BioGeometry NEWS

BioGeometry Meeting

On June 5-6, 2003, the BioGeometry group met at Stanford for a semiannual project meeting. It featured technical presentations by many of the 25 students and postdocs in the program. The meeting ended with an overwhelming feeling that considerable progress has been achieved in the genuine integration of computer science and biology, as evidenced by a deepening of the research with a clear focus on a few major themes as follows:

DOCKING & BINDING, including protein-protein interaction, protein-drug interaction, and analysis of interface surfaces. Speakers in this area included: Andrew Leaver-Fay (UNC), Johannes Rudolph (Duke), Vicky Choi (Duke), and Yusu Wang (Duke).

MAINCHAIN & BACKBONES, including homology modeling, protein design, and the dynamics of long chains (biomolecules or robot arms). Speakers in this area included: Kimberly Noonan (UNC), Rachel Kolodny (Stanford), and An Nguyen (Stanford).

POTENTIALS & ENERGY CALCULATIONS, including statistical potentials and the development of faster and more accurate versions of standard molecular forces, with emphasis on electrostatics and hydrophobicity. Speakers in this area included: Patrice Koehl (Stanford), Daniel Russel (Stanford), and Leo Liu (UNC).

COMPARISON & SIMILARITY MEASURES, including proximity in transformation space and probabilistic road-maps. Comparisons abound in biology (sequences, structures, pathways). Speakers in this area included: Itay Lotan (Stanford).

It is clear that the project has converged on the right topics. The next stage of research requires an intensified push to deepen the research on all four topics. The group feels confident this will lead to significant contributions that leave a lasting mark on the field of structural biology and, at the same time, a lasting contribution to computer science in terms of general ideas and software artifacts:

COMPUTATIONAL METHODS, including categories of data structures (kinetic, road-maps, proximity, and alpha shapes), sampling techniques for continuous spaces, and concrete mathematical structures (combinatorial Morse theory and Jacobi sets). Speakers in this area included: Alper Ungor (Duke).

SOFTWARE, including area and volume derivatives for implicit solvent modeling, specialized data structures for proximity detection, a suite for protein docking, etc.

In keeping with the diverse nature of the group and the need to explore new frontiers, two of the fourteen talks at this meeting were in areas that are related to but not part of these tight foci. The talk by Ben Wong (Stanford) described "Modeling and Simulation of Lymph Node Germinal Center Reaction," whereas that by Jeff Roach (UNC) described "Local Squaring Equations: Real/Reciprocal Space".

In addition to such a full lecture schedule, participants got to know each other much better at the mixer lunches, the Byte Café breakfasts and coffee and the conference dinner at Janta, a local Indian restaurant.

Student Projects

Students are very involved in the BioGeometry project this summer.

SHANTANU SHARMA, an undergraduate from IIT(Kanpur), is working with Jeff Roach and Charlie Carter in the Department of Biochemistry and Biophysics at UNC on a project developing an efficient way to project three-dimensional protein structures into one dimension for the purpose of compression and comparison.

MATT MIAN, an undergraduate from the Howard Hughes Research Fellows Program, is at Duke with Herbert Edelsbrunner and Johannes Rudolph preparing an interface to the exhaustive search docking algorithm created by postdocs Sergei Bespamyatnikh and Vicky Choi. Using the new interface and the algorithm, he will put the protein-protein docking method through new tests designed to probe the radius of convergence for correct answers and conformational flexibility.

ANDREW BAN is working at Duke with Johannes Rudolph and Herbert Edelsbrunner. The focus of his work is the deepening of our understanding of interface surfaces and their physical meaning.

SERKAN APAYDIN is working at Stanford with Jean-Claude Latombe, Doug Brutlag, and Amit Singh on non-uniform sampling techniques for probabilistic roadmaps.

ITAY LOTAN is working at Stanford with Jean-Claude Latombe, Vijay Pande, and Patrice Koehl on the simulation of the interaction of collections of proteins and on the generation and classification of decoy sets.

TAMMY BAILEY is working at Duke with Herbert Edelsbrunner. She explores structural similarity measures, including the use of hierarchical deformations.

BEN WONG is working at Stanford with Peter Lee and Arancha Casal on the simulation of large collections of cells.

IBRAHIMA MBAYE, an undergraduate from NCAT Physics is working at Duke Computer Science with Pankaj Agarwal and Herbert Edelsbrunner on the representations of rigid body orientations using quaternions.

KEVIN WEDDERBURN and under-graduate **SEWYALEW TADDELE** from NCAT's Department of Physics are working at Duke's Department of Chemistry with Professor Weitao Yank on computing accurate electrostatic potential charges of biomolecules with density function methods.

YUSU WANG is working at Duke with Pankaj Agarwal and Herbert Edelsbrunner on fast docking with persistent critical points. One focus is the quantitative assessment of samples of the space of rigid motions, another is the computation of a new function, the elevation over the surface of a molecule.

ABHIJIT GURIA is working at Duke with Herbert Edelsbrunner. He is finishing up his project on sampling the space of rotations. A question of particular interest is the sampling of the 3-sphere with locally BCC-like configurations.

Student Profile: Andrew Ban

Yih-En Andrew Ban is a third-year PhD student in the Structural Biology and Biophysics Program at Duke University. His official affiliation is with the Department of Biochemistry and he works with Johannes Rudolph (Biochemistry) and Herbert Edelsbrunner (Computer Science). He came to Duke from the University of Texas at Austin, where he received a Bachelor of Science in Mathematics and in Biology.

At Austin, Andrew did a research project with William C. Gardiner in the Department of Chemistry. The goal of the project was the use of molecular dynamics simulations to analyze the energy transfer in the reaction of HIV-1 Protease. A distinguishing feature of that project was the attempt to use RRKM theory to model the reaction mechanism.

His initial project at Duke was with Johannes Rudolph aimed at the enzymology of Cdc25B phosphatase. In this project, Andrew used enzyme kinetics studies of Cdc25B phosphatase to probe the reaction mechanism on both natural and artificial substrates. This work contributed to a publication on the subject [1].

At present, Andrew works on protein-protein interfaces. The goal is to define and compute geometric representations of such interfaces, and to use that representation to obtain detailed information about the structure and the mechanism of the interaction. As an example, consider vipoxin, a complex of a neurotoxin and its inhibitor, in Figure A.

The trouble with the representation is that the particular stage of the interface is hardly visible. The situation does not improve much when we display one or both proteins transparent or as wire frames or ribbon diagrams. A common method is to take the complex apart and to show the two proteins side by side. We can see the areas along which the proteins interact, but it is cumbersome at best to determine which residues interact and how properties of the interface varies over the area of the interaction.

To overcome these limitations, Andrew defines and computes an interface surface that weaves itself between these two proteins. The surface of the vipoxin complex of Figure A is shown in Figure B.

An unusual feature of this particular interface surface are three tunnels: the surface is a genus-3 2-manifold with boundary. This is remarkable because each tunnel separates two linking circles, like two links along a metal chain. The existence of these links suggests a strong bond between the two proteins, and indeed this particular complex is quite stable.

[1] M. Wilborn, S. Free, A. Ban and J. Rudolph. The C-terminal tail of the dual-specificity Cdc25B phosphatase mediates modular substrate recognition. Biochemistry 40 (2001), 14200-14206.
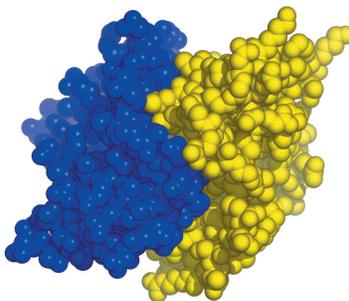
- Profile by Herbert Edelsbrunner

Figure A. The neurotoxin protein in yellow and its inhibitor in blue. Both are shown as van der Waals diagrams in which each atom is displayed as a sphere with the van der Waals radius.

Figure B. The interface surface of the complex in Figure A.