Cortical Neurons and Circuits: A Tutorial Introduction

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Abstract. This paper is a tutorial review of the structure, composition, and statistical modeling of the organization of the neocortex. It begins with a general overview of the layered structure of the neocortex and its organization as a network of interconnected functional columns. Next it discusses the various classes of neurons that populate the neocortex using as a classification system the several generic types of signals produced by cortical neurons. This is followed by a discussion of characteristics in neuron-to-neuron signaling. Finally, it reviews some of the general trends found in the cortical organization.

I. Introduction

The neocortex is that part of the brain which makes up the outer 2 to 4 mm of the cerebral hemispheres. It is the 'gray matter' of the brain lying atop the cerebral 'white matter' composed of myelinated axons that interconnect different regions of the brain. All the higher-level psycho-physical functions sensory perception, object- and event-representation, planning, and decision making are believed to take as their biological substrate the activities of interconnected and distributed networks of neurons in the neocortex. Although it is quite thin, the cortex structure is highly folded with many grooves (called 'sulci'). This folded arrangement allows for a far greater volume of cortical matter to be contained within a given-sized brain cavity than would be possible if the cortex were laid out in a 'sheet' directly beneath the skull. The sulci provide convenient 'landmarks' for helping anatomists to classify different regions of the cerebral cortex. Figures 1 and 2 illustrate some of the general anatomical structures of the human brain.

All sensory information reaching the neocortex is conveyed through a sub-cortical (below the cortex) structure called the thalamus. Other signals, thought to be primarily 'control' signals that modulate cortical activity, also come into the neocortex from approximately 20 sub-cortical regions of the brain. The neocortex also sends signals back to these other areas via the thalamus and the basal ganglia. Part of the neocortex, called the primary motor cortex, also outputs signals that control the movement of skeletal and visceral muscles. It sends some of these signals to the brain stem or directly to the spinal cord, and others indirectly by way of the cerebellum. Different regions of the neocortex appear to be specialized to participate in specific types of psycho-physical functions, e.g. the visual cortex, the auditory cortex, the primary motor cortex, the language area, etc. However, it must be fully appreciated that no single area of the brain has been successfully identified as the sole functional area of any psycho-physical phenomenon. Rather, the brain appears to have a highly distributed functionality with many different areas of the brain (both cortical and non-cortical) making important contributions to every such function.

At a finer level of detail, experimental evidence strongly suggests that the neocortex divides itself up into small local processing units called **functional columns**. Each functional column is thought to be responsible for some one or few highly dedicated signal processing tasks. Functional columns appear to extend down through the entire thickness of the neocortex and to occupy lateral areas of only a few tenths of a millimeter in diameter. Interestingly, however, it appears that functional column structures are dynamic, i.e. that there is not an anatomical division of the cortex into fixed and permanent functional columns. Rather, it appears to be the case that the cortical circuits effectively 're-wire' their lateral connections in response to modulatory control signals (probably of non-cortical origin) so that at least some neurons are capable of 'being part of' many different possible functional columns. Some of the strongest evidence of this

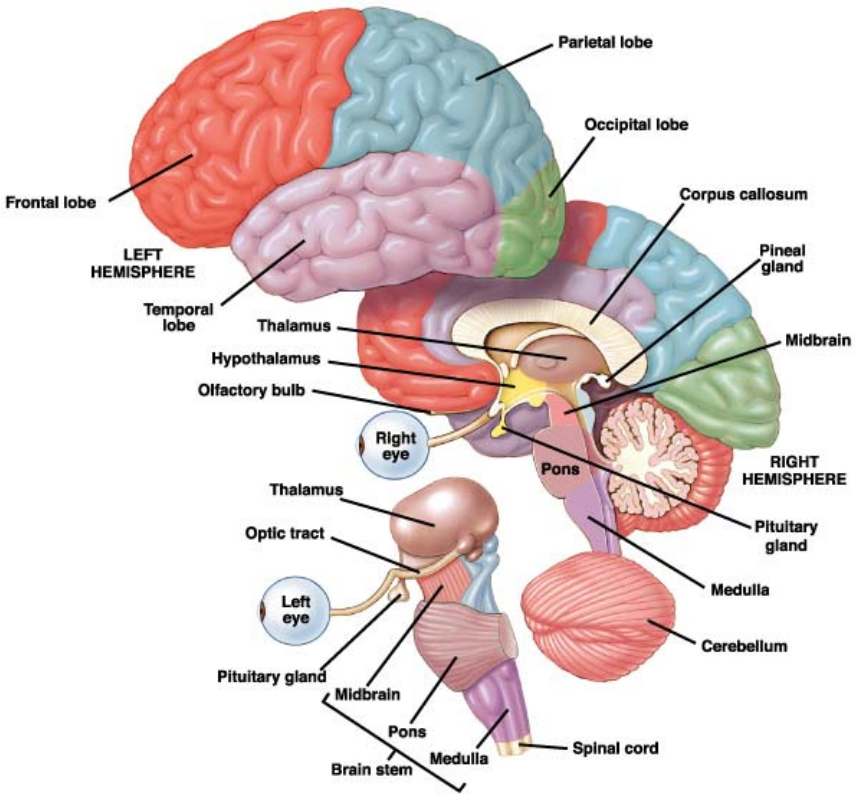

Figure 1. General anatomical structure of the human brain visible from sectioning along the sagittal plane. The neocortex is the outer volume of the cerebrum. The cerebrum is divided into two hemispheres. Four different regions, called lobes, are distinguished according to the primary functions associated with cortical processing in these regions. These are called the frontal, parietal, occipital, and temporal lobes. Not visible along the sagittal plane are three deep-lying structures that make up the rest of the cerebrum. These are: the basal ganglia, the hippocampal formation, and the amygdala. The thalamus and hypothalamus are sub-cortical structures not belonging to the cerebrum.

has come from studies of the visual cortex, where experimenters have succeeded in estimating the approximate number of functional columns. The experimental evidence hands us the interesting fact that there appears to be more functional columns in the visual cortex than there is room to hold all the neurons that would have to be present in order to 'build' these columns if the columns had a 'fixed' structure [1]. This has led to the present-day view of looking at the neocortex in terms of anatomical **cell groups** (physical neurons making physical synaptic connections to each other) that are in a sense 'soft-wired' and capable of dynamically modulating the strength of their interconnections in order to form functional **cell assemblies**.

This putative property of the neocortex is called the **dynamic link architecture** (DLA) hypothesis [2]-[4]. Although the DLA hypothesis has been around for more than twenty years, it has only gained wider acceptance in theoretical neuroscience in the past few years. This has been due primarily to new experimental findings that strongly implicate it, and to more recent issues of a theoretical and mathematical nature that appear to demand a mechanism such as DLA in order to explain the possibility of neural network capabilities for representing object composition as a coordinated correlation of many individual 'feature fragments' [3], [5]-[6].

Going down to the next level of detail, the neocortex has a laminar structure with six distinctive layers. Different features of these layers are revealed by different staining methods, as

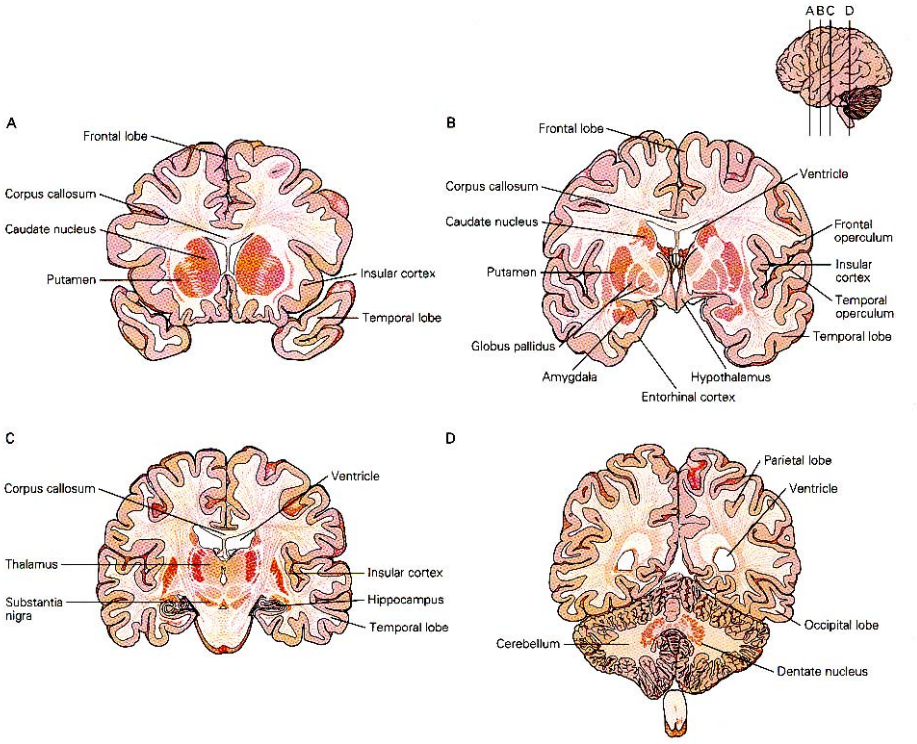

Figure 2. Coronal sections of the brain showing various deep structures. The neocortex is the thin outer layer. A. The corpus callosum is part of the white matter and is the major pathway for connecting the two cerebral hemispheres. The putamen and caudate nucleus are part of the basal ganglia. B. The globus pallidus is part of the basal ganglia. The amygdala is also visible in this section. C. The substantia nigra is part of basal ganglia. The hippocampus is visible in this section. D. Section showing the cerebellum. The neocortex and its white matter comprise 80% of the volume of the brain. The cerebellum contains 50% of all its neurons.

illustrated in figure 3. Layer I, the outermost layer, is often called the molecular layer or, somewhat misleadingly, the 'acellular' layer. As shown by the Nissl stain in figure 3, it does contain a few neurons. These neurons are all inhibitory neurons and synapse mainly to dendrites of neurons from the deeper layers. The principal structures found in layer I are dendrites and axons from neurons in the deeper layers. These run horizontally in layer I for short distances and interconnect with neighboring columns located at distances within a fraction of a millimeter. Intra-columnar axons in layer I are thought to belong exclusively to pyramidal cells (the output cells of the neocortex) mostly likely located in layers II and III of the neocortex. Dendrites in layer I not belonging to the sparse population of layer I inhibitory cells are apical dendrites from deeper-lying pyramidal cells.

Layer II, the external granular cell layer, contains a mix of small pyramidal cells and some inhibitory neurons, mainly bipolar cells and double bouquet cells. It also contains apical dendrites from pyramidal cells whose cell bodies are found in layers V and VI.

Layer III contains a variety of cells essentially consisting of almost all cell types found in the neocortex except the excitatory spiny stellate cell and cells found exclusively in layer I (the Cajal-Retzius cell and small unclassified inhibitory cells). The majority of cells in layer III are small pyramidal cells.

Layer IV is the exclusive location of a class of small excitatory cells called spiny stellate cells. It also contains a variety of inhibitory cells. Layer IV is the principal receiving layer for input signals coming into the neocortex from the thalamus. Typically the neurons in layer IV are strongly intercoupled. In some locations the layer IV neurons form a distinctive structure called a

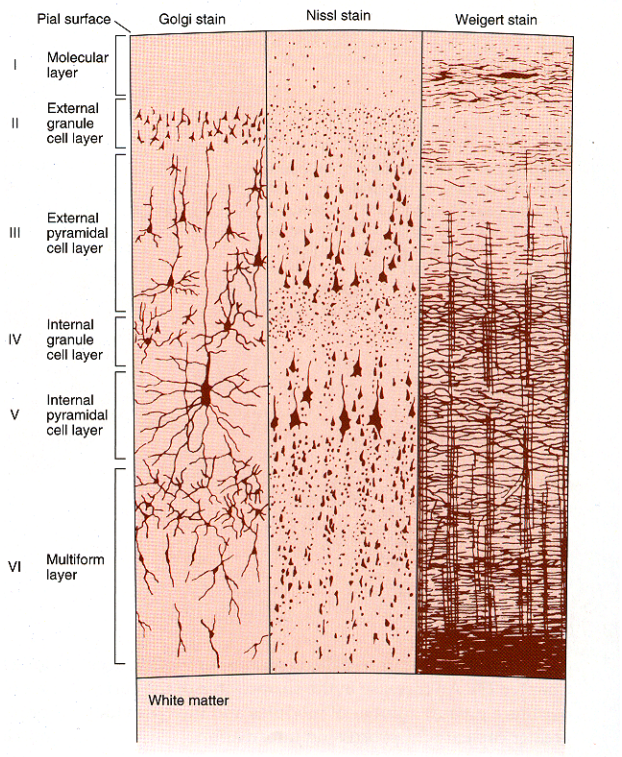

Figure 3. Layers in the neocortex as revealed by different staining methods. The Golgi stain reveals neuronal cell bodies and dendritic trees. The Nissl stain shows cell bodies and proximal dendrites. The Weigert stain reveals patterns of axonal distribution.

'barrel.' It is thought that barrel structures form the central core of functional columns in at least some locations within the neocortex, particularly some locations in the primary sensory cortices. Where they occur, barrels are surrounded by formations of other cells. One hypothesis is that barrel structures might form the nucleus of a functional column, with neurons located in between barrel locations possibly being dynamically transferable from one barrel to another as functional columns are 're-wired' in response to different signaling and control conditions. When they occur, barrels are found exclusively in layer IV.

Layer V is composed mainly of large pyramidal cells with a smaller population of inhibitory cells. Axons and possibly basal dendrites of non-spiny bipolar cells (which are inhibitory) are also found in layer V. Chandelier cells, which are inhibitory cells that make synaptic connections only to the axons protruding from other neurons, are often found in layer V. Layer V pyramidal cell axonal outputs to the white matter make long projections that leave the cortex and target the basal ganglia, brain stem, and spinal cord.

Layer VI is a heterogeneous layer of various neurons that blends gradually into the white matter. Most of the cells in layer VI are large pyramidal cells that project their axons back to the thalamus. Layer VI also contains a class of inhibitory neurons called Martinotti cells whose axonal outputs make long projections across all layers of the neocortex. After layer IV, layer VI is the next principal target of thalamic inputs to the neocortex.

An overview of the known neural populations found in the neocortex is given by Table I. It should be noted that no claim is made for this table being complete, nor are all known types of cortical neurons represented in this table (for example, the small unclassified layer I cells). New discoveries are constantly being made in regard to cortical organization. The data provided in this

Table I: Brief Summary of Cortical Neuron Classes

Cell Type	Signaling Class	Primary Neurotransmitter	Co-localized Neuropeptide	Location of Cell Body	Dendritic Location	Principal Axonal Targets
PC	RS	glutamate	SOM, CCK	layers II-VI	all layers	WM, dendrites.
PC	IB	glutamate		V	all layers	WM, dendrites.
SSC	RS	glutamate		IV	IV	dendrites in II-IV.
LBC	FS, RS	GABA	NPY, CCK	III, V		soma and proximal dendrites with sparse intra-laminar and intra-columnar projections and long inter-columnar projections.
SBC	FS, RS	GABA	VIP, CCK	III-V		local soma and proximal dendrites with dense intra-laminar and intra-columnar projections.
NBC	FS, CB, RS	GABA	NPY, SOM CCK	III, V		local soma and proximal dendrites with sparse to dense intra-laminar and intra-columnar projections.
BTC	FS, CB, RS	GABA	SOM, CCK, VIP			intra-columnar over all layers
BPC	FS, IS, CB, RS	GABA	VIP	II-IV	all layers	dendritic shafts over all layers but few and very restricted target cells.
e-BPC	?	glutamate?	?	II-IV	?	dendrites.
DBC	FS, CB	GABA	VIP	II/III	?	dendrites over all layers in a column.
e-DBC	?	glutamate?	?	II-V	?	dendrites.
NGC	FS	GABA		I, III/IV	local layer	dendritic shafts in the same layer, column.
MC	FS, CB, IS	GABA	NPY, SOM CCK NPY+SOM	VI	VI +?	dendrites with intra-laminar and intra-columnar projections and inter-columnar projections.
CRC	?	GABA		I	I	local dendrites.
ChC	FS, CB	GABA		III, V	III, V/VI	local axons in same layer and column.

PC=pyramidal cell; SSC=spiny stellate cell; LBC=large basket cell; SBC=small basket cell; NBC=nest basket cell; BTC=bitufted cell; BPC=bipolar cell; e-BPC=excitatory bipolar cell (putative); DBC=double bouquet cell; e-DBC=excitatory bitufted cell (putative); NGC=neurogliaform cell; MC=Martinotti cell; CRC=Cajal-Retzius cell; ChC=chandelier cell; RS=regular spiking; FS=fast spiking; CB=continuous bursting; IS=irregular spiking; GABA=gamma aminobutyric acid; NPY=neuropeptide Y; VIP=vasoactive intestinal peptide; SOM=somatostatin; CCK=cholecystokinine; WM=white matter.

table is therefore to be regarded as a summary of presently known facts. Most of the information in this table is taken from [7].

Various researchers have from time to time proposed circuit models for the neocortex. None of these models are complete and in some cases the connections described in them are hypothetical rather than known for a fact. It is very difficult to determine the exact connectivity of neurons in the neocortex. The attending technical difficulties are described in [1]. Furthermore, it

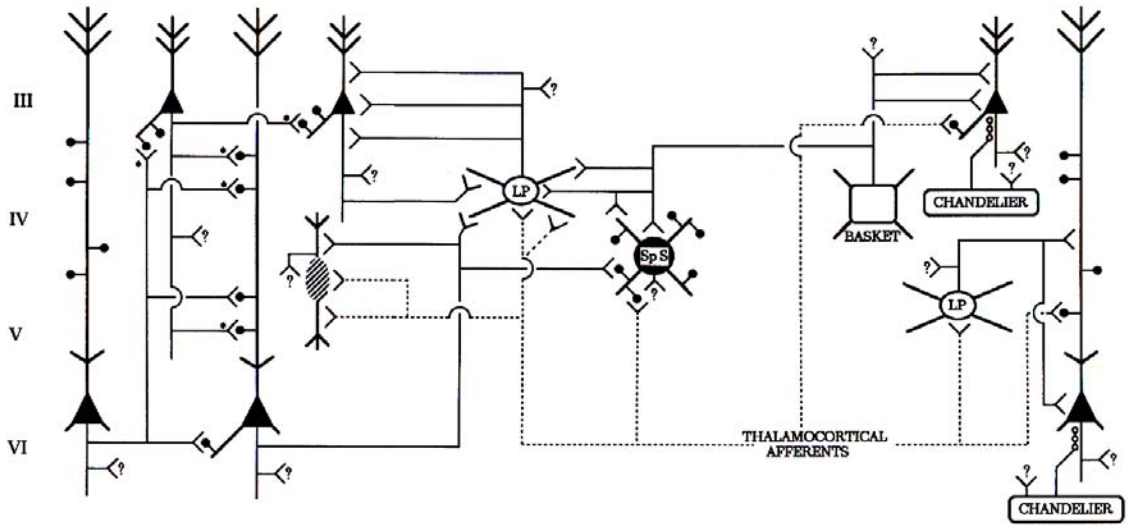

Figure 4. Known synaptic connections verified experimentally in the neocortex. This figure does not try to present a complete circuit model of cortical organization, and the neocortex contains many connections not shown in this figure. The dark cells are excitatory neurons; the white cells are inhibitory interneurons. The dark triangle-shaped cells are pyramidal cells. Their axons are drawn coming from the base of the triangle. Lines emerging from the corners represent dendrites. Sp S is a spiny stellate cell. It's axon is drawn protruding from the bottom. The other protrusions are dendrites. BASKET denotes a basket cell (either large, nested, or small basket cell). CHANDELIER denotes a chandelier cell. LP stands for 'local plexus'. This is not the name for a particular neuron class but rather is a catch-all for a variety of neurons characterized by having a multipolar shape, axonal ramifications that include a local plexus in the immediate vicinity of the cell body and dendrites either coextensive with it or located slightly above or below it. The LP designation excludes basket, chandelier and bipolar cells. The cross-hatched symbol represents a non-spiny bipolar cell. The figure also shows some known connections from the thalamus.

needs to be emphasized that all of these models are misleading in the sense that none of them accurately represents the true proportion of different neuron types. At best these models might describe known instances where one neuron type has been found to make synaptic connection to another neuron type. Figure 4 illustrates some of the experimentally verified neuronal connections in the neocortex [1]. Although some researchers prefer to refer to neocortical inter-connections as 'random,' cortical organization does seem to follow some relatively simple rules [1]. White's rules are as follows.

Rule 1. Every neuron within the target area of a projection receives input from the projection.

Corollary to Rule 1. Axon terminals from any extrinsic or intrinsic source synapse onto every morphological or physiological neuron type within their terminal projection field. In practice this means that a pathway will form synapses with every element in their target region capable of forming the type of synapse normally made by the pathway (i.e., asymmetrical or symmetrical).

Rule 2. Different dendrites of a single neuron form similar synaptic patterns; that is, the numbers, types proportions, and spatial distribution of synapses is similar, provided the dendrites are exposed to similar synaptic inputs.

Corollary to Rule 2. Axonal pathways form similar synaptic patterns onto all the dendrites of a single neuron, provided the dendrites occur within the target region of the axonal pathway.

Rule 3. Neuronal types receive characteristic patterns of synaptic connections; the actual numbers, proportions, and spatial distribution of the synapses formed by each neuronal type occur within a range

of values.

Corollary to Rule 3. Different extrinsic and intrinsic synaptic pathways form specific proportions of their synapses with different postsynaptic elements (spines vs. dendritic shafts, one cell type vs. another).

Rule 4. The receptive field properties of every cortical neuron are shaped by the spatial and temporal integration of inputs from a variety of excitatory and inhibitory sources. Inputs from a single source cannot be the sole determinant of the receptive field properties of cortical neurons.

Rule 5. Only a fraction of the synaptic inputs to a cortical neuron are activated at one time. Therefore, the receptive field properties of cortical neurons are transitory and are determined by the cortical circuitry active at a given time.

Rule 6. Excitatory and inhibitory synaptic interactions between cortical neurons preferentially link neurons situated in close proximity to one another, and these interactions typically link neurons having similar receptive field properties. Synaptic interactions between closely spaced neurons, having similar receptive field properties, provide a basis for the similarity of receptive field properties of neurons within a functional column.

Pyramidal cells (PCs) are the projection neurons of the neocortex, i.e. they are the 'output' neurons. Excepting projections they make via the white matter, the projection radii of PCs is quite limited in spatial extent. In mouse neocortex 90% of all PCs make no synaptic connections to neurons beyond a distance of 0.2-0.3 mm and only 9% of them make a single synaptic connection at this range [8]. This sets for us an approximate lateral range for the size of a functional column. All connections made by inhibitory neurons are 'local' (primarily within the functional columns to which they belong).

II. Cortical Neuron Fundamentals

In some basic ways cortical neurons are all alike. Their cell membranes all exhibit an electric potential difference (the membrane voltage) between the inside (cytoplasm) and outside (extracellular region) of the cell. Their membrane voltage varies in response to the flow of ions through dedicated proteins, called **channels**, that are embedded in the cell membrane. In a sense the channel proteins act like ionic valves and can be caused to open or close by various biophysical mechanisms. Different proteins are selective as to the type or types of ions they will allow to flow, and these differences determine if the channel current is **excitatory** (tends to make the neuron fire a pulse) or **inhibitory** (tends to prevent the neuron from firing a pulse). The inward flow of Na^+ or Ca^{2+} ions makes the membrane voltage more positive ('depolarizes' the membrane), while the outward flow of K^+ ions makes the membrane voltage more negative ('hyperpolarizes' the membrane). Figure 5 illustrates the 'valve action' of channel proteins according to the main biophysical mechanisms for opening and closing ion channels.

All neurons have a cell body (soma) that integrates incoming signals to produce variations in membrane potential. Neuron-to-neuron signaling occurs at connections, called synapses, where an action potential (AP) pulse from the signaling neuron (the 'presynaptic cell') is converted to a membrane response in the neuron that is signaled to (the 'postsynaptic cell'). Synapses made on the soma are generally inhibitory. Cortical neurons have an extensive network of extruded fibers, called dendrites, that serve as connection points for synapses and 'receive' incoming signals. All excitatory connections are made on the dendrites, and about 31% of all inhibitory synapses likewise occur on the dendrites. Almost all cortical neurons extrude another long fiber, called the axon, that serves as the 'wire' carrying the neuron's output signal (its AP). The axon can branch to make contact with synapses on multiple target neurons.

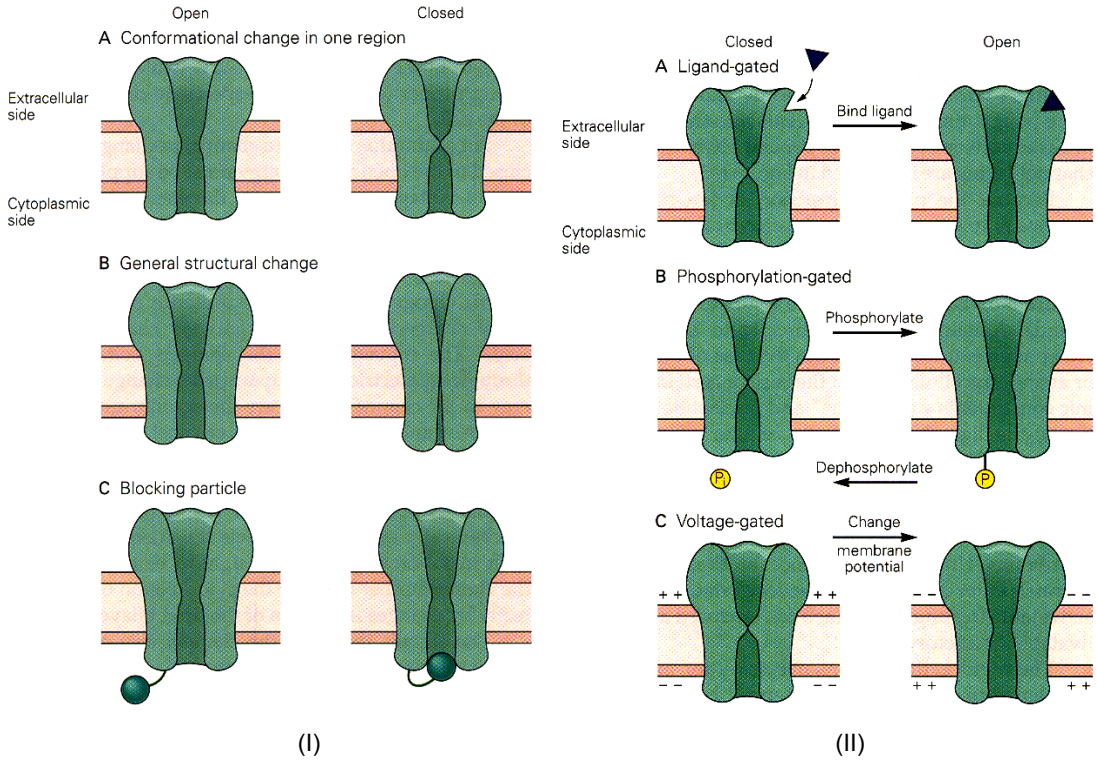

Figure 5. Principal channel mechanisms in neuronal membrane. (I) The three physical models for the opening and closing of ion channels. A and B are typical of channels said to be 'persistent' channels. C is typical of channels said to be 'inactivating' channels. (II) Principal mechanisms for causing channels to open and close in the neocortex. A. Ligand gated channels are opened by the binding of a chemical neurotransmitter molecule. These channels occur at chemical synapses and are responsible for neuron-to-neuron signaling. B. Phosphorylation-gated channels are opened by the binding of a phosphate to the channel protein on the cytoplasmic side. These types of channels are opened and closed by metabotropic processes going on inside the neuron that determine its internal chemical state. They are involved in metabotropic processes stimulated by external neuron-to-neuron signaling that act as modulation and control processes in the neocortex. C. Voltage-gated channels are channels that open or close in response to the cell's membrane potential. These are the channel types responsible for the generation and propagation of the action potential.

Figure 6 summarizes these main common features of neural signaling. Neurons come in many different sizes and shapes and contain different kinds of channel proteins at their synaptic junctions and in the region of the soma where action potential are generated. These differences produce a wide variety of different neuron types, some of which transmit excitatory signals, others of which transmit inhibitory signals. This diversity has led to a variety of different ways of classifying cortical neurons according to either a cell's morphology, to the types of AP signals it generates, or to the types of molecules it uses as its neurotransmitter. In this paper we are mainly interested in neuronal signaling, and so we will classify neurons according to their signaling type. Even here, however, there is more than one signal classification system in use. The more widely used system is the one we have used in Table I, which we will here call the Connors-Gutnick or CG system [9]. However, in some ways this classification system is too simple and so other more ad hoc classifications have also arisen. Toledo-Rodriguez et al. use such a system in [7], and we will likewise adopt elements of the 'T-R system' here. It is also worth mentioning that yet another taxonomy, based on the mathematics of models of different neuronal signaling patterns, has also been introduced by Rinzel [10]. However, we will not use that system in this paper.

At a physiological level the signaling behavior of a neuron is determined by the numbers and

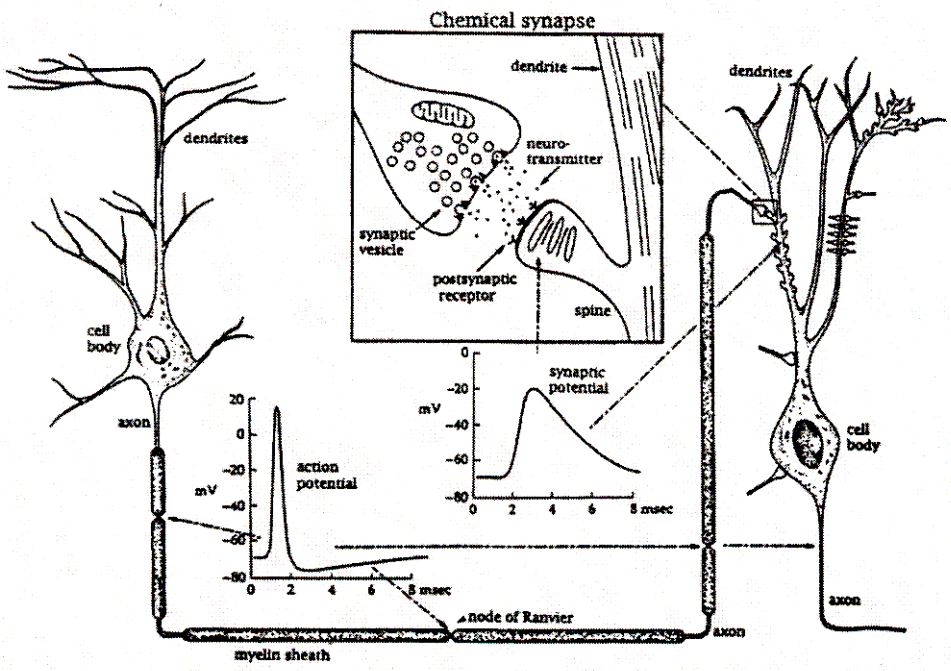

Figure 6. Canonical signaling scheme in neural networks. The action potential (AP) is generated at the axon hillock in response to excitatory signals received by the neuron's dendrites. (The axon hillock is the part of the soma where the axon protrudes from the cell body). It is propagated down the myelinated axon by being regenerated by voltage-gated ion channels at the nodes of Ranvier. The AP is an all-or-nothing spike. Its rising edge (depolarization) is produced by the opening of voltage-gated Na^+ channels in the cell membrane. At higher voltage levels voltage-gated K^+ channels open and the Na^+ channels inactivate, thus producing hyperpolarization and the down-swing of the AP pulse. The chemical synapse is the most commonly-occurring type of synapse in the neocortex. When the AP arrives at the synaptic terminal (end of the axon) it stimulates the release of a chemical neurotransmitter (NTX). The NTX molecules are called ligands. The ligands bind with receptor proteins in the postsynaptic cell membrane. These respond by opening ion channels, which produces a postsynaptic potential (PSP) in the target cell. The PSP decreases in amplitude and spreads out in time as it travels down the dendrite to the cell body, being typically less than 1 mV in cortical neurons by the time it reaches the soma. Note that the PSP is much wider than the AP that produced it. To a first approximation, PSPs from multiple synapses add. As suggested in the figure, synapses can form at dendritic spines, on the dendrite shaft, and at the cell body itself. Synapses on the cell body are usually inhibitory. Most dendritic synapses are excitatory, but a minority of them are inhibitory. Synapses on the dendrite are called axo-dendritic synapses. Those on the cell body are called axo-somatic. A synapse can also be formed between the axon and the axon of another neuron. These are called axo-axonic synapses, and they are usually either inhibitory or modulatory. In the neocortex only pyramidal cells (PCs) project axons into the white matter, which is composed entirely of myelinated axons. Most cortical neurons express branches in their axons prior to the myelin sheath. These make local interconnections. The axon usually branches at its far end as well as makes multiple synaptic connections to many target neurons.

types of protein channels it contains and on how these are distributed. For our purposes, it is sufficient to distinguish three types of channels. These are called the ionotropic channels (ICs), the voltage-gated channels (VGCs), and the metabotropic second-messenger channels (MSMs). In this paper we will need only a light and qualitative description of these channels. Slightly more detail in tutorial form can be found in [11], and a much more detailed discussion is given in [12]-[13].

Ionotropic channels are located at synapses. An action potential arriving at the end of an axon stimulates the release of neurotransmitter (NTX) into a tiny gap, called the synaptic cleft, between the presynaptic and postsynaptic neurons. The NTX molecules bind to receptor proteins on the postsynaptic cell. This causes the protein channel to open and an ion current to flow. This current in turn causes a change in the membrane voltage of the postsynaptic neuron. This change is called the postsynaptic potential (PSP). A positive increase in voltage is called an excitatory PSP

(EPSP); a negative change is called an inhibitory PSP (IPSP). The amount of change for a single synaptic transmission is typically very small (less than 1 mV) by the time the signal reaches the soma. In the case of excitatory ICs, it generally takes many action potentials arriving more or less simultaneously at many synapses to stimulate the receiving neuron enough to fire its own AP. One rough rule of thumb is that a typical cortical neuron in monkey requires about 125 EPSPs randomly distributed throughout its dendritic tree and arriving within about 1 msec of each other in order to stimulate a firing response. To put this in perspective, it has been crudely estimated [14, pp. 58-59] that in the monkey neocortex each neuron has a total of approximately 20,000 synapses on the average. Of these, about 9,000 are excitatory synapses connected with local neurons, another 9,000 are excitatory synapses connected to remote neurons via the white matter, and about 2,000 are inhibitory synapses (all from connections made by local neurons).[1] Thus, only on the order of 0.7% of the neurons capable of sending excitatory APs to a particular postsynaptic neuron need fire at any given time in order to stimulate a response.

The ionotropic channel is modeled as a change in conductance. Conductance is the ratio of current to voltage, so the ion channel current is expressed as

$$I(t) = G(t) \cdot \left[V_m(t) - E_{syn} \right] \tag{1}$$

where I is the ion current, $G(t)$ is the time-varying synaptic conductance, V_m is the membrane voltage, and E_{syn} is an electromotive force (a voltage) characteristic of the types of ions that flow through the channel. For the principal excitatory ionotropic channel (called the AMPA channel), $E_{syn} = 0$; for the main inhibitory ionotropic channel (called the $GABA_A$ channel), $E_{syn} = -75$ mV. The overall channel conductance for most ionotropic channels is approximated accurately enough by the expression

$$G(t) = G_{\max} \frac{t - t_i}{\tau} \cdot \exp\left(1 - \frac{t - t_i}{\tau} \right) \cdot H(t - t_i) \tag{2}$$

where $G_{\max}$ is the maximum channel conductance, t_i is the arrival time of the action potential, τ is a time constant for the channel, and $H(x)$ is the Heaviside unit step function. $H = 1$ for $x > 0$ and $H = 0$ for $x < 0$. The maximum channel conductance occurs at $t = t_i + \tau$.

The dynamics of the membrane voltage response to ionotropic current $I(t)$ is a complicated function of other channels, namely the voltage-gated channels, present in the cell's membrane [11]. Every cortical neuron has three main classes of VGCs characterized by the ion current they conduct. These are: 1) Na^+ channels; 2) K^+ channels; and 3) Ca^{2+} channels. These channels are heavily concentrated in the trigger zone of the neuron. The mathematical description of the physiology of voltage-gated channels was first discovered by Hodgkin and Huxley and published in a landmark paper in 1952 [15]. For this work Hodgkin and Huxley received the Nobel Prize in medicine in 1963. A summary of the Hodgkin-Huxley (H-H) model is provided in [16]. All present day mathematical models of the physiology of VGCs in neurons are based upon extensions of the H-H model to accommodate the various types of VGCs that characterize a particular neuron. Examples of such extensions can be found in [17]. In addition to the voltage-dependent ion channels, the neuronal membrane has an intrinsic capacitance that determines a voltage-dependent time constant characteristic of the PSP. Roughly speaking, the postsynaptic neuron acts like an integrator of the EPSPs and IPSPs produced by the ICs. Figure 7 illustrates the membrane voltage response for several increasingly high levels of excitatory synaptic inputs as modeled by the Wilson version of the H-H model [18].

[1] In comparison, these numbers are all doubled in human neocortex. In mouse cortex each neuron receives roughly 8,000 synapses. Of these, 3600 are local excitatory, 3600 are remote excitatory, and 800 are local inhibitory. In humans these numbers are: 40,000; 18,000; 18,000; and 4000, respectively.

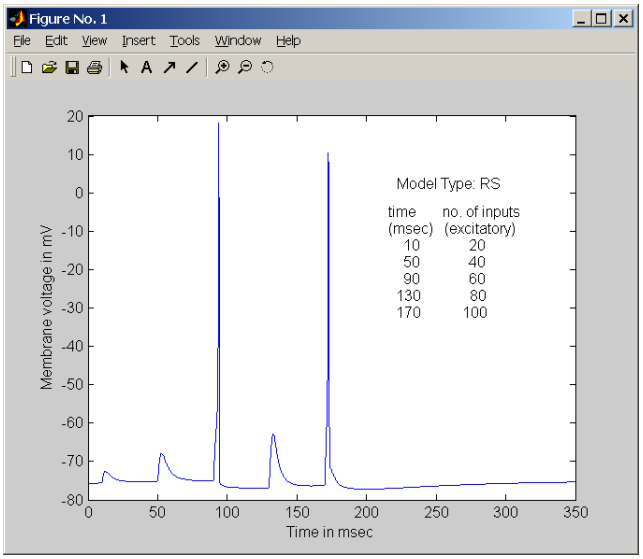

Figure 7. Response of a Wilson RS-type neuron model to excitatory inputs. The arrival time and number of simultaneous excitatory inputs is given in the figure. The IC time constant was 2 msec. Note the integrator-like response of the membrane potential for $t = 10$ and $t = 50$ msec. Note also that the response is not linear. At $t = 90$ msec the arrival of a volley of 60 synaptic inputs opens enough voltage-gated Na^+ channels to stimulate an action potential. However, a volley of 80 inputs at $t = 130$ is not sufficient to trigger another AP. This is because the first AP has opened all the K^+ channels and these have not all deactivated by $t = 130$. (Note the slight hyperpolarization of the membrane potential around $t = 100$ msec and again at around $t = 180$ msec). Their inhibitory effect outweighs the excitatory synaptic input and no AP is produced. This phenomenon is called the relative refractory time of the neuron. Note that the membrane voltage's time constant is smaller (faster) at $t = 130$ compared to $t = 10$ and $t = 50$. This is because of the increased K^+ channel conductance. At $t = 170$ the combination of more input APs and decreased K^+ conductance results in the generation of a second action potential.

To invoke a firing response the membrane voltage at the trigger zone must exceed a threshold level sufficient to turn on the Na^+ VGCs in that region. Although the EPSP is attenuated as it travels along the dendrite, there is relatively little attenuation of this signal in the soma. The firing threshold is a function of the density of primarily Na^+ VGCs in the cell membrane (or, in some cases, to the density of Ca^{2+} VGCs). Thus, there is a relatively high threshold in regions away from the axon hillock (trigger zone), and the threshold drops sharply at the trigger zone. This is illustrated in figure 8.

Unfortunately, the computational complexity of H-H-like neuron models prevents our using them in the simulation of even modestly-sized neural networks of a few hundred neurons because of the amount of computer time required. To combat this, while at the same time trying to preserve as much of the complex dynamics shown in figure 7 as possible, a variety of simpler phenomenological models have been developed. Two important examples of this are the Eckhorn model [19] and, more recently, the Rulkov model [20]. These models aim at keeping most of the dynamical effects produced by VGCs but do so by ad hoc equations that cannot be easily tied to physiological mechanisms.

Our final class of channels is the MSM-class. These, too, are synaptic channels but, unlike ICs, they do not directly cause any ion currents to flow across the cell membrane. Rather, their action is primarily modulatory. Although in some cases they have been known to indirectly cause certain types of ion channels (primarily K^+ channels) to open or close, in most cases they change the sensitivity of IC receptor proteins to binding with NTX molecules, modulate the cell's resting potential, or modify the membrane voltage threshold at which an action potential is generated [11]. MSMs produce a complicated biochemical chain reaction inside the postsynaptic cell that alters its chemical state, producing a change in its metabolic properties. (This is why these

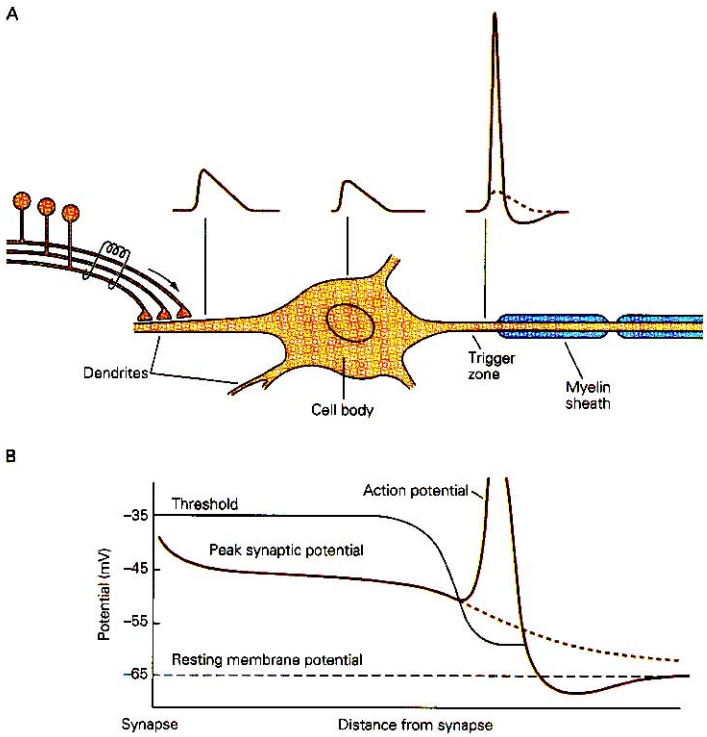

Figure 8. Variation of firing threshold with position in the neuron. The threshold is a function of the density of voltage-gated channels, particularly Na^+ and Ca^{2+} channels, in the neuron. In most cortical neurons the firing threshold is about 10 mV above the cell's resting potential. Trigger zones are repeated at the nodes of Ranvier in myelinated axons. PSPs generally decay rapidly with distance along a synapse. Thus, synapses on distal dendrites (far from the soma) generally produce smaller PSPs at the cell body, while synapses on proximal dendrites (near the soma) produce large responses.

channels are called 'metabotropic' channels). The most important neurotransmitters (which are called neuromodulators when they bind to an MSM receptor protein) are the neuropeptides and the small molecule monoamines dopamine (DA), serotonin (5-HT), and norepinephrine (NE; also known as noradrenaline) as well as acetylcholine (ACh) and histamine. Metabotropic effects are slow in onset and have a much longer duration than IC or VGC effects. They are also known to sometimes have very long-lasting effects, including the growth of new synapses and the increasing of the number of ionotropic receptor proteins in existing synapses. It is thought that monoaminergic neurons located in the brain stem (neurons that project axons to all parts of the neocortex and use monoaminergic neurotransmitters for their 'output chemical') are responsible for controlling the sleep-wake cycle. The metabotropic signaling sequence inside the cell has very high 'gain' in the sense that even the binding of a single neuromodulator molecule at the synapse can produce a very large response in the postsynaptic cell.

The magnitude of the PSP produced at an ionotropic synapse is directly proportional to the amount of neurotransmitter released into the synaptic cleft. NTX release is quantized by the fact that it is due to the breaking-open of the synaptic vesicles that contain the NTX molecules in the presynaptic terminal. The number of vesicles that break open with a given AP appears to be a random variable following the famous binomial probability distribution function. Figure 9 illustrates the experimental evidence that points to the fact that signaling at the synapse is 'noisy.' This data was actually obtained at the neuromuscular junction where axons from spinal motor neurons contact the skeletal muscles. However, similar effects take place at synaptic junctions in the neocortex. Thus, a synapse is characterized by its 'release probability.'

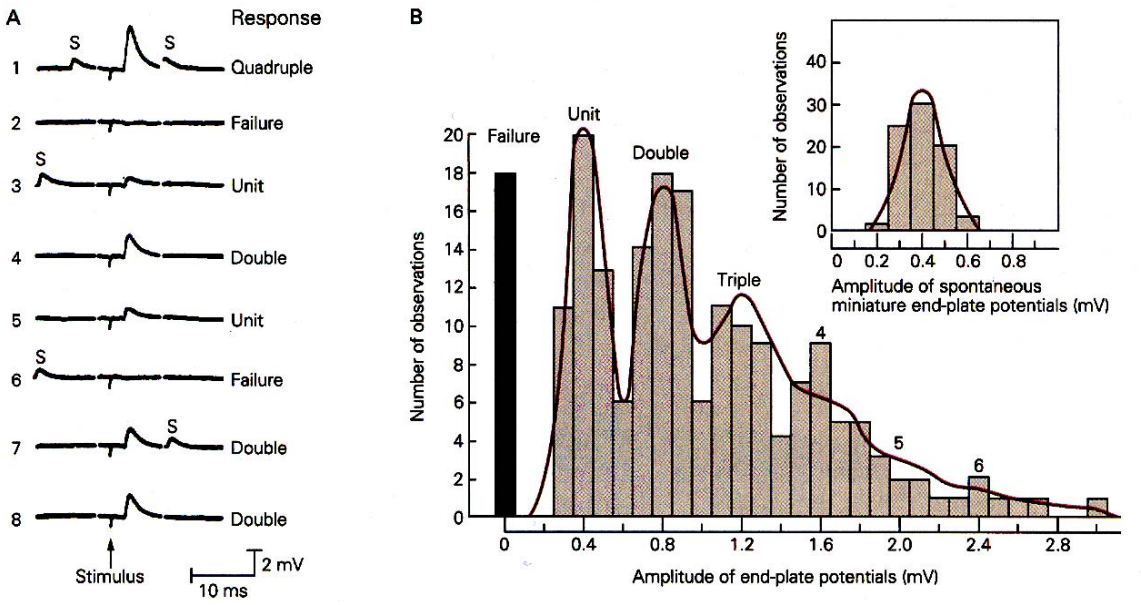

Figure 9. Experimentally observed responses to neurotransmitter release measured at neuromuscular junction. In the neuromuscular junction the response is called an 'end plate potential' rather than a postsynaptic potential. A. Measured voltage responses. The stimulus event is marked by the arrow in the figure. Note that spontaneous NTX release (S) is sometimes observed (1, 3, 6, and 7). Note also that the stimulus sometimes fails to produce a response (2 and 6). B. Histogram of responses. The histogram clearly shows quantized response levels. The hypothesis explaining this effect is that a unit response corresponds to release from one synaptic vesicle in the presynaptic terminal. The data is empirically fitted very well by the binomial probability distribution function.

III. Classes of Cortical Neurons

Despite the great variety of neuron types that occur in the nervous system, all neurons can be subsumed under a standard signal processing schema involving four elements: input element, integrative element, conductile element, and output element. This is illustrated by figure 10 and discussed in the caption. There are only two important deviations from the general model of figure 10. Some cortical neurons lack an axon as the conductile element. Instead they make direct dendrite-to-dendrite or dendrite-to-soma connections to other neurons. These connections are called dendro-dendritic and dendro-somatic synapses, and they can be either of the chemical synapse type or the electric gap junction type. In the case of the latter, the connection is strongly attenuating, with attenuations of 10:1 at low frequencies and as much as 100:1 for action potential spikes. It is therefore difficult to see what role, if any, gap junctions might play in the neocortex, although that question is currently under investigation. It might be that gap junctions provide a path for Ca^{2+} or other molecular transport. So far gap junctions in the neocortex have been documented only among inhibitory interneurons. Furthermore, at present it appears that gap junctions only form among neurons of the same firing type, i.e. RS-type neurons to RS-type neurons and LTS-type neurons to LTS-type neurons[2] but not RS-type to LTS-type neurons [21].

The other exception occurs for the case of axo-axonal synaptic coupling. Here the synaptic connection is made directly to the axon of the target neuron, usually at a point near where the target axon emerges from the cell body. These connections appear to be exclusively inhibitory. A

[2] LTS stands for 'low threshold spiking neurons'. LTS neurons exhibit post-inhibitory rebound (PIR), i.e. they fire a spike after being released from hyperpolarization. The LTS class includes sparsely spiny bitufted and Martinotti cells.

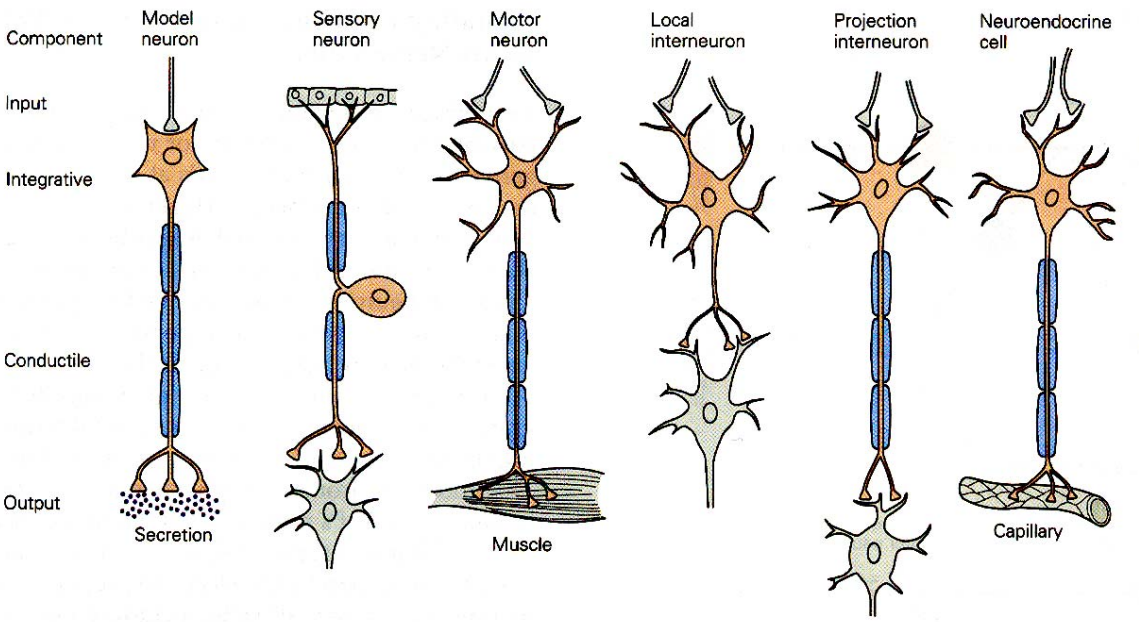

Figure 10. Standard neuronal signal processing model. The standard model is shown on the far left. The neocortex contains local interneurons (INs) and projection interneurons (PIs) as well as a few motor neurons that control eye movement. Sensory neurons are found in the peripheral nervous system and in the retina, olfactory, and auditory systems. Most motor neurons are found in the ventral horn of the spinal cord. Neuroendocrine cells are located primarily in the hypothalamus and secrete hormones into the blood stream. In the neocortex only pyramidal cells serve as projection neurons. Some local INs lack a conductile element and make direct dendro-dendritic or dendro-somatic connections. In some cases this is by means of electric gap junctions, which can be viewed as voltage-dependent resistors that directly couple between cells. Chemical synapses are by far the most common type of connection in the neocortex and it is not known what the relative density of gap junctions is in the cortex. Where they exist, gap junctions have so far been found only between inhibitory INs of the same class. Specifically, FS-type neurons make gap junctions only with other FS-type neurons, and low-threshold spiking interneurons (LTS neurons) make gap junctions only with other LTS neurons. Neurons connected by gap junctions sometimes act as though they were equivalent to one large neuron with many output pathways, all of which fire synchronously.

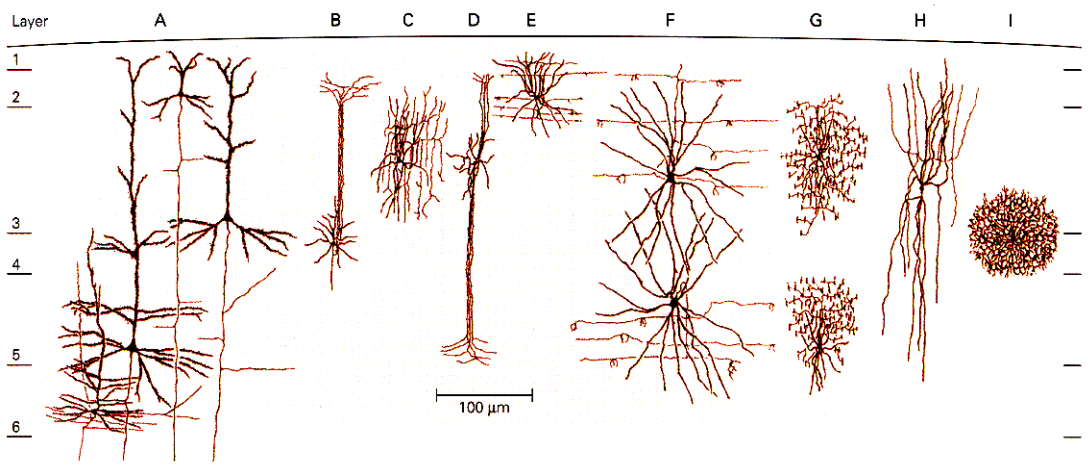

Figure 11. Some varieties of cortical neurons found in monkey cerebral cortex. (A) Pyramidal cells. The structures projecting vertically upward are apical dendrites. The structures projecting down to the white matter are axons. (B) Spiny stellate cell. The structure projecting into layer 2 is its axon bundle. (C) Bitufted cell. The branching 'arcades' running vertically make up the cell's axon arborization. (D) Double bouquet cell. The long structures are axon fibers. (E) Small basket cell. (F) Large basket cells. (G) Chandelier cells. (H) An undesignated cell, sometimes called a long stringy cell. This cell transmits neuromodulators, either neuropeptides or acetylcholine. (I) Neurogliaform cell.

connection so made by-passes the target cell's integrative unit and acts as a direct inhibitory gating mechanism preventing the target cell from transmitting its action potential. In the neocortex the chandelier cell makes only this type of synaptic connection.

Within the generality of this basic neuronal schema we find a great diversity of different cell types (Table I). Figure 11 illustrates some of the cell types that have been documented in the cerebral cortex of monkey. Our next task is to discuss the types of signaling differences that set these different neurons apart from one another [7], [8], [21].

A. Pyramidal cells (PCs). Pyramidal cells make up about 65% of all neurons in the neocortex. They are the only neurons that send signals out of their local area to other regions of the brain. For this reason they are called projection neurons. Most, but not all, PCs belong to the regular-spiking or RS-type class of neurons. This signaling-type classification, like the others, was defined by experimental observations of the neuronal response when it is injected with a constant excitatory current (by means of microprobe impalement). Under these test conditions, the neuron initially fires at a relatively high rate (determined by the amount of injected current) but soon slows its firing rate and settles into a constant-frequency firing pattern. This behavior is called 'accommodation' by some researchers and 'adaptation' by others. Its principal physiological mechanism is thought to be the slow activation of Ca^{2+}-dependent K^+ channels. Many neurons contain high-voltage-gated Ca^{2+} channels in their cell membranes. These VGCs normally cannot be opened by EPSPs due to synaptic inputs. However, when the cell fires an AP sufficient voltage is generated to open these VGCs. This results in an influx of Ca^{2+} ions which bind to sites on the cytoplasmic side of the proteins that make up the Ca^{2+}-dependent K^+ channels, thereby opening these channels and hyperpolarizing the cell. The amount of resulting firing rate adaptation depends on the number and density of these channels and on the number and density of the high-voltage Ca^{2+} VGCs. Figure 12 models RS-type firing under laboratory test conditions.

Not all PCs are of the RS-type. Some PCs found in layer V exhibit Class-1 IB-type signaling. IB stands for 'intrinsic bursting' behavior, which is illustrated under laboratory conditions in figure 13. The primary mechanism for IB-type firing is thought to be a transient low-threshold calcium current produced by low-voltage-gated Ca^{2+} channels. It is this current rather than an Na^+

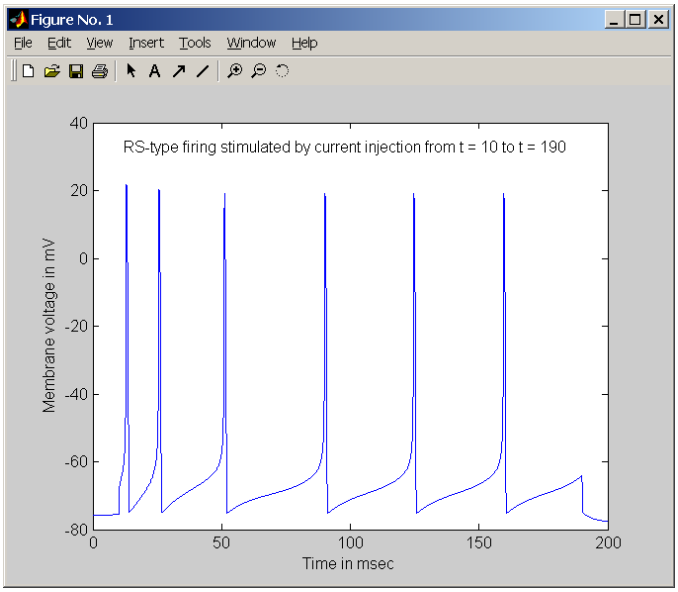

Figure 12. RS-type firing under laboratory test conditions stimulated by injection of an excitatory current from $t = 10$ to $t = 190$ msec.

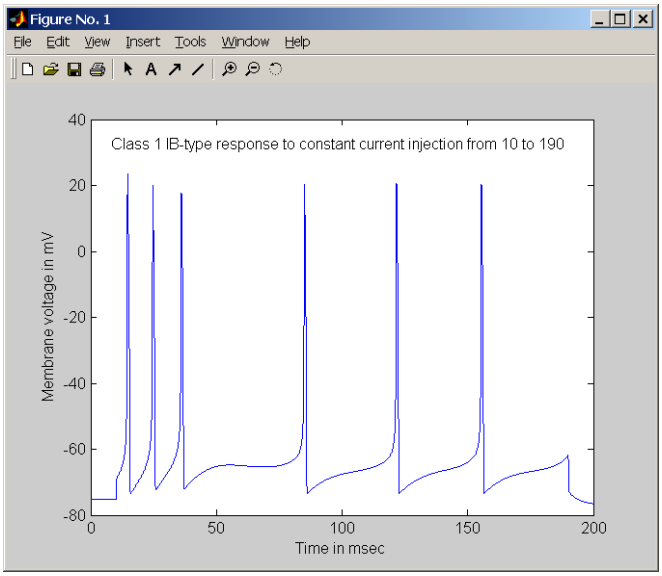

Figure 13. Class-1 IB-type firing pattern in response to constant current injection from $t = 10$ to $t = 190$ msec.

current alone, that produces the burst action. However, the Ca^{2+} channel is a slowly inactivating (transient) VGC and it soon ceases to conduct any more current until its inactivation is reset by hyperpolarizing the cell. Under laboratory test conditions with constant-current injection the neuron fires a burst of 3 to 5 action potentials, followed by a quite period, and then resumes firing at a lower and more or less constant rate. Other PCs exhibit Class-2 IB firing, where the neuron fires a burst, followed by a pause, then fires another burst, repeating this while the stimulus lasts.

The accommodation response in RS-type signaling may be either weakly accommodating (the most typical behavior) or strongly accommodating. Strongly accommodating means the steady-state firing rate under constant-current injection is much lower than the initial firing rate. Some PCs in layers IV-VI belong to the strongly accommodating subclass, which is usually called RS2.

B. Spiny Stellate Cells (SSCs). SSCs make up the other type of excitatory neurons in neocortex. They are found only in layer IV and make up about 20% of the total population of neurons. SSCs are local interneurons only. Their axonal projections never leave the immediate region in which they are located, although their axons do project vertically all the way to layer II (see figure 11). SSCs are RS2-type neurons so far as their signaling behavior is concerned.

C. Class I Inhibitory Neurons. The remaining 15% of cortical neurons are local inhibitory interneurons (IINs). 50% of these neurons are classified as Class-I GABAergic cells (so called because their neurotransmitter is gamma-aminobutyric acid or GABA). They are found in all cortical layers. Class-I IINs belong to the fast-spiking or FS-type category. As shown in Table I, almost all morphological classifications of IINs contain species of neurons belonging to Class-I. The classical FS-type neuron is non-accommodating, i.e. its spiking frequency does not change when the neuron is injected with an excitatory constant current. Thus some researchers prefer the designation NAC (non-accommodating) to the designation FS for these neurons [7].

Figure 14 illustrates the classical FS response. As can be seen, the FS-type neuron's firing rate is significantly faster than that of the RS-type. Examination of the onset of the firing pattern has led to the distinguishing of three subclasses of FS-type response, called b-NAC, c-NAC, and d-NAC. Figure 14 illustrates the c-NAC (constant non-accommodating) subclass. The b-NAC subclass is characterized by a brief 3 to 5 spike very-high-frequency burst at onset which quickly

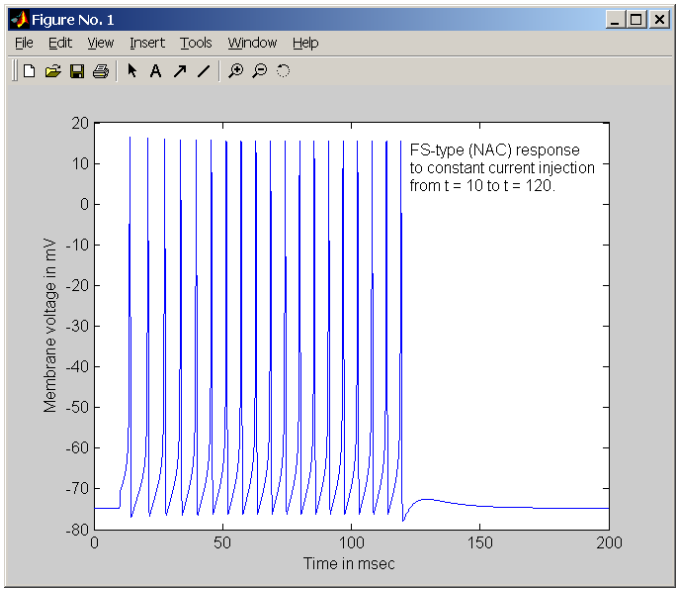

Figure 14. RS-type response to constant current injection from t = 10 to t = 120 msec. This response is characterized by lack of accommodation in the firing rate and by high-frequency spiking. There are three subclasses of RS response. The firing pattern illustrated here belongs to the c-NAC subclass.

settles into the constant steady-state firing pattern. It is not entirely clear what the mechanism is for this bursting-NAC response. The d-NAC or delayed-NAC response is characterized by a brief delay between the application of the stimulus and the onset of firing. There is an initial strong depolarization of the membrane voltage followed by a brief interval before AP spiking begins. Most likely this is caused by the presence in the trigger zone of a particular type of transient K^+ VGC known as the "A-current" or I_A [22]. Large basket cells (LBCs) and nested basket cells (NBCs) of different subspecies exhibit all three subclasses of NAC signaling. Bitufted cells (BTCs) and small basket cells (SBCs) have species exhibiting both d-NAC and c-NAC. Neuroglioform cells (NGCs) and Class-I chandelier cells (ChCs) are d-NAC FS-type cells, while Class-I Martinotti cells (MCs) are c-NAC FS-type cells [7]. FS-type cells tend to make synapses to the soma or to the shafts of proximal dendrites at their target cells and will form synapses with any other type of cell. The exception to this rule is the Class-I NGC, which targets only axons.

D. Class II Inhibitory Neurons. About 17% of IINs in the neocortex are Class-II GABAergic cells. Some of these neurons exhibit a low spiking threshold and so are known as low threshold spiking (LTS) cells. Class-II cells are found in layers II-VI of the neocortex. The Class-II response shows adaptation during tonic firing, and therefore is called an AC (accommodating) response. This is similar to the RS-type firing pattern except for two things. First, the firing rate is higher for AC-type than for RS-type. Second, the onset of accommodation is slower to appear than in the case of the RS-type cells. The AC signaling class also shows three subspecies, called b-AC, c-AC, and d-AC where the prefix designator means the same thing as above for the NAC class. Class-II NBCs have subspecies that exhibit all three firing subclasses. Class-II BTCs and MCs have subspecies that exhibit b-AC and c-AC signaling. Class-II LBCs have subspecies exhibiting d-AC and c-AC signaling. Class-II double bouquet cells (DBCs) exhibit c-AC signaling. The c-AC type is also sometimes called the RSNP (regular spiking non-pyramidal) type.

An interesting feature of LTS Class-II neurons (BTCs and MCs) is that they exhibit post-inhibitory rebound (PIR). PIR is the firing of a single AP spike upon release from hyperpolarizing

inhibition. The mechanism for PIR is an inactivating low-threshold Ca^{2+} VGC, commonly called a "T-current" or I_T. The I_T channel is normally open at the cell's resting potential, and the resulting Ca^{2+} current causes a slow depolarization of the cell's membrane potential, rising to the spiking threshold of the neuron. The neuron then fires an AP, in the process of which the I_T channel is inactivated. The channel will not deactivate (release from the inactivation state) until the cell membrane is hyperpolarized, and will not activate again until the membrane recovers from hyperpolarization. LTS cells co-localize the neuropeptide SOM (somatostatin).

Class III Inhibitory Neurons. Class-III IINs make up another 17% of all IINs in the neocortex. They co-localize the neuropeptide VIP (vasoactive intestinal peptide) and display an irregular spiking (IS) pattern [21]. Some mathematical modelers refer to this as a 'chaotic' firing pattern [23]. An illustration of an IS pattern is provided in [7]. The Wilson models are not very successful at producing an IS pattern. They require an ad hoc sinusoidal oscillator to be added to the model dynamics to produce a chaotic response [24, pp. 180-183]. Rulkov has demonstrated irregular (chaotic) spiking by his map-model neuron [23]. Class-III IINs include DBCs, BPCs, and BTCs. Of these, vertically-oriented BPCs are the most common.

Other Inhibitory Neurons. The three classes just described make up 84% of all IINs. The remaining 16% have not been given a specific classification, but their firing patterns can still be grouped into 3 major categories. Continuous spiking (CS) neurons respond to a constant stimulus of injected current with a burst firing pattern. This pattern is sometimes denoted as the BST class. Figure 15 illustrates the CS-type firing pattern of neurons in this class. Species of neurons exhibiting this firing pattern are found among the ChC, BPC, and DBC IIN cells.

Stuttering cells (STUT cells) make up a second interesting group of unclassified neurons. The STUT-type cells respond to a constant-current stimulus injection with high-frequency clusters of APs, showing little or no accommodation, interspersed with periods of silence of unpredictable length. Some LBC, NBC, BTC, MC, and BPC neurons have subspecies of STUT-type cells. To date the modeling of STUT-type cells has not been very successful in that the unpredictability of

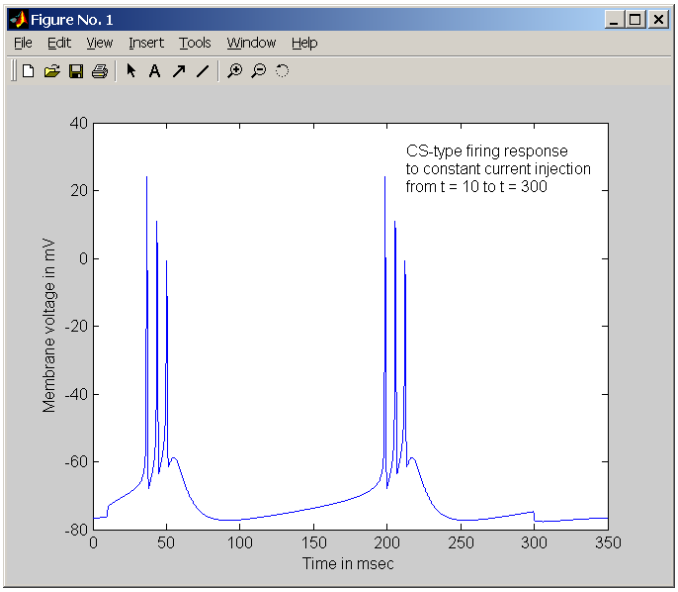

Figure 15. CS-type firing response to a constant-stimulus injected current.

the silent interval has not been successfully reproduced. [7] provides an illustration of a STUT-type firing pattern.

Finally, some IINs exhibit an AC response to constant stimulus current injection yet do not fall under the Class-II designation. This is because Class-II classification uses a particular molecular category system, and IINs of the type we are now discussing do not fall into that molecular category. We will call them 'other AC' (OAC) types. ChC, SBC, and BPC neurons exhibit subspecies that fall into the OAC-type category. For practical purposes, we can regard these as simply AC-type neurons and view them as a fast species of RS-type signaling.

The population percentages among CS-type, STUT-type, and OAC-type cells is not reliably known. The best we can presently say is that taken in total they add up to 16% of the total IIN population. Table II summarizes the mix of classifications that the various morphological IINs exhibit.

IV. Cortical Connections and Circuits

The functional column organization of the neocortex suggests that a natural way to look at the organization of connections is to categorize them in terms of subcortical afferents and efferents (inputs and outputs), cortico-cortical (inter-columnar) connections, and intra-columnar (local) connections. Anatomical studies have shown that synapses can be classified according to certain morphological features into two categories: asymmetric and symmetric. At the present time it is thought that all asymmetric synapses are excitatory and all symmetric synapses are inhibitory. However, it is not known how or if this classification extends to metabotropic synapses. Using the synapse category as a guide, it is estimated [25] that 84% of all synaptic connections in the neocortex are excitatory and 16% are inhibitory. It is further hypothesized, on the basis of relative axon densities in the white matter and gray matter, that the majority of signal projections within a functional column are local (intra-columnar) projections. It is estimated that one cubic millimeter of white matter contains about 9 meters of axon, whereas one cubic millimeter of gray matter contains about 3000 meters of axon [25]. These areal densities ($9 \cdot 10^3$ axons/mm^2 vs. $3 \cdot 10^6$ axons/mm^2) seems to suggest that only about 0.3% of axonal traffic is involved in signaling between non-neighboring functional columns. This figure does not, of course, speak to the density of axonal traffic between neighboring functional columns since this signaling is possible

Table II: Classes of Inhibitory Neurons

Neuron	Class-I (NAC)	Class-II (AC)	Class-III (IS)	CS-type	STUT-type	OAC-type
SBC	X		?			X
NBC	X	X			X	
LBC	X	X			X	
DBC		X	X	X		
BPC			X	X	X	X
NGC	X					
BTC	X	X	X		X	
MC	X	X			X	
ChC	X			X		X

X denotes that a subspecies of the neuron is found among the indicated types.
The Cajal-Retzius (CRC) cell is not classified. The CRC is found only in layer I.

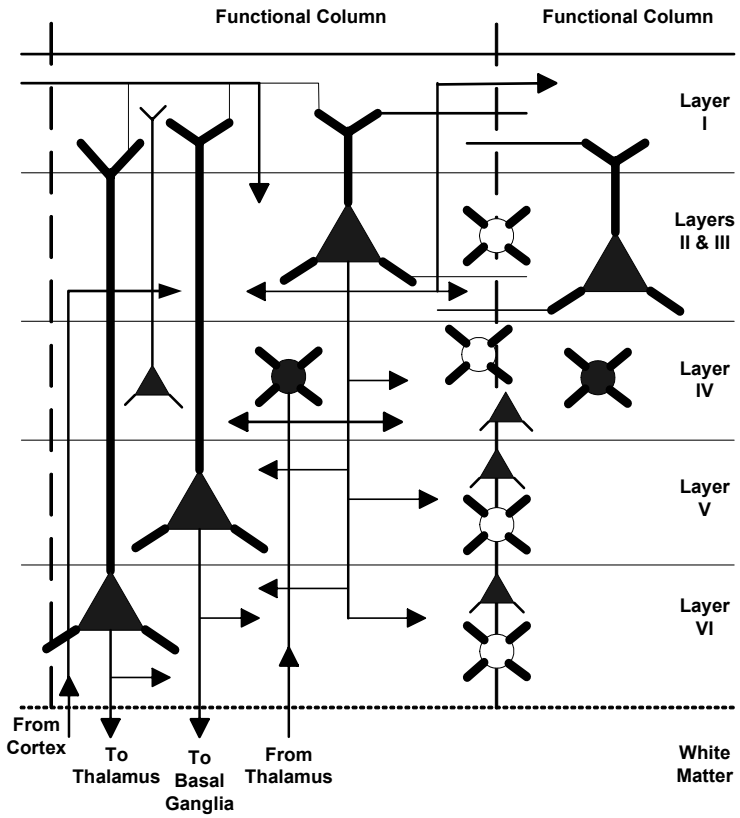

Figure 16. Simplified schematic view of functional column interconnections. Dark symbols represent excitatory neurons (PCs and SSCs). Unfilled symbols represent general inhibitory interneurons. Neurons drawn on the boundary between functional columns denote 'neuron sharing' at the boundaries of the columns. Column-to-column gray matter connections are primarily from axon projections from layers II/III PCs. Dendritic arbors may cross column boundaries at all layers but only over a limited distance. Cortico-cortical connections via the white matter are primarily sourced by PCs in the superficial layers (II/III) and primarily target neurons in these layers at the destination. The other primary inputs to a column are projections from the thalamus, which makes connections in all layers, but primarily targets layer IV SSCs and inhibitory interneurons. 90% of PCs make no synaptic connections via the gray matter to neurons beyond distances of 0.2 to 0.3 mm.

by means of axonal and dendritic projections that remain entirely within the gray matter. This general scheme is illustrated in figure 16, which is meant to convey only the general idea of inter-columnar connection pathways and not specific connections. With a few exceptions, the boundary line between functional columns is not as crisp as the figure might suggest, and it is more correct to speak of boundary zones between functional columns rather than of boundary lines.

A. Thalamic and Other Sub-Cortical Afferents. More than 20 subcortical areas make projections into the neocortex [25]. Most of these pathways have not yet been studied enough to permit a schematization of the connections they make. One of the main pathways, which carries all or nearly all 'specific' information (e.g. sensory information from throughout the body) reaching the neocortex, is sourced from the thalamus. Other important sources include regions in the brain stem (especially in the pons and medulla) and the basal forebrain (deep-lying nuclei lying beneath the basal ganglia and part of the cerebrum but not regarded as part of the neocortex [26, pp. 149-154]). Many of these non-thalamic sources project monoaminergic (NE, DA, and 5-HT) or cholinergic (ACh) signals to the neocortex, which means their signaling is metabotropic and regulatory rather than constituting ionotropic 'data pathway' signaling of specific processed

information. Thus the thalamus is the principal ionotropic 'data pathway' into the neocortex.

Thalamocortical axons made excitatory synaptic connection to both RS- and FS-type cells. Their strongest signals are registered in layers IV and VI, where most of these axons terminate. Their EPSPs are large, although these are an average as twice as large for synapses with FS-cells as for those made with excitatory neurons. The average thalamic axon makes seven synapses to each excitatory cell it contacts [21].

The thalamus pathway accounts for about 10% of all excitatory synapses to spiny stellate cells in layer IV. Another 30% of these synapses arise from other SSCs in layer IV, and an additional 40% are due to layer VI pyramidal cells. About 90% of the inhibitory synapses made with layer IV SSCs come from layer IV basket cells [25].

EPSPs from thalamic synapses show pronounced tetanic depression [12] at high pulse rates. Typically the first EPSP pulse is quite strong (averaging 2 mV peak on SSCs, 4 mV peak on FS-cells), but subsequent pulses occurring within 25 msec produce EPSPs attenuated by a factor of about 4:1 [21]. EPSPs from thalamic connections are generally far stronger, by a factor of 5 or more, than are the responses between neocortical neuron connections.

B. Sub-cortical Efferents. The main output signals from a cortical column to sub-cortical areas of the brain are produced by pyramidal cells in layers V and VI. Layer V PCs project mainly to the basal ganglia, brain stem nuclei, the superior colliculus in the midbrain (which controls eye movements), and to the spinal cord. Layer VI PCs project mainly back into the thalamus. Some layers V/VI PCs also make projections to the corpus callosum (and thence to the other cerebral hemisphere) and to the ipsilateral ('same side') cortex via the white matter [1].

C. Cortico-cortical and Intra-Cortical Projections. Most cortico-cortical signaling originates from PCs in layers II/III and projects by way of the white matter. These PCs can also make gray matter projections to nearby-neighboring functional columns via axon collaterals running through layer I. These projections mainly target neurons in the superficial layers (layers I-III). EPSPs on synapses connecting excitatory cells in mature cortex range from mildly depressing to mildly facilitating [12]-[13]. Synaptic connections from RS- to LTS-INs show pronounced facilitation when activated at frequencies above 20 Hz, but exhibit a high failure rate for signaling below 1 Hz [21]. This suggests that the primary role of LTS-type IINs is that of a 'governor' circuit that activates only in response to high signaling activity within the functional column.

EPSPs at synapses connecting RS- to FS-type neurons are relatively reliable and stable at firing rates below 0.2 Hz, but are depressed for firing rates above 5 Hz [21]. This suggests that whatever the role of the FS-neurons may be in a functional column, it is a low-frequency role insofar as cortical dynamics are concerned. IPSPs at synapses connecting FS- to RS-type neurons tend to be strong and reliable and show little depression or facilitation. IPSPs for connections of LTS-type neurons to RS-type neurons are moderately strong and show pronounced facilitation at high frequencies activations, typically doubling the peak IPSP over time and within a few cycles at 40 Hz activation rates [21].

The typical pyramidal cell draws most of its inhibitory inputs from layer I cells, basket cells, and chandelier cells. It draws the majority of its excitatory inputs from other PCs within the column and from SSCs in layer IV. EPSP responses range from mildly depressing to mildly facilitating. A reasonable 'average' treatment for these connections is to treat them as if they were stable (i.e. as if they showed neither depression nor facilitation). The IPSP responses are those just described above for LTS- to RS- responses and for FS- to RS-type responses. It has not been

reliably documented whether or not synaptic connections made to IB-type excitatory cells show depression or facilitation.

V. Summary

This paper has presented a tutorial overview of the neocortex. Our viewpoint has been that of characterization of the signal processing pathways present in neocortex, and of the signaling characteristics of the neurons which make it up. Additional and more detailed information can be obtained from the references and from their citations.

The outstanding organizational feature of the neocortex is its organization into dynamical functional columns. The vast majority of all neuron-to-neuron connections in the neocortex are intra-columnar connections. Only a small percentage of cortical connections are made up of signals coming into the functional column from other regions of the brain. Thus the makeup of connectivity in the neocortex can be characterized as 'sparse' insofar as column-to-column or column-to-noncortical connections are concerned. The exception to this rule is the possibility of higher percentage connectivity between a functional column and its immediate neighbors. The exception comes about because of the general 'fuzziness' of definition of the boundary zone of cortical cells between functional columns.

Computational models of functional columns should be based in part upon the statistical distributions of different neuron types found in neocortex. In this paper we have documented the known population statistics of the various neuron types, grouped according to signaling class. It has proven to be quite difficult to experimentally track down the detailed connections among neurons in the neocortex. Indeed, there is some evidence that suggests that in mature neocortex the 'wiring' of a functional column may be experience-dependent, which is a consequence of neuronal plasticity [12]-[13]. Our best evidence, therefore, for probing the organization of the neocortex is through measurable and known signaling activities as measured by such methods as electroencephalograms (EEGs) and subdural microelectrode grids. These measure averaged activities, and the reasonable assumption is that network models that produce these same averages must in some significant way capture the functional nature of the neocortex.

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