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The role of synapses in cortical computation

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Summary

The synapse, first introduced as a physiological hypothesis by C. S. Sherrington at the close of the nineteenth century, has, 100 years on, become the nexus for anatomical and functional investigations of interneuronal communication. A number of hypotheses have been proposed that give local synaptic interactions specific roles in generating an algebra or logic for computations in the neocortex. Experimental work, however, has provided little support for such schemes. Instead, both structural and functional studies indicate that characteristically cortical functions, e.g., the identification of the motion or orientation of objects, involve computations that must be achieved with high accuracy through the collective action of hundreds or thousands of neurons connected in recurrent microcircuits. Some important principles that emerge from this collective action can effectively be captured by simple electronic models. More detailed models explain the nature of the complex computations performed by the cortical circuits and how the computations remain so remarkably robust in the face of a number of sources of noise, including variability in the anatomical connections, large variance in the synaptic responses and in the trial-to-trial output of single neurons, and weak or degraded input signals.

Introduction

The analyses of the structure and function of the synapse rank amongst the highest achievements of modern neuroscience. The original physiological discoveries that led to the formulation of the concept of the synapse raised many deep questions that remain to be answered. Some of these important questions relate to the integration of synaptic input by single neurons within a network. In the neocortex, the circuits are strongly recurrent. This raises especial problems for the analysis of synaptic interactions and for attempts to develop synthetic, simplified models that effectively capture basic principles of cortical operation. In this paper we discuss the development of ideas of cortical computations by synapses and review the experimental data in support of these ideas. Finally, we provide a synthetic account of the actions of synapses in the recurrent circuits of the neocortex and discuss their importance in cortical computations.

Synapse as a physiological hypothesis

The concept of the synapse, that so physical of junctions between neuron and neuron, was an historical imperative demanded by physiologists at the close of the nineteenth century. The word 'synapse' was first introduced by Sherrington (1897) in his contribution to the section on the 'Central Nervous System' in Foster's 7th edition of *A Text Book of Physiology* in 1897. 'Synapse' ('clasp') was actually coined by the Euripidean scholar Verrall, as a more elegant and grammatically tractable alternative to Sherrington's suggestion of 'syndesm' ('connection'; see Fulton, 1949). The physiological controversies surrounding the synapse: whether transmission was chemical or electrical (see Eccles, 1964; Whitteridge, 1993), were well in the future. Meanwhile, Sherrington and Foster's introduction of the term 'synapse' and its associated functional implications provided physiologists with a means of explaining what Foster called the 'busy time' of the spinal cord, and enabled them to identify mono- di- and polysynaptic reflexes. Neuroanatomists, then still embroiled in the controversy of the neuron doctrine, however, were slow to accept the term. Ramón y Cajal, for example, minutely described the morphology of axonal boutons, but the word 'synapse' does not appear once in the edited English translation of his lengthy autobiography (Ramón y Cajal, 1989). He also made no attempt to identify the possible classes of inhibitory neurons that

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physiologists, by the time of his writing, had clearly shown to exist as a separate functional class.

The hypothesized existence of the synapse provided Sherrington with an explanation for how postsynaptic excitation and inhibition might be effected. In his book of 1906, *The Integrative Action of the Nervous System*, Sherrington explained that by designating a set of central afferent terminations on a motoneuron as specifically 'inhibitory' he meant that changes in stimulus intensity, or mode of stimulation of these afferents produced only inhibition. He argued that inhibition, "in all probability is ... situated at points of synapsis". Thus, Sherrington's introduction of the concept of a 'synapse' was an important stepping stone in his work to establish that inhibition was an active process, not simply an absence of activity, and that inhibition acted at a particular point in time and space. However, for the origin of this concept of active inhibition in tandem with active excitation, Sherrington credits Descartes (see Sherrington, 1940, p. 186). This same issue is of direct relevance in understanding the control of excitation in the neocortical circuits.

The transference of these fundamental concepts of synapses and inhibition and excitation to other parts of the brain, especially the cerebral cortex, were surprisingly slow. Anatomically, terminal boutons were first convincingly demonstrated in the cerebral cortex by Meyer and Meyer (1945). In his discussion of the circuits of the neocortex, Lorente de No (1949) makes no mention of synaptic inhibition. Only with the development of intracellular recording methods was evidence presented that inhibitory synapses were present in the neocortex. The earliest intracellular recording, made by Albe-Fessard and Buser (1953, 1955) from cortical neurons showed hyperpolarising events that were so much longer than the inhibitory post synaptic potentials (ipsps) seen in the spinal motoneurons that their genuineness as synaptic events was initially doubted. However, antidromic stimulation of the Betz cells in the cat's motor cortex during intracellular recording by Phillips (1959) demonstrated convincingly the existence of recurrent excitatory and inhibitory synapses at the level of single neurons.

The advent of the era of the electron microscope confirmed the hypothesis that the terminal boutons were the sites of the synapses. Gray subsequently established the morphological criteria for distinguishing these two types in the electron microscope (EM) in the neocortex that are still used today (Gray, 1959). These two morphological types, called type 1 and type 2, correlate with the excitatory and inhibitory synapses respectively (Uchizono, 1965), and confirm Sherrington's early hypothesis. These ultrastructural findings provided one of the hooks to which current concepts of the operations of synapses attach. The development of the electron microscope as a tool of the neuroanatomists triggered the beginning of the modern era of research on the microcircuitry of the neocortex, which began with a series of papers that used the classical technique of Golgi-staining to identify the different morphological types of neurons in the cortex (e.g., Valverde, 1971; Lund, 1973; Szentágothai, 1973; Jones, 1975).

It is an interesting question why these modern Golgi studies had such an impact, given that Ramon y Cajal, Lorente de No and others luminaries had applied the same technique to the same material for their classical studies. The answer is that the view provided by the EM of the ultrastructure of neurons and their synaptic input led to a need to identify the sources of the images seen in the high magnification of the electron microscope (Jones, personal communication). Thus the modern Golgi studies were certainly more direct in their approach and provided more detailed descriptions of the different cell types in order to match their light appearance to the patterns seen in the electron micrographs. Technical developments allowed the ultrastructure of Golgi-stained neurons to be studied in the electron microscope (Blackstad, 1975; Fairén *et al.*, 1977). It is clear that these studies planted the seeds for the rich harvest of anatomical and neurochemical data we now have for cortical neurons.

Synapses as elementary devices for computation

While many careful experimental studies have added greatly to our knowledge of the details of excitatory and inhibitory neurons and their synaptic connections, such analyses as these provide only the elemental functional units of the cortical circuits. If we wish to understand the collective actions of synapses and their consequences, then we need to confront the same fundamental questions about the excitatory and inhibitory synapses faced by Sherrington and his peers in studying the spinal reflexes. In modern terms, we need to understand the computations being carried out within the neural circuits. Computation, of course, is ultimately a physical process, whether it is carried out by neurons or by transistors, and necessitates that elements necessary for the computation be brought together at the same physical locus. This necessity has been somewhat misunderstood in the light of modern notion that computations in the brain are carried out in a distributed and parallel fashion. Parallel paths do converge in the brain. Sherrington conceived this in synaptic terms as a convergence towards a final common path: the means of the convergence of the inhibitory and excitatory pathways was through their synapses formed with their target neuron (see below). Thus, from studies of the spinal reflexes, Sherrington (1908) concluded

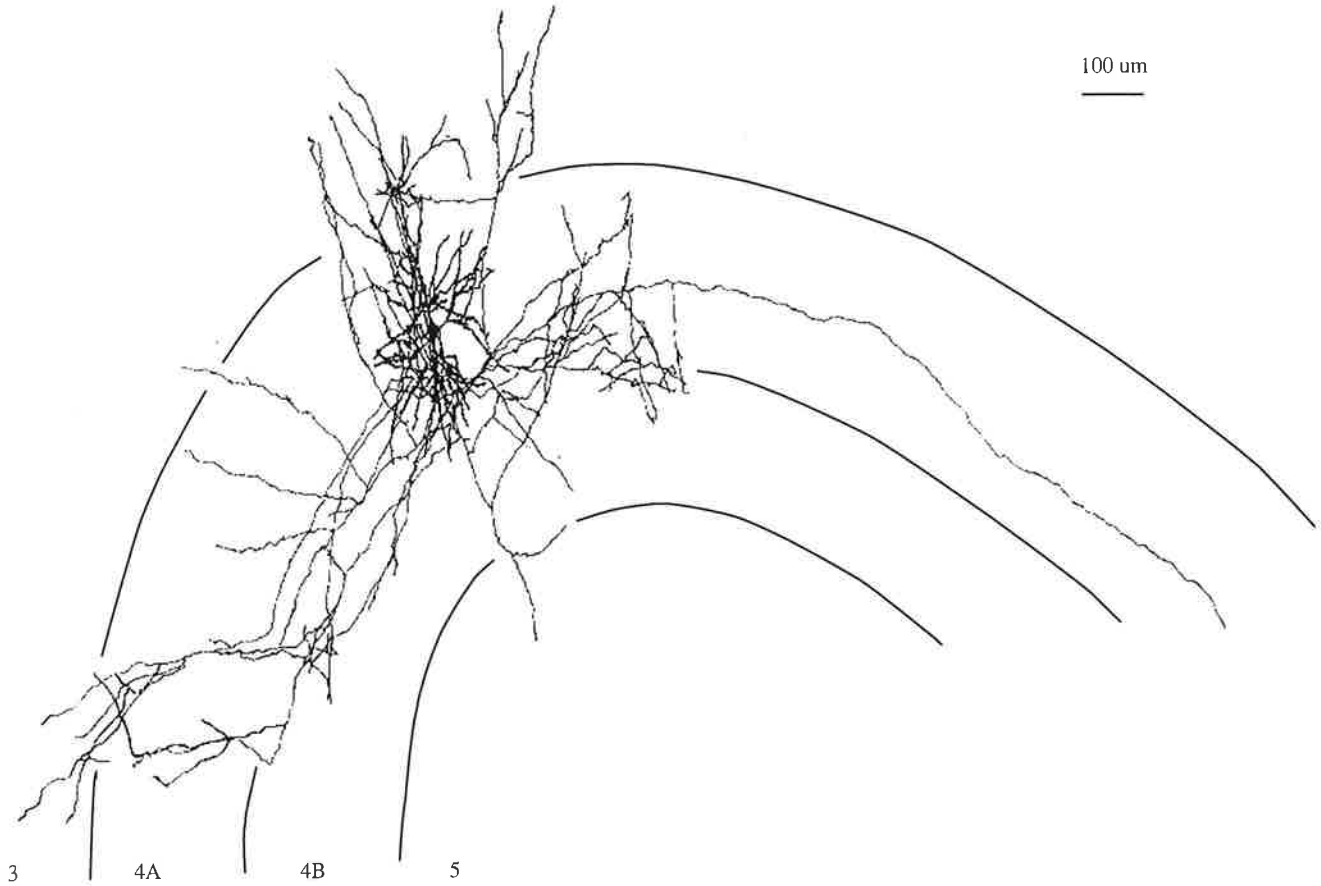

Fig. 1. Spiny stellate neuron of layer 4A of cat visual cortex. These neurons are the major recipients of monosynaptic excitation from the lateral geniculate nucleus and have simple receptive fields. As in this example, their dendrites are largely confined to layer 4 and their axonal arborisation is mainly in layers 3 and 4.

excitation and inhibition add up algebraically:

> The net change which results there when the two areas are stimulated concurrently is an algebraic sum of the plus and minus effects producible separately by stimulating singly the two antagonistic nerves.

This was the important first step towards developing a theoretical account of the computations being implemented by the interaction of inhibitory and excitatory synapses.

Arithmetic operations of synapses: linear summation

Theoretical studies of computations in neocortical neurons stem from the investigations on the subthreshold biophysical properties of excitation and inhibition that might lead to logical or arithmetic operations of the nerve cell (Blomfield, 1974; Jack *et al.*, 1975; Rose, 1977; see also Koch & Poggio, 1985). The synaptic events are in some sense the elementary 'bits' of the brain. In neural modelling, each synapse performs a probabilistic multiply-add. The multiplication factor is given by the synaptic weight while the addition occurs in the dendrite. The probabilistic element derives from the fact that at any one central synapse, a presynaptic spike only causes the release of a synaptic vesicle with a given probability (see Jack *et al.*, 1990). Real synapses, of course, have additional interesting behaviours, not only because of their dynamic properties, which are determined by the receptors and ion channels, but because they are modifiable over a range of milliseconds to years. In addition to dynamics and learning, synaptic interactions on the dendritic tree could compute a large range of logical functions. These synaptic interactions could be carried out by very local operations, involving only one or a few synapses (e.g., the *synaptic microcircuits* of Shepherd 1972, 1978). Both pre- and postsynaptic mechanisms contribute to the variety of physiological responses produced by individual synapses.

Sherrington's view is the simplest: neurons simply sum algebraically the voltages generated by the excitatory and inhibitory synapses they receive. If the sum of the excitation (pluses) and inhibition (minuses) exceeds the action potential threshold, the neuron produces an output. In such simplified model neurons, referred to as integrate-and-fire neurons, the dendritic tree acts a linear device to convert input current into firing frequency. The important corollary of the

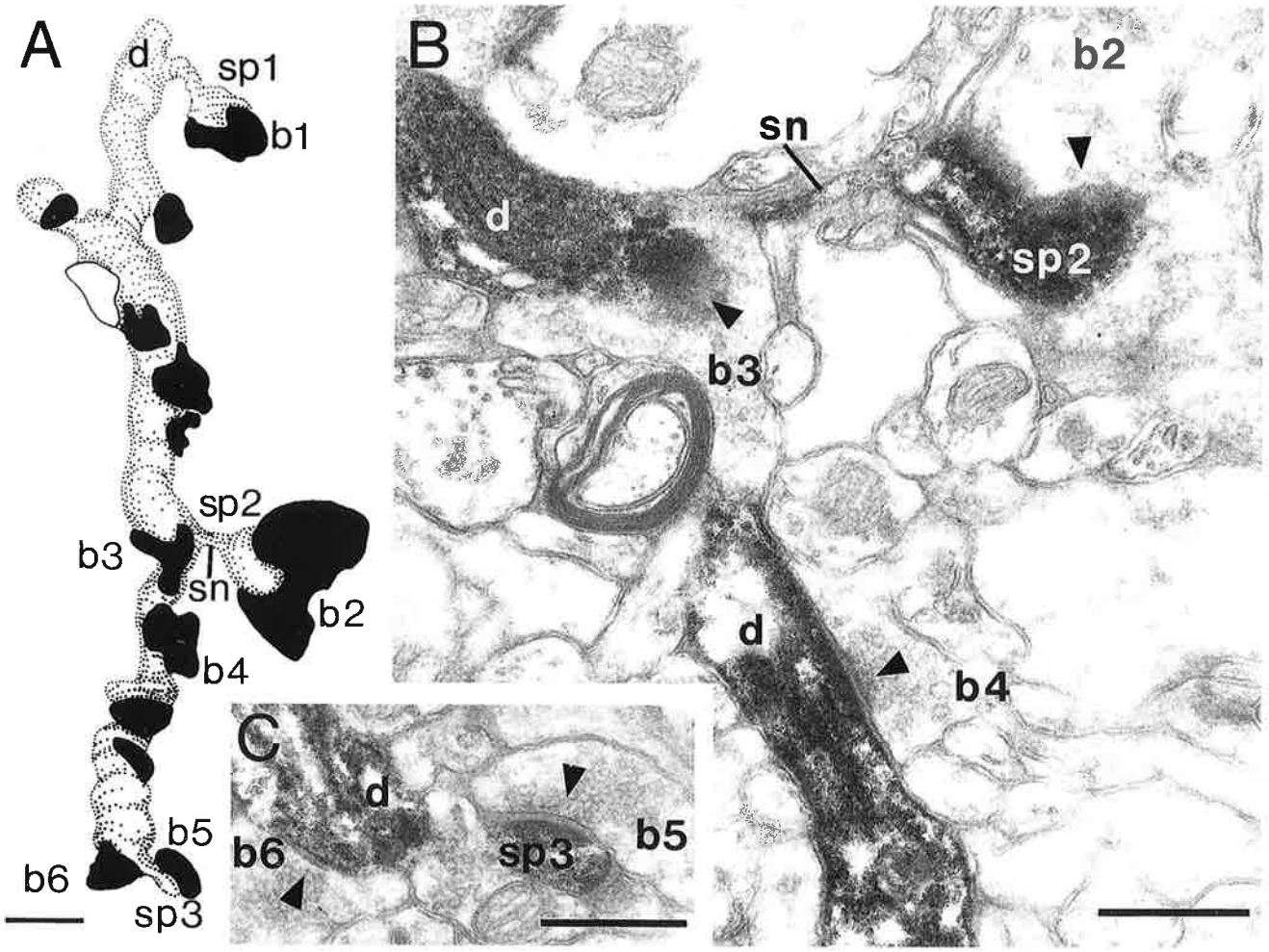

Fig. 2. (A) Reconstruction of distal dendrite of a spiny stellate neuron in layer 4 of cat visual cortex showing synaptic boutons (black = forming Gray's type 1 synapses, white = forming Gray's type 2 synapses), annotated features can be seen in the micrographs. Spine 3 (sp3) is proximal, spine 1 (sp1) is more distal. (B) An electron micrograph taken from a point about midway along the length of the reconstruction in (A). A slender spine neck (sn) gives rise to the spine (sp2), which forms a type 1 synapse (arrowhead) with a large bouton (b2). The dendritic shaft (d) forms type 1 synapses with boutons b3 and b4 (arrowheads). (C) The dendritic shaft (d) forms a type 1 synapse (arrowhead) with b6, which is very close to the point at which a small spine (sp3) emerges. Bouton b5 forms a type 1 synapse (arrowhead) with sp3 and the dendritic shaft (d) forms a type 1 synapse (arrowhead) with bouton b6. Scale bars (A) = 1 μm; (B, C) = 0.5 μm.

algebraic summing is that both inhibitory and excitatory processes are graded. The solution of the equation depends on the relative magnitude of the opposed processes. If the excitation is intense, then threshold will be reached even in the face of strong inhibition. Since the discharge rate of the neuron itself depends on the magnitude of the net excitatory current, once threshold is reached, the sum of the synaptic current of the excitatory and inhibitory synapses will continue to determine the firing frequency.

There is evidence for linear summation of synaptic input within the receptive fields of simple cells in the visual cortex of the cat. These neurons are found mainly in or near the zones of thalamic input to the visual cortex (Fig. 1). When tested with sine wave grating these neurons behave approximately as linear filters (Movshon *et al.*, 1978). Or more precisely, a sine wave input to these neurons gives a spike output that is halfway rectified. The rectification is explained by the action potential threshold: the underlying membrane potential is a sine-wave that passes through the action potential threshold to produce the rectified output signal. Such linearity is a feature only of neurons with simple receptive fields, since the other varieties of receptive fields – complex and end-inhibited, are not linear. However, the very fact that there is a class of neurons that exhibits quasi-linear behaviour is a puzzle, because in addition to the action potential threshold there are so many sources of non-linearities in neurons.

Convergence of synaptic pathways on single neurons

A model system for studying synaptic interactions in the neocortex is layer 4 of sensory cortex, which is the main zone of termination of the axons of the relay neurons of the thalamus. It was Hubel and Wiesel (1962) who not only discovered that a profound transformation in the receptive field properties of neurons occurs within layer 4 of cat visual cortex, but also offered a powerful explanatory model of the means by which the centre-surround receptive fields of the relay neurons of the visual thalamus (principally the lateral geniculate nucleus) are transformed into the simple receptive fields of layer 4 neurons. The computations carried out within layer 4 of the primary visual cortex has, and continues to be, one of the most active and important (and occasionally contentious, see below) areas of cortical research.

Although it was well known on anatomical and electrophysiological grounds that neurons with simple receptive fields form synapses with the specific afferents of the dorsal lateral geniculate nucleus of the thalamus (see Martin, 1984, 1988), these synapses only contribute a minority (less than 20%; see below) of the excitatory synapse formed with the layer 4 neurons. The remaining synapses are largely from intracortical sources. Recent detailed mapping of the synapses formed with the dendrites of the spiny stellate neurons of layer 4 (Fig. 1; Ahmed *et al.*, 1994; Anderson *et al.*, 1994) have provided the first quantitative estimates of the contribution of synapses from sources other than the lateral geniculate nucleus. Figure 2 illustrates the rich synaptic input to the distal portions of the spiny stellate cells' dendrites. An analysis of the size and location of the boutons that form synapses with the spiny stellate dendrites (Ahmed *et al.*, 1994) indicated that the small boutons that form Gray's type 1 synapses (filled boutons, Fig. 2) with the dendritic shaft derive mainly from the layer 6 pyramidal cells. Other spiny neurons within layer 4 itself provide most of the medium sized boutons that form Gray's type 1 synapses with dendritic spines. Only about 6% of the Gray's type 1 synapses formed with spiny stellate dendrites originated from the lateral geniculate nucleus. These synapses are formed by the largest boutons (e.g. b2 in Fig. 2).

The small percentage of synapses from the relay cells of the lateral geniculate nucleus is in general agreement with other estimates. (Garey & Powell, 1971; LeVay, 1986; Peters & Payne, 1993). Two studies have reported substantially higher numbers of 22–28% (LeVay & Gilbert, 1976; Einstein *et al.*, 1987). So much higher percentages are surprising, given that the tracers used in these studies were radiolabelled amino-acids, which are acknowledged to be less sensitive tracers than the wheat-germ agglutinin used by LeVay (1986) who obtained a figure of only 5% in this later study. LeVay (1986) offered several possible technical reasons for the discrepancy between his two studies and concluded that the estimate of 28% may be too high and the estimate of 5% too low! Further work with better techniques obviously needs to be done if the precise number is to be established for the neuropil of layer 4, but the estimate for the spiny stellate dendrites clearly indicates that other cortical neurons provide the major part of the found 4000–5000 excitatory synapses on spiny stellate dendrites. The inhibitory synapses arise entirely from cortical neurons and are distributed about 50 : 50 between the soma-proximal dendrites and the distal dendrites. The smooth neurons (basket cells) of layer 4 also receive excitatory input from the same sources – the lateral geniculate nucleus (LeVay, 1973; Martin *et al.*, 1983; Freund *et al.*, 1985; Einstein *et al.*, 1987), layer 6 pyramidal cells (McGuire *et al.*, 1984; Somogyi, 1989), from other layer 4 neurons (Anderson *et al.*, 1994b), and a tiny input from the claustrum (LeVay, 1986). The quantitative contribution of each different source remains to be determined for the basket cells.

How these anatomical figures translate into function is of course a major question. Stratford and colleagues (1989) have suggested that the presence of multiple classes of synaptic input might enhance the computational power of cortical neurons if the synapses show different efficacies and time courses. Stratford and colleagues (1996) have recorded from layer 4 of cat visual cortex maintained *in vitro* to determine whether this is so for spiny stellate cells. The recorded single fibre inputs to the same class of spiny stellate cells that were studied anatomically by Ahmed and colleagues (1994). They used both extracellular 'minimal stimulation' techniques and intracellular recordings between pairs of cortical neurons to examine the excitatory connections in layer 4 neurons and between the layer 6 pyramids and the layer 4 neurons. Because the axons of the geniculate relay cells were severed, intracellular recordings could obviously not be made between pairs of geniculate relay neurons and cortical neurons. However, single cut fibres of geniculate relay neurons could be electrically stimulated within the slice by extracellular bipolar electrodes. Together these techniques revealed the existence of three functionally distinct classes of fast excitatory synaptic input to the spiny stellate cells of layer 4. These three classes differed not only in basic attributes, such as conduction velocity and refractoriness, but also in the mean amplitude and dynamics of the excitatory postsynaptic potential (epsp, Fig. 3). The peak amplitudes of the epsps evoked by the layer 6 pyramidal cells in the layer 4 spiny neurons varied from 0.08–0.8 mV, which is in the range of those previously reported for cortical neurons in other cortical layers (Mason *et al.*, 1991; Thomson *et al.*, 1993). In contrast to the paired-pulse depression more

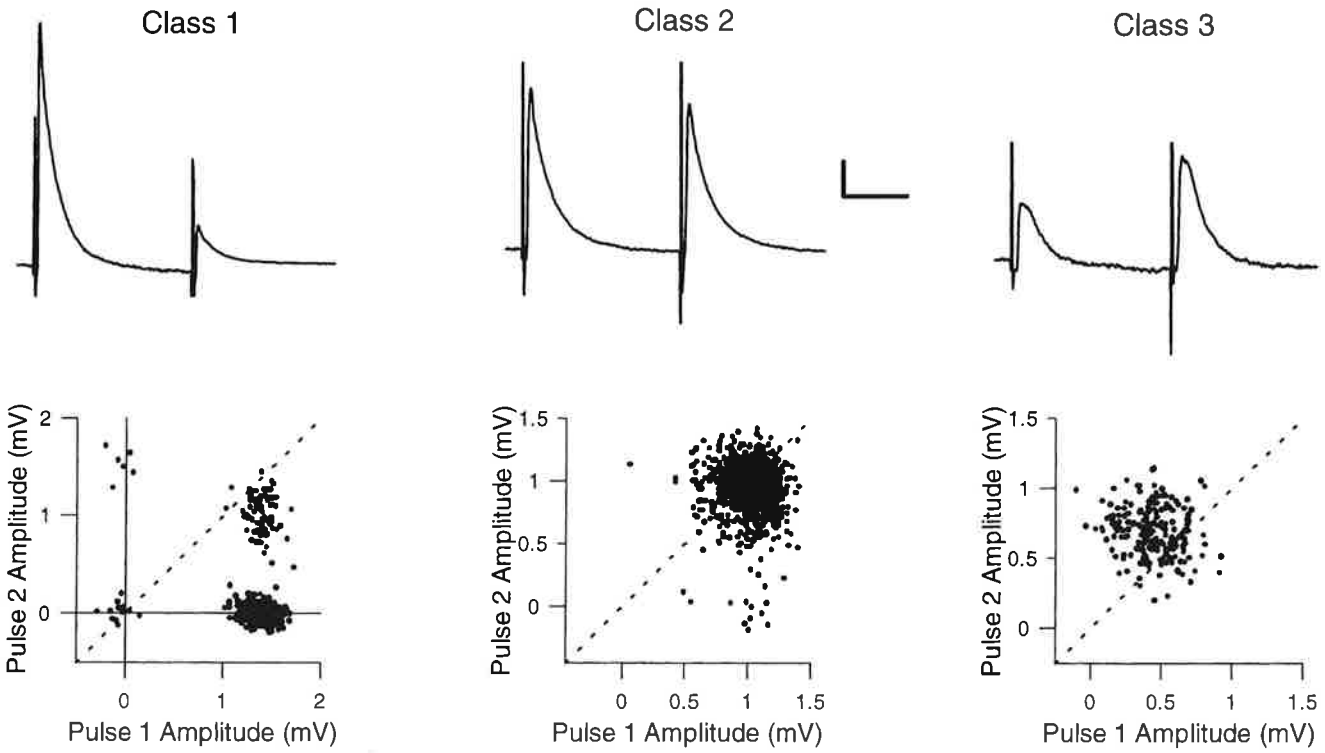

Fig. 3. Examples of the three classes of fast excitatory synaptic input recorded in spiny stellate cells in cat visual cortex *in vitro*. Upper panels: averaged traces of typical single fibre epsps for the three classes show that a paired pulse protocol (at 50 ms pulse interval) results in a net depression for Class 1 input (1650 trials), slight depression for class 2 (800 trials) and facilitation for Class 3 (1200 trials). Lower panels: paired pulse scattergrams showing the relationship between individual presentations of the paired pulse protocol. For Class 1 inputs (left) the first stimulus evoked a constant amplitude response (CV 6%) and on most occasions there was no response to the second stimulus, probably due to refractoriness in the axon being stimulated. If the second stimulus did evoke a response, it was smaller than the first (points below diagonal). If only the second stimulus evoked a response, the response was full-sized. For Class 2 (centre) the stimulus commonly evoked nearly equal-sized epsps (CV 14%). In the case of Class 3 (right) most points on the scattergram lie above the diagonal, indicating that the second stimulus usually evoked a larger response than the first. Both responses fluctuate considerably (CV 43%). Scale bars = 200 μV and 200 ms.

commonly recorded for cortical excitatory synapses, the layer 6 pyramidal synapses exhibited powerful paired-pulse facilitation. The other two classes of epsps, which originated from putative geniculocortical synapses and from spiny stellate synapses, did show depression on the paired-pulse protocol (Fig. 3).

The AMPA receptor mediated epsps originating from other layer 4 excitatory neurons were three times larger on average than those evoked by layer 6 pyramidal cells. However, the largest epsps were evoked by stimulation of the putative geniculocortical fibres, which had a mean amplitude of about 2 mV. These fibres were also the most rapidly-conducting of the three classes. Nevertheless, the most striking differences between the classes was in the variance in the amplitude of the epsp from trial to trial. The layer 6 pyramidal synapses had large coefficients of variation CVs – up to 110%. The synapses between layer 4 neurons have lower CVs – up to 40%. The putative geniculocortical synapses have astonishing low CVs – below 16% with some near zero. Thus, the primary sensory input to the visual cortex in the cat is delivered through synapses that are powerful and unusually invariant for central synapses. On face value this would imply that the geniculocortical synapses might indeed provide the dominant excitatory drive to the simple cells as suggested in the original linear summation model of (Hubel & Wiesel, 1962) for the input to layer 4.

However, these functional data have to be factored by the number of synapses actually provided by the geniculate afferents. The total number is less than 300 and of course only a subset of these originate from the relay cells whose receptive field centres align with the specific ON or OFF subfields of the simple cell (Bullier *et al.*, 1982; Tanaka, 1983; Reid & Alonso, 1995). During the activation of the simple receptive field by a visual stimulus, perhaps only tens of geniculocortical synapses will be activated as the stimulus passes over a receptive subfield, but because of the divergence and convergence within the cortical circuits (see Martin, 1984, 1988) many more cortical synapses will be

activated by the same stimulus. The net current provided by the synapses of cortical neurons is in all probability substantially in excess of the excitatory current provided by the geniculocortical synapses. Thus, the recurrent exitatory pathways in the cortex provide the means of amplifying the relatively weak and noisy signal delivered by the geniculocortical synapses. This manner of operation, encapsulated in the functional microcircuit proposed by Douglas and colleagues (1988) and Douglas and Martin (1991) receives strong support from physiological studies showing that the layer 6 pyramidal cells provide an augmenting response to the simple cells (Ferster & Lindström, 1985; Stratford *et al.*, 1996), that the layer 4 neurons are connected in recurrent excitatory circuits (Stratford *et al.*, 1996), and that reducing the activity of the cortical neurons that excite layer 4 simple cells strongly depresses the response of simple cells (Grieve & Sillito, 1991; Ferster *et al.*, 1996).

Even if all these synaptic events could be summed linearly on the dendritic tree, the dynamics of the various synapses are also important in determining the linearity of the response: each presynaptic neuron sends a barrage of impulses down its axon that produces different degrees of depression or facilitation of the synapse, depending on the particular synapse and the rate of activation of the bouton (Thomson *et al.*, 1993; Markram & Tsodyks, 1996; Stratford *et al.*, 1996). Although the initial excitation to the simple cell arises from the geniculocortical fibres, this would be rapidly amplified by the addition of excitation from neighbouring layer 4 neurons and further facilitated by the augmenting activity of the layer 6 pyramidal synapses (Ferster & Lindström, 1985). It is therefore difficult to see how strict linearity could be maintained through these changing conditions.

Non-linearities on the dendritic tree

Neurons that have complex receptive fields do not exhibit the linearity seen in simple cells. Complex cells form a large proportion of the receptive field types in the primary visual cortex and form the vast majority of receptive fields in the extrastriate cortex. Although the form of the non-linearities are not well defined, non-linearities other than the action potential threshold have been proposed on theoretical grounds. For example, simply the existence of active synapses means that there are conductances distributed through the dendritic tree. These will increase the input conductance of the neurons significantly from their lowest value, derived from a passive, unstimulated dendritic tree that has been traditionally used in many theoretical simulations of synaptic action (Bernander *et al.*, 1991). The increase in input conductance could be significant when several hundred synapses are simultaneously active at physiological rates (≈ 50 spikes s^{-1}). This increases the electrotonic length of the dendrites, so that the more distal synapses become relatively less effective (Bernander *et al.*, 1991). All neurons are in this dynamic electrical state, so that in addition to the history-dependent response of the synapses themselves, the conductances activated by the synapses are elements that contribute to potentially strong non-linearities in the summation of the synaptic potentials.

The dendritic tree itself may be functionally compartmentalised so that the local interactions taking place between synapses lead to non-linear outputs (Mel, 1994). Ohzawa and colleagues (1990) have proposed a model of stereodisparity selectivity in complex cells that relies on the grouping of binocular pairs of simple cells with a squaring nonlinearity. This nonlinear grouping could be implemented by placing the synaptic input from the subunits on the same dendritic branch of the complex cell and providing some active mechanism for amplifying the current delivered to the soma when both inputs are simultaneously active.

Synapses can activate voltage-sensitive sodium and calcium conductances in the dendrites, which may also serve to amplify the synaptic inputs to different parts of the dendritic tree (Shepherd *et al.*, 1985; Huguenard *et al.*, 1989; Pockberger, 1991; Bernander *et al.*, 1994; Hirsch *et al.*, 1995; Markram & Sakmann, 1994; Yuste *et al.*, 1994). Bernander and colleagues (1994) have suggested that the active conductances could serve to linearize the synaptic inputs to avoid saturation of the dendrites by synchronous inputs. Inhibition can modify this dendritic excitation (Kim *et al.*, 1995) by reducing the sodium and calcium spikes produced by excitation of the dendrites. The timing of the response to the inhibitory synapses influences the timing of the spike generation in the dendrites and can delay or accelerate the timing of the dendritic spikes. Although these results obtained under the controlled conditions of *in vitro* recording lead naturally to theoretical considerations of temporal coding of outputs, it should be admitted that there is still deep ignorance about whether similar conditions ever prevail to control the timing of spikes *in vivo* (see Shadlen & Newsome, 1994).

The timing of spikes may be relevant to the issue of the computation role of the propagation of the spike generated at the axon hillock back into the active dendrites (Stuart & Sakmann, 1994). What the computational role actually is is presently speculative, but Yuste and Denk (1995) have found that temporal coincidence between an excitatory synaptic input and the antidromic spike produces accumulations of calcium within dendritic spines, and suggest that short term or long term modifications to the synaptic 'weight' might be enabled by this mechanism.

However, if the sodium action potential is blocked by intracellular QX-314 (Gustafsson *et al.*, 1987), the potentiation persists. Further explorations of this pairing paradigm (Markram & Tsodyks, 1996) have drawn attention to the relevance of the synaptic depression induced during trains of impulses, which may significantly alter the signal transmission properties of the synapse over short time periods. Finally, it should be recalled that even when the results of all the dendritic computations are brought together at the zone of spike generation at the axon hillock, the morphology of the dendritic tree itself shapes the pattern of firing and limits the maximum firing frequencies of the neuron with both passive dendiritc trees (Douglas & Martin, 1990) or in trees with active conductances (Mainen & Sejnowski, 1996).

Dividing with inhibitory synapses

One central idea that emerged from theoretical studies was the possibility of inhibition not simply subtracting from the excitation, as Sherrington conceived it, but dividing. This idea of divisive inhibition emerged from consideration of the biophysics of the inhibitory conductances, and their location on the dendritic tree. The inhibitory synapses act by increasing the conductance of the membrane to ions whose reversal potential is generally more negative than the resting membrane potential (Eccles, 1964). When these synapses are activated, the depolarizing effects of the excitatory synapses are, of course, opposed by the inhibitory current. However, the size of the conductance required to balance the excitatory synapses will depend on the reversal potential of the ions involved at the inhibitory synapse. If the ion has a reversal potential that is substantially negative to the resting membrane potential, as is the case for a potassium conductance (the ionophore associated with GABAb receptor), then a small increase in the conductance would be sufficient to generate an inhibitory current able to move the resting potential further from threshold and so decrease the effectiveness of the excitatory synapses. If the reversal potential of the ion is at, or near, the resting potential, e.g., the case of the chloride ionophore associated with GABAa receptor, (Eccles, 1961, 1964; Krnjević & Schwartz, 1967), then a large increase in the conductance is required to produce the same reduction in the excitation. In this case the inhibition cannot act by moving the membrane further from the resting potential. It must act by shunting the excitatory current through low resistance pathways through the membrane. Such a mechanism was observed in the crayfish by Fatt and Katz (1953). The size of the inhibitory conductances thus determine to some degree the arithmetic operations that could be performed by nerve cells.

The analysis of Blomfield on the arithmetic operations performed by cortical neurons (Blomfield, 1974) indicated that not only the size of the conductance, but the position of the synapses were important in determining the nature of the arithmetic function. If the inhibitory conductances were located proximally on the dendritic tree and were large, then the interaction between the excitatory and inhibitory synapses would be non-linear. The inhibitory conductances would 'shunt' the excitatory currents significantly and thus would appear to act 'divisively'. Small inhibitory conductances located on the proximal regions of the neuron, or inhibitory conductances located on distal portions of the dendritic tree would interact linearly with the excitatory synapses and produce the appearance that the inhibition was subtracting the excitatory current arriving at the neuron (Blomfield, 1974). Experimental evidence in favour of the non-linear inhibitory operation was not long in coming: Rose (1977) determined the orientation tuning curves of neurons in the cat's visual cortex while iontophoresing different amounts of GABA onto the neurons. GABA reduced the response of the cell, measured as spikes per trial. However the number of spikes per trial was reduced more for the optimal orientation (i.e. the strongest response) than for the non-optimal orientations. This is the result predicted by Blomfield (1974) if the inhibitory synapses are acting in a non-linear 'divisive' mode.

Complementary evidence was obtained by Morrone and colleagues (1982) who examined changes in the orientation tuning curve resulting from the addition of a conditioning stimulus at the non-optimal orientation. The non-optimal stimuli induced inhibition in the neuron and so reduced its responsiveness to the optimal stimulus. As in the case of the GABA iontophoresis, the change in the tuning curve produced by the presence of the conditioning stimulus was suggestive of a divisive rather than a subtractive inhibitory process at work. Carandini and Heeger (1994) proposed a model that uses divisive conductance changes to explain these contrast normalization effects as well as changes in simple cell response latency as a function of contrast. Dean and colleagues (1980) looked at the role of inhibition in direction selectivity. They obtained similar results, but used a synaptic rather than a pharmacological technique. Their experiments might give a more realistic view of the synaptic processes involved in the tuning of cortical neuronal responses. Nevertheless, the conclusion from both kinds of experiments is that the cortical mechanism of inhibition is divisive. However, it should be clearly pointed up that the theory applies to the subthreshold responses of neurons, whereas the experimental analyses were of the action potential discharge.

Synaptic logic

It has also been suggested that the local interaction of small numbers of excitatory and inhibitory synapses can implement logical functions of OR and AND (Shepherd & Brayton, 1987), and AND-NOT (Koch *et al.*, 1982). Koch and Poggio considered the case of shunting synapses located on the head of a spine, where they would be able to interact directly with the excitatory input arriving on the same spine head (Koch & Poggio, 1987). They showed through simulation that the non-linear interactions between the inhibitory and excitatory synapse on the same spine could emulate an AND-NOT logical operation. Such an operation had been suggested by Barlow and Levick (1964) in their original analysis of directionality in the rabbit retina. This operation would occur at a site that was electrically distant from the soma and thus might be relatively invisible to a micro electrode located at the soma. They referred to this as 'synaptic veto' or 'silent' inhibition. Other non-linear functions such as multiplication or division can be mediated by different synaptic receptor types or voltage-dependent membrane conductances in the dendrites. For example the NMDA or dendritic calcium channels can both implement a form of multiplication (Mel, 1993, 1994).

Extensive experimental tests of this and similar propositions (Douglas *et al.*, 1988; Berman *et al.*, 1991; Dehay *et al.*, 1991; Pei *et al.*, 1991; Ferster & Jagadeesh, 1992) have indicated that as a general class, the varieties of shunting inhibition proposed by theorists do not occur in practice. The physiological experiments employed a variety of techniques to examine the magnitude of the shunt produced during visually-evoked or electrically-evoked inhibition *in vivo*. The results of all the studies agreed that the increase in conductance during visually-evoked inhibition is only about 20%, which is certainly too small to be used for shunting all the excitatory current that arrives (see below and Fig. 6). Dehay and colleagues (1991) used anatomical techniques to explore the hypothesised spine-based mechanism. They examined the spines that were the postsynaptic targets of the geniculate relay cells. If a synaptic veto mechanism were located on a spine head then most spines that formed synapses with the axons of geniculate relay cells should form a second synapse with an inhibitory cell. Dehay and colleagues (1991) found that only 7% of the population of spines had such a dual input. Thus, the vast majority of geniculate input cannot be gated at the level of the spine.

The conclusion of the intracellular recording and ultrastructural studies is that synaptic veto, or 'silent' inhibition, cannot explain the experimental findings with respect to subfield antagonism of simple cells, or their orientation selectivity and directionality. The problem remains, however, of how to account to the extracellular observation of a divisive, shunting type of inhibition for both orientation and direction selectivity (Dean *et al.*, 1980; Morrone *et al.*, 1982). Thus, some fundamental disparity was evident at the level of the experimental data, for which there was no reasonable theoretical analysis. In the final section below we outline a synthetic model that offers an explanation of the paradoxes between the biophysics of single cells and their performance with visual stimuli. The model remains true to the principles of connectivity provided by the anatomical discoveries and provides some insights into the computational advantages offered by such recurrent circuits.

Recurrent circuits in theory

The fundamental formulation of our model of cortical microcircuits (Douglas *et al.*, 1989, 1995; Douglas & Martin, 1991) is that large number of excitatory and inhibitory neurons are connected in recurrent circuits. The details of the overall pattern synaptic connections from one cell to another have been explored in a simplified model of the connections between layer 4 spiny stellates. The chief point of interest is whether the pattern of excitatory connections between spiny stellate neurons might be a significant factor in determining the stability of the recurrent circuit.

If we take the radial density of synaptic boutons generated by the axon collaterals of a single spiny stellate neuron, then the primary cluster of boutons extends from the soma to a distance of about 500 μm with additional clusters lying further from the soma. The radial density of synaptic boutons on the cluster surrounding the neuron can be characterised by a three dimensional Gaussian distribution. The standard deviation of the distribution of the primary cluster is about 100–150 μm (Douglas *et al.*, 1995). Thus, the major output of the neuron is to its nearest neighbours. However, the neuron's neighbours have similar morphology and thus the neuron may receive excitatory connections back from neighbours to which it has given connections. Such 'first-order' reciprocal connections between pairs of neurons have been reported between pyramidal cells in rat visual cortex, for example Mason and colleagues (1991). These constitute the most direct circuit for positive feedback. Of course, di- and polysynaptic loops may be constituted in the same way, but at present the circuits are unknown.

In a similar vein, the inhibitory neurons may also be connected within such loops to produce a negative feedback circuit. The more smooth neurons that are reciprocally connected to a given spiny stellate neuron, the higher will be the inhibitory current received by a given spiny stellate neuron. If there are many inhibitory cells receiving excitatory input from the spiny stellate, each of which provides an inhibitory

connection back to that spiny stellate, then the convergence of inhibitory synapses will produce a recurrent inhibition of sufficiently large magnitude to prevent the spiny stellate from firing altogether, or at least reduce greatly the degree of amplification allowed by the recurrent excitatory circuits. Thus the overall 'gain' of the system is to some degree embedded in the physical connections. Of course, issues of the physiology of synapses and neurons are also important, but these must act within the context of the circuit. The problem for theoretical analyses of these properties is that so little is known about the three dimensional organization of neurons and rules governing their synaptic connections. However, simplified models based on the biology can provide some view of the significance of the problem.

The number of neuron pairs involved first-order connections depends on several factors, including the density of synapses and any specificity of innervation there might be. We have derived these data from an analysis of the input to the spiny stellate neurons (Ahmed *et al.*, 1994; Anderson *et al.*, 1994a; Douglas *et al.*, 1995) and from counts of neuronal densities in layer 4 (Peters & Payne, 1993). In layer 4 there are approximately 4×10^4 spiny stellate cells per cubic millimeter. Of the 5000 synapses formed with the soma and dendrites of spiny stellate cells, 1000–1500 of which probably derive from other spiny stellates. Each makes about 5000 synapses, of which about 1200 are made with other spiny stellate cells. We have assumed that about one third of the boutons occur in the primary cluster and that they are homogenously distributed in the three-dimensional space. If we make the simplifying assumption that local connections are made between spiny stellates on a random basis (Braitenberg & Schüz, 1991), then the number of such first-order recurrent connections can be estimated precisely from the density of the synaptic boutons and the total number of such synapses made with the dendrites of the target neuron.

Given these statistics and these simplifying assumptions, we have calculated that for axonal arbors whose primary clusters have standard deviations of 100 μm, the spiny stellate neuron would participate in 117 first-order recurrent connections. If the standard deviation of the primary cluster increases to 150 μm, which effectively reduces the synaptic bouton density, then a given spiny stellate would participate in only 34 such pairs (Douglas *et al.*, 1995). While it is obvious that the more first-order connections a given neuron is involved in, the stronger will be the synaptic current it receives from those neurons, this is a very interesting case for consideration, because the effects of the feedback may differ significantly between the two cases. It might be expected intuitively that if the excitatory current is sufficient to drive the interconnected neuron to threshold, then, in the absence of any inhibition, the neurons in the network will be driven to their maximum discharge rates. Inhibition, it seems, is essential. Surprisingly, however, analysis of these first-order excitatory networks indicates that in some configurations they can be stable, in the sense that they remain bounded without the restraint of saturation, without the addition of inhibition. The analysis of the conditions under which this is achieved is explored in the following section. The essential problem is how to control the gain, or amplification, that is inherent in these recurrent excitatory circuits.

Electronic equivalent circuit for recurrently connected neurons

These ideas of recurrence, amplification and control of gain, are encapsulated in a simple electronic circuit that represents a recurrent network of excitatory and inhibitory neurons. The representation is simple, but the biology it captures is far from simple. The excitatory neurons are represented as single conductances (G, in Fig. 4). The current (I_g) dissipated through this conductance (G), generates a voltage (F) that represents the 'firing frequency' of the neuron. Thus the current-voltage relationship gives a straight line of slope $1/G$ (Fig. 4). Conservation of current demands that the current entering the 'neuron' is exactly matched by the current leaving the neuron via the passive membrane conductances and the action potential conductances, which are very much larger than the membrane conductances. The action potentials themselves are thus significant sinks of synaptic current in this model. The source of the excitatory current is from two pathways: one from a feedforward input, which represents the geniculate input to layer 4, the second being a feedback pathway, which represents the intracortical recurrent excitatory circuits. In addition, there is a recurrent inhibitory pathway that arises from the cortical basket cells, which themselves are driven by the cortical excitatory neurons.

The recurrent pathways are expressed in the electronic circuit model (Fig. 4) by two sets of otherwise identical neurons, that differ only in having synapses of opposite sign. Since all the excitatory neurons are identical, their synapses can be represented as a single lumped excitatory synapse. In the electronic circuit, this lumped synapse is approximated as a current source whose magnitude is proportional to the firing rate of the point neuron, F. This recurrent excitation generates an effective 'network conductance' α, represented in the circuit by a current source that is controlled (grey arrow) by the output voltage across the conductance, G. The $1/\alpha$ curve represents the dependence of the excitatory feedback current I_{rec}, measured in a particular neuron, on the average output rate of neurons in the population. For an external observer measuring the input

current provided to a neuron and the voltage out, it will appear as if the conductance of the neuron has decreased. The effective conductance of the neuron, G_{eff}, will be $G - \alpha$ and the slope of the current-frequency relationship will now be $1/(G - \alpha)$.

It is the relationship of this $1/\alpha$ curve to the $1/G$ curve, that is crucial to the stability of a recurrent circuit of purely excitatory neurons. As long as this curve lies to the left of the $1/G$ curve, then the circuit will remain stable because the individual neurons will be able to 'sink' all the synaptic current supplied by the feedforward and recurrent circuits. This 'sink' is provided by the action potentials themselves as explained above. In this condition the output of the network will remain proportional to the feedforward current. If the feedforward current falls to zero, the activity in the network will also rapidly fall to zero. In electrical engineering terms this means that the 'open loop' gain is less than 1. However, if the $1/\alpha$ lies to the right of the $1/G$ curve, then any feedforward current supplied to the network will be amplified by the recurrent circuit to a degree that it will increase the firing of individual neurons until they reach saturation. Under these conditions, the open loop gain is greater than 1 and there is no proportionality between the feedforward current and the output of the network. Under such conditions, stability could only be achieved through the addition of other 'sinks', for example, inhibition.

In the electronic circuit the inhibitory circuitry is similarly represented to the excitatory circuit, but in place of the α of the excitatory circuit we have a second constant, β, which, like α, also acts as a network conductance, but has the opposite sign. We treat the inhibition as a linear, hyperpolarizing current, neglecting the shunting aspects of inhibitory inputs, since they have been difficult to observe experimentally (see above). With the inhibitory circuit added, the effective conductance of the neuron, G_{eff}, is the sum of the

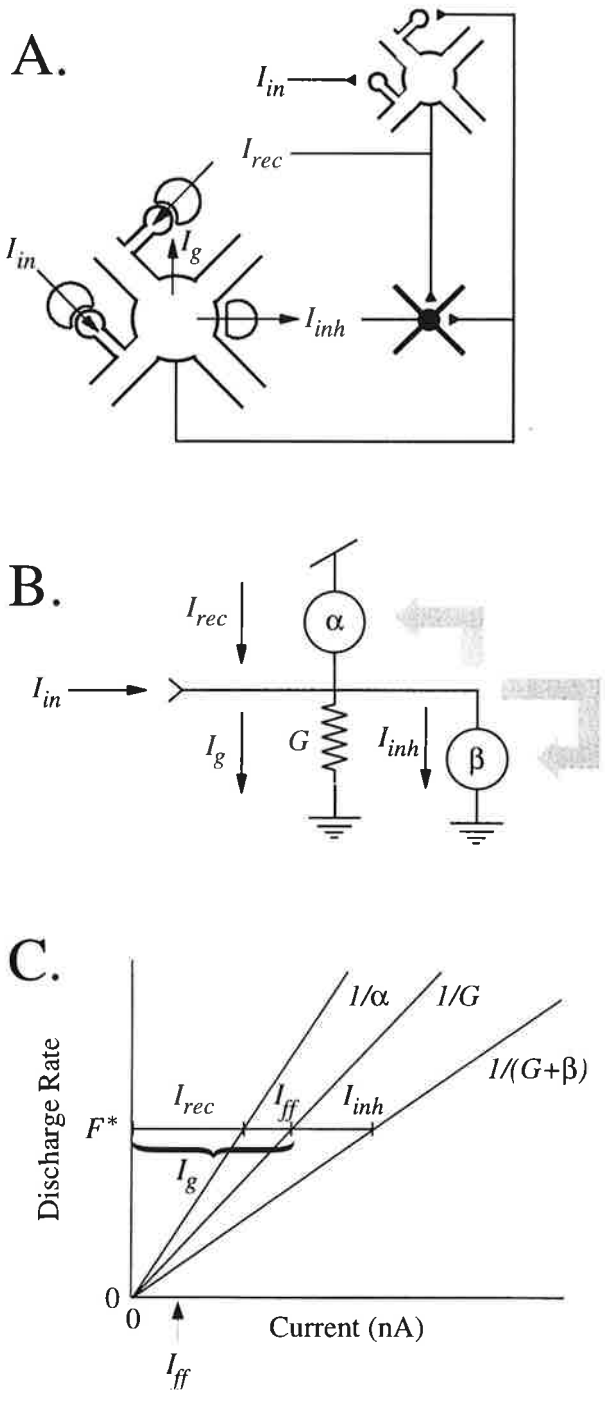

Fig. 4. A circuit for the simple cells of layer 4. (A) A spiny stellate neuron receives inward excitatory synaptic current from two sources, the synapses of the relay neurons of the lateral geniculate nucleus (I_{in}) and the synapses of other cortical neurons (I_{rec}). The basket cells of layer 4 are the source of the outward inhibitory current (I_{inh}). The frequency of firing, F, if determined by the net current (I_g) at the axon initial segment. (B) The electronic circuit analogue of the biological circuit represented in (A). The spiny stellate is represented as a single conductance G. The currents are as in (A). Grey arrows indicate the recurrent inhibitory and excitatory circuits. α represents the 'network conductance' for the recurrent excitatory circuit, β the 'network conductance' for the recurrent inhibitory circuit. (C) Current-discharge relations characterizing the behaviour of the cortical amplifier. The $1/G$ line, corresponding to the current-discharge curve, expresses the amount of current I_g that dissipated across the somatic membrane by spike currents at discharge rate F^*. The $1/(G + \beta)$ curve indicates the increased current, $I_g + I_{inh}$, required to maintain a given discharge rate in the presence of inhibition that is proportional to the output of the neurons. The $1/\alpha$ curve expresses the dependence of the excitatory feedback current I_{rec}, measured in a particular neuron, on the average output rate of neurons in the population. For any particular input current I_{ff} the steady state discharge rate F^* occurs where the equation $I_{rec} + I_{ff} = I_g + I_{inh}$ is satisfied. At F^* the input current I_{ff} is exceeded in amplitude by the recurrent current I_{rec}.

individual neuron conductance G, and the two network conductances, α, for the excitatory circuit, and β for the inhibitory circuit. These two network conductances naturally have opposite signs. The effective conductance of the neuron is therefore $G - \alpha + \beta$. The magnitude of the inhibitory current is βF and the total recurrent current arriving at the soma is given by $I_{rec} = (\alpha - \beta)F$ and the output firing frequency of the neuron, F, is given by $I_{ff}/(G + \beta - \alpha)$.

The effects of the inhibitory network on the input-output functions of the neuron can be represented graphically (Fig. 4). For an isolated neuron the current-frequency relationship is linear with a slope $1/G$. In the presence of an inhibitory network where the inhibition applied is proportional to the output of the neuron, the total current sunk by the neuron will be the sum of the load current and the inhibitory current, $I_g + I_{inh}$. Consequently, the slope of the spike frequency versus current (FI) curve will be $1/(G + \beta)$. Although the synapses themselves are linear, the change in slope of the FI curve during recurrent inhibition appears as a divisive process, because the inhibition is proportional to the output of the neuron. Interpreted physiologically, feedback inhibition that acts through approximately linear 'subtractive' synapses nevertheless generates a network conductance that appears as a shunting-like inhibition of the output of the neuron. This inhibition changes the gain of the cortical response to a given input current. This crucial insight provides the solution to the problem posed by the experimental data. It explains how shunting, or divisive inhibition can be revealed in the spike discharge of the neuron (Rose, 1977; Dean *et al.*, 1980; Morrone *et al.*, 1982), while intracellular recordings indicate the shunts associated with inhibitory events are extremely modest (Douglas *et al.*, 1988; Ferster, 1988; Berman *et al.*, 1991; Pei *et al.*, 1991) and largely induce small amplitude hyperpolarizations.

Computation of orientation

The dry abstraction of an electronic circuit may seem a long way from the actual organization and workings of the wet biology. However, the principles of operation that have been outlined above link directly to more realistic models of functions that are carried out by visual cortical neurons. The computations carried out by the neurons in layer 4 of the cat's visual cortex are amongst the most beguiling that have so far been observed in the neocortex. 'Beguiling', because while they seem quite simple and obvious, efforts to understand how the neuronal machinery is achieving its results have blunted the sharpest instruments available.

The computation that has been a canonical example for two generations of neuroscientists is that of orientation selectivity. This is the computation that transforms the non-oriented centre-surround receptive fields into the simple cells can be considered as filters that effectively 'select' a limited set of the information from the representation of the stimulus supplied to layer 4 by the relay neurons of the lateral geniculate nucleus. At the level of single cells this cortical representation may appear reduced compared to the geniculate neurons, as indicated by the select number of features to which the cortical cell responds. However each cortical cell represents a location in a multidimensional space; each neuron responds not only to a particular stimulus orientation, but also stimulus size, direction of motion, velocity, depth, and so on. Hubel and Wiesel, who first discovered this role of layer 4, also provided the 'simplest' model of the simple receptive field, of which Sherrington might well have approved: a row of geniculate relay neurons converging on a layer 4 cortical neuron, which linearly sums the excitatory synaptic currents. In their model the cardinal properties of the simple receptive field are generated entirely by the spatial convergence of the excitatory geniculate synapses whose activity is summed linearly by the poststynaptic neuron.

However, such a simple addition is insufficient account for the sophisticated processes being carried out in layer 4. For example, it is clear from such a feedforward system that the degree of orientation tuning will be highly dependent on the strength of the geniculate input and it will be very susceptible to noise. A strong stimulus presented at the non-optimal orientation should have the same effect as a weaker stimulus presented at the optimal orientation, for example. Experimentally, however, orientation tuning of cortical neurons remains largely unchanged over considerable changes in the contrast of the stimulus (Sclar & Freeman, 1982) and is surprisingly robust in the face of potentially confounding stimuli e.g., simultaneous presentations of a second stimulus at a different orientation over the same receptive field (Morrone *et al.*, 1982). Such invariance in the face of noise is in fact a cardinal property of cortical processing and visual perception. The computations to achieve invariance are clearly present even at the earliest stage of cortical processing. Hidden in the maze of synaptic connections within layer 4 are these rather powerful operations.

The computational role of the amplification mechanisms described in the sections above was explored in the context of the layer 4 simple cell (Douglas *et al.*, 1994, 1995). Models with similar recurrent architectures have recently been explored by Somers and colleagues (1995), Ben-Yishai and colleagues (1995) and Suarez and colleagues (1995). For our exploration we extended the model described above to include aspects of the local interneuronal connections of the spiny stellate neurons. The connectivity is represented in a one-dimensional array of 40 neurons, represented

as a ring of filled black symbols in Fig. 5. As determined experimentally (Ahmed *et al.*, 1994), the spiny stellate receive their major functional input from other cortical neurons and a minor input from the lateral geniculate nucleus. Following the anatomical analysis of bouton distribution described above, the connections in the model were organised so that each excitatory neuron connected to its neighbours with a strength, or weight, determined by their distance apart. Neurons that encoded similar orientations were reciprocally connected with weights that were a Gaussian function of their similarity of orientation preference (indicated by 'proximity' curve in Fig. 5). Nearest neighbours interconnected with more/stronger synapses than more distant pairs. This pattern of connections is also consistent with the ice-cube model of the functional architecture of area 17 (Hubel & Wiesel, 1977), in which neighbouring neurons have closely similar functional properties and interconnect most strongly. Although simple cells code a multidimensional space, we consider only the orientation domain. However, a model with similar has been explored for directionality and velocity (Suarez *et al.*, 1995).

We did not differentiate between the cortical component of excitation produced by spiny stellate from that of the layer 6 pyramids and we did not attempt to replicate the varieties of synaptic dynamics, because the kinetics of these synapses have yet to be specified with sufficient detail to be incorporated in a model. Thus, we used a simplified continuous output, firing rate model, rather than using detailed models of spiking neurons, with their considerable overhead in parameterization. (Note however, that the recurrent model recently simulated by Somers *et al.*, 1995, uses spiking neurons and gives similar results). The strength of the reciprocal connections between two excitatory neurons i and j is given by α_{ij}, here assumed to be a Gaussian function of the preferred stimulus angle between the coupled neurons i and j. Unlike the spiny neurons, the lateral clusters of the axons of inhibitory neurons do not connect exclusively to iso-orientation zones (Kisvarday *et al.*, 1995). Instead, they appear connect all orientation zones. Thus, in our

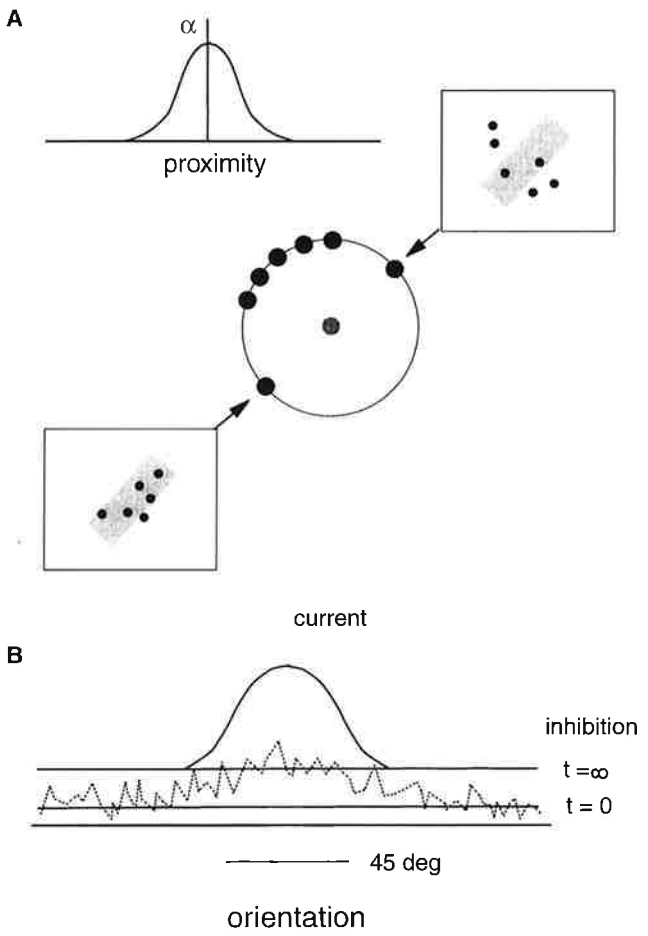

Fig. 5. Orientation tuning in the presence of noisy signal, and/or noisy connections. (A) Forty simple cells (large filled circles, examples indicated) each receive convergent feedforward excitation from a group of geniculate relay cells, whose receptive field positions (small filled circles, examples indicated) fall along an oriented axis in visual space (large rectangles). A light bar stimulus (shaded rectangle) excites the geniculate cells. If the orientation of the stimulus activates most of the geniculate cells that converge on the simple cell (e.g. lower left group) then the simple cell will be optimally excited. If however the stimulus is orthogonal to the bias of the geniculate receptive fields (upper right group), then the excitatory drive to the simple cell will be much weaker. Neurons that prefer similar orientations are located near each other and are connected reciprocally with synaptic weights (α_{ij}) that are a Gaussian function of their distance apart, as indicated in the 'proximity' curve. (B) The response of the 40 simple cells to presentation of the oriented stimulus. Cells 1–40 are plotted along the absiscae, synaptic current along the ordinate. The dashed line indicates the response of the neurons when only the feedforward geniculate input is activated. The continuous dark line indicates the response with the recurrent circuits connected. The geniculate input is noisy because the connections are imprecise and because the signal may be noisy. The level of inhibition at $t = 0$ (horizontal line) is insufficient to suppress noisy peaks at off-orientations. Nevertheless, there is a better response of simple cells near the preferred orientation, and the positive feedback is strongest there. The increased activity of preferred populations increases the average inhibition, and suppresses more of the weakly activated cells. Elimination of the outliers improves the correlations amongst the survivors, and enhances their gain (resulting in increased inhibition indicated by horizontal line $t = \infty$). This process converges on a narrow bandwidth tuning curve (solid line in B), indicating that this model is able to extract signals from noise. It does this by expressing the tuning curve implicit in the nearest neighbour rule of cortical connectivity.

model all the neurons that contribute to the recurrent inhibitory loop can be lumped into a single 'inhibitory neuron' that receives excitation from all 40 neurons and recurrently provides equal numbers of 'inhibitory synapses' to all 40. This global 'inhibitory neuron' is represented as a grey dot in the centre of the circle of Fig. 5A.

The relay neurons of the lateral geniculate provided all the feedforward current to layer 4. This component is represented in the model by the current, I_{ff} or I_{in} (Fig. 4). The pattern of the connections between the geniculate relay neurons and the simple cells was generated by drawing a random sample from an oriented binormal spatial distribution, which represented a portion of the two-dimensional visual space. The concentric centre-surround receptive fields of the geniculate relay neurons that provide a biased input to two of the simple cells, are represented by the scattered dots in the boxes of Fig. 5A. The aspect ratio of the binormal distribution was 1.6, which is typical for subfields of simple cells. The principle axis of the binormal distribution was rotated through 180°, and samples were taken at 40 different orientations within that range. These samples then provided the geniculate input to a single subfield of the simple cell (arrows from boxes in Fig. 5A). Thus, following the basic connections of the Hubel and Wiesel model, the input to the 40 simple cells is provided by a row of relay cells aligned along a slightly different principal axis to that of its neighbour. When an oriented stimulus is presented (grey rectangle in Fig. 5), it will activate most the geniculate neurons that converge on some simple cells (e.g. lower arrowed neuron in Fig. 5A), but only a few for other simple cells (e.g. upper set in Fig. 5A). This bias in the geniculate input provides for the differences in the strength of the response when the stimulus is presented, as indicated by the undulating dotted line in Fig. 5B. This line plots the response amplitude for each of the 40 excitatory neurons in the ring. The neurons most strongly excited are those whose orientation tuning provided by the pattern of feedforward connections most closely matches the stimulus orientation, but all neurons respond to some degree because the geniculate neurons respond to all orientations. Thus the population of cortical neurons expresses only weak orientation preference (Fig. 5B, dotted line).

The recurrent excitatory current was expressed in the simple electronic model as αF, because all neurons had identical connectivity. The situation in the more elaborate orientation model is more difficult to calculate, because the excitatory neurons connect to each other unequally, with strengths related to their distance apart. In addition, some of the neurons will be below threshold and so will not contribute synaptic current to the network. The synaptic current provided by a neuron to any one of its target neurons is a product of its firing frequency and the coupling coefficient α_{ij}. At the limits it is apparent that the recurrent current in a given neuron is maximal, i.e. the gain of the amplifier is greatest when all neurons connected to it are above threshold, and zero when all are below threshold. The synaptic currents arising from all the different neurons are then summed by the given target neuron.

In this circuit, the inhibitory neuron acts as a summing device and provides the same inhibitory current to all 40 spiny neurons, in proportion to the total activity in the circuit. Virtually all 40 spiny neurons are active initially, because geniculate relay neurons will response to a stimulus of any orientation (Fig. 5, dotted line). As the total activity in the network increases due to the positive feedback, the excitatory drive to the inhibitory neuron increases. Neurons that are just above threshold will thus be silenced by inhibition and they will no longer contribute to the total excitation (threshold at $t = 0$ and $t = \infty$ are indicated by horizontal lines in Fig. 5B). However, the pattern of connectivity ensures that they will continue to receive an inhibitory input, and so their threshold for activation will continue to be raised as the total activity in the circuit increases through the recurrent excitation between the remaining active members. The inhibited neurons will always be those who were most weakly driven by the stimulus and thus received the least amount of feedforward synaptic current from the geniculate relay neurons. The neurons who were most biased for the stimulus orientation will receive the most feedforward current. They will produce the most activity and re-excite each other most strongly and thus remain above threshold despite the recurrent inhibition. In this way the initially small input from the lateral geniculate relay neurons will be amplified selectively by a subgroup of the total 40 excitatory neurons to provide a robust orientation signal (continuous bell-shaped curve in Fig. 5B).

Once the stimulus is presented, the tuning of the inhibition rapidly changes from broad band to narrow band. Progressively it becomes more strongly tuned to the orientation of the remaining active neurons. At convergence, or steady state, the orientation tuning of the inhibitory neuron is that of the net tuning of the surviving active members of the excitatory group. The amount of inhibition experienced by a given neuron is obviously proportional to the number of active neurons in the network. The question naturally arises as to how long this convergence takes. Somers and colleagues (1995) have performed a detailed simulation of a recurrent circuit of layer 4 with 2205 cortical neurons and 882 geniculate relay cells and have determined the speed at which the network converges to a stable solution. Their simulations indicated that sharp orientation selectivity in the membrane potential of a given test neuron emerged just after the

test neuron produced its first spike. Neurons whose geniculate input was biased to the stimulus orientation will have a head start on those whose input bias is for a different orientation. These latter neurons therefore have to rely more on temporal integration to reach threshold, but they may never respond, because of the recurrent lateral feedback inhibition arising from activity in the optimally biased neurons. This 'delay' effect contributes to the rapid suppression of the neurons whose geniculate input is biased for non-optimal orientations, and the rapid emergence of sharp tuning in the 'winners.' In their simulations the weakest tuned cortical neuron had a stronger orientation tuning than the best tuning provided by the feedforward convergence of the geniculate relay cells.

In the recurrent configuration of Fig. 5, it is interesting to note that the role of inhibition changes over time. Initially, it is used as a means of setting a threshold to extract the best estimate of the signal arising from the visual input. Later, inhibition assists in stabilizing the recurrent excitation of the active population: as the excitation grows, so the inhibition grows proportionately and acts as a divisor. This proportionality is important in helping to maintain a balance between inhibition and excitation. Obviously, when the neuron responds, the sum of the inhibitory and excitatory currents do not cancel out, for excitation exceeds inhibition. Similarly, when the cortical neuron is shut off in the face of activity in the relay cells, the cortical inhibition exceeds the excitation. However, too much inhibition would make the response to the optimal stimulus weak, while too little inhibition may broaden the tuning curve. Because of the gain provided by the recurrent excitation, small swings in the balance between excitation and inhibition are amplified. This is a useful attribute because it makes neurons more sensitive to both the input excitatory current and reduces the amount of inhibition required to have a given effect. This result is illustrated in Fig. 6.

In models that receive all their excitation from a feedforward pathway, as in Hubel and Wiesel's simple cells, the magnitude of the inhibition has to equal that of the excitation to prevent the neuron from firing. In the case of the recurrent circuit, however, there are two components of excitation, one from the feedforward pathway and the other of larger magnitude from the recurrent pathway. Since all the cortical neurons are in the recurrent circuit, the amplification by the recurrent circuit is exactly proportional to the output of a given neuron. Similarly, the amount of current supplied by the recurrent pathway is exactly proportional to, and dependent on, the amount of synaptic current supplied by the feedforward pathway (Fig. 6). Thus, the decrease in firing of a neuron reduces the total feedback current, which further

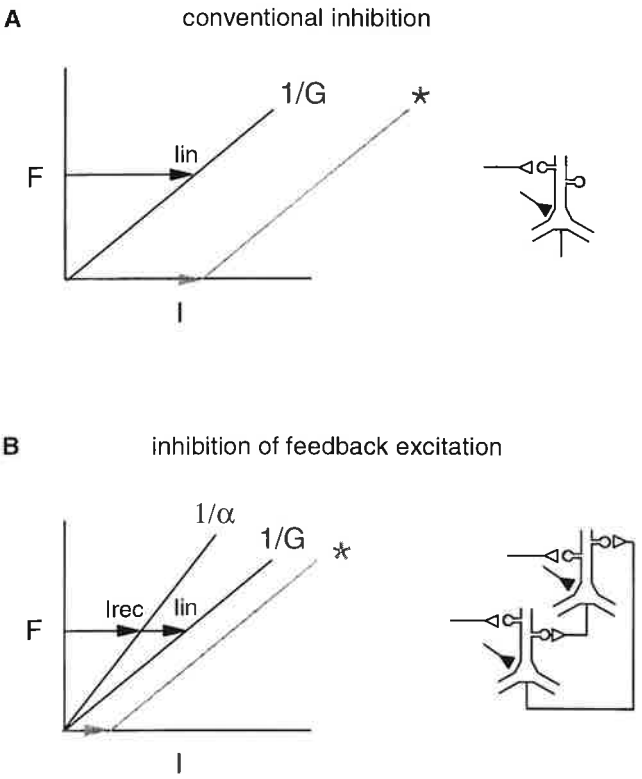

Fig. 6. Neurons are more sensitive to inhibition in the presence of current gain. (A) A conventional, feedforward (inset, right), view of cortical neurons in which all of the input current, I_{in}, must be controlled by inhibition. In this case complete inhibition of F requires that an inhibitory current, at least as large as I_{in}, raise the current threshold by displacing the FI curve to the right (asterisk). (B) When the neurons are embedded in a recurrent circuit (inset, right), they cooperate to provide current amplification in each neuron. In the presence of this current gain, the same value of F is achieved with a much smaller I_{in}, because a substantial fraction of the total current is due to a recurrent current, I_{rec}. Under these conditions complete inhibition of discharge also requires that the inhibitory current be at least as large as I_{in}. But because I_{in} is smaller than the feedforward case, so is the required inhibitory current.

reduces the firing and so on until a new steady state is achieved. To reduce the firing of the neuron to zero, the inhibition has only to be the magnitude of the smaller feedforward component of the excitation.

There are a number of features that become apparent in this simulation. First, the system is robust in the face of noise. The pattern of intracortical connectivity ensures that even if the stimulus is embedded in noise, there will be a subpopulation of 'winners'. The selective, noise resistant properties arise out of the actual pattern and weighting of the synaptic connections between the cortical neurons, here modelled as a Gaussian weighting. This property does not arise out of feedforward circuits. Secondly, the circuit performs a version of gain control or 'normalization'. The average activity in the excitatory

network determines the strength of the recurrent inhibition and thus the threshold for spike activity. When the network has converged, then the inhibition is essentially divisive – strong inhibition is seen for strong excitation, weak inhibition for weak excitation. This extraction of invariance is one cardinal feature of cortical operations that feedforward models lack. Thirdly, it is obvious that the current threshold required to produce a minimal discharge for a given neuron will vary according to the amount of recurrent inhibition it receives at any moment. In this respect, the circuit responds dynamically to the incoming stimulus. Finally, this form of circuit provides a reconciliation of the disparity we detected in the experimental data: the observation of divisive or shunting inhibition (Rose, 1977; Dean *et al.*, 1980; Morrone *et al.*, 1982), with the failure to detect this shunt biophysically (Douglas *et al.*, 1988; Berman *et al.*, 1991; Pei *et al.*, 1991; Ferster & Jagadeesh, 1992). The division arises out of the network conductance generated by the recurrent inhibition and not, as was previously thought, out of the individual inhibitory synaptic conductances on the neuron.

The recurrent microcircuit described here gives a more robust computation of the variable, orientation, by employing the strategy of amplifying only the portion of the incoming signal that provides the best estimate of the orientation of the actual visual stimulus. This best estimate originates from a bias provided by the convergence of a patterned input from the relay neurons of the lateral geniculate nucleus, perhaps in the manner originally suggested by Hubel and Wiesel (1962), but avoids the problems of noise and ambiguity that is inherent in a purely feedforward system. The recurrent circuit also permits the excitation to be controlled by small levels of inhibition, provided that the inhibition is provided to all members of the excitatory circuit. This provides an explanation for why strong inhibition is not seen in cortical networks during activation with natural stimuli. These principles may be generally applied to new models of cortical networks that exploit the features of recurrency (Douglas *et al.*, 1994, 1995; Ben-Yishai *et al.*, 1995; Somers *et al.*, 1995; Suarez *et al.*, 1995).

Recent discussions of the merits of the purely feedforward and recurrent models have concluded that purely feedforward mechanisms are sufficient and that the recurrent cortical circuitry is redundant for the generation of orientation selectivity and perhaps direction selectivity as well (Das, 1996; Ferster *et al.*, 1996; Hubel, 1996). While it is quite true that orientation and direction selectivity can theoretically be achieved by purely feedforward mechanisms, what is omitted entirely from these discussions is a consideration of how the observed robustness of these computations comes about. The simple feedforward circuits are not noise tolerant. The emergent properties of the recurrent circuits that we have emphasised above, such as extraction of meaningful patterns from noisy or incomplete input patterns and invariance, seem to be characteristic of what we think to be neocortical functions. The additional power of the recurrent circuit models is not just that they capture more of the principles of organization of the biological microcircuits than the feedforward models, but that they offer simple explanations for experimental results beyond the phenomenon of orientation selectivity itself. Of course, in proposing here that the microcircuits of the neocortex actually do more than simply sum their synaptic inputs, we make no novel claim. Hubel and Wiesel put it succinctly in the opening sentences of their classic paper of 1962, when in echoing Lorente de Nó (1949), they wrote:

> What chiefly distinguishes cerebral cortex from other parts of the central nervous system is the great diversity of its cell types and interconnexions. It would be astonishing if such a structure did not profoundly modify the response patterns of the fibres coming into it.

Indeed it would be, but fortunately it does, by microcircuits that use novel computational principles that we are only just beginning to explore.

Conclusion

In this paper we have moved from the development of the concept of the synapses by Sherrington, through the theory of the possible computational operations that can be carried out by neurons, to the anatomical and physiological details of the circuits in the input layer of visual cortex, to abstract electronic models of cortical recurrent circuits and finally to a synthetic model that encapsulates some essential principles of cortical anatomy and physiology. One of the pleasing aspects of progress in the development of these many links between the different levels of analysis is that it leads us back to where Sherrington started – with behaviour. And of course for Sherrington (1908): "Motor behaviour would seem to be the cradle of recognizable mind". This is the task and challenge that we have set ourselves: that as neuroscientists we are bound to explain how the multiple facets of ourselves – our perception, attention, memory, thought, emotion and consciousness – are created by the operations of neurons and their synaptic interactions.

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