Learning objectives and outcomes:

This problem set investigates the role of synapses in two-compartment cell models. In particular, we will analyze how the location of an inhibitory synapse affects the computational properties of a cell in a circuit mediating an escape response. More fundamentally, we will analyze how these biophysical and computational changes mediate different behaviors and are thus fundamental for survival of the species.

The role of synapses and the computational properties of 2-compartment models are discussed in lectures 6 & 7. Furthermore, this PSET is based on the assigned reading for lecture 7 (Vu and Krasne, 1992).

The expected learning outcomes for this PSET are:

- Analyze two-compartment cell models and write current balance equations using Krichoff's and Ohm's law.
- Be acquainted with shunting inhibition.
- Use the current balance equations to understand and analyze the different behaviors that arise when inhibition is located out on a dendrite or near the soma.
- Make plots to visualize relative and absolute suppression in 2-compartment cell models.
- Disentangle in which scenarios excitation can override inhibition.
- Be able to present your results as a cohesive and well-structured report.

MATLAB functions you will need:

This PSET deals mostly with analytical work and plotting functions in MATLAB. As a reminder the main plotting functions are: `figure, plot, subplot, xlim, ylim, title, xlabel, ylabel, legend, hold on, hold off.`
To generate plots with a logarithmic scale on the x-axis use `semilogx.` To generate a vector whose elements are logarithmically spaced use `logspace.`

For more information on MATLAB functions and commands, check the provided cheat sheet or the more extensive MATLAB documentation.

SYNAPSES AS COMPUTATIONAL DEVICES

Escape response in the crayfish: computational roles of somatic (proximal) and dendritic (distal) inhibition

Vu and Krasne (1992) studied the role of inhibition at two locations relative to the soma: near the soma (proximal configuration) and out in the dendrite (distal configuration). The

main point of their study is to understand how inhibition location affects the initiation of the LG escape response in the crayfish[1].

In their analysis they argue that proximal (called "recurrent" in Vu and Krasne) inhibition can mediate an absolute suppression of the escape behavior. In contrast, distal (called "tonic" in Vu and Krasne) inhibition mediates a relative suppression that can always be overridden by sufficient strong excitatory input. These mechanisms are important to distinguish different behavioral scenarios. For an animal, it is often necessary to suppress certain behaviors completely, while under other conditions the threshold for initiating a behavior should only be elevated but the behavior should not be completely suppressed. Altogether, once an escape response is initiated no other escape reflex should be triggered. However, during feeding or exploratory behaviors the threshold for an escape response should be set accordingly. This gives the biological background for the observed absolute and relative suppression.

In the next exercise we follow the analysis by Vu and Krasne. We will work on proximal and distal inhibition configurations on a two-compartment cell model to understand how absolute and relative suppression arise in each of these scenarios.

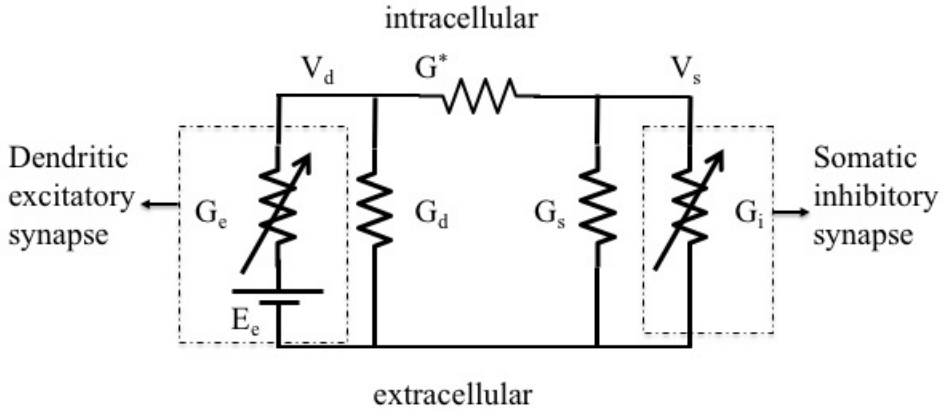
An inhibitory synapse produces different effects on the target cell depending on the value of the synaptic reversal potential (E_{syn}). If the synaptic reversal potential is below the target cell resting potential, inhibition will be hyperpolarizing and therefore will have a subtractive effect. In contrast, if the synaptic reversal potential is identical (or very close) to the membrane resting potential, inhibition will have a "shunting" effect. Shunting inhibition is termed "shunting" because the synaptic conductance short-circuits currents that are generated at adjacent excitatory synapses. If a shunting inhibitory synapse is activated, the input resistance is reduced locally and, following Ohm's law, the amplitude of subsequent excitatory postsynaptic potentials (EPSPs) is reduced. In this case inhibition per se does not affect the membrane potential as much as in the hyperpolarizing case, however it makes it harder to excite the cell.

For simplicity, and to be consistent with lecture notes we will call the inhibition locations somatic (proximal in the paper) and dendritic (distal in the paper). It is important to notice that crayfish neurons have a ganglionic morphological organization and that action potentials are not initiated in the soma but rather in a dendrite near the soma. This is the origin of the proximal and distal nomenclature, to refer to dendritic locations near and far from the soma respectively.

Problem 1: Somatic inhibition

In the circuit below we depict a two-compartment model where the inhibitory synapse is located in the somatic compartment (proximal configuration).

[1] Check https://www.jove.com/video/1297/recordings-of-neural-circuit-activation-in-freely-behaving-animals for a video exhibiting the behavior (Heberholz, 2009)



Notice that G^* is a longitudinal resistor linking/coupling the two compartments. Also, to simplify the analysis we have set the resting membrane potential at 0 mV. As inhibition is of the shunting type we have set E_i to 0 mV and thus there is no need to include a battery for this synapse. V_d and V_s are labels to indicate the membrane potential at the dendritic and somatic compartments respectively.

With this information answer the following questions:

1. **Using Kirchoff's and Ohm's law, write two equations, each one expressing the sum of currents at the dendritic and somatic compartments respectively.**
2. **Combine the above two equations to get a single expression for the voltage at the somatic compartment that does not depend on the voltage at the dendritic compartment. (i.e to eliminate V_d). You should reach the following expression:**

$$V_s = \frac{G_e G^* E_e}{G^* G_d + G_s G_d + G_s G^* + G_e\left(G^* + G_i + G_s\right) + G_i\left(G_d + G^*\right)}$$

3. **Next consider the following parameter values:**

$$G_d = G_s \quad G^* = \frac{1}{9} G_s \quad G_s = 1$$

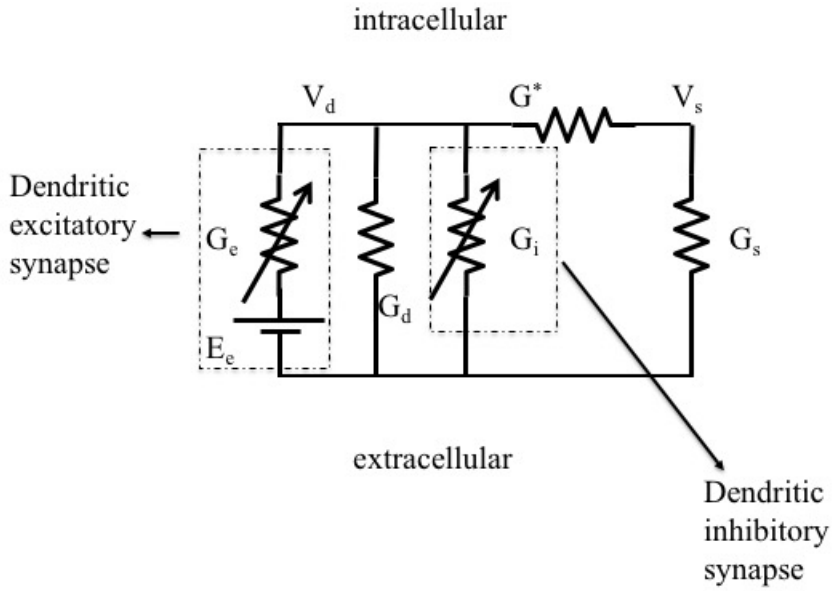
$$\alpha = \frac{G_i}{G_d} = \{0, 0.2, 0.5, 1, 2, 5\} \quad E_e = 100\text{mV}$$

where α controls the inhibitory strength. Simplify the above expression for V_s using these parameter relations.

4. **Using the expression from question 3, plot the voltage at the soma as a function of G_e for each level of inhibition. Use a logarithmic scale on the x-axis and set its range between 0.01 and 1000. Overlay all the curves in a single panel. This should look similar to figure 1A in Vu and Krasne (1992)[2].**
5. **Note that in the previous plot, strong inhibition is always capable of suppressing the voltage at the soma. To show this, take the limit of G_e going to infinity on the simplified equation for V_s. Write down the expression you got for this limit. In this limit, is V_s dependent or independent of inhibition? Explain and relate to the plot in question 4. What type of suppression is this?**

Problem 2: Dendritic inhibition

In the circuit below we depict a two-compartment model where the inhibitory synapse is located in the dendritic compartment with the same considerations as in problem 1.



With this information answer the following questions:

1. **Using Kirchoff's and Ohm's law, write two equations, each one expressing the sum of currents at the dendritic and somatic compartments respectively.**
2. **Combine the above two equations to get a single expression for the voltage at the somatic compartment that does not depend on the voltage at the dendritic compartment. (i.e. to eliminate V_d). You should reach the following expression:**

[2] As in the paper, consider that the threshold for initiating an escape response is 9 mV.

$$V_s = \frac{G_e G^* E_e}{G^* G_d + G_d G_s + G^* G_s + G_e\left(G^* + G_s\right) + G_i\left(G^* + G_s\right)}$$

3. **Next consider the following parameter values:**

$$G_d = G_s \quad G^* = \frac{1}{9} G_s \quad G_s = 1$$

$$\alpha = \frac{G_i}{G_d} = \{0, 0.2, 0.5, 1, 2, 5\} \quad E_e = 100\text{mV}$$

where α controls the inhibitory strength. Simplify the above expression for V_s using this parameter relations.

4. **Using the expression from question 3, plot the voltage at the soma as a function of G_e for each level of inhibition. Use a logarithmic scale on the x-axis and set its range between 0.01 and 1000. Overlay all the curves in a single panel. This should look similar to figure 1A in Vu and Krasne (1992)[3].**
5. **Note that in the previous plot, strong excitation is always capable to overcome inhibition. To show this, take the limit of G_e going to infinity on the simplified equation for V_s. Write down the expression you got for this limit. In this limit, is V_s dependent or independent of inhibition? Explain and relate to the plot in question 4. What type of suppression is this?**

References:

Vu, E. T. and Krasne, F. B. (1992). Evidence for a Computational Distinction Between Proximal and Distal Neuronal Inhibition. *Science* **255**(5052): 1710-2.

Herberholz, J. (2009). Recordings of Neural Circuit Activation in Freely Behaving Animals, *Journal of Visualized Experiments* 29, e1297.

[3] As in the paper, consider that the threshold for initiating an escape response is 9 mV.

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