



## THE SIGNIFICANCE OF PRECISELY REPLICATING PATTERNS IN MAMMALIAN CNS SPIKE TRAINS

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**Abstract**—Neuronal spike trains from both single and multi-unit recordings often contain patterns such as doublets and triplets of spikes that precisely replicate themselves at a later time. The presence of such precisely replicating patterns can still be detected when the tolerance on interval replication is shortened to a fraction of a millisecond. In this context we examine here data taken from various parts of the central nervous systems of anesthetized rats, cats and monkeys. The relative abundance of replicating triplets varies from centre to centre, and is nearly always significantly greater than obtained in Monte-Carlo simulations of either a Poisson-like process or a renewal process having the same interspike interval distribution as the neuronal data. However, a remarkable exception is found in the activity of retinal ganglion cells. Significant deviations were found in the primary visual cortex and, even more so, in the lateral geniculate body and the mitral cells of the olfactory bulb. Using a fixed tolerance for the replication of intervals (0.5 ms) it is usually observed that replicating patterns are produced in excess (with respect to renewal process models) mostly in low firing rate episodes ( $\leq 100$  Hz). However, using a tolerance that varies in direct proportion to the mean interval (i.e. as the reciprocal of the firing rate), one generally observes that replicating triplets occur with higher than expected frequency in comparable proportions at all firing rates. This observation suggests the existence of a scale invariance principle in these phenomena with respect to certain neuronal codes. In order to decrease the influence of the estimated neuronal firing rate on the results of the comparisons, we computed also the ratio NT2/ND3, of the number of replicating triplets to the number of doublets replicating three times [Lestienne R. (1994) *Proc. Soc. Neurosci.* **20**, 22; Lestienne R. (1996) *Biol. Cybern.* **74**, 55–61], using both a fixed or a variable tolerance. In spike trains obeying a Poisson process, NT2/ND3 ratios should be nearly independent of the frequency, especially when using a variable tolerance. These studies supported previous results: significant deviations from the models are found in all the spike trains examined, except in the case of retinal ganglion cells, and the most significant deviations are found in recordings from the lateral geniculate nucleus and the mitral cells of the olfactory bulb. Removing spikes that belong to bursts having large “Poisson surprise” values [Legéndy C. R. and Saleman M. (1985) *J. Neurophysiol.* **53**, 926–939] (except the very first spike of the burst) significantly decreases NT2/ND3 ratios in the record from the lateral geniculate nucleus, suggesting that in this case bursty episodes greatly contribute to the production of replicating patterns, but such a removal does not affect results from the piriform record. Finally, in both the lateral geniculate nucleus and in the mitral cells of the olfactory bulb records, perturbing the timing of spikes by applying to interspike intervals small jitters of uniform probability density with amplitude up to 3 ms, very significantly decrease NT2/ND3 ratios in these centres, but does not change much the NT2/ND3 ratios in other neuronal recordings.

Implications of these findings for a possible role of precisely replicating patterns in temporal coding of neuronal information is discussed, as well as possible mechanisms for their production. © 1997 IBRO. Published by Elsevier Science Ltd.

**Key words:** triplets, repeating patterns, intervals, temporal coding.

In recent years, much attention has been paid to insufficiencies in the classical model of an integrate and fire neuron,<sup>16,29,30</sup> whereby dendritic fields of neurons passively collect excitatory postsynaptic potentials and inhibitory postsynaptic potentials (IPSPs), summing them algebraically and emitting action potentials when the summated voltage crosses some threshold. Such a model could often not account for the variability of spikes,<sup>44</sup> and was unable

to satisfy the precision required for many sensory systems, from the sonar of the bat to human vision (for a review, see Ref. 7). At the same time, more data were obtained on the existence of active dendritic computation,<sup>31,45</sup> and  $\text{Ca}^{2+}$  spikes in dendritic arborizations were shown to take place to a much larger extent than was previously thought.<sup>20</sup> More recently, metric space techniques have been devised to quantify the information content of spike trains.<sup>55</sup>

The existence of precise temporal organization in spike trains in the form of precisely replicating patterns does not seem as surprising as a decade earlier.<sup>3,13,48</sup> These can be interpreted as a sign that, far from being purely stochastic, neurons embedded

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in neuronal networks and processing sensory information carry information in the details of their spike sequences, not only in the low frequency domain (as first demonstrated several years ago by B.J. Richmond *et al.*,<sup>39</sup> using principal component techniques, and more recently confirmed by Victor and Purpura,<sup>55</sup> using metric space techniques), but also in much higher frequency bands. In some cases they most probably also imply that a neuron has received, at different times, the same sequences of inputs, and this is suggestive of possible repeated excitations in the very same networks of neurons. For example, a neuron could receive several repetitions of essentially the same excitatory synaptic input sequence on its soma and dendrites, leading to approximate repetitions of the input current and hence emit the same pattern of spikes several times. Another example is provided by specific conductance mechanisms, which when activated can lead to bursts or other specific spike sequences.

However, several questions are raised by the very existence of repeated neuronal repeated firing patterns. It is difficult to speculate confidently on their function, even though in the frontal cortex a correlation between their frequency and attention in a goal directed motion had been reported.<sup>54</sup> We re-examine here the question of their production: are such replicating patterns produced by special mechanisms that ensure timing of spikes at a sub-millisecond precision, as was earlier envisaged,<sup>27</sup> or is their presence due to general, statistical and electrophysiological mechanisms that make spike trains depart from, for example, Poisson-like renewal processes? To get new insights into this issue, we have examined spike trains from various centres of the CNS of animals in different conditions and have assessed their propensity to contain precisely replicating patterns relative to their expected frequency in simple stochastic models (which include appropriate refractory periods). We have also looked for a correlation between this propensity and the presence or not of networks containing inhibitory interneurons, which couple a neuron to its neighbours. Finally, we have assessed whether such temporal organization was robust to jitters in the timing of spikes, in order to see if the patterns were sensitive to small perturbations.

The present study compares the fine temporal organization of single-unit and/or multi-unit recordings from various CNS centres of anaesthetized rats, cats, and monkeys. Our aims here are not only to compare the frequencies of replicating patterns within a given centre with the predictions of certain renewal processes, but also to compare these frequencies in the various nervous system centres.

#### DATA ACQUISITION

All the data taken into consideration here were recorded using a spike discriminator or a threshold

trigger that recorded times of events at a precision of 0.1 ms. In order to accumulate enough statistics to get reliable pictures, not of single neurons whose input/output characteristics may be very special, but of the collective behaviour of neurons in a given area of the brain of animals, we concatenated the various records obtained from the same or different cells of the same area, recorded under the same experimental conditions by the same experimental team. Of course, this may introduce some degree of mixing of responses of cells, for instance cells of different layers in the case of cortical recordings, but all efforts have been made to record only from principal cells and to keep this mixing to a minimum. Thus, the search for replicating patterns was performed in all these records as if they were a single long record, except that of course a break time was introduced between each original record, so as not to mix spikes of different recordings in the analysis.

The data labelled LSUM- and RSUM- were provided by Dr Mukherjee and Prof. Kaplan from Rockefeller University. LSUM- is an aggregate file made of the juxtaposition (one after the other) of 28 recordings from single-units in the lateral geniculate nucleus (LGN). The animal was kept under anaesthesia by perfusion of urethane or pentothal, and its visual system was stimulated using drifting luminous sinusoidal gratings centred on the receptive field of the recorded cell. The total number of spikes in this record was 17061. RSUM- is the aggregate file made of the juxtaposition of files from S-potentials impinging on the same lateral geniculate cells. They therefore represent spike trains emitted by retinal ganglions cells, and are strongly believed to represent single-unit data.<sup>10</sup> The total spike count was 291290 spikes. Details from the preparation and stimulation of the visual system of the animal may be found elsewhere.<sup>34</sup>

The data labelled BOCXT- were provided by J.-C. Beaux and Michel Imbert from Institut des Neurosciences in Paris. They represent single-unit spike trains from 82 infragranular layer cells of V1, constituting an extended sample of the data used in an earlier paper.<sup>27</sup> The animal was maintained under anaesthesia and paralysis through injection of Saffan (0.3 ml/kg per h) and flaxedil (10 mg/kg per h). Visual infragranular cortical cells were also stimulated by drifting gratings centred on the receptive field of the cell under study. The total number of spikes in this set was 255883, comprising successive episodes of visual stimulation and rest between stimulations, where the screen was reset to a uniform grey of the same luminance as its mean value over the grating bands. More details on the preparation may be found in Beaux *et al.*<sup>5</sup>

The data labelled RUNSUM consist of single-unit recordings from 18 cells, mostly recorded in the supragranular cells of area 17 from an anaesthetized cat, provided by Ralph Siegel of Rutgers University. The stimulation was provided by luminous bars,

crossing the receptive field of the recorded cell. The total number of spikes is 147527. Details about the preparation of the animal and electrophysiological observations may be found in Siegel.<sup>43</sup>

The data labelled V1MSUM are a juxtaposition of multi-unit recordings from area V1 of an anaesthetized monkey, and V2MSUM is similarly a juxtaposition of multi-unit recordings in V2. Here again the visual stimulation consisted of luminous bars crossing the visual field. Anaesthesia was maintained using nitrous oxide/oxygen (70/30) supplemented with small regular injections of fentanyl (5 µg/kg per h). There were 244990 spikes from 19 cells in V1MSUM, and 211874 spikes from nine cells in V2MSUM. Details about the preparation and electrophysiological observations in this animal can be found in Nowak *et al.*<sup>35,36</sup>

We have gathered in the record K00C-spikes from a single electrode penetration, but as a multi-unit record, taken in the prefrontal cortex of ketamine-anaesthetized Sprague–Dawley rats. These data were taken during simultaneous recording of activity in the prefrontal cortex and in the locus coeruleus, by Anne Hervé-Minvielle and Susan Sara (Paris). Details about this preparation may be found in Sara and Hervé-Minvielle.<sup>40</sup>

Finally, data coming from single-unit recordings of mitral cells in the olfactory bulb of anaesthetized adult Wistar rats were provided by N. Buonviso, M. Chalansonnet and M. Chaput, from Lyon I University. The total number of spikes was 222925, coming from 41 cells. Anaesthesia was provided through injections of equithesin (mixture of pentobarbital sodium and chloral hydrate at 3 ml/kg). Stimulation was provided by exposing the animal to various chemical odorants through a flow dilution olfactometer. The record SUM4TM cumulates records under olfactive stimulation, and records, of about the same length of time, when the olfactometer was not in action. The times of presentation of odours were separately recorded, so that it was easily possible to distinguish between records in the presence or absence of odour stimulation. Furthermore, the respiratory cycles were also monitored and recorded, so that responses to odour could be located within such cycles. We shall not present here the detailed results that follow from such partitions, but simply characterize the global propensity of spike trains from cells of the mitral cells of the olfactory bulb to contain replicating patterns, as in the other examples above. Details about the preparation and electrophysiological observations may be found in Chaput *et al.*<sup>9</sup>

It is to be noticed that our samples all come from anaesthetized animals. Anaesthesia might of course modify to a considerable extent the fine details of neuronal responses to a given stimulation. Replicating patterns have already been observed under a wide range of conditions in awake animal recordings,<sup>17,26,54</sup> but few data on awake animals are

presently available with the sub-millisecond precision required here. We believe that limiting ourselves in the present study to a sample of data from anaesthetized animals, but recorded with a uniform precision of 0.1 ms, would provide us with an interesting and homogeneous basis for comparison.

Finally, let us emphasize once again that because we are combining sequentially records made in various cells of the same area, our purpose is not to characterize a particular neuron, but rather to extract general tendencies in the temporal organization of spike trains emitted by neurons of a particular region of the CNS. Particular studies of individual cells and the modelling of their propensity to emit replicating patterns is the object of another study, currently in progress, and which will be published later.

#### DETECTION OF PRECISELY REPLICATING TRIPLETS

After the discovery that cortical cells emit a large number of precisely repeating patterns, a systematic study<sup>5,23–25,49</sup> of the evoked responses of anaesthetized and awake monkeys and cats has shown that :

- (1) Many individual infragranular visual cortical cells had a large propensity to emit such patterns: precisely repeating doublets, triplets, quadruplets and up to sextuplets have been detected.<sup>23</sup> However, the propensity for the replication of patterns seems to be very labile. Even in an episode where the cell responses to a visual stimulus contained many repeats, the propensity for a cortical cell to emit copies of a given triplet, for instance, usually disappeared within about 25 ms,<sup>23</sup> even though the visual stimulus was presented for a much longer period of time. Then after a fraction of a second, the same neuron usually generated other, quite different repeating patterns.
- (2) Repeated patterns did not occur in isolation. In particular, in the same period of time where one found two copies of a given triplet (the corresponding interspike intervals of which replicate themselves within a given tolerance  $\Delta$ ), one usually found also, in the same train of spikes, several other doublets whose intervals duplicated, to the same tolerance, one or other of the intervals that constitute the recent triplets. That is, if a repeating triplet has constituent successive intervals  $a$  and  $b$ , doublets are often emitted in the vicinity of both copies of the triplet with an interval of either  $a$ ,  $b$ , or  $a+b$  (see Fig. 1). Such accompanying doublets were called “ghost” doublets.<sup>49</sup>

In the analysis of this section we mainly focus our attention on the production of replicating triplets. In order to assess and compare their occurrence among neuronal spike trains emitted by neurons or groups

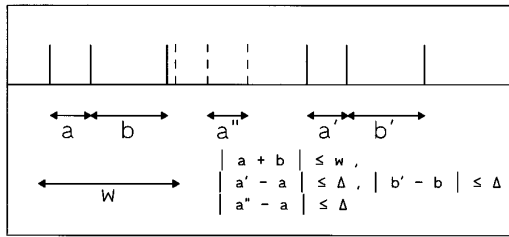


Fig. 1. Definition of replicating patterns. Nine spikes are present in the window of duration  $T=100$  ms here depicted. A triplet with constituent intervals  $a$  and  $b$  (such that the total span  $a+b$  was  $\leq w$ ) was replicated by a triplet whose interspike intervals  $a'$  and  $b'$  reproduced, within the tolerance  $\Delta$ , the intervals of the former triplet. Spikes not belonging to the replicating triplet are shown as dashed lines. Among them, a doublet interval  $a''$  (termed a "ghost doublet") replicated, within the same tolerance, one of the intervals of the replicating triplet.

of neurons in various centres of the CNS, we systematically examined replicating triplets using the two following measures:

A): The number of replicating triplets per spike of the train, counted in successive non-overlapping windows of duration  $T=100$  ms, having a maximum duration (i.e. the time interval between the last and first spikes of the triplet)  $w=25$  ms, and using a uniform tolerance  $\Delta=0.5$  ms for the replication of intervals.

B): The number of replicating triplets per spike of the train, counted in the same manner except that the tolerance  $\Delta$  was frequency dependent. More precisely  $\Delta$  was given by  $\Delta(\text{ms})=5/n$ , where  $n$  is the number of spikes in the window. In other words, the tolerance was inversely proportional to the average firing rate in the window; e.g., at a mean firing rate of 50 Hz,  $\Delta=1$  ms, but at a mean firing rate of 250 Hz,  $\Delta=0.2$  ms.

The choice of a rather narrow time window ( $T=100$  ms) and a correspondingly small time span for the patterns ( $w=25$  ms) was suggested by our previous observation that replicating patterns were most likely to be found within such a temporal framework<sup>23</sup> as was also found to be true in the present investigation. However, we are not implying that larger values of  $w$  and  $T$  would not be appropriate for other preparations, such as those of Abeles<sup>2,3</sup> or Vaadia *et al.*<sup>54</sup>

The number of possible replicating patterns which may occur in a window of fixed time duration depends strongly on the number of spikes in that window, and hence to a large extent on the average firing rate of the neuron. For this reason our measurements are always carried out, and our results always displayed, as a function of the firing rate in spikes per second (sp/s). This parameter was estimated from the count of spikes in the 100 ms window, so that the firing rate was ten times the number of spikes. Note that such estimates suffer from possible errors, due both to non-homogeneity in the spike distribution in the window, and to

statistical fluctuations in the number of spikes in a window. For this reason, the search for relative measures of occurrences of replicating patterns that are as independent as possible of the firing rate, is important.

Results on the detection of replicating triplets in experimental spike train data are displayed as the logarithm of number of replicated triplets detected per spike in Fig. 2a–h, parts A and B, where experimental points are shown as filled triangles, together with their statistical S.D. (no error bar means that statistical deviation is smaller than the size of the triangle).

The number of replicating patterns detected in any experiment can be compared with the results obtained from a model representing a null hypothesis. Although we know that real spike trains rarely have the properties of a renewal process, we seek a set of standard processes to make a comparison. For that purpose only, we systematically used two kinds of Monte-Carlo generated data:

#### Poisson-like model

The times of successive events are generated by drawing successive intervals from an exponential distribution and adding a refractory period  $t_R$  (the value of which is set to 1.5 ms). In other words, if  $t_0$  is the time of a given event, the probability density  $p(t)$  of the time of occurrence of the next event is given by:

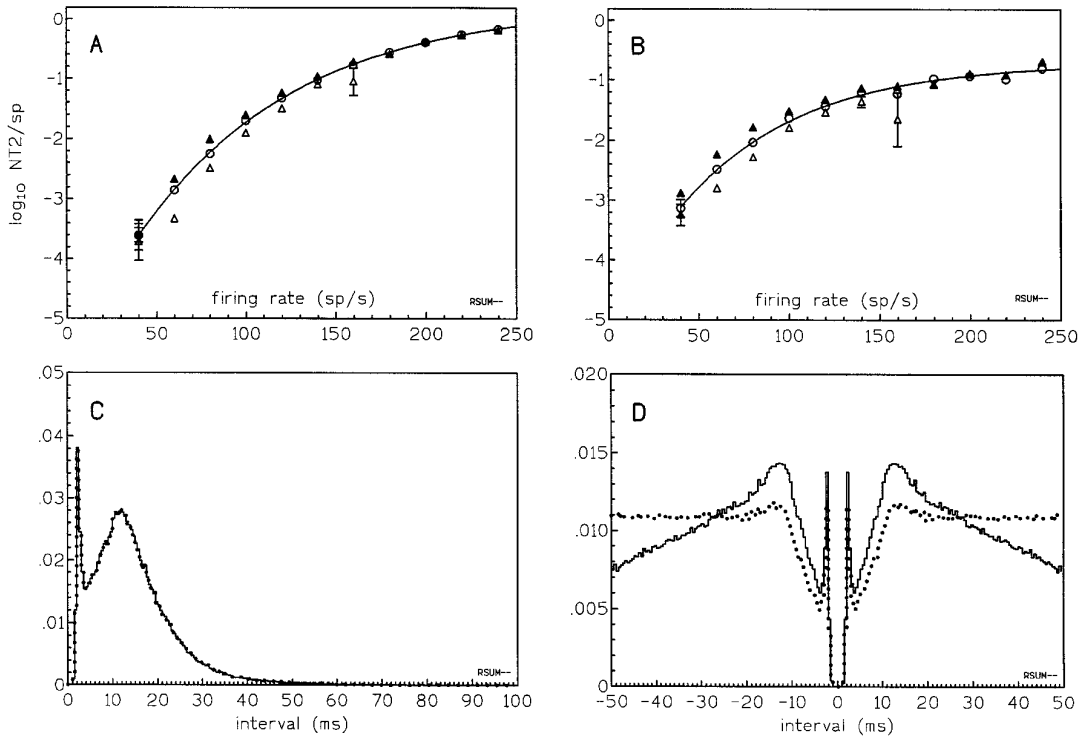
$$p(t) = \begin{cases} 0, & 0 < t - t_0 < t_R \\ \mu \exp[-\mu(t - t_0 - t_R)], & t - t_0 \geq t_R \end{cases}$$

where  $1/\mu + t_R = 1/\lambda$ , and  $\lambda$  is the current average firing rate. Results obtained with this model are displayed as open circles in Fig. 2a, and simply repeated as a continuous line (obtained by analytical fitting through the circles of Fig. 2a) in all subsequent figures.

*Renewal model with the same interval distribution as the physiological data.* The times of successive events are generated by drawing successive intervals according to the time interval histogram (TIH) of real events, as displayed in the lower left of Fig. 2a–h. Results obtained using this model are displayed as open triangles in the figures, whereas physiological data are always represented by filled triangles. The probability density was defined by the TIH, normalized to unity. The bin width of the TIH was 0.5 ms and the probability density was assumed to be uniform within each bin. This procedure is an inevitable consequence of our approximating a supposed underlying continuous distribution of intervals by a discrete one.

It is to be noticed that, although both physiological data and Monte-Carlo generated data according to

**a** NT2/sp - RETINAL GANGLION CELLS (S pot) - Anesth. cat - Rec RSUM



**b** NT2/sp - LATERAL GENICULATE NUCLEUS - Anesth. cat - Rec LSUM--

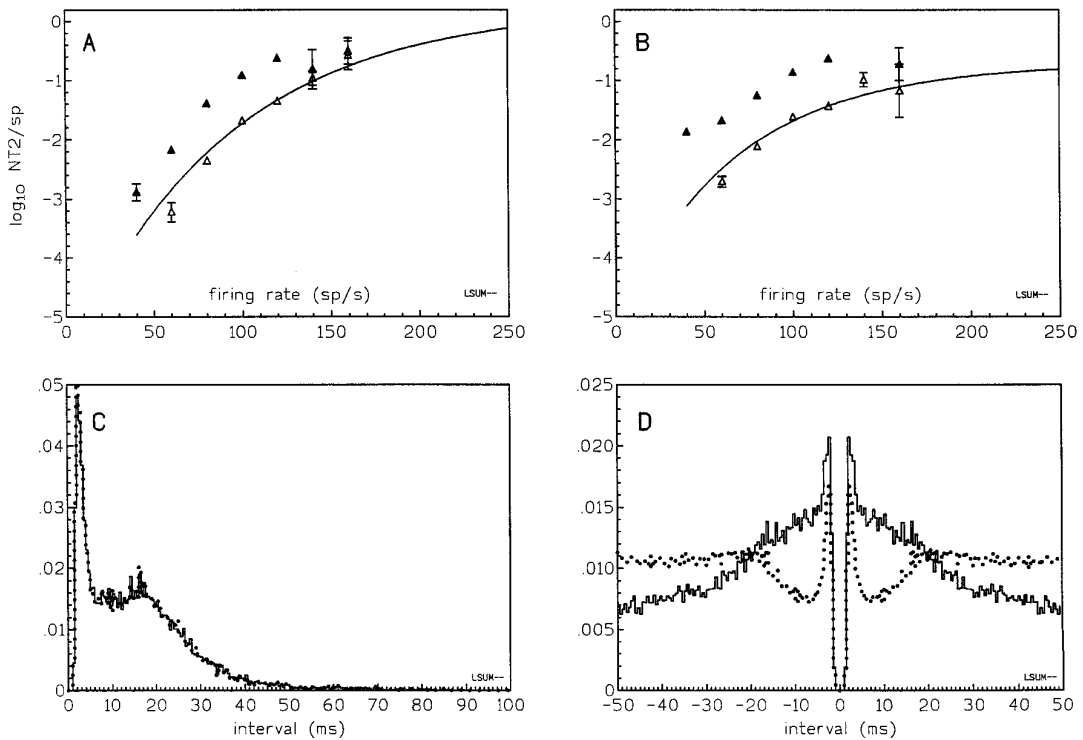


Fig. 2 (a, b).

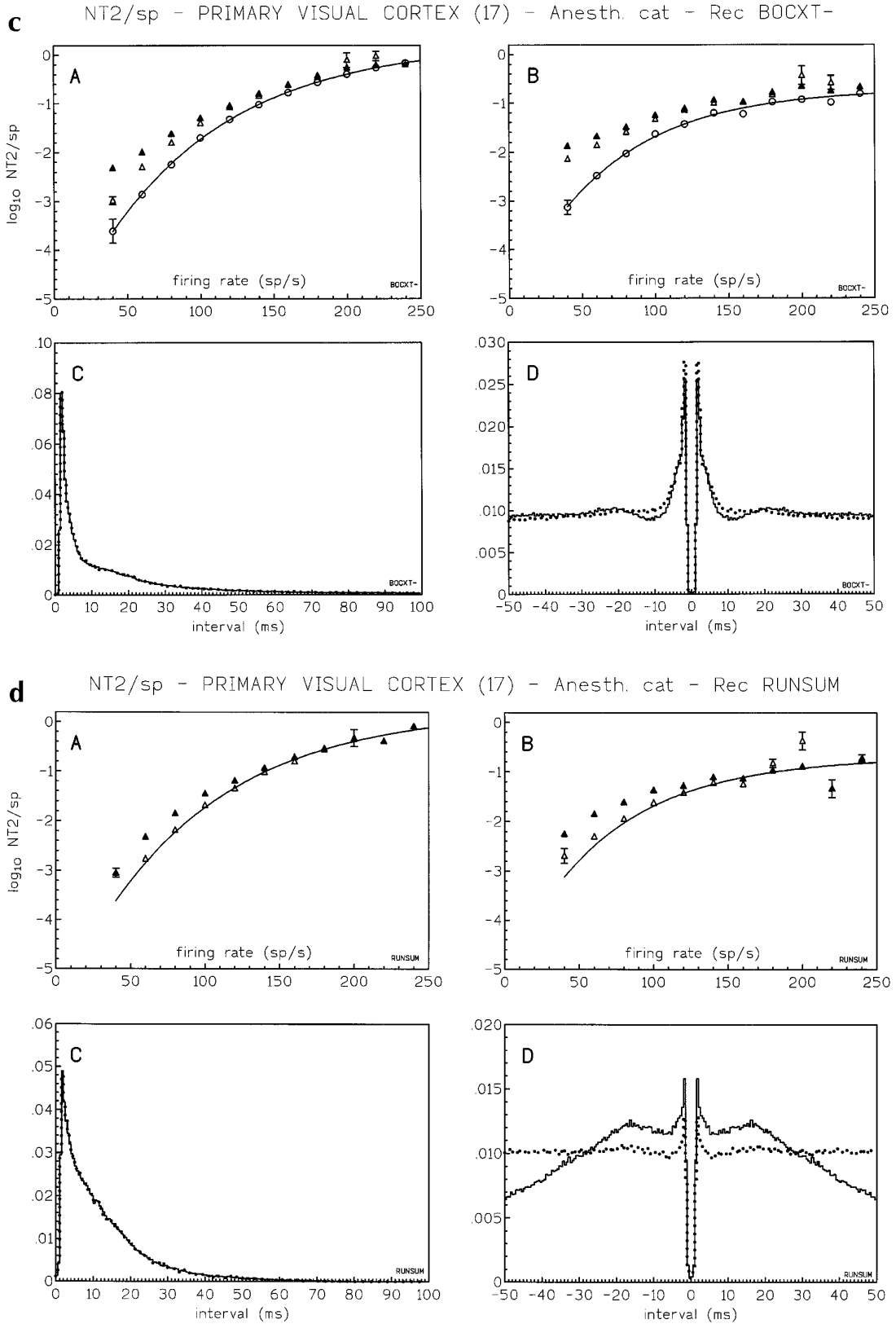


Fig. 2 (c, d).

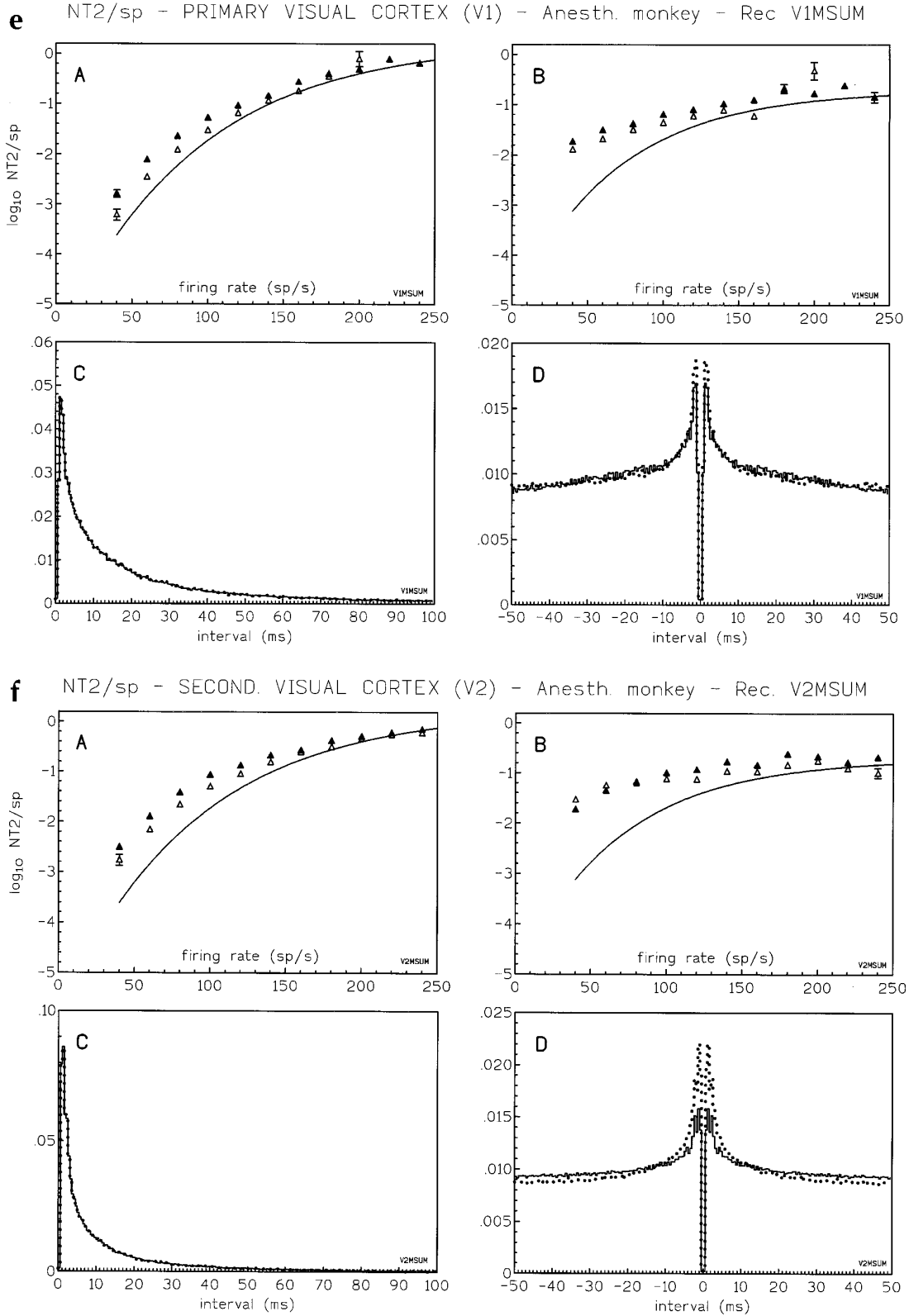


Fig. 2 (e, f).

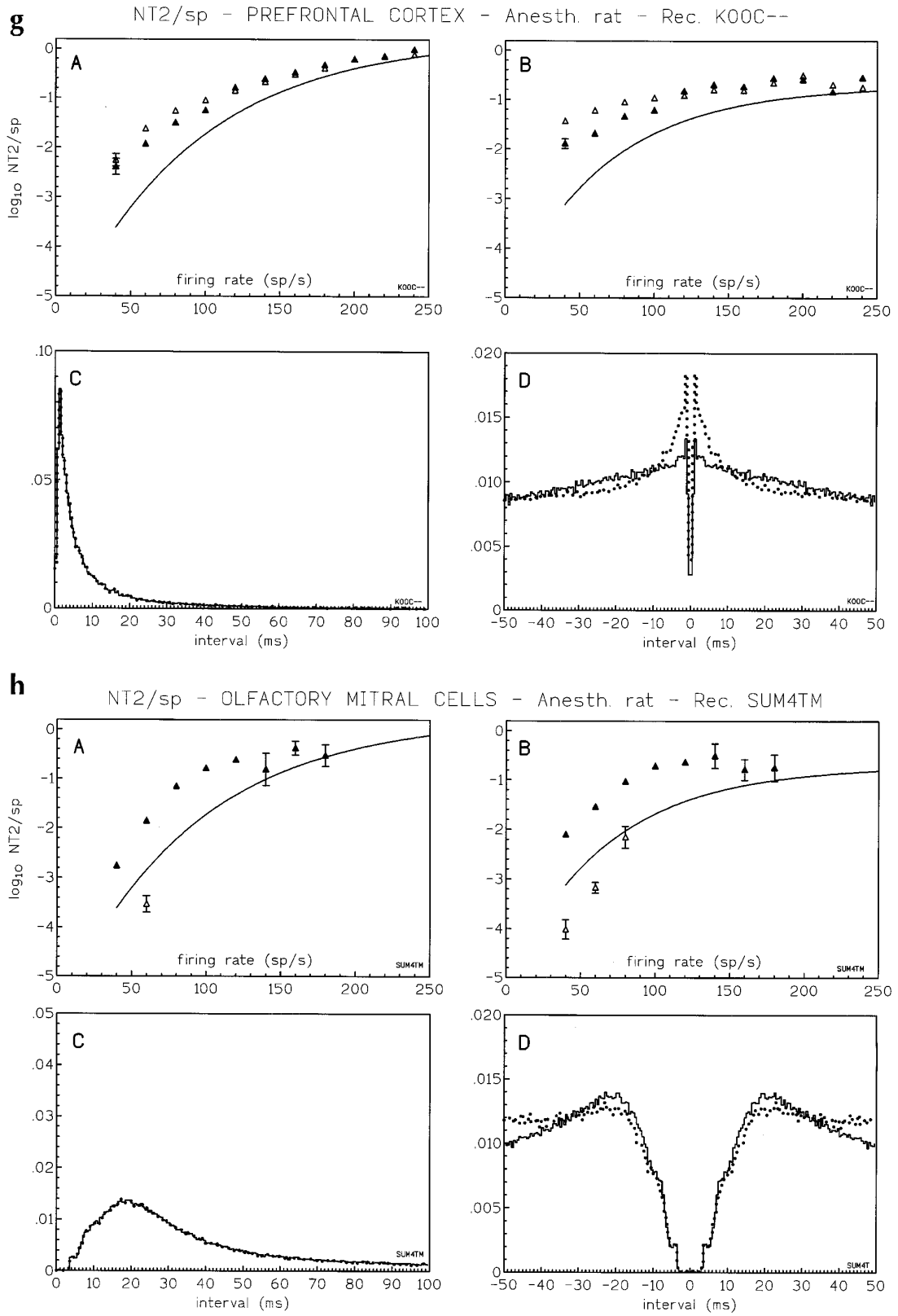


Fig. 2 (g, h).

this model display almost identical TIH (Fig. 2, part C), as expected their autocorrelograms may be quite different (Fig. 2, part D). These differences are manifestations of the non-renewal process nature of spike trains which carry information not only in their mean rate and interval distribution, but also in their temporal correlations.

## RESULTS

Applying the same choices of parameters for all the sets of data at our disposal, that is using a tolerance for replication of 0.5 ms, a maximum span for replicating patterns of 25 ms and a time window of  $T=100$  ms, we observe (Fig. 2a–h, parts A) the presence of a clear excess of replicating triplets, measured by the total number of replicating triplets divided by the total number of spikes ( $NT_2/sp$ ) – both counted in all windows corresponding to the same firing rate bin—with respect to the renewal Poisson-like process (exponential density for intervals with a refractory period of 1.5 ms and the same average frequency) in all centres examined, except in the data from S-potentials (afferent spikes to LGN from retinal ganglion cells).

Whereas in part A of Fig. 2a is shown the result of counting replicating triplets with a uniform tolerance of 0.5 ms, in part B is shown the result of counting them with a frequency-dependent tolerance. Open circles and the curve display the expected frequencies for Poisson-like simulated data, while open triangles display results for a renewal process using the same TIH as the actual spike train in the 0–100 ms range (lower left). The number of replicating triplets detected per spike in the real data is generally consistent with or slightly higher than expectations for a Poisson-like process, which is itself in this case consistently higher than simulations based on the TIH. Note the perfect consistency, by construction, of TIHs of the real data (full line histogram) and the renewal model (dotted line), as opposed to the

differences observed in the autocorrelograms (Fig. 2, part D). Simulated data exhibit in this case a flatter distribution at large intervals and a slightly lower peak at small intervals in the autocorrelogram, as compared with real data.

Figure 2b presents corresponding results for recordings made in the lateral geniculate body of the same animal. The differences from the case of retinal S-potentials are striking. Here the excess of replicating triplets detected is large, with respect to both renewal models, at almost all except perhaps the highest firing rates (140–160 sp/s), and the difference is even clearer when using a tolerance that decreases with the firing rate (part B). Note that in this case the differences observed in the autocorrelogram are even greater than in the previous case, with the absence, in the real data, of a trough between the peak at small intervals and the plateau at large intervals.

Figure 2c shows the results obtained for the sample BOCXT- of recordings under stimulation by drifting gratings, in the infragranular layers of primary visual cortex. While the difference between the number of replicating triplets detected per spike is apparent with respect to both models, the renewal model which uses the actual TIH gives results which clearly depart from the Poisson-like model and come closer to observations on the real data. In this case the autocorrelograms are also very similar. Note also that whereas in the count of replicating triplets using a uniform tolerance of 0.5 ms, the real data come close to the Poisson expectation at high frequencies (part A), when using a variable tolerance, the deviation between the data and the Poisson results is still apparent. The same holds, however, for the renewal model with the same TIH as the spike train.

Figure 2d presents results obtained with recordings in supragranular cells of the primary visual area when the animal was stimulated with drifting light bars. Qualitatively the results are similar to those obtained in the previous case, but with a lower excess of replicating triplets whether using constant or

Fig. 2. a–h) Analysis of the frequency of replicating triplets. Part A. Ordinate:  $\log_{10}$  of the ratio of the number  $NT_2$ , of repeating copies of triplets found in successive windows of width  $T=100$  ms, to the total number of spikes in the corresponding windows. Abscissa: firing rates in the corresponding window, estimated as  $n/T$ , where  $n$  is the number of spikes in the window. Filled triangles: physiological data; open triangles: Monte-Carlo data from a renewal model with successive intervals obeying the TIH distributions shown in part C; open circles: Monte Carlo data from a renewal model (stationary Poisson process) of successive intervals, modified to introduce a refractory period of 1.5 ms and to have the same firing rate; solid curve: an analytical fitting through the open circles. Part B. Same as in parts A, but instead of detecting replicating triplets with a constant tolerance  $\Delta=0.5$  ms, a tolerance decreasing reciprocally with the firing rate  $\lambda$  ( $\Delta=50/\lambda$  ms) was used. Part C. Time Interval Histograms (TIH) for the data (full line histogram) and for the Monte-Carlo data from a renewal model with the experimental TIH (dotted histogram). Part D. Autocorrelograms of the same spike trains, respectively. a) Retinal ganglion cell recordings (S potentials afferent to LGN). b) Lateral geniculate nucleus recordings (single units). c) Primary visual cortex recordings (area 17, single recordings). d) Another example of primary visual cortex, single unit recordings. e) Primary visual cortex recordings from an anaesthetized monkey (multi-unit recordings). f) Secondary visual cortex recordings from the same animal and under the same conditions. g) Recordings from the prefrontal cortex of an anaesthetized rat (multi-unit recordings). h) Single-unit recordings from the mitral cells of the olfactory bulb of anaesthetized, freely breathing rats. As in the other figures, the analysis was performed by concatenating records made successively on several cells of the same structure and several animals (see data acquisition).

variable tolerance. Note that in this case the difference observed between the autocorrelograms of the real data and the renewal process is greater than in the previous case, but not as dramatic as for Fig. 2b (LGN).

Figure 2e shows the results from recordings made in the visual cortex area V1 of the anaesthetized monkey. One can notice the similarity of each of the results for this figure with the corresponding results in Fig. 2c (primary visual cortex of anaesthetized cat). Here again we have a clear excess of replicating patterns relative to the Poisson-like model. In the count of replicating triplets using a fixed value of tolerance (part A), this excess is more pronounced at low frequencies and tends to vanish at high frequencies. Using a variable tolerance (part B) the difference remains discernible at all frequencies except for the last point at 240 sp/s. Deviations from the Poisson model, nearly as large as those observed in the data, are however obtained in the renewal model with the same TIH as the neuron.

The TIH for recordings made in area V2 (Fig. 2f, lower left) seems even more peaked than the corresponding TIH for recordings taken in area V1 (note the change in ordinate scale). Accordingly, the peaks at short intervals in the autocorrelogram (Fig. 2f, lower right) in the renewal simulation (dotted line) are even more pronounced than in the real data, and the excess of replicating triplets, while still present with respect to the Poisson model, has practically disappeared with respect to the renewal process with the neuron's TIH.

The same trend, even more accentuated, is seen in Fig. 2g, where the results of analysis of recordings in multi-unit recordings from the prefrontal cortex of anaesthetized rat are presented. Here the number of replicated triplets in the recordings, although again clearly greater than expected from the Poisson-like model, is less than predicted from the renewal model with the neuron's TIH. Note that, in this figure as in all previous ones, the excess of replicating triplets as compared with the Poisson-like model seems to vanish at high frequencies when the count is made with a fixed tolerance (part A), while it remains large for a much larger range of frequencies when the count is made using a relative tolerance (part B).

Finally, Fig. 2h presents the results for the interesting case of the mitral cells of the olfactory bulb of anaesthetized rats. We observe here a radical change in the TIH distribution. The average frequency of discharge is lower, no spike interval is observed over a wider range of small intervals (up to about 4 ms), and there is no sharp peak in the distribution. Under these circumstances, it is not surprising to see that replicating patterns found in the Monte-Carlo process with the same TIH are rare and their number clearly below the prediction of the Poisson-like model with a refractory period of 1.5 ms. However, the number of replicating triplets found in the data is on average about one order of magnitude greater than

predicted by the latter model, except in the few windows where the firing rate was near or over 150 sp/s. Note also that the autocorrelogram (Fig. 2h, lower right) obtained with real data does not differ widely from that obtained from the renewal process with the neuron's TIH. Except for the absence of horns at short intervals, both autocorrelograms are reminiscent of those observed in Fig. 2a for data on S-potentials in the retina, where few if any excess of replicating patterns were found.

Thus, we have observed that precisely replicating triplets in neuronal records generally exceed in number those that would be expected from random processes of emission of spikes, except in the sensory receptor stage of the visual system (the retina). At the same time, this excess seems to reach a maximum at the LGN in the visual system and at the mitral cells in olfactory system, and then to decline at higher levels. While some excess may be readily accounted for by the sharp peaks present in both the TIH and autocorrelograms, this cannot be the case for the olfactory bulb and, most probably, for the LGN. However, the highly non-linear dependence of the number of replicating triplets on the firing rate may also be a source of distortions in the analysis, which we will now attempt to remedy.

#### RATIOS OF TRIPLETS AND DOUBLETS

One of the main difficulties encountered in the interpretation of the occurrence of replicating patterns resides in the fact that, even if the cell discharges at random according to a Poisson process, the number of copies of replicating patterns expected within a time window  $T$ , varies greatly with the average firing rate of the cell. Using the same notations as above, Abeles and Gerstein<sup>1</sup> have calculated that for a stationary Poisson process, the expected number of patterns repeating themselves  $r$  times in a time window of duration  $T$  is:

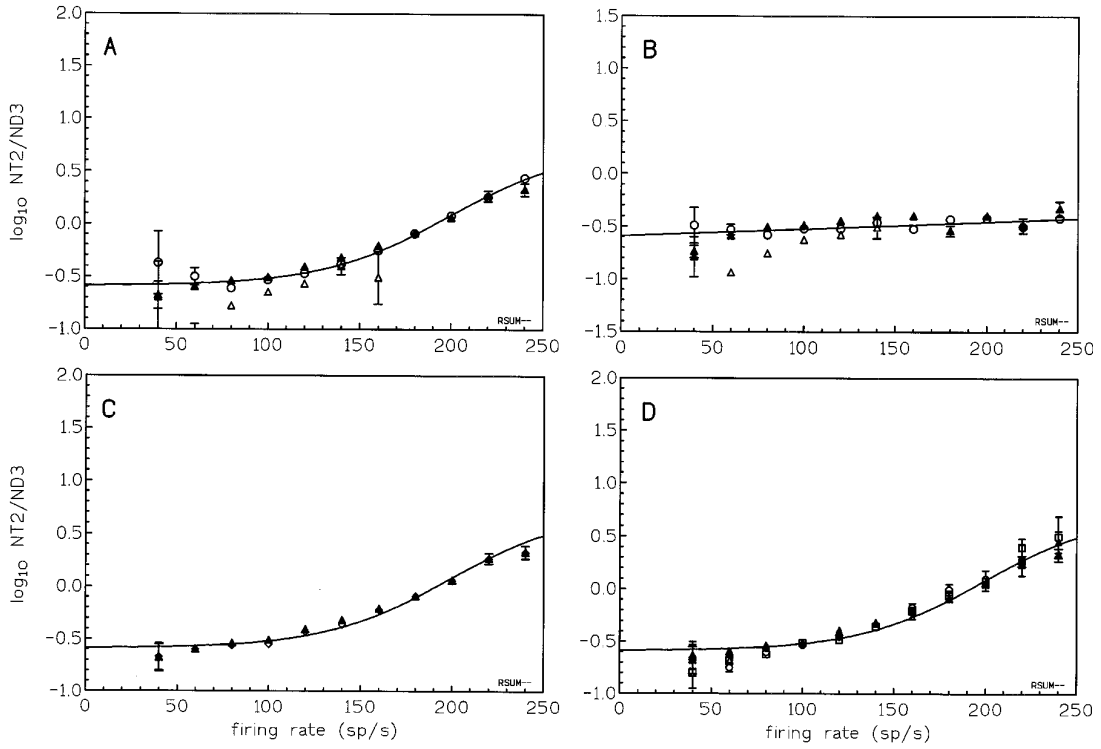
$$N_c^{(r)} = \frac{(w/\Delta)^{c-1} (T\Delta^{c-1}\lambda^c)^r}{(c-1)!r!} \exp(-T\Delta^{c-1}\lambda^c) \quad (1)$$

where  $\lambda$  is the mean firing rate, and  $c$  is the number of spikes comprising the pattern (i.e. 2 for doublets, 3 for triplets, etc.).

Thus, for a stationary Poisson process with an average firing rate  $\lambda$ , the expected number of triplets replicating two times ( $c=3, r=2$ ), in a given window of duration  $T$  seconds, rises roughly as the 6th power of  $\lambda$ . Since cell discharges are usually far from being stationary, this peculiarity makes it difficult to draw conclusions about the real significance of the presence of repeated patterns in spike trains.

A possible frequency-insensitive measure of a neuron's propensity to emit replicating patterns is obtained on noting that in a stationary Poisson process the expected number of doublets repeated

**a** NT2/ND3 - RETINAL GANGLION CELLS (S pot) - Anesth. cat - Rec. RSUM--



**b** NT2/ND3 - LATERAL GENICULATE NUCLEUS - Anesth. cat - Rec. LSUM--

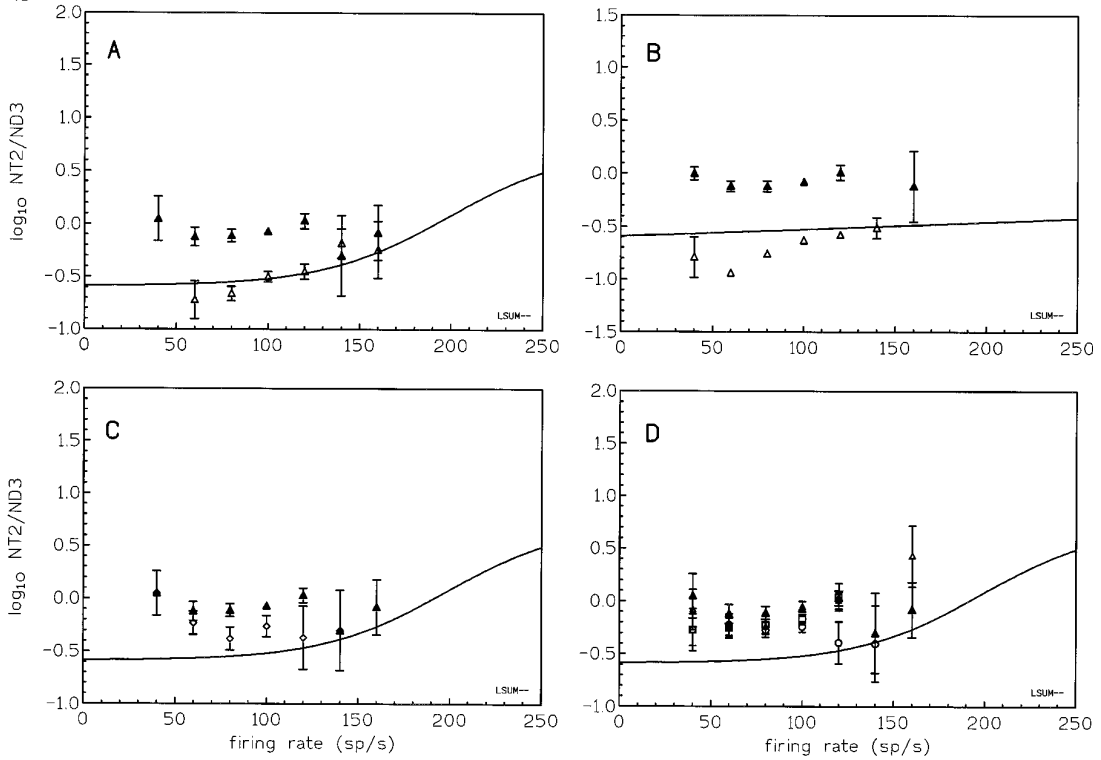


Fig. 3 (a, b).

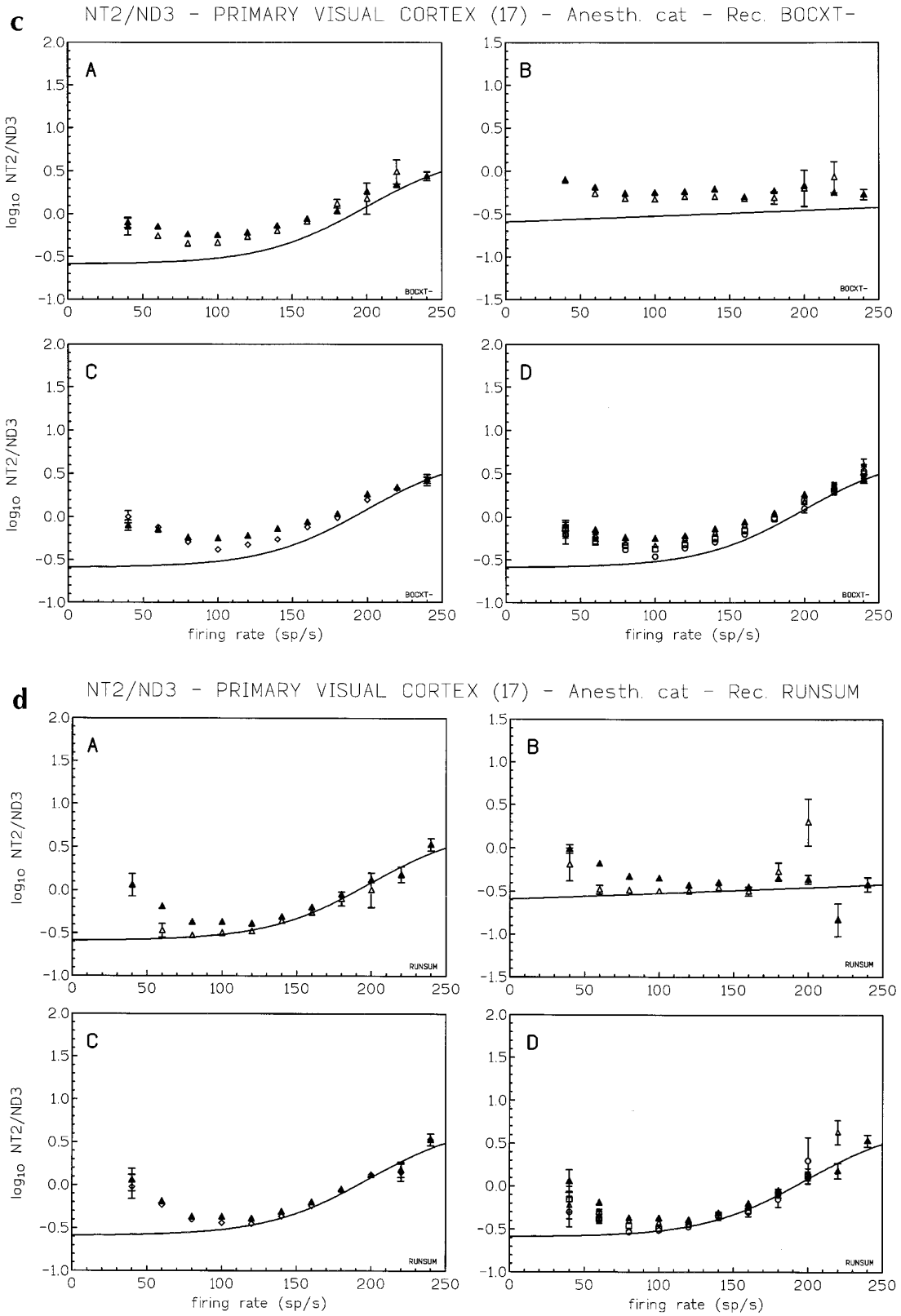


Fig. 3 (c, d).

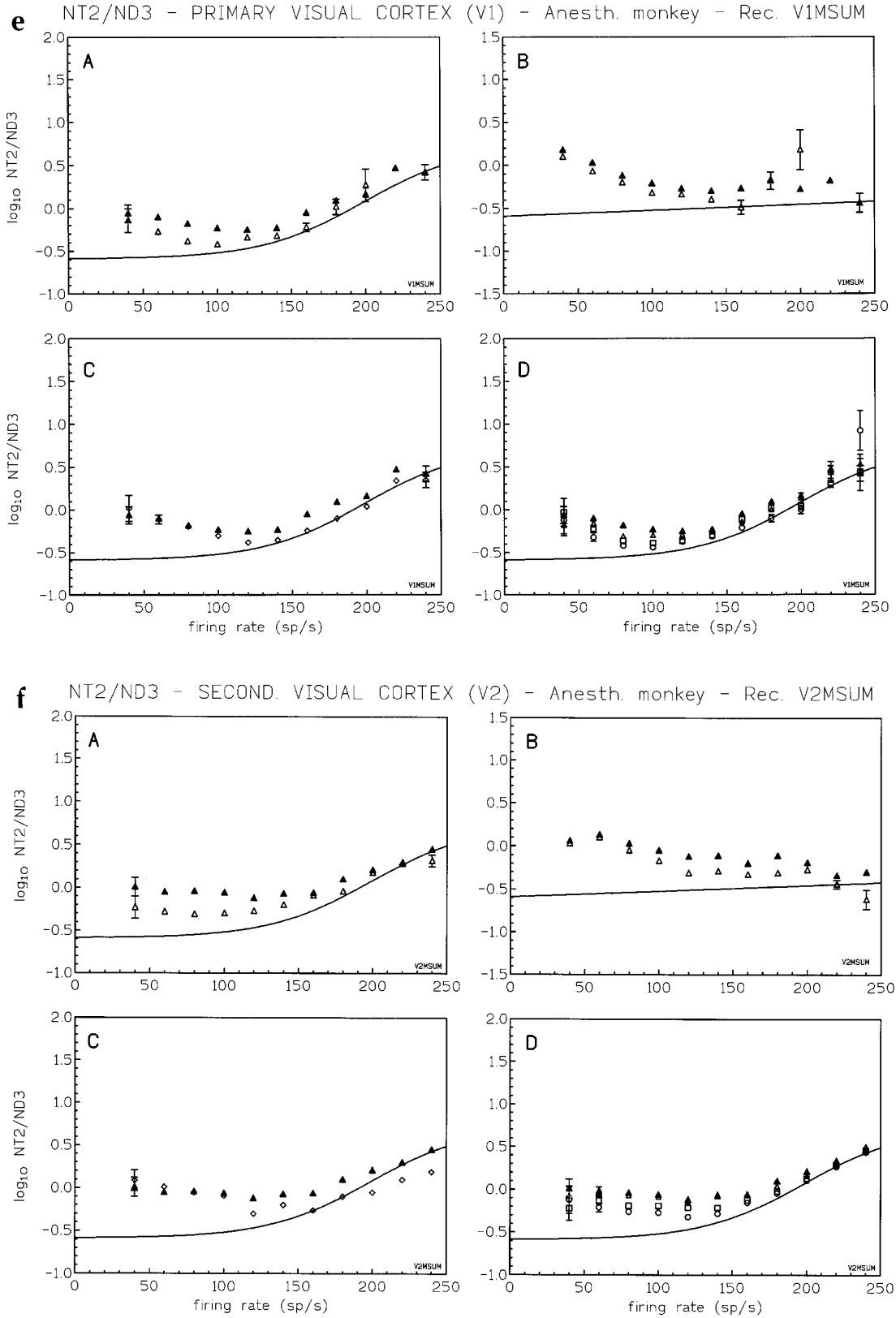


Fig. 3 (e, f).

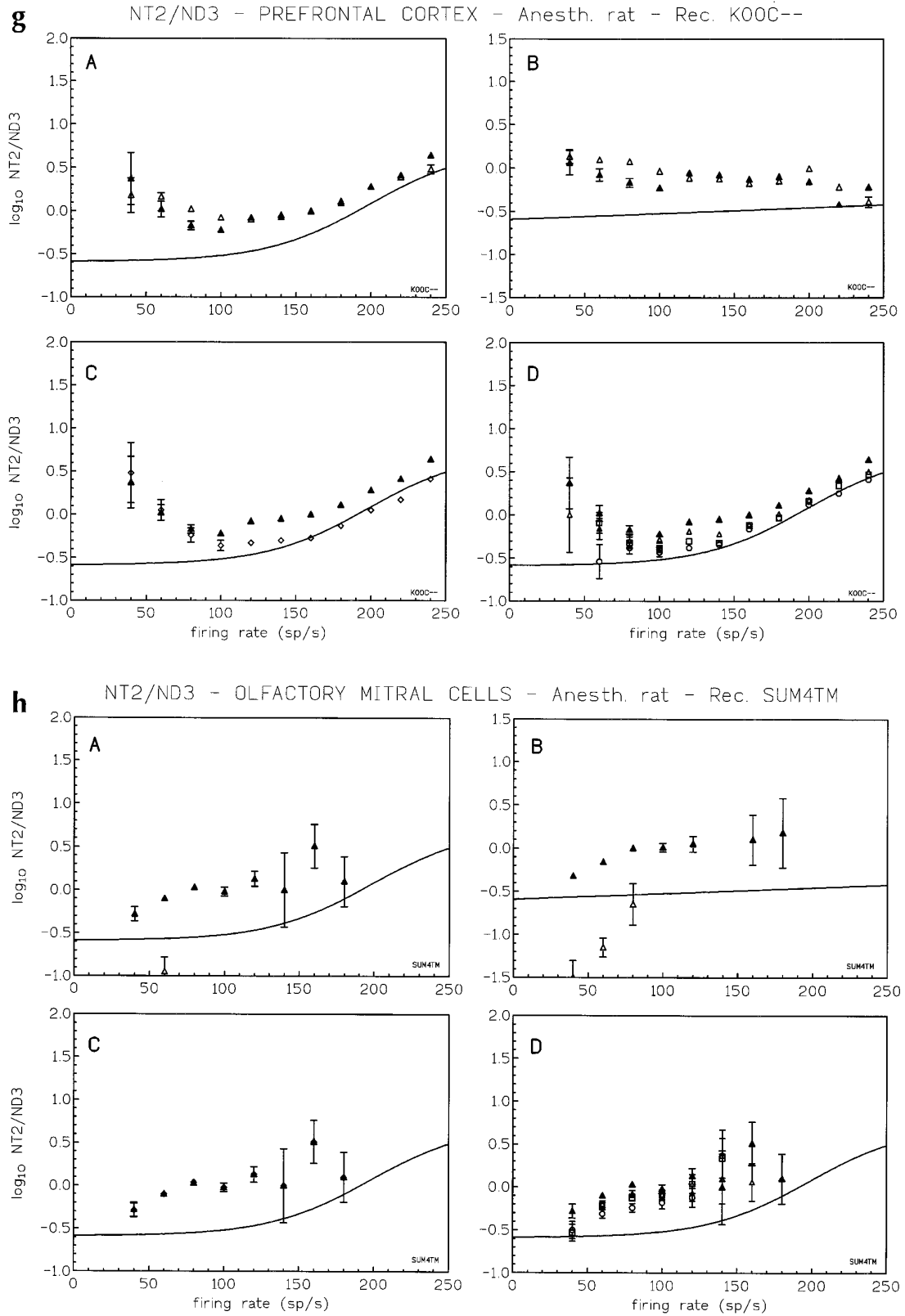


Fig. 3 (g, h).

three times ( $c=2$ ,  $r=3$ ) within the same window of time also rises roughly as the 6th power of  $\lambda$ . It is therefore quite natural to introduce as a test statistic the ratio NT2/ND3 of the number of triplets repeated two times to the number of doublets repeated three times.<sup>26</sup> Indeed, we have observed that cortical discharges present a definitely higher index NT2/ND3, or NQ2/ND4 (ratio of the number of quadruplets present two times to the number of doublets present four times in the same window, see Lestienne<sup>26</sup>) than synthetic Poisson-like spike trains.

The above measure of the propensity of a neuron to emit replicating patterns is, however, strictly frequency independent only as long as the exponents in the Abeles–Gerstein formula (1) remain low.\*

By using the NT2/ND3 ratio as a test statistic, it was possible to show, in the case of recordings taken in the area 17 of anaesthetized cats, that there was still a significant excess of replicating patterns when the tolerance for replication was restricted to a few tenths of a ms, but that such an excess was hardly discernible when the tolerance was increased to 2 ms.<sup>27</sup> The standard for comparison taken in such analyses was a Poisson-like model, as defined above.

In the present section we still use the same standard process, and also the renewal process with the empirical TIH distribution. We measured the NT2/ND3 ratios using both a fixed tolerance  $\Delta=0.5$  ms and a variable tolerance  $\Delta=5/n$  (ms). The latter case is particularly interesting, because with a tolerance which varies as the inverse of the firing frequency  $\lambda$ , NT2/ND3 as given by (1) reduces to:

$$\frac{NT2}{ND3} = \frac{3w}{2T} e^{Tk(1-k)\lambda},$$

\*That is, when  $\lambda < 1/\sqrt{(TA)}$ . For  $T=100$  ms,  $\Delta=0.5$  ms, this ensures a frequency insensitivity of NT2/ND3 or NQ2/ND4 only up to an average frequency of  $\sim 140$  Hz.

where we have put  $\Delta=k/\lambda$ . Since  $k=0.05$ , it follows that:  $NT2/ND3=3/2 w/T e^{0.00475\lambda}$ , giving a slow quasi-linear increase with  $\lambda$  in the range  $\lambda \in [40, 250]$  Hz here considered. Such a quasi-linear increase was effectively found using Poisson-like Monte-Carlo data in Fig. 3b (Fig. 3 uses the same symbol conventions as Fig. 2).

## Results

Figure 3a–h display the results for NT2/ND3, the ratio of the number of triplets present two times to the number of doublets present three times, for the same sets of recordings as in Fig. 2a–h, and for the stochastic models.

As for the number of precisely replicating triplets per spike, the observed excess in NT2/ND3 for the data relative to the Poisson-like model is generally greater at low frequencies, and gradually decreases at high frequencies. Globally, the temporal structure of nervous discharges, i.e. the departure from the Poisson model in terms of replicating patterns, again seems to be particularly large in the mitral cells of the olfactory bulb and in the LGN, and, to a lesser extent, in the primary visual cortex.

By contrast, no such propensity to emit replicating patterns (above the prediction of the renewal processes) was found in the case of the S-potentials (incoming spikes) recorded at the level of input to LGN cells, shown in Fig. 3a. Those S-potentials can be reliably identified with spike trains of retinal ganglion cells.<sup>34</sup>

In Fig. 3a, part A compares observations in spike trains from the retinal ganglion cells (filled triangles) to observations in Monte-Carlo generated data, generated either by a Poisson-like process (open circles and curve obtained from analytical fitting) or by a renewal process using the empirical TIH (open triangles). Part B presents the same results, but using

Fig. 3. Analysis of the ratios NT2/ND3 of replicating triplets to the number of triple copies of doublets found in successive windows,  $T=100$  ms wide. Part A. Ordinate:  $\log_{10}$  NT2/ND3. Abscissa: firing rates in the corresponding window, estimated as  $n/T$ , where  $n$  is the number of spikes in the window. Filled triangles: physiological data; open triangles: Monte-Carlo data from a renewal model with successive intervals obeying the TIH distribution, shown in parts C; open circles: Monte-Carlo data from a steady Poisson process, modified to introduce a refractory period of 1.5 ms and with the same firing rate; the solid curve was drawn by analytical fitting through the open circles. Part B. Same as part A, but instead of detecting replicating triplets with a constant tolerance  $\Delta=0.5$  ms, a tolerance decreasing reciprocally with the firing rate  $\lambda$  ( $\Delta=50/\lambda$  ms) was used. Note that practically all variation with firing rate has disappeared. Part C.  $\log_{10}$  NT2/ND3, for the original records (filled triangles), and for the same data where all spikes belonging to bursts having an *a priori* probability lower than 0.01 (“Poisson surprise” values  $>4.603$ ; see text) were removed, except the very first spike of the burst (open diamonds). Part D.  $\log_{10}$  NT2/ND3, for the original record, and for the same record where successive intervals have been jittered by adding a pseudorandom interval of time in the interval [0.1 ms] (open triangles), [0.2 ms] (open squares), and [0.3 ms] (open circles). a) Retinal ganglion cell recordings (S-potentials afferent to LGN). b) Lateral geniculate nucleus recordings (single-units). c) Primary visual cortex recordings (area 17, single recordings). d) Another example of primary visual cortex, single-unit recordings. e) Primary visual cortex recordings from an anaesthetized monkey (multi-unit recordings). f) Secondary visual cortex recordings from the same animal and under the same conditions. g) Recordings from the prefrontal cortex of an anaesthetized rat (multi-unit recordings). h) Recordings from mitral cells of the olfactory bulb of anaesthetized, freely breathing rats. As in the other figures, the analysis was performed by concatenating records made successively on several cells of the same structure, and several animals (see data acquisition).

a relative tolerance, changing reciprocally with the average firing rate according to the  $\Delta=5/n$  rule as in Fig. 2, part B.

While observations on actual data from retinal ganglion cells closely matches expectations from the Poisson-like model, the model based on a random sample from the TIH predicts a lower value of NT2/ND3 at low firing rates. Parts C and D of Fig. 3 are explained and discussed below.

Figure 3b presents corresponding results for data recorded from the dorsal part of the LGN. In this case a large excess of replicating patterns is seen, both using a fixed tolerance  $\Delta=0.5$  ms (part A) or a relative tolerance (part B), when the comparison is made with both the Poisson-like model (continuous line) or with the model based on the renewal process with the neuron's TIH (open triangles).

Figure 3c, d and e contains results obtained from recordings in the primary visual area of anaesthetized cats (Fig. 3c, d) or anaesthetized monkey (Fig. 3e) and are quite similar to each other. In all these figures, an excess of replicating triplets in terms of NT2/ND3 is visible, although it is generally much higher when the comparison is made with the Poisson-like model than with the renewal process model. When calculating NT2/ND3 using constant tolerance (parts A), this excess is clearly greater at low frequencies and seems to vanish at high frequencies. But values of NT2/ND3 determined using a relative tolerance (parts B) show an excess even at high discharge frequencies (Fig. 3c and e; the same is true for Fig. 3f, g and h).

Figure 3f and g display corresponding results from area V2 of an anaesthetized monkey, and from the prefrontal cortex of an anaesthetized rat, respectively. Results are generally very similar to those observed in primary visual areas, both in terms of departures from the Poisson-like model or from the renewal process model, and in terms of fixed or relative tolerances. It should be noted, however, that in the case of prefrontal cortex recordings, the model using the TIH predicts a higher value of NT2/ND3 than actually seen in the data (it predicts also a higher NT2/sp ratio, see Fig. 2h). This should be related to the particularly peaked TIH and autocorrelogram at small intervals (Fig. 2h, insets C and D, dotted histograms). The particularly sharp peak in the TIH in this case is probably related to nearly synchronous discharges from several cells in this multiple-unit recording.

Figure 3h presents results obtained from the single-unit recordings in the mitral cells of the olfactory bulb. Findings here are similar to those observed using single-unit recordings in the LGN. Significantly large NT2/ND3 ratios are found with respect to the Poisson-like model. The excess is even higher with respect to the renewal model using the TIH, from which very few or, at most frequencies, not even a single replicating pattern was found. This is to be related to the much more dispersed TIH observed in

this case (Fig. 2h, part C), and to the absence of peaks at short intervals, both in the TIH and the corresponding autocorrelogram.

In summary, an excess of replicating patterns measured in terms of NT2/ND3, with respect to the two standard random models used for comparison, are again observed for all CNS areas here analysed, except for the S-potentials coming from retinal ganglion inputs to the LGN. The fact that this excess is observed in terms of NT2/ND3 ratios and even more, in terms of NT2/ND3 ratios combined with a tolerance that decreases as the inverse of the firing rate, seems to rule out the possibility that the excess is artifactually produced by a biased estimation of the instantaneous frequency (if the spike trains contained high frequency bursts interspersed with long silences, the firing rates could be largely underestimated when measured by the number of spikes in windows of 100 ms).

It had been reported in earlier publications<sup>49</sup> that replicating triplets in spike trains were usually accompanied by "ghost" doublets, i.e. doublets that reproduce one or other of the intervals comprising a replicating triplet. This effect was confirmed in the present analysis, in the sense that, by removing in both the experimental data and the simulations, these "ghost" doublets, the deviations of NT2/ND3 values with respect to both the Poisson process and the renewal process based on the empirical TIHs were systematically and significantly increased, in all recordings except in the retinal ganglion cells.

#### EFFECT OF LOCAL "POISSON SURPRISES"

In a spike train, the departure from a Poisson process can be characterized in a quantitative manner, by application of the criterion of "Poisson surprise", introduced over a decade ago by C. R. Legédy and M. Salcman.<sup>22</sup>

For each window containing  $k$  spikes (spanning a time interval of duration  $\theta$ ), the probability  $P$  to obtain in a Poisson process of the same average firing frequency,  $k$  or more spikes during that time interval  $\theta$  is simply given by:

$$P = e^{-\mu\theta} \sum_{i=k}^{\infty} \frac{1}{i!} (\mu\theta)^i$$

where  $\mu$  is the average frequency of the discharge in the window considered.

The removal from a spike train of all spikes belonging to bursts having a probability of occurrence in a Poisson process lower than 0.01 (i.e., having a level of Poisson surprise  $S = -\text{Log } P$  higher than  $S = -\text{Log } (0.01) = 4.605$ ), leaving only spikes not belonging to such bursts and the very first spike of the burst, somewhat decreases NT2/ND3 ratios (Fig. 3, parts C). This is particularly the case for records in the LGN (Fig. 3b, part C). On the other hand, data

taken in the mitral cells of the olfactory bulb are not affected by the removal of bursts, which are rare anyway in these data.\*

#### THE INTRODUCTION OF JITTER IN THE TIMING OF EVENTS

The increased propensity of replicating triplets and doublets to occur in neuronal spike trains relative to the Poisson-like model is suggestive of mechanisms of precise timing of action potentials. Although little is known about the real mechanisms by which such a precision could be achieved in real neurons or about the possible use of replicating patterns for transmission of information in a network of neurons, a few mechanisms have been suggested (see for example Softky<sup>45</sup> for production mechanisms, and Lestienne and Strehler<sup>23</sup> for a possible decoding mechanism).

However, if such mechanisms were implemented in real neurons, then it would be expected that neurons be tuned for the emission of a well-defined variety of patterns, and that addition of noise in the duration of interspike intervals would considerably disturb the detection of replications.

This hypothesis was tested in the various records at our disposal. For each window of time, a small random perturbation, whose amplitude was uniformly distributed over a time interval of either [0,1], [0,2] or [0,3] in units of ms was added to each interval, and the jittered spike data were processed again for the detection of replicating patterns (perturbations were restricted to positive values only, in order to avoid introducing intervals that could be smaller than the refractory period; another test was also performed, allowing both positive or negative perturbations, but rejecting perturbations that would result in intervals smaller than the refractory period; results were qualitatively similar to the present test).

It is to be noted that introducing such a random perturbation in spike times amounts to performing a convolution of the spike time density with a given uniform density. This results not only in a change in the distribution of intervals, but also in a change in the correlation coefficients of successive intervals.

More specifically, if  $\{T_k, k=1,2,\dots\}$  is a sequence of interspike intervals in an original record and  $\{N_k, k=1,2,\dots\}$  is a sequence of such independent uniformly distributed noise variables on  $(0,a)$ , then the perturbed intervals:

$$T'_k = T_k + N_k,$$

have means

$$E[T'_k] = E[T_k] + a/2,$$

variances

$$Var[T'_k] = Var[T_k] + a^2/12,$$

and covariances

$$Cov[T'_j, T'_k] = Cov[T_j, T_k].$$

That is, the mean and the variance of the intervals are increased whereas covariances remain the same. However, the correlation coefficients change according to the prescription:

$$\rho[T'_j, T'_k] = \frac{\rho[T_j, T_k]}{\sqrt{(1+a^2/12\sigma_j^2)(1+a^2/12\sigma_k^2)}},$$

where  $\sigma_j^2 = Var[T_j]$ .

Thus, when  $a$  is very small, the correlation coefficients are practically unaltered, but when  $a$  is large, any correlation between intervals is decreased.

To our surprise, we found that, with the exception of the record taken in the LGN and the mitral cells of the olfactory bulb, the introduction of such a noise in the timing of events does not dramatically change either the absolute numbers of replicating patterns detected, or the ratios NT2/NT3. This robustness of the propensity for replication of patterns is illustrated in Fig. 3a-h, part D, comparing the ratios NT2/ND3. It is only with a jitter of amplitude 2 ms that the NT2/ND3 ratios begin to be systematically affected, except of course in the case of S potentials for which the number of replicating patterns in spike trains already does not depart from the Poisson-like model. It would seem likely from this observation that high NT2/ND3 ratios in visual cortical spike trains are not the result of precise mechanisms, but only the result of a deviation of the probability distribution of spike times from a Poisson process, as the examination of triplets counting in the renewal model based on the TIH had already suggested. Such a deviation makes replications more probable than could be expected, but adding a little noise only changes the type of patterns that are detected, not their number.

On the other hand, data coming from the mitral cells of the olfactory bulb and the LGN do behave as we should expect if the exact timing of events was significant: introducing a jitter significantly decreases both the total number of detected replications and the NT2/ND3 ratios, toward their expected value for a Poisson-like process. Note that in the case of the mitral cells of the olfactory bulb, the decrease in the number of replicating patterns detected after removal of bursts of high Poisson surprise is quite a lot smaller than in other cases. This would confirm that in this case bursts are not chiefly responsible for the appearance of replicating patterns.

\*The removal of bursts of a Poisson surprise  $>4.605$  reduces the number of spikes in SUM4TM by only 1 per 1000 spikes (from 53,579 to 53,516), whereas it decreases the number of spikes in LSUM- by more than 7% (from 17,056 to 15,766).

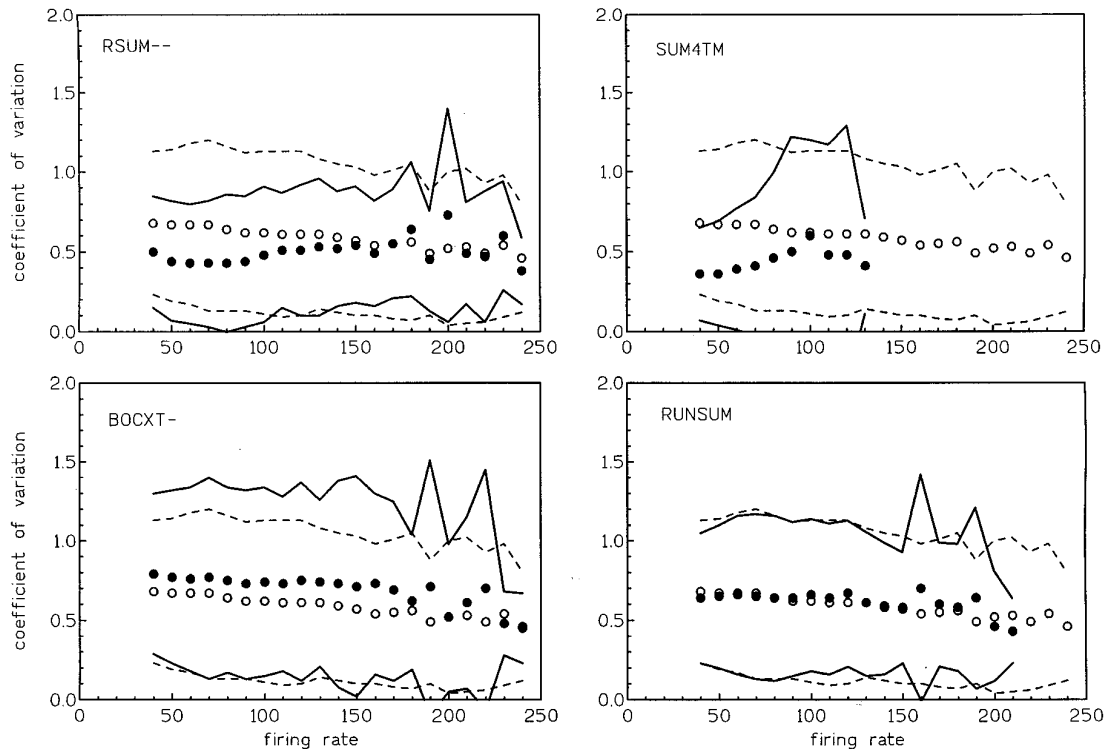


Fig. 4. The coefficient of variation (CV) of the interspike interval for four preparations: CV is the ratio of S.D. to the mean for intervals within windows of duration  $T=100$  ms. The average values of CV (filled circles) are here plotted against average local firing rate across windows, together with the CV S.D.s (full lines), and compared with values obtained for simulated Poisson-like spike trains (open circles: mean values; S.D. dotted lines). In the larger part of the frequency range, variability is smaller than expected for a Poisson-like spike train for S-potentials from retinal ganglion cells (record RSUM-) and mitral cells of the olfactory bulb (SUM4TM). In records from the primary visual area, variability is higher (BOCXT-) or about the same magnitude (RUNSUM) as in Poisson-like spike trains. Note that the CV computed in successive windows is consistently less than 1 for a Poisson-like process, for which the exact coefficient of variation is given by  $1/(1+\lambda_{TR})$ .

#### PATTERN REPLICATION AND THE VARIABILITY OF SPIKE DISCHARGES

It has long been known that the variability of the neuronal discharges is not consistent with a Poisson process. Softky and Koch have also argued by analysis of several models, that the classical integrate and fire models of nervous cells are often inadequate.<sup>46</sup> We therefore examined the variability of the discharges in our samples, taking, in each successive window, the ratio of the standard deviation of the intervals to their mean. In Fig. 4 we show plots of the coefficient of variation of the spike interval versus the frequency of spike discharge in various preparations. It is seen that S-potentials coming from retinal ganglion cells (record RSUM-) are much more regular (less variability) than would be expected for a Poisson process modified by including a refractory period (for a more detailed discussion of variability in retinal g ganglion cell responses, see Ref. 11). By contrast, records from the primary visual area are more variable (BOCXT-) or about as variable (RUNSUM) as would be expected for a Poisson-like process. However, in the case of data from cells of the

mitral cells of the olfactory bulb (SUM4TM), the variability is again definitely lower than expected for a Poisson process; nevertheless their propensity to emit replicating patterns is higher than for any other data. We may conclude therefore that there is no systematic relation between the propensity to emit replicating patterns and the variability of the interspike interval.

#### DISCUSSION

As was recognized a long time ago, many examples of time coding can be found in neurophysiology (see for example Ref. 7), and some of them imply a very fine precision of spike timing. In the terms of Theunissen and Miller:<sup>11,51</sup> The ability of neurons to phase lock to a stimulus signal is exemplified by high-frequency auditory fibres: single neurons can phase lock to stimulus frequencies of up to 7 kHz<sup>33</sup> (although no single neuron could fire at every cycle). Another remarkable example of phase-locking neurons is found in bats, where the variance in the latency of spiking neurons to the onset of the stimulus is in the sub-millisecond range.<sup>11,12</sup> Several

examples of what has been termed “hyperacuity” have been described in the past literature (see for instance Ref. 8): the avoidance reflex of jammed frequencies by electric fish, the precision of localization of targets by the auditory system of the owl, and the range and texture detection of targets by the bat. Recently, a possible theory for the accurate detection of inter-aural delays by nucleus laminaris neurons of the barn owl has been proposed by Gerstner *et al.*,<sup>19</sup> which is consistent with a sub-millisecond organization of spike trains. These examples are, however, probably no more difficult to understand than the more familiar example of the precision of the visual or auditory systems of humans. The clearest signal discovered so far in the mutual information problem (between visual stimulation and the time structure of cortical visual cells) in primates has probably been given a few years ago by Barry Richmond and his group,<sup>39</sup> who detected a code for the low frequency part of the neuronal messages (<30 Hz). Some suggestions of codes at a higher frequency band were found in insects, such as the blow fly<sup>6</sup> and the cricket<sup>32</sup> and they both imply precise spike timing, but in a way that differs from the use of precisely replicating triplets. The remaining codes for high frequencies, that is, in situations characterized by high precision in spatial patterns and/or highly dynamic stimulations, which are of course real life situations, as opposed to simple and relatively static stimulations tested in most experiments of electrophysiology, remain to be discovered. Whatever were our hopes ten years ago,<sup>23,48</sup> it is not obvious how the search for precisely replicating patterns will help in this direction. This is not to say, however, that replicating patterns cannot be correlated with general states of the brain,<sup>41</sup> but replicating patterns of a much wider separation in time between replicas are not likely to be good candidates for the encoding of the high frequency part of the sensory stimulations.

Our results, agreeing with others previously published, suggest that in all hierarchical levels of processing of sensory data, spike trains possess a fine temporal organization that enhances the presence of replicating patterns in their spike train. In the case of the retina, however, spike trains, although not completely compatible with certain paradigm random processes, display fewer replicating patterns than all other centres of CNS here tested. There are, however, several other parameters, other than the hierarchical level of processing, that can influence the presence of replicating patterns. Single or multi-unit recordings, type of stimulation, etc. may also play a role. The first distinction may be particularly important, since the interpretation of replicating patterns in the two cases should be distinguished: recurring states of inputs of single cells on the one hand, and synfire-like properties of networks on the other. It is known that external inputs constitute a very small proportion of all afferents within most cortical columns and hence

the cerebral cortex communicates to a large extent with itself. This property led Moshe Abeles and his group to develop a model of richly interconnected networks, where synchronous modes of discharge are likely to occur and to give rise to repeated patterns in multi-electrode recordings of neuronal discharges.<sup>2-4</sup> As Abeles pointed out, patterns of activity involving different neurons can only be detected using multiple micro-electrodes. On the other hand, the patterns that we have observed occur in single-electrode recordings of both multi- and single-unit activity, which could easily be subsequences of patterns in neural assemblies. However, if repeated patterns detected in single-units were only a consequence of population spatio-temporal patterns, their precision would be expected to be the same, if detected in a single neuron or in a local population. The fact that in our study most evidence for replicating patterns was found in two samples of single-unit recordings (LSUM- and SUM4TM) is perhaps an indication that other mechanisms are involved in the production of the kind of replicating patterns here considered.

We note that in multi-unit recordings, detection of replicating patterns does not necessarily reflect synfire mechanisms, since there is no guarantee that spikes in original patterns and their subsequent copies come from the same neurons. On the other hand, since microelectrodes usually distinguish spikes from a few neurons in their immediate neighbourhood, mixing only occurs to a limited extent. Finally, let us note that if one had access to spike amplitudes as well as times of occurrence, this problem could be easily resolved.

#### *Is local inhibition instrumental in the production of replicating patterns?*

Clearly, inhibition and excitation are not separable events in the processing of neuronal information, “because individual neurons are embedded in micro-circuits that contribute strong population effects”.<sup>15</sup> There are arguments in favour of the idea that local inhibitory interactions are chiefly responsible for many of the details of the temporal organization of spike trains. The first reason is the observation that local inhibitory interneurons are faster spiking neurons than excitatory neurons.<sup>21,28</sup> The second reason is the diversity of interneuron types and the non-random patterning of their synapses with pyramidal neurons. Some interneurons (chandeliers) synapse in particular with the initial segment of pyramidal neurons, and are evidently able to shut down in a fast manner any initiating or initiated action potential. The cut-off of tail potentials by use of inhibitory IPSPs occur frequently in many systems, including the corticothalamic pathways in the visual system<sup>47</sup> or in the auditory cortex of the owl<sup>18</sup> or the bat.<sup>50</sup>

Clearly, inhibitory interneurons are one of the many factors responsible for the departure of spike trains from Poisson and the other standard processes

and may contribute to the existence of specific spike sequences. As a matter of fact, massive inhibition by local interneurons have been demonstrated in the LGN (see for instance Refs 42 and 37), and in the olfactory cortex as well.<sup>38,52</sup> In the latter structure, mitral cells interact with inhibitory interneurons through serial and reciprocal excitatory-inhibitory synapses at the level of the glomerular layer and reciprocal synapses in the plexiform layer, and it has been recognized that these inhibitory local circuits, which involve both GABA and glycine receptors, play a major role in shaping the activity of the bulb.<sup>53</sup> There is also the possible control of thalamic discharges by corticothalamic inputs, which are both excitatory and inhibitory,<sup>14</sup> and were shown to exert a powerful effect on the replicating patterns detected in the LGN.<sup>5</sup> In the visual cortex, the inhibitory connections are supposed to exert a stronger influence on deep cortical layers than on supragranular layers,<sup>15</sup> and this observation parallels our observation that replicating patterns were more abundant in infragranular layers.<sup>25</sup>

On the other hand, GABA receptor density in the retina seems lower than in most structures of the CNS, and retinal ganglion cells do not project forward inhibitory pathways to the next stage of nervous integration (LGN).

Thus, the question of the relationship between the pattern of spike discharges and the presence of a large amount of inhibitory inputs to nervous cells is posed. Inhibition not only avoids over-excitation in cortical centres, but plays a much more important role in molding patterns from excitatory phenomena, just as a sculptor carves a statue by precisely removing those parts of the marble that mask the most recognizable traits of the model. To check whether, in the absence of local inhibition, neuronal spike trains might be more Poisson-like and/or would produce less replicating patterns, it would certainly be interesting to compare the presence of replicating patterns in the same nervous centres under stimulation, before, under and after local injection of bicuculline. We intend to make such analysis in our laboratory in the near future.

## CONCLUSION

While demonstrating that spike trains emitted by certain centres of the CNS do contain a precise temporal organization of the kind which is not present at an entry level such as retinal ganglion cells, the present study does not allow us to decide whether replicating patterns are a reflection of network properties and their modes of information processing (for example, the syn-fire mode) or were largely due to factors intrinsic to neurons themselves, linked perhaps to the dynamics of the various ionic channels. It should be noted, however, that in at least one example, the effects of external inputs were clearly demonstrated. In the analysis of simultaneous recordings from a cell in LGNd and a connected cortical cell, it was observed that the temporal organization of the LGNd cell discharges was profoundly and reversibly affected when the corticothalamic loop was interrupted by the iontophoretic application of GABA at the cortical level.<sup>5</sup> In order to advance our understanding it is desirable to not only further analyse repeating patterns in different preparations (with pharmacological controls of specific channels), but also to undertake a detailed modelization of networks of neurons, that includes details for each unit with regard to its various and specific conductances.

*Acknowledgements*—We are indebted to the various groups who generously provided their carefully taken data, with the specific purpose of searching for replicating patterns and their significance, and in particular to Dr Pratik Mukherjee and Ehud Kaplan from the Rockefeller University (New York), Jean-Christophe Beaux and Michel Imbert, from Institut des Neurosciences (Paris), Ralph Siegel from Rutgers University (New York), Lionel Nowak and Jean Bullier, from Cerveau and Vision, INSERM U371 (Bron), Nathalie Buonviso, Monique Chalansonnet et Michel Chapat from Physiologie Neurosensorielle, CNRS-Université Lyon I, and Anne Hervé-Minvielle and Susan Sara, Institut des Neurosciences (Paris). One of us (HCT) appreciates the support of a Fellowship from the Ministère des Affaires Étrangères, Paris and the French Embassy in Canberra, Australia. This work has been supported by Centre National de la Recherche Scientifique (CNRS), Paris, France.

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(Accepted 28 May 1997)