An adaptive controller of reliable neuromodulation on mixed feedback systems

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1 Neurons as mixed feedback systems

Hodgkin and Huxley pioneered mathematical modeling of neuronal excitability using conductance-based models, representing the neuronal membrane as a nonlinear resistor-capacitor circuit. These models portray an excitable cell biophysically, with ion channel types expressed through voltage- and time-dependent conductance $g_{\text{ion}}(V,t)$, determined by $\bar{g}_{\text{ion}}$ linked to channel availability. The current flowing through the membrane can be divided into two components: I_C, associated with charging the membrane capacitance (*i.e.*, the current flowing into the passive membrane, comprising the capacitor and leakage conductance), and I_{int}, resulting from the movement of ions across the membrane through various ion channels in the neuronal model. This approach enables the representation of conductance-based models as mixed feedback systems. Here, the capacitor and leakage conductance (the membrane itself) are regarded as the passive plant, while all the active ion channels constitute a controller. Each ion channel can be represented as a parallel block within the overall controller. This mixed feedback system is termed as such because certain ion channels produce global negative feedback, while others produce localized positive feedback. These feedback systems exhibit excitability: subthreshold excitation results in a small response, whereas suprathreshold excitation leads to a large amplitude response, known as the spike [2].

2 Neuromodulation as adaptive control

Brain activity undergoes constant modulation through the actions of various neuromodulators and neuropeptides, including dopamine, serotonin, and histamine [1]. These neuromodulators dynamically influence single neuron activity and input/output properties, providing a means to continuously adapt neuronal network activity in response to ever-changing needs, contexts, and environments. To achieve this modulation, neuromodulators dynamically reshape the density, dynamics, and kinetics of many single-cell ion channels. Consequently, the robustness and reliability of neuromodulation mechanisms at the molecular and cellular levels become crucial for the overall functional signaling of the brain. In essence, neuromodulation is a physiological mechanism that constantly adjusts the parameters $\bar{g}_{\text{ion}}$ to align the activity of neurons and circuits with a desired state, dictated by the concentration of neuromodulators. Recently, a neuromodulation model incorporating an adaptive control layer, which tunes the intrinsic gains of neurons, has been demonstrated to be highly robust against neuronal parameter variability [3]. This adaptive layer essentially computes new values for neuromodulated ion channel conductances from a target firing pattern (dictated by the concentration of neuromodulators) to dynamically achieve target firing pattern.

3 Results

First, numerous control systems regulate ion channel expression, with homeostasis and neuromodulation being the two major players. We have demonstrated that, despite potential contradictions between these two control actions, the adaptive control layer [3] and a previously published homeostatic controller [4] synergize to enhance neuronal robustness.

Second, the adaptive control layer finds versatile applications, from analyzing ion channel correlations to implementing gait control in a quadruped robot. Specifically, we showcase the the ability of the adaptive controller to enhance robustness in a simple gait control network by integrating a neuromodulatory network.

References

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