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6 November 2003

Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 117
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Dear Colleagues:

It is a pleasure to write in support of Dr. Richard Henchman, whom you are considering for an Assistant Professorship.

Richard excelled in research at the undergraduate level in Australia and, under a prestigious Commonwealth Scholarship, at the graduate level in England. At the undergraduate level, Richard developed water models for computational studies of hydrophobicity and completed theoretical analyses of small-molecule diffusion in polymers. At the graduate level, his work involved *ab initio* quantum chemical calculations and molecular simulation studies of the solvation and behavior of different types of chemical systems. He developed new mathematical methods for choosing electrostatic charges for molecular models and new statistical mechanical methods or the computation of free energies of hydration. In addition, he performed state-of-the-art computational studies on molecular recognition.

Richard started postdoctoral work in our group in 2000. In recognition of his exceptional achievements during his first two years here, he was advanced to a Research Associate position in the Howard Hughes Medical Institute in 2002. During his time at UCSD, Richard has gained an extensive knowledge of molecular and cellular biology, and he has built upon his superb background in computational chemistry to develop and apply new methods for computational biology. As an initial project, Richard undertook an analysis of solvent water dynamics in a 10 ns molecular dynamics simulation of the enzyme acetylcholinesterase (AChE). AChE has a long channel that extends from the surface of the enzyme to its active site. Richard's work, published in *Biophys. J.* in 2002,

significantly clarified the mechanisms by which the water molecules in this channel move to allow entry of substrate and expulsion of products. In this particular project, Richard invented and developed the most revealing analytical methods currently available for defining the hydration sites of proteins, and the traffic of solvent molecules among these sites. At the same time, Richard helped to guide a graduate student (Kaihsu Tai, now a postdoc at Oxford) in molecular dynamics studies of AChE and the complex it forms with the snake venom toxin Fasciculin 2. A notable part of this work was the introduction of "porcupine plots" – clever representations invented by Richard and Kaihsu to display the correlation of the residue displacements throughout AChE with the transient opening of a bottleneck region in the substrate access channel. These plots were used to demonstrate that there is an important collective character in the motions that lead to opening of the channel, providing insight into the allosteric properties that are known experimentally for AChE. The simulations also revealed that, contrary to common assumptions about the consequences of ligand binding, the thermal fluctuations of the atoms in AChE *increase* in magnitude when Fasciculin 2 binds.

In addition to the work described above, Richard has introduced important new methods for the analysis of liquid structure and thermodynamics, and for the structure-based design of new pharmaceuticals. In the former area, Richard recognized that recent developments in the computer simulation of liquids make it possible to revive an early class of theoretical models for liquids, the so-called cell models, and to use these to provide a deeper understanding of liquid behavior. Richard's work in this area was stimulated in part by his work on protein hydration. Indeed, it looks very likely that Richard will be able to capitalize on his new insights in the next few years to create valuable new methods for the quantitative analysis of biomolecular solvation. In the drug discovery area, Richard helped again to guide the work of a graduate student (Julie Schames). Richard and Julie worked with an experimental group in bioinorganic chemistry to create a new hybrid computational-experimental approach for predicting how ligands will bind to metalloenzymes. The initial publication on this work appeared in the leading chemistry journal *Angew. Chemie* in 2003.

During the past year, Richard has embarked on yet another very high profile line of research, viz., molecular dynamics simulation of nicotinic acetylcholine receptors. These intrinsic membrane proteins occur throughout the central and peripheral nervous systems, and at neuromuscular junctions. Each receptor comprises five protein subunits, the sequences of which depend on the tissue type. Given their large size and their association with membranes, the experimental characterization and computational analysis of these receptors has been extremely challenging. But recent x-ray crystallographic studies of a soluble acetylcholine binding protein have shed light on the structures of the homologous ligand-binding domains of the receptors, and recent electron crystallographic studies of the neuromuscular junction receptors have provided a sense of the overall structure of the receptors. Richard has responded to the opportunities afforded by these new data, and by advances in computing power, to conduct a variety of simulations of the alpha 7 receptor – which is of great interest as a potential target of neurological and psychiatric drugs. In work that is now in press in *Biophys. J.*, Richard has demonstrated that large-scale conformational changes occur in the pentameric ligand-binding domains upon ligation.

Richard has material for additional publications that compare the effects of agonist and antagonist binding, etc., and he is conducting additional simulations on models of entire receptors in their membrane environments.

As the above should make clear, Richard is a gifted and energetic researcher, with a wide range of expertise. He is fully capable of independent work, from the formulation of good research projects to the final polishing of excellent manuscripts for publication. As mentioned above, he has successfully mentored several graduate students in our group. He also gives excellent presentations at our group meetings, at the UCSD Pharmacology Research Discussions, and at other meetings. Richard also shows outstanding traits as a scientific citizen and leader, having organized our group's weekly research discussion meetings and other activities.

Alumni of my group now have tenured or tenure-track faculty positions at a number of leading institutions. Within the US, the latter include the Universities of California (4), Illinois, Maryland, Michigan, North Carolina, Oklahoma, and Texas, New York University, Washington University (2), and Vanderbilt. Elsewhere, these include University College Dublin, the EMBL/EML in Heidelberg, the ETH Zürich, the IIT Bombay, the International University Bremen, Philipps-Universität Marburg, Saarland University, and the University of Toronto. These faculty members have won about 20 NSF CAREER Awards, NIH Research Career Development Awards, EMBO Young Investigator Awards, Sloan Research Fellowships, Beckman Young Investigator Awards, and similar awards. I fully expect that Richard will follow such a trajectory, and emerge as an international leader in computational structural biology.

Sincerely yours,

J. Andrew McCammon