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Cortical columns as devices for maximizing neuronal diversity

Rafael Malach

Columns are a fundamental feature of cerebral cortex organization, yet the function served by this architecture remains elusive. Here it is proposed that the columnar organization of the cortex serves to maximize diversity of neuronal connections in supragranular cortical layers.

Rafael Malach is at the Dept of Neurobiology, Weizmann Institute of Science, Rehovot, Israel 76100.

With the discoveries by Mountcastle[1] and Hubel and Wiesel[2], it was recognized that a fundamental feature of the cortical architecture is its columnar organization – that is, the organization of neurons having similar properties in columns running perpendicular to the cortical surface. The columnar organization of the cortex, which was initially deduced on physiological grounds, received further confirmation with the demonstration of histologically defined columns or modules[3,4]. A particularly striking example of such modules are the cytochrome oxidase (CO) dense 'blobs', which were subsequently associated with color-information processing[5]. Tract-tracing experiments have shown that axonal projections throughout the cerebral cortex tend to be organized in vertically aligned clusters or patches, indicating that the columnar organization is a ubiquitous aspect of neocortical architecture[6–11]. It should be noted, though, that whether the cortical columns constitute discrete elements or blend smoothly into one another has remained an open question. In several cases, a direct correlation between the axonal patches and functionally determined columns has been demonstrated[5,12,13]. Thus, it can be safely concluded that the columnar organization is a fundamental feature of both the anatomy and physiology of the cerebral cortex. However, the function served by this organization in cortical processing remains enigmatic. This problem was put forward most explicitly by Purves and colleagues[14] who argued that the columnar organization serves no function and is merely an 'incidental consequence' of developmental rules.

Here I propose that, regardless of the developmental processes that lead to column formation, a powerful consequence of the columnar organization in the adult brain is the maximization of the connectional diversity of cortical neurons. More explicitly, the columnar organization ensures that every neuron in the upper cortical layers will be different from its neighbors.

The importance of column size

The argument originates from the observation that the width of cortical columns, at least those defined by CO blob staining or by the patchiness of axonal projections, is closely matched to the average diameter of individual dendritic arbors of upper-layer pyramidal neurons[10,15]. Figure 1 illustrates this point by showing a tangential view of the basal dendritic arbor of a pyramidal neuron and an axonal patch, both taken from area V1 of the macaque. Note the similar tangential spread of the two structures. Measurements in area V1 of the macaque reveal that average tangential spread of upper-layer pyramidal neurons is 213 ± 79 μm (unpublished observation), and the average tangential width of axonal patches is essentially identical (230 ± 98 μm)[10]. Recently, Lund and colleagues[16] demonstrated that the correlation between column size and dendritic spread is a fundamental cortical property that holds true throughout various neocortical areas and species. Furthermore, it appears that the size of axonal patches, revealed by tracer injections, remains invariant irrespective of the size of the injection. This suggests that patch size has an upper limit which is not determined by the number of neurons feeding the patch[10].

The size match between axonal patches and dendritic arbors leads to maximum diversity of dendritic sampling in the neuronal population. To appreciate this it is easiest to consider a simple scheme of a cortical net, built up of a set of patchy axonal inputs surrounded by a set of inter-patch inputs, and a population of neurons which sample from these two sets of inputs. An example of such a set might be the CO blobs which are innervated selectively by thalamic and feedback projections from area V2 (Refs 5 and 17) but any other set of axonal patches could be considered as well. Fig. 2A depicts such a scheme, based on empirically derived dimensions for the sizes of axonal patches and dendritic arbors for macaque V1. It illustrates how pyramidal neurons sample axonal afferents clustered into patches. Only a few representative neurons are shown, but in fact, as it is in real cortical tissue, the entire area should be considered to be densely packed with pyramidal neurons. The graph,

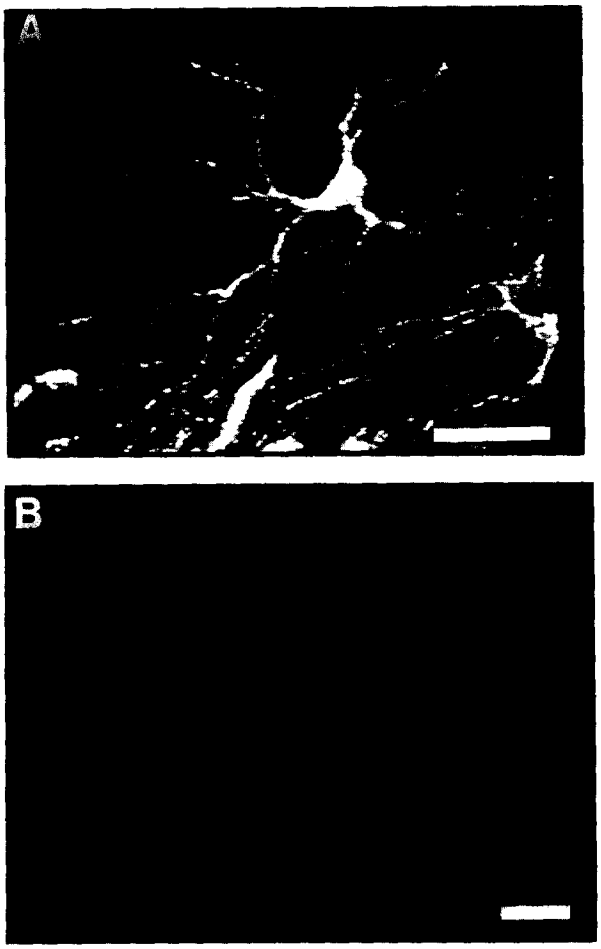

Fig. 1. *Examples of a dendritic arbor and an axonal patch.* **(A)** *Confocal laser scanning microscope image of the basal dendritic arbor of a pyramidal neuron. The neuron was Golgi-impregnated and the image is an 'extended view' composite produced by adding 16, 3 μm thick, optical sections through the arbor*[15]. **(B)** *Dark-field photomicrograph showing an axonal patch, anterogradely labeled by an injection of biocytin in area V1 (Ref. 10). Both A and B are top views of tangential sections through supragranular cortical layers in area V1 of the macaque monkey. Note the similarity in the size of the two structures. Scale bars, 50 μm.*

which will be termed here the 'population sampling profile', shows how the mix of inputs feeding each neuron with a cell body located on the white line changes as one moves from left to right across the axonal patches. At each point along the line, a neuron will differ from its neighbors in the mix of patch–interpatch inputs it receives. The sampling mix changes smoothly from neurons whose dendrites are completely outside the patches and thus receive pure interpatch inputs, through neurons situated on the border of axonal patches and receive mixed patch–interpatch inputs, to neurons whose dendrites are fully confined within the axonal patches and receive exclusively patch inputs.

What might be less apparent is that the match between patch size and dendritic spread generates the maximum possible sampling diversity in this population. This can be best illustrated by considering the two alternative situations in which the size match between dendritic arbors and axonal patches is violated. Figure 2B shows a case in which the size of the axonal patches exceeds that of the dendritic spread. In this case, most dendritic arbors are either fully confined within an axonal patch (that is, receive purely patch input) or are completely outside it (that is, receive purely interpatch input). This leads to a large redundancy in the neuronal population – neurons belong either to one type or another – and is reflected in the 'flattened' peaks in the population sampling profile. Figure 2C shows the opposite case where the diameter of the dendritic arbors greatly exceeds the size of axonal patches so that all neurons receive mixed patch–interpatch inputs. In such a case, neighboring neurons might still sample different mixtures of inputs but the range of possible patch–interpatch combinations is reduced since the possibility of pure patch or interpatch inputs onto a neuron is excluded. This is reflected in a shallow amplitude of the population sampling profile. Thus, maximum diversity is achieved only when the size of dendritic arbors matches that of the axonal patches (Fig. 2A). It is striking that of all the possible relationships between dendrites and axons, this size match is the one that is found most consistently in the upper layers of the cerebral neocortex.

Conditions necessary for neuronal diversity

It is important to note that the situation described in the proposed scheme can exist only if two conditions are met. First, dendritic arbors of cortical neurons have to cross freely through column boundaries. If column borders were to form true barriers, preventing dendritic crossing, then the population of neurons will be split into two distinct homogenous groups, which is an equivalent situation to the one shown in Fig. 2B. We have studied this point by analysing the relationship of dendritic arbors of cortical neurons to the borders of CO blobs and found no statistically significant reduction in dendritic crossing from blob to interblob territory[15]. Figure 3 illustrates this point by showing an example of dendritic arbors in area V1 of the macaque and their relationship to the CO borders. Note that while an occasional neuron appears to be affected by blob borders, the overall trend is of free dendritic crossings. Bolz and colleagues[18] found a small population of neurons which were 'repelled' by CO-blob borders, but the majority of dendritic arbors in their study appear to be randomly distributed with respect to blob boundaries. A similar phenomenon of dendritic crossing was also observed in the relationship of dendritic arbors to orientation domains in the macaque[13]. Therefore, it can be concluded that dendritic arbors of upper-layer neurons are, for the most part, nonspecific with regards to column boundaries.

A second implicit assumption in the proposed scheme is that dendrites that cross column boundaries sample inputs with equal probability from both compartments. In qualitative observations of blob neurons whose dendrites cross into interblob territory, no clear reduction was observed in the spine

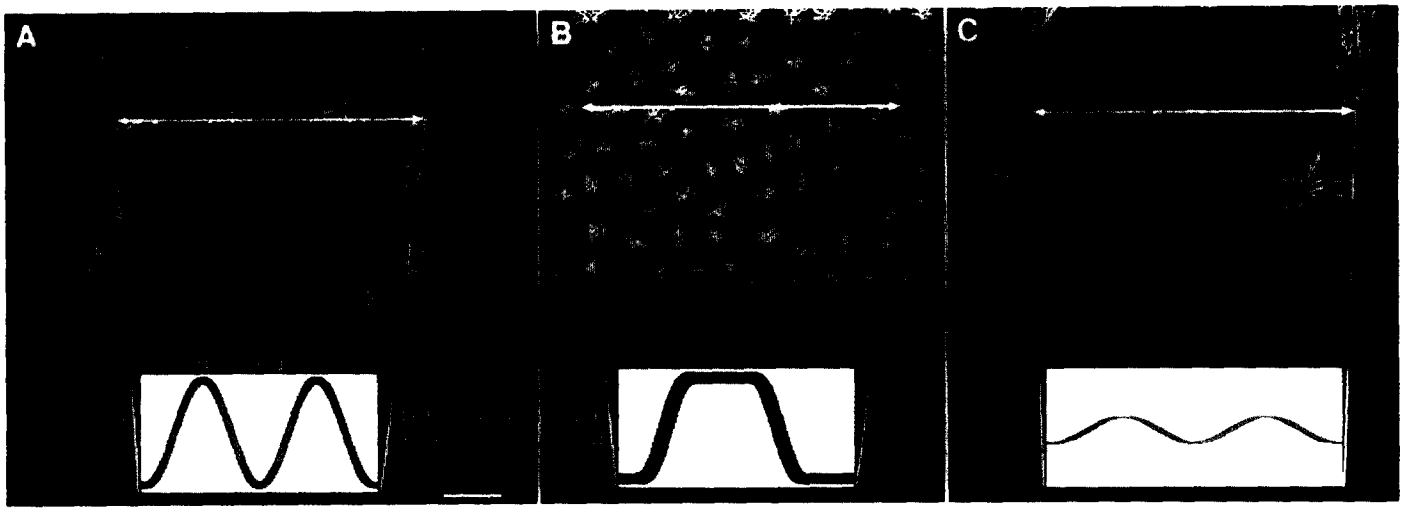

Fig. 2. *Dendritic sampling from axonal patches: macaque area V1.* **(A)** *A scheme depicting how dendritic arbors of upper-layer pyramidal neurons sample from incoming inputs clustered into patches (red). Only a few representative neurons are shown (yellow), whereas in the real tissue the area is densely packed with pyramidal neurons having highly overlapping dendritic fields. The neurons and patches were generated from examples revealed by anterograde and retrograde transport of biocytin in area V1 of the macaque monkey. Note the similarity in size of the dendritic spread of individual neurons and the width of axonal patches. In this case, only a few neurons at the center of a patch or interpatch will receive 'pure' inputs while all the others will sample different mixes of patch–interpatch inputs. Below is the population sampling profile which shows the mix of patch–interpatch inputs to each neuron along the white line. The x-axis corresponds to position along the white line, while the y-axis shows the ratio of patch–interpatch inputs. Note that the population sampling profile oscillates smoothly between pure interpatch inputs and pure patch inputs, thus generating maximum neuronal diversity. Scale bar, 100 μm.* **(B)** *Dendritic sampling from oversized axonal patches. A depiction of a hypothetical case in which the size of the axonal patches greatly exceeds the spread of dendritic arbors. Note that, in this case, most dendritic arbors will be confined either to the patch or to the interpatch compartments. Only a small fraction of the neuronal population will integrate information from both compartments. The graph below shows the population sampling profile for this case. Note that, unlike the case shown in (A), here the peaks of the population sampling profile are flattened leading to redundant sampling by neighboring neurons.* **(C)** *Dendritic sampling from undersized axonal patches. Depiction of a hypothetical case in which the size of dendritic spread greatly exceeds the width of axonal patches. Note that in this case all neurons receive mixed patch–interpatch inputs so that the range of possible mix ratios is reduced. This is reflected in the shallow population sampling profile.*

density of dendrites protruding into the interblob compartment[15]. Similarly, quantitative measurements of the density of synaptic boutons on axons show that it remains the same regardless of whether the axons are on their way to a patch, in an environment populated purely by dendrites of the 'wrong', interpatch, neurons or within the targeted patch itself[10]. Finally, quantitative studies of EM material in rat somatosensory cortex reveal that the various dendritic branches of individual cortical neurons contain similar densities and proportions of synaptic contacts[19]. All these findings strongly suggest that dendrites of upper-layer pyramidal neurons sample inputs in their vicinity regardless of the compartment in which the neuronal cell body itself is located.

A crucial caveat to this argument regards the strength and efficacy of synaptic contacts. The scheme presented here deals only with the existence or absence of these contacts; it says nothing about their strength or functional impact. Mechanisms which modulate synaptic strength such as long-term plasticity or dynamic processes of population coding and formation of cell assemblies[20–22] might all operate upon the connectional substrate provided by the axonal projections.

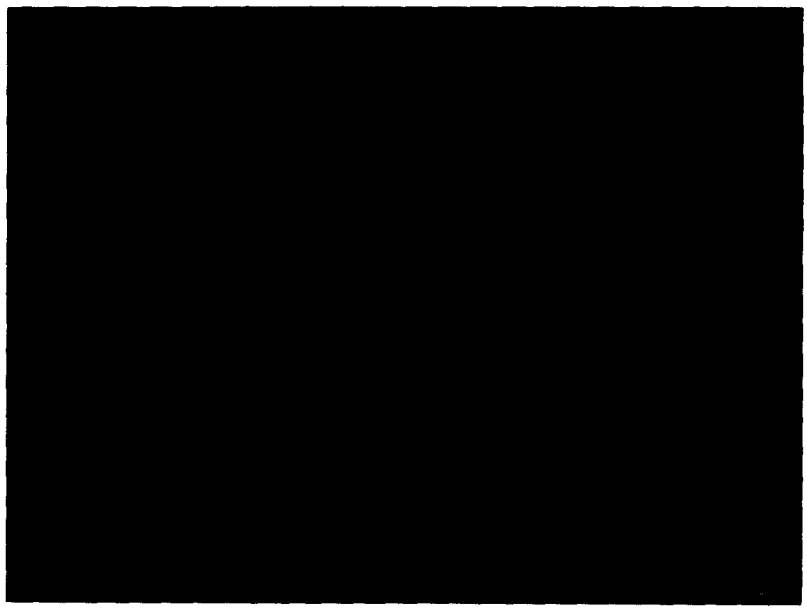

Fig. 3. *Relationship of dendritic arbors to cytochrome-oxidase (CO) blobs. The basal dendritic arbors of upper-layer pyramidal neurons in area V1 of the macaque monkey that were retrogradely labeled by a nearby biocytin injection are shown in yellow. The borders of the CO blobs from a neighboring section stained for CO are drawn in red. Note that, for the most part, dendritic arbors cross CO-blob boundaries without interruption. Scale bar, 100 μm.*

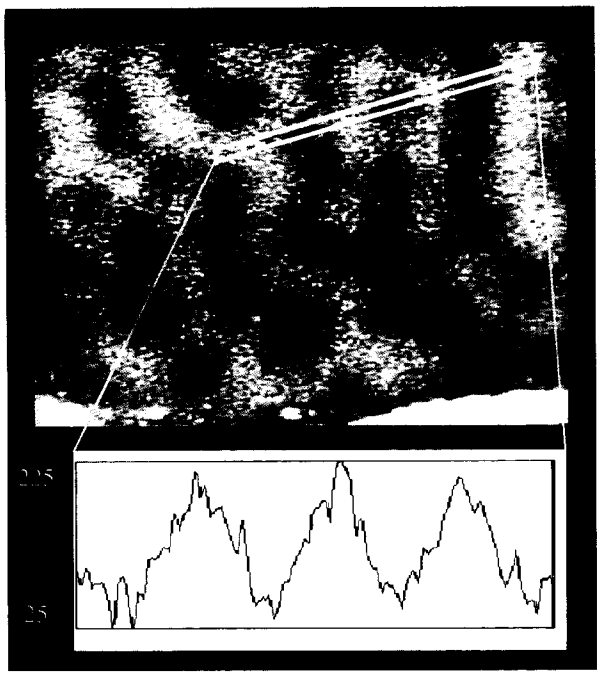

Fig. 4. *The pattern of activation produced by a single visual stimulus. This is a deoxyglucose (2-DG) autoradiograph of a tangential cortical section from area V1 of the owl monkey following stimulation by moving gratings of a single orientation. The histogram shows, quantitatively, the profile of 2-DG uptake along the indicated band. The neuronal responses as reflected by the 2-DG uptake oscillate smoothly across the line, and neighboring sites always differ slightly in their responsiveness. Note the similarity of this histogram to the population sampling profile shown in Fig. 2A.*

Functional manifestations of sampling diversity

If sampling diversity is such a fundamental characteristic of the cortical tissue, one would expect to see it reflected in the functional properties of cortical neurons. Figure 4 illustrates that this might indeed be the case for upper-layer cortical neurons. The figure shows the pattern of deoxyglucose (2-DG) uptake of cortical neurons in area V1 of the owl monkey during visual stimulation by a grating pattern presented at a single orientation. Using an image-analysis program, the profile of activation, as reflected in uptake of 2-DG, was measured along a line, in an analogous fashion to the scheme presented in Fig. 2A. Note that cortical responsiveness to the visual stimulation oscillates smoothly between maximum responsiveness at the center of the activated regions, and minimal responsiveness in between. Although the 2-DG pattern reflects the average neuronal activity at each cortical site, it is nevertheless remarkably compatible with the scheme of neuronal activation proposed in Fig. 2A.

Concluding remarks

It is proposed here that the current account of the striking order manifested by clustering and segregation of axons into isolated patches should be modified. Axonal patches are not devices for segregating neurons into separate processing streams; rather, they are the basis for maximizing neuronal diversity. That order should be a prerequisite for producing diversity might seem puzzling. However, consider the following metaphor: in trying to reproduce the full richness of natural colors, a painter must start with a set of pure colors that he can then mix at various proportions to create the infinite number of required hues. If these pure colors, by some unfortunate accident, got mixed, then the potential of the painter to produce a wide range of novel hues would be greatly diminished. Similarly, the purity of inputs introduced by the orderly clustering of axons into patches provides the basis for maximizing diversity of input mixtures sampled by the cortical neurons. The merits of maximizing diversity of cortical neurons is still a matter of speculation, but some instructive suggestions can be gained from recently developed cortical models (for example, see Ref. 23).

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