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

Project title

Development of Artificial Intelligence Methods for Molecular Dynamics Simulations

1.1. Project goals

- To improve substantially the methodology of biomolecular or material science computer simulations of complex systems
- To find out the most suitable machine learning (ML) methodology to select optimal collective variables used in the characterization of molecular transitions
- To test selected ML methods in simple model systems
- To solve selected biophysical problems involving organic ligand diffusion through proteins or ion channels

1.2. Outline

Modern science requires computer modeling. In physics, we model the dynamics of complex systems (solid state, swarms of stars, atoms in DNA or in proteins) by solving the equations of motion. Due to the huge complexity of conformational space (thousands of degrees of freedom), it is far from trivial. Machine Learning (ML) or artificial intelligence (AI) methods can facilitate the investigation of interesting large systems in a very efficient way.

Computational physics witnessed tremendous progress in understanding nature at the atomistic level. Processes involving biomolecules determine our life and health. Time evolution, related to, for example, metabolism in cells, requires efficient computational methods. Current modeling methods of all-atom simulations suffer from very short time scales (nanoseconds) that are accessible for modeling. The mismatch between computational and experimental regimes spans through some 10 orders of magnitude. Fortunately, enhanced sampling methods allow us to reduce this gap. In this project, we will develop new methods for the extraction of meaningful data from unbiased and biased simulations of atomistic systems. Classical and ab initio molecular dynamics, or Monte Carlo methods, will be used.

Selected statistical and numerical methods will be used to implement open-source codes for the extraction of slow modes in atomistic dynamics. New functionalities will be added to the widely used software PLUMED2 (Tribello et al., 2014). Hopefully, these efforts will bring new, fast, and versatile tools that will allow for the effective usage of computational simulations in physics, biophysics, chemistry, molecular medicine, and material science.

1.3. Work plan

(Years 1-4:)

1. Mastering molecular dynamics methodology, Monte Carlo methods and elements of statistical physics. Study on basic ML and AI methods as currently used in physics and modeling.
2. Finding new general methods for ML based selection of slow modes in conformational transitions.

3. Optimizing computational efficiency of the existing and used in the group ML-based methods and programing the new method.
4. Testing new approaches on specific biological problems: finding ligand unbinding pathways in protein channels, reduction of noise in molecular dynamics trajectories, reaching millisecond timescales of large/functional conformational transitions in allosteric or stress induced conditions. Writing Thesis.

1.4. **Literature** (max. 10 listed, as a suggestion for a PhD candidate)

[1] Rydzewski, J., Jakubowski, R., Nowak, W., & Grubmüller, H. (2018) J. Chem. Theory Comput., 14, 2843.
[2] Rydzewski, J., & Nowak, W. (2016) J. Chem. Theory Comput., 12, 2110.
[3] Rydzewski, J., & Nowak, W. (2017a) Sci. Rep., 7, 7736.
[4] Rydzewski, J., & Nowak, W. (2017b) Phys. Life Rev. 22, 58.
[5] Rydzewski, J., & Valsson, O. (2019) J. Chem. Phys. 150, 220901 (2019); https://doi.org/10.1063/1.5092590.
[6[Tribello, G. A., Bonomi, M., Branduardi, D., Camilloni, C., & Bussi, G. (2014) Comput. Phys. Commun., 185, 604.
[7] Valsson, O., & Parrinello, M. (2014) Phys. Rev. Lett., 113, 090601.
[8] J Rydzewski, The Journal of Physical Chemistry Letters 14 (22), 5216-5220; Spectral map: Embedding slow kinetics in collective variables; (2023).
[9] J Rydzewski, T Gökdemir; The Journal of Chemical Physics 160 (9) (2024); Learning Markovian dynamics with spectral maps.

1.5. Required initial knowledge and skills of the PhD candidate

- Analytical thinking
- Great programming skills
- Curiosity, willing to learn new things
- Basic understanding of physics, chemistry, mathematics and to some extent biology

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

Throughout the project, the candidate will expand his/her knowledge and skills in:

- Advanced computational modeling techniques
- Understanding Machine Learning (and some AI) methods – useful in modern job market
- Programing and computing skills
- Effective scientific/computer science communication through reports, presentations, and manuscript preparation
- Developing critical thinking, problem-solving abilities,