UNIVERSITY OF MINNESOTA

Twin Cities Campus | *Department of Biomedical Engineering* | *7-105 Basic Sciences and Biomedical Engineering Building (BSBE)*
312 Church Street S.E.
Minneapolis, MN 55455
Office: 612-624-4507
Fax: 612-626-6583
http://www1.umn.edu/bme

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Dear Faculty Search Committee Chair,

I am very pleased to write this letter in support of Dr. Vincent VanBuren, who has applied for a faculty position in your department. I have known Vince for over seven 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_BT, respectively). In addition, he estimated the mechanical energy stored as strain in the GDP-tubulins to be ~ 2 k_BT. 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 ~3-4 k_BT and a slight weakening of the lateral bond by ~1 k_BT 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 ~1 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. I think this is one of the best papers that I have co-authored, and I give the credit to Vince for providing the drive and vision to take the analysis in directions that neither Lynne nor I had envisioned. A group at the University of Michigan (Prof. Alan Hunt, Dept. of Biomedical Engineering) is now using Vince's model to compare to nanoscale fluctuations of microtubule length during assembly under mechanical load. I expect that the impact of the model will continue to increase over time, especially considering the work done by Vince in the second part of his dissertation.

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 nanoscale 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. The work was recently published (VanBuren et al., *Mechanochemical Model of Microtubule Structure and Self-Assembly Kinetics,* Biophysical Journal, **89**, 2911-2926 (2005)). The article was chosen by the editors from the ~60 articles in the November issue to be highlighted as "New & Notable". Vince's results are the first step toward a recent call for an integration of mechanics and chemistry in the modeling of microtubule dynamics (Mahadevan and Mitchison, *Cell biology: powerful curves.* Nature, 2005. **435**(7044): p. 895-7).

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.

In conclusion, there is a growing recognition of the need for the integration of informatics knowledge with the physical underpinnings of complex cellular processes, such as cell division or cell growth. 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 to operate 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 department.

Sincerely,

David J. Odde

David J. Odde, Ph.D.
Associate Professor