UTMB
The University of Texas Medical Branch

HUMAN BIOLOGICAL CHEMISTRY & GENETICS

D. W. Bolen

5.154 Medical Research Bldg.

November 29, 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 Faculty Search Committee:

This letter is in recommendation of Dr. Jörg Rösgen for the position you have advertised. I met Dr. Rösgen in early 2001 when I visited the laboratory of Prof. Hans-Jürgen Hinz at Westfälische-Wilhelm Universität, Münster, GDR. As a result of mutual research interests we continued discussions, and several months later he joined my laboratory as a Keck Postdoctoral Fellow. Keck Fellowships are highly sought after and they are designed to support young scientists who want to work at the interface between the physical and the biological sciences. Two mentors are required for the Fellowship, an experimentalist and a theorist. I serve as the experimentalist and Prof. Montgomery Pettitt (Cullen Distinguished Professor in the Departments of Chemistry, Physics, Computer Science, Biology and Biochemistry, and Director of the Institute for Molecular Design, at the University of Houston) serves as his mentor in matters of theory. We both are very pleased with Jörg Rösgen's work – he combines intelligence, imagination, and a consuming work ethic, with superior ability in mathematics, the physical sciences and biology. This gives him a perspective that is unusual and insightful, placing him in the highest tier of young scientists worldwide.

In the field of biochemistry, essentially all thermodynamic and kinetic measurements of binding and chemical reactions have been performed in dilute solution. The reason for restricting such measurements to dilute solutions is that in this regime, thermodynamic quantities can be obtained using *concentrations* of products and reactants in place of *chemical activities*. However, while it is convenient to perform experiments in the ideal dilute solution regime, the intracellular environment of living cells is known to be highly non-ideal. The interior compartments of cells, such as the cytosol, generally contain highly concentrated protein (upwards of 400 mg/ml) and numerous small molecules and ions, giving a concentrated solution of relatively low water content. While it has been known for decades that non-ideality of the cell cytosol contributes considerably to molecular processes, it is common practice to take results obtained from dilute solution experiments and assume they apply in the cell. The practice is offered as a first approximation, for without activity coefficients there is no way of knowing what the actual thermodynamics of cellular events and processes are in living systems.

Office (409) 772-0754 FAX (409) 747-4751 E-Mail dwbolen@utmb.edu

The field of Systems Biology is in various stages of defining networks of reactions that comprise living organisms. The next step is to understand the networks of reactions in the context of the highly non-ideal crowded environment of intracellular compartments. Jörg Rösgen's goal is to establish a means of evaluating chemical activities of compounds and proteins in non-ideal conditions like those existing in the cell cytosol.

Upon joining my laboratory Jörg Rösgen undertook two parallel projects, one designed to experimentally evaluate activity coefficients of biological molecules in two and three component solutions, and another to develop a statistical thermodynamic basis for understanding and interpreting the origin of non-ideal behavior of biological molecules. Progress has been made in both areas, but advancements in the statistical thermodynamic approach are particularly noteworthy. Our first publication on the statistical thermodynamic approach appeared in the Journal of Physical Chemistry (Part B), and a second paper submitted to Biochemistry is in press. A third paper relates the efficacy of organic osmolytes as protein stabilizing and destabilizing agents to their effects on the native-to-denatured transition and solution structure. I hasten to add that the development of the theory in these papers all belongs to Jörg Rösgen. Monte Pettitt and I only gave occasional advice and discussed the results with him.

What is particularly notable about this body of work by Dr. Rösgen is that he has developed an isobaric partition function which gives analytical expressions that can be used to fit two-component solution activity data over the full solubility range, from dilute to the solubility limit. Regardless of solute type, experimental fits of activity data to the analytical expressions require fewer parameters and give smaller standard deviations than the models (mostly heuristic) devised by Pitzer and a host of other researchers in the twentieth century. Other advantages of the approach are that it is physically based, it takes into account the effective solvent interactions with the solute and between solute molecules, and it provides a statistical thermodynamic foundation for interpreting the results. Further developments of the approach show it can be extended to three and four component solutions. Only a small fraction of the possible applications of the approach to solution thermodynamics has been explored, and linkages of the approach to other solution theories are under investigation.

As is clear from his publications, Jörg Rösgen is prolific experimentalist, having published some 11 papers from his graduate work. He recognized very early the importance of understanding non-ideality in living systems and he intends to focus his career on this seminal problem in biology. If biology is to progress beyond the ideal solution regime, as it clearly must, new approaches, concepts and methods must to be developed that will set this new area of research into motion. Given his exceptional abilities in theory and experiment, I have no doubt that Jörg Rösgen will figure most prominently in its development. He is the best young faculty prospect I've seen, and whichever department hires him will be fortunate indeed.

Finally, I must make mention of personal qualities of Dr. Rösgen that add favorably to his ability in science, qualities that make him a delightful person to be around. He is very likeable, and graduate students and postdocs are naturally attracted to him because of his

Office (409) 772-0754 FAX (409) 747-4751 E-Mail dwbolen@utmb.edu

personality and his insight into their own work. He is the kind of person who brings out the best in those with whom he is associated. Since having him in my lab, students throughout the Department come to him for advice on their projects, and they have thrived from the experience. He will be a co-author on several papers from other laboratories, and professors in Structural Biology and Molecular Biophysics are delighted with the results of his collaboration with their students. He has natural teaching abilities, and is very well read and well-grounded in physics, chemistry, and biology. From this vantage point, he always has insightful comments and asks interesting and penetrating questions in any scientific discussion. He is the complete package, and there are few that can match him.

Sincerely,

Wayne Bolen, PhD.
Professor
Dept. of Human Biological Chemistry & Genetics
Sealy Center for Structural Biology

Office (409) 772-0754 FAX (409) 747-4751 E-Mail dwbolen@utmb.edu