Depicting fast voltage gating in Connexin hemichannels with Coarse-grain simulations.

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Connexins are tetra-membrane spanning proteins that assemble into plasma membrane hemichannels and Gap Junctions, which mediate intercellular communication. A complete understanding of the gating mechanism of these channels is still lacking, despite a vast amount of genetic, cellular and biochemical data including low-resolution structures.

We used Coarse-grained molecular dynamics simulations to study the fast Voltage gating of Cx26 hemichannel in the multi microsecond time scale under externally applied transmembrane voltage. Completely unbiased simulations reveals conformational transitions passing form a semi-closed to closed and open states. The presence of explicit solvent and simple electrolytes allows for the calculation of the open channel’s conductance, which is comparable to that measured in electrophysiology experiments. Our modeling approach provided the first model of the fully open state of the channel offering a structural frame to evaluate the effect of point mutants related to polymorphisms and a number of genetic diseases.