



Ram Samudrala, Ph.D., Assistant Professor
Computational Genomics
Department of Microbiology
University of Washington
P: 1-206-732-6122
F: 1-206-732-6055
E: ram@compbio.washington.edu
W: <http://compbio.washington.edu>

October 20, 2005

Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142, 1001 E 3rd Street
Bloomington, IN 47405-7005

Dear Dr. Brun:

It is my immense pleasure to recommend Yu Xia for a faculty position in your department. I have known Xia for over seven years, and we have worked together to devise methods to produce *de novo* models of protein structure starting with sequence alone, using lattice-based approaches.

I first started working with Xia in 1998 when I was a post-doctoral fellow with Michael Levitt at Stanford University, where we decided to develop a hierarchical method to make *de novo* predictions of protein structure using a combination of techniques available to us. Xia was responsible for generating all possible enumerations of small protein sequences using tetrahedral lattice models and producing a limited subset of models, some of which would possess native-like topologies. These models were then used for detailed model building and filtering to extract the native-like conformations.

Our method was among the best at the third meeting on the Critical Assessment of Structure Prediction methods, which was the first time *de novo* methods did consistently well in blind prediction experiments. The results were published in the CASP3 *Proteins: Structure, Function, Genetics* special issue (Samudrala, Xia, Huang and Levitt, 3S: 194-198, 1999) and another, more complete, publication with Xia as first author was published in the *Journal of Molecular Biology* (Xia, Huang, Levitt and Samudrala, 300: 171-185, 2000).

From this research it became clear that a central challenge in protein structure prediction is to find the right energy function that can discriminate native-like from non-native conformations. Xia subsequently focused himself on this challenge and independently initiated a new project in the lab. He developed an approach that systematically trains an energy

function to improve its predictive power, and showed that the optimal energy function parameters can be reliably obtained in this way (Xia and Levitt, *Journal of Chemical Physics* 113: 9318-9330, 2000). Further research along these lines produced several improved energy functions for protein structure prediction (Fain, Xia and Levitt, *IBM Journal of Research and Development* 45: 525-531, 2001; Fain, Xia and Levitt, *Protein Science* 11: 2010-2021, 2002).

Xia then expanded his research to address the evolutionary origins of protein folding, using simplified models for proteins. Instead of studying protein folding mechanisms one sequence at a time, he mapped out protein folding thermodynamics and kinetics for all sequences that fold to the same structure. These maps provided crucial insights into how protein sequence space is organised globally (Xia and Levitt, *Proteins: Structure, Function, Bioinformatics* 55: 107-114, 2004), and how such large-scale organisation in sequence space effects population dynamics of protein evolution (Xia and Levitt, *PNAS* 99: 10382-10387, 2002).

Xia's post-doctoral work with Mark Gerstein at Yale focuses on mapping and understanding molecular interaction and control networks within a cell through a combination of genome-wide data integration and mining, physical simulation, and evolutionary study. Xia's unique background with a strong emphasis on protein structure, combined with his rigorous quantitative skills, will greatly help in solving the open problems in this area.

Xia's work ethic is admirable. When we were at Stanford together, he would work almost every day. He was always on the ball when I was working with him and we never missed a single deadline.

Xia is a terrific and personable intellectual companion. He is extremely bright, open-minded, and highly critical, which will make him a valuable asset to your department. He is patient, thoughtful, and courteous, and is a pleasure to work with.

I believe Xia has the intellectual capacity and commitment to be a scientist of the highest calibre. I recommend him wholeheartedly for a faculty position without any reservations whatsoever, and I expect that he will be an excellent addition to your department.

Should you have any questions or would like further comment, please feel free to contact me.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ram Samudrala', with a stylized flourish at the end.

Ram Samudrala