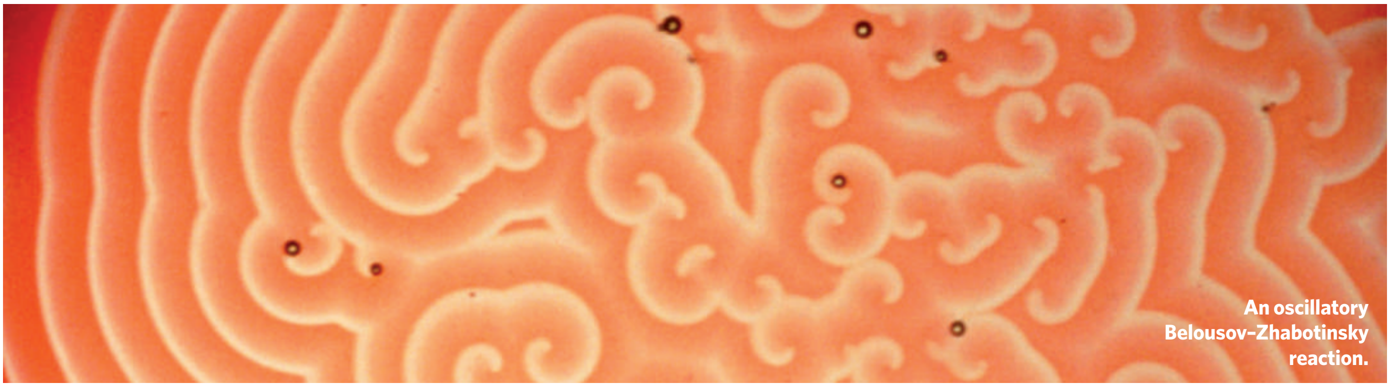
Q&A


An oscillatory Belousov–Zhabotinsky reaction.

P. PLAILLY/SPL

SYSTEMS CHEMISTRY

Molecular networks come of age

Jonathan R. Nitschke

The advent of sophisticated analytical tools enables the collective behaviour of networks of interacting molecules to be studied. The emerging field of systems chemistry promises to allow such networks to be designed to perform complex functions, and might even shed light on the origins of life.

What is systems chemistry?

It's the study of complex systems, or networks, of molecules. Tools for analysing complex networks are being developed and employed in fields as diverse as computer science and sociology. By applying these tools to systems of interacting molecules — molecules that might link together into larger superstructures, or catalyse one another's formation — chemists can investigate how interactions between members propagate through networks, allowing complex behaviour to emerge.

So what questions are systems chemists asking?

There are two main questions. The first is how the complex networks of molecules found on the prebiotic Earth might have crossed the threshold of life. Research into this area seeks possible mechanisms for how the biochemical building blocks of life were selected, and how biomolecules developed to have only one 'handedness' (chirality). The second question is how collections of molecules self-assemble into complex structures, and how secondary interactions between molecules and competition for molecular building blocks lead to complex behaviour within self-assembling systems. Such systems of molecules might sort themselves, for example, by pairing up in the same way as complementary DNA bases, or they might adapt to the addition of a substrate by combining in such a way as to create a strong binding pocket for that substrate.

Why the increased interest just now?

Recent strides in analytical methods allow complex mixtures of compounds to be picked apart and their constituents quantified without isolating each one individually. Using techniques such as high-performance liquid chromatography coupled to mass spectrometry and multidimensional nuclear magnetic resonance, up to 1,000 or so individual compounds can be identified within a mixture. The chemical evolution of mixtures over time can be tracked, allowing complex transformations to be followed and kinetic relationships between network members to be deciphered. Discoveries, ideas and tools from systems biology have also informed and inspired work in systems chemistry. Chemists can help to define the bedrock on which systems biology is built by showing how interactions between molecules lead to the emergence of function.

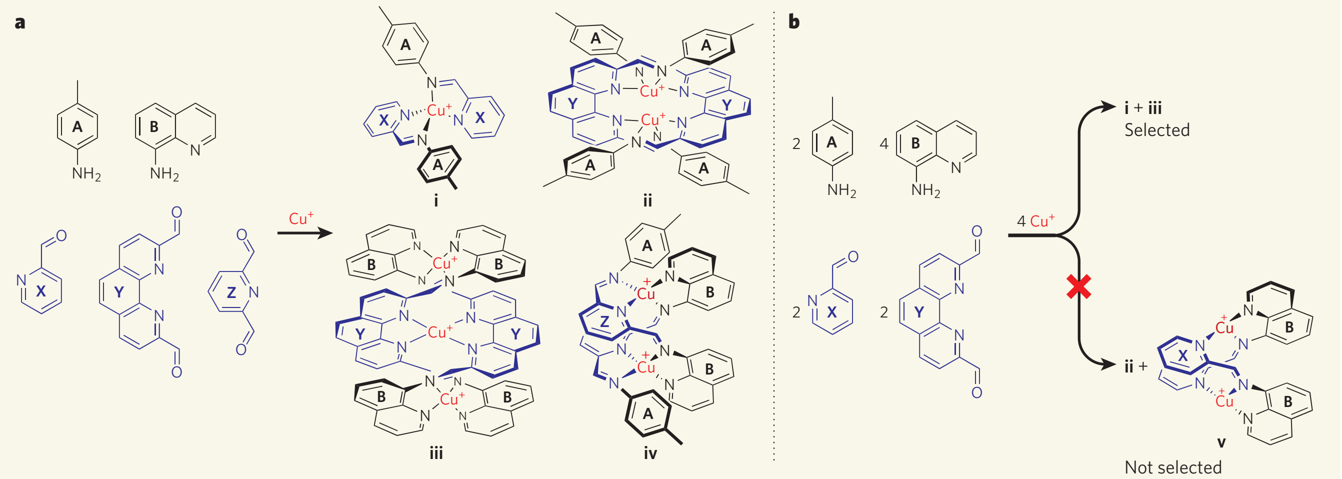
What do you mean by 'emergence'?

Emergence occurs when a complex system exhibits properties that can't be predicted by considering its subcomponents in isolation. For example, consciousness emerges when neurons come together into a brain, and the recent global recession was a consequence of vast numbers of interwoven individual financial transactions. Predictability is subjective, however, so calling a property 'emergent' is uncomfortably close to saying 'I wasn't clever enough to predict it', or worse — 'it is mystical'. Perhaps a better definition of 'emergent' is 'interesting and counter-intuitive', which highlights the necessary subjectivity and ties the elucidation of emergent phenomena directly to the scientist's role in unravelling the predictive rules that underlie everyday phenomena.

And what do you mean by 'complexity'?

In systems chemistry, perhaps the most useful definition is borrowed from information science: complex systems require more information to describe them than do simple systems. Specifically, complex chemical systems are richer in connections between members than simple ones. The complexity of a single molecule is necessarily limited by the number of bonds that individual atoms may form with others. But the complexity of a collection of molecules can be more than the sum of the complexities of each individual molecule, if the molecules can interact in different ways. Such interactions might be supramolecular, with molecules fitting together like locks and keys; or they might involve the exchange of molecular subcomponents; or they could be catalytic if one molecule catalyses the formation of several others. It becomes easier for complex behaviour to emerge from networks as the connections between members grow denser, because networks can then respond to stimuli in more complicated ways — the addition of a single chemical signal to a system can affect many of its members through the transmission of the signal from one member to another.

Box 1 | A thermodynamically controlled chemical system



Boundary conditions (input)
$[\mathbf{A}] - [\mathbf{X}] - [\mathbf{Z}] \geq 0$
$[\mathbf{B}] - [\mathbf{Z}] \geq 0$
$[\mathbf{Y}] = 2[\mathbf{A}] + 2[\mathbf{B}] - 2[\mathbf{X}] - [\mathbf{Z}]$
$[\mathrm{Cu}^+] = [\mathbf{A}]/4 + [\mathbf{B}]/2 + [\mathbf{X}]/4 + [\mathbf{Y}]/2 + [\mathbf{Z}]/4$

Quantities of products (output)
$[\mathbf{i}] = [\mathbf{X}]/2$
$[\mathbf{ii}] = ([\mathbf{A}] - [\mathbf{X}] - [\mathbf{Z}])/4$
$[\mathbf{iii}] = ([\mathbf{B}] - [\mathbf{Z}])/4$
$[\mathbf{iv}] = [\mathbf{Z}]/2$

In thermodynamically controlled systems, networks of reversible reactions lead to the generation of the most stable set of products. **a**, In this system, amines **A** and **B** react reversibly with aldehydes **X**, **Y** and **Z** and with copper ions to form copper complexes that contain imine (C=N) groups. In principle, a large number of products could form. But in practice, two empirical self-assembly rules are observed: the system generates the smallest possible structures that are not unduly strained, and the products are all coordinatively saturated (all the copper ions are bound to four imines, and each imine is bound to a copper ion). Only structures **i–iv** satisfy these rules. **b**, Additional selection rules arise in cases where several products form simultaneously. In this system, for example, **Y** preferentially pairs with **B** to make **iii**, so that **A** and **X** are left to generate **i**. Even though **A** could pair with **Y** to make **ii**, **B** and **X** would then be forced to make **v**, which is not coordinatively saturated. The system may thus be seen to carry out logic operations during self-assembly, described by the boundary conditions and equations shown. [**A**] represents the concentration of **A**, [**B**] that of **B**, and so on. **J.R.N.**

What kinds of chemical system exhibit complex behaviour?

There are two main categories. The first involves systems of molecules undergoing thermodynamically controlled reactions (reversible reactions that lead to the generation of the most stable set of products), which approach equilibrium in a complex way. In these systems, numerous interactions between the molecules may act together to determine the most stable set of products from the network as a whole. The second category involves sets of kinetically controlled reactions (irreversible reactions proceeding along the most expeditious paths available), in which one reaction's products modulate another reaction's rate within the system.

How can an approach to thermodynamic equilibrium be complex?

When there are several different ways in which a pool of building blocks can come together to form a collection of products, the formation of one structure may leave behind a set of building blocks that can't form a stable product. The collective stability of all product structures within a system must thus be considered, which can be a complicated undertaking. The rules that govern the behaviour of a self-sorting system may be traced through and expressed in the form of algorithms or equations (Box 1).

What kinds of complex system evolve under kinetic control?

Those that contain autocatalytic reactions, in which a product catalyses its own formation, and those that involve cross-catalytic reactions, in which one product catalyses another's formation. Cross-catalytic reactions can give rise to oscillations, as a system periodically switches between discrete states (Box 2, overleaf). Feedback between coupled oscillators can be used to carry out computations, as happens in our own neural circuitry.

Do any systems exhibit both thermodynamic and kinetic complexity?

Biological systems do. Complex self-assembly processes operating under thermodynamic control are used to construct many of the complex forms of biomolecular systems. The protein subunits of viral capsids (their outer shells), for example, are held together in highly symmetric assemblies by many discrete, reversible interactions. In many cases, viral genetic material serves as a template for capsid formation — negatively charged nucleic acids attract positively charged capsid-forming proteins, which then arrange themselves into a capsid through the thermodynamic equilibration of van der Waals attractions, hydrophobic effects and hydrogen bonds, among other forces. Alongside such thermodynamically controlled processes, complex kinetics underlies all biological signalling networks. The simplest biological systems are therefore much more complicated than the most intricate synthetic chemical systems currently known. This begs the question of which chemical systems on the prebiotic Earth might have developed sufficient complexity to become alive.

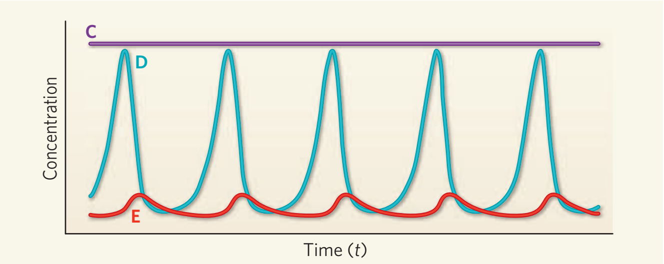
Do we know the answer?

Not yet, but ideas abound — such as the hypothesis that self-replicating RNA-like molecules, able both to encode information and to act as catalysts, served as an intermediate stage between naturally occurring mixtures of complex organic molecules and living systems. But we cannot yet follow our own story back to its beginning. This is a primal quest for chemists, and one that is likely to spin off much new knowledge along the way.

Can chemical systems perform complicated tasks?

Definitely. For example, a molecular 'motor' has been made in which a rotor spins unidirectionally about a double bond when irradiated with ultraviolet light (Fig. 1, overleaf). When the motor is dissolved in a thin film of liquid-crystal (LC) matrix, molecular interactions between the turning rotor and the matrix lead to a continuous reorganization of the overall LC system. This causes micrometre-scale corrugations on the LC surface to

Box 2 | Kinetically controlled chemical systems



$d[\mathbf{D}]/dt = k_1[\mathbf{D}][\mathbf{C}] - k_2[\mathbf{D}][\mathbf{E}]$

$d[\mathbf{E}]/dt = k_3[\mathbf{E}][\mathbf{D}] - k_4[\mathbf{E}]$

Kinetically controlled complex chemical systems contain autocatalytic reactions, in which a product catalyses its own formation, and cross-catalytic reactions, in which one product catalyses another's formation. The graph shows the changes in concentration of the components of a hypothetical chemical system containing three compounds — **C**, **D** and **E** — described by the rate equations under the graph. [**C**] indicates the concentration of **C**, [**D**] that of **D**, and so on; *t* is time; k_1 to k_4 are constants. The system is both autocatalytic, because the rate of increase of [**E**] is proportional to [**E**], and cross-catalytic, because the rate of increase of [**E**] is proportional to [**D**]. As long as [**C**] is kept constant, the system will oscillate regularly.

Ecologists will recognize the equations as the Lotka–Volterra 'predator–prey' equations of population dynamics in ecosystems, where **D** is prey, **E** is predator, **C** is food and the constants reflect rates of prey reproduction (k_1), predation (k_2), predator reproduction (k_3) and predator mortality (k_4). The polymath Alfred Lotka originally conceived the equations to describe chemical oscillations; only later were they applied to ecosystems. No known chemical reactions follow these equations, but slightly more complex autocatalytic and cross-catalytic systems, such as the oscillatory Belousov–Zhabotinsky reaction, are described by similar mathematics.

The myriad auto- and cross-catalytic biochemical reactions that take place during the cell cycle may be seen as constituents of a highly complex chemical oscillation in which an entire cell is duplicated. A fundamental link thus connects the kinetics of the biochemical reactions underpinning the exponential growth of cells (and by extension, organisms) to the dynamics of populations of organisms within ecosystems. **J.R.N.**

rotate clockwise, which in turn can rotate a macroscopic object embedded in the matrix. Interactions between the components of the system thus cooperate to transform light energy into torque. Light has also been used to push a different chemical system out of equilibrium, by allowing ring-shaped molecules to travel easily in one direction along molecular shafts, but creating a dynamic barrier to their return. This system is described as an information ratchet by its creators, because it can process information about the ring's position, and the barrier can be raised or lowered accordingly. Such a mechanism could form the basis of a component for information-processing molecular machines.

What other problems might be addressed using systems chemistry?

Many advanced materials, such as composites, consist of systems of intermingled basic materials (metals, ceramics, polymers and so on) that interact in complex ways. Understanding the chemical nature of these interactions is essential for tuning and designing the properties of advanced materials. Synergistic drug interactions — interplay between different drugs in the body that can cause biological effects not seen when the drugs are taken individually — likewise emerge from complex networks of drug molecules and biomolecules. Insight into such networks will underpin our understanding of the pharmacology of drug combinations.

Biological structures such as the ribosome (nature's protein-making machinery) also provide clues to how chemical systems might be used as molecular assembly lines to effect multi-step transformations, as a substrate is passed from one component of a catalytic system to another, with each component bolting on a new molecular subunit.

What will be needed to meet these goals?

Perhaps the most useful tool would be a 'retrosynthetic' methodology that can be used to reverse-engineer chemical systems. This would facilitate the design of links between the members of chemical networks, in the same way that sequences of chemical bonds may be planned and constructed in the syntheses of complex organic molecules. Such a methodology for systems chemistry is still a long way off, but its foundations are being laid as the basic rules that govern interactions between members of molecular networks are deciphered. ■

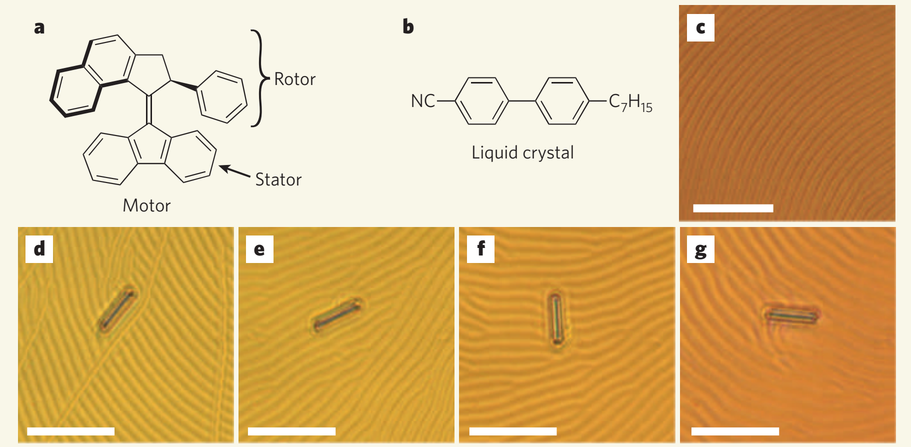


Figure 1 | Systems chemistry in a spin. a, When this molecular 'motor' is irradiated with ultraviolet light, the rotor turns relative to the stator. **b, c,** If the motor molecules are dissolved in a thin film of a liquid crystal (LC; **b**) at a concentration of 1% by weight, a 'cholesteric' phase (**c**) is created, in which the LC molecules stack in a helical fashion, parallel to the surface they cover. This results in a sinusoidal surface corrugation of the film, with a peak-to-peak distance that corresponds to the helices' pitch. Light-driven twisting of the motor within the LC matrix lengthens the optimal helical pitch of the cholesteric LC matrix, 'winding' tension into the system. **d–g,** As the LC molecules rearrange to release this tension, the surface corrugations rotate clockwise. The resulting torque is sufficient to rotate a cylindrical glass rod (5 × 28 micrometres in size), as shown in this series of pictures taken at intervals of 15 seconds. The transformation of light energy into torque thus emerges out of a complex system formed by two simple molecules. Scale bars, 50 micrometres. (Images taken from R. Eelkema *et al.* *Nature* 440, 163; 2006.)

Jonathan R. Nitschke is in the Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK.
e-mail: jrn34@cam.ac.uk

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