

Membrane currents contributing to variability of neuronal firing: implications for disease

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Recent studies suggest that increases in the variability of firing in cerebellar Purkinje cells is a critical factor leading to ataxia in Ca^{2+} channel mutants, and regular firing of neurons is an important part of the normal behavior of many neuronal cells. However, the mechanism that links Ca^{2+} channel function to firing regularity is unknown. Computational simulations of neural dynamics can add key insights into this problem. Inspired by experimental work on neuronal ion channels, we have constructed a model neuron with fast sodium, delayed rectifier potassium, calcium, calcium-dependent potassium, and persistent sodium channels. The gating properties of these channels were based on experimental observations, and the channel densities were chosen to reproduce physiological electrical activity. We found that, in a tonically firing state, decreasing the calcium current results in an increase in firing variability, quantified as the coefficient of variation of the inter-spike interval. Decreases in calcium current can be produced either by a direct reduction in calcium conductance or a shift in the voltage-activation curve. This result provides a potential explanation for the loss of regular firing observed in cerebellar Purkinje cells in *leaner* and *tottering* mutant mice, which display a shift in the voltage dependence of calcium channel activation. We have also observed that including Ca^{2+} channels in the model can produce bistability of the membrane potential over a time scale of several seconds, resulting from the interplay between persistent sodium and calcium-dependent potassium channels. This resembles some of the bursting properties of Purkinje cells described in previous experimental studies.

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