Title: **Molecular kinetics of chemosensory receptors**

Hosting lab: Institut de Chimie de Nice (ICN) - UMR7272 CNRS – UCA
collaborator: Institute of Physics (IP) - University of Freiburg (Allemagne)

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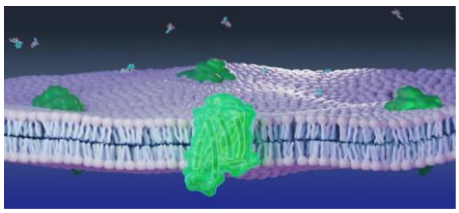
Financial support: ~580 euros per month
duration: 6 months



Application deadline: 20 November 2023

Scientific details: Our brain perceives our olfactory and gustatory environment thanks to chemosensory receptors, and more specifically those of the G Protein Coupled Receptor (GPCR) family. From a pharmacological point of view, a molecule that gives rise to an odour or taste must assemble with a sensory receptor on the same principle as the key-lock association. We have around 400 olfactory receptors and around thirty gustatory receptors. It is only in recent months that the first experimental structures of three chemosensory receptors have become available. In addition, spectacular advances in machine learning for protein structure prediction (such as AlphaFold2) have made it possible to generate 3D models of proteins with a high degree of accuracy. Solid foundations have therefore been laid for understanding, at the atomic level, the interaction between these receptors and odorant or sapid molecules [1-4]. However, analysing the dynamics of these receptors is essential to better understand their function and predict new ligands. To do this, powerful high-performance computing (HPC) architectures are now available, enabling the dynamics of systems to be modelled on a timescale of several µs. The aim of this internship is therefore to analyse the binding kinetics of a ligand and the allosteric mechanism associated with the activation of a GPCR using molecular dynamics simulations. The post-processing treatment of data extracted from MD simulations to extract the structural and kinetic parameters [5] will be partly carried out in collaboration with our partner at the University of Freiburg.

References:

[1] *Odorant receptor 7D4 activation dynamics.* C.A. de March, **J. Topin**, E. Bruguera, G. Novikov, K. Ikegami, H. Matsunami, J. Golebiowski. Angew. Chem. Int. Ed., **2018**, 57, 4554-4558
[2] *Mammalian class I odorant receptors exhibit a conserved vestibular-binding pocket.* C. Bushdid, C.A. de March, **J. Topin**, M. Do, H. Matsunami, J. Golebiowski. Cell. Mol. Life Sci., **2019**, 76, 995-1004.
[3] *Functional Molecular Switches of Mammalian G Protein-Coupled Bitter-Taste Receptors.* **J. Topin**, C. Bouysset, J. Pacalon, Y. Kim, M. Rhyu, **S. Fiorucci**, J. Golebiowski. Cell. Mol. Life Sci., **2021**, 78, 7605-7615
[4] *Agonists of G Protein-Coupled Odorant Receptors are Predicted from Chemical Features.* C. Bushdid, C.A. de March, **S. Fiorucci**, H. Matsunami, J. Golebiowski. J. Phys. Chem. Lett., **2018**, 9, 2235-2240.
[5] Multisecond ligand dissociation dynamics from atomistic simulations. S. Wolf, B. Lickert, S. Bray. Nat. Commun. **2020**, 11, 2918.

Keywords: GPCR, molecular simulations, statistical mechanics, big data, kinetics

Methods: molecular dynamics, Langevin models.

Candidate profile: The candidate should have a physical-chemistry or biochemistry background and have a strong interest in biomolecular simulations. Knowledge of structural biology is essential for understanding the systems studied. Experience with Linux and Python programming environments will clearly be a plus.