Sujet de thèse – proposition
In silico design of protein-targeting aptamers

Funding: doctoral contract

Duration: 3 years (October 2020 – September 2023)

Location: UMR 7025 CNRS, Génie Enzymatique et Cellulaire, Université de Technologie de Compiègne, France

Direction : I. Maffucci (co-direction with either B. Bihan-Avalle or S. Padiolleau – to be defined)

Background

DNA or RNA aptamers are single-stranded oligonucleotides able to bind molecular targets (small molecules, proteins, nucleic acids, phospholipids up to cells, tissues and bacteria) with high affinity and specificity by adopting specific secondary and tertiary structures, as antibodies do. They share with these latter dissociation constants in the nano- to picomolar range, while showing advantages as compared to them: i) a less time consuming, more reproducible and cheaper production, ii) the lack of immunogenic response, iii) a lower molecular weight allowing faster uptaking and broader range of targets, iv) a higher stability and v) the possibility of being structurally modified without negatively affecting the binding affinity. It is therefore clear that aptamers can have appealing diagnostic and therapeutic applications.

Classically, aptamers are selected through the Systematic Evolution of Ligands by EXponential enrichment (SELEX) *in vitro* procedure, consisting of multiple rounds of selection and amplification of a DNA/RNA library incubated with the target. Although successful SELEX procedures have been reported, the process is tedious, it highly depends on the initial oligonucleotide library and it often fails in enriching high affinity aptamers. In the last decade, much effort has been made to overcome these limits, also exploiting computational methods. Indeed, *in silico* approaches have been developed and applied to model aptamers, with particular interest for those binding proteins, a crucial target for therapeutic and diagnostic applications. Nevertheless, the reported works have been mostly focused on isolated aspects related to SELEX: aptamers library design, retrospective validation of aptamer-target complexes or structure prediction. This does not allow to avoid SELEX and the few promising attempts to design from scratch aptamers with a specific protein target haven't been extensively validated.

Objectives

This work has the general aim of overcoming SELEX limits by developing a *in silico* protocol for the *de novo* design of aptamers given a specific target of interest. With this aim, the work will be divided in:

1. A benchmark step focused on:
   - Assessing the ability of different methods, including enhanced sampling molecular dynamics, in reproducing experimentally available aptamers' secondary/tertiary structures;
   - Testing different protein-DNA/RNA docking algorithms to obtain a reliable protocol for the prediction of protein-aptamer complexes and of their binding affinities.
2. A procedure set-up phase, during which a system of interest will be used as study case. Taking into account the outcomes of the previous phase, this phase will lead the optimization of an *in silico* workflow to obtain a series of aptamers able to bind the chosen target.
3. Eventually performing *in vitro* experiments to validate the obtained results.

This work will, therefore, provide a generally exploitable procedure for aptamers design for diagnostic/therapeutic applications without SELEX. In addition, it will enrich the fundamental knowledge on both aptamers 3D structures and protein-aptamer interactions.

Candidate profile

The candidate will have a strong biology/biochemistry/biophysics background; in addition, the candidate will have bioinformatics (sequences and/or structural) and, possibly, computer programming (python) skills. Wet lab experiences and/or interests together with experiences in drug design will be an advantage. This PhD project is compatible with a handicap situation.