Systems Biology at Harvard's Bauer Center for Genomics Research

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The Bauer Center for Genomics Research, at Harvard University, is a new interdepartmental initiative whose goal is to identify general principles underlying the structure, behavior and evolution of cells and organisms. Although we carry the "genomics" label, what we do could just as well be described as "systems biology". The unifying themes of our research are a system-level approach to biology, and close interactions among experiment, theory and computation. Our scientists come to biology from many disciplines, including physics, mathematics and computer science.

Research at the Bauer Center is done by Fellows — young scientists appointed for up to five years, who lead their own small research groups. The Fellows form a truly collaborative group of scientists; at last count, there were ten pairwise collaborations among the eight groups currently in the center. Interactions among the Fellows are promoted both by what they share (an interest in uncovering general principles in biology, and a commitment to interdisciplinary research) and by their differing backgrounds and expertise, allowing them to tackle problems together in ways that none of them would have devised separately.

Physicists and other quantitatively inclined scientists can contribute to molecular and cell biology in various ways — for example, by formulating mathematical and computer models and analytical tools, developing sensitive and accurate techniques for data collection, and bringing to the subject a predilection for reducing complex problems to their essentials. The eleven Bauer Center Fellows include two mathematicians, a biophysicist, and a computational biologist who are already at the center, and two physicists who will be arriving over the next eight months. Their work exemplifies these types of contribution.

Lani Wu and Steven Altschuler, pure mathematicians by training who spent six years at Microsoft working on problems ranging from video compression to speech recognition before being drawn into biology, have a number of collaborations with experimental biologists both inside and outside the center. In one, with Professor Rong Li of Harvard Medical School, they are investigating the self-organizing processes that underlie the establishment and maintenance of cell polarity in budding yeast. Experiments had suggested the existence of a positive feedback loop involving an activated form of the protein Cdc42, required for cell polarization, and the Cdc42-dependent assembly of actin cables,

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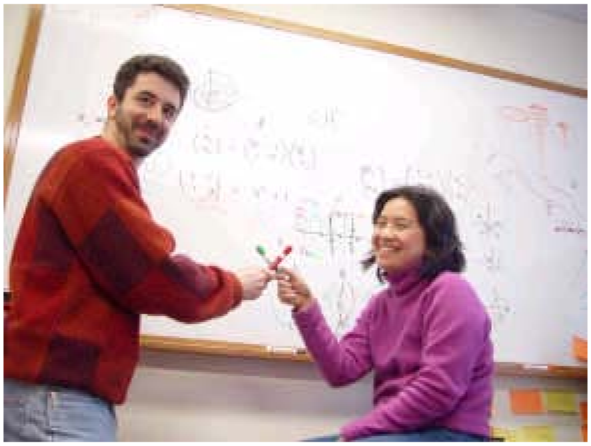
which deliver Cdc-42 to the cell membrane. In this picture, a stochastic increase in the local concentration of activated Cdc42 on the membrane increases the probability of actin polymerization, and hence further promotes the accumulation of Cdc42 at the site. Wu and Altschuler simulated this process mathematically, and were able to predict



Mathematicians Steven Altschuler and Lani Wu.

conditions (subsequently verified experimentally) in which yeast cells would develop one, two or more polar caps of Cdc42 (ref. 1). In nature, cell polarization is usually controlled by spatial signals, but the intrinsic polarization mechanism modelled by Wu and Altschuler may be used to amplify a small initial asymmetry.

Roy Kishony, a postdoctoral fellow with Stanislas Leibler at Rockefeller University, will be joining the center as a Fellow in August. Kishony has a Ph.D. in theoretical physics (his thesis was about the ignition criterion in inertial confinement fusion), but for the past four years he has been working as an experimental biologist. Kishony is addressing fundamental questions in evolutionary genetics, using new techniques for obtaining quantitative physiological data. In particular, he has developed a bioluminescence technique that allows accurate, automated measurements of bacterial growth rates at very low cell densities, and has used the technique to study the interaction between environmental stresses and deleterious mutations in the bacterium *E. coli* (ref. 2). At the Bauer Center, Kishony will extend this work to budding yeast, using his growth rate assay to perform a comprehensive and quantitative perturbation analysis of fitness with respect to both internal (genetic) and external (environmental) perturbations. He will use these data to reconstruct genetic circuits in yeast, and to generate testable hypotheses regarding the nature of interactions between pairs of genes.

Another physicist making the transition into biology is Sharad Ramanathan, a theoretical physicist on the technical staff at Bell Labs, who will be starting as a Bauer Center Fellow early next year. Ramanathan hopes to transfer insights from work he has done on electronic communication networks to the problem of signal transduction in biology. In particular, he is interested in questions

Meeting of minds: the Bauer Center café.

related to fidelity and cross-talk in the mitogen-activated protein (MAP) kinase cascades in yeast. Another Fellow, biophysicist Kurt Thorn, is approaching signaling in yeast from a different angle, developing fluorescence-based techniques such as fluorescence resonance energy transfer (FRET) to monitor the association of signaling proteins in living yeast cells. His new techniques should allow many proteins to be monitored simultaneously in real time, providing data to which computational tools can be applied to decipher the structure of signaling pathways.

Many of the Fellows share an interest in reconstructing biological networks, and will benefit from collaborating with the center's latest arrival, computational biologist Aviv Regev. Regev is using computational approaches to look for modular organization (ref. 3) in biological networks, and to characterize the behavior of modules (ref. 4).

It will not have escaped the notice of DBP members that there is a new influx of physicists and other physical and computational scientists into biology (see http://www.aps.org/apsnews/1102/110204.html). The Bauer Center's Systems Biology program (http://cgr.harvard.edu/research/systems_biology.html) aims to facilitate such career transitions, with jointly mentored postdoctoral fellowships designed to integrate quantitative scientists into biology, and a two-week summer school featuring lectures and laboratory experiments that will introduce postdocs and advanced graduate students from physics, mathematics, computer science and engineering to experimental biology. One of the center's main aims is to promote an intimate symbiosis between theory and experiment, of the kind that is normal in physics, but has been all too rare in molecular and cell biology. In addition to welcoming theorists into the Systems Biology program, we also encourage visits, ranging from one month to two years, from theorists who are interested in interacting strongly with the experimental biologists in the center.

Biophysicist Kurt Thorn.

There are of course many types of barrier — caused by differences of language, culture, assumptions and philosophy — that need to be surmounted when scientists from different disciplines start to work together. By bringing Fellows from many fields into the same building to work closely together, we are learning how to lower these barriers. But we will not be content merely to do successful interdisciplinary research within the center's walls. Instead, our aim is to catalyze fruitful interactions between the center's Fellows and faculty in the surrounding departments, and among faculty in different departments. To this end, we hold a weekly series of "Genomics Talks", at which the speakers are asked to make themselves intelligible to a mixed audience, and where there is no such thing as a stupid question. Although we have a long way to go, we consider it a sign of success that two of the most dependable audience members at these talks are condensed-matter theorists from Harvard's physics department. An equally important venue for interdisciplinary interactions is the Bauer Center's café — after all, scientists from all disciplines have to eat!

References

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