



Note

Obituary: Nobuhiko Saitô, a man who understood protein folding in his own way

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Nobuhiko Saitô (Fig. 1), a pioneer in the field of biophysics in Japan, passed away in Tokyo, Japan on May 2, 2015 at the age of 96. He was a leading scientist in the field of statistical physics of both chaos and macromolecules, including biomolecules. After graduating from Tokyo Imperial University, he devoted his time to the physics of macromolecules. The scientific details of his achievements are well narrated in the accompanying paper by Yukio Kobayashi in this special issue [1]. To complement Dr. Kobayashi's review and complete the picture of Nobuhiko Saitô's role in biophysics, I will describe other aspects of his life and work.

Prof. Saitô's career started at Syoten Oka's Lab in the Kobayasi Institute of Physical Research in 1949. Syoten Oka is perhaps best known amongst the younger generation for his Japanese translation of *What is Life*, written for the layman by the physicist Erwin Schrödinger. The institute was founded in 1940 as a place for research of pure and applied physics, but later focused on acoustics. Nobuhiko Saitô extended his theoretical study of polymers during those days. In 1952 he was invited to the Department of Applied Physics in Waseda University as an associate professor. At that time, the department was still in the process of growth and it was only in the late '60s that the department settled into its current structure. Nobuhiko Saitô held the lectureship in statistical physics throughout his career in the department, and I was one of his students.

His extensive studies on macromolecules were crystallized

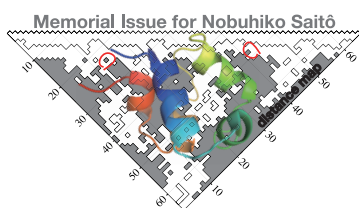


Figure 1 Portrait of late Prof. Nobuhiko Saitô. I assume that this was his own hand-drawing. Reprinted with permission from “Nobuhiko Saitô, From My Recent Works. *Kobunshi* 33, 302–303 (1984)”.

in the book *Kobunshi Butsurigaku* (Introduction to Polymer Physics), published in Japanese in 1958. This book, once out of print, was revived in 1986 and remains the standard for the study of macromolecules in Japan. Prof. Saitô's work on polymer physics was praised and he received a number of prizes, including the SPSJ Award for Outstanding Achievement in Polymer Science and Technology (1979) from the Society of Polymer Science, Japan. Once, Nobuhiko Saitô mumbled that the equations in his book had many errors and he would like to revise them. I once saw his book with numerous corrections noted in his writing in pencil. He also mentioned publishing the book in English, although neither of these aspirations were accomplished. However, it should be noted that some of his books were published in English by Springer, such as *Statistical Physics I: Equilibrium Statistical Mechanics* with Morikazu Toda and Ryogo Kubo.

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Prof. Saito's biggest achievement, before he became deeply involved in the protein folding problem, was the theoretical study on the effect of the Brownian motion of solutes on the viscosity of solvents in 1951 [2,3], which pointed out mistakes in the existing theories and established a new one. The same problem was independently explored by two other groups in the 1950's using different formulae, but Saitô and Sugita [4] proved that all of these were equivalent. The theoretical background of the relationship between the structure of the solute and the viscosity of the solvent was fully established by their work. In 1955, Harold A. Scheraga gave a numerical answer to Saitô's equation [2] using the state-of-the-art Mark I computer [5]. In those days, the hydrodynamic property of proteins was an important issue in the field, and these studies led to the foundation of the Scheraga-Mandelkern relation [6].

Nobuhiko Saitô spent time at the University of Oregon between 1958 and 1960 as a visiting professor by the courtesy of Terrell L. Hill, and then started his studies in biophysics. At the same time, he started to study the origin of irreversibility, which paved the way to the study of chaos. In retrospect, the first step to this study may have been documented in his manuscript with Mikio Namiki in 1956. They extensively discussed the analogies found amongst the theories of Brownian motion, quantum mechanics and quantum statistics [7]. The details of what Nobuhiko Saitô considered at Oregon can be glimpsed in the afterword section of the manuscript he published in 1987 [8]. His study in biomolecules took the form of understanding the mechanism of protein folding, which was awarded the Toray Science and Technology Prize in 1986. The first series of his outstanding study on protein structure was on helix-coil transition with Mitiko Gô, published between 1965 and 1970 [9,10]. Then came the concept of the "island model", proposed by Hiroshi Wako and Nobuhiko Saitô in 1978 [11,12], which contributed significantly to the understanding of protein folding. The details are elucidated in the accompanying paper by Masaki Sasai, George Chikenji and Tomoki P. Terada in this special issue [13].

Prof. Saito's passion for pursuing an understanding of protein folding continued to the last moment of his life. He had submitted a manuscript on secondary structure prediction to *Biophysics and Physicobiology* and was pursuing discussions and rebuttals with reviewers. Unfortunately, the manuscript has not been published during his lifetime. However, there are a couple of points that are worth sharing with the biophysics community to let us understand how he viewed the study of protein folding. The following is a relatively long quote from the introduction section of his last draft:

"... theoretical determination of the tertiary structure has been attempted with two aspects in mind; one is to know the mechanism of the formation of the protein structure and the other is to replace or reduce the hard work of experimental method. The works by Lewis et al. for alpha-helix and beta-

bends were those among the early attempts to predict the secondary structures, or more generally, the tertiary structures of proteins from the amino acid sequences. The attempts suggested two ways of research to the structure prediction from the amino acid sequence. One is to use the accumulated data of protein structures to inquire the similarity of sequences. By virtue of the increase in structures determined, and the establishment of the Protein Data Bank (PDB), the scope of the research has reached to the extent to inaugurate a new science called bioinformatics. This approach has been proved to be useful to the studies of molecular evolution. Nevertheless, it is not yet sufficient for the structure prediction of proteins. Another way is the prediction or determination of protein structure by means of the physicochemical basis of the formation of secondary and tertiary structures of proteins, but it is also behind the progress. As regards the secondary structures, one may say that the prediction by either method has not yet been made to the scope to be useful for the determination of protein structures. On the other hand, the determination of tertiary structure, when the secondary structures are given in advance, has been successively performed in some proteins by means of the island model for introducing hydrophobic interactions. Furthermore the detailed structure and its behavior in the folding process of a protein, in particular, occurrence of two-state or three-state transition, are treated for various examples by the statistical mechanical theory. They can be reproduced quite similarly with the results obtained by experiments. Thus once the primary structure is determined, the remaining problem for the determination of the tertiary structure would be to develop new methods of the prediction of the secondary structure elements."

It is not so apparent in the quotation above, but Nobuhiko Saitô believed and often stated that a prediction should be formed on the physicochemical basis that could lead to an understanding of the mechanism of protein folding. He admitted that the information of sequence evolution had great power in structure prediction, but in the real world, a protein folds without that information. In addition, the above quotation evidently stated that the prediction of the tertiary structure of (small) proteins had been solved. In his mind, the remaining issue in the prediction was the secondary structure prediction, and once the secondary structure prediction was perfected, then the structure prediction from an amino acid sequence would be complete. This is apparently a controversial statement, but he understood protein folding in his own way.

In the draft, he continued to analyze the pattern of the appearance of hydrophobic amino acid residues in the primary structure of an alpha-helix. The pattern was further applied to a prediction of the location of alpha-helix on an amino acid sequence. In other words, what Prof. Saitô aimed at was a rule-based method for the alpha-helix prediction. Unfortunately, at the time, his method was not implemented in a computer program that could show its generality. Based

on the draft, I tried to implement the method in a computer program, but in vain; perhaps there was a missing description in the draft. In the draft though, it is evident that Prof. Saito put stress on hydrophobic interactions, which he stated were the most important interactions for secondary and tertiary structure formation.

Nobuhiko Saitô served many roles at Waseda University (he was a head of the Department of Applied Physics, when the Department of Physics was founded at the university) as well as in the scientific community. He was the vice-president of the Biophysical Society of Japan in 1985 and contributed significantly to the growth of the society. He is sorely missed by the biophysics community in Japan. Those who were lucky enough to know him personally will keep alive his way of venturing into the unknown in the physical world.

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