Molecular Dynamics Simulation of HIV-1 Reverse Transcriptase

Abderrahmane Benghanem[1,2], Maria Kurnikova[3]

[1]*Bioengineering & Bioinformatics Summer Institute, Dept. of Computational Biology, University of Pittsburgh, 15260*

[2]*Rensselaer Polytechnic Institute , 12180*

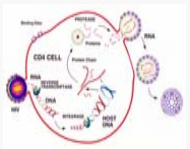
[3]*Department of Chemistry, Carnegie Mellon University, 15213*

Abstract (optional)

HIV-1 reverse transcriptase (RT) has been in the center of attention in the treatment of AIDS for many years. Understanding its structure will prove essentially useful in the design of new antiviral agents. The unliganded structure has been studied by Molecular dynamics techniques showing the flexibility and rigidity of HIV-1 reverse transcriptase. Solving the flexibility of HIV-1 RT is essential in determining controlling mechanisms of polymerases, binding of inhibitors, and developing more efficient drugs in the treatment of AIDS. The AMBER module was used to carry out the molecular dynamics studies. All calculations are performed using AMBER and its force fields as well as the Ptraj analysis package.

Introduction

HIV-1 reverse transcriptase has been in the center of attention in the treatment of AIDS. The function of The enzyme reverse transcriptase is used by retroviruses to transcribe their single-stranded RNA genome into single-stranded DNA and to subsequently construct a complementary strand of DNA (see figures below).



Functional HIV-1 reverse transcriptase is a heterodimer (see figure above) containing subunits of 66 kDa (p66) and 51 kDa (p51) . p66 contains two domains, the N-terminal polymerase domain (440 residues) and the C-terminal RNase H domain (120 residues). p51 is processed by proteolytic cleavage of p66 and corresponds to the polymerase domain of the p66 subunit. Portions of both p51 and the polymerase domain of p66 can be described as a "right hand" that contains three subdomains: fingers, palm, and thumb.

Comparing static structures can lead only to the conclusion that there is a Hinge – bending displacement, motion can only be analyzed by protein dynamics. ED method is able to extract large concerted atomic motion from an MD trajectory which allows us to solve the structure of HIV-1 reverse transcriptase. The dynamic structure will help determine ways of control of polymerases, binding of inhibitors, and developing more efficient drugs in the treatment of AIDS.

Method

Essential Dynamics is used to determine the structure of HIV-1 reverse transcriptase because it is able to extract large concerted atomic motion from a molecular dynamic trajectory. MD utilizes force fields to define the parameters of a certain molecule. Force Fields can be interpreted in terms of a relatively simple four component picture of the intra and inter molecular forces with in the molecular system. Energetic values are associated with the deviation of bonds and angles away from their reference or equilibrium values. There is a function that describes how the energy changes as bonds are rotated and also the force field contains terms that describe the interaction between non bonded parts of the system. Force field methods or molecular mechanics ignore the electronic motions and calculate the energy of a system as a function of the nuclear positions only making this method efficient in performing calculations on systems containing significant numbers of atoms.

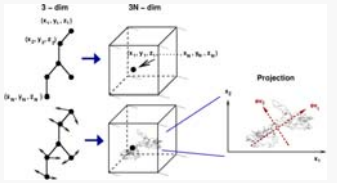
In MD, atoms interact with each other. These interactions originate forces which act upon atoms, and atoms move under the action of these instantaneous forces. As the atoms move, their relative positions change and forces change as well. In MD successive configuration of the system are generated by integrating Newton's laws of motion. The result is a trajectory that specifies how the positions and velocities of the particles in the system vary with time.

$$= \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_\theta (q - q_0)^2 + \sum_{improper} \frac{1}{2} K_\chi (x - x_0)^2 + \sum_{dihedral} K_\phi \left[1 + \cos(n_j - d)\right] + \sum_{ij} \left[\frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} - \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon_r r_{ij}} \right]$$

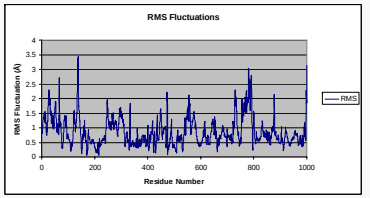
Potential Energy Function

$$\begin{bmatrix} a & b \\ c & d \end{bmatrix} \xrightarrow{\text{diagonalization}} \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix} \quad \begin{matrix} \text{eigenvalue} \\ \text{eigenvector} \end{matrix}$$

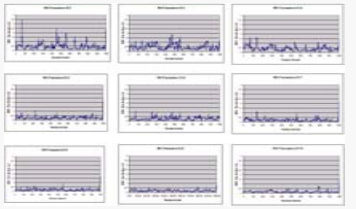
Covariance Matrix



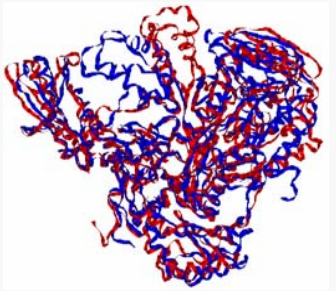
Results



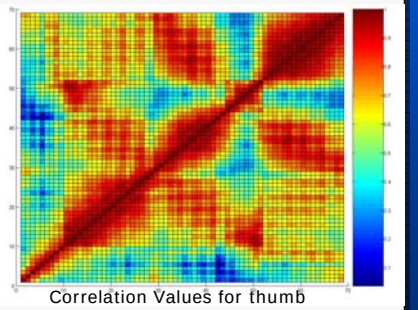
RMS Fluctuation for EV 1



RMS Fluctuations for EV 2-10



Thumb Flexibility



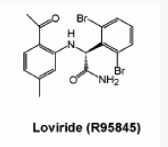
Correlation Values for thumb region (residues 243 -311)

Summary and Future Work

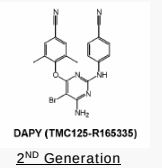
Molecular Dynamics was used to determine the structure of HIV-1 RT. Understanding the conformation flexibility of HIV-1 RT is essential in

- Controlling mechanism of polymerase
- Binding of inhibitors
- Developing more efficient drugs

New methods of drug design are now being developed to hinder the RT.



Loviride (R95845)



DAPY (TMC125-R165335)

1st Generation
Effective against wild type HIV-1 but not mutants

2ND Generation
(more flexible)
Binds RT in many conformations & escapes drug-resistance mutations

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