On testing neural network models

Rafael Yuste

In my recent Timeline article, I described the emergence of neural network models as an important paradigm in neuroscience research (From the neuron doctrine to neural networks. *Nat. Rev. Neurosci.* **16**, 487–497 (2015))[1]. In his correspondence (Neural networks in the future of neuroscience research. *Nat. Rev. Neurosci.* http://dx.doi.org/10.1038/nrn4042 (2015))[2], Rubinov provides some thoughtful comments about the distinction between artificial neural networks and biologically inspired ones and about how a strictly data-driven approach may succeed at providing a general theory of neural circuits. I thank Rubinov for these comments and note that this theory agnosticism is a methodological approach that we respect and indeed sponsored in our Brain Activity Map proposal that led to the BRAIN Initiative[3]. Also, although in my Timeline article I tried to provide a brief summary of the history of artificial neural network models, I am not yet personally convinced that there are clear instances in which a biologically inspired neural network model has yet been validated ("…it is unclear whether existing neural network models have enough predictive value to be considered valid or useful for explaining brain circuits." (REF. 1)). There are many exciting areas of progress in current neuroscience detailing phenomenology that is consistent with some neural network models, some of which I tried to summarize and illustrate, but at the same time we are still far from a rigorous demonstration of any neural network model with causal experiments. I therefore could not agree more with Rubinov that we still have "largely not bridged the gap between elegant theory and neuroscientific observation". But when will we know that we have bridged that gap? This is a difficult question to answer, depending on the particular viewpoint, and I would leave this open to the reader's own interpretation. In my mind, a successful neural model should have quantitative accuracy in predicting either the behaviour, mental or perceptual state of the animal, or at least the future internal dynamics of the system. Another characteristic of a successful model could be its effective use in designing therapies of brain-based diseases. On the other hand, one of my mentors, David Tank, argued that for a true understanding of a neural circuit we should be able to actually build it, which is a stricter definition of a successful theory (D. Tank, personal communication) Finally, as mentioned in the Timeline article, one will also need to connect neural network models to theories and facts at the structural and biophysical levels of neural circuits and to those in cognitive sciences as well, for proper 'scientific knowledge' to occur in the Kantian sense.

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Neural networks in the future of neuroscience research

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Neural networks are increasingly seen to supersede neurons as fundamental units of complex brain function. In his Timeline article (From the neuron doctrine to neural networks. *Nat. Rev. Neurosci.* **16**, 487–497 (2015))[1], Yuste provides a timely overview of this process, but does not clearly differentiate between biological neural network models (broadly and imprecisely defined as empirically valid models of (embodied) neuronal or brain systems, which enable the emergence of complex brain function through distributed computation) and artificial neural network models (a relatively well-defined class of networks originally designed to model complex brain function[2] but now mainly viewed as a class of biologically inspired data-analysis algorithms useful in diverse scientific fields[3]).

A distinction between biological and artificial neural network models is important as the neuroscience network paradigm is mainly driven by the aim of uncovering biologically valid mechanisms of neural computation. Artificial neural networks were initially proposed as candidate models for such computation but, despite being enthusiastically researched at the end of the twentieth century, they have largely not bridged the gap between elegant theory and neuroscientific observation[4,5]. In this context,

Yuste's emphasis on some classic artificial neural network models does not seem to be supported by the evidence of, or the promise for, the problem-solving capacity of these models in neuroscience[6].

What could be an alternative promising approach to biologically valid neural network modelling? At present we can only speculate, but the ongoing development of high-resolution high-throughput brain imaging technologies — including those being developed as part of the BRAIN Initiative[7] — and the consequent availability of increasingly large structural[8] and functional[9] imaging data sets, make it appealing to initially search for patterns in such data in less theory-bound and more data-driven ways[10,11], and to subsequently construct theories a priori constrained on these discovered patterns[12]. A famous example of this approach in biology is the formulation of the theory of evolution by natural selection; this theory arose from an initial aim to catalogue all living biological organisms on earth, and from a subsequent careful analysis of the obtained diverse biological data[13]. Interestingly, artificial neural networks may yet prove to be important in this quest but in the role of powerful tools for analysing complex imaging data sets[14], rather than as a theoretical foundation for how the brain computes.

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PERSPECTIVES

From the neuron doctrine to neural networks

Rafael Yuste

Abstract | For over a century, the neuron doctrine — which states that the neuron is the structural and functional unit of the nervous system — has provided a conceptual foundation for neuroscience. This viewpoint reflects its origins in a time when the use of single-neuron anatomical and physiological techniques was prominent. However, newer multineuronal recording methods have revealed that ensembles of neurons, rather than individual cells, can form physiological units and generate emergent functional properties and states. As a new paradigm for neuroscience, neural network models have the potential to incorporate knowledge acquired with single-neuron approaches to help us understand how emergent functional states generate behaviour, cognition and mental disease.

In a way, the history of neuroscience is the history of its methods. This is evident in the case of the neuron doctrine, which states that the structural and functional unit of the nervous system is the individual neuron[1]. The neuron doctrine was first enunciated by Cajal[2] and Sherrington[3] (FIG. 1) and has served as the central conceptual foundation for neuroscience[1]. This focus on the properties of individual neurons was a natural consequence of the use of single-cell anatomical and physiological techniques, such as the Golgi stain[4] or the microelectrode[5]. The piecemeal reconstruction of neuronal circuits into their individual neuronal components using these methods enabled researchers to decipher the structural plan and design logic of many regions of the brain, with the analysis of the retina providing a remarkable early example[6] (FIG. 2a). Furthermore, single-neuron recordings opened up the possibility of functional studies of the cerebral cortex[7]. Nevertheless, in spite of the enormous advancements in knowledge facilitated by these techniques, a general theory of brain function with the explanatory power to account for behavioural or cognitive states, or to explain mental pathologies, remains elusive. It is possible that the neuron doctrine, with its focus on individual neurons, may be partly to blame.

Unlike the neuron doctrine, neural network models assume that neural circuit function arises from the activation of groups or ensembles of neurons[8]. According to these models, these ensembles generate emergent functional states that, by definition, cannot be identified by studying one neuron at a time. In fact, it is thought that the brain, unlike other body organs, could be specifically built to generate emergent functional states[9]. Although the earliest neural network models were formulated in the 1940s[10,11], they have only recently become experimentally testable as a result of the development of new optical, electrophysiological and computational tools[12–15]. Using data generated by these novel methods, neural network models could incorporate the phenomenological insights acquired using single-neuron approaches and also explain phenomena that do not easily fit within single-neuron frameworks.

In this Perspective I describe how the neuron doctrine arose and flourished as a result of the use of single-neuron techniques and consider the resulting limitations of its view of neural circuits. The subsequent growth of neural network models is discussed, highlighting results obtained with new multineuronal recording methods. I suggest that neuronal network models could

be a useful paradigm, or act as guideposts, to understand many brain computations. This article does not provide an exhaustive review but instead illustrates with a small number of examples the transition between these two paradigms of neuroscience.

History of the neuron doctrine

Origins. Many neuroscience textbooks begin by explaining Cajal's proposal that the unit of the structure of the nervous system is the individual neuron[2,16,17] (FIGS 1,2a). This idea, actively debated at the time, contrasted with the 'reticular theory' — defended by Golgi himself — which hypothesized that neurons were linked in a single overarching syncytium[1]. Cajal's keen observations of physical discontinuities between neuronal processes were proven correct: decades later, the introduction of electron microscopy[18] demonstrated synaptic clefts between neurons[19,20]. The neuron doctrine was the logical extension of Virchow's cell theory, which itself arose from the works of Leeuwenhoek, Hooke, Schleiden and Schwann, among others, who, using microscopes, described the cell as the basic unit of the structure, reproduction and pathology of all biological organisms[21]. Partly thanks to an influential review by the renowned anatomist Waldeyer[22], the neuron doctrine became widely accepted and developed into the essential conceptual basis for the piecemeal description of the structure of nervous systems[6] carried out by early anatomists and many subsequent researchers.

The functional aspect of the neuron doctrine — the hypothesis that individual neurons are also the unit of function in the nervous system — evolved in parallel and was spearheaded by Sherrington[3]. Closely linked to this was the concept of the receptive field, originally formulated by Sherrington as the area of skin from which a scratch reflex is elicited. This concept was cemented with the development of techniques that enabled investigators to record activity from individual nerve fibres[23], revealing that different neurons responded specifically to different sensory stimuli[24]. Thus, each neuron had its own receptive field: a specific feature of the sensory world that activates it and defines its function.
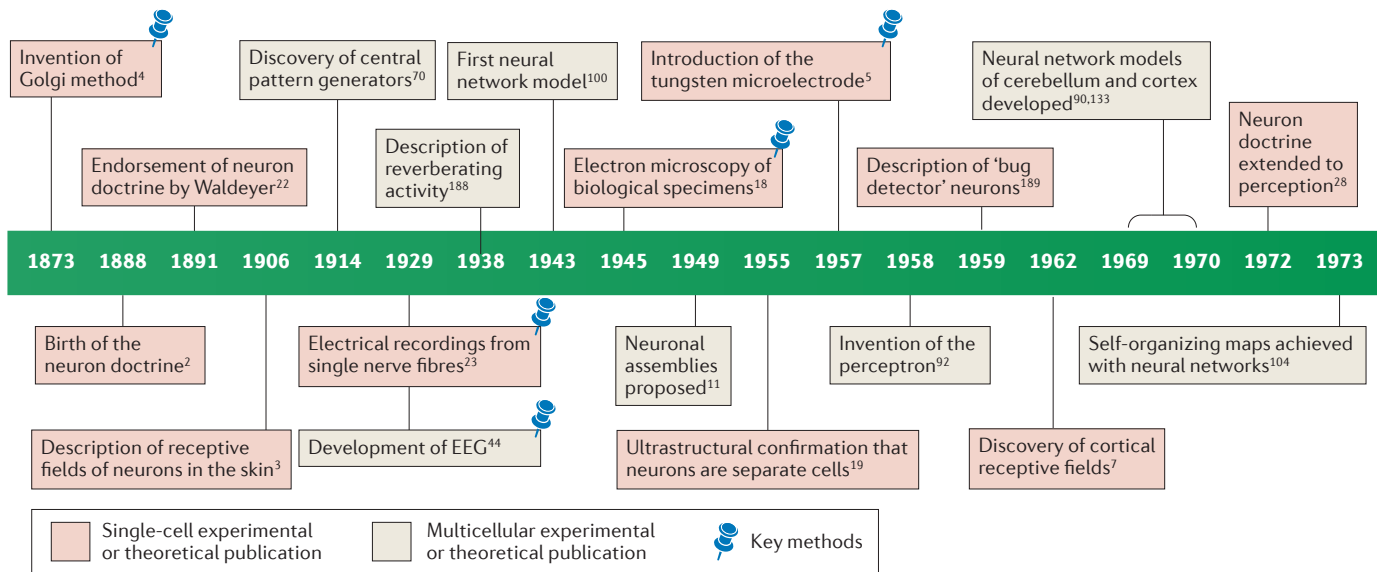
Figure 1 | **Historical evolution of the neuron doctrine and neural network models.** Historical summary of the key single-cell or multicellular experimental or theoretical publications used to support the neuron doctrine or neural network paradigms. CCD, charge-coupled device; EEG, electroencephalography.

One example of this concept was the discovery of 'bug detector' neurons in the frog retina: neurons with small, motion-sensitive, receptive fields that appeared perfectly designed to detect moving flies[25] (FIG. 2b–d).
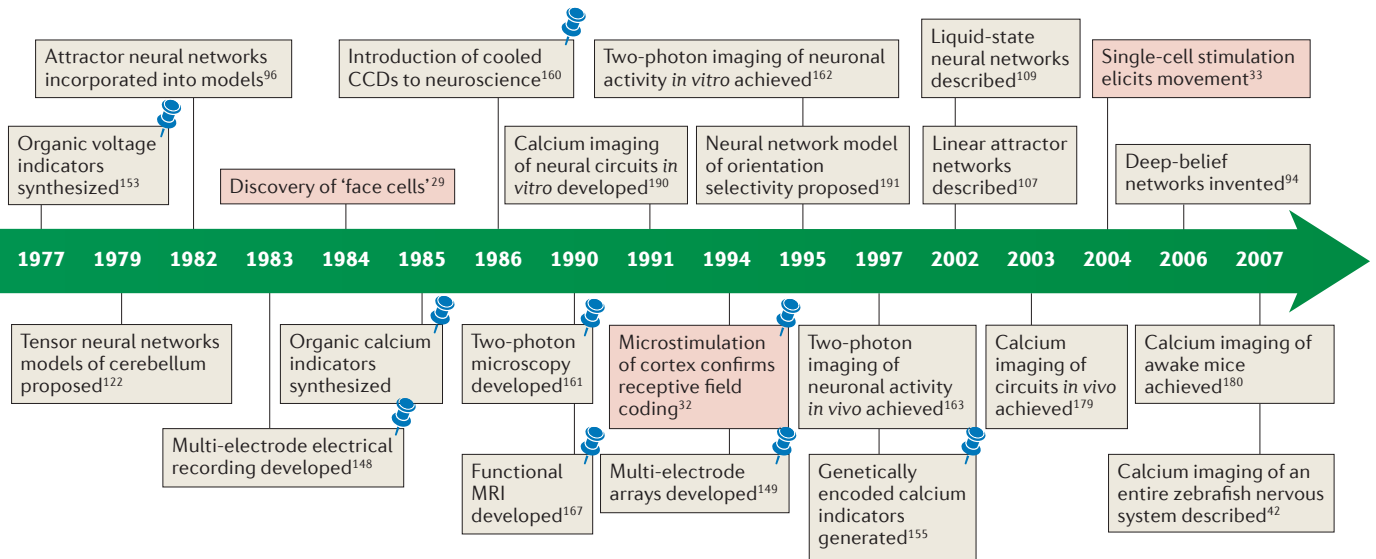
Over the decades, the focus on single neurons and receptive fields became the cornerstone of electrophysiology, especially after the introduction of the tungsten microelectrode by Hubel[5]. A rich tradition of single-cell recordings, which continues to this day, has mapped receptive fields throughout the brain. Particularly influential were the discoveries of topographically organized receptive fields in cortical 'columns' described by Mountcastle[26] and by Hubel and Wiesel[7,27]. These successes crystalized conceptually the idea that the single neuron was not only the anatomical and functional unit of the brain but also its perceptual unit[28]. Following this logic, for example, at the top of the hierarchy of the mammalian visual system one could find 'grandmother cells' that were responsible for the perception of our grandmother[28]. Consistent with this, 'face cells' that responded to images of specific individuals were found in the temporal cortex of monkeys and humans[29–31]. Moreover, electrical stimulation of a very small number of cortical neurons[32], or even of individual neurons[33,34], can lead to behavioural alterations in monkeys and rodents, suggesting that the functional properties of individual neurons could represent the functional units of the perception or even the behaviour of the animal.

Limitations. A century after Cajal and Sherrington, it is clear that the nervous system is built out of individual neurons and that their responses can be correlated with particular sensory stimuli, motor actions and behaviours. There is no question that work based on the basic assumptions made by the neuron doctrine has been ground-breaking. At the same time, when examining the historical evolution of neuroscience, one appreciates the direct links between the neuron doctrine and the use of single-neuron methods[1]. The neuron doctrine was cemented by the Golgi stain[4], which enabled investigators to visualize with relative completeness the morphologies of isolated neurons, and by electrodes[5], which provided routine recordings of individual neurons in whole brains. It therefore seems quite natural that neuroscientists emphasized the importance of individual neurons in the brain's structure and function. As in other fields of science, there is a direct link between the techniques used and the concepts and paradigms that arose from these studies[21], as investigators cannot make discoveries beyond those that their techniques reveal[35]. However, as with every established scientific paradigm[36], over the years the neuron doctrine may have become limiting.

It is possible, for example, that the concept of receptive fields may have led to an underestimation of the true complexity of neuronal function[37]. The fact that neurons are specifically activated by particular inputs may not necessarily mean that this is their role in the circuit. It may be too narrow or simplistic to

equate neuronal function with the fact that a neuron fires in response to a stimulus: its function could be related to its firing, to the exact time at which it fires, to whether or not it fires in synchrony with or builds a dynamical pattern with other neurons, or even to its lack of firing[37]. Indeed, even in primary sensory areas, and particularly in awake animals, neurons do not always respond in the same way to identical sensory stimuli[38,39], suggesting that their coding could be more sophisticated than originally thought. In fact, organized spontaneous activity appears to be prevalent in many brain regions[40–43], particularly in humans[44,45]. This spontaneous activity, already described in the first electroencephalography (EEG) recordings[44], cannot be easily explained from the perspective of receptive fields, as it occurs in the absence of sensory inputs, and thus indicates that neurons could be engaged in intrinsic functions unrelated to sensory stimulus or motor action (FIG. 3).

In addition, when interpreting 'face neuron' data[31], perhaps one of the strongest pieces of evidence for feature selectivity in receptive fields, it is difficult to understand how the investigators can be lucky enough to find a neuron that codes for the face of a particular person when recording from one neuron at a time in a cortical area that contains hundreds of thousands, or even millions, of neurons. It is more likely that coding for any particular face is distributed across large populations of neurons. A similar argument has been made for finding place cells in the hippocampus[46]. Thus, the receptive field could be reinterpreted

Timeline boxes (above axis):
- Attractor neural networks incorporated into models[96]
- Introduction of cooled CCDs to neuroscience[160]
- Two-photon imaging of neuronal activity *in vitro* achieved[162]
- Liquid-state neural networks described[109]
- Single-cell stimulation elicits movement[33]
- Organic voltage indicators synthesized[153]
- Discovery of 'face cells'[29]
- Calcium imaging of neural circuits *in vitro* developed[190]
- Neural network model of orientation selectivity proposed[191]
- Linear attractor networks described[107]
- Deep-belief networks invented[94]

Timeline years: 1977 1979 1982 1983 1984 1985 1986 1990 1991 1994 1995 1997 2002 2003 2004 2006 2007

Timeline boxes (below axis):
- Tensor neural networks models of cerebellum proposed[122]
- Organic calcium indicators synthesized
- Multi-electrode electrical recording developed[148]
- Two-photon microscopy developed[161]
- Functional MRI developed[167]
- Multi-electrode arrays developed[149]
- Microstimulation of cortex confirms receptive field coding[32]
- Two-photon imaging of neuronal activity *in vivo* achieved[163]
- Genetically encoded calcium indicators generated[155]
- Calcium imaging of circuits *in vivo* achieved[179]
- Calcium imaging of awake mice achieved[180]
- Calcium imaging of an entire zebrafish nervous system described[42]

more generally as the single-cell manifestation of distributed circuit states: that is, the activation of a large number of neurons by a stimulus or a location. If this is the case, we should re-examine the assumption that single neurons are the functional units of the nervous system, and instead focus our attention on groups of neurons[11,47].

Moving to neural circuits
Structural evidence for distributed circuits. Is there any evidence that groups of neurons, rather than single neurons, serve as functional units in neural circuits? Indeed, there is anatomical evidence to support the notion that most neural circuits, particularly in the mammalian brain, are built with a distributed connectivity: that is, as a connectivity matrix in which each neuron receives inputs from many other neurons while sending its outputs to large populations of cells[48,49]. Furthermore, the majority of the excitatory connections in the brain are weak, as though each neuron is trying to integrate as many excitatory inputs as possible without saturation[50]. For example, the average pyramidal cell neuron in the mammalian cortex probably receives inputs from and connects to tens of thousands of other cells[51]. More dramatically, each Purkinje cell in the cerebellum probably receives a single input from as many as several hundred thousands of granule cells, and each granule cell itself connects with as many Purkinje cells as it can, given its axonal length[52]. This distributed design, which did not escape Cajal's notice (he compared it to telegraph lines)[6], appears to be built to enhance the distribution of information. A distributed design principle is also prominent in inhibitory neurons. Most subtypes of cortical GABAergic interneurons

(with the exception of vasoactive intestinal peptide-expressing interneurons)[53] appear to connect with as many excitatory neighbours as possible, with a connectivity approaching the physical limit (connection to 100% of local targets)[54–56]. Moreover, inhibitory neurons are often linked to each other by gap junctions[57–59], as though they are designed to work as a unit. In addition, some interneurons release GABA directly onto the neuropil[60], affecting all of their local neighbours. Thus, inhibitory neurons appear to be designed to extend a 'blanket of inhibition' onto excitatory cells[56].

This distributed connectivity plan is also reflected in the biophysical properties of neurons. For example, many mammalian neurons are covered with dendritic spines, which receive essentially all excitatory inputs[61]. The fact that these excitatory inputs choose to connect on spines and not on neighbouring dendritic shafts indicates that spines must have a fundamental role in neuronal integration[62]. One possibility is that spines facilitate distributed connectivity by maximizing the assortment of different axons that dendrites can connect to[63]. Also, by avoiding input saturation, spines could enable the independent integration of each excitatory input while simultaneously allowing the neuron to alter the synaptic strength of each input individually[64]. These properties only make sense if the neuron is trying to integrate as many different inputs as possible.

Now, if one assumes that neural circuits are built to maximize connectivity, one could then argue that the more connected a neuron is, the less important it becomes in the circuit[9]. If every neuron is connected with every other neuron, any individual neuron becomes dispensable (like an individual vote

in a democracy). Because of this, individual neurons in the mammalian brain are likely to be irrelevant for the overall circuit function, which must depend instead on interactions among a large number of neurons. This design is unique among other organs in the body, as the overall function of organs such as the liver, kidney, lung, skin or muscle can, in principle, be comprehended by understanding the function of each of their cells, whereas for the brain one may need to consider the activity of selected populations of cells.

The situation in the nervous system — in which many elements are connected and contribute structurally or functionally to a larger structure — is characteristic of physical systems that generate emergent properties[8,65]. Emergent properties arise from interactions among elements but are, by definition, not present in the individual elements. Even something as mundane as watching a movie on a TV screen is an example of the importance of emergent properties: one cannot comprehend the scene by looking at individual pixels but instead needs to simultaneously view many pixels to decipher the image. Although the neuron doctrine and single neuronal techniques have focused on the exhaustive analysis of the individual 'pixels' of the brain, it is possible that the function of neural circuits may not be apparent unless one can visualize many, or most, 'pixels' in the screen.

Neuronal assemblies and spontaneous activity. The idea that neural circuits are built for an emergent function is not new. As early as the 1930s, Cajal's disciple Rafael Lorente de Nó argued that the structural design of many parts of the nervous system is one of recurrent connectivity whose purpose could be
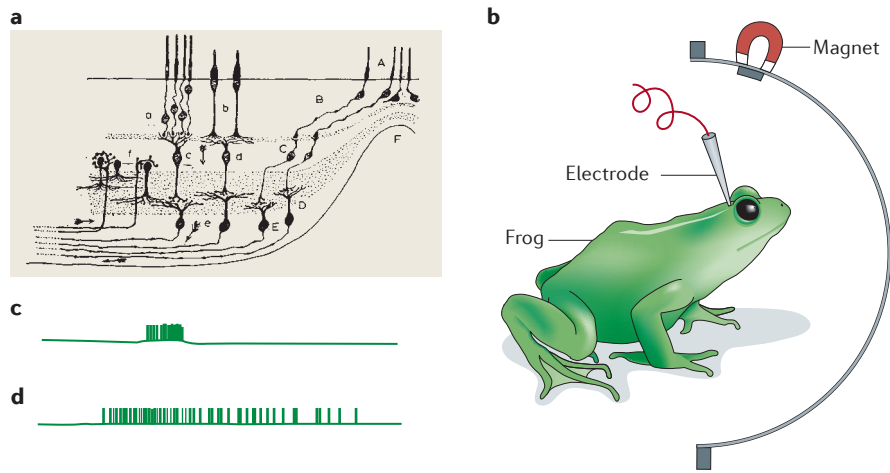
Figure 2 | **Anatomical and physiological examples of the neuron doctrine. a** | Cajal's schematic illustration of a section of a bird retina, depicting individual neurons that were assumed to be the units of the circuit. The arrows indicate the direction of electrical impulses, correctly deduced by Cajal's application of the neuron doctrine and the law of dynamic polarization. **b–d** | Physiological application of the neuron doctrine. The diagram of the experiment (panel **b**) shows the electrical activity of a ganglion cell in a frog's retina recorded while a visual stimulus is moved with a magnet over a screen (panel **c**), as well as the electrical activity in response to a stationary stimulus (panel **d**). Note how the neuron responds vigorously to the moving stimulus but only weakly to the stationary stimulus. The neuron was defined as a 'bug detector', because its receptive field matches the movement of a physiological prey of the frog. Thus, the single neuron would have a very specific function, in agreement with the idea that single neurons are the functional units of the circuit. Part **a** adapted, with permission, from REF. 192 © The Nobel Foundation 1906. Parts **b–d** adapted, with permission, from REF. 25 © 1960 Maturana *et al. Journal of General Physiology.* 43:129–175. doi:10.1085/jgp.43.6.129.

to generate functional reverberations (patterns of neuronal activity that persist after the initial stimulus has ceased) among groups of neurons[66,67]. This idea was embraced by Donald Hebb, who proposed that neural circuits worked by sequentially activating groups of neurons, which he called 'cell assemblies'[11]. According to Hebb, these recursive and reverberating patterns of neuronal activation, firing in closed loops, would be responsible for generating functional states of the brain, such as memories or specific behaviours[11]. He proposed that synaptic connections between neurons could be altered by a learning rule (a local change in synaptic strength governed by correlated patterns of activity), thus linking neurons into an assembly[68]. In doing so, the circuit has 'learned' a pattern of activity, storing it into its altered repertoire of synaptic connections.

In parallel with these ideas, a rich phenomenology demonstrated the presence of intrinsic, spontaneous activity in many neural circuits (FIG. 3). Rhythmic types of activity are generated by central pattern generators (CPGs), which are responsible for stereotypical behaviours such as digestion, locomotion or respiration[69]. The concept of CPGs originated with Sherrington's student, Graham Brown, who observed the persistence of spinal cord activity in the absence

of sensory stimuli[70,71]. Although the idea ran contrary to Sherrington's view that neural circuits operate through an input–output sequence of reflexive actions, Sherrington himself later appeared to be open to the importance of intrinsic activity patterns[72]. Thus, the scientists responsible for the neuron doctrine, Cajal and Sherrington, trained the early pioneers of the alternative viewpoints.

A related line of experimental work, which began with the first use of EEG by Berger[44], led to the description of spontaneous electrical oscillations throughout the brain[40,73,74]. These rhythmic modulations in neuronal activity, which can arise from the dynamical properties of neurons[75,76], have been linked to a variety of important functional roles, including attention, brain states, sensory or computational processing, decision-making, perceptual binding and consciousness[77–87]. The role of spontaneous activity in brain function could be basic and ancient: during evolution, the function of the CNS may have resulted from the encephalization of simpler fixed action pattern rhythms[88]. From this point of view, repeated or oscillatory firing patterns may no longer correspond to simple rhythmic movements but could have acquired a symbolic or computational meaning[88].

Emergent circuit properties

The first neural network models. Neuronal reverberations, neuronal assemblies, ensembles, CPGs and oscillations are examples of functional emergent states that may be of great importance but cannot be captured within a single-neuron framework. These ideas have attracted many theorists, who, over the decades, formalized these emergent models, creating the concept of a neural network[8,89,90]. The term 'neural network' has become synonymous with models of distributed neural circuits in which neurons are abstracted into nodes and linked by connections that change through learning rules[8] (FIG. 4). Typically, neurons in neural networks are connected in an all-to-all or a random fashion and integrate inputs linearly, leading to a threshold nonlinearity that causes the cell to fire and activates its outputs.

In the first neural network models[10], neurons merely summed inputs to reach a threshold and fire action potentials. If the threshold is set at a high level, the neuron will only fire if many (or all) of its inputs are active. This strategy corresponds to the AND logical function and could be used, for example, to build neurons that are very selective to the conjunction of inputs and to detect and recognize a pattern or particular object. At the same time, if one sets the threshold to a low level, the neuron would fire whenever any of its inputs is active. This corresponds to the logical OR function and enables neurons to respond to a set of inputs, thus generating an invariant response, even if inputs are changing. Hence, even these simple circuits could implement Boolean logic, the mathematical foundation of digital calculus and computers, as demonstrated by Turing[91]. Neural networks have, in principle, the computational abilities of the most sophisticated computers. Importantly, these networks generate emergent computations: the overall logic and function implemented in the circuit (for example, object recognition or invariant response) depends on the activity — or lack of activity — of all of its components.

Over the ensuing decades, more complex models were created. These belonged to two basic types, based on their architecture: feedforward networks, which are governed by one-way connections (FIG. 4a), and recurrent networks, in which feedback connectivity is dominant (FIG. 4b). Feedforward networks (sometimes referred to as multilayer perceptrons) are organized in layers and linked by unidirectional connections[92]. Such circuits can solve effectively problems such as categorization or classification of inputs.
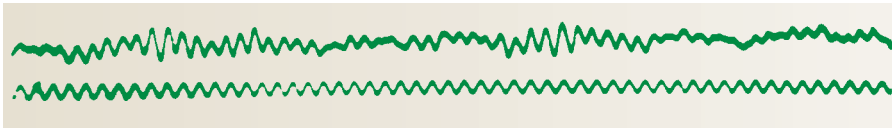
Figure 3 | **Spontaneous cortical activity.** The figure illustrates one of the first electroencephalograms by Hans Berger (1929)[44], recorded from his son Klaus (15 years old). The upper trace represents a sample of the 'alpha rhythm' (a sinusoidal rhythm of approximately 10 Hz), often found in the visual cortex when the eyes are closed (thus in the absence of visual stimulation). The lower trace is a generated 10 Hz sine wave, for reference[44]. Patterned spontaneous activity is present throughout the nervous system and is an example of a phenomenon that cannot be easily explained by the Sherringtonian physiological neuron doctrine because it occurs in the absence of sensory inputs. Rather, spontaneous activity is likely to be generated by interactions among groups of neurons and indicates that neurons could be engaged in intrinsic functions, unrelated to a sensory stimulus or motor action. Adapted from REF. 44, Steinkopff-Verlag, with kind permission from Springer Science and Business Media.

Although originally viewed with suspicion by the artificial intelligence community[93], feedforward networks have recently undergone a renaissance in computer science, through the development of novel training rules, an expansion in the number of layers and the access of large-scale datasets and better hardware implementations (convolutional or deep belief networks)[94,95].

Recurrent networks, however, emphasize feedback connections between pools of neurons. In some models, the recurrent connectivity enables these networks to generate intrinsic activity, which becomes stable at particular points in time, termed attractors[96]. Attractor models were inspired by the Ising model of ferromagnetism, in which individual atomic spins interact with neighbouring spins and spontaneously align into emergent states by minimizing an energy variable[97]. Likewise, in a recurrent neural network with symmetric connections (in which synapses between any pair of neurons have the same synaptic strength), one can define an 'energy' function that assigns a value to any activity pattern to measure the propensity of the network to change its activity. It can be demonstrated mathematically that this energy tends to decrease, endowing the network with a dynamical trajectory that coalesces into several lower energy states. Because of this, the activity map for such networks contains multiple stable points, which 'attract' the activity; hence the term 'attractors'[96,98] (FIG. 4c). Attractors are another example of the emergent states of the activity of the network and could serve to implement associative memories, decision-making, or — more generally — solutions to optimization or other computational problems[99,100]. Moreover, the trend towards lower energy states endows these networks with pattern completion properties: that is, the internal dynamics of the system can 'complete' a spatiotemporal pattern of activity when provided with a partial stimulus. Pattern completion is found in memory recall and many neuroethological fixed action patterns[101,102].

Recent neural network models. Starting with the original models of McCulloch and Pitts[10], neural networks were traditionally based on circuits that had an all-to-all connectivity or were widespread, where the exact spatial pattern of the connections did not matter. At the same time, connections in the brain often have particular spatial properties. For example, inhibition tends to mostly affect local neighbours (known as lateral inhibition)[103]. This was explored in one set of neural network models, in which adding a spatial local profile to the connectivity enabled networks to implement competitive 'winner takes all' algorithms, in which individual neurons stand out among their neighbours, stifling their activity. These algorithms perform pattern separation: that is, they differentiate similar inputs by having them excite different sets of neurons, thus 'placing' them into different locations of the activity map of network[104,105]. Interestingly, these excitatory–inhibitory networks were able to spontaneously assemble into self-organizing maps in which the computational variables of the input space became systematically ordered onto the planar physical structure of the network[106]. This may be particularly interesting for neurobiologists because many areas of the brain have sensory, motor or cognitive maps, and perhaps lateral inhibitory connections could help to build these maps spontaneously during development.

Continuing with this trend, recent generations of neural network models have tried to better capture known structural and functional features of brain circuits[107–113]. In fact, unlike the original attractor networks (which assumed all-to-all, symmetric connections

between neurons, and were deterministic as they were locked into discrete stable activity states), an entirely new type of recurrent neural networks (which are stochastic, not deterministic) allows weights to be asymmetric and exhibits transient dynamical patterns without stable states[109]. Moreover, the asymmetry in the synaptic connectivity matrix naturally endows these models with temporally organized activity[89]. In fact, many of these newer dynamical networks models can produce repeated temporal patterns in the firing of the neurons[114], which — because of the recurrent connectivity — can be generated in the absence of input to the network. Spatiotemporal patterns of activity are produced in recurrent dynamical models by spike-timing-dependent synaptic plasticity and could be used as an emergent substrate for neural coding[115].

Through these refinements, newer neural networks are becoming useful for experimentalists as models of neural circuits, capturing effectively the recurrent nature of excitatory neural connections and the intrinsic firing of neurons in the absence of stimuli, as observed, for example, during working memory tasks[116,117]. Furthermore, recurrent models can also be used to explain binary circuit states, such as those that must occur during decision-making[111], or provide continuous solutions to computational problems, as often observed during smooth physiological responses[107].

Importantly, in neural network models the computation is an emergent collective property, carried out by the assembly of neurons rather than by single cells[96,118]. In fact, individual neurons can participate in different functional groups, flexibly reorganizing themselves and diluting the concept of the receptive field. This combinatorial flexibility, originally proposed by Hebb[11], is a natural consequence of synaptic plasticity and it also allows the modular composition of small assemblies into larger ones. Because of this flexibility, neural circuits may never be able to be in the same functional state twice, responding differently even if the exact same sensory stimulus is presented. Neural circuits could be constantly changing, as if they were a 'liquid state' machine[109,119]. This could be used as an emergent mechanism to encode time[120], providing different time stamps to different moments[121].

Experimental evidence for emergent properties. The possibility that neural circuits generate emergent states of activity is fascinating, but is there any evidence that biological neural circuits actually operate as such
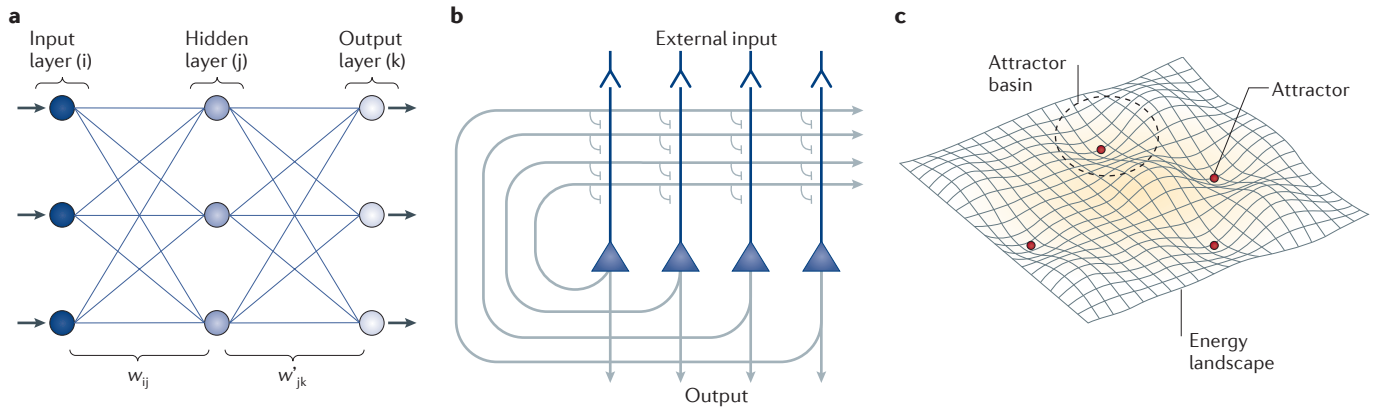
Figure 4 | **Neural networks.** Examples of common types of neural network models. **a** | Feedforward network. The diagram shows a multilayer perceptron, consisting of three sequential layers of neurons (represented by circles), in which every neuron from each layer is connected to every neuron of the next layer. Each connection has an associated synaptic strength or 'weight' (w_{ij} or w'_{jk}) that changes according to a learning rule that is applied to all the connections; w has a numerical value and is indexed by the presynaptic neuron and the postsynaptic neuron, which generate the connection. In this network, inputs are sequentially processed layer by layer in a unidirectional fashion, from the input layer on the left, to the 'hidden' layer in the middle, to the output layer on the right. The simple addition of synaptic weights in the output layer results in the generation of selective responses. The computation is an emergent property of the activity of the entire network. **b** | Recurrent network: an example of an attractor (feedback) neural network in which four pyramidal neurons (blue) are connected to themselves through recurrent axons (thin lines) with synaptic weights (w_{ij}) that change owing to a learning rule. The network receives an external set of inputs (top connections) and generates an output (bottom arrows). In networks with recurrent and symmetric connectivity the activity becomes 'attracted' to particular stable patterns. **c** | Recurrent network: an activity map of an attractor neural network (Hopfield model). Each point in the grid represents a particular state of activity of the entire network, and the three-dimensional height of the map represents the 'energy' of the network in that particular activity pattern. This energy is a mathematical function that captures the propensity of the network to change its activity. The landscape thus represents all possible activity patterns, where the 'valleys' (red dots) are circuit attractors, which represent stable (that is, low energy) states of activity. The dashed circle represents an attractor 'basin' in which the network activity patterns converge into the attractor. Part **b** reproduced, with permission, from REF. 193, by permission of Oxford University Press. Part **c** reprinted from REF. 194.

neural networks? From a naive point of view, if one assumes that a neural network simply consists of interconnected neurons, every neural circuit is indeed a neural network, and no experimental evidence is needed. A more relevant question is whether these feedforward or recurrent neural network models have any validity in explaining the phenomenology measured in brain circuits. Is there any evidence for emergent states of activity that may make it necessary to use these neural network models? Are neural network models helpful for understanding how neural circuits operate?

One could argue that traditional single-cell circuit models can be explained as particular examples of feedforward or recurrent neural networks. For example, the Hubel and Wiesel model for orientation selectivity is equivalent to a multilayer perceptron performing conjunction or disjunction[89]. Likewise, oscillatory dynamics present throughout the CNS can be reinterpreted as reverberating activity patterns generated by recurrent neural networks with stable dynamical trajectories[73,88,122].

In some cases, neural network models have already been used by researchers to help design and interpret their experiments. In particular, the circuit architecture of the mammalian hippocampus has been

proposed to represent a series of sequential feedforward and recurrent neural networks[123], which generate attractors[46,124]. Attractor networks have also been used to model grid cells in the entorhinal cortex[125–127] and to explain their remapping in new environments[128] — something that is hard to understand from a single-neuron point of view. Pattern separation, pattern completion and replay, which are well-known properties of recurrent neural networks[100,123], are also found in hippocampal activity[129,130]. Furthermore, network models are being used to guide the optogenetic manipulation of hippocampal circuits in mice to enable feats that include activating a memory[131] or implanting 'false' memories by activating a neuronal ensemble[132].

Similarly, neural network models have been used to understand emergent functional properties of the cerebral cortex[133,134]. For example, repeated temporal sequences of action potentials described *in vivo*[135–137], and even in brain slices[138], could result from recurrent neural network architecture. In fact, some of these stimulus-evoked activity patterns are similar to those that occur spontaneously[41,43,139–141], as would be predicted from some dynamical network models[115]. Also, neural network models based on the multidimensional representation of

information by neuronal ensembles have been recently used to explain, for example, context-dependent coding[114], multidimensional selectivity in the functional responses of neurons in the prefrontal cortex[142], and complex motor actions in awake behaving monkeys[143]. In these studies, multidimensional activity patterns appear to repeat in systematic fashion during the performance of the behavioural task (FIG. 5a).

Recent evidence for the existence of emergent circuit states in the mammalian cortex comes from experiments on mice navigating a virtual maze[144] (FIG. 5a). Researchers used two-photon calcium imaging to measure the activity of groups of neurons in the parietal cortex while the mouse made a behavioural choice, based on visual cues. Although single-neuron activity could not be used to explain decision-making, the temporal trajectory of the population of neurons could be used to decode the behaviour, indicating the possible existence of an emergent code. Strikingly, the temporal sequences of firing were predictive of the behavioural choice (FIG. 5b). These experiments echo earlier work on the behavioural switching of leeches between swimming and crawling, in which the dynamical activity of a population of neurons in the ganglion could be used to decode and predict a behavioural choice[145].
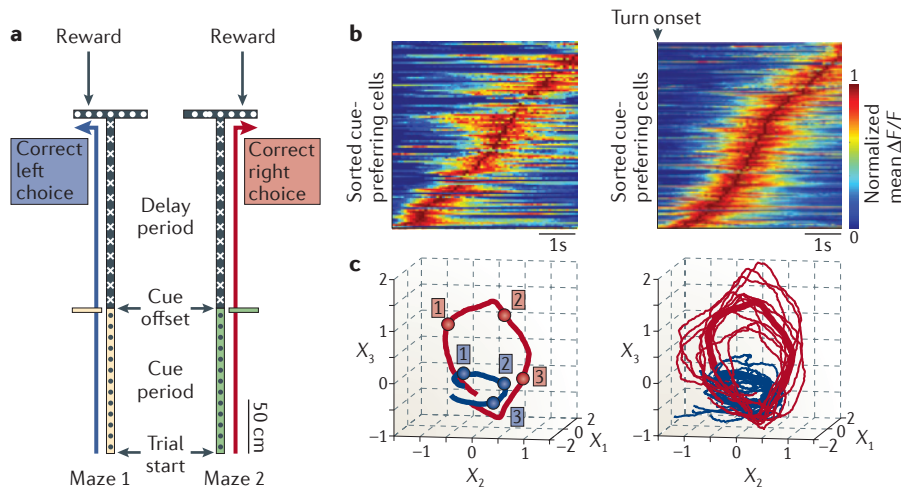
Figure 5 | **Emergent functional states in multineuronal dynamics during virtual navigation. a** | A virtual navigation task is shown. A T-maze is projected in a virtual reality arena. A mouse runs along a linear track and has to choose to turn right or left depending on the cue that is presented to it via patterns present on the virtual maze walls. **b** | Repeated spatiotemporal dynamics are observed during behaviour. The colour panels show the activity of a population of neurons in the mouse parietal cortex during the virtual navigation task, measured using two-photon calcium imaging. Each panel displays the calcium-related fluorescence ($\Delta F/F$) in pseudocolour for every individual cell (y axis), as a function of time. The multineuronal activity from 101 cue-preferring cells (left) or 170 turn-preferring cells (right) is aligned to the trial start and turn onset, and displays a smooth progression in time of the activity through the population. Whereas individual neurons are activated at variable times, the overall activity faithfully tracks the behaviour of the animal. **c** | Choice-specific multineuronal trajectories. Analysis of similar data to that shown in part **b**. Here, the multineuronal activity is now condensed into three-dimensional plots of principal component axes. The left panel shows the time course of average multidimensional dynamical trajectories on the right (red) and left (blue) choice trials from one session. Points labelled 1, 2 and 3 correspond to the times of the cue offset, turn onset and trial end, respectively. The right panel superimposes several individual (thin lines) and mean (thick lines) trajectories for correct trials. Note how the trajectories of the activity of the neuronal population differ on the right and left trials, yet are similar within each type of trial. Thus, one can decode the behaviour of the animal from the multineuronal activity patterns, as an emergent property of its dynamics. Figure modified from REF. 144, Nature Publishing Group.

New methods to study networks

It is not an accident that the experiments that provide the strongest support for neural network properties have been performed with multineuronal recording techniques[56,146,147], highlighting the ties between techniques and scientific paradigms[35]. Moving beyond the microelectrode[5], advances in electrical recordings — such as the EEG[44], the development of tetrodes[148], multi-electrode arrays[149] and nanofabricated high-density complementary metal-oxide semiconductor (CMOS) arrays[150] — have enabled neurophysiologists to record population-wide activities and decipher coding properties and the functional connectivity of circuits such as those in the retina[151]. A similar case could be made for optical recordings of neuronal activity. From the initial development of organic calcium[152] or voltage[153,154] indicators to the more recent genetically encoded indicators[155–158], it has become possible to measure the activity of many — or, in some cases, most[42,159] — neurons in a neural

circuit. These advances in optical probe design and synthesis have been accompanied by a similar revolution in optical hardware. From the introduction of cooled charge-coupled device (CCD) cameras[160], which enabled quantitative optical imaging from different regions of a neuron, to the development of ultrafast infrared lasers that enabled two-photon microscopy[161], which allowed imaging of neurons deep into living brain circuits[162,163], and to more recent optical designs for three-dimensional imaging of neural activity[42,164], these new methods are bringing not just a quantitative change in the amount of data acquired but a qualitative modification in the mindset with which neuroscientists approach neural circuits. Besides microscopy, new optical or magnetic methods to image the activity of entire cortical areas should be also highlighted, although they do not yet possess the spatial resolution to visualize individual neurons. For example, intrinsic signal imaging[165] has enabled visualization of the functional architecture

of cortical areas with unprecedented resolution[166]. Also, the development of functional MRI[167] has enabled the pinpointing of critical regions of the brain involved in specific behaviours, mental states or disease processes in human subjects. These large-scale imaging methods are starting to build bridges between neural circuits and topics at the core of psychology[168] and as complex as consciousness[169].

Novel techniques have also been developed to optically alter the activity of neural circuits, such as optogenetics[12] or opto-chemistry[170,171]. This optical large-scale manipulation of neural circuits can be carried out while preserving single-cell resolution[172–174], while simultaneously imaging neuronal activity[172,175], thus allowing one to 'play the piano' with neuronal circuits in order to generate spatiotemporal patterns of activity with the same precision as the ones encountered naturally.

Finally, novel computational and analytical approaches have been developed to analyse and decipher the meaning of multineuronal datasets. Using dimensionality reduction methods[143], dynamical systems analysis[176], information theoretic frameworks[177] and a rich variety of other novel theoretical tools[15,113], researchers can visualize and understand multidimensional neuronal dynamics in ways that enable them to probe brain circuits at the multicellular level.

Challenges and outlook

Despite the very good progress made over more than a century using the neuron doctrine as a foundation, neuroscience still lacks a general theory of how neural circuits operate, how they generate behaviour or mental states, and how their dysfunction leads to mental or neurological diseases. I would argue that this may be due partly to the methodological focus on single cells, which — despite propelling the field forward — has left multicellular phenomenology and its corresponding emergent properties relatively unexplored. Although one can, in principle, study circuit-level properties with single-neuron techniques (such as local field potentials that monitor the aggregate activity of groups of neurons, or even whole-cell recordings that provide access to the population of excitatory or inhibitory inputs onto an individual cell), one may still miss emergent circuit properties unless more comprehensive measurements of population activity are made. In this respect, the above-mentioned new methods to measure multineuronal activity *in vitro* or *in vivo*[14,149,178–180] or to analyse and model multidimensional

and dynamical activity[37,109,181] may usher in a Kuhnian 'scientific revolution'[36], in which the single-neuron doctrine taught in textbooks is replaced by a new neural network paradigm that assumes that assemblies of neurons are the basic building blocks of the function of the brain.

However, the adoption of neural networks as a new paradigm faces some potential challenges, at least when one considers current models. For example, it is unclear whether existing neural network models have enough predictive value to be considered valid or useful for explaining brain circuits. Given the nonlinearity of the interactions among neurons present in most neural network models, numerical simulations can result

in vastly different outcomes if they have too many free parameters. Alternatively, the same outcome can be generated from many different network simulations, underspecifying any biological predictions. Thus, it could become difficult to disentangle how current models of neural circuits generate dynamical structured or emergent functional states. Because of this, it is possible that although artificial neural networks could operate well in principle and even be very useful for engineering applications, in order to be applied rigorously to realistic neural circuits they may need to be constrained with quantitative data, which are still not available. In this respect, although there is increasing evidence supporting some of these neural network

models, the data are still correlative and critical experiments to demonstrate their importance or disprove them have not yet been carried out. Novel methods to systematically modify or manipulate neuronal activity at the population level are key, because they can directly reveal causal interactions and test the validity of these emergent-level models. Perhaps the new tools generated by the BRAIN initiative[182,183] to measure, manipulate or analyse multineuronal activity could critically contribute to the refining and proper testing of neural network models. It should also be pointed out that in addition to gathering and analysing the data it is equally important to generate an organizational framework to store, distribute and share these data in a fashion whereby knowledge could be gained from the parallel efforts of the entire research community.

Simply recording from more neurons, or even manipulating large numbers of them, may not suffice and may only be a first step. Developing an understanding of how neural circuits work may require integration of essential knowledge from many — or all — levels, with a detailed characterization of the way in which the elements at different levels work together and interact. This is not a new idea: Marr emphasized the interconnectivity of the different levels as a necessity for acquiring a proper knowledge of how vision works[118]. Earlier than this, Kant pointed out that science is a ladder in which every rung is connected to those above and below it, and it is only once the facts become properly connected to the ladder that they finally become knowledge[184]. To be truly paradigm shifting, neural circuit models must assimilate the knowledge of single-cell properties and interactions that was painstakingly acquired by the past century of research, as well as multineuronal data acquired with EEGs, local field potential and multi-electrode recordings. Moreover, a proper synthesis needs to be carried out, integrating the new anatomical and physiological large-scale datasets (termed 'structural' and 'functional' connectomics), and evaluating how neuromodulators can alter their function[185,186].

Finally, it should be noted that research based on the principles of the neuron doctrine is far from being finished[1,16]. There are still some important questions remaining about the function of individual cells, like, for example, what local computations are carried out by dendrites[187] (which in some cases serve as both input and output devices)[49]. The future integration of different levels of analysis by neural network models should be

Glossary

Attractors
Stable or semi-stable states in the temporal dynamics of the activity of a neuronal population. They arise naturally in neural networks that have a recurrent (feedback) architecture with symmetric connections.

Boolean logic
A form of algebra in which all values are reduced to either true or false. Boolean logic is especially important for computer science because it fits nicely with its binary numbering system. Boolean logic depends on the use of three logical operators: AND, OR and NOT.

BRAIN initiative
The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative is a decade-long large-scale scientific project, sponsored by the White House, to accelerate the development and application of innovative neurotechnologies to revolutionize the understanding of the brain.

Activity map
In a neural network context, the activity map is a three-dimensional representation of all the activity states of the network, where the depth dimension corresponds to the energy function of the activity, which captures the propensity of the network activity to change. This topological representation provides an intuition of how the activity of the circuit evolves in time, as it progresses through this energy landscape to find its lower-energy (attractor) points.

Ensembles
A group of neurons that show spatiotemporal co-activation. Ensembles provide an example of an emergent state of the circuit.

Gap junctions
Cellular specializations that allow the non-selective passage of small molecules between the cytoplasm of adjacent cells. They are formed by channels termed connexons, which are multimeric complexes of proteins known as connexins. Gap junctions are structural elements of electrical synapses.

Golgi stain
A staining technique introduced by Camillo Golgi in 1873 that involves impregnating the tissue with silver nitrate. This labels a random subset of neurons, allowing the entire cell and its processes to be visualized.

Grid cells
Neurons in the rodent entorhinal cortex that fire when the animal is at one of several specific locations in an environment; these locations are organized in a grid-like manner.

Learning rule
The alteration of the strength of a synaptic connection in a neural network, as a consequence of the pattern of activity experienced by that synapse (or the network).

Neuronal assemblies
Originally proposed by Hebb; groups of neurons that become bound together owing to synaptic plasticity, and whose coordinated activity progresses through the circuits, often in a closed loop.

Pattern completion
A process by which a stored neural representation is reactivated by a cue that consists of a subset of that representation.

Pattern separation
A process by which overlapping neural representations are separated to keep episodes independent of each other in memory.

Perceptrons
Multilayer feedforward artificial neural networks in which activity flows unidirectionally from one layer to the next. Multilayer perceptrons are often used to implement classification problems.

Place cells
Hippocampal neurons that specifically respond to stimuli in certain spatial locations. Their firing rate increases when an animal or subject approaches the respective location.

Recurrent connectivity
The concept that neurons within a class connect with one another, implying feedback communication within the network.

Replay
Recapitulation of experience-dependent patterns of neural activity previously observed during awake periods.

able to incorporate and explain, from a circuit perspective, this neuron subcompartment phenomenology.

In closing, neural network models based on the conjoint activity of groups of neurons could explain the phenomenology described with single-neuron approaches, but may also go beyond that and help understand observations that did not fit the single-neuron mould. If successful, neural network models could help to reveal the nature of the neuronal code and reformulate classical — yet still unanswered — questions in neuroscience, such as the physiological basis of learning and memory, perception, motor planning, ideation and mental states; for example, in an emergent theoretical framework. A new framework may help us to take a fresh look at data, reveal novel phenomena, and perhaps help generate a unified theory about how neural circuits give rise to behaviour and mental or pathological states.

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Competing interests statement
The author declares no competing interests.