On the Fluctuation of Threshold of the Nerve Fibre

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Probability phenomena in the nervous system have been mentioned for the first time by Adrian[1]. He assumed that irregular fluctuations in the threshold of the nerve fibre might account for the irregular injury discharge. Probability aspects of firing have been mentioned or investigated for instance by Towé and Amassian[16] for the cerebral cortex and for the spinal cord by Lloyd and McIntyre[10] and by Hunt[7]. In the peripheral nerve fibre it is shown that low frequency stimulation of about threshold strength, gives occasional responses of the axon (Fig.1). The significance of this phenomenon was recognised only by Pecher[12-14]. Here we would like to describe some aspects of this probability phenomenon.

METHODS

Technical procedures

The observations were made on the most rapidly conducting axons of sciatic-phalangeal nerve preparations *(Rang esculenta)* suspended in mineral oil. In the experiments 18 axons were used. The usual way of stimulating and recording was employed. During any series of observations the frequency was kept at one negative square pulse per two seconds.

From all the axons the relationship between stimulus strength and probability of reaction were determined in two ways: with a pulse of short duration (0.25 msec) and high intensity, and with a pulse of longer duration (2.5 msec) and therefore lower intensity. Each of these 36 observations was made, increasing the intensity from zero probability with steps of about 0.5 % threshold intensity, until the probability became about one. At each step 50 trials were made.

From 8 axons, continuous series of reactions were registered. They varied from 200 to 600 responses.

Statistical procedures

The 8 series of reactions were subjected to the run test[8], to determine whether the sequence of positive and negative reactions is random or not.

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The 36 above-mentioned relationships were subjected to the probit transformation. This was done to determine whether the integral of the function of De Moivre[5], usually connected with the normal distribution, can be considered as a useful working hypothesis for this relationship.

Then from each of the 36 observations the two parameters of this integral could be fitted by means of the probit analysis. Their quotient will be called the Relative Spread, and will be given in arbitrary units.

These Relative Spreads, consisting of 18 pairs, were subjected to Wilcoxon's test for symmetry[8]. This was done to examine whether the 18 differences between the pairs, taking their signs into account, can be considered as being distributed symmetrically around zero.

In all the tests we use a level of significance of 5 %.

RESULTS

The application of the run test to the 8 series of reactions shows, that in none of the 8 sequences can the null hypothesis of randomness be rejected (Table I). This means that the observations are not in conflict with the theory that the successive reactions of a nerve are independent (using this low frequency of stimulation.) Therefore we are justified to speak of a probability of reaction.

TABLE I

RESULTS OF THE RUN TEST, APPLIED TO CONTINUOUS SERIES OF REACTIONS OF 8 AXONS

Number	N	m_1	m_2	u_o	μ_u	σ^2_u	T_o	$P_D(T_o)$
1	590	169	421	240	242.2	98.4	0.17	0.87
2	300	149	151	140	150.9	74.7	1.19	0.23
3	297	171	126	138	146.1	70.6	0.90	0.37
4	261	95	166	120	121.8	55.7	0.18	0.86
5	281	153	128	130	140.4	68.8	1.19	0.23
6	211	103	108	96	106.4	52.4	1.37	0.17
7	227	149	78	110	103.4	45.9	0.90	0.37
8	196	105	91	108	98.0	47.7	1.38	0.17

$\alpha = 0.05$

N = total number of trials = m1 + m2
m_1 = total number of positive reactions
m_2 = total number of negative reactions
μ_o = total number of runs

$$\mu_u = \frac{2\, m_1\, m_2}{N} + 1 \qquad \sigma^2_u = \frac{2\, m_1\, m_2\, (2\, m_1\, m_2 - N)}{N^2\, (N - 1)}$$

$$T_o = \frac{|\, u_o - \mu_u \,| - \frac{1}{2}}{\sigma_u}$$

Null hypothesis is in no case rejected, because $P_D(T_o) > \alpha$.

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A second aspect is the relationship between stimulus strength and probability of reaction. This is a sigmoid curve and bears a close resemblance to the above-mentioned integral. To test this, the 36 sets of observations were each subjected to the probit transformation. They then appeared to fit very closely to a straight line. This would be expected, if the integral of the function of De Moivre[5] can be accepted as a useful working hypothesis.

Therefore we can characterise the relationship between stimulus strength and probability of reaction with the two parameters of this integral (Fig. 1).

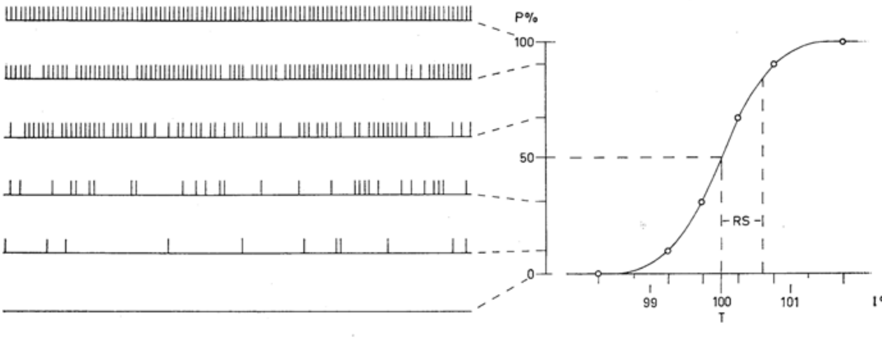

Fig. 1. The occasional responses of an axon and their relation to stimulus strength (in % of threshold). Stimulus frequency 1 per 2 sec.

The first is the threshold which is defined [3] as the strength of the negative square pulse on which the nerve fibre reacts with a probability of *50%,* when stimulated with a frequency of one per 2 sec. The second parameter is called the spread. This is a measure of the width of the curve and is also expressed in current strength. The quotient of spread and threshold is called the Relative Spread (RS) and has no dimensions.

The RS was thought to be independent of the stimulus duration. To test this, the 18 pairs of Relative Spreads were subjected to Wilcoxon's test for symmetry (Table II). The result shows that the distribution of the differences between the pairs has a point of symmetry not significantly different from zero. So the RS has not been found to be dependent on the stimulus duration.

DISCUSSION

The first observation that low-frequency stimulation of the nerve fibre gives occasional responses has been made by Blair and Erlanger[2] and by Monnier and Jasper[11]. Blair and Erlanger[3] noted that the phenomenon is due to spontaneous fluctuations in the irritability of the nerve fibre and not to variations in shock strength or duration. This was demonstrated by Pecher[13]. Monnier and Jasper[11] already stated explicitly that this phenomenon may follow the law of chance. Pecher[12, 14], however, seems to be the only one who tried to prove this statement. This assumption was thought in

TABLE II

WILCOXON'S TEST FOR SYMMETRY, APPLIED TO 18 PAIRS OF OBSERVATIONS

Number of axons	Coefficient + with a duration of 0.25 ms	2.5 mse	Difference +	--	Rank +	--
1	0.72	0.70	2		4	
2	0.75	0.88		13		16
3	0.40	0.32	8		10	
4	0.45	0.38	7		9	
5	0.26	0.25	1		1.5	
6	0.56	0.47	9		11	
7	0.30	0.27	3		6	
8	0.21	0.17	4		7	
9	0.19	0.21		2		4
10	0.36	0.55		19		17.5
11	0.35	0.48		13		15
12	0.55	0.46	9		12	
13	0.35	0.23	12		14	
14	0.34	0.32	2		4	
15	0.87	0.97		10		13
16	0.44	0.25	19		17.5	
17	0.37	0.38		1		1.5
18	0.16	0.21		5		8
					+96	- 75

$V_o = +96 - 75 = 21$; $V_{(n=18,\alpha=0{,}05)} = 91.$

Null hypothesis is not rejected, because $V_o \leqslant V_{n(=18,\alpha=0.05)}$.

+ Relative spread in arbitrary units.

general to be true without evidence[4, 6, 9, 15]. As Pecher's argument does not hold*, we tested this hypothesis, with the result that the successive reactions can be considered as independent.

Pecher[14] also noticed that the relationship between stimulus strength and probability of reaction closely resembles the integral of De Moivre. We found this to be a useful working hypothesis and we used the Relative Spread as a parameter of this relationship. We observed that the RS seems to be independent of stimulus duration, which was also noticed by van Lier[9]. We indeed did not find the RS to be dependent on the stimulus duration. And as the RS is by definition not dependent on current strength, it is now possible, given a strength-duration curve, to construct a theoretical strength-duration-probability graph (Fig. 2a). From this graph, and from its projection to the horizontal plane, the i - t plane (Fig. 2b), we can deduce some properties of the duration-probability relationships:

* Pecher made an analysis of the distribution of responses, determined completely by chance (which means that the successive reactions are independent). From this it followed that a linear relationship exists between the log (number of groups) and the group number. But the reverse of this statement (that a linear relationship proves that the distribution depends solely on chance) is not logically true.

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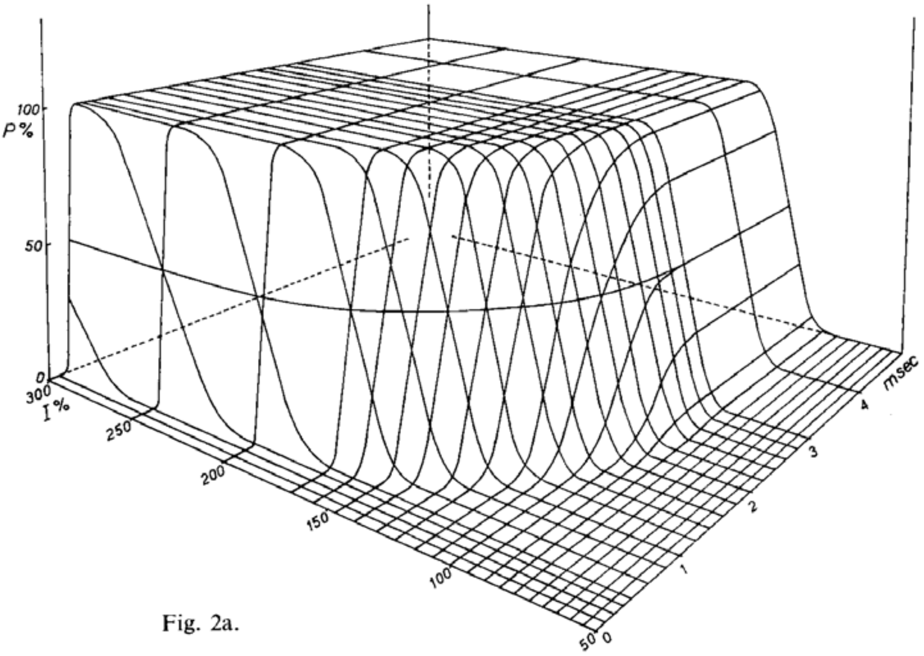

Fig. 2a.

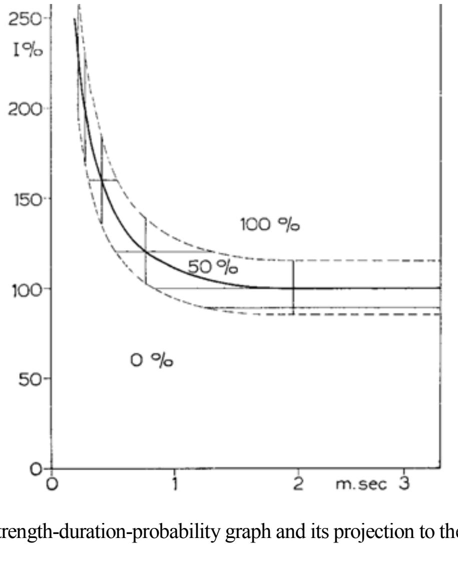

Fig. 2b.

Figs. 2 a and b. Strength-duration-probability graph and its projection to the horizontal plane.

(a) The higher the intensity, the "steeper" the curve is (around the bending point the first derivative is larger).
(b) The curves are asymmetrical, because the slope is "steeper" below, and less "steep" above the 50 point.

(c) With stimulus intensities about rheobasic level the curves never reach the 100 % probability.

In determining duration-probability relationships of a nerve fibre, these characteristics are easily shown (Fig. 3). Therefore we are justified to consider the RS a parameter of the threshold fluctuation of the peripheral axon.

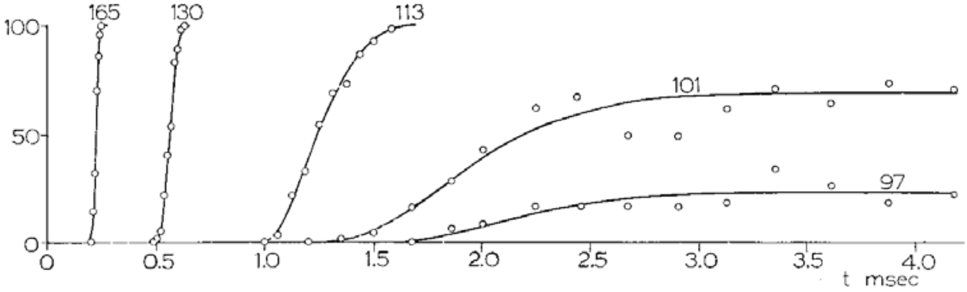

Fig. 3. Duration-probability curves of a nerve fibre. Strength in % of rheobase. Ordinate: P in percentage.

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SUMMARY

Summarising our results on probability phenomena of the peripheral nerve fibre of the green frog, we have seen that, with low-frequency stimulation

(a) The successive reactions can be considered as independent.
(b) The integral of the function of De Moivre can be considered a useful working hypothesis for the relationship between stimulus strength and probability of reaction.
(c) The Relative Spread, defined as the quotient of the two parameters of this integral, can be considered to be a parameter of the threshold fluctuation of the nerve fibre, not dependent on strength and duration of the stimulus current.

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DISCUSSION

R. LORENTE DE NÓ: I don't know if you are justified to speak about random variation; there are always continuous changes in the membrane potential. Nerve fibres never have a constant potential. They are oscillating and the oscillations can become synchronous. The random variation would then be associated with the changes in membrane potential.

A. A. VERVEEN: I have given only a description of the phenomenon, omitting the cause. Blair and Erlanger (1933) have already stated that this appearance of randomness could be caused by the interference of a supposed oscillation of the membrane potential and a cycling stimulus. As yet, I cannot think such an interference would result in a statistical appearance of randomness. Pecher (1939) proposed the idea of the discontinuity of matter to be responsible for this phenomenon. I am inclined to favour this hypothesis, because it can explain all the known features of this phenomenon. Probably processes like membrane oscillations-which I indeed did not measure- may interfere with this probability phenomenon and so may give alterations in the value of the probability, with subsequent alterations of the response pattern.