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

Project title:

Computer Modeling Approach to Processes in Brain. Towards Understanding of Molecular Foundations of Memory.

Project goals

The main goal of this project is to develop an efficient computational pipeline to study dynamics and mechanical properties of selected proteins involved in brain functioning and storing information.

1.1. Outline

Brain is the most critical structure for learning and intelligence. Short and long term memory is indispensable for that. During learning new connections between neurons are formed, thus new synapses arise. To keep information for a longer time complex chemistry is involved. In connecting neurons numerous proteins are involved. What proteins "store"

or control information? How can I remember equations, formulas etc.? The main goal of this project is to develop an efficient computational pipeline to study dynamics and mechanical properties of selected proteins involved in brain functioning and storing information. Following literature we want to study a few major protein players in this process, such as: ROBO1, secretogranin-2, ADAM10, CaMKII, AMPAR . At the same time we will delineate what minimal computational data are required to have an effective tool to study possible abnormalities and pathological process induced by point mutations in that critical systems.

In our theoretical molecular biophysics group we have an extensive experience in using molecular dynamics methods for protein modeling [1-6]. Recently a virtual atomic force microscope set of programs (V_AFM) has been developed to study mechanical anisotropy of proteins. That system together with classical (NAMD) and non-classical (metadynamics, GROMACS) MD simulations tools will be used for this PhD project. As an accompanying/training activities modeling of *E.Coli* L-asparaginase interactions with graphene oxide – a promising anti-cancer system will be studied (bionanotechnology). Mechanical properties of proteins also are adapted to their functions, how mechanical stress modifies protein architecture is very basic question. This problem can be studied computationally using Steered Molecular Dynamics (SMD) simulations. We plan to get detailed picture of mechanical anisotropy of ROBO1 – a protein guiding neurons during brain development. It is possible to use SMD to enforce rare conformational changes in proteins. We will adopt this method to mimic large pore formation in P2X7 purinergic receptor, activation of this protein is considered currently as possible strategy for glioma (brain cancer) treatment. With glioma is also related ubiquitous enzyme ADAM10, it releases in pathological conditions a mitotic agent NLG3. Due to the recent determination of human ADAM10 atomic structure we plan to prepare computer models of this important systems in open and close forms, this may help to develop selective inhibitors of this secretase. Very recently a gene coding for secretogranin-2 protein has been identified as playing a major role in learning process and establishing new spine-spine connections (rearranges of F-actin in neurons). As a part of this project a novel computational model of secretogranin-2 will be created and hopefully its dynamics will be studied. Finally , a central player in memory formation , namely calcium–calmodulin-dependent protein kinase II will be modelled. Several paper described its properties but based on proteins fragments. We will try to prepare a complete model of this system, which might be used to study phosphorylation process in other steps of storing information at molecular level. Finally we will try to construct a model of a critical in LTP receptor AMPA. The ultimate part of these efforts will be a collection of best, most effective practices, leading to formation of semiautomatic route (pipeline) for routine (a gray box) MD simulations of various memory-linked proteins.

Work plan

1.3.1 Literature search for molecules involved in long lasting memory formation
1.3.2. Literature search for structure and function of secretases.
1.3.3. MD/modeling training – simulations of L-asparaginase/GO surface.
1.3.4. Modeling of ROBO1 – SMD training- neuron guidance protein-nanomechanics.

1.3.5. Modeling of P2X7 purinergic receptor (closed and open form, SMD applications – exploratory study, link with cancerous glioma treatment).
1.3.6. Modeling of dynamics and function of ADAM10 secretase (Disintegrin and metalloproteinase domain-containing protein 10, structure 8ESV, link with glioma).

1.3.7. Modeling of dynamics and function of secretogranin-2 (Alphafold2 P13521 structure)
1.3.8. Building of calcium–calmodulin-dependent protein kinase II (CaMKII) protein model.

1.3.9 Building of AMPA receptor model
1.3.10 Summary of the best modeling practices useful for memory-related proteins. Computational pipeline recommendation.
1.3.11 – Thesis writing

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

[1] Applications of computational methods to simulations of proteins dynamics
W Nowak, Handbook of Computational Chemistry, 1-43 , Springer, 2016

[2] Nanomechanical unfolding of α-neurexin-a major component of the synaptic junction

K Mikulska, J Strzelecki, A Balter, W Nowak
Chemical Physics Letters 521, 134-137 (2012)

[3] Nanomechanics of multidomain neuronal cell adhesion protein contactin revealed by single molecule AFM and SMD
K Mikulska-Ruminska, AJ Kulik, C Benadiba, I Bahar, G Dietler, W Nowak
Scientific reports 7 (1), 8852 (2017)

[4] Moreno A. Molecular mechanisms of forgetting.
Eur J Neurosci. 2021 Oct;54(8):6912-6932. doi: 10.1111/ejn.14839.

[5] SYNAPTIC MEMORY AND CaMKII; Roger A. Nicoll and Howard Schulman
Physiol Rev 103: 2897–2945, 2023

[6] **Understanding the physical basis of memory: Molecular mechanisms of the engram**;
Clara Ortega-de San Luis et al., J. Biol. Chem. Volume 298, Issue 5, May 2022, 101866

[7] Mechanisms of CaMKII action in long-term potentiation. Lisman J, Yasuda R, Raghavachari S; Nat Rev Neurosci. 2012 Feb 15;13(3):169-82. doi: 10.1038/nrn3192.

Required initial knowledge and skills of the PhD candidate

Great interest and motivation in doing good science. Background in biochemistry, chemistry, physics and/or computer science. Reasonable programming skill, knowledge of Linux is a plus. Ready to work hard.

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
- -protein interactions and their role in the brain and memory formation. Some drug design.
- 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 proteins, programming proficiency, and effective communication skills. These abilities will pave the way for a successful career in biophysics/ biomedical research and related disciplines.