DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Laboratory of Chemical Physics, NIDDK
Building 5, Room 112
Bethesda, Maryland 20892-0520
November 19, 2004

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

Dear Search Committee:

I am writing in support of **Dr. Nathan Oyler's** application for a faculty position in your department. Nathan has been a postdoc in my research group for about 3½ years. Nathan is a very smart individual with a great deal of experience and expertise in the theoretical and experimental aspects of modern solid state NMR, which he has developed in his Ph.D. research with Gary Drobny and his postdoctoral research with me. In his postdoctoral research, Nathan has made several important and original contributions to solid state NMR methodology, particularly in the context of structural studies of amyloid fibrils associated with Alzheimer's disease, a major project in my group since 1999. Of the current members of my group, Nathan has the deepest understanding of the mathematical and quantum mechanical basis for modern solid state NMR techniques. For this reason, I rely on him particularly for the conceptual development, numerical simulation, and experimental demonstration of new NMR pulse sequence methods. These methods contribute directly to our investigations of amyloid structure, but are also of quite general applicability to other biochemical systems in noncrystalline solid states.

Nathan's main current project is the development of techniques for extracting molecular structural constraints from solid state NMR measurements on amyloid fibrils that are aligned by deposition on planar substrates (*e.g.*, mica sheets). All previous solid state NMR measurements on amyloid fibrils, both in my group and in other solid state NMR groups, have been performed on samples that were unaligned. Measurements on aligned samples are qualitatively different, because in principle they permit the absolute orientation of specific chemical functional groups and bond vectors to be determined relative to the fibril morphology. For these experiments, Nathan has developed new experimental protocols for achieving a high degree of fibril alignment in multi-milligram samples of fibrils formed by the 40-residue β-amyloid peptide associated with Alzheimer's disease ($A\beta_{1\text{-}40}$). He has explored various pulse sequences for obtaining structurally significant data with high sensitivity and high resolution, both experimentally and in numerical simulations (using sophisticated simulation programs written by him, which incorporate a variety of effects uncovered by his own investigations). Nathan has also synthesized and purified the $A\beta_{1\text{-}40}$ peptides required for his experiments. These experiments are really very challenging, and they are entirely Nathan's work. His initial results, which confirm the existence of the "cross-β" structure in the $A\beta_{1\text{-}40}$ fibrils that is suggested by x-ray scattering data, have been published recently in a very beautiful Communication in the *Journal of the American Chemical Society* (vol. 126, pp. 4478-4479, 2004). Nathan is currently extending these results to the quantitative characterization of non-β-strand conformations in these fibrils, which have proven to be difficult to determine by more conventional approaches. I expect that Nathan's work on solid state NMR of aligned fibrils will contribute new

information that is essential for the full determination of the molecular structures of $A\beta_{1-40}$ fibrils, as well as amyloid fibrils formed by other polypeptides.

In an earlier project, published in the *Journal of Physical Chemistry B* (vol. 106, pp. 8382-8389, 2002), Nathan developed a new method for exciting and detecting high-order multiple quantum transitions in solid state ^{13}C NMR of biochemical systems under high-speed magic-angle spinning. This project was originally motivated by the idea that multiple quantum ^{13}C NMR spectra of proteins with uniformly ^{13}C-labeled amino acid residues could be used to determine the backbone and sidechain conformations of the labeled residues, provided that high-speed magic-angle spinning was used to resolve the ^{13}C NMR signals of distinct carbon sites. Although this specific idea turned out not to be as successful as we had hoped (for reasons identified by Nathan in the course of this work), the techniques devised and demonstrated by Nathan are the most general and most efficient techniques for multiple quantum excitation reported to date, and they will certainly find applications in other contexts. This work also included a detailed investigation of the effects of chemical shift differences and anisotropic chemical shifts on ^{13}C-^{13}C dipolar recoupling under magic angle spinning, with results that are of general significance in structural studies by solid state NMR. Again, this project was entirely Nathan's work.

Nathan is a very well-balanced and personable individual, with good communication and leadership skills. Combined with the breadth and depth of his scientific skills (theory, simulation, experimental implementation of novel solid state NMR techniques, peptide synthesis and characterization, etc.), these personal qualities will help him succeed as an independent investigator and educator. I fully expect that Nathan will establish a productive research program and quickly develop into a leading figure in the biomolecular solid state NMR field. I recommend him to you without reservations.

Please feel free to contact me if you would like any additional information concerning Nathan's accomplishments.

Sincerely yours,

Dr. Robert Tycko
phone: 301-402-8272
fax: 301-496-0825
e-mail: robertt@niddk.nih.gov