Exercise 6: T-type Ca^{2+}-channels

In this exercise, you will explore the properties of an ion channel type called T-type Ca^{2+} channels (hereby called T-channels). T-channels may generate so called Ca^{2+}-spikes, which in turn may lead to bursts of action potentials such as that seen in Fig. 1B. A neuron's T-channel mediated response does not only depend on the total amount of T-channels that it possesses, but also on how these are distributed over the somatodendritic membrane. In the computational study by Allken et al. 2014 [1], we explored the relationship between T-channel distribution and different neuronal response properties. In this exercise you will perform a simplified version of that project.

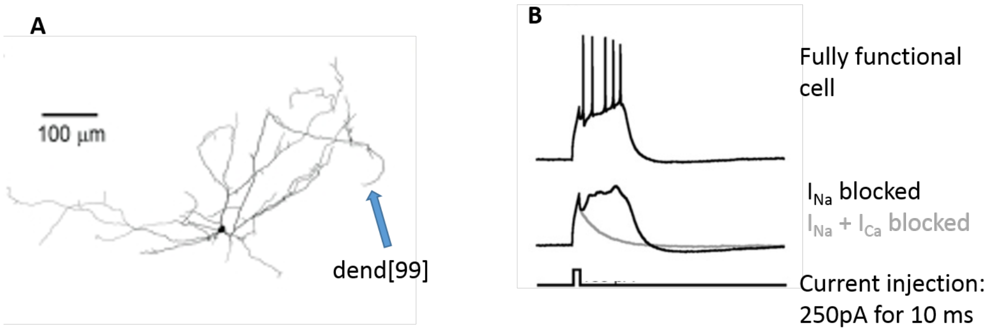

Figure 1: Model of an interneuron in the visual thalamus. **A** Morphology. dend[99] refers to a compartment in the distalmost tip of a dendrite. **B** "experimental" data (manipulated for use in this exercise). A brief (10 ms), strong (0.25 nA) current injection to the soma evoked the following qualitative response features: (1) The fully functional neuron responded with a burst containing a few APs (top). (2) When Na-channels were blocked, the APs were eliminated (middle, black line), and a Ca-spike (bump) underlying the burst was revealed. (3) When T-channels were blocked, a passive response could be observed (grey line).

You will be given an example script, `exercise_6.py`, that you can develop further to solve this exercise. The example script contains:

- A model of a thalamic interneuron with a detailed morphology (Fig. 1A).
- Three types of ion channels: Na^+ and K^+ channels for action-potential generation, and T-channels. The conductances (g_{Na}, g_{Kdr} and g_{CaT}) are currently set to zero, so that the neuron is passive.
- A current clamp inserted in the soma. You must set its amplitude and duration.
- A synapse inserted at the tip of a dendrite. You must activate it.
- A figure that plots the membrane potential at 4 different locations (soma + 3 locations along a selected dendritic branch).

[1] Allken et al. (2014) *The subcellular distribution of T-type Ca^{2+} channels in interneurons of the lateral geniculate nucleus* PLoS ONE 30;9:e107780

1) Model calibration
You will now try to adapt the model so that it roughly reproduces the experimental data in Fig. 1B. For this part of the exercise, only the somatic response is relevant.

a) Make the following assumptions: (1) Only the soma contains Na^+ and K^+-channels. All other segments have g_{Na} and g_{Kdr} equal to zero. (2) T-channels are uniformly distributed over the membrane, so that g_{CaT} has the same value in all segments, including the soma [2]. Run a series of simulations where you regulate (by trial and error) the nonzero conductances g_{Na}, g_{Kdr} and g_{CaT} of the different ion channels. Try to find a set of values that give model responses as similar as possible to that seen in Fig. 1B.

P.s. You will not get a perfect match, but you should be able to reproduce essential qualitative aspects (1-3 in Fig. 1B.)

b) Describe the relative roles that the involved ion channels have in generating the burst.

c) Was the resting membrane potential the same in (1) and (2) above? Comment on the result.

2) Dendritic signalling
You will now study how signals propagate from the soma to the distal dendrites and vice versa. Keep the values for g_{Na}, g_{Kdr} and g_{CaT} that you found above.

a) In the simulations you ran in part 1 of the exercise, describe how different aspects of the somatically evoked response changed during its propagation through the dendrite. Compare the propagation of the action potentials with the propagation of the Ca^{2+}-spike (bump).

b) Instead of using a somatic current injection, explore the response to a synaptic input in the distal dendrite of the neuron (you will find the synapse implemented in the code, but must set its weight to e.g., $w = 0.015$). Describe how the synaptic response changes during its propagation towards the soma.

c) Compare the two simulations a)-b). In which direction is it easiest for a signal to travel?

3) How does the distribution of T-channels affect the neural response properties?
Experiments have been inconclusive regarding how T-channels are distributed in INs. One experiment indicated a uniform distribution [3] like the one we have considered so far in this exercise. However, another experiment indicated that the T-channel density increases with distance from soma [4]. You will now compare these two distributions.

a) Change the distribution of T-channels, so that the T-channel density increases linearly with distance (d) from the soma:

$$g_{CaT}(d) = \beta \cdot (1 + 0.04d), \tag{1}$$

where d is inserted with units of μm. The constant β should be determined so that the distribution in Eq. 1 gives the same total number of T-channels as our previous (uniform)

[2] g_{Na} and g_{Kdr} typically have values in the range 0.01 - 1 S/cm^2 (NEURON units). g_{CaT} typically has values in the range $10^{-5} - 10^{-3}$ cm/s (NEURON units). For technical reasons, g_{CaT} has units of a permeability and not conductance

[3] Parajuli et al. 2010 *Subcellular distribution of α 1G subunit of T-type calcium channel in the mouse dorsal lateral geniculate nucleus.* J Comp Neurol, 518(21), 4362–4374

[4] Munsch et al. 1997 *Voltage-activated intracellular calcium transients in thalamic relay cells and interneurons* Neuroreport, 8(11), 2411–2418

distribution. Otherwise it would not be meaningful to compare results. For the particular distribution and cell morphology that we have here, it can be shown that the normalization constant is:

$$\beta = 0.1054 \cdot \tilde{g}_{CaT}, \tag{2}$$

where $\tilde{g}_{CaT}$ is the value that you found for the uniform conductance in exercise 1a.

P.s. In the example code, the command *h.distance()* was used to set the soma compartment as the reference point for distance measures. In other segments, use the command *h.distance(0.5)* to obtain the distance between the reference point (soma) and the midpoint (0.5) of the relevant segment.

b) Repeat the simulations in exercise 1 and 2 using the new T-channel distribution. Determine which of the two distributions (*uniform* versus *linearly increasing with distance*) that are facilitates the following response properties:

- The somatic response to somatic current injections (paragraph 1).
- The response in distal dendrites to somatic current injections (paragraph 2).
- The response in the soma to synaptic input in a distal dendrite (paragraph 3).

4) Optional: Dendritic Na^+ and K^+ channels

Presumingly, your simulations in Paragraph 1 showed that action potentials (evoked in the soma) only gave rise to small voltage deflections in the tip of the dendrite. Conversely, experiments have shown that the action potential shape and amplitude are fairly well preserved when they propagate from the soma to the distal dendrites in these interneurons [5]. This indicates that not only the soma, but also the dendrites contain a nonzero density of Na^+ and K^+ channels.

a) Insert Na^+ and K^+ channels (with some density/conductance) in the dendrites, and see if you can can make the model account for this observation.

b) How is the response to a synaptic input when you have the dendritic Na^+ and K^+ conductances that you found above?

5) Optional: Other distributions of T-channels

Try to implement some other distributions for the T-type Ca^{2+} channels. In order to do this, you need to make an algorithm to calculate the normalization (cf. eq. 2), so that the total conductivity in the cell remains the same when you change from one distribution to another. Generally, the total conductivity of an ion cannel x in the cell is given by

$$G_x^{tot} = \sum_k g_{x,k} A_k, \tag{3}$$

where the sum is taken over all neural segments k, and where $g_{x,k}$ and A_k are the conductance area of segment k.

[5] Casale et al. 2011 *Active Action Potential Propagation But Not Initiation in Thalamic Interneuron Dendrites.* Journal of Neuroscience, 31(50), 18289–18302