A survey of structure and dynamics in HIV-1 Reverse Transcriptase

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Abstract
HIV-1 reverse transcriptase (RT) is a critical drug target for HIV treatment, and understanding the exact mechanisms of its function and inhibition would significantly accelerate the development of new anti-HIV drugs. Structural information on reverse transcriptase alone has proven to be insufficient. It explains the mechanism of inhibition and drug resistance of non-nucleoside reverse transcriptase inhibitors. Elastic network modeling provides a technique to rapidly probe and compare protein dynamics. Combining elastic network modeling with hierarchical clusters of both structural and dynamic data reveals a wealth of novel information. Here we present an extensive survey of the dynamics of reverse transcriptase bound to a variety of ligands with a number of mutations, revealing a novel mechanism for drug resistance to non-nucleoside reverse transcriptase inhibitors, where hydrophobic core mutations subtly shift the structural balance of RT to differences in the structural and dynamic functional regions of HIV-1 RT. This model arises out of a combination of structural and dynamic information, rather than exclusively from one or the other.

Structure of HIV-1 RT
- RNase H domain
  - Thumb subdomain
- p51 subunit
- p66 subunit
- Palm subdomain
- Thumb subdomain
- Connection domain
- DNA-bound
- Unliganded
- Hydrophobic core residues
- Entry blocker residues

States of HIV-1 RT
- Unliganded HIV-1 RT (red)
- DNA-bound HIV-1 RT (blue)
- NNRTI-bound HIV-1 RT (green)
- P51 subunit (gray)
- Thumb subdomain (red)
- Connection domain (orange)
- Palm subdomain (blue)
- DNA-bound (dark blue)

Elastic Network Models
- All-atom Molecular Dynamics (MD) too slow
- Coarse-grained model, Ca resolution, fast
- "Beads on springs"
- Single harmonic potential: \[ V_0 = k(r_{ij} - r_{ij}^0)^2 \]

Structural Differences are Subtle
- Pre-active structures
- Inactive structures
- Structures all in hyperextended conformation
- Fingers, thumb, and RNase H domains all subtly different
- Other structures largely unchanged

Deformation of Drug Binding Pocket Alters Thumb Position
- Plot of significant differences in covariance between inactive and pre-active cluster
- Motion correlated in Inactive only (blue)
- Motion correlated in Pre-active only (red)

Mapping Changes in Covariance onto Structure
- Residues colored by number of significantly varying covariances
- Changes in correlation motions do not correlate in domain connectivity
- Fingers and palm subdomains rigid in Inactive cluster
- RNase H domain correlated with polymers in Pre-active

Conclusions
- Subtle changes in structure can lead to larger changes in dynamics
- Hydrophobic core mutations can cause a change in structure/dynamics
- Rotation of thumb
- Restores unliganded motions
- Small changes in structure can lead to distinct changes in dynamics

Work done in LOOS (Lightweight Object Oriented Structure analysis library), an open-source C++ library designed and maintained by the Grossfield lab. LOOS provides a concise, adaptable framework for designing analysis tools that interfaces with native file formats of most simulation packages.

http://loos.sourceforge.net