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Modeling and Simulations of Calcium Channels

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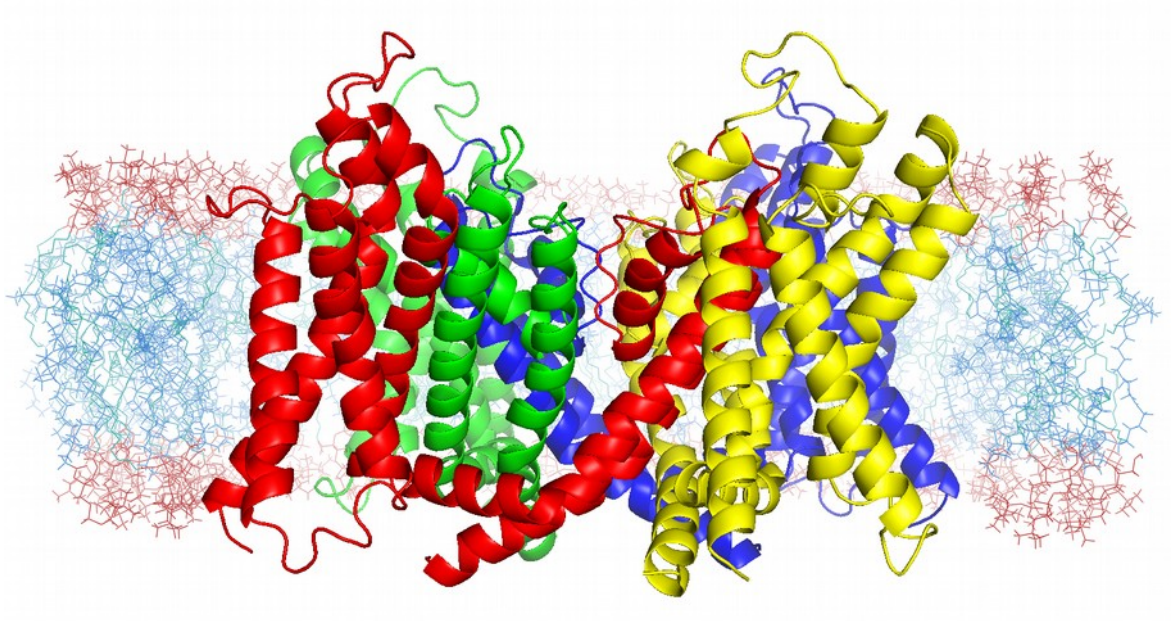

Voltage-gated calcium channels are involved in several diseases and the investigation of their mechanism is based on an atomic-detailed study of the protein 3D structure. Since X-ray structures are not yet available for the pore-forming α_1 subunit, molecular modeling can be applied to predict potential functional changes of mutations in the voltage sensors.

Firstly, homology modeling allows to predict the transmembrane segments of the membrane protein: it starts from the X-ray structure of another homologous ion channel, sharing close sequence similarity. Several states can be modeled editing the sequence alignment, in order to get different positions of key charged residues in the voltage sensors. Then, the loops are modeled by ab initio methods (e.g. Rosetta), using sequence information only, because they differ for each ion channel.

Afterwards, the structural models are minimized in a periodic box including lipids, water molecules and ions, and then submitted to molecular dynamics simulations in order to investigate the development of the interactions in time. Molecular dynamics simulations investigate specific functions of the protein, such as the mechanism of activation or changes in the structure upon mutations. As an example the simulation of a mutant of the voltage sensor has shown the formation of a wire of water molecules in the resting state of the mutant, that is not present in the wild-type protein.