LETTER TO THE EDITOR

Obituary Fumio Oosawa 1922–2019

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Abstract

Prof. Fumio Oosawa passed away in Nagoya on March 4, 2019, at the age of 96. As two of his former students we, like a great many scientists both in Japan and around the world, were much inspired and influenced by him. We have, at the request of the journal, penned this note to describe some of his major scientific contributions and also provide the readers of Biophysical Reviews with an idea of the remarkable personality and character traits that he displayed throughout his life. Fumio Oosawa (or Oosawa-san as he preferred to be called) was a physicist who initially entered the area of biophysics through studies in the field of condensed matter phenomena. Although a remarkable human being, he was, first and foremost, one of the leading scientists of his generation, making many original contributions that could, by any measure, be described as scientific breakthroughs. Therefore, before providing a short biography of his life in and around science, we thought it most appropriate to begin this Letter by first summarizing his major scientific contributions.

Depletion force

Oosawa developed the physical formulation of the depletion interaction—an attractive force observed to be exerted between two otherwise inert particles when immersed within a solution of macromolecules (Asakura and Oosawa 1954, 1958). The analytical expressions constituting the depletion force provided a theoretical basis for a variety of previously observed solution condensation phenomena induced by the addition of high concentrations of chemically inert polymers. Examples of such polymer-induced condensation phenomena included protein crystallization, blood cell agglutination in blood, bacterial aggregation in bacterial suspension, and soil particle flocculation in soil slurries. In his formulation of the depletion force Oosawa assumed two phases, one is the space between two particles, where polymer molecules are excluded because the space is too narrow to accommodate them, and the other is the rest of the polymer solution. The difference of osmotic pressure between the two phases exerts an attractive force between the particles, aggregating the particles. This theory was long time forgotten, being re-discovered 40 years later in a research news in Science (Kestenbaum 1998). In the mean-time, the force is referred to as “the depletion force.” It has been understood that in living cells, the depletion force should contribute to protein folding, bundling of the actin filaments and DNA, and the crowding of macromolecules. By employing novel microscope techniques, the force was quantitatively measured and the theory was proved (Crocker et al. 1999).

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Polyelectrolytes

Oosawa formulated a theory on the distribution of counter-ions on the surface of anisotropic macromolecules having many ionizable groups (polyelectrolytes), the phenomena typified by actin filaments and DNA (Oosawa 1957, 1971). While the distribution of polyelectrolytes and counter-ions is usually treated by use of the Poisson–Boltzmann equation, Oosawa instead employed the two-phase approximation and deduced the counter-ion condensation. Moreover, the theory accounts for the additive law of the activity of counter-ions (chapter 7 of (Oosawa 1971)) and predicts the assembly of rod-like polyelectrolyte molecules (chapter 9 of (Oosawa 1971)). The monograph (Oosawa 1971) summarizing the theory has gone on to become a highly influential textbook in polymer science.

Actin polymerization

Although not the first scientist to investigate actin polymerization, Oosawa was the first to study the behavior of actin from the viewpoint of a condensation phenomenon in statistical physics (Oosawa and Asakura 1975). Previously, it was known that actin could be prepared as monomeric globular G-actin in solutions containing low concentrations of salt. It was also known that monomeric G-actin could be induced to self-assemble into filamentous F-actin upon addition of salt. In the late 1950s Oosawa and his group began experimental studies of actin polymerization, preparing their own actin samples from the skeletal muscle of rabbits. At a small local scientific meeting, a member of the group presented an electrophoresis experiment which showed both a main peak, corresponding to the very large F-actin, and also a much smaller peak. Although they initially thought that this small peak must be denatured actin (thought present as a contaminant due to their lack of technical skills) a meeting attendee pointed out that the data could also indicate that monomeric actin may co-exist with filamentous actin. Prompted by this comment Oosawa realized that all their collected data might be interpreted by assuming that actin could transition between G- and F forms according to a definite kinetic and thermodynamic relationship (Oosawa and Kasai 1962) (Oosawa and Asakura 1975).

During these early investigations Oosawa found that actin exists as a mixture of G-actin and F-actin (i.e., as just two states) in a phase transition type relationship that was defined by a salt-dependent G-actin critical concentration (Cc). Below the Cc only G-actin exists, while above Cc, some actin exists in the G-actin form (equal to the Cc concentration) with all excess actin existing in the F-actin form. Oosawa and his group demonstrated that each actin molecule undergoes a cyclic transfer between G-actin and F-actin, making the system a dynamic steady-state. These results indicated that the polymerization of actin followed a condensation mechanism physically analogous to the behavior observed for water; i.e., as water vapor pressure increases above the critical vapor pressure, the excess steam condenses to form liquid water. Based on this understanding Oosawa and his group constructed a theoretical framework for the polymerization of actin based on nucleated-condensation principles. This conceptualization enabled them to propose a structural model of F-actin that configured the fiber as a helical polymer (Oosawa and Kasai 1962), and which suggested that the F-actin length distribution should be exponential. These proposals were later experimentally proven. In 1972, it was established that both the polymerization of tubulin into microtubules, and the polymerization of flagellin into bacterial flagella, followed an identical “helical polymer”-based theoretical framework. Since then, the concept “polymerization as a condensation phenomenon” has been accepted in the community as one of successful examples of the biophysical approach (Oosawa and Asakura 1975).

Outline of his scientific career

Oosawa was born in 1922 in Osaka. In September 1944, during wartime, he graduated from the physics department in the University of Tokyo. After his graduation, he moved to take an Assistant Professor position in the physics department of Nagoya University. After the war, the faculty of physics was completely restructured under the leadership of the renowned elementary particle physicist Prof. Shoichi Sakata. After that reform, if a proposal was approved, any scientific staff was allowed to organize a laboratory under his/her own leadership (in contrast to the old system where only professors were entitled to be PIs). Oosawa persuaded the pro-reform faculty to organize his laboratory for colloidal science. That was in 1950 when Oosawa was the age of 28.

In 1959, he was promoted to full professor in the section of physics at Nagoya University. In 1961, he created the Institute of Molecular Biology as a graduate school within the Department of Sciences, leading one of the two laboratories that constituted the Institute. In 1973, he started another laboratory in the newly founded Section of Biophysical Engineering in the Department of Engineering Sciences, Osaka University. Since that time, he was at Nagoya University in the first half of the week and was in Osaka during the second half of the week. He maintained this arrangement up until his retirement from the two universities.

In 1960, he and his colleagues at Nagoya University organized the Biophysics Society of Japan (BSJ) with 1500 members. This was about the same time as the International Union for Pure and Applied Biophysics (IUPAB) was founded and was also roughly congruent with the timing of the first annual meeting of the Biophysical Society in the USA (held in 1957).
**Inspired by Josiah Willard Gibbs**

Who was Oosawa-san’s teacher? We suppose that the scientist who provided the most profound inspiration was Josiah Willard Gibbs (1839–1903). As students we once saw three old notebooks which were kept by Oosawa-san. We were impressed that the three notebooks were completely filled with Oosawa-san’s beautiful handwriting. He had copied the entire book “Elementary principle of Statistical Mechanics” by Gibbs (Gibbs 1902). The notebooks were made by Oosawa-san at his age of 18, right after he started his physics study in the University of Tokyo. In his autobiography (Oosawa 2005), he describes:

> “I wrote down the entire text with every mathematical equation after I followed the meaning. However, after completing the transcription, I realized that I did not fully comprehend what was written in this book. It is really difficult to explain how and what is difficult to comprehend with this book. Dirac’s Text book “Quantum Mechanics” is simply not comprehensible. The difficulty in comprehending Gibbs’s book is somewhat different from this. Each equation and segment of the text is comprehensible. However, I was not able to understand for what purpose the author described the text. The book was very much fascinating.”

It was the Gibbs’ book that inspired Oosawa-san to start his studies in statistical thermodynamics.

**Shifts of research interests**

Soon after he started research in colloidal science, Oosawa’s research interests widened to include polymer science. In the polymer science field, he had chances to exchange ideas through personal contacts with Paul J. Flory (a Nobel Prize laureate in chemistry). When Flory visited Japan in 1953, he stayed for a couple of days with Oosawa in Nagoya, and it was during this time that Flory encouraged Oosawa to publish the theory of the depletion force (Asakura and Oosawa 1954). Later, Flory invited Oosawa to a scientific meeting on polymer contractility held in Pittsburgh. During that time Oosawa stayed with Flory and through him had the chance to meet and interact with Werner Kuhn, the inventor of the entropy elasticity model. Around this time Oosawa’s interests branched out to include the study of polyelectrolyte theory. In approaching this problem he adapted the two-phase approximation successfully employed to formulate the depletion force. Therefore, the polyelectrolyte study was a natural extension of his earlier work.

**Start of actin studies**

While Oosawa was still actively making major theoretical contributions, he was fascinated by the study of muscle contraction. In 1954, his group started to sacrifice rabbits to prepare actin by themselves in the physics department. It was his belief that in their experimental works actin should be prepared by themselves. This shift of research interests was encouraged through personal contacts with two physicists, Reiji Natori in Tokyo and Noburo Kamiya in Osaka. Natori invented a novel experimental system of the de-membranated single fiber of skeletal muscle, which permitted experimenters to directly investigate both the contractile apparatus (actin and myosin) and the regulatory apparatus (T-tubules and sarcoplasmic reticulum), without physical barriers of the plasma membrane. With his sound physics background, Natori advised Oosawa to study actin, since actin should be easier to both prepare, handle, and model by physicists. Kamiya started quantitative physiological studies of protoplasmic streaming using slime molds. Later Sadashi Hatano, a pupil of Kamiya, joined the Oosawa lab to isolate actin from the slime mold (Hatano and Oosawa 1966). That was the first isolation of actin from non-muscle cells, making it clear that actin is ubiquitous.

**Thoughts on biological studies by physicists**

Once we asked Oosawa-san about whether he had to change his mindset when moving from the field of theoretical physics to the field of experimental biology, he said that the lesson he learned most during this time came from observing the failure of many famous physicists to appreciate the correctness of the sliding filament hypothesis of muscle contraction proposed by Huxley (Huxley 1957). He noted that many renowned physicists of the day assumed that the contractility of muscle should originate from the properties of the individual molecules themselves, such as was the case for rubber elasticity. In the contractility meeting in 1960 described above, both Flory and Kuhn presented hypotheses along this line of thought. As the lone biophysist supporting the sliding filament hypothesis, Jean Hanson was also invited to talk at the meeting. This general paucity of talks advancing the sliding filament hypothesis indicated that even 6 years after its initial proposal in 1954 (Huxley and Niedergerke 1954; Huxley and Hanson 1954) it was still not widely accepted. At that time Oosawa-san was himself convinced of the general veracity of the sliding filament theory. Microscopic observations showed two kinds of filaments in parallel arrays and that contraction is associated with sliding between the two kinds of filaments, without requiring a change in length of individual filaments. Oosawa-san added that this example provided a microcosm of what was happening at the time. After the war, many physicists got
interested in biological research and moved into the field. However, many failed. That was because many were not aware of the fundamental differences between physics and biology in two aspects. First, any biological system has hierarchical structures and a particular function originates from a particular structural layer. A good grasp of the correspondence between a function and layer is essential. The contracting force is generated on the structural layer of arrays of filamentous aggregates, not the layer of individual molecules. Second, biological macromolecules, especially proteins, are individually distinct from each other. Therefore, we (biophysicists) should spend time and effort to understand and describe the properties of each protein. In this sense Oosawa-san postulated that biological studies are more like chemistry rather than physics. Therefore, questions to be addressed from a physics standpoint may be best formulated on the basis of the knowledge acquired by chemical and biological studies. Indeed, Oosawa-san understood well the importance of structural elucidation of proteins and protein complexes stating that physics can begin once the structure is elucidated. Within the laboratory Oosawa-san instructed PhD students to study a series of seminal papers by Max Perutz on hemoglobin structure and oxygen transport and encouraged them to pursue their own project in structural biology.

Life in the Oosawa laboratory

Oosawa-san attracted many young physicists, chemists, and biologists to biophysical research. His style in organizing his laboratory was extremely unique. First of all, there was no special professor’s room. Instead he had one small desk in an office shared with the students. He had no big book shelf either. As PhD students who shared a room with him, we did not know when and where he read or studied. Someone once told us that he often spent a couple of hours in a coffee shop off the campus reading important publications by others. Otherwise, he spent hours in talking science with other scientists that was observed everywhere within the university campus.

Only to a newly joining Master’s course student would he suggest a scientific project while every PhD student was encouraged to develop their research plan by themselves. While Oosawa-san did not provide students detailed instructions on their scientific project, he encouraged them to visit specialists for technical help in other laboratories both nationally and internationally. In this context, it was an enormous help for PhD students that we were allowed to communicate freely with scientists in Prof. Setsuro Ebashi’s lab in Tokyo and Prof. Yuji Tonomura’s lab in Osaka. Among muscle protein researchers in Japan during the 1970s to 1980s, every student was treated as a student of the community, not just of one particular laboratory.

The internal laboratory meeting of the Oosawa group was also something special. Every second week, all the scientists of four labs, two in the Department of Physics and two in the Institute of Molecular Biology, sat together for scientific discussions about each on-going project. Almost 30 scientists attended, consisting of about 7 or 8 staff scientists, more than 10 post-doctoral fellows, and about 10 PhD (in Japan DSc) students. While Oosawa-san did not interrupt discussions almost at all, the staff scientists and post-doctoral fellows engaged in critical analysis with each other that ranged from general observations right down to the fine details (including solution conditions in each experiment). Such meetings could continue for quite a long time, frequently running from 10 a.m. and to 9 p.m. with two breaks for meals. It was Oosawa-san’s belief that enthusiastic and noisy discussions among young scientists were a key to creativity.

The major roles played by Oosawa-san in the laboratory meeting included presenting insightful summaries of progress in research activities (both ours and others) and providing a new perspective on emerging questions. In either case, he always made clear a concept, rather than just presenting individual facts. We were fascinated by his way of formulating a new concept. Some of these conceptual formulations originally presented during laboratory meetings (and then later expounded upon in the literature) are recalled below.

“One function-one molecule”

Setsuro Ebashi convinced the research community of the calcium theory of the regulation of muscle contraction through his isolation of troponin, the calcium ion receptor bound on the muscle thin filament (the actin filament) (Ebashi et al. 1968). Oosawa was impressed by Ebashi’s work and proposed that there should be a general rule ‘one function-one molecule’; that is, if you identify a particular elementary function, then you should be able to find a specific protein molecule, which performs the function. Perhaps this proposal is an extension of his understanding of evolutionary requirement principles of living cells.

“Molecular machine”

A living cell is a collection of working blocks (blockworks) each performing an elementary function. The cellular function is additive; namely, it arises from the sum of functions of the individual working blocks. In Oosawa’s explanation each piece of a block corresponded to a protein molecule which he referred to as a “molecular machine.” The genetic information contains plans for these individual parts, not the entire system. Therefore, a living cell is a parts defined system with emergent properties.

The concept “the molecular machine” was first proposed and defined by Oosawa in a review article (Tonomura and...
machines. Oosawa suggested that molecular machines are flexible through random solution collisions. Thus molecular machines can better harness energy from the environment through thermal energy (later, Berg et al. reported that the threshold is approximately 0 mV (Manson et al. 1980)). This Oosawa provides an approximate free energy difference of the order of 30 mV which (based on the Nernst relation) is a thermal ratchet model is one important possible mechanism of energy transformation (Vale and Oosawa 1990).

The actomyosin sliding motor is also “loose coupling”

Toshio Yanagida, who worked together with Oosawa at Osaka University, reported that in the contractile apparatus, the hydrolysis of one ATP molecule drives the sliding of the actin filament over 600 Å, when no extra load is applied to the motor (Yanagida et al. 1985). It is known that as an extra load applied increases, the sliding distance per ATP hydrolysis decreases, eventually going to zero. Therefore, with the actomyosin sliding motor, the ratio between influx (the free energy from the ATP hydrolysis) and efflux (the sliding distance) is variable, which is another example of loose coupling. In other words, each step of the ATP hydrolysis reaction path does not necessarily correspond to a particular change in the physical state of myosin. In this experiment (Yanagida et al. 1985), they employed the sarcomeres in which the actin filaments are allowed to slide into the adjacent sarcomere. These interesting results prompted them to try and characterize a single molecular machine reconstituted from one myosin molecule and a single actin filament. By employing advanced techniques, they obtained results showing that each cycle of ATP hydrolysis can bring about multi-step sliding on the actin filament of between 2 and 5 steps (each of 53 Å in step size) for a total sliding distance of 110 to 300 Å (Kitamura et al. 1999).

The actomyosin sliding motor is a molecular machine which transforms the chemical energy stored in ATP into mechanical work. The mechanism of the energy transformation has still not yet been completely elucidated. For further investigations, the concepts formulated by Oosawa may play a helpful role.

(i) A living cell is a block work, and the cellular functions are a sum of functions of individual molecular machines.
(ii) A molecular machine is flexible.
(iii) The influx and efflux of a molecular motor may be loosely coupled (Oosawa and Hayashi 1986).
(iv) In a molecular motor, chemical reaction steps and physical states may also be loosely coupled.
(v) A thermal ratchet model is one important possible mechanism of energy transformation (Vale and Oosawa 1990).

In summary we would like to state that the concepts and theoretical investigations outlined by Oosawa-san were both highly original and incisive. They reflect Oosawa-san’s view of a living cell from the standpoint of statistical mechanics. Many leading scientists around the world have openly reminisced that they were inspired by discussions with, and talks
given by, Oosawa-san. Oosawa-san has surely influenced the thinking of many scientists and it is this, perhaps, that is the most important aspect of his legacy to the scientific community.

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**References**

Asakura S, Oosawa F (1954) On interaction between two bodies immersed in a solution of macromolecules. J Chem Phys 22:1255–1256  
Asakura S, Oosawa F (1958) Interaction between particles suspended in solutions of macromolecules. J Polym Sci 33:183–192  
Crocker JC, Matteo JA et al (1999) Entropic attraction and repulsion in binary colloids probed with a line optical Tweezer. Phys Rev Lett 82(21):4352–4355  
Ebashi S, Kodama A et al (1968) Troponin. I. Preparation and physiological function. J Biochem 64(4):465–477  
Fujime S (1970) Quasi-elastic light scattering from solutions of macromolecules. II. Doppler broadening of light scattered from solutions of semi-flexible polymers, F-actin. J Phys Soc Jpn 29(3):751–759  
Gibbs JW (1902) Elementary principles in statistical mechanics: developed with special reference to the rational foundations of thermodynamics. Charles Scribner’s sons, New York  
Hatano S, Oosawa F (1966) Isolation and characterization of plasmodium actin. Biochim Biophys Acta 127(2):488–498  
Huxley AF (1957) Muscle structure and theories of contraction. Prog Biophys Biophys Chem 7:255–318  
Huxley H, Hanson J (1954) Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. Nature 173(4412):973–976  
Huxley AF, Niedergerke R (1954) Structural changes in muscle during contraction; interference microscopy of living muscle fibres. Nature 173(4412):971–973  
Kestenbaum D (1998) Gentle force of entropy bridges disciplines (research news). Science 279(5358):1849  
Kitamura K, Tokunaga M et al (1999) A single myosin head moves along an actin filament with regular steps of 5.3 nanometres. Nature 397(6715):129–134  
Manson MD, Tedesco PM et al (1980) Energetics of flagellar rotation in bacteria. J Mol Biol 138(3):541–561  
Matsuura S, Shioi J et al (1977) Motility in Bacillus subtilis driven by an artificial protonmotive force. FEBS Lett 82(2):187–190  
Nagashima H, Asakura S (1980) Dark-field light microscopic study of the flexibility of F-actin complexes. J Mol Biol 136(2):169–182  
Oosawa F (1957) A simple theory of thermodynamic properties of poly-electrolyte solutions. J Polym Sci 23(103):421–430  
Oosawa F (1971) Polyelectrolytes. Marcel Dekker, New York  
Oosawa F (2005) Hyou-hyou rakugaku; in this way fresh studies could be born one after the other (in Japanese). Tokyo, Hakujitsu-sha  
Oosawa F, Asakura S (1975) Thermodynamics of the polymerization of protein. Academic Press, New York  
Oosawa F, Hayashi S (1986) The loose coupling mechanism in molecular machines of living cells. Adv Biophys 22:151–183  
Oosawa F, Kasai M (1962) A theory of linear and helical aggregations of macromolecules. J Mol Biol 4:10–21  
Oosawa F, Fujime S et al (1973) Dynamic property of F-actin and thin filament. Cold Spring Harb Quant Biol 37:277–285  
Tonoura Y, Oosawa F (1972) Molecular mechanism of contraction. Annu Rev Biophys Bioeng 1:159–190  
Vale RD, Oosawa F (1990) Protein motors and Maxwell’s demons: does mechanochemical transduction involve a thermal ratchet? Adv Biophys 26:97–134  
Yanagida T, Arata T et al (1985) Sliding distance of actin filament induced by a myosin crossbridge during one ATP hydrolysis cycle. Nature 316(6026):366–369

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