New experiments will model HIV protease more accurately
Docking to flexible targets will improve our ability to identify novel inhibitors.

We have started a new set of experiments on the World Community Grid that will help to model the HIV protease even more accurately than our previous experiments.

Until recently, our experiments have treated the ligand—the small molecule that could be a candidate drug—as a flexible molecule. The HIV protease, on the other hand, is treated as a rigid molecule.

The Relaxed Complex method will be used in many of the new experiments performed on the FightAIDS@Home grid. This will allow us to evaluate potential drugs by docking fully-flexible versions of known and potential inhibitors against an ensemble of hundreds to thousands of different conformations of the target protein. In other words, we examine how well a potential drug binds to and blocks a massive collection of many of the different shapes that the drug target can sample as it wiggles and jiggles in a warm, watery environment. Proteins are very flexible polymers, and some potential drugs might not bind well to the average conformation that is represented in a particular crystal structure. Thus, by including the many different shapes that the target protein can display when we evaluate potential drugs, the drug design process can become more realistic and more accurate.

Molecular Dynamics simulations (or other methods for sampling the drug target’s conformational space) are first used to generate that massive collection of thousands of different snapshots of the shapes that the protein target can sample as it dances around. For descriptions of the Molecular Dynamics technique (MD, for short), the drug-resistance problem, and the particular collections of shapes that will be targeted in these new FA@H experiments, check out this link: http://legacy.sdsc.edu/Press/03/032504_HIV.html.

By AutoDocking fully-flexible inhibitors to the massive ensembles of conformations that were harvested from these MD simulations, the flexibilities of both the potential drugs and their target can be incorpo-
rated into the drug design and evaluation process. Including this flexibility can be especially important when one is trying to inhibit a highly dynamic target such as HIV protease.

The FightAIDS@Home distributed computing network provides unparalleled resources that will enable virtual high-throughput screening of libraries of thousands of different compounds from the NCI against ensembles of hundreds to thousands of different conformations from several of the worst multi-drug-resistant mutants (MDR) of HIV protease. Such mind-bogglingly complex experiments are thought to be impossible by most scientists in the drug design community. We would not be able to perform these experiments without the computational resources that you help provide. Thank you for helping us push the boundaries of what can be accomplished with current technology.

The ensembles of conformations of different multi-drug-resistant mutants of HIV protease will be used for two different drug design projects that use the Relaxed Complex method. In one line of research, the NCI diversity set of compounds (as well as other lead compounds developed at TSRI or discussed in the literature) will be docked against the active site of the ensembles of shapes of these MDR mutants of HIV protease. When you are running the FightAIDS@Home project on your computer, these experiments will show the little colored spheres docking to the large cavity in the center of the ribbon diagram of HIV protease. Structural modifications to the best-performing compounds will be performed and tested both in silico and in vitro in a collaborative, iterative process, in order to aid in the development of new drugs that should be effective against these multi-drug-resistant mutants.

In the second line of new experiments, the NCI's library of small molecules will be used in Relaxed Complex experiments that focus on a novel binding site. This site can be identified by AutoLigand, shown here as the grey, blue and yellow spheres on the right-hand side of the ribbon diagram of HIV protease. This software is designed to identify binding sites in proteins, and was developed in the Olson Laboratory by Rodney Harris and David S. Goodsell, building on a idea from a former member of the laboratory, Albert Beuscher. This binding site is on the outside of HIV protease, and we call it the “exo site”. When you are running the FightAIDS@Home project on your computer, you might recognize these experiments by looking for the little colored spheres that dock to the sides of the protease molecule.

To learn about the initial experiments that tested the idea of trying to target this potential new drug binding site and to find some molecular art that helps to explain it, read the following press releases:
http://www.hhmi.org/news/perryman_mccammon20060310.html and http://www.aumag.org/lifeguide/THApril06.html. A news article that discusses this exo site and that presents the unbiased comments from a couple of scientists who were not involved in these projects can be found on pages 3 and 4 of this document:

Thank You
Dr. William “Lindy” Lindstrom has recently completed his postdoctoral training and research in the Olson Laboratory. Dr. Lindstrom has taken the position of Principal Scientist at Acelot, a chemical informatics start-up company in Santa Barbara, California, which focuses on novel graph-based methods for characterizing and classifying libraries of chemical compounds.
Dr. Lindstrom’s contributions to FightAIDS@Home have been very significant and highly impactful. He served as the mainstay in organizing and running all of the computational experiments. We will miss his diligence and ingenuity as well as his cheerful and helpful nature—which we know will all serve him well in his new endeavors.

We are happy to have recruited Dr. Alex Perryman to the project, who is taking over Lindy’s role, and as described above, is introducing new approaches to FightAIDS@Home.

Thank you very much for your interest in science and for your assistance in the fight against AIDS. We couldn't do this research without your help.

Prof. Arthur J. Olson
Dr. Garrett M. Morris
Dr. William Lindstrom
Dr. Alex Perryman
Dr. Rodney Harris
Alexandre Gillet

References

1. The Relaxed Complex Method:  
   http://www.npaci.edu/Press/02/052202_shortentime.html
2. Molecular dynamics:  
   http://legacy.sdsc.edu/Press/03/032504_HIV.html
3. AutoLigand:  