Chapter Six

Nonlinear Dynamics and Signal Processing in Neurons

6.1 INTRODUCTION

How do living systems process, respond, remember, and adapt to information from their environment? The prior chapter described ways that bacteria, like *E. coli*, sense chemical gradients in a way that enables them to spend more time in good environments and less time in bad environments. This sensing is enabled by a nonlinear kinase cascade circuit connecting signals at the surface with changes in regulatory dynamics and of physical dynamics (the counter-clockwise or clockwise rotations of the flagellar bundle). In that sense, perhaps the "brain" of *E.coli* can be thought of as nothing more than a nonlinear kinase cascade circuit. Yet what *E. coli* does seems rather remarkable. The evolution of such kinase cascades includes many components and feedbacks operating in different regimes such that a bacterium can sense/respond even without an actual brain, i.e., without white matter, dark matter, neurons, or glia cells. Hence, it would seem that the example of *E. coli* does something else. It illustrates - in an important real-life system - that the capability of sensing is embedded not in one particular "sensing" protein, but rather in the system itself.

This substrate-independent approach to information processing is even more apparent when transitioning from chemotaxis in bacterial cells to signal processing in the brain. This transition would seem to require a new vocabulary corresponding to the parts list, not just of neurons but of neural circuits. This chapter will indeed introduce new components, however it will not begin and end with parts. Instead, the tack of this chapter continues to follow the rule that it is not just structure that begets function, but rather that it is feedback that begets dynamics and principles. Neurons are not just components of complex living systems with highly specialized components. They are more: living dynamical systems where the sum is far greater than the parts. Such a dynamical perspective is not universally adopted in introductory courses on neuroscience, but it is the perspective espoused by certain theoretical neuroscientists including Eugene Izhikevich, who offered this sage advice:

> Information processing depends not only on the electrophysiological properties of neurons but also on their dynamic properties.
>
> Even if two neurons in the same region of the nervous system possess similar electrophysiological features, they may respond to the

> same synaptic input in very different manners because of each cell's bifurcation dynamics.
> -Eugene Izhikevich (Izhikevich 2007)

In my view, this quote suggests that answers to deep problems in information processing will not be found by looking at cellular structure alone. Worse yet, we might even find the wrong answer if only turning to cell physiological differences to explain observed differences in behavior. Instead, the physiological system, and particularly its feedbacks, might enable the system - whether a bacteria, neuronal cell, or cardiac cell - to exhibit emergent dynamics that are not characteristic of lower scales of organization. Moreover, this concept applies to systems of cells, i.e., such that a brain or heart exhibits emergent, systems level behaviors that reflect both the local rules as well as emergent properties.

Yet, this quote does not mean we should forego the details of the physiology. Instead, this information is essential to understand the basis for the kinds of feedbacks that govern different classes of (potential) dynamical behavior. Indeed, evolutionary adaptations have fixed and proliferated precisely because of the expanded dynamical features that could be accessed via a new set of physiological mechanisms. These physiological mechanisms extend from cells to whole organisms. For example, in the classic example of perturbations to a zebrafish larvae, a stimulus experienced at the tail end is sensed within milliseconds by sensory neurons. Signals are then transmitted through the larvae's nervous system to the central nervous system where the larvae reacts through a combination of motor neurons and muscle neurons, rapidly changing its body conformation and swimming away from the experimental water pulse. These kinds of evolved adaptations have many benefits, in this particular case, rapid sensing of changes in the fluid context provides protection from the actions of potential predators. Figure 6.1 depicts the movement of the zebrafish larvea away from an experimental water pulse stimulus (left panel) and away from a larval dragonfly (right panel), with individual movements depictedover a 30 ms time series (bottom panel). This kind of integrative response has a core template: the reaction of individual neurons to stimulus.

Hence, this chapter will focus on understanding neuronal dynamics as a first step towards understanding what a brain does. This first step will be enabled by recognizing that a key template for learning is the notion of "excitability". That is we will examine excitable systems that can filter out small perturbations, while reacting to sufficiently large perturbations via extended, often sharp, departures from its rest state and relax back slowly, over time. Such excitability is a template for information processing occuring at the level of single neurons (see Figure 6.2. This Figure, reproduced from Hodgkin and Huxley's class and Nobel Prize winning work, shows the change in associated conductance in a squid axon given a fixed voltage. The use of an isopotential experiment meant that Hodgkin and Huxley (HH, hereafter) could systematically change voltage differences and measure the response of the system. The large size and accessibility of the axon made it ideal for the direct evaluation of changes in the

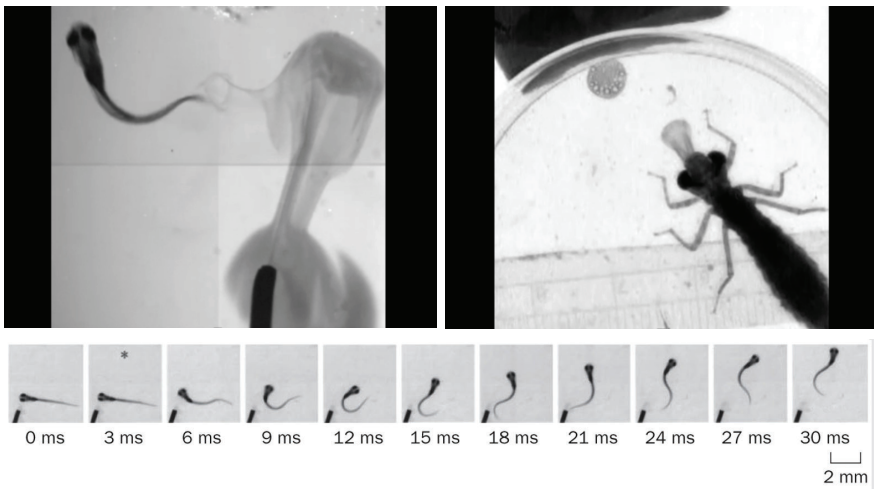


Figure 6.1: Electrical signaling in the central nervous system underlies the rapid reaction of organisms to external stimuli. The sequence of images, reprinted from (**?**), illustrate the rapid reaction of a zebrafish larvae to experimental stimulus (water pulse) as well as the action of a potential predator (a dragonfly larvae). Reproduced from (Luo 2015).

action potential and comparison to model predictions. Critically, the response is highly nonlinear, incluhding a rapid spike in current followed by a slower relaxation. It is worth noting that the numerical calculations were enabled via a hand operated Brunsviga mechanical calculator (for a historical perspective, see (Schwiening 2012)).

Thankfully, there is a deep foundation to build upon to understand excitability and information processing in neurons, beginning with the classic work of Hodgkin and Huxley. That then is our next step: trying to make sense of the Hodgkin-Huxley model – at first glance, what seems like an impenetrable work from a different time. But it has stood the test of time precisely because the theory corresponds to the real world. As Jim Peebles, the Nobel Prize winning cosmologist remarked (Peebles 2019):

> [I]t is so easy for us theorists who build wonderful castles, beautiful ideas. Sometimes, it is remarkable, sometimes these beautiful ideas prove to be close to what the observations tell us. But often and also they turn out to be wrong. No great surprise, but time will tell, and it is the measurements that tell us.

The work of Hodgkin Huxley is a beautiful, but complicated, it is beautiful because the idea has turned out to be right. The goal then of this chapter is to

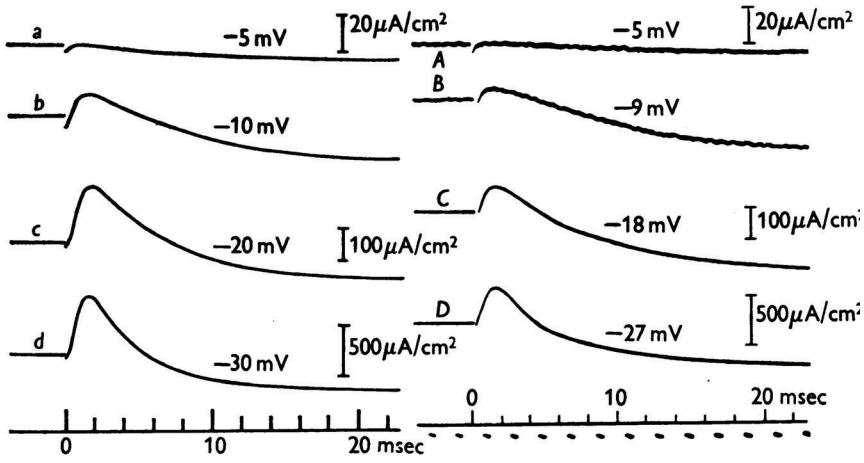


Figure 6.2: Rapid changes in transmembrane current enabled by holding the transmembrane potential at a fixed voltage, enabled by the use of a voltage clamp. As sodium ions enter the cell during the initial depolarizaion, the release of potassium ions during the fall of the action potential. Note that the relaxation to rest state occurs much later (Hodgkin and Huxley 1952). The sequence of images include numerical calculations of model predictions (left) with experimental measurements (right) given variation in the externally fixed potential difference, a significant advance over prior (related) work by Cole and Curtis (1939) (Cole and Curtis 1939).

decipher the following set of equations:

$$\begin{aligned} I &= C\frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_K n^4 (V - E_K) + ... \\ &\quad \bar{g}_{Na} m^3 h (V - E_{Na}) + \bar{g}_l (V - E_l) \qquad (6.1) \\ \frac{\mathrm{d}n}{\mathrm{d}t} &= \alpha_n(1-n) - \beta_n n \qquad (6.2) \\ \frac{\mathrm{d}m}{\mathrm{d}t} &= \alpha_m(1-m) - \beta_m m \qquad (6.3) \\ \frac{\mathrm{d}h}{\mathrm{d}t} &= \alpha_h(1-h) - \beta_h h. \qquad (6.4) \end{aligned}$$

These are the HH equations. The expected value of the current, I, is precisely what was measured and compared to experiment as shown in Figure 6.2. These equations don't fit in the usual T-shirt size aphorisms ($E = mc^2$ and the like), and they are sufficiently opaque as to suggest the intent of invoking them is to admire them. Hence, for now, think of these equation as a reference point;

something to refer to, or name, but naming is not equivalent to understanding. To understand requires more work.

This chapter will aim deeper, shedding light on the basis of behavior, learning, memory beginning with the information processing of a single neuron. Hence, the first part of this chapter will walk in the path of Hodgkin and Huxley to understand what these equations mean, how they were derived, and how they can help to explain the dynamical behavior of single neurons. Then, using the potential processing features of a single neuron, the second part of the chapter will make a link both towards collective behavior, learning, amd memory in the central nervous system but also explain how productive analogies to learning *in vivo* are the basis for learning (deep or otherwise) *in silico*.

6.2 THE BRAIN: MEMORY, LEARNING AND BEHAVIOR

6.2.1 What is the Brain For? Really

The nervous system is an information processing machine that serves as a gateway between two physical environments – the body and the outside world. This gateway is important. Although what the brain does can be abstracted strictly in terms of information and signal processing, it is critical to recognize that the brain is not a disembodied entity. Hence the processes of signalling, communication, memory, learning, and behavior all are part of an extended, complex system. Conventionally this system is broken down into two categories: the central nervous system (CNS) and the peripheral nervous system (PNS). For humans, the central nervous system, aka the brain, is connected to the body via a system of nerves (e.g., cranial nerves and spinal nerves) as well as a spinal cord. This extended system also provides context for the flow of information. Interactions with the environment are mediated by sensory receptors, which initiate signals that are transmitted to the CNS via what is termed the afferent path. Then, signals reflecting the outcome of neuronal interactions in the CNS alter the state of the CNS and also can trigger signals propagating from the CNS to effector cells and tissue via an efferent path. Such processes take time, are conducted in the presence of noise, and uncertainty, but are also the basis for behavior, learning, and memory.

What does the brain do? In brief, the brain-body interactions enable behavior, but it is the brain that enables modifications to behavior via learning and memory. It would seem that terms so universally used as learning or memory require no definition. But definitions will help center our goals. Here are a few:

Behavior: Actions taken by an organism, usually in the context of its environment.

Learning: Adaptive change in behavior resulting from experience.

Memory: The retention of learning, allowing learning (i.e., adaptive behavior) at a later time.

These three intertwined words are critical to placing the neuron, neuronal dynamics, and the brain and cognitive sciences in context. In order for there to be adaptive behavior, there must be some way for an organism to adapt. And, to adapt requires that an organism recognizes an environmental context that is related to prior experiences and then potentially does something different. This recognition implies an internal represention of experience, that is a map (or transformation) of sensory input from the environment that can then be used as the basis for computations. Indeed, that is what the nervous system does. The nervous takes in experiences via sensory receptors and then transmits those signals to the brain where the brain generates neural output patterns that inform responses and changes in behavior. That unidirectional flow, from environment to behaviors, becomes a circuit, when a set of the outputs is directed at the brain itself, thereby modifying behavior. This learning requires representations of the environments, at least in a statistical sense, that can be used as the basis for recognition of similar environments and/or contexts. Hence, learning requires a computation - first comparing a prior experience (via memory) to a present experience - and then the adaptive change requires that the outputs of the brain modify itself (see Figure 6.3).

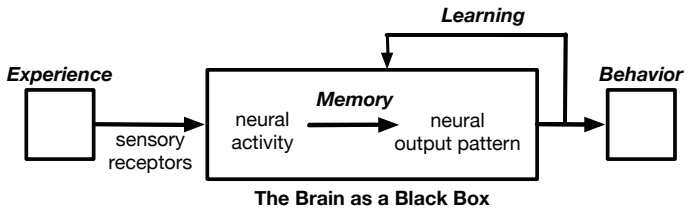
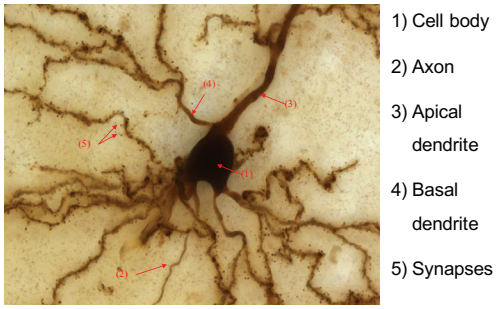
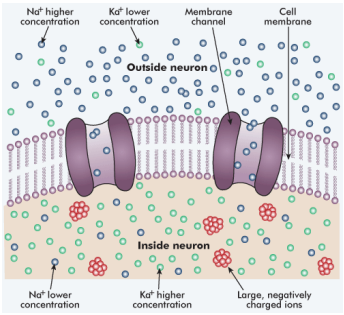


Figure 6.3: Schematic of behavior, memory, and learning in the brain. Experiences are detected by sensory receptors (and sensory neurons) that than transmit information to the central nervous system. Neural activity is then encoded as an output pattern which is transmitted back to sensory, motor, and muscle neurons that can change behavior. The outcome of behavior then modifies the very neural activity and output patterns that drive behavior, connecting learning to long-term changes (i.e., memory).

A full description of the parts list of the nervous system lies outside the scope of this chapter – but can be found in any one of many standard neuroscience textbooks (e.g., (Luo 2015)). In brief, the pathway from the environment (including both the internal and external components) involves the propagation of information and signals via sensory receptors at the surface of the body and internally via nerves and ganglia. This information is then transmitted to the central nervous system where it is processed and then outputs are directed both to the CNS as well as to motor components. The transmission of signals via the efferent path include motor nerves as well as components of the visceral motor



histological staining of a single neuron in a rat brain (photo credits: Cristiaan de Kock, CNCR, VU, Amsterdam)



Credit: Principels of Neurobiology, Garland

Figure 6.4: Two view of a neuron. (Left) Histological staining of a single neuron by C. de Kock, including cell body, axon, apical dendrite, basal dendrite and synapses (). (Right) View of ion exchange across the membrane of neurons (Luo 2015).

system leading to changes in what are term 'effectors' including muscles and glands. This repeated process links information and behavior, the physical and biological world, and yet at its core requires templates of computation. These templates are neurons, and they deserve their own introduction.

6.2.2 Neurons, A Synopsis

Neurons are cells essential to behavior, learning, and memory. There are many kinds of neurons, differing in their location (brain, somewhere else), their structure (size and connectivity), and function (e.g., motor neuron, sensory neuron, pyramidal cell). Neurons are composed of a cell body, with electrical input coming from other neurons via axons and transmitted forward via dendrites. The connections between axons and dendrites are called synapses. This electrical input represents information, transmitted from other neurons. The dendrites collect this information, integrate it, and then the firing of the neuron transmits a new signal (and new information) to other neurons.

Figure 6.4 provides two views of a neuron. The first is a histological stain of components. The second is a schematic of the localization and distribution of ions on either side of the neuron's cell membrane. As is apparent, there are different concentrations of ions on either side of the cell membrane. And, as you may recall from basic electricity and magnetism, a difference in charged particles implies there is a difference in the *electrical potential*, what in the parlance of neuroscience is termed the 'transmembrane potential' or 'transmembrane voltage". Differences in electrical potentials lead to forces, and forces lead to changes in the mobility and positions of particles, in this case ions.

In vertebrates, information generally flows from dendrites to cell bodies to

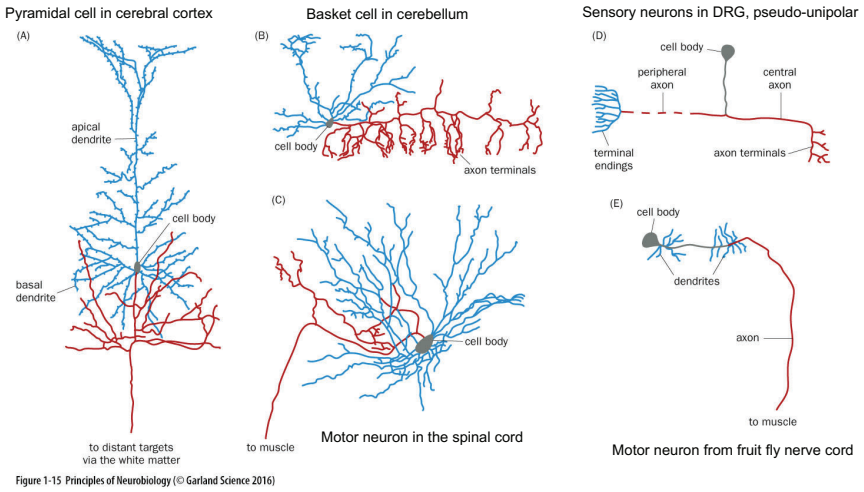


Figure 6.5: Neurons in a vertebrate context. Each of these examples reveals the position of a neuron in its context, spanning neurons in the brian, to sensory neurons, to motor neurons (Luo 2015).

axons as part of networks. A few examples of these networks can be seen in Figure 6.5. . As is apparent, the input can involve the integration from multiple dendrites and outgoing signals can then split, enabling distribution of signals to multiple neurons. For example, sensory information transmitted from a sensory neuron through nerves in the spinal cord would be transmitted via the brain stem and thalamus to the primary somotasensotyr cortex, and after processing a signal would be relayed via the primary motor cortex through nerves in the spinal cord to a motor neuron which would trigger the movement of muscales and - voila - voluntary movement. Indeed, this example is precisely one of many drawn in SnapShot (timescales in cell biology) by Ron Milo and colleagues as part of their BioNumbers project (Milo et al. 2010). In this example, they ask the question "How fast can olympic athletes respond to the starter's pistol". Here is their answer

> Upon hearing the shot, athletes process and propagate an electric impulse from the brain all the way to their feet (1 m). Considering the speed of the action potential (10-100 m/s), this implies a latency of 10-100 ms regardless of other processes, such as the speed of sound and signal processing in the brain. The best athletes respond after 120 ms, and a reaction time below 100 ms is immediately disqualified as a false start.

This insight is telling. It connects a biophysical process at one scale (action potential propagation) to a behavior that seems familiar, while placing limits

on the behavior precisely because of the biophysical nature of the nervous system. This example reinforces the idea that the nervous system is not just an information processing system; it is part of a living organism (i.e., a complex bio-chemical-physical system). Yet the insight is also limited. Why is the speed of the action potential 10-100 m/s? What enables the action potential to propagate? How does a signal turn into a response in the first place? These are deeper problems and taking a distance divided by a velocity to get a time will provide an answer, but an incomplete one. A deeper answer requires delving in to the neuron itself.

In walking the path of HH, we will zoom in to the neuron itself and specifically to the dynamics associated with the movement of ions across the membrane given an electrical signal that arrives via the dendrites to the neuronal cell body. This process provides the basis for an answer not just to the question raised by Milo and colleagues but to a whole class of problems related to information processing and excitability.

6.3 WALKING IN THE PATH OF HODGKIN AND HUXLEY

6.3.1 The HH equations: a far-off destination

The 1952 paper by Hodgkin and Huxley is remarkable on many levels. It combines theory and experiment. It is quantitative. It remains deeply influential. And yet, it is also difficult to read and, at some level, intimidating. It arrived on the scene, *sui generis*, well ahead of its time, and yet done so well that it could influence a field that could not necessarily recapitulate the key steps of the mathematical model. Here are the central equations, what are now known as the Hodgkin-Huxley (HH) model:

$$\begin{aligned} I &= C_M \frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_K n^4 (V - V_K) + ... \\ &\quad \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l) \qquad (6.5) \\ \frac{\mathrm{d}n}{\mathrm{d}t} &= \alpha_n (1 - n) - \beta_n n \qquad (6.6) \\ \frac{\mathrm{d}m}{\mathrm{d}t} &= \alpha_m (1 - m) - \beta_m m \qquad (6.7) \\ \frac{\mathrm{d}h}{\mathrm{d}t} &= \alpha_h (1 - h) - \beta_h h \qquad (6.8) \end{aligned}$$

At this stage I will forgo much by way of a typical introduction, including omitting overbraces to explain the terms. Suffice it to say that V is voltage and m, n, and h are other response variables of the neuron. The purpose of the next series of sections is to break down this model, part by part, and reconstruct it, so that at the end of this chapter you will understand what these equations means and have some biological as well as biophysical insight as to how a neuron - operating given these principles - could exhibit an astonishing array of dynamical behaviors, including nonlinear response to stimuli and excitability.

6.3.2 Where do the ions go?

In order to understand the dynamics of neurons, let's first consider what would happen if there was an imbalance of particles to inside vs. outside of a cell. A cellular membrane is permeable to the passage of certain molecules (like water), while many molecules include sugars like glucose or charged ions, may only pass through via specialized transport mechanisms including facilitated diffusion, transporter, and/or channels. In the event that passage is feasible, consider the concentration just inside the membrane to be n_{in} and the concentration just outside the membrane to be n_{out}. A typical molecule may have a probability per unit time k to cross the membrane. In that case, the number per unit time per area (or flux) leaving the cell would be $J_{in\to out} = kn_{in}$ and the flux entering the cell would be $J_{out\to in} = kn_{out}$. Hence, the net flux out of the cell should be proportional to the difference in concentration, i.e.,

$$J = -k\left(n_{out} - n_{in}\right), \tag{6.9}$$

where the proportionality is due to the fact that the speed of transport introduces an additional factor. When there is a higher density outside then these molcules should flow inwards and vice-versa. If we assume that the actual concentration is a function of length (perpendicular to the surface), then $n(x + \mathrm{d}x) = n(x) + \frac{\partial n}{\partial x}$, i.e., the concentration a small distance away is equal to the current concentration plus the chemical gradient multiplied by the distance away. Hence the difference between internal and external concentrations can be written as $n_{out} = n_{in} + \frac{\partial n}{\partial x} w_m$ where w_m is the membrane width. Given a fixed length across the membrane then we can also write this as:

$$J = -D\nabla_r n(r,t) \tag{6.10}$$

where D is the diffusivity of the molecules and ∇_r denotes the derivative of the concentration with respect to the radial direction. The negative sign denotes the fact that flux moves in the opposite direction of the concentration gradient (from high to low concentrations). When there is a higher concentration outside then the net flux is negative (molecules move into the cell), where there is a higher concentration inside than the net flux is positive (molecules move out of the cell). Here D has units of area per time, $n(r,t)$ has units molecules per volume such that J has units of molecules per unit area per unit time. Now, if the molecules were uncharged and were not differentially produced inside or outside, we would expect that over time any imbalance in concentration would disappear. That is to say: diffusion of molecules would enable the inside and outside concentrations to reach an equilibrium, n^*. However, these molecules are charged. And that makes a difference.

Consider a case where there is an excess of potassium ions inside the cellular cytoplasm compared to the concentrations in the extracellular medium. Hence, according to Fick's law, these ions should diffuse out. However, potassium ions are positively charged. Hence, as potassium ions diffuse out there will be a slight

excess of net positive charge just outside the cell membrane and, by extension, a slight excess of negative charge just inside the cell membrane. As a consequence, there will be an electric field, ϕ, and associated force proportional to the gradient of the electric field, $\nabla\phi$, driving ions back inside the cell. The flux of charged ions resulting from interactions with the electric field should be

$$J^{(e)} = -qn\hat{\mu}\nabla\phi. \tag{6.11}$$

Hence, each particle should move in a direction at a velocity proportional to the applied force, namely, $v \sim \vec{F}$ where $\vec{F} = q\vec{E}$ given q the valence (e.g., positive, negative, and degree of valence) of the charge in units of electron charge and $\vec{E}$ is the electric field. But the electric field is the derivative of the potential, i.e., $\vec{E} = \nabla\phi$ where ϕ is the electric potential. Note that the proportionality constant is $\hat{\mu} = D/(k_B T)$ is the mobility constant where D is the diffusivity of the particle, k_B is Boltzmann's constant, and T is temperature. This logic applies to all ionic types.

As is evident, imbalances in ionic density leads to two fluxes working in opposite directions: (i) diffusion driving an excess of ions out of the cell; (ii) electrical force driving charged ions back into the cell. So, rather than just counting the diffusivity of neutral particles, we must account for both contributions to the flux of charged ions across the membrane:

$$J^{(e)}_{tot} = \overbrace{qn\mu\nabla\phi}^{\text{electrostatic flow}} - \overbrace{qD\nabla n}^{\text{diffusive flow}} \tag{6.12}$$

Hence, if there are more positive ions inside the cell than outside the cell, then there should be more diffusion flow from in to out (the second term above should large and negative). However, there should also be an electrical field that points inwards (the first term should be large and positive). This is known as the "Nernst-Planck" equation. At equilibrium, the total flux of charge should be zero, in other words:

$$-qn\hat{\mu}\frac{\mathrm{d}\phi}{\mathrm{d}x} = qD\frac{\mathrm{d}n}{\mathrm{d}x} \tag{6.13}$$

where the derivative is in a direction perpendicular to the membrane and q denotes charge and $\hat{\mu}$ denotes the mobility of the ions. Integrating this equation yields:

$$\int \left[-qn\hat{\mu}\frac{\mathrm{d}\phi}{\mathrm{d}x} = qD\frac{\mathrm{d}n}{\mathrm{d}x}\right] \tag{6.14}$$

or

$$\int \mathrm{d}\phi = \int \frac{D}{\hat{\mu}}\frac{\mathrm{d}n}{n} \tag{6.15}$$

$$\phi_{out} - \phi_{in} = \frac{D}{\hat{\mu}}\log\frac{n_{in}}{n_{out}} \tag{6.16}$$

or equivalently

$$\phi_{out} - \phi_{in} = \frac{k_b T}{q}\log\frac{n_{in}}{n_{out}} \tag{6.17}$$

where we identify $E = \phi_{out} - \phi_{in}$ as the Nernst potential specific to each ion. The last equivalency leads to a set of equations specific to neuronal cells given a range of typical ionic concentrations in neurons. That is, given known differences between intracellular and extracellular ionic concentrations, implies the following typical values of Nerst potentials, e.g.,:

$$E_{Na^+} = 62 \log \frac{145}{5} = 90\text{mV} \tag{6.18}$$

$$E_{Na^+} = 62 \log \frac{145}{15} = 61\text{mV} \tag{6.19}$$

given variation in internal potassium ion concentrations from 5 to 15 nM,

$$E_{K^+} = 62 \log \frac{5}{140} = -90\text{mV} \tag{6.20}$$

$$E_{Cl^-} = -62 \log \frac{110}{4} = -89\text{mV} \tag{6.21}$$

and given variation in external calcium concentrations from 2.5-5 mM:

$$E_{Ca^{2+}} = 31 \log \frac{2.5}{10^{-4}} = 136\text{mV} \tag{6.22}$$

$$E_{Ca^{2+}} = 31 \log \frac{5}{10^{-4}} = 146\text{mV}. \tag{6.23}$$

These Nerst potentials correspond to the resting state of a system with only one kind of diffusing, charged molecule. But, a neuron has more than one kind of ion. In order to understand how a system of ions interacts with signals (in the form of currents incoming from axons), one has to begin to connect the links in the entire neuronal 'circuit'.

6.3.3 Feedback between voltage, capacitance, and conductance

In order to understand how ions move across the membrane, it is essential to view the inside and outside of the cell as part of an electrical circuit. The total current flowing across the membrane is equal to the sum of ionic currents (associated with each of the different charged ions) and the "capacitive current". The capacitance, C, quantifies the ability of the membrane to store charge, and the associated current, $C\dot{V}$, quantifies the current arising from changes in the voltage across the membrane, or what is termed the "transmembrane potential". According to Kirkhoff's law, the applied currents must equal the sum of currents across the membrane:

$$I = C\dot{V} + I_{Na} + I_{Ca} + I_K + I_{Cl} \tag{6.24}$$

or, by switching the location of the terms, we can write this as a dynamical system

$$C\dot{V} = I - I_{Na} - I_{Ca} - I_K - I_{Cl}. \tag{6.25}$$

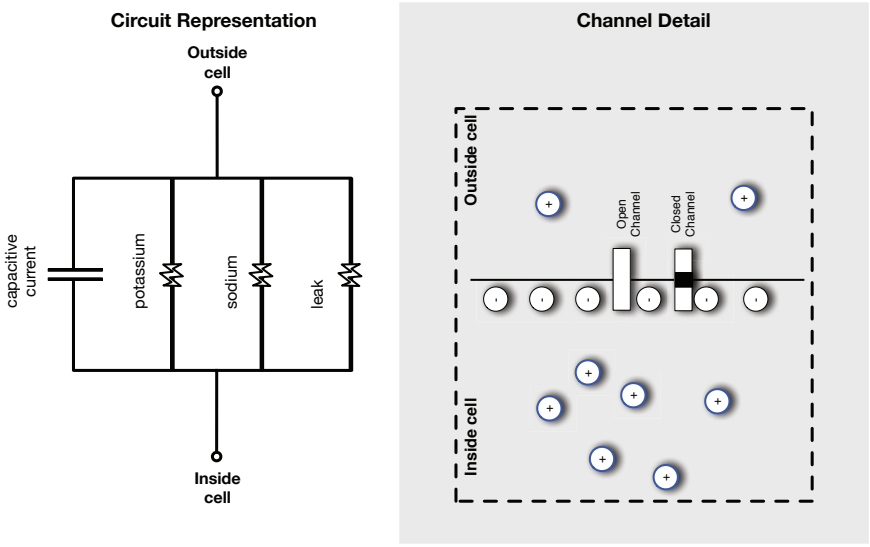


Figure 6.6: Circuit diagram schematic of neuron and membrane. (Left) Original depiction from Schematic, illustrating the ability of the membrane to store charge as well as the ion-specific conductance of sodium, potassium, and chloride (i.e., 'leak'). (Right) Schematic of the configuration space of ion-specific gates enabling passage of ions across the membrane, the switching rates are voltage dependent.

This appears to be the start of a *linear* differential equation. Here, we should recall the old relation from Physics 102 (i.e., introduction to electricity and magnetism), i.e, that $V = IR$ or that $I = V/R$, that is given a voltage difference, the current will increase (decrease) with decreasing (increasing) resistance. Extended treatment of this and other ways in which eletricity and magnetism impacts biological systems are described in detail in (Benedek and Villars 2000a) (part of a larger series of an out-of-print series, a shame given the range of contributions (Benedek and Villars 2000c, b)). Note that the inverse of resistance is conductance, $R = 1/g$. Hence, in this example we should write that the current associated with the movement of pottasium ions will be:

$$I_K = g_K(V - E_K). \tag{6.26}$$

In essence, if this were the only ion and there were no applied current, then the dynamics would have an equilibrium when $\dot{V} = 0$ such that the transmembrane potential, V, would converge to the Nerst potential, E_K. But there are other ions. For multiple ions the dynamics of current can be rewritten as:

$$\begin{aligned} C\dot{V} &= I - g_K(V - E_K) - g_{Na}(V - E_{Na}) \\ &\ldots \quad -g_{Ck}(V - E_{Cl}). \end{aligned} \tag{6.27}$$

When $\dot{V} = 0$, then the resting potential is at the center of "mass", i.e., weighting the Nerst potentials by the conductances:

$$V^* = \frac{g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl}}{g_K + g_{Na} + g_{Cl}}. \tag{6.28}$$

If the conductances of these ion-specific gates were fixed irrespective of changes in voltage, then it is unlikely that I would be writing this chapter or that you would be reading it. Instead, the conductances are voltage-dependent, and that voltage dependence is essential to understand why neurons have nonlinear feedback properties.

The central point is that transmembrane channels can be in either open or closed configurations (see Figure 6.6). An open configuration requires that multiple gates in the channel permit the passage of ions. Technically there are both opening and closing gates, and the open gates must be open while the closing gates must not be closed (a double-negative and confusing to be sure!). In essence, think of these gates as representing the effective coordination number of the channel. The open or closed configuration status of these gates can change with time. For example, if x is the proportion of open gates of a certain type, then the dynamics of x can be thought of representing the expected value arising via a two-state transition process, between off to on and between on to off. Given transition rates of k_{on} (from off to on) and k_{off} (from on to off), then the dynamics of open gates are:

$$\begin{aligned}
\dot{x} &= k_{on}(1-x) - k_{off} x && (6.29)\\
&= k_{on} - (k_{on} + k_{off})\, x && (6.30)\\
&= \left(\frac{k_{on}}{k_{on} + k_{off}} - x \right) / \tau && (6.31)\\
&= (x^* - x)\,/\tau && (6.32)
\end{aligned}$$

where the time constant for relaxation is $\tau \equiv 1/(k_{on} + k_{off})$ and the equilibrium is $x^* = k_{on}/(k_{on} + k_{off})$. This relaxation implies that the frequency of on gates would relax from any initial configuration back to the equilibrium as

$$x(t) = x_0 e^{-t/\tau} + x^* \left(1 - e^{-t/\tau}\right). \tag{6.33}$$

The Technical Appendices present a brief derivation of the relaxation dynamics in this class of kinetic problem. In this example, the kinetic constants are fixed, but for neurons, the kinetic constants are voltage dependent, i.e., $k_{on} = k_{on}(V)$ and $k_{off} = k_{off}(V)$. This dependency has significant consequences.

Returning to the original work of HH, if a voltage is clamped it is possible to isolate the interaction between a fixed voltage and the change in the frequency of gates that gives rise to a change in current. In that way, the frequencies of gates will change, and the current will change depending on the extent to which charged ions pass through the changing congifuration of gates. But, in an open

system, the voltage will also change, leading to a potential intensification of the system's dynamics (i.e., to excitability). The voltage dependency is, in essence, an empirical problem, linking evolved cellular physiology to system dynamics. The equations for the voltage dependent on rates and off rates, denoted using $\alpha(V))$ and $\beta(V)$ respectiely, where empirically measured by HH and represented as:

$$\alpha_n(V) = 0.01\frac{10-V}{e^{\frac{10-V}{10}}-1} \tag{6.34}$$

$$\beta_n(V) = 0.125e^{-V/80} \tag{6.35}$$

$$\alpha_m(V) = 0.1\frac{25-V}{e^{\frac{25-V}{10}}-1} \tag{6.36}$$

$$\beta(m)(V) = 4e^{-V/18} \tag{6.37}$$

$$\alpha_h(V) = 0.07e^{-V/20} \tag{6.38}$$

$$\beta_h(V) = \frac{1}{e^{\frac{30-V}{10}}+1}. \tag{6.39}$$

The quantitative dependencies of these rates are shown in Figure 6.7. As is apparent, at negative voltages, off rates for both K and Na are high, whereas the off rate for the leak current is low. In contrast, at high voltages then on rates for both K and Na are high, whereas the on rate for the leak current is low.

Finally, we can return to the original HH equations, but hopefully with a newfound sense of understanding. The equations below include overbraces to denote the meaning of each component, albeit here shifting the voltage dynamics to the left-hand side to clearly delineate the nonlinear nature of the dynamics:

$$\begin{aligned}\overbrace{C_M\frac{\mathrm{d}V}{\mathrm{d}t}}^{\text{capacative current}} &= \overbrace{I}^{\text{applied current}} - \overbrace{\bar{g}_K n^4 (V-V_K)}^{\text{potassium current}} \ldots \\ &\quad - \overbrace{\bar{g}_{Na} m^3 h (V-V_{Na})}^{\text{sodium current}} - \overbrace{\bar{g}_l (V-V_l)}^{\text{leak current}}\end{aligned} \tag{6.40}$$

$$\overbrace{\frac{\mathrm{d}n}{\mathrm{d}t}}^{\text{potassium channels}} = \overbrace{\alpha_n(1-n)}^{\text{on}} - \overbrace{\beta_n n}^{\text{off}} \tag{6.41}$$

$$\overbrace{\frac{\mathrm{d}m}{\mathrm{d}t}}^{\text{sodium channels}} = \overbrace{\alpha_m(1-m)}^{\text{on}} - \overbrace{\beta_m m}^{\text{off}} \tag{6.42}$$

$$\overbrace{\frac{\mathrm{d}h}{\mathrm{d}t}}^{\text{leak channels}} = \overbrace{\alpha_h(1-h)}^{\text{on}} - \overbrace{\beta_h h}^{\text{off}} \tag{6.43}$$

In essence, the HH model arises via the following biophysical feedbacks: (i) Ohm's law, i.e., that a voltage is equal to the current multiplied by the resis-

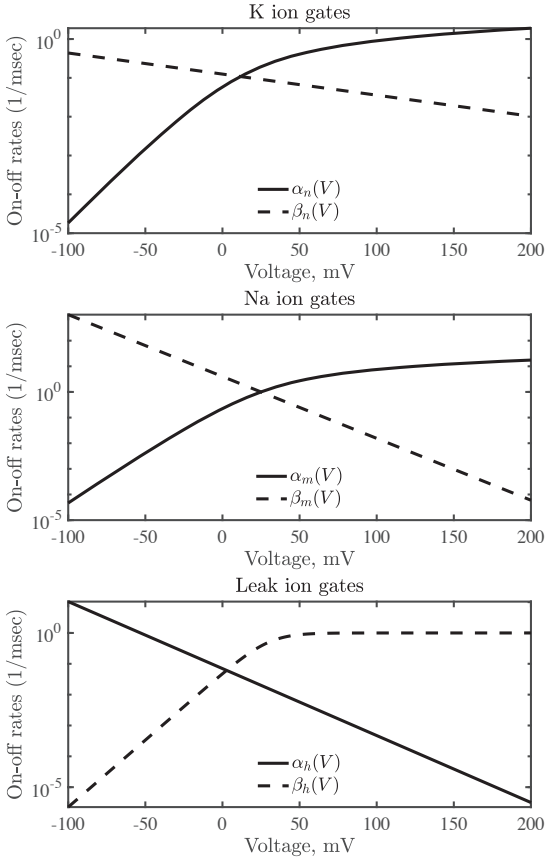


Figure 6.7: Transmembrane ion channels can be in an open and closed configuration, such that switches between states (e.g., between open and closed states of the channel) are voltage dependent. Quantitative switching rates for K, Na, and leak ions where α_n, α_m, α_h denote on rates, and β_n, α_m, and β_h denote off rates.

tance (or the inverse of capacitance); (ii) Kirchoff's rule, i.e., that currents are conserved; (iii) the opening and closing of ionic channels are voltage-dependent; (iv) ionic channels modify current flow in a nonlinear fashion. A beautiful theory that, *sensu Peebles*, is beautiful because it is true.

6.4 DYNAMICAL PROPERTIES OF EXCITABLE NEURONAL SYSTEMS

6.4.1 Overview

The HH model exhibits excitability and other features as a direct result of the feedback between gate status and voltage dynamics. Some of these features include (i) filtering of small perturbations; (ii) excitability given sufficiently large perturbations; (iii) refractory periods; (iv) beating. In addition to exploring each of these below, each of these features is also explored at length in the accompanying computational lab (and in the problems at the end of this chapter). In all of the examples below, the constituent HH equations are simulated using a standard set of parameters such that the resting voltage is 0. These parameters are $\bar{g}_K$=36 mS/cm^2, $\bar{g}_{Na}$=120 mS/cm^2, $\bar{g}_L$=0.3 mS/cm^2, E_K=-12 mV, E_{Na}=120 mV, E_L=10.6 mV, and C = 1 muF/cm^2. In addition, the initial conditions in these examples varies, but includes both the initial voltage (equivalent to the transmembrane potential) and the initial gating states, i.e., $V(0)$ as well as $n(0)$, $m(0)$, and $h(0)$. In the event that the neuron is initially at rest, then $V(0) = 0$ and $n(0) = n^*$, $m(0) = m^*$, and $h(0) = h^*$. Note that at equilibrium, the activation and inactivation processes must be in balance - which themselves depend on the voltage V^*. For this to hold, then:

$$\begin{aligned} n^* &= \alpha_n(V^*)/\left(\alpha_n(V^*) + \beta_n(V^*)\right), \\ m^* &= \alpha_m(V^*)/\left(\alpha_m(V^*) + \beta_m(V^*)\right), \\ h^* &= \alpha_h(V^*)/\left(\alpha_h(V^*) + \beta_h(V^*)\right). \end{aligned}$$

At these particular values, the system will be at rest. If not, then the gates will begin to open, conductances will increase, the membrane depolarizes and then repolarizes and the system will appear to fire even if no stimulus or a weak stimulus is applied.

6.4.2 Filtering and Excitability - The System and Its Input

Initially, at rest (V^*, n^*, m^*, h^*), the application of a small current perturbs the membrane (via a proceed term depolarization). This is insufficient to trigger a response and the membrane repolarizes. A larger current, however, depolarizes the membrane, which then changes conductances. This feedback further depolarizes the membrane. Hence, there is inward Na+ current, followed by outwards K+ current, and small leak current. The neuron is "excited" and fires – as is evident in the examples below. These two examples also help to reveal a way of

looking at the entire system from top to bottom. Each panel represents the voltage dynamics, the gating variables, the conductances, currents, and then applied currents. As is apparent in the first image, there are two applied currents but only one action potential (or "spike"). The reason is that the smaller current does not sufficiently depolarize the membrane. Instead, a larger current, however, depolarizes the membrane, which then changes conductances. This feedback further depolarizes the membrane (see Figure 6.9). Hence, there is inward Na+ current, followed by outwards K+ current, and small leak current. The neuron is "excited" and fires. This firing of the neuron includes a large voltage spike - the basis for signal propagation, information processing, and the interaction between neurons as part of a connected system (for more on connected neurons and excitable cells, see the next chapter).

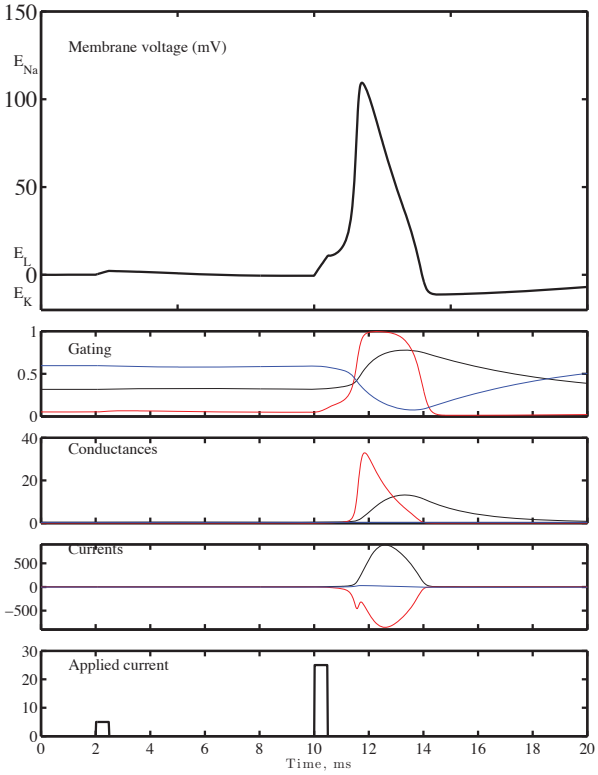


Figure 6.8: Filtering and spiking of a neuron. Note that this instance of dynamics includes a weak applied current (from 2 to 2.5 ms) followed by a stronger applid current (from 10 to 10.5 ms). The first current is filtered, whereas the second current leads to a spike of the transmebrane voltage associated with rapid changes in conductance.

The excitability of the system denotes a particular feature of the response. The neuronal system, i.e., $V(t), n(t), m(t), h(t)$ undergoes a long trajectory away from its initial state and then eventually returns close to it. Locally, however, the system is stable, insofar as small perturbations lead to the relaxation of the system back to the fixed point without long excursions. This difference between small and large perturbations is precisely the mechanism underlying the ability of neurons to filter sufficiently small input and react non-linearly with an impulse-like output to sufficiently large output. The excitability also implies that there is a critical point between large and small outputs rather than a smooth change in dynamics with increasing input size. This discontinuity in response the following two images which differ only in that the applied current is applied from time 2 to 2.5 ms, and in the two cases there is a current of 12 vs. 14 μA/cm^2, respectively. Yet this small difference leads in the first case to filtering of a signal and in the second case to an excitation. The full dynamics take place in 4 dimensions - but as is apparent, it is the relaxation of the gating variables slowly while the voltage changes quickly is a hallmark of the neuronal excitable response.

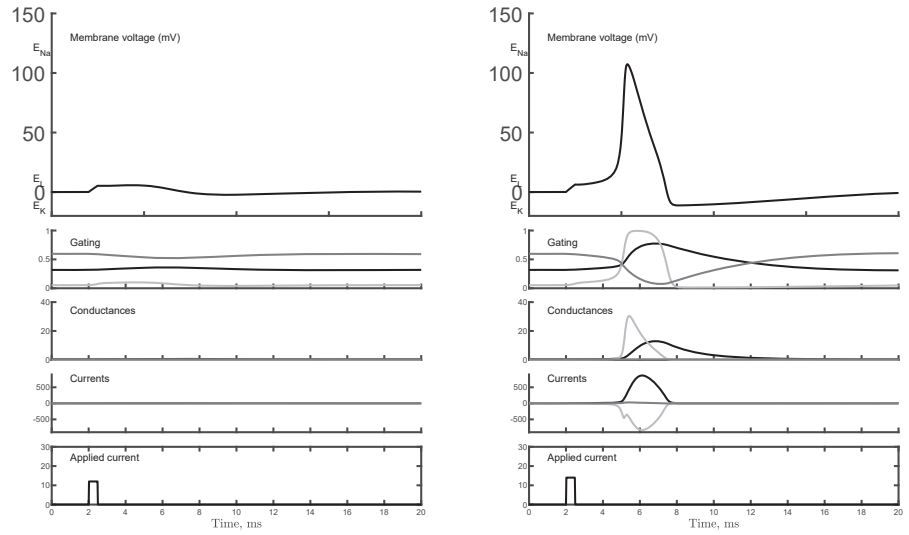


Figure 6.9: Excitability implies that small differences in perturbations near the critical point can lead to large changes in response. In both cases a current is applied from 2 to 2.5 ms, albeit of 12 vs. 14 $\mu A/\text{cm}^2$. This slight difference leads to a dramatic change in output. The first current is filtered, whereas the second current leads to a spike of the transmembrane voltage associated with rapid changes in conductance. Note that the difference can be made even smaller, resulting in a discontinuity (which the homework problems explore in detail).

6.4.3 Refractory period

The concept of excitability is usually accompanied by a refractory period. The reason is that excitability involves a long deviation in state space from a resting condition, given a sufficiently large initial perturbation. However, given that the HH system's K, Na, and leak current gates begin to relax over longer time scales, the subsequent addition of an external current after an initial excitation can lead to transient changes in voltage. Given the voltage-dependent changes in activation and incativation, it is notable that this may have little to no effect on gating, and therefore on conductances and currents. Instead the system continues to relax in the four dimensional state space until the membrane (and gates) have returned closer to their rest state. Hence given the appropriate physiological constants, when the inter-perturbation interval increases from 10 ms to 30 ms, then the gating variables will have relaxed sufficiently close to their rest state that a subsequent input of applied current could lead, once again, to a large scale deviation (see Figure 6.10). Like excitability, there is often a sharp transition, such that there exists a critical timing between input before a second spike can generate (again, another problem examined at depth in the homeworks). The concept of a refractory period in excitable systems will also be explored in greater depth in the context of a simplified model inspired by the HH model of neuron dynamics.

6.4.4 Beating

Given the concepts of filtering, excitiability and a refractory period, it is possible to begin to understand how neurons can exhibit persistent oscillatory dynamics given a constant input. A beating neuron is one that exhibit oscillatory behavior, repeatedly initiating spikes, followed by the slow relaxation towards (but not reaching) a rest state. Figure 6.11 shows one such example using the same initial conditions and physiological parameters as used in this chapter, yet with a constant applied current of 25 μA/cm^2. The result is not a constant output or convergence to a fixed point, but rather an oscillatory or beating signal. Consider the initial portion of the input. This can be viewed as a sufficiently large input that can initiate an excitatory response. However, because of the refractory nature of the dynamics, the continued application of current will not necessarily lead to another excitation until the gating variables relax sufficiently close to their rest states, and then, yet again, the system spikes. This process leads to the phenomena of beating which is the concatenation of a sequence of excitations and refractory periods given a constant input.

6.5 FROM NEURONS TO NEURAL NETWORKS AND INFORMATION PROCESSING

The excitable dynamics of individual nerve cells are then connected as part of complex neural networks in the central nervous system and embedded as part

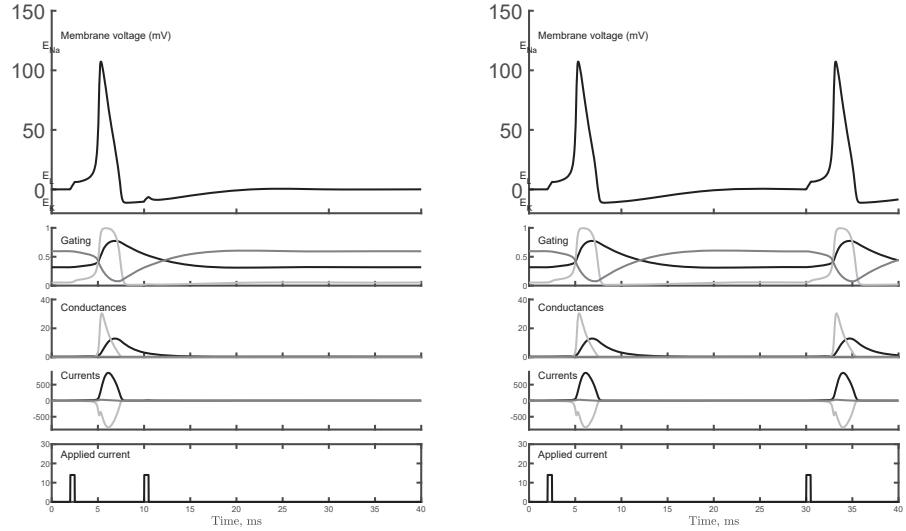


Figure 6.10: Refratory periods after an initial excition. In both cases an initial large amplitude current of 14 $\mu A/\text{cm}^2$ is applied between 2 to 2.5ms. The left and right panels depict a second pulse of equal amplitude applied between 10 to 10.5 ms (left) and 30 to 30.5 ms (right). Note that the second stimulus only leads to an action potential spike in the case of the larger interval (which the homework problems explore in detail).

of integrative physiological systems (including sensory, motor, and muscle neurons). A full treatment of neural networks and collective information processing is beyond the scope of this chapter (and indeed, of this book). The next chapter goes further in a formal sense to link what happens at one location with collective phenomena, albeit in cardiac cells. Yet, it is worth taking at least a small step in this direction by examining some of the potential activities that multiple groups of neurons can enable – by connecting highly nonlinear input-output relationships. In doing so, we will have to make certain simplification, i.e., rather than considering the full nonlinear dynamical profile of an excitatory system, we will assume that such a profile represents a type of integrate and fire mechanism. The integration is that of accumulating application of an external current and the firing is that of an action potential. Such action potentials, if connected to other neurons, can lead to information processing – in a universal sense.

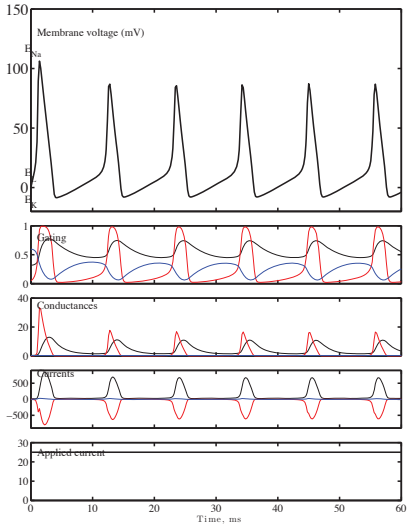


Figure 6.11: Beating phenomena in a single neuron given a constant applied current of 25 μA/cm^2.

6.5.1 Integrate and Fire

The dynamics of the transmembrane potential, i.e., the voltage V, change according to the following generic form:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = I - \sum_i g_i(V - E_i). \tag{6.44}$$

where i denotes one of the ions that is exchanged across the membrane. Although the full set of equations include multiple ions, it is instructive to focus on one as a means to reduce the complexity of the HH equations into what is tantamount to an integrate and fire model. First, note that the resistance is defined as the inverse of the conductance $R_i = 1/g_i$. Hence, assuming there is one particular ion and dividing both sides by g_i yields

$$\tau\frac{\mathrm{d}V}{\mathrm{d}t} = E_i - V + R_i I \tag{6.45}$$

where τ is a characteristic timescale C/g_i. In this light, the variables g_i which denote the state of the gating variables are a form of feedback control, changing the passage of ions that enable a rapid spike – including an increase and then decrease, with overshoot, of the voltage – followed by a slow relaxation of the gating variables. A simplified view of these dynamics would be to replace the gating responses with a rule: $V(t_c) = V(t_c) + V_s$ where V_s is a spike (akin to the rapid increase in action potential). The critical point would correspond to

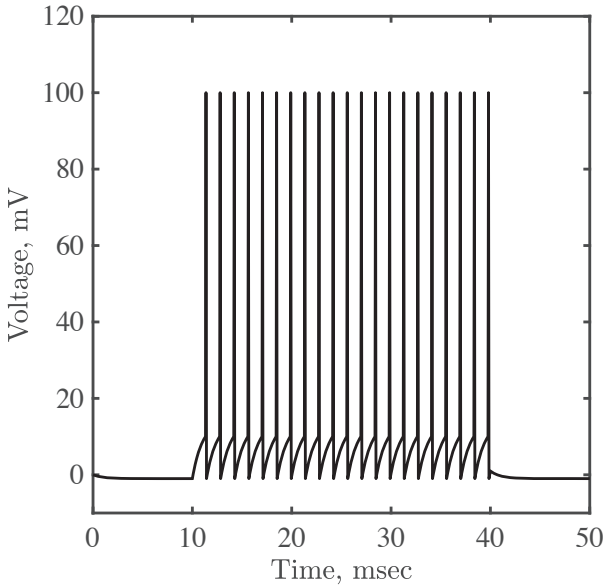


Figure 6.12: Dynamics in an integrate and spike neuron model. Here, there is a constant applied current of 10 μA/cm^2 applied from 10 to 40 ms, otherwise there is 0 applied current. Here, we use an illustrative model with g_i = 1 mS/cm^2 and E_i=-1 mV, where the simulation includes a spike of 100 mV in a 0.5 ms pulse. As is apparent, the dynamics build up and then fire during the period of applied current and not otherwise.

the moment when V exceeds a critical value V_c. Following the spike, the system is reset at $V(t_c + \delta t) = 0$, i.e., there is a small duration spike, followed by a reset. In the limit of a strong applied current, then the time between spikes should be $\frac{CV_c}{R_i I_c g_i}$ assuming δt is much less than the time to integrate and fire. Figure 6.12 provides an example of the resulting dynamics. This approximation provides a simplified view of neuronal dynamics, but it also provides a link between detailed physiological dynamics of single neurons to an information processing perspective, where the action of a single neuron can be essentialized in terms of whether the incoming current exceeds a critical threshold. If it does, the neuron fires – in other words, outputting a positive bit – and if not the neuron remains quiescent – in other words, outputting a negative bit. This link provides a map from physiolological signals to information, computation, and perhaps even cognition.

6.5.2 The Basis for Neural Logic to Computation

The integrate and fire mechanism is a simplifcation of neuronal dynamics. Nonetheless it provides a route to explore the basis for information processing and, more