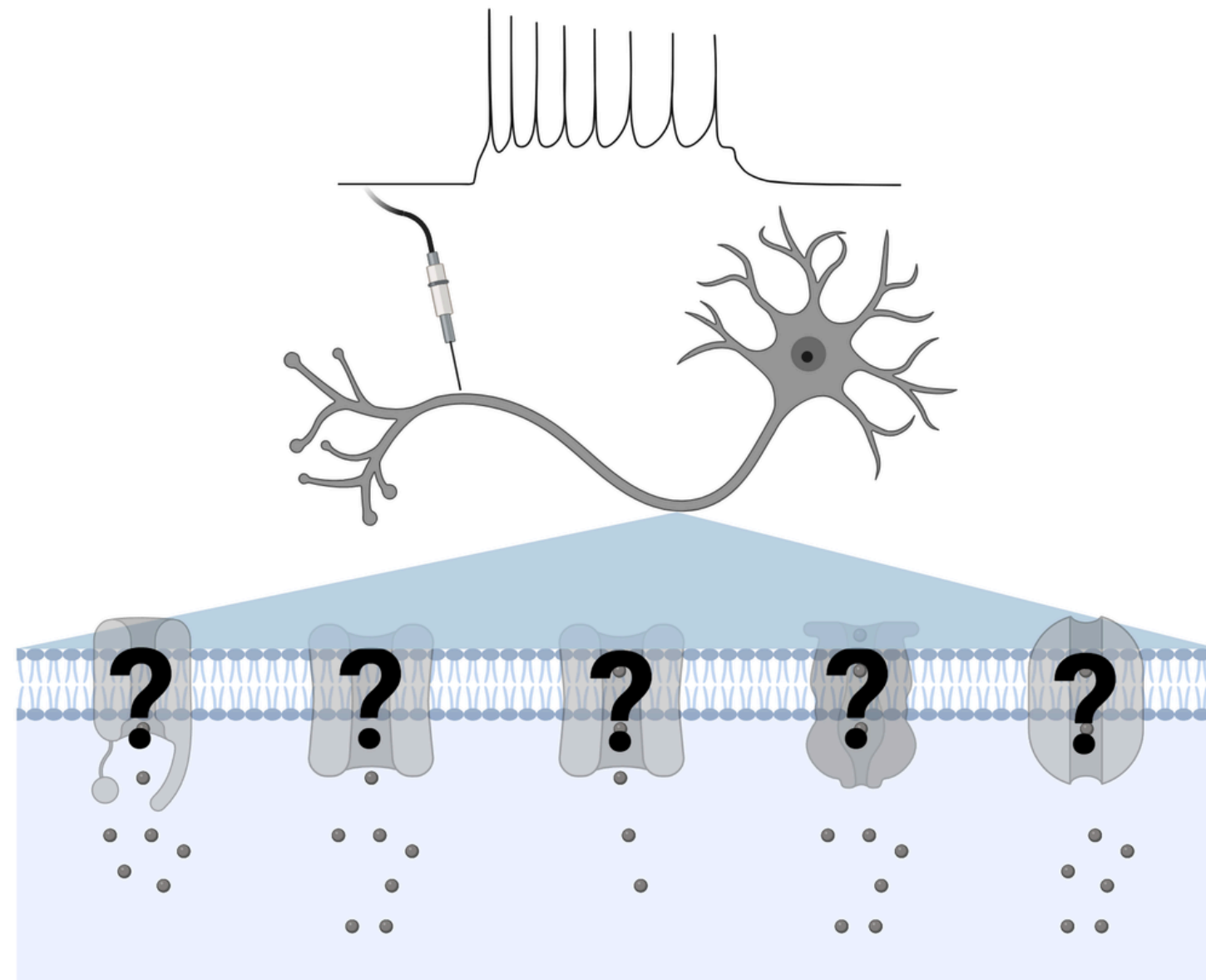


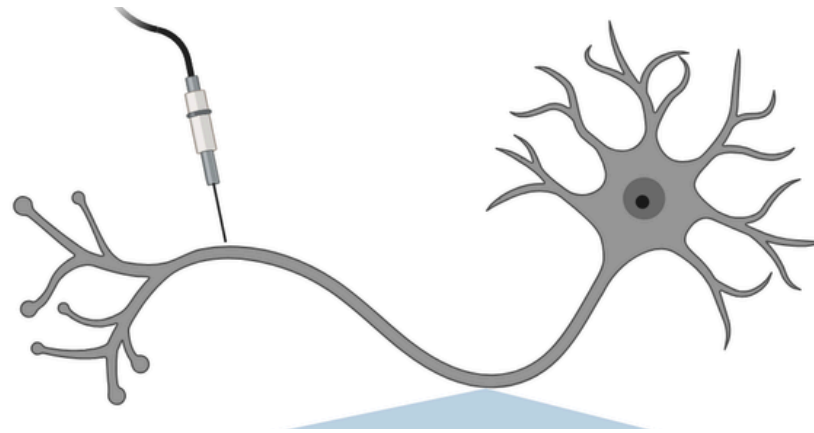
Inferring neuromodulatory targets and conductance parameters from neuronal spike times

J. Brandoit • P. Sacré • D. Ernst • A. Fyon • G. Drion
University of Liège

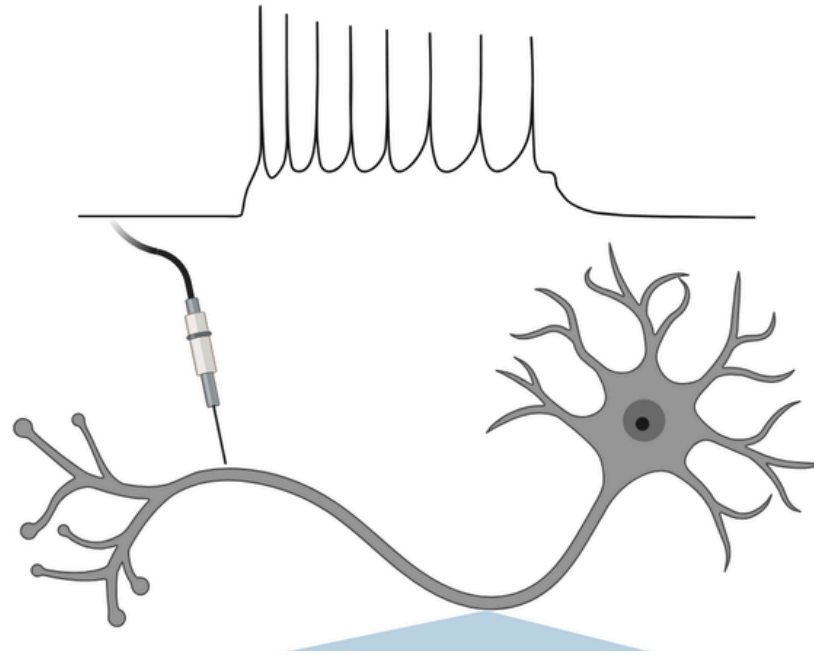
Let's play **a million-dollar game** together



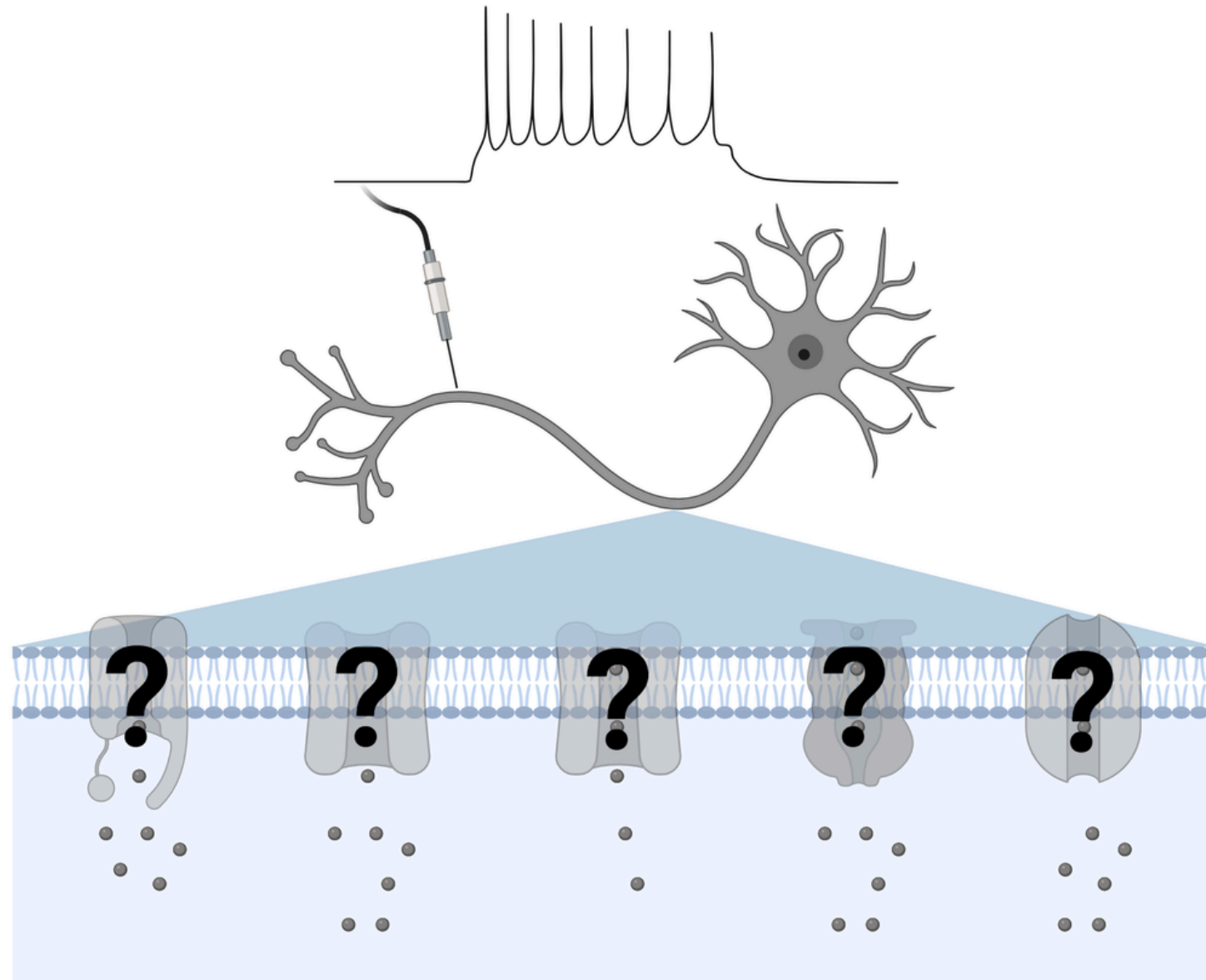
Let's play a million-dollar game together



Let's play a million-dollar game together



Let's play **a million-dollar game** together



This million-dollar game is very simple:

I give you an activity, and you tell me the exact membrane composition.

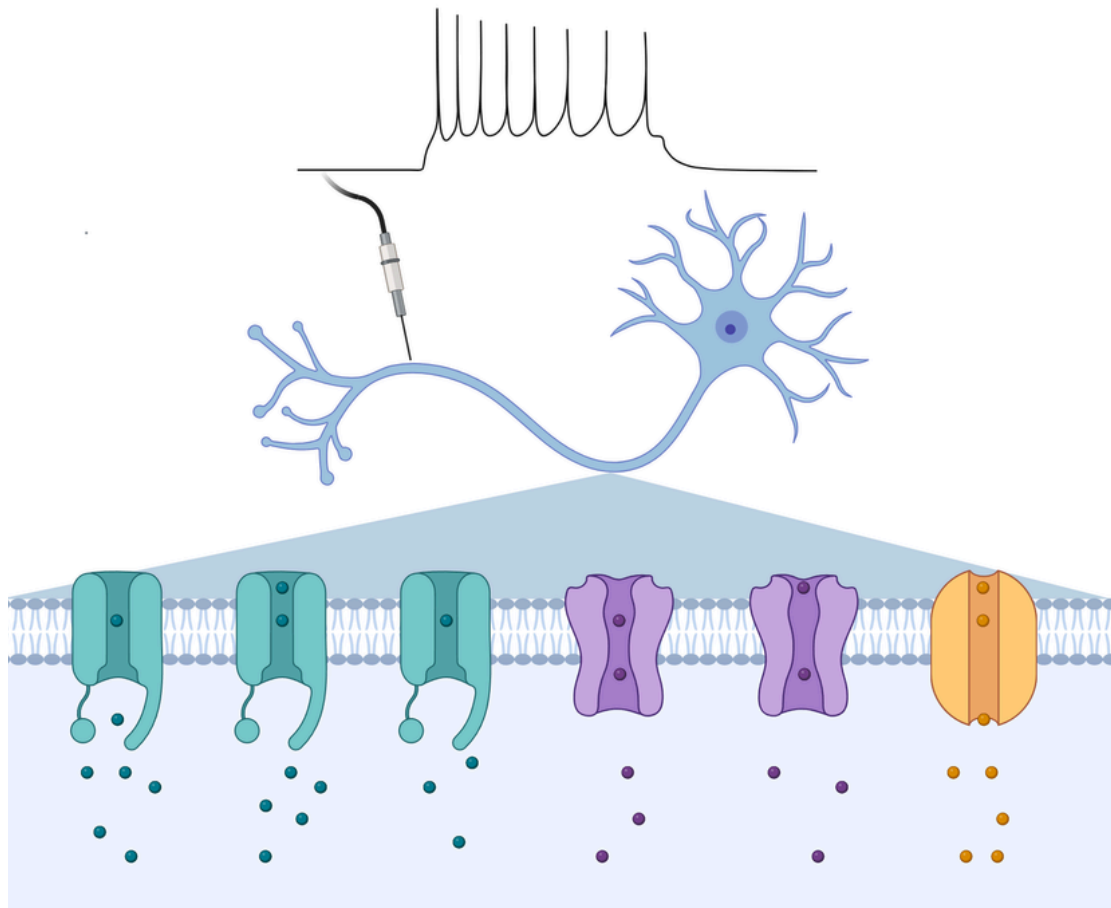
If you're right, you win; if not, I win.



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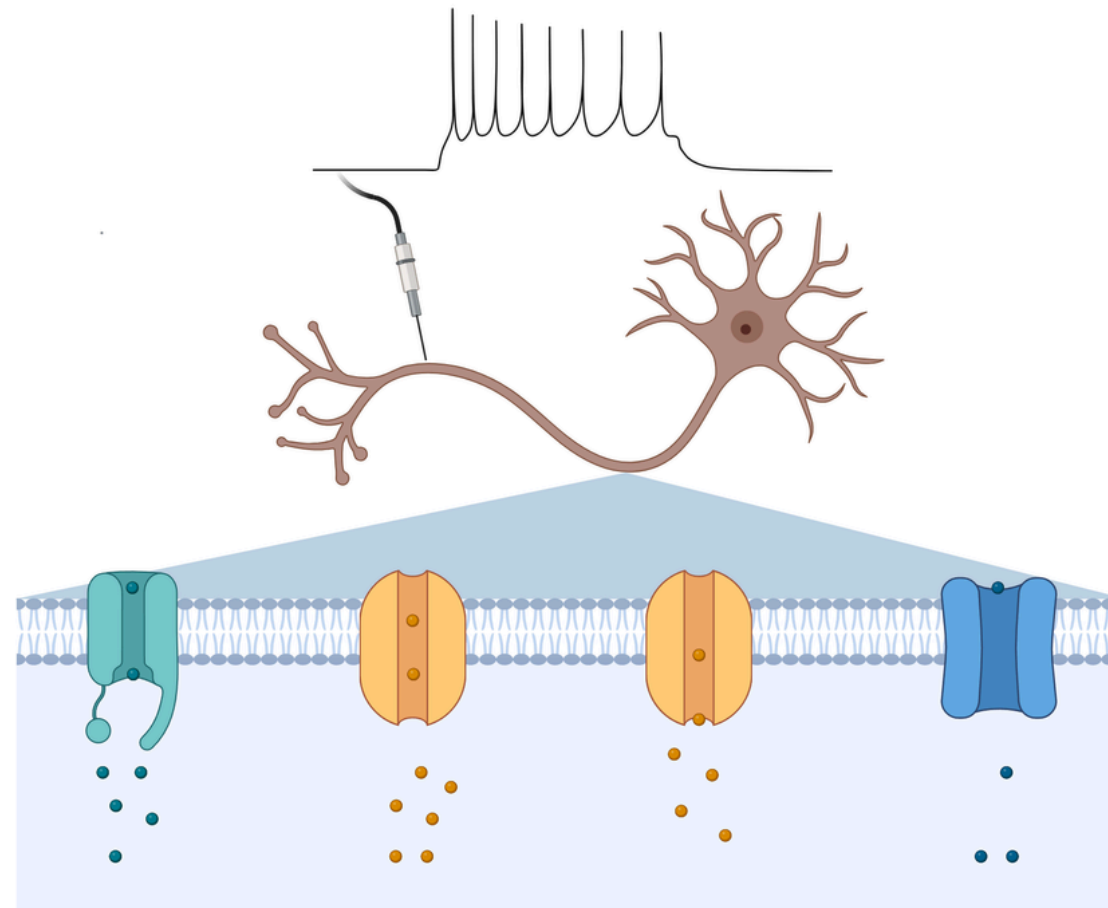
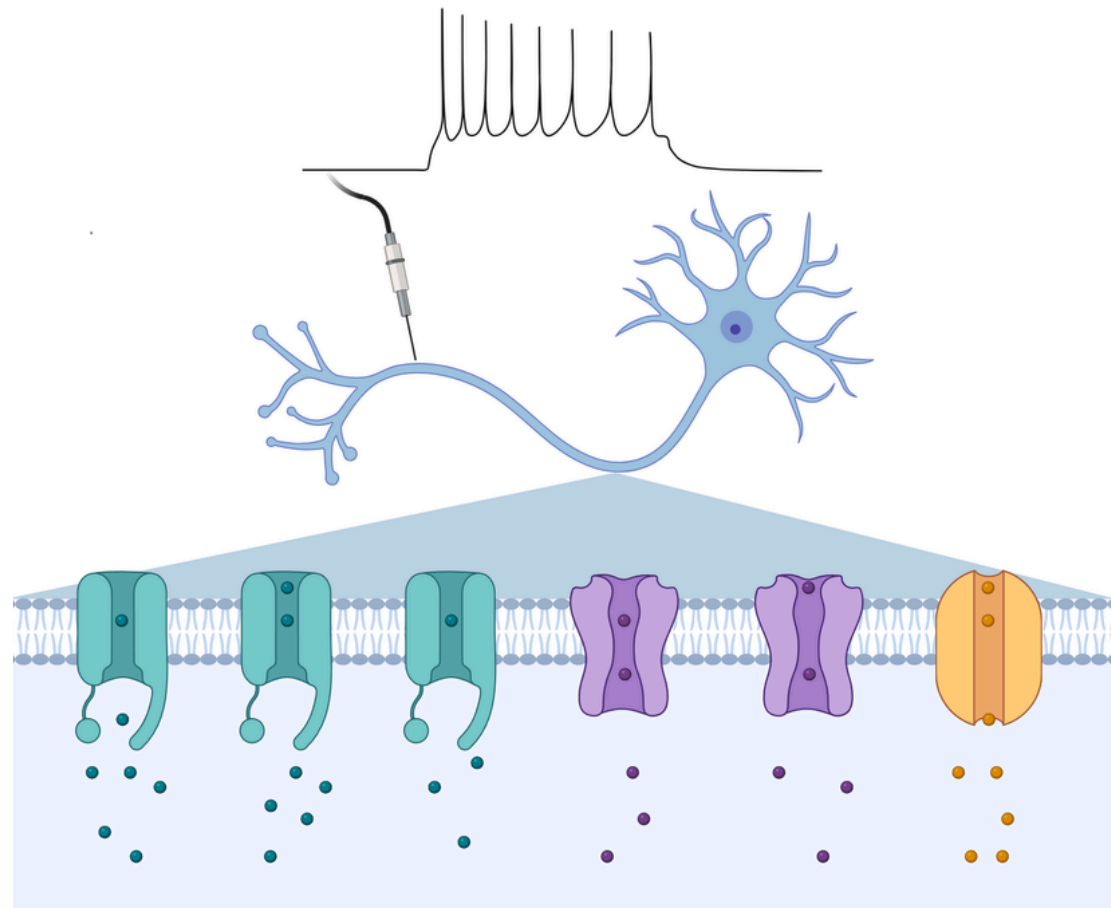
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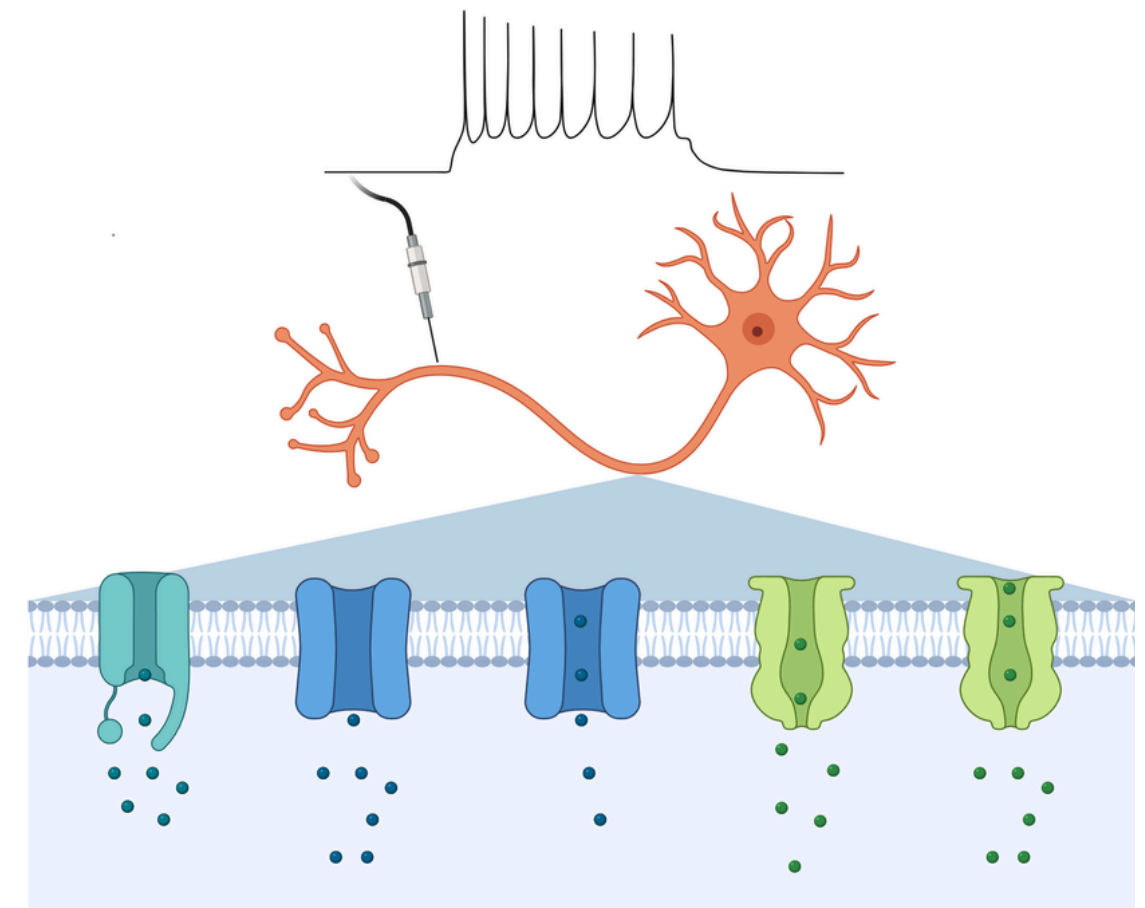
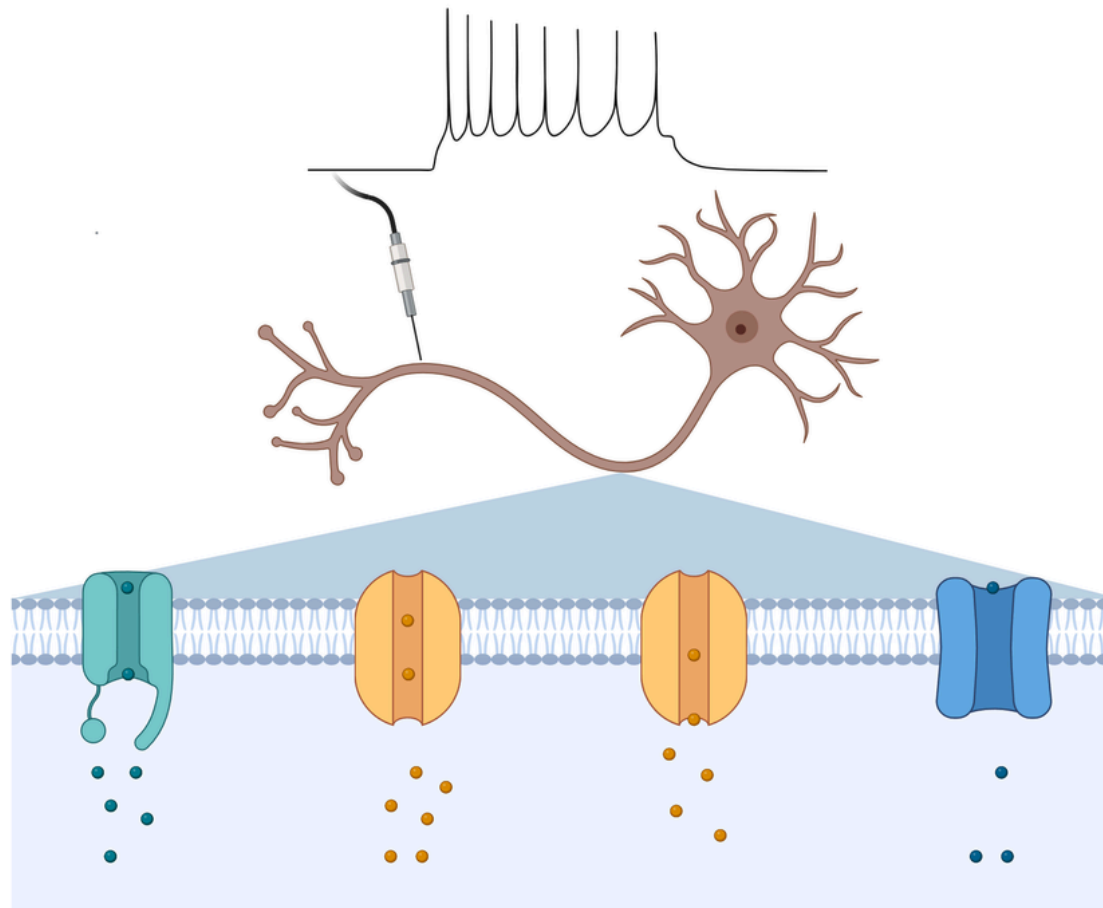
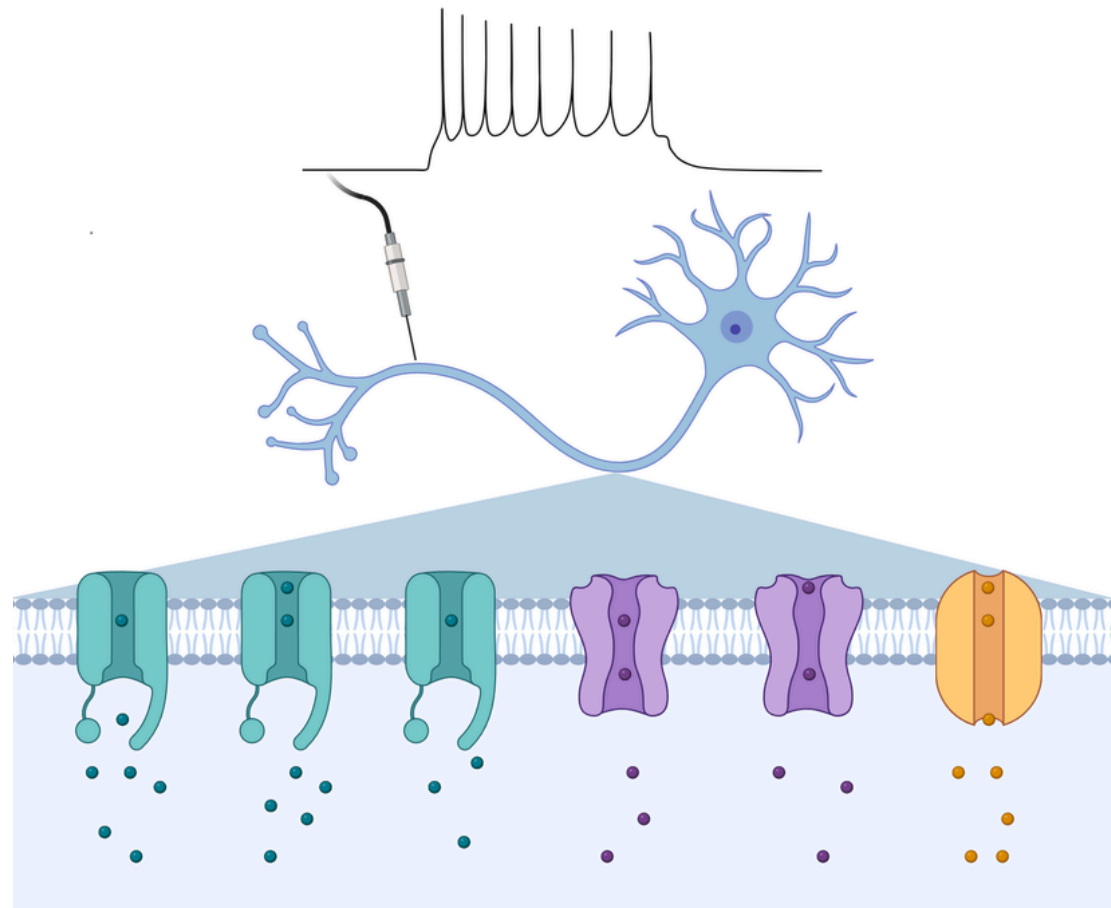
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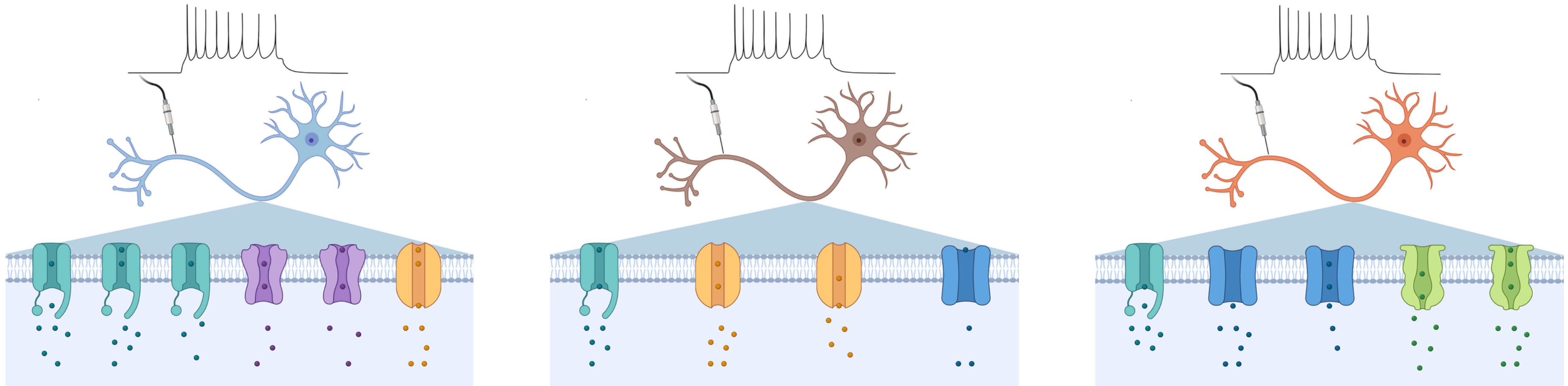
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No biologist would bet on this game

Neurons as parameterized dynamical systems

Degeneracy arises from **functional overlaps** between ion channels

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

$$\tau_i(V) \frac{dx_i}{dt} = x_i^\infty(V) - x_i, \quad x_i \in \{m_i, h_i\}$$

Neurons as parameterized dynamical systems

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$$\bar{\mathbf{g}} = [\bar{g}_1, \dots, \bar{g}_{|\mathcal{I}|}] = ?$$

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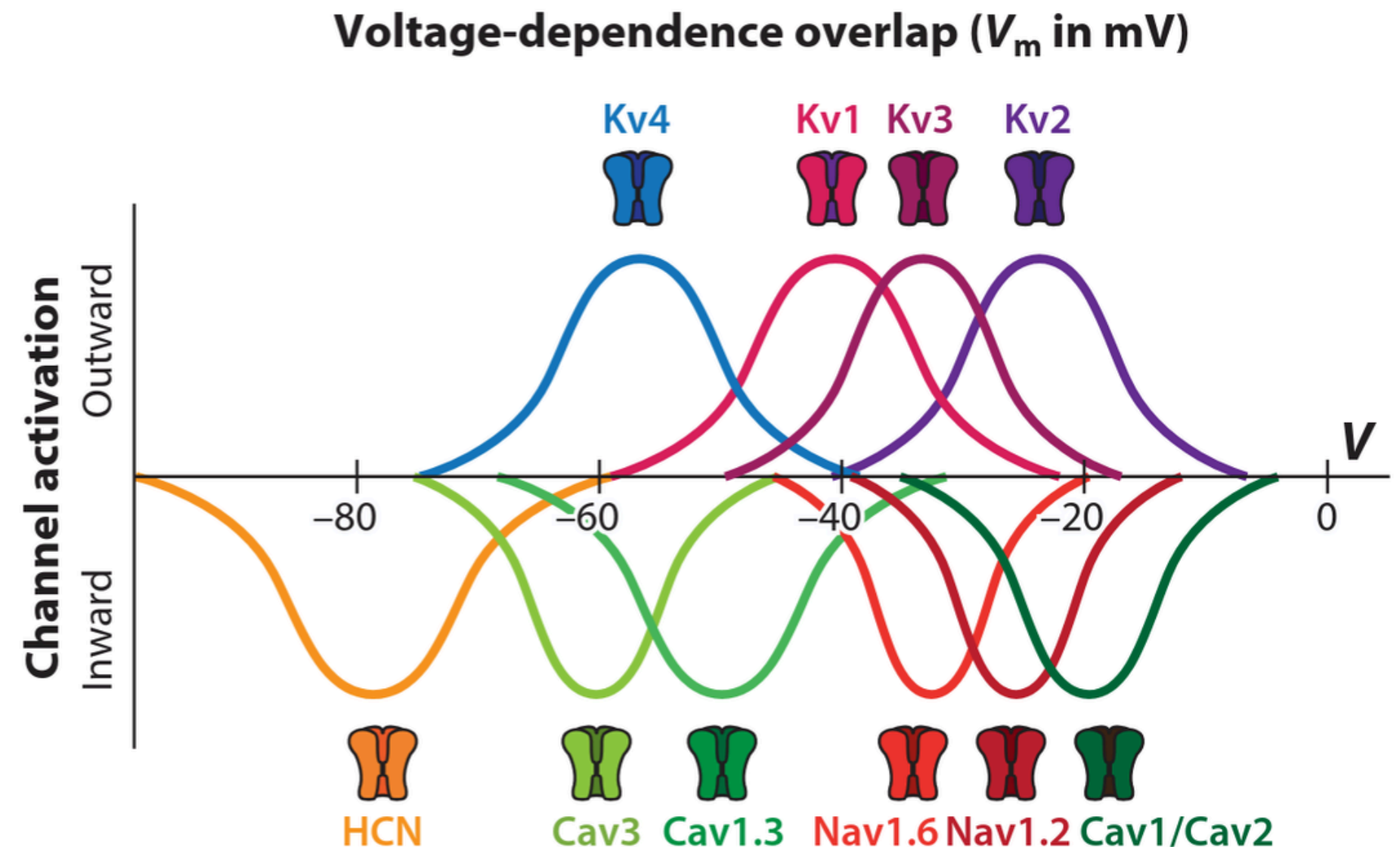
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We need to identify all possible solutions!

Simulation-based inference captures degeneracy

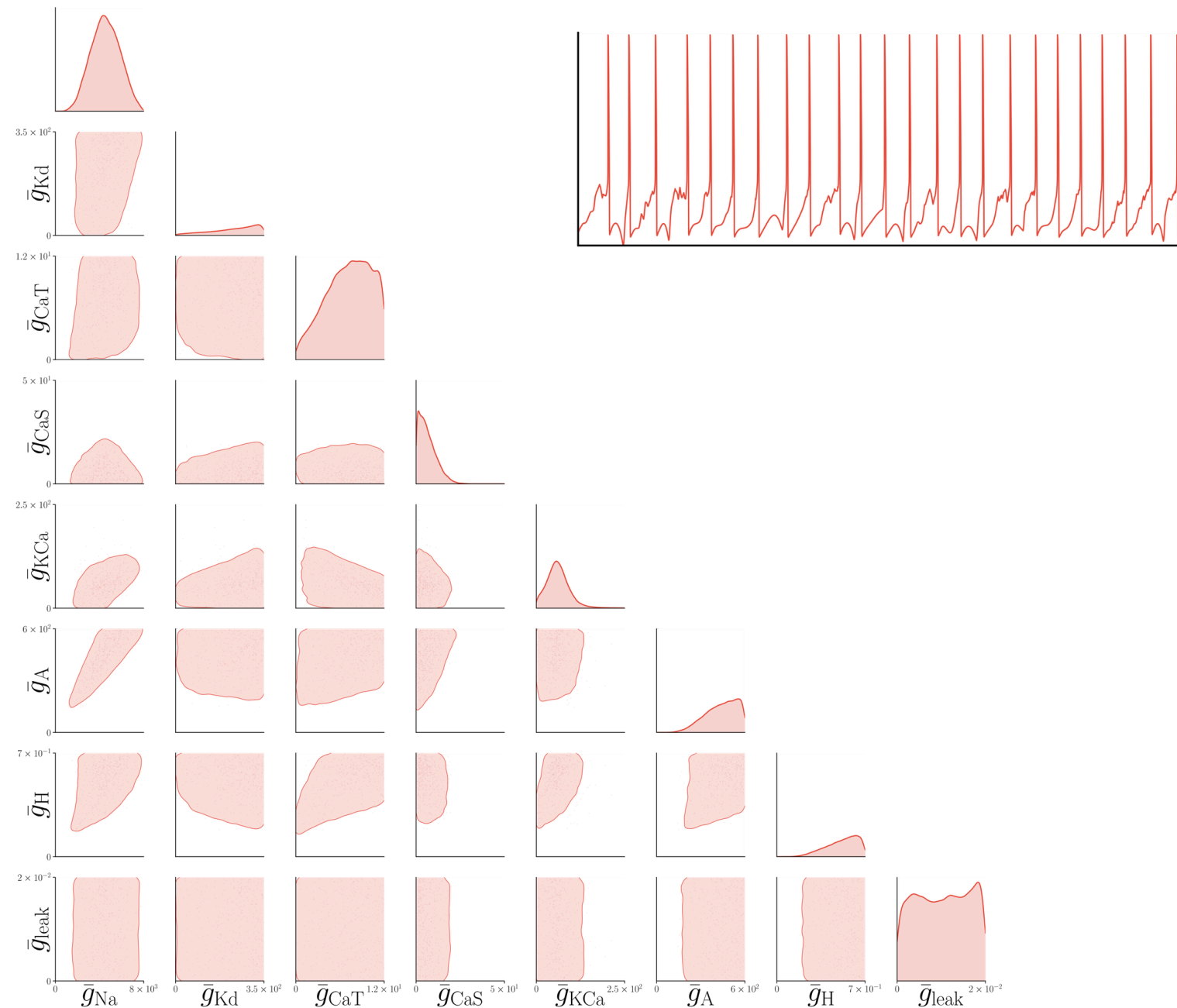
$$q_{\phi}(\bar{\mathbf{g}} \mid \mathbf{s}) \approx p(\bar{\mathbf{g}} \mid \mathbf{s})$$

where q_{ϕ} is a neural network, and $\mathbf{s}$ is the recorded spike train.

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So what? Is the problem solved?!

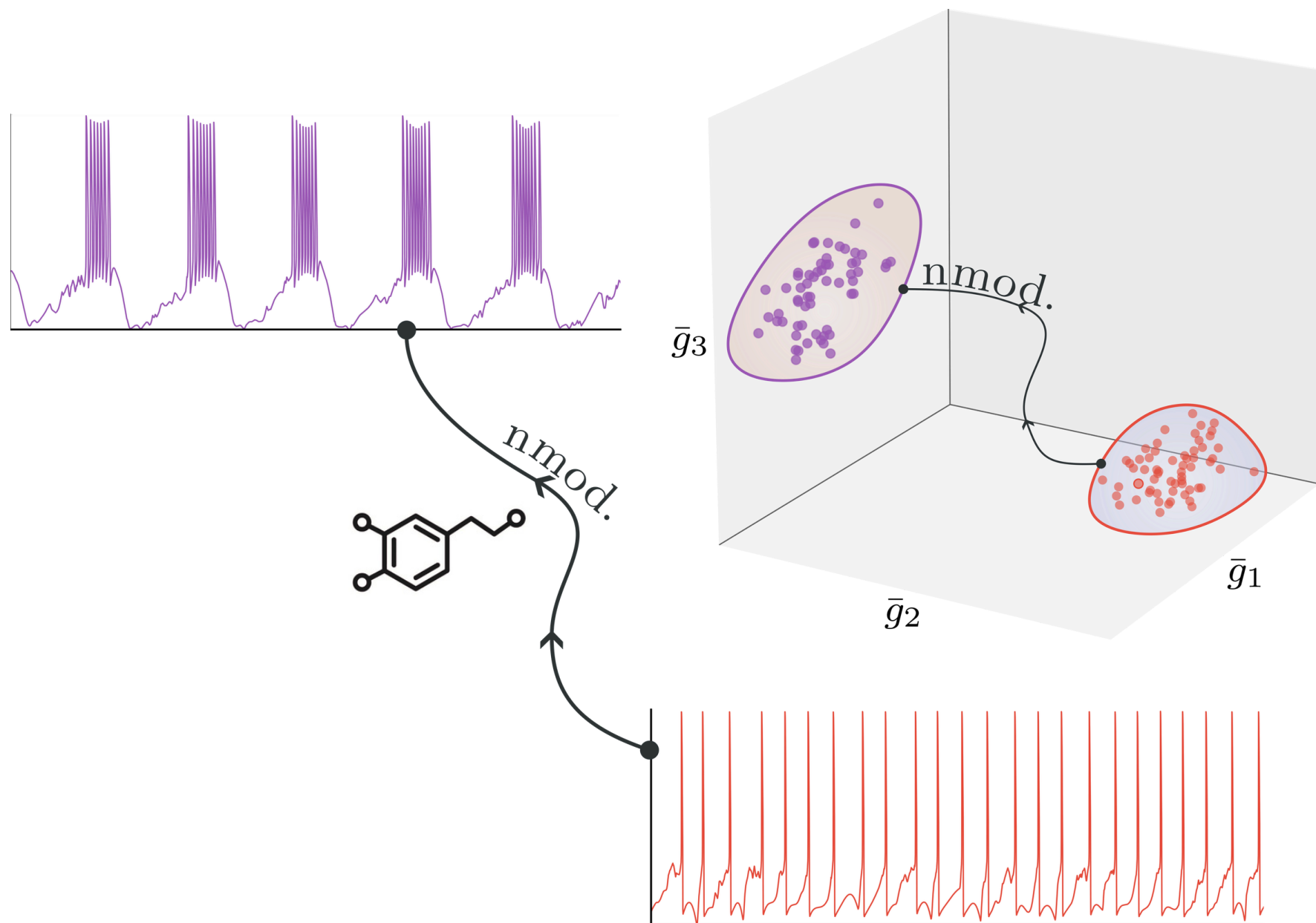
Where's my million dollars?

So what? Is the problem solved?!

**This provides very little useful information for biologists.
The real million-dollar game is about functional understanding.**

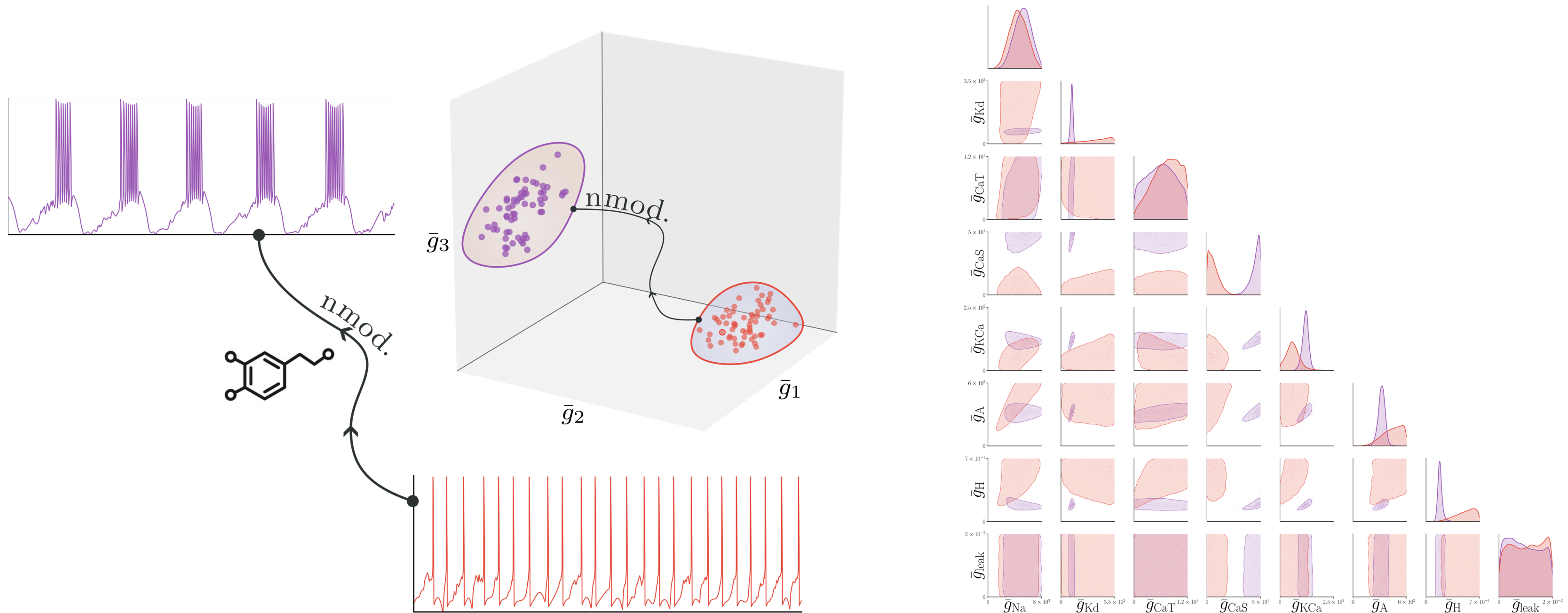
Neuromodulators continuously reshape conductances

Under neuromodulation, the degeneracy game is not static anymore.



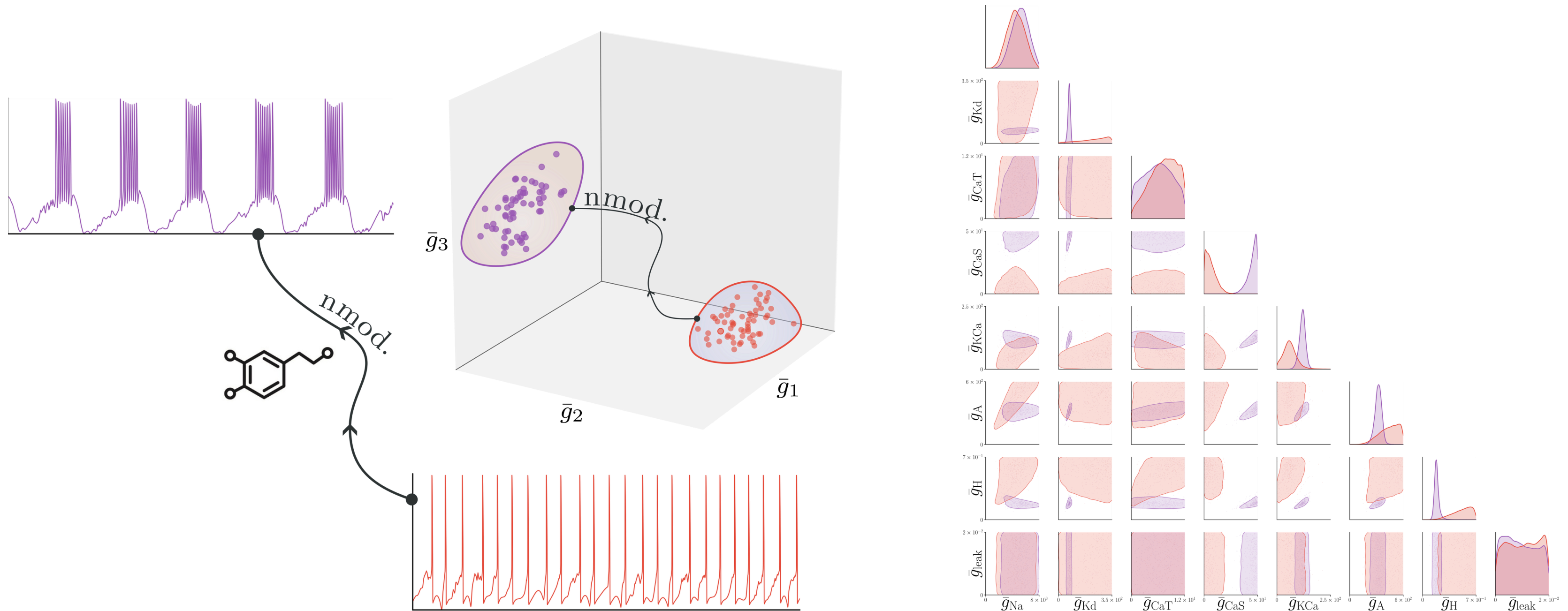
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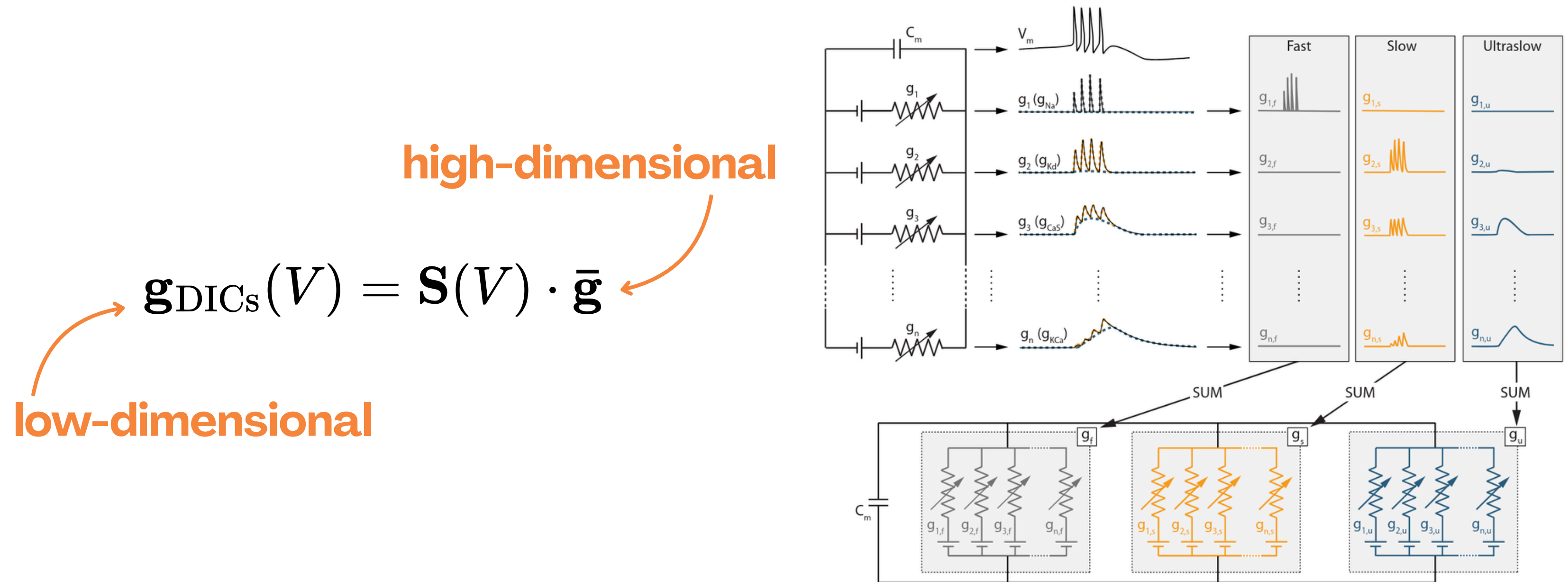
Under neuromodulation, the degeneracy game is not static anymore.



We want to identify the targets of neuromodulation

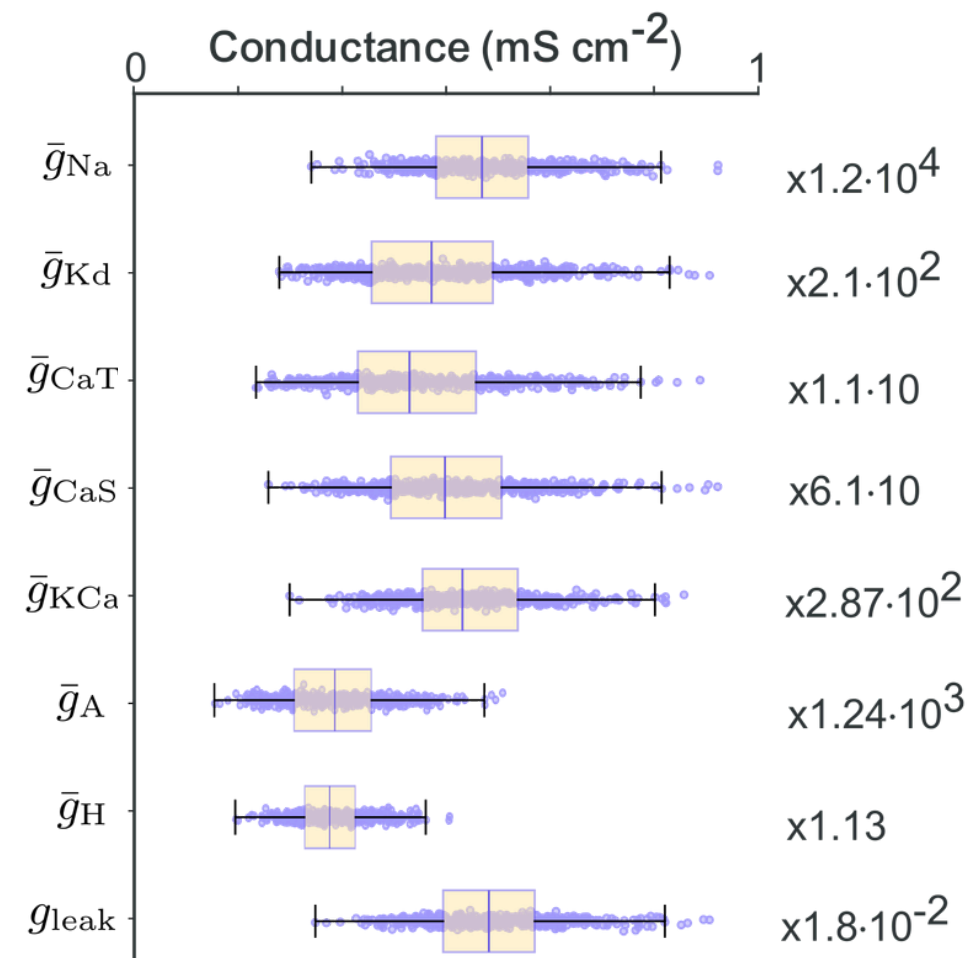
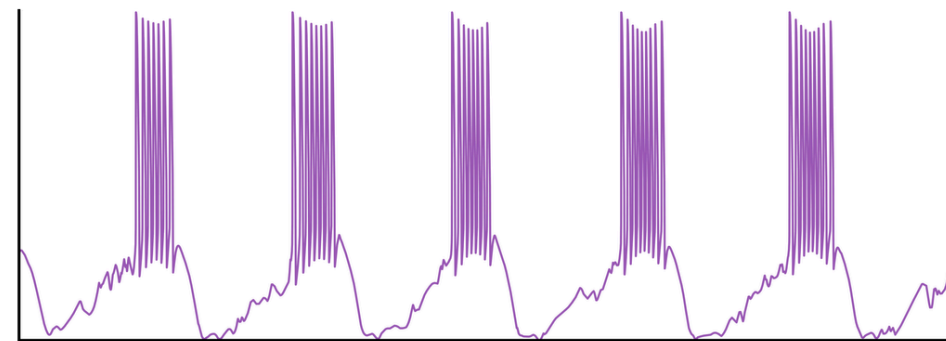
Dynamic Input Conductances (DICs) reduce ion channel dynamics to interpretable components

They are derived from the model equations; projecting on timescales.



Degenerate activities collapse onto similar DICs

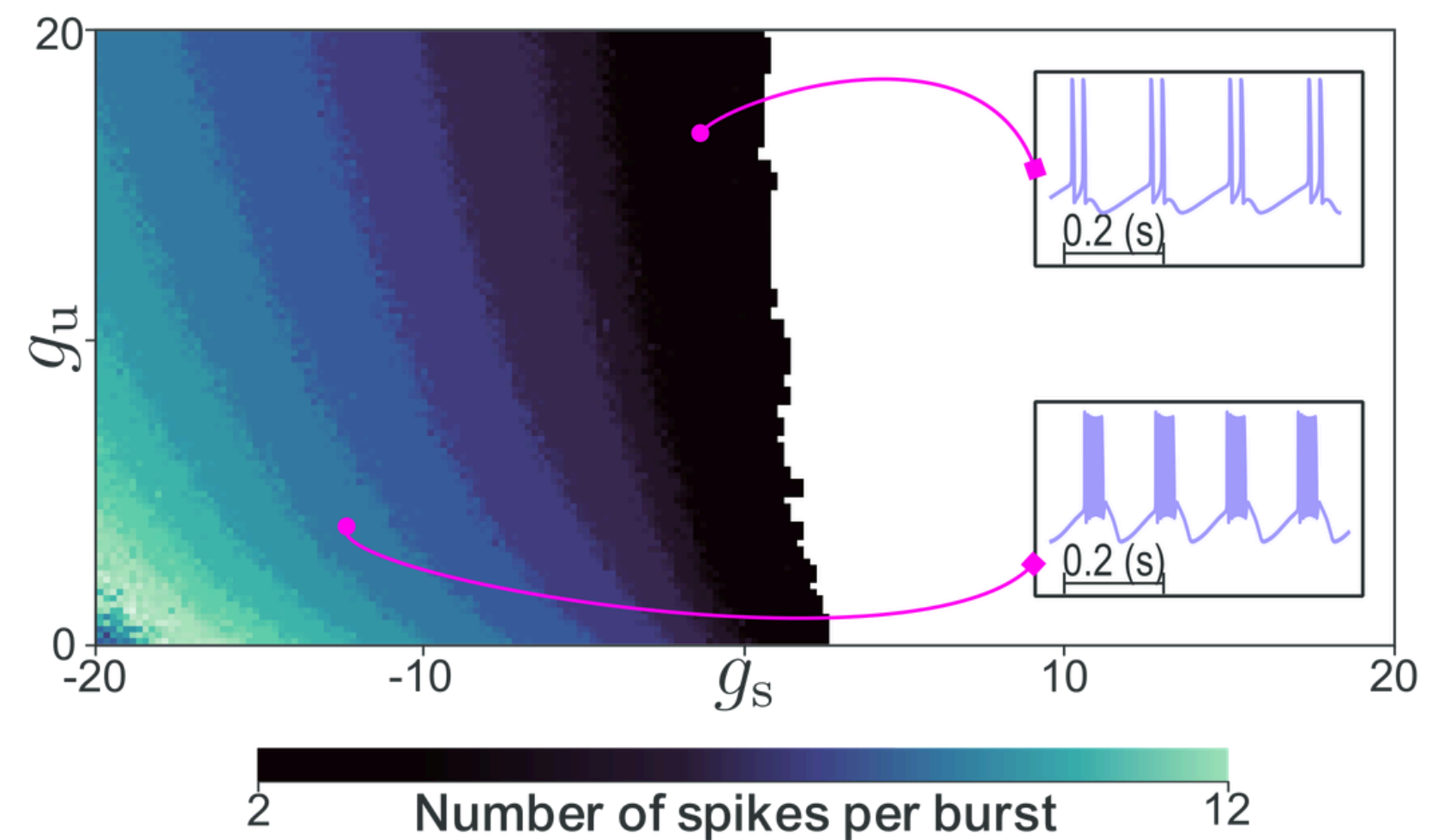
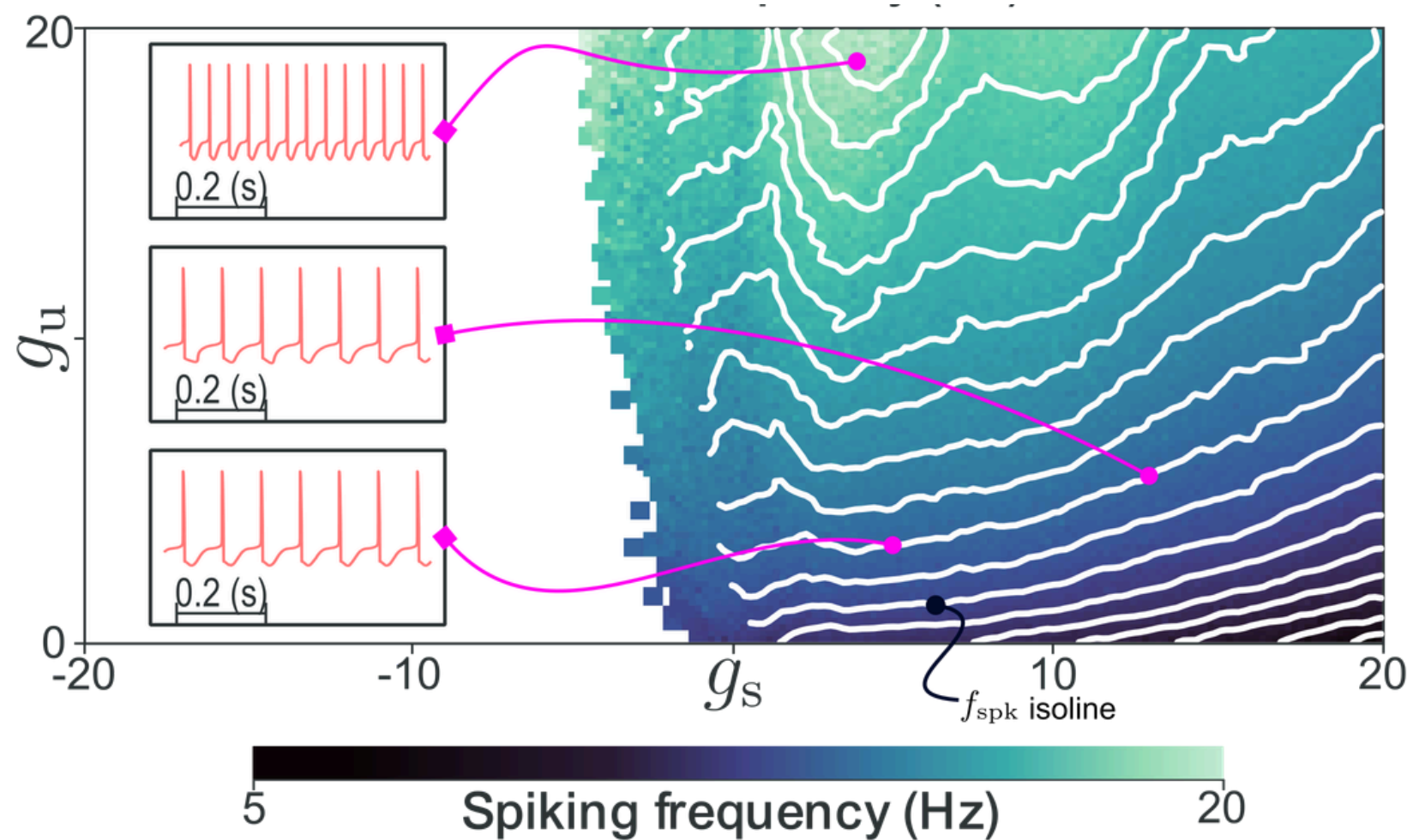
We focus on the, very informative, threshold voltage V_{th} .



$$\mathbf{g}_{DICs}(V_{th}) = \mathbf{S}(V_{th}) \cdot \bar{\mathbf{g}} \approx \begin{bmatrix} -15.0 \\ 5.0 \end{bmatrix}$$

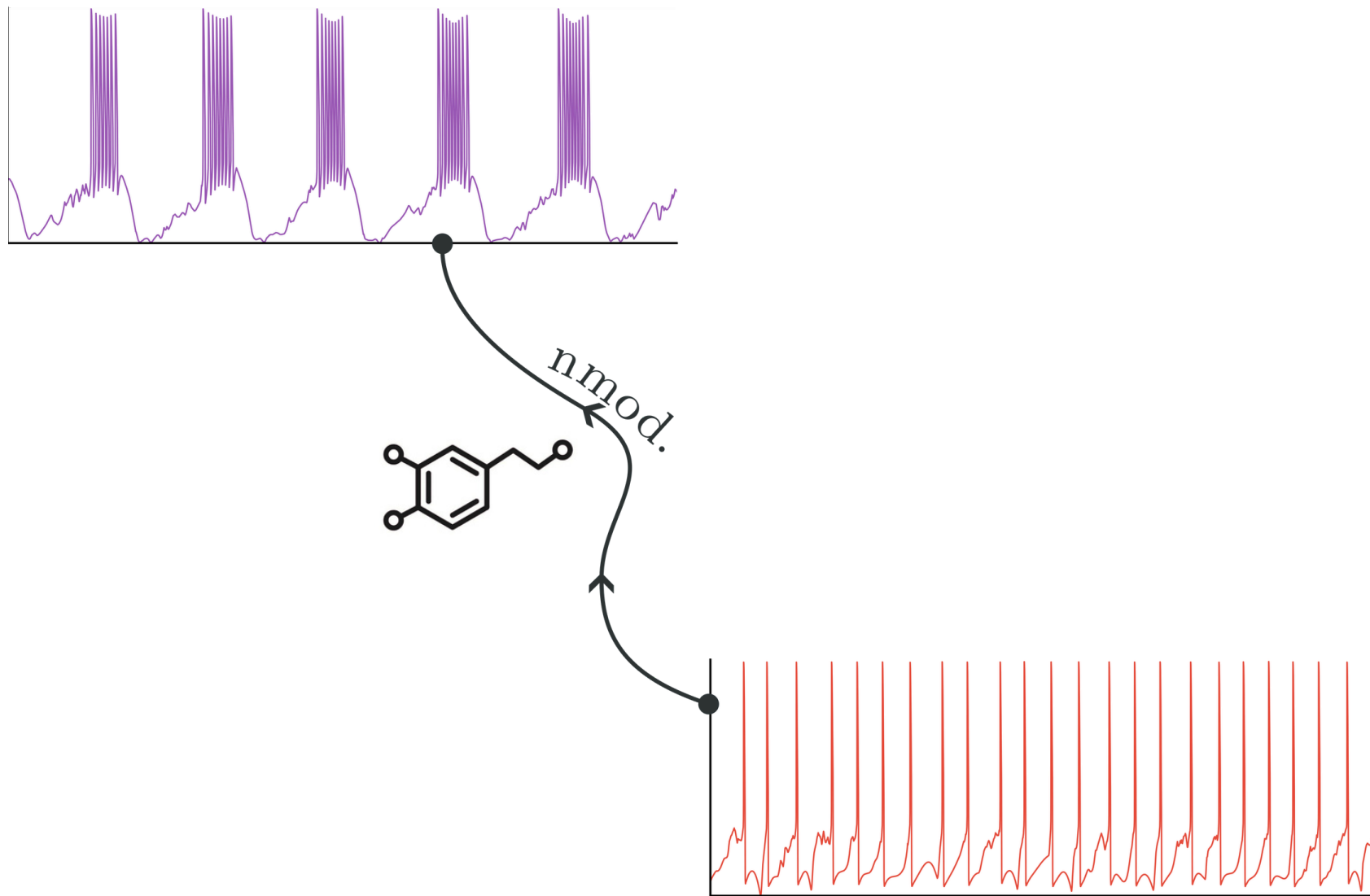
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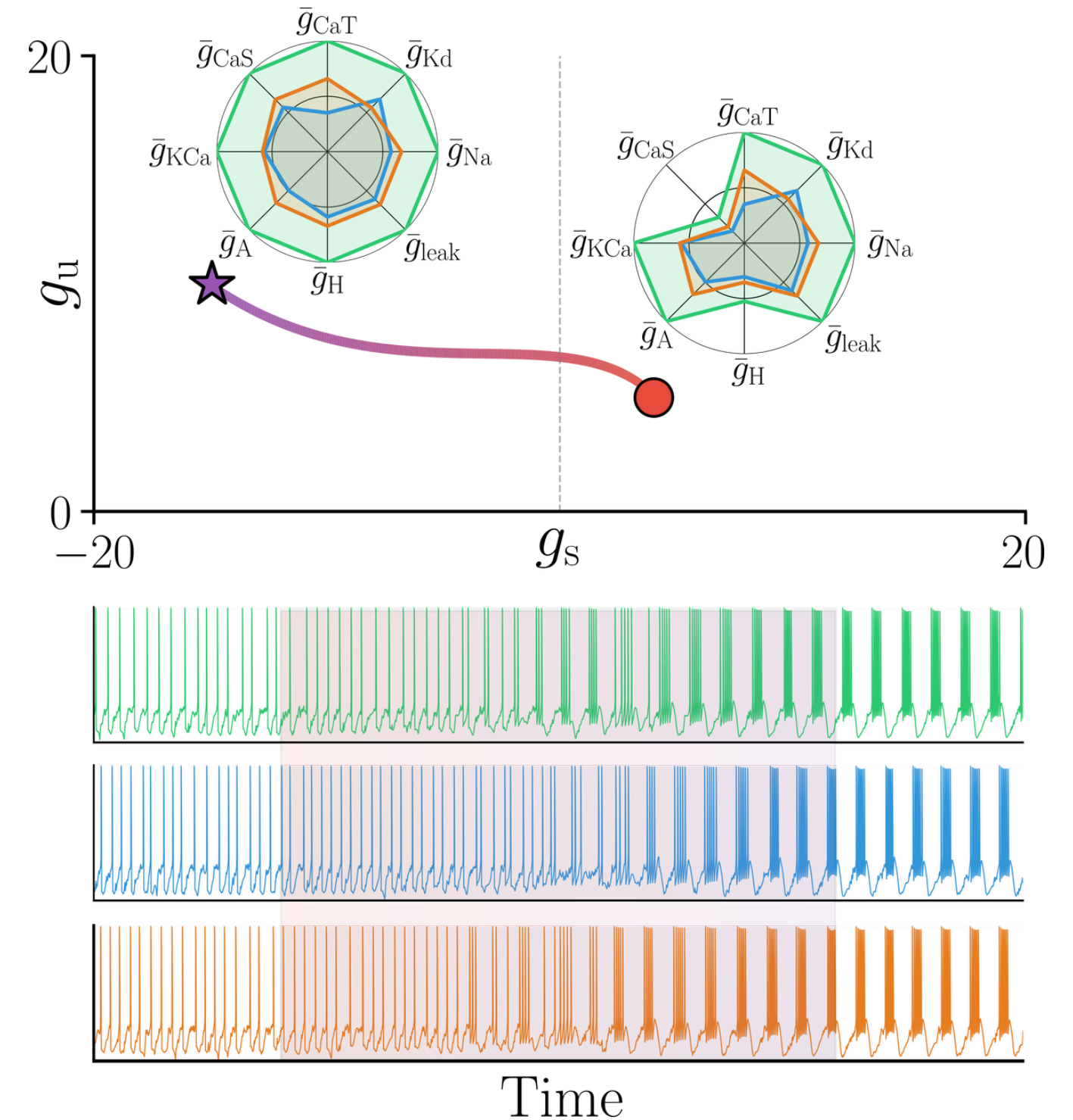
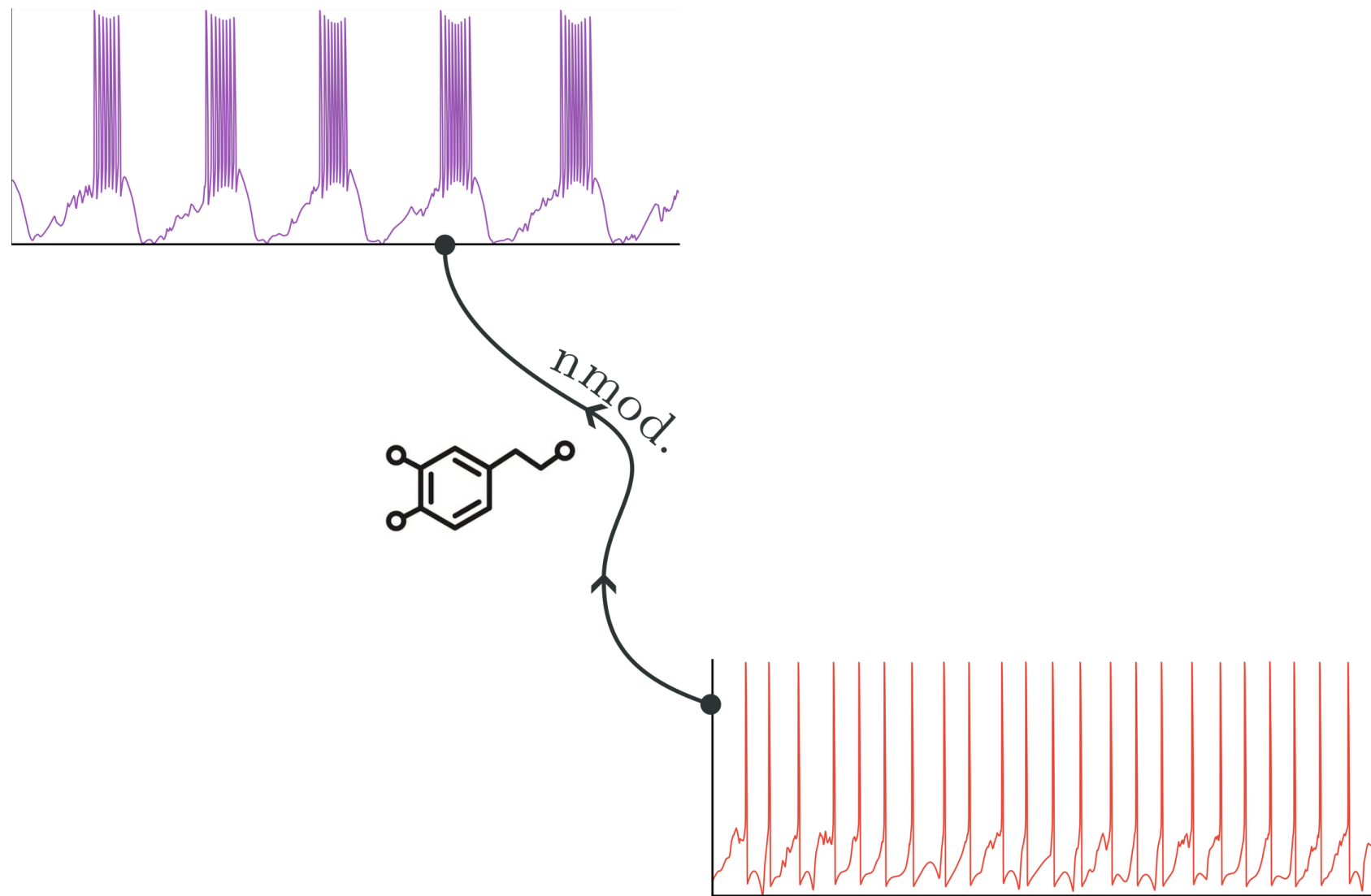
Neuromodulation traces a path in DIC space

Through DICs, we obtain a degeneracy-aware view.



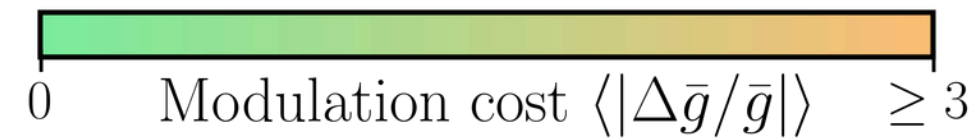
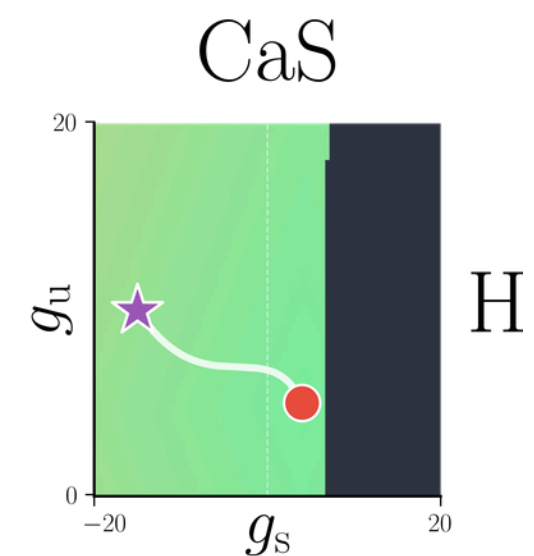
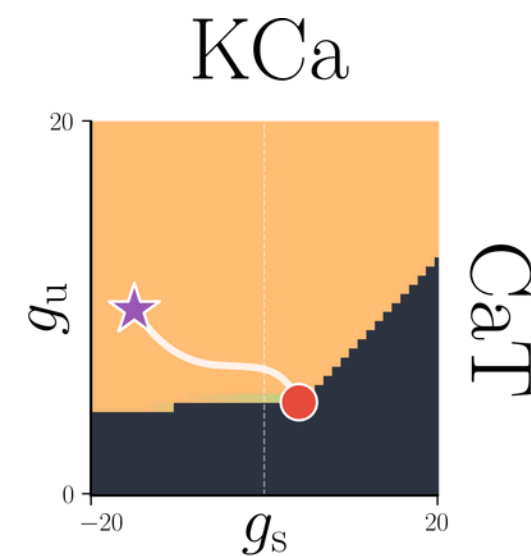
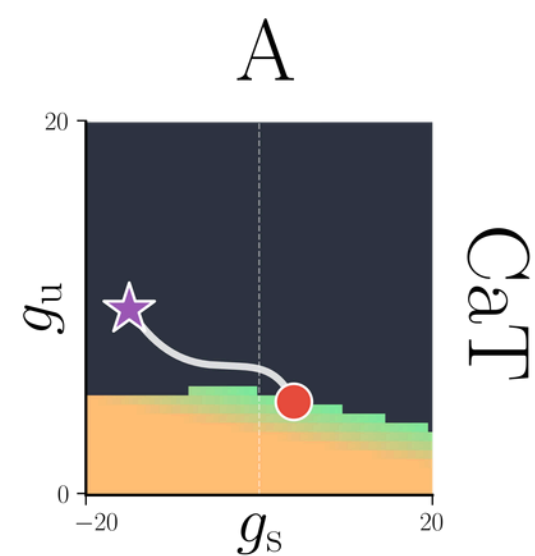
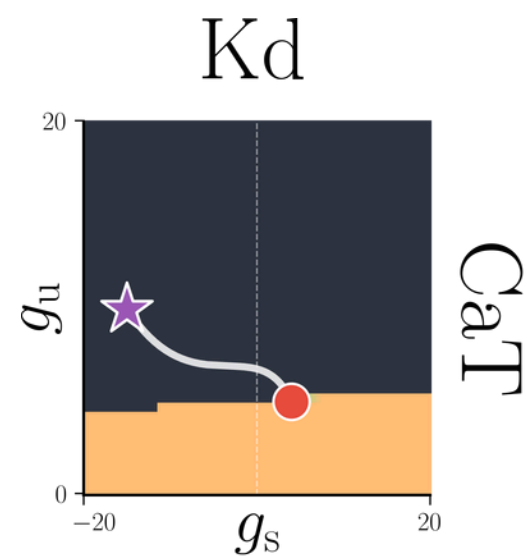
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Through DICs, we obtain a **degeneracy-aware** view.



Reachability maps identify the most plausible neuromodulation targets

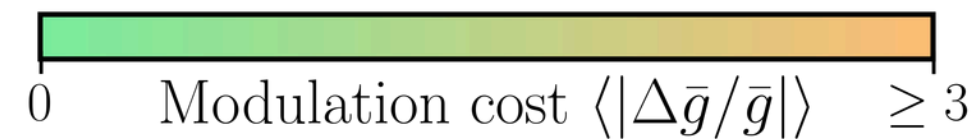
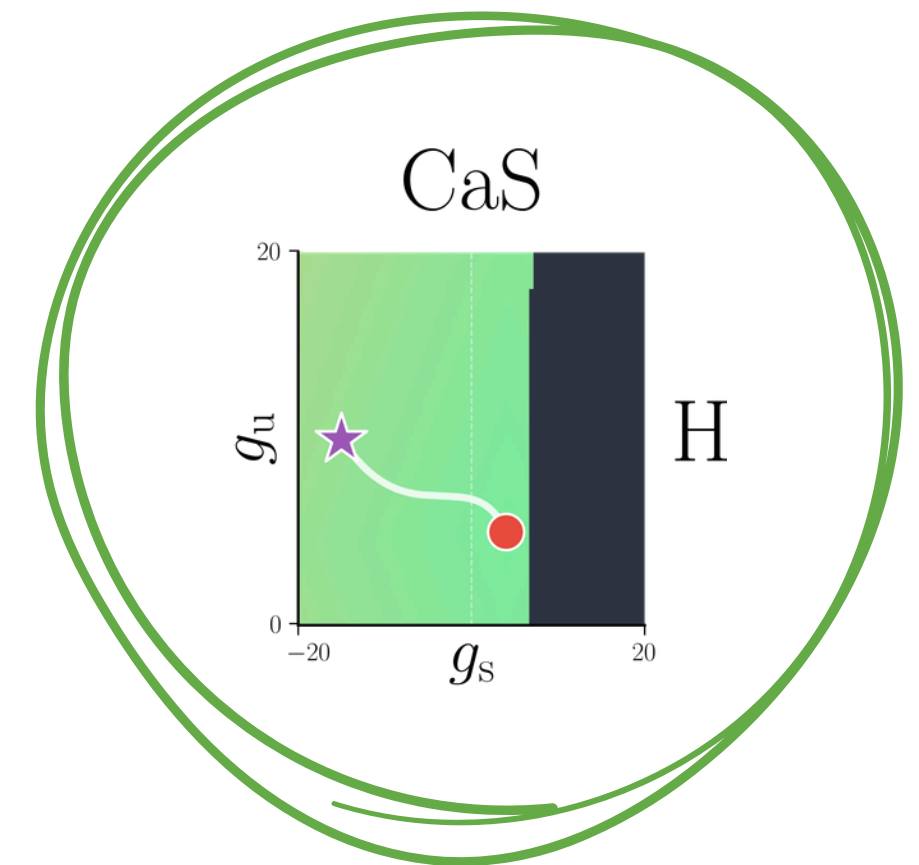
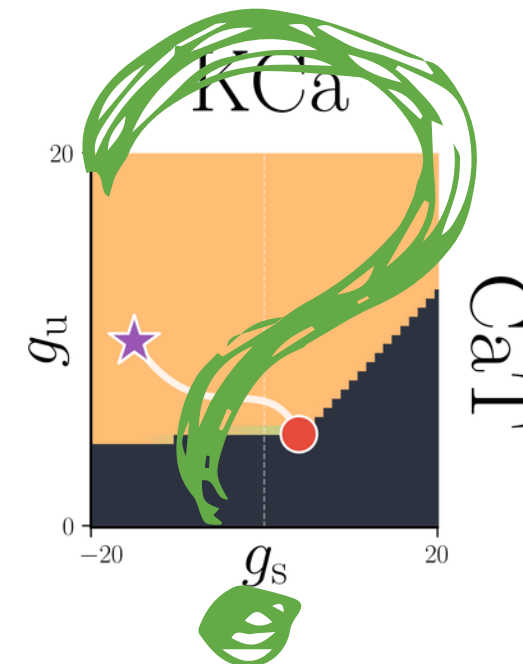
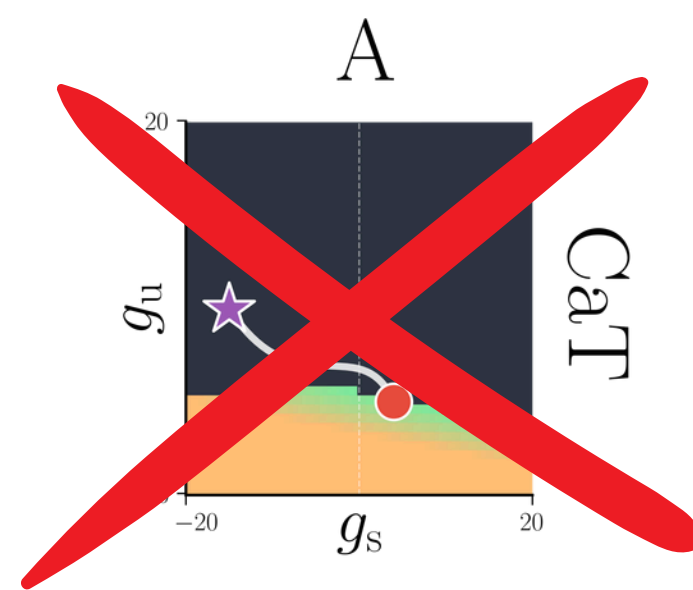
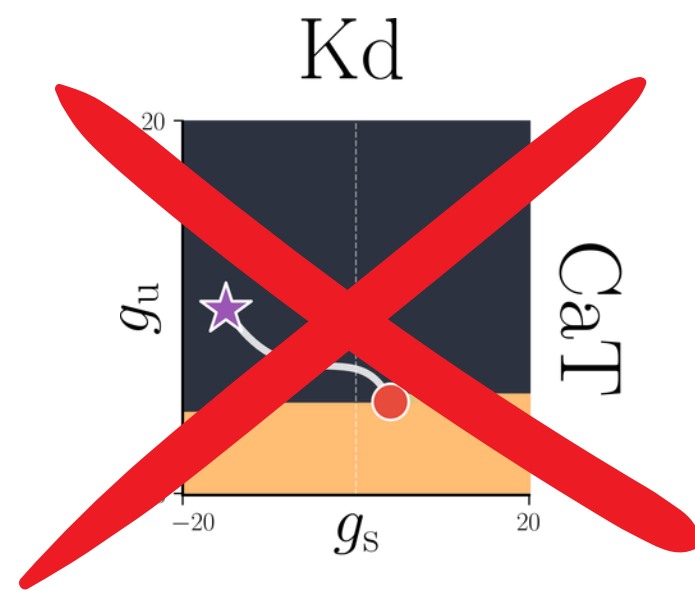
Only certain conductances are allowed to vary,
some subsets are not compatible with the path.



Unreachable
($\bar{g} < 0$)

Reachability maps identify the most plausible neuromodulation targets

Only certain conductances are allowed to vary,
some subsets are not compatible with the path.



Predicting is not understanding !

