Neuromodulation and Homeostasis: Complementary Mechanisms in Ion Channel Expression Adaptation for Robust Neural Function

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Neurons and circuits undergo significant changes in their firing patterns and responsiveness to external stimuli through the process of neuromodulation (Marder, 2012). The proper functioning of many functions in the nervous system relies on consistent neuromodulation, despite the physiological variability often observed in the characteristics of neurons targeted by neuromodulators (Grashow et al., 2009; Marder et al., 2014). Recently, reliable neuromodulation has been achieved through the incorporation of an adaptation mechanism that modulates the expression of ion channels in conductance-based models, by fine-tuning the correlations, or ratios, between ion channel expression (Fyon et al., 2023).

Moreover, neurons and circuits possess an extraordinary ability to regulate and sustain their electrical signaling properties in the face of various disruptions, including protein turnover and external disturbances. This crucial function is accomplished through the mechanism of homeostatic regulation (O'Leary et al., 2014). A previously published model of homeostasis involves the maintenance of a baseline intracellular calcium level by simultaneously adjusting the conductances of all ion channels, either up or down, while preserving predetermined correlations between each conductance (O'Leary et al., 2014).

These two computational models present contrasting perspectives. Neuromodulation primarily adjusts the correlations between pairs of conductances within a subset of neuromodulated ion channels in a neuron, thereby influencing neuron dynamical properties (Fig. 1A). On the other hand, homeostatic regulation aims to maintain existing correlations and reach a predetermined calcium level by adjusting all conductances in the same direction, thereby modifying neuron passive properties (Fig. 1B). Despite these differences, biological neurons successfully implement both mechanisms in a robust manner. This study seeks to understand the mechanisms behind such robust interaction between neuromodulation and homeostasis in a computational framework. Whereas it is known that homeostasis alone can lead to pathological losses of function (Fig. 1C, left), we show that combining reliable neuromodulation mechanisms with homeostasis permits to robustly achieve and sustain a specific firing pattern provided as input to the model (Fig. 1C, right).

References

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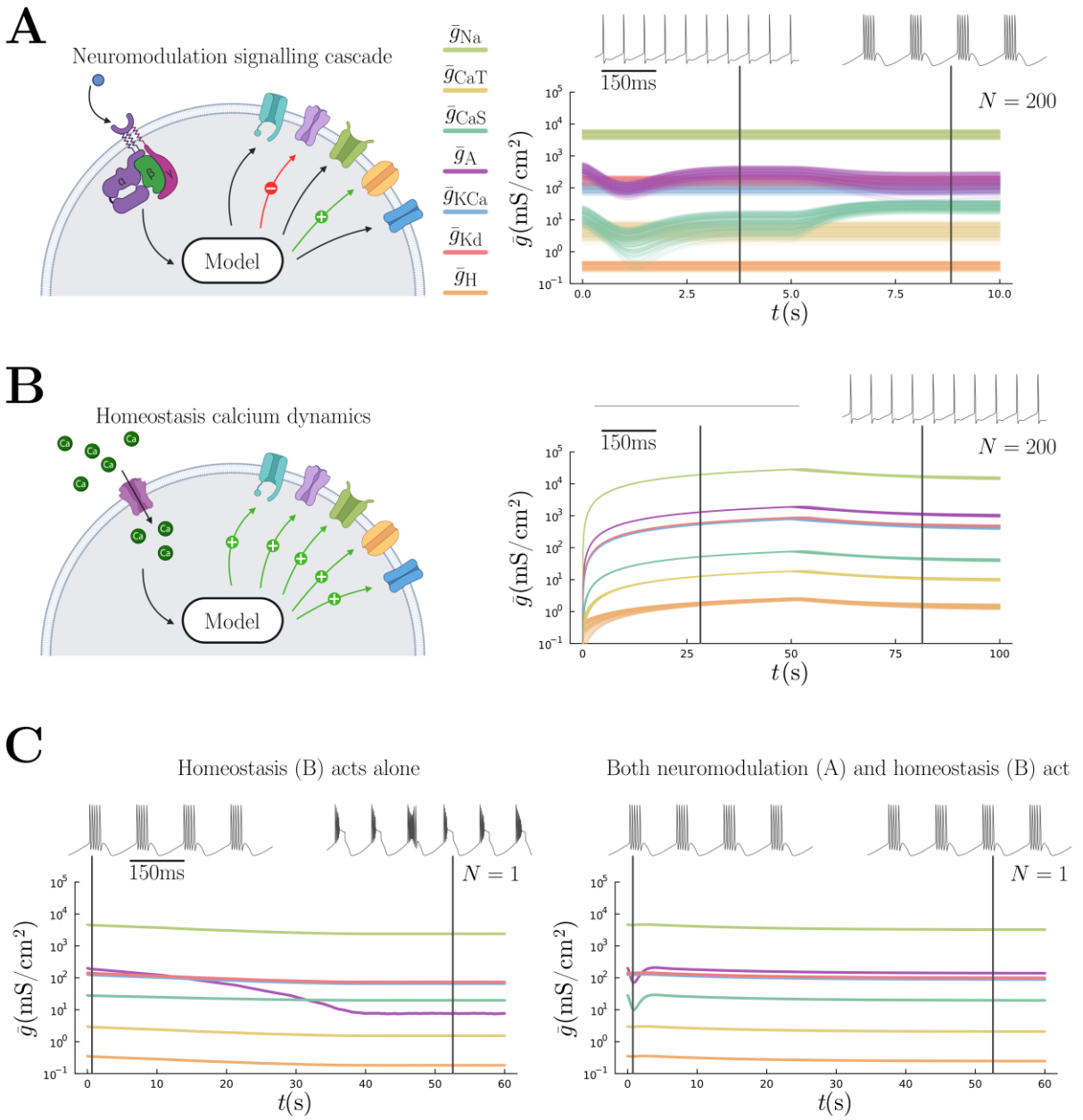

Figure 1. *Neuromodulation and homeostasis both affect ion channel expression correlation in a complementary way.* The neuromodulation model developed in Fyon et al., 2023 (A, left) tunes the correlations between a subset of ion channels (specifically, between A-type potassium channels and slow calcium channels) to achieve a target firing pattern (A, right). On the other hand, the homeostasis model developed in O'Leary et al., 2014 (B, left) preserves the correlations, or ratios, between all ion channels of the considered conductance-based model (B, right) in order to achieve a target calcium level. When starting from a bursting neuromodulated state (C, left and right), the homeostasis mechanism is pathological if it acts alone (C, left), whereas the bursting neuromodulated state is preserved when both mechanisms act together (C, right).