METHOD FOR CALCULATING THE DISTRIBUTION DENSITY OF THE NUMBER OF RECEPTORS IN A CERTAIN FIELD BASED ON THE FREQUENCY OF THEIR GENERATED IMPULSES

(UDC 612.815.1.014.421.7)

B. I. Balanter

Institute of Normal and Pathological Physiology (Director-Active Member of the Academy of Medical Sciences of the USSR Prof. V. V. Parin), Moscow
(Presented by Active Member of the Academy of Medical Sciences of the USSR V. V. Parin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 6, pp. 120-124, June, 1966
Original article submitted December 31, 1964

Electrical stimulation of a nerve evokes a potential composed of the action currents of all fibers. If orthodromic receptor impulses move along afferent fibers counter to the evoked potential, hereafter called antidromic potential, they can "collide" with the antidromic impulses with a certain probability. As a consequence of this the amplitude of the antidromic potential decreases as it moves toward the receptor field. This phenomenon permits evaluating the total activity of the receptors of a given field [3, 4]. The results of experiments with stimulation of a nerve by repeated impulses of a different frequency enable determination of the relative number of receptors generating impulses of a different repetition rate [1, 2].

It is shown in this work that this problem is solved by analyzing the results of experiments with stimulation of the nerve by single impulses, and a method of calculation is proposed.

Douglas and Ritchie [3] found that the value of the antidromic potential decreases with an increase of the interelectrode distance between the stimulating and recording electrodes. As was shown earlier [2], for a nerve trunk model consisting of afferent fibers conducting orthodromic impulses with the same frequency f and an equal conduction velocity v, the following dependence holds true:

$$f = \frac{rv}{2d}, \tag{1}$$

where d is the length of the interelectrode distance, $r = (A_{max} - A)/A_{max}$ where A is the arithmetic mean (from a number of repeated samples) of the values of the antidromic potential for a certain d, A_{max} is the arithmetic mean of the maximal values of the antidromic potential.

Formula (1) is derived on the basis of calculating the probability P of the encounter of impulses in the interelectrode space in a single fiber:

$$P = \begin{cases} \frac{2d}{l} \; (2d < l) & (2) \\ 1 \; (2d \geqslant l), & (3) \end{cases}$$

where l is the distance between two adjacent impulses (excited sections of the nerve).

For a real nerve formula 1 can be used only when determining the lower boundary of the frequency spectrum, f_{min} [2]. In this case:

$$d = \frac{l_{max}}{2}, \text{ where } l_{max} = \frac{v_m}{f_{min}}. \tag{4}$$

In formula 4 v_m is the conduction velocity corresponding to the maximal point of the antidromic potential (mode of the velocity distribution V in the nerve).

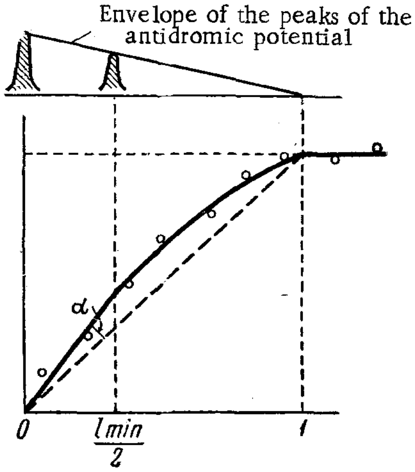

Fig. 1. Curve of the dependence r = r(d). On the x-axis is plotted d (length of the interelectrode distance); on the y-axis is r (the value of the relative drop of the antidromic potential).

From the results of the experiments with stimulation of a nerve by single impulses [4] we can determine the function r = r(d). It is shown below that from the curve r = r(d) (Fig. 1) we can also derive the value of the maximal frequency f_{max}. Let us assume that impulses of a certain repetition rate (different in different fibers) pass in each of the n fibers of the nerve model and the conduction velocity v_m = const. Let us examine the region of change d from 0 to l min/2. In this section an obligatory encounter of impulses in the interelectrode space does not occur in a single one of the fibers, the probability of encounters in the fibers is found from formula 2 and depends on the frequency in each of the fibers (i.e., on l). The increase of the function r(d) with an increase of d (see Fig. 1) is obviously determined by the fact that in each fiber the probability of an encounter increases with an increase of d. Let us divide the range of the change in the quantity $l/2$ into k discharge intervals and examine the ratio$(n_j/n)(j = 1, 2 ..., k)$, where n_j is the number of fibers conducting impulses with a frequency corresponding to the value $l/2$ from the j-th discharge interval.

We determined above the quantity:

$$r = \frac{A_{max} - A}{A_{max}} = \frac{B}{A_{max}}, \text{ where } B = A_{max} - A. \tag{5}$$

Let us designate in terms of a the value of the component of the antidromic potential in one fiber. Then:

$$a = \frac{A_{max}}{n}. \tag{6}$$

The drop in the value of the antidromic potential in the j-th group of fibers corresponding to the j-th discharge interval is equal to:

$$B_j = a \cdot \sum_{i=1}^{n_j} \rho_i \quad (j = 1,2,...\kappa), \tag{7}$$

where k is the number of discharge intervals, ρ_i is a discrete random quantity having the following distribution law:

$$\rho_i \quad \frac{1}{P_i = \frac{2d}{l_j}} \quad \frac{0}{1 - P_j = 1 - \frac{2d}{l_j}}, \tag{8}$$

where in the upper line are the possible values of the random variable and in the lower line the probabilities with which ρ_i will take these values.

Let $l_j/2$ be a certain average value of $l/2$ corresponding to the j-th discharge interval. Then l_j and P_j are equal to const.for a fiber of the j-th interval.

The mathematical expectation (mean value) of the quantity B_j is equal to:

$$\bar{B}_j = a \cdot n_j [1 \cdot P_j + 0 \cdot (1 - P_j)] = a \cdot n_j \cdot P_j, \quad (j = 1,2,...,k). \tag{9}$$

Since the section of change from 0 to $l_{min}/2$ is being examined, then by substituting the value of P_j (8) into formula 9, we obtain

$$\bar{B}_j = a \cdot n_j \frac{2d}{l_j}, \quad (j = 1,2,...,k). \tag{10}$$

Since $B = \sum_{j=1}^{k} B_j$ then, considering B_j to be independent random variables, we can find the average value of the quantity B:

$$\overline{B} = \sum_{j=1}^{k} \overline{B}_j = \sum_{j=1}^{k} a \cdot n_j \frac{2d}{l_j} = A_{max} \sum_{j=1}^{k} \frac{n_j}{n} \cdot \frac{2d}{l_j}. \tag{11}$$

Consequently,

$$\frac{\overline{B}}{A_{max}} = \sum_{j=1}^{k} \frac{n_j}{n} \cdot \frac{2d}{l_j}. \tag{12}$$

By virtue of the law of large numbers we can assume for a sufficiently large n that

$$\overline{B} \cong B. \tag{13}$$

Therefore, from formulas 12, 13, and 5 we obtain:

$$r(d) = \sum_{j=1}^{k} \frac{n_j}{n} \cdot \frac{2d}{l_j}. \tag{14}$$

n_j/n was the mean distribution density for $(\Delta l)_j = \Delta l = l (j = 1, 2, \ldots, k)$ where $(\Delta l)_j$ is the length of the j-th discharge interval of the change $l/2$.

Let us go over to the true distribution density. For this purpose we must turn to $\Delta l \to 0$. Then we can find the equation to determine the distribution density which we will designate by $P(z)$, where $z = l/2$. Upon passing to the limit in the right-hand side of (14) we obtain:

$$r(d) = \lim_{\Delta l \to 0} \sum_{j=1}^{k} \frac{n_j}{n} \cdot \frac{1}{\Delta l} \cdot \frac{2d}{l_j} \Delta l = \lim_{\Delta z \to 0} \sum_{j=1}^{k} \left(\frac{n_j}{n} \cdot \frac{1}{\Delta z} \right) \cdot \frac{d}{z} \Delta z = \int_{z_{min}}^{z_{max}} P(z) \frac{d}{z} dz, \tag{15}$$

where

$$z_{min} = \frac{l_{min}}{2}, \quad z_{max} = \frac{l_{max}}{2}.$$

In formula (15) the unknown distribution density $P(z) = \lim_{\Delta z \to 0} \frac{n_j}{n} \cdot \frac{1}{\Delta z}$, and in the same formula we can take d out of the integral side:

$$r(d) = d \int_{z_{min}}^{z_{max}} P(z) \cdot \frac{1}{z} dz. \tag{16}$$

Since the integral in the right part of (16) gives a certain constant number:

$$\frac{r(d)}{d} = \int_{z_{min}}^{z_{max}} P(z) \cdot \frac{1}{z} dz = \text{const}. \tag{17}$$

then it is clear that in the section $0 \leq d \leq z_{min} = l_{min}/2$ the curve of the function $r = r(d)$ should represent a straight line passing through the origin of the coordinates (in the plane zor).

For the simplest case, $P(z) = \text{const}$, we can find in the following manner the approximate value of the upper limit of the frequency spectrum:

$$P(z) = \frac{1}{z_{max} - z_{min}}. \tag{18}$$

Here and henceforth we will consider that the condition of normalization is fulfilled for $P(z)$:

$$\int_{\infty}^{\infty} P(z) dz = 1. \tag{19}$$

Then we obtain:

$$\frac{r(d)}{d} = \int_{z_{min}}^{z_{max}} \frac{1}{z_{max} - z_{min}} \cdot \frac{dz}{z} = \frac{\ln z_{max} - \ln z_{min}}{z_{max} - z_{min}}. \tag{20}$$

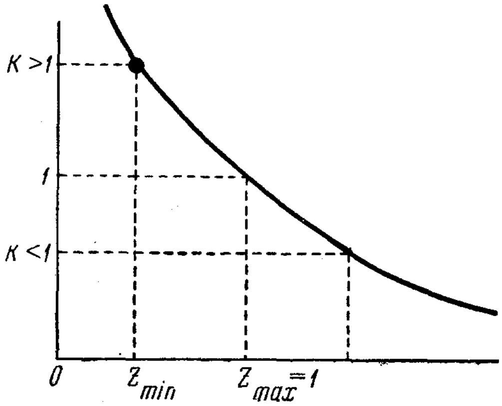

Fig. 2. Method of the graphic solution of equation 20. On the x-axis are the values the independent variable x; on the y-axis are the values of the function $\varphi(x) = \ln x/(x-1)$.

We know that z_{max} is determined from the curve $r = r(d)$ as the abscissa of the point of transition of the curve $r(d)$ into a plateau, where $r(d) = 1$. From Eq. 20 we can obtain the value of z_{min}. Actually, according to Eq. 17, the curve of the function $r = r(d)$ in the section $0 \leq d \leq z_{min}$ is a straight line. Using, for example, the method of least squares, we can find the regression line for the experimental points $r(d)$ close to the origin of the coordinates and the angular coefficient of the regression line K.

Let us set up the curve of the function:

$$\varphi(x) = \frac{\ln x}{x-1}, \tag{21}$$

where $x = z_{min}$; we will consider that the scale along the x-axis is selected to that $z_{max} = 1$ (Fig. 2). The unknown value of z_{min} is defined as the abscissa of the point of intersection of the curve of the function (21) with the straight line $y = k$. In order to understand how the points z_{min} and z_{max} are mutually arranged we must find the value of $\varphi(x)$ at the point $z_{max} = 1$

$$\lim_{x \to 1} \varphi(x) = \lim_{x \to 1} \frac{\ln x}{x-1} = \lim_{x \to 1} \frac{1/x}{1} = 1$$

(the L'Hospital rule was used to determine the limit).

Hence it follows that the angular coefficient of the regression line for the empirical dependence $r = r(d)$ should be greater than one. When $K = 1$ we obtain a straight line connecting the origin of the coordinates (0, 0) with the point (1, 1) of the plane zor, where $z_{max} = 1$, $r = 1$ corresponds to this point (1, 1) in a certain scale along the z and r axes. Consequently, the frequency spectrum degenerates into one point: $f_{min} = f_{max}$.

When $K < 1$ $z_{min} > z_{max}$, which is impossible. Thus, it is established that $K > 1$ and the value of the angle $\alpha = \arctan K - \pi/4$ determines the width of the frequency spectrum.

Let us pass on to an examination of the second section of the change d: $z_{min} \leq d \leq z_{max}$ on the nerve model. At any point of this section the probability of the encounter of impulses in the interelectrode space in some fibers is 1, and in the remaining portion of the fibers this probability is equal to $2d/l$. Consequently, we can determine the value $r(d)$ by dividing the set of n fibers into two groups: a group of fibers with an impulse frequency f corresponding to the probability of encounter $P_1 = 1$, and a group of fibers with an impulse frequency corresponding to $P_1 = 2d/l$. In the same manner that we obtained Eq. 15, we can find the equation for determining the unknown distribution density in the second section of change d:

$$r(d) = \int_{z_{min}}^{z_{max}} P(z) P_1(d, z)\, dz, \quad z_{min} \leqslant d \leqslant z_{max}, \tag{22}$$

where

$$P_1(d, z) = \begin{cases} d/z\left(d < z = \dfrac{v}{2f}\right), & (23) \\ 1 \quad (d \geqslant z). & (24) \end{cases}$$

We obtained above formula 9 which holds true both for the first and for the second section of the change of d. Analogous to the conversion from formula 9 to formula 15 for the first section, we can easily change from Eq. 9 to Eq. 22 for the second section.

Substituting P_1 from 23 and 24 into Eq. 22 and dividing the integral in the right side of (22) into two integrals, we obtain:

$$r(d) = \int_{z_{min}}^{d} P(z) \cdot 1 \cdot dz + \int_{d}^{z_{max}} P(z) \cdot \frac{d}{z} dz. \tag{25}$$

Integral Eq. 25 determines the dependence of the unknown distribution density P(z) on the empirical function r = r(d).

This equation is easily solved if at first we determine the boundaries of the spectrum as was indicated above. An analytical solution of Eq. 25 is possible if we assume that by means of regression analysis the experimental values of r for various values of d in the second section of the change of d are smoothed out and the smoothed curve is approximated by some analytical function.

Assuming the possibility of representing the regression line for the empirical points r in the second section of the change of d in the form of a polynomial of the n-th power, we can obtain the distribution density P(z), having solved integral Eq. 25 in the form of a polynomial of degree n−1.

In the case of representing r(d) in the form of a polynomial of the second degree we can easily obtain the formula for the value of the upper limit of the frequency spectrum and thus eliminate the need to solve the equation for z_{min} (20). In this case we obtain the following formula for determining z_{min}:

$$z_{\min} = \frac{2}{K} - 1. \tag{26}$$

Differentiating Eq. 25, we obtain:

$$r'(d) = P(d) \quad P(d)\cdot\frac{d}{d} + \int_{d}^{z_{\max}} P(z)\cdot\frac{dz}{z}. \tag{27}$$

This integral equation does not contain z_{min}. It follows from Eq. 27 that r(d) should not be represented by means of a linear approximation in the second section of the change of d, otherwise we would obtain from Eq. 27:

$$\int_{d}^{z_{\max}} P(z)\cdot\frac{dz}{z} = c \quad \text{const.} \tag{28}$$

Differentiating Eq. 28, we obtain P(d)/d = 0, i.e., P(d) = 0, which is impossible.

For practical application it is convenient to solve Eq. 25 without an analytical representation of the regression line r = r(d). As the result of S experiments let points $r_1, r_2 \ldots, r_m$ be obtained, where each r_i is the arithmetic mean from S values at a given d_i. Then to solve Eq. 25 we substitute the value of the pairs (d_i, r_i) into it:

$$\int_{z_{\min}}^{d_i} P(z)dz + \int_{d_i}^{z_{\max}} P(z)\cdot\frac{d_i}{z}\,dz = r_i, (i = 1,2,\ldots,m). \tag{29}$$

To solve system 29 we can use one of the numerical quadrature formulas, for example the formula of a trapezium. Let us use this formula. For this purpose we need a change of the distance d in the experiments such that the following relationships are fulfilled:

$$d_i = d_{i-1} + \Delta z, \quad d_1 = z_{\min}, \quad d_n = z_{\max} = 1 (i = 1,2,\ldots,m), \tag{30}$$

where Δz = const is the step of separating the interval (z_{min}, z_{max}). Let us denote $P_i = P(d_i)$. Using the formula of a trapezium, we obtain:

$$\int_{d_i}^{d_i} P(z)dz = \Delta z\left(\frac{P_1}{2} + P_2 + \ldots + \frac{P_i}{2}\right), (i = 2\ldots, m), \tag{31}$$

$$\int_{d_i}^{d_m} P(z)\frac{d_i}{z}\,dz = \Delta z\left(\frac{P_i}{2d_i} + \frac{P_{i+1}}{d_{i+1}} + \ldots + \frac{P_m}{2d_m}\right)d_i, (i = 1,\ldots,m-1). \tag{32}$$

Therefore, system 29 by means of Eq. 31 and 32 can be represented in the form:

$$\left.\begin{aligned} & d_1 \cdot \triangle z\left(\frac{P_1}{2d_1}+\frac{P_2}{d_2}+\ldots+\frac{Pm}{2d_m}\right)=r_1, \quad \ldots. \\ & \triangle z\left(\frac{P_1}{2}+P_2+\ldots+\frac{P_k}{2}\right)+d_k\cdot\triangle z\left(\frac{P_k}{2d_k}+\frac{P_{k+1}}{d_{k+1}}+\ldots+\frac{P_m}{2d_m}\right)=r_k \\ & \ldots \triangle z\left(\frac{P_1}{2}+P_2+\ldots+\frac{P_m}{2}\right)=r_m \end{aligned}\right\} \qquad (33)$$

Thus, a system of m linear Eq. 33 relative to m unknown $P_1, \ldots P_m$ is obtained. By solving this system we find m ordinates of the curve of the distribution density of the number of fibers (receptors) with respect to the quantity $z = l/2 = v_m/2f$. It is easy to change from the density obtained to the unknown histogram of the distribution of the number of receptors based on the repetition rate of the impulses.

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