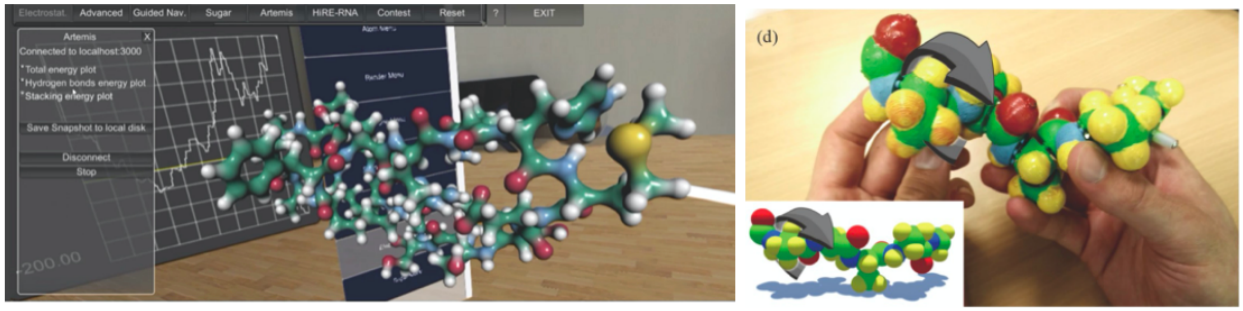
Université Paris Cité

Two M2 internships (5/6 months each)

Physical characterization of protein/ligands binding sites for augmented reality visualization

Medical conditions are often related to dysfunction of biomolecules. Many drugs have been developed to rescue function through interaction with one or more of these biomolecules, hence called target. However there remain large unmet medical needs and side effects.
Virtual approaches based on computations are now used routinely used to find new drugs and have shown impressive successes. Among these techniques, Virtual Screening (VS) allows one to consider millions of molecules. VS requires a model with which it will filter a large database of molecules, a process that can be performed using a 3D-pharmacophore, i.e. a 3D representation of molecular properties.
In our group we develop a method that combines the potential of virtual screening with human expert knowledge of the interaction between known ligands and a target. To that aim we will develop an interactive approach to virtual screening using a mixed-reality 3D-pharmacophore. The underlying hypothesis is that the possibility for an expert to design the 3D-pharmacophore interactively should improve the potential of 3D-pharmacophores. Furthermore, it should benefit from human 3D pattern recognition potential and interaction technology coming from Virtual and Augmented Reality.

As part of this large project, we propose two internships to develop methods to compute physical properties associated with the binding site of the protein (internship A) and to visually highlight possible unused binding interactions that would enhance the affinity of the binding of a ligand and optimize the interactions (internship B). The tools developed in these internships will then be used to develop the interactive approach for drug design to guide researchers in finding new molecules that have an enhanced binding affinity with the target.



Left: virtual reality visualization of a molecule using UnityMol; Right: augmented reality of a tangible molecule

Internship A: We will first characterize at the atomistic level the most common physical properties such as electrostatic interactions, hydrogen bonding, and available space, by computing the properties of the volume of the cavity (and not just on its surface as done by other approaches). Other interaction terms such as stacking of aromatic rings, hydrophobicity, and polarization are harder to assign at the atomistic level. Using our experience in designing coarse-grained models for biomolecules, we will develop a coarse-grained representation of the proteins which will allow us to define and easily compute these terms.

Internship B: We will implement in our molecular visualization software UnityMol the visualization of these physical interactions in space to guide the user to the optimization of the pharmacophore and to the search of new ligands that would better fit into the binding pocket. This will require also envisioning an intuitive way of presenting the interactions and proposing ergonomic solutions to present data in a densely occupied 3D space.

For internship A the applicant should be at ease with concepts of molecular interactions and the basic physical laws governing them, have some experience of molecular visualization and python programming.
For internship B the applicant should have some experience of molecular visualization and python programming and have the interest in learning programming tools based on the Unity platform (used also for videogames).

Each internship will last 5/6 months, and the student will receive an allowance of approximately 500 euros/month. For programs that require longer internships, it is possible to envision a single internship grouping all proposed work lasting up to one year.

If interested, please send a motivation letter, a CV and recent record transcripts to:
samuela.pasquali@u-paris.fr

Samuela Pasquali
Physics professor
Laboratoire Biologie Fonctionnelle et Adaptative, CNRS UMR 8251
Equipe Modélisation Computationnelle des Interactions Protéine-Ligand
Bâtiment Lâmarck A, bureau 418
35 rue Hélène Brion, 75205, Paris Cedex 13
tel: 0157278279