BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 2—1940

AN APPROACH TO THE MATHEMATICAL BIOPHYSICS OF BIOLOGICAL SELF-REGULATION AND OF CELL POLARITY

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In a cell, in which the permeability to a metabolite is a function of the concentration of that metabolite, situations may occur, in which the diffusion field will exhibit certain assymetric patterns, even though the cell may possess geometrically spherical symmetry. This pattern results in a polarity of the cell. Moreover, the pattern being the result of a dynamic equilibrium, it possesses the property of self-regulation. Dividing the cell in two results in the appearance of a similar pattern in each half-cell.

Another case when such self regulation and polarity occur is given by considerations of the action of the diffusion forces upon colloidal particles, which affect catalytically the metabolic reactions. A simple case is treated mathematically.

The problem of biological self-regulation offers many different aspects. One of the most fundamental of these, and at the same time one of the most difficult is that of the development of regulation eggs. Most drastic interference with the visible internal structure of these eggs may leave them still capable of producing normal embryos (Harvey, E. B., 1932, 1936). Such self-regulation has perhaps been *the* phenomenon, upon which claims of the existence of non-physical elements in biology have been based. While much has been written on the physical aspects of self-regulation and it has been pointed out, that even relatively simple physico-chemical systems may at times possess the property of self-regulation, yet all these general considerations and analogies do not bring us much nearer to the solution of the problem. If we are to incorporate eventually these phenomena into the field of mathematical biophysics, we must proceed by studying *theoretical models, which are sufficiently specific* to be applied not only to the phenomenon of self-regulation in general, but to some definite biological case of it. Of course, when such a model is developed, it is by no means to be regarded as *the* explanation of the particular phenomenon, for which it is intended as a model. Most likely there is a large number of different possible explanations. It is only by studying systematically all theoretically possible cases and by a comparison

of the mathematical deductions from each of those cases with available experimental data, that we may in the future arrive at a decision as to which, if any, of the theoretically studied situations actually occurs.

With this in mind, we shall now investigate a problem, which is suggested by such observations, as for instance those by E. B. Harvey (1932, 1936) on centrifuging *Arbacia* eggs. Subjecting them to a force 10,000 times that of gravity not only produces a definite stratification of the content of the egg, according to the specific gravity of the different constituents, but results eventually in a breaking up of the egg in two and even in four parts, each part containing *different* visible components. Yet, when fertilized, all four parts can give rise to normal embryos.

The early differentiation of the fertilized egg indicates definitely the preexistence of some sort of nonuniformities. At the same time these nonuniformities obviously cannot be connected with or even related to the visible material. Moreover, whatever latent nonuniformity pattern may have existed in the normal egg, the breaking of the latter into four parts of very different gross constitution must have resulted in each part acquiring again the same latent pattern, which characterized the original normal egg.

A suggestion has been made that the pattern responsible for the early differentiation is contained not in the cell volume, but on the surface in the cell membrane (Weiss, 1939). The latter being of a much more rigid nature than the more liquid interior of the egg, the centrifugal forces used in the experiment may not be sufficient to upset the inner structure of the membrane. Since there is a direct microscopic evidence for a superficial localization of the early noticeable differentiation of the egg (Weiss, 1939), it appears of interest to investigate this possibility more quantitatively.

It must however be remembered, that while there is good evidence for a more solid-like consistency of the egg membrane as compared with the interior of the egg, yet the membrane certainly cannot be considered as a solid bag, containing a liquid interior. For in such a case a force strong enough to break the egg into parts would simply tear the solid membrane, leaving the interior to flow out. The microphotographs taken by E. B. Harvey (1932, 1936) and reproduced by P. Weiss (Weiss, 1939, p. 191) show that under the influence of the centrifugal force the egg elongated and then divided by constriction in the middle. In other words the membrane at the equatorial region fuses together as only a liquid would do. If however the membrane is merely a very viscous liquid, sufficiently strong forces would upset its internal structure also.

I

Let us consider a spherical cell of radius r_0 cm., producing a substance at a constant rate q gm cm^{-3} sec^{-1}. Let the external concentration of the substance be c_0 gm cm^{-3} and the external diffusion coefficient D_e be very large, so that we may put $D_e = \infty$. This merely simplifies the calculations, without introducing any essential limitations. Let the internal diffusion coefficient be D cm^2 sec^{-1}. Assume further, that the membrane of the cell is not uniform in its physical constitution and that therefore its permeability is not the same at every point. Let the structure of the membrane possess an axial symmetry, thus imparting a polarity to the cell. Let at one pole the permeability have the value h_1 cm sec^{-1}, while at the other pole let that value be h_2 cm sec^{-1}. Due to such a nonuniform and asymmetric distribution of the permeability, the distribution of concentration of the produced substance within the cell will also not be spherically symmetric. In particular the concentration inside the cell at the membrane will vary from point to point.

To calculate the average concentration distribution in such a cell we shall use the usual approximation method (Rashevsky, 1940). Let $\bar{h}_1$ denote the *average* permeability in one hemisphere (Fig. 1), while

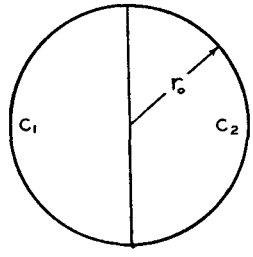

FIGURE 1

$\bar{h}_2$ denotes the average permeability in the other one. Correspondingly we shall denote by c_1 and c_2 the *average* concentrations *at the membrane* inside the cell in each hemisphere. Denoting by $\bar{c}$ the average concentration within the cell, we have

$$2D\frac{\bar{c}-c_1}{r_0} = \bar{h}_1(c_1 - c_0) \; ; \tag{1}$$

$$2D\frac{\bar{c}-c_2}{r_0} = \bar{h}_2(c_2 - c_0) \; ; \tag{2}$$

$$\frac{4}{3}\pi r_0^3 q = 2\pi r_0^2 \times 2D\frac{\bar{c}-c_1}{r_0} + 2\pi r_0^2 \times 2D\frac{\bar{c}-c_2}{r_0} \; . \tag{3}$$

Equations (1) and (2) give:

$$c_1 = \frac{2D\bar{c} + r_0\bar{h}_1 c_0}{2D + r_0\bar{h}_1}\,; \qquad c_2 = \frac{2D\bar{c} + r_0\bar{h}_2 c_0}{2D + r_0\bar{h}_2}\,. \tag{4}$$

Hence

$$\bar{c} - c_1 = \frac{r_0\bar{h}_1(\bar{c} - c_0)}{2D + r_0\bar{h}_1}\,; \qquad \bar{c} - c_2 = \frac{r_0\bar{h}_2(\bar{c} - c_0)}{2D + r_0\bar{h}_2}\,. \tag{5}$$

Introducing equation (5) into equation (3), we find after rearrangements:

$$\bar{c} = c_0 + \frac{r_0 q}{3D}\,\frac{(2D + r_0\bar{h}_1)(2D + r_0\bar{h}_2)}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,. \tag{6}$$

For $\bar{h}_1 = \bar{h}_2 = h$, that is for a uniform membrane, equation (6) reduces to

$$\bar{c} = c_0 + \frac{qr_0}{3\bar{h}} + \frac{qr_0^2}{6D}\,, \tag{7}$$

as should be the case*.

Equation (6) introduced into equation (4) gives

$$c_1 = c_0 + \frac{2r_0 q}{3}\,\frac{2D + r_0\bar{h}_2}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,;$$

$$c_2 = c_0 + \frac{2r_0 q}{3}\,\frac{2D + r_0\bar{h}_1}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}\,. \tag{8}$$

Thus an asymmetry of the cell membrane will result in an asymmetry of the diffusion field within the cell. For the approximate calculation of this field we considered two discrete *average* values $\bar{h}_1$ and $\bar{h}_2$ of the permeability. The actual value of the permeability is assumed to vary continuously along the meridian. If this variation is monotonic, then a division of the cell into several parts by sections parallel to the equator will produce smaller cells, each having a similar polarity.

We have here a model which may reproduce some of the properties of actual cells. Yet this model does really not show any regulation. It is essentially a "mosaic" model, the mosaic being attributed to the membrane and possessing a rather simple pattern. The above

* The equations derived for a spherically symmetrical cell previously (Rashevsky, 1940) differ from equation (7) in the values of the numerical coefficients, which are respectively 2/9 and 1/9. This is due to the fact that we considered there actually a cylinder whose length equals its diameter.

considerations suggest however an interesting possibility of actual regulation, which we shall mention here.

Suppose that the permeability h of the membrane is itself influenced by the concentration c of the metabolite in its vicinity. Such a supposition is biologically rather plausible. Let this influence be such, that an increase of c results in a decrease of h. Let the permeability be originally uniform all over the membrane. Then the diffusion field will possess spherical symmetry. Let now the concentration become, because of some disturbance, slightly higher at one region of the membrane. This will result is a decrease of permeability in that region, thus creating a condition similar to the one discussed above. But in that case the concentration c at the membrane will be larger in the region with smaller h. This can be readily seen from equations (8), which give:

$$c_1 - c_2 = \frac{2r_0^2 q(\bar{h}_2 - \bar{h}_1)}{\bar{h}_1(2D + r_0\bar{h}_2) + \bar{h}_2(2D + r_0\bar{h}_1)}. \tag{9}$$

Equation (9) shows, that when $\bar{h}_1 < \bar{h}_2$, then $c_1 > c_2$. Thus the resulting change in permeability will result in a further increase of c at that place, thus enhancing the asymmetry. We may ask whether under such conditions stable asymmetric configurations may not be obtained.

Mathematically the problem reduces to the following. Let h be a prescribed function of c, $h = f(c)$. We then have $\bar{h}_1 = f(c_1)$ and $\bar{h}_2 = f(c_2)$. Denote the right hand side of the first equation (8) by $u_1(h_1, h_2)$ and the right hand side of the second equation (8) by $u_2(\bar{h}_1, \bar{h}_2)$. Then, since $\bar{h}_1$ and $\bar{h}_2$ are functions of c_1 and c_2, we find that $u_1(\bar{h}_1, \bar{h}_2) = u_1[f(c_1), f(c_2)] = v_1(c_1, c_2)$; and similarly $u_2(\bar{h}_1, \bar{h}_2) = v_2(c_1, c_2)$. We must now look for *stable* solutions of the system of equations:

$$\begin{aligned} c_1 &= v_1(c_1, c_2), \\ c_2 &= v_2(c_1, c_2), \end{aligned} \tag{10}$$

other than $c_1 = c_2$, which corresponds to a spherical symmetry. It can be shown that when $f(c)$ is monotonic, only spherically symmetric solutions are possible. Physically this is due to the fact that when an asymmetric configuration is obtained in a manner described above, then any slight increase of c at the *lower* end will result in a decrease of h at that end, with a resulting further increase of c, until it reaches the same value as at the higher end. However we cannot *a priori* ex-

clude the possibility that for some special types of the function $f(c)$ asymmetric solutions of the system (10) may exist. The problem now is to investigate whether this is possible and if so, for what forms of $f(c)$. Furthermore we shall have to ascertain, that if such possibilities exist, the necessary form of $f(c)$ is biologically plausible or at least possible.

For given $\bar{h}_1$ and $\bar{h}_2$, the values $c_1 = u_1(\bar{h}_1, \bar{h}_2)$ and $c_2 = u_2(\bar{h}_1, \bar{h}_2)$, as expressed by equations (8), are obtained by considerations of material balance in a stationary state. Therefore when $c_1 > u_1$, c_1 will decrease until it reaches the value u_1. Conversely if $c_1 < u_1$, c_1 will increase until it reaches the value u_1. A similar thing holds for c_2. Therefore the conditions of stability require that any small increment of c_1 would result in a lesser increment of $u_1(\bar{h}_1, \bar{h}_2)$ or, which is the same, of $v_1(c_1, c_2)$, so that $\partial v_1/\partial c_1 < 1$; and similarly $\partial v_2/\partial c_2 < 1$. For the symmetrical case, when $c_1 = c_2$, it may happen that the configuration will be stable for a simultaneous equal increase or decrease of c_1 and c_2, but unstable for an increase of c_1 accompanied by a decrease of c_2 or vice versa.

If asymmetric stable solutions of the system (10) exist for some forms of $f(c)$, and if they exist for a sufficiently large range of values of r_0, then we have a case of a true self-regulation. No matter how we divide such a cell, whether equatorially or meridionally, no matter how we stir up its content, the cell or each part of it within the admissible range of r_0, will automatically reconstitute the asymmetry of the diffusion field.

We have however rather formulated a problem than given a solution. A consideration of a different physical mechanisms leads us to a simpler solution of this type of problem.

II

Consider again a spherical cell, producing a substance. Let however now the permeability be a constant, h. Let moreover the cell contain a catalyst, which *inhibits* the reaction, so that the higher the concentration n of the catalyst, the smaller the rate of production q. If the molecules of the catalyst are rather large, or if the latter is present in a colloidal state, with a particle size $> 2 \times 10^{-7}$ cm., then as we have seen elsewhere (Rashevsky, 1938), due to the action of the diffusion forces, these particles will show a pronounced nonuniformity of distribution, their concentration n being larger in regions of smaller concentrations c of the diffusing metabolite. For a produced substance, when the negative gradients are directed outwards, the catalyst will accumulate at the periphery, decreasing there the rate of pro-

duction and still enhancing the gradient of c. However, for a spherically symmetric distribution of the catalyst, everything will remain spherically symmetric and the *average* rate of production q will be the same in any arbitrarily chosen half of the cell. If however, for some reason, in one of the hemispheres the average concentration $\bar{c}$ increases, this will result in an increase of n in the other hemisphere at the expense of the first. This will cause a further increase of $\bar{c}$ in the first hemisphere, enhancing the asymmetry. To investigate the possibilities in this case, let us first investigate what effect a variation of q from point to point in a cell will have upon the diffusion field.

Referring again to Fig. 1, denote the *average* concentration *in one hemisphere* by $\bar{c}_1$, in the other by $\bar{c}_2$. Denote the average rate of production in the first hemisphere by q_1, in the second by q_2. We now have

$$2D\frac{\bar{c}_1 - c_0}{r_0} = h(c_1 - c_0) \ , \tag{11}$$

$$2D\frac{\bar{c}_2 - c_2}{r_0} = h(c_2 - c_0) \ . \tag{12}$$

The material balance equation is now however somewhat modified. Due to the different values of $\bar{c}$ in the two hemispheres, there will now be not only an outflow of the metabolite from the cell, but also an inner flow, from one hemisphere to another. Since the average gradient for this flow is approximately $(\bar{c}_1 - \bar{c}_2)/r_0$, and the area through which the flow takes place is πr_0^2, that of the equatorial circle, the total inner flow is equal to $\pi r_0 D(\bar{c}_1 - \bar{c}_2)$. We now have for the first hemisphere

$$\frac{2}{3}\pi r_0^3 q_1 = 2\pi r_0^2 \times 2D\frac{\bar{c}_1 - c_1}{r_0} + \pi r_0 D(\bar{c}_1 - \bar{c}_2) \ , \tag{13}$$

and for the second

$$\frac{2}{3}\pi r_0^3 q_2 = 2\pi r_0^2 \times 2D\frac{\bar{c}_2 - c_2}{r_0} - \pi r_0 D(\bar{c}_1 - \bar{c}_2) \ . \tag{14}$$

Equations (11) and (12) give

$$c_1 = \frac{2D\bar{c}_1 + r_0 h c_0}{2D + r_0 h} \quad ; \quad c_2 = \frac{2D\bar{c}_2 + r_0 h c_0}{2D + r_0 h} \ . \tag{15}$$

Introducing (15) into equations (13) and (14) we find after rearrangement:

$$3D(2D + 5r_0h)\bar{c}_1 = 3D(2D + r_0h)\bar{c}_2 + 12Dr_0hc_0 + 2(2D + r_0h)r_0^2q_1 ;$$
$$3D(2D + 5r_0h)\bar{c}_2 = 3D(2D + r_0h)\bar{c}_1 + 12Dr_0hc_0 + 2(2D + r_0h)r_0^2q_2 . \tag{16}$$

Solving we find:

$$\bar{c}_1 = c_0 + \frac{r_0^2(2D + r_0h)[(2D + r_0h)q_2 + (2D + 5r_0h)q_1]}{12Dr_0h(2D + 3r_0h)} ,$$
$$\bar{c}_2 = c_0 + \frac{r_0^2(2D + r_0h)[(2D + r_0h)q_1 + (2D + 5r_0h)q_2]}{12Dr_0h(2D + 3r_0h)} . \tag{17}$$

Hence

$$\bar{c}_1 - \bar{c}_2 = \frac{r_0^2(2D + r_0h)(q_1 - q_2)}{3D(2D + 3r_0h)} . \tag{18}$$

The difference $\bar{c}_1 - \bar{c}_2$ vanishes for $q_1 = q_2$. When $q_1 > q_1$, then $\bar{c}_1 > \bar{c}_2$.

Now let us investigate the effect of such an asymmetric concentration distribution of the metabolite upon the concentration n of the catalyst. Denoting by V the volume of the particle, by N — Avogradro's number, and by M — the molecular weight of the diffusing metabolite, and putting

$$\alpha = \frac{3}{2}\frac{NV}{M} , \tag{19}$$

we have (MB, p. 67), for the ratio n_1/n_2 of the concentrations of the catalyst in the two hemispheres

$$\frac{n_1}{n_2} = e^{-\alpha(\bar{c}_1 - \bar{c}_2)} . \tag{20}$$

Denoting by n the average concentration of the catalyst in the whole cell, and remembering that the total amount of the catalyst $\frac{4}{3}\pi r_0^3 n$ is constant, we have

$$n = \frac{n_1 + n_2}{2} . \tag{21}$$

Putting

$$\bar{c}_1 - \bar{c}_2 = x , \tag{22}$$

we find from equations (20) and (21)

$$n_2 - n_1 = 2n \tanh \tfrac{1}{2}\alpha x . \tag{23}$$

For the effect of the catalyst on the reaction rate q let us consider the simplest possible relation, a linear one.
Let

$$q = q_0 - an , \tag{24}$$

where a is a constant. Then

$$q_1 - q_2 = a(n_2 - n_1) . \tag{25}$$

If an asymmetric distribution is to be possible, it must be represented by a stable root of the equation, obtained by introducing (23) into (25) and then introducing the latter into (18). Putting

$$\frac{r_0^2(2D + r_0 h)}{3D(2D + 3r_0 h)} = A , \tag{26}$$

we thus find

$$x = 2Aan \tanh \tfrac{1}{2}\alpha x. \tag{27}$$

If, as will usually be the case, αx is rather small, we may expand the hyperbolic tangent keeping only the lowest nonvanishing power. Equation (27) then becomes

$$x = Aan\alpha x\left(1 - \frac{1}{12}\alpha^2 x^2\right) , \tag{28}$$

which, besides $x = 0$, has a positive root:

$$x^* = \frac{2}{\alpha}\sqrt{\frac{3(Aan\alpha - 1)}{Aan\alpha}} , \tag{29}$$

provided

$$Aan\alpha > 1 . \tag{30}$$

That the root (29) corresponds to a stable configuration is seen by graphing equation (28). The curve which represents the right hand side of (28), is nothing else but the right hand side of equation (18). By a similar argument as before we must have for stability

$$\frac{d}{dx} Aan\alpha x\left(1 - \frac{1}{12} x^2\alpha^2\right) < 1 \quad \text{for} \quad x = x^*$$

which is actually the case.

The model discussed here does exhibit true selfregulation. No

matter how the cell is divided or how its content is stirred, the characteristic asymmetry of the diffusion gradient will be automatically reestablished. By considering the presence of several catalysts with different particle size, and affecting different reactions, we may obtain complex asymmetric patterns of the diffusion field, which thus may represent a rather intricate latent self-regulating structure.

It must be noted that the diffusion force per unit volume, $-(RT/M)$ grad c may be of the order of $10^7 - 10^8$ dyn. cm^{-3}, (Rashevsky, 1938), which is not only comparable, but even may exceed the centrifugal forces used in the above mentioned experiments. Moreover while the effect of the centrifugal forces upon a particle is proportional to the difference in specific weights of the particle and of the surrounding liquid and vanishes when the two specific weights become identical, no such restriction holds for the effect of diffusion forces. The model discussed here may in principle be mutilated beyond the point when self-regulation is possible, by applying such a strong centrifugal force, that all the catalyst is driven into one cell fragment. But this may require centrifugal forces far in excess of those available now.

III

Another important result of this study is that it leads us into the theory of cell polarity. A cell like the one discussed in section II always possesses a "polarity," and it is known that polarity is rather the rule in cell biology. The asymmetric distribution of the metabolite and therefore of the diffusion forces will in general result in asymmetries of all other important physical properties of the cell. Aggregates of such polar cells will themselves exhibit polar properties and a way is thus indicated for a mathematical biophysics of different types of tissues.

A polarity considered in section II is of a dynamic nature. But due to the irreversibility of some biological reactions, it may result after a lapse of time in a permanent polarity of a static nature, as discussed in section I.

The author is indebted to Dr. A. S. Householder for a discussion of this paper and checking of the calculations.

The publication of this paper was made possible by a grant from the Rockefeller Foundation to the University of Chicago.

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