19

Group Report: Neocortical Microcircuits

UPs and DOWNs in Cortical Computation

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INTRODUCTION

A remarkable feature of the vertebrate brain is the key role played by cerebral cortex in the versatility of computation during cognitive operations and the adaptive control of the organism's actions when immersed in a novel environment. In particular, as advocated by William James as early as 1890, there seems to be an almost quantitative "fit" between the preeminence of cerebral cortex and the "complexity" of the cognitive repertoire specific to each species. Since then, searching for regional cortical uniqueness versus uniformity has been considered a primary axis of study. Two concepts of cortical organization are classically opposed: on one hand, phrenology and now functional brain imaging have given some credence to the delineation of specialized "organs of the mind" by singularizing regional variations of anatomy, metabolism oxygen consumption, and hemodynamic flow across the cortical mantle (Spurzheim 1824; Dehaene, Dehaene-Lambertz, and Cohen 1998). It has been argued that this parcellation in distinct functional areas, and the specialization of the columnar motifs that pave the cortical gray matter sheet, may be entirely genetically determined (Rakic 1988). On the other hand, network statistics reveal a number of structural regularities, which, to a certain extent, are found repeated across the whole cortex (Bok 1936; Sholl 1956; White 1989). Since then, numerous studies have tried to look for canonical building blocks and to define quantitative criteria for an area-specific articulation of these elementary processing units. The ultimate goal is to decide which ones, between the most probable intra- and inter-area

interactions derived from cortical anatomy and physiology, form a semantic basis for implementing specialized cortical computations.

A supplementary twist in this debate is the possibility that a diversity of building blocks coexists in the same anatomical network. Dynamic selection processes may enforce order on synaptic interactions, ensuring formation and dissolution in time of specific functional circuits (Woolsey in White 1989). It is therefore likely that the reductionist dream of molecular biologists who propose that "from the DNA sequences stored *in silico*, one may be able to compute the main features of the species-specific functional organization of the brain" is far from being fulfilled. Not only additional quantitative markers at the molecular and genomic levels are needed, but reproducible state-dependent contexts must be defined before one may seriously envision dissecting out waxing and waning forests of nested circuits during the time-course of a mental event.

This chapter summarizes our group's discourse on neocortical circuits at the 93rd Dahlem Workshop. We begin with a conceptually driven discussion and address the problem of decomposition of cortical structure, function, and computation in canonical elements. The comparison of taxonomies established at various integration levels raises the question of continuum versus clusterization; new techniques are now available to search in real-time for the transient switch-on of cortical microcircuits not only within, but also across anatomical microcolumns. Thereafter we focus on the identification of the format of the information processed by the cortex and the relevance of a multiplicity of temporal scales in coding schemas. Possible links are presented between the horizontal spread of depolarized "UP" states in cortical neurons, the transient synchronization of active assemblies repeated according to stereotyped temporal motifs, and the recent reinterpretation of the existence of temporal sequences of fixed microstates in the dynamics of global EEG maps (initially observed by Lehmann 1971). Since high conductance states appear to be generated *in vivo* by intense synaptic recurrence in the cortical network, models and electrophysiological experiments based on dynamic clamp techniques are now testing the possibility that attentional processes control cortical gain by changing membrane properties such as membrane potential and its synaptically driven variance. A third issue is more hypothetical and refers to plausible neural architecture for the emergence of cognition, and even access to consciousness. The last section illustrates one feature that is specific to the think-tank sessions as practiced at a Dahlem Workshop: interdisciplinarity enriches the field of study by borrowing concepts, tools, and analogies from other disciplines. New paradigms for the study of brain computation can be suggested on the basis of experience provided by computer science and theoretical physics. Evolutionary considerations using language as an example can also validate certain circuit architectures maintained through phylogeny. Even though the reader will not find decisive conclusions on the elusive existence of cortical microcircuits in this chapter, we hope to provide a fair view of consensus, controversies, and challenges that may guide future research.

CONCEPTS: CANONICAL DECOMPOSITION OF BRAIN STRUCTURE, FUNCTION, AND COMPUTATION

Although its existence is not guaranteed, modularity in brain organization can be studied at different structural levels, ranging from molecular ensembles to sets of interconnected neuronal networks. Its functional expression can also be searched for on different timescales in the nonrandomness of temporal patterns of activity arising from gene expression to coordination of neural activity between cell assemblies.

A first issue is to find ways of *reducing the level of complexity* of the biological system under study (membrane compartment, cell, network, map) by detecting stereotypes in the space and time domains. A second issue will be to show that the whole system organization and functional repertoire can be integrated in a hierarchy of elementary building blocks. If one accepts the possibility that such decomposition exists and, in addition, is linear, the functional output can be predicted from the convolution of the transfer function of each basic module and its input. A cartoon view of these concepts of modularity and segmentation, detailed in Figure 19.1, would be to imagine that the cortex, whatever its functional specificity, is composed of an array of identical modules replicated all over its surface (see Figure 19.1, case "$1 \times N$"). The specialization of cortex into identifiable sensory, association, and motor areas would result from specific combinations of basis modules. Another possibility is that the building block set is heterogeneous (see Figure 19.1, case "$N \times 1$"). If, in addition, some cross-talk occurs between elementary processes (see Figure 19.1, cases "Overlaid" and "Nested"), a nonlinear interaction is expected between modules and has to be taken into account. This can be done by defining additional binding principles and identifying specific relational architectures.

Another issue is the *preservation of the elementary function* of each module while progressively segmenting the whole network. The "invariance-by-segmentation" property may not be verified in highly recurrent networks, such as cortex, where an elementary processing module may be nested in a hierarchy of subnetworks of variable recurrence. Cutting one of the loops might alter, or even cancel, the global functional attributes of the cortical network. The case of the primary visual cortex illustrates the principle of recurrence. Most connections originate from within cortex even for cells that receive the direct impact of extrinsic inputs, a feature which has long been underestimated. For instance, a layer IV spiny stellate cell in cat area 17 receives only 6% of feedforward thalamo-cortical inputs, whereas 94% correspond to recurrent and feedback connections (Ahmed et al. 1994; Binzegger et al. 2004). Further studies may show that it is necessary to envision primary visual cortical modules not only as highly recurrent networks but also as encapsulated in a larger ensemble of thalamo-cortico-thalamic and long-distance corticocortical loops. Continuing to study the properties of cortical cells independently of the anatomical context
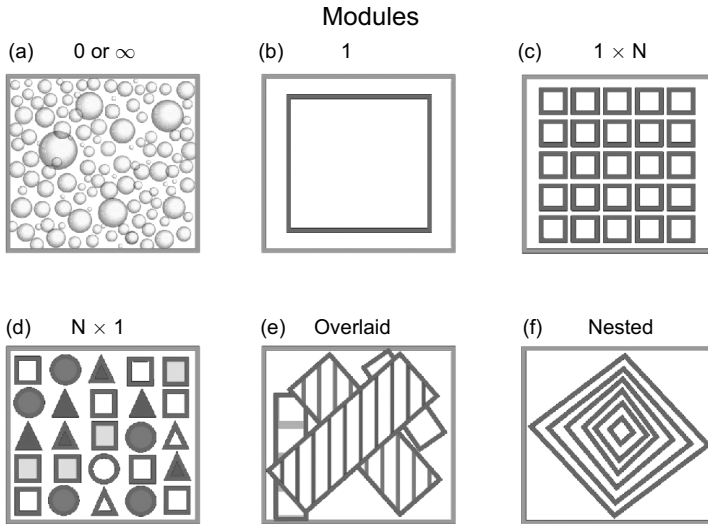
Modules

(a) 0 or ∞   (b) 1   (c) 1 × N

(d) N × 1   (e) Overlaid   (f) Nested

Figure 19.1   Modules: Several theoretical possibilities may be explored in the decomposition of cortex into an array of basic elements at the structural and/or functional levels. (a) "0 or ∞": These elements may be infinite in number, which is the equivalent of saying that, at the lowest level of organization, each and every element is unique and that no module is replicated. (b) "1": The cortex is the module itself. (c) "1 × N": Only one type of elementary module exists, replicated *n* times spatially all over cortex. This uniform tiling would not exclude the variant that a local combination of several basis modules would be responsible for the specialization of cortical areas into identifiable sensory, association, and motor areas. (d) "N × 1": The building block set is heterogeneous but finite. (e) "Overlaid": The building blocks are not independent and share elements. (f) "Nested": The modules are defined at different levels of integration and can be integrated in a compositional way in nested architectures.

of the recurrent network in which they are embedded may falsify our search for understanding the genesis of the specificity of cortical computations.

Canonical Structural Circuits (Static Circuits)

The search for microcircuits requires looking at repetitions of elementary units in terms of constituents (molecular–anatomical level) and invariant topological motifs in the connectivity pattern between these constituents. The most intuitive version of canonical circuits can be found in the radial columnar architecture of the cortex and its structure in six layers. In the case where the input projects in a regular topographic way onto the laminar plane and the location of cortical receptive fields is invariant along the cortical depth, the temptation is to collapse the 3D network into a 2D network, where each integration point represents an elementary cortical microcolumn. One of the most studied examples is the

cortical mosaic of input–output modules juxtaposed in the somatosensory cortex of some rodents. Each module embodies the imprint of the parcellation of the sensory periphery onto the cortical field; each cortical barrel represents one individual whisker in the somatosensory cortical matrix organized in rows and arcs and has the same respective location as the whisker in the snout (Woolsey and Van der Loos 1970). Other mapping examples, more continuous in nature, can be found in the visual cortex, although some debate was initially raised concerning the mosaic/distributed aspect of the global cortical network (Albus 1975).

Canonical Activity Processes (Dynamic States)

The Metacolumn Concept

In the Hubel and Wiesel model of the "hypercolumn" in primary visual cortex (Hubel and Wiesel 1963), the anatomical extent of the circuit should roughly correspond to the cortex volume activated by an impulse-like input (cortical spread function). However, the use of voltage-sensitive dye imaging techniques or intracellular recordings *in vivo* shows that the visual activity evoked by a point or bar-like stimulus spreads far beyond the classical radius of the anatomical column defined by vertical integration process along the cortical depth and extends laterally over long distances (Grinvald et al. 1994; Frégnac and Bringuier 1996; Bringuier et al. 1999). On distinct grounds, theoreticians have introduced the functional concept of "metacolumn" (see Figure 19.3, bottom left), where, in addition to the radial column characterizing vertical integration, a chunk of cortex spreading horizontally in superficial layers has been added in order to provide the contextual intracortical input required for completing the functional integration (Somers et al. 1998). Without this extended environment, the functional selectivity of the cortical module (e.g., its direction orientation selectivity or preference) would be lost.

The Temporal Signature of Spike Trains

Independently of the spatial location of the elements in the cortical tissue, another approach is to develop in time the activity of each member of the recruited assembly and search for some form of invariance in the temporal patterns of spike trains. Such stereotypy can be expressed either in a stimulus-locked fashion (time coding) or in the phase-relationship of spike activity across the different cells forming the assembly (relational coding). Multiple simultaneous recordings in the awake behaving monkey motor cortex have shown replication above chance level of temporal motifs composed by composite intervals between spikes of different units with a precision in the 2 ms range. The occurrence of such motifs has been found to be correlated with the nature of the

behavioral task (Go vs. No-Go in Vaadia et al. 1995) and could carry information related to the probability of expected reinforcement (Riehle et al. 1997). Stereotypy in time could then represent the signature of canonical operations specific to the relational (binding) topology of the activated graph, but not of the anatomical identity and location of the elements composing its nodes. This point will be developed further below (see section on FORMAT OF INFORMATION AND RELEVANCE TO TEMPORAL SCALE).

Canonical Computations and Compositionality Issues

Whatever the chosen level of integration, the next question is: How many modules can be extracted? Possible answers, detailed in Figure 19.1, are none, one (the cortex), many (the columns), or an infinity (the cell). The so-called "hypercolumn" can be seen as an example, in primary visual cortex, of a unitary module composed by the grouping of a finite set of anatomical columns whose boundaries are defined by the spatial spread of thalamic afferents representing the same point in space seen through each eye (Hubel and Wiesel 1963). However, the task becomes more daunting if the aim is to extract the subcircuits responsible for each elementary operation performed by the cortex. A group of neurons collaborating to perform one operation may not necessarily collaborate to perform a different operation (Swindale et al. 2001).

   In the case where the answer is not "one" but "many," is it possible to look for compositionality, that is, an alphabet and a grammar (Cavanagh 2003)? Can we predict the network performance on the basis of a functional syntax combining chains of elementary processes? This problem is compounded by the fact that multiple operations can be multiplexed in time in the same network. For instance, at a given point in time the spiking of a given cell may participate in two parallel computations, which engage transiently the same cell in different assemblies. An interesting theoretical development would be to search for scale-free architectures where similar binding rules operate at different integration levels (nested architectures). What applies between cell members of the same assembly may apply to interaction rules between compartments of a given dendrite (Mel 2003).

Validation of a Canonical Process/Circuit/Computation

Validation should be performed by comparing circuit stereotypes across different cortical areas within one species as well as across homologous cortical areas within different species. Phylogenetic and ontogenetic perspectives can serve to strengthen the argument of equivalence across circuit types and help define the functional attributes of new circuits that emerge during development and evolution (see section on EVOLUTIONARY CONSIDERATIONS USING LANGUAGE AS AN EXAMPLE).

TAXONOMY WITHIN AND ACROSS INTEGRATION LEVELS: CONTINUUM OR CLUSTERS

Continuum of Variability or Categorization of Diversity?

One may, or may not, believe in canonical modules. In spite of the generally limited confidence in such matters, the measure of variability against generic diversity should be evaluated with quantitative methods, not only across constituents within a given cortical area, but also across different functional areas and across species. In the latter case, one must accept some stratification hypothesis with evolution, where abrupt changes of primary principles are rarely observed, and refinement, elimination, or addition tend to be the rule. This argument, for instance, may advocate the use of the tree shrew model, where numerous functional streams afferent to V1 remain more segregated in the cortex at the anatomical level than in other mammalian species, and where the detection of a correlation with function and laminar location may be facilitated (Fitzpatrick 1996; Mooser et al. 2004).

Over the past few years, more attention has been given to inhibitory processes in the shaping of cortical functional selectivity, and a significant set of data reveals the computational diversity that may exist in inhibitory circuits (*in vitro*: Gupta et al. 2000; Monyer and Markram 2004; *in vivo*: Monier et al. 2003). Concerning the taxonomy of GABAergic interneurons, the following questions are still a matter of debate:

1. Is there a finite number of interneuron subtypes, and what criteria are necessary to classify GABAergic interneurons?
2. What is the minimal set of criteria that can help identify distinct subpopulations of GABAergic interneurons?
3. Why would so many types of interneurons be useful?
4. What approach allows for a systematic study of identified interneurons?

During the Dahlem Workshop, our group partially answered the first and last questions; however, no decisive consensus was reached for the others.

Morphological Taxonomy

There is great diversity of interneurons based solely on the morphology of their somata and of their dendritic and axonal arborizations. There is, however, no established convention for assessing which morphological characteristics of a neuron are essential to pertain to a given cell type or, in other words, which morphological differences are functionally important. Nevertheless, a positive consensus was reached for the first question, since certain interneurons can be recognized by their unique morphological characteristics, or on the basis of their patterns of axonal arborization, or the synaptic connections they establish with other interneurons and/or with pyramidal cells. Further, interneurons are not

solely connected by point-to-point chemical synapses and are often electrically coupled within specialized gap junction networks (Galarreta and Hestrin 2001).

Even if interneurons are differentiated into subtypes, some either lack or display a great variability profile when compared across different species. One of the best studied examples is the *double bouquet cell*. There is considerable interest in studying this interneuron, because it forms a widespread and regular microcolumnar structure spanning from superficial to deep layers, and because it appears to represent a key component of the minicolumnar organization of the primate neocortex (see section on SEARCH FOR CORTICAL MICROCIRCUITS). However, these neurons are less numerous in the cortex of other species or may even be absent (e.g., in mouse and rat, although this is still a matter of debate). In addition, there are significant variations in the number of neurons and the proportion of excitatory (glutamate) and inhibitory (GABA) neurons and synapses within the minicolumn in different areas and species (DeFelipe et al. 2002).

Molecular Determinants and Multiparametric Taxonomy

Recent studies have extended the dimension to the classification search. Experts in the field still think that GABAergic interneurons can be further subdivided into distinct subtypes if sufficient criteria are considered and cross-correlated. The most frequent parameters that have been used so far are morphological features (e.g., soma shape, dendritic and axonal arborization, axonal targets), neurochemical markers (calcium-binding proteins, neuropeptides, neurotransmitters or their synthesis enzymes), intrinsic electrical properties (e.g., firing pattern, firing frequency, action potential width and amplitude, input resistance), synaptic dynamics (connectivity and its plasticity, decay time constants of EPSPs and IPSPs), as well as a specific repertoire of expressed proteins (e.g., ion channels, receptors).

The minimal number of required criteria has not yet been assessed but most experts agree that it will vary depending on which cell types are studied. Thus, fast-spiking cells can be predicted to be somatostatin-negative, since this marker has not been found in this frequently studied cell population so far. However, they can also be subdivided in subclasses if other parameters are taken into account, for example, axonal arborization and synaptic properties. Recent attempts at correlating firing properties with protein expression corroborate the existence of clear-cut GABAergic interneuron subtypes (Toledo-Rodriguez et al. 2004; Monyer and Markram 2004). Present data also suggest the existence of molecular determinants underlying oscillatory and synchronous network activity and lead to the conclusion that different types of interneurons may subserve distinct functions, for example, by participating in the generation of oscillatory activity in different frequency bands (Blatow et al. 2003; Whittington and Traub 2003). This may have a decisive impact on controlling the precision of spike timing (see below) and more studies on this issue are expected *in vivo*.

METHODOLOGICAL CONSTRAINTS IN CLUSTER ANALYSIS

The use of multiple criteria raises an interesting combinatorial issue. As illustrated in Figure 19.2, the assumption is made that all diversity of the repertoire should be found in a "hypercolumn cube" of $1 \times 1 \times 2$ mm, which is a rough estimate of the volume of cortex required to process one point in visual space through both eyes and a complete preference set of orientation filters. The number of classes given in Figure 19.2 is based on the most recent studies performed *in vitro* (Toledo-Rodriguez et al. 2004). If the profiles observed for each classification type (anatomical, genomic, electrophysiological) were to be independent, the basic element of the neocortical microcircuit can be considered the cell itself and its singularity, since the number of neurons and potential categories are roughly comparable! Also, armies of postdoctoral fellows, working *in vitro,* might get depressed by the simple thought experiment of guessing the number of cells to be recorded before reaching statistical significance level.

Cluster analysis provides a quantitative method with which to measure in a multidimensional space how similar neurons are to one another. The group of Rafael Yuste has recently applied this approach to a population of neocortical interneurons from mouse primary visual cortex with the goal of examining how many distinct classes of interneurons exist (Dumitriu et al., submitted; Yuste 2005). The sample of interneurons included parvalbumin (PV)-positive, somatostatin (SS)-positive, and neuropeptide Y (NPY)-positive cells, as selected from transgenic animals expressing GFP under the control of these three promoters. These neurons were patched and their intrinsic electrophysiological parameters measured, as well as the time constants of the spontaneously received EPSPs and IPSPs. The neurons were also filled with biocytin and reconstructed morphologically after fixation. For each neuron, a series of ~100 different morphological parameters were measured. The morphological and physiological
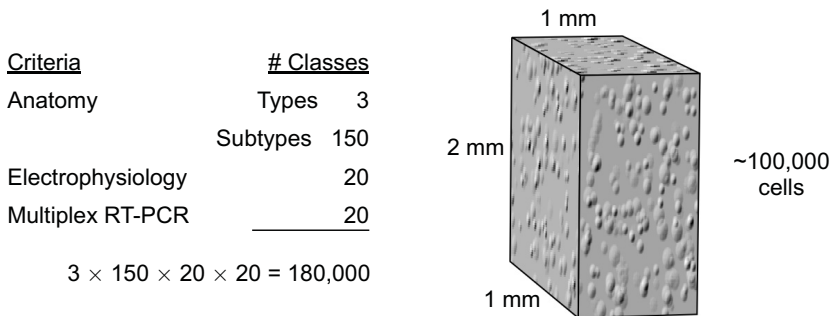

Criteria	# Classes	
Anatomy	Types	3
	Subtypes	150
Electrophysiology		20
Multiplex RT-PCR		20

$$3 \times 150 \times 20 \times 20 = 180,000$$

1 mm

2 mm

1 mm

~100,000 cells

Figure 19.2 Taxonomy and the hypercolumn: The volume of the cortical tissue chunk is the size of a functional hypercolumn (Hubel and Wiesel 1963). The number of neurons is roughly of the order of the number of classes (180,000) based on anatomical, electrophysiological, and genomic criteria (see text for the choice of parameters).

parameters were then used to generate two cluster trees: one based on the morphology and the other on the physiology. Interestingly, both trees had three major branches, which corresponded quite accurately to the three groups of PV, SS, and NPY interneurons.

From these results, it can be concluded that at least *three* distinct different classes of neocortical interneurons exist in mouse primary visual cortex. Further, there is a correspondence between the biochemical, morphological, and electrophysiological characteristics of the neurons within those groups, since the clusters found with the electrophysiological analysis can be used to predict the morphological clusters and they correspond to the expression of these three marker proteins.

One disadvantage of cluster analysis is that it always results in clusters and does not provide a natural cutoff in the classification, which in principle can be pursued with subsequent subdivisions until each cluster has a single individual. At the same time, the use of independent measurements with which to cluster a data set can help in distinguishing important clusters from the noise. Overall, the arguments in favor of the real existence of distinct classes of neocortical neurons are very compelling in the case of neocortical interneurons. There are striking correlations between the morphologies of the axon and dendrites, the firing patterns and spike and AHP characteristics, the EPSP and IPSPs kinetics, the synaptic dynamics, the coupling through gap junctions to neurons of the same class, and the expression of distinct protein markers. It is very probable, like the interneurons in the spinal cord, as demonstrated by Jessell and colleagues (Tsuchida et al. 1994), that different classes of neocortical interneurons could differentiate under the control of different promoters and play specific circuit roles. In general, if the circuit is built with specific elements, it appears absolutely essential to come to terms with this diversity in order to understand the function of the circuit.

Standing Issues

To a certain extent, numerous studies, whether at the anatomical or functional level, have for a long time erased the variability content of their data by looking for average morphological structures or average temporal response profiles, without analyzing the computational impact of possible diversity. This makes the comparison between previously treated databases obtained in distinct laboratories difficult. No effort has been made to reconcile the classification methods and criteria used by different groups. Therefore, it is important that some benchmark is proposed to validate the classification of data. An international database is clearly needed. The criteria of classification should be widely accepted and regularly updated (see the collective document which has been proposed by 35 scientists at http://www.columbia/cu/biology/faculty/yuste/petilla), taking into account the rapidity of the techniques in that field.

The multiplex RT-PCR technique has limitations. The first is quantitative and concerns the existence of high probabilities of false negatives. Second, mRNA measurement in the slice looks like a "photograph" made after a massive disturbance of activity imposed by the slicing process itself, which may result in spurious activity-dependent regulation of gene expression that may vary according to the experimental protocol. A third, fundamental issue is that one should not limit oneself to cytoplasmic mRNA harvesting. The search should be extended to the proteome and membrane-bound proteins in order to establish the cell-by-cell distribution of receptor and ions. In other words, it is likely that multiplex RT-PCR will not give access to the "molecular shape" of the neuron. A question of importance in terms of cellular computation remains the subcellular distribution of the balance between GABA and glutamate receptors across the dendritic compartments.

Genetic approaches that allow the marking of interneuron subclasses with an *in vivo* fluorescent protein are a promising avenue that is being taken in order to identify even rare subtypes in the slice preparation and *in vivo*. They will certainly promote the systematic study of GABAergic interneurons at the cellular and system levels.

SEARCH FOR CORTICAL MICROCIRCUITS: WITHIN OR ACROSS COLUMNS?

Within Columns (Vertical)

The issue of whether or not there is a canonical microcircuit in the neocortex is of the utmost importance. The possibility of a common transfer function performed on any cortical input could be the equivalent of a DNA helix model of the brain. As conceptualized earlier, the canonical microcircuit hypothesis can be articulated as the existence of a common single operator (or transfer function) of cortical function, one which would be similar in different cortical regions and in different species. This hypothesis was first explicitly articulated by Hubel (Hubel and Wiesel 1974) and has been most developed in the writings of Douglas and Martin (1991, 2004; Douglas et al. 1989).

Brief History of the Columnar Consensus

In spite of the diversity of neuronal elements and the profusion of connections within the cortical network, one should recognize that there are strong arguments in favor of a canonical microcircuit, especially linked with phylogeny and ontogeny. Like in other systems in the evolution of the body plan, it is likely that the neocortex arose by manifold duplication of a similar circuit module. The relatively short evolutionary history of the neocortex, together with the prodigious increase in size it has experienced in mammals, make this idea appealing. Also,

developmentally, all cortices of all animals arise through a very stereotypical sequence of events: from neurogenesis in the ventricular zone, through migration along radial glia, depositing of neuroblasts in cortical layers, and emergence of axons, dendrites, and dendritic spines. These events occur in some cases with nearly identical timing in different parts of the cortex and in different animals, so it is not unreasonable to argue that they result in the assembly of an essentially identical circuit.

The Radial Microcolumn

Anatomically, the presence of vertical chains of neurons defining small columnar structures has been noted at least since Lorente de Nó (1938). Cyto- and myelo-architectonic studies from even earlier dates show presence of vertical aggregates of neurons and vertical bundles of axons. This radial arrangement is frequently referred to as the micro- or minicolumnar organization. Similar bundles of apical dendrites have been noticed more recently using a variety of techniques. Therefore, this arrangement defines an anatomical module, consisting of a vertically oriented group of interconnected cells, which are contained in a vertical cylinder of tissue with a diameter ranging approximately from 25 to 50 μm (depending on the cortical area and/or species). These structural modules appear in many different parts of the cortex in many different species (see schematized representation in Figure 19.3b). Dendritic bundles of apical dendrites of pyramidal cells have been described in various areas of the mouse, rat, rabbit, cat, and monkey, the size and number of dendrites forming the bundles depending on the cortical area and species being variable (e.g., Peters and Walsh 1972; Fleischhauer 1978). Since there are significant variations in the number of neurons as well as in proportion to the excitatory (glutamate) and inhibitory (GABA) neurons and synapses within the minicolumn in different areas and species (DeFelipe et al. 2002), we can conclude that the radial minicolumns should be considered dominantly as regularly distributed vertical aggregates of pyramidal excitatory neurons.

The Functional Column

The basic functional element of the neocortical microcircuit can be defined primarily by the vertically dominant integration flow of activity evoked by thalamic input (see Figure 19.3c). The electrophysiological recordings since Mountcastle and Edelman (1982) and Hubel and Wiesel (1977) have emphasized the invariance of receptive fields along vertical electrode penetrations, in terms of spatial location in the visual field and orientation preference property. These pioneering studies led to the specific proposal of functional columns of different scales. The macrocolumn is defined as a complex processing and distributing unit that links a number of inputs to a number of outputs via overlapping internal processing chains (minicolumns) (Mountcastle 1997). One should
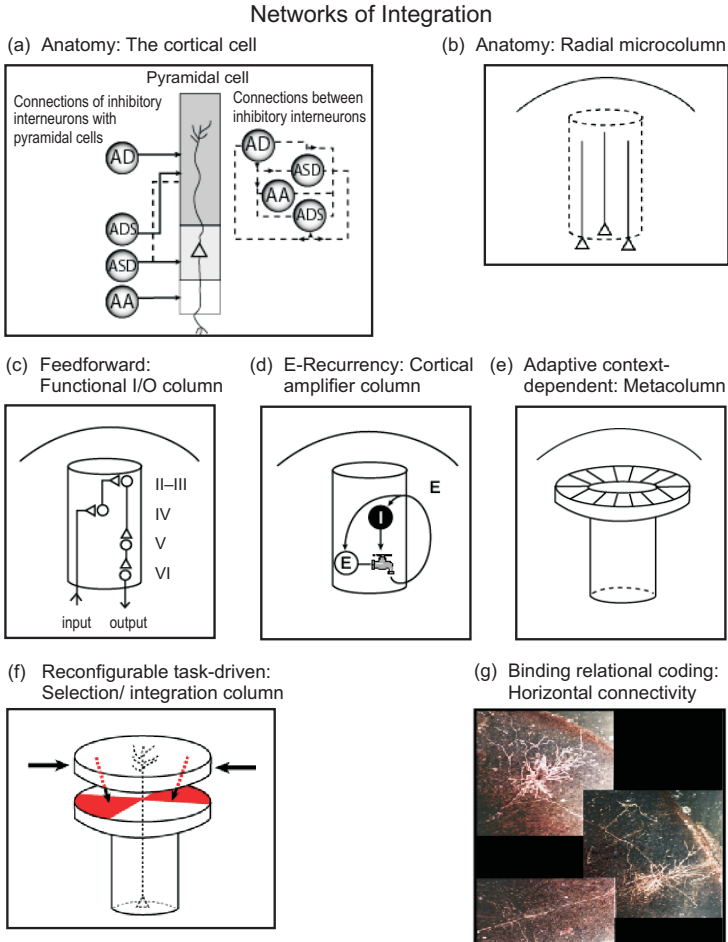
Networks of Integration

(a) Anatomy: The cortical cell

(b) Anatomy: Radial microcolumn

(c) Feedforward: Functional I/O column

(d) E-Recurrency: Cortical amplifier column

(e) Adaptive context-dependent: Metacolumn

(f) Reconfigurable task-driven: Selection/ integration column

(g) Binding relational coding: Horizontal connectivity

Figure 19.3 Networks of integration. (a) The cortical pyramidal cell and its membrane compartments represent an elementary site of synaptic convergence. (b) Bundles of axons of pyramidal cells form radial microcolumns. (c) One of the best-studied input–output circuit characterizes the serial processing of layer IV afferents by first-order targets, the stellate cells in layer IV. After a series of successive relays in layer II/III and layer V, these terminate on layer VI neurons, which send their axons out of the functional column (Gilbert and Wiesel 1979). (d) The canonical microcircuit exemplifies the high level of recurrence of excitatory local connections whereas the inhibitory interneurons control the gating of the avalanche of excitatory amplification (Douglas and Martin 1991). (e) The concept of metacolumn, introduced by Somers et al. (1998), corresponds to the network influence carried via long-distance horizontal connections in the supragranular layers (see g), that needs to be added to the column to predict its context-dependent behavior. (f) The hypothesis of selection of computational circuits (red volume) by the neuromodulatory action of ACh fibers running in layer I. (g) Inverted contrast picture of two biocytin-labeled layer II/III pyramidal cells connected by horizontal axons (Frégnac and Friedlander, unpublished).

note, however, that the definition of the functional column applies to the in-put–output circuit formed exclusively by serial excitatory links from layer IV (input layer) to layer VI (one of the output layers). The laminar relay description (IV → II–III → V → VI) within the column is based on the assumption that ax-ons are connected to neurons whose somata were located in the layer to which the axon projects (Gilbert and Wiesel 1983).

Standing Controversies

Although most Cajal lovers dream of wandering in a forest of pyramidal cells, recognizing here and there a repetitive anatomical motif, there are perhaps even more compelling reasons "against" than "for" the "columnar" canonical hy-pothesis. It is indeed hard to imagine that there is a common denominator in all of the different computational problems that the cortex is solving. In some cases, these problems are essentially mathematically irreducible, such as the 3D visual processing, as compared with auditory speech perception, for example. Also, the exact nature of the structure of the cortical modules is elusive to define. Ana-tomical techniques do not reveal any clear borders between modules, and physi-ological approaches reveal a combination of maps superimposed onto one an-other with different metrics, such as orientation ocular dominance or spatial frequency (Basole et al. 2003). Recent intracellular *in vivo* recordings in V1 cor-tex show that the computation of orientation preference, thought to be internal-ized in columnar modules according to the feedforward model of Hubel and Wiesel, is in fact the result of a diversity of combinations of excitatory and inhib-itory inputs. This diversity reflects mostly the anatomical nonuniformity of the intracortical input context provided by the orientation map ("metacolumn" con-cept considered above; Figure 19.3e, f) in which the cell is embedded (Schum-mers et al. 2002; Monier et al. 2003; Frégnac et al. 2003). Finally, the detailed anatomical comparison of cortical neurons sampled from different regions re-veals that each cortical region is endowed with specific subtypes of pyramidal neurons, as revealed by Elston, DeFelipe, and Yuste (Elston et al. 2001; Elston and DeFelipe 2002; DeFelipe et al. and McCormick and Yuste, both this volume).

Across Columns (Horizontal)

As noted earlier, a strong historical bias can be found in favor of the description of modular circuits respecting the laminar organization and organized along the depth (vertical) dimension of the gray matter. Similarly, at the functional level, a strong bias can be noted in the elucidation of feedforward sequential streams in processing. An analogy can, however, be made with computers and the problem of minimization of the wire length (Peters and Kaiserman-Abramof 1970; Chklovskii et al. 2002; Mitchison 1991; Mead 1989). To avoid a complete

connectivity pattern and reduce the physical size of the global system, a hardware configuration often used is to stack-over interface bus-cards, each dedicated to input only or output only. In that respect, the vertical dimension does not carry processing, and only the lateral dimension is used to wire the computing architecture. This analogy suggests that, rather than looking for vertically organized columns, one should concentrate on the pattern of horizontal connectivity (Figure 19.3e, f) to characterize the functional specialization of the cortical network under consideration.

Excitatory horizontal connectivity from visual to prefrontal cortex exhibits a patchy layout: the interpatch spacing is roughly double that of the patch diameter. This patchy architecture has been studied extensively in primary visual cortex and shows a strong correlation between anatomy and function. Cells that are connected through long excitatory links tend to belong to columns with the same functional preference. Some authors, however, have moderated the impact of the principle "those alike tend to wire together." This schema neglects the spatial organization of axons and dendritic structure of the target cell. The matching of the composite size of the axonal terminal distribution from the presynaptic cells with that of the dendritic spread of the target cell could be the result of an optimization process maximizing the diversity of inputs collected by a given neuron (Malach 1992).

Several arguments can be listed to support the fit between the function and the anatomy of the horizontal network. During development in strabismic cats, anomalous horizontal connectivity links are formed between distant cortical territories corresponding to the same eye-dominance (Schmidt et al. 1997; Trachtenberg and Stryker 2001). Another example can be observed with a sensory substitution protocol imposing a rewiring of the input to the auditory thalamus at an early stage of development. If visual input is provided to auditory thalamus at that time, the auditory cortex develops a visual competence and an orientation preference map. The horizontal connectivity anatomy in the rewired A1 cortex resembles that of a control area V1, in terms of anteroposterior/mediolateral biases, and not to that of a normal auditory cortex (Sharma et al. 2000). To progress in this direction, work must be undertaken to characterize the factors, linked with activity and the sensory code, that determine the number of patches, the extent of their distribution, their input distribution, and their output distribution, both during normal and abnormal development.

Standing Consensus

The cortex looks like a multifaceted structure where some stratification and crystal-like regularity is apparent, depending on the view angle (vertical, horizontal) and the nature of the module for which one is looking (anatomical, functional). To the dismay of most experimenters, this remarkable versatility of

changing its crystalline motif adapts to the computational task on demand. In other words, cortical modules appear highly reconfigurable, and the autonomous structural entity that forms the grain of the lattice has a virtual boundary defined by the nature of the computation. Figure 19.3f illustrates a recent hypothesis made in favor of a reconfigurable selection network, where "the superficial layer neurons within and among patches, and within and among areas, cooperate to explore all interpretations of input and to select an interpretation consistent with their various subcortical inputs" (Douglas and Martin 2004). More work is also needed to elucidate the controversial role attributed to various ascending neuromodulatory influences and the still mysterious or controversial implication of layer I.

FORMAT OF INFORMATION AND RELEVANCE TO TEMPORAL SCALE

To extract computational steps in network processing, most experimenters and theoreticians have focused their attention on measures derived from spike activity, since this is the component of the neuronal integrative process that is broadcast through axons and synapses to the rest of the network. The most commonly used measures are based on:

- The *rate of action potential* generation per relevant unit of time. The relevant unit of time in terms of sensory coding is thought to vary from a few tens of milliseconds for processing simple features to several hundreds in the case of the construct of a mental percept.
- The *precise timing of action potentials* during this unit of time. Temporal reproducibility of stimulus-locked activity in response to a continuous flow of full field patterns gives some indication of the precision in spike occurrence time coding. In such stimulation context, precision, at least in retina and thalamus, narrows to the 2–5 ms range (Reinagel and Reid 2000; Frégnac et al. 2005). Associative forms of synaptic plasticity in cortical networks have also been shown to depend on the temporal order and delay between pre- and postsynaptic activities, with a precision in the order of a few ms (Markram et al. 1997).
- The spatiotemporal distribution of the activity in the network and the relative phase of firing between cells of the same assembly (Abeles and Gerstein 1988).

Although the following arguments concern coding by spike activity, it is important to note that recent efforts have been carried out to retrieve network state dynamics and information transfer measurements from the analysis of membrane potential trajectories of cortical cells (intracellular recordings; see reviews in Shapley et al. 2003 and Frégnac et al. 2003) and from optical imaging of

supragranular layer activity (voltage sensitive dyes: see, e.g., Arieli et al. 1996; Sharon and Grinvald 2002).

Rate versus Time Coding

Experimental support for a neuronal doctrine based on rate coding (Barlow 1972) is found in the stability of cortical measures of feature selectivity when using, as the output signal, the rate of discharge or total number of spikes evoked as a function of the orientation of the stimulus in V1 (Hubel and Wiesel 1962) or the direction of the planned movement in M1 (Georgopoulos et al. 1986). Despite this evidence, for the past ten years there has been a growing claim that information is also encoded in the timing structure of spike trains of single neurons. The study of statistical moments of higher order than the mean shows evidence for temporal precision in the order of a few milliseconds (review in Abeles 1991). Thus, multiple coding schemes may coexist in spike train patterns, accounting for different aspects of the functional dynamics of cortical networks. The prevalence of time versus rate coding in the same structure could depend on several factors, such as the density and statistics of the input regime and its associated computational load, the context of sensory adaptation, the internal state of the cortex (e.g., level of desynchronization in the EEG), and the dynamic regime imposed by the balance between recurrent excitation and inhibition.

Despite four decades of research characterizing the response properties of sensory neurons in primary cortical areas, we still do not have a good picture of how cortical neurons really operate under realistic conditions (i.e., how, for instance, natural scenes are encoded by cortical activity patterns). Much of our current knowledge is derived from experiments using reduced stimuli (i.e., impulse-like stimuli, such as spots, white noise, or sinewave gratings for the visual system). The main problem with this is that under the continuous influence of the feedforward drive and massive recurrent intracortical activity produced by natural images, cortical neurons are forced into a high conductance dynamic regime where their behavior may become highly nonlinear. More work is needed to compare the actual subthreshold and spiking activity of sensory cortical neurons in response to natural scenery movies or continuous sound tracks to predictions based on linear estimates of receptive field properties established by conventional methods.

The Synfire Chain Signature of Cortical Songs

Independent of the spatial location of the elements in the cortical tissue, another approach to describe a functional assembly is to develop the activity of each member of the recruited assembly in time and look for specific temporal cross-relationships. After more than twenty years of continuous research, Abeles and his group identified the replication above chance level of temporal motifs of a

few hundred milliseconds of total duration, composed by a chain of feedforward and recurrent excitations (Abeles 1982, 1991; Vaadia et al. 1995; Rieke 1999). These temporal motifs can eventually be found in high-order statistics of the spike train of a single cell, since the same element of the synfire assembly can participate several times in the activation chain. A continuous version of these discrete patterns has been reported recently in intracellular whole-cell recordings in voltage clamp mode *in vitro* and in intracellular current clamp recordings *in vivo* (Ikegaya et al. 2004), although the functional significance of such events remains to be clarified. Several features are remarkable, in the sense that these motifs become more precise in the timing of individual action potentials with the repeats and can sometimes bind transiently to each other. This last finding is reminiscent of the theoretical prediction that suggests compositionality of synfire chains through activity-dependent plasticity, which would affect the finally stabilized probability of connections between cortical cells (Delage 1919; von der Malsburg 1981; Bienenstock and Doursat 1991). Support for this view could eventually come from the morphological study of branching patterns of dendrites and axons, considered here as a read-out of the past association processes (Bienenstock 1996). An extreme view would be to consider that the temporal motifs of cortical spike trains form a "cortical song" by itself, which becomes independent of the absolute physical location of the cell in the network. Stereotypy in time would then represent the signature of canonical operations specific to the binding topology of the activated graph, but not of the anatomical identity and location of the elements composing its nodes.

RELATIONSHIP BETWEEN UP AND DOWN CELLULAR STATES, TRANSIENT SYNCHRONIZATION OF ASSEMBLIES, AND GLOBAL DYNAMICS IN EEG MAPS

UP and DOWN States

A recent revival of attention has been accorded to membrane potential dynamics in cortical cells and the capacity of cells to engage in persistent activity for time periods up to a few seconds, compatible with the buildup of a working memory. If such behavior is well established in the striatum and prefrontal cortex, the presence of bistable units has been long disputed in primary and association cortex. UP states are not characterized by a specific pattern of persistent or synchronized activity; rather, they are associated with a high conductance state due to an intense afferent or recurrent synaptic bombardment. This ongoing bombardment sets the membrane potential of the target cell in a constantly depolarized state, just below the spike firing threshold. During this behavior, cortical and striatal cells exhibit bimodality in the distribution of their membrane potential values, defining two states: one in the vicinity of –70 to –80 mV (DOWN state) and one more depolarized by +15–20 mV (UP state). This behavior has been observed both *in vivo* and *in vitro*.

Although it has been strongly suggested that the tonic influence of attention-related and neuromodulatory signals, present in the awake and behaving animal, would force cortical cells to operate in the UP state most of the time (Stériade et al. 2001), most evidence for the description of bistable cells *in vivo* comes from the anesthetized preparation. Under xylazine and ketamine, spontaneous UP state periods last up from a hundred ms to up to several seconds. In slice preparations from ferrets, where the network is severely deafferented, the spontaneous occurrence of UP state episodes is rarely observed for normal artificial cerebral spinal fluid (ACSF) concentrations: the experimenter needs to promote the excitability of the cortical tissue by changing the potassium and calcium concentrations in order to reveal reproducible UP and DOWN transitions (Sanchez-Vives and McCormick 2000). However, in slices from mouse neocortex, UP and DOWN transitions are readily observed in normal ACSF.

The definition of UP and DOWN states, although based on the intracellular membrane potential dynamics of a single cell, may also be reflected in the level of recurrent activity in the local network, detectable by depth EEG recording (Paré et al. 1998). Indeed, positive EEG dips are the inverted image of the intracellular Vm behavior. Similarly, in the thalamus, the occurrence of UP states can be monitored by the detection of episodes of sustained burst multiunit activity. Divergent and recurrent connectivity leads to a strong self-modulatory influence of the cortex upon itself. An as yet unaddressed theoretical aspect is whether two-state dynamics are the only solution or whether the network state can wander across a larger but finite number of recurrence levels.

The part taken by intrinsic membrane properties and extrinsic drive, such as the balance between excitation and inhibition, remains to be clarified during UP states. In the pharmacologically activated cortical slice, McCormick's group finds an almost perfect balance between gI and gE during the UP state in prefrontal cortex. This voltage clamp-derived measure differs from theoretical estimates, based on ongoing activity in the primary visual cortex in the anaesthetized preparation (gI = $4 - 6 \times$ gE; Rudolph and Destexhe 2001; review in Destexhe et al. 2003), or from continuous conductance measurements done during visual activation (Monier et al. 2003). In the latter case, the UP state can also be evoked by nonoptimal stimuli, and the balance is often reached in terms of current and not conductance, clamping Vm just below spike initiation (for a theoretical prediction, see Shelley et al. 2002).

Is the UP State Instrumental in Building Up Synchrony?

What is the functional consequence of UP states in terms of spiking behavior and processing capacity of cortical neurons? On one hand, the ongoing bombardment due to massive recurrent activity during UP states may change the input–output transfer function of cortical neurons; this will be discussed in more depth later. On the other hand, because of the depolarized state, one may expect that synchrony in spike activity will be more easily detected when cells are

already in the UP state. This last question has been addressed both in the prefrontal cortex during the spontaneous generation of UP and DOWN states and in the primary visual cortex in response to a visual stimulus. Spike-triggered average records reveal that the UP states or visual responses are composed of two components: a large broad base of depolarization (which is termed "base" or "bias") and a 3–5 mV event lasting about 10–20 ms, which triggers the action potential. These results suggest that action potentials are triggered by the synchronous firing of a subset of presynaptic neurons (Nowak et al. 1997). More direct evidence has been obtained independently in single electrode voltage clamp, showing that for a specific set of stimulus features (velocity, direction, orientation), a light moving bar often evokes periodic bursts of excitatory inputs without or shifted in phase with inhibitory inputs. These packets of synchronous events last 10–20 ms and their phase onset can vary from trial to trial, suggestive of a reverberating process of intracortical origin (Bringuier et al. 1997).

Another set of observations, from McCormick's and Frégnac's laboratories, suggests that the inhibitory network is very important in the control of spike timing. In spontaneously active cortical networks, McCormick's study compares the IPSCs measured in voltage clamp of cortical pyramidal cells to 0 mV to EPSCs at –75 mV, and finds that IPSCs contain a much higher level of power at all frequencies above approximately 10 Hz (Hasenstaub et al. 2005). During visual stimulation, Frégnac's group examined the trial-by-trial frequency-time behavior of subthreshold membrane potential trajectories as a function of orientation and direction of the stimulus. High-frequency oscillatory behavior (40–90 Hz) is evoked during UP states in current clamp, while, in the same cell and under the same stimulus condition, the continuous voltage clamp measurement of excitatory and inhibitory conductances shows the presence of shunting inhibition (Monier et al. 2003; Russier et al. 2002).

One function of precise spike timing is to reduce the number of coactive afferents necessary to elicit a postsynaptic spike and increase selectivity of the association process: only closely spaced action potentials, emitted in the course of highly reproducible spike train patterns, will temporally summate and efficiently drive postsynaptic neurons. It is hypothesized that axoaxonic and basket GABAergic neurons may control precisely not only spike rate but also spike timing and thus may play an important role in both rate and time codes. Taking into account the fact that fast-spiking inhibitory interneurons are capable of transmitting higher-frequency information, the varying results summarized above suggest that high-frequency synchronized IPSPs are important for controlling rapid transitions in membrane potential and input conductance, leading to a high level of temporal precision in spiking behavior of pyramidal neurons.

Possible Functions for UP States

The functional role of the UP state remains open to conjecture. Are two states an epiphenomenon of network dynamics, a view shared by some of the participants

of our group, or are they a functional operating feature of the cerebral cortex, mediating working memory, attention, sensorimotor coordination, and other cortically generated computations? In support of the latter view, it has been proposed that a synchronous transition in the UP state may signal the general activation of a given microzone by a behavioral event and enable more easily the generation of action potentials (Stern et al. 1998). However, a review of the experimental evidence, partly unpublished, points to the diversity of effects of sensory stimulation on the dynamics of cortical UP and DOWN states. For instance, the sustained presentation of a full-field input (drifting grating) increases the UP state duration, preferentially in complex cells (Anderson et al. 2000). This effect appears specific to the neurons that share the same orientation preference. The authors suggest that UP states might participate in the cortical presentation of stimuli, or at least in stochastic resonance facilitating the integration of subthreshold inputs (see next section).

This interpretation differs from observations made in somatosensory cortex by correlating optical imaging and intracellular recordings. Subthreshold sensory synaptic responses evoked while a cortical area was engaged in an UP state were reported to be smaller in amplitude, shorter in duration, and spatially more confined (Petersen et al. 2003). These effects recorded at the single-cell level were correlated with local changes of cortical activity measured using optical imaging. The interpretation of these data, however, remains ambiguous since the lack of detectable change in the optical imaging signal—when the network is already in the UP state—is not surprising. A quantitative study of visual cortical receptive fields conditional to the membrane potential state occupied just before the arrival of the thalamic input shows on average a more neutral conclusion (Huguet et al. 2004). Two separate mechanisms of activation are revealed. The first is focal and transient and is linked specifically with sensory processing; when applying the appropriate reference statistics, subthreshold receptive fields are comparable in size when evoked from the DOWN state or the UP state. A more global activation process is triggered conjointly when one column in the cortical map switches from a DOWN state to an UP state. It corresponds to the slow lateral propagation of the UP state through horizontal connectivity and may be considered as nonspecific in terms of information processing. This viewpoint contradicts Petersen et al.'s (2003) conclusion; they interpret both activation processes as information specific and claim that both sensory-evoked PSPs and spiking are inhibited by spontaneously occurring UP states.

Functional Microstates in the Human Brain

Thus far, our discussion has been limited to the dynamics observed in the membrane potential of a single cell, or averaged across a cortical column extension, through optical recording with a spatial precision of 50–100 μm. Synchronicity and oscillatory behavior, however, is often more easily detected when averaging

over larger spatial scales and using macroprobes, such as local-field potential and EEG.

The term *functional microstate* is used to describe a particular, but very stable, empirical observation when recording multichannel human EEG (Lehmann et al. 1987). It is the observation that the spatial configuration of the global scalp electric field always shows stimulus-locked periods of stability separated by short transitions, which last on average around 80–120 ms. Based on this observation some authors have proposed that information processing is parsed into sequential episodes and that these episodes represent the basic building blocks underlying spontaneous or evoked information processing (Michel et al. 1999).

Distributed linear inverse solutions applied to these microstates show that each state is characterized by the activity of a distributed neuronal network implicating different areas of the brain. It is assumed that the duration of the segment corresponding to a fixed spatial pattern reflects the computation time that this particular network needs to accomplish a particular part of the task, that is, a step of information processing. The abrupt switch from one state to the other would be mainly due to the exclusion and inclusion of new modules in this network, leading to a dynamic relational reconfiguration of the large-scale cerebral neural network over time.

Methodologically, these functional microstates are confirmed when applying cluster analysis on the multichannel EEG data. It usually reveals that a limited set of electric field configurations (EEG maps) are sufficient to explain a given period of EEG activity (determined by cross-validation). Fitting these cluster maps to the data by spatial correlation analysis results in a discrete distribution of these maps, each one being present for a given duration. This procedure is independent of the strength of the activity since all maps are normalized to unitary strength. The cluster analysis thus only looks at the topography, the landscape of the scalp electric field. Nevertheless, segment borders typically (but not always) appear during low field strength, that is, during periods of low signal-to-noise ratio. It is not known whether these periods reflect low neuronal activity or highly nonsynchronized activity. Disease, drugs, external stimulation, or cognitive tasks can influence both the duration as well as the sequence of the microstate. Thus, the syntax with which these basic building blocks are put together may be crucial for the behavioral outcome.

Several questions were raised during the meeting, which remain to be solved:

- What characterizes the transition period? The duration of the switch from one microstate to the next may be affected by the algorithm used to detect sequential states. One should include in the search analysis the possibility that at certain times no stable EEG map is observed.
- Do the modules of the neural network during a microstate synchronize or not? If yes, in which frequency and is it phase-locked or not? Time-frequency analysis based on wavelets could be used to answer this question (Le Van Quyen et al. 2001).

- To what extent are spontaneous and evoked microstates comparable? A key issue is the possible "phase resetting" of ongoing EEG induced by the sensory stimulus, which may result in the presence of temporal segmentation into distinct microstates in the evoked case (Shah et al. 2004).
- How can the syntax of microstates be analyzed formally?
- Are microstates related to consciousness and do they support the workspace model introduced by Dehaene and Changeux (see below)?
- Can the UP and DOWN states observed at the cellular level participate in the buildup of these microstates? We note that UP and DOWN states have been observed mostly in the anesthetized and sleeping preparation, and that the eventual presence of synchronized depolarization spreading over large cortical areas should be detectable with the EEG.

NETWORK RECURRENCY, CORTICAL GAIN CONTROL, AND ATTENTIONAL PROCESSES

Attention and Sensory Processing

Because of its well-documented limitation in processing multiple tasks in parallel, the brain, and more specifically the cortex, has to find a way to select the relevant stimulus and allocate enough computing resources to the task. Attention during active behavior is a focalization process that seems critical for the detection of complex objects or even "pre-attentive" features of objects in low-level vision. Classically, a distinction is made between two forms: (a) *attentional selection* refers to the focus in attention targeted to an individual stimulus out of an array of competing stimuli, and (b) *attentional facilitation* refers to the performance increase in the detection of a single stimulus when it appears alone at an attended location. An electrophysiological correlate of this latter process has been found by the observation, in V4 of the macaque monkey, that behavioral attention directed to a location in the visual field increases the responsiveness of V4 cells to stimuli shown at that location (Reynolds et al. 2000). Responses to weaker stimuli are enhanced by attention, whereas those to stronger stimuli are unchanged. This observation provides an intriguing analogy with the possible role of ongoing synaptic intracortical bombardment and the local level of recurrence in the control of the cortical gain.

The results obtained in Reynolds's study favor the "contrast gain model," according to which the neuronal response is scaled as if the effective input stimulus strength had been increased multiplicatively by a constant factor. This corresponds to a lateral shift in the log-contrast-input–response function (transition from the dark gray (control) to the black curve in the left panel of Figure 19.4c). Evidence for such behavior pleads for a saturating or normalization mechanism in response strength, thus leading to a limitation in the ability to enhance output at high levels. Another model, supported by McAdams and Maunsell (1999) and
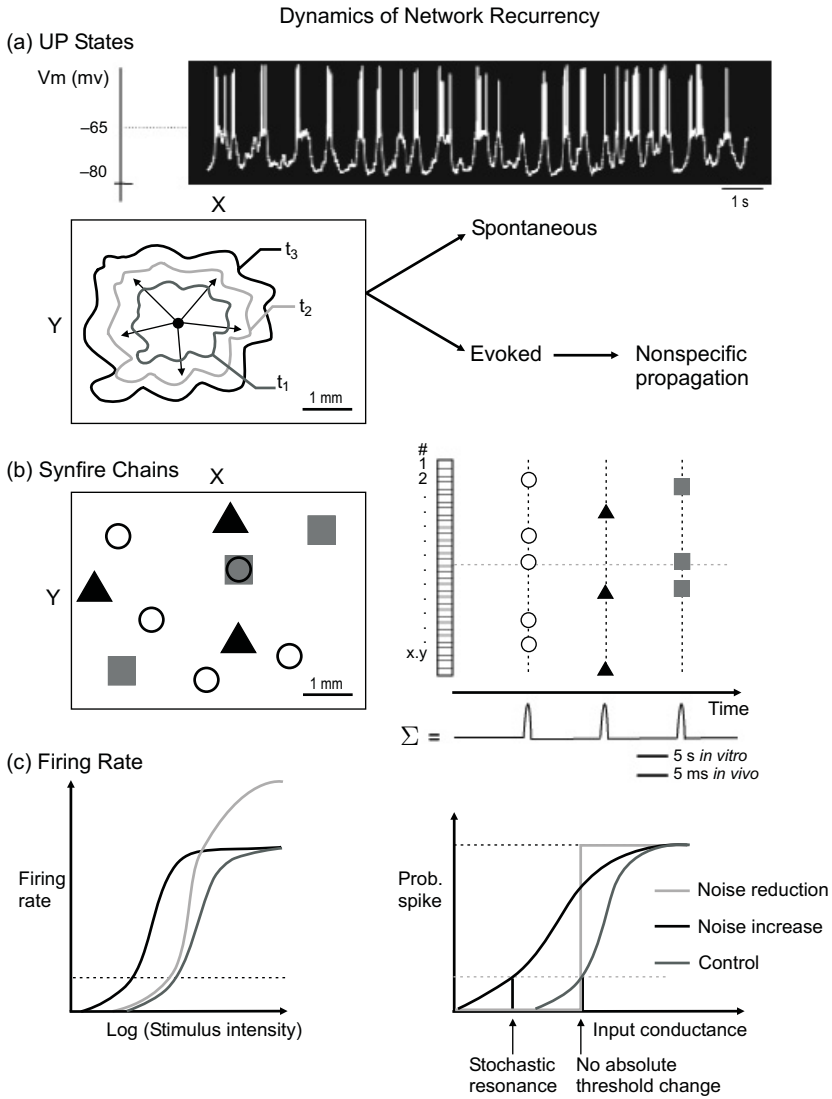
Figure 19.4 Recurrent networks = UP and DOWN states vs. synfire chains. (a) UP states: Recording of a V1 cell showing bistability in its membrane potential dynamics. The inset represents a spatial view of the laminar plane of cortex (X, Y) and the spatial spread of "UP"-state at different points in time (t_1, t_2, t_3). (b) Synfire chains. Left: sparse spatial distribution of cells belonging to the same synfire chain. Cells which are coactive during the same temporal window (defined on a 2 ms bin) are labeled by the same symbol. Right: raster view of the time course of the propagation of synchrony packets (symbols) across the cortical network (for N cells = x, y). $\sum$ = evolution with time of the total spike activity of the network (integrated over space). *Caption continues on next page*.

called "response gain model," proposes that attention causes a multiplicative increase in firing rate output (transition from the black (control) to the light gray curve in the left panel of Figure 19.4c). According to this model, it is the response neuronal firing rate that is multiplied by a constant gain factor.

A Cellular Analog of Attentional Facilitation

Background ongoing synaptic activity, misleadingly called "noise," emerges naturally in biological recurrent neural networks and can be recorded in the variance of membrane potential values in single cells in the awake or anesthetized animal (review in Destexhe et al. 2003). As seen earlier, the characteristics of the background activity vary with the level of alertness (sleep vs. awake and attentiveness) and also with the level and nature of anesthesia. The processing of input signals during sensory activation is not only affected by changes in the mean membrane potential (e.g., depolarization) due to the addition of a DC component but also by nonlinear effects due to the high-frequency content of the fluctuation spectrum as well as to changes in input conductance. The contextual impact of background activity on the probability of a spiking response to a test input has been studied intracellularly, both *in vivo*, when the membrane potential shifts to an UP state (see above), and in the *in vitro* situation under certain pharmacological conditions which facilitate the recruitment of reverberating intracortical activity and the generation of "UP-like states" (Shu et al. 2003a, b).

The following controversies remain:

- Most available experimental data show that the input–output probability curve measured in response to pulses of input conductance is smoothed and shifted towards weaker inputs compared to the control quiescent condition when the network is in the highly recurrent mode (high conductance state). Such input–output curve is used in sensory electrophysiology to measure the neurometric transfer function of the cell under study and can be compared to psychometric curves used in psychophysics, relating the

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Figure 19.4 (*continued*)   (c) Hypothetical modulatory effects of the network recurrence level on the transfer function of cortical neurons. The control input–output characteristics linking postsynaptic firing rate (left) or spiking probability (right) as a function of input strength are represented by dark gray curves. The "contrast gain model" (left panel, black curve) posits that the postsynaptic discharge rate is scaled as if the effective input stimulus strength had been increased multiplicatively by a constant factor. The "response gain model" proposes that attention causes a multiplicative increase (light gray curve) as if the response neuronal firing rate had been multiplied by a constant gain factor. Right: the equivalent effect found at the level of the probabilistic transmission by cortical neurons. If attention reduces the variance level, the threshold for spiking is unchanged but the input–output curve becomes a steep Heavyside function (Chance et al. 2002). If attention increases the variance level, the slope of the i/o curve is further smoothed and the threshold of significance for detecting weak input (dotted line) is improved (Destexhe et al. 2003).

percentage of correct choice with stimulus intensity. In the present case, the leftward shift of the neurometric curve (cf. the black [high conductance state] and dark gray [control quiescent state] curves in the right panel of Figure 19.4c) indicates that the detectability for weak inputs is increased by a lowering of the absolute spiking threshold (see arrows and dotted line in Figure 19.4c). This effect, reminiscent of stochastic resonance, is accompanied by a decrease of the slope of the neurometric function, suggestive of compensatory decrease in the cortical gain. This prediction was first formulated with theoretical models (Rudolph and Destexhe 2003).

- Another theoretical model attributes an opposite effect to attention-related processes by reducing, rather than increasing, noise variance (Chance et al. 2002). Background synaptic recurrent activity tunes the input–output gain of neurons and enhances the slope of the neurometric function without changing the absolute sensitivity threshold (light gray step-function curve in Figure 19.4c).

Whichever mechanism is put into play, both viewpoints predict an input rescaling, that is, a change in the dynamic range of input levels, which are coded in graded fashion by the output spiking probability. It remains to be established which effect is more likely in the behaving awake animal, and whether such gain control mechanisms at the neuronal level may be beneficial at the population coding level.

FROM CORTICAL SPACE TO DYNAMIC RECONFIGURATION OF PERCEPTUAL REPRESENTATIONS

The distribution of excitation in the cerebral cortex occurs in identified clusters of hot spots, suggestive of localized reverberation processes. It occurs locally, for example, through recurrent activation within the minicolumn, and clustering of activity is thought to propagate across the cortical network via patchy excitatory long-distance horizontal and cortico-cortical connections. Inhibition between minicolumns is mediated via different kinds of local inhibitory GABAergic interneurons, driven by afferent input as well as via synapses from local and distant pyramidal cells. Such anatomy of circuit architecture (Figure 19.5, top) is, of course, not specific to sensory and motor cortex. Similar layouts can be found, for instance, in the lamprey spinal locomotor CPG (see Kiehn et al., this volume). The basic building block here is an "excitatory core" of mutually excitatory premotor interneurons (EINs) connected by glutamate synapses having AMPA and NMDA receptors. Each hemisegment of the spinal cord has such a core, and long-distance reciprocal (glycinergic) inhibition between them secures left–right alternation, whose functional action is similar to long-range excitation of local inhibition in visual cortex. Two of the other motor systems
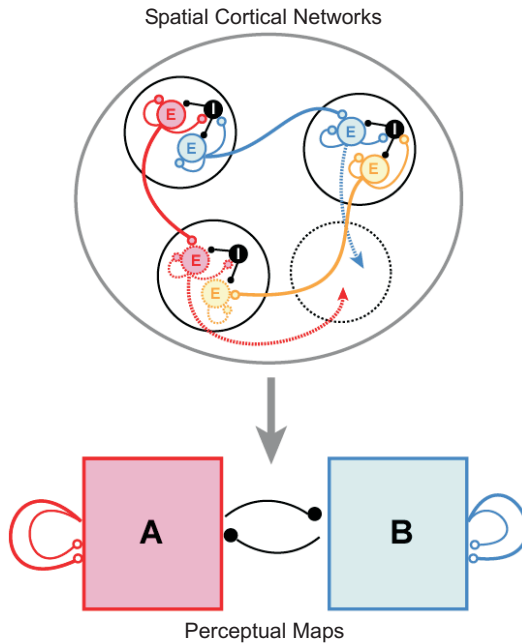
Figure 19.5 Building a perceptual space. Top: spatial schematic representation of activity in cortical networks. Cortical cells can be excitatory (E) or inhibitory (I) and situated in the same or different columns (circle). The same color for the E-cells represents coactive cells belonging to the same functional assembly. Bottom: representation of the dynamics between two color-coded assemblies in an abstract perceptual referential, through long- and short-distance excitatory and inhibitory connections. In addition to short-distance inhibitory connections, the model assumes the existence of a second type of local inhibitory interneuron (bipolar or double bouquet) that is driven mainly by long-range excitatory connections from pyramidal cells. These connections are important for achieving rhythmic activation of attractors and competition between them.

discussed during the workshop—the vertebrate respiratory oscillator in the brainstem and the saccade generator of the superior colliculus—also comprise an excitatory core. However, the precise composition and properties of these networks differ in important respects. For example, the respiratory excitatory core, the pre-Bötzinger complex, lacks NMDA transmission and relies on persistent sodium channels for burst buildup and plateau maintenance. The burst termination mechanism involves inactivation of the sodium-persistent I_{NaP} channels. The saccade generator of superior colliculus has a core of mutually exciting neurons in its deep layer. Here, AMPA and NMDA transmission is important for fast-burst initiation and to maintain a high-bursting frequency. The burst duration, however, is tightly controlled by externally provided disinhibition, possibly generated by long-distance connections recruiting the feedback action from the cerebellum.

Full-scale biophysical simulations (including compartmental cell models and AMPA and NMDA type synaptic transmission) in the lamprey locomotor CPG and a network model of layer II/III of visual cortex (Fransén and Lansner 1995 and unpublished observations) show clear similarities in their dynamic behavior. A way to give a possible functional relevance of this patchy pattern of excitation across the anatomical network is to project cells according to their degree of synchrony into an abstract "perceptual" space (bottom part of Figure 19.5). Elements of the cortical network synchronous at a given epoch in time (same-colored cells in the upper cartoon of Figure 19.5), which belong to the same or distinct "minicolumns" (circular clusters in Figure 19.5) and are synaptically connected, will define the Hebbian assembly participating in the broadcasting of an identified percept ("A" or "B" in the bottom part of Figure 19.5). If we assume the existence of several facilitated neural assemblies within the same network (color coded in Figure 19.5), they would compete in a kind of winner-take-all manner (as do the left–right sides in the spinal CPG). As one neural assembly wins and becomes active, it inhibits the others through local connections; its pyramidal cells are in an UP state but gradually hyperpolarize until activity terminates. This enables the emergence of some other neural assembly. Additional control will be imposed by afferent inputs that bias activation towards more stimulated assemblies. This analogy between neocortex and the spinal cord lends continuous dynamics to the attractor memory network paradigm (Yuste et al. 2005).

A PLAUSIBLE NEURAL ARCHITECTURE FOR THE EMERGENCE OF COGNITION AND ACCESS TO CONSCIOUSNESS

So far, only a few models have addressed the emergence of conscious cognitive processes in the human brain (review in Koch 2004). At this Dahlem Workshop, Jean-Pierre Changeux reviewed the basic concepts of hypothetical networks that could subserve the genesis of "higher-order" mental states and tried to relate predictions of the model with the observation of cellular UP states and synchrony microstates in the EEG (discussed above).

Selection of "Adequate" Actions and Decisions

The model, initially proposed by Dehaene and Changeux (1991; Dehaene, Dehaene-Lambertz, and Cohen 1998), assumes that the elementary mechanism of selection by a self-evaluated reward is restricted to a set of clusters of prefrontal neurons encoding for a repertoire of behavioral rules, the activation of which controls a lower-level sensorimotor network. Clusters are postulated to exhibit a high level of spontaneous activity together with strong recurrent

connectivity and thus to display two *stable* modes of activity: one in which the cluster is inactive, and the other similar to the UP state, in which activity, once initiated, remains at a high level for a prolonged period.

Action selection may be implemented by a stabilization–destabilization mechanism (see Dehaene and Changeux 1991). Negative reinforcement is assumed to cause a *fast synaptic desensitization* on a timescale of a few tens of milliseconds, which allows synapses to recover spontaneously their original strength on a slower timescale of a few seconds. The net result of this mechanism is that whenever negative reinforcement is received, recurrent connections within the currently active cluster decrease rapidly in strength, thus releasing the neighboring clusters from lateral inhibition. Spontaneous activity then propagates from one cluster to another, giving the full network/organism the chance to test different prerepresentations or behavioral options. Thus, reward signals function as effective *selection signals* and either maintain or suppress active prefrontal representations as a function of their current adequacy.

Distinction between Conscious and Nonconscious Processings

During sleep and deep general anesthesia, the subject is nonconscious with the notable, though limited, recall of the dreaming episodes. Even when awake, alert subjects may not be aware that they are carrying on intense *nonconscious* processing. Particular experimental evidence in favor of nonconscious processing (among many others) is the phenomenon of *semantic priming* (Dehaene, Naccache et al. 1998; review in Dehaene and Naccache 2001). Visual words, when flashed briefly before a masking stimulus, are not perceived consciously; that is, the subject/observer does not report their presence. Nevertheless, they still induce a priming effect since they facilitate the subsequent processing of related words by the same subject/observer. Brain imaging techniques reveal that such stimuli have a measurable influence on brain activation patterns, in particular in the areas involved in motor programming, which are covertly activated (Dehaene, Naccache et al. 1998). Moreover, these patterns differ dramatically when the subject (according to his/her reports) sees the stimulus in a fully conscious compared to a nonconscious manner.

The central proposition made by Changeux and Dehaene is the neural embodiment in the brain of two main distinct computational spaces. The first is a *processing network* composed of parallel, distributed, and functionally encapsulated processors organized from cortical *microcircuits.* These processors range from primary (or even heteromodal) sensory processors to motor processors and include long-term memory stores of semantic databases, the "self," autobiographical and personal data, as well as attentional and evaluative systems including motivation, reward, and, in general terms, the emotions. The second computational space, referred to as a *global workspace*, is assumed to consist of a distributed set of cortical neurons, which integrate physically the multiple

processors by their ability to receive from and send back long-range excitatory axons to homologous neurons dispersed in other cortical areas (Figure 17.1, this volume). These projections interconnect, at the brain scale, distant areas in the same hemisphere and between hemispheres through the *corpus callosum*. The early observations of Cajal (1909) and Von Economo (1929), which are supported by a large body of recent observations (see Mountcastle 1997), indicate that pyramidal cells from layers II and III of the cerebral cortex (among others) possess *long axonal processes* that they send within and between hemispheres. They are postulated to contribute to the neural workspace in a privileged manner. An important consequence of this postulate, already noticed by Von Economo (1929), is that pyramidal neurons of layers II and III are especially abundant in dorsal lateral prefrontal and inferoparietal cortical areas and thus offer, at the brain-scale level, a regional correlate of this cellular hypothesis in terms of a topology of activated cortical areas. As a result, these selective contributions might be directly evaluated by brain imaging techniques.

The model posits that, in a conscious effortful and attentive task, workspace neurons become spontaneously coactivated, forming discrete though variable spatiotemporal patterns of activity, giving rise to some kind of *global prerepresentation*. Such "brain-scale" representations would mobilize neurons from multiple brain processors in a reciprocal manner and be subject to regulation by vigilance and attention neuromodulators and to selection by reward signals. Their eventual recording as "functional microstates" in the EEG was discussed above.

WHAT SYSTEM NEUROSCIENCE CAN LEARN FROM INTERDISCIPLINARITY

A Need for New Paradigms for the Study of Brain Computation

Our understanding of brain complexity is often limited by the lack of a theoretical framework specifically adapted to the neural embodiment of computation, and experimenters often address key issues on the basis of anecdotal (since devoid of context) observations or intuitive speculations. It is desirable for theory and modeling in neuroscience to be carried out in a dedicated and systematic manner rather than in an ad hoc fashion, taking into account available information and know-how from other relevant disciplines, such as computer science, robotics, and mathematics. Such interdisciplinary pooling of information is especially needed for a transition from currently existing descriptive models for computation in neural microcircuits (that may, for example, describe activity streams resulting from a particular input) to functional models that can—on the basis of general principles—guarantee that the circuit carries out a desirable computational task for *all* (in general, exponentially many) possible inputs. For example:

- To make educated guesses about which computational problems are solved by the brain (e.g., by mice), one can learn quite a bit from the real-time computing problems regarding motor control and processing of complex sensory input streams that are encountered in robotics. The difficulty of such computational tasks is easily underestimated because evolution has solved these problems so well, and the complexity of the underlying computation problems are hidden from us.
- To evaluate the power of computational problems, one needs to take into account results from computational complexity theory.
- To evaluate the difficulty of learning-specific problems (and the difficulty of generalizing learned knowledge), one needs to take into account results from statistical learning theory and empirical results from machine learning.
- To design new tests for analyzing the structure and progress of computations in a neural system (besides looking for neurons whose response in a trained animal can be related directly to its behavior), one needs to take into account methods from system identification and dynamical systems theory. Typically, these methods require probing the response of the system (or parts of the system) for a much richer ensemble of quasi natural stimuli (with the same statistics and addressing the full real-time parallel processing capacity of the sensory cortical analyzer).

Reviving Liquid Computing

High-level cognitive functions in the human brain involve the activation of processes (from the activation of the ACh receptor to memory) with time constants covering 13 orders of magnitude (from microseconds to years). These microcircuits implement massively parallel computations, where the inputs consist of multimodal input streams stemming from a rapidly changing environment, and results of computations have to be provided at any time. In contrast, nearly all of the previous theoretical approaches to understand how such systems can possibly provide the basis for cognition and learning (e.g., Dayan and Abbott 2001) have been based on highly simplified and homogenized neurons and synapses as well as on simplified connection patterns, and they result in simple dynamics converging towards a set of point attractors. New paradigms of computation that depart significantly from this concept are needed, where the complexity expressed in the recurrent ongoing activity of the network is the determining part of the computational process rather than something to be avoided.

Over several decades, a number of theoretical frameworks have been proposed to understand how collective and complex behavior of large populations of units may lead to a distributed representation of information (Longuet-Higgins 1968; Gabor 1969; Kohonen 1977; Hinton and Anderson 1981; Hopfield 1982). These now classic "holographic" theories have recently been the subject

of renewed interest addressing the framework of complex dynamical systems, such as the "dynamics-based computing" (Sinha and Ditto 1998), computing using neuronal diversity (Buonomano and Merzenich 1995), or the "liquid computing" (Maass et al. 2002) paradigms. The goal of this latter approach is to provide a conceptual framework for analyzing emerging real-time computing capabilities of neural microcircuits and to produce better quantitative methods for testing computational capabilities of neural microcircuits *in vitro* and *in vivo*.

Theoretical predictions and computer simulations suggest that under certain conditions the current state of a dynamical system contains information about current and recent inputs injected into the system, and, furthermore, that even the results of nonlinear computations on the components of this input can be read out and extracted by linear methods (i.e., by a weighted sum, or by a perceptron in the case of a classification task) from the current state of such a dynamical system. One condition for this is that the dynamical system contains sufficiently diverse components (e.g., as provided by a rich repertoire of different types of neuronal time constants and synaptic kinetics). Another condition is that the circuit has a sufficiently complex connectivity structure (containing connections to nearest neighbors as well as a distribution of midrange connections). Hence, many dynamical systems constructed by theoreticians (which often consist of stereotypical simple components and all-to-all or only-to- neighbors connections) do not satisfy these conditions, but reasonably realistic models for neural microcircuits tend to satisfy these conditions.

Computer simulations show that an optimization of the computational power of such neural microcircuit models requires that these circuits are sufficiently activated by the input stream. An idea that emerged from this Dahlem Workshop, which has been already tested on computer models, is that UP states of neural microcircuits constitute activity regimes that enhance specifically their capability for fast nonlinear computations on time-varying firing rates (Maass et al. 2005). Another topic of current research is the impact of readout neurons, which extract information from such microcircuits and project their output back into the circuit. It can be shown that they create high-dimensional attractors of the circuit state that provide longer memory spans for selected input patterns (Maass et al. 2006). This still leaves other components of the circuit state free for online processing of new information. This approach using realistic neural microcircuit models suggests new ways of understanding emergent computations while processing continuously different input streams. It underlines the role of hierarchies of cortical areas where higher-level circuits are optimized for processing on a slower timescale the output streams provided by neural readouts from lower-level circuits.

Evolutionary Considerations Using Language as an Example

Evolution by natural selection is the only known force to build up complex adaptations. Hence it makes sense to think that the nervous system is also the result

of evolution, and that it fulfills many different roles. This is not to say, however, that every aspect of it is selectively significant, let alone perfect. Evolutionary optima do not necessarily coincide with engineering ones for at least three reasons: (a) there are several entrenched state characters, so-called hang-ups from former evolution; (b) the available genetic variation may be limited (so-called constraints), and (c) in the process of selection, only relative (rather than absolute) fitness matters. Thus, having a modern mammalian neocortex may render the hippocampus obsolete from an engineering point of view, but evolution cannot go back to the drawing board and start all over again. Evolution is a process of "irrational design" (Sydney Brenner), often reminiscent of tinkering (*bricolage,* François Jacob). It is not yet known to what extent various aspects of the nervous system are selectively neutral or maladaptive from an engineering point of view.

Cumulative selection can produce complex adaptations, as Darwin and Wallace already recognized, but this is not always obvious. In the case of the optical structure of the eye, Darwin had no choice but to assume that natural selection would have driven the populations through a series of incremental improvements, acting on appropriate genetic variation (Darwin 1859). Nilsson and Pelger (1994) did demonstrate about 130 years later that Darwin was essentially correct. They applied computer simulations to generate eyes, and selection was based on the quality of the imaging capacity of the structure. Fortunately, biophysics is advanced enough to make this calculation, which was then used later to calculate the relative fitness of each eye. It turned out that starting with only three cell layers (a transparent, a pigment, and a sensitive layer), they could reconstruct how the eye of, say, a fish could have arisen in a surprisingly small time in evolution. Of course, they did not consider the visual analyzer, but this had not been their task in the first place.

A relevant question is, therefore, to ask how the neural structures fulfilling certain (occasionally quite complicated) styles could have evolved. Ultimately, one would like to simulate such evolution. Leigh Van Valen said that evolution was the control of development by ecology. In a less telegraphic form, one can imagine the following algorithmic process (see Figure 19.6). What are the relevant traits for a simulated evolution of nervous systems? An essential ingredient is the genetic determination of neuronal types by the following traits: number of
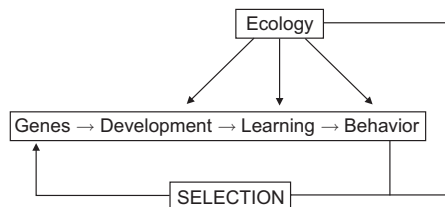

Figure 19.6   Schematic depicting the control of development by ecology.

types, number of cells in each type, cell shape, projection pattern, synaptic rules, and electric properties. One has to start with a simple architecture and to see the evolution of a network that shows a required behavior as a result of selection on the population of networks. This approach is not entirely novel: Floreano has used it to generate control networks for robots (Floreano and Urzelai 2000), and Rolls and Stringer (2001) evolved an autoassociative network. However, one should attempt more complex networks as well.

The issue of the origin of natural language constitutes an appropriate field of application of such theories to the emergence of higher cognitive functions. For example, Fitch and Hauser (2004) have shown that tamarind monkeys are, in contrast to young human infants, insensitive to violation of input described by phrase structure grammar $(AB)^n$, whereas they are proficient at discerning patterns from finite state grammar $A^n B^n$. What could be the neuronal background to this important difference? At present, we do not know, but we might learn it through simulated evolution of neural architectures.

Finally, an interesting mechanism, likely to have played a role in the evolution of language, is worth mentioning; namely, genetic assimilation (or Baldwin effect). In our context it is a mechanism whereby learning can guide evolution, rather than vice versa. Imagine a flat fitness landscape with a needle-like peak somewhere. There is no way genetic evolution can find the needle, unless the individuals are plastic (in the sense of genetics—this includes learning as well). Plastic individuals have a fair chance to "sense" the needle through their phenotypic range and thus be subject to directional selection towards it. It is interesting to note, however, that plasticity becomes maladaptive as soon as the genotypes come sufficiently close to the needle: plasticity is costly then without advantage. Then the trait is fully genetically assimilated (it was once learned; now it is fixed). For complex traits evolving on complex fitness landscapes, one dimension may favor the loss of plasticity whereas in another, learning might always be the best. In the case of language, vocabulary is stored in the environment and is subject to rapid change. In contrast, certain procedural operations behind syntax are likely to be innate. How did they evolve? One mechanism may be genetic assimilation, which could have led to an appropriate fixation of certain rather widespread network properties of the human brain. Regulatory genes acting on neurons are likely to have been involved.

CONCLUSION

Although some stereotypy was found in the molecular determinants and anatomical substrate of cortical circuits, it is likely that the expression of cortical computation cannot be easily decomposed in stable—time-invariant and space-invariant—modules. We propose that the modularity lies not in the structural arrangement but in the dynamical signature of the activity that circuits sustain. Cortical computation, and the emergence of cognitive functions, should be

envisioned as a dynamic coordination of reconfigurable modules coexisting within a finite number of regular structural architectures.

A central theme of our discussions was to clarify distinct scales in the spatial and temporal selectivity of synchrony. Recently, some confusion seems to have arisen between synfire chains, hot spots of synchronized activity, and UP states. The conclusion reached at this Dahlem Workshop is that these different synchronization processes differ significantly in terms of spatial spread in the cortical tissue, propagation mode, and propagation speed:

- Synfire chains are the sparse version of an assembly, where the reproducibility of temporal motifs is in the millisecond range and is found in the phase relationships between activities of individual cells. The highly reproducible intervals can last up to several hundred of milliseconds, irrespectively of the spatial separation of the cortical units. It is best described by a reverberation of activity in a local network where the same cell can participate several times in the propagation of the same synfire chain.
- Bistability in the membrane potential is often observed in cortical cells, both *in vitro* and *in vivo*. UP states are usually triggered by intense feedforward activity. Their initial spatial spread is compact, and the local initiation of an UP state gives rise to a slow propagating wave of depolarization in the surrounding cortical tissue, most likely through horizontal connectivity. Their occurrence cannot be considered as signaling a bursty event of spike synchrony at a given node of the network, since they characterize more a membrane potential state defined with a temporal precision in the second range than a specific pattern of spiking activity.
- A mixed version of synfire chains and UP states has been revealed recently using spike or membrane potential recordings paired with calcium imaging. The spatial spread that results from this process is locally compact, with additional hot spots that are sparsely distributed across the network. The propagation of activity jumps from one spot to the next and transitions dates form temporal motifs similar to those observed in synfire chains.

In summary, "synfire chains" are defined by phased-locked activity between few members of the cortical assembly, forming temporal motifs with a precision in the order of milliseconds. UP states are defined by the observation of correlated or synchronous depolarization in the membrane potential of cortical cells clustered in a restricted cortical neighborhood. Chains of propagation of UP states can be viewed as the analog version of synfire chains when one spike is replaced by an UP state transition of cortical columns in a high conductance mode favoring spike activity. These transitions, occurring at different times in distant spatial locations of the network, would shape the temporal sterotypy of the cortical song.

UP states may prove to be an epiphenomenon of recurrent networks. However, the possibility exists that they are essential to the binding of sensory

information: they may be the microcircuit substrate underlying what Yves Delage has described as the "parasynchronization" process necessary for the emergence of mental imagery and dreams (Delage 1919).

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