

4. The Theory of Open Systems in Physics and Biology

L. von Bertalanffy

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From the physical point of view, the characteristic state of the living organism is that of an open system. A system is closed if no material enters or leaves it; it is open if there is import and export and, therefore, change of the components. Living systems are open systems, maintaining themselves in exchange of materials with environment, and in continuous building up and breaking down of their components.

So far, physics and physical chemistry have been concerned almost exclusively with processes in closed reaction systems, leading to chemical equilibria. Chemical equilibria are found also in partial systems of the living organism - for example, the equilibrium between hemoglobin, oxyhemoglobin, and oxygen upon which oxygen transport by blood is based. The cell and the organism as a whole, however, do not comprise a closed system, and are never in true equilibrium, but in a steady state. We need, therefore, an extension and generalization of the principles of physics and physical chemistry, complementing the usual theory of reactions and equilibria in closed systems, and dealing with open systems, their steady states, and the principles governing them.

Though it is usual to speak of the organism as a "dynamic equilibrium", only in recent years has theoretical and experimental investigation of open systems and steady states begun. The conception of the organism as an open system has been advanced by von Bertalanffy since 1932, and general kinetic principles and their biological implications have been developed (4, 6). In German literature, Dehlinger and Wertz (15), Bavink (1), Skrabal (31), and others have extended these conceptions. A basically similar treatment was given by Burton (12). The paper of Reiner and Spiegelman (28) seems to have been inspired by conversations of the present author with Reiner in 1937-8. Starting from problems of technological chemistry, the comparison of efficiency in batch and continuous reaction systems, Denbigh *et al.* (16) have also developed the kinetics of open reaction systems. The most important recent work is the thermodynamics of open systems by Prigogine (25, 26).

In physics, the theory of open systems leads to fundamentally new principles. It is indeed the more general theory, the restriction of kinetics and thermodynamics to closed systems concerning only a rather special case. In biology, it first of all accounts for many characteristics of living systems that have appeared to be in contradiction to the laws of physics, and have been considered hitherto as vitalistic features. Second, the consideration of organisms as open systems yields quantitative laws of important biological phenomena. So far, the consequences of the theory have been developed especially in respect to biological problems, but the concept will be important for other fields too, such as industrial chemistry and meteorology.

General Characteristics of Open Systems

Some peculiarities of open reaction systems are obvious. A closed system *must*, according to the second law of thermodynamics, eventually attain a time-independent equilibrium state, with maximum entropy and minimum free energy, where the ratio between its phases remains constant. An open system *may* attain (certain conditions presupposed) a time-independent state where the system remains constant as a whole and in its phases, though there is a continuous flow of the component materials. This is called a steady state.^[1] Chemical equilibria are based upon reversible reactions. Steady states are irreversible as a whole, and individual reactions concerned may be irreversible as well. A closed system in equilibrium does not need energy for its preservation, nor can energy be obtained from it. To perform work, however, the system must be, not in equilibrium, but tending to attain it. And to go on this way, the system must maintain a steady state. Therefore, the character of an open system is the necessary condition for the continuous working capacity of the organism.

To define open systems, we may use a general transport equation. Let Q_i be a measure of the i -th element of the system, e.g. a concentration of energy in a system of simultaneous equations. Its variation may be expressed by:

$$\frac{dQ_i}{dt} = T_i + P_i$$

P_i is the rate of production or destruction of the element Q_i at a certain point of space; it will have the form of a reaction equation. T_i will be expressed by Fick's diffusion equation. A system defined by the system of equation 1 may have three kinds of solutions. First, there may be unlimited increase of the Q_i 's; second, a time-independent steady state may be reached; third, there may be periodic solutions. In the case that a steady state is reached, the time-independent equation:

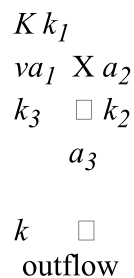
$$T_i + P_i = 0 \quad 2$$

must hold for a time $t \rightarrow \infty$. If both members are linear in the Q_i and independent of t , the solution is of the form:

$$Q_i = Q_{i1}(x, y, z) + Q_{i2}(x, y, z, t) \quad 3$$

where Q_{i2} is a function of time decreasing to 0 for certain limiting conditions.

We may consider the following simple case of an open system (4, 6). Let there be a transport of material a_1 into the system which is proportional to the difference between its concentrations X outside and x_1 inside ($X - x_1$). This imported material may form, in a monomolecular and reversible reaction, a compound a_2 of concentration x_2 . On the other hand, the substance a_1 may catabolized, in an irreversible reaction, into a_3 . And a_3 may be removed from the system, proportional to its concentration x_3 . Then we have the following system of reactions:



and equations:

$$\frac{dx_1}{dt} \sim K(X - x_1) - k_1 x_1 + k_2 x_2 - k_3 x_1 - x_1$$

$$\frac{dx_2}{dt} = k_1 x_1 - k_2 x_2 \quad 4$$

$$\frac{dx_3}{dt} = k_3 x_1 - k x_3$$

Solving these equations for the steady state by equating to 0 we obtain that:

$$x_1 : x_2 : x_3 = 1 : \frac{k_1}{k_2} : \frac{k_3}{k} \quad 5$$

Immediately we seen some interesting consequences. First, the composition of the system in the steady state remains constant, though the ratio of the components is not based upon a chemical equilibrium of reversible reactions, but the reactions are going on and are, in part, irreversible. Second, the steady state ratio of the

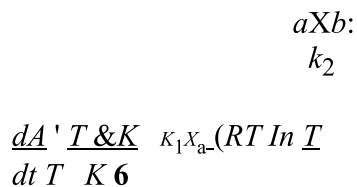
components depends only on the system constants, not on the environmental conditions as represented by the concentration X .

Third, we find $x_1 = \frac{KX}{K + k_3}$. Let us assume that a disturbance from outside, i.e.

biologically speaking, a "stimulus", raises the rate of catabolism, amounting to an increase of constant k_3 . Then x_1 must decrease. But since import is proportional to the difference of the concentrations X & x_1 , influx must increase. The system therefore manifests forces which are directed against a disturbance of its steady state. In biological language, we may say that the system shows adaptation to a new situation. Physicochemically, open systems show a behavior which corresponds to the principle of Le Chatelier.

But these characteristics of steady states are exactly those of organic metabolism. In both cases, there is first maintenance of a constant ratio of the components in a continuous flow of materials. Second, the composition is independent of, and maintained constant in, a varying import of materials; this corresponds to the fact that even in varying nutrition and at different absolute sizes the composition of the organism remains constant. Third, after a disturbance, a stimulus re-establishes its steady state. Thus, the basic characteristics of *self-regulation* are general properties of open systems.

The energy need for the maintenance of a steady state is, in the simplest case of a monomolecular reversible reaction



where x_a^* is the concentration in the steady state, k_1 the reaction velocity in the steady state, $K = k_1/k_2$ the equilibrium constant, $T = k_1/k_2$ the steady state constant. A similar expression applies to systems of n reaction partners (6).

Though at present this expression can hardly be used quantitatively in respect to cell problems, some general considerations are not without interest. Even the resting cell, performing no perceptible work, needs a continuous energy supply, as demonstrated by the fact that a deprivation of oxygen stops life in the (aerobic) cell. This maintenance work of the living cell is, of course, partly physicochemical, as in maintenance of osmotic pressure, and of ion concentrations different from those in the environment (17). But the chemical side must also be taken into account. Apart from the photosynthesis, which needs considerable energy that is yielded by sun radiation, the anabolism of cell materials consists mainly of processes of dehydrosynthesis, such as the building up of proteins from amino acids and of polysaccharides from monosaccharides. Considered from the usual static viewpoint, these processes need little energy. But the situation is different in that these processes are to be considered not merely as reversal of hydrolytic splitting, but the high molecular compounds must be maintained in a concentration very far from equilibrium. In the catalytic reactions, sugars X polysaccharides, amino acids X proteins, the equilibrium is almost completely on the side of the splitting products, as shown simply by the ease of hydrolysis and the difficulty, even impossibility, of dehydrosynthesis *in vitro*. Therefore, the steady state constant T is very different from the equilibrium constant K (35). The energy need for synthesis is demonstrated by numerous facts showing the coupling of anabolic and oxidative processes (6, p. 218 ff.). On the other hand, the efficiency of the "living machine" appears to be rather low. Since the organism works as a chemodynamic system, theoretically an efficiency of 100 per cent, i.e. complete transformation of free energy into effective work, would be possible in isothermic and reversible processes, the condition of isothermy being almost ideally realized in the living organism. But the efficiency of the organic system in performing effective work, except in photosynthesis, does not much surpass that of man-made thermic machines. It appears that we have to take into account, in the balance of cell work, not only effective work but also conservation energy, i.e. the energy needed for the maintenance of the steady state.

If these considerations are correct, it is to be expected that there is heat production in the transition from the steady state to equilibrium, i.e. in cell death. In contradiction to earlier work of Meyerhoff, this is true according to Lepeschkin (20), whose investigations, however, need confirmation. Possibly a combined study of reaction heat in cell death and of oxygen consumption of the resting cell, and the application of equation 6 can lead to a deeper insight into the problem of maintenance work of the cell.

Equifinality

A profound difference between most inanimate and living systems can be expressed by the concept of *equifinality*. In most physical system, the final state is determined by the initial conditions. Take, for instance, the motion in a planetary system where the positions at a time t are determined by those of a time t_0 , or a chemical equilibrium where the final concentrations depend on the initial ones. If there is a change in either the initial conditions or the process, the final state is changed. Vital phenomena show a different behavior. Here, to a wide extent, the final state may be reached from different initial conditions and in different ways. Such behavior we call equifinal. It is well known that equifinality has been considered the main proof of vitalism. The same final result, namely, a typical organism, is achieved by a whole normal germ of the sea urchin, a half-germ, or two fused germs, or after translocations of cells. According to Driesch, this is inexplicable in physicochemical terms: this extraordinary performance is to be accomplished only by the action of a vitalistic factor, an entelechy, essentially different from physicochemical forces and governing the process by foresight of the goal to be reached. Therefore, it is a question of basic importance whether equifinality is a proof of vitalism. The answer is that it is not (4, 6).

Analysis shows that closed systems cannot behave equifinally. This is the reason why equifinality is, in general, not found in inanimate systems. But in open systems which are exchanging materials with the environment, in so far as they attain a steady state, the latter is independent of the initial conditions; it is equifinal. This is expressed by the fact that if a system of equations of the form 1 has a solution of the form 3 the initial conditions do not appear in the steady state. In an open reaction system, irrespective of the concentrations in the beginning or at any other time, the steady state values will always be the same, being determined only by the constants of reactions and of the inflow and outflow.

Equifinality can be formulated quantitatively in certain biological cases. Thus growth is equifinal: the same species-characteristic final size can be reached from different initial sizes (e.g. in litters of different numbers of individuals) or after a temporary suppression of growth (e.g. by a diet insufficient in quantity or in vitamins). According to quantitative theory (p. 73), growth can be considered the result of a counteraction of the anabolism and catabolism of building materials. In the most common type of growth, anabolism is a function of surface, catabolism of body mass. With increasing size, the surface-volume ratio is shifted in disfavor of surface. Therefore, eventually a balance between anabolism and catabolism is reached which is independent of the initial size and depends only on the species-specific ratio of the metabolic constants. It is, therefore, equifinal.

Equifinality is found also in certain inorganic systems which, necessarily, are open ones (6, 9, 10). Such systems show a paradoxical behavior, as if the system "knew" of the final state which it has to attain in the future.

Thermodynamics of Open Systems

It has sometimes been maintained that the second law of thermodynamics does not hold in living nature. Remember the sorting demon, invented by Maxwell, and Auerbach's doctrine of ectropy, stating that life is an organization created to avert the menacing entropy-death of the universe. Ectropy does not exist. However, thermodynamics was concerned only with closed systems, and its extension to open systems leads to very unexpected results.

It has been emphasized by von Bertalanffy (4,6) that, "according to definition, the second law of thermodynamics applies only to closed systems, it does not define the steady state". The extension and generalization of thermodynamical theory has been carried through by Prigogine (11, 25, 26, 30). As Prigogine

states, "classical thermodynamics is an admirable but *fragmentary* doctrine. This fragmentary character results from the fact that it is applicable only to states of equilibrium in closed systems. *It is necessary, therefore, to establish a broader theory, comprising states of non-equilibrium as well as those of equilibrium.*" Thermodynamics of irreversible processes and open systems leads to the solution of many problems where, as in electrochemistry, osmotic pressure, thermodiffusion, Thomson and Peltier effects, etc., classical theory proved to be insufficient. We are indicating only a few, in part revolutionary, consequences.

Entropy must increase in all irreversible processes. Therefore, the change in entropy in a closed system must always be positive. But in an open system, and especially in a living organism, not only is there entropy production owing to irreversible processes, but the organism feeds, to use an expression of Schrödinger's, from negative entropy, importing complex organic molecules, using their energy, and rendering back the simpler end products to the environment. Thus, living systems, maintaining themselves in a steady state by the importation of materials rich in free energy, can avoid the increase of entropy which cannot be averted in closed systems.

According to Prigogine, the total change of entropy in an open system can be written as follows:

$$dS = d_e S + d_i S, 7$$

$d_e S$ denoting the change of entropy by import, $d_i S$ the production of entropy due to irreversible processes in the system, like chemical reactions, diffusion, and heat transport. The term $d_i S$ is always positive, according to the second law; $d_e S$, however, may be negative as well as positive. Therefore, the total change of entropy in an open system can be negative as well as positive. Though the second law is not violated, or more precisely, though it holds for the system plus its environment, it does not hold for the open system itself. According to Prigogine, we can therefore state that: (a) Steady states in open systems are not defined by maximum entropy, but by the approach of minimum entropy production. (b) Entropy may decrease in such systems. (c) The steady states with minimum entropy production are, in general, stable. Therefore, if one of the system variables is altered, the system manifests changes in the opposite direction. Thus, the principle of Le Chatelier holds, not only for closed, but also for open systems. (d) The consideration of irreversible phenomena leads to the conception of thermodynamic, as opposed to astronomical, time. The first is nonmetrical (i.e. not definable by length measurements), but arithmetical, since it is based upon the entropy of chemical reactions and, therefore, on the number of particles involved; it is statistical because based upon the second law; and it is local because it results from the processes at a certain point of space.

The significance of the second law can be expressed also in another way. It states that the general trend is directed toward states of maximum disorder and leveling down of differences, the higher forms of energy such as mechanical, chemical, and light energy being irreversibly degraded to heat, and heat gradients continually disappearing. Therefore, the universe approaches entropy death when all energy is converted into heat of low temperature, and the world process comes to an end. There may be exceptions to the second law in microphysical dimensions: in the interior of stars, at extremely high temperatures, higher atoms are built up from simpler ones, especially helium from hydrogen, these processes being the source of sun radiation. But on the macrophysical level, the general direction of events toward degradation seems to be the necessary consequence of the second law.

But here a striking contrast between inanimate and animate nature seems to exist. In organic development and evolution, a transition toward states of higher order and differentiation seems to occur. The tendency toward increasing complication has been indicated as a primary characteristic of the living, as opposed to inanimate, nature (2). This was called, by Woltreck, "anamorphosis", and was often used as a vitalistic argument.

These problems acquire new aspects if we pass from closed systems, solely taken into account by classical thermodynamics, to open systems. Entropy may decrease in open systems. Therefore, such systems may spontaneously develop toward states of greater heterogeneity and complexity (11, 25, 26, 30). Probably it is just the thermodynamical characteristic of organisms as open systems that is at the basis of the apparent contrast of catamorphosis in inanimate, and anamorphosis in living, nature. This is obviously so for the transition toward higher complexity in development, which is possible only at the expense of energies won by oxidation and other

energy-yielding processes. In regard to evolution, these considerations show that the supposed violation of physical laws (13) does not exist, or, more strictly speaking, that it disappears by the extension of physical theory.

As emphasized by Prigogine, "the thermodynamics of irreversible phenomena is an indispensable complement to the great theories of macrophysics, giving the latter a unification hitherto lacking". Not since De Vries and Pfeiffer's work on osmosis have basic developments in physical theory been instigated by biological considerations. Not only must biological theory be based upon physics; the new developments show that the biological point of view opens new pathways in physical theory as well.

Biological Applications

Generally speaking, the basic fundamental physiological phenomena can be considered to be consequences of the fact that organisms are quasi-stationary open systems. Metabolism is maintenance in a steady state. Irritability and autonomous activities are smaller waves of processes superimposed on the continuous flux of the system, irritability consisting in reversible disturbances, after which the system comes back to its steady state, and autonomous activities in periodic fluctuations. Finally, growth, development, senescence, and death represent the approach to, and slow changes of, the steady state. The theories of many physiological phenomena are, therefore, special cases of the general theory of open systems, and, conversely, this conception is an important step in the development of biology as an exact science. Only a few examples can be briefly mentioned.

Rashevsky's theoretical cell model (27), representing a metabolizing drop into which substances flow from outside and undergo chemical reactions, from which the reaction products flow out, is a simple case of an open system. From this highly simplified abstract model, consequences can be derived which correspond to essential characteristics of the living cell, such as growth and periodic division, the impossibility of a "spontaneous generation", an order of magnitude similar to average cell size, and the possibility of nonspherical shapes.

Permeation of substances into the cell, leading to a composition of the cell sap different from that of the surrounding medium, to the selective accumulation of salts, and to volume increase, was studied by Osterhout and his co-workers (23, 24) in large plant cells and physical models. The conditions are again those of open systems, attaining a steady state. The mathematical treatment of this system, as given by Longworth (22), is interesting because it agrees with and confirms the inferences, drawn from quite different physiological considerations, in von Bertalanffy's theory of growth (6).

The conception of open systems has been applied, by Dehlinger and Wertz (15), to elementary self-multiplying biological units, i.e. to viruses, genes, and chromosomes. A more detailed model was indicated by von Bertalanffy (7). According to this model, self-duplication in viruses and genes results from the fact that they are metabolizing a periodic crystals. If degradative processes are going on, then, according to the derivations of Rashevsky, repulsive forces must result which eventually can lead to division and self-multiplication. At least in respect to chromosomes, this conception appears to be well founded, since tracer investigations with radiophosphorus show that the nucleoproteids of the cell are continually worn out and regenerated.

Tracer studies of metabolism, in particular, helped in this country to popularize the conception of the organism as a steady state.

The discovery and the description of the dynamic state of the living cells is the major contribution that the isotope technique has made to the field of biology and medicine . . . The proteolytic and hydrolytic enzymes are continuously active in breaking down the proteins, the carbohydrates and lipids at a very rapid rate. The erosion of the cell structure is continuously being compensated by a group of synthetic reactions which rebuild the degraded structure. The adult cell maintains itself in a steady state not because of the absence of degradative reactions but because the synthetic and degradative reactions are proceeding at equal rates. The net result appears to be an absence of reactions in the normal state; the approach to equilibrium is a sign of death. (29)

Compare this with the following statement, derived from the investigation of animal growth:

Every organic form is the expression of a flux of processes. It persists only in a continuous change of its components. Every organic system appears stationary if considered from a certain point of view; but if we go a step deeper, we find that this maintenance involves continuous change of the systems of next lower order: of chemical compounds in the cell, of cells in multicellular organisms, of individuals in super-individual life units. It was said, in this sense . . . that every organic system is essentially a hierarchical order of processes standing in dynamic equilibrium . . . We may consider, therefore, organic forms as the expression of a pattern of processes of an ordered system of forces. This point of view can be called *dynamic morphology*. (5)

In fact, we have inferred, from quantitative analysis and theory of growth, and before the investigations of Schoenheimer and his co-workers, just the essential conclusions reached by the tracer method, namely, (a) that protein metabolism goes on, particularly in mammals, at much higher rates than classical physiology supposed, and (b) that there is synthesis and resynthesis of amino acids and proteins from ammonia and nitrogen-free chains (3). These predictions were rather hazardous at that time; but they have been fully confirmed by later isotope work, especially with N¹⁵.

To apply the conception of open systems quantitatively to phenomena in the organism-as-a-whole, we have to use a sort of generalized kinetics. Since it is impossible to take into account the inextricable and largely unknown processes of intermediary metabolism, we use balance values for their statistical result. This procedure is in no way unusual. Already in chemistry, gross formulas - for example, those for photosynthesis or oxidation - indicate the net result of long chains of many partly unknown reaction steps. The same procedure is applied on a higher level in physiology when total metabolism is measured by oxygen consumption and carbon dioxide and calorie production, and bulk expressions, like Rubner's surface rule, are formulated; or when in clinical routine the diagnosis of, say, hyperthyroidism is based upon determination of basal metabolism. A similar procedure leads to exact theories of important biological phenomena.

Thus, a quantitative theory of growth has been developed. Growth is considered to be the result of the counteraction of anabolism and catabolism of the building materials. By quantitative expressions, using the physiological values of anabolism and catabolism and their size dependence, an explanation of growth in its general course, as well as in its details, and quantitative growth laws have been established. This theory is almost unique in physiology, for it permits precise quantitative predictions which have been verified, often in a very surprising way, by later experiments. The conceptions of dynamic morphology have been applied to a large number of problems, including the quantitative analysis of growth in microorganism, invertebrates, and vertebrates, the physiological connexions between metabolism and growth, leading to the establishment of metabolic types and corresponding growth types, allometry, growth gradients and physiological gradients, pharmacodynamic action, and phylogenetic problems (8).

Spiegelman (32) has given a quantitative theory of competition, regulation, dominance, and determination in morphogenesis, based upon a generalized kinetics of open systems and the gradient principle. The steady state and turnover rate of tissues are investigated by Leblond and his group (19a).

Excitation has already been considered by Hering a reversible disturbance of the processes going on in the living organism. The conception that organic systems are not in equilibrium, but in a steady state, has been advanced by Hill (17), mainly upon considerations of the osmotic nonequilibrium in living cells. Hill's theory of excitation (18), which is formally identical with that of Rashevsky (27), concerns a special case of steady states.

Under certain conditions, the approach in open systems to a steady state is not simply asymptotical, but shows an "overshoot" or "false start", as demonstrated by Burton (12), and Denbigh *et al.* (16). These phenomena are missed in ordinary physical chemistry, but are common in biological phenomena, e.g. in the sequence of after potentials following the spike potential in nerve excitation, in after discharge after inhibition, and in supernormal respiration after entering an oxygen debt.

Also the theory of feedback mechanisms (36), much discussed in the last few years, is related to the theory of open systems. Feedbacks, in man-made machines as well as in organisms, are based upon structural arrangements. Such mechanisms are present in the adult organism, and are responsible for homeostasis. However,

the primary regulability, as manifested, for example, in embryonic regulations, and also in the nervous system after injuries, etc., is based upon direct dynamic interactions (9, 10).

In pharmacology, a conception corresponding to that of open systems has been applied by Loewe (21); quantitative relations have been derived for systems corresponding to the action of certain drugs ("put in", "drop in", >block out" systems). A deduction of the several laws of pharmacodynamic action from the organismic conception (von Bertalanffy) and a general system function was given by Werner (34).

Conceptions and systems of equations similar to those of open systems in physicochemistry and physiology appear in biocoenology, demography, and sociology (14, 19, 33).

The formal correspondence of general principles, irrespective of the kind of relations or forces between the components, leads to the conception of a "General System Theory" as a new scientific doctrine, concerned with the principles which apply to systems in general.

Thus, the theory of open systems opens a new field in physics, and this development is even more remarkable because thermodynamics seemed to be a consummate doctrine within classical physics. In biology, the nature of the open system is at the basis of fundamental life phenomena, and this conception seems to point the direction and pave the way for biology to become an exact science.

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[1] In German, the term *Fliessgleichgewicht* was introduced by von Bertalanffy.

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