BIOGRAPHICAL MEMOIRS

Martin Karplus

March 15, 1930–December 28, 2024
Elected to the NAS, 1967

A Biographical Memoir by R.J. Petrella

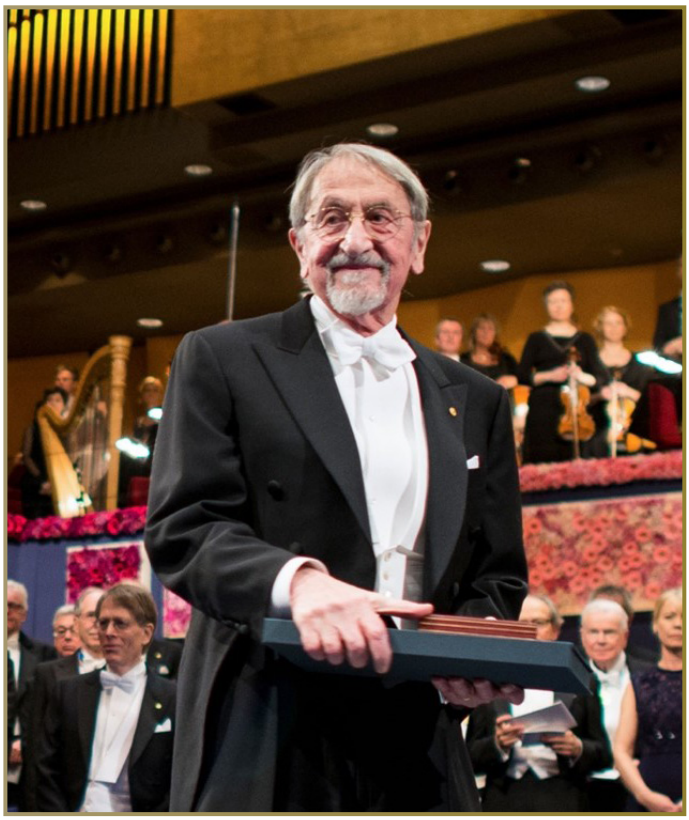

Figure 1 Nobel Prize ceremony, Stockholm, 2013. *Copyright © Nobel Prize Outreach 2013. Photo: Alexander Mahmoud*

Martin Karplus was arguably the greatest scientist who most people have never heard of. A theoretical and computational biochemist, long-time professor at Harvard University, and winner of the 2013 Nobel Prize in Chemistry,[1] he was a true pioneer, a giant in his field, and no doubt one of the most influential scientists of the last half-century. Owing mostly to his lack of interest in self-promotion, he was not well-known outside of scientific circles, but his work was transformative.

Karplus spearheaded the development of computational molecular biophysics, a field that is dedicated to explaining the mechanisms of biological processes in a very fine-grained way. It uses math, physics, and computers to analyze the structure and action of biological molecules—such as DNA, carbohydrates, drug molecules, and proteins—at the atomic level. The fundamental understanding that its methods thereby enable is important to the advancement of many other fields, not the least of which are human physiology and medicine. And although the discipline's impact has already been significant, it will no doubt increase in the future as computational techniques improve and processing power continues to expand.

Karplus's contributions in theory and computation, detailed in nearly 900 publications, have benefitted research areas spanning a number of different categories, a partial list of which is as follows:

- **Molecular dynamics methods**—methods for simulating the motion of molecules at the atomic scale, many of which were incorporated into the biomolecular simulation package called CHARMM beginning in the late 1970s.[2]
- **Empirical energy functions**—realistic mathematical models for use in physical simulations of biological molecular systems, such as DNA, lipid membranes, proteins, or their complexes.[3]
- **J-coupling constants and structure.**[4] After a postdoctoral fellowship at Oxford, and before joining the faculty at Columbia, Karplus became a junior faculty member at the University of Illinois Urbana-Champaign in 1955. There, he discovered the

relationship between the positions of nearby (vicinal) hydrogen atoms in molecules and the corresponding coupling constants used in NMR, which help to determine structure and conformation. This relation is known as the Karplus Equation.[5]

- **Crystallographic refinement**—using theoretical models and computation to refine crystallographic (i.e., experimentally determined) structures of large biological molecules such as proteins.[6,7]
- **Combined quantum mechanical-molecular mechanical methods.** These methods include semiclassical methods—so-called multiscale models—that blend quantum and classical approaches and that Karplus developed in the 1960s and early 1970s with colleagues.[8-11] This is the work that led to his Nobel Prize. These combined methods also include quantum mechanical-molecular mechanical ("QM/MM") calculations that partition a molecular system into parts treated classically and parts treated quantum-mechanically.[12-13]
- **Protein and peptide dynamics and kinetics**—essentially, how proteins move.[14] With colleagues, he published the first-ever atomic-level simulation of a protein (BPTI)[15] in 1977 and, in the following decades, applied these methods to study many protein systems, such as hemoglobin, which transports oxygen in the blood, titin,[16] an important component of muscle, and GroEL,[17] which is a "chaperone" protein that protects other newly formed proteins.
- **Thermodynamics of macromolecules**[18]—methods for calculating the energy and free energy differences between different states of a system, as well as the entropy,[19] which is the multiplicity or numeracy of the states. The free energy, a function of both the energy and entropy, determines how likely each state is to occur.[20]
- **pKa's of biomolecules**[21]—determining the acid/base status of biologically important molecules and their components and how it varies with changes in their structure or environment.
- **Protein structure analysis and prediction**—predicting the structure of a folded protein[22] based on its amino acid sequence, often with molecular dynamics methods, but also using other methods such as neural networks.[23,24] The latter were used for this purpose in his research group for predicting protein secondary structure as far back as the late 1980s.
- **Small molecule binding to proteins.**[25] He helped establish methods for developing drug leads by modeling the interactions between small molecules and drug targets like protein enzymes.[26-28]

His Nobel Prize, which he shared with fellow chemists Arieh Warshel and Michael Levitt, was granted specifically for the development of methods that combine classical and quantum mechanical approaches into a single calculation.[29,30] These methods by themselves paved the way for the study of a wide range of reactive biochemical processes, such as the catalysis of reactions and the conversion between different forms of energy in the cell. Yet they represent just a single constellation of approaches within the much larger methodological universe that Karplus helped introduce. The Nobel Foundation does not grant lifetime achievement awards, but Karplus was the prime mover in the establishment of the entire field of biomolecular simulation, which has transformed the way much of chemistry and molecular biology research is carried out.

Karplus's contributions went well beyond his scientific findings and method developments, however. He mentored nearly 250 graduate students and postdoctoral fellows, many of whom are leaders in academia and industry today. And more than teaching good science, Karplus taught people how to be good scientists. In his view, the latter meant going beyond a mastery of the subject and fulfilling one's responsibilities to the field, to scientific integrity, and to other people. More than once in our conversations, he expressed his belief that scientific endeavor, in itself, was orthogonal to morality, because it is essentially a tool that can be used for good or ill, and that the responsibility for making the right choices rests in the scientist's hands.

This attitude might have had roots in Karplus's childhood. He was born on March 15, 1930, in Vienna, and his family fled Austria in 1938, a few days after Hitler's *Anschluss*.[31] His father, Hans, a banker, was forced to stay behind, having been imprisoned by the Nazis, and had to turn over all his possessions before finally being released about six months later. Although Karplus's immediate family managed to escape and waited for him in France,[32] his great aunt, Eugenie Goldstern, a prominent Viennese archeologist, was later killed in the Sobibór extermination camp in Poland. In October 1938, the family finally made it to the United States, settling in the Brighton neighborhood of Boston.[33] They later moved to the suburb of Newton, where Karplus began his science education at Newton High School, from which he was accepted to Harvard. Karplus respected authority but carried a healthy skepticism of it, whether it resided in government, business, or academia. He believed there was usually a right answer to which one could arrive, regardless of what the authorities or anyone else declared. Outwardly, this notion was about science, a technical idea rooted in the scientific method, but it was clear to those who knew him that he held the same belief about human dignity as well.

Figure 2 California, 1956, at age 26. © *Martin Karplus Photography.*

Karplus studied small molecules early in his career [34,35]—initially, the bifluoride ion under his third and principal graduate advisor, Linus Pauling—but he held a longstanding interest in biology, which eventually led him to pursue research in larger, more complex biological molecules. As a teenager, he had studied ornithology, winning the Westinghouse Science Talent Search of 1947 for his work on alcids (seabirds) of the eastern U.S. seaboard, and had soon thereafter entered Harvard College with a plan to study for a medical career.[36] Notably, a number of his forebears had been involved in the medical field. Both of his grandfathers—Johann Paul Karplus and Samuel Goldstern—were physicians in Vienna. His mother, Lucie Isabella (Goldstern) Karplus, a dietician, and his aunt Lene Goldstern, also a physician, had both worked at his maternal grandfather's medical clinic. And preceding his graduate work with Pauling, Karplus had been studying protein charge fluctuations under John Kirkwood at the California Institute of Technology, until Kirkwood left for Yale University.

Karplus considered the refocusing of his work on biological systems in the 1970s, several years after he accepted a professorship at Harvard, his "homecoming."[37] But it was the insights he gained from his early work with small molecules that led to success in his later work on biomolecules by demonstrating to him that the introduction of experimental data into a model could make it more accurate and computationally tractable. In the 1950s, working as a graduate student under Pauling, he learned that small systems could be accurately modeled by combining empirical data with quantum mechanical calculations.[38,39] At Columbia University in the early 1960s, he helped develop the Porter-Karplus surface for the description of the hydrogen exchange reaction ($H + H_2 \rightarrow H_2 + H$),[40] again by combining experimental data and quantum mechanical rules. These results convinced him that classical mechanics (Newton's laws) could be used to describe molecular motion if the potential energy surface (i.e., the model) could be made accurate enough through a combination of theory and experimental data. Moreover, it indicated to him that these same principles and methods could be extended to much larger molecular systems, such as proteins and their complexes. This is the idea that gave birth to the now-thriving field of biomolecular computer simulation.

Today, many experimental scientists routinely use the results of molecular simulation studies to help interpret or direct their experiments.[41,42,43] But in the 1970s, when Karplus began his groundbreaking work in this area, the notion that biology could be successfully reduced to physics (that biological behavior could be predicted using Newton's laws of motion and quantum mechanics, or approximations thereof) sounded fanciful even among scientists. Friends and colleagues tried to convince him that such physics-based, atomic-level calculations would never be accurate enough to model a complex biological system, and that even if they could be made to be, the results would not be interesting.[44,45]

Karplus explained in later years that what helped him persevere though the skepticism was faith in the idea that valid theories should eventually work—however remote that eventuality might appear.[46] Though not a religious man, he believed that scientists must have their own kind of faith: a belief that the world can be understood and that the door to discovery will be left open just far enough.[47] As a result, he went on to publish the first-ever atomic-level simulation of a protein,[48] oversee the development of the highly influential CHARMM program,[49,50,51] and make many important contributions not only to new computational methods, but also to our understanding of many chemical and molecular biological systems and processes.

As mentioned, Karplus also held a decades-old interest in applying machine-learning methods such as neural networks—what today is called *artificial intelligence*—to molecular biology and made significant contributions there.[52,53] But the bulk of his work involved physics-based studies. Machine-learning methods provide insights by recognizing statistical patterns, often without explaining the underlying mechanisms. Biophysical methods, on the other hand, yield predictions and explanations based on physical models, providing a clear, detailed picture of how the molecular parts of a living system act, react, and interact. In this way, physics-based

methods—often ones Karplus helped develop—have shed light on everything from how hemoglobin functions in red blood cells,[54,55] how viruses attach themselves to and enter cells,[56,57] how the body's biochemical reactions are catalyzed,[58,59] and how a protein folds itself from a long strip of amino acids into a complex three-dimensional structure.[60,61,62]

In addition, because simulations can predict a system's behavior under different conditions, they can help scientists decide what experiments are most likely to bear fruit. The results of those experiments then feed the next round of simulations, which can then help guide the design of the next round of experiments, and so on. Simulation and experiment now go hand in hand, complementing one another in a way that seemed far-fetched even thirty years ago. The impact that all of this has on the rest of science and our lives in general is real and growing. For instance, the field of computer-aided drug design[63] has evolved out of these methods and has aided in the discovery of new medications, including new treatments for HIV[64] and other viral infections,[65,66] psychiatric conditions,[67] and cancer.[68]

To his collaborators and students, Karplus brought passion that inspired, but also a rigor that demanded certainty. He usually granted his students and postdocs fairly broad leeway to pursue the research paths that excited them, helping to direct them along the way. He taught them to follow their intuition, an insight he said he had gained from Pauling.[39] But his mentees had to get the science right—and by his lofty standards. His approach was a double-edged sword: it was the reason his lab saw not only the birth of many important developments over the years but also the inevitable demise of many flawed projects that may have seemed promising at first. It was why so many high-achieving scientists trained there, but also why many of his students spent five to ten years completing their degrees. For most everyone he worked with, he was paradoxically both the vehicle and the barrier to success, productively brilliant, yet more exacting than the scientific journals.

As has been said, great men seek truth, not applause. Karplus was not interested in notoriety, especially among non-scientists, and was not keen on self-promotion. On the contrary, in his talks and papers, he presented his work dispassionately and often self-critically, pointing out its weaknesses and limitations almost as eagerly as its strengths and applications.

The first time I heard him speak was in New York in 1989 or 1990. He showed a short molecular dynamics trajectory of part of a protein with some surrounding water molecules that were vibrating in place. Someone in the audience asked why the water molecules seemed "stuck." Karplus noted the time scale was in femtoseconds, quadrillionths of a second, which meant that the water didn't have time to move around very much. But then he said something unexpected—shocking, one might say—for someone in a theoretical field: "But remember, this is a simulation. This is just our best guess as to what is going on at the atomic level."

No one is entirely objective, especially about his own work, but he came as close as one will ever see. In addition to his scientific abilities, this authenticity is what attracted hundreds of colleagues and students to him over a career spanning nearly seven decades. His exemplary training of so many scientists, on its own, leaves a lasting mark on the field.

In addition to the Nobel Prize, Karplus received an array of awards and distinctions over his career. He was elected to the National Academy of Sciences in 1967 and the Royal Society, as a foreign member, in 2000. He received the American Chemical Society's Irving Langmuir Prize in Chemical Physics in 1987 for outstanding interdisciplinary research in chemistry and physics, the Protein Society's Christian B. Anfinsen Award in 2001 for excellence and outstanding achievements in the multidisciplinary fields of protein science, and the American Chemical Society's Linus Pauling Award in 2004 for outstanding achievement in chemistry. In 2024, he was awarded the Grand Decoration of Honour for Services to the Republic of Austria in Gold with Sash, which is the highest honor that can be bestowed on a non-head of state. Yet, despite these and many other distinctions, his major scientific achievements, his long list of publications, which includes three books,[69,70,71] and his having trained hundreds of scientists, his contributions to science and society have thus far remained largely unknown to the general public.

Those of us who were fortunate enough to have been able to join Karplus in his scientific venture, or part of it, were able to witness how greatness works. Greatness never rests on its laurels. It filters ideas before pursuing them wholeheartedly so as not to waste time but then drives worthwhile projects to completion. It states facts but doesn't argue. It generally doesn't sacrifice quality for speed. It is trustworthy and conscientious. It brings out the best in others by promoting their strengths. It is fair. When wronged, it doesn't whine but takes corrective action. It minds its own business but also takes opportunities to expand into new areas when it can. It is confident but not vain. And, above all, it is steadfast in its pursuit of truth.

Martin Karplus died on Saturday, December 28, 2024, at the age of ninety-four. He leaves behind his loving wife, Marci, who was his long-time support and lab administrator, as well as three children, Reba, Tammy, and Mischa, and a grandchild, Rachel. He was a talented photographer—his stunning stills of the Southwest from the 1950s, for example, have been part of multiple exhibitions—and something of a French chef. He had a remarkably productive and long life, from which the scientific world and the world in general have

gained greatly. He conducted research until his last days—as of this writing, his lab remains up and running. We are all diminished by his absence.

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