THE EQUILIBRIUM SUPRAMOLECULAR THERMODYNAMICS OF QUASI-CLOSED BIOLOGICAL SYSTEMS. ON THE THERMODYNAMIC DIRECTION OF CELL DIFFERENTIATION AND ORGANISM DEVELOPMENT

© 2002 **G.P. Gladyshev**

N.N. Semenov Institute of Chemical Physics, RAS
117977 Moscow, up. Kosygina, 4. E-mail: academy@endeav.org

Abstract

The law of temporal hierarchies makes it possible to identify quasi-closed systems in open biological systems and to use the approaches of hierarchical quasi-equilibrium thermodynamics to establish the direction of ontogenesis and the evolutionary processes. A short review of the achievements of thermodynamics of biological evolution and aging are presented. The application of the principle of stability of matter to the structures of adjacent hierarchies constitutes additional proof that quasi-equilibrium thermodynamics can be applied to the biological systems in the real world.

It is assumed that cell differentiation, the development of multicellular organisms, and the emergence of structures of the higher hierarchies of the biological world are determined by the thermodynamic direction of these processes.

An organism's cells contain identical genes. Only some of them, however, function in the course of differentiation and development. Gene induction and repression during differentiation are determined by the position of newly emerging cells, whose properties depend on their functional position. The manifestations of these properties are determined by the thermodynamic parameters of the cells' environment (thermostat), whose components and physicochemical characteristics affect gene induction and repression.

The holographic (three-dimensional) design of the future organism (higher structures of the biological world) is determined by thermodynamic demand for certain genes. The latter's operation is stimulated by their environment. One of the well-known examples that corroborate the presented model is the change of gene transcription as the nature of lipids and other metabolites contained in cells changes.

Key words: Biological evolution, aging, second law, law of temporal hierarchies, caloric restriction, differentiation of cells

The Thermodynamic Theory of Evolution and Development

The study of the processes that lead to the origin and development of living systems in terms of hierarchical structures and identification of the law of temporal hierarchies gives reason to assert that the direction of the processes of the development and evolution of living beings can be ascertained on the basis of thermodynamic (thermostatic) principles formulated by the classics of the natural sciences, R. Clausius, J. Gibbs and others [2, 6-8, 22, 24-26].

The formation of structural hierarchies in open natural biosystem within the framework of the model of quasi-closed systems can be described in terms of hierarchical thermodynamics (thermostatics).

In the course of the evolution of open natural systems, each higher hierarchical level *j* is formed as a result of thermodynamic self-organization (self-assembly) of lower-level, *j*-1, structures. This self-assembly occurs through the stabilization of level *j*. The latter is connected with the fact that the Gibbs specific function of the formation of structure *j* tends to a minimum.

The cycle – the relative matter circulation in nature can also be studied from the stand of hierarchical thermodynamics. Fig. 1 presents the scheme of the change of Gibbs function (Gibbs' free energy of the formation of structures of the biological world). Obviously, the motive force of the *non-spontaneous processes* of the cycle of matter, first of all, is connected with the Sun. In terms of "dark" *spontaneous processes*, the motive force of the self-assembly and evolution of biological structures at all hierarchical levels is "thermodynamic forces." In conformity with the principle of energy differentiation (and the law of temporal hierarchies), the specific values of Gibbs function of self-assembly (thermodynamic self-organization) at different hierarchical levels differs significantly. Thus, there exist the series

$$\ldots \gg \Delta\Delta\overline{\overline{G}}^{\,j} \gg \Delta\Delta\overline{\overline{G}}^{\,j+1} \gg \ldots, \qquad (1)$$

where $\Delta\Delta\overline{\overline{G}}^{\,j}$ and $\Delta\Delta\overline{\overline{G}}^{\,j+1}$ are the changes of the specific values of Gibbs function of the formation of structural hierarchies *j* and *j* + 1 calculated for a unit of volume or mass. In other words, the coordinate axes of the scheme presented in Fig. 1 are of different scale in a significant degree.

Gibbs function of the formation of molecules and supramolecular structures as complex systems often coincide, in the conditions of the Earth, with the Gibbs function of the

formation of the corresponding simple systems. In view of this, the asterisk in ΔG^{*i} may be omitted.

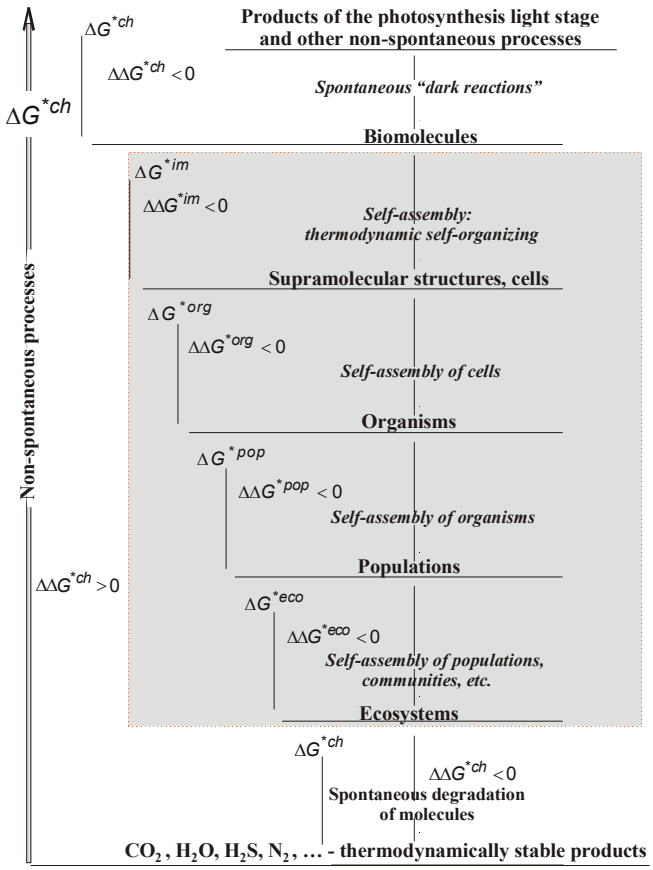


Fig. 1. Scheme of the change of Gibbs function of the formation of complex systems, ΔG^{*i} during the emergence and degradation of chemical (*ch*) and supramolecular structures (*im*), as well as organisms (*org*), populations (*pop*), communities (*com*), and ecosystems (*eco*).

The law of temporal hierarchies [2, 7, 22-24] makes it possible to identify quasi-closed thermodynamic systems (subsystems) in open biosystem. It is possible to study their development (ontogenesis) and evolution (phylogenesis) by studying the changes of the value of specific (per unit of volume or mass) Gibbs function of the formation of the given higher hierarchical structure out of lower-level structures. Thus, it was established that in ontogenesis (or phylogenesis), the specific Gibbs function of the formation of supramolecular structures of an organism's tissues, $\overline{\widetilde{G}}_i^{im}$, tends to minimum:

$$\overline{\widetilde{G}}_i^{im} = \frac{1}{V}\int_0^V \frac{\partial \widetilde{G}^{im}}{\partial m}(x,y,z)dxdydz \to \min \qquad (2)$$

where V is the volume of the system; m is the mass of the identified micro-volumes; x, y, z are coordinates; symbol «--» means that value $\overline{\widetilde{G}}_i^{im}$ is specific; and symbol «~» emphasizes the heterogeneous character of the system. Let us note that equation (2) implies taking account of all supramolecular interactions in all hierarchical bio-tissue structures (intracellular, intercellular and others). This is fully justified because the structural hierarchy does not always coincide with the temporal hierarchy. Thus, some types of cells do not divide and, like organisms, age simultaneously with the organism. However, any supramolecular hierarchy (j-1) has some higher hierarchy ($j + x$), so that

$$t^{j-1} << t^{j+x},$$

where t^{j-1} and t^{j+x} are the mean life times (life spans) of elementary structures of the corresponding structural hierarchies in a living system, $x = 0, 1, 2, \ldots$, etc.

The use of equality (2) means, in fact, that we apply the law of temporal hierarchies as:

$$\ldots << t^{m} << t^{im} << t^{organism} << t^{pop} << \ldots . \qquad (3)$$

Here, t^{m} (t^{ch}) is the average life span of an organism's molecules (chemical compounds) that take part in metabolism. t^{im} (t^{supra}) is the average life span of any supramolecular structures of an organism's tissues that are renewed in the process of its growth and development. $t^{organism}$ is the average life span of an organism in a population. And t^{pop} is the population's average life span. The series of strong inequalities (3) does not include the life span of cells (*cell*) and some other supramolecular structures. However, this series of course tallies well with reality and reflects the existence of temporal hierarchies in the living systems. The latter rigidly substantiates the possibility of identifying quasi-closed systems (subsystems) in open biological systems.

The thermodynamic theory of biological evolution and the aging of living beings accords with numerous facts and with mankind's empirical experience [2, 3, 7, 24, 25].

A graphic example of the accord between theory and observations is connected with the well-known medical recommendation to include vegetable oil and seafood (cold seas) into

one's diet.[1] These products add "young chemical matter" to the biotissues [7], "building material" that corresponds to the composition of a young organism. In thermodynamic terms (and in the light of known facts), this rejuvenates the organism's tissues. This is easy to see having analyzed the approximate equation — an analogue of Gibbs-Helmholtz equation:

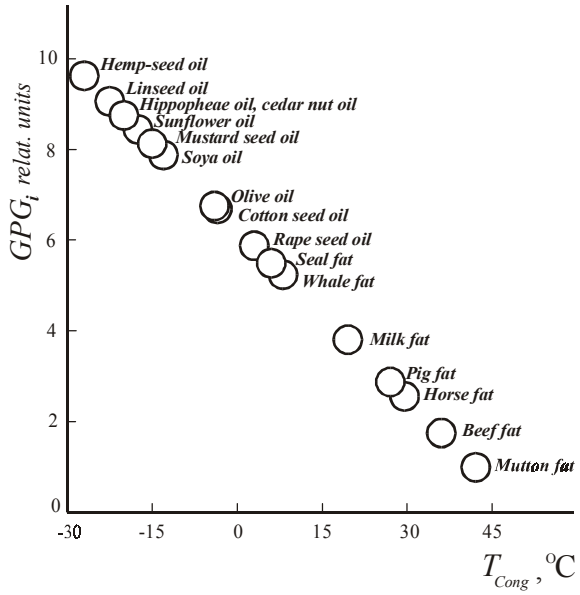
$$\Delta\overline{\widetilde{G}}_i^{im} = (\Delta\overline{\widetilde{H}}_{m_i}^{im} / T_{m_i})(T_{m_i} - T_0) = \Delta\overline{\widetilde{S}}_{m_i}^{im}\Delta T\,, \qquad (4)$$

where $\Delta\overline{\widetilde{G}}_i^{im}$ is the specific Gibbs function (Gibbs specific free energy) of the formation of the condensed phase of matter i, $\Delta\overline{\widetilde{H}}_{m_i}^{im}$ and $\Delta\overline{\widetilde{S}}_{m_i}^{im}$ are the change of specific enthalpy and entropy during the solidification of natural fat (oil), T_{m_i} is the melting or freezing point, and T_0 is the standard temperature (e.g., 37° C) at which the comparison of values $\Delta\overline{\widetilde{G}}_i^{im}$ is done.

It follows from equation (4) that, at a certain approximation, there should be a correlation between $\Delta\overline{\widetilde{G}}_i^{im}$ (calculated for the standard temperature) or the indicator of the product's anti-aging (gerontological) value, GPG_i [3, 5], and the fats or oils' congeal (pour or freezing, or melting) point [11, 15, 36]. Let me note that the GPG_i indicator is proportionate to value $\Delta\overline{\widetilde{G}}_i^{im}$ [5, 7, 23]. Indeed, such a correlation does exist. This is confirmed by the known data presented in Fig. 2. We can see that as a rule, vegetable oils have a relatively low pour point and, consequently, higher $\Delta\overline{\widetilde{G}}_i^{im}$ values (as compared to fats). According to the theory, they have heightened anti-aging value. It is common knowledge that these oils are recommended for use as food during various diseases and to prolong the duration of healthy life [21, 33]. Needless to say, the correlation presented in Fig. 2 can be specified by a strict evaluation of $\Delta\overline{\widetilde{G}}_i^{im}$ and the GPG_i indicator. *The latter's value, as well as a product's congeal point T_{cong} (T_{m_i}), depend on the environment and the age of the plant or animal used as food* [5]. To emphasize this point, the data in Fig. 2 are presented as large circles. Let me note that such calculations are easy to perform in relation to proteins and carbohydrates, as well as the food additives and medicines.

A convincing argument in favor of the thermodynamic theory of aging is a well-known phenomenon, namely, medical recommendations to reduce the caloric intake. In will

[1] This example may help the reader believe in the effectiveness of the thermodynamic theory when ascertaining the direction of the evolution and development of the living organisms.



be in order here to quote prominent gerontologists [30] saying in the popular scientific magazine : «Investigators have know for decades that caloric restriction extends life and the

Fig. 2. Dependence of "anti-aging (gerontological) value" of edible oils and fats, GPG_i, on their congeal point, T_{cong}. GPG_i and T_{cong} depend on the environment and age of plants and animals. A ten-point GPG_i scale is used. It is assumed that ten GPG_i points are given to the oil with a congeal point of -30°C; no points are given to fat with a pour point of 47°C.

duration of good health in all species in which it has been studied, as long as the diet includes enough nutrition for routine maintenance of the body. These findings suggest that caloric restriction might have similar effects in humans». These researchers believe, however, that there is no indicator, which would make it possible to objectively assess the rate of aging in humans or other species. The thermodynamic theory of aging introduces such an indicator or yardstick, which can help established the degree of aging of tissues in living organisms. This yardstick is the GPG_i index, which is calculated by measuring value $\Delta\widetilde{\overline{G}}^{im}$ for various types of tissues. Then the less negative value of $\Delta\widetilde{\overline{G}}^{im}$, i.e. the higher the value of indicator GPG_i, the younger the tissue is. Reducing the caloric intake helps keep the value of index GPG_i of

human, animal, and plant tissues higher (cf. the scheme of the changes of value $\Delta\overline{\widetilde{G}}^{im}$ in the process of aging [3, 6, 7]). This reminds us yet again that nutrition significantly affects human longevity in the state of health. There is reason to believe that gerontologically good nutrition also has a favorable effect on overall longevity.

It is shown that the principle of stability of matter - the feedback principle is applicable to all biological systems (their hierarchies) [7, 8, 24, 25]. The core of this principle is as follows: during the formation (self-assembly) of the *most stable structures* at the highest hierarchical level (*j*), for example, the supramolecular level, nature spontaneously uses predominantly the *least stable structures* (accessible to the given local segment of the biosystem), e.g., the molecular level (*j*-1). It has been quantitatively proved that the principle works at the molecular and the supramolecular levels of the biotissue. There are also facts confirming its applicability to the social hierarchies. Thus, hierarchical thermodynamics of complex systems can help explain the social management techniques developed over centuries, such as "divide and rule" [7, 8, 25], etc.

Further on, this work uses multicellular living organisms to examine the general scheme of the development of organisms, as well as the structures of the higher hierarchies of biosystems (populations, communities, etc.) from the stand of equilibrium (quasi-equilibrium) hierarchical thermodynamics of complex quasi-closed systems.

The melting point of the organisms' supramolecular structures

As the author repeatedly stressed, the soundness of the thermodynamic theory of evolution and aging is corroborated by numerous generally known facts relating to the change of the ratio of high- and low-melting structures in an organism's tissues as its body temperature (the temperature of the habitat) changes. Nevertheless, many gerontologists and other researchers disregard this fact.

It would be useful to draw the specialists' attention to the models whose study makes one believe in the prognostic value of the theory.

The simple two-state model is:

$$N = D, \tag{5}$$

where N – is the native (associated) state of the supramolecular structure, and D is the unfolded state.

In this simplest case, we can apply the obvious equation:

$$(c_{\mathrm{N}})/(c_{\mathrm{D}}) = \exp\left(-\Delta\widetilde{\widetilde{G}}_i^{im}/RT\right), \quad (6)$$

where (c_{N}) и (c_{D}) - concentration of N и D structures R - gas constant, T - temperature. There are other long known simplified models representing the melting of nucleic acids, proteins, and their complexes. These models were previously used only in the study of closed laboratory systems with variable composition (substances of the same type). No one tried to apply these models to open real systems. After the law of temporal hierarchies (3) had been discovered, it became obvious that many known models can, with good reason, be applied to those open biological systems which can be treated as quasi-closed at certain time periods.

For example, the equilibrium transformation between double- and single-helix DNA examined in old classical works [12, 18] can be presented as:

$$\mathrm{M_n \cdot D} \leftrightarrow \mathrm{M_{n'} \cdot S_1} + \mathrm{M_{n''} \cdot S_2} + \Delta\mathrm{nM}\ , \quad (7)$$

where M is a small molecule, $\mathrm{S_1}$ and $\mathrm{S_2}$ are single helixes, and D is a double helix. According to the limiting model, during the melting $\Delta\mathrm{n} = \mathrm{n} - \mathrm{n}' - \mathrm{n}''$ M molecules are released or are bound.

The equilibrium or self-assembly constant for the process (7) can be presented as:

$$K_{\mathrm{s-ass}} = (\mathrm{M_n \cdot D})/(\mathrm{M_{n'}}\, S_1) \cdot (\mathrm{M_{n''}} S_2) \cdot (\mathrm{M})^{\Delta\mathrm{n}} = \exp(-\Delta G^0/RT)\,.$$

The dependence of ln$K$ on the concentration of small molecules, ligands, can be defined from equation:

$$\partial\left(\ln K_{\mathrm{s\text{-}ass}}\right)/\partial[\ln(\mathrm{M})] = -\Delta n \quad . (8)$$

The dependence of $K_{\mathrm{s\text{-}ass}}$ on melting point T_{m} ($T_{\mathrm{s\text{-}ass}}$) of the supramolecular structures participating in equilibrium (7) is defined by the well-known equation:

$$\frac{\partial(\ln K_{\mathrm{s\text{-}ass}})}{\partial T_{\mathrm{m}}} = \frac{\partial}{\partial T_{\mathrm{m}}}\left(\frac{-\Delta G^0}{RT_{\mathrm{m}}}\right) = \frac{\Delta H^0}{RT_{\mathrm{m}}^2}\,. \quad (9)$$

Equation (9) is correct when the change of enthalpy ΔH^0 of the reaction does not depend on temperature. This is quite true of type (7) processes. But the use of this equation for the cases of self-assembly of different-type substances requires additionally taking into account that for the different substances ΔH^0 can be notably different.

If all variables except $\ln(\mathrm{M})$ do not depend on *T*, it can be assumed that:

$$\frac{\partial T_{\mathrm{m}}}{\partial[\ln(\mathrm{M})]} = -\Delta n \frac{RT_{\mathrm{m}}^2}{\Delta H^0}. \qquad (10)$$

Values ΔH^0 and Δn in equations (9) and (10) belong to the kinetically independent (cooperative) unit that takes part in the processes of melting and coupling (self-assembly).

The presented type (9) and (10) dependencies can also be used if the calculations are made for a unit of mass (volume) of supramolecular structures. In other words, if a researcher do not like to use some mean values of $K_{\text{s-ass}}$, constant of self-assembly, ($\overline{\widetilde{K}}_{\text{s-ass}}$), he or she may use the values $\Delta\overline{\widetilde{G}}_i^{im}$ and others. This is convenient, since it is not easy to measure the concentration of kinetically independent units. In addition, this value is not constant for different microvolumes of supramolecular structures. As was already noted, in supramolecular thermodynamics, values ΔG, ΔH, ΔS and others are designated as $\Delta\overline{\widetilde{G}}_i^{im}$, $\Delta\overline{\widetilde{H}}_i^{im}$, $\Delta\overline{\widetilde{S}}_i^{im}$, etc. It should be noted that the values of "ΔG " and "*RT*" in equation (6) and others should be related to the same units (mole, cooperative unit, kinetic independent unit, gram, grams in liter and so on).

It is important that an increase of the concentration of small molecules in the environment of DNA structures (chromatin) causes a rise of T_{m}, if these molecules tend to bind with double and not single helixes. When small molecules tend to bind with single helixes, a decrease of T_{m} is observed. In principle, this conclusion is true of any supramolecular structures that contain DNA, RNA, proteins, polysaccharides, and many other molecules [12]. Some aspects of the interaction between genetic structures and small molecules are discussed in a short paper dealing with gene and aging thermodynamics [4].

The author [3] demonstrated the existence of dependence $K_{\text{s-ass}} = f(T_{\mathrm{m}})$ using the solidification (congealing) of a number of fatty acids with different T_{m} and ΔH_m^0 values as

a example[1]. The high-melting supramolecular structures or substances have, as a rule, high values of T_{m} and ΔH_m^0 ($\Delta \widetilde{\overline{H}}_m^0$)[2].

I would like to give the long-known examples[36]. Butterfat has a T_m of 28-36 ^{o}C and the heat of fusion 81.6 J/g. Cottonseed oil has a T_m from –1 ^{o}C to –6 ^{o}C and the heat of fusion 86.0 J/g. Peanut oil has a T_m of -3 ^{o}C and the heat of fusion 90.9 J/g. Fully hardened cottonseed oil (Iodine value ca. 1) has a T_m of 40 ^{o}C and the heat fusion 185.0 J/g.

These high-melting substances (structures) with decreasing temperature of an organism's tissues (the temperature of the environment) are *freezed out and their role in the processes of metabolism and structure formation is decreased.*

This conclusion fully corresponds to the classical equilibrium thermodynamic theory of solutions. Thus, for ideal solution of a solid in a physiological liquid, by using the Gibbs-Helmholtz equation, one can obtain:

$$\left(\frac{\partial \ln x}{\partial T}\right)_{p,sat} = \frac{\overline{\mathrm{Q}}}{RT^2}, \qquad (11)$$

were x is the solubility of the solid, p- pressure, sat is saturated solution, $\overline{\mathrm{Q}}$ is the heat of solution of a mole of a substance in a saturated solution (differential or partial heat of solution). For ideal solutions the heat of solution $\overline{\mathrm{Q}}$ is equal to the heat of fusion of the solid: $\overline{\mathrm{Q}} = \lambda_f = -\Delta H_f$. In accordance with equation (11) one can see that the temperature dependence of solubility of solid is determined first of all by its heat of fusion ΔH_m^0.

To demonstrate the effect of the change of the ratio of the concentrations of low- and high-melting supramolecular structures during temperature changes in an organism's tissues, let us consider Fig. 3. The example presented in it can help foster belief in the correctness of the thermodynamic theory as applied to open (quasi-closed at certain points) systems.

Although the scheme presented in Fig. 3 is simplified it, strictly speaking, graphically demonstrates the following. As the organisms' body temperature (both in ontogenesis and phylogenesis) goes down, the relative amount of fatty acids, fats (lipids) and other supramolecular structures with increased ΔH_m^0 and T_m in the tissues of these organismsв

[1] The presented example was complex and non-informational for understanding. However, the conclusions were true.

[2] However, the common dependence between T_{m} and ΔH_m^0 does not exist.

should decrease in a greater measure than the relative amount of low-melting structures. And the other way around, the relational content of supramolecular structures with decreased ΔH_m^0 and T_m should go up as the organism's temperature does down. This is in line with the Le Chatelier - Braun principle.

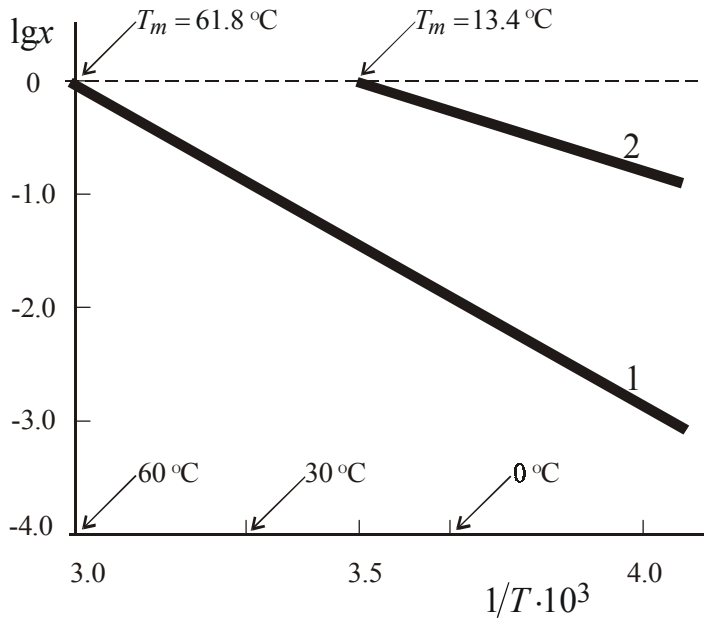


Fig. 3. Temperature dependence of solubility of two substances . Illustrative ideal model .

1 – palmitic acid (T_m = 61.8 °C, $\overline{Q}$ = 50.7 cal/g);
2 – oleic acid (T_m = 13.4 °C, $\overline{Q}$ = 25.5 cal/g);
x – solubility; $\overline{Q}$ - heat of solution; for ideal solution $\overline{Q} = -\Delta H_f$

As was already noted, natural fats and oils with low-melting points (slip points) are accumulated in the tissues of organisms with decreasing body temperature (temperature of the environment). The fats and oils with low-melting points contain non-saturated acid residues basically[1]. That is why the concentration of non-saturated bonds in these products (their Iodine values) is increased with decreasing the body temperature of living beings.

[1] As a whole, one should take into account that the melting point generally increases with increasing proportion of long chain fatty acids or decreasing proportion of short chain or unsaturated fatty acids. Besides, the latent heat of fusion increases with increasing chain length and increasing degree of saturation [36].

As was already noted, this important conclusion prompted by the theory is in accord with a vast number of known facts [1, 7, 16, 34]. Many new research findings can be found in Internet.

This is a proper place to give a long-known example of the variation in the structure and composition of collagen. It has been established that the temperature of denaturation (melting point) of collagen in homothermous animals is close to their body temperature, and in poikilothermous animals, to the temperature ceiling of their habitat (i.e., the animal's highest body temperature). Fig. 4 shows the dependence of denaturation temperature T_{d} (T_m) of the collagen molecule on body temperature (homothermous animals) or the temperature ceiling of the environment (poikilothermous animals) T_{en} [16, 34]. The presented dependence is in line with correlations (11) and, of course, the data in Fig. 3.

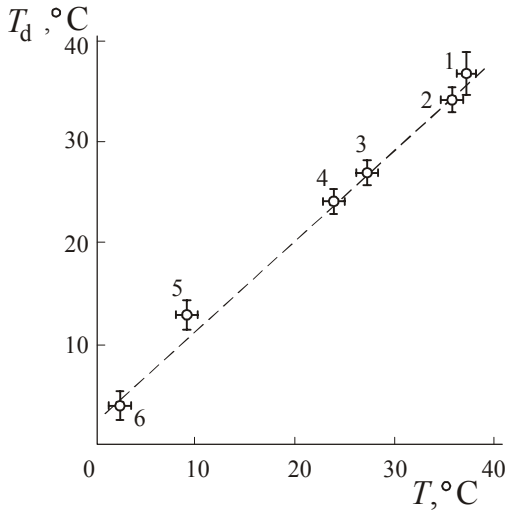


Fig. 4. The relationship of the denaturation temperature (T_{d}) of collagen molecules to the body temperature (homothermous animals) or to the upper temperature limit of the environment (poikilothermous animals): (1) pig, parasitic nemathelminthic worms - Ascaris and Acanthocephala; (2) human, rat, cow; (3) snail; (4) tuna; (5) cod; (6) ice-fish.

Decreasing body temperature or the temperature of the environment promotes the accumulation of low-melting collagen structures in an organism's tissues. Thus, the data in Fig. 4 also constitute irrevocable proof of the correctness of the thermodynamic theory of evolution and aging.

There are also examples of "adaptation" of T_m nucleic acids, their complexes, and chromatin to the body temperature of homothermous living beings or the temperature of the environment of poikilothermous living beings (cf. [2]). Due to its relative stability, this DNA adaptation is observed extremely slowly and is not obvious at certain points of an organism's life. The RNA structure should adapt relatively faster. Nevertheless, it turns out that in the process of phylogenesis (evolution), the organisms' DNA (RNA) structure changes noticeably as the temperature of the environment (and other factors) change. All this confirms the general proposition of our physical (physicochemical) theory of evolution: evolutionary changes in the biological world (and in inorganic nature) are determined by internal (the organisms' genetics) and external (parameters of the environment) factors. *The relative contribution of these factors depends on the selected time scale (as we observe some changes or others) and the stability of the examined structures.* This is a manifestation of the unity of general laws of nature (the law of energy conservation, a private case of which is the first principle of thermodynamics, the second principle of thermodynamics, and the law of temporal hierarchies).

Genetic regulation of development

It is assumed, with good reason, that most multicellular plants and animals begin their life cycle with one cell, a zygote (fertilized ovum). Multiple mitotic divisions lead to the formation a complex highly differentiated organism. This process is called growth and development, and involves differentiation. As a result of the latter, a cell acquires a certain structure and, multiplying, produces other cells of the same type. Various tissues (organs) are formed in a multicellular organism, and a complex organism evolves. The origin of this phenomenon is not clear [9]. However, growth and development are certainly linked to gene induction and repression. It is assumed that differentiation manifests itself through complex interactions among the cell's nucleus, cytoplasm, and environment. Various stages of the differentiation mechanism have been examined in literature. Naturally enough, there are many of them.

The phenomenon of differentiation has not, on the whole, been examined in terms of thermodynamics. The thing is that there used to exist a ban of sorts on the use of classical (equilibrium) thermodynamics for revealing the "motive forces" of differentiation. It was connected mainly with the open character of the living biosystems. It should be noted that at the same time, classical thermodynamics was (still is) widely used in the study of closed

"laboratory" biological systems" [12]. The rapid headway of bioorganic physical chemistry and the other adjacent disciplines is associated with this circumstance.

As was already noted, in the past few years it became possible to make a substantiated study of open living systems with the help of thermodynamic (thermostatic) quasi-closed models. The latter are analogues of the models of chromatographic systems based on the use of methods of classical thermodynamics [13].

It is indicative that the processes of growth and development can be examined in terms of the change of the specific Gibbs function during cell differentiation, etc.

It is known that all cells in an organism contain the same genes. But only some of them function during differentiation. This leads to the formation of different tissues.

Embryonic development

Embryonic development begins with fertilization and is made up of cleavage, gastrulation, organogenesis, and the emergence of the functions of the organs' tissues. During cleavage, an equi-hereditory nuclei division takes place. But the division of the cytoplasm, which differs depending on the part of the ovum, is not equal. These primary distinctions in the cytoplasmic environment of the ovum are believed to determine the early stages of the embryo's differentiation. During gastrulation, the embryonic leaflets are separated and an overall plan of the organism's structure (a "holographic" blueprint) is formed. Than during organogenesis the appearance of tissue germs and organ systems in embryonic leaflets take place. Although the embryo's cells receive the full complement of genes during division, only some of these genes function in each type of tissue.

After division, each cell finds itself in an "environment of its own," which has certain specific properties. The latter may be connected (directly or indirectly) with water concentration in the system, the amount of carbon dioxide, oxygen, and other components of the atmosphere, the presence of biologically active hormone molecules and other metabolites, and with a number of other factors. The latter include temperature, the intensity and spectrum of penetrating radiation, and the values of electromagnetic gradients. It is assumed that these factors can affect differentiation through the cytoplasm, which, in turn, affects genes. There is reason to assume that the distinctions between these factors arise from the different position of cells in a living heterogeneous system. A simple analogy between the position of a cell in developing embryonic tissue and the growth of a plant (e.g., tree) leaf would be in order here. The growing leaf orientates itself in space guided by the maximum intensity of the solar energy flow. The amount of the solar energy accumulated by the leaf is determined by both

the direct access of sunlight and the flow of dissipated light, which depends on the spatial position of the leaf among its neighbors (other leaves). The latter perform the role of components of the inner environment of the leaf in question. They are, if you will, the surrounding "cells." This analogy makes it easier to comprehend the phenomenon of the differentiation and development of an embryo's cells.

If we approach the issue from the stand of supramolecular thermodynamics, a question would arise: are the seemingly minor changes in the biomass micro-volume during embryonic development sufficient for affecting the thermodynamic direction of differentiation and development? The answer is clear: quite sufficient. Numerous facts described in manuals and monographs confirm this opinion. Thus, insignificant temperature fluctuations can produce a noticeable change in the morphological structure of tissue, because kinetically independent particles (along with low-molecular ones) are, here, constituted by enormous supramolecular formations. Their rearrangement or redistribution in the system is easy to see with a naked eye. It is clear that minor temperature changes (around several hundredth of a degree) can significantly affect the transformation of the gene structure. What is more, they can substantially change the rate of synthesis of individual enzymic processes due to their high energy of activation.

Insignificant fluctuations of PH and the concentration of various substances are also known to affect the functioning of genes (chromatin). The differences in PH can be determined by the location of dividing cells.

Having appeared "in a place of its own," each new cell finds itself surrounded by other cells in physiological (intercellular) liquid. The other (previously formed) cells and the physiological environment are the habitat (thermostat in the physical sense of this term) of the new cell. According to the parameters of the habitat, the cell's genetic apparatus is "transformed": only certain genes go into action. Another division follows, and the new cells receive a new command from its thermostat, etc.

Each cell (chromatin) micro-local volume (i) has "thermodynamics of its own" determined by the trend of $\Delta\overline{\widetilde{G}}_i^{im}$ towards minimum. The local micro-volume must contain a sufficient number of particles (low-molecular substances and kinetically independent fragments of supramolecular structures) to make the laws of statistics and, correspondingly, the second law of thermodynamics applicable.

Since thermodynamic laws operate in each local micro-volume, correlation (2) is applicable to any tissue macro-fragment.

Individual facts

Examples that confirm the possibility of regulating gene activity under changes in their environment include the studies of chromatin transformation under the impact of chemical agents and physicochemical factors [14, 28]. Even insignificant fluctuations of chromatin's environmental parameters result in its observable changes. Heterochromatinization of chromosomes is observed in ontogenesis and is a fact that determines an organism's aging (development) [14, 28].

Convincing proof of the influence of the cell membranes' structural component, lipids, on gene transcription is provided by numerous experimental studies [19]. It has been proved absolutely that lipids perform an important role not only in signal transduction and intercellular transport, but also in gene transcription. Since living organisms (their biotissues) quickly adapt to the character of fats and oils used as food [27], it is clear that the character of nutrition affects the work of the genetic apparatus. Such effect can, in principle, result not only in the transformation of the work of the genetic apparatus but also gradually fix individual genetic characters. The latter accords with the existence of feedback between the biostructures in different hierarchies [7, 8, 24-26].

A well-known example is animals changing their coloring with a change of the environment's background coloring. Some rodents' changing their fur color at insignificant temperature changes (around 1°C) have been described.

The optimal rate of the germination of seeds of some plants also frequently lies within the 1°C range of temperature fluctuations. A commonly known fact is the effect of insignificant temperature changes upon the function of testes in animals and humans. All this confirms the high sensitivity of genes to the changes in the parameters of their intracellular environment and the environment of cells and organisms.

There is no doubt that all phases of the process of embryonic development are governed by thermodynamics. Thus, the "mitoticspinalle" model viewed as a self-made machine can be presented as a series of consecutive stages of structure formation. The implementation of each of these stages can, without question, be regarded as a process directed towards a decrease of $\Delta\widetilde{\overline{G}}_i^{im}$ in each local zone of the developing structure. Unfortunately, many researchers continue to believe that "the biochemical and physical principles that govern the assembly of this machine are still unclear. However, accumulated discoveries indicate that chromosomes play a key role"[28]. It would, of course, be interesting to examine the stages of the functioning of the self-made machine using the DSC method and others.

There is reason to believe that the genome of embryonic stem cells retains totipotency, the ability to choose an appropriate development program [17], which, in my view, is determined by the functioning of genes through the "mechanism" of thermodynamic demand. It has been established that there exist totipotency proteins that help preserve the special structure (conformation) of chromatin. It is also believed that the design of a future organism is written down in the totipotent cells in the language of mRNA.

It is known that supramolecular structures are often formed without direct participation of, for example, the structures of nucleic acids and proteins. Thus, the "protein - RNA interactions are mediated by the specific recognition of widened major groove and the tetraloop without any direct protein-base contacts and include a complex network of highly ordered water molecules" [37]. This confirms yet again the need to study the changes in the specific averaged values of thermodynamic potentials (functions) within the framework of supramolecular thermodynamics. The latter's action should extend to all types of supramolecular structures interacting in a living organism. Proof of this are the numerous proven facts studied by information biology and medicine. A number of physically substantiated examples can be found, for instance, in the monograph [10] and the work [35].

In my view, both the information theory and supramolecular thermodynamics support the theory of Poitevin [31]. He believes that an organism is a sum of interacting systems that exchange information in the course of rhythmic action. A special place is allocated to electrical and chemical signals. The organism is treated as a generalized information exchange system. In such a living system, the distinctions between the brain and the other parts of the organism are disappeared (no "distinction between mind and body"). This point of view corroborates the theory on the establishment of partial chemical and supramolecular equilibrium in the organism and the helpfulness of studying the summary variation of the chemical composition of both individual tissues and the organism at large [2, 3, 22]. As the author wrote in his earlier works, such variation is a consequence of the thermodynamic direction of the evolution of supramolecular structures, as well as the higher hierarchical levels of the biological world.

The environment also determines behavioral reactions at the level of organisms and populations. Operating here, however, are not only physicochemical factors but also all the parameters of the thermostats of complex thermodynamic systems. In human societies, human behavior is also affected (apart from the known material factors) by the parameters of Popper's 3rd world [32].

Although my conclusions are general, they show that there are no principle contradictions between known facts and the conclusions of supramolecular thermodynamics

on the trend of differentiation processes. It follows that this trend is determined by "thermodynamic demand" for genes on the part of the environment (structures of higher hierarchies), which stimulates (induces and represses) the genes' directed functioning.

Thus, the overall potential program of cell differentiation is contained in genes. However, this program is transformed (corrected) under the impact of the environment. It is determined by the parameters of the environment (the medium) of the genes themselves.

Thus, the thermodynamic model of cell differentiation and the behavior of organisms, populations, and higher structures of the biological world does not, of course, make it possible to draw conclusions regarding the mechanisms of processes. But it can help identify their direction and degree of completion. Awareness of the thermodynamic (thermostatic) aspects of the development of open biological systems can be useful for comprehending the phenomenon of life within the framework of general laws of nature.

References

1. Александров В.Я. Клетки, макромолекулы и температура. Л.: Наука, 1975. 330 с.
2. Гладышев Г.П. Термодинамика и макрокинетика природных иерархических процессов. М: Наука, 1988. 287 с.
3. Гладышев Г.П. Термодинамическая теория эволюции живых существ. М: Луч, 1996. 86с.
4. Гладышев Г.П. Супрамолекулярная термодинамика генов и старение // Успехи геронтол. 1999. Вып. 3. С. 63-65.
5. Гладышев Г.П. Способ измерения геронтологической ценности биоактивных веществ и композиций, преимущественно пищевых и косметических продуктов. Патент РФ, RU 2147370, Российское агентство по патентам и товарным знакам. 29.06.1999; 10.04.2000. Бюл. № 10.
6. Гладышев Г.П. Термодинамическая теория старения выявляет причины старения и смерти с позиций общих законов природы // Успехи геронтологии. 2001. Вып. 7. С. 42-45.
7. Гладышев Г.П. Супрамолекулярная термодинамика – ключ к осознанию явления жизни. Что такое жизнь с точки зрения физико-химика //В сб. Наука и фигурное катание. М.: Фонд им. М.Ю.Лермонтова, 2002. http://www.endeav.org/evolut .
8. Гладышев Г.П. О принципе стабильности вещества и обратных термодинамических связях в иерархических системах биомира //Изв. РАН. Сер. биол. 2002. № 1. С. 5-9.

9. Грин Н., Стаут У, Тейлор Д. Биология. В 3-х т. М.: Мир, 1993. Т. 3. С. 221.
10. Зилов В.Г., Судаков К.В., Эпштейн О.И. Элементы информационной биологии и медицина. М.: МГУЛ, -2000. - 248 с.
11. Иоффе Д.В. Жиры животные. Химическая энциклопедия. М.: Сов. Энциклопедия, 1990. Т. 2. С. 306-309.
12. Кантор Ч., Шиммел П. Биофизическая химия. В 3-х т. М.: Мир, 1984, 1985.Т. 1. 336 с. Т. 2. 493 с. Т. 3, 534 с.
13. Киселев А.В., Пошкус Д.П., Яшин Я.И. Молекулярные основы адсорбционной хроматографии. М.: Химия, 1986. 272 с.
14. Лежава Т.А. Функциональные особенности хромосом человека и старение // Успехи геронтол. 2001. Вып. 8. С. 34-43.
15. Паронян В.Х. Растительные масла. Химическая энциклопедия. М.: Сов. Энциклопедия, 1995. Т. 4. С. 376-383.
16. Никитин В.Н., Перский Е.Э., Утевская Л.А. Возрастная и эволюционная биохимия коллагеновых структур. Киев: Наук. Думка. 1977. 280 С.
17. Репин В.С. Стволовые клетки и старение: идеи и реальность // Клиническая геронтол. 2001. Т. 7, № 12. С. 9-36.
18. Франк-Каменецкий М.Д., Карапетян А.Т. Молекулярная биология. 1972. Т. 6. С. 621-627.
19. Chong L., Marx J. Lipid Biology, Lipids in Limelight // Science. - 30 November 2001. V. 294. P. 1861-1885.
20. Flory P. Principles of Polymers Chemistry. Ithaca. New York. Cornell University Press, 1953.
21. Food, Nutrition and the Prevention of Cancer: a Global Perspective. World Cancer Research Fund. // American Institute for Cancer Research. 1759. R.St. NW Washington, DC 20009. ISBN: 1 899533 05 2. 1997. P. 670.
22. Gladyshev G.P. On the Thermodynamics of Biological Evolution // J.Theoret.Biol. 1978. V. 75. P. 425-441.
23. Gladyshev G.P. Thermodynamics of Aging // Biology Bull. 1998. V. 25. № 5. P. 433-441.
24. Gladyshev G.P. The Hierarchical Equilibrium Thermodynamics of Living Systems in Action, 17th IUPAC Conference on Chemical Thermodynamics, Rostock, Germany. 2002. AsCt02-340.
25. Gladyshev G.P. Thermodynamics of Biological Evolution and Aging //Advances in Gerontol. 2002. V. 9.

26. Gladyshev G.P. Thermodynamics of Biological Evolution and Aging // Electron. J. Math. Phys. Sci. 2002. Sem. 2. P. 1-15. USA. www.ejmaps.org .
27. Goodnight S.H. The Fish Oil Puzzle // Science & Medicine. - September/October. 1996. P. 42-51.
28. Karsenti E., Vernus I. The Mitotic Spindle: A Self-Made Machine // Science. 19 October 2001. V. 294. P. 543-547.
29. Lezhava T. Chrosome and Aging: Genetic Conception of Aging // Biogerontology. 2001. № 2. C. 253-260.
30. Olshansky S.J., Hayflick L., Cames B. No Truth to the Fountain of Youth //Essay. Scientific American. June 2002. P. 78-81.
31. Poitevin B. Mechanism of Action of Homeopathic Medicines // Brit. Homeopath. J. 1995. V. 84. No 2. P. 102-107.
32. Popper Karl R. Evolutionary Epistemology //Evolut. Theory: Path into the Future /Ed. Y J.W.Pollard. John Wiley & Sons, Chichester and New York. 1984. ch. 10. P. 239-255.
33. Preventing Cancer Worldwide. Science News. World Cancer Research Fund International. Issue 32. February 2002. www.wcrf.org .
34. Rigby B.J. The Thermal Stability of Collagen: Its Significance in Biology and Physiology //Chem. Dynamics. 1971. No 4. P. 537.
35. Tchuraev R.N. On Storing, Coding, Passing and Processing the Hereditary information in Living Systems // Computational Technologies. 2000. V. 5. Special Issue. P. 100-111.
36. Thomas A. Fats and Fatty Oils. Weinheim: Ullmann's Encyclopedia of Industrial Chemistry. VCH. 1987. V. A10. P. 173.
37. Wild K., Sinning I., Cusack S. Crystal Structure of an Early Protein. RNA Assembly Complex of the Signal Recognition Particle // Science. 19 October 2001. V. 294. P. 598-601.