Method: Sensitivity Analysis of Model Parameters on Simulated Features

To understand how each model parameter influences specific simulated features, we conducted a sensitivity analysis aimed at capturing the effects within the complex, non-linear landscape of our model equations. Because the responses are highly sensitive to the delicate balance among parameters, a global sensitivity approach was more appropriate than traditional local perturbation tests (e.g., delta tests). This approach allowed us to leverage the byproduct of the genetic optimization process: the extensive set of simulated trial results. We applied a first-order Sobol analysis to each feature utilized in the optimization, enabling us to quantify the individual impact of each parameter.

Given the diversity in parameter scales and units, as well as similar variability in the feature ranges, establishing appropriate parameter boundaries and normalizing the data presented a significant challenge. To address this, we selected the top 100 performing models from each optimization set as a reference group, or "model citizens." We then defined the bounds for each parameter using the maximum and minimum values from this high-performing group, which allowed us to filter out nearly half of the data that was either unrealistic or non-informative for the sensitivity analysis. For the remaining models, which we considered "reasonable," we established normalization ranges for each feature, based on the range observed in these high-quality simulations.

To generate a final sensitivity matrix for each cell, we averaged the same feature across various clamping currents into a single representative value. We then combined the matrices of all cells within the same cell type, producing a cell type-specific sensitivity matrix. Due to the high degree of similarity in results across different seeds and the substantial computational demands, we limited this sensitivity analysis to one seed per cell type. This approach provided an efficient yet reliable insight into parameter sensitivity across different cell types, helping us identify which parameters most strongly influence specific features within each model.