Contents

Part I

Modelling of Cellular Physiology

Chapter 1

Passive Membrane

1.1 Diffusion

We will start considering diffusive processes that take place near the cellular membrane. On the two sides of this structure, charged particles are constantly moving thanks to Brownian motion, a process crucially dependent on the temperature of the solution. The mean displacement of a particle $\langle x \rangle$ is given by:

$$\langle x \rangle = \sqrt{Dt} \tag{1.1}$$

Since x is a length and t a time, we can easily figure out the units of measurement for D:

$$[D] = \frac{m^2}{s}$$

The Einstein relation, which links diffusive processes with thermodynamic quantities, tells us that the diffusive constant D is proportional to:

$$D = \mu k_B T \tag{1.2}$$

with the new constant μ. We know that $k_B T$ is an energy, measured in joules (J), or newton-meter Nm. From this and from the units of D, we can find the units of μ:

$$[\mu] = \frac{m^2}{s \cdot J} = \frac{m^2}{s \cdot N \cdot m} = \frac{m}{s \cdot N} = \frac{speed}{force}$$

We can see that μ is a parameter that indicate how much a particle moves when a force is applied to it.

1.1.1 Diffusive Currents

The change in the concentration of particles due to diffusive processes in a point of the space is given by:

$$\boldsymbol{J}_d = -D \nabla c \tag{1.3}$$

Where c is the concentration of the molecule. In the monodimensional case the this simply reduces to:

$$J_d = -D\frac{dc}{dx} = -\mu k_B T \frac{dc}{dx} \tag{1.4}$$

1.1.2 Electric Currents

If we have a diffusive current of charged particles through channels in the membrane, an electric field will be generated across the membrane[1]. In order to derive the electric field that will be generated, we need to introduce the membrane capacitance. The capacitance of the membrane tells us how many charged particles have to be accumulated on one of its sides to produce a given potential difference across its depth:

$$C = \frac{Q}{V} \tag{1.5}$$

Capacitance has its own unit, the farad (F). With a capacitance of 1 F, 1 C (Coulomb) of charge will produce a potential difference of 1 V (volt).

The capacitance of a cell membrane depends on its surface: the bigger the cell, the more we can spread out the charges thus reducing the electric field. To account for this, we can introduce a membrane specific capacitance that gives us the capacitance per unit of area:

$$C_{sp} = \frac{C}{S}$$

In neuronal cells its value is usually considered to be 1 $\frac{\mu F}{cm^2}$.

The electric field generated across the membrane will in turn affect the movements of charged ions in the channel, producing a net electric current. In particular, since we know that the constant μ tells us the velocity of particles given the force that acts on them, we can write the following equation for the electric current across the membrane:

$$J_e = \mu F_e c$$

Where c is the concentration of particles and F_e is the force acting on each particle, which can be written as qE. Then:

$$\begin{aligned} J_e &= \mu F_e c \\ &= \mu q E c \\ &= \mu q \frac{dV}{dx} c \end{aligned} \tag{1.6}$$

Where for the last passage we used the definition of the electric field as the spatial derivative of the potential.

[1] he volume that enclose the entire system is still electrically neutral, we only have an electric field across the membrane.

If we can assume a constant potential across a membrane of length d, which is usually a valid approximation for the membrane, then we have:

$$J_e = -\frac{\mu q V}{d} c \tag{1.7}$$

The total current once we consider both diffusive and electric currents will be:

$$J = J_d + J_e \tag{1.8}$$

1.2 Nernst Equation

We will start by considering only the equilibrium situation, in which the net flow of charges is 0:

$$J = 0$$

By substituting equation 1.4 and equation 1.6 into equation 1.8, we get:

$$J = -\mu k_B T \frac{dc}{dx} - \frac{\mu q V}{d} c = 0 \tag{1.9}$$

Then:

$$\begin{aligned} \mu k_b T \frac{dc}{dx} &= -\frac{\mu V}{d} c \\ \frac{dc}{dx} &= -\frac{qV}{dk_B T} c \end{aligned} \tag{1.10}$$

This is a linear differential equation in c, with a simple exponential decay solution:

$$c(x) = c_0 e^{-\frac{qV}{dk_B T} x} \tag{1.11}$$

Where c_0 is the concentration of the ion at the 0 point, i.e. the intracellular compartment. Even if the concept of a ionic gradient across the membrane is purely theoretical, we can use this equation to calculate the concentration of the ion on the extracellular side. Remembering that d is the thickness of the membrane,

$$c(d) = c_0 e^{\frac{qV}{dk_B T} d} = c_0 e^{\frac{qV}{k_B T}} \tag{1.12}$$

We can than write the following relationship between the intracellular concentration c_{in} (or c_0), the extracellular concentration c_{out} ($c(d)$) and the potential across the membrane:

$$\begin{aligned} -\frac{q}{k_B T} V &= \ln\left(\frac{c_{out}}{c_{in}}\right) \\ V &= \frac{k_B T}{q} \ln\left(\frac{c_{in}}{c_{out}}\right) \end{aligned} \tag{1.13}$$

Sometimes, this is written in units more familiar to chemists and by using E (in this case NOT an electric field!) instead of V:

$$E = \frac{RT}{zF} \ln\left(\frac{c_{in}}{c_{out}}\right) \tag{1.14}$$

Note that in this final equation we are dealing with moles and not absolute numbers of particles, but this will not affect the result after taking the ratio.

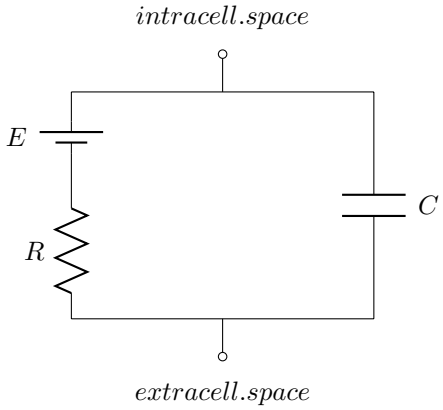

Figure 1.1: The equivalent circuit

The simple scheme of the equivalent circuit for a membrane. The capacitance C is equivalent to the total capacitance of the membrane, E is the potential generated by the ions concentrations and R represent the channels that ions can use to cross the membrane, generating a current according to the resistance of the channel.

Important remark: in this derivation we are considering the 0 of our potential to be in the intracellular side of the membrane. Usually the convention in electrophysiology is to consider the 0 of the potential at the extracellular side. This means that we switch the numerator and denominator in the concentration ratios of equations 1.13 and 1.14, resulting in a sign change of the equilibrium potential: 1.13 and 1.14

$$V = \frac{k_B T}{q} \ln\left(\frac{c_{out}}{c_{in}}\right)$$
$$E = \frac{RT}{zF} \ln\left(\frac{c_{out}}{c_{in}}\right)$$

1.3 Equivalent circuit

1.3.1 Building the Equivalent Circuit

We now want to introduce a different representation if the membrane and diffusion processes. We can deal with it in a much more tractable way by thinking about it in terms of electrical elements. In the simple circuit that we will draw, we will have a membrane capacitance C, a battery (the potential from the Nernst equation) and a resistance, the channels where charges can cross the membrane.

We will start studying the current/voltage relation for the resistance R. If we assume we are in an Ohmic regime (where the Ohm's law $V = RI$ holds), this relation is linear [2].

[2] In general, near the zero we can always approximate this function as linear for the ionic concentrations that we usually find in a cell. For ions that are strongly unbalanced, like Ca^{2+}, this approximation is not appropriate.

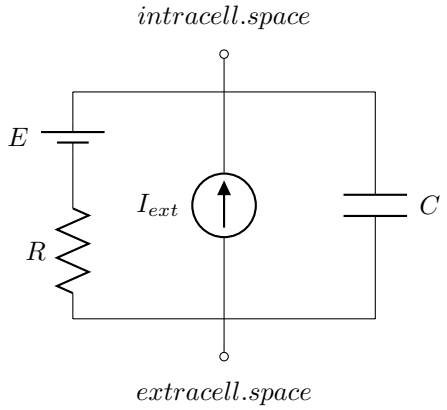

Figure 1.2: Equivalent circuit with current source

The equivalent circuit with the addition of a current I_{ext} that is controlled experimentally.

We can than write:

$$I(V) = gV + b$$

We know that by definition at the resting potential E the current through the membrane is 0:

$$I(E) = gE + b = 0$$

Then $b = -gE$ and

$$I(V) = g(V - E) \tag{1.15}$$

Here, g is the conductance of the membrane, a parameter that tells us how strong is the current given the potential. It is the inverse of the resistance, and it is measured in siemens:

$$S = \frac{A}{V} = \frac{1}{\Omega} \tag{1.16}$$

Now that we have the current/voltage relation for the resistence R, we can study the equivalent circuit of fig. 1.1. In 1.2 we see a similar circuit where we have added the possibility of injecting with an electrode a current I_{ext}. In order to satisfy Kirchhoff's current law and maintain the conservation of charge, the sum of all the currents at every node of the circuit must be 0. Then:

$$I_C + I_R - I_{ext} = 0 \tag{1.17}$$

Where the sign of the electric current that we inject is negative by convention. The capacitative current I_C is defined as:

$$I_C = \frac{dQ}{dt} = C\frac{dV}{dt} \tag{1.18}$$

I_C is not a current flowing through the membrane: it just indicates the accumulation of ions on the two sides of the membrane. It is induced by changes in

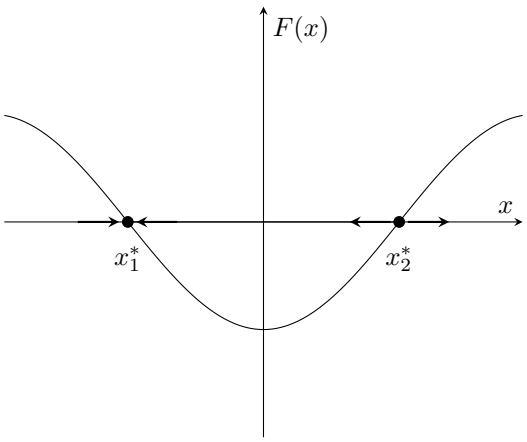

Figure 1.3: Graph of a sample function $F(x) = \frac{dx}{dt}$

voltage, and, in turn, describes how the membrane voltage changes in time as ions flow across the membrane (i.e. as the capacitor is charged/ discharged).

Substituting this equation in equation 1.17 we get:

$$C\frac{dV}{dt} + g(V - E) + I_{ext} = 0 \tag{1.19}$$

This is a differential equation where the dynamic variable is V, and we have three parameters C, g, E, I_{ext}.

1.3.2 Linear One-Dimensional Differential Equations

When we have a first-order (autonomous) differential equation, we have to solve the general problem:

$$\frac{dx}{dt} = F(x) \tag{1.20}$$

Where x is a function of t. That is, by analysing the function F with respect to the value of x we can see how the *rate of change of* x changes with respect to x. Let's take as an example the function $F(x)$ represented in fig. 1.3. In this example, $F(x)$ crosses the 0 two times in x_1^* and x_2^*. This means that at these points the rate of change of the solution $x(t)$ is 0, i.e. it is constant. For this reason those two points are called stationary solutions or fixed points.

To see what happens when the value of $x(t)$ is different from x_1^* or x_2^*, we have to study the sign of the function $F(x)$. When it is positive, the rate of change of x is positive and x is an increasing function of t. When it is negative, the rate of change of x is negative and x decreases. This behaviour is represented with the arrows of fig. 1.3. In this way we can see that if the function $x(t)$ slightly moves away from the point x_1^* in either direction it goes back to the fix point. We call this fix point *stable point*. On the other side, when it moves from point x_2^* it keeps moving away: this point is an *unstable point*.

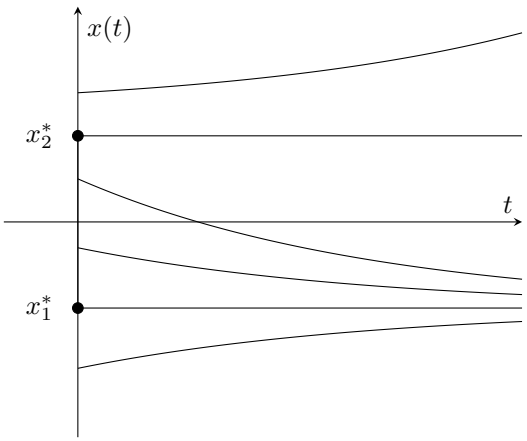

Figure 1.4: Solutions for the differential equation of fig. 1.3 for different starting values x_0.

Fig. 1.4 shows the evolution over t of several solutions $x(t)$ of this differential equation. Here we clearly see that the evolution of this function depends on the initial value x_0. When it coincides with one of the two fix points $x(t)$ is constant. If $x_0 > x_1^*$ $F(x)$ is positive and the solution diverges to infinity. For $x_0 < x_1^*$, all the solutions converge to the stable point x_2^*, as can be deduced from the sign of $F(x)$ around this problem. This can be alternatively stated in terms of the derivative $\frac{dF}{dx}$:

$$\frac{d}{dt}F(x^*) < 0 \qquad \text{stable fix point}$$
$$\frac{d}{dt}F(x^*) > 0 \qquad \text{unstable fix point}$$

1.3.3 Passive Membrane

Now that we know how to deal with these simple differential equations we can turn back to the problem of the passive membrane of eq. 1.19. Rearranging the terms, we can obtain:

$$\frac{dV}{dt} = -\frac{gV}{C} + \frac{gE + I_{ext}}{C} = -\frac{V}{\tau} + J$$

Where

$$\tau = \frac{C}{g} \qquad J = \frac{gE + I_{ext}}{C} \tag{1.21}$$

We can see that the rate of change $\frac{dV}{dt}$ is a linear function of V, with a slope $-\frac{1}{\tau}$ and an x-intercept at $V^* = \tau J$ (fig.1.5). Moreover, since $\frac{dV}{dt}$ is positive below V^* and negative above, V^* is a stable fix point.

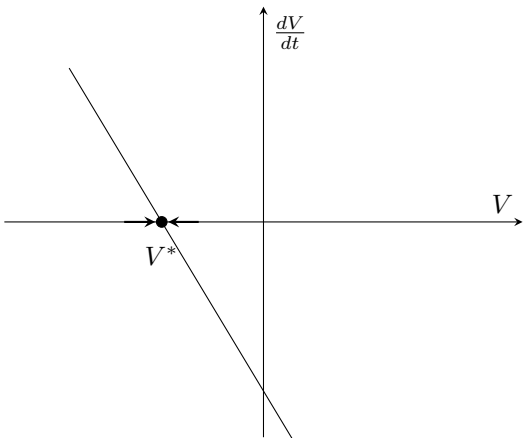

Figure 1.5: Graph ofdV/dt. The fix point V^* is always stable. A current injection would shift this line upward.

We can also analyse how the stable solution change as a function of the initial parameters. As we have seen:

$$V^* = \tau J$$

Using the definition of J, in the case of $I_{ext} = 0$:

$$V^* = \tau J = \tau \frac{gE}{C} = E$$

I.e., without an external current the resting potential E is a stable solution of equation 1.19.

To find an explicit form for a full solution of this differential equation we will try again to see if a given form

$$V(t) = Ae^{BT} + C \tag{1.22}$$

can satisfy equation 1.19. Taking the derivative of $V(t)$:

$$\frac{dV}{dt} = \frac{d}{dt}(Ae^{Bt} + C) = ABe^{Bt} \tag{1.23}$$

If we plug this into equation 1.19 we get:

$$ABe^{Bt} = -\frac{A}{\tau}e^{Bt} - \frac{C}{\tau} + J \tag{1.24}$$

For this equivalence to hold the constant terms and the terms depending on t must be separately equal:

$$ABe^{Bt} = -\frac{A}{\tau}e^{Bt}$$
$$0 = -\frac{C}{\tau} + J$$

It immediately follows:

$$B = -\frac{1}{\tau}$$
$$C = \tau J$$

A remains to be determined, since it is a free parameter that we set by fixing the initial conditions for the potential:

$$V(0) = Ae^{-\frac{0}{\tau}} + \frac{J}{\tau} = A + \frac{J}{\tau}$$

It follows that:

$$A = V_0 - \tau J$$

Now we have:

$$\begin{aligned} V(t) &= (V_0 - \tau J)e^{-\frac{t}{\tau}} + \tau J \\ &= V_0 e^{-\frac{t}{\tau}} + \left(\frac{gE}{C} + \frac{I_{ext}}{C}\right)\tau(1 - e^{-\frac{t}{\tau}}) \\ &= V_0 e^{-\frac{t}{\tau}} + \left(E + \frac{I_{ext}}{g}\right)(1 - e^{-\frac{t}{\tau}}) \end{aligned} \tag{1.25}$$

Now let's take a cell at the equilibrium potential E and inject a current I_{ext} with an electrode. Setting $V_0 = E$ we have

$$\begin{aligned} V(t) &= Ee^{-\frac{t}{\tau}} + \left(E + \frac{I_{ext}}{g}\right)(1 - e^{-\frac{t}{\tau}}) \\ &= E + \frac{I_{ext}}{g}(1 - e^{-\frac{t}{\tau}}) \end{aligned}$$

For $t \to \infty$ this tends to

$$V_{t\to\infty} = E + \frac{I_{ext}}{g} = E + RI_{ext}$$

The velocity by which $V(t)$ goes to this final value depends on the exponential term, i.e. τ. The larger τ the slower the increment. We can see that the resistance (and its reciprocal, the conductance) is a factor in both the important parameters for this function: it influences the maximum depolarization as well as the rate of depolarization.

1.3.4 Equivalent Circuit with Multiple Conductances

One approximation of our previous equivalent circuit model is that it considers only one ionic species. The next step could be consider multiple ion channels, each one with its resting potential and conductance.

We can start by considering a sodium-specific conductance (g_{Na}, with the potential E_{Na}) and a "leakage conductance" g_L, with E_L, that considers all the

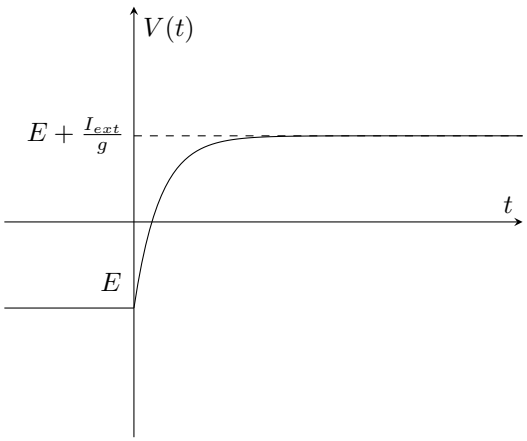

Figure 1.6: Evolution in time of an equivalent circuit after application of the external current I_{ext} at time $t = 0$.

other ionic movements (mostly potassium). As shown in (fig.). We only have to add this new branch of the circuit to equation 1.19

$$\begin{aligned} C\frac{dV}{dt} &= g_L(E_L - V) + g_{Na}(E_{Na} - V) + I_{ext} \\ &= g_L E_L + g_{Na} E_{Na} - (g_L + g_{Na})V + I_{ext} \\ &= (g_L + g_{Na})\left(\frac{g_L E_L + g_{Na} E_{Na}}{g_L + g_{Na}} - V\right) + I_{ext} \\ &= g_{tot}(E_{tot} - V) + I_{ext} \end{aligned} \tag{1.26}$$

As this expression is equivalent to equation 1.19, with two new constants that consider all the conductances and the potentials:

$$\begin{aligned} g_{tot} &= g_L + g_{Na} \\ E_{tot} &= \frac{g_L E_L + g_{Na} E_{Na}}{g_L + g_{Na}} \end{aligned}$$

E_{tot} is a weighted mean of the two resting potentials, therefore it is always bound to assume an intermediate value between them. For this reason, the equation will always have a stable solution as equation 1.19. Note that this can be repeated for every combination of passive channels we can introduce.

1.4 Voltage-Dependent Conductances

1.4.1 Voltage-Dependent Na Conductance

In real neurons, the most important conductances for the generation of the action potential are voltage-dependent sodium channels. To start modelling

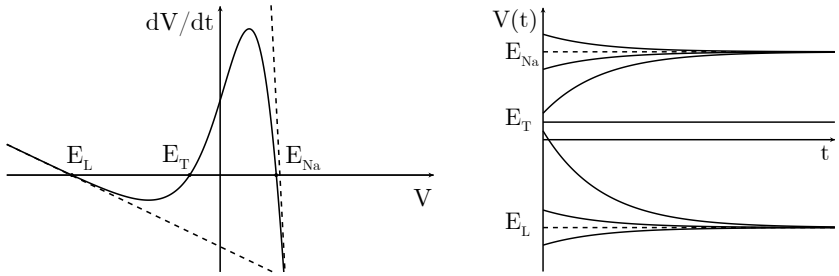

Figure 1.7: (*Left*) Plot for $\frac{dV}{dt}$ for a cell with an ideal voltage-dependent sodium channel. Note how near the stable points E_L and E_{Na} the function tends to the linear relation we have been studying before. (*Right*) Evolution in time of a membrane with a voltage-dependent sodium conductance.

more interesting dynamics, we can think about introducing a voltage dependence in our sodium conductance, now modelled as some simple function $g_{Na}(V)$. We will not deal with its analytical expression; for now it is enough to know that it goes to 0 around the leakage resting potential E_L (usually around -60 mV) and tends to an asymptotic value g_{Na} as the voltage increase. An important assumption is that the asymptotic value of g_{Na} is $\gg g_L$. Substituting in equation 1.19 we get:

$$C\frac{dV}{dt} = g_L(E_L - V) + g_{Na}(V)(E_{Na} - V) + I_{ext} \tag{1.27}$$

This time we cannot simplify the equation. To understand the stability of the system we can study the function $C\frac{dV}{dt}$ even without an analytical solution.

We will start by ignoring the current I_{ext}. When it is close to E_L the conductance $g_{Na}(V)$ is close to 0, and the equation reduces to the case of the passive membrane we have seen before, where the intercept has an abscissa of E_L (left dashed line of fig. 1.7). On the other hand, since $g_{Na} \gg g_L$, when the function goes near to E_{Na} it approximates a passive membrane with an intercept E_{Na} (right dashed line of fig. 1.7). It follows that near those zero points the function has to approximate the simple passive membrane, i.e. it must have a negative derivative. In order to do that, if we want it to be a "well-behaved" differentiable function it has to cross again the abscissa at some point $E_L < E_T < E_{Na}$ with a positive slope (fig. 1.7). This provides the differential equation with another fix point, but this time it is unstable. We will call it the *threshold point*: below this value every starting value would lead the cell toward the resting potential E_L, and above it toward E_{Na}.

The solutions for such a system are shown in fig. 1.7.

Now we can consider again the role of the applied current I_{ext}. As reported in the plot of fig. 1.8, its value shifts the curve up and down. This means that changing it we can set the number of fix point solutions from three, to two, or only one single solution. To represent this dependence we can use a bifurcation diagram that shows the number and positions of the fixed solutions as a function of the parameter I_{ext} (fig. 1.8).

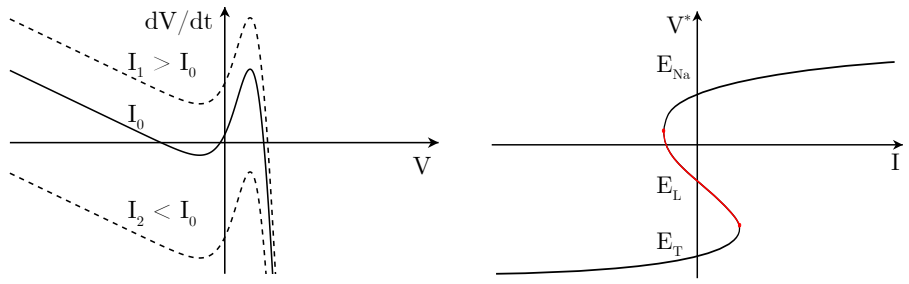

Figure 1.8: (*left*) Shift of the curve of fig. 1.7 for different I_{ext} values. Note the changes in the x axix intercepts.(*right*) Bifurcation diagram showing the behaviour of the stable solutions V^* as a function of I_{ext}.

1.4.2 One-Dimensional Neuronal Models

In the previous section we have been qualitatively analysing the behaviour of a system whose equation $\frac{dV}{dt}$ we did not specify. Here are some examples of how this function can be defined to determine the dynamics of a simple one-dimensional model.

Leaky integrate-and-fire (LIF)

In this case, we use a simple passive membrane model with the leakage conductance g_L and we set a spike voltage V_s. Every time that the neuron reach this value we count one action potential, and we set again its voltage at a reset value V_r.

Quadratic integrate-and-fire (QIF)

In the quadratic model we try to use a better approximation of a voltage-dependent sodium channel, i.e. we try to preserve the fact that there is a change in the slope of the curve $\frac{dV}{dt}$ between E_L and E_T. This means that the negative drive will become smaller near E_T, instead of becoming always bigger as in the LIF. Again, once we reach a threshold value we put back the cell to the reset potential V_r. The equation for the potential derivative in this case will be:

$$\tau \frac{dV}{dt} = (V - E_R)(V - E_T) + IR \tag{1.28}$$

Note that since the growth of the derivative become supra-linear, even if we do not reset the voltage it will become infinite in a finite amount of time (hyperbolic growth). This makes the precise choice of the threshold point not too relevant (it can be even infinite).

Exponential integrate-and-fire (EIF)

The problem with the quadratic model is that it makes the arbitrary assumption that the potential is symmetric around the point $(E_R + E_T)/2$ (the vertex of the parabola). To make a slightly better model we can use something more similar to the function we have plotted in fig 1.7. This can be done by using an exponential term in the function for the voltage, such as:

$$\tau \frac{dV}{dt} = (V - E_R) + \alpha e^{\frac{V - E_T}{\alpha}} + IR \tag{1.29}$$

This model gives a more satisfactory description of the physiological properties of a cell in the sub-threshold regime. Still, as long as we remain in the domain of one-dimensional systems, we cannot properly derive the amplification followed by the reset of the resting potential which characterize the full action potential.

1.5 Nernst Potential from Vokker-Planck Equation

We provide here a more complete derivation of the Nernst equation, in a framework that will make possible to test the validity of the assumption (made in the passive membrane model) about the Ohmic nature of the membrane conductance.

1.5.1 Continuity Equation

We start by the same simplified one-dimensional sketch for the membrane geometry we used in section 1.3.3: we have a membrane of width d that divides the outside of the cell ($x < 0$) from the inside ($x > d$). In any arbitrary interval of this space we can calculate the number of particles as:

$$N(t) = \int_a^b C(t, x) dx \tag{1.30}$$

Where $C(t, x)$ is the concentration of particles for each x at the time t, and we assume that it can change in time. For it to change in time we must have an inflow or an outflow of particles at the boundaries of the considered interval $[a, b]$. If the particles are charged, we can indicate these flows as the currents at the two boundaries $J_a(t)$ and $J_b(t)$. Therefore:

$$\frac{dN(t)}{dt} = \int_a^b \frac{\partial C(x,t)}{\partial t} dx = J_a(t) - J_b(t) = -\int_a^b \frac{\partial J(x,t)}{\partial x} dx \tag{1.31}$$

Where the sign in the current difference depends on the arbitrary definition of positive current flowing from low to high x, and the last identity holds for the

fundamental theorem of calculus. Since $[a, b]$ is an arbitrary interval that can be made arbitrary small, we can eliminate the integrals to get:

$$\frac{\partial C(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x} \tag{1.32}$$

This equation is called continuity equation. It states that any change in particles concentration in time in one point of the space corresponds to a change in the derivative of the current in that point of the space, as we have discussed in section 3.4. In more than one space dimensions this generalizes to:

$$\frac{\partial C(\boldsymbol{x},t)}{\partial t} = -\nabla \cdot \boldsymbol{J}(\boldsymbol{x},t) \tag{1.33}$$

1.5.2 Vokker-Planck Equation for the Cellular Membrane

We have already seen that the current J can be divided in two components: a purely diffusive one, that depends on a non-homogeneous distribution of particles in the space, and an electric one, that corresponds to a drift under the effect of some electric potential $\phi(x,t)$. If the potential is constant in time ($\phi(x,t) = \phi(x)$), remembering the derivations made in section 1.3.3, we can write:

$$J = J_{el} + J_{diff} = -C(x,t)\mu q\frac{d\phi(x)}{dx} - \mu k_b T\frac{\partial C(x,t)}{\partial x} \tag{1.34}$$

If we remain in the membrane interval $[0, d]$ and we assume that in this region the potential decrease in a linear way, we know that $-\frac{d\phi(x)}{dx} = -\frac{V}{d}$, where V is the potential difference between the inside and the outside of the cell. We can plug this definition of the current in the continuity equation to get:

$$\frac{\partial C(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x} = \frac{\mu q V}{d}\frac{\partial C(x,t)}{\partial x} + \mu k_b T\frac{\partial^2 J(x,t)}{\partial x^2} \tag{1.35}$$

This is an example of a Fokker-Planck equation, a partial differential equation that describe the time evolution of the distribution of particles under the effects of Brownian motion and a drifting force, in this case electrical.

1.5.3 Solutions of the Vokker-Planck at Equilibrium

We can try to have a look at the equilibrium states of the system, *i.e.* states that do not change over time. For an equilibrium state:

$$\frac{\partial C(x,t)}{\partial t} = 0$$
$$\frac{\partial J(x,t)}{\partial x} = 0$$

This means that the current is constant, with a value that we can call J_0. We can substitute these values in equation 1.34 and divide by $\mu k_b T$ to get:

$$\frac{J_0}{\mu k_B T} = -\frac{qV}{\mu k_B T} C(x) - \frac{dC(x)}{dx} \tag{1.36}$$

This is the same linear differential equation for $C(x)$ we have seen in section 1.3.3, which has a solution:

$$C(x) = C(0) e^{\frac{-qV}{k_B T}\frac{x}{d}} - \frac{J_0 d}{\mu q V}(1 - e^{\frac{-qV}{k_B T}\frac{x}{d}}) \tag{1.37}$$

We can use this function to find an expression for the ion concentration in the cell, which correspond to $C(d)$ and is a value that we can evaluate experimentally:

$$C(d) = C(0) e^{\frac{-qV}{k_B T}\frac{d}{d}} - \frac{J_0 d}{\mu q V}(1 - e^{\frac{-qV}{k_B T}\frac{d}{d}})$$

From here, we can obtain an explicit expression for the steady current across the membrane J as a function of the membrane potential difference V:

$$J(V) = \frac{\mu q V}{d} \frac{C_d - C_0 e^{\frac{-qV}{k_B T}}}{1 - e^{\frac{-qV}{k_B T}}}$$

Where C_d and C_0 are $C(d)$ and $C(0)$. To have a nicer form, we can finally use a rescaled voltage u defined as $u = \frac{q}{k_B T}$, identical to V but for a constant scaling term.

$$J(u) = \frac{k_B T \mu}{d} u \frac{C_d - C_0 e^{-u}}{1 - e^{-u}} \tag{1.38}$$

1.5.4 GHK Flux Equation

In equation 1.38 $\frac{k_B T \mu}{d}$ is a constant term that scales the amount of current given the potential u. Therefore we will call it P, or permeability constant. Multiplying everything by e^u we get the final form:

$$J(u) = Pu \frac{C_0 - C_d e^u}{1 - e^u} = P \frac{u}{1 - e^u}(C_0 - C_d e^u) \tag{1.39}$$

This equation is called the Goldman–Hodgkin–Katz (GHK) flux equation (not to be confused with the Goldman–Hodgkin–Katz voltage equation). To write the passive membrane equations, we have assumed that this dependence was a linear one, *i.e.* that $J(u) = g(V - E)$ where E was the resting potential of the considered ionic specie.

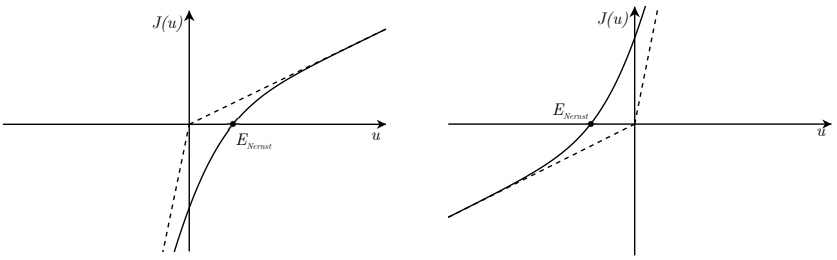

Figure 1.9: Graphics for the GHK flux equation with $C_0 > C_d$ (*left*) and $C_d > C_0$ (*right*).

We need to see when the equation that we have obtained for $J(u)$, which is not linear, can be considered reasonably linear under some limit approximation. For example, we can start by analysing what happens near the reversal potential, the potential at which the current across the membrane cross the zero and changes its sign. This means that we have to look at 0-crossing points of equation 1.39. We can analyse separately the two terms $\frac{x}{1-e^x}$ and $(C_0 - C_d e^u)$. The first term is always negative, and for $x \to 0$ goes to:

$$\lim_{u\to 0^+} \frac{u}{1-e^u} = \lim_{u\to 0^+} \frac{1}{-e^u} = -1 \lim_{u\to 0^-} \frac{u}{1-e^u} = \lim_{u\to 0^-} \frac{1}{-e^u} = -1$$

Where to solve the indefinite limit we have turn to l'Hôpital's rule. Note that even if both limits are behaving properly, strictly speaking the function is not defined for $x = 0$, but it is a discontinuity of the first type and it can easily be dealt with by defining separately the 0 value of the function.

The 0 crossing therefore must be given by the second term, $(C_0 - C_d e^u)$. By setting this equal to 0, we find:

$$u = ln\left(\frac{C_0}{C_d}\right) \tag{1.40}$$

And this formula is equivalent to the Nernst equation.

Now we can look at the limits for $u \to \pm\infty$ to draw this function.

$$\lim_{u\to+\infty} Pu\frac{C_0 - C_d e^u}{1-e^u} = PC_d u$$
$$\lim_{u\to-\infty} Pu\frac{C_0 - C_d e^u}{1-e^u} = PC_0 u$$

For both $\pm\infty$ we have two linear asymptotes with different slopes that are proportional to the external and internal concentrations. This behaviour is shown in Figure 1.9 for both $C_0 > C_d$ and $C_d > C_0$.

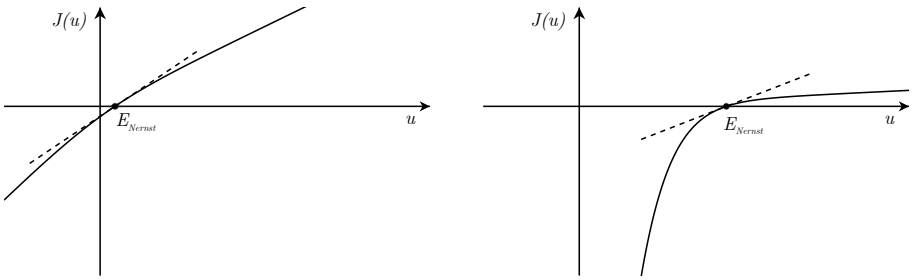

Figure 1.10: Graphics for the GHK flux equation with $C_0 \sim C_d$ (*left*) and $C_0 \gg C_d$ (*right*).

1.5.5 GHK Flux Equation and the Ohmic Approximation

For our linear approximation $J \approx g(E - V)$ to hold around the Nernst potential, the two lines must have a similar slope. This means that the two ionic concentrations cannot be too different from each other. This can be graphically appreciated in Figure 1.10: when the two lines are extremely different, the bending around the zero crossing makes the error of the linear approximation bigger. This is for example why the GHK flux equation is used to calculate the resting potential for the Ca^{2+} ion, since the intracellular concentration is orders of magnitude lower than the extracellular concentration. For all the other ions though the Ohmic approximation does not depart too much from the GHK curve.

1.5.6 GHK Potential

Finally, we can use this equation to derive the current flow when the membrane is permeable to more than one chemical specie. In this case,

$$J_{tot} = \sum_x J_x q_x = \sum_x q_x^2 P_x \frac{\frac{V}{k_b T}}{1 - e^{\frac{q_x V}{k_b T}}} (C_x(0) - C_x(d) e^{\frac{q_x V}{k_b T}}) \tag{1.41}$$

Where q_x and P_x are the charge and the permeability of each specific ion.

This cannot be always simplified. But in the special case that we have when all the q_x have the same absolute value, we can find an expression for the voltage that makes the total current $J_{tot} = 0$. With some algebra we obtain:

$$V_{GHK} = \frac{k_b T}{|z|e} ln \left(\frac{\sum_{x,z>0} P_x C_x^{out} + \sum_{x,z<0} P_x C_x^{in}}{\sum_{x,z>0} P_x C_x^{in} + \sum_{x,z<0} P_x C_x^{out}} \right) \tag{1.42}$$

And this is the famous GHK potential, where the resting potential is calculated keeping into account the permeability of the cell to each of the involved ionic species.

Chapter 2

Hodgkin-Huxley Model

2.1 Voltage-gated Channels

2.1.1 Gating Variables

In the previous section an important approximation that we were using is that the changes in the conductances were instantaneous. In the true biophysical situation, the opening of a channel require a conformational change in the protein, a process that is described by its own temporal kinetics. If we want to take this into account, we need to introduce a gating variable x that tells us at any time t what is the fraction of open channels (it goes from 0 to 1). In this way, to describe the temporal evolution of the opening of the channel, we need to write the differential equation for x.

To describe its dynamics, we need to introduce an opening rate ($\alpha_x(V)$) and a closing rate $\beta_x(V)$. They are a function of V since we know that the gating process will depend on the voltage of the cell membrane. If we assume that the gating process follows a fist-order kinetics, the evolution in time of x will be described by:

$$\frac{dx}{dt} = (1-x)\alpha_x(V) - x\beta_x(V)$$

Where $(1-x)$ is the fraction of closed gates, and x is the only dynamic variable. By rearranging it we can write

$$\begin{aligned}
\frac{dx}{dt} &= \alpha_x(V) - x(\alpha_x(V) + \beta_x(V)) \\
\frac{dx}{dt} &= \alpha_x(V) - \frac{x}{\tau_x(V)} \\
\tau_x(x)\frac{dx}{dt} &= \tau_x(V)\alpha_x(V) - x \\
\tau_x(x)\frac{dx}{dt} &= x^{\infty}(V) - x
\end{aligned}$$

Where:

$$\tau_x(V) = \frac{1}{(\alpha_x(V) + \beta_x(V))}$$
$$x^\infty(V) = \tau_x(V)\alpha_x(V)$$

This is a very simple differential equation of the same type we have encountered before, with a linear dependence of the derivative of the function on the function itself. it will be a stable solution at $x = x^\infty(V)$, and it will always converge to this value (derivative is always negative) with a time constant $\tau_x(V)$. The bigger the time constant, the slower the process.

2.1.2 Gating of the Sodium Channel

Hodgkin and Huxley, studying the dynamics of the sodium channel, came up with a model for its kinetics with two different mechanisms: an activation gate m and an inactivation gate h. Each of these gates is voltage sensitive, with its own parameters; therefore we will have two equations:

$$\frac{dm}{dt} = \frac{m^\infty(V) - m}{\tau_m(V)} \tag{2.1}$$
$$\frac{dh}{dt} = \frac{h^\infty(V) - h}{\tau_h(V)} \tag{2.2}$$
$$\tag{2.3}$$

The two gating variables m and h compose together to give the equation for the total sodium conductance $g_{Na}(t)$:

$$g_{Na} = \overline{g}_{Na} m^3(V) h(V)$$

In this function, the activation gating variable m has an exponent 3 as a result of the fitting of the experimental data. One possible way to interpret this is to think that there are three independent gates of the type m and one of the type h on each channel protein, and they all have to be open for the channel to have non-zero conductance (i.e., their probabilities multiply). Still, since the motivations for the choice of the exponent 3 are purely experimental and do not derive from considerations on the structure of the channel, this interpretation should not be taken too literally. Modern models include often other values between 2 and 3.

Now we can have a look at the voltage dependences of the two gating variables (fig. 2.1). The limit value $h^\infty(V)$ for the activation gate starts at 1 for low voltages and it decreases to 0 for increasing voltages; on the other hand, $m^\infty(V)$ will start at 0 and increases to 1 for high voltages. To be more precise, since the conductance is dependent on the cube of the gating variable m in the equation we should look at the graph for $m^{\infty 3}$, which grows slightly less than m^∞. There is a window of voltages in which both curves are much higher than 0; this can be seen in the graphic for the limit value of the total sodium conductance $g^\infty_{Na}(V)$

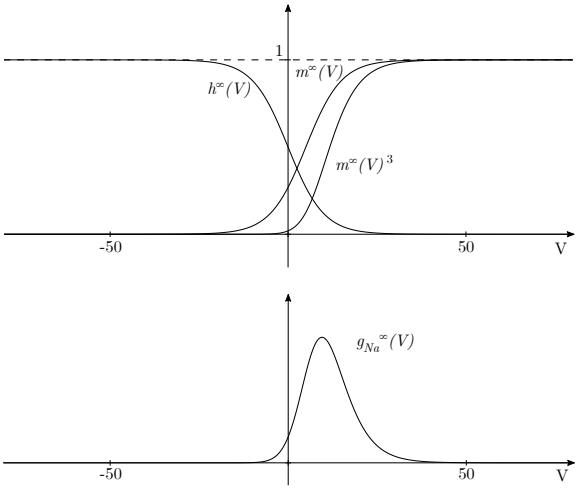

Figure 2.1: *(top)* voltage dependency of the gating variables parameters $m^\infty(V)$ and $h^\infty(V)$; *(bottom)* voltage dependency of the resultant limit conductance $g^\infty_{Na}(V)$.

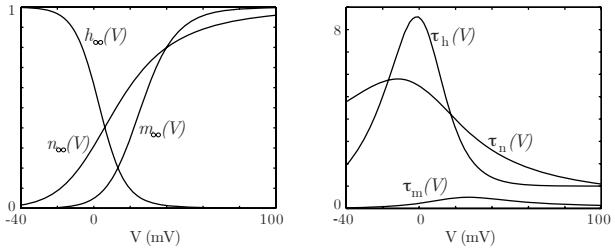

Figure 2.2: Numeric values for the limit value (*left*) and time constant (*right*) for the sodium activation, the sodium inactivation and potassium gate. Note that these values change with channel type and specific neuron physiology (from Dynamical Systems in Neuroscience; Eugene M. Izhikevich, 2007).

that combines the previous two functions. As for the time constants $\tau_m(V)$ and $\tau_h(V)$, the most important thing is that the former is much faster than the latter, as can be appreciated in fig. 2.2.

2.1.3 Voltage-clamp Experiments

Now we can try to figure out what happen with an ideal voltage-clamp experiment, i.e. an experiment in which we assume to be able to adjust instantaneously the voltage of the cell to a desired value (fig. 2.3). In such an experimental condition, we can think of moving a cell at its resting potential E toward a voltage value V_0 around 0. The value of $m(V)$ is initially 0 since $m^\infty(E) \sim 0$. With increasing voltages it will exponentially go to $m^\infty(V_0)$ (slightly less than 1 for $V_0 \sim 0$) with a time constant $\tau_m(V_0)$. The value of $h(V)$ (initially 1) will ex-

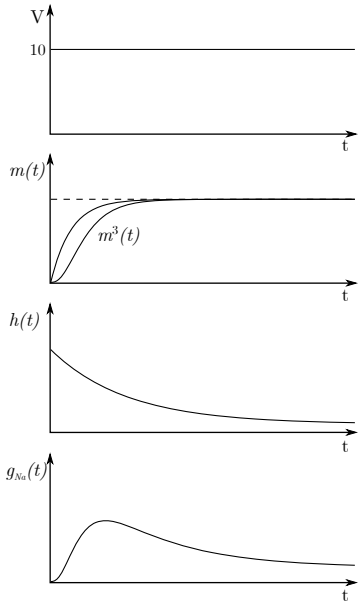

Figure 2.3: Ideal voltage clamp experiment. From top to bottom: the voltage step that we apply to the cell; time evolution ot the gating variable $m(V)$ (note the difference of the cubic term); time evolution ot the gating variable $h(V)$; combination of the two gating variables in the total conductance $g_{Na}(V)$

ponentially go to $h^{\infty}(V_0)$ (slightly more than 1 for V_0 0) with a time constant ($\tau_h V_0 < \tau_m V_0$).

If we now look at the composition of these two different functions that determine g_{Na} we will have two opposite dynamics: in the beginning the fastest time constant for the activation gate will drive an initial increase in the conductance; after some time, this will be followed by a decrease in the conductance due to the slower action of the inactivation channel, that will drive the conductance to 0 or to a similar value according to the choice of V_0. If we plot the value reached by g_{Na} at its peak, we can have the graphic of figure (fig. 2.4). For small values of V_0 it will be almost 0, than it will increase to stabilize eventually around a constant value. Now that we have described the voltage dependency of the sodium conductance, we can draw the I/V curve for this ion (measured at the time of the conductance peak), that is a product of the conductance and the driving force of the ion. The result can be appreciated in fig. 2.5. It is almost 0 for low voltages, it goes to negative values as soon as the conductance begins to increase (the voltage is still lower than the equilibrium potential for sodium), and it follows a linear relationship $g(V - E)$ when we reach the limit value of the peak conductance g_{peak}.

2.1.4 Gating of the Potassium Channel

The potassium channel has a much simpler dynamics, in that it has only an activation gate (modelled by the gating variable n). Experimental results show

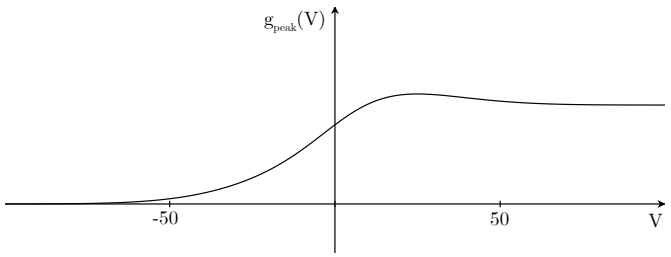

Figure 2.4: Peak value reached by $g_{Na}(V)$ in the voltage clamp experiment.

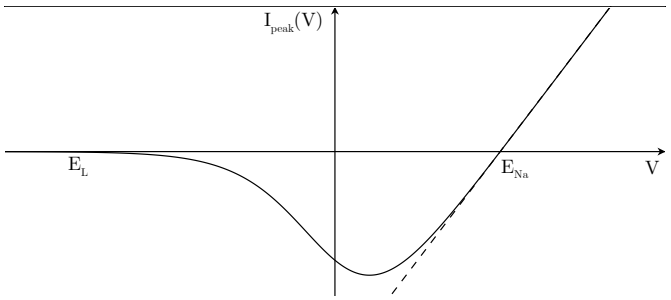

Figure 2.5: Voltage/current plot for the voltage-gated sodium conductance

that sodium conductance is proportional to n^4:

$$g_K(t) = \overline{g}_K n^4(t)$$

with

$$\tau_n(V)\frac{dn}{dt} = n^{\infty}(V) - n$$

The graphic of this function and its fourth power is very similar to the sodium gating variable parameter $m^{\infty}(V)$, as can be seen in fig. 2.2. The I/V curve for potassium currents is represented in fig.2.6: the higher the voltage the more the slope of the true current get close to the ideal linear relationship of a voltage independent potassium conductance.

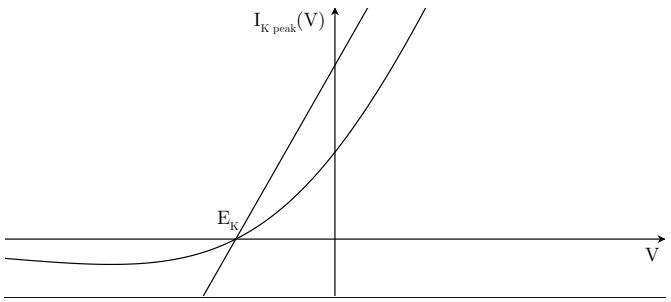

Figure 2.6: Voltage/current plot for the voltage-gated potassium conductance

2.2 Building the H-H model

2.2.1 Conductances Functions

The functions that we will use for describing the conductance kinetics ($m^\infty(V)$, $\tau_m(V)$, etc.) will simply be fits on electrophysiological recordings. One typical model function for an activation curve (for example $n^\infty(V)$) is a sigmoid function:

$$n^\infty(V) = \frac{1}{1 + e^{-\frac{V - V_0}{k}}} \tag{2.4}$$

This function has the limits that we expect, in that:

$$\lim_{V \to +\infty} n^\infty(V) = 1$$
$$\lim_{V \to -\infty} n^\infty(V) = 0$$

And the parameters that describe the steepness and the flexing point of the curve (k and V_0) are easily fitted from experimental data. There may be other possible functions used in more advanced models, but even a simple sigmoid catch the salient features of the behaviour of the conductance.

2.2.2 H-H Equations

Now we have all the ingredients to compose the full H&H model. As we have previously seen, for the equivalent circuit of the cell we can use the Kirchhoff's current law to write:

$$C\frac{dV}{dt} + I_L + I_K + I_{Na} = I_{ext} \tag{2.5}$$

Where:

$$I_L = g_L(V - E_L) \tag{2.6}$$
$$I_{Na} = g_{Na}(V - E_{Na}) = \overline{g}_{Na} m^3 h (V - E_{Na}) \tag{2.7}$$
$$I_K = g_K(V - E_K) = \overline{g}_{Na} n^4 (V - E_K) \tag{2.8}$$

And the evolution in time of the gating variables m, n and h will be given by:

$$\tau_m(V)\frac{dm}{dt} = m^\infty(V) - n$$
$$\tau_h V)\frac{dh}{dt} = h^\infty(V) - n$$
$$\tau_n(V)\frac{dn}{dt} = n^\infty(V) - n$$

The full H&H system will therefore be:

$$\frac{dm}{dt} = \frac{m^{\infty}(V) - n}{\tau_m(V)}$$
$$\frac{dh}{dt} = \frac{h^{\infty}(V) - n}{\tau_h V)}$$
$$\frac{dn}{dt} = \frac{n^{\infty}(V) - n}{\tau_n(V)}$$
$$\frac{dV}{dt} = \frac{g_L}{C_m}(V - E_L) + \frac{\overline{g}_{Na}}{C_m} m^3 h(V - E_{Na}) + \frac{\overline{g}_{Na}}{C_m} n^4 (V - E_K) + \frac{I_{ext}}{C_m}$$

This is a 4-dimensional dynamical system - *i.e.*, a system of differential equations (in this case, ordinary differential equations) that describe the evolution over time of 4 different variables..

2.2.3 Qualitative Analysis of Spiking in the H-H Model

The qualitative evolution of the four variables during an action potential is described in figure 2.7. When an external current is applied through an electrode, there is a initial depolarisation of the cell. This depolarisation recruit quickly the fast gating variable $m(t)$; this, in turn, sustains and amplifies the depolarisation even after the end of the current injection thanks to the flow of sodium ions. This self-amplified depolarisation gives rise to the upstroke of the action potential. After a while, two other events with slower timescales and activating voltages take place. On one side, the depolarisation trigger the closing of the slow gating variable $h(t)$ of the sodium conductance, which determines the closing of previously opened sodium channels. On the other, slow potassium conductances are opened (gating variable $n(t)$) and mediate the repolarization of the cell. The repolarization does not stop at the resting potential: since a large number of potassium conductances are recruited, the cell temporarily goes to a voltage closer to the potassium resting potential (more negative than the resting potential). This produces the so-called after-hyperpolarization.

Two things prevent the immediate repolarization of the cell. Initially, in the absolute refractory period, sodium conductances are still inactivated, and the gating variable h is still closed, and the generation of a new spike is completely blocked. Then, even when all $h(t)$ gates are opened again, the hyperpolarization of the cell due to the potassium conductances is still present, and stronger inputs will be required in order to trigger the action potential. This is the so-called relative refractory period.

2.2.4 Generalization of the H-H Model

The current-balance equation we wrote (equation 2.5) is valid for an arbitrary number of currents that contribute to the membrane voltage:

$$C\frac{dV}{dt} + \sum_x I_x = 0 \tag{2.9}$$

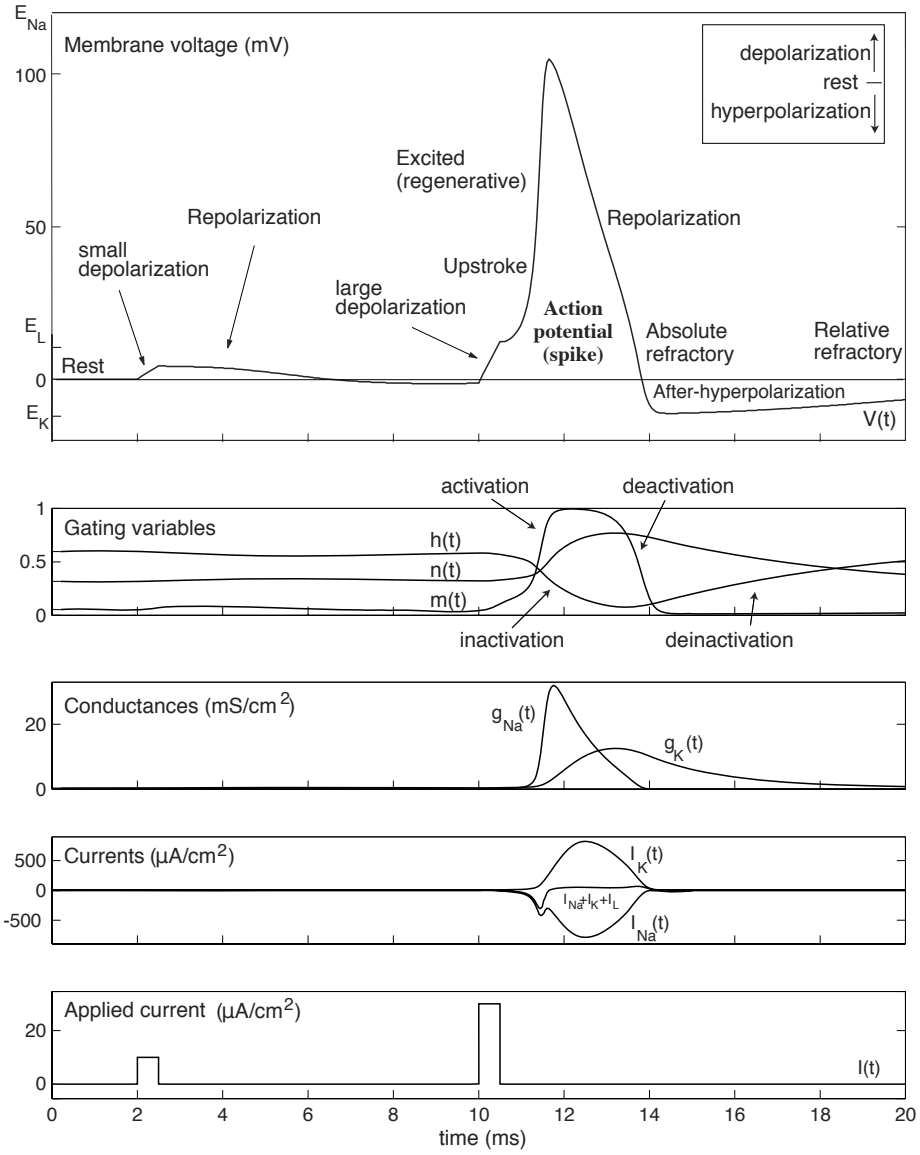

Figure 2.7: Time evolution of membrane potential and ionic conductances during an action potential as described by the H&H equations (see text for description).

where I_x can include many sodium, potassium, chloride, calcium currents, each with any kind of complicate dependence on voltage or other factors, and it can be expressed in a general form as:

$$I_x = \overline{g}_x \prod_k a_k^{n_k} (V - E_x) \tag{2.10}$$

Were the productory on k take into account an arbitrary number of gating variables a_k with exponents n_k. this can be very useful to provide numerical description for different cells having particular firing patterns that emerge as the combination of specific types of ionic conductances with different gating mechanisms.

2.3 2D Reduction of H-H Model

We have seen that in the H&H model we have 4 dynamical variables interrelated in a dynamical system ($V(t)$, $g(t)$, $h(t)$ and $n(t)$). To analyse the behaviour of this system we would like to describe it in the terms we were using for simpler 1-D differential equations (find fixed points, draw the bifurcation diagram, etc.), but the number of dimensions make this hard. One possible approach is trying to reduce the dimensionality of the system while preserving its salient features. A possible approach for this simplification starts by noting that the four variables involved in the H&H model have two different time scales: Those variables are characterized by different time scales:

- V and m have fast time constants;
- h and n have slow time constants.

We can think about reducing the four-dimensional system to one 2D system with two variables that sums up the slow and fast dynamics of the system.

For example, if by looking back at equation 2.1 we know that the derivative of the sodium conductance in time is:

$$\tau_m(V) \frac{dm}{dt} = m^\infty(V) - m \tag{2.11}$$

Since we know that the time constant for the sodium $\tau_m(V)$ is always small compared to $\tau_n(V)$ and $\tau_h(V)$, we can assume m to be always at its equilibrium value $m^\infty(V)$:

$$m \approx m^\infty(V(t)) \tag{2.12}$$

A more complicated approach must be taken for the two slow variables. Since they both have a slower dynamics, we can assume that they are similarly always at equilibrium with a new dynamical variable $U(t)$ with the same dimensionality as $V(t)$ and a slower temporal evolution:

$$n(t) \approx n^\infty(U(t))$$
$$h(t) \approx h^\infty(U(t))$$

Now the problem is to find a function for relating U and V, which supposedly should take into account also all the numerical parameters that we include in the H&H model. To do this, we will use a simplified argument based on (Kepler&Abbott, 1992).

As a starting point, we can use the current balance equation (equation 2.9) to derive a function F that binds the dynamical variables of the original H&H system:

$$\frac{dV}{dt} = -\frac{\sum_x I_x}{C} \tag{2.13}$$

This equation lets us define the function F as:

$$\frac{dV}{dt} = -\frac{\sum_x I_x}{C} = F(V, m, n, h) \tag{2.14}$$

So far we have not introduced any simplification. Now, if our hypothesis is true though, we can assume it exist another function that approximates F[1]

$$F(V, m(V), n(V), h(V)) \approx f(V, \bar{m}(V), \bar{n}(U), \bar{h}(U)) \tag{2.15}$$

Now our aim is to prove that there exists an expression for dU/dt, under the above assumptions. Once we have it, we just need to plug it into the functions for $\bar{n}$ and $\bar{h}$ (fitted on experimental data) to describe entirely the model.

The general strategy is based on the fact that if the approximation holds true:

$$\frac{dF}{dt} = \frac{df}{dt} \tag{2.16}$$

We start by defining dF/dt using the multivariate chain rule:

$$\frac{dF}{dt} = \frac{\partial F}{\partial V}\frac{dV}{dt} + \frac{\partial F}{\partial m}\frac{dm}{dt} + \frac{\partial F}{\partial h}\frac{dh}{dt} + \frac{\partial F}{\partial n}\frac{dn}{dt} \tag{2.17}$$

Since V and m will reach their equilibrium value almost immediately compared to h, n and U, we can treat them as constants. In this way dV/dt and dm/dt are zero. So we are left with:

$$\frac{dF}{dt} = \frac{\partial F}{\partial h}\frac{dh}{dt} + \frac{\partial F}{\partial n}\frac{dn}{dt} \tag{2.18}$$

Note that here n and h are functions of the voltage V ($n(V)$ and $h(V)$). At this point, we need to know dh/dt and dn/dt. In the original H&H model, we have the two equations:

$$\tau_n(V)\frac{dn}{dt} = \bar{n}(V) - n \tag{2.19}$$

$$\tau_h(V)\frac{h}{dt} = \bar{h}(V) - h \tag{2.20}$$

$$\tag{2.21}$$

[1] $\bar{x}$ will be used instead of x^∞

Substituting here our simplifications $n \approx \bar{n}(U)$ and $h \approx \bar{h}(U)$, we find:

$$\tau_n(V)\frac{dn}{dt} = \bar{n}(V) - \bar{n}(U) \tag{2.22}$$

$$\tau_h(V)\frac{dh}{dt} = \bar{h}(V) - \bar{h}(U) \tag{2.23}$$

$$\tag{2.24}$$

Substituting everything in equation 2.18 we get:

$$\frac{dF}{dt} = \frac{\partial F}{\partial n}\left(\frac{\bar{n}(V) - \bar{n}(U)}{\tau_n(V)}\right) + \frac{\partial F}{\partial h}\left(\frac{\bar{h}(V) - \bar{h}(U)}{\tau_h(V)}\right) = A(V,U) \tag{2.25}$$

Where $\partial F/\partial h$ and $\partial F/\partial n$ are to be evaluated at $\bar{h}(U)$ and $\bar{n}(U)$.

To find the derivative for the approximated function f we can use the chain rule in a similar way to write:

$$\frac{df}{dt} = \frac{\partial f}{\partial V}\frac{dV}{dt} + \frac{\partial f}{\partial \bar{m}}\frac{d\bar{m}}{dt} + \frac{\partial f}{\partial \bar{h}}\frac{d\bar{h}}{dt} + \frac{\partial f}{\partial \bar{n}}\frac{d\bar{n}}{dt} \tag{2.26}$$

We can eliminate the V and m term as in equation 2.17. In this way,

$$\frac{df}{dt} = \frac{\partial f}{\partial \bar{h}}\frac{d\bar{h}}{dt} + \frac{\partial f}{\partial \bar{n}}\frac{d\bar{n}}{dt} \tag{2.27}$$

Because, by our above assumptions, h and n are functions of some variable $U(t)$, we can again apply the chain rule to get:

$$\frac{df}{dt} = \frac{\partial f}{\partial \bar{h}}\frac{d\bar{h}}{dU}\frac{dU}{dt} + \frac{\partial f}{\partial \bar{n}}\frac{d\bar{n}}{dU}\frac{dU}{dt} = \frac{dU}{dt}\left(\frac{\partial f}{\partial \bar{h}}\frac{d\bar{h}}{dU} + \frac{\partial f}{\partial \bar{n}}\frac{d\bar{n}}{dU}\right) = \frac{dU}{dt}B(V,U) \tag{2.28}$$

Thus:

$$\frac{dF}{dt} = \frac{df}{dt} \tag{2.29}$$

$$A(V,U) = B(V,U)\frac{dU}{dt} \tag{2.30}$$

And we arrive to our complicated expression for the U derivative:

$$\frac{dU}{dt} = \frac{A(V,U)}{B(V,U)} = g(V,U) \tag{2.31}$$

Where:

$$A(V,U) = \frac{\partial F}{\partial n}\left(\frac{\bar{n}(V) - \bar{n}(U)}{\tau_n(V)}\right) + \frac{\partial F}{\partial h}\left(\frac{\bar{h}(V) - \bar{h}(U)}{\tau_h(V)}\right) \tag{2.32}$$

$$B(V,U) = \frac{\partial f}{\partial \bar{h}}\frac{d\bar{h}}{dU} + \frac{\partial f}{\partial \bar{n}}\frac{d\bar{n}}{dU} \tag{2.33}$$

Therefore there exists and expression for dU/dt that is a function of V and U.

Our final system will then contain the expressions for the derivatives of V and U:

$$\frac{dV}{dt} = f(U,V)$$
$$\frac{dU}{dt} = g(U,V)$$

2.3.1 2D Dynamical Systems

We have to analyse now the two dimensional system described by the equation:

$$\frac{d}{dt}\begin{pmatrix} V(t) \\ U(t) \end{pmatrix} = \begin{pmatrix} f(V,U) \\ g(V,U) \end{pmatrix} = \boldsymbol{R}(V,U) \tag{2.34}$$

To think about this system we need to introduce the concept of phase space. The phase space for the system in equation 2.34 is the plane containing all the couple of values (U,V). The state of the system at the time t will be determined by the pair of values of the two dynamic variables $((U(t),V(t)))$. Consequently, we can think about the evolution in time of the system as a trajectory described in the phase space, containing every point $(U(t)V(t))$ touched by the system at the time t during its evolution, as depicted in fig. 2.8. In one-dimensional systems we have been studying the plot of the derivative as a function of the state of the system (for example in fig.1.3). Here, we have to extend to two dimensions that line of thinking.

Let's assume we know that the system at t_0 is at the initial point (V_0,U_0). For each of the two dynamic variables we want to know what will happen next. Will it increase? Will it decrease? To find out we need to know what is the value of the derivative of that dynamic variable at the time t_0. This is exactly what is expressed in equation 2.34: here the vector of the derivatives of the two dynamic variables is expressed as a function of the two dynamic variables themselves. This means that this equation associates a vector $(\frac{dV}{dt}, \frac{dU}{dt})$ (also called $\boldsymbol{R}(V,U)$) to every point (V,U) in the phase space; therefore, it describe a two dimensional vector field on the phase space. We can visualise a vector field as a collection of arrows with a given magnitude and direction, each attached to a point in the plane. Each state of the system (a point in the phase space) will be associated with an arrow, the vector $\boldsymbol{R}(V_0,U_0)$ from this vector field. This arrow is exactly what will describe for us the evolution of the trajectory of system at the next temporal step (fig.2.8). If the system at t_0 is at the point (V_0,U_0), in the next temporal step dt it will moves in the direction of the arrow $\boldsymbol{R}(V_0,U_0)$. This means that the trajectory of the system in the phase space is at each time t tangent to the vector field $\boldsymbol{R}$.

In our previous analysis the zero crossings of the function for the derivatives played a central role: they were telling us where the fix points of the system were. Those points were stable or unstable, depending on the slope of the function at the zero crossing. In our two-dimensional system the equivalent for

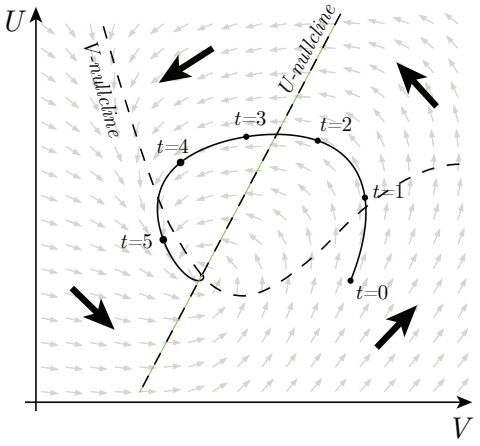

Figure 2.8: Phase plot for a dynamical system in the two variables U and V. The evolution of the system at various times $t = 0, 1, 2..$ is represented by the continuous line; dashed lines indicate the nullcines for the two variables. Note that the nullclines divide the space in subregions where the orientation of the arrows of the vector field is roughly the same.

these fix points are the points in the phase space at which the derivative (i.e., the vectors of the vector field) is zero along one or both dimensions.

To find them we just have to write:

$$\frac{d}{dt}\begin{pmatrix} V(t) \\ U(t) \end{pmatrix} = \begin{pmatrix} f(V,U) \\ g(V,U) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \tag{2.35}$$

The solutions of this equation are described by the two implicit equations:

$$g(V,U) = 0$$
$$f(V,U) = 0$$

Let's focus on the first equation. It tells us that for every point (V_i, U_i) for which $f(V_i, U_i) = 0$ the derivative with respect to the first dimension V will be 0 - this means that the vector field component along this dimension is 0, and in the following time step dt the system can move only along the dimension U. If the equation $f(V_i, U_i) = 0$ has an explicit form[2] , these points will be the values of some function $U = f_{V-null}(V)$ plotted on the phase space. We will call the line represented by this function as the *nullcline* of V: on this line, the derivative with respect to V will be 0, and every time we cross this line the sign of this derivative will change. This happens in the graph presented in fig.2.8. Here the V nullcline is a cubic curve on the phase space. Below it, all the arrows are pointing right; above it, they point left. When we are exactly on the nullcline

[2]This is not necessarily true. In this form, the equation in general describes a manifold, not a function. (To think about that, consider the circle of equation $x^2 + y^2 = 1$. It is not a function - for each value of x there are two possible values of y, and has no explicit form $y = f(x)$. It is a manifold. On the other side, $y - x = 0$ has an explicit form $y = x$, therefore it can describe a function)

the arrows will have no left-right component: the system can move only up or down, along the U dimension.

The nullclines for each dimension will not be fix points: the system (its trajectory in the phase space) will keep moving along the other dimension. A special case is represented by the crossing of the two nullclines: at these points the vector field will be 0 along each dimension. This means that these points will be the fix points of our system: once the trajectory reach one intersection of the nullclines, the vector field that drives it is 0 on that point and the system will remain there, at equilibrium.

Moreover, we can think of the nullclines as partitioning the phase space into several regions; in each region, the vectors of the vector field $\boldsymbol{R}$ will all point roughly in the same direction (north-east, south-west, etc.). We can easily imagine that if around the fix point the vector field arrows will be pointing toward it in every surrounding region, the fix point will be stable; perturbations around it will be always pushed back to the fix point. On the other hand, if vectors around the fix point are pointing outward, displacements from this point will be amplified and the system will move far from the equilibrium point: in this case the fix point will be unstable.

Supplementary note: in the two-dimensional case the fix point can behave in more interesting ways than just being stable or unstable. We can have a fix point that is stable for movements on one direction, but unstable for movements on the other; or we can have fixed points around which the system will periodically oscillate remaining always in the same orbit; finally, we can have points around which the trajectory of the system will "swirl", either inward toward the point (stable focus) or outward (unstable focus). To know exactly what kind of fix point our fix point will be, we have to linearise the system around the fix point and analyse the eigenvalues of the matrix that describe our new linear system. For a more detailed (but still intuitive) dissertation see (*Dynamical Systems in Neuroscience*, Eugene M. Izhikevich, 2007, Chapter 4).

2.3.2 Phase Plot for the Reduced H-H Model

The phase plot of fig. 2.9 is the system that describe our simplified two-dimensional system (we have not specified so far the two functions $g(V,U)$ and $f(V,U)$, so note that you have to trust Kepler&Abbott about the fact that those nullclines actually correspond to $g(V,U) = 0$ and $f(V,U) = 0$). But we will not bother with finding a form for them, and we will start our analysis taking for granted this shape of the vector field and the nullclines. As we were mentioning, the four regions divided by the V and U nullclines correspond to different orientations of the vector field. in the figure there are also some examples for trajectories starting at different points: we can clearly see that the trajectory swirls inward around the fix point: this means that the point is a stable focus. No matter how far we will move the system from its fix point, it will always come back to that state.

Now, we want to see what happens to our system when we inject a current, as we were doing in the one-dimensional case. Firstly, note that injecting a

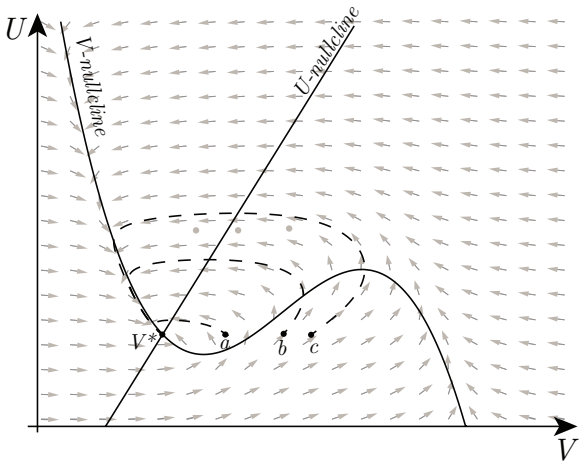

Figure 2.9: Phase plot for the symplified H&H model, built from the two equations for $g(U, V)$ and $f(U, V)$, with no current injection. The trajectory of the system starting from three different points a,b and c is represented by the dash lines. Note that in every case it converges to the resting value V_*, the intercept of the two nullclines.

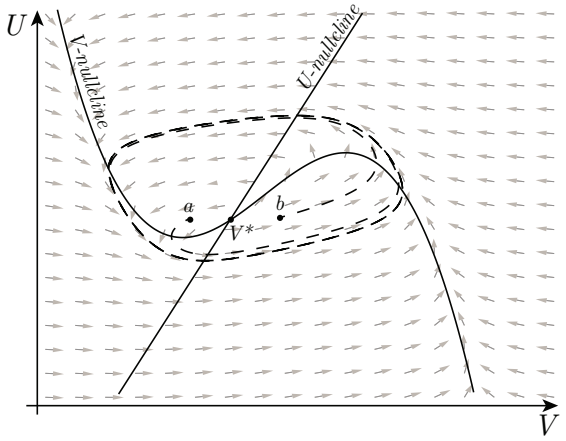

Figure 2.10: Phase plot for the symplified H&H model, built from the two equations for $g(U, V)$ and $f(U, V)$, with current injection. The trajectory of the system starting from the two points a,b is represented by the dash lines. In both cases the system move far from the fix point and get attracted by the limit orbit.

current will change only one of the two nullclines: remember that the expression for $g(V,U)$ came out of a time derivative, which eliminates an eventual I_{ext} constant in time[3]. Therefore, an increasing current will simply move the V nullcline upward. The phase plot for the system with the current injection is represented in fig. 2.10 As we can see from the trajectories starting from the two points a and b, now even small deflections from the fixed point V^* will make the system move far from it. It will not move indefinitely far: as we can see in the figure there is a cyclic attractor, a circular orbit where the system will get caught. As long as the current is injected in the neuron, it will remain in this cyclic orbit - i.e., it will be firing. How can we see this from the graph?

By looking at the trajectory in fig. 2.10 we can know what part of the action potential is described by each part of it: the sharp transition leftwards (an increase in the voltage variable V) is the upward stroke, and the transition rightwards is the repolarisation. Note that the slowest transition is the one on the left of the V-nullcline. Here the system stays for a long time close to a nullcline: here the amplitude of the vectors of the vector field are low, and this translates into a slow time evolution of the system. This corresponds to the time during which the neuron is back to the resting potential, and it is depolarizing again until reaching threshold. Therefore, the time spent on this part of the trajectory will determine the firing frequency of the neuron.

If we imagine of gradually increasing the current, we can expect to have a certain threshold current I upon which there is a transition: for $I < I_{thr}$ the trajectory swirls inward; for $I > I_{thr}$ the trajectory swirls outward to the cyclic attractor. This means that at this critical point at which we encounter a bifurcation, similarly to what we where seeing in the one-dimensional case. At this value, the fix point changes from a stable focus to an unstable focus[4]; this transition is called a *Hopf bifurcation.*

Supplementary note: looking at the graph one may have the intuition that the transition depends on the slope of the V-nullcline at the intercept with the U-nullcline, that from negative become positive. This is true only if the case when the U-nullcline is perfectly vertical; for every other situation it is not necessarily true - the only way to know is to compute the eigenvalues of the system linearised around the fix point. Anyway, when $U \ll V$, that is usually the case for this system, this become negligible, and the transition happens almost at the local minimum of the V-nullcline.

2.4 Type I and Type II neurons

We have seen that depending on the level of the current injection, the intersection of the two nullclines will move and this will determine a transition from a stable fix point to a unstable fix point with a limit cyclic attractor. This

[3] Put in another way, we assume that and injected current will change the voltage so quickly compared to changes in U, that we can treat is as a constant when trying to find an expression g(V,U) = dV/dt.

[4] The system is not completely divergent, it enters a stable limit cycle.

corresponds to what we were seeing in the one-dimensional case, and it is again an Hopf bifurcation.

Note: To be precise, the transition can be also subcritical, i.e. there are certain currents that produce both a stable fix point and a limit attractor, and the system will converge to one of the two depending on the initial condition. In this case in the phase space we can distinguish with a separatrix the region where the system will be attracted by the fix point from the region where the system will be attracted by the cyclic orbit. This is again negligible when $U \ll V$.

What we now want to see is how this is linked to the experimental observation of neuronal firing in response to currents. This is done by computing the so called F/I curve, where the firing rate is plotted as a function of increasing currents injected experimentally in the cell. The F/I response is a classic electrophysiological parameter, and it has been characterized for a big number of cells. In general, there are two big families of neurons grouped by the shape of their F/I curve:

- Type I neurons
- Type II neurons

2.4.1 Type II Neurons

Type II neurons are characterized by a discontinuity in their F/I curve, that is actually what we get from an Hopf bifurcation (fig. 2.11). Increasing the current in the beginning will trigger no action potentials, but crossed a certain threshold the firing rate will jump to some discrete value. This is typical of pyramidal cells, fast sensory neurons in the brainstem, coincidence detectors and rhythm generators.

2.4.2 Type I Neurons

Type I neurons, on the other side, do not show such a discontinuity in the curve: the firing frequency at the transition point is infinitely low and it increase assuming every arbitrarily low value of firing frequency (fig. 2.11). The neurons belonging to this category are typically interneurons and neurons that act as signal integrators. They are cells with low input resistance. The property of having arbitrary low firing rates seems to be in conflict with the concept of Hopf bifurcation we had. How should the derivatives vector field and the nullclines be shaped in order for the neurons to have this property?

First of all, since the function for the V term derive from the current balance equation, it is reasonably the same also for this kind of neurons. The nullcline that is affected the most by the composition in channels is the U-nullcline. For having arbitrarily low firing rates we need a broad region of the phase space where the length of the derivative vectors - i.e. the rate of change of the system - is low. Since the length of this vector along the two axes is 0 along the nullclines, we can expect it to be low near the nullclines. Since we need to be

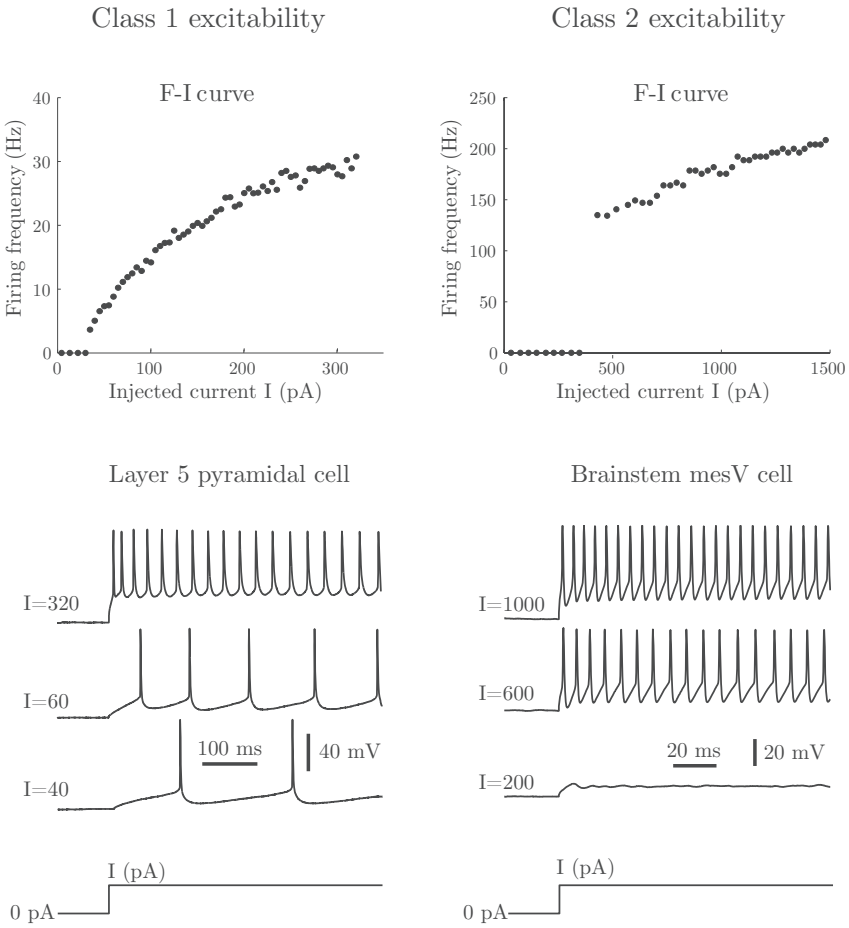

Figure 2.11: F-I curves for neurons of type (class) I and II. Below, example traces from which the data points where calculated. Increasing currents in type I neurons produce arbitrarily slow firing frequencies. On the opposite, In type II neurons there is a discontinuity at a critical current I_{thr}

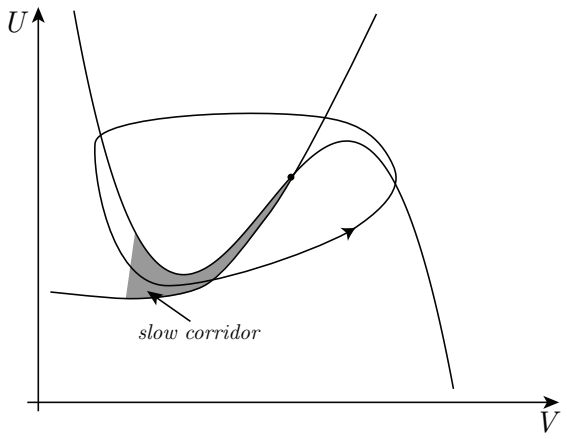

Figure 2.12: Phase space for neurons of the first type. They spend most of the time in the part of the trajectory depicted in gray, the slow corridor near the nullclines. Here we are close to both the nullcline, and so the vector field is small in both the dimention, and the system is moving slowly.

close to both nullclines, we can expect that the shape of this new U-nullcline follows in at least part of the phase space the V-nullcline.

This is actually what happens in the Type II neurons phase space. In the part of the space when the two nullclines run close to each other we have a "slow corridor" where the system is moving extremely slow. Note also that the system is progressing in this region between one spike and the other: this means that the dynamic of the action potential itself is very similar for the two types, and what changes the most is just the evolution of the potential between spikes.

This bending in the shape of the U nullcline will change the behaviour of the system when the current is 0: we will have now three different fix points instead of one. As we increase the current, two of them will collapse in one single point and then vanish, similarly to what was happening for the quadratic integrate-and-fire model. This is the so called saddle-node bifurcation. Even when the two fixed point have vanished, their "ghosts" represents regions where the system is evolving extremely slowly, in the slow corridor.

What does this difference means in terms of the behaviour of the neurons? To understand that, we need to introduce the concept of phase response curves.

2.4.3 Phase Response Curves (PRCs)

Let's assume that when injected with some current I a neuron fire with some period $T(I)$ between spikes. Now we can think of "perturbing" (changing slightly the value of the voltage, e.g. with an EPSP) the evolution of the membrane potential and see how this deviation from the periodic orbit affect the time of the following spike. The effect of the perturbation will depend both on its amplitude and its time during the cycle between two spikes. What we want to analyse is then $T_I(t^*, \epsilon)$, where t^* is the time of the perturbation and ϵ its

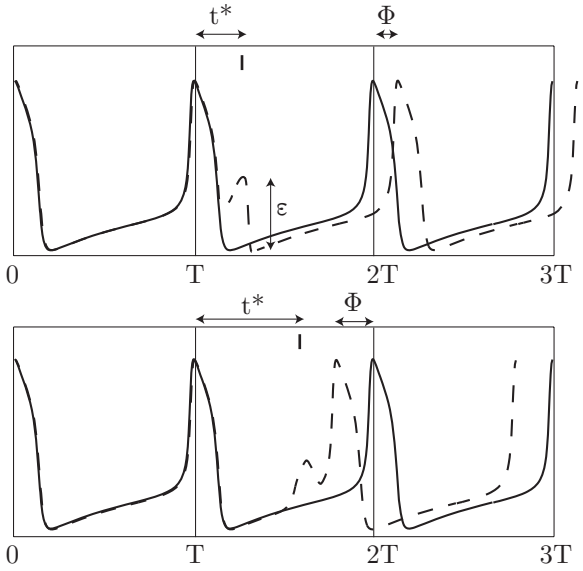

Figure 2.13: Perturbation of a neuron firing periodic action potentials. We can imagine the perturbation as an EPSP of amplitude ϵ that falls at a time t^* from the beginning of the cycle (set to the action potential in the graph). Depending on the exact time t^*, the system can prolong the period, thereby shifting negatively the phase of the following oscillations (*top*), of shorten it, shifting the phase positively (*bottom*).

amplitude. If we assume that the perturbation is very small, we can linearly approximate it near $\epsilon = 0$:

$$T_I(t^*, \epsilon) = T(I) + \epsilon \left. \frac{dT(t^*, \epsilon)}{d\epsilon} \right|_{\epsilon=0} \tag{2.36}$$

$$= T(I)(1 - \epsilon\phi(t^*)) \tag{2.37}$$

Where the term $\phi(t^*)$ is simply the calculated derivative from the first equation. This term is called the *phase response curve* (PRC): its sign will tell us if the period is made longer compared from the initial value $T(I)$ or shorter. Note that once we have done the linear approximation it has became a function of the sole term t^*.

If we imagine the spiking of the neuron as a cyclic oscillation, we can think of an elongation or shortening of the period as movement in one direction or the other of the phase of the oscillation. A longer period will correspond to a backward shift in the phase:

$$\phi < 0$$
$$T(t^*, \epsilon) > T(I)$$

So far we have not related this analysis in any way to our model; what would happen if we do this kind of PRC analysis for neurons of the two types?

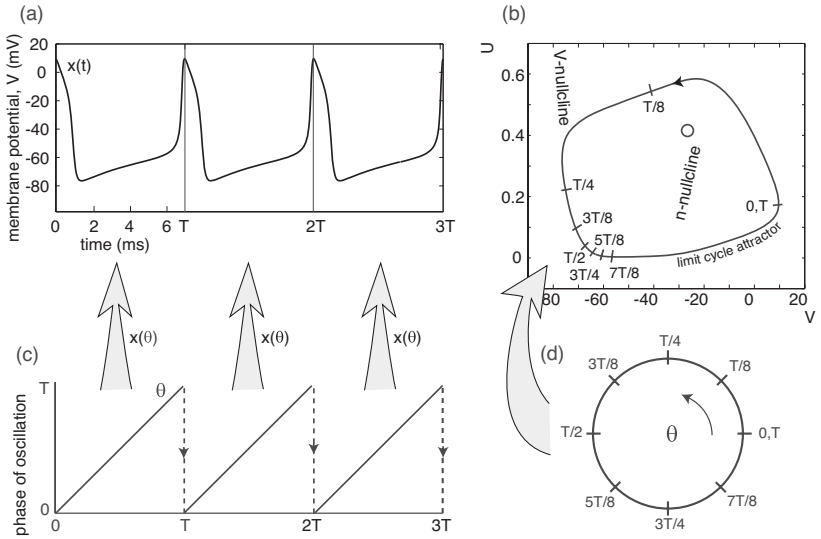

Figure 2.14: The figure shows how the cyclic spiking of a neuron can be though in terms of an oscillation with its phase. On the right, the mapping of different points of the oscillation of period T that goes from the end of an action potential to the begin of the new one, mapped onto the cyclic trajectory of the system in the phase space.

2.4.4 PRC for Type I Neurons

To have an intuition about the effects of a perturbation we need to consider the phase space and how move the system in a certain direction for the perturbation will affect its trajectory. If we apply a positive perturbation in the voltage, we will shift the system toward the right in our phase space; this means that it will accelerate it when it is moving rightward (anticipation of the phase, $\phi > 0$), and slow it down when it is moving rightward (delay of the phase, $\phi < 0$). Moreover, remember that the time of the perturbation during the cycle of one oscillation is indicated by the value t^*. A type II neuron spends a significant amount of time in the slow corridor region, where the perturbation anticipate the phase; this means that for most values t^* the shift will be positive, and only for a short initial time it will be negative.

2.4.5 PRC for Type II Neurons

Type II neurons on the other side spend most of their period in the region on the left of the V nullcline. in this region rightward deflections of the trajectory will move the system far from its orbit. This means that it will need some time to go back to the cyclic attractor before continuing in the oscillation, i.e. there will be an elongation of the period or backward shift of the phase ($\phi(t^*) < 0$). At certain point of the orbit t^* the perturbation will shift again the system in the direction of its trajectory, thereby producing a progression of the phase ($\phi(t^*) < 0$). Still, the part of the curve below zero will be much longer for a

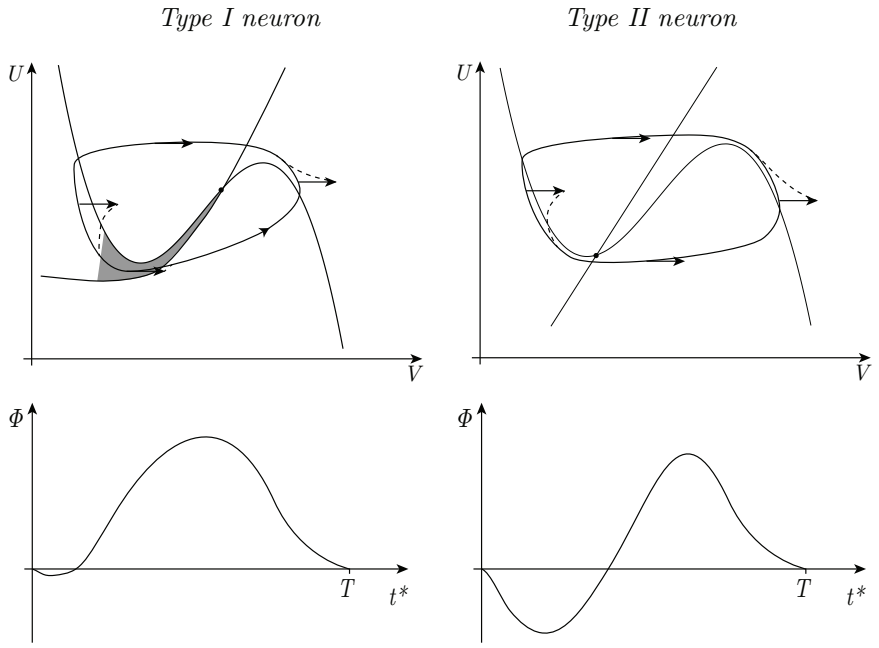

Figure 2.15: (*above*) A schematic of how the perturbation can affect the system in different points of the cyclic trajectory. (*below*) The effects on the phase as reported in the phase response curve. Note that in the case of Type I neurons there is a broad range of values that produce always positive shifts, due to the time that the system spends in the the slow corridor where the perturturbation accelerates the system. On the other side, type II neurons spend a lot of time in the region on the left of the V nullcline, where the perturbation moves the system far from its attractor and makes the period longer.

Type II neuron compared to a Type I one.

2.5 Dynamics of Type I II Networks

. What happens if we try to link together more neurons of the same type with inhibitory or excitatory synapses? We can observe the effects they have onto each other by postulating a steady-state condition for the starting firing frequency of the two neurons and pretending that synaptic EPSPs act as perturbations of the oscillation. In this way, we can simply look at the graph for ϕ in order to understand what will happen to the network.

Excitatory Coupled Type I Neurons

The situation for this first kind of simple network is schematised in fig. 2.16. We assume that the two neurons are firing with some steady state frequency spikes that are represented by the continuous lines in the figure. Each spike acts as a perturbation on the other neuron, with positive sign since the synapses are excitatory.

The first spike produced by the neuron 1 (1.1) will fall immediately before the spike of the second neuron; by looking at this point in the phase response curve we can see that it should produce a delay (point a), therefore the true spike of neuron 2 (dashed line, 2.1) will be delayed. In turn this will fall at the beginning of the oscillation of neuron 1, producing a very small anticipation. This will move backward the spike 1.2, that in turns will delayed even more the phase of spike 2.2. The two processes keep balancing in opposite directions, and they will never end up synchronized. Moreover, the final frequency will be lower than the initial one.

Excitatory Coupled Type II Neurons

In the case of excitatory coupled neurons of type II things changed given the difference in the PRC. The spikes are driven in opposite directions in the two neurons. One will gradually anticipate, while the other will be more and more delayed, and they will eventually end up synchronized.

Inhibitory Coupled Type I Neurons

In the case of inhibitory coupled neurons, the PRC is flipped upside down for the change of sign of the perturbation. In this case, spikes of neuron 2 will become gradually less delayed over time, and it will eventually be reached by the progressive delay of spikes of neuron 1. In the end they will be synchronized, and the final frequency will be smaller than the initial one. This is the mechanism that is hypothesized be the base for gamma oscillations (the so called ING model for gamma oscillations).

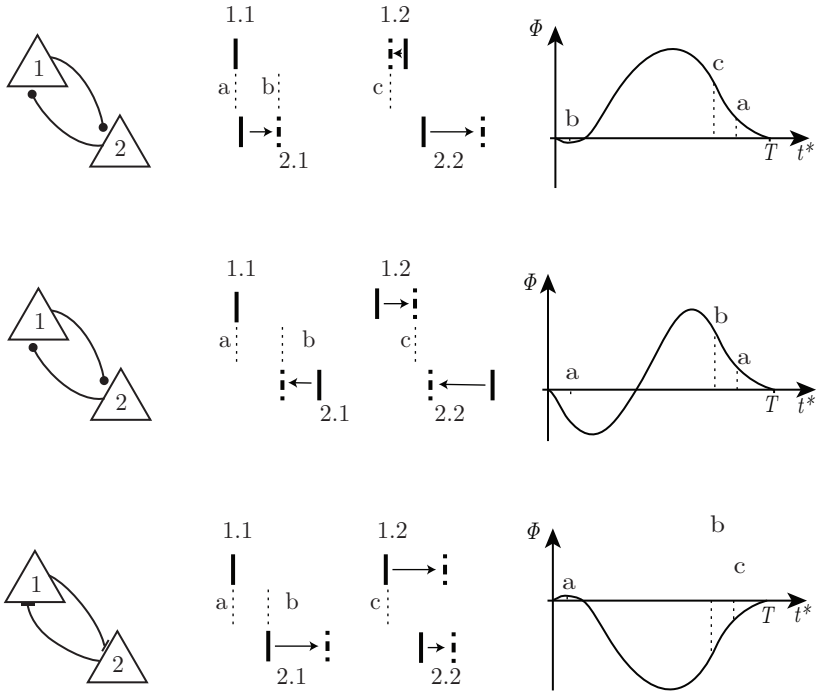
1
2
1.1
a
b
2.1
1.2
c
2.2
Φ
b
c
a
T
t*
1
2
1.1
a
b
2.1
1.2
c
2.2
Φ
a
b
a
T
t*
1
2
1.1
a
b
2.1
1.2
c
2.2
Φ
b
a
c
T
t*

Figure 2.16

Chapter 3

Cable Theory

3.1 Derivation of the Cable Equation

So far we have been working with point neurons. We now address the following question: what happens when we give spatial dimensions to our neuron?

We can begin with approximating a dendrite to a cable of infinite length, with diameter d. The capacitance per unit of length will therefore be:

$$c_m = \pi d C_m$$

Where C_m is the specific capacitance (F/m^2) and c_m, the linear specific capacitance will be F/m. Similarly, if the specific membrane resistance is R_m in $\Omega \cdot m^2$, the linear membrane resistance will be:

$$r_m = \frac{R_m}{\pi d}$$

With units $\Omega \cdot m$. The greater the circumference of the dendrite, the greater the area for charge to escape through its membrane, and therefore the lower the membrane resistance; and the more membrane available to store charge, therefore the higher the capacitance. Finally, we know that ions can flow through the intracellular space. The resistance of a cable is proportional to its length divided by the area, therefore the resistance per unit of length is:

$$r_i = \frac{R_i}{d^2/4\pi}$$

And it will have the dimension of a resistance per unit of length (Ω/m - therefore R_i is in $\Omega \cdot m$).

We can imagine that each point of the dendrite over time can have a different voltage; *i.e.*, voltage is a function of both space and time, $V(x,t)$. For each point x we can have two different kind of currents: one current $I_m(x)$ across the cell membrane, and one current $I_i(x)$ flowing inside the dendrite according to differences in voltage of different sections of the dendrite. At a certain time t,

$I_i(x)$ will be given for each segment dx by the infinitesimal difference in voltage dV:

$$I_i(x) = \frac{1}{r_i}\frac{dV}{dx} \tag{3.1}$$

Where r_i is the intracellular resistance of the cable.

To calculate $I_m(x)$, the fundamental intuition is that for the Kirchhoff current law, the sum of all the currents that enter an infinitesimal segment dx must be 0. The currents that enter one segment are $I_i(x)$, $-I_i(x+dx)$ and $I_m(x)dx$ (this last term is multiplied by dx because $I_m(x)$ is flowing for each unit of length). Therefore:

$$I_i(x) - I_i(x+dx) + I_m(x)dx = 0 \tag{3.2}$$

Or:

$$I_m(x) = \frac{I_i(x+dx) - I_i(x)}{dx}$$

That is exactly the definition of the derivative $dI_i(x)/dx$. Using equation 3.1:

$$I_m(x) = \frac{dI_i(x)}{dx} = \frac{d}{dx}\left(\frac{1}{r_i}\frac{dV}{dx}\right) = \frac{1}{r_i}\frac{d^2V}{dx^2} \tag{3.3}$$

But we also know that (assuming $E_r = 0$?) the current through a passive membrane is equal to:

$$I_m(x) = \frac{1}{r_m}V(x) + c_m\frac{\partial V}{\partial t} \tag{3.4}$$

Equating 3.1 with 3.3 we get:

$$\frac{1}{r_i}\frac{d^2V}{dx^2} = \frac{1}{r_m}V(x) + c_m\frac{\partial V}{\partial t} \tag{3.5}$$

And rearranging the terms:

$$\frac{r_m}{r_i}\frac{d^2V}{dx^2} = V(x) + \tau_m\frac{\partial V}{\partial t} \tag{3.6}$$

Where $\tau_m = r_m c_m$ is the time constant of the membrane. This is a partial differential equation that gives us the evolution of the voltage $V(x,t)$ in space and time.

3.2 Steady-state Solution for the Cable Equation

We can study our system in the simple steady-state situation, where the system has reached equilibrium and is stable over time ($\partial V/\partial t = 0$). In this case 3.6 reduces to:

$$\frac{r_m}{r_i}\frac{d^2V}{dx^2} = V(x) \tag{3.7}$$

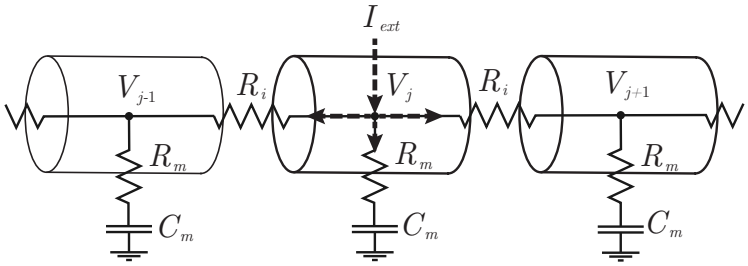

Figure 3.1: Compartmental modelling.

This is a simple second order linear differential equation. It is trivial to verify that the solution is:

$$V(x) = V(0)e^{-\frac{x}{\lambda}} \tag{3.8}$$

Where

$$\lambda = \sqrt{\frac{r_m}{r_i}}$$

This solution tells us that if at a point $x = 0$ the cell voltage is V_0, this potential will propagate to adjacent compartments decaying exponentially with a space constant λ. The bigger λ, the better the propagation of the potential. Using the definition we had for r_i and r_m λ can be written as:

$$\lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{R_m d^2\pi}{R_i 4d\pi}} = \sqrt{\frac{4}{d}\frac{R_m}{R_i}} \tag{3.9}$$

Where, remembering that $[R_m] = \Omega \cdot m^2$ and $[R_i] = \omega \cdot m$:

$$[\lambda] = \sqrt{m \cdot \frac{\Omega \cdot m^2}{\Omega \cdot m}} = m$$

Therefore, λ has the unit of a length (m or cm, depending on the definition of R_i and R_m). This means that the bigger the constant λ, the longer the potential propagate in the steady state. As we can imagine, a large R_m means that the current leakage across the membrane will be low and the potential will propagate better; on the other side, increasing the intracellular resistance will decrease the intracellular flow of current compared to the current leakage across the membrane, and will make the propagation of the potential worse.

3.3 Compartmental Model for Dendrites

The equation we have derived in the previous paragraph applies only to the very simplified case of a linear dendrite of infinite length and homogeneous biophysical properties. For dealing with more realistic models of dendrites, with the possibility to introduce dendrite branching points and variate conductances and other features in different part of the cell, we can introduce the tool of compartmental modelling.

Compartmental modelling build on the idea that we can chunk the dendrite in a discrete number of segments that can be treated as point (fig. 3.1). Each punctiform segment will be connected to its neighbours, and from each segment the current can flow either in the adjacent compartments or outside the cell. Therefore, remembering that the current flow into neighbours compartments is driven by differences in voltage, for every compartment j we can write the current-balance equation as

$$I_j^{ext} = (V_j - E_L)g_L + (V_j - V_{j-1})g_i + (V_j - V_{j+1})g_i \tag{3.10}$$

Rearranging the terms we get:

$$(g_L + 2g_i)V_j - g_i V_{j-1} - g_i V_{j+1} = I_j^{ext} + E_L g_L \tag{3.11}$$

This is valid for every compartment except for the first one, $j = 1$, which will have no V_{j-1} term:

$$(g_L + g_i)V_1 - g_i V_2 = I_1^{ext} + E_L g_L \tag{3.12}$$

And the last one, $j = N$, which will have no V_{j+1} term:

$$(g_L + g_i)V_N - g_i V_{N-1} = I_N^{ext} + E_L g_L \tag{3.13}$$

3.3.1 Analogies with the Analytical Solution

Now, we can see that using linear algebra there is a much shorter way to write together the equations for all compartments at once. We can define the vector with the voltages for every segment j:

$$\boldsymbol{v} = (V_1, V_2, ..., V_{N-1}, V_N) \tag{3.14}$$

Then, by looking at the terms that multiply the voltages in equation 3.13, we can think of introducing a matrix designed in this way:

$$\boldsymbol{M}_{N,N} = \begin{pmatrix} g_i + g_m & -g_i & 0 & 0 & \cdots & 0 & 0 \\ -g_i & 2g_i + g_m & -g_i & 0 & \cdots & 0 & 0 \\ 0 & -g_i & 2g_i + g_m & -g_i & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 2g_i + g_m & -g_i \\ 0 & 0 & 0 & 0 & \cdots & -g_i & g_i + g_m \end{pmatrix}$$

We can now see that the right term of equation 3.13 can be written as the product $\boldsymbol{Mv}$. Finally, we introduce two other vectors for the injection and the leakage currents $\boldsymbol{i}_{ext}$ and $\boldsymbol{i}_L$, such as:

$$\boldsymbol{i}_{ext} = (I_1^{ext}, I_2^{ext}, ..., I_{N-1}^{ext}, I_N^{ext})$$
$$\boldsymbol{i}_L = (I_1^L, I_2^L, ..., I_{N-1}^L, I_N^L)$$

Now equation 3.13 can be entirely restated in a vectorial form as:

$$\boldsymbol{Mv} = \boldsymbol{i}_{ext} + \boldsymbol{i}_L \tag{3.15}$$

Now, note that the matrix $\boldsymbol{M}$ can be also rewritten separating the g_m from the g_i terms in this way:

$$\boldsymbol{M}_{N,N} = -g_i \begin{pmatrix} -1 & 1 & 0 & 0 & \cdots & 0 & 0 \\ 1 & -2 & 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & -2 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & -2 & 1 \\ 0 & 0 & 0 & 0 & \cdots & 1 & -1 \end{pmatrix} + g_m \boldsymbol{I}$$

Where $\boldsymbol{I}$ is the identity matrix,

$$\boldsymbol{I} = \begin{pmatrix} 1 & 0 & 0 & \cdots \\ 0 & 1 & 0 & \cdots \\ 0 & 0 & 1 & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

The interesting thing about this expression is that, in the case of external current $I_j^{ext} = 0$ for all compartments, if we rescale the potential to maje $E_L = 0$, once we plug it back into 3.15 we get:

$$\boldsymbol{M}_{N,N} = -g_i \begin{pmatrix} -1 & 1 & 0 & 0 & \cdots \\ 1 & -2 & 1 & 0 & \cdots \\ 0 & 1 & -2 & 1 & \cdots \\ 0 & 0 & 1 & -2 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix} \boldsymbol{v} + g_m \boldsymbol{I}\boldsymbol{v} = 0$$

Now, the general form of this equation is strikingly similar to the steady state analytical solution (equation 3.7), when we had:

$$-g_i \frac{\partial^2 V}{\partial t^2} + g_m V = 0 \tag{3.16}$$

In this case the matrix with -2 on the diagonal 1 nearby takes the place of the second derivative. We can imagine then that apply a matrix of this form to a vector $\boldsymbol{v}$ is the discrete analogue of calculating its second derivative.

3.3.2 Implementing Temporal Dynamics

So far we have excluded capacitances from our model, and, with them, any interesting evolution of the system in time. If we want to reintroduce them , it is quite easy: we just have to add the capacitative current to our current balance equation:

$$(g_L + 2g_i)V_j + C_m \frac{\partial V_j}{\partial t} - g_i V_{j-1} - g_i V_{j+1} = I_j^{ext} + E_L g_L \tag{3.17}$$

Using discrete time steps Δt

$$C_m \frac{\partial V_j}{\partial t} \approx C_m \frac{V(t) - V(t-1)}{\Delta t}$$

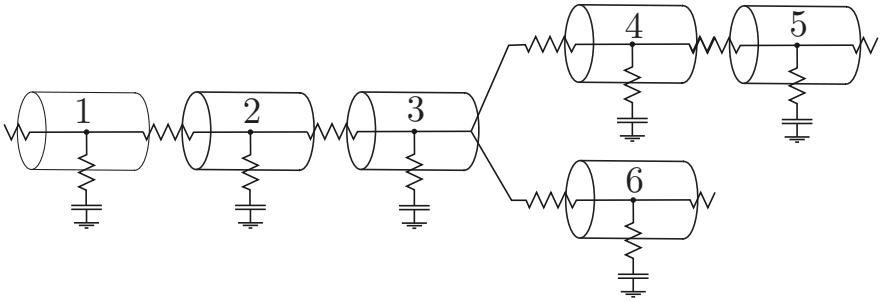

Figure 3.2: Branching compartments.

We can then rearrange the current balance equation to:

$$(g_L + 2g_i + \frac{C_m}{\Delta t})V_j - g_i V_{j-1} - g_i V_{j+1} = I_j^{ext} + E_L g_L + \frac{C_m}{\Delta t} V_j(t-1) \quad (3.18)$$

And this can be again translated in the matrix form, with the addition of $C_m/\Delta t$ on the diagonal terms and the new vector of values at the previous time step $\boldsymbol{v}(t-1) = (V_1(t-1), V_2(t-1), ..., V_N(t-1))$

3.3.3 Branching Compartments

The power of the matrix form for the compartment model become clearly evident when we analyse the case of branching compartments. In this case, the first step is to find a convenient way to numerate the compartments. Once we have done that, describe new connections between non-consecutive compartments can be accomplished simply by adding new $-g_i$ terms in the respective positions in the equivalent matrix. We will now write the connection matrix for the branching scheme reported in fig. 3.2. Here the compartment n.3 is connected on one side to compartment n.2 and on the other on compartment n.4 and 6. To implement this configuration in our matrix, we will just have three off-diagonal terms $-g_i$ in the 4th row and column (in the positions 3, 4 and 6). Note that we also have to increase by one the $2g_i$ term on the diagonal: the sum of each column and row must remain 0. For our example then the connection matrix will be:

$$\boldsymbol{M}_{N,N} = -g_i \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 1 & -2 & 1 & 0 & 0 & 0 \\ 0 & 1 & -3 & 1 & 0 & 1 \\ 0 & 0 & 1 & -2 & 1 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 0 & 0 & -1 \end{pmatrix} \boldsymbol{v} + g_m \boldsymbol{I}\boldsymbol{v} = 0$$

The connection matrix reproduces in a synthetic way the connectivity of the compartments. No matter how complicate the wiring diagram, this approach will always gives us a convenient way to deal with the evolution of voltages in every compartment of the model.

3.3.4 Active Compartments

Another crucial tool for compartmental modelling is the possibility to make some compartments active. Implementing this numerically in our model is quite easy. We can just assume that the conductances of one specific compartment are affected only by the voltage at that compartment. Therefore, we will just have to introduce some new vectors $\boldsymbol{m}(t)$, $\boldsymbol{h}(t)$ and $\boldsymbol{n}(t)$ that will give us the state of gating variables at each compartment of the cell. We can implement this numerically simply by setting the starting values for the voltage ($\boldsymbol{v}_0$) and for the gating variables ($\boldsymbol{m}_0$, $\boldsymbol{h}_0$ and $\boldsymbol{n}_0$) and then on a step by step basis use their value at the time $t-1$ to predict their current value at time t. In this way we can analyse a wide spectrum of cases where we can make one, a few, or all compartments active to study the propagation of the action potential.

3.4 Another View on the Cable Equation

We have seen that the cable equation that describes the propagation of a potential in space and time throughout a cylindrical dendrite of infinite length has this form:

$$\tau \frac{\partial}{\partial t} V(x,t) = V(x,t) + \lambda^2 \frac{\partial^2}{\partial x^2} V(x,t) \tag{3.19}$$

As we have said, this is a partial differential equation, and it contains a leak term $-V(x,t)$, which describe the flow of ions across the membrane, and a diffusion term $\partial_{xx} V(x,t)$, which tells us how diffusion is happening inside the cable under a certain configuration of the potential. We can look at it as the function describing the diffusion of ion charges along the cable. Why diffusion should goes with the second derivative of the voltage? If we imagine to have a voltage that grows linearly throughout the cable, for every point x_0 there will be the same number of particles moving toward it on one side and far from it on the other, because the difference of potential will be the same between $x_0 + dx$ and $x_0 - dx$ for a straight line. In this case we will have only an exponential decay of the potential through the membrane, happening at the same pace at all points of the line, and at any time t the potential at every point of the cable $V_t(x)$ will still be linear.

If we want to have some significant effect of diffusion on the concentration of charges at one point $x_0 + dx$ and $x_0 - dx$ must be different. This happens have some bending of the curve, which in mathematical terms translates into a non-zero second derivative.

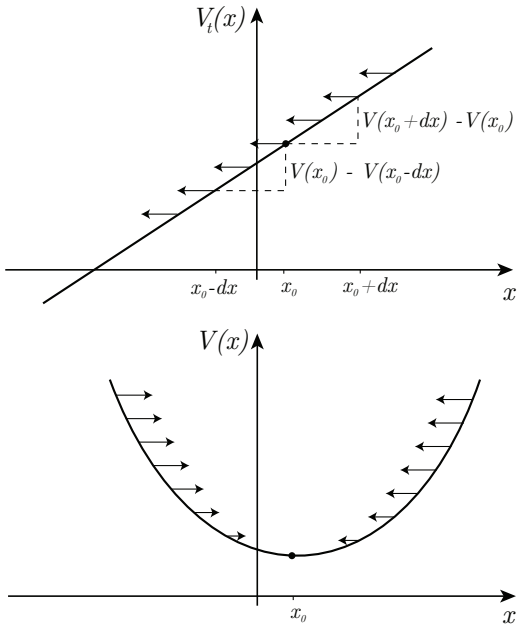

Figure 3.3: Effects of distribution of intracellular potential along the linead dendrite and diffusion of charges. Here $V_t(x)$ is the potential at a certain time t as a function of x. (*above*) linear case: the second spatial derivative $\partial_{xx}V_t(x) = 0$: the number of particles that flow into the point x_0 on one side is balanced by the number of charges leaving it on the other, and the net diffusion is 0. (*below*): nonlinear case; here $\partial_{xx}V_t(x) > 0$, and we will have a net influx of charges at the point x_0.

Chapter 4

Modelling Synapses

4.1 Synaptic Currents

We can describe a generic synaptic current as:

$$I_{syn} = g_{syn}(V - E_{syn}) \tag{4.1}$$

Where each neurotransmitter will have its own conductance and resting potential. For example, the resting potential for a typical glutamatergic synapse E_{glut} will be around 0. Since it is permeable to several ions (sodium, potassium, calcium), this voltage is some weighted average of the resting potentials for these ions. For GABAergic synapses, permeable to chloride and carbonate, $E_{GABA} \approx -90$.

The conductance is the term that confer to the synaptic current its temporal evolution. It is a term that somehow sums up all the processes that are at work between the action potential of the presynaptic neuron and the synaptic potential of the postsynaptic neuron. These processes are arbitrarily complicated (voltage-gated presynaptic calcium conductances, exocytosis, diffusion, binding of the neurotransmitter, post-synaptic channels opening) amd they involve huge number of parameters (calcium channel kinetics, exocytosis dynamics, diffusion constants, kinetic of post-synaptic channels opening, etc.). Still, since we can experimentally observe the typical shape of the post-synaptic potential for a given neurotransmitter and a given neuron, we can fit a curve with a shape that describe it. A typical equation can be a difference of exponentials:

$$g(t) = \omega(e^{-\frac{t}{\tau_1}} - e^{-\frac{t}{\tau_2}}) \tag{4.2}$$

A very simple way to deal with synaptic inputs in a neuron is to keep fixed the shape of this curve for each synapse of a given neurotransmitter, and change only the parameter ω, that describes the synaptic strength, or the amplitude of the curve.

4.2 Dynamical Synaptic Transmission

Here we want to find some mathematical description of the processes that undergo synaptic transmission. A synaptic terminal is described mainly by three parameters:

- Number of vesicles, R;
- Probability of release after action potential, p;
- Post-synaptic response amplitude for one vesicle, q.

With this parametrization, the final amplitude of the post-synaptic response will be

$$A = Rpq \tag{4.3}$$

And in the literature, this model is called the RPQ model for synaptic transmission.

4.2.1 Synapse Dynamics: Synaptic Depression

The first thing that we will characterize about the synapse is the dynamics of the pool of vesicles, of size R. We can do it starting from these assumptions:

- The resting state dimension of the pool is R_0;
- The dynamics of the pool follows a first order kinetics;
- Each action potential trigger the release of a constant fraction of the available pool, thereby decreasing the number of available vesicles by uR (u can be roughly considered a probability of release - even though it is not exactly that, for reasons that I do not recall).

Under these assumption, the equation that will describe the change of vesicles over time (postulating a continuous number of vesicles):

$$\frac{dR}{dt} = \frac{R_0 - R}{\tau_V} - \delta(t - t_{sp})uR \tag{4.4}$$

Where the first term drive an exponential recovery of the storage after every depletion, while the second term at any time t_{sp} when a spike happens subtracts the amount uR to the existent pool.

The evolution of the system is represented in fig. 4.1. Here, $R(t^+_{sp_1})$ represents the value of the store immediately after the first spike. We do not consider anything before this point; instead, we look at the values $R(t^-_{sp_2})$ (vesicles immediately before the second spike) and $R(t^+_{sp_2})$ (immediately after).

$R(t^-_{sp_2})$ and $R(t^+_{sp_2})$ will differ only for the amount of vesicles depleted by the second action potential, which are $uR(t^+_{sp_2})$:

$$R(t^+_{sp_2}) = R(t^-_{sp_2}) - uR(t^-_{sp_2}) \tag{4.5}$$

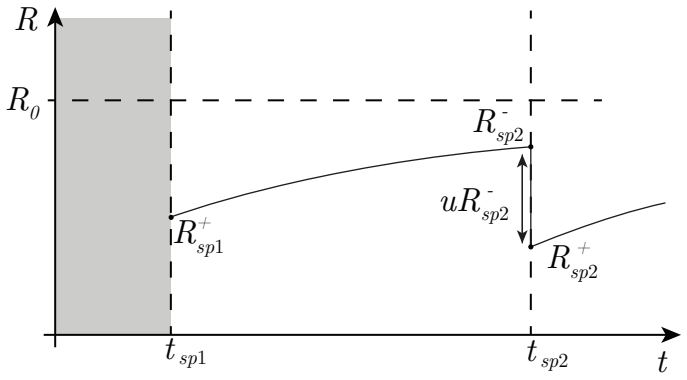

Figure 4.1: Temporal evolution of the pool size R when pre-synaptic spikes happen at the times t_{sp_1} and t_{sp_2}. The exponential recovery tend to the resting value R_0.

To find out the value $R(t^-_{sp_2})$ we need to analyse the recovery dynamics from the previous spike. We know that the solution for the differential equation 4.4 is an exponential; can drop some algebraic passages and write:

$$R(t^-_{sp_2}) = (R(t^+_{sp_1}) - R_0)e^{-\frac{t^+_{sp_1} - t^-_{sp_2}}{\tau_V}} + R_0 \tag{4.6}$$

And pooling together these two equations we arrive to:

$$R(t^-_{sp_2}) = (R(t^-_{sp_1}) - uR(t^-_{sp_1}) - R_0)e^{-\frac{t^+_{sp_1} - t^-_{sp_2}}{\tau_V}} + R_0 \tag{4.7}$$

This has become a discrete dynamical system: even if we started with a continuous time, now the value before any new spike n is just a function of the value before the precedent spike $n-1$:

$$\begin{aligned} R_n &= R(t^-_{sp_n}) \\ R_{n+1} &= ((1-u)R(t^-_{sp_n}) - R_0)e^{\frac{\Delta t^n}{\tau_V}} + R_0 \end{aligned}$$

where $\Delta t^n = t^+_{sp_{n-1}} - t^-_{sp_n}$.

This equation recurrently applies to all the pre-synaptic spikes of the time series, and in order to find the value R_i we need to know the times of all the previous spikes:

$$\{t_s p^{(i)}\} \rightarrow R_i \tag{4.8}$$

We can analyse the behaviour of the system under the assumption of a constant firing rate r, so that:

$$\Delta t^n = \frac{1}{r} = const.$$

In this situation we know that the system will eventually reach a steady state, *i.e.*, a situation where the number of vesicles becomes constant:

$$R_{n+1} = R_n = R^* \tag{4.9}$$

Knowing this:

$$R^* - R_0 = ((1-u) - R_0)e^{-\frac{1}{\tau_V r}} \tag{4.10}$$

After a few algebraic passages we can rearrange the equation in terms of R^*:

$$R^* = R_0 \frac{1-\delta}{1-\delta(1-u)} \tag{4.11}$$

Where $\delta = e^{-\frac{1}{r\tau_V}}$.

The term δ is a function of the firing rate r. Its limits are the following:

$$\lim_{r \to +\infty} \delta = 1$$
$$\lim_{r \to 0} \delta = 0$$

And, once plugged in equation 4.11 they make sense, since for infinite firing rates the vesicles are completely depleted and for firing rate 0 they are untouched:

$$\lim_{r \to +\infty} R^* = 0$$
$$\lim_{r \to 0} R^* = R_0$$

The shape of the function $R^*(r)$, the vesicle pool dimension as a function of the firing rate r, is depicted in fig.X. This function depends on the parameters τ_V and u, and they can be fitted from experimental data. A typical value for τ_V is about 100 ms.

Since, before reaching the steady state, the size of the pool will decrease at every new action potential ($R_{n+1} < R_n$), this phenomenon is called synaptic depression: it will drive a decrease of post-synaptic potentials for later spikes of the train.

4.2.2 Synapse Dynamics: Synaptic Facilitation

The dimension of the vesicle pool R is not the only parameter that can change over time. Also the *pq* term, also grouped under one single variable y (they are difficult to isolate experimentally). Since both the probability of release and the post-synaptic amplitude depends on intracellular calcium concentration, we can imagine that they will have a facilitating dynamics with the increasing of firing rate: previous spikes will leave high intracellular calcium concentrations that in turn will produce higher release amplitudes for the subsequent spikes. The equivalent of equation 4.4 for the release probability will now be:

$$\frac{du}{dt} = \frac{y_0 - y}{\tau_f} + \delta f(y_{max} - y) \tag{4.12}$$

The first term gives the recovery dynamics of calcium; the second term the increase in release probability given by any new spike. Note that the presence

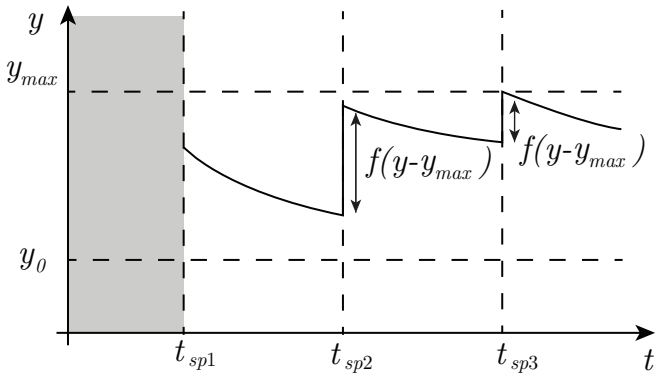

Figure 4.2: Temporal evolution of transmission efficacy y when pre-synaptic spikes happen at the times t_{sp_1}, t_{sp_2} and t_{sp_3}. The exponential recovery tend to the resting value y_0, while the ceiling effect limit the effects of the spikes for increasing y to the max y_{max}.

of y_{max} gives a ceiling effect: the facilitation will not grows indefinitely, but only to a maximum value y_{max}. The evolution of this system is depicted in fig. 4.2

By passages that are fully analogous to the previous case of synaptic depression, we can come out with this equation (equivalent to equation 4.7)

$$y_{n+1} = (y_n(1-f) + f y_{max})e^{-\frac{\Delta t}{\tau_f}} + y_0(1 - e^{-\frac{\Delta t}{\tau_f}}) \tag{4.13}$$

Again, we can analyse the case of a constant firing frequency r at the steady state, when $y_{n+1} = y_n = y^*$. Again, with some algebraic passages that we are dropping here, we arrive to:

$$y^* = \frac{y_0(1-\delta) + f y_{max}\delta}{1 + \delta(1-f)} \tag{4.14}$$

in this new case:

$$\lim_{r \to +\infty} y^* = y_{max}$$
$$\lim_{r \to 0} y^* = y_0$$

With increasing firing rate the function for y will exponentially go to y_{max}.

4.2.3 Combining Facilitation and Depression

We know that the post-synaptic amplitude is a function of both the dynamics for R and y. What happens when we combine them? We can compute each of the two independently, since they are not interdependent, to calculate the steady state amplitude $A^* = R^* y^*$. Depending on the dimensions of the two time constants τ_f and τ_V we can have two different cases, represented in fig. 4.3:

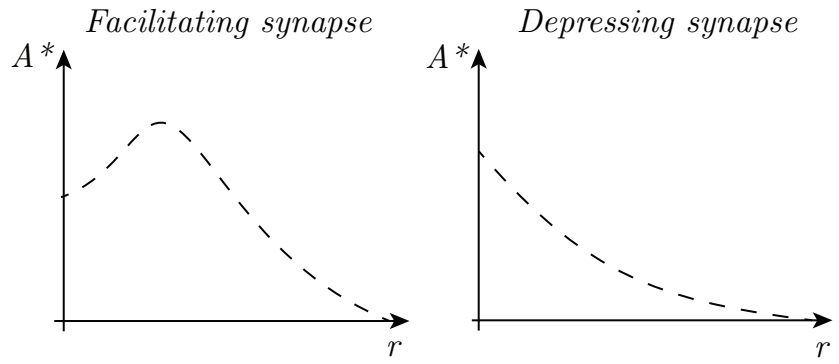

Figure 4.3: Amplitude of post-synaptic potential as a function of input rate r for facilitating and depressing synapses.

- $\tau_f > \tau_V$: facilitating synapses. In this case the replenishment of the vesicle pool has a short time constant - i.e., it happens very fast and the depletion of the storage is negligible at low r; we will have an immediate phase of facilitation, followed by a depression for increased frequencies;
- $\tau_f < \tau_V$: depressing synapses. In this case the facilitation happens slower than the depletion, and the net result will be a decrease to 0 to the post-synaptic amplitude. Note that this happens even if we still have the facilitating term.

The facilitating synapse acts as a frequency filter: inputs coming with the correct frequency will produce an increase in post-synaptic amplitudes compared to other input frequencies. This may have physiological relevance, and indeed it has been observed in electrically active fishes, where the electrosensitive neurons are matched in terms of optimal synaptic response frequency with the frequency they use for producing the electric field with the electric organs.

This kind of models for synaptic facilitation and depression are known under the name of Tsychyhs-Markram models, from the names of the people that made them famous.

4.3 Local Field Potential (LFP)

4.3.1 Electric Fields in the Vacuum

We start this section with a brief recap about electric fields in the vacuum. In general, a point charge q will produce an electric field that goes with the inverse square of the distance from the point (bold variables are vector quantities):

$$\boldsymbol{E} = \frac{q}{|\boldsymbol{r}|^2}\frac{\boldsymbol{r}}{|\boldsymbol{r}|} \tag{4.15}$$

Instead of using the vector field $\boldsymbol{E}$ we can define a scalar function ϕ such as its gradient (derivative in more dimensions) will gives us the electric field:

$$\boldsymbol{E}(\boldsymbol{r}) = -\nabla\phi(\boldsymbol{r}) \tag{4.16}$$

This function is called the electric potential. For a point charge,

$$\phi(\boldsymbol{r}) = \frac{q}{\boldsymbol{r}} \tag{4.17}$$

In the case of multiple charges, they will add linearly:

$$\phi(\boldsymbol{r}) = \sum_i \frac{q_i}{|\boldsymbol{r} - \boldsymbol{r}_i|} \tag{4.18}$$

Now we can substitute the presence of discrete charges q_i with a continuous charge density $\rho(\boldsymbol{r})$, which will give us the charge per unit of volume for every point of the space $\boldsymbol{r}$. In this way, the sum becomes an integral:

$$\phi(\boldsymbol{r}) = \int_V \frac{\rho(\boldsymbol{r})}{|\boldsymbol{r} - \boldsymbol{x}|} d\boldsymbol{x} \tag{4.19}$$

This equation comes as a solution for a partial differential equation called the Poisson equation:

$$-\nabla^2\phi = 4\pi\rho(\boldsymbol{r}) \tag{4.20}$$

Where the operator ∇^2, the so-called Laplacian, is defined as the sum of the second-order spatial derivatives in the three dimensions:

$$\nabla^2 = \partial_{xx} + \partial_{yy} + \partial_{zz} \tag{4.21}$$

4.3.2 Electric Fields in Biological Tissues

All these equations hold in the vacuum. In matter things are more complicated: the presence of an electric field will make the charges move, which in turn will change the electric field. Still, to describe the movement of charges under the influence of the field we can use a big simplification that has been proved quite valid for biological tissue, *i.e.*, that it acts as an Ohmic material. In an ohmic material the relationship between charge movements and the electric field is linear:

$$\boldsymbol{j}(\boldsymbol{r}) = \sigma\boldsymbol{E}(\boldsymbol{r}) \tag{4.22}$$

Where $\boldsymbol{j}$ is the vector field which describe the flow of current in every point of the space $\boldsymbol{r}$, $\boldsymbol{E}$ is the electric potential and σ is the conductivity, which tells us the efficacy of the electric field in generating a current (when it is 0, we will have no charge movement). Then, using our definition for ϕ:

$$\boldsymbol{j} = \sigma(-\nabla\phi) \tag{4.23}$$

Now we can apply to both sides the operator *divergence*[1]. Calculating the divergence requires taking the scalar product of the vector with a vector of its

[1]The divergence of a vector field tells us how many particles or charges are leaving from one point. If we imagine the vector field to be arrows, a point with high divergence will have many arrows pointing outwards, and only a few pointing towards it. A point with 0 divergence will have as many arrows pointing toward it as arrows pointing outwards.

derivatives:

$$\nabla \cdot \boldsymbol{j} = \begin{pmatrix} \partial_x \\ \partial_y \\ \partial_z \end{pmatrix} \begin{pmatrix} j_x \\ j_y \\ j_z \end{pmatrix} = \left(\frac{\partial}{\partial x} + \frac{\partial}{\partial y} + \frac{\partial}{\partial z} \right) \boldsymbol{j} \tag{4.24}$$

For the potential term:

$$\nabla \cdot (-\sigma \nabla \phi) = -\sigma \begin{pmatrix} \partial_x \\ \partial_y \\ \partial_z \end{pmatrix} \begin{pmatrix} \partial_x \\ \partial_y \\ \partial_z \end{pmatrix} \phi = -\sigma \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) = \nabla^2 \phi$$

where the term $nabla^2$, the so-called Laplacian (also indicated as Δ), is a new operator, the sum of the the second derivatives of the scalar function ϕ.

Plugging back these two new definition in the original equation, we get:

$$\frac{1}{\sigma} \nabla \cdot \boldsymbol{j} = -\nabla^2 \phi \tag{4.25}$$

And this is equivalent to the Poisson equation we were talking about for the void case, equation 4.20. It will therefore have a similar solution, *i.e.* a solution in the form of equation 4.19:

$$\phi(\boldsymbol{r}) = -\frac{1}{4\pi\sigma} \int_V \frac{\nabla \cdot \boldsymbol{j}}{|\boldsymbol{r} - \boldsymbol{x}|} d\boldsymbol{x} \tag{4.26}$$

This means that in the tissue the description of the voltage is very similar to the void case once we replace the charge density ρ with the divergence of the current density $\nabla \cdot \boldsymbol{j}$.

As we were previously mentioning, divergence is the measure of "how many arrows" are coming out of each point of the vector space. But if in one point of the space the current arrows pointing inward are less than the current arrows pointing outward, it means that there is more charge leaving the point than charge entering it, *i.e.*, we will have a change in the charge density for that point, and viceversa. Then, in general, the divergence of the current field $\boldsymbol{j}$ tells us the time derivative of the charge density:

$$\frac{\partial \rho(\boldsymbol{r}}{\partial t}) = -\nabla \cdot \boldsymbol{j} \tag{4.27}$$

[here, a brief useless mention to the Gauss theorem].

We can conclude that, in general, in the case of matter the term $\nabla \cdot \boldsymbol{j}$ take the role of ρ in the vacuum. We will call this term current source density, since, as we mentioned, it tells us how many charges are sourcing or sinking in a point of the space.

4.3.3 Current Source Density and Compartment Models

This is extremely important, since it is a way to link the potential of the extracellular media to the current sources that occupies it, i.e. neurons. Any time some neural activity is going on, charges will enter or leave the neurons, thereby generating current fields with non-zero divergence[2]. We have already studied models for the currents that are moving in and out neuronal compartments. In general, we have the equation

$$C\frac{dV}{dt} = \sum_x I^x + I_{ax} \tag{4.28}$$

That can be applied for every single compartment (I^x are currents of different ionic nature flowing through the membrane, and I_{ax} is the current flowing through the dendritic cable). We can simply plug the term for membrane currents into equation 4.26 to get:

$$\phi(\boldsymbol{r}) = -\frac{1}{4\pi\sigma}\sum_i \frac{\sum_x I_x^{(i)}}{|\boldsymbol{r} - \boldsymbol{r}_i|} \tag{4.29}$$

For every dendritic compartment i and its x_i transmembrane currents .

From this we can conclude that:

- The local field potential drops as $1/\boldsymbol{r}$
- The local field potential is deeply affected by the geometrical relationships of the considered neurons. For example, if one neuron is moving out positive charges, and another one negative one, there will be a strong field between these two neurons. Anyway, as soon as ve move a little bit far from them they will cancel out with each other, and we will have a very small final effect[3].

To observe strong signal in the local field potential (and in the EEG as well) therefore we need:

- Strong temporal synchronization;
- Strong spatial synchronization.

Many neurons in the same area must respond in the same way for us to see them.

[2] If we look at the channel from outside, it is a point where charges from all the space are coming in (arrows toward) or coming out (arrows outward) - i.e., a point of non-zero divergence

[3] In this case they act as a dipole, whose field far from the charges drops as $1/|\boldsymbol{r}^3|$