Single Neuron Computation

September 18, 2024

Introduction

Whereas the brain function at the level of neural circuit remains largely a mystery, a great deal is known about the biophysical mechanisms responsible for generating electrical activity at single neuron level. This knowledge provides the building blocks for constructing neural circuit models. In the following few weeks, we will discuss the basic electrical properties of neurons and the mathematical models by which the rich neuronal dynamics can be described and explained quantitatively. We will present simple but useful model neurons, such as the integrate-and-fire model, as well as the more substantially detailed Hodgkin-Huxley model based on the presence of many voltage-dependent conductances. Finally, we will discuss, despite the tremendous success in constructing detailed conductances-based models (albert with many adjustable parameters) to explain the experimental data, we lack a clear understanding how a single neuron can fine-tune itself to generate the stereotypical activity pattern.

Electrical Properties of Neurons

The cytoplasm of a neuron is packed with a variety of ions ($\sim 10^8$), molecules ($\sim 10^7$) , proteins ($\sim 10^5$), etc. Numerous ion-conducting channels are embedded in the membrane of a cell. Many, but not all, channels are highly selective, allowing only a single type of ion to pass through them. The permeability of ions across the membrane together with the difference of the concentration of these ions largely determine the membrane potential of a neuron. By convention, the potential outside a cell is set to 0. Because the cell membrane is more permeable to positive ions such as K^+ and because there is higher concentration of K^+ inside the neuron, K^+ tend to diffuse to the outside (up to a point, as we will explain later) and the excess internal negative charge causes the potential inside the cell membrane to be negative.

Membrane potential, capacitance and resistance

What determines the typical scale of neuronal membrane potential? The membrane potential should be small enough to allow neurons to take advantage of

the thermal energy to transport ions across the membrane, but should also be large enough so that the thermal fluctuation does not destroy the electrical signaling in a neuron. These conditions imply that when an ion traverses across the membrane, the energy it gains or loses due to the potential difference may be on the same order of the thermal energy. The thermal energy of single ion is given by k_BT, where k_B is the Boltzman constant. Let's denote q as the charge of a single proton, we have

$$qV \sim k_BT \tag{1}$$

. Plugging into the real numbers, $k_B = 8.6 \times 10^{-5}$ eV/K, $T = 300$ K, we found that $V \sim 26$ mV. This sets the overall scale of the membrane potential. Experimentally, the membrane potential of a neuron varies between +50 mV to -80 mV, which is +2 to -3 times the estimated voltage.

Neurons with less complex morphologies have more uniform membrane potentials. These neurons are called electronically compact. When we could ignore the spatial variation of membrane potentials (or they do not seem to play a very important role), the electrical properties of a neuron is largely determined by its membrane capacitance and resistance (or conductance). The membrane capacitance C_m is proportional to the total surface area of a neuron, and the proportionality constant is called the specific membrane capacitance c_m is roughly the same for all neurons, $c_m \approx 10$ nF/mm^2. Surface area of neuron ranges between 0.01-0.1 mm^2, so the membrane capacitance for a whole neuron is typically 0.1-1 nF.

The membrane capacitance determines how much current is required to be injected to a neuron in order to make the membrane potential to change at a given rate. The membrane resistance R_m determines how much the voltage will shift from its current value (ΔV) when a small current is injected into a neuron ($\Delta V = I_m R_m$). The resistance is inversely proportional to the membrane surface area, and the specific membrane resistance r_m is around 1MΩ mm^2. For total surface area ranges between 0.01-0.1 mm^2, the total membrane resistance is about 10-100 MΩ.

The product of membrane capacitance and membrane resistance is called the membrane time constant, $\tau_m = R_m C_m = r_m c_m$, which is independent of the total membrane area of the neuron. It sets the basic time scale for changing the membrane potential, and it typically falls within 10-100 ms.

Reversal potential,Resting state and Equilibrium

Electric forces and diffusion are responsible for driving ions across the cell membrane. When a neuron is at its resting state, the current flow due to electric force should cancel the current flow caused by diffusion. What is the membrane potential at the resting state? Can we calculate it specifically? Without losing generality, Let us consider one case for an positive ion (i.e., K^+) with a negative membrane potential. The ion stays inside the cell and the potential outside the

cell is higher than that inside. A positive ion inside the cell can cross the membrane only if it has sufficiently large thermal energy to overcome the electrical barrier. In other words, it must have a thermal energy at least $-zeV$ (where $ze > 0$ is the electric charge of the ion, and $V < 0$ is the membrane potential of the neuron. The probability that an ion has thermal energy E follows the Boltzmann distribution $\frac{1}{Z}\exp(-E/k_BT)$, and the probability that the ion can go cross the barrier is simply $\exp(zeV/k_BT)$: this is determined by integrating the Boltzmann distribution for energies $E \geq -zeV$. A concentration of ions inside the cell, n_{in}, that will be able to move across the membrane would be proportional to $n_{in}\exp(zeV/k_BT)$, and this should balance the ions flowing inside the cell, which will be proportional to n_{out}. Putting these things together, we obtain

$$n_{out} = n_{in}\exp(zeE/k_BT). \tag{2}$$

Solving this equation, we have

$$E = \frac{k_BT}{ze}\ln(\frac{n_{out}}{n_{in}}). \tag{3}$$

Equation 3 is the Nernst equation. The potential we derived is also called the reversal potential: the current flow for a particular type of ion switches its direction when crossing the reversal potential. The reversal potential for a K^+, denoted as E_K typically falls in the range between -70 and -90 mV; the reversal potential for Na^+, E_{Na}, is 50 mV or even higher; and E_{Ca}, for Ca^{2+} channels, is even higher, around 150 mV. Cl^- reversal potential are typically around -60 to -65 mV.

The Nernst equation only take into account one type of ion. However, some channels are not quite selective, and we need to combine the current flow from multiple ions, and the result is the Goldman-Hodgkin-Katz formula for reversal potential. I will write down the equation here, and it is your homework to provide the derivation of this formula.

$$E_m = \frac{k_BT}{e}\ln\left(\frac{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{out} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{in}}{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{in} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{out}}\right). \tag{4}$$

Sodium Anomaly, Ion Pumping and Membrane Current

Now let's go back and revisit the Nernst equation. In the literature, Equation 3 is also called the equilibrium potential: a steady-state membrane potential when the net current flow for a given type of ion is zero. The measured membrane potential of a neuron at the resting state is $\Delta V = -60\ mV$; the equilibrium potential for a K^+, typically falls in the range between -70 and -90 mV; Cl^- equilibrium potential are typically around -60 to -65 mV. Both are fairly close to the resting potential of a neuron. However, there are exceptions.

The equilibrium potential of sodium (+50 mV) is much more positive than the

actual resting potential of a neuron.

All animal cells have a **sodium anomaly** of this type.

One possible explanation for such sodium anomaly might be that sodium and other ions such as calcium simply cannot permeate the membrane on the time scale of our experiment. This is partially true. In the resting state,

$$g_{\mathrm{K}^+} \approx 25 g_{\mathrm{Na}^+} \approx 2 g_{\mathrm{Cl}^-}$$

. However, the permeability of sodium is not exactly zero. On a longer timescale, the equilibrium would eventually be reached. How could we resolve this paradox?

The term "equilibrium potential" is actually quite misleading. A living cell is not at an equilibrium. Equilibrium is not life; it is death! Cells are constantly burning energy, and to combat to drive towards equilibrium. In fact, a specific molecular machine embedded in the cell membranes is constantly hydrolyzing ATP, then uses some of the resulting energy to pump sodium ions out of the cell. The active outward pumping current is compensating inward leakage sodium current so that the net current at the resting state is zero. At the same time the pump imports potassium, partially offsetting the loss of electric charge from the exported sodium. As a consequence, this working machine keeps $[\mathrm{K}^+]_{in} \gg [\mathrm{K}^+]_{out}$, and $[\mathrm{Na}^+]_{in} \ll [\mathrm{Na}^+]_{out}$.

When a neuron is not at the resting state, the total current flowing across the membrane through all of its ion channels is called the membrane current of the neuron. By convention, the membrane current is defined as positive when positive ions leave the neuron and negative when positive ions enter the neuron. Let us label different types of channels that may have selective permeability of specific types of ions with ndex i. As we discussed before, when the membrane potential of a neuron equals to the reversal potential E_i, $V = E_i$, the net current that traverses that channel becomes zero. For many channels, the current increases or decreases linearly with small difference of $V - E_i$. When we add the contribution from different type of ion channels, we have

$$I_m = \sum_i g_i (V - E_i), \tag{5}$$

where g is the ion channel conductances. In Equation 5, we must distinguish two types of conductances. Many ion channels embedded in the membrane are voltage-gated, and therefore the conductances g_i is also voltage-dependent. Some other conductances may be well approximated as voltage independent, such as the current from ion pump, as well as other leaky ion currents. These time-independent conductances could be lumped together by a single term $\bar{g}_L$, and the leaky membrane current I_L is given by:

$$I_L = \bar{g}_L (V - E_L), \tag{6}$$

where E_L is the resting potential of the neuron. Putting everything together, we may write down

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) - \bar{g}_L(V - E_L) + I_e. \tag{7}$$

Integrate-and-Fire Models

Neurons possess a large repertoire of voltage-gated ion channels that regulate the membrane conductances, making the neuronal activity higher nonlinear. One prominent feature in the activity pattern of many invertebrate and vertebrate neurons is the existence of action potential, or spike. In mammalian brains, action potential is the basic unit for information transmission. Clearly, the above-mentioned RC circuit cannot be used to describe such nonlinear dynamics. It was in 1952, through a series of elegant experimental and theoretical papers, Hodgkin and Huxley provides a detailed biophysical description of action potential generation and propagation. This work won them the Nobel Prize in 1963.

We will ignore Hodgkin and Huxley, temporarily. On the other hand, neuron models can be simplified and simulations can be accelerated dramatically if the biophysical mechanisms responsible for action potentials are not explicitly included in the model. Integrate-and-fire model (I-F model) is a much simplified, but extremely useful model to describe spike generation. It is widely used in the neuroscience community. In the I-F model, we ignore the voltage dependent term in Equation 12. We only include the linear leaky term together with an *ad-hoc* spiking event. Here the spike is modelled as the point event and it does not have temporal width. The timing of a spike is defined as the time where the membrane potential V reaches the firing threshold value, V_{th}, from below. Whenever a spike occurs the voltage is reset immediately to a lower value, which for simplicity will be taken as $V_{reset} = E_L$. In other words, $V(t^-_{spike}) = V_{th}$, and $V(t^+_{spike}) = V_{reset}$. Now if we define a new variable

$$\tilde{V} = (V - V_{reset})/(V_{th} - V_{reset}),$$

and denote

$$I_c = g_L(V_{th} - V_{reset}),$$

the RC equation together with the resetting event can be rewritten as

$$\begin{aligned} \tau \frac{d\tilde{V}}{dt} &= -\tilde{V} + \frac{I_e}{I_c} \\ \tilde{V}(t^-_{spike}) &= 1 \\ \tilde{V}(t^+_{spike}) &= 0 \end{aligned} \tag{8}$$

To understand the input-output relationship of a neuron, an important quantity that needs to be derived is the dependence of the firing rate, f, on the applied external current I_e. This can be calculated straightforwardly. The time that required to reach the threshold membrane potential is simply given by

$$\frac{I_e}{I_c}(1 - \exp(-t/\tau)) = 1 \tag{9}$$

Rearrange this equation and note that $f = 1/t$, we obtain

$$f = -\frac{1}{\tau \ln(1 - I_c/I_e)}. \tag{10}$$

For large current I_e, using $\ln(1 + x) \approx x$, the f-I relationship reduces to

$$f \approx \frac{I_e}{I_c \tau} \tag{11}$$

The firing rate grows linearly with the input current for large I_e.

Now let us examine some experimental data. Real neuron exhibits spike-rate adaptation: the interspike intervals lengthen over time when a constant current is injected into the cell, before a steady-state value is reached. Nevertheless, if one only uses the first two spikes fired by the neuron in response to the injected current, the results agree quite well with the I-F model. The steady-state firing rate can also be fitted by an I-F model, but using a different set of parameters. Another important factor we have not taken into account in our simplest model is the refractory effect: the probability that a neuron fires significantly reduced for a short period of time after the appearance of a spike. This can also be incorporated into the model.

Hodgkin-Huxley Model

What makes the electrical properties of a neuron so interesting, including the ability to generate and propagate action potentials, arise from nonlinearity associated with active (voltage-dependent) membrane conductances, as denoted by g_i in the following equation

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) - \bar{g}_L(V - E_L) + I_e. \tag{12}$$

The fact that we can experimentally observe currents entering single channels is truly amazing. The technology that allows an accurate measures of the amplitude of single-channel currents is called *patch clamp recording*, developed by Erwin Neher and Bert Sakmann. Neher and Sakmann won the Nobel prize in 1991 for their seminar contribution to patch clamp method. In patch clamp recording, the tip of a small glass pipette (with a diameter of 1 μm) is sealed to the membrane of a cell. Under ideal condition, with slight suction on the

pipette, a seal resistance can be as high as a few GΩ (10^9 ohms). With a state-of-the-art amplifier, small currents across the patch of membrane inside the pipette tip can be recorded. The high resistance seal ensures that such currents flow through the amplifier rather than escaping through the rim of the patch. When recording, an online feedback control system holds the membrane potential of the cell almost instantaneously. This is done by (1) calculate the difference between the current membrane potential with the desired membrane potential. (2) Apply a feedback current to exactly compensate the membrane current flowing across the cell, so that the membrane potential is always hold at a constant value.

Patch clamp recordings of the current flowing through single channels indicate that channels fluctuate rapidly between open and closed states in a stochastic manner. However, the neuronal dynamics model we discuss so far is deterministic. This is justified because the conductance of a given ion channel type arises from a large number of channels. If these channels fluctuate independently of each other, the fraction of channel open at any given time is approximately equal to the probability P that any single channel is open. Let's denote $\bar{g}_i$ as the maximum conductance for a given type of ion channel, the actual conductance $g_i = \bar{g}_i P_i$. Understanding active conductance now reduces to understanding how the channel open probability depends on voltage, neurotransmitter concentration, etc.

This is the structure of a delay-rectifier K^+ channel (show the 3D movie), which is comprised of four identical subunits. The opening of the channel appears to require all four units to undertake a structural change. In reality, the gating mechanisms underlying the conformational change of the subunit as well as the ion selectivity is complex and delicate. However, if our goal is to understand the current-carrying ability of a channel, it suffices to introduce a swinging gate picture: all four gates need to be opened simultaneously for a channel to open. if the movement of each gate is independent from each other, then we have

$$P_{\mathrm{K}} = n^k, \tag{13}$$

where n is the probability that any one of the gate opens, and we choose $k = 4$. Hodgekin and Huxley chose this formation of equation and use $k = 4$ to fit their experimental data, 40 years before the membrane protein structure of the potassium channel was determined. Indeed, Roderick MacKinnon, who solved the structure of the voltage-activated potassium channel, won the Nobel Prize in Chemistry in 2003.

Now let's describe the transition of each subunit gate from close to open using a simple kinematic model. The transition from closed $\rightarrow$ open occurs at a forward voltage-dependent rate $\alpha_n(V)$, and open $\rightarrow$ close occurs at the voltage-dependent rate $\beta_n(V)$. The probability to find a subunit gate open over short period time is $\alpha_n(1-n)\Delta t$; the probability to find a subunit gate close over

short period time is $\beta_n n \Delta t$. The change of open probability over time $n\Delta t$ is given by the difference of the above two terms. Putting things together, we have

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n. \tag{14}$$

By introducing a steady-state probability

$$n_\infty(V) = \frac{\alpha_n}{\alpha_n + \beta_n},$$

and

$$\tau_n = \frac{1}{\alpha_n + \beta_n},$$

Equation 14 can be rewritten as

$$\tau_n \frac{dn}{dt} = n_\infty - n. \tag{15}$$

What can we say about the voltage-dependence of n_∞ and τ_n ? In the simplest model, the opening of a gate can be viewed as moving an effective charge qe across the membrane, and the free-energy difference between open and close gates will be $\Delta F = F_0 - qeV$. Thus, from statistical physics, we have

$$\frac{n_\infty}{1-n_\infty} = \exp(-\Delta F/k_B T).$$

Solving for n_∞, we have

$$n_\infty = \frac{1}{1+\exp[(F_0 - qeV)/k_B T]}. \tag{16}$$

Note that we do not know the exact value of F_0 and q. They are chosen to best-fit the experimental data. I will leave students as a homework to determine the functional form of τ_n based on the experimental data.

The delay-rectified potassium channel has persistent conductances: the channel are slowly activated upon depolarization and are slowly closed upon hyperpolarization. Some other channels, such as voltage-gated sodium channels, only open transiently when the membrane potential is depolarized because they are gated by two processes with opposite voltage dependence. For such channel, the probability to open the ion channel is given by

$$P_{\mathrm{Na}} = m^k h. \tag{17}$$

Here m is similar to n for the potassium channel. Hodgkin and Huxely used $k = 3$ to fit their model. Upon depolarization, m will increase towards one. However, h has the opposite dependence on voltage. Depolarization causes h to

decrease and hyperpolarization causes h to increase. Thus to turn on a transient conductance maximally, it may first be necessary to hyperpolarize the neuron below its resting potential, this would open the gate for h. In the second step, upon depolarization, m will increase. Only when m and h are both nonzero, the channel will be opened.

The Hodgkin-Huxley model for generation of an action potential is constructed by a summation of leaky current, a delayed-rectified K^+ current, and a transient Na^+ current, and Equation 12 becomes

$$C_m \frac{dV}{dt} = -\bar{g}_{\rm K} n^4 (V - E_{\rm K}) - \bar{g}_{\rm Na} m^3 h (V - E_{\rm Na}) - \bar{g}_L (V - E_L) + I_e. \quad (18)$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V) n \quad (19)$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V) m \quad (20)$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V) h. \quad (21)$$

Below I will provide detailed parameter values used in Hodgkin and Huxley model. It is your homework to simulate the dynamic equations and check whether it could generate action potentials.

$$\alpha_n = \frac{0.01(V+55)}{1-\exp(-0.1(V+55))},\ \beta_n = 0.125\exp(-0.0125(V+65)),$$

$$\alpha_m = \frac{0.1(V+40)}{1-\exp(-0.1(V+40))},\ \beta_m = 4\exp(-0.0556(V+65)),$$

$$\alpha_h = 0.07 exp(-0.05(V+65)),\ \beta_h = \frac{1}{1+\exp(-0.1(V+35))}.$$

Two-Dimensional Nonlinear Systems

The HH model is difficult to be understood analytically. We thus consider a simplified model

$$C_m \frac{dV}{dt} = -\bar{g}_{\rm K} n (V - E_{\rm K}) - \bar{g}_{\rm Na} m_\infty(V) (V - E_{\rm Na}) - \bar{g}_L (V - E_L) + I_e. \quad (22)$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n. \quad (23)$$

Note that there are several simplifications we have made. First, we assume that the sodium current is persistent by eliminating the h variable. Second, we drop

the exponent in the gating variable of the potassium channel. Third, we shall assume that for a given voltage, the sodium current reaches the steady state instantaneously. In what condition can we make such an assumption?

Before we discuss how to analyze the above two-dimensional system, I would like to briefly introduce some mathematical methods that we will use. This is the minimum requirement you need to understand the lecture.

Nonlinear differential equation

The neural dynamics we deal with are generally nonlinear. The most general differential equation we consider takes the form

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(x) \tag{24}$$

where $\mathbf{x}$ is an N component vector and $\mathbf{f}$ is vector of functions. Unless it is unstable, the behaviors of the dynamics fall into three classes. For one class, called stable fixed points or point attractors, $\mathbf{x}(t)$ approaches a time-independent vector $\mathbf{x}(\infty)$, when $t \to \infty$. In another class, called the limit cycle, $x(t)$ becomes periodic at large times and repeats itself indefinitely. For the third class of solutions, the chaotic ones, $x(t)$ never repeats itself but the trajectory of the system lies in a limited subspace of the total space of allowed configurations called a strange attractor. Chaotic solutions are extremely sensitive to initial conditions.

Below we shall consider the point attractor, in which $\mathbf{x}_\infty$ is called the fixed point of the system, when $f(\mathbf{x}_\infty) = 0$. Near the fixed point, we can perform perturbation analysis by expanding f to the first order near the fixed point

$$\mathbf{f}(\mathbf{x}(t)) = \mathbf{f}(\mathbf{x}_\infty) + \mathbf{J}\epsilon(t), \tag{25}$$

where $\mathbf{J}$ is the Jacobian matrix, whose elements are given by

$$J_{ij} = \frac{\partial f_i(\mathbf{x})}{\partial x_j} \tag{26}$$

Thus the dynamics that need to be analyzed near the fixed point is given by

$$\frac{d\epsilon}{dt} = \mathbf{J}\epsilon \tag{27}$$

We know how to analyze this linear equation. The fixed point $\mathbf{x}_\infty$ is a stable fixed point only when the real part of all eigenvalues of the Jacobian matrix $\mathbf{J}$ are negative. Here, let's consider a very simple scenario, where the system we are considering is two-dimensional.

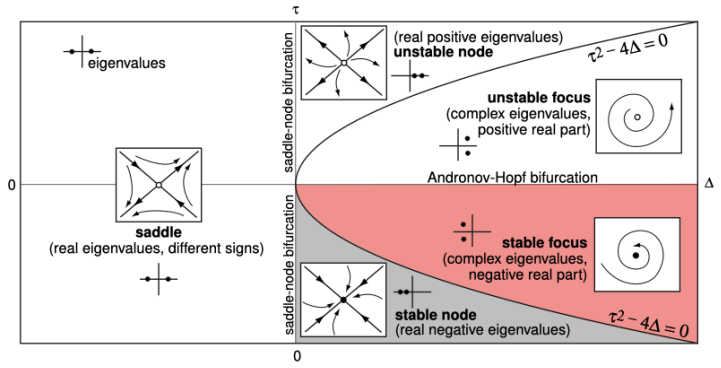

Figure 1: phase diagram of fixed point stability (2D)

Analysis of a two-dimensional nonlinear system near the fixed point

Let's now consider a very simple case: the Jacobian matrix $\mathbf{J}$ is two-dimensional. In this case, we have

$$\mathbf{J} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

The characteristic equation becomes

$$\det \begin{bmatrix} a-\lambda & b \\ c & d-\lambda \end{bmatrix} = 0$$

Expanding the determinant yields

$$\lambda^2 - \tau\lambda + \Delta = 0 \tag{28}$$

where $\tau = \mathrm{Tr}\mathbf{J} = a + b$ and $\Delta = \mathrm{Det}\mathbf{J} = ad - bc$. Then we have

$$\lambda_{1,2} = \frac{\tau \pm \sqrt{\tau^2 - 4\Delta}}{2} \tag{29}$$

Vector field and phase trajectory

A vector function $(x(t), y(t))$ is a solution of the two-dimensional system

$$\dot{x} = f(x, y), \tag{30}$$

$$\dot{y} = g(x, y), \tag{31}$$

starting with an initial condition $(x(0), y(0)) = (x_0, y_0)$. This requirement has a simple geometrical interpretation: a solution is a curve $(x(t), y(t))$ on the phase plane which is tangent to the vector field.

Poincare-Bendixson Theorem

See slides.

Now let us go back to the two-dimensional model. Let us determine the null-clines of the $I_{Na,p} + I_K$-model. The V-nullcline is given by the equation

$$I_e - \bar{g}_L(V - E_L) - \bar{g}_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n(V - E_{\mathrm{K}}) = 0 \tag{32}$$

which has the solution

$$n = \frac{I_e - \bar{g}_L(V - E_L) - \bar{g}_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}})}{\bar{g}_{\mathrm{K}}(V - E_{\mathrm{K}})} \tag{33}$$

It typically has the form of a cubic parabola. The steady state of the gating variable n defines the n-nullcline, given by

$$n = n_\infty(V) \tag{34}$$

The $V-$ and $n-$nullclines partition the phase plane into four regions, in each of which the vector field has a different direction:

(a) Both V and n increase.

(b) V decreases but n still increases.

(c) Both V and n decrease.

(d) V increases but n still decreases.