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

Project title:

Dynamics and Functional Mechanisms of ATP-Sensitive Potassium (KATP) Channels: AI supported computer modeling related to medical problems.

1.1. Project goals

The project is related to biophysics and medicine. Physical sciences, especially computer modelling supported these days by Artificial Intelligence (AI) and Machine Learning (ML) contribute a lot to understanding basic facts of life and human health. The Department of Biophysics has an extensive experience in applications of such methods in studies of medically relevant proteins, we are a team in Emerging Field called Biophysics in Nanoscale. We publish results in high-impact journals (JACS, PNAS, etc.)

ATP-sensitive potassium channels play a critical role in many physiological processes, i.e. insulin release and cardiac muscle contraction. The conductance of potassium regulates human brain as well. Some medical conditions are related to malfunctioning of these highly organized protein complexes. Molecular mechanisms of KATP channels activity are not well understood yet.
The primary goal of this Ph.D. project is to investigate the structural dynamics and functional mechanisms of ATP-sensitive potassium (KATP) channels. The project aims to unravel the intricate interplay between the channel components, ligand binding, and membrane environment to understand the regulation of KATP channel activity. Specific objectives include:

- Characterizing the structural features and conformational dynamics of KATP channels using computational modeling techniques, such as molecular dynamics simulations.
- Exploring the interactions between different subunits of KATP channels and understanding their roles in channel gating and modulation.
- Investigating the binding mechanisms and allosteric regulation of ligands, including ATP, ADP, and PIP2, in KATP channels.
- Assessing the influence of membrane composition and lipid interactions on the stability, function, and dynamics of KATP channels.
- Integrating computational findings with available experimental data to validate and refine models, providing insights into the complex behavior of KATP channels.

1.2. Outline

The project will be organized into the following key components:

A. Literature Review and Model Development: Conduct an extensive literature review on KATP channels, focusing on their structure, function, and regulatory mechanisms. Studies of up-to date modern Artificial intelligence based methods used in protein modeling. Developmentof accurate computational models of KATP channels based on available experimental data, structural information, and models already developed in our group.

B. Molecular Dynamics Simulations and Analysis: Perform molecular dynamics simulations to investigate the conformational dynamics, interactions, and ligand binding properties of KATP channels. Analyze simulation trajectories to gain insights into the mechanisms underlying channel gating, ligand-induced conformational changes, and membrane interactions.

C. Membrane Composition and Lipid Interactions: Explore the influence of membrane composition, lipid types, and concentrations on the stability, function, and dynamics of KATP channels. Investigate the role of specific lipids in modulating channel behavior and elucidate the molecular mechanisms involved.

D. Validation and Integration: Validate the computational models and findings by comparing them with available experimental data. Integrate computational and experimental data to refine the models and gain a comprehensive understanding of KATP channel structure-function relationships.

E. Thesis Writing and Defense Preparation: Summarize the research findings in a comprehensive thesis. Prepare for the defense by presenting the results and implications of the study to the scientific community.

Work plan

Phase 1: Literature Review and Model Development (12 months)
Phase 2: Molecular Dynamics Simulations and Analysis (12 months)
Phase 3: Membrane Composition and Lipid Interactions (12 months)
Phase 4: Validation and Integration (6 months)
Phase 5: Thesis Writing and Defense Preparation (6 months)

***Literature** (max. 7 listed, as a suggestion for a PhD candidate preliminary study)*

- Ashcroft, F. M. ATP-sensitive potassium channelopathies: focus on insulin secretion. *J. Clin. Invest.* **2005**, *115*, 2047– 2058, DOI: 10.1172/jci25495
- Sung, M. W.; Driggers, C. M.; Mostofian, B.; Russo, J. D.; Patton, B. L.; Zuckerman, D. M.; Shyng, S.-L. Ligand-mediated Structural Dynamics of a Mammalian Pancreatic KATP Channel. *J. Mol. Biol.* **2022**, *434*, 167789, DOI: 10.1016/j.jmb.2022.167789
- Driggers, C. M.; Shyng, S.-L. Mechanistic insights on KATP channel regulation from cryo-EM structures. *J. Gen. Physiol.* **2023**, *155*, e202113046 DOI: 10.1085/jgp.202113046
- Zhao, C.; MacKinnon, R. Molecular structure of an open human KATP channel. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, *118*, e2112267118 DOI: 10.1073/pnas.2112267118
- Structural insights into ATP-sensitive potassium channel mechanics: a role of intrinsically disordered regions. K Walczewska-Szewc, W Nowak, bioRxiv, 2022.08. 03.502592
- Photo-switchable sulfonylureas binding to ATP-sensitive potassium channel reveal the mechanism of light-controlled insulin release, K Walczewska-Szewc, W Nowak, The Journal of Physical Chemistry B 125 (48), 13111-13121

Required initial knowledge and skills of the PhD candidate

The "optimum" candidate for this Ph.D. project should have a background in physics or chemistry. biophysics, some molecular biology, computational modeling. Essential skills include:

- Some proficiency in programming (or eager to learn), particularly in Python, MATLAB, or C/C++
- Strong communication skills for presenting research findings and collaborating with interdisciplinary teams

While expertise in specific areas mentioned in the project is not required, the candidate should demonstrate an eagerness to learn and engage in interdisciplinary research. The project will provide opportunities to develop knowledge and skills in computational modeling using AI based methods, membrane biophysics, and other relevant areas.

Expected development of the PhD candidate's knowledge and skills

Throughout the project, the candidate will expand their knowledge and skills in:

- Advanced computational modeling techniques, including knowledge on artificial intelligence methods
- Understanding lipid-protein interactions and the influence of membrane composition on channel dynamics, role of modeling in medicine related research
- Enhancing scientific communication through reports, presentations, and manuscript preparation
- Developing critical thinking, problem-solving abilities, and experimental design skills
- By the end of the Ph.D. program, the candidate will have a strong foundation in computational modeling, expertise in studying KATP channels, programming proficiency, and effective communication skills. These abilities will pave the way for a successful career in biophysics research and related disciplines.