

# Networking opportunity

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A neglected mathematical theory is enjoying new popularity, thanks to its relevance to network dynamics in biological systems. The beating of a leech's heart is just one example that has a mathematical basis in 'groupoid theory'.

The historically uneasy relationship between biology and mathematics has improved markedly in recent years, as it has become increasingly clear that our understanding of biological systems can benefit from mathematical input and insight. Examples include the spatial and temporal behaviour of ecosystems, the geometry of protein folding, the informatics of DNA, the dynamics of the cytoskeleton and the mechanisms of visual perception. In such areas, biologists can accumulate the key data, delineate the important interactions and suggest possible mechanisms, but at some point the questions migrate to realms that are more congenial to physicists and mathematicians. Conversely, biology poses stimulating challenges for mathematics. A case in point is network dynamics. Networks arise naturally in many areas of science, and there are numerous examples in biology: gene regulation<sup>1</sup>, protein networks<sup>2</sup>, epidemiology<sup>3</sup>, ecological food webs<sup>4</sup>, neural networks for locomotion<sup>5</sup>, vision<sup>6</sup>, speciation<sup>7-9</sup> and the synchronous flashing of fireflies<sup>10</sup>.

Many phenomena of pattern formation are common in the dynamics of networks, especially synchrony and phase-locking<sup>11-13</sup>. Understanding the generalities of such patterns requires a formal theory of network dynamics to act as an intellectual framework. This stimulus from biology has encouraged a new approach<sup>14</sup> to the problem, in terms of the mathematical theory of 'groupoids'<sup>15</sup> — a flexible form of symmetry, which is the main subject of this article. The aim is to illustrate how biological motivation can suggest novel mathematics. Along the way, there are also glimpses of possible trade in the opposite direction.

## The leech heart

Even small networks can be puzzling. A fascinating example<sup>16</sup> — not fully explained, even by the theory to be described, but still excellent motivation — is the heart of the medicinal leech, *Hirudo medicinalis*. The heart consists of two lateral sinuses, each a tube-like series of chambers, located in the third to eighteenth segments of the leech's body (Fig. 1a). Each sinus contracts in a coordinated pattern: in one sinus, all chambers beat synchronously, in the other there is a rear-to-front travelling wave in

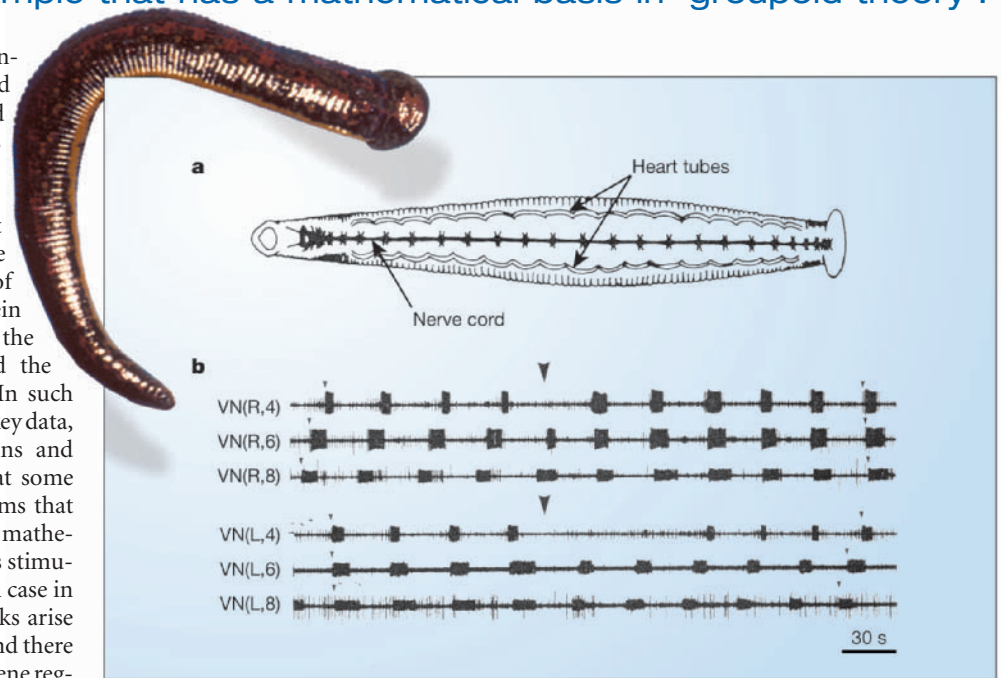


Figure 1 The heart of the leech *Hirudo medicinalis*: a, the physiology and b, the observed patterns of neural activity. Traces are shown for segments 4, 6 and 8 of the left (L) and right (R) vascular nerves (VN). The left side of the figure shows travelling waves on the right side of the heart and synchrony on the left; the right side of the figure shows the reverse, with the switch occurring at the points marked with arrowheads. The rapid 'bursting' dynamics of the neurons might be triggered by a slow dynamic with the same pattern of phase shifts<sup>18</sup>. (Graphic derived from ref. 16.)

which successive chambers contract in turn. Roughly every 50 beats, the two sides switch roles (Fig. 1b). One possible evolutionary/physiological reason for this pattern is that systolic pressure is high in the travelling wave but lower in the synchronous contractions. But what is its mathematical basis?

A mapping of the relevant neural connections has shown that this curious pattern is coordinated by a small network of neurons at the rear of the animal<sup>16,17</sup>. Four of these, in segments 3 and 4, form a 'timing oscillator' that drives three pairs of interneurons (which cross-connect neural pathways) in segments 5, 6 and 7. The interneurons organize the two waveforms and control switching between them<sup>17</sup>; motor neurons transfer the timing patterns to the heart chambers. The actual signals are high-frequency bursts; these are probably driven by a slow dynamic with the same pattern of phase shifts, in which case it should be sufficient to understand the slow dynamic<sup>18</sup>.

Even though the architecture of this network of neurons has been mapped, mathematically there are unanswered questions. In

particular, it would be useful to understand how travelling waves and synchrony arise here and in networks in general, and how the network architecture produces the distinct coordinated states and switches between them. Groupoid theory goes some way towards such an understanding.

A real network has two main ingredients. First, there are 'agents', usually in profusion (for the leech heartbeat, these are various motor neurons and interneurons). Second, these agents interact, and influence one another's behaviour (for the leech, through their synaptic interconnections). The key observation that makes an abstract theory of networks possible is that the topology of those interactions — the 'architecture' of the network — can have a systematic influence on network behaviour that is more or less independent of the precise details of the agents and their interactions. An infection, for example, is transmitted more rapidly by people who have many contacts than by people who have few; with a few caveats about incubation times and the like, this is true whatever the disease might be. An associated

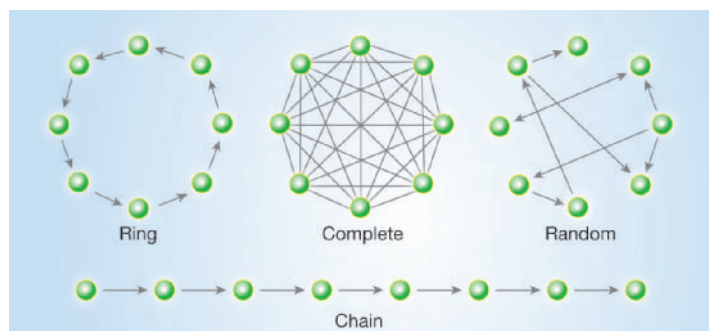


Figure 2 **Common network architectures.**

observation is the occurrence of ‘motifs’ — small subnetworks with specific patterns of interconnection that are unusually common<sup>19,20</sup>, and may represent significant building blocks for network function.

The leech heart illustrates two important types of pattern in network behaviour: synchrony and phase-locking. The chambers along one side of the animal are synchronized — they all do the same thing at the same instant. Meanwhile, the other chambers follow the same dynamics, but shifted by some regular amount. Many notions of synchrony are found in the literature<sup>12</sup>. Here I focus on the simplest idealization, in which two nodes are synchronous if their states are identical at all times. More realistic forms of synchrony can be viewed as perturbations of this ideal case.

**Network architecture**

Mathematically, a network can be idealized as a graph<sup>21</sup>, which consists of nodes (vertices) linked together by edges (links, connections, arrows). The nodes represent the agents, the edges represent their interactions. Two nodes are joined by an edge if, and only if, they interact. Edges may be bidirectional (interactions go both ways) or unidirectional (A influences B but not the other way round). The unidirectional case yields a so-called directed graph, whose edges are usually drawn as arrows. The edges may carry ‘weights’ to indicate the strength of the interaction. They may be of different kinds (fox predated on rabbit is different from rabbit predated on vegetation) or they may be nominally identical (fox A predated on rabbit X is near enough the same as fox B predated on rabbit Y). These distinctions can be taken into account by labelling the nodes and edges so that ‘identical’ nodes or edges carry the same label. Important architectures include chains, rings, complete graphs (all-to-all coupling) and random graphs (Fig. 2). Couplings can be to nearest neighbours, near neighbours (so many steps removed) or long-range.

We can investigate networks in the abstract (using graphs), in concrete mathematical models where the nodes and edges have additional structure, and in real networks with real agents and interactions. These three contexts are closely associated, but it is important to bear in mind that they

are different. As long as we do that, we can safely employ the same words in all contexts — for example, talking of a rabbit as a node in a food-web and drawing it as a dot.

Different people use networks for different purposes and ask different questions about them. An early pioneer was Kauffman<sup>22</sup>, who employed binary switching circuits (each node can be either on or off) to model gene interactions in a cell. He found that the dynamics of the network depended critically on the average number of edges linked to each node. The literature includes innumerable types of network: discrete (cellular automata<sup>23</sup>), continuous (differential equations<sup>24</sup>), probabilistic (Markov chains<sup>25</sup>), fractal (iterated function schemes<sup>26</sup>) and complex systems<sup>27</sup>. A radically new network architecture that has attracted attention is the ‘small world’: a regular network with near-neighbour connections, in which some edges are randomly rewired to become long-range connections, or some nodes become ‘hubs’ that are connected to an unusually high number of other nodes<sup>28</sup>.

There are several general theories of network structure and behaviour. Among them is a huge body of graph theory, invented by pure mathematicians<sup>21</sup>. Intensive work on the statistical properties of random graphs<sup>29</sup> has shown that, as the probability of including any given edge increases, there is a ‘phase transition’ at which most of the nodes suddenly link up into a single, giant component. This result shows, metaphorically at least, that if the probability of disease transmission becomes sufficiently great, almost everyone will be exposed. Less obviously, it shows that there is a sharp threshold, below which the infection remains in numerous small ‘pools’ isolated from one another, and above which nearly everyone is exposed.

Another approach, followed by Kuramoto<sup>30</sup>, analyses network dynamics in the special case of phase oscillators with weak, linear coupling. That is, the only dynamic variable is the phase of the oscillation; the effect of any node on any other to which it is linked by an edge is small and is proportional to the state of the node or the difference between states. Think of a disease whose likelihood of being transmitted is very small, for instance. With these assumptions, useful quantitative predictions can be made about the behaviour of the network and its stability.

However, in real-world networks strong coupling and nonlinearity are rife. But these issues can be tackled. One approach, once a specific model is agreed upon, is computer simulation. An alternative is to formalize general elements of mathematical structure. In this case, the results typically apply only to special, often idealized, networks, but they can be proved with logical rigour and provide deeper understanding than just “the computer says so”.

An example of general structure in a network is symmetry. Mathematically speaking, a symmetry of a network is a permutation of its nodes that preserves labels, directions and the network topology. These permutations form a group: the permutations can be inverted (still preserving the network topology); and if any two are performed in turn, the result is equivalent to performing another permutation that is a member of the group. This symmetry group of a network has a very strong influence, and the catalogue of possible behaviour is largely independent of the specific dynamics of nodes and couplings. Symmetry principles have been applied to network dynamics in locomotion<sup>5</sup>, vision<sup>6</sup>, speciation<sup>7–9</sup> and many areas of physical science<sup>24</sup>. However, such a concept of symmetry is too rigid for many applications. As we shall see, a more flexible view can be taken, which still preserves the structural principles of pattern formation.

**Mathematical description**

In the formalism<sup>14</sup> that follows, each node determines a system of differential equations, and directed edges specify couplings. To illustrate the principles, Fig. 3 shows three simple networks: a ring, a chain and a modified chain with feedback. In these examples, all nodes are equivalent (they obey the same equations) and all couplings are equivalent (interconnected nodes affect one another in the same way). For each network there is a class of ‘compatible’ differential equations, describing the behaviour of each node over time. In Fig. 3a, for example, we assume that the state of any node, *i*, is determined by the variable *x<sub>i</sub>*. (For simplicity we assume that each node has one degree of freedom, so *x<sub>i</sub>* is a number.) The equations compatible with the ring network are shown in Fig. 3a, with the same function *f* throughout. The first variable of *f* represents the internal state of the node, and the second represents the node from which it receives an input.

The most striking mathematical feature of these equations is their symmetry. The graph is symmetric under cyclic permutations of the nodes, and so are the equations. The typical patterns of time-periodic states in symmetric systems are predicted by theory<sup>24</sup>. For this ring network, one common pattern is a clockwise rotating wave: a periodic oscillation in which successive cells differ by a phase shift of one-third of a period. Another

possibility is an anticlockwise rotating wave (with a phase shift of two-thirds of a period).

Next, consider the chain shown, with its set of equations, in Fig. 3b. Note that node 1 has no inputs and therefore requires a distinct function  $g$ . Despite the regular appearance of the network, there is no symmetry. Each node occupies a distinct place in the chain. Indeed, with one degree of freedom for each node, the network cannot support a non-steady periodic state.

Finally, the chain in Fig. 3c is modified to include feedback. The equations contain only one function,  $f$ , because now node 1 receives an input from node 3. This network also has no symmetry; nevertheless, it supports periodic oscillations with a striking pattern. To see why, suppose that nodes 1, 4 and 7 are in synchrony, that nodes 2 and 5 are in synchrony, and that nodes 3 and 6 are in synchrony (indicated by the colours in Fig. 3c). That is, define  $y_1 = x_1 = x_4 = x_7$ ,  $y_2 = x_2 = x_5$  and  $y_3 = x_3 = x_6$ . The first three equations for the modified chain become:

$$\begin{aligned} dy_1/dt &= f(y_1, y_3), \\ dy_2/dt &= f(y_2, y_1), \\ \text{and } dy_3/dt &= f(y_3, y_2). \end{aligned}$$

These are the same equations as for the ring of Fig. 3a, with the  $x_i$  replaced by  $y_i$ ; the remaining four equations in Fig. 3c just repeat one or other of these equations. So, from what we know about symmetry in the simple ring network, in this network with feedback there exists a periodic state in which nodes 1, 4 and 7 are in synchrony; nodes 2 and 5 are in synchrony with each other but are one-third of a period out of phase with nodes 1, 4 and 7; and nodes 3 and 6 are in synchrony with each other but are two-thirds of a period out of phase with nodes 1, 4 and 7 (for appropriate choice of  $f$ ). That is, there are travelling-wave states in which successive nodes along the chain differ only by a phase shift of one-third of a period.

This observation is striking: hitherto, travelling waves have mainly been associated with symmetric networks. The network in Fig. 3c has no symmetry, and neither do its associated equations. But when we restrict our considerations to the ‘synchrony subspace’ (with the assumption that  $y_1 = x_1 = x_4 = x_7$ ,  $y_2 = x_2 = x_5$  and  $y_3 = x_3 = x_6$ ), a hidden ‘rotational’ symmetry becomes apparent. A travelling wave can be generated whatever the size of the feedback loop and however long the chain. Moreover, a synchronous oscillation of the entire chain arises if, instead of node 3 connecting to node 1, the first node feeds back to itself. Qualitatively, these two patterns resemble those observed in the leech heartbeat, and neurological studies<sup>16,17</sup> have added important detail, as already described.

The general formalism that underlies this kind of hidden symmetry is simple but influ-

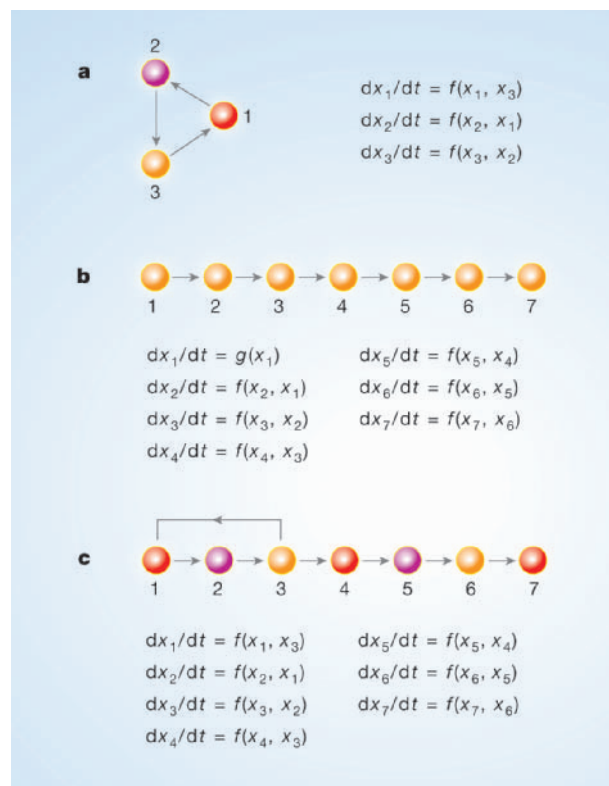


Figure 3 Describing a network. a, The behaviour of three identical nodes connected in this directed ring is rendered in the three differential equations shown. b, For a linear chain of seven identical nodes there are seven such equations. As node 1 has no inputs, its behaviour must be described with some different function, and the symmetry of the equations is broken. c, If feedback is introduced from node 3 to node 1, the symmetry of the equations is restored. The nodes are coloured to reflect the ‘equivalence classes’ that define a ‘quotient network’ — that is, this equivalence makes the dynamics in c equivalent to the dynamics in a (the inputs follow the pattern orange to pink, pink to yellow and yellow to orange in both).

ential. The root cause of the hidden symmetry in the modified chain network of Fig. 3c is not symmetries of the entire network, but symmetries between special subsets of the network, namely, the input sets — all nodes that emit an arrow pointing to a given node. For example, in Fig. 3a and c every node receives an input from exactly one other node. All nodes are identical and all edges are identical, so the input sets are all ‘isomorphic’. In contrast, the network in Fig. 3b has two types of input structure: node 1 receives no inputs, whereas nodes 2–7 receive inputs from one other node. This difference is reflected in the appearance of a different function  $g$  for the dynamics of node 1, whereas nodes 2–7 are governed by the same function,  $f$ .

### From groups to groupoids

As discussed above, the symmetries of a network — those permutations of its nodes that preserve edges, labels and directions — form a group in the usual algebraic sense<sup>31</sup> if any two symmetries performed in turn produce another symmetry of the network. Input isomorphisms are similar, but they permute only a subset of nodes, namely, those whose arrows point to a given node. The corresponding algebraic structure is no longer a group but a groupoid, a concept introduced by Brandt<sup>32</sup> in 1927. Groupoids have, on the whole, been somewhat removed from the mathematical mainstream — few undergraduate courses mention them, for example. However, they are the ideal tool for describing symmetries that apply only to parts of systems. Groupoids are more flexible and often more appropriate than the better-known

groups, and they have been unduly neglected.

To use groupoid terminology, the network in Fig. 3c has a synchrony subspace in which the dynamics is that of the network in Fig. 3a because it has a ‘quotient graph’: in this, the nodes are identified in three ‘equivalence classes’ — {1,4,7}, {2,5} and {3,6} — that respect the groupoid structure. Associated with any such quotient graph is a synchrony subspace in which states of nodes that belong to the same equivalence class are identical. The synchrony subspace is invariant under the dynamics of the network (that is, synchronized initial states remain synchronized indefinitely), and the dynamic restricted to that subspace has the form determined by the quotient graph.

Using the groupoid formalism, all robust patterns of synchrony in a network can be worked out<sup>14</sup> — that is, patterns that occur (stably or unstably) for all differential equations compatible with the network architecture. These patterns are given by the so-called balanced equivalence relations. Informally, imagine colouring the nodes so that synchronous nodes are the same colour (as in Fig. 3c). Each colour corresponds to an equivalence class. The colouring is balanced if any two nodes with the same colour have input sets that are isomorphic via a permutation that keeps all colours fixed — for example, if any one red node has inputs from three green nodes and two yellow ones, then every red node has inputs from three green nodes and two yellow ones. Intuitively, this condition makes good sense: it means that the dynamics of any red node is given by the same function of red, green and yellow

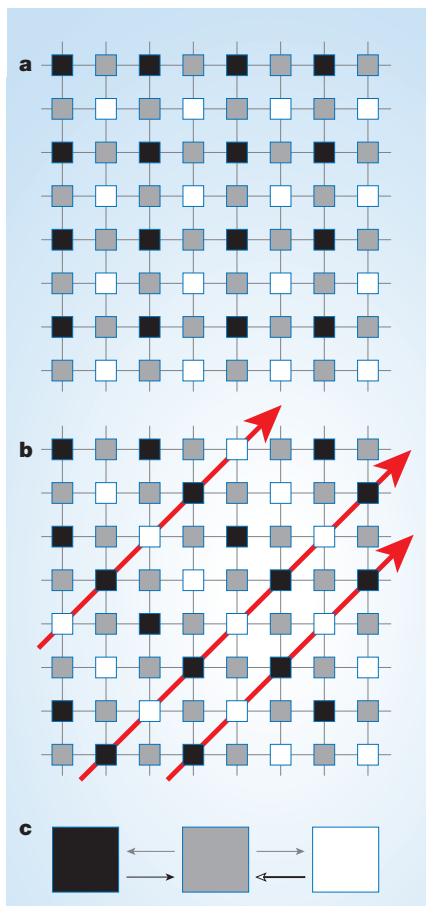


Figure 4 A square lattice, with nearest-neighbour coupling between nodes. a, The balanced equivalence relation is indicated by the three-colour scheme. All couplings are bidirectional, and nodes of the same colour are synchronous. b, Arbitrary parity changes along diagonals (red arrows, interchanging black and white squares) also produce a balanced equivalence relation. c, The quotient network has three nodes and is the same in all cases. Its left-right symmetry implies that there are robust, 'multirhythm', time-periodic states, in which the black and white nodes are half a period out of phase and the grey node has twice the frequency. Networks a and b therefore possess corresponding states in which identically coloured nodes are synchronous, and which can all be stable simultaneously<sup>33</sup>.

nodes, which is a necessary and sufficient condition for synchrony to be maintained.

A more extensive example<sup>33</sup> is a square lattice of nodes with nearest-neighbour coupling. Here all nodes are identical, and all couplings are identical and bidirectional. The groupoid structure reveals a host of time-periodic patterns of synchrony in which three colours occur. One is highly symmetric (Fig. 4a); the rest are asymmetric (such as Fig. 4b) and can be obtained by choosing some subset of diagonal lines and interchanging the colours. However this is done, every grey node receives an input from two black and two white nodes, and every black (or white) node receives an input from

four grey ones, so the colouring is balanced. The quotient graph (Fig. 4c) is therefore the same in all cases, so all patterns can coexist in the same network. In fact, the typical periodic state here is a 'multirhythm' in which the grey nodes have twice the frequency of the black and white ones, and the latter are half a period out of phase<sup>24</sup>. Thus, elements of pattern and randomness coexist in such states.

### A way forward

Network architecture can impose significant constraints on the dynamics of the system, but the groupoid formalism makes it possible to approach network dynamics within a coherent theoretical framework. Just as group theory has illuminated pattern formation in symmetric systems, so groupoid theory can illuminate pattern formation in systems with repeated subunits: mathematically, the groupoid structure generalizes the group structure.

An important question is stability. Balanced equivalence relations specify robust patterns of synchrony, but 'robust' here does not equate with 'stable' in the usual dynamical sense. Further analysis, exploiting the groupoid structure, shows that the travelling waves in the chain of Fig. 3c and the patterns in the square lattice can, in fact, all occur stably for a wide range of compatible equations<sup>33</sup>. The effect of symmetry on stability is significant and well understood<sup>24</sup>; the relevant principles should generalize (though not directly) to the groupoid case. One application of such principles is food webs: although specific webs can be studied numerically, there remains a need for general ecological principles that guarantee stability<sup>4</sup>.

But network dynamics is far richer than merely steady and periodic states. Quasiperiodic behaviour, combining oscillations of incommensurable periods, are common. So is 'synchronized chaos', in which distinct nodes pursue identical but chaotic dynamics — a phenomenon widely studied because of its potential application in secure communications<sup>13</sup> and its possible role in neural communications where certain nerve cells fire together (chaotically or regularly)<sup>34</sup>. The groupoid classification of patterns of synchrony includes these more exotic types of behaviour. Subtle phenomena that occur in chaotic dynamics — such as 'bubbling', where nodes repeatedly almost synchronize only to diverge again<sup>35</sup> — probably underlie some notions of approximate synchrony.

The phenomena that are typical in networks differ in many ways from those that are typical in a general dynamical system. The network architecture not only selects particular patterns and behaviours, but permits patterns that would not normally arise at all. Philosophically, networks are a marvellous way to make exotic dynamics and patterns robust and controllable. Perhaps this is why nature makes so much use of networks.

At any rate, it places the understanding of networks high on the biomathematical agenda. The groupoid formalism is one promising route to such understanding.

Of course, specific networks governed by explicit equations can be studied through computer simulations. But in many areas, especially biology, there is no widely accepted choice of equations. In these areas — neuroscience, evolutionary biology, cell biology, ecology — general principles relating qualitative dynamics to network architecture are vital. The development of this theory will require many modelling issues to be addressed (such as approximate versus exact identity of components or states): to do so, input from both biology and mathematics will be needed. In this respect, network dynamics is a striking instance of the growing spirit of collaboration between these two major areas of science. ■

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