- **Title** : Novel ligand docking algorithms
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- **Group leader** : Stephane Redon, stephane.redon@inria.fr
- **Laboratory** (+working place) : NANO-D, INRIA Rhone-Alpes Research Center

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- **If a PhD is forseen** : yes

Internship presentation :

Structure-based drug design [1] relies on knowledge of the three dimensional structure of the biological target obtained through methods such as X-ray crystallography, which is used as a basis for designing new ligands by applying accepted principles of molecular recognition. The basic assumption underlying structure-based drug discovery is that a good ligand molecule should bind tightly to its target. Thus, one of the most important principles for designing or obtaining potential new drugs is to predict the binding affinity of a certain ligand to its target and use it as a criterion for selection. The binding affinity can be approximated with certain physics-based empirical functions or using knowledge– driven potentials [2]. Another very important direction of research in structure-based drug design is the development of new sampling algorithms that predict binding poses of different drugs on the surface of a protein receptor molecule.

State-of-the-art methods [3] allow to accurately predict binding poses and affinities only for small rigid molecules. More precisely, there are no methods that successfully predict binding of flexible (more that six rotatable bonds) ligands [4]. This is due to both deficiency of accurate potentials and efficient sampling schemes.

Internship objectives:

The overall research topic of the proposal is to extend the state-of-the art methods for accurate binding predictions of large flexible ligands. This includes

- the development of new algorithms for flexible ligands. In particular, it implies molecular mechanics in the internal space (bond lengths are fixed, but bonds can rotate) in combination with (1) rotameric search for protein side- chains, (2) off-rotameric search, (3) accounting for global protein flexibility.
- and also consists in applying motion-planning methods [5] to enhance the efficiency of global search algorithms. In particular, we will implement a search engine based on the RRT method [6,7].

All the developed algorithms will be designed as individual modules for the SAMSON software platform developed in our team. Algorithms will be validated using a number of standard benchmarks and blind docking competitions (CAPRI, GPCR Dock, CSAR Dock).

Requirements :

We are looking for creative, passionate and hard-working individuals from applied math / computer science background with exceptional talent for computer science and mathematics. Excellent oral, written and interpersonal communication skills are essential (working language will be English – knowledge of French is a plus). Good knowledge of C++ will be an asset.

References:

[1] T. L. Blundell, “Structure-based drug design,” Nature, (1996), 384, 23.

[2] H. Gohlke, M. Hendlich, and G. Klebe, “Knowledge-based scoring function to predict protein-ligand interactions,” Journal of molecular biology, (2000), 295, 337.

[3] Yuriev, E. and Ramsland, P. A., “Latest developments in molecular docking: 2010–2011 in review,” J. Mol. Recognit., (2013), 26, 215.

[4] O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010) 455-461.

[5] Motion planning algorithms for molecular simulations: A survey, Al-Bluwi et al., Computer Science Review, 2012.

[6] Rapidly-Exploring Random Trees: Progress and Prospects, by S. M. Lavalle , J. J. Kuffner , Jr. Algorithmic and Computational Robotics: New Directions, 2000.

[7] A randomized tree construction algorithm to explore energy landscapes. Journal of Computational Chemistry, L. Jaillet, F. J. Corcho, J.-J. Pérez, and J. Cortés, 32(16):3464– 3474, 2011.