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A Thermodynamic Approach towards the Question “What is Cellular Life?”

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Abstract: The question “What is life?” has been asked and studied by the researchers of various fields. Nevertheless, no global theory which unified various aspects of life has been proposed so far. Considering that the physical principle for the theory of birth should be the one known for the unanimated world, and that the life processes are irreversibly selective, we showed by a deductive inference that the maximum entropy production principle plays an essential role for the birth and the evolution of life in a fertile environment. In order to explain the survival strategy of life in a barren period of environment, we also proposed that life had simultaneously developed a reversible on and off switching mechanism of the chemical reactions by the dynamics of equilibrium thermodynamics. Thus, the birth and evolution of life have been achieved by the cooperation between the driving force due to the non-equilibrium thermodynamics and the protective force due to the equilibrium thermodynamics in the alternating environmental conditions.

Keywords: birth and evolution of life; non-equilibrium thermodynamics; maximum entropy production principle; self-replication; multi-cellular life

1. Introduction

It has been generally accepted that the four elements, metabolism, self-replication, evolution, and common cell structures, are indispensable for the principle of life. There have been innumerable efforts to theoretically describe each of these phenomena separately by various fields of scientists. Nevertheless, no theoretical viewpoint which had unified all these elements of life including the birth of life has been proposed so far.

Physicists among them had been eager to find some fundamental concepts in this charmingly complex world [1–10]. Schrödinger [3] discussed the “negative entropy” of the life, a new concept at that time. But it was not explained where it comes from and how life was created. Prigogine [4,5] derived entropy production and its fluctuation and stability of the local steady non-equilibrium systems, but the formalism was limited near equilibrium. Watson and Click discovered DNA experimentally and showed that DNA is universal among the all lives [11]. Since this epoch-making discovery, enormous progress has been achieved around DNA central dogma in biological science. Nevertheless, the theoretical question how the life was born and how it has evolved has not been clarified, in spite of the efforts of experimental researchers of the field including RNA world [12,13], and theoretical researchers including Eigen [6,7] who kept through his life asking the physical meaning of Darwin’s natural selection [1] and tried to answer the question “who does the selection?”
In addition, necessity of a comprehensive theory of life has recently increased in view of the present problematic situation of the lives on our planet. To make research of “What is life?” is not only of academic interest, but it is also important for the future of the relation between the mankind and other species.

To study the birth and evolution of life we clarify the following three basic standpoints. First of all, because life was basically born from unanimated material when some necessary conditions were satisfied, we should not expect a new physical principle specialized for the birth and evolution of life. The process cannot be something which follows quite different principle observed in unanimated world. Secondly, we notice that the life phenomena are, in principle, not reversible but one-directional in spite of the neutrality of gene mutation. Thirdly, the self-replication chemical system was selectively evolved. The first two points strongly imply that the life phenomena should be based on the thermodynamics far from equilibrium. The third selectiveness implies that the second law of thermodynamics is not sufficient.

This is the very reason why we took, in this paper for the problem of birth and evolution, a thermodynamic approach using maximum entropy production principle known as the pattern selection principle in the unanimated phenomena such as convection patterns or growth pattern of snowflakes. In Section 2, we review the past research for the complex system based on the maximum entropy production principle. In Section 3, we overview the important steps of birth and evolution of life. In Section 4, we show intuitively how maximum entropy production principle is derived from the second law of thermodynamics. We discuss in section 5, deductive outcomes from maximum entropy production principle.

Biological structures, however, cannot be described only by the force of the thermodynamics far from equilibrium, because the environment changes were common all over the surface of the earth, and did not guaranteed the fertile condition. The life had simultaneously developed a reversible on-and-off switching mechanism of chemical reaction by the dynamics of equilibrium thermodynamics for survival under the barren environment. This development had helped the activity of the living organism much better than starting again from zero. In Section 6, we discuss thermodynamics of multi-cellular organism together with the altruistic behavior. In Section 7, we discuss the remaining problems and conclude.

2. Thermodynamic approach to a complex system far from equilibrium

2.1. Dynamical system approach and thermodynamic approach

In a dynamical system of a few components one may discuss what kind of modes exist and how fast each mode grows by calculating Lyapunov exponents. The mode with largest Lyapunov exponents grows fastest among others. The molecular dynamics, however, in the birth and evolution dynamics of life involves too many chemical reactions with many unknown chemical reaction constants to analyze, and one cannot derive dynamical equations to obtain Lyapunov exponents.

Thermodynamic researches, in contrast, utilize macroscopic variables of the ensemble. In equilibrium systems, the minimum free energy principle for any systems at equilibrium was well established, and has been widely used to study successfully the structure of the materials. In contrast, almost all of the biological structures and functions are fundamentally irreversible and characteristic to non-equilibrium thermodynamics. The present status of the researches in non-equilibrium physics of biology was recently reviewed in detail [14], which showed the non-equilibrium nature of each biological phenomena. It also suggested that the researches have been localized in each phenomena of biology, and have not yet approached to the present global question of the life.

The maximum entropy production principle has been used for the self-organized dynamical structures and the corresponding functions of open systems far from equilibrium [15,16], as the natural extension of the second law of thermodynamics. Maximum entropy production principle is the algorithm of the nature to achieve the final equilibrium state of any localized system most efficiently, as shown in the later
section of the present article. This principle may work as the physical basis of “Survival of the Fittest” of C. Darwin [1].

2.2. Past researches on the maximum entropy production and related topics

The applicability of the maximum entropy production principle has been reported in various fields [15,16]. In the studies of pattern formation of a chemical reaction [17] and electrical convection patterning [18], computer simulation showed that the pattern modes drifted from given initial conditions towards the mode of largest entropy production among the possible modes under the given thermodynamic potential. In other words, the total system consisting of the local open system together with the reservoirs were observed to follow the maximum entropy production principle. Recently, a theoretical research of the selection rule of open systems far from equilibrium was reported based on the stochastic least-action principle, which showed that in a multi-stable system, the steady state with the highest entropy production is favored [19]. Among statistical theories of evolution, a model [20] was recently proposed to give the relation between the maximum growth rate of individual number and statistical variations of the attribute, the offspring and the environmental factors. The maximum growth rate is certainly related to the maximum entropy production. A statistical approach may be powerful for discussing evolution once we obtain the transition probability.

3. Breakthrough processes of the birth and evolution of life

Figure 1 shows the important steps generally accepted as the birth and evolution of life. Our present interest is to know if there are some common features in the processes, although they might look at first as if each process took place with no relation to each other. This paper focusses not on the physical mechanism of each process, but on the physical principle by which nature selected a path shown by heavy frames and thick arrows among others in Figure 1.

[Process 1]. Accidental accumulation of amino-acid, sugar, fat, nucleic acids in the varieties of planetary and geophysical phenomena such as meteorite bombardment, volcanic activities, temperature fluctuation occurred on the surface of the earth. Stage was prepared geophysically for the birth of life.

[Process 2]. Quasi-stable vesicles were created to decrease free energy of the amphiphilic molecules in water [21]. Among the various vesicles produced in different environment, some happened to contain high density of useful chemicals. Density of these chemicals reached high enough to set the cells in the thermodynamic state far from equilibrium and various chemical reaction modes were excited inside, including formation of RNA world [12,13].

[Process 3]. The vesicles finally became biological cell membrane, which had provided a stable dense chemical reaction tanks. The well-developed cell structure started developing self-replication double-stranded DNA with structure/catalysis by proteins or other chemical compounds.

[Process 4]. Exponential increase of the organism was achieved by the self-replication of the chemical information by the stable double strand DNA molecules together with corresponding cell division. Great improvement of metabolism was necessary for this process. The exponential number growth made visible the very small probability of natural mutation and also made possible the “Preservation of Favoured Races in the Struggle for Life” by Darwin [1].

[Process 5]. Frequent cell division gave a choice of life style whether as independent single cells or as cooperative group cells, depending on the environmental condition.

[Process 6]. Invention of tools and acquisition of languages of mankind (The latest evolution, which resulted in considerable increase of entropies on the surface of the earth).

Although each of these steps may be the research target by dynamical models, and even if some success be obtained by constructing good models, one still wants to know the super rule to drive all
these dynamics in order to understand “what is life”. It is why we try to approach this problem by thermodynamics.

Figure 1. Breakthrough processes of the birth and evolution of life. Heavy frames and thick arrows are the main line of birth and evolution of lives. The figure is by no means complete, with many other missing important steps of evolution such as the transition from asexual to sexual regeneration in this figure.
4. The Second law of thermodynamics and maximum entropy production principle

4.1. Intuitive derivation of maximum entropy production principle

Considering the neutrality of mutation, one directionality of the evolution may be phenomena related to the second law of thermodynamics. The features of these major steps of life may suggest us an inductive inference: The various aspects of life are the structure and the activity of the open systems far from equilibrium, and the birth, self-replication and evolution are consistent with a thermodynamic principle.

The only well-known principle for a closed non-equilibrium system is the second law of thermodynamics. The law, however, indicates only the direction of the thermodynamic state of a closed system, and does not indicate how processes of life make progress as described above. Therefore, only the second law is not sufficient to account for the birth and evolution of life. All the processes except the preparation stage give us an impression that the processes follow a selection rule such that they always evolve toward the direction of increasing “activity”, or increasing entropy production. Therefore, we try to investigate if the birth and evolution is explained by the maximum entropy production principle [15,16,22,23], which was proposed for nonlinear open systems far from equilibrium as a lemma of second law of thermodynamics.

Let us intuitively describe the mode-selective nature of the entropy production for an open system far from equilibrium, apart from a recent theoretical research on the same principle [20]. According to the second law of the thermodynamics, the entropy of a closed system of particles with random distribution in momentum space always increases, and the ensemble approaches to Boltzmann distribution,

\[ S(t + \Delta t) - S(t) > 0, \]  

because the larger the entropy is, the more probable the state is.

Suppose that this closed system is divided into a small closed subsystem and some reservoirs separated by the walls, each of which is in the equilibrium independently from each other. Furthermore, each reservoir is, by definition, very large and homogeneous defined by thermodynamic potentials \( X \) such as temperature, pressure and chemical potentials, and will not produce entropy by itself. When the walls in contact with the small sub-system are replaced by semi-permeable walls at a time \( t_1 \), the small subsystem, which happens to have a thermodynamic potential different from the reservoirs in contact, will be driven to produce a thermodynamic current \( J \) inside and thereby produces some entropy within the subsystem. Produced entropy may be extracted to the reservoirs to keep the subsystem steady, and the entropy of the total system will increase.

Let us discuss a subsystem hereafter, assuming for simplicity that all the subsystems are equal. Suppose a variety of active modes \( i \) are possible for a given \( X \) which is the thermodynamic potential far from equilibrium, the increase of the total entropy \( S(t) \) for \( t > t_1 \) depends on the mode which the subsystem chooses. If \( \sigma_i \), the entropy production per unit time of the \( i \)-th mode is greater than \( \sigma_j \), that of the mode \( j \), then \( \Delta S(X, t) = \Delta t \cdot \sigma \) by definition we get,

\[ \Delta S_i(X, t) > \Delta S_j(X, t), \]  

and

\[ S_i(X, t + \Delta t) > S_j(X, t + \Delta t) \quad \text{for} \quad t > t_1. \]  

Then the mode \( i \) of the local sub-system will be selected, because it is more probable. This is maximum entropy production principle which is a natural extension of the second law (see Figure 2).
Entropy production is equivalent to metabolic energy divided by the temperature for living organism. The former, however, is a concept which is useful quantity for living or nonliving systems, while the latter is a terminology used for living system only. That is why entropy production plays a fundamental law for the birth of life. Also, the difference is important for the [Process 6 of Figure 1]. The energy dissipation for the body action to the environment using a tool is counted in metabolic energy, but the resultant increase of the environmental entropy is not counted in metabolic energy. However, it should also be counted as the entropy produced by the living object who used the tool.

4.2. Entropy production and chemical structures in the open chemical reaction systems far from equilibrium

The second law of thermodynamics is concerned with a closed system at a non-equilibrium state. A simplest non-equilibrium state is composed of two local systems different in the thermodynamic variables connected within a totally closed system. In the relation (2) of the previous section we described a non-equilibrium system separated spatially from the reservoir. However, the local non-equilibrium system, in general, may be separated by momentum space or the chemical component space. An example of the spatially separated system is two boxes of the same molecules but different temperatures $T_1$ and $T_2$, connected with each other. If energy flow is allowed between the two boxes, the total system will move to the direction to equalize the temperatures as fast as possible [23–27]. An example of the separation in chemical component space is one box of the same temperature, but with two different kinds of molecules $A_1$ and $A_2$ with different chemical potentials $\mu_1$ and $\mu_2$, interchangeable irreversibly from one to the other by reaction. When a chemical reaction from $A_1$ to $A_2$ or vice versa is allowed, the chemical reaction will proceed to equalize the chemical potentials.

It is important to notice that the thermodynamic current realized at a condition far from equilibrium generally forms a structure in the relevant space. For a non-equilibrium system whose thermodynamic force is separately given in a real space, a spatial current structure such as convection is observed. While, for a non-equilibrium system whose thermodynamic force is separately given in a chemical component space, an associated structure of reaction flows will be observed in chemical components space. The self-replication chemical reaction structure in the problem of birth and evolution of life is also an example
of the structure in a chemical component space generally associated for the maximum entropy production principle in a non-equilibrium system far from equilibrium.

When the spatial variation of the temperature, the pressure, the concentration or any other thermodynamic force can be neglected compared to the chemical potential difference of the composing molecules, one may write the entropy change as,

\[ T ds = -\mu_1 dN_1 - \mu_2 dN_2. \] (4)

More generally, the entropy production \( \sigma(R, t) \) of an ensemble of organisms in the area \( R \) which is much larger than the body size of the organism (see Figure 3), may be written at time \( t \) as,

\[ \sigma(R, t) = \sum_i \sum_k J_{i,k}(R, t) \cdot X_{i,k}(R, t) \] (5)

where \( J_{i,k} \) and \( X_{i,k} = A_{i,k}/T \) are the reaction rate and the generalized thermodynamic force for the \( k \)-th chemical reaction of \( i \)-th organism, respectively. And, the chemical affinity \( A_{i,k} \) is written as,

\[ A_{i,k} = -\sum_j v_{i,k,j} \mu_{i,k,j}, \] (6)

where \( v_{i,k,j} \) is the \( j \)-th component of \( k \)-th reaction of \( i \)-th organism. \( \mu_{i,k} \) is the chemical potential difference of \( k \)-th reaction of the \( i \)-th organism. These equations will be used for the discussion in the next section.

**Figure 3.** Schematic drawing for a thermodynamic system at niches \( R, R', \ldots \), far from equilibrium, consisting of a reservoir which is characterized by a thermodynamic force \( X(R) \) and some small open organisms with thermodynamic currents \( J_i \).

5. Deductive outcomes from maximum entropy production principle

5.1. Thermodynamic deductive scenarios

In a simple thermodynamic system where the dynamical equation can be written down, such as the case of a convection system, or the case of model chemical reaction system such as Brusselator [4,5], the thermodynamic force \( X_k \) and the thermodynamic current \( J_k \) can be specified. On the other hand, chemical
reaction systems related to the birth and evolution of life are so complex that it is nearly impossible to specify all the dynamics of reactions. Since any bottom up theoretical treatment may not be perfect for the birth and evolution of life, we intend to present in the next section a top down thermodynamic approach and compare with the important processes observed for the birth and evolution of life.

We intend in this section to deduce the possible results when we assume the maximum entropy production principle as a guiding principle for the nonlinear open system far from equilibrium. We propose a physical model that the principle of maximum entropy production explains not only the mode selection of unanimated open systems far from equilibrium, but also most of the indispensable features of lives. By limiting the discussion here for only one kind of organisms in a local area and summing in Equation (5) over $i$, we get,

$$\sigma(R,t) = N(R,t) \langle J(R,t) \cdot X(R,t) \rangle$$

(7)

where $N$ is the number of organisms, and $\langle J \cdot X \rangle$ is the inner product of vectors $J$ and $X$ in $k$-space. Since thermodynamics of each area is independent from each other when each area is not interacting, one can discuss the entropy production of an area and the principle of maximum entropy production requires to maximize $\sigma$ of each local area. From Equation (7) the change of the entropy production $\sigma(R,t)$ has three terms,

$$\Delta \sigma(R,t) = \Delta N \langle J(R,t) \cdot X(R,t) \rangle + N(R,t) \langle \Delta J(R,t) \cdot X(R,t) \rangle + N(R,t) \langle J(R,t) \cdot \Delta X(R,t) \rangle$$

(8)

Equation (8) implies that maximum entropy production principle is decomposed into three scenarios.

[ΔN–scenario.] The first term of Equation (8) is the contribution to the increase of the entropy production by increasing number $N$. The number of the subsystems may increase even in unanimated systems such as vortices in fluid system, although the mechanism of the birth of a new eddy is independent of each other. The specialty of the ΔN–scenario of the animated systems is the achievement of self-replication and therefore the born subsystems are identical to each other.

[ΔJ–scenario.] The second term of Equation (8) is the contribution to the increase of the entropy production by increasing thermodynamic current $J$. The chemical reaction rates were improved by the transition of the modes to higher entropy production shown in Figure 2 introducing various kinds of enzymes and new reactions before or after the completion of the self-replication cycle. Geometry, membrane and size of the cells were adjusted for the highest efficiency of the metabolism after the self-replication cycle was completed.

[ΔX–scenario.] The third term of Equation (8) is realized by improving the mismatch of the position $R$ of the cell and the more fertile environment.

$$\Delta X(R,t) = \Delta R \cdot \nabla_R X(R,t)$$

(9)

The cell may move to a better environment to increase entropy production if the cell is equipped sensors to sense $\nabla_R X(R,t)$ and mobile function to realize $\Delta R$. For this strategy to function for a cell, the sensor and locomotive mechanism must be developed.

Now, let us try to compare these deductive possibilities with the processes shown in Figure 1. We realize that the Process 1 and 2 correspond to $\Delta J$-scenarios, and that Process 3 and a part of Process 4 corresponds to $\Delta N$–scenarios. Process 5 may correspond to a $\Delta X$–scenario. The three scenarios were obviously not planned by the biological system. It is only the result of the selection among the products of various mutation to satisfy the maximum entropy production principle. Process 6 is obviously beyond the scope of the present paper.
5.2. Self-replication in chemical systems and the maximum entropy production

In a complex molecular structure, one cannot expect to make a direct copy of it, because a molecule of one kind avoid to be near the same molecules. However, one can expect to make a copy of the original, by the first use of a negative copy which is complemental to the original and a second use of the negative copy of the negative. If this cycle works well (ΔJ-scenario), the original complex molecular structure will be doubled, and the continuation of this process will lead to exponential increase of ΔN (ΔN-scenario) by creating a fastest reaction mechanism of this self-reproduction process shown in Appendix A and in Figure 4. We notice a surprising similarity between the self-replication reaction currents in the chemical component space (Figure 4) and the convection currents of fluids in the spatial coordinate (Figure 5). They are both the results of the maximum entropy production of each system at a condition far from equilibrium.

**Figure 4.** Chemical reaction current in a chemical component space of the self-replication dynamics shown in Appendix A under a thermodynamic condition far from equilibrium. The chemical reactions are shown in Appendix A. X and X* are the single strand gene polymer and its counterpart. XX* and X*X are equivalent double strand gene polymers. C is law molecules, and E, E', and E'' are enzymes.

**Figure 5.** Convection current of a liquid layer in real space under a condition far from equilibrium.
This chain reaction produces RNA exponentially with time and guarantees the fastest possible increase of the number $N$, and thereby, the maximum of entropy production. No other reactions can make the entropy production higher. Self-replication of RNA information was an indispensable step [Process 3 of Figure 1] for the evolution of life, as the RNA is considered to be the first pre-biotic self-replicating molecules which carry information [13].

5.3. An example of scenarios for the birth of cellular life

An important question is in what conditions the self-catalytic reaction can stably continue. First of all, there must be accumulation of high concentration of law materials for the self-catalytic reaction [Process 1 of Figure 1]. An open space may be difficult for this condition, as the law chemical molecules should be diluted in an open space by the water flow and winds. Pores in the rock might be better, which may be related to the DNA multiplication experiments by Braun et al. [30]. The key point for the successful results of their experiments is due to the combinatorial usage of the principle of maximum entropy production principles, one in the chemical component space shown in Figure 4 and the other in the real space shown in Figure 5. The temperature oscillation of the enzymes in the convective current (Figure 5) could be controlled to synchronize with the reaction times of melting and fusing of DNA molecules (Figure 4).

Secondly, the produced self-replicated polymers must flow out from the pore before the law chemical materials are depleted. For this purpose, small windows connected from the pore to the external world are necessary so that the exponentially increasing products can enjoy in a fresh and nourishing environment. Thirdly, if the exit of the window of the pore is covered by phospholipid membrane [19], the self-replicated polymers may be covered at the exit by the membrane balls like the soap bubbles [Process 2 and 3 of Figure 1]. The membrane might have played the role of a vehicle for the self-replicated products until it finds a new environment for further evolution. And after a long time, this membrane finally might have grown into a biological cell membrane [31], and Process 4 of Figure 1 was realized. An example of this scenario is shown in Figure 6.

**Figure 6.** Schematic drawing of hypothetical formation of prebiotic self-replicating organism in a pore covered by phospholipid membrane. The produced self-replicated RNA like polymers flew out from the pore before the law chemical materials are depleted. If the exit of the window of the pore happened to be covered by phospholipid membrane, the self-replicated polymers could have been covered at the exit by the membrane balls like the soap bubbles [Process 2 and 3 of Figure 1]. The bubble membrane might have played the role of a vehicle to protect the self-replicated products until it finds a new environment for further evolution. And after a long time, this membrane finally might have grown into a biological cell membrane [31], and Process 4 of Figure 1 was realized.
Great improvement of metabolism by using variety of enzymes were necessary [ΔJ-scenario.] for the Process 2, 3 and 4, and in addition to the additional functional structures such as lysosomes or mitochondria underlie the Process 5 of Figure 1. Paramecium [31] is known as a model unicellular life which has temperature sensor and cilia for swimming which may have been developed as one of [ΔX-scenario] which is included in the Process 5 of Figure 1. These comparison shows that the most of the possible scenarios deductively driven from the maximum entropy production principle are found in the main processes of life at least of the unicellular organism.

6. Thermodynamic stability of the living structures shown by multicellular organisms

6.1. Multicellular organism

Nature had invented multi-cellular systems, which are more favored for evolution in some case than the assembly of independent uni-cellular system [Process 5 of Figure 1]. During the long history of evolution, the lives which could have survived against the severe environment change must have equipped with a system which can maintain the structure and genome. Because the non-equilibrium thermodynamics of an open system does not necessarily guarantee the stability of the structure when the thermodynamic force X in Equation (7) decreases by the environmental change, it is absolutely necessary for the living organism to prepare some protection mechanism of self-organized structure to survive. More accurately, a living organism had survived through the severe environment only when it happened to have a structure reversible for the environmental change. Because the reversibility is not achieved by any structures functioning in non-equilibrium state, the cell must have been protected by a system of equilibrium structure. This thought on crisis management is not surprising considering the fact that the cell membrane of a uni-cellular organization itself was originally not the product of non-equilibrium states. It has worked as the protecting wall of the self-replication machine of genes at early stage of life by some process shown in Figure 6, as an example.

6.2. Morphology of multicellular organism and entropy production

Because each cell and its environment is not an independent open system far from the equilibrium any more, and the total entropy production is no more equal to the sum of that of each cell. The multi-cellular system is one thermodynamic system. The geometry of the collected cells can be in principle either one-dimensional array, two-dimensional sheets or three-dimensional aggregates. To obtain sufficient chemicals necessary for metabolic conditions, the collection of the cells needs enough surface. For this purpose, two-dimensional structure is best, because one dimensional array may be mechanically weak. Among various possible forms of two dimensional, the effective surface area of the collection of cells can be calculated for a sheet, a tube or a sphere of single layer of cells. The results tell us all the three forms of two-dimensional structure have 1/3 of the total surface area of individual cells. However, the quantity of incoming chemicals into a small sphere of single cell by diffusion is severely reduced by the pinching effect of flow line, compared to that of incoming chemicals to the two-dimensional structure. Among them tube and sphere are superior to the plane because the they can form internal space, and tube is superior to the sphere because it is convenient for the liquid to flow from inlet to outlet. In fact, a tubular geometry is most often found in morphogenesis of primitive multi-cellular organism, such as coelenterates [32,33].

6.3. Pattern selection and entropy production of multi-cellular organism

Reaction-diffusion chemical system is known to produce spatial pattern. This mechanism may give us a hint to understand an early stage of evolution to multi-cellular system, although genetic information
and positional information play important roles in addition to this mechanism for the morphogenesis of present multi-cellular organism.

When the cells interact only by diffusion of the molecules, the entropy production may be written as,

\[ P = \frac{1}{T} \int \left[ \sum_i A_i W_i + \sum_i \mu_i \sum_j \nabla (D_j \nabla \rho_{ij}) \right] dV \quad (10) \]

where \( T \) is temperature, \( A_i \) is the chemical affinity, \( W_i \) is chemical reaction rate, and \( \mu_i \) is the chemical affinity of \( i \)-th reaction. \( D_i \) is the diffusion constant, and \( \rho_{ij} \) is the density of \( j \)-th component of \( i \)-th reaction. By using the Brusselator [4,5] for the chemical reaction as a morphogenesis model of a multi-cellular system, it was found by simulation that the state of the chemical component of the maximum entropy production \( P \) is most stable among others starting from various initial conditions [14]. This observation will support a viewpoint that the [Process 5 of Figure 1] may be related the maximum entropy production principle, and that the pattern formation of multi-cellular system may be determined by the maximum entropy production principle, when the environmental condition such as chemical potential is maintained high enough.

Multi-cellular organism is characterized by differentiation. When a group of cells form a tubular structure, the cells at the openings experience different environmental situation from the cells far from openings. Among the various multi-cellular organization which mutation of genes would have created, tubular type of organism might have been selected.

6.4. Altruistic behaviors based on switching in the organism from maximum entropy production principle to minimum free energy principle

Some strategies obtained in the early history of evolution associated with the system such as germ cells in hydra or differentiation into spore-stalk in slime molds. Hydra shifts reversibly from vegetative growth to sexual reproduction by sacrificing amount of epithelial cells under the starving condition [34]. From life cycle of slime molds, we may also learn how multi-cellular organisms adapt in a restrictive environment [35]. When resources such as food are limited in the surrounding environment, population of single cells of independent amoebas is converted to a multi-cellular slugs, within which only the pre-spore cell become spore. During the phase of amoebas, differentiation to germline cells is not determined yet. In response to starvation, amoebas start to aggregates and only a certain ratio of cell in the aggregation become pre-spore cells [35]. This means that limited number of cells is potential for revival later in their life cycle and the others contributes only as structural components. In the higher multi-cellular organisms, germ cells are differentiated at earlier time of growth independently of the environmental condition.

Altruistic examples as seen in life cycle in slime molds are commonly observed in the multicellular society. Groups of cells sacrifice for the others to survive. Sacrifice of a fraction for the total does not appear to be consistent with maximum entropy production principle. However, the restrictive environment for living organisms forced the system to shift from a far-from equilibrium condition to an equilibrium condition. Thereby, thermodynamic principle for selection also switches from ‘the maximum entropy production principle’ to ‘the minimum free energy principle’. If the germ cells are more stable in the equilibrium state than the somatic cells, or if the germ cell can create not only germ cell itself but also somatic cells in the future mellow period, then one can be sure that the altruistically looking behavior of the multi-cell system follows the thermodynamics.

6.5. Seeds and Molecular structure of the living state and dormant state

Formation of seeds is one of the strategies of the differentiation to survive for plants. We want to know if the structure of the seeds is stable in the equilibrium state in which no chemicals penetrates
through the shell. Surprisingly, some seeds of lotus, known as Ooga Lotus [36], which had been buried over 2000 years in an old ruin, successfully budded after immersed in water and finally bloomed. How do we thermodynamically understand this miraculous strength of life?

The most of multicellular animals become mobile for survival. However, particular animals adopt a strategy for survival similar to the seed of plants. The body of Tardigrades is the most famous for being able to survive in the extreme conditions that would be fatal to nearly all other known life forms, such as exposure to extreme temperatures and pressures (both high and low), air deprivation, radiation, dehydration and starvation [37]. In the ‘open’ state the lotus seed or tardigrades body consist of structure which is metabolically active and undergoes events for living such as budding, growing, flowering, etc. Thermodynamically speaking, they are in an open system far from equilibrium and follows maximum entropy production principle in the normal living state. In the dormant or frozen state, on the other hand, a lotus seed is closed by a strong testa and exhibits no metabolic activity as if it were a stone. Thermodynamically it should be in a closed equilibrium system with the lowest Helmholtz free energy, because the ‘seed’ is devoid of entry and exit of molecules and thus thermally separated from outside [38].

Figure 7. Switching between a living state and a dormant state of a cell exhibited by Ooga lotus and Tardigrades, as examples. A self-organized living state is symbolically expressed by a chemical reaction $X$ to $Y$ separated in a chemical component space in an open non-equilibrium state with input and output. By dehydration, the living system switches to a dormant state by closing the reaction wall between $X$ and $Y$. The dormant state is stable for more than two thousand years for the Ooga lotus seed. The process can be reversed by hydration to the living state. A possible mechanism may be related to the onset and offset of the activity of enzymes related for the reactions, although the phyico-chemical mechanism has not yet clarified.

Interestingly, being supplied with water, the seed quickly becomes ‘open’ status and start to enables pass of molecules though the shell. This event resembles an electric machine in which input of electricity changes the function without changing the macroscopic structure. The structure of dormant state of seeds, spores or a total body cannot be very different from when they are active in the ‘open’ state. At the same time the structure must be stable in a poor state as if it were a stone. In Figure 7 is shown a schematic picture of switching between a living state and a dormant state of a cell, exhibited by Ooga lotus and Tardigrades, as examples. Here, a self-organized living state is symbolically expressed by a chemical reaction $X$ to $Y$ separated in a chemical component space in an open non-equilibrium state with input and output. By dehydration, the living system switches to a dormant state by closing the reaction wall between $X$ and $Y$. The dormant state is stable for more than two thousand years for the Ooga lotus seed.
The process can be reversed by hydration to the living state. A possible mechanism may be related to the onset and offset of the activity of enzymes related for the reactions. Suggested glassy state [39] and disordered proteins [40], which is very viscous in the absence of water and fluidic in the presence of water, may give the answer consistent with two different thermodynamic principles. Yet, no microscopic research of molecular structures of this transformation has been tried experimentally or theoretically to the authors’ best knowledge.

7. Discussion and Conclusion

We presented in this paper a unified thermodynamic theory of the “Birth and Evolution of the life”. By inductive and deductive inference, we showed that the thermodynamic force, which has been known to increase the entropy production of the open system far from equilibrium, should have played a critical role for creating life and driving the evolution. In the early prebiotic stage, the entropy production is associated with chemical reactions of the molecular level, while in the successive stage after gene molecules are formed, the entropy production is due to the metabolic activity of each cell created by its own genetic information.

The generation of self-replication system and resulting exponential increase of number of organisms, which is certainly the most efficient pathway to increase entropy with no other comparison, is fundamentally distinct from non-life activities, and is reasonably called the birth of life. In fact, this is the basis of evolution of life to miraculous complexity of living phenomena. The history of evolution, however, did not progress so simply. The fluctuation of environment sometimes did not keep the condition for the living organisms satisfying “far from equilibrium”. The foods for the organisms may have depleted temporarily or locally. Nature has also given the fluctuation among existing organisms by mutation. Some organisms had obtained seed-like cells or locomotive cells in the multi-cellular structure. These organisms which survived under starving condition, either by closing themselves or escaping to better environments, started growing their sizes or numbers again when the environment recover the “far from equilibrium” situation. Therefore, the driving force for the birth and evolution of life is achieved by the alternation of the non-equilibrium thermodynamic driving force for developing liveliness at a period of rich environment and protective structure of equilibrium thermodynamic force at a period of poor environment, as summarized in Figure 8.

In short, life is a product of the thermodynamics which prevails in the universe together with the abundant useful chemical substance on the earth. The birth of our universe is in the present paradigm of cosmology described by “inflation”, in which some space-time region experienced exponential expansion. The universe, however, was not endowed with the self-replication mechanism like biological life.

A question may arise; is this theory any better than a tautology that the statistically most probable phenomenon dominates, or that of “the survivals of the fittest” by Darwin? Our answer is yes; we presented for the first time in this paper a thermodynamic driving force which initiated the birth and has driven the evolution, and thereby we could discuss the condition for the possibility of dominant processes in evolution. Birth of self-organized structures and competition among the various possible modes in nonlinear open systems far from equilibrium have been well established in various inanimate systems. We believe that it is important to explain the birth and evolution by the same principle which has been shown valid in the inanimate laboratory systems far from equilibrium. Darwin’s theory did not include origin of life nor driving force of the evolution.

Secondly, is the directionality of the thermodynamic principle contradictory with the neutrality [41] of genetic mutation? Our answer is no. The mutation of gene is neutral. Among the various products by neutral mutation of genes, the organism of the maximum entropy production is selected, when the environmental condition is fertile.
Another question may be; is there predictability of the present theoretical work? We say yes in the relation of Process 6 of Figure 1, where the evolution of life finally created tools. Tools including fire has provided mankind the most efficient pathway for increasing entropy production, and have made mankind enjoy the results of using them. Only recently, they started worrying if the produced entropy might threaten themselves in future. A consistent thermodynamic viewpoint on life from Process 1 to 6, is potentially useful to predict the future of mankind.

Finally, if we admit a thermodynamic principle is the motive force for creation of life, shouldn’t there be other types of lives in some other stars which were made by the same principle but by different materials and evolved differently? Our answer is that there is no reason to say no.

**Figure 8.** Themodynamics for the birth, evolution and survival of life. Birth of life was achieved by the driving force of nonequilibrium thermodynamics, and the evolution was achieved by the competition between the thermodynamic force for increasing entropy production and destructive force of environmental change.
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Appendix A

Among possible chemical reactions in the evolution, the RNA is considered to be the first pre-biotic self-replicating molecules which carry information [20]. Let us write RNA as \(XX^*\), where \(X\) is combined with \(X^*\) which is a counter copy of \(X\). The solution in a chemical reaction tank contains original RNA and the law nucleotides molecules \(C\) and enzymes \(E\), \(E'\) and \(E''\) which could be some proteins. The enzyme \(E\) dissolves the original RNA \(XX^*\) into \(X\) and \(X^*\). The reaction rate is \(k_d\) with help of enzyme.

\[
XX^* \xrightarrow{k_d(E)} X + X^*
\]  

(A1)

Subsequently, after the reaction (A1) is over, \(X\) and \(C\) reacts to make a \(XX^*\). The reaction rate is \(k_c\) with help of \(E'\).

\[
X + C \xrightarrow{k_c(E')} XX^*
\]  

(A2)

Simultaneously with the reaction (A2), \(X^*\) and \(C\) react to make a \(X^*X\). The reaction rate should be the same that of (A2),

\[
X^* + C \xrightarrow{k_c(E'')} X^*X
\]  

(A3)

Since \(XX^*\) is identical to \(X^*X\), the value of \(XX^*\) is doubled during the sum of the reaction times of (A1) and (A2) or (A1) and (A3), the number of RNA molecules, single stranded or double stranded increases exponentially with time constant \(\tau = k_d^{-1} + (Ck_c)^{-1}\).

The self-catalytic reaction rate of \(XX^*(t)\) and therefore the entropy production increases exponentially. No other reactions can make the entropy production higher. Self-replication of RNA information by self-catalytic reaction was an indispensable step [Process 3 of Figure 1] for the evolution of life. The fastest growth of numbers of molecules [6,7] can be achieved only by the self-replication (\(m = 1\)) type among all possible chemical reaction systems of the type; \(dN/dt = kN^m\). At the same time, this type of chemical reactions maximizes the entropy production, as we see in Section 5.

In the forgoing discussion, we did not discuss where the enzymes came from. If we include the reaction in which \(X\) and \(X'\) produce proteins which works as the enzymes, \(E\) and \(E'\), the network of reaction may be similar to one of the hyper-cycle [6,7].

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