Chapter 10

Modeling the Nerve Action Potential

10.1 Electrical Behavior of Excitable Tissue

Excitable tissues like nerves and muscles possess the property that when stimulated beyond some threshold an all-or-none *action potential* can be observed. This action potential is a local depolarization of the normally polarized cell membrane on the axon. The local depolarization causes the depolarization of adjacent regions of the cell; the continuation of this process results in propagation of the action potential over the axon. This propagating action potential is an important means of information transmission in animals; nerve cells communicate by means of such action potentials propagating along axons. Information between cells is usually conveyed across a *synapse* in which the action potential from one nerve causes the release of a transmitter chemical which in turn generates excitatory or inhibitory post-synaptic potentials. Sufficient excitatory post-synaptic potential amplitude will in turn evoke another action potential in the receiving cell. Sensory receptors like retinal cells, touch receptors, etc., transduce external physical signals into depolarizations in the receptor ultimately resulting in action potentials which carry the information to the brain. On the other hand activity of neurons in the motor cortex results in action potentials being conveyed to spinal neurons which impinge on muscle fibers and evoke muscle fiber action potentials. The muscle fiber action potential leads to a sequence of activity which ultimately produces muscle contraction, force production and locomotion. The process of generation of action potentials in all these various types of cell is essentially the same.

The generation of the action potential is important from the point of pure scientific curiosity as well as from the medical point of view where pathological defects of action potential propagation are to be understood and

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treated. In this chapter we will look at some experiments on the electrical behavior of excitable tissue and also some models of nerve excitation derived from the experimental observations.

10.1.1 Excitation of Nerves: The Action Potential

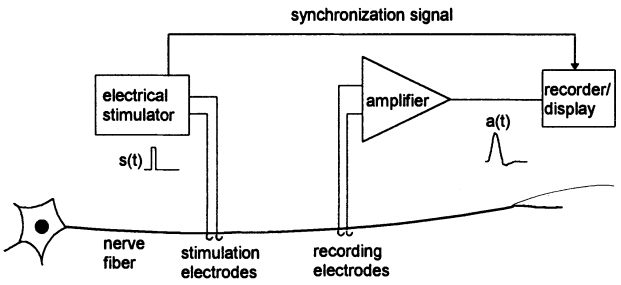


Figure 10-1. Recording a nerve action potential. The stimulus s(t) initiates an action potential which is observed as a(t).

A nerve action potential can be recorded from a section of nerve axon using the arrangement shown schematically in *Figure 10-1*. An action potential may be initiated quite simply by stimulating a portion of the axon with a rectangular pulse of current injected across the membrane. The propagating action potential may be recorded at another point along the axon. The recording may be done either by (a) placing electrodes across the membrane and observing the voltage signal, or (b) placing the electrodes externally and recording the potential difference between two closely placed electrodes. The first recording method is rather difficult as it will require placing an electrode inside the nerve axon, and hence the second one is usually used. A schematic of the arrangement with external electrodes is shown in *Figure 10-1*. The electrical stimulator generates a rectangular pulse of voltage (or current) that is applied to the nerve axon. If the strength of the stimulus exceeds the required threshold, then an action potential is generated. The action potential propagates in either side of the point of initiation. The region of depolarization which forms the action potential travels at a velocity of several meters per second away from the point of initiation. When the region of depolarization is sufficiently close to the position of the recording electrodes, an appreciable voltage is induced which can be observed on the recorder/display system. The entire sequence of events takes a few milliseconds. A synchronization signal from the stimulator to the recorder ensures that the recording system captures the

events correctly. If recording commences from the instant of stimulation, the time latency of the observed action potential will be the time taken for the propagating action potential to traverse the distance between the stimulation and recording electrodes.

10.1.2 Extracellular and Intracellular Compartments

In order to understand the generation of the nerve action potential we must first understand the ionic environment of the nerve that produces the polarization of the resting state and also the depolarization of activation.

The nerve cell is surrounded by extracellular fluid lying outside the membrane. The three ions that are important from the point of this discussion of excitable tissues, viz., sodium, potassium and chloride are present in different concentrations inside and outside the cell. The concentration difference of sodium and potassium is maintained by an active (i.e., energy utilizing) molecular pump in the membrane. The ion concentration difference results in a potential difference across the membrane. This potential which is present even in the unexcited or unstimulated nerve is called the *resting membrane potential.* Since, the extracellular space is very large compared to the intracellular space movement of ions to and from any cell does not affect the extracellular concentrations significantly. It is therefore, common to assume the extracellular space to be a constant reference. The resting membrane potential in nerve and muscle cells is negative with respect to the extracellular space. When ionic movement occurs in any nerve cell the ionic currents result in a local potential change across the membrane with the inside of the cell going positive with respect to the extracellular space.

10.1.3 Membrane Potentials

The action potential is caused by the movement of ions across the nerve membrane. It is therefore of primary importance to understand the ionic concentrations inside as well as outside the cell. Three main ions are involved in the electrical activity of nerve cells, *viz.*, Na^+, K^+ and Cl^-. In a nerve cell at rest (no action potential) the concentrations of these ions are unequal inside and outside. Typical values are shown in *Table 10-1.*

Table 10-1. Ion concentrations for an illustrative cell

Ion	Inside	Outside
K^+	397 mM/l	20mM/l
Na^+	49mM/l	440mM/l
Cl^-	48mM/l	480mM/l

Nernst potential: For each of the ions mentioned above the concentration difference results in an effective electric field across the membrane. The *Nernst potential* is the potential at which the particular ion is at equilibrium with its diffusional force. The Nernst potential is calculated for cations C^+ or anions A^- as follows:

$$E_N = \frac{RT}{ZF}\ln\left(\frac{[C^+]_e}{[C^+]_i}\right), \qquad E_N = \frac{RT}{ZF}\ln\left(\frac{[A^-]_i}{[A^-]_e}\right) \tag{10.1}$$

R is the gas constant, R=8.314 Joules/K mole at 27°C,
T is the absolute temperature in Kelvin
F is the Faraday constant, F=96487 absolute Coulombs/gram equivalent
Z is the magnitude of the valence of the ion,
(Z=1 for all the three ions, Na^+, K^+ and Cl^-)
$[]_e$, $[]_i$ are the extracellular and intracellular concentrations of the ion.

This voltage is positive if the inside of the cell is more positive than the outside, or $V_m=V_i-V_e$, where the subscripts refer to *extracellular* and *intracellular*. Using this equation we can calculate the Nernst potentials for the above mentioned concentrations of the ions, K^+, Na^+ and Cl^- as:

E_K = 77 mV, E_{Na} = -57 mV, E_{Cl} = -59.5 mV

Ionic permeabilities and conductances: The permeability of the membrane to a certain ion is defined as: $P=D\cdot\beta/d$, where β is the partition coefficient or the ratio of the ion concentrations just inside the membrane to just outside it (at the boundary), d is the thickness of the membrane and D is the diffusion constant or Fick's constant.

The relative permeability of the resting membrane to the three ions is approximately: $P_K : P_{Na} : P_{Cl} = 1.00 : 0.035 : 1.4$.

With a transmembrane potential of V_m, the ionic current density (current per unit area of membrane), J, for a monovalent (positive) ion may be calculated as

$$J = \frac{PV_m F^2}{RT}\cdot\frac{[C]_e - [C]_i e^{V_m F/RT}}{1 - e^{V_m F/RT}} \tag{10.2}$$

The conductance of the membrane is then $g=J/V_m$ in mhos/unit area.

Goldman equation: With all the three ions being present simultaneously, the total effective potential across the membrane may be calculated for the steady state condition using the *Goldman equation*,

$$V_m = \frac{RT}{F} \ln\left(\frac{P_K[K]_e + P_{Na}[Na]_e + P_{Cl}[Cl]_i}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_e}\right) \tag{10.3}$$

where P_K, P_{Na} and P_{Cl} are relative permeabilities of the three ions. Note that since chloride is a negative ion the intracellular concentration is in the numerator and the extracellular concentration in the denominator. For the nerve cell at rest we may use, $P_K : P_{Na} : P_{Cl} = 1.00 : 0.035 : 1.4$
With these values the *Resting Membrane Potential* is V_m = -60mV

10.1.4 Electrical Equivalent of the Nerve Membrane

Treating the Nernst potentials as voltage sources and the permeabilities as conductances an electrical equivalent of the nerve membrane can be drawn, *Figure 10-2*. The effective membrane potential can be determined from this electrical circuit in terms of the individual ionic Nernst potentials and the ionic permeabilities. The ionic current in each branch (i.e., the current due to each of the ions) can be calculated from this circuit.

$$\begin{aligned} I_{Na} &= (V_m - E_{Na})\, g_{Na} \\ I_K &= (V_m - E_K)\, g_K \\ I_{Cl} &= (V_m - E_{Cl})\, g_{Cl} \end{aligned} \tag{10.4}$$

Here, the g's represent conductances of the membrane for each ion. At equilibrium there is no net flow of current across the membrane and thus applying Kirchhoff's current law at either of the two nodes,

$$\begin{aligned} I_{Na} + I_K + I_{Cl} &= 0 \\ (V_m - E_{Na})g_{Na} + (V_m - E_K)g_K + (V_m - E_{Cl})g_{Cl} &= 0 \end{aligned} \tag{10.5}$$

Rearranging Eq.(10.5) we obtain

$$V_m = \frac{E_{Na}\, g_{Na} + E_K\, g_K + E_{Cl}\, g_{Cl}}{g_{Na} + g_K + g_{Cl}} \tag{10.6}$$

For a "typical" axon at rest the conductances are approximately: g_K=0.3m*mho*/cm^2, g_{Na}=0.04m*mho*/cm^2, g_{Cl}=0.5m*mho*/cm^2. Using the above formula we can calculate the resting membrane potential of such a membrane as V_m = -60 mV.

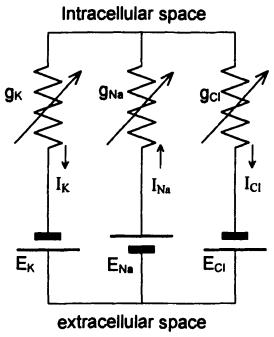


Figure 10-2. Electrical equivalent of ionic potentials and conductances in a nerve cell membrane.

Membrane conductance and excitability: The generation of the action potential involves movement of ions across the nerve cell membrane and a change from the resting membrane condition. This movement of ions results from change in the ionic conductances of the membrane. These conductances are found to be functions of the membrane voltage which is why an action potential can be initiated by an electrical pulse. The electrical stimulus causes a change in the ionic conductances initiating a chain of events observed as the action potential.

The cell membrane capacitance: We must also note that since the cell membrane itself is a lipid bilayer and an insulator, its passive electrical property may be represented by a capacitor. If there is a potential change across the membrane then a capacitive current flows. Conversely, the voltage across the capacitor may be calculated from the current flowing through it.

$$C\frac{dV_m}{dt} = I_C \tag{10.7}$$

When the membrane is at rest, I_c=0 and dV_m/dt=0.

Maintenance of ion concentration – Sodium-Potassium pump: We can see that the resting membrane potential is close to the chloride potential therefore the chloride ion is almost at equilibrium. Potassium and sodium on the other hand are not in equilibrium since the Nernst potential of these ions is different from the resting membrane potential. For sodium there is a driving potential is V_m-E_{Na}=-117 mV, and for potassium the driving potential

is V_m-E_K=+14 mV. The ion current that will result from this is offset by an active molecular pump that pumps sodium outside and potassium inside the cell. This molecular pump being an active mechanism consumes energy during its operation. This is called the sodium-potassium pump. The electrical equivalent circuit is expanded by including the Na-K pump and drawn in *Figure 10-3*.

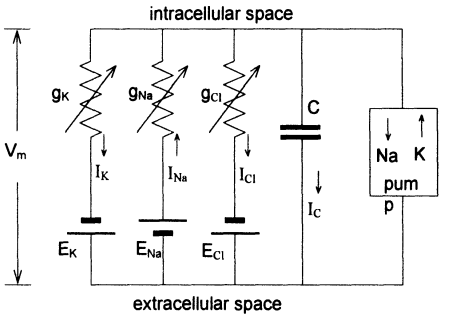


Figure 10-3. Electrical equivalent of a nerve membrane.

The action of the sodium-potassium pump is such as to maintain the ionic gradients by compensating for the passive diffusion of each ion across the membrane. The Na-K pump current is thus equal in magnitude but opposite in direction to the passive flow of each ion across the membrane, resulting in a net zero current. (The ratio of sodium to potassium transported by the Na-K pump is found to be 3:2). Therefore, the Na-K pump as well as the passive movement of ions across the membrane is ignored in further discussion.

Movement of chloride ion: We can see that the chloride ion is almost at equilibrium at rest, since $E_{Cl} \approx V_{rest}$. The concentration of chloride ion inside the cell is also very small; which means that even large percentage changes of chloride ion (to achieve large changes in E_{Cl}) require only very small quantities of actual flow of the ions; i.e., I_{Cl} is always quite small. In sum, the contribution of the chloride ions to the resting membrane potential as well as to the membrane current is negligible.

Conceptual model of the action potential: Assuming that the influence of the chloride ions on the action potential generation is negligible, a block schematic of the membrane behavior may be drawn highlighting the role of the sodium and potassium ions and the membrane capacitance. If an external current is injected across the membrane then the net ionic current will equal the injected current. The total current in the membrane including any

externally injected current can be determined by extending Eqs.(10.5) and (10.7) suitably as follows:

$$I_K + I_{Na} + I_C = I_S$$
$$I_C = I_S - (I_K + I_{Na}) \tag{10.8}$$

$$C\frac{dV_m}{dt} = I_S - (I_K + I_{Na}) \tag{10.9}$$

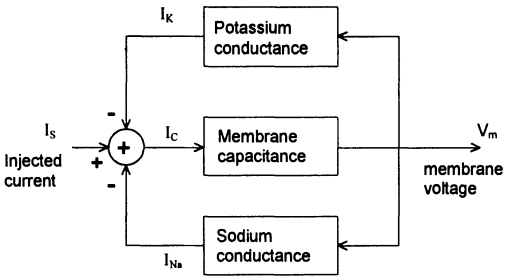


Figure 10-4. Block schematic of the main components contributing to current flow across a nerve membrane.

This conceptual model of the electrical behavior of the nerve membrane is shown schematically in *Figure 10-4*. An important aspect of the diagram in *Figure 10-4* is the separation of the sodium and potassium conductances. This is a key assumption made by Hodgkin and Huxley in their investigation of the nerve action potential, that the sodium and potassium conductances are independent of each other.

10.2 The Voltage Clamp Experiment

Since the action potential is generated because of the voltage sensitive nature of the cell membrane's ionic conductances, it is of interest to study the characteristics of these ionic conductances. This can be done by varying the cell membrane voltage and then observing the resulting change in the ionic currents. If a step signal is input and the ionic current is observed, then the membrane conductance can be calculated. However, any net current flowing through the capacitor will tend to change the membrane voltage. This problem is solved by the *Voltage-Clamp experiments* devised by Hodgkin and Huxley.

10.2.1 Opening the Feedback Loop of the Membrane

The voltage clamp apparatus maintains a constant membrane voltage at any desired level by injecting a transmembrane current that will compensate for any change in membrane voltage from the desired value. This is achieved by closed loop control as indicated schematically in *Figure 10-5*. This voltage clamp apparatus was used by Hodgkin and Huxley to apply a precisely controlled step change of voltage across a nerve membrane.

Comparing the voltage clamp schematic of *Figure 10-5* with the earlier block diagram in *Figure 10-4* showing the membrane conductances and capacitance, we see that the main goal of the voltage clamp apparatus is to open the loop between the membrane current and the membrane voltage; i.e., dissociate the membrane voltage from the membrane current. This is achieved by injecting a current $I_s=I_K+I_{Na}$ so that $I_c=0$ and consequently $dV_m/dt=0$, and the membrane voltage is held constant at the desired clamp voltage V_c. The experimental arrangement used by Hodgkin and Huxley for the nerve membrane voltage clamp (on the giant axon of the squid, *Aplysia*) is shown schematically in *Figure 10-6*. As seen in *Figure 10-6* a current injecting electrode and a voltage sensing electrode are inserted into the nerve axon. The giant axon of the squid is almost 1 mm in internal diameter permitting the insertion of these electrodes. Another electrode in the extracellular medium acts as the reference. Using this closed loop control arrangement any desired input signal can be applied as the membrane voltage. Recording the membrane current will give the ionic current flow resulting from this input signal. The current recording is not shown explicitly in *Figure 10-6* in order to keep the schematic simple. The current may be recorded by a number of different ways, viz., it may be obtained from the voltage-to-current converter, or it may be deduced from the voltage drop across a known resistance placed in the current path. The latter method was used in the Hodgkin-Huxley experiment.

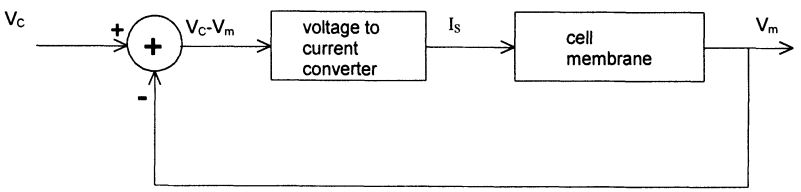


Figure 10-5. Block schematic of the experiment for voltage clamping a membrane.

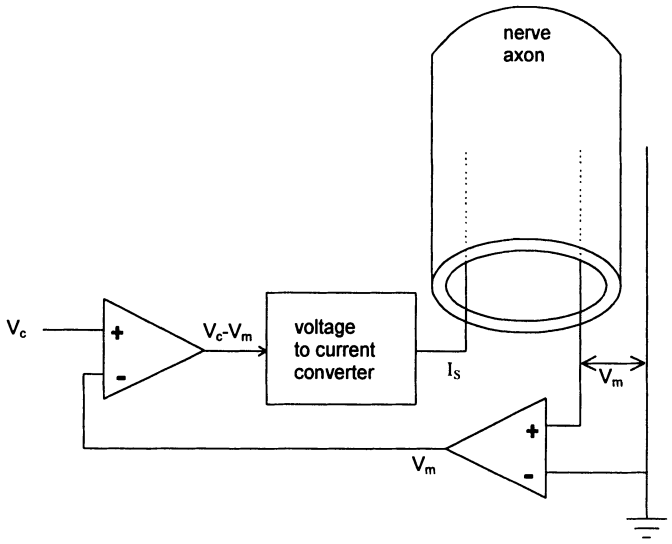


Figure 10-6. Schematic of the voltage clamp experiment.

Immediately after the application of the step change in membrane potential there will be a large capacitive current as the membrane capacitor assumes the new voltage V_c; since $V_c=V_m+dV_m/dt=V_m+I_c/C$. This large current is seen as a large spike in the current recording. This initial spike is ignored in further analysis since it is not related to the sodium and potassium currents. After this large spike, the voltage clamp apparatus acts to inject a current $I_s=I_{Na}+I_K$ so that $I_c\approx 0$. Note that since the voltage-to-current converter generates a non-zero current I_s during the course of the voltage clamp, the input to this voltage-to-current converter, V_c-V_m, is not exactly equal to zero but has a very small value. This variation in V_c is negligibly small. In order for the initial current spike to be very brief in duration and also for the variation in clamp value to be small the voltage-to-current converter must be a good one – i.e., it must have a fast response time and adequately large gain.

10.2.2 Results of the Hodgkin-Huxley Experiments

The following discussion uses the same membrane as mentioned above with E_{Na} = -57 mV, and V_{rest} = -60 mV. Application of a step voltage, V_c, of step amplitude, say, 56 mV (V_c-V_{rest}=56 mV), and recording the current gives the total current due to potassium and sodium ions. In other words, this produces the step response, to a 56mV step, of the sodium+potassium conductances (*Figure 10-7*a). In order to observe only one of the two

conductances, Hodgkin and Huxley replaced 90% of the extracellular sodium with choline. This makes $E_{Na} \approx -1$ mV and a step of 56 mV makes $V_m - E_{Na} \approx 0$ and therefore, sodium being essentially at equilibrium there is negligible sodium current. The observed current response to the voltage clamp step is then solely due to potassium (*Figure 10-7*b). The sodium current response to the 56 mV step voltage input can be deduced by simply subtracting the potassium current from the total current (*Figure 10-7*c).

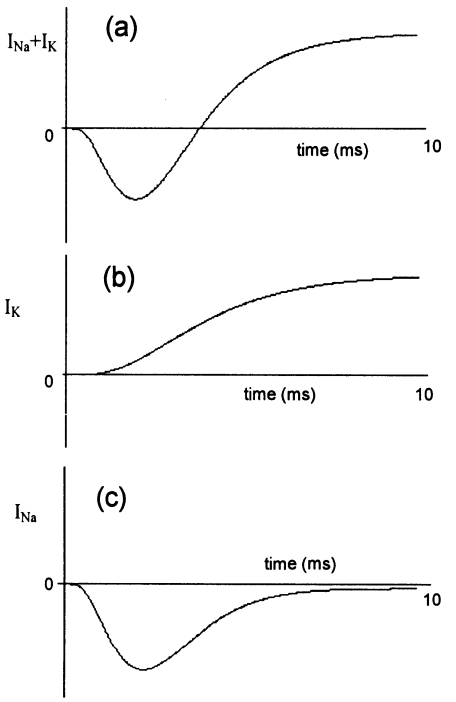


Figure 10-7. Voltage clamped membrane currents. (a) potassium and sodium current, (b) potassium current, (c) sodium current calculated as the difference of the first two. (Adapted from A.L.Hodgkin and A.F.Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, *J.Physiol.* **117:** 500-544, 1972.)

The ionic conductance can be calculated from these graphs simply as

$$g_K(t) = \frac{I_K(t)}{V_C(t) - E_K}, \quad g_{Na}(t) = \frac{I_{Na}(t)}{V_C(t) - E_{Na}} \tag{10.10}$$

10.3 Interpreting the Voltage-Clamp Experimental Data

10.3.1 Step Responses of the Ionic Conductances

First we should determine functions that will describe the step responses of the potassium conductance and the sodium conductance. From experience with simple first and second order systems we can see that these step responses can be approximated by combinations of exponentials.

Potassium conductance: The potassium conductance step response is approximately of the familiar form,

$$S_{gK}(t) = c_K[1-e^{t/\tau_K}]u(t) \tag{10.11}$$

This is a first order step response. The main difference between this function and the actual data is the gradual and delayed rise at the onset. The delay can be incorporated using a simple time shift but this will not account for the gradual rise of the actual data. Moreover, as explained later the coefficients c_K and τ_K are not constant which makes such a linear function approach untenable.

Sodium conductance: The sodium step response has a rising and falling portion each of which may be described by an exponential Thus the sodium conductance step response may be expressed as the product of two exponentials, one a rising exponential and the other a falling exponential,

$$S_{gNa}(t) = c_1[1-e^{-t/\tau_b}][c_2+e^{-t/\tau_a}]\cdot u(t) \tag{10.12}$$

Again the main difference between these functions and the actual data is the slow onset of the actual data in contrast to the abrupt rise of the proposed function. The delay can be incorporated with a time shift, but this does not adequately model the behavior of the sodium conductance, since the coefficients are voltage dependent. Again, apart from the inadequate accounting of the slow onset, the coefficients c_1, c_2, τ_1 and τ_2 are not constants, making the linear function approach useless.

Extending the above model: The above proposed simple functions can be extended to have a slow onset. In addition, further experiments by Hodgkin and Huxley indicated that the magnitude coefficients c and the time constants τ are voltage dependent. Thus, the resulting expanded model developed by Hodgkin and Huxley is a nonlinear model.

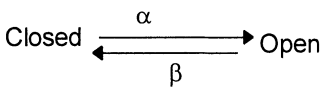
10.3.2 Hodgkin and Huxley's Nonlinear Model

Hodgkin and Huxley used the results of the voltage clamp experiments obtained from the large axon of the squid to develop a model of nerve excitation. The model proposed by Hodgkin and Huxley (*H-H model*) is explained below.

Potassium conductance: In the Hodgkin-Huxley model the potassium conductance step response is represented by a function of the form selected above, raised to the fourth power,

$$s_K(t) = \{c_n[1 - e^{-t/\tau_n}]\}^4 \cdot u(t) \tag{10.13}$$

Raising to the fourth power ensures that the rise of the function is gradual as seen in the experimental data. *Figure 10-8* shows the potassium conductance for a 56 mV step fit to a first order function and also its fourth power. Note how $n(t)$ rises abruptly from t=0 whereas using $n^4(t)$ introduces a slower rise, with an inflection and more accurately represents the actual potassium conductance step response. A physical explanation for the first order expression raised to the fourth power can be assumed by considering four first order responses that act in combination. Each first order term represents the solution to a first order process. The potassium conductance can be explained in physical terms of potassium *gates* whose opening permits the passage of potassium ions and therefore changes the ionic conductance. If, as Hodgkin and Huxley did, we assume that each potassium channel contains four sub-gates each of which has a first order response then the opening and closing of each sub-gate may be represented as



Let $n(t)$ be the fraction of the total number of sub-gates that are open; or, we may say that $n(t)$ is the probability of a particular sub-gate being open. The rate of gate opening can be written as

$$\frac{dn(t)}{dt} = [1 - n(t)]\alpha_n - n(t)\beta_n$$

$$\frac{dn(t)}{dt} + [\alpha_n + \beta_n]n(t) = \alpha_n \tag{10.14}$$

The steady state solution (step response) for this differential equation is of the form,

$$n(t) = \frac{\alpha_n}{\alpha_n + \beta_n}[1 - e^{-(\alpha_n + \beta_n)t}] \cdot u(t) \tag{10.15}$$

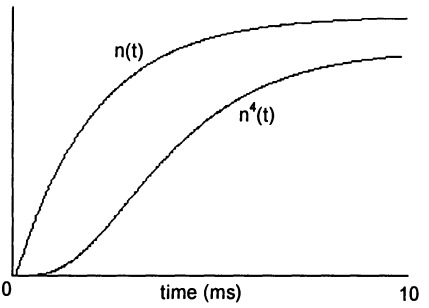


Figure 10-8. Potassium conductance following a step change of voltage.

In order for a particular potassium channel to be open, all four sub-gates must be open. Therefore, the total probability of a particular gate being open is the product of the probabilities of all its four component sub-gates being open, i.e., $n^4(t)$. (It is also assumed that all four sub-gates have identical properties). Thus the potassium conductance in the H-H model is represented by the following equation (with G_K being a constant scale factor):

$$g_K(t) = G_K n^4(t) \tag{10.16}$$

Sodium conductance: We saw that the sodium conductance during the voltage clamp can be expressed as the product of a rising exponential and a falling exponential. Hodgkin and Huxley used a similar form with the extension that the rising exponential was raised to the third power in order to account for the slow rise, i.e.,

$$\begin{aligned} S_{Na}(t) &= c_1[1 - e^{-t/\tau_1}]^3 \cdot [c_2 + e^{-t/\tau_2}] \cdot u(t) \\ &= m^3(t) \cdot h(t) \end{aligned} \tag{10.17}$$

where $m(t)$ and $h(t)$ represent the two first order responses.

The sodium conductance functions $m(t)$ and $h(t)$ for a voltage clamp experiment using $V_1 = V_{rest}$ =-60 mV and $V_2 = V_{rest}$+56 mV are shown in *Figure 10-9*. The product $m^3(t)h(t)$ is shown in *Figure 10-10* (vertical scales are different from *Figure 10-9*) and its shape is clearly a good description of the sodium conductance. Again the biophysical explanation for these four terms can be obtained by assuming four sub-gates in each sodium channel, three of which open in the step response (rising exponential produced by sub-gates m) and the fourth closes in the step response (falling exponential produced by sub-gate h).

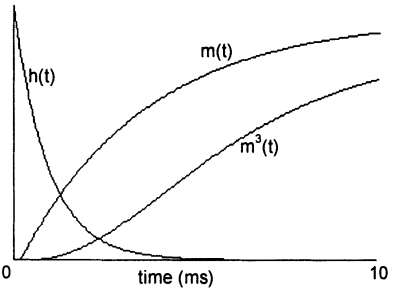


Figure 10-9. Components of sodium conductance following a step change in membrane voltage.

The step responses of both sub-gate h and sub-gate m can be construed as solutions of first order behavior described by the rate equations,

$$\frac{dm(t)}{dt} + [\alpha_m + \beta_m] \cdot m(t) = \alpha_m$$
$$\frac{dh(t)}{dt} + [\alpha_h + \beta_h] \cdot h(t) = \alpha_h \qquad (10.18)$$

The steady state solutions (step responses) of these first order differential equations are of the form,

$$m(t) = \frac{\alpha_m}{\alpha_m + \beta_m}\left[1 - e^{-(\alpha_m+\beta_m)t}\right] \cdot u(t)$$
$$h(t) = \left[\frac{\alpha_h}{\alpha_h + \beta_h} + e^{-(\alpha_h+\beta_h)t}\right] \cdot u(t) \qquad (10.19)$$

The probability of a sodium ion channel with its four sub-gates being open is then the cumulative probability of each sub-gate being open. The sodium conductance is thus expressed by the H-H model as

$$g_{Na}(t) = G_{Na}\, m^3(t)h(t) \tag{10.20}$$

where G_{Na} is a constant scale factor and $m(t)$ and $h(t)$ represent the probability of each sub-gate being open.

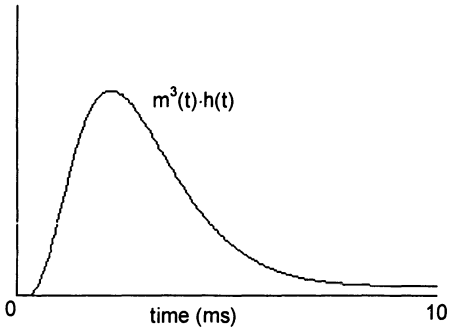


Figure 10-10. Function describing the sodium conductance following a step change in membrane voltage.

Calculation of the function parameters: The voltage clamp involves change of the membrane voltage from V_1 to V_2 at t=0.

$$V_m(t) = \begin{cases} V_1 & t \le 0 \\ V_2 & t \ge 0 \end{cases} \tag{10.21}$$

Each of the terms, $n(t)$, $m(t)$ and $h(t)$ has two coefficients to be determined. From the experimental data an amplitude constant and a time constant can be determined. These constants are uniquely related to the biochemical reaction rates α and β.

$$c = \frac{\alpha}{\alpha + \beta}, \quad \tau = \frac{1}{\alpha + \beta} \tag{10.22}$$

From the experimental data the functions $n(t)$, $m(t)$ and $h(t)$, which are the first order step responses, are estimated and the c's calculated as: $n(\infty)=c_n(V_2)$, $m(\infty)=c_m(V_2)$, $h(\infty)=c_h(V_2)$. The τ's at V_2 are obtained from the rise and fall *rates* of the curves.

10.3.3 The Voltage Dependent Membrane Constants

Proceeding as outlined above Hodgkin and Huxley obtained values for the membrane constants c_n, c_m, c_h, τ_n, τ_m, τ_h for different values of V_m. These are drawn as functions of the membrane voltage in *Figure 10-11* and *Figure 10-12*.

The coefficients α and β are related to c and τ as follows:

$$\begin{aligned} \alpha(V_m) &= \frac{c(V_m)}{\tau(V_m)} \\ \alpha(V_m)+\beta(V_m) &= \frac{1}{\tau(V_m)} \\ \beta(V_m) &= \frac{1-c(V_m)}{\tau(V_m)} \end{aligned} \qquad (10.23)$$

From the curves obtained for α and β, Hodgkin and Huxley used analytical functions to describe them.

$$\alpha_n(V_m)=\frac{-0.01(58+V_m)}{e^{-(58+V_m)/10}-1} \quad , \quad \beta_n(V_m)=0.125e^{-(V_m+68)/80} \qquad (10.24)$$

$$\alpha_m(V_m)=\frac{-0.1(43+V_m)}{e^{-(43+V_m)/10}-1} \quad , \quad \beta_m(V_m)=4e^{-(V_m+68)/18} \qquad (10.25)$$

$$\alpha_h(V_m)=0.07e^{-(V_m+68)/20} \quad , \quad \beta_h(V_m)=\frac{1}{e^{-(38+V_m)/10}+1} \qquad (10.26)$$

These functions are, of course, specific to the membrane studied by Hodgkin and Huxley; they will be different for membranes from different types of cells although the general form may be expected to be similar.

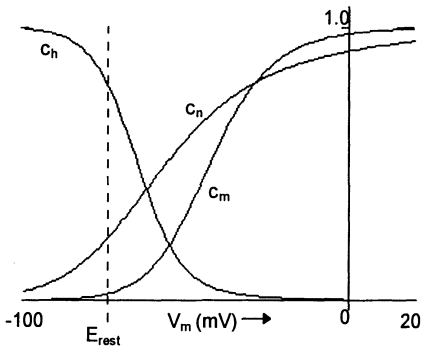


Figure 10-11. The amplitude constants plotted against the membrane voltage.

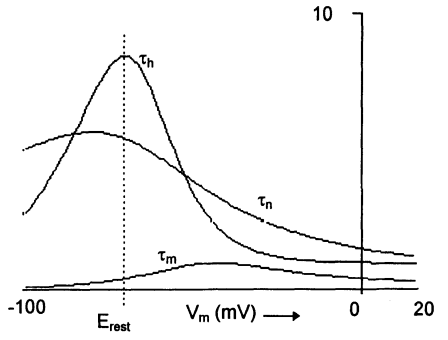


Figure 10-12. The time constants plotted against membrane voltage.

10.3.4 Simulation of the Hodgkin-Huxley Model

Using the first order differential equation describing the ion channel dynamics, the values of the functions $n(t)$, $m(t)$ and $h(t)$ can be recursively calculated for any given set of initial conditions. The differential equation can be solved for consecutive values of time as follows (with time increments of Δt). Rearranging Eq.(10.14) using $\Delta n = dn$ and $\Delta t = dt$ we have

$$\begin{aligned} \Delta n(t) &= \Delta t \cdot \{[1-n(t)] \cdot \alpha_n(V_{\mathrm{m}}(t)) - n(t) \cdot \beta_n(V_{\mathrm{m}}(t))\} \\ n(t+\Delta t) &= n(t) + \Delta n(t) \end{aligned} \tag{10.27}$$

where we have also made explicit that the membrane voltage V_{m} is also a function of time. Similarly, for the sodium conductance functions m and h,

$$\begin{aligned} \Delta m(t) &= \Delta t \cdot \{[1-m(t)] \cdot \alpha_m(V_{\mathrm{m}}(t)) - m(t) \cdot \beta_m(V_{\mathrm{m}}(t))\} \\ m(t+\Delta t) &= m(t) + \Delta m(t) \end{aligned} \tag{10.28}$$

$$\begin{aligned} \Delta h(t) &= \Delta t \cdot \{[1-h(t)] \cdot \alpha_h(V_{\mathrm{m}}(t)) - h(t) \cdot \beta_h(V_{\mathrm{m}}(t))\} \\ h(t+\Delta t) &= h(t) + \Delta h(t) \end{aligned} \tag{10.29}$$

For these equations the values of α and β are calculated for the current membrane voltage V_{m} using the empirical functions determined by Hodgkin and Huxley. Once the gate probabilities are known the conductances may be calculated. Using the conductances the ionic currents may be calculated using the electrical network model. The total current through the capacitor will be the sum of the ionic currents and the stimulus current injected from an external source. Finally, the new membrane voltage is calculated as the solution to the differential equation describing the capacitor. That is,

$$\frac{dV_{\mathrm{m}}(t)}{dt} = \frac{1}{C} \int I_C(t) dt \tag{10.30}$$

Discretizing Eq.(10.30) we get

$$\Delta V_{\mathrm{m}}(t) = \frac{1}{C} \cdot I_C(t) \cdot \Delta t \tag{10.31}$$

The voltage at the next point in time can be calculated using this ΔV_{m}.

$$V_{\mathrm{m}}(t+\Delta t) = V_{\mathrm{m}}(t) + \Delta V_{\mathrm{m}}(t) \tag{10.32}$$

This sequence of calculations is repeated for the duration of the simulation.