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Frontiers in Computational Biophysics: A Symposium in Honor of Martin Karplus

Meeting Review

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A symposium in honor of Martin Karplus (Figure 1) and 50 years of scientific contributions was organized by Bernard Brooks, Toshiko Ichiye, and Richard Pastor and held at the National Institutes of Health on April 30, 2005. Since the start of his career in academic research on the chemistry faculty at the University of Illinois in 1955, Martin has published 735 scientific papers and two books and has worked with nearly 220 students, postdoctoral associates, and visiting scientists.

Martin was born in Vienna in 1930, destined by family tradition to become a physician. But times were changing in Austria, and nine years later the Karplus family fled to the United States to escape persecution by the Nazis. They settled near Boston, and Martin attended Newton High School, where his remarkable intellectual abilities soon became evident. His first major foray into science came as the result of a gift of a pair of binoculars, and Martin used them to observe the activities of the local bird populations. At the age of 16 he had a long article on alcids (a species of seabirds that includes auks) published in the Bulletin of the Massachusetts Audubon Society. These studies also took him to the White House, as a winner of the Westinghouse Science Talent competition, to be congratulated by President Truman. After graduating from high school at the top of his class, Martin went to Harvard on a scholarship and rapidly came to the conclusion that to understand biology one needs to have a firm grasp of physics and chemistry, a message that much of the rest of the world is only now beginning to understand.

After Harvard Martin moved to the California Institute of Technology, having received advice from J. Robert Oppenheimer (Princeton University) and Linus Pauling, the latter eventually becoming his Ph.D. supervisor. Following his graduate work on hydrogen bonding, Martin won an NSF scholarship that allowed him to travel to Oxford in 1953 and become a postdoctoral fellow with Charles Coulson. From there he rediscovered Europe and began a lifelong passion for its culinary as well as scientific traditions. During his travels throughout Europe, Martin cultivated his interest in photography, armed with a Leica IIIC camera he received as a gift from his family for his Ph.D. His extraordinary talent as a photographer, unknown to many, was evident from the exhibition at the Symposium of images he photographed from 1954 to 1956, including the photo of the Temple of Apollo in Corinth, Greece, shown in Figure 2.

Martin returned to the United States as an Instructor at the University of Illinois, where he carried out the studies that revealed that NMR coupling constants are related to bond torsion angles through the famous equation that now bears his name. This work demonstrated in a dramatic manner the power of bringing theory and experiment together in order to probe the structures and dynamics of molecules in solution. Indeed, it gave birth to a new field of conformational analysis and was the first of many seminal discoveries by Martin Karplus that have changed the face of modern chemistry and structural biology. From Illinois he moved to Columbia in 1960, before returning to Harvard as a Professor in the Chemistry Department in 1966. He now divides his time between Harvard and the Université Louis Pasteur, Strasbourg, France, and runs highly productive research groups in both places. Marci Karplus, as wife and administrative assistant, has been a key factor in Martin's life for the past 25 years. Her competence and flair have contributed greatly to Martin's work, and her affection is vital to his well-being. Martin and Marci's partnership of mutual devotion, respect, and commitment is truly unique.

The Symposium included four sessions chaired by Lee Pedersen, Alex MacKerell, Ron Levy, and Peter Rossky. The diversity in the presentations by former students and postdocs reflected the remarkable variety of areas to which Martin has made pioneering contributions. These fields span quantum mechanics, chemical dynamics, magnetic resonance spectroscopy, and the statistical behavior of biomolecules. Since around 1970, Martin's research activities have focused on an understanding of the physical behavior of biomolecules. He has been a leader in the development of molecular dynamics simulation methods as a means to gain detailed, atomic-level information about complex systems. Martin's scientific influences and the impact of computer simulations on biophysics and chemical physics were clearly evident in the contributions at the Symposium. Several speakers remarked on Martin's genuine scientific curiosity to understand the nature of molecules in atomic detail, and expressed appreciation of his infectious enthusiasm for scientific research.

Martin's earlier work in classical trajectory studies of gas-phase chemical reaction rates was highlighted by Gabriel Balint-Kurti (University of Bristol), who spoke on classical and quantum dynamics of molecular motion. Balint-Kurti described a wave-packet treatment to define the potential surface for the reaction Li + HF → LiF + H, and the reactive cross-section of nonadiabatic reactive scattering of $O(^1D) + H_2 \rightarrow OH + H$. In addition, the photodissociation of ozone and the design of laser pulses to prepare molecules in desired quantum states were presented. Overall, Balint-Kurti stressed

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Figure 1. Photograph of Martin Karplus at the Symposium

the breadth of Martin's accomplishments and their importance in applying quantum and, particularly, classical dynamics to modeling, and understanding chemical and biological systems.

Protein solvation and the behavior of water molecules around proteins have drawn the attention of many researchers. The role of water is fundamental to biological systems; proteins must function in environments as diverse as the aqueous cytoplasm and a hydrophobic membrane bilayer. Three of the speakers at the symposium exploited the unique capability of molecular dynamics simulations to investigate the physical properties that underlie the complex behavior of water.

Stefan Boresch (University of Vienna) reported an analysis of the structure and dynamics of water molecules near the surface of proteins determined from molecular dynamics simulations. The proteins investigated—ubiquitin, apo-calbindin, and phospholipase C-γ1 SH2 domain—differ in net charge and fold, and thus provide structural variability for the analysis. Long simulation times (>15 ns) and larger than usual solvent boxes allowed for reliable assessment of radial distribution functions, orientational correlation functions, mean residence times, and frequency-dependent dielectric constants of the protein solutions. Boresch found that in the first solvation shell these properties depend strongly on the type of amino acid at the protein surface and that the first shell greatly dampens the otherwise large dipole moment of the protein. Further, the protein was found to exert a greater influence than previously recognized on solvent properties beyond the second solvation shell.

Monte Pettitt (University of Houston) discussed the molecular basis of the hydrophobic effect by examining solvation of apolar surfaces and the question of whether dewetting occurs at contact distances longer than that defined by steric considerations. Density profiles of water molecules around two hydrophobic plane surfaces were used to characterize the behavior and the energetic dependence of the distribution of intervening water molecules. Pettitt showed that an apparent dewetting only occurs with either purely repulsive or weakly attractive solute-solvent interaction potentials, but not when polarity and attractive dispersive forces are introduced. Accordingly, dewetting-induced collapse does not apply at hydrophobic surfaces of protein interfaces.

Lennart Nilsson (Karolinska Institutet and Lund University) exploited molecular dynamics simulations to gain insight into the relaxation behavior of the protein solvation shell. The time-dependent fluorescence Stokes shift relaxation is observed to slow 10- to 100-fold when a chromophore is bound to a macromolecule. This observation has been interpreted in terms of a layer of "biological water" that surrounds the macromolecule and is in slow exchange with bulk solvent. The FSS effect is in contrast to magnetic relaxation dispersion (MRD) data, which show a modest 2- to 3-fold retardation of the solvent dynamics near the macromolecule. Nilsson and coworkers found that the slow component of the FSS relaxation is mainly due to chromo-

Figure 2. Photograph of the Temple of Apollo in Corinth, Greece
Taken by Martin Karplus in April, 1955.

phore and protein motions, whereas water relaxation around the protein is in general quite fast, consistent with the MRD data and other MD simulations of water dynamics.

A lifelong endeavor of Martin's has been a theoretical treatment to explain experiments including various spectroscopic measurements. Attila Szabo (NIH) presented a number of new theoretical approaches based on diffusion equations and related them to single-molecule fluorescence and force spectroscopy. He remarked on the similarity of the mathematical methods applied to the variety of physical problems discussed in his talk.

Aaron Dinner (University of Chicago) spoke on theoretical approaches to describe signal amplification in T cells, and the high sensitivity of T cells to small numbers of pathogen-derived peptides in the presence of much larger numbers of self-derived peptides. Recent experiments with soluble covalently linked heterodimers of major histocompatibility complex molecules (MHC) presenting agonist and null peptides demonstrate that such ligands can activate T cells even though high-affinity monomeric ones cannot. Dinner introduced a stochastic model to describe signal amplification in vivo and to account for the effects of mutations that prevent the coreceptor CD4 from binding MHC in soluble dimers. In the model, agonist and null peptide-MHC are spatially localized with CD4, which allows the associated kinase Lck to phosphorylate the many T cell receptors that are only briefly in complex with the low-affinity species. The results explain how T cells harness the display of relatively many self-derived peptides to detect relatively few pathogen-derived peptides.

Andrej Sali (UCSF) addressed the problem of structural characterization of macromolecular assemblies. Sali is developing a framework for computing 3D models of a given protein assembly that are consistent with all available information about its composition and structure. In contrast to structure determination of individual proteins, structural characterization of macromolecular assemblies usually requires diverse sources of information, which may vary greatly in terms of their accuracy and resolution, and include data from both experimental and computational methods. The proposal was illustrated by the use of low-resolution single-particle cryo-EM, immuno-EM, affinity chromatography, and theoretical considerations to model the configuration of proteins in the yeast nuclear pore complex.

Charles Brooks (Scripps Institute) presented an approach to explore the mechanism and kinetics of protein folding that utilized molecular models on multiple levels of resolution, from full atomic detail to residue-based Go-like models. Detailed calculations on helical and α-β proteins were used to describe the mechanism of folding and the role of solvent. Brooks suggested that small, single-domain proteins fold without significant free energy barriers. He further demonstrated that proteins containing mostly helical structure can fold by commensurate collapse and native structure formation, whereas more β-containing proteins must first collapse to a relatively unstructured globule and then fold to the native state. Water plays a role as a "lubricant" and must be expelled late in folding. More simplified representations called Go-like models were applied to further illustrate the strong relationship between folding mechanism and protein topology, but they also demonstrated the role of sequence in modulating the existence of intermediates in folding of proteins of analogous topologies. A hypothesis to link the presence of folding intermediates and functionally important conformations was related to observations on the folding of two different proteins.

Molecular dynamics methodology has also been exploited to help solve a variety of practical problems, including ligand docking and macromolecular structure determination. Andrew McCammon (UCSD) discussed the application of MD to structure-based drug design. McCammon is taking advantage of the thermally averaged population of structures generated by MD, along with a fast docking protocol and rescoring of protein-ligand complexes, to help in the design of better inhibitors. Ligand docking to a set of simulation "snapshots" was reported to be more effective than docking to a single average structure. Targeted proteins discussed included FKBP, HIV integrase, and acetylcholine receptor. McCammon suggested that the MD fluctuations reveal intermittently exposed regions of the protein that can be exploited in the design of new inhibitors. McCammon's results explain how seemingly similar inhibitors of the HIV integrase exhibit different sensitivity to resistance mutations in the active site region.

NMR structure determination depends on molecular dynamics to generate conformations consistent with experiment. Wilfred van Gunsteren (ETH) discussed the agreement of protein structure and dynamics from molecular dynamics simulations with NMR data and pointed out the difficulty of assessing the accuracy of structures determined using NMR data. He suggested that structural results should be assessed in terms of the NOE-derived distances rather than a direct comparison of atomic coordinates.

MD simulations of large systems are being tackled by Klaus Schulten (University of Illinois). Schulten presented a brief historical perspective over thirty years of molecular biophysics in his laboratory. Beginning with elementary chemical processes involving three-atom reactions and electronic excitations of visual chromophores, Schulten moved into investigations of the physical mechanisms of cellular processes and biomolecular assemblies in their native environment. Schulten's outline of MD simulations of large systems started with a large patch of membrane (36,000 atoms) in 1993, the in situ aquaporin membrane channel (106,000 atoms), and ended with ongoing simulations of over 300,000-atom systems like the lac repressor-DNA complex, the ankyrin gating spring of hair cells in the inner ear, and the hemolysin channel. His presentation demonstrated that large-scale simulations, just like smaller scale ones, have assisted many computational-experimental collaborations in identifying the atomic-level mechanisms underlying the molecular machines of complex cellular processes.

Another large simulation system was described by Carol Post (Purdue University). Post is using simulation methods to examine the effects of antiviral compounds that bind a buried hydrophobic cavity in the capsid pro-

tein of human rhinoviruses, a causative agent of the common cold. Dissociation trajectories of a WIN compound from human rhinovirus 14 (HRV14) calculated using an adiabatic, biased MD method show that WIN exits in a series of steps. Small, transient packing defects in the protein are sufficient for dissociation. A number of torsion angle transitions of the antiviral compound are involved, which suggests that flexibility in antiviral compounds is important for binding. Further, dissociation is associated with an increase in the conformational fluctuations of residues never in direct contact with WIN 52084 over the course of dissociation. These residues are located in the interior of the capsid near the icosahedral 5-fold axis. The observed changes in dynamics may be relevant to structural changes associated with virion uncoating and its inhibition by antiviral compounds. Only simulation methods will provide a molecular explanation of these long-range effects.

The Symposium concluded with an evening banquet and three presentations with more personal comments. Richard Pastor focused on "The Karplus Group." He recounted memories of the original "Prince House" (a yellow house on Divinity Avenue at Harvard) and the "New Prince House" at Harvard and fondly remembered Mike Cook. Slides from the past illustrated that the Symposium was indeed a family reunion. Chris Dobson gave an appreciation of the first 75 years of Martin's life and work and showed how his ideas have led to new paradigms in chemistry, physics, and biology. The task of giving Martin his birthday gift fell to Bernard Brooks. In recognition of Martin's hobby of photography, Martin was presented with a toy camera, and was assured that a real one was on the way.

Martin's work over the past 50 years has led to unprecedented advances in our understanding of molecular properties and how they have been exploited through the evolution of living systems. As well as producing a flood of elegant and highly innovative papers, Martin's enthusiasm and insight have informed, trained, and inspired a whole generation of scientists throughout the world.