Chapter 3

Background: The Biophysics of Neuronal Activity

In this chapter, we present a brief description of the biophysics that underlies the activity of a biological neuron. A basic understanding of this material should facilitate any evaluation of the strengths and weaknesses of the model of the neuron that we propose in Chapter 4. Familiarity with this material is, however, not a prerequisite to the comprehension of the contents of the thesis.

3.1 The Brain: Basic Features

The brain is an exceptionally complex organ. It can be regarded at various levels of organization and detail. From a functional perspective, the brain can be partitioned into (i) the cerebral cortex, responsible for all higher order functions, (ii) the thalamus, which acts as a processing gateway to all information bound for and departing the cerebral cortex, and (iii) the perithalamic structures comprising the hypothalamus, the reticular formation, the nigrostriate formation, the cerebellum, the hippocampus, and the colliculus, each performing peripheral tasks essential to the proper functioning of the system as a whole.

At the highest level of abstraction, the brain is a device that is composed of numerous copies (approximately 3×10^{10} in the human brain) of a lone functional unit, the *neuron* (or the *nerve cell*).[1] This outlook, however, changes drastically when the brain is viewed at a more concrete level. Physiological and anatomical investigations have established that neurons in the brain come in an overwhelming variety of shapes, forms, and functional types. Furthermore, there is extensive evidence both of structure and the lack thereof in the layout of connections between

[1] The other category of cell known as the *glial* (or *neuroglial*) *cell* outnumbers the neuron eight or nine times to one, and is believed to serve as a structural and metabolic support element, a role played by connective tissue elsewhere in the body.

individual neurons (Braitenberg & Schüz, 1991; Schüz, 1992; Shepherd, 1998).

Notwithstanding the great variety of neurons present in the various structures enumerated above, and significant variations in cytoarchitecture both between and within each structure, the basic principles that govern the operation of their constituent neurons are substantially the same. This fortuitous finding has led to the formulation of the *model neuron*, a construction that embodies the general characteristics of the majority of the neurons.

3.2 Morphology of the Biological Neuron

A model neuron can be partitioned into four morphological regions: the soma, the dendrites, the axon, and the presynaptic terminals. The *soma* or the *cell body* contains the organelles (subcellular components) necessary for cellular function. The soma gives rise to the *axon*, a tubular process that in most instances extends over a considerable distance. For example, the axons of pyramidal neurons in layers 2/3 of the cortex extend to distances of 100 μm to 400 μm. At the distal end the axon divides into fine branches (axonal arborization) that have specialized terminal regions called *presynaptic (axonal) terminals*. Terminals convey information regarding the activity of the neuron by contacting *dendrites* that are receptive surfaces of other neurons. Dendrites typically consist of arborizing processes, that is, processes that divide repeatedly to form a treelike structure, that extend from the soma. The point of contact between two neurons is labeled a *synapse*. It is formed by the presynaptic terminal of one cell (the presynaptic neuron) and the receptive surface on the dendrite of the other (the postsynaptic neuron). Figure 3.1 displays a schematic diagram of a pair of model neurons and their various morphological regions.

Electrical signals known as *action potentials*[2] travel down the axon and arrive at presynaptic terminals, whereupon they are transmitted to the dendrite of the postsynaptic neuron through a chemically mediated process. The electrical signal in the dendrite then spreads to the soma (the impulse has by now lost its localized form) where it is integrated with signals arriving from other such presynaptic neurons, and in certain cases signals generated intrinsically. When the potential at the soma exceeds the *threshold* of the neuron, the soma generates an action

[2] Also known as *spikes*, each such nerve impulse is a roughly triangular solitary wave of amplitude 100 mV that lasts approximately 1 msec.

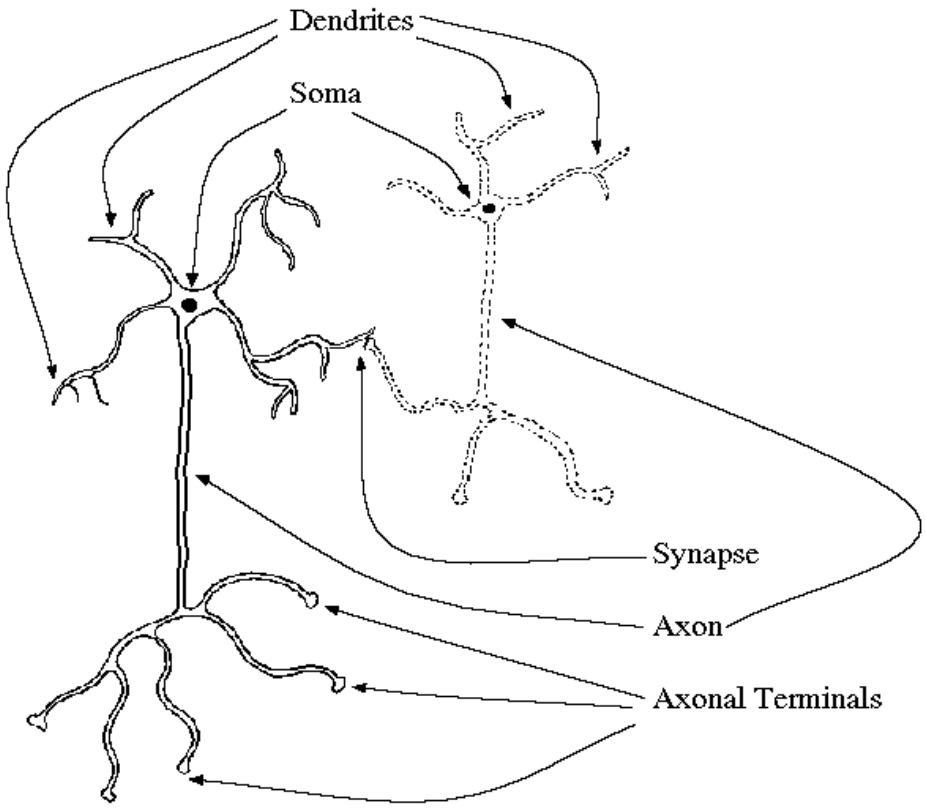

Figure 3.1: Schematic diagram of a pair of model neurons.

potential that travels down its axon.

From a systems perspective, a neuron transforms multiple series of input action potentials arriving at its various afferent (incoming) synapses and in addition, in certain cases intrinsic signals, into a series of output action potentials on its axon. It is this view of the neuron that we adopt in the upcoming chapters.

In order to build a *viable* model of the biological neuron, we impose several formal constraints on the noted transformation, constraints that we enumerate in Chapter 4. Evaluating the veridicality of the constraints, however, requires a basic understanding of the functioning of the neuron. In the remainder of this chapter we therefore shed light on the nature of this transformation by describing briefly the biophysics that underlies the various stages of the process described above. Readers who desire a more comprehensive exposition of the material should consult (Kandel, 1976; Cronin, 1987; Tuckwell, 1988; Koch, 1998; Zigmond et al., 1999).

3.3 The Membrane Potential

The cell membrane of a typical neuron ranges in thickness between 30 and 50 Å and consists of two layers of phospholipid molecules. This insulating bilipid membrane is interspersed with membrane spanning protein molecules with water filled pores that act as *ionic channels*, that is, conduits through which ions can pass. At its resting state a neuron maintains a potential difference across its cell membrane, the inside of the cell being negative in relation to the outside. This potential difference, known as the *membrane potential*, ranges between -40 and -70 mV (with the mode at -60 mV) depending upon the organism as well as the classification of the neuron (Bernstein, 1902; Hodgkin & Huxley, 1939; Curtis & Cole, 1942).

The potential difference is derived primarily from an unequal distribution of K^+ and Na^+ ions across the cell membrane. The membrane is selectively permeable and allows ions to diffuse through the specific and sparsely distributed ionic channels at rates determined by the permeability of the membrane to the particular ion, the electrical gradient across the membrane, and the concentration gradient of the ion across the membrane. The membrane maintains numerous electrogenic[3] Na^+–K^+ pumps (also known as Na^+, K^+-ATPase) that actively transport Na^+ ions out of the cell and K^+ ions into the cell. It is primarily the effect of these pumps and the differential permeability of the membrane to Na^+ and K^+ ions at resting state that results in the membrane potential.

Due to the concentration gradient generated by the pumps, K^+ ions diffuse across the membrane. This is, however, not accompanied by the entry of an equal quantity of positive charge (borne by cations such as Na^+) into the cell or the exit of negative charge (borne by anions such as Cl^- and other organic anions) out of the cell, the permeability of the membrane to these ions being very low at resting state. There is therefore a buildup of electrical charge across the membrane. At steady state, there is a net balance between flow of charge into the cell (Na^+ ions drawn in due to the equilibrium potential difference and its concentration gradient across the membrane) and flow of charge out of the cell (K^+ and Cl^- ions driven out for like reasons). The equilibrium potential difference is given by the solution to the Goldman-Hodgkin-Katz

[3]Three Na^+ ions are expelled for every two K^+ ions drawn into the cell. This unequal transport of ions leads to a hyperpolarizing potential, and the pump is therefore electrogenic.

equation (Goldman, 1943)

$$V_m = \frac{RT}{F} ln \frac{P_{\mathrm{K}}[\mathrm{K}^+]_o + P_{\mathrm{Na}}[\mathrm{Na}^+]_o + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_i}{P_{\mathrm{K}}[\mathrm{K}^+]_i + P_{\mathrm{Na}}[\mathrm{Na}^+]_i + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_o} \tag{3.1}$$

where R is the gas constant, T the absolute temperature, F the Faraday constant, $[\cdot]_o$'s and $[\cdot]_i$'s the concentrations of the ions outside and inside the cell respectively, and $P_{\cdot}$'s the permeability of the membrane to the ions.

3.4 Passive Conductance of Synaptic Potential across Dendrites

Synaptic potentials, generated by the arrival of action potentials at synapses, are conducted passively over the dendrites to the soma. This passive conductance is generally modeled using cable theory (Rall, 1960).

The dendrite is modeled as a uniform cylindrical core conductor with length much larger than diameter. Membrane properties such as resistivity and capacitance are assumed to be uniform. The gradient of the membrane potential v_m along the axis of the cable can then be expressed as

$$\frac{\partial v_m}{\partial x} = -ri \quad \text{and as a result} \quad \frac{\partial^2 v_m}{\partial x^2} = -r\frac{\partial i}{\partial x}, \tag{3.2}$$

where x represents the distance along the axis of the cable, i the current flowing along the axis, and $r = (r_i + r_o)$ the compound resistance per unit length of the cable (r_i is the intracellular and r_o the extracellular resistance per unit length). If there is no current injected by an intracellular electrode, and i_m is the membrane current density per unit length of the cylinder (current flowing perpendicular to the axis of the cable), then

$$i_m = -\frac{\partial i}{\partial x}. \tag{3.3}$$

Equations 3.2 and 3.3, when combined, yield

$$\frac{\partial^2 v_m}{\partial x^2} = r i_m. \tag{3.4}$$

Finally, a unit length of the membrane is modeled as an equivalent circuit (Figure 3.2) consisting of two components connected in parallel. The first is the membrane capacitance, and the second is a compound component that consists of the membrane resistance and a cell

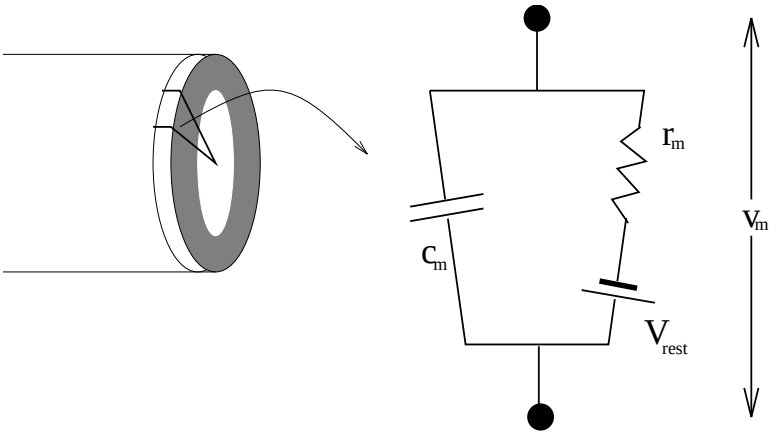

Figure 3.2: Schematic diagram of the equivalent circuit for a passive membrane.

(modeling the resting potential) connected in series. This results in the equation

$$i_m = c_m \frac{\partial v_m}{\partial t} + \frac{v_m}{r_m} \quad \text{or} \quad i_m = c_m \frac{\partial v_m}{\partial t} + g_m v_m, \tag{3.5}$$

where c_m is the membrane capacitance per unit length, and $g_m = \frac{1}{r_m}$ is the membrane conductance per unit length. The partial differential equations 3.4 and 3.5 together form the basis of cable theory. The equations have been solved for various boundary conditions. One such solution (MacGregor & Lewis, 1977) uses the Laplace transform method to yield

$$v_m(x,s) = v(0,s)\cosh[\sqrt{rg_m + rc_m s}\, x] - \sqrt{\frac{r}{g_m + c_m s}} i(0,s)\sinh[\sqrt{rg_m + rc_m s}\, x], \tag{3.6}$$

$$i(x,s) = i(0,s)\cosh[\sqrt{rg_m + rc_m s}\, x] - \sqrt{\frac{g_m + c_m s}{r}} v(0,s)\sinh[\sqrt{rg_m + rc_m s}\, x]. \tag{3.7}$$

Assuming a short circuit at the soma, that is, $v_m(l,s) = 0$, a synaptic impulse at the near end, that is, $i(0,s) = I_{syn}(s) = Q$, and a semi-infinite dendrite ($l \to \infty$) so that higher order terms in the solution may be disregarded, one arrives at the solutions,

$$i(x,t) = [\frac{Q\sqrt{rc_m x^2}}{2\sqrt{\pi t^3}}] e^{-rc_m x^2/4t} e^{-(g_m/c_m)t}, \tag{3.8}$$

$$v_m(x,t) = [\frac{Qr}{\sqrt{rc_m x^2 \pi t}}] e^{-rc_m x^2/4t} e^{-(g_m/c_m)t}. \tag{3.9}$$

The membrane potential at the soma is computed by integrating the impact of the PSP's (postsynaptic potentials) generated by the arrival of spikes at the various synapses on the dendritic tree. An advantage of using cable theory to model subthreshold response at the soma is that the equations are linear. In other words, if V_1 is the solution to the equation

$V_t = V_{xx} - V + I_1$, with initial value $v_1(x)$ (I_1 is introduced as injected current density at $\langle x, t \rangle$), and V_2 is the solution to the equation $V_t = V_{xx} - V + I_2$, with initial value $v_2(x)$ and the same boundary conditions, then the solution to $V_t = V_{xx} - V + I_1 + I_2$, with initial value $v_1(x) + v_2(x)$ and the same boundary conditions is $V(x,t) = V_1(x,t) + V_2(x,t)$.

While spatiotemporal integration of PSP's on a single dendritic branch is linear (the consequence of the linearity of cable theory), spatiotemporal integration of PSP's on an entire dendritic tree is in general not so. It has, however, been shown in (Walsh & Tuckwell, 1985) that if all dendritic terminals are at the same distance from the origin, and at all branch points on the dendritic tree $\text{diameter}^{3/2}_{\text{parent-cylinder}} = \sum \text{diameter}^{3/2}_{\text{daughter-cylinder}}$, then the entire dendritic tree can be mapped onto a single nerve cylinder, in which case integration of PSP's over the entire dendritic tree becomes linear.

Dendritic trees do not, in general, satisfy the above criterion. Passive conductance of synaptic potential across structurally complex dendritic trees is therefore computed using compartmental modeling. The main assumption in the compartmental approach is that small pieces of the neuron can be treated as isopotential elements. The continuous structure of the neuron is approximated by a linked assembly of discrete elements (compartments), and the resulting coupled partial differential equations are solved numerically.

In order to determine how reasonable the boundary conditions are that lead to the closed form solution of (MacGregor & Lewis, 1977), we compared it to simulations of subthreshold response in a neuron to synaptic inputs on an implementation of the compartmental approach, NEURON v2.0 (Hines, 1993).[4] We constructed a toy neuron with the soma and axon modeled as a single compartment and six dendritic branches connected irregularly to form a tree of depth two. Synaptic inputs were applied at various locations on the dendrites and the responses at the soma were noted. Figure 3.3 displays the result of one such experiment. As seen in the figure, we found a good fit between the simulation results and the closed form solution (with parameters set at optimal values).

[4]NEURON, like GENESIS, is a neuronal simulation software that, given a compartmental model of a neuron, simulates its dynamics by solving numerically a coupled set of the Hodgkin-Huxley equations for each compartment. It is a freeware and is available at "http://neuron.duke.edu/".

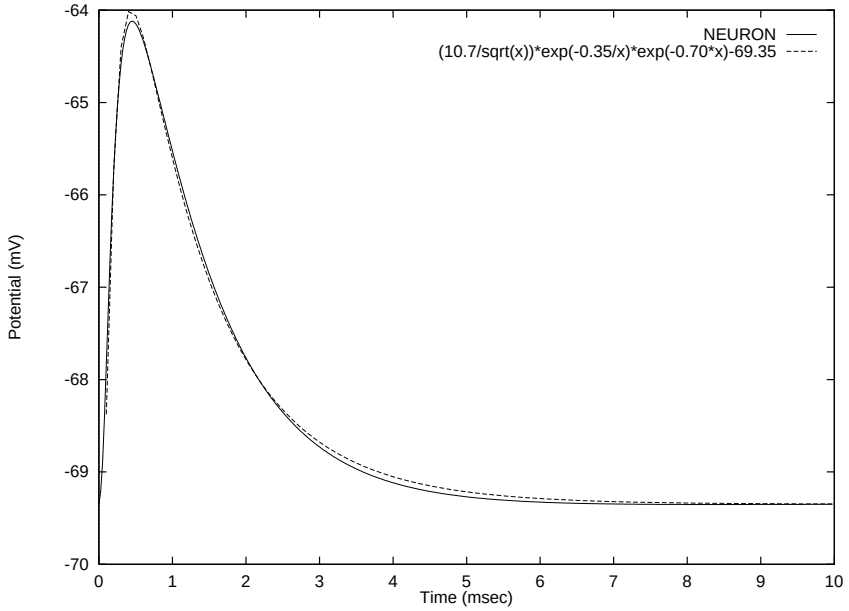

Figure 3.3: Comparison of PSP traces: Simulation on NEURON v2.0 versus Closed form solution.

We also tested the results of linear summation of PSP's against simulations on the toy neuron described above (the toy neuron violated the assumptions delineated in (Walsh & Tuckwell, 1985)) and found an agreeable fit. Figure 3.4 displays the result of one such experiment.

The results of the simulation experiments that are presented in Chapter 7 are based on a model of a neuron, the membrane potential of which is computed as a linear summation of the above noted closed form solution to passive conductance of potential across individual dendrites. It should, however, be noted that the model of the neuron that we formulate and analyze in this thesis is not so constrained. The potential in the simulation experiments is computed as a linear summation for reasons of tractability. Moreover, as will become clear in Chapters 8 and 9, this issue does not play a significant role in the determination of the generic qualitative dynamics of systems of neurons.

3.5 Generation and Conduction of Action Potentials

If the cell membrane is depolarized (the membrane potential is driven towards 0 mV by injecting a current) by a critical amount, it generates a large but brief ($\approx$ 1 msec) active response known as an *action potential* or *spike*. The membrane potential at which the action potential

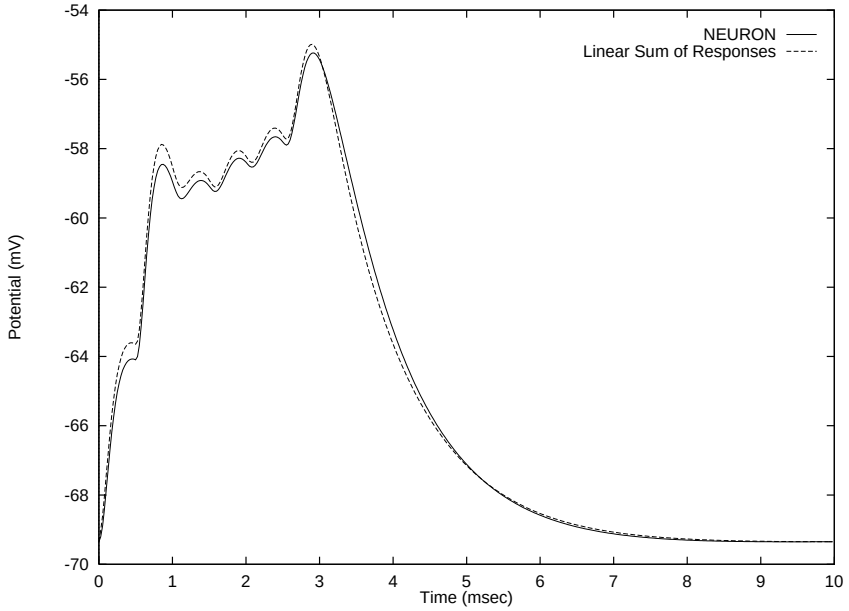

Figure 3.4: Comparison of PSP integration: Simulation on NEURON v2.0 versus Linear summation of individual solutions.

is triggered varies from -55 to -45 mV (depending on the morphological class of the neuron) and is called the *threshold*. The action potential is generated in an all-or-none fashion; increase in current strength (to depolarize the membrane) above the threshold does not increase the amplitude of the action potential or change its shape (Adrian & Zotterman, 1926). The action potential not only eliminates the resting potential (at ≈ -60 mV) but actually reverses the membrane potential for an instant, raising it to approximately $+55$ mV. Upon reaching this peak, the potential rapidly repolarizes to a value below the resting potential in a process referred to as *afterhyperpolarization*. Following afterhyperpolarization, the potential gradually (over several msec) decays to the resting level. Unlike the passive conductance of PSP's described in the previous section, the action potential is conducted without any loss of amplitude.

The generation of an action potential is the result of a dramatic, albeit transient, increase in the ionic conductance of the membrane (an approximately forty-fold increase resulting from the activation of voltage sensitive ionic channels). The initial increase in the ionic conductance during the action potential is due to a sudden reversal in the permeability characteristics of the membrane; it temporarily becomes more permeable to Na^+ ions than to K^+ ions. Depolarization of the membrane increases Na^+ permeability, producing an influx of Na^+ ions into the cell and causing further depolarization, which increases Na^+ permeability even more.

This catastrophic event, known as Na^+ current *activation*, eventually reverses the membrane potential.

The sudden reversal of the membrane potential is, however, transient. The progressive depolarization described above shuts off the Na^+ permeability in due course, a process labeled sodium current *inactivation*. This is accompanied by an increase in the already high K^+ permeability, a process labeled *delayed rectification*. Na^+ current inactivation and delayed rectification together result in the afterhyperpolarization of the membrane potential. At this point the repolarization of the membrane potential leads to the *deactivation* of the K^+ and Na^+ channels and the membrane potential gradually returns to its resting level. The removal of the depolarization also leads to the *deinactivation* of the Na^+ channels and the membrane is ready for the next action potential.

Immediately following an action potential there is a time interval of approximately 1 msec during which no stimulus, however strong, can elicit a second action potential. This is called the *absolute refractory period*, and is largely mediated by the inactivation of the sodium channels. After the absolute refractory period there is a *relative refractory period* during which an action potential can be evoked only by a stimulus of much larger amplitude than the normal threshold value, a condition that results from the persistence of the outward K^+ current.

The above process is modeled by replacing the partial differential equation 3.5 derived in the previous section to model passive conductance of potential across dendrites, by the more general equation

$$i_m = c_m \frac{\partial v_m}{\partial t} + g_{\text{Na}}(v_m - V_{\text{Na}}) + g_{\text{K}}(v_m - V_{\text{K}}) + g_{\text{L}}(v_m - V_{\text{L}}), \tag{3.10}$$

where $g_.$'s are the voltage sensitive membrane conductances for the respective ions and $V_.$'s their respective equilibrium potentials (L denotes leakage and is a variable that represents Cl^- and all other organic ions lumped together). Furthermore, the relation between the various conductances and the membrane potential is modeled based on empirical data. One such set of equations (Hodgkin & Huxley, 1952a-d; Hodgkin, Huxley & Katz, 1952),

$$i_m = c_m \frac{\partial v_m}{\partial t} + \bar{g}_{\text{Na}} m^3 h(v_m - V_{\text{Na}}) + \bar{g}_{\text{K}} n^4 (v_m - V_{\text{K}}) + \bar{g}_{\text{L}}(v_m - V_{\text{L}}), \tag{3.11}$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m, \tag{3.12}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h, \tag{3.13}$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n, \tag{3.14}$$

called the Hodgkin-Huxley equations, agrees well with physiological data. $\alpha_m, \beta_m, \alpha_h, \beta_h, \alpha_n$ and β_n are functions of v_m given as

$$\alpha_m = \frac{0.1(v_m+25)}{e^{\frac{v_m+25}{10}}-1}, \qquad \beta_m = 4e^{\frac{v_m}{18}}, \tag{3.15}$$

$$\alpha_h = 0.07e^{\frac{v_m}{20}}, \qquad \beta_h = \frac{1}{e^{\frac{v_m+30}{10}}+1}, \tag{3.16}$$

$$\alpha_n = \frac{0.01(v_m+10)}{e^{\frac{v_m+10}{10}}-1}, \qquad \beta_m = 0.125e^{\frac{v_m}{80}}. \tag{3.17}$$

There have been several attempts to reduce the complexity of these equations while maintaining their qualitative properties (Fitzhugh, 1961; Nagumo, Arimoto & Yoshizawa, 1962). The prospect of a closed form solution to the above process, however, remains bleak.

3.6 Beyond the Basic Model

The true electrophysiology of neurons in the central nervous system (CNS) is substantially more complex than the basic electrophysiology elucidated in the previous sections. The variations in the electrophysiology of morphologically distinct classes of neurons in the CNS allows them to operate in different firing modes. Several of these modes have been cataloged and their electrophysiological basis identified.

The simplest mode of behavior (manifest by the model described in the previous sections) is called “regular-firing” and is characterized by the generation of action potentials one at a time. Motor neurons in the brainstem and the spinal cord are examples of neurons that lie in this category. Such neurons also exhibit a brand of linearity of behavior: the longer the depolarization of their somas, the longer their discharge, and the more intense the depolarization, the higher the frequency of their discharge.

A slight modification of this basic behavior is characterized by neurons that, upon sustained depolarization of their somas, generate spike trains that exhibit a marked decay in spike frequency over time, a process known as *spike frequency adaptation.* Examples of cells that discharge in this manner are cortical and hippocampal pyramidal neurons (McCormick et al.,

1985; Connors & Gutnick, 1990). The basis for this behavior has been identified to be the activation of a slow K^+ afterhyperpolarization current that builds up over several action potentials.

A third category of behavior is characterized by an intrinsic propensity to generate bursts of spikes instead of single action potentials. Thalamic relay neurons, some pyramidal and stellate cells, and neurons in the inferior olive spike in this manner (Connors & Gutnick, 1990). The clusters of action potentials are generated by the activation of specialized Ca^{2+} currents that, by virtue of their slow kinetics, allow the membrane potential to remain depolarized for sufficiently long periods of time so as to generate several regular $Na^+ - K^+$-dependent action potentials.

Yet another category of behavior is characterized by relatively short duration (< 1 msec) action potentials that discharge at relatively high frequencies ($> 300\ Hz$). Inhibitory interneurons in the cortex, the thalamus, and the hippocampus display this kind of behavior (Connors & Gutnick, 1990).

Finally, there is a class of neurons called *pacemaker* neurons that spontaneously generate relatively low frequency ($1 - 10\ Hz$) spike trains. These neurons innervate wide regions of the brain and appear to set the "state" of the entire local network.

It is now well recognized that these diverse behaviors are the result of the wide variety of ionic channels that are present in the neurons in addition to the basic Na^+ and K^+ channels described in the previous sections. Some of these channels activate and rapidly inactivate, whereas others do not inactivate. Some are fast acting while others display very slow (> 1000 msec) kinetics. Some are directly activated by variations in the membrane potential while others require second messengers for activation.

Several of these ionic channels have been identified, and the search and classification of others remains an integral part of ongoing research in the field.

3.7 Synaptic Transmission

The effects of an action potential arriving at a presynaptic terminal is transferred to the postsynaptic neuron through a chemically mediated process. Currents for excitatory (encouraging

the neuron to spike) and inhibitory (discouraging the neuron to spike) synaptic actions are generated in the postsynaptic neuron via changes in membrane conductance (Fatt & Katz, 1951, 1953). The biophysical processes involved in several aspects of synaptic transmission are not yet completely understood, and the phenomenon continues to inspire intense research.

Synaptic transmission is fairly rapid (synaptic delays range from 0.3 to 0.5 msec). The nervous system achieves such speeds by confining transmitter molecules to *synaptic vesicles* (rather than leaving them free floating in the plasma) that are docked in specialized sites along the presynaptic membrane called *active zones*.

The depolarization that results from the arrival of an action potential at a synaptic terminal leads to the activation of Ca^{2+} channels that are strategically co-located with the synaptic vesicles in the active zones. The opening of the Ca^{2+} channels causes an intense rise in Ca^{2+} ion concentration in the immediate vicinity of the channels, thus creating Ca^{2+} rich fields known as *microdomains*.

The intense rise in Ca^{2+} ion concentration triggers the fusion of the synaptic vesicles with the plasma membrane (a process known as *exocytosis* that is believed to be mediated by several calcium-binding proteins) which results in the transmitter molecules being released into the *synaptic cleft*. The released transmitter molecules drift across the cleft and bind with receptors on the postsynaptic membrane. This leads to opening/closing of various chemically gated Na^+ and K^+ channels on the postsynaptic membrane giving rise to a postsynaptic current (PSC). The resultant effect can be one of an excitatory postsynaptic potential or one of an inhibitory postsynaptic potential.

It was discovered around fifty years ago that the release of synaptic vesicles from their respective sites in the presynaptic terminal takes place in a stochastic manner (Fatt & Katz, 1951). This led to the postulation of the *quantal hypothesis* (del Castillo & Katz, 1954), according to which neurotransmitter molecules are released from single presynaptic terminals in quantal packets corresponding to synaptic vesicles, and the strength of a synaptic transmission is the product of three parameters: *Strength* $= pnq$, where p is the probability of triggering quantal release during a presynaptic action potential, n is the number of readily releasable quanta available (which depends upon the number of release sites in the presynaptic terminal), and q is the response (which can be excitatory or inhibitory) of the postsynaptic neuron to a single quantum

of neurotransmitter.

Excitatory postsynaptic potentials (EPSP's) are generated by a sudden increase in g_{Na} often accompanied by an increase in g_{K}. These increases are simultaneous and not sequential. Moreover, the increase in g_{Na} is not voltage dependent as in the case of action potentials. Because g_{Na} and g_{K} increase simultaneously, the EPSP is a compound potential that lies midway between E_{Na} ($+55$ mV) and E_{K} (-75 mV). In other words, an excitatory synaptic action drives the membrane potential from its resting value (-60 mV) past the threshold (-45 mV) to a value of approximately -10 mV (that is, about 50 mV above resting potential).

Inhibitory postsynaptic potentials (IPSP's) are generated by sudden increases in g_{K} and g_{Cl}. IPSP's inhibit neurons from firing in two different ways. First, by increasing the conductance to Cl^-, synaptic inhibition increases the overall conductance of the membrane. Any EPSP generated by a postsynaptic current is subsequently lowered. This process is labeled *shunting* or *short circuiting*. Second, inhibitory synaptic action due to increased conductance usually hyperpolarizes the membrane, moving it further away from threshold.

3.8 The Neuron-Synapse Ensemble: Should it be Modeled as a Deterministic or a Stochastic Unit?

Modeling any physical system entails making choices. The first decision that confronts our undertaking is whether the neuron-synapse ensemble ought to be modeled as a stochastic or a deterministic unit.[5] We have elected to pursue a deterministic model. In the remainder of this section we present the reasons that led to this choice.

Whether the neuron-synapse ensemble should be modeled as a stochastic or a deterministic unit is an issue that is closely related to the question of the reliability of the nervous system. There is now mounting evidence that the mammalian (as well as others) nervous system is highly reliable. For example, responses to the arrival of *single* photons in retinal receptor cells have been shown to be highly reproducible (Baylor, Lamb & Yau, 1979; Baylor, Nunn & Schnapf, 1984). Based on data pertaining to the spontaneous noise in these cells, it has been

[5] At issue is whether a fixed input into a neuron should produce a fixed output, or a variable output based on some probability distribution.

demonstrated that the limits to the reliability of night vision are set by the photoreceptor cells, that is, little additional noise is introduced by subsequent neuronal processing (Barlow, 1988; Donner, 1989; Bialek & Owen, 1990; Rieke, Owen & Bialek, 1991). Similar results have been reported for spatial discrimination (Parker & Hawken, 1985) and somatosensory tasks (Valbo, 1995).

The neuron-synapse ensemble has traditionally been modeled as a stochastic unit for the simple reason that repeated presentation of the same sensory stimulus elicits variable response. This apparent noise can, however, be the result of the ineluctable noise in the stimulus itself, as well as information feedback from systems that are not driven by the same stimulus, for example, when recording from the primary and secondary sensory cortex (these areas are of the order of four synapses removed from the sensory receptors). A second reason for the choice has been the apparent stochastic nature of spike train recordings from neurons in the cortex. However, as shall be demonstrated in Chapter 7, such recordings can also be elicited from a deterministic system.

If the neuron-synapse ensemble is indeed an unreliable unit (a case that warrants the use of a stochastic model for the unit), there are two possible courses that the nervous system can adopt in order to maintain reliability: (i) reduce the noise-induced variance in the signal by choosing the number of times the neuron spikes in a relatively large time window as the relevant variable (rate coding), or (ii) reduce the variance by choosing the instantaneous spike rate averaged over a large population of neurons as the relevant variable (population coding).

In order for rate coding to be a viable scheme, modulations in the signal must be slow compared to the average spiking rate of the neuron. It has, however, been shown that not only do modulations in natural signals occur over time scales comparable to typical interspike intervals (ISI's) recorded in the cortex, but also that behavioral decisions are made over the same time scale (for example, sonar detection by bats (Simmons, 1989; Dear, Simmons & Fritz, 1993), bat evasion by moths (Roeder, 1963), preattentive discrimination by monkeys and cats (Knierem & van Essen, 1992; Reid, Soodak & Shapley, 1991), and tactile discrimination by rats (Fee & Kleinfeld, 1994).).

Population coding, on the other hand, can reduce the noise induced variance in the signal significantly only if the activity of the ensemble of neurons from which the average spiking

rate is computed, is uncorrelated. There is, however, strong evidence that this is not the case (Zohary, Shadlen & Newsome, 1994). Although there exist more robust schemes (such as maximum likelihood estimates) that can extract the appropriate variable under such conditions, they are based on the availability of the entire joint probability distribution of the spike rates of the neurons. Over the time scales under consideration, these schemes approach temporal coding (where spike times are relevant).

It is now widely held that cortical neurons are quite reliable. Experimental results have demonstrated that cortical neurons are capable of extraordinary precision (to within ≈ 1 msec) when transforming injected currents into spike trains (Mainen & Sejnowski, 1995). Propagation of action potentials on axons has likewise been shown to be relatively noise-free (Lass & Abeles, 1975).

Noise and transmission failure at synapses is, however, a hotly debated issue. Some in the field have reported that excitatory synapses in the cerebral cortex and the hippocampus are extremely unreliable; the value of p (from the equation *Strength* $= pnq$) in response to a single spike has been estimated at 10% or lower (Rosenmund, Clements & Westbrook, 1993; Hessler, Shirke & Malinow, 1993; Allen & Stevens, 1994; Stevens & Wang, 1994, 1995; Dobrunz & Stevens, 1997), whereas others have reported that synapses in the same areas are quite reliable (p is estimated upwards of 80%) (Thomson, Deuchars & West, 1993; Markram, Lübke, Frotscher, Roth & Sakmann, 1997; Larkman, Jack & Stratford, 1997). In an attempt to explain this disparity Hardingham & Larkman (1998) have demonstrated that quantal transmitter release is temperature dependent in cortical synapses, and that experiments performed at room temperature could lead to an exaggerated impression of their unreliability.

Finally, the notion that spike timing across an ensemble of cells plays an important role in encoding various aspects of a stimulus is gaining support from experiments in a variety of systems such as locust olfaction, electric fish electrosensation, cat and monkey vision, audition and olfaction (Chung, Raymond & Lettvin, 1970; Freeman, 1975; Strehler & Lestienne, 1986; Abeles, 1990; Richmond, Optican & Spitzer, 1990; Krüger, 1991b; Bialek, Rieke, de Ruyter van Steveninck & Warland, 1991; Bialek & Rieke, 1992; Bair, Koch, Newsome & Britten, 1994; Singer & Gray, 1995; Bair & Koch, 1996; Decharms & Merzenich, 1996; Laurent, 1996; Wehr & Laurent, 1996; Gabbiani, Metzner, Wessel & Koch, 1996; Lisman, 1997).

The apparent contradiction between evidence of unreliable synaptic transmission and that of reliable spike trains may be the outcome of short term synaptic plasticity. That the strength of synapses change in a history dependent manner during short term plasticity is well documented (Magleby, 1987; Zucker, 1989; Fisher, Fischer & Carew, 1997; Dobrunz & Stevens, 1997; Markram & Tsodyks, 1996; Tsodyks & Markram, 1997; Abbott, Varela, Sen & Nelson, 1997; Varela, Sen, Gibson, Fost, Abbott & Nelson, 1997; Zador & Dobrunz, 1997). Since most central synapses have very few release sites (n ranges from 1 to 5 (Raastad, Storm & Andersen, 1992; Gulyas, Miles, Sik, Toth, Tamamaki & Freund, 1993; Bolshakov & Siegelbaum, 1995; Schikorski & Stevens, 1997)), it is conceivable that in order to achieve a rapid and wide range of efficacy, synapses modulate transmission in a deterministic history dependent manner.

Since the temporal sequence of ISI's is abstracted away in a stochastic model, there is little hope that such a model would shed light on all aspects of information processing in a neuronal system. Second, while thermodynamic noise in the guise of random miniature postsynaptic potentials do exist, their mean amplitude is at least an order of magnitude smaller than the mean amplitude of the postsynaptic potential elicited by the arrival of a spike at a synapse. The impact of such noise on the dynamics of the system is best identified by contrasting the dynamics of a noise-free model to that of a model augmented with the appropriate noise. We have therefore chosen to investigate a deterministic model for the neuron.

3.9 Summary

The neuron constitutes the basic building block of the nervous system. In this chapter, we have briefly described the biophysical processes that underlie the dynamics of a neuron, including the generation of the membrane potential, the passive conduction of synaptic input across the dendritic arborization, the generation of the action potential and the transmission of the action potential across a synapse.

While we do not deny that the neuron-synapse ensemble, like any other physical device, must admit some noise, we have argued that in the light of the evidence supporting the relevance of spike timing in information representation and transmission, it is logical to begin with the analysis of a deterministic system.