Molecular Dynamics Simulations to Map the Conformational Changes in the HIV-1 Tat Protein

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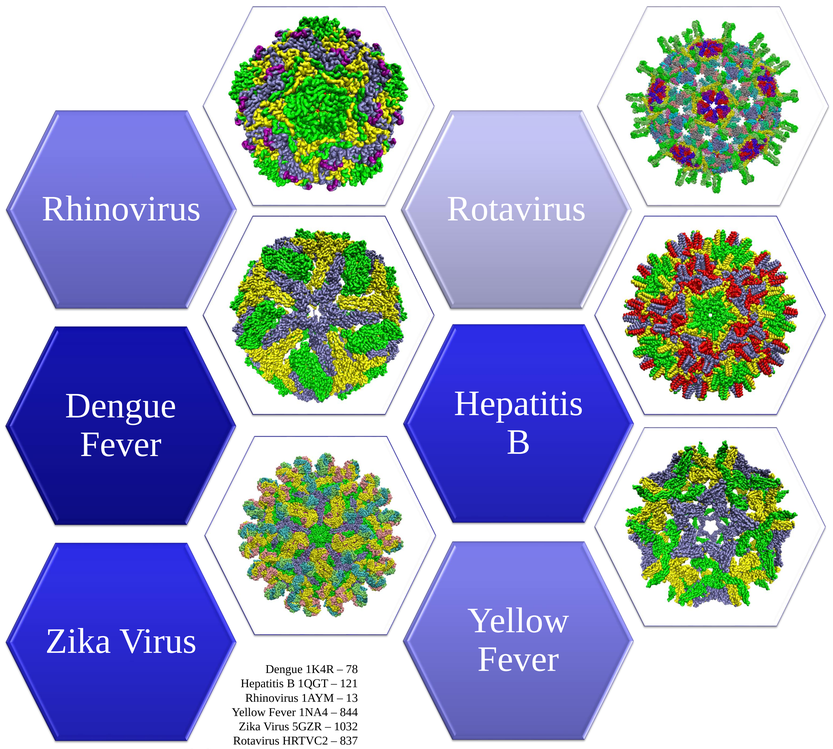
Abstract

Viruses are infectious biological agents that rapidly replicate inside of host cells and are responsible for many human disease outbreaks such as Dengue fever, Hepatitis B, and most recently the Zika virus. Viral genetic material is stored inside and protected by the viral capsid. Viral capsids are composed of different proteins and take on many complex structures. With the advancement in computing powers, only recently have the complex viral capsid structures been able to been modeled computationally. Still full viral capsid simulations remain computationally expensive. In order to gain a holistic understanding of viruses, the human immunodeficiency virus Type-1 Tat protein was chosen as a model system and studied via a classical molecular dynamics (MD) simulation. The Tat protein is responsible for binding the transactivation response (TAR) RNA in the HIV -1 genome, producing a conformational change, and promoting viral replication. A short 28 ns long MD simulation was performed and analyzed against other known structures of the Tat protein to understand the mechanism by which Tat binds to TAR RNA.

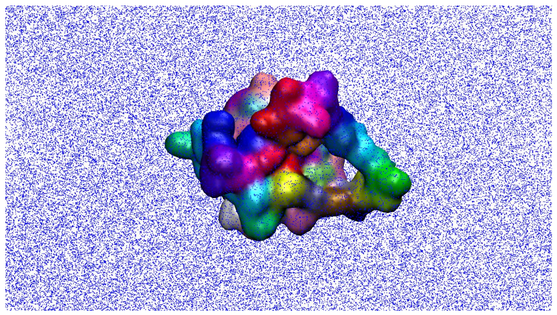
Viral Capsid Structures



Dengue 1K4R – 78
Hepatitis B 1QGT – 121
Rhinovirus 1AYM – 13
Yellow Fever 1NA4 – 844
Zika Virus 5GZR – 1032
Rotavirus HRTVC2 – 837
The figures/data were obtained from VIPERdb (http://viperdb.scripps.edu)

Goal

The main goal of this project was to study the Tat protein at an atomistic level, through molecular simulation, to gain insight into its conformational landscape when it is unbound to TAR RNA.



HIV-1 Tat protein unbound in a water box. (1TIV)

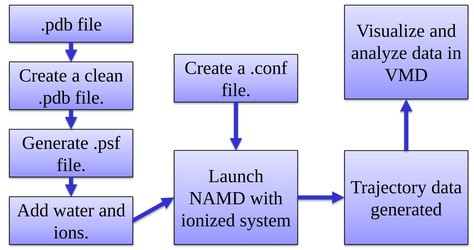
System size: 17020 atoms

Methods

Molecular Dynamics Simulation

The integration of Newton's equations of motion at small time steps for each atom in the simulation.

Simulation Preparation



Software

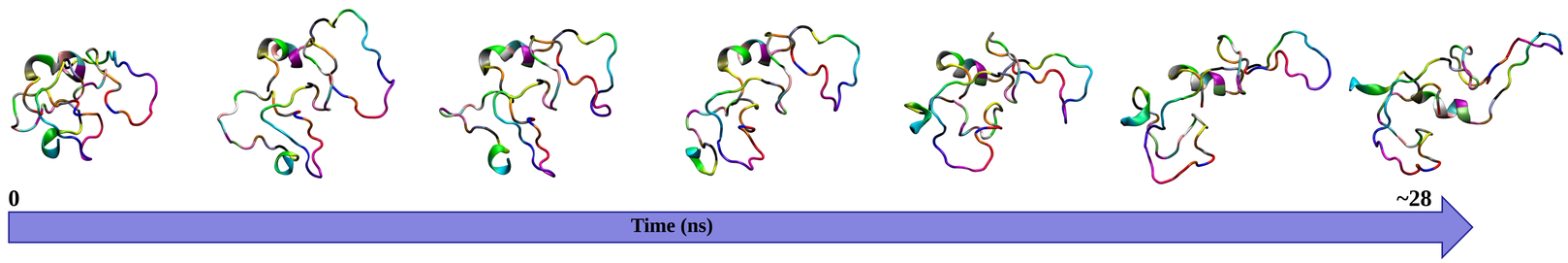
Visualization Software: **V**isual **M**olecular **D**ynamics (VMD)

Simulation Software: **NA**noscale **M**olecular **D**ynamics (NAMD)

The system was simulated in a CHARMM (**C**hemistry at **HAR**vard **M**acromolecular **M**echanics) 36 force field with the TIP3P water model.

Produced by the Theoretical and Computational Biophysics Group at the University of Illinois-Urbana-Champaign.

Results



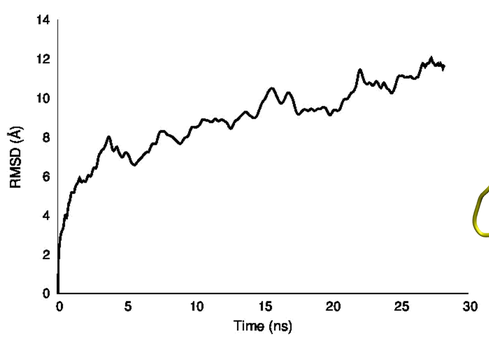


Figure 1: Root Squared deviation in angstroms calculated from the starting structure (1TIV)

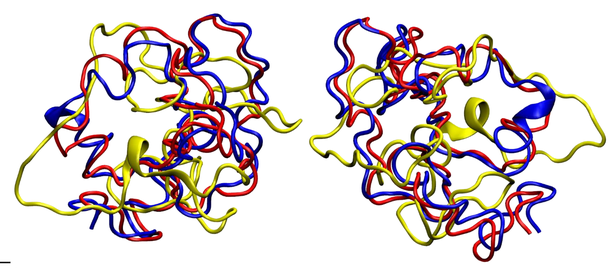


Figure 2: Aligned structures of Tat used for comparison. 1TIV (Yellow) 1TAC (Blue) 1TBC (Red)

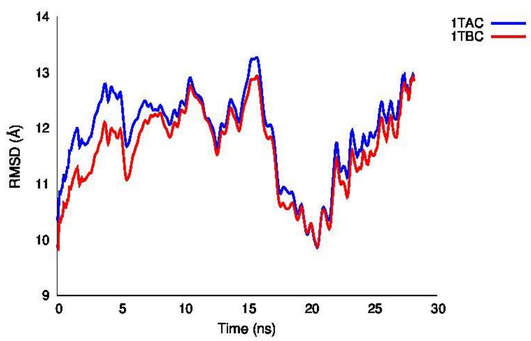
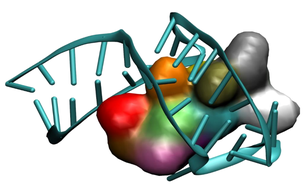


Figure 3: Root Squared deviation in angstroms calculated from two other known structures of Tat.

Introduction

Introduction/Background

- HIV-1 Tat protein interacts with TAR-RNA as a key step of replication.
- Understanding this process could led to better, more effective methods of blocking this process, halting HIV-1 replication.



HIV-1 Tat Protein bound to TAR-RNA. (5J1O)

Conclusions/ Future Work

- The Tat protein simulation did not show any definitive configurations that could allow for binding with TAR-RNA.
- Longer MD simulation is suggested.

Acknowledgements

This research was supported with funding from the National Science Foundation's Research Experience for Teachers in Engineering Grant (ENG-1132648).

Thanks to Vashisth Lab and Altai Perry.

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