Protein Folding and Dynamics—An Overview on the Occasion of Harold Scheraga’s 100th Birthday

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This virtual special issue of Journal of Physical Chemistry B is devoted to a survey of protein folding and dynamics, on the occasion of the 100th birthday of Harold A. Scheraga. This dedication is especially apt. Harold’s career in protein science began in 1946 when he became a postdoctoral fellow in the laboratory of John Edsall, at a time when the most important question in the field was whether proteins are molecules or colloidal aggregates, and the first three-dimensional structure of a protein by X-ray crystallography was 8 years in the future. He left us shortly before his 99th birthday, in August 2020. At the time of his passing his research had been continuously supported by the National Institutes of Health, under the same award, for 64 years, and he had papers in submission, in press, and newly published in leading journals. He presided over the advancement of the field of protein physical chemistry, with magisterial vision and legendary intensity, from the earliest, precrystallographic efforts to determine protein structure hydrodynamically, through pathbreaking experiments on protein folding, to his most recent, cutting-edge work in computational protein chemistry and protein bioinformatics. He carried out seminal work on the elucidation of the blood clotting cascade and on the structure of water. In addition to experimental work, he pioneered the fields of theoretical protein science, protein bioinformatics, computational structure prediction, and protein molecular dynamics. All current efforts in these fields rest on the shoulders of Scheraga’s early work. He joined the faculty of Cornell University in 1947 as an Instructor in Chemistry, and ended his career there 73 years later as the George W. and Grace L. Todd Professor of Chemistry Emeritus. His bibliography includes almost 1400 publications, he mentored over 400 graduate students and postdoctoral fellows, and he was honored with almost every award the field, and the chemical community at large, had to offer. He was truly a giant of science.

The papers included in this virtual special issue, contributed by numerous colleagues, reflect the breadth of Harold’s interests and attainments. There are studies of folding mechanisms and of chaperone function; of intrinsically disordered proteins; and of basic peptide and protein biophysical chemistry. There are experimental and computational studies, and new developments in bioinformatics and in the applications of artificial intelligence in protein structure prediction. Every active worker in protein science is likely to find something of interest in this list.

This collection appears at a particularly appropriate time. The field of computational protein science is undergoing an urgent reevaluation, as a result of the recent impressive success of artificial intelligence algorithms for the prediction of structure from sequence. The initial furor occasioned by these results has now moderated, as a result of studies which are beginning to delineate the limitations of artificial intelligence as a tool for the study of proteins. Recent work and recent observations have made it clear that there is a difference between the prediction of fold, using data from a sequence/structure database, and an understanding of protein folding derived from basic physical considerations. Viewed in this light, Scheraga’s early and continued insistence that a physics-based approach is fundamental to true understanding can be seen as prescient.

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We bring this exciting collection to the attention of the research community in gratitude for Harold Scheraga’s legacy, and in the certainty that that legacy will live and grow in the work of colleagues currently active in the field, and colleagues yet to come.

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ASSOCIATED CONTENT

Supporting Information
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Notes
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