Department of Brain and Cognitive Sciences
Harvard-MIT Division of Health Sciences and Technology
Massachusetts Institute of Technology
77 Massachusetts Avenue, 46-6079
Cambridge, MA 02139
Tel: (617) 324-1880; Fax: (617) 324-1884
Email: enb@neurostat.mit.edu
Web: http://web.mit.edu/bcs/people/brown.shtml

Emery N. Brown, M.D., Ph.D.
Professor of Computational Neuroscience (MIT)
Professor of Health Sciences and Technology (MIT)
Warren M. Zapol Professor of Anaesthesia (HMS)
Anesthetist (MGH)

April 5, 2012

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

RE: Zhe "Sage" Chen, Ph.D.

Dear Dr. Sheinberg:

I am pleased to offer my support for the application of Dr. Zhe "Sage" Chen for a tenure-track position as Assistant Professor in the Dept. Neuroscience at Brown University. Sage is a computational neuroscientist with a strong mathematics background who is doing very creative work in the area of neural signal processing. In addition to successful new methodology development he is one of the most collaborative postdoctoral fellows I have had in my laboratory. Sage would be a welcome addition to your faculty.

Sage joined my laboratory two years ago after having spent two years at the RIKEN Institute in Japan working with Shun-ichi Amari and Andrzej Cichocki. Since joining my laboratory Sage's work has focused in two areas. The first is developing dynamic algorithms to characterize neural spiking activity using the theory of point processes and state-space modeling. The second is the use of this same theory to characterize the dynamic properties of human heart beats. Since joining my laboratory Sage has published several substantial papers on each of these topics.

An important question in neuroscience is understanding how neural systems respond to various stimuli as a function of the brain's background states. It is now widely appreciated that the cortex constantly passes through a series of up and down states and that its responsiveness to external stimuli can vary appreciably depending upon its state. To date, there have been no methods to identify these up/down states in a principled manner and use them to characterize brain states. Using the theory of point processes, Sage developed an efficient algorithm to identify up and down states by modeling the neural responses as a point process modulated by a two state Markov process with non-exponential holding times. He then used variable dimension Markov chain Monte Carlo methods to estimate the transition points between the states and the model parameters. He performed a detailed study of the algorithm's performance on simulated data and then used it to analyze spiking activity from the somatosensory cortex of a rat performing a spatial navigation task. This manuscript was published in *Neural Computation* in 2009.

In his second project, Sage studied the problem of tracking autonomic control and respiratory sinus arrhythmia (RSA) from electrocardiogram and respiratory measurements. This is an important problem in cardiovascular control. Sage developed a point process adaptive filter algorithm based on an inverse Gaussian model to track heart beat intervals that incorporates respiratory measurements as a covariate and provides an analytic form for computing a dynamic estimate of RSA gain. He demonstrated the properties of the new dynamic estimate of RSA in the analysis of simulated and actual heart beat data. The latter were recorded from subjects in a four-state postural study of heart beat dynamics: control, sympathetic blockade, parasympathetic blockade, and combined sympathetic and parasympathetic blockade. In addition to giving an accurate description of the heart beat data, the adaptive filter algorithm confirmed established findings pointing at a vagally mediated RSA, and it provided a new dynamic RSA estimate that can be used to track cardiovascular control between and within a broad range of postural, pharmacological and age conditions. The new paradigm provides a framework for designing a device for ambulatory monitoring and assessment of autonomic control in both laboratory research and clinical practice. This manuscript has appeared in *IEEE Transactions on Biomedical Engineering*.

In addition to these substantial papers, Sage has become actively involved with a number of other projects with other members of my group. To illustrate, he is currently collaborating with my postdoc Gordon Pipa on a new tomographic reconstruction algorithm for estimating the receptive fields of neurons in primary visual cortex in response to moving bar stimuli. Their new results show that V1 neurons are more direction specific and have larger receptive fields in their responses than previously appreciated. Gordon and Sage recently presented this work as an invited talk at the 2009 Cosyne meeting. A manuscript is under review for consideration of publication in *Neural Computation*.

With David Putrino, one of my postdocs who recently arrived from Australia, Sage has been developing a multivariate point process model to analyze the activity of neurons in the cat primary motor cortex. The algorithm which Sage has developed to analyze these data is a novel state-space extension of the multivariate point process algorithm we published four years ago (Okatan et al., *Neural Computation*, 2005). With this new algorithm, which provides an L^2 regularization for the model parameters, Sage and David have been able to characterize specific differences between the fast spiking (presumptive interneurons) and regular spiking (presumptive pyramidal neurons) in primary motor cortex. In particular, they have been able to identify for the first time clearly distinct network dynamics between movement and non-movement phases of a motor task for these neurons. This work was presented at the recent 2009 IEEE Engineering in Medicine and Biology Society Conference (EMBC’09) in Minneapolis. A related work was also published in *IEEE Transactions on Neural Systems and Rehabilitation Engineering*.

Furthermore, Sage has worked jointly with Wei Wu, one of my visiting students from Tsinghua University in Beijing, to develop a new robust version of the common spatial patterns (CSP) algorithm. The algorithm is widely used in a number of areas of computer sciences and engineering where reliable pattern recognition is a primary objective. Currently, CSP algorithms can be very sensitive to outliers and as a consequence, give quite distorted results. Sage and Wei used the multivariate t-distribution to design a robust form of this algorithm. In a series of simulated and real data examples they clearly demonstrate the superior performance of the robust version of the algorithm with respect to stray or outlying measurements. These results were also presented at the EMBC’09 conference and published in *NeuroImage*.

In addition to these several projects, Sage has extended his hidden Markov model work to the analysis of the dynamic properties of miniature post synaptic current recordings. This is a collaboration that he has established with Martha Constantine-Paton’s laboratory in the Department of Brain and Cognitive Sciences at MIT. The results of the analysis from this work were just submitted to the *Journal of Neuroscience* for publication. Sage is also working on a methodology paper based on this work. He has also used his point process filter algorithms for heart beat analysis to develop novel characterizations of the autonomic nervous system in different states of general anesthesia. This new analysis holds promise for identifying a novel signature of autonomic function which may allow a more refined assessment of the arousal state of patients undergoing general anesthesia for surgery or other medical procedures.

I have given details about each one of these projects because they show the enormous energy and breadth Sage has. In this regard, he is impressive. Sage has actively sought out and made good on collaborations with both experimentalists and quantitative scientists interested in methodology development. In particular, his ability to interact successfully with both experimentalists and junior colleagues demonstrates his strong pedagogical ability. His collaborative spirit is exactly the type of perspective that will lead to successful research at an interdisciplinary institute. As I stated at the outset, I believe that Sage would be a welcome addition to your faculty and I reiterate my endorsement for his application.

Sincerely,

Emery N. Brown, M.D., Ph.D.
Professor of Computational Neuroscience
Department of Brain and Cognitive Sciences

Professor of Health Science and Technology
Harvard-MIT Division of Health Sciences and Technology

Warren M. Zapol Professor of Anaesthesia
Harvard Medical School

Anesthetist
Massachusetts General Hospital