Laboratoire d'Ingénierie des Systèmes Biologiques et des Procédés

UMR INSA/CNRS 5504 – UMR INSA/INRA 792

# *Master Internship*
# Computational Design for the development of Thermostable Lipases

Over the next decades, it is expected that enzyme-driven methods will play an increasing role in manufacturing, by replacing existing chemical processes, thus driving the bioeconomy forward. The use of enzymes represents the best environmentally friendly scenario in the development of sustainable manufacturing. However, despite great potential of enzymes, their industrial applications can be hampered by their unsuitable properties in terms of specificity, catalytic efficiency and stability. To overcome such shortcomings, a variety of enzyme engineering approaches to generate biocatalysts with desired properties have been developed. Especially, Computer-aided (or Computational) Protein Design has been attracting increasing attention to fully rationalize enzyme engineering and speed-up the production of new enzymes while reducing the human and financial costs.

Computational Protein Design (CPD) uses the tight relationships existing between the function and the structure of a protein to design novel functions by searching in the immense sequence space, the amino-acid sequences compatible with a known 3D scaffold and that will lead to the desired functional properties. This *in silico* search for the best sequence candidates that will empower the enzymes with the targeted properties is extremely challenging due to the astronomically large size of the search space. The CIMES team of LISBP, Toulouse, in collaboration with specialists in artificial intelligence (UMIAT, INRA Toulouse) has developed new methods that handle search spaces which are out of reach of classical CPD methods [1-4]. These methods speed-up search by several orders of magnitude, find the minimum energy design and generate exhaustive lists of near-optimal sequences, defining small mutant libraries. These new CPD approaches have been evaluated on various types of test benchmarks, and are currently used to optimize the stability of several enzymes.

In this framework, the objective of the internship is to apply these CPD methods to guide the engineering of lipases (triacylglycerol acyl hydrolases) that find an increasing interest in biotechnology. More specifically, this project involves two main tasks: (i) the use of various molecular modelling methods (i.e. comparative modelling, molecular dynamics,…) to build 3D models of the targeted lipases and explore their dynamics; (ii) the use of our automated CPD methods to sample mutations (and their conformation) in order to search for the most promising combinations of mutations enabling to improve the stability of lipases. The predicted stabilized mutant sequences will be experimentally evaluated by the IATE Montpellier. Feedback of these tests and evaluations will enable to improve the models and methods.

**Requirements:** Candidates should have a background in molecular modelling, computer science, structural biology and be enthusiastic about science! Research internship is available for Master 1 or Master 2 students.

**Duration:** The internship will have duration of 5 months from March 2017.

**Location:** Laboratoire d'Ingénierie des Systèmes Biologiques et des Procédés (LISBP) UMR - CNRS 5504 - INRA 792 – Equipe de Catalyse et Ingénierie Moléculaire EnzymatiqueS (CIMES)
Institut National des Sciences Appliquées - 135 Avenue de Rangueil - F-31077 Toulouse Cedex 04 France

**Contact:** If you are interested in this position you can send your letter of application and resume to:

Sophie Barbe - E-mail : Sophie.Barbe@insa-toulouse.fr

1- Traoré S, Roberts KE, Allouche D, Donald BR, André I, Schiex T, Barbe S* (2016). Fast search algorithms for Computational Protein Design. J Comput Chem. (12) 1048-58.
2- Traoré S, Allouche D, André I, Schiex T, Barbe* (2016). Deterministic search methods for Computational Protein Design. In Computational Protein Design. Springer. 1529:107-123.
3- Simoncini D, Allouche D, de Givry S, Delmas C, Barbe S, Schiex T* (2015) Guaranteed Discrete Energy Optimization on Large Protein Design Problems. J Chem Theory Comput 11(12):5980-9.
4- Traore S, Allouche D, Andre I, De Givry S, Katsirelos G, Schiex T*, Barbe S* (2013). A new framework for computational protein design through cost function network optimization. Bioinformatics, 29 (17), 2129-2136.