Modeling an Experimentally Observed Effect of Microgravity on Action Potential Interspike Interval

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Summary

With the prospect of commercial spaceflight becoming widely available in the near future, understanding the neurological consequences of spaceflight is imperative. Particularly we need to understand the neurophysiological changes that occur in microgravity (~0g). Published work provides evidence that the properties of action potentials (APs) are sensitive to changes in gravity. For example, the interspike interval (ISI) (AP frequency^{-1}) of spontaneously firing leech neurons was found by Meissner & Hanke (2005) to be reduced to approximately 62.5% of its 1g duration upon exposure to microgravity. Since the underlying mechanisms driving this observed reduction in ISI remain unclear, we have used a neuronal model to evaluate several alternative explanations for the change in ISI in microgravity. Since problems of gravitational biology are difficult to address experimentally, we pursued our objective computationally using Hodgkin-Huxley (HH) AP simulation. We identified four potential mechanisms that could reduce ISI: [1] increased membrane excitability, [2] more rapid ion channel gating activity, [3] decreased mean open state probabilities of ion channels (experimentally observed by Goldermann & Hanke, 2001), and [4] ion leakage through an imperfect patch-clamp/membrane seal, resulting from the drop-tower methodology of Meissner & Hanke (2005). Each was separately implemented via HH parameter changes: [1] by decreasing K^+ conductance, decreasing leak conductance, and increasing Na^+ conductance; [2] by increasing rate constants for ion channel gating activity; [3] by decreasing open probabilities for ion channel activation gates; [4] by transforming the leak current parameters to represent a hole in the membrane. The average ISI of each simulation was computed and compared to that of a control simulation. We found that all proposed mechanisms caused a decreased ISI when parameters where changed within a biologically reasonable range; however, only [4] produced an ISI reduction similar to that observed experimentally.

References

1) Meissner K, Hanke W. (2005) Action potential properties are gravity dependent. *Microgravity Sci Technol.* XVII-2, 38-43.
2) Goldermann M, Hanke W. (2001) Ion Channel are Sensitive to Gravity Changes. *Microgravity Sci Technol.* XIII-1, 35-38.

Additional Detail

To illustrate our methods and findings, we present example analyses of mechanisms [1] and [4], corresponding to increased membrane excitability and an imperfect patch-clamp/membrane seal (membrane hole), respectively. We reasoned that, in terms of HH parameters, [1] could result from one or more of the following: decreased K^+ conductance (g_K), decreased leak conductance (g_{leak}), and/or increased Na^+ conductance (g_{Na}). We therefore conducted HH simulations to establish the relationships between these parameters and ISI (Figs. 1, 2b). We found that such parameter changes did reduce ISI; however, obtaining the reduction to 62.5% observed experimentally[1] required large relative changes to g_K, pushing it beyond physiological relevance (Fig. 1a), and was not possible by changing g_{Na} (Fig. 1b) or g_{leak} (Fig. 2b).

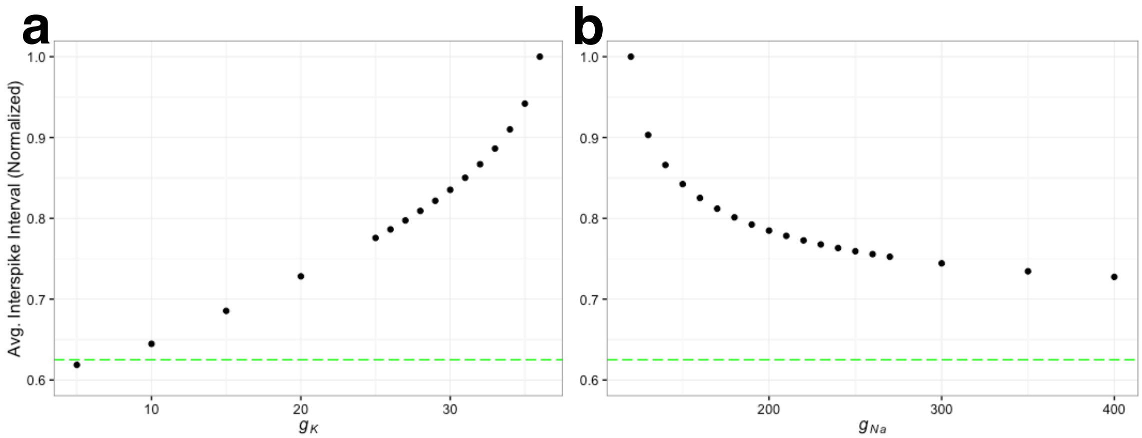

Figure 1. Evaluating the effect of decreasing g_K (**a**) or increasing g_{Na} (**b**) on ISI (normalized to control). The green dashed line represents the ISI decrease observed experimentally. Note the difference in horizontal scale.

We simulated [4] through manipulating the HH leak current parameters E_{leak} and g_{leak}. We used the Goldman Equation with $P_{Na} = P_K = P_{Cl}$ to estimate the effect of a nonselective opening in the present membrane on E_{leak}. Substituting the modeled value (–9.4 mV) for E_{leak} in place of its control value (–54.4 mV) yielded an ISI 63.7% of the control duration (Fig. 2a), comparable to that observed experimentally (62.5%).[1] Implementing changes to g_{leak} representative of [4] required a different approach than E_{leak}, as such changes could not be quantitatively predicted, although we reasoned that it should increase in the given context. We therefore implemented a range of values to assess the relationship between g_{leak} and ISI with E_{leak} at both its control value and at –9.4 mV (Fig. 2b). We found a negative relationship between g_{leak} and ISI when E_{leak} = –9.4 mV, unlike the positive relationship when E_{leak} = –54.4 mV (control), altogether supporting our hypothesis that [4] may explain the experimental decrease in ISI.

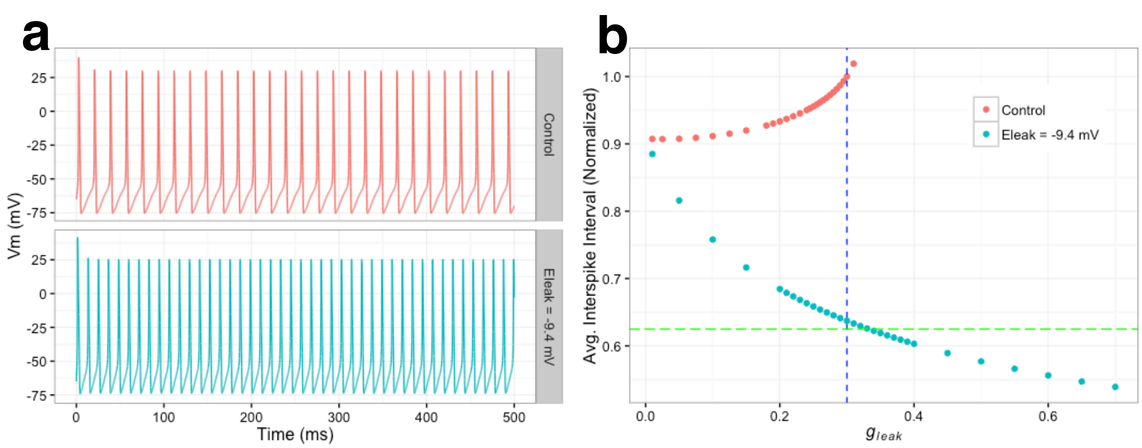

Figure 2. Evaluating the influence of [4] on ISI; **a**, HH simulation outputs for membrane potential (V_m) vs. time with control parameters (red) or E_{leak} = –9.4 mV (blue). The corresponding average ISIs are respectively 18.17 ms and 11.58 ms (63.7%); **b**, analysis of ISI (normalized to control) vs. g_{leak} with control parameters or E_{leak} = –9.4 mV. The green dashed line represents the ISI decrease observed experimentally; the blue dashed line represents the control value of g_{leak}.