

Tribute to Klaus Schulten



Klaus Schulten was a true leader in modern computational biophysics, who devoted over 40 years of his life to establishing the physical mechanisms underlying processes and organization in living systems from the atomic to the organism scale. Klaus was a strong proponent of the use of simulations as a “computational microscope”,³⁰¹ to augment experimental research, and to lead to discoveries that could not be made through experiments alone. (Please see “Selected Publications of Klaus Schulten” (DOI: 10.1021/acs.jpbc.7b02902), also included in this issue, for the references cited here.) Being genuinely passionate, and quite successful, in applying physical principles and computational methodologies to biological problems through advanced algorithms exploiting modern hardware architectures, his research spanned diverse areas, ranging from application of quantum physics to vision and magnetoreception to some of the largest ever molecular simulations of whole cells and cellular scale structures and processes. During his impactful career, Klaus published more than 700 research articles, cited nearly 100,000 times, earning him an *h*-index of 140 (Google Scholar, April 2017).

Klaus Schulten’s passion for the biology of living organisms can be traced back to his youth in Westphalia, Germany, and the reading of the classic by Nobel laureate Karl von Frisch, *Du und das Leben* (von Frisch, K. *Du und das Leben*—Eine Moderne Biologie für Jedermann and Andere; Deutscher Verlag: Berlin, 1936), wherein the chapter illuminating how photosynthesis is utilized by cells to produce ATP exerted

fascination on the schoolboy. Very early on, he realized that complete understanding of cellular processes at a fundamental level would require a solid background in mathematics, physics, and chemistry. At the time, scientific disciplines were well compartmentalized, and the concept of interdisciplinarity was somewhat incongruous amidst the academic community. Still, future Nobel laureate Martin Karplus stood as a notable exception, combining physics and chemistry to study the biology of living organisms. Endowed with a Volkswagen scholarship and armed with a strong training in physics, Klaus embarked in 1969 for the United States to join the Karplus research group at Harvard, which, to a large extent, shaped the field of computational biophysics. Back then, human vision and the role played by polyene chromophores like retinal constituted a major research avenue at the Harvard laboratory. During the years that he spent in Massachusetts, Klaus relentlessly applied electron correlation to polyenes and showed that inclusion of doubly excited configurations alters absorption spectra significantly, leading to a seminal article that remains one of his most cited contributions.¹

After completing his Ph.D., Klaus returned to Germany and joined the Max–Planck Institute for Biophysical Chemistry in Göttingen, which, at the time, was administered by Albert Weller, a chemist focused on the primary processes connected with electron-transfer reactions in the excited state. Electron transfer was already familiar to him, as it occurs in photosynthesis within a protein referred to as the reaction center, which uses sunlight energy to transfer electrons. In Göttingen, he studied with Albert Weller the effect of the magnetic field on electron–transfer reactions.² Göttingen was also the place where he published his first paper on photosynthesis. In many respects, the Max–Planck Institute for Biophysical Chemistry shaped his scientific direction amidst such influential scientists as Nobel laureate Manfred Eigen. However, since permanent positions in Max–Planck institutes were scarce then, Klaus moved to Bavaria and joined the physics department of the Technical University of Munich as a newly appointed professor. Southwest of Munich, another Max–Planck Institute—for biochemistry—was the theater of exciting research led by future Nobel laureate Hartmut Michel for solving the complete structure of the photosynthetic reaction center (Michel, H. Three-dimensional crystals of a membrane protein complex. The photosynthetic reaction center from *Rhodospseudomonas viridis*. *J. Mol. Biol.* **1982**, *158*, 567–572). The groundbreaking work of Michel opened new vistas for Klaus, who would now be able to return to the field of photosynthesis. With a homemade parallel computer in his backpack, he left Munich in 1988 to join the physics department of the University of Illinois at Urbana–Champaign, where, in 1989, he founded the Theoretical and Computational Biophysics Group, one of the inaugural research groups housed

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at the Beckman Institute for Advanced Science and Technology.

Klaus's research interests were very broad. It is nearly impossible to list exhaustively his many contributions to the field of theoretical and computational biophysics, for, in the course of his career, he touched so many subjects, from nonequilibrium statistical mechanics¹³⁷ to cybernetics⁶ and from human vision²¹⁶ to virus maturation.⁴⁰⁶ His interest in human vision as well as energy production in the purple membrane started with his Ph.D. work in the research group of Martin Karplus at Harvard, leading to milestone papers rationalizing the experiments of Bryan Kohler, notably the origin of low-lying forbidden transitions in polyenes.¹ Working with Albert Weller in Göttingen, he brought to light the influence of magnetic fields on geminate recombination of radical ion pairs in polar solvents, which resonated in the experimental community, as it was now possible to distinguish tight ion pairs from solvent-separated radical ion pairs. With this breakthrough, Klaus would also realize that, like other visionary scientists before him, many of his ideas were too bold or came too early to be fully appreciated by his peers at the time. Initially submitted to *Science*, his paper was thrashed by the scientific gatekeepers, before getting eventually published in the more modest *Zeitschrift für Physikalische Chemie*.² The work on radical ion pairs was the seed to the concept of compass sensor, which Klaus had long anticipated to be key to magnetoreception in migratory birds, albeit could not yet prove where and how the chemical reaction occurred. The hypotheses on magnetoreception had to mature for 12 years to come to fruition, explaining the role the eye plays in an avian magnetic compass and why cryptochrome was the perfect candidate molecule for this compass.⁸²

As a young professor established in Munich, Klaus got acquainted in the early 1980s with future Nobel laureate Hartmut Michel, who, at the time, was striving to crystallize a membrane protein. The structure of the first membrane protein, the photosynthetic reaction center, offered Schulten perspectives beyond the wildest dreams of any theoretical biophysicist. Studying in atomic detail the reaction center in its natural membrane environment would, however, require the kind of computational infrastructure that, at the time, was largely inaccessible to the average scientist. To circumvent this obstacle, he built with two of his Munich students, Helmut Heller and Helmut Grubmüller, an affordable parallel machine,^{4,5} on which they ran what is still viewed as the first realistic-size and time scale membrane simulation.⁷ With this simulation, Klaus was pushing the boundaries of computational biophysics, pioneering the exploration of uncharted territories of very large, complex molecular assemblies in biology. Far from disregarding experiment, he was, and remained, a proponent of large-scale, atomistic simulations as a complement to experiment. Teaming up with leading experimentalists, he applied this concept successfully over the years to such diverse biological objects as light-harvesting complexes,^{250,466} aquaporin water channels,¹²⁴ mechanical proteins,^{81,239} the ribosome,²⁸² and, more recently, the entire capsid of a virus.⁴⁰⁶

Even though Klaus Schulten was a true leader in computational biophysics, pioneering several methodologies and technologies in this area, he maintained at all times high regards for experiments and worked very hard to genuinely bring together computing and experiment. He collaborated very closely with a large number of experimental biophysicists from a wide range of techniques and systems, very often with

significant contributions from the theory to fundamental understanding of the problem. Some prominent examples of this effective synergy include his close collaborations at the Max Planck Institute resulting in one of the first structures of a membrane protein,²⁰ and the more recent solution of the entire HIV capsid structure⁴⁰⁶ through an unprecedented level of integration of electron microscopy (EM) data into the model, made possible by the advanced methodology specifically crafted for this problem. Being cognizant of the key role of experiment in biophysics, Klaus always identified key areas in which computing was needed to help experiments. For example, recognizing the rapidly increasing role of EM in the field, he immediately started to work on specific methods, such as the flexible fitting molecular dynamics (MDFF) algorithm,²⁶⁸ to enable a better model development and fitting computational tool for EM data. It comes as no surprise that several of his students ended up working in experimental settings after completing their training with Klaus—from Axel Brünger in the early 1980s to, more recently, Marcos Sotomayor, Peter Freddolino, and Elizabeth Villa in the late 2000s. Klaus was also very successful in making the power of computing known to his collaborating and other experimental biophysicists. Oftentimes, his experimental collaborators became true believers of the power of computing and its strong complementarity to experiments after interacting with him.

Klaus Schulten was a scientist pursuing a dream—the dream of disentangling the complexity of the cell machinery with exquisite atomic detail, using the laws of physics. What fundamentally distinguishes him from many other theorists is that the wonderful tools he has imagined and developed over the years, and made available to the community, were aimed at attaining this dream. When the structure of the reaction center got published, he rapidly saw the potential of molecular simulations for the study of membrane proteins, notably those of the photosynthetic apparatus. However, such large-scale simulations would involve a number of atoms about an order of magnitude larger than was commonly handled back then. Going big at a time when supercomputers were in their infancy would require creative thinking to acquire the desired computational power at a cost amenable to a small research group. Quite ahead of his time, Klaus had realized the importance of parallel computing if one were to attempt molecular dynamics simulations on large sets of atoms. This realization was the impetus for assembling his own parallel computer, the T60 transputer, and developing a specific operating system and molecular dynamics program, EGO.⁸ In 1992, only a few years after his bold move to the United States, he received support from the National Institutes of Health to start a center for computational biology—an inspired desire to bring physics, biology, and computer science together by removing barriers between disciplines. It became quickly apparent that, in order to overcome the limitations of parallel-programming paradigms, Klaus would have to team up with leading computer scientists, resulting in the Bell-award winning program NAMD,^{71,195} the design of which stood the test of time. To this date, NAMD remains the most widely used molecular dynamics program at national supercomputing centers, scaling on hundreds of thousands of computing units. Both NAMD and the popular visualization platform VMD¹⁷ were key to the scientific agenda of Klaus Schulten—as time went on, the different pieces of a gigantic jigsaw puzzle fell into place one after the other to culminate with the fully

atomistic simulation of an entire chromatophore, the organelle where photosynthesis occurs.

Klaus Schulten was also a great mentor who trained a generation of computational biophysicists, many of them currently running their own research groups around the world. During his scientific career, he trained nearly 100 Ph.D. students and mentored more than 50 postdoctoral researchers (see the accompanying List of Colleagues in this issue). He would often point to the archetypical professors who relentlessly siphon off all the energy from their young people, and while jokingly wondering if some saw him like this, he felt he offered something more in return. “The most important thing I can do as a professor is give somebody a good research problem”, he would counter. “A good research project, that is the hardest thing to find, but that is actually the best thing you can give to a young person”. He was always the most enthusiastic and excited person about a project, and his infectious excitement would immediately transmit to and deeply permeate his junior colleagues. Despite his extremely busy schedule, he would always make time for students to engage in detailed discussions and lengthy derivations. In addition to scientific research, the group led by Klaus was a perfect example of a conducive environment for future faculty members to get full training in other aspects, such as mentoring more junior co-workers, full engagement in scientific collaborations with experimental and other computational groups, participation in team-organized events, teaching opportunities at workshops, and, probably most important, grant writing.

Klaus Schulten left us on October 31, 2016, after living an exemplary scientific life that continues to inspire generations of theoretical and computational biophysicists. Through his countless accomplishments, he has revolutionized the field of computational biophysics in many ways, not only through inventing and introducing novel theories and innovative methodologies but also by his passion to constantly push forth the boundaries of biological systems and cellular processes that could be studied computationally. The field of computational biophysics would not be the same without his groundbreaking methodological and technological contributions. He was a pioneer and a leader in bringing parallel computing to molecular dynamics simulation of biological systems, a legacy that will last forever. He was a genuine biophysicist, working tirelessly to marry physics with relevant biological questions, and passionate to make discoveries. He respected the complexity of biological systems and the importance of the most detailed description for a thorough understanding of biological phenomena. Klaus Schulten and his impactful contributions have been recognized by numerous awards and honors. At Illinois, he was Swanlund Professor of Physics and was affiliated with the Department of Chemistry as well as with the Center for Biophysics and Quantitative Biology; he was Director of the Biomedical Technology Research Center for Macromolecular Modeling and Bioinformatics as well as Co-Director of the Center for the Physics of Living Cells.

We conclude this tribute with a quote from Klaus that truly reflects on his lifelong passion for computational biophysics and scientific discoveries. “When I was a young man, my goal was to look with mathematical and computational means at the inside of cells, one atom at a time, to decipher how living systems work. That is what I strived for and I never deflected from this goal.”

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