# Biophysics and Physicobiology

*Note*

# Professor Nobuhiko Saitô's contribution to statistical mechanics of biopolymers

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Polymer science, which studies the structure and properties of biopolymers and synthesized polymers, developed rapidly during the 20th century. One of the notable achievements in the 1950s was the discovery of the helix-coil transition of polypeptides [1]. At about the same time, in 1953, James Watson and Francis Crick reported on the double helix of DNA [2], which soon came to be a major subject within polymer science.

In 1958, Prof. Nobuhiko Saitô wrote a famous book in Japanese titled "Introduction to Polymer Physics" [3]. This book explained the properties of polymers based on physical laws, providing information essential to understanding the nature of polymers. His book has been read by many researchers and students for more than half a century. Indeed, if the book had been translated into English, it might be read world-wide and regularly referred to by numerous international scientists.

Prof. Saitô started his research on the helix-coil transition, a kind of phase transition, in the 1960s. I was then a graduate student in the Department of Physics at Nagoya University, and in 1964, was fortunate to be able to undertake theoretical research on the helix-coil transition of polypeptides under the guidance of Prof. Saitô at the Department of Applied Physics of Waseda University. Shneior Lifson and Antonio Roig had already published their elegant paper on the statistical mechanics of helix-coil transition based on the molecular structure of polypeptide chains [4].

Prof. Saitô encouraged me to pursue these questions by studying the helix-coil transition of D,L-copolymer, a copolymer consisting of D- and L-amino acid residues. Although natural proteins consist of 20 kinds of L-amino acid residues, the theoretical study of denaturation or renaturation of such proteins is not easy. So, we started to study D,L-copolymers as a simple model [5]. L-amino acid residues tend to lead to right-handed helices, while D-amino acid residues create left-handed ones. It was found, however, that D-amino acid residues in D,L-copolymers can have right-handed helices, depending on the number of continuous D-amino acid residues present. Although no copolymers of D,L-amino acid residues are found in nature, we conjectured that a slight change in the structure of polypeptides will lead to quite different conformations, which may cause different biological functions as well. It was my first experience enjoying theoretical studies, which allow a researcher to imagine and predict characteristics of polymers that cannot be determined through experimental study.

The interesting behavior of D,L-copolymer led me to study DNA and RNA, where Adenine and Thymine are connected alternately [6]. I introduced quasi-grand partition function as an extended version of the method of grand partition function, taking into account intra- and inter-molecular interactions.

The conformation of polypeptides in a helix-coil transition region is not Gaussian. Gaussian is a molecular chain whose end-to-end distance <R> follows normal distribution. In my subsequent work under Prof. Saitô, we adopted an


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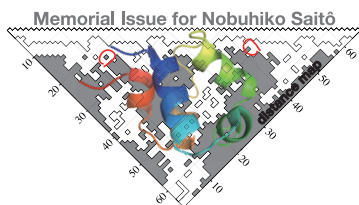
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interrupted helix model of a polypeptide chain in which random coil parts and rod-like helix parts were connected alternately by universal joints. Under certain conditions, shallow minima appeared in the second and fourth moments, $<R^2>$ and $<R^4>$, at the transition region. The deviations of $<R^2>$ and $<R^4>$ from Gaussian was calculated and the polypeptide chain in the transition region were shown to have a conformation of the swollen Gaussian type [7,8]. In organisms, proteins are always surrounded by many molecules and they are continuously synthesized and folded. They are also discarded, and overall, the conformational changes of proteins are thought to play a role on such occasions.

Prof. Saitô and I went on to study the helix-coil transition of polypeptides under external forces at the ends of the chain [9]. The following is an excerpt from the abstract of our paper on this research:

"It is shown that when the mean square end-to-end distance of a chain has a minimum at the transition region, the helical fraction increases at the helix-side and decreases at the coil-side of the transition region on applying the force. The critical value of the force to make the helical content almost vanish is estimated and the implication of this phenomenon in the mechanical denaturation of polypeptides such as polyglutamic acid and silk fibroin is discussed."

As described in this paper, Prof. Saitô also was deeply involved with the experimental results of the mechanical denaturation of polypeptide. He maintained close communication with Professors Yukichi Go and Eisaku Iizuka, who were engaged in the mechanical denaturation of a solution of polyglutamic acid and silk fibroin under shear stress [10].

The details of the linkage between our theoretical calculations and these experiments were described in the following paragraph from the same paper:

"Prof. Y. Go and his collaborators showed the final stage of mechanically denatured polypeptides is the fibrous aggregate of molecules by forming β-structures. However, the first stage of the mechanical denaturation is to unfold the molecule, or to decrease the helical content of polypeptides and the next stage is to form intermolecular β-structures between neighboring molecules which have unbounded -CO and -NH groups. These -CO and -NH groups are made free from intrachain bonding by the application of the external force in the manner described above, but still have the affinity to make the hydrogen bonds intermolecularly. Our calculation is concerned with the first step of the mechanical denaturation."

I was introduced to statistical mechanics of polypeptides and trained as a graduate student by Prof. Saitô from 1964–1967. I went on to earn a doctoral degree in Physics from Nagoya University. I had the privilege to work under Prof. Saitô again in 1970–1971 after returning to Japan from Cornell University where I had been working for Prof. Harold A. Scheraga as a post-doctoral research associate. I sincerely appreciate Prof. Saitô for his constant support of my research, and particularly for showing no sign of discrimination against women. If I had not had the chance to meet Prof. Saitô, I believe I could not have survived as a woman scientist. I deeply acknowledge the value of the training in statistical mechanics I gained at Prof. Saitô's laboratory and the style of his physical insights into biopolymers, which he taught me at a crucial, early stage of my research life.

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