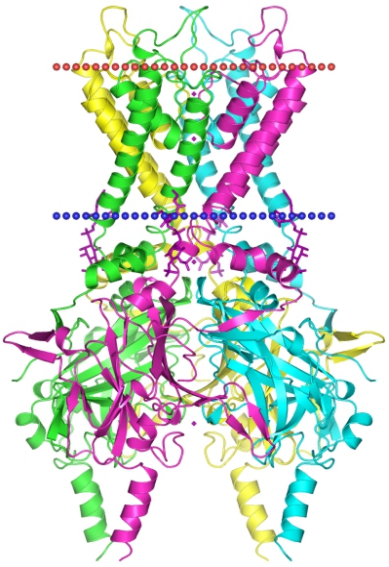
Title : How anionic lipids regulate lipid-gated ion channels: an *in silico* study

[submitted to **Biochemistry MSc.**]

Workplace: BioISI-FCUL (C8, 8.5.50D) **Duration:** 12 months
Supervision: Miguel Machuqueiro (machuque@ciencias.ulisboa.pt)
Webpage/ORCID: mms.rd.ciencias.ulisboa.pt / 0000-0001-6923-8744



Lipid-gated ion channels are a class of the voltage-gated ion channel superfamily whose conductance of ions through the membrane is modulated by lipid binding. The most common mechanisms are mediated by PIP, PA, or PG lipids in the inner leaflet of the plasma membrane, that, due to their anionic charges, are able to change the local membrane potential and trigger the channel ion permeabilities. Other mechanisms include the mechanosensitive ion channels that respond to lipid tension, thickness, and hydrophobic mismatch [1]. Several structures of these lipid-gated ion channel proteins have been resolved, including the K^+ channel K_{ir} 2.2 (see Figure) [1] and the K_v7 [2], both in complex with PIP2 lipid.

The goal of this project is to study at the molecular level the role of these anionic lipids in triggering the ion conductance along these channels. We will use our state-of-the-art constant-pH molecular dynamics method extended to deal with lipid bilayers (CpHMD-L) [3] and the project will have the following tasks:

1- Parameterization of the anionic lipids and calibration of their pK_a values;

2- Setup the Kir2.2 channel (PDB ID: 3SPG) in a POPC membrane environment containing PIP2 lipids in the inner leaflet and retaining them in crystallographic positions;

3- Perform CpHMD-L simulations at physiological pH of ion channel in the presence and absence of anionic lipids to equilibrate their active and inactive states;

4- Calculate the K^+ channel permeability in both lipid-bound and lipid-unbound states using CpHMD-L simulations coupled with an umbrella-sampling protocol.

5- Write the thesis and prepare a scientific manuscript for publication.

[1] Hansen, S.B. (**2015**) *Biochimica et Biophysica Acta*, 1851, 620
[2] Sun J., MacKinnon R. (**2020**) *Cell*, 180, 340.
[3] Teixeira, V. H., Vila-Viçosa, D., Reis, P. B. P. S., Machuqueiro, M., (**2016**) *J. Chem. Theory Comput.*, 12, 930-934.