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Cell Types, Circuits, Computation

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How does the connectivity of a neuronal circuit, together with the individual properties of the cell types that take part in it, result in a given computation? We examine this question in the context of retinal circuits. We suggest that the retina can be viewed as a parallel assemblage of many small computational devices, highly stereotypical and task-specific circuits afferent to a given ganglion cell type, and we discuss some rules that govern computation in these devices. Multi-device processing in retina poses conceptual problems when it is contrasted with cortical processing. We lay out open questions both on processing in retinal circuits and on implications for cortical processing of retinal inputs.

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Introduction

The mammalian brain is assembled from thousands of neuronal cell types [1], organized into distinct circuits that perform computations relevant to behavior. Sophisticated local circuits exist in all brain regions and they act in concert in the behaving animal. In order to gain mechanistic insights into brain function, it is crucial to uncover *what* these local circuits are computing and *how* computations are achieved. Furthermore, understanding the changes that occur in those neuronal circuits involved in specific brain diseases may help design strategies for therapy. One of the most intriguing questions about local neuronal circuits pertains to the relation between structure and function: How does the connectivity of a circuit, together with the individual properties of the cell types that take part in it, result in a given computation? Here, we review recent developments, which begin to answer this question, in examples of mammalian retinal circuits in which structure and function can be approached by means of genetic tools as well as by imaging and physiological techniques.

The retina as a model system

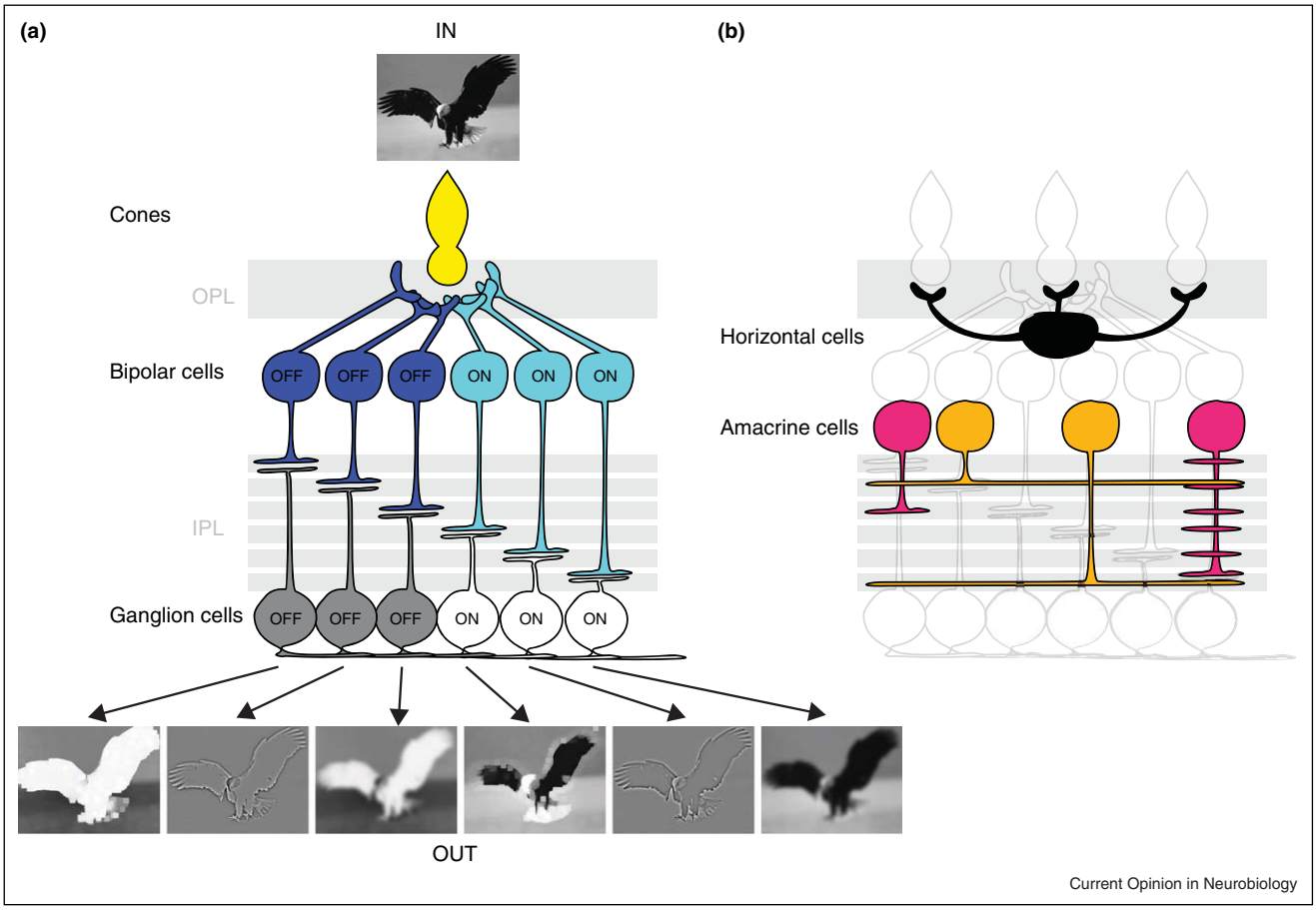
The first steps of visual processing take place in the retina [2,3], which also serves as a unique model system to study the relationship between structure and function. The retina is a self-contained system in the sense that, if the retina is involved in a particular neuronal computation, then one can understand the mechanisms of this computation through the study of retinal circuits alone. This is owing to the fact that, unlike fish [4] and bird [5], mammals have minimal feedback from higher brain centers that possibly carries only modulatory commands [4]. It is easy to isolate and maintain a healthy retina *in vitro*, and its natural inputs, dynamically evolving light patterns, can be presented to it in a controlled and quantitative manner. In probing the retina, neuronal activity from any cell class can be recorded.

In the past few decades, many investigations [2,3] have pointed to the existence of specialized cell types and have found that these cell types are organized in local circuits. Cell types and circuits are ordered in neuronal layers in the retina (Figure 1), which greatly simplifies the study of connectivity between neurons. The emerging picture is that each retinal output neuron, a ganglion cell, of a given type has an afferent circuit in which a few other cell types take part. Ganglion cell types are arranged in mosaics [2,3] (Figure 2), with various degrees of overlap between the dendritic fields of the individual cells of the same type.

The 'what' and the 'how' of retinal computation

Recent work from several groups suggests that the retina acts as the sum of many small devices – the circuits of different ganglion cell types – each highly stereotypical and task-specific [7,8••,9,10••,11••,12–16]. It appears that an appreciable fraction of these circuits is devoted to the analysis of different categories of motion. Eight types of direction-selective ganglion cells (four ON–OFF types [14,17–19], three ON types [14,18], and one OFF type [10••]) report either the direction of lateral object motion or the direction of global image drift. Approach motion is detected by at least one ganglion cell type [11••] and other ganglion cell types respond to differential motion relative to global background motion [12]. In all three cases of motion sensitivity – direction selectivity, approach sensitivity, and differential-motion sensitivity – the ganglion cells respond most vigorously to a so-called preferred

Figure 1

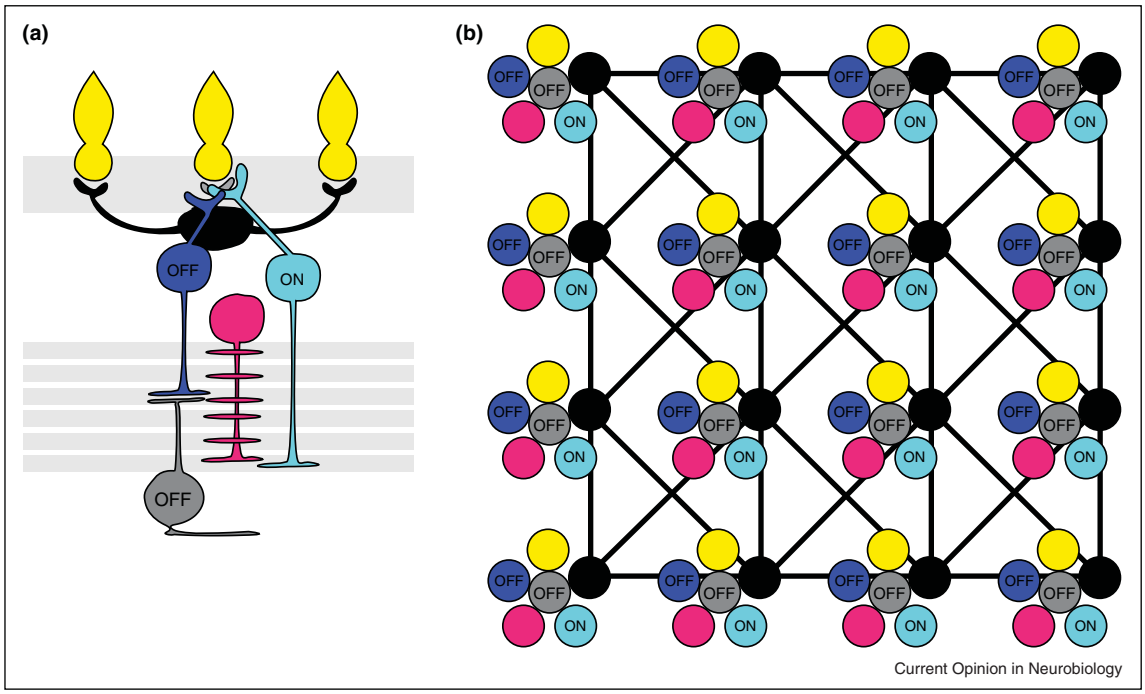


Functional organization of the mammalian retina. **(a)** The retina can be viewed as a parallel image processor that acquires movies (top panel) with its array of photoreceptors, and uses its internal circuits to compute dozens [2,3,6] of different neuronal representations (bottom panels) of the visual world. These are sent to higher brain centers via axons of the ganglion cells. Cone photoreceptors (middle panel, yellow), which are the light sensors in daylight, connect to about ten types of bipolar cells. Half of the cone bipolar cells are activated by decrease (OFF cells, blue) and the other half by increase (ON cells, cyan) in light intensity. Axon terminals of OFF and ON bipolar cells settle at different depths within the inner plexiform layer (IPL): OFF terminals in the distal part and ON terminals proximally. Order exists at an even finer scale: bipolar cell terminals occupy one or a few of IPL strata (horizontal gray bars in the IPL). Dendrites of more than a dozen types of ganglion cells arborize in these strata and receive excitatory input from co-stratified bipolar cell terminals. The response polarity of a ganglion cell is determined by the types of bipolar cells that provide input to it: ON (white), OFF (gray) or ON–OFF. **(b)** The photoreceptor-to-bipolar synapse in the outer plexiform layer (OPL, top gray horizontal bar) is regulated by inhibitory horizontal cells (black). Similarly, excitatory synapses between bipolar and ganglion cells are modulated by inhibitory amacrine cells. These cells receive excitatory input from bipolar cells, and they provide feedback and feedforward signals to bipolar terminals and ganglion cell dendrites respectively. Amacrine cells are the most diverse of the retinal cells: more than 30 morphological types have been described [2]. As yet, the functions of most of them are unknown. Amacrine cells are either GABAergic or glycinergic. GABA-releasing cells have long processes and are therefore called wide-field cells. Glycine-releasing cells have short processes, which often span several strata; these cells are often referred to as narrow-field cells. This architecture is further enriched by amacrine–amacrine cell inhibitory connections and by various electrical synapses within and among cell types.

stimulus, while their responses to so-called null stimuli are suppressed. In the case of the three motion categories, the preferred stimuli are lateral motion in a given direction, approach motion, and spatially differential motion, respectively, whereas null stimuli are lateral motion in the opposite direction, receding and lateral motion, and coherent whole-field motion, respectively. Yet another type of motion sensitivity consists in the suppression of response, in a few ganglion cell types, to the rapid image shifts [13] that occur during wide-angle, fast eye movements, the so-called saccades. Here the null stimulus, global image motion, is similar to that of the differential-motion sensitive cells, except that a high speed of global motion is required.

It is important to note that in general ganglion cells are broadly tuned: 'sensitivity' does not mean 'exclusivity'. Indeed, motion-sensitive cells do not respond *only* to their preferred stimulus. For example, an OFF direction-selective, approach-sensitive, or differential motion-sensitive cell will respond vigorously to a dark flash, like any other OFF ganglion cell. The essence of motion

Figure 2



Retinal circuits are arranged in a mosaic. **(a)** Our current view of a retinal circuit: a few bipolar and a few amacrine cell types are involved in the circuit afferent to a ganglion cell. **(b)** These ganglion cell circuits are modular, since ganglion cells belonging to the same morphological and physiological type are arranged in a mosaic, each type with a different extent of dendritic overlap. (Color-coding of retinal cells as in Figure 1).

sensitivity lies in the suppression of responses to null stimuli; that is, in what the motion-sensitive cell does *not* respond to.

When circuits afferent to motion-sensitive ganglion cells are examined in detail, the same two key elements of the computation emerge: first, the *temporal or spatial modulation* of response due to *inhibition* from amacrine cells; second, *nonlinearities* at bipolar cell terminals and in the way excitatory inputs from bipolar cells and inhibitory inputs from amacrine cells combine to produce spiking in the ganglion cell. (Other forms of nonlinearities are also relevant to retinal computation.) Owing to the spatio-temporal offset between excitation and inhibition, and the manner in which the two inputs are summed, certain dynamical visual stimuli – the null stimuli – result in maximum inhibition and minimum excitation, while others – the preferred stimuli – generate minimum inhibition and maximum excitation.

Intriguingly, but not surprisingly, the geometries of inhibitory cell types appear to be tailor-made for given computations. *Starburst amacrine* cells [20,21] that provide inhibitory input to ON–OFF direction-selective ganglion cells [22–24] are star-like, with long radial processes. The asymmetric inhibitory connectivity of these long processes to direction-selective ganglion cells [23,25••], together with preferential release of neurotransmitters when the direction of motion points from the cell body to the tip of the processes [26], serve to produce direction selectivity. *AII amacrine* cells [27] are 'bushy' and, therefore, they span several retinal strata. This morphology allows these inhibitory cells to capture ON-bipolar inputs in daytime (cone-mediated) vision [28,29] at the proximal strata, and to deliver it to approach-selective ganglion cells [11••], which arborize in distal retinal strata. The dendritic trees of *polyaxonal amacrine* cells [30,31] remain close to the cell body, while several axons radiate away from it. The ability to broadcast local input via long axons in all directions is required for inhibiting the response to global motion [12,13]. The remarkable match between structure and function in these examples of retinal circuits suggests a long evolutionary process during which the tinkering with details resulted in remarkably sophisticated computing devices.

The presence of diverse forms of nonlinearities is another factor that allows for the existence of task-specialized neuronal circuits. The active dendrites involved in direction selectivity provide maybe the most striking example [26]. In approach sensitivity and differential-motion sensitivity, nonlinear thresholding in bipolar or amacrine cells is key to the respective computations. Nonlinear thresholding results in a nonlinear summation of inputs to

the ganglion cell that originate from different subunits within its receptive field. As a result, the symmetry between ON and OFF stimuli, and hence between excitation and inhibition, can be broken. Furthermore, an array of nonlinear subunits feeding into a ganglion cell enables it to distinguish between (edge) motion and diffuse or wide-field temporal changes in light intensity.

The relation between cell types, computation, and coding: open questions

Despite success in uncovering the categories of visual features that some ganglion cell types extract, and despite the isolation of some elements of the neuronal circuits that give rise to the relevant computations, we are still in an early phase of the understanding of the detailed structure of the retina and of the array of mechanisms that rule its computational power. Three major sets of questions remain open.

First, at a physiological level, one would like to understand the functional role of all cell types involved in a given circuit. This program is ambitious, especially because of amacrine–amacrine interactions, which complicate the analysis. But the corollary, simpler problem, namely, that of the functional role of cell types that synapse onto a ganglion cell type, is amenable to study [25••,32•]. In much the same way as the discovery of the detailed structure of hemoglobin paved the way to revealing a great deal about the organization of amino acids into proteins, the elucidation of the computational role of the complete set of amacrine and bipolar cell types that belong to one identified ganglion cell type circuit may teach us basic principles about the roles of cell types in neuronal circuits.

Second, in order to understand vision at a more abstract, computational level, one would like to identify the preferred and null stimuli corresponding to each of the many ganglion cell types. But how can the wealth of the space of visual features be explored in a systematic and efficient way once a given ganglion cell type has been pinpointed? A number of methods have been devised to approach the problem of 'feature selection' in the retina, such as linear-nonlinear models [33–40], covariance models [41], generalized linear models [42•], and search procedures for maximally informative filters [43]. Typically, these methods are designed to extract one or a few 'features' – spatio-temporal light patterns – to which a ganglion cell or set of ganglion cells are responsive, out of a set of random stimuli. As experiments are now beginning to probe one cell type at a time and explore phenomenology that goes beyond mere 'feature selection', it is likely that theory, too, will require new machinery for extracting principles of computations. Currently, neither the choice of an appropriate set of stimuli nor the investigation of spatio-temporal nonlinearities is approached in either a systematic or a cogent manner.

Third, the message that a ganglion cell type conveys to higher brain centers is coded in the spatio-temporal pattern of spikes [37,44] produced by the entire mosaic of all ganglion cells of that particular type. What is the nature of the transformation that maps a visual movie into precisely timed spikes in all the members of a given cell type and into correlations [37,44–52] across cells of a same type [42•,53]? In order to begin answering this question, it will be desirable to develop methodologies that will allow the simultaneous recording of the spiking activity from a large fraction of the ganglion cells belonging to a genetically identified and morphologically confirmed mosaic of a given cell type.

New technologies that relate structure to function

The emergence of new technologies points to the hope of approaching some of these questions in the near future. The specialized tasks that each of the many ganglion cell types are carrying out can only be studied in detail, in a reasonable time frame, if one can examine the same cell type whenever it is required. This technical challenge has hindered our understanding of ganglion cell computations for a long time, but in the past years more than 100 mouse lines have been made and screened in which green fluorescent protein (GFP) is expressed in specific inner retinal (bipolar, amacrine, and ganglion cell) neuronal types or in combinations of a few types [8••,9,10••,54,55•,56–58]. Since GFP can be detected in live retinas, with the help of two-photon microscopy one can now target many of the cell types for physiological recordings [8••,26,32•,55•,59–63]. In this context, the development of two-photon microscopy [64,65] has been essential, since its infrared laser does not bleach the photoreceptors and, therefore, light-evoked responses can be measured at different ambient intensities. These targeted recordings, together with visual stimulations, allow the 'what' of the circuit computation to be addressed.

Once the visual features relevant to a ganglion cell type are identified, one would like to explain the corresponding computation from the connectivity and the individual properties of the cell types that participate in the circuit. Technologies that enable efficient investigation of this 'how' question are arising on the horizon. Currently, two different approaches are being pursued: one relies upon 3D electron microscopy reconstructions [25••,66] and the other uses transsynaptic viruses [59,67–69]. Here we discuss the latter. The main requirement is that of a transsynaptic tracer that passes from the postsynaptic cell to the presynaptic cells, in a retrograde manner, and preferably monosynaptically [68]. The difficulty lies in the initiation of the tracer from the ganglion cell type of interest. There are several ways of addressing this issue. First, in the rare scenario in which only one or a few ganglion cell types project to a specialized brain nucleus or initiate a reflex pathway, one can initiate the tracer from the target sites *in*

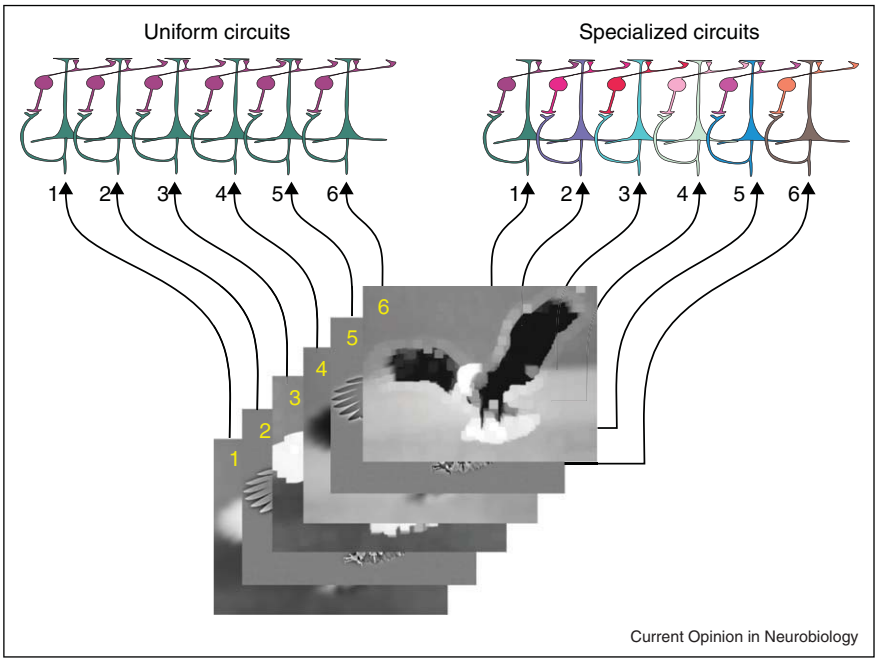
vivo [70]. The retinal circuits of melanopsin-containing [59,71] and ON direction-selective cells [32•], for example, was investigated in this way. Second, if the ganglion cell type of interest expresses Cre recombinase, the possibility for conditional initiation of the tracer *in vivo* exists [72•]. Third, jump-starting the tracer from a recorded single ganglion cell [73] *ex vivo*, and culturing the retina for a few days, would allow for the visualization of the presynaptic cells after each recording. Confirming functional connectivity between the virus-labeled cells requires dual patch clamp experiments or, perhaps preferably, the development of tracers that express light activated channels. Since, at present, the tracers are viruses that can be genetically engineered, equipping them with light-activated channels [74–76] or pumps [77] and/or Ca sensors [78–80] would allow synaptic strengths to be determined [32•], as well as dendritic and axonal activity patterns to be imaged. Finally, an important step in relating the activity of a presynaptic cell type to the visual features extracted by a ganglion cell efferent to it would be the ligand-mediated silencing of the presynaptic cell type during the corresponding visual computation [81].

The fate of 'retinal movies'

The existence of a large number of parallel features extracted from visual scenes and projected by the retina to higher brain centers, poses an obvious conceptual problem: How are these dynamical representations processed downstream of the retina? Some features, such as ones extracted by ON direction-selective cells and by melanopsin-containing ganglion cells are transmitted to a variety of subcortical nuclei involved in specialized reflex pathways. A great number of features are analyzed by cortical circuits and it is unlikely that the features extracted by the retina are combined in a simple manner by cortical circuits. This would 'waste' the effort put in by the retina in making up parallel channels. The divergence from retina to cortex – the fact that cortical visual areas taken together use a larger number of neurons and synapses to process retinal information, and hence can deploy a higher computational power – also argues against such a scenario. For example, the four ON–OFF direction-selective cells, corresponding to the four compass directions, project to the lateral geniculate nucleus [8••]. Geniculate cells relay information to primary or higher-order visual cortices. This begs the question of how the four motion features follow their 'processing route' within the cortex. A likely scenario, in analogy with retinal processing, is that distinct features extracted by the retina interact with each other in cortex via inhibitory neurons: features are subtracted from each other, possibly according to nonlinear computations, resulting in more sophisticated neuronal representations.

The logic and biological significance of feature recombination, as well as its interaction with orientation selectivity [82] and other types of cortical selectivity, are currently a mystery. A specific but central open question relates to the signals incoming from the lateral geniculate nucleus, driven by different types of retinal ganglion cells. Do these

Figure 3



Parallel 'retinal movies' from different ganglion cell types are relayed by the LGN to the visual cortex. These may couple to a uniform cortical circuitry (left). Alternatively, they may be processed by sets of specialized circuits (right).

couple to a uniform cortical circuitry or are each routed through highly specific circuit paths (Figure 3)? In both scenarios, features recombine with each other, but in the former the 'feature calculus' has regularities, while in the latter it can take advantage of irregularities subject to feature-specific evolutionary and plastic refinements.

The retina can be pictured as a parallel assemblage of a multitude of small computational devices. Is the cortex similarly to be viewed as made up of highly designed and specialized computational devices, or are randomness, plasticity, and large-scale coupling the rules of the game? More specifically, how do local computations fit with the adaptive and plastic nature of cortical circuits, and with the presence of strong feedback from remote areas and top-down control? Currently, there exists no unified answer to this question. And indeed the answer probably will depend upon the specific cortical area and function. The methodologies highlighted above in the context of retina are opening a window on the realm of cortex [83–86].

It is customary to make parallels between brain and digital computer, in an effort to understand the former. For example, wiring cost is often invoked as a constraint that matters in the designs of both: accordingly, circuits ought to minimize total wire length. But brains and computers are dramatically different from a functional and computational point of view. Biological processing units – neurons, or even subcellular units such as dendrites or synapses – are computationally sophisticated, specialized, and diverse. By contrast, digital computers are assembled from a few kinds of processing units, which are parallelized or serialized. Microcircuits in the brain capitalize on the richness of the basic machinery to yield a zoology of cell types. This insures sophistication, specialization, and diversity on a higher computational plane, that is, over broader temporal, spatial, and functional domains. The oft-quoted parallels between brain and computer may be overemphasizing 'hardware constraints' invoked to understand their make-up that, in reality, may be tempered by – possibly functionally more important – requirements from function and computation.

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