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## Recommendation letter on behalf of Dr. Paul Miller

I am writing this letter in support of Dr. Paul Miller's application for a faculty position at your Institution.

Paul received higher education from the University of Cambridge and Bristol, England. He was a postdoc in Physics at Georgetown University when he decided to change the field to Computational Neuroscience. He joined my lab in September 2000. In his first year, Paul took a number of courses in introductory, cellular, systems neuroscience. At the same time, Paul taught a course in the Physics Department, which was very well received. He also successfully applied to a five-year NIH Mentored Award grant, which supports a young scientist in transition to become an independent investigator under the mentorship of an advisor.

Over the last three years, Paul's research has been focused on the cortical network mechanisms of working memory, the brain's ability to actively hold and manipulate information 'on-line' for a few seconds. Dr R. Romo and colleagues have discovered, in a monkey physiological experiment, that some neurons in the prefrontal cortex encode and maintain the memory of an analog sensory signal (the frequency of a vibrotactile stimulus), with a monotonic tuning curve of mnemonic activity, a phenomenon called 'parametric working memory'. Paul and I decided to investigate a biologically-based neural network model of 'line attractor' for parametric working memory. Paul developed a large-scale recurrent network model, involving tens of thousands of noisy spiking neurons, that reproduced the salient physiological observations of Romo's experiment. This work, published in *Cerebral Cortex* was co-authored with R Romo and C Brody, but Paul did all the model construction and computer simulations. Moreover, it was known that the realization of a line attractor requires fine-tuning of parameters, but the precise meaning of this fine-tuning was unclear. To address this question, Paul carried out a mean-field analysis of of the spiking neuron model, and found that the fine-tuning condition mathematically corresponds to a precise alignment of multiple 'cusps' (a cusp, in the jargon of bifurcation theory, is a particular point in a two-parameter (say recurrent excitatory connection and external input amplitude) space corresponding to the onset of bistability). He showed that this conclusion holds true also for a line attractor model of neural integrators in the oculomotor system developed by HS Seung and collaborators.

Previous modeling studies have been concerned with the average firing rates of neurons in a line attractor network. In a second manuscript, Paul studied the stochastic fluctuations of neural activity in his parametric working memory model. Interestingly, he found unusual features of a line attractor dynamics, such as scale-invariant correlation function and Fano factor, that are characteristic of a random walk process. His results also have specific predictions about the trial-to-trial noise correlation between neurons in a parametric working memory network. Furthermore, Paul extended his model to a larger model for the entire somatosensory discrimination task to investigate the following question: when two stimuli f1 and f2 are presented sequentially, separated by a delay period, how can f1 and f2 be compared, so that the output of the system reflects a categorical choice (f1>f2 or f1<f2)? Paul proposed a clever scheme for this discrimination computation, based on a novel concept of 'integral feedback control'. This idea will be the basis of a third paper.

In addition to research on working memory, I suggested Paul to look at a seemingly totally different problem, that of synaptic long-term potentiation (LTP) believed to be a cellular basis of long-term memory in the brain. In actuality, the problem can be conceptually formulated as persistent activity (sustained over a long period of time–years) in a bistable molecular switch. The intriguing question is, given a small number of molecules at the postsynaptic density of a synapse, how can a potentiated state be maintained in spite of stochastic fluctuations and protein turnover? Paul took this problem in stride. He mastered Gillespie's stochastic simulation algorithm, and applied it to a biologically realistic CamKII-based model of LTP. Given the known kinetic properties of phosphorylation and dephosphorylation reactions, Paul quantitatively estimated the expected lifetime of a memory state and how it depends on the number of CamKII holoenzymes. Importantly, Paul showed, for the first time, that a CamKII-based switch can still function despite protein turnover. This work is now in revision for the top-ranking journal *PloS*. Paul clearly enjoyed doing this project. In fact, I think he is attracted to this type of problems beyond neurobiology, in the broader field of 'systems biology' (studies of gene and protein networks, networks of transcriptional factors, etc).

Paul genuinely likes teaching; his lectures and seminars are clear and pedagogical. He is conscientious and spends a lot of time with students. His teaching record prior to and at Brandeis has been consistently good. He would be an effective teacher. Let me add that Paul is more than a good citizen in the lab. He is extremely good at computers and played a major role in setting up a PC cluster in my lab, which now has 80 CPUs. He is always helpful to others in the lab, especially newcomers; and he is a most interactive participant at lab meetings. I think he would be a valuable and congenial colleague in a scientific community he'll be part of.

In summary, Paul has demonstrated a broad range of knowledge and experience in theoretical neuroscience, and he has exciting ideas about a future research program at the interface between biology, physics and applied mathematics. He is ready for a faculty position.

Sincerely yours.

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