JOHNS HOPKINS
UNIVERSITY

School of Medicine

725 North Wolfe Street / Baltimore MD 21205-2185
(410) 955-8333 / FAX (410) 955-0461

Department of Physiology

2 December 2004

Biocomplexity Faculty Search, c/o C. Howard
Department of Physics, Indiana University
Swain West 117, 727 East 3rd Street
Bloomington, IN 47405-7105

Dear Search Committee,

This is a letter to recommend Hyunbum Jang for your faculty position. Hyunbum joined my group after his thesis work in New Zealand and after an initial postdoctoral position with Carol Hall's group. He arrived with a good grasp of how to run a CHARMM computational chemistry calculation and with a strong physics background from his thesis work.

We've been pursuing problems in computational membrane biophysics. This has been my group's main focus point and Hyunbum was recruited to tackle these kinds of computations. This required a real shift from his previous work, because the membrane setting is a very difficult heterogeneous solvation environment and we chose to go after large membrane proteins in an explicit (all-atom) simulation setting. Hyunbum thus has had to learn a great deal about the types of questions that we were addressing and to understand the challenges associated with the computations. His analysis and computational skills have been an important part of the success of our work in this area. In particular, the *Biophysical Journal* paper on the two states of bacteriorhodopsin was largely due to the efforts of Hyunbum to produce, equilibrate, and analyze the very large simulations.

In addition, and as part of the overall project, Hyunbum elected to continue a project on dynamic importance sampling that we've been pursuing within the group. This project fit in very nicely with the large computational project, because it deals with large conformational changes. Ideally, we want to be able to simulate two major states of a system (e.g. bacteriorhodopsin in two states) and then to understand how, biologically, the system moves between these two states. Most forced transition algorithms create a systematic error by sampling along only one transition pathway and by their very construction force *a-priori* assumptions onto the dynamics. In our dynamic

JOHNS HOPKINS
UNIVERSITY

School of Medicine

725 North Wolfe Street / Baltimore MD 21205-2185
(410) 955-8333 / FAX (410) 955-0461

Department of Physiology

importance sampling (DIMS) approach, the biased sampling is determined from a probability distribution. This enables us to correct for the bias, similar to Monte Carlo importance sampling, and also creates the ability to independently sample on a large number of trajectories that connect the starting point with the ending point. In the process, we can comment on kinetics, pathways, and relative free energy differences with this type of calculation. Our problem, as is very frequent in the computational literature, is scaling things up from small model systems to larger protein systems. Hyunbum has been very involved with the testing and analysis of this idea and we plan for a JCP paper to be submitted soon on our approach.

In preparation and as further testing of the DIMS concepts Hyunbum has been the central figure in our efforts to make a first effort at understanding the details of gating in K-channels. This work is based on the x-ray structures of the MacKinnon group and also on our computational procedures for mixing domains and addressing the issues of the membrane solvation setting. As you may already know, the initial x-ray structures of the pore domain did not include aspects of the voltage sensor and the coupling of the sensor to the pore. More recent structures, while providing some insights into the voltage gating structure, are also problematical due to the antibodies used to help solve the structure. This lack of a clear starting point has created an additional challenge for this project. It could be that this is also an opportunity for us to comment on likely structures and coupling in the system, but our sampling is very slow and we view the project mainly as a first attempt to understand the gating behavior. Thus, while the work has been difficult to this date, we are planning on a paper reporting on our progress and hope to use it as the first basis point for DIMS calculations that even more directly get at the coupling between gate changes and pore open/close transitions.

In another on-going project, we've been looking at the pH driven transition of the influenza hemagglutinin fusion domain using a combination of all-atom computations of each state and eventual DIMS calculations. This provides an excellent testing ground for the utility of the approach to computing large scale computational changes and Hyunbum has been instrumental in getting this system set-up and in performing the large amount of analysis that is needed for the idea to turn into reality. The approach is based on structural work that used pH to gate the transition. While the computations do not directly use pH to gate, the type of transition that is reflected in the structures may occur under a set environmental condition. Thus, we are addressing the question of

JOHNS HOPKINS
UNIVERSITY

School of Medicine

725 North Wolfe Street / Baltimore MD 21205-2185
(410) 955-8333 / FAX (410) 955-0461

Department of Physiology

how this particular transition might occur under the conditions of constant pH that we can readily simulate on the computer. The results should help us to understand the power and the limitations of our algorithms and to comment on the likelihood of similar transitions in other fusion domains.

While here at Hopkins, Hyunbum has not had the opportunity to teach directly, but he has been active at our lab meetings and our computational journal club. In these settings I have observed the quality and the amount of time that he puts into his public presentations. He is also very effective at computers and web-page design and that should further benefit his teaching and grant-writing skills. Thus, I believe that he will be a good teacher and that he will be effective at communicating his ideas and results.

In short, I recommend Hyunbum for your open position. Please do not hesitate to contact me if I can be of further help in your candidate search.

Yours truly,

Thomas B. Woolf, Associate Professor
woolf@groucho.med.jhmi.edu
410 614-2643