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A CONTRIBUTION TO THE SEARCH OF GENERAL MATHEMATICAL PRINCIPLES IN BIOLOGY

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A somewhat different approach to the principle of biotopological mapping, discussed in previous publications, is given. The organism is considered as a set of properties, each of which is in its turn a set of numerous subproperties which are logically included in the corresponding properties. Topology is introduced by an appropriate definition of neighborhoods, and four postulates are stated which concern the mapping of the spaces corresponding to higher organisms on those of lower ones. A number of conclusions are drawn from the postulates. Some of them correspond to well-known facts. For example, in man and some higher organisms appropriate emotional stimuli should produce gastrointestinal or cardiovascular disturbances; or some microorganisms should produce substances harmful to other microorganisms (antibiotics). Some other conclusions are still awaiting verification. One of them is, for example, that there must exist unicellular organisms which produce antibodies to appropriate antigens.

In a series of publications (Rashevsky, 1954, hereinafter referred to as I; 1955a—II; 1955b—III; 1955c—IV; 1955d—V; 1956a—VI; 1956b—VII; 1956c—VIII; 1957a—IX; 1957b—X), we have suggested and outlined a topological approach to general biology. The aim is to emphasize the relational aspects of biology and to express the unity of the organic world. This approach is in no way intended as a substitute for the biophysical, metric approach used hitherto in mathematical biology. The two should rather supplement each other. Great as are the advances of the current metric physicomathematical approach to biology, they leave entirely outside of their scope a large number of important relational phenomena. They also do not express the basic similarities between the most different organisms. Such phenomena as sensitivity to stimuli, some

forms of motion, digestion, excretion of wastes, etc., are present in one form or another in every organism, unicellular or multicellular. The quantitative aspects and frequently the physicochemical mechanisms of any of these properties are very different in different organisms. Yet they not only are present in all organisms, but the basic relations between those properties are the same for all organisms.

This general observation leads to the formulation of the principle of biotopological mapping, as discussed in I. In some way all organisms can be mapped on each other and all of them on some conceivable simplest organism, which may either exist or have existed or which may be conceived as an abstraction possessing the minimum number of properties which makes us recognize an organism as such. For lack of a better name, we designated this simplest organism as the primordial. If the relational structure of the primordial organism were known and if the mathematical nature of the mapping were known, we would be in a position, barring purely mathematical difficulties, to describe the relational aspects of *all* organisms.

The purpose of the present paper is to give a somewhat more general and yet a somewhat more precise formulation of the principle of biotopological mapping and to show how a number of known biological facts follows rather directly from this formulation and new phenomena are predicted by it.

In I we pointed out that an organism is a set of what we called "biological functions," connected with each other by certain relations which impart on that set an "organization." Examples of "biological functions" are sensitivity, locomotion, digestion, secretion, etc. We say, for example, that the function of the stomach is to digest, the function of a gland is to secrete. In a mathematical discussion we have to use frequently the word "function" in an entirely different sense, namely, as the mathematician understands it, e.g., $x = f(y)$. Though in I we agreed to use the word function in the mathematical sense, while explicitly using the combination of words "biological function" in the sense in which the biologist uses it, yet the notation is not a convenient one. Some "biological functions" are characterized by their intensity, for example, the intensity or rate of secretion. Situations may arise where we would have such monstrous expressions as "the inten-

sity of a biological function is a function of the intensity of another biological function."

We shall therefore henceforth change our previous terminology and denote such things as sensitivity, locomotion, digestion, absorption, secretion, etc., by the word "property" of an organism. We shall denote different properties by the letter P provided with a capital Latin subscript to designate the specific property. Thus P_S stands for sensitivity to external stimuli; P_C—for property to conduct excitation; P_M—for orderly movement (as contrasted with random thermal agitation); P_A—for absorption, etc. Lower case Latin letters will be used for running subscripts. Thus we shall write P_i, $(i = S, C, M \ldots)$.

In a unicellular organism the one cell, which constitutes it, possesses all the basic properties P_i. Those properties are related in a manner to be discussed below. One of the characteristics of multicellular organisms is that different cells specialize in different properties. Some cells retain some properties and lose others. The relation between two different properties P_i and P_k, whether they belong to the same cell of a multicellular organism or to different cells, remains the same as in a unicellular organism. For example, one type of cell may be sensitive to external stimuli, but may not be motile; another cell may not be sensitive but may possess motility. Yet just as in a unicellular organism a stimulus under certain conditions produces a movement, so will a stimulus applied to the sensory cell result in a movement of the motile cell.

Another characteristic of more complex multicellular organisms is the much larger number of different properties as compared with the simpler or unicellular ones. Thus a sensory cell in a lower organism may be sensitive to chemical stimuli in general. In a higher organism, different sensory cells may be sensitive to different chemical stimuli. For example, different taste cells of the human tongue are sensitive to salt, sour, sweet, and bitter. In I we designated those additional properties as "subsidiary biological functions." In our present terminology it is more appropriate to speak of "subproperties." The sensitivity to bitterness, which we shall denote by P_{S_1}, and the sensitivity to sourness P_{S_2} are included in the sensitivity P_S. Thus P_S is a set of subproperties $P_{S\alpha}$ $(\alpha = 1,2 \ldots)$. The $P_{S\alpha}$'s are subsets of P_S, or elements of P_S. The same holds for any other property P_i. Denoting a "subprop-

erty" by $P_{i\alpha}$ ($i = S,C,M\ldots$; $\alpha = 1,2,3\ldots$)(in other words numbering the subproperties in an arbitrary manner) we have

$$P_{i\alpha} \subset P_i . \tag{1}$$

When we examine the mapping of different organisms on each other, we see that the set $S_1(P_{i\alpha})$ of the subproperties of P_i in one organism maps on the set $S_2(P_{i\beta})$ of another organism; and both map on the set P_i of the primordial. The set P_i is thus the largest or the most inclusive of all subsets $P_{i\alpha}$.

The sets P_i may be conceivably infinite. Thus P_S contains amongst its subsets the sensitivity $P_{S\lambda}$ to radiation of wave length λ. Thus P_S has, at least theoretically, the power of the continuum. Actually, however, in any given concrete organism, the sets P_i are all finite, though some of them may have very large cardinal numbers. An arbitrary ordering of the subsets $P_{i\alpha}$, as done above, does not present therefore any practical difficulty.

It must be also noted that two subsets $P_{i\alpha}$ and $P_{i\beta}$ of P_i are not necessarily disjoined, so that we may have

$$P_{i\alpha} \cap P_{i\beta} = 0 . \wedge . P_{i\alpha} \cap P_{i\beta} \neq 0 , \tag{2}$$

where $\wedge$ denotes the exclusive "or." As an example we have the secretion of proteins and the secretion of regulatory substances. Both are included in "secretion" in general. *Some* secreted proteins are regulatory substances, and *some* regulatory substances are proteins.

Let us examine more closely some of the sets P_i.

We have already discussed some of the subsets $P_{S\alpha}$ of P_S. As a further example let us consider that a painful stimulus may be a stimulus of any modality with an intensity above a certain injurious limit. This does not contradict the known fact that there are special nerve fibers for conduction of pain. Let $P_{S\alpha_i}$ denote the sensitivity to a stimulus of modality α_i, while $P_{S\alpha_i(\beta)}$ denotes the sensitivity to the stimulus of modality α_i and intensity β. Then we have

$$P_{S\alpha_i(\beta)} \subset P_{S\alpha_i} \tag{3}$$

and the sensitivity to pain caused by stimuli of modality α_i is represented by

$$P_{S\alpha_i(\pi)} = \bigcup_{\beta \geqslant \beta_0} P_{S\alpha_i(\beta)} \tag{4}$$

where β_0 is the threshold of pain. The sensitivity to painful stimuli of any modality is then represented by the subset of P_S:

$$P_{S\pi} = \bigcup_{P_{S\alpha_i} \subset P_S} P_{S\alpha_{i(\pi)}}. \tag{5}$$

The set which represents the property of conduction, P_C, consists of subsets $P_{C\alpha}$ which are conductions at different rates. Other subsets are conductions mediated chemically and conductions mediated electrophysiologically.

Of special interest is the set P_M of all orderly movements. In this set are included such movements like those of cilia and flagella, as well as the movement involved in the protrusion of a pseudopod. The fact that different pseudopoda may succeed each other in a rather random fashion does not make the movements in each pseudopod disorderly or random. On the other hand, movements of transport due to either diffusion or to active transport, secretion or absorption, are also subsets of P_M. Thus one important subset of P_M is the set P_{M_1} of all movements which may be called movements on the physically molar level. Another important set is the set of orderly movements P_{M_2} on the molecular level.

The set P_A of properties of absorption includes as subsets the absorption P_{A_1} of building substances for the organism and the absorption P_{A_2} of energy-yielding substances. The absorption P_{A_3} of energy is an element of P_A. That absorption may either proceed through absorption P_{A_4} of radiant energy directly, like in autotrophic plants, or through absorption of energy-yielding substances, P_{A_2}. We have

$$P_{A_3} \subset P_{A_2} \text{ and } P_{A_3} \subset P_{A_4}. \tag{6}$$

Hence

$$P_{A_2} \cap P_{A_4} \neq 0. \tag{7}$$

This gives us another example of (2).

The set P_{Me} of the properties of metabolism includes as subsets the anabolism or synthesis P_{Me_1}, catabolism P_{Me_2}, and storage P_{Me_3}. Those contain other subsets. Thus, for example, synthesis of proteins is included in P_{Me_1}; storage of fats and storage of sugars are both included in P_{Me_3}, etc.

How are the different sets, P_S, P_M, etc., related in the primordial organism? We do not know the full answer to that question, but certain partial relations may be inferred from the logical analysis of what is usually meant by the concept of organism. An organism is a set S_0 of sets P_i in which certain relations of "immediate succession" are established. Therefore those relations between the sets P_i of S_0 can be best represented by a directed graph (cf. I).

We define one biological property P_k as immediately succeeding another, P_i, if the manifestation of P_i causes the manifestation of P_k without involving the manifestation of any third property P_l ($l \neq i$; $l \neq k$). As examples we may give excitation and conduction. However, to the extent that both P_i and P_k contain subsets $P_{i\alpha}$ and $P_{k\beta}$, a sequence of manifestations of *different* subsets may be involved in the sequence $P_i \rightarrow P_k$. Thus, for example, the excitation of a nerve is immediately followed by conduction of an impulse. But in different types of nerves both the excitation and the conduction may represent a sequence of somewhat different physicochemical processes. If P_k succeeds P_i, then we say that P_i preceeds P_k.

There will be a general agreement at least on the structure of some parts of the primordial graph. Thus we have in general $P_S \rightarrow P_C$, and $P_C \rightarrow P_M$. In some organisms we have only P_{M_2}, while in others both P_{M_1} and P_{M_2} are present, but at least one of the two sets of properties is exhibited by *all* organisms. As a result of P_{M_1} as well as of P_{M_2} we have in general ingestion, P_F, or excretion of substances. Thus $P_M \rightarrow P_F$. The process of digestion, which corresponds to a set P_D of properties, occurs either as a result of P_{M_1} or of P_{M_2} or both. Hence we also have $P_M \rightarrow P_D$. Then again $P_A \rightarrow P_{Me}$. Metabolic processes being essential to the proper performance of sensitivity, conduction, and motion, we have also $P_{Me} \rightarrow P_S$; $P_{Me} \rightarrow P_C$; $P_{Me} \rightarrow P_M$. The metabolic processes are also essential for the reproduction P_R of the organism. Hence $P_{Me} \rightarrow P_R$, and by the same token, $P_M \rightarrow P_R$.

There is even in the primordial organism also a set P_H of properties of homeostasis. The connection between P_H and the other P_i is not directly evident from *a priori* considerations. However, undoubtedly there is a connection $P_{Me} \rightarrow P_H$, as well as a connection of P_H to nearly all other P_i's.

We have already remarked that in a multicellular organism the different $P_{i\alpha}$ ($\alpha = 1,2,3\ldots$) map on the P_i of the primordial. We

have studied previously (I,V) different kinds of possible mappings. We shall consider here the most general conceivable mapping. Let S_0' be the set of sets P_i which represents a multicellular organism, and S_P'—the set of sets P_i which represents the primordial organism.

Those sets are not yet spaces, since no topology has been introduced into them. By connecting the different points P_i of S_P or $P_{i\alpha}$ of S_0 by appropriate arrows, which indicate the relations of immediate succession, we obtain a one-dimensional continuous space, if we consider the arrows as continuous lines or as one-dimensional simplexes. But actually those arrows merely indicate the relation of immediate succession. As simplexes they have no *physical* meaning. It is therefore much more logical to construct spaces S_0 and S_P by introducing into the sets S_0' and S_P' a topology by an appropriate definition of neighborhoods. Considering the $P_{i\alpha}$ and P_i as points in the topological spaces S_0 and S_P, respectively, this this can be done in the simplest manner by defining the neighborhoods in S_0 and S_P in the following way:

The neighborhood of a point in S_0 *(or* S_P*) consists of the point itself and of all those points which it immediately precedes.*

Since the relation of immediate succession can be represented by an arrow of a graph, we see that to each S_0 and to S_P there is a corresponding graph. Instead of saying that a point a immediately precedes b, we may say that "a is connected to b by an arrow." Then the above definition of neighborhoods can be stated thus: the neighborhood of a point in S_0 (or S_P) consists of the point itself and of all points to which arrows originate from it.

We shall subject the mapping of S_0 onto S_P only to the condition of being continuous. If now the graph of the primordial organism is given, the possible spaces S_0 are obtained in the following manner:

As we have remarked above (p. 73), the more complex an organism the "narrower" the specialization of its cells; in other words, the smaller a subset P_i that each cell type represents and therefore the larger the number n of subsets. Denote by $P_i^{(n)}$ *any* set of n subsets of P_i. Denote by $P_{i\alpha_r}^{(n)}$ $(r = 1,2,3,\ldots,n)$ the n subsets of $P_i^{(n)}$. For example, if $i = S$, and $n = 2$, and if P_S had only three possible subsets, P_{S1}, P_{S2}, P_{S3}, which denote respectively the sensitivities to light, sound, and touch, then $P_S^{(2)}$ would be either (P_{S1}, P_{S2}), or (P_{S1}, P_{S3}), or (P_{S2}, P_{S3}). Actually, of course, each P_i includes much more than two subsets. We now proceed as follows:

(A). For each set P_i in S_P, which is represented by a point on the corresponding graph, we choose n_i subsets $P_{i\alpha}^{(n_i)}$. These subsets, for all possible values of i, will be the points of the space S_0. If in S_P the point P_i is connected by an arrow to the point P_k, then in S_0 *at least one* point $P_{i\alpha}^{(n_i)}$ is connected by an arrow to *at least one* $P_{k\beta}^{(n_k)}$, the directions of the arrows being properly preserved. If in S_0, $\overline{P_i \rightarrow P_k}$, then no $P_{i\alpha}$ is connected to any $P_{k\beta}$. ($\bar{a}$ means "not a".)

In this manner neighborhoods of S_0 are mapped on neighborhoods of S_P. The mapping is continuous.

The proposed representation of S_0 and S_P as topological spaces, in which neighborhoods are defined in the above manner, is more consistent than their representation by one-dimensional complexes or graphs. In the graphs used in I-VI the directed lines, or arrows, stand only to represent certain relations between the biological properties, namely, relations of immediate precedence and immediate succession. As one-dimensional complexes those lines have no physical meaning. To the extent, however, that to each S_0, as well as to the S_P, there *corresponds* a graph, we may conveniently use the terminology of graphs in our discussion. But actually while a graph, considered as a one-dimensional complex, is a polyhedron in a metric space, S_0 and S_P are topological spaces, which are not metrized up to this point. This point of view is in line with Alexandroff's and Hopf's (1935) attitude of not separating the combinatorial and set-theoretical methods in topology.

The above procedure of constructing S_0 from S_P does not prevent the possibility that more than one $P_{i\alpha}^{(n_i)}$ will be connected to a $P_{k\beta}^{(n_k)}$, or that one $P_{i\alpha}^{(n_i)}$ is connected to several $P_{k\beta}^{(n_k)}$. The total number of possibilities for prescribed values of n_i ($i = S,C,M,$ etc) is very large. To each possible set of connections permitted by (A) there corresponds a different multicellular organism. Moreover, it must be remembered that the set P_i can be divided in many different ways into $P_{i\alpha}^{(n_i)}$ subsets. Thus we may have two sets S_0 which are homeomorph, but in which two topologically identical points $P_{i\alpha_r}^{(n_i)}$ represent different subsets of P_i. Such two sets represent again different multicellular organisms.

It is an interesting combinatorial problem to determine the total number N of possible different sets S_0 which correspond to a given S_P. This number will give us the total number of possible or-

ganisms. If any of the P_i's are infinite sets, then of course N will be infinite. As we remarked, actually for any given organism, n_i are always finite. But inasmuch as theoretically some, if not all, of the P_i's may be infinite and even not enumerably infinite, we have here a possibly interesting problem in set theory. Namely, for given cardinal numbers of the P_i's what is the cardinal number of the set of possible sets S_0?

The organism may be considered as the more complex, the more connecting arrows there are in S_0 between the different $P_{i\alpha}^{(n_i)}$ and $P_{k\beta}^{(n_k)}$. The maximum degree of complexity is obtained when each point $P_{i\alpha}^{(ni)}$ is connected by an arrow to each $P_{k\beta}^{(nk)}$. We shall call such a S_0 the *maximal* S_0.

The rule (A) for constructing S_0 from S_P is very general and contains only the restriction of continuity. We shall, however, add to it another restriction. A space S_0, constructed according to (A), is not necessarily connected. To see this we may consider the particular case when all n_i's are equal ($n_i = n$). We may then connect each point $P_{i\alpha}^{(n)}$ of S_0 to just one corresponding point $P_{k\beta}^{(n)}$ in such a manner that we have n disjoined graphs, each of which is homeomorph with S_P. It is to be noted that with the above definition of neighborhoods in S_0 a connected graph implies a connected space S_0, in the more general topological meaning of the word "connection." Biologically this would mean that a multicellular organism simply consists of n separate organisms, which in no way interact with each other. To avoid this absurdity we add the requirement:

(B). S_0 is connected.

Requirement (B) implies some geometrical and combinatorial relations in S_0, relations which are in general by no means simple, but which may have definite biological predictive value. We shall not discuss here this question in detail, but merely illustrate its nature on an example.

Let again $n_i = n$, and consider the graph of S_0. In the absence of requirement (B) this graph may consist, as we have seen, of n disjoined identical graphs.

Because of $n_i = n$, we can conveniently number all the $P_{i\alpha_q}^{(n)}$ and $P_{k\alpha_r}^{(n)}$ in such a manner that $q = r$, in other words, so that $P_{i\alpha_r}^{(n)} \rightarrow P_{k\alpha_r}^{(n)}$.

To make the whole graph connected, we must have at least $n-1$ lines joining *different* non-corresponding points of the n identical graphs. Let such a cross-connection be made between the points $P^{(n)}_{i\alpha_r}$ and $P^{(n)}_{k\alpha_{r+1}}$. Since we already have $P^{(n)}_{i\alpha_{r+1}} \longrightarrow P^{(n)}_{k\alpha_{r+1}}$, therefore the point $P^{(n)}_{k\alpha_{r+1}}$ will have two predecessors, namely, $P^{(n)}_{i\alpha_r}$ and $P^{(n)}_{i\alpha_{r+1}}$. Each of the last two points will have at least one immediate predecessor.

We call a point a a predecessor of b, if a precedes b. However, a may precede b either immediately by being connected to b by an arrow $a \longrightarrow b$, or not immediately by being merely connected to b by a sequence of arrows, or by a directed way (III, p. 114). Accordingly we shall speak of immediate and non-immediate predecessors. Hence, requirement (B) assures us that of the n points which correspond to P_i, $n-1$ points will have more predecessors in S_0 than P_i has in S_P. In other words, while a certain point P_k in S_P may be reached from only one point P_i, in S_0 we shall have at least $n-1$ points corresponding to P_k, each of which will have at least two immediate or non-immediate predecessors. The maximal S_0 is of course always connected.

If P_i is a predecessor of P_k, then anything that affects P_i is going to affect P_k. Hence the biological meaning of the above is that in a multicellular organism, due to requirement (B) the number of biological properties which affect a given property is greater than in a unicellular organism.

As in I, we prove in quite a similar manner the following:

Theorem I. The rules (A), when applied to two different primordial graphs S_P result always in different graphs S_0.

On the other hand, the theorems in IV require some modification. The general situation is now much more complicated. For the case of a maximal S_0 we have the following:

Theorem II. If in the graph of S_P there is a way (III, p. 114) from P_i to P_k, which goes through one or more intermediate points P_e, then in the maximal S_0 the number of disjoined ways from any point $P^{(n_i)}_{i\alpha_q}$ to any $P^{(n_k)}_{k_r}$ is equal to $n_{\min}$, where $n_{\min}$ is the *smallest* of all n_e's, which belong to any of the intermediate points P_e.

Proof. If $n_{\min}$ is the smallest of all n_e's, then we can pick out $n_{\min}$ points amongst every of the n_e's, and construct $n_{\min}$ disjoined ways from $P^{(n_i)}_{i\alpha_q}$ to $P^{(n_k)}_{k\alpha_r}$. More than $n_{\min}$ disjoined ways are im-

possible, because some of them would have common points amongst the $n_{\min}$ points of $P_{m\alpha}^{(n_m)}$.

How about unicellular organisms? They exhibit a great variety of properties P_i, and they also map on each other and on the primordial. Some microorganisms, as we remarked above (p. 76), do not have any P_{M_1} (non-motile microorganisms), but all of them have P_{M_2}. Similarly different microorganisms have different $P_{S\alpha}$, but at least some elements of P_S occur in all of them. Generalizing by induction, it is natural to postulate:

(C). The spaces S_{0u} which represent all possible unicellular organisms are obtained from S_P by assigning to one cell any possible space S_0, with the exception of such elements $P_{i\alpha}^{(n_i)}$ or combinations thereof as would be incompatible with the size of a cell or with physical laws.

The last restriction is essential for example in the following case: Consider the property P_H of homeostasis. Amongst its elements the set P_H contains the subset P_{H_t} of temperature regulation. While some microorganisms show other homeostatic properties P_H, for example osmoregulation (Prosser, 1950), no unicellular organism can show temperature regulation, because, as simple calculations show, the maintenance of any appreciable difference in temperature between a single cell and its environment would require such rates of heat producing reactions as are incompatible with known physicochemical laws, because of the tremendous specific surface of a single cell.

In addition to (C), we postulate:

(D). All possible multicellular organisms are represented by S_0, and conversely, any organism which corresponds to an S_0 is possible.

A number of interesting conclusions follow almost immediately from (A)-(D), without a more detailed specification of the structure of the primordial space S_P.

From (A) it follows that if we have an S_0, in which $P_{i\alpha} \longrightarrow P_{k\beta}$, then in the primordial we have $P_i \longrightarrow P_k$. Hence, from (D) it follows that there exist organisms, in which $P_{i\mu} \longrightarrow P_{k\nu}$, where μ and ν are in general different from α and β. From (C) it follows that there exist unicellular organisms, in which $P_{i\mu} \longrightarrow P_{k\nu}$, unless the exist-

ence of either $P_{i\mu}$ or $P_{k\nu}$, or both, is incompatible with the size of a single cell.

Thus from observations of some relations within an organism, we may infer the existence of other organisms in which different but corresponding relations exist.

Let us consider the sequence $P_S \longrightarrow P_C \longrightarrow P_M$. As we have seen, an important subset of P_M is P_{M_1}, the subset of molar orderly movements. In a unicellular organism this may be represented by amoeboid movements or ciliary or flagellary movements, which we shall denote correspondingly by P_{M_a}, P_{M_c}, P_{M_f}. We have

$$P_{M_a} \subset P_{M_1}; \qquad P_{M_c} \subset P_{M_1}; \qquad P_{M_f} \subset P_{M_1}. \tag{8}$$

In a higher animal different cells specialize in the three different subsets; the leucocytes, for example, in P_{M_a}; cells of respiratory epithelium in P_{M_c}; spermatozoids in P_{M_f}.

A subset of P_{M_1} is represented by contractile muscular tissues.

A movement of a unicellular organism, for example an amoeboid movement, plays several roles in the life of the organism.

(a) It propels the organism as a whole in space, towards food or away from the enemy;

(b) it orients the organism differently with respect to different stimuli, thus

(c) changing possibly the effectiveness of the stimulus;

(d) it helps ingestion of food into the digestive vacuole, and

(e) it may cause an eventual movement of food in the latter. It also

(f) in general affects the transport of substances inside the cell.

The sets of movements which produce correspondingly the effects (a), (b), (c), (d), (e), and (f) are included in P_{M_1}. In line with (A), (B), and (D), different cell types specialize in some higher organisms in each of those subsets of movements, which we shall denote correspondingly by $P_{M(a)}$; $P_{M(b)}$; $P_{M(c)}$; etc. We have

$$P_{M(a)} \subset P_M \tag{9}$$

and similarly for $P_{M(b)}$ and the others.

The skeletal muscles are general representatives of $P_{M(a)}$; they also represent the subset $P_{M(b)}$. The ciliary muscle of the eye or the muscles of the tympanic membrane have properties which belong to $P_{M(c)}$.

Instead of the general sensitivity P_S we also have in a higher animal several subsets of P_S, some of which we discussed above. The same holds for P_C.

Let P_{Sv} denote the set of visual sensitivities of all kind. We have

$$P_{Sv} \subset P_S . \tag{10}$$

In a primordial we have $P_S \rightarrow P_C \rightarrow P_M$. Hence it follows from (A) that in *some* higher organisms we must have:

$$P_{Sv} \rightarrow P_C \rightarrow P_{M(d)} . \tag{11}$$

In words: There exists higher organisms, in which gastrointestinal movements are affected by visual stimuli. A well-known example is the vomiting at the sight of some unpleasant things. By the same argument, we have more generally

$$P_{S\alpha} \rightarrow P_C \rightarrow P_{M(d)}, \tag{12}$$

which states that in some animals different sensory stimuli affect the gastrointestinal motility.

As we have seen, the more complex an animal, the more subsets $P_{i\alpha}$ are connected to a given subset $P_{k\beta}$, if $P_i \rightarrow P_k$. Hence, the higher the animal, the greater the variety of sensory stimuli, which affect the gastrointestinal motility. Man is the highest of the presently existing animals, though there is no reason to assume that it is represented by a maximal S_0. We should, however, expect the human gastrointestinal tract to be more sensitive to a great variety of sensory stimuli, than in any of the other animals.

To the extent that our psychological experiences are manifestations of a complex interplay of sensory activities, we may state that it follows from (A), (B), and (D) that in man, as well as in some animals, psychic disturbances produce gastrointestinal troubles. This is a well-known fact. This does not follow, however, and cannot follow from any metric biophysical theory, unless specifically assumed. It does follow, however, from the general principle of biotopological mapping, as formulated here. It cannot be deduced from considerations of natural selection, since its adaptive value is, if anything, negative, at least for the usual occupations of man.

By the same argument we see that there exist animals, in which sensory stimuli and specifically in man, psychic disturbances,

affect the cardiovascular phenomena. We merely substitute in (12) $P_{M(f)}$ for $P_{M(d)}$. In this connection it is interesting to note that "stimulation of almost any afferent nerve of the body can affect the heart rate" (Carlson and Johnson, 1953, p. 161).

From $P_S \longrightarrow P_C \longrightarrow P_M$ it follows, according to (A), that

$$P_{S\alpha} \longrightarrow P_{C\beta} \longrightarrow P_{M\gamma}, \tag{13}$$

where $P_{M\gamma}$ is any subset included in P_M.

Hence we may substitute for $P_{M\gamma}$ any subset contained in P_{M_2}. But P_{M_2} represents the different molecular orderly movements, such as, secretion. In particular the set P_{M_ϵ} of "secretions of different digestive enzymes" is included in P_{M_2} and hence in P_M. Therefore we have

$$P_{S\alpha} \longrightarrow P_{C\beta} \longrightarrow P_{M_\epsilon}. \tag{14}$$

In words: In some animals sensory stimuli affect the secretion of digestive enzymes. In men we should expect psychological states to affect such a secretion.

A biological property of an organism is affected whenever any predecessor is affected. If a given $P_{i\alpha}$ has, say, n predecessors and if we assume equal probability for any of them being disturbed, then the probability that an observed disturbance of the property $P_{i\alpha}$ is actually due to a disturbance of a predecessor, and not of $P_{i\alpha}$ itself, is $(n-1)/n$. To know the total number of predecessors for a given $P_{i\alpha}$ we must know the structure of S_P which we do not know. But even from a simple general consideration as that made on page 76 we see that for P_M, and therefore for any $P_{M(d)}$ or P_M, $n \geqslant 4$, at the very least. Hence the probability of a given gastrointestinal disturbance being due to disturbances of other parts of the organism is greater than 0.75. To the extent that the psychological disturbances involve $P_{S\alpha}$'s and $P_{C\beta}$'s, we can infer that the percentage of all observed gastrointestinal disturbances, which is due to psychic disturbances, is greater than 60%. It is said to be actually over 80%. Consider now in S_P the relation of P_M to some following P_i's. Molar movements are followed by feeding reactions P_F. So are the molecular orderly movements, because diffusion gradients and active transport bring food from the surroundings towards the cell in non-motile cells. Hence

$$P_M \longrightarrow P_F \tag{15}$$

in the primordial. Denote by $P_{M(\text{sec})}$ the subset of P_M which contains all the secretory properties. Since $P_{M(\text{sec})} \subset P_M$, therefore from (15) and from (A) and (B) it follows:

$$E(S_0)\colon P_{M(\text{sec})} \subset S_0.P_{F\alpha} \subset S_0.P_{M(\text{sec})} \rightarrow P_{F\alpha}. \tag{16}$$

In words: There are organisms in which secretory phenomena produce feeding reactions. An example of this is offered by *Urechis* which secretes mucous bags that filter out food particles and are eventually swallowed (Prosser, *loc. cit.* p. 145). Another example is the secreted spider-web which catches the prey.

In some unicellulars the movements P_{M1} affect the transport of substances both within the cell (by stirring "the protoplasm") and outside of it. (Ingestive movements of cilia.) Denoting phenomena of transport in general by P_T, we thus have:

$$E(S_{0u})\colon P_{M1} \subset S_{0u}.P_T \subset S_{0u}.P_{M1} \rightarrow P_T. \tag{17}$$

Hence it follows from (A) and (C):

$$P_M \subset S_P.P_T \subset S_P.\supset.P_M \rightarrow P_T, \tag{18}$$

where $\supset$ is the sign of implication. Hence, in the primordial we have $P_M \rightarrow P_T$. But then it follows from (A):

$$E(S_0)\colon P_{M1\alpha} \subset S_0.P_{T\beta} \subset S_0.P_{M1\alpha} \rightarrow P_{T\beta}. \tag{19}$$

Put for $P_{M1\alpha}$ the movements of skeletal muscles, which are propelling the organism in space. Put for $P_{T\beta}$ the set of circulatory phenomena. Then (19) states that in some higher organisms such movements of skeletal muscles affect the circulation. Example: The venous circulation in man is largely due to the "kneading" action of skeletal muscles. Effects of body musculature on circulation are also known in a number of lower animals (Prosser, *loc. cit.*).

The general principles (A)-(D) apply to both animals and plants. The latter are perhaps characterized by the fact that $P_{M_{11}} = 0$; the subset of all amoeboidal movements of the cell is empty. We have $P_{M_{11}} \subset P_{M_1}$. But $P_{M_1} \neq 0$, since we have the flow of water in plants. The set of flagellate movements is not empty in lower unicellular plants. Similarly the subset of P_C which contains the conduction due to electrochemical phenomena (nerve conduction) is empty in plants. However, from $P_S \rightarrow P_C \rightarrow P_M$ in the primordial it follows:

$$E(S_0)\colon P_{S\alpha} \subset S_0 . P_{C\beta} \subset S_0 . P_{M\gamma} \subset S_0 . P_{S\alpha} \longrightarrow P_{C\beta} \longrightarrow P_{M\gamma} . \quad (20)$$

This applies to plants as well as to animals. If $P_{S\alpha}$ denotes any sensitivity to external stimuli, $P_{C\beta}$—chemical mediation, and $P_{M\gamma}$ denotes either the movement of water through tracheae or the movement of food-containing solvents through sieve cells, then (20) states that adequate stimulation of plants, say by light, affects both the flow of sap and the translocation of metabolites.

The subset of all secretions, which is included in P_{M2}, includes such subsets as secretion of wastes, secretion of poisons, secretion of substances useful to other organisms, and secretion of substances lethal or otherwise harmful to other organisms. From (C) it follows that there must exist microorganisms which secrete substances that are either lethal or otherwise harmful to some other organisms. The toxins of some pathogenic bacteria is one example. The set of substances harmful to some other organisms includes the subset of substances harmful to some microorganisms. The antibiotics, like penicillin, are an example.

By the same token there must exist microorganisms which produce substances that are useful to other organisms, which is a well known fact.

The finding of different possible subsets of a set P_i may be a matter of logic. A set P_i consists of all conceivable subsets included in it, as long as the existence of such subsets is compatible with physical laws. Sometimes the possibility of a subset $P_{i\alpha}$ is shown by experiment.

In many relatively higher animals there are cells which upon stimulation with appropriate substances, the antigens, produce special proteins, the antibodies. The production of antibodies is thus a subset of the set P_{Me} of metabolic phenomena. The sensitivity to antigen is a subset of the set P_S. We shall designate the former by $P_{Me(a)}$, the other by $P_{S(a)}$. From (C) it follows that there must exist unicellular organisms which produce antibodies when stimulated by an appropriate antigen. So far no such microorganism has been definitely found, though there is a report of antibody production by yeast (Fox and Plaisted, 1953; Cushing and Campbell, 1957).

This is an example of prediction made from the general principles proposed here.

Another conclusion is also interesting. We have $P_{S(a)} \subset P_S$ and $P_{Me(a)} \subset P_{Me}$. We also have in higher organisms:

$$P_{S(a)} \rightarrow P_{i\alpha} \rightarrow \ldots P_{m\gamma} \rightarrow P_{Me(a)}, \tag{21}$$

where $P_{i\alpha} \rightarrow \ldots P_{m\gamma}$ denotes the possible intermediate sequence of points of S_0, which as yet are unknown. From (A) and (21) it follows that in a primordial

$$P_S \rightarrow P_i \rightarrow \ldots P_m \rightarrow P_{Me}, \tag{22}$$

and then again from (A) that there exist multicellular organisms in which

$$P_{S\mu} \rightarrow P_{i\nu} \rightarrow \ldots P_{m\omega} \rightarrow P_{Me(a)}. \tag{23}$$

Here $P_{S\mu}$ stands for sensitivity to any stimulus, such as light, heat, etc. Expression (23) states that *in some cases* antibodies may be formed in multicellular organisms by "physical stimuli." This reminds us of the "physical allergy" phenomena (Boyd, 1956), which seem, at least in some cases, to be connected with actual formation of "something" that can be transferred passively by the serum (Sherman and Seebohm, 1950). Alternative explanations of the observed phenomena seem, however, possible (Boyd, *loc. cit.*). Thus the above conclusion cannot be regarded as verified. Neither does it seem to be yet disproved.

By the same line of reasoning we should expect that some plants produce antibodies. Indications of the existence of such a phenomenon have been found (Wallace, 1950). Again, however, a different interpretation of Wallace's observation has been suggested (Luria, 1950). The evidence against production of antibodies by plants is considered by some to be conclusive (Cushing and Campbell, *loc. cit.*). However, in view of the fact that still very few plants have been investigated, the search would be worth while to be continued. Should, however, such a search fail definitely, this would lead to definite conclusions which are again verifiable by experiments. As has been remarked, in plants the set $P_{M_{11}}$ of amoeboid movements is empty. There are other subsets $P_{i\alpha}$ which are empty in plants. Plants are characterized by the set P_0 of subsets $P'_{i\alpha}$ which are empty in them. If plants do not produce antibodies, then $P_{Me(a)}$ is empty in plants. Either then $P_{Me(a)}$ is an

element of P_0, and in a sense enters into the definition of plants, or there must be some physicochemical relation between some of the $P'_{i\alpha}$ and $P_{Me(a)}$, such that the absence of $P'_{i\alpha}$ implies the absence of $P_{Me(a)}$. The first possibility does not seem very likely. The second possibility suggests immediately a possible physicochemical connection between $P_{M_{11}}$ and $P_{Me(a)}$. There may be a common biophysical or biochemical factor involved in certain type of movements of the cell and production of antibodies. It may, perhaps, be significant that antibodies are apparently produced by reticuloendothelial cells which resemble more than others some amoeboid forms. If there is a relation between $P_{M_{11}}$ and $P_{Me(a)}$, then, however, we should look for antibody production by unicellulars not to yeasts, but rather to amoebae.

The above is meant to illustrate that even in its immediate and simplest consequences, the postulates (A)-(D) do have a predictive and heuristic value. More of this should be found by further elaborating the set-theoretical properties of S_0 and S_P.

We have considered two subsets of P_C: the subset of what may be called nervous conduction and the subset of humoral chemical conduction. We shall denote the former by P_{C1}. The set P_{C1} includes two important subsets, P_{C1_0} and P_{C1h}, such that

$$P_{C1_0} \subset P_{C1} \quad \text{and} \quad P_{C1h} \subset P_{C1}. \tag{24}$$

The first one, P_{C1_0}, we shall call, for lack of a better term, nonhysteresis conduction; the second, P_{C1h}, hysteresis conduction. The first is characterized by independence of a given conduction phenomenon on the past history. The other is characterized by the fact that the character of the conduction depends on past conductions. No more detailed specifications are necessary here. In its simplest form a hysteresis conduction may manifest itself merely by the fact that a given response to a given stimulus is facilitated by repetition. In its most complex manifestations hysteresis conduction may result in most complicated phenomena of learning in higher animals. Whatever physiological or biological theory of learning we accept, whether we consider it based on the existence of self-circuited neurons (Rashevsky, 1948) or on synaptic changes of a physical or chemical nature (Shimbel, 1950), or any other different conceivable mechanism, in all of them we deal with hysteresis conduction in the central nervous system. Conduction

here is understood not only along a nerve-fiber, but including synaptic transmission as well.

From (C) it follows that there must exist unicellular organisms which exhibit some form of hysteresis conduction. The turning around of a paramecium in a capillary tube with fewer turns after several trials is an example of this (Prosser, *loc. cit.*, p. 842). Whether we call such phenomena elementary acts of learning or not is immaterial. Relationally they are isomorphic to the more complex phenomena of learning in higher animals.

So far as relations between the different P_i's and $P_{i\alpha}$'s are concerned, we have considered only the relation of immediate precedence R, and immediate succession $\breve{R}$, its converse. If we represent S_0 and S_P by directed graphs then we have here a graphical representation of the class of relations R. We can apply to this some standard expressions of the theory of relations, but we do obtain only relatively trivial results. We give here just two illustrations.

Thus, if we use the rather convenient notations of J. Riguet (1948) and denote by pr_1 the argument of the relation R, we have the formula:

$$pr_1\, SR \subset pr_1\, R\,, \tag{25}$$

where SR denotes the product of the relations S and R.

In particular we have

$$pr_1\, R^2 \subset pr_1\, R\,. \tag{26}$$

If R is the relation between $P_{i\alpha}$ and $P_{k\beta}$ when $P_{i\alpha}$ immediately precedes $P_{k\beta}$, then R^2 is the relation between two points such that there is a third one, immediately preceding the second one and immediately succeeding the first. We shall say that the second point is a second-order successor of the first one. In that case (26) states that the number of points P_i which have immediate successors is less or equal to the number of points which have second-order successors.

Consider the property: "Cells are sensitive to different forms of light" as a relation between the cell c and light l. In symbols cRl.

Let in the relation xRy, $R(x)$ denote the set of all y's, such that xRy. Let

$$R(X) = \bigcup_{x \in X} R(x); \qquad R[X] = \bigcap_{x \in X} R(x)\,. \tag{27}$$

Then (Riguet, *loc. cit.*) we have:

$$X_1 \subset X_2 . \supset . R(X_1) \subset R(X_2) , \tag{28}$$

$$X_1 \subset X_2 . \supset . R[X_2] \subset R[X_1] . \tag{29}$$

$R(c)$ is the set of all forms of light to which a given cell is sensitive. If X is a given set of cells, then $R(X)$ is the set of all forms of light to which we find sensitivity amongst cells of the set X; while $R[X]$ is the set of all forms of light, such that every cell of X is sensitive to all of them. If X_2 is the set of all cells of an organism and X_1 a set of cells of a part of it, then expressions (28) state that the number of different forms of light to which we find sensitivity amongst the cells of a part of the organism is less or equal to the number of all forms of light to which we find sensitivity amongst cells of the whole organism. Expression (29) states that the number of different forms of light such that every cell of a given part of an organism is sensitive to it is greater or equal to the number of different forms of light such that every cell of the organism is sensitive to all of them.

By applying expressions (28) and (29) to the inverse relation $\breve{R}$ (different forms of light affect different cells), we find even more trivial statements:

The number of cells which are sensitive to any wave length of light is greater or equal to the number of cells which are sensitive to only some selected spectral range. And: The number of cells which are sensitive to all wave lengths within a given spectral range is less than or equal to the number of cells which are sensitive to all wave lengths within a wider spectral range.

The above statements while true have no predictive or heuristic value. It is, however, rather likely that by studying in a similar manner more complicated relations between pairs of points in S_0 and S_P we shall arrive at much more valuable conclusions.

A systematic application of theory of relations to biology and an attempt to build an axiomatic biology on this basis has been made in the noteworthy research of J. H. Woodger (1937). Though Woodger's approach differs seemingly very radically from ours, the possibility cannot be denied that the further development of both approaches may establish a number of points of contact between them. In any case, to Woodger belongs the credit of having clearly emphasized the importance of relational aspects in biology and to

have made the first systematic mathematical study of those relational aspects.

The principal difficulty found in the present approach is that the graphs of S_P or S_0 do not represent merely such simple relations as immediate succession. Two biological properties of which one immediately succeeds the other are usually characterized by other relations which are more inclusive than the relation R of immediate succession.

No elaborate scientific system can be developed on the basis of one or two general principles only. Other principles or postulates will have to be added in the future to those presented here. Some of them are likely to be of a restricting nature, reducing somewhat the generality of (A) or (C), just as (B) does restrict (A). As we have already suggested in I, the principle of maximum simplicity, introduced by us (Rashevsky, 1948), or as David Cohn (1954, 1955) aptly calls it, the principle of optimal design, may be used as another general mathematical principle, together with the principle of biotopological mapping. The principle of optimal design may possibly eliminate some of the possibilities presented by (A).

The general formulation presented here, unlike the ones suggested in I-VI, does not give any indications as to arrangements of various differentiated cells into organs. It seems that an additional rule of a relational character must be added to (A)-(D).

It may be asked as to whether we should not expect on the basis of the foregoing to have organisms which are sensitive to X-rays or γ-rays, or which can perform other tasks than those so far observed. The answer is in the affirmative, since, for example, sensitivity to γ-rays is included in sensitivity to radiation. Does it then follow that we must predict organisms to develop in the future, which will have such properties? Not necessarily.

Through science and technological invention man has found means to detect γ-rays and to perform numerous tasks which no organism can do directly. All such performances we do not consider as part of the biological properties of the human organism. But all such performances are definitely the result of biological manifestations of the human organisms, in particular of the brain. And *relationally* it is quite consistent to extend the notion of organism to include the results of the direct biological properties. Relationally there is no difference between the *Urechis* secreting a mucous bag which catches food and then swallowing it, or the

spider secreting its web, and a human-being manufacturing as a result of his brain-work a machine which processes food and makes it possible for it to be swallowed.

Such an extension of the relational principles will necessitate a more detailed study of relations between an organism and its surroundings, which thus far have been considered only sketchily. The principle of optimal design may then lead to the conclusion that organisms which perceive X-rays or γ-rays directly may not develop, because it is simpler to develop an appropriate brain which can invent technological devices for the performance of such tasks than to develop an organism which performs them directly.

An extension of the relational principles, such as mentioned above, will also include many aspects of social relations, both in man and animals.

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LITERATURE

Alexandroff, P. and H. Hopf. 1935. *Topologie*. Vol. I; Berlin: J. Springer.

Boyd, W. C. 1956. *Fundamentals of Immunology*. Third Ed. New York: Interscience Publishers.

Carlson, A. J. and V. Johnson. 1953. *The Machinery of the Body*. Fourth Ed. Chicago: The University of Chicago Press.

Cohn, David. 1954. "Optimal Systems: I. The Vascular System." *Bull. Math. Biophysics.*, **16**, 59–74.

———. 1955. "Optimal Systems: II. The Vascular System." *Ibid.*, **17**, 219–27.

Cushing, J. E. and D. M. Campbell. 1957. *Principles of Immunology*. New York: McGraw-Hill.

Fox, S. W. and E. Plaisted. 1953. "The Precipitability of Two Modified Proteins." *Proc. Soc. Expl. Biol. Med.*, **84**, 392–94.

Luria, S. E. 1950. "Comment [on the Paper by J. M. Wallace]." In *Viruses*, pp. 98–99. (M. Delbrück, Ed.) Pasadena: California Institute of Technology.

Prosser, C. L. 1950. *Comparative Animal Physiology*. Philadelphia: W. B. Saunders Co.

Rashevsky, N. 1948. *Mathematical Biophysics*. Rev. Ed. Chicago: The University of Chicago Press.

———. 1954. "Topology and Life. In Search of General Mathematical Principles in Biology and Sociology." *Bull. Math. Biophysics*, **16**, 317–48.

———. 1955a. "Note on a Combinatorial Problem in Topological Biology." *Ibid.*, 17, 45–50.

———. 1955b. "Some Theorems in Topology and Possible Biological Interpretation." *Ibid.*, 19, 111–26.

———. 1955c. "Some Remarks on Topological Biology." *Ibid.*, 17, 207–18.

———. 1955d. "Life, Information Theory, and Topology." *Ibid.*, 17, 229–35.

———. 1956a. "The Geometrization of Biology." *Ibid.*, 18, 31–56. Erratum: *Ibid.*, 18, 233–35.

———. 1956b. "Contributions to Topological Biology: Some Considerations on the Primordial Graph and on Some Possible Transformations." *Ibid.*, 18, 113–28.

———. 1956c. "What Type of Empirically Verifiable Prediction Can Topological Biology Make?" *Ibid.*, 18, 173–88.

———. 1957a. "A Note on Geometrization of Biology." *Ibid.*, 19, 201–04.

———. 1957b. "Remark on an Interesting Problem in Topological Biology." *Ibid.*, 19, 205–07.

Riguet, J. 1948. "Relations Binaires, Fermetures, Correspondances de Galois." *Bull. Soc. Math.*, (France), 76, 114–55.

Sherman, W. B. and P. M. Seebohm. 1950. "Passive Transfer of Cold Urticaria." *J. Allergy*, 21, 414–24.

Shimbel, A. 1950. "Contributions to the Mathematical Biophysics of the Central Nervous System, With Special Reference to Learning." *Bull. Math. Biophysics*, 12, 241–75.

Wallace, J. M. 1950. "Immunological Properties of Plant Viruses." In *Viruses*, pp. 93–98. (M. Delbrück, Ed.) Pasadena: California Institute of Technology.

Woodger, J. H. 1937. *The Axiomatic Method in Biology.* Cambridge: Cambridge University Press.

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