Simulations at PSC Show Joint-Like Motion in Key HIV Protein

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Introduction

- ✓ The agent that causes AIDS (Acquired Immunodeficiency Syndrome) is the human immunodeficiency virus, HIV.
- ✓ FDA approved drugs to treat AIDS bind to either HIV-1 protease or HIV-1 Reverse Transcriptase (RT). These drugs can stop the virus replication, but only for a short period of time.

Anti-AIDS drugs

- ✓ HIV lacks a proofreading mechanism, and therefore it is prone to errors. Mutations arise by chance and RT continues duplicating ignoring the error. The drug cannot bind to some of these mutations ('drug resistant mutations'). The population of drug resistant mutations grows faster.
- ✓ Combination therapies or "cocktails" targeting both RT and protease are more effective.

HIV-1 RT

- This talk will concentrate on one of the targets of anti-AIDS drugs, HIV-1 Reverse Transcriptase. RT is an enzyme that takes part in the cycle of reproduction of the HIV virus.
- Starting from a single strand of RNA, RT makes double-stranded DNA, which is then assimilated into the host-cell (T-cell).
- If we could inhibit RT from working, we could cure AIDS.

HIV-1 RT Crystal Structures

- ✓ Several crystal structures exist of RT unliganded, and bound to DNA or to inhibitors.
- ✓ The crystal structures show that the subdomains that contain the active site and the binding site for the inhibitors resemble a human hand.

RT Crystal structures

- Two crystal structures of RT, with and without DNA, reveal a striking difference:
- With the hand grasping DNA, the thumb is extended and open, making space for the DNA to fit into the palm. Without DNA, the thumb is closed.

Flexibility and function

- This joint-like flexibility of the thumb region has implications for RT function and possibly for the design of new drugs:
- Flexibility might play an important role by allowing the translocation of RT along the nucleic acid.
- Certain anti-AIDS drugs might act by inhibiting this motion (molecular arthritis model). Like sand in a gear, they might lock the thumb in an open position, so that the enzyme cannot function normally.

Molecular Dynamics

- ✓ The crystal structures are snapshots of different conformational states.
- ✓ Molecular dynamics provide an ideal technique to study at atomic detail the movements from one configuration to another.

Molecular dynamics

- Objective: Can MD simulate large conformational changes in RT?
- Starting structure: crystallographically determined structure of RT/DNA, from which the DNA was removed.
- Will the thumb subdomain close, adopting a conformation similar to that reported for the crystal structure of unliganded RT ?

Details of MD simulations

- AMBER on CRAY T3D and T3E
- RT has 1,000 amino acid residues. Total number of atoms: 9,924.
- Eight 1-ns simulations in vacuum, starting with different random velocities of the atoms each time.
- Each 1ns simulation required 41 hours of computing time on 16 CRAY T3E processors.

Results

- For six of the eight simulations, the thumb subdomain closed down over the palm in close agreement to the crystallographic structure, strongly suggesting this is the native state.
- The simulations show a large subdomain rearrangement (the tip of the thumb moves approximately 30 A) occurring in a short time scale (30 to 200 ps), suggesting that MD is an effective technique to study RT subdomain mobility

Biological significance

- ✓ The fact that the thumb subdomain closes down in the majority of the simulations investigated indicates that, for unliganded RT, the closed down configuration is the favored one with this molecular dynamics model. This is consistent with two independently determined structures of unliganded RT.

The future

- ✓ These studies are only a first step in simulating RT mobility.
- ✓ Want to make simulations more realistic by surrounding the molecule in a water bath.
- ✓ Study the effect on RT mobility of bound DNA and drugs.

Collaborators

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- Jianping Ding and Eddy Arnold, Center for Advanced Biotechnology and Medicine, and Rutgers University Chemistry Dep.