

Neurophysiological Basics, a Digression

Consistent with the above, allocating space for detailed anatomical and cell-physiological facts about the brain is superfluous, as "too much anatomy has been found to order for theoretic purposes, even by the anatomists."¹⁸¹ But, as young William James once wrote in a letter from the Amazonas (1865) while serving in a party led by Jean Agassiz: "No one sees farther into generalization than his own knowledge of details extends."¹⁸² Therefore, several cell-physiological facts are highlighted below in the form of points that wrap together only the bare essentials for the dialogue. Readers who are familiar with the basic matters of cortical and subcortical dimensions, electrical phenomena in neurons, and synaptic communication, are encouraged to leaf through or skip this section.

Dimensions. The adult cortex is a convoluted plate that, unfolded, would occupy an area more-or-less equivalent to a 50x50 cm screen, 1.5–4.5 mm thick.¹⁸³ Having a well-defined anatomical division of the cortex to the right and left hemispheres, with complex relations between them, gave rise to fascinating and useful clinical neurology observations that are most relevant to issues of symptom localization, as discussed above. A considerable share of the clinical work in the field of neurology is dedicated to mapping behavioral symptoms to brain coordinates of suspected lesions such as hemorrhage, blood clot, tumor, or local infection; this is a first step in the formulation of diagnosis and application of physical, localized treatment. But we are already equipped with what is required in order to understand that neuroanatomical localization in general, and brain bi-laterality in particular, are of no immediate relevance to our intended dialogue. We simply take it as given – backed by ample experimental evidence – that psychological functions distribute within the total available neural space according to genetic, developmental, and adaptive constraints.

¹⁸¹ James (1950[1890], Volume 1, p. 81–2).

¹⁸² The Letters of William James, 1920, vol. I, p. 65.

¹⁸³ Readers interested in a more detailed account on cortical scales are encouraged to consult Corticonics: Neural circuits of the cerebral cortex (Abeles, 1991).

The cortex is densely packed with two types of cells: nerve (neurons) and glial cells. While glial cells are abundant, in fact outnumbering neurons,¹⁸⁴ the activity of neurons is unequivocally accepted as the major physiological correlate of behavior; we therefore neglect glial cells in our discussion.¹⁸⁵ The average number of neurons within one cubic millimeter of cortex is ca. 30,000 in the human (compared to 200,000 per cubic millimeter in the mouse). Estimates of the total number of neurons in the entire human cortex converge to ca. 20 billion; to intuit how large the number is, consider this: at the neuronal death rate of 50,000 per day – a realistic rate – it would take about 1,000 years to clear the cortex from neurons altogether. For all practical purposes the distribution of this huge number of neurons across the entire cortex is even. Thus, the reader is invited to picture the cortex, on the large scale, as a thick, homogeneous sheet, a symmetric structure that looks the same from wherever one chooses to observe it. An expert neuroanatomist would have to stretch his imagination in order to convince himself that he can tell one piece of cortex from another.

Subcortical entities are in general more structured, less symmetric. Note that the cortex holds ca. 18% of the entire population of neurons in the brain, packed within 70% of the brain's volume. It is in the cerebellum (the "little brain"), a structure that occupies about 10% of the brain's volume, situated at the lower-back region of our skulls, where the vast majority of the brain's neurons – ca. 80% – are situated. Cerebellar activity is mostly correlated with timing and control of fine movements. All other subcortical entities¹⁸⁶ are populated by only ca. 2% of the total number of neurons in the brain. The fact that these 2% of neurons (buried deep within the skull) are packed in well-structured and anatomically resolved clusters (nuclei), has made them targets for intensive applied neurophysiological research and industry investment, a direct consequence of availability bias. The development of the cerebellum and these other subcortical nuclei do not show evolutionary changes that match the

¹⁸⁴ See, for instance, a review article "How many neurons do you have? Some dogmas of quantitative neuroscience under revision" by Lent et al. (2012); see also "The human brain in numbers: a linearly scaled-up primate brain" by Herculano-Houzel (2009).

¹⁸⁵ Albeit intriguing reports on the involvement of glial cells in behaviorally relevant activities, their role in such processes remains marginal; glial cells' main function in the brain is supportive (biochemically and biophysically).

¹⁸⁶ Basal ganglia, thalamus, sub-thalamus, hypo-thalamus, dorso-thalamus, midbrain, pons, and medulla.

emergence of human traits. Following up on our discussion on localization, this last statement does not mean that subcortical entities are irrelevant to human-specific traits.

Salinity and its consequences – the origin of electrical phenomena in neurons. On the more microscopic scale one finds that, like practically all other tissues inside our body, the space between cells in the cortex is filled with a watery solution. This *extra-cellular* watery environment is salty, mainly due to the abundance of sodium and chloride ions, the dissolved components of table salt. The borders of a neuron, as every other cell in our body, are spatially defined by the *cell membrane*, a thin lipid covering that separates the interior of the neuron from its exterior. Having a markedly different composition of salts inside compared to the surrounding outside is the hallmark of a living cell. While the dominant ions composing the extra-cellular environment are sodium and chloride, the intracellular milieu is dominated by potassium ions and charged amino acids in proteins. There exist physiological reports claiming that as much as half the total neuronal energy expenditure is invested in maintenance of intracellular salt concentrations that differ from the extra-cellular ones.¹⁸⁷ A cell that loses its capacity to maintain an interior composition that differs from the exterior is dead, an association-provoking fact of the life sciences.

Ions are electrically charged atoms or molecules. The difference of ionic compositions between intra- and extra-cellular solutions leads to a major consequence, entailed by well-founded conservation relations: practically *all the cells in our body* maintain a negative electric potential inside, relative to the outside. It is safe to say that the average value of intracellular potential is roughly 0.06 volts negative compared to the extra-cellular potential.¹⁸⁸ This is called (in the physiological jargon) the *resting potential*. Most cells maintain a more-or-less stable negative resting potential that is used as an energy source for different biological activities. Neurons belong to a special class of cells that make use of this potential energy to generate electric signaling; the class is called *excitable cells*. Among the other members in the class of excitable cells one finds muscle cells, heart cells, hormone (for instance, insulin or adrenaline) secreting cells. Excitable cells are equipped with a machinery enabling them to transiently move away from the resting state, generating a positive, pulse-like, short change in

¹⁸⁷ Howarth, Gleeson, and Attwell (2012).

¹⁸⁸ Readers might wish to develop a sense for “how much is” 0.06 volts in terms of everyday life: considering the fact that this value of electric potential is focused across a thin cell membrane, the resulting electric field is close to the electric field that gives rise to bolts of lightning in a thunderstorm.

membrane potential known as *action potential*. In cells of the heart and other body muscles, action potentials cause contraction in a beautifully organized process that translates electrical energy to movement; in hormone releasing (endocrine) cells the action potential brings about secretion of the hormone, which in turn spreads in body fluids and impacts the activity of target organs. In nerve cells, the action potential is a means to: (1) transmit external and internal sensory signals into the brain; (2) communicate among neurons within the brain; and (3) carry neuronal activity to muscles, hence generating movement, behavior.

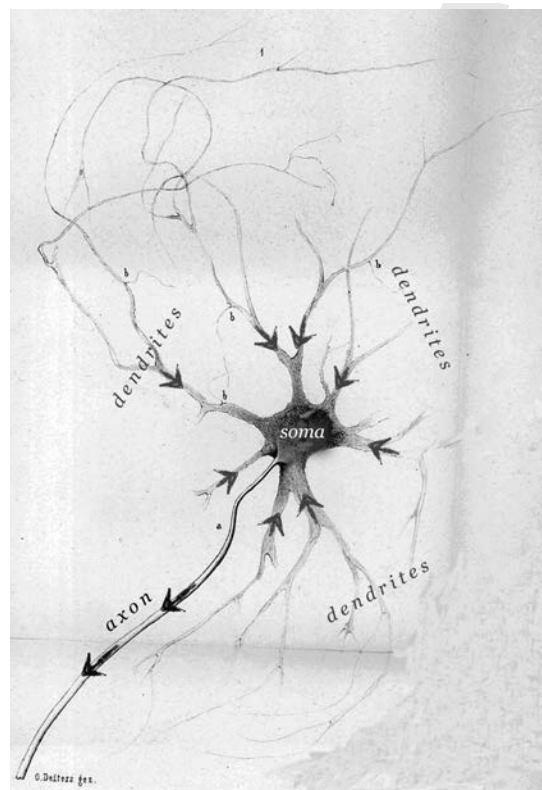


Figure 5.2: A nerve cell drawing by Otto Friedrich Karl Dieters (1834–1863); added arrows and text depicting dendrites and one axon.

The integrative nature of neurons – synapses (excitatory and inhibitory), dendrites, and axons. The structure of a single neuron, when observed through a microscope, is complex. For our purposes it is useful to picture a generic form that has a set of receptive and effector branches (Figure 5.2). Receptive branches, called dendrites due to their tree-like shape, sense the

activity of other (“upstream”) neurons and propagate a modified form of this sensation to the cell body, the *soma*. If the integrated effect of the input to the soma crosses a *threshold* value (invariably more positive compared to the negative resting potential), an action potential is evoked in (and nearby) the soma. The mechanism of action potential generation in the soma of excitable cells is *the* canonical example of a well-understood phenomenon in the life sciences, mathematically, physically and biologically. This action potential, once evoked in the soma and its vicinity, is propagated through the effector branches that are called *axons* (a mnemonic for their axial shape), and impacts dendrites of many other, “downstream” neurons, which will be discussed shortly. The names *dendrite* and *axon* should not be taken too seriously as reflecting the actual shapes found under the microscope; the variability between different cortical neurons in this regard is immense.

The dendrites of each cortical neuron are decorated with many, probably thousands, of contact points with other neurons; these contact points are called *synapses*. Each synapse should be conceived as a sensor that detects the occurrence of an action potential in one given upstream (pre-synaptic) neuron somewhere in the cortex. When an action potential occurs in a given neuron, it travels down the axon of that neuron and releases packets of chemicals (neurotransmitters) in the synapses that the axon forms with other cells. The neurotransmitter molecules bind to the post-synaptic, dendritic side of the synapse, giving rise to a transient change in the local (near the synapse) intracellular potential. The transient effect of this *synaptic potential* relaxes back to the resting state after a fraction of a second.

The impact of the transient local synaptic potential depends on the identity of the pre-synaptic neuron, which may be one of the following: (1) an *excitatory neuron* – that is, a neuron that releases neurotransmitters that push its post-synaptic, downstream partners *toward the threshold*; or (2) an inhibitory neuron – that is, a neuron that releases neurotransmitters that push its post-synaptic, downstream partners *away from the threshold*. Excitatory and inhibitory neurons differ in the identity of the neurotransmitters that they synthesize and release. Thus, the direction of the effect in a given synaptic connection is fixed – that is, an inhibitory synapse remains inhibitory and an excitatory synapse remains excitatory; this is a property of the upstream neuron that is capable of synthesizing and releasing a uniquely-defined

neurotransmitter.¹⁸⁹ Many different kinds of neurotransmitters are known to act in the cortex, but for practical purposes we may classify them all as being either excitatory or inhibitory. There are thousands of synapses on the dendrites of any given cortical neuron; those that are activated by incoming excitatory neurons are accordingly denoted *excitatory synapses*; those that are activated by inhibitory incoming neurons are called *inhibitory synapses*. On top of its identity as excitatory or inhibitory, each synapse has one more identifier, that is – its “strength,” the amplitude of the synaptic potential. Thus, the two identifiers of any given synapse are the direction of action (excitatory or inhibitory) and the strength of the change (strong or weak effects).

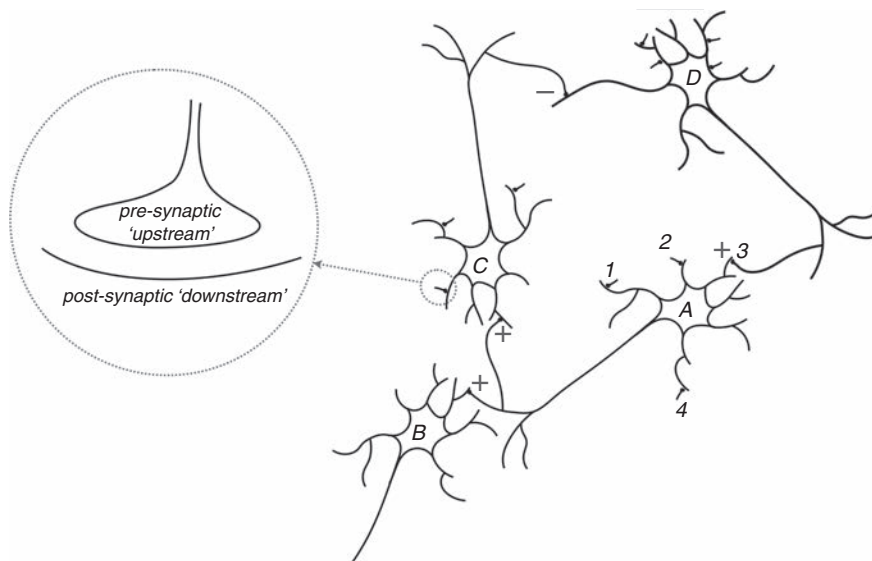


Figure 5.3: Considering neuron A, only four (depicted 1 to 4) out of thousands of incoming synapses are depicted on its dendrites. Synapse number 3 is contributed by a branch of the axon of neuron D. Let us assume that neuron D is an excitatory neuron (depicted by positive sign in its outgoing synapses). Neuron A integrates the input from all of its synapses; if the integrated activity causes deviation from the resting potential beyond a threshold level, an action potential is evoked in neuron A. The action potential propagates down the axon of neuron A and activates the many synapses that this neuron contributes to other neurons. Let us assume that neuron A is an excitatory neuron. In the scheme of this figure, neuron A contributes synapses to neurons B and C. It also contributes synapses to hundreds or even thousands of other neurons, but we highlight only neurons B and C here. If the integrated activity of all the synapses on neuron C drives the neuron above threshold, then C generates an action potential. Let us assume that C is an inhibitory neuron. This means that the contribution of neuron C to the integration of neuron D is negative, inhibitory, pushing it away from the threshold potential, hence resisting its activation by other neurons. In the cortex, a neuron may contribute several synapses to another neuron. A scaled representation of a single synapse is shown to the left.

¹⁸⁹ For completeness, note a counter example, a very special case that is irrelevant to our discussion reported in Wagner, Sagiv, and Yarom (2001), and references therein.

The transient synaptic potential (excitatory or inhibitory) propagates down the dendrite toward the cell body. It may safely be assumed that activation of one excitatory synapse is not enough to cause a cortical neuron to cross the threshold value and evoke an action potential. Estimates converge to several, maybe tens of excitatory synapses that need be active more-or-less simultaneously in order to drive the electrical potential in the soma above threshold. Thus a single synapse should be thought of as one point of entry into the cell, a point of entry that is either excitatory or inhibitory; one “vote” (for or against), counted by the downstream neuron. If the sum of votes amounts to above threshold, the neuron says “Aye” and emits an action potential. In that sense, a single neuron is said to be an integrator.¹⁹⁰

Global neuromodulation. There is one more source of cortical neuronal activity modulation: chemicals that are “sprayed” onto the cortex, released from axons of subcortical neurons and change the cortical neuronal states globally. These chemicals are called neuromodulators and include dopamine, serotonin, norepinephrine, acetylcholine, and others. Their global effects on cortical neuronal activities do not lend themselves to any simple classification of the kind that serves us so well in the discussion of inhibitory and excitatory synapses. It is maybe useful to think of neuromodulators as nonspecific generators of variance, but let us defer discussion on this point to a more proper place in the text.

The Neuron Doctrine, Associationism, and the Network School

The neuron doctrine is a general term used to designate the understanding that brains are made of separate entities, neurons; the brain is not one spatially continuous compartment. The doctrine is a result of a collective effort that extended over 100 years, involving many scientists. It started with the development of advanced optical technology in the 19th century, which made it possible to observe specimens at high enough resolution. The technology was rapidly adopted by biologists; the leading physiologists in this context are people that we all know from cellular entities and cell-biology techniques called after

¹⁹⁰ This entire process is not deterministic; the critical role of “noisy” or “background noise” activity – that is, activity evoked by random variations in the dynamical constituents of the system, at practically each and every scale – is a subject matter for intensive research in physiology.