Dr. Andrew B. Goryachev
Research Scientist & Team Leader
Systems Biology Group, Bioinformatics Institute
30 Biopolis St., Singapore 138671

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Dr. Yves Brun,
Department of Biology,
Indiana University,
Bloomington IN, USA

Dear Sir,

I wish to apply for a position of an Assistant Professor in Computational Systems Biology. I am especially interested in this position as I am excited about the excellent interdisciplinary research opportunities provided by Indiana University. I strongly believe that the research I plan in the area of computational systems biology perfectly matches the goals of the Department. In particular, I am proposing a research program in computational modeling of bacterial decision networks and complex cooperative behavior in bacterial populations. My interests in microbial systems biology, developmental mechanisms and function of gene networks are highly congruent with the research interests of the members of the Department. I am confident that my research could make a worthy contribution to the research of the Department of Biology.

I have a long-standing interest in understanding biological systems on the systemic level. To equip myself with tools matching the complexity of the goal, I completed my basic education in biophysics. I chose to specialize in synergetics (non-linear dynamics), an interdisciplinary physical science that aims to develop generalized mathematical description for complex self-organizing systems. Through my graduate studies, I developed a solid background in mathematical modeling and computer simulations. Working on a variety of projects ranging from competing species to chemical reactive media, I developed an expertise in dealing with the complexity of real systems through building their abstract description, simulation and interpretation of model predictions. This background enables me to efficiently approach the subject of my proposed research.

To obtain practical experience in biological research, I elected to conduct my postdoctoral studies at the Microarray Centre of the Ontario Cancer Institute. Based on my study of experimental errors and variability, I developed a comprehensive statistical approach to the pre-processing and analysis of microarray data. In close collaboration with several research groups I applied microarray technology to study gene expression in yeast, mouse and human. My role in these projects varied from consultant to the key contributor and was primarily focused on rational design of experiments, data acquisition, analysis and data mining. In the large collaborative effort together with A. Edwards (University of Toronto) and K. Furuya (now at Pennsylvania State University) we performed expression analysis of a pediatric liver disease, biliary atresia. Based on my analysis of microarray data, I was able to link the etiology of the disease to a defect in morphogenesis of biliary epithelial cells. Working on this project, I began to plan an independent research program in computational modeling of morphogenetic processes with a single cell resolution.

Upon successful completion of an industrial research and development position with a leading bioinformatics software development company, GeneData AG, I was able to pursue my scientific goals as a Research Scientist at the Bioinformatics Institute of Singapore. This position, fully funded by the government, gave me a unique opportunity to start my independent research program and assemble a group that presently consists of a postdoctoral fellow, a Ph. D. student and two research associates. In the short time period at the Bioinformatics Institute we developed the first prototype of the novel parallel computational platform for the simulation of multiple communicating cells and successfully applied it to the analysis of quorum sensing, the cooperative phenomenon in a bacterial population (see *Research Proposal*).

I am keenly interested in shaping the minds of the future generations of researchers, today's students. In my present position of an adjunct faculty at the National University of Singapore I designed, developed and delivered graduate courses and modules in systems biology and mathematical modeling. I propose to further develop and teach comprehensive as well as special focus courses in biophysics as well as computational and systems biology.

In conclusion, I strongly believe that the unique blend of my background, research interests and multifaceted experience makes me a highly qualified candidate for a faculty position. I would greatly appreciate the chance to present my research and qualifications at an interview on the university campus.

Enclosed are a copy of my curriculum vitae, along with the statements of research and teaching interests and the list of references. Thank you for your time and consideration.

Sincerely,

Andrew B. Goryachev, Ph.D.

Andrew B. Goryachev

Understanding Communication and Cooperation of Cells through Computational Modeling

Many normal and pathological processes in higher eukaryotes, such as morphogenesis and oncogenesis, are fundamentally cooperative phenomena that stem out of the complex pattern of multiple cell-cell and cell-environment interactions. Recently it has become evident that bacteria also communicate and coordinate their activities by means of chemical signals. Cooperation of prokaryotic organisms can go as far as the formation of fascinating multicellular bodies that consist of profoundly differentiated cells. This complex behavior is a phenotypical manifestation of the operation of intracellular circuitry composed of signal transduction and gene expression networks. Experimental accessibility and abundant genomic information make prokaryotic organisms the systems of choice for studying how intracellular networks define communicative and cooperative abilities on the multicellular level. The understanding of these links is paramount for our fundamental biological knowledge and important for biomedical applications, such as the control of infectious diseases.

My research is driven by the passion for understanding complex cooperative phenomena in biological systems by means of computational modeling. The ultimate goal of my research is to quantitatively describe the interaction between the intracellular and extracellular environments of a unicellular organism and understand how this interaction results in the emergence of cooperative behavior and multicellularity. The overwhelming complexity of these questions defies our naked intuition. It is my strong belief that their complete understanding can only be achieved through the quantitative approach that integrates biological experiments with the methods developed by physical and computational sciences.

Past and present research

Until recently, intracellular phenomena and the dynamics of multicellular populations have usually been considered separately. The research in my group focuses on bridging this artificially created gap. We work towards elucidating the relationships between intracellular processes and multicellular phenotypes that are displayed by bacterial populations in natural and experimental conditions.

Recent progress in computational cell biology has established the basis for the development of computational methods suitable for the biologically realistic simulation of systems comprised of many interacting biological cells. Simulation of multicellular ensembles poses an algorithmically complex and resource-consuming computational problem. The need for a parallel computation platform capable of managing large, dynamically changing collections of interacting cells has emerged recently but has not yet been adequately addressed by the systems biology community. We created a parallel computing platform [1] for the simulation of a bacterial population in which individual cells possess their internal biochemical environment as well as the abilities to move, divide and chemically communicate through the common extracellular environment. The prototype of the system has been already successfully applied for the simulation of the transition to quorum sensing in a population of plant pathogen *Agrobacterium tumefaciens* [2]. The intracellular dynamics of more than 100,000 cells was computed stochastically with the direct Gillespie method on multiple parallel processors. These simulations, for the first time, explicitly revealed the extent of the stochastic variability in gene expression across the entire bacterial population. This difficult to measure information is usually lost in experiment when the population-averaged values are obtained.

Quorum sensing (QS), the phenomenon that allows bacterial populations to coordinately activate certain gene expression programs once some critical population density has been achieved, provides an excellent example of cooperative behavior in bacteria. To achieve quantitative understanding of QS, I reconstructed from the experimental publications the layout of the molecular network responsible for the transition to quorum in *Agrobacterium tumefaciens* and created a mathematical model describing its dynamics [2]. Through the analytical and computational analysis of this model I demonstrated that the QS network operates as an "on-off" gene expression switch and investigated in detail the molecular mechanisms that are responsible for this threshold behavior. I further demonstrated that the network layout, while enabling sensitivity to subtle variations in extracellular concentration of the signaling molecule, at the same time provides surprising robustness to molecular noise that is inherent in the bacterial intracellular environment. Building upon this intracellular model, we simulated the transition to quorum in an exponentially growing *Agrobacterium* population using our parallel computational platform [2]. We demonstrated that while individual cells exhibit sharp transitions, the population-wide transition to quorum is spread over a wide range of population densities as was observed in experiment. We also compared the transition to quorum in a freely suspended population versus a population growing as a biofilm and concluded that quorum is not likely to be achieved in the first case. On the basis of these quantitative predictions we hypothesized that the previously elusive ecological and evolutionary function of the QS phenomenon in *Agrobacterium* is to serve as the detector of the formation of plant-attached biofilm.

Inspired by the intricate layout of the QS network of *Agrobacterium*, I set out to compare it with other known QS networks to determine what functional benefits are provided by the particular elements of the network. The task of mapping structural elements of the network to its function is not trivial because the overall function of the network is not just a linear combination of its parts. In the report of the preliminary results of this analysis [3], I compared several potential layouts of the QS network with the aim to determine differences in their functional fitness. Specifically, I considered the influence of the dimerization of the transcription factor and the presence of the extra positive feedback loop on the robustness of the networks under the influence of molecular noise. Surprisingly, this analysis demonstrated that all network elements, including those that on the first glance appear to be unimportant, contribute to the robustness, sensitivity and the overall functional fitness of the QS network.

Future plans

Based on the solid foundation of already developed computational tools and modeling approaches, I propose to further advance our understanding of complex cooperative behavior observed in bacterial populations. The success of this research program is critically dependent on close collaboration with experimental groups.

The exigent goal of systems biology is to map structural organization of molecular networks on the phenotypes they control. To bring closer the achievement of this goal, I plan to further the research efforts directed towards reverse engineering, modeling and analysis of intracellular decision circuits, in particular networks involved in cell-cell communication and cooperation. Recent advances in various bacterial systems provide rich material for comparative functional analysis of molecular networks. In particular, I plan to build on my expertise in quorum sensing networks to continue analysis of various existing QS layouts. This work will serve to improve our understanding of how various network layouts evolved to precisely fit specific biological tasks under various ecological conditions. The next challenge is to understand how multiple decision circuits integrate their activity to control complex behavior. For example, in *Vibrio harveyi* three QS networks operate in parallel. Existing experimental evidence indicates that this layout is necessary for the bacterium to differentiate between several environmental conditions and make complex behavioral decisions. In a different system, *Bacillus subtilis*, antagonizing QS circuits control the switch between competence and sporulation.

While studying the dynamics of intracellular molecular networks responsible for communication and cooperative action, it is important to consider the function of these networks in the ecologically relevant population-wide context. Thus our simulation results predict that the phenomenon of bacterial quorum sensing is likely to play an important role if bacteria grow as a biofilm. Recent experiments also highlight the existence of multiple connections between QS and the emergence, maintenance and life cycle of biofilms. My immediate research goal is to extend the already created modeling methodology to simulate transition to quorum in the conditions of a biofilm. In particular, I want to explore how the heterogeneity of cell density typical to natural biofilms affects the transition to quorum and whether the QS phenomenon plays any morphogenetic role in the formation of biofilms. Our preliminary results indicate that signaling with acyl-homoserine lactones (AHSL) typical to Gram-negative species has poor morphogenetic potential due to the high diffusivity of AHSL molecules. This may prevent them from forming the sharp concentration gradients necessary to provide positional information for cellular differentiation. Therefore, it is interesting to consider other signaling mechanisms, for example those based on polypeptides that are typical for Gram-positive bacteria.

In addition to chemical communication, bacterial cooperation and formation of multicellular structures relies on active motion of bacterial cells. Recent experimental results indicate that bacteria may actively move to form a quorum. I plan to use computational modeling, in particular the developed parallel computational platform, to explore the potential role of chemotaxis in formation of biofilms and the possible interplay of active motion and chemical signaling in various phenomena of bacterial communication and cooperation.

In these and many other fascinating prokaryotic systems, computational modeling and analysis will become instrumental for achieving fundamental understanding of complex cooperative behavior on both intracellular and population-wide scales.

References*:

1. D.-J. Toh *et al.*, Parallel computing platform for the agent-based modeling of multicellular biological systems. In: K. M. Liew *et al.* (Eds.) Parallel and distributed computing: applications and technologies. (2004) Springer, Heidelberg.
2. A. Goryachev *et al.*, Transition to quorum sensing in an *Agrobacterium* population: A stochastic model. PLoS Computational Biology **1**(4), (2005)
3. A. Goryachev, D.-J. Toh, T. Lee, Systems analysis of a quorum sensing network: design constraints imposed by the functional requirements, network topology and kinetic constants. To appear in BioSystems (2005).

* **(reprints are available at *http://web.bii.a-star.edu.sg/~andrewg/*)**

Andrew B. Goryachev

SUMMARY OF TEACHING INTERESTS AND EXPERIENCE

Teaching Philosophy

I strongly believe that the ultimate goal of university education is to help students discover methods for lifelong learning and professional development. I remember my own instructors saying that the primary goal of a teacher is to show a student how to formulate and approach real-life problems. This attitude distinguishes an education that merely transfers technical knowledge to students from one that challenges them to think. Committed to the latter principle of education, I see it as my task to instill in students an inquisitive and persevering mind capable of courageous exploration of novel ideas and solutions.

To this end, I constantly work on cultivating active and deep learning. It is my fundamental persuasion that students will only be able to absorb material that excites and stimulates them. My role as a teacher is to help activate the student's interest in the subject and the process of learning itself. I always actively encourage an interactive environment and break my monologues often to re-establish the contact by asking questions. From both my learning and teaching experiences I know that it is often a psychological block that prevents a student from enjoying learning. The teacher has to learn appropriate pedagogic techniques to create a psychological contact with a student that will eventually help to overcome the block. I clearly remember an episode in class when I asked students to solve a photochemisty problem related to laser radiation of a certain wavelength. I sensed the boredom and to break the mood I asked what, in their opinion, was the color of the beam. After a short surprised silence, a vivid discussion ensued, the ice was broken and the rest of the tutorial went in cheerful and productive atmosphere.

Another way to encourage students' creativity and active attitude is through integration of independent research into the coursework. I discovered that nothing better stimulates the learning than the opportunity to participate in independent research. The role of the teacher here is to skillfully guide the process, introduce correct research practices and help to avoid common pitfalls. For example, I found that much frustration and end-term anxiety can be spared if work on the term project is started early, the students are given ample time to select the topics of interest and perform a thorough literature search. I encouraged students to contact me outside of office hours to discuss the progress in their projects.

To further promote independent intellectual growth and self-realization of students, the teacher needs to adopt a broad interdisciplinary approach and systems perspective. In the short term, students should be able to understand how a particular course contributes to their education portfolios and brings them closer to their goals. In the long run, the ability to see their studies in a "bigger picture" is vital for students' career decisions. The highly interconnected and fast-paced nature of modern science demands from the teacher to always be up-to-date and somewhat of a visionary. This is especially true for rapidly evolving interface sciences such as bioinformatics and computational biology. I feel privileged to work on the cutting edge of modern biology and to be able to bring students the latest results from its frontiers. The feeling of being contemporary to the exciting developments is very important for the motivation of students, especially in the course of their graduate studies. To promote this feeling, I plan to organize journal clubs, research seminars and discussion groups.

An important responsibility of the teacher is to help students develop strong interpersonal and communication skills. I always encouraged active participation of students in the class by requesting them to demonstrate on the board how they solved the problem. Some students commented that after fighting the initial discomfort of public appearance, they eventually felt more satisfaction and fulfillment than when they would simply have shown their solution to the instructor.

I have greatly enjoyed my experiences as a teacher, and I understand that they form only the beginning of a lifelong learning process. I believe that teaching is a vital part of academic life and I look forward to further developing my talents as a teacher while I foster the excitement that will stimulate future generations of thinkers.

Teaching Experience and Interests

My first introduction to teaching dates back to my undergraduate years when I was organizing competitions in biology for high-school students. In the course of my graduate studies I had ample opportunity to develop my teaching skills as a teaching assistant. I conducted more than 400 classroom hours of tutorials, laboratory practicum and lectures. In particular, I taught several courses in general and physical chemistry to life sciences students.

In addition, I volunteered my time as a one-on-one tutor for undergraduate students requiring personal attention. I enjoyed this type of individual teaching just as much as I did working with large classes. Often I had to search for alternate explanations and reinterpret the course materials to ensure that concepts were understood. I also used the feedback from these sessions to fine-tune the content and style of my classroom tutorials. During my appointment as an industrial scientist and manager I refined my teaching skills by conducting customer training and mentoring my colleagues.

My current position of Adjunct Assistant Professor at the Division of Bioengineering, National University of Singapore gives me an excellent opportunity to fully utilize and further develop my teaching potential. I independently designed and conducted a module of the graduate course in systems biology. In addition to 20 hours of lectures I developed several problem sets and conducted tutorials where the solutions to the assigned problems were interactively discussed with the class. The lecture slides pertinent to the course are posted on my website and the complete course notes are available on request. In addition to this large effort I also contributed several guest lectures to the graduate course "Quantitative physiology principles in bioengineering". At the moment I am developing a module for a course in computational biomechanics.

My teaching interests reflect my multifaceted educational background and interdisciplinary research interests and experience. With profound formal training in mathematics, physics, chemistry and biophysics, I can teach a variety of undergraduate courses pertaining to these disciplines. In particular, my strength lies in the application of these disciplines to biology. Also I propose to develop senior-level undergraduate and graduate courses related to the areas of my research interests and specialization. These disciplines include but are not restricted to systems biology, computational biology, bioinformatics, data mining and mathematical modeling of biological systems.