"You keep on learning and learning, and pretty soon you learn something no one has learned before."

— Richard Feynman

1 Introduction

Neural models range from highly detailed to very simplified descriptions. The level of complexity of them depends on the specific scale at which we want to study the biological system. In this notes we will deal with single-compartment models where we treat the whole neuron as a point-like object and leave aside all space variability across neurites and soma.

1.1 Electrical properties of intracellular medium

The intracellular medium of neurons has a huge number of ions and molecules, which are separated from the extracellular medium by the neuron membrane. Since the concentration of these charged particles is not even across the cell, the membrane acquires a non-zero potential at rest. Moreover, due to the action of ion-channels, these particles can be exchanged between inside and outside the neuron which produces changes in the membranes voltage. These membrane potentials are not uniform across the neuron, but they can take different values in different places. This difference in voltage produce ions to flow *inside* the neuron which leads to the so called **longitudinal current** I_L and the intracellular medium provides a resistance to such flow known as **longitudinal resistance** R_L. These features allow us to model neurites as cables, and so the aforementioned quantities are related via Ohm's law

$$V_2 - V_1 = I_L R_L \,, \tag{1.1}$$

where V_2 and V_1 are two voltage at the extremes of the cable. The longitudinal resistance is well modeled by

$$R_L = r_L \frac{L}{\pi a^2} \,, \tag{1.2}$$

which tells us that R_L is proportional to the length of the segment L and inversely proportional to its area πa^2. The constant of proportionality is called the **intracellular resistivity** r_L. As a consequence of (1.2) we get that the resistance is higher for long and narrow dedritic or axonal cables. Neurons that have few of these high-resistance neurites may have relatively uniform membrane potentials across their surfaces (see (1.1)). Such neurons are dubbed **electronically compact** and they can be entirely described by a single membrane potential. In these notes we will deal with models for this kind of neurons leaving aside any space variability along the membrane!

1.2 Electrical properties of the membrane

As we mentioned before, ions are blocked inside the cell by the neuron membrane. Due to this charge-separating feature, it acts effectively as a capacitor creating the so called **membrane capacitance** C_m. The amount of excess charge Q is related to the membrane potential via the capacitor equation

$$Q = C_m V \,, \tag{1.3}$$

where V is the voltage across the membrane. C_m is proportional to the area of the membrane A and the constant of proportionality is called **specific membrane capacitance** c_m, $C_m = c_m A$. In the same way the intracellular medium provides a resistance R_L for ions flowing inside the cell, the cell membrane provides a **membrane resistance** R_m for these charges particles moving across the neuron. R_m is inversely proportional to the membrane area $R_m = \frac{r_m}{A}$ with r_m the **specific membrane resistance**. The product

$$R_m C_m = r_m c_m \equiv \tau_m \tag{1.4}$$

has units of time and is known as the **membrane time constant**, it sets the basic time scale for changes in the membrane potential. In principle the membrane is essentially impermeable, which can be associated with an infinite membrane resistance or, equivalently, zero membrane conductance. However, the membrane is not fully impermeable but it contains several ion-channels which allow the interchange of particles. This lowers the effective membrane resistance, which ultimately depends on the density and type of ion-channels. The total flow of charged particles across all these channels defines the **membrane current** I_m, which is related to the **membrane current per unit area** i_m by $I_m = i_m A$. This current can be related to the current flowing across each different channel type. Labeling each type with an i subscript, the membrane current per unit area due to the type i channels is given by $g_i(V - E_i)$, where g_i is the channel **conductance per unit area**, E_i its reversal potential and $(V - E_i)$ the driving force. Summing these currents over all different types of channels we obtain the total membrane current per unit area

$$i_m = \sum_i g_i(V - E_i)\,. \tag{1.5}$$

In general, the membrane conductances g_i are far from being static objects. They usually change over time and they depend on many factors like current membrane potential V, intracellular messengers and extracellular neurotransmitters or neuromodulators. The currents carried by ion-pumps also contribute to the variability of the membrane conductance. Even though much of the complexity and richness of neuronal dynamics come from these variations, some of the factors that contribute to the total membrane current can be modeled as relatively constant. These time-independent contributions are lumped together into what is called **leakage current**

$$i_L = \bar{g}_L(V - E_L)\,. \tag{1.6}$$

In this approximation, E_L and $\bar{g}_L$[1] usually do not correspond with any specific ion channel but they have to be kept as free parameters and fixed later depending the cell we are modeling. The leakage conductance $\bar{g}_L$ is called passive, while the variable conductances are termed active.

1.3 Single-Compartment models

Models that describe the membrane potential of a neuron by a single variable V are called **single-compartment models**. These models do not capture spatial variability in the membrane potential, which is the job of **multi-compartment models**. The basic equation for single-compartment models is obtained by differentiating (1.3) w.r.t. time

$$C_m \frac{dV}{dt} = \frac{dQ}{dt}\,. \tag{1.7}$$

Equation (1.7) describes the change of membrane potential due to the flow of charges *across the membrane*. This rate at which charge builds up inside the cell is nothing but the amount of current entering the neuron. This current is the combination of the membrane current (1.5) (due to all ion channels and synaptic conductances) and possible external currents injected into the cell through an electrode I_e. Diving by the membrane area we arrive at the basic equation for all single-compartment models

$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}\,. \tag{1.8}$$

By convention current that enters the neuron through an electrode is defined as positive-inward while I_m is positive-outward. This is the reason for the different signs in (1.8). The membrane current in (1.8) is nothing but (1.5). The system of equations must be completed with additional equations for the conductances g_i because they usually vary in time. The structure of this model is the same as an electrical circuit, which is called the **equivalent circuit**. Such circuit contains a capacitor c_m, several sources E_i and voltage-dependent conductances g_i.

[1] The bar on top of this quantity is used to indicate it has a constant value. The same notation will be used later for other quantities.

2 Integrate-and-Fire models

A neuron typically fires an action potential when its membrane potential reaches a threshold that ranges from -55 to -50 mV. Neuron models can be simplified and simulations can be accelerated dramatically by excluding the biophysical mechanisms responsible for these action potentials. This is exactly the case for **Integrate-and-Fire models** (Lapicque 1907) which are dedicated to study purely sub-threshold membrane potential dynamics and action potentials are treated just as binary (all-or-none) events. Firing then occurs whenever the membrane potential reaches a certain value V_{th} and afterwards V is reset to a value $V_{\text{reset}} < V_{\text{th}}$. The description of sub-threshold dynamics can be done with various levels of rigor.

2.1 Leaky Integrate-and-Fire

The simplest version of this model ignores all active conductances and model the entire membrane current as a passive leakage term (1.6), $i_m = \bar{g}_L(V - E_L)$. This is known as the **leaky integrate-and-fire (LIF) model**. For this particular single-compartment model equation (1.8) simplifies to

$$\tau_m \frac{dV}{dt} = E_L - V + R_m I_e \,, \tag{2.1}$$

where apart from using the leakage current (1.6) we multiplied by r_m which in this case coincides with $r_m = \frac{1}{\bar{g}_L}$. Equation (2.1) needs to be supplemented with the threshold and reset rules

$$\text{If} \quad V > V_{\text{th}} \quad \Rightarrow \quad \text{fire} \quad \Rightarrow \quad V = V_{\text{reset}} \,. \tag{2.2}$$

In this model E_L corresponds to the resting potential of the cell.

The only dynamical quantity in (2.1) is the sub-threshold membrane potential $V(t)$. The external current $I_e(t)$ is taken as an already known time-dependent function, meaning that we do not have to model its dynamics too. Except for some simple cases of $I_e(t)$, (2.1) cannot be solved analytically so we have to rely on numerical methods. One of the few simple-enough cases to solve (2.1) analytically is when the external current remains constant $I_e(t) = I_0 = \text{const}$. In this case, the solution is given by an exponential decay regulated by τ_m

$$V(t) = (V(0) - A)e^{-\frac{t}{\tau_m}} + A \,, \quad A \equiv E_L + R_m I_0 \,, \tag{2.3}$$

Since these simple models only describe subthreshold dynamics, the only information they offer about action potentials is the precise time at which they occur. This information is crucial however because it encodes the firing pattern of each neuron which is the main quantity to take into account for information transmission across cells. In order to study these patterns it is useful to introduce the **interspike interval** t_{isi} and its inverse, the **firing rate** $r_{\text{isi}} = \frac{1}{t_{\text{isi}}}$. The former is nothing but the time difference between two consecutive spikes and the firing rate encodes the same information but in a frecuency format (Hz).

2.2 Adaptation and Refractoriness

The LIF model we described so far relies on two separate approximations: simplified description of action potentials and linear (leaky) approximation for the total membrane current. An option to move into more accurate descriptions is to keep omitting details about action potentials but increase the complexity of the membrane current. These generalizations already allow us to include more realistic effects. One of them is **spike-rate adaptation**, which is the mechanism by which interspike intervals lengthen over time when a constant current is injected into the cell and then settle to a steady-state value. Another biological mechanism neurons exhibit is called **refractoriness**, which describes the decrease in firing probability after a previous action potential occurred. This phenomena is divided into two periods. **Absolute refractory period**: is a certain period of time the neuron cannot fire at all, this happens immediately after an action potential took place.

Relative refractory period: after the absolute refractory period took place, firing is possible but initially less likely and after some time the membrane recovers its normal firing probabilities.

Spike-rate adaptation can be modeled by extending the LIF model (2.1) to include an additional current

$$\tau_m \frac{dV}{dt} = E_L - V - r_m g_{\text{sra}}(V - E_K) + R_m I_e \,. \tag{2.4}$$

This spike-rate adaptation current g_{gsa} is modeled as a K^+ conductance which slows any action potential after a previous firing. Equation (2.4) must be supplemented with (2.2) and an equation for the time-dependent conductance g_{sra}. It is common to assume it relaxes to zero exponentially with a time constant τ_{sra}. This is behavior can be obtained as the solution of the equation

$$\tau_{\text{sra}} \frac{dg_{\text{sra}}}{dt} = -g_{\text{sra}} \quad \Rightarrow \quad g_{\text{sra}}(t) = g_{\text{sra}}(0) e^{-\frac{t}{\tau_{\text{sra}}}} \,. \tag{2.5}$$

On top of this, after each spike we increase the conductance by the rule

$$\text{If} \quad V > V_{\text{th}} \quad \Rightarrow \quad g_{\text{sra}} = g_{\text{sra}} + \Delta g_{\text{sra}} \tag{2.6}$$

After repetitive firing the current builds up in a sequence of steps causing the firing rate to adapt!

Regarding refractoriness, the simplest way to include an absolute refractory effect in the LIF model is by extending the crossing rule (2.2) to impose that after each firing the membrane potential clamps to the reset value for a certain time τ_{ref}. Refractoriness can be included into (2.1) in a more realistic way by adding an additional conductance like we did to incorporate adaptation. For this effect, however, we need a fast recovery time (τ small) and larger conductance increment (Δg large). The latter basically clamp the voltage to E_K after each firing, mimicking an absolute refractory period. After this, the conductance will decay exponentially fast making firing possible but less likely. When the recovery is completed, normal firing can resume. Finally, yet another way of modeling refractoriness is by promoting V_{th} to a dynamical variable which raises after each firing and then relax back to its normal value.

[Maybe add the full model here including these two modifications to (2.1) and (2.2)]

2.3 Generalized Integrate-and-Fire

To be continued...

2 References

[1] Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems - Laurence F. Abbott, Peter Dayan - MIT Press, 2005.

[2] Neuromatch Academy