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

November 24, 2003

Dear Professor de Ruyter van Steveninck,

I am writing to apply for the recently advertised Assistant Professor position in the Biocomplexity Institute at Indiana University, Bloomington. My previous training and research interests in computational neuroscience and nonlinear dynamics fit those described in the advertisement. As an independent investigator, I plan to study the dynamics of biological neural networks, responsible for motor control and information processing.

I become interested in nonlinear dynamics of neural networks as a result of my graduate work with Dr. Mikhail Rabinovich at the University of California, San Diego and Institute for Applied Physics of the Russian Academy of Science. The focus of my thesis work was on chaotic and regular dynamics of mathematical models of networks of coupled nonlinear oscillators. I studied how spatial inhomogeneities can alter network's dynamics. The primary focus of my postdoctoral fellowship with Dr. Kopell at Boston University and Dr. Sigvardt at the University of California, Davis, is on the mathematical description of the basal ganglia networks, which are involved in the control of motor programs in mammals. I developed a biophysically-based mathematical model of basal ganglia motor control circuits as well as time-series analysis methods. The latter are aimed at characterization of intermittent dynamics of brain-muscles synchronization in order to understand the structure and dynamics of basal ganglia motor control circuits. This work has given me an appreciation for the power of cross-disciplinary collaboration of mathematicians and biologists.

I plan to develop mathematical theory of neuronal networks, which control motor programs in mammals. My primary approach will be to develop two interconnected research projects. One is aimed at the construction of the realistic models of the real networks, their numerical analysis and utilization of dynamical systems methods to analyze generic types of network's behavior. The other is to support the first one by the analysis of the complex oscillatory brain dynamics data observed in patients. Please, see details, provided in the research statement, which is included. While there is a strong practical interest in the development of there projects, grounded in the fact, that these networks are affected by Parkinson's disease, these projects will serve an advancement of a much broader fundamental issue of neuroscience: identification of generic features of the structure and dynamics of living networks, which make them very stable and, at the

same time, very adaptable to complex environment and amenable for control and information processing.

I hope that you will consider my application for the opened position. My research goals complement those already established in the Biocomplexity Institute, while adding a new perspective to the studies in biocomplexity. I have included my research statement and curriculum vitae in this application. Recommendation letters should follow soon from Dr. Karen Sigvardt at the University of California, Davis (kasigvardt@ucdavis.edu; 530-757-8520), Dr. Nancy Kopell at Boston University (nk@bu.edu; 617-353-5210), and Dr. Mikhail Rabinovich at the University of California, San Diego (mrabinovich@ucdavis.edu; 858-534-6753).

Thank you for your time and consideration.

Sincerely,

Leonid L. Rubchinsky, Ph.D.

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Research Statement

Leonid L. Rubchinsky, Ph. D.

My research interests lie in the area of biomathematics and nonlinear dynamics. I am using mathematical and computational methods to analyze the dynamics of the nervous system to get insights into its function. The focus of my research is on the dynamics of networks of nonlinear oscillators and neuronal assemblies.

Research history

Dynamics of nonlinear oscillatory media

Periodic temporal evolution of spatial disorder – a state en route from static disorder to spatio-temporal chaos in nonlinear oscillatory media was identified and characterized in the framework of the complex Ginzburg-Landau equation. Since complex GL equation is a generic model for behavior of any distributed system in the vicinity of Hopf bifurcation, it may be applicable to dynamics of a wide class of real spatially distributed oscillatory systems near the onset of instability of static spatial distribution.

Modeling of simple neural systems

An approach to model simple neural systems as finite automata was developed and applied to the modeling of stomatogastric central pattern generator of lobster – well-known model preparation that has been widely used to study mechanisms of central rhythm generation in the nervous system. This approach allows studying how dynamics of central pattern generators is affected by variation of parameters with minimal computational efforts.

Dynamics of networks of coupled nonlinear oscillators

Studies of chains of oscillators with different types of spatial inhomogeneity led to conclusions on how this inhomogeniety (whether introduced into a system as a spatial variation of parameters or formed in nonlinear oscillatory network under appropriate inhomogeneous initial conditions) may affect the behavior of oscillators. I found that chains of chaotic bistable oscillators can establish regular dynamics in strongly inhomogeneous regime, while preserving chaos in homogeneous regime, and described networks, in which an introduction of spatial inhomogeneity into parameters of the network increases intensity of oscillations. I also considered a transition from propagation to non-propagation of fronts in bistable active media. An intermittent dynamics of fronts was described and the types of underlying intermittency were characterized.

Current research

My current research is concentrated on dynamics of basal ganglia – brain nuclei, which control motor programs and are impacted in Parkinson's disease (characterized by tremor – oscillations in limbs and inability to control motor programs properly). Despite the large amount of factual knowledge about basal ganglia at all levels – from cells to behavior – little is understood about principles of function of basal ganglia in Parkinson's disease (and other diseases involving basal ganglia) and even in normal conditions. There is mounting experimental evidence that complex collective dynamics of interaction of various ionic channels and various cells are responsible for normal basal ganglia operation and pathological variations of these dynamics are responsible for disease.

Minimal models of basal ganglia motor control circuits

A minimal biophysically-based model of basal ganglia motor control circuits was developed by me. This is the first attempt to develop a mathematical model of basal ganglia circuits controlling motor programs, which connects the cellular biophysics with the motor program execution and, thus, behavior. The model consists of sets of coupled ODEs, each describing dynamics of individual groups of basal ganglia cells. This

model makes it possible to study basal ganglia motor control with mathematical and numerical methods. Importantly, the model developed generates several predictions, which can be tested experimentally, and which may be relevant to the possible therapy in Parkinson's disease.

Synchronous dynamics of parkinsonian tremor

Synchronization phenomena in the experimentally observed oscillatory electrophysiological data from parkinsonian patients are studied to reconstruct the structure of the neural networks, which control motor programs in health and supports tremor in pathology. A methodology for detection of short-term phase synchrony between tremor in the limbs and tremor-related activity in the brain was developed and now we are studying the structure of this variable, intermittent synchronous activity. I collaborate with neurologists and neurosurgeons from UC Davis School of Medicine and Kaiser Permanente Medical Center in Sacramento, and participate in brain surgeries in parkinsonian patients as a consulting electrophysiologist, performing electrophysiological recordings from brain and muscles.

Influence of brain surgeries on brain activity of parkinsonian patients

A study of small group of parkinsonian patients, who have undergone a second surgical intervention in basal ganglia revealed the differences in the basal ganglia activity of these patients and the same (and other) patients during the first surgery. This has allowed us to making conjectures about the mechanisms of anti-parkinsonian surgeries, which is still an open question (in spite of usage of these surgeries in clinical practice).

Research plan

Modeling basal ganglia motor control circuitry

I propose to continue modeling of basal ganglia motor control circuitry. The developed minimal model (a result which has been recently published in PNAS) appears to be scalable. The goal is to develop biologically relevant large realistic network models (in the form of coupled ODE systems). They should adequately describe interactions of many motor programs in basal ganglia and will allow us to study how various modifications of network elements and topology of coupling (which represent different changes in real basal ganglia) affect them. They also should be able to lead to experimentally testable predictions. These realistic models will be compared to available experimental and clinical data (including our own data) on basal ganglia dynamics and motor control in parkinsonian patients and animals. The other goal is to reduce these complex network models to more simple models, such as coupled maps lattices and low-dimensional ODEs, which would capture generic behavior of the network in the vicinity of some crucial bifurcation points. Then analytical and numerical studies of bifurcations in these simple dynamical systems will be carried. I (together with Dr. Sigvardt and Dr. Kopell) plan to write an NIH (or possibly NSF) grant application to develop and study such network models by numerical simulation and to perform reduction to low-dimensional ODE systems, which may yield generic results about principles of the function of such neuronal motor control system as basal ganglia. At minimum, this project will require modest computing facilities and participation of graduate students. Extensive present collaboration with clinicians studying Parkinson's disease will provide an extremely important background for relating modeling results with experimentally observed reality.

Intermittent synchronization in parkinsonian tremor and structure of tremor-supporting networks

While characterization of tremor in limbs and tremor-related activity in brain is of independent interest for neurology, Parkinson's disease and its motor symptoms constitute a unique nature-created experiment, which presents a window for looking at the basic principles of the basal ganglia motor control operation. The methods we developed to analyze tremor dynamics point to the intermittent character of tremor oscillations and synchronization of them. I will continue the work on characterization of intermittent tremor dynamics.

The goal here is to understand the nature of this unstable, variable behavior and I am working on hypothesis why transiently synchronous oscillations can arise in the networks, controlling motor programs. Mathematically, it is interesting to understand whether this tremulous behavior corresponds to the dynamics in a vicinity of some "simple" manifold, which could correspond to completely synchronous state, and study associated instabilities. It may happen that some specific topological organization of the network is needed to exhibit such a behavior. Understanding this problem will help to construct large-scale model networks and to derive simple generic models for motor control or tremor oscillations, which can be analyzed in the framework of dynamical systems theory. The analysis of these generic systems, their stability and bifurcations, will assist our understanding of neuronal motor control.

The plan for the future is to advance both modeling and data analysis research to the level at which model networks will be able to adequately describe complex dynamics of synchronization observed *in vivo*. There is a potential for building up new collaboration with mathematicians, studying dynamical systems and with neurologists and neurophysiologists interested in basal ganglia disorders and motor control. A particularly interesting line of research would be a biomedical engineering project aimed at optimization of deep brain stimulation for Parkinson's disease and other disorders. At the present time, deep brain stimulation is characterized by application of basically the same large-current stimulus to all patients and has been a purely empirical procedure without theoretical ground. Understanding of basal ganglia dynamics may open the way for developing deep brain stimulation techniques, which will be a small-force control of basal ganglia dynamics. This approach can be potentially extended to other types of neuronal systems.

The aforementioned set of research projects provides ample opportunities for participation of graduate and undergraduate students of different backgrounds: from those who are interested in theoretical biophysics and nonlinear dynamical systems to those who are interested in electrophysiology, data analysis or numerical simulations of large networks.

Further perspectives

My research plans are devoted to the development of biophysical description of neuronal systems, to the much-awaited advancement of biological science from the level of verbal reasoning and descriptive data to the level of physical theoretical background and mathematical rigor. While these plans are concentrated on the basal ganglia and Parkinson's disease (in particular due to the wonderful collaboration with biologists and clinical scientists at UC Davis), the long-term goals are not limited to the studies of basal ganglia. These projects will serve an advancement of a much broader fundamental issue: identification of generic features of the structure and dynamics of living networks, which make them very stable and, at the same time, very adaptable and amenable for control and information processing. Similar phenomena in neuronal networks are observed in many other areas of science, in particular, life science (gene regulation pathways, protein networks and intra- and inter-cell signaling networks etc.). There is some evidence, that what distinguishes these living networks is a specific topology. The dynamics of the networks with "real" topology (e.g. scale free networks, small-world networks) and formation of these networks appears to be an important direction of future research.