Modeling of polygenic effects in layer V pyramidal cells: applications to schizophrenia pathophysiology

Computer Exercises using the NEURON Simulator

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Introduction

Layer V pyramidal cells (L5PCs) are a principal computational element of the cerebral circuit. An L5PC extends throughout the cortical depth with the soma located in layer V and the apical dendrite branching into the "apical tuft" in layer I, and its long axon may project to non-local cortical and subcortical areas. The apical tuft of an L5PC integrates non-local synaptic inputs, and is considered a biological substrate for cortical associations providing high-level context for low-level (e.g., sensory) inputs that arrive at the perisomatic compartments. Therefore, the ability of L5PC to integrate the apical and perisomatic inputs has been proposed as one of the mechanisms that could be impaired in hallucinating patients [Larkum 2013].

Schizophrenia (SCZ) is a polygenic mental disorder. The actual symptoms of SCZ (hallucinations, delusions, social withdrawal) are complex, but the disorder is associated with more easily quantifiable biomarkers such as deficits in prepulse inhibition (PPI), among many others. PPI is a phenomenon where the startle response, i.e. an involuntary contraction of muscles caused by a strong sensory stimulus, is weakened by presenting a relatively weak sensory stimulus (prepulse) 30 – 500 ms in advance. PPI has been shown to be diminished in SCZ patients [Turetsky et al. 2007].

More than a hundred genetic loci are implicated with the risk of SCZ [Ripke et al. 2014]. These loci include many ion-channel-encoding genes that are expressed in L5PCs. In this exercise, building upon the approach of [Mäki-Marttunen et al. 2016], we study the effects of SCZ-associated ion-channel and calcium-transporter-encoding genes on L5PC electrophysiological properties. In particular, we explore how the variants of SCZ-associated genes affect the response to a pair of inputs at the apical dendrite of an L5PC, drawing a possible link to the clinically observed endophenotype PPI.

Assignment

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The neuron model of [Hay et al. 2011] is used. The user interface allows certain variants from [Mäki-Marttunen et al. 2016] to be implemented as changes of model parameters. These variants are taken from functional genomics literature and downscaled so that each of them (when implemented separately) only has a small effect on the firing frequency and action potential shape of the L5PC. The model parameters that these model variants affect typically control the half-voltage, slope or time constants of ion channel activation and inactivation. The transmembrane currents that the considered genes affect are the following: high-voltage activated (HVA) Ca^{2+} current (*CACNA1C*, *CACNB2*, and *CACNA1D*),

low-voltage activated (LVA) Ca^{2+} current (*CACNA1I*), transient Na^{+} current (*SCN1A*), transient and persistent Na^{+} currents (*SCN9A*), persistent K^{+} current (*KCNB1*), Ca^{2+}-activated K^{+} current (*KCNN3*), and non-specific cation channel (*HCN1*). The genes encoding for Ca^{2+} transporters (*ATP2A2* and *ATP2B2*), however, affect the intracellular Ca^{2+} dynamics, and their effects are conveyed by model parameters controlling the contribution of Ca^{2+} to the free cytoplasmic Ca^{2+} and the rate of expulsion of Ca^{2+} from the cytoplasm to the extracellular medium. Here, we study the effects of the implicated model parameters on neuron's response to somatic and apical stimuli.

1) Go to the directory and compile the membrane mechanisms by command "nrnivmodl". Open the GUI of the simulator by command "nrngui init.hoc".
2) Click the *CACNA1C* variant and unclick other variants and run the first simulation "Simulate response to somatic DC". The program simulates the neurons, namely both the control (blue) and variant (red) neuron, and opens four windows. These windows show the somatic membrane potential (left), membrane potential at the apical dendrite (middle-left), intracellular [Ca^{2+}] at the soma (middle-right), and the SK currents into the soma (right). In the command prompt window, the information on the changed model parameters is printed:

   CACNA1C variant: ['offma_Ca_HVA', 'offmb_Ca_HVA']: -0.047*25.9 mV, ['offha_Ca_HVA', 'offhb_Ca_HVA']: -0.047*27.0 mV

   This means that the half-activation voltage of both activation and inactivation of the high-voltage activated Ca^{2+} currents are decreased by 1.21 and 1.27 mV, respectively. In these Ca^{2+} channels, the activation is much quicker (time constant < 10 ms) than the inactivation (time constant > 150 ms), and thus the variant strengthens the Ca^{2+} currents. This can be seen in the middle-right window showing an increased intracellular [Ca^{2+}] responses at the soma.

   As the intracellular [Ca^{2+}] is increased, the Ca^{2+}-activated K^{+}-currents (SK currents, shown in the right-hand panel) are increased as well. How does this effect reflect on the firing frequency (left-hand panel)? Why?

3) Click the *ATP2B2* variant and unclick other variants and run the first simulation again. In the command window, the information on the changed model parameters is printed:

   ATP2B2 variant: ['decay_CaDynamics_E2']: *1.97^0.11

   This means that the decay constant of the intracellular [Ca^{2+}] is slightly increased (multiplied by 1.97^0.11 = 1.077, i.e., increased by 7.7%). How can this be observed in the plotted data? Which of the observed effects can be considered primary, and which ones secondary or tertiary?

4) Check the variants one by one, simulate, and decide whether they increase or decrease the firing frequency. Click all the ones that increased the firing frequency to see the combined effect of the variants. Do the variants have cumulative effects? What about the combination of all the variants that decreased the firing frequency?

5) Now, choose the variants that increased the firing frequency, and run the second simulation “Simulate sensitivity to second apical stimulus". In this experiment, the apical dendrite is first given a suprathreshold, spatially distributed (3000 synapses randomly located from 300 um to the end of the apical dendrite) stimulus. 60 ms later, the same synapses are activated, now conducting 2-, 2.5-, 3-, 3.5-, 4-, or 4.5-fold stronger currents compared to the first stimulus (each response is plotted with a different color). The left-hand figure shows the membrane potential at the soma, and the right-hand figure at the apical dendrite, 400um from the soma. How is the neuron’s sensitivity to second apical stimulus affected by the variants, compared to control neuron? In other words, does the amplitude of the second stimulus have to be larger or smaller to produce an additional spike following the second stimulus? Note that in this experiment, the control case is not explicitly shown, but it has to be separately simulated by unclicking all variants. Repeat the experiment by choosing the opposite set of variants (namely, those that decreased the firing frequency in (3). Do you observe opposite effects?

6) Discussion. What mechanisms seem to have largest effects? Can the same mechanisms play role in the PPI deficits observed in schizophrenia patients? On what conditions? What other mechanisms could be at play?

References:

Hay, E., Hill, S., Schürmann, F., Markram, H., & Segev, I. (2011). Models of neocortical layer 5b pyramidal cells capturing a wide range of dendritic and perisomatic active properties. *PLoS Comput Biol*, *7*(7), e1002107.

Larkum, M. (2013). A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex. *Trends in neurosciences*, *36*(3), 141-151.

Mäki-Marttunen, T., Halnes, G., Devor, A., Witoelar, A., Bettella, F., Djurovic, S., Wang, Y., Einevoll, G. T., Andreassen, O. A., Dale, A. M. (2016). Functional effects of schizophrenia-linked genetic variants on intrinsic single-neuron excitability: A modeling study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1;1(1):*49-59.

Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans P, et al. (2014): Biological insights from 108 schizophrenia-associated genetic loci, *Nature 511*.7510: 421–427.

Turetsky, B. I., Calkins, M. E., Light, G. A., Olincy, A., Radant, A. D., & Swerdlow, N. R. (2007). Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophrenia bulletin*, *33*(1), 69-94.