

STATISTICAL ANALYSIS OF THE MULTICELLULAR ACTIVITY OF NEURONS

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Abstract

The paper describes three related statistical methods. These include the estimation of the interrelationship of impulse trains in neurone systems; a quantitative estimation of the correspondence of the impulse train to functioning of the neuron group; and a quantitative estimation of the interference of action potentials. The joint application of these methods contributes to a correct analysis of multicellular activity of neurons.

1. Introduction

An adequate interpretation of the results of neurophysiological studies is known to be rather sensitive to the level of correctness in treatment of initial data (Sherry and Klemm, 1984). This is especially true in analyzing the multicellular activity of neuron systems. In this connection three main problems may be distinguished. These include:

- separation of impulse trains belonging to different neurons;
- the definition of the probability of their interference;
- the analysis of the interrelation of the separated impulse trains.

The present paper describes new methods which allow in some instances for a successful solution of the above-mentioned problems.

2. The Method for Estimation of Interrelation of Impulse Trains in Neuron Systems

For estimation of interrelation of neuron impulse trains the following techniques are used. These include the methods of correlation analysis, the

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methods based on the application of the mutual function of expectation and the cross-interval interrelations (Lyamin, 1968; Moore *et al.*, 1970; Dickson, Gerstein, 1974; Holden, 1976). The mentioned methods are confined to the assumption about the stationarity of impulse trains and give only a generally required condition of the presence of the dependence. Other constraints of these methods cover the requirements for the ordinarity of impulse trains and the absence of the after-effects, etc. For example, Keder-Stepanova *et al.* (1976) used in her paper the method based on reliable difference between the regular density distribution and a real histogram for interimpulse intervals at the segment $0 < t \leq \tau_{\min}$, where τ_{\min} is the minimal period among refractory periods of comparable neurons. However, the reliability of the estimation obtained with this criterion is strongly decreased in case when the statistically significant difference from the straight line ("overshoot") is observed in the vicinity of τ_{\min} .

It should be emphasized that none of the mentioned methods is versatile. For this purpose the aim of the present paper is to develop a method allowing in a number of cases to avoid the mentioned limitations.

Let us consider the algorithm and the peculiarities of the method. We start with a simple case: it is necessary to estimate the functional interrelation of two neurons. Let the following conditions be met: an investigator has simultaneous recordings of impulse activity from each individual neuron and that of two neurons. This means that for the closely-located neurons the impulse activity can be recorded with one microelectrode while neurons distantly-located from each other require the use of two microelectrodes.

Let this condition be satisfied, then the algorithm of the estimation of interrelation can be described by the following steps:

1) Let us make the hypothesis H_1 : the functioning of each neuron satisfies the model of the threshold element (Kryukov, 1976). If x is an interspike interval of the output impulse train from a neuron, then the probability density $f(x)$ in this model is described as:

$$(1) \quad f(x) = \frac{x^{N-1}}{(N-1)!} v^N \exp(-vx),$$

where $N = \text{Const.}$, $v = (\lambda - \mu) \geq 0$, λ is the parameter of the Poisson distribution, μ is the parameter of the exponential distribution. The choice of this model is not essential: according to the first step of the algorithm it is necessary to have an analytical description of the interspike interval distribution. The Erlang distribution (1) is applicable for approximation of many histograms of interspike intervals characterized by mono-modality and the positive asymmetry coefficient.

2) For testing of the hypothesis H_1 we use the method of the maximal likelihood and χ^2 test. Let $x_i^{(j)} > 0$, $i = \overline{1, n}$ be the sequence of values of interspike intervals of the spike activity of the j -th neuron; $j = 1, 2$. The likelihood function for this sequence assumes the form:

$$(2) \quad L(x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}, N, v) = \prod_{i=1}^n f(x_i^{(j)}) = \frac{\left(\prod_{i=1}^n x_i^{(j)N-1} \right)}{[(N-1)!]^n} v^{nN} \exp \left\{ -v \sum_{i=1}^n x_i^{(j)} \right\}$$

The values of parameters v and N providing the maximum for the function L can be found from the conditions

$$(3) \quad \begin{aligned} L'_v(x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}, N, v) &= 0 \\ \max L(x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}, N, v), \end{aligned}$$

in that $v \geq 0$ is continuous and N is discrete.

Solve the system (3). Denote

$$\prod_{i=1}^n x_i^{(j)} = b^{(j)} > 0.$$

Let us compose the ratio of Eqn (2) for $N = k$ and $N = k - 1$; $k = 2, 3, \dots$

$$(4) \quad \frac{L(x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}, k, v)}{L(x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}, k-1, v)} = b^{(j)} \left(\frac{v}{k} \right)^n$$

If $v < 1$ and $b^{(j)} < 1$, then $k = N = 2$ delivers the maximum to Eqn (4). If $v \geq 1$, $b^{(j)} \geq 1$ or if only one of these parameters is greater than or equal to 1, then the number $k = k_0$ can be found starting from which the Eqn (4) will be less or equals to 1. To see this,

$$k_0 = E\{v[b^{(j)}]^{1/n}\} + 1,$$

where $E(\cdot)$ is an integral part of a number (\cdot). Thus, in place of (3) we have the following system of finding the estimates for the parameters v and N :

$$(5) \quad \begin{aligned} v &= \frac{nN}{\sum_{i=1}^n x_i^{(j)}} \\ N &= E \left[v \left(\prod_{i=1}^n x_i^{(j)} \right)^{1/n} \right] + 1 \end{aligned}$$

3) Suppose that for a realization of $x_1^{(j)}, x_2^{(j)}, \dots, x_n^{(j)}$; $j = 1, 2$ these estimates appeared to be equal to N^* and v^* . By applying the χ^2 test we check whether the sample agrees with the hypothesis that the interspike interval is distributed according to the law (1) with parameters $N = N^*$ and $v = v^*$.

4) Let us suppose that the hypothesis H_1 is not rejected. Then the probability density of interspike intervals of the set of two independent impulse trains can be calculated as follows (Cox and Lewis, 1966).

$$(6) \quad f(x) = \frac{d}{dx} \left(\exp(-v^*x) \sum_{k=0}^{N^*-1} \frac{(xv^*)^k}{k!} \left[m \int_x^\infty \exp[-v^*x] \sum_{k=0}^{N^*-1} \frac{(xv^*)^k}{k!} dx \right] \right),$$

where m is an intensity of impulse train following the distribution (1). Hence

$$F(x) = \int_{-\infty}^x f(x) dx$$

for the more interesting case $N^* = 2$ assumes the form

$$F(x) = 1 - \frac{1}{2}(1 + v^*x)(2 + v^*x) \exp[-2v^*x]$$

5) Interrelation between impulse trains does not exist if the values of interspike intervals z_1, z_2, \dots, z_n , obtained in simultaneous recordings from two neurons are distributed in accordance with the integral function $F(x)$. This fact is checked with the Smirnov-Kolmogoroff's test. Otherwise the dependence exists. In case of recording with two microelectrodes the array of z_1, z_2, \dots, z_n is formed due to the superposition of all recorded impulses on the time axis.

Remarks

(a) If the estimates of the parameter v^* appeared to be different for $j=1$ and $j=2$, then $F(x)$ is found as the convolution of two Erlang distributions with different parameters values of v_1^* and v_2^* according to the following formula

$$F(x) = 1 - \frac{1}{2} \left[\frac{2b + 2(c+d)(xa+1) + b(x^2a^2 + 2xa + 2)}{a^2} \right] \exp[-ax],$$

where

$$\begin{aligned} a &= v_1^* + v_2^*; \\ b &= v_1^* v_2^*; \\ c &= (v_1^*)^2; \\ d &= (v_2^*)^2 \end{aligned}$$

(b) The estimation of interrelation of a large number of neurons results in the estimation of the pair interrelation.

3. Quantitative Estimation of the Correspondence of the Impulse Train to Functioning of the Group of Neurons

The records obtained in microelectrode recording show generally the activity of several neurons. The separation of the units are performed with the amplitude discriminator (Berry *et al.*, 1978; Fetz and Finacchio, 1975; Gasanov, 1981), according to the shape of a spike (Schwartz *et al.*, 1976) or with linear filtration technique (Abeles and Goldstein, 1977). The amplitude discrimination technique is more frequently used in neurophysiological studies: the spikes are assigned to

$k > 1$. However, errors of two types may be observed in this case. The error of the first type is made when impulse activity is attributed to one neuron, the spikes of which differ by less than k times while this is actually the activity of neurons located in a close vicinity. The error of the second type is made when the impulse activity of a single neuron characterized by the amplitude changes of more than k times is attributed to that of two neurons.

Let us consider the statistical method allowing under a number of assumptions to minimize the error of the first type.

We will analyse extracellularly the activity in respect to which it is not known in advance whether this activity is the impulse sequence of several or single neurons. Suppose that this impulse sequence satisfies the properties of the renewal process and does not contain an average frequency trend. We choose the spike amplitude and the length of interspike interval as independent information parameters of the impulse train.

We form two impulse subtrains from the initial impulse train using the amplitude discrimination with two non-intersecting "windows" (Fetz and Finacchio, 1975; Berry *et al.*, 1978; Gasanov, 1981), whereas we choose the width of the "windows" significantly smaller than the maximal value among the amplitudes of impulses in neurograms. If we know the law of distribution of amplitudes of a general impulse train $F(z)$, then the procedure of organization of the first impulse subtrain is equivalent to the operation of thinning the initial impulse train with probability

$$p_1 = \int_{a_1}^{a_2} f(z) dz,$$

where $[a_1, a_2]$ is the width of the first "window" (just with this probability were left the events of the thinned impulse train). The procedure of organization of the second subtrain is equivalent to the thinning of the initial train with probability

$$p_2 = \int_{b_1}^{b_2} f(z) dz,$$

where $[b_1, b_2]$ is the width of the second "window". It is evident that $p_1 + p_2 \leq 1$. Suppose that with such a neurogram the absolute inequality $p_1 + p_2 < 1$ is satisfied. Then on performing the above-mentioned limitations a randomized procedure of shaping the impulse subtrains forms statistically independent subtrains in the case where the initial impulse train belongs to a single neuron.

We may then deduce the following rule of estimation of the belonging of the impulse train to a group of neurons: if in the result of statistical estimation of subtrains plotted according to the criterion described in part I, they appeared to be interdependent, then the analyzed activity does not belong to a single neuron; that is, it belongs to the group.

The testing of the method based on the rule formulated above was carried out for situations when due to the separation of impulse trains by microelectrode displace-

ment in electrophysiological experiments we succeeded in obtaining the pre-information whether one or two neurons "work". By such a test the validity of the proposed method can be checked. Two variants were considered:

1) impulse activity is visually subdivided into two subtrains (the amplitudes differed not less than 1.5 times) and according to neurograms there are good grounds to attribute their functioning to two closely-located receptors; electrophysiological experiments with displacement of a microelectrode showed that these were two receptors. The impulse activity presented in Fig. 1b will be referred now as neurogram 1.

2) impulse activity is visually characterized by a weak impulse-to-impulse amplitude change (1.1 times less). In this case there are grounds to attribute this activity to functioning of one neuron. According to the results of experiments with displacement of a microelectrode this is one receptor. The impulse activity presented in Fig. 1a will be referred as neurogram 2.

Both neurograms do not display a marked trend of average frequency. Corresponding time series plotted for interspike intervals at neurogram magnification are smoothed by the zero degree polynomial according to the method of the least squares; the significance level was chosen to be equal to 0.05.

In the proposed method the system of equations (5) from Section 2 is the key system for application of the criterion of interrelation. Substitute in this system the values of sequential (arranged in the order of recording) interspike intervals (expressed in absolute units) first for X_1 and then for the subtrain Y_1 of neurogram 1. In the resulting solution of the system we have the following parameters values

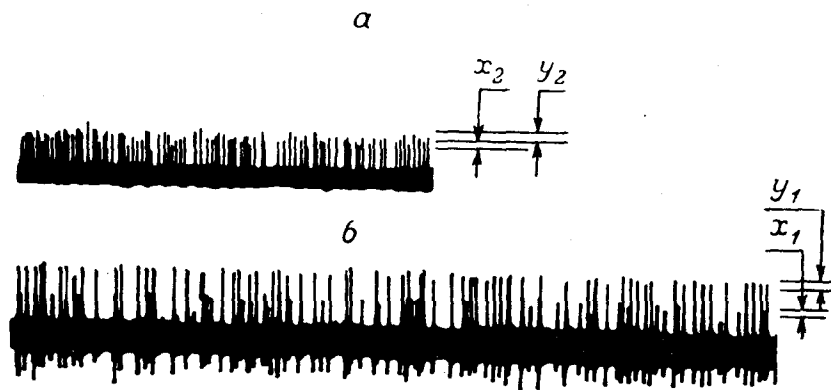


Fig. 1. The neurograms of the antennal receptors of the American cockroach after prolonged deviation of the flagellum relative to the pedicel.

Two types of recordings received from different insects are shown.

(a) The first second of mechanical stimulation.

The amplitudes of the impulse subtrains X_2 and Y_2 differ in less than 1.1 times.

Calibration for all neurograms: 100 μ V, 100 ms.

(b) The fifth second of mechanical stimulation.

The amplitudes of the subtrains X_1 and Y_1 differ in not less than 1.5 times.

(simultaneously for X_1 and Y_1): $v_1 = 0.06$; $N_1 = 2$. For these parameters values we can construct the following function of the distribution of interspike intervals using the formula (6)

$$F_1(x) = 1 - 0.50(1 + 0.06x)(2 + 0.06x)\exp(-0.12x)$$

The index 1 in $F_1(x)$ means that all considerations are referred only to the neurogram 1. The comparison of the function $F_1(x)$ and the sample Z_1 (the sample Z_1 presents the sequential values of interspike intervals of the total impulse train including X_1 and Y_1 of the neurogram 1) leads to the following results according to the Smirnov-Kolmogoroff's test

$$D_{(130)} = \max |F_n^{(1)} - F_1(x)| = 0.134,$$

where $F_n^{(1)}$ is the empirical function of distribution, plotted for interspike intervals of the sample Z_1 . This allows us to estimate the value based upon the Smirnov-Kolmogoroff's test

$$\lambda_0^{(1)} = n^{1/2} D_{(130)} = 130^{1/2} \cdot 0.134 = 1.53$$

Then, using the distribution table for the function $1 - K(\lambda)$, where $K(\lambda)$ is a special function introduced by A. N. Kolmogoroff, we get:

$$1 - K(\lambda_0^{(1)}) = 1 - K(1.53) < 0.05.$$

The obtained results show that with the significance level of 0.05 the hypothesis of interdependence of the subtrains X_1 and Y_1 is rejected, that is, the neurogram 1 corresponds to the impulse activity of the group of neurons. Similarly, using the above-mentioned algorithm on the data of neurogram 2 we get $v_2 = 0.11$; $N_2 = 2$ for X_2 and Y_2 , simultaneously. Then

$$F_2(x) = 1 - 0.50(1 + 0.11x)(2 + 0.11x)\exp(-0.22x),$$

$$D_{(100)} = \max |F_n^{(2)}(x) - F_2(x)| = 0.049,$$

$$\lambda_0^{(2)} = 100^{1/2} \cdot 0.049 = 0.490;$$

$$1 - K(0.490) > 0.05$$

Therefore, the hypothesis of interdependence of impulse trains X_2 and Y_2 is not rejected. Thus, the processed data are not in contrast with the hypothesis that the neurogram 2 corresponds to impulse activity of one neuron, although there are no given reasons to state that this hypothesis holds true.

Thus, a comparison of conclusions of the statistical analysis of the neurogram 1 and neurogram 2 on the one hand, and electrophysiological experiments on the other hand shows good agreement.

The proposed method as seen from its description is not universal and available for all experimental situations. The same may be said about the methods of separation of

impulse trains according to a spike shape and on the base of the optimal linear filtration (Schwartz *et al.*, 1976; Abeles, 1977). The application of a combination of these methods will probably allow us to analyze impulse trains in a rather valid way. Thus, for analysis of impulse responses from two elements which do not differ in their amplitudes, attempts should be made to use the method of spike shape differences. However, the following situation may arise: suppose different-amplitude spike recordings of the functioning of one neuron are imply discarded as unavailable and containing the "additives" from other neurons. In this case important information can be excluded from consideration. As far as the displacement of a microelectrode at extracellular recording does not always result in separation of impulse activity of one neuron, the application of the proposed method allows in a number of instances to fill this gap.

4. The Quantitative Estimation of Interference of Action Potentials

In processing the impulse activity of a neuronal population as recorded with one microelectrode it is important to determine quantitatively the probability of interference of individual impulses from different excitable units. This is due to the fact that if at the segment of the nervous tissue interference of impulse trains from different neurons takes place, then the neurogram shows not two but three impulse trains with different amplitudes. The processing of such a neurogram performed by the techniques of the amplitude discriminator or the probability criterion (Gerstein, 1970; Moore *et al.*, 1970; Dickson and Gerstein, 1974; Kovbasa, 1980) will lead to quantitatively inaccurate results.

Let us obtain a quantitative estimate of the interference of impulse trains using the method of estimation of functional interrelation of neurons, described in Section 2.

Suppose that in the result of applying this method to the records of impulse trains from the studied pool units we do not reject the hypothesis with the selected significance level concerning interdependence. Then and only then the possibility arises of estimating the effect of interference by calculating the interference coefficient, which is the ratio of pulse overlap frequency to the total pulse frequency from the whole pool. The coefficient of interference K_n for the case of n mutually independent stationary impulse trains is known to assume the form (Sedyakin, 1975)

$$(7) \quad K_n = - \frac{\frac{\partial^{K+1}}{K! \partial \lambda^K \partial \delta} \prod_{s=1}^n [Q_s(\delta) + \lambda P_s(\delta)] \Big|_{\lambda=0}}{\sum_{i=1}^n \bar{\mu}_i}$$

where K is the number of overlapping impulses; δ is the duration of overlapping; $Q_s(\delta)$ and $P_s(\delta)$ are expressed in terms of density distribution of interspike intervals in impulse trains $\beta_s(\tau)$ and density distribution of the impulse length $\alpha_s(\tau)$.

$$P_s(\delta) = \bar{\mu}_s \int_{\delta}^{\infty} dx \int_x^{\infty} \alpha_s(y) dy;$$

$$Q_s(\delta) = \bar{\mu}_s \int_{\delta}^{\infty} dx \int_x^{\infty} \beta_s(y) dy;$$

$$\bar{\mu}_s = \frac{1}{\bar{\tau}_s + \bar{\theta}_s};$$

$$\bar{\tau} = \int_0^{\infty} \tau \alpha_s(\tau) d\tau;$$

$$\bar{\theta}_s = \int_0^{\infty} \theta \beta_s(\theta) d\theta.$$

The action potentials are characterized by the following properties:

- the length of impulses is fixed, denote it as τ_0 ;
- impulses are not overlapped in one impulse train due to refractoriness.

Let us suppose that the average value of the interspike interval is little changed from train to train. Denote it by θ_0 . In any case an average magnitude of the average values of interspike intervals can be regarded as θ_0 . Furthermore, suppose that $n=K$.

Then in place of (7) we have

$$(8) \quad K_n = \left(\frac{\tau_0 - \delta}{\tau_0 + \theta_0} \right)^{n-1}$$

From this equation it follows that the major contribution to the action potential interference is from the superposition of one impulse on the other and the probability of simultaneous superposition of three, four and more impulses is decreased according to the law of geometric series with the common ratio equal to $\frac{\tau_0 - \delta}{\tau_0 + \theta_0} < 1$. In addition, it is important that microelectrodes usually record not more than four impulse trains. The contribution to the interference of the impulses from neurons located at a distance more than the cell radius (the diameter of the electrode tip is less than $2 \mu k$) is so insignificant that it may be neglected (the amplitude of action potential is at the level or below the level of noise) (Towe, 1973; Schwartz *et al.*, 1976). Taking into account these factors let us find the equation for the "extended" coefficient of interference $K_n^{(n)}$ which gives a quantitative estimate of coincidence of two impulses only. This can be easily done if we remember that impulse trains were considered as being interdependent and a total number of different "pairs" of impulse

trains equals to C_n^2 which is the number of combinations from n taken by two. Thus we have

$$(9) \quad K_2^{(n)} = C_n^2 \frac{\tau_o - \delta}{\tau_o + \theta_o}$$

Let us refer to a geometrical interpretation. Fig. 2a demonstrates an idealized situation where the neurogram shows two impulse trains X_1 and X_2 with the identical amplitude as well as the impulse train X_3 , the impulse amplitude of which exceeds the level of amplitudes of the impulse trains X_1 and X_2 . Fig. 2b shows the situation when there are four impulse trains characterized by different values of amplitudes.

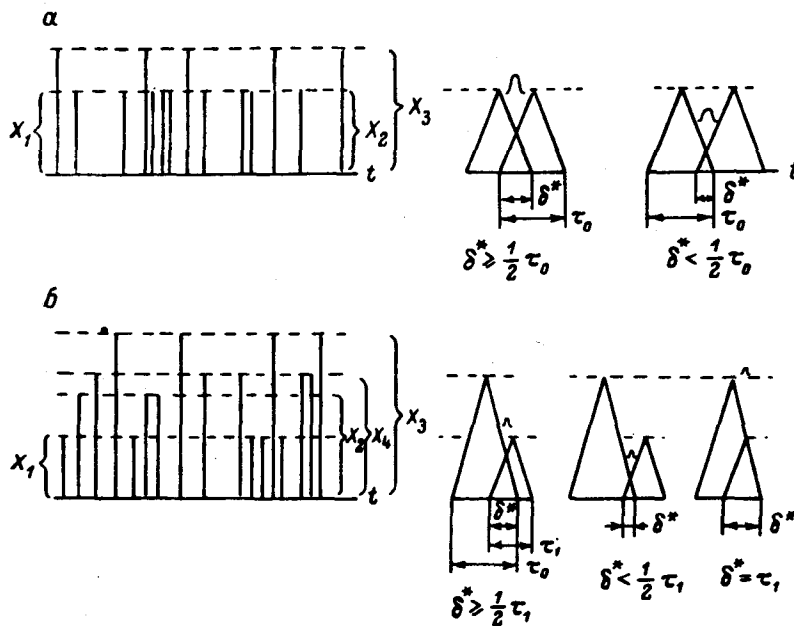


Fig. 2. Dependence of the amplitude of the recorded signal on the impulse pile-up value (Schematic representation).

- (a) X_1, X_2 — the impulse trains from neurons located at the identical distance from the recording microelectrode. X_3 — the impulse train is probably connected with interference of X_1 and X_2 impulse trains.
- (b) X_1, X_2 — the impulse trains from neurons located at different distance from the recording microelectrode. X_3 and X_4 — the impulse trains are probably connected with interference of X_1 and X_2 impulse trains.

The impulses in the first approximation are regarded as the isosceles triangles.

δ^* — impulse pile-up value

τ_o — length of impulse with the larger amplitude

τ_1 — length of impulse with the lesser amplitude.

Let us make two hypotheses:

- 1) The impulse train X_3 (and X_4) was formed due to interference of impulse trains X_1 and X_2 .
- 2) The impulse train X_3 (and X_4) is not connected with interference of the impulse trains X_1 and X_2 .

The problem is to decide between the two hypotheses. The solution of the problem will be constructed by estimating the magnitude of interference of action potentials. Taking into consideration that the duration of the action potential is significantly less than its amplitude (at measurement by the identical units) action potentials in the first approximation are regarded as isosceles triangles. In the figures a real correlation of the impulse height and its base was not especially required to obtain clear evidence. From Fig. 2a it can be easily seen that the value of impulse overlap $\delta = \delta^*$ included in the interval $(0.5\tau_o, \tau_o)$ and only this value will lead to the situation that the impulse produced due to superposition of the impulse trains X_1 and X_2 will have higher amplitude than that of impulses of these trains. With the values δ^* related to the interval $(0, 0.5\tau_o)$ superposition of impulses will initiate the impulse with the amplitude not higher than that of any impulses of the trains X_1 and X_2 . Due to short duration of action potential the impulse generated in the result of such interference will not differ from impulses which initiated it and the larger δ^* , the higher will be the amplitude of the impulse originated due to interference. However, as it directly follows from (9) the larger δ^* , the less is the value of "extended" interference coefficient. With $\delta^* = \tau_o$, $K_2^{(n)}$ is equal to zero. This indicates that if interference takes place, then due to superposition the impulses (forming the impulse train X_3) will be produced. These will slightly exceed the amplitude of the unsuperimposed trains X_1 and X_2 .

Let us consider the most favourable situation leading to the initiation of the impulse train X_3 due to interference. It is obvious that this situation occurs when the condition $\delta^* = (0.5 + \epsilon)\tau_o$ is satisfied, where ϵ is an infinitesimal positive value (the extended interference coefficient is maximal while the impulse initiated due to interference exceeds by the infinitesimal value the impulses which gave rise to the impulse τ_o , $\theta_o = \text{Const.}$). In this case

$$K_2^{(n)} = \frac{C_n^2 (0.5 + \epsilon) \tau_o}{\tau_o + \theta_o}$$

Moreover, let $\theta_o = 0$ (impulse trains contacting each other). Then $K_2^{(n)} = 0.5 C_n^2$ with $\epsilon \rightarrow 0$. For $\theta_o = \tau_o$, $K_2^{(n)} = 0.25 C_n^2$, for $\theta_o = 9\tau_o$, $K_2^{(n)} = 0.05 C_n^2$, and for $\theta_o = 99\tau_o$, $K_2^{(n)} = 0.005 C_n^2$. This indicates that even with the value of an average interspike interval which is 10 times larger than the impulse length ($\theta_o \geq 10\tau_o$) $K_2^{(n)} \leq 0.05 C_n^2$ that constitutes only 5% of the maximal possible value of the "extended" interference coefficient equal to C_n^2 . Let us now consider the case corresponding to Fig. 2b. It can be easily recognized by analogy with the previous example that the impulse train X_3 (and X_4) arises due to interference only in case

when the value of overlapping δ^* belongs to the interval $(0.5 \tau_1, \tau_1)$, where τ_1 is the length of the impulse with lesser amplitude $\tau_1 < \tau_0$. Elementary calculations show that

$$\frac{\tau_1}{\tau_1 + \theta_0} \leq \frac{\tau_0}{\tau_0 + \theta_0}$$

with $\tau_0 > \tau_1$, $\tau_0 > 0$, $\tau_1 > 0$, $\theta_0 \geq 0$. This means that with the uniform amplitude the value of the "extended" interference coefficient is larger than that with different amplitude.

Thus, in processing of neurograms of interdependent impulse trains recorded extracellularly by microelectrodes, for which the ratio $\theta_0 \geq 10 \tau_0$ is satisfied, the interference of these impulse trains may be neglected.

5. Conclusions

The algorithm of the proposed methods can be easily realized as the program for an electronic digital computer. However, the methods cannot answer the question regarding the type of dependence (excitation or inhibition) between neurons. The number of interspike intervals is of essential importance: not less than 50 intervals are required to obtain reliable estimates. At the same time the methods allow (that is rather essential and presents the main distinction from previously known methods) to compare two or several recordings and receive qualitative estimation of stochastic dependence between neurons without large limitations in respect to the structure and recording of impulse trains.

References

- Abeles, M. and Goldstein, M. H. (1977). Multispikes train analysis. *Proceedings of the IEEE* **65**, 762-773.
- Berry, S. D., Rinaldi, P. C., Thompson, R. F. and Verzeano, M. (1978). Analysis of temporal relations among units and slow waves in rabbit hippocampus. *Brain Res. Bull.* **3**, 509-518.
- Cox, D. R. and Lewis, P. A. W. (1966). *The statistical analysis of series of events*. Wiley, New York. 312 pp.
- Dickson, J. W. and Gerstein, G. L. (1974). Interaction between neurons in auditory cortex of the cat. *J. Neurophysiol.* **37**, 1239-1261.
- Fetz, E. and Finocchio, D. V. (1975). Correlation between activity of motor cortex cells and arm muscles during operantly conditioned response patterns. *Exp. Brain Res.* **23**, 217-240.
- Gasnov, U. G. (1981). *The systemic activity of the cortex neurons in learning*. Nauka Publ., Moscow, 110 pp. (In Russian.)
- Gerstein, G. L. (1970). Functional association of neurons: detection and interpretation. In *Neurosciences Communication and Coding in the Nervous System*, New York, 648-661.
- Holden, A. (1976). *Models of the stochastic activity of neurones*. Lecture notes in Biomathematics. Springer-Verlag, 312 pp.
- Keder-Stepanova, J. A., Ponomarev, V. A. and Chetaev, A. N. (1976). On the dependence in the action of medulla oblongata respiratory neurons. *Biophysics* **11**, 123-129. (In Russian.)
- Kryukov, V. (1976). Wald's identity and random walk models for neuron firing. *Adv. Appl. Prob.* **8**, 257-277.
- Kovbasa, S. I. (1980). On mutual dependent pulse fluxes appreciation in neuron systems *Biophysics* **25**, 1086-1090. (In Russian.)
- Lyamin, E. A. (1968). Estimation of impulse flow dependence. *Biophysics* **13**, 827-834. (In Russian.)
- Moore, G. P., Sequendo, J. P., Perkel, D. M. and Levitan, H. (1970). Statistical signs of synaptic interaction in neurons. *Biophys. J.* **10**, 876-900.
- Schwartz, E. L. and Ramos, A. (1976). Single cell activity in chronic unit recording: a quantitative study of the unit amplitude spectrum. *Brain Res. Bull.* **1**, 57-68.
- Sedyakin, N. M. (1975). The elements of the theory of random impulse fluxes. In *Soviet Radio*, Moscow, 250 pp. (In Russian.)
- Sherry, C. J. and Klemm, W. R. (1984). What is the meaningful measure of neuronal spike train activity? *J. Neurosci. Methods* **10**, 205-213.
- Towe, A. L. (1973). Sampling single neuron activity. In *Bioelectric Recording Techniques*. Part A. New York, London, pp. 79-93.