Proposition de stage M2

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Encadrant : Dirk Stratmann
Contact : dirk.stratmann@sorbonne-universite.fr
Homepage: https://dirkstratmann.github.io/
Laboratoire : BFA, CNRS UMR 8251, INSERM ERL U1133, Université Paris Cité
Équipe : TPM2PI (Therapeutic Peptides: Modulation of Protein-Protein Interactions): https://bfa.u-pariscite.fr/tpm2pi/
Lieu du stage : bât Lamarck A, 35 rue Hélène Brion, 75205 Paris Cedex 13
Ecole doctorale: ED 563 - Médicament, Toxicologie, Chimie, Imageries
https://ed563.u-paris.fr/

Advanced MD simulations of protein - cyclic peptide complexes

Peptides have attracted increasing attention over the past decade as a viable alternative to small molecules for developing drug molecules capable of interfering with protein-protein interactions particularly well. While linear peptides composed of only natural amino acids suffer from degradation, cyclic peptides display a stronger resistance to the proteases. In addition, their conformational space is usually more restricted than that of linear peptides, reducing the entropy loss upon binding, and leading to a stronger binding affinity.
The conformational space explored by cyclic peptides can be characterized *in-silico* with molecular dynamics, Monte-Carlo simulations and other sampling methods. In the past our group worked on sampling algorithms for cyclic peptides inspired from robotics (Jusot et al., 2018); as well as on advanced molecular dynamics (MD) simulations of cyclic peptides using replica-exchange MD (REMD) and simulated tempering (ST) (Murail et al., 2025).
For this internship, we propose to go one step further by simulating the association and dissociation of protein – cyclic peptide complexes using another class of advanced molecular dynamics simulations: the metadynamics approach using collective variables to accelerate the process of association and dissociation. The metadynamics approach has been invented already more than 20 years ago by the group of Parrinello (Laio and Parrinello, 2002) and with more than 6.000 citations this physics based method has been widely used and is continuously improved. The success of a metadynamics simulation depends often on the careful choice of collective variables (CVs) that describe the *a priori* unknown slow motions. Suboptimal CVs cause long convergence times and makes the application of a standardized metadynamics protocol to many systems impractical. Therefore, the Parrinello group developed recently an improved metadynamics method, named “On-the-fly Probability Enhanced Sampling” (OPES) (Invernizzi and Parrinello, 2020), reducing the convergence times for suboptimal CVs. Building on that, the group of Gervasio combined OPES with REMD into “OneOPES” (Rizzi et al., 2023) to further reduce convergence times. They applied OneOPES to predict with a high accuracy the free energy of binding of protein – ligand (=small molecules) complexes (Karrenbrock et al., 2024) and demonstrated also on small ligand receptors that this method can be automatized (Febrer Martinez et al., 2024).
Here, we would like to apply OneOPES to a small set of protein – cyclic peptide complexes for which the experimental free energy of binding is already known. The goal is to explore the association and dissociation mechanisms, as well as to predict the free energy of binding.

Skills required :

- having followed a computational physics course or a course on molecular dynamics simulations
- basic programming skills, preferably in python

Skills that will be acquired during the internship :

- molecular dynamics simulations with GROMACS
- metadynamics OneOPES protocol with PLUMED
- analysis of the MD trajectories with mdanalysis python package, pymol and VMD
- usage of a computational cluster via SLURM

Some presentations to know more on :

- Funnel-metadynamics: https://www.plumed-tutorials.org/lessons/22/001/data/NAVIGATION.html Click on “Lecture I” for an introduction to kinetics and free energy of binding
- OPES: https://www.plumed-tutorials.org/lessons/22/003/data/NAVIGATION.html
- PLUMED: https://www.plumed-tutorials.org/masterclass.html

References:

Febrer Martinez, P., Rizzi, V., Aureli, S., Gervasio, F.L., 2024. Host–Guest Binding Free Energies à la Carte: An Automated OneOPES Protocol. J. Chem. Theory Comput. 20, 10275–10287. https://doi.org/10.1021/acs.jctc.4c01112

Invernizzi, M., Parrinello, M., 2020. Rethinking Metadynamics: From Bias Potentials to Probability Distributions. J. Phys. Chem. Lett. 11, 2731–2736. https://doi.org/10.1021/acs.jpclett.0c00497

Jusot, M., Stratmann, D., Vaisset, M., Chomilier, J., Cortés, J., 2018. Exhaustive Exploration of the Conformational Landscape of Small Cyclic Peptides Using a Robotics Approach. J. Chem. Inf. Model. 58, 2355–2368. https://doi.org/10.1021/acs.jcim.8b00375

Karrenbrock, M., Borsatto, A., Rizzi, V., Lukauskis, D., Aureli, S., Luigi Gervasio, F., 2024. Absolute Binding Free Energies with OneOPES. J. Phys. Chem. Lett. 15, 9871–9880. https://doi.org/10.1021/acs.jpclett.4c02352

Laio, A., Parrinello, M., 2002. Escaping free-energy minima. Proc. Natl. Acad. Sci. 99, 12562–12566. https://doi.org/10.1073/pnas.202427399

Murail, S., Sawmynaden, J., Zemirli, A., Jusot, M., Pietrucci, F., Chomilier, J., Tufféry, P., Stratmann, D., 2025. Robust Conformational Space Exploration of Cyclic Peptides by Combining Different MD Protocols and Force Fields. J. Chem. Theory Comput. 21, 10018–10034. https://doi.org/10.1021/acs.jctc.5c01123

Rizzi, V., Aureli, S., Ansari, N., Gervasio, F.L., 2023. OneOPES, a Combined Enhanced Sampling Method to Rule Them All. J. Chem. Theory Comput. 19, 5731–5742. https://doi.org/10.1021/acs.jctc.3c00254