Teaching Interest

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During graduate school, I served as a teaching assistant at the University of California, San Diego. In doing so, I discovered that I really enjoyed teaching for a number of reasons. First, I took great pride in the fact that I was directly contributing to the students' comprehension of the subject (physics, e.g.). It is indeed of great pleasure to watch and to participate in the process in which the students become mature, creative, and capable of handling problems and subjects independently. Second, while preparing the lectures that the students could easily digest, I needed to condense the material at hand into a simple and comprehensible talk. I greatly enjoyed this challenge because it helped me to understand the material from different perspective. In other words, I was not only teaching the students, but they also helped me to learn more. Indeed, I would like to try to concentrate my own research into a subject in the lecture. By doing so, the students can be inspired by the recent research activity, and their feedback can help me to acquire a new understanding of a problem that I am interested.

In general, I prefer courses that are structured such that they contain many examples of the concepts being covered and many opportunities for students to apply their new-found knowledge to complete small projects. I have found that students comprehend material more easily when it is connected to appropriate examples and when they have ``hands-on" experience dealing with the subject material independently. When supervising students, I like to spend time with them on a one-to-one basis. This helps me to identify their strength and weakness as individuals. In addition to tracking a student's scientific progress, I also feel that contributing maturation to his/her personality is of equal importance to advancing his/her intellectual growth. Finally, I would advise students to participate in a variety of conferences within or without their fields, because a wide depth and breadth of experience are both important for the maturation of an independent and creative scientist.

Research Plan **Chinlin Guo**

Modeling Self-Organization in Biological Networks

General interests & overview Life depends on the ability to respond to environmental cues despite stochastic fluctuations in the abundance and distribution of intracellular components and extracellular molecules. These responses often depend on self-organized molecular networks. Through positive feedbacks and collective dynamics, self-organization provides the cooperative spatial-temporal control that allows a cell to integrate events that are stochastic at the level of individual molecules into a robust response. Re-wiring or fine-tuning feedback loops can further enhance the plasticity of responses and allow for evolutionary adaptation. My general interest is in studying how self-organization can give rise to spatial-temporal control, and in discovering what design principles have been involved in these systems. In particular, I am interested in how self-organizing processes of different time/length scales are integrated and what types of biological consequences would result from such integration. Below, I present three research topics. These projects are all related to self-organization, and explore scales ranging from molecular to multicellular. I have and will continue to collaborate with both theoretical physicists and experimental biologists, thereby introducing new topics and new insights into both communities.

Background of proposed questions

(A) In eukaryotes, cellular polarity formation is an important process during cell growth and development. Failure of proper polarity formation can lead to tissue malfunction and cancer formation. Current models of polarity formation depend on persistent extracellular gradients of signaling molecules or intracellular heterogeneity, as well as a reaction-diffusion scheme in which a short-lived activation spreads out more slowly than a longer-lived inhibition[1]. This class of models, however, has several problems. First, they cannot explain the observation that budding yeast cells treated with uniform pheromone concentration form a single polarized projection without persistent intracellular heterogeneity[2]. Second, they predict that depending on the relative length scale of the cell to the reaction-diffusion scheme of activation-inhibition, the cell can alternatively form regular distributions of active/inactive regions (i.e., pattern formation). This, however, is not found in elongated yeast cells exposed to a low dosage of pheromone treatment[2].

(B) In addition to single cell polarity formation, spatially and temporally coordinated multicellular responses appear in cell-cell and cell-matrix interactions. Examples include wound healing and epithelial cell differentiation, in which cells need to integrate local information into a global response. How this is achieved is not well understood. The current model suggests that through mechano-regulation of the cytoskeleton between and inside the cells, biochemical activities at different locations can be altered simultaneously to reach a global response (the tensegrity model)[3]. Although this model is attractive, general evidence of such mechano-chemical coupling is lacking. Moreover, it is not obvious how this model can account for the observation that cells can switch to different phenotypes by changes in cell polarity and shape[4].

(C) The third question I wish to address is protein aggregation. Proteins are normally folded into native structures. However, they can form pathological aggregates in neurodengerative diseases[5]. Most studies on protein aggregation are performed *in vitro*[6], where self-organized thermodynamics appears to be important[7]. However, these reactions have a large kinetic barrier and cannot explain how aggregation occurs *in vivo* on a reasonable timescale. In particular, it is not clear whether active *in vivo* processes can participate in the onset and progression of the disease, and whether there is transition between pathological aggregates and functional fibrils, speculated to be important for synapse memory[8].

Proposed research

(A) Self-organization in single cell polarity formation I have proposed that self-organization based on a novel long-range mechanism is required for polarity formation. This mechanism allows different regions of the cell to compete directly with each other for limiting factors[2]. I have identified this mechanism as actin-based transport and discovered that it is involved in two distinct self-organizing processes[2]. A nonlinear partial differential equation (PDE) was constructed to address the dynamics of these two processes, in which I showed that their behavior depends on a restriction of diffusion[2]. I plan to include stochasticity to study how robustly these processes can give rise to polarity formation in the absence of a gradient. In particular, the effective length scale and the strength of direct competition of long-range transport will be varied to explore the phase diagram. In addition, I will investigate how well the coupling between these two processes can help cells detect gradients. It is clear that the restriction of diffusion can help cells search for a point (the mating partner, e.g.)[2]. However, it is not apparent whether this restriction would weaken or enhance gradient detection. To address this, I will vary the coupling and the effective diffusion of these two processes to see how the gradient response is altered.

(B) Collective dynamics in cell-cell and cell-matrix interactions I propose that the multi-cellular, global response is mediated by collective dynamics through long-range cytoskeleton biomechanics, long-range transport, and short-range biochemical cooperativity. Short-range cooperativity can be found in the oligomerization of cell surface molecules such as integrins[9], whereas actomyosin is involved in both cytoskeleton biomechanics[10] and actin-based transport that in turn regulates local biochemical events. This provides a clue of how mechno-chemical coupling is established. In other words, mechanical interaction affects cytoskeleton dynamics, leading to a perturbation of active transport and hence to a switching of the biochemical response. To verify this and to explore how robustly this can occur, I will construct a nonlinear PDE and incorporate both the fast-changing randomness of individual cells and the slow-varying roughness of the extracellular matrix. The major goal here will be to show that the single-cell polarity formation (by transport) can be correlated with a multi-cellular, global response. Analysis will first take place at the mean-field level and stochasticity will subsequently be taken into account. I expect a synchronized formation of multi-cellular polarity in a stochastic environment, and plan to explore how robust it is, and if it is correlated with a global, phenotypic switch.

(C) *in vivo* dynamics of protein aggregation I propose to incorporate both the protein thermodynamics and the non-equilibrium kinetics of protein interacting network to study protein aggregation *in vivo*. Specifically, I will include the interaction between amorphous intermediate (an ill-defined, pre-fibril state)[5] and fundamental cellular functions such as chaperonin-assisted folding and ubiquitination-mediated scavenging[5,11]. The basic ingredients contain the thermodynamics of aggregation-prone proteins, short-range protein-protein interactions, and long-range active transport involved in protein scavenging. In addition, thermal fluctuation (in protein thermodynamics) and shot noise (in gene expression, transport, and protein interaction) will be included. The goal is to identify the role of active transport and protein interaction in the onset and progress of cellular toxicity, and in the transition between pathological and functional states of the aggregate[8].

Goals of research I am excited to learn that your department offers a great opportunity for conducting interdisciplinary research. The study of the proposed projects requires a researcher with excellent analytical and experimental skills in order to collaborate with both the biologists and physicists. Given my training in medicine, electrical engineering, theoretical physics, and molecular and cellular biology, I am confident that my interaction with the physicists, chemists, bioengineers,

and medical researchers at your institute will not only facilitate the understanding of fundamental biophysical issues, but also have a profound impact on multiple disciplines.

Reference

1. Meinhardt H. (2003) *C. R. Biol.* **326,** 223-237.
   Rappel W-J, *et al.*, (2002) *Biophys. J.* **83,** 1361-1367
   Roland W, *et al.* (2003) *Science* **299,** 1231-1235;
2. Guo C, Piel M, Murray AW. (2004) in preparation.
3. Ingber DE. (2003) *J. Cell Sci.* **116,** 1157-1173, 1397-1408.
4. Numaguchi Y, *et al.* (2003) *Angiogenesis* **6,** 55-64.
5. Stefani M, Dobson CM. (2003) *J. Mol. Med.* **81,** 678-99.
6. Serio TR, *et al.* (2000) *Science* **289,** 1317-1321.
7. Lindquist S., *et al.* (2001*) Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356,** 169-176.
   Krobitsch S, Lindquist S. (2000) *Proc. Natl. Acad. Sci. U S A.* **97,** 1589-1594.
   Jimenez JL, *et al.* (1999) *EMBO J.* **18,** 815-821.
8. Si K, Lindquist S, Kandel ER. (2003) *Cell* **115,** 879-91.
9. Li R, *et al.* (2003) *Science* **300,** 795-798.
10. Balaban NQ, *et al.* (2001) *Nat. Cell Biol.* **3,** 466-472.