Neuronal population inference reveals how neuromodulation reshapes conductance space

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Summary: Neuromodulators such as dopamine, serotonin, and histamine continuously reshape neuronal excitability by acting on ion channel densities and kinetics. While this process is central to brain function, it remains difficult to characterize experimentally: metabotropic signaling cascades make the mapping from neuromodulator to ion channel nontrivial, and direct measurements of all affected conductances are rarely feasible. Moreover, ion channel densities vary considerably across neurons of the same type, so the effect of a given neuromodulator cannot be understood from a single "average" model. A key obstacle is neuronal degeneracy: distinct combinations of ion channels can generate similar spiking patterns. Standard approaches that attempt to fit a unique model from data, therefore, miss the richness of possible solutions. To address this challenge, we introduce a computational tool that reconstructs rich populations of conductance-based models (CBMs) from spike times, the most widely available form of experimental data. The method combines deep learning with Dynamic Input Conductances (DICs), a compact representation that aggregates the dynamical influence of ion channels on excitability, enabling fast and interpretable inference of diverse conductance sets from activity. By design, the reconstruction preserves degeneracy, producing heterogeneous ion channel configurations that all reproduce the observed dynamics. With this capability, neuromodulation can be investigated at the population level. Instead of treating modulation as isolated parameter changes, the tool reveals how entire distributions of conductances move through parameter space under modulatory action. This makes it possible to identify which channels are likely targeted and how robustness emerges from shifting populations rather than fixed parameters. Applied to distinct CBMs, the method shows that different modulators reorganize excitability regimes by moving whole populations in conductance space, providing a new perspective on the interplay between variability, robustness, and modulatory control.

Problem statement: We consider a known CBM, whose membrane dynamics read: $C\frac{dV}{dt} + g_{\text{leak}}(V - E_{\text{leak}}) = -\sum_{i\in\mathcal{I}} \bar{g}_i m_i^{p_i} h_i^{q_i}(V - E_i) + I_{\text{ext}}$, where V is the membrane potential, C the capacitance, g_{leak} and E_{leak} the leak parameters, and each ionic current i depends on its maximal conductance $\bar{g}_i$, gating variables m_i, h_i with exponents p_i, q_i, and reversal potential E_i.

The unknown parameters are the maximal conductances $\bar{g} = [\bar{g}_1, \ldots, \bar{g}_{|\mathcal{I}|}, g_{\text{leak}}] \in \mathcal{G} \subseteq \mathbb{R}_{\geq 0}^{|\mathcal{I}|+1}$, while all other parameters are assumed to be known. Experimental data are usually limited to spike times $x = [t_1, \ldots, t_{N_{\text{spikes}}}]$ recorded over a finite window, which depend both on $\bar{g}$ and on possible time-varying modulatory influences. Due to neuronal degeneracy [1], the inverse map $x \mapsto \bar{g} \in \mathcal{G}^*(x)$ is not unique: multiple conductance vectors yield similar activity, so the feasible solution set is a subset $\mathcal{G}^*(x) \subset \mathcal{G}$ [2]. Our objective is, therefore, not to recover a single estimate, but to infer the population of models that reproduce observed spike trains. For each data segment x, we construct a set $\mathcal{P}_x = \{\bar{g}^{(1)}, \ldots, \bar{g}^{(P)}\}$ sampled from $\mathcal{G}^*(x)$, thereby capturing degeneracy. To address this inverse problem, we adopt an intermediate strategy that avoids both collapsing to a single solution and attempting to reconstruct the full high-dimensional space directly [3]. The key step is to use DICs [4], a low-dimensional representation that aggregates the dynamical influence of ion channels. For any CBM, the DICs write $g_{\text{DICs}}(V) = S(V; \bar{g}) \cdot \bar{g}$, where S is a sensitivity matrix. The three DIC components $g_{\text{f}}(V)$,

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$g_s(V)$, and $g_u(V)$ capture fast, slow, and ultraslow contributions to excitability. Evaluated at threshold, $g_{\text{DICs}}(V_{\text{th}})$ provides a compact 3D signature of the spiking dynamics [4]. Our approach proceeds in two steps. First, a deep learning architecture learns the mapping $x \mapsto g_{\text{DICs}}(V_{\text{th}})$, enabling inference in a tractable space. Second, from predicted DIC values, we generate valid conductance vectors $\bar{g} \in \mathcal{G}^*(x)$ via a state-of-the-art knowledge-based iterative compensation algorithm [3]. In short,

$$x \xrightarrow{\text{Deep learning}} g_{\text{DICs}}(V_{\text{th}}) \xrightarrow{\text{Compensation algorithm}} \mathcal{G}^*(x) \xrightarrow{\text{Sampling}} \mathcal{P}_x,$$

yielding full populations of degenerate CBMs consistent with recorded spike trains and their modulatory variations. Under neuromodulation, the observed activity x evolves with time, which implies that the underlying conductance vector $\bar{g}$ also evolves; our approach makes it possible to directly observe how populations of conductances reorganize in response to modulatory inputs.

Choosing appropriate conductances: In the method described above, the deep learning architecture infers $g_{\text{DICs}}(V_{\text{th}})$ from recorded spike times. Each point in the DIC space corresponds to neuronal activity, summarizing how all ionic conductances interact to generate a particular firing regime. Thus, before and after neuromodulation, two spike trains x_{before} and x_{after} map to two distinct DIC points and, consequently, to two corresponding solution sets $\mathcal{G}^*_{\text{before}}$ and $\mathcal{G}^*_{\text{after}}$. Since neuromodulation affects only a subset of ion channels, the difference between these sets is expected to be localized to specific conductances. However, biology shows that various subsets of ion channels can be targeted even within the same neuronal type [2]. As a result, multiple candidate subsets $\mathcal{G}^*_{\text{after}}$ may lead to the same x_{after}, reflecting alternative modulatory pathways. In other words, several subsets of $\bar{g}$ can be modified along neuromodulation while still satisfying the DIC constraints. To resolve this ambiguity, the method automatically selects the most plausible candidate subset by minimizing a cost associated with changes in $\bar{g}$ between before and after modulation, while ensuring that the resulting conductance values remain physiologically plausible (e.g., positive and within reasonable ranges). To visualize these possibilities, we built reachability maps that display the region of the DIC space that can be reached without aberrant $\bar{g}$ values, given variations in a particular subset of conductances. These maps also encode the magnitude of changes required to reach a target DIC point, thereby linking the geometry of the DIC space to feasible modulatory transitions between neuronal states.

Implications of the work: This work introduces a framework that reconstructs populations of conductance-based models directly from spike times before and after neuromodulation (see Fig. 1). By mapping activity to DICs and then back to full conductance vectors, the method provides degenerate populations consistent with observed firing patterns, but also candidate ion channel subsets most likely to be modulated. These candidates can be directly visualized in conductance space, making it possible to track how populations reorganize under modulation rather than reducing effects to isolated parameter changes. For experimentalists, this opens the possibility of inferring which conductances are targeted by neuromodulators from spike recordings, without requiring voltage-clamp measurements or full conductance characterization. Importantly, degeneracy is not treated as a limitation but as an asset: different conductance solutions that reproduce the same spike times are preserved, offering a richer view of how robustness emerges from variability. In this way, the approach provides a practical and interpretable bridge between experimental recordings and the mechanistic conductance space, giving new insights into how neuromodulation reshapes neuronal excitability at the population level.

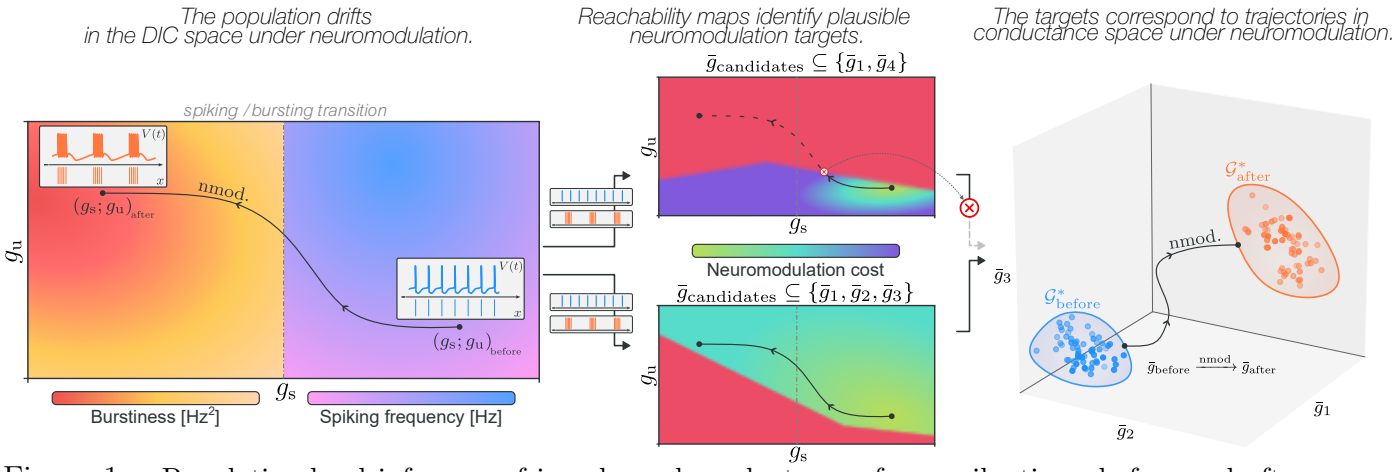

Figure 1: Population-level inference of ion channel conductances from spike times before and after neuromodulation, with automatic identification of the most plausible conductance targets. Unreachable regions are shown in red; reachable regions (green-purple) are colored by neuromodulation cost.

[1] Marder, E., & Taylor, A. L. (2011). Multiple models to capture the variability in biological neurons and networks. *Nature neuroscience*, 14(2), 133-138.

[2] Marder, E. et al. (2014). Neuromodulation of circuits with variable parameters: single neurons and small circuits reveal principles of robust neuromodulation. *Annual review of neuroscience*, 37(1), 329-346.

[3] Author et al. (2025). Fast reconstruction of degenerate populations of conductance-based neuron models from spike times. *arXiv preprint arXiv*:2509.12783.

[4] Drion, G. et al. (2015). Dynamic input conductances shape neuronal spiking. *eNeuro*, 2(1).