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A statistical method for the estimation of neuronal response latency and its functional interpretation

JOHN SEAL1,*, DANIEL COMMENGES2, ROGER SALAMON2 and BERNARD BIOULAC1

Groupe Motricité, 1Laboratoire de Neurophysiologie, and 2Département d’Informatique, Université de Bordeaux II, 146 rue Léo Saignat, 33076 Bordeaux Cedex (France)

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The functional role of many central nervous structures has been inferred from the temporal relationship of a neuronal response with the different sensory and motor events in an experimental design such as when an animal performs a trained movement in response to a conditioned stimulus. However, this kind of data analysis leads to problems in estimating the occurrence and latency of any neuronal response. We examine these problems and propose a novel technique of data analysis to estimate the point of change in a sequence of neuronal discharge. Furthermore, data can be tested to see whether the neuronal response is related to the conditioned stimulus or the motor act. The method can also be used in the simple situation of determining the latency of a neuronal response after a stimulus.

The basis of many neurophysiological experiments in behaving animals is to record single neuronal discharge during the execution of a conditioned movement. The temporal relationship between the modulation of neuronal activity and the sensory or motor events in this type of experimental design has been extensively used to infer the functional role of numerous structures in the central nervous system. In this kind of experiment, unit activity is generally analyzed using perirestponse or peristimulus histograms depending on whether the recorded units were located in a supposed motor or sensory structure. Using such histograms, an attempt can be made to detect changes in discharge of the recorded unit and to estimate the latency of any change with respect to the stimulus or the movement.

In the analysis of neuronal discharge, there are essentially 3 problems. The first is to decide whether or not there has been a neuronal response. Secondly, if there has been a response, it is necessary to evaluate at what moment in time the change occurred. Thirdly, in the case of a change in activity after the stimulus but before the movement, it may be necessary to decide whether the change is related to the stimulus or to the movement. This is because the change may be the sensory response to the stimulus or part of the motor activity which gives rise to the movement, depending on the structure in which the recording is made. It is not sufficient to say that a change in activity before the movement represents motor activity. This problem is all the more relevant now that there are several reports of stimulus-related changes in activity recorded in brain structures which were previously considered to have essentially a motor function.

A brief perusal of the methods section in any of the recent papers in sensorimotor physiology will show that numerous techniques and statistical tests are used to detect changes in unit activity, e.g. the widely used interspike interval distribution method of Tanji and Evarts12, the transformation of a spike train into a continuous function3 and the application of the Kolmogorov-Smirnov test to determine the onset time of modulation in discharge rate7. However, the different methods available propose only empirical solutions. Many techniques include a subjective selection of a threshold for significance of changes in unit activity or the assumption of spike interval distribution which is assumed although the case and the interval distribution may be skewed.

Tanji and Evarts12, have used the distribution of the interspike intervals to determine the number of discharges during the period of time and the subsequent period was made for peak likelihood to occur at the length of the period, it was decided to use the method. The onset of the criterion was when a deviation
of changes in unit activity. Often, a normal distribution of spike intervals during the pre-stimulus period is assumed although in reality this may not be the case and the interval distribution for spontaneous activity may be skewed.\(^6\)^\(^{10}\)

Tanjii and Evarts\(^3\), for instance, compared the distribution of the interspike intervals for the neuronal discharge during the pre-stimulus period with that of the subsequent post-stimulus period. Several tests were made for periods of growing size. If a deviation occurred at the level \(P < 0.001\) for a particular period, it was decided that a response had taken place. The onset of the response was said to have occurred when a deviation at the level \(P < 0.01\) was obtained.

A similar technique was proposed by Mano and Yamamoto\(^7\) using the Kolmogorov-Smirnov test which, being a non-parametric test, is independent of normality assumptions. However, the approach illustrated by these two examples is clearly empirical: as several tests are made, the power and the actual probability level of the test is unknown.

Concerning the third problem, it is difficult to interpret changes in neuronal activity which precede the onset of movement on the basis of histograms only. In clearcut cases, the decision of whether a change in activity is better related to the stimulus or the movement can be made after examining the form of the peri-stimulus and peri-response histograms. A change in activity which gives rise to a movement (as seen in the precentral motor cortex, for example) will appear more punctual in a peri-response histogram than with a peri-stimulus histogram (see Fig. 1). The converse is true for a modulation of activity related to the stimulus. However, the comparison of histograms is purely arbitrary and this technique is of limited use when recording from structures which present both stimulus- and movement-related events. In an attempt to solve this particular problem, Mano and Yamamoto\(^7\) proposed to estimate the latency of the response in each trial and then to study the correlation between the latency of the response with respect to the stimulus and the behavioral reaction time. These authors concluded that a high correlation indicates the response is related to the movement. Although interesting, this method has a severe defect:

\[ Z \]

\[ X \]

\[ Y \]

\[ \text{Stimulus} \]

\[ \text{Neuronal response} \]

\[ \text{Movement} \]

X and Y may both be correlated to Z. In such a case, the conclusion of the authors that the response is related to the movement is incorrect because it does not take into consideration the correlation of Y and Z. We propose a novel technique of analyzing data trial by trial to precisely determine the interval at which there is a change in the discharge of a neuron. Data analyzed in this way can be tested so as to decide whether the change in activity is a response to
the stimulus or whether it is related to the movement.

The situation of detecting a response in a sequence of action potentials corresponds to a problem known to statisticians as the change-point problem which can be stated as follows: a sequence of random variables \(X_i, i = 1, \ldots, n\) is given in which a change in the distribution possibly occurs at an unknown point: \(X_i, i = 1, \ldots, r\) has the distribution \(F_1(r)\), and \(X_i, i = r + 1, \ldots, n\) has the distribution \(F_2(r)\).

It is first necessary to test the 'no change' hypothesis, \(F_1 = F_2\), and then if this hypothesis is rejected, an attempt can be made to estimate the point of change, \(r\). In our problem, the random variables are the time intervals between subsequent action potentials. These intervals are obviously positive. Furthermore, the means and the standard deviations of the intervals are approximately linearly related for most examples of neuronal discharge\(^{10}\).

Thus, we propose the following model as being most likely to fit the real situation:
\[
F_1 = \Gamma(\gamma, a_1); F_2 = \Gamma(\gamma, a_2)
\]
where \(\Gamma\) is the gamma distribution. This distribution was chosen because it appears to fit the data well\(^4\) and gives robust estimators even when the data distribution is not a gamma function\(^2\). Little work has been published on the problem of testing the 'no change' hypothesis. Most of the tests proposed\(^{1, 3, 9}\) concern the case where the variance of the variables is known. We have proposed Bayesian procedures for solving the problem with unknown variance\(^2\).

When a response was detected, we have estimated the point of change in neuronal discharge using the maximum likelihood approach. The estimator, based on the gamma distribution, is the value of \(r\) which maximizes:
\[
X_{1r}^{(n-r)} X_{2r}^{(n-r)}
\]
where \(X_{1r}\) is the mean of the \(r\) first intervals and \(X_{2r}\) is the mean of the \((n-r)\) remaining intervals.

Fig. 2. Histograms and a raster display representing the activity of a neuron located in the posterior parietal cortex. The discharge of this neuron increased at about 160 ms before the movement, as shown by the peri-response histogram (A), and approximately 160 ms after the stimulus, as shown by the peri-stimulus histogram (B). From a simple comparison of the form of the two histograms, it is not possible to say whether the neuronal response is related to the movement or to the stimulus. However, these two histograms served to determine the 'window' which was fixed at 100 ms after the stimulus and 100 ms before the movement. The estimate of the onset of the neuronal response for each trial is shown by the filled circle in the raster display (C). The onset of the movement is shown by an open circle. Arrows indicate trials in which no change was detected. See text.

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4 Glaser, E. M. and Randles, H. R., A test of the null hypothesis that two samples are drawn from normal populations with equal variances, *Biometrics*, 35 (1979), 35–43.
the mean of the \( (n - r) \) following intervals. We have applied this method to estimate the latency of the change in neuronal activity for each trial recorded for an individual neuron. In the case of one change in the frequency of discharge, the problem is easily solved. The same is true if the number of change-points is known although the number of operations becomes impractical if this value is high. Often, the number of change-points is unknown. A solution to this problem is to reduce the time period over which a search for a change is made so as to include only one point of change. We determined this 'window' after referring to the peri-stimulus and peri-response histograms constructed from all of the trials recorded for the neuron under test (Fig. 2). To avoid any bias, the limits of the 'window' must be fixed symmetrically with respect to the stimulus and the movement.

To decide whether a neuronal response is related to the stimulus or the movement, we have used the variance of the time periods: stimulus to change-point \((X)\) and change-point to movement \((Y)\). When the hypothesis of equal variance is rejected, we can conclude that the change in activity is related to the stimulus if the variance of \( X \) is smaller and to the movement if the variance of \( Y \) is smaller\(^2\). For a particular neuron, the change-point in a sequence of neuronal activity can be determined for each trial recorded. We then have a series of paired estimates of the time periods, \( X \) and \( Y \). The variances of these time periods can be compared using the non-parametric test of Kepner and Randles\(^4\). The statistic obtained with this test is either negative or positive, which indicates whether the variance of \( X \) of \( Y \) is the smaller. We have chosen this test because the classical techniques for the comparison of variance are sensitive to gross departures from the mean and may give incorrect results. We have studied the complete testing procedure with both simulated and experimental data with the number of trials as low as twenty.

A limit of our technique concerns testing the 'no change' hypothesis. There may be several points of change in a sequence of neuronal discharge and procedures based on one point of change may be misleading. We are at present engaged in finding a more acceptable solution for the 'no change' hypothesis.

An example using experimental data is given in Fig. 2. This neuron was located in area 5 of the posterior parietal cortex where changes in neuronal activity related to both the stimulus and the movement have been reported\(^8,11,12\). From the two histograms, it can be seen that there was an increase in neuronal activity approximately 160 ms before the onset of movement and approximately 160 ms after the onset of the stimulus. Trial by trial analysis using the method described above gave the mean latency of the neuronal response as being 167 ms after the stimulus and 131 ms before the movement. There was a significant difference between the variances of these two values \((P < 0.05)\) and the sign of the statistic was negative which indicated that the variance of the period stimulus to change in activity was the smaller. We can therefore say that the modulation of activity recorded in this neuron was related to the stimulus.

A Fortran program for the technique presented in this article is available from D. Commenges.

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Using an isolated neonatal CNS preparation for mammalian central nervous system (CNS) (0.001–0.004%) can effectively recover tissue viability. Adequate tissue oxygenation is recognized to be of paramount importance for tissue viability. This is even more so for the central nervous system (CNS), which is known to be very sensitive to anoxia. The importance of tissue viability today with the increase in CNS preparations. One approach to maintaining the viability of CNS tissue by Linas and coworkers was using hydrogen peroxide (H₂O₂) as an oxygen source in the superfusing saline solutions. They found that by administering hydrogen peroxide to the saline superfusing gassed with O₂, the viability of these preparations could be improved. In experiments conducted using gassed saline, the saline was not brought into contact with the oxygen source. Furthermore, hydrogen peroxide (0.003%) was necessary for tissue survival in vitro, and perfused in vivo, for example, in an adult guinea pig.

A detailed study of the role of hydrogen peroxide as an oxygen source of molecular oxygen in CNS preparations has been undertaken. The importance of the general significance of this study has been carried out successfully, and the protocol has been conducted using the isolated neonatal CNS, since, in addition to small preparations, large groups of neonatal CNS can provide insights into the factors affecting tissue viability.

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* Current address: Zoology Department, University of Pretoria, Pretoria.