Abstract Submitted
for the MAR09 Meeting of
The American Physical Society

In Silico Docking of Ligands to Drug Oxidation Enzymes Cytochrome P450 3A4 and Cytochrome P450 1A2. DAVID SMITH, JONATHAN GUGLIELMON, MARSCH GLENN, GUENGERICH F. PETER, GROVE CITY COLLEGE BIOPHYSICS RESEARCH TEAM — Cytochrome P450 3A4 (CYP3A4) and Cytochrome P450 1A2 (CYP1A2) oxidize most drugs in humans. Protein modeling toolkits from OpenEye Scientific Software were used to examine the interaction of drug substrates with CYP3A4 and CYP1A2. Conformers and partial atomic charges were generated for each drug molecule. User-defined volumes were defined around CYP3A4 and CYP1A2 active sites. Ligands were docked assuming protein and substrates as rigid bodies. To assess rigid docking accuracy, x-ray diffraction coordinates of CYP3A4-erythromycin and CYP3A4-metyrapone complexes were obtained. Rigid re-docking of erythromycin and metyrapone into CYP3A4 yielded poses similar to the crystal structures. Rigid docking revealed two other energetically-favorable CYP3A4-metyrapone poses. The best poses were obtained by using all the Open Eye scoring functions. Optimization of protein-ligand interactions within 5-10 Angstroms of the docked ligand was then performed using the Merck Molecular Force Field in which the protein was assumed to be flexible and the ligand to be rigid. Nearby protein residues pulled slightly closer to the substrate, reducing the volume of the active site.

David Smith
Grove City College

Date submitted: 15 Dec 2008 Electronic form version 1.4