

Molecular modelling studies of HIV protease drug resistance

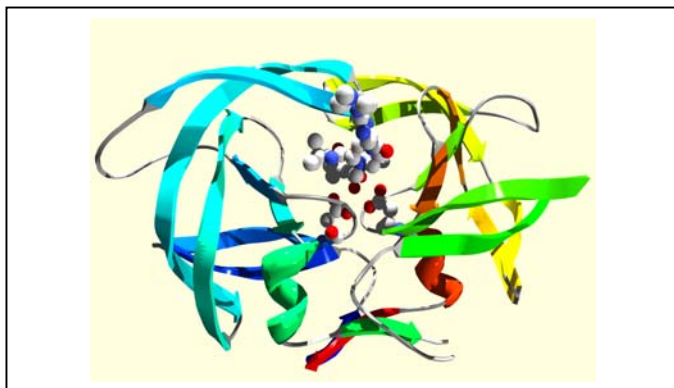


Figure 1 HIV protease with inhibitor

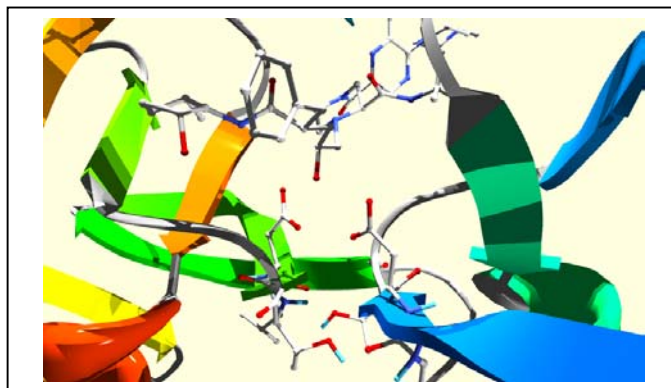


Figure 2 Active site of HIV protease

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Objective:

To understand mechanism of resistance to human immunodeficiency virus (HIV) protease specific drugs, and use this information to aid in drug choices for patients currently undergoing HIV therapy.

Background:

HIV is a global disease affecting some 38.6 million people at the end of 2002 according to the World Health Organization. Although antiviral drugs are available, the rise of drug-resistant HIV strains has decreased their efficacy and is becoming an increasing health concern. HIV protease, which is a crucial dimer protease enzyme for the replication of HIV in host cells, is one of the key targets of current drug therapies. Depending on the type of drug used in treatment, multiple amino acid mutations can occur in the protein structure of the HIV protease, conferring resistance through often poorly understood mechanisms. By modelling these mutations and understanding their mechanisms it is hoped that drug therapies can be tailored to patients with drug resistant HIV strains.

Method:

The solved crystal structure of HIV protease was used as a starting model for molecular minimization and dynamics simulations (PDB code 2BPY). After adding approximately 20,000 water molecules and minimizing the system, multi-nanosecond simulations of the wild type and mutant HIV protease were run using NAMD* 2.5 at VPAC. Each simulation typically used 8 processors and ran for about 7 days or about 1400 CPU hours.

Analysis of the dynamics simulations using VMD** revealed certain mutations increased instability at the active site, possibly contributing to weakening the affinity for the protease drugs. Other modelled mutations sites presented clear steric hindrance for certain protease inhibitors such as glycine 48 to valine giving resistance to Saquinavir.

Outcomes:

Our dynamics simulations have identified possible key mutations responsible for HIV protease dimer stability which in turn, along with active site mutations, are implicated in reduced drug affinity. Verification is hoped to be gained with experimental work, providing more insight into resistance mechanisms and eventual implemented in designing more effective drug regimes for the treatment of HIV.

* NAMD Laxmikant Kalé, Robert Skeel, Milind Bhandarkar, Robert Brunner, Attila Gursoy, Neal Krawetz, James Phillips, Aritomo Shinozaki, Krishnan Varadarajan, and Klaus Schulten. NAMD2: Greater scalability for parallel molecular dynamics. *Journal of Computational Physics*, 151:283-312, 1999.

**VMD Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", *J. Molec. Graphics*, 1996, vol. 14, pp. 33-38.