

High performance computing was used to investigate the effects of resistance mutations within a crucial enzyme of Human Immunodeficiency Virus (HIV) towards a range of antiviral drugs. New methods of assessing drug binding using averaging molecular interactions over longer molecular dynamics simulations of the drug and enzyme in a solvated environment correlated well with clinical experience. This method is hoped to be useful in assessing treatment options for patients presenting with new drug resistance profiles.

<<< Molecular Modelling of HIV Protease Mutations

HIV currently affects approximately 40 million people worldwide and although a number of antiviral drugs are available for treatment, the virus often develops resistance to these medications. Changing to alternate drugs can often lead to further resistance until no drug choices remain for the patient, and thus can not be used as a long term strategy to overcome this issue. As it is difficult to predict what resistance mutations will arise upon starting a new antiviral treatment, it is desirable to have a model system upon which to test the existing range of drugs to assess which drug is most suitable to treat that particular strain of the virus.

HIV protease is an enzyme essential in HIV viral replication. Numerous antiviral drugs have been developed targeted towards inhibiting the HIV protease but unfortunately, all are prone to encourage drug resistant mutations. The difficulty in patient treatment arises as more drug resistance mutations accumulate; fewer of the protease drugs remain effective as a result.

Molecular modelling of drug interactions in the active site of the enzyme can offer some indication of which drug would be most effective for a particular ensemble of resistance mutations, greatly optimising a treatment regime.

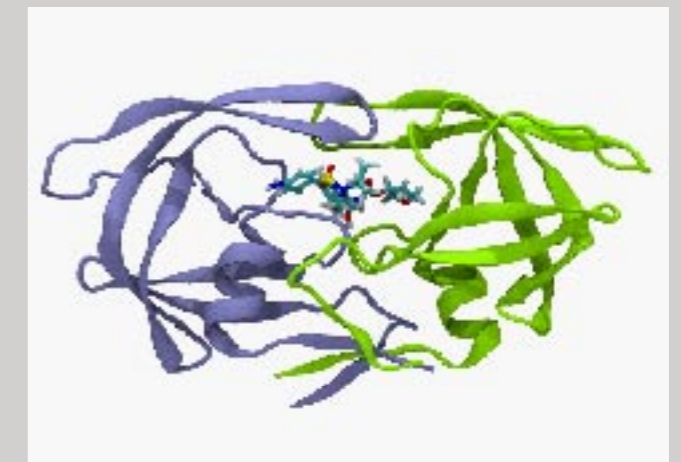
In collaboration with the Victorian Infectious Disease Reference Laboratory, VPAC investigated this approach using a fully solvated model of the HIV protease enzyme using molecular dynamics simulations. It was found that better results were obtained using longer simulations (in the order of nanoseconds) and averaging the interaction energies. This required a significant amount of high performance computing (HPC) resources. VPAC combated this issue by using Grid technology. The Grid is an emerging technology in HPC whereby researchers can enjoy shared access to computer, database and instrument resources securely across the web, greatly improving infrastructure utilisation and research output.

The simulation of the antiviral drug Amprenavir with various HIV protease mutations gave a range of energy interaction levels that correlated extremely well with what is known at the clinical level.

HIV simulation solvation interaction energy with Amprenavir

HIV protease strain	kcal/mol
V84I	-52.9
I50V	-56.7
I50V_V82I	-59.2
I47A	-61.7
I48V	-63.1
Wild type	-64.6
D30N	-73.1

The strains depicted in red are known to be resistant to Amprenavir and thus are expected to have a lower interaction energy than the wild type (-64.6 kcal/mol). The strains depicted in blue are known to be not resistant towards Amprenavir.



HIV Protease with Apv

The longer simulations used in this methodology have highlighted the continual conformational change in the active site between the protein, drug and aqueous environment suggesting why the time averaged approach appears more successful than earlier attempts which used much shorter time frames.

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Close up of the aprenavir binding site showing water interactions

Further Information

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