Early Stage Researcher Project

"Rational design of positive and negative allosteric modulators of pLGICs"

in

University of Strasbourg (Unistra), France

You want to participate in a training programme in and beyond the fields of physical chemistry of biological systems, theoretical and computational chemistry, biological chemistry, biochemistry, targeted drug delivery/discovery and medicinal chemistry?

14 Early Stage Researcher (ESR) positions are available within the EU-funded Marie Skłodowska Curie Innovative Training Network on **Allo**stery in **D**rug **D**iscovery (**ALLODD**) under Grant Agreement No. 956314.

The ALLODD project is a collaboration between 13 academic and industrial organizations with 14 ESR/PhD students in total. The aim of ALLODD is to train a new generation of scientists to exploit the concept of allostery in drug design, putting together a whole array of technologies to identify and characterize allosteric modulators of protein function that will be applied to therapeutically relevant systems.

Project Description

Nicotinic acetylcholine receptors (nAChRs) play a central role in the intercellular communication in the brain and the nervous system and are involved in fundamental processes such as attention, learning, and memory.[1] They are oligomeric protein assemblies that convert a chemical signal into an ion flux through the postsynaptic membrane and their pharmacological modulation is currently developed for the treatment of Alzheimer's, Parkinson's, schizophrenia and depression.[2] Very recently, we proposed a straightforward extension of the popular Monod-Wyman-Changeux (MWC) model for the allosteric transitions of synaptic receptors and found that pharmacological attributes such as potency, efficacy and selectivity of the modulatory ligands can be expressed in terms of the ligand-binding affinity for the active, resting and desensitized states of the receptor.[3] In addition, thanks to the recent improvements in the structural determination of synaptic receptors at high resolution, a number of high-resolution structures of nAChRs in different physiological states and in complex with modulatory ligands (i.e. agonists, antagonists and positive and negative allosteric modulators) have been deposited.[4] Both the recent theoretical and structural advances on the allosteric regulation of synaptic receptors open to a novel paradigm for the identification of neuroactive compounds by modeling and simulations, which we referred to as *computational neuropharmacology*.[3] In this context, the establishment of accurate and efficient numerical methods for the calculation of conformation-based ligand-binding affinities is essential.

Goal(s): In light of the above, the goals of the project are: (1) Demonstrate that accurate ligand-binding affinity predictions in nAChRs can be obtained using Molecular Dynamics simulations. (2) Provide a proof of principle that potency, efficacy, and selectivity of known nAChR modulators can be accessed from ligand-binding free energy calculations. (3) Implement strategies for the design of neuroactive compounds with a controlled pharmacological profile in the context of virtual screening.

Responsibilities: The successful candidate will be in charge of implementing protocols for rigorous binding free energy calculations using Gromacs.[1] Given the size, complexity and flexibility of the molecular systems under investigation, enhanced sampling approaches will be considered. The opportunity to rely on relative binding free energy calculations based on single-topology or dual-topology setups will be explored.

Requirements:

1. Master degree in physics, physical chemistry, or theoretical/computational chemistry.
2. Experience in modeling and simulations of proteins.
3. Interest in the theoretical understanding of protein-ligand binding.
4. Proficiency in English oral and written.

This project is part of the EU-funded MarieSkłodowska Curie Innovative Training Network on Allostery in Drug Discovery (ALLODD) under Grant Agreement No. 956314.[2] The ALLODD project is collaboration between 13 academic and industrial organizations with 14 ESR/PhD students in total. The aim of ALLODD is to train a new generation of scientists to exploit the concept of allostery in drug design, putting together a whole array of technologies to identify and characterize allosteric modulators of protein function that will be applied to therapeutically relevant targets.

Eligibility: The ESR will be enrolled in the Ph.D. program of University of Strasbourg (Unistra). Applicants must be in the first 4 years after obtaining their Master's degree and/or Bachelor's degree and must not have resided or carried out their main activity (work, studies, etc.) in the host country (France) for more than 12 months in the 3 years immediately before the recruitment date. In addition, local regulations of the host countries may apply.

Remarks: The position is **available from February 2022** at the earliest. The **salary** is **3780 €/month** (before taxes). Only highly motivated candidates and on focus with the project will be considered. Experience with free energy calculations is considered as an asset. Applications including a cover letter, a CV, and one or two reference letters should be sent to:

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Laboratoire d'Ingenierie des Fonctions Moléculaires
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1. Changeux, J.-P.; Christopoulos, A., Allosteric Modulation as a Unifying Mechanism for Receptor Function and Regulation. *Cell* **2016,** *166* (5), 1084-1102.
2. Cecchini, M.; Changeux, J.-P., The nicotinic acetylcholine receptor and its prokaryotic homologues: Structure, conformational transitions & allosteric modulation. *Neuropharmacology* **2015,** *96*, 137-149.
3. Cecchini, M.; Changeux, J.-P., Nicotinic receptors: From protein allostery to computational neuropharmacology. *Molecular aspects of medicine* **2021**, 101044.
4. Gharpure, A.; Noviello, C. M.; Hibbs, R. E., Progress in nicotinic receptor structural biology. *Neuropharmacology* **2020,** *171*, 108086.

[1] http://www.gromacs.org
[2] http://www.drugdesign.gr/allodd.html