THE JOURNAL OF PHYSICAL CHEMISTRY B

Special Issue Preface

pubs.acs.org/JPCB

Autobiography of J. Andrew McCammon

I was born in Lafayette, Indiana, on a snowy February 8, 1947. My mother Jean McClintock McCammon and father Lewis Brown McCammon, Jr., had been undergraduates at Purdue; my maternal grandfather was Professor of Horticulture there. My dad started graduate study in civil engineering at Purdue but was called up for US army service in Burma after Pearl Harbor. My older brother, Lewis III, arrived in 1943 and my younger brother, Thomas, arrived in 1950, all in Lafayette, where my dad had returned to complete his Ph.D. Two of my earliest memories were of my dad leaning against the kitchen doorframe, talking with my mom at the hospital by phone a day or two after Tom's birth, and—later—of my mom's father teaching me how to graft buds to grow new branches onto fruit trees. The latter helped to trigger my lifelong interest in biology. Another influence that developed only later was my dad's enthusiasm for mathematics, gained from one of his Ph.D. advisors, Charles Ellis, a structural dynamicist who designed the Golden Gate Bridge in San Francisco, California. This later influence was to save me from academic disaster, as described below.

INAUSPICIOUS BEGINNINGS

Soon after Tom's birth, our family moved to Alhambra, California, where my dad worked at an engineering firm while completing his thesis. I largely grew up in Alhambra, though we had a two-year diversion to Evanston, Illinois, where my dad taught at Northwestern University before returning to engineering practice in Alhambra. My early educational pursuits during these years were unpromising in the extreme. My parents had arranged for me to start preschool two years early at the Purdue Lab School, but I was held back for a year, apparently due to my efforts to organize the students to do the opposite of what the teacher directed. My subsequent school years in Alhambra and Evanston were largely spent in disciplinary time, sitting in a back corner of the room. My reading developed well, though I had an inordinate interest in comic books. However, I seemed incapable of arithmetic, finally flunking the fourth grade around 1954—defeated by multiplication....

Everything changed after July 1955, when President Eisenhower announced the US earth satellite program. Walt Disney was a great supporter of space exploration, and one of the comic books I read soon after was a Disney classic about human exploration of space. Solar mirrors that focus sunlight were part of the mix. I was intrigued, and asked my dad how such mirrors were made. He pulled out volume "P" of the encyclopedia, showed me the basic equation for parabolas, and proceeded to plot a parabola on graph paper. With this as a guide, he used a jig saw to make parabolic wood frames, applied aluminum foil, and—voila!—we had a solar mirror. I never had trouble with math again. On October 4, 1957, the Soviet Union launched the first Sputnik satellite. July 1957 through December 1959 was also the first International Geophysical Year, with lots of attention to sun spots and other cool stuff. I became hooked on science.

As a student at San Gabriel High School in Alhambra, I was allowed to take chemistry a year early and then to volunteer as a teaching assistant for the class the following year. This provided unsupervised access to the supply room, resulting in a variety of pyrotechnic explorations that would not be allowed today. Thermite reactions with steel wool wrapped in aluminum foil drew a stern reprimand due to the holes left in the street asphalt. I was fortunate enough to win the LA Times Scholarship in Science in 1965, with an embarrassing amount of publicity. An organic chemistry professor, Corwin Hansch, convinced me that Pomona College was the right place for my undergraduate work. Many benefits resulted, most important of which was meeting my future wife, Anne Woltmann, but also including opportunities for summer research at Pomona, MIT, Berkeley, and Harvard.

In 1969, I started graduate school in chemical physics at Harvard, with the threat of the draft hanging over my head. The Vietnam War was in full force. I had secured conscientious objector status but was still liable to be called up. Indeed, when my draft number for 1970 was assigned, I was certain to be called, so I elected to volunteer to start my alternative service at the end of the 1969−1970 academic year. Such service was typically done in a hospital, so I found the easiest place to get to by subway—the Massachusetts General Hospital. For the next two years, I worked as a technician in the MGH thyroid biochemistry lab, mostly doing clinical assays but also helping with research projects. I wound up coauthoring my first two papers, one in the *Annals of Internal Medicine* and one in *Endocrinology*. The latter involved a bit of basic research, pointing to the possibility of cooperative effects in the binding of antigens to antibodies. The possibility that such effects might involve the relative motion of the antigen-binding arms of the antibody molecule stimulated my thinking about models of protein dynamics.

Upon returning to the Ph.D. program in 1972, I started a project on computational study of protein conformations with Martin Karplus. Martin soon decided to relocate to Paris, possibly a permanent move. I approached John Deutch, who was on sabbatical from MIT at Harvard; John kindly agreed to become my day-to-day thesis supervisor, with Martin as cochair of my thesis committee. I proceeded to work on a simple model of phase transitions in lipid bilayers, and more extensively on theoretical hydrodynamics of biopolymers, completing my Ph.D. in 1976. In the process, I had accidentally learned the basics of equilibrium and nonequilibrium statistical mechanics, which proved handy in later work.

MOLECULAR AND BROWNIAN DYNAMICS

Martin did return to the Harvard Faculty, and agreed to accept me as a postdoctoral fellow. His group had recently started developing computational tools for studying conformational

Special Issue: J. Andrew McCammon Festschrift

Published: August 25, 2016

DOI: 10.1021/acs.jpcb.6b00834
J. Phys. Chem. B 2016, 120, 8057−8060

changes in proteins. I was encouraged to try to come up with a new problem to which these tools could be applied. A few days later, I found myself paging through a biochemistry text in the chemistry library, and stopped at a picture of the enzyme lysozyme. Lysozyme's two lobes, divided by its active site cleft, brought to mind a tuning fork, and reminded me of the possible arm-waving of antibody molecules we had considered at MGH. Using Bruce Gelin's molecular mechanics software, which provided estimates of the potential energy of different protein conformations, we produced a harmonic oscillator model for the opening and closing of the lysozyme active site. With advice from Peter Wolynes on the solvent frictional behavior, we developed a simple dynamical model for the overdamped fluctuations of the active site that appeared in *Nature* in 1976. Bruce, Martin, and I began working at the same time on software to simulate the unconstrained dynamics of all of the atoms in a protein—a "molecular dynamics" (MD) simulation. Anees Rahman and Frank Stillinger had reported the first MD simulation on liquid water in 1971, and Anees was kind enough to provide code for the predictor-corrector algorithm for integrating Newton's equation of motion. My job was to combine the protein molecular mechanics software with the dynamics software, which we had working by May 1976, and then to use this to conduct and analyze the first protein MD simulation during a two-month workshop at CECAM in Orsay, France, during May–July 1976.

My original plan for protein MD was to study protein folding and unfolding, which was a popular topic at the time. I deleted the covalent bonds associated with the three disulfide groups in the 58-residue protein, bovine pancreatic trypsin inhibitor (BPTI), and initiated the dynamical simulation. Disaster ensued! I had neglected to separate the bonded sulfur atoms to a nonbonded distance before beginning the dynamics. The prodigious forces acting on these atoms led them, and the associated polypeptide chain, to rocket apart and flail around wildly. Chastened, I decided instead to investigate the dynamics of the folded protein. This simulation revealed a fluid-like motion of the atoms in the protein interior, and other features seen in innumerable subsequent simulations. The BPTI simulation was described in *Nature* in 1977. The CECAM meeting was very important in my career. Beyond the MD work, I met Don Ermak, with whom I developed Brownian dynamics simulation methods for diffusional simulations. I also met Herman Berendsen, a wonderful person who had many far-sighted ideas about simulations; Wilfred Van Gunsteren, just starting his postdoc with Berendsen; Michael Levitt; Anees Rahman; and many other stellar scientists.

My postdoc years at Harvard, 1976–1978, also provided my first exposures to the federal grant funding process. Soon after our paper on protein MD appeared, Martin asked me to help evaluate a remarkable NSF proposal from Kent Wilson, a visionary scientist at UCSD who would later have a major influence on my career trajectory. Kent's proposal included futuristic features for protein MD simulations, including a haptic interface by which one could sense on one's fingers the stiffness of different parts of the structure. Also, several Harvard structural biologists, including Martin, Steve Harrison, and Don Wiley, submitted an NIH proposal for an early VAX computer from the Digital Equipment Corporation. Martin was away during the site visit, and asked me to represent the theoretical side of the work. The most vivid memory I have of the site visit was of the eminent protein crystallographer, Paul Sigler, who was a member of the review group. Sigler was initially very skeptical of MD simulations, but by the end of the visit, he was bubbling over with ideas about how they could be used.

HOUSTON: COMPUTATIONAL ALCHEMY AND DRUG DISCOVERY

I started my first faculty position at the University of Houston in 1978. While assembling a small research group (postdocs Scott Northrup, Mike Pear, Boryeu Mao, and Max Berkowitz) and writing lectures and grant proposals, I was able to stay closely involved in research efforts focusing on how to simulate activated processes, diffusional motions of polypeptides including helix–coil transitions, and other basic phenomena. Steve Harvey joined the group for a sabbatical in 1981, and led efforts in the area of RNA—including the first study of tRNA flexibility and the first MD simulation of RNA, which appeared in *Nature* and *Science*, respectively. Steve and I subsequently wrote a monograph, "Dynamics of Proteins and Nucleic Acids" (Cambridge University Press, 1987). The challenges of authorship were rewarded by treats such as dinner at an excellent Thai restaurant in Houston.

My focus on basic research expanded in the early 1980s when the wife of a close colleague developed cancer. I became very interested in the possible use of molecular dynamics simulations for drug discovery. How could one calculate relevant thermodynamic quantities, such as the free energy of binding an inhibitor to an enzyme? An answer came during another CECAM meeting in Orsay, in July 1983. Herman Berendsen was describing the use of thermodynamic perturbation theory to calculate the change in the free energy of spherical cavities in water with increasing cavity radius. It was a warm afternoon; my mind was wandering a bit. However, suddenly I visualized the use of thermodynamic perturbation theory to calculate the change in free energy of an enzyme–inhibitor complex, when the inhibitor is changed into a slightly different molecule while bound to the enzyme. With a corresponding calculation for the inhibitors in water, one could use thermodynamic cycle arguments to compute the relative binding strengths of the inhibitors—something that should be useful in drug discovery. Bhalu Tembe, a postdoc, soon completed a demonstration simulation with an extremely simple model. It was rejected by *Nature*, for lack of general interest, and published in an obscure computational chemistry journal in 1984. Another postdoc, Terry Lybrand, completed the first such "computational alchemy" study of molecular recognition with an experimentally characterized host–guest model the next year. Ironically, it was rejected by *Science* because the idea had already been described, so the work appeared in *PNAS* in 1986. The first applications to enzymes were done by Chung Wong, who had recently joined the group following his Ph.D. studies at the University of Chicago. Chung calculated the effects of placing a fluorine atom in the para position of the inhibitor benzamidine; this was shown to reduce the inhibitor's affinity for trypsin, largely due to unfavorable solvation effects. Chung subsequently used alchemical methods to model a mutation into trypsin and calculate the resulting change in ligand binding affinity.

During these early years in Houston, another major motivation for working on drug discovery developed, with the appearance of the HIV/AIDS epidemic. The NIH responded to this crisis with a bold program, the AIDS-Related Structural Biology Program, to promote the discovery of antiviral therapies based on structures of the molecular components of HIV. A group of UCSD faculty members had

DOI: 10.1021/acs.jpcb.6b00834
J. Phys. Chem. B 2016, 120, 8057–8060

started Agouron Pharmaceuticals, the first company focusing on structure-based drug discovery, in 1984, and Agouron immediately began to plan a program targeting the HIV protease enzyme. I was recruited as a consultant to develop Agouron's computer-aided drug discovery efforts and to help write their grant proposal in response to the new NIH program. The proposal led to a site visit, and the chair of the site visit team was Pete von Hippel of the University of Oregon. When I described our ideas of using computational methods for drug discovery, the experience was eerily similar to the Harvard VAX site visit. Von Hippel was skeptical at first but soon the most enthusiastic of the visitors. Fortunately, the grant was awarded, my postdoc Russ Bacquet joined Agouron as its first computational scientist, and Agouron went on to develop nelfinivir (Viracept), for many years the most widely prescribed protease inhibitor for HIV infections.

Research work in Houston also continued on development of theory and computational methods for molecular biophysics. With postdocs Scott Northrup and Stu Allison, we developed theory for using Brownian dynamics simulations, combined with analytical methods, to calculate rate constants for diffusion-controlled enzymatic reactions, using realistic models for the enzymes and their interaction with substrate molecules. Our University of Houston Brownian Dynamics (UHBD) software package was created thanks to Jeffry Madura, Jim Briggs, Rebecca Wade, Malcolm Davis, Brock Luty, and others. Libby Getzoff's group at The Scripps Research Institute used UHBD to engineer superoxide dismutase enzyme mutants with predictably modified catalytic rates, described in *Nature* in 1992. Our own studies of substrate diffusion to acetylcholinesterase (AChE) were soon followed by molecular dynamics studies of this superefficient enzyme, which is critical to nerve and muscle action. This work ultimately led to Anne and me moving to San Diego, California. The AChE work caught the attention of the strong group of young structural biologists who had coalesced in Toronto. I was invited to speak at a symposium there in 1993 to represent the field of computational structural biology. Mike Gilson, a gifted postdoc who had joined our group in 1991, was using molecular dynamics to discover a possible "back door" in the enzyme that might be important in its function. This work led to a cover article in *Science* in 1994, and I was able to present some of the preliminary results in my lecture in Toronto. Susan Taylor of UCSD was invited to speak at the Toronto meeting on protein crystallography—her group had recently determined the first structure of a catalytic subunit of a protein kinase. She mentioned that Palmer Taylor of UCSD was very active in experimental studies of AChE, which I knew, but I was embarrassed a bit when she also mentioned—but I had not known—that they were married. I was soon recruited to UCSD for a joint position in Pharmacology (chaired by Palmer Taylor) and in Chemistry & Biochemistry (chaired by Katja Lindenberg). A significant inducement was the Joseph E. Mayer Endowed Chair in Theoretical Chemistry created by Kent Wilson, whose NSF proposal I had reviewed as a postdoc at Harvard.

UCSD: NEW TOOLS AND GIFTED COWORKERS

It is common knowledge that time seems to go faster as one ages, and the twenty-plus years (late 1994 to date) at UCSD have indeed been something of a blur. However, surely, the exceptional students, postdocs, and collaborators who have kept me hopping contributed to this feeling. Much of the work at UCSD has involved the development of new theory or simulation methods. Our studies of diffusional processes such as protein−protein encounters benefitted from new methods for calculating electrostatic interactions in large systems—the Adaptive Poisson−Boltzmann Solver (APBS)—developed by Nathan Baker in collaboration with Mike Holst of UCSD's math department, and for simulating Brownian motion—embodied in the BrownDye software developed by Gary Huber. Xiang Zhou, now at Florida State University, spent several mini-sabbaticals in our group. One result has been a deeper understanding of gated diffusion-influenced reactions. For example, we were able to show that, although the entry channel to the enzyme AChE is closed most of the time, it opens frequently enough that the kinetics of normal substrate binding are hardly affected. Jung-Hsin Lin, Alex Perryman, and Julie Schames developed the "relaxed complex scheme" in which many conformations of a drug target from MD simulations are used in virtual screening of small-molecule libraries, allowing for the effects of target flexibility. Rommie Amaro greatly increased the efficiency of the relaxed complex method by introducing a clever way to select representative target conformations. Donald Hamelberg and John Mongan invented "accelerated MD" (aMD), which allows greatly enhanced sampling of molecular conformations. This method has been enhanced with the invention of Gaussian aMD by Yinglong Miao; GaMD allows for the efficient calculation of free energy landscapes of proteins and other large molecules. John Mongan in collaboration with Dave Case from TSRI also developed a constant-pH MD method, which allows for changes in the protonation states of solute molecules during MD simulations. Olivia Kim and Pat Blachly showed how such methods can be used to compute the pH dependence of binding affinities of ligands and receptors. Joe Dzubiella and Jessica Swanson created a variational model of implicit solvation, which allows for balanced treatment of polar and apolar contributions. Joe and Bo Li of UCSD's math department led efforts that turned this model into a useful tool for studying the solvation of proteins and other complex solutes.

In addition to the development of new methods, the group at UCSD has been very active in applying theory and simulations to elucidate biochemical mechanisms and to advance drug discovery. Ady Elcock used Brownian dynamics to show how electrostatically restrained diffusion of charged intermediates can lead to "channeling" from one active site to another in a bifunctional enzyme. Dave Sept used APBS and Brownian dynamics to deepen our understanding of actin polymerization, and Barry Grant used them to show how electrostatics may contribute to kinesin migration on microtubules. MD studies by Heather Carlson, Richard Henchman, and Julie Schames led to the discovery that the very flexible active site region of HIV integrase can bind multiple poses of inhibitors; this contributed to the development of the first FDA-approved HIV/AIDS drug targeting that enzyme. Other work related to drug discovery included Rommie Amaro's use of the relaxed complex scheme to find drug leads for African sleeping sickness, Alex Gorfe and Barry Grant's discovery of the remarkable flexibility of the small G-protein Ras—opening the way to discovery of allosteric modulators, Yinglong Miao's similar discoveries for the much larger, membrane-bound G-protein-coupled receptors, and Steffen Lindert's identification of prospective antibiotics (with Bill Sinko and Cesar Oliveira, in collaboration with Eric Oldfield's group at UIUC) and modulators of cardiac activity

DOI: 10.1021/acs.jpcb.6b00834
J. Phys. Chem. B 2016, 120, 8057−8060

(in collaboration with Brian Sykes's group at University of Alberta).

Looking back on the tricostal adventures outlined above, I find—as so many teachers have before—great pleasure in following the careers of my former students and collaborators. There have been far more of these than I could mention here, and they are primarily responsible for our group's progress. As I have often said in seminars, much of my activity as time has gone on has been in areas that I was never trained for: small businessman, matchmaker (usually unwittingly), immigration counselor, and psychologist, to name a few. It has been a pleasure to provide gifted students an environment in which so many could thrive.

J. Andrew McCammon

DOI: 10.1021/acs.jpcb.6b00834
J. Phys. Chem. B 2016, 120, 8057−8060