Roskilde University, Universitetsvej 1
4000 Roskilde Denmark

Project in Science
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Modeling of signal propagation through networks of neurons

Anakin Diermayr, Alex Winter, Konstantina Kalagia, Svetlana Rusnakova, Kenni Abild, and Ana Helena Vieira de Melo Gomes Prata
Supervisor: Carsten Lunde Petersen

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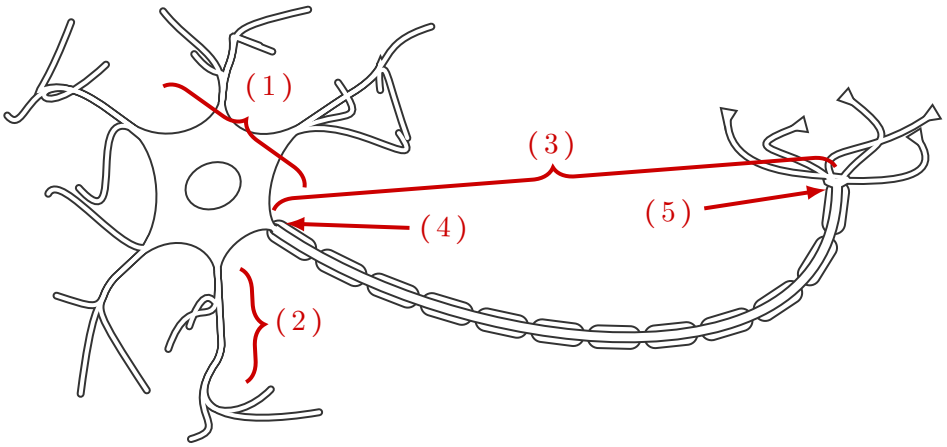


Figure 1.1: A simplified representation of a neuronal cell, with labels for each of the important features. (1) the soma of the cell; (2) a dendrite; (3) the axon; (4) the axon hill-lock; (5) the axon terminal.

The human body is composed of a vast number of cells and complex interactions, how could anyone ever expect these meaty lumps we call '*people*' to coordinate properly without an equally complex system for the transfer of information? Neurons are information highways made manifest in multi-cellular organisms. There exist many distinct types of neurons, however, the underlying mechanisms of function stay the same.

1.1 Cellular Structures

1.1.1 - Organelles

1. **The Nucleus** is mainly found in the centre of the cell and is responsible for distinguishing between eukaryotic and prokaryotic cells - existing only in the first ones. It functions as the key factor in the cell's activities, it contains the cell's gentic information (DNA), and is where the DNA replication, transcription, and RNA processing all happen.
2. **The Ribosomes**
3. **The Golgi-Apparatus**
4. **The Endoplasmic Reticulum**
5. **The Lysosome**

1.1.2 - Specialized Neuronal Structures

There exist a number of important features that are foundational to the specialized functions found in the neurons;

1. **The soma** is the main body of the neuron. It is the space in which the nucleus resides, and by extension where protein production occurs. The nucleus can range from 3 µm to 18 µm in diameter.
2. **The dendrites** of a neuron are extensions of the membrane with many branches. This overall shape and structure are metaphorically referred to as a '*dendritic tree*'*. This is where the majority of neuron inputs are received, and carried by the 'dendritic spine' down to the soma [<**empty citation**>].
3. **The axon** is a finer tendril that can extend tens, if not tens of thousands of times, the diameter of the soma in length. The axon primarily carries nerve signals away from the soma and carries some types of information back to it. Most neurons have only one axon, but this axon will be able to undergo significant branching, enabling communication with many target cells.
4. **The axon hill-lock** is the part of the axon where it emerges from the soma. The region contains the greatest density of voltage-dependent sodium channels. This makes it the most easily excited part of the neuron [<**empty citation**>].
5. **The axon terminal** is found at the terminus of the axon and contains synapses.
6. **The myelin sheathe** is a lipid and protein comprised substance excreted from ??? cells that 'sheathes' the axon, creating additional insulation for capacitance [<**empty citation**>].

1.2 The Resting Membrane Potential

A fundamental component of cells is the cell membrane, composed of what is known as a '*lipid bilayer*'†. A lipid bilayer creates a strong electrical insulation, which confers it the property of 'capacitance'- the capability of an object to store electrical charge [<**empty citation**>]. In a neuron, the overall charge in the intracellular space is negative relative to the extracellular space. This difference in charge is known as the resting membrane potential, and it is essential for the neuron's ability to transmit electrical signals.

The ions found to be involved in the membrane potential include Na^+, potassium (K^+), chlorine (Cl^-), and, to a limited degree, calcium (Ca^{2+}). In the extracellular space the concentrations of Na^+ and Cl^- are kept much higher then in the cytoplasm, whereas K^+ is found in much higher concentrations in the cytoplasm compared to the extracellular space. During rest, their concentration gradients are actively regulated and maintained at constant values by 'ion pumps', that chemically transport ions from one side of the membrane to the other [<**empty citation**>].

*Greek root word '*dendron*' meaning tree, translates to 'tree tree'.

†Latin root word 'bi' meaning two, translates to 'lipid two-layer'

This separation of charges is what creates a voltage difference across the cell membrane, with the inside being negatively charged relative to the outside. The usual resting membrane potential is found to be around −70 millivolts (mV) in neurons, however, it varies depending on the cell type and conditions [<**empty citation**>].

Another structure embedded in the lipid bilayer includes 'ion *channels*' that permit electrically charged ions to diffuse across the membrane gradient. Ion channels are only permeable to a specific ion [<**empty citation**>]. Some ion channels are voltage gated, meaning that they can be switched between open and closed states by altering the voltage difference across the membrane. Others are 'ligand gated', meaning that they can be switched between an open and a closed state by interacting with ligands that travel through the extracellular fluid.

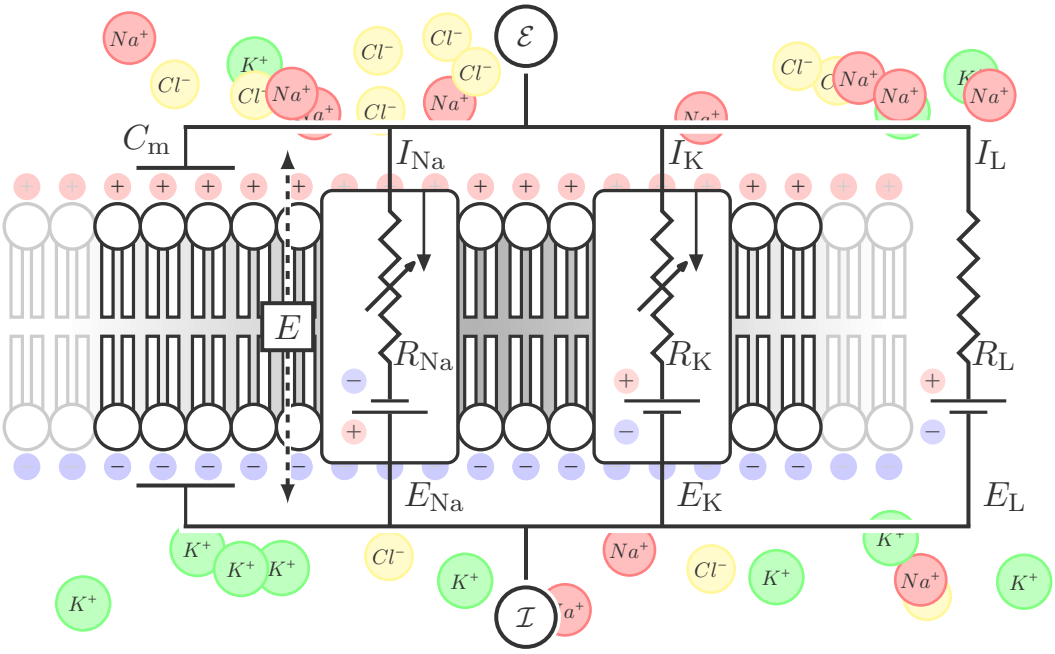


Figure 1.2: The Hodgkin-Huxely circuit diagram overlaid with the relevant structures found in the cell membrane. $\mathcal{E}$ and $\mathcal{I}$ denote the extra-cellular space and the intra-cellular space respectively. Capacitance of the membrane (C_m) is given by the charge difference on either side of the lipid bilayer. Ion channels for Na^+ and K^+ are shown with the relevant variables, resistor type, and battery. Additional ion channels and other leaked is represented as a lone resistor and battery outside of the membrane region. The K^+ ions are shown in green, Na^+ are shown in red, and Cl^- ions in yellow; distributed in approximately relative concentrations on either side of the membrane.

The voltage has two functions: first, it provides a power source for an assortment of voltage-dependent protein machinery that is embedded in the membrane; second, it provides a basis for electrical signal transmission between different parts of the membrane.

1.3 Ions Passively Diffuse Down Their Electrochemical Gradient

To predict the direction of the passive diffusion of ions through an open channel, both the concentration gradient of the ion and the membrane potential have to be known. The resultant of these two forces is called the electrochemical gradient.

Suppose that membrane potential is null (Vm=0mV), there is no difference of potential between the two faces of the membrane, so ions will diffuse according to their concentration gradient only (Figure3a). since the extracellular concentrations of Na^+, Ca^{2+} and Cl^- are higher than the respective intracellular ones, these ions will diffuse passively towards the intracellular medium (when Na^+, Ca^{2+} or Cl^- permeable channels are open) as a result of their concentration gradient. In contrast, K^+ will move from the intracellular medium to the extracellular one (when K^+ permeable channels are open).

If we suppose that there is no concentration gradient for any ions (there is the same concentration of each ion in the extracellular and intracellular media), ions will diffuse according to membrane potential only: at a membrane potential Vm=-30mV (Figure3b), positively charged ions, the cations Na^+, Ca^{2+} and K^+, will move from the extracellular medium to the intracellular one according to membrane potential. In contrast, anions (Cl^-) will move from the intracellular medium to the extracellular one.

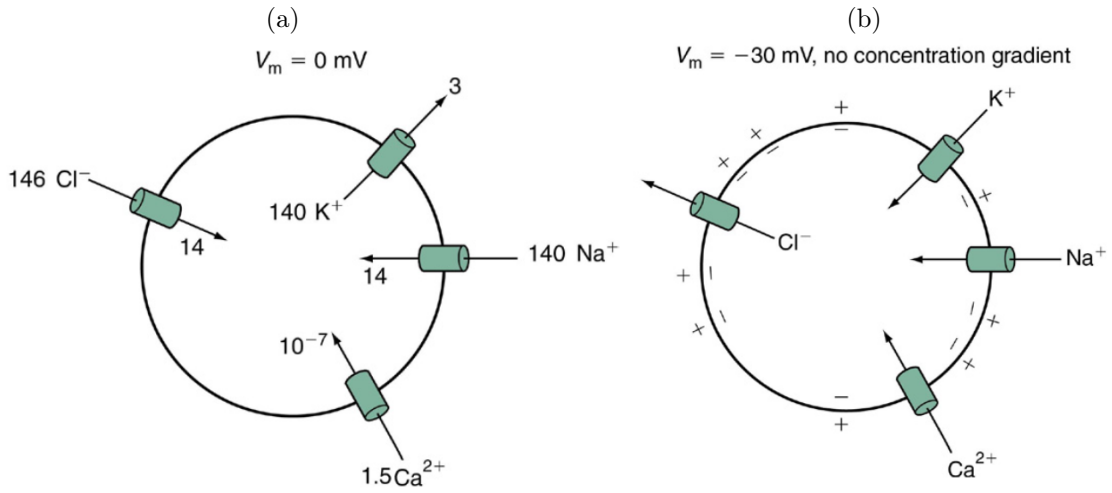


Figure 1.3: Passive diffusion of ions. Passive diffusion of ions according (a) their concentration gradient only, or (b) to membrane potential (electrical gradient) only (Vm = -30mV).

In physiological conditions, both the concentration gradient and membrane potential determine the direction and amplitude of ion diffusion through an open channel. since concentration gradient is constant for each ion, the direction and amplitude of diffusion varies with membrane potential. When comparing Figure3 a and b it appears that at a membrane potential of -30mV, concentration gradient and membrane potential drive Na^+ and Ca^{2+} ions in the same direction, toward the intracellular medium, whereas they drive K^+ and Cl^- in reverse directions. The resultant of these two forces, concentration and potential gradients, is the electrochemical gradient. To know how to express the electrochemical gradient, the equilibrium potential must first be explained.

1.4 Equilibrium Potential of a Given Ion

All systems yearn for their equilibrium, the fabled *steady state*. This divine relation of the components in a system, one achieved, the system no longer needs to evolve, it has been perfected by entropy. The value of the membrane potential is constantly fluctuating depending on the relative distribution of charged particles that cross the membrane. When the direction of the gradient is perfectly balanced at net zero, it is referred to as the '*equilibrium potential*' of the given ion ($E_{\mathbf{ion}}$), alternatively, as the '*reversal potential*' of the ion $E_{\mathbf{rev}}$. $E_{\mathbf{ion}}$ of the relevant ions can be calculated using the *Nernst* equation:

$$E_{\mathbf{ion}} = \left(\frac{\mathcal{R} \cdot \mathcal{T}}{z \cdot \mathcal{F}} \right) \ln \left(\frac{[\,\mathbf{ion}\,]_{\mathcal{E}}}{[\,\mathbf{ion}\,]_{\mathcal{I}}} \right) \tag{1.1}$$

Where $\mathcal{R}$ is the ideal gas constant $\left(8.31\,\mathrm{m^3\,Pa\,K^{-1}\,mol^{-1}} \right)$; $\mathcal{T}$ is the temperature in kelvin ($x\,^{\circ}\mathrm{C} \cong 273.15 + x\,\mathrm{K}$); $\mathcal{F}$ is the Faraday constant $\left(96\,500\,\mathrm{C\,mol^{-1}} \right)$; z is the valence of the ion; and [**ion**] is the concentration of the given ion in the extracellular ($\mathcal{E}$) or intracellular ($\mathcal{I}$) medium. As most of the terms are constants, its simple to reduce the equation down in dimensional complexity:

$$E_{\mathbf{ion}} = \left(\frac{8.31\,\mathrm{m^3\,Pa\,mol^{-1}\,K^{-1}} \cdot \mathcal{T}}{z \cdot 96\,500\,\mathrm{C\,mol^{-1}}} \right) \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \tag{1.1 i}$$

dividing and rearranging the terms:

$$E_{\mathbf{ion}} = \left(\frac{\mathcal{T}\mathrm{K^{-1}\,m^3\,Pa}}{z \cdot 11\,612.52\,\mathrm{C}} \right) \cdot \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \tag{1.1 ii}$$

converting the unit of pressure, pascal (Pa) to the base units representing mass over an area over time $\left(\mathrm{kg\,m^{-1}\,s^{-2}} \right)$, as well converting the unit for charge, a coulomb (C), to the base units denoting the quantity of current in a second, (A s), gives the substitution:

$$E_{\mathbf{ion}} = \left(\frac{\mathcal{T}\mathrm{K^{-1}\,m^3\,kg\,m^{-1}\,s^{-2}}}{z \cdot 11\,612.52\,\mathrm{A\,s}} \right) \cdot \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \tag{1.1 iii}$$

at this point we're only left with base SI units, so we need to be a little silly, the unit of magnetic flux is defined $\mathrm{Wb} = \mathrm{kg\,m^2\,s^{-2}\,A^{-1}}$, implying through substitution $\mathrm{kg\,m^2\,s^{-3}\,A^{-1}} = \mathrm{Wb\,s^{-1}}$:

$$E_{\mathbf{ion}} = \frac{\mathcal{T}\mathrm{K^{-1}}}{z \cdot 11\,612.52} \cdot \left(\mathrm{Wb\,s^{-1}} \right) \cdot \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \tag{1.1 iv}$$

a unit describing the rate of change of magnetic charge per second, which is equivalent to a Volt, $\mathrm{Wb\,s^{-1}} = \mathrm{V} = \mathrm{kg\,m^2\,s^{-3}\,A^{-1}}$, the combination of units found through deconstruction is the literal base unit definition of a volt:

$$E_{\mathbf{ion}} = \frac{\mathcal{T}\mathrm{K^{-1}}}{z \cdot 11\,612.52} \cdot \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \mathrm{V} \tag{1.1 v}$$

With minor adjustments to eq. (1.1 v), the now derived form of eq. **(1.1)**, one is able to get

$$E_{\mathbf{ion}} = \frac{\mathcal{T}\mathrm{K^{-1}}}{z} \cdot \ln \left(\frac{[\mathbf{ion}]_{\mathcal{E}}}{[\mathbf{ion}]_{\mathcal{I}}} \right) \cdot 11.61^{-1}\ \mathrm{mV} \tag{1.2}$$

Plugging the relative concentrations, measured in millimols (mmol), of each ion into eq. (**1.2**), as well as choosing an arbitrary temperature, such as room temperature $\approx 20\,°\mathrm{C}$ ($(20 + 273.15)\,\mathrm{K}$), the equilibrium potential of each ion follows as:

$$E_{\mathrm{Na}} = 293.15\ \ln\left(\frac{140}{14}\right)\cdot 11.61^{-1} = 58.13\,\mathrm{mV} \tag{1.2$_{\mathrm{i}}$}$$

$$E_{\mathrm{K}} = 293.15\ \ln\left(\frac{3}{140}\right)\cdot 11.61^{-1} = -97.01\,\mathrm{mV} \tag{1.2$_{\mathrm{ii}}$}$$

$$E_{\mathrm{Cl}} = \frac{293.15}{2}\ \ln\left(\frac{1.5}{10^{-4}}\right)\cdot 11.61^{-1} = 121.37\,\mathrm{mV} \tag{1.2$_{\mathrm{iii}}$}$$

$$E_{\mathrm{Ca}} = -293.15\ \ln\left(\frac{146}{14}\right)\cdot 11.61^{-1} = -59.19\,\mathrm{mV} \tag{1.2$_{\mathrm{iv}}$}$$

These equations can be interpreted such that when K^+ channels open in the membrane, the efflux of K^+ ions will hyper-polarize the membrane until $V_m = E_K \approx -97\,\mathrm{mV}$, at which point the net flux of K^+ is null being that K^+ ions have exactly the same potential to move towards the extracellular space as the intracellular space. The efflux of K^+ will be exactly compensated by the influx of K^+ and the membrane potential will stabilize at E_K for as long as the K^+ channels stay open. Assuming only Na^+ channels are open, the membrane potential will move toward $V_m = 58\,\mathrm{mV}$, the potential at which the net flux of Na^+ is null. Similarly, when $V_m = E_{Ca} \approx -59\,\mathrm{mV}$, the net flux of Cl^- is null. By extension, should $V_m \neq E_K$, the net flux of K^+ will no longer be null. This holds true for all ions: when $V_m \neq E_{\mathbf{ion}}$ there is a net flux of the ion [<**empty citation**>]. The difference $(V_m - E_{ion})$ is called the electrochemical gradient. It is the force that makes the ions move through an open channel.

1.5 Ionic currents

The passive diffusion of ions through an open channel is a movement of charges through a resistance (resistance here is a measure of the difficulty of ions moving through the channel pore). Movement of charges through a resistance is a current. Through a single channel the current is called 'single-channel current' or 'unitary current', i_{ion}. The amplitude of i_{ion} is expressed in amperes (A) which are coulombs per seconds (C.s-1).

In general, currents are expressed following ohm's law: U=RI, where I is the current through a resistance R and U is the difference of potential between the two ends of the resistance. For currents carried by ions (and not by electrons as in copper wires), I is called i_{ion}, the current that passes through the resistance of the channel pore which has a resistance R (called r_{ion}). But what is U in biological systems? U is the force that makes ions move in a particular direction; it is the electrochemical gradient for the considered ion and is also called the driving force: $U = (V_m - E_{ion})$. According to ohm's law, the current i_{ion} through a single channel is derived from

$$(V_m - E_{ion}) = r_{ion} \times i_{ion}$$

So:

$$i_{ion} = 1/r_{ion}(V_m - E_{ion}) = \gamma_{ion}(V_m - E_{ion})$$

γ_{ion} is the reciprocal of resistance; it is called the *conductance* of the channel, or unitary conductance. It is a measure of the ease of flow of ions (flow of current) through the channel pore. Whereas resistance is expressed in ohms (Ω), conductance is expressed in siemens (S). By convention i_{ion} is negative when it represents an inward flux of positive charges (cations) and i_{ion} is positive when it represents an outward flux of positive charges. It is generally of the order of pico-amperes (1 pA=10-12 A). At physiological concentrations, γ_{ion} varies between 10 and 150 pico-siemens (pS), according to the channel type.

In physiological conditions, however, several channels of the same type are open at the same time in the neuronal membrane. Suppose that only one type of channel is open in the membrane, for example Na^+ channels, the total current I_{Na} that crosses the membrane at time t is the sum of the unitary currents i_{Na} at time t:

$$I_{Na} = Np_o i_{Na}$$

where N is the number of Na^+ channels present in the membrane; p_o is the probability of Na^+ channels being open at time t (Np_o is therefore the number of open Na^+channels in the membrane at time t); and i_{Na} is the unitary Na^+ current.

More generally:

$$I_{ion} = Np_o i_{ion}$$

By analogy, the total conductance of the membrane for a particular ion is:

$$G_{ion} = Np_o \gamma_{ion}$$

and from $i_{ion} = \gamma_{ion}(V_m - E_{ion})$ above:

$$I_{ion} = G_{ion}(V_m - E_{ion})$$

I_{ion} and i_{ion} can be measured experimentally. The latter is the current measured from a patch of membrane where only one channel of a particular type is present. Iion is the current measured from a whole cell membrane where N channels of the same type are present.

1.6 Action Potential

Functionally all eukaryotic cell membranes maintain a difference in voltage between the extracellular and intracellular space, this difference is called the 'membrane potential'. An expected membrane potential in human cells is −70 mV [<**empty citation**>]. AP is the measure of the potential that causes action.

An AP occurs when the potential of an excitable cell's membrane rapidly rises and falls. This depolarization then causes adjacent locations to similarly 'depolarize', creating a chain reaction in the form of a 'wavelet'. The voltage fluctuations take the form of a rapid upward spike followed by a rapid fall.

"All-or-none" principle

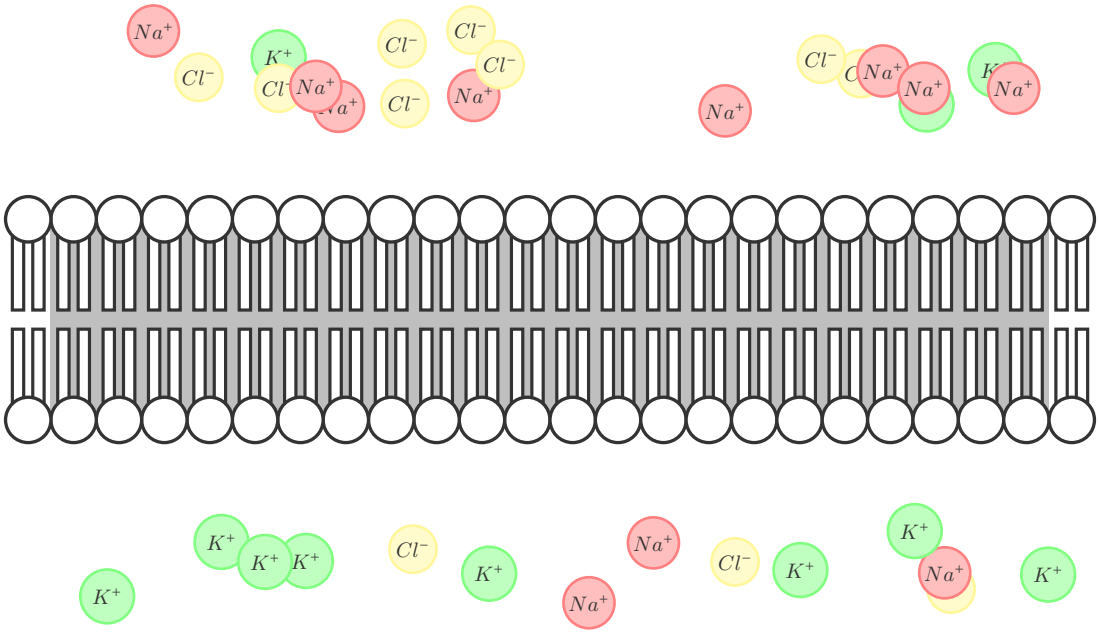


Figure 1.4: ⟨temp⟩

The AP is a sudden and rapid depolarization of the membrane as a result of positive inward current entering the axon initial segment. In neuronal somas and axons, these positive inward currents are most commonly carried by Na^+ cations (positively charged ions).

The ionic basis for neuronal excitation was first described in the squid giant axon by Hodgkin and Huxley (1952) using the voltage clamp technique. They observed a key phenomenon, that the AP is underlied by two separate voltage-dependent currents: an early transient inward Na^+ current which depolarizes the membrane, and a delayed outward K^+ current largely responsible for repolarization. The resulting voltage waveform takes the shape of a rapid upward spike followed by a rapid inactivation that eventually slightly hyperpolarizes the membrane before returning to resting membrane potential Figure (1.5).

Up to a threshold level of membrane depolarization (called the threshold potential), only passive ohmic response can be recorded, but when the membrane is depolarized just above threshold, an AP can be evoked. Increasing the intensity of the stimulating current pulse does not increase the amplitude of the AP, the AP is all or none.

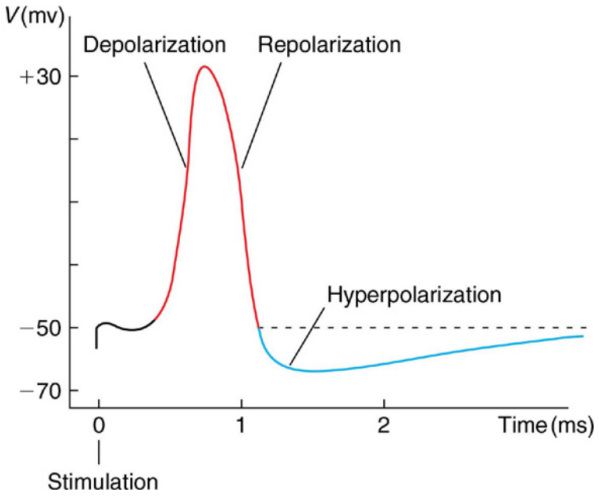


Figure 1.5: The AP spike, indicating the different phases.

1.6.1 - The depolarization phase of Na^+-dependent AP results from the transient entry of Na^+ ions through voltage gated Na^+ channels.

The threshold for initiation of Na^+-dependent action potential is due to the fact that voltage-gated Na^+ channels open only in response to a depolarization positive of −50 mV to −40 mV, hence the name 'voltage-gated'.

In response to a depolarization to the threshold potential, the closed Na^+ channels of the axon initial segment begin to open. The flux of Na^+ ions through the few open Na^+ channels depolarizes the membrane more and thus triggers the opening of other Na^+ channels. In consequence, the flux of Na^+ ions increases, depolarizes the membrane more and opens other Na^+ channels until all the Na^+ channels of the segment of membrane are opened, which is when the depolarization phase is at its peak. Na^+ channels are opened by depolarization and once opened, they contribute to the membrane depolarization and therefore to their activation: it is a self-maintained process, which is why the Na^+-dependent action potential is all or none. Once initiated, the AP propagate along the axon without decaying, with a speed varying from $1\,m\,s^{-1}$ to $100\,m\,s^{-1}$ depending on the type of axon. It propagates without attenuation since the density of voltage-gated Na^+ channels is constant along the axon as well as due to the presence of the insulating myelin sheathe. Once the channels inactivate, they may not reopen, which ensures that AP only propagates unidirectionally forward. The time during which the Na^+ channel stays open varies around an average value, τ_0, called the mean open time. The functional significance of this value is the following: during a time equal to τ_0 the channel has a high probability of staying open.

The I_{Na}/V relation is obtained by plotting the amplitude of the unitary current (I_{Na}) versus membrane potential (V_m). It is linear between −50 mV to 0 mV. For membrane potentials more hyperpolarized than −50 mV, there are no values of I_{Na} since the channel rarely opens or does not open at all. Quantitative data for potentials more depolarized than 0 mV are not available.

When the activity of a single Na^+ channel is recorded at different test potentials, it was observed that the amplitude of the inward unitary current (I_{Na}) diminishes as the memrane is further and further depolarized. The critical point of the current/voltage relation is the membrane potential for which the current is zero; i.e. the reversal potential of the current (E_{rev}). If only Na^+ ions flow through the Na^+ channel, the reversal potential is equal to E_{Na}. From $-50\,mV$ to E_{rev}, I_{Na} is inward and its amplitude decreases. This results from the decrease of the Na^+ driving force $(V_m - E_{Na})$ as the membrane approaches the reversal potential for Na^+ ions. For membrane potentials more depolarized than E_{rev}, I_{Na} is now outward. Above E_{rev}, the amplitude of the outward Na^+ current progressively increases as the driving force for the exit of Na^+ ions increases.

The linear I_{Na}/Vrelation is described by the equation $I_{Na} = g_{Na}(V_m - E_{Na})$, where V_m is the test potential, E_{Na} is the reversal potential of the Na^+ current, and g_{Na} is the conductance of a single Na^+ channel (unitary conductance). The value of g_{Na} is given by the slope of the linear I_{Na}/V curve. It has a constant value at any given membrane potential. This value varies between 5 ps to 18 ps depending on the preparation.

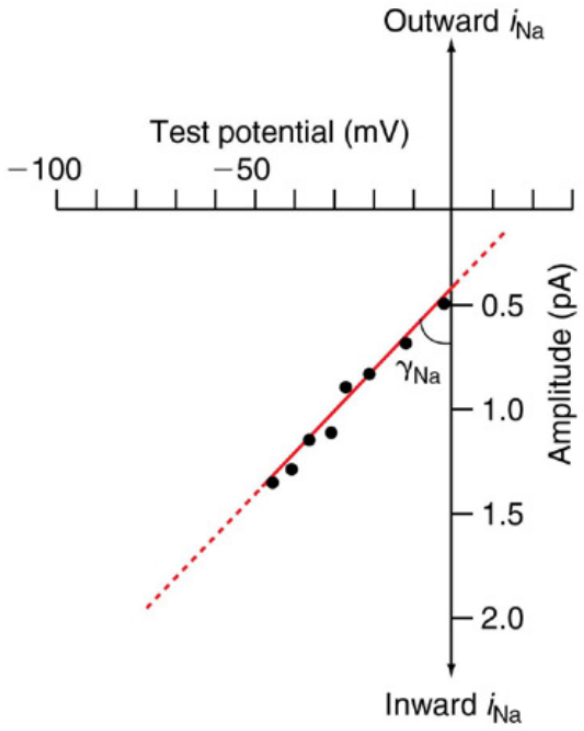


Figure 1.6: The single-channel current/voltage (I_{Na}/V) relation is linear.

The open probability of the voltage-gated Na^+ channel is voltage and time dependent. During cell recordings of Na^+ channels, it was observed that when the membrane potential is depolarized, the probability of the Na^+ channel being in the open state increases with depolarization to a maximal level. The higher is the depolarizing step, the higher is the probability of the Na^+ channel opening. It also varies with time during the depolarizing step: openings occur more frequently at the beginning of the step. It was observed that after 4 ms to 6 ms the probability of the Na^+ channel being in the open state is very low, even with large depolarizing steps: the Na^+ channel in-activates in 4 ms to 6 ms. The probability of the Na^+ channel being in the open state at time $t = 2$ ms, for example, increases with the amplitude of the depolarizing step. To generalize, at −30 mV the open probability is maximum, and the channels inactivate in 4 ms.

I_{Na} is the macroscopic current, or the sum of all unitary currents, I_{Na} flowing through all the open Na^+ channels of the recorded membrane. In Figure 7b, an average of 300 unitary Na^+ currents elicited by a 40 mV depolarizing pulse is shown. For a given potential, the 'averaged' inward Na^+ current has a fast rising phase and presents a peak at the time $t = 1.50$ ms. The peak corresponds to the time when most of the Na^+ channels are opened at each trial. Then the averaged current decays with time because the Na^+ channel has a low probability of being in the open state later in the step (owing to the inactivation of the Na^+ channel). At each trial, the Na^+ channel does not inactivate exactly at the same time, which explains the progressive decay of the averaged macroscopic Na^+ current. A similar averaged Na^+ current is shown in Figure 4.8b.

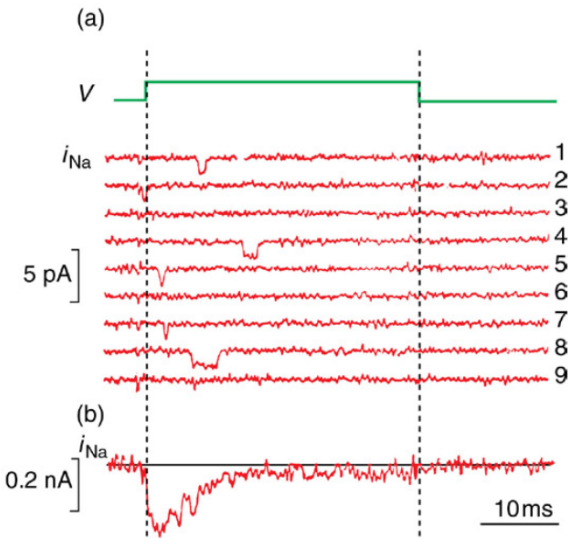


Figure 1.7: Single Na^+ channel openings in response to adepolarizing step. (a) Nine successive recordings of single channel openings (iNa) in response to a 40mV depolarizing pulse (V trace in green) applied at 1s intervals from resting membrane potential. (b) Averaged inward Na^+ current from 300 elementary Na^+ currents as in (a).

The more numerous are the Na^+ channels opened by the depolarizing step, the smoother is the total Na^+ current. The value of I_{Na} at each time t at a given potential is:

$$I_{Na} = Np_{(t)}i_{Na}$$

where N is the number of Na^+ channels in the recorded membrane and p(t) is the open probability at time t of the Na^+ channel; it depends on the membrane potential and on the channel opening and inactivating rate constants. I_{Na} is the unitary Na^+ current and Np(t) is the number of Na^+ channels open at time t.

Subsequently, the relation of the macroscopic Na^+ current I_{Na} and voltage V is not linear, but rather has a clear bell shape, with a peak at around −40 mV.

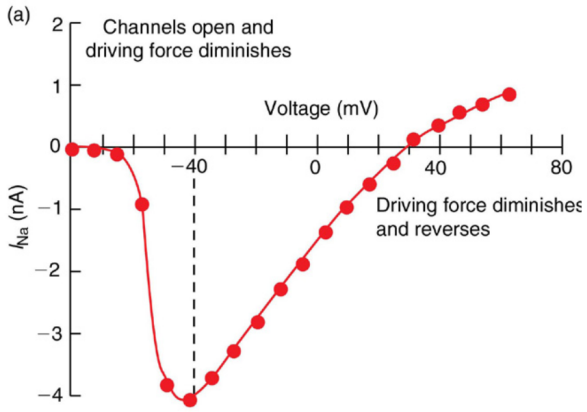


Figure 1.8: The INa-V relation has a bell shape. (From Chiu Sy, ritchie JM, bogart rb, Stagg d (1979) A quantitative description of membrane currents from a rabbit myelinated nerve. J. Physiol.292, 149–166)

For small steps, the peak current amplitude is small (0.2nA) and has a slow time to peak (1ms). At these potentials, the Na^+ driving force is strong but the Na^+ channels have a low probability of opening. Therefore, INa is small since it represents the current through a small number of open Na^+ channels.

As the depolarizing steps increase in amplitude (to -42/-35mV), the amplitude of INa increases to a maximum (-3nA) and the time to peak decreases to a minimum (0.2ms). Larger depolarizations increase the probability of the Na^+ channel being in the open state and shorten the delay of opening. Therefore, though the amplitude of iNa decreases between −63 mV and −35 mV, the amplitude of INa increases owing to the large increase of open Na^+channels.

After this peak, the amplitude of INa decreases to zero since the open probability does not increase enough to compensate for the decrease of iNa. The reversal potential of INa is the same as that of iNa since it depends only on the extracellular and intracellular concentrations of Na^+ ions.

INa changes polarity for Vm more depolarized than Erev: it is now an outward current whose amplitude increases with the depolarization

Activation and inactivation curves

Activation rate is the rate at which a macroscopic current turns on in response to a depolarizing voltage step. The Na^+ current is recorded in voltage clamp from a node of rabbit nerve. Depolarizing steps from -70mV to +20mV are applied from a holding potential of -80mV. When the ratio of the peak current at each test potential to the maximal peak current (I_{Na}/I_{Namax}) is plotted against test potential, the activation curve of INa can be visualized. The distribution is fitted by a sigmoidal curve. In this preparation, the threshold of Na^+ channel activation is -60mV. At -40mV, INa is already maximal (INa/INamax = 1). This steepness of activation is a characteristic of the voltage-gated Na^+ channels.

Inactivation of a current is the decay of this current during a maintained depolarization. To study inactivation, the membrane is held at varying holding potentials and a depolarizing step to a fixed value is applied where INa is maximal (0mV, for example). The amplitude of the peak Na^+ current is plotted against the holding potential. INa begins to inactivate at -90mV and is fully inactivated at -50mV. Knowing that the resting membrane potential in this preparation is around -80mV, some of the Na^+ channels are already inactivated at rest.

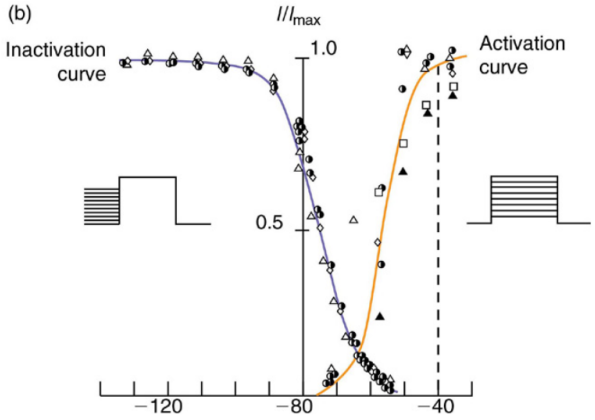


Figure 1.9: Activation (right curve) and inactivation (left curve) curves obtained from nine different experiments. The voltage protocols used are shown in insets. In the ordinates, I/Imax represents the ratio of the peak Na^+ current (I) recorded at the tested potential of the abscissae and the maximal peak Na^+ current (Imax) recorded in this experiment. (From Chiu Sy, ritchie JM, bogart rb, Stagg d (1979) A quantitative description of membrane currents from a rabbit myelinated nerve. J. Physiol.292, 149–166)

1.6.2 - The repolarization phase of the sodium-dependent AP results from Na^+ channel inactivation and partly from channel activation

The voltage-gated Ka+ channel type that participates in membrane repolarization are the so called delayed rectifiers, which activate after a delay following membrane depolarization and inactivate slowly. The function of the delayed rectifier channel is to transduce, with a delay, membrane depolarization into an exit of K+ ions.

The gating behavior of the delayed rectifier channel is different from that of the Na+ channel. Whereas all four voltage-sensitive domains in K+ channels must be activated in order for pore opening to occur, Na+ channel pore opening requires activation of only three voltage-sensitive domains. Thus, part of the difference in activation speed between Na+ and K+ channels may be due to the lesser number of voltage-sensitive domains required to move in Na+ channels.

The average open time τ_O measured in the patch illustrated in Figure10 is 4.6ms. The mean closed time τ_c is 1.5ms. As seen in the figure, during a depolarizing pulse to 0mV the delayed rectifier channel spends much more time in the open state than in the closed state: at 0mV its average open probability is high (po=0.76).

In order to test whether the delayed rectifier channels show some inactivation, long-lasting recordings are performed. Though no significant inactivation is apparent during test pulses in the range of seconds, during long test depolarizations (in the range of minutes) the channel shows steady-state inactivation at positive holding potentials (not shown). Therefore, in the range of seconds, the inactivation of the delayed rectifier channel can be omitted: the channel fluctuates between the closed and open states:

$$C \rightleftharpoons O$$

The transition from the closed (C) state to the open (o) state is triggered by membrane depolarization with a delay. The delayed rectifier channel activates in the range of milliseconds. In comparison, the Na+ channel activates in the range of submilliseconds. The O to C transitions of the Na+ channel frequently happen though the membrane is still depolarized. It also happens when the membrane repolarizes.

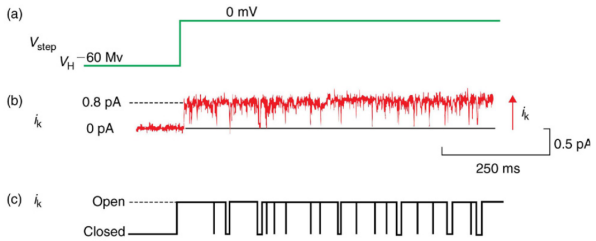


Figure 1.10: Single K+ channel openings in response to a depolarizing step. The activity of a single delayed rectifier channel expressed from rat brain is recorded in patch clamp (inside-out patch). A depolarizing step to 0mV from a holding potential of -60mV(a) evokes the opening of the channel (b). The elementary current is outward. The channel then closes briefly and reopens several times during the depolarization, as shown in the drawing (c) that interprets the current trace. bathing solution or intracellular solution (in mM): 100 KCl, 10 eGTA, 10 HepeS. pipette solution or extracellular solution (in mM): 115 NaCl, 2 KCl, 1.8 CaCl2, 10 HepeS. Adapted from Stühmer W, Stocker M, Sakmann bet al. (1988) potassium channels expressed from rat brain cdNA have delayed rectifier properties. FEBS Lett.242, 199–206, with permission.

The K+ channel has a constant unitary conductance γ_K. In Figure 11a, unitary currents are shown in response to increasing depolarizing steps from -50 to +20mV from a holding potential of -80mV. It can be observed that both the amplitude of the unitary current and the time spent by the channel in the open state increase with depolarization.

When the mean amplitude of the unitary K+ current is plotted versus membrane test potential, a linear i_K/V relation is obtained. This linear i_K/V relation (between -50 and +20mV) is described by the equation $i_K = \gamma_K(V - E_K)$, where V is the membrane potential, E_K is the reversal potential of the K+ current, and γ_K is the conductance of the single delayed rectifier K+ channel, or unitary conductance.

Linear back-extrapolation gives a reversal potential value around -90/-80mV, a value close to E_K calculated from the Nernst equation. This means that from -80mV to more depolarized potentials, which correspond to the physiological conditions, the K+ current is outward. For more hyperpolarized potentials, the K+ current is inward. The value of γ_K is given by the slope of the linear i_K/Vcurve. It has a constant value at any given membrane potential. This value varies between 10 and 15pS depending on the preparation.

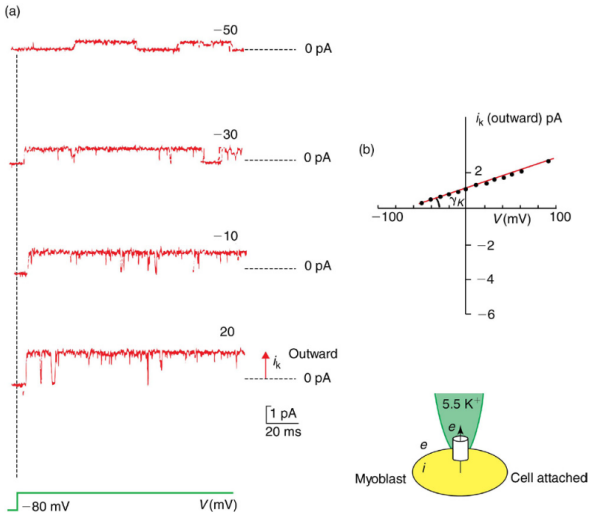


Figure 1.11: The single-channel current/voltage (iK/V) relation is linear.delayed rectifier K+ channels from rat brain are expressed in a myo-blast cell line. (a) The activity of a single channel is recorded in patch clamp (cell-attached patch). unitary currents are recorded at different test potentials (from -50mV to +20mV) from a holding potential at -80mV. bottom trace is the voltage trace. (b)iK-V relation obtained by plotting the mean amplitude of iK at the different test potentials tested. iK reverses at =-75mV and gK=14pS. Intrapipette solution (in mM): 145 NaCl, 5.5 KCl, 2 CaCl2, 2 MgCl2, 10 HepeS. Adapted from Koren G, liman er, logothetis deet al. (1990) Gating mechanism of a cloned potassium channel expressed in frog oocytes and mammalian cells. Neuron2, 39–51.

The macroscopic delayed rectifier K+current (IK) has a delayed voltage dependence of activation and inactivates within tens of seconds. Whole cell currents start to activate at potentials positive to -30mV and their amplitude is clearly voltage dependent. When unitary currents recorded from 70 successive depolarizing steps to 0mV are averaged (Figure4.20b), the macroscopic outward current obtained has a slow time to peak (4ms) and lasts the entire depolarizing step. The whole cell current amplitude at steady state (once it has reached its maximal amplitude) for a given potential is

$$I_K = Np_o i_K,$$

where N is the number of delayed rectifier channels in the membrane recorded, p_o the open probability at steady state and iK the elementary current. The number of open channels Npo increases with depolarization (to a maximal value) and so does IK.

The IK/V relation shows that the whole cell current varies linearly with voltage from a threshold potential which, for those conditions, is around -40mV . When the membrane is more hyperpolarized than the threshold potential, very few channels are open and IK is equal to zero. For membrane potentials more depolarized than the threshold potential, IK depends on p_o and the driving force state (V-EK) which augments with depolarization. once p_o is maximal, IK augments linearly with depolarization since it depends only on the driving force.

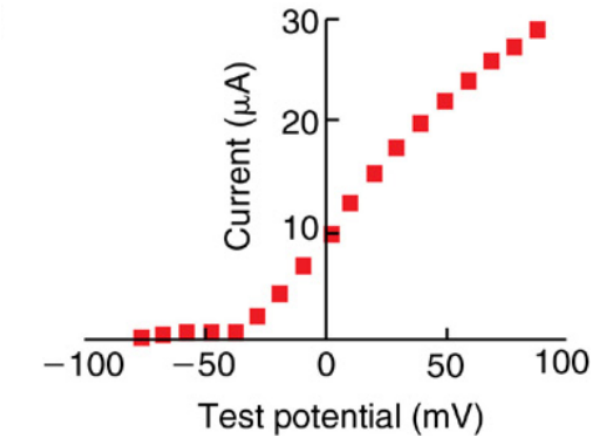


Figure 1.12: Characteristics of the macroscopic delayed recti-fier K+ current. The amplitude of the current at steady state is plotted against test potential. The potential threshold for its activation is -40mV.

In conclusion, owing to their delay of opening, delayed rectifier channels open when the membrane is already depolarized by the entry of Na+ ions through open voltage-gated Na+ channels. Therefore, the exit of K+ ions does not occur at the same time as the entry of Na+ ions. This allows the membrane to first depolarize in response to the entry of Na+ ions and then to repolarize as a consequence of the exit of K+ ions.

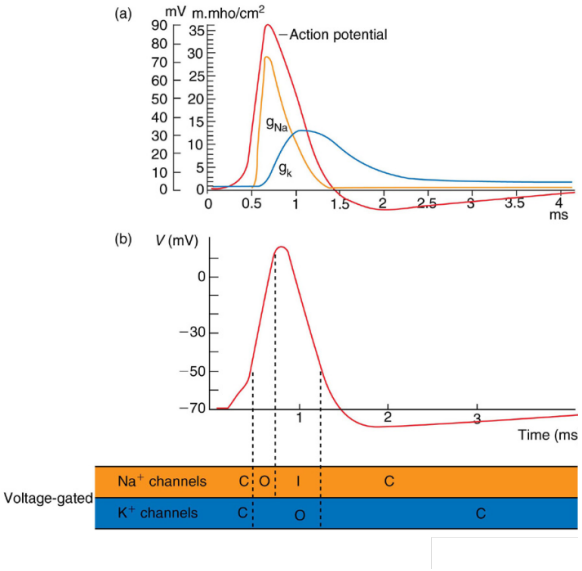


Figure 1.13: Gating of Na+ and K+ chan-nels during the Na+-dependent action potential.(a) Interpretation of the manner in which the con-ductances to Na+ and K+ contribute to the action potential. (b) State of the Na+ and K+ voltage-gated channels during the course of the action potential. o, channels open; I, channels inactivate; C, channels close or are closed. Trace (a) adapted from Hodgkin Al, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol.117, 500–544.

2 Electromagnetism

2.1 Circuits

The circuit for the Hodgkin-Huxley model can be seen in Figure (2.1).

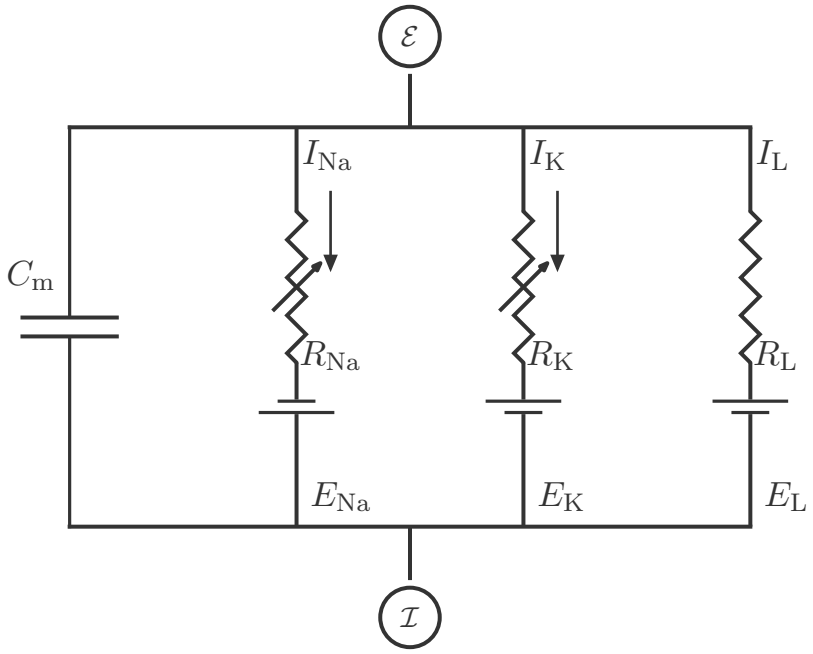


Figure 2.1: The circuit diagram of the Hodgkin-Huxely (HH) model [1].

There are five elements to this circuit diagram. These are the batteries, capacitor, resistor, variable resistor, and wire.

The batteries are symbolised by two parallel lines where one is longer than the other. The shorter end is the negative side (anode) and the longer end is the positive side (cathode). In this model, there are three batteries placed in different directions. The task of the batteries is to store energy and push said energy through the wire. When batteries are placed in parallel like this, the voltage does not get increased. However, the current capacity increases, so the batteries last longer. The unit of batteries is watt-hours (Wh) or milliamp-hours (mAh) [<**empty citation**>].

The symbol for the capacitor is two parallel lines of equal length. Much like the batteries, the capacitor stores electrical charge. However, a capacitor cannot store as much energy as a comparable-sized battery. But in return, capacitors can charge and discharge faster. Capacitance is measured in Farads (F) [<**empty citation**>].

resistors are represented by zig-zag lines. These work against the batteries and the resistor as it removes energy from the equation and turns it into heat. The resistor has a fixed value of resistance. This is measured in ohms (Ω) [<**empty citation**>].

Variable resistors, also called varistors, are a type of resistor. These are also represented by a zig-zag line, however, they have an arrow through them. Unlike the normal resistor, the varistors have almost infinite resistance before a certain voltage. Here they act like an insulator allowing almost no current through. After it has reached a certain voltage, it slowly starts to act like a conductor, having almost no resistance [<**empty citation**>].

The lines connecting the pieces together are the wire. Much like what is shown in the figure, the wire connect all the parts of the model. The wire are in theory considered to have no resistance. But in reality, they always have some, even if it is very little [<**empty citation**>].

2.2 Voltage + Current

The flow of charge is called current. Current is measured by the number of charges that pass through a boundary per unit of time. The symbol for current is I and its unit is Ampere. The formula for current is derived from Ohm's law. Ohm's law is $V = IR$, where V is the voltage, I is the current, and R is the resistance. Voltage is synonymous with electric pressure. This pressure pushes the current through a loop in order for it to produce some kind of work [<**empty citation**>].

3 Mathematical Modeling

The attempt to find an equation which can accurately describe the behavior of a chosen system is one of the most fundamental aspects of mathematics.

A model is a series of mathematical equations capable of replicating the behavior of a system. A role of these models, known as dynamic systems, is to bring light in the gaps of understanding and explain the underlying mechanisms behind some function. The construction of a model requires equations complex enough to accurately describe the dynamics of interest yet, preferably, simple enough so that mathematical tools exist to analyze the equations*. There exists any number of limitations in the pursuit of this task, some inherent to the system, others inherent to our modern construction of mathematics.

3.1 Scale of model

In scaling processes the complexity of a system will often change. Scaling neural models is a multidimensional challenge involving trade-offs between model complexity, computational efficiency, and the ability to provide meaningful insights into neural function. As can be seen in figure3.2 the

cf. appendix[fig. (1)] on the summery of different spiking scenarios.

For neural networks scaling up involves increasing the number of neurons interacting and To capture the realism the number of parameters will have to increase as well.

*The best model of a cat is a cat. Preferably the same cat†.-'*Philosophy of Science, 1945, Arturo Rosenblueth (1900-1970)*'

†If man could be crossed with the cat, it would improve man, but it would deteriorate the cat.-'*Mark Twain*'.

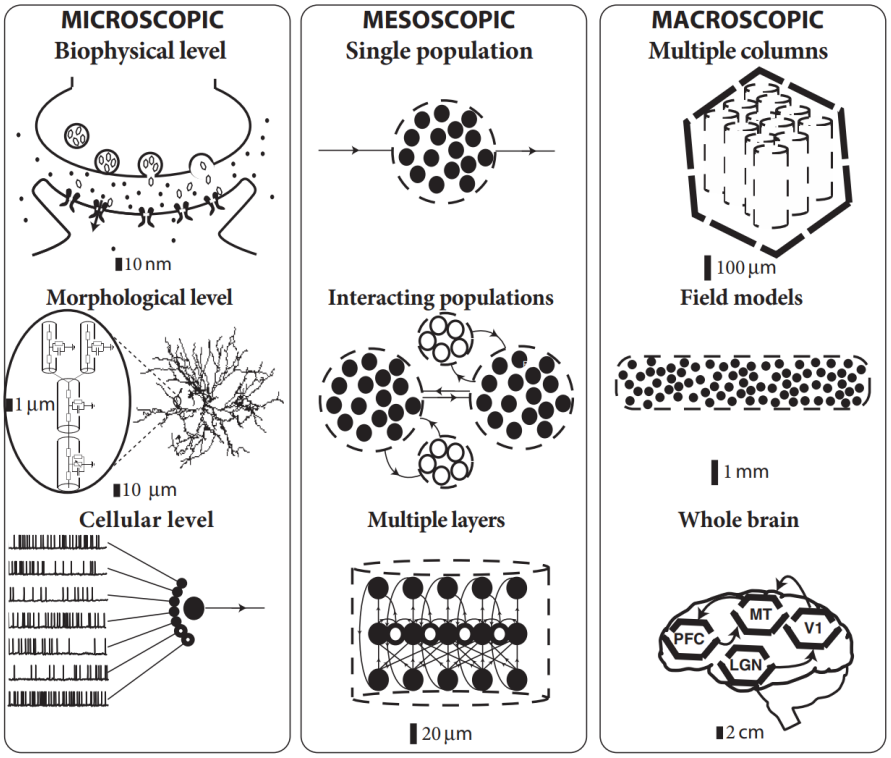
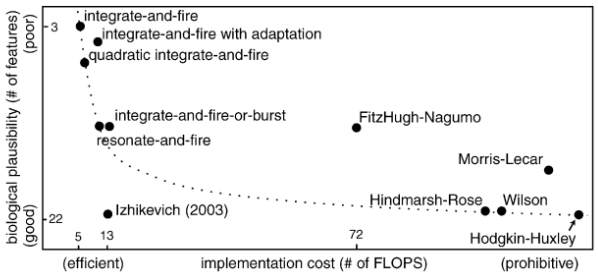


Figure 3.1: Level of description, [2].

....



Models	biophysically meaningful	tonic spiking	phasic spiking	tonic bursting	phasic bursting	mixed mode	spike frequency adaptation	class 1 excitable	class 2 excitable	spike latency	subthreshold oscillations	resonator	integrator	rebound spike	rebound burst	threshold variability	bistability	DAP	accommodation	inhibition-induced spiking	inhibition-induced bursting	chaos	# of FLOPS
integrate-and-fire	-	+	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	5
integrate-and-fire with adapt.	-	+	-	-	-	-	+	+	-	-	-	-	+	-	-	-	-	+	-	-	-	-	10
integrate-and-fire-or-burst	-	+	+		+	-	+	+	-	-	-	-	+	+	+	-	+	+	-	-	-		13
resonate-and-fire	-	+	+	-	-	-	-	+	+	-	+	+	+	+	-	-	+	+	+	-	-	+	10
quadratic integrate-and-fire	-	+	-	-	-	-	-	+	-	+	-	-	+	-	-	+	+	-	-	-	-	-	7
Izhikevich (2003)	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	13
FitzHugh-Nagumo	-	+	+	-		-	-	+	-	+	+	+	-	+	-	+	+	-	+	+	-	-	72
Hindmarsh-Rose	-	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	120
Morris-Lecar	+	+	+	-		-	-	+	+	+	+	+	+	+		+	+	-	+	+	-	-	600
Wilson	-	+	+	+			+	+	+	+	+	+	+	+	+		+	+					180
Hodgkin-Huxley	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+			+	1200

Figure 3.2: "# of FLOPS" is an approximate number of floating point operations (addition, multiplication, etc.) needed to simulate the model during a 1 ms time span. Each empty square indicates the property that the model should exhibit if the parameters are chosen appropriately, [3].

3.2 Dynamic System Fundamentals

When looking at the brain in abstract form it can be seen as a multi-dimensional dynamical system governed by an independent set of system variables, such as neuronal membrane potentials, which change in time based on a set of deterministic equations with system parameters that either do not change in time (e.g. maximal conductance of the ion channels on the neuronal membrane) or whose evolution happens on a much slower time scale relative to the evolution of the system variables [4].

Fundamentally, a dynamical system is a system that evolves over time. This system is dependent on fixed rules which govern the evolution of the system. Thus a dynamical system is the opposite of a static system, which, unlike dynamical systems, does not depend on the past inputs. A simple example of a dynamical system can be that of a pendulum swinging back and forth [<**empty citation**>].

There are different types of dynamical systems. A system can be deterministic or stochastic, discrete or continuous, linear or nonlinear, and autonomous or non-autonomous [<**empty citation**>].

If a system is deterministic, it is possible to predict each following state given an initial state. It is also possible for a system to have an element of randomness to it. In this case, the system is said to be stochastic [<**empty citation**>].

A discrete system is one where there is only measured a position of the integer values of time. On the other hand, is a continuous system, where the positions are measured continuously (ie. for every possible time) [<**empty citation**>].

A linear system is one where it is only composed of linear functions and a nonlinear system contains at least one nonlinear component [<**empty citation**>].

Lastly, there is the difference between an autonomous system, which is one where it does not depend on the independent variable t [<**empty citation**>], and a non-autonomous system, which does depend on t [<**empty citation**>].

When analysing differential equations *phase space* analysis is an important concept and tool. Phase space is the space spanned by the system's variables and the trajectories it contain are those variables traversing time. When a neuron transitions from rest to firing a qualitative change in the dynamical behavior of the system will occur. A qualitative change can be associated with phenomena such as *bifurcations*, *phase transitions*, emergence of (new) *attractors*, or shifts in stability.

Bifurcations constitutes critical points where the stability of a system changes, leading to abrupt transitions in the system's behavior. As will be shown these transitions can provide insights into the onset of seizures and their characteristics [link to network analysis section]

Let's consider a simple two-variable system where the variables represent the activity of excitatory and inhibitory neurons. A phase plane for such a system could help visualize the dynamics.

Here's a simple set of differential equations to represent this system:

dxdt = alpha * (1 - x**2) - beta * y dydt = gamma * x - delta * y

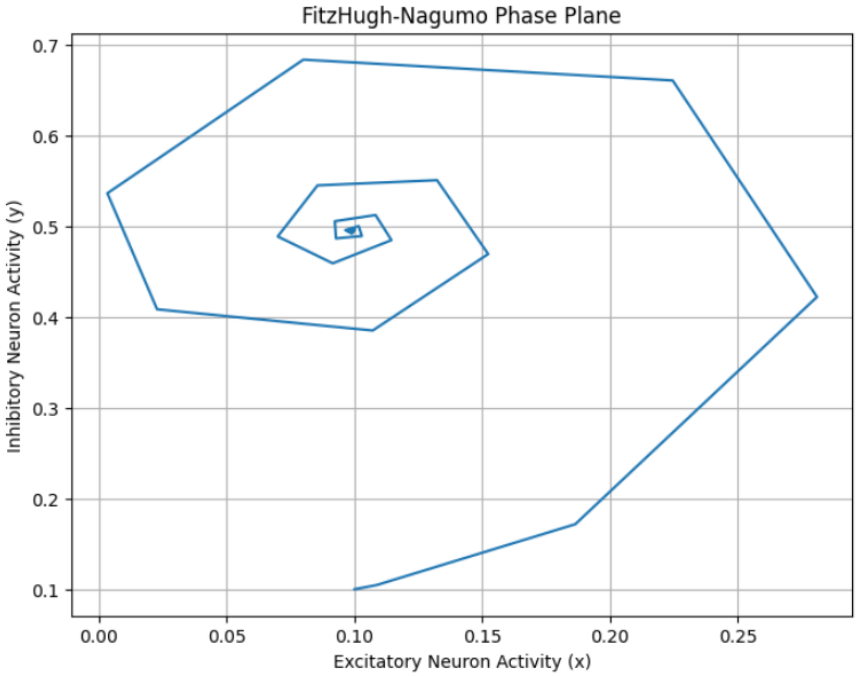


Figure 3.3: Caption

Notes: - Time delays can be the source of instabilities and bifurcations in dynamical systems and are frequently observed in biological systems such as neural networks. - with qualitative change in the dynamical behavior of the system we mean - The bifurcation constitutes a 'dividing event' and is associated with modifications to the system parameters such as membrane capacitance and ion channel parameters etc. [4]. - The reduced, two dimensional Hodgkin-Huxley model constitutes what is called a relaxation oscillator. Oscillator because solutions oscillate, there is a limit cycle. "building up tension" as it were, then all of the sudden the tension is "released" when the trajectory shoots over from the left branch of the v-nullcline to its right branch. See example

Bifurcations are critical points where the stability of a system changes, leading to abrupt transitions in the system's behavior. These transitions can provide insights into the onset of seizures and their characteristics. Identifying bifurcation points in neural systems helps to understand the mechanisms underlying the transition from normal brain activity to a seizure state.

Dimensionality reduction

A neuron model, such as the HH model, uses a system of four differential equations to simulate a complex network this can quickly amount to an insurmountable task with contemporary computer technology...

Modeling Neuronal Networks

A complex system can be described by a network or a graph with complex topology, whose nodes are the elements of the system and whose edges represent the interactions among them. 'One significant recent discovery in the field of complex networks is the observation that a number of large-scale and complex networks are scale-free, that is, their connectivity distributions have the power-law form' [5].

Self-organized criticality has been proposed as a framework to understand various phenomena in nature ranging from earthquakes, forest fires to neuronal activity in the brain. Avalanche Dynamics: In self-organized critical systems, events or disturbances can lead to cascading effects, causing a series of interconnected events or "avalanches." The size distribution of these avalanches often follows a power-law distribution [6, 7].

The power-law form in connectivity distributions refers to a specific mathematical relationship that characterizes the distribution of connections or links among elements in a network. In a power-law distribution, the probability of a node having k connections (degree) is proportional to k raised to the power of a negative exponent.

Mathematically, the power-law distribution is often expressed as: $P(k) \sim k^{\gamma}$

$$P(k) \sim k^{\gamma} \tag{3.1}$$

$P(k)$ is the probability that a node has k connections. γ is the exponent characterizing the power-law distribution.

from the article : "FitzHugh-Nagumo oscillators on complex networks mimic epileptic-seizure-related synchronization phenomena":

Notes: - a smallworld network - ...

When analysing seizures, bifurcation points helps to understand the mechanisms underlying the transition from normal brain activity to a seizure state. The change in parameter can be factors like synaptic strength, excitability of neurons, or network connectivity [8].

Network connectivity and topology

Modeling brain processes can be advantages because of the difficulties performing certain experiments and it is therefore possible to simulate certain scenarios without the need of conducting large scale exploratory experiments. Aspects like ethical barriers...

The practical barriers to simulating brain processes are to do with the modeling framework of the particular question of interest together with the computational resources needed to run complex simulations. Fortunately Moore's Law are still holding and with the emergence of AI the modeling framework have been propelled foreword. Large-scale brain simulation projects, like the Human Brain Project[‡], leverage AI and high-performance computing to simulate the behavior of billions of neurons and their connections.

[‡] `https://www.humanbrainproject.eu/en/brain-simulation/`

3.3 Building up to Hodgkin-Huxley

The HH Model of Neuron Action Potential is regarded as being a part of the great achievements of 20th-century biophysics. Receiving the Nobel Prize in Physiology or Medicine for what is inarguably an incredible feat of human ingenuity. However, the authors of this paper are students, and therefore such a sophisticated model might be beyond the direct reach of abilities within the given timeframe. As such, the exploration begins by investigating simplified HH derived models to see what insights can be built. These models are only going to be presented for now, and discussion regarding their details are to be saved for Chapter (**8**).

3.3.1 - FitzHugh-Nagumo

"The models in this category are highly simplified toy models that qualitatively describe the membrane voltage as a function of input. They are mainly used for didactic reasons in teaching but are not considered valid neuron models for large-scale simulations or data fitting".[§]

$$\frac{\mathrm{d}V}{\mathrm{d}t} = V - \frac{V^3}{3} - w + I_{ext} \tag{3.2-A}$$

$$\tau \frac{\mathrm{d}w}{\mathrm{d}t} = V - a - b\,w \tag{3.2-B}$$

3.3.2 - Chay

In 1985, T.R. Chay proposed a model of three-dimensional nonlinear differential equations based on the HH model to study chaotic behavior and show ionic events in excitable membranes.

$$\frac{\mathrm{d}V}{\mathrm{d}t} = g_{\mathrm{I}} m_{\infty}^3 h_{\infty} \left(V_{\mathrm{I}} - V \right) + g_{\mathrm{K,V}} n^4 \left(V_{\mathrm{K}} - V \right) + g_{\mathrm{K,C}} \frac{C}{1+C} \left(V_{\mathrm{K}} - V \right) + g_{\mathrm{L}} \left(\mathrm{V_m} - V_{\mathrm{L}} \right) \tag{3.3-A}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{n_{\infty} - n}{\tau_n} \tag{3.3-B}$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \rho \left[m_{\infty}^3 h_{\infty} \left(V_c - V \right) - k_C C \right] \tag{3.3-C}$$

where V, n, and C are membrane potential, probability of the voltage-sensitive K^+ channel, and intracellular concentration of Ca^{2+} ions, respectively. The Chay model parameters are adopted from *'paper'* and collected in Table

[§]Wikipedia

The m_∞, h_∞, and n_∞ are calculated by $y_\infty = \alpha_y/(\alpha_y + \beta_y)$ formula, and the explicit expressions for $\alpha_m, \beta_m, \alpha_h, \beta_h, \alpha_n, \beta_n$, and τ_n are given by:

$$\alpha_m = 0.1\frac{25+V}{1-\exp(-0.1V-2)}, \quad \alpha_h = 0.07\exp(-0.05V-2.5), \quad \alpha_n = 0.01\frac{20+V}{1+\exp(-0.1V-2)}$$

$$\beta_m = 4\exp\left(-\left(\frac{V+50}{18}\right)\right), \qquad \beta_h = \frac{1}{1+\exp(-0.1V-2)}, \qquad \beta_n = 0.125\exp\left(-\frac{V+30}{80}\right),$$

$$\tau_n = \frac{1}{r_n(\alpha_n+\beta_n)}$$

3.3.3 - Hodgkin-Huxley

The HH model of Action Potential is a system of nonlinear differentiable equations with four state variables with respect to time, $\mathrm{V_m}(t)$, $n(t)$, $m(t)$, $h(t)$ [1]. The model is built from approximating the characteristics of excitable cells, such as neurons, to a circuit-like construct [fig. (1.2)].

Through long term experimentation, the duo of Hodgkin and Huxley divined a model built from the observations of smooth current change as a function of pores (or channels) that were either open or closed. By using a statistical approach, H&H generated predictions for the probability of channels being open or closed at a given time in the process [9]. H&H presented the model as a set of four Ordinary Differentials (ODEs) with respect to time.

$$C_m\frac{\mathrm{dV_m}}{\mathrm{d}t} = I_m - \left(\bar{g}_\mathrm{K}n^4(\mathrm{V_m}-V_\mathrm{K}) + \bar{g}_\mathrm{Na}m^3h(\mathrm{V_m}-V_\mathrm{Na}) + \bar{g}_\mathrm{L}(\mathrm{V_m}-V_\mathrm{L})\right) \tag{3.4-A}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(\mathrm{V_m})(1-n) - \beta_n(\mathrm{V_m})n \tag{3.4-B}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(\mathrm{V_m})(1-m) - \beta_m(\mathrm{V_m})m \tag{3.4-C}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(\mathrm{V_m})(1-h) - \beta_h(\mathrm{V_m})h \tag{3.4-D}$$

The 'gating' variables m and h, part n describe the time dependent kinetics of the voltage The ion channel activation/inactivation[¶] probabilities, denoted by α_p, $\beta_p : (n,m,h) \in p$, are defined such that:

$$\alpha_p(\mathrm{V_m}) = p_\infty(\mathrm{V_m})/\tau_p \tag{3.5}$$

$$\beta_p(\mathrm{V_m}) = (1-p_\infty(\mathrm{V_m}))/\tau_p \tag{3.6}$$

With p_∞ and its inverse $1-p_\infty$ being the steady state values for activation and inactivation respectively [1]. In the original paper by Hodgkin and Huxley, the relationships of α_p, and β_p were defined as:

$$n \Rightarrow \begin{cases} \alpha_n(\mathrm{V_m}) = 0.01\,\dfrac{10-V}{\exp(10-V)-1} \\ \beta_n(\mathrm{V_m}) = 0.125\exp\left(-\dfrac{V}{80}\right) \end{cases}$$

Where $V = V_{\text{rest}} - \mathrm{V_m}$ represents the polarization in mV

$$m \Rightarrow \begin{cases} \alpha_m(\mathrm{V_m}) = 0.1\dfrac{25-V}{\exp\left(\dfrac{25-V}{10}\right)-1} \\ \beta_m(\mathrm{V_m}) = 4\exp\left(-\dfrac{V}{18}\right) \end{cases}$$

$$h \Rightarrow \begin{cases} \alpha_h(\mathrm{V_m}) = 0.07\exp\left(-\dfrac{V}{20}\right) \\ \beta_h(\mathrm{V_m}) = \dfrac{1}{\exp\left(\dfrac{30-V}{10}\right)+1} \end{cases}$$

¶ activation gives α, bnactivation gives β, really these are the obvious choices

4 Mathematical Modeling

Seizure

Seizures can be primarily interpreted as a dynamical disease [10, 11] and computational models have been successful in gaining insight into and generate hypothesis to the cellular and network level brain mechanisms of seizures [12].

Definition and classification of seizures

The role of neuronal networks in seizure generation

(or network effects)

- network properties influence seizure dynamics –> connectivity and coupling strengths

Some notes: - The role of neuronal networks in seizure generation - Models for simulating seizures - A chaotic process can be classified according to its fractal dimensions and Lyapunov exponent [13]. - Identifying bifurcation points in neural systems

When modeling neuronal interactions, and in particular modeling of seizures, the model must reflect the fact that thousands of neurons need to interact in order to display seizure-like activity. The first major roadblock becomes the quantity of neurons involved, it is not possible to measure the activity of every individual neuron, even assuming one could do so, it would be a monumental task to extract useful information from the bulk. Therefore we must be smart about creating a model, choosing the 'right' approach to simplify the equations can save astronomical amounts of time and effort.

1. **Model average activity**
2. **Reduce parameter space**
3. **Tackle a smaller problem**

A system can be modeled deterministicly or contain stochasticly. When collecting data, measurements will rarely be completely deterministic. This is not because forces act in unpredictable manner, rather that there exists far too many elements in the 'real' world for any model to fully account for them. As a consequence, many models will incorporate both deterministic and stochastic elements to more accurately reflect the observed data.

1. **Model simplification**
2. **Stochastic activity**
3. **stochastic Inputs**

4.1 Physiological Parameters

It's important to determine what is even being modeled, which features can be parameterized and which can not.

4.2 Parameters of Neural Models

When it comes to modelling the brain activity it is essential to present a set of variables and parameters apropos of the previously chosen dynamic model. The model usually consists of a system of equations, able to describe and predict a model behavior over some specific time frame. But simulating any kind of brain dynamics is in principle a challenging task and therefore one should follow some guidelines for deciding upon the complexity of the model. The goal is to make it as composite as possible to sufficiently describe its machinery but at the same time adequately easy, to be computable by current computing methods. The latter is in fact a prerequisite.

$$\frac{d\mathbf{z}(t)}{dt} = P(\mathbf{z}(t), \kappa(t), u(t), t) \tag{4.1}$$

Each dynamic brain model may be represented by the continuous-time state-transition equation. In this standard format, one may determine the intricacy of the model, by means how much detail should or should not it be included, by varying its components. The formula depicts the development of the state $\mathbf{z}(t)$, with a parameter set $\kappa(t)$, and an input $u(t)$. The model's behavior is then determined by the mapping P.

- In the process of studying the model, the aim is to investigate changes in the system *variables*, which, in dynamical models, are absorbed in the state $\mathbf{z}(t)$. These changes happen only via the evolving relationships encoded in mathematical formulas, while alterations in parameters arise from external sources beyond the model's scope.
- *Parameters* $\kappa(t)$, on the other hand, are attributes of the state, that can be empirically measured. They are placeholders that constitute to values in the group of maps P (mapping or mapplet) [Informatica® Cloud Data Integration November 2023 Mappings]. They are used when it is necessary to keep values constant in time, or during desired observation. In real life, however, the values of parameters (and variables) can vary, but parameters deviate at a different pace than variables. It is reasonable that the parameters and time-dependency are to be related.

There exists no predetermined set of rules dictating what features ought to function as parameters and which should operate as variables, however, a certain group of general instructions can be considered.

1. It can be acknowledged that parameters may exhibit very steady variations, compared to the relevant temporal horizon, for instance, the network's neuron count remains relatively stable, when working in short time intervals. Yet, in a lifespan of a couple of years, some neurons will annihilate, affecting the overall number of brain cell communities. Hence, it is necessary to match a specific time scale with a corresponding parameter, failing to do so may justify its classification as variables. Nevertheless, parameters are typically considered to remain constant over the interval. At certain times, this holds accurately. An example would be an axon's length, that stays fairly permanent as time evolves. It brings some degree of simplicity into the model, particularly in the course of analysis.

2. Usually, reasonable approximations already exist for both variables and parameters. The values of parameters can normally be determined from observational data. In cases where values are not obtainable, there still happen to be lifelike limitations. Variables, on the contrary, are investigatory quantities with a broad range of plausible values. Even if estimates are available, it proves challenging to see the impact of minor changes on a system.

4.2.1 - One neuron

In the spatial scale of one neuron, the choice of the model itself decides on the parameters that are to be used. The integrate-and-fire model is relatively straightforward. The excitatory and inhibitory currents representing the input are entering the branches of dendrites. They are added up at the soma, which embodies the integration process. If the value reaches a certain threshold, the action potential is fired to serve as the resultant outcome. The relevant set of parameters are ones responsible for producing the action potential.

5 Our Approach

5.1 The inspiration

5.2 Input

Since we want want minimize the effects of a possible bias in our data, it makes sense to use the Gaussian white noise signal as an input. But why?

Gaussian white noise is a stationary and ergodic random process with zero mean. Considering an ergodic process is useful in a sense that one can infer meaningful statistics of the process given only that same process. Having a zero mean will just make the data analysis even simpler as well since the model will describe only the fluctuations of the input received by a neuron.

Ergodic process: the expected value of an observable A is not dependent on time and its time average converges to its value(the average behavior over time is the same as the average potential behavior at a point in time).

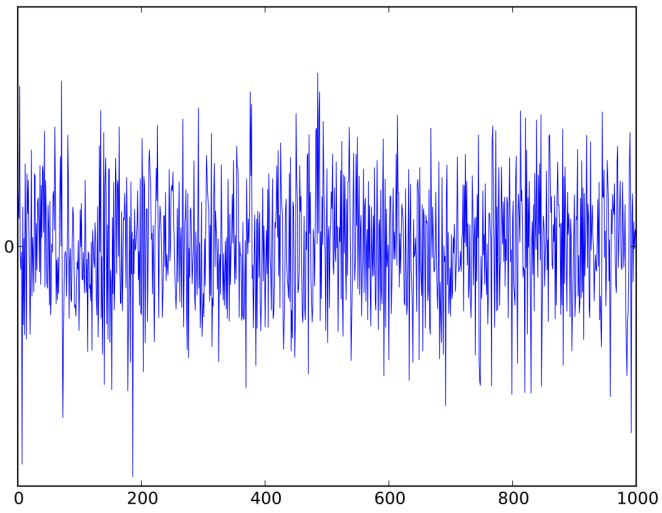


Figure 5.1: The waveform of a Gaussian white noise signal plotted on a graph [<**empty citation**>].

5.3 Neuronal Motif

Effectively studying the dynamics of neurons becomes very complex in big systems if one takes as basis the Hodgkin-Huxley model. In opposition to this, studying the behaviour of one neuron will not give a reasonable representation of the neuronal dynamics. For this reason, it makes sense to consider small neuronal motives to serve as basis of study for neuronal dynamics while being able to take in consideration the biological characteristics of neurons. Such characteristic network building blocks are also prevalent in biological networks [14]

Using nodes to represent neurons in a system, one can consider different types of connections between nodes as in the figure below:

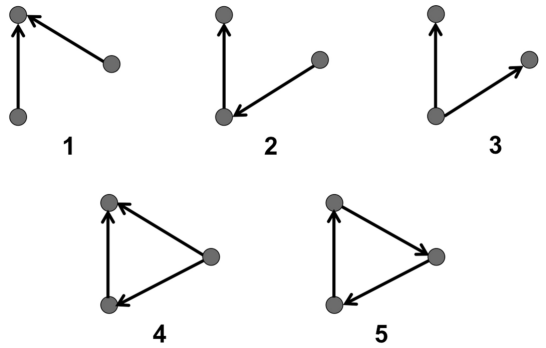


Figure 5.2: Possible unidirectional 3-node network motifs. [15]

5.4 How will these neuronal populations behave?

Let's take the example of two nodes.

Excitatory synapses: If one connects them mutually with excitatory synapses the two populations will synchronize(more or less depending on external input and the strength of mutual connections).

Inhibitory synapses: If one connects them mutually with inhibitory synapses the two populations will "compete" resulting in one suppressed node and a winner one.

Excitatory and inhibitory synapses: If the nodes are connected by a excitatory and inhibitory synapses, the resulting behaviour will be oscillatory.

UNTIL EACH NUMBER SHOULD I WRITE? WHAT DETAILS WOULD BE NICE?

INSERT FIGURE TYPES OF MOTIVES(write about their connections)

6 Methodology

In order to investigate further the models in terms of applicability, scalability and accuracy, among other factors, there was a need to run computer simulations where parameters can be easily changed and their effects on models are easier to compare.
Python was the chosen language to do so. It is of free-access, unlike Mathlab which requires a license, more prominent than Octave(so more resources are available), and very versatile. Since, machine learning was also considered, R was deemed as not as suitable as Python. It is a statistical programming language. Moreover, the numba and numpy libraries which are based on C/C++ code make it relatively fast.
As such, python simulations were performed as this language is very well-documented, approachable and already widely used in data analysis. From the scripts, one can create phase planes and graphs to better visualize the behaviour of variables within the model.

7 Results

Part II

Discussion

8 Model Discussion

8.1 Fithugh-Nagamo

The FitzHugh-Nagumo model can be written in many ways, one of which is as follows.

$$\dot{V} = V - \frac{V^3}{3} - W + I \tag{8.1}$$

$$\dot{W} = \phi(V + a - bW) \tag{8.2}$$

The original values for the constants are $a = 0.7$, $b = 0.8$, and $\phi = 0.08$ [<**empty citation**>]. For these values, the nullclines look like Figure (8.1).

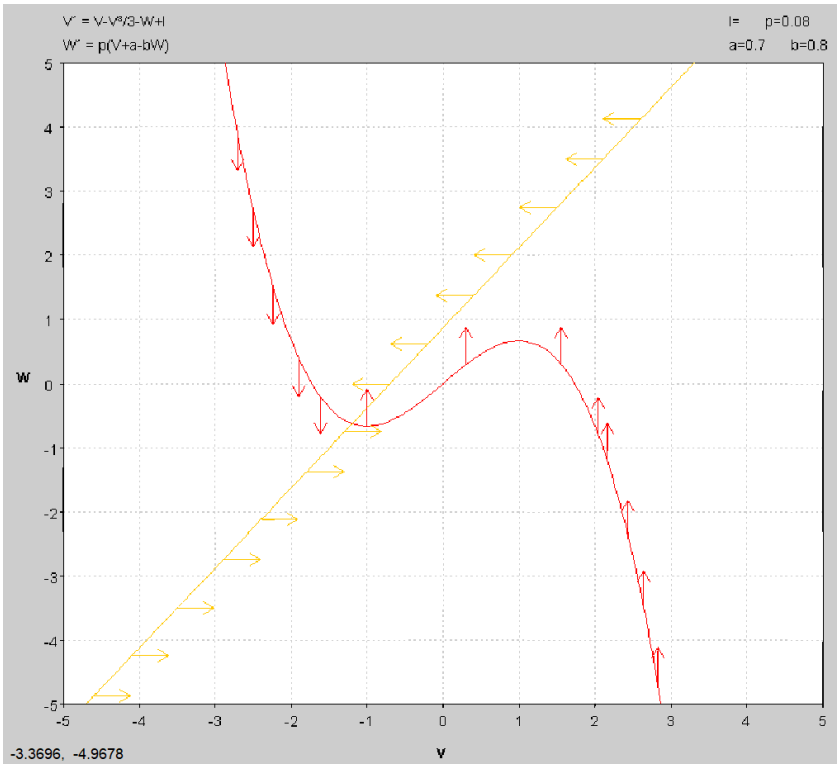


Figure 8.1: Nullclines for $I = 0$, $a = 0.7$, $b = 0.8$, and $\phi = p = 0.08$

As can be seen in Figure (8.1) there is only one equilibrium. This is located at $(-1.1994, -0.62426)$. This is a spiral sink.

It is also possible for the model to have three equilibria. This is for example the case if b is changed to -0.8. This can be seen in Figure (8.2).

Here the equilibria are at $(-2.376, 2.0949)$, $(-0.39825, -0.37719)$, and $(2.7742, -4.3428)$. The first and last are saddle points and the middle is a nodel source.

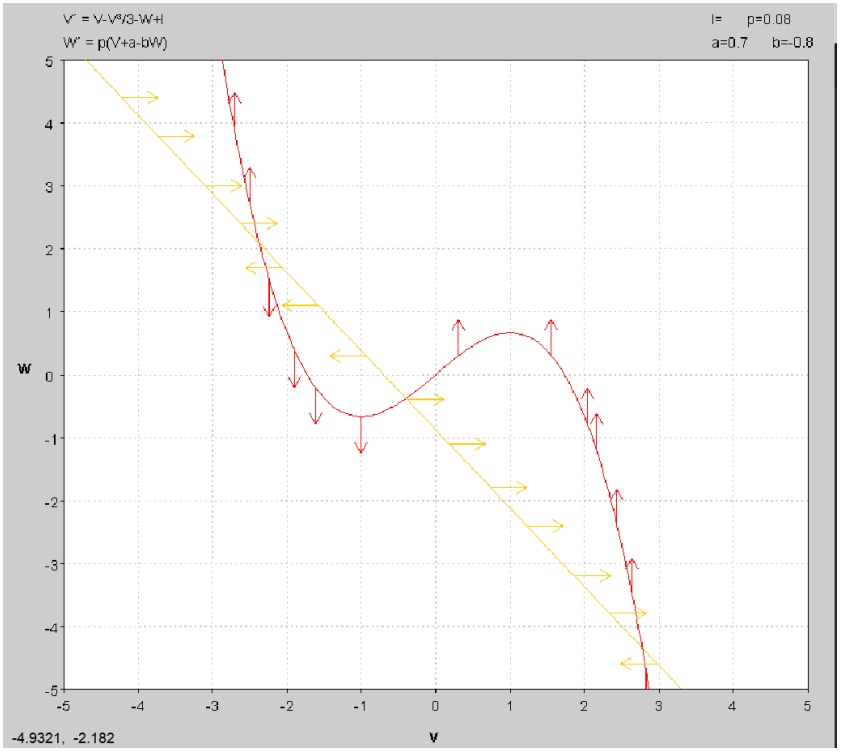


Figure 8.2: nullclines for $I = 0$, $a = 0.7$, $b = -0.8$, and $\phi = p = 0.08$

The parametric solution to this system is $V + a = bW$ and $W = V - V^3/3 + I$.

This change from one to three equilibria changes at b>0.

8.2 Chay

The Chay Model, developed by T.R. Chay in 1958, is a mathematical model designed to capture the dynamic behavior of excitable cells. Based on the Hodgkin-Huxley model, it offers a set of differential equations describing the changes in membrane potential (V), the probability of opening the voltage-sensitive K^+ channel (n), and the dynamics of the intracellular concentration of Ca^{2+} ions (C) over time. The model includes crucial elements such as voltage-gated ion channels, steady-state variables, and capacitive variables, providing a comprehensive description of the mechanisms related to cellular excitability. This model is uaseful in computational neuroscience and, due to its three-dimensionality, presents a more realistic portrayal of the dynamic processes within excitable cells compared to other known models that are two-dimensional. One representation of the Chay model is provided below [16].

$$\frac{\mathrm{d}V}{\mathrm{d}t} = g_{\mathrm{I}} m_{\infty}^3 h_{\infty} \left(V_{\mathrm{I}} - V \right) + g_{\mathrm{K,V}} n^4 \left(V_{\mathrm{K}} - V \right) + g_{\mathrm{K,C}} \frac{C}{1+C} \left(V_{\mathrm{K}} - V \right) + g_{\mathrm{L}} \left(V_m - V \right) \tag{8.3}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{n_{\infty} - n}{\tau_n} \tag{8.4}$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \rho \left[m_{\infty}^3 h_{\infty} \left(V_c - V \right) - k_C C \right] \tag{8.5}$$

The equations presenting the rate constants are given by:

$$\alpha_m = 0.1 \frac{25+V}{1-\exp\left(-0.1\,V-2\right)}, \quad \alpha_h = 0.07 \exp\left(-0.05\,V-2.5\right), \quad \alpha_n = 0.01 \frac{20+V}{1+\exp\left(-0.1\,V-2\right)}$$

$$\beta_m = 4 \exp\left(-\left(\frac{V+50}{18}\right)\right), \qquad \beta_h = \frac{1}{1+\exp\left(-0.1\,V-2\right)}, \qquad \beta_n = 0.125 \exp\left(-\frac{V+30}{80}\right),$$

$$\tau_n = \frac{1}{r_n \left(\alpha_n + \beta_n\right)}$$

In this context, V_I, V_K, and V_L represent the reversal potentials for a combination of Na^+ and Ca^{2+}, K^+, and leakage ions, respectively. C represents the concentration of intracellular Ca^{2+} ions divided by their dissociation constant from the receptor. The terms g_I, $g_{K,V}$, $g_{K,C}$, and g_L refer to the maximal conductances divided by the membrane capacitance. Here, the subscripts I, (K,V), (K,C), and (L) specifically address to the voltage-sensitive K^+ channel, the Ca^{2+}-sensitive K^+ channel, and the leakage channels, respectively. Additionally, τ_n represents the relaxation time and n_{oo} is the steady-state value of n. Furthermore, m_{oo} and h_{oo} are set to be the probabilities of activation and inactivation of the mixed channel. [16].

Analyzing deeper the dynamics of the Chay model, our exploration now extends to the Jacobian matrix, a mathematical tool that illustrates the behavior of the system around equilibrium points.

$$J = \begin{pmatrix} \frac{dV}{dV} & \frac{dV}{dn} & \frac{dV}{dC} \\ \frac{dn}{dV} & \frac{dn}{dn} & \frac{dn}{dC} \\ \frac{dC}{dV} & \frac{dC}{dn} & \frac{dC}{dC} \end{pmatrix}$$

$$= \begin{pmatrix} -g_{\mathrm{I}} m_\infty^3 h_\infty - g_{\mathrm{K,V}} n^4 - g_{\mathrm{K,C}} \frac{C}{C+1} - g_{\mathrm{L}} & 4 g_{\mathrm{K,V}} n^3 (V_{\mathrm{K}} - V) & \frac{1}{(1+C)^2} g_{\mathrm{K,C}} (V_{\mathrm{K}} - V) \\ 0 & -\frac{1}{\tau_{\mathrm{n}}} & 0 \\ -\rho m_\infty^3 h_\infty & 0 & -\rho K_{\mathrm{C}} \end{pmatrix}$$

We now focus on extracting the eigenvalues from the Jacobian matrix, using its determinant. These eigenvalues are key to exploring the stability of the model.

$$|J - \lambda I| = \begin{vmatrix} -g_{\mathrm{I}} m_\infty^3 h_\infty - g_{\mathrm{K,V}} n^4 - g_{\mathrm{K,C}} \frac{C}{C+1} - g_{\mathrm{L}} - \lambda & 4 g_{\mathrm{K,V}} n^3 (V_{\mathrm{K}} - V) & \frac{1}{(1+C)^2} g_{\mathrm{K,C}} (V_{\mathrm{K}} - V) \\ 0 & -\frac{1}{\tau_{\mathrm{n}}} - \lambda & 0 \\ -\rho m_\infty^3 h_\infty & 0 & -\rho K_{\mathrm{C}} - \lambda \end{vmatrix} = 0$$

Negative real parts of eigenvalues indicate stability, while positive real parts indicate instability. Although it's difficult to find the eigenvalue signs of the Chay model, we notice that the trace of the Matrix is negative.

Table 8.1: Parameters' values and significations of Chay neuron model.

Parameters	Significations	Values
VI	Reversal potentials for mixed Na^+ - Ca^{2+} ions	100 mV
VK	Reversal potentials for K^+ ions	−75 mV
VL	Reversal potentials for leakage ions	−40 mV
VC	Reversal potentials for Ca^{2+} ions	100 mV
gI	Maximal conductance of mixed Na^+ - Ca^{2+} channel	1800 ms/cm^2
gK,V	Maximal conductance of K^+ channel	1700 ms/cm^2
gK,C	Maximal conductance of Ca^{2+} - sensitive K^+ channel	12 ms/cm^2
gL	Maximal conductance of leakage channel	7 ms/cm^2
rn	Relaxation time of the voltage-gated K^+ channel	230 ms
kc	Rate constant for the efflux of intracellular Ca^{2+} ions	3.30/18 /ms
ρ	Proportionality constant	0.27

8.3 Hodgkin-Huxley

Mathematically, the flow of current is represented as:

$$I_c = C_m \frac{\mathrm{dV_m}}{\mathrm{d}t} \tag{8.6}$$

and the current through a given ion channel is the product of that channel's conductance and the reversal potential for the specific ion

$$I_{\mathbf{ion}} = g_{\mathbf{ion}}(\mathrm{V_m} - \mathrm{V_{\mathbf{ion}}}) \tag{8.7}$$

where $\mathrm{V_{ion}}$ is the reversal potential of the specific ion channel. Thus, for a cell with sodium and potassium channels, the total current through the the membrane can be defined by:

$$I = I_c + \sum_{i=1}^{p} I_i = I_c + \sum_{i=1}^{p} g_{\mathbf{ion}} \cdot (\mathrm{V_m} - \mathrm{V_{\mathbf{ion}}}) \tag{8.8}$$

with I representing the total membrane current per unit area;

$$I = \quad I_c \quad + \quad I_{\mathrm{K}} \quad + \quad I_{\mathrm{Na}} \quad + \quad I_{\mathrm{L}} \tag{8.9}$$

$$\Rightarrow \quad I = C_m \frac{\mathrm{dV_m}}{\mathrm{d}t} + g_{\mathrm{K}}(\mathrm{V_m} - V_{\mathrm{K}}) + g_{\mathrm{Na}}(\mathrm{V_m} - V_{\mathrm{Na}}) + g_{\mathrm{L}}(\mathrm{V_m} - V_{\mathrm{L}}) \tag{8.10}$$

Where C_m the membrane capacitance per unit area; and g_{K}, V_{K}, along with g_{Na}, V_{Na} make up the conductance and reversal potential of $\mathrm{K^+}$ and $\mathrm{Na^+}$ respectively. The directly time dependent element of this equation is $\mathrm{V_m}$, with g_{Na}, and g_{K} are time dependant by virtue of explicit dependence on the membrane voltage ($\mathrm{V_m}$).

In order to characterize the ion-channels, the equations can be fitted to voltage clamp* data.

*An assay that measures the flow of current through a neuronal cell membrane by 'clamping' the potential at an unchanging value.

8.4 Choice of model

8.4.1 - FitzHugh-Nagumo

8.4.2 - Chay

8.4.3 - Hodgkin-Huxley

8.4.4 - Other possible models

Table 8.2: Parameters of the Hodgkin-Huxely model

Parameters	Significations	Values
I	Membrane Current Density 0A/cm2 during spac clamp	
C_{m}	Membrane Capacitance	1 µF/cm2
$\mathrm{V_m}$	Membrane Potential	mV
$\bar{\mathrm{g}}_{\mathrm{K}}$	maximal conductance for potassium	36 m mho/cm2
$\bar{\mathrm{g}}_{\mathrm{Na}}$	maximal conductance for sodium	120 m mho/cm2
$\bar{\mathrm{g}}_{\mathrm{L}}$	maximal conductance for "leaking" ions	$0.30/(\mathrm{m}\Omega\,\mathrm{cm}^2)$
$\mathrm{V_K}$	Resting Potential of potassium	12 mV
$\mathrm{V_{Na}}$	Resting potential for Sodium	−115 mV
$\mathrm{V_L}$	Resting potential for "leaking" ions	−10.61 mV
n	Proportion of particles in neuron involved wit opening of potassium gate	
m	proportion of particles in neuron affecting opening o sodium gate	
h	proportion of particles outside of neuron affectin closing of "2nd" sodium gate	
α_{n}	Voltage dependent rate for potassium ions to ente the cell per ms	
β_{n}	Voltage dependent rate for potassium ions to exit th cell per ms	
α_{m}	Voltage dependent rate for sodium to enter the cel per ms via the "1st" gate	
β_{m}	Voltage dependent rate for sodium to exit the cel per ms via the "1st" gate	
α_{h}	Voltage dependent rate for sodium to exit the cel per ms via the "2nd" gate	
β_{h}	Voltage dependent rate for sodium to enter the cel per ms via the "2nd" gate	

Name	Biophysically relevant	Number of operations per ms	Dimensions	Number of neurons in a network
FitzHugh-Nagumo	No	72	2	Thousand
Chay	Yes		3	
Hodgkin-Huxley	Yes	1200	4	Tens
Standard integrate and fire	No	5	1	Thousands
Integrate and fire adaptations	No	7-13	1-2	Thousands
Izhikevich	No	13	2	Thousands
Moris-Lecar	Yes	600	2	
Hindmarch-Rose	No	120	3	
Wilson	No	180	4	

9 Coupling

To couple things

10 Conclusion

Appendix

.1 Images

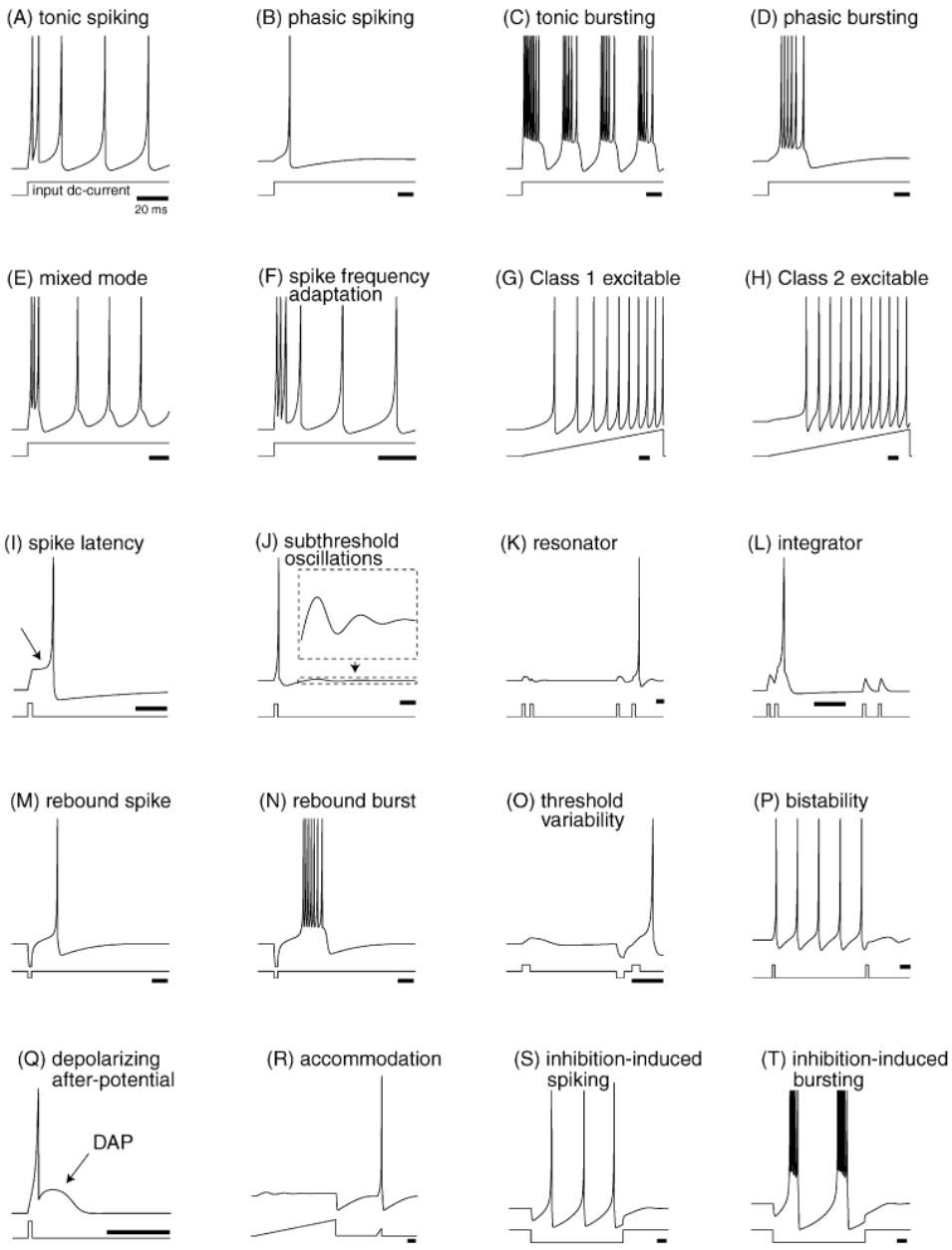


Figure 1: Summary of the neuro-computational properties of biological spiking neurons. Shown are simulations of the same model (1) and (2), with different choices of parameters. Each horizontal bar denotes a 20-ms time interval, [3]

NEURO-COMPUTATIONAL FEATURES: This figure shows 20 of the most prominent features of biological spiking neurons and depicts the spiking behavior of individual neurons in response to simple pulses of dc current, [3].

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