

## Physical aspect of microscopic behaviour of biomolecules

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I studied theoretical physics in the University of Tokyo and got a Doctor of Science degree in 1969. My thesis dealt with a theoretical analysis of nonlinear wave propagation on a liquid layer. After that I have been working until recently in the Department of Mechanical Engineering, Toyko University of Agriculture and Technology. From about 1980 I have been interested in mechanisms of pattern formations in physical systems, and have also been engaged in running the Society for Science on Form in Japan. Thanks to this activity, I have had many chances to meet scientists from other fields, especially the biological sciences.

Several years ago I had a graduate student, who had been a medical doctor and wanted to analyse the structure of human lung airways. She got a Doctor of Engineering degree on the basis of this work and we wrote a joint paper on the subject (Kitaoka *et al* 1999). Since then, I have maintained an interest in the problem of formation of macroscopic organ shapes. Originally, the behaviour of microscopic elements in biological systems was unfamiliar to me. However, the thermal motions of molecules were familiar. Would they not be negligible in the microscopic world; and might they destroy microscopic order? This article is a result of my speculations on the effect of thermal motions of molecules in biological systems.

### 1. Introduction

It would be appropriate to start this article by mentioning the contribution of Erwin Schrödinger, who wrote a famous book, “*What is Life?*” (1944), based on a series of lectures that he gave in Trinity College, Dublin in 1943. In this book he pointed out something important about the nature of the gene, long before the discovery of the double helical structure of DNA by Watson and Crick (1953). Schrödinger said that though the gene was of molecular dimensions, it should not be influenced by thermal fluctuations, whether of itself or of the surrounding molecules (he

expressed this by saying that the gene should have a zero effective temperature). This requirement is almost impossible to be fulfilled except for crystals, which have periodic and stable molecular configurations even at high temperatures. However, since biomolecules, in contrast to crystals, have no periodic structure, his claim worked as a suggestion to develop a new field of statistical physics, that is, to investigate the behaviour of molecules with aperiodic structures.

Here, I must confess that I am not a specialist of biophysics, but have been engaged in problems of pattern formation in fluid dynamics and thermodynamics. The only contact point between this and “gene science” is that the shapes of objects play essential roles in both. Nevertheless, I am trying to say something about the behaviour of biomolecules. It may be worth pointing out that Schrödinger began his lectures by expressing a desire to discuss biological problems even though he was not a specialist.

An important point in his book is an assertion that the food we eat everyday contains negative entropy. Since biological order is destroyed slowly by thermal effects, we must always continue to repair damaged parts in our body, and the negative entropy (contained in materials with high molecular order) should be taken in as ‘exchange parts’. Until that time food was considered to be an energy source for activity and materials to build up our bodies, the latter not being related to thermal effects. Schrödinger’s way of putting it was unique because he drew attention to two seemingly contradictory functions of food, one to produce energy (hence produce heat) and another to suppress the effect of heat.

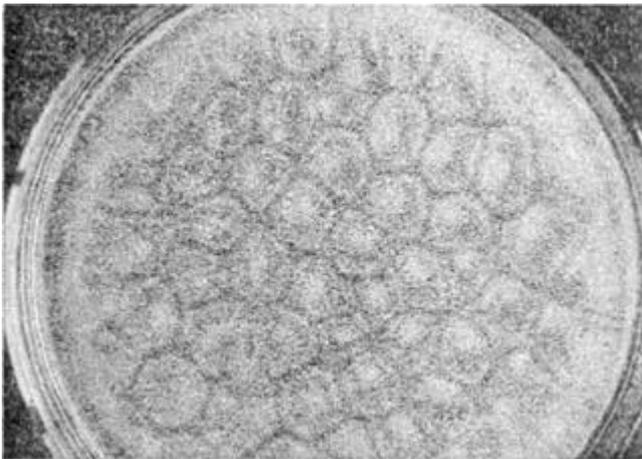
His book triggered studies of the molecular basis of genes, and eventually led to the discovery of the double helix. Since then, highly organized microscopic processes have been elucidated, including, for example, the roles of RNA, enzymes and proteins. The functions of these biomolecules are associated with rather complicated but well-organized biochemical reactions. Taken as a whole these

organized processes have given rise to the belief that, because they proceed deterministically, there is no scope for the thermal motions of molecules to be effective. (An additional reason to neglect thermal motions would be that they are much too complicated to allow an estimation of their effects.)

## 2. Recent progress in physics – dissipative structures

It is worthwhile here to note some important advances in physics in the past half century, that is, after the book of Schrödinger. A concept of dissipative structure in thermally non-equilibrium systems was proposed by Ilya Prigogine and his group (Glansdorff and Prigogine 1964, 1971), which without doubt enriched our understanding of nature. They developed a thermodynamical theory in which the thermal motion of molecules can produce a certain kind of order, which appears as a macroscopic coherent motion of materials. There are many examples of these ordered motions, other than well known ones, i.e. thermal convection within a fluid with non-uniform temperature distribution, the formation of dendrite shapes in crystal growths or aggregation of diffusing materials and the oscillating chemical reaction called the Belousov-Zhabotinski reaction. Thermal convection refers to fluid motion within a container with long range order (see figure 1), and its driving force is buoyancy owing to the thermal expansion. Therefore, it is certainly an example of order originating in thermal motions of molecules.

The “order” in these structures has macroscopic sizes. In the microscopic scale thermal motions of molecules dominate their states; we do not see any order. Each mole-



**Figure 1.** Thermal convection of silicone oil between two horizontal boundaries, where the lower one was given a higher temperature. The flow was visualized by mixing aluminum powder (from Takaki and Sano 1988). Each aluminum particle was undergoing Brownian motion, as will be seen by the use of a microscope, which shows microscopic disorder.

cule does not know that it is a member of macroscopic ordered structure. This is an essential difference between dissipative structures and the order maintained by biomolecules. Here arises the problem of how the order in the latter is preserved in spite of existence of their thermal motions.

## 3. Types of thermal motions of biomolecules – translation and rotation

There are several kinds of thermal motions. One is a translational motion of a molecule, whose energy is  $3kT/2$  ( $k$  is the Boltzmann constant, and  $T$  is the absolute temperature). The energy  $E$  is expressed also in terms of the mass of the molecule  $M$  and the velocity of translation  $v$  as follows:

$$E = \frac{1}{2}Mv^2, \quad \text{hence} \quad v = \sqrt{\frac{3kT}{M}}. \quad (1)$$

It is possible to make a rough estimation of this velocity by assuming the value of  $M$ . The other parameters can be fixed to  $k = 1.38 \times 10^{-23}$  J/T and  $T = 300^\circ\text{K}$ .

In order to estimate the value of  $v$ , let us assume that a typical molecular weight of a biomolecule is 1000 (here big molecules, such as DNA, are excluded). Then we have  $M = 1.7 \times 10^{-24}$  kg. However, we should keep in mind that a biomolecule is always interacting with nearby molecules and its motion must be associated with many of these molecules. Then, the thermal motion of the molecule is looked upon as a motion of a group of molecules, where the size of the group should be specified. We assume further that the group is 10 times as large as  $M$ . The factor 10 is chosen here, because in the close packing of equal spheres a sphere contacts 12 neighbours. Then, by substituting the value of this effective mass  $M = 1.7 \times 10^{-23}$  kg into Eq. (1), we have  $v = 27$  m/s. Translational thermal motion of this velocity causes the diffusion of molecules, since the direction of motion is chosen randomly. This velocity is rather large, as can be understood from the following note.

If we assume a molecular size of 1 nm, it takes a time of  $10^{-10}$  s for the molecule to move by a distance of the order of the size. On the other hand, the typical time of biochemical reaction is much longer; for example, a typical half-time of catalysis by an enzyme is  $10^{-3}$  s (Alberts *et al* 1994). Thus diffusion plays an important role in biochemical reactions, since it assures that a molecule meets the right “counterpart” molecules.

The second type of thermal motion is a rotation of the molecule. The energy of the rotational thermal motion is  $3kT/2$ , which is also expressed in terms of the moment of inertia  $I$  and the angular velocity of rotation  $w$  as follows:

$$E = \frac{1}{2}Iw^2, \quad \text{hence} \quad w = \sqrt{\frac{3kT}{I}}. \quad (2)$$

The moment of inertia  $I$  is a quantity which stands for an inertia associated with rotational motion and has a value of the same order as the product of mass  $M$  and the square of the molecular size. Here, we have the same problem of molecular group as is met in the translational thermal motion i.e. a molecule is rotating together with nearby molecules. It would be natural to consider that the group size in rotational motion is smaller than that in translational motion, because the rotating molecule does not push many other molecules (in the case of a molecule with spherical shape, the molecule slips at contact points with other molecules, hence it moves only by itself). We assume that  $M = 1.7 \times 10^{-24}$  kg, that the effective mass is equal to  $M$  and that the rotation radius of the molecule is 1 nm. Then, we have  $I = (1.7 \times 10^{-24}) \times (1 \times 10^{-9})^2 = 1.7 \times 10^{-42}$  kg·m<sup>2</sup>, and  $\omega = 8.5 \times 10^{10}$  rad/s, which means about  $10^{-10}$  s per one turn. This time is also much shorter than the reaction time. This rapid molecular rotation is considered to work to let the molecule reach its right posture for reaction with other molecules.

Here, an important feature of reaction between biomolecules should be discussed. A molecule chooses the right counterpart by shape i.e. it chooses by trying to fit one part of its surface to one part of the surface of another molecule. For that purpose, both molecules should rotate around a variety of axes rapidly and look for a correct combination of their postures. Therefore, rapid thermal rotation is necessary in order that chemical reactions proceed without delay.

#### 4. Deformation of molecule as thermal motion

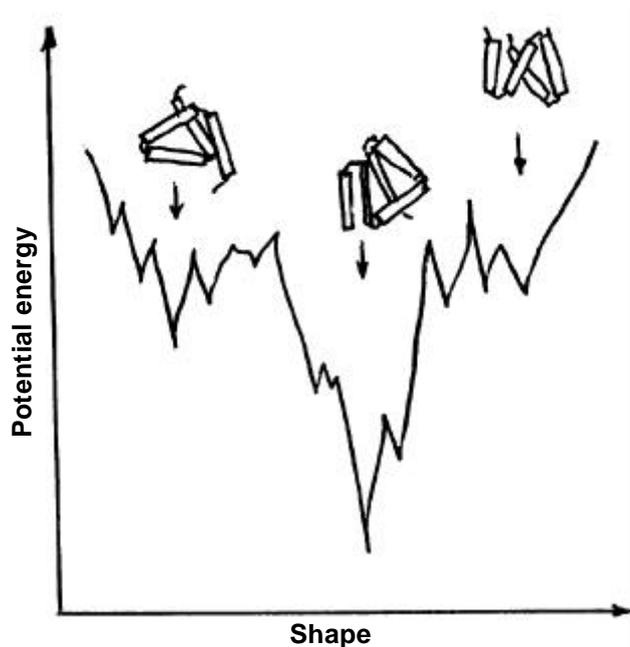
The third type of thermal motion is the random change of molecular shape. It often occurs in flexible molecules which are constructed by folding a long chain of components. In the folded chain two components come close through folding, but they interact each other rather weakly and the molecule has a room to change its shape as a whole. How does a molecule change its shape or how much is the probability of shape change? This is quite a difficult problem in physics, and little is known. The main problem which has been attracting the interest of physicists is how an elongated chain of elements folds itself to a correctly folded shape. At each joint of folding there are many possibilities of choosing folding angles, and if the chain has many joints it has a great number of possible shapes. It would take a very long time to test all of these shapes, but biomolecules attain correct shapes very rapidly. It is a mystery how the chain can “know” the correct shape beforehand.

A model analysis of folding mechanisms was made by Sasai (1997). He calculated the potential energy owing to forces between elements and guessed a process of folding by assuming that the folding proceeds so that this potential

energy decreases. However, the theory is not convincing enough because the potential function has many minima, whence the chain has a variety of stable shapes (see figure 2).

But this same figure is highly suggestive for our purpose, which is to consider thermal fluctuations of molecular shape. It should be noted that the potential minima (called also potential wells) are very sharp and that a molecule, once fallen into the bottom of a potential well, can not get out of it easily. The sharpness means that thermal fluctuation of a trapped molecule are not large and it maintains a nearly constant shape. But, the probability of a molecule to receive a strong thermal agitation is not zero (although very small); with this probability the molecule will be pushed above the potential wall and shifted to a neighbouring well. It means that the molecule has changed its shape appreciably owing to a strong thermal agitation. This possibility is the main point of what I am trying to get across.

This kind of shape fluctuation may occur also in biomolecules which recognize other molecules by their shapes. Hence mistakes of recognition will occur with a small but nonzero frequency. The fluctuation will be reduced by a certain degree by the presence of other nearby molecules as is the case for the translational and the rotational motions. However, this suppression effect on shape fluctuation will be smaller than those on translation and rotation, because the shape change is considered to occur freely in a narrow space surrounded by other molecules.



**Figure 2.** Potential energy of a folded chain molecule (a rough sketch of the figure in Sasai's paper (1997)). The abscissa indicates conceptually the variety of folded shapes.

I must apologize for discussing molecular shape fluctuation with so many speculations. Theoretical progress in this field is poor and no well-founded discussion is available.

### 5. Strategy of biological systems to prevent wrong processes

Is the shape fluctuation of biomolecules a serious problem or not? There may be the objection that its influence is negligible since it occurs very rarely. However, a general idea that the effect of very rare events is small may be correct only in random systems (or macroscopically ordered systems). In biological systems with microscopic order a very rare event in a single molecular might lead to a large deviation from the normal state. For example, a signal molecule in the nucleus may choose a wrong site on DNA and may produce a wrong mRNA, which might act as a trigger to many wrong processes. Hence biological systems should have developed a strategy to eliminate the effects of shape fluctuations or to destroy wrong products. What principle might lie behind this strategy? I will try to suggest one.

A general property of biochemical processes is that they are always associated with a great number of chemical reactions. It means that the system of biochemical processes is looked upon as a highly complex system. The concept of "complex systems" has been developed recently as an interdisciplinary research field. It is another major development since the time of Schrödinger's lecture. A good introduction to complex systems in the field of biochemistry is given by Cramer (1988). A necessary condition for a complex system is that it should contain many elements interacting nonlinearly with each other. The nonlinearity prevents the system from being arranged to a new set of variables with simple behaviour; hence one can not establish a simple understanding of the system. Examples of complex systems are ecological systems, economical systems, neural networks in the brain, etc. The theory of complex systems is not yet developed enough to be applied to microscopic behaviour in biological systems. I hope that development of the theory will cast light on the a mystery of microscopic order in biological systems.

In general, how is order recovered in systems full of thermal fluctuations? In ensembles of molecules, increasing their number makes thermal fluctuations less effective. If a system is composed of  $N$  molecules, the deviation of an averaged quantity has a strength which is  $\sqrt{N}$  times smaller than the average itself. Hence, as  $N \rightarrow \infty$ , the fluctuation becomes negligible relative to the average. However, this logic is not useful in microscopic biological systems, where the number of molecules is not very large. Then, what ensures microscopic order?

A hint to the solution of this problem might be that the number of chemical reactions is huge. Moreover, these mutually connected chemical reactions are highly organized. Because of the large number of reactions, deviations from correct process might be always suppressed and a normal route to the favourable goal might be maintained. By increasing the number of reactions (not the number of molecules), ordered behaviour of the system would be enhanced. This idea is just an extension of the analysis of the Belousov-Zhabotinski reaction, which is an oscillating chemical reaction (Winfree 1974). In the analysis this phenomenon is associated with several reactions and shows an orderedness which is not expected in simpler systems with a smaller number of reactions.

Can a new type of statistical physics be constructed for systems with a great number of reactions among components, with the number not large enough to allow conventional statistical treatment? I do not know what this new theory will look like, but can imagine that it will be an extension of the present theory of complex systems. This new theory will contribute to understanding the microscopic order in biological systems. It will predict how much is the effect of unfavourable products coming from shape fluctuations of a biomolecule.

For example, suppose that a mRNA has been produced from a wrong gene. Then, a group of chemical reactions will be triggered and will produce molecules to attack this mRNA. At a certain stage, before it passes through the nuclear membrane, or after that (or while it is synthesized), this mRNA will be eliminated.

### 6. Concluding remarks

Biomolecules do not always behave correctly; they sometimes make mistakes because of shape fluctuations. On the other hand, a mechanism constructed of a complex network of biochemical reactions could work to correct mistakes.

This idea will lead to a proposition of a new physical problem: what are the properties of such complex networks? It will meet the doubt "Are mistakes actually occurring in biochemical processes owing to shape fluctuations?" It should suggest new activity to detect the production of biomolecules in real biological systems. In addition, it would be interesting to insert a wrong component into a system with normal processes and to observe how this component provokes abnormal reactions.

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