Note to answers - Assignment 1: AMPA and NMDA

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Question 1 (5 points) Show how you calculated the value for nseg. How does nseg depend on the membrane leak?

Answer: λ is about 350μm (see lecture notes for equation), so we need about 27 segments. (for the soma one segment suffices)

Question 2 (5 points) First consider a case where the synapse is on the soma. Model the AMPA receptor as an exponential synapse with a 5ms timeconstant, and the NMDA receptor as one with a 100ms timeconstant. Although our neuron model does not spike, assume that the neuron fires whenever the voltage reaches a certain value. Consider two extreme limits: a very short and a very slow membrane time-constant. How should the conductances of AMPA and NMDA be related in either case to be equally responsible for a spike (i.e. give the same depolarization)? Compare your findings to simulations and discuss any mismatch.

- In the limit of short τ_{mem} the voltage is directly following the synaptic current, so peak voltage produced by NMDA should equal the peak produced by AMPA if their peak conductances are the same.
- In contrast for very slow τ_{mem} it is the charge $Q = \int_0^\infty I(t)dt$ that determines the final membrane voltage. In other words AMPA needs to be a factor τ_{NMDA}/τ_{AMPA} bigger. (Another way of seeing that is to note that the fast AMPA components are filtered out by the membrane).
- If we assume that the current does not depend on post voltage (justifyable because spike thresholds are typically far from the reversal potential of NMDA or AMPA), you can use the equation for $V(t)$ from the I&F chapter which gives it as a difference of exponentials. You can determine the peak time t_p for which $\frac{dV(t)}{dt} = 0$. This then gives you the peak voltage and how it relates to τ_{ampa}.
- Simulation notes: 1) Note that due to saturation of the postsynaptic voltage for very strong conductances, differences might be hard to see. 2) When changing g_pas, you need to do that throughout the neuron, not just the soma. Otherwise the current just leaks away via the dendrite. 3) If you use small enough conductances, the response will be linear in the AMPA (or NMDA) conductance. So you can easily estimate the amount need to reach certain level.

Question 3 (10 points) How would the above arguments change if the synapse were on the dendrite, and the membrane time-constant were manipulated by altering the membrane leak everywhere uniformly in the neuron? Again test with simulations.

- For the (almost) leak free cable, you should retrieve the same as the above question (AMPA/NMDA ratio of timeconstants). The reason is that in this case the cable can be seen as a single compartment.

- In the limit of very strong leak, the result is also not affected (i.e. AMPA and NMDA ratio should be the same). In this case both AMPA and NMDA are much slower than the cable filter and are filtered similarly.
- Interestingly, for intermediate g_{pas}, you should see that the AMPA is filtered more strongly than NMDA.
- Note that if you simulate this case you should adjust nseg (although a too bug nseg does not hurt; it just takes more CPU time).

Next, we model more realistic synaptic responses. [...]

Question 4 (10 points) Place the synapse at various location on the dendrite. Examine the voltage response in the soma as a function of the distance of the synapse. Explore the various components that determine the time-course and the amplitude of the response and justify your claims.

- The amplitude generally decreases when the synapse is further away. (Not quite exponentially as this isn't an infinite cable), however, when the synapse is placed at the very tip, the somatic response is higher again. This unexpected effect is due to release of the Mg block. The local voltage in the dendrite is higher when it is placed at the tip of the dendrite, boosting the NMDA current. You don't see this for AMPA-only synapses.
- The AMPA component becomes less, the further the synapse is.
- You can also see changes in the peak time as the synapse is moved.

Question 5 (10 points) Make two synapses (identical, and both with AMPA and NMDA) on the dendrite, one on the far tip, one in the middle. Activate them with a variable time delay and examine the somatic response as a function of the delay. Explain your findings.

- Here you should see that the sequence of activation matters. You get the maximal response if the nearby synapse is activated about 1-2ms after the first one. You can calculate the approximate number with the cable equation.
- In addition, the response is non-linear (the response is bigger than the sum of the individual responses). The reason is again the voltage dependence of the NMDA receptor.

Question 6 (5 points) For which values of the AMPA and NMDA conductances is the effect(s) of the previous question the biggest. Give reasoning behind your findings.

- The width of the coincidence window depends on the time-constant of the synapses. As a result it becomes narrower if there is relatively more AMPA.
- The supra-linearity depends on the NMDA component.