SELF-ASSEMBLY

Complexity from small molecules

Chemical oscillations emerge during the chemically fuelled self-assembly of a perylene diimide derivative as a result of simple feedback mechanisms.

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Oscillations in the concentrations of molecules and molecular assemblies play an important role in the functioning of the biological cell[1]. For example, microtubules in the cytoskeleton oscillate between periods of growth and collapse to maintain a dynamic network[2]. Likewise, before the division of the rod-shaped bacterium *Escherichia coli*, the concentration of a set of three proteins (the Min proteins) oscillates between the bacterium's two poles in order to determine its centre and thereby ensure the formation of two equal daughter cells[3]. Inspired by such dynamic structures and functions in biology, supramolecular chemists have long been engineering molecules that can assemble into ordered structures. Recently, however, the field has focused on the formation of dynamic molecular structures that require constant dissipation of energy to exist[4]. The goal is to develop out-of-equilibrium self-assembly systems that show behaviour of a kind that we typically associate with living things. Now, writing in *Nature Nanotechnology*, Leira-Iglesias et al. report a system in which abiotic chemicals spontaneously oscillate between an assembled and a disassembled state in response to a flux of chemical energy[5].

The researchers use a perylene diimide derivative (PDI, Fig. 1a)[6] which assembles and disassembles in response to a set of redox reactions[7]. When exposed to atmospheric oxygen, the PDI oxidizes, becomes uncharged and can stack into nanofibres that subsequently organize into micrometre-sized colloids. In contrast, a reducing agent renders the PDI anionic, resulting in a mostly disassembled state (Fig. 1b). The assembly and disassembly rates show nonlinear dependencies on the size of the structures. On the one hand, the self-assembled structures exert a positive feedback on their growth: the assembly is initially slow, because of the lack of stable nuclei that can initiate the growth; but once the first assemblies form, the growth proceeds at ever-increasing rates because the assemblies can fragment and serve as new nucleation sites. On the other hand,

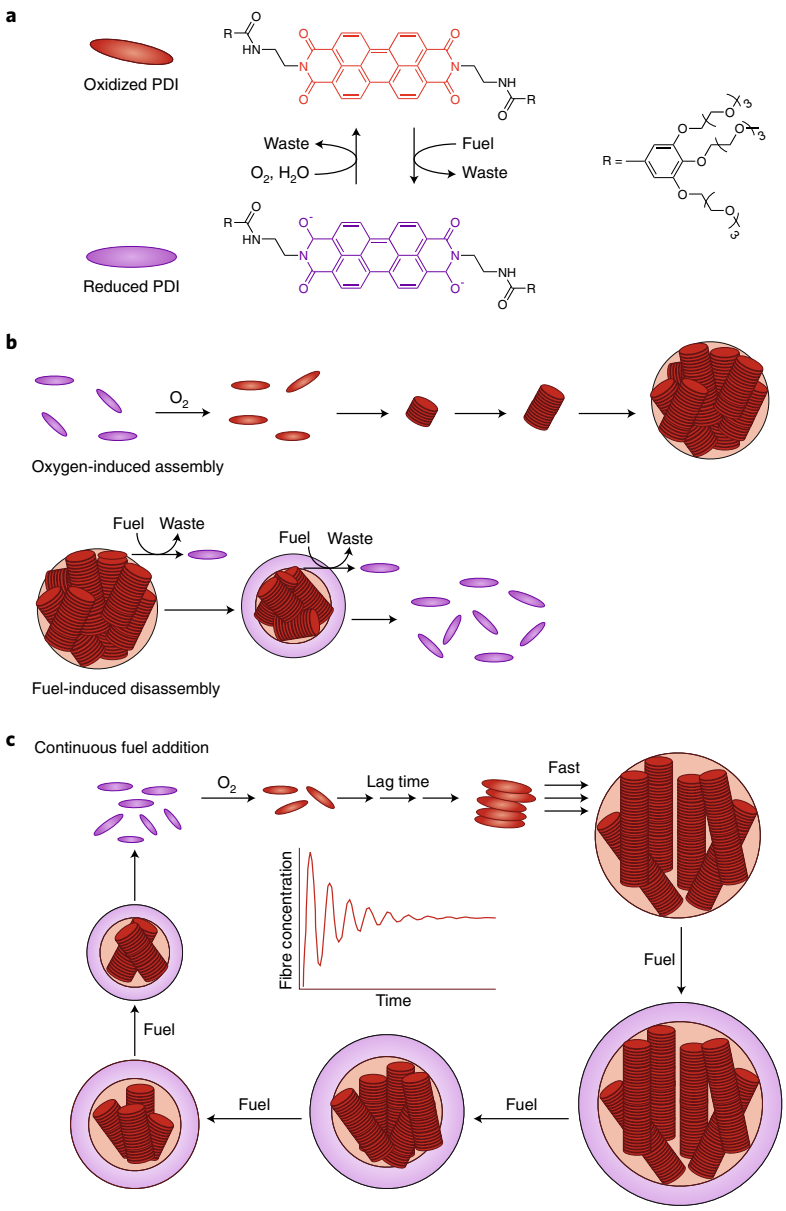

Fig. 1 | Chemical oscillations in self-assembling systems. a, Molecular structures of oxidized (red) and reduced (purple) PDI derivatives. **b**, Exposure to oxygen induces the assembly of the reduced PDI into fibres that subsequently form colloids. Conversely, reducing agents fuel the disassembly of the colloids, yielding reduced PDI that is free in solution. The diffuse purple-shaded layer indicates molecules that have been reduced but have not immediately left the assembly. **c**, Oscillations between an assembled and disassembled state emerge on continuous addition of fuel to oxygen-exposed solutions of PDI.

the disassembly of the colloids induced by a reducing agent follows a surface erosion mechanism in which only the PDI at the surface of the colloids is available for chemical reaction. The consequence is that the colloids severely slow the reduction of PDI, which is effectively a form of negative feedback. The beauty of the work is that both modes of feedback rely on relatively simple mechanisms triggered by the assembly of the molecules, instead of enzymes or rare autocatalytic reactions.

Chemical oscillations are the result of the interplay between these positive and negative feedbacks. Leira-Iglesias et al. screen for such behaviour by sustaining the system out of equilibrium. They fuel a solution of PDI continuously with reducing agent. At relatively low fluxes, they obtain a steady state — a dynamic state in which concentrations are stable because reduction equals oxidation. However, when they dial up the flow beyond a threshold value, oscillations in concentration, structure and colour start to emerge. That means that the influx of chemical energy is a measure for how far the state is from equilibrium, and therefore a way to control emergent behaviours.

Starting in the form of a purple solution of PDI in a monomeric state, the molecules react with molecular oxygen and rapidly self-assemble to form a reddish colloidal solution. At this point, despite the continuous influx of the reducing agent, the colloids do not reduce immediately; the feedback delays the reduction and the disassembly. The solution remains red for several minutes before rapidly switching to the initial purple and restarting the cycle (Fig. 1c). These oscillations exist for several hours under continuous influx of fuel, but eventually die out, and the system reaches a steady state.

Recent work has shown that oscillatory behaviour can be designed in non-biological networks of chemical reactions[8], but this relies on relatively rare autocatalytic reactions. In contrast, Leira-Iglesias et al. demonstrate that the oscillatory behaviour can directly emerge from feedback mechanisms induced by the nature of the assemblies themselves. The fact that oscillations can emerge from rather simple chemistry suggests that emergent, life-like behaviour could be a general feature of self-assembly systems that are continuously pushed out of equilibrium.

The next step in this line of investigation would be to add functionality. For instance, the forces generated by oscillating structures could serve as an artificial cytoskeleton that induces the division of a phospholipid vesicle, thus coupling the division of artificial cells to an externally fuelled clock. ❐

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