1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan, all in English)

Project title:

Regulation of ATP-sensitive ion channels by ligands and membrane lipids

1.1. Project goals

- To develop the multiscale molecular dynamics methods for ion channels computer modelling
- To gain fundamental understanding at molecular level how activity of ion channels are regulated by small molecules present in the cellular environment
- To check computationally what is a role of physical and chemical properties of biological membranes in regulating ion channels dynamics and structure

1.2. Outline

The project is in the area or theoretical molecular biophysics. Adenosinotriphosphate (ATP) is well known and abundant "energy storage" molecule. ATP-activated ion channels have been found in a wide variety of cells. They have two main physiological functions: to stabilize the resting membrane potential and to facilitate the transport of ions through the membrane [1]. The physiological activity and functions of ATP-regulated ion channels depend on precise regulation of a pore opening and the ion flux. Major factors that regulate the pore opening include nucleotides (ATP and others) and a variety of membrane lipid modulators (PIP, cholesterol, etc.).

The project aims to gain a fundamental understanding of how substrates present in the typical ATP-regulated ion channel affect the channel activity and how this process is influenced by changing the chemical composition of a biological membrane. For this purpose, molecular dynamics (MD) methods will be used as a main research tool. However, the microsecond time scale of the transition from open to close state of the channel calls for using either advanced computational sampling MD methods such as metadynamics [2] or rex-GaMD [3], or coarse-grained (CG) MD approach [4].

Within this PhD project, a variety of computational approaches will be used to simulate the dynamics of ion channels alone and upon ligand binding. Especially, to reduce the negative effects of deteriorated accuracy CG simulations, we will use one of the hybrid models – so-called Fixed Resolution method [5] (FR). In such a method, the molecular system is represented as a combination of elements with different levels of a detail. The crucial parts of proteins, which are likely to play an important role in processes we are interested in, are represented in a full atomistic detail. In contrast, the rest of the system, such as solvents or membranes, are simulated with the coarse-grained resolution. Combining high-resolution atomistic simulations with a low-resolution CG description is a challenging task. However, it has been successfully applied in simulations of membrane processes [6], protein folding [7], and G-protein coupled receptors ligands binding [8] studies. Here we will extend the area of applications of such methods into ion channel modelling area.

Using MD simulation we recently have gain better understanding of Kir62/Sur1 potassium ion channel involved in control of glucose level and diabetes [9,10]. Successful application of these approaches in ion channel systems can open new perspectives in complex systems simulations in biology, chemistry, physics, bioengineering, and all other disciplines in which multiscale MD methods may bring better understanding of physics of living matter..

1.3. Work plan

- Mastering methods of molecular dynamics, Monte Carlo and statistical physics
- Building series of ATP-regulated ion channels models
- Developing a computational scheme for metadynamics/rex-GaMD method in the ion channel system
- Developing a computational scheme for CGFR method in the ion channel systems
- Testing the approaches, reaching millisecond timescales of simulation or enhancing the

slow conformational change of closing and opening of the channel.

- Systematic review of membrane and ligand possible effects on ATP-regulated ion channel dynamics

1.4. Literature

1. Kew, J.N.C. and C.H. Davies, *Ion Channels: From Structure to Function*. 2010: Oxford University Press.
2. Branduardi, D., G. Bussi, and M. Parrinello, *Metadynamics with Adaptive Gaussians.* Journal of Chemical Theory and Computation, 2012. **8**(7): p. 2247-2254.
3. Huang, Y.M., J.A. McCammon, and Y. Miao, *Replica Exchange Gaussian Accelerated Molecular Dynamics: Improved Enhanced Sampling and Free Energy Calculation.* J Chem Theory Comput, 2018. **14**(4): p. 1853-1864.
4. Shih, A.Y., et al., *Coarse grained protein-lipid model with application to lipoprotein particles.* J Phys Chem B, 2006. **110**(8): p. 3674-84.
5. Rzepiela, A.J., et al., *Hybrid simulations: combining atomistic and coarse-grained force fields using virtual sites.* Phys Chem Chem Phys, 2011. **13**(22): p. 10437-48.
6. Genheden, S. and J.W. Essex, *A Simple and Transferable All-Atom/Coarse-Grained Hybrid Model to Study Membrane Processes.* Journal of Chemical Theory and Computation, 2015. **11**(10): p. 4749-4759.
7. Han, W. and K. Schulten, *Further Optimization of a Hybrid United-Atom and Coarse-Grained Force Field for Folding Simulations: Improved Backbone Hydration and Interactions between Charged Side Chains.* Journal of Chemical Theory and Computation, 2012. **8**(11): p. 4413-4424.
8. Leguèbe, M., et al., *Hybrid Molecular Mechanics/Coarse-Grained Simulations for Structural Prediction of G-Protein Coupled Receptor/Ligand Complexes.* PLOS ONE, 2012. **7**(10): p. e47332.
9. Structural Determinants of Insulin Release: Disordered N-Terminal Tail of Kir6.2 Affects Potassium Channel Dynamics through Interactions with Sulfonylurea Binding Region in a SUR1 Partner, Walczewska-Szewc K., Nowak W., J. Phys. Chem. B 2020, 124, 29, 6198–6211.
10. Photo-switchable Sulfonylureas Binding to KATP Ion Channel Reveals Mechanism of Light-controlled Insulin Release, Walczewska-Szewc K., Nowak W., JACS (2021) submitted.

Required initial knowledge and skills of the PhD candidate

- Analytical thinking
- Basic programming skills, willing to learn more
- Good understanding of physics, basic understanding of chemistry, mathematics and biology
- Curiosity

1.5. Expected development of the PhD candidate's knowledge and skills

- Deep understanding of advanced modelling methods used in computational biophysics
- Understanding of potassium channel architecture and physiology
- Improvement of programming skills (Python, Unix)
- "Fluency" in work in international scientific settings