

## LECTURES 1 AND 2. THE LEAKY-INTEGRATOR NEURON

In this lecture the basic voltage equation for a leaky-integrator neuron is derived and its response to a step change in current calculated.

- CAPACITANCE OF A NEURON

The charge  $Q$  (in coulombs C) on a membrane of capacitance  $C$  (in farads F) is proportional to the potential difference across the membrane (membrane voltage)  $V_m$  measured in volts (V)

$$Q = CV_m \quad (1)$$

where  $V_m = V^i - V^e$  with  $V^i$  the internal and  $V^e$  the external voltage. Injection of a current  $I$  (measured in Amperes, A) into a neuron will charge it up (by convention  $I$  is positive for charge flowing into the cell for injected current). Assume for now that the membrane is closed so no charge leaks out. Then

$$C \frac{dV_m}{dt} = I \quad \text{with a solution} \quad V_m(t) = \int_{-\infty}^t \frac{dt'}{C} I(t'). \quad (2)$$

Such a leakless neuron would be a perfect integrator. Neurons, however, also have channels on their membranes that allow ions to pass and are therefore leaky. The internal potential of a neuron is lower than the external potential (so there is a resting charge on the membrane) - a feature that is also due to transmembrane ionic currents  $I_{ion}$ . By convention these are positive for current flowing out of the cell so that

$$C \frac{dV}{dt} + I_{ion} = I. \quad (3)$$

We now consider the form of this ionic current.

- IONIC CURRENT: CHEMICAL AND ELECTRICAL POTENTIALS.

Neurons have pumps on their membranes that keep the concentrations of ions far from equilibrium between the inside and outside of the cell. Neurons also have channels that allow specific ions to pass across the membrane. There is a high concentration of potassium  $K^+$  ions inside the cell and very low concentration outside the cell. Conversely, there is a very high concentration of both sodium  $Na^+$  and chloride  $Cl^-$  ions outside the cell (like salt water) and very low concentrations of these ions in the cell. At rest the cell membrane is permeable to potassium ions due to membrane channels with a total conductance  $g_K$ . Imagine that the voltage inside the cell is initially 0mV. Potassium will move out of the cell through potassium channels because it will flow down the concentration gradient - call this current  $g_K E_K$  where  $E_K$  is a constant. As soon as positive potassium ions leave the neuron the voltage will become negative inside the cell and the potassium ions will feel a retarding electric force that leads to a current  $g_K V$  in the opposite direction of the motion down the concentration gradient. The total current is therefore

$$I_K = g_K(V - E_K). \quad (4)$$

At some voltage these two forces will be equal and the net potassium current out of the cell will be zero. This occurs when the voltage satisfies  $V = E_K$ . Given that the potassium ions are positively charged it must be that  $E_K < 0$  and in fact it is typically around  $-80\text{mV}$ . Neurons also have other channels open at rest that allow chloride ions (and to a lesser extent) sodium ions to cross the membrane. The reversal potentials for these ions are  $E_{Na} \simeq +50\text{mV}$  and  $E_{Cl} \simeq -70\text{mV}$ . The currents are in parallel so we can define a net *leak* current  $I_L$

$$I_L = g_L(V - E_L) = g_K(V - E_K) + g_{Na}(V - E_{Na}) + g_{Cl}(V - E_{Cl}) \quad (5)$$

where  $g_L = g_K + g_{Na} + g_{Cl}$  and  $E_L = (g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl})/g_L$ . The conductance of the cell membrane to sodium at rest is very small, which explain why neurons have a negative membrane voltage around  $E_L = -70\text{mV}$ . The total leak membrane resistance  $R_L$  is just given by  $g_L = 1/R_L$ .

- VOLTAGE EQUATION FOR A PASSIVE MEMBRANE AND RESPONSE TO A CURRENT STEP  
Combining equation (5) with the membrane voltage equation (3) we have

$$C \frac{dV}{dt} + g_L(V - E_L) = I \quad \text{or more usually} \quad C \frac{dV}{dt} = g_L(E_L - V) + I. \quad (6)$$

On dividing this equation through by  $g_L$  a quantity with units of time can be found  $\tau = C/g_L$ . This is the membrane time constant. The voltage equation now looks like

$$\tau \frac{dV}{dt} = E_L - V + IR_L. \quad (7)$$

Now lets consider the solutions to this equation when the current  $I$  is zero before  $t = 0$  but at  $t = 0$  is switched on to the constant value  $I_0$ . The general solution of the equation in this case for  $V(t > 0)$  is

$$V(t) = E_L + I_0 R_L (1 - e^{-t/\tau}). \quad (8)$$

Note that the initial condition is “forgotten” over a timescale of the order of the membrane time constant  $\tau$  so unlike equation (2) this model does not have an infinite memory and will act as a coincidence detector over a timescale  $\tau$  which typically in the range 5 – 50ms.

## LECTURES 2 AND 3. VOLTAGE-GATED CURRENTS I AND II

In these lectures we will examine voltage-gated channels that are active in the voltage range around  $-80$  to  $-50\text{mV}$ . We will not consider spike-generating currents, but only the subthreshold effects voltage-gated channels can have on steady states and stability.

### • IONIC CURRENT WITH A SINGLE ACTIVATION VARIABLE

We consider a species of ionic channel that has two states: open and closed. The rate a closed channel opens is  $\alpha(V)$  and the rate an open channel closes is  $\beta(V)$  - the rates are voltage dependent. Let  $n$  be the fraction of open channels. The rate of increase of  $n$  is equal to the difference between the total opening and closing rates

$$\frac{dn}{dt} = \alpha(V)(1 - n) - \beta(V)n. \quad (9)$$

This equation may be rewritten in a more convenient form

$$\tau_n \frac{dn}{dt} = n_\infty - n \quad \text{where} \quad n_\infty = \frac{\alpha(V)}{\alpha(V) + \beta(V)}. \quad (10)$$

The time constant  $\tau_n = 1/(\alpha + \beta)$  is weakly voltage dependent; however, here it will be approximated as being constant. The quantity  $n_\infty(V)$  gives the fraction of channels open in the steady state (at fixed voltage  $V$ ). The time constant  $\tau_n$  measures how quickly  $n$  tracks the voltage-dependent target  $n_\infty$  as the voltage changes. Experimentally  $n_\infty$  takes the form

$$n_\infty = \frac{1}{1 + e^{-(V-V_{1/2})/\Delta_V}} \quad (11)$$

which is a sigmoidal activation function with  $V_{1/2}$  being the voltage where half the channels are open and  $\Delta_V$  the width of the activation curve. The sign of  $\Delta_V$  determines the type of channel: for  $\Delta_V$  positive it is a *depolarisation* activated channel (it opens when the voltage increases towards  $0\text{mV}$ ); for  $\Delta_V$  negative it is a *hyperpolarisation* activated channel (opening when the voltage decreases away from  $0\text{mV}$ ).

The ionic current flowing out of the cell through this gated channel is

$$I_n = g_n n (V - E_n) \quad (12)$$

where  $g_n$  is the total conductance per unit area of membrane through these channels when they are all open. The reversal potential  $E_n$  of the channel depends on which species of ion it carries.

### • A TWO-VARIABLE MODEL AND THE STEADY STATES

The dynamics of the membrane voltage are now governed by two equations; a voltage equation for the charging of the membrane due to the ionic currents and the dynamics of the activation variable  $n$

$$C \frac{dV}{dt} = g_L(E_L - V) + g_n n (E_n - V) + I_{app} \quad (13)$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n. \quad (14)$$

In the steady state the activation variable is given by  $n^* = n_\infty(V^*)$  where, for  $I_{app} = 0$ , the steady-state voltage  $V^*$  satisfies

$$V^* - E_L = \frac{(E_n - E_L)g_n n^*}{g_L + g_n n^*}. \quad (15)$$

The resting potential  $V^*$  is higher or lower than the leak reversal depending on the sign of  $(E_n - E_L)$ . If  $(E_n - E_L) > 0$  it is a *depolarising* current because it increases the voltage from its leak value. If  $(E_n - E_L) < 0$  it is a *hyperpolarising* current because it decreases the voltage from the leak value.

• PHASE-PLANE ANALYSIS

A convenient way to analyse equation (15) is to rewrite the equations in the form

$$\tau_v \frac{dV}{dt} = V_\infty(n) - V + RI_{app} \quad (16)$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n. \quad (17)$$

where  $\tau_v = CR$  and  $R = (g_L + ng_n)^{-1}$  has units of resistance and  $V_\infty(n)$  is found from (15) to be

$$V_\infty(n) = \frac{E_L g_L + E_n g_n n}{g_L + g_n n}. \quad (18)$$

We continue with the  $I_{app} = 0$  case. When  $n = n_\infty$  the rate of change of  $n$  is zero. When  $V = V_\infty$  the rate of change of voltage is zero. These lines in the  $V, n$  plane are called *nullclines* and the fixed points are found at their intersections. The nullclines are better written as functions of  $V$  by inverting the function  $V = V_\infty(n)$  so that  $n_1 = V_\infty^{-1}(V)$  and  $n_2 = n_\infty(V)$

$$n_1 = \frac{g_L}{g_n} \left( \frac{V - E_L}{E_n - V} \right) \quad n_2 = \frac{1}{1 + e^{-(V - V_{1/2})/\Delta V}}. \quad (19)$$

On plotting these two equations on a graph of  $V$  ( $x$ -axis) versus  $n$  ( $y$ -axis) it is straightforward to see that there are two cases: (i) if the gradients of  $n_1$  and  $n_2$  have the same sign (a hyperpolarisation-activated hyperpolarising current or a depolarisation-activated depolarising current) it is possible to have one or three fixed points; (ii) if the gradients have different sign (a hyperpolarisation-activated depolarising current or a depolarisation-activated hyperpolarising current) it is only possible to have one fixed point. Case (i) for which the gradients have the same sign corresponds to positive feedback - when the voltage moves away from rest the voltage-gated currents amplify the change. Case (ii) for which the gradients have different signs corresponds to negative feedback - when the voltage moves away from rest the voltage-gated currents act to counter the change.

• LINEARISATION OF THE TWO-VARIABLE MODEL

Equations (16) and (17) are non-linear and hard to study analytically. One method is to linearise the equations near a fixed point. The forms of the eigenfunctions of the two-variable system then give information on the fixed-point stability. On writing  $V = V^* + \delta V$  and  $n = n^* + \delta n$  we get

$$\tau_v \frac{d\delta V}{dt} = \left. \frac{dV_\infty(n)}{dn} \right|_{n^*} \delta n - \delta V \quad (20)$$

$$\tau_n \frac{d\delta n}{dt} = \left. \frac{dn_\infty(V)}{dV} \right|_{V^*} \delta V - \delta n \quad (21)$$

where  $\tau_n$  and  $\tau_v$  are constants:

$$\tau_v = \frac{C}{g_L + g_n n^*}. \quad (22)$$

It proves convenient to convert  $\delta n$  to a voltage-like variable  $y = \delta n / (dn_\infty / dV|_{V^*})$  and also to rescale time by  $t = s\tau_n$ . Writing  $\delta V$  as  $v$  we get

$$\frac{dv}{ds} = -Pv + Qy \quad (23)$$

$$\frac{dy}{ds} = v - y \quad (24)$$

where

$$P = \frac{\tau_n}{\tau_v} \quad \text{and} \quad Q = \frac{\tau_n}{\tau_v} \left. \frac{dV_\infty(n)}{dn} \right|_{n^*} \left. \frac{dn_\infty(V)}{dV} \right|_{V^*}. \quad (25)$$

It can be noted that the sign of  $Q$  signifies whether the feedback is positive or negative (see the previous section) and that the gradients can be related to the tangents of the phase-plane analysis via

$$\left. \frac{dV_\infty(n)}{dn} \right|_{n^*} = \left( \left. \frac{dn_1(V)}{dV} \right|_{V^*} \right)^{-1}. \quad (26)$$

The eigenfunctions  $\lambda_\pm$  of this equation set satisfy

$$\lambda^2 + (P+1)\lambda + P - Q = 0 \quad \text{so that} \quad \lambda = \frac{1}{2} \left( -(P+1) \pm \sqrt{(P+1)^2 + 4(Q-P)} \right) \quad (27)$$

from which the stability of the equations may be analysed. If  $\lambda$  is real then an instability can occur when  $\lambda_+ > 0$  which happens when  $Q > P$ . Complex roots (damped oscillations in the voltage) appear when

$$(P-1)^2 + 4Q < 0 \quad \text{so that} \quad Q < -\frac{1}{4}(P-1)^2. \quad (28)$$

If  $P+1 < 0$  the complex roots are unstable and spontaneous oscillations are possible. For the cases considered so far  $P > 0$  (see Eq 25). However, there are circumstances where the effective conductance can become negative (see Questions). It can be noted that  $Q < 0$ , the case of negative feedback, is required for damped oscillatory solutions, though this is not sufficient.

## LECTURES 4. THE LEAKY-INTEGRATE-AND-FIRE NEURON

In this lecture we will derive and analyse the firing rate for the most commonly used mathematical model of a spiking neuron: the leaky integrate-and-fire model.

- DEFINITION OF THE LEAKY INTEGRATE-AND-FIRE NEURON

The model comprises a leaky, passive subthreshold dynamics characterised by a timescale  $\tau_L$ ,

$$\tau \frac{dV}{dt} = E_L - V + \frac{I}{g_L}. \quad (29)$$

If the voltage ever reaches a threshold  $V_{th}$  then a spike is registered, the voltage is instantly reset at  $V_{re}$  and the dynamics continue. It sometimes proves convenient to absorb the current into the effective fixed point or resting potential  $E_0 = E_L + I/g_L$ . If  $E_0 < V_{th}$  there is stable fixed point but the model is excitable - a current pulse that brings the voltage above  $V_{th}$  releases a spike. If  $E_0 > V_{th}$  the neuron is spontaneously firing - it is a non-linear oscillator. The critical value of the resting potential is  $E_0 = V_{th}$  which corresponds to a critical current  $I^* = g_L(V_{th} - E_L)$ .

- FIRING-RATE OF THE LIF NEURON

The firing-rate of the neuron for  $E_0 > V_{th}$  can be calculated by remembering the form of the response of a passive neuron (Eq. 29) for a relaxation from an initial state at  $t = 0$ . Choosing the initial voltage to be  $V_{re}$  we have

$$V(t) = E_0 + (V_{re} - E_0)e^{-t/\tau}. \quad (30)$$

A single period of duration  $T$  takes the neuron from the reset  $V_{re}$  to the threshold  $V_{th}$  so that

$$V(T) = V_{th} = E_0 + (V_{re} - E_0)e^{-T/\tau} \quad \text{giving} \quad T = \tau \log \left( \frac{E_0 - V_{re}}{E_0 - V_{th}} \right). \quad (31)$$

The inverse of the period is the firing rate  $r$ ; thus

$$r = \frac{1}{\tau \log \left( \frac{E_0 - V_{re}}{E_0 - V_{th}} \right)}. \quad (32)$$

We now consider the firing in various limits. First a case where the neuron is just starting to fire, which occurs when  $E_0 = V_{th} + \epsilon$  where  $\epsilon$  is small and positive. In this case the rate is

$$r \simeq \frac{1}{\tau \log \left( \frac{V_{th} - V_{re}}{\epsilon} \right)} \quad (33)$$

which gives a zero firing rate as  $\epsilon \rightarrow 0$  from above. Hence the LIF neuron can fire at an arbitrarily low rate. We now consider the other extreme, the high-firing rate limit when  $E_0$  is very large. Consider two variables  $\theta = V_{th} - V_{re}$  and  $\mathcal{E} = E_0 - (V_{th} + V_{re})/2$ . In terms of these variables the firing rate can be written

$$r = \frac{1}{\tau \log \left( \frac{\mathcal{E} + \theta/2}{\mathcal{E} - \theta/2} \right)} \simeq \frac{1}{\tau \log (1 + \theta/\mathcal{E})} \simeq \frac{\mathcal{E}}{\tau \theta} = \frac{E_0 - (V_{th} + V_{re})/2}{\tau(V_{th} - V_{re})}. \quad (34)$$

Hence for strong current the firing rate grows linearly with  $E$ . This is unrealistic as the firing rate in real neurons saturates. This feature can be dealt with by including a refractory time:

after the spike the neuron stays at  $V_{re}$  for a time  $\tau_r$  before the dynamics restarts. By considering the full period as  $T_r = T + \tau_r$  we can write the firing rate for a refractory neuron as

$$r_r = \frac{r}{1 + r\tau_r}. \quad (35)$$

When  $r\tau_r \ll 1$  the firing rates of the refractory and non-refractory neuron are similar  $r_r \simeq r$ . For  $r\tau_r \gg 1$  the firing rate for the refractory neuron becomes  $r_r = 1/\tau_r$  and hence a maximal firing rate has been enforced.

## LECTURES 5. NON-LINEAR INTEGRATE-AND-FIRE NEURONS

The leaky integrate-and-fire model has the linear subthreshold behaviour seen in experiment, but the spike is absent (there is just a hard threshold mechanism). Here we will first introduce an abstract one-dimensional model with an explicit spike and then show how a compromise between it and the leaky integrate-and-fire model can capture the spikes of real neurons.

- QUADRATIC INTEGRATE-AND-FIRE MODEL

Consider a neuron model with a voltage equation of the form

$$\frac{dV}{dt} = qV^2 + I \quad (36)$$

where  $q > 0$ . The dynamics allows the voltage to run off to infinity in finite time. We supplement the equation by stating that if the voltage is at  $+\infty$  we re-insert it at  $-\infty$ . This will allow oscillations, and something that looks a bit like a spike. We will now examine the fixed point structure of equation (36) and consider its dynamics.

*Subthreshold response and excitability.* When  $I < 0$  there are two fixed points, at

$$V_* = \pm \sqrt{\frac{-I}{q}}. \quad (37)$$

The lower fixed point is stable and the upper unstable, as can be seen from the eigenvalues at these fixed points:

$$\lambda_{\pm} = \pm 2\sqrt{-Iq}. \quad (38)$$

If the voltage is between  $-\infty$  and  $\sqrt{-I/q}$  it will relax to the lower stable fixed point. However if the voltage is above the upper unstable fixed point  $V > \sqrt{-I/q}$  the voltage will go off to  $+\infty$ , be reinserted at  $-\infty$  and then relax to the lower fixed point from below. For  $I < 0$  the model has a stable fixed point but is *excitable*, current pulses that add up to a total voltage larger than  $2\sqrt{-I/q}$  will cause the neuron to fire once.

*Approach to the critical point.* As  $I \rightarrow 0$  the eigenvalues approach 0. Because the response of the system near the fixed point are governed by a time-scale that is the inverse of the eigenvalue, the dynamics become very slow near  $V_*$  (which also approaches 0). At  $I = 0$  the stable and unstable fixed points “collide” and annihilate, and so for  $I > 0$  no fixed point exists. The derivative is always positive and all motion is towards more positive  $V$ . For small positive  $I$  the dynamics are still very slow near  $V = 0$  as can be seen by directly evaluating the voltage rate of change (36) at  $V = 0$  which scales with  $I$ .

*Spontaneous oscillations.* We will now derive the form for the oscillations for the unstable case when  $I > 0$ . On rescaling voltage by  $V = x\sqrt{I/q}$  and time by  $t = s/\sqrt{qI}$ , the dimensionless voltage equation becomes

$$\frac{dx}{ds} = x^2 + 1. \quad (39)$$

The solution of this equation between times  $s_a, s_b$  and voltages  $x_a, x_b$  is

$$\arctan(x_b) - \arctan(x_a) = s_b - s_a \quad (40)$$

and if, when  $s_a = 0$  we have  $x_a = 0$ , then the voltage takes the simple form

$$x = \tan(s) \quad \text{or} \quad V = \sqrt{\frac{I}{q}} \tan\left(t\sqrt{Iq}\right). \quad (41)$$



From this it is straightforward to extract the period of the oscillation, which is the time it takes to go from  $0 \rightarrow \infty$  and then  $-\infty \rightarrow 0$ . This is just

$$T = \frac{2}{\sqrt{Iq}} \lim_{V \rightarrow \infty} \left( \arctan \left( V \sqrt{\frac{q}{I}} \right) \right) = \frac{\pi}{\sqrt{Iq}} \quad (42)$$

which gives a firing rate  $r$  that scales with the square-root of the current

$$r = \frac{\sqrt{Iq}}{\pi}. \quad (43)$$

• EXPONENTIAL IF (EIF) MODEL

An important recent improvement to the LIF and QIF is to include an exponential term that accounts for the near instantaneous activation of the sodium current's  $m$  variable. The voltage equation takes the form

$$\tau \frac{dV}{dt} = E_L - V + \Delta_T \exp^{(V-V_T)/\Delta_T} + \frac{I}{g_L} = F(V). \quad (44)$$

In this case the ultimate threshold is at  $V_{th} = \infty$  (when the spike starts the voltage diverges in finite time) with a subsequent reset to  $V_{re}$ . The voltage range for spike initiation is  $\Delta_T$  and the effective threshold is measured by  $V_T$ . There are two cases: if the current is below a critical value there are two fixed points, the lower one is stable and the upper unstable - the model is excitable; if the current is above the critical value there are no fixed points and the model is spontaneously oscillating. At the critical current the fixed points merge, the RHS of equation (49) is zero and so is its derivative with respect to voltage:

$$E_0^* - V^* + \Delta_T \exp^{(V^*-V_T)/\Delta_T} = 0 \quad \text{and} \quad -1 + \exp^{(V^*-V_T)/\Delta_T} = 0. \quad (45)$$

From the second equation the critical voltage is  $V_T$  and the critical effective resting potential is

$$E_0^* = V_T - \Delta_T. \quad (46)$$

Consider the case where  $E_0$  is just above  $E_0^*$ . The voltage dynamics are very slow near  $V = V_T$  as this is where  $dV/dt$  almost touches the  $x$  axis. If we expand the voltage around that point as  $V = V_T + v$  then

$$\tau \frac{dV}{dt} = E_0 - V_T - v + \Delta_T \exp^{(V_T+v-V_T)/\Delta_T} \quad (47)$$

$$\tau \frac{dV}{dt} = E_0 - V_T - v + \Delta_T \left( 1 + \frac{v}{\Delta_T} + \frac{1}{2} \frac{v^2}{\Delta_T^2} + O(v^3) + \dots \right) \quad (48)$$

$$\tau \frac{dV}{dt} = E_0 - E_0^* + \frac{1}{2} \frac{v^2}{\Delta_T} + \dots \quad (49)$$

we reach a form that is (to second order) identical to the QIF model in equation (36). On comparing this last form with that of the QIF we can see that the assignments  $I = (E_0 - E_0^*)/\tau$  and  $q = 1/2\tau\Delta_T$  can be made which can be inserted into equation (43) to calculate the firing rate near the critical point for the EIF model.