MASTER « *In Silico* Drug Design »

1ère année

PROPOSITION DE STAGE
Année Universitaire 2020 / 21

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Titre du stage : Characterization of the structural asymmetry in the HIV-2 protease

Description du sujet (quelques lignes) : HIV-2 is a retrovirus discovered a few years after HIV-1. HIV-2 infections are restricted mainly to West Africa. HIV-1 and HIV-2 are currently treated with the same therapeutic arsenal, which consists of drugs targeting integrase, reverse transcriptase, fusion protein and protease (PR). However, HIV-2 is naturally resistant to all non-nucleoside inhibitors of reverse transcriptase or fusion inhibitors. HIV-2 has also demonstrated reduced susceptibility to protease inhibitors (PIs) [1–4].
PR is an effective therapeutic target for treating HIV infection because of its essential role in hydrolysing the viral precursor polyprotein during infectious viral particle maturation. PR is an homodimer of 99 amino acid per monomers. Ligand (Substrats and IPs) bound the PR in a pocket located at the monomer interface. Ligand binding induces structural deformation allowing the closing of ligand-binding pocket. In the aim to study the natural resistance of PR2 against IPs, we have previously developed in silico protocols to characterize PR2 structure and flexibility [5], its structural asymmetry [6-7], to compare PR1 and PR2 complexes [8] and their PI-binding pockets [9]. During these analysis, we have shown that although PR2 is an homodimer its two monomers exhibit different global and local conformations [6-7, 9-10]. This structural asymmetry is induced by ligand binding [6], crystal packing [7, 9], intrinsic flexibility of PR2 [6-7]. This asymmetry is important for the recognition, specificity and ligand binding [6].
In this study, we will explore the link between the structural asymmetry of PR2 and its intrinsic flexibility. To do so, we will study and compare the PR2 structural asymmetry during molecular dynamics simulations ran under different conditions (protonation, implicit or explicit solvant, …). More precisely, we will locate structural asymmetry residues in the different structures extracted from the generated trajectories and will analyze their position according to the flexible regions. We will also study the impact of protonation and water-molecule interactions on the PR2 asymmetry. For these analyses, student will use python and R programming languages and PyMoL software.

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