Internship Position Opening

Title : Development of novel algorithms for structure-based drug design.

Place: NANO-D research group, INRIA (MInatec CEA) http://nano-d.inrialpes.fr

Internship topic description

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. State-of-the-art methods 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 [2]. This is due to both deficiency of accurate potentials and efficient sampling schemes. 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 following two subjects:

1. 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.
2. Applying motion-planning methods [3] to enhance the efficiency of global search algorithms. In particular, we will implement a search engine based on the RRT method [4,5].

Requirements

We are looking for creative, passionate and hard-working individuals 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).

- Strong computer science background
- Strong knowledge of applied math and physics
- Strong oral, written and interpersonal communication skills (working language: English – knowing French is a plus)
- Good knowledge of C++
- Ability to work independently and with a team

Supervisors:

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Leonard Jaillet (leonard.jaillet@inria.fr)

Duration

4-8 months, continuation for PhD is possible

References:

[1] T. L. Blundell, “Structure-based drug design,” Nature, (1996), 384, 23.
[2] Yuriev, E. and Ramsland, P. A., “Latest developments in molecular docking: 2010–2011 in review,” J. Mol. Recognit., (2013), 26, 215.
[3] Motion planning algorithms for molecular simulations: A survey, Al-Bluwi et al., Computer Science Review, 2012.
[4] Rapidly-Exploring Random Trees: Progress and Prospects, by S. M. Lavalle , J. J. Kuffner , Jr. Algorithmic and Computational Robotics: New Directions, 2000.
[5] 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.