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Virtual Screening of Inhibitors Targeting HIV-1 Reverse Transcriptase

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Abstract

HIV (Human Immunodeficiency Virus) weakens the immune system and has resulted in 30 millions lives lost, without any established cure discovered. This project's approach targeted an enzyme belonging to HIV called Reverse Transcriptase, which plays an important role in viral replication. In the first project, a virtual software called AutoDock was first validated for its effectiveness by comparing its results to already experimentally determined ligands. In the second project, AutoDock will be used to analyze developed fragment-based inhibitors to see if they successfully bind to HIV-1 Reverse Transcriptase. It was also observable that the virtual software FTrees could be used to create a larger inhibitor by matching and linking the fragments with other chemically favorable molecules. These results show that *in silico* research has the potential to be as effective in HIV drug discovery as lab-based procedures, as long as further analysis of the results is conducted.

Introduction

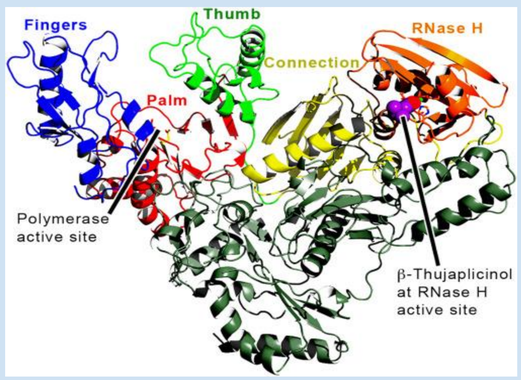
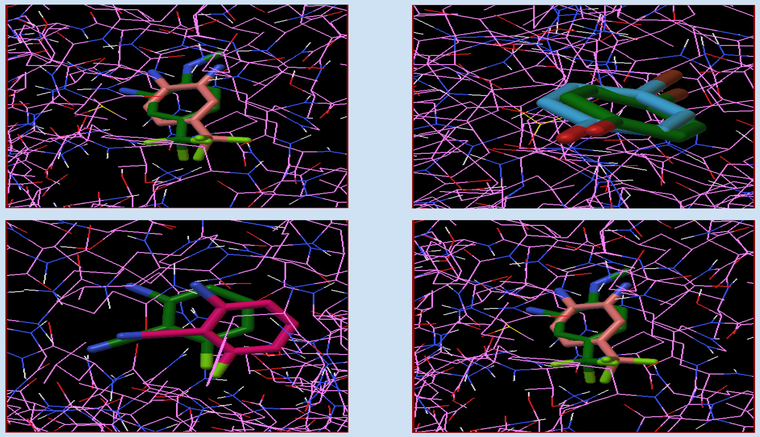


Figure 1: A Protein Data Bank 3D Model of HIV 1 Reverse Transcriptase

HIV (Human Immunodeficiency Virus) is a retrovirus that attacks the human immune system. Currently, the only drugs on the market are used to prolong life and mitigate symptoms. One popular target in the research community's goal to discover a treatment for HIV is Reverse-Transcriptase, an enzyme that is essential to viral replication. RT has 2 key subunits (p66/p51), and many pockets that make the structure analogous to a right hand

Results

- It was found that AutoDock generated multiple (usually 7-9) different virtual conformations for each fragment, each with a different orientation and binding affinity
- As shown in Figures 2 and 3, some (but not all) of the conformations were extremely similar to the experimentally-generated ligand
- The binding affinities vs the average distance of each conformation from the best fit for HL31 (ranked by AutoDock) was plotted, showing a positive correlation
- However, the virtual models in Figures 2 -5, which are closest in orientaiton to the experimental ligand, have a lower binding energy compared to some alternatives



Figures 2-5: Results from AutoDock shown in its user interface "Python Molecular Viewer" for both the experimental (green) and the virtually generated (blue/orange) fragments

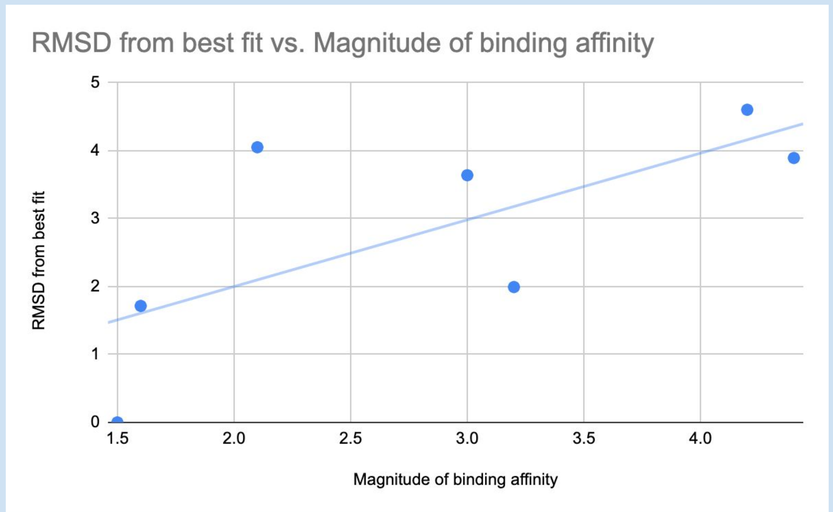


Figure 6: Scatter plot of Halo31, plotting each conformation's RMSD from the best fit with its binding affinity to HIV RT

Conclusion

- After comparing the molecular models generated by AutoDock to the ones experimentally developed through X-ray crystallography and diffraction, it was seen that some (however, not all) of the conformations generated by AutoDock were very similar to the experimental results.
- These findings show that *in silico* based drug discovery research has the potential to be as effective as lab-based experimental procedures, as long as the results are carefully analyzed
- In the future, we would like to use AutoDock to develop the fragments into a stronger inhibitor based on the restulting molecules suggested by the software FTrees

Materials and Methods

Project 1: Validate the effectiveness of online docking software by comparing its results to an already experimentally tested library

- Four ligands (HL 20, 23, 31, 43) and the receptor (HIV RT) were inputted into AutoDock, as well as the specific coordinates that the software will analyze for potential binding sites.
- Several possible conformations were generated and then compared to the experimental results

Project 2: Develop new fragments into HIV RT inhibitors

- Selected ragments from Project 1 were run against a database with over 100 million other molecules through the software FTrees
- The software then compared molecules linked to the fragment with already existing drugs in the market

References

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