Curvature

We established that high concentrations of glycine also influenced solutions of DNA by changing the temperature of fusion of the latter on thermal denaturing. Table 2 presents the T_{fusion} of DNA of phage T2 at different concentrations of glycine in solution.

Investigations are now being carried out into the hydrodynamic properties of DNA and DNP and their thermal denaturing in solutions containing high concentrations of glycine and different concentrations of salts.

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BIOPHYSICS OF COMPLEX SYSTEMS. MATHEMATICAL MODELS

MECHANISM OF THE FORMATION OF CLOSED PATHWAYS OF CONDUCTION IN EXCITABLE MEDIA[*]

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A model of a two-dimensional excitable medium reproducing the properties of the contractile myocardium has been constructed. Experiments on this model have shown that the formation of closed pathways of conduction of excitation in a homogeneous medium is directly due to the action of local currents. The conditions for the existence of self-sustained activity in such a medium are considered and the methods of obtaining it described.

In investigation of excitable media in connexion with the problems of the origin and maintenance of sustained activity in the myocardium various formalized models of such media have come into wide use (see, for example, [1–6]). Such models have, in

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particular, demonstrated the importance of closed pathways of conduction of excitation (reverberators) for self-sustained activity. However, for a fuller understanding of the mechanism of the formation of reverberators in actual conditions it is of interest to investigate the processes of spread of excitation in non-formalized models of excitable media which maintain as far as possible a large number of the collective properties of the actual excitable tissue of the myocardium principally, the cable properties, and are not confined to a formal representation of merely its individual properties.

In solving such a problem by the methods of mathematical modelling considerable difficulties of calculation arise connected with the large volume of the necessary calculations. These difficulties may be largely circumvented by using the method of hybrid modelling (analogue-numerical) of excitable networks proposed in [7, 8]. This opens the way to devising a model of a two-dimensional excitable medium of sufficient size with maintenance of sufficient completeness both of the local properties of the elements of the medium and the laws of transmission of excitation from one portion of the medium to another. The present paper is concerned with the application of such a model for investigating the self-sustained activity in excitable media.

STRUCTURE OF THE MODEL AND TECHNIQUE OF MODELLING

The model of an excitable medium realized in line with the technique in [7, 8] with a hybrid computer constitutes a square network consisting of 961 excitable elements (Fig. 1*A*) each of which imitates the behaviour of a small region of the medium. As such an element in the present work we adopted the model of the homogeneous zone of the membrane of the contractile myocardium proposed in [9] (equations (6)–(10) in [9]). (This model is somewhat simplified as compared with the models in [9–11] for similar processes although it fully reproduces the electrical properties of the membrane of the myocardium). The interaction of the elements comes about in line with the theory of local currents which with the discrete concept of the medium adopted are described in the model by the equation

$$[I_m(t)]_{i,j}=\frac{V_{i-1,j}(t)-V_{i,j}(t)}{R}+\frac{V_{i+1,j}(t)-V_{i,j}(t)}{R}+\frac{V_{i,j-1}(t)-V_{i,j}(t)}{R}+\frac{V_{i,j+1}(t)-V_{i,j}(t)}{R}, \tag{1}$$

where $(I_m)_{i,j}$—local current arriving at the element with the coordinates (i,j) (Fig. 1*B*); $V_{i,j}$—potential of this element; $V_{i\pm1,\,j\pm1}$—potentials of the adjacent elements; R—the equivalent passive resistance between the adjoining portions of the medium. The value R in the model was such as to ensure the reliable transmission of excitation with normal spread of the wave. The sign of the current in (1) was so chosen that we consider as positive for the element (i,j) the depolarizing current and negative the repolarizing. With the modelling technique adopted (see [7, 8]) equations describing the individual

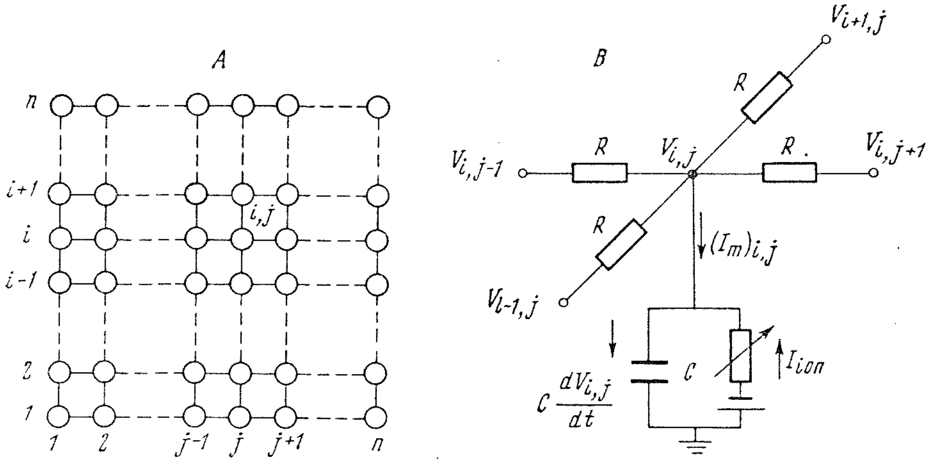


FIG. 1. Model of excitable medium: *A*—structural diagram of excitable network; *B*—equivalent circuit of node of network (element (i, j) and resistance of links R).

excitable elements were solved continuously in time whereas the local currents (1) were approximated stepwise with step of $\Delta t = 2{\cdot}5$ msec.

In modelling we recorded the values of the potentials of the elements of the network and where necessary in addition the values of other phase coordinates and local currents.

PROPERTIES OF MODEL OF EXCITABLE MEDIUM

The properties of an excitable medium are determined both by the properties of the individual excitable elements forming this medium and the character of the link between them. Fundamental to the model adopted in the present work is the presence of constant links between the adjacent elements, which reflects the character of interaction of the adjoining regions of the actual excitable tissue between which a local current appears whenever a potential difference exists between them (see equation of links (1)). On spread of excitation the local currents act on the elements of the medium in principle throughout the period of their generating an a.p. Therefore it is very important that in the present work we use a model of the individual excitable element which, as shown by the investigation, reproduces not only such properties of the homogeneous portion of the membrane of the myocardium as the form of the a.p., threshold, refractoriness, latency, etc. but also its reaction to the positive and negative external agents applied at different phases of the a.p.

This reaction corresponds to the character of the "strength-duration" curve for cathode and anode stimulation. It must be emphasized that the action of prolonged negative external current on the excited element causes acceleration of repolarization and reduction in the duration of the a.p. which is more clearly manifest the greater the negative external current. We would also note that on excitation of the element in the state of relative refractoriness the rate of depolarization and the duration of the generated a.p. diminish.

We shall now enumerate a number of important properties observed in the model of the excitable medium.

1. The form of the spreading a.p. in normal conditions was close to that of the a.p. generated by an isolated element.

2. The rate of spread of excitation depended on the curvature of the wave front. In the concave parts of the front the speed of movement was higher than in the convex, which is to be explained by the action of the local ~~currents~~ [12].

3. By delivering a depolarizing stimulus to the portion of the medium in the zone of relative refractoriness after the traversal of the excitation wave and with appropriate choice of the value and duration of the stimulus and the phases of its application it is possible to obtain a new excitation wave spreading only to one side, opposite to the direction of movement of the first wave, i.e. only towards those elements the excitability of which is largely restored.

4. It is particularly important to note a further property of the medium manifest on approach of the spreading wave to the zone with reduced excitability. Let in a certain zone of the medium the properties of the elements or their states be so changed that the excitability of this zone is reduced (for example, the elements have a raised threshold, reduced rate of depolarization, amplitude and duration of a.p.). Then in the region adjoining such a zone we would also observe fall in the rate of depolarization, reduction in duration and amplitude of the spreading a.p. and the speed of spread of excitation. This fact is directly connected with the repolarizing action of the local currents appearing between the zones with normal and reduced excitability as the front of the wave runs on. It is important that by virtue of the constantly acting links the influence of these currents affects not only the behaviour of the elements directly contiguous with the zone with reduced excitability but embraces a whole region surrounding this zone. Thus, each portion of the medium in which excitability is reduced through the parameters of the inherently excitable elements (or their state) is surrounded by a fringe of elements the excitability of which is reduced only through the links with the first region. As we move away from such a region its influence gradually weakens and the excitability of the elements of the fringe approaches the normal. We would note that in the one-dimensional case a similar phenomenon was obtained for the giant axon using calculations from cable equations [13].

MODELLING OF THE PROCESSES OF FORMATION OF CLOSED PATHWAYS OF CONDUCTION

The self-sustained activity in the medium to be modelled is connected with the existence of such pathways of spread of the excitation wave when the (possibility of repeat stimulation by the excited portion of the medium of those regions which have already had time to come out of the state of excitation (and refractoriness) appears. Below we describe three model experiments in which it was possible to obtain a closed pathway of conduction of excitation in three different ways. To present and explain the results of modelling we shall first introduce the concept of the "excited region" and outline certain qualitative notions on the dynamics of its boundary.

The excited region in the present work will be considered to be the region of the medium the potential of the elements in which exceeds $V_{\text{bound}} = 20$ mV (a value approximately corresponding to the threshold potential of the normal element). The region where the potentials are less than V_{bound} will be called the non-excited region. Everywhere in the figures the excited region in hatched. For example, Fig. 2*A* shows the position of the excited region on spread of excitation wave running from the left upper corner. The potential of the elements lying at the boundary of the excited region is by definition equal to V_{bound}. (This refers only to the portions of the boundary not coinciding with the boundary of the medium to be modelled, i.e. to the portion separating the excited and non-excited regions and changing on movement of the wave.) On generation of an a.p. the value V_{bound} is reached twice; in the initial phase of rapid depolarization when a large depolarizing ionic current develops and in the final stage of the phase of repolarization (see Fig. 2*B*). Correspondingly, at the boundary of the excited region it is possible to isolate two zones. The first zone is the set of depolarized boundary points. Since here $\frac{dV}{dt} > 0$, the boundary at this site is shifted towards the previously non-excited region. This zone of the boundary must naturally be considered to be the front of the excitation wave. In all the Figures we will isolate it by a bold line (*ab*, Fig. 2*A*). The other part of the boundary consists of the repolarized points where $\frac{dV}{dt} < 0$ and which by virtue of this emerge from the region of excitation. Therefore, such a zone will always be shifted towards the excited region and we will call it the posterior front or the "tail" of the excitation wave (*cd*, Fig. 2*A*).

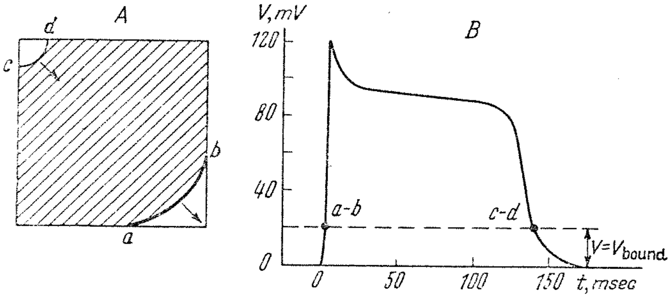


FIG. 2. Determination of "excited region": *A*—position of excited region with normal spread of wave (*ab*—front of wave; *cd*—"tail" of wave); *B*—position of boundary points in a.p.

We shall now turn to the direct description of the results of modelling. In the experiment illustrated in Fig. 3 at the initial moment of time $t = 0$, a normally spreading a.p. (wave *I*) was induced. The position of the wave *I* at the moment $t = 150$ msec is shown in Fig. 3*A*. Then, to the portion in the zone of relative refractoriness evoked by this wave (point S in Fig. 3B) was applied additional external stimulation. The moment of application and the value of the stimulus was so chosen as to give a new excitation wave (wave *II*) spreading only to one side opposite the direction of movement of the first wave (see property *3* of the excitable medium). Since the stimulated elements were in a state of relative refractoriness the a.p. generated by them was shortened. At the moment when the excitability of the region surrounding wave *II* was completely restored part of the excited region adjoining the portion qr at the boundary of this wave was already in the phase of repolarization and at $qr\ \frac{dV}{dt}<0$. Therefore, the portion qr constituted the tail of the wave *II* and was shifted towards the excited region embraced by this wave (Fig. 3C and D). At the same time, the other portion of the

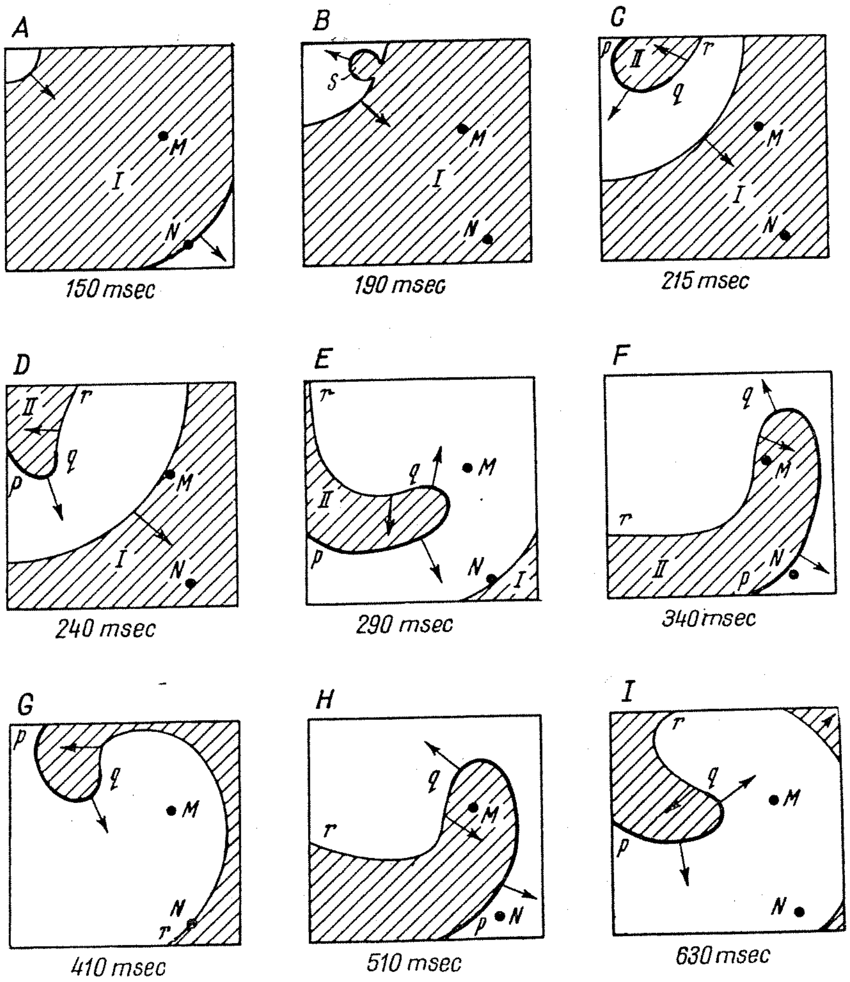


FIG. 3. Origin of closed pathway of conduction of excitation in a homogeneous medium after delivery of additional stimulus to point S at $t=183$ msec (explanations in text).

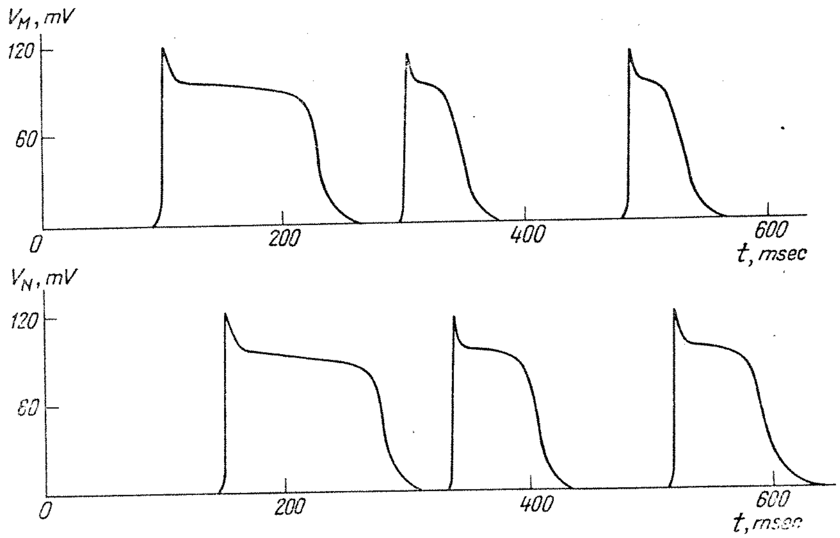


FIG. 4. Action potentials V_M and V_N at the points M and N (see Fig. 3) respectively.

boundary pq moved, passing to the resting part of the medium. This is the front of the wave *II*. As can be seen from Fig. 3*C–E* the portions of the front and tail of wave *II* move in opposite directions, which leads to bending of the boundary of the excited region and ultimately to the appearance of a closed pathway of spread of excitation—a reverberator (Fig. 3*F–I*).

We would note that obtaining a reverberator by means of an additional stimulus applied in the zone of relative refractoriness is similar to the method described by Wiener and Rosenbluet [1] of excitation of sustained circulation by the wave about a physical inhomogeneity. However, unlike [1] here the closed pathway of conduction is formed in a completely homogeneous medium.

It is necessary in particular to emphasize the following facts directly associated with such a character of spread of the wave:

A. As can be seen from Fig. 3, that starting from a certain time on movement of the wave *II* there exists portions of the boundary pq and qr in contact the direction of movement of which in relation to the excited region is mutually opposed. Because of the fact that the front and tail of the wave are in contact, at each moment of time the wave tends to turn about the point q separating the depolarized and repolarized parts of its boundary. We will use q to denote the point of change in phase. It should be noted that on normal spread of excitation the boundary does not contain the points of change in the phase—the front and the tail of the wave do not touch (see Fig. 3*A*). In this case the wave does not only not tend to bend the boundary but on the contrary, evens out the small bumps of the front appearing for certain reasons (property *2* of the model of the medium).

B. The wave of excitation circulates about a certain region of finite dimensions (not necessarily fixed). The front of the wave does not pass to this region because of the influence of the near-lying refractory zones of the tail forming about themselves a quite large fringe—zone of reduced excitability (see property *4* of excitable medium).

C. On modelling the reverberator we observe reduction in the duration of the a.p. as compared with the duration of excitation of the elements with normal spread of excitation. This effect was manifest more strongly in those elements which were closer to the inner side of the circulating wave. Figure 4 shows the a.p. calculated at the points *M* and *N* the position of which can be seen in Fig. 3.

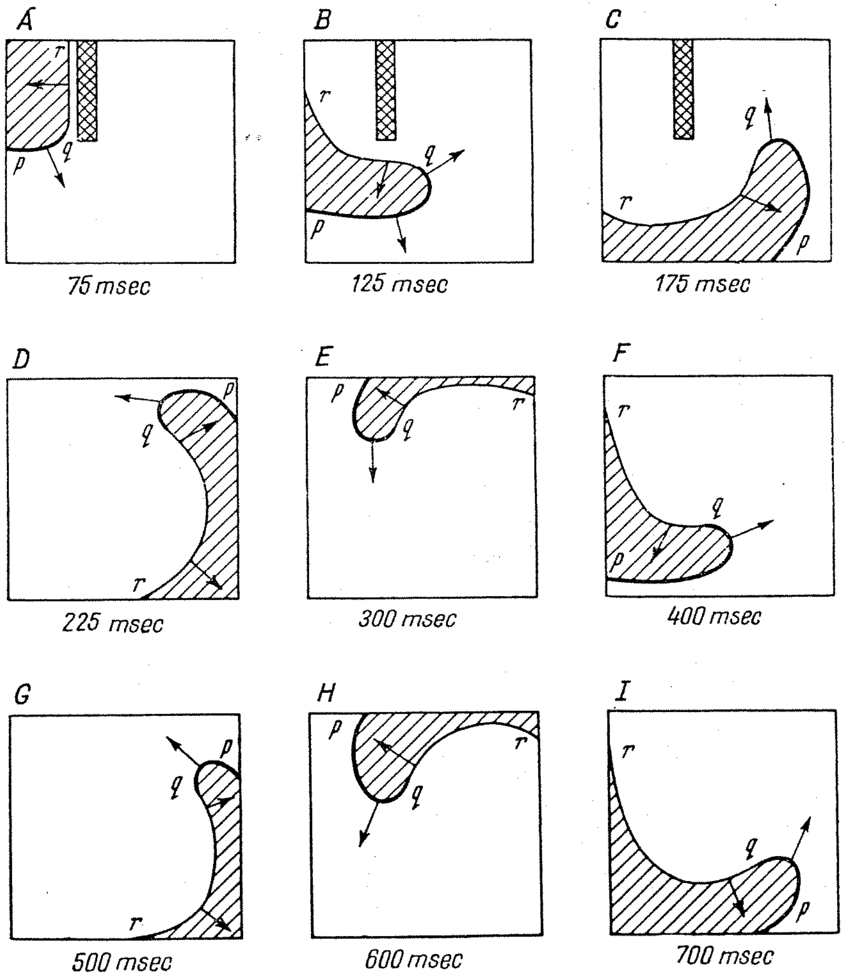
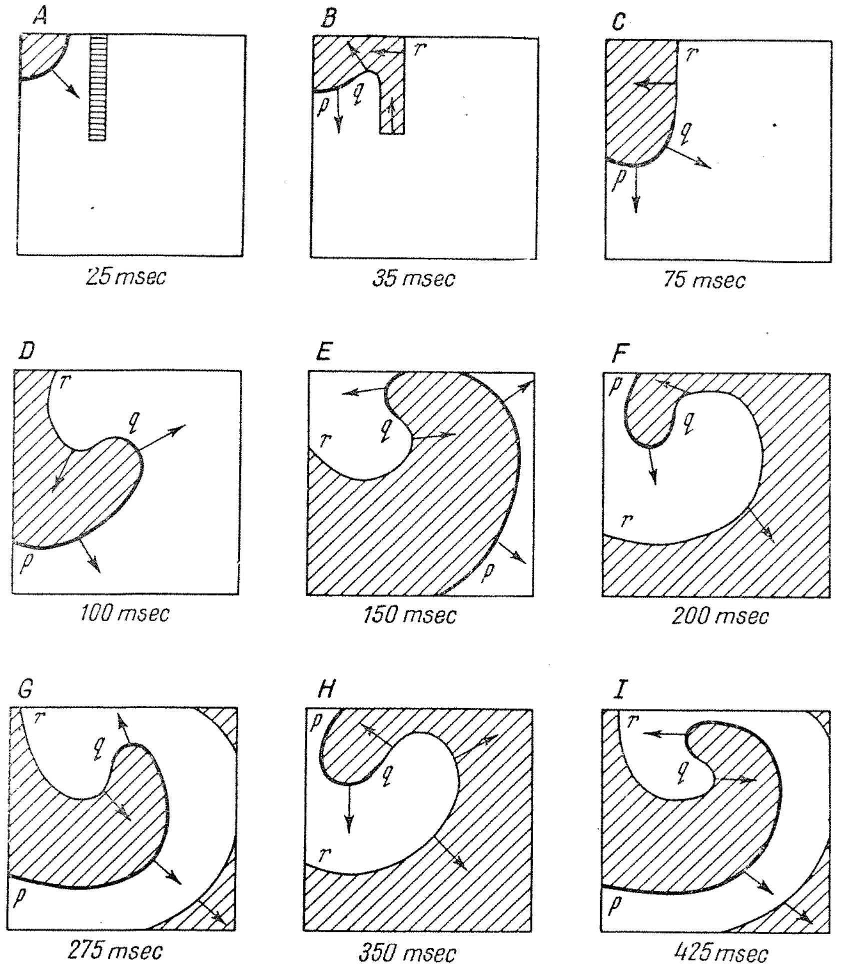


FIG. 5. Obtaining reverberator by means of temporarily "inhibited" zone (explanations in text).

The effects described are also observed with other methods of obtaining closed pathways of conduction. Figure 5 illustrates the model experiment in which before the front of the normally spreading wave a temporarily non-excitable zone was produced where the potential was artificially maintained at the level of the resting potential (posi-



25 msec 35 msec 75 msec

100 msec 150 msec 200 msec

275 msec 350 msec 425 msec

FIG. 6. Circulation of excitation induced by additional stimulation of portion of homogeneous medium before the front of the spreading wave (explanations in text).

tion of the inhibited zone is shown in Fig. 5 by cross-hatching). In line with property *4* of the model of the excitable medium, about this zone a fringe of reduced excitability forms in which considerable reduction in the duration of the a.p. is observed. Therefore, in the portion *qr* of the boundary of the spreading wave repolarization rapidly develops whereas the portion *pq* moving in the medium with normal excitability consists of depolarized elements (Fig. 5*A*). Thus, at the boundary of the excited region a point of change in phase separating the front of the wave and its tail appears. Figure 5*B* and *C*, shows the spread of the wave enveloping the inhibited zone. At the moment $t = 200$ msec the excitability of the inhibited zone was restored. However, the bending of the path of spread of the wave continued even after this because of the presence at its boundary of the point of change in phase. As can be seen from Fig. 5, *D* and *E*, the front of the wave without hindrance passed through the previously inhibited region in the reverse direction, forming a reverberator. Figure 5, *F–I* shows the further circulation of the wave over a closed pathway of conduction of excitation. We would note that this model experiment reproduces the qualitative conditions for obtaining the closed pathway of conduction described by Rozenshtraukh *et al.* in [5] where a temporarily non-excitable zone causing bending of the front of the wave was produced in the frog heart by stimulating the vago-sympathetic trunk.

In a further experiment on a model it proved possible to produce a temporarily non-excitable zone without resorting to the introduction into the medium of an inhomogeneity—artificially inhibited zone. For this, in a completely homogeneous medium before the front of the spreading wave was a zone stimulated externally and the position of which is shown in Fig. 6*A* by horizontal shading. The value of the external stimuli was such that although the stimulation led to increase in the potential in the stimulated zone it was insufficient to obtain an excitation wave spreading from there (this imitates the arrival of an extrasystolic action producing in the zone considered only a local response). Since the elements in the stimulated zone passed into a state of refractoriness, then the approaching wave could not pass through it and in the zone of reduced excitability, repolarization developed and the tail of the wave *qr* formed (Fig. 6*B* and *C*). The further process of bending of the wave as shown in Fig. 6*D–I* and the appearance of a reverberator qualitatively in no wise differ from similar processes described above.

The reverberator obtained by any of the three methods described above could exist in the experiment with the model for as long as desired. However, self-sustained activity may be stopped by immediately applying to all the elements of the medium an external stimulus of sufficient strength. In such an experiment, imitating the action of a defibrillator, we observe simultaneous excitation of the whole region about which the wave had circulated until then. With passage of time the elements of the medium gradually repolarized. Although the emergence of various parts of the medium from excitation occurred not simultaneously (the first to be repolarized are those regions which before the application of the defibrillating stimulus were covered by excitation) nevertheless at this time the boundary of the excited region is formed only by the repolarized points where $dV/dt < 0$. Therefore, no new excitation can ensue and any activity in the medium ceases.

DISCUSSION OF RESULTS AND MODELLING

The investigations carried out firstly show the possibility determined by the action of local currents of the appearance in an homogeneous two-dimensional excitable medium of closed pathways of conduction over which excitation may circulate without abatement. Analysis of the results of modelling revealed the main conditions for the existence of sustained activity the most important of which are: *1*) contact of the depolarized and repolarized portions of the boundary of the excited region, i.e. the presence at the boundary of a point of change in phase; and *2*) the existence of a fringe of refractoriness (region of reduced excitability adjoining the refractory regions of the tail of the wave).

As shown by modelling, condition *1* in particular, is fulfilled if stimulation of the portion of the medium at the tail of the traversing wave (in the zone of refractoriness) produces a new wave of excitation spreading at first only in the direction opposite to the movement of the first wave or in the same direction if before the front of the wave a portion is formed with a temporarily reduced excitability which is restored when the wave runs round it.

Condition *2* is peculiar to the excitable medium considered here although it has significant influence only in the presence of anomalous spread of excitation. Suppression of the action of the fringe contributes to the arrest of the self-sustained activity. To show in principle the importance of condition *2* we carried out a special model experiment. The fringe was artificially eliminated by changing the law (1) of formation of local current: if during calculation from formula (1) the current $(I_m)_{i,j}$ was negative, then in the model it was taken as equal to zero. This artificially rendered the excitable element insensitive to the action of the repolarizing local currents. If such a modification of the character of the linkage of the elements was carried out, with normal movement of the wave no significant changes were noted. If it was carried out after the formation of the reverberator, then the excitation spread in the region about which until then the wave had circulated and then approximately the same pattern appeared as on "defibrillation" described above.

The results indicate that on modelling of the processes of anomalous conduction of excitation it is necessary to reproduce correctly the reaction of the portions of the excitable medium both to depolarizing and repolarizing local currents during all the phases of generation of the a.p. The model of the excitable medium devised and used in the present study unlike the formalized model satisfies this requirement at least qualitatively. Thus, it may be considered that on modelling the main qualitative properties peculiar to such an actual excitable medium as the myocardium were maintained. This, in turn, determines the applicability of the results of the work to investigation of the process of fibrillation.

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INVESTIGATION OF ONE MECHANISM OF ORIGIN OF THE ECTOPIC FOCUS OF EXCITATION IN MODIFIED HODGKIN–HUXLEY EQUATIONS*

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The paper studies the mechanism of origin of a point source of pulsation (ectopic focus of excitation) in the system of the cells of the heart each of which as such does not possess automatic activity. It investigates the behaviour of a system of two interacting cells of such a type. It is assumed that the membrane of each cell is described by a set of differential equations of the BvP. type.

1. INTRODUCTION

In the present work we studied the mechanism of origin of an ectopic focus of excitation of the "echo" type. Such a mechanism was investigated in simple mathematical models in [1, 2]. It is shown how in a medium not possessing automatic activity a point source of pulsation may appear. As follows from these studies such a source, for example, may be two adjacens cells exciting each other. This mechanism of excitation will be investigated in a more detailed model where each cell is described by a set of differential equations of the BvP. type. (According to the terminology adopted in [2] this mechanism will be called "echo"). In [3] it is shown that the BvP. system is a convenient qualitative description of an excitable membrane.

2. MODEL

We shall consider the following set of differential equations:

$$\left.\begin{array}{ll}
(2.1\text{a}) & \begin{cases} \mu\dot{u}_1 = f(u_1) + v_1 - z(u_1 u_2) \\ \dfrac{1}{\mu}\dot{v}_1 = \varphi(u_1, v_1) \end{cases} \\[2ex]
(2.1\text{b}) & \begin{cases} \mu\dot{u}_2 = f(u_2) + v_2 - z(u_2, u_1) \\ \dfrac{1}{\mu}\dot{v}_2 = \varphi(u_2, v_2) \end{cases}
\end{array}\right\} \qquad (2.1)$$

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