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Professor Robert R. de Ruyter
Chair, Biocomplexity Search Committee
Department of Physics
Swain Hall West 117
Indiana University
Bloomington, IN 47405-7105

Dear Dr. de Ruyter,

This is a letter of recommendation for Dr. **Weiquan Peng's** application of a junior faculty position in biological physics in your department.

Dr. Peng joined the biophysics theory group at UCSD in the fall of 2001, right after completing his Ph.D. study in statistical physics from the University of Illinois, Urbana/Champaign. During the past two plus years, he worked primarily with Herb Levine and myself, on various aspects of molecular evolution. He also participated the full duration of an intense 3-month program on "biomolecular network" organized by Boris Shraiman at the Kavli Institute for Theoretical Physics (KITP) in Santa Barbara last winter.

Weiquan is well trained in theoretical physics, and is quite capable in both analytical and numerical investigations. Moreover, he has accumulated a large body of knowledge in many aspects of molecular biology and population genetics. As a result, his biological sophistication is much beyond that of a typical biophysics post-doc. In the past year, I frequently consulted him on issues related to population genetics. Indeed, our collaborations have mostly centered on applying ideas in population genetics to molecular systems, e.g., protein-DNA interaction, gene regulation, and genetic circuits. I believe the interface of molecular biophysics, systems biology, and evolution is an area of tremendous opportunities in the next decade. Weiquan's experiences and expertise put him in a perfect position to exploit these opportunities.

The two projects that Weiquan has written papers on were carried out within his first year at UCSD. The first project was on the evolutionary dynamics of DNA sequences motifs, as inspired by a recent experiment performed by the Libchaber group at NEC. In that experiment, DNA sequences were selected progressively *in vitro* according to their binding affinities to a certain protein. The project combined the steady-state analysis of protein-DNA interaction that I studied earlier with another post-doc, and the type of nonequilibrium growth dynamics Herb Levine's group studied in depth. Weiquan showed that the dynamics of the DNA sequence evolution could be simply described by the propagation of a *decelerating pulse* in an appropriate sequence space. More importantly, Weiquan elucidated the essential ingredients responsible for this type of dynamics, with generality encompassing a large class of "breeding" problems (see more below). This beautiful result was not anticipated by either Herb or I. Weiquan worked out the problem mostly on his own after being introduced to it.

Through this problem, Weiqun became exposed to a large number of other directed evolution experiments, especially the DNA shuffling approach that is bringing on a revolution in the pharmaceutical industry. Weiqun was surprised that there had been virtually no theoretical studies on the DNA shuffling experiment. He developed a toy model which incorporated recombination, a key feature of DNA shuffling, into his work on pulse propagation. Weiqun's model is one of the very few models of recombination that can actually be solved. He generated a large number of results described in a long paper later. I was only marginally involved in this work, contributing mainly in the initial phase during the formulation of his simple model, and in the final phase, guiding him to write up what he had generated instead of continuing to generate more results.

Weiqun's apparent productivity dropped in his second year for a number of reasons: (i) The birth of his first child last year slowed him down for several months. (ii) The intense "bio network" program at KITP got him thinking about all kinds of biological problems. They hadn't led to any clear output so far, but I think the experience greatly contributed to his maturity in biology. (iii) He looked into a number of bioinformatic projects concerning the discovery of DNA sequence motifs in the *E. coli* and human genomes. In particular, he extended sequence alignment algorithms to include advanced models of DNA sequence evolution (e.g., those with neighbor-dependent mutation processes). However to generate biologically useful results, it is necessary to preprocess a large amount of sequence data for a number of genomes. The latter, being carried out by a collaborator, is taking longer than expected.

The projects Weiqun has been working on the past several months are perhaps the most exciting ones I have been engaged in. Recently, I started a wet-lab to perform molecular evolution experiments using *E. coli*. We were able to evolve a promoter very quickly *de novo* by "guiding" the evolution process through appropriate manipulation of environmental factors. Weiqun recognized that the essence of our guiding strategy was very similar to that of the propagating pulse problem mentioned earlier. He showed that with proper guidance, the speed of evolution could be much faster than what's usually regarded for fast evolution, i.e., the steady ascent on a smooth fitness landscape. We are currently relating these findings to the very rapid evolution of antibacterial drug resistance occurring in the real world. More generally, we are evaluating the extent to which evolutionary processes can be completely dominated by rare environmental fluctuations. Unexpectedly, the latter problem has some intriguing analogy with spin-glass problems: Certain types of environmental fluctuations may greatly increase the evolution rate, thereby dominating the evolutionary dynamics despite their rare occurrence, much like how the thermodynamics of a spin glass may be dominated by a few low-lying states. Weiqun is now testing these ideas by simulating the evolution of complex promoters and gene circuits. If successful, these findings stand to reshape the way we think about evolution.

Overall, I believe Weiqun is ready scientifically to start on his own. He has a good sense of the basic issues in molecular biology and population genetics. This sense will guide him to work on interesting and relevant problems at the interface of biophysics and evolution. And he certainly has the necessary technical skills to supervise students/post-docs to get the job done. He will benefit a lot from further growth in some of the non-scientific but nevertheless important areas (e.g., assigning priorities and promoting his results) for a successful career in the academia. I feel that the responsibilities that come with a faculty position would help to push his development in those areas. I hope he gets this opportunity and support his application strongly.

Sincerely yours,

A handwritten signature in black ink, appearing to be 'Terence Hwa', written in a cursive style with a long horizontal line extending to the right.

Terence Hwa