# Molecular Dynamics Simulation of HIV-1 Reverse Transcriptase

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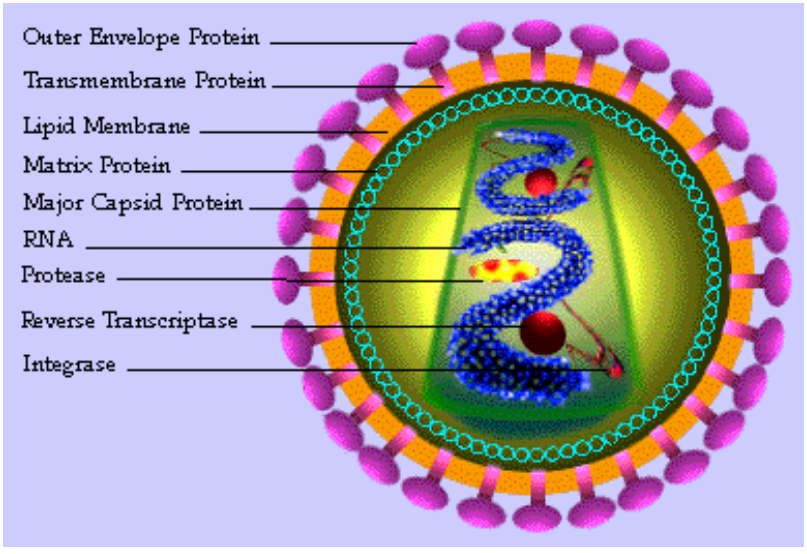
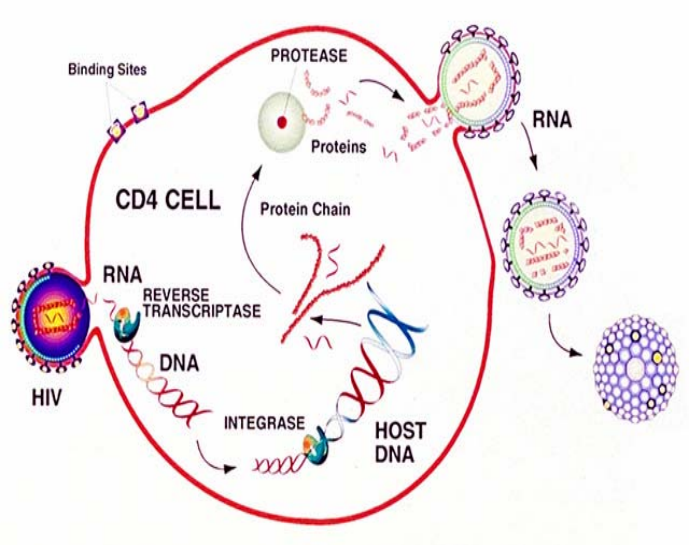
June 16, 2006

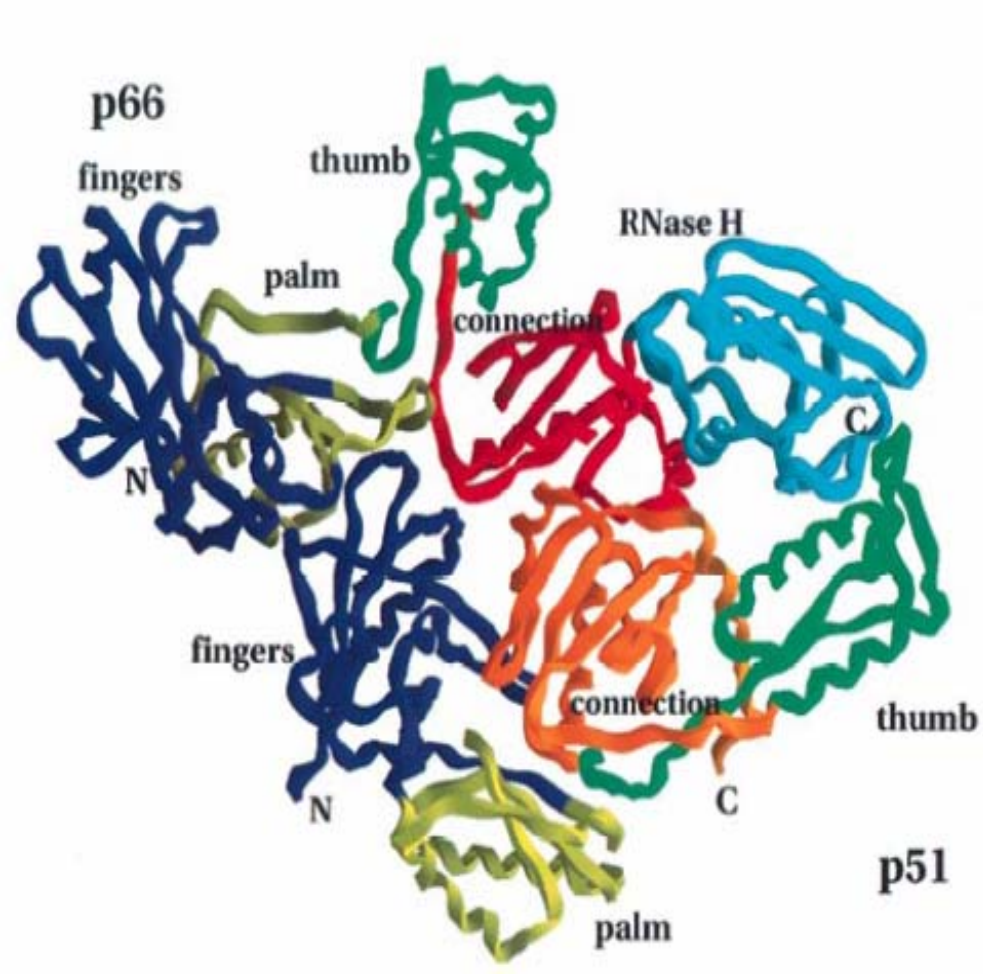
## Introduction

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 below) 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 strucs 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.

**Methods**

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. Molecular dynamics 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 molecular dynamics, 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 molecular dynamics 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. Newton's laws of motion can be stated as follows.

1. a body moves in a straight line with constant velocity unless perturbed.
2. force equals the rate of change of momentum
3. every action has an equal and opposite reaction

Trajectory is obtained by solving the differential equations embodied in Newton's second law F=MA:

$$\frac{d^2 r_i}{dt^2} = F_i(r_1, r_2, \cdots, r_n) \Big/ m_i$$

$$F_i(r_1, r_2, \cdots, r_n) = -\nabla V(r_1, r_2, \cdots, r_n) \qquad i = 1, 2, \cdots, N$$

$$V_i(\vec{r}) = V_i(\vec{r_1}, \vec{r_2}, \vec{r_3}, \ldots, \vec{r_N})$$

$$= \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_q (q - q_0)^2 + \sum_{improper} \frac{1}{2} K_x (x - x_0)^2 +$$

$$\sum_{dihedral} K_j \left[ 1 + \cos(n_j - d) \right] + \sum_{ij} \left[ \frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} - \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon_g r_{ij}} \right]$$

Formula explanation:

First term= models the interaction between pairs of bonded atoms, modeled here by a harmonic potential that gives the increase in energy as the bond length *b* deviates from the reference value $b_0$.

The second term and the third term= is a summation over all valence angles in the molecule, again modeled using a harmonic potential (a valence angle is the angle formed between three atoms A-B-C, A and C both bonded to B).

The fourth term= is a torsional potential that models how the energy changes as a bond rotates.

Fifth term = is the non-bonded term. Calculated between all pairs of atoms (i and j) that are in different molecules or that are in the same molecule but separated by at least three bonds. In a simple force field the non bonded term is usually modeled using a coulomb potential term for electrostatic interactions and a lennar-jones potential for van der waals

interactions.

Essential motions determine low energy modes of protein movement, They reflect preferred deformation pathways of the protein, which can be related to the function of protein.

**Expected Results**

Studying HIV-1 reverse transcriptase using Molecular Dynamics will determine the dynamic structure, which contains vital information to help understand its conformation flexibility. This is essential in determining controlling mechanisms of polymerases, binding of inhibitors, and developing more efficient drugs in the treatment of AIDS.

**References**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