VS 265: Problem Set 1

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today

1 Problem 5: Membrane Equation

Implementation

Simulate the membrane equation to show how the voltage across the cell membrane will change in response to a step input current, I(t). Numerically simulate the solution for a duration of least 500 milliseconds with the following parameters:

- Initial Condition $V(0) = V_{rest} \equiv 70mV$
- Membrane capacitance: $C = 100pF$
- $I_{in}(t) \equiv I(t) = \begin{cases} 100pA & t \geq 100ms \\ 0pA & t < 100ms \end{cases}$
- $G_{Leak} = 5nS$.

You may find it easiest to run this simulation using the Euler method, but you are free to use convolution or any other method.

- Try different values of G_{Leak} and C to explore how these parameters affect the rise time and resulting membrane voltage. Plot the results of your simulation and interpret your findings.
- Now examine the effect of adding a single synaptic input that opens a set of sodium channels (ΔG_{Na}). Sweep ΔG_{Na} from $0nS$ to $50nS$ and plot the resulting equilibrium membrane potential (by solving for V at $\frac{dV}{dt} = 0$) over this range.

- Now do the same for an inhibitory synaptic input that opens a set of potassium channels by varying ΔG_K over the same range and superimpose on the plot above.

- Finally, in a second plot, show the effect of shunting inhibition by simulating an inhibitory synaptic input that causes chloride channels to open by some amount (say $\Delta G_{Cl} = 10nS$) and now sweep ΔG_{Na} over the same range as above. How does this compare to what you would expect from a linear superposition? (plot as a dashed line). Explain your results.

1.1 Simple LIF with Input Current

We begin by studying the membrane equation

$$\tau \frac{dV}{dt} + V = V_r + \frac{I(t)}{G_{leak}}, \tag{1}$$

with initial condition and parameter values defined above. Here, $\tau = \frac{C}{G_{leak}}$ and the constant $G_{leak} = G_{Na} + G_K + G_{Cl}$ represents the ambient level of open channels. We would like to study how the membrane potential V is affected by the input current, the number of open ambient channels, and the capacitance C of the membrane. Naturally, if we wanted to we could extend (1) to a spiking model by introducing some threshold V_{th}. Then the input current would increase the membrane potential until the threshold is reached, followed by a spike and a resetting of the membrane potential to its resting potential. In the standard integrate-and-fire model there is no time-dependent memory term in the equation, i.e. the second term on the left hand side of (1) is absent, which is a shortcoming of the model. Without this term, any signal that is below the threshold will keep its voltage indefinitely, which is not plausible. This problem is solved by the above leaky integrate-and-fire (LIF) model in (1). In this case, the voltage of below-threshold signals slowly decreases or "leaks" due to the natural diffusion of ions.

To simulate (1) numerically, we use the well-known constant step size 4^{th}-order Runga-Kutta scheme (RK4) presented below. Consider an ordinary differential equation (ODE)

$$\begin{aligned} \frac{dy(t)}{dt} \equiv y'(t) &= f(y(t), t) \\ y(t_0) &= y_0. \end{aligned}$$

For a constant step size $h = \Delta t$, we aim to find an approximate solution $\hat{y}$ to the ODE at time $t_0 + h$. Once the solution is found for one time step, the algorithm may be applied iteratively to find the solution up to some final time t_f . The RK4 scheme uses four slope approximations of the function at time t_0:

$$\begin{aligned} k_1 &= f(y_0, t_0) \\ k_2 &= f(y_0 + k_1 \frac{h}{2}, t_0 + \frac{h}{2}) \\ k_3 &= f(y_0 + k_2 \frac{h}{2}, t_0 + \frac{h}{2}) \\ k_4 &= f(y_0 + k_3 h, t_0 + h) \end{aligned}$$

Then a 4^{th}-order approximate solution for the ODE at time $t_0 + h$ is given by

$$\hat{y}(t_0 + h) = y_0 + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4).$$

In order to iterate to achieve an approximate solution at the $(n+1)^{th}$ time step, we replace y_0 by $\hat{y}_n = \hat{y}(t_0 + nh)$, the approximate solution at the n^{th} time step, and t_0 by $t_n = t_0 + nh$, the n^{th} time step.

Now that we have an appropriate numerical scheme for simulating (1), we can explore the effects the conductance and capacitance. We consider two cases: 1) a fixed capacitance $C = 100pF$ and varying conductance $G = 3, 5, 10nS$, and 2) a fixed conductance $G = 5nS$ and varying capacitance $C = 50, 100, 200, 300pF$. The results are given in Figure 1.

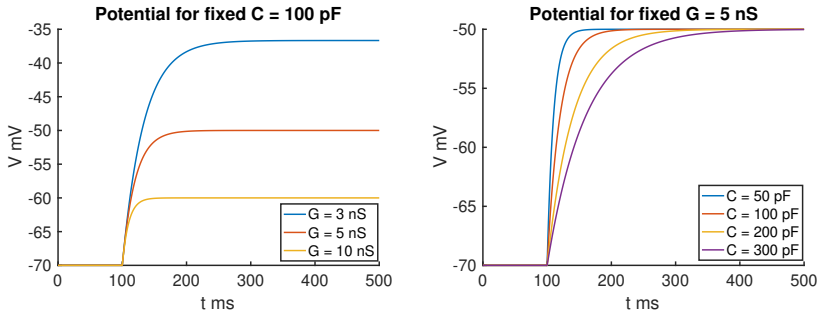

Figure 1

Let's first examine the plot where the capacitance is fixed and the conductance varies. We see that as the conductance increases, the resulting membrane potential decreases. This should come as no surprise since as a result of Ohm's law, we know that conductance is inversely proportional to voltage. Biologically, increasing the conductance G_{leak} amounts to a larger number of ions being able to "leak" or diffuse through open ambient channels, which lowers the membrane potential closer to the resting potential.

Moving on to the case for a fixed conductance and varying capacitance, we see that an increase capacitance has no effect on the limiting/maximum membrane potential. However, as capacitance increases we do see a delay in reaching the limiting potential. Both of these are due to the fact that the only place C arises in (1) is in the numerator of τ. Hence, it should only effect the growth/decay rate of the potential. This should also come as no surprise since when current begins flowing, an increased capacitance means the capacitor will take longer to charge, resulting is a slower time to reach a stable membrane potential.

1.2 Adding Na and K synaptic channels

By adding a Na (sodium) synaptic channel, equation (1) becomes

$$\tau \frac{dV}{dt} + V = \frac{V_r G_{leak} + V_{Na} \Delta G_{Na} + I(t)}{G_{tot}}, \tag{2}$$

where $V_{Na} = 55mV$ is the reversal potential of Na, $G_{tot} = G_{leak} + \Delta G_{Na}$ is the total conductance, and $\tau = \frac{C}{G_{tot}}$. We aim to explore the effects of Na synaptic input against the ambient level of open channels, hence, the ΔG_{Na} term. We also aim to study the effect of separately adding a K (potassium) synaptic channel. In this case, the equation for the membrane equation is identical to (2) but with $V_{Na}\Delta G_{Na}$ replaced by $V_K \Delta G_K$, and the new total conductance becomes $G_{tot} = G_{leak} + \Delta G_K$. Here, $V_k = -92mV$ is the reversal potential of K. In order to study the separate effects of these two synaptic channels, we leave $C = 100pF$ and $G = 5nS$ fixed and vary ΔG_{Na} and ΔG_K from 0 to $50nS$.

Instead of simulating equation (2) directly, we study the equilibrium solution, i.e. we set $\frac{dV}{dt} = I(t) = 0$. Furthermore, we consider the superposition-like effect of combining both Na and K synaptic inputs with the same level of conductance, i.e. $\Delta G_{Na} = \Delta G_k$. In this case, the equilibrium solution is

given by

$$V = \frac{V_r G_{leak} + V_{Na}\Delta G_{Na} + V_K \Delta G_K}{G_{tot}}.$$

The results are given in Figure 2.

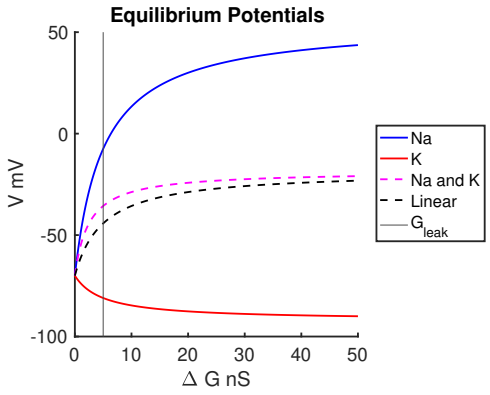

Figure 2

First, we see that Na (blue) exhibits an excitatory response by depolarizing the membrane while K (red) is inhibitory and hyperpolarizes the membrane. Furthermore, we see that changing either ΔG_{Na} or ΔG_K has a nonlinear response on the membrane potential due to the nonlinearity introduced by G_{tot} in the denominator of the membrane equation. We also notice that as either ΔG increase, both Na and K responses plateau. If we consider just the case for Na, sending $\Delta G_{Na} \to \infty$ in the equilibrium membrane equation shows that the potential approaches the reversal potential of Na. Physically this makes sense because for large ΔG_{Na}, the Na ions are near equilibrium. An analogous statement can be made for K. We also see that K plateaus much more quickly than Na. This is due to the fact that K has a reversal potential that is closer to the membrane's resting potential.

When combining both Na and K (dashed magenta), we do see that the excitatory response is decreased by the inhibitory response. This happens almost by linear subtraction (in an arithmetically averaged sense) due to the fact that both of the reversal potentials of Na and K are not very close to the membranes resting potential. When trying to determine whether or not a function can predicted linearly by two other functions, the notion of pure additivity is not typically considered, possibly outside of waves and group theory. In our case, it's immediately clear that the membrane potential can

never be purely additive with respect to synaptic inputs due to the initial conditions. The potential from either Na or K alone is V_r when $\Delta G_{Na} = \Delta G_K = 0$. Hence, the sum of the two potentials will result in $2V_r$, and thus, violating the fact that the potential for the combined synaptic inputs must also be V_r when each synaptic conductance is zero. In general, we want to consider linear combinations of predictors or bases. This is particularly seen in linear algebra, linear regression, and linear ODEs and PDEs. It should also be clear just from examining the equilibrium equations that this doesn't work either. The potential resulting from both Na and K cannot be written as a linear combination of the potential resulting from Na alone and the potential resulting from K alone, even if $\Delta G_{Na} = \Delta G_K$. This is inherently due to the nonlinearity arising from G_{tot}. However, we can get pretty close. Without going through the details of solving the optimization problem, the two coefficients seem close to one half. Therefore, I will just refer to the arithmetic average (dashed black). In this case, the membrane potential with both synaptic inputs is

$$\frac{2V_r G_{leak} + \Delta G(V_{Na} + V_K)}{2(G_{leak} + \Delta G)},$$

and the sum of the two individual inputs gives

$$\frac{V_r G_{leak} + \Delta G(V_{Na} + V_K)}{G_{leak} + 2\Delta G}.$$

We see that the two are close, but slightly off due to the nonlinearity of G_{tot}, i.e. there is some inherent divisive inhibition going on, even if it's only a small amount. This is reflected in Figure 2.

1.3 Shunting inhibition of Cl

We now explore the effects of adding a Cl (chloride) synaptic input. For simplicity, we consider only the interaction between Na and Cl. In this case, $V_{Cl} = -65mV$ is the reversal potential of Cl. In Figure 3, we compare a Na input (blue), a Cl input (red), the combined inputs of Na and K (dashed magenta), and a linear combination (average) of Na and Cl inputs (dashed black).

The first thing to notice is that the reversal potential of Cl is very close to the resting potential of the membrane. Hence, Cl has only a minute

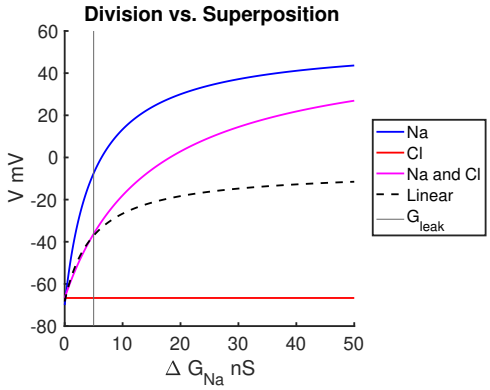

Figure 3

effect on the membrane potential. However, $\Delta G_{Cl} = 10nS$ does increase the total conductance G_{tot}, which again gives rise to divisive, or shunting, inhibition of the membrane's potential. As per my comments in the previous section, it's obvious (for the same reasons) that the potential resulting from the combined inputs of Na and Cl cannot be equal to the sum of the two individual potentials. Hence, again I looked at a linear combination and used an average for simplicity. Unlike in the case for Na and K, the actual combined potential for Na and Cl and the linear guess, agree up to G_{leak}, but quickly diverge after that, i.e. G_{leak} is the ambient level at which point the inhibition transitions from linear to divisive. This seems to support Weber's law where G_{leak} is the difference threshold, i.e. "the minimum amount by which stimulus intensity must be changed in order to produce a noticeable variation in sensory experience." [USD coglab]