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Onto-biology: clarifying also the spatiotemporal structure

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Abstract: A protocol describing the origins and evolutions of life is outlined, based on the seven principles of information, topology, function, diversity, discontinuity, temporal cycle, and metabolic conservatibity. This is derived based on the nonequilibrium quantum chemistry on time-dependent electron clouds: the general mobilization of thermo-fluid dynamics, stochastic mechanics, traditional quantum mechanics, chemistry, and mathematics as warp and the biologies related to molecular biology, morphogenesis, bioinformatics, origin of life, and medicine as weft. This also reveals the procedure to generate left-right asymmetric liver and symmetric kidneys and also the standard clock common to stem-cell cycle and circadian clock.

Keywords: Protocol, Seven principles, Life, Origin, Evolution

I. INTRODUCTION

Frontiers [1,2] showed how to generate amino acids and nucleic acids artificially. Yanagawa et al. artificially generated something like a cell membrane in a high-pressure chamber. [3] Ricardo and Szostak wrote a comprehensive review of recent studies on artificial production of elementary components. [4]

The polymerase chain reaction (PCR) is widely used to replicate DNA sequences in vitro, using an enzyme called DNA polymerase and nTP as elements. [5] This may be the first milestone toward achieving artificial replication of life. However, in PCR, the enzyme is not replicated automatically, though the DNA sequence is. A closed cycle of chemical reactions, which is a hyper-cycle like that shown by Eigen et al. [6], is not achieved in PCR.

Joyce and Orgel [7] demonstrated that various RNA polymers can be generated randomly without enzymes. Instead of enzymes, metal, such as magnesium ions, is necessary for catalyzing the synthesis of RNA polymers. In this system, a metallic catalyzer may deteriorate, because metal is not regenerated. Synthesis based on metal is also prebiotic because of the noncyclic reactions.

Thus, researchers have still not found a definite way and principle for generating the minimum hyper-cycle capable of replicating both information and functional molecules. The road to an artificial cell may be long. We still do not know the design diagram of life over billions of years.

The design diagram of life should be outlined based on the seven key principles of (I) information, (II) topology (structure), (III) function, (IV) diversity, (V) discontinuity, (VI) temporal cycle, and (VII) metabolic conservativity. Our previous reports [8-16] show the principles on (I), (III), (V), and (VI).

Although traditional quantum mechanics yields the static state of the electron cloud, the cyto-fluid dynamic theory [8, 9, 10] for (I) and (III) describes the time-evolution process of the unstable cloud, which can be non-equilibrium quantum chemistry. Some mysteries on biological information and function are clarified by the theory. Our previous studies on (V) and (VI) [12, 15, 16] reveal some temporal aspects. Thus, in the following sections, we will show the bio-principles on (II), (IV), and (VII).

II. TOPOLOGY

It is well known that the electron cloud is not spherical around an atom heavier than helium (He). Thus, non-spherically electron cloud induces string-like and ring-like molecules in amino acids and nitrogenous bases, without spherical connections of carbons. Nitrogenous bases without a spherical electron cloud generate string-like DNA and RNA. This is an essential principle of chemistry.

The string-like connections of non-spherical particles can be also seen in cells. Here, let us separate cell aggregation into two parts: the internal side around the center of the aggregation and the external side close to the surface. External cells close to the surface move relatively easily, because one part of the cell is free without any connection to other cells. However, internal cells often receive forces from many directions due to the presence of other cells, making it relatively difficult for them to move relative to the origin on the earth. Thus, inner cells deform relatively easily without any translational motion. [10,12,15] This deformation brings the discrepancy from a complete sphere, i.e., its scabrous shape, which induces a string-like connection of deformed cells, although parcels with less deformation connect as a spherical aggregation or a spherical surface aggregation in two- or three-dimensional space (Fig. 1). It should be stressed that there will also be three sub-types of strings: straight strings, rings, and bifurcation strings of deformed cells (Fig. 2). One of these three types of strings will be

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chosen based on the cell deformation rates and the types of molecules lying between cells such as cell adhesion molecules (CAMs), morphogens, and extracellular matrix (ECM).

Then, an aggregation of long strings (straight strings, rings, and bifurcation strings) will be close to the next larger sphere like yarn waste because of their flexibility. Repeats of strings and spheres are natural, because we can see the repeats in several levels of living beings.

It is no wonder that spherical biological cells such as bacteria include string-like DNA and also connections of spherical cells become a string-like shape such as intestine and blood vessel again.

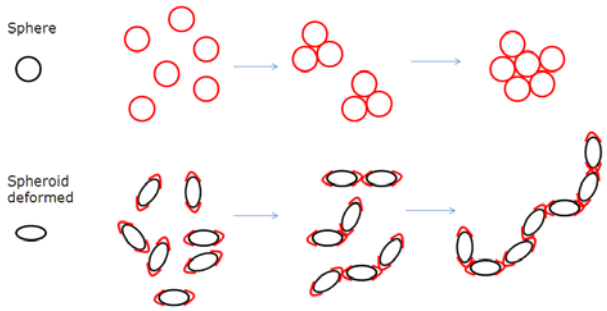

Fig. 1. Two types of aggregations. Upper: sphere, lower: string

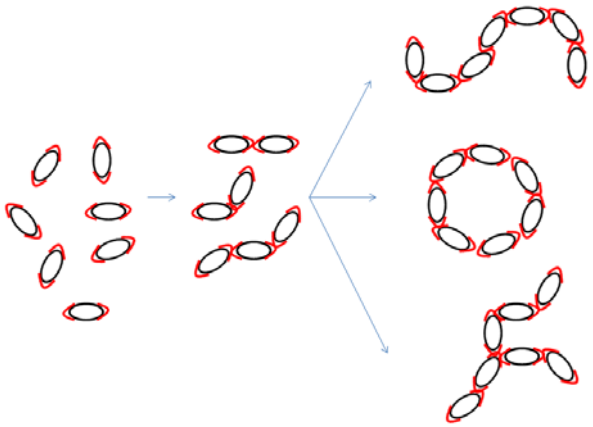

Fig. 2. Three types of strings. a: string, b: ring, c: bifurcation string

The representative length of a string is relatively longer than that of a sphere or a surface, when the weight of the string is equal to that of the sphere. This is because the diameter of the sphere is proportional to the cubic root of the string length (Fig. 3). This leads to compression buckling of the string inside the sphere: the conclusion that the string must bend inside the sphere. A representative example of this is the intestines inside the human body.

Blood vessels resemble the string type at first glance. Thus, the heart and liver, representing two parts connected to blood vessels, are distorted due to the buckling effect, leading to the left-right asymmetric distribution. However, the other parts of blood vessels are left-right symmetric, because vessels bifurcated at a lot of points in a tree structure are mathematically close to a three-dimensional dense sphere.

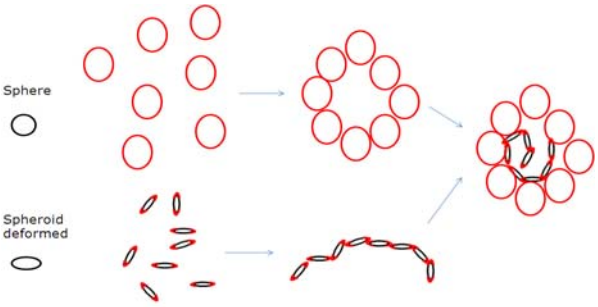

Fig. 3. Buckling of a string inside a sphere.

II. Diversity

The molecular weights of the twenty types of amino acids show a threefold variation between 240 of cysteine as the maximum and 75 of glycine as the minimum, although that of purines and pyrimidines among nitrogenous bases varies by only about 1.5 times. The frequency ratios of hydrophilic and hydrophobic amino acids in proteins are also more stochastic than those of purines and pyrimidines in nucleic acids. Although there are only five main types of nitrogenous bases in living beings, there are many types of proteins. How is this variety determined?

Information carriers such as DNA are relatively deterministic, because accurate conservation of information is necessary. It is stressed that accurate conservation of information is achieved by the relatively hard structure of DNA. Thus, DNA maintains a certain spiral shape having a fixed width and pitch. In contrast, functional molecules such as proteins and RNA provide a variety of functions for several environmental changes. This variety of functions comes from the flexible shapes of the molecules.

This concept of "hard deterministic" and "soft stochastic" can be validated by the stochastic determinism, representing new dynamics, at the triple point of the Boltzmann, Langevin, and Schrodinger equations. [17,18]

First, let us recall the cyto-fluid dynamic theory derived from continuum mechanics [8,9,10], which describes the motions of deformation and translation for a flexible parcel consisting of a nitrogenous base and water molecules surrounding the base. (See Eq. 1a.) We must rethink whether the parcel can be a continuum or not. It is apparent that the parcel is not a continuum, because it is on a very small scale. Larger windows for averaging in continuum mechanics cannot resolve the phenomenon in principle. The scale for averaging, i.e., the minimum scale representing the phenomenon, will be between the atomic scale and the size of the base, because the spatial distribution of the deformation rate in the parcel should be analyzed. Let us define this minimum scale representing the phenomenon as the

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stochastic determinism window (SDW). When this SDW is used for averaging, the density and also the other physical variables have indeterminacy because of molecular discontinuity. Then, the stochastic governing equation having indeterminacy (Eq. 1b) shows a slightly vague solution for the phenomenon. This indeterminacy also implies that variations of molecular sizes are possible in a limited range.

$$d^2x/dt^2=(e\text{-}1)(dx/dt)^2+(e^3\text{-}3)x+q(t) \quad (1a)$$

$$d^2x/dt^2=(e\text{-}1)(dx/dt)^2+(e^3\text{-}3)x+q(t)+\varepsilon(t) \quad (1b)$$

where the parameters e, q(t), and ε(t) denote the size ratio of the two parcels connected under equilibrium conditions, the time-dependent force generated by the other connected parcel, and random fluctuation due to indeterminacy, respectively. [17,18]

The quantum mechanics of the Schrodinger equation is based on an indeterminacy principle. The presence of electrons is given in a certain area, not at a deterministic point. This vague viewpoint with indeterminacy shows an outline of a possible solution. We can obtain the value solution in exchange for abandoning the determinant solution. Although this stochastic determinism for biomolecules is based on a governing equation different from that for the Schrodinger equation, a weak indeterminacy lying at the triple point of the Boltzmann, Lanvevin, and Schrodinger equations leads to new findings underlying living beings, when we also use the quasi-stability concept of life.

An important point of the indeterminacy principle is generally that the level of indeterminacy determined by the averaging window size implies the level of variety in natural phenomena.

Hard systems such as DNA will experience less deformation, leading to a relatively larger stochastic determinism window, i.e., a larger representative scale. On the other hand, soft molecules such as RNA and proteins will have large curvature (severe bending) locally, which leads to the necessity of a smaller SDW. As a result, the difference in SDWs produces manifold variety.

VII. Metabolic conservation

We must consider the five components necessary for a living cell: (Group 1) a DNA group including genes, (Group 2) an RNA group, (Group 3) molecules for the cell wall, (Group 4) a protein group including enzymes, and (Group 5) a lipid group.

Let us consider the relation between these five molecular groups and the five types of nTPs (ATP, GTP, CTP, TTP, UTP). ATP is used as the main energy carrier for the five molecular groups, while UTP, GTP, and CTP are also employed for generating polysaccharides of the cell wall, proteins, and lipids, respectively. It is also known that DNA uses A, T, G, and C as components, while RNA employs A, U, G, and C as components.

Thus, the reaction scheme for the five groups (cell wall, proteins, lipids, DNA, and RNA) per generation is described by Eq. (4), by using [A], [U], [G], [C], and [T] for adenine, uracil, guanine, cytosine, and thymine.

$$\begin{aligned}
&[\text{Cellwall}] \leftarrow m_1[A]+n_1[U]\\
&[\text{Protein}] \leftarrow m_2[A]+n_2[G]\\
&[\text{Lipid}] \leftarrow m_3[A]+n_3[C]\\
&[\text{DNA}] \leftarrow \{(1-\alpha)([A]+[T])+\alpha([G]+[C])+2k_1[A]\}\omega\\
&[\text{RNA}] \leftarrow \{(1-\beta)\{[A]+[U]\}+\beta\{[G]+[C]\}+k_2[A]\}\omega
\end{aligned} \quad (4)$$

where $\alpha, \beta, m_i, n_i, k_i,$ and ω denote the rate of GC pairs inside DNA, the rate of GC pairs inside RNA, the rate of A as the energy supplier for generating the cell wall, proteins, and lipids, the rates of U, G, and C as the energy suppliers for generating the cell wall, proteins, and lipids, the consumption rate of A as the energy supplier for generating DNA and RNA, and the number of loci in nucleic acids, respectively.

The consumption rate of purines during a cell division will be on the order of that of pyrimidines. This constraint and Eq. 4 lead to the relation

$$(2k_1+k_2)\omega+(m_1+m_2+m_3)\approx n_1+n_3-n_2$$

which yields some interesting results. The increases in k_i, i.e., the acceleration of DNA replication, leads to a decrease in GTP, thus reducing n_2. The natural tradeoff between nucleic acid generation by ATP and protein generation by GTP is seen in Eq. 4. The five frameworks (cell wall, protein, lipid, DNA, RNA) do not increase at the same time. Guanine functions as the switch for changing the phases of DNA replication and protein generation.

The alternating generation of DNA and protein also leads to the spatial asymmetry of molecular distributions, although the simultaneous generation of DNA and protein will induce a symmetric distribution. This spatial asymmetry also causes cell deformation.

IV. CONCLUSION

Thought experiments based on data pertaining to life lead to the conclusion that life can be tentatively defined as the object controlled by all of the seven principles mentioned above. The prebiotic self-replication systems without cell walls do not represent life, because they only involve four principles of (I), (II), (III), and (I V). More than seven principles or detailed algorithms within the seven explained here may be necessary to produce an artificial cell in vitro. The present protocol shows the minimum scenario.

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