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Special Issue Preface

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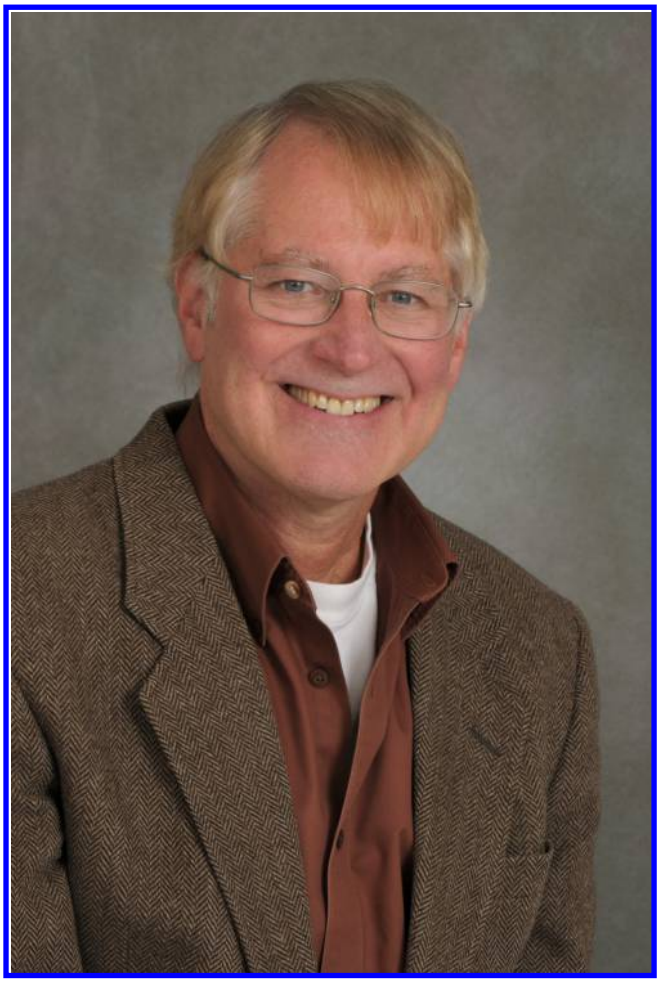
Tribute to Ken A. Dill



Jeanne Neville, Photographer

It is our privilege and a great pleasure to honor professor Ken A. Dill with this special issue of *The Journal of Physical Chemistry B* on the occasion of his 70th birthday that he celebrated in December 2017, as well as for his wide-ranging contributions to science.

Ken's work was originally focused on protein-folding problems, but his research interest is much broader than that. Besides exploring stability and function of proteins, he is also interested in elucidating the structure and physical properties of water, and its role in biology. He is developing simplified statistical-mechanical models to understand the physicochemical properties of pure water, hydrophobic interactions, and ion hydration. Recently he has also become involved in the field of systems biology. It is difficult to give all his achievements the full credit they deserve in such a limited space. We will therefore only give a brief overview of the main milestones in his career. We believe his work speaks for itself. And it does have a lot to say.

Ken is known for his discovery in 1985 that the hydrophobic effect is the primary structure-causing force in protein folding. The earlier view, from Kauzmann, Scheraga, and others, was that hydrogen bonding was the structure-specifying force in proteins and hydrophobicity was just nonspecific "glue", a compactifying force. Ken reversed that understanding. He showed the folding code had to be in the side chains, not the backbone. Using lattice models, Ken showed that folding was mainly a binary hydrophobic-polar code. Experimental proof of the binary code idea came in 1993 (Kamtekar et al. *Science* **1993**, *262*, 1680). Later, based on these principles, Ken (together with Ron Zuckermann at Lawrence Berkeley National Laboratory, CA) developed the first nonbiological foldamers (peptoids), which are now a growing field of materials.

Ken was also instrumental in developing the concept of protein-folding funnels which was an offshoot of his work on folding entropies and densities of states. Folding funnels now provide faster conformational search methods for molecular dynamics, and they explain folding speeds and mechanisms (Levinthal's paradox). The Dill group's current suite of programs, called MELD (Modeling Employing Limited Data) enables incorporation of this philosophy. Incorporating nonspecific insights such as "make a good hydrophobic core" or "make secondary structures consistent with web server predictions" is made possible by MELD in free energy simulations. This has been applied successfully to the community-wide blind protein structure prediction experiment CASP.

Working on protein folding, Ken realized the importance of water in shaping the native states of proteins which opened another area of his research interest, water and its role in the solvation processes. He has advanced the understanding of the physics of water, biology's solvent, over the past 20 years. He has been a leader in showing how water properties derive from the structure of the water molecule and its energies and from the organization of water molecules into a collective hydrogen-bonding network. Of course, water had been studied extensively. But, atomistic simulations are expensive and were not giving sufficient conceptual understanding of how water's structure maps to its pT phase diagram, volumetric anomalies, hydrophobic effect, or ion hydration. And, liquid-state theories, which treated water as radially symmetric or dipolar (without orientational hydrogen-bonding arms), had not revealed how water's properties are encoded in its molecular structure and orientational hydrogen bonding. By rediscovering simple water models, such as the "Mercedes-Benz" (first proposed by A. Ben-Naim in 1971), Ken has overcome these shortcomings. Using statistical-mechanical modeling he managed to explain how water's molecular hydrogen-bonding structure encodes its properties. Together with colleagues he developed SEA (Semi Explicit Assembly), a fast and accurate new computational model for computing the solvation free energies of nonpolar, polar, and charged solutes in water, relevant for chemistry and

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biology. His modeling explains why large versus small solutes switch from entropy to energy domination, how Hofmeister effects arise from a balance between water hydrogen-bond caging and electrostatics, and how water's asymmetry (water's dipolar center is offset from its mass center) is critical for modeling ion−solvent interactions. His SEA model is as accurate as explicit atomistic water models (e.g., TIP3P water), is as computationally efficient as implicit Poisson−Boltzmann models, and has recently been shown to be among the best solvation models in two blind community-wide annual solvation-modeling competitions called SAMPL.

Protein aggregates are among the most important biological states, not only in the realm of disease, but in related industrial applications: amyloid fibrils and protein aggregates are central in aging and Alzheimer's and Parkinson's diseases. And moderating the viscosities of antibody solutions is one of the most critical challenges for formulating biotech drugs. As a responsible scientist Ken is aware of the importance of these drugs for curing otherwise uncurable diseases; he put his genius mind to work and has tackled the problem with great enthusiasm. He has, together with co-workers, pioneered modeling the physics of aggregated proteins: in liquid−liquid phase equilibria, and in states of amyloid and antibody aggregation.

Becoming the director of the Laufer Center for Physical and Quantitative Biology at Stony Brook University in 2012, he started exploring the fields of systems biology. His group developed a simplified model to explain the evolutionary optimization of the balance of energy and protein synthesis in bacterial growth. They are also developing mathematical models to understand causes of biological aging, pointing to the fact that random modification of side chain charge of proteins could be a major source of protein stability loss in aging cells. Ken has also been intrigued by the long-standing question of the origin of life: Which came first, proteins or nucleic acids? Using the above-mentioned hydrophobic-polar lattice model, he and his PhD students proposed proteins as the original self-replicating biomolecule, and experiments are being performed now to test this hypothesis.

Ken Dill's achievements did not go unnoticed. In 2008, he was elected a member of the National Academy of Sciences (USA), and in 2013 he was elected to the American Academy of Arts and Sciences. He is a Fellow of the American Physical Society, the Biophysical Society, and the American Association for the Advancement of Science (AAAS). Among many services, he was a founding cochair of the Gordon Conference on Stochastic Physics in Biology in 2011, Acting Director of UCSF Biophysics Program from 1994 to 1995, and President of the Biophysical Society in 1998. In the early 2000s, he cofounded and directed (with Mary Barkley) Bridging the Sciences, a federal funding initiative that led to new funding for deep innovation programs at NSF and NIH, and for which Ken was awarded the Distinguished Service Award of the Biophysical Society. To mention just a few honors, Ken received the Hans Neurath Award in 1998 (Protein Society, inaugural award) for contribution of exceptional merit to basic protein research, and in 2012 he received the Emily Gray Award (Biophysical Society) for significant contributions to education in biophysics for his textbook *Molecular Driving Forces* with Sarina Bromberg. He is/was on the editorial/advisory board of many journals related to biophysics and physical chemistry, such as *Annual Review of Biophysics*, *Protein Engineering*, *Physical Biology*, *Multiscale Modeling and Simulation*, *Structure*, *Biopolymers*, *Biophysical Chemistry*, *Journal of Molecular Recognition*, *The Journal of Chemical Physics*, *Annual Review of Physical Chemistry*, *Chemical Physics*, and others. Ken has given 25 named lectures, including the 2016 CN Hinshelwood Lecturer in Chemistry at Oxford. He was the 53rd Annual Distinguished Lecturer at UCSF, and is a Distinguished Professor at both UCSF and Stony Brook University. Ken has published more than 300 peer-reviewed papers in journals such as *Proc. Natl. Acad. Sci. U.S.A.*, *J. Chem. Phys.*, *J. Phys. Chem. B*, *J. Am. Chem. Soc.*, *Phys. Chem. Chem. Phys.*, *Biophys. J.*, *Biopolymers*, *Biochemistry*, *Phys. Rev. Lett.*, *Science*, *J. Mol. Biol.*, and others. He has a Google h-index of 100, with over 41,000 citations. Last year he (together with I. Bahar and R. L. Jernigan) published the textbook *Protein Actions: Principles and Modeling*.

We all have the pleasure of working with Ken on some aspects of his wide-ranging opus, and by spending time with him, sharing scientific views, one can understand how he achieved so much. He always knows the right questions to be asked. He is never satisfied until he gets to the bottom of things. He truly believes that simple explanations supercede any complicated theory. It is said only those who understand the physics behind the extraordinary phenomena in the world can explain them to a three-year old. This "common sense" view cannot be substituted by any complex theory and is a broad, solid foundation for the pyramid of knowledge.

Saying all that, it is not surprising that Ken has touched so many scientists, in the beginning of, as well as established in, their resarch careers. The fantastic response that we received to the call for contributions to this issue reflects what a remarkable impact Ken has on the scientific community, as well as on all the people he has collaborated, and is still collaborating, with. Honoring Ken Dill with this special issue of *The Journal of Physical Chemistry B* is our way of thanking him for all that he has taught us throughout these years, and of wishing him many more years of scientific discoveries.

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