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

Project title:

New mechanisms of ion channels control through classical and photoactive ligands

1.1. Project goals

- To develop the multiscale molecular dynamics protocols for ion channels computer modelling
- To gain understanding, at molecular level, how functions of medically important ion channels are regulated by small molecules (ATP, lipids) present in the cellular environment
- To search computationally and via single molecule experiments for new possibilities of optical control of ion channels by light-activated ligands

1.2. Outline

The project is focused in the area or theoretical molecular biophysics but some AFM and Magnetic Tweezers experiments for single molecules are also planned. In many organs (brain, pancreas) a large protein structures called ion channels regulate electric potentials between cells interior and exterior [1]. Closing and opening of ion channels may be regulated by natural ligands and exogenous drugs. (ATP) is well known and abundant "energy storage" molecule. ATP-activated ion channels have been found in a wide variety of cells. 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.). Very recently a complex chemical molecules which undergo light-induced conformational changes were also proposed as tool for steering activity of ion channels (sodium, potassium).

The project aims to gain a fundamental understanding of how substrates, both natural (ATP, PIP2, etc.) and exogenous (photoactive azo-compounds), affect the model channel activity and how this process is affected by a particular composition of a biological membrane. For this purpose, classical all-atoms 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], 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, one of the hybrid models – so-called Fixed Resolution method [5] (FR) will be used. 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 simulationour group 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 other ion channel systems (for example P2X7, NaV channels) 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 and statistical physics
- Construction of a 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 ligands' possible effects on ion channels dynamics

1.4. Optional: nanomechanics single molecule study (AFM, Magnetic Tweezers) or selected related protein systems. 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.

Required initial knowledge and skills of the PhD candidate

- Analytical thinking
- At least basic programming skills, willing to learn more
- Good understanding of physics, basic understanding of chemistry, mathematics and biology
- Curiosity
- Eager to work hard

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/sodium channel architecture and physiology
- Improvement of programming skills (Python, Unix)
- "Fluency" in work in international scientific settings