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Prof. James A. Glazier
Director, Biocomplexity Institute
Department of Physics
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Re: **Recommendation for Lingchong You**

Dear Dr. Glazier:

I am happy to share my impressions of Lingchong You, who has applied for a faculty position in your department. Having served as his research advisor, I feel qualified to evaluate his accomplishments and potential. Lingchong possesses the intellect, vision, drive, commitment to excellence, and personal skills that have not only made his doctoral studies at University of Wisconsin highly productive, but will also enable him to continue to have a significant impact as an independent researcher.

I first met Lingchong in Fall of 1997, when he joined our graduate program in Chemical Engineering at UW-Madison. He had completed a B.E. in Chemical Engineering at Chengdu University of Science and Technology (CUST) and an M.S. in Molecular Biology at University of Science and Technology of China (USTC), while earning awards in physics, mathematics, and chemistry. His strong academic performance continued in our department, where, following his first term, he performed at the top of his class in our qualifying exams covering kinetics and catalysis (1st of 17), process control (1st of 11), thermodynamics (2nd of 16) and transport phenomena (3rd of 16). In addition, he excelled in his course work, completing not only our core graduate-level chemical engineering courses, but also in his cross-disciplinary selection of courses such as Introduction to Data Structures (Computer Science) and Regulation of Gene Expression in Prokaryotes, a graduate course in Bacteriology, while earning a 3.9/4.0 grade-point average.

During the Spring of his first year I got my first taste of Lingchong's solid motivation and intellect when he asked me if I might suggest an open-ended problem that he could pursue as a term project for his reactive-systems course, a graduate chemical engineering course. Several years earlier I had studied the spread of viruses on stationary host cells, modeled it as a three-species reaction-diffusion system and developed several limiting-case analytic expressions for velocities of propagation. I suggested he numerically solve this PDE system to verify my original ansatz---that a travelling-wave solution should exist---and also that he confirm my analytical solutions. With little input from me he carried out these tasks and found that his numerical result was consistent with all but one of my analytical solutions. He then went on to reveal an error in my original analysis. My taste of humble pie was more than compensated by the improved understanding I gained from Lingchong's analysis. We published his term project in *Journal of Theoretical Biology*.

Lingchong's doctoral work has had two broad thrusts: (1) to employ a computer simulation of a virus genomic system to explore a diversity of fundamental and applied problems and (2) to develop a general computational tool to facilitate the simulation and analysis of dynamic networks of interacting components, with an emphasis on genomic systems. The problems of the first thrust arose naturally from broad research interests in my group. Since Lingchong far exceeded my expectations in completing these projects, I encouraged him to define and pursue a project along a direction he found most exciting, and this self-defined project became his second major thrust.

The first thrust of Lingchong's work employed, expanded, and refined a computer simulation of virus growth to explore three directions. The simulation integrates several decades of biochemical, genetic, and biophysical data to account for the developmental dynamics of a very well-studied experimental system---the intracellular growth of phage T7, a virus that infects bacteria. In essence, by accounting for the dynamics of biological information processing (DNA to mRNA to protein), as well as protein-protein interactions, kinetics of host-cell and virus enzymes, genetic regulatory loops, and virus assembly processes, we have able to capture *in silico* the overall development of the virus in its host cell. Lingchong sought in his initial project to develop ways to infer likely genetic regulatory components and protein-protein interactions when provided dynamic global expression data of a form provided by DNA arrays and proteome profiles. Using simulated data from our T7 model he suggested algorithms for processing the data and showed how they could reveal likely genetic regulatory loops and protein-protein interactions. The broader lesson from this work was that genome-to-organism simulations provide a useful *in silico* system to test new algorithms for mechanistic inference. This work was published in *Metabolic Engineering* and a broader overview of our virus simulation work in the *Proceedings of the Pacific Symposium on Biocomputing 2001*.

In the second project Lingchong and I sought to probe the nature-versus-nurture problem from a quantitative genomic systems perspective. Again, using the T7 model, we wondered to what extent the resources provided by the host cell (nurture) could influence the dynamics of the genome-encoded phage development (nature). This work was performed in collaboration with another graduate student, who measured in the lab how the physiological state of the host, as defined by its specific growth rate, influenced the phage growth. Remarkably good agreement was found between the experiments and simulations. Lingchong's analysis extended these results to suggest that the limiting host-resource was the level and processivity of the host translation machinery. This result has been indirectly suggested in the last five years by other groups, but to my knowledge, Lingchong's work is its first quantitative demonstration. Aside from the fundamental interest of this result, it serves as a foundation to better understand how the physiological state of more complex mammalian-cell hosts may limit the productivity of bioprocessing for the production of viral vaccines or gene therapy vectors. We published this work in *Journal of Bacteriology*, and it was highlighted in *Science* (Editor's Choice, 296:219, 2002). In an extension of this work Lingchong has used the T7 model discover a key role that finite host resources played in the design of the phage. In short, he used the model to generate thousands of *in silico* phage mutants and simulated their growth under conditions of finite (realistic) and infinite host resources. He found that wild-type T7 was overall more efficient (less wasteful of resources) than the vast majority of mutants in either environment. Moreover, this efficiency correlated strongly with the phage growth rate (fitness) only under finite resource conditions. In other terms, wild-type is a winner because its high efficiency enables it to grow well under finite resource conditions. We are currently preparing this work for publication.

Lingchong's third project illustrates his uncanny ability to move into a new research area and rapidly make advances. Without knowing in detail how to implement the idea, I suggested to him three years ago that our virus model might be useful to quantitatively shed light on how genetic interactions behave at the population level, a problem that is extremely labor intensive to study in the laboratory. It has, however, been a long-standing problem in population genetics how deleterious mutations interact. Lingchong dove head-first into a completely new area for him and me---

population genetics, he learned the principles and terminology, and developed an implementation of our model that provided a molecular mechanistic basis for probing fundamental questions in epistasis, genetic system robustness, population fitness, and the evolution of genetic recombination. Lingchong showed how epistasis may be synergistic or antagonistic, depending on the environmental resources and the severity of the mutations in their effects on fitness. We published this work in *Genetics*.

Lingchong's work has opened doors for me in understanding better the challenges and opportunities of computational biology. Along these lines, what is perhaps most exciting to me is the long-term vision Lingchong has for his research and the very feasible path he has defined to achieve it. By implementing efficient *in silico* methods to dissect the behavior of different biological systems he aims ultimately to shed light on the functional modules that are the building blocks of bio-molecular networks. In the second thrust of his graduate work he has developed *Dynetica*, a computational tool to facilitate the efficient modeling and analysis of dynamic networks, focusing on genetic systems. An applications note on *Dynetica* has been accepted for publication in *Bioinformatics*. I think Lingchong has correctly diagnosed that the limited ability of the scientific and engineering communities to efficiently create, share, test, and compare models has significantly hindered the adoption of integrated and computational approaches in the study and application of biological systems. Since Lingchong has been the vision behind the creation of *Dynetica*, I have encouraged him to continue developing it and its applications as he builds his own independent research program. I do not plan to develop it further, though I certainly foresee it becoming a useful modeling and educational tool in my own research group.

Lingchong is a born leader. His was elected President by the 500 members of the UW-Madison Chinese Student and Scholar Association, and he served from 1999-2000. Further, Lingchong was one of twelve Knapp House Fellows (and the sole engineer) selected from a campus-wide competition. Knapp House Fellowships provide free housing for graduate students from diverse disciplines to live in a former Wisconsin governor's mansion and share research, cultures and interests. Lingchong edited the Knapp House Newsletter, which is sent to 200 alumni across the world. Lingchong's initiative is uncommon. For example, I organize a seminar series "Advances in Biotechnology" that brings a few distinguished speakers to campus each term. Three years ago I thought it would be good for the graduate students to take the lead deciding on a speaker, and handling the invitation and visit. So I offered the opportunity to our more than 30 chemical engineering graduate students working at the engineering-biology interface, and Lingchong was the only one to volunteer. He polled graduate students, came up with a list of speakers and invited a distinguished speaker, Adam Arkin of UC-Berkeley, who came to campus and gave a stimulating talk that attracted students and faculty from Chemical Engineering, Biomedical Engineering, Computer Science and the Biological Sciences. On a more personal note, Lingchong got along well with his coworkers, and I easily imagine that as a faculty member he will be a dependable departmental citizen.

In summer 2002 Lingchong completed this PhD at UW-Madison and joined Frances Arnold's group at Caltech, where he is working to design and implement genetic circuits in living cells. I am very enthusiastic about his prospects for making a significant impact in this area and I have no reservations about recommending him for a faculty position. Please contact me if I may be of further assistance.

Sincerely,

John Yin
Associate Professor & Cargill Faculty Fellow