HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 2

Electrical Activity from the Neuron to the EEG and EM

EDITOR: O. CREUTZFELDT

Max-Planck-Institute for Biophysical Chemistry, Göttingen-Nikolausberg (West Germany)

PART B

Basic Neurophysiology of Neuronal and Glial Potentials

EDITOR: C. F. STEVENS

University of Washington Medical School, Seattle, Wash. (U.S.A.)

ELSEVIER

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Editor-in-Chief: **Antoine Rémond**
Centre National de la Recherche Scientifique, Paris (France)

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PART B

BASIC NEUROPHYSIOLOGY OF NEURONAL AND GLIAL POTENTIALS

Editor: **C. F. Stevens**
University of Washington Medical School, Seattle, Wash. (U.S.A.)

Collaborators:

M. W. Cohen, *Department of Physiology, McGill University, Montreal (Canada)*

K. Krnjević, *Department of Research in Anaesthesia, McGill University, Montreal (Canada)*

R. Llinás, *Division of Neurobiology, University of Iowa, Iowa City, Iowa (U.S.A.)*

C. Nicholson, *Division of Neurobiology, University of Iowa, Iowa City, Iowa (U.S.A.)*

C. F. Stevens, *University of Washington School of Medicine, Seattle, Wash. (U.S.A.)*

Preface

Volume 2, Part B, Basic Neurophysiology of Neuronal and Glial Potentials, presents the background material required for understanding electrical activity of the nervous system. In Section I the passive and active electrical properties of nerve cells are treated. This Section, in introducing the basic notions required for the succeeding Sections of the Part, covers the resistance–capacitance properties of nerve membranes, their behavior as cables, and the ion concentration gradients and permeability changes that underlie action potentials and synaptic activity.

Synaptic phenomena are at the very heart of nervous system function, and this important topic is covered in detail in Section II. Here synaptic morphology, the electrophysiological basis for synaptic potentials, the properties of synaptic potentials observed in experiments, and the role of neurotransmitters are all considered.

Because the electrical activity of glial cells is less dramatic than that of neurons, these important cellular elements have in the past often been neglected. In Section III, the criteria for electrophysiological identification of glial cell recordings is presented and glial contributions to the electrical activity of the nervous system are evaluated.

The recording of voltage changes produced by single neuronal elements is, of course, very valuable; often, however, the potentials generated by neuronal populations are of interest, both because field potential measurements are technically less difficult or disruptive, and because information about simultaneous activity in a large group of neurons is required. The basis for interpreting such field potentials is considered in Section IV where the various sources for these potentials are enumerated, the effects of neuronal geometry and environment are reviewed, and the problems of obtaining and interpreting field potential are surveyed.

This Part will be of particular interest to those who wish to review the electrophysiological basis of nervous system function, and to survey the recent advances in this field. The material contained in this Part forms the logical basis for much of what follows, and is thus of importance both in the theoretical interpretations of cellular electrical activity and in understanding the practical advantages and limitations of the electrophysiological method.

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Section I. Electrical Phenomena of Nerve Cells and Fibers

A. PASSIVE NEURON PROPERTIES

1. Passive properties of neuronal membrane

A current passed through a nerve membrane produces a voltage difference across the membrane; when the current is switched on, the final voltage is not achieved instantaneously, however, but rather is approached exponentially[1]. The direction of the voltage change reverses as the direction of the current flow is reversed, and the amplitude of the voltage change is proportional to the current magnitude, the proportionality constant being termed the *membrane resistance.* As the final voltage is approached exponentially, the rapidity of the voltage response is specified by the membrane *time constant*, τ. In τ seconds after a current is applied, the voltage has approached about 67% of the way to its final value, and in 2τ seconds, the relaxation to the steady voltage is about 86% complete. For example, if one were to apply to a neuron membrane with a 5 msec time constant a current sufficient to produce a final voltage displacement of 10 mV, the voltage would change by 6.7 mV after 5 msec and by 8.6 mV after 10 msec. The passive electrical properties of a membrane patch, then, are completely specified by only two quantities, the membrane resistance, and membrane time constant. Cat spinal motoneurons, for example, have a membrane resistance of approximately 2000 Ω (for a square centimeter patch), and a time constant of approximately 5 msec (Lux *et al.* 1970b; Barrett and Crill 1971; Burke and ten Bruggencate 1971); the time constant of pyramidal cells in cerebral cortex appears to be slightly longer (5.2–11.5 msec) than that of motoneurons (Creutzfeldt *et al.* 1964). The resistance of a square centimeter of squid giant axon membrane is about 1000 Ω, and its time constant about 1 msec (see Hodgkin and Huxley 1952c). Passive responses of neuron membrane to current pulses are illustrated in Fig. 1.

The plasma membrane is an approximately 100 Å thick lipoprotein structure with a very low permeability to water and electrolytes, and consequently a high resistance. Because it is principally composed of high dielectric constant, non-conducting material separating two conductors, the membrane has an associated capacitance through which displacement current can flow. Thus, the membrane's equivalent circuit is that of a parallel resistance R and capacitance C. For the squid membrane $R = 1000\ \Omega\ \text{cm}^2$ and $C = 1\ \mu\text{farad/cm}^2$; estimates for the cat motoneuron membrane are $R = 2000\ \Omega\ \text{cm}^2$ and $C = 2.5\ \mu\text{farad/cm}^2$.

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[1] References usually are provided in this Section only where information is new and not "standard". For a more detailed treatment of standard material, the reader may consult Ochs (1965), Ruch and Patton (1965), Stevens (1966), Mountcastle (1968) and Aidley (1971).

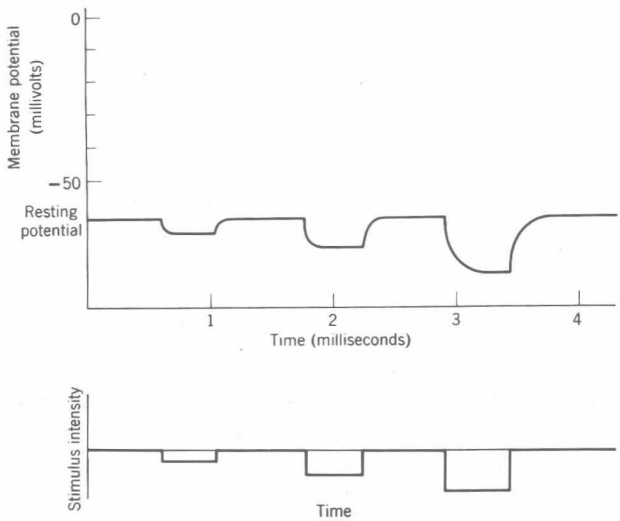

Fig. 1. Current pulses applied to a patch of neuron membrane are shown in the lower part of the figure, and the passive voltage responses are illustrated above. Note that the final response magnitude is proportional to stimulus intensity, but that the final voltage is approached exponentially.

As the nerve membrane is represented by a parallel resistance and capacitance , its voltage–current relationship is specified by the differential equation

$$C\frac{dV(t)}{dt}+\frac{1}{R}V(t)=I(t) \tag{1}$$

where $I(t)$ is the applied current, $V(t)$ is the voltage across the membrane at time t, and R and C are the membrane resistance and capacitance. This equation may be solved for the voltage response to give

$$V(t)=\frac{1}{C}\int_0^t e^{-(t-z)/RC}I(z)dz+V(0)e^{-t/RC} \tag{2}$$

The membrane time constant τ is equal to RC. For the special case of a step of current applied at time 0 with amplitude I, the voltage approaches its final value exponentially:

$$V(t)=IR(1-e^{-t/RC}) \tag{3}$$

2. Cable properties

In some instances the passive electrical properties of neurons may be adequately approximated by a simple patch of membrane described above. More generally, however, it is necessary to take neuron structure into account in order to obtain an adequate description. Axons and dendrites can often be idealized as long cylinders, so that an adequate description of their passive electrical properties specifying, for current injected at one site, the voltage at all positions and for all times along the cylinder. Because the mathematical treatment of a cylindrical axon or dendrite is like that of transmission cables studied by electrical engineers, the passive electrical

properties of these structures are termed cable properties (see Hodgkin and Rushton 1946; Rall 1959); use of *cable properties* will be made in Sections II, III and IV.

When current is injected into one site of an axon or dendrite, it can flow out through immediately adjacent membranes, or, by passing along the longitudinal axis of the structure, through more remote areas of membrane. Because current tends to follow the path of least resistance, most current flows out through the membrane closest to the site at which current is injected, and progressively less current flows out through more distant locations. As indicated above, the voltage change produced by a current flowing through a nerve or dendrite membrane depends on the magnitude of the current: thus, current injected into a long cylindrical structure causes a large voltage change near the site of injection and progressively smaller voltage changes at distances away from the site of current injection. For a long, uniform cable, the magnitude of the effect decreases exponentially with distance from the site of the injection. As attenuation with distance is an exponential, it may be specified by a single number, the *length constant* λ. In one length constant a signal is decreased by about 67% and by two length constants it has declined to 86% approximately of the original value. For example, if sufficient current was passed into a long dendrite to cause a 10 mV depolarization at the site of current injection, and if the dendrite had a length constant of 0.5 mm, a 3.7 mV depolarization would exist 0.5 mm from the site of current injection, and a 1.4 mV depolarization would be found at a distance of 1 mm.

The length constant λ depends on the dimensions and properties of the cylindrical structure under consideration, and is given by the formula[1]

$$\lambda = \sqrt{r_m/r_l} \tag{4}$$

Here r_m is the membrane resistance (Ω cm) and r_l is the longitudinal resistance of the cytoplasm ($\Omega\ cm^{-1}$). Longitudinal resistance ρ ($\Omega\ cm^{-1}$) depends, for a cylindrical process, upon fiber diameter d and the cytoplasm specific resistivity r_s (Ω cm) according to the formula

$$r_l = \frac{4r_s}{\pi d^2}$$

and membrane resistance R (Ω cm) is related to the specific membrane resistance R_M ($\Omega\ cm^2$) and fiber diameter d by the formula

$$r_m = \frac{R_m}{\pi d}$$

For example, the apical dendrite of a cortical pyramidal cell would have a length constant of 535 μ if the specific membrane resistance is taken as 2000 $\Omega\ cm^2$, the radius 2 μ, and the cytoplasm specific resistivity 70 Ω cm.

The equation governing the electrical properties of a cable such as that described

[1] It has been assumed here that the external medium has negligible resistance; if this assumption is not made, the external resistivity r_e ($\Omega\ cm^{-1}$) also appears in the expression for the length constant: $\lambda = \sqrt{r_m/(r_l + r_e)}$.

above can be derived as follows. According to Ohm's law, the longitudinal current i_l down a cable is proportional to the voltage gradient

$$i_l = -\frac{1}{r_l}\frac{\partial V(x,t)}{\partial x} \tag{5}$$

x is longitudinal distance along the cable and r_l is the cytoplasmic resistivity ($\Omega\ cm^{-1}$). As all current must flow either through the membrane or longitudinally, the membrane current i_M is the derivative of longitudinal current with distance

$$i_M = -\frac{\partial i_l}{\partial z}$$

This membrane current consists of a capacity (displacement) component $C(\partial V/\partial t)$ and resistive component $(1/r_m)V$ because of the membrane properties described above; r_m is the membrane resistance (Ω cm) and C the membrane capacitance ($F\ cm^{-1}$). Thus, the membrane current, from equation (5) above is

$$\frac{1}{r_l}\frac{\partial^2 V(x,t)}{\partial x^2} = C\frac{\partial V(x,t)}{\partial t} + \frac{1}{r_m}V(x,t) \tag{6}$$

This is the cable equation.

To predict the passive responses of a dendrite or axon, the cable equation given above must be solved. For an infinitely long cylindrical structure with homogeneous properties, the response to a step applied current of magnitude I at position $x=0$ is given by

$$V(x,t) = Is\lambda\left[e^{-x/\lambda}\,\mathrm{erfc}\left(\frac{x/\lambda}{2\sqrt{t/r}} - \sqrt{t/r}\right) - e^{z/\lambda}\,\mathrm{erfc}\left(\frac{z/\lambda}{2\sqrt{t/r}} + \sqrt{t/r}\right)\right] \tag{7}$$

The symbol *erfc* denotes the complementary error function (see Magnus and Oberhetinger 1949, for properties), $\lambda = \sqrt{r_m/r_l}$, and $\tau = r_m C$. This solution is qualitatively like that described for a membrane patch on page 3, and in the steady state, that is, when all time varying transients have died out, the voltage change at $x=0$ is attenuated exponentially with distance. Thus, for the steady state, equation (7) approaches

$$V(x,\infty) = Ir_l\lambda e^{-x/\lambda}$$

The solution for the cable equation depends, of course, on the geometry of the structures to which it is applied. Thus, to understand how the voltage change in one part of a neuron affects the voltage in other parts, it is necessary to solve the equation for the specific neuron under consideration. Typical neurons have a large number of dendritic branches—typically between 10 and 100—and to treat the passive electrical properties of such a structure, it would be necessary to, as a first approximation, treat each dendritic branch separately and match the voltages and currents where branches connect. Thus, to treat a typical neuron, one would need to solve 10–100 simultaneous cable equations, a difficult task indeed. Rall (1962) has shown that, in certain idealized cases, the dendritic branching pattern may be treated as equivalent to a simple cable.

Thus, a crude approximate solution similar to equation (7) above may be useful in semi-quantitative discussions.

B. ACTIVE NEURON PROPERTIES

1. Dependence of membrane voltage on ionic permeabilities and concentrations

The active responses of nerve and muscle membranes depend upon ion specific permeability changes, that is, upon increases and decreases in the permeability of specific ions, most notably sodium potassium, and calcium. In order to describe active membrane properties, it is therefore convenient to start by discussing the properties of a membrane patch which is permeable, first to only a single ion, and then, to only two ions. Suppose a membrane patch has different ion concentrations on its inside and outside as follows: 100 mM sodium chloride, and 10 mM potassium chloride outside, and 5 mM sodium chloride and 100 mM potassium chloride inside. We suppose that, at first, the membrane is totally impermeable to all ions and then, at an arbitrary 0 time, suddenly channels which permit only potassium ions to move through the membrane are opened. Sodium and chloride ions will not move, of course, since they cannot permeate the membrane, but potassium ions, which are in high concentration on the inside and low concentration on the outside will start to flow through the membrane. Each potassium ion that moves through, however, moves a unit positive charge from the inside to the outside and thus makes the inside negative with respect to the outside (the outside potential is, by convention, set at 0). As the inside becomes progressively more negative with the loss of potassium ions, it becomes increasingly more difficult for additional potassium ions to move out because of the work associated with moving positive ions away from a negative voltage. Thus, after a voltage exists across the membrane, two factors determine the movement of potassium ions. First, they tend to move outward because of the concentration gradient, and second they tend to move inward because of the opposing voltage difference caused by the preceding movement of potassium ions. When these two opposing tendencies are exactly equal, that is, when the movement of potassium ions by diffusion is exactly balanced by the opposite movement of potassium ions because of voltages, the net transport of potassium through the membranes will cease and the voltage will remain constant. The voltage at which this occurs is known as the underlying *equilibrium potential*, and is determined by an important formula known as the *Nernst equation*

$$V = \frac{RT}{zF} \log_e \left(\frac{C_o}{C_i} \right) \tag{8}$$

Here, V is the membrane potential, that is the inside–outside potential difference, C_o is the outside potassium ion concentration, C_i is the inside potassium ion concentration, R is the gas constant, T the absolute temperature, F is the Faraday, and z gives the number and sign of unit charge borne by ions ($z = +1$ for potassium ions).

The Nernst equation (8) just discussed specifies the voltage which arises from an

ionic concentration difference across a membrane. This equation is of central importance for nervous system function because nerve cells, like other cells, do generally maintain different inside and outside ion concentrations. These concentration differences are produced and maintained by the energy requiring pumping mechanisms, the chief one of which is the sodium pump. Because this sodium pump generates electrical currents, it also can produce contributions to a nerve cell's membrane potential (Thomas 1972: see also Sections II and III).

Two points in connection with the preceding discussion deserve particular stress. First, although potassium ions are moving through the membrane, *no* significant change in the bulk potassium concentration generally occurs because the excess ions that move through are held close to the outside surface of the membrane by the voltage difference and are not free to move through the solution[1]. Second, the Nernst equation applies only to the permeate ions and not to the sodium and chloride ions which cannot move through the channels.

The Nernst equation given above is essentially a re-statement of the Boltzmann distribution of statistical mechanics. According to the Boltzmann distribution, the ratio of potassium concentrations on the inside (C_i) and outside (C_o) depends exponentially on the energy difference E of a potassium ion between the inside and outside:

$$\frac{C_o}{C_i} = e^{-E/RT}$$

where k is Boltzmann's constant and T is the absolute temperature. The energy difference E between the inside and outside is the work to move a positive charge across the membrane which is

$$E = -z\varepsilon V$$

Here, ε is the unitary charge, z denotes the number and sign of the charges borne by the ion, and V is the membrane potential ($V_{inside} - V_{outside}$). Thus, the equilibrium concentration ratios and voltage are related by the equation

$$\frac{C_o}{C_i} = e^{z\varepsilon V/kT}$$

which may be rewritten for a mole of ions by multiplying the numerator and the denominator of the exponent by Avogadro's number N

$$\frac{C_o}{C_i} = e^{zFv/RT}$$

Here $F = N\varepsilon$ is the Faraday and $R = Nk$ is the gas constant. This equation, then, relates the equilibrium concentrations to the membrane potential. Taking the

[1] "Significant" change in concentration here means that no neuron function is generally (although not always) unaffected. Some implications of concentration changes which do occur as the result of neuronal activity are considered in Section III.

logarithm of this relation yields the Nernst equation:

$$V = \frac{RT}{zF} \log_e\left(\frac{C_o}{C_i}\right) \tag{8}$$

For normal body temperature this equation may be rewritten as

$$V = \frac{61.5}{z} \log_{10}\left(\frac{C_o}{C_i}\right)$$

where the natural logarithms have been converted to base 10 and constants have been evaluated; V is expressed in mV.

It should be noted especially that the equilibrium potential just discussed does not depend on the number of *ion selective channels* that are open. If one channel opens or if a million open, the membrane will finally reach the same equilibrium potential. How rapidly the equilibrium potential is reached will, however, vary with the number of channels open. If only a few channels are present, the diffusional movement of ions from the high to the low concentration side will be slow and the build-up of voltage will take a relatively long time; if very many channels open, the balance between the diffusional forces moving ions from the high to the low concentration region and the opposing electrical forces built up by the accumulation of excess charges on one side of the membrane will rapidly be achieved.

As more channels become open, the ions of the type selected by the channel move more freely through the membrane. The ease with which ions move through the membrane is generally specified by the *conductance* g for the ion in question. This conductance is the inverse of the electrical resistance of a system containing only the permeate ion. The conductance g_{Na} for sodium ions, for example, increases as the number of sodium-selective channels increases.

Generally biological membranes contain a number of different types of channels, each selectively permeable to a different ion species. Thus, it is important to investigate the behavior of membrane potential in an instance where different ionic channels are participating. We suppose as before that the membrane patch has the ion concentration on its inside and outside as follows: 100 mM sodium chloride, and 10 mM potassium chloride outside; 5 mM sodium chloride, and 100 mM potassium chloride inside. If we were to open simultaneously a large number of potassium channels and a small number of sodium ion channels, both ions would begin moving from the high to low concentration regions. Therefore, the sodium ions would move from outside to inside, and the potassium ions would move in the reverse direction. If only potassium ion channels were open, the membrane potential would approach the potassium equilibrium potential which is, according to the Nernst equation, -61 mV for this example. If only sodium ion channels were to open, the membrane potential would approach the sodium ion equilibrium potential, in this case 80 mV. Because more potassium ion channels are open than sodium ion channels, the situation approaches most closely that of one in which only potassium ion channels are open, and the membrane potential would approach, but not reach, the potassium equilibrium potential. As might be expected, the membrane potential is driven toward the sodium or the

potassium equilibrium potential according to the relative conductances of the membrane to the sodium and potassium ions. Specifically, the final membrane potential V is given by the equation

$$V = \frac{g_k}{g_k + g_{Na}} E_k + \frac{g_{Na}}{g_k + g_{Na}} E_{Na}$$

where g_{Na} and g_K are the sodium and potassium ion *conductances* and E_{Na} and E_K are the sodium and potassium ion *equilibrium potentials* as given by the Nernst equation. Thus, by varying the relative sodium and potassium conductances, the membrane potential can be moved to any value between E_{Na} and E_K.

Biological solutions contain a variety of different ions, and biological membranes have a number of different channel types that are selectively permeable to specific ions. For example, most of the ions which permeate one particular type of nerve membrane would pass through sodium, potassium, and calcium-selective channels. In general, the membrane potential is a weighted sum of all ion equilibrium potentials, the weight being determined by relative conductances of the ion. Thus if a number of different channel types are all present, the membrane potential will be given by

$$V = \sum_j \frac{g_i}{\left(\sum_k g_n\right)} E_j \tag{9}$$

where E_j is the equilibrium potential of the jth ion as given by the Nernst equation and g_j is the conductance of the jth ion.

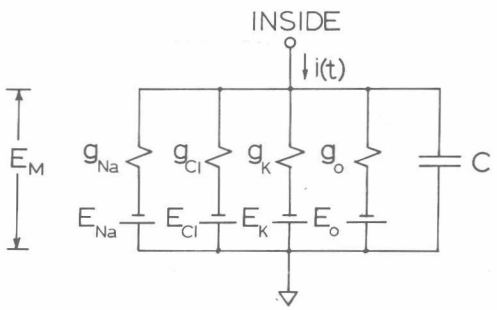

Fig. 2. Equivalent circuit for neuron membrane; this circuit is a representation of the relationships embodied in equation (9). E_M is the membrane potential, and the other E's signify the equilibrium potentials for the indicated ions; sodium (Na), chloride (Cl), potassium (K), and other (0)—such as calcium. Membrane current is represented by $i(t)$, and the membrane capacitance by C. The conductances of the various ions are denoted by the g's.

Because ions move independently through the membrane and because the total ionic current is the sum of the contributions from individual ionic currents, one may represent the membrane by an equivalent circuit as illustrated in Fig. 2. From this equivalent circuit the relationships given above are immediate consequences of Kirchhoff's laws. A more complete justification for this equivalent circuit is given by Finkelstein and Mauro (1963), and may also be found in Stevens (1966).