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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 117
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Dear Dr. de Ruyter van Steveninck:

It is a great pleasure to write on behalf of ***Sridhar Raghavachari***, who has been a postdoctoral fellow in my laboratory for the last 3 years. As you may be aware, Brandeis has a strong program in computational neuroscience. As a result, I have met many young people in this field. Of these, I would put Sri near the top of this group. I hold this opinion for several reasons. First, Sri has had an unusually high degree of previous training in mathematics and physics, which he puts to very good use. When particular types of computation are required, Sri is able to classify them mathematically and consult the mathematics and physics literature about how best to deal with such computations. As a result, Sri comes rapidly to technically sound and rigorous methods. Since he is adept at mathematics, he can derive new statistical or analytical tests as needed to suit the particular problem. Second, Sri is a very quick learner and has had no reluctance to jump into new problems. As you will see below, Sri has been involved in 5 very different projects in my laboratory, making a very strong contribution in each case (and leading to publication). It seems that within weeks after digging into topic he is knowledgeable and wise about it. Thus, Sri has developed expertise in an unusually broad range of topics in computational neuroscience. Finally, Sri has a wonderful warm and competent way about him. As a result, Sri is the person that people turn to for advice and insight into their scientific problems. These qualities make him an excellent collaborator.

I would now like to review the specific contributions that Sri has made in my laboratory. Since all his papers have been collaborative, I will indicate what Sri has contributed in each case.

1. **Working memory analyzed by intracranial recording arrays**. This methodology generates a formidable amount data; the local EEG is recorded at up to 256 sites at high time resolution during repeated cognitive tests. Sri developed new ways of filtering the data and detecting interesting patterns of activity linked to cognitive performance. It was this that led to his discovery of the phenomenon of theta "gating", the sharp increase in theta power at the beginning of the working memory period and its decline at the end. Sri developed statistically rigorous ways to detect brain sites where gating occurred. Sri is

clearly the "lead person" in this analysis project and is the first author on our article in ***Journal of*** Neuroscience. Sri has published another article in this area with Kaplan and Kahana. Sri is now working a final paper in this series which analyzes the synchronization between nearby and distant cortical sites. Again Sri developed sophisticated methods related to principle component analysis for detecting common mode signals (but with phase offset) at nearby sites. This will be an important paper because it demonstrates why theta is so difficult to detect at the scalp (cortical theta is NOT synchronized over large areas). Furthermore, it appears that the paper will provide a new explanation of the evoked potential (cortical theta is reset in a spatially coordinated process over distances of several cm). In summary, Sri now has very solid credentials of EEG data and will have made a series of important contributions to the understanding of the cognitive role of theta oscillations.

2. **Neural integrators consisting of bistable units.** This was a project done in collaboration with Alexei Koulakov, then at Salk (now at Cold Spring Harbor), and Adam Kepecs in my laboratory. Sri developed a simulation platform to look at the network interactions of biophysically realistic neurons (voltage-dependent conductances; complex synaptic conductances; several neuronal compartments). This platform allowed us to determine the conditions that lead to bistability of individual neurons and allow a recurrent network to produce integration. In my lab, Adam and Sri contributed equally to this work, which has appeared recently in ***Nature Neuroscience***. The underlying issues of how synaptic biophysics leads to functionally important network behavior is one that fascinates Sri. He is developing a project on his own trying to understand how integrator function could explain properties of temporal perception. I have been impressed with the avidness with which he has attacked the psychological literature on this issue.

3. **Phototransduction cascades.** In the ongoing work on phototransduction in my laboratory, we developed an intuition that feedback regulation might explain some surprising experimental observations. The pathways were too complex to be sure about this and we needed a model. Literally within minutes, Sri found the appropriate software for analyzing coupled differential equations and forced us to define each reaction involved in the transduction cascade. Over the course of a week, he developed a useful model by which we could test our intuitions. This work is described in Lisman, J.E., Richard, EA, Raghavachari, S, Payne, R.: Chapter 31-Simultaneous roles for Ca^{2+} in excitation and adaptation of Limulus ventral photoreceptors, in Advances in Experimental Medicine and Biology – Photoreceptors and Calcium, 2002, edited by Wolfgang Baehr and Krzysztof Palczewski; 514:507-538.

4. **The microphysiology of quantal transmission.** Experimental work in our laboratory has pointed us to the possibility that transmission at hippocampal synapse may be multiquantal. But how exactly would the glutamate released by two nearby vesicles interact? There have been many models of glutamate diffusion in the cleft and the binding of glutamate to AMPA channels. However, in reviewing the literature, we became aware that recent dendritic recordings by Magee revealed that the rising edge of the mEPSC is an order of magnitude faster than previously thought. We therefore set out to develop a new model that would be consistent with this finding, but also constrained by the multitude of additional knowledge about glutamate release, glutamate diffusion, and the activation and desensitization properties of AMPA channels. Sri has been dogged

about identifying these constraints and developing a model that can account for them all. Many modelers are satisfied to develop either an analytical model of the response (which is fast to compute, but gives no insight into variation) or Monte-Carlo models (which are slow because they follow each molecule, but do give insight into variation). Sridhar quickly developed both classes of models. As I write this letter, we are coming to the conclusion of this work. I believe it gives fundamentally new insight into the functional significance of the cooperative activation of the channel by glutamate, its desensitization properties and the glutamate "spike" that exists in the cleft for 10's of microseconds after vesicle fusion. The model also shows that only AMPA channels localized near the site of release are efficiently activated, accounting for the fast rise time of the mEPSC. This localization has important implications for multiquantal release: multiple quanta released at the same synapse act on independent groups of AMPA channels and therefore can summate effectively. Of further importance is the finding that the correlation of rise-time and amplitude of mEPSCs cannot be explained according to the hypothesis that amplitude variability stems from variability in vesicle glutamate content. This hypothesis has recently been proposed by leaders in the field (Franks, Stevens and Sejnowski). However, we find that the rise-time/amplitude correlation can be explained on the assumption that some mEPSCs are multiquantal, as recently proposed at other central synapses. This explanation has been pursued by Sri and satisfactorily explains a broad range of experimental results. This is work on which Sri will be the first author has been submitted to J. Neurophysiology.

5. **The "up-state" and "down-state" of cortical neurons and their role in contextual processing and schizophrenia.** This work again relates to the biophysics of the NMDA channel: its voltage dependence can lead to bistable membrane properties. Sri and Adam Kepecs have done this work on their own without my input. The focus on this work is not on recurrent network connections (as in project 2), but on the interaction of the intrinsic bistable properties with external inputs representing specific information and "contextual information". Through NMDA-mediated processes, the contextual input puts the neuron in the "up state", where it is gated "on" to respond to the specific informational inputs. Again, what fascinates Sri about this is the potential to relate this biophysical computation to cognitive functions in which contextual gating plays a role. Sri has plans to pursue this line of research, especially as it relates to the NMDA hypofunction theory of schizophrenia and the known abnormalities in contextual processing in schizophrenics. In recognition of the importance of understanding this linkage to Schizophrenia, Sri was recently award the prestigious Young Investigator Award by NARSAD.

In closing, I wish to emphasize what a pleasure it has been working with Sri. He has both a brilliant mind and the nitty gritty capability of bringing a vast array of methods to bear on a problem. He is a perfect gentleman. He has a deep love for the rigor of science and the passion to move it forward.

Sincerely yours,

John E. Lisman, Ph.D.
Professor, Biology Department