UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

CENTER FOR NEUROSCIENCE
(530) 757-8708
FAX: (530) 757-8827

1544 NEWTON COURT
DAVIS, CALIFORNIA 95616

November 24, 2003

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

Dear Members of the Biocomplexity Faculty Search Committee,

I am writing in strong support of Dr. Leonid Rubchinsky's application for a tenure-track position in the Indiana University Biocomplexity Institute at Indiana University Bloomington. Dr. Rubchinsky's expertise is in mathematical biology, particularly computational neuroscience.

Dr. Rubchinsky has been a postdoctoral fellow with me since March 1, 2001, working collaboratively with me and Dr. Nancy Kopell, my long-time mathematics collaborator at Boston University. His focus is on the development of biophysically based dynamical models of the basal ganglia-thalamocortical networks and the dysfunction of these networks in Parkinson's disease.

Dr. Rubchinsky has an excellent academic record. He received his B.S. in Physics from University of Nizhny Novgorod, Russia in1995. Upon graduation Dr. Rubchinsky received a Russian Presidential Fellowship, which is a highly prestigious national award given to only 50 students in Russia per year, which gives the awardees $35,000 of support for studies at an academic institution anywhere in the world. Leonid chose to study applied physics at the University of California at San Diego, and received his Master's Degree in Physics. It is at the UCSD that Leonid began his work in computational neuroscience. Dr. Rubchinsky also received a number of other awards during graduate school, all of which were highly competitive national or regional awards.

Dr. Rubchinsky has been in my lab for almost three years. As I was trained as a biologist and neuroscientist, my contribution to our collaboration and my comments on Leonid's abilities are from a biologist's perspective. Dr. Rubchinsky has a comprehensive knowledge of the neuroscience literature relevant to motor control, the basal ganglia, cellular biophysics and computational models in neuroscience. His knowledge has developed from his avid and regular reading of the relevant neuroscience literature, his discussions with me and Nancy and his attendance at seminars here at the

Center. He has also attended a number of workshops and meetings, most importantly a two-week formal workshop on Dynamics of Neuronal Networks: From Biophysics to Behavior, where the faculty included many of the leaders in field of computational neuroscience. This past spring Dr. Rubchinsky was invited to present his recent modeling studies at the workshop on the Sensory-Motor System at the Mathematical Biosciences Institute at Ohio State University, a workshop that brought together leading researchers studying sensorimotor integration, and focused primarily on work on the basal ganglia. He has also attended the Society for Neuroscience meetings and Computational Neuroscience meetings where a young person with Leonid's energy and enthusiasm benefit greatly from the depth and breadth of material presented. When Leonid returns from these meetings he always gives our lab an amazing (at least to me) summary of the presentations that he saw and conversations that he had about results or methods of interest to our research program.

Dr. Rubchinsky has now taken the lead in the computational component of my collaborative research with Nancy Kopell - our theoretical work on Parkinson's Disease. He has done most of the work to develop our first biophysically based network model of the circuitry. To put that work in the context of neuroscience: Much is known about the cellular biophysics, anatomy, neurophysiology, pharmacology and behavioral output of the basal ganglia motor circuits in the brain that are dysfunctional in Parkinson's disease (PD). However, it is not understood how the loss of dopaminergic innervation of these circuits, the underlying deficit of PD, results in its devastating symptoms. Current models of basal ganglia motor circuits are simple "box and arrow" models representing the anatomical interconnections between the component structures of the network. Therefore the power of these static models in providing explanations of the motor symptoms of PD has severe limitations, primarily because of the dynamic nature of the pathophysiology and motor symptoms of PD. Our modeling efforts are focused on the development of a biophysically based dynamic computational model of the basal ganglia network that incorporates the vast amount of experimental data available at different levels (from biophysics to behavior) to provides a single framework for investigating the mechanisms underlying of different motor symptoms of the disease.

While I provided the biological framework and Dr. Kopell provided the primary hypothesis about the over-all structure of our initial model, Leonid has done all of the work that led to the implementation of our first efforts, the results of which were recently published in PNAS and were presented at the recent Society for Neuroscience meeting, and were well received when Leonid presented them at the workshop in Ohio. In the model the biophysical properties of the neurons in the network are represented by coupled ODEs and the output is seen as patterns of neural activity that can be interpreted as driving particular types of behavior, either normal or parkinsonian. These first efforts are very interesting, as they have led to predictions about the structure of the network and the contribution of particular biophysical properties to network behavior. Dr. Rubchinsky's doctoral work involved a number of studies of the dynamics of inhomogeneous networks of nonlinear oscillators. The knowledge and intuition he gained in his studies of nonlinear oscillatory networks in his graduate work contributed greatly to his success in his most recent work. While I cannot speak directly to Dr. Rubchinsky's mathematical abilities, I do know that he worked very independently on the development of this model and was creative and persistent in seeking solutions to the problems encountered along the way.

Both testing and development of the model involve comparing the model output to real output - spiking patterns observed within the structures being modeled and the timing within the networks

relative to movement during behavior. Dr. Rubchinsky's abilities and expertise have been critical to our work in two other aspects of our research program which are relevant to his career goals. First, Leonid, after a period of training with me, has recently become a consulting electrophysiologist for our functional neurosurgery cases. We are responsible for implementing the microelectrode recordings that are necessary to map the borders of the basal ganglia and surrounding structures before the neurosurgeon lesions these structures or implants stimulating electrodes into them. This has given Leonid first-hand experience in recording and interpretation of electrophysiological signals and also provided him with direct knowledge of the patterns of activity that we use to constrain our models. While this experience is not absolutely necessary for Leonid to pursue his research goals, I believe that first-hand knowledge, at some point, greatly strengthens the biomathematician's expertise and intuition in terms of the nature of the scientific questions and the biological data and the difficulties associated with each.

A second contribution of Leonid's is in the development of data analysis techniques. The time scale and nature of the patterns of output from the nervous system are not always visually observable, but instead require sophisticated analysis techniques for full characterization. Leonid has contributed, along with Dr. Jose M. Hurtado, another postdoctoral fellow in my lab, to the development of a statistical method for the detection of phase locking in pairs of neural signals, data that we collect during the surgical procedures. These methods are particularly important to our studies because phase entrainment can be of very short duration and because phase entrainment between neural signals is relevant to the nature of coupling and dynamics of the networks under study. A manuscript on these methods has been submitted and another manuscript on the properties of the basal ganglia-thalamocortical network revealed by the data analyzed in this way is in revision and soon to be submitted.

It is really quite remarkable that Dr. Rubchinsky has been so productive and made so many contributions since he joined my laboratory, when he had to devote so much time to learning basic neuroscience, all the literature related to the basal ganglia and PD and to training in electrophysiological recording techniques. However, given the number of studies that he published in his five years as a graduate student, I shouldn't be surprised. He came to my lab having read (and understood) a good proportion of the most relevant literature and was, therefore, able to immediately begin working on the rudimentary components of the model (models of the cellular biophysics). He is now working to scale up the model to a network with larger number of neurons so that we can address other hypotheses that we have about the relationship between the pathophysiology of the nuclei in the network and the activity of the normal network. Dr. Rubchinsky is also currently working on several other projects (some near completion), including one with Dr. Hurtado on the intermittent nature of tremor related units in the brain, and one with a student in the lab on the implications for network function of an interesting finding from our neurosurgical cases. I should also mention that during the past year Dr. Rubchinsky has provided a significant proportion of the ideas and written text for a grant proposal on modeling dynamics of the basal ganglia motor control network and its dysfunction in PD. He seems to write both manuscripts and grant applications easily and efficiently. Leonid's command of the English language is remarkable, his vocabulary more sophisticated that his native English-speaking peers, and most of what he writes needs little editing (except for prepositions, the rules for which are somewhat illusory).

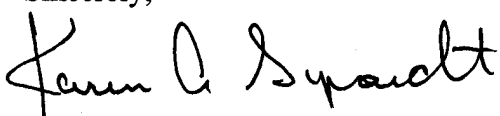
Dr. Rubchinksy and I plan to continue our collaboration into the future. Leonid has taken the lead in our current work and Leonid is welcome to take this project as his own, as my contributions to computational neuroscience have always been in providing the biological framework and the data needed to constrain the models. Dr. Kopell, as well as Dr. Conrad Pappas and Dr. Vicki Wheelock, our physician colleagues in the functional neurosurgery program, are all very supportive of Leonid's continued efforts in this regard.

I cannot comment directly on Dr. Rubchinsky's abilities as a teacher in a formal classroom, though I do know that he has done a significant amount of teaching, both as a lecturer at University of Nizhny Novgorod and as a teaching assistant at UCSD. Nonetheless, I can comment on some of his skills and abilities that are relevant to teaching. Leonid has played an important part in the education and training of the students in my lab. He has kindly given hours of his time to support and guide students in experimental design, statistical analysis and interpretation of results. He is very good at translating the complex ideas and techniques of nonlinear dynamics and neuroscience into language that the students can understand. He is respectful and patient, and is very good at providing encouragement as well as giving constructive feedback. Leonid is an always an active and interested participant in intellectual discussions, in the lab, around the Center for Neuroscience and at meetings. He asks penetrating questions and is very effective at communicating his own ideas.

In summary, Dr. Rubchinsky is a wonderful and exceptional young colleague with a very promising future; he has contributed enormously to the success of my research program. He has a broad-based knowledge of mathematics, computation and neuroscience and excels in both the creative and practical aspects of research. He is very self-disciplined, sets realistic goals, and has shown a strong personal commitment to successfully completing the work that he undertakes. Leonid is energetic and enthusiastic about both work and life in general, loves discussion, but is always respectful of other's views. I am absolutely certain that he will be an excellent academic colleague, lecturer and mentor and a wonderful addition to your department faculty.

I give him my highest recommendation.

Sincerely,



Karen A. Sigvardt, Ph.D.
Adjunct Professor of Neurology
Center for Neuroscience
University of California Davis
Phone: (530) 757-8520
E-mail: kasigvardt@ucdavis.edu