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 (~ 1Hz) [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=-60mV and V_high=-30mV). 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 ICa and Ih. 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, ICa is difficult to measure and therefore a top-down approach is adopted to elucidate the contributions of ICa and Ih to MPR in PD and LP. Because resonance depends on the kinetics of ICa and Ih, 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, ICa and Ih 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, V½_Ca_act, V½_Ca_inact and τ_Ca_inact. Additionally, strong correlations were observed between τ_Ca_act and τ_Ca_inact (negative), between V½_Ca_act and V½_Ca_inact and between g_Ca and V½_Ca_act (negative). In models with low Ih, f_max correlated strongly with the frequency which ICa peaked, which is controlled by τ_Ca_act and τ_Ca_inact. The parameter sensitivities also support the sensitivity to ICa 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 Ih 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 timescales 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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