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A Tribute to Attila Szabo

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Photo by Irina V. Gopich

It is a great pleasure for us to guest-edit this special issue in honor of our colleague, Attila Szabo. The articles in this issue testify to the many friends Attila has made in science over the years and reflect his interest and contributions to so many areas of physical chemistry, ranging from quantum chemistry and statistical mechanics to studies of the self-assembly and function of biological macromolecules. We have not only had the good fortune to know and collaborate with Attila, but we have also enormously benefited from almost daily discussions with him for many years (10 for G.H., 20 for R.W.Z., and almost 30 for W.A.E.). Attila is extremely generous with his time and is always willing to immediately stop whatever he is doing to listen carefully and to think hard about someone else's problem. As a result, his name appears in the acknowledgement section of over 100 papers from the Laboratory of Chemical Physics. His generosity has been extended not only to us and our colleagues in the Laboratory but also to any scientist who asks him a question or seeks his opinion about his or her research. The benefit of discussions with Attila stems not only from his sharp mind and keen insights but also from his extremely broad knowledge of both theoretical and experimental science, as is evident from his bibliography and from the summary of the highlights of his research presented below. Much of Attila's research has been closely tied to experiment, connecting new measurements to existing theory, developing new theoretical methods, and suggesting experiments that critically test theoretical ideas.

Attila's first important research came as a graduate student with Martin Karplus, when he developed a mathematical model for the Perutz stereochemical mechanism on how hemoglobin binds oxygen cooperatively. His use of the grand canonical partition function and his attention to experimental detail made this the most sophisticated theoretical modeling of any protein studied up to that time. Thirty-five years later, the SK model still serves as a paradigm for modern theoretical and experimental studies on hemoglobin, as well as other cooperative, multi-subunit proteins. Attila has maintained an interest in hemoglobin and has made several additional contributions to the subject, including the first application of linear free energy relations to protein kinetics and the development of an elegant theoretical model for explaining the stochastic kinetics of sickle hemoglobin polymerization observed in one of our labs (W.A.E.), which was his first work dealing with "single molecules". While working on his hemoglobin project as a graduate student, Attila also published papers in atomic physics and quantum chemistry. Interactions with his office mate, Neil Ostlund, resulted in what has become a widely used graduate-level textbook: *Modern quantum chemistry: Introduction to advanced electronic structure theory*, originally published by Macmillan in 1982, with a revised edition published by McGraw-Hill in 1989 and reprinted as a Dover paperback edition in 1996.

Attila is perhaps best known for his work on analyzing NMR relaxation measurements, carried out with his student Giovanni Lipari. The conventional approach had been to interpret the data using specific models, such as wobbling in a cone or jumping between two distinct states. Attila recognized that if the internal motions are sufficiently fast there is certain information in these NMR experiments that is independent of any specific model. This was the foundation of his "model free" approach, which has been universally adopted by NMR spectroscopists and has resulted in a residue-by-residue picture of the internal dynamics of proteins. Subsequently, he has extended this approach to analyze complex internal motions, such as the nature of the slow inter-domain motions of calmodulin. In collaboration with Ron Levy, he performed one of the first quantitative comparisons between molecular dynamics simulations and experiment, and to this day, the agreement between measured and calculated order parameters serves as an important test of force fields.

As can be seen from his bibliography, Attila has continued this pattern of working on a wide variety of problems. At least in his mind, these problems are not as unrelated as it appears at first sight, as illustrated with three widely recognized non-NMR papers. The first deals with the theory of fluorescence depolarization of probes attached to macromolecules or embedded in membranes. The second, done in collaboration with Klaus and Zan Schulten, presents the theory of first passage times with application to the end-to-end kinetics of polymers. This work has attracted considerable interest recently because of its relevance to intramolecular contact formation in polypeptides, a fundamental process that is part of all protein folding mechanisms. The third is a paper with his student David Shoup on the chronoamperometric current at microdisk electrodes.

One of Attila's lifelong interests has been understanding the role of diffusion in the kinetics of reversible and irreversible biomolecular chemical reactions. He began by extending the classical theory of Smoluchowski to handle anisotropic reactivity, rotational diffusion, and

“gating”. He then started thinking about the many-particle nature of the problem and how to generalize the theory to treat reversible reactions. One interesting aspect of diffusion-influenced reversible bimolecular reactions is that the concentrations do not relax to equilibrium with an exponential time course but rather follow a power law. On the basis of computer simulations, Attila first conjectured the analytic form of this relaxation and later, in collaboration with Irina Gopich, determined the exact power-law amplitude for $A + B \leftrightarrow C$ for arbitrary diffusion coefficients.

In recent years, Attila has focused on developing the theory required to analyze fluorescence and force spectroscopy of single biomolecules. These experimental studies require sophisticated theories to provide accurate molecular information. With Irina Gopich, he has developed a comprehensive theory of the most common single-molecule optical experiments—Förster resonance energy transfer (FRET) of immobilized molecules or the more complex case of FRET measurements on molecules diffusing in and out of the illuminated volume of a confocal microscope. This work shows how to extract intramolecular distances and the rates of conformational changes in individual molecules from the FRET efficiency, after taking into account the various sources of intensity fluctuations that result in “noise” in the experimental data. In collaboration with one of us (G.H.), Attila has contributed to the analysis of single-molecule mechanical measurements. By extending Jarzynski’s identity, he showed how one could rigorously extract equilibrium thermodynamic information from non-equilibrium pulling experiments. To extract accurate kinetic information from single-molecule pulling experiments, he developed a formalism built on the Kramers theory of diffusive barrier crossing.

It would be unfair to Attila not to mention tennis. Tennis is by far Attila’s major leisure activity. It comes in all forms—playing the game, watching tennis on television and at tournaments, particularly the French Open at Roland Garros in Paris which he has attended more than 10 times. Because of his charm and encyclopedic knowledge of the history of tennis, he has hobnobbed with tennis greats. At Roland Garros, he befriended Don Budge, and he has even played singles with the likes of Pancho Gonzales and doubles with Rod Laver and Roy Emerson. Attila’s huge collection of tennis books is reputed to be rivaled only by the collection at Wimbledon.

Finally, as anyone can testify who has spent time talking to Attila in his invariably disheveled office or at meetings, his delightful wit and disarming approach to all subjects make discussions with him an incredibly enjoyable experience. One of the great joys of working at the NIH is that, at any time we want, we get to talk to Attila! Thus, on behalf of all of his friends and colleagues, we wish him all the best in the future, hope that his tennis game keeps improving, and look forward to many more years of discussing and laughing with him.