

Self-assembling life

In 1944, Erwin Schrödinger posed the question “How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?” Studying out-of-equilibrium chemical systems may take us closer to an answer.

Scientists are, like most people, fascinated by life. Yet, a commonly accepted definition of ‘life’ still escapes us. We can intuitively distinguish living and non-living things, but drawing a clear line between the two remains elusive. Chemists, for example, used to divide substances into two categories: organic (which were found in living organisms) and inorganic (which were found in inanimate matter, such as rocks, sea and soil). Organic compounds were thought to possess a special property (a *vis vitalis*, or ‘vital force’) that bestowed life on organisms, in contrast to inorganic compounds. The synthesis of urea from inorganic reagents in 1828 meant that according to the paradigm of the time, scientists could create living matter from non-living substances. As it was evident that synthetic urea was no different from natural urea, the notion of *vis vitalis* became obsolete and was gradually abandoned.

Fast forward almost 200 years. The discovery of viruses, the development of genomic manipulation techniques and the advent of synthetic biology (with the demonstration of a self-replicating microorganism containing purely artificial DNA), have further blurred the line between living and non-living things. This makes it almost impossible to define life, and it could be argued that it is even a moot exercise. Yet, we can jot down a list of features that are typically encountered in living organisms: self-replication, natural selection, adaptability. Interestingly, most, if not all, of these features have been observed in what we consider non-living systems as well: molecules can self-replicate, supramolecular aggregates can evolve to maximize fitness and reaction networks can show oscillatory behaviour similar to a circadian rhythm.

So how does inanimate matter become alive? What is the physicochemical driving force behind this? In his book *What is life?*, Schrödinger used thermodynamic principles to try to answer these questions and it is now clear that a central feature of living organisms is that they (we!) operate out of equilibrium: that is, a continuous supply of energy — which is then dissipated, producing entropy — is needed to be kept alive. Equilibrium equals death. In a more recent book (also entitled *What is life?*, 2012), Addy Pross adds kinetic principles,



Basket of Fruit by Caravaggio.

arguing living systems are characterized by a dynamic kinetic stability in which a stationary state arises from competing reactions (or networks of reactions) that create and destroy organized matter at equal rates. But this is not enough. As first conceptualized by Francisco Varela and Humberto Maturana in the 1970s, a living system is also characterized by a boundary, a semipermeable membrane that defines an ‘in’ and an ‘out’ and the relationship between the two.

Despite the fact that we are made of molecules, chemists are generally not conversant with out-of-equilibrium systems. In fact, more than two centuries of studying chemical reactions has resulted in a great deal of understanding of chemical equilibrium, since that is where reactions proceed towards, with only the occasional insight into specific out-of-equilibrium situations, mainly limited to oscillating reactions and photostationary states. Recently, however, chemists have started tackling out-of-equilibrium chemical systems head on. This new direction comes off the back of more than 30 years of research in supramolecular chemistry, which deals with interactions weaker than covalent bonds. The wonderful thing here is that under the right conditions, multiple interactions between molecules lead to the formation of large aggregates that just self-assemble. Non-covalent interactions

allow these nanometre-scale aggregates to respond to environmental changes, and can thus become adaptable and start to display emergent properties characteristic of living systems. The next obvious step would be to merge self-assembly chemistry with out-of-equilibrium, dissipative conditions, and to do so in confined environments.

One tool that is still lacking though, is a firm grasp of the physical chemistry of out-of-equilibrium systems. Similarly to what happened at the beginning of the twentieth century, when physical chemistry took the centre stage and scientists went on to define chemical equilibrium and chemical reactivity from thermodynamics, a new generation of physical chemists is likely to be needed to connect supramolecular chemistry to the out-of-equilibrium thermodynamic concepts being developed by theoretical physicists. This will perhaps bring us closer to answering Schrödinger’s question and towards a clearer understanding of what life is.

Over the past few years, *Nature Nanotechnology* has published a set of commissioned Reviews, Perspectives and Commentaries on this topic, which we have now collected in a web focus (<http://www.nature.com/nnano/focus/self-assembly/index.html>). We hope that these pieces will serve to inspire and guide future explorations of out-of-equilibrium systems at the nanoscale. □