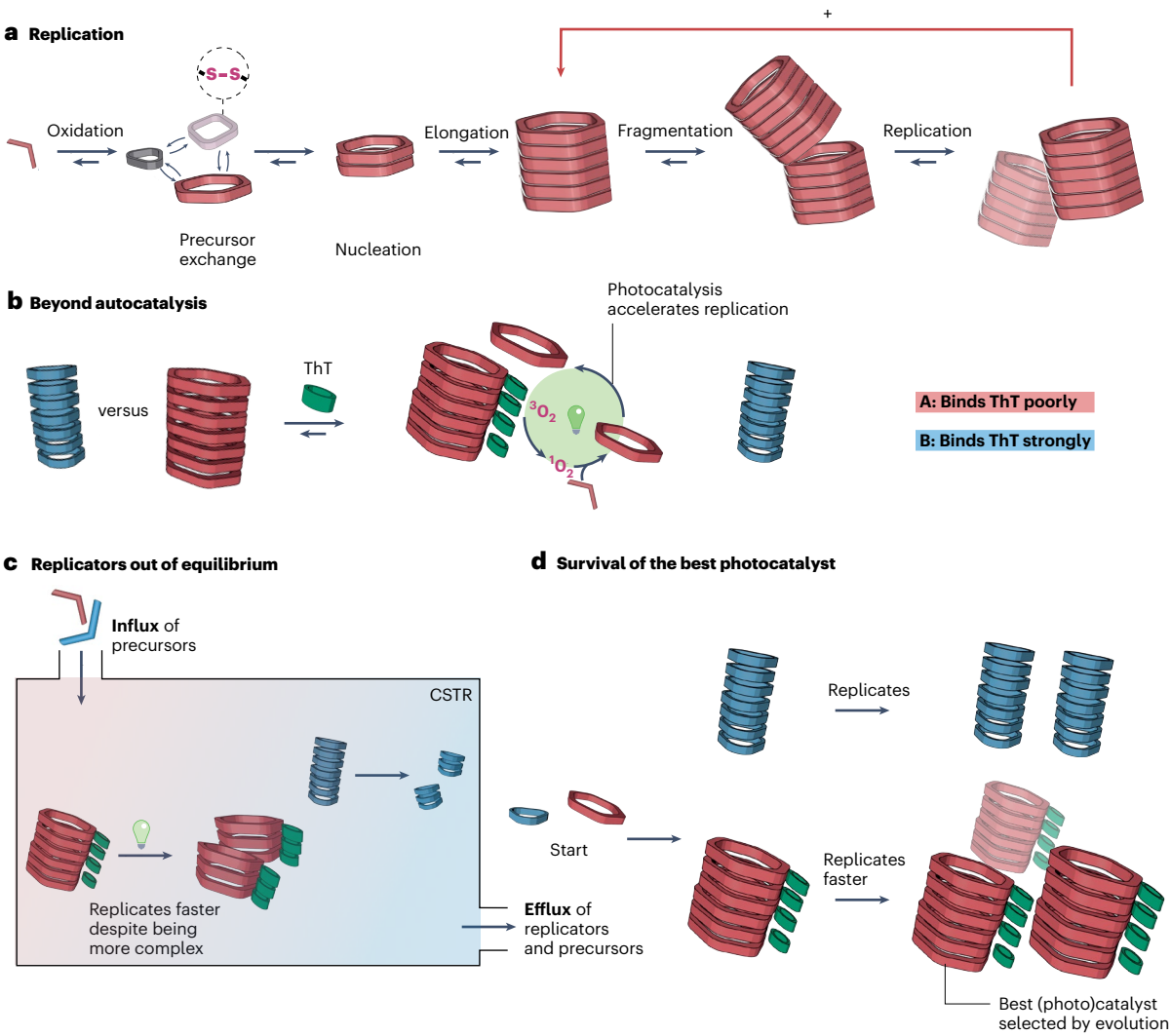

Fig. 1 | Synthetic Darwinian evolution guides catalyst optimization. **a**, Mechanism for the self-replication of stacks driven by self-assembly. **b**, The binding of Thioflavin-T (ThT) to the hexamer stacks and the production of singlet oxygen species that catalyse the formation of more hexameric stacks close to the fibres. **c**, Experiment in the CSTR where hexamer stacks bind ThT and replicate faster, biasing product distribution. **d**, The capacity to replicate faster outcompetes CSTR efflux, yielding hexamers as the best catalyst.

expertise in catalysis with the replicating stacks, we expect further optimization of a range of catalysts and their combination using the principles of natural selection[4]. In other words, recombination creates better catalysts that are amplified and selected. Ideally, such studies would eventually give rise to completely de novo catalysts that can be used for future technologies. Imagine materials that heal themselves, chemical sensors that evolve in response to pollution, or even forms of synthetic life designed from scratch.

Héctor Soria-Carrera ✉ **& Job Boekhoven** ✉
Department of Bioscience, School of Natural Sciences, Technical University of Munich, Garching, Germany.
✉e-mail: hector.soria@tum.de; job.boekhoven@tum.de

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Competing interests

The authors declare no competing interests.