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The Self-regulation of Metabolism, taking into Account the Optimal Regulation and the Energetics of the Processes

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Abstract: *In this study the metabolic network of cell energetics are investigated as a self-regulating system, the control which is described with non-classical variation method - the Bellman's equation (also known as a dynamic programming equation), on the basis of the thermodynamics of irreversible processes and the kinetics of the biochemical reactions.*

Keywords: *Metabolic network, Thermodynamics of irreversible processes, Self-regulating system, Dynamic programming.*

Introduction

In a series of works [4, 5, 13, 14], an attempt was made to investigate the metabolic network and its self-regulation, on the basis of a model constructed on the cell energetics, from the point of view of the thermodynamics of irreversible processes and the kinetics of the biochemical reactions, examined as a self-regulating system, the control which is based on the non-classical variation methods. The properties of the entity in the transitory state after the disturbance of the steady state have been examined. The main conclusion that was drawn subordinated the free energy to the system of Bellman's equation of dynamic programming [1, 9]:

$$dG/dt = -\min\sum[(\partial G/\partial x_j)(dx_j/dt)]. \qquad (1)$$

In the course of the discussion of the relationship found, the necessity to answer the following question was felt: “What is the place of the above-mentioned relationship in the thermodynamic terminology applied to biology?” It is obvious, that the expression (1) contains something more than a quantitative characteristic of a thermodynamic quantity. In particular, the formulation of an equation by the non-classical calculus of variations gives us the right to assert that the processes of the living entities are an object of cybernetics (and, more specifically: of optimal control methods).

The present work is an attempt to make an accurate evaluation of the result (1), by way of more general considerations than those that helped for its finding.

Entity characteristics

We shall begin with the thermodynamic characteristic. The living system can exist only by a continuous exchange of materials and energy with the environment, i.e., it is an open system.

As Passinsky [10] has stressed, the majority of the cell processes are irreversible and because of the interdependence among all processes, irreversibility is a non-ignorable feature of the system. At first sight, the two characteristics mentioned above require the application of the thermodynamics of irreversible processes. There are, however, a considerable number of works [10, 15, 17] showing that the state away of equilibrium is inherent to the processes in the biological entities. This is sufficient to preclude that the thermodynamic analysis of the entity, as the theory of irreversible processes, does not yet surpass the frames of Onsager's ratios, furthermore, a purely thermodynamic characteristic is insufficient also because of the fact that thermodynamics do not investigate the mechanism of the processes and for this reason cannot explain by itself the specific peculiarity of the biological processes. Consequently, the quantitative characteristics of the thermodynamic quantities that will be used have to submit to the rule not to depend on their distance from the equilibrium of the system. There is a class of thermodynamic quantities – thermodynamic potentials – which are very suitable for the description of the development of the system, due to their strict orientation regardless of their distance from the point of equilibrium. Of the quantities indicated, entropy is undoubtedly the most appropriate. The use of entropy and free energy, for example, is not equivalent – entropy is more general to the effect that it gives us the possibility to interpret not only the degree of energy degradation but, as we shall see, it describes the properties of organization [11].

Entity characteristics from the point of view of the theory of systems (cybernetic characteristics)

The analytical approach in metabolism investigations [7, 16] led to the accumulation of an enormous amount of experimental material for the different reactions and raised the question of the examination of the interactions between the various reactions. The qualitative, examination led do the concept of a metabolic network [7]. The discovery of the feedback mechanism in biology was the prerequisite for the treatment of this metabolic network, as a system strictly coordinated in space and time, where the disturbance of one link results inevitably in general functional disturbances [17]. The optimum state of functioning at given conditions is determined experimentally [10, 17].

During the last decades, with the investigation of protein functions the thought of an important property – teleonomy has been growing spontaneously [8, 12]. The discovery of the genetic code put this concept on a scientific basis. The availability of feedback and the coding of the information in the gene make the organisms controllable self-regulating entities and become the theoretical prerequisite for the investigation of cell processes, using the methods of cybernetics (of optimal control).

The processes of control are possible only as a result of the transmission and transformation of the respective information. This concept scientifically derived concept is strictly quantitative in nature. It is related to the concept of informational entropy – a measure for disorganization. The change of informational entropy is inversely proportional to the change of information contained in the system. Such an alteration of the informational entropy always appears as an indicator of substantial changes in the organization of the system and its structure. We have, therefore, a quantitative characteristic for the most important feature of our entity – the controllable organization (for instance, the synthesis of macromolecules – bodies arranged in space in a strict order).

So, the quantities necessary for a full qualitative and quantitative characteristic of the entity are the two entropies – the thermodynamic and the informational one [18].

The most general definition of Gibbs of the entropy of unbalanced states is:

$$S_T = -k \ln \varpi^*, \qquad (2)$$

where

$$\varpi^* = \varpi(X, t) = \int g(X - Y)\, \varpi(Y, t) dY. \qquad (3)$$

The transition from the determination of the entropy for the balanced state to that for the unbalanced state is related to the determination of the probability density for unbalanced state. The distribution of the probabilities for the unbalanced state differs from the balanced distribution, by the fact that it requires additional parameters, i.e., more precise knowledge of the quantities determining the system. The above-mentioned will be corroborated in (4) by fixing the time t, i.e., ϖ^* is transformed into function only of X:

$$\varpi^* = \varpi(X). \qquad (4)$$

We assume that for a system of measurements we are given full knowledge of the quantity $\Phi(X) = \Phi$, while for all the others that supplement Φ to a complete set of quantities necessary for the system, we chose to have only the statistical averages for a balanced ensemble of values – $\varpi_0(X)$. Then, the unbalanced probability density may be represented as

$$\varpi_\Phi(X) = \varpi_0(X)(\delta(\Phi - \Phi(X))/W(\Phi)). \qquad (5)$$

Here $W(\Phi)$ is the probability density $\Phi(X)$ to have a value of Φ.

If, however, the quantity Φ is not known exactly, but with some probability density of $g(\Phi)$ then, instead of (5), we have

$$\varpi_{g(\Phi)}(X) = \int g(\Phi) \varpi_\Phi(X) d\Phi = \varpi_0(X)(g(\Phi(X))/ W(\Phi)) \qquad (6)$$

Obviously, the expressions (5) and (6) $\varpi_0(X)$ and $\varpi_{g(\Phi)}(X)$ coincide only in the case when $g(\Phi) \equiv W(\Phi)$ i.e., we have no additional information about the quantity $\Phi(X)$ except those that we have for a system in equilibrium. In this way, the unbalanced systems contain more information about the system than the balanced ones. But, to an unbalanced ensemble always corresponds lesser entropy (in a thermodynamic sense), than to the balanced one. Consequently, the greater the thermodynamic entropy of a system, the less our information is about it, i.e., the larger is the quantitative measure of informational entropy. Recently, instead of entropy in the theory of information wide popularity enjoys the measure of negentropy H, determined by Leon Brillouin [3] by means of

$$H = -S \qquad (7)$$

Then, greater information corresponds to a larger value of H.

Thus, we proved that to thermodynamic entropy corresponds a definite amount of information of the system, i.e. definite informational entropy. Now, let us prove the same correspondence.

In the information theory, for a maximum possible amount of information about a quantity transmitted through a given system, we have the expression:

$$I_\phi = k\{\int[\ln \varpi_\phi(X)]\,\varpi_\phi(X)dX - \int[\ln\ \varpi_0(X)]\,\varpi_0(X)dX\}, \qquad (8)$$

whose second member reflects the so-called noise, accepted as a balanced state caused by the fluctuations.

The expression (8) might be given a simpler form

$$I_\phi = (-S_\phi) - (S_0) = S_0 - S_\phi \qquad (9)$$

It is obvious from (9) that $I_\phi \sim \Delta S = S_0 - S_\phi$, i.e., at a fixed noise S_0, I_ϕ is a minimum when $S_\phi = S_0$, i.e., S_ϕ has a maximum in the equilibrium state caused by the fluctuations. This condition, as well as the fact that the fluctuations fixing the level of S_0 are thermal in all informational systems without exception, together with the first proof adduced ***enable us to investigate on the one hand the energy characteristics of our entity, and on the other, the structural and organizational aspects, characterizing it as a cybernetic system with one and the same quantity – entropy.***

It is interesting to note, that the viewpoint expressed on the problem of equivalence between the informational and the thermodynamic entropies is prevailing nowadays [2, 6]. Brillouin [3], for instance, through considerations differing fundamentally from those quoted here, has reached the conclusion that the averaged value of H has all the properties ascribed to entropy in thermodynamics. This conclusion by itself is sufficient for us because of the macroscopicity, the poly-atomic nature of the organism. In a system consisting of a small number of particles the static fluctuations would destroy any organization.

Let us discuss more thoroughly the physical content of the result achieved. We pointed out above that only a thermodynamic analysis of the living systems is not sufficient. The processes in the organism are controllable and each parameter, including the thermodynamic one, must take into account this condition. We pointed to S_T as the most general thermodynamic characteristic; analogically to the organization to which are subjected the energy transformations – S_i. A qualitative description of the organization, the arrangement in space and time is the characteristic of S_i. Besides, in our case the term organization includes both the strict coordination of the cell processes and the presence of arranged structures – macromolecules. On its part, S_T is a characteristic of the energy transformations of the same processes. The equivalence between the two entropies (i.e., the so-called entropy of Bolzman-Shennon) is, therefore, a characteristic sufficient for the cell analysis with both necessary conditions taken into account.

After the achievement of this result, we would like to determine the cell processes from the point of view of their quantitative evaluation through entropy. The most general definition would be that they are chemical reactions and material transfer (active and passive transfer). Both proceed along the two possible ways of realization – with an increase or decrease of entropy. For the active transfer, in particular, this means that there is a material flux against the concentration gradient. Without limiting the general validity we may formally reduce the transfer to a pseudo-chemical reaction, being interested, furthermore, in the entropy effect of the processes. Then, for all processes we have the possibility of introducing the same quantities, for example the set:

A – chemical affinity,

μ – chemical potential,

v – rate of reaction,

as well as relations between these quantities, relating them to S of the chemical thermodynamics, while, naturally, keeping in mind the mandatory condition to use them only for those for which the distance from the equilibrium is of no importance.

Until recently it was assumed that the organisms incessantly create arranged structures [15]. Passinsky [10] specified that the organisms derive from the environment not arrangement, but free energy. There are no mechanisms in metabolism that give the possibility to the organism to utilize the arrangement alteration in the transformation of the high-molecular compounds into low-molecular ones.

On the basis of the above-said the generalized set of chemical reactions in the cell may be divided in two classes. On the one hand, those are the energy releasing reactions (as well as all other processes proceeding in accordance with their chemical affinity A). On the other hand, the reactions of the synthesis of macromolecules, or more generally, all reactions proceeding against their chemical affinity. It is accepted that they should be called conjugated reactions, as their existence on their own is impossible – it would contradict the second thermodynamic principle.

We can find the exact quantitative expression for the alteration of the entropy by connecting the entropy and the characteristics of a chemical reaction:

$$Td_iS/dt = Av \qquad (10)$$

Since we have already mentioned that the entropy balance of the system is related to two types of processes of which the first increases the entropy, while the others decrease it, we have for the whole generalized system:

$$Td_iS/dt = \sum_{\rho=1}^{k} A_\rho v_\rho - \sum_{\rho=k+1}^{n} A_\rho v_\rho \geq 0 \qquad (11)$$

To expression (11), that repudiates only the entropy alterations resulting from the generalized chemical processes, we must put in also the entropy alterations resulting from the annihilation (at the time of the destruction) and the creation (at the synthesis) of the macromolecules and the stabilization of the metabolic organization after the disturbance, i.e., the full effect will be:

$$Td_iS/dt = \left(\sum_{\rho=1}^{k} A_\rho v_\rho + S_1\right) - \left(\sum_{\rho=k+1}^{n} A_\rho v_\rho + S_2\right) > 0 \qquad (12)$$

In a transitory process to a steady state S_1 and S_2 are naturally quantities changing with time.

The ratio $|A|/RT >> 1$ is valid for the sum $\sum_{\rho=1}^{k} A_\rho v_\rho$ in (11) as a totality, which is sufficient to allow us to apply to it Prigogine's theorem [11]. Thus, in the steady state $Td_iS'/dt = \sum_{\rho=1}^{k} A_\rho v_\rho$ is minimum.

Let us now examine the system without the conjugated reactions. Then, the dissipation of free energy is maximal. With the inclusion of the conjugated reactions, the system begins to organize itself functionally. The optimum organization is reached in a steady state [5, 10], i.e., the sum $\sum_{\rho=k+1}^{n} A_\rho v_\rho$ reaches its maximum there.

Consequently, in a steady state we have:

$$Td_iS/dt = \min \sum_{\rho=1}^{k} A_\rho v_\rho + S_3. \tag{13}$$

As $dx_j/dt = \sum \upsilon_{j\rho} v_\rho$ then (13) is converted into

$$Td_iS/dt = -\min\sum(d_ix_j/dt)\mu_j + S_3. \tag{14}$$

The full entropy alteration with time is given for open systems [11, 17] by:

$$dS/dt = d_iS/dt + d_eS/dt, \tag{15}$$

i.e.

$$TdS/dt = -\left(\sum(d_ex_j/dt)\mu_j + \sum(d_ix_j/dt)\mu_j\right) + S_3 \tag{16}$$

Here, the first sum designates the alteration of the entropy of the environment as a result of processes relevant to our entity.

For a steady state

$$TdS/dt = -\left(\sum(d_ex_j/dt)\mu_j + \sum(d_ix_j/dt)\mu_j\right) + S_3 = 0, \tag{17}$$

the first member characterizes the exchange of the entropy with the environment through metabolism. It depends directly on time, i.e.

$$dS_e/dt = -1/T\sum(d_ex_j/dt)\mu_j \tag{18}$$

Then, with respect to (14), (17) and (18) we get

$$dS/dt = \min[1/T\sum(d_ix_j/dt)\mu_j] + S_3. \tag{19}$$

This dependence is analogical to Bellman's equation of dynamic programming [9].

It is immediately seen that the equation written at the beginning (1) is a special case of (19). If we are interested in the free energy of the system, which is a factor reflecting only the generalized chemical processes, then, from the relations

$$Td_iS/dt = -d_iG/dt \tag{20}$$

and

$$\mu_j = (\partial G/\partial x_j)_{\rho T} \tag{21}$$

from (19) we have (with $S_3 = 0$):

$$dG/dt = -\min\{\sum[(\partial G/\partial x_j(d_i x_j/dt)]\} \tag{22}$$

The dependence (19) derived cannot be interpreted only from the standpoint of thermodynamics. It subjects the processes in the transitory state to a definite dependence on the mathematical apparatus of the optimal processes, i.e., to a proceeding along trajectories determined by the requirement of a minimum for *dS/dt*. Consequently, for the transition towards a steady state (and in itself too) on account of the genetically predetermined set of reactions, the element statisticity, giving only an interpretation of entropy in thermodynamics, cedes place to optimal control, i.e., to motion on a definite course. From the theorems of equivalence which we proved, it follows that the negentropy of the system becomes higher and higher. The corollary (22) concerning a purely thermodynamic quantity *G*, also permits us to make a well-grounded assertion in the sense that for the mathematical apparatus describing the development of a similar parameter, a variation method should be applied. The entropy of Bolzman-Shennon gives a strictly divided criterion for the difference between inorganic and living nature. The former is characterized by its stay in the most probable for it chaotic (i.e., equilibrium) state, with possibilities for statistical interpretation of the determining macroparameters. On the contrary, living nature is characterized by a state of unbalance connected to the information weight increase, i.e., with a reduction of statisticity. Expression (19) speaks unambiguously in favour of that. ***And more than that – it characterizes the living system as a final case of the informational system – a system whose processes are optimized.*** Consequently, the statistical thermodynamics cannot be applied to the quantitative evaluation of the development of the thermodynamic quantities for the entire entity without entailing a considerable error.

In this sense, we think that in view of the thermodynamic analysis of metabolism as a complete system it is necessary to form non-statistical (phenomenological) thermodynamics, whose mathematical apparatus describes ***the entity as controllable***. In particular, the non-classical calculus of variations could be such an apparatus.

We interpret expression (22) together with the first principle of thermodynamics as a possible basis of such a theory.

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