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Biocomplexity Faculty Search Committee
c/o Prof. Rob de Ruyter van Steveninck
Biocomplexity Institute
Swain Hall West 117
Bloomington, IN 47405-7105

Dear Prof. de Ruyter van Steveninck,

I am very pleased to write this letter in support of Dr. Vincent VanBuren, who has applied for a faculty position in your Biocomplexity Institute. I have known Vince for over six years having served as a member of his doctoral dissertation committee, although in fact I functioned more as his co-advisor.

I was introduced to Vince by his doctoral dissertation advisor, Lynne Cassimeris, with whom I have worked for many years on modeling quantitative, physical aspects of microtubule dynamic instability. In our collaboration, Lynne has conducted microscopy experiments amenable to quantitative analysis, and I have developed computer models to simulate the experimental behavior and test various hypotheses about microtubule self-assembly and its regulation. About six years ago, Lynne asked if I would be willing to work with Vince, who had a strong interest in computer modeling and its application to cellular and molecular biology. After initial meetings with me, Vince worked largely on his own at Lehigh with periodic input from me.

Vince's dissertation project was to develop an integrated mechanochemical model for microtubule self-assembly. Current models of microtubule assembly assume tubulin subunit addition/loss processes linked to GTP hydrolysis that gives rise to dynamic instability. As a result, previous computer simulation models (e.g. the Monte Carlo simulation models of Hill and Chen, and later of Bayley and co-workers) considered only the kinetic/thermodynamic aspects of tubulin subunit addition/loss and GTP hydrolysis. And yet, it has been known for over twenty years from electron microscopy studies that there are characteristic structures at the microtubule tip that correlate with either the growing or the shortening states, clearly reflecting a change in the mechanical energy state of the terminal tubulin subunits. Prior to Vince's dissertation research, this mechanical energy component had not been integrated into a chemical kinetic/thermodynamic model for dynamic instability. As a result, previous models did not accurately predict the structural/mechanical state of the microtubule tip during dynamic instability nor did they consider the influence of mechanical stress on the chemical kinetics/thermodynamics.

Drawing on the existing literature for quantitative constraints on his model, Vince first developed a Monte Carlo computer simulation that allowed estimation of the strength of the lateral and longitudinal bond energies between adjacent tubulin dimers in the microtubule lattice (~ -4 and -8 $k_B T$, respectively). In addition, he estimated the mechanical energy stored as strain in the GDP-tubulins to be ~ 2 $k_B T$. He then went on to investigate the effect that the microtubule-associated protein XMAP215 has on dynamic instability, finding that a strengthening of the longitudinal bond by $\sim 3-4$ $k_B T$ and a slight weakening of the lateral bond by ~ 1 $k_B T$ accounted for the experimentally

observed growth and shortening rates. Finally, he incorporated mechanical effects into a chemical kinetic model for dynamic instability. The mechanical component of the model allowed us to correctly predict the size of the GTP cap at the growing tip of microtubules, and led us to estimate the hydrolysis rate to be $\sim 1 \text{ s}^{-1}$. The work was published in VanBuren, V., D.J. Odde, and L. Cassimeris, *Estimates of lateral and longitudinal energies within the microtubule lattice*. Proceedings of the National Academy of Sciences USA, 2002. **99**: p. 6035-6040.

In the second part of his dissertation research, Vince made a major improvement in our mechanical model to explicitly account for the deformation of tubulins in the lattice. This three-dimensional mechanochemical model of dynamic instability allowed Vince to correctly predict, for the first time, the ultrastructural features of both growing and shortening microtubule tips that were first observed by electron microscopy over twenty years ago. In addition, the model makes the prediction that the Young's modulus is an important parameter in microtubule stability, which may explain how taxol (which softens microtubules) stabilizes microtubules. Vince has prepared a manuscript that we are currently editing and intend to submit soon to *Biophysical Journal*. Even though the work has not yet been published, other groups have expressed their enthusiasm about using the model. As a result, we are currently working with two other groups to apply Vince's mechanochemical model to understanding the stall force of microtubule assembly (with Alan Hunt's group at U. Michigan) and the kinetochore tension-dependent stabilization of kinetochore microtubules (with Ted Salmon's group at U. North Carolina).

In all his work I found Vince to be simultaneously imaginative and careful. He was able to keep the big picture in mind, while also dealing with the details of the model. As a result, I think his modeling represents a major advance in the understanding of the role of mechanics in microtubule dynamic instability. In addition, he created beautiful three-dimensional computer-based renderings of the microtubule structure and mechanochemical energy state, which will further aid our understanding of this complex process. He is a pleasure to work with and his research has taught me much. His oral dissertation defense was excellent and so I believe he would make an excellent instructor. Since completing his dissertation, Vince has been working in the bioinformatics area at NIH, and I leave it to experts in this field to judge his contributions there.

As evidenced by your creation of a new institute, there is a need for the integration of informatics knowledge with the physical underpinnings of complex cellular processes, such as microtubule array reorganization. The primary new tool that has enabled this integration is the digital computer, which simultaneously facilitates the organization/manipulation of biological information and facilitates the simulation of the complex physical processes underlying cell behavior. Dr. VanBuren is well-qualified in both of these arenas and therefore very likely to make important new connections between them. I highly recommend him for a faculty position in your institute.

Sincerely,



David J. Odde, Ph.D.
McKnight Land-Grant Professor