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TRIBUTE TO WILLIAM C. SWOPE

It is a distinct honor to co-edit this Festschrift on the occasion of the 60th birthday of William (Bill) Swope, who has been a long time friend and colleague to us and the many who have contributed articles in this special edition of JPC-B. A definitive majority of scientists who have been honored previously in this journal have come from academia, leaving behind a legacy of not only original ideas and their impactful execution embodied in a vitae, but also a group of mentored students and postdocs who define a “school” of thought in their area discipline. However, Bill is one of only two industry scientists to be honored in J. Phys. Chem. (the other being Frank Stillinger who was originally from Bell Labs). Nonetheless, while not having his own research group in the traditional sense, Bill has influenced a diverse community of both senior and junior scientists, both inside and outside IBM, which provides a different model of research impact that we attempt to highlight here. We sincerely thank Hans Andersen, Hans Horn, Jed Pitera, and Fritz Schafer who helped to provide a complete history of Bill’s scientific efforts and accomplishments over the decades for this Festschrift introduction, in which we highlight their contributions through direct attributes.

One of Bill’s early achievements as a researcher was to find his way into the groups of intellectual leaders of theoretical chemistry, first as a graduate student with Fritz Schaefer at Berkeley and later with Hans Andersen at Stanford. As Fritz summarizes: “In the Autumn of 1975, Bill Swope coming from Harvard, and Bernie Brooks arriving from MIT, entered the Ph.D. program in chemistry at Berkeley and joined my research group. It was a very good year! Notwithstanding their obvious promise, little could I have known that these two would become superstars in the (just emerging in 1975) important field of biomolecular simulations. Surely, neither of them learned anything biological from me.”

“My first remembrance of many meetings with Bill was his passion to know “why.” Although Bill was a quick learner, he always wanted to know why a problem I suggested was important. For a no nonsense person like myself, these discussions were occasionally longer than I desired, but they helped the science and certainly made for much clearer introductions to the papers we wrote.” This early training and curiosity certainly developed into a hallmark of Bill’s scientific persona, which is his ability to explain not only difficult content in a clear and insightful way (very much like Frank Stillinger) but to place that scientific content into a larger context.

The methodological problem Bill worked on at Berkeley involved the rigorous treatment of degenerate point group symmetry in multi-reference configuration interaction methods.¹ Bill had become friends with Yuan-Pern Lee, a gifted student with George Pimentel, and coincidentally the younger brother of Berkeley faculty colleague Yuan Tseh Lee. Yuan-Pern was trying to measure and understand very complicated electronic spectra of the diatomic molecules S_2 and SO .^{2,3} Working with Bill and his powerful methodology, the two of them characterized virtually all of the low-lying electronic states of S_2 and SO ; the theoretical work not only helped the Pimentel group with their experiments, but also provided new predictions later confirmed by other spectroscopists”. About six months before the canonical four years of his Ph.D. studies, Bill received a postdoctoral offer that was just too hard to refuse.

Fritz’s friend and colleague Hans Andersen at Stanford gave Bill his entree to statistical mechanics during a time when the transitions from quantum to statistical mechanics were very infrequent. Hans Andersen “had just started doing computer simulations with a recently purchased DEC PDP 11; the PDP computer was augmented by the Floating Point Systems Array Processor, which could achieve ~2-4 mega ops in a molecular dynamics calculation, provided that the inner loops in the program were written in a very complicated assembly language! This allowed simulations of systems of 512 water molecules at the blinding speed of about one molecular dynamics time step per wall clock second”. With this capability, Bill and Hans were one of the first

to calculate absolute solvation free energy by simulation⁴; the study employed thermodynamic integration with a coupling parameter, and carefully treated statistical uncertainty. However, the language employed to describe the methodology involved solubility and chemical potential rather than "free energy", as the methods later came to be known.

In collaboration with Peter Behrens and Kent Wilson, he and Hans developed a method of calculating equilibrium constants for the formation of molecular clusters in the gas phase⁵. More importantly, perhaps, was the fact that in this work they developed the velocity form of the Verlet algorithm, now commonly known as the velocity Verlet algorithm. Since particle positions and velocities are available at the same instant in time with this algorithm, it was straightforward to implement thermal control in a molecular dynamics program in a way that supported the proper simulation of canonical ensembles. In addition to the better organization of dynamical variables, the algorithm represented a symplectic transformation in phase space and avoided numerical problems with round-off error, thereby becoming an industry standard for molecular simulation. The details of the velocity Verlet algorithm were relegated to the Appendix of the 1982 paper in *J. Chem. Phys.*⁵, thereby obscuring the origin of this important contribution to molecular simulation, which we excavate here.

After this Bill went to work for IBM, first on the East Coast, and then back on the West Coast in the late 1980's at a location near the Stanford campus. At that time, he began working on a molecular dynamics program that was well organized and capable of being compiled to efficient code for computer systems that had very large memory. When Hans Andersen asked Bill how many particles his program could deal with on available IBM computers, he thought for a while and then answered, "A million". This system size scale was so unprecedented, that it took a while to define a problem that truly would benefit and be adequately studied by computer simulation. The result was a paper on homogeneous nucleation in a million-particle system⁶, and later, with Ken Bagchi, the freezing transition in two dimensions for disks with repulsive forces^{7,8}, which were among the largest such systems simulated to that date."

In the early 90s Bill transferred to IBM's Almaden Research Center in San Jose. There he joined a group of computational chemistry pioneers such as Bowen Liu, Doug McLean, Megumu Yoshimine, Byron Lengsfeld, Bob Nesbet, John Barker, and the young Julia Rice. At Almaden, a new business unit was formed aimed at creating a "best of breed" suite of computational chemistry programs, named "Mulliken" – by rewriting core quantum chemical and molecular simulation algorithms from scratch. Such an undertaking (competing with the "big" guys, such as Gaussian and Spartan) had its own set of intense challenges, including night and weekend shifts to meet deadlines. During this time, Bill developed many improved techniques for accurate calculation of solvation free energies using molecular dynamics simulations, including a method for automated detection of equilibration, as well as a method that allowed simulations to run until a preset target statistical precision was obtained for a set of specific computed results; all pioneering capabilities that were industry-first for years to come. Even today, the Mulliken code is used to prototype new algorithms within IBM.

In the years, 1996 through 1999, Bill became an expert in SQL and relational database technologies while collaborating with Almaden's Computer Science department. During this period he and Julia were two of a small group of researchers who participated in the formation of IBM's Life Sciences business, which first focused on scientific data integration⁹. Then, starting in 1999 and continuing through the early 2000s, Bill was a member of IBM's Blue Gene research project¹⁰ that aimed to develop a general-purpose supercomputer suitable for physical simulations such as protein folding, leading to the successful development of three generations of high performance Blue Gene systems. As a senior member of the science team, Bill kept the project focused on high-quality, careful work modeling the thermodynamics and kinetics of protein folding. Some early promising

results using replica-exchange molecular dynamics performed by Bill and Jed Pitera suggested that thermodynamic studies could efficiently use even massively parallel computer resources.¹¹ Kinetic studies were still problematic, however, as the eventual limits to scalability meant it made more computational sense to generate an ensemble of short trajectories rather than a single long trajectory. As summarized by Jed, “Bill was among the first to recognize how the Master equation could be applied to a state-based analysis of protein folding kinetics from ensembles of trajectories and the first to develop a clear formal basis for the method.”¹² With collaborators at IBM, Stanford (Pande group) and UCSF (Dill group), he worked on a number of subsequent developments including validation in simple systems¹³, automatic state identification¹⁴, and dynamical reweighting¹⁵.” These approaches, now more popularly called Markov State Models, have been widely adopted in the biomolecular simulation community.

With the advent of improved treatment of long-range Coulomb interactions (via Ewald summation) becoming main-stream in the early 2000s and the large-scale protein folding simulations undertaken in the context of the Blue Gene project, it soon became apparent that conventional water models (that were developed in the 80s without consideration of long-range electrostatics) were not robust enough for experimental comparisons in some cases. Bill and his colleagues took the best fixed charge water model available at the time, Bill Jorgensen’s TIP4P model, and, using experimental density and heat of vaporization data over a range of temperatures relevant for the liquid phase, retuned its parameters for use in simulations that use Ewald and Lennard-Jones corrections. The resultant water model, TIP4P-Ew, is one of the best general purpose fixed-charge water models to date.¹⁶ By construction, it reproduces the experimentally observed density maximum at $T \approx 4^\circ\text{C}$. But beyond the parametrization, it also determines phase equilibrium properties such as vapor pressure, and boiling and melting point¹⁷, and it can even predict critical phenomena (critical temperature, density and pressure) as well as supercritical properties.

In 2008, collaboration with Marti Head and Dan Price of GlaxoSmithKline (GSK), led to the computation of hydration free energies for ~ 300 small and/or drug-like molecules with several of the popular force fields and water models. This study exposed a wide range in the accuracy of predicted results, which, in turn, led Bill and Julia Rice to look at ways to improve force fields based on high quality quantum chemistry calculations; this has initiated work that explores the effect of solvent on the electronic polarization of solute molecules.¹⁸⁻²¹ To advance this effort, Bill, Julia and Hans Horn have also developed in the Mulliken software package the capability for hybrid quantum mechanics/molecular mechanics (QM/MM) simulations where sub-regions of a periodic system are treated with localized basis set quantum calculations surrounded by material to be treated classically. They have also formulated methodology for hybrid simulations where sub-regions are treated with a classical model for electronic polarization and other regions are treated with a fixed charged model.

Currently, IBM has a leading program in the development of star polymers for a range of applications including surface coatings through to biomedical applications such as drug delivery.²² Driven by recent advances in polymer synthesis to employ a diverse set of chemistries for the diblock polymeric arms attached to different chemical “cores”, one can imagine a materials genome of possibilities for these nanoparticle systems; however controlling their functional outcomes based on composition or thermodynamic controls such as temperature or pressure, is currently challenged by a lack of fundamental understanding of their physical chemistry. Bill is leading the effort, working with Julia, to provide a more detailed understanding of a wide range of star polymers and investigating where in the nanoparticle a drug might reside.²³ In addition, in collaboration with Teresa Head-Gordon and graduate student Lisa Felberg, they are attempting to answer, through both experiment (SAXS) and molecular simulation, questions such as the size and shape of these nanoparticles as a function of composition (e.g., how changing the molecular structure of the

hydrophobic and hydrophilic components of the diblock copolymeric arms alters the morphology of the macromolecule), the size and shape of the nanogel core, and how these shape and size features change with temperature and solvent composition. By answering these questions and working in conjunction with the IBM experimentalists, their ultimate goal is to design star polymeric nanoparticles more rationally for suitability as drug delivery vehicles. Bill has also cleverly developed a coarse-grained, reactive chemical model for the polymerization process of the nanogel core that is leading to new insights into the complexity of the core. It is notable that, while star polymers seem to bear little resemblance to biopolymers, Bill has brought the many principles learned from protein folding to aid in the understanding the complex thermodynamic and kinetic behavior of these non-biological nanoparticles, pictures of which suitably grace the cover of this Festschrift.

In summary, Bill Swope's record of achievement in computational chemistry is impressive, in which he has been a frontrunner in developing molecular simulation models and methodology whose impact and popularity has stood up over decades. Bill is too modest to emphasize these accomplishments himself, instead preferring to talk about his current research and learning about what other scientists are doing. Speaking for ourselves, and on behalf of the Festschrift contributors, we thank Bill for his collegiality and the many enjoyable scientific interactions over the years, and we look forward to many more of them!

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(1) Swope, W. C.; Schaefer, H. F.; Yarkony, D. R. A GENEALOGICAL ELECTRONIC COUPLING PROCEDURE INCORPORATING THE HARTREE-FOCK INTERACTING SPACE AND SUITABLE FOR DEGENERATE POINT GROUPS - APPLICATION TO EXCITED-STATES OF BH₃. *Journal of Chemical Physics* **1980**, *73*, 407-415.

(2) Swope, W. C.; Lee, Y. P.; Schaefer, H. F. DIATOMIC SULFUR - LOW-LYING BOUND MOLECULAR ELECTRONIC STATES OF S₂. *Journal of Chemical Physics* **1979**, *70*, 947-953.

(3) Swope, W. C.; Lee, Y. P.; Schaefer, H. F. SULFUR OXIDE - LOW-LYING BOUND MOLECULAR ELECTRONIC STATES OF SO. *Journal of Chemical Physics* **1979**, *71*, 3761-3769.

(4) Swope, W. C.; Andersen, H. C. A MOLECULAR-DYNAMICS METHOD FOR CALCULATING THE SOLUBILITY OF GASES IN LIQUIDS AND THE HYDROPHOBIC HYDRATION OF INERT-GAS ATOMS IN AQUEOUS-SOLUTION. *Journal of Physical Chemistry* **1984**, *88*, 6548-6556.

(5) Swope, W. C.; Andersen, H. C.; Berens, P. H.; Wilson, K. R. A COMPUTER-SIMULATION METHOD FOR THE CALCULATION OF EQUILIBRIUM-CONSTANTS FOR THE FORMATION OF PHYSICAL CLUSTERS OF MOLECULES - APPLICATION TO SMALL WATER CLUSTERS. *Journal of Chemical Physics* **1982**, *76*, 637-649.

(6) Swope, W. C.; Andersen, H. C. 10(6)-PARTICLE MOLECULAR-DYNAMICS STUDY OF HOMOGENEOUS NUCLEATION OF CRYSTALS IN A SUPERCOOLED ATOMIC LIQUID. *Physical Review B* **1990**, *41*, 7042-7054.

(7) Bagchi, K.; Andersen, H. C.; Swope, W. Computer simulation study of the melting transition in two dimensions. *Physical Review Letters* **1996**, *76*, 255-258.

(8) Bagchi, K.; Andersen, H. C.; Swope, W. Observation of a two-stage melting transition in two dimensions. *Physical Review E* **1996**, *53*, 3794-3803.

(9) Haas, L. M.; Schwarz, P. M.; Kodali, P.; Kotlar, E.; Rice, J. E.; Swope, W. C. DiscoveryLink: A system for integrated access to life sciences data sources. *Ibm Systems Journal* **2001**, *40*, 489-511.

(10) Fitch, B. G.; Germain, R. S.; Mendell, M.; Pitera, J.; Pitman, M.; Rayshubskiy, A.; Sham, Y.; Suits, F.; Swope, W.; Ward, T. J. C.; Zhestkov, Y.; Zhou, R. Blue Matter, an application framework for molecular simulation on Blue Gene. *Journal of Parallel and Distributed Computing* **2003**, *63*, 759-773.

(11) Pitera, J. W.; Swope, W. Understanding folding and design: Replica-exchange simulations of "Trp-cage" fly miniproteins. *Proceedings of the National Academy of Sciences of the United States of America* **2003**, *100*, 7587-7592.

(12) Swope, W. C.; Pitera, J. W.; Suits, F. Describing protein folding kinetics by molecular dynamics simulations. 1. Theory. *Journal of Physical Chemistry B* **2004**, *108*, 6571-6581.

(13) Swope, W. C.; Pitera, J. W.; Suits, F.; Pitman, M.; Eleftheriou, M.; Fitch, B. G.; Germain, R. S.; Rayshubski, A.; Ward, T. J. C.; Zhestkov, Y.; Zhou, R. Describing protein folding kinetics by molecular dynamics simulations. 2. Example applications to alanine dipeptide and beta-hairpin peptide. *Journal of Physical Chemistry B* **2004**, *108*, 6582-6594.

(14) Chodera, J. D.; Singhal, N.; Pande, V. S.; Dill, K. A.; Swope, W. C. Automatic discovery of metastable states for the construction of Markov models of macromolecular conformational dynamics. *Journal of Chemical Physics* **2007**, *126*.

(15) Chodera, J. D.; Swope, W. C.; Pitera, J. W.; Seok, C.; Dill, K. A. Use of the weighted histogram analysis method for the analysis of simulated and parallel tempering simulations. *Journal of Chemical Theory and Computation* **2007**, *3*, 26-41.

(16) Horn, H. W.; Swope, W. C.; Pitera, J. W.; Madura, J. D.; Dick, T. J.; Hura, G. L.; Head-Gordon, T. Development of an improved four-site water model for biomolecular simulations: TIP4P-Ew. *Journal of Chemical Physics* **2004**, *120*, 9665-9678.

(17) Horn, H. W.; Swope, W. C.; Pitera, J. W. Characterization of the TIP4P-Ew water model: Vapor pressure and boiling point. *Journal of Chemical Physics* **2005**, *123*.

(18) Cerutti, D. S.; Rice, J. E.; Swope, W. C.; Case, D. A. Derivation of Fixed Partial Charges for Amino Acids Accommodating a Specific Water Model and Implicit Polarization. *Journal of Physical Chemistry B* **2013**, *117*, 2328-2338.

(19) Mobley, D. L.; Liu, S.; Cerutti, D. S.; Swope, W. C.; Rice, J. E. Alchemical prediction of hydration free energies for SAMPL. *Journal of Computer-Aided Molecular Design* **2012**, *26*, 551-562.

(20) Swope, W. C.; Horn, H. W.; Rice, J. E. Accounting for Polarization Cost When Using Fixed Charge Force Fields. I. Method for Computing Energy. *Journal of Physical Chemistry B* **2010**, *114*, 8621-8630.

(21) Vosmeer, C. R.; Rustenburg, A. S.; Rice, J. E.; Horn, H. W.; Swope, W. C.; Geerke, D. P. QM/MM-Based Fitting of Atomic Polarizabilities for Use in Condensed-Phase Biomolecular Simulation. *Journal of Chemical Theory and Computation* **2012**, *8*, 3839-3853.

(22) Appel, E. A.; Lee, V. Y.; Nguyen, T. T.; McNeil, M.; Nederberg, F.; Hedrick, J. L.; Swope, W. C.; Rice, J. E.; Miller, R. D.; Sly, J. Toward biodegradable nanogel star polymers via organocatalytic ROP. *Chemical Communications* **2012**, *48*, 6163-6165.

(23) Swope, W. C.; Carr, A. C.; Parker, A. J.; Sly, J.; Miller, R. D.; Rice, J. E. Molecular Dynamics Simulations of Star Polymeric Molecules with Diblock Arms, a Comparative Study. *Journal of Chemical Theory and Computation* **2012**, *8*, 3733-3749.