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Measuring spike pattern reliability with the Lempel–Ziv-distance

Markus Christen[a,*], Adam Kohn[b], Thomas Ott[a], Ruedi Stoop[a]

[a] *Institute of Neuroinformatics, University/ETH Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland*
[b] *Center for Neural Science, New York University, NY, USA*

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Abstract

Spike train distance measures serve two purposes: to measure neuronal firing reliability, and to provide a metric with which spike trains can be classified. We introduce a novel spike train distance based on the Lempel–Ziv complexity that does not require the choice of arbitrary analysis parameters, is easy to implement, and computationally cheap. We determine firing reliability in vivo by calculating the deviation of the mean distance of spike trains obtained from multiple presentations of an identical stimulus from a Poisson reference. Using both the Lempel–Ziv-distance (LZ-distance) and a distance focussing on coincident firing, the pattern and timing reliability of neuronal firing is determined for spike data obtained along the visual information processing pathway of macaque monkey (LGN, simple and complex cells of V1, and area MT). In combination with the sequential superparamagnetic clustering algorithm, we show that the LZ-distance groups together spike trains with similar but not necessarily synchronized firing patterns. For both applications, we show how the LZ-distance gives additional insights, as it adds a new perspective on the problem of firing reliability determination and allows neuron classifications in cases, where other distance measures fail.

Keywords: Spike train distance measure; Spike pattern; Lempel–Ziv-complexity; Clustering; Neuron classification; Firing reliability; Visual system; Macaque monkey

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1. Introduction

Measuring the similarity of neuronal firing is required for solving two problems of spike train analysis. First, the reliability of neuronal firing can be measured by calculating the mean distance among a set of spike trains obtained from multiple presentations of the same stimulus. The larger the mean distance, the less reliable is the neuron's firing. Second, in combination with a clustering algorithm, neurons can be classified in terms of firing similarity. This is critical for gaining information about the functional connectivity of a probed neuronal network. A classic example is the discrimination between simple and complex cells in the primary visual cortex based on response modulation (Skottun et al., 1991). To solve these problems, a variety of distance measures has been proposed (see Fig. 1). Almost all these measures introduce a bias by predefining analysis parameters. Only the simplest measure, the *spike count distance* that measures similarity as the difference in the total number of spikes evoked, is free from any bias—but this measure does not take the temporal structure of the spike train into account. *Information distances* – e.g. those that rely on the Kolmogorov complexity (Bennett et al., 1998; Li et al., 2001) or the Kullback–Leibler distance (Johnson et al., 2001; Samonds et al., 2003) – require that spike trains are transformed into bitstrings (see Section 2). Binning introduces a bias that can only be neglected for a sufficiently small binsize, such that spikes are well-separated (see Section 2.1). Other distance metrics, however, introduce more severe biases. The *firing rate distance* requires the predefinition of a time interval T_{rate} over which the local firing rate is calculated. *Cost-function distances* need a predefined cost-function to determine the cost of transforming one spike train into another by moving, deleting and inserting spikes (Victor and Purpura, 1997). *Correlation distances* measure coincident firing of spike trains (Perkel et al., 1967), expressed for example by synchronized activity measured by gravitational clustering (Gerstein et al., 1985), or by calculating the dot product or the integral of spike trains convolved with a Gaussian (Schreiber et al., 2004) or exponential (Van Rossum, 2001) kernel. These distance measures depend on the choice of the specific functions involved, such as the width of the Gaussian kernel, and may generate results that are difficult to interpret when applied to cells with very different firing rates, because coincidence may just appear

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[*] Corresponding author. Tel.: +41 44 635 3062; fax: +41 44 635 3053.
E-mail address: markus@ini.phys.ethz.ch (M. Christen).

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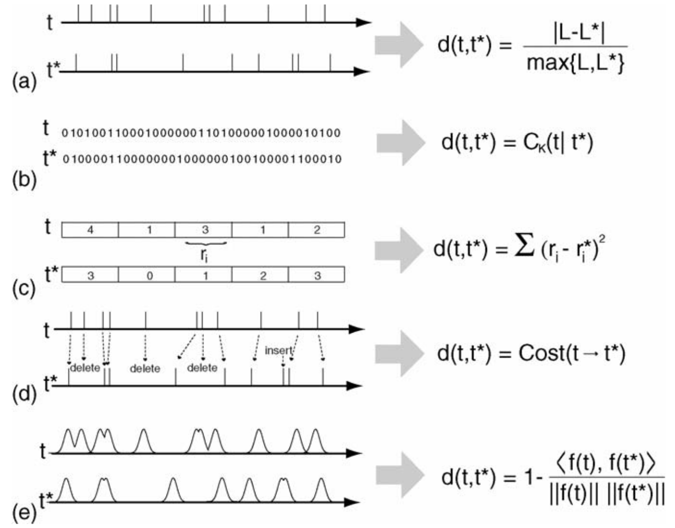

Fig. 1. Spike train distance measures (t, t^*: spike trains). (a) Spike count distance: $d(t, t^*) = \frac{|L-L^*|}{\max\{L,L^*\}}$ (L, L^* are the numbers of spikes in each train). (b) Example of an information distance: $d(t, t^*) = C_K(t|t^*)$ ($C_K(t|t^*)$ is the Kolmogorov complexity of train t given train t^*). (c) Example of a rate distance: $d(t, t^*) = \sum_i (r_i - r_i^*)^2 \{r_1, \ldots, r_n\}$ is the sequence of local firing rates of spike train t partitioned in n time intervals of length T_{rate}). (d) Cost-function distance: $d(t, t^*) = \text{Cost}(t \rightarrow t^*)$. (e) Example of a correlation distance (C-distance): $d(t, t^*) = 1 - \frac{f(t) f(t^*)}{||f(t)|| \, ||f(t^*)||}$ ($f(t)$ is the spike train t convolved with a Gaussian kernel function $f(\cdot)$).

due to chance and not due to structural or functional connectivity (Meissen and Epping, 1987). For both firing rate measurement and neuron classification, the biases discussed above may affect the analysis.

The available distance measures give different insights into the two basic problem types mentioned. Most common, however, are those distances that focus on the precise timing of spikes and consider spike trains as close with a large degree of synchronous spikes. But other research questions, like the search for precisely replicating sequences in neuronal firing (Abeles and Gat, 2001), require alternative distance measures. We introduce a novel distance based on the Lempel–Ziv-complexity (Lempel and Ziv, 1976) that does not require the choice of arbitrary analysis parameters, is easy to implement, and computationally cheap, as it is based on well-known and widely used compression algorithms. Compared e.g. to the C-distance (see Fig. 1(e)), the calculation of the Lempel–Ziv-distance (LZ-distance) is four to six times faster, depending on the length of the spike train. The measure is applied to spike trains that are transformed into bitstrings. As the methodology used for defining the LZ-distance is similar to the one applied in compression algorithms (Gersho and Gray, 1992), the metric considers strings as similar if they have similar compression properties. Due to this character of the metric, we will show that the LZ-distance considers spike trains with similar but possibly delayed firing patterns as close. This is advantageous when firing reliability of single neurons under in vivo conditions is considered, as the LZ-distance accounts for delays of firing patterns that may appear in different responses to multiple presentations of a single stimulus. Such differences may result from influences to the neuron under investigation that are, in the in vivo condition, beyond the experimenter's control. In this way, the LZ-distance allows one to address an alternative aspect of firing reliability compared to distance measures that focus on synchronous firing.

The *classification* of spike trains basically requires two ingredients: a distance measure and a clustering algorithm. The former defines the *type of similarity* that is taken as the basis for neuronal group identification, the latter defines how the clusters are actually found. As it is a priori unknown how many neurons form a single group and how many such groups are present in the probed neuronal network, the algorithm should not require information about the number or the size of clusters. We have developed the sequential superparamagnetic clustering algorithm that satisfies these requirements. The algorithm operates in analogy to a self-organizing Potts-spin system (Ott et al., 2005). Essentially, it only requires the determination of a minimal cluster size (which is two in our case) and a minimal cluster stability S_θ—latter indicates the minimal density of a cluster given a certain distance measure. In this way, no substantial bias is set upon the clustering procedure. In the application of the LZ-distance for neuron classification, we will show that the measure groups together spike trains with similar but possibly delayed firing patterns. This is important because, due to the complex neuronal connectivity in cortex, similar firing patterns may occur as delayed patterns in different neurons. Distance measures that focus on synchronized firing would not classify such cells as firing similarly. In this way, the LZ-distance supplements the available methods for spike train classification.

2. Materials and methods

2.1. Definition of the LZ-distance

For our analysis, spike trains given as sequences of neuronal spike-times $t = \{t, \ldots, t_n\}$ are translated into bitstrings. For this translation, the measurement time interval $[0, T]$ is partitioned into n bins of width $\Delta\tau$ ($n\Delta\tau = T$). If at least one spike falls into the ith bin, the letter "1" (and otherwise the letter "0") is written to the ith position of the string. Usually, $\Delta\tau$ is chosen so that maximally one spike falls into one bin. This can be achieved by setting $\Delta\tau = 1$ ms, because of the neuronal refractory period. We found that our analysis is not effected by the choice of $\Delta\tau$ as long as this criterion is fulfilled. The resulting bitstring is denoted by X_n, a substring starting at position i and ending at position j is denoted by $X_n(i, j)$. Such a bitstring can be viewed as being generated by an information source. For this source, we want to find the optimal coding (Cover and Thomas, 1991; Steeb and Stoop, 1997). This coding is based on a parsing that partitions the string into non-overlapping substrings called *phrases*. The set of phrases that results from a parsing of a bitstring X_n is denoted by P_{X_n}. To calculate the LZ-complexity, two distinct codings have been introduced (Lempel and Ziv, 1976; Ziv and Lempel, 1978). We use the coding that sequentially parses the string such that the new phrase is not yet contained in the set of phrases generated so far (Ziv and Lempel, 1978). As an illustration, the string 0011001010100111 is parsed as 0|01|1|00|10|101|001|11. It can be shown that this procedure, hence called *LZ-coding*, is the appropriate coding for calculating the LZ-distance of spike trains as it is noise robust (Christen et al., 2004). In addition, it is computationally cheap. The Lempel–Ziv-complexity is then defined as follows:

Definition 1. For a bitstring X_n, the Lempel–Ziv-complexity $K(X_n)$ of X_n is

$$K(X_n) = \frac{c(X_n)\log c(X_n)}{n}$$

where $c(X_n)$ is the number of phrases that results from the LZ-coding of X_n.

If a bitstring X_n is the result of a stationary, ergodic process with entropy rate H, then the LZ-complexity is asymptotic optimal, i.e. $\limsup_{n\to\infty} K(X_n) \leq H$ with probability 1 (Cover and Thomas, 1991). Stationarity of neuronal firing, which is required if the LZ-complexity is used for estimating the entropy rate of a spike train (Amigö et al., 2004), is not critical for calculating the LZ-distance.

To explain the LZ-distance, we assume two strings X_n, Y_n of equal length n. From the perspective of LZ-complexity, the amount of information Y_n provides about X_n is given as $K(X_n) - K(X_n|Y_n)$, where $c(X_n|Y_n)$ is the size of the difference set $P_{X_n} \backslash P_{Y_n}$ If Y_n provides no information about X_n, then the sets P_{X_n} and P_{Y_n} are disjoint, and $K(X_n) - K(X_n|Y_n) = 0$. If Y_n provides complete information about X_n, then $P_{X_n} \backslash P_{Y_n} = \phi$ and $K(X_n) - K(X_n|Y_n) = K(X_n)$. The LZ-complexity approximates the Kolmogorov complexity $C_K(X_n)$ of a bitstring and a theorem in the theory of Kolmogorov complexity states that $C_K(X_n) - C_K(X_n|Y_n) \approx C_K(Y_n) - C_K(Y_n|X_n)$ (Li and Vitányi, 1997). In practical applications with bitstrings of finite length, however, this symmetry does not hold when the LZ-complexity is used. Therefore, we have to calculate $K(X_n) - K(X_n|Y_n)/K(X_n)$ as well as $K(Y_n) - K(Y_n|X_n)/K(Y_n)$ and we take the minimum in order to ensure $d(X_n, X_m) > 0$ for $n \neq m$. Theoretically, this asymmetry may be used to gain further information on causal relationships between neurons, although in our applications, the difference is usually only small such that no specific information can be gained from it. Furthermore, the expression $K(X_n) - K(X_n|Y_n)$ is normalized by $K(X_n)$ (and by $K(Y_n)$, respectively) such that the distance $d(X_n, Y_n)$ ranges between 0 and 1. This leads to the following definition of the *LZ-distance*:

Definition 2. For two bitstrings X_n and Y_n of equal length, the Lempel–Ziv-distance $d(X_n, Y_n)$ is:

$$d(X_n, Y_n) = 1 - \min\left\{\frac{K(X_n) - K(X_n|Y_n)}{K(X_n)}, \frac{K(Y_n) - K(Y_n|X_n)}{K(Y_n)}\right\}$$

In summary, the LZ-distance compares the set of phrases generated by a LZ-coding of two bitstrings originating from corresponding spike trains. A large number of similar patterns appearing in both spike trains should lead to a large overlap of the sets of phrases. Thus distances between spike trains with similar patterns are expected to be small, whereas distances between trains with different patterns are expected to be large.

2.2. Firing reliability as deviation from a Poisson reference

The *firing reliability* is measured by determining the mean of the pairwise distance between all spike trains obtained from one neuron in response to multiple presentations under equal stimulus conditions. We use both the C-distance (according to Schreiber et al. (2004), see also Fig. 1) and the LZ-distance in order to obtain complementary information about firing reliability. The C-distance measures the degree of coincident firing of two neurons. Therefore, a small mean C-distance indicates high timing reliability, whereas a large mean C-distance indicates low timing reliability and/or a large variability in firing rate. The LZ-distance measures the degree of firing-similarity in terms of spike patterns. A small mean LZ-distance indicates the presence of similar (and possibly delayed) firing patterns, whereas a large mean LZ-distance indicates the absence of similar firing patterns within the different spike trains and/or a large variability in the firing rate.

The main problem for both the C-distance and the LZ-distance is the interdependence between mean distance and firing rate, because a higher firing rate increases the chance of coincident spikes and leads, for example, to smaller mean C-distances. We therefore need a reference to calculate the reliability of neuronal firing independently of the firing rate. This reference is provided by a Poisson process, the most random distribution of events in time (Cox and Lewis, 1966). Mean distances obtained by analyzing real data of a specific neuron can then be compared with mean distances of a set of Poisson spike trains with similar rate. The larger the deviation, the more reliable (in terms of the distance used) is the neuron's firing.

To investigate the dependence of the C-distance and the LZ-distance on firing rate in more detail, we generated by means of a Poisson process 72 sets of 10 spike trains with similar firing rate each (duration: 10 s per train, sampled with a resolution of 1 ms). The majority of the trains had (physiologically meaningful) firing rates of 1–100 spikes/s. To analyze the limit behavior, higher firing rates up to 1000 spikes/s were also used. For each set, we measured the mean C- and LZ-distance (Fig. 2). For the C-distance we see that distance is basically linearly related for small firing rates and that it asymptotically approaches $d(t, t^*) \simeq 0$ for large firing rates. This is plausible, as the probability that the convolved trains overlap scales linearly with the increase in number of (randomly distributed) spikes for small firing rates (i.e. when for the convolved trains $f(t) = 0$ holds for most parts of the spike train) and saturates asymptotically for large firing rates. By testing several fit-functions (polynomials, exponential and power-law functions) we found that a fourth order polynomial of the type $p(x) = ax^4 + bx^3 + cx^2 + dx + e$ provided the best fit in terms of minimized mean-square errors (for a firing rate of 0, the function has a point of discontinuity, as the mean distance would be zero). This function is taken as the Poisson reference for the C-distance.

The relation between the LZ-distance and the firing rate is more complex. For small firing rates (up to -10 spikes/s) we find a steady increase of the mean distances up to -0.2, which is followed by a very slow further increase until the firing rate reaches $\sim$500 spikes/s. This is the point, where the bit-coded

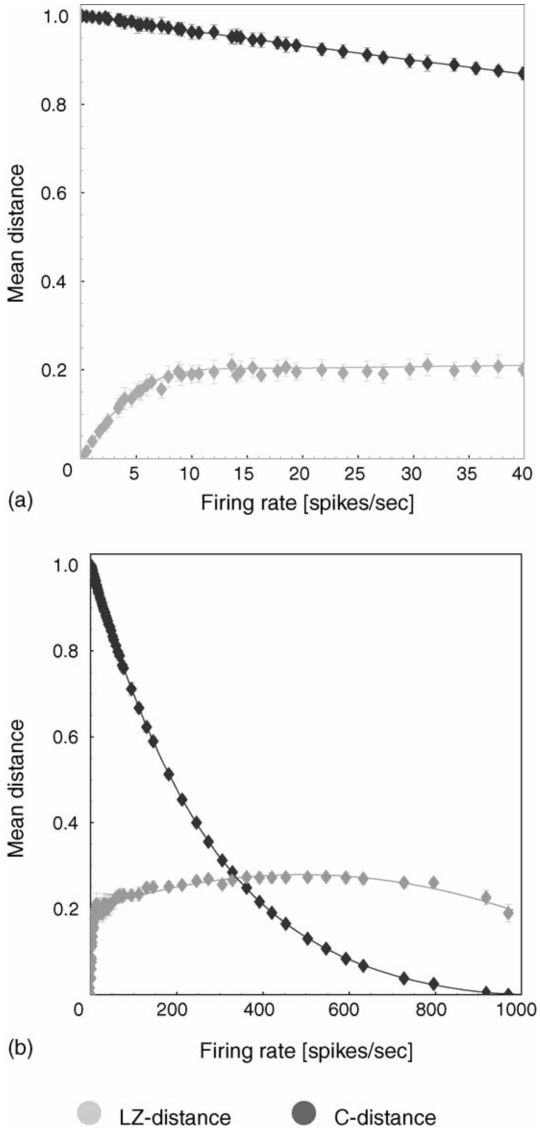

Fig. 2. Relation between the C/LZ-distances and the firing rate for Poisson spike trains: (a) small firing rates, (b) asymptotic behavior for large firing rates. For the C-distance, the width of the Gaussian kernel was let unchanged.

spike trains have an equal number of ‘0’ and ‘1’. For larger firing rates, we find a symmetry along the vertical axis $x = 500$, because in the bit-coded spike trains a switch between the letters ‘0’ and ‘1’ is observed as the spike train predominately consists of spikes. We obtained the best fit to this function by a fourth-order polynomial for the interval [0, 20] spikes/s and a quadratic function for the interval [20, 980] spikes/s. We use this composed function as the Poisson reference for the LZ-distance. The deviation of the neuronal data to these two Poisson reference functions is our measure for the reliability of firing in terms of the C/LZ-distances. It is calculated as follows: For a fixed stimulus parameter, several spike trains are obtained in an experiment. We calculate the mean distance of these spike trains and the mean firing rate. For this mean firing rate, the Poisson reference provides us the mean distance from a set of Poisson spike trains. The absolute value of the difference between these two mean distances is the deviation. For different stimulus parameters, we obtain a distribution of deviations, from which the mean deviation – the reliability of the cell independent of the stimulus used to evoke the response – is calculated. Note, that this measure of reliability can be refined by distinguishing between deviations that exceed the Poisson reference and those that are smaller than the reference. The former indicates that, in the C-distance paradigm, systematic de-synchronization beyond Poisson firing appears in the different trials, whereas latter indicates a higher degree of synchronization compared to the Poisson reference. In our analysis (Section 3) we however forwent this further distinction, as this would complicate the interpretation of the results.

2.3. Sequential superparamagnetic clustering

To group spike trains into classes, we use the *sequential superparamagnetic clustering* algorithm, whose conceptual idea can be outlined as follows: data points are interpreted as particles to which a Potts-spin is assigned. Each particle can interact via its spin with the particles of a defined neighborhood (usually *k*-nearest neighbors). The particles tend to align the direction of their spins depending on the interaction strength, whereas thermal fluctuation opposes this tendency. The interaction strength is a decreasing function of the distance between the points. Groups of particles with aligned spins form clusters, whose size diminish with increasing temperature T. Groups of particles with strong interaction are able to resist this tendency of disintegration. Thus, the size of this cluster is stable over a broad range of T. Clustering is applied for a certain range of $T = 0, \ldots, T_{\max}$ in steps of ΔT. Usually at $T = 0$, one cluster is present, which breaks up into smaller clusters for increasing T. The sequential approach allows one to take inhomogeneities in the data space into account: The data points of the densest cluster are removed and the clustering algorithm is reapplied to the remaining data set as well as to the removed cluster. The application of superparamagnetic clustering algorithm requires the determination of several parameters. The most important ones are minsize (the minimal size of clusters) and S_θ (the minimal required cluster stability), which define the resolution of the clustering procedure. The other parameters are only of minor interest and basically influence the efficiency of the algorithm. In this way, the clustering algorithm comes equipped with an intrinsic measure for cluster stability S, with $0 \leq S \leq 1$. It sequentially reveals clusters according to their stability, i.e. the most stable cluster is detected first. The result of clustering is displayed in a dendrogram that indicates how larger clusters break apart into smaller clusters. Furthermore, the size of the cluster N, $T_{\max}$ (the temperature, where all clusters have disintegrated), the cluster stability S (the temperature range over which the cluster remains stable relative to $T_{\max}$), T_{cl} (the temperature range over which the cluster remains stable) and T_{ferro} (the temperature, where the cluster is still in the ferromagnetic phase, i.e. all spins are aligned) are displayed. For a formal description of the algorithm, we refer to Ott et al. (2005).

2.4. Experimental procedure

Neural recordings were performed in anesthetized (with sufentanil citrate at 4–8 μg/kg/h), paralyzed (with vecuronium bromide at 0.1 mg/kg/h) macaque monkeys. Vital signs (EEG, EKG, end-tidal PCO_2, lung pressure, and temperature) were monitored continuously. All experimental procedures were approved by the New York University Animal Welfare Committee. Recordings were made with tungsten-in-glass or platinum/tungsten electrodes. Signals were amplified, band pass filtered (typically 300 Hz to 10kHz) and fed into a hardware dual time-amplitude window discriminator. Spike times were saved with a resolution of 0.25 ms. Analysis was performed on previously published recordings in the lateral geniculate nucleus (LGN; Movshon et al., 2005), primary visual cortex (V1; Kohn and Smith, 2005), and in area MT (Kohn and Movshon, 2004). Detailed methods for the recordings can be found in those references.

3. Results

3.1. Distinguishing timing and pattern reliability

We investigated the performance of the LZ-distance for determining the reliability of neuronal firing under in vivo conditions from measurements obtained at different stages of the visual information processing pathway. We used recordings of nine LGN neurons, ten complex neurons in V1 (V1C), six simple neurons in V1 (V1S) and seven neurons in area MT stimulated by drifting gratings of different orientation (V1, MT) or frequency (LGN). For the LGN-cells, six to seven different temporal drift frequencies of grating were presented. However, only two to three trials per stimulus were recorded, which limits the significance of the results obtained for this class of cells. For the V1 cells, ten repetitions of each stimulus (five orientations) were recorded in each cell. For the MT cells, six trials were measured (16 orientations). For each set of spike trains emerging from trials performed on a specific cell and using a specific stimulus, the mean C- and LZ-distance between the trains was calculated (the standard deviation of the Gaussian kernel used for convolving the spike train before applying the C-distance was 1 ms).

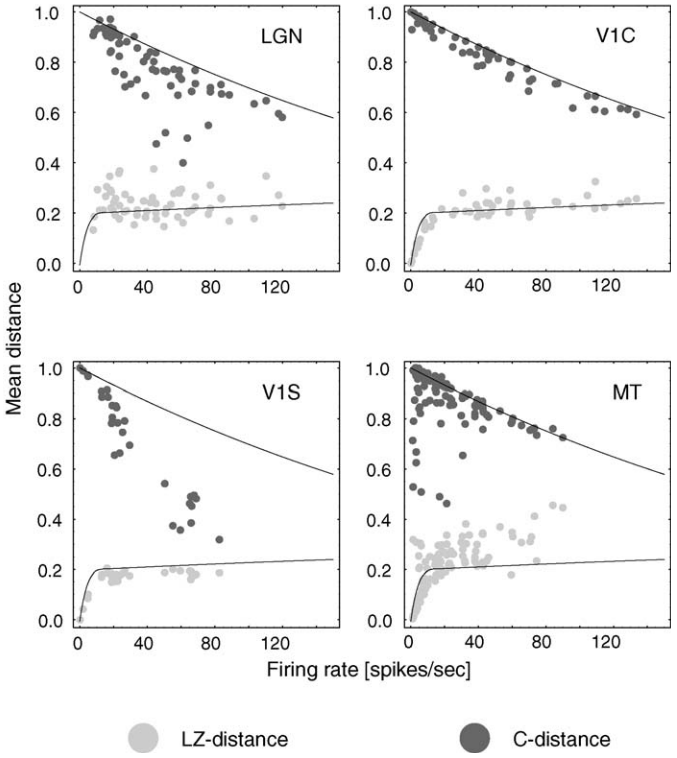

Fig. 3. Relation between the C/LZ-distances and the firing rate for spike trains obtained from neurons of areas LGN, V1 (complex: V1C and simple: V1S), and MT in macaque monkey.

The results of the analysis for the four cell types investigated are displayed in Fig. 3. Each point in the graph reflects the mean distance of all trials of a single stimulus parameter (drift frequency or orientation) for a single neuron calculated using the LZ-distance measure (light grey) or the C-distance measure (dark grey). The curves shown are the Poisson reference functions described in Section 2. We then determined the deviations of the mean distances of each trial from the Poisson reference for the C-distance (‘timing reliability’) and the LZ-distance (‘pattern reliability’) and for each class of neurons. As the standard deviations of the data sets obtained in this way (LGN, V1C, V1S, MT) were high, we pairwise tested the null-hypothesis that two sets of deviations derive from the same distribution using the non-parametric Wilcoxon–Mann–Whitney U-test with significance levels $p<0.05$ and $p<0.001$ (two-sided). The results are displayed in Fig. 4. For the C-distance, the data sets obtained from the MT-cells and the V1 complex cells are not distinguishable at the $p<0.05$ and $p<0.001$ level, whereas the other sets are recognized as distinct distributions. For the LZ-distance and a significance level of $p<0.05$, the data sets V1C and V1S, as well as V1S and LGN are not distinguished, but MT was classified as distinct. For the higher significance level $p<0.001$, the data sets V1C, V1S, and LGN, as well as LGN and MT

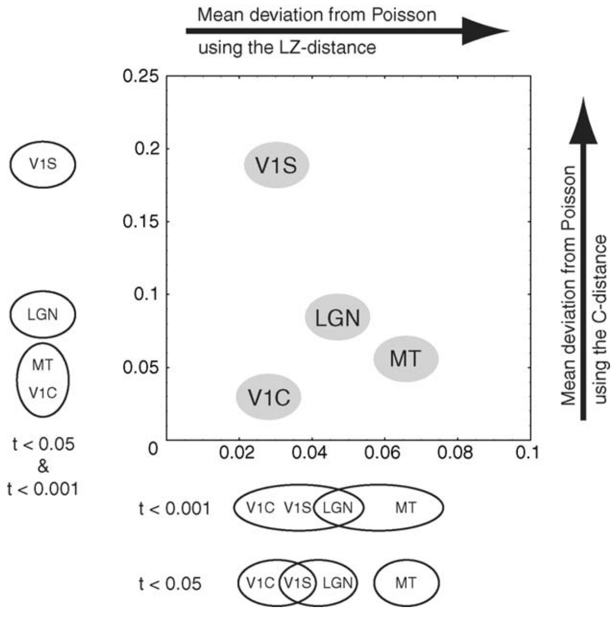

Fig. 4. Mean deviation from the Poisson reference of the LZ- and C-distance of spike trains originating from neurons measured in areas LGN, V1 (complex/simple cells) and MT.

were not distinct. In summary, the results suggest the following interpretation: in terms of the ‘timing deviation’ of the data from the Poisson reference, the V1 simple cells have the highest value (i.e. have the highest ‘timing reliability’), followed by the LGN cells and the MT/V1 complex cells. In terms of the ‘pattern deviation’ of the data from the Poisson reference, the MT neurons have the highest value (i.e. have the highest ‘pattern reliability’), followed by the LGN, V1 simple and complex cells. Thus, the complex cells are closest to the Poisson model in both respects, whereas the MT cells have a considerable ‘pattern reliability’ and the V1 simple cells a considerable ‘timing reliability’. The LGN cells display both characteristics up to some degree, although the number of trials per stimulus conditions in this case is low and thus requires a careful interpretation.

3.2. *Classifying spike trains with non-synchronous patterns*

To investigate the performance of the LZ-distance in spike train classification, we proceed in two steps: we test whether the LZ-distance sorts spike trains of physiological and simulated data and we compare the performance of the LZ-distance with the C-distance when clustering artificial spike trains with similar, but not synchronous patterns. For the first step, we generated a set of spike trains consisting of in vivo and model data of comparable firing rate (80–90 spikes/s), as classes of spike trains that differ substantially in firing rate are easily recognized using the LZ-distance. Our multi-train data set contains the following five classes, each represented by nine spike trains of length 2400 ms. Class (A) spike trains of a complex cell (macaque monkey visual cortex data, for further explanation see preceding section) driven by gratings drifting at 6.25 Hz. Class (B) spike trains of a simple cell driven by gratings drifting at 12.5 Hz. Class (C) spike trains of a homogeneous Poisson process with refractory period that models the firing of the recorded complex cells. The absolute refractory period is 1 ms, the relative refractory period is tuned such that the interspike interval histogram is similar to the one of the original data. Class (D) spike trains of an inhomogeneous, step function driven Poisson process with refractory period that models the firing of the recorded simple cells. The frequency of the modulation is 12.5 Hz, the base rate is 0 spikes/s and the peak rate is tuned such that it is similar to the original data. Class (E) Poisson spike trains containing weakly synchronized burst patterns. The burst pattern is formed by sequences of three bursts of five spikes per burst and interburst-distances of ∼70 and ∼100 ms. The corresponding spikes of each burst of the pattern of each train are uniformly distributed within an interval of ±2 ms and ∼50% of the remaining spikes derive from a low-rate Poisson process that has been tuned such that the overall firing rate is similar to that of the other four classes. We randomized the order of the spike trains in order to obtain a multi-train data set (Fig. 5(a)). After calculating the LZ-distance between all trains (for the resulting distance matrix and the distribution of distances see Fig. 5(b)), clustering led to the following result: The classes B, D and E formed one cluster each, whereas the classes A and C fell into a single cluster (Fig. 3(c)). When the algorithm was applied to the latter cluster for a decreased minimal cluster stability S_θ, only an incomplete separation between spike trains of the classes A and C occurred, as two smaller clusters of five (spike trains of class C) and 13 elements each (spike trains of classes A and C) emerge (not shown). Two main conclusions can be drawn from this result. First, the metric is able to classify correctly spike trains with comparable firing rate, but differing temporal structures. Second, we are able to interpret classifica-

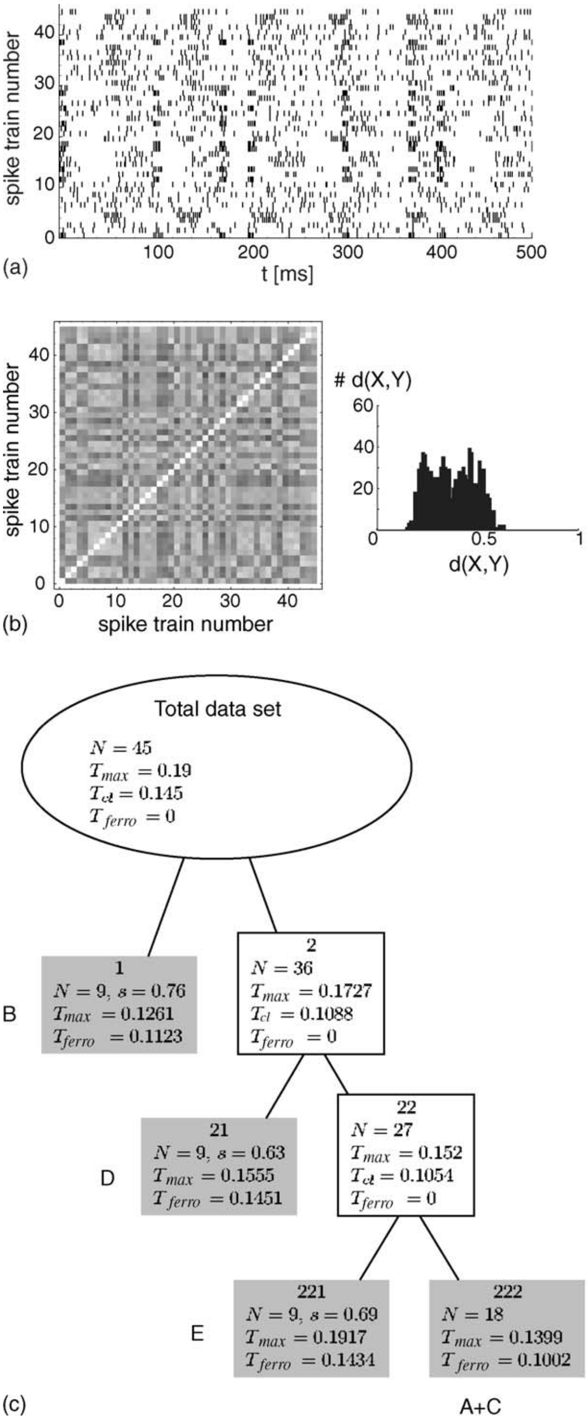

Fig. 5. Clustering of multi-train data. (a) Raster plot of initial spike set. (b) Distance matrix (white: $d(X, Y) = 0$, black: $d(X, Y) = 1$) and histogram of distances obtained after calculating the pairwise LZ-distance. (c) Dendrogram outlining the result of clustering.

tion failures as in the incomplete separation between spike trains of the classes A and C. Here, the spike trains C derive from a model of the firing of a complex cell and the incomplete separation from the spike trains of the complex cell indicates that the firing behavior of the cell appears to be (in a first approximation) properly modelled by a Poisson process with refractory period. The sinusoidal firing of the simple cell, however, could be distinguished from the inhomogeneous Poisson process driven by a step function, as the two classes B and D are separated by the clustering algorithm.

In a second step, we clustered model spike trains of similar firing rate that contain different types of repeating sequences of interspike intervals (interval patterns). The repeating sequences within spike trains of a single class characterized by one type of interval pattern are not synchronized, but randomly distributed within each train. This challenging task for spike train clustering is performed using the LZ-distance and the C-distance, the latter is a common distance measure for spike train clustering problems (Fellous et al., 2004). We generated five classes of spike trains, characterized by the following interval patterns. Class (A) (4, 4), Class (B) (13, 13, 13), Class (C) (5, 20, 3), Class (D) (3, 16, 3, 16), and Class (E) (1, 4, 7, 2, 6, 11). Each spike train (five per class) was generated such that 50% of the interspike intervals of the train originate from the sequence and 50% from a homogeneous Poisson process. The rate of the Poisson process was adapted for each class in order to generate almost identical mean firing rates for all spike trains (92–94 spikes/s). The order of the spike trains was again randomized to generate a multi-train data set (Fig. 6(a)). To this data set, sequential superparamagnetic clustering was applied, using both the LZ- and the C-distance (the standard deviation of the Gaussian kernel used for convolving the spike train before applying the C-distance was 1 ms). We found a clear difference in performance between the two distance measures: Whereas the LZ-distance allowed a clear-cut separation of all five classes (Fig. 6(c)), the use of the C-distance did not lead to any classification. This noticeable difference in performance becomes apparent if the distribution of the distances is compared (Fig. 6(b)). For the LZ-distance, the range of distances is ∼0.4 with a multi-modal distribution (indicating the structure within the data set), whereas for the C-distance the range is ∼0.1 with a unimodal distribution. The latter observation implies that a re-scaling would not increase performance and that the classification-failure is independent of the clustering algorithm used. This demonstrates that the LZ-distance is a measure that classifies spikes trains with delayed patterns. The C-distance, which focuses on synchronized firing, fails in such situations. In contrast, if synchronization were the desired criterion to classify spike trains, the C-distance would be more appropriate than the LZ-distance. Generally, two spike trains that are very close in the C-distance paradigm for a sufficiently small gaussian kernel (width: 1–2 ms) share many coincident spikes and thus consist basically of the same spike patterns. Therefore, these trains are also close in the LZ-paradigm, whereas two trains that are close using the LZ-distance can be distant using the C-distance—e.g. when a considerable phase-shift is present. In that sense, the LZ-distance is more general.

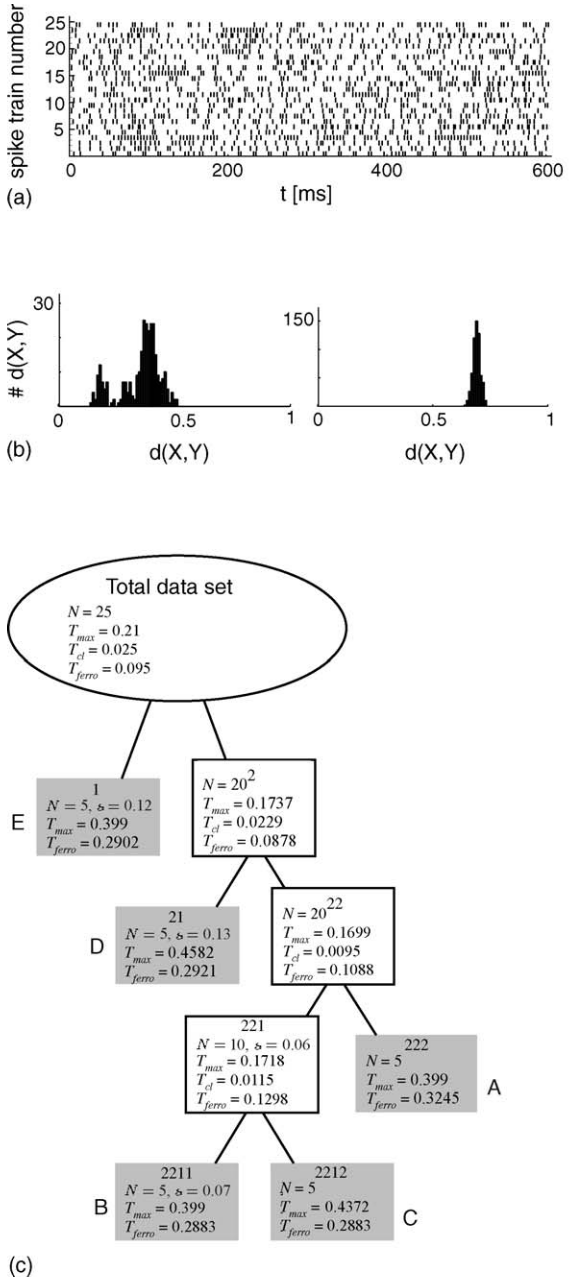

Fig. 6. Comparison of distance measures. (a) Test trains, (b) distributions of LZ-distances (left) and correlation-based distance, and (c) Dendrogram of clustering the spike train set using the LZ-distance: all five classes are clearly recognized.

4. Discussion

We have introduced a novel spike train distance measure, the LZ-distance. We find that this distance provides additional insights into firing reliability determination and spike train classification, compared to the common spike train distance measures. For the first problem type, the LZ-distance determines a complementary aspect of neuronal firing reliability compared to spike timing. In combination with the C-distance, we are able to distinguish between firing reliability in terms of spike timing and firing reliability in terms of spike patterns. Our findings on spike timing agree with the results of earlier studies that claim a high timing precision in LGN (Reinagel and Reid, 2002) and simple cells of V1 (Kara et al., 2000). The reliability deviations in terms of patterns provides an additional insight that needs a more careful interpretation, because the mean distance of some spike trains obtained in multiple presentations of a single stimulus condition is higher than the Poisson reference—especially in area MT. Thus, the neurons may deviate from the reference function not in the sense that certain specific firing patterns are replicated in the different trials, but that *different* firing patterns are present in different trials of a single stimulus condition. This interpretation may be explained within our framework of neural coding and computation within dynamical systems theory (Stoop and Stoop, 2004; Stoop et al., 2000a,b, 2002). This framework is based on coupled, noise-driven neuronal limit cycle firing, where neuronal computation shows up as distinct firing patterns that result from locking of these limit cycles. In the in vitro condition, the appearance of these firing patterns of periodicity one up to five has been demonstrated (Stoop et al., 2000c), whereas fast but coherently changing modulations of the driving of two locked neurons in the in vivo condition hide the patterns in the sense that the periodicity is not visible from eye, although – as model studies using detailed compartment models and Hodgkin–Huxley-neurons demonstrated (Stoop et al., 2004a,b) – the locking between the two neurons is preserved. The LZ-distance is expected to consider spike trains that emerge from a neuron under in vivo conditions performing always the same computation in different trials as close, because the firing patterns – although the periodicity is hidden – should not differ considerably. However, locked neurons in higher cortical areas (as area MT), where different types of computation may take place, display different types of patterns, whose actual presence and weighting in different trials of a single stimulus condition may change in the in vivo condition. This type of firing would, however, be well distinguished from Poisson firing. Our findings are compatible with this prediction, although further experimental work would be required to test our theoretical framework.

For spike train classification, we have shown that the LZ-distance, in combination with the sequential superparamagnetic clustering algorithm, classifies spike trains with similar but delayed firing patterns. Distance measures that focus the precise timing of spikes fail in such cases. This demonstrates, that the application of the LZ-distance for the neuron clustering task provides novel insights. This is also shown for an in vivo study using data from electrodes array recordings in the olfactory system of rats in vivo. In this analysis we have shown that clusters of neurons under the LZ-distance-paradigm are more stable when an olfactory stimulus is presented to the animal than during spontaneous activity (Christen et al., in preparation). This stabilization effect is much weaker when the neurons are clustered under the synchronization paradigm. This result indicates, that the presence of an odor increases the stability of firing patterns beyond simple coincidence firing and demonstrates, how additional insight is obtained by our novel measure in a neuron classification task.

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References

Abeles M, Gat I. Precise firing sequences in experimental data. J Neurosci Methods 2001;107(1/2):141–54.

Amigö JM, Szczepański J, Wajnryb E, Sanchez-Vives MV. Estimating the entropy rate of spike trains via Lempel–Ziv-complexity. Neural Comput 2004;16:717–36.

Bennett CH, Gács P, Li M, Vitányi PMB, Zurek WH. Information distance. IEEE Trans Inform Theory 1998;44(4):1407–23.

Christen M, Ott T, Stoop R. Spike train clustering using a Lempel–Ziv distance measure. In: Proceedings of the international symposium on nonlinear theory and its applications (NOLTA); 2004. p. 379–82.

Cover TM, Thomas JA. Elements of information theory. New York: John Wiley and Sons Inc; 1991.

Cox DR, Lewis PAW. The statistical analysis of series of events. London: Methuen and Co. Ltd; 1966.

Fellous J-M, Tiesinga PHE, Thomas PJ, Sejnowski TJ. Discovering spike patterns in neuronal responses. J Neurosci 2004;24(12):2989–3001.

Gersho A, Gray RM. Vector quantization and signal compression. Boston: Kluwer Academic Publishers; 1992.

Gerstein GL, Perkel DH, Dayhoff JE. Cooperative firing activity in simultaneously recorded populations of neurons: detection and measurement. J Neurosci 1985;5(4):881–9.

Johnson DH, Gruner CM, Baggerly K, Seshagiri C. Information-theoretic analysis of neural coding. J Comput Neurosci 2001;10:47–69.

Kara P, Reinagel P, Reid RC. Low response variability in simultaneously recorded retinal, thalamic and cortical neurons. Neuron 2000;27: 635–46.

Kohn A, Movshon JA. Adaptation changes the direction tuning of macaque MT neurons. Nat Neurosci 2004;7:764–72.

Kohn A, Smith MA. Stimulus dependence of neuronal correlation in primary visual cortex of the macaque. J Neurosci 2005;25(14):3661–73.

Lempel A, Ziv J. On the complexity of finite sequences. IEEE Trans Inform Theory 1976;IT-22:75–81.

Li M, Vitányi P. An introduction to Kolmogorov complexity and its applications. Berlin: Springer Verlag; 1997.

Li M, Bádger JH, Chen X, Kwong S, Kearney P, Zhang H. An information-based sequence distance and its application to whole mitochondrial genome phylogeny. Bioinformatics 2001;17(2):149–54.

Meissen WJ, Epping WJM. Detection and estimation of neural connectivity based on crosscorrelation analysis. Biol Cybern 1987;57:403–14.

Movshon JA, Kiorpes L, Hawken MJ, Cavanaugh JR. Functional maturation of the macaque's lateral geniculate nucleus. J Neurosci 2005;25: 2712–22.

Ott T, Kern A, Steeb W-H, Stoop R. Sequential clustering: tracking down the most natural clusters. J Stat Mech Theory E 2005:P11014.

Perkel DH, Gerstein GL, Moore GP. Neuronal spike trains and stochastic point processes II. Simultaneous spike trains. Biophys J 1967;7: 419–40.

Reinagel P, Reid RC. Precise firing events are conserved across neurons. J Neurosci 2002;22(16):6837–41.

Samonds JM, Allison JD, Brown HA, Bonds AB. Cooperation between area 17 neuron pairs enhances fine discrimination of orientation. J Neurosci 2003;23:2416–25.

Schreiber S, Fellous J-M, Whitmer D, Tiesinga, Sejnowski TJ. A new correlation-based measure of spike timing reliability. Neurocomputing 2004;52–54:925–31.

Skottun BC, de Valois RL, Grosof DH, Movshon JA, Albrecht DG, Bonds AB. Classifying simple and complex cells on the basis of response modulations. Vision Res 1991;31(7/8):1079–86.

Steeb W-H, Stoop R. Exact complexity of the logistic map. Int J Theor Phys 1997;36:943.

Stoop R, Stoop N. Natural computation measured as a reduction of complexity. Chaos 2004;14(3):675–9.

Stoop R, Schindler K, Bunimovich LA. Neocortical networks of pyramidal neurons: from local locking and chaos to macroscopic chaos and synchronization. Nonlinearity 2000a;13(5):1515–29.

Stoop R, Schindler K, Bunimovich LA. Noise-driven neocortical interaction: a simple generation mechanism for complex neuron spiking. Acta Biotheor 2000b;48:149–71.

Stoop R, Schindler KA, Bunimovich LA. When pyramidal neurons lock, when they respond chaotically, and when they like to synchronize. Neurosci Res 2000c;36:81–91.

Stoop R, Blank DA, Kern A, van der Vyver J-J, Christen M, Lecchini S, et al. Collective bursting in layer IV: synchronization by small thalamic inputs and recurrent connections. Cognitive Brain Res 2002;13:293–304.

Stoop R, Buchli J, Christen M. Phase and frequency locking in detailed neuron models. In: Proceedings of the international symposium on nonlinear theory and its applications (NOLTA); 2004a. p. 43–6.

Stoop R, van der Vyver J-J, Christen M, Kern A. Where noise and precision join forces: coding of neural information via limit cycles. In: Proceedings of the international symposium on non-linear theory and its applications (NOLTA); 2004b. p. 375–8.

Van Rossum MCW. A novel spike distance. Neural Comput 2001;13:751–63.

Victor JD, Purpura KP. Metric-space analysis of spike trains: theory, algorithms and application. Network: Comp Neural 1997;8:127–64.

Ziv J, Lempel A. Compression of individual sequences by variable rate coding. IEEE Trans Inform Theory 1978;IT-24:530–6.