MS03.05.04 EFFICIENT DOCKING OF MACRO-MOLECULES BY EXHAUSTIVE ENUMERATION OF CONFIGURATIONS. Lynn F. Ten Eyck[1,2], Igor Tsigelny[1], Victoria Roberts[3], and Jeffrey Mandell[2]. [1] Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, California, [2] San Diego Supercomputer Center, San Diego, California, [3] Department of Molecular Biology, The Scripps Research Institute, La Jolla, California

New approaches to macromolecular docking are being developed in several laboratories which use convolution and correlation methods to evaluate the interaction energy between two molecules over all space for any given orientation. These methods use Fast Fourier Transforms to compute the correlation functions, so they scale well as the size of the problem increases. This paper describes the development and use of a new computer program, DOT, which computes the solvated electrostatic energy and the van der Waals interaction energy for two molecules of arbitrary size, as a function of position and orientation. The computation is efficient, enumerating billions of configurations in minutes on a parallel supercomputer, or in a few hours on a group of networked workstations. Exhaustive enumertion shows all possible binding locations, within the limitation of the grid chosen. A large portion of the statistical mechanical partition function can be calculated from this data, which gives a measure of the significance of the best results. The method is well suited to screening of possibilities, with the best values being fed into a more detailed calculation for further refinement.

The use of exhaustive enumeration on a grid instead of statistical sampling in a continuum means that the method has different properties from standard energy minimization methods, and suggests different uses. DOT has been used in systems which show electrostatic steering, and systems which show tight docking. Limitations, optimal uses, and possible enhancements of the method are presented.

MS03.05.05 AUTOMATED PROTEIN-PROTEIN AND SUBSTRATE-PROTEIN DOCKING. Arthur J. Olson, Ph.D., Department of Molecular Biology, The Scripps Research Institute, La Jolla, California

We have developed methods to computationally dock proteins with other proteins and with flexible small molecules and have predicted the correct interactions both in known test cases, and in unknown cases that have subsequently been verified by experiment. Prediction of biomolecular interactions is critical in the understanding of fundamental biological processes as well as in the design of bioactive compounds for medicine, agriculture and other technological applications. Because of the complexity of the systems involved, computational approaches to the docking problem must balance the need for an accurate physical description with the requirements of computational feasibility.

This paper describes the approaches we have taken in the codes AutoDock (1), for docking flexible ligands to protein receptors and SurfDock, for predicting protein-protein interactions. In each case we describe the nature of the models built, the scoring functions developed and the approximations used, as well as the strategies for searching the large configurational space involved. AutoDock uses atomic affinity grids for rapid energy evalutation of intermolecular interactions and has the option of two search strategies; simulated annealing and a local/global search based on a genetic algorithm.

SurfDock uses an analytical surface-based representation of protein shape and properties based upon the expansion of spherical harmonic functions(2). It performs a multi-resolution search of the positional and orientational degrees of freedom using an evolutionary programing algorithm.

Examples involving HIV protease and inhibitors, Human Tissue Factor complexes, and beta lactamase with a protein inhibitor will be discussed.

PS03.05.06 MODELING OF THE SPATIAL STRUCTURE OF EUKARYOTIC ORNITHINE DECARBOXYLASES. Nick V. Grishin, Margaret A. Phillips, Elizabeth J. Goldsmith, University of Texas Southwestern Medical Center, Dallas, TX, 75235

Based on sequence analysis the pyridoxal phosphate (PLP) dependent enzyme eucaryotic ornithine decarboxylase (ODC) is predicted to have a β/α barrel fold. We found that the sequences of reported PLP dependent enzymes (313 in total) fall into seven fold types, three of which were previously described crystallographically. ODC and alanine racemases were shown to be related and display 15% identity. These enzymes have no detectable sequence identity with any protein of known spatial structure, but match secondary structure and hydrophobicity profiles of a β/α-barrel template. Through the analysis of known barrel structures we developed a topographic model of ODC active site. Out of 11 active site residues in glycolate oxidase, an FMN-dependent enzyme with known structure, 9 are invariant in the ODC model. Our model predicts the phosphate group of the PLP is located between the Ctermini of the seventh and eighth strands, bound to a Gly-rich region in the loop after strand 7 and the N-terminus of a small helix with Arg277 after strand 8. The model suggests that Glu274 or Asp233 may interact with the pyridoxal nitrogen. Characterization of the Glu274 to Ala mutant *Trypanosoma brucei* ODC demonstrated that Glu274 functions to stabilize the positive charge on the pyridoxal nitrogen, and Arg277 to Ala mutant displayed lower affinity to PLP, supporting the model. Crystals of *Tryponosoma brucei* ODC were obtained ($P2_1$, a=67, b=152, c=85, β=103; R_m 7.5%, 99% complete to 3Å resolution). The work on phase determination is in progress.

PS03.05.07 A FAST AND EFFICIENT PROGRAM FOR LOOPS. Yuzhen Han, Hongyu Zhang, Luhua Lai, Leyu Wang and Youqi Tang, Institute of Physical Chemistry, Peking University, Beijing 100871, China

We developed an efficient Monte Carlo Simulated Annealing (MCSA) program for modelling protein loops with high speed. The total conformational energy in each step of MCSA simulation consists of two parts: the nonbonded atomic interaction represented by a simple softsphere potential and the harmonic distance constraint to ensure the smooth connection of the loop segment to the rest protein structure. The softsphere potential was a quite simplified potential that has been successfully used by the authors in modelling the carbohydrate part of glycoprotein systems. It only considers the purely repulsive steric interactions to avoid artificial attractive forces between the atoms in the absence of solvent molecules in modelling. The N-terminal of the loop segment was connected to the bulk protein part, and two dummy main chain atoms N and Cα immediately following the C-terminal of the loop segment were constrained to their real positions in the crystal structure, which not only assures the correct geometry of loop-protein connection but also is more rigorous than the previous work. To improve the speed, two strategies, local region method and grid-mapping method, were devised to accelerate the computing of environmental interaction that is responsible for the major part of the computing consumption. The grid-mapping method can reduce computing time dramatically. Conformations with rational steric packing and smooth connection to the rest protein structure were generated by the MCSA program, and then were refined in the empirical force field CHARMm. Finally, we got the conformations with high precision to the crystal structure for all the loops of bovine pancreatic trypsin inhibitor (BPTI). With the criteria of CHARMm energy, near-native conformations can be selected, for example, the backbone root mean square deviation (RMSD) 0.93 Å from the crystal structure was gotten for the longest 9-residue loop.