Dear editor(s),

We hereby submit the manuscript “An electrodiffusive neuron-extracellular-glia model with somatodendritic interactions” by Marte J. Sætra, Gaute T. Einevoll, and Geir Halnes, and ask that it is considered for publication as a research article in PLoS Computational Biology. We suggest Kim “Avrama” Blackwell as the associate editor to handle the submission.

Within the field of computational neuroscience, there has been a strong focus on simulating the electrical activity of neurons and neural networks, often neglecting processes in other components of brain tissue, such as the extracellular space and glial cells. Within this programme, we have seen the development of ever larger and more sophisticated network models, such as those provided by the Blue Brain Project [Markram et al. 2015; Cell, 163(2):456-492] or Allen Brain Insititute [Arkhipov et al. 2018; PLoS Comput. Biol. 14(11):e1006535], including thousands of detailed multicompartmental neurons.

Standard multicompartmental neuron models typically assume that the concentrations of the main charge carriers (K+, Na+, and Cl-) do not vary over the simulated period, so that concentration-dependent effects on ionic reversal potentials, electrical potentials, and neuronal firing properties are not accounted for. Consequently, these models do not lend themselves to simulate scenarios where concentrations *do* deviate from baseline, which happens to a dramatic extent under pathological conditions such as epilepsy and spreading depression, but also to a moderate extent during non-pathological periods of enhanced activity.

Our group has, through a series of computational studies, investigated the consequences that ion concentration dynamics have on various aspects of neuronal, glial, and extracellular dynamics, with several publications on the topic [Halnes et al. 2013. PLoS Comp Biol 9(12) e1003386; Halnes et al. 2016: PLoS Comp Biol, 12(11), e1005193; Halnes et al. 2017: J Neurophysiol 118: 114–120; Solbrå et al. 2018: PloS Comp Biol, 14 (10), e1006510; Ellingsrud et al. 2020 Front. Neuroinform. 2020;14:11; Sætra et al. 2020 PloS Comp Biol 16(4) e1007661]. Based on the formalism established through those publications, we here present the electrodiffusive neuron-extracellular-glia (edNEG) model, which we believe is the first model to combine multicompartmental neuron modelling with an electrodiffusive formalism for the dynamics of electrical potentials, ion concentrations and homeostasis in a (two-compartmental) neuron and the surrounding medium consisting of extracellular space and a glial syncytium.

Technically, the edNEG model expands one of our previous models [Sætra et al. 2020 PloS Comp Biol 16(4) e1007661], by adding effects not present there of (1) glial ion concentration regulation and (2) osmotically driven neuronal and glial swelling or shrinkage. Focusing on the novel functionality, we have devoted the major part of the current work to exploring the role of glia in making the neuron more tolerable to hyperactive firing and in limiting neuronal swelling during various firing conditions within a locally closed system. However, we also discuss how the edNEG model can be integrated with previous spatial continuum models of (global) tissue dynamics, and how we believe that such an integration can lead to an improved understanding of the pathophysiology of spreading depression.

Yours sincerely,

Geir Halnes (corresponding author)