Mathematical Biophysics

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THE application of physico-mathematical methods to biology has been advocated now and again by scientific workers; but until recently no systematic attempt to create a mathematical biology has been made, and the advocates of this 'science to come' have confined themselves to outlining the possibilities of such an approach. True, there is a wealth of literature on the application of mathematical statistics to various biological phenomena; but the whole of this field of research lacks almost completely the physical point of view. General physics is accepted as of paramount importance in the study of biological phenomena; the application of physical methods has already resulted in important biological discoveries. But most of this application is restricted to the use of physical apparatus in biological experiment; and very little attempt has been made to gain an insight into the physicochemical basis of life, similar to the fundamental insight of the physicist into the intimate details of atomic phenomena. Such an insight is possible only by mathematical analysis; for our experiments do not and cannot reveal those hidden fundamental properties of Nature. It is through mathematical analysis that we must *infer*, from the wealth of known, relatively coarse facts, to the much finer, not directly accessible fundamentals. The greatest advances of modern physics are due to such men as Einstein, Bohr, Heisenberg, Dirac, who unravel the mysteries of the physical universe by the power of their thought, using mathematics as their tool.

The objection has been frequently raised that mathematical methods, however useful in physical science, are inapplicable to biology, because of the tremendous complexity of biological phenomena. But this argument should really be used in favour of, rather than against, the application of mathematics to biology. A simple phenomenon can be understood by mere 'inspection', but it requires mathematical analysis to see through a complex system. The main thing is to apply mathematics methodologically correctly, by first studying abstract, over-simplified cases, which may even perhaps have no counterpart in reality. Afterwards the various complexities of the case have to be taken into account gradually, as second, third and higher approximations. This use of abstract conceptions in the beginning is *the* characteristic of the physico-mathematical method. Violation of this rule, and all attempts to start with actual cases in all their complexity, result in failure and have contributed to a sceptical attitude towards mathematical methods*.

The following brief review of my own researches in mathematical biophysics may serve to illustrate the fruitfulness of a mathematical approach to this field.

The fundamental living unit is the cell; hence it is with the study of a cell that we must begin. But, faithful to our rule, we must start with a mathematical description not of any given type of actual cell, but of an abstract concept of a cell. Not only are there innumerable varieties of cells, but also no two cells are quite alike. They differ in size and structure and chemical composition. Most of them possess a nucleus; some have several, others have none. Some cells consume oxygen, some not. Some metabolise one type of substance, others a different type. If we discard all such properties of a cell as are not common to absolutely *all* cells, we arrive at the following definition of a cell, which holds for *all* cells whatsoever and which we take as defining our abstract conception of a cell.

A cell is a small liquid or semi-liquid system, in which physico-chemical reactions are taking place, so that some substances enter into it from the surrounding medium and are transformed, through those reactions, into other substances. Some of these other substances remain within the system, causing it to increase in size; some diffuse outwards.

Such a system is no longer so complex as to forbid any application of mathematical analysis, and we shall proceed to investigate mathematically various properties of such systems, or in other words, various consequences of the above definition.

At a first glance not much can be done with such a general definition, but actual analysis shows quite the opposite. As in geometry extremely simple axioms and definitions lead us to very complex propositions by reasoning, so will the same mathematical reasoning lead to important conclusions from the above definition of the cell[1].

First of all, it is easily demonstrated that whenever a system consumes or absorbs any kind of substance in solution in the surrounding medium, the concentration of this substance will not remain uniform, either in the system itself, or in the surrounding medium. The concentration outside of the system will have a gradient towards the system: in the system itself there will be a

* Cf. my article in "Philosophy of Science", 1, 176; 1934.

gradient from the periphery towards the inside. The reverse holds true whenever the system produces a substance which diffuses outwards into the *milieu externe*. The concentration will be greatest inside, and will decrease towards the periphery, and will then further decrease with increasing distance from the system. The exact variation of the concentrations from point to point will depend on a number of factors, such as the size and shape of the system, the diffusion constants inside and outside, the permeability of the boundary, the type of reaction producing the gradient, etc. But whenever a reaction producing or absorbing a substance takes place in the system, *as is always the case with a living cell*, such gradients of concentration are present.

Any dissolved substance produces an osmotic pressure, which for dilute solutions is proportional to the concentration of the solute; hence, whenever concentration gradients are present, they result in non-uniformity of osmotic pressure. This in its turn results in forces, acting on each element of volume, and proportional to the gradients of pressure. Thus the very general and simple fact that *every cell metabolises* leads to the existence of a system of forces within and without the cell. Like the gradients of concentration, the exact distribution of these forces will vary from case to case; but they are always there.

Having thus deduced the existence of these forces, we must now investigate their possible effects. To this end we must investigate various possible cases, which open up an unexplored field to the mathematician.

We start with the simple case of a spherical homogeneous cell, which either absorbs or produces some substance at a constant rate per unit volume: this rate being independent of the concentration of the substance. The distribution of concentrations within and without the cell has in this case a spherical symmetry and can be easily calculated: the resultant force will be *zero*. But things are different if the cell is slightly deformed from its spherical shape. Mathematical investigation of the forces produced by such a deformed cell shows that, for substances absorbed by the cell, the forces are such as tend to restore the spherical shape; but for substances which are produced by the cell, the forces are such that they tend to increase the departure from the spherical and to *divide* the cell into smaller ones. Since in an actual cell substances are both produced and absorbed, the net result will depend on which forces prevail. This, again, is determined by various physical constants of the cell, the rates of reaction, etc.

Let us consider the more interesting case, when the *dividing* forces prevail. It can be shown that even in this case the cell will only become unstable and divide spontaneously when its size is greater than a certain critical value; for when the cell is below that size, surface tension, which opposes division, always prevails. This critical size can be calculated in terms of the above-mentioned constants of the cell. Although we do not know these constants with any accuracy, we have a fair knowledge of their order of magnitude, and can estimate the order of magnitude of the critical size at which a cell will divide, if it divides at all. The sizes thus calculated happen to be the same as the sizes of actual living cells[2]. We thus see that, merely by virtue of its metabolism, every cell contains in itself factors which may cause its division into two, whensoever in the course of its growth it comes to exceed a definite critical size. The half-cells grow on until they in turn divide, and so on.

As our next step, we must consider more complex cases of cells consisting of two phases, nucleus and cytoplasm. The mathematical treatment here becomes much more complicated, but the general results remain the same.

A further step leads us to non-spherical cells. At a first glance the existence of free, non-supported, liquid systems with a non-spherical shape sounds like nonsense, since we know from the laws of capillarity that in such a case the only stable shape of equilibrium is a sphere. But this holds true only when forces other than a *constant* surface tension are absent. Now, the presence of concentration gradients produces non-uniformities in the surface tension of the cell; this modifies the situation and makes non-spherical shapes of equilibria possible. But those non-spherical shapes are possible *only* so long as the cell metabolises; as soon as the cell dies its metabolism stops, the gradients disappear and the cell assumes a spherical shape. An illustration of this is found in many unicellular organisms, which possess oblong and sometimes eccentric shapes during life, but round up after death[3].

We have seen that the forces discussed above do not always produce division of the cell. In such a case, however, a cell will not grow indefinitely. As it increases its specific surface decreases, and the relative rate of growth decreases too. A stage will be reached when anabolism just balances katabolism, and no further growth will result.

The osmotic forces are not the only ones produced by concentration gradients. Other forces, due to attraction between various molecules, enter into play whenever concentration gradients are present. These forces may be of opposite sign to the osmotic ones. Taking them into account makes the whole picture much more complex, but the general conclusions remain as given above. We see that our apparently simple definition of a cell necessarily implies a complexity reminding one of the actual conditions in biological systems ![2]

An objection has been raised to all the above considerations that, in actual cells, protoplasmic streamings are often observed, which should stir the interior of the cell and even out the concentration gradients. This objection is based on fallacy. Not only does the existence of protoplasmic streaming constitute no argument against the existence of gradients, but it is a positive proof for their existence. Where there are streamings, there are the forces which produce them ; and if everything were homogeneous, no such forces could be produced. It is true that the occurrence of streamings will modify the distribution of forces, and so far this complication has not been taken into account ; it is one of the next problems on our programme. It has been already suggested that such a further generalisation of the theory may throw light on the mechanism of locomotion in the Protozoa.

Thus far we have been considering the effect of the forces produced by the cell on the cell itself ; but the concentration gradients outside the cell result also in forces between one cell and another. All those forces being of the same origin, there is a close relation between them. Whenever we have an aggregate of cells in which the dividing factors prevail, they will repel each other. On the other hand, when the 'restoring' factors prevail, cells attract each other. Of all cells, the neurones have most completely lost their property of dividing ; we should expect forces of attraction between them. Indeed the existence of such forces has been inferred by a number of neurologists, notably Ariens Kappers and Ramon y Cajal, from various observations. The peculiar irregularity in shape of the neurones and the existence of a great number of interneuronic connexions is also to be accounted for by those forces. It has been suggested that a formation of new anatomical connexions between neurones may be the cause of conditioned reflexes and learning. Calculation shows that the above forces may account for it. Under certain conditions they will produce an actual new connexion in a very small fraction of a second.

This leads us towards a mathematical theory of nervous functions. We find that, under very general conditions, aggregates of cells such as are studied above will possess many properties characteristic of the brain. These include differential discrimination of spatial and temporal patterns by learning, and what is known in psychology as 'Gestalt-transposition'. For details we must refer to the original papers[4].

Finally, the theory of intercellular forces has been applied to the form of cellular aggregates, forming multicellular organisms. It has been shown that those forces account in a general way for the various stages of embryonic development (blastula, gastrula, neurula), and for the gross features of the forms of various classes of animals[5].

Having thus started from a study of the most general properties of a cell, we arrive in a deductive, synthetic way at a possible understanding of such problems as "why we behave as we do" and "why we are shaped as we are".

We have not mentioned at all the 'mechanism-vitalism' controversy. The problems discussed here are entirely independent of its issue, if there be an issue[6]. Whether the present-day concepts of physics will prove sufficient to provide an exhaustive explanation of life, or whether new principles will be introduced in the future, the treatment of those problems will of necessity be mathematical, if it is to be exact and scientific and not to resolve itself into mere verbal disputes.

Much remains to be done, but there can be little doubt of the fruitfulness of this approach. The further we proceed, the more difficult become the mathematics involved ; but the results compensate for all difficulties. C. F. Gauss, "rex mathematicorum", derived many an inspiration for his purely mathematical discoveries from the study of physical phenomena. The time has come when mathematicians may find their problems in the ever-inspiring realm of living Nature.

[1] *Protoplasma*, **14**, 99 ; 1931. **15**, 427 ; 1932. **16**, 387 ; 1932. *Physics*, **1**, 143 ; 1931.
[2] Cold Spring Harbor Symposia on Quantitative Biology, **2** ; 1934.
[3] *Physics*, l.c.
[4] Forthcoming in "Philosophy of Science" and in the *Journal of General Psychology*.
[5] Protoplasma, **20**, 180 ; 1933.
[6] Cf. concluding paragraphs in "Philosophy of Science", l.c.

Racial Studies in Britain

THE proposals put forward by the Royal Anthropological Institute for an organised anthropometric survey of Great Britain (see NATURE, 135, 463; 1935) revives a project in anthropological research of which too little has been heard in recent years. It is a project which has had a curiously chequered history ; and its fate up to the present has been less than is deserved both by its intrinsic merits and by the enthusiasm and strenuous efforts of those who, from time to time, have endeavoured to bring it to practical effect. The story covers more than half a century