Biocomplexity Faculty Serach Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University, Swain Hall West 117
Bloomington IN, 47405-7105

**Re: Faculty Position/ Biocomplexity** November 4, 2003

Dear Sir, Members of the Search Committee,

In applying for a faculty position I am pleased to offer your Institute my expertise and enthusiasm for computational biology, in research and in teaching.

I obtained a PhD degree in mathematics at the University of Göttingen/ Germany in 1993, specialising in mathematical thermodynamics; soon after that I began to devote myself to projects in behavioral and biomedical sciences, beginning as a data analyst. During my work and research over the last 7 years I have had ample opportunity to refine my skills in addressing issues in biomedical research - collaboratively with clinicians and researchers - that profit from the biologically informed use of computational and bioinformatic tools. At present I am working on the level of a senior research associate in microarray gene expression studies at the University of Toronto.

I have formulated a research agenda that focuses on mathematical biology in a general sense, encompassing microarray gene expression studies, statistical genetics, and neurobiology. This program would extend my current work in genomic investigation of posttranscriptional gene regulation, and at the same time build on my prior work in physiological models for behavior and neural circuitry. From the biocomplexity perspective, it projects new ideas in nonparametric statistics towards distinguishing primary and secondary effects in gene expression regulation and functional annotation of genes and protein domains (see the attached FunSpec article in BMC Bioinformatics, 2002).

If needed, I would be able to teach courses in bioinformatics and computational biology in a resourceful way. My analytical skills and expertise together with my well-developed talents in communicating with professionals from various backgrounds would very likely strengthen your institution's unique theoretical and practical agenda. I'll be happy to send you further references and information on request and look forward to hearing from you.

Best regards

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# A Research Agenda in Bioinformatics and Computational Biology

***Managerial/ Administrative:***

For a researcher in bioinformatics, the constant and close contact with biology is essential in developing new computational and formal methods that are relevant for discovery. For original research in the area of bioinformatics, access to facilities of data generation is needed, i.e. a core "wet lab". As a prospective leader at your department towards pioneering new methods of bioinformatics I propose

- to establish and maintain core lab facilities for generating genomic gene expression data with academically or commercially available cDNA or oligonucleotide microarrays, or have access to such facilities as a PI. For this, financial support is needed for 1 postdoc and 1 technician, both with university degrees in Molecular Biology or a related field.

- to establish a bioinformatics lab for the analysis of high-volume genomic data and for modeling and simulation studies. Here, financial support for 1 technician/ system administrator is needed, with a university degree in Computer Science.

***Scientific:***

As a postdoctoral fellow at the Hughes Lab/ Banting and Best Institute Toronto I designed and applied a new method to investigate the genome-wide turnover of messenger RNAs (mRNAs). This method is based on cDNA microarrays and uses rank and goodness-of-fit statistics to identify groups or categories of genes that represent specific biological functions affected in their mRNA life-time. I propose to apply this method in original research projects in the following areas:

Disturbances in mRNA stability as causative factors in human oncogenesis. - Mutations in many human protooncogenes and lymphokines are pathological by affecting the life-time of mRNAs. Similarly to the yeast mutants used in this study, human genes can be knocked out in tissue culture cells using small interfering RNAs (siRNAs). We determined 28 human genes - many of which documented in the cancer research literature - that are homologous to yeast genes involved in mRNA turnover.

MRNA turnover is regulated by the 3' and 5' untranslated regions (UTRs) that flank the protein-coding body of the mRNA. The cis-acting sequence and secondary RNA structure motifs in these regions both serve as anchors in subcellular localisation and lend specificity to trans-acting factors (RNA-binding proteins) in mRNA turnover. The analysis of RNA secondary structure motifs requires sophisticated mathematical algorithms for their detection and further statistical analysis in their phylogenetic comparison and evaluation. In the human transcriptome, the issue of regulatory regions in mRNAs is largely unaddressed, but holds great potential in enhancing the understanding of regulatory variation in general, and as a contributing factor to complex human diseases. (While only ~1.5% of the human genome codes for proteins, it is estimated that a further 4-4.5% represent noncoding regulatory DNA.) One aim of my research on mRNA stability will be to establish an accurate inventory of human mRNA UTRs.

Related subjects of my work in this area should include:

- Integrating genomic expression profiles of human diseases with standards of reliability and reproducibility that are used in clinical trials and in FDA drug research regulation.

Once this research program is established, opportunities will likely arise to link bioinformatics with other methods in computational modeling and behavioral/ psychological research. I am prepared to pursue emerging opportunities in this direction, in collaboration with neuroscientists, based on my considerable success and experience in the area of behavioral data analysis and computational neuroscience. –

***Teaching:***

There is no higher task than educating young people and provide challenges for expectant minds to refine both intellect and character. In bioinformatics, the challenge consists in balancing the development of skills in operating with high-volume data, on the one hand, and nurturing the respect that is essential for a student to learn and to apply in dealing with any living being that he or she will encounter in his/ her career. This balancing aim can be reached, for instance, by complementing and presenting a bioinformatic subject such as BLAST search with information on the phylogenetic background of a nucleotide sequence, or by acquainting the student at an early stage even with the philosophical issues that are at the core of integrative efforts in genomics such as Gene Ontology - and, maybe most importantly, by gathering data for subsequent bioinformatic analysis in projects of field work. In summary, bioinformatics needs to be presented to the next generation of practitioners not only as an assemblage of databases, but as enabling to pose new questions on origin and destination of biological entities, in a more comprehensive way than previously possible. Those questions will arise from nowhere else but the student's mature mind and ability to analyze and thoroughly reflect on a subject of study or work.

Toronto/ Canada, October 2003


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