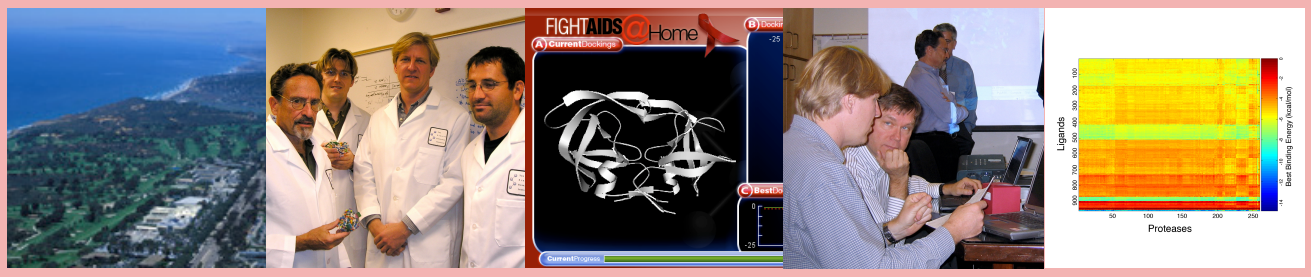
FightAIDS@Home News



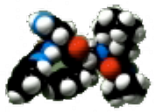
May 10th, 2007 Volume 3

First Results of FightAIDS@Home Research Published

We have published the initial analysis of the vast number of docking results from our FightAIDS@Home computations.

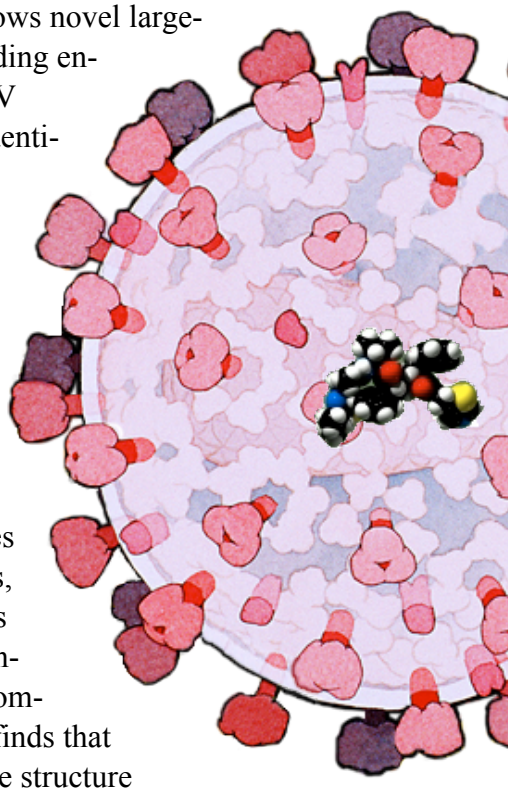
This week the first peer-reviewed scientific paper reporting results from our research using FightAIDS@Home is being published. As we continue to test experimentally the first batch of compounds identified in our first computational experiment, we have been able to analyze the broader computational results to give us more information about the entire range of mutations to the HIV viral protease and how they respond to a large class of diverse chemical compounds.

This analysis, and how we can use it is the subject of the paper that appears in the *Journal of Chemical Information and Modeling*. The paper is titled: "Analysis of HIV wild-type and mutant structures *via in silico* docking against diverse ligand libraries." The authors are Max Chang, Lindy Lindstrom, Arthur Olson, and Richard Belew.

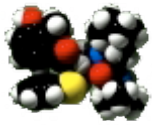


The abstract of the paper reads as follows:

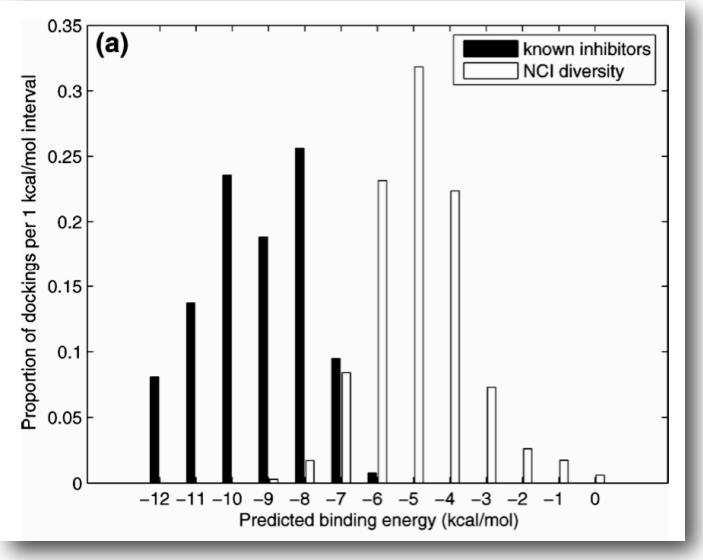
"The FightAIDS@Home distributed computing project uses AutoDock for an initial virtual screen of HIV protease structures against a broad range of 1,771 ligands including both known protease inhibitors and a diverse library of other ligands. The volume of results allows novel large-scale analyses of binding energy profiles for HIV structures. Beyond identifying potential lead compounds, these characterizations provide methods for choosing representative wild-type and mutant protein structures from the larger set. From the binding energy pro les of the PDB structures, a PCA-based analysis identifies seven "spanning" proteases. A complementary analysis finds that the wild-type protease structure 2BPZ best captures the central tendency of the protease set. Using a comparison of known protease inhibitors against the diverse ligand set yields an



AutoDock binding energy significance threshold of -7.0 kcal/mol between significant, strongly binding ligands and other weak/non-specific binding energies. This threshold captures nearly 98% of known inhibitor interactions while rejecting more than 95% of suspected non-inhibitor interactions. These methods should be of general use in virtual screening projects, and will be used to improve further FightAIDS@Home experiments.

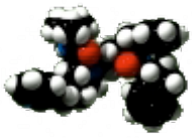


In simple terms, the results from FightAIDS@Home has given us the ability to classify both protease mutants and potential chemical inhibitors so that the docking calculations that we do in the future will be more targeted and efficient. We will, for instance, be able to use a small set of mutant protease structures to represent a much larger set of HIV mutants in our docking analysis. This will allow us to screen much larger chemical libraries more efficiently, or enable us to use more sophisticated models of the mutant structures, that incorporate flexibility into their representation.



Comparison of the distribution of binding energies for known inhibitors and NCI Diversity Set compounds.

While this is principally a technical break-through, it means that we can get more reliable and meaningful results in the computations that we will now be pursuing . This should speed us to our goal of finding new HIV therapeutics that are effective in the face of drug resistance. These results would not have been possible without the computing resources of the World Community Grid, and the generous support of the FightAIDS@Home volunteers. We are most grateful to all of you, and your contributions are acknowledged in the paper.



Prof. Arthur J. Olson
Dr. Garrett M. Morris
Dr. William Lindstrom
Alexandre Gillet
Dr. Richard K. Belew
Max W. Chang

References

Max W. Chang, William Lindstrom, Arthur J. Olson, and Richard K. Belew (2007) “Analysis of HIV Wild-Type and Mutant Structures *via in Silico* Docking against Diverse Ligand Libraries” *J.Chem. Inf. Model.* http://pubs.acs.org/cgi-bin/abstract.cgi/jcisd8/asap/abs/ci700044s.html