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Using multi-objective evolutionary algorithms to predict the parameters that determine membrane resonance in a biophysical model of bursting neurons

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Many neurons exhibit membrane potential resonance (MPR), a peak in the membrane impedance amplitude ($|Z|$) in response to oscillatory inputs at nonzero frequency (f_{max}) [1]. MPR arises from nonlinearity and timescales of voltage-gated currents and may set frequency of network oscillations. Pacemaker PD neurons of the crab pyloric network show MPR whose f_{max} is correlated with the network frequency (~ 1 Hz) [2]. In contrast, the LP follower neuron shows a higher f_{max} of ~ 1.4 Hz. The impedance profile of biological PD and LP neurons and the model neuron was measured using a logarithmic ZAP function ($f_{min}=0.1$ Hz, $f_{max}=4$ Hz) in voltage clamp ($V_{low}=-60$ mV and $V_{high}=-30$ mV). The f_{max} in biological PD neurons increases if either V_{low} or V_{high} are increased [3], whereas the LP neuron f_{max} is only sensitive to V_{high} . Additionally MPR in the PD neurons is sensitive to blockers of I_{Ca} and I_h . We hypothesize that: (1) many combinations of parameters can produce MPR in PD and LP neurons; (2) The MPR mechanism in LP is distinct from PD.

Experimentally, I_{Ca} is difficult to measure and therefore a top-down approach is adopted to elucidate the contributions of I_{Ca} and I_h to MPR in PD and LP. Because resonance depends on the kinetics of I_{Ca} and I_h , a brute-force sampling of the parameter space is computationally unfeasible and, therefore, we search for model parameters using a genetic algorithm. The biological data were used to constrain the range of leak, I_{Ca} and I_h parameters in a single-compartment model. The genetic

algorithm, NSGA-II [4] was used to optimize the MPR profile and produce a population of optimal models. A sensitivity analysis of MPR attributes on model parameters was done in these models.

The distributions of optimal parameters were tightly constrained for g_{leak} , $V_{\frac{1}{2}Ca_{act}}$, $V_{\frac{1}{2}Ca_{inact}}$ and $\tau_{Ca_{inact}}$. Additionally, strong correlations were observed between $\tau_{Ca_{act}}$ and $\tau_{Ca_{inact}}$ (negative), between $V_{\frac{1}{2}Ca_{act}}$ and $V_{\frac{1}{2}Ca_{inact}}$ and between g_{Ca} and $V_{\frac{1}{2}Ca_{act}}$ (negative). In models with low I_h , f_{max} correlated strongly with the frequency which I_{Ca} peaked, which is controlled by $\tau_{Ca_{act}}$ and $\tau_{Ca_{inact}}$. The parameter sensitivities also support the sensitivity to I_{Ca} time constants, demonstrating potential targets for neuromodulation.

The MOEA was also used to optimize the f_{max} shifts with V_{low} and V_{high} to produce two model groups with properties that correspond to the differences between PD and LP. These results suggest that f_{max} shift is due to different activation rates of I_h and therefore these two neurons may generate MPR through different mechanisms; a result which we aim to test experimentally.

Many neurons display emergent properties in response to oscillatory inputs, such as amplified responses in certain frequency bands. These properties may be important in shaping coherent network activity. The underlying nonlinearities and time scales that shape specific features of impedance profiles can be used to link sub-threshold dynamics to supra-threshold voltage responses. We have used an MOEA to understand the multiple underlying ionic mechanisms that generate resonance and explained how PD, and not LP, f_{max} can be adjusted according to different input amplitudes.

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