Molecular Dynamics Analysis of the HIV-1 Protease Enzyme

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Acquired immunodeficiency syndrome (AIDS), a disease caused by the human immunodeficiency virus (HIV), has been a worldwide threat to people's health since the 1980s. The World Health Organization estimates that over 34 million people are currently infected and living with the virus. The HIV protease is a critical part of the viral life cycle of HIV. The protease functions to cleave pre-viral gag and gag-pol polyproteins that develop into the mature virus. There are nine FDA-approved protease inhibitor drugs available; however, the high replication rate of the virus has led to drug-resistant mutants. Research has shown that even minor changes in the protease sequence away from the active site result in a decrease in drug binding efficiency. The goal of this project is to utilize long time scale molecular dynamics simulations to study the conformational dynamics of the wild type and Flap+ mutant of the HIV-1 protease enzyme. Simulations were conducted using the two force fields: Amber99SB and Charmm27 with three starting structures "open" (1odw.pdb), "curled" (2hb4), and semi-open (1HHP). Conformational results sampled the "closed", "semi-open" and "open" states of wild type and Flap + mutant of the HIV-1 protease enzyme. Overall, the Flap + hexa-mutant of the HIV-1 protease enzyme was more dynamic and had a backbone that was more flexible than the wild-type enzyme. The results from this experiment will shed light on the flap dynamics of HIV-1 protease and help scientists develop drugs that can inhibit the protease more efficiently.