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DEPARTMENT OF CHEMISTRY

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Yves Brun, Systems Biology/Microbiology Faculty Search,
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Dear Search Committee:

Mr. Dat Nguyen is an outstanding young man who I am delighted to recommend for a faculty position. He graduated from UC Davis with a B.S. major in chemistry and an outstanding grade point average in 1997. He entered our chemistry graduate program and accumulated a superb record in his course work. The courses he chose to take are themselves indicative of a superior individual as they cover the two most diverse sub-areas of chemistry, both organic and physical chemistry with outstanding performances in both. Dat chose to undertake his dissertation research in theoretical chemistry under my supervision.

Beginning with summer 1998 and completing his Ph.D. in Summer 2002, Dat became our expert on the AMBER suite of programs for molecular simulation of biologically important molecules. He implemented the program under a variety of UNIX operating systems from LINUX to HP UNIX , Silicon Graphics IRIX, and the IBM SP3 UNIX. He wrote and implemented scripts that enable AMBER to interface with DELPHI to solve the Poisson-Boltzman equations for the biological solute molecule. For some of the application problems that I discuss below, Dat has also needed to use the electronic structure program Gaussian 98 in order to obtain force-field parameters for the AMBER force-field for some carbohydrate side-chains and to examine molecular changes between a free and an RNA bound complex of malachite green. In the general area of computer expertise, Dat was without parallel in the chemistry department. He functioned as our group's network administrator, built our first Beowulf cluster and configured our second. He gradually tightened our security holes, as we recovered from hacker invasions, maintained the group web-page, and created the website for the 2001 West Coast Theoretical Chemistry Conference, which we hosted in Davis. He completed the requirements for a master's degree in computer science simultaneously with the completion of his Ph.D. in theoretical chemistry. Computation is his forte, but it is applications that keep his interest and enthusiasm for computation going with the prospect of solving important biological problems.

The applications comprising Dat's thesis work all involve molecular dynamics simulations of biological problems. He started with examination of simulations of the dissolved state of biological antifreeze molecules, went on to simulations of candidates for improved DNA cross-linking anticancer drugs, and lastly examined the nature of binding of certain dyes to RNA aptamers. He held a graduate fellowship supported by the Lawrence Livermore National Laboratory after passing his qualifying examination, and has worked in the Biomedical Technology Group there under Dr. Michael Colvin's joint supervision. In each of these application projects, Dat worked largely independently while coming for guidance and keeping me apprised of the progress of the work. He worked extremely well in this mode, and it was a pleasure to have him as my student. He was the carrier of the projects, including preparing the initial drafts of manuscripts for publication. He organized the work logically for presentation and worked hard on his initial drafts, accepted the revisions suggested by his co-authors, and re-edited the manuscripts utilizing modern tools for composition and collaboration.

Dat began work on the biological antifreezes, compounds that interfere with the kinetics of ice formation and maintain a condition of metastable equilibrium below the thermodynamic freezing point seemingly indefinitely. By identifying a charge complementarity of the sidechains when Type I antifreeze protein (AFP) is oriented as an anti-parallel dimer, he speculated that this orientation may be important for its function and proceeded to investigate the energetics of the dimer as a function of the relative orientation ~~of~~ the two monomers. Since little modeling effort had been directed at the inter-molecular interactions of the AFP, it was an important point to pursue. He obtained some very interesting results that suggest the dimer may have an attractive bound condition that is nearly energetically neutral with the dissociated state. While the simulations are simply of the molecule in solution, not at the ice/water interface, the existence of dimer states energetically neutral with a dissociated state has led us to speculate that there may be a previously unrecognized role of energy transfer characteristics in the function of these biological antifreezes in addition to their role as a mass shield against the incoming flux of water molecules to the ice surface(Biopolymers **75**, 109, *2004*). Because recent NMR studies of antifreeze glycoprotein (AFGP) found an absence of long-range order in the molecular structure, we proceeded to examine these molecules by molecular dynamics simulations of their solvated condition. The molecular dynamics studies also illustrate an extremely flexible molecule in solution, consistent and supportive of the newer NMR interpretations. In order to be able to compare relative energetics of conformational snapshots during the simulations, Dat interfaced the DELPHI program for solution of the Poisson-Boltzmann equation with the AMBER generated trajectories so that he could calculate the continuum model solvation energies for snapshots along the trajectory. These in turn enabled us to quantitatively assess the relative equilibrium populations of conformations generated during the MD simulations and identify the lowest energy ones among them. Among these lowest energy conformers is an enormous diversity of structures, consistent with the absence of long-range order. The multiplicity of energetically equivalent states also suggests that there may be a role for energy transfer in AFGP as well as for AFP (Biophysical Journal **82**, 2892, *2002*).

In his studies of prospective candidates for new anti-cancer therapies, Dat has been able to design some clever molecular dynamics simulations that explore the question of the probability of occurrence of proper molecular geometry for cross-linking reactions to occur and to be able quantitatively to compare these probabilities for both existing drug therapies and for some new candidates. Along with the reactive energetics, these studies permit a computational ranking of potential new candidates for DNA cross-linking therapeutics. In this work, Dat clearly demonstrated the ability to take an extremely tenuous, loosely-defined criterion of drug efficacy and design molecular dynamics simulations that not only address the qualitative questions, but result in a quantitative comparison. This ability to convert a biological question into a computational problem is a skill that can perhaps be learned but not taught. It is a skill that Dat will have with him as he addresses future challenging biological problems.

The original challenge in the RNA aptamer-dye binding problem was simply to account for the observed changes in the optical spectrum of the dye when it binds to the RNA and to see whether there were corresponding electronic structure changes that also correlate with the NMR chemical shifts upon binding. Again, Dat was able to abstract the intractably large electronic structure computation into one that simply provided an electrostatic model of the RNA's influence on the electronic structure of the dyes. This extremely simplified model proved successful in accounting for all the experimental observations (J. Am. Chem. Soc. **124**, 15081,*2002*). However, Dat realized that by extending the work to include molecular dynamics simulations and examination of the potential of mean force, the role of ring-base stacking interactions in the stability of the complex could also be examined (J. Phys. Chem. B **108**, 1279, *2004*).

Dat Nguyen is an impressive young scientist with the aptitude for enormous future success in computational biology and biochemistry. Recognizing the importance of the newly developing field of bioinformatics and feeling that his background and preparation were very strong for pursuit of a career in this new area, he applied for and won an extremely prestigious DOE-Sloan fellowship to further develop his background in bioinformatics, which he is pursuing in the laboratory of Professor George Church at Harvard Medical School. I am not technically versed enough in bioinformatics to comment on this work intelligently, but it appears that in addition to clearing up some issues regarding information portability, Dat has also developed an approach to prediction of gene expression and regulation that is extremely promising.
I believe that Dat Nguyen is an outstanding young scientist who has the potential to make profound contributions to human knowledge and will be an excellent citizen of academia. I recommend him most enthusiastically for a faculty position.

Sincerely yours,

William H. Fink

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P.S. I have prepared this while on travel in Newfoundland. phone (709) 884-1312