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Research Report

Double sliding-window technique: A new method to calculate the neuronal response onset latency

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ABSTRACT

Neuronal response onset latency provides important data on the information processing within the central nervous system. In order to enhance the quality of the onset latency estimation, we have developed a 'double sliding-window' technique, which combines the advantages of mathematical methods with the reliability of standard statistical processes. This method is based on repetitive series of statistical probes between two virtual time windows. The layout of the significance curve reveals the starting points of changes in neuronal activity in the form of break-points between linear segments. A second-order difference function is applied to determine the position of maximum slope change, which corresponds to the onset of the response. In comparison with Poisson spike-train analysis, the cumulative sum technique and the method of Falzett et al., this 'double sliding-window, technique seems to be a more accurate automated procedure to calculate the response onset latency of a broad range of neuronal response characteristics.

1. Introduction

Peristimulus time histograms (PSTHs; developed by Gerstein and Kiang, 1960) are commonly used to visualize the effect of a stimulus on the neuronal activity in extracellular recordings. Estimation of the neuronal response onset latency may provide important data concerning the information flow within the central nervous system (Berson, 1987; Dreher and Sefton, 1979). Despite the fact that the response onset latency comprises a source of data with which to resolve the information coding in the central nervous system alternative to the well-discussed properties of neuronal responses, i.e. the neuronal firing frequency, response duration and stimulus threshold, only a small proportion of neuronal recordings are generally analyzed from this aspect, possibly because of the weakness of automated latency estimation methods.

In the automation of the estimation of latency, a basic problem is to extract a signal from the spontaneous activity, which is determined by environmental and physiological noise. Mathematically, two solutions exist: counting the number of impulses discharged in some fixed interval (counting method) and detecting the time for the discharge of a fixed number of impulses (timing method) (Wandell, 1977). Poisson spike-train analysis is currently the most frequently applied method of latency estimation (Legéndy and Salcman, 1985). The neuronal response onset is calculated by averaging the time positions of some arbitrarily chosen bursts in the proven trials. The cumulative sum (CUSUM) technique was the first method in which the latency of neuronal responses was calculated via the analysis of PSTHs (Ellaway, 1978). The value of this method lies in the detection of change in the mean level of the activity. Since the change in

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Abbreviations: CUSUM, cumulative sum; EE, estimation error; PSTH, peristimulus time histogram; SOD, second-order difference

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the mean could be small relative to the variation in the individual values, an arbitrary threshold level (usually 1, 2 or 3 standard deviations (SD) above the mean of the spontaneous activity condition) is often chosen to quantify the start-point of the increment in the CUSUM curve (Ouellette and Casanova, 2006). The CUSUM technique has the weakness that it is not possible to determine precisely which temporal component of the response should be analyzed. Accordingly, Falzett et al. (1985) introduced a combination of the CUSUM technique with a second-order difference (SOD) function. However, despite the numerous methods proposed (Table 1), none of them can be applied reassuringly as a universal latency estimation method.

Is it possible to develop an estimation method for onset latency whereby the estimation becomes a clear objective statistical procedure? Can this new statistical function contribute to the applicability and reliability of automated latency estimation? Is it possible to keep the computational time-cost low? In an attempt to answer these questions, we have developed a 'double sliding-window' technique with which to calculate the neuronal response onset latencies. The double sliding-window technique analyzes trial-by-trial data on PSTHs and combines the advantages of mathematical methods with the reliability of standard statistical processes. In order to check on the validity of the technique, we calculated the visual response onset latencies of neuronal responses obtained in a large number of extracellular single-unit recordings and compared them with visually quantified latencies and with the latencies provided by Poisson spike-train analysis, the CUSUM technique, and the advanced method of Falzett et al.

2. Results

For measurement of the latency of neuronal response onsets, we developed a software program, the double sliding-window

Table 1 – Methods for estimating neuronal response onset latencies

χ^2-test within a different time window	(Fournier et al., 1986; Marque et al., 2001)
Significance level set to a specific threshold of spontaneous activity	(Tamura and Tanaka, 2001; Edwards et al., 2003)
Cumulative sum technique (CUSUM)	(Ellaway, 1978; Butler et al., 1992; Forlano et al., 1993; Rolls et al., 1993; Ouellette and Casanova, 2006)
Advanced CUSUM (method of Falzett et al.)	(Falzett et al., 1985; Day and Sibbald, 1989; Akeyson et al., 1990; Knuepfer and Holt, 1991; Holt et al., 1991; Drew et al., 1996; Hernandez et al., 2002)
CUSUM with Monte Carlo technique	Ushiba et al. (2002)
Poisson spike-train analysis	(Legéndy and Salcman, 1985; Hanes et al., 1995; Sáry et al., 2006)
Maximum likelihood estimation	(Seal et al., 1983; DiCarlo and Maunsell, 2005)
Artificial neuronal network	Churchward et al. (1997)

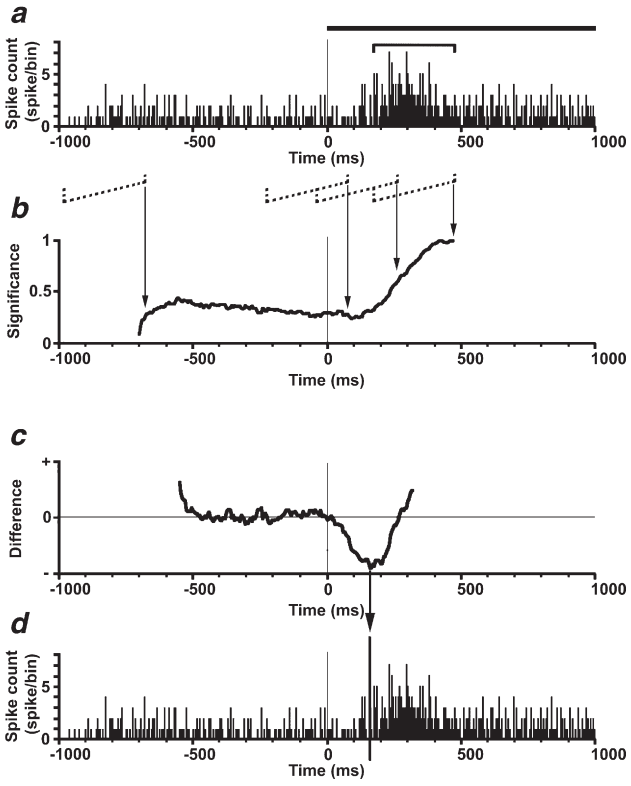

Fig. 1 – Estimation of neuronal response onset latency with the double sliding-window technique. (a) Peristimulus time histogram (PSTH) of an excitatory neuronal response. A PSTH consists of a prestimulus and a peristimulus period; the time-scale is presented on the abscissa (ms). The duration of visual stimulation is indicated by a thick horizontal black line above the PSTH. The beginning of visual stimulation is the zero time point. The ordinate demonstrates the cumulated spike count in each 5 ms wide bin. The solid black clamp above the PSTH denotes the position of the 300 ms wide reference window, where it overlaps the highest neuronal activity. (b) Significance curve calculated by the series of t tests. Four specific positions of the 300 ms wide sample window corresponding to different activity levels of the neuron are indicated by dotted clamps, while the arrows denote the corresponding significance values. The first two positions relate to cases when the sample window contains only pure spontaneous activity, while the third contains the transition between the pure spontaneous activity and the neuronal response to visual stimulation. The fourth marker shows the final position, when the reference and the sample windows overlap each other (the significance level of the t test is 1). The ordinate denotes the result of the series of paired t tests between the activity in the reference window (shown in part A) and the activity within each actual sample window in 5 ms (one bin) steps. (c) Curve of the second-order difference function (SOD) derived from the significance curve (n=30). The ordinate demonstrates the positivity or negativity of the SOD results. The minimum point of this curve coincides with the maximum slope change of the significance curve, and thus approximates to the onset of the neuronal response. (d) PSTH with marked response onset (thick vertical line). Accordingly, the visual response onset latency of the demonstrated neuron was 160 ms.

technique, which slides two windows along the PSTHs. The first window (reference window) slides through the peristimulus period in 1 bin steps, and selects the portion that represents the maximum (or the minimum) frequency (depending on the excitatoric or inhibitoric characteristic of the neuronal response). A second window (sample window) then slides through, also in 1 bin steps. After each step, the program calculates the significance level between the spike frequencies of the two windows with the *t* test. The latency of the responses is calculated from the time function of these *p* values. A curve is fitted to the *p* values, and the response onset latency is provided as the time interval between the start of the stimulation and the first point of the rising segment of the p curve, which is estimated by a SOD function (Fig. 1).

2.1. *Response onset latency estimation using the double sliding-window technique*

A total of 681 extracellular single-unit recordings (PSTHs) were analyzed by using the double sliding-window technique. All these PSTHs were selected from among our earlier recordings with regard to two criteria: the PSTH had to demonstrate a significant neuronal response to visual stimulation, and the response onset latency from the PSTH could be determined by subjective visual estimation. Latencies were calculated for each neuronal response subjectively by visual evaluation and by using the double sliding-window technique with 135 different parameters (10 different window widths, from 10 to 100 bins, and the possible corresponding *n* values in the SOD function, from 2 to 50; Fig. 3a). Fig. 2 depicts the characteristics of three different excitatory (Figs. 2a–c) and one inhibitory (Fig. 2d) neuronal response, with their associated significance and the SOD curves produced by the latency analysis. The automatically determined response onsets are indicated by vertical arrows.

The difference between the subjectively determined latency and the latency estimated by using the double sliding-window technique was defined as the estimation error (EE) of a measurement. If the *n* value was higher than a limit (10–12) and the window width was in an appropriate range (30–60 bins), there was not a significant difference between the computed EEs (Fig. 3a). Furthermore, calculation of the median

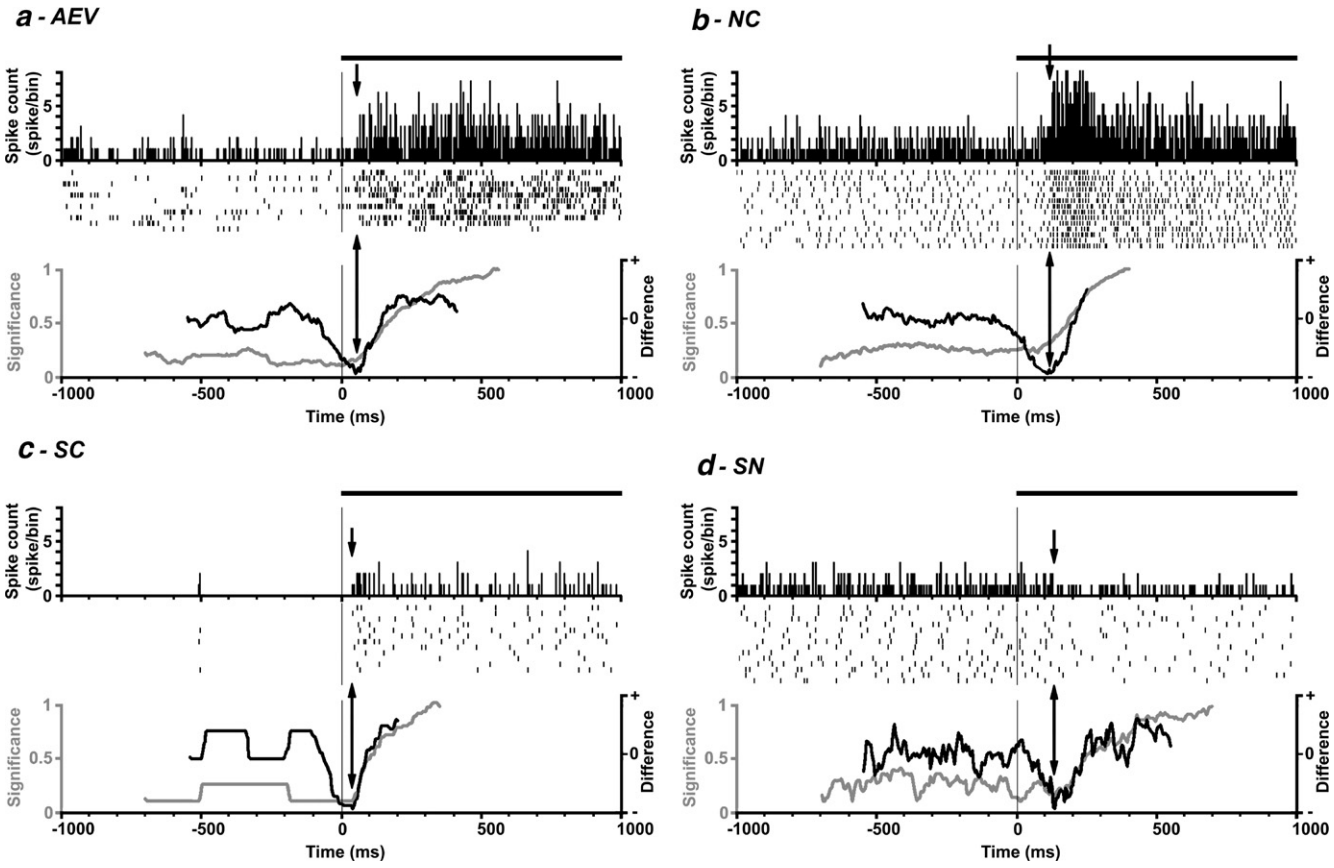

Fig. 2 – Application of the double sliding-window technique. Calculation of the visual onset response latencies of excitatory neuronal responses in the anterior ectosylvian visual area (a), the caudate nucleus (b) and the superior colliculus (c), and an inhibitory response in the substantia nigra pars reticulata (d). Each part contains the summed neuronal activity in the form of PSTHs (uppermost part), the trial-by-trial activity in raster form (each row visualizes one trial, where each small dash means one neuronal excitation; middle part) and the two calculated curves (lower part), the significance (gray) and the SOD curve (black). The arrows show the minimum point of the SOD curve that depicts the neuronal response onsets. The conventions are the same as in Fig. 1.

of the acquired onset latencies by using the highest mathematically possible *n* values with different window widths furnishes higher internal stability, this smoothing leading to the most accurate onset latencies. Use of the median instead of the mean to estimate the central tendency is more accurate in this case, since sporadic disturbances in a data set (estimation inaccuracy for a single *n* value) distort the final latencies less. The mean of the medians of the EEs when the double sliding-window technique was used was 35.98 ms ($n=681$; SD: ±58.48 ms).

2.2. *Response onset latency estimation with other automated methods*

The visual response onset latencies of the same 681 neuronal recordings (PSTH) were also estimated by using Poisson spike-

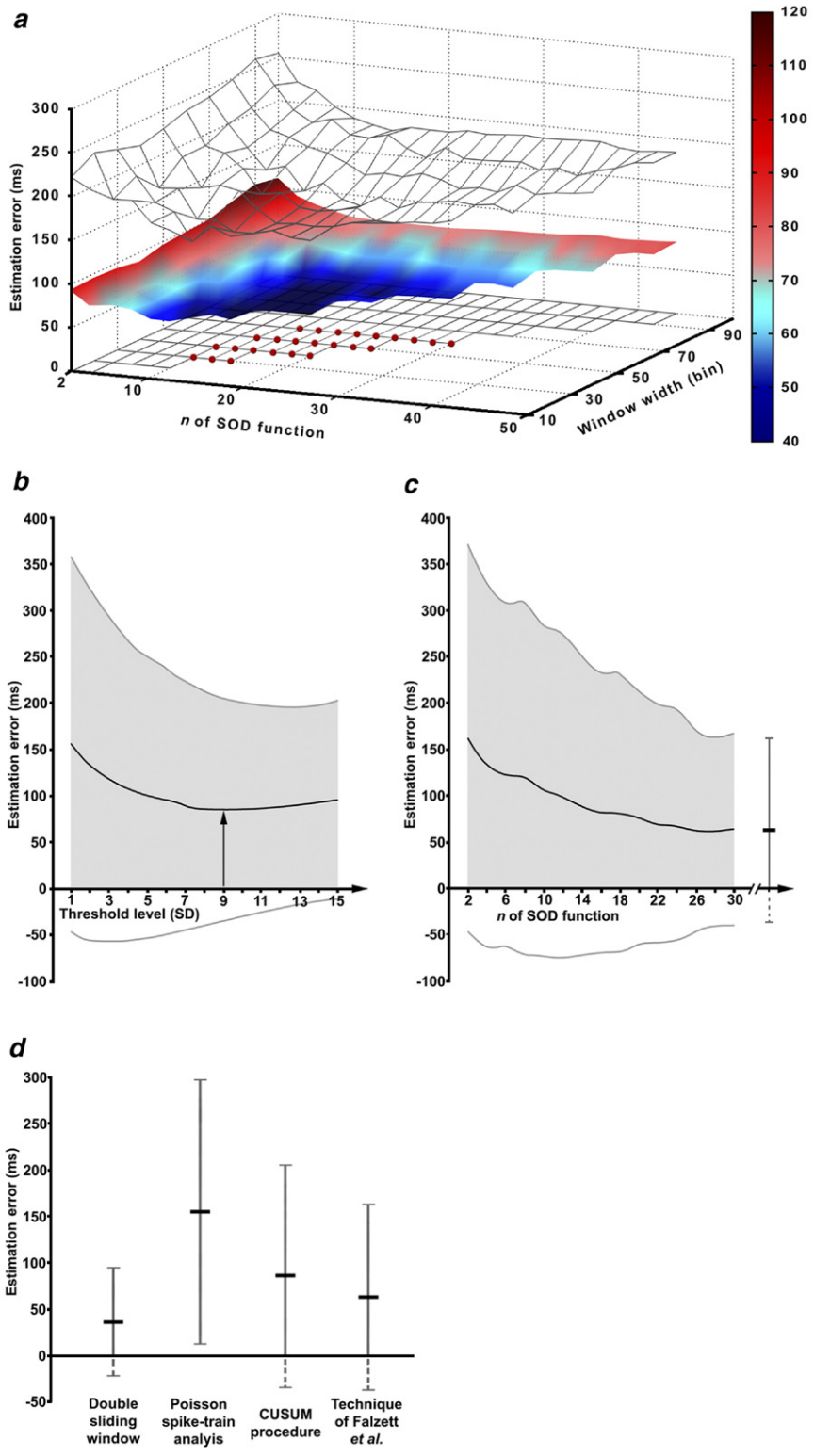

Fig. 3 – Effectivities of the four investigated latency estimation methods. The double sliding-window technique (a) was tested by using 135 different parameter combinations (10 different window widths from 10 to 100 bins and the corresponding possible SOD parameters) on 681 extracellular single-unit recordings. A solid color-shaded surface was constructed from the means of the estimation errors (EEs) of the 681 neurons as a result of using each 135 parameter combination; the ±1 SD range is marked with the two meshes (the lowest limit for this range was defined as 0 since the result of the EE calculation equation cannot be negative). The measurement parameter combinations that were constantly used to calculate the mean of the medians of the EEs (see part d) are marked with red dots. The CUSUM method (b) was also tested on the same 681 recordings using 15 different parameters 1–15 SDs above the mean firing rate as threshold level. The mean+9 SD threshold level (denoted by an arrow) provided the most accurate latency values. The technique of Falzett et al. (c) was tested with 15 different SOD parameters on 681 recordings, and a continuous graph was constructed from the calculated average EE values of the acquired data in ms. The mean of the medians of the EEs (when $n=22$–30 was applied, which yielded the most accurate latency result) is indicated as a discrete range on the right side of the graph. (d) Comparison of the effectiveness of the four latency estimation methods, using the most accurate parameter(s) for each method. The ordinate shows the EEs in ms. Thick horizontal lines denote the mean EE. From left to right, the EEs of the double sliding-window technique, Poisson spike-train analysis, the CUSUM procedure and the technique of Falzett et al. are presented, while the whiskers show the ±1 SD EE range for each method.

train analysis, the CUSUM method and the extension described by Falzett et al. (1985). In some cases, Poisson spike-train analysis estimated the response onset before the onset of the stimulus. We excluded these registrations from our comparison (none of the other methods could provide 'negative' latencies for technical reasons). The mean EE of the Poisson spike-train analysis was 154.41 ms (n=576; SD: ±141.81 ms; Fig. 3d).

In CUSUM analysis, 1, 2 or 3 SDs above the mean spontaneous activity are usually used as the threshold level for this process (Ouellette and Casanova, 2006; Butler et al., 1992). We found that this method tested with 1–3 SDs thresholds consistently underestimated the latencies. We therefore tested our data set with 15 different SD parameters (the threshold was varied in the interval 1–15 SDs). The most accurate latencies and therefore the smallest EE could be calculated by using 9 SDs as threshold. Below and above this threshold, the EEs were higher (Figs. 3b, d). The mean EE with the most accurate (9 SDs) threshold was 85.26 ms (n=681; SD: ±120.11 ms).

The method of Falzett et al. combined the advantages of the CUSUM process with the same SOD function as used in our double sliding-window technique. Fig. 3c illustrates the mean EEs on the use of different n values of the SODs. Similarly as with the double sliding-window technique, the method of Falzett et al. provides the most accurate response onset latencies when high n values are used (n>22; Figs. 3c, d). The median calculation of the acquired onset latencies using different high n values (n=22–30) provided the most accurate values. The mean of the medians of the EEs by the method of Falzett et al. was 62.87 ms (n=681; SD: ±99.98 ms).

2.3. *Comparison of the confidence of the double sliding-window technique with Poisson spike-train analysis, the CUSUM procedure and the method of Falzett et al.*

Since the EE data sets did not reveal normal distribution, we used the Wilcoxon test for the correlated samples to compare the effectiveness of the double sliding-window technique with that of Poisson spike-train analysis, the CUSUM procedure and the method of Falzett et al. The distributions of the EEs observed when the four investigated techniques were used are presented in Fig. 3d. The double sliding-window technique appears to be the most accurate automated latency estimation method in the sense that the EE provided by this technique (mean: 35.98 ms; n=681; SD: ±58.48 ms) was significantly smaller (in all cases p<0.01) than those resulting from Poisson spike-train analysis (mean: 154.41 ms; n=576; SD: ±141.81 ms), the CUSUM procedure (mean: 85.26 ms; n=681; SD: ±120.11 ms) and the advanced method of Falzett et al. (mean: 62.87 ms; n=681; SD: ±99.98 ms).

3. Discussion

The new method described here, the double sliding-window technique, allows the rapid, reproducible, accurate and automated estimation of the neuronal response onset latency. Our results show that the double sliding-window technique can yield more accurate latency data than Poisson spike-train analysis (Legéndy and Salcman, 1985), the CUSUM procedure (Ellaway, 1978) and the method of Falzett et al. (1985) in the sense that the EEs of the latencies calculated by the double sliding-window technique are significantly smaller than those of these most commonly used methods. Furthermore, the double sliding-window technique seems to be able to determine the latency of both excitatory and inhibitory neuronal responses since it detects conformity changes between two data sets regardless of the direction of change.

Poisson distribution (Legéndy and Salcman, 1985) expresses the probability of a number of rare events occurring in a fixed period of time if these events occur with a known average rate, and are independent of the time since the last event. The weakness of Poisson spike-train analysis, i.e. the overestimation of the response latency, may occur for several reasons. The neuronal excitations in a spike train are not independent of each other, and if the spontaneous activity of a single unit is relatively high, and thus the estimated parameter λ of the method is higher than a particular limit, the Poisson spike-train analysis may not work properly. Poisson spike-train analysis is suitable only for the calculation of onset latencies of neurons with low or no spontaneous activity. However, a noteworthy population of neurons has high spontaneous activity, and for these, Poisson spike-train analysis furnishes inaccurate latencies.

As concerns the CUSUM method (Ellaway, 1978), it appears that the most commonly used 1 or 2 SDs above the main spontaneous discharge rate chosen as threshold level is not sufficient to calculate the response onset latency. The mean +9 SD threshold level allows an estimation of the most accurate onset latencies whereas the mean+2 SD threshold level results in an underestimation of the response onset latencies. However, even if we choose a statistically abnormal high 9 SD threshold level, the CUSUM method is still a poorly reliable technique. In the modification of the CUSUM procedure (method of Falzett et al., 1985), the most sensitive problem is the choice of the appropriate n value for the SOD. A 100 ms binwidth and n=3–5 were chosen in the original publication of Falzett et al. as producing the most reliable onset latencies. In our analysis we used a 5 ms binwidth, and found that n=22–30 is the most appropriate parameter with which to calculate the response onset latencies by the method of Falzett et al. Thus, it seems that the correct level of n has to be chosen for the binwidth. Despite the arbitrarily chosen n value, the method of Falzett et al. still appears to be the most reliable of the three techniques discussed above for numerous neuronal response characteristics.

In order to exclude the subjective, arbitrary selection of the parameters, the n value of the SOD and the window width, the double sliding-window technique calculates the latencies by using a series of constant parameters, and the median of the latencies estimated for 25 constant parameter combinations (see Results) defines the response onset latency of a single neuron. It should be noted that the optimal parameter combination set used here to calculate the response onset latency may be valid only for this particular study and may differ from the optimal parameter combinations for other areas of the central nervous system. Another weakness of automated response onset latency estimation procedures is that the arithmetical accuracy of latency value does not correlate with the uncertainty of the estimation. In order to reduce such false

estimations, preliminary visual inspection of the recordings or preliminary, basic statistical probes are recommended.

With regard to its advantages and disadvantages, the double sliding-window method offers a practical alternative to other methods, such as subjective visual estimation, Poisson spike-train analysis, the CUSUM procedure and the method of Falzett et al. (1985). The reliability and reproducibility of the double sliding-window method allow its use in the daily, routine calculation of neuronal response onset latencies.

4. Experimental procedures

The method presented here was specifically developed for the analysis of neuronal activity stored in PSTHs (Eördegh et al., 2005). The original temporal resolution of the recoded data was 1 ms, which was converted to a 5 ms binwidth for faster processing. Each PSTH consisted of a prestimulus interval and a peristimulus interval. The prestimulus interval contains the genuine spontaneous activity of a neuron, while the peristimulus interval contains both the spontaneous activity and the responses of a neuron to the stimulation. The duration of the spontaneous activity in the peristimulus interval defines the onset latency of the neuronal response.

4.1. *Response onset allocation via the t test*

The first element of this computational method is a double sliding-window technique with repetitive application of the *t* test for dependent samples. A computer program slides two virtual time windows with specific width along the spike frequency histogram. The first window, called the reference window, slides through the peristimulus histogram in 1 bin steps (5 ms in our analysis), and the portion is selected where the difference between the content of the reference window and the average activity during the prestimulus period is the highest. The reference window in this specific position represents the maximum frequency (or the minimum frequency if an inhibitory response is investigated) of the peristimulus interval (Fig. 1a). The content of this window is declared to be the 'pure response' and is applied later as a reference in the *t* test. A second window, called the sample window, slides from the beginning of the prestimulus period (pure spontaneous activity) to the position of the reference window in 1 bin steps. For each 1 bin step, a paired *t* test is carried out between the spike rate of the reference and the sample windows, and the level of significance (*p* value) calculated from the *t* value is stored and plotted on a graph. The accurate definition of the lengths of the windows is reasonable, since a too narrow reference window may not compensate the frequency variability inside the spontaneous activity (i.e. a stochastic simultaneous excitation in several trials may lead to an erroneous response identification when the sample window is too narrow to compensate it), while a too broad sample window may include pure spontaneous activity in addition to the response (especially when the window width is broader than the duration of the neuronal response).

This method calculates the similarity between a reference window containing a pure neuronal response and a moving sample window, which at the beginning of the evaluation contains only pure spontaneous activity; later, it contains both spontaneous and stimulated activity; and finally only pure stimulated activity is present. Initially, when no response occurs inside the sample window, the similarity is minimal (the significance level is low). Afterwards, the sampling window slides into the response period, finally reaching total equivalence (significance level 1) as the two windows overlap each other. A curve is fitted to the *p* values, in a theoretical case this being a sigmoid curve (Fig. 1b). The time interval between the start of the stimulation and the first point of the ascending segment of this curve provides the response onset latency.

4.2. *Estimation of the onset of elevation*

When a response occurs, the significance curve mentioned above no longer fits one straight line, but consists of several linear segments, each with a different slope. Each segment of the curve produced by the sliding-window function describes a different period of the neuronal activity and the slope of each segment gives an estimate of the change in the neuronal discharge rate during that segment according to the fixed reference window. In Fig. 1b, the first segment represents pure spontaneous activity, while the second component represents the time segment when the sample window slides onto the response period and contains spontaneous activity and also neuronal responses. Finally, the third segment represents the stage when the sample window clearly overlaps the response. The slope of the second segment is steeper than that of the first, indicating a 'positive conformity change' between the two window contents. The elevation of the significance curve is indifferent as regards the direction of the neuronal discharge rate change, and thus our method can be used to estimate the onset latency of both excitatory and inhibitory neuronal responses. To estimate the latency quantitatively, a SOD is calculated from the sliding-window function to determine the first point of the elevating segment of the significance curve. The aim of this function is to locate breaks and discontinuities between linear segments.

Eq. (1) is used to produce such a function according to Falzett et al. (1985):

$$SOD_{(t)} = |(X_{(t-n)} - X_{(t)})| - |(X_{(t+n)} - X_{(t)})| \quad (1)$$

where X = the significance level; t = the actual time component of the function; and $n = \Delta t$, an arbitrary time offset. $SOD_{(t)}$ is computed for each point on the significance curve (Fig. 1c).

A zero value of this difference function means that no change occurs in the steepness of the observed curve in the vicinity of moment $X_{(t)}$. The peaks in the SOD curve furnish estimates of the positions of maximal slope change, and thus define the endpoints of each linear segment. The latency of the response can be calculated by subtracting the time of the stimulus onset from the minimum in $SOD_{(t)}$.

In order to eliminate sporadic disturbances in measurement (estimation imprecision in the case of a single *n* value), the method calculates the response onset latencies as a median of 25 measurements per registration, using 25 selected different parameter combinations that provided the most

accurate latencies for our data sample (4 different window widths from 150 to 300 ms, and the corresponding highest possible n values of SOD; Fig. 3a).

For the cell shown in Fig. 1, the maximum possible n offset of SOD function (30 bins) was applied (which is equal to half of the t test window width (300 ms, 60 bins) as otherwise the SOD function may run out of the range of the t test results), because this value produced a relatively smooth SOD with well-defined peaks. The analysis began with the 31st point of the significance curve ($t=31$; $n=30$), with computation as defined by the equation ($SOD_{(31)}=|(X_{(1)}-X_{(31)})|-|(X_{(61)}-X_{(31)})|$). The next point of the significance curve to the right of point 31 was then selected and the process was repeated until the entire difference curve had been generated ($SOD_{(32)}=|(X_{(2)}-X_{(32)})|-|(X_{(62)}-X_{(32)})|$).

4.3. *Statistical evaluation of onset latencies*

Visual latency estimation was performed independently by all three authors (experienced neurophysiologists). The mean of the three subjectively quantified latencies was regarded as the gold standard during the comparison, and EE was calculated for each latency by different techniques via the following equation:

$$EE = |L_t - L_s| \quad (2)$$

where L_t is the onset latency acquired by the automated latency estimation method used, and L_s is the visually quantified gold standard value.

The EE results did not indicate a normal distribution according to the Lilliefors test ($p<0.01$), and the Wilcoxon test for correlated samples was therefore used to compare the EE results of the different calculation methods.

4.4. *Recording and stimulation*

The visual responses of 681 neurons (10 in the suprageniculate nucleus, 238 in the anterior ectosylvian visual area, 20 in the caudate nucleus, 228 in the substantia nigra, 80 in the superior colliculus and 105 in the primary visual cortex) of the feline brain were analyzed in this study. The animal preparation, the surgery and the other details of data collection were described in our earlier papers (Eördegh et al., 2005; Nagy et al., 2005; Paróczy et al., 2006).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brainres.2007.08.041.

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