BACKGROUND

G-Protein Coupled Receptors (GPCRs) form a large family of membrane proteins that constitute key privileged targets for the design of new drugs. Despite a large set of available structures, their regulation mechanism at the molecular scale still requires to be characterized. This is principally due to the fact that this mechanism involves the modulation by different partners (ligands, lipids, ions, intra-cellular effectors, etc…) of the equilibria between different intrinsic conformations, some features that are hard to be captured by structural methods. Things are even more complicated if we consider homo- or hetero-dimers of GPCRs. Only a few structures in the PDB describe the possible orientation of GPCR protomers in such assemblies. Some years ago, we proposed a model of the Ghrelin:Dopamin hetero-dimer in which each receptor was bound to its favorite G-protein partner at the same time. This model was experimentally validated by the measurement of crossed distances between the two receptors and the two G-proteins. Thanks to the "Grand Challenge" phase on the Jean-Zay machine provided by GENCI, we already performed extensive simulations of this dimeric model and its isolated entities. The objective of these simulations is to understand the cross-talk that operates in such large molecular assemblies and help to the design of new potent ligands.

We propose here an **18 months** contract, funded by FRM (foundation pour la recherche médicale) for a highly motivated post-doctoral fellow, ideally beginning in **January 2023**. The objective of the recruited post-doc will be to analyze the already obtained data and run complementary molecular dynamics simulations to provide a global mechanical view of how these complex systems behave at the membrane surface. The work will be performed in close collaboration with experimentalists in the laboratory, including biochemists and chemists for validation purposes. This collaboration could include the production of protein variants and the synthesis/testing of new ligands.

CANDIDATE PROFILE

The seeked candidate would ideally have a good experience in running / analyzing molecular dynamics simulations of peptides and proteins, and a validated PhD in a related field. She/He will have good knowledge of classical force-fields and MD codes and especially Gromacs; a plus would be to already have practiced coarse-grained force-fields (MARTINI FF). The candidate must be autonomous under the linux environment, and know at least one scripting language to analyze all produced data (python, R, etc …). The candidate must be fluent in English and able to present her/his results either to specialists or non-specialists.

Contact us @ nicolas.floquet@umontpellier.fr for further detail and planification of an interview.

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Some of our last publications in the field :

(1) Louet, M.; Casiraghi, M.; Damian, M.; Costa, M. G.; Renault, P.; Gomes, A. A.; Batista, P. R.; M'Kadmi, C.; Mary, S.; Cantel, S.; Denoyelle, S.; Ben Haj Salah, K.; Perahia, D.; Bisch, P. M.; Fehrentz, J.-A.; Catoire, L. J.; Floquet, N.; Banères, J.-L. Concerted Conformational Dynamics and Water Movements in the Ghrelin G Protein-Coupled Receptor. *Elife* 2021, *10*, e63201. https://doi.org/10.7554/eLife.63201.

(2) Damian, M.; Louet, M.; Augusto Severo Gomes, A.; Mkadmi, C.; Denoyelle, S.; Cantel, S.; Mary, S.; Bisch, P.;

Fehrentz, J.-A.; Catoire, L.; Floquet, N.; Banères, J.-L. Allosteric Modulation of Ghrelin Receptor Signaling by Lipids. ***Nature communications*** 2021.

(3) Bous, J.; Orcel, H.; Floquet, N.; Leyrat, C.; Lai-Kee-Him, J.; Gaibelet, G.; Ancelin, A.; Saint-Paul, J.; Trapani, S.; Louet, M.; Sounier, R.; Déméné, H.; Granier, S.; Bron, P.; Mouillac. Structure of the Antidiuretic Hormone Vasopressin Receptor Signalling Complex. ***Science Advances*** 2021.

(4) Renault, P.; Louet, M.; Marie, J.; Labesse, G.; Floquet, N. Molecular Dynamics Simulations of the Allosteric Modulation of the Adenosine A2A Receptor by a Mini-G Protein. ***Sci Rep*** 2019, *9* (1), 5495. https://doi.org/10.1038/s41598-019-41980-x.

(5) Ferré, G.; Louet, M.; Saurel, O.; Delort, B.; Czaplicki, G.; M'Kadmi, C.; Damian, M.; Renault, P.; Cantel, S.; Gavara, L.; Demange, P.; Marie, J.; Fehrentz, J.-A.; Floquet, N.; Milon, A.; Banères, J.-L. Structure and Dynamics of G Protein-Coupled Receptor-Bound Ghrelin Reveal the Critical Role of the Octanoyl Chain. ***Proc. Natl. Acad. Sci. U.S.A.*** 2019, *116* (35), 17525–17530. https://doi.org/10.1073/pnas.1905105116.

(6) Damian, M.; Pons, V.; Renault, P.; M'Kadmi, C.; Delort, B.; Hartmann, L.; Kaya, A. I.; Louet, M.; Gagne, D.; Ben Haj Salah, K.; Denoyelle, S.; Ferry, G.; Boutin, J. A.; Wagner, R.; Fehrentz, J.-A.; Martinez, J.; Marie, J.; Floquet, N.; Galès, C.; Mary, S.; Hamm, H. E.; Banères, J.-L. GHSR-D2R Heteromerization Modulates Dopamine Signaling through an Effect on G Protein Conformation. ***Proc. Natl. Acad. Sci. U.S.A.*** 2018, *115* (17), 4501–4506. https://doi.org/10.1073/pnas.1712725115.