Title: Optimization Techniques for Protein Docking

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Abstract:

I shall present my group's recent work motivated by a fundamental and challenging problem in computational structural biology. Protein-protein interactions play a central role in metabolic control, signal transduction, and gene regulation. Determining the 3-dimensional (3D) structure of a complex from the atomic coordinates of two interacting proteins (the receptor and the ligand) is known as the protein docking problem. Experimental techniques can provide such 3D structures but are time-consuming, expensive, and not universally applicable. As a result, solving these problems computationally is critical and has attracted a lot of attention.

Nature being efficient, protein docking can be formulated as a the problem of minimizing the Gibbs free energy of the complex. Optimization is performed over translations and rotations of the ligand with respect to the receptor (a nonlinear manifold), as well as, over conformational changes (especially side-chains at the interface). However, the free-energy functional is very complex having multiple deep funnels and a huge number of local minima of less depth that are spread over the domain of the function. We present a systematic multi-stage method for performing this optimization. The entire conformational space of ligand translations and rotations is explored using simplified energy potentials to produce clusters of promising conformations. Optimization of side chains is formulated as a combinatorial optimization problem for which we propose a new distributed algorithm based on graph-theoretic ideas. The energy landscape in the space of ligand translations and rotations is explored using dimensionality reduction approaches, which reduces the domain of further optimization. Finally, cluster refinement is done using a new stochastic global optimization method we have developed, the so called Semi-Definite programming based Underestimation (SDU) method. We will discuss the algorithms, provide convergence guarantees, comparisons with related work, and an array of computational results illustrating our approach.

About the speaker:

Yannis Paschalidis is a Professor of Electrical & Computer and of Systems Engineering at Boston University, a Co-Director of the Center for Information and Systems Engineering (CISE), and the Academic Director of the Sensor Network Consortium (SNC) - an industry consortium he spearheaded which currently consists of 14 companies focusing in sensor networks. He obtained a Diploma (1991) from the National Technical University of Athens, and an M.S. (1993) and a Ph.D. (1996) from the Massachusetts Institute of Technology (MIT), all in Electrical Engineering and

Computer Science. In September 1996 he joined Boston University where he has been ever since. His current research interests lie in the fields systems and control, networking, applied probability, optimization, operations research, computational biology, and bioinformatics.

Prof. Paschalidis' work on communication networks has been recognized with a CAREER award (2000) from the National Science Foundation and the second prize in the 1997 George E. Nicholson paper competition by INFORMS. He was an invited participant at the 2002 Frontiers of Engineering Symposium, organized by the National Academy of Engineering.

His recent work on protein docking has been recognized by a 1st prize in the Protein Interaction Evaluation Meeting (2007) and an invitation to a select workshop at the Institute for Mathematics and Its Applications (IMA) on Molecular and Cellular Biology (2008). He has served in the program/organization committees of many conferences, has been a past associate Editor of the IEEE Trans. on Autom. Control and of the Operations Research Letters, and is currently an associate editor of the SIAM Journal on Control and Optimization.