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Multi-objective evolutionary algorithms for model neuron parameter value selection matching biological behavior under different simulation scenarios

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In our previous work, we systematically explored a 12-dimensional parameter space of a 2-compartment model of the AB (anterior burster) neuron, which is one of the two cells that form the pacemaker kernel in the pyloric network in the lobster stomatogastric ganglion (STG). Our computational exploration started with a hand-tuned AB model [1] and systematically varied maximal conductances of membrane currents, one at a time with all the other conductances kept constant at their hand-tuned values, to determine ranges and variation steps that produced physiologically realistic behavior. Every parameter set representing an individual model neuron in this grid-based parameter space was simulated and classified as functional if it produced biologically realistic bursting activity. Specifically, we looked at the period, burst duration, spike and slow wave amplitude, number of spikes per burst, spike frequency, and after-hyperpolarization potential, which all had to be within limits determined in physiological experiments. Furthermore, in order to be classified as "good," the models had to exhibit proper responses to STG deafferentation (*i.e.*, neuromodulator deprivation) as well as current injections both in the presence and in the absence of neuromodulation. After applying all the criteria, not only have we determined that many different parameter sets performed successfully under all tested conditions, but we have also found several very interesting relationships between parameters, which may indicate the existence of co-regulations in the investigated system [2]. However, the question has always remained: are the ranges determined by varying just one maximum conductance at a time suitable and representative of the solution space of the real AB neuron? Perhaps, if two or more conductances were varied at the same time, the ranges would have been different. Unfortunately, the answer to this question cannot be found by simply extending the ranges of parameter values to some arbitrary limits and simulating all the resulting combinations; this would be unrealistic computationally. Therefore, we utilize an approach alternative to the strict grid determination of the parameter search space, based on an application of Multi-Objective Evolutionary Algorithms (MOEA) to generate a population of neuron models meeting the above selection criteria. In MOEA, the algorithm searches for pseudo-optimal solutions by trying to optimize several, sometimes conflicting, objectives at the same time. In this case, all the selection criteria were implemented as separate objectives in the end-VEGA (elitist non-dominated Vector-Evaluated Genetic Algorithm), previously proposed by the authors [3]. The ranges of variation from the hand-tuned values were set between -100% and +400%. This allowed for an extensive and ample exploration of the parameter space. The results from the simulation of the spontaneous activity alone [4], as well as all the remaining scenarios, on the one hand confirmed our observations about the possible existence of coregulations between some currents, but on the other hand, some of the relationships seen before seem to have disappeared over the extended ranges of values. This may indicate that some of the interactions observed with the grid approach were just local relationships. Conversely, the analysis of the expanded search space allowed for identification of relationships that were not seen in the previous stages of our study.

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