Protein interfaces and assembly of heteromeric Nav1.8 ion channels

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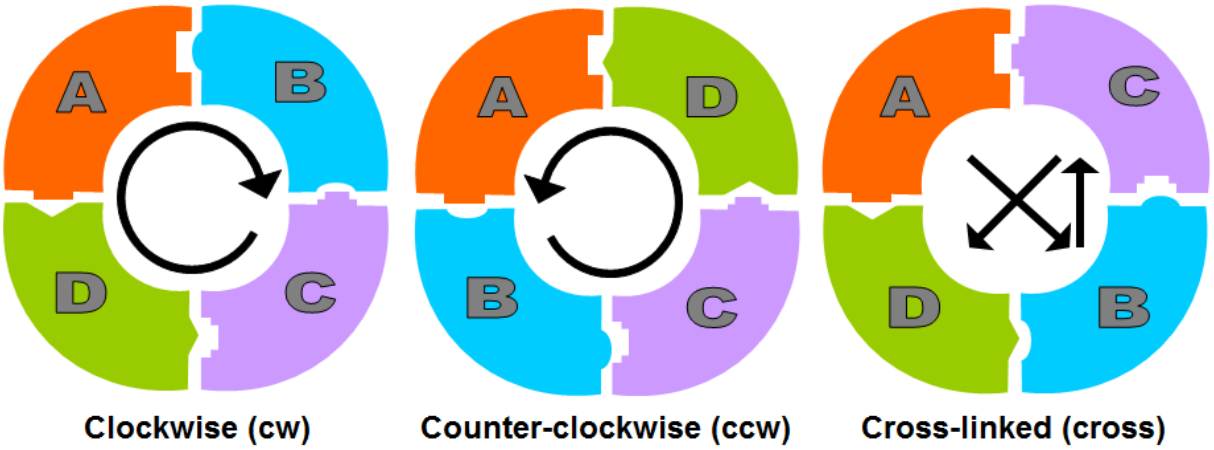

In this work we analyse the formation of heteromeric voltage gated ion channels. In contrast to bacterial homomeric ion channels that have been investigated in the last decade by crystallographic methods, the assembly of heteromeric human ion channels has yet to be studied. Subsequently, we have built homology models of human Nav1.8 sodium channels with all possible associations to study their assembly by computational methods. This includes the possible orientations of clockwise, counter-clockwise and cross-linked models. The side chain conformational landscape has been explored with molecular dynamics simulations.

The focus of the presentation will include the analysis of protein interfaces between the domains as well as the formed patches of these models with various energetic measures. Herein the Rosetta program suite including implemented scores and forcefield energies at different time points play a decisive role.

As a result the key drivers for the domain associations will be summarized with respect to the applied methods.

[1] Rosetta program suite: A. Leaver-Fay, M. Tyka, S. Lewis, O. Lange, J. Thompson, et al., Methods Enzymol., 2011, 487, 545–574.
[2] R. A. Li, I. L. Ennis, R. J. French, S. C. Dudley Jr., G. F. Tomaselli, E. Marbán, J. Biol. Chem., 2001, 276, 11072-11077.
[3] S. C. Dudley Jr., N. Chang, J. Hall, G. Lipkind, H. A. Fozzard, R. J. French, J Gen Physiol., 2000, 116, 679-690.
[4] Molecular Operating Environment (MOE), 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2013.