Neuromodulation and homeostasis: complementary mechanisms for robust neural function

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1 Introduction

Brain activity is continuously shaped by neuromodulators and neuropeptides, including dopamine, serotonin, and histamine [2]. Neuromodulators dynamically influence single-neuron activity, input-output properties, and synaptic connection strength and dynamics, enabling neuronal networks to adapt to changing needs, contexts, and environments. To achieve this modulation, neuromodulators dynamically reshape the density, dynamics, and kinetics of many single cell transmembrane proteins, making whole brain functional signaling strongly dependent on the robustness and reliability of neuromodulation mechanisms at the molecular and cellular levels. As such, studying neuromodulation is a very arduous task, both experimentally and computationally, which explains our limited understanding of its underlying mechanisms.

Neuromodulation coexists with cellular homeostasis, a mechanism that gradually adjusts neuronal membrane properties to maintain a target activity level. Neuronal cells are dependent on homeostatic mechanisms to maintain optimal functionality throughout the extended useful life of mammals [1]. Despite continuous turnover of transmembrane proteins, such as ion channels and receptors, occurring on varying temporal scales ranging from hours to weeks, the robustness and excitability of neurons must remain undisturbed. By monitoring calcium, the neuron orchestrates the regulation of all its conductances through homeostatic self-tuning rules. This raises the question of how two different mechanisms acting on the same targets (ion channels), each potentially having divergent goals, can co-exist and complement each other harmoniously.

2 Results

Homeostasis stabilizes neuronal activity by adjusting ionic conductances, whereas neuromodulation dynamically modifies ionic properties in response to external signals. Combining these mechanisms in conductance-based models often produces unreliable outcomes, particularly when sharp neuromodulation interferes with homeostatic tuning. This study explores how a biologically inspired neuromodulation controller [3] can harmonize with homeostasis [4] to ensure reliable neuronal function. Using computational models of stomatogastric ganglion and dopaminergic neurons, we demonstrate that controlled neuromodulation preserves neuronal firing patterns while maintaining intracellular calcium levels. Unlike sharp neuromodulation, the neuromodulation controller integrates activity-dependent feedback through mechanisms mimicking G-protein-coupled receptor cascades. The interaction between these controllers critically depends on the existence of an intersection in conductance space, representing a balance between target calcium levels and neuromodulated firing patterns. Maximizing neuronal degeneracy enhances the likelihood of such intersections, enabling robust modulation and compensation for channel blockades. We further show that this controller pairing extends to network-level activity, reliably modulating central pattern generators in crustaceans. These findings suggest that targeting neuromodulation pathways—rather than ion channels directly—may offer safer pharmacological strategies to manage neuronal dysfunctions. This study highlights the complementary roles of homeostasis and neuromodulation, proposing a unified control framework for maintaining robust and adaptive neural activity under physiological and pathological conditions.

References

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