time the device returns to equilibrium.

Spintronic oscillators have a few key properties: they are tens to hundreds of nanometres in size; they are nonlinear (they can exhibit stable isolated oscillations); they can be analysed using signal-processing methods; and they produce analog, rather than digital, signals. Spintronic oscillators also have useful capabilities. For example, they can perform many distinct tasks simultaneously by combining (multiplexing) signals and they are capable of phase locking — a property that stabilizes the oscillations. The transistors used in conventional computing can be as small as spintronic oscillators, approaching the size of a single atom. However, a network of transistors that emulates the properties of a spintronic oscillator would be larger and more complex than the corresponding oscillator.

The approach of using oscillations for computations is based on biology. Recordings of electrical activity in the brain show that neurons transmit signals whose oscillations have a wide range of frequencies. Furthermore, biological rhythms operate on time scales ranging from milliseconds to months[3]. These oscillations are forms of analog information processing. One notable feature, which spintronic oscillators share, is that the oscillations are remarkably stable in the presence of noise and other perturbations.

In the 1940s and 1950s, the mathematician John von Neumann proposed using microwave-frequency oscillators for general-purpose computations[4]. By using one oscillation in voltage to represent '0' and the antiphase oscillation to represent '1', von Neumann showed that all arithmetic operations can be performed using simple electronic circuits called NAND gates. However, his proposal came immediately before the advent of transistors. Transistors took over the computing world because they are simple in design and, with ingenious engineering, can be interconnected to form complex switching circuits that perform the required arithmetic operations.

In the past decade, there has been an explosion in applications of artificial intelligence, machine learning and, in particular, 'deep' learning that require powerful computers to simulate massive artificial neural networks. At the same time, there have been concerns that transistors are reaching their limit in terms of size, functionality and cost effectiveness. New types of transistor and alternative technologies are being investigated throughout the computing industry, with the aim of producing ever-smaller computer circuits. Some researchers are revisiting von Neumann's ideas to use oscillators for arithmetic computation[5], whereas others are developing computers based on quantum mechanics[6]. Torrejon and colleagues' work is the first step in a different direction — it suggests that spintronic oscillators could pave the way to building specialized chips for large-scale neural networks. The present era feels similar to that of 60 years ago, when transistors were first used to replace vacuum tubes in computing machines.

Torrejon *et al.* used an approach called reservoir computing, which is derived from studies of neural networks in the prefrontal cortex of primate brains[7]. In this approach, an input signal is fed into a computing system called a reservoir. Another computer is trained to read the state of the reservoir and map this state to the desired output.

The authors' reservoir is a spintronic oscillator comprising a non-magnetic material sandwiched between two magnetic layers (Fig. 1). As the input signal, the authors used an audio file of an isolated digit (0 to 9) pronounced by one of five different speakers. They then transformed the audio signal into an electrical current using signal-processing methods (the pre-processing stage). The current drives the oscillator, producing a voltage that measures the deflection of the magnetization from equilibrium. Finally, the authors identified the spoken digit (the output) from this voltage using machine-learning methods (the post-processing stage).

Torrejon *et al.* achieve digit-recognition rates of up to 99.6%, independent of the speaker — a result that is competitive with other state-of-the-art technologies[2]. Currently, the pre-processing of inputs and the post-processing of outputs rely on digital computation, so the authors' system is a hybrid digital–analog machine. The reservoir cannot be tuned during the recognition process, but the pre- and post-processing systems can be (for example, during training).

Neuromorphic computers might not become general-purpose computational machines. It is more likely that they will make up arrays of specialized computers that communicate and synchronize their activities — much like the brain does — but at speeds of gigahertz rather than hertz, and on length scales of nanometres rather than micrometres. Such computers could also be hybrids of digital and analog devices, thereby taking advantage of the strengths of both technologies.

A natural next step for the authors is to investigate networking of spintronic oscillators to design and build more-complex arrays that have greater functionality. Connections between such oscillators could be achieved using electrical or optical pathways, or through excitations called spin waves that propagate in a common magnetic medium. In addition, input and output processing might eventually reach the scale and functionality of spintronic oscillators. Torrejon and colleagues' system is a breakthrough in terms of using oscillators for computing. The system works, and it holds promise for major gains in classification, computation, control and switching. ■

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1. Torrejon, J. *et al. Nature* **547,** 428–431 (2017).
2. Yildiz, I. B., von Kriegstein, K. & Kiebel, S. J. *PLoS Comput. Biol.* **9,** e1003219 (2013).
3. Buzsaki, G. *Rhythms of the Brain* (Oxford Univ. Press, 2011).
4. von Neumann, J. Nonlinear capacitance or inductance switching, amplifying, and memory organs. US patent 2815488 (1957).
5. Hoppensteadt, F. C. & Izhikevich, E. M. *Phys. Rev. Lett.* **82,** 2983–2986 (1999).
6. Lin, Z. R. *et al. Nature Commun.* **5,** 4480 (2014).
7. Dominey, P. F. *Biol. Cybern.* **73,** 265–274 (1995).

NEUROBIOLOGY

Synapses get together for vision

A sophisticated analysis in mice of how inputs to neurons from other neurons are distributed across individual cells of the brain's visual cortex provides information about how mammalian vision is processed. **SEE LETTER P.449**

TOBIAS ROSE & MARK HÜBENER

A typical pyramidal neuron in the brain's visual cortex receives thousands of excitatory signals from other neurons, transmitted across connections called synapses. These inputs from presynaptic neurons end on tiny protrusions called spines on the postsynaptic neuron's tree-like processes (dendrites). In principle, when a sufficient number of inputs are active at the same time, the postsynaptic neuron will fire. But not all inputs are equal: it matters where on the dendritic tree an input is located, and whether it is activated by similar stimuli to those that activate its neighbours, allowing simultaneously active inputs to team up for greater impact[1]. On page 449, Iacaruso *et al.*[2] describe how inputs activated by stimuli at different locations in visual space are mapped onto the dendrites of neurons in the visual cortex.

Neurons in the visual cortex respond to specific attributes of visual stimuli, including

particular contour orientations, the presence or absence of light, or a combination of factors. Importantly, each neuron responds only to visual stimuli in a small, defined region of the scene, known as that neuron's receptive field. The visual cortex as a whole contains a systematic representation of the visual scene, such that neighbouring neurons have receptive fields close to or overlapping one another, and neurons farther apart have distant receptive fields. One aspect of neuronal organization in the visual cortex that has remained unclear is whether synaptic inputs that are activated together cluster on dendrites. Previous studies[3–5] have reached divergent conclusions.

Iacaruso *et al.*[2] took a fresh look at this issue. They used small black-and-white squares as stimuli that they presented at different locations in a mouse's field of view to activate synaptic inputs from presynaptic neurons. They then painstakingly mapped a fraction of the active inputs to individual postsynaptic neurons. This was achieved by measuring brief increases in calcium-ion concentration, which occur in response to input activation, in dendritic spines. The researchers observed that spines located close to one another on a dendrite did tend to respond to stimuli in overlapping regions of visual space (Fig. 1). However, not all stimulus features were equally relevant — clustering was not determined by the orientation of contours, in agreement with earlier results in mice[3,4].

Next, the authors focused on spines that respond to stimuli from distant regions of the visual scene. Although neurons respond best to stimuli in their receptive field, their activity can be modulated by visual stimulation elsewhere in the visual scene[6]. These modulatory inputs are thought to provide contextual information, which might help in perceptual grouping — the process that determines which pieces of highly localized information belong together when objects extend over large regions of the visual scene, spanning many receptive fields[6,7].

Iacaruso *et al.* found that long-range synaptic inputs from presynaptic neurons that respond to distal regions of the visual field are not random. Instead, the presynaptic neuron is frequently tuned to the same orientation as the postsynaptic neuron, and responds to stimuli located in a part of the visual field that is 'co-linear' with the preferred orientation of the postsynaptic neuron. For instance, if a postsynaptic neuron prefers horizontal contours, the presynaptic neuron is activated by horizontal stimuli positioned in the visual scene along a horizontal axis (a co-linear axis) from the receptive field of the postsynaptic neuron. Anatomical[8] and functional[9] data from other animal models have suggested a similar set-up for long-range connectivity in the visual cortex, but Iacaruso *et al.* are the first to demonstrate this complex connectivity directly.

Finally, the authors observed that nearby and remote presynaptic neurons terminate at different dendritic locations on the postsynaptic neuron — remote, long-range inputs target distal dendrites, whereas inputs from cells that have receptive fields next to that of the postsynaptic neuron are located closer to the cell body (Fig. 1). This finding further supports the idea that visual space is mapped onto the dendrites in an organized way.

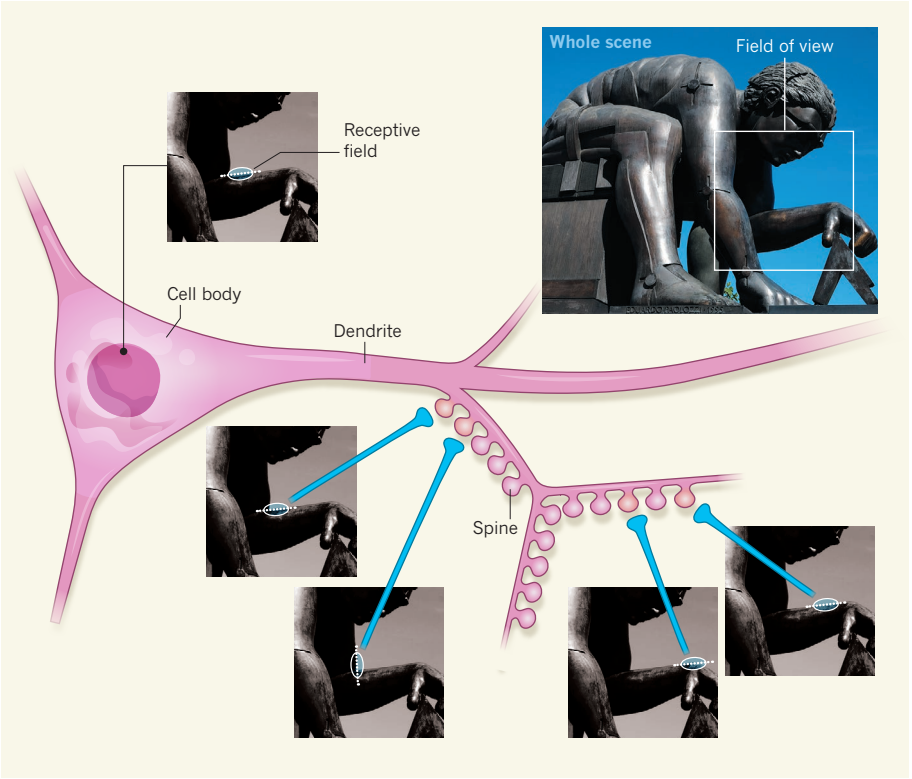

Figure 1 | Mapping visual space onto individual neurons. In a whole scene, the field of view is the portion processed by the eyes at any one time. Neurons in the brain's visual cortex (such as that in pink) are activated by light–dark boundaries of particular orientations in a small region of the field of view, known as their receptive field (orientation preference is indicated by the dotted line). Neurons receive information from others (blue) via small protrusions called spines on branched processes called dendrites. Iacaruso *et al.*[2] report that the arrangement of these inputs across dendrites in mice depends on the stimuli that activate the neurons involved — both those that send inputs and the postsynaptic neuron that receives them. Inputs from neurons that have overlapping receptive fields cluster on dendrites, regardless of their orientation preference. Inputs whose receptive field lies in regions of the scene close to that of the postsynaptic neuron tend to terminate close to the cell body, whereas those whose receptive fields lie in a distant part of the scene terminate farther from the cell body. These remote inputs tend to share the orientation preference of the postsynaptic neuron, and their receptive fields lie along an axis in the field of view formed by that orientation.

Iacaruso and colleagues' data set provides a starting point for further investigation of the relationship between the spatial arrangement of synaptic inputs and neuronal outputs, in the visual cortex and beyond. However, many questions remain. For instance, how does the clustering of similar inputs shape the way in which a neuron integrates information from all of its inputs? Does co-activation of neighbouring, spatially correlated inputs lead to dendritic amplification of like signals, which has been suggested to enhance orientation selectivity in the visual cortex in ferrets[5] and mice[10]? Do the synaptic inputs that provide information about remote, co-oriented and co-linear regions of the visual scene contribute to Gestalt phenomena — the rules by which our brain attempts to parse meaning from our perceptions of the surrounding world, for example by instantly identifying figures in otherwise randomly distributed lines[7]?

Answering these questions will probably require a drastic increase in the throughput of the difficult experiments undertaken by Iacaruso and co-workers. Individual cells must be stimulated with a wide array of more-complex visual stimuli, and activity recorded from many more spines and neurons. Ideally, these analyses would be performed in awake animals; mice were lightly anaesthetized in the current study, prohibiting analysis of neuronal activity during behaviour.

A final question is how such intricate connectivity arises during brain development. Some evidence[11] suggests that the well-established theory that neurons that fire together wire together might come into play here, causing the clustering of co-activated synaptic inputs during development. Alternatively, dendritic organization might be the result of activity-independent processes. Indeed,

sister cells derived from the same neuronal progenitor in the visual cortex are more likely than unrelated neurons to be connected and have similar orientation preferences[12,13]. Insight could come from classic experiments involving animals reared in particular visual environments (such as complete darkness or high-contrast contours), together with functional input mapping as used by Iacaruso and colleagues. ■

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1. London, M. & Häusser, M. *Annu. Rev. Neurosci.* **28,** 503–532 (2005).
2. Iacaruso, M. F., Gasler, I. T. & Hofer, S. B. *Nature* **547,** 449–452 (2017).
3. Chen, T.-W. *et al. Nature* **499,** 295–300 (2013).
4. Jia, H., Rochefort, N. L., Chen, X. & Konnerth, A. *Nature* **464,** 1307–1312 (2010).
5. Wilson, D. E., Whitney, D. E., Scholl, B. & Fitzpatrick, D. *Nature Neurosci.* **19,** 1003–1009 (2016).
6. Gilbert, C. D. & Li, W. *Neuron* **75,** 250–264 (2012).
7. Field, D. J., Hayes, A. & Hess, R. F. *Vision Res.* **33,** 173–193 (1993).
8. Bosking, W. H., Zhang, Y. & Schofield, B. & Fitzpatrick, D. *J. Neurosci.* **17,** 2112–2127 (1997).
9. Schwarz, C. & Bolz, J. *J. Neurosci.* **11,** 2995–3007 (1991).
10. Smith, S. L., Smith, I. T., Branco, T. & Häusser, M. *Nature* **503,** 115–120 (2013).
11. Winnubst, J., Cheyne, J. E., Niculescu, D. & Lohmann, C. *Neuron* **87,** 399–410 (2015).
12. Li, Y. *et al. Nature* **486,** 118–121 (2012).
13. Ko, H. *et al. Nature* **496,** 96–100 (2013).

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ORGANIC CHEMISTRY

Molecular structure assignment simplified

An innovative combination of chemical synthesis, theory and spectroscopy could simplify determination of the structures of naturally occurring, biologically active molecules, which are often leads for drug discovery. SEE LETTER P.436

SEVERIN K. THOMPSON & THOMAS R. HOYE

Nature has long served as a source of biologically active molecules called natural products, many of which help to combat diseases[1]. In some instances, natural products have become approved drugs, whereas in others, close structural analogues have emerged as the optimal therapeutic agents. Knowledge of the molecular structure of a natural product is essential for drug-discovery efforts, but structure determination is still difficult for many complex molecules. On page 436, Wu *et al.*[2] describe the re-elucidation of the molecular structures of the baulamycins A and B — two natural products that are potentially important leads for antibiotic discovery. The authors' approach could be applicable to determining the structures of other complex natural products.

When a drug is presented to a relevant biological receptor, the drug's unique chemical structure results in a selective binding event and a pharmacologically beneficial modulation of the receptor's function. Structural features that affect such binding include the sequence of chemical bonds in the drug and the array of chemical groups that define its molecular constitution. Perhaps the most essential structural feature is the 3D spatial (stereochemical) orientation of those bonds and groups. Molecules that contain one or more stereocentres, which are typically carbon atoms bonded to four different chemical appendages, can exist in multiple 3D forms called stereoisomers that often have distinct biological activities.

Baulamycin A and B were isolated from the bacterium *Streptomyces tempisquensis* in 2014, and their molecular structures were proposed[3] (Fig. 1a). Each molecule contains 7 stereocentres and can therefore exist as one of 128 (2^7) stereoisomers. Wu *et al.* devised and implemented an efficient synthesis (comprising just ten steps) of the proposed structures, only to find that the spectroscopic properties of the resulting compounds were not identical to those of the natural materials. They concluded, as had researchers doing parallel work[4], that the structures of the natural products had been misassigned — a not uncommon dilemma for chemists[5]. Wu and colleagues therefore undertook a series of studies that culminated in the deduction of the correct structure of the baulamycins (Fig. 1b).

Nuclear magnetic resonance (NMR) spectroscopy is currently the most powerful spectroscopic method used to deduce the stereochemical features of organic compounds. A common approach for deducing the relative

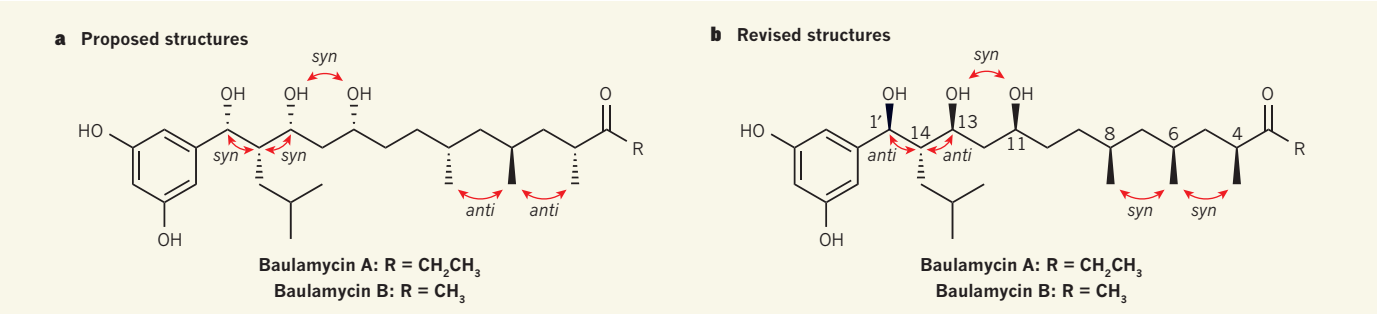

Figure 1 | Previously proposed and actual molecular structures of the baulamycins. a, The molecular structures of baulamycin A and B were first proposed[3] in 2014. Key features include the relative 3D geometrical alignments (stereochemical relationships) of the bonds, which are drawn as solid wedges (projecting above the plane of the page) or hashed wedges (projecting below). Pairs of bonds that project in the same direction are said to be in a *syn* relationship, whereas those that project in opposite directions are in an *anti* relationship. **b**, Wu *et al.*[2] now report corrected structures for the baulamycins, which the authors confirmed by synthesizing the molecules. In the corrected structures, the carbon atoms (C), indicated by numbers, are called stereocentres. Variation of the relationships among these 7 stereocentres means that the baulamycins could take any of 128 different 3D forms (stereoisomers). The authors revised the relative geometry of the C14 and C1′ stereocentres on the basis of a parameter known as the coupling constant, or *J* value, which was obtained using nuclear magnetic resonance (NMR) spectroscopy. Deduction of the stereochemical relationship in the C11–C14 portion was guided by another NMR technique, called ROESY, and the stereochemical relationship in the C4–C8 region was determined by synthesizing a mixture of unequal amounts of stereoisomers and then comparing the NMR spectrum of the mixture with that of a natural sample of baulamycin A or B.