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Investigating Ion Channel Gating Through Md Simulations and Network Analysis

Carlo Guardiani [1], Flavio Costa [1], Alberto Giacomello [1]

[1] Sapienza university, Rome, Italy

Gating is a key property of ion channels whose misregulation causes channelopathies and that could be leveraged for the design of controllable artificial nanopores. Here we investigate the gating of the heart channels hERG and Kv7.1. While the gating mechanism of domain-swapped channels is now known, gating of non-domain-swapped channels like hERG is still controversial. On the other hand, while inactivation of Kv7.1 is operated by residues on the extracellular side, it is modulated by the intracellular CaM and PIP2 ligands suggesting an allostericregulation.

We adopted a graph approach computing paths of minimal length between critical source and sink regions of the protein network. Residues with high centrality index lie on pathways connecting coupled regions. The application of this approach to hERG revealed the presence of non-canonical inactivation pathways in agreement with patch clamp measurements. The application to Kv7.1 on the other hand, showed that the paths connecting CaM and PIP2 to the Selectivity Filter (SF), converge to the final part of the S4-SF

inactivation pathway thus explaining the long-range influence of CaM and PIP2 on inactivation.