Reprinted from

BRAIN THEORY

BIOLOGICAL BASIS AND COMPUTATIONAL PRINCIPLES

Edited by

A. AERTSEN
Department of Neurobiology
The Weizmann Institute of Science
Rehovot, Israel

V. BRAITENBERG
Max-Planck-Institut
für Biologische Kybernetik
Tübingen, Germany

1996

Brain Theory - Biological Basis and Computational Principles
A. Aertsen and V. Braitenberg (Editors)

Microarchitecture of Neocortical Columns

Rodney J. Douglas and Misha A. Mahowald and Kevan A.C. Martin*

MRC Anatomical Neuropharmacology Unit,
Mansfield Road,
Oxford OX1 3TH, United Kingdom

The neocortical system, with its exquisite variety of function, is built on a series of column-like structures that aggregate to form slabs and pinwheel patterns. The basic unit of the column is a vertical chain of neurons where later stages of the chain reconnect with earlier stages to form a series of recurrent circuits. We present a simple electrical circuit analogy to represent this recurrent chain and show how stability in the circuit can be achieved through the known biophysical mechanisms of the neuron and synapses. The possible role of recurrent excitation and inhibition is then explored in the context of extracting a signal embedded in noise. The example demonstrates how the recurrent circuits of the neocortex, with neurons connecting on a nearest neighbour basis, provide a means of representing the signal in a relatively noise-free neural code and of allowing the restored signal to scale with the magnitude of the input from the periphery.

1. MAPS, AREAS AND COLUMNS

A brief history of neurophysiological research on the neocortex would reveal three interrelated strands that dominated the research over many decades. The first strand is the work that established the existence of topographic maps of the sensory and motor world on the surface of the neocortex. The best known example is the topographic map described for primate area 17 by Daniel and Whitteridge [15]. From data derived from electrophysiological mapping of area 17 they were able to develop a simple mathematical model that predicted the both the form of the representation of the visual field upon the striate visual cortex of the monkey and the unfolded shape of area 17. Their map revealed that neighbouring regions in visual space were represented in neighbouring regions of the visual cortex and this principle remains true for all sensory and motor maps in the cortex. Through the concept of magnification factor, i.e. the factor that relates the surface of the cortex devoted to a unit size of the sensory space, they were able to suggest a direct relationship between visual acuity and the amount of cortex devoted to the presentation of the fovea. This relationship was a necessary precursor of the notion of a cortical 'hypercolumn' (see third strand below).

*We thank Bashir Ahmed, John Anderson and Charmaine Nelson for their contributions to the work described in this chapter. We acknowledge the financial support of The Royal Society, the Medical Research Council, the US Office of Naval Research, the EC, and the Wellcome Trust.

The second dominant strand is the existence of multiple cortical areas devoted to a single sensory domain, such as vision or audition. These areas began to be mapped physiologically in some detail in the early part of this century [12,1]. Many of these areas were originally defined by the fact that they have a complete or partial topographic map of the sensory surface. In the visual system, for example, Cowey [13] was able to demonstrate the existence of a topographic map in area 18, and showed that the border of area 17 and 18 followed the same principle of nearest neighbour mapping. Obviously to achieve this, the visual field representation was mirrored along the border between the two areas. All sensorimotor systems have multiple representations in cortex. The size of the individual cortical areas varies as does the grain of the maps in the different areas. The largest single area, area 17 in the primate, for example, has the most most precise retinotopic representation of the visual field, whereas in area MT, a much smaller anterior visual area in the primate, has a much coarser retinotopic representation of visual space. In addition, within a single area there may be repeated segments of the same basic representation. The visual field is doubly represented in layer 4 of each eye has a full representation of the whole visual field [34]. Even in this instance, local neighbourhood relations are maintained because the maps are retinotopic and interleaved with each other in a series of alternating left and right eye Zebra-like stripes [35]. These stripes appear as patches, blobs, or columns when cut in cross section.

These local mapping strategies form the third dominant strand of investigation. The columnar systems in the primary visual cortex have been a major preoccupation of neurobiologists of all hues. With the development of sophisticated 2-D and 3-D methods of functionally mapping these columns using metabolic markers [35] and optical recording methods [8,24] and of anatomical methods of mapping the columns [35], the two dimensional nature of the columnar map has become clearer. The actual form of the columns varies and depends on the actual function being mapped. For example, in the primary visual cortex of both the cat and monkey at least three varieties of columns have been described. One is the the slab-like arrangement found in the ocular dominance columns [34]. A second is the circular 'pinwheel' arrangement that form of part of the orientation map [10]. The third is the arrangement of the cytochrome oxidase 'blob' [28] - a column that lies at the centre of the ocular dominance columns and which also aggregates neurons that have functional properties in common [41].

These columnar structures are all superimposed on the retinotopic map of the visual field and these mapping are united in the inspired invention of the notion of hypercolumns [33]. A hypercolumn is the minimal unit that contains all the machinery necessary to process all the values of a particular variable for each part of the visual field. In the case of the orientation system it consists of a full set of slabs subserving the 180 degree cycle, for ocular dominance it consists of a left eye slab and a right eye slab. Since the size of the visual receptive fields and their scatter scales with the magnification factor, it transpires that a move of 2-3 mm along the surface of the primate are 17 in any direction will lead out from one region of the visual field to an entirely new, but neighbouring region of the field. Thus, independently of which part of the visual field is being represented, a region of visual cortex 2mm by 2mm in surface area and extending from pia to white matter will contain the neuronal machinery to analyse that small region of visual field.

Although the visual cortex was the arena in which the major development of this key concept of columns took place, it is now appears that the cortical column is ubiquitous. In all species that have been examined, anatomical, histochemical, or functional columns can be found throughout the neocortex. Although the simplest illustration is the spatial neighbourhood relations preserved in the retinotopic representation of visual space in the cortex, the same nearest neighbour relations also run along a other dimensions, like orientation and ocular dominance, i.e. any given neuron is likely to be tuned to similar parameters to its neighbours. Columns form a fundamental unit of cortical organization. It is no surprise then that they have received close attention from theoreticians, who have for the most part produced models in which the afferents self-organize into the columnar pattern through activity-dependent competitive mechanisms (e.g. [66]). These theories provide a description of the development the columns in all their forms, blobs, slabs, pinwheels etc., but they do not express a view about why one pattern rather than another should be associated with a particular cortical function. The functional 'usefulness' of the mapping is not really addressed, neither is the issue of whether the cortical circuits have any role in determining the form of the afferent mapping.

The single principle that unites these three strands is the preservation of neighbourhood relations. The fundamental organization of neocortex is that aggregates of neurons with common connectivity and functional properties are organized in coherent, repeated patterns.

2. MAP FORMATIONS

Experimentally it is very difficult to decide whether the pre-or postsynaptic elements are pre- eminent in determining the form of the map. Generally, the line has been taken that it is the presynaptic elements alone that determine the form of the projection. For example, the retinotopic map of the visual field on the striate cortex is thought to be due to self-ordering of the thalamic projection to layer 4. The arbors of individual thalamic afferents in the sensory areas form a non-uniform, patchy projections, which underly the ocular dominance columns seen with bulk tracing techniques or optical recordings in the visual cortex. In these instances, it seems, the cortical circuits need have only a relatively uniform structure, since the functional ocular dominance columns are in fact imposed by the relative right and left eye afferent arbors arising from subcortical neuron populations in the lateral geniculate nucleus. Even in the clear cases where the cortical neurons are involved, as in the whisker barrel fields in the the mouse somatosensory cortex in which the aggregates of neurons that respond selectively to the activation of one particular whisker can be seen in a simple Nissl-stained section [65].

The problem is of course, that viewing these aggregates in the adult says nothing about the mechanism of their development. In the case of the barrel fields, there is actually strong evidence that the barrels are induced by the afferents. Changes in whisker number, for example, will be reflected in a congruent change in the barrel field map in the cortex [65]. This view of cortex was stated in a strong form by Hubel and Wiesel [33], who proposed that the whole visual cortex contained repeated units of the same basic machinery and that the local differences in function were provided by differences in the pattern and function of the afferents supplying any local piece of the cortical machinery. The great attraction of this view is that the genetic instructions that build neocortex,

which after all constitutes over 80% of the brain volume in humans, need not specify many thousands of unique modules. However, we cannot assume that the neocortex is simply a tabula rasa upon which the subcortical projections to scratch their idiosyncratic graffiti during development. The possibility cannot be excluded that the cortex has some protomap that guides the development of particular form of afferent mapping [59,37].

The protomap hypothesis can itself be considered at at least two scales. One is the cortical mantle itself - how does it divide itself up into the 100 or so distinct areas? There is now convincing experimental evidence that there is some predisposition to form areas in the absence of subcortical input, but that this predisposition can be strongly influenced by the presence of the thalamic afferents. Thus the most distinctive cortical area - area 17 of the primate - develops highly abnormally *in utero* if the eyes are removed [60,17,38]. Neverthless, islands of histologically normal looking area 17, with its distinctive laminar pattern still develop.

At another level is the possible protomap within a single area. It is simply not known whether there are protomaps for the columnar patterns, such as ocular dominance stripes, cytochrome blobs, or the orientation system, but studies of the plasticity of these systems in longitudinal studies of the same animal suggest that there is some basic framework that guides the particular organization in that particular animal. It is as though a 'fingerprint gene' was determining a basic form within which individual variations were possible through epigenetic interactions.

3. ELEMENTS OF CORTICAL MICROCIRCUITS

Considerations like this beg the question of what actually are the cortical circuits that make up these different functional aggregates of neurons. Does the same circuit simply get repeated through a cortical area, as Hubel and Wiesel suggested, or does the precise circuit vary according to the afferent innervation? In the case of ocular dominance columns the simplest explanation would be that a neuron's ocular dominance is determined by the relative number of synapses formed on that neuron that derive from right or left-eye driven LGN afferents. The form of the local cortical circuit at any point within the ocular dominance map would be the same. A similar argument would of course hold for the orientation columns - they could reasonably be set up by the specific geometric arrangement of the thalamic afferents converging on the target cells. If the cortical microcircuits were examined at any position in the map of orientation columns, the prediction is that they would be the same. If the cortical circuits are the same for these two cardinal functions, then it is reasonable to suppose that a multidimensional mapping of various attributes could operate on the same principle. This would leave the Hubel and Wiesel notion of a basic uniformity in the cortical machinery intact. But what is the evidence that the cortical machinery is repeated over and over, like a crystal? Experimentally it is clear that single neurons respond to a variety of stimulus attributes, including orientation, motion, contrast, depth and velocity. Somehow the circuits of the cortex are arranged to permit such multidimensional function. And what is the possible function of the cortical circuits if the pattern of thalamic afferent input is so important in determining the basic functional properties?

The data for the uniformity of the cortical machinery can be approached at several

different scales and levels of sophistication. One line of evidence has come from simple counts of Nissl-stained sections of different cortical areas in different species. Rockel Hiorns and Powell [61] reported that counts of the number of neurons under a millimetre of surface of various areas of cortex sampled from mouse, rat, cat monkey and man, was approximately constant. The number was about 100 000 neurons, with the exception of the primate visual cortex which had about double the number. The claim was that the absolute number of neurons under a unit area of cortical surface was genetically determined and this genetic instruction had been preserved though mammalian evolution [58]. This is a bold claim and not surprisingly, several dissenting voices have been heard [55]. But even the counter-claims that there are differences between areas in the absolute number of neurons per unit surface area do not offer figures that are more than about 2 fold different from those suggested by Powell and his coworkers. But even were there exact agreement on this particular point, no-one has offered any hypothesis as to why evolution might have arrived at this or any other number. Can it simply be a number arrived at through some serendipity of the evolutionary process, or does the number, whatever is exactly, have a functional significance? To get any hint at this answer we need to explore another level of organization. Powell's hypothesis was not based simply on counts of neurons in Nissl-stained sections. A second strand to his argument was that the composition of neuronal types in the different areas of neocortex was also conserved through evolution. That is, when examined in the electron microscope, about two thirds of the neurons appear to be pyramidal cells and about one third are non-pyramidal intereneurons [58]. The proportions produced by Powell and his coworkers have never been seriously challenged, although they ran counter to the dogma of Ramon y Cajal who, on the basis of Golgi-stained sections, supposed that the number of non-pyramidal neurons increased greatly from mouse to man (see discussion by DeFelipe and Jones ([16], pp. 590-599). With the advent of immunochemical methods Ramon y Cajal's view has had to be modified. It has been shown that smooth 'non-pyramidal' neurons contain the synthesizing enzyme for gamma amino butyric acid (GABA) and are immunopositive for antibodies directed against GABA itself. Both in rat and in primate, the GABA-positive neurons form about 20% of the total in all cortical areas [29,26,55]. These neurons include the basket cells, the chandelier cells, double bouquet cells and various other subclasses. An additional population of non-pyramidal spiny neurons are found in the primary sensory areas. These are the spiny stellate cells that are found exclusively in layer 4, which form about 5-10% of the neurons. They do not contain GABA. Thus, even in area 17 of the primate, the relative proportions of the different cell types seems to have remained approximately constant. However, what Ramon y Cajal certainly saw was an increasing elaboration of the dendritic or axonal arborization of the population of smooth neurons, i.e., their morphology and connectivity was evolving, but modern studies have shown that their proportion remains constant.

4. VERTICAL COLUMNAR MICROCIRCUITS

It was Lorente de No [42] who, on the basis of his Golgi studies, emphasized the vertical organization of chains of neurons, which he saw as the functional unit of cortical organization. This theme of verticality was taken up by the physiologists whose discovery

of topographic maps in the sensory areas gave a teleological reason for this arrangement: neighbouring neurons processed signals arising from neighbouring regions of the sensory space [53,15]. Another dimension was added when Hubel and Wiesel [32] showed that within a single column there were different receptive field types that were aggregated in different layers of the column. To them this suggested a chain of processing in the vertical dimension, i.e. a hierarchical tier of processing within a local column of grey matter extending from the white matter to the pial surface. This was a concept of great synthetic power and subsequent anatomical work gave further clarity to this view of the organization.

Tracing methods showed that the projections to other cortical and subcortical regions were provided by neurons in different layers, e.g. corticothalamic projection arose from layer 6 pyramidal cells, corticocollicular projections arose from layer 5 neurons (e.g. [44]). The columnar principle remained however. In a given column, the neurons that project to the thalamus are activated by much the same stimuli as those projecting to the colliculus. Essentially all the projections to the areas involved in motor control (tectum, striatum, pons, medulla, spinal cord) arise from a small percentage (10% in cat visual cortex) of neurons located mainly in layer 5. From the layer 6 projection back to the thalamus, the cortex can influence the pattern of sensory activity it receives. Since the transmission times from cortex to thalamus and back are only about twice as long on average as between cortical neurons themselves, the thalamic relay cells could almost be considered a sublayer of neocortex itself.

The pattern of projection within the column has been studied mainly using the Golgi technique applied in immature animals. In adults, degeneration and tract tracing techniques have also been exploited. The most vivid and complete picture of the 3-dimensional structure of cortical neurons in both immature and adult neocortex, has however come from intracellular filling of single neurons *in vivo* [23,51]. If the enzyme horseradish peroxidase is injected intracellularly, it is transported through the finest dendritic and axonal processes of that neuron. Subsequent histochemical processing reveals the complete dendritic and axonal arborization of a single neurons, without all the problems of incompleteness or immaturity that plague the Golgi technique. Furthermore, the axons of the different types of neurons are not labelled together as in the tract-tracing methods.

Clearly there must be some agreement between the conventional neuroanatomical and electrophysiological methods and the complete structure-function picture of single neurons provided by the intracellular HRP techniques. The different techniques do in fact agree (see [48,20,7,40,43]. The main thalamic projections are to the middle layers of the cortex, principally, but not exclusively to layer 4. The spiny neurons of layer 4 project vertically to the superficial layers, which in turn project to the deep layers. The pyramidal cells in the deep layer project to each other and upwards to layers 1-4. The basic vertical pattern of interlaminar connections of the spiny neurons is conserved through all cortical areas. The pattern of projection of the smooth neurons has been less intensively studied. In general, the axonal arbors of the smooth GABAergic cells appears to be more compact than that of the spiny cells, but many of the the interlaminar projections patterns of smooth neurons are equivalent and congruent to those for spiny neurons. This is interesting because the targets of the smooth cells are their neighbours, i.e. the smooth neurons lie in the same column as the neurons they inhibit.

5. LATERAL ORGANIZATION OF MICROCIRCUITS

Lest the impression be given that there are no connections between columns, it should be emphasized that the physiology and the anatomy show clearly that there are lateral connections. For example the monocular fields of the layer 4 neurons lying in segregated left and right eye columns become binocular in the upper and lower layers of the visual cortex [32]. This mixing of left and right eye can only occur through some lateral interaction. Similarly, the work of Powell and coworkers, in which they made microelectrode lesions in different cortical areas, showed that there was dense terminal degeneration extending for a few hundred microns from the lesion and thereafter becomes moderate and extends, usually asymmetrically for 2-3 mm, depending on the lamina. This pattern was seen in all cortical areas tested in cat and monkey [19,22]. Significantly, the pattern remained the same even when the lesion was placed next to an architectonic boundary between two different cortical areas. The efferent fibres form a tight bundle running perpendicularly to the surface of the cortex.

The quantitative distribution of synapses in these patchy projections has yet to be determined, but a first approximation was given by Fisken *et al* [19] who made minimal lesion in area 17 of the monkey to produce degenerating terminals of axons of neurons in the lesion area. They found that nearly 40% of asymmetrical (excitatory) synapses and 30% of the symmetric (inhibitory) synapses were found less than 500 um from the site of the lesion. Nearly 70% of the degenerating asymmetric synapses and 60% of the symmetric synapses were found within 1mm of the lesion. The symmetric synapses formed about 11% of the degenerating synapses and did not fall off so rapidly with distance. The distribution of degenerating synapses might include those of boutons from fibres of passage damaged by the lesion, but nevertheless the point is that the major connections were local. Similar qualitative observations have been made by Lund Yoshioka & Levitt [45], and Malach ([46], this volume) in their experiments, which used biocytin rather than degeneration to label the terminals.

More recent studies in which chemical tracers have been used rather than degeneration have added little to the vertical dimension of this picture but have derived a clearer picture of the pattern of the lateral projections. These lateral projections are not uniformly distributed but form patchy projections. Comparative studies [45,3] in the macaque monkey revealed that the patchy lateral projections in the superficial cortical layers were similar in dimensions and 'patchiness' in areas as diverse as visual (area 17, 18, 19), somatosensory (areas 1, 2, 3b), motor area 4, and area 9 and 46 in the frontal cortex. The dimensions and spacing of the lateral patches was within a factor of two in species as diverse as monkeys, tree shrews and cats. The intrinsic pattern of connectivity revealed by this technique does not match precisely the patterns produced by afferents such as those arising from the thalamus or from other cortical areas. The intrinsic mosaic of connections is slightly smaller in scale than those of the extrinsic systems, a device which Lund et al (1993) suggest, might allow for more heterogenous sampling of inputs. A similar argument has been advanced by Malach (1992; this volume) to account for the equivalence in the size of the dendritic arbors and the size of the patches formed by neurons in area 17 of marmosets and squirrel monkeys. Both Malach [46,47] and Lund *et al* [45] found a positive correlation between the size of the dendritic spread and the size

of the patches. Malach ([46,47], this volume) pointed out that this comparability in size allows a maximization of the spread of sampling of different proportions of inputs from the different functional compartments delineated by the patches.

6. FEEDFORWARD HIERARCHIES

The pattern of connectivity and the proportions of the different component neurons and synapses outlined above leads inexorably to the conclusion that in terms of anatomical connectivity the activity of any single neuron in a column is dominated by excitatory synapses provided by monosynaptic or disynaptic activation from neighbouring neurons. This raises the interesting question of how this excitation is organized. Based on his view of the anatomical connections, Lorente de No [42], concluded that the chains of neurons connected so that they could repeatedly re-excite the same neurons. An alternative view was taken by Hubel and Wiesel [30,34] in their early formulation of the cortical circuits for vision. In their scheme the interconnections within the columns were organized in a feedforward hierarchical fashion, so that the chains of neurons never reconnected to form a re-excitatory loop.

A similar plan was suggested by Gilbert and Wiesel [23] in their seminal study of the structure and function of cat visual cortex. Their schema closely followed that of Hubel and Wiesel [30,31] except that an inhibitory feedback loop was incorporated from layer 6 to layer 4 (see below). Indeed, traditionally it has been supposed that the recurrent collaterals of pyramidal cells are involved in a recurrent inhibitory pathway to control excitation within the cortex [57,58]. In the excitatory feedforward case originally proposed by Hubel and Wiesel [30], the activity of the cortical circuit was dependent on the pattern of activity of the thalamic afferents. By contrast, Lorente de No's were circuits of recurrently connected excitatory neurons containing no inhibitory neurons [42]. His view was that the effect of impulses entering the cortex depended entirely on the state of the existing activity of the chains of cortical neurons. Although the two models, one of feedforward excitation, the other of recurrent excitation are diametrically opposed, it has been difficult to distinguish either experimentally or theoretically between these two versions of the basic cortical circuit. Generally the feedforward version has been preferred over that of the recurrent excitatory model of Lorente de No for the obvious reason of simplicity and functional stability. However, recent work from our laboratory has suggests that Lorente de No's view needs to be re-considered. Both within and between lamina we have found recurrently connected excitatory neurons, which may contribute greatly to the effect of activity entering the cortex from the thalamic afferents.

7. RECURRENT EXCITATION AND INHIBITION IN LAYER 4

The new experimental evidence turns on the projection of layer 6 pyramidal cells to layer 4 and between the spiny stellate cells of layer 4 itself. The question of the organization of the layer 6 recurrent pathway to layer 4 had originally been addressed by Gilbert and Wiesel and coworkers. Their suggestion that the layer 6 pyramidal cells were involved in a recurrent inhibitory pathway to layer 4 was supported by two independent strands of evidence. The first was their detailed ultrastructural examination of the synapses formed by the layer 6 pyramids in layer 4 [52] in which they found that most of the layer 6 pyramidal cell boutons form asymmetric synapses on dendritic shafts. This is a very unusual arrangement since most pyramidal cells form their synapses with dendritic spines. By serial electron microscopic reconstructions they discovered most of the target dendrites were sparsely spiny, which they supposed to originate from GABAergic, inhibitory neurons. Their model of end-inhibition was essentially that proposed by Hubel and Wiesel [31]. This hypothesis they followed up by physiological experiments in which they examined the effect of blocking activity of the layer 6 pyramids on the activity of layer 3 and 4 neurons [9]. They found that end-inhibition was considerably reduced when layer 6 was blocked. Their conclusion was that the basic function of the layer 6 pyramidal cells was to provide a recurrent inhibition to layer 4.

Our new observations were obtained from single neurons that had been filled with horseradish peroxidase by intracellular recordings and injections *in vivo*. We began by filling various afferents of layer 4 and studying them at the light microscopic level. The neurons that have axonal arbors in layer 4 include the relay cells of the thalamus, the layer 6 pyramidal cells, and the spiny stellate cells themselves, which are only found in layer 4. The axons of each of these types distribute in a characteristic way. The thalamic afferents form dense clumps of terminals, about 0.5 mm in diameter [21,36]. The layer 6 pyramidal cells have a rich innervation of the region of layer 4 radially above the soma of the pyramidal cells, i.e. around the apical dendrite of the layer 6 pyramid as it passes through layer 4, and a collateral innervation of adjacent areas [23,51]. The tangential appearance of the layer 6 pyramidal axonal arbor is that it is less clumped and more diffuse than the thalamic afferents. The spiny stellates have a rich innervation of the area within and above their dendritic tree as well as laterally-directed branches that form clusters in layer 4 and layer 3 [23,51]. These clusters are of similar dimensions to those of the thalamic afferents and also form clumps spaced by 1mm. Thus the basic picture of a columnar innervation is in accordance with the columnar principle of nearest neighbours connect. But to what do they connect? The details of the circuit were discovered through a detailed ultrastructural analysis of the pre- and postsynaptic elements.

Before our study, it was not known whether the spiny stellate cells in layer 4 of cat cortex form synapses with all the possible presynaptic elements in layer 4. Peters & Feldman [56] and Peters [54] proposed a 'rule' that geniculate afferents contacted dendrites in layer 4 in the statistical probability of occurrence of pre- and post-synaptic elements. Braitenberg and Schüz [11] generalized Peter's 'rule' for all pre- and postsynaptic elements. We adopted their generalization and hypothesized that all types of boutons in layer 4 would form synapses with spiny stellate cells. In order to demonstrate that this polysynaptic innervation did occur, we defined the ultrastructural signature of the presynaptic elements based on the type of synapse, its location (spine or dendritic shaft), and size of presynaptic bouton [4]. After detailed comparison with the synapses formed on the spiny stellate cells, we were able to show that the dendrites of the spiny stellate neurons are polysynaptic innervated by all the presynaptic elements we identified in layer 4. The spiny stellates form most of their asymmetric (excitatory) synapses with the layer 6 pyramidal neurons (45%) and other spiny stellate neurons (30%) and only about 6% with the thalamic afferents [2]. The remainder of synapses could not be identified with certainty, but other minor sources like the claustrum could be involved. The small basket cells of layer 4 appeared to provide the majority (90%) of the symmetric (inhibitory) synapses

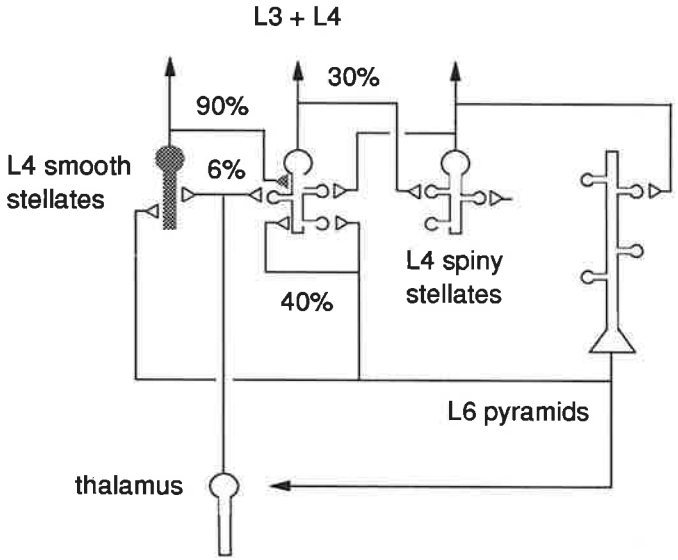

Figure 1. Schematic of some of the elements of the layer 4 circuits of neocortex. The inhibitory neurons (small basket cells) are indicated in shaded profiles, the excitatory neurons in open profiles. The percentages refer to the proportion of synapses formed between the various elements and the spiny stellate neurons. Inhibitory and excitatory percentages calculated separately.

[2]. These connections are summarized in Fig. 1.

8. MICROCIRCUITS OF LAYER 4

A microcircuit could now be assembled from these elements and their interconnections. This circuit is similar in concept to the 'elementary unit' of Lorente de No [42], which contained all the necessary elements in cortex for transmitting impulses from the afferent fibre to the efferent axon. Although only a subcircuit is being considered here, the same principle applies: we have identified the chain of neurons that are required to excite and inhibit the spiny stellate cells within a single column. From our electrophysiological work in the cat we know that the thalamic afferents excite monosynaptically the spiny stellate cells, the layer 6 pyramidal cells and the small layer 4 basket cells [50,51]. Our anatomical work showed that the layer 6 pyramids and the spiny stellates form excitatory synapses

relax to zero if there is no thalamic excitatory current.

The thalamic synaptic current is amplified by the recurrent excitatory network with a gain that is expressed as $I_{in}+I_{rec}/I_{in}$, which can be alternatively expressed as $G+\beta/G_{eff}$. This gain can be much greater than one and as the value of the excitatory network conductance (α) approaches $G+\beta$, the output is largely due to the current delivered by the spiny stellate network of excitatory synapses (I_{rec}) rather than the thalamic synapses. Thus, this circuit encapsulates and solves analytically the issue raised 45 years ago by Lorent do No: how does the activity of the cortical column influence the impulses entering the column from afferent systems like the thalamus? In this modern formulation, the output of the spiny stellates is always proportional to the thalamic excitation, but the magnitude of the effect of the thalamic synapses on the spiny stellates, and hence the columnar circuit, depends on the gain of the cortical network at that point in time, i.e. the factor by which the thalamic input is amplified. This gain factor is affected by the activity existing in the network. The gain is highest when all the neurons in the column are above threshold and its gain is zero when all the neurons are below. Many pre- and postsynaptic factors determine the state of activity of the network. Presynaptically, amongst the many different factors that need to be considered is the issue of the synaptic efficacy. With repeated stimulation a synapse may potentiate or depress. This process is also dependent on the rate the synapse is stimulated by action potentials. Postsynaptically, issues of receptor saturation, the concentration of ions in small compartments like the spine, and the processes of adaptation will all have an affect on the gain of the circuit. The adaptive processes may be especially significant. The probability that a given spiny stellate cell will produce an action potential will depend on when it last produced an action potential. The action potential discharge of the spiny stellate neurons adapts rapidly and this adaptation is due largely to a calcium-dependent potassium current that has a time constant of about 20ms. Thus, the production of just one action potential by a spiny stellate will affect its response to the next volley from the thalamic synapses. The number of active synapses on the spiny stellate will also have a considerable effect on the input conductance of the neuron [5]. These numerous factors are changing dynamically and their cumulative effects need to be assessed through more detailed models than that presented here.

10. WHAT RECURRENCE IS GOOD FOR: A NEW ORIENTATION

The possible role of the columnar recurrent circuit can now be considered in the context of the attribute of orientation selectivity in the visual cortex. The property of orientation selectivity has been studied in much detail at the level of the receptive fields of single cells and in the geometric arrangement of columns described above. Orientation selectivity of single neurons is quite robust in the face of changes in spatial and temporal frequency and in stimulus contrast of the stimuli. Bars and gratings give similar tuning curves and the orientation selectivity of binocular neurons is the same tested through either eye. It is clear that these properties do not reside in the physiological properties of the thalamic afferents, nevertheless the geometry of the thalamic afferent synapses are thought to be a necessary condition in setting up orientation selectivity [30,6]. The issue of what the role of the intracortical circuitry is in this system is rather contentious. One view is that of Hubel and Wiesel [30], which is that the intracortical circuitry does not

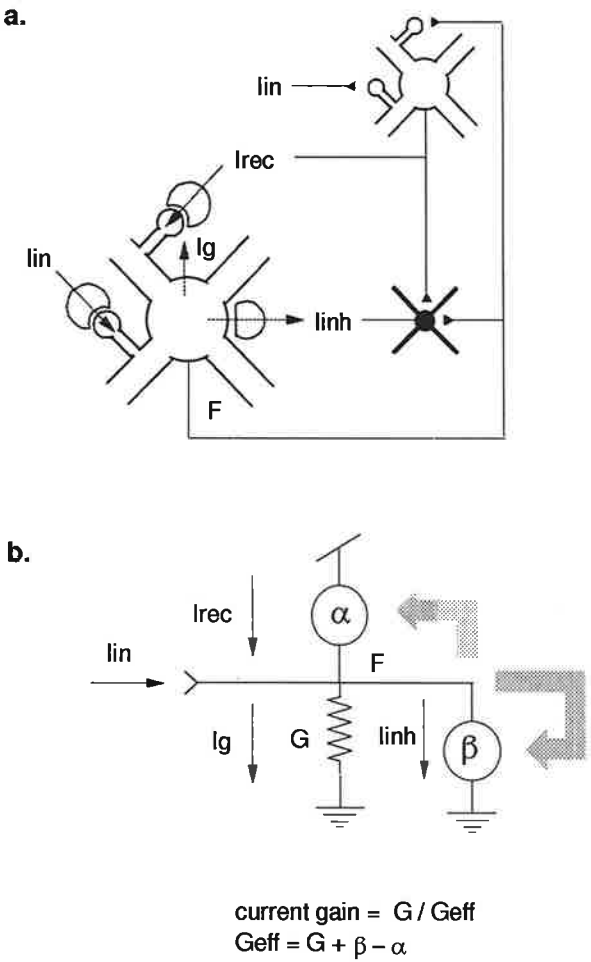

Figure 2. Reduced spiny stellate microcircuit for layer 4. a. Spiny stellate neurons form synapses with thalamic afferents and other spiny stellates and with inhibitory basket cells (shown in black). The excitatory synapses provide an inward current, Iin from thalamic afferents and Irec for recurrent spiny neurons. The basket cells provide an outward current Iinh. Ig is the current flowing across total conductance of the spiny stellate and the output is given by the frequency of discharge F. b. Equivalent electrical circuit. The spiny stellate net conductance is G. Currents as in a. α is the network conductance of the excitatory portion of the circuit and β is the network conductance of the inhibitory portion of the circuit.

contribute to the basic receptive structure of simple and complex cells. A contrary view is that the thalamic afferents provide a non-oriented or weakly oriented excitation that is shaped by inhibitory neurons in the cortex [62,63,25,6]. In this view the inhibitory neurons provide a powerful 'cross-orientation' inhibition that is the critical functional component producing orientation selectivity. We have previously reviewed the evidence for both mechanisms and will not review our conclusion that neither of these extremes gives a coherent account of the cortical mechanisms of orientation selectivity [49]. Instead, we start from an acceptance of the existence of recurrently connected columnar circuits and attempt to understand the manner in which these circuits might interact with the thalamic input to produce orientation selectivity in columns in cat visual cortex.

Our tool for exploring these interactions is a simple model of layer 4. In this model (Fig. 3), 40 spiny stellate cells were connected together in a ring: these could be considered to be components of an orientation 'pin-wheel'. All the spiny stellate cells received monosynaptic excitation from a group of thalamic afferents. The receptive fields of the group of thalamic afferents forming synapses with any single spiny stellate neuron were roughly arranged along an axis in visual space (Fig. 3b). The preferred axis of each array of thalamic neurons shifted in an orderly fashion so that the full 180 degrees of the orientation domain was spread across the 40 neurons. The intracortical connections of the spiny stellates were arranged so that nearest neighbours had the strongest connections with each other and more distant neurons were weakly interconnected. These connections were distributed according to a simple gaussian function (Fig. 3a). The spiny stellates were recurrently connected to a pool of inhibitory neurons, i.e. they provided a convergent excitatory input to the inhibitory neuron pool, which provided a divergent and equal strength inhibitory connection to all the spiny stellates. For simplicity this pool was considered as a single neuron (Fig. 3b, grey neuron). This provided for an interesting analysis of the role of intracortical inhibition in orientation specificity. Since we were not studying the dynamics of the circuit, we did not provide for a feedfoward inhibitory pathway driven by the thalamic afferents. The orientation tuning of the population of spiny stellate neurons was tested under various conditions of connectivity. The 'recordings' are the results that would be obtained if the net activity of the whole ring of spiny stellates could be seen simultaneously as they were being stimulated with one orientation. This recording is in effect a one-dimensional optical recording of the voltage of the array of 40 neurons.

In the first condition, the spiny stellate ring was connected only to the geniculate afferents and the afferents were stimulated with a weak stimulus at one orientation. The resultant activity profile showed that the orientation tuning of the array was very broad and that the signal-to-noise ratio was poor (Fig 3c, dotted line). This is what would be expected from the 'jitter' in the thalamic afferent connectivity. A very different profile was obtained when the intracortical circuitry was engaged (Fig. 3c solid curve). Here the same weak, noisy stimulus gave a well-tuned and robust response. The explanation of this result derives directly from the analysis of the recurrent circuitry of the column (Fig. 2).

The process is as follows: the oriented stimulus activates all the thalamic afferents. Those converging on the cells with a receptive field biased along the principle axis of the stimulus will be slightly more excited than those tuned to other orientations. The

neurons reaching threshold will produce action potentials and excite their neighbouring spiny stellate cells, which in turn will excite the inhibitory neuron pool. The inhibitory neuron pool, because it connects to all the spiny stellates, will apply the same inhibition to all neurons ((Fig. 3c; inhibition 'strength' $t = 0, t = \infty$). Weakly driven spiny stellates will be completely inhibited, but more strongly activated spiny stellates will continue to fire and provide positive feedback to their neighbours. Neurons that are non-optimally activated will become more inhibited and fall silent, while the positive excitatory feedback between the optimally activated neurons will amplify the weak and noisy thalamic afferent signal. The result is a relatively noise-free and robust signal.

The mechanism of action of the inhibitory neuron in this process is very interesting. It acts in at least two modes, depending on the state of the network. Initially, it acts as a thresholding device to extract the best estimate of the noisy input signal. As the network converges to the optimal solution, the inhibitory neuron pool will be strongly activated and will therefore be orientation tuned. In the final state, the inhibition is proportional to the degree of excitation of the active population of spiny stellates. This proportional inhibition stabilizes the co-operative excitation established within the ring.

The neurons in the model circuit act co-operatively [27,64,18] to vote on their best decision as to the orientation of the stimulus. Although this co-operative action is in some senses a democratic one, it is not the democracy of the ballot box, where each neuron makes its own independent decision before adding its individual secret vote to the box. Instead the voting is done on the town hall model, where a show of hands decides the issue. Here each member is subject to the influence of its fellow's vote. A member (in this case a neuron) intending to vote differently from their immediate neighbours will be influenced by neighbours to change their vote to agree with those of its neighbours. This peer pressure is not the only factor. Unlike the town hall, in this cortical model there is active suppression of members whose local support is small. Nevertheless, as in most democracies, the winners take all.

11. COLLECTIVE MEMORY AND MODELS

It is important to note that the connectivity of the model circuit predisposes it to behave in the selective way described. It acts as a correlation detector for a predetermined set of patterns, amplifies the correlated signal and suppresses the noisy uncorrelated signal. Thus, even before the weight of the synapses is considered, the 'weight' of the specific connections is having a powerful influence on the result. This embedding of an expectation of the nature of the stimulus in the hardware of the neocortex is not too long a long march from Craik's view that the brain constructs of a working model of reality [14]. Thus, the principle of organization and function of the cortical columnar systems outlined here could apply equally well to most of the other processes we know about in the cortex, whether they be sensory or motor, hardwired or plastic. The same architecture could be used to generate coherent action to take the noisy and ambiguous individual signals arising from the sense organs, shape it into some coherent form according to previous experience, and generate an appropriate response.

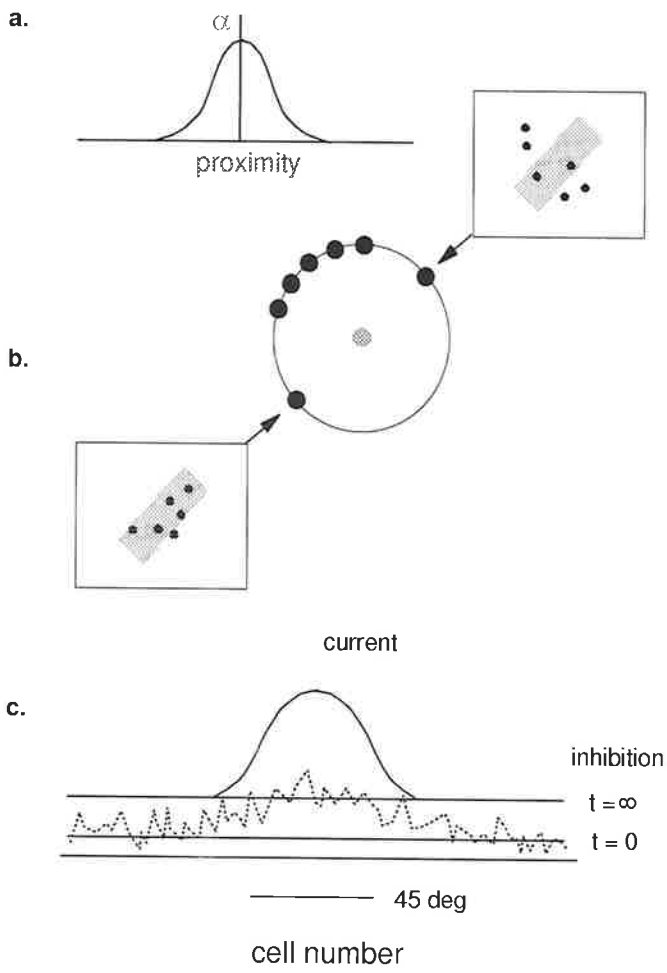

Figure 3. Reduced model of orientation map. a gives the distribution of excitatory connections of a given spiny stellate neuron. b. 'Ring' of 40 spiny stellate cells interconnected according to distribution given in a. Shaded symbol in centre is an inhibitory neurons to which all spiny stellates are recurrently connected. Boxes indicated topographical distribution of receptive fields of thalamic afferents connecting to spiny stellates indicated. All spiny stellates were 'stimulated' with bar indicated by shaded rectangle. c. Activity profile of 40 spiny stellate neurons when connected only to thalamic afferents (dotted line) and with spiny stellate intereconnections engaged (solid line). Magnitude of inhibition shown by horizontal lines at time $t = 0$ and in steady state $t = \infty$.

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