• Los Alamos
NATIONAL LABORATORY

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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 Professor de Ruyter van Steveninck:

It is a pleasure to write a recommendation letter in support of Hugh Nymeyer's application for a tenure track position at Indiana University. Hugh Nymeyer has been a postdoctoral fellow in my group for the past two years. I have known Hugh since 1996 when he was starting his PhD thesis work with Jose N. Onuchic at UCSD. Jose's group and I started collaborating at that time and Hugh's was directly involved in the work done between the two groups. After he finished his PhD Hugh joined my group and started working on full atomic models of proteins. For this work Hugh has developed software and analyzed the limits of applicability of enhanced sampling methods for studying protein folding. Hugh has an excellent combination of talents. He is very bright, has a strong mathematical and physics background, and can uniquely translate his ideas into working computer codes. Hugh also has a very good eye for identifying good problems. I offer a strong support to his application with great enthusiasm.

Shortly after meeting Hugh, Onuchic's group and I started working on off-lattice minimalist models of proteins and published a crucial paper in protein folding. In this paper we described a framework that quantitatively distinguished good and bad folders. We studied two sequences that have the same native structure, but one of them is minimally frustrated whereas the other one exhibits a high degree of frustration. This manuscript has over 100 citations. Hugh contributions to this work were very crucial to its success. He worked out the details of the simulation data analysis, and determined which parameters were relevant for describing glassy and non-glassy dynamics of the protein.

Hugh joined my group in July 2001 as a postdoctoral fellow. He was the recipient of a Director's Postdoctoral Fellowship, and a finalist for the Feynman computational physics fellowship. Shortly after joining my group Hugh developed a new version of the replica exchange code that makes use of a sockets code for paralelization. This implementation of the REMD method is much simpler and faster than the

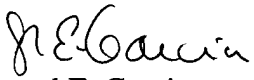
one we had developed. Also, it has the advantage of being portable. Hugh has implemented the REMD into CHARMM, and Amber codes. Hugh is very interested in validating enhanced sampling algorithms. He has explored the limits of applicability of the REMD method. For example, he discovered that the commonly used Berendsen thermostat does not produce sampling from a Boltzmann distribution, but that the Andersen and Nose-Hoover method do. He also showed that the rate at which exchanges are attempted does not affect the sampling—an issue that has been incorrectly brought up by CL Brooks and Vijay Pande.

Two main projects in which Hugh has used the REMD method involved a side-by-side comparison of the generalized Born/Surface area approximation (GB/SA), an extensively used implicit solvent model, and explicit solvent models. In this manuscript, now in press in PNAS, Hugh showed that the GB/SA incorrectly describes the unfolded state of peptides, and improperly weight alpha helical conformations at low temperature. This manuscript will be very important since the GB/SA is broadly used by the biomolecular simulation community and has not been thoroughly tested.

More recently Hugh has been studying protein/membrane systems. In a recent work, in collaboration with Tom Woolf (Hopkins), we studied the insertion and folding of a peptide into a lipid bilayer. This work involved the use of the new LANL computer, using up to 1024 cpu. This project was one of four projects chosen to benchmark and highlight the performance of the LANL Q machine —the second fastest computer in the world. The results from this project have been highlighted in the Supercomputing 2003 meeting in Baltimore. The results from this calculation are very surprising since we observed that the peptide inserts into the membrane unfolded and folds inside the lipid. The currently accepted hypothesis, postulated by SH White (Irvine), assumes that folding occurs in the water phase before insertion. However, our simulation results are not inconsistent with existing data. To test our prediction we have started a new calculation of a peptide from diphteria toxin which is being studied by SH White. For this work we got an extra allocation of 250 k cpu hrs in the LANL computer. Without Hugh's expertise with computers and insights we could not have done this calculation. I am in the process of nominating Hugh for a Distinguished Postdoctoral Fellow Performance Award for his outstanding work in this project.

At this pointing his career Hugh has a very strong formation in theoretical and computational biophysics, and has a very strong physics and mathematics background. Hugh has a friendly personality. I believe that he will be a great addition to your department. I recommend him for a tenure track position without any reservations.

Sincerely,



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