« PROPOSITION DE STAGE ET/OU DE THESE »

Laboratoire : Laboratoire d'Optique et Biosciences (LOB), Ecole Polytechnique

Adresse : Route de Saclay, Palaiseau

Responsable de stage : Alexey Aleksandrov

Adresse électronique : Alexey.Aleksandrov@polytechnique.fr

Profil recherché : Skills in theoretical physics and engineering/computer sciences will be considered as an asset

Possibilité de poursuite en thèse : OUI

Si oui financement envisagé : funded by ANR ATMCADD

Titre du stage : Accurate Atomistic Models for Computer-Aided Drug Design

Résumé :

We propose an internship for 6 month in the LOB laboratory of Ecole Polytechnique. For a motivated student this internship will be followed by a doctoral thesis financed by **ANR project ATMCADD**.

Drug discovery and development are very time and resources consuming processes, which are significantly facilitated by computer-aided drug design (CADD) methods. Structure-based CADD methods use three-dimensional atomistic structures of protein targets to evaluate ligand-target affinities to identify possible drugs. These methods fundamentally rely on scoring functions to approximate ligand-target affinities. Currently used scoring functions are not accurate enough to reproduce ligand-target interactions in the complex heterogeneous protein-solvent environment. Computational capacity has increased dramatically over the last two decades making possible the introduction of more sophisticated and computationally intensive methods in computer-aided drug design. The primary goal of this internship is to develop and implement in CADD a new generation of mechanistic models based on solid physical principles. It is related to the recent advances in next generation atomistic simulation models explicitly treating electronic polarizability[1]. Current scoring functions neglect polarization effects, which are expected to be important for ligand binding to hydrophobic protein surfaces. The student will develop new methods for solvent treatment in CADD combined with the cutting-edge methods for treatment of polarization. Treatment of solvent, which plays a key role in drug-target binding remains challenging in CADD due to the complex nature of the heterogeneous protein-solvent environment. Continuum dielectric medium methods can accurately capture direct electrostatic effects due to solute atomic charges and surrounding polarized continuum solvent[2]. However, the total ligand-protein binding free energy also includes an additional non-polar contribution, largely responsible for hydrophobic effects playing a key role in protein stability and ligand binding. Most of the CADD methods today treat the total non-polar contribution by simple empirical functions such as proportional to the solute surface area. In this project, the student will contribute to lifting several technological barriers by designing new non-polar solvation models.

Skills in theoretical physics and engineering/computer sciences will be considered as an asset. Previous experience with the Linux environment and basic script programming is desired, but not mandatory.

References:

1) Lemkul JA, Huang J, Roux B, MacKerell AD Jr. An Empirical Polarizable Force Field Based on the Classical Drude Oscillator Model: Development History and Recent Applications. *Chem Rev.* 2016 116(9):4983-5013

2)Aleksandrov A, Lin FY, Roux B, MacKerell AD Jr. Combining the polarizable Drude force field with a continuum electrostatic Poisson-Boltzmann implicit solvation model. *J Comput Chem.* 2018 39(22):1707-1719

Contact:
Dr. Alexey Aleksandrov,
e-mail: Alexey.Aleksandrov@polytechnique.fr