Human Immunodeficiency Virus (HIV), which causes Acquired Immunodeficiency Syndrome (AIDS), has infected 70 million people worldwide since the beginning of the epidemic. In 2011, an estimated 34 million people had HIV, and in the same year, 1.7 million people died from AIDS. Working towards prevention is not enough; treatment is necessary for the millions of people who are currently living with HIV infection. Discovery of new types of drugs against HIV is especially urgent since multi-drug-resistant mutants of HIV are constantly evolving and spreading throughout humanity. Additionally, scientists have shown that treating HIV with effective drugs helps decrease the probability of spreading infection. Helping us advance the discovery of new anti-HIV drugs will both assist in the treatment of current HIV patients and prevent the spread of this deadly virus.

MGL and the HIVE. The Molecular Graphics Laboratory (MGL), led by Professor Arthur Olson, is part of the HIV Interaction and Viral Evolution (HIVE) Center, under a National Institutes of Health grant. Part of the research done by MGL is to computationally search for compounds targeting the variants (or mutants) of HIV proteins. This is done with software tools created by MGL, AutoDock and AutoDock Vina. AutoDock and Vina “dock” flexible models of small molecules to predict (a) where these compounds prefer to bind on a protein target, (b) how tightly these compounds may bind, and (c) which molecular interactions are formed between a compound and a protein target. Predicting small molecules that bind tightly to HIV proteins aid in advancing the discovery of new anti-HIV drugs. The FightAids@Home Project uses the volunteered power of IBM’s World Community Grid (WCG) to dock millions of small molecule libraries to different HIV protein structures. Since 2005, the WCG has provided over 200,000 run-time years equating to approximately 400 million dockings.

2. World Health Organization (http://www.who.int/gho/hiv/en/)
**Progress**

The “wet lab” experimental work on FAAH hits is ongoing. Some of the compounds mentioned in the last newsletter have had little to no activity or have been difficult to crystallize. Others have shown some promise. However, there is much data still to analyze.

In fact, part of our efforts include streamlining the processing and analyzing of the incoming FAAH data, which includes creating a database to enable more efficient analysis of our virtual screenings.

Since the last newsletter, AutoDock Vina has been implemented on FAAH, and because of its speed, Experiments 42 – 71 are almost all completed. Due to the rapid computational turn-around, we have decided to now use Vina’s flexible receptor feature (discussed below). To give an idea of Vina’s efficiency, recent AutoDock jobs, Experiments 72 – 78 are only about 30% finished although all of these jobs were submitted within a few months of the almost completed Vina jobs.

**AutoDock Vina is now on Android**

As of July 2013, FightAIDS@Home can be run on mobile devices. This is possible via a new app for BOINC on Android. With the default settings, Vina calculations only run when the device is charging and has access to Wi-Fi, but these settings can be changed. Although currently limited to AutoDock Vina and Android devices, this new concept of “mobile volunteer computing” will surely grow.³

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**Optimizing the use of AutoDock**

Experiments 72–84 were recently designed to investigate how changes to our docking protocols may improve our results. While AutoDock and Vina have already been calibrated and tested, we are continually looking for new ways to improve performance characteristics such as speed, accuracy, and scope of use. Historically, virtual screening was applied to more traditional sites of a protein where the targeted region would have a well-defined pocket where a substrate binds. In recent years, computational scientists have been pushing the limits by learning to apply docking to less traditional sites in previously unidentified locations and/or in pockets that are shallower and less well-defined.

Our computational HIV research, is being done in collaboration with multiple experimental laboratories. For example, the Arnold Lab at Rutgers has found allosteric sites for HIV RT by using X-ray crystallographic fragment screening.⁴ The Arnold Lab is one of our collaborators in the HIVE Center. Structures from this work are being used for the FightAIDS@Home Project.

We strive to improve our computational tools by analyzing the data from these docking experiments and eventually comparing this to experimental data from our collaborators. Due to WCG and its donors, massive amounts of data are being generated to help us understand these less traditional protein sites, so effective drugs may be developed to affect specific protein-protein interactions and disrupt the HIV life cycle.

³Go to [http://www.worldcommunitygrid.org/about_us/viewNewsArticle.do?articleId=318](http://www.worldcommunitygrid.org/about_us/viewNewsArticle.do?articleId=318) for more information.
IN takes the viral DNA and incorporates it into human DNA. This structure has been constructed using a similar protein bound to DNA in order to show relative placement of DNA bound (left).

HIV integrase forms a tetramer in its functional form, able to bind to 2 strands of DNA. These two proteins enable HIV to replicate, which, in turn, drives proliferation and persistent infection.

Beyond HIV protease: HIV reverse transcriptase and integrase

HIV reverse transcriptase (RT) and HIV integrase (IN) proteins are added foci to the FightAIDS@Home experiments. Studying these proteins is part of the goals of the HIVE Center. Specifically, the interactions of RT and IN with other HIV proteins are of important for understanding the workings of the virus and how it can evolve to evade existing drug therapies. RT enables HIV to generate complementary DNA from viral RNA, and IN takes the viral DNA and incorporates it into human DNA into human DNA. These two proteins enable HIV to replicate, which, in turn, drives proliferation and persistent infection.

Both proteins have several challenging targets (see next page for more in-depth information). Myriad crystal structures are available for each protein, and several are used in our computational experiments. Using the data from these experiments can ultimately lead to new anti-HIV drugs by helping to characterize suitable receptor structures for use with docking programs.

TARGET: HIV Reverse Transcriptase

HIV reverse transcriptase (RT, left) is responsible for copying viral DNA. RT is a heterodimer, which means that it is composed of 2 different proteins. Multiple Protein Data Bank (PDB) structures were used to show all sites of interest in RT as well as where DNA binds. DNA¹ is shown with a molecular surface (A, red), and is removed along with the molecular surface of on monomer to show a close-up (B) of the non-nucleoside RT inhibitor² (NNRTI, cyan), NNRTI adjacent³ (orange), incoming nucleotide binding⁴ (green), and knuckles⁵ (magenta) sites. Images created with PMV* and PDB ID’s ¹2HMI, ²4I2Q, ³4KFB, ⁴3JYT, ⁵4IG3.

TARGET: HIV Integrase

HIV integrase (IN) incorporates viral genes into host DNA. It is a large protein with several domains. Our current focus is on the catalytic core domain (CCD, shown right). The CCD is a homodimer, which means that it is composed of 2 proteins that are identical. It interacts with human protein LEDGF. The image depicts the homodimer in blue and white for each of the monomers. IN has 3 sites of interest: FBP (orange), LEDGF (magenta), and Y3 (cyan) sites. Because of its symmetry, there are actually 2 of each site on this protein. This can be seen when the rendered molecular surface (C) is removed to reveal a cartoon representation (D). Images created with PMV* and PDB ID ³NF8.

*PMV is Python Molecular Viewer developed by MGL (http://mgltools.scripps.edu).
AutoDock Vina and flexible docking on WCG

AutoDock Vina was created by Dr. Oleg Trott at MGL at The Scripps. Its accuracy was observed to be comparable to 6 commercially available docking programs, and it is among the fastest docking codes available.

Flexible receptor docking is a feature of Vina that we are implementing on FAAH with the help of WCG. It will allow us to sample more variations in the target protein structure and may potentially lead to more accurate docking results.

AutoDock Vina flexible receptor docking. One test case is shown of the compound ZINC00284524 docked into the LEDGF site of HIV IN. Nearby residues in the site (labeled below) were given partial flexibility.

Flexible residues allow more sampling. Arrows show relative differences in flexible residues and a small molecule between two Vina docked poses. Molecular surface only rendered on rigid atoms. Flexible residues are in sticks and ligands are in ball and stick representations.

Images created with PMV (http://mgltools.scripps.edu).
We could not perform this much research without the help of World Community Grid or your donated computer time. Thank you very much for helping us advance the fight against multi-resistant drug HIV and for helping us improve the tools and techniques that many other labs use in their own research against other diseases.

We also wish to extend our gratitude to Scott Kurowski and Tim Cusac from Entropia for proposing the initial idea to create the FightAIDS@Home Project in 2000 in partnership with Professor Art Olson and Dr. Garrett Morris.

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