Inferring neuromodulatory targets and conductance parameters from neuronal spike times

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Neuromodulators such as dopamine and histamine continuously reshape neuronal excitability by acting on ion channel densities and kinetics. This process is central to brain function; however, it remains difficult to characterize experimentally: metabotropic signaling cascades make the mapping from neuromodulator to ion channel nontrivial, and direct measurements of affected conductances are rarely feasible.

A key obstacle is neuronal degeneracy: distinct combinations of ion channels can generate similar spiking patterns, so neuromodulatory effects cannot be understood from a single "average" model. Standard approaches that attempt to fit a unique model from data therefore miss the richness of possible solutions [1].

We consider conductance-based neuron models, in which membrane dynamics are governed by ionic currents,

$$C\frac{dV}{dt} + g_{\text{leak}}(V - E_{\text{leak}}) = -\sum_{i\in\mathscr{I}} \bar{g}_i m_i^{p_i} h_i^{q_i}(V - E_i) + I_{\text{ext}},$$

where the unknown parameters are the maximal conductances $\bar{g} = [\bar{g}_1, \ldots, \bar{g}_{|\mathscr{I}|}, g_{\text{leak}}]$. Due to degeneracy, the set of solutions consistent with a given activity forms a manifold rather than a point.

We introduce a computational framework that reconstructs populations of conductance-based models directly from spike times, a widely available experimental data. The method relies on Dynamic Input Conductances (DICs), an interpretable three-dimensional mixed-feedback representation that aggregates fast, slow, and ultraslow dynamical contributions of ion channels to excitability [2]. A deep learning model maps spike trains to DICs, from which populations of degenerate conductance vectors consistent with activity x are efficiently generated [3].

Under neuromodulation, as spike patterns evolve from x_{before} to x_{after}, entire populations shift in parameter space. We identify plausible modulatory targets by minimizing parameter changes while maintaining physiological constraints. Reachability maps visualize accessible regions of DIC space and encode the cost of reaching target states, linking output changes to feasible parameter transitions (fig. 1).

By treating degeneracy as an asset rather than a limitation, the framework reveals how robustness emerges from shifting populations rather than fixed parameters, offering new insights into how neuromodulation reshapes neuronal excitability at the population level.

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References

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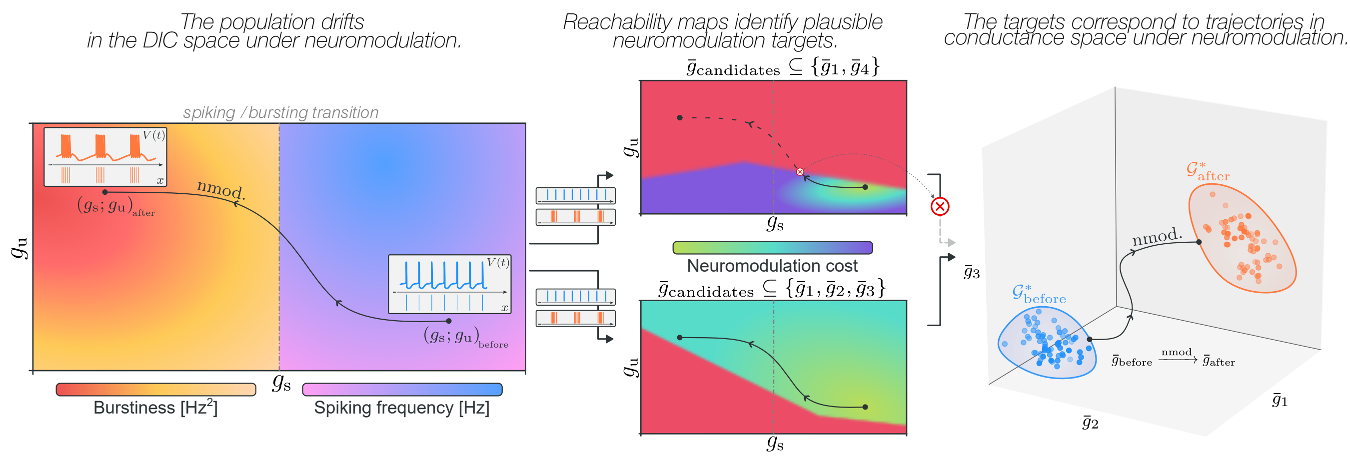

Figure 1: Population-level inference of ion channel conductances from spike times before and after neuromodulation, with automatic identification of the most plausible conductance targets. Unreachable regions are shown in red; reachable regions (green-purple) are colored by neuromodulation cost.