

COMMENTARY

Recollection

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I would like to thank Carol Post and Charlie Brooks for organizing this special Festschrift issue of *Protein Science* in my honor and I thank Brian Matthews and the Protein Society for approving it. I am very glad to have an opportunity in this recollection to look back briefly on my work and my associations. I have E. Bright Wilson to thank as the person who pointed me in a direction that had such a formative effect on my career path. As a student in the Graduate Program in Biophysics at Harvard in the 1970s, I was taking courses that I liked, and was involved in a research project that I did not. I took a course from Professor Wilson and sought advice from him about new research opportunities in biophysics. He suggested that I try to find Martin Karplus to speak with the next time Martin was in town. I took Wilson's advice and the conversation with Martin eventually led to a four-year postdoctoral stay in his lab which launched my career. I found the environment in New Prince House exhilarating. Thinking back on that time, I am often struck by the fact that the friends and competitors I was interacting with during that period included several of the people who would form my professional community for more than thirty years. I thank Martin for creating and fostering that environment. After a very brief stint in old Prince House where

my office mate was Peter Rossky, my first office mate in the newly-renovated space in Mallinckrodt was Bruce Gelin whose generosity in sharing programs helped break the ice for me. Also in the Karplus group at the time were Andy McCammon, Peter Rossky, Dave Case, Wilfred van Gunsteren, Toshicko Ichiye, and Bernie Brooks, to name some of the people whose lives have intersected with mine many times over the succeeding decades. I think about my interactions with Peter Wolynes back then, how enthusiastic he was to talk about science and how rewarding the discussions were to me.

I think of myself as one of the founding members of the group of scientists who developed molecular dynamics simulations of proteins into the powerful technique used in biophysics and structural biology that it is today. I take pride in the early work I did to connect molecular dynamics simulations of proteins with Nuclear Magnetic Resonance relaxation probes of protein dynamics. My interest in that subject grew out of a then unpublished manuscript that Martin gave me to read by Wittbert and Szabo on the jump model for NMR relaxation¹; this led to extended discussions about the subject with Attila and to two papers written together that I highly value.^{2,3} Our common interests in NMR experiments on proteins and molecular dynamics simulations was the initial basis for my friendship with Carol Post, a friendship that has been sustained by many scientific discussions over the years and by her incredibly warm personality and our shared interests in wine futures.

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In 1982, totally by chance, I met Richard Friesner at a conference in Austin, Texas. From that first day, Rich talked with passion about his vision for the place of theoretical chemistry in rational drug design. In the 1990s, as a member of the Center for Theoretical Biophysical Chemistry that Rich established at Columbia University, my many interactions with Rich, Bruce Berne, Barry Honig, and Bill Jorgensen had a large influence on the direction of my research program during that era and beyond. My work on solvation effects in chemistry and biophysics, which started in the 1980s, picked up momentum from my interactions with the group at Columbia. Work on linear response theory and the dielectric properties of proteins,⁴ on the hydrophobic effect,⁵ and my initial interest in implicit solvent effective potentials developed during this period as well.

I have had a long association as a scientific advisor to Schrodinger LLC, watching with great respect as it has grown from a company with fewer than a dozen employees in 1995 to one with three hundred employees today. My association with Schrodinger has inevitably sparked my interest in aspects of structure-based drug design that are linked with statistical mechanics. The Binding Energy Distribution Analysis Method (BEDAM)⁶ is a free energy method Emilio Gallicchio and I developed based on Widom's potential distribution theorem, to predict enrichment factors for focused ligand libraries; it occupies a niche between docking on one hand, and more computationally intensive free energy methods on the other. While in the 2013 SAMPL4 challenge, it proved to be the most successful approach to identifying active compounds, we are well aware of how challenging the problem is and how much room there is for improvement. This is an active area of research in my group. BEDAM is implemented in the molecular dynamics simulation program IMPACT (Integrated Modeling Program Applied Chemical Theory)⁷ started in my group in the 1980s. For many years, the IMPACT code formed a core part of Schrodinger's GLIDE docking program very widely used in industry.

While Charlie Brooks and I co-organized a meeting in 1992 on protein folding in San Juan, Puerto Rico, which Bill Eaton has referred to as a seminal event in the field, I actually didn't become very interested in the problem until much later on, in the early 2000s. On the subject of folding, I like our recent papers in *Protein Science* and *PRL*^{8,9} which resolve the paradox of why mean first passage times of unfolded miniproteins can be so long, yet their folding is still two state. Working on protein folding fueled my interest in advanced sampling algorithms, especially replica exchange and Markov State Models. Our 2007 *PNAS*¹⁰ paper on "simulations of simulations" of Replica Exchange proved a point I have frequently made, that while it is easy to implement Replica Exchange, it is harder to use it wisely. I am

actively interested in developing more powerful advanced sampling and analysis algorithms to study rare events. Our papers^{11,12} this year (2015) on asynchronous replica exchange and on stochastic methods for solving the WHAM equations are two examples.

I have had fifty graduate students, postdocs, and research scientists work in my group since starting out as an Assistant Professor of Chemistry at Rutgers University in September 1980. A list of all of my former and present group members can be found at: https://ronlevygroup.cst.temple.edu/levygroup_people.html. While science is at times a solitary pursuit, it is also a social and collaborative one. I learned so much from interacting with everyone in my group, posing and solving problems together, and I hope they learned from me and absorbed some of my enthusiasm, even passion, for being a scientist and for the field. I want to mention by name a few that have had an especially strong effect, for one reason or another, on the direction my research took: Fumio Hirata, Douglas Kitchen, Francisco Figuerido, Nobuyuki Matsubayashi, Emilio Gallicchio, Michael Andrec, and Nanjie Deng—thank you, and I thank all of the present and former members of the Levy group!

As I write this recollection, I am sitting in my office on the seventh (top) floor of a beautiful new glass and steel Science Education and Research Center with a wonderful view of downtown Philadelphia. I am excited by my recent move to Temple University, not least the interactions with my new next door neighbors, Mike Klein, John Perdew, and their research groups. The opportunity to help build world class computational science at Temple is both energizing and one that I am familiar with. I take much satisfaction in looking back at my time at Rutgers, at the leadership role I played there in recruiting top junior and senior faculty, as well as in my many collaborations with the structural biologists at Rutgers. I am glad that this volume will include contributions from some of them.

My parents always wanted to hear me say that I enjoy my work—that it makes me "happy." I was never able to give them the satisfaction of saying exactly that. To me, doing science is too intense an activity to be described in quite this way. Fulfilling—yes, very stressful—definitely. I think they eventually came to appreciate my feelings and to understand that my career as a scientist has been deeply sustaining and rewarding to me.

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