Membrane Currents Contributing to Variability of Neuronal Firing: Implications for Disease

CASE WESTERN RESERVE UNIVERSITY EST. 1826

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Introduction

Computational models of neuronal acitivity have become powerful tools to help understand brain behavior, and often lead to insights about neural physiology. We created a computational model to study variability in spontaneous firing to gain insight into the biophysical mechanisms underlying the regularity of neuronal firing. This has gained attention recently because experimental studies on ataxic mice have shown that irregular firing in Purkinje Cells correlates with ataxia. There is also a particular strain of mutant mice with a 10mV shift in the activation and inactivation curves (Fig. 1) of the mice's Calcium channels, which have been shown to have ataxia and an increased variability in the spontaneous firing of their Purkinje Cells. Thus the increase in variability is believed to be a cause for ataxia . We sought to recreate this shift in Calcium activation in our model to study what effect it was having on the variability of neuronal activity.

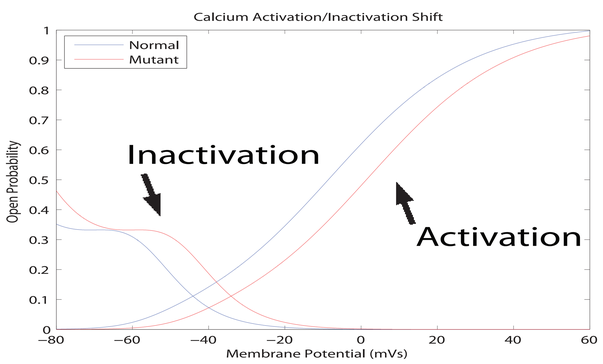

Fig 1: Our model's normal and mutant (10mV shift) activation and inactivation Calcium curves

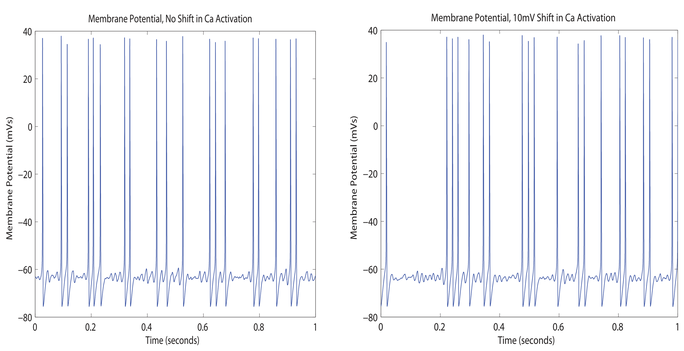

Fig 2: Membrane traces of the normal (left) and mutant (right) model

Results

Our model successfully recreated the increase in the Coefficient of Variation (CV, see methods) and showed a reduction in CV when Calcium dependent Potassium conductance was increased, as observed in mice by Ref 3. We then analyzed the increase in CV by comparing different current behavior at subthreshold peaks (or failed attempts) to actual action potentials; figure 5 shows the subthreshold peak locations, figures 6 and 7 show the CV in the Calcium and Calcium-Dependent Potassium currents in both mutants and normal cases at Action Potentials and subthreshold peaks. We found a significant increase in the CV of the mutant when a spike did not occur, though there was no difference when a spike did occur.

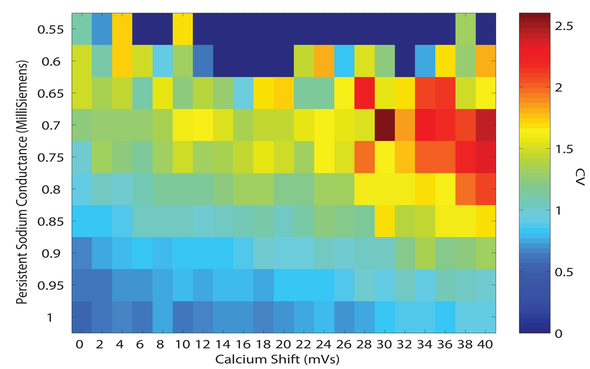

Fig 3: The Coefficient of Variation in the model's firing rates (measure over about 16 seconds of spontaneous activity) at different shifts in Calcium activation (x axis) and Persistent Sodium (y axis). Persistent Sodium was used as a way to change the baseline activation rate of the neuron without dramatcially changing it's properties.

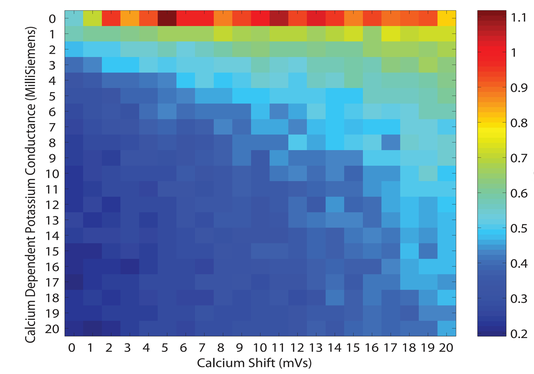

Fig 4: The Coefficient of Variation in the model's firing rates (measured over about 16 seconds of spontaneous activity) at different shifts in Calcium activation (x axis) and Calcium dependent Potassium (y axis). We can see recovery (reduction in CV) in the coefficient of variation at various Calcium shifts.

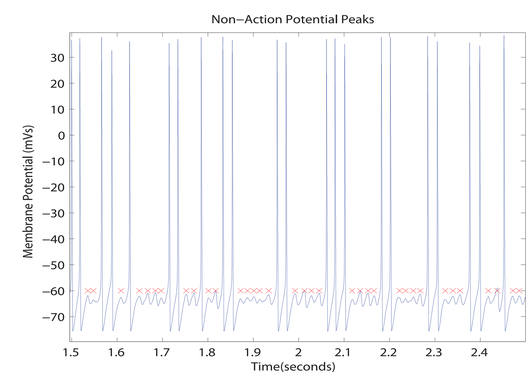

Fig 5: Membrane traces of the model, with what we defined to be subthreshold peaks marked with a red x.

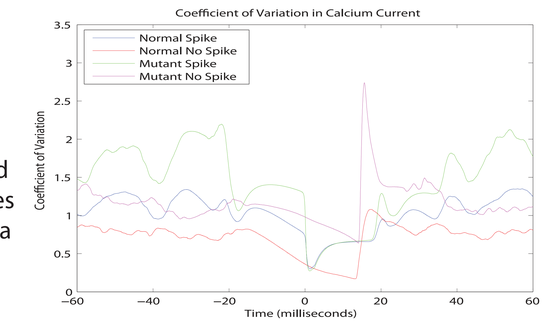

Fig 6: The Coefficient of Variation (CV) in the Calcium current, around when a spike occurred (blue-normal, green-mutant) or around when a subthreshold peak (failed spike) occurred (red-normal, purple-mutant)

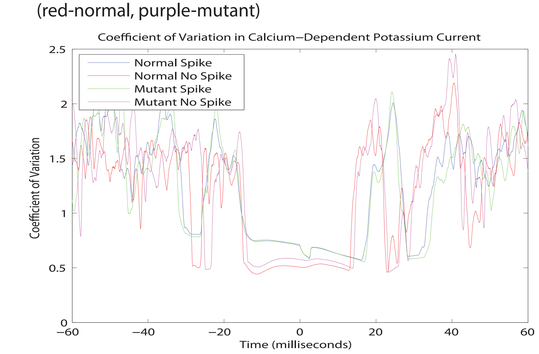

Fig 7: The Coefficient of Variation (CV) in the Calcium-dependent Potassium current, around when a spike occurred (blue-normal, green-mutant) or around when a subthreshold peak (or a failed spike) occurred (red-normal, purple-mutant)

Methods

Variability was defined bythe coefficient of variation, which is the standard deviation divided by the mean of the interspike interval.

Our model included fast Sodium, delayed-rectifier Potassium, voltage-gated Calcium, Calcium-dependent Potassium, and persistent Sodium. All ionic conductances and opening and closing rates were taken from Ref.1, except persistent Sodium, which was based on experimental descriptions by Ref. 2. Simulations were run on a computer assembled by the author.

To obtain physiological behavior, channel densities were adjusted until the membrane features matched those of experimental recordings (examples from the model are in fig. 2)

Conclusions

Our model has demonstrated that shifts in the Calcium activation curve are sufficient to recreate the variability in neuronal firing that has been linked to ataxia, and thus we have a better insight into the physiology behind the disease.

Acknowledgements

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References

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2. Magistretti J & Alonso A. Fine Gating Properties of Channels Responsible for Persistent Sodium Current Generation in Entorhinal Cortex Neurons. *J. Gen. Physiol*. **120**, 855-73 (2002)
3. Walter, Joy et. al. Decreases in the precision of Purkinje cell pacemaking cause cerebellar dysfunction and ataxia. *Nature Neuroscience*. **9**, 389-397 (2006)