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Research Project

Ion channels are transmembrane proteins that regulate the movement of ions across cell membranes. The ion channels-mediated currents are involved in a plethora of biological processes, including cardiac contraction, nerve transmission, and cell homeostasis. Thus, there is a great interest in numerical techniques for simulating the activity of ion channels. Nowadays, there are two approaches that are commonly used to model these proteins. The functional properties are usually described by Markov Models (MMs) estimated from experimental data. These MMs reproduce quantitatively the membrane currents, but they do not reveal how channels operate at the atomic level. Conversely, Molecular Dynamics (MD) simulations reproduce the behaviours of proteins at atomic level, but because of the high computational cost, they cannot be routinely used to simulate membrane currents. Thanks to an increase in computational resources and theoretical advancements, it is now possible to estimate MMs directly from MD simulations. The aim of this project is to estimate the currents through ion channels using MMs based on MD simulations, and to compare these in-silico estimates with in-vitro data obtained under different conditions in term of membrane potential, combination of ion species and ion concentrations.

Plan of activities

The research plan includes the following activities: - Firstly, MD simulations will be performed for different ion channels under different experimental conditions. The set of atomistic simulations will investigate the dependency of the channel behaviours on lipid compositions, permeating ion species, ion concentrations in the extracellular and intracellular comportment, and membrane potential; - Then, these atomic trajectories will be used to estimate kinetic models of the ion channels at the various experimental conditions. These models will need to describe both the dynamics of the channel protein (possible transitions among different states) and of the permeating ions; - Finally, estimated currents will be compared with experimental data. Single channel currents will be obtained by patch-clamp experiments in giant liposomes, and/or measurements in planar artificial lipid bilayers using channels produced by heterologous expression in bacterial cells. The comparison between simulated currents and experimental data will be used to optimize the modelling methods