1. PHD PROJECT DESCRIPTION

Project title:

How Ligands and Membranes Regulate Inwardly Rectifying Potassium Channels? A Computer Modelling Approach.

Project goals

- To gain understanding of how small molecules and drugs regulate Kir channels activity and how this process is affected by the composition of a membrane
- To develop the multiscale molecular dynamics methods suitable for effective modelling of ion channels

1.1. An outline

Living organisms depend on ion channels – large protein systems present in biological membranes. Usually ion channels are selective and conduct effectively only one type of ions, for example, sodium or potassium. Ion channels discovered so far are classified into tens of different groups. In this project we will focus on specific potassium ion channels belonging to the Kir family (seven sub-families – Kir1-7). These channels, in contrast to "standard" potassium channels, conduct positive charges better into a cell than outside. Such inwardly rectifying (IR) potassium channels have been found in a wide variety of cells: cardiac myocytes, neurons, pancreatic beta-cells. They stabilize the resting membrane potential near the K^+ equilibrium potential, and facilitate the transport of K^+ through the membrane [1]. The physiological activity of a Kir channel depends on regulation of the pore opening and an ion flux. Major natural factors that regulate the pore opening include nucleotides, such as ATP, and a variety of membrane lipid modulators (PIP2, cholesterol etc.).

The aim of the project is to understand how various small molecules interacting with Kir regulate the channel activity and how this process is affected by the physical properties of a membrane.

This issue is related to famous allosteric effects. For that purpose, the computational molecular dynamics methods will be used. However, the problem is ambitious, since the physiological microsecond time scale of the transition from open to close state of the channel requires usage of either advanced all-atom MD sampling methods such as metadynamics [2] and rex-GaMD [3], or the coarse grained (CG) approaches [4]. Within this PhD project a few enhanced sampling methods will be applied to simulate the dynamics of Kir channels upon a ligand (for example phosphatidylinositol 4,5-bisphosphate - PIP_2) binding. We will use one of hybrid models – so called Fixed Resolution method [5] (FR). In that method crucial parts of

proteins are shown in full atomistic detail, whereas the rest of the system is simulated with a cheaper CG resolution. Supercomputer centres will be used to run calculations. Combining high resolution atomistic simulations with low resolution CG description is a challenging task, but it has been successfully applied in simulations of membrane processes [6], protein folding [7] and GPCR ligands binding [8]. Here such a hybrid approach will be tested for Kirs for the first time. In our group we have a good knowledge of Kir6.2, a channel related to glucose metabolism, based on our recent NCN OPUS project [9]. Thus, a PhD candidate will have a head start into high level research. Successful implementation of modern MD approaches into Kir channel systems dynamics studies will open new perspectives in medically important simulations. If successful, and time permitting, we will use the new methodology in studies of prospective light activated drugs regulating the Kir channels.

1.2. Work plan

- Mastering MD methods and statistical physics
- Building Kir channels models; 1st: Kir6.2/SUR1 complex
- Developing a computational scheme for metadynamics/rex-GaMD in the Kir channel
- Developing a computational scheme for CGFR method in the Kir channel systems
- Testing, reaching millisecond timescales MD or enhancing conformational changes
- Large scale tests of ligands/prospective drugs, including photoactive, on the Kir activity

1.3. Literature

1. Kew, J.N.C….., *Ion Channels: From Structure to Function*. 2010: Oxford University Press.
2. Branduardi, et al. JCTC 2012. **8**(7): p. 2247-2254.
3. Huang, Y.M., et al. JCTC 2018. **14**(4): p. 1853-1864.
4. Shih, A.Y., et al., J Phys Chem B, 2006. **110**(8): p. 3674-84.
5. Rzepiela, A.J., PCCP, 2011. **13**(22): p. 10437-48.
6. Genheden, S. et al. JCTC 2015. **11**(10): p. 4749-4759.
7. Han, W. and K. Schulten, JCTC, 2012. **8**(11): p. 4413-4424.
8. Leguèbe, M., et al., PLOS ONE, 2012. **7**(10): p. e47332.
9. K. Walczewska-Szewc, W. Nowak *"**Structural determinants of insulin release: disordered N-terminal tail of Kir6.2 affects potassium channel dynamics through interactions with sulfonylurea binding region in SUR1 partner**"*, J Phys Chem B (2020) subm.

Required knowledge and skills of the PhD candidate

- Fan of computers
- Analytical thinking
- Some programming skills
- Basics of physics, chemistry, math and biology
- Curiosity