DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY
HARVARD UNIVERSITY
OFFICE OF THE CHAIR

Andrew W. Murray
Professor, Molecular and Cellular Biology
Director, Bauer Center for Genomics Research
Chair, Department of Molecular and Cellular Biology

Room 3000, 16 Divinity Avenue
Cambridge, MA 02138
Phone: (617) 496-1350
Fax: (617) 496-1541
Email: amurray@mcb.harvard.edu

November 10, 2004

Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Department of Physics
Indiana University, Swain Hall West 117
Bloomington, IN 47405-7105

Dear Search Committee:

Chinlin Guo is a theoretical physicist who took the ambitious step of doing a post-doc in an experimental biology lab. His training in physics has been rigorous and his PhD advisor and other physicists who have interacted with him lavish superlatives on his intellectually ability and creativity. An example of the breadth of his interests is that during his PhD he made excellent progress on two very different theoretical problems, the initial reactions that nucleate protein folding and the role of receptor clustering in cellular signaling.

The latter work is directly relevant to Chinlin's current interest, determining how a gradient in the extracellular concentration of mating pheromones leads to yeast cells forming a single polarized mating projection, the first step in the act of conjugation. I was particularly excited by Chinlin's arrival for two reasons. He is committed to combining three approaches to cell polarization, experiment, simulation, and theory, and he is dedicated to searching for general principles that help to explain biology.

Chinlin has more than lived up to his promise. When he arrived in the lab, he began by thinking very generally about how cells detect their mating partners, and then set out to compare different models for their ability to detect concentration gradients and to produce a unique direction of polarization when exposed to spatially uniform concentrations of pheromone. His theoretical work argues that this problem can be solved by coupling of locally non-linear amplification to local cooperation and competition mediated by the actin cytoskeleton. The ideas and their development are all Chinlin's and my role has been restricted to rather general discussions about the biology of gradient detection and providing initial summaries about what was experimentally known.

On the experimental front, Chinlin has worked in close collaboration with Matthieu Piel, another post-doc, who is an outstanding microscopist. Matthieu built a microscope that could follow tens of cells for up to 12 hours and coupled this with microfluidic chambers that produce stable, precisely controlled pheromone gradients. Together they learnt yeast molecular genetics and constructed a wide range of strains in which different proteins involved in cell polarity were connected to fluorescent molecules and combined with different genetic perturbations. Their experiments reveal novel intermediates in the polarization of cells to uniform concentrations and pheromone gradients and argue strongly for the model that Chinlin has proposed. In particular three predictions of the model are verified: actin filaments are absolutely required to concentrate the earliest markers of the unique polarization axis, an initial phase of cooperation between adjacent sites of stimulation depends on the diffusion of critical components in the membrane, and a later phase where the deposition of other proteins prevents this diffusion converts local cooperation into a long range, rich-get-richer competition that leads to a unique site of polarization. This work is currently being written up and I expect it to make a major contribution to understanding how eukaryotic cells detect gradients of chemical signals.

Either Chinlin's theoretical or experimental contributions would be remarkable, but taken together they are astonishing. His experimental accomplishments would be impressive for a seasoned experimental biologist working in a lab dedicated to gradient detection. They are truly remarkable coming from a theorist working in a lab where this is a new area of research. He has the boundless energy and killer instinct that allows him to find the crucial experiments that will discriminate between different models and is utterly fearless in assembling the knowledge, equipment, and reagents needed to conduct them. He has absorbed a tremendous amount of biology in a very short time and now has the unusual ability to have unwatered down conversations with both physicists and biologists. This allows him to get the most out of his current environment and will make him a wonderful bridge between physics and biology as a faculty member.

Chinlin has been a joy to have in the lab. As the first theorist to join the group, I have learned more from him than he has from me. He is endlessly inquisitive and creative. For example, I have been worrying about how the strength of selection affects models that ascribe the beneficial effects of sex to rescuing good mutations from bad genetic neighborhoods. Chinlin and I had a five-minute discussion about the topic, and two weeks later he was back with simulations shedding light on the problem. He manages to combine great enthusiasm with great rigor, both qualities that will be necessary to connect models to experimental observations. He interacts with all other members of the group, and has nucleated a small group of theorists within the lab, thus providing mutual encouragement, without walling them off from their experimental colleagues. I am not the best person to assess his strengths in terms of the mathematics behind theory, but I have been greatly impressed by two things, his ability to take a simple verbal description, go away, think, and come back with models that are directly relevant to biology, and his ability to produce simple, intuitive explanations of his theory.

In summary, Chinlin Guo is an outstanding young person at the border between physics and biology. His combination of theoretical skills and fearlessness about experiments suggests that he will go on to make the same sort of contributions that Stanislas Leibler has made. He has my strongest recommendation.

Yours sincerely,

AW Murray

Andrew W. Murray
Herchel Smith Professor of Molecular Genetics
Chair, Department of Molecular and Cellular Biology
Professor of Molecular and Cellular Biology