

Stochastic Nature of Precisely Timed Spike Patterns in Visual System Neuronal Responses

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Oram, M. W., M. C. Wiener, R. Lestienne, and B. J. Richmond. Stochastic nature of precisely timed spike patterns in visual system neuronal responses. *J. Neurophysiol.* 81: 3021–3033, 1999. It is not clear how information related to cognitive or psychological processes is carried by or represented in the responses of single neurons. One provocative proposal is that precisely timed spike patterns play a role in carrying such information. This would require that these spike patterns have the potential for carrying information that would not be available from other measures such as spike count or latency. We examined exactly timed (1-ms precision) triplets and quadruplets of spikes in the stimulus-elicited responses of lateral geniculate nucleus (LGN) and primary visual cortex (V1) neurons of the awake fixating rhesus monkey. Large numbers of these precisely timed spike patterns were found. Information theoretical analysis showed that the precisely timed spike patterns carried only information already available from spike count, suggesting that the number of precisely timed spike patterns was related to firing rate. We therefore examined statistical models relating precisely timed spike patterns to response strength. Previous statistical models use observed properties of neuronal responses such as the peristimulus time histogram, interspike interval, and/or spike count distributions to constrain the parameters of the model. We examined a new stochastic model, which unlike previous models included all three of these constraints and unlike previous models predicted the numbers and types of observed precisely timed spike patterns. This shows that the precise temporal structures of stimulus-elicited responses in LGN and V1 can occur by chance. We show that any deviation of the spike count distribution, no matter how small, from a Poisson distribution necessarily changes the number of precisely timed spike patterns expected in neural responses. Overall the results indicate that the fine temporal structure of responses can only be interpreted once all the coarse temporal statistics of neural responses have been taken into account.

INTRODUCTION

To relate neuronal responses to higher functions such as perception and memory it is critical to know what aspects of neuronal responses can carry information. Because extracellularly recorded neuronal responses can be regarded as a series of impulses or spikes it is natural to wonder whether temporal characteristics as well as firing rate of spike trains vary in a systematic way across experimental conditions. It has been shown that information is coded in the temporal characteristics of responses when the times of the spikes are represented at relatively low temporal precision (~20 ms) (Eskandar et al.

1992a,b; Heller et al. 1995; McClurkin et al. 1991a–c; Richmond and Optican 1990; Richmond et al. 1987). It has been proposed that precisely (~1 ms) timed spike patterns carry information unavailable from spike count and play a central role in important psychological processes such as linking or binding of parts of objects falling on different retinal receptors (Abeles 1991; Engel et al. 1992; Singer and Gray 1995; von der Malsburg 1995; von der Malsburg and Schneider 1986). Several experiments have suggested that an independent process might exist that controls the times of some of the spikes within responses of neurons in frontal and visual cortices and thalamic areas (Abeles et al. 1993; Aertsen et al. 1989; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Prut et al. 1998; Riehle et al. 1997). Such an independent process could encode the information needed for these psychological processes.

Precisely timed spike patterns can carry information beyond that carried by spike count only if the precise spike patterns are controlled rather than occurring by chance. We examined responses of single neurons from the lateral geniculate nucleus (LGN) and primary visual cortex (V1) for three classes of precisely timed patterns of spikes previously studied in frontal and primary visual cortices and thalamic areas of rat, cat, and monkey (Abeles et al. 1993; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Prut et al. 1998). The precisely timed patterns were found to carry some stimulus-related information, but the same information was available from spike count. This suggested that the precisely timed patterns were predictable from a model using the spike count and slow variation in firing rate, leading us to search for such models.

The variation in the number and timing of spikes occurring across trials is large, giving ample possibility for different stimuli to elicit different numbers and types of spike patterns. The large number of possible spike patterns makes it a complex statistical problem to determine whether the spikes occurred precisely when they did by chance or whether it is necessary to postulate some process controlling the spike times. Statistical models with simple response measures, e.g., spike count, peristimulus time histograms (PSTHs), and interspike intervals (ISIs), have been developed to reduce the complexity of this problem. These models are used to determine the number and type of internal temporal structures that can be expected by chance (Abeles 1991; Abeles and Gerstein 1988; Abeles et al. 1993; Aertsen et al. 1989; Dayhoff and Gerstein 1983a,b; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Vaadia et al. 1995). The simplest of these, the uniform Poisson

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model, assumes a Poisson process with a uniform firing rate. Another class of model shuffles the ISIs. These shuffled ISI models directly examine the tendency for interval length b to follow interval length a . Finally, time-varying or nonhomogeneous Poisson process (NHPP) models are based on the changes of the observed stimulus-elicited firing rate over time (Abeles and Gerstein 1988; Aertsen et al. 1989; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Victor and Purpura 1996). None of these models matched the precise temporal structures observed in the neural data in past studies nor, as we show subsequently, do they match the data from our experiments in the LGN and V1.

Previous stochastic models, which assume that the spike counts follow a Poisson distribution (Abeles and Gerstein 1988; Abeles et al. 1993; Aertsen et al. 1989; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998), predicted fewer precisely timed spike patterns than seen in our V1 and LGN data. A new stochastic model, which extends an earlier model (NHPP) only in that it replaced the assumed Poisson distribution with the observed distribution of spike counts, predicted almost exactly the observed numbers and types of precisely timed patterns. We show that any deviation, no matter how small, from a Poisson distribution of spike counts necessarily induces changes in the numbers and types of spike patterns in and between neuronal responses of both single and, by simple extension, multiple neurons. The results demonstrate that the precise temporal patterns observed in our data can arise by chance. The match between the observed and predicted temporal patterns makes this model a potentially valuable tool for understanding the mechanisms underlying the temporal properties of neuronal responses.

METHODS

Using standard techniques, we recorded activity from LGN and V1 neurons from a rhesus monkey performing a fixation task. Spike data from single neurons were collected with 1-ms resolution. Up to 64 different images were used as stimuli for LGN recordings: bars at four orientations and dots at four sizes, each at up to eight different contrast levels. Up to 274 stimuli were used when recording V1 neurons: bars at 8 orientations at 5 contrast levels, gratings at 8 orientations and 5 spatial frequencies at up to 5 contrast levels, Walsh patterns at up to 5 contrasts, and 32 digitized photographs.

Each stimulus was presented for 300 ms centered on the receptive field. The stimuli covered the excitatory receptive field and extended into the near surround. Reward was delivered after every one to four stimulus presentations if the monkey maintained fixation within 0.5° . LGN parvocellular neurons were recorded with receptive field centers varying between 3 and 20° eccentricities in the lower contralateral hemifield. Striate cortical neurons in the calcarine sulcus had receptive fields between 5 and 10° from the fovea in the upper contralateral hemifield. The animal procedures followed USPHS guidelines and were approved by the NIMH Animal Care and Use Committee.

Data analysis

Analysis was performed on the period -200 to $+200$ ms peristimulus onset, with spikes times measured with 1-ms precision. This interval was chosen because it provided equal pre- and poststimulus onset sample periods while capturing the majority of the available information in the responses. We identified and counted all triplets and quadruplets with intervals of ≤ 25 ms in each response. A replicating triplet (Lestienne and Strehler 1987; Lestienne and Tuckwell

IDENTIFICATION OF REPEATING TRIPLETS

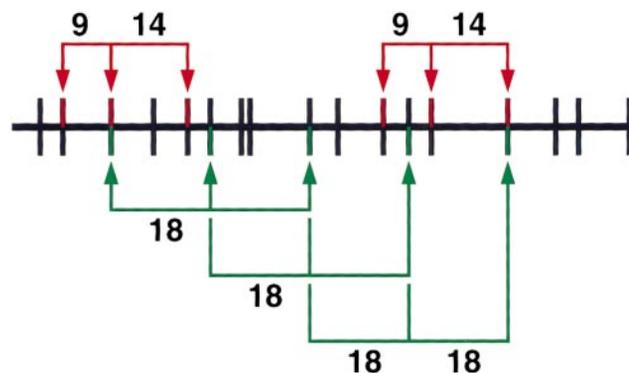


FIG. 1. Detection of repeating triplets. Pairs of interspike intervals (ISIs) were examined to see if they repeated within individual spike trains (horizontal bar). Two sets of repeating triplets are illustrated, one identified by red arrows and the other (repeating 3 times) by green arrows.

1998) occurs when any spike triplet with intervals a and b ($0 < a, b \leq 25$ ms) appears at least twice in a single stimulus-elicited spike train (see Fig. 1). Note that “extra” spikes could appear both within triplets and between the repeats of triplets. Each spike can participate in any number of repeating triplets, making it possible for the number of repeating triplets to be greater than the number of spikes. To investigate the general applicability of models, we also identified the number of each of the 15,625 possible replicating quadruplets with intervals a, b, c ($0 < a, b, c \leq 25$ ms) provided that the quadruplet type appeared at least twice in a single stimulus-elicited spike train. We also counted the number of triplets across responses regardless of whether the triplet repeated within an individual trial. To enable the use of standard parametric statistical tests, the number of patterns found was transformed with natural logarithms to remove the strong dependency of the variance on the mean and establish homogeneity of variance (Snedecor and Cochran 1980).

Spike count-matched model

The model we propose generates random spike times while preserving both the spike count distribution assessed over a long (400 ms) time period and the observed stimulus-elicited firing rate profile for each stimulus. The spike count distribution is preserved by stepping through the experimental data trial by trial and forcing each simulated trial to have the same spike count as the corresponding experimental trial. We refer to this model as the spike count-matched model because of the forced matching of the spike count distribution.

The responses from each cell to each stimulus are used to generate a spike density function by convolution of the PSTH with a Gaussian (Fig. 2, top). The results used a Gaussian of $\sigma = 5$ ms (Richmond et al. 1987). Results with Gaussians of $\sigma = 2$ or 10 ms were indistinguishable from the results with $\sigma = 5$ ms. Smoothing the stimulus-elicited spike trains with Gaussians of $\sigma \geq 20$ ms reduced the predicted number of repeating triplets.

We used a standard method to generate random numbers (spike times) with a known probability distribution (spike density function) (Press et al. 1992). The spike times are generated randomly by taking uniform random numbers in the interval $(0-1)$ and applying the inverse of the cumulative probability distribution (Fig. 2, bottom). Specifically, the spike density function is transformed into a cumulative spike density function (CSDF) for each stimulus at each time point t

$$\text{CSDF}(t) = \left[\sum_{i=1}^t \text{SDF}(i) \right].$$

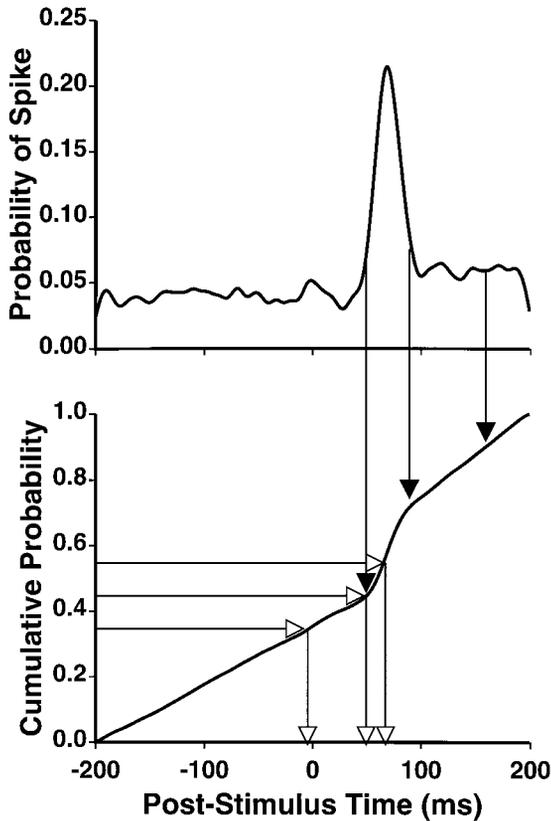


FIG. 2. Spike count-matched model. *Top*: spike density function calculated from the responses of 1 lateral geniculate nucleus (LGN) neuron to a single, effective stimulus. *Bottom*: summation of the spike density function from the *top panel* gives the cumulative spike function over the sample period. Normalization so that the total probability = 1 gives the cumulative spike probability function. Cumulative spike probability function allows random numbers drawn from a uniform distribution to be transformed into the distribution of spike arrival times given by the spike density function (*top section*). To generate a trial with, say, 3 spikes, 3 uniformly distributed random numbers between 0 and 1 are drawn. These random numbers are then transformed with the cumulative spike probability function to obtain the times at which the spikes will occur in the simulated spike train. The arrows show an example of the transformation of 3 evenly spaced random numbers (y-axis) into the spike times (x-axis) appropriate for the spike density function shown. Spikes in the resulting train are not evenly spaced.

Normalization by the value of the CSDF at the end of the sample period ($t = T$) gives the cumulative spike probability function

$$\text{CSPF}(t) = \frac{\text{CSDF}(t)}{\text{CSDF}(T)}$$

(Fig. 2, *bottom*). The CSPF gives the probability with which any given spike in a train will have occurred within t ms of stimulus onset. The time bin (width δt , here 1 ms) in which a spike occurs, t_{spike} , in a simulated train is determined from a uniform random distribution $R_{[0,1]}$ such that t_{spike} satisfies $\text{CSPF}(k) \leq (R_{[0,1]} < \text{CSPF}(k + 1))$, the time of the k th bin being between $k\delta t$ and $(k + 1)\delta t$ (arrows in Fig. 2, *bottom*). As with the NHPP model, only one spike is allowed in each time bin; when a spike was assigned to an already occupied bin, a new random number was drawn and the spike was re-assigned.

Correction of ISIs

The number and type of patterns seen in modeled responses are known to depend on the ISI distribution, which in turn is influenced

by the refractory period (Berry and Meister 1998; Berry et al. 1997). We adjusted the spike count-matched model to account for this effect. An overall frequency ISI histogram for each cell was compared with the frequency histogram of the simulated spike trains when no correction for refractory period was used. The probability of allowing a 1-ms ISI was then set to be the ratio of the number of 1-ms intervals in the data to the number in simulated data (p). Then a new set of simulated spike trains was generated allowing spikes to be 1 ms apart only if a uniform random number (0–1) fell below p , and a new ISI histogram was generated. Then the same procedure was used to correct the probability for the 2-ms ISI. An example of the ISIs obtained from the spike count-matched model and the corresponding ISI from a striate neuron are shown in Fig. 3. After correcting for the 1- and 2-ms ISIs the simulated data for both LGN and V1 neurons had ISI frequency histograms that were indistinguishable from the neuronal data (nonsignificant deviations, Kolmogorov-Smirnov test, $P > 0.05$).

Information measures

To assess the potential role of precisely timed spike patterns for cognitive or psychological processing we used an information theoretical approach. Transmitted information is a statistical measure quantifying how well a set of inputs (here visual stimuli) can be distinguished from each other using the corresponding outputs (here the responses of the neurons). The amount of information calculated to be in a neuron's response depends on the code used to interpret the response (e.g., spike count). We measured the information carried when the number of spikes (spike count) in a trial was used as the response code, when the number of precisely timed spike patterns was used as the response code, and when the two measures together were used as the response code. If, as has been suggested (Abeles 1991; Engel et al. 1992; Lestienne and Strehler 1987; von der Malsburg and Schneider 1986), precisely timed spikes play a special role in processing, then some of the information they carry should be unavailable from considering the spike count alone. We were therefore interested in whether there was stimulus-related information carried by the triplet code and whether the dual code of precisely timed spike patterns and spike count carried more information than that carried by spike count alone.

Details of information theory can be found elsewhere (Cover and

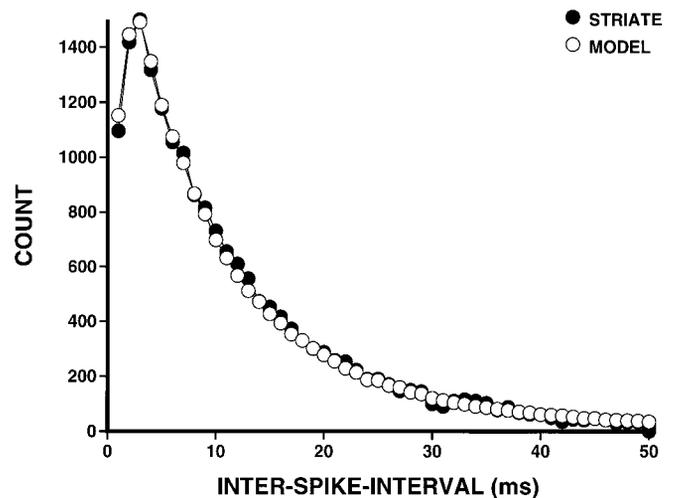


FIG. 3. Matching ISIs of the spike count-matched model and the neuronal data. ISI histograms from a primary visual cortical (V1) neuron (●) and the corresponding spike count-matched model (○) are shown. The ISI distributions of all neurons obtained from the spike count-matched model were statistically indistinguishable (Kolmogorov-Smirnov test, $P > 0.05$) from those of the corresponding neurons.

Thomas 1991; Shannon 1948). In brief, we asked how well the neuronal responses could, in principle, tell us which stimulus elicited a response. Information is defined as

$$I_{(S;R)} = \sum_S \sum_R \left[p(r)p(s|r) \log_2 \left(\frac{p(s|r)}{p(s)} \right) \right] \quad (1)$$

where $I_{(S;R)}$ is the information transmitted about the set of input stimuli S . The outer sum ranges over all the stimuli S . The inner sum ranges over the set of all observed responses R . For the terms of the inner product, $p(r)$ is the probability of observing response r independent of the input stimulus. $p(s|r)$ is the probability of response s being the input stimulus having observed response r , i.e., the conditional probability of stimulus s being present based on observing response r in a particular trial. $p(s)$ is the a priori probability of the stimulus s , which is determined by the frequency with which the stimulus was presented in the experiment.

Although $p(s)$ is controlled by the experimenter, $p(r)$ and $p(s|r)$ must be estimated from the neuronal data. Because of limited sample size $p(r)$ and especially $p(s|r)$ are subject to misestimation (Carlton 1969; Kjaer et al. 1994; Miller 1955; Optican and Richmond 1987; Panzeri and Treves 1996). Several methods have been developed to correct for limited sample size and calculate an accurate estimate of $I_{(S;R)}$ (e.g., Kjaer et al. 1994; Panzeri and Treves 1996; Victor and Purpura 1996; see Golomb et al. 1997). We used the method of Kjaer et al. (1994).

RESULTS

Number of precisely timed spike patterns depends on response strength

We searched spike trains for three classes of precisely timed (1-ms precision) patterns that have been studied by others (Abeles 1991; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Prut et al. 1998). The classes of precisely timed spike patterns we examined were 1) the triplets and 2) the quadruplets that repeat within single neuronal responses (see Fig. 1) and 3) the total number of triplets found across

different responses regardless of how many times the pattern repeated within a single response. The data were collected from 32 LGN neurons and 19 supragranular complex cells in V1 of an awake fixating monkey.

We begin by examining the number of precisely timed repeating triplets independent of stimulus and the particular pattern type. At least 60% of the spikes in the excitatory responses of both LGN and V1 (Fig. 4) neurons are associated with repeating triplets. Previous work (Abeles and Gerstein 1988) suggests there will be a strong, nonlinear relationship between the mean number of repeating triplets within individual responses and the spike count, as we find in both LGN and V1 neuronal responses (Fig. 5).

Information carried by precisely timed spike patterns

The strong dependency of the number of repeating triplets on the number of spikes within a response does not, of course, preclude the possibility that the precisely timed patterns carry information that is unavailable from spike count because the number of precisely timed patterns could also vary with stimulus condition. We therefore directly measured the information carried by 1) the spike count, 2) the number of repeating triplets, and 3) the dual code of spike count and number of repeating triplets together.

To calculate the stimulus-related information (Eq. 1) we require a measure of the precisely timed spike patterns in each trial. We used the number of spikes in each trial as one response measure and the number of repeating triplets in each trial as another response measure. The information carried by spike count alone was on average >2.5 times the amount of information carried by the number of precisely timed repeating triplets [Fig. 6, left and middle bars, LGN: 0.36 ± 0.047 (mean \pm SE) vs. 0.14 ± 0.03 ; V1: 0.41 ± 0.023 vs. 0.15 ± 0.013]. Inclusion of the number of repeating triplets with spike count to form a dual code with two numbers (spike count and

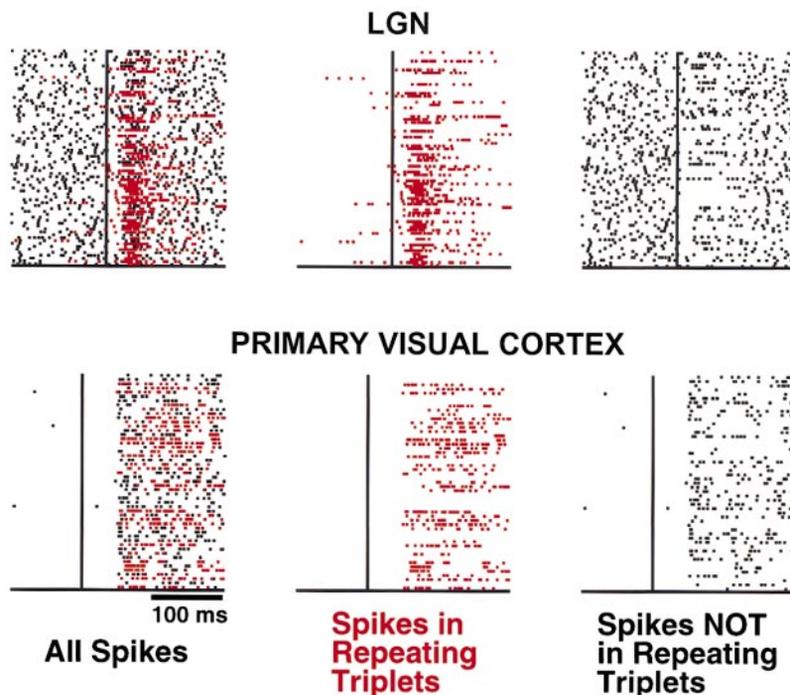


FIG. 4. Rastergram displays of individual responses of cells. *Left rastergram*: all spikes (black and red vertical ticks) in each trial (horizontal trace). *Middle rastergram*: only those spikes associated with repeating triplets (red ticks). *Right rastergram*: same trials after removal of the spikes from repeating triplets. Vertical bar in each indicates stimulus onset. *Top*: responses of an LGN neuron to a bright square covering the excitatory receptive field. Almost every spike associated with the excitatory response is also associated with a repeating triplet, yet very few repeating triplets are present before response onset. *Bottom*: responses of a V1 neuron. Note the high variability in the number of spikes associated with repeating triplets for different trials, ranging from none to all spikes in a trial.

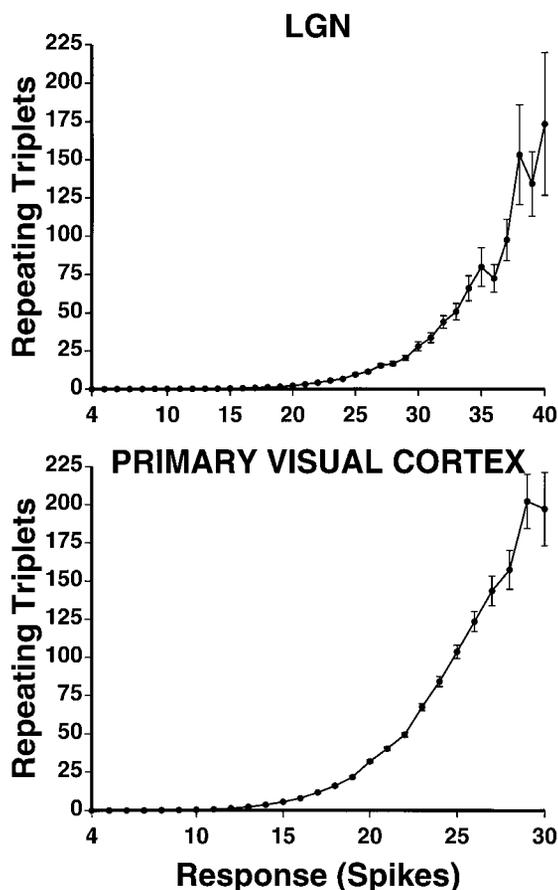


FIG. 5. Number of repeating triplets depends on spike count. Number of repeating triplets (mean \pm SE) in neuronal responses is plotted as a function of the number of spikes within the responses. Note the nonlinear relationship between mean number of repeating triplets and the response. *Top*: LGN data. *Bottom*: V1 data.

number of repeating triplets) associated with each trial provided no additional information about which stimulus was present beyond that available from spike count (left and right histogram bars of Fig. 6, LGN: 0.36 ± 0.047 vs. 0.36 ± 0.047 ; V1: 0.41 ± 0.023 vs. 0.41 ± 0.022), indicating that the stimulus-related information available from the number of repeating triplets is completely redundant with the information from spike count for both LGN and V1 neurons. We present only the results from the analysis of repeating triplets but note that qualitatively the same results were obtained with repeating quadruplets; the information carried by repeating quadruplets is much less than and completely redundant with the information carried by spike count.

Models predicting repeating spike patterns

The redundancy of the information from the number of repeating triplets with the information from spike count suggests that the distribution of the numbers of precisely timed (1-ms accuracy) spike patterns is directly related to slow variations (>20 -ms accuracy) in firing rate as characterized by the spike density function and spike count. To investigate whether the stimulus-elicited repeating triplets are predictable from the stimulus-elicited spike count we examined models of the relationship of the numbers and types of precisely timed spike

patterns with the spike count and slow variation in firing rate. Table 1 shows the relevant properties of the models we used to investigate the expected numbers of repeating triplets expected by chance.

The uniform Poisson and NHPP models both assume that the spike counts follow a Poisson distribution. A Poisson distribution of spike count has a variance numerically equal to the mean. In our data the variance of the LGN and striate neuronal responses was greater than the mean (Fig. 7). On average the Fano factor (variance/mean) was 1.44 ± 0.03 for the responses of the LGN neurons and 2.90 ± 0.03 for the V1 neurons, indicating the spike count distributions were not Poisson (Snedecor and Cochran 1980). These values are similar to those reported for the spike count distribution from recordings in LGN, V1, TE, MT, parietal, and frontal areas (Bradley et al. 1987; Buracas et al. 1998; Gershon et al. 1998; Levine and Troy 1986; Mechler et al. 1998; Reich et al. 1997; Tolhurst et al. 1983; Victor and Purpura 1996; Vogels et al. 1989).

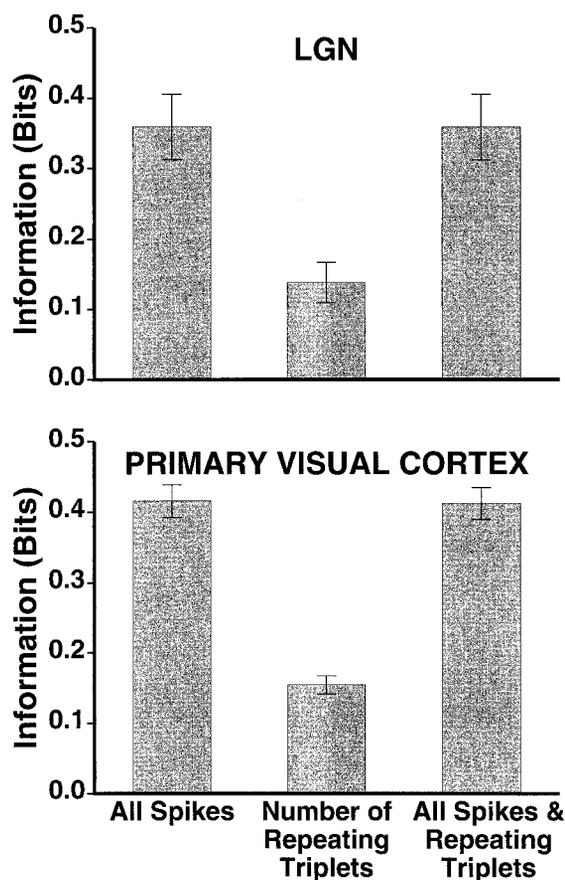


FIG. 6. Information measures from the number of repeating triplets are inherent in the total spike count. Three measures of the mean information are shown. Information from total spike count (All Spikes) is higher than the information from the number of repeating triplets (Number of Repeating Triplets). If the presence of repeating triplets were independent of the first-order statistics of the spike trains then the information from Spikes + Triplets would be the sum of the information from All Spikes and the information from the Number of Repeating Triplets. The information from a joint code containing all spikes and the number of triplets (Spikes + Triplets) is no different from the information from the spike count (All Spikes). *Top*: LGN data, ANOVA: effect of code $F_{[2,42]} = 56.1$, $P < 0.0005$. *Bottom*: V1 data, ANOVA: effect of code $F_{[2,36]} = 78.5$, $P < 0.0005$.

TABLE 1. Comparison of models used to assess significance of precisely timed spike patterns

Model	Process	PSTH	ISIs	Spike Count Distribution
Uniform Poisson	Uniform rate Poisson process	No	No	No (Poisson)
Shuffled ISI	Shuffle ISI trial by trial	No	Yes	Yes
NHPP	Time-varying Poisson process	Yes	No	No (Poisson)
Spike count matched	As NHPP, but trials selected to have particular spike counts	Yes	Yes	Yes

Three models commonly used to examine the statistical significance of precisely timed spike patterns are listed along with the new spike count-matched model described here. A brief description of the process used to generate the artificial spike trains is given (see text and Fig. 2) along with whether or not the model is constrained to match the peristimulus time histogram (PSTH), the interspike interval (ISI) distribution, and the spike count distribution. Of these models, only the spike count-matched model uses all 3 constraints, and only the spike count-matched model predicts the observed numbers and types of precisely timed spike patterns observed in LGN (lateral geniculate nucleus) and primary visual neural responses. NHPP, nonhomogeneous Poisson process.

Comparison of models with neuronal data

Figure 8 shows the mean number of all types of repeating triplets (intervals $a, b \leq 25$ ms) found in recorded spike trains from the LGN (*top*) and V1 (*bottom*) and the spike trains simulated using the four different models (uniform Poisson, shuffled ISI, NHPP, and spike count-matched models; see INTRODUCTION) (Abeles 1991; Abeles and Gerstein 1988; Abeles et al. 1993; Aertsen et al. 1989; Dayhoff and Gerstein 1983a,b; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Vaadia et al. 1995). The numerical differences between the observed and predicted numbers of repeating triplets from the uniform, shuffled ISI, and NHPP models are small but highly significant ($P \ll 0.0005$). In contrast, the spike count-matched model predicted numbers of repeating triplets that were indistinguishable from those observed in both LGN and V1 data ($P > 0.2$ each comparison). The spike count-matched model also predicted the number of triplets across responses observed in the neural data. The spike count-matched model differs in two ways from previous models in that we matched both the spike count distribution and the influence of the refractory period on the ISIs. The effect on the number of repeating triplets of adjusting the spike count distribution from Poisson (NHPP) to that observed was considerably larger than the effect of adjusting the ISIs (9 times larger with the V1 data).

Previous reports have noted that the occurrence of precisely timed spike patterns varies with stimulus (Abeles 1991; Abeles et al. 1993; Engel et al. 1992; Prut et al. 1998; Riehle et al. 1997; Singer and Gray 1995; Vaadia et al. 1995). We also examined the number of precisely timed spike patterns found in the responses of LGN and V1 neurons to individual stimuli. Each point in Fig. 9 shows the number of repeating triplets measured (in the neuronal data) and predicted (by the spike count-matched model) in the responses to one stimulus of one neuron. The figure shows the data from all neurons. Figure 9 shows that the regression line of the number of repeating

triplets predicted by the spike count-matched model on the observed number was statistically indistinguishable from equality (the regression lines are hidden by the equality line). To assess the accuracy of the NHPP model we calculated the ratio of the number of repeating triplets from the model to that observed in the neural data. For both LGN and V1 data sets the spike count-matched model predicted the numbers of repeating triplets more accurately than the NHPP model (Fig. 9, *insets*). The spike count-matched model also accurately predicted the number of repeating quadruplets (not shown) within the responses of LGN (intercept = 0.005, slope = 1.12, $R^2 = 0.94$) and V1 neurons (intercept = -0.002, slope = 0.998, $R^2 = 0.95$).

Finally, to investigate the possibility that particular patterns in the responses to individual stimuli may occur more frequently than expected by chance (Abeles 1991; Abeles et al. 1993; Prut et al. 1998; Riehle et al. 1997; Vaadia et al. 1995) we examined the numbers of each repeating triplet type found in the responses and compared the results to the numbers predicted by the spike count-matched model. We counted the number of times each of the 625 types of repeating triplet occurred in the neuronal and simulated data for each stimulus. Figure 10 shows a high ridge of repeating triplets with equal

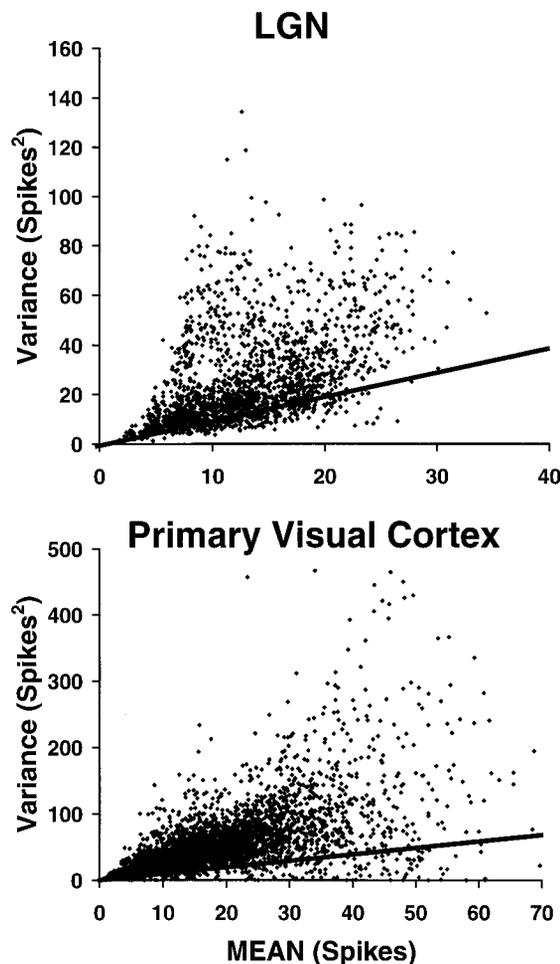


FIG. 7. Responses of LGN and V1 neurons are not Poisson distributed. Scatter plots of the response variance against the mean response to each stimulus of each cell for the neural data. The thick line represents equality ($\mu = \sigma^2$), a property of Poisson distributions. Most points lie above the equality line for both the LGN (*top*) and V1 data (*bottom*).

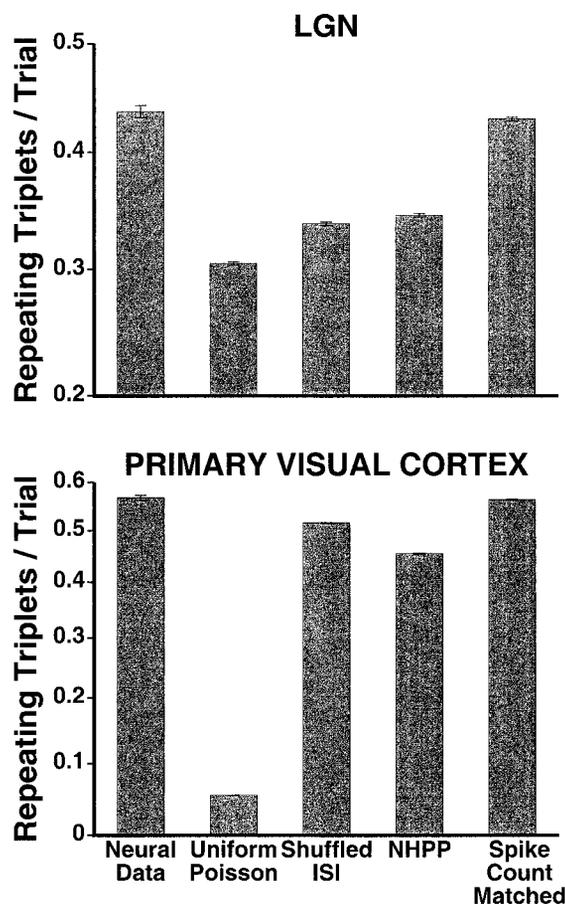


FIG. 8. Comparison of the number of repeating triplets found in neuronal and modeled data. The mean number of repeating triplets per trial found in the spike trains from the neuronal and modeled data sets is shown on a logarithmic scale. *Top*: repeating triplets from LGN neuronal and modeled responses. Modeled data sets contain 20 times more trials than the LGN data sets. Post hoc testing revealed that the spike count-matched model gave results that were statistically indistinguishable from the LGN data ($P > 0.1$). The other models predicted fewer repeating triplets than seen in the LGN data ($P < 0.01$ each comparison). ANOVA: overall effect of source of triplets $F_{[4,124]} = 13.8$, $P < 0.00005$. Effect of cell: $F_{[31,124]} = 12,775.0$, $P < 0.00005$. Interactions: $F_{[124,2069640]} = 84.4$, $P < 0.00005$. *Bottom*: repeating triplets from V1 neuronal and modeled responses. Modeled data sets contain 20 times more trials than the V1 data sets. Post hoc testing revealed that the spike count-matched model gave results that were statistically indistinguishable from the V1 data ($P > 0.1$). Other models predicted fewer repeating triplets than seen in the V1 data ($P < 0.01$ each comparison). ANOVA: overall effect of source of triplets $F_{[4,72]} = 32.2$, $P < 0.00005$. Effect of cell: $F_{[18,7785787]} = 45,800.6$, $P < 0.00005$. Interactions: $F_{[72,7785787]} = 2,200$, $P < 0.00005$.

intervals (diagonal) and relatively few repeating triplets with a short interval (< 2 ms) in both the neuronal and simulated data sets. The large proportion of triplets with equal intervals is expected. Given a single triplet with equal intervals, for example, 5 and 5 ms, only one additional spike with the same interval (continuing the example, 5 ms) forms a second triplet of the same type, that is, a repeating triplet. All other triplet types require at least two spikes at particular times before forming a repeating triplet (see Fig. 1). The refractory period reduces the number of repeating spike patterns containing intervals of < 2 ms. For the same reasons, the number of repeating quadruplets with equal intervals was larger than that of the other quadruplet types, and the number of repeating quadruplets with very short (< 2 ms) intervals was small in

both the modeled and the neuronal data. Not surprisingly, very similar distributions of triplet types were observed for the total numbers of triplets across all responses.

Estimating significance of particular spike patterns

To estimate the statistical significance of the numbers of repeating triplets found in the neuronal data, a Monte Carlo approach was used. For each cell and each stimulus we generated 10,000 “runs” of the spike count-matched and NHPP models, with each run containing the same number of trials as in the neuronal data set. Figure 11 shows that the spike count-matched model predicts larger numbers and greater variability in the numbers of each repeating triplet type found per trial than is predicted from the NHPP process. The number of each of the 625 repeating pattern types was noted in each of the 10,000 simulations, giving the predicted distributions of the numbers of each of the individual triplet types. The number of a particular repeating triplet type that could be accepted as occurring by chance was taken to be any number that fell within the 95% confidence limits of the predicted distribution of that repeating triplet type (Fig. 12). The spike count-matched model predicted the number of triplets across responses in addition to the number of repeating triplets within responses (not shown).

The estimation of significant deviations from the expected numbers of individual precisely timed patterns both within and between responses is prone to problems associated with multiple comparisons. Figure 13 illustrates this point for repeating triplets. The large peak found in the responses of one cell to one stimulus indicates that this repeating triplet type (intervals 16;15 ms) occurred more frequently than any other (large peak in Fig. 13, *top graph*). Individual runs of the spike count-matched model also showed particular repeating triplet types with the same high frequency of occurrence (Fig. 13, *bottom graphs*). The peaks from the simulated data were found at a variety of triplet types in different runs (e.g., 9;7, 16;15, 2;2, and 3;6). The large variability of the triplet types arising from the spike count-matched model illustrates the danger of assuming that a single extreme peak in the neuronal data is significant. By accepting the peak in the neuronal data as significant one would be forced to assert that the large peaks in the example simulations, which we know arise from a stochastic process, were also significant. Thus the parsimonious conclusion is that the large peaks in the neuronal data are consistent with a stochastic process.

The average number of significant peaks across stimuli in the neuronal data, as assessed by using the spike count-matched model, was indistinguishable from that expected by chance (31.2 of 625 at the $P = 0.05$ significance level). In contrast, with the NHPP model we would have concluded that many of the neuronal responses contained individual repeating triplet types that occurred more frequently than expected by chance.

DISCUSSION

Summary of results

We examined three forms of previously studied (Abeles 1991; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Prut et al. 1998) precisely timed spike patterns in LGN

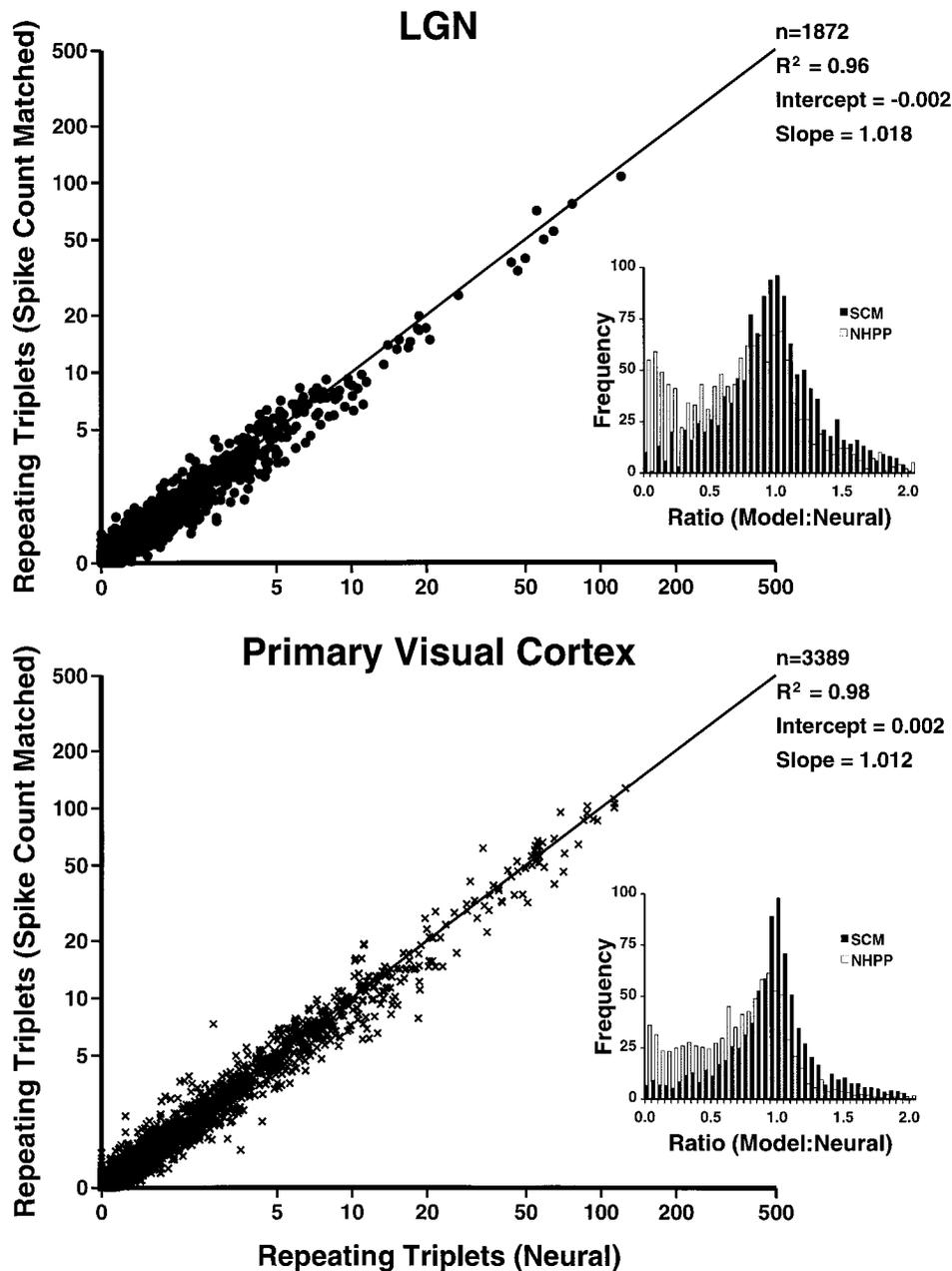


FIG. 9. Spike count-matched model accurately predicts the number of repeating triplets in neuronal data. Scatter plots of the number of repeating triplets from the spike count-matched model against the number of repeating triplets found in the neuronal data on a logarithmic scale are shown. Each point shows the data and prediction from 1 stimulus from 1 neuron. One was added to the number of repeating patterns to allow use of trials where no repeating patterns were present. *Top*: mean number of repeating triplets per trial from the spike count-matched model and LGN neuronal data for each stimulus and each of the 32 cells on a logarithmic scale ($n = 1,872$). Points from the cumulative spike probability function are scattered around the equality line (diagonal), indicating excellent predictive value of the spike count-matched model. *Bottom*: mean number of repeating triplets per trial from the spike count-matched model and V1 neuronal data for each stimulus and each of the 19 cells on a logarithmic scale ($n = 3,389$). Points from the cumulative spike probability function are scattered around the equality line (diagonal), indicating excellent predictive value of the spike count-matched model. *Insets*: frequency plot of the ratio of the number of repeating spike patterns predicted by the spike count-matched model to that seen in the neuronal data. Note the tight distribution of this ratio of ~ 1.0 obtained with the spike count-matched model compared with the flatter distribution extending down to 0.0 from the nonhomogenous Poisson process (NHPP) model for both LGN and V1 data sets.

and V1 neuronal responses, triplets and quadruplets that repeat within single neuronal responses and triplets that repeat across different responses. We used static stimuli that evoked responses ranging from strongly inhibitory to strongly excitatory. Our results were found to apply across all response strengths. Given the large number of precisely timed spike patterns we found, it is not surprising that we find that many ($\sim 60\%$) of the individual spikes are associated with precisely timed spike patterns.

Previous reports have emphasized only those spikes occurring in patterns thought to have been above chance levels (e.g., Abeles 1991; Prut et al. 1998). Had we restricted our analysis to using previous analysis methods we would also have concluded that a small number of spikes was associated with those precisely timed spike patterns occurring above chance levels. However, we stress that the spike count-matched model indi-

cates that the patterns we observed were consistent with a stochastic process.

The large number of stimuli used and the large numbers of precisely timed triplets facilitated information theoretical analysis of the number of precisely timed spike patterns. The analysis showed that the information carried by the total number of repeating precisely timed spike patterns was redundant with that carried by the spike count (Fig. 6). The redundancy of information implies a relationship between the spike count and the distribution of the numbers and types of repeating patterns.

We first compared our data with the predictions from three commonly used models. As found in earlier studies of many brain areas (Abeles 1991; Abeles and Gerstein 1988; Dayhoff and Gerstein 1983a,b; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998) these models predicted significantly fewer repeating patterns than were observed in our data (Fig. 8). Had

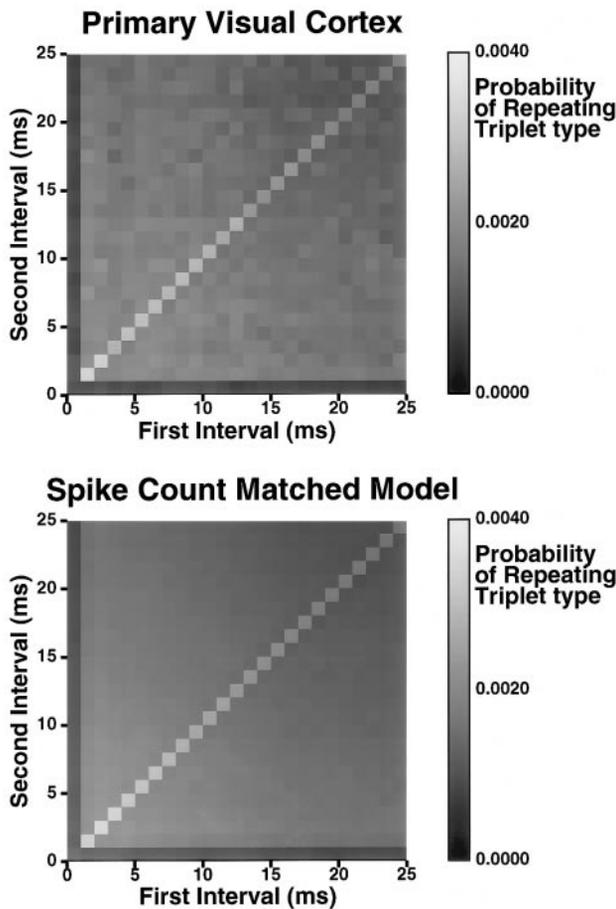


FIG. 10. Comparison of repeating triplet type. Frequency of occurrence of each of the 625 examined types of repeating triplet of the V1 neuronal data and the associated spike count-matched model data. *Top*: probability of each repeating triplet type is shown as a gray scale for the neuronal data (lighter = higher probability). *Bottom*: probability of each repeating type estimated from the simulated spike trains from the spike count-matched model. Note the decreasing probability of triplets with increasing intervals, the relatively high probabilities for triplets with equal intervals (diagonals), and the relatively low probability of triplets with very short (<3 ms) intervals for both the neuronal and modeled data. Modeled data appear smoother (less variable) than the neuronal data because 20 times as many trials were simulated were present in the neuronal data.

we relied on these models we might have postulated a special role for the repeating patterns. Adjusting a previous model (NHPP) by forcing the spike counts and ISIs in the model to match the experimental data (Figs. 2 and 3) demonstrates that a stochastic process can give rise to the fine temporal structures observed here (Figs. 8–13). Note that if the observed distribution of spike counts is truly Poisson, the spike count-matched and NHPP models are identical.

We observed that the mismatching of the ISI distribution had a small but still significant effect on the predicted numbers of precisely timed spike patterns (~10% of the size of mismatching the spike count distribution). Others have also observed a significant effect of changes in the ISI distribution on the precise temporal structure of responses (Berry and Meister 1998; Berry et al. 1997). A previous model that matches both the spike count distribution and the time-varying firing rate but not the ISI distribution does not match the fine temporal structures of V1 responses (Victor and Purpura 1996). The performance of the spike count-

matched model with other types of data, e.g., from rhythmic neurons, bursting neurons, or neurons with a long refractory period and low firing rates, has not yet been assessed. Thus the relative importance of the ISI distribution in these situations remains unknown.

The spike count-matched model, which matches the spike count distribution, the ISIs, and the time-varying firing rate, predicts the distribution of each particular triplet type found in the data (Figs. 8–13). This leads to the conclusion that the observed numbers of repeating triplets in the neuronal data are consistent with chance; this is very different from the conclusion that would be reached with Poisson-based models.

Firing rate profile, response variance, and precisely timed spike patterns

The number of precisely timed triplets and quadruplets increases in a roughly combinatorial fashion with the spike count (Abeles and Gerstein 1988). Figure 5 shows that high firing rates are also associated with very large numbers of repeating triplets. The difference between the number of repeating spike patterns associated with high and low response strengths implies that slow variations in firing rate (spike density function) must be incorporated into models used to predict the expected numbers of such patterns (Lestienne and Strehler 1987).

The nonlinear relationship between the number of spikes within a response and the number of repeating triplets (Fig. 5) also offers an intuitive explanation of the differences between the NHPP and spike count-matched model in situations, as here, where the response variance is numerically greater than the response mean (in the following section we give the more

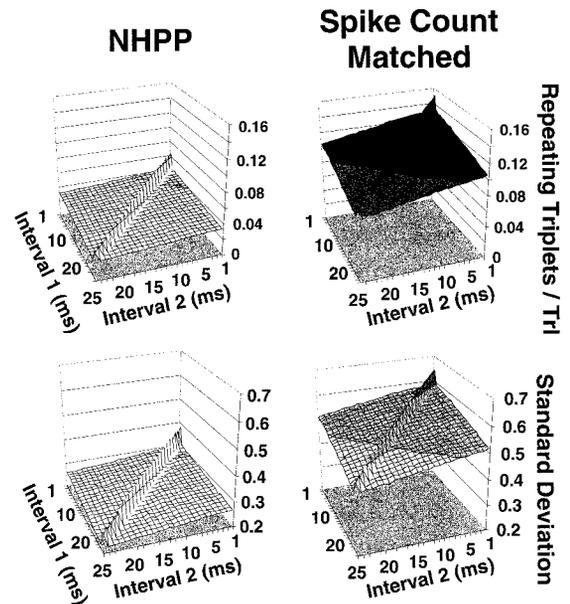


FIG. 11. Predicted mean and variance of repeating triplet types are higher in spike count-matched model than in NHPP model. Mean and variance of the number of each of the 625 examined repeating triplet types predicted by NHPP and spike count-matched models in the responses of a single V1 cell to a single stimulus are shown. *Top left*: mean number of repeating triplets by triplet type predicted by NHPP model. *Top right*: mean number of repeating triplets by triplet type predicted by spike count-matched model. *Bottom left*: SD of the number of repeating triplets by triplet type predicted by NHPP model. *Bottom right*: SD of the number of repeating triplets by triplet type predicted by spike count-matched model.

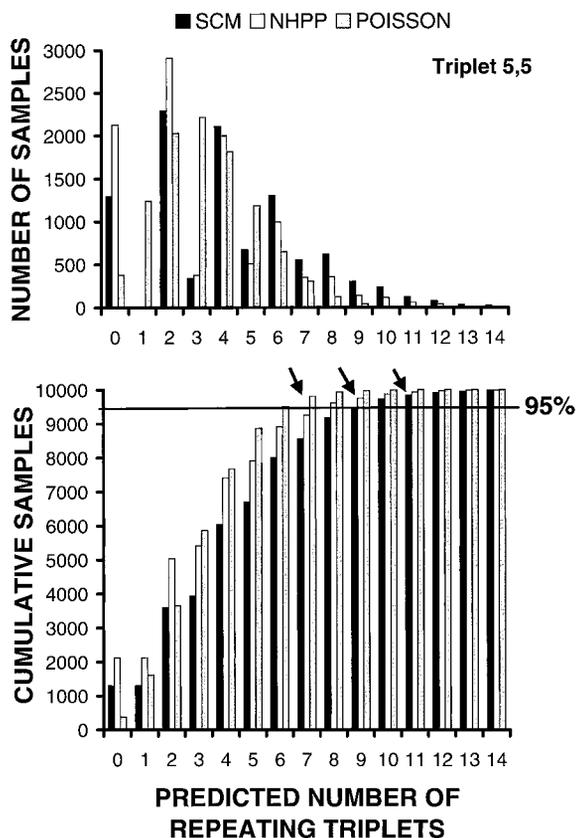


FIG. 12. Determination of significance for 1 repeating triplet type. The method used to determine the distribution of expected numbers of 1 triplet type (intervals 5;5 ms) for the responses of a single V1 neuron to 1 stimulus is shown. *Top*: Monte Carlo simulations of the spike count-matched (SCM) and NHPP models produced a frequency histogram of the number of samples (of 10,000) in which the triplet type 5:5 was observed 0,1,2, . . . ,13,14 times. Poisson distribution based on the mean from the NHPP model is also shown. *Bottom*: cumulative plot of the data in the top panel. Value after the cumulative plot crossed the 95% level (9,500 samples) was taken as the upper limit ($P < 0.05$) for the expected number of repeating triplets of type 5:5 to occur by chance (Poisson distribution = 7; NHPP = 9; SCM = 11).

formal and general case). Changes in the number of simulated trials with low spike counts will have little effect on the expected number of precisely timed spike patterns because low spike counts are associated with relatively few precisely timed spike patterns. The nonlinearity means, however, that the predicted number of precisely timed patterns is underestimated because high spike counts are associated with very large numbers of such patterns. Thus the expected number of precisely timed spike patterns is very sensitive to the distribution of the spike count.

Dependency of repeating patterns on spike count distribution

Here we show that, by necessity, the number of precisely timed spike patterns is critically dependent on the distribution of the trial-by-trial spike count. We stress at the outset that the following argument applies no matter what the mean firing rate; the dependency can be shown from consideration of the spike count distribution, not the spike counts per se. Furthermore, the argument applies to spike count distributions with small or large variability.

Precisely timed patterns of spikes reflect temporal relation-

ships or correlation within and between responses. At the temporal resolution we used (1 ms), responses can be described as binary events (spike or not) with a low probability of a spike occurring. If the small time bins within a response are independent, the mean and variance of spike count over extended periods are simply the sum of the means and sum of variances of the short interval bins. As small time bins have a Poisson distribution of spike count, a response with independent bins also has a Poisson distribution of spike count. Whenever the observed spike count distribution over homogenous repeated trials deviates from a Poisson distribution there must be co-variation between periods of a response because the individual small bins cannot be independent. Thus, because the spike count-matched model used a different spike count distribution than that used in the NHPP model, the numbers of precisely timed spike patterns must be different between these two models.

The dependency of the internal structures of responses applies to deviations from a Poisson distribution. It is insufficient to show that the variance is numerically equal to the mean because distributions that are not Poisson can have this property. The NHPP model, by definition, gives rise to simulated responses with numerically equal mean and variance of spike

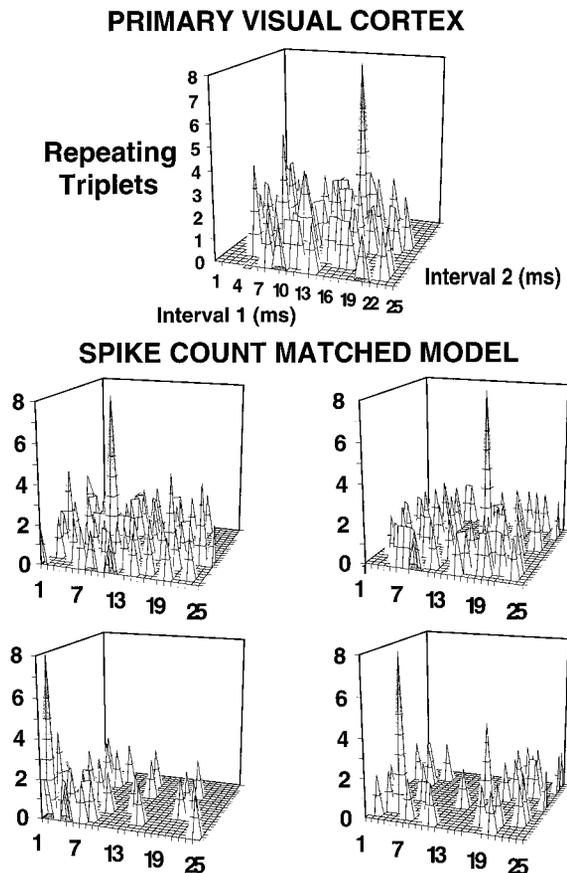


FIG. 13. Spike count-matched model predicts large variability in the number of particular repeating triplet types. Distributions of each repeating triplet type show that the spike count-matched model matches the neuronal data including the occasional large numbers of particular triplet types. *Top*: number of times each triplet type, defined by the first and second intervals, was found in the responses of 1 striate cortical neuron to 1 stimulus. *Bottom*: distributions of expected numbers of repeating triplets from 4 runs of the spike count-matched model. Model shows large variability in the numbers of particular repeating triplet types from run to run.

count. We note that non-Poisson distributions of spike count have been reported in responses of neurons in the retina, LGN, V1, TE, and parietal and frontal lobes (Baddeley et al. 1997; Berry and Meister 1998; Berry et al. 1997; Bradley et al. 1987; Britten et al. 1997; Buracas et al. 1998; Gershon et al. 1998; Lee et al. 1998; Levine and Troy 1986; Reich et al. 1997; Snowden et al. 1992; Tolhurst et al. 1983; Victor and Purpura 1996; Vogels et al. 1989). Indeed all the reports of which we are aware show that the spike count distribution is different from a Poisson distribution, indicating that the NHPP model will necessarily misestimate the expected numbers of precisely timed spike patterns for all these brain areas.

Precision of temporal codes

Reports on other systems, most notably the auditory systems of the owl and bat and the motion system of the fly, have shown that the precise times of individual spikes are directly related to the stimulus (de Ruyter van Steveninck and Bialek 1988; Ferragamo et al. 1998; Olsen and Suga 1991; Suga 1989; Sullivan and Konishi 1984; Takahashi and Konishi 1986; Takahashi et al. 1989). We have examined the potential role of precisely timed patterns of spikes in information coding of static stimuli, not the role of the precise times of individual spikes to rapidly changing or moving stimuli (Buracas et al. 1998; de Ruyter van Steveninck and Bialek 1988; Rieke et al. 1996).

In the past it has been shown that there is information in the coarse (<30-Hz bandwidth) temporal variation of a response that is unavailable from the spike count alone (Eskandar et al. 1992a,b; Heller et al. 1995; McClurkin et al. 1991a–c; Optican and Richmond 1987; Richmond and Optican 1990; Richmond et al. 1987, 1990; Tovee et al. 1993). These new results (~1 KHz bandwidth) do not affect those conclusions because of the difference in the precision of the proposed codes. Although we do not know the temporal precision of mechanisms used to decode the information contained within responses, that the precisely timed spike patterns are predictable from spike count and firing rate profile shows that information unrelated to spike count cannot be contained by the precisely timed spike patterns we observed.

Precisely timed spike patterns in single and multiple neuronal spike trains

We have considered the fine temporal structure of the responses of single neurons. Many reports of precisely timed spike patterns have found that the numbers of precisely timed repeating patterns of spikes found between the responses of different neurons also exceed the number predicted by NHPP-based models (Abeles and Gerstein 1998; Abeles et al. 1993; Aertsen et al. 1989; Riehle et al. 1997; Vaadia et al. 1995). The results presented here show that deviations of the spike count distribution from a strict Poisson distribution will necessarily introduce temporal correlation into the responses of the individual neurons. These temporal correlation structures will appear as covariation between the probabilities of spikes occurring between different time bins. The expected numbers of precisely timed spikes between responses of different neurons are generally estimated by cross-multiplication of probabilities of a spike occurring in individual bins in the responses of the

different neurons (Abeles and Gerstein 1988; Aertsen et al. 1989; Vaadia et al. 1995). The estimated cross-product probability will therefore necessarily be influenced by covariation between the bins of the responses of the individual neurons. Thus it is critical to use the correct spike count distribution to predict the expected numbers of precisely timed spike patterns across neurons just as it is within single neuronal responses.

Information processing and information transmission

We are concerned here only with the information content of the neuronal responses (information encoding), not the mechanisms by which the information may be transferred (information transmission). Exquisite arrangements of synapses (Thomson and Deuchars 1994) and complex structures of feedforward and feedback inputs (Carr and Konishi 1988, 1990) suggest that precisely timed spikes, especially synchronous volleys of spikes, could have enhanced effects on postsynaptic cells compared with temporally disjoint spikes (Douglas et al. 1991; Gochin et al. 1991; Softky 1994; Softky and Koch 1993). Although it is possible that mechanisms exist that preferentially utilize precisely timed patterns, we stress that such mechanisms can only provide an alternative for conveying the same information (at a lower rate, Fig. 6) as that available from the spike count if, as in LGN and V1 neuronal responses reported here, the fine temporal structure is a consequence of coarse temporal measures.

CONCLUSIONS

Although mechanisms may be identified that impose and maintain exact relations among interspike intervals, it is critical to identify the simplest models consistent with observed data. In that vein, we have reported here that a simple stochastic model predicts the numbers and types of repeating patterns in our data without needing to invoke a specific mechanism to establish the observed relationships among spike times. Previous studies have frequently assumed a Poisson distribution of spike count (Abeles and Gerstein 1988; Abeles et al. 1993; Aertsen et al. 1989; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Prut et al. 1998; Riehle et al. 1997; Vaadia et al. 1995). This study has shown that changing the spike count distribution (from Poisson to observed) affects the predicted numbers and types and therefore the interpretation of precisely timed patterns. We conclude that the exactly timed patterns seen here are directly related to the coarse (<30-Hz bandwidth) firing rate modulation and the spike count distribution. The spike count-matched model requires only enough data to estimate the firing rate profile to determine the numbers and types of precisely timed spikes expected by chance. Thus it potentially provides a straightforward method of testing, for example, the consistency between precisely timed patterns generated by a biophysical model and the distribution of precisely timed patterns that can be inferred with the matched model from a small number of experimental trials.

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