Complexity in Neuronal Networks

Yves Frégnac*, Michelle Rudolph, Andrew P. Davison and Alain Destexhe

Unité de Neurosciences Intégratives et Computationnelles (UNIC), UPR CNRS 2191, 1 Avenue de la Terrasse, 91 198 Gif-sur-Yvette, France

*Corresponding author E-mail: Yves.Fregnac@unic.cnrs-gif.fr.

Published in : Frégnac, Y., Rudolph, M., Davison, A. and Destexhe, A. (2007). Complexity and level hierarchy in Neural networks. In « Biological networks », Editor : F. Képès, In « Complex systems and interdisciplinary Science » Series, World Scientific. pp. 291-340.

Introduction

The brain can be thought of as a collective ensemble ranging in the spatial domain from microscopic elements (molecules, receptors, ionic channels, synapses) to macroscopic entities (layers, nuclei, cortical areas, neural networks) (Figure 1). The same multi-scale analysis can be replicated in the temporal domain, when decomposing brain activity in a multitude of dynamic processes with time constants ranging from microseconds (molecule transconformation, channel opening) to years (postnatal cell replacement, for example in the bird song system; long-term memories, for example in vertebrate hippocampus). A tantalising challenge to the field of system and computational neuroscience is to bind in a coherent way these different hierarchies of organisation on the basis of experimentally defined descriptors, each of which is endowed with a specific spatio-temporal domain and measurement precision.

An issue central to the theme of complexity in biological systems concerns the inferences that can be made from one level of integration to the next, along reductionist top-down (from macroscopic to microscopic) or synthetic bottom-up (from microscopic to macroscopic) axes. The question addressed by combining computational and system neuroscience tools is `to what extent can properties specific to one level of organisation be predicted by those demonstrated at lower levels of organisation?', or, in other words, is the `whole' the sum of the `parts'? This question applies not only at the structural level but also at the functional level. In the latter case, one wants to assess to what extent can the global systemic behaviour (e.g. network dynamics) be reproduced on the basis of knowledge of the `intrinsic reactivity' of the elements (ion channels, neurons) and the `extrinsic' relational links established between them (synapses)? Any failure of the linear/additive synthetic approach opens the Pandora's Box of complexity.

As underlined by Tomaso Poggio in a famous essay [2], one of the main reasons explaining the conceptual distance between brain theoreticians and biologists is the relative ignorance of the nature and properties of the biophysical substrate that implements the elementary stages of neural information processing. The classical vision of the neuron and its integrative function as a summating unit, with multiple input lines, static synaptic gains, a postsynaptic threshold and a single `all-or-none' spiking output reflects our incapacity to recognise the necessity of non-linear operations on graduated, analogue input signals. Theoreticians dealing with McCulloch-Pitts [3] assemblies were initially tempted to use only additions and subtractions, while the neuronal machinery of the brain is obviously capable of non-linear input-output relationships, such as temporal integration and division of excitation by inhibition, and thus of more elaborate computations. The existence of distributed local non-linearities in the process of assembly making is a first indication of the complexity of living networks.

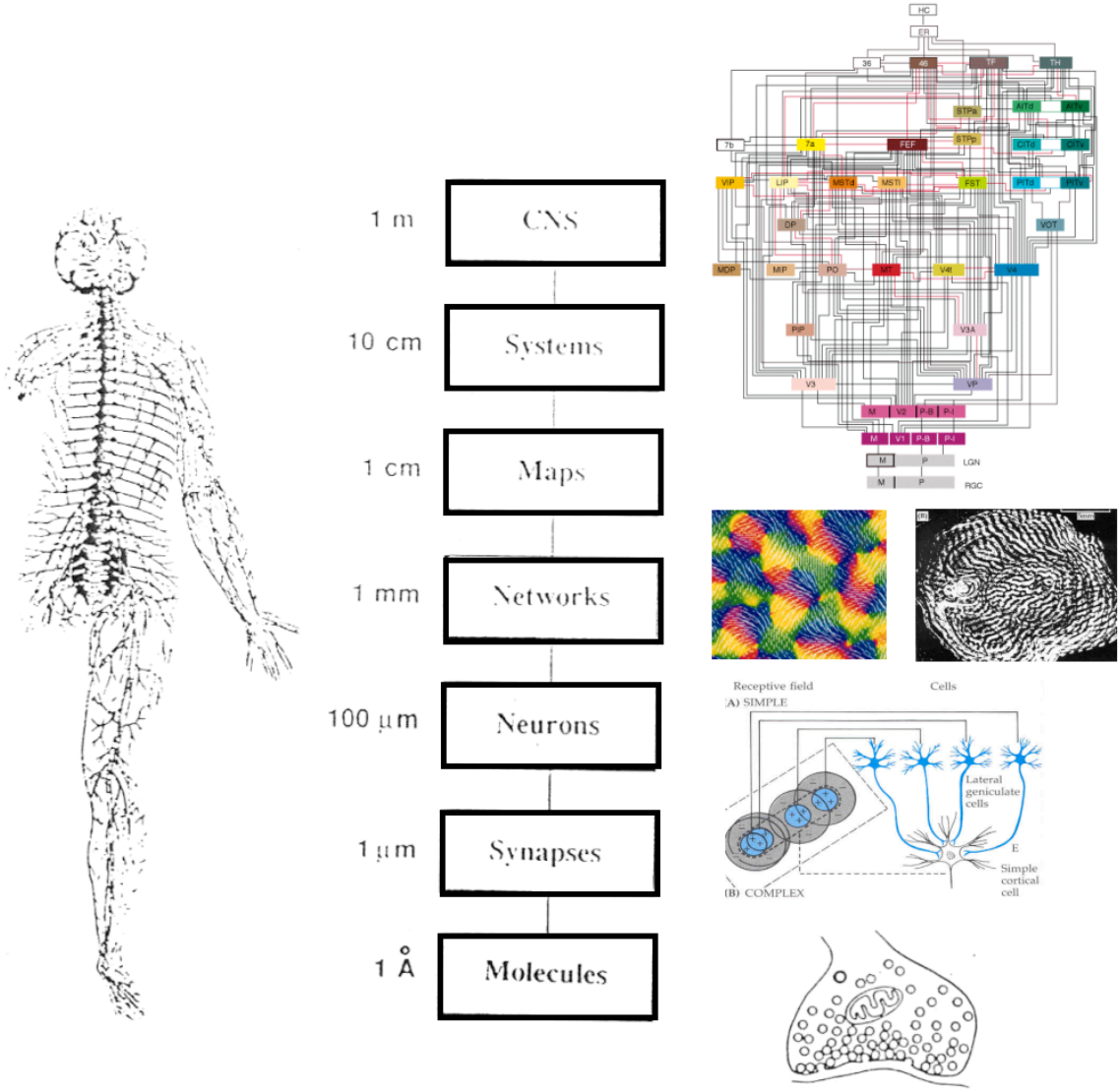

Figure 1: *Schematic levels of spatial integration in the nervous system. The spatial scale at which anatomical organizations can be identified varies over many orders of magnitude. Icons to the right represent structures at distinct levels in a bottom-up fashion: (bottom) a chemical synapse, (middle-bottom) a network model of how thalamic afferent cells could be connected to simple cells in visual cortex, (middle-top) maps of orientation preference and ocular dominance in a primary visual area; (top) the subset of visual areas forming visual cortex and their interconnections (adapted from ref. [1]).*

An additional difficulty in crossing bridges between different organisational levels is the lack of systematic methods for reducing complexity. The problem here is to define methods and rationales for separating informationless or `noisy' variability from structural diversity capable of providing distinct biophysical substrates for different functions. This chapter will present a review of the structural and functional complexity of neurons and networks, with an emphasis on the vertebrate brain and more specifically neocortex. We will also point out major unsolved issues that limit a bottom-up synthetic approach, such as the lack of separability between intrinsic excitability of neurons and extrinsic modulation by synaptic activity.

A third problem is whether current knowledge of brain processes is advanced enough to allow the derivation of function from structure. The classical engineering approach, the so-called black-box system approach, relies only on the study of input-output relationships and inference of transfer

functions. The link with biological `hardware' is not guaranteed and proceeds mostly from analogy (e.g. lateral inhibition and Mexican hat profile of sensory receptive fields). A fallacious strategy followed by many cortical physiologists for the last 50 years has been to map operational engineering models onto the biological structure and ignore the `hidden' structural complexity. By doing so, one may transpose wrongly at a more `microscopic' level the additive/linear nature of the global computation realized at a more integrated level [4], without realizing that non-linear interactions between non-linear elements can subserve a global linear transform [5,6,7]. For instance, the functional study of sensory perception in the brain shows numerous abuses of mapping ad-hoc serial linear-non-linear (L-NL) engineering models onto biological recurrent networks, whose topological architecture is composed mostly of non-linear reverberating loops.

Interacting partners

As has been clear since Golgi and Cajal, the principal components of the vertebrate brain are neurons. Neurons are a particular class of cells, endowed with excitable membranes and specialised compartments (soma, dendrite and axon in the vertebrate brain, soma and neuropile in the invertebrate brain), and secreting neurotransmitter molecules across synapses. The action potential they emit and which propagates along axons controls neurotransmission and as such is considered as the major `signal' source in the network. However, supporting glial cells, to which one attributes a dominant importance in metabolic maintenance, also play a role in the slower dynamics of the brain [8]. In contrast to neurons, glia do not transmit spikes although they are heavily involved in the capture, transport, diffusion and clearance of ions and transmitters. Electrically, the graded potential of glia reflects the local extracellular potassium concentration modulated by the spiking behaviour of neighbouring cells. For the sake of simplicity, the putative role of glia in signal processing and synaptic communication will be ignored in the rest of the chapter, although strong evidence points to its importance in regulating network plasticity [9]. Note also that not all neural-based computations are expressed at the spiking level. In some neuron types (e.g. olfactory bulb granule cells) different regions of the dendritic arbour function relatively independently, so that sub-neuronal structures could be also considered as the relevant interacting partners (see below) [10].

As alluded to in the Introduction, the prevailing view in understanding network function is to use a Lego-type approach, and reproduce the collective behaviour of neural ensembles by combining elementary bricks. This is usually done by progressing in a bottom-up and hierarchical fashion across various scales of spatial integration, from ion channel, conductance, membrane compartments to the full network range [1]. Two hidden assumptions, whose validity will be disputed in this chapter, should be stated clearly: 1) to a certain degree, one is expecting that the `whole' assembly behaviour can be simulated by `adding' together the different `parts' (synapses and neurons); 2) intrinsic excitability properties of neurons, i.e. their electrical reactivity to intracellularly injected electrical currents, are separable from the modulation of neuronal integrative properties by the activity-driven synaptic inputs of the other partner-neurons in the network studied.

According to these views, and keeping in mind their limitations, the intrinsic properties of individual neurons studied in isolation can be thought of as cellular `building blocks' that contribute to how a specific neuron will respond to a given synaptic input. Such a reductionist approach has often been attempted in simplified preparations such as *in vitro* slices maintained in artificial cerebro-spinal fluid (ACSF) [11,12] or cultures [13]. Until recently, such reference networks were studied in the absence of external drive and devoid at rest of spontaneous or ongoing activity, mostly because of the massive deafferentation in the slicing process and the ionic concentrations chosen for the ACSF. If the network was found to be spontaneously active, the influence of the rest of the network was further suppressed by pharmacological blockade of

synaptic transmission. In the case of paucineuronal nets, such as invertebrate sensorimotor ganglia composed of Giant cells with invariant morphology, the size of the network may become so reduced that the total blockade of the afferent connectivity to any given cell can be obtained by injecting fluorescent compound in the other somata and then photoinactivating all the putative synaptic partners. Early experiments in the molluscan invertebrate revealed that isolated neurons could generate oscillatory bursts of action potentials and it soon became clear that individual neurons from all species display a large variety of intrinsic membrane potential patterns such as bursting, plateaux, post-inhibitory rebound, and spike-frequency adaptation [14].

Interestingly, although the importance of intrinsic properties for circuit dynamics has been accepted by the entire community of small (mostly invertebrate) circuit researchers for almost twenty-five years, until relatively recently most workers studying large cell assemblies in the vertebrate brain, both experimentalists and theoreticians, have continued to assume that circuit dynamics depend exclusively on synaptic connectivity and synaptic strength. This view has changed in the last five years, mainly for two reasons: 1) patch recording techniques are no longer restricted to the soma and now allow recording simultaneously from several points distributed along the dendritic structure in the same neuron. More and more recordings from central neurons have shown the prevalence of complex voltage- and time-dependent firing properties which must shape, to a certain extent, circuit function; 2) digital computer simulation power has increased tremendously and allows simulation in real-time of the kinetics of the spatial distribution of voltage change and calcium influx across the entire neurite. The neuron is no longer considered as a point-like integrator receiving multiple input lines and emitting a thresholded binary output [3], but as a complex tridimensional spatio-temporal integrator [15]. Consequently, the complex morphology of central neurons must be taken into account to fully understand their integrative properties.

Classic theoretical work on integration in passive cables [16,17,18,19] has shown the strong filtering exerted by passive dendritic structures. In particular, synaptic inputs are differentially attenuated or distorted according to their position on the dendrite. Recent dendritic recordings have revealed that, as proposed 30 years ago [20], dendrites are not simple passive structures, but contain a myriad of ion channel types [21,22,23,24,25]. Dendrites can have regenerative properties [26,27,28,29] and initiate Na^+ or Ca^{2+} spikes, propagating towards or away from the soma [21,25] (Figure 2). The presence of dendritic ion channels may also contribute to the renormalisation of synaptic inputs [30,31,32,33], correcting for dendritic filtering, or may produce more subtle effects such as establishing coincidence detection [34,35]. The emergence of efficient techniques for 3D morphological reconstruction of single neurons, combined with sophisticated numerical tools for simulating cable equations in such structures [36,37,38] has revolutionised this area as such tools now become standard [36,37,39]. Computational studies are now able to incorporate measurements from *in vitro* and *in vivo* studies [40,41,42] and infer the function of dendritic trees under such *vivo*-like conditions. One of the main findings is that the dendritic tree may function in fundamentally different modes of integration in these states (see below), and consequently that the network might perform qualitatively different operations during *in vivo*-like states [42].

Even considering only neocortex, a huge variety of neuronal types can be discriminated based solely on the diversity of morphology and of the intrinsic properties of cortical neurons [43,44]. The most commonly established correlation between morphology and excitability revealed by current injection is `regular-spiking'. Neurons with this property display responses with a prominent spike-frequency adaptation (regular increase in interval between successive spikes). These neurons correspond mostly to a spiny pyramidal cell morphology. Other neuron types include different variants of bursting cells, such as the `intrinsically-bursting' cells of layer V, the `fast rhythmic bursting' or `chattering', and the `low-threshold spiking' cells. The latter types correspond to either excitatory (pyramidal) cells or various types of interneurons [45].

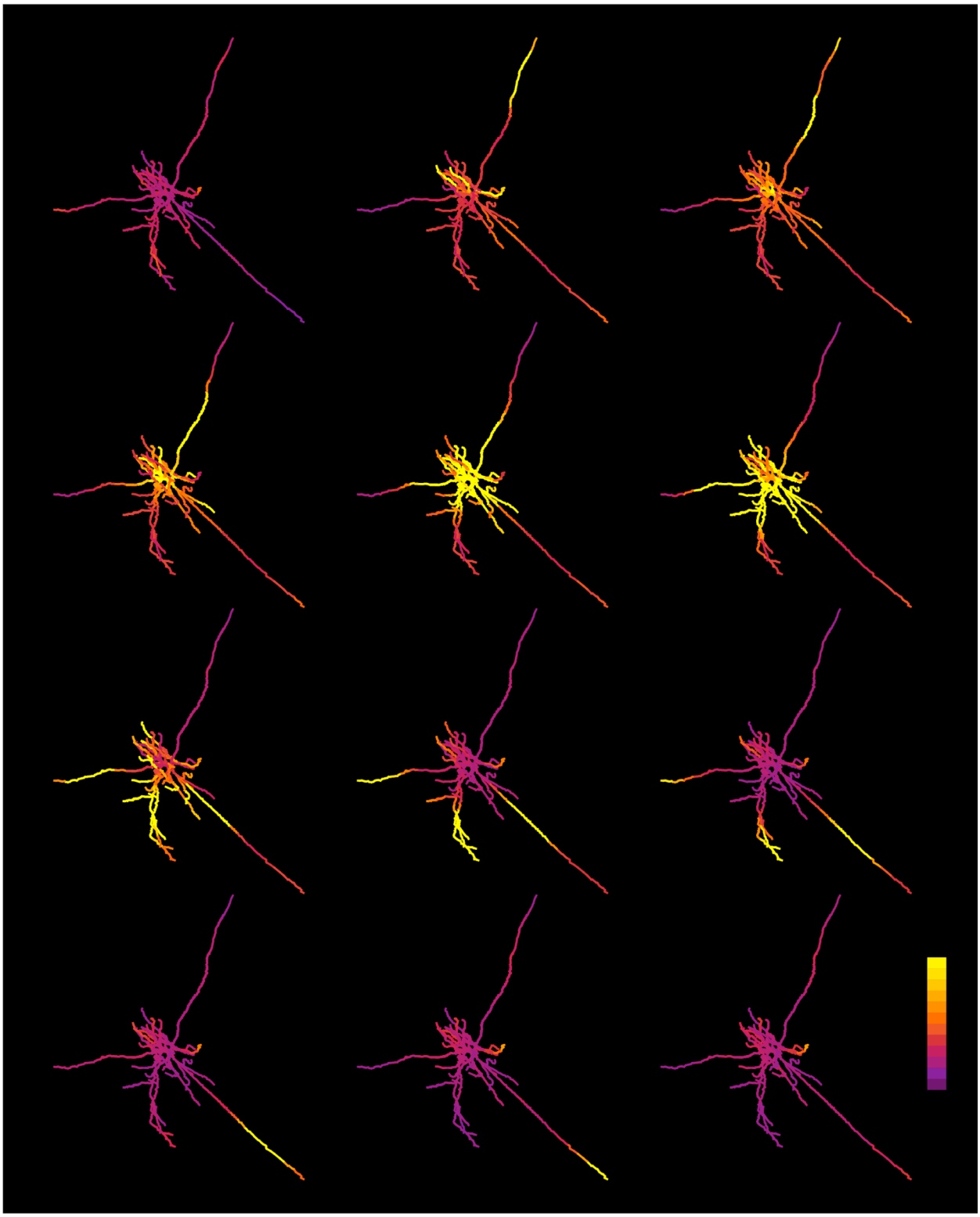

Figure 2: *Snapshots of the distribution of membrane potential in a cat cortical (layer VI) pyramidal neuron during simulated in vivo activity. The colors indicate the membrane potential (from violet, -80 mV, to yellow, -25 mV; see scale). Time runs from left to right, then top to bottom (steps of 0.5 ms, except first frame which was taken 4 ms earlier). The simulation shows a dendritic action potential which propagates forward to the soma and evokes a backpropagating action potential in all other dendrites. These forward-propagating action potentials may play an important role in the integrative properties of pyramidal neurons during in vivo like states (modified from [42], with permission).*

More recent, extensive studies show that structural diversity of cortical neurons is not limited to

the stereogeometry of axons and dendrites or to the multiple excitability patterns that a step of depolarising current produces in the recorded cell, but extends also to neurochemical markers (calcium-binding proteins, neuropeptides, neuro-transmitters or their synthesis enzymes), synaptic dynamics (connectivity and its plasticity, decay time constants of EPSPs and IPSPs), as well as to a specific repertoire of expressed proteins (e.g., ion channels, receptors). The genomic expression identity profile can be revealed in the patch-recorded cell by harvesting the cytoplasmic content at the end of the recording session and by applying off-line multiplex RT-PCR. Although initial cortical cell classifications concerned mostly excitatory cells (which represent 80% of the whole population), more refined attempts have been made in the case of inhibitory interneurons (the remaining 20%), and in this latter case a consensus in taxonomy has almost been reached [46,47]. Recent attempts correlating firing properties with protein expression corroborate the existence of clear-cut GABAergic interneuron subtypes [48,49]. Present data also suggest the existence of molecular determinants underlying oscillatory and synchronous network activity and lead to the conclusion that different types of interneurons may subserve distinct functions, for example by participating in the generation of oscillatory activity in different frequency bands [50,51]. These examples illustrate striking high-order correlations between the morphologies of the axon and dendrites, firing patterns, spike and AHP characteristics, EPSP and IPSPs kinetics, synaptic dynamics, coupling through gap junctions to neurons of the same class, and the expression of distinct protein markers. It is very probable, as was demonstrated for interneurons in the spinal cord by Jessell and colleagues [52], that different classes of neocortical interneurons differentiate under the control of different promoters and play specific roles in the building-up of circuits. In general, if one assumes the existence of repeated modules with some degree of structural invariance, it appears absolutely essential to come to terms with neuronal diversity in order to understand the function of so-called canonical circuits (review in [53].

There are however several caveats with this descriptive approach of structural diversity. The number of neurons in an anatomical cortical column [54] or functional hypercolumn [55] is roughly on the order of the number of classes based on anatomical, electrophysiological, and genomic criteria, implying that to a certain extent some neurons may be the sole exemplars of their class. Furthermore, the multiplex RT-PCR technique has its own experimental limitations. The first is quantitative and concerns the existence of high probabilities of false negatives. The second is that mRNA measurement in the slice looks like a static `photograph' made after a massive disturbance of activity imposed by the slicing process itself, which may have already resulted in spurious activity-dependent regulation of gene expression. A third, fundamental issue is that in principle one should not limit oneself to cytoplasmic mRNA harvesting. The search should be extended to the proteome and membrane-bound proteins in order to establish the cell-by-cell distribution of receptors and ions. In other words, it is likely that multiplex RT-PCR will not give access to the `molecular shape' of the neuron (Changeux, personal communication).

Modes of interaction

Synaptic transmission

The dominant mode of interaction between neurons in the brain for fast information processing is via synapses. Of these, the most important type are chemical synapses, in which a presynaptic depolarisation of the cell membrane triggers the release of chemical neurotransmitters, which diffuse across a small gap and bind to receptor proteins embedded in the membrane of the postsynaptic neuron. This leads to the opening of ion channels, which may lead to depolarisation or hyperpolarisation of the postsynaptic cell membrane, or to shunting of other currents entering the cell. Besides chemical synapses, electrical synapses (gap junctions), which provide direct contact (in the Angström range) between cell membranes and allow current to flow between the

cells through a purely resistive link (with almost zero time-constant), play an important role in many brain regions. In neocortex, electrical synapses are involved in synchronisation of neuronal activity of specific classes of inhibitory interneurons [56,57,58].

There is a great diversity of chemical synapse types, with different neurotransmitters and many different types of receptor proteins, each of which may also have subtypes, with different subtypes expressed in different neuron types. In the central nervous system, the principal neurotransmitters involved in fast information transmission are glutamate, associated with excitatory synapses (those producing a depolarisation of the postsynaptic membrane), and γ-amino butyric acid (GABA), associated with inhibitory synapses (those that generally produce a hyperpolarisation of the postsynaptic membrane).

Synaptic receptor proteins may either be ionotropic (the binding site is on an ion channel protein and causes the opening of the channel - also known as ligand-gated ion channels) or metabotropic (the binding triggers an intracellular signal cascade which leads indirectly to ion channel opening). Ionotropic receptors tend to operate with a more rapid time course. Ionotropic receptors that bind glutamate include α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, which have a rapid time course of opening/closing (sub-millisecond rise time and decay time constants below 10 ms), and N-methyl-D-aspartic acid (NMDA) receptors, which are both ligand-gated and voltage-gated, and have a slower time course (decay time constants from a few tens to a few hundreds of milliseconds). There is only one type of ionotropic receptor that binds GABA, the $GABA_A$ receptor, which has a rapid time course.

The exact effect that the opening of a synaptic ion channel has on the postsynaptic membrane potential depends on the value of the membrane potential during the opening and on the reversal potential of the channel, which in turn depends on the permeability of the channel to different ion species and on the concentrations of the ions on either side of the membrane. The reversal potential of glutamatergic receptor channels is around 0 mV, which means that activation of such receptors almost always leads to an inward flow of current and depolarisation of the cell membrane (the exception is near the peak of the action potential when the membrane potential exceeds 0 mV). The reversal potential of $GABA_A$ channels is near -70 mV, which is near the resting membrane potential of the cell, and above the reversal potential for potassium ion-gated channels. This means that if the cell is strongly hyperpolarised by a potassium current, then opening of a $GABA_A$ channel leads to depolarisation of the cell, an excitatory effect. If the membrane potential is near the $GABA_A$ reversal potential, the main effect of the channel is an electrical shunt, increasing the total conductance of the membrane and clamping the membrane potential to the $GABA_A$ reversal potential. Thus, starting from this resting condition, when inhibition is applied alone, no change in the resting potential will be seen, hence the denomination of `silent' inhibition. In the case where excitation occurs concomitantly with inhibition, the excitatory evoked depolarisation will be reduced in amplitude and shortened in time-course, hence the term `divisive or shunting inhibition'. Although disputed for a long time (e.g., ref. [59]), there is now clear evidence for the existence and the role of shunting inhibition in shaping cortical functional selectivity *in vivo* [5,7].

Until recently it was thought that all synapses of a neuron release only one type of neurotransmitter (Dale's Law [60]), although there is now evidence to the contrary. Neurons are usually described as `excitatory' or `inhibitory' depending on the effects of the neurotransmitter they principally release. The almost-fixed association which is usually made between the synaptic type and the electrical `sign' of the synaptic effect (i.e. depolarisation vs hyperpolarisation) is to be interpreted with care. As pointed out above, the functional effect will depend on the resting state of the neuron and of the degree of invariance of the reversal potentials of ions whose transport through the membrane is responsible for the voltage change. For instance, in developing networks in the neonate, inhibitory $GABA_A$ synapses become depolarising, due to a much more positive chloride reversal potential than in adult neurons, and have in fact a positive effect in

driving spiking activity [61]. Furthermore, in the invertebrate, synaptic gain can be occasionally reversed in sign by appropriate conditioning events [62]. Another important feature worth noting is the large proportion of anatomically-identified synaptic contacts which are functionally silent in the resting condition, and can become expressed functionally once the neuron becomes strongly engaged by depolarising input and activation of specific subtype of receptors [63,64]. This effect is most preeminent in the immature vertebrate brain.

The interaction types discussed above are those which are most generally considered when discussing fast information processing in neuronal networks. Besides these, however, there are other possible fast interactions, e.g., between neurons mediated by current flow through the extracellular space (ephaptic interactions) that may be of importance in certain structures or circuits, and very many slower interactions: mediated via glia or through diffusion of signalling molecules (e.g. nitric oxide, hormones).

Synaptic dynamics and plasticity

The conductance change associated with synaptic transmission is generally characterised by its rise time, decay time constant, and peak amplitude. However, one should not consider that synaptic transmission is reduced to a simple static multiplicative factor. The efficacy or `gain' in transmission at a given synapse should in fact be seen as a dynamic variable, which is regulated by its past synaptic activity (homosynaptic plasticity) and the global state of network dynamics (heterosynaptic plasticity and network-driven homoeostasis).

At many synapse types, these descriptive parameters have their own dynamics on a time scale of tens of milliseconds, determined by the pattern history of presynaptic spikes. In addition to the genomic, electrical and morphological diversity that we reviewed earlier (see Section 2), the synaptic interactions between different neuronal types also display various short-term plasticity mechanisms, such as facilitation or depression, which result from the modulation to various degrees of conductance amplitude, the size of the available pool of neurotransmitter and its release probability [65,66,67,45]. On longer time scales, from minutes upwards, the efficacy of synapses (probability of transmitter release in response to a presynaptic action potential and size of postsynaptic conductance change) may be changed by activity-dependent and/or by homoeostatic processes (reviews in refs. [68,69]).

The most classical forms of synaptic plasticity found in neocortex are induced by convergence of synchronous activation sources acting at the pre and/or postsynaptic levels (review in ref. [70]: Long-term potentiation (LTP) [71,72,73] and depression (LTD) [74,75,76,77] are found both in hippocampus and neocortex. Although it was initially assumed that synchrony between presynaptic activity and postsynaptic depolarisation was the key event in plasticity induction, more diverse and reversible forms of associative plasticity have been reported and result from various patterns of time-locked associations between presynaptic input and the postsynaptic spike [78,69]. For instance, spike-timing-dependent plasticity (STDP), initially demonstrated *in vitro* in hippocampus [79] but immediately forgotten (!), was rediscovered in neocortical slices from young animals and in hippocampal organotypic cultures. The synaptic change rule differs from the classical correlation-based postulate, since the sign of the change of synaptic strength depends critically on the temporal order between pre- and post-synaptic spikes. More specifically, in cortical and hippocampal excitatory synapses, when the presynaptic event precedes the postsynaptic event by less than 50 ms, synaptic strength is augmented, whereas the reverse temporal order leads to a reduction in synaptic strength [35,80,81]. Reverse-sign STDP rules have also been found, in cerebellum-like structures in the electric fish [82]. However, the impact of multiple correlations and spontaneous activity in the pre- and post-synaptic cells, the existence of STDP *in vivo* and its applicability in the intact brain are still debated, which motivates building computational models.

The obvious consequence of the diversity that may exist in associative synaptic plasticity rules is that 1) not all synapses follow a unique rule and 2) the same network can use multiple forms of adaptation for different purposes, through each one of these different plasticity algorithms. For instance, LTP is considered as a major substrate of associative memory formation [83]. In spite of the fact that its implication in behavioural learning remains disputed, this rule obeys the general principle that `neurons that fire together, wire together' and has been considered as responsible for functional epigenesis in sensory neocortex [84,85,86]. Microcircuits that incorporate spike-timing dependent plasticity (STDP) rules account most accurately for the emergence of causal chains within neuronal assemblies and best support phase sequence learning [87] or multimodal coordinate transformation [88]. Other circuits which incorporate a mirrored form of STDP may be used for enhancing novel information and filtering out expected changes in sensory environment due to motor exploration. Hypothetically, these different plasticity algorithms could coexist together in the same network and operate in a synergistic fashion, for instance by acting on different synaptic types and cell targets on different time scales.

In addition to these dominant forms of plasticity, other processes are designed to stabilise the integrative function of the cell within a reference working range. Five forms of `homoeostasis' are generally recognised [89]. The simplest form regulates the efficacy of transmission around a mean synaptic gain or between two boundary values. When evaluated on a longer time scale, the fast input-dependent regulation of synaptic transmission, described earlier, results in maintaining average synaptic efficacy approximately constant in the face of rapid changes in the probability of transmitter release [90]. Furthermore, the probability of inducing potentiation, depression or depotentiation depends on the previous stimulation history of the network (`metaplasticity' in ref. [91]) and on the initial efficacy state of the synapse. A second form of homoeostasis, predicted in many models of learning, acts more globally, at the neuronal level [92]. It assumes that the sum (or sum of squares) of all the synaptic weights of synapses impinging on the cell remains constant. A third form of homoeostasis limits the anatomical divergence of growing axons and corresponds to the conservation of the sum of the synaptic weights of all contacts made in the network by the same parent axon [93]. The fourth form of homoeostasis concerns the capacity of a cell to maintain a similar output (e.g., its firing level) in spite of strong alterations in the activity pattern of the network [94,95] (review in ref. [89,96]). This last regulatory process involves activity-dependent tuning of postsynaptic sensitivity. Examples so far come from the regulation of intrinsic conductances. A last form of homoeostasis concerns possible changes in the site of impulse initiation and the direction of impulse propagation in the dendrite [97].

Interdependency between intrinsic excitability and extrinsic synaptic factors

Knowledge of the intrinsic conductance repertoire of the cell under study and of the biophysical conditions of expression (voltage-dependency, activity priming) is generally used to reinterpret the role of intrinsic properties in the functional context of the full network. For example, in many rhythmic central pattern generating circuits, the timing of the neurons within a circuit is often governed by the intrinsic post-inhibitory rebound properties of the neurons in the circuit [98]. Similarly, it is clear that neurons with strong plateau properties can turn a rapid synaptic input into more sustained firing, thus changing the timing of discharge between the presynaptic neuron and follower neuron [99,100]. One of the first suggestions that the intrinsic properties of individual cortical neurons might be crucial for understanding network behaviour comes from the early work of Bremer [101,102] who suggested that the rhythmic activity seen in the electroencephalogram (EEG) might result from the interactions among neurons that display an intrinsic propensity to oscillate, as is now thought to be the case [103,104]. Bremer further suggested that the cortex should not be viewed as a system passively driven by its inputs, but rather as a system having spontaneous, intrinsic activity which is modulated by sensory inputs [101], a theme which has

been explored in detail [105,106]. A striking illustration of this last point in mammalian neocortex is the discovery of the implication of intrinsic high frequency oscillatory properties of cortical neurons in the functional binding of their activity during the transient time course of a percept [107]. Such intrinsic oscillatory potential had in fact been observed *in vitro* much earlier [108], but totally ignored until *in vivo* studies suggested they could be the hallmark of a specific class of cells, chattering type, involved in the genesis of gamma band activity during sensory processing [109].

At a more microscopic level, active properties intrinsic to the neuronal membrane, such as dendritic action potentials, may play a central role in synaptic plasticity because they provide the strong depolarisation necessary to establish coincidence of pre- and post-synaptic activity required for inducing synaptic changes [35,72]. Interestingly, this coincidence can be established by local dendritic spikes, without participation of the soma, which opens the possibility for local dendritic computations - or associations - to occur without participation of the cell body [68,110]. These problems are heavily investigated today. In addition, the efficacy of a synaptic input depends on the conductance state of the neuron and its dendrites, and therefore will depend on the level of network activity. The responsiveness to a given input has been shown, both experimentally and theoretically, to strongly depend on background inputs (reviewed in ref. [42]). This `contextual' dependence of integrative properties is of primary importance to understand cellular operations. The impact of such dependence at the network level still remains a subject largely uncharacterised, both theoretically and experimentally.

Evidence that network-driven activity may even control the intrinsic repertoire of conductances of any given neuron comes from the field of invertebrates [111,112,113]. This process can be thought of as an extreme case of contextual control resulting from the non-synaptic diffusion of neuromodulators or hormones in the network, and its implication in the reorganisation of cortical network dynamics has not yet been addressed. Pioneering work in the invertebrate motor ganglia, in particular in the stomatogastric ganglion of the lobster, showed that the repertoire of intrinsic conductances could in fact change dramatically in the presence of neuromodulatory signals secreted by specific cells in the afferent sensory network [114]. The activity of such cells was found to be a determinant in triggering the expression of active conductances in cells which are part of a central motor program generator assembly. The turning on and off of neuromodulation was found to reorganise the dynamics of the full network in distinct functional assemblies associated with different motor behaviours [115,112] (see Figure 3).

These data support the hypothesis of the existence of `orchestra leader'-like neurons, whose activity conditions and formats merging and segmentation across functional assemblies. Their identification, or even evidence of their existence, in larger networks such as mammalian neocortex is still lacking, but there is already ample evidence that modulatory signals linked with various amines and acetylcholine change the repertoire of expressed conductances. Like central pattern generators, thalamic circuits are subject to neuromodulatory influences [116]. In this case, neuromodulators such as acetylcholine, norepinephrine or serotonin affect intrinsic currents and switch the circuit from an oscillatory mode to a `relay mode' in which oscillations are abolished [117]. These neuromodulators are present in activated states, promoting the relay of sensory information by the thalamus, while their diminished levels during slow-wave sleep promote the participation of the thalamus in the genesis of large-scale synchronised oscillations in the entire thalamocortical system. Some aspects of these mechanisms, in particular the type of processing of sensory information that thalamic neurons perform, are still unclear and subject to current investigation [118]. We conclude from this brief review that, to a certain extent, both in invertebrate ganglia as in vertebrate brain, the separability of intrinsic and extrinsic factors in the control of cellular excitability is doomed to fail. Thus, the `whole' cannot be the sum of the `parts'.

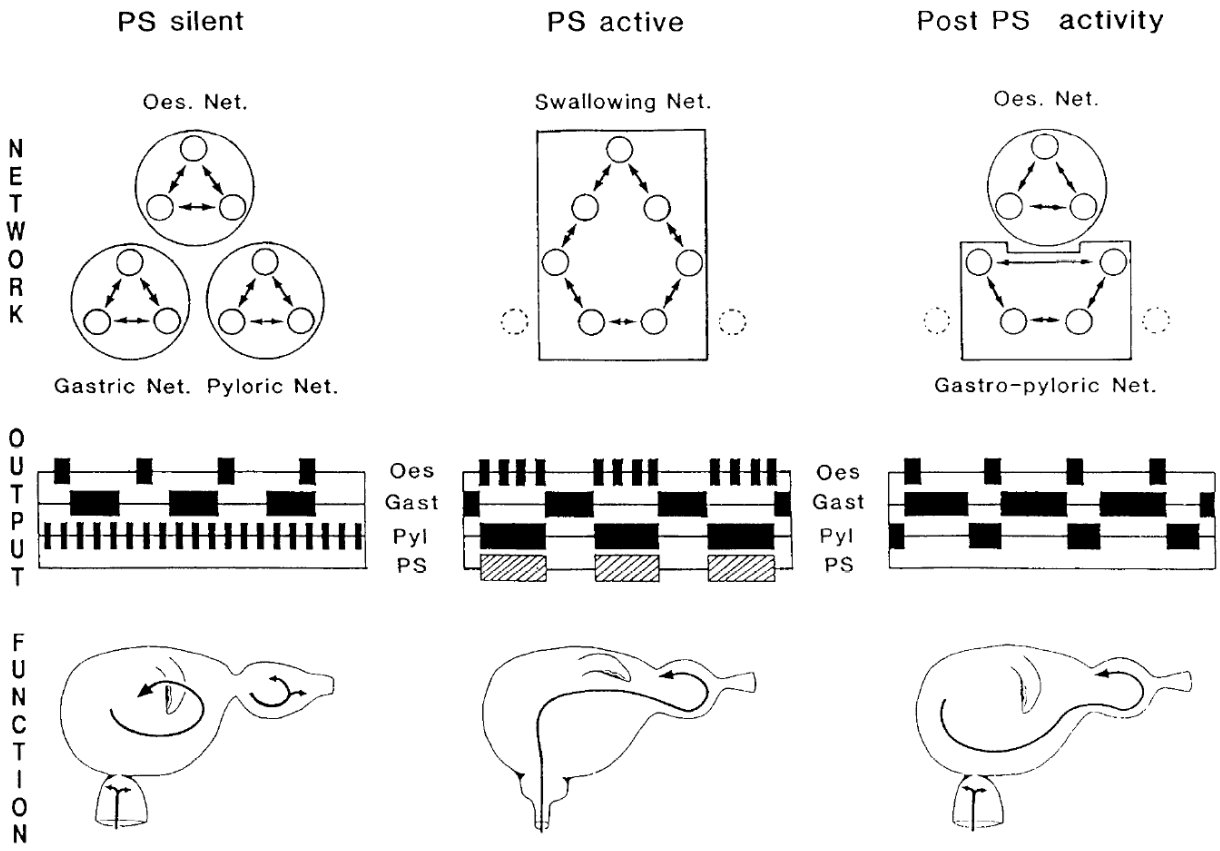

Figure 3: *Reconfiguration of network dynamics under the influence of orchestra-leader cells (called PS here). The same network is functionally reorganized in independent assemblies depending of the activity state of neuromodulating cells (PS) (upper row). These assemblies are characterized by specific excitability patterns expressed by each of the composing cells and specific phase relationships between them (middle row). The functional role of each assembly during the swallowing stomatogastric cycle is depicted in each cartoon below.* ***A****, When PS is silent, the oesophageal, gastric, and pyloric networks (top) generate independent rhythmic output patterns (middle) involved in regionally specific and separate behavioural tasks (bottom).* ***B****, When PS is rhythmically active, it drives opening of the oesophageal valve (bottom), and by breaking down preexisting networks and using certain neurons, it constructs a single novel network (top) that generates a coordinated motor pattern (middle) appropriate for swallowing behaviour.* ***C****, When PS is again silent, the oesophageal valve closes (bottom) and motor units immediately resume their original network activity while units (i.e., gastric and pyloric) controlling regions more caudal to the sphincter continue to generate a single pattern before resuming their separate activities (adapted from ref. [112]).*

Computational modelling

We give here only a brief overview of computational modelling of neuronal networks. More complete treatments may be found in, for example, refs [38], [119] and [120].

Modelling cells and synaptic interactions

We will consider here only that class of neuron models in which the action potential is explicitly represented (spiking models), and neglect traditional neural network-type models and mean-field models which represent only the time-averaged mean activity of neurons or populations. The class of spiking models may be further subdivided into biophysically-realistic models and simplified

models (integrate-and-fire, spike response models).

The concept of the integrate-and-fire model dates back to Lapicque [121]. In its standard form, the model represents a purely passive membrane with no non-linear properties until the membrane potential reaches a fixed spike threshold, at which point the potential is reset to some sub-threshold value. To match the model behaviour more closely to that of real neurons, sub-threshold non-linearities (e.g. quadratic [122], exponential [123]), a second state variable [124,125], and approximations of the effects of background synaptic activity [126] have variously been added. Integrate-and-fire-type neurons are usually point models, although multi-compartment models have also been used (e.g., ref. [127]).

Biophysically realistic models build on the work of Hodgkin and Huxley, who developed a mathematical description of the kinetics of sodium and potassium channels [128] which is still the basis of almost all ion channel models used today, and of Rall, who introduced compartmental modelling of spatially-extended structures such as dendrites[15].

The level of detail in modelling synaptic interactions covers a large range, from a step change in the postsynaptic potential to modelling of biochemical pathways, quantised neurotransmitter release and uptake, and post-synaptic binding and channel kinetics. The most commonly used representation is that a presynaptic action potential causes a postsynaptic conductance change with a fixed time course.

Modelling networks

Traditionally, neural networks are viewed as being composed of simple neuronal units interconnected in large and specifically structured networks, hence forming complicated systems. Mathematical tools borrowed from statistics and physics provide in many cases an effective, possibly stochastic or probabilistic, description of the dynamics of these complicated systems. Classical examples date back to Anderson, Cooper and Hopfield (review in ref. [129]), who showed that such networks can be described by a formalism analogous to spin-glasses (Ising models), or the mean-field description of networks of interconnected oscillators and linear neurons. However, an unfortunate common aspect of this approach is also that when departing from idealised model systems by endowing single neuronal units with more realistic, non-linear dynamic behaviours, the availability of mathematical tools which allow an exact or even a statistical description ceases quickly.

Looked at carefully, it is exactly this now experimentally evidenced non-linearity in the dynamical behaviour of neuronal units which might, or does, in fact constitute the crucial ingredient for the immense computational power of the biological neuronal circuitry. Starting from the simplest description of neurons as threshold or integrate-and-fire units, in the past decades much experimental and theoretical work was done in filling up these neurons with a plethora of biophysical and functional properties giving rise to the wealth of observed dynamic behaviours. The level of detail is already now sufficient to provides a theoretical picture of single neuron dynamics which comes very close to its biological original, but with the caveat that at the same time also the border towards complex systems is passed. The latter renders many exact and statistical mathematical tools useless, and linearisations or approximate numerical descriptions remain the only way to access a vanishingly small regime of possible dynamic behaviours.

Similar to the statistical description of networks composed of many, but simply- behaving, components, systems with only few, but highly non-linear, components can be accessed with mathematical tools borrowed from chaos theory (e.g., refs [130,131]). Indeed, such systems can be viewed as low-dimensional deterministic chaotic systems. Corresponding measures and

notations were successfully applied to characterise the behaviour observed in isolated neuronal systems such as bursting [132] or spontaneously discharging neurons in the mammalian cortex (for a recent review see ref. [133]).

However, in order to approach a real understanding of the brain or macroscopic functional sub-structures of it as complex systems, it is not sufficient to restrict to small isolated units. Instead, the dynamic aspect of neural behaviour has to be exported to whole networks comprised of such units. A first attempt in this direction was the characterisation of the large-scale dynamic behaviour of the brain in the context of chaotic systems using experimental data from available electroencephalographic (EEG) studies and new distributed imaging techniques such as functional magnetic resonance imaging (fMRI). Indeed, studies dating back two decades indicate the presence of low-dimensional chaos in human EEG data [134]. Although still subject to dispute, this suggestion found much support afterwards (e.g., ref. [135,136]).

In the absence of useful analytical tools for studying large, biophysically-detailed neuronal networks, numerical simulation is the most widely used tool. Large scale models of specific cortical or sub-cortical regions [137,138,139,140] have given insights into the functioning of these regions. A more general approach aims to understand the behaviour of generic cortical circuits, comparing numerical results with available analytical predictions where possible (e.g., ref. [141]).

Complexity in structural and functional network topology

Diversity of structural network topology

As noted above, there are at least dozens, and possibly hundreds, of distinct cell types in neocortex. The connectivity between cell types, however, is far from random. A broadly similar distribution of neuron types and similar local connectivity is found throughout neocortex, although there are regional variations and specialisations. Neocortex is divided into six layers on the basis of histological studies; some layers are further sub-divided. Most cell types, defined narrowly, have cell bodies that are only found in a single layer, and have dendrites and axons that have a layer-specific pattern of ramification. The layered structure of cerebral cortex has also motivated the introduction of microcircuits (review in ref. [142]). This is based on the high specificity of intracortical inter-layer connections [143], and the fact that thalamic inputs end preferentially in layers I, IV and VI and systematically avoid other layers [144,145]. Long-range intracortical connections are made quasi-exclusively by layer II-III cells [146], and cortico-thalamic input originates exclusively from layer VI and the lower part of layer V. This highly specific arrangement has motivated the conceptual introduction of cortical microcircuits [147,148,149], although there is no clear `cortical module' but rather a continuum with clear connectivity templates [150,151] (review in [53]).

In parallel with this modular decomposition based primarily on anatomical descriptions of the circuit, similar arrangements have been validated on a functional basis. One way to identify primary functional modules is to follow, step by step, the vertically dominant integration flow of activity evoked by thalamic input (see Figure 4, third top left drawing). EPSP/IPSP sequences show stereotyped behaviour as a function of layer in cortex [149] (but see ref. [152]). At a more integrated level, numerous studies of sensory evoked responses using single unit electrophysiological recordings, since the pioneering work of Mountcastle [153,154] in somatosensory cortex and Hubel and Wiesel [155] in visual cortical areas, have emphasised the invariance of receptive fields along vertical electrode penetrations (orthogonal to the layer planes).

In visual cortex, this `columnar' arrangement holds not only in terms of spatial location of the receptive fields in the visual field, defined primarily by the thalamic afferent input, but also in terms of orientation preference, a property profoundly influenced by intracortical recurrency.

These pioneering studies led to the specific proposal of functional columns of different scales. The macrocolumn is defined as a complex processing and distributing unit that links a number of inputs to a number of outputs via overlapping internal processing chains (minicolumns) [156]. One should note, however, that the definition of the functional column initially applied only to the input/output circuit formed by serial excitatory links from layer IV (input layer) to layer VI (one of the output layers). The laminar relay description (IV→II-III→V→VI) within the column is based on the assumption that axons are connected to neurons whose somata are located in the layer to which the axon projects [157]. Since these initial studies, other definitions of columnar entities have been given, in which all coexist within the same network, giving a crystalline organisational architecture whose elementary motif depends on the computation under study (review in ref. [53]). These different views are summarised in Figure 4.

If one extends the search for modules to the scale of the whole cortex, it is clear that different areas are specialised for different computations, each with a different role in sensory perception, generation of motor commands, memory, or other areas of cognition. The basis of this functional diversification may in part reflect differences in individual neuron properties or in the distributions of neuron types, but is presumably mainly due to differences in connectivity, although very little is known about any such connectivity-computation correlations. Although there is strong evidence that the morphological lay-out of these dedicated networks operates under strong genetic constraints, there is also ample evidence for a shaping of cortical circuit anatomy by activity. The most remarkable illustrations can be found in the developing thalamocortical pathway, during a `critical' period during which sensory experience shapes to a certain extent cortical organisation [160]. In an imaginative experiment performed in the developing ferret, the group of Mriganka Sur was able to turn an auditory cortical area (A1) into a new visual area by 1) depriving, early in development, the auditory thalamus (which feeds the primary auditory cortex) from its normal input, and 2) substituting this input for rerouted visual afferents [161,162]. Without going into the details of such a complex and artificial operation, this rewiring of afferent pathways resulted in two major restructurings. The first, expressed at the functional level, was the genesis of visual receptive fields in an `auditory' cortex, showing all the attributes of a normal visual cortical area: a large proportion of the rewired A1 cells were found to be orientation selective, and the orientation network visualised with optical imaging techniques showed the progressive shift in orientation preference and the existence of pinwheel singularities that is characteristic of the normal topology of the V1 visual network. The second, seen at the structural level, was a rewiring of intracortical long-distance `horizontal' connectivity according to a pattern normally seen only in the V1 area. Thus, the imposition of a drastic change in sensory activation and patterns of afferent activation (in sensory thalamus at an early stage of development) induced a structural reorganisation in the rewired A1 area, resulting in a binding-architecture anatomy indistinguishable from that found in a normal V1 visual cortical area. We conclude from this example that sensory cortical circuits are capable of profound activity-dependent reorganisation, in such a way as to realize a computational `fit' with the statistical nature of the information to be processed.

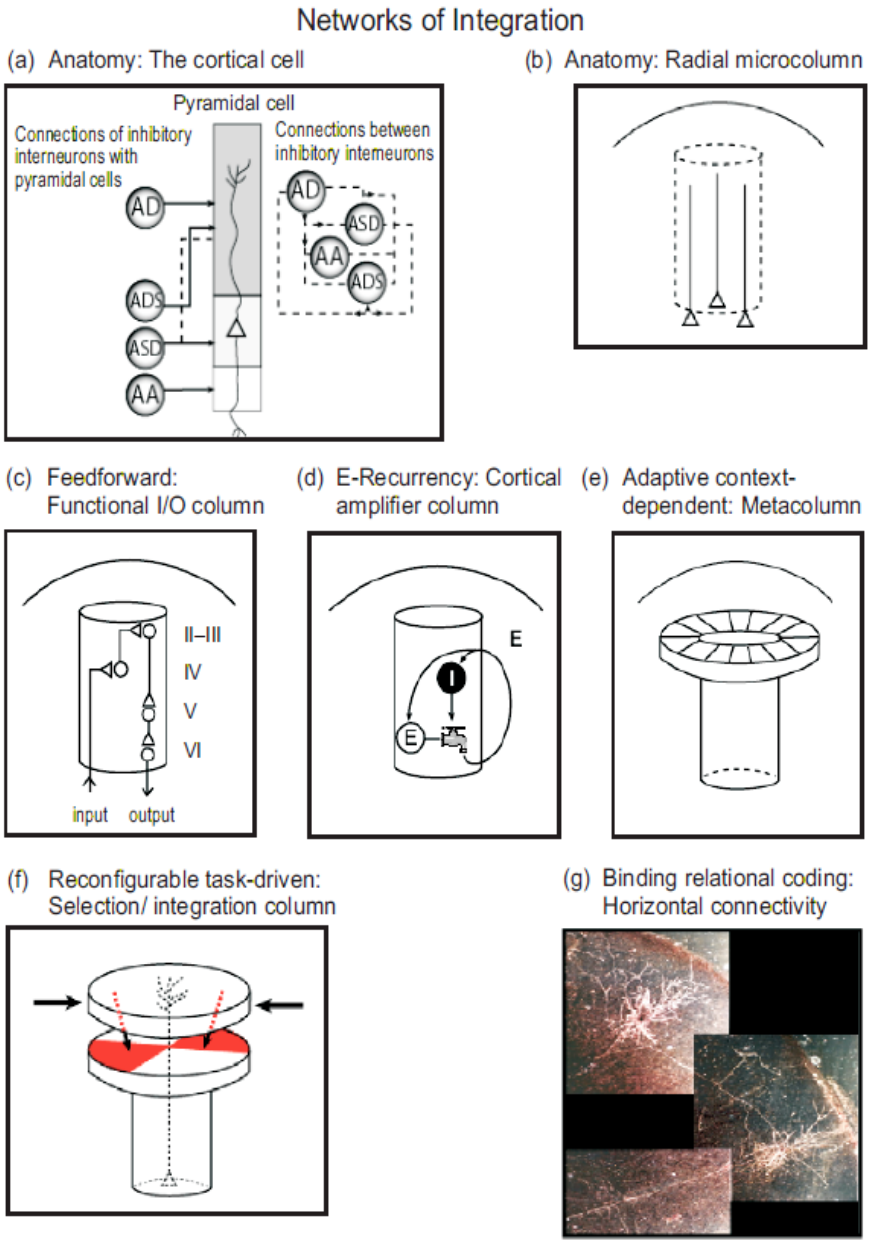

Figure 4: *Different levels of integration are schematised from left to right and top to bottom: a) The cortical pyramidal cell and its membrane compartments represents an elementary site of synaptic convergence; b) Bundles of axons of pyramidal cells form radial microcolumns; c) One of the best studied input/output circuit characterises the serial processing of layer IV afferents by first-order targets, the stellate cells in layer 4, which, after a series of successive relays in layer II-III and layer V, terminate on layer VI neurons who send their axons out of the functional column [158]; d) The canonical microcircuit exemplifies the high level of recurrency of excitatory local connections whereas the inhibitory interneurons control the gating of the avalanche of excitatory amplification [149]; e) The concept of meta-column, introduced by Somers et al. [159], corresponds to the network influence carried via long-distance horizontal connections in the supragranular layers (see inset), that needs to be added to the column to predict its context-dependent behaviour; f) This last schema summarises the hypothesis of selection of computational circuits (red volume) by the neuromodulatory action of ACh fibres running in layer I; g) Inverted contrast picture of two biocytin-labelled layer II/III pyramidal cells connected by horizontal axons (Frégnac and Friedlander, unpublished). (taken from ref. [53], with permission)*

Complexity of structural network topology

Turning now from specificities, and differences between cortical areas, we now consider the commonalities between brain regions and the regularity in cortical structure, to ask what we can learn from a more theoretical view of cortical connectivity and topology, and to what degree cortical networks resemble other complex networks found in physics, biology and sociology.

In general, it is true to say that although an increasing amount is known about the connectivity of local circuits in cortex, at least in a statistical sense (the probabilities of connection between pairs of nearby neurons of given types), and the general strengths of connectivity between different cortical areas [163], much less is known about medium-to-long range connections in cortex, although much experimental work has been done to reveal anatomical connectivity patterns in a variety of brain networks [164]. The term anatomical connectivity refers here to the set of physical or structural, i.e. synaptic, connections which link all neuronal units comprising the network [142]. Among the most notable early studies in this direction is the quantitative neuroanatomical work of the group around Braitenberg [165], which analysed cortical tissues of mice with respect to principal connectivity patterns and connection probabilities. Based on the idea of a rather homogeneous distribution of excitatory neurons, these investigations revealed a high short-range intra-cortical connection probability, which decays exponentially with a decay length of a few hundred micrometres, as well as a more sparse, patchy, long-range cortico-cortical connectivity. Interestingly, although each given neuron connects to tens of thousands of other neurons in their near vicinity, the probability that more than one contact is made with another neuron at the same time was found to be vanishingly small. These results suggest that the cortical network is comprised of interconnected, rather local, processing units or cortical microcircuits, containing a few hundred thousands of densely connected neurons.

More recently, extensive anatomical studies revealed comparative aspects of neocortical circuitry in different species, ranging from mice over giraffes [166] to humans, with respect to the number (density) of neurons and their synaptic terminals as well as to patterns of neuronal interconnectivity. The reported results highlight a vast variability in density within the neuronal populations that constitute cortical microcircuits across cortical areas and in different species. Viewed in the light of results obtained in earlier studies, these findings suggest that this variability in the topological structure goes hand in hand with functional differences in the specific cortical circuits, and is the result of evolutionary adaptation of circuits in different species to particular functions (review in [53]).

Structural network topology and the `small-world' analogy

Given the limitations of the classical approaches noted above - studying either large, regular networks of simple units or small networks with complex units - in understanding the behaviour and the emergence of behaviour in large, complex networks, we now ask whether the anatomical studies briefly reviewed above provide support for a view of the cortex as a small-world, scale-free system such as has been linked in other fields with self-organisation and emergent properties of complex systems. Szentágothai's module concept shows at least that the cortex consists of integrative units densely packed with neurons and linked with each other by long-range connections. Together with Braitenberg's statistical investigations of the long-range anatomical connectivity, this suggests indeed the existence of a cortical network topology with properties similar to those found in small-world networks, namely high clustering due to modules and small connectivity length due to long-range connections. Concrete support in this direction, although not explicitly linked to the small-world phenomenon, follows from numerous neuroanatomical studies of large-scale cortico-cortical pathways in different mammalian species. Most notable here are the investigations of Angelucci, Kennedy, Lund, Rakic, White, and many others in the cerebral cortex,

in particular the macaque and cat visual cortex, as well as experimental studies of the group around Scannell in the cat cortico-cortical and cortico-thalamic system [167,168], and in the rat hippocampus by Burns and Young [169]. All these anatomical investigations provided maps of large-scale pathways in the investigated brain areas and graphically confirmed earlier findings which show a highly hierarchically organised structure with `streams' and `systems' with connections which mostly link to nearest neighbours [170]. Moreover, these densely intra-connected systems reflect functionally specialised sets of cortical areas, suggesting once more that function and structure are closely linked at the system level [171].

However, these early studies did not go far beyond drawing of large-scale connectivity maps of neuronal populations. Only recently were these maps of network pathways re-examined with specific graph-theoretical tools [172] in order to find a decisive answer to the question whether the brain network, or at least parts of it, shares properties of scale-free, small-world networks otherwise so commonly found in nature. For this purpose, anatomical maps are represented as directed graphs [170,173] in which vertices, or nodes, describe neuronal units (neurons, population of neurons, brain areas) and (directed) edges describe connections (synaptic or `streams') between these units. With this, the average path length and cluster index can be calculated and compared with that typical for random, lattice or small-world networks. As mentioned above, two criteria must be fulfilled for the latter [174]. First, the average path length should be small and comparable with that of random networks. Second, the cluster index should be larger than that of highly ordered networks, such as lattice networks.

Recently, Sporns and Zwi investigated the large-scale cortical connectivity maps obtained from previous neuroanatomical studies in the macaque and cat cortex [175]. They found indeed that in all cases the cortical connectivity patterns had properties of small-world networks. Pairs of neuronal units are linked together by short paths, as in random networks, despite the spatial extent and rather sparse connectivity of the network. Moreover, neighbouring neuronal units shared many more interconnections than typical for random networks, resulting in a correspondingly high cluster index (see Fig. 5). However, and this must be viewed as a rather surprising result, in this study no clear evidence was found for scale-free degree distributions in the large-scale connection maps. In fact, the investigated networks exhibit a rather homogeneous degree distribution. This, indeed, could be a major setback in the argumentation outlined above which could potentially prove that brain networks indeed form complex systems. Even more crucial, does this mean that the brain, or its substructures, obey rules which deviate from that seen in so much abundance in other natural and social systems? In fact, experiments done in sensory systems of various species long before the investigations of topological connectivity patterns in mammalian cortices indicate differently. Specifically, studies of functional, rather than structural, aspects of sensory coding do provide strong evidence for a power-law, i.e. a scale-free, behaviour.

Functional network topology and the `scale-free' analogy

Investigations showing power-law behaviour in neuronal systems date back to the early second half of the last century. For example, Landgren [176] investigated the response of cat carotid sinus baroreceptor units during constant intrasinusal pressure stimuli and found a power-law scaling in the impulse frequency as a function of time. Similar findings were reported in the transient response (impulse frequency) as a function of time as well as the impulse frequency modulation (sensitivity) as a function of the forcing frequency in cockroach mechanoreceptors [177], the decay of the response impulse frequency of a slowly adapting stretch receptor following step stretches and the peak impulse frequency as a function of the velocity of stretching in the stretch receptor of crayfish [178], or the gain as a function of the light modulation frequency in the lateral eye of the limulus [179]. More recently, an investigation of Teich and colleagues [180] showed

that the discharge statistics of cat retinal ganglion cells and lateral-geniculate nucleus cells show long-duration power-law correlations.

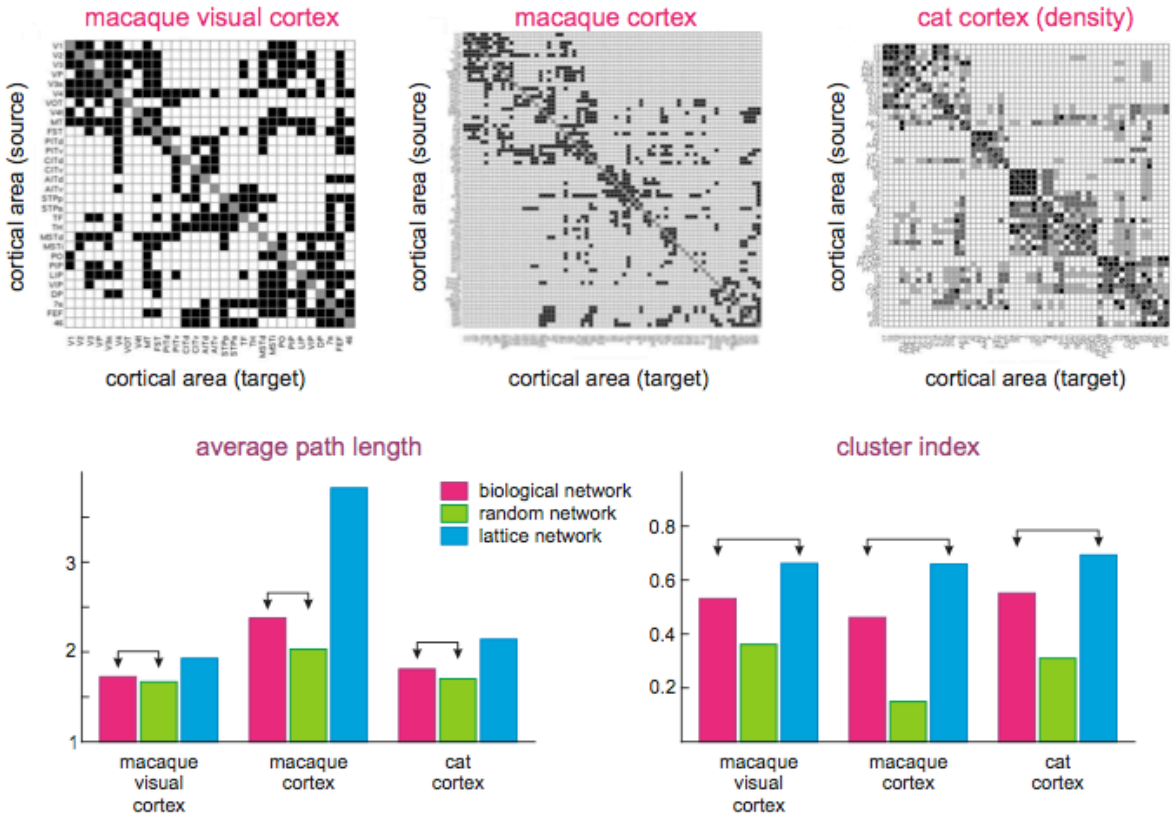

Figure 5: *Topological connectivity pattern in biological neural systems. Top: Large-scale connectivity matrices of the macaque visual cortex, the macaque cortex and the cat cortex. In the latter case, the density-based connectivity is shown. Bottom: Average path length (left) and cluster index (right) deduced from the large-scale connectivity matrices of cortico-cortical pathways. Results from the macaque visual cortex, the macaque cortex and the cat cortex are shown, along with the average path length and cluster index for corresponding random and lattice networks. The arrows indicate that the small average path length observed in the biological systems is closer to that seen in random networks, whereas the cluster index in biological systems is closer to that of corresponding lattice networks. Figures and data modified from ref. [175].*

In most of these cases, the power-law behaviour was linked to how sensory information is coded, i.e. to a specific functional aspect of sensory processing. These findings suggest the possibility that the presence of specific scaling-laws might be true for functional networks in higher brain areas, such as the cortex, where the investigation of topological connectivity patterns did not reveal such a structural signature. With the availability of recording techniques which cover spatially separated brain regions, such as distributed multielectrode EEG recordings or fMRI, as well as new mathematical analysis methods, which allow the effective activity in such spatially extended systems to be screened and characterised [181], the experimental and theoretical basis now exists to address this possibility. Among the first clear indications that, indeed, the functional dynamics in macroscopic brain networks might be governed by power-laws was the work of Jung and collaborators [182]. In their study of spiral chemical waves mediated by the network noise in cultured networks of glial cells, they found that these waves could cover a few centimetres and persist for many seconds. In turn, a power-law distribution of wave sizes was reported along with the argumentation that the processes which create these waves do not exhibit a preference for a specific spatial or temporal scale, i.e. are scale-free.

Recently, similar results were reported in experimental investigations of the propagation of spontaneous activity in mature organotypic cultures and acute slices of the rat cortex [183]. By continuously recording spontaneous local field potentials using a multielectrode array, Beggs and Plenz showed that these waves of activity are similar to avalanches, a phenomenon well-known to exhibit power-law amplitude distributions. Indeed, the propagation of these `neuronal avalanches' in terms of size and lifetime obeyed a power law [184]. Moreover, their spatio-temporal patterns were stable and significantly repeatable for hours of recordings [183]. The authors suggested that these avalanches may constitute a novel mode of activity in cortical networks which differs profoundly from those known for a long time, such as oscillatory or synchronised network states.

The presence of scale-free or avalanche dynamics is, however, unclear for association cortex. In a recent analysis (C. Bedard, H Kroger and A. Destexhe, submitted), we found no evidence for avalanche or scale-free dynamics in neuronal activity from parietal cortex of awake cats, but rather that the dynamics shows exponential scaling, as if neuronal discharges were described by Poisson stochastic processes. This corroborates the work of Softky & Koch showing that the statistics of neuronal discharges in another type of association cortex (area MT) is similar to Poisson processes. It still remains possible that the cortex switches from Poisson-like to scale-free dynamics as a function of its state of attention or arousal, but such a hypothesis has not been tested yet. Thus, there is presently no direct in vivo evidence for scale-free dynamics in association cortex, but the only evidence so far was obtained in primary sensory cortex or thalamus, suggesting that this type of dynamics may be mostly relevant to sensory pathways.

At the level of functional interactions, direct evidence that the cortical network of functional interactions *in vivo* is not homogeneous but rather is segregated into mutually interacting functional assemblies comes from the work of Stephan and colleagues in the macaque cerebral cortex [185]. Functional connectivity refers here to deviations from statistical independence in the activity between spatially separated neuronal units, and measures their temporal correlation or spectral coherence [186]. Stephan *et al*. systematically collected and investigated data from many earlier studies on the spread of activity after strychnine-induced disinhibition and indeed found, using graph-theoretical tools, that the functional cortical network is closer to a small-world than to a random or lattice network (see Fig. 6). These findings are in good agreement with results obtained in investigations of the anatomical connectivity patterns in the mammalian cerebral cortex (see above), and demonstrate once more strong arguments for the close link between functional and structural connectivity. However, in the cited study, again no evidence for a scale-free, but for a rather single-scaled degree distribution was found.

Finally, using fMRI data, the network of functionally correlated, spatially separated brain sites in humans was investigated [187]. It was found that both the distribution of functional connections and the probability of finding a link as a function of distance between vertices closely followed a scale-free behaviour (see Fig. 6). In conjunction with the finding that the average path length between vertices in this fMRI network was very small and accompanied by a clustering coefficient which was much larger than that of equivalent random networks, these findings suggest that, indeed, the large-scale functional connectivity in the brain follows that typically seen in scale-free small-world networks.

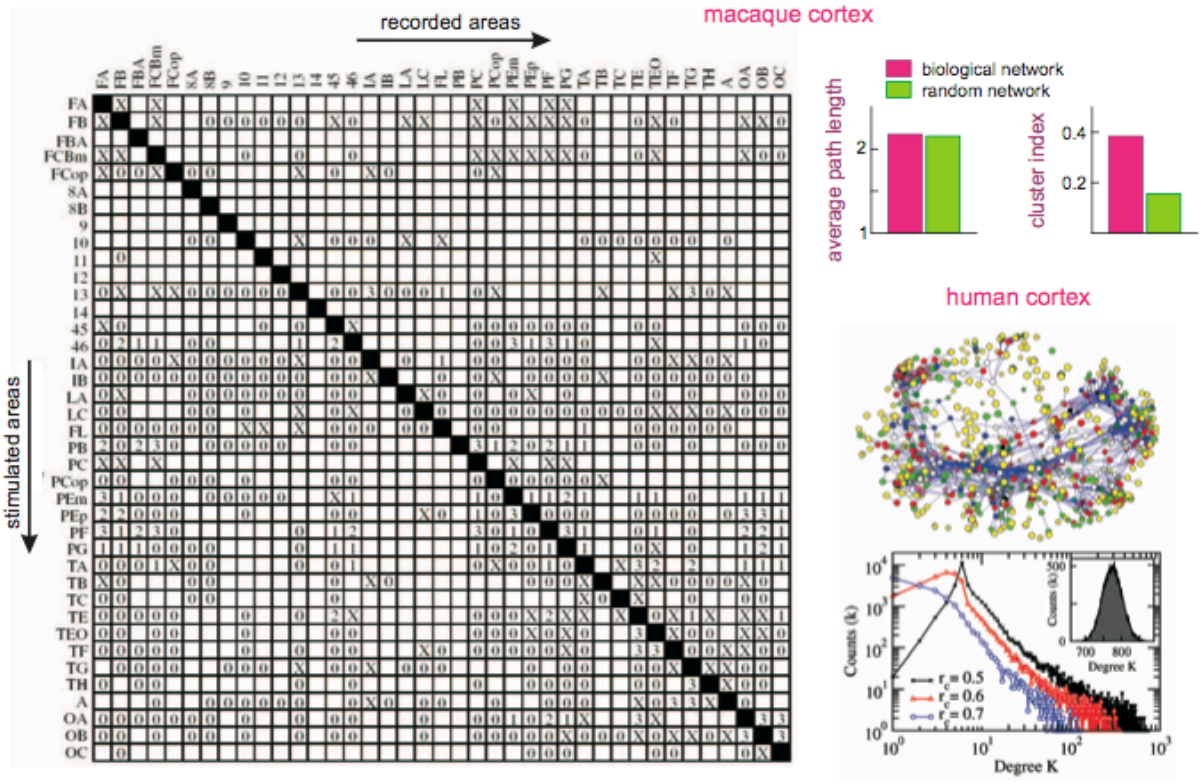

Figure 6: *Functional connectivity pattern in biological neural systems. Left: Matrix of functional connectivity in the macaque cortex deduced from the spread of activity between cortical areas as determined by strychnine neuronography (figure taken from ref. [185]). Right top: Average path length and cluster index deduced from the functional connectivity matrix in comparison with the values for a corresponding random network (data from ref. [185]). Whereas the average path length of the biological functional network was small as in a corresponding random network, the cluster index was markedly larger, suggesting a functional connectivity with small-world structure. Right bottom: Functional network (top) and degree-distribution (bottom) extracted from functional magnetic resonance imaging data on the human cortex during a behavioural task. The degree-distribution shows a scale-free behaviour. Figure taken from preprint by Eguíluz et al, with permission.*

Complexity in network dynamics

A possible role of `noise' in the functional dynamics of cortical networks

One of the most striking differences between cerebral cortex and central pattern generating networks is that cortical neurons *in vivo* show a considerable degree of apparent randomness in their activity. The membrane potential of cortical neurons is subject to highly fluctuating activity (Fig. 7A), mostly of synaptic origin [188], consistent with the extremely dense connectivity in cortex [150,189,142]. An essential characteristic of this `synaptic noise' is that it sets the membrane in a `high-conductance state', which may impact considerably on the integrative properties of cortical neurons [42]. Computational models have predicted that in high-conductance states cortical neurons follow several `computational principles' [42]. First, their responsiveness is strongly modulated by synaptic noise, and in some cases it may boost the response to synaptic inputs[190] (Fig. 7B), similar to stochastic resonance phenomena [191]. Some of these predictions were confirmed experimentally using dynamic-clamp [192,193,194]. Second, complex interactions

between synaptic noise and dendritic ion channels may considerably reduce the dependence of the efficacy of synaptic inputs on their location in dendrites [195], resulting in a more `democratic' dendritic tree in which each synapse would have an approximately equal vote in firing an action potential in the axon (Fig. 7C). This scheme is, however, only valid for isolated inputs, and the integration of multiple inputs may reveal the existence of `dendritic subunits', as suggested by experiments [196] and models [197]. Third, high-conductance states sharpen temporal resolution, allowing cortical neurons to detect millisecond coincidences and therefore resolve precisely timed inputs [42,198]. However, how cortical neurons integrate thousands of inputs distributed in their dendrites still remains an open problem. Finally, an obvious consequence of synaptic noise is that cortical neurons display a high trial-to-trial variability in their responses [190], a feature often seen *in vivo*. Consequently the only measures that makes sense for a cortical neuron *in vivo* are probabilities, and indeed probabilities have been used for several decades to characterise responses recorded in cortex *in vivo*, under the form of `post-stimulus time histograms' [199]. There is also a whole family of computational models of cortical coding based on probabilistic models [200], some of which will be mentioned below.

The property of noise-induced enhancement of responsiveness [190], or gain modulation by noise [193], suggests two possible views about the computational role of synaptic noise. It could be that the apparently stochastic membrane potential fluctuations result from the processing of a large number of `meaningful' signals. Assuming that these signals are weakly correlated, any given input sees the other inputs as `noise', and can be boosted by these other inputs. The neuron would therefore multiplex many such weakly correlated signals [201]. Alternatively, it may be that the cortical network produces self-generated stochastic activity in order to be in a regime of enhanced responsiveness where afferent inputs can be processed efficiently. Here, synaptic noise is viewed as the result of a particular network state where responsiveness is optimised, perhaps related to attentional mechanisms ([190,194], see discussion in ref. [53]).

These lines of evidence suggest that `noise' is one of the building blocks that need to be taken into account to understand cortical computations, in addition to the intrinsic and synaptic properties introduced earlier. In contrast to what is usually thought, the effect of `noise' may be not detrimental but possibly beneficial for near-threshold signalling and decision making. However, other theoretical frameworks, which are no longer limited to the classical Shannonian transmission of a signal source by a noisy channel, should also be considered. When studying the impact of `noise' no longer at the level of input/output operations performed by the single cell but at the level of assembly dynamics, network-driven `noise' reflects the activity of all unseen units and depends on the degree of redundancy/sparseness achieved by the population code. Under such dynamic regime, `noise' no longer acts as an additive or multiplicative constant at the cell level, but becomes embedded in the global dynamics of the system [202]. Recent work in visual cortex, based on the trial-by-trial reliability of the spike pattern as well as of the subthreshold membrane potential trajectory, indicates that `noise' covaries as a function of the global uncertainty provided by the sensory context ([203]; Baudot, Marre, Levy and Frégnac, to be submitted). The variability of the network dynamics can be derived from the respective dimensions of the sensory input information to be processed, i.e. its complexity and the intrinsic information capacity of the network.

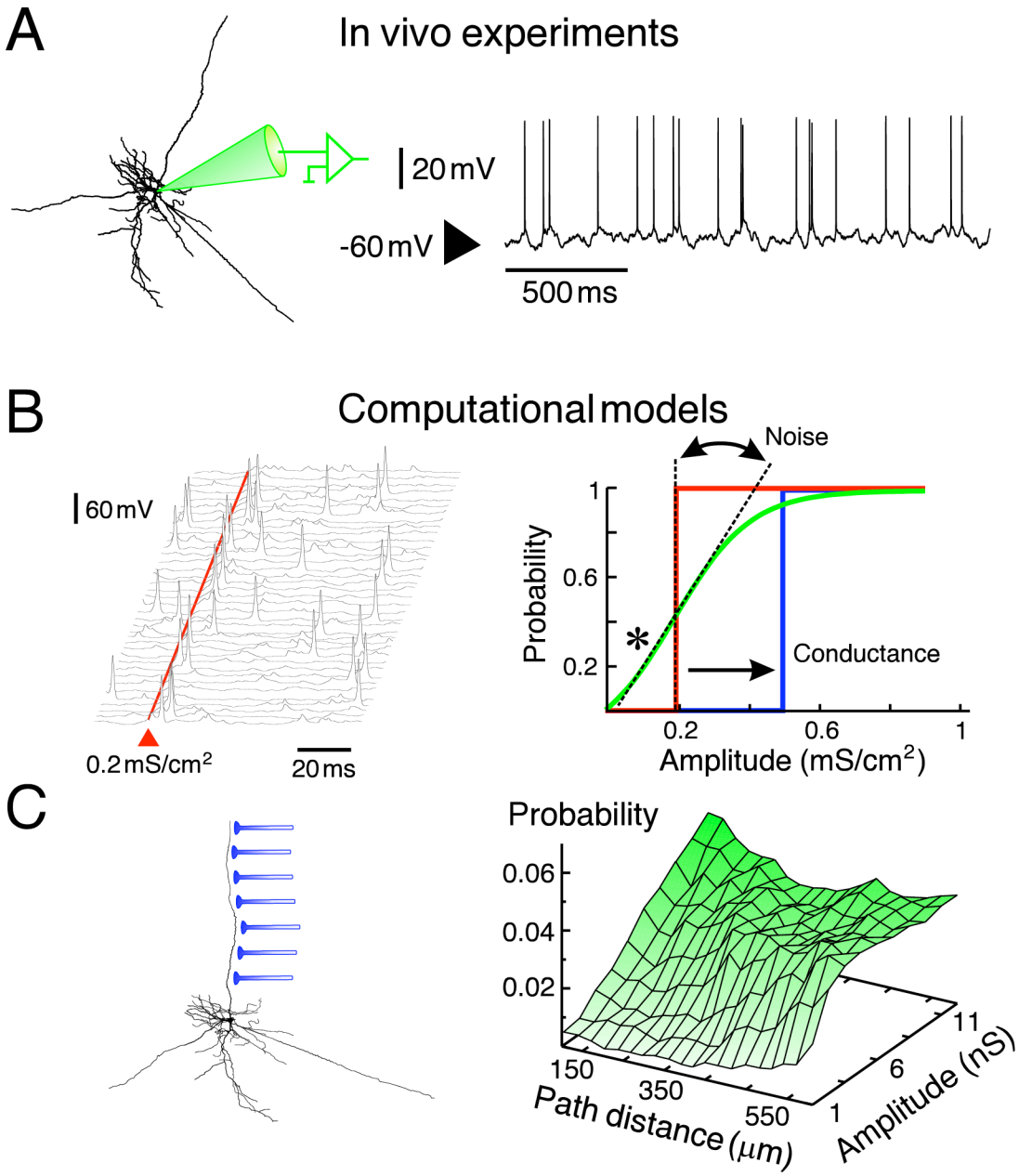

Figure 7: *Synaptic noise as a building block of neocortical circuit computations. A. Intracellular recordings in cat parietal cortex in vivo showing the sustained membrane potential fluctuations during activated states. B. Enhancement of responsiveness by synaptic noise. Computational models of pyramidal neurons simulated synaptic noise from the random release of thousands of glutamatergic and GABAergic synapses distributed in soma and dendrites. Left: the response to additional excitatory inputs leads to probabilistic responses (red line; 40 trials shown). Right panel: response curve of the neuron without noise (red), with noise (green) and with the equivalent leak conductance (blue). Synaptic noise changed the gain of neurons and enhanced the responsiveness to low-amplitude inputs (*). C. Equalisation of synaptic efficacies by synaptic noise. Synaptic inputs were simulated at different distances from the soma (left scheme). The response probability is shown as a function of input strength (Amplitude) and localisation with respect to soma (Path distance). Input efficacy was weakly dependent on the location of the input in dendrites. Modified from ref. [42].*

Self-organisation and adaptive properties in network dynamics

The concept of self-organisation dates back to the British psychiatrist and engineer W.R. Ashby [204], who became one of the founding fathers of systems theory and cybernetics in the late 1940s [205]. Based on the work of Ashby and his successors, we can now formulate several principles that are linked to the dynamics of self-organisation. First, self-organising systems exhibit a balance between positive feedback, which leads to an acceleration of the development of the system, and negative feedback, which is required to stabilise the system. Second, self-organising systems show an adaptation to their environment. For that, the system needs a huge variety of stable states, i.e. the number of states must be large enough to allow the system to react to environmental perturbations yet remain stable. Third, the process of self-organisation is equivalent to an increase in coherence or synchrony which can span the whole system and is accompanied by a decrease of statistical entropy. Interestingly, this principle points, apparently, towards the well-known thermodynamic paradox. However, according to Ashby, dynamic systems always tend to evolve to a specific attractor state, which can be viewed as a specific state of equilibrium which reduces the uncertainty about the system's state and, therefore, minimises the system's statistical entropy. This argumentation, indeed, circumvents the paradox. Fourth, in self-organising systems, only correlation or coherence patterns which can maintain themselves can result from the inherent dynamics and, therefore, continue to exist. This property is a manifestation of the concept of closure and self-sufficiency.

It has been shown that many physical and chemical systems develop a hierarchical, structured, i.e. complex, architecture. Finally, this organisational closure turns a collection of interacting elements into an individual coherent whole, which has properties that arise out of its organisation and that cannot be reduced to the properties of its elements. This is the birthplace of emergent properties.

In generalisation of this last point of organisational closure, self-organisation also means adaptation of system constituents, populations or sub-components to themselves. This leads, naturally, to the concept of self-regulation or self-control. This requires that, first, the system is able to produce a sufficient variety of actions to cope with possible perturbations (external and intrinsic) and, second, that the system selects the most adequate counter-action for a given perturbation. Here, variety keeps the system far from equilibrium, i.e. endows it with many possible attractor states, characteristic of chaotic systems. In contrast, selectivity pushes towards a sufficiently small number of attractor states in order to ensure stability, as is typical for deterministic systems. The coexistence, or union, of variety and selectivity leads to the idea that complex adaptive systems tend to reside on the edge of chaos [206,207], a regime between chaotic disorder and deterministic order. Moreover, the mechanism by which complex systems tend to maintain themselves on this critical edge is called self-organised criticality [208]. Interestingly, as has been shown to be the case in many natural and social contexts, the system's behaviour on this edge is typically governed by power laws. This closes the loop of argumentation, although with many remaining holes of explanation, for a connection between the definition of a system as being complex and the property of possessing a topological or functional small-world structure which follows a power-law distribution in some of its characteristic properties.

Conclusion and perspectives: Complexity as a computational principle?

An alternative to attempting to explain cortical function on the basis of canonical microcircuits is to exploit the phenomenal diversity of cortical structure and dynamics. Cortical neurons display a wide diversity of morphologies and intrinsic properties [45], and synaptic dynamics are highly variable and show properties from facilitating to depressing synapses [65]. The essential feature of

cortical anatomy may be precisely that there is no canonical pattern of functional connectivity, consistent with the considerable apparently-random component of cortical structural connectivity templates [150,151]. Taking these observations together, one may argue that the cortex is a circuit ever-adapting to the functional task that seems to maximise its own complexity, both in terms of recruitment of distributed elementary intrinsic properties at the single-cell level and in terms of relational topology at the network connectivity level. Along with this view, computational models are now emerging, in which the goal is to take advantage of the special information processing capabilities - and memory - of such complex systems. Such large-scale networks can transform temporal codes into spatial codes by self-organisation [209], and computing frameworks have been proposed which exploit the capacity of such complex networks to cope with complex input streams [210,211]. In these examples, information is stored in the ongoing activity of the network, in addition to in its synaptic weights.

Progress in the study of complex systems may also be crucial for understanding cortical computations. We have mentioned above the idea that cortical wiring is given by the repetition of canonical microcircuits [53,147,148,149] which was contrasted with the idea that cortical wiring templates are highly variable [150,142,151]. We can go further and note that the nervous system is perfectly able to wire well ordered, almost crystalline structures, suggesting that the considerable variability and diversity found in neocortex is important for its computations. We may have to abandon the usual concept of `large networks of identical units' and replace it with the idea that the cortex consists of `large networks of diverse elements', guided by a continuum of properties, rather than of prototypical units or microcircuits.

Advances in this field will depend on combined progress in molecular tagging, instrumentation (e.g. two-photon [212]) and in multiple-scale monitoring of brain activity. New methods are already available to link levels of integration and visualise the collective dynamics of large distributed ensembles of spiking elements. Such tools find a natural field of application in the delineation of parts of the brain, and more specifically of cortical areas, involved in specific cognitive functions and in the genesis or processing of mental representations [213]. However their present use and repeated abuse illustrate the fact that most advanced brain imaging techniques (calcium imaging with two-photon, PET, fMRI, BOLD, EEG-MEG) rely on explicative variables (metabolic, haemodynamic) which differ greatly from those used to decipher the neural code and information transfer at a more microscopic level (current source density, evoked potentials, spike counts). Increased efforts have to be made in establishing correlations and when possible transfer functions between variables collected at different levels of integration and scales of observation [214,215]. The ignorance, of minoration, of elementary sources of complexity in the living brain has already attributed specific locations to consciousness and we should not wait long for the pineal gland to be reinstated as the centre of mind/soul. It is only when the complexity of brain processes will be fully recognised that one may hope to go beyond the past errancy of phrenology and system behaviour linearisation.

This review work has been supported by the European Union under the Bio-inspired Intelligent Information Systems Programme, project reference IST-2004-15879 (FACETS).

Bibliography

1. Churchland, P. & Sejnowski, T. (1988). Perspectives on cognitive neuroscience. *Science* **242**, 741-745.

2. Poggio, T. . (1983). Visual algorithms. In: O. J. Braddick & A. C. Sleigh (eds.), *Physical and Biological Processing of Images*, pp. 128-153. Springer-Verlag, Berlin.

3. McCulloch, W. & Pitts, W. (1943). A logical calculus of the ideas immanent in nervous activity. *Bull. Math. Biophys.* **5**, 115-133.

4. Ferster, D. & Miller, K. D. (2000). Neural mechanisms of orientation selectivity in the visual cortex.. *Annu. Rev. Neurosci.* **23**, 441-471.

5. Borg-Graham, L. & Monier, C. (1998). Visual input evokes transient and strong shunting inhibition in visual cortical neurons. *Nature* **393**, 369-373.

6. Shapley, R., Hawken, M. & Ringach, D. L. (2003). Dynamics of orientation selectivity in the primary visual cortex and the importance of cortical inhibition. *Neuron* **38**, 689-699.

7. Monier, C., Chavane, F., Baudot, P., Graham, L. J. & Frégnac, Y. (2003). Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. *Neuron* **37**, 663-680.

8. Oliet, S., Piet, R. & Poulain, D. (2001). Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. *Science* **292**, 923-926.

9. Todd, K., Serrano, A., Lacaille, J. & Robitaille, R. (2006). Glial cells in synaptic plasticity. *J. Physiol.* **99**, 75.

10. Jacobs, R. (1999). Computational studies of the development of functionally specialized neural modules. *Trends Cogn. Sci.* **3**, 31-38.

11. Connors, B., Gutnick, M. & Prince, D. (1982). Electrophysiological properties of neocortical neurons *in vitro*. *J. Neurophysiol.* **48**, 1302-1320.

12. Hille, B. (1991). *Ionic channels of excitable membranes*. Sinauer Associates, Sunderland, 2nd edn.

13. Gähwiler, B. H. (1981). Organotypic monolayer cultures of nervous tissue. *J. Neurosci. Meth.* **4**, 329-342.

14. Kandel, E. (1976). *Cellular basis of behavior: an introduction to behavioral neurobiology*. W.H. Freeman.

15. Rall, W. (1964). Theoretical significance of dendritic tree for input-output relation.In: R. F. Reiss (ed.), *Neural Theory and Modeling*, pp. 73-97. Stanford University Press, Stanford.

16. Rall, W. (1967). Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *J. Neurophysiol.* **30**, 1138-1168.

17. Rall, W. (1969). Time constants and electrotonic length of membrane cylinders and neurons. *Biophys. J.* **9**, 1483-1508.

18. Rall, W. & Rinzel, J. (1973). Branch input resistance and steady attenuation for input to one branch of a dendritic neuron model.*Biophys. J.* **13**, 648-687.

19. Segev, I., Rinzel, J. & Shepherd, G. M. (eds.) (1995). *The Theoretical Foundation of Dendritic Function. Selected Papers of Wilfried Rall with Commentaries.* MIT Press, Cambridge, MA.

20. Llinás, R. (1975). Electroresponsive properties of dendrites in central neurons. *Adv. Neurol.* **12**, 1-13.

21. Johnston, D., Magee, J. C., Colbert, C. M. & Christie, B. R. (1996). Active properties of neuronal dendrites. *Annu. Rev. Neurosci.* **19**, 165-186.

22. Migliore, M. & Shepherd, G. M. (2002). Emerging rules for the distributions of active dendritic conductances. *Nat. Rev. Neurosci* **3**, 362-370.

23. Segev, I. & Rall, W. (1998). Excitable dendrites and spines: earlier theoretical insights elucidate recent direct observations. *Trends Neurosci.* **21**, 453-460.

24. Yuste, R. & Tank, D. W. (1996). Dendritic integration in mammalian neurons, a century after Cajal. *Neuron* **16**, 701-716.

25. Stuart, G., Spruston, N. & Häusser, M. (eds.) (2000). *Dendrites*. MIT Press, Cambridge, MA.

26. Wong, R. K., Prince, D. A. & Basbaum, A. I. (1979). Intradendritic recordings from hippocampal neurons. *Proc. Natl. Acad. Sci. USA* **76**, 986-990.

27. Benardo, L. S., Masukawa, L. M. & Prince, D. A. (1982). Electrophysiology of isolated hippocampal pyramidal dendrites. *J. Neurosci.* **2**, 1614-1622.

28. Regehr, W., Kehoe, J. S., Ascher, P. & Armstrong, C. (1993). Synaptically triggered action potentials in dendrites. *Neuron* **11**, 145-151.

29. Andreasen, M. & Lambert, J. D. (1995).Regenerative properties of pyramidal cell dendrites in area CA1 of the rat hippocampus. *J. Physiol.* **483 (Pt 2)**, 421-441.

30. Schwindt, P. C. & Crill, W. E. (1995). Amplification of synaptic current by persistent sodium conductance in apical dendrite of neocortical neurons. *J. Neurophysiol.* **74**, 2220-2224.

31. Stuart, G. & Sakmann, B. (1995). Amplification of EPSPs by axosomatic sodium channels in neocortical pyramidal neurons. *Neuron* **15**, 1065-1076.

32. Berger, T., Larkum, M. E. & Lüscher, H. R. (2001). High I(h) channel density in the distal apical dendrite of layer V pyramidal cells increases bidirectional attenuation of EPSPs. *J. Neurophysiol.* **85**, 855-868.

33. Williams, S. R. & Stuart, G. J. (2000). Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons. *J. Neurophysiol.* **83**, 3177-3182.

34. Stuart, G. J. & Sakmann, B. (1994). Active propagation of somatic action potentials into

neocortical pyramidal cell dendrites. *Nature* **367**, 69-72.

35. Markram, H., Lübke, J., Frotscher, M. & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213-215.

36. Hines, M. L. & Carnevale, N. T. (1997). The NEURON simulation environment. *Neural Comput.* **9**, 1179-1209.

37. Hines, M. L. & Carnevale, N. T. (2001). NEURON: a tool for neuroscientists. *Neuroscientist* **7**, 123-135.

38. Koch, C. & Segev, I. (eds.) (1998). *Methods in Neuronal Modeling*. MIT Press, Cambridge, MA.

39. Bower, J. M. & Beeman, D. (1997). *The Book of GENESIS: Exploring realistic neural models with the GEneral NEural SImulation System*. TELOS, Springer-Verlag, New York, 2 edn.

40. Steriade, M., Timofeev, I. & Grenier, F. (2001). Natural waking and sleep states: a view from inside neocortical neurons. *J. Neurophysiol.* **85**, 1969-1985.

41. Matsumura, M., Cope, T. & Fetz, E. (1988). Sustained excitatory synaptic input to motor cortex neurons in awake animals revealed by intracellular recording of membrane potentials. *Exp. Brain Res.* **70**, 463-469.

42. Destexhe, A., Rudolph, M. & Paré, D. (2003). The high-conductance state of neocortical neurons *in vivo*. *Nat. Rev. Neurosci* **4**, 739-751.

43. Nowak, L. G., Azouz, R., Sanchez-Vives, M. V., Gray, C. M. & McCormick, D. A. (2003). Electrophysiological classes of cat primary visual cortical neurons *in vivo* as revealed by quantitative analyses. *J. Neurophysiol.* **89**, 1541-1566.

44. Connors, B. W. & Gutnick, M. J. (1990). Intrinsic firing patterns of diverse neocortical neurons. *Trends Neurosci.* **13**, 99-104.

45. Gupta, A., Wang, Y. & Markram, H. (2000). Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. *Science* **287**, 273-278.

46. Yuste, R. (2005). Origin and classification of neocortical interneurons. *Neuron* **48**, 591-604.

47. Alonso-Nanclares, L., Anderson, S., Ascoli, G., Benavides-Piccione, R., Burkhalter, A., Buzsaki, G., Cauli, B., DeFelipe, J., Fairen, A., Feldmeyer, D., Fishel, G., Frégnac, Y., Freund, T. F., Fukuyi, K., Glarreta, M., Goldberg, J., Helmstaedter, M., Hensch, T., Hestrin, S., Kisvarday, Z., Lambolez, B., Lewis, D., McBain, C., Marin, O., Markham, H., Monyer, H., Muñoz, A., Petersen, C., Rockland, K., Rossier, H., Ruby, B., Somogyi, P., Staiger, J. F., Tamas, G., Thomson, A., Toledo-Rodriguez, M., Wang, X.-J., Wang, Y., West, D. & Yuste, R. (2005). Nomenclature of features of GABAergic interneurons of the cerebral cortex. *Petilla. Classification endorsed by the American Society for Neuroscience*.

48. Toledo-Rodriguez, M., Blumenfeld, B., Wu, C., Luo, J., Attali, B., Goodman, P. & Markram, H.. (2004). Correlation maps allow neuronal electrical properties to be predicted from single-cell gene expression profiles in rat neocortex. *Cereb. Cortex* **14**, 1310-1327.

49. Monyer, H. & Markram, H. (2004). Interneuron diversity series: Molecular and genetic tools

to study GABAergic interneuron diversity and function. *Trends Neurosci.* **27**, 90-94.

50. Blatow, M. and Rozov, A. and Katona, I. and Hormuzdi, S.G. and Meyer, A.H. and Whittington, M.A. and Caputi, A. and Monyer, H. (2003). A novel network of multipolar bursting interneurons generates theta-frequency oscillations in neocortex. *Neuron* **38**, 805-817.

51. Whittington, M. A. & Traub, R. D. (2003). Interneuron diversity series: inhibitory interneurons and network oscillations *in vitro*. *Trends Neurosci.* **26**, 676-682.

52. Tsuchida, T., Ensini, M., Morton, S. B., Baldassare, M., Edlund, T., Jessell, T. M. & Pfaff, S. L. (1994). Topographic organization of embryonic motor neurons defined by expression of LIM homeobox genes. *Cell* **79**, 957-970.

53. Frégnac, Y. R., Blatow, M., Changeux, J. P., DeFelipe, J., Markram, H., Lansner, A., Maass, W., McCormick, D., Michel, C. *et al*. (2006). Ups and downs in the genesis of cortical computation. In: Grillner, S. *et al*. (ed.), *Microcircuits: The Interface between Neurons and Global BrainFunction Microcircuits:*, vol. 93 of *Dahlem Workshop Report*, pp. 397-437. MIT Press, Cambridge, MA.

54. Szentágothai, J. (1975). The `module-concept' in cerebral cortex architecture. *Brain Res.* **95**, 475-496.

55. Hubel, D. H. & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.* **160**, 106-154.

56. Dudek, F., Andrew, R., MacVicar, B., Snow, R. & Taylor, C. (1983). Recent evidence for and possible significance of gap junctions and electrotonic synapses in the mammalian brain. In: *BasicMechanisms of Neuronal Hyperexcitability*, pp. 31-73. A. Liss, New York.

57. Galaretta, M. & Hestrin, S. (1999). A network of fast-spiking cells in the neocortex connected by electrical synapses. *Nature* **402**, 72-75.

58. Gil, Z., Connors, B. & Amitai, Y. (1997). Differential regulation of neocortical synapses by neuromodulators and activity. *Neuron* **19**, 679-686.

59. Douglas, R., Martin, K. & Whitteridge, D. (1988). Selective responses of visual cortical cells do not depend on shunting inhibition. *Nature* **332**, 642-644.

60. Dale, H. (1935). Pharmacology and nerve-endings. *Proc. R. Soc. Med. (Lond)* **28**, 319-332.

61. Cherubini, E., Gaiarsa, J. L. & Ben-Ari, Y. (1991). GABA: an excitatory transmitter in early postnatal life. *Trends Neurosci.* **14**, 515-519.

62. Alkon, D., Sanchez-Andrés, J. V., Ito, E., Oka, K., Yoshika, T. & Collin, C. (1992). Long-term transformation of an inhibitory into an excitatory GABAergic synaptic response. *Proc. Natl. Acad. Sci. USA* **89**, 11862-11866.

63. Liao, D., Hessler, N. & Malinow, R. (1995). Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. *Nature* **375**, 400-404.

64. Malenka, R. C. & Nicoll, R. A. (1997). Silent synapses speak up. *Neuron* **19**, 473-476.

65. Thomson, A. M. (2000). Facilitation, augmentation and potentiation at central synapses. *Trends Neurosci.* **23**, 305-312.

66. Markram, H. & Tsodyks, M. (1996). Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature* **382**, 807-810.

67. Tsodyks, M., Pawelzik, K. & Markram, H. (1998). Neural networks with dynamic synapses. *Neural Comput.* **10**, 821-835.

68. Frégnac, Y. (1999). A tale of two spikes. *Nature Neurosci.* **2**, 299-301.

69. Frégnac, Y. (2002). Hebbian synaptic plasticity. In: M. A. Arbib (ed.), *The Handbook of Brain Theory and Neural Networks, 2nd edition*, pp. 515-522. MIT Press, Cambridge, MA.

70. Brown, T., Ganong, A., Kairiss, E. & Keenan, C. (1990). Hebbian synapses: biophysical mechanisms and algorithms. *Annu. Rev. Neurosci.* **13**, 475-511.

71. Bliss, T. V. & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* **232**, 331-356.

72. Kelso, S. R., Ganong, A. H. & Brown, T. H. (1986). Hebbian synapses in hippocampus. *Proc. Natl. Acad. Sci. USA* **83**, 5326-5330.

73. Bliss, T. V. P. & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31-39.

74. Artola, A., Bröcher, S. & Singer, W. (1990). Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of the rat visual cortex. *Nature* **347**, 69-72.

75. Mulkey, R. & Malenka, R. (1992). Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* **9**, 967-975.

76. Dudek, S. & Bear, M. (1992). Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. *Proc. Natl. Acad. Sci. USA* **89**, 4363-4367.

77. Kirkwood, A., Dudek, S., Gold, J., Aizenman, C. & Bear, M. (1993). Common forms of synaptic plasticity in hippocampus and neocortex *in vitro*. *Science* **260**, 1518-1521.

78. Bi, G. & Poo, M. (2001). Synaptic modification by correlated activity: Hebb's postulate revisited. *Annu. Rev. Neurosci.* **24**, 139-166.

79. Levy, W. & Steward, O. (1983). Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. *Neuroscience* **8**, 791-797.

80. Bi, G. & Poo, M. (1998). Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J. Neurosci.* **18**, 10464-10472.

81. Feldman, D. (2000). Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron* **27**, 45-56.

82. Bell, C., Han, V., Sugawara, Y. & Grant, K. (1997). Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature* **387**, 278-281.

83. Hebb, D. O. (1949). *The Organization of Behavior*. John Wiley and Sons, New York.

84. Frégnac, Y., Shulz, D., Thorpe, S. & Bienenstock, E. (1988). A cellular analogue of visual cortical plasticity. *Nature* **333**, 367-370.

85. Frégnac, Y. & Shulz, D. (1999). Activity-dependent regulation of receptive field properties of cat area 17 by supervised Hebbian learning. *J. Neurobiol.* **41**, 69-82.

86. Kirkwood, A., Lee, H. & Bear, M. (1995). Co-regulation of long-term potentiation and experience-dependent synaptic plasticityin visual cortex by age and experience. *Nature* **375**, 328-331.

87. Mehta, M., Quirk, M. & Wilson, M. (2000). Experience-dependent asymmetric shape of hippocampal receptive fields. *Neuron* **25**, 707-715.

88. Davison, A. & Frégnac (2006). Learning cross-modal transformations through spike timing-dependent plasticity. *J. Neurosci.* **In press**.

89. Frégnac, Y. (1998). Homeostasis or synaptic plasticity? *Nature (News and Views) 391* **391**, 845-846.

90. O'Donovan, M. J. & Rinzel, J. (1997). Synaptic depression: a dynamic regulator of synaptic communication with varied functional roles. *Trends Neurosci.* **20**, 431-433.

91. Abraham, W. & Bear, M. (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* **19**, 126-130.

92. Glanzman, D., Kandel, E. & Schacher, S. (1991). Target-dependent morphological segregation of Aplysia sensory outgrowth *in vitro*. *Neuron* **7**, 903-913.

93. Willshaw, D. & Von der Malsburg, C. (1976). How patterned neural connections can be set up by self-organization. *Proc. R. Soc. Lond. B Biol. Sci.* **194**, 431-445.

94. Turrigiano, G., Abbott, L. & Marder, E. (1994). Activity-dependent changes in the intrinsic properties of cultured neurons. *Science* **264**, 974-977.

95. Turrigiano, G., Leslie, K., Desai, N., Rutherford, L. & Nelson, S. (1998). Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* **391**, 892-896.

96. Miller, K. & MacKay, D. (1996). The role of constraints in Hebbian learning. *Neural Comput.* **6**, 100-126.

97. Chen, W. R., Midtgaard, J. & Shepherd, G. M. (1997). Forward and backward propagation of dendritic impulses and their synaptic control in mitral cells. *Science* **278**, 463-467.

98. Getting, P. A. (1989). Emerging principles governing the operation of neural networks. *Annu. Rev. Neurosci.* **12**, 185-204.

99. Hartline, D. K., Russell, D. F., Raper, J. A. & Graubard, K. (1988). Special cellular and synaptic mechanisms in motor pattern generation. *Comp. Biochem. Physiol. C* **91**, 115-131.

100. Kiehn, O. & Eken, T. (1998). Functional role of plateau potentials in vertebrate motor neurons. *Curr. Opin. Neurobiol.* **8**, 746-752.

101. Bremer, F. (1938). L'activité électrique de l'écorce cérébrale. *Actualités Scientifiques et Industrielles* **658**, 3-46.

102. Bremer, F. (1949). Considérations sur l'origine et la nature des ``ondes'' cérébrales. *Electroencephalogr. Clin. Neurophysiol.* **1**, 177-193.

103. Destexhe, A. & Sejnowski, T. J. (2003). Interactions between membrane conductances underlying thalamocortical slow-wave oscillations. *Physiol. Rev.* **83**, 1401-1453.

104. Steriade, M. (2003). *Neuronal Substrates of Sleep and Epilepsy*.Cambridge University Press, Cambridge, UK.

105. Llinás, R. R. (2002). *I of the Vortex: from Neurons to Self*. MIT Press, Cambridge, MA.

106. Llinás, R. R. & Paré, D. (1991). Of dreaming and wakefulness. *Neuroscience* **44**, 521-535.

107. Singer, W. & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* **18**, 555-586.

108. Stafström, C. E., Schwindt, P. C. & Crill, W. E. (1984). Repetitive firing in layer V neurons from cat neocortex *in vitro*. *J. Neurophysiol.* **52**, 264-277.

109. Gray, M. & McCormick, D. (1996). Chattering cells: Superficial pyramidal neurons contributing to the generation of synchronous oscillations in the visual cortex. *Science* **274**, 109-113.

110. Golding, N. L., Staff, N. P. & Spruston, N. (2002). Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* **418**, 326-331.

111. Hooper, S. & Moulins, M. (1989). Switching of a neuron from one network to another by sensory-induced changes in membrane properties. *Science* **244**, 1587-1589.

112. Meyrand, P., Simmers, J. & Moulins, M. (1991). Construction of a pattern-generating circuit with neurons of different networks. *Nature* **351**, 60-62.

113. Le Masson, G., Marder, E. & Abbott, L. (1993). Activity-dependent regulation of conductances in model neurons. *Science* **259**, 1915-1917.

114. Dickinson, P. & Nagy, F. (1983). Control of a central pattern generator by an identified modulatory interneurone in crustacea: II. induction and modification of plateau properties in neurones. *J. Exp. Biol.* **105**, 59-82.

115. Dickinson, P. S., Mecsas, C. & Marder, E. (1990). Neuropeptide fusion of two motor-pattern generator circuits. *Nature* **344**, 155-158.

116. Steriade, M., Jones, E. G. & McCormick, D. A. (eds.) (1997). *Thalamus*. Elsevier, Amsterdam.

117. McCormick, D. A. (1992). Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* **39**, 337-388.

118. Sherman, S. M. & Guillery, R. W. (2001). *Exploring the Thalamus*. Academic Press, New York.

119. Gerstner, W. & Kistler, W. (2002). *Spiking Neuron Models*. Cambridge University Press, Cambridge, UK.

120. Feng, J. (ed.) (2003). *Computational Neuroscience: A Comprehensive Approach*. Chapman & Hall/CRC, Boca Raton, FL.

121. Lapicque, L. (1907). Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation. *J. Physiol. Pathol. Gen.* **9**, 620-635.

122. Ermentrout, B. (1996). Type I membranes, phase resetting curves, and synchrony. *Neural Computation* **8**, 979-1001.

123. Fourcaud-Trocmé, N., Hansel, D., van Vreeswijk, C. & Brunel, N. (2003). How spike generation mechanisms determine the neuronal response to fluctuating inputs. *J. Neurosci.* **23**, 11628-11640.

124. Izhikevich, E. M. (2004). Which model to use for cortical spiking neurons? *IEEE Trans. Neural Networks.* **15**, 1063-1070.

125. Brette, R. & Gerstner, W. (2005). Adaptive exponential integrate-and-fire model as an effective description of neuronal activity. *J. Neurophysiol.* **94**, 3637-3642.

126. Rudolph, M. & Destexhe, A. (2006). Integrate-and-fire neurons with high-conductance state dynamics for event-driven simulation strategies. *Neural Comput.* **In press**.

127. Bressloff, P. (1995). Dynamics of a compartmental model integrate-and-fire neuron with somatic potential reset. *Physica D.* **80**, 399-412.

128. Hodgkin, A. L. & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**, 500-544.

129. Anderson, J. & Rosenfeld, E. (eds.) (1991). *Neurocomputing: Foundations of Research*. MIT Press.

130. King, C. C. (1991). Fractal and chaotic dynamics in nervous systems. *Prog. Neurobiol.* **36**, 279-308.

131. Faure, P. & Korn, H. (2001). Is there chaos in the brain? I. Concepts of nonlinear dynamics and methods of investigation. *C. R. Acad. Sci. III* **324**, 773-793.

132. Schiff, S. J., Jerger, K., Duong, D. H., Chang, T., Spano, M. L. & Ditto, W. L. (1994). Controlling chaos in the brain. *Nature* **370**, 615-620.

133. Korn, H. & Faure, P. (2003). Is there chaos in the brain? II. Experimental evidence and related models. *C. R. Biol.* **326**, 787-840.

134. Babloyantz, A., Salazar, J. & Nicolis, G. (1985). Evidence of chaotic dynamics of brain activity during the sleep cycle. *Phys. Lett. A* **111**, 152-156.

135. Freeman, W. J. (2000). Mesoscopic neurodynamics: from neuron to brain. *J. Physiol. (Paris)*

94, 303-322.

136. Pritchard, W. S. & Duke, D. W. (1995). Measuring "chaos" in the brain: a tutorial review of EEG dimension estimation. *Brain Cogn.* **27**, 353-397.

137. Maex, R. & De Schutter, E. (1998). Synchronization of Golgi and granule cell firing in a detailed network model of the cerebellar granule cell layer. *J. Neurophysiol.* **80**, 2521-2537.

138. Davison, A. P., Feng, J. & Brown, D. (2003). Dendrodendritic inhibition and simulated odor responses in a detailed olfactory bulb network model. *J. Neurophysiol.* **90**, 1921-1935.

139. Rangan, A. V., Cai, D. & McLaughlin, D. W. (2005). Modeling the spatiotemporal cortical activity associated with the line-motion illusion in primary visual cortex. *Proc. Natl. Acad. Sci. USA* **102**, 18793-18800.

140. Traub, R. D., Contreras, D., Cunningham, M. O., Murray, H., LeBeau, F. E. N., Roopun, A., Bibbig, A., Wilent, W. B., Higley, M. J. & Whittington, M. A. (2005). Single-column thalamocortical network model exhibiting gamma oscillations, sleep spindles, and epileptogenic bursts. *J. Neurophysiol.* **93**, 2194-232.

141. Brunel, N. (2000). Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *J. Comput. Neurosci* **8**, 183-208.

142. White, E. L. (1989). *Cortical circuits*. Birkhauser, Boston.

143. Thomson, A. M. & Bannister, A. P. (2003). Interlaminar connections in the neocortex. *Cereb. Cortex* **13**, 5-14.

144. Herkenham, M. (1980). Laminar organization of thalamic projections to the rat neocortex. *Science* **207**, 532-535.

145. Peters, A. & Jones, E. (eds.) (1985). *Cerebral cortex.*, vol. 3. Plenum, New York.

146. Gilbert, C. & Wiesel, T. (1989). Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. *J. Neurosci.* **9**, 2432-2442.

147. Mountcastle, V. B. (1979). An organizing principle for cerebral function: the unit module and the distributed system. In: F. O. Schmidt & F. G. Worden (eds.), *The Neurosciences: Fourth Study Program*, pp. 21-42. MIT Press, Cambridge, MA.

148. Hubel, D. H. & Wiesel, T. N. (1963). Shape and arrangement of columns in cat's striate cortex. *J. Physiol.* **165**, 559-568.

149. Douglas, R. & Martin, K. (1991). A functional microcircuit for cat visual cortex. *J. Physiol.* **440**, 735-769.

150. Braitenberg, V. & Schüz, A. (1998). *Cortex: statistics and geometry of neuronal connectivity*.Springer-Verlag, Berlin.

151. Silberberg, G., Gupta, A. & Markram, H. (2002). Stereotypy in neocortical microcircuits. *Trends Neurosci.* **25**, 227-230.

152. Contreras, D., Dürmüller, N. & Steriade, M. (1997). Absence of a prevalent laminar

distribution of IPSPs in association cortical neurons of cat. *J. Neurophysiol.* **78**, 2742-2753.

153. Mountcastle, V. (1957). Modality and topographic properties of single neurons in a cat's somatosensory cortex. *J. Neurophysiol.* **20**, 408-434.

154. Mountcastle, V. B. (1982). An organization principle for celebral function: The unit module and the distributed system. In: V. Mountcastle & V. Edelman (eds.), *Mindful Brain: Cortical Organization and the Group-Selective Theory of Higher Brain Function*, pp. 7-50. MIT Press, Cambridge, MA.

155. Hubel, D. & Wiesel, T. (1977). Functional architecture of macaque monkey visual cortex. *Proc. R. Soc. Lond. B Biol. Sci.* **198**, 1-59.

156. Mountcastle, V. (1997). The columnar organization of the neocortex. *Brain* **120**, 701-722.

157. Gilbert, C. D. & Wiesel, T. N. (1983). Clustered intrinsic connections in cat visual cortex. *J. Neurosci.* **3**, 1116-1133.

158. Gilbert, C. & Wiesel, T. (1979). Morphology and intracortical projections of functionally characterized neurones in the cat visual cortex. *Nature* **280**, 120-125.

159. Somers, D., Todorov, E., Siapas, A., Toth, L., Kim, D. & Sur, M. (1998). A local circuit approach to understanding integration of long-range inputs in primary visual cortex. *Cereb. Cortex* **8**, 204-217.

160. Wiesel, T. (1982). Postnatal development of the visual cortex and the influence of the environment (Nobel lecture). *Nature* **299**, 583-591.

161. Sharma, J., Angelucci, A. & Sur, M. (2000). Induction of visual orientation modules in auditory cortex. *Nature* **404**, 841-847.

162. von Melchner, L., Pallas, S. & Sur, M. (2000). Visual behaviour mediated by retinal projections directed to the auditory pathway. *Nature* **404**, 871-876.

163. Binzegger, T., Douglas, R. J. & Martin, K. A. C. (2004). A quantitative map of the circuit of cat primary visual cortex. *J. Neurosci.* **24**, 8441-53.

164. Felleman, D. J. & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* **1**, 1-47.

165. Braitenberg, V. & Schüz, A. (1991). *Anatomy of the cortex*. Springer, Berlin.

166. DeFelipe, J., Alonso-Nanclares, L. & Arellano, J. I. (2002). Microstructure of the neocortex: comparative aspects. *J. Neurocytol.* **31**, 299-316.

167. Scannell, J. W., Blakemore, C. & Young, M. P. (1995). Analysis of connectivity in the cat cerebral cortex. *J. Neurosci.* **15**, 1463-1483.

168. Scannell, J. W., Burns, G. A., Hilgetag, C. C., O'Neil, M. A. & Young, M. P. (1999). The connectional organization of the cortico-thalamic system of the cat. *Cereb. Cortex* **9**, 277-299.

169. Burns, G. A. & Young, M. P. (2000). Analysis of the connectional organization of neural

systems associated with the hippocampus in rats. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **355**, 55-70.

170. Young, M. P. (1992). Objective analysis of the topological organization of the primate cortical visual system. *Nature* **358**, 152-155.

171. Hilgetag, C. C., Burns, G. A., O'Neill, M. A., Scannell, J. W. & Young, M. P. (2000). Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **355**, 91-110.

172. Bienenstock, E. (1996). On the dimensionality of cortical graphs. *J. Physiol. (Paris)* **90**, 251-256.

173. Sporns, O. (2002). Graph theory methods for the analysis of neural connectivity patterns. In: R. Kötter (ed.), *Neuroscience Databases. A Practical Guide.*, pp. 171-186. Klüwer, Boston, MA.

174. Watts, D. J. & Strogatz, S. H. (1998). Collective dynamics of `small-world' networks. *Nature* **393**, 440-442.

175. Sporns, O. & Zwi, J. D. (2004). The small world of the cerebral cortex. *Neuroinformatics* **2**, 145-162.

176. Landgren, S. (1952). On the excitation mechanism of the carotid baroceptors. *Acta. Phys. Scandinav.* **26**, 1-34.

177. Chapman, K. & Smith, R. (1963). A linear transfer function underlying impulse frequency modulation in a cockroach mechanoreceptor. *Nature* **197**, 699-700.

178. Brown, M. & Stein, R. (1966). Quantitative studies on the slowly adapting stretch receptor of the crayfish. *Kybernetik* **3**, 175-185.

179. Biederman-Thorson, M. & Thorson, J. (1971). Dynamics of excitation and inhibition in the light-adapted Limulus eye in situ. *J. Gen. Physiol.* **58**, 1-19.

180. Teich, M. C., Heneghan, C., Lowen, S. B., Ozaki, T. & Kaplan, E. (1997). Fractal character of the neural spike train in the visual system of the cat. *J.Opt. Soc. Am. A Opt. Image Sci. Vis.* **14**, 529-546.

181. Lachaux, J., Rodriguez, E., Martinerie, J. & Varela, F. (1999). Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* **8**, 194-208.

182. Jung, P., Cornell-Bell, A., Madden, K. S. & Moss, F. (1998). Noise-induced spiral waves in astrocyte syncytia show evidence of self-organized criticality. *J. Neurophysiol.* **79**, 1098-1101.

183. Beggs, J. M. & Plenz, D. (2004). Neuronal avalanches are diverse and precise activity patterns that are stable for many hours in cortical slice cultures. *J. Neurosci.* **24**, 5216-5229.

184. Beggs, J. M. & Plenz, D. (2003). Neuronal avalanches in neocortical circuits. *J. Neurosci.* **23**, 11167-11177.

185. Stephan, K. E., Hilgetag, C. C., Burns, G. A., O'Neill, M. A., Young, M. P. & Kötter, R. (2000).

Computational analysis of functional connectivity between areas of primate cerebral cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **355**, 111-126.

186. Sporns, O., Chialvo, D. R., Kaiser, M. & Hilgetag, C. C. (2004). Organization, development and function of complex brain networks. *Trends Neurosci.* **8**, 418-425.

187. Eguíluz, V. M., Chialvo, D. R., Cecchi, G. A., Baliki, M. & Apkarian, A. V. (2005). Scale-free brain functional networks. *Phys. Rev. Lett.* **94**, 018102.

188. Paré, D., Shink, E., Gaudreau, H., Destexhe, A. & Lang, E. J. (1998). Impact of spontaneous synaptic activity on the resting properties of cat neocortical pyramidal neurons *in vivo*. *J. Neurophysiol.* **79**, 1450-1460.

189. DeFelipe, J. & Fariñas, I. (1992). The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs. *Prog. Neurobiol.* **39**, 563-607.

190. Hô, N. & Destexhe, A. (2000). Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons. *J. Neurophysiol.* **84**, 1488-1496.

191. Wiesenfeld, K. & Moss, F. (1995). Stochastic resonance and the benefits of noise: from ice ages to crayfish and SQUIDs. *Nature* **373**, 33-36.

192. Destexhe, A., Rudolph, M., Fellous, J. & Sejnowski, T. (2001). Fluctuating synaptic conductances recreate *in vivo*-like activity in neocortical neurons. *Neuroscience* **107**, 13-24.

193. Chance, F. S., Abbott, L. & Reyes, A. D. (2002). Gain modulation from background synaptic input. *Neuron* **35**, 773-782.

194. Shu, Y., Hasenstaub, A., Badoual, M., Bal, T. & McCormick, D. A. (2003). Barrages of synaptic activity control the gain and sensitivity of cortical neurons. *J. Neurosci.* **23**, 10388-10401.

195. Rudolph, M. & Destexhe, A. (2003). A fast-conducting, stochastic integrative mode for neocortical neurons *in vivo*. *J. Neurosci.* **23**, 2466-2476.

196. Wei, D. S., Mei, Y. A., Bagal, A., Kao, J. P., Thompson, S. M. & Tang, C. M. (2001). Compartmentalized and binary behavior of terminal dendrites in hippocampal pyramidal neurons. *Science* **293**, 2272-2275.

197. Mel, B. W. (1994). Information processing in dendritic trees. *Neural Computation.* **6**, 1031-1085.

198. Softky, W. (1994). Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* **58**, 13-41.

199. Moore, G. P., Perkel, D. H. & Segundo, J. P. (1966). Statistical analysis and functional interpretation of neuronal spike data. *Annu. Rev. Physiol.* **28**, 493-522.

200. Rao, R., Olshausen, B. & Lewicki, M. (eds.) (2002). *Probabilistic Models of the Brain*. MIT Press, Cambridge, MA.

201. Rudolph, M. & Destexhe, A. (2001). Do neocortical pyramidal neurons display stochastic resonance? *J. Comput. Neurosci* **11**, 19-42.

202. Rieke, F., Warland, D., de Ruyter van Steveninck, R. & Bialek, W. (1997). *Spikes: Exploring the Neural Code*. MIT Press, Cambridge, MA.

203. Marre, O., Baudot, P., Levy, M. & Frégnac, Y. (2005). High timing precision and reliability, low redundancy and low entropy code in V1 neurons during visual processing of natural scenes. In: *Soc. Neurosc. Abstr. 285.5., Washinton D.C.*, p. 285.5. Washinton D.C.

204. Ashby, W. (1947). Principles of the self-organizing dynamic system. *J. Gen. Psych.* **37**, 125-128.

205. Ashby, W. (1956). *An Introduction to Cybernetics.* Chapman and Hall, London.

206. Langton, C. (1990). Computation at the edge of chaos: Phase transitions and emergent computation. *Physica D* **42**, 12-37.

207. Kauffman, S. (1993). *Origins of Order: Self-Organization and Selection in Evolution.* Oxford University Press, Oxford.

208. Bak, P. (1997). *How Nature Works: The Science of Self-organized Criticality.* Oxford University Press, Oxford.

209. Buonomano, D. V. & Merzenich, M. M. (1995). Temporal information transformed into a spatial code by a neural network with realistic properties. *Science* **267**, 1028-1030.

210. Maass, W., Natschläger, T. & Markram, H. (2002). Real-time computing without stable states: a new framework for neural computation based on perurbations. *Neural Comput.* **14**, 2531-2560.

211. Bertschinger, N. & Natschläger, T. (2004). Real-time computation at the edge of chaos in recurrent neural networks. *Neural Comput.* **16**, 1413-1436.

212. Ohki, K., Chung, S., Ch'ng, Y. H., Kara, P. & Reid, R. C. (2005). Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. *Nature* **433**, 597-603.

213. Dehaene, S. & Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition* **79**, 1-37.

214. Logothetis, N., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412**, 150-157.

215. Grinvald, A. (2005). Imaging input and output dynamics of neocortical networks *in vivo*: exciting times ahead. *Proc. Natl. Acad. Sci. USA* **102**, 14125-14126.