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## **Macrothermodynamics of Biological Evolution and the Aging of Living Organisms. Physicochemical Dietetics**

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### **Abstract**

The author sets forth-general considerations pertaining to the thermodynamic theory of biological evolution and the aging of living organisms. It becomes much easier to comprehend the phenomenon of life scrutinizing the formation of structural hierarchies of biological matter applying different temporal scales. These scales are 'identified' by nature itself, and this is reflected in the law of temporal hierarchies. The author discusses some misunderstandings in thermodynamics and evolutionary biology. He postulates that the origin of life and the evolution of living systems can be studied using the known functions of state within the framework of quasi-closed models with the help of quasi-equilibrium macrothermodynamics (hierarchical thermodynamics). A simple physicochemical model of biological evolution and the development of living beings is proposed. The adequacy of this model to reality is proved. The considered theory makes it possible to use physicochemical evaluations to develop effective anti-aging diets and to recommend food additives and medicines effective in the treatment of some diseases.

**Key words:** thermodynamics, temporal hierarchies, supramolecular thermodynamics, biological evolution, aging and gerontology, dietary

*"One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity."*

J. Willard Gibbs

*"... the properties of living things are the outcome of their chemical and physical composition and configuration."*

Thomas Hunt Morgan

## **1. Introduction**

The past years have witnessed considerable progress in the understanding of the phenomenon of life in terms of universal laws of nature and the laws and principles of physical chemistry. It has been proved that a thermodynamic description of ontogenesis and phylogenesis does not require a discovery of new universal laws. There is every reason to believe that the second law of thermodynamics as formulated by R. Clausius and J.W. Gibbs, the law of temporal hierarchies, the principle of stability, and a number of other well-known concepts suffice to reveal the "motive forces" in the origin and development of living organisms [1]. What is more, these laws and principles make it possible to explain the existence of enormous biological diversity, which is a consequence of the thermodynamic need in the appearance of a variety of living organisms. The greatest headway in the understanding of the phenomenon of life was made in the development of hierarchical thermodynamics (macrothermodynamics) and identification of *quasi-closed* systems (subsystems) in open biological systems.

An important general remark which, I believe will help to better understand the theory discussed in this paper is in order here.

It should be remembered that the meaning of most ideas and concepts in scientific circulation is, in a measure, relative. This is true of the concepts of equilibrium and non-equilibrium of systems and processes, the closed and quasi-closed character of systems, the stationary and non-stationary character of processes, and many other things. Depending on the purpose and objectives of a study and the chosen *time scales*, models implying different approximations are built. This is why, designing models, reservations and explanations are usually required. This circumstance must be taken into account in the study of such a complex phenomenon as life. Otherwise it would certainly be impossible to make definite and substantiated conclusions. This is confirmed by the well-known ideas regarding the relative possibility of cognizing the world.

## 2. General

Over a quarter of a century has passed since the time when the author of this paper suggested that the origin of life and biological evolution be examined in terms of equilibrium (quasi-equilibrium) classical thermodynamics of quasi-closed systems[1].

Later, thermodynamics which studies real biological structures came to be known as hierarchical thermodynamics or macrothermodynamics. The new term, macrothermodynamics, introduced by the author, does not at all intend to emphasize that thermodynamics naturally describes the behavior of systems at macrolevel alone. It was introduced to stress that the study extends to complex heterogeneous biological objects (in principle, heterogeneous objects of any origin). A special importance was identification of supramolecular thermodynamics as an area of study in its own right. Its significance becomes obvious if one recollects that the phenomenon of life is observed within a narrow temperature range where “functioning,” relatively stable supramolecular formations can come into being. Any organism is essentially a sum of such supramolecular formations, which

interact and unite into more complex structures, i.e., cells, tissues, and organs that constitute the organism proper.

The necessity of introducing the concept of macrothermodynamic (heterogeneous) systems is fully justified and substantiated. The thing is that the interactions among all atoms in the molecules and among the molecules themselves in a biological (heterogeneous) system cannot be registered even in the case of microvolumes due to the unbelievable (as I see it) complexity of the system. In this case, statistical thermodynamics is practically powerless. However, the phenomenological macrothermodynamic approach makes it possible, for instance, to identify real quasi-closed supramolecular systems (subsystems) in open (as a whole) living systems. It provides an opportunity to experimentally calculate the changes of the thermodynamic functions of supramolecular formations. Thus, when studying living supramolecular systems (subsystems), it is convenient to use the Gibbs or Helmholtz function of the unit of volume or the mass of biological objects. Naturally enough, this is also true of the systems (subsystems) at any hierarchical level. This answers the question of why it was necessary to introduce the term macrothermodynamics [1].

Thus, hierarchical thermodynamics (macrothermodynamics) came to be used in the study of equilibrium systems, that is, systems that are close to the state of equilibrium. To emphasize this, the author began to refer to “equilibrium hierarchical thermodynamics” implying the thermodynamics of systems approaching the state of equilibrium. The latter include objects in which phase-transition-type processes are occurring: crystallization from a state of supercooling (supersaturation), association, aggregation, self-assembly (thermodynamic self-organization) of structures in different hierarchies, etc. As is well known, the study of such systems and processes may use classical thermodynamic methods, which imply that the functions of state of the examined systems have real meaning, that is, it can be assumed with good enough approximation that the differentials of these functions are total.

At the same time, the systems studied in hierarchical equilibrium (quasi-equilibrium) thermodynamics can be regarded as linear dynamic systems. Due to the weak non-equilibrium processes, hierarchical structures are naturally bound by dynamic links (as the author has frequently pointed out). These links manifest themselves not only “inside” the set hierarchies but also at the “junction” of different-scale structure-forming processes of adjacent hierarchies. Recently J. Collier introduced the concept of *physical information system* as a system consisting “of a number of relatively stable units that can combine more or less freely to form somewhat less stable structures which have a capacity to carry information in a more or less arbitrary way.” This definition accords with the author’s idea of hierarchical thermodynamics in the framework of which temporal hierarchies are examined [1].

It should be noted that in terms of mechanism, the evolution of natural biological structures is avalanche-condensation structure formation – a phenomenon opposite, as regards direction, to the branched processes, e.g., ones that occur during gas discharge or branching chemical and nuclear reactions. In a sense, life is like a gravitational collapse, which unites “small-scale” structures into large bodies.

Building my theory, I was clearly aware that it would become much easier to understand the phenomenon of life if the formation of structural hierarchies of biological matter is examined using different time scales. I refer, in fact, to the formation of “kinetic thermodynamics” of near-to-equilibrium processes occurring on different time scales. The methods of kinetic thermodynamics can be used to study, on each concrete time scale, the corresponding *non-stationary* structure-formation processes in terms of the changes of the function of state (changes in the degree of the processes’ completeness). The model implies that the differentials of the examined functions with acceptable approximation are total. Thermodynamic kinetics is, of course, unable to make conclusions on molecular and other “dynamic” mechanisms of phenomena. At the same time, we can study the change in the degree of the completeness of structure formation processes or the change in thermodynamic

stability of structures within the framework of ontogenesis and phylogenesis. It would make sense, for example, to build a dependence of the Gibbs specific function of the formation of the aggregated phase of supramolecular structures of biological tissues,  $\Delta\widetilde{G}_i^{im}$ , on time ( $t$ ) in ontogenesis and phylogenesis. This method can also be used to study the change of the other components of the Gibbs function during the evolution of any hierarchical structure of the biological world.

To avoid misunderstandings, I would like to note that my concept of **thermodynamic self-organization** (self-assembly) differs in principle from I.Prigogine's **dynamic self-organization**, which can be observed in systems remote (far from) from the state of equilibrium. Since structure formation (origin and evolution of hierarchical structures) in the biological world takes place in conditions that are close to the state of equilibrium, the dynamic self-organization models (used to describe dissipative structures and oriented towards non-linear modeling) should not, as a rule, be used in the study of biological evolution and the development (aging) of living organisms. I.Prigogine's theory deals, on the whole, with generation (production) of entropy in systems of any origin far removed from equilibrium. In this situation, entropy (Prigogine's entropy) is not a function of state, since its differential is not total. It follows that in the general case, Prigogine's evolutionary theory is kinetic and not thermodynamic. I would also like to note that, using the term "self-organization," both Prigogine and his followers in fact mean dynamic self-organization. I already said that this should be borne in mind to avoid confusion!

Moreover, to clearly understand the author's concept (which rests on the foundation of classical natural sciences), one must specially mention the existing misunderstandings in the use of the concept of "thermodynamic functions", first of all, entropy, by different researchers. I have already discussed this issue in a number of publications but, because of its exceptional importance, will consider it in the next section of this paper.

### **3. Biological Evolution, Entropy, and the Gibbs Function (Gibbs free energy)**

Some of the publications expressed many opinions that were in contradiction to the classic science and, in particular, to the general laws of nature. This flow really overcrowds the science and provokes on my opinion the essential damage to education.

One of the fashionable tendencies in the scientific activity of some naturalists and philosophers is the development of the unproved conceptions of entropy, of its production, orderliness and complexity. Many outstanding scientists, including the Members of the Royal Society, members of some academies of scientific organizations are opposed to this negative tendency. The works by K. Denbigh and his colleagues [2-4] should be noted especially<sup>1</sup>.

During last years I try also, at least to a small degree, to correct the situation which has been formed and connected with misunderstanding as for the notion of entropy, complexity, orderliness etc [1].

The main part of authors of new concepts in this field seem do not understand seriously the works of classics - Clausius, Gibbs, Plank and many other [1-5]. Some of them probably neglect the encyclopedic reviews and the textbooks of high quality [6-13]. I should like to note that I will not deliberately to mention the author's names of the uncorrected works as I have no right to judge them negatively - their theoretical and experimental works in some other branches of science sometimes are worthy. Moreover, I believe that many of them are under delusion very sincerely because of the complexity of the interdisciplinary branch of knowledge.

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<sup>1</sup> However, I have to say that by reading of these outstanding papers one should bear in mind that they were written before the time, when the law of the temporary hierarchies has been formulated in its final form. This law allows to select the quasi-closed systems in the open biological systems and to study their evolution using the methods of the hierarchic thermodynamics- macrothermodynamics [1].

Having no possibility to discuss in a short communication even small part of misunderstandings I should like to point only some tendencies that bring about many of evidently erroneous and deadlock, or, in the better case, of non-effective [13]. Some of these theories are related to the wrong ideas on the entropy production and about the connection between entropy and such the notions as ‘organization’, ‘complexity’ and ‘orderliness’. [1-4].

For the beginning it seems reasonable to remind the readers that there exist many types of entropy. It is evident that the using of the general semantic terms does not imply that in each specific case one deals with the one and the same notion.

It is well known that the classic entropy according to Clausius and Gibbs, which is used in the phenomenological thermodynamics, differs from the statistic entropy by Gibbs and from the statistic entropy according to Boltzmann and Plank [1-3]. These well-known distinctions do not distort the ‘physical structure’ of the classic thermodynamics and its conclusions. All these types of entropy, being well founded, are denoted by one symbol  $S$ .

It is also well known the notion of the information entropy or Shannon entropy,  $H$ , which has its own independent meaning and from the physical point of view has nothing common with Clausius-Gibbs entropy, statistical entropy by Gibbs and statistical entropy by Boltzmann-Plank [1-2].

Further, the entropy by Prigogine is known, which, as distinct from the classic thermodynamics in the general case has no full differential and because of it can not be considered as the function of the state (for convenience we shall denote this entropy as  $S'$ ). This entropy is a kinetic function. It's possible to discuss some other concepts about entropy, which have no direct relation to the classic definition of thermodynamic entropy. To know more about various types of entropy used in exact science I refer to the mentioned above Denbigh works [[2-4] and (for example) to the comprehensive paper by Dr. Zubarev and Dr. Morozov [15] where the extensive literature references may be found.

The existence of the principal distinctions between classical and information entropy is accepted by the most part of professional mathematicians, physicists, chemists and other. Modern encyclopaedias and textbooks as a rule do not content any mishmash on this subject [1]. However many authors up to now do not distinguish information entropy  $H$  and classical entropy  $S$ . Many investigators, as the reader knows for sure, also identify the classical Clausius-Gibbs entropy and Prigogine entropy  $S'$  despite the latter has no relation to the second law of thermodynamics. [1,4,16]. From the said above follows that this kinetic function, strictly speaking, can not serve as parameter whose change, from the thermodynamic point of view, reveals the trend and estimates the degree of the completeness of spontaneous processes occurring even in the simple isolated real systems.

Considering the open biological systems I. Prigogine's and colleagues discuss the question about the entropy production inside the system itself and entropy supply from the surroundings. The growth of entropy of the total system is discussed, this system being consisted of the system itself and surroundings. For the simple system [14] close to the equilibrium state such a position seems to be rightful, but needs the averaging entropy changes on micro- and macro levels what is difficult to prove. The supply of the "negative entropy" into the living systems (which is not simple) is connected with the heat exchange between the system and surrounding. From this follows that the system becomes thermodynamically and kinetically quasi-closed [1] only at small times when the substance exchange between the whole system (thermostat plus the system itself) and surrounding may be neglected. Such a system is an analogue of the equilibrium (quasi-equilibrium) chromatograph column where the substance flow of the constant composition enters to. The direction of spontaneous processes in such a system is determined not by the change of its entropy but by the change of the Gibbs function,  $G$  or Helmholtz function,  $F$  (Gibbs or Helmholtz free energies). Really, it is evident! Besides, the second law in its classical form states the increase in entropy  $S$  may be observed

only in non-equilibrium isolated system where only the work of expansion proceeds or no work at all. This important circumstance needs some additional substantiation of the “thermodynamic” model in relation to the entropy production. Thus the Prigogine concept due to many unproved and experimentally non-corroborated postulates is not in conformity with the second law of thermodynamics.

In editorial paper published in a very authoritative journal “Entropy” the editor-in-chief Dr. Shu-Kun Lin has written [16]:

"...it is not surprise that an honest chemist (among any other educated chemists, biologist, etc.) will tell you that he has never found an application of this entropy theory in chemistry (or in biology, physics, engineering...)" . Author bears in mind "the Prigogine's dissipative structure theory". Dr. Shu-Kun Lin concludes: "I have a clear opinion regarding this entropy theory. Its main problem is that it does not conform with the Second law of thermodynamics". I personally fully agree with this point of view.

The apologists of the theory of the entropy production and of dissipative structures (which really exist in the system far from the equilibrium state) discuss sometimes the question about the production and accumulation of some “low-entropy product “ in the evolutionizing biological systems. Some authors believe that the principle of the minimum entropy production ( $S'$ ) at some circumstances may be equivalent to the principle of maximum production of this “low-entropy product”. However, if to speak about the classical entropy ( $S$ ) all above mentioned arguments must be rejected as deprived of the physical sense.

The change in entropy of the living system itself ( $S$ ), even if it is observed, does not speak anything about the trend to the state prescribed by the second law of thermodynamics. I have already noted that in the given case one may speak, probably, about the minimization of the Gibbs (or Helmholtz) function together with some other functions. The entropy (classical,  $S$ ) by evolution of a living system may either diminish or increase.

The creators of the new theories, using the entropy production concept, write sometimes not only about the accumulation of the “low entropy products” in the evolutionizing systems but about the increasing the complexity or the orderliness of these systems. Such a supposition, as I understand, is reasonable if there is the definite connection between the entropy and the complexity. Meanwhile it is well known that entropy is not obligatory connected to orderliness, complexity or organization. These questions have been thoroughly discussed in the classical monographs and reviews of one of the creator of the non-equilibrium thermodynamics, kinetics of open systems and modern science on the phase equilibrium, K.Denbigh, as well in works of other classics of the modern thermodynamics and chemical kinetics [1- 4].

It should be especially noted that the notion of the “orderliness” itself has no strict definition from the mathematics point of view and because of it can not serve as any quantitative characteristics of the degree of completeness of any processes.

To avoid the vain discussion with the colleagues, who do not know the subject of consideration in more detail, I should like to present only one example well known to any physicists and chemists.

Discussing the formation of the supramolecular structures in the living nature some authors often speak about increasing the orderliness of the system by evolution in the living nature due to the accumulation (production) of the “low-entropy product”. Meanwhile it was established long ago that many aggregation processes (self-assembly or thermodynamic self-organization of macromolecules and cells) are entropy-controlled, i.e. are accompanied by the entropy growth [17]. Thus the entropy of the system increases as well. The latter fact testifies to the increasing amount of the “high-entropy product” but in no way of the “low-entropy product”. It may seem that by proceeding of the processes mentioned the entropy should be diminished because of the growth of the orderliness in the system, which is observed visually. However, on many reasons, it is not true! Other examples the reader may have found in the works [1-4, 18-20] and in Internet.

In such a way, if to have forgiven the author of these remarks the lack of some important and additional digressions and more precise definitions, the following conclusion can be drawn. The notion about the entropy production in the living systems and about the increasing in the course of evolution of their “orderliness” or “complexity” (being mathematically not well defined) disagree with well known general laws of the nature. If to account for both the lack of the conventional terminology and for extraordinary importance of the problem, one may assert the following: these incorrect concepts bring about unbelievable mishmash into the science. It’s a great pity that some new and probably correct and inspiring ideas in the field of the mechanisms of the biological evolution and the life origin can not get the proper development due to the presence of the annoying and crude errors. Such the errors of some naturalists are circulated and distributed by the poorly educated philosophers. As a result many colleagues do not desire to study the subject itself which makes the situation worse and do harm to the education.

I believe that during last years it becomes possible to develop non-contradictory and non-conflicting thermodynamic theories of the biological evolution, the life origin and the aging of living beings. These theories are based on the fundamental principles of the classical thermodynamics [4, 21-27].

The theory intends to use the concept of the classical entropy,  $S$  and other functions of state,  $G$ ,  $F$  (Gibbs and Helmholtz functions whose differentials are full). It is evident this theory gives no information about the molecular and similar “dynamic” mechanisms of the evolution processes. Besides, this theory uses some postulates and in such a way has approximate character. In spite of this, its conclusions meet very well the experimental data and, generally, the whole experience of science.

The substantiation of the thermodynamic model of the biological evolution (phylogenies) and aging (ontogenesis) becomes possible due to the discovering the law of the temporary hierarchies and due to the development of basic ideas of the hierarchic thermodynamics. The selection (identification) of the quasi-closed

thermodynamic and kinetic systems in the living world [4] allows studying the biological evolution (on all the hierarchic levels) and the organism aging with the account for the principle of the minimization of the specific value of Gibbs (Helmholtz) function.

The formulation of the “principle of the substance stability “gives the possibility to explain (unfortunately up to now only on a qualitative level) the reasons for the existence of the reverse thermodynamic connections between various hierarchies of the living matter. The possibility of the practically infinite development of the bioworld (on the time scale comparable with the time - the duration of biological evolution) may be also explained.

As I understand, in the framework of the modern conception, it may be taken for granted that from the point of view of the energy source, the Sun is the driving force of the evolution of living (and dead) matter, of the origin and of the supporting life on the Planet. Of course, there are other energy sources feeding the circulation (cycle) of matter. From the point of view of “dark” spontaneous processes of the arising and evolution of living beings, the driving force is so called “thermodynamic force” [1]. As some scientists claim the new results are in concordance with ideology (Weltanschauung) of Galileo, Maxwell, Gibbs, Darwin and the author of this paper as for the general, total nature laws. The theory allows the predictions to be made even on the sociological level and considers the history as the process, which is rather predictable (on a definite scale of time), whose direction is predetermined by the second law in its classical (classical and hierarchical thermodynamics) formulation. This theory is valid for all levels of biomatter organization. The thermodynamic theory of the biological evolution facilitates the choice between the ideas of creationism and science of favor of the latter. If to connect creationism only with the problem of the origin and development of life (but, does not connect with the origin of universe mater and energy before the probable Big Bang), then, as I believe, such a choice seems to be grounded.

It should be noted that some particulate problems of the thermodynamics of the biological evolution have been solved only qualitatively. The detail investigations in many branches of this interdisciplinary science are only at their start. However, there are the reasons to believe that an essential progress in the development of the corresponding apparatus may be achieved very soon and then the quantitative treatment becomes possible.

It becomes also evident that the new “science building” about the arrangement of the bioworld, based on classical science, is rather strong. This science building, I am sure, will resist any winds arising under the influence of some fashionable one-day models of various dreamers which try to create, as the say, “post-non-classical science” and neglect the knowledge of the many centuries history.

I understand that various points of view have their right for existence. However brainless eclectic mixing up of even well established scientific concepts (presented on the mathematical language) hardly might be approved. As for the mentioned mixing of various concepts, neglecting general laws of the nature, it can not be excused as enhances the destruction of the intellectual potential of a new generation of researches. The main part of works dedicated to the development of some eclectic concepts contains mainly the quotations from some other works where contradictory positions are presented. Authors of such paper are not capable to formulate sharply their own positions. It is clear that any works and even textbooks may contain discussion statements. However, the first duty of the authors, as I am sure, should be not to give any disinformation to the readers. At least, authors should make a reservation, if their statements do not correspond to the general nature laws or are not proved. The neglecting these criteria by writing scientific work often determines that the interesting in principle investigations, containing the important scientific information, are accompanied by the erroneous interpretation and may happen to be rejected at all. It is clear that the researcher, who for the first time begins to study any discipline, cannot distinguish the serious statements from mishmash and, sometimes, mockery in relation to classics. Before to risk and

propose something fresh (novel) in science, it is reasonable, as I understand, to study carefully the stable textbooks (which, usually, have been writing for some tens of years and improving for centuries). It is worthy to follow the well-established scientific schools having their origin in ancient days. Proposing new concepts and theory it is also clever, as I believe, to use the whole experience of the world science.

As the next step, I should like to examine one of the simplified physicochemical models that imitate biological evolution and individual development of organisms.

#### **4. The Physicochemical Model of Biological Evolution and the Development of Living Organisms. A Comparison with Reality**

The idealized model will, hopefully, be comprehensible to any researcher with a grasp of the foundations of physical chemistry. I believe that it will convince the readers that the phenomenon of life can be easily understood on a quantitative foundation in terms of classical physical chemistry, physicochemical biology, and other classical scientific disciplines. This model also facilitates the assimilation of the thermodynamic theory of biological evolution and the aging of living organisms, which is considered in many works by this author [1].

Let us visualize a glass filled with a diluted aqueous solution containing certain inorganic and organic substances. The organic compounds may include alcohols, acids, lipids, peptides, sugars, and nitrogen bases.

Let us add activated charcoal or some other sorbent, e.g., a natural mineral with a active surface.<sup>2</sup> Let us designate the particles of the sorbent as the system proper or just the system. The sorbent, of course, sorbs (adsorbs and/or absorbs) the dissolved substances. Assuming that diffusion restrictions are absent, substances with heightened affinity to the used sorbent will be predominantly sorbed. According to

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<sup>2</sup> Interesting works by G. Arrhenius examine the possible role of minerals in phosphates, which, in his view, performed an important role in the origin and development of life. [28].

the author's principle of the stability of substance [1], the most energy-intensive (the high energy capacity, in chemical terms) substances will constitute such compounds, above all. Of course, the stability of supramolecular formations (sorber—substance) will be determined by the change of the Gibbs function,  $G$  (Gibbs' free energy), or the Helmholtz function at sorption. The substances that form the most stable supramolecular structures (which emerge as a result of interactions marked by the most negative or the least positive values,  $\Delta G^{supra}$  at sorption) will be characterized by relatively heightened sorption (distribution) constant values.

Let the sorber (the system of interest to us) have properties of a catalyst of chemical transformation. Such a sorber may be a catalyst of oxidation and other processes facilitating complete oxidation of some compounds resulting in the formation of  $H_2O$ ,  $CO_2$  and other relatively stable chemical substances. In this case, in the presence of oxygen (or other oxidants), the substances in the system are oxidized, at least in part, turning into compounds that are easy to remove from the sorbing system, such as carbon dioxide. If new portions of the initial substances reach the system from the environment (incidentally, they may be synthesized in the environment under the impact of light or other energy sources), the complete solution—sorber system, as well as the system proper, become open; the stationary state is established in them over relatively short time periods and with a certain approximation. Over long enough time periods, if the composition of the system proper (e.g., due to the accumulation of chemically energy-intensive substances) changes, it should be treated as *non-stationary*. In this case, the system proper can be regarded as a kinetically quasi-closed chromatographic column in which chemical transformations accompanied by the accumulation of new substance occur.

The processes in the examined system resemble (model) the phenomenon of metabolism in a living system. This system (as a *non-stationary* one) is gradually transformed, becoming enriched with thermodynamically stable supramolecular

structures. The latter are formed with predominant participation of chemically energy-intensive substances delivered to the system or formed in it (as a result of a number of thermodynamically advantageous chemical reactions). The energy-intensive substances accumulated in the system can, in principle, include various nucleotides, complex peptides and sugars, lipids, and some others. The chemical equilibrium constants of the formation of such compounds (e.g., from lower-molecular substances reaching the system from solution) are usually quite small. However, this is not an obstacle to the accumulation of these substances in the system: sorption processes remove them from the “reaction zone” causing a shift of chemical equilibria towards the formation of these compounds. Thus, “removing” the formed (as a result of chemical transformations) components from the reaction zone, thermodynamics of supramolecular interactions promotes a shift of non-advantageous chemical processes towards the formation of the reaction products mentioned above. When individual supramolecular structures are isolated, chromatin-type structures may, in principle, be formed due to the emergence of primitive membranes and other, complex supramolecular formations. These structures should remain in the system for a long enough period due to the high supramolecular stability.

It is evident that the more stable a supramolecular structure, the longer it can survive in a system where metabolism takes place. Indeed, nucleic acids (chromatin) form the most stable supramolecular structures in living organisms. This makes it possible to retain the genetic information accumulated in the course of evolution for a long time, passing it on through inheritance.

Most protein supramolecular structures are less stable than similar structures of DNA and its complexes. This assumption is confirmed by many physicochemical studies, for instance, works using of differential scanning calorimetry (DSC). Changes in protein structures occur over relatively short time periods often comparable with the life span of a living organism.

As for the lipids, which form relatively non-stable supramolecular structures, their chemical composition in tissues may change quite rapidly. This is why it is sometimes said that the composition of many lipids in an organism's tissues is tightly controlled by genetics and promptly adapts to the changes in the environment (e.g., temperature and the character of food). Such adaptation can often be observed in the organisms' (plants and animals) lifetime. It should be noted here that enrichment of an organism's tissues with non-stable (usually low-melting) supramolecular lipid-containing structures stimulates the performance of the genes (which become more thermodynamically necessary) responsible for the synthesis of proteins that take part in the formation of relatively non-stable supramolecular structures. Such gene stimulation (expression) is made possible by thermodynamic feedback among biological structures in different hierarchies, which manifests itself in the principle of stability of substance mentioned above.

The following qualitative assumption can, therefore, be made: the food that contains low-melting oils and lipids (vegetative food, food made from the biomass of plants and animals inhabiting cold regions) rejuvenates tissues relatively quickly. This fact is well known to dieticians (see [32]).

At the change of a protein diet, rejuvenation of proteins is much slower, although it can be observed over relatively long periods of a person's life. Such reasoning can be continued. All these ideas are completely in line with the macrothermodynamic theory. Generally speaking, it should be borne in mind that all metabolites and their supramolecular formations can, in principle, change their composition and structure over time. However, depending on the intrinsic chemical stability of substances and the stability of the supramolecular structures formed by them (by metabolites), as well as the stability of the higher hierarchies of living matter, the nature on these substances and structures changes at widely varying rates. Thus, the nature and composition of biological tissues (and organisms) may be transformed in varying measures as the character of the environment changes. It is interesting that the conclusions drawn from the thermodynamic theory of

biological evolution and the aging of living organisms [1] have recently been corroborated by the works of the well-known scientist L.Heiflick, who wrote to the author:

“I believe, as you do, that aging in biological material is caused by the thermodynamic instability of molecules. This instability increases at rates faster than capacity for repair. I have described this in some recent papers that are attached.” In this case, the reference is to the chemical instability of substances, which oust water from the organisms’ biological tissues in the course of aging. The process of accumulation of non-stable (energy-intensive) chemical compounds in tissues takes place because the specific value of the Gibbs function of the formation of supramolecular structures strives towards minimum in ontogenesis. This interpretation of Heiflick’s idea is obviously in line with the author’s thermodynamic theory (formulated in 1976 and subsequently developed), as well as with the principle of stability of substance [1, 21, 24].

It follows that there are no obstacles of principle to the understanding of the phenomenon of life, its origin and evolution, within the framework of classical natural scientific approaches. There is no need to “artificially invent” new universal laws and principles. One may safely say that the known universal laws of nature are applicable to all hierarchies of living and inorganic matter.

Some attention should be paid to a frequently posed question, namely, which theory is correct—the widely recognized Darwin’s theory or the well known but less generally accepted Lamarck’s theory? Unlike Darwin, Lamarck maintained that the characters acquired by an individual during its lifetime are inherited, that is, passed on to the progeny.

The question I formulated above is not complete or, in terms of the macrothermodynamic theory, even correct. When such questions are asked, one must specify, not only which characters are implied but also the conditions of observation, first of all, set the *time scale* on which we want to make these observations. If the time period over which we want to examine a certain process

(biological processes or phenomena are no exception) is not indicated, asking such questions is often pointless. It should be clear from above that thermodynamic stability of biological structures determines the time scale on which authentic observations of the changes in the world of living nature of interest to us are possible. To be more convincing, I would like to give some simple model quantitative estimates.

One may well assume that the *relation* of retention periods of molecular structures  $t'_R(1) / t'_R(2)$  (type 1 and 2 molecules or their fragments in the relevant supramolecular environment) *correlates with the relation* of the periods of noticeable (e.g., reliably established) changes in the nature of these molecular structures in ontogenesis and phylogenesis. Here is a model comparison of the periods of evolutionary changes in DNA structure and some lipid structure at the body temperature of a warm-blooded animal. It would be convenient to use an equation that is well known from chromatography [1]:

$$\Delta(\Delta G) = -RT \ln(t'_R / t'_{st}),$$

where  $\Delta G$  is the change of the Gibbs function during sorption,  $t'_R$  is the time of retention of the examined substance, and  $t'_{st}$  is the time of retention of standard substance. There is reason to believe that noticeable changes (at the level of 1%) in the chemical composition of individual lipids in humans is already observed one of two months later once a person changes the oils and fats in his/her diet. This happens because of the relatively low supramolecular stability of lipid structures. To simplify matters, one may assume that under insignificant nutritional changes, the stability of these structures (chosen as the standard) often corresponds to a relatively insignificant (close to zero) change of  $G$  (i.e.,  $\Delta G$ ). However, DNA strands contain a large number of areas that are relatively stable. In other words, at an organism's body temperature, most of these areas are fairly stable, that is, the relevant  $\Delta G$  values differ significantly from zero. Assuming that in one particular case, for some DNA area  $\Delta G$  is equal to -5 kcal/mol, the relation of retention time

for DNA ( $t'_R$ ) and lipid ( $t'_{st}$ ) equals approximately  $30 \times 10^2$ . If  $\Delta G$  for the DNA area is  $-8$  kcal/mol, this relation is  $40 \times 10^4$ . Such estimates can be continued, and corresponding nomograms can be built. But even a comparison of the quoted figures obtained on the basis of experimental data, corroborates known facts. Our simplest calculations indicate that a significant change of the composition of DNA fragments (for instance, under the impact of environmental changes and other known factors) takes place over hundreds and tens of thousands of years. In actual fact, individual DNA fragments are even more stable than the analyzed example implies. It follows, therefore, that DNA is able to retain the structure of individual areas for millions of years.

My estimates draw attention to the fact that various areas of DNA (and of lipid structure) evolve at different rates. This indicates that the rate of inheritance of genetic characters is not the same either. The analyzed example is merely a demonstration. One may conclude, however, that the process of transmission of genetic (and practically inherited) information takes place on different time scales. These time scales, which usually change gradually, may differ by many orders of magnitude. This conclusion should open up broad opportunities for the study of genetics from the angle of thermodynamic dynamics of transmission of hereditary (thermodynamic) characters of living organisms in the course of evolution.

I have presented some general arguments pertaining to the rate of changes in the chemical and supramolecular structure of DNA (RNA), proteins, and lipids in the process of evolution and ontogenesis of individuals. I would like to repeat that, differing as to supramolecular stability, the structures formed by these molecules show transformation rates (in living organisms) varying within a very wide range. To make things clearer, let me say that the changes in the composition and structure of the above-mentioned chemical compounds at molecular level, and of the supramolecular structures and the structures of higher hierarchies formed by them, take place on different time scales. Correspondingly, the role of these changes

manifests itself in phylogenesis (evolution) in different ways. Moreover, the informational feedback between any structures of higher and lower hierarchies (e.g., between population and DNA) [1] proceeds at a much slower rate than the transition of information from DNA to proteins and other biomolecules, and onwards to supramolecular structures, such as organisms, populations, etc. This becomes clear if one recollects that during self-assembly, equilibriums (for instance, ones between liquid-phase structures and the self-assembled ones, associated by the same structures in the aggregated phase) usually shift towards the aggregated phases. This happens during the crystallization of a substance from the state of overcooling or from an oversaturated solution. In such cases (weakly non-equilibrium transitions), an exchange of molecules in the liquid and solid phase always takes place. The more the liquid (solution) is overcooled, the greater the distinction in the rate of molecular exchange between the phases. In other words, in such a situation, the rates of exchange processes between the phases are different. Under equilibrium conditions, the rates are equal. These are, I believe, well known obvious facts.

To avoid misunderstandings, I would like to stress that, using the term “information,” I referred to the transmission of characters (features of composition and structure, properties, characteristics) between structures of the same type (e.g., between macromolecules, such as DNA and protein) inside one structural hierarchy or between structures belonging to different hierarchies (e.g., between supramolecular structures and organisms). This interpretation of information is widely used in biology. It must not be identified with the concept of information used in information theory, which is a department of mathematics constituting a significant part of cybernetics. The mathematical interpretation of information is not used in the discussed thermodynamic theory of biological evolution, since, as was pointed out in the preceding section, this information bears no conscious relation to classical thermodynamics. There are also other ideas regarding

information, e.g., the well-known hierarchical dynamic information used by Collier in the quoted work in the study of biological systems [29].

This arguments can, I believe, convince the reader that there is very real need to identify different time and energy scales and types of hierarchy (as well as the size of the examined system) when looking for answers to the questions about the origin and development of living matter.

It goes without saying that in this section, I have presented a general approximate and simplified thermodynamic model, a scheme of biological evolution and the aging of living organisms, and formulated general physicochemical concepts. I drew only on the findings of the classical natural sciences. The reader is likely to have many questions (mainly, I trust, concerning particulars) prompted by both this section and the paper generally. I am sure, however, that most of them can be convincingly answered from the stand of classical science. Also, the proposed model may be specified and adjusted to fit known facts.

## **5. On the Choice of Anti-aging Diets**

The thermodynamic model of biological evolution and the aging of organisms described in the previous section, as well as the materials included in the paper and monographs [1, 24, 27], makes it possible to provide practical recommendations on a quantitative foundation.

Rejuvenation, or the formation of renovated, young (in terms of physiology and macrothermodynamics) tissue structures, can be achieved by their direct (quick) enrichment with relatively low-molecular components of definite chemical origin. Such enrichment is observed when creams and ointments are applied, or when the diet includes foods, which contain components (e.g., water, hormones, oils, and embryonic tissue elements) that are easily absorbed by tissues. Due to their heightened concentration in an organism's tissues, these components may partially

replace substances that take part in the formation of relatively stable supramolecular structures. Chemical composition and conformational changes in tissue macromolecules and supramolecular structures can be observed quite early. What is more, the existence of thermodynamic feedback between the different hierarchies of the living world (in our case, between supramolecular and molecular hierarchies) gives reason to assume that this rejuvenation effect can be slowly “registered” by the structure of chromatin and DNA at molecular level. With a significant enough change of the composition and the conformational properties of its environment, the chemical composition of DNA is forced (in conformity with the second law or the Le Chatelier—Braun principle) to adapt to the components that are newly formed in tissues (cells). Let me note that the effect of low-molecular substances on the conformation and, possibly, chemical composition of DNA fragments need not require direct contact of this substance’s molecules with the molecular environment of DNA (and with DNA itself). It is well known that interaction among molecules in solutions and in biological systems can extend to hundreds of  $\text{Å}^0$ . Thus, it has long been established that in colloid systems formed by spherical particles in electrolyte solutions, these particles may occupy a stable position in relation to one another. They sometimes form a hexagonal net called a periodic structure. Their properties are known well enough. Their existence is corroborated by the presence of strong forces of physicochemical origin [30].

However, as I have already pointed out, the discussed DNA adaptation to its immediate environment at molecular level should proceed too slowly. It can become noticeable only under a systematic impact of the rejuvenating components described above (like changes in the organisms’ habitat), as a rule, over many generations.

Referring to tissue rejuvenation under the impact of chemically low-active compounds (which do not do noticeable damage to the organism), I mean, first of all, the shift of the specific value of the Gibbs function of the supramolecular structures of an organism’s tissues towards the least negative (more positive) values

[1]. Such shift cannot, of course, be illimitable or even comparatively large. Thermodynamics and kinetics (direct and reverse information) impose severe restrictions on the possible extent of rejuvenation.

I would also like to remind the readers that there is a large body of facts indicating that genes may determine the aging (ontogenesis) of organisms only indirectly. Writes L.Heiflick [31]: “Aging is not a programmed process governed directly by genes. Studies in lower animals that have led to the view that genes are involved in aging have not shown a reversal or arrest of the inexorable expression of molecular disorder that is the hallmark of aging. Those studies are more accurately interpreted to have impact on longevity determination because the results alter physiological capacity and occur before the aging process begins.” This point of view is, in principle, in line with my theory, which ties thermodynamic stability of supramolecular structures with the time of the information exchange among the various structures “inside” the same hierarchy, on the one hand, and in different hierarchies, on the other.

Basing oneself on qualitative theoretical assessments and a large body of reliable empirical experience, one can most probably assume that the effect of rejuvenation of individual human tissues and organs may reach, on average, 10—15 years in middle-aged persons. Specialists believe (on an empirical basis) that, given the right diet and life routine, the average healthy human life span can be extended by 15-20 years. As for overall average longevity, it may rise 7 – 10 years in the near future. However, this figure is likely to be revised.

The links between molecular structures that retain and transmit genetic information and the structures in different hierarchies can, in the general case (multicellular organisms), be presented as the following simplified scheme:

**Molecular structures** (nucleic acids → proteins, other biological polymers) →  
**Supramolecular structures** → **Cells** → **Organisms** → **Populations** →  
**Communities** → **Ecosystems, etc.** (1)

In view of the presence of feedback among the structures in different hierarchies, this scheme should be presented as:

**Molecular structures** (nucleic acids ↔ proteins, other biological polymers) ↔  
**Supramolecular structures** ↔ **Cells** ↔ **Organisms** ↔ **Populations** ↔  
**Communities** ↔ **Ecosystems, etc.** , (2)

where arrows ↔ indicate the possibility of reading off direct and reverse (backward) information. As was repeatedly stressed, the rate of transmission of reverse information is, for the examined reasons, low as compared with that of direct information.

Scheme (2) accords with the well-known facts pointing to the relatively slow effect of the environment on the structure and characteristics of populations (on the time scale of their life) and, in the final analysis,- on the supramolecular and chemical structure of nucleic acids.

Talking about the effect of diets and various substances on the length of healthy life (and longevity generally), the following becomes obvious. A reasonable increase, in the diet, of the amount of the foods that contain non-stable (“young”) supramolecular structures (whose stability depends, of course, of their chemical composition) of tissues of living organisms has a positive effect. Thus, a permissible (physiologically acceptable for the given individual) increase of the amount of water, low-melting lipids, some natural compounds, and medicines in the organism’s tissues often decreases the supramolecular stability of these tissues. The latter means, in terms of thermodynamics, that the given tissue is rejuvenated, that is, becomes relatively young. The most indicative example (already mentioned) is probably an improvement in the state of health in patients whose tissues contain the maximum allowable amount of water. In this case, the stability of a number of supramolecular structures is somewhat lowered, since the tissues become

rejuvenated. As was noted above, this information is transmitted to gene level quite slowly, so that the structural changes are, for this reason, difficult to observe within an individual's lifetime. But a normal water intake is beneficial to the patients' health, that is, the length of their healthy life. Medics are well aware of the hazards of dehydration, which in some countries unfortunately affects a larger part of the population.

These considerations and facts accord well with the latest findings of the study aimed at prolonging the life span of yeast cells, and with other observations [32]: "Several naturally occurring small molecules extend the life of yeast cells by approximately 70% and offer some protection to cultured human cells exposed to radiation, researchers reported online in *Nature* on 24 August. The molecules belong to a family of chemicals known as polyphenols, some of which are prominent components of grapes, red wine, olive oil, and other foods." (*Full story at <http://www.sciencemag.org/cgi/content/full/301/5637/1165?etoc>* ). I will note, however, that these compounds may also affect longevity in an indirect way, e.g., by changing the speed of some metabolic processes in an organism.

The supramolecular stability of the tissues of a natural food (as of an organism's tissues) is assessed on the basis of its gerontological value indicator,  $GPG_i$ , calculated by determining the Gibbs specific function of the formation of the supramolecular structure of this food or its ingredients. A 10-point scale first described in patent [33] can be used for this purpose. The higher the  $GPG_i$  indicator, the more gerontologically valuable (anti-aging) the food is. Drinking water can also be evaluated on the basis of its gerontological quality, its purity [34]. One should remember that the known gerontological characteristics of foods and drinking water are supplementary indicators, which do not obviate the need to examine the quality and safety of food and water on the basis of other accepted standards. What is more, designing a diet, one should always take account of the possible medical recommendations which, as was said above, are often strictly individual.

With account of schemes (1) and (2), the thermodynamic theory of aging makes it possible to qualitatively (and, if necessary, quantitatively) assess the gerontological value of lipids, proteins, carbohydrates, and other components of food and food additives. The most indicative example of the effectiveness of such an assessment is determination of the anti-aging properties of natural oils and fats.

It follows from the thermodynamic theory that the changes in the Gibbs specific function when supramolecular structures are formed, as well as the values of the  $GPG_i$  index connected with it, can be easily assessed from the approximated Gibbs – Helmholtz – Gladyshev equation [35], which is an **analogue** of the classical Gibbs – Helmholtz approximated equation. As applied to natural fats and oils, it can be written down as:

$$\Delta\widetilde{G}_i^{im} = (\Delta\widetilde{H}_{m_i}^{im} / T_{m_i})(T_{m_i} - T_0) = \Delta\widetilde{S}_{m_i}^{im} \Delta T, \quad (3)$$

where  $\Delta\widetilde{G}_i^{im}$  is the Gibbs specific function (Gibbs specific free energy) of the formation of the substance condensed phase  $i$ ,  $\Delta\widetilde{H}_{m_i}^{im}$ ;  $\Delta\widetilde{S}_{m_i}^{im}$  is the change of specific enthalpy and entropy during the solidification of natural fat (oil);  $T_{m_i}$  is the pour or melting point; and  $T_0$  is the standard temperature (e.g., 25, 0, - 25, - 50 ° C) at which values  $\Delta\widetilde{G}_i^{im}$  (and, consequently,  $GPG_i$ ) are compared. Value  $T_0$  must be lower than value  $T_{m_i}$ . When assessing the gerontological value of a food, the choice of  $T_0$  is determined by the value of melting point of the lowest melting-point substance in the series of compared products. It is assumed that the low melting-point substances take part in the formation of corresponding low melting-point (as a rule, relatively non-stable) supramolecular structures in an organism's tissues.

Let me note that the Gibbs – Helmholtz equation is correct for an individual substance in a closed system in which chemical, phase or other transformations may take place. The **analogue** of this equation, often with a good approximation, can be applied to various substances of the same type and variable composition systems. The Gibbs – Helmholtz equation and its **analogue** (3) was used, with good results,

by the author of this paper when determining the thermodynamic direction of evolutionary processes [1]. Such relationships, in fact by default, are widely used in the study of synthetic copolymers, biological polymers, and some other variable composition systems [1, 27].

It follows from equation (3) that a correlation between  $\Delta\widetilde{G}_i^{im}$  (calculated for standard temperature) and the pour (melting) point of fats or oils,  $T_{m_i}$  should often be observed, with acceptable approximation [1]. Such a correlation should, of course, be also observed between the indicator of the anti-aging (gerontological) value of the food in question,  $GPG_i$  and  $T_{m_i}$  [1]. Indeed, such a correlation does exist [1, 27]. Knowing the pour point of vegetable oils and fats, we can build the series:

**Hempseed oil, linseed oil, sea buckthorn oil, cedar oil, sunflower oil, mustard oil, olive oil, cottonseed oil, seal oil, bottle-nose oil, butter oil, lard, horse fat, beef fat, mutton fat** (4)

This series, from the highest to the lowest gerontological value of the foodstuffs, can be substantially expanded. It accords with the fact that, as compared to fats, vegetable oils usually have relatively low pour points and, consequently, less negative or more positive (as compared to fats)  $\Delta\widetilde{G}_i^{im}$  values. According to theory, they have heightened anti-aging value. They are recommended for use in the case of various diseases and to prolong *healthy human life* [see, for instance, manuals on dietetics; 1, 21, 24, 36]. Theory is in complete accord with many known qualitative medical recommendations based on practical experience. Some of them, it is true, apparently contradict the sequence of foods in the series. But in actual fact this is not so. Much of medical advice is determined by various pathologies, the way and conditions of life, and other factors. Circumstances sometimes make it desirable to reduce the intake of some gerontologically valuable foods. Series (4) relates to

average gerontological value indicators (the exact values significantly depend on the age of the plant or animal, the specifics of the environment inhabited by the organisms used as sources of food, and some other unaccounted-for factors).

The approximated correlation presented by series (4) can, of course, be adjusted at a strict assessment of  $\Delta\widetilde{G}_i^{im}$  and indicator  $GPG_i$  (members of the series may, within limits, change places). Such an assessment is easy to make taking into account the distinctions in the  $\Delta\widetilde{H}_{m_i}^{im}$  values for different oils and fats (it was concluded, as the series was built, that values  $\Delta\widetilde{H}_{m_i}^{im}$  were the same for all foods), as well as some other facts. *The  $GPG_i$  value, like pour point  $T_{solid}(T_{m_i})$  of a product, depends on the character of the environment and the age (ontogenetic and phylogenetic) of the plants or animals whose biomass is used as food [1, 21, 24].*

This explains the high gerontological value of the foods made from the biomass of young plants and animals inhabiting cold (including cold seas) and Alpine regions. The gustatory quality of such food is usually high. It accords with the thermodynamic theory and mankind's long experience.

## 6. Practical Advice

The arguments presented in this paper (in my view, well-substantiated) indicate that practically all concrete (detailed) recommendations relating to nutrition are individual. They should be formulated on the basis of general and anti-aging medicine (gerontology) and should factor in the findings of physicochemical dietetics.

Nevertheless, the thermodynamic theory of biological evolution and the aging of living organisms (built on the foundation of classical science) provides an opportunity to formulate general concepts pertaining to nutrition and helping prolong healthy human life.

The diets promoting a long and healthy life should, of course, comprise only ecologically clean foods. They should be balanced as to composition and calorific value. It is extremely important for a diet to include cold (deep) sea foods and foods made from plants and animals inhabiting cold and Alpine regions. It is also desirable that the biomass used should be that of young plants and animals. What is more, we should use predominantly food prepared from the biomass of ancient species, living organisms with a low phylogenetic development level (standing at early stages of phylogenesis). The food for which young (ontogenetically and phylogenetically) plants and animals were used is not only gerontologically valuable but also, for obvious reasons, has a low calorific value. It is also known to prolong healthy life and is certain to increase general longevity. One should use pure practically salt-free drinking water. Medicinal mineral waters should be specifically indicated.

Generally speaking, it is advisable to use the foods and water which meet the general up-to-date standards developed on a strictly scientific foundation. It is also desirable that these foods and water should be recognized to have high anti-aging value, and that the water should be “gerontologically pure”. Specific recommendations, which are an object of recent research, are also available.

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