2013 Workshop on Computational Structural Bioinformatics

Sunday, September 22, 2013 — Washington DC
Workshop W2 Location: Harmony
Jing He, Amarda Shehu, Nurit Haspel, Brian Chen, Co-Chairs

8:30 – 10:30 Session 1 Session Chair: Nurit Haspel. Co-chair: Bahar Akbal-Delibas
8:30-8:55 - Arrival, poster setup
8:55-9:00 – Welcome and opening remarks (Jing He)
9:00-10:00 – Keynote by Ruth Nussinov: Amyloid Toxicity and Ion Channel Formation in Alzheimer's Disease
10:00-10:20 - **Rudy Clausen** and Amarda Shehu: Exploring the Structure Space of Wildtype Ras Guided by Experimental Data
10:20-10:40 - Dong Luo and **Nurit Haspel**: Multi-Resolution Rigidity-Based Sampling of Protein Conformational Paths
10:40-11:00 Coffee Break
11:00-12:30 Session 2 Session chair: Amarda Shehu. Co-chair: Rudy Clausen
11:00-12:00 – Keynote by Lenore Cowen: Practical Markov Random Field Methods to Detect Remote Protein Homologs
12:00-12:20 - **Kamal Al Nasr**, Lin Chen, Desh Ranjan, M. Zubair, Dong Si, and Jing He: A Constrained K-shortest Path Algorithm to Rank the Topologies of the Protein Secondary Structure Elements Detected in CryoEM Volume Maps
12:20-12:40 - Filip Jagodzniski, **Bahar Akbal-Delibas** and Nurit Haspel: An Evolutionary Conservation and Rigidity Analysis Machine Learning Approach for Detecting Critical Protein Residues
12:40-2:00 Lunch (Provided by ACM-BCB)
2:00-4:00 Session 3 Session Chair: Brian Chen. Session Co-chair: Dong Si
2:00-2:20 - **Majid Masso**: Fast and Accurate Structure-Based Prediction of Resistance to the HIV-1 Integrase Inhibitor Raltegravir
2:20-2:40 - **Brian Orndorff** and Filip Jagodzinski: A Combined Molecular Dynamics, Rigidity Analysis Approach for Studying Protein Complexes
2:40-3:00 - Jeffrey Chyan, **Mark Moll** and Lydia Kavraki: Improving the Prediction of Kinase Binding Affinity Using Homology Models
3:00-3:20 – **Irina Hashmi** and Amarda Shehu: Informatics-driven Protein-protein Docking
3:20-4:20 – poster session and coffee break
4:20-5:00 Session 4 Session Chair: Jing He Session Co-chair: Irina Hashmi
4:20-4:40 – Dong Si and **Jing He**: Beta-sheet Detection and Representation from

Medium Resolution Cryo-EM Density Maps
4:40-5:00 – closing remarks (Jing He) and poster session

Speaking times:

17 + 3 minutes for Q/A

Poster session information:

We will hold two informal poster sessions. Please make a poster for every talk, plus any other work you wish to present. Here are some additional posters:

1. Title: Single Evolutionary Insertions or Deletions Within Membrane Segments can be Crucial for Membrane Protein Function.

Authors: Marcus Stamm and Lucy Forrest

2. Title: How do influenza strain-specific properties of the M2 channel determine its affinity for aminoadamantane anti-influenza agents?

Authors: Nadine Homeyer, Antonios Kolocouris and Holger Gohlke

Keynote information:

Speaker: Lenore Cowen, Tufts University, Boston MA.

Title: Practical Markov Random Field Methods to Detect Remote Protein Homologs

Abstract:

Hidden Markov Models (HMMs) are among the most popular and successful methods for the identification of remote protein homologs. However, they are not mathematically powerful enough to model statistical dependencies between amino-acid residues that are close in space but far apart in the protein sequence sequence. On the other hand, there is evidence that such dependencies can be important folding determinants in many cases, for example, in protein structures that contain beta-sheet secondary structure. It was all the way back in the 1990s that James White, Ilya Muchnik, Rick Lathrop and Temple Smith proposed generalizing HMMs to Markov Random Fields (MRFs) in order to model more mathematical complex dependencies. However, when generalizing from an HMM to an MRF, several design difficulties emerge, stemming from sparse training data on the one hand, to computational complexity on the other. With Matt Menke and Bonnie Berger, we introduced SMURF, an extremely simple MRF

that generalizes profile HMMs by incorporating beta-strand dependencies. We give several alternative strategies for how challenges stemming from sparse training data and computational complexity can be overcome for SMURF, and show that we can improve the detection of remote protein homologs as compared to existing profile HMMs, profile-profile HMMs and threading methods using our ideas. We discuss remaining open problems sand challenges for the field.

Bio: Dr. Lenore J. Cowen is a Professor in the Computer Science Department at Tufts University. She also has a courtesy appointment in the Tufts Mathematics Department. She received a BA in Mathematics from Yale and a Ph.D. in Mathematics from MIT. After finishing her Ph.D. in 1993, she was an NSF Postdoctoral Fellow and then joined the faculty of the Mathematical Sciences department (now renamed the Applied Mathematics and Statistics department) at Johns Hopkins University where she was promoted to the rank of Associate Professor in 2000. Lured by the Boston area, and the prospect of making an impact in a growing young department, she joined Tufts in September, 2001. Dr. Cowen has been named an ONR Young Investigator and a fellow of the Radcliffe Institute for Advanced Study. Her research interests span three areas: Discrete Mathematics (since high school), Algorithms (since 1991 in graduate school) and Computational Molecular Biology (since 2000). She is on the editorial board of SIAM Review.

Speaker: Ruth Nussinov, Center for Cancer Research, National Cancer Institute, Frederick MD, and Department of Human Genetics, Tel Aviv University School of Medicine, Tel Aviv, Israel.

Title: Amyloid Toxicity and Ion Channel Formation in Alzheimer's Disease

Abstract:

Alzheimer's disease (AD) is a protein misfolding disease characterized by a buildup of β-amyloid (Aβ) peptide as senile plaques, uncontrolled neurodegeneration, and memory loss. AD pathology is linked to the destabilization of cellular ionic homeostasis and involves Aβ peptide-plasma membrane interactions. Recent evidence suggests that fibril-like, small Aβ oligomers are the toxic species in AD. These oligomers contain β-sheet structure and present exposed hydrophobic surface. Oligomers with this motif are capable of penetrating the cell membrane and gathering to form toxic ion channels. Understanding the exact nature by which these channels conduct electrical and molecular signals could aid in identifying potential therapeutic targets for the prevention and treatment of AD. Since no experiment-based Aβ channel structures at atomic resolution are currently available, molecular dynamics (MD) simulations have successfully provided the atomic-level details of three-dimensional Aβ channel conformations embedded in the membranes. The predicted structural models by MD support that the Aβ channel is an assembly of loosely associated mobile β-sheet subunits. The emerging

picture from our large-scale simulations is that toxic ion channels formed by β-sheets spontaneously break into loosely interacting dynamic units that associate and dissociate leading to toxic ionic flux. Our observations support the amyloid channel hypothesis that Aβ oligomers can irreversibly insert into a membrane and spontaneously form an ion channel, leading to cell death in AD. We further suggest that Aβ-directed therapeutics should consider a combination therapy that targets the toxic Aβ oligomers on the membrane before they are inserted, and, in parallel, the oligomers that have already penetrated into the membrane, where these agents could prevent toxic channel formations.

Bio:

Dr. Ruth Nussinov is a Professor in the Department of Human Genetics, School of Medicine, Tel Aviv University, Tel Aviv, 69978 Israel, and a Senior Principal Scientist and Principal Investigator at the National Cancer Institute. She has received her B. Sc degree in Microbiology from the University of Washington (Seattle, Washington) and her Ph.D. in Biochemistry from Rutgers University (NJ). She was a Fellow at the Weizmann Institute, and a visiting scientist at the chemistry department at Berkeley and at the Biochemistry department at Harvard. She joined the Medical School at Tel Aviv University in 1985 as an Associate Professor. In 1990 she became a Full Professor. Her association with the NIH started in 1983, first with the NICHHD and since 1985 with the NCI. Currently, she has a large group of graduate students in Tel Aviv, in collaboration with Prof. H. Wolfson, from the School of Computer Science. Additionally, she has a group at the NCI. She is an author of over 440 scientific papers.