VS 265: Problem Set 1

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

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).

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, $\tau = \frac{C}{G_{leak}}$. 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 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 is 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 iteratlvely 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:

$$\begin{aligned} k1 &= f(y_0, t_0) \\ k2 &= f\left(y_0 + k_1\frac{h}{2}, t_0 + \frac{h}{2}\right) \\ k3 &= f\left(y_0 + k_2\frac{h}{2}, t_0 + \frac{h}{2}\right) \\ k4 &= f(y_0 + k_3 h, t_0 + h). \end{aligned}$$

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: a fixed capacitance $C = 50[pF]$ and varying conductance $G = 3, 5, 10[nS]$, and a fixed conductance $G = 5[nS]$ and varying capacitance $C = 50, 100, 200, 300[pF]$. The results are given in Figure 1. Let's first

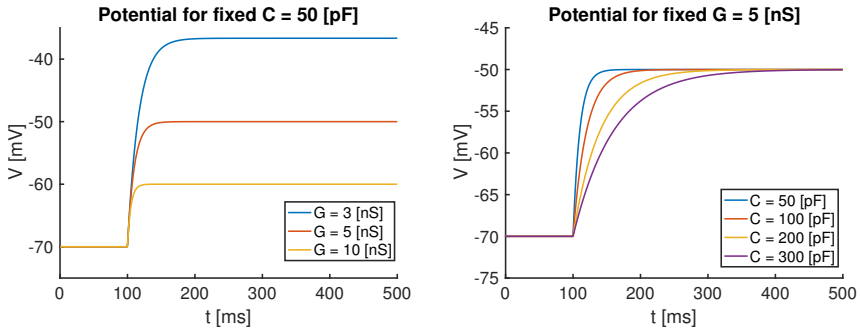

Figure 1

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. 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. 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 $V_{Na} = 55[mV]$ is the reversal potential of Na, the total conductance is $G_{tot} = G_{leak} + \Delta G_{Na}$, 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 capacitance becomes $G_{tot} = G_{leak} + \Delta G_K$. Here, $V_K = -92[mV]$ is the reversal potential of K. In order to study the separate effects of these two synaptic channels, we leave $C = 50[pF]$ and $G = 10[nS]$ fixed and vary ΔG_{Na} and ΔG_K from 0 to $50[nS]$.

Instead of simulating equation (2) directly, we study the equilibrium solution, i.e. we set $\frac{dV}{dt} = 0$. We compare the contrasting results of Na and K on the equilibrium membrane potential in Figure 2. In the first plot, we see that Na (solid lines) exhibits an excitatory response by depolarizing the membrane while K (dashed lines) is inhibitory and hyper-polarizes the membrane. Furthermore, we see that changing either of the differences ΔG_{Na} or ΔG_K has a nonlinear response on the membrane potential, i.e. changing a difference effects the denominator G_{tot}. In fact, by directly examining the equilibrium solution to (2), we see that sending $\Delta G_{Na} \to \infty$ results in $V \to V_{Na}$. An analogous statement can be said for K. Both of these behaviors are seen in the first plot of Figure 2.

Additionally, in the second plot in Figure 2, we observe the superposition principle, i.e. a decrease in the excitatory potential of Na by the linear subtraction of K. An equilibrium potential for only Na ($\Delta G_{Na} = 50$) is plotted in blue and an equilibrium potential for only K ($\Delta G_K = 50$) is plotted in red. The potential when considering both Na and K is the dashed line, i.e. for

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

The weighted subtraction effect of combing both the Na and K results from the fact that Na is excitatory, K is inhibitory, and that both of their reversal potentials are not close to the membrane's resting potential, i.e. an increase in each of their conductance differences changes the potential is opposite directions.

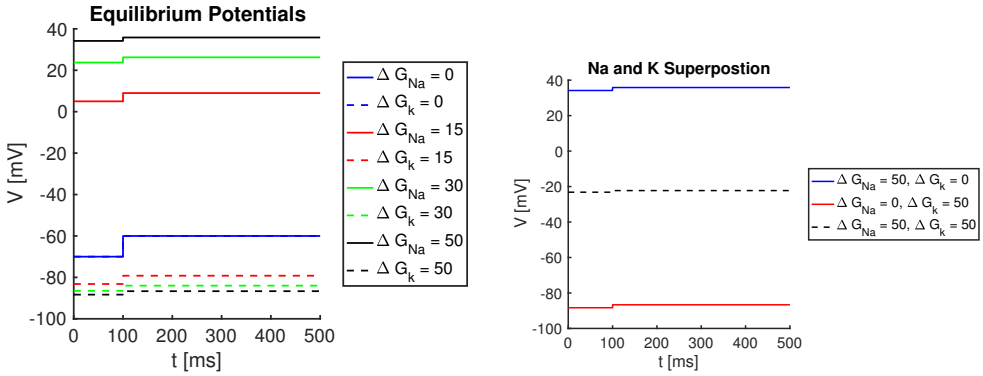

Figure 2

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. We study equation (2) with $V_{Cl}\Delta G_{Cl}$ added to the numerator and $G_{tot} = G_{leak} + \Delta G_{Na} + \Delta G_{Na}$. Here, $V_{Cl} = -65[mV]$ is the reversal potential of Cl. In Figure 3, we compare a Na synaptic input to that of combined Na and Cl synaptic inputs for fixed $\Delta G_{Cl} = 10[nS]$. The potentials resulting only from Na are plotted with solid lines while the dashed lines correspond to adding in Cl. Each color corresponds to distinct values of ΔG_{Na}.

The most obvious result is for case with no Na, i.e. the blue lines. We see that Cl has little to no effect on the membrane potential. This is the result of Cl's reversal potential being nearly identical to the membrane's resting potential. However, as seen below, adding in Cl increases the membrane's total conductance G_{tot}, which effectively decreases the effect of Na (or K) by division. This gives us the shunting inhibition effect of Cl.

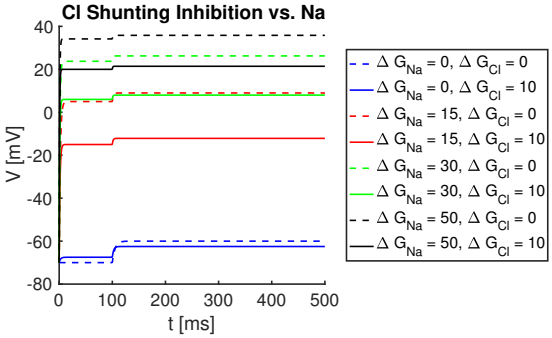

Figure 3

While Figure 3 shows the effects of shunting inhibition on Na, in Figure 4 we verify that the effect of Cl on Na is indeed not a result of linear subtraction. The blue line is the membrane potential with only Cl input while the red line is the potential with only Na input. The solid black line is the actual result of using both Na and Cl inputs while the dashed black line is what we would expect from linear superposition/subtraction. Clearly, adding a Cl input with Na does not result in linear subtraction as it does for K.

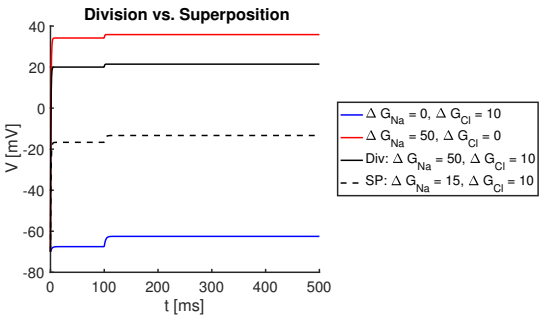

Figure 4