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DEPARTMENT OF PHYSICS
Center for Theoretical and Biological Physics
9500 GILMAN DRIVE, MC 0319
LA JOLLA, CA 92093-0319
http://www-physics..ucsd.edu

PROFESSOR JOSE N. ONUCHIC
Tel: (858) 534-7067 FAX: (858) 822-4560
EMAIL: jonuchic@ucsd.edu

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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 177
Bloomington, IN 47405-7105

Dear Dr. van Steveninck,

It is with great pleasure that I support Hugh Nymeyer for an Assistant Professorship at your department. Hugh has been one of my two best graduate students during my stay at UCSD. I have been impressed with his scientific abilities and creativity, and I have high hopes he will turn out to be one of the leading scientists in theoretical and computational biophysics and biochemistry. During the last few years I had four outstanding postdoctoral fellows in my group. This quartet has been greatly responsible for our success. They are all currently assistant professors at major places: Joan Shea (UCSB), Nick Socci (Albert Einstein School of Medicine), Cecilia Clementi (Rice) and Steve Plotkin (British Columbia). Hugh is someone in the same class. At this stage of his career, he is really at the top compared to any other people in this field. You will be very fortunate if you are able to hire him, and I am sure he will become one of your successful stories. I am certain that he will perform impressive research since he is already did that as a graduate student and continued as a postdoctoral fellow at Los Alamos.

In my group, Hugh played a key role in moving our simple models from lattice simulations to off-lattice realistic models. He was central in establishing the connections between energy landscape theory and the funnel concept with experiments. His Ph.D. research work was outstanding. Hugh has focused on different aspects of the protein folding problem. First he has worked on the development of the landscape theory for protein folding. Working with a combination of analytical calculations and lattice models simulations, he has been able to clarify how the interplay between energetic and "topological" frustration controls the folding of proteins. These results have been published on Physica D and in PNAS where he really resolved the major issues in the field: how to choose appropriate reaction coordinates, how to relate thermal quantities to kinetic ones, and how much energetic and/or topological frustration can a sequence tolerate and still fold. He knew, however, that lattice models were not totally realistic. He generalized all these results for off-lattice models and the results were published at PNAS in 1998 (this paper has already over 100 citations). After developing all this theoretical understanding, he felt comfortable in applying all these ideas towards a quantitative understanding of real proteins. Working together with CeciliaClementi, they have published a paper at the J. Mol. Bio.where they explained how most of the observed structural heterogeneity observed in the transition state ensemble of these proteins were more a consequence of topological factors the energetic frustration (with almost 100 citations). I have also written a review in protein folding jointly with him (published at Adv. Prot. Chem.) where his participation was vital. This effort would be impossible without his overall understanding of theoretical and experimental aspects of the problem.

During his postdoctoral work, he switched the emphasis of his research from minimalist models to detailed all-atom with explicit solvation simulations. This new experience has made him complete in terms of protein simulations. He has been able to move towards larger systems by enhancing sampling methods; especially those based on the multi-canonical or replica exchange methods. These methods have

revolutionized the computer studies of peptides and small proteins. Utilizing thee approaches, he has been the first one able to apply these methods to membranes and peptides interacting with membranes. Their results are the first demonstration from simulation of spontaneous insertion of a peptide into a membrane and folding of a peptide inside a membrane. He has also been able to measure free energies, enthalpies, or entropies of a peptide/membrane/water system as a function of peptide structure and location without using continuum approximations. I believe that these simulations are one of the few that are completely redefining the field of protein/membrane simulations. Hugh has been the main force behind this work. With the aid of these methods, he has also attacked other problems such as globular proteins and water-soluble helices. Much has been learned about water mediated protein fluctuations and folding.

As you can see from the description above that he is not your conventional young scientist. It is not only the quality of his work, but also the breath and novelty of it. I conclusion, I believe that HughNymeyer is an outstanding candidate for this assistant professor position. It will be almost impossible for you to find someone else with his analytical and computational skills, great knowledge of functional and structural molecular biology and biochemistry, ability to collaborate with experimentalists, and it the top of it an amazing creativity. He really deserves this opportunity! Give it to him and you will be proud of his accomplishments. Please feel free to contact me if you need any further information.

Sincerely,

José N. Onuchic
Professor of Physics