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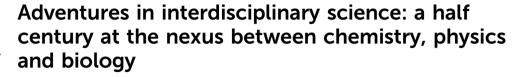
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Judith Herzfeld

science, my overwhelming feeling is one of having been extraordinarily lucky. Fortunate from the start, I was born in a time of optimism, to a family of German Jewish refugees eager to bring old world values and ideas to new world opportunities. By the time I finished elementary school, the space race was on and the New York City public schools were putting new oomph into teaching science. By the time I finished college, some were beginning to think that graduate education of women was not necessarily "wasted". By the time I was in graduate school, biophysics was a nascent field, equipped by recent developments in chemistry, physics and computer technology to explore the mysteries of molecular structure and function in biology. By the time I was on the job market, a few chemistry departments were newly open to diversifying their tenure track facul-

ties, including a venerable men's college

that had yet to admit female students.

Around the same time, a guy showed up

who seemed to sincerely believe that

being married to a woman active in

science would be a positive rather than

a nuisance. By the time I was applying for

faculty fellowships, interviewers were not

necessarily disbelieving of the research

plans of a woman who showed up visibly

As I look back on over five decades in

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pregnant. And, despite the demands of academic science, the long hours were flexible enough to allow at least one parent to be home as needed. To be sure, some developments were silver linings on ugly clouds, clouds that almost propelled me out of science half-way through graduate school. But the silver linings won out. And the forces at play are much clearer in retrospect than they were at the time.

Formative years

It surprises many to hear that I consider growing up in New York City to have been a great experience. Although the singlefamily homes were small, our street on the eastern side of Queens was wide, treelined and quiet enough for kids to play street games, while the postage stamp lots allowed for a bit of creative gardening. In addition, two very large parks near home offered skating in winter and tennis otherwise, while long, sandy beaches lined the southern coast of Long Island.

What distinguished all of this from generic suburbia was superb public institutions. On a personal scale, it is difficult to imagine what my childhood would have been like without a well-stocked, -staffed and -furnished public library close by (for borrowing and studying) and the Girl Scouts of America, from 6-year-old Brownies through 15-year-old Mariner Scouts and the international Senior Round Up in 1962 (for team work, outdoor skills, and self-paced learning1). At the grand end of the spectrum, the cultural institutions of the city, including top-notch theater, worldclass art museums, and the formidable American Museum of Natural History were enormously influential. Winter solstice holidays also brought annual science lectures at the then Rockefeller Institute. Happily, by 12 years old I was deemed old enough and responsible enough to take public transportation into Manhattan, whether by myself or with friends (before the advent of cell phones!).

Of course, schools are the most central of all the public institutions growing up. I benefited from attention paid to individual differences and a long-standing NYC program that selected capable students to complete grades 7-9 (usually ages 12-15) in two years. In addition, when I reached that level in 1961, the impetus of Sputnik had led the schools to also offer some of the accelerated students a year of earth science during those same two years. Since the elementary schools were science deserts in the 1950's, I didn't know what to expect in the new program, but the fit (recommended by my teachers and agreed to by my parents) was a good one. And, although I didn't take notice at the time, in retrospect I have often thought that it made a difference for the girls in the class that the new science program was entrusted to an enthusiastic female teacher, Esther Daly, the only female science teacher I had until I got to a women's

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college years later. On the negative side, girls were not offered a shop class until high school. However, Home Economics had its moments, particularly the topological exercise of transforming 2D clothing patterns into 3D garments and the operation of sewing machines.

The only subject with which I became bored in those two years of middle school was math and my mother (then a history teacher and guidance counselor) kept my interest from atrophying by starting to teach me algebra at home. Mom's one pedagogic disappointment was that she could not teach me to play bridge because my mind kept wandering to things that seemed more interesting. She finally gave up when I declared that I really couldn't care less who had which cards! Among Dad's pedagogic achievements was teaching me to ride a bicycle and drive the family's manual shift car. He was also a model of life-long, selfeducation: although he had not had the chance to finish high school and English was his third language, his English vocabulary was greater than that of most native speakers based on daily front-toback reading of the New York Times (in part to stay informed of the doings of his most famous business customers).

In high school, teachers saw to it that I was placed in challenging classes, worked on the school science and math magazine (as the science editor during my senior year), and participated in science fairs (including the 1964 National Science Fair with award of the 1st Army Prize). Choosing a college was relatively simple because the closest of the Seven Sisters happened to be the one with the best track record of sending its students to graduate school. Barnard College would combine the benefits of the attention afforded by a small college with access to the broad offerings of the rest of Columbia University.

Applying to graduate school was more complicated. I consider it a testament to the support that I received in the NYC public schools and at Barnard that, when my Nobel Laureate physics professor at Columbia responded "It doesn't matter." to my inquiry about which graduate program I should choose, I assumed that he meant that they were all indistinguishably excellent. As it happened, my accomplished

Barnard advisor, Bernice Segal, knew him well and explained that what he meant was that he thought that graduate education was wasted on women "out of bitterness" that his physicist daughter had "stayed home with her children". That his was an emotional reaction explained his turning to the window as he spoke his three words and remaining silent as I said good-bye. Still, I naively assumed that this was an isolated case. It was later, in Cambridge, that I realized that many leading scientists in the 1960's considered graduate education for women to be a doubtful experiment. All that I can say in their defense is that few of them had ever interacted with a female scientist and most therefore had no idea what to expect of their protégées. On the other hand, as scientists, they had enough respect for data that they could gradually be persuaded by numbers that eventually came forth. However, the process was slow and the burden of proof was clearly on the women.

My move from Barnard College to MIT in 1967 would begin a pattern of oscillating between general and technical institutions. From MIT, I went to study at the Harvard Kennedy School (1971-1973) and then to teach and carry out research at Amherst College (1973-1974), Harvard Medical School (1974-1985) and Brandeis University (1985-present). This peripatetic trajectory was driven by two factors. The first was that my years at MIT coincided with protests against the Vietnam war, growing concern about the environment, and outright alarm about global population growth. Among veterans of the Manhattan Project, the atomic physicist Jerrold Zacharias took time to mentor MIT students concerned about the social context of science and, with a public policy degree from the Harvard Kennedy School under my belt, Amherst College hired me with the idea that I could teach science policy as well as chemistry. However, I then did what everyone in those days said a woman would do if you hired her, which was leave to marry: since my fiancé wanted very much to stay at MIT, even though his was a research staff position at that time, I returned to Boston, first taking a position at Harvard Medical School and then settling at Brandeis. (Amherst College did replace me with another woman, but a married one with a "portable" spouse.) Although my peregrination was unconventional, it was also rewarding. Each environment was stimulating in its own way, making for many interesting experiences in the lab, in classrooms, and on committees with a very wide range of mandates. Indeed, my book on navigating obstetrical care arose from the circumstance of being pregnant while on a medical school faculty, with access to a medical library.2

Experiment and theory

My first research experiences were experimental: under the auspices of a high school research program, I spent the summer of 1963 collecting ORD data on gramicidin in Murray Goodman's lab, at that time at the then Brooklyn Polytechnic Institute; and, under the auspices of a college research program, I spent the summer of 1966 taking EPR spectra of small free radicals in Jack Freed's lab, at Cornell University. These were wonderful introductions to the power of spectroscopy to probe the characteristics of molecules. On the other hand, in college courses I became enamored of the ability of theory to concisely explain and synthesize a wide range of observations. After introductory physics courses elaborated the scope and power of classical mechanics and electromagnetic theory, physical chemistry (with Bernice Segal) and quantum chemistry (with Bruce Berne) boasted the ability of wave mechanics to come to grips with such apparently disparate phenomena as electron diffraction, the lines of atomic spectra, the radii of atoms, and the structure of the periodic table.

When I arrived at MIT in 1967, there were two theoreticians in the chemistry department, Irwin Oppenheim and Robert Silbey. But theory was also being applied to biological molecules in Eugene Stanley's group in the physics department, and I found the scope and freshness of those interdisciplinary questions particularly compelling. Thus, Gene became my research advisor, Bob my program advisor and Irwin the chair of my committee. In the course of my doctoral work on allostery, I learned a great deal about proteins.

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I also learned that theory's place in the nascent field of biophysics was a bit marginal: without oversimplifying, there were few biomolecular problems that could be modeled with the computing power available in the 1970's. In the interest of hewing closely to experimental observations by avoiding "spherical cow approximations". I decided that, to stay in biophysics, I should be open again to experiments. Spectroscopy was still attractive and nuclear magnetic resonance in particular has the special capability of providing both chemical information (from chemical shifts) and structural information (from dipolar interactions), in mixtures as well as pure samples, without any need to incorporate potentially perturbing probes. It also happened that (my by-then husband) Robert Griffin was establishing a lab for obtaining high resolution NMR spectra from solid samples. This was just what was needed to study biological membranes. So as convergence between evolving technology and evolving questions came into view, my biophysical chemistry research program developed along both theoretical and experimental tracks.

Allostery in oligomeric proteins

Readily available in abundance, myoglobin and hemoglobin were studied early and thoroughly, generating an abundance of data to tempt theoreticians. Functionally, monomeric myoglobin has a simple oxygen saturation curve suitable for a storage protein, while tetrameric hemoglobin has a sigmoid oxygenation curve that facilitates loading and unloading in environments that differ only modestly in pO_2 . By the time that I joined Gene Stanley's group at MIT, three mechanisms had been proposed for the tetramer's homotropic cooperativity. Because it seemed to us that there was no reason for nature to choose just one, we developed a general model that incorporated all three modes of coupling and demonstrated its utility in analyzing data for different hemoglobins under different conditions.3 We also modeled heterotropic cooperativity, in particular the physiologically important effects of pH and phosphates on oxygenation,

providing the first notice of, and explanation for, biphasic saturation curves. Rama Bansil, the successor graduate student on this project, then investigated the effects of phosphate on the kinetics of oxygenation.4

After leaving MIT, I turned my attento glyceraldehyde 3-phosphate dehydrogenases.5 The flexibility of the general model of cooperativity was necessary to comprehensively describe the more complex behavior of these enzymes, including both positive and negative cooperativity and half-of-the-sites reactivity. Further work explored half-of-thesites reactivity in other oligomeric enzymes, confirming that, taking the possibility of metastability into account, halfof-the-sites reactivity could occur in the absence of either oligomer asymmetry or pairwise interactions between sites.⁶

Energy transduction in a light-driven ion pump

After I arrived at Arthur Solomon's Biophysical Laboratory at Harvard Medical School in 1974, Jonathan Cohen, a colleague in the Department of Pharmacology, called my attention to recent papers by Dieter Oesterhelt and Walther Stoeckenius reporting that purple patches in the cell membranes of the Halobacterium salinarum contained a single protein with a retinal chromophore that used light to create a pH gradient across the membrane.^{7,8} Here was an abundantly available integral membrane protein that effectively selfpurified in its native membrane (and happened to be unusually stable)! Not only was this "bacteriorhodopsin" ideal for solid state NMR (ssNMR) studies, but there were sure to be studies forthcoming from other labs using complementary techniques. Enthusiasm carried the day, as my proposal to NIH for ssNMR studies of isotopically labeled samples was met with a positive review that included the foreshadowing comment "This will be difficult, but we should let her try."

The first step was isotopic substitution with spin = 1/2 nuclei. ¹⁵N-histidine seemed a good first target because histidines tend to be important and resonance assignments would be relatively easy as amino acid analyses indicated that there were only one or two histidine residues. However, radio tracers showed no incorporation of label from either histidine or histidine precursors. The nature of this dead-end became clear when DNA sequencing by Gobind Khorana's group showed that there actually is no histidine in the protein! Our next target was lysine; although there were seven, one was unique in forming the Schiff base with the retinal and 15N at that location provided abundant information about the active site. Eventually we also introduced 13C labels on various amino acid sidechains and replaced the native retinal with specifically ¹³C-labeled retinals prepared by Johan Lugtenburg's group in Leiden. In addition, inhouse synthesis produced model compounds that could be used to interpret the 15N and 13C chemical shifts observed in bacteriorhodopsin.

On the instrumental side, the challenges were such that various collaborators were able to use our isotopically labeled samples to assign vibrational spectra before we were able to obtain NMR spectra. Our first instrumental challenge was to spin samples in magic angle rotors fast enough to obtain high resolution spectra. At that time, 3 kHz was pushing the state of the art. Another instrumental challenge was guiding laser light to the spinning sample in order to generate photocycle intermediates that could be trapped at low temperatures. In addition, the Griffin group worked on new ssNMR methods, in particular pulse sequences to obtain dipolar interactions that reflect internuclear distances and dynamic nuclear polarization to vastly improve signal intensities. From my end, contributions to wresting information from NMR measurements were methods for obtaining chemical shift anisotropies from the intensities of spinning sidebands9 and for constructing bias-free multidimensional spectra from data acquired by efficient non-linear sampling. 10-12

The key issue in understanding the ion transport mechanism in bacteriorhodopsin boiled down to understanding how the protonated Schiff base remained connected to the extracellular side of the membrane after light-induced chromophore isomerization and yet spontaneously

changed connectivity to the intracellular side immediately after deprotonation. The NMR data showed that, after photoisomerization, torsion developed in the retinal as the still protonated Schiff base found a new, and stronger, counterion.13 This indicated that the decisive switch in connectivity on deprotonation is due to unwinding of the twisted chromophore as soon as the electrostatic attraction of the Schiff base to the new counterion is voided by proton transfer. We finally determined that, as in the resting state, the counterion is a complex, in this case of a threonine that is hydrogen bonded to aspartic acid on the extracellular side of the membrane.14 In a nice confluence between experiment and theory, the mechanism indicated by NMR was one of the three pathways for which Bondar et al. had previously found viable activation barriers in detailed QM/MM simulations of bacteriorhodopsin.¹⁵

Entropically-driven order in crowded, reversibly self-assembling systems

This project, ultimately funded by The American Heart Association and then NIH, began with a phone call from Robin Briehl at the Einstein College of Medicine. Robin had been studying sickle cell hemoglobin (HbS) and wondered if I could help him pursue his hypothesis that the growth of HbS polymers and their spontaneous alignment are mutually reinforcing. In short order, we were able to demonstrate this coupling for rigid, linear polymers, using Edmund DiMarzio's lattice model¹⁶ to describe the effects of crowding on the entropy of the solutions.

After Robin returned to his experiments, I realized that I could generalize Ed's lattice model to polymers wider than monomers, allowing both lateral and longitudinal contacts, as necessary to describe filament nucleation. In this construct, the lattice spacing could also be shrunk to zero, affording a continuum of particle sizes and translational positions. Of course, the particle orientations were still restricted to three mutually orthogonal lattice axes, a limitation eventually lifted by adopting Cotter and Wacker's formulation of scaled particle

theory¹⁸ and the development of a reliable algorithm for optimizing particle orientation distributions.¹⁹

With a decent model of HbS polymers in hand, we could ask how the behavior of HbS in the heterozygous condition (sickle cell trait) differs from that in the homozygous condition (sickle cell disease). We found that, while a phase of aligned polymers still formed, it was shifted to concentrations even higher than those prevalent in erythrocytes, consistent with the absence of pathology in sickle cell trait.

Since mixtures of polymerizing and non-polymerizing proteins also occur in cells more generally, we turned our attention to the behavior of microtubules and actin filaments crowded by other cytosolic proteins. We found that, under the crowded conditions prevalent in cells, the reversibly assembled polymers will spontaneously form bundles that expel nonpolymerizing proteins.20 In addition, taking differences in diameters and persistence lengths into account, we found that the narrower and more flexible actin filaments and the wider and stiffer microtubules will spontaneously sort into separate bundles.21 This meant that, contrary to the then prevalent dogma, the accessory proteins for these filaments were controlling bundling rather than producing it. We showed specifically that capping proteins could keep filaments short enough to avoid bundling,22 and proposed that molecules cross-linking filaments in parallel could be responsible for controlling the polarity, spacing and register in bundles, while molecules cross-linking filaments at large angles would frustrate bundling.

With our refined lattice model, we were also able to consider the behavior of lyotropic liquid crystals, in particular the phase diagrams of micellar solutions. Taking into account the thermodynamics of forming disk- and rod-shaped micelles, we were able to reproduce the occurrence of columnar and lamellar nematic phases vs. concentration and temperature.²³

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Floatation organelles are functional amyloids

After years of growing *H. salinarum* for its bacteriorhodopsin, we became curious about the gas vesicles that allow these organisms to adjust their depth in the water column. With spindle shaped walls consisting almost exclusively of a single protein, it was unknown how the vesicles could resist pressure or how they could be permeable to water molecules without filling with liquid water. Support for finding out came from NIH and then NSF. Because organisms that live in deeper water have stronger gas vesicles and photosynthetic organisms readily allow uniform isotope substitution, we chose to first study the gas vesicles of Anabaena flos-aquae. Diffraction had detected anti-parallel βsheets and the strength of the vesicles had been attributed to the orientation of the H-bonds at the "magic angle" relative to the vesicle axis. A clue as to how this could be consistent with stabilizing aromatic and electrostatic side chain interactions was detection of duplicate NMR resonances that revealed the presence of an asymmetric dimer.24 The amyloid model that resulted from chemical shift secondary analysis and correlation spectroscopy also indicated a preponderance of hydrophobic residues on the interior surface that would inhibit the nucleation of liquid water. 25,26 The significance of the investment in dimorphism by the deepdwelling A. flos-aquae was underscored by further NMR studies showing that there was no such dimorphism in the relatively weak vesicles of the shallow-dwelling H. salinarium.27

The structures of pre-biotic polymers

Long intrigued by ideas about the origins of life, I noticed that speculation about the roles of amorphous polymers that form readily in the supposed "prebiotic soup" was not matched by any structural information. This led to a short

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NASA-funded project to characterize polymers formed under mild conditions by HCN and by sugars.

We polymerized H¹³C¹⁵N (prepared by a method suggested by my Brandeis colleague Barry Snider) under a variety of conditions. The chemical shifts did not correspond to any of the three structures proposed in the literature. Instead, they indicated three other structures: simple linear and "chicken-wire" polymers formed by direct monomer addition under base catalysis in solution,28 and a polymer with cyclized side chains formed on heating crystals of the HCN tetramer that form in alkaline solution.29

In the case of the sugar polymers, the chemical shifts confirmed the presence of the expected furans, with implications for the formation of pyrroles in the presence of amines. However, selective 13C substitution, ¹H-dephasing, and double quantum filtration revealed that intact sugar molecules are responsible for cross-linking the rings into a network.30

Force fields for semiclassical valence electrons

This research arose out of serving as an examiner for a doctoral thesis on atomistic force fields in 2003. Although simple atomistic force fields, with harmonic potentials for bond lengths and bond angles, and periodic potentials for bond torsion, were originally developed to model the conformations and vibrational modes of small molecules, the force fields were gradually being elaborated to address more demanding scenarios. In addition to defining and parameterizing multiple atom types for each element (e.g., aromatic C vs. aliphatic C, vs. amide C, etc.), the elaborations involved adding and parameterizing models for polarization and even reactivity. Acceptance of these accumulating costs of avoiding an explicit description of the electrons was based on the notion that the only alternative was some form of onerous wave mechanics. However, chemists have routinely gotten lots of mileage from semiclassical descriptions of valence electrons and these "Lewis dots" accord well with

highly localized orbitals derived from wave mechanics. It therefore seemed worthwhile to explore the degree to which the semi-classical picture could be rendered quantitative. It was a long, mostly unfunded, slog to find good potential forms for the interactions of semiclassical valence electrons with each other and with kernels, but a path gradually became clear enough to garner a round of NSF funding at the end.

We began with water, comprising protons, oxygen kernels and valence electron pairs. With three independently mobile types of particles, we eventually found six pairwise potentials (three between like particles and three between unlike particles) that would reproduce the structures and relative energies of water and water dimer in all protonation states (without different atom types). This LEWIS force field actually gave a better description of polarizability, ion diffusion, surface charge, and acid-base reactions in bulk water than DFT had.31-35

To generalize beyond water, we had to allow electrons to have variable cloud diameters as well as spatial coordinates.36-38 For potential forms taking electron spread into account, we eventually generalized from the analytical functions corresponding to Coulomb and exchange integrals for floating spherical Gaussian orbitals.39 The new LEWIS-B potential for "breathing" valence electron pairs (parametrized on the structures and relative energies of small hydrocarbons, without atom types) is able to not only describe larger hydrocarbons, including linear, branched, and cyclic compounds in various protonation states, but also efficiently simulates carbocation addition to a double bond and cation migration to a neighboring carbon.40

Finally, after sorting contributions corresponding to Coulomb and exchange integrals, we arrived at pairwise potentials for single valence electrons that take spin into account. Although not trained to do so, these potentials produced Linnett-type structures for acetylene and benzene.41 Dubbed LINNETT, the force field shows that semi-classical electrons can provide an efficient alternative to ab initio methods in predicting the separation of electron pairs in diamagnetic hydrocarbons. Given these encouraging results, it is gratifying to see that a new generation is beginning to explore subatomistic force fields based on the concept of semi-classical electrons. 42

Teaching

If anything, the importance of helping young people to learn about science has only become more compelling in recent years and teaching is a satisfying way to honor past teachers and pay it forward. Aside from outreach to local schools, the biggest audiences that academic scientists have is usually in the introductory courses and the courses for non-science students. It is also the case that there are wonderful opportunities for creativity in these courses. In a course for non-science students interested in the environment, I interleaved lessons on environmental chemistry with John Lovelock's writing about his "Gaia Hypothesis". For a firstyear seminar, which is supposed to include disciplines outside the sciences, I chose the topic of behavioral determinism, with reading on neuroscience and neural networks bookended by Mark Twain's two-man play What is Man? at the start and the concluding chapters of Derk Pereboom's philosophical work Living Without Free Will at the end. Although the content of general chemistry is mandated, I undertook two efforts to improve engagement, starting in 1995. One was to reorder the topics to thread a history of our material world from nucleogenesis to anthropic perturbations, a progression that had been appreciated in my environmental chemistry course. The other change was to flip the classroom for active learning, primarily by creating a comprehensive set of "ConcepTests" with which to implement Eric Mazur's Peer Instruction method across all topics,43 but also by developing games with natural rules44,45 and drawing exercises focused on central concepts and details of apparati. Teaching innovations were well received and I hope to find time in retirement to broaden access to relevant materials.43 The most recent is a short, open-access primer for classical and statistical thermodynamics.46

Privilege

Profile

Perhaps all scientists think that the era in which they were active was exceptional, but I can't help but marvel at what science has learned in the past half century. In any case, it has been an enormous privilege to have participated in that puzzle-solving enterprise. This includes the opportunity to work alongside young people on campus and engage with peers around the world. The public is often unaware of how social and entrepreneurial science is. I am particularly grateful to the graduate students who joined each project in its earliest stages, when there was no guarantee that it would fly, and the exceptional reviewers who saw merit in risky projects that were outside of the mainstream. Awards bestowed along the way, were the icing on the cake. The one regret is how fast the time goes by. On the other hand, that is an understood measure of having fun.

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