MASTER « *In Silico* Drug Design »

2ème année

PROPOSITION DE STAGE
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Ecole doctorale de rattachement : 2MIB

Spécialité du stage : Recherche ☑ Professionnel ☐

Indiquez par quelques mots clés, l'orientation scientifique du sujet :

ADN G-quadruplexes, docking, dynamique moléculaire

Titre du stage :

Développements méthodologiques pour adapter le docking à des structures de quadruplexes G4.

Ce sujet constitue-t-il un premier pas vers un travail de thèse : Oui

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Description du sujet (quelques lignes):

Non-canonical DNA and RNA structures, such as *G-quadruplexes (G4)* are implicated into a variety of biological processes, comprising the development of a number of pathologies. G4-DNA structures are involved in regulation of transcription of a number of genes (including proto-oncogenes such as *MYC*, *KIT*, *KRAS* and others), DNA replication (through recruitment of the origin recognition complex) and induction of genome instability and DNA damage (including telomere-targeted DNA damage). G4-RNA structures are involved in a number of post-transcriptional mechanisms through disabling or sequestration of RNA G4-binding proteins, translational blockade of mRNA, or atypical (non-AUG) translation. From the therapeutic point of view, an important property of non-canonical DNA and RNA structures is their ability to form stable complexes with small molecules (ligands), leading to modulation of their physiological roles through, for example, transcriptional or translational blockade, disruption of complexes with disease-linked proteins, conformational change (in the case of polymorphic motifs) or ligand-induced degradation of the toxic nucleic acid structure. For these reasons, development of novel ligands for G-quadruplexes represents an active research area and in our laboratory, the combinatorial chemistry will be used to create a small molecules library targeting specific G4-DNA structures. However, the complementary docking algorithms have been poorly developed for such structures.

In docking algorithms, the scoring functions are generally developed and parametrized based on protein targets. The performance of these programs is also tested and compared using protein datasets. To our knowledge, such tests and comparisons were not made for nucleic acids, making high-throughput docking studies for these macromolecular targets more problematic. In order to choose the best-performing program or to create a specific strategy, we will compare the performance of popular docking algorithms (Glide, Gold, Surflex and FlexX) based on *in vitro* affinity data, obtained from biophysical studies with a set of reference ligands (developed in the laboratory) and well-characterized G4-DNA targets. This is necessary to be able to take into account the accuracy of docking scores and computational requirements. We will also combine docking approaches with molecular dynamics, since in the latter the parameters are more adapted to the study of DNA. However, if the results are still unsatisfactory because the parameters were not developed to the particular structures of G4-DNA, we plan in the longer term to undertake a QM/MM study on parts of G4-DNA in order to adjust these parameters.

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