Chapter 2

The Hodgkin-Huxley Neuron

2.1 Introduction to Modeling Biological Neurons

2.1.1 Historical Timeline

The biology of nerve cells is grounded in three principles that represent the core of the brain's functional organization:

- The *neuron doctrine*: the nerve cell or neuron is the fundamental building block and elementary signaling unit in the brain.
- The *ionic hypothesis*: individual nerve cells generate electrical signals, called action potentials, that can propagate over considerable distance within a given nerve cell.
- The *chemical theory of synaptic transmission*: a nerve cell communicates with another by releasing a chemical signal called a neurotransmitter; the second cell recognizes the signal and responds by means of a specific molecule in its surface membrane called a receptor.

Morphology deals with the form and structure of neurons without consideration of function. Electrical *signaling* is the means by which nerve cells communicate with each other. In short, electrical signaling is the language of the mind. Historically, the signaling function of neurons was investigated in the last 200 years and proceeded over four phases

- discovery of electrical activity and its speed of propagation in animals,
- study of the form of the signaling activity and its role in encoding information,
- postulation of the membrane hypothesis,
- postulation and verification of the ionic hypothesis.

Electrical Activity and its Speed of Propagation in Animals

In 1791 Luigi Galvani

- discovered electrical activity in animals and
- brought nervous activity out of the realm of vital forces and into the natural sciences.

Hermann von Helmholtz by 1859

- brought the rigorous methods of physics into brain science and
- succeeded in measuring the speed at which electrical messages are conducted. He found that electricity conducted along a living axon is fundamentally different from the flow of electricity in a copper wire.

Subsequently, it was demonstrated that nerves sacrifice speed of conduction for active regeneration.

Form of the Signal and its Role in Encoding Information

Edgar Douglas Adrian (1920s) argued that

- action potentials are all-or-none events that encode information about the stimulus,
- action potentials generated by the same cell exhibit about the same shape and amplitude regardless of the strength, duration and location of the stimulus,
- intensity results from the frequency with which action potentials are emitted,
- the nature of information conveyed depends on the type of nerve fibers that are activated and the specific brain systems to which those fibers are connected.

  Thus, visual information is different from auditory information because it activates different pathways.

The Membrane Hypothesis

Julius Bernstein following up on his Ph.D. thesis of 1902

- determined that the potential difference across the cell membrane is about -70 mV,
- postulated that in resting state, the membrane presents a barrier to all ions except one - potassium. As potassium moves out of the cell, it is drawn back by the positive charge left behind. The resulting ion balance maintains the membrane potential at -70 mV.

- the selective permeability of the cell membrane breaks down very briefly during the action potential, allowing all ions to enter and leave the cell freely and reducing the resting membrane potential to *zero*.

The Ionic Hypothesis

Allan Hodgkin and Andrew Huxley (1952)

- confirmed Bernstein's inference that the action potential was about -70 mV and that it depends on the movement of potassium ions through ion channels,
- discovered that the amplitude of the action potential is 110 mV and not 70 mV as predicted by Bernstein,
- major implication: Bernstein's hypothesis that the action potential represents a generalized breakdown of the cell membrane's permeability to all ions had to be incorrect.

2.1.2 Ion Channels

The *cell membrane* provides a boundary separating the internal working of the cell from its external environment. It consists of a lipid bylayer about 7.5 nm thick that is a very strong insulator. The membrane contains water filled pores and protein-lined pores called channels. In addition to ion channels, ion pumps are also embedded in the cell membrane. The ion pumps tap into the energy generated in the cell and use it for ion transport across the cell membrane, e.g., from the inside of the cell to the outside of the cell.

Ion channels are transmembrane protein molecules that form aqueous pores. These channels undergo conformational changes that allow ion passage (gate open) or prohibit ion passage (gate closed). There are four ion channel types in the nervous system:

- sodium (Na^+),
- potassium (K^+),
- calcium (Ca^{2+}) and
- chloride (Cl^-).

The energy source of ion movement is the ionic concentration gradient across the membrane. This gradient is maintained by active transport (ion pumps) and by passive distribution of ions. Due to the activity of ion pumps, a concentration difference between the inside of the cells and its surrounding fluid is established. For sodium the concentration inside of the cell is 50 mM while the concentration on outside of the cell is 440 mM. For potassium the concentration is higher inside, 400 mM, and lower outside, 20 mM.

2.1.3 Graded and Action Potentials

Neural signals, either electrical or chemical, are the messengers used by the nervous system for all of its functions. Electric signals in excitable membranes are transmitted from one part of the cell to another in two ways, by:

- passive spread of *graded potentials*. Graded potentials are:
  - observed in interneurons that transmit signals over short distances,
  - carried by ions that diffuse down their electrochemical gradients. The magnitude of the signal varies with the ion currents.
- propagation of all-or-none *action potentials*. Action potentials are
  - used by neurons that bear far-reaching processes (axons), carrying signals over long distance,
  - carried by voltage- and time-dependent conductances that generate transient all-or-none potential changes (spikes).

2.2 The Equilibrium Potential

2.2.1 Physical Laws Dictate Ion Movement

The principles of ion permeability and channel gating are the cornerstones of our understanding of neural signaling.

- Based on thermodynamic principles, ions tend to flow from regions of high concentration to regions of low concentration - a phenomenon known as *diffusion*.
- Since most plasma membranes are permeable to some ion species but not to others, a *separation of charge* occurs. This separation results in an electric field across the membrane that influences the movement of ions through pores and channels situated in the plasma membrane.
- The concentration differences are caused by active ion transporters (*pumps*) and selective permeabilities of ions of the plasma membrane.

Fick's Law

For *diffusion* of particles *caused by concentration differences* is given by

$$J_{diff} = -D\frac{\partial[C]}{\partial x},$$

where J_{diff} is the diffusion flux (molecules/s·cm^2), D is the diffusion coefficient (cm^2/s) and $[C]$ is the concentration of ions (molecules/cm^3).

Ohm's Law

For *drift* of ions *caused by potential differences* is given by

$$J_{drift} = \partial_{el} E = -\mu z[C]\frac{\partial V}{\partial x},$$

where J_{drift} is the drift flux (molecules/s·cm^2), ∂_{el} is the electrical conductivity (molecules/V·s·cm), E is the electric field (V/cm), V is the electric potential, μ is the drift mobility (cm^2/V·s) and z is the valence of the ion (dimensionless).

Einstein's Relation

The frictional resistance exerted by the fluid medium at thermal equilibrium is the same for diffusion and drift processes. This relationship formally states that the *diffusion and drift processes in the same medium are additive*. In addition,

$$D = \frac{kT}{q}\mu,$$

where k is the Boltzmann's constant ($1.38 \cdot 10^{-23}$ Joule/°K), T is the absolute temperature (°K) and q is the charge (C).

Space-Charge Neutrality

The total charge of cations (positively charged ions) is equal to the total charge of anions (negatively charged ions) in a given volume.

Example 1 [Charge Neutrality Breaks Down in the Plasma Membrane] What is the the fraction of uncompensated ions on each side of the membrane required to produce 100 mV in a spherical cell with a radius of 25 μm?

Assumptions: the membrane capacitance is $1\mu F/cm^2$ and the concentration of ions inside and outside is $0.5M$. The number of ions needed to charge up 1 cm^2 membrane to 100 mV is

$$\frac{q \cdot 1(cm^2)}{e} = \frac{10^{-6}(CV^{-1}cm^{-2}) \cdot 10^{-1}(V) \cdot (cm^2)}{1.6 \cdot 10^{-19}(C)} = 6 \cdot 10^{11}.$$

Thus, the total number of uncompensated ions needed for the cell is

$$6 \cdot 10^{11}(cm^{-2}) \cdot 4\pi(0.0025)^2(cm^2) = 4.7 \cdot 10^7.$$

Since the total number of ions in the spherical cell is

$$(0.5 \cdot 6.02 \cdot 10^{23}) \cdot 10^{-3}(mL^{-1})) \cdot \frac{4}{3}\pi(0.0025)^3(mL) = 2 \cdot 10^{13},$$

the fraction of uncompensated ions amounts to $4.7 \cdot 10^7 / 2 \cdot 10^{13}$ or 0.000235%.

2.2.2 Nernst-Planck and Nernst Equations

The Nernst-Planck Equation

$$J = J_{drift} + J_{diff} = -\mu z[C]\frac{\partial V}{\partial x} - D\frac{\partial [C]}{\partial x},$$

and by using Einstein's formula for the diffusion coefficient

$$J = -(\mu z[C]\frac{\partial V}{\partial x} + \frac{\mu kT}{q}\frac{\partial [C]}{\partial x}).$$

The current is the product of the ion flux and the charge it carries:

$$I = J/N_A \cdot zF = -(uz^2F[C]\frac{\partial V}{\partial x} + uzRT\frac{\partial [C]}{\partial x}),$$

where N_A is Avogadro's number ($6.02{\cdot}10^{23}$/mol), R is the gas constant (1.98 cal/°K·mol); F is Faraday's constant (96,480 C/mol); u is μ/N_A: molar mobility (cm^2/V·s·mol); and I is the current density (A/cm^2).

The Nernst Equation

Under what conditions is the cross-membrane current zero?

$$J = -(\mu z[C]\frac{\partial V}{\partial x} + \frac{\mu kT}{q}\frac{\partial [C]}{\partial x}) = 0$$

or

$$\frac{\partial V}{\partial x} = -\frac{RT}{zF}\frac{1}{[C]}\frac{\partial [C]}{\partial x}.$$

Therefore, by integrating on $[x_1, x_2]$ on both sides

$$V_2 - V_1 = -\frac{RT}{zF}\ln\frac{[C]_2}{[C]_1},$$

that is

$$V_{in} - V_{out} = \frac{RT}{zF}\ln\frac{[C]_{out}}{[C]_{in}}.$$

2.2.3 The Nernst Equilibrium Potential

The *equilibrium potential* for ion i is defined as the cross-membrane potential at which the membrane current carried by ion i equals zero:

$$E_i = V_{membrane}(I_i = 0) = V_{in} - V_{out} = \frac{RT}{zF}\ln\frac{[C]_{out}}{[C]_{in}}.$$

Example 2 At room temperature ($T = 20°C$) and $z = 1$, the Nernst potential in mV is given by

$$E_i = 58 \cdot log_{10} \frac{[C]_{out}}{[C]_{in}}.$$

In the squid axon, the concentration of potassium is (400, 20) and sodium (50, 440) in mM. Therefore, the equilibrium potential is -75 mV for K and 55 mV for Na.

As shown in the example above, the Nernst potential for sodium (E_{Na}) is about +55 mV. If the membrane voltage is smaller than the value of the Nernst potential E_{Na}, more Na^+ ions flow into the cell so as to decrease the concentration difference. If the membrane voltage is larger than the Nernst potential, ions would flow out of the cell. Therefore, the direction of the current is reversed when the membrane voltage is large then E_{Na}. This is the reason why the equilibrium potential E_{Na} is also called the *reversal potential*. For potassium, the equilibrium or reversal potential is $E_K = -75mV$.

2.3 The Hudgkin-Huxley Neuron

As we already discussed in Chapter 1, neurons are cells that consist of a cell body or soma, and extensions called neurites. The neurites are distinguished as dendrites, the receiving end or antennae of the neuron, and an outgoing trunk called the axon. The concentration of ions inside the cell is different from the concentration of ions outside of it. This difference in concentration generates a potential difference whose quantitative characterization will be described next.

2.3.1 Ionic Currents and Channel Conductances

Let E_{Na}, E_{Ca}, E_K and E_{Cl} denote the Nernst equilibrium potentials for the sodium potassium, calcium and chloride channels, respectively. The total K^+ current amounts to

$$I_K = g_K(V - E_K),$$

where the positive parameter g_K is the conductance and $(V - E_K)$ is the driving force. By Ohm's law, the total current I flowing across a patch of a cell membrane is the sum of the membrane capacitive current CdV/dt and all the ionic currents (assuming that they are independent)

$$I = C\frac{dV}{dt} + I_{Na} + I_{Ca} + I_K + I_{Cl}$$

or

$$I = C\frac{dV}{dt} + g_{Na}(V - E_{Na}) + g_{Ca}(V - E_{Ca}) + g_K(V - E_K) + g_{Cl}(V - E_{Cl}).$$

Resting Potential and Input Conductance

The equivalent "equilibrium" potential is given by

$$E_{equiv} = \frac{g_{Na}E_{Na} + g_{Ca}E_{Ca} + g_K E_K + g_{Cl}E_{Cl}}{g_{Na} + g_{Ca} + g_K + g_{Cl}}.$$

Thus, Ohm's law can be rewritten as

$$C\frac{dV}{dt} = I - g_{inp}(V - E_{equiv}),$$

where

$$g_{inp} = g_{Na} + g_{Ca} + g_K + g_{Cl}$$

is the *input conductance*. Finally, the *resting membrane potential* is given by

$$V_{rest} = E_{equiv}|_{I=0,dV/dt=0}.$$

Typically,

$$E_K < E_{Cl} < V_{rest} < E_{Na} < E_{Ca}.$$

The resting potential is usually in the range $-60mV$ to $-70mV$. Again, this value is the result of the equilibrium between ion flow through the channels and the active ion transport.

2.3.2 Conductances and Voltage-Gated Channels

Model of a Giant Squid Axon Patch

The Hodgkin-Huxley model provides a good description of the electrophysiological properties of the giant axon of the squid. The model captures the essence of the spike generation of sodium and potassium ion channels. The basic mechanism is essentially preserved in higher organisms. Cortical neurons, however, exhibit a much richer repertoire of electrophysiological properties than the squid axon studied by Hodgkin and Huxley.

In Figure 2.1, the membrane voltage is the potential difference between the inside and the outside of the cell, the conductance g_i models the ion channels associated with ion i, $i = K, Na, L$, the membrane capacitance C models the dielectric properties of the membrane bilayer and E_i denotes the equilibrium potential of ion i.

Voltage-Gated Channels

The individual ion channels are controlled by gating variables. The gates switch the channels between open and closed states and might be modulated by

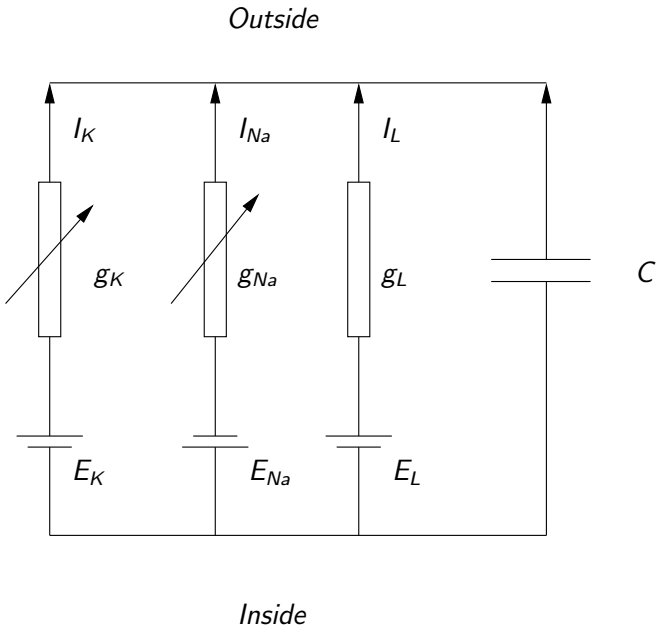


Figure 2.1: The Hodgkin-Huxley Model of the Giant Squid Axon

- membrane potential;
- intracellular agents (e.g., second messengers);
- extracellular agents (e.g., neurotransmitters).

The current I generated by an ensemble of (a large number of) identical channels is given by

$$I = \bar{g}p(V - E),$$

where p is the average proportion of channels in the open state, $\bar{g}$ is the maximal conductance of the population and E is the Nernst potential.

When gating variables are sensitive to the membrane potential, the channels are said to be voltage-gated. Gates either activate, that is open channels, or inactivate or close them.

- the probability of an activation gate to be in the open state is denoted by m or n.
- the probability of an inactivation gate being in the open state is denoted by h.

The proportion of open channels in a large population is

$$p = m^a h^b,$$

where a is the number if activation gates and b is the number of inactivation gates per channel.

Dynamics of the Activation and Inactivation Variables

The dynamics of the activation variable m are described by the first order differential equation

$$\frac{dm}{dt} = -(m - m_\infty(V))/\tau(V),$$

where $m_\infty(V)$ is the activation function and $\tau(V)$ is the time constant. Both can be measured experimentally. The dynamics of the inactivation variable h is given by

$$\frac{dh}{dt} = -(h - h_\infty(V))/\tau(V).$$

Inactivation kinetics is usually slower than activation kinetics.

If the voltage is kept constant (voltage clamp) then:

$$m(t) = m_0 - (m_0 - m_\infty)(1 - \exp(-\frac{t}{\tau_m}))$$
$$h(t) = h_\infty + (h_0 - h_\infty)\exp(-\frac{t}{\tau_h})$$
$$n(t) = n_0 - (n_0 - n_\infty)(1 - \exp(-\frac{t}{\tau_n})).$$

Although the solution for n, m and h has the same mathematical structure, the respective solutions above have been written in a slightly different form because of differing boundary conditions: $h_0 > h_\infty$ whereas $n_\infty > n_0$ and $m_\infty > m_0$.

2.3.3 The Hodgkin-Huxley Equations

Hodgkin and Huxley determined that in the squid axon:

- the potassium current is carried by voltage-gated channels with four activation gates;
- the sodium current is carried by voltage-gated channels with three activation gates and one inactivation gate;
- a chloride current is carried by Ohmic (leak) channels.

The complete set of equations is given by the system of differential equations

$$C\frac{dV}{dt} = -\bar{g}_{Na}m^3h(V - E_{Na}) - \bar{g}_K n^4(V - E_K) - g_L(V - E_L) + I(t)$$
$$\frac{dm}{dt} = -\frac{1}{\tau_m(V)}[m - m_\infty(V)]$$
$$\frac{dh}{dt} = -\frac{1}{\tau_h(V)}[h - h_\infty(V)]$$
$$\frac{dn}{dt} = -\frac{1}{\tau_n(V)}[n - n_\infty(V)],$$

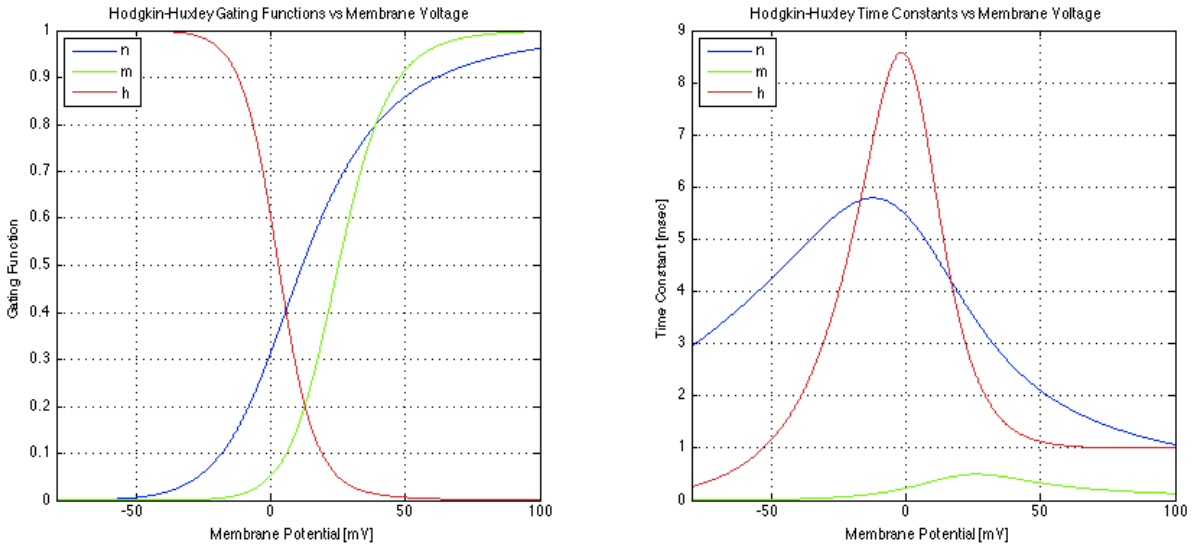


Figure 2.2: The Form of the Gating Functions and the Time Constants.

where $\bar{g}_{Na}$ and $\bar{g}_K$ are the maximum conductances of the sodium and potassium channels, respectively. g_L is the value of the leaky conductance. The variable n describes the activation of the postassium channel. The variables m and h describe the activation and inactivation of the sodium channel, respectively.

A simple transformation of the form

$$\alpha_l = l_\infty/\tau_l, \qquad \beta_l = (1 - l_\infty)/\tau_l$$

for all $l, l = h, m, n$, leads to the gate model of the Hodgkin-Huxley neuron:

$$\begin{aligned} C\frac{dV}{dt} &= -\bar{g}_{Na}m^3h(V - E_{Na}) - \bar{g}_K n^4(V - E_K) - g_L(V - E_L) + I(t) \\ \frac{dm}{dt} &= \alpha_m(1 - m) - \beta_m m \\ \frac{dh}{dt} &= \alpha_h(1 - h) - \beta_h h \\ \frac{dn}{dt} &= \alpha_n(1 - n) - \beta_n n. \end{aligned}$$

Hodgkin-Huxley experimentally evaluated α_l and β_l, $l = h, m, n$, as a function of transmembrane voltage and fitted the following empirical equations:

$$\begin{aligned} \alpha_n(V) &= 0.01(10 - V)/(e^{\frac{10-V}{10}} - 1), \\ \beta_n(V) &= 0.125\ e^{\frac{-V}{80}} \end{aligned} \tag{2.1}$$

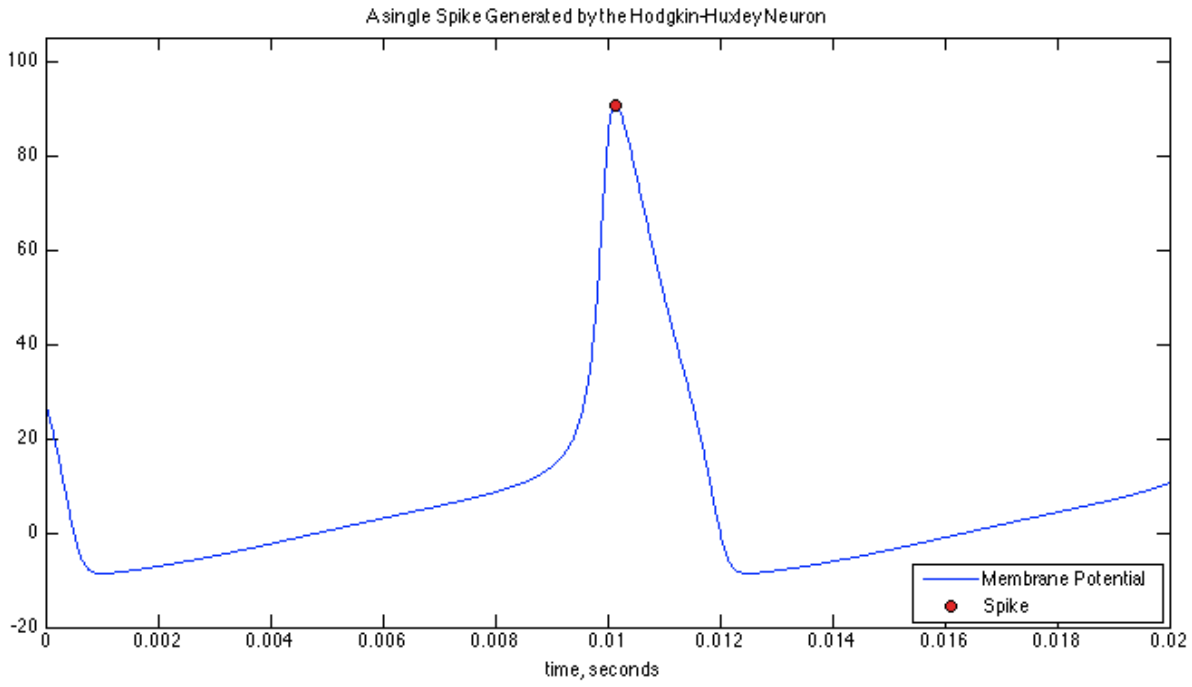


Figure 2.3: The Hodgkin-Huxley Model Predicts the Shape of the Spikes.

and

$$\begin{aligned} \alpha_m(V) &= 0.1(25-V)/(e^{\frac{25-V}{10}}-1), \\ \beta_m(V) &= 4e^{\frac{-V}{18}} \end{aligned} \tag{2.2}$$

and finally

$$\begin{aligned} \alpha_h(V) &= 0.07e^{\frac{-V}{20}}, \\ \beta_h(V) &= 1/(e^{\frac{30-V}{10}}+1). \end{aligned} \tag{2.3}$$

These parameters, first provided by Hodgkin-Huxley, correspond to the membrane potential shifted by 65 mV so that the resting potential is zero. The shifted Nernst potentials are $E_K = -12mV$, $E_{Na} = 120mV$ and $E_L = 10.6mV$. Note that this shift, introduced for the sake of convenience, has led to substantial confusion over the years.

2.3.4 The Gate Model Underlying the Hodgkin-Huxley Equations

The *gate model* of Hodgkin-Huxley described in the previous section can be directly postulated using the assumptions that

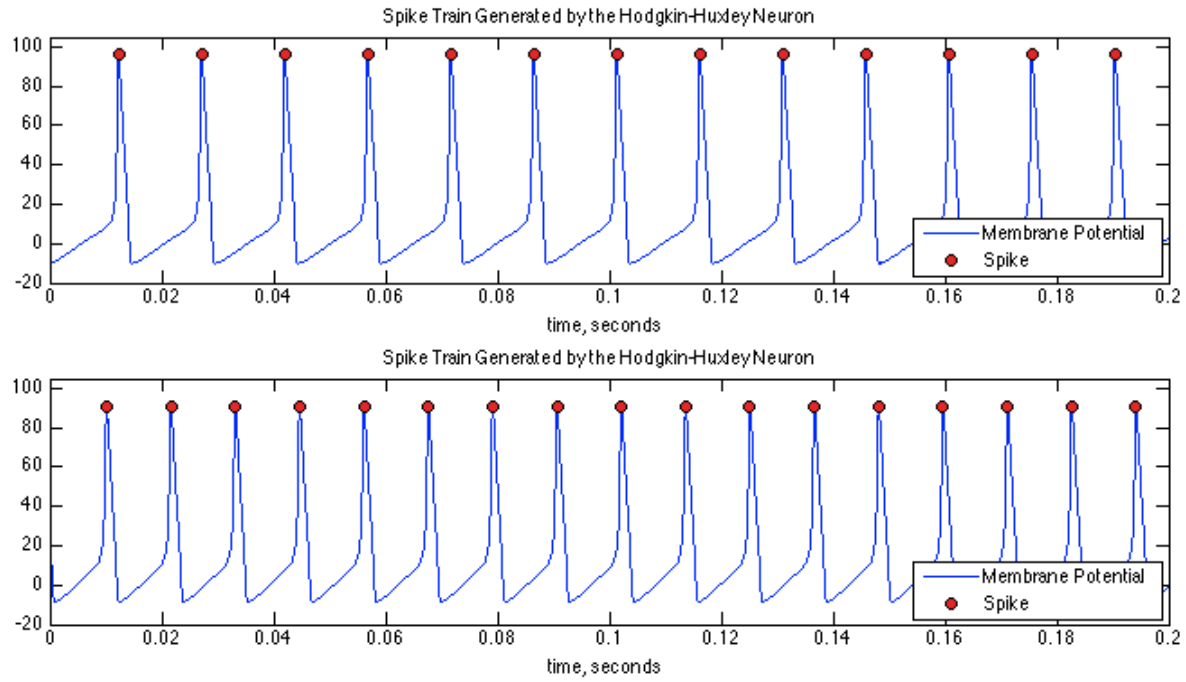


Figure 2.4: The Effect of the Injected Current (a) lower and (b) higher DC value of the injected current.

- ion currents are flowing through transmembrane channel proteins that form pores through which ions can diffuse
- pores have "gates" that are controlled by voltage sensitive gating charges or gating particles

Furthermore:

- Ionic channels undergo a conformational change in response to variations of the electric field. This conformational change will cause the channel to move from open to closed states or vice versa. $\alpha(V)$ and $\beta(V)$ are the rate coefficients associated with the closed and open states, respectively.
- The reaction between open and closed states is a first-order reaction.

Let p be the probability of the gating particle to be in the open state and $1-p$ the probability of the closed state. Then

$$\frac{dp}{dt} = \alpha_p(1-p) - \beta_p p.$$

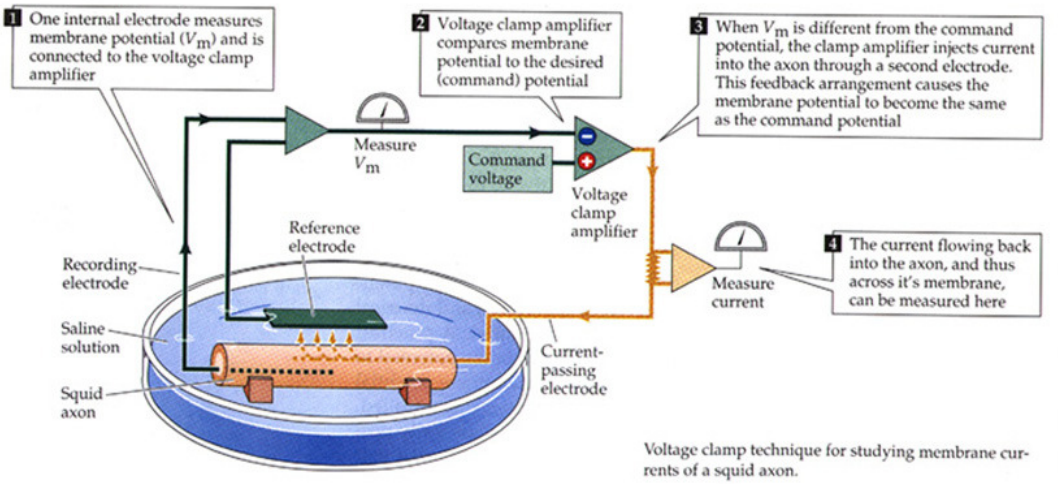
Clearly:

$$p(t) = p_0 + (p_\infty - p_0)[1 - \exp(-(\alpha_p + \beta_p)t)].$$

Setting $p = m, n$, or h, we obtain the equations of the activation and inactivation gating variables discussed in the previous section. As before, if there are a independent gating particles involved in gating a channel, then the channel will follow the time course $[p(t)]^a$.

2.4 The Voltage, Current and Dynamic Clamp

2.4.1 The Voltage Clamp



Voltage clamp technique for studying membrane currents of a squid axon.

The voltage clamp was the key experimental tool used by Hodgkin and Huxley to reveal the ionic mechanisms underlying the generation of action potentials.

- the voltage clamp permits the experimenter to "clamp" the membrane potential at predetermined levels.
- The voltage gated ion channels continue to open or close in response to changes in membrane potential, but the voltage clamp prevents the resultant changes in membrane current to influence the membrane potential.
- The experiments in the squid axon enabled the estimation of the instantaneous conductances without the influence of voltage-dependent parameters.

2.4.2 The Current Clamp

The current clamp is closely related to the voltage clamp. The difference is that while the value of the voltage is continuously monitored, the value of the injected current is

kept fixed. By keeping the value of the current constant, however, the voltage value is now variable. The current clamp is realized with a circuit with an adjustable impedance whose value multiplied with the (constant) injected current amounts to the value of the measured voltage.

2.4.3 The Dynamic Clamp

The dynamic clamp is a real-time feedback control systems that functionally replaces a biological conductance (group of ion channels) with a virtual conductance. The virtual or programmable conductance functionally depends on the membrane voltage. The value of the injected current is the product of the desired conductance value and the driving force. The latter is the difference between the membrane potential and the reverse potential. This is to be contrasted with the voltage or current clamp recordings whereby a current is injected into the neuron and the membrane voltage is simultaneously measured. The dynamic clamp enables the emulation of (i) voltage-independent conductances, (ii) voltage-dependent conductances, (iii) synapses between neurons, (iii) biological-silicon hybrid circuits, and (iv) in-vivo synaptic input.

As with the traditional current and voltage clamp techniques, limitations in applying the dynamic clamp are due to imperfections of the electrode resistance and capacitance. These imperfections can be minimized by using low-resistance electrodes, by using separate electrodes for voltage recording and current injection, or by temporally separating recording and injection through a single electrode using the discontinuous (switched) current clamp technique. The voltage measurement error is proportional to the amount of current flowing through the nanoactuator. Compensation methods to reduce this error have been developed.

2.5 The Geometry of the Hodgkin-Huxley Models

The behavior of high-dimensional differential equations is difficult to visualize - and even more difficult to analyze. Two-dimensional differential equations, however, can be studied in a transparent manner by means of phase plane analysis. A reduction of the four-dimensional equation of Hodgkin and Huxley to a two-variable neuron model is therefore, highly desirable.

The Reduced Rinzel Model

The Hodgkin-Huxley equations can be simplified by noting that τ_m only takes small values and by observing that the rate of inactivation of Na^+ channels is nearly reciprocal to the rate of activation of K^+ channels, and therefore, $h = 1 - n$. Therefore, the

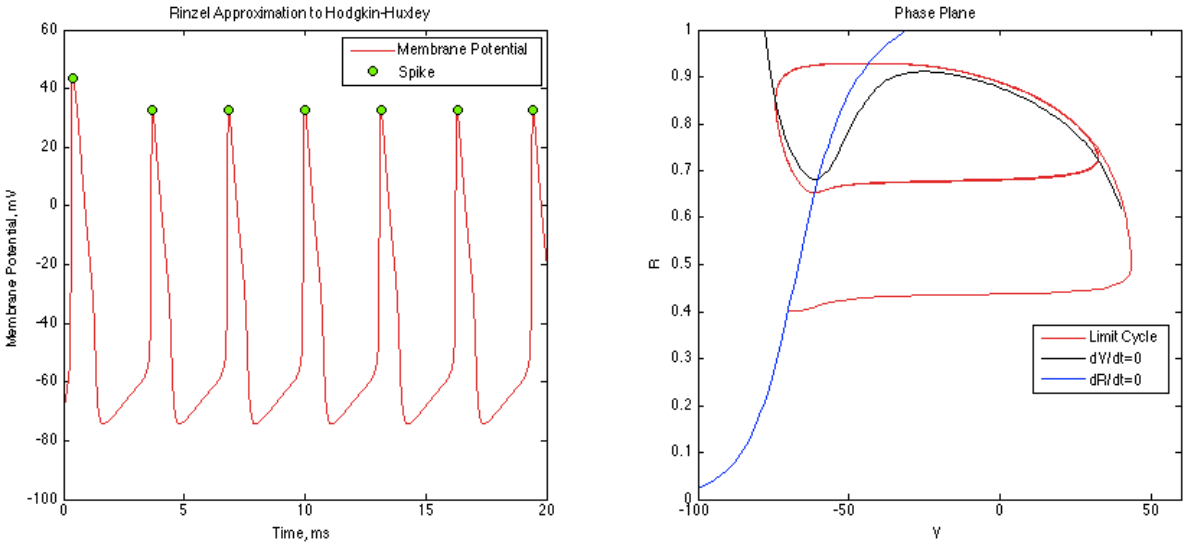


Figure 2.5: Rinzel model: spiking behavior and phase plane.

Hodgkin-Huxley equations can be reduced to:

$$C\frac{dV}{dt} = -g_{Na}m_{\infty}^{3}(V)(1-R)(V-E_{Na}) - g_{K}R^{4}(V-E_{K}) - g_{leak}(V-E_{leak}) + I(t)$$
$$\tau_{R}\frac{dR}{dt} = -[R-R_{\infty}(V)]; \quad \tau_{R} = 1+5\exp[\frac{-(V+60)^{2}}{55^{2}}].$$

Here, R describes the K^{+} channel opening and Na^{+} channel closing, which together constitute the recovery variable.

The Reduced Wilson Model

Wilson proposed a set of reduced Hodgkin-Huxley equations of the form:

$$C\frac{dV}{dt} = -g_{Na}(V)(V-E_{Na}) - R(V-E_{K}) + I(t)$$
$$\tau_{R}\frac{dR}{dt} = -[R-R_{\infty}(V)]$$

Here, R describes the recovery of the membrane potential.

By restricting $g_{Na}(V)$ to a quadratic polynomial and $R_{\infty}(V)$ to a quadratic term,

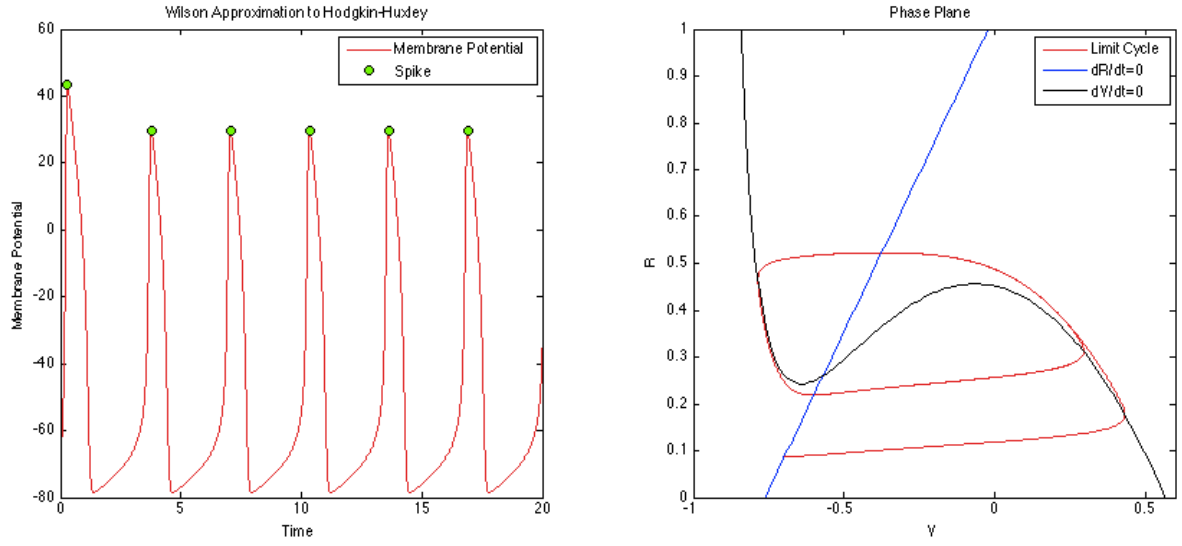


Figure 2.6: Wilson model: spiking behavior and phase plane.

the following explicit formulation is obtained:

$$\begin{aligned} C\frac{dV}{dt} &= -(17.81 + 47.71V + 32.63V^2)(V - 0.55) - \\ &\quad - 26.0R(V + 0.92) + I(t) \\ \tau_R\frac{dR}{dt} &= -R + 1.35V + 1.03, \end{aligned}$$

where the capacitance $C = 1\mu\text{F/cm}^2$ and $\tau_R = 1.9\text{ms}$. As the simulations show, the reduced set of equation above behave to a large extent in the same way as the Hodgkin-Huxley equations.

Wilson Model and Chaos

By adding a sinusoidal component to the stimulus current:

$$\begin{aligned} C\frac{dV}{dt} &= -(17.81 + 47.71V + 32.63V^2)(V - 0.55) - \\ &\quad - 26.0R(V + 0.92) + I(t) \\ \tau_R\frac{dR}{dt} &= -R + 1.35V + 1.03 \\ I(t) &= I_0 + A\sin(2\pi\omega t) \end{aligned}$$

the behavior of the reduced Hodgkin-Huxley equations leads to chaos.

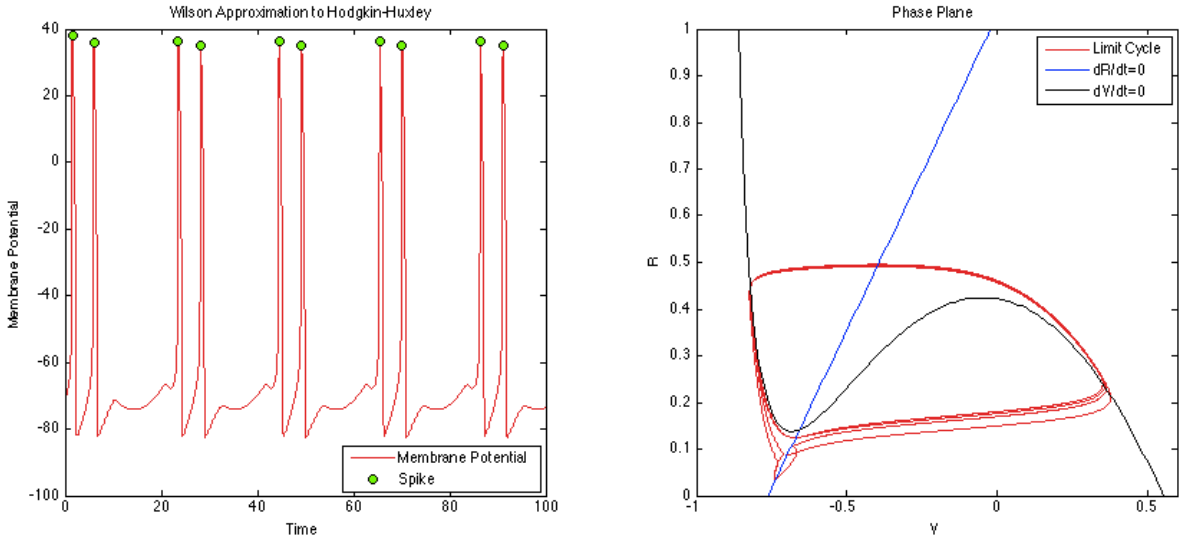


Figure 2.7: Wilson model of chaos: spiking behavior and phase plane.

2.6 Nonlinear Oscillations and Limit Cycles

This section gives a flavor of some elementary theoretical considerations arising in nonlinear systems. The field itself is vast.

2.6.1 What is an Oscillation?

A system oscilates when it has a nontrivial periodic solution

$$\mathbf{x}(t+T) = \mathbf{x}(t),$$

for all $t \in \mathbb{R}_+$ for some $T > 0$. Here $\mathbf{x}$ is a vector of appropriate dimension. T is the period of the oscillation.

Nonlinear oscillations or rythms are ubiquitous in living organisms and arise as circadian rhythms, cardiac rhythms, hormonal cycles, the rhythms of breathing and locomotion.

Fundamental Problems with Linear Oscillations

In linear systems the only possible oscillations involve sines and cosines. There are two fundamental problems with linear oscillators (i) the linear oscillator is not structurally stable (not robust) and (ii) the amplitude of the oscillation depends on the initial conditions. In addition, noise could alter the amplitude of the linear oscillation. These fundamental problems can be eliminated in nonlinear oscillators. For this reason alone,

it is safe to say that biological rhythms have evolved to be inherently nonlinear. The generation of action potentials in single neurons is the result of inherently nonlinear oscillations.

2.6.2 The Poincaré-Bendixon Theorem

The limiting behavior of nonlinear oscillations is, in general, hard to visualize and to derive. For nonlinear differential equations the problem is not completely understood. The planar case, however, is intuitively simple.

Definition 1 (Limit Cycles) *An oscillatory trajectory in the state space of a nonlinear system is a* **limit cycle** *if all trajectories in a sufficiently small region enclosing the trajectory are spirals. If these neighboring trajectories spiral towards the limit cycle as $t \to \infty$, then the limit cycle is* **asymptotically stable**. *If, however, neighboring trajectories spiral away from the limit cycle as $t \to \infty$, the limit cycle is* **unstable**.

Theorem 1 (Poincaré-Bendixon) *Bounded trajectories in the plane will have to approach periodic orbits or equilibrium points as time goes to infinity.*

Example 3 (The Van der Pool Oscillator) The Van der Pool relaxation oscillator considered here is described by:

$$\begin{aligned} dx_1/dt &= x_2 \\ dx_2/dt &= \beta(1 - x_1^2)x_2 - \alpha^2 x_1 \end{aligned}$$

For $\alpha = 500$ and $\beta = 0.5$ this non-linear system of equations has a periodic attractor.

Remark 1 The Van der Pool oscillator and the reduced Hodgkin-Huxley neuron are central to the study of oscillators arising in physics and engineering and, neuroscience, respectively. Their study in the phase plane shows that they exhibit limit cycles. This common characteristic is a bridge between seemingly disparate fields. We shall build upon it.

2.7 Appendix: Estimating the Parameter Values of the Hodgkin-Huxley Equations

This section is included for completeness.

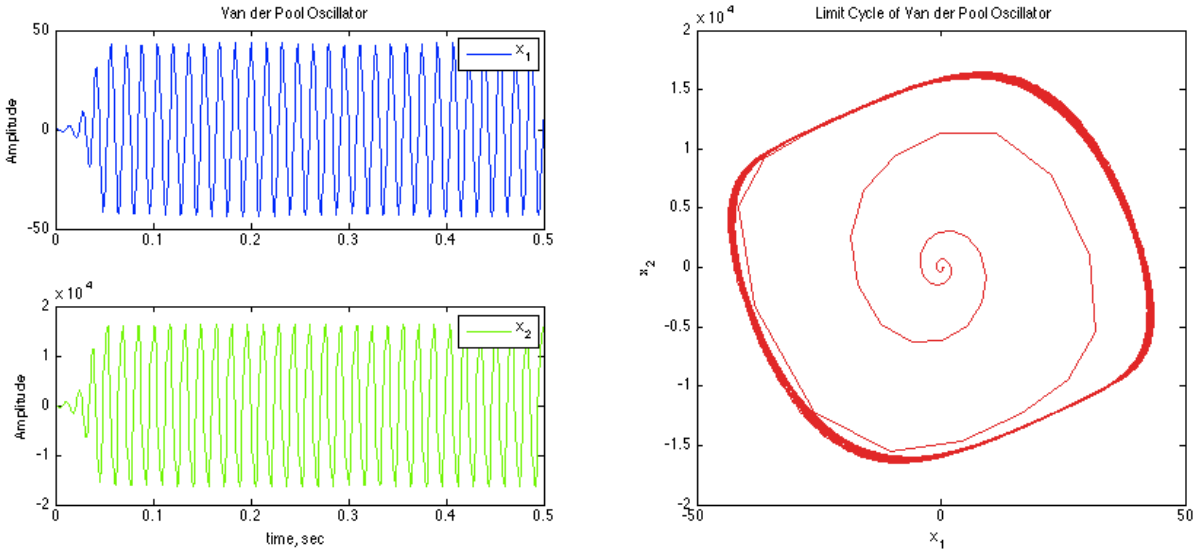


Figure 2.8: Van der Pool oscillator: spiking behavior and phase plane.

2.7.1 Estimating the Parameters of the K^+ Channel

Hodgkin and Huxley postulated that the conductance of the Potassium channel is of the form

$$g_K = \bar{g}_K n^a(t, V),$$

where a is an integer exponent. As before the activation variable is of the form

$$\frac{dn}{dt} = -\frac{1}{\tau_n(V)}[n - n_\infty(V)].$$

Hodgkin and Huxley found the exponent a, and the functional forms of n_∞ and τ_n via a combination of theory and experiment. First, by inserting a wire into the squid axon, the membrane voltage value along the axon patch was constant and, therefore, they achieved a space clamp. Second, by using a voltage clamp, the capacitive current had the value zero. Finally, chemically they disabled all currents except the Potassium current. Using the voltage clamp, the membrane potential was kept fixed at some prestep (holding) potential value V_h and then stepped to a new value V_c (command voltage). Thus,

$$g_K(t_j; (V_h, V_c)) = I_K(t_j)/(V_c - E_K),$$

where $(t_j), j = 1, 2, ..., N$, are the times at which the current was measured. Note also that given the postulated form of the activating variable and $n_0 = n_\infty(V_h)$

$$n(t; (V_h, V_c)) = n_\infty(V_h) - (n_\infty(V_h) - n_\infty(V_c))(1 - \exp(-\frac{t}{\tau_n})).$$

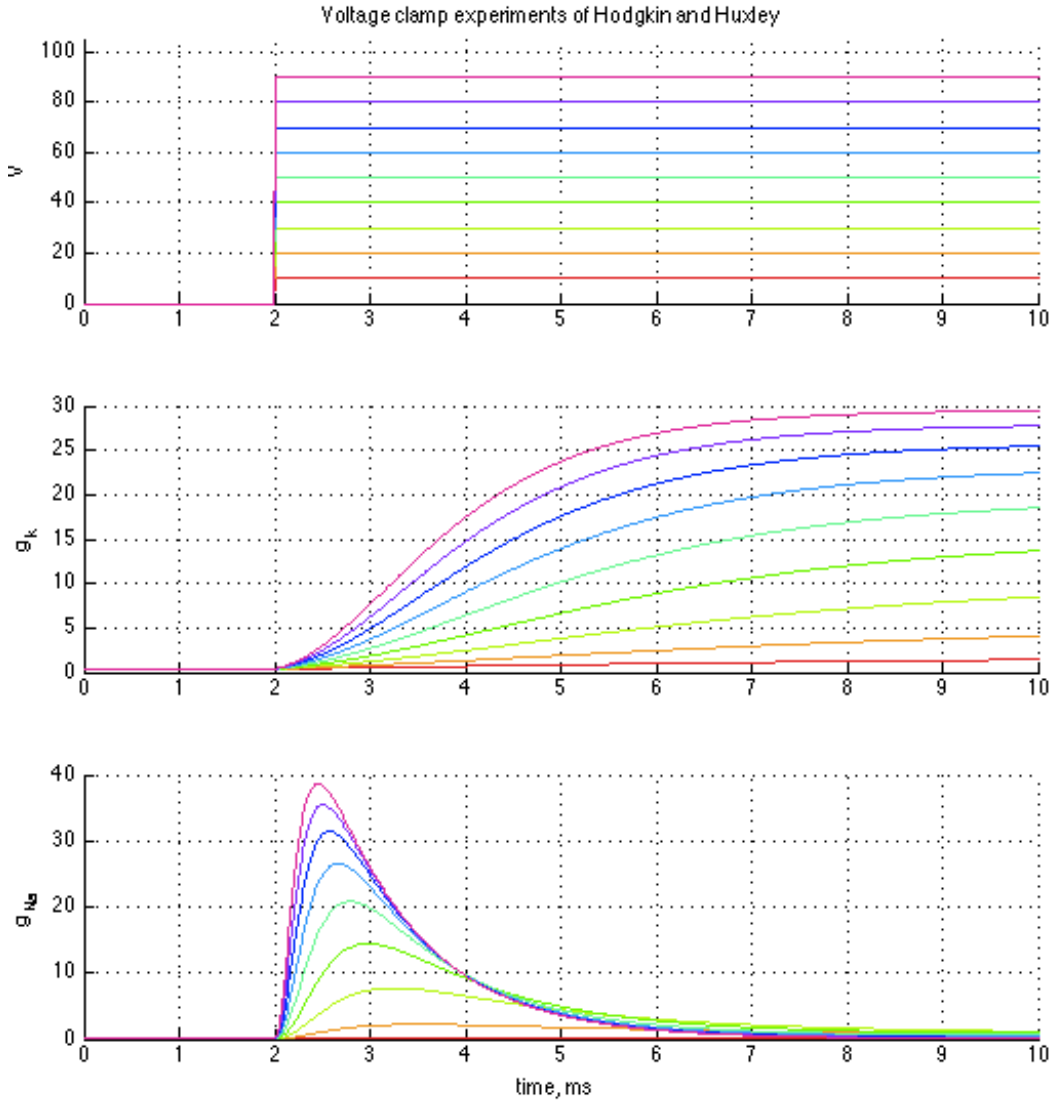


Figure 2.9: Voltage clamp experiments of Hodgkin and Huxley.

The parameters $\bar{g}_K$, n_∞, τ_n and a can be determined by minimizing (for fixed a) the quadratic sum

$$\sum_{(V_h,V_c)} \sum_{j=1}^{N} |\bar{g}_K[n_\infty(V_c) + (n_\infty(V_h) - n_\infty(V_c)) \exp(-\frac{t}{\tau_n})]^a - g_K(t_j; (V_h, V_c))|^2,$$

where the outer sum is over all pairings of V_h and V_c. The power a is chosen such that the quadratic sum is further minimized; recall that $a = 4$. An example is provided in Figure 2.9.

2.7.2 Estimating the Parameters of the Na^+ Channel

With only the sodium current present (the current associated with the other ions chemically disabled), the sodium conductance quickly went up and then fell off. Hodgkin and Huxley postulated that this conductance can be modeled with two voltage gated variables. The conductance takes the form

$$g_{Na} = \bar{g}_{Na} m^a(t; V) h^b(t; V).$$

with

$$\frac{dm}{dt} = -\frac{1}{\tau_m(V)}[m - m_\infty(V)] \quad \text{and} \quad \frac{dh}{dt} = -\frac{1}{\tau_h(V)}[h - h_\infty(V)].$$

As before

$$m(t; (V_h, V_c)) = m_\infty(V_h) - (m_\infty(V_h) - m_\infty(V_c))(1 - \exp(-\frac{t}{\tau_m}))$$
$$h(t; (V_h, V_c)) = h_\infty(V_h) - (h_\infty(V_h) - h_\infty(V_c))(1 - \exp(-\frac{t}{\tau_h})).$$

Finally, the activation and inactivation variables are obtained by minimizing the quadratic sum

$$\sum_{(V_h,V_c)} \sum_{j=1}^{N} |\bar{g}_{Na} m^a(t; (V_h, V_c)) h^b(t; (V_h, V_c)) - g_{Na}(t_j; (V_h, V_c))|^2.$$

An example is provided in Figure 2.9.