



CHEMICAL PHYSICS THEORY GROUP

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TORONTO
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September 14, 2005

Dr. Yves Brun
Systems Biology /Microbiology Faculty Search
Department of Biology
Indiana University
Jordan Hall 142, 1001 E 3rd Street
Bloomington Indiana 47405-7005

Dear Dr. Brun:

I am writing this letter in support of Andrew Goryachev's application for a position at Indiana University.

Andrew Goryachev is an excellent scientist who has shown that he can carry out significant research in a variety of fields. I'll begin by describing some of the work he carried out in the course of his graduate studies in my group in Toronto. He came to Toronto well prepared, having obtained a Master's degree in computational biophysics from the prestigious Moscow Institute of Physics and Technology. His technical skills are superb and his knowledge of biophysics, chemistry and mathematics is excellent.

For his thesis, he carried out a major original investigation on the nature of spiral waves in chemically reacting systems that support complex local oscillatory or excitable dynamics. Spiral wave patterns are ubiquitous in chemical and biological excitable and oscillatory systems. In the course of this work he discovered the existence of synchronization defect lines, new types of line defects where the phase of the oscillation changes suddenly. His theoretical predictions stimulated attempts by other groups to experimentally verify the phenomena. These attempts were successful and synchronization defect lines have now been observed in experimental studies on the Belousov-Zhabotinsky reaction. Furthermore, these line defects may be implicated in some cardiac arrhythmias that arise from electrochemical wave patterns called alternans. This line of research is under active investigation in several groups.

Not only did he discover this phenomenon through numerical simulations of wave patterns, but he also carried out a sophisticated analysis of their structure and origin using ideas from knot theory. The results of his research has been published in a series of papers, most notably portions of the work appeared in three papers in Physical Review Letters, the most prestigious journal in physics.

He was one of our best graduate students and was awarded two prizes for his graduate work, the Dignam Travel Award and the D.J. LeRoy Prize which is given to the top graduate student in physical chemistry.

After leaving my group in Toronto, Andrew went on to pursue work in bioinformatics and computational biology. His training in a variety of fields including biology, physics, chemistry and mathematics gives him an enviable background for work in this area. I have followed his work and am impressed with the results he has obtained.

Andrew is able to communicate his results to others in a very clear manner. His oral presentations are models of organization and clarity. He is able to interact well with others and he carried out research collaborations with other scientists during his graduate studies. I enjoyed working with Andrew very much. He is bright, he works hard and he develops his own ideas. He is firm in defending his own ideas but not to the exclusion of other approaches.

There is little doubt in my mind that he has both the drive and intellectual abilities to make him a very successful scientist with the ability to supervise students and attract funding for his work. I can recommend him for the position in the highest terms.

Sincerely yours,

A handwritten signature in cursive script that reads "Raymond Kapral".

Raymond Kapral
Professor of Chemistry



UNIVERSITY OF TORONTO

CHARLES H. BEST INSTITUTE 112 COLLEGE STREET TORONTO, ONTARIO, CANADA M5G 1L6

September 16, 2005

Dr. Yves Brun,
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Reference for Andrew Goryachev

Dear Dr. Brun,

It is a great pleasure to be able to write this letter of support for Andrew Goryachev's application.

Andrew was a post-doctoral fellow in my group after his having received his PhD in physical chemistry and modeling of complex systems.

When Andrew came to my group, his knowledge of biological systems was limited to high-level knowledge of gene regulatory networks. In my lab, he spent his time working on the analysis of microarray data and gained an in depth understanding of all of the practical aspects of data reduction and data interpretation. Although he was swimming in an area in which he had not been trained, it was abundantly clear that Andrew is quite a brilliant guy. He grasped concepts quickly, even in areas beyond his expertise, and he asked extraordinarily insightful questions.

He single-handedly and independently initiated the analysis of the microarray experiments in my lab, which led to three publications in that area. Importantly, in the late 1990's, while the local community was talking about microarrays and the hype, Andrew was doing. In terms of intellect, demonstrated capacity for research and work ethic, Andrew was outstanding and it was clear that he has many of the attributes to be a successful PI.

Andrew then spent a couple of years at GeneData, where he was responsible for a number of microarray-related software packages and participated in a number of external collaborations with pharmaceutical companies (in which he provided the bioinformatics

support). He and I continued to collaborate on the transcription profiling of biliary atresia, a childhood liver disease. In this project, Andrew discovered that the transcription profiles in this disease suggest a link to situs inversus (an inversion of the lefty-right asymmetry). Interestingly, in 20% of biliary atresia patients, there are associated left-right phenotypes. These results led Andrew to the provocative hypothesis that biliary atresia is not in fact a disease of the biliary tree, but is a manifestation of some underlying defect in patterning.

Finally, I should comment on what I perceived as the most dramatic improvement in Andrew development as a scientist since he left my lab. In my group, Andrew worked rather independently and may not have as effectively communicated with others as well as he could have. As a result, at the time he left my group, I had worries as to his ability to interact with colleagues in the academic setting. I have been very impressed with his progress in this area. His communication style is now very professional, probably as a result of his experiences at GeneData as a Group Leader. The transformation that has occurred has been quite remarkable. In addition, his training in physical chemistry and modeling provides an excellent foundation for systems analysis, which is doubtless the future of bioinformatics.

With all this in mind, I must note the relative lack of productivity that he has had as an independent investigator in Singapore. I don't know the reason; there are tens of perfectly valid reasons that a new principal investigator would get off to a slow start, but it certainly caught my attention, as it doubtless did yours as well.

All said, I am confident that you would be extremely happy with Andrew as a colleague. His theoretical chemistry/physics background will bring a completely different perspective than would classical "DNA-sequence-based" bioinformaticians. Please feel free to phone me if you require further information.

Yours sincerely

A handwritten signature in black ink, appearing to read "Aled Edwards". The signature is fluid and cursive, with a large, sweeping initial letter 'A'.

Aled Edwards
Banbury Chair of Medical Research
Banting and Best Department of Medical Research
University of Toronto



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September 15, 2005

Dear Chair and members of Search Committee,

RE: Dr. Andrew Boris Goryachev

It is my great pleasure to provide this reference letter to support Dr. Andrew Boris Goryachev, who is keen to apply for the faculty position in microbial systems biology available at your department. I have been collaborating with Andrew on computational modelling of bacterial quorum sensing since September, 2003, shortly after he took up the position of Team Leader at the Bioinformatics Institute in Singapore. He has also been serving as an Adjunct Assistant Professor in the National University of Singapore since 2003, for which he constantly gives lectures to undergraduate and graduate students.

Andrew is a brilliant and well-trained computational scientist and has a strong interest in microbial systems biology. During our frequent oral discussions and email exchanges, I have always been impressed by his quick wisdom in understanding the details of complicated biological phenomenon but without losing the grasp of general mechanisms. Our common interest is the bacterial community behavior and its origin of evolution. In principle, a biological phenotype is the display of the collective functions of a set of orderly expressed gene products. However, many this kind of intracellular activities are known to be regulated at the community level. For example, the quorum sensing-dependent Ti plasmid conjugal transfer in *Agrobacterium tumefaciens* depends on production, release and sense quorum sensing signals, and these events lead to subsequent expression of a set of *tra* genes, which then enables the transfer of Ti plasmid from donor cells to recipient cells. The modern art of molecular genetics is not enough to explain why *A. tumefaciens* cells have to evolve the quorum sensing mechanism, which synchronizes the expression of *tra* genes among donor cells, to complete the conjugal transfer process; and how the bacterial cells could be synchronized in quorum sensing as they are varied in age and generation times, and hence in the critical concentrations of quorum sensing modulators. To address these important issues, Andrew cleverly used an integrated computational approach. He first developed a detailed model of intracellular



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control network and demonstrated that it functions as an “on-off” switch for expression of *tra* operon in responses to changing concentrations of quorum sensing signals. Based on that, he further assembled an agent-based stochastic population model in which each bacterial cell is given a unique copy of an intracellular network. As the stochastic model also monitors bacterial motion and cell divisions, it hence describes logically both the dynamics of individual cells and the population behavior in quorum sensing. This model predicts that the transition to quorum sensing requires a much higher threshold cell density in liquid medium than in biofilm, which is consistent with the reported experimental observations. More importantly, based on the model he proposed that *Agrobacterium* quorum sensing serves as the detector of biofilm formation, which seems to provide a reasonable explanation of its ecological and evolutionary significance. The key paper has recently been accepted in PLoS Computational Biology.

Andrew is also recommended as an effective communicator and excellent collaborator. He has demonstrated his strong ability to lead projects by effectively coordinating *in silico* analysis and wet lab experiments. He is currently supervising a team of 5 scientists including a PhD student. In less than 2 years time, his team got first batch of three papers published or accepted for publication with more in the pipeline.

In summary, Andrew has demonstrated his ability as a high calibre computational biologist and a strong principle investigator. I believe that his extensive knowledge and skills in computational biology, experience in teaching and supervision, and demonstrated track record would make him a strong contender for an assistant professor position in the area of Systems biology. I hereby provide my full endorsement.

Yours sincerely,

Lian-Hui Zhang, PhD
Principle Investigator &
Associate Professor



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Dear Dr. Brun,

Dr. Andrew Goryachev asked me to write a letter to support his application for a faculty position in your department, and I am more than happy to oblige.

I first met Andrew briefly when he was still a graduate student in a famous lab (his PhD supervisor is Ray Kapral of the University of Toronto), and have come to know him more closely since I took a leave of absence from Boston University and joined the Bioinformatics Institute (BII) in Singapore (BII is part of the Biopolis complex). In the course of his graduate studies Andrew successfully demonstrated the power of the modeling approach to complex systems. Based solely on his simulation results he predicted a totally new class of chemical patterns which was later found by several experimental groups.

Earlier this year, Andrew solicited my comments on his paper on bacterial quorum sensing which was about to be submitted for publication. I find the work solid, creative, and very interesting. It is an excellent example of how theory and computation can provide tremendous help in elucidating complex biological mechanisms. The parallel computational platform that Andrew developed to implement the quorum sensing project is a technical accomplishment in itself.

My discussions with Andrew (mostly focused on the abovementioned quorum-sensing paper) led me to believe that he welcomes interdisciplinary collaborations - and have demonstrated it so by working with experimentalists, biologists, and computer scientists in order to carry out the quorum-sensing project. Furthermore, his skill in independent research management is clearly exhibited by his excellent employment record in a bioinformatics company in Switzerland where he was in-charge of developing a gene microarray data pre-processing and analysis software that successfully reached the commercial market.

In Singapore, Andrew heads a group composed of a postdoc, several research associates, and PhD students. His reputation among students and research associates is that of a hardworking, intense, thorough, and clever fellow. I concur with these descriptions, and I have confidence that he would be an asset to any research institution, both at the team level as well as at the individual level. If one looks at Andrew's curriculum vitae closely, one sees a scientist equipped with the analytical prowess of a physicist who is not afraid to ask and tackle difficult biological questions. Andrew was raised in a strong Russian scientific tradition, and coupled with his familiarity and experience in working in Canada, Europe and Asia, he should clearly be somebody to pay attention to.

Andrew and I have already started regular discussion on a possible collaborative project involving TGF- β signaling. If you have further questions, please do not hesitate to contact me by email (baltazar@bii-sg.org or bdaguda@bu.edu) or call me at +65 6478 8298.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Baltazar D. Aguda', written in a cursive style.

Baltazar D. Aguda



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September 28, 2005

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Dear Dr. Brun:

I am writing this letter of reference on behalf of Dr. Andrew Goryachev. I have known Dr. Goryachev since 1999 when we became collaborators on a cDNA microarray project at the University of Toronto, Canada. I highly recommend him for a position in your Institution.

We collaborated on a project examining gene expression in patients with extrahepatic biliary atresia and compared it with normal human liver and diseased liver samples in order to obtain some insight into the etiology and pathogenesis of this disease. It is the most common cause for liver transplantation in children. Dr. Goryachev provided the essential bioinformatic analysis on the data derived from the microarrays performed on our human liver samples. He used both hierarchical and k-means clustering as well as principal component analysis. The majority of the work was done in Toronto, however, he continued to work on this project in his spare time after taking a job with GeneData AG in Basel Switzerland. It was due in part to his continued efforts with respect to our collaboration that this project was finished despite the miles located between our Institutions (at the time I was working at the University of North Carolina and he was in Switzerland). Our manuscript involving this work was published in *Hepatology* 2003;38:567-576.

With my not having a background in bioinformatics or statistics, Dr. Goryachev was extremely patient and knowledgeable in explaining to me the analytical methods used for our paper at a level which I could understand. Thus, I feel that he would be able to teach on his subject with clarity.

Over all it was a pleasure to work with Dr. Goryachev and without his scientific input and his drive our microarray project would not have been completed.

If you have any questions please do not hesitate to contact me.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'K. Furuya', with a long horizontal flourish extending to the right.

Katryn Furuya, MD, FRCPC
Associate Professor of Pediatrics,
Penn State University,
Milton S. Hershey Medical Center