Computational Simulations of the Human Immunodeficiency Virus Rev-RRE Complex

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People newly infected with HIV

Total: 4.9 (4.3–6.4) million

UNAIDS epidemic update, December 2004
Deaths caused by AIDS globally

Total: 3.1 (2.8–3.5) million
Introduction

- There are many drugs to fight AIDS but due to its high mutation rate, not all strains of HIV are susceptible to drug therapy; therefore, new drug treatments are needed. A better understanding of how HIV works will be required in order to develop new drugs.
RNA is a Polymer of Ribonucleotides
The Structure of Nucleic Acids

- Nucleic acids can form double stranded regions, and in 3D are helical molecules consisting of a sugar-phosphate backbone and four different nitrogenous bases.
Current Drug Targets

Reverse transcriptase inhibitors: target HIV during reverse transcription preventing the RNA from being reverse transcribed into DNA.

Protease inhibitors: target HIV during the process of budding and stop the protein protease from cleaving the gag and pol polyproteins and forming a mature viral particle.

Summers *JMB* 1999.
Rev in early phase of HIV
Rev in the late phase
**Minimal Rev-RRE complex**

a) **Rev**

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DTRQARRNRRRRWWRERQRAAAAR
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b) **RRE**

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g g U c U G G G C G C G C A G C G U C G gc
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- important for *in vitro/in vivo* binding
- non-specific *in vivo*
- important phosphate
- *in vitro* selection studies
Amino acid structure
The Rev-RRE complex has chains of amino acids hanging off the molecule in different directions called arginine side chains.

Understanding the position of these side chains in the complex is essential in understanding how Rev-RRE functions in vivo.
Objectives/Goals

- One part of understanding how HIV works is knowing how the Rev protein binds to the RRE section of mRNA to transport it out of the nucleus.
- We accomplished this by using molecular dynamics in the program AMBER to simulate the protein nucleic acid complex.
Methods

- Molecular dynamics simulations make a movie of the molecule.
- 4000 snapshots (1 every picosecond) for 3 models were collected.
Molecular dynamics

- Surround with water and Na+ (24,000 atoms)
- Balls and springs
- Cornell et al. force field
The simulations were visualized with the computer program VMD, which shows the motion of the molecule as a movie.
Results

- Model 4 has 1000-4800 picoseconds.
- Model 8 has 600-4600 picoseconds.
- Model 14 has 800-4800 picoseconds.
Atomic fluctuations for model 4

![Graph showing atomic fluctuations for model 4]
Atomic fluctuations for model 8

[Graph showing atomic fluctuations for model 8]
Atomic fluctuations for model 14

[Graph showing atomic fluctuations with residue numbers on the x-axis and fluctuation (Å) on the y-axis.]

- X-axis: Residue #
- Y-axis: Fluct (Å)
- Graph title: Atomic fluctuations for model 14
RMSD starting structures for all models

RMSD all models for 4000 ps

Time (ps)

Model 4
Model 8
Model 14
This project has given us a better idea of how Rev hydrogen bonds to the RRE of mRNA and an idea of how much the atoms involved in the binding fluctuate. This information will hopefully give the next person working on characterizing the arginine side chains a good place to start.
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