An analysis of neural spike-train distributions: determinants of the response of visual cortex neurons to changes in orientation and spatial frequency

D. Berger, K. Pribram, H. Wild, and C. Bridges

Center for Brain Research and Informational Sciences, Radford University, Radford, VA, USA

Summary. A previously unexploited method of examining neural spike-trains was applied to data obtained from cells in the visual cortex. Distributions of interspike intervals recorded extracellularly from cat visual cortex under four conditions were analyzed. Stimuli were gratings differing in orientation and spatial frequency. The probability density function of first passage time for a random walk with drift process, which is defined by its barrier height and drift coefficient, was used to characterize the generating process of axonal discharge under resting and stimulus conditions. Drift coefficient and barrier height were derived from the sample mean and standard deviation of the measured inter-spike intervals. For cells with simple receptive fields, variations in the drift coefficient were produced by changes in orientation and spatial frequency. Variations in barrier height were produced only by changes in orientation of the stimulus.

Key words: Visual cortex - Spike train analysis - Cat

Introduction

Neurons of the primary visual cortex have been found to respond to a variety of visual and non-visual sensory stimuli (see DeValois and DeValois 1988 for review). The question therefore arises as to whether these responses to different stimuli are equivalent. The question has two subsidiaries: 1) Do different stimuli have different effects on the generation of spikes? And 2) Do spike train patterns identify various stimuli? This report concerns the first of these subsidiary questions: and another report (Bierre, Wild, Bridges and Pribram, in preparation) deals with the second. In this preliminary communication a hitherto unexploited approach is applied to analyze the distribution of intervals in order to address the issue of the origin of spike generation. Ordinarily, the record of interspike intervals is presented in terms of a histo-

Offprint requests to: K. Pribram (address see above)

gram of the firing rate versus time. Such a display yields a moving portrait of firing rate.

In this paper a different approach to the analysis of neural activity that emphasizes properties of the distribution of inter-spike intervals is presented. The random walk with positive drift model for simulating the inter-spike interval distribution is used to describe the unknown underlying process. This model incorporates two parameters that specify the temporal distribution of the first passage time of a diffusion process. These specify the temporal distribution of the first passage time of a diffusion process. These parameters, the drift coefficient and barrier height, are derived from the measured mean and standard deviation of the actual neural spike train intervals. The model is therefore a device for describing the underlying process.

If the process generating the interspike interval is stationary, without a temporal change in the probability density, an analysis based on a random walk with drift is potentially relevant. An early study indicated the random walk with positive drift yields an excellent fit to experimental data of inter-spike intervals recorded from spontaneous neural activity (Gerstein and Mandelbrot 1964). There are therefore theoretical and experimental reasons to believe the model based on the first-passage time of walk with positive drift realistically describes the process generating spike-train statistics.

When the spontaneous activity of neurons measured by extracellular recordings had been analyzed it was observed that the temporal distributions of inter-spike intervals resemble the distribution of the first passage time of a random walk with drift process (Lansky 1983; Lansky and Lanska 1987; Lansky and Radil 1987; Tuckwell 1976; Kryokov 1976; Yang and Chen 1978; Tuckwell and Cope 1980). The forward Kolmogorov equation or Fokker-Planck equation provides a formalism whose solution gives the probability density function of the process (Harrison 1985; Karlin and Taylor 1975). The forward equation is recovered whenever any of several types of random noise are assigned as the inputs to the Hodg-

kin-Huxley equations (Tuckwell 1986). The distribution for the first passage time of random walk with positive drift has also been referred to as the inverse Gaussian distribution (Wasan 1969; Johnson and Kotz 1970).

When viewed as a neuronal-spike generating process, the membrane potential of the neuron changes from the resting potential to threshold, at which time an action potential is initiated; after a brief refractory period the process is reset to the resting potential to begin another drift toward the threshold. In the formal model of spike generation the resting potential is considered the process origin and the threshold voltage as the absorbing barrier. Drift reflects the voltage change resulting from input current and membrane conductance. It is the probability density function of this process that is observed as the sequence of inter-spike intervals recorded extra-cellularly during the experiment. The spike-generating process is influenced by the collective dendritic activity of the entire neuron. The model process, which is a representation based on the formalism of the forward equation, provides the statistics describing the spike-rain intervals.

Methods

Subjects

Subjects were eight adult cats obtained from the cattery at the University of California at Davis. A total of 339 spike trains from 110 cells were recorded. 8 spike trains were of sufficient duration and completeness to be useful for the analysis presented here.

Apparatus

The stimulus, consisting of sine wave gratings of variable spatial frequency, drift velocity and contrast, was displayed on a Tektonix type 602 XY oscilloscope. Orientation of gratings was varied mechanically. The display was maintained at a distance of 50 cm from the subject's head. The neural response was picked up using Haer tungten microelectrodes with impedance from one to six MegaOhms. A combination of an RCA 3140IC chip provided first amplification, constant input current of 5 picoamps, and a low output impedance. This device was fastened via alligator clip directly to the electrode. A large bore hypodermic needle inserted through the animal's scalp provided the ground. The signal was transmitted to the input of a Grass P511 J AC preamplifier with gain set at 10k, low pass at 3 Hz, high pass at 300 Hz, and a 50 Hz notch filter. This combination of settings allowed operation without a Faraday cage although partial screening around the animal's head was sometimes necessary. The output of the Grass amplifier was divided: one output went to an A-to-D converter input of a PDB11 computer; another went to an adjustable Schmitt trigger; a third to a Tektronix model 5111A oscilloscope; and a fourth to an audio monitor. The output of the Schmitt trigger, set to fire when a spike appeared above background noise, was in turn sent to the alternate trace of the oscilloscope and audio monitor. A software window discriminator allowed setting two voltage windows for accepting spikes. Two separate records of interspike intervals were thus kept when two units were defined. Interspike interval lengths were rounded to the nearest millisecond.

Procedures

Surgical. Craniotomy and implanation of two 6.5 mm tubular electrode chambers were performed under halothane anesthesia and sterile conditions. A 1/4″-20 bolt was embedded in a cranial cap made of dental acrylic and fastened to the skull by four to six stainless steel screws. Trephine holes were centered at sterotaxic coordinates posterior 2.0 cm and left and right 0.5 cm. The trephine holes were thus placed over areas 17 and 18, and included, at their medial margins, cells activated by stimuli in the midline of the cat's visual field. It is these cells from which most of the recording were made.

Experimental. The animal was allowed to recover from surgery for at leasts one week. Once the morning of the experiment subjects were anesthetized with Ketamine and Valium, intubated, and fastened to the Kopp stereotactic apparatus by the head bolt. Subjects were paralyzed with 10 mg/kg Flaxedil to prevent muscle action. Respiration and temperature were stably maintained; heart rate and anal temperature were recorded every 15 min. Subsequent medication during the experimental session was limited to intravenously administered Valium and Flaxedil, titrated to the condition of the animal: Valium was administered when heart rate began to rise; Flaxedil was administered when hind leg muscle tension began to increase. One electrode chamber was opened and coordinates for the placement of the electrode were determined. Contact lenses with zero correction were inserted in both eyes, the eye ipsilateral to the recorded hemisphere was occluded. The electrode was then set with the stereotax to touch the surface of the brain where a small cut in the dura had been made.

The experimental room was darkened and recording commenced. A Wells hydraulic drive was used to slowly lower the electrode. A small flashlight, masked to project an oblong patch of light onto a ground glass or white paper screen at about 20 cm distance from the cat, was used as a search stimulus. When a responding unit was found an unaltered flashlight was used to illuminate a 50 cm by 38 cm stimulus card with 2.5 cm wide alternating black and white stripes, to hand-map the response of the unit. For this study only spike trains from cells whose receptive fields showed "simple" properties were used. The XY display monitor was positioned at the orientation which provided the best response of the unit. Using maximum contrast (0.8 on a scale were 1 equals maximum brightness on a background of total darkness) the frequency of the sine wave gratings and the velocity of their drift were varied until a maximum response was obtained; the direction of movement of black and white stripes over the visual field was reversed to check for directional selectivity.

Testing. The intent of the experiment was to contrast the stimulus which included the maximal response (determined by an online sample as the histogram with maximum amplitude) with suboptimal stimuli whose parameters were changed over one dimension at a time. After the optimal stimulus parameters has been determined, the experimenal procedure was as follows: Recordings were made while the animal was in darkness; then the optimal condition was displayed twice; then again the dark-condition. After this, the variations of single stimulus parameters were carried out in the following order: variation 1; darkness; variation 1; darkness; variation 2; darkness; variation 2; darkness; variation 3; darkness; variation 3; darkness; etc., until all effective values of that variable were explored. At this point a new stimulus parameter was varied leaving the previously manipulated variable at optimum. The dark-conditions preceding and following each comparison made it possible to detect linear drift of the spontaneous firing rate and to search later for stationarity in an analysis of covariance of firing rates. Presenting the optimal condition each time before and after a series of variations allowed for additional tests of stationarity for the conditions with stimulation. The first stimulus variable to be systematically changed was spatial frequency; the next was the velocity of the grating (temporal frequency); systematic changes in orientation and contrast followed if the unit held up long enough. After completion of the procedure search began for a seconde unit, and the sequence was repeated. When an electrode track was no longer productive the electrode was moved 2 mm laterally, or moved to the other chamber to begin a new search. After about four hours the administration of Flaxedil was discontinued and the animal allowed to recover.

Analytic

The temporal stability of the distribution of inter-spike intervals is essential to all consideration of reproducibility of experimental results. If this criterion is not met, either some aspect of the experimental preparation is changing, or the instrumentation is not recording the activity correctly. If the conditions of time invariance for the distribution of inter-spike intervals and a low level of first order auto-correlation are met, a two-parameter fit of the data can be based on the random walk with drift model of neural activity. This approach uses the derived values of drift coefficient and barrier that can generate probability densities which have the same mean and variance as the measured spike trains.

Calculated values of mean and standard deviation from the measured inter-spike intervals were determined from the following expressions:

The mean of the measured inter-spike intervals.

$$T_m = \sum_{i=1}^{N} \frac{T_i}{N}. \tag{1}$$

The standard deviation of the measured inter-spike intervals.

$$S_d = \left\{ \sum_{i=1}^{N} \frac{(T_i - T_m)^2}{(N-1)} \right\}^{1/2}. \tag{2}$$

The random walk with positive drift process is illustrated in Fig. 1. A sample path beginning with the origin at X_0 is seen to advance towards the absorbing barrier at X_a. The distance between the origin and the absorbing barrier, $Z = X_a - X_0$, will always be referred to as the "barrier height" in this paper. The problems are to determine 1) the density of this processing path, 2) its first moment or expectation value, and 3) the second moment from which the variance is calculated. Using sample values for the mean inter-spike interval T_m and the standard deviation S_d then the the drift coefficient μ and barrier height Z can be derived for the first passage time of random walk with positive drift process. A normalized diffusion constant, $\sigma^2/2 = 1.0$, is assumed in the derivation of the drift coefficient and barrier height. This normalization scales the process to ensure the consistency of the units of the derived parameters.

The solution of the forward equation, Eq. (3), is the probability density function of the first passage time of random walk with positive drift.

$$\frac{\partial P}{\partial t} = -\mu \frac{\partial P}{\partial x} + \frac{\sigma^2}{2} \frac{\partial^2 P}{\partial x^2}. \tag{3}$$

The probability density function that is a solution of the forward equation is given by:

$$P(\mu, Z, \sigma; t) = \frac{Z}{\sqrt{2\pi}\sigma t^{3/2}} \exp\left\{ \frac{-(Z - \mu t)^2}{2\sigma^2 t} \right\}. \tag{4}$$
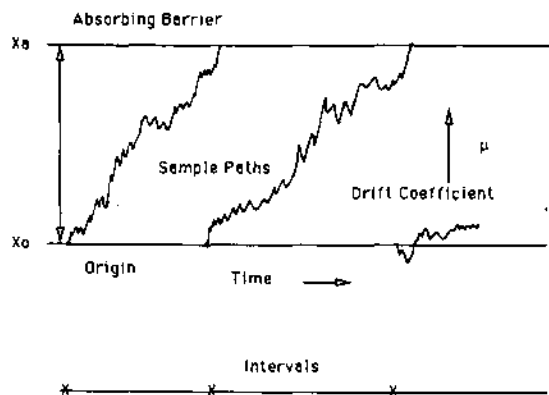

Fig 1. First passage time of random walk with drift is illustrated for positie drift coefficient μ and barrier height $Z = X_a - X_0$. The probability distribution function for the first passage time intervals is determined by these parameters

The first moment or expectation value the second moment and the variance of the probability density function are given by Eqs. (5, 6 and 7).

$$E[t] = \frac{Z}{\mu} \tag{5}$$

$$E[t^2] = \frac{\sigma^2 Z}{\mu^3} + \frac{Z^2}{\mu^2} \qquad \frac{\sigma^2}{2} = 1.0 \tag{6}$$

$$E[t^2] - E[t]^2 = \frac{2Z}{\mu^3}. \tag{7}$$

To obtain derived values of drift coefficient μ and barrier height Z the sample mean, T_m is set equal to the expectation value of the probability density function and the sample standard deviation S_d is set equal to the square root of the variaince of the probability density function. In this way a calculated probability density function with the same mean and variance of the measured inter-spike interval distribution is obtained. The derived drift coefficient of the model process is given by equation 8 and the derived barrier height is given by Eq. (9).

$$\mu = \frac{\sqrt{2 T_m}}{S_d} \tag{8}$$

$$Z = \mu T_m. \tag{9}$$

The main objective of this report is to illustrate the activity of neurons under different stimulus conditions as graphs of Z and μ; this will provide insight into the changes in the spike-generating process. If sufficient stationarity during recording of experimental data is observed it is believed that this method for investigating neural activity will yield a substantially correct description of the inter-spiked interval statistics in a concise form.
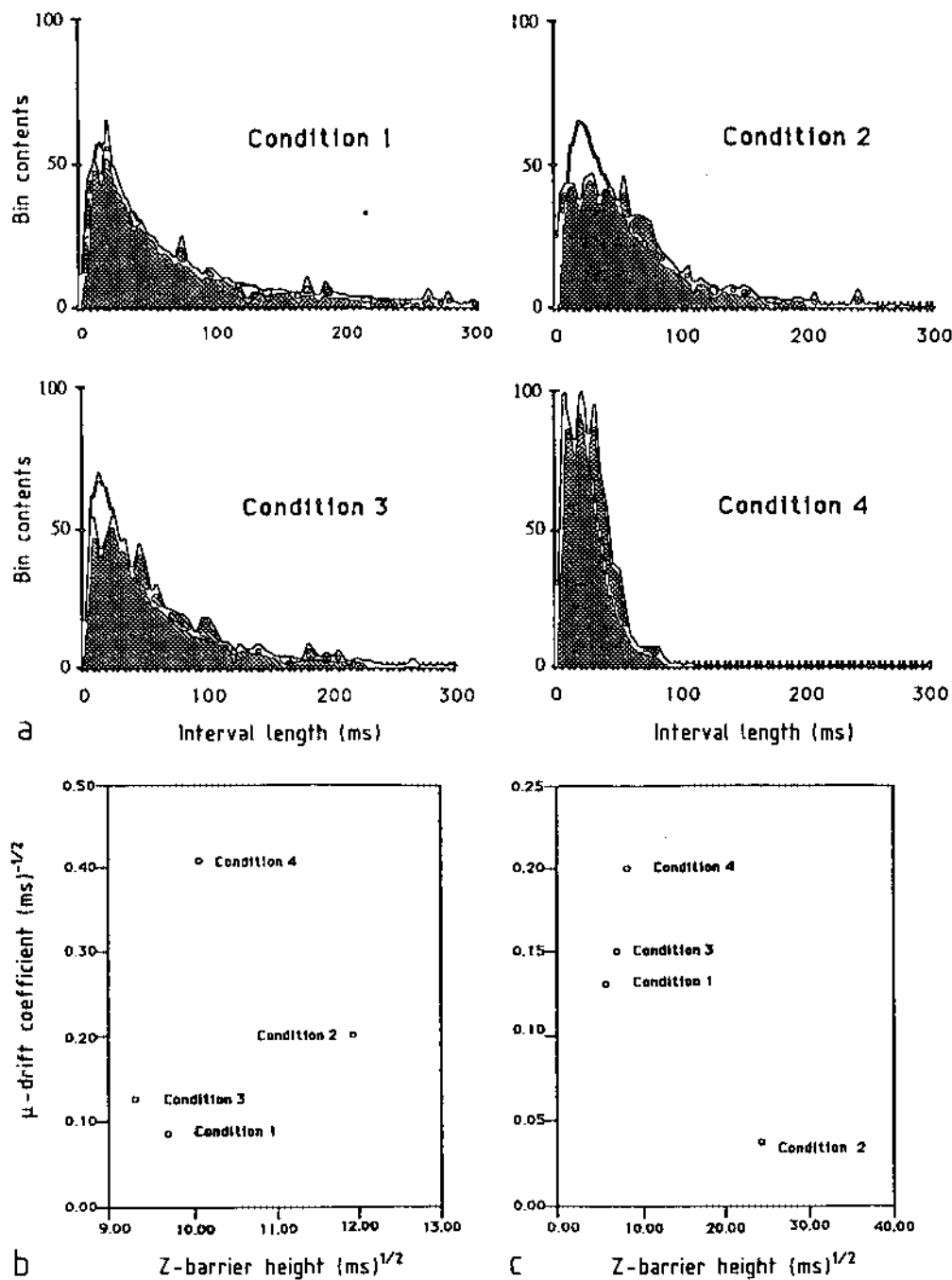
Fig. 2. a The interspike interval histograms for the four stimulus conditions are shown by the shaded areas. The solid line shows the calculated pdf for the first passage time of random walk with positive drift with the same mean and variance as the measured histograms. b The barrier height and drift coefficient for the cell with the interspike interval histograms illustrated in a is shown. c Another cell is presented which shows a large increase in barrier height for the 90 degree orientation change of Condition 2

Experimental Results

The methods described were applied to the inter-spike intervals of recorded data for ten cells that were under similar experimental conditions. The four conditions can be summarized as follows

Condition 1. No stimulus presentation and a corresponding spontaneous neural discharge-rate.

Condition 2. Orientation change with the same spatial frequency as Condition 4.

Condition 3. Spatial frequency change with the same orientation as Condition 4.

Condition 4. Condition of orientation and spatial frequency for maximal discharge rate.

The inter-spike interval histograms for a selected cell are shown in Fig. 2a. These histograms show that a given stimulus condition results in a unique distribution of inter-spike intervals. Figure 2b illustrates the derived values of drift coefficient μ and barrier height Z for this cell. For condition 2, for which the stimulus orientation is changed by 90 degrees relative to conditions 3 and 4, an increase in barrier height Z is seen for the process. Another cell with an even greater Z shift is shown in Fig. 2c. The condition 3 for change in the spatial fre-

quency is primarliy associated with a decrease in drift coefficient μ in both figures. The Z and μ values shown in Fig. 2b were evaluated for 800 measured intervals for each of the four conditions. The statistical significance of the change in Z values between condition 2 and condition 3 of Fig. 2b is an an important issue. To examine this problem the measured intervals were divided into ten equal segments of 72 intervals each 'for both condition 2 and condition 3. The mean and variance of the derived values of Z of each collection of intervals was calculated. The results of a one-tail T-test showed the confidence level for eighteen degrees of freedom to be ($T = 2.09$, $P < 0.05$). This would indicate that the Z shift is probably statistically significant and that changes in orientation and spatial frequency are indexed separately. (Sillito et al. 1980; Ramoa et al. 1986). The limits of hyperpolarization and depolarization correspond to changes in the barrier height of the process if other factors are unchanged.

The histogram of the intervals shown in Fig. 2a has some spikes in the distributions. It is of interest to determine if this structure is a permanent feature related to the stimulus conditions or if it an unrelated artifact. An extensive examination of histograms using segmented data and auto-correlograms did not reveal any permanent feature that could be attributed to the representation of relevant information. The structure of the probability density function derived from the measured histograms appears to contain all the significant information in terms of representation of the stimulus. Clearly a sufficiently low rate of temporal change in the stimulus conditions would create variations in the probability density function and auto-correlograms but under the nearly stationary conditions of these experiments no temporal sequences provided evidence for an additional mode of stimulus representation.

Conclusion

Spike trains recorded from visual cortex neurons reflect three separable influences: 1) those, such as the sensory stimuli which characterize the input to the neuron 2) those which parameterize the properties of the ensemble of dendritic activities of the neuron, and 3) those which directly determine the output of the neuron at the axon hillock (Pribram, Lassonde and Ptito 1981). Receptive field properties (no 2 above) can be characterized as filters resonating to spatial (and temporal) frequencies (DeValois and DeValois 1988) which are specified as sinusoids in the spectral domain. These sinusoids are limited by a Gaussian envelope which reflects the spatial characteristic of the receptive field, specifically, orientation. The result is best described as a Gabor elementary function. (Marcelja 1980; Pribram and Carlton 1986; Daugman 1988). The analyses undertaken in this study indicates that these two separable characteristics of the receptive dentritic field, responses to changes in spatial frequency and orientation, have different effects on the processes generating neural impulses at the axon hillock.

The barrier height and drift coefficient derived from the measured interspike intervals parameterize these two characteristics of the dendritic network. For a given stimulus condition a dendritic environment is generated from the excitatory and/or inhibitory character of the dendritic events. The assignment of a weighted rate process to the events of this dendritic microprocess reflects their degree of influence on the generating of spikes by the cell being examined. The neuron is thus conceived as a processor of stochastic dendritic events which displays its computed output as the statistics of the sequence of inter-spike intervals.

The cells studied in this paper were sufficiently stationary to be analyzed by the spike interval distributions. Such distributions can be used to determine a derived barrier height and drift coefficient process. The first two moments of the sample distribution are sufficient to characterize the underlying diffusion process if stationarity is observed. This property is indicated by the time invariance of the inter-spike interval distributions for a given stimulus condition. Because of this requirement transients and fluctuations in the drift coefficient and barrier height cannot be examined directly.

The analyses made in this study indicate that inter-spike interval distributions are changing with different inputs and are doing this in a consistent and reproducible manner. The changes are reflected in the probability density of the first passage time of the underlying process. Interpretation of these changes is made in terms of the random walk with drift model. The rate of neural firing is the slope from origin to the data point in plots of barrier height and drift coefficient. Shifts in threshold, changes in polarization levels and stimulation rate can therefore be inferred from changes in the barrier height and drift coefficient of the process if the variance parameter does not change for different stimulus conditions. The analysis showed that, in the sample of cells studied, the variation of spatial frequency only changed the drift coefficient and that barrier height was changed only by changes in orientation.

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