

EXAMPLES OF THE INVESTIGATION OF NEURAL INFORMATION PROCESSING BY POINT PROCESS ANALYSIS

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ABSTRACT

*The firing of neurons is studied via recorded spike trains. A technique for estimating the summation function, the decay function and the firing probability function of a neuron model, on the basis of recorded output and corresponding input spike trains, is described and illustrated for the neuron L3 of *Aplysia californica* firing under the influence of the neuron L10. The procedure of employing partial coherences to "remove" the effects of a common stimulation on pairs of neurons is validated by applying the technique to neurons of the cat's auditory thalamus. In this case, the data were collected for the neurons firing first in a spontaneous fashion and then in response to stimulation. Finally, coherences within groups of eight neurons are averaged together on the basis of known anatomy to enhance discernment of patterns. In some cases, significant peaks were found in partial coherences where no signs of association were observed during spontaneous firing. It is concluded that the techniques presented here provide a valuable improvement in detecting associations between neurons which are modulated by a stimulus, but are not necessarily time-locked to its time course.*

INTRODUCTION

This paper focuses on three basic problems: the analytic description of the firing of a single stimulated neuron, the understanding of how the relationships within pairs of neurons are affected by stimulation and isolating the common behavior expressed by neurons resident in particular regions of the brain.

The fundamental unit of neural information processing is the *neuron*. This type of cell is generally composed of the cell body, the *soma*, and by the appendices called the *dendrites* and the *axon*. A very important characteristic of neurons is the fact that they are electrically polarized cells. The cell surface, the *membrane*, is negatively charged inside the cell and positively charged outside because of different ionic concentrations inside and outside the cell. In order to keep these ionic differences at a constant level, the cell spends most of its energy in activating special proteins at the cell membrane, which are called electrogenic pumps. In a steady state, without external influence, the *membrane potential* is called the resting potential and fluctuates around a constant level, usually close to $-70mV$. The cell body contains the *nucleus* with the genetic description of proteins and the organelles required

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for the synthesis of proteins and their turnover. The dendrites form the largest part of the cell appendages. They may have very different shapes, clustered together in bundles or in discs, and represent the major sites of obtaining input signal from other cells. The ensemble of dendrites is often referred to as the dendritic tree and is characterized by passive electrical membrane properties. This means the input signals, in the range of few millivolts, are generated at special places of the dendritic membrane, called *postsynaptic elements*, and passively transmitted through the dendritic tree to the cell body. The passive transmission means that integration of several inputs might be viewed as being essentially a summation of the input potentials with the resting potential. In a special place of the membrane of the cell body, referred to as the *trigger zone*, there are voltage sensitive ion channels. Whenever the cell is in the resting state and the membrane potential becomes larger than a certain *threshold*, the channels open and a fast depolarization occurs. Such an event is referred to as a *spike* and its magnitude is generally larger than 100mV. The membrane of the axon is characterized by active electrical properties because of its voltage sensitive channels. Therefore, the *spike* can propagate along the axonal membrane without modifications to reach the axon terminals and it represents the way the neuron sends output signals. The axon may have several branches, but all of them propagate the same signal, that is the *spike*. The junction of an axonal terminal with a portion of the dendritic membrane is called a *synapse*.

The sequence of spikes of a neuron is referred to as its "*spike train*". Neurophysiologists often have been satisfied with observing whether there are several or only a few spikes over a relatively prolonged time interval. Important concepts and findings have been clarified by using the overall mean rate as a measure of neuronal activity. The slow integration time of neuronal cells, operating in the milliseconds range (about a hundred thousand times slower than presently available supercomputers), and the large number of connections established by a single neuron suggest that neural information is transmitted by simultaneous discharge of sets of neurons. Then one can raise the question whether the overall mean rates of firing are sufficient to infer or to predict the experimental observations.

The next section of this chapter presents a stochastic model for neuron firing and the results of fitting that model to experimental data from the sea hare, *Aplysia*. The section "Partial Coherence Analysis" describes the technique of partial coherence analysis, as well as experiments concerning neurons in the auditory thalamus of the cat, and then presents the results of three such analyses for these experiments. The section "Averaging Within Groups of Neurons" is concerned with neurons resident in particular regions of the brain and presents average coherences and partial coherences for pairs of neurons from those regions. The chapter concludes with discussion of the main findings and their implications for the analysis of neurophysiological data.

AN ANALYTIC NEURON MODEL

The threshold of a neuron may be viewed as a time-varying quantity that is reset to a high level on the neuron's firing and is then subject to slow decay. One effect of the reset is to prevent firing recurring immediately and hence to incorporate the phenomenon of *refractoriness*. Consider the following analytic model: let $M = \{\sigma_j\}$ refer to the times at which an input spike is received by the neuron N . Given the summation function $a(\cdot)$, consider the following time-varying state variable:

$$U(t) = \sum_{\sigma_j \leq t} a(t - \sigma_j). \quad (1)$$

The quantity $U(t)$ is meant to represent the membrane potential at time t at the trigger zone of the neuron whose firing is of interest. The function $a(\cdot)$ is meant to represent the various

processes involved in the stimulus' influencing N 's firing. The character of the function affects whether the firing of the stimulus M increases (excites) or decreases (inhibits) the chance of the neuron N firing. The decaying threshold will be represented by a function $b(\cdot)$.

Figure 1 is a layout of the situation. The bottom two panels give hypothetical $a(\cdot)$

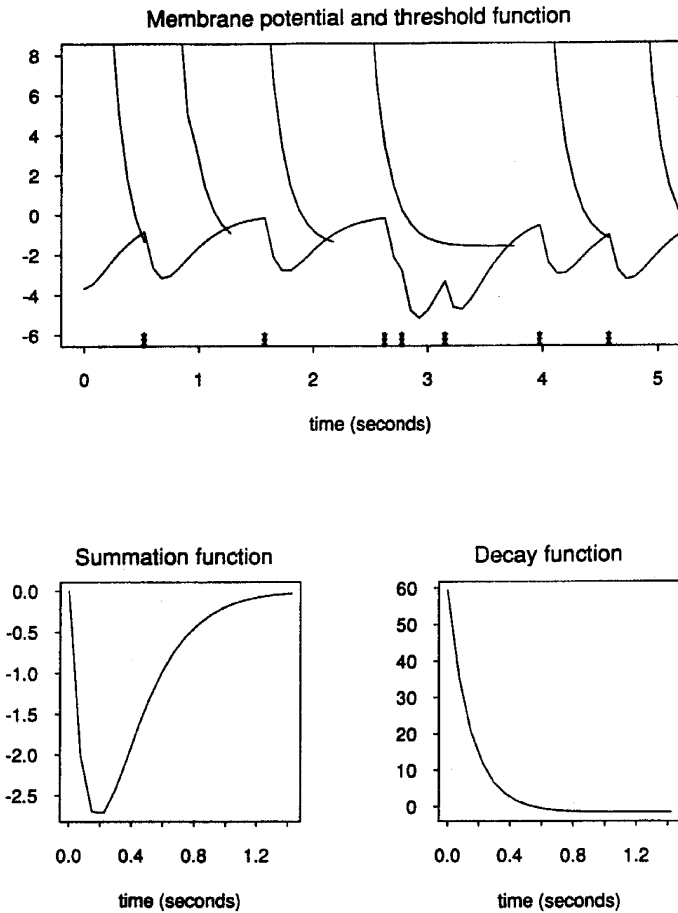


Figure 1 The lower curve of the top panel gives $U(t)$ of Eq. (1) with $a(\cdot)$ given by the lower left function. The hook-shaped functions of the top panel are translates of the function of the lower right panel initiated each time the curve $U(t)$ is crossed.

and $b(\cdot)$ for the case of an inhibitory synapse. (Shortly empirical estimates of $a(\cdot)$ and $b(\cdot)$ will be provided). The vertical piles of asterisks in the top plot are meant to represent the firing times of the input stimulus, M . The hook-shaped curves are the translates of the decay function $b(\cdot)$, with a new translate introduced for each firing of the neuron, N . If γ_t denotes the time elapsed since N 's last firing, then the threshold curve may be represented by

$\theta(t) = b(\gamma_t)$. The lower continuous curve of the figure is $U(t)$. One is concerned with the membrane potential, $U(t)$, crossing $\theta(t)$.

Consider next the development of a stochastic version of this model and of a corresponding likelihood function to employ in analyzing the available data. Suppose that the point processes are simplified to discrete time series ($t=0, \pm 1, \pm 2, \dots$) of binary values. That is, a sampling interval of small length is selected such that only one point may occur within each interval; and one defines $M_t=1$ if there is a point in the sampling interval t , and $M_t=0$ otherwise. Corresponding discrete versions of N and $a(\cdot)$ are similarly defined. Now

$$U(t) = \sum_{\sigma_j \leq t} a(t - \sigma_j) \approx \sum_u a_{t-u} M_u \quad (2)$$

and it is convenient to represent the effect of the threshold by

$$\theta_t = \sum_{v=1}^{\gamma_t} b_v N_{t-v} \quad (3)$$

with γ_t again is the time elapsed since the last N -firing.

Suppose that there is noise, with c.d.f. $P(\cdot)$, superposed on the threshold. This makes the model stochastic. The conditional probability of the neuron firing given the past is taken to be

$$P_t = \text{Prob}\{N_t=1 | \text{the past}\} = P(\psi_t) \quad (4)$$

where

$$\psi_t = \sum_u a_u M_{t-u} - \theta_t. \quad (5)$$

Suppose that the noise comes from an unknown probability distribution and that it is desired to estimate this distribution. It is convenient to write that distribution as

$$P(\psi) = \Phi(g(\psi)) \quad (6)$$

where Φ is the standard normal cumulative, with the consequence that $g(\cdot)$ will be linear if the noise is in fact normal.

The estimation procedure employed is locally weighted maximum likelihood. The computations are carried out recursively. To begin, set $\hat{g}(\psi) = \psi$ and set the derivative $\hat{g}'(\psi) = 1$.

Step 1. Given $N_t, \hat{g}(\cdot), \hat{g}'(\cdot)$ obtain estimates of the remaining parameters of the model, and in particular $\hat{\psi}_t$, by ordinary maximum likelihood.

Step 2. Given $N_t, \hat{\psi}_t$ obtain $\hat{g}(\cdot), \hat{g}'(\cdot)$ to maximize the locally weighted loglikelihood

$$\sum w(\psi - \hat{\psi}_t) [N_t \log P_t + (1 - N_t) \log(1 - P_t)] \quad (7)$$

with $w(\cdot)$ a weighting function, concentrated near 0, and with $g(\psi) = \alpha + \beta\psi$ assumed (locally) linear. The weighting function focuses the local estimation towards the center of the function's support. The estimate of $g(\psi)$ is now taken to be $\hat{\alpha}_\psi + \hat{\beta}_\psi \psi$ and of the derivative taken to be $\hat{\beta}_\psi$.

Step 3. Return to Step 1 until convergence is achieved. More details of this procedure are provided in Brillinger (1992).

This procedure will be illustrated for data collected on *Aplysia californica*, the sea hare. The basic experiments and data collection procedures are described in Bryant et al., (1973) and Brillinger et al., (1976). For the particular data set analyzed, neuron L3 was firing and the input was the sequence of firing times of neuron L10. Figures 2 and 3 present the results

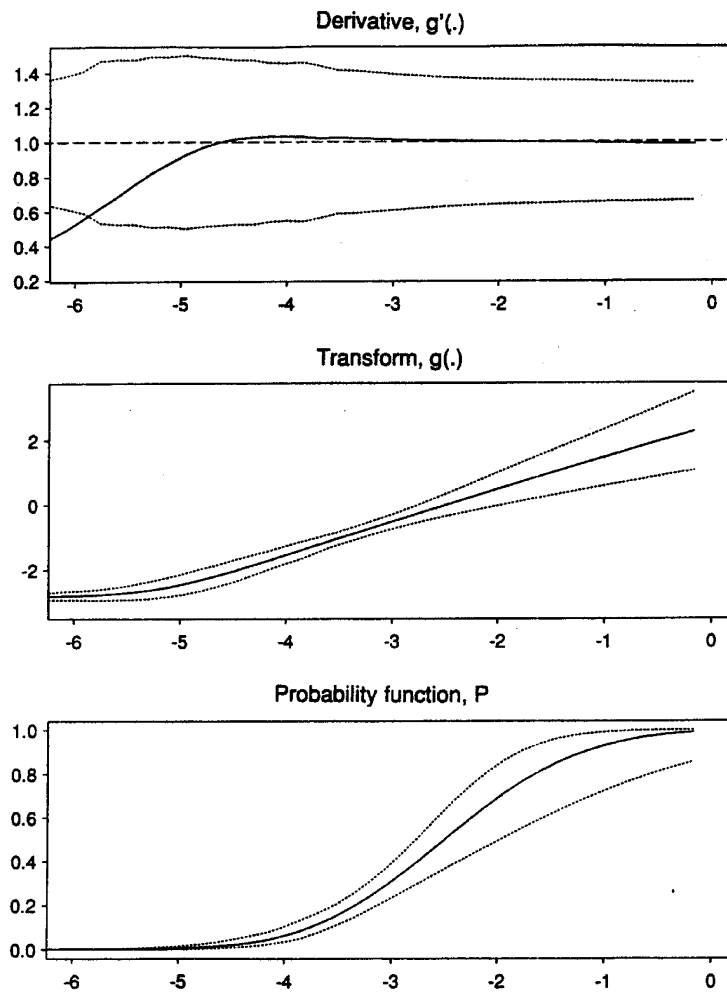


Figure 2 Estimates of the functions $g(\cdot)$ and $P(\cdot)$ of Eq. (6) and of $g'(\cdot)$ the derivative of $g(\cdot)$.

of the computations. The dashed lines give estimated ± 2 standard-error limits. In the case of $\hat{g}'(\cdot)$, they are placed about the level 1.0. The derivative estimate $\hat{g}'(\cdot)$ is seen to not deviate much from 1.0 in the region of apparent probability mass. Thus, the computations are seen to support an assumption of linearity of $g(\cdot)$ and hence of normality of the noise.

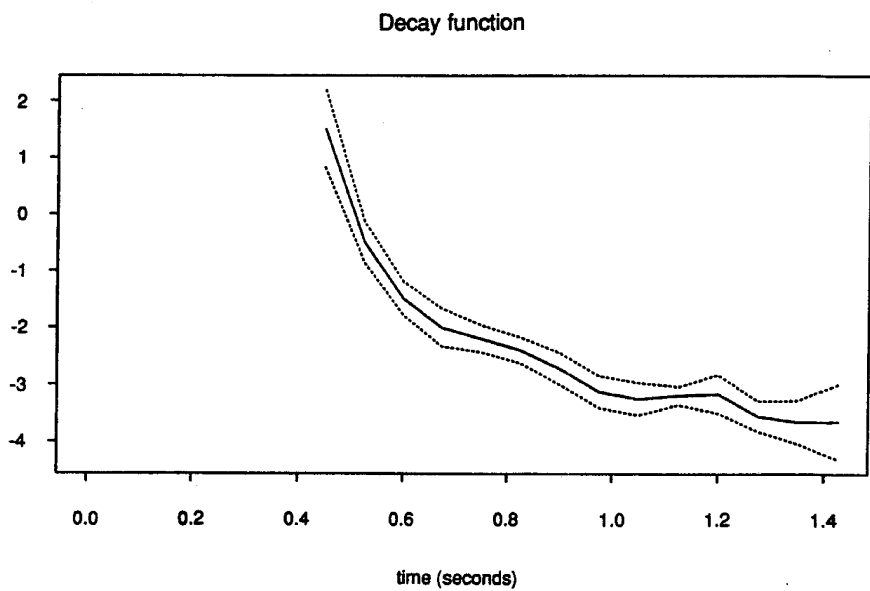
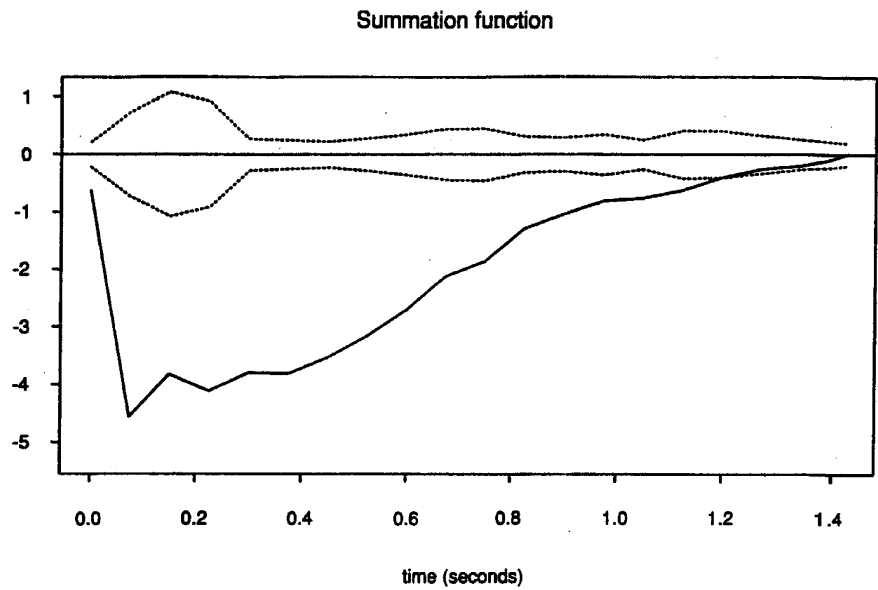


Figure 3 Estimates of a_u and b_u for the case of unknown $P(\cdot)$.

For this particular data set, the fitting of the model described appears quite successful. It has led to results in accord with the preconceptions of the neurophysiologists and allowed estimation of quantities of substantive interest.

The model and fitting technique may be extended directly to the case of several inputs.

PARTIAL COHERENCE ANALYSIS

The thalamus is the major source of sensory information for the cerebral cortex. Merely considered as a relay station for a long period, current research experiments showed that the thalamo-cortical loop is likely to play a major role in the processing of the sensory information (Steriade and Llinas, 1988; Villa et al., 1991). The search for spatiotemporal firing patterns provided evidence that an excess of patterns does exist and that acoustical stimulation increased their number (Villa and Abeles, 1990). Therefore, neuronal circuitry within the auditory thalamus is functionally defined by complex patterns of firing and its study might provide important clues in understanding information processing in the brain. The reticular nucleus occupies a special place among the various nuclei which form the auditory thalamus (Villa, 1990). Indeed this nucleus is formed almost exclusively by inhibitory neurons. It receives its major inputs from the collaterals of the thalamo-cortical fibers and sends its inhibitory output to the other auditory thalamic nuclei. In addition, as well as any other thalamic nucleus, the reticular nucleus of the thalamus receives afferent input from the cerebral cortex too. Given the above knowledge of complex processing taking place in the auditory thalamus, it is important to assess more precisely whether the effect of the stimulus affects the association between units at particular rates of firing. Recordings of neuronal activities were made with glass-coated platinum-plated tungsten microelectrodes advanced in the auditory thalamus of four anesthetized cats. The firing times of up to eight single units were measured with accuracy of 1ms and stored digitally for off-line analyses. The stimulus consisted of a white noise burst, 200ms in duration with a rise and fall time of 10ms. Stimuli were delivered at a rate of 1 per second at an intensity of 60dB SPL. For more details on the methods see Villa (1990).

Now, suppose that a stimulus is applied simultaneously and repeatedly to neurons M and N . Then it will often appear that the spike trains of the two neurons are related, even though they are not physically so. The association is caused by the joint influence of the common stimulus. Partial coherence analysis, Brillinger (1975a, 1975b) is one means of studying such a situation.

The *coherency* at frequency λ , $R_{MN}(\lambda)$, between two spike trains $M=\{\sigma_j\}$ and $N=\{\tau_k\}$ may be defined as follows

$$R_{MN}(\lambda) = \lim_{T \rightarrow \infty} \text{corr}\{d_M^T(\lambda), d_N^T(\lambda)\} \quad (8)$$

where

$$d_M^T(\lambda) = \sum_{0 < \sigma_j \leq T} e^{-i\lambda\sigma_j} \quad (9)$$

is the empirical Fourier transform of the points of M in the interval from time 0 to time T , at frequency λ , with a similar definition for d_N^T . The *coherence* is the modulus-squared, $|R_{MN}(\lambda)|^2$. It is a measure of the association of the trains at frequency λ . It satisfies $0 \leq |R_{MN}|^2 \leq 1$, taking the value 0 if the trains are independent and value 1 if M is able to (linearly) predict N .

The *partial coherency* at frequency λ of point processes M and N , given the point process S , is defined to be

$$R_{NM|S} = \frac{R_{NM} - R_{NS}R_{MS}}{\sqrt{(1 - |R_{NS}|^2)(1 - |R_{MS}|^2)}} \quad (10)$$

suppressing the dependence on λ . The partial coherency may be interpreted via

$$R_{NM|S} = \lim_{T \rightarrow \infty} \text{corr}\{d_N^T - \alpha d_S^T, d_M^T - \beta d_S^T\}. \quad (11)$$

Here α and β are the regression coefficients of d_N^T on d_S^T and of d_M^T on d_S^T , respectively. The intent of their inclusion is to remove the (linear) effects of the Fourier transform of S from those of N and M . The partial coherence also satisfies $|R_{MN|S}|^2 \leq 1$.

In the present case, the point process S refers to the periodic times at which the stimulus is applied. The coherency and partial coherency are estimated in the manner described in Brillinger, Bryant and Segundo (1976). The computation of percentage points of the null distribution of the estimated coherence is also described in that reference.

In the first set of analyses, coherences and partial coherences are estimated in the case of no stimulation. The spike train S is taken to be the times at which the stimulus might have been applied. The null levels derived from the approximate distributions appear quite appropriate for this case (where by construction the stimulus has no effect). Further, because one has experiments in both stimulated and unstimulated cases, one can examine the extent to which the estimated partial coherence in the stimulated case actually resembles the unstimulated coherence.

Three illustrative examples will now be presented. In case the two units are firing independently during spontaneous activity, the coherence and partial coherence are flat and similar, for example see Fig. 4 (bottom half). During stimulus delivery, both units might be excited all along and their response is referred to as of *sustained* type. In the example of Fig. 4 (top half), the firing activity of the two units is associated at low frequencies, that is below 10Hz , during stimulation. This suggests that the two units are not associated when they fire in high frequency bursts of spikes. Such an association might be produced by the common stimulus (which occurs once per second) and the sustained type of response. Indeed the partial coherence during stimulation "removes" the most significant peaks below 10Hz (Fig. 4, second row). A secondary peak remains at 3Hz , which may represent a meaningful sign of association or may be due to "incomplete" removal of common stimulus effects by the partial coherence analysis.

In another example, both units exhibit a strong response to the stimulus, but with a different pattern of response (Fig. 5, first row). Unit 1 is excited the whole time the stimulus is present, and is exactly time-locked to the stimulus offset (at 200ms). It is then inhibited for almost 200ms after the stimulus offset. Unit 3 is only excited at the onset and the offset of the stimulus. The coherence analysis does show the units are associated during stimulus delivery (Fig. 5, second row on the left), but the association is totally due to the common stimulus, as shown by the partial coherence analysis (Fig. 5, second row on the right). No sign of association is visible during spontaneous activity, as evidenced by the flat figures of coherence and partial coherence shown in Fig. 5 (third row). Note that the raster display of unit 3 does show some weak signs of instability during the stimulated condition, but the partial coherence analysis proves to be robust in this respect.

If two units are recorded from the same electrode tip, it often happens that their discharges are associated during spontaneous activity (Villa, 1990; Villa et al., 1991). In one such example (Fig. 6, bottom half) units 7 and 8 are associated over a wide range of frequencies, from $1 - 40\text{Hz}$. Note that a weak sign of association is also detectable at 85Hz . Because of significant association during spontaneous firing, one might expect that the units are associated also during the acoustical stimulation. Both units exhibit a sustained response during stimulus delivery, followed by a brief inhibition at stimulus offset followed by a later offset excitation. The association of firing in the stimulated condition (Fig. 6, second row, on the left) extends roughly over the same range of frequencies observed during spontaneous activity. To the contrary of previous examples, the partial coherence analysis here "removes" only a fraction of the association below 10Hz observed during stimulation. In this case, the comparison of partial coherence during stimulated and spontaneous firing becomes extremely meaningful. Many signs of association observed during spontaneous activity (Fig. 6, third row) are no

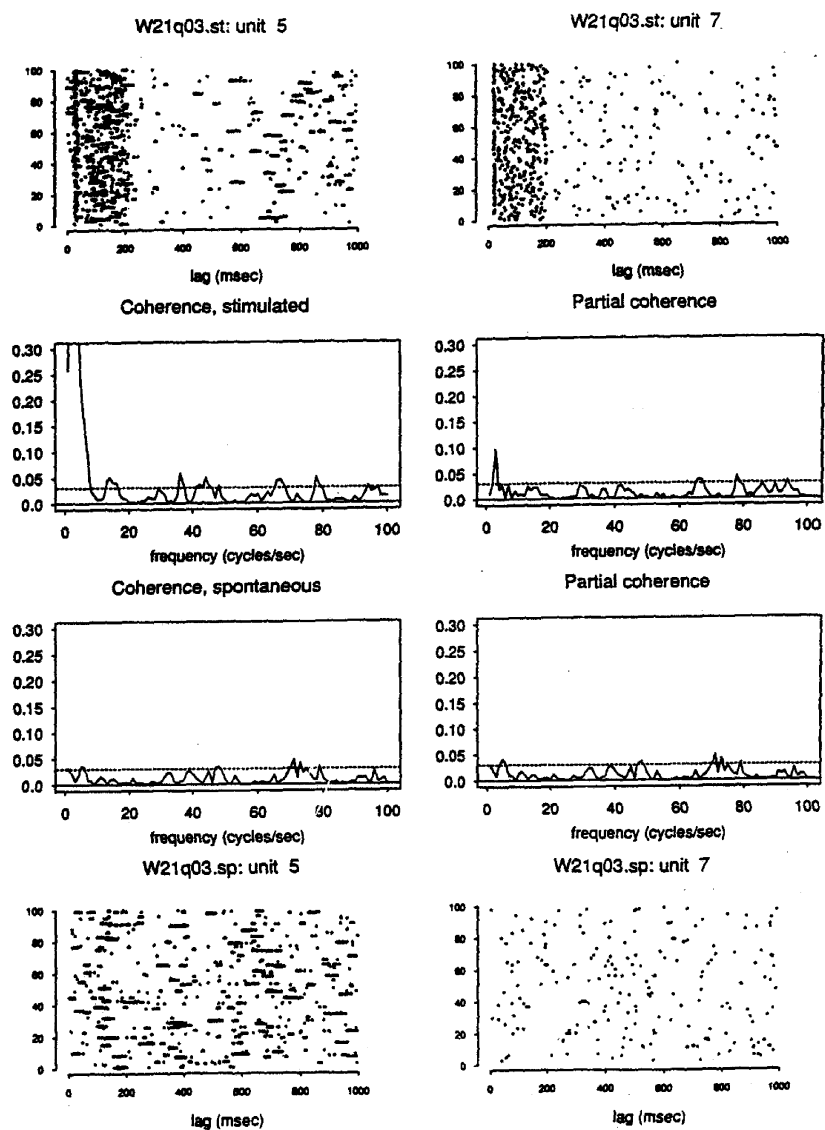


Figure 4 Raster plots of the firing times of two neurons in the case of stimulated (top) and spontaneous (bottom) firing together with computed estimates of the coherence and partial coherence. The dashed line provides the 95% point of the null distribution in the case of independently firing cells.

longer noticeable in the partial coherence at the stimulated condition except at very low frequency (below $5Hz$) and at the peak of $23Hz$.

This example indicates that the partial coherence analysis proves to be an essential tool to distinguish association of firing which depends on the stimulus point process (that is, in the present case, dependent on the auditory ascending pathway) from association of firing due to intrinsic circuitry, not the common stimulus.

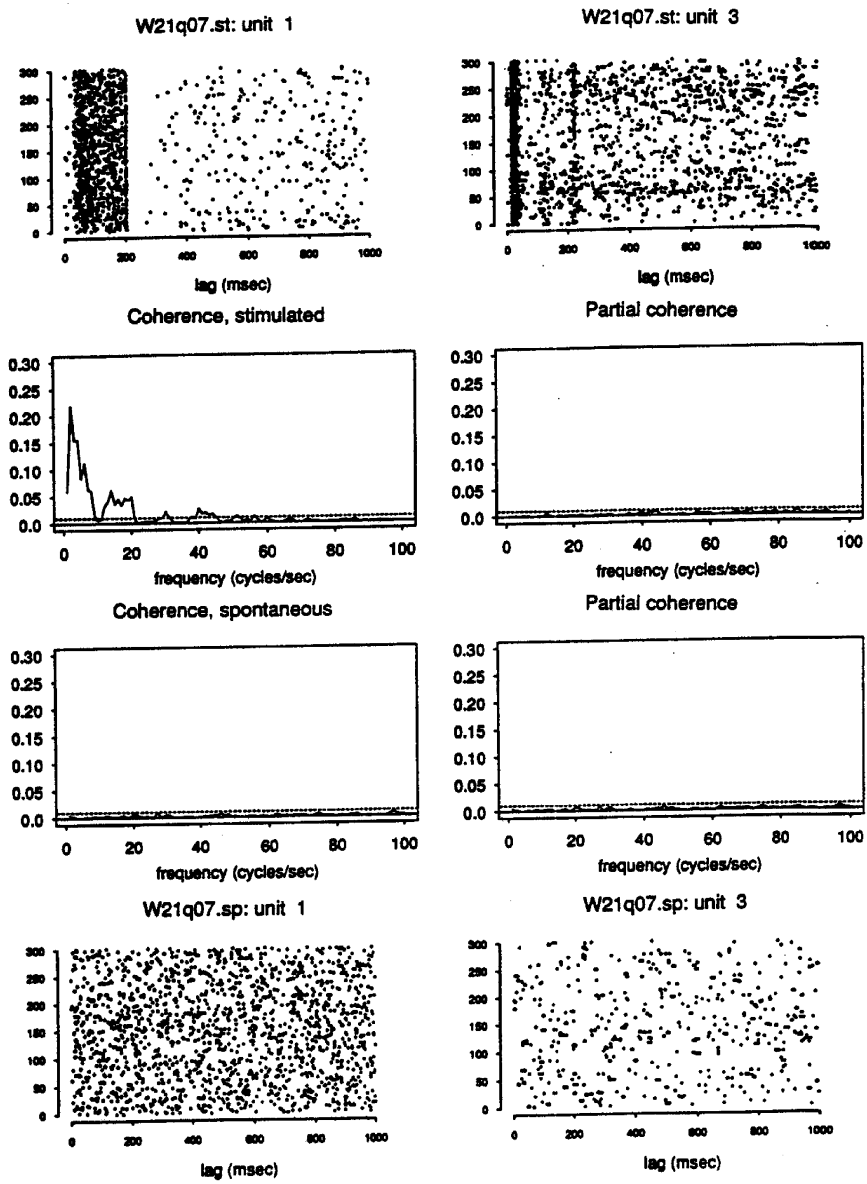


Figure 5 As in Fig. 4, but for a different pair of neurons.

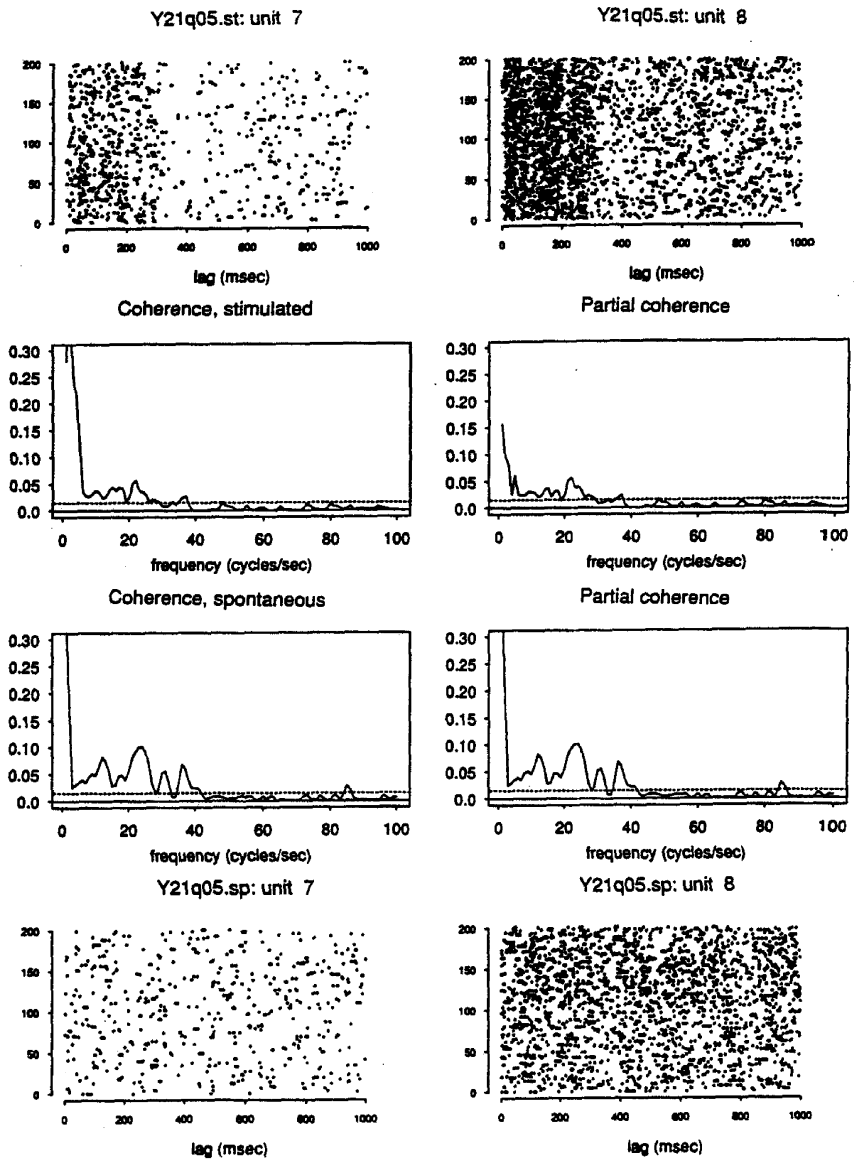


Figure 6 As in Fig. 4, for two units recorded from the same electrode.

AVERAGING WITHIN GROUPS OF NEURONS

The thalamic nuclei belonging to the cat auditory pathways are the medial geniculate body, the lateral part of the thalamic posterior complex (PO), the nucleus of the brachium of the inferior colliculus (BIN), and the reticular nucleus of the thalamus (RE). Based on histological characterization, the medial geniculate body of the cat has been subdivided into dorsal (D), ventral (V), and medial (M) divisions (Morest, 1964). These subdivisions roughly correspond to parallel ascending auditory pathways (Calford and Aitkin, 1983). The ventral division is further subdivided into *pars lateralis* (LV) and *pars ovoidea* (OV). Given the very special position of RE with respect to the other nuclei, it was important to assess whether significant differences appear between groups of unit pairs, where one unit is in RE and one in another thalamic nucleus. The groups were labeled RM for pairs of RE and M divisions, RL for pairs of RE and LV divisions, and so forth.

Data from the M division are particularly interesting to analyze. This thalamic subnucleus is known to participate in cerebral circuits involved in emotional responses to sounds (Ledoux et al., 1983) and rate-sensitive associations of firing with RE may be extremely important with respect to Hebb's theory of learning (Hebb, 1949). There were 32 pairs of units in group RM. During stimulus delivery, RE and M were associated at very low frequencies (below 5 Hz) and near 15 Hz (Fig. 7, top half on the left). Removal of linear effects by partial coherence (Figure 7, top half on the right) suppresses almost entirely the very low frequency peak, but leaves a significant peak near 15 Hz. The comparison of this curve with coherence analysis during spontaneous activity (Fig. 7, bottom half) strongly indicates that the 15 Hz is totally induced by stimulus presentation.

In addition to mixed pairs RE and medial geniculate cells, those pairs of units with both cells belonging to RE were also analyzed. Because of the inhibitory nature of RE units, one can expect to obtain further validation of the partial coherence method. Indeed another method commonly used to assess association of firing proved to be very sensitive to inhibitory links when compared to excitatory links (Aertsen and Gerstein, 1985). Two data sets were used for this classification. One data set contains pairs of units simultaneously recorded from the same microelectrode tip, which means that the units were very close together. This group is labeled R1 and consisted of 17 pairs. The other data set is formed by pairs of units belonging to RE and simultaneously recorded from two different microelectrodes. This group is labeled R2 and consisted of 24 pairs.

Figure 8 shows that the association of firing between pairs of units of the R1 group is mainly restricted to very low frequencies. This pattern of association is present during spontaneous activity and is remarkably unaffected by the stimulus delivery. In contrast, the R2 pairs, as seen in Fig. 9, exhibit a strong association over the entire range of frequencies, although at very low frequencies the peak is much higher than at other frequencies. However, a unique feature of this group is the inverse relation between coherence and frequency in the range 5–80 Hz. The higher the frequency of firing, the lower the association of the discharges between pairs of RE units recorded from different electrodes. Note that R2 pairs, as well as R1 pairs, are only weakly affected by stimulus delivery, even though the responsiveness to the stimuli is well established by raster plots and peri-stimulus time histograms (Villa, 1990).

DISCUSSION

The present paper extends previous results of the application of point process analysis, in the frequency domain, to neurophysiological data (Brillinger, 1975b; Brillinger et al., 1976). An analytic neuron model which incorporates refractoriness, the typical neuronal feature, is shown to fit experimental spike train recordings. Validation of partial coherence analysis is

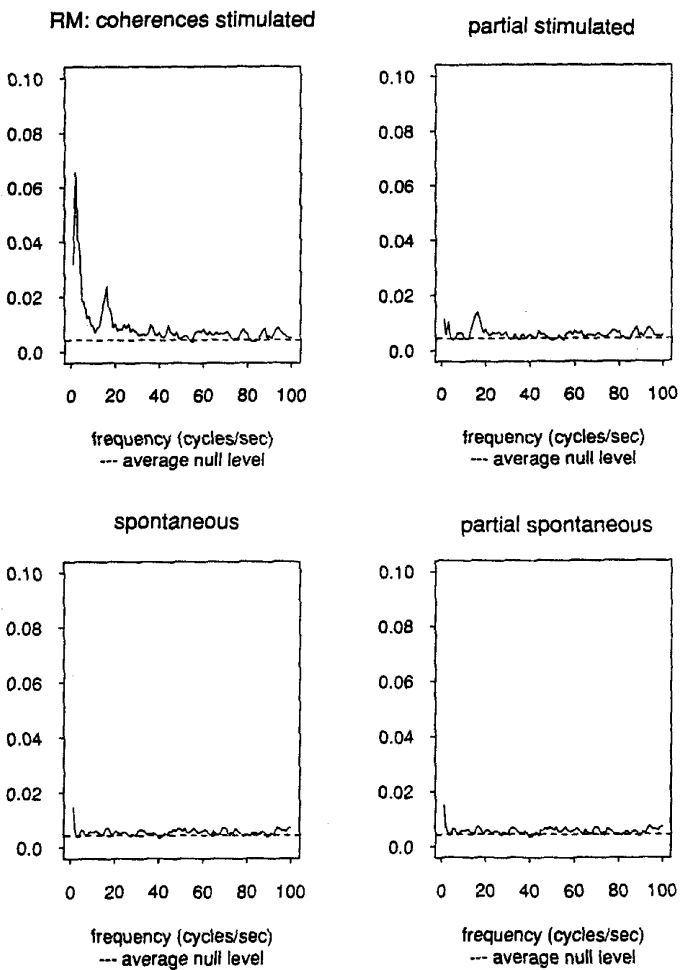


Figure 7 The averages of coherences and partial coherences for the cells from the RM region, in both the stimulated and spontaneous cases. The horizontal dashed line provides the average level to be expected in the case that the cells are firing independently of each other.

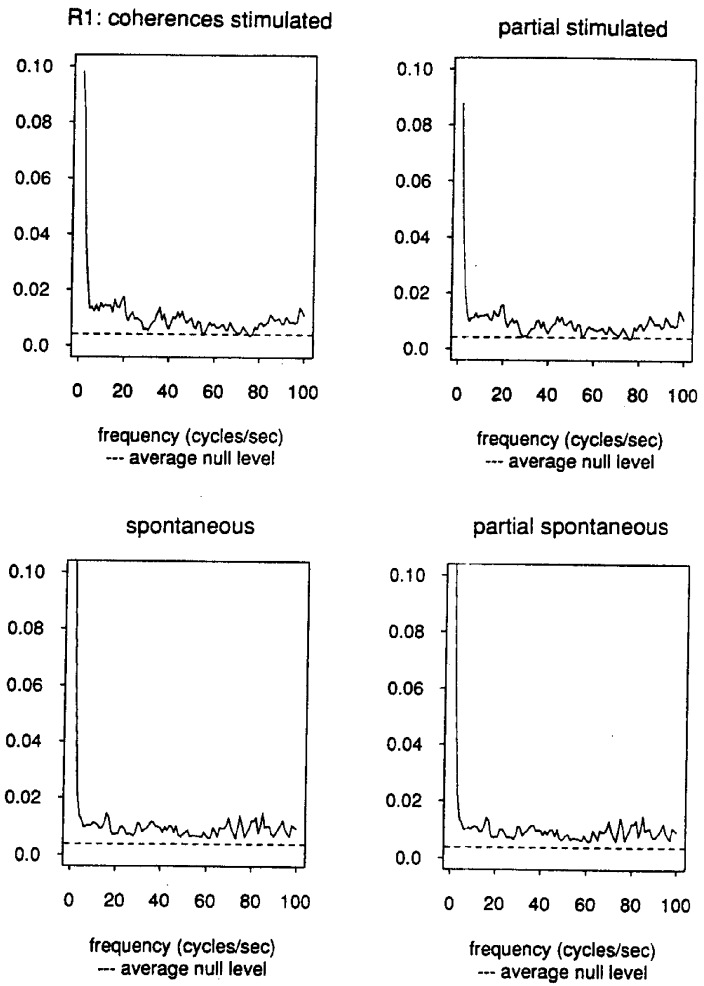


Figure 8 The averages of coherences and partial coherences for the cells from the R1 group (17 pairs, each pair recorded from the same electrode), in both the stimulated and spontaneous cases.

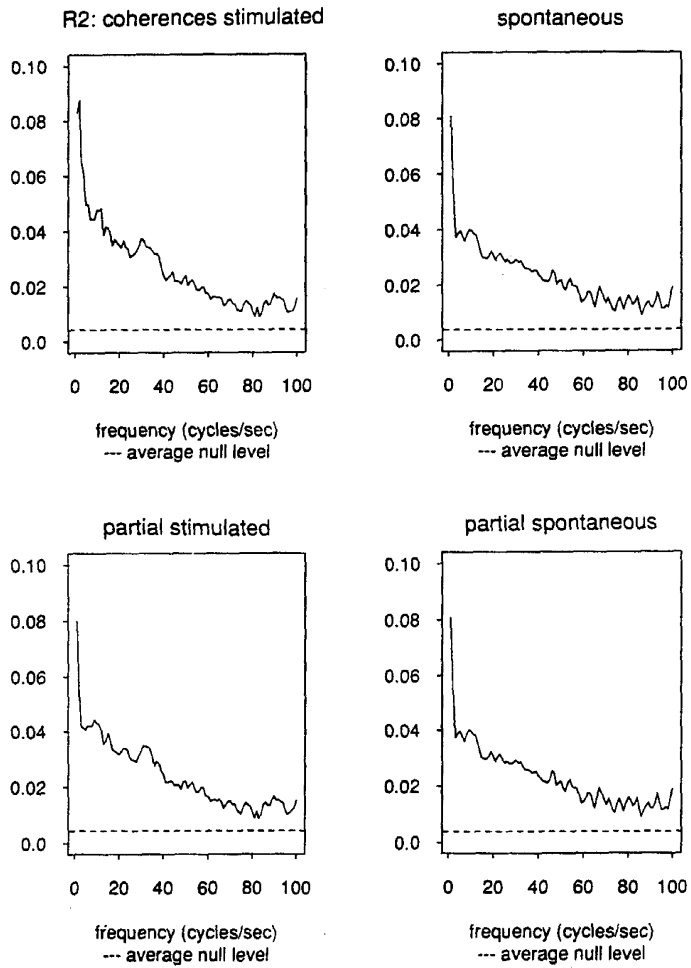


Figure 9 The averages of coherences and partial coherences for the cells from the R2 group (24 pairs, each pair recorded from two different electrodes), in both the stimulated and spontaneous cases.

carried out by means of comparison of spontaneous activity with stimulated condition, and "removal" of linear effects of the stimulus point process.

Evidence has been presented that the discharge pattern of pairs of units may be affected selectively by an external stimulation. These rate sensitive effects might represent a correlate of basic mechanisms of learning as suggested by Hebb (1949), and are being investigated in on-going studies.

The statistical procedures employed are based on minimal assumptions (stationarity and mixing of the basic processes) and, in particular, do not require Poisson distributions. They provide formal indications of the uncertainties of the estimates and, for example, allow specific examination of the hypothesis of no association. The general character of the parameters employed in these procedures makes them widely applicable and well suited for interdisciplinary studies which require collaborative efforts of statistics, engineering and neurophysiology. Indeed, the development of new techniques of acquisition of electrophysiological data with further extensions of the statistical methods described here, might allow the researcher to detect selected signs of associated firing in real neuronal assemblies. In the meantime, the new issues suggested by this approach to information processing, might be studied with "pseudo spike trains" generated within a framework of artificial neural networks (see Villa, 1992).

It is concluded that the techniques presented here provide a valuable tool for detecting and understanding associations between neurons which are modulated by a common stimulus, but are not necessarily time-locked to its time course.

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