THERMODYNAMICAL METHOD IN BIOLOGY

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The author of this paper has been studying the thermodynamics of transient phenomena and the results are summarized in his work and dissertation.[1] He has endeavoured to apply his idea to the problem of biophysics.[2]

I. *On the Method of Biophysics*

If we take account of the world consisted of living materials and their surroundings, the Gibbs' free energy of the world must undoubtedly be decreased. Therefore there must be no fear of the inapplicability of thermodynamical principle. There is, however, some necessity of considering the part of the world to the thermodynamical study of life and then we must stand for the confusing nature of the world which comes from the thermodynamical interaction of *very long range*.[3] (The interaction is presented by μ-field of III).

On the other hand, such an interaction is the most interesting feature which is called *cooperative* and considered as the key to solve the mystery of life. For instance, if there is a droplet of water suspending in its supersaturated vapour, then the whole system can no longer stay in its metastable equilibrium state (see section (ii) of III).

Let us now consider virus or such an ambigous material. These materials constitute a part of the world of living material, "fauna and flora," consuming the chemical free energy of the surroundings and have a distinguished character from lifeless matter like inorganic substance or pure protein.[4]

From the thermodynamical point of view, what is explained above is the *criterion*, whether virus is a sort of lifeless substance or not. The *definition of life* might be also considered from this point.

The characteristic nature of the theory of thermodynamics is a large scale

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[1] "Thermodynamik der nicht reversiblen Erscheinungen," *Proc. Phys. Math. Soc. Japan 3*, Vol. **15** (1933), p. 12; *Neturikigaku Sinkō* (New Lecture on Thermodynamics), Tokyo, 1942; *Thermodynamics of Transient Phenoemena* (in Japanese, Tokyo, 1950, Dissetation sent to Kyoto University).

[2] The greater part of this paper is written in Japanese in *Seibutu Kagaku*, Vol. **2**, No. 1 (1950).

[3] This *cooperativeness* is the keen contrast to the dynamical system in which we can consider a part or a material point of mass m isolated from other part and the correlations are substituted by force f expressed by the equation of motion $f=ma$ where a is the acceleration. However, f is not of such a *long range nature* as the thermodynamical interaction.

[4] See section (v) of VI.

net-work of logics enclosing the whole world. We can not forget the importance of this methodological point.

On the other hand, if we extract the characteristic point of the living system by the *method of induction* and if we apply it to virus, then the *criterion* might meet some difficulties. It would not be correct from the methodological point, either, to discuss the definition of life in such an *inductive manner.*

In some individual system the character of the total system is seen approximately near and in such case the inductive method is no longer inadequate. In general, however, such a *narrow way of thinking* like induction is very dangerous. The thermodynamical consideration will make clear the methodological point.

II. *The Theory of Transient Phenomena*

The process of decreasing of free energy G of the world containing the lives is the *transient phenomena* describing the part of the history of the earth.

In the natural science the *reproducibility* is in general recognized but even in the simple case of crystal-formation the initial period is different from the final period and the state of the initial period is no more reproducible in the course of that experiment.

The phenomena of life is an experiment of nature continuing for billions of years from its origination to the future from the thermodynamical point of view. If we want to reproduce, we must wait for the origination of a new solar system and reproduce the history of the earth, although it will take inestimable years. The specialty of the phenomena of life is such an extraordinary character with the long range character of mutual action. Therefore we must take as well the *total system of animate world* into account as the *total history of the world* and not individually.

But in some case we can find the special nature of life, that of total history by observing only the period of an *individual life* which is considered as a period of *relaxation oscillation* of the total system. (For instance, in the evolution of individual the evolution of the system is repeated). What is relaxation oscillation will be described later. On the other hand, if we conclude inversely the *nature of the total period* from the observation of a period of life, which is the section of long history of lives, by induction, then such a *mechanical method* is very dangerous.

Instances of the *relaxation oscillation* proposed by van der Pol are cell division, evolution and death and also our life itself, if we translate it to the word of thermodynamics. The evolution of lives itself, which is an ensemble of individuals, is under mutual cooperating action, and also a sample of this oscillation. Therefore, there occured many times jump-like evolutions.

Further the *functional form of relaxation oscillation* is different from sinusoidal curve so that it is dangerous to estimate the nature of total development from the observation of only a limited period of time (see section (v) of III).

For instance, the *intermediate substance* between animate and lifeless material might have been able to exist in the early stage but in these days the living materials have already been developed in such a way as to adapt the present stage and cooperative to the whole system even though taking the simplest form. Therefore such an intermediate material cannot be found if we want to find the *bridge* between two worlds, and there exists a deep chasm. Nevertheless such a deep chasm does not hinder the relation between biology and physics or chemistry. The bridge connecting the two domains may easily be found by thermodynamics. On the other hand, it is dangerous to unify the domains mechanically or by the method of simple induction.

III. *The Field of Chemical Potential*

The living system is composed of atoms, ions and molecules as well as lifeless substances and there can be seen complicated chemical composition, decomposition and diffusion of matter. In the transient phenomena of lifeless system we consider the *field of chemical potential* conducting these physical and chemical reactions. My consideration[1] on this matter how to formulate the molecular statistics and to define the chemical potential in transient phenomena will be described later. We will suppose here that *the fields conducting these reactions as well as in the living system as in the lifeless system are both the field of ch. p.* (chemical potential).

Whether the field in the living system has the same thermodynamical nature with that in the lifeless system or not is a question. On this question we will, however, confess some *affirmative* reason.

(1) The chemical reaction in the body which has lost its life must be conducted by the ordinary ch. p. On the other hand, the reactions before the death was conducted by the field of biological ch. p. Then whether there occurred an *abrupt change* of chemical potential or not is a question from the thermodynamical point of view.

(2) We know the *reversal of the field* when a snow-flake is in its period of growth or of destruction. The *abrupt-like* change considered above might be such a reversal described in section (v).

(3) On the other hand, the atoms and molecules are moving in the *phase space* and the living system must have its position in the space as a *molecular aggregation* although they are a very complicated one. Therefore we can consider the field in both system from the point of *molecular statistics.* Further, there might be nothing inadequate but a benefit in considering common nature of the field if the thermodynamics are applied only *correctly.*

Many biologists have asked me how to calculate the ch. p. in the living system. It is, however, a matter of biology, and thermodynamics is really indifferent to such a detailed calculation. On the other hand, the *quantitative* calculation of such a function from the point of molecular statistics is very difficult and quite powerless for such a complicated case (see (6.15′) of VI).

Qualitatively the idea of ch. p. is, however, a very powerful weapon of thermodynamics and molecular statistics of transient phenomena and we have good reason to recommend the application of this idea to the study of biology. Therefore, let us illustrate the interesting properties and the way of application of this idea.

(i) The field has a character with *very long range interaction* as it is seen, for instance, in the case of crystal formation. The disturbance in cooperative phenomena might be recovered by this field. The *totality of living system* might be also explained by this *cooperative character* of the field.

(ii) If we adopt the method of μ-field (μ means ch. p. of reacting or diffusing substance), the *quasithermodynamical treatment*[1] *of inhomogeneous colloidal system as well as transient phenomena* can now be possible, which was formerly thought impossible.

(iii) The development of beautiful and curious form of some crystal composed of simple molecules or even atoms, can be explained by *mutual induction of the μ-field and the development.* That is, the development may be conducted by the field and the development induces the field to its surrounding so that the crystal develops like a rolling snow-ball by this mutual induction. The theory of predestination by biologists might be critisized from this point of view.

(iv) The crystallit of curious snow-flake must have extraordinary *large free energy* or *small entropy* corresponding to its curious form. Therefore, we can now explain the *negative increase of entropy* of small part in the system in transient state.

(v) The *field of development* of such a crystal under enough supply of vapour molocule will disappear and unstable equilibrium of vapour and crystallit might be seen, if the vapour supply becomes poor. And then the field *reverses* its sense and it will become the *field of destruction,* if the supersaturation of the surrounding vapour disappears.

Such a *reversal* can be considered as one of the causes of *relaxation oscillation.* We have also suspected that such a reversal might be seen before and after death of a system (see section (iii) of VI).

(vi) We can avoid the *paradox* which is inevitable if we do not comprehend the theory of *rate process.* The *reaction velocity might depend on this field* describing how far the system is apart from the equilibrium, for the field must disappear when the system is in its equilibrium. Let us call the field the *circumstance of the equilibrium theory* which depends on the *thermodynamical quantity.* But there are many paradoxical facts that the reaction is not intense though the system is very apart from the equilibrium.

They say that there must be large *resistance* for the reaction and the velocity depends on the field strength as well as on the resistance.[5] Therefore, the *process of weaker field occurs priorily*, if the resistance of this process is much smaller, and in this case *paradoxical aspect* may be seen.

Let us call the largeness of resistance the *circumstance of the theory of rate process*, and this circumstance can not be considered thermodynamically. We must distinguish two circumstances in the theory of transient phenomena; and if we confuse these, we must meet the *paradox* which is very dangerous for biology.

(vii) The nature of metastability, false equilibrium, and of the relaxation phenomena becomes clear if we recognize the theory of rate process.[1]

(viii) This field cannot be seen by the naked eyes of an observer. It can only be perceived by statistical observation of *certain long interval.* The length of this interval is a very important quantity and the so-called *time of relaxation* is an instance of such an interval.

For instance, let us consider Langevin's equation of Brownian movement, which can be written in the form

$$Kv = -\, grad\mu \qquad (3.1)$$

where v is the mean velocity of diffusing particle, Kv is the resistance and μ the chemical potential of the particle. Such a velocity v and the field, grad μ, can no longer be perceived by direct observation. It asserts that the centre of Brownian movement of the particle is drived statistically by the field. Detailed consideration of this time interval will be stated later.

The field represents the *necessity running through the individual contingencies*. Therefore we might see the *field of evolution* statistically and also the *field of origination* when there was nothing on the earth. The latter is similar to that of nuclear formation in metastable state (Keimbildungsfeld).

(ix) The nature of semi-permeability and specialty of biochemical processes can be explained qualitatively by our method.

IV. *Negative Increase of Entropy*

In the case of snow formation it is said that the greater the supersaturation, the more complicated form the crystallit takes, in order to increase the *rate of disappearance* of supersaturation.

In spite of the largeness of free energy of each crystallit, the rate of decreasing of free energy of the *total system* composed of crystallits and the surrounding is accelerated by the snow-flakes.

This circumstance is described as *mutual induction* like a snow-ball rolling down a slope if we adopt the explanation (iii) of III.

In other words, it may be said that the crystallit acts like the *autocatalizer.*

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[5] Jouguet, *Ann. de physique*, **5** (1926), 5; see foot note 16 and (6.7) of VI.

That is, the surface of the crystallit play a role of passage for the colliding molecules to be carried to each nib, where they deposit. The supersaturation stabilizes itself temporarily through an *instability* which speedily takes away the chemical stress of total free energy. The formation of such an unstable form with small entropy might be seen *purposely* by the observer with naive eyes.

Our body is composed of complicated molecules with delicate behaviour like enzyme, hormone and others and such molecules take so delicate an arrangement that the free energy of such a system must be very large.

But the larger the free energy of such a system is the larger may be the *catalytic action* accelerating the consumption of free energy of the surrounding by this body. On the other hand, the body is synthetized by a part of free energy consumed in the body, like the tax at the customs house. This is the common feature of the transient phenomena, the passage having *small entropy* or *large* free energy is built with vigour like rolling snow-ball by the *part of free energy* which is consumed by the passage.[4]

These molecular aggregations are shaken by thermal agitation, if the inherent thermal agitation should be considered conveniently like a virtual action of external body, so that molecules fall down from the nib and the curious form contracts to an ordinary ice block, if the vapour supply becomes deficient to develop the nib. (The process may be either re-evaporation from the nib and condensation at the stem of crystal or the creeping of the reevaporated molecule from the nib along the surface to the stem). Then the catalytic action of the flake may be lost and this is the *common nature* of such a system with *delicate arrangement* or with small entropy and is called *reversal* of field according to the expression of (v) of III.

We Japanese are able to visualize the dovelopment of such an unstable structure with large free energy if we remember the crowded passenger car during the war. The unstable vapour molecules crowding on the nib of snowflakes are shattered by thermal agitation but the *total system is now in an unstable state with large free energy* and molecules are like the people wanting to be free but hanging at the window or sitting on the roof of their car at the risk of their lives.

If this is the general nature of the *negative increase of entropy* or *increase of free energy*, our body and our life must also be an unstable one. In other analogy, the small entropy can be seen as a narrow gate through which only the *aggregations with favourable form* are permitted to go. Molecules moving freely can scarcely have the *chance* to aggregate in such a form in the phase space. Such a chance and small entropy are related together.

This small chance determines the velocity of the decrease of total free energy. The metastability or false equilibrium are explained by the smallness of this velocity. The aggregates taking such a limited form by chance can be considered like the people in austerity. Such a life is not comfortable but the uneasy state must be indispensable for future. The molecules are also struggling through the difficult passage and then the chemical stress of total system is released by the austerity.

The *dynamical equilibrium*, which was discussed by Bertalanffy and will be discussed on another occasion, can be considered as a pulsating flow of matter through such gates.

The systems with small entropy like cluster, crystal-flake or living-system are not *closed system*, so that the application of *grand partition function* might be suitable. The application of the function in transient state is not yet perfect for us, but the phenomenological theory of cluster[6] suggests the way of qualitative and approximate treatment[7] of this case although the quantitative calculation of the number of complexion (corresponding to the mixing entropy in Frenkel's theory) including lives can no longer be carried in our case (see (6.15′) of VI).

Usually the number of complexion is really defined only in the case of equilibrium state. If we, however, consider a limited part of the phase space[1,7] (*cut off* method) we can enumerate the number of complexion corresponding to a definite macroscopic transient state, which will be discussed later.

V. *On the Possibility to Consider The 4th Law of Thermodynamics*

In the foregoing paragraph we have considered that the system in the transient state has large free energy and also that the discharge of the free energy is hindered by the bottle-neck.

If the bottle-neck is so narrow that the states dwell on as if they were in equilibrium, then they are called in the states of *metastable* or in *false equilibrium*. The so-called *time of relaxation* depends on the narrowness of the bottle-neck which is determined by the *free energy of activation*.[8] But the narrowness is not unchangeable and even has the tendency to enlarge itself at the cost of free energy of the total system, discharging through this passage. In the simplest case of supersaturated vapour, cluster or crystallit suspending in it is the passage and their development makes the bottle-neck large. In this *evolution of passage* we might find the key to solve the strange idea in natural science, *fitness*.[9]

By the way, let us think here the circumstance deeply. According to the 2nd law of thermodynamics, Gibbs' free energy, G, of the world has the tendency to decrease in isothermal and isopietic change. On the other hand, we

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[6] J. Frenkel, *J. Chem. Phys.*, **7** (1939), p. 536.

[7] Sugita, "Thermodynamics of Metastability and the Origin of Life" (in Japanese), *Kagaku* (*Science*), **18**, No. 5 (1948).

[8] The energy part of this free energy determines the potential barrier of the process and the entropy part depends on unstable or curious form of aggregation.

[9] Sugita, "On the Idea of Fitness in Natural Phenomena" (in Japanese), *Ikkyo-ronso* (*Hitotsubashi Rev.*), **22**, No. 3 (1949).

can find the tendency that the *velocity of decreasing* of G, i.e. $\dot{G}$ wants to take a large value as far as possible. This might be a general principle of nature which I should like to call temporarily the 4th law of thermodynamics.

The foundation of such a large principle will be discussed later, and we can suggest here that it is very important and a beneficial idea that the nature of the transient phenomena as well as the living system may be clarified and explained uniformly by this principle.

There are many delicate problems concerning human thought if we propose to clarify the nature of life on the basis of physics and chemistry. In any way the matter looks as if it were concerned in the 4th law.

The adequacy of the 1st law there is no one who doubts but on the 2nd law some objection or scepticism was seen, for the thermodynamics of transient phenomena are not perfect formerly. Also it might be feared to clarify with vigour the mysterious veil covering the nature of life. But now the thermodynamics of transient phenomena are perfect as well as inadequate[1] and the problem is shifted to the 4th law. It might be a progress of theory though it looks like only shifting the matter.

I do not want to claim that the special and complicated matter of life can be solved only by thermodynamics but that the biologist has now a powerful weapon in thermodynamics to proceed to his last purpose.

There is no doubt that the free energy, G, has the tendency to decrease. There might be struggle of life like origin of life, evolution or conscious action of higher animal and so on, to accelerate[10] the tendency on the earth. The *activity of the mind* concerns this acceleration of natural tendencies.[9] The fundamental problem of philosophy also concerns the matter, whether to permit the *initiative* of human mind, which is accelerating the natural course, *absolutely or not.*

Here let us see many instances suggesting this large principle of thermodynamics.

(i) The cascade principle (Stufenregel) found by W. Ostwald shows that the nature has the tendencies as if it wanted to take the pass of smaller resistance or make a de tour and want to establish the equilibrium as fast as it could.

(ii) Generalizing further the rule described above, it might be said that the nature prefers the line of least resistance, if there are ways side by side for the equilibrium.

(a) According to Volmer,[11] for instance, the crystal formation shows that such a pass is taken actually.

(b) Eyring[12] and others called such a process *rate determining.*

(c) Electric current in conductor takes the distribution that heat loss is minimum if the total current takes a given value. Therefore the heat genera-

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[10] As if we are endeavouring to shorten the time of termination of epidemics which has arisen, though it would terminate itself in the natural course.

[11] Volmer, *Kinetik der Phasenbildung* (Berlin, 1939).

[12] Eyring and others, *The Theory of Rate Processes* (N.Y., 1941).

tion must be maximum if the potential difference will be taken as constant. Therefore, if a cell is applied to drive the current, it will take the distribution to dissipate the free energy of the cell as fast as it can.

(d) Onsager[13] has derived his reciprocal relation from the *principle of least dissipation function.* This principle might be considered to the maximum velocity of entropy increase which will be considered later.[14]

(iii) If a new passage is built independently which has less resistance than others already existing, then the circumstance above described, that might be the 4th law of thermodynamics, may also be seen from our common sense.

(a) The new way may be considered having delicate catalytic action, therefore, large free energy of activation or small entropy. The free energy of activation determines the rate of development of such a passage acting as if the initial cost to construct a highway. That is why the construction of the way of small resistance is retarded. Nevertheless, it becomes rate determining when it is performed and the old ways become only bipass or will be ruined.

(b) The idea of natural selection or struggle for life of biology may be considered as having the relation to this principle. That is the free energy discharged through the old passage is used to the free energy of activation of new way, and the material itself constituting the old way may be used also as the material of construction (see (v) of VI).

(c) Such a circumstance like natural selection can be seen also in the inorganic worlds. For instance, let us observe the nuclear formation of ice in supersaturated water vapour under freezing point, and containing super-cooled water droplets. If the crystal nucleous is formed, not only the condensation occurs on this nucleous, but the super-cooled droplets vapourize and disappear. This is the consequence of the 4th law and the same phenomena can be seen on the discharged plate of Pb SO_4 of battery and also in the case of recrystallization of metals and others, and they are playing a role to *promote the tendency* to the thermodynamical equilibrium.

VI. *Mathematical Theory and Conclusion*

Neither from the empirical point nor from the point of molecular statistics can we systematize the 4th law immediatedly and thoroughly. But the possibility is in our hand.

(i) On the base of microscopic reversibility Onsager[13] has shown that

$$\delta(\dot{S}-\Phi) \geqq 0 \qquad (6.1)$$

where $\dot{S}$ is the velocity of entropy increase of the total system and Φ is the dissipation function. On the same base as Onsager, Landau and Lifshitz has shown

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[13] Onsager, *Phys. Rev.*, **37** (1931), p. 405. **38** (1932), p. 2265.

[14] See section (i) of VI.

that
$$\dot{G} = -2\Phi \qquad (6.2)$$
in their *statistical physics.*

(ii) Let n_i denote the parameter expressing the transient state, and let us assume that G is expressed by n_i using the *cut off* method, then
$$\dot{G} = \Sigma\mu_i\dot{n}_i, \qquad \mu_i = \frac{\partial G}{\partial n_i} \qquad (6.3)$$
where μ_i is the chemical potential of the i th component, and $\dot{n}_i$ is the reaction velocity. Let us consider quasi-chemical processes
$$\sum_j \nu_{js}A_j \rightleftarrows \sum_k \nu_{ks}A_k, \qquad s = 1, 2, \ldots \qquad (6.4)$$
between the components. Denoting $\dot{q}_s$ the reaction velocity of the process s from left to right, the reaction velocity $\dot{n}_i$ can be written in the form
$$\dot{n}_i = \sum_s \nu_{is}\dot{q}_s \qquad (6.5)$$
Through this linear transformation the variables n_i are transformed to q_s. The number of new parameter q_s may be less than n_i (see iv) and they may be independent variables.[15]

Then
$$\dot{G} = \sum_s (\sum_i \mu_i\nu_{is})\,\dot{q}_s \qquad (6.6)$$
where
$$\sum_i \mu_i\nu_{is} = \sum_j \nu_{js}\mu_j - \sum_k \nu_{ks}\mu_k$$

From the theory of rate process of chemical reaction $\dot{q}_s$ can usually be written in the form[16]
$$\dot{q}_s = \frac{1}{R_s}\left\{e^{\Sigma\nu_{js}\mu_j/kT} - e^{\Sigma\nu_{ks}\mu_k/kT}\right\} \qquad (6.7)$$
where R_s represents the so-called chemical resistance of the process s, which corresponds with the *circumstance of the theory of rate process*, and the quantity in the bracket represents the μ-field, that corresponds with the *circumstance of the theory of equilibrium.*

Inserting the expression of $\dot{q}_s$ in (6.6) we can see that $\dot{G}$ is equal to $kT\dot{H}$ where H is Boltzmann's H-function. If the mean value of H is taken in the momentum space and if it is assumed that s represents only the rate determining processes in the individual processes and that the higher term of $\dot{H}$ is negligible (see iv), then
$$\dot{G} = kT\dot{H} = \sum_s \frac{\Sigma\mu_i\nu_{is}}{R_s}\left\{e^{\Sigma\nu_{js}\mu_j/kT} - e^{\Sigma\nu_{ks}\mu_k/kT}\right\} \qquad (6.6')$$
The proceedure, which neglected the higher term, corresponds with the *cut off* method.[1] The summation of the right hand side of (6.6′) may be interpreted as 2Φ, where Φ is the dissipation function of the quasi-chemical processes, and it may be considered as the virtual heat source.[1]

From this relation, however, we cannot see the validity of the 4th law intuitively. Let us consider the matter on another occasion.

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[15] If we neglect smaller one, which is not rate determining, then q_s may be interpreted as a sort of ξ parameter of de Donder (l'Affinité).

[16] The statistical foundation of this form appears to be not yet sufficient. It may be assumed, however, from the thermodynamical consideration of Jouguet,[5] de Donder and the author.[1]

(iii) The reversal of the μ-field can be interpreted if we consider the transition from the stage

$$\Sigma\nu_{js}\mu_j>\Sigma\nu_{ks}\mu_k \quad \text{to} \quad \Sigma\nu_{js}\mu_j<\Sigma\nu_{ks}\mu_k \qquad (6.8)$$

(iv) From the relation (6.7) we can see that $\Sigma\nu_{js}\mu_j-\Sigma\nu_{ks}\mu_k$ must be small enough if $\dot{q}_s$ is very small. Then the product of both term must be the small quantity of higher order and therefore the higher terms of (6.6′) can be reasonably neglected. Therefore the system in transient state can be defined by certain number of parameters $\dot{q}_s$ and q_s from the point of macro-physics[17]. Thus the *cut off* method of quasithermodynamics is supported.[1] "The thermodynamics and molecular statistics of transient phenomena" will be translated in English in the near future.

(v) We can see easily the circumstance that the molecules or the cluster of large free energy is developing consuming the free energy of the surrounding world.

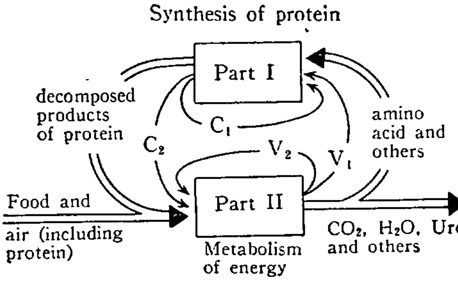

Fig. 1.

Part I corresponds with the production of capital goods (protein). See p. 21.

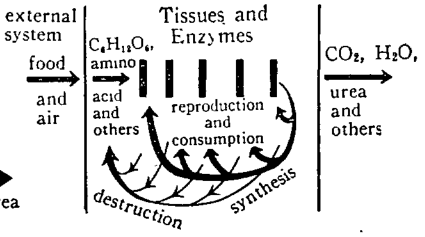

Fig. 2.

Part II corresponds with the production of consumer goods (A.T.P. corresponds also with labourer).

Let us consider this synthetic reaction in details. In every instant such molecules, cluster and tissues are degrading. The reaction of this type is denoted by $\Sigma x_iA_i\rightarrow\Sigma x_i'A_i'$ (1), where x_i is integer and A_i is components with large free energy like A.T.P. or some protein molecule. By this reaction (1) the large free energy is liberated, which is utilized as the free energy of activation for the digestion and absorption of food and for the decomposition of glycogen in our body. The reaction of the latter type is denoted by $\Sigma y_jB_j\rightarrow\Sigma y_j'B_j'$ (2). If the body is in a steady state, the consumption of matter and free energy due to the reaction (1) must be recovered by the synthetic reaction $\Sigma z_kC_k\rightarrow\Sigma z_k'C_k'$ (3), in which

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[17] If $\dot{q}_s$ is rate determining, then it is called decomposition or reaction coordinate. On the other hand, the higher term of (6.6′) satisfy the condition of detailed balance approximately (then $\dot{q}_s\sim 0$), which corresponds the microscopic reversibility.

$$\Sigma z_k\mu_k < \Sigma z_k'\mu_k'.$$

The field of this reaction (3) shows reversal. But if we consider the combined reaction of (2) and (3) and further idealize the process of energy transfer from (2) to (3), then

$$\Sigma y_j\mu_j + \Sigma z_k\mu_k = \Sigma y_j'\mu_j' + \Sigma z_k'\mu_k' \tag{6.9}$$

But the reaction velocity might not be large enough, if it is represented by (6.7). Let us consider now the combined reaction[18] of (1), (2) and (3).

$$\Sigma x_iA_i + \Sigma y_jB_j + \Sigma z_kC_k \rightarrow \Sigma x_i'A_i' + \Sigma y_j'B_j' + \Sigma z_k'C_k' \tag{6.10}$$

$$\Sigma x_i\mu_i + \Sigma y_j\mu_j + \Sigma z_k\mu_k > \Sigma x_i'\mu_i' + \Sigma y_j'\mu_j' + \Sigma z_k'\mu_k' \tag{6.9'}$$

Then the reaction (3) must be promoted by (2) and (1), the field of this reaction is estimated by (6.9′) and the reaction velocity is represented by (6.7).

The consumption of free energy in our body is from (6.6) and (6.9)

$$\dot{G} = kT\dot{H} = \Sigma(\Sigma x_{is}\mu_i - \Sigma x_{is}'\mu_i')\,\dot{q}_s\,^{19} \tag{6.11}$$

On the other hand, the reproduction of free energy due to the process (3) will be written in

$$\sum_t(\Sigma z_{kt}\mu_k - \Sigma z_{kt}'\mu_k')\,\dot{q}_t. \tag{6.12}$$

Let us consider the metabolizm of component i. The consumption of free energy[20] of i is from (6.11)

$$\sum_s(x_{is}\mu_i - x_{is}'\mu_i')\,\dot{q}_s$$

and the reproduction must be from (6.12)

$$\sum_t(z_{it}\mu_i - z_{it}'\mu_i')\,\dot{q}_t.$$

Then the following relation

$$\sum_i{}'\sum_s(x_{is}\mu_i - x_{is}'\mu_i')\,\dot{q}_s = \sum_t(z_{it}\mu_i - z_{it}'\mu_i')\,\dot{q}_t \tag{6.13}$$

might be obtained in the steady state, which is *analogous* to the equation of simple reproduction of economics. Let us assume that $s=t=1$ corresponds with the synthesis of protein and $s=t=2$ with that of A.T.P. (adenosine triphosphate) and also that $i=A$ corresponds with A.T.P. and $i=P$ with protein. Then from (6.13)

$$\left.\begin{aligned}(x_{1A}\Delta\mu_A + x_{1P}\Delta\mu_P)\,\dot{q}_1 &= (z_{1P}+z_{2P})\,\Delta\mu_P\dot{q}_1\\ (x_{2A}\Delta\mu_A + x_{2P}\Delta\mu_P)\,q_2 &= (z_{1A}+z_{2A})\,\Delta\mu_A\dot{q}_2\end{aligned}\right\} \tag{6.13'}$$

where $\Delta\mu_A = \mu_A - \mu_A'$, $\Delta\mu_P = \mu_P - \mu_P'$

Then in steady state $x_{1P}=z_{1P}$, $x_{2A}=z_{2A}$ and

$$\frac{x_{1A}}{z_{2P}} = \frac{z_{1A}}{x_{2P}} = \frac{\Delta\mu_P}{\Delta\mu_A} \tag{6.14}$$

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[18] This corresponds with the model of multiple collision of many components. Our body is a mixture of many components like vitamin, hormone, enzyme and others, therefore the above consideration might be reasonable from this point of view. If we consider the energy transfer of the combined reaction and if we assume that the energy liberated by (1) is converted to the energy of activation of (6.10), then the prominent action of enzyme will be interpreted in this manner.

[19] Let us assume that $x_{is}\mu_i - x_{is}'\mu_i'$ is easily defined, like $\Delta\mu_A$ of $\Delta\mu_P$ of the equation (6.13′).

[20] It is my opinion that the quantity $\dot{G}$ has a similar property to the utility function of mathematical economics, which wants to take as large a value as possible (see V).

From (6.13′) we can get also

$$z_{1A}\Delta\mu_A\dot{q}_2 = x_{1A}\Delta\mu_A\dot{q}_1 \tag{6.15}$$

Then from (6.14) $z_{1A}\Delta\mu_A = x_{2P}\Delta\mu_P$ and

$$x_{2P}\Delta\mu_P\dot{q}_2 = x_{1A}\Delta\mu_A\dot{q}_1. \tag{6.15′}$$

If we put here (see N.B.)

$$V_1 = x_{1A}\Delta\mu_A\dot{q}_1 = z_{1A}\Delta\mu_A\dot{q}_2, \qquad V_2 = x_{2A}\Delta\mu_A\dot{q}_2 = z_{2A}\Delta\mu_A\dot{q}_2,$$

$$C_1 = x_{1P}\Delta\mu_P\dot{q}_1 = z_{1P}\Delta\mu_P\dot{q}_1 \quad \text{and} \quad C_2 = x_{2P}\Delta\mu_P\dot{q}_2 = z_{2P}\Delta\mu_P\dot{q}_1$$

then (6.13′) and (6.15′) may be written in the following form

$$\begin{aligned} C_1 + V_1 &= C_1 + C_2 \\ C_2 + V_2 &= V_1 + V_2 \end{aligned} \tag{6.13″}$$

and

$$V_1 = C_2 \tag{6.15″}$$

which is in similar form to that of economics (see fig. 1).

We can also get from (6.13′)

$$\frac{x_{2P}}{z_{2P}} = \frac{\dot{q}_1}{\dot{q}_2} = \frac{z_{1A}}{x_{1A}}. \tag{6.16}$$

Therefore, if the correlation of $\dot{q}_1$ and $\dot{q}_2$ is known from the measurment in the steady state, we can *estimate* $\Delta\mu_P$ and thus the entropy[21] of the protein molecules in living body. The phenomena of life may be interpreted as the *correlation* of $\dot{q}_s$ of the metabolizing components.

N.B. (6.13) and (6.13′) may be obtained by the maximum principle of $|\dot{G}|$, i.e. the 4th law. (6.15) follows from the relations $x_{2A} = z_{2A}$ and

$$x_{1A}\dot{q}_1 + x_{2A}\dot{q}_2 = (z_{1A} + z_{2A})\dot{q}_2$$

for the conservation of the components. Thus $x_{1A}\dot{q}_1 = z_{1A}\dot{q}_2$, and (6.15) and (6.16) can be obtained.

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[21] The quantity can not be measured chemically, because the system can no longer be alive if we seperate it from the body to measure the value. See p. 12 and p. 15.