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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
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To Whom It May Concern:

It is a pleasure to write on behalf of Paul Miller. I have worked closely with Paul over the last two years and feel that I have a good sense of his capabilities. In a nutshell, I feel that he is one of the best computational neuroscientists I have seen at Brandeis. Importantly, he is now one of the few computational neuroscientists who has training in the simulation of biochemical reactions. As I will explain later, I believe this is a hot field.

The work that Paul has undertaken in collaboration with Dr. Zhabotinsky and myself has to do with a fundamental biological entity, a molecular switch. There is good reason to believe that such switches are involved in synaptic memory, but there are likely to be many other biological processes that require information storage and that may use switch-like biochemistry to achieve such storage. For over 15 years I have been trying to understand how coupled reactions involving Calcium-calmodulin kinase (CaMKII) and the phosphatase, PP1, could form a switch. The models of such switches are both increasingly constrained by data and have increasing experimental support. In trying to understand such switches, a fundamental problem relates to their stability. We do not expect a light switch to spontaneously switch from the "on" to the "off" state (or vice versa), but a switch is a macroscopic entity. A molecular switch, by contrast, would be composed of only a few molecules and stochastic processes must necessarily lead to spontaneous transitions that place limits on the stability of the stored information. What Paul's work has done is provide the first deep exploration of this problem. For instance, although it is obvious that increasing the number of molecules that participate in switch reactions will increase stability, the functional relationship has not been clear. What Paul's work shows is that stability increases *exponentially* with molecule number. This means that relatively small increases in molecular content can have enormous impact on stability. As I mentioned above, in modeling the CaMKII/PP1 switch we are constrained by a great deal of data, which, though not airtight, gives reasonable estimates of expected reaction rates. For this reason, Paul was able to derive estimates of the absolute stability of switches of various sizes. Since we know that a postsynaptic density contains about

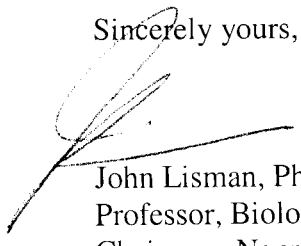
10-20 CaMKII holoenzymes, it was of particular interest to know what stability could be achieved by a switch of this size. Paul's simulations and calculations indicate that such a switch could be stable for more than 10 years and thus indicates the suitability of such switches for long-term memory storage. Because of the novelty of this work and its general importance for neuroscience and cell biology, we have thought it appropriate to aim for publication in a very high level journal. The paper was therefore submitted to the open access journal PLOS, which has a selectivity comparable to Nature and Science, and the first round of reviews were quite positive.

Paul's contributions to this work have been both conceptual and technical. Even though not trained as a biochemist, he has rapidly developed a deep understanding of the biochemical issues relevant to the simulations. His analytical skills are keen, well honed by study of Physics. He is thus always looking for the deep insights and the underlying principles. In the particular simulations that were done, many technical issues arose regarding hugely variable time scales for reactions, "non classical" effects of small numbers of molecules and cumulative calculation errors. Paul stayed on top of all this. What particularly impressed me has been his continual efforts to simplify the problem to the point that he could crosscheck Monte Carlo simulations with analytical equations. Perhaps most important, was Paul's use of his physics background to provide analytical approximations of the final results; having such expressions is very valuable when one is trying to explore new variants of the model or incorporate switch processes into larger neuronal simulations. I wish to emphasize this point because in hiring a new faculty member one is trying to find the person who has sufficient depth and creativity to make important contributions in the future. I think Paul has those qualities.

In closing, I would like to explain why I think the modeling of cellular reactions is a hot new field. The basic argument is that we have reached the point where a substantial fraction of the molecules involved in biological processes have been identified. Thus the major hurdle ahead is to understand how these molecules work together as a chemical system to achieve a desired result. This is an idea that has been pushed recently by the "Systems Biology" movement, with good reason.

Paul is one of the few young scientists with the tools required to push this effort forward. I suspect that, as he has done at Brandeis, his optimal approach will be to work with investigators who already have well established expertise in particular cellular/biochemical processes. They will find Paul a delight to work with; he is smart, friendly, honest and hard working---a great collaborator. His results can be trusted.

Sincerely yours,



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