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April 27, 2012

David Sheinberg, Ph.D.
Search Committee Chair
Department of Neuroscience
Brown University
Providence, RI 02912

RE: Robert Haslinger, Ph.D.

Dear Search Committee:

I am pleased to offer my support for the appointment of Robert Haslinger, Ph.D. for a tenure-track position as Assistant Professor in the Department of Neuroscience at Brown University. I have known Rob, now for 7 years. During this time he has been a post-doctoral fellow and more recently, an Instructor in the Martinos Center for Biomedical Imaging in the Department of Radiology at Massachusetts General Hospital (MGH) and Harvard Medical School. During this time, Rob has developed several, new computational neuroscience results that offer new perspectives on how ensembles of neurons represent and transmit information. Rob's accomplishments in understanding neuronal networks make him a superb selection for this position at Brown University.

In his first neuroscience project, Rob studied how the temporal dynamics of ongoing Up and Down states influenced the sensory evoked response of rat somatosensory (barrel) cortex to vibrissae deflection. During general anesthesia, the barrel cortex exhibits strong, low frequency (< 1Hz) oscillations in local field potential (LFP) caused by synchronized depolarizations and hyperpolarizations (Up and Down states) of neuronal membrane potentials. Using LFPs and multi unit activity (MUA) recorded simultaneously by linear depth electrodes, Rob showed that the size of the MUA response varied smoothly as a function of LFP phase. Prior studies, both at the population and single neuron levels, had only considered the response as a function of Up state, versus Down state. That is, only in terms of the LFP's polarity. By showing that there was in fact a continuum of response properties of the neuronal ensemble, Rob's work makes explicit the importance the ongoing dynamics of the neural system in characterizing its response, particularly in experiments performed under general anesthesia. This work was published in the *Journal of Neurophysiology* and inspired single neuron studies of Up and Down states.

In a subsequent computational study, Rob developed a method for inferring the dynamical states of single neurons from their output spike trains. The approach clustered temporal patterns of spike histories based upon how they predicted the future evolution of spike trains, and generated a hidden Markov model (HMM) that used the clusters as predictive states. Firmly grounded in information theory, these HMMs not only captured the computational structure inherent in the spike train, they could be used to estimate the computational complexity of the spike train. This approach complemented more traditional analyses based upon firing rates, or spike train entropy. Rob published this work in *Neural Computation*.

Historically, the problem of neural coding has been most extensively studied in the context of single neurons. In the visual systems the dogma is that primary visual cortex (V1) neurons receive input from small regions of the visual field called their "classical receptive field" (CRF) and are insensitive to stimuli outside the CRF (in the "surround"). However, this conclusion has been reached using simple grating-type stimuli. Natural scenes possess strong spatial correlations. It is possible that these are already integrated in V1 through lateral connections. In collaboration with Professor Wolf Singer's group at the Max Planck Institute in Frankfurt Germany, Rob designed an experiment to test the primacy of CRFs. Awake macaque monkeys viewed unaltered natural scenes movies and then the same movies with the surround obscured. Using detailed statistical analysis based upon point process Generalized Linear Model (GLM) techniques, Rob determined the extent to which the spiking of single neurons was dictated by the CRF, the surround, and the ongoing LFP that reflected coherent network dynamics. He found strong modulation in both the surround and the LFP, showing that the many efforts to understand natural scenes based solely on stimuli within the CRF give an inaccurate picture. This observation has significant implications for understanding visual coding. A report on these findings was submitted to *PLoS Computational Biology* and is now being revised.

Model-based analyses of neural spike trains, whether explicit or implicit, must assess goodness-of-fit prior to using the model to make inferences. A commonly used Kolmogorov-Smirnov test for assessing goodness-of-fit based upon the time-rescaling theorem transforms a neuron's interspike intervals with respect to the explicit or implicit conditional intensity function used in the analysis. If the model is correct, then the transformed intervals will be independent and identically distributed exponential random variables. This theorem applies to spike trains recorded in continuous time. However, neural spike train models are fit to data that have finite precision. Hence, they are recorded in discrete time. During the course of the natural scenes study, Rob analyzed many neurons with high firing rates using point process GLMs. He noticed that the continuous-time approximation broke down, leading to misleading goodness-of-fit evaluations. Rob developed a discrete time correction for time-rescaling theorem-based goodness-of-fit analyses. The key insight is that with discretization, the exponential probability density becomes a geometric probability mass function. An appropriately scaled geometric probability model is what results when discrete observations are transformed rather than an exponential probability model. This methodological correction is important because the time-rescaling theorem is routinely used for evaluating statistical models of neural spiking activity and such evaluations must be accurate. Rob published this work in *Neural Computation*. In a related paper which he co-authored with Professor Gordon Pipa formerly at the Max Planck, Rob extended the time-rescaling theorem to test goodness-of-fit for population spiking models. This work was also published in *Neural Computation*.

Rob's current work focuses on deciphering population codes in large networks of neurons. In this research he has taken different approaches. The first involves developing and fitting L^1 regularized GLMs to devise parsimonious graphical representations of the functional interactions among neurons in an ensemble. Working with Dr. Ziv Williams, a neurosurgeon and neurophysiologist at MGH, Rob has used these models to investigate the role of network interactions in coding sensory-motor associations in the pre-motor cortices of awake, behaving monkeys. He found that during learning, models based on interactions could not decode which association was being made. However, during subsequent recall of the same task, neuronal interactions were far more valuable for accurate decoding than individual neuronal spiking rates.

Presumably, once learned, the pre-motor cortices store associations in a type of population code. Since the majority of investigations in pre-motor and other frontal cortical areas used either imaging or studies of single neurons, this demonstration that interactions encode information is exciting. Rob and Ziv plan to submit a report on these findings to *Nature*.

In a clever extension of this work Rob is modeling directly how different patterns of spiking activity across a neuronal population depend upon the input stimulus. This is fundamental (and challenging) problem because the number of possible spike patterns is potentially boundless. Rob has created a regression tree algorithm which recursively splits the observed patterns into smaller clusters. He has shown that within these smaller clusters member patterns covary with the stimulus in an identifiable manner. Rob used this algorithm to show that population spiking in V1 neurons in anesthetized cats is not only better described by patterns, as opposed to the spiking of independent neurons, but that the patterns provide better decoding capabilities. This is perhaps the first method capable of understanding direct encoding and decoding by patterns in large neuronal ensembles. As such I expect that this work, which he is submitting to *PNAS*, will have significant impact.

As Rob's several projects indicate, he has successfully collaborated with a broad range of experimentalists and quantitative scientists on different aspects of the fundamental computational neuroscience problem of understanding how ensembles of neurons represent and transmit information. Rob is a careful, patient scientist who takes the extra time to make his ideas clear to his non-mathematical colleagues. In this regard, he is a natural pedagogue. I predict that just as he did here at MGH and beyond, Rob will catalyze collaborations across the campus at Brown. This quality coupled with his several accomplishments in understanding neuronal networks makes Rob an ideal choice to be a tenure track faculty member at Brown University. For these reasons, I am pleased to restate my support for his appointment.

Sincerely,

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