

State-dependent computations: spatiotemporal processing in cortical networks

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Abstract | A conspicuous ability of the brain is to seamlessly assimilate and process spatial and temporal features of sensory stimuli. This ability is indispensable for the recognition of natural stimuli. Yet, a general computational framework for processing spatiotemporal stimuli remains elusive. Recent theoretical and experimental work suggests that spatiotemporal processing emerges from the interaction between incoming stimuli and the internal dynamic state of neural networks, including not only their ongoing spiking activity but also their ‘hidden’ neuronal states, such as short-term synaptic plasticity.

Perceptron

A simple linear neuron model that computes a weighted sum of its inputs, and outputs 1 if the weighted sum is larger than some threshold, and 0 otherwise. Weights and thresholds can be learned by the perceptron learning rule.

Multi-layer perceptron

A feedforward network of units, the computational function of which is similar to that of a perceptron, except that a smooth function (instead of a threshold) is applied to the weighted sum of inputs at each unit. Weights and thresholds can be learned by the back-propagation learning rule.

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All sensory stimuli generate spatiotemporal patterns of action potentials (spikes) that are conveyed to the CNS by sensory afferents. A fundamental goal of neuroscience is to understand how neural networks extract information from both the spatial and the temporal structure of these complex spike patterns; however, our understanding is currently biased towards the processing of spatial information. Indeed, it is not even known whether the spatial and temporal dimensions of stimuli are processed by the same or different networks. Temporal information is crucial to most forms of sensory processing; for example, in the visual modality, the temporal structure of stimuli is crucial in determining not only the direction and velocity of objects, but also the duration and interval between sensory events. In the somatosensory system, temporal structure contributes not only to motion detection, but also to object and texture discrimination¹. However, it is perhaps in the auditory system that temporal processing is most prominent; for example, both the spatial (spectral) and the temporal structure of animal vocalizations — from frog calls to bird song to monkey calls — encode information². Similarly, speech is rich in spatiotemporal structure, and removing either spatial or temporal information impairs speech recognition^{3,4}. The importance of the temporal structure of speech, and the brain’s ability to process complex temporal stimuli, is evidenced by the fact that language can essentially be reduced to a single-channel temporal code — as in Morse code. Given the importance of temporal information for the processing of natural stimuli, it is not surprising that neural responses are often strongly dependent on temporal features of stimuli^{5–7}. Indeed,

many neurons respond selectively to specific spatiotemporal stimuli, such as birdsong motifs or patterns of simple stimuli^{8–12}. Together, the universal presence of spatiotemporal patterns in natural stimuli and the sensitivity of cortical neurons to spatiotemporal structure argue that any general model of cortical processing must account for the ability of the cortex to process both spatial and temporal information.

How do we discriminate lines of different orientations? Any neuroscience textbook provides an answer to this question by describing the mechanisms that contribute to the orientation selectivity of V1 cells to a bar of light. However, the answer to the equally sensible question ‘How does the brain discriminate between different durations of a bar of light?’ remains largely unanswered. Indeed, relatively few models address this simple question. Early artificial neural-network models, such as the perceptron¹³ and later multi-layer perceptron¹⁴, proved capable of classifying complex spatial patterns; however, they were ill-suited to performing even a simple interval-discrimination task because there was no representation of time — the patterns being processed were static and not time-varying. Later models processed sequences of spatial patterns by either creating an explicit representation of time by transforming it into an additional spatial dimension (BOX 1), or by taking into account preceding network states through the incorporation of recurrent connections^{15–17}. It has proved difficult to develop these abstract models into more realistic models that are based on spiking neurons (such as integrate-and-fire neurons) and in which time is continuously represented. In parallel, spiking models of the sensory cortex also

Box 1 | Spatialization of time

Traditional artificial neural networks, such as the perceptron¹³ and multi-layer perceptrons¹⁴, were designed to process static spatial patterns of inputs — for example, for the discrimination of handwritten characters — and the network structure therefore had no need to implicitly or explicitly incorporate time. When these models began to be used for the discrimination or production of time-varying stimuli, such as speech, the first approach was simply to assume that time was an additional spatial dimension¹⁷. For example, in one well-known model that converted written letters into artificial speech¹⁰⁵, the input was represented by 26 units (each representing a specific letter of the alphabet) and the temporal context was encoded by dividing time into 'bins' and then replicating the input layer of 26 inputs; that is, to encode 7 time bins ($t-3, t-2 \dots t+3$) there would be a total of 182 (26×7) inputs to the network. As the simulation progressed this 7-bin time window would slide forward bin by bin. In essence, time was 'spatialized' by transforming it into an additional spatial dimension. A spatial representation of time was also used in more biology-based models, such as those that simulated the fact that many forms of classical conditioning generated motor responses at the appropriate point in time; such 'delay-line' or 'labelled-line' models assume that in response to a stimulus specific neurons will respond with specific hardwired delays^{106–108}. Biologically speaking it is clear that time is not treated as an additional spatial dimension at the level of the inputs — that is, the sensory organs. However, in the CNS there is likely to be a spatial representation of some temporal features, particularly simple features such as the interval between two events. Thus, the question is not whether time can be centrally represented in a spatial code, but how this is achieved.

A second approach in artificial neural-network models was to implicitly represent time using recurrent connections, which allowed the state of the previous time step to interact with the input from the current time step, thus providing temporal context^{15,17}. These networks still treated time as a discrete dimension composed of time bins that were updated according to a centralized clock; the units themselves were devoid of any temporal properties. Together, these features have made these models difficult to generalize to biologically realistic continuous time models composed of asynchronous spiking neurons.

focused primarily on spatial processing. These models successfully accounted for the ability of cortical neurons to develop selective responses to the spatial properties of stimuli, such as retinotopy, somatotopy and orientation selectivity^{18,19}. But again, they were not designed to cope with the inherent spatial and temporal structure of natural stimuli.

In this Review, we describe a framework in which spatiotemporal computations emerge from the time-dependent properties of neurons and the inherent dynamics in cortical networks^{20–22}. These models posit that spatial and temporal processing are inextricably linked and that information is encoded in evolving neural trajectories (FIG. 1). Thus, in this framework the computation is in the voyage through state space as opposed to the destination. Additionally, we examine the predictions generated by this framework, including that the state of a network at any point in time encodes not only the present but also the past.

Inputs interact with internal states

The response of a population of neurons in a network is determined not only by the characteristics of the external stimulus but also by the dynamic changes in the internal state of the network^{12,21,23–26}. In other words, whether a neuron responds to a tone depends not only on the frequency of the tone but also on whether the neuron is receiving additional internally generated excitatory and inhibitory inputs and on the current strength of each

of its synapses (which vary on a rapid timescale). This general point can be intuitively understood by making an analogy between neural networks and a liquid²⁰. A pebble thrown into a pond will create a spatiotemporal pattern of ripples, and the pattern produced by any subsequent pebbles will be a complex nonlinear function of the interaction of the stimulus (the pebble) with the internal state of the liquid (the pattern of ripples when the pebble makes contact). Ripples thus establish a short-lasting and dynamic memory of the recent stimulus history of the liquid. Similarly, the interaction between incoming stimuli and the internal state of a neural network will shape the population response in a complex fashion. However, defining the internal state of a neural network is not straightforward, and it will thus be useful to distinguish between two components, which we will refer to as the active and the hidden states.

Active and hidden internal states. Traditionally, the internal state of a network is defined as the population of active neurons — we will refer to this as the active state. At any time t we can think of a network of N neurons as an N -dimensional vector that is composed of zeros and ones (depending on the size of the time bin we can also represent each value as a real number representing the firing rate). Such a vector forms a point in N -dimensional space and defines which neurons are active at corresponding time point t . Over the course of multiple time bins these points form a path (a neural trajectory) through state space (FIG. 1a). In a network that is driven by an ongoing external stimulus, a complex trajectory will form that represents the temporal evolution of active states. At each point $t+1$ the response of the neuronal population is dependent not only on the synapses that are directly activated by the input, but also on the ongoing activity in the network: owing to the recurrent nature of cortical circuits, activity in the network provides an additional source of synaptic inputs (the active state from other brain regions can also contribute to the response of a network, but from the perspective of any given local network this is equivalent to an additional time-varying input). *In vivo* recordings demonstrate that different stimuli elicit distinct spatiotemporal patterns of activity^{24,25,27,28} — that is, different neural trajectories (FIG. 1b, see below). These time-varying changes in the active state can be driven directly by the stimulus structure or by internally generated dynamics produced by the recurrent connectivity. Indeed, in some cases even if the stimulus (for example, a constant odour or steady auditory tone) is not varying in time, the neural trajectories that represent the network's active state continue to change^{24,29}, which could contribute to computations such as the encoding of intensity or time. For example, because trajectories evolve through time in a reproducible manner for a given stimulus²⁴, any given point has the potential to provide information not only about the stimulus presented but also about time itself — such as how much time has elapsed since the onset of the stimulus (FIG. 1a).

The response of a network is, however, more complex than the interaction between the external input and the ongoing pattern of activity in the network.

Integrate-and-fire neuron

A simple model of a spiking neuron. It integrates synaptic inputs with a passive membrane time constant. Whenever the resulting membrane voltage reaches a firing threshold, it generates an output spike.

Retinotopy

A spatial arrangement in which neighbouring visual neurons have receptive fields that cover neighbouring (although partly overlapping) areas of the visual field.

Somatotopy

A spatial arrangement in which neighbouring sensory neurons respond to the stimulation of neighbouring receptors in the skin.

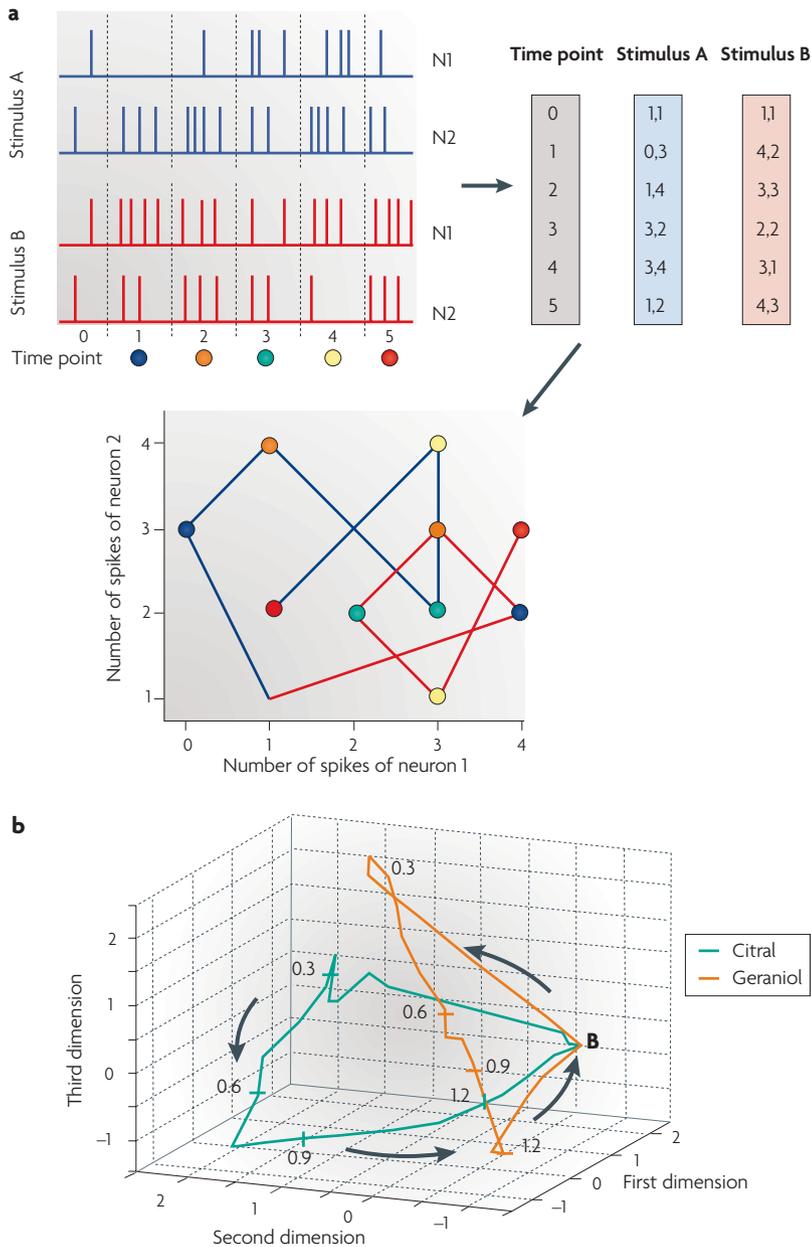


Figure 1 | Trajectories of active and hidden states. a | A schematic of a neural trajectory. If we consider the firing pattern of two neurons over five time bins, we can visualize the trajectory of this two-neuron network by plotting the number of spikes of each neuron during each time bin on the axes of a two-dimensional plot. The spikes generated by two different hypothetical stimuli are represented in blue and red, and each produces a different neural trajectory (lower plot). Importantly, each point on the trajectory can potentially be used to determine not only which stimulus was presented, but also how long ago the stimulus was presented (colour-coded circles). Thus, the neural trajectory can inherently encode spatial and temporal stimulus features. The coordinates represent the number of spikes of each neuron at each time bin (derived from the upper plot). **b** | An example of the active trajectory of a population of neurons from the locust antennal lobe. For a large number of neurons it is possible to use mathematical techniques to visualize their trajectory. In this case 87 projection neurons from the locust were recorded during multiple presentations of 2 odours (citral and geraniol). These data were used to calculate the firing rate of each neuron using 50 ms time bins. The 87 vectors were then reduced to 3 dimensions. The resulting three-dimensional plot reveals that each odour produces a different trajectory, and thus different spatiotemporal patterns of activity. The numbers along the trajectory indicate time points (seconds), and the point marked B indicates the resting state of the neuronal population. Part **b** is modified, with permission, from REF. 24 © (2006) Cell Press.

Neurons and synapses have a rich repertoire of time-dependent properties — the network’s hidden internal state — that are shaped by previous activity and that can in turn influence whether a neuron fires. For example, synapses undergo depression or facilitation for the duration of a timescale of hundreds of milliseconds^{30–33} (FIG. 2a); because short-term synaptic plasticity is often of the same magnitude as long-term plasticity³⁴, it should have significant effects on local neural computations. Thus, in the same manner that long-term potentiation provides a long-lasting memory of coincident pre- and postsynaptic activity, short-term synaptic plasticity can provide a memory of the recent stimulus history of the network. If we consider a brief sensory event presented to a network that is composed of excitatory and inhibitory neurons, a certain subpopulation of neurons will fire in response to that input (FIG. 2b). The brief sensory event could be a short tone, a flash of light or a tap to a whisker. In addition to eliciting action potentials in a subpopulation of neurons A, the stimulus will trigger changes in a series of time-dependent cellular and synaptic properties of the activated neurons that last on the order of hundreds of milliseconds. Thus, if the same brief stimulus is repeated 100 ms later, when neurons are no longer firing (the active state has returned to ‘baseline’), the network will nevertheless be in a different internal state (lower row in FIG. 2b). Consequently, it is possible that a different (albeit overlapping) subpopulation of neurons A’ will respond to the second (but identical) stimulus — thus providing information about the inter-stimulus interval.

It is important to stress that short-term synaptic plasticity is but one of many time-dependent neuronal properties that have the potential to provide a memory of the recent stimulus history in a network. In principle any neural or synaptic activity-triggered property that can shape the output of a neuron and that operates over the relevant timescale could contribute to the hidden state — and thus potentially to the encoding of time-varying stimuli. Other such cellular and synaptic properties include slow inhibitory postsynaptic potentials (IPSPs)^{35,36}, metabotropic glutamate currents³⁷, ion channel kinetics³⁸, Ca²⁺ dynamics in synaptic and cellular compartments^{39,40}, and NMDA (*N*-methyl-D-aspartate) channel kinetics⁴¹ (indeed, the membrane time constant can also contribute to the hidden state of a network, albeit over a shorter timescale). We refer to these neuronal and synaptic properties as the hidden network state, because they are not accessible to the downstream neurons (or to the neuroscientist performing extracellular recordings) but can influence the response of neurons to stimuli.

Because both the active and the hidden states influence the response of a local cortical network to a stimulus, the true internal state is a combination of both. In contrast to the active state, the hidden state provides a memory trace that can span periods of network quiescence. Thus, the active state that is produced by a second stimulus event will be influenced by the time that has elapsed since the previous stimulus (because of the hidden state), and it can therefore be used to determine the interval between stimuli⁴².

Membrane time constant
A physical measure that reflects the time it takes the voltage of a neuron to achieve 63% of its final value for a steady-state current pulse.

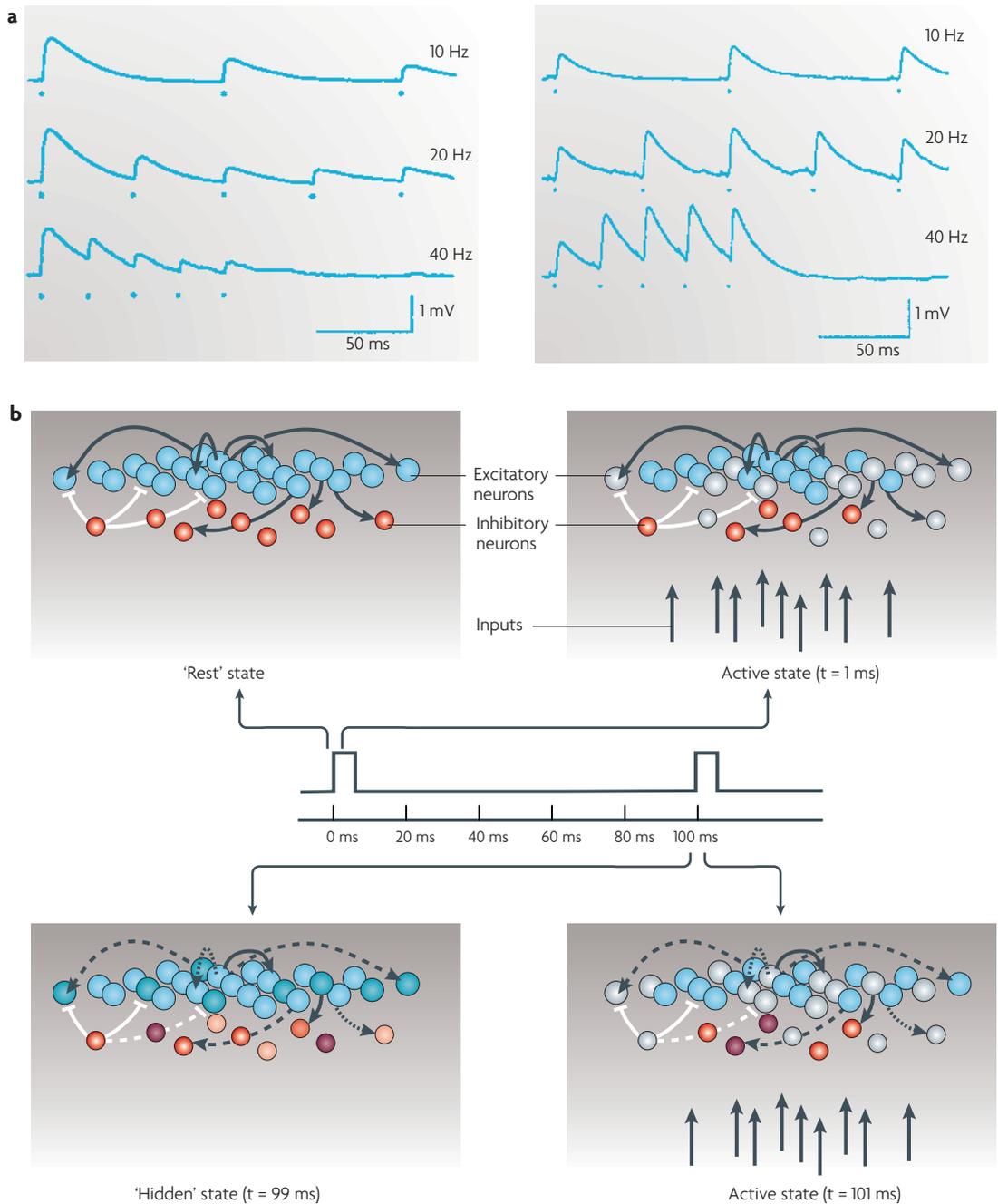


Figure 2 | Active and hidden network states. **a** | An example of short-term plasticity of excitatory postsynaptic potentials (EPSPs) in excitatory synapses between layer 5 pyramidal neurons. Short-term plasticity can take the form of either short-term depression (left) or short-term facilitation (right). The plots show that the strength of synapses can vary dramatically as a function of previous activity, and thus function as a short-lasting memory trace of the recent stimulus history. The traces represent the EPSPs from paired recordings; each presynaptic action potential is marked by a dot. **b** | Hidden and active states in a network. The spheres represent excitatory (blue) and inhibitory (red) neurons, and the arrows represent a small sample of the potential connections. The baseline state ('rest' state, top left panel) is represented as a quiescent state (although in reality background and spontaneous activity must be taken into account). In the presence of a brief stimulus the network response will generate action potentials in a subpopulation of the excitatory and inhibitory neurons (light shades), which defines the active state of the network (top right panel). After the stimulus, the neurons in early cortical areas stop firing. However, as a result of short-term synaptic plasticity (represented by dashed lines) and changes in intrinsic and synaptic currents (represented by different colour shades), the internal state may continue to change for hundreds of milliseconds. Thus, although it is quiescent, the network should be in a different functional state at the time of the next stimulus (at $t = 100$ ms) — this is referred to as the 'hidden' state (bottom left panel). The fact that the network is in a different state implies that it should generate a different response pattern to the next stimulus (bottom right panel), even if the stimulus is identical to the first one (represented as a different pattern of blue spheres). Part **a** is reproduced, with permission, from REF. 31 © (1999) Society for Neuroscience.

The interaction between internal states and time-varying external inputs has been proposed to be a key step in cortical function^{20–22,29,43}. Some theoretical models, with varying degrees of biological plausibility, have relied on this principle for the processing of spatio-temporal stimuli. In some of the models, the encoding of past stimuli was based solely on ongoing changes in the active state produced by the recurrent architecture^{17,44–47}. In other models, the memory of previous events was contained in the active and/or hidden states^{20,22,42,48,49}. In the context of neuroscience and machine learning, several instantiations of the general framework discussed in this Review have emerged, including liquid-state machines^{20,50}, echo-state networks⁴⁵, state-dependent networks^{2,22} and reservoir computing⁵¹. As is explained in the next section, a key result that arises from these models is that trajectories of active network states can, in spite of their complexity, be used for noise-robust computations on time-varying external inputs.

Decoding neural trajectories

In response to a stimulus, the active state of a network of neurons typically changes on a fast timescale of tens of milliseconds. How can downstream systems extract useful information about the external stimulus, such as the identity of an odour or of a spoken word, from these trajectories of transient states?

This decoding problem becomes less formidable if one considers it from the perspective of a downstream or ‘read-out’ neuron. Read-out neurons, which extract information from upstream areas and project it to downstream systems, are typically contacted by a large set of input neurons — thus each read-out neuron receives a high-dimensional sample of the active state of the upstream network. From a theoretical perspective, the high-dimensionality of the sample space facilitates the extraction of information by read-out neurons (see below). Let us assume for simplicity that read-out neurons are modelled by perceptrons — that is, that they have the discrimination capability of a linear discriminator. Such a linear discriminator, when applied to a point $x_1, x_2 \dots x_d$ from a d -dimensional state space (which corresponds to the active state of a population of d presynaptic neurons), computes a weighted sum $w_1x_1 + w_2x_2 + \dots w_dx_d$ at each time point, where $w_1, w_2 \dots w_d$ are the weights of the discriminator (corresponding to the synaptic weights of each presynaptic input); it outputs 1 whenever the weighted sum is above the threshold, and 0 otherwise. In this fashion, linear read-out neurons can classify the time-varying active states of presynaptic neurons according to the external stimuli that caused these active states — in other words, the read-out neurons become a detector, in that their activity reflects the presence of a specific stimulus. An example of such a separation of trajectories of active states is shown in FIG. 3.

Robust separation of the trajectories is difficult in few dimensions (that is, few presynaptic inputs) (see BOX 2 figure, part a), but mathematical results demonstrate that a linear separation of trajectories becomes much easier when the state space has many dimensions (see BOX 2 figure, part b). In particular, linearly inseparable

classes of external stimuli tend to become linearly separable once they are projected nonlinearly into a higher-dimensional state space⁵² (BOX 2). The nonlinearity of the projection of stimuli into high-dimensional space is a product of the inherent complexity and nonlinear nature of the interaction between the internal state and external stimuli. Indeed, from a theoretical perspective⁶⁴ it is not the precise nature of the transformation itself, but rather the increase in the dimensionality of the representation that is crucial to the computation. As mentioned above, because a typical read-out neuron in a cortical area receives synaptic input from thousands of neurons, it has a high likelihood of being able to separate the trajectories of active states of its presynaptic neurons according to the external stimuli that caused these trajectories.

Can read-out neurons learn to decode time-varying active states? Experimental and theoretical results to date indicate that read-out neurons are in principle able to separate complex trajectories of active states of presynaptic neurons if their synaptic weights are determined by a suitable learning rule (see below)^{44,53–55}. It remains unknown, however, whether the appropriate set of synaptic weights can be learned *in vivo*.

In the case in which a read-out neuron is modelled by a linear discriminator, if one assumes that the read-out neuron is informed during learning which trajectory resulted from stimulus class A and which from class B (a process known as supervised learning), then traditional learning rules (such as the perceptron learning rule or backpropagation)^{13,56} converge to a weight vector that achieves the desired separation — provided that such a set of weights exists. Traditional artificial neural network learning rules do not capture information that is contained in previous time steps — that is, information encoded in the temporal pattern of active states; however, some supervised-learning rules have also proved effective in allowing spiking read-out neurons to extract information from the spatiotemporal pattern of inputs generated by different stimuli⁵⁷.

Additionally, it is plausible that a biological read-out neuron can learn to decode the active states of a recurrent network through trial and error in a reward-based setting. For example, it has been shown that reward-modulated spike timing-dependent plasticity (STDP) allows spiking neurons to learn to discriminate different trajectories using reinforcement learning^{58,59} — a form of learning in which the animal or network receives a global positive or negative feedback signal based on its performance.

In a third model for decoding spatial or spatiotemporal patterns of activity, read-out neurons learn to separate trajectories in the absence of a ‘teacher’ and of rewards — that is, in an unsupervised fashion. One such model, termed slow-feature analysis, takes advantage of the observation that stimuli remain present on time-scales that generally exceed those over which the neural trajectories are changing. It has been shown that a spiking read-out neuron can learn through STDP to extract the slow features from the trajectory of active states of presynaptic neurons under certain conditions⁶⁰. This approach has been applied to unsupervised learning of

Liquid-state machine

A class of computational model that is characterized by one or several read-outs applied to some generic dynamical system, such as a recurrent network of spiking neurons. Whereas the dynamical system contributes generic computational operations, such as fading memory and nonlinear combinations of features that are independent of concrete computational tasks, each read-out can be trained to extract different pieces of the information that is accumulated in the dynamical system.

Echo-state network

A class of artificial neural network model that is based on recurrent connections between analogue units, in which the connection weights are random but appropriately scaled to generate stable internal dynamics. These models can encode temporal information as a result of the active state but do not have hidden states.

State-dependent network

A class of model that is based on the characteristics described in this Review. The state-dependent network model proposes that cortical networks are inherently capable of encoding time and processing spatiotemporal stimuli as a result of the state-dependent properties imposed by ongoing activity (the active state) and as a result of time-dependent neural properties (the hidden states).

Reservoir computing

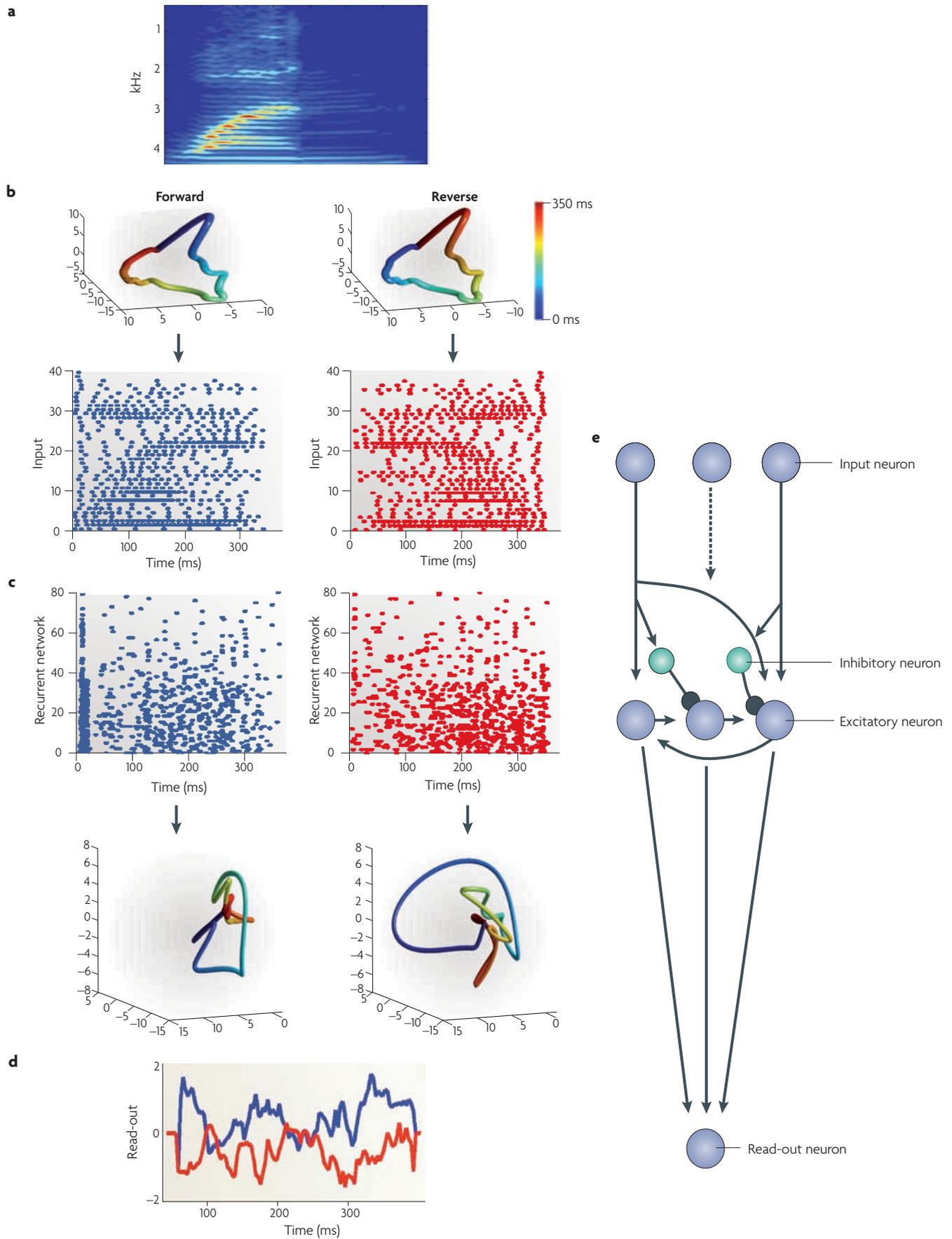
A general term used primarily in machine learning to refer to models that rely on mapping stimuli onto a high-dimensional space in a nonlinear fashion. Such models include echo-state machines, liquid-state machines and state-dependent networks.

Linear discriminator

A type of classifier that can be computed by a perceptron.

Synaptic weights

The strength of synaptic connections between neurons.



Learning rule

A rule that governs the relationship between patterns of pre- and postsynaptic activity and long-term changes in synaptic strength. For example, spike timing-dependent plasticity.

Recurrent network

A network in which any neuron can be directly or indirectly connected to any other — the flow of activity from any one initial neuron can propagate through the network and return to its starting point. By contrast, in a feedforward network information cannot return to the point of origin.

Spike timing-dependent plasticity

(STDP). Traditionally, a form of synaptic plasticity in which the order of the pre- and postsynaptic spikes determines whether synaptic potentiation (pre- and then postsynaptic spikes) or depression (post- and then presynaptic spikes) ensues.

invariant pattern classification of moving visual inputs by linear discriminators⁶¹.

A question related to how read-out neurons learn to respond in a stimulus-specific manner is whether the read-out neurons exhibit robust generalization — indeed, the ability to properly respond to a novel stimulus and to similar instances of the same stimulus is fundamental for effective sensory processing. Theoretical results from statistical learning theory⁶² imply that linear read-outs exhibit better generalization than highly nonlinear neurons, because they have fewer degrees of freedom during learning⁶³. Analysis of network properties that favour robust generalization of trained read-outs to new network inputs shows that a necessary and sufficient condition for generalization is that the inputs that need to be classified differently by a read-out neuron result in trajectories that stay farther apart than two trajectories that are caused by two trials with the same external input⁶⁴.

It should be noted that to date there is little direct experimental evidence regarding how neurons *in vivo* learn to extract information from upstream areas. However, the theoretical work reviewed above suggests that variations on experimentally described forms of synaptic plasticity could in principle suffice. Finally, it should be pointed out that models related to the framework described here — in which linear discriminators are used to read out information from complex recurrent artificial neural networks — have proved to be a powerful tool in engineering and machine-learning applications, such as time series prediction, speech classification and handwriting recognition^{45,51}.

Noise, chaos and network dynamics. *In vivo* recordings demonstrate that there is significant variability in network activity in response to nominally identical experimental trials²⁵. For example, FIG. 4b shows the variability of spike trains from a neuron in the primary visual cortex for 50 trials in which exactly the same visual stimulus was shown to an anaesthetized cat. This variability is generally attributed to internal noise and different initial internal states. In the context of recurrent networks, noise can reduce the ability to encode information about past stimuli (the memory span). Furthermore, theoretical and modelling studies have shown that recurrent networks can exhibit chaotic behaviour^{64–69} — specifically, in simulations the removal of a single spike can cause large changes in the subsequent spiking activity⁶⁷.

Computational models of recurrent networks establish that certain regimes — particularly when the strength of recurrent connections dominates network dynamics — can be highly sensitive to noise and exhibit chaotic behaviour^{66,67}. However, it is clear that cortical neural networks, although they are recurrent, are not chaotic in the sense that trajectories of neural states are not dominated by noise^{24,25,53,70}. For example, in the experiment described in FIG. 4, a read-out unit (FIG. 4c) could determine from a single trial not only the identity of the current stimulus but also that of a past stimulus that is no longer present, despite the noise in the system. How the brain creates these non-chaotic states in recurrent networks is a fundamental issue that remains to be fully addressed.

However, it is known that the complex dynamics that are associated with chaotic regimes can be avoided by appropriately scaling the synaptic weights^{45,47,64}. Furthermore, numerous computational models have shown robust pattern recognition in the presence of noise using recurrent networks and linear read-outs^{20,22,48,71–73}. Additional theoretical work shows that under certain conditions randomly connected networks can encode past information in the ongoing dynamics of the active states, and the duration of this fading memory increases with network size^{74,75}. In addressing the influence of noise on the framework described here, it is important to consider a number of other factors. First, the external stimulus can limit the sensitivity of the neural network to noise because it also actively shapes the neural trajectory, and can in effect entrain the dynamics. Indeed, the relative strength of the recurrent connections in relation to the input connections is crucial to determining the behaviour of the network. Notably, the recurrent connections do not need to be strong enough to generate self-maintaining activity in order to contribute to spatiotemporal computations: during the presentation of time-varying stimuli even weak recurrent connections provide an interaction between the current and immediately preceding sensory events. Second, for time spans over which sensory information is often integrated (hundreds of milliseconds), generic models of recurrent cortical microcircuits can store information about past stimuli^{50,75}. Third, theoretical analyses generally do not take into account the contribution of the hidden states. Specifically, time-dependent properties, such as short-term synaptic plasticity and

◀ **Figure 3 | Discrimination of complex spatiotemporal patterns.** **a** | A sample spectrogram of the spoken word 'one'. **b** | A spatiotemporal pattern of action potentials representing the word 'one'. Cochlear models can be used to generate a spatiotemporal pattern of spikes generated by the word 'one' (left lower panel). This pattern can be reversed (right lower panel) to ensure that the network is discriminating the spatiotemporal patterns of action potentials, as opposed to only the spatial structure. One can perform a principal-component analysis on the spikes of the input patterns, and by plotting the first three dimensions create a visual representation of the input trajectory. The upper panels show that the trajectories are identical except that they flow in opposite temporal directions. Time is represented in colour: note the reverse colour gradient. **c** | Active states in a cortical microcircuit model. The raster of the recurrent network in response to the forward (blue) and the reverse (red) direction is plotted. The fact that the spatiotemporal spike patterns are no longer simply reverse representations of each other can be seen in the neural trajectories (lower plots). The response shown represents a subsample of the 280 layer-5 neurons of the model described by Hauesler and Maass⁴⁸. The trajectory calculations plotted the fourth, fifth and sixth dimensions of the principal-component analysis to improve visualization. **d** | A linear read-out can distinguish between the original speech input and its time reversal at most points in time. A single linear read-out that received synaptic inputs from all neurons in the circuit was trained to produce large output values for any active state that occurred when the word 'one' was spoken, but low output values at any time during the time-reversed version of 'one'. The resulting output values of the read-out are shown for a new trial that included noise injections into the neurons. The fact that this simple linear read-out can distinguish at most time points the original spatiotemporal spike inputs from their time-reversed version demonstrates that not only does the circuit process the spatial aspects of these input patterns, but every active state also transmits information about the temporal context of each spatial input pattern. **e** | A schematic of the cortical microcircuitry model, with the components aligned with the relevant sections of parts **b–d**. Several neurons provide input to excitatory neurons that are part of a recurrent network. The excitatory neurons in this network send a multi-dimensional signal to a single downstream read-out neuron. Part **a** is based on simulations by S. Klampf.

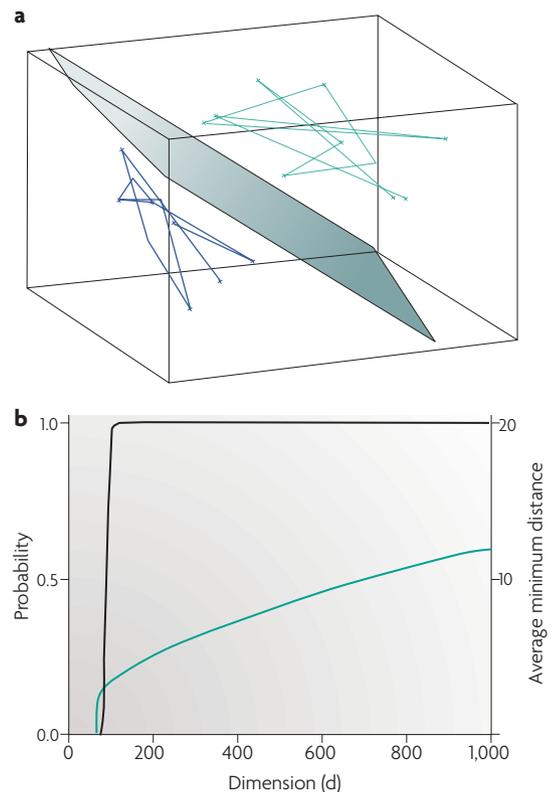
Box 2 | **Encoding in high dimensions**

Consider two neural trajectories, T_A and T_B , in d dimensions (see the figure, part a), both of which are defined as paths that linearly connect sets of N randomly drawn points in the d -dimensional hypercube $[0,1]^d$. A point x in this space represents the active state of presynaptic neurons at a specific time point t . Its i^{th} coordinate could represent, for example, the firing rate of the i^{th} presynaptic neuron in a time bin centred at t . An alternative method for representing the contribution of presynaptic neuron i is to convolve the spike train of neuron i with an exponential function (for example, an exponentially decaying kernel with a time constant of 20 ms) and take the output value of the resulting linear filter at time t (scaled into $[0,1]$) as the i^{th} component of the active state⁵⁵.

The read-out of the active states can be modelled by a perceptron^{15,109}, which computes a weighted sum $w_1x_1 + w_2x_2 + \dots + w_dx_d$ of the inputs x . Geometrically, those points (x_1, x_2, \dots, x_d) at which the weighted sum is exactly equal to the threshold form a hyperplane in the d -dimensional input space. Such a hyperplane is shown as a grey surface in part a of the figure for the case $d = 3$, together with a trajectory T_A (the green curve) and a trajectory T_B (the blue curve). The linear discriminator assigns the output value 1 to the points on one side of the hyperplane, where the weighted sum is larger than the threshold, and 0 to the points on the other side. The values of the weights and the threshold of the linear discriminator define the position of this hyperplane. Complete separation of T_A and T_B would imply that there is a linear read-out that could output the value 1 for all points in T_A , and the value 0 for all points in T_B . This extreme case is illustrated for $d = 3$ in part a of the figure. However, such perfect separation can in general not be expected (for example, a read-out neuron might not be able to separate presynaptic active states in a reliable manner immediately after stimulus onset), and it suffices if the hyperplane separates the trajectories during some given time window.

Although robust separation of complex trajectories is difficult in low dimensions, results from mathematical theory imply that a linear separation of trajectories becomes much easier when the dimension of the state space exceeds the 'complexity' of the trajectories³². Part b of the figure shows that most pairs of trajectories defined by paths through any 2 sequences of 100 points can be separated by a linear discriminator as the dimension d becomes larger than 100. The probability that 2 trajectories that each linearly connect 100 randomly chosen points can be separated by a hyperplane is plotted in black. The green curve gives the average of the minimal Euclidean distance between pairs of trajectories. It shows that the distance between any two such trajectories tends to increase as d grows. Thus, at higher dimensions not only is it more likely that any two such trajectories can be separated, but also they can be separated by a hyperplane with a larger 'safety margin'. A larger margin implies that noisy perturbations of these two trajectories can be classified by the linear discriminator in the same way as the original trajectories. One should note that projections of external inputs into higher-dimensional networks are quite common in the brain. For example, ~1 million axons from the optic nerve inject visual information from the lateral geniculate nucleus into the primary visual cortex, in which there are ~500 million neurons. Thus, the primary visual cortex gives rise to trajectories in a much higher dimensional space than those generated by the retinal ganglion cells. Theoretical results⁶⁴ suggest that the way these trajectories are generated is not all that important for the resultant computational capability of the network: it is primarily the linear dimension of the space that is spanned by the resulting trajectories that is crucial.

slow IPSPs, also provide a memory on the timescale of hundreds of milliseconds. This memory is likely to contribute to the representation of past information in a fashion that is less susceptible to noise because it is not necessarily amplified as a result of the positive feedback that is inherent to recurrent connectivity. For example, as mentioned above, sensory cortical areas do not generally exhibit self-maintaining activity, and after a brief stimulus they return to low-level firing rates; in these cases the hidden state can provide a memory that bridges the gap between stimuli^{42,76}, and this memory should be relatively insensitive to noise as the network is silent.



Invariant pattern classification

The discrimination of patterns in a manner that is invariant across some transformation. For example, recognition of the same word spoken at different speeds or by different speakers.

Chaos

In theoretical work this term is applied only to deterministic dynamical systems without external inputs, and characterizes extreme sensitivity to initial conditions. In neuroscience it is also applied more informally to systems that receive ongoing external inputs (and that are subject to noise and hence are not deterministic), and characterizes neuronal systems with a trajectory of neural states that is strongly dependent on noise and less dependent on external stimuli.

Hyperplane

A hyperplane is a generalization of the concept of a plane in a three-dimensional space to d -dimensional spaces for arbitrary values of the dimension d . A hyperplane in d dimensions splits the d -dimensional space into two half spaces.

Most theoretical analyses of dynamics have considered recurrent networks in which both the connectivity and the weights are randomly assigned. However, given the universal presence of synaptic plasticity^{77,78} and known connectivity data^{79,80}, it is clear that synaptic connectivity and strengths are not random in cortical circuits. Indeed, one of the fundamental features of the cortex is the fact that synaptic strength and neural circuit structure are modified as a function of sensory experience⁸¹⁻⁸⁴. These forms of long-term and experience-dependent plasticity probably play a crucial part in shaping network dynamics and producing stable and reproducible neural

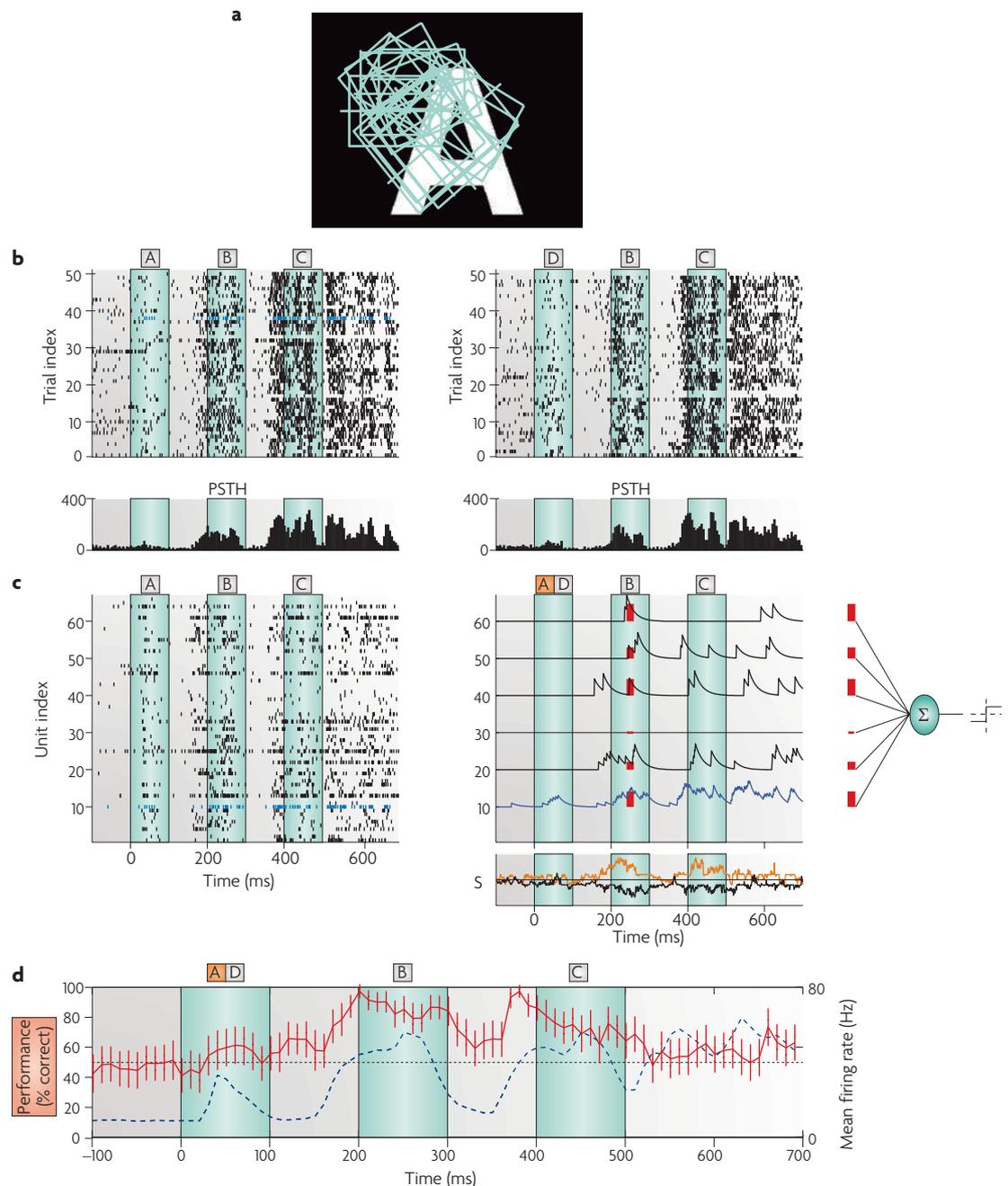


Figure 4 | Population activity from the cat visual cortex encodes both the current and previous stimuli. **a** | A sample stimulus, with the receptive fields (squares) of the recorded neurons superimposed. **b** | The spike output of neuron number 10 for 50 trials with the letter sequence A, B, C as the stimulus and 50 trials with the letter sequence D, B, C as the stimulus. The temporal spacing and duration of each letter is indicated through green shading. The lower plot is a post-stimulus time histogram (PSTH) showing the response of neuron 10 (shown in blue in part **c**) over the 50 trials shown. **c** | The spike response of 64 neurons during trial number 38 (indicated in blue in part **b**) for the letter sequence A, B, C (left-hand plot), and the read-out mechanism that was used to decode information from these 64 spike trains (upper right-hand plot). Each spike train was low-pass filtered with an exponential and sent to a linear discriminator. Traces of the resulting weighted sum are shown in the lower right-hand plot both for the trajectory of active states resulting from stimulus sequence A, B, C (black trace) and for stimulus sequence D, B, C (orange trace). For the purpose of classifying these active states, a subsequent threshold was applied. The weights and threshold of the linear discriminator were chosen to discriminate active states resulting from letter sequence A, B, C and those resulting from the letter sequence D, B, C. The blue traces in parts **b** and **c** show the behaviour of neuron 10. **d** | The performance of a linear discriminator at various points in time. The red line shows the percentage of the cross-validated trials that the read-out correctly classified as to whether the first stimulus was A or D. The read-out neuron contained information about the first letter of the stimulus sequence even several hundred milliseconds after the first letter had been shown (and even after a second letter had been shown in the meantime). Note that discrimination is actually poor during the A and D presentation because of the low average firing rate (blue dashed lines). Part **a** is reproduced, with permission, from REF. 55 © (2007) MIT Press. Parts **b-d** are partly based on data from REF. 55.

trajectories that improve the encoding and read-out of behaviourally relevant stimuli. Effectively incorporating plasticity into recurrent networks that are composed of spiking neurons has proved to be a challenge, but recent studies have shown that certain learning rules can help to embed neural trajectories in recurrent networks⁸⁵, and work on reward-modulated STDP^{58,59,86} has also begun to address this issue. Additionally, it has been shown that the time span over which networks can encode previous events can be increased in models with spiking neurons through long-term synaptic plasticity⁷¹.

Computing with trajectories

The framework reviewed above proposes that cortical networks are inherently capable of processing complex spatiotemporal stimuli as a result of the interaction between external stimuli and the state of the internal network. Additionally, it suggests that sets of read-out neurons can extract information from the time-varying neural trajectories represented in high-dimensional space. As was recently stressed by a number of groups^{21,29,87}, this notion marks a significant departure from the traditional hypothesis that cortical computations rely on neural networks that converge to steady-state attractors^{88,89} — that is, states in which neural firing rates remain constant for a minimal period of time. Although there is evidence that in higher-order cortical areas these fixed-point attractors play a part in working memory^{90–92}, few data suggest that they contribute to the pattern recognition of complex time-varying stimuli. Thus, earlier cortical areas, the computational task of which is to decide what stimulus is present, could extract information from neural trajectories. This framework is well suited to the fact that most complex forms of sensory processing take place in real-time in the presence of ever-changing sensory stimuli.

We next review experimental data from different neural systems that support the notion that neural computations arise from state-dependent computations and are represented in the trajectory of the active states in high-dimensional space.

Olfactory system. The mechanism that underlies the discrimination and coding of olfactory information has proved to be a valuable system for the study of neural dynamics in recurrent circuits⁹³. Studies in the locust suggest that even when it is presented for a prolonged period, a given odour is encoded in a characteristic trajectory of active states (FIG. 1b). Specifically, the projection neurons (PNs) in the antennal lobe exhibit complex time-varying changes in firing rate in response to a tonic stimulus. For each odour, a complex spatiotemporal pattern is formed across the approximately 800 recurrently connected projection neurons that represents a trajectory in a high-dimensional space⁵³. The trajectory is reproducible for a given odour at a given concentration. This trajectory can evolve for a few seconds and then converge to a fixed point. The cells that are located in the next processing stage — the Kenyon cells in the mushroom bodies — create a sparse code of olfactory stimuli that also changes with time. Furthermore, the Kenyon cells, which can be

thought of as read-outs of the PNs, decrease their firing when the active state of the PNs has converged to an attractor. That is, the Kenyon cells, which transmit the ‘output’ of the computation of the PNs, respond preferentially while the PN trajectory is in motion but respond less when it is in the steady state. Additionally, as it can take up to a few seconds for the fixed point to be achieved, the fixed point is unlikely to contribute to behavioural decisions *in vivo*. Consistent with the predictions of the framework discussed above, the response of the network to an odour B was distinct from the response to the same odour when it was preceded by odour A²⁴, reflecting the state dependency of the trajectory of the active states of PNs and suggesting that the network has the potential to encode not only the current stimulus but also past stimuli. The fact that the neural trajectories are dynamic even when the stimulus is not suggests that the internal dynamics have a critical role in the ongoing computations²⁹. Together, these results provide experimental evidence that the critical computation in olfactory discrimination resides in the voyage of the network through high-dimensional state space, as opposed to it residing in the arrival at a specific location in state space.

Timing in the cerebellum. Experimental evidence suggests that the cerebellum regulates some types of motor timing^{94,95}. Although the mechanisms that underlie timing are not fully understood, it has been shown that small lesions in the cerebellar cortex can alter the timing of a motor response⁹⁶. Consistent with these findings, it has been proposed that timing relies on the spatiotemporal dynamics of the granule cell population and that these dynamics arise from the interaction between cerebellar input and the internal state of the cerebellar network^{44,97}. In the cerebellum, granule and Golgi cells are part of a negative-feedback loop in which granule cells excite Golgi cells, which in turn inhibit granule cells. In response to a constant stimulus, conveyed by the mossy fibres, the granule cell population response is not only a function of the current stimulus, but also depends on the current state of the granule cell–Golgi cell network. Simulations reveal that, as a result of the feedback loop, a dynamically changing trajectory of active granule cells is created in response to a stimulus^{44,46,98}. This pattern will trace a complex trajectory in neuron space, and as each point of the trajectory corresponds to a specific population vector of active granule cells, the network inherently encodes time. Time can then be read out by the Purkinje cells (the ‘read-out’ neurons), which sample the activity from a large population of granule cells. Importantly, the Purkinje cells can learn to generate timed motor responses through conventional associative synaptic plasticity coupled to the reinforcement signal from the inferior olive⁹⁹. In this framework, the pattern of granule cell activity would be expected not only to encode all potentially relevant stimuli, but also to be capable of generating a specific time stamp of the time that has elapsed since the onset of each potential stimulus. This scheme clearly requires a very high number of distinct granule cell patterns. Indeed, the fact that there are over 5×10^{10} granule cells in the human cerebellum¹⁰⁰

Attractor

The state of a dynamical system to which the system converges over time, or the state that ‘attracts’ neighbouring states.

Sparse code

A neural code in which only a small percentage of neurons are active at any given point in time.

suggests that they are uniquely well suited and indeed designed to encode the large number of representations that would arise from having to encode the time from onset for each potential stimulus.

State-dependent cortical responses. Studies in the auditory cortex have demonstrated that some neurons respond preferentially to a given sensory event when it is preceded by another event. These cells are sometimes referred to as temporal combination-sensitive cells, and have been observed in the auditory systems of a number of species, including songbirds^{8,11,101}, rats¹⁰, cats^{9,102} and monkeys^{12,103}. In some of these studies, cells exhibited a facilitated response to tone B if it was preceded by tone A by a specific interval. This spatiotemporal selectivity tends to be highly nonlinear and thus not predictable on the basis of the linear combination of the response generated by the two tones independently. For example, recently it was shown that neurons in the auditory cortex of monkeys that were trained to recognize a specific sequences of tones can exhibit dramatic facilitation to the target sequence¹⁰⁴. Specifically, a neuron could respond strongly to the sequence AB, but not to A or B alone. Interestingly, the percentage of such cells was higher in trained monkeys, indicating that experience-dependent plasticity optimizes the encoding of behaviourally relevant neural trajectories. In many of the experimental studies cited above, there was no observable ongoing activity in the network between tone presentations. Thus, it is possible that here the state-dependent facilitatory responses are the result of changes in the hidden state of the local neural network, or they could be a result of ongoing stimulus-specific activity in other brain regions.

State-dependent temporal processing. A few studies have set out specifically to test predictions that have been generated by state-dependent models^{26,55} (see below). In one study these predictions were examined using human psychophysics⁷⁶. Specifically, state-dependent models predict that the interval between two brief tones can be encoded in the population response to the second tone. Thus, two distinct inter-stimulus intervals (of, for example, 100 ms and 200 ms) can be discriminated by comparing the network responses to the second stimulus⁴². However, the state-dependency of this framework poses a potential problem: if the same 100 ms interval is preceded by a 'distractor' tone (that is, an additional tone before the two that define the interval), the representation of the simple 100 ms interval should be altered. In other words, the network does not have an absolute representation of a 100 ms interval, because each event is encoded in the context of the previous event. Thus, one prediction that emerges is that if temporal processing relies on state-dependent mechanisms as opposed to an 'internal clock', it will be difficult to directly compare the absolute interval between two stimuli if they are presented in close temporal proximity — one can think of this as being because the network would not have time to 'reset' between stimuli. Psychophysical results revealed that if two intervals (each of approximately 100 ms) were presented 250 ms apart, the ability to determine

which was longer was significantly impaired compared with when they were presented 750 ms apart⁷⁶. Importantly, when the two intervals were presented 250 ms apart, but the first and second tones were presented at different frequencies (for example, 1 kHz and 4 kHz), interval discrimination was not impaired. This could be interpreted as preceding stimuli being able to 'interfere' with the encoding of subsequent stimuli, but with there being less interference if the stimuli are processed in different local cortical circuits (as a result of the tonotopic organization of the auditory system). These results are consistent with the notion that timing relies on the interaction between incoming stimuli and the internal state of local cortical networks.

Visual cortex. The hypothesis that the response of a neuronal network to a stimulus encodes that stimulus in the context of the previous stimuli implies that the neural population code could be used to determine the nature of the previous stimuli. This prediction has recently been explicitly tested in the cat primary visual cortex using a sequence of visual stimuli (letters). Specifically, Nikolić *et al.*⁵⁵ showed that the neuronal response of 60–100 neurons to the second stimulus contained information not only about the letter being presented but also about the preceding letter. In fact, the identity of the first and the second letters could be recovered with high reliability by a simple linear read-out from the simultaneously recorded spike trains of neurons in area 17, both during and after the presentation of the second stimulus (FIG. 4). This effect could be viewed as imprecision in the neural code for the second letter. However, it can also be seen as a potential mechanism for integrating information from several frames of visual inputs, as is needed for the analysis of dynamic visual scenes.

Conclusions and future directions

A general model of cortical function should account for the ability of neural circuits to process stimuli in real time, and to classify and discriminate these stimuli based on their spatiotemporal features. Here we have reviewed an emerging framework that could provide a theoretical foundation to meet this goal. This framework is characterized by four key features. First, networks of neurons are inherently capable of encoding complex spatiotemporal stimuli as a result of the interaction between external stimuli and the internal state of the network. This internal state is determined both by ongoing activity (the active state) and time-dependent changes in synaptic and cellular properties (the hidden state). It is this state dependency that allows networks to encode time and spatiotemporal structure. Second, the inherent diversity of neuronal properties and the complexity of cortical microcircuits contribute to computations by projecting network responses into high-dimensional representations, which amplifies the separation of network trajectories generated by different stimuli. Third, the high dimensionality of stimulus representations in neuron space, together with massive convergence onto downstream 'read-out' neurons, allows for decoding by appropriately adjusting

Psychophysics

Studies based on perceptual decisions regarding the physical characteristics of stimuli, such as the intensity or duration of sensory stimuli.

Tonotopy

A spatial arrangement in which tones that are close to each other in terms of frequency are represented in neighbouring auditory neurons.

the synaptic weights between these groups of neurons. Finally, the multiplexing of computational processes in cortical circuits is an emergent property in this framework, because different read-out neurons can extract different features of the information (for example, spatial or temporal features) present in the trajectory of active network states.

The above framework provides an initial step towards a general model of cortical processing; however, a number of fundamental issues remain to be elucidated. These include how downstream neurons acquire the appropriate weights to read out the relevant active states, the mechanisms by which cortical circuits create reproducible neural trajectories and avoid chaotic regimes, and the role of long-term and experience-dependent plasticity in

sculpting and optimizing neural trajectories. Although future research will have to continue to address these and other issues, the notion that cortical microcircuits are inherently capable of processing spatiotemporal features of stimuli as a result of their active and hidden internal states provides a unified model of spatial and temporal processing and generates explicit experimental predictions. One prediction, that we hope will continue to be the target of experimental tests, is that the population response of cortical networks should not be interpreted as simply encoding the current stimulus, but rather as generating a representation of each incoming stimulus in the context of the previous stimuli²². In this fashion, networks would be able to encode the combination of past and present sensory events.

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FURTHER INFORMATION

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