1

Definition of the neuron

1.1 The biologist

The shapes of the dendritic arborization of vertebrate neurons is a unique property which differentiates the nervous tissue from all the other tissues of the organism. The neuron doctrine, which we owe to Santiago Ramón y Cajal (Ramón y Cajal, 1904, 1911), was established 50 years after the cellular theory proposed by Schwann in 1839. This long period of trial and error and of vigourous opposition by the adherents of the reticularism is simply explained by the great difficulty of recognizing a nerve cell on histological preparations (Figure 1.1).

It was only after the discovery of the Golgi method, which is a selective technique for visualizing nerve cells and their prolongations that Ramón y Cajal established the first fundamental concept of neuroscience:

> All becomes clear in our minds. Why do dendritic arborizations exist, why are they so varied, so abundant, so extensive? We understand now. Simply to enable the cell to receive, and to transmit to its cylinder-axis, the greatest possible variety of signals, from as many different sources as possible; put simply, to make of the cell a microcosm whose connections to the interior and exterior worlds are as numerous and complex as possible.

He called the nervous tissue the most intricate structure known in the living world. He observed a great number of neurons stained with the Golgi method in a variety of species. The comparison of dendritic morphologies of neurons located in homologous regions of the brains of different animals led him to formulate what we call the '*shape hypothesis*'. It was in the darwinism context of the time and tuned with the comparative phylogenetic approach. During evolution, the structural complexity of the dendritic arborization is greatly increased and he also illustrated the idea that the ontogenetic history of a neuron replicates its phylogenetic history (Figure 1.2).

The evolutionary aspects of the shapes of cellular structures were also studied in the Moscow Brain Institute, where the concept that the higher we ascend the

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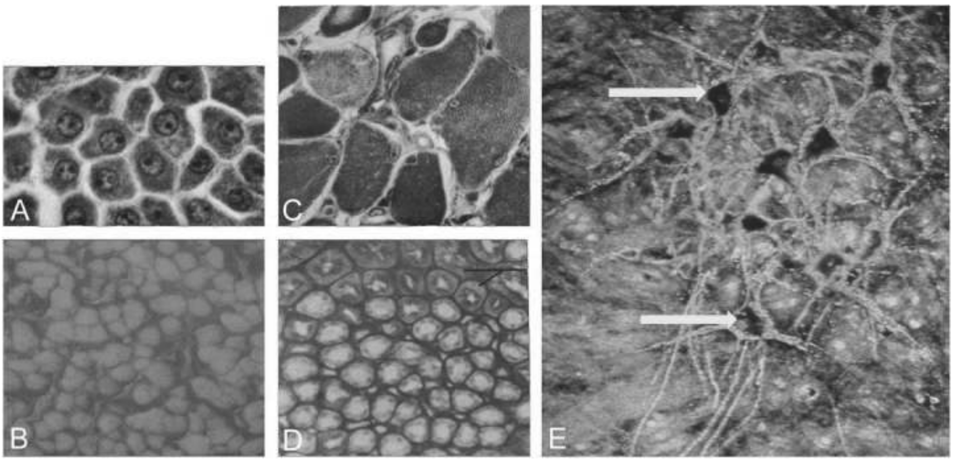

Figure 1.1 (Plate 1) The shape of all living cells of all tissues that make an organ are regular, similar and simply geometrically patterned. A: epithelial cells; B: tendon cells; C: muscular fibres; D: renal cells; E: the cellular bodies of the neurons are dark (arrows) with thick dendritic stems which divide into fine branches, the origin of which becomes soon unidentified.

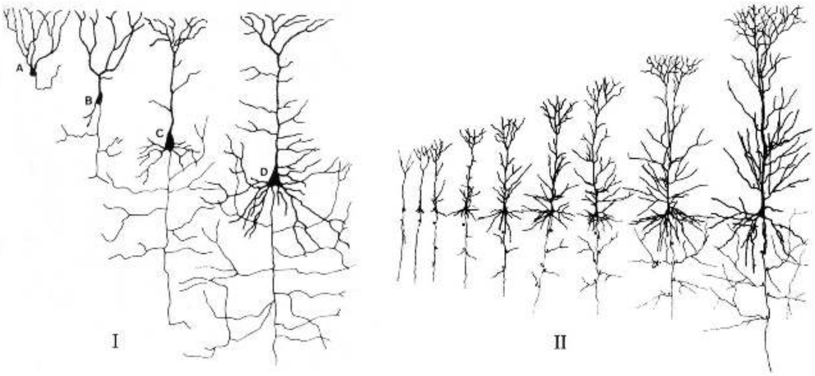

Figure 1.2 Dendrites of pyramidal cells observed in the course of phylogenesis (I) and ontogenesis (II). I: A: frog, B: green lizard, C: rat, D: human. The dendrites become increasingly important and complex. II: Growth of the the dendritic arborization of a pyramidal cell observed at different stages of development of the human embryo. (Adapted from Ramón y Cajal, 1911.)

phylogenetic ladder, the more complex become the dendritic and axonal structures of the neurons was developed by Sarkisov (1960). A definitive nervous system first appears unequivocally in the coelenterates (including hydroids, jellyfish, sea anemones and comb jellies) some 1500 million years ago. The nerve cell types evolve from unipolar to bipolar, multipolar and heteropolar types (Figure 1.3). The

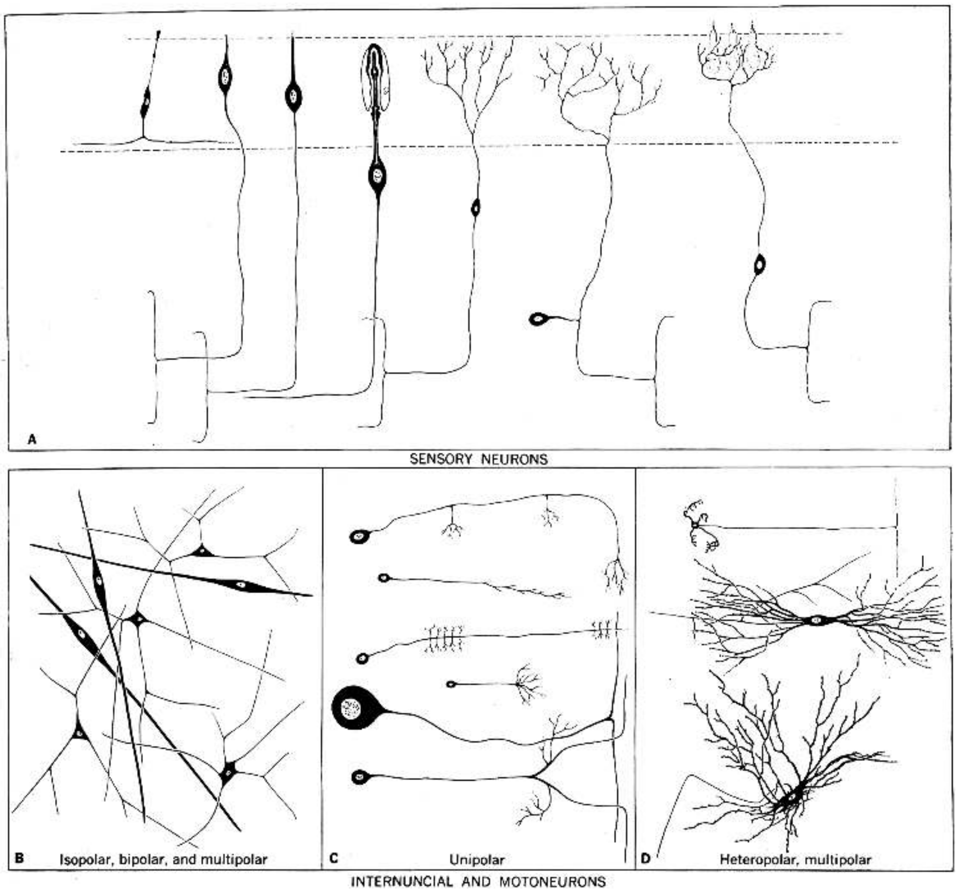

Figure 1.3 Types of neurons based on the number and differentiation of processes. A: Sensory neurons. The most primitive (left) send axons into a superficial plexus. In animals with central nervous systems the commonest type is a similar bipolar cell in the epithelium with short, simple or slightly elaborated (arthropod) distal process and an axon entering the central nervous system and generally bifurcating into ascending and descending branches. A presumably more derived form is that with a deep-lying cell body and long branching distal process with free nerve endings. In vertebrates such cells secondarily become unipolar and grouped into the dorsal root ganglia. B: Isopolar, bipolar and multipolar neurons in the nerve net of medusa. These may be either or both interneurons and motoneurons: differentiated dendrites cannot be recognized. C: Unipolar neurons representative of the dominant type in all higher invertebrates. Both interneurons and motoneurons have this form. The upper four are examples of interneurons and lower two of motoneurons. Dendrites may be elaborated but are not readily distinguished from branching axonal terminals. The number and exact disposition of these two forms of endings and of major branches and collaterals are highly variable. D: Heteropolar, multipolar neurons. These are the dominant types in the central nervous system of vertebrates. The upper two represent interneurons and the lower a motoneuron. (Adapted from Bullock and Horridge, 1965.)

excellent seminal book by Bullock and Horridge (1965) provides a review of early nervous systems.

The shape hypothesis is a concept within other principles operating in evolution. The evolution of progressively more complex functions has been made possible by the evolution of more complex structural patterns, hence more complex connectivity and greater differences between individual neurons. From lower to higher animals there is a scale of increasing complexity in connectivity patterns that is made possible by greater structural specificity and resolution in the morphogenetic mechanisms by which neurons become a highly complex system. How neurons grow into the fantastic patterns of connections that bring about their properties, which make in turn their richness of behaviours, remains unknown. We know that the driving forces of evolution have created the conditions for an enormous increase in the number of elements, in particular those in between receptors and motor neurons, the number and profusion of their branching processes together with the differentiation of shapes and connections. This structural complexity is the background that provides for complex manipulations of signals representing internal and external worlds.

An important contemporary concept of the neuron doctrine is that the neuron is made of several regions of different functional capacity facultatively interacting in complex ways, which will be discussed in later chapters. Some of the functionally diverse regions correspond to the anatomically distinct parts of the cell. The *axon* is a process specialized to distribute or conduct nerve impulses generally over great distances. It is smooth and only sends off branches at long intervals, if at all. It is commonly surrounded by a barrier of non-nervous cells called neuroglia inside the central nervous system and Schwann cells outside.

The *dendrites* are processes specialized for collecting information from other neurons, glial cells, circulating hormones and extracellular signals. Vertebrate dendrites are commonly highly branched, irregular in thickness, thorny and filled with cytoplasm more like that of the soma than that of the axon. No other cells can compete with neurons and their dendritic arborizations for sheer complexity of form and the extraordinary range of sizes that they display (Van der Loos, 1967) (Figure 1.4).

The *membrane*: all known organisms (excluding viruses) are composed of cells with membranous boundaries composed of lipid molecules. The membrane that surrounds every living cell is essentially such a lipid sheet formed into a bubble. The lipids are the primary component of cell membranes. Particularly abundant are the phospholipids, a class of lipids that consist of a sugar molecule (glycerol) linked to two fatty acids and to a polar alcohol molecule via a phosphodiester

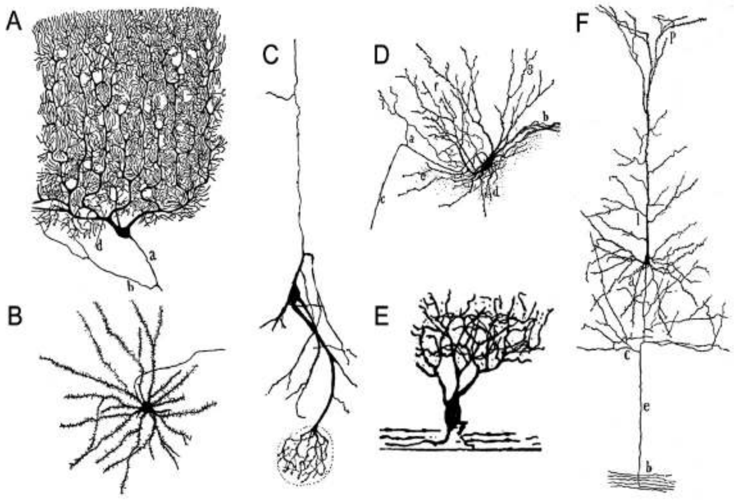

Figure 1.4 Drawings by Ramón y Cajal to illustrate the great diversity of the shapes of dendritic arborizations of the neurons. A: Purkinje cell (adult human); B: spiny neurons from the striatum; C: cell from the olfactive bulb (cat); D: motoneuron (cat foetus); E: ganglion cell fron the retina (adult chicken); F: pyramidal cell (adult mouse). (Adapted from Ramón y Cajal, 1911.)

bond. These molecules are amphiphilic, containing both polar and non-polar domains. Phospholipids form sheets by lining up with non-polar domains inward and polar domains outward. Channels are macromolecular pores lodged in the lipid bi-layer that make up the cell membrane and are positioned in a transmembrane orientation such that one end is in contact with the environment and the other end is located in the cellular interior. Integral membrane proteins consist of one or several transmembrane (TM) regions connected by extra-membrane segments. TM regions are 15–20 amino acids in length; just enough to span the lipid bilayer. They mediate the transport of ions and small molecules across the cell membrane along their chemical potential gradient. The other membrane components are carriers, which bind to a solute and move it across the membrane and protein pumps, which transport ion species against the chemical potential gradient expending energy in the process. Most channels in contemporary cells are highly selective to only one type of ion: Na, K, H, Ca, Mg or Cl. The selectivity is encoded in the amino acid sequence. The ligand-gated superfamily of channels is activated in response to specific interactions with small molecules.

1.1.1 Evolutionary history

Astrobiology, a new interdisciplinary field in science, explores the origin, evolution and distribution of life in the universe (see NASA's exobiology program: http://exobio.ucsd.edu/NSCORT.htm). Research is focused on tracing the pathways taken by the biogenic elements, leading from the origin of the universe through the major epochs in the evolution of living systems and their precursors. These epochs are: (1) the cosmic evolution of biogenic compounds, (2) prebiotic evolution, (3) the early evolution of life and (4) the evolution of advanced life. The principal goal of research in the area of the cosmic evolution of biogenic compounds is to determine the history of the biogenic elements (C, H, N, O, P, S) from their birth in stars to their incorporation into planetary bodies. The discussion deals with current evidence for the development of complexity, both chemical and structural, through the 4.5 billion years of Earth's history.

It is interesting to look at the recent results obtained by astrobiologists in this field and to learn about the emergence of membrane proteins, which are assumed to be essential for evolution from simple vesicules in the membrane to the simplest form of cellular life. Peptides are likely the first precursors of biopolymers (Pohorille *et al*., 2005). The main thesis is that the emergence of simple ion channels is protobiologically plausible. In fact, molecules capable of forming vesicules constitute a large fraction of organic material extracted from the Murchison meteorite (Deamer and Pashley, 1989), and were also obtained in laboratory simulations of interstellar or cometary material (Deamer *et al*., 2002). The current discussion is how peptides have partitioned into membranes self-organized into functional structures and evolved towards increasing efficiency and specificity for adaptation and diversity. For example, the family of potassium channels exist in organisms from all three domains of life, eukarya, bacteria, archae, which speaks for their antiquity. Recently, structures of several K channels have been resolved from eukaryotes (Jiang *et al*., 2003; Kuo *et al*., 2003), revealing that the ion conduction pore and the mechanisms of selectivity are conserved within the family (Lu *et al*., 2001). Analysis of the rapidly growing databases of sequences reveal that many eukaryotic channels have homologues in both bacteria and archea (Lu *et al*., 2001). Many channels have been identified that resemble those in higher animal phyla (Hille, 2001). Given the enormity of time separating us from the actual events thousands of millions of years ago, only speculation is possible. Nevertheless, current opinion is that channels evolved from a common ancestor and that their evolution is extremely slow. The message that we shall keep in mind is that the main characteristic of the evolutionary history of channels is their remarkable conservation throughout phyla. The emergence of neuronal complexity relies not on channels, but on their organization and their distribution in more and more complex dendritic structures.

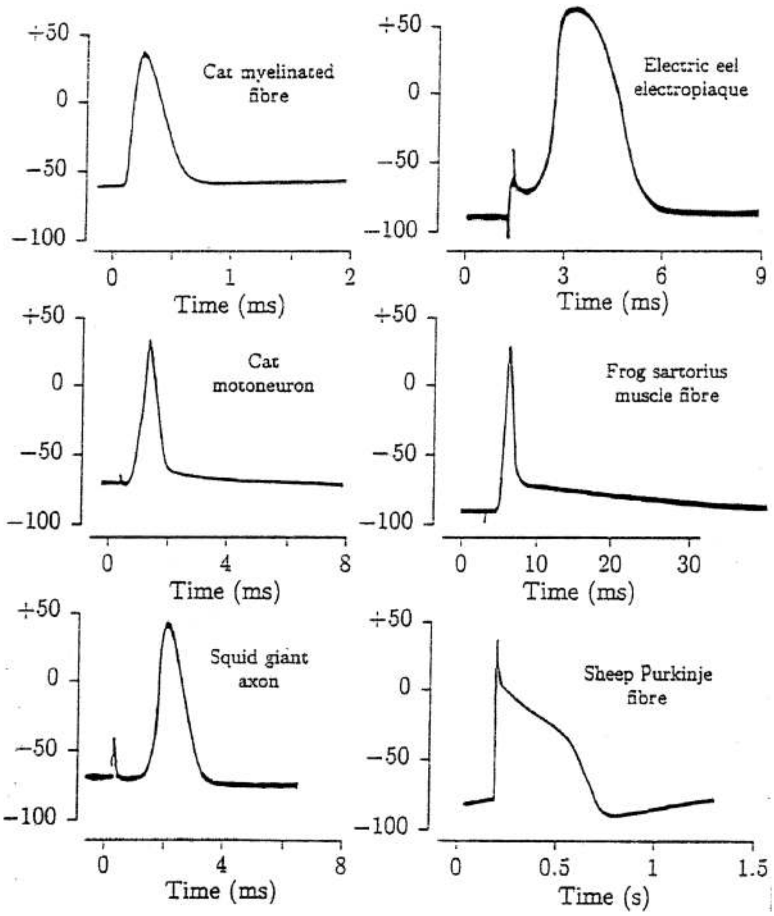

Figure 1.5 Intracellularly recorded resting and action potentials from several nerve cells: cat myelinated nerve fibre at 37 °C; cat motoneuron at 37 °C excited antidromically by stimulation of motor axon; squid giant axon at 16 °C; electric eel electroplaque at 27 °C; frog sartorius muscle at 22 °C; sheep Purkinje fiber at 32 °C. (Adapted from Bullock and Horridge, 1965.)

1.1.2 Neuronal excitability

Up to now, the properties common to all neurons can only be stated on the basis of a small sample studied electrophysiologically. All neurons so far examined are capable of an all-or-nothing brief electrical membrane change called the action potential propagating without decrement along the axons (Figure 1.5). As yet little can be said definitively about the evolutionary history of the signals used in nervous tissues except that the most characteristic of these signals, the action potential, is already present in the simplest nervous systems yet studied, those in jellyfish. Its common feature is universal without differences throughout phyla, although there are some slight variations in detail and mechanism.

To generate an action potential, the neuronal membrane uses some ionic channels. This operation is normally done by an intact neuron integrated in a live system, but it can also be performed by neurons extracted from their natural environment to be recorded in vitro and even by a small patch extracted from the neuronal membrane and sucked on the recording pipette (Safronov *et al*., 1997; Wolff *et al*., 1998; Safronov *et al*., 1999). This observation indicates that the action potential is not only universal, but also the most primitive nervous signal.

1.2 The physicist

The neuron is a highly complex system. The concept of system is defined by a set of interacting elements, the structure of which gives its principle of organization. The term ‘principle’ indicates that the system is not fully described, but that data allow one to consider that the system is organized. The scale of observation determines the level of organization that is considered. A scale measured in tens of microns or even in millimetres deals with the macrostructure of the neuron, which is itself made of a microstructural organization explored by electron microscopy focusing on the smallest parts of the structure at a scale of tenths of micrometres or even less. The different spatial scales of the neuronal system span a range of three orders of magnitude. The crucial notion is that all these parts, from the smallest molecular to the largest cellular elements, are linked together to constitute an individual united whole. Any mechanical damage to a single part kills the whole as an operating unit.

Considered as an electrically distributed system, the neuron is defined by its active plasma membrane in which macromolecules, acting as intrinsic generators, are lodged. The macromolecular assemblies play the key role in the communication between intra- and extra-cellular spaces. Intrinsic generators are carriers of electric current which move the ion across the plasma membrane. Channels in the open state let ions passively cross the membrane along the concentration gradient. Ion pumps transfer the ions actively against their concentration. In such an electrically distributed system, the whole neuron is a functional structure made of linked elements. Any change occurring in a single element by the action of a current or a voltage produced by intrinsic generators is followed by an immediate characteristic change in the state of all the other elements. As in the structural notion of the united whole, we deal here with the same crucial notion of a functional unit made of electrically inseparable elements. Consequently every site of the neuronal space operates as a generator and a load at the same time. When the membrane generators produce unequal transmembrane potentials in different elements of the neuron, the

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voltage difference between the elements generates a current that flows between them. It is called the lateral current that is conducted through the extra- and intracellular space. The lateral current added to the currents flowing through the plasma membrane pictures the electrical space of the whole neuron. The main property of the neuron is to produce electrical signals which are funnelled into axonal and dendritic tubes. The shapes of these tubes determine the way the signals are distributed spatially within the neuron. Most important of all, the neuronal space provides the neuron with its specific electrical morphology and shapes the intracellular conductor through which all elements are connected.

1.3 The physicist and the biologist

Taking for granted that the action potentials and their instantaneous frequency at the output of the neuron is the neuronal code, this system of signals must be considered as the final product of a chain of stochastic events occurring continuously at the soma–dendritic membrane of the neuron. These transient discharges and their transmission through highly specialized synapses made electrophysiologists hover on the brink of major discoveries that Eccles (1957) made in the late 1950s. Intracellular recordings from mammalian spinal motoneurons and their synaptic potentials were a major breakthrough in neuroscience that came with new ideas opening the way for decades of intensive investigations. The drawback of such an important discovery is that it quickly establishes dogma acting as a barrier to progress. In his time Ramón y Cajal commented on this type of attitude:

> That an idea may be mistaken or that a fact may be wrong matters little! The fact is simple, the idea is inspired, an illustrious scientist has put them forward; fashion, that indefinable something made up of idleness in judgement and deed, of respect for authority and total abdication of responsibility for oneself, takes over, influences other scientists by suggestion, and then, throughout their work, you see nothing but reflections of the trend they are following, nothing but proofs of the fact, confirmation of the idea.

Electrophysiologists have been fascinated by the recordings obtained with their tool – the intracellular or the patch electrode – and one of the dogmas in electrophysiology is to believe that the study of the transfer function between single or a few synaptic inputs and the output discharges is capable of explaining how a neuron operates. They forget that the output discharges constitute the space integral of all dendritic events occurring in the whole arborization and that they provide no information about how active dendritic sites contribute to the generation of these output discharges. Then the difficult question of finding out the mechanisms by which the complex processing performed by the interconnected active dendritic sites remains open.

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If one assumes that the firing neuron is a functional unit that plays in time and space, one must admit that electrophysiology describes the phenomenon in time but not in space. Our hypothesis proposes to fill the gap between the temporal and spatial aspects of the same phenomenon by introducing the concept of dendritic space. We believe that the transfer function of the neuronal system, that is the functional link connecting a diversity of synaptic inputs with the adapted output discharges, will be further understood in terms of membrane mechanisms distributed in the dendritic space. As we know that the commonality in structural and functional design of membrane channels is antique and exist in all domains of life, it is only their organization in space, their distribution in the complex architecture of the dendritic arborization that can support neuron processing. We predict that the generation of all types of specific output discharges triggered by an immense variation of synaptic inputs can only be produced by an arborization in which a differential plastic contribution of all its dendritic parts is continuously selected by its electrical states.

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