Master's Thesis Biophysical Chemistry • From Jan/Feb 2024

Group of Guillaume Stirnemann, École Normale Supérieure, Chemistry Department, Paris

Toward a molecular understanding of the effect of drug binding on GPCR function

Subject GPCRs are transmembrane- proteins that regulate a large array of intracellular signaling cascades, in response to neurotransmitters, hormones, etc. Because of their essential role in physiology and diseases they are the targets of about one third of the marketed drugs. Ghrelin is a 28-amino acid peptide hormone that is tightly involved in the control of growth hormone secretion, food intake, reward-seeking behaviors, and glucose homeostasis. All these effects are due to the interaction with a single GPCR: the GHSR. This receptor is thus a major target to treat cachexia, obesity, diabetes, and addiction. However, no compound that would bind GHSR and modulate its behavior has so far reached the market of therapeutic intervention, probably due to fragmentary knowledge of how signaling efficacy and selectivity are regulated. In collaboration with experimental groups performing single-molecule force spectroscopy measurements, we will aim to characterize GHSR affinity for various ligands (agonists, inverse agonists, and antagonists) using a combination of enhanced sampling and out-of-equilibrium molecular dynamics simulations. If time allows, we will also characterize how ligand binding may allosterically affect the binding of GHSR to G-proteins.

Techniques/Methods The candidate will gain strong experience in molecular dynamics simulations (no previous experience is required), using a widely-employed and distributed code, as well as advanced techniques to accelerate the sampling of the conformational space of biomolecules. Tools: Molecular dynamics simulations with state-of-the-art forcefields; enhanced sampling methods; non-equilibrium steered molecular dynamics; programming tools, and simulation analysis tools.

Research environment Research will take place in the group of Guillaume Stirnemann, at École Normale supérieure. It is located in the very stimulating research environment of the Latin Quarter, at the heart of Paris. Our group have extensive experience in applying advanced simulation and theoretical tools to tackle a variety of questions, ranging from water ultrafast dynamics in aqueous solutions to the mechanical and thermal stability of proteins. We have access to state-of-the-art computing facilities that include a local mesoscale computer cluster. More information about the lab and the research groups are available here: https://sites.google.com/view/. This internship will take place in strong collaboration with the group of Charlie Gosse at the Institute of Biology at ENS and that of Laurant Catoire at IBPC.

Extension into a PhD can be considered upon mutual agreement, although a funding is not yet secured. The current internship is funded by a PSL-Qlife grant (2023-2025).

Contact information Interested candidates should contact Guillaume Stirnemann **as soon as possible** (guillaume.stirnemann@ens.psl.eu), together with a curriculum vitae and contact information for one or two references.