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Conditional cross-interval correlation analyses with applications to simultaneously recorded cerebellar Purkinje neurons

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Two conditional cross-correlation techniques are described for the analysis of two simultaneously recorded neuronal spike trains. The *conditional interspike interval histogram* describes the distribution of interspike intervals of a neuron conditioned by a preceding spike in another neuron. The *conditional cross-interval histogram* describes the distribution of cross-intervals of two neurons conditioned by a preceding spike in one of the neurons. These techniques could be used to reveal the temporal coupling in the discharge of two neurons recorded simultaneously. The techniques augment the description of the correlation obtained with conventional cross-correlation measures. When applied to the simple spike discharge of simultaneously recorded cerebellar Purkinje neurons, the methods reveal temporal interactions between neurons that are not readily apparent from conventional cross-correlograms. The patterns observed suggest a tightly coupled, temporal surround-inhibition among nearby Purkinje neurons.

Introduction

Recently, there has been renewed interest in the use of simultaneous recording of multiple cerebellar neurons to elucidate spatiotemporal interactions among cells (Ebner and Bloedel, 1981b; Bloedel et al., 1983; Bower and Llinas, 1983; Sasaki and Llinas, 1985). Analytical techniques used to evaluate simultaneously recorded multiunit data have relied primarily on conventional cross-correlation analyses (Perkel, 1965; Moore et al., 1966; Perkel, et al., 1967; Knox, 1974, 1981), extensions of cross-correlation analyses (Ebner and Bloedel, 1981a; Lindsey, 1982), joint interval analyses (Segundo et al., 1966; Gerstein and Perkel, 1969, 1972; Perkel et al., 1975) and most recently more novel approaches (Gerstein et al., 1985). In this paper we introduce two representations of joint interval correlation, the *conditional interspike interval histogram* and the *conditional cross-interval histogram*, to analyze simultaneously recorded multiple spike train data.

The techniques presented in this report are extensions of the joint-interval histogram technique for analyzing a single spike, except that two simultaneously recorded spike trains are used. Both new techniques can be used to describe the temporal correlation between the discharge of two simultaneously recorded neurons. They can also be used to describe the primary and secondary effects of neuronal interactions (Moore et al., 1970). In brief, the conditional interspike interval probability density function (p.d.f.) describes the interspike interval distribution of one neuron conditioned by a preceding spike in another simulta-

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neously recorded neuron. Similarly, the conditional cross-interval p.d.f. describes the first order forward cross-interval distribution conditioned by a preceding spike in the other simultaneously recorded neuron. The p.d.f.'s can also be defined with an alternative definition of the reference spike (see Appendix B for details). The intervals used in the conditional correlation p.d.f.'s are a subset of the intervals in the cross-correlation function, which considers all nth order intervals (Perkel et al., 1967). In the conventional cross-correlation, interactions reflected in the first and second order intervals could become obscured since all combinations of conditional firing probability are summed together. The two measures we describe are based on conditional relations between first and second order intervals, emphasizing only the successive temporal firing patterns of these two neurons associated with these intervals.

The correlation statistics were applied to the simple spike discharge of simultaneously recorded pairs of cerebellar Purkinje neurons. Based on the highly structured cerebellar cortical circuitry, many have theorized the existence of precise temporal firing patterns among nearby Purkinje neurons (Braitenberg, 1961, 1967; Eccles et al., 1967; Marr, 1969; Pellionisz, et al., 1977). However, attempts to detect temporal correlations in Purkinje cell simple spike discharge using conventional cross-correlation techniques have yielded only limited results (Freeman and Nicholson, 1970; MacKay and Murphy, 1976; Ebner and Bloedel, 1981b). When we applied conditional correlation techniques to Purkinje cell simple spike activity, precise temporal relationships were observed which augmented the information obtained from conventional cross-correlation analysis. An abstract of some results was presented earlier (Tam et al., 1985).

Materials and Methods

Conditional interspike interval histogram

The conditional interspike interval distribution function is described in Appendix A and its construction presented in Fig. 1. It is similar to the joint-interval histogram for a single spike train (Rodieck et al., 1962), except that the backward cross-interval preceding the reference spike is used as the first or conditioning interval. The cross-interval is defined as the time interval from a reference spike in one train (Train A of Fig. 1A) to the nearest spike in another train (Train B of Fig. 1A), and is equivalent to the first-order "waiting-time interval" (Perkel et al., 1967). Since there are two cross-intervals with respect to a reference spike, one preceding it and another succeeding it, they are referred to as the backward cross-interval and forward cross-interval, respectively. As illustrated in Fig. 1, to construct the conditional interspike interval histogram from two spike trains, A and B, select a reference spike in train A and determine

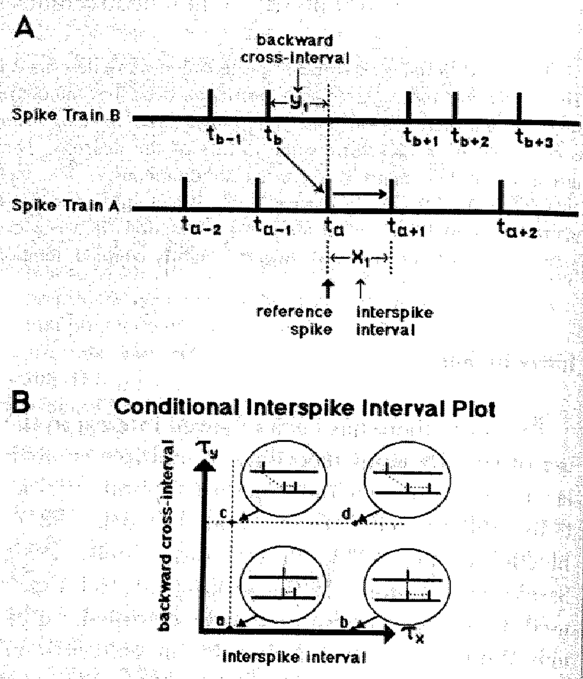


Fig. 1. Diagrammatic illustration of the generation of the conditional interspike interval histogram from two spike trains A and B. A: the backward cross-interval with respect to the reference spike in train A denoted as y_1, and the succeeding interspike interval in A as x_1. B: mapping of interspike and backward cross-interval pairs into an $x-y$ plot showing the relationships between select interspike intervals and backward cross-intervals in the insets. A conditional interspike interval histogram is constructed from the cumulated counts of the interspike cross-interval pairs for all reference spikes in train A.

the backward cross-interval (y_1). Next determine the interspike interval, x_1, from the same reference spike to the succeeding spike in A. This "interspike, cross-interval pair" (x_1, y_1) is then mapped into an x–y plot, with the backward cross-interval as the ordinate, and the succeeding interspike interval as the abscissa (Fig. 1B). By repeating the above procedure for all spikes in A, a conditional interspike interval histogram is obtained from the cumulated counts of the interspike cross-interval pairs (x_1, y_1). The interspike interval can be plotted on the y-axis alternatively (see Appendix C for details). Although a scatter plot could be used to display the interspike cross-interval pairs (Gerstein and Perkel, 1969, 1972), displaying in a histogram form provides a more useful representation of the estimated joint p.d.f.

The conditional interspike interval histogram may be regarded as a set of interspike interval histograms of neuron A (parallel to the x-axis) given that the nearest spike in neuron B occurred with the backward cross-interval indicated on the ordinate. Thus, the interspike interval distribution along the x-axis (Fig. 1B, line through a and b) represents the interspike interval histogram of neuron A when neuron B fires simultaneously with neuron A. Points distributed along a line parallel to the x-axis (Fig. 1B, line through c and d) represent the interspike interval distribution of the neuron A when the reference spike fires at a lag time given by the backward cross-interval on the ordinate. A clustering a points around a region suggests that *both* the backward cross-interval, y_1, and the subsequent interspike interval, x_1, are correlated with the preceding spike in neuron B at those specific intervals. Finally, if the points lie parallel to the y-axis (Fig. 1B, points a and c), this suggests that neuron A has a relatively constant interspike interval independent of the preceding spike occurrence in neuron B. It should be noted that the conditional interspike interval histogram essentially reduces to the conventional interspike interval histogram by "compressing" the x–y plot onto the x-axis (see Appendix A for details).

Having found the estimated joint p.d.f., it is of central interest to determine how this joint p.d.f. differs from one obtained from two uncorrelated (control) spike trains with the same firing frequency p.d.f. In particular, we want to find out whether there is an increase or decrease in the correlation independent of the underlying p.d.f. of either spike train. One way to uncover the increase or decrease in correlation is to subtract a conditional interspike interval histogram of two uncorrelated spike trains from the original histogram. However, the uncorrelated spike trains used for the control must have the same interspike interval distributions (p.d.f.'s) as the original spike trains. This is achieved by randomly shuffling the interspike intervals of the original spike trains (Perkel et al., 1967; Mountcastle et al., 1969). This procedure removes any serial correlation between spikes and eliminates any temporal correlation between the spike trains. Therefore, the conditional interspike interval histogram computed from the shuffled spike trains produces the required baseline control histogram for subtraction. The "difference" conditional interspike interval histogram is computed from the difference between the conditional interspike interval histogram of the original unshuffled spike trains and that of the shuffled trains. Consequently, positive or negative values in the difference histogram reflect an increase or decrease in the estimated conditional probability of a spike above or below the baseline level of random coincidence, respectively, independent of the underlying p.d.f.'s of the original spike trains. If there is no correlation, the difference histogram would appear essentially flat, with zero height at all time intervals. Note, if a scatter plot is used, the amplitude of the difference histogram is difficult to represent.

Conditional cross-interval histogram

While the conditional interspike interval histogram describes the relationship between the backward cross-interval and the interspike interval, the conditional cross-interval histogram describes the relationship between the backward and forward cross-intervals of two neurons. As depicted in Fig. 2A the backward cross-interval is given as y_2 and the forward cross-interval as x_2. The conditional cross-interval histogram is constructed from the cumulated counts of the cross-interval pairs (x_2, y_2) for all spikes in train A (Fig. 2B). A *difference* conditional cross-interval histogram is constructed by subtracting the conditional cross-interval histogram of the shuffled trains from the original unshuffled one as described earlier. Derivation of the conditional cross-interval distribution function is given in Appendix A.

In the conditional cross-interval histogram for points above (Fig. 2B, point c) or below (Fig. 2B, point b) the diagonal line of slope 1, the backward cross-interval is longer or shorter, respectively, than the forward cross-interval. Uncorrelated spike trains in the conditional cross-interval histogram will have a joint p.d.f. which reflects the underlying stochastic process of each cell. Correlated spike trains will have a distribution of points lying along the preferred intervals. Points lying along a line parallel to the x-axis (Fig. 2B, line through a and b) imply neuron A follows the firing of neuron B at a constant interval, but not vice versa. Similarly, if points distribute along a line parallel to the y-axis (Fig. 2B, line through a and c), then the backward cross-interval varies independently with a fixed forward cross-interval. Note that the sum of the backward and forward cross-interval ($y_2 + x_2$) equals the intervening interspike interval of

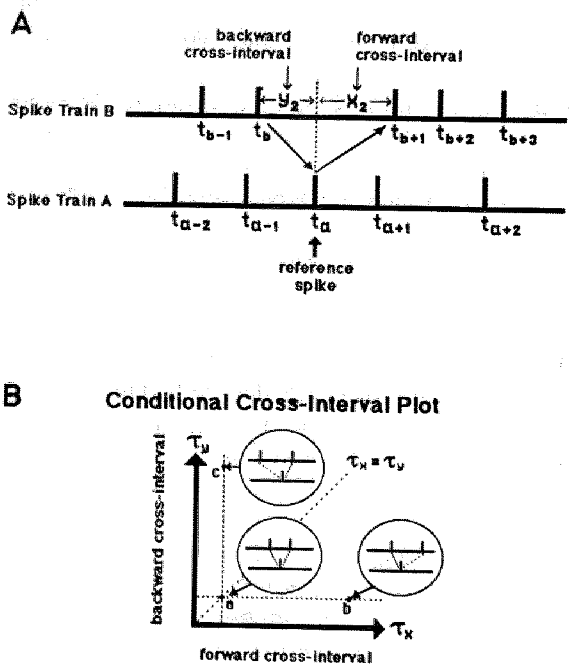


Fig. 2. Diagrammatic illustration of the generation of the conditional cross-interval histogram from two spike trains A and B. A: The backward cross-interval with respect to the reference spike in train B, denoted as y_2, and the forward cross-interval as x_2. B: mapping of select cross-interval pairs into an $x-y$ plot showing the relationships between the forward and backward cross-intervals in the insets. A cross-interval histogram is constructed from the cumulated counts of all cross-interval pairs obtained from each reference spike in train A.

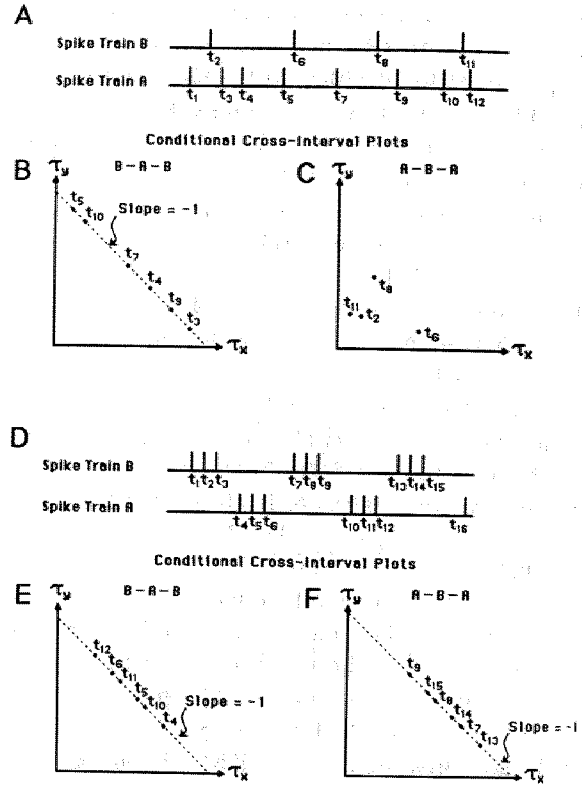


Fig. 3. Two examples of the firing patterns resulting in points distributed along the line with a slope of −1 in the conditional cross-interval plots. A: when neuron B discharges with a constant interspike interval and neuron A discharges irregularly, points will lie on the line with slope = −1 when train A is used as the reference train (B), but not when train B is used as the reference (C). The notation B–A–B denotes the sequence of spikes considered are from train B to A and then to B, with train A as the reference train. Similarly, A–B–A denotes train B used as the reference. Similar notation is used to indicate the reference spike train in the conditional cross-interval plots of Figs. 4–6. The times of spike occurrence are indicated by t_i, $i = 1, 2, \ldots$ next to the spike trains. D: When neurons A and B fire with regular alternating bursts, points will lie on the line with slope of −1 in both conditional cross-interval plots using either train A or B as the reference.

train B. If points distribute along a line with a slope of -1, this implies that the reference spike in neuron A discharges anywhere within the same intervening interspike interval of neuron B. Two possible sets of spike trains with these characteristics are shown in Fig. 3. If one of the spike trains exhibits regular firing rate (spike train B, Fig. 3A) and the other irregular firing (spike train A, Fig. 3A) points will distribute along a line with slope of -1 in the conditional cross-interval plot when the irregular firing train is used as the reference (Fig. 3B), but not reciprocally (Fig. 3C). If regular alternating bursts of impulses occur for the neuron pair (Fig. 3D), for example, (Perkel and Mulloney, 1974) then points will lie along a line with slope of -1 in both conditional interspike interval plots when train A or B is used as the reference train (Fig. 3E, F). Thus, these conditional histograms can be used to characterize and distinguish the temporal coupling in the discharge of two neurons.

Data display techniques

To display the difference histograms with easily discernible increases and decreases in correlation, the values of the histogram were pseudo-color coded and displayed as a three-dimensional (3D) plot. We employed a scheme which mapped red onto positive values and blue onto negative values. In addition the amplitudes were intensity coded (see Figs 4–6). Since we wished to emphasize the absence of correlation, an inverse-intensity color coding scheme for green was used in which the green tone was maximized for zero values. Thus, the intense red peaks in Figs. 4–6 represent an increase of correlation above the control and the intense blue peaks represent a decrease. Green regions represent no correlation. Three-dimensional rotation of the histograms permitted the visualization of the salient features of the plots. In particular, edge-on views showed the relative heights of the histogram bars, and views from the z-axis showed the coordinates of the peaks and valleys. Contour plots could have been used but would have required interpolation between data points resulting in loss of local details of interest. A similar problem arose when pseudo-colored contour plots were used, the interpolation greatly reduced the visual contrast of neighboring peaks and valleys.

Experimental procedures

Experiments were performed on 14 unanesthetized adult cats decerebrated at the intercollicular level. The animals were initially anesthetized with halothane and then when decerebrate artificially respired via a tracheostomy and paralyzed with gallamine triethiodide. The methods of animal preparation, decerebration, and maintenance of physiological parameters have been described previously (Ebner et al., 1983). A posterior fossa craniotomy was performed under warm saline drip (37 °C), exposing the vermal and paravermal regions of lobules V and VI. Agar was placed on the cerebellar cortical surface after removal of the dura to minimize pulsation. Two independently mounted glass pipette microelectrodes were used to record simultaneously from two Purkinje neurons on the cerebellar surface folia (Ebner and Bloedel, 1981a). Distances between electrodes were determined from a micrometer eye piece in a dissecting microscope. The simple and complex spike discharge from each Purkinje cell were discriminated and recorded using time-amplitude and waveform discrimination techniques. Occasionally, two Purkinje cells were recorded from the same electrode and discrimination based on amplitude and waveform differences. Only simple spike activity was used in this study, since the firing rate of the complex spike was too low for the correlation analysis. Spike train data were collected with a sampling interval of 1 ms and analyzed on-line with a PDP-11 laboratory computer. Additional graphic displays were performed off-line, with a Silicon Graphics IRIS 2400 workstation.

Simultaneous recordings were made of the spontaneous discharge of 72 pairs of Purkinje cells. For some pairs of cells, the ipsilateral median or the radial nerve was electrically stimulated. The nerves were gently dissected out, placed on bipolar hook electrodes, and bathed in warm mineral oil. Stimulation consisted of suprathreshold, 1 ms pulses. Poisson distributed intervals were used to avoid introducing any periodicity into the spike train discharge.

Results

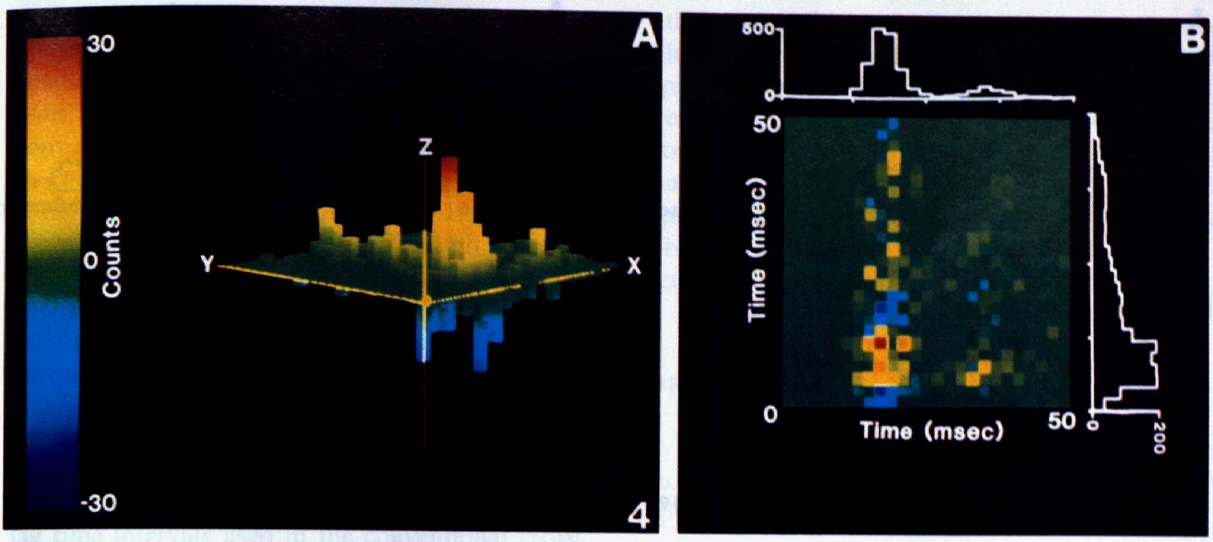
An example of conditional interspike and conditional cross-interval analyses on the spontaneous simple spike activity of a pair of simultaneously recorded Purkinje neurons is shown in Figs. 4 and 5. The two Purkinje neurons were located in lobule V and were separated by approximately 100 μm. We will refer to one neuron as A and the other as B in the following discussion. Fig. 4A shows a 3D view of the difference conditional interspike interval histogram, using train B as the reference train, and Fig. 4B shows the pseudo-colored x–y plot of the same histogram. The histograms were displayed using 2-ms bin widths, and spanned 50 ms on the x- and y-axes. Two positive peaks surrounded by adjacent negative valleys which run parallel to the y-axis are evident with an interspike interval of 18 ± 4 ms. When neuron A fired from 7 to 11 ms before B, neuron B was more likely than random to fire another spike with an interspike interval of 18 ± 4 ms (red peaks). In contrast, when neuron A fired at 4 or 18 ms before B, neuron B was less likely than random to discharge with an interspike interval of 18 ± 4 ms (blue regions). This suggests that the interspike interval distribution of Purkinje cell B was *dependent* on the time of occurrence of the preceding spike in neuron A. Since the other regions of the plot have little structure (green regions), this implies the interspike interval in Purkinje cell B is relatively independent of the preceding spike occurrence in A at those intervals, the histograms projected on the x- and y-axes of the pseudo-colored x–y plot are the estimated p.d.f.'s of the interspike interval and backward cross-interval distributions, respectively. They show the underlying distribution of spikes occurring at those intervals.

Fig. 5A,B shows two views of the difference conditional cross-interval histogram with train A as the reference constructed from the same Purkinje cell shown in Fig. 4. This histogram revealed an intricate temporal relationship between the simple spike discharge of the two neurons, with two positive peaks surrounded by negative peaks. The highest peak occurred at the cross-interval pair of $x_2 = 7$ ms and $y_2 = 11$ ms, implying that Purkinje neuron A was more likely than random to fire 11 ms after Purkinje neuron B fired, and also that 7 ms later neuron B discharged again. In other words, since the sum of the backward cross-interval and the forward cross-interval is equal to the intervening interspike interval of B, A was likely to fire 11 ms after neuron B when the interspike interval of B was 18 ms. Similarly, the second positive peak at $x_2 = 11$ ms and $y_2 = 7$ ms shows that neuron A fired 7 ms after B with a higher probability than random. The prominent negative peaks imply that when the interspike

Fig. 4. A: 3D view of the pseudo-colored difference conditional interspike interval histogram of the spontaneous simple spike discharges of two Purkinje neurons with train B as the reference. Note the two positive peaks surrounded by negative peaks along the band of 18 ms interspike interval. In this view the amplitude of the peaks and valleys are evident. B: planar view of the same pseudo-colored histogram in A but viewed from the z-axis. In this view the coordinates of the peaks and valleys are evident. The interspike interval histogram is displayed parallel to the x-axis, the backward cross-interval histogram parallel to the y-axis. The values of the histograms are in counts. Color scale for z-axis shown on left, values are in counts. Bin width = 2 ms. Length of spike trains = 46,542 ms.

Fig. 5. A: 3D view of the pseudo-colored difference conditional cross-interval histogram with train A as the reference constructed from the same spike train pair as used in Fig. 4. Two positive peaks surrounded by negative peaks along the band of 18 ms interspike interval of train B are evident. B: planar pseudo-colored view of the same cross-interval histogram shown in A. The forward cross-interval histogram is displayed parallel to the x-axis, the backward cross-interval histogram parallel to the y-axis. Bin width = 2 ms.

Fig. 6. A: 3D view of the difference conditional cross-interval histogram of the simple spike discharge recorded from same neurons in Figs. 4 and 5 with train A as the reference during ipsilateral median nerve stimulation with a Poisson pulse train with a mean rate of 1 Hz. General structures observed with spontaneous activity remain (compare with Fig. 5) but with some decrease in amplitude and sharpness of the positive peaks. Note the change of amplitude scale compared to Figs. 4 and 5. B: planar pseudo-colored view of the same histogram shown in A. The forward cross-interval histogram is displayed parallel to the x-axis, the backward cross-interval histogram parallel to the y-axis. Length of spike trains = 60,218 ms.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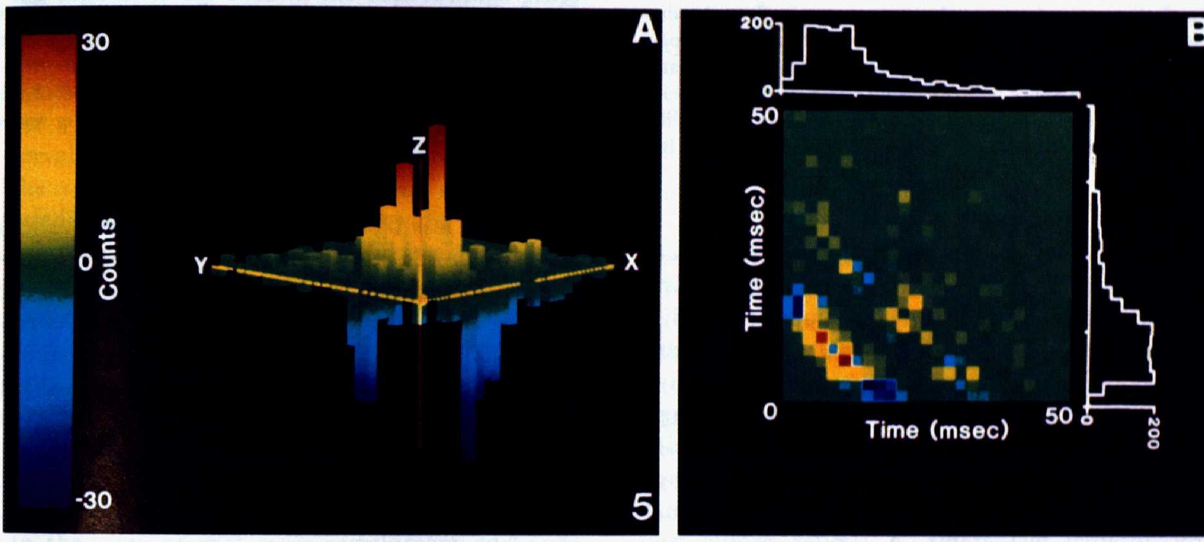
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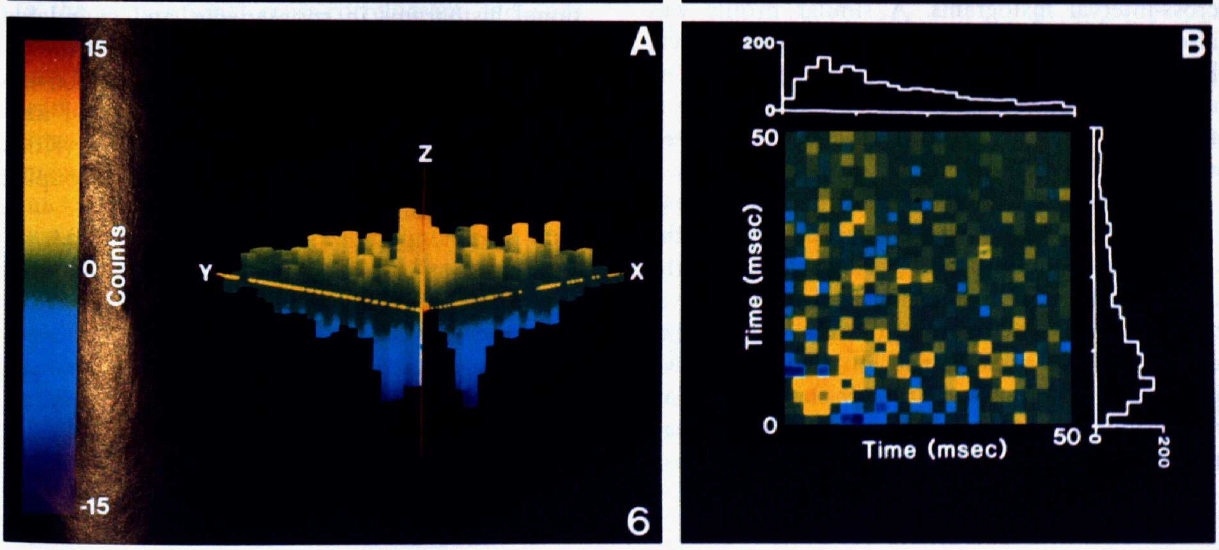
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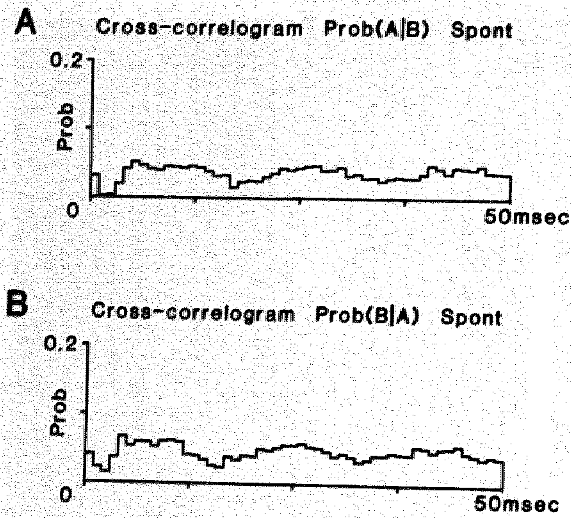

Fig. 7. Cross-correlograms of spontaneous simple spike discharge constructed from the same Purkinje cell spike train pair used in Figs. 4 and 5 using train A as the reference in A, and train B as the reference in B. Although a rhythmicity is present, the joint correlation of the backward cross-intervals with the forward cross-intervals is not revealed by this method. Bin width = 1 ms.

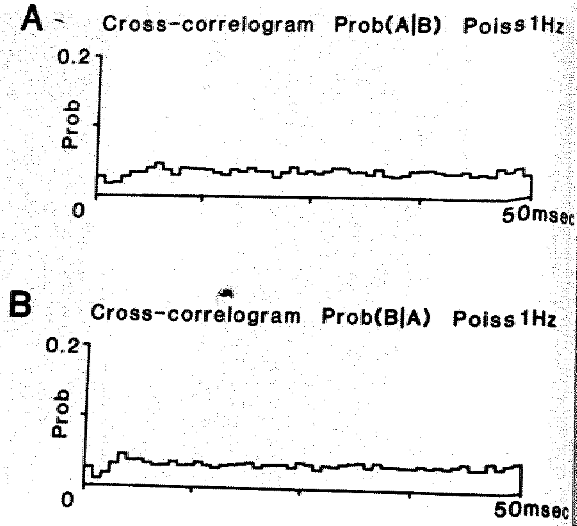

Fig. 8. Cross-correlograms during median nerve stimulation constructed from the same spike trains used in Fig. 6. No clear structure is present during stimulation in the cross-correlograms, yet peaks and valleys are discernible in the plots of the conditional cross-interval histogram (see Fig. 6). Bin width = 1 ms.

interval of B was 18 ms, neuron A was less likely to discharge at 3 ms or at 15 ms after B. The temporal coupling between the simple spike discharge of the two neurons appeared to be very tight as suggested by the closeness of the positive and negative peaks (only 4 ms apart). Although the cross-correlograms (Fig. 7) show a periodicity of 16–18 ms, it did not reveal the detailed temporal coupling observed in the conditional cross-interval histograms. A similar profile was also observed for the conditional cross-interval histogram when neuron B was used as the reference (not displayed here). This symmetry suggests there is a mutual reciprocal correlation between these two Purkinje cells.

An additional example is presented in Fig. 6 to contrast the correlation features revealed by the conditional cross-interval histogram and the cross-correlogram. The conditional cross-interval histogram was constructed from the simple spike discharge of the same pair of Purkinje cells shown in Figs. 4 and 5, but during ipsilateral median nerve stimulation with a Poisson pulse train (mean rate of 1 Hz). During stimulation the peaks were somewhat less distinct and the peaks and valleys somewhat wider, but the temporal coupling relationships were similar to the spontaneous case (see Fig. 5). In contrast, the conventional cross-correlogram (Fig. 8) shows little structure during stimulation. The only obvious structure was a slight decrease in probability at short lag times (2–3 ms).

Thirty-seven percent (17 out of 46 pairs completely analyzed) showed structure in the conditional histograms in spontaneous and stimulated conditions. Although the profiles were not identical from pair to pair, just as profiles of conventional cross-correlograms among individual neurons differ in other populations of neurons (Knox et al., 1977), a common feature was the coupled surround-inhibition profile.

Discussion

Conventional cross-correlation techniques have been widely used to analyze simultaneously recorded neurons (for example, Perkel et al., 1967; Knox, 1974, 1981; Ebner and Bloedel, 1981b;

Murphy et al., 1985a, b). When applied to the analysis of cerebellar Purkinje cells (Ebner and Bloedel, 1981b), cross-correlation techniques have revealed some correlation. However, more interactions among Purkinje neurons are expected based on known connectivity and hypothesized function of the cerebellar cortex (Braitenberg, 1967; Eccles et al., 1967; Freeman, 1969; MacKay and Murphy, 1976; Pellionisz et al., 1977). Since the cross-correlation function is only a function of a single variable, the lag time, this function may not be adequate to describe the conditional joint probability density function of the subset of the lag time intervals. The two conditional histograms described in this paper are estimates of the conditional joint probability functions of a subset of the lag time intervals used in the conventional cross-correlation function. In addition, the difference conditional histograms allow one to estimate the conditional increase (or decrease) in excitability for a pair of intervals. Conditional interspike interval histograms, such as those in Fig. 4, revealed the recurrent firing characteristics of a neuron conditioned by the precise backward cross-interval. Conditional cross-interval histograms, such as in Fig. 5, revealed reciprocal interactions between two neurons.

Although both of these joint p.d.f.'s consider only the immediately adjacent spike occurrences, the same techniques can be generalized to include all subsequent spike occurrence times with respect to the reference spike (i.e. include all forward nth order waiting times or interspike intervals) similar to the conventional cross-correlogram and auto-correlogram. If all subsequent intervals are taken into account, the conditional cross-interval histogram would become a "generalized" conditional cross-correlogram and the conditional interspike interval histogram a "generalized" conditional auto-correlogram.

Application of the conditional interspike interval and conditional cross-interval to the simple spike discharge of neighboring Purkinje neurons revealed more intricate temporal correlations than those revealed by the conventional cross-correlograms (Freeman, 1969; MacKay and Murphy, 1976; Ebner and Bloedel, 1981b). Not only did the application of the techniques demonstrate their utility, it suggested the existence of strongly coupled temporal interactions between the simple spike discharge of Purkinje cells not previously described. Purkinje cell discharges were tightly coupled not only to the first subsequent discharge, but also to the second subsequent discharge of spike. The tightly coupled temporal correlation observed in the simple spike discharge suggests a temporal surround-inhibition.

Appendix A

A formal description of the conditional correlation function is given below. Let the stationary spike trains A and B be represented by:

$$f_A(t) = \sum_{a=1}^{N_a} \delta(t - t_a) \tag{1}$$

and

$$f_B(t) = \sum_{b=1}^{N_b} \delta(t - t_b) \tag{2}$$

respectively, where $\delta(t)$ is a Dirac delta function, and N_a and N_b are the number of spikes in trains A and B, respectively, and they are large numbers. Each delta function (of unit area) is located at the time of occurrence of the spike in the original train, i.e. at times t_a for train A and at times t_b for train B. The conditional cross-interval histogram may be written as:

$$I_{BAB}(\tau_x, \tau_y) = \sum_{a=1}^{N_a} \delta(t_{b+1} - t_a - \tau_x)\delta(t_a - t_b - \tau_y) \tag{3}$$

for all t_a and t_b that satisfy $t_b \le t_a < t_{b+1}$. The subscripts BAB of I are used to describe the sequence of spikes considered from train B to A and then to B. Similarly, the conditional interspike interval histogram may be written as:

$$I_{BAA}(\tau_x, \tau_y) = \sum_{a=1}^{N_a - 1} \delta(t_{a+1} - t_a - \tau_x) \times \delta(t_a - t_b - \tau_y) \tag{4}$$

for all t_a and t_b that satisfy $t_b \le t_a < t_{b+1}$. The subscripts BAA are used here to describe the sequence of spikes considered, i.e., from train B to A and then A again. Discrete time is used, following the usual convention (Gerstein and Kiang, 1960; Rodieck et al., 1962). To avoid confusion between the intervals involved, the cross-interval pairs (x_2, y_2) were used throughout the paper, which are equivalent to (τ_x, τ_y) of $I_{BAB}(\tau_x, \tau_y)$ and the interspike cross-interval pairs (x_1, y_1) are equivalent to (τ_x, τ_y) of $I_{BAA}(\tau_x, \tau_y)$.

The conditional interspike interval histogram will reduce to a conventional interspike interval histogram when one sums up I_{BAA} for all τ_y:

$$\sum_{\tau_y=0}^{\infty} I_{BAA}(\tau_x, \tau_y) = \sum_{a=1}^{N_a-1} \delta(t_{a+1} - t_a - \tau_x) \doteq I(\tau_x) \qquad (5)$$

where $I(\tau_x)$ represents the interspike interval histogram or interval histogram (Rodieck et al., 1962).

Appendix B

Note that the condition $t_b \leq t_a < t_{b+1}$ used in the formulation of the histogram does not exclude the possibility there may exist more than one intervening spike in train A falling within the interspike interval from t_b to t_{b+1} of train B. That is, there may exist spikes $\delta(t - t_a)$, $\delta(t - t_{a+1}), \ldots,$ that satisfy $t_b \leq t_a < t_{a+1} \cdots < t_{b+1}$. The existence of these spikes would not alter the definitions of the conditional cross-interval histogram or the conditional interspike interval histogram, even though the probability of firing of the reference spike becomes dependent on the probability of firing of the preceding intervening spikes. Thus, for example, the present definition of conditional interspike interval histogram may be redefined alternatively using the preceding spike in train B as the reference spike. Then the intervals (τ_x, τ_y) in our definition will become the first and second order waiting times instead of the backward waiting time and forward interspike interval as described throughout the paper. If intervening spikes with the backward cross-interval exist, the cross-interval would be described by the higher-order waiting times in this alternate definition. Since our primary objective is to correlate the interval from an arbitrary reference spike in train A to the nearest preceding spike in train B with the subsequent firing interval in either train B or train A, the original definition is preferred.

Appendix C

Alternatively, the interspike interval could be plotted on the y-axis, and the backward cross-interval on the x-axis in the conditional interspike interval plots. We choose to plot interspike interval on the x-axis, even though somewhat unconventional for a dependent variable. The purpose is to display the interspike interval distribution on the x-axis conditioned by the preceding or backward cross-interval plotted on the ordinate. In this context it appears more "natural" to place the preceding or conditioning event on the ordinate. Also, when the conditional interspike interval is compressed onto the x-axis the resultant histogram is the interspike interval histogram of spike train A (see Fig. 4 and Appendix A). Similarly, the forward cross-interval can be plotted on the y-axis and the backward cross-interval on the x-axis, alternatively, in the conditional cross-interval plots. Again we elected to plot the backward cross-interval on the y-axis.

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