Deep Learning-Powered Prediction of Voltage Gating: The Case of Kv7.1

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Voltage-gated ion channels (VGICs) are crucial for cellular excitability, undergoing complex conformational changes to regulate ion flow. Understanding their transient intermediate states is vital for drug design and elucidating channelopathies, yet remains a significant challenge for both experimental and traditional computational methods. While AlphaFold-based approaches excel at static structure prediction, they are not inherently designed to systematically map the dynamic gating pathways of VGICs.

To address this, we have developed and refined a deep learning-based pipeline that integrates AI with biophysical insights to predict intermediate conformations of VGICs. Our approach utilizes a 1D convolutional autoencoder to learn a low-dimensional representation of the channel's conformational landscape from structural data of its open and closed states, typically derived from molecular dynamics simulations. New conformations along the transition pathway can then be generated from this learned manifold. A key innovation is our physics-informed loss function, $L = \alpha_1 L_{\text{MSE}} + \alpha_2 L_{\text{phys}} + \alpha_3 Q_{\text{path}} + \alpha_4 Q_{\text{lin}}$, which incorporates not only geometric consistency (MSE) and classical potential energy terms (L_{phys}), but also novel terms (Q_{path}, Q_{lin}) based on gating charge — a critical collective variable for VGICs.

This work focuses on the Kv7.1 channel, a vital cardiac potassium channel, investigated in the presence of its modulator PIP_2. We present, for the first time, an *in silico* estimation of Kv7.1 gating charge parameters, consistent with experimental measurements. These parameters were subsequently used to guide the prediction of Kv7.1's gating transitions. Furthermore, to enable the study of full tetrameric channels, we successfully addressed a critical computational bottleneck by implementing a custom CUDA kernel for the efficient calculation of non-bonded interaction terms within our physics-based loss. This optimization significantly reduces GPU memory demands, allowing the application of our pipeline to larger, more physiologically relevant systems. Our findings demonstrate the pipeline's capability to generate plausible intermediate states for Kv7.1, offering new insights into its gating mechanism and showcasing the potential of this AI-driven approach for broader applications in VGIC research.