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October 27, 2005

Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142
1001 E 3rd Street
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Dear Dr. Brun:

I am writing to give Yu Xia (Brandon) my highest possible recommendation for the tenure-track faculty position. Currently a Jane Coffin Childs postdoctoral fellow, Brandon joined my lab two and half years ago after finishing his Ph.D. from Stanford University, where he worked under the guidance of Prof. Michael Levitt. With Michael, Brandon worked on several fundamental problems in computational molecular biophysics, such as *ab initio* protein structure prediction, energy function optimization, and simulation of protein folding and evolution using simple protein models.

Since joining my lab, Brandon has expanded his focus from modeling protein sequence-structure relationships to modeling all aspects of the entire proteome. The main theme of Brandon's research is to understand and predict biologically important protein attributes through integrated probabilistic modeling of diverse genomic datasets. In particular, he took on the challenge of predicting the membrane protein interactome, the set of all interactions between membrane proteins. This project is immediately relevant to biomedical and cancer research, since the unraveling of protein-protein interactions, particularly those involving membrane receptors, is very important in elucidating the signal transduction pathways that underlie a variety of diseases, including cancer. Unfortunately, experimental determination of membrane protein interactions is very difficult, due to the unusual physical chemical properties of membrane proteins. Brandon developed a novel logistic regression procedure to predict interactions among yeast membrane proteins by optimally combining fourteen pieces of evidence based on diverse genome-wide information such as sequence, function, localization, abundance, regulation, and phenotype. Applying the optimized classifier genome-wide, Brandon constructed a comprehensive map of predicted membrane protein interactome in yeast. These predictions are of high quality; many of them have been found to be truly interacting according to literature, even though they were not included in the training dataset. By studying the high-level organization of the interactome map, Brandon was able to identify a number of putative membrane protein complexes. This work was the first effort to computationally map the membrane protein interactome in an organism, and can serve as a guide for prioritizing further

experimental mapping efforts. In addition, the predicted interactome provides a scaffold upon which three-dimensional atomic details can be added through structural modeling.

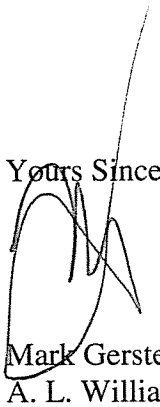
A second new direction that Brandon independently conceived and spearheaded is to combine genomic data integration and structural modeling to understand protein evolution. Brandon has a long-term interest in protein evolution. During his Ph.D. work, Brandon studied the evolutionary dynamics of lattice proteins. His current interest is to understand the evolution of real proteins by systematically surveying how fast- and slow-evolving proteins differ from other proteins in terms of their sequence, structural, and functional properties. Brandon's new idea is to integrate all these properties into a unified statistical framework, thereby revealing the previously hidden inter-dependencies among all protein properties and protein evolutionary rate. This strikes me as very exciting, as this is the first systematic study on the determinants of protein evolutionary rate.

Brandon is highly independent, creative and productive. In addition to the above two projects, he has also worked on integrated prediction of transcriptional regulatory networks and on biological network analysis. Brandon has an impressive publication record with over twenty papers published to date. He is also working on a number of manuscripts that will lead to publications very soon. In addition to focusing on his own projects, Brandon has applied his bioinformatics expertise to a variety of biological problems by forming extensive interdisciplinary collaborations with experimental biologists. For example, he has collaborated with Profs. Daniel DiMaio and Donald Engelman here at Yale University on sequence motif discovery for interacting transmembrane helices, Prof. Jon Beckwith at Harvard University on translocation signals, and Prof. Judith Frydman at Stanford University on network analysis of chaperon substrates and interactors, all of which have led to significant publications.

Brandon is one of the few scientists with solid background in all three areas of computational molecular biology: sequence analysis, structural modeling/biophysical simulation, and analysis of functional genomic datasets. As such he is in a great position to carry out integrated research in bioinformatics. In addition to algorithms in computational biology, Brandon has a deep knowledge in modern theories of statistical machine learning, optimization, and statistical physics. More importantly, he has a keen sense for fundamental and important problems in biology that can be tackled by computational means. Brandon is also generous in sharing his knowledge with his colleagues; many people in my laboratory have benefited from his insights into their own projects.

Brandon has greatly impressed me with his exceptional talents and insights into a whole variety of biocomputing questions, as well as his easygoing and pleasant manner. With the genomic and proteomic training he has gotten here coupled with his extensive background in classical structure prediction and biophysical simulation, Brandon is an exceptional candidate for a faculty position focusing on bioinformatics and computational biology. I am certain that you will be as impressed with his credentials and his research as I am. I give you my highest recommendation for him with the knowledge that Brandon will make very important contributions to the field of computational biology as well as your department for many years to come. If you have any further questions, please feel free to contact me.

Yours Sincerely,



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