MINIREVIEW

Cross-Correlation Analysis of Neuronal Activities

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In physiological studies, nerve impulses are generally regarded as spike train and statistically analyzed by use of various kinds of so-called time series analyses. The general survey on time series analysis referred to here was reported by YAMAMOTO and NAKAHAMA [88].

Cross-correlation analysis reviewed in this paper is a time series analysis. Cross-correlation analysis is used to reveal temporal and/or spatial relationships between more than two spike trains in the neuronal circuit, in which two neurons are synaptically connected or two neurons are independent but receive a common input.

1. CROSS-CORRELATION HISTOGRAMS

Synaptically mediated interactions between neurons have been investigated using two different types of recording. Intracellular recording of post-synaptic potentials (PSPs) evoked by activation of presynaptic cells has revealed synaptic connectivity in terms of excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) [18]. A considerable range of shapes and sizes of PSPs has been suggested to correspond to the differences in the effectiveness of underlying synaptic connections. Alternatively, extracellular recordings have shown that the changes in the firing probability of the postsynaptic cell can be used to document the synaptic input from presynaptic cells. In this case, the interaction between neurons can be detected by cross-correlating the input events with the output spike train of the postsynaptic cell.

Cross-correlation histogram [64] is sometimes called the cross-correlogram or the pre- and post-stimulus time histogram. For neurons pairs, this is a histogram of the times of occurrence of all output spikes relative to the times of occurrence of all input spikes (or stimulus pulses). The presence of peaks or troughs in such histograms indicates the probability of more or less firing than that expected by chance, and thus can reveal the functional connections between cells. Certain features of the cross-correlograms have been used to infer different types of

underlying synaptic connections [13, 31, 39, 49, 64, 65, 72].

2. PRIMARY AND SECONDARY EFFECTS

The “primary effect” [65] is the peak and/or trough nearest the time of onset of the presynaptic spike ($\tau=0$ in the cross-correlogram) and the size and shape normally depends more on the synaptic potentials produced by the connection than on the firing characteristics of the relevant cells. When two neurons are synaptically connected, the primary effect appears with a lag-time corresponding with the latency. The significance of the shape of the primary effect will be discussed later. On the other hand, when two neurons receive excitation from a common source, the primary effect appears at time zero and the shape is generally symmetrical about zero.

The “secondary effects” [65] are the correlogram features farther from the primary effect, which reflect periodicities in the firing of pre- and post-synaptic cells. Therefore, the “secondary effects” have been used in conjunction with autocorrelograms of the firings of pre- and post-synaptic cells [12, 13, 49, 65, 72]. This article is mainly concerned with the primary effect, which has been called the primary peak [65], the primary correlation kernel [48], the primary correlation operator [40], the primary structure [24], the lag-time distribution [35], or the primary mode [30].

3. THE TIME COURSE OF THE PRIMARY EFFECT

It is of interest to know the relationship between the shapes of primary cross-correlogram features and the underlying PSPs. If the transform is known, the shapes of underlying PSPs can be inferred from the cross-correlogram. The possible relationships between the shapes of the PSP and cross-correlogram features have been analyzed theoretically, but empirical data have remained relatively indirect. Three different transforms have been proposed on a theoretical basis.

MOORE *et al.* [65] have reported, based on the results obtained from Aplysia neurons, that the shape of the primary correlogram peak produced by an EPSP resembles the waveform of the underlying EPSP due to the inverse relationship of the instantaneous firing probability of a neuron and the instantaneous distance between the membrane potential and threshold. A similar notion has been suggested by LINDSEY and GERSTEIN [53] in crayfish claw motoneurons.

On the other hand, theoretical analysis of neural models have led to the conclusion that EPSP produces correlogram peaks that resemble their temporal derivative. This analysis takes into consideration the fact that the membrane trajectory of the postsynaptic cell typically crosses the threshold of the firing level during the rising phase of the EPSP. For a neuron model that reaches the threshold firing level by summation of EPSPs, and resets the membrane trajectory after firing, KNOX [48] and HOMMA *et al.* [35] found that the resulting correlogram peak resembles a derivative of EPSP shape. This argument has been confirmed in cat

motoneurons by FETZ and GUSTAFSSON [23], in which they mentioned the relationship between the trough which follows the peak and the falling phase of the EPSP. Assuming such a relation, many researchers have used the integral of post-stimulus firing probability of human motor units to infer the shape of underlying PSPs in motoneurons [3–6, 10, 32, 68]. The time course of generator potentials elicited in muscle spindle primary endings was also investigated under similar assumptions in man [36] and in cats [33].

The third possibility was suggested by KIRKWOOD and SEARS [40] in their analysis of the synaptic events underlying the average common excitation potential in inspiratory motoneurons. They proposed that the primary correlogram peak is the sum of two linear terms: one proportional to the EPSP, the second proportional to its temporal derivative. The two proportionality constants could be chosen to provide good theoretical matches with the observed average common excitation potentials [40] and short-term synchronization of intercostal motoneurons [75]. Compiling cross-correlograms between intercostal afferents and ventral root efferents during respiration, KIRKWOOD and SEARS [42] found correlogram peaks with shapes which could plausibly resemble the sum of such terms, given the shapes of single-fiber EPSPs documented in separate experiments. GUSTAFSSON and MCCREA [26] reported that the shape of the primary correlation peak seems well described by a linear summation of the shape of the EPSP derivative and that of the EPSP itself, and that a leaky integration of the correlation peaks gives time courses that closely resemble the shape of the EPSPs.

The relationship between the primary correlogram trough and the underlying IPSP has not yet been theoretically studied. HOMMA and NAKAJIMA [31] measured post-stimulus responses of gastrocnemius motor units in the cat, integrating the primary correlogram peak evoked by the muscle stretch and also the primary correlogram trough evoked by the stretch of the antagonistic muscle. They showed that aggregated IPSPs generated correlogram troughs wider than the peaks produced by EPSPs of comparable duration. These results, and the fact that the correlogram trough produced by large IPSPs was not simply related to the shape of the IPSP or its derivative [23, 26] mean that the transforms from the IPSP shape to the primary correlogram trough or vice versa are still unclear.

Since presynaptic inhibition also decreases the firing probability of the postsynaptic cell, the effect is shown as a correlogram trough. The cross-correlogram alone does not suffice to distinguish between pre- and postsynaptic inhibition. A possible method for the detection of presynaptic inhibition is proposed by PERKEL [71] and PERKEL *et al.* [73].

4. SENSITIVITY OF CROSS-CORRELATION

Sensitivity of cross-correlation histogram depends on the length of recording (e.g. numbers of pre- and postsynaptic spikes) and the bin width of the correlogram. Although cross-correlation analysis is commonly used, only a few papers discuss the

sensitivity of the cross-correlation histogram. KIRKWOOD [39] estimated that the amplitude of the smallest EPSP that would be detected by a cross-correlogram of motoneuron discharge with 10,000 input spikes would be about $30\text{ }\mu\text{V}$ if many spikes are counted and an appropriate bin width is chosen.

When the synaptic effect is weak, a large number of postsynaptic spikes in each bin of the histogram is necessary to reveal significant peaks. As an alternative to using long periods of recordings to obtain sufficient data, it is possible to use multi-unit spikes, treating all discharges from a group of neurons as one [40, 75]. But in this case, the interpretation of cross-correlograms is limited.

On the other hand, AERTSEN and GERSTEIN [1] proposed a method to estimate the relative connectivity between pre- and postsynaptic cells using a neuron model. The neuronal connectivity is expressed in terms of connecting probability which can either enhance the probability of firing of postsynaptic cell or suppress it. According to them, a probability for connections with a strength larger than 0.02–0.05 is commonly detectable in a cross-correlogram in the case of excitation. But in the case of inhibition, a strength of less than 0.8 is undetectable in a cross-correlogram.

5. QUANTITATIVE EXPRESSION OF CROSS-CORRELATION

AERTSEN and GERSTEIN [1] suggested that the synaptic strength of an excitatory connection is given by the ratio of the number of correlated spikes (the spikes in the area of the peak in the cross-correlogram) and the number of presynaptic spikes. This measured parameter has been proposed as the “effectiveness” or “dynamic potency” of the particular excitatory synapse by LEVICK *et al.* [52], and used by LINDSEY and GERSTEIN [53] and MASTRONARDE [57]. On the other hand, the parameter given by the ratio of the number of correlated spikes relative to the number of the postsynaptic spikes has been proposed as the “contribution” by LEVICK *et al.* [52]. Although this parameter cannot express the synaptic connectivity [1], this measured parameter has been used by many investigators to express the connectivity [63, 82–84]. KWAN *et al.* [51] have proposed the combination of these two ratios to express synaptic strength. Furthermore, the term k , the ratio of the peak count to the mean counts in a region away from the peak is proposed for cross-correlograms which involves multi-unit recordings with variable numbers of units in the neuronal populations [75]. Inhibitory strength is proposed as the ratio of the ordinate values inside and outside of the trough [1].

A simple statistical method to compare two cross-correlograms on a bin-by-bin basis and to evaluate the reliability has been proposed by DÖRRSCHEIDT [21]. This method is also applicable to cases where the original spike data are not available (e.g. published cross-correlograms). Another method to test the independency of two spike trains has been proposed by JOHNSON and KIANG [38].

6. CROSS-CORRELATION EXTENSION TECHNIQUES

Postsynaptic spikes, which are time-locked to the presynaptic spikes or stimuli, compose the primary correlation peak, while the spikes not time-locked are distributed beyond the peak. These spikes are called the locked and unlocked spikes, respectively [28]. By using cross-correlograms and a special gate circuit, HIRAYAMA *et al.* [28] and WATANABE and HIRAYAMA [86] separated, in man, motor unit spikes elicited by muscle vibration under voluntary contraction into two spike trains: one is a spike train of locked spikes, which are elicited by tonic vibration reflex [27], and the other a spike train of unlocked spikes, which are supposedly elicited by voluntary command from the supraspinal center. This type of cross-correlogram extension technique has been used in spike trains recorded from the nucleus parabrachialis medialis to reveal changes of neuronal activity during sleep and waking states [24].

Another extension technique has been proposed by SCHNEIDER *et al.* [74] to characterize the interneuronal and stimulus-response coupling changes of two periodically driven and simultaneously recorded units. In this technique, the coupling measure is derived from the cross-correlation functions without the subsequent time-averaging (which would give the ordinary cross-correlogram).

BORISYUK *et al.* [11] proposed another method for identification and evaluation of the interconnections in a neuronal network from several simultaneously recorded spike trains. The characteristic of this method is that it is sensitive to relatively small sample spikes without the assumption of a stationary spike train.

7. CROSS-CORRELATION ANALYSIS USED IN NEUROPHYSIOLOGY

The cross-correlation analysis is widely used in neurophysiology since the cross-correlograms can reveal three main characteristics of discharge dependency between two cells: 1) the direction of dependency; 2) the latency of interaction; and 3) the type of functional connections between the cells as indicated by the shape of the primary correlation effect.

In the fields of motor control, cross-correlation analysis was performed between γ efferent stimulation and primary muscle spindle afferent spikes [37, 66], which revealed functional differences among the γ motor fibers. Cross-correlation analysis between motor efferent stimulation and muscle receptor afferent spikes revealed some mechanical coupling [7–9]. From these research works, the concept of “sensory partitioning” of a muscle was suggested [15]. Further analysis using cross-correlograms of muscle receptor discharges showed that the “sensory partitioning” is strongly dependent on the general condition of the experimental animals, such as the level of anaesthesia [70]. The effect of muscle mechanoreceptors on γ motoneurons [22] and coactivation of α and γ motoneurons [17] have also been investigated using cross-correlation.

Using an intramuscular needle electrode, it is possible, in man, to record the

action potentials of a single motor unit activated by a voluntary contraction or stimulation of peripheral nerves. Since the single motor unit spikes reflect the spike train of a single motoneuron, it is possible to perform cross-correlation analysis during repetitive stimulation of peripheral nerves. Thus, cross-correlation analysis of the stretch reflex was used to derive information about postsynaptic events in human motoneurons [14, 25, 47, 50, 56, 62, 81, 87]. The inhibitory effect of acupuncture on vibration-induced finger flexion reflex was clearly revealed in man by the disappearance of the primary correlation peak seen in the control [34, 46].

The behaviour of intercostal motoneurons during respiration has been extensively analyzed by use of cross-correlograms between the pairs of afferent spikes [41], and between the efferent and afferent spikes [42]. Three types of synchronization—short-term, broad-peak, and high-frequency oscillation—were found in the cross-correlograms between the efferent spikes [43, 45]. Cross-correlograms between spikes of inspiratory bulbospinal neurons and phrenic or external intercostal motoneurons revealed peaks which could be divided into three groups on the basis of the time course: narrow, medium-width, and high-frequency oscillation [19, 20]. Intercostal muscle activity during purring of the cat was also analyzed [44]. Response of pulmonary mechanoreceptors to high-frequency pressure stimulation applied to the airway was investigated by use of cross-correlation to reveal the relationships of the rapidly and slowly adapting receptors and the negative and positive pressure changes [29, 30]. Neuronal activity, phase-locked to the respiration, in the brain stem is analyzed by use of cross-correlograms [16, 55, 76, 77, 79].

Cross-correlation analysis is also generally applied to ganglion cells of the retina [57–59], to the lateral geniculate nucleus [60, 61], to the geniculostriate projection [82], and to the visual cortex [83, 84]. Other applications include the following: between neurons in the hypothalamus [69]; between somatosensory thalamic activity and cortical activity [85]; between thalamic neurons [78]; between mesencephalic reticular neurons [54, 80]; between hippocampal neurons [67] and between hippocampal neurons and septal units [2]; between precentral cortical neurons [51].

SUMMARY

Nerve impulses are generally regarded as spike train and analyzed by use of various kinds of so-called time series analyses. Cross-correlation analysis is used to reveal temporal and/or spatial relationships between more than two spike trains in the neuronal circuit, in which two neurons are synaptically connected or two neurons are independent but receive a common input. Three main characteristics of discharge dependency between two neurons become clear from the cross-correlation histogram: 1) the direction of dependency; 2) the latency of interaction; and 3) the type of functional connections between the neurons. We reviewed the cross-correlation analysis from these points of view: 1) what is cross-correlation analysis;

2) what are primary and secondary effects; 3) what kinds of functional information can be obtained from the shape of the primary effect; 4) how sensitively cross-correlation can detect neuronal interaction; 5) how to express quantitatively the primary effect; 6) what kinds of extension technique are available from cross-correlation; and 7) research trends using cross-correlation analysis.

Key words: cross-correlation, primary correlation effect, postsynaptic potential, neuronal connectivity, quantitative expression.

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