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Biocomplexity Faculty Search
c/o Ms. Yana Teterina
Department of Physics
Indiana University
Swain West 117
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USA

Encl.: Statement of research interests; statement of teaching philosophy

Dear Sir/Madam,

I am currently a post-doctoral fellow with Dr. Dennis Bray at Cambridge University working in the field of computational cell biology. Please consider me as a candidate for Junior Faculty Position at the Biocomplexity Institute, Indiana University.

I have several years of experience in modeling cellular signaling and regulatory systems using a variety of modeling methods, both theoretical and simulation. If hired for this position, I intend to establish an independent research program as outlined in the attached research statement. I have experience teaching Quantitative Biology at the University of Cambridge and look forward to taking part in teaching activities of the Department, especially in the multidisciplinary programs.

Given the opportunity I would be pleased to discuss with you how I can contribute to activities at the Institute.

I have arranged for two letters of recommendation to be sent under separate cover. My third reference is Dr. Dennis Bray who is able to send his letter of recommendation only upon personal request. His contact email address is db10009@cam.ac.uk.

Thank you very much for consideration.

Sincerely,

Sergej Aksenov

Statement of research interests

My main research interest lies in mathematical modelling of cellular regulatory networks. In particular, I am interested in elucidating the relationship between the structure and function of spatial aggregations of cell surface receptors, covalent modification pathways, and gene regulation networks. I would like to understand the mechanisms of these regulatory phenomena, and how these spatially and temporally segregated pathways couple to each other to produce an integrated and efficient response.

Current research

My current research is analysis of signalling by cellular surface receptors using stochastic modelling. In particular, I am studying the role of receptor oligomerization in conditioning responses when the cell is simultaneously presented with several different ligands. I was motivated for this work by studying bacterial chemotaxis receptors with Dr. Dennis Bray. Each of these receptors has its own distinct set of cognate ligands, and receptors of different specificity appear to stably associate into trimers. The question is how such physical organization of receptors helps bacterium to find its way in a medium containing gradients of several attractant and repellent chemicals. To answer this question I have constructed a model of conformational coupling in oligomeric rings of receptors, which is conceptually based on the generalized model of allostery by Duke, Le Novère, and Bray[1]. I am also using a stochastic simulation of swimming bacterial cells to study response to different signals at a behavioural level.

Future plans

In my future work, I plan to continue to study signalling by cell surface receptors by (i) extending my model to account for other design features of receptor signalling, and (ii) constructing integrated models of specific pathways.

(i)

To answer questions about the general mechanisms of receptor signalling, I plan to consider design features found in eukaryotic receptors that present a considerable complication to our understanding of receptor functioning in comparison with bacterial receptors.

For example, eukaryotic receptors form much more dynamic oligomers/aggregates that also involve a diverse array of accessory proteins. I plan to study the dynamics and control of formation of such physically coupled "signalosomes" of varying composition, and the effect of design of such "signalosomes" on signalling.

There is evidence that many receptors go through several different signalling conformational states. I will incorporate this feature in my model of conformational coupling, which is currently formulated for two-state receptors (i.e., those that exist in a thermodynamic equilibrium between two signalling conformations).

Finally, I will use stochastic simulation of receptor signalling to analyze the effects of noise on receptor function. Noise is in fact the driving force of signalling, because receptors flip between defined signalling conformations in a random fashion. We previously found that in a simple regular lattice of coupled two-state receptors response to step changes in ligand concentration exhibits a phenomenon analogous to stochastic resonance[2]: receptor cluster has optimal high signal-to-noise ratio at intermediate levels, but degrades at both low and high levels of internal noise.

(ii)

I plan to use my models of receptor signalling to gain useful insight into cellular regulation of particular responses that have pharmacological significance. Cell surface receptors can be in fact considered gateways into the cell for the ligand-initiated responses; following activation or inhibition of receptors signal transmission then proceeds via intracellular second messenger cascades to control expression of sets of genes. I plan to identify a number of experimentally well-studied signalling pathways (for example, receptor tyrosine kinases that control cell cycle, migration and survival[3]), and construct detailed mechanistic models by putting together insight from my studies of generic receptor models and the existing knowledge of the downstream pathways. The necessary background for such integrative modelling is provided by the experience that I gained as a Ph.D. student working on the SOS gene regulatory network in *Escherichia coli* and as a postdoctoral researcher working with Prof. Michael Savageau on the comparative analysis of covalent modification cascades.

References

1. Duke, T. A., Le Novère, N. & Bray, D. (2001). Conformational spread in a ring of proteins: a stochastic approach to allostery. *J Mol Biol* 308, 541-553.
2. Shimizu, T. S., Aksenov, S. V. & Bray, D. (2003). A spatially extended stochastic model of the bacterial chemotaxis signalling pathway. *J Mol Biol* 329, 291-309.
3. Schlessinger, J. (2000). Cell signaling by receptor tyrosine kinases. *Cell* 103, 211-25.

Statement of teaching philosophy

Learning process

I think that the most important result of learning a discipline is to acquire its general concepts and understand their interconnection. This will enable the student to achieve an overall integrated command of the subject. Alongside with learning such a framework, a student needs to acquire the ability to recognize and use these general concepts and ideas in particular situations and examples. Introducing worked examples that illustrate and illuminate all facets of a particular concept will provide firm and usable grasp of the subject.

My concept of teaching

To facilitate such learning process my idea of teaching is to go through a gradual and logical build-up of general foundations of a discipline, in parallel with working through particular examples and setting problems. Examples will serves a double purpose of motivating the learning and illustrating application of abstract concepts to real-life problems. With this I would like to provide students with a learning model for (re)use in their professional life, which nowadays involves constant probing and learning new disciplines. I will also try to place each new idea/example in a broader context of the subject and the scientific field in general. This requires the teacher to be broadly educated and knowledgeable, which I will strive to become and maintain. The most successful teacher is a scholar, which ensures that he/she always stays aware of the subject he/she teaches by being active in his/her own field of research. Effective teaching skills can and should be developed, and I am prepared to continuously learn how to teach effectively.

Setting goals for students

I would like to encourage students to learn the subject thoroughly and think critically, constantly challenge assumptions of particular concepts and models, and evaluate their results in the context of possible real-life applications. Another important goal for efficient learning is to help student learn to prioritize their time.

Relationship with students

I think it is important (if not obvious) to treat students with respect. It is important to recognize that there will always be students with different abilities and pace of learning, and to adjust the teaching style appropriately. I will make an effort to include every student of the class in the learning process and will try to use a variety of teaching styles to achieve this effectively. I will try to be always available to students to provide academic and sometimes personal support, keep track of their academic progress and regularly provide constructive feedback to them.