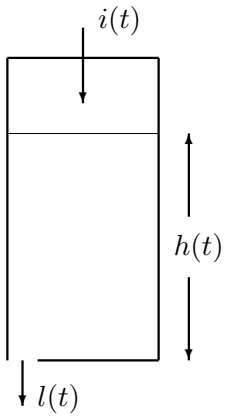
Introduction

In neuroscience computational methods are used in analyzing data and in modeling, which is what we aim to discuss here. Modeling, in turn, is both a tool for testing out ideas about the functional significance of an experimental discovery and a language for phrasing ideas about brain function. This lecture is about the first of these two: modeling as a tool for testing functional significance. The idea here is that a neuroscience might be interested in a neuroscientific phenomenon, for example, very fast oscillations in the hippocampus and may have discovered a possible explanation for how the phenomenon occurs, in the hippocampus example, axon-to-axon gap junctions. Modeling might then be useful in seeing if the potential explanation is likely to be correct. Gap junctions, for example, are very difficult to block, so it might be hard to resolve this issue experimentally and so an alternate approach would be to use a computer to try to simulate a network of neuron with axon-to-axon gap junctions to see if the network supports very fast oscillations. Precisely this approach is described in [1].

The challenge then is to simulate the behavior of neurons and networks of neurons. In fact, a lot is known about how neurons behave, but when simulating a trade-off needs to be made between a very accurate and detailed model which may be very slow to simulate and may contains lots of parameters which are hard to fix using experimental data, and very simple models that are easier to simulate and contain few parameters, but are inaccurate and may not incorporate important aspects of the dynamics.

Buckets of water

In the simplest model of neurons their voltage dynamics is similar to the dynamics of a bucket with a leak and the class of equations that apply in this case will also be applied to synapses, for example.



Consider a bucket, with straight sides which is filled to a height h with water. Imagine the water leaks out of a hole in the bottom. The rate the water leaks out depends on h; the larger

h is the larger the pressure at the bottom is and hence the faster the water pours out. In other words

$$l(t) \propto h(t) \tag{1}$$

or

$$l(t) = Gh(t) \tag{2}$$

where G is a constant which will depend on the size of the hole and complicated things like the viscosity of water. Of course, we are also ignore lots of other complicated stuff, like turbulence and so forth, but since we are interested in the equation rather than the amount of water in a bucket, this is fine. Imagine water also pours in the top at a rate $i(t)$. This means the total rate of change of the amount of water is $i(t) - Gh(t)$.

Now, $h(t)$ is the height of the water not the volume: the volume is $Ch(t)$ where C is the cross-sectional area of the bucket. The rate of change of the volume is therefore

$$\frac{dCh(t)}{dt} = i(t) - Gh(t) \tag{3}$$

or

$$\frac{dh}{dt} = \frac{1}{C}(i - Gh) \tag{4}$$

In other words, the rate that the height of the water changes is proportional to the amount of water flowing in minus the amount flowing out.

Constant input

This equation can be solved analytically if the current flowing in is constant, but we won't try that calculation here since it only works for this specific special case, normally we have to solve numerically, using a computer. The solution is

$$h(t) = [h(0) - i/G]e^{-t/\tau} + i/G \tag{5}$$

where $\tau = C/G$. This makes sense, when $h = i/G$ then the equation says $dh/dt = 0$ so this is an equilibrium point, a value where everything stops changing. The dynamics describe the systems as decaying exponentially to the equilibrium.

These dynamics make good intuitive sense; the more water there is in the bucket, the higher the pressure will be at the leak and the quicker the water will pour out. If there is just the right about of water the rate the water pours out the leak will precisely match the rate it pours in, this is the equilibrium. If there is more water than required for equilibrium it will pour out faster than the flow coming in, if there is less, it will pour out slower. Either way, as time passes the height of the water will reach the equilibrium. The plot in Fig. 1 illustrates this.

Variable input

We have only discussed constant inputs; the variable input case where i depends on time is harder and although it can sometimes be solved it is often easier just to compute it numerically, we will look briefly at how to do this, but first note that the effect of variable inputis that the solution kind of chases the input with a timescale set by τ, that is for very small τ is chases it quickly, so it is close to the input, but for large τ it lags behind it and smooths it out. This is sometimes described by saying that it *filters* the inout. There is an illustration in Fig. 2.

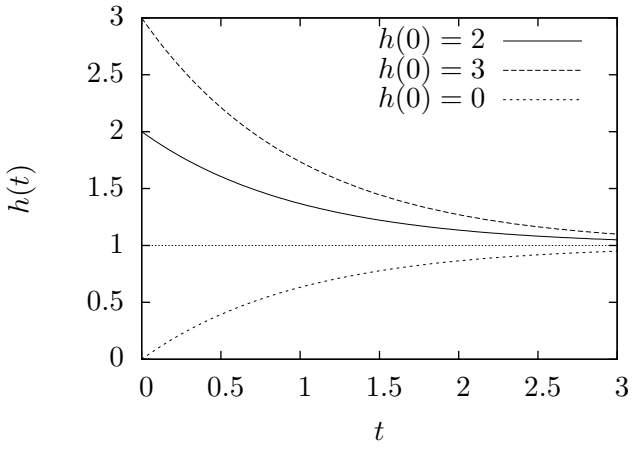


Figure 1: Exponential relaxation. The dynamics described by the 'bucket equation' is very common. Here $h(t)$ is plotted with $i = G$, $\tau = 1$ and three different values of $h(0)$. $h(t)$ relaxes towards the equilibrium value, the closer it gets, the slower it approaches.

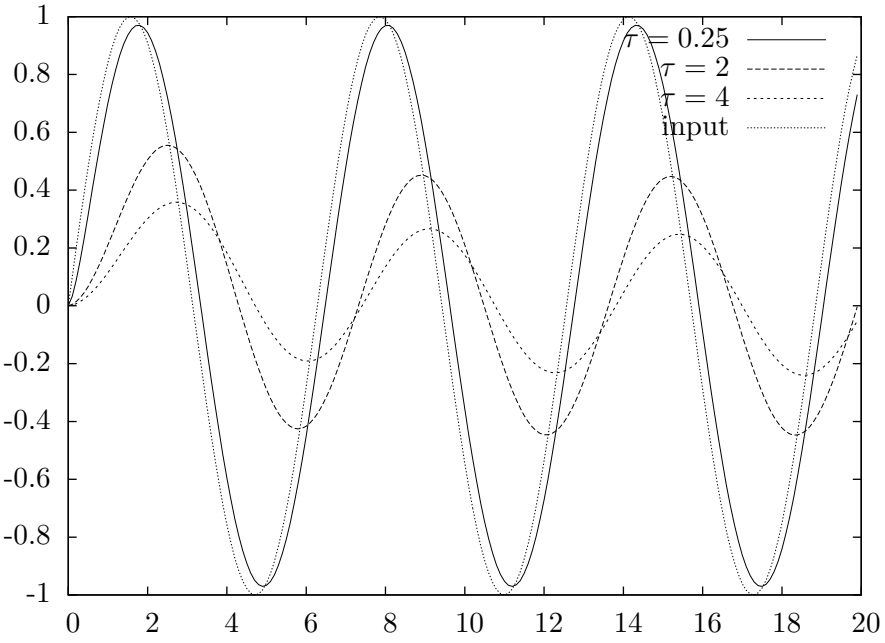


Figure 2: Variable input. Here the input is a sine wave $i(t) = \sin t$ and the equation is evolved with $h(0) = 0$ and three different τ values. For $\tau = 0.25$ we see $h(t)$ closely matches the input whereas for larger τ it is smoother and lags behind.

Numerical solutions

Consider the problem of solving a general first order differential equation

$$\frac{df(t)}{dt} = F(f,t) \tag{6}$$

This includes our bucket case if we replace f with h and $F(f,t)$ with $(i-Gh)/C$. Now consider the situation where we want to solve this but can't do it analytically, as will be the case for many values of the time dependent input $i(t)$ or, indeed, if $i(t)$ itself is only known numerically.

The simplest numerical approach is Euler's method. Say you know the value of $f(t)$ and want to approximate $f(t+\delta t)$ where δt is some small increment in time. Now, it is known that

$$f(t+\delta t) = f(t) + \delta t \frac{df(t)}{dt} + O(\delta t^2) \tag{7}$$

That is, it changes by its rate of change multiplied by how long it is changing for. The $O(\delta t^2)$ says there are δt^2 sized errors in this approximation, this comes about because dh/dt is itself changing but our approximation assumes it is fixed still. Now we know what $df(t)/dt$ is, it is $F(f,t)$ from the equation, so

$$f(t+\delta t) = f(t) + \delta t F(f,t) + O(\delta t^2) \tag{8}$$

so approximating $f(t+\delta t)$ with $f(t)+\delta t F(f,t)$ is actual to first order in the time step δt. This is the Euler approximation. More formally if we have an initial condition $f(t_0)$ and write

$$f_n = f(t_0 + n\delta t) \tag{9}$$

$$t_n = t_0 + n\delta t \tag{10}$$

then the Euler approximation is

$$f_{n+1} = f_n + \delta t F(f_n, t_n) \tag{11}$$

Thus, in the case we are interested in here

$$h_{n+1} = \frac{[i(t_n) - Gh_n]\delta t}{C} \tag{12}$$

Of course, this is just the easiest way to do the integration, there are more sophisticated approaches like Runge-Kutta or backwards Euler which are more complex and computational costly for each step, but which are also much more accurate.

Electrical properties of a neuron

The potential inside a neuron is lower than the potential on the outside; this difference is created by ion pumps, small molecular machines that use energy to pump ions across the membrane seperating the inside and outside of the cell. One typical ion pump is Na+/K+-ATPase (Sodium-potassium adenosine triphosphatase); this uses energy in the form of ATP, the energy carrying molecule in the body, and through each cycle it moves three sodium ions out of the cell and two potassium ions into the cell. Since both sodium and potassium ions have a charge of plus one, this leads to a net loss of one atomic charge to the inside of the cell lowering its potential. It also creates an excess of sodium outside the cell and an excess of potassium inside it. We will return to these chemical imbalances later. The potential difference across the membrane is called the membrane potential. At rest a typical value of the membrane potential is $E_L = -70\text{mV}$.

Spikes

So the summary version of what happens in neuons is that synapses cause a small increase or decrease in the voltage; excitatory synapses cause an increase, inhibitory synapses a decrease. This drives the internal voltage dynamics of the cell, these dynamics are what we will learn about here. If the voltage exceeds a threshold, say $V_T = -55$ mV there is a nonlinear cascade which produces a spike or action potential, a spike in voltage 1-2 ms wide which rises above 0 mV before, in the usual description, falling to a reset value of $V_R = -65$ mV, the cell then remains unable to produce another spike for a refractory period which may last about 5 ms. We will examine how spikes are formed later, this involves the nonlinear dynamics of ion channels in the membrane; first though we will consider the integrate and fire model which ignores the details of how spikes are produced and simplifies the voltage dynamics.

The bucket-like equation for neurons

We will now try to extend the bucket-like equation we looked at before so that it applies to neurons. First off we replace h, the height of the water, by V the voltage in the cell and C will be replaced by C_m, the capacitance of the membrane, the amount of electrical charge that can be stored at the membrane is $C_m V$. The amount of electrical charge is the analogue of the volume of water. Thus, voltage is like height, charge is like the amount of water.

The leak is a bit more complicated, because of the chemical gradients, that is the effects of the differing levels of ions inside and outside the cell along and their propensity to diffuse, the voltage at which there is no leaking of charge is not zero, it is $E_L = -70$mV, roughly. This is an important aspect of how neurons behave: you might at first expect that if the voltage inside the cell was, say, -60 mV then even if there was a high conductivity for potassium at the membrane, the potassium ions would stay in the cell: they are positive ions after all and so a negative voltage means the electrical force is attracting them to the inside of the cell. However, this isn't quite what happens, there is a high concentration of potassium inside the cell and because of the random motion of particles associated with temperature, these have a tendency to diffuse, that is to increase the entropy of the situation by spreading out. It takes a force to counteract this. This is the reversal potential, E_L, the voltage required for zero current even if there is some conductivity. It turns out that the normal Ohm's law applies around the reversal potential so that the current out of the cell is proportional to $V - E_L$.

G is now G_m, a conductance, measuring the porousness of the membrane to the flow of ions, in other words, it gives the constant of proportionality for the leak current: the leak current out of the cell is $G_m(V - E_L)$. We actually divide across by the conductance, and write $R_m = 1/G_m$, the resistance. Finally, we write $\tau_m = C_m/G_m$ to get

$$\tau_m \frac{dV}{dt} = E_L - V + R_m I \tag{13}$$

I might end up being synaptic input, but traditionally we write the equation to match the *in vivo* experiment where I is an injected current from an electrode, so we write I_e, 'e' for electrode. τ_m is a time constant.

The equation above leaves out the possibility that there are other non-linear changes in the currents through the membrane as V changes. This is a problem since there are other non-linear changes in the currents through the membrane as V changes. The equation above leaves these out, in fact, the nonlinear effects are strongest for values of V near where a spike

is produced, so one approach is to use the linear equation unless V reaches a threshold value and then add a spike 'by hand'. This has the effect of changing the voltage to a reset value, this mimics what happens in the neuron, or in the Hodgkin Huxley model which we will look at next and which includes the full non-linear dynamics which makes the spike. Anyway, in summary

- V satisfies
$$\tau_m \frac{dV}{dt} = E_L - V + R_m I_e \tag{14}$$
- If $V \geq V_T$ a spike is recorded and the voltage is set to a reset value V_R.

The reset value, the voltage after the spike is often set equal to the leak potential. This is the leaky integrate and fire model, a surprisingly old model first introduced in [2]. It lacks lots of the details important in the dynamics of neurons, but is useful and often used for modeling the behavior of large neuronal networks or for exploring ideas about neuronal computation in a relatively straight-forward setting.

This model is easy to solve; if I_e is constant we have already solved it above up to messing around with constants:

$$V(t) = E_L + R_m I_e + [V(0) - E_L - R_m I_e] e^{-t/\tau_m} \tag{15}$$

If I_e is not constant it may still be possible to solve the equation, but in any case the equation can be solved numerically on a computer. An example in given in Fig. 3.

One thing to notice is that there are no spikes for low values of the current. Looking at the equation

$$\tau_m \frac{dV}{dt} = E_L - V + R_m I_e \tag{16}$$

so the equilibrium value for constant I_e, the value where V stops changing, is

$$\bar{V} = E_L + R_m I_e \tag{17}$$

Now if this value $\bar{V} > V_T$ then as the neuron voltage increased towards its equilibrium value, $\bar{V}$, it would reach the threshold, V_T, and spike. Hence, if $\bar{V} > V_T$ the neuron will spike repeatedly. However if $\bar{V} < V_T$ then the neuron will not spike for that input because it will never reach threshold. We won't do it here[1], but, in fact, since we can solve the equations for constant I_e we can work out the $f-I$ curve, the relationship between the firing rate and the input current. It is plotted in Fig. 4.

The Hodgkin-Huxley equation

The nonlinear dynamics that neurons rely on to form spikes arise from the voltage-gated channels; these are ion channels whose conductance varies as the voltage varies. They are, crucially, are ion selective: only sodium ions can pass through a sodium gate, only potassium ions through a potassium gate. This means that there are different currents for each type of ion, whereas in the integrate-and-fire neuron there is just the leak current, and the conductances of these currents aren't constant, as they are for the leak, but rather have complicated, non-linear

[1] This calculation is described in `note_on_the_f-I_curve.pdf`

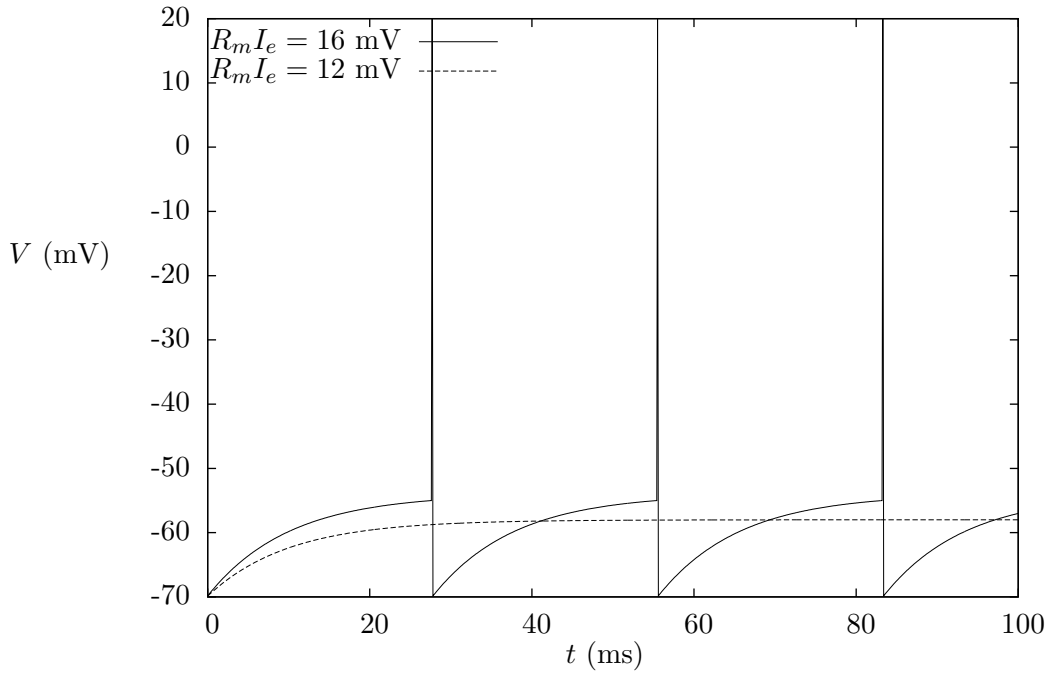


Figure 3: An integrate and fire neuron with different inputs. For $R_mI = 12$mV the voltage relaxes towards the equilibrium value $V = E_L + R_mI_e = -58$ mV. It never reaches the threshold value of $V_T = -55$mV. For $R_mI = 16$ mV the voltage reaches threshold and so there is a spike; the spike is added by hand, in this case by setting V to 20 mV for one time step. The voltage is then reset. Here $\tau_m = 10$ ms.

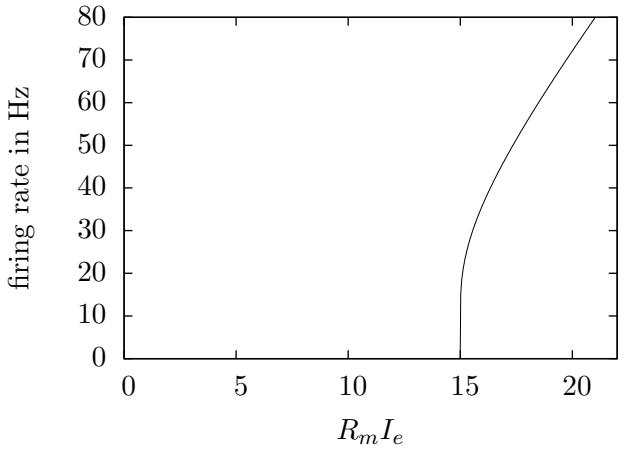


Figure 4: The firing rate, that is spikes per second, for the integrate and fire neuron with different constant inputs with $\tau_m = 10$ ms, $V_T = -55$ mV and both the leak and reset given by -70 mV. Notice how there is no firing until a threshold is reached and after that the firing increases very quickly.

function. These currents together gives the Hodgkin-Huxley equation, basically it equates the rate of change of V to a set of currents, the leak current giving the roughly linear behavior below threshold we saw in the integrate and fire model and the gated channels which become important near the threshold and whose behavior gives rise to the action potential:

$$C_m \frac{dV}{dt} = \text{currents} \tag{18}$$

The currents depend on the conductances for the different ions and so the Hodgkin-Huxley model is referred to as a conductance based model; since the conductances depend on gated channels the equations describing them are called gating equations.

The Hodgkin-Huxley equation has only one voltage, it pretends the neuron is just a point. More complicated models include the spatial extent of neurons and model the neuron as being composed of compartments, with a Hodgkin-Huxley equation in each compartment and what is called a cable equation describing how the compartments are linked together.

Computational tools

People in computational neuroscience usually use either MATLAB or Python or they use a specialized simulation tool such as GENESIS or NEURON or NEST. These simulation tools are optimized to efficiently simulate large complicated neurons, in the case of GENESIS or NEURON, or large and complicated networks of neurons, in the case of NEST. The simulation tools have been writen over many years and can be quite complicated and idiosyncratic, however, NEURON at least, now has a Python interface.

MATLAB has some advantages, it has a very large user base across many parts of applied mathematics, a huge collection of libraries and package. There is a free community authored version called Octave, they are not completely compatible and Octave lacks many libraries and features. Matlab uses a matrix paradigm which is easy to use and quick when you get used to it. Python is a proper programming language, with a nicer language structure than Matlab, it is free and open and has many libraries, though perhaps not as many as Matlab.

The most specialized tools include

- Brian, a python package for writing neuron simulations.
- NEURON for large biophysical simulations of neurons.
- GENESIS, the rival to NEURON.
- NEST, for simulating very large networks of simple neurons: http://www.nest-initiative.org/
- XPP, a powerful tool for investigating dynamical systems of the sort found in neuroscience.
- Open Source Brain, a set of tool for sharing neuronal simulations.
- NeuroML, a markup language for neuron models.

References

[1] Traub RD, Bibbig A. (2000). A model of high-frequency ripples in the hippocampus based on synaptic coupling plus axonaxon gap junctions between pyramidal neurons. The Journal of Neuroscience, 20: 2086–2093.

[2] Lapicque, L. (1907). Recherches quantitatives sur l'excitation lectrique des nerfs traite comme une polarisation. J. Physiol. Pathol. Gen, 9:620–635.