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Application of Lempel–Ziv complexity to the analysis of neural discharges

J Szczepański[1,2], J M Amigó[3], E Wajnryb[1] and M V Sanchez-Vives[4]

[1] Institute of Fundamental Technological Research, Warsaw, Poland
[2] Centre of Trust and Certification, CENTRAST SA, Warsaw, Poland
[3] Centro de Investigación Operativa, Universidad Miguel Hernández, Elche, Spain
[4] Instituto de Neurosciencias, Universidad Miguel Hernández–CSIC, Alicante, Spain

E-mail: jszczepa@ippt.gov.pl, jm.amigo@umh.es, ewajnryb@ippt.gov.pl and mavi.sanchez@umh.es

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Abstract

Pattern matching is a simple method for studying the properties of information sources based on individual sequences (Wyner *et al* 1998 *IEEE Trans. Inf. Theory* **44** 2045–56). In particular, the normalized Lempel–Ziv complexity (Lempel and Ziv 1976 *IEEE Trans. Inf. Theory* **22** 75–88), which measures the rate of generation of new patterns along a sequence, is closely related to such important source properties as entropy and information compression ratio. We make use of this concept to characterize the responses of neurons of the primary visual cortex to different kinds of stimulus, including visual stimulation (sinusoidal drifting gratings) and intracellular current injections (sinusoidal and random currents), under two conditions (*in vivo* and *in vitro* preparations). Specifically, we digitize the neuronal discharges with several encoding techniques and employ the complexity curves of the resulting discrete signals as fingerprints of the stimuli ensembles. Our results show, for example, that if the neural discharges are encoded with a particular one-parameter method ('interspike time coding'), the normalized complexity remains constant within some classes of stimuli for a wide range of the parameter. Such constant values of the normalized complexity allow then the differentiation of the stimuli classes. With other encodings (e.g. 'bin coding'), the whole complexity curve is needed to achieve this goal. In any case, it turns out that the normalized complexity of the neural discharges *in vivo* are higher (and hence carry more information in the sense of Shannon) than *in vitro* for the same kind of stimulus.

1. Introduction

The transmission of information in the nervous system takes place in multiple stages. We consider this process at the stage of the information being transmitted among neurons by trains

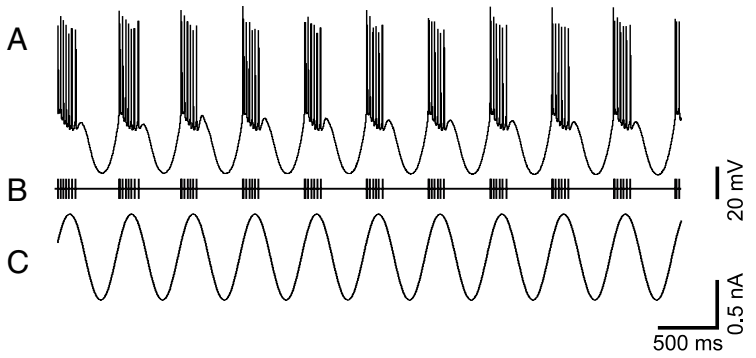

Figure 1. Intracellular recording from a cortical cell *in vitro* during sinusoidal current injection. (A) A membrane potential trace showing the trajectory while intracellular sinusoidal current was injected. During the depolarizing phase the membrane potential value reached threshold, inducing a train of spikes or action potentials. (B) Spikes as acquired in a separate channel to be used for the analysis presented here. (C) Sinusoidal current injected into the cell.

of action potentials or spikes, which are sharp voltage peaks of about the same amplitude, eventually in clusters or bursts, with comparatively long periods of silence between them (figure 1). In this paper we will focus on the responses of visual cortical neurons to different stimuli. One peculiarity of this particular process is the fact that stimulus and response are not one-to-one related, i.e. there is a variability in the occurrence of the spikes induced by the repetition of the same stimulus. This variability accounts for the introduction of internal states in the deterministic models of neuronal communication and might indicate that the information is basically comprised in the temporal spike patterns or, rather, in some invariant features of them. One ultimate goal of computational neuroscience is precisely to find out what kinds of encoding and decoding mechanisms are concealed behind spiking. In some approaches to neuronal communication, the neuron plays the role of an information source or encoder, the spike trains become messages generated by it and the modeller worries about entropy, number of internal states or compression ratios, just to mention a few keywords. In other approaches, the attention shifts to the relation between stimulus and response as expressed by conditional probabilities, correlations, mutual information and the like. We will follow here the first approach.

The mathematical modelling of nervous systems is as old as the first physical and chemical models of the action potentials (Hodgkin and Huxley 1952). In fact, only four years after Shannon's seminal work (1948), MacKay and McCulloch (1952) estimated the entropy of spike trains in what was probably the first application of information theory to neuroscience. Since then, the theory of information has become a major tool in the mathematical approach to the nervous phenomena and, in particular, to the communication among neurons.

Pattern matching is a combinatorial approach to understanding the properties of information sources (Wyner *et al* 1998). One of the main roles in this approach is played by the complexity as defined by Lempel and Ziv (1976), which counts the number of different patterns along a sequence, time series or, in more physical terms, digital signal output by a source. A related quantity, the normalized complexity, measures the rate of generation of new patterns. We will see below that the normalized complexity is on average a lower bound of the source entropy, so, in general, the higher the normalized complexity of a spike train, the more Shannon information it conveys. Moreover, if the source is stationary and has 'good' statistical properties (specifically: ergodicity, which allows one to calculate mean values as

time averages), the normalized complexity of a single signal gives with high probability a close estimate of the source entropy, which is the average Shannon information in bits per second (bits s^{-1}) generated by the source. But observe that, whereas entropy is a property of sources and thus difficult to evaluate, complexity is a property of individual sequences which can be calculated straightforwardly and independently of the source properties. Further advantages of the normalized complexity when applied to the analysis of neural responses include its practical invariance under repetition of the same stimulus.

The reader must be cautioned at this point that there are different definitions and measures of complexity in the literature (Ebeling *et al* 2000, Gonzalez Andino *et al* 2000, Rapp *et al* 1994). Historically, the early works linked the complexity of a sequence to that of the simplest algorithm able to produce it, a notion which goes nowadays by the name of Kolmogorov–Chaitin algorithmic complexity (Chaitin 1982). More concretely, the algorithmic complexity of a symbol sequence is given by the number of bits of the shortest computer program that outputs the said sequence. However, there is no general recipe for such a minimal program. Instead, Lempel and Ziv proposed a complexity measure that does not necessarily deliver the length of the shortest program generating the sequence in question but, rather, a number that is a useful bound of this length (Rapp *et al* 2001). Other quantitative measures of complexity assess the level of disorder or randomness, very much in the same way as thermodynamic entropy does. These include, for example, the entropies associated with the names of Shannon, Renyi and Gelfand-Yaglom. Finally, still other measures stem from non-linear dynamics or Chaos theory (Lyapunov exponents, fractal dimensions of attractors etc). Let us mention in passing that, unlike Lempel–Ziv complexity, most of them are difficult to apply because they are numerically demanding or suffer from other drawbacks such as requiring long time series or exhaustive sampling. Sequences which are complex by one definition need not be complex by the other, since these definitions may target distinct aspects of what is actually meant by complexity. Hereafter, complexity is always meant in the sense of Lempel and Ziv (1976)[5]. Roughly speaking, time series with a repetitive or simple pattern structure (e.g. periodic or quasi-periodic) have a low normalized complexity, while those unfolding a rich pattern diversity as time goes on (e.g. random sequences) have a normalized complexity very likely around 1.

In this paper we show that the complexity can be used to discriminate the responses of single neurons to different kinds of stimulus. The recordings were made from simple cells of the primary visual cortex *in vivo* and from layers 2/3 and 4 *in vitro*. The stimuli consisted of visual stimulation by sinusoidal drifting gratings (only *in vivo*) and intracellular injections of sinusoidal and random currents (*in vivo* and *in vitro*). The results show that the neural discharges have different degrees of complexity depending on the kind of stimulus and the experimental preparation (*in vivo*, *in vitro*), so, in general, one can identify both of them by just measuring the normalized complexity of a single discharge. In particular, it turns out that the normalized complexities of the responses *in vivo* are higher (and hence carry more Shannon information) than *in vitro* for the same kind of stimulus.

2. Encoding of spike trains

The application of information theory to neuronal discharges poses some problems on its own. To begin with, spike trains are, from a mathematical point of view, continuous signals with two very dissimilar timescales. On a millisecond scale, the spikes are bumps of the same height and width; on a scale comparable to the train duration though, a spike train is practically an

[5] The reader may not be aware that a concept of complexity related to but developed later (Ziv and Lempel 1978) is widely implemented in information technologies for lossless data compression (e.g. 'WinZip', 'PK-Zip').

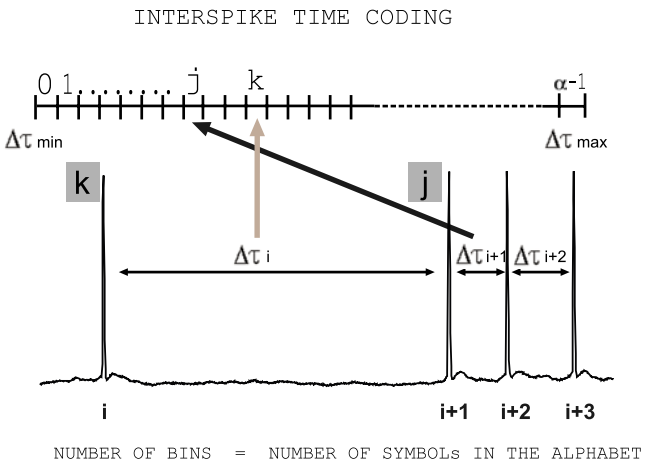

Figure 2. Divide the interval $[\tau_{\min}, \tau_{\max}]$ between the minimal and maximal interspike times of a given spike train in α time bins $\Delta\tau_n, 0 \leqslant n < \alpha - 1$, of the same length $L = (\tau_{\max} - \tau_{\min})/\alpha$. Let τ_i be the time elapsed between the ith and $(i+1)$th spikes and suppose $\tau_{\min} + kL \leqslant \tau_i < \tau_{\min} + (k+1)L$ so that τ_i belongs to the time bin $\Delta\tau_k$. In this case, assign the 'letter' k to the spike i. Analogously, if τ_{i+1}, the time elapsed between the $(i+1)$th and $(i+2)$th spikes, belongs to the time bin $\Delta\tau_j$, then the spike $i+1$ is assigned the letter j. The length of the message is the number of spikes. The resulting alphabet has α letters: $0, 1, \ldots, \alpha - 1$.

all-or-none signal. This explains why there have been in computational neuroscience two different approaches to spike train analysis based on continuous and discrete methods. For the first approach (including differential entropy and clustering reconstruction), see for example McFadden (1995), Victor and Purpura (1997) or Victor (2002). In this paper we follow the second approach, but making use of complexity theory rather than discrete information theory (Rieke *et al* 1998). A first technical difficulty in this pursuit is the fact that a spike train is not digital in the sense needed (figure 1), i.e. a sequence of finitely many symbols or 'letters' called a *message* or *word*. The transformation of a spike train into a *bona fide* message is called the *codification* of the signal and the procedure, the *(en)coding*. In the following, whenever we talk about spike trains as messages, we mean that the signal has been previously codified.

Codification can be achieved in a variety of ways. Hereafter we will consider only two of the many codings proposed in the literature:

(1) *Interspike time coding* (figure 2). Let $\tau_{\min}$ and $\tau_{\max}$ be the minimal and maximal *interspike* times, respectively, in the signal. Divide the interval $[\tau_{\min}, \tau_{\max}]$ into α slots $\Delta\tau_i$ $(1 \leqslant i \leqslant \alpha)$ of the same length. If τ_j is the interspike time following spike s_j and τ_j belongs to, say, the kth slot $\Delta\tau_k$, then assign to the spike s_j the k-symbol a_k from a set $A = \{a_1, \ldots, a_\alpha\}$ of α symbols (Rapp *et al* 1994). In this way, we get an α-nary message whose length equals the number of spikes.

(2) *Bin coding* (figure 3). Let the first spike of a train occur at time 0 and the last one T time units later. The time interval $[0, T]$ is then split into n bins Δt_i $(1 \leqslant i \leqslant n)$ of the same length. If there are N_k spikes in the bin Δt_k, then assign the number N_k to Δt_k (Dan *et al* 1996, Rieke *et al* 1998, Zador 1998). The result is a message of length n with no more than n different letters. If, instead, each bin Δt_i is coded by 0 or 1 according to whether it contains no or at least one spike, respectively, the message will be binary. Whenever necessary, the latter method will be called *binary* bin coding to distinguish it from the former one, the *general* (multi-symbol) bin coding. Notice that, when n is so

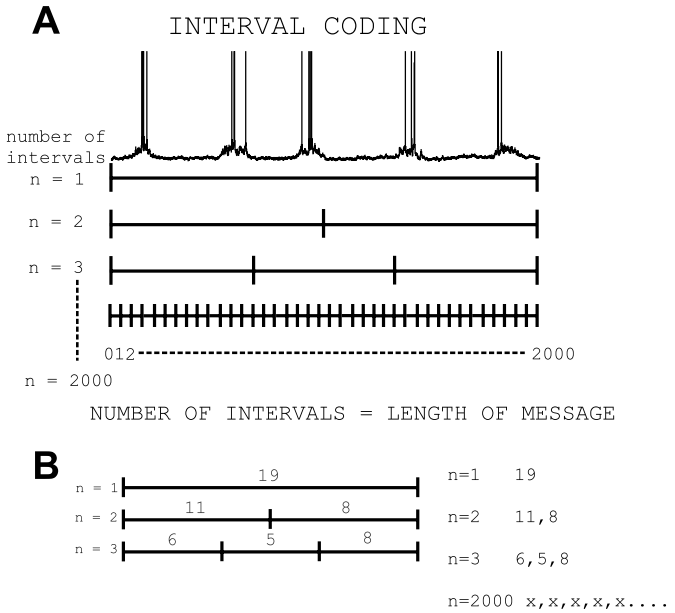

Figure 3. Divide the time duration T of the spike train into N subintervals Δt_n, $0 \leqslant n < N-1$, of the same length $L = T/N$. If N_k spikes occur in the subinterval Δt_k, then assign the 'letter' N_k ($0 \leqslant N_k \leqslant N$) to the subinterval Δt_k. The length of the ensuing (in general, multi-symbol) message is N, the number of subintervals. A binary message results instead if Δt_k is coded by 0 or 1 according to $N_k = 0$ or $N_k > 0$, respectively.

large (or, equivalently, the bin length so small) that only one spike at most occurs in each Δt_i, the two bin codings coincide. This happens for $n \geqslant T/\tau_{\min}$.

For other methods (such as the median coding), see for example Rapp *et al* (1994). Codings turn out to be like microscopes resolving the structure of spike trains at the scale set by the number of letters (interspike time coding) or the word length (bin coding). It is clear that the information-theoretic properties of *encoded* spike trains related to the stimuli depend, in general, on the parameters of the encoding method used (Amigó *et al* 2001). This entails different codings catching different features of the spike trains or, rather, of the stimuli, since the properties of inputs and outputs must be related. Needless to say, these 'by-hand' codifications are not meant to model the codification(s) that the neurons might employ to communicate, but they are necessary artefacts of the mathematical approach. Observe also that neurons codify input signals in real time, whereas our codifications require the whole spike train to be previously given.

3. Information sources and entropy

Once a spike train has been codified into a message, this can be viewed as emitted by an information source (Gallanger 1968), the source comprising everything preceding the message, namely, the stimulus (S), the neuron or neuronal network (N) and, last but not least, the encoding technique (E). This formal counterpart of the neuron considered as an information source will be called sometimes a *SNE source* to highlight the dependence of the encoded neural responses on both stimulus and codification. Any source property applied to a neuron or neuron network makes sense only if referred to the corresponding SNE source. By the same token, source

properties evaluated from neural outputs should only be compared if codified with the same technique; the numerical differences can then be traced back to differences in the stimuli.

The most important property of a source S is its *entropy* (Borst and Theunissen 1999, Cover and Thomas 1991, Shannon 1948), which can be interpreted as the average information generated by the source per unit of time (assuming that one letter is produced at every time unit). Suppose that S generates words $x_1^n := x_1 x_2 \cdots x_n$ of length n whose letters x_i $(1 \leqslant i \leqslant n)$ belong to a set $\mathcal{A} = \{a_1, \ldots, a_\alpha\}$ of size $|\mathcal{A}| = \alpha < \infty$, called the source *alphabet*. The entropy of S is then defined as

$$H_b(S) = -\frac{1}{n} \sum_{x_1^n} p(x_1^n) \log_b p(x_1^n)$$

where $p(x_1^n)$ denotes the probability of the word x_1^n happening and the sum is over all words of length n (α^n in total, although some of them could have zero probability). The subscript b stands for any real constant $b > 1$ and refers to the base of the logarithm. If $b = 2$, the entropy is measured in bits s^{-1}. Of course, the entropy can always be expressed in bits s^{-1} via the formula

$$H(S) := H_2(S) = H_b(S) \log_2 b. \tag{1}$$

In the special case that the letters are independently generated (i.e. there are no correlations among letters in the words) and p_i is the probability for the letter a_i to occur, then $H_b(S)$ simplifies to

$$H_b(S) = -\sum_{i=1}^{\alpha} p_i \log_b p_i.$$

Such sources are called *memoryless*. If, moreover, all letters have the same probability $p_i = 1/\alpha$, the source is called *symmetric*. In this case, $H_b(S) = \log_b \alpha$. Finally, if words can be arbitrarily long, one has to let n go to infinity:

$$H_b(S) = -\lim_{n\to\infty} \frac{1}{n} \sum_{x_1^n} p(x_1^n) \log_b p(x_1^n)$$

provided the limit exists.

4. Complexity

The entropy is a property of sources and, therefore, difficult to evaluate. In fact, the estimation of all probabilities involved in its calculation requires an extensive sampling which very often cannot be performed, not to mention the reproducibility of the test conditions. In contrast, *complexity*, as formulated by Lempel and Ziv (1976), is a property of individual sequences which can be used to estimate the entropy or, more generally, to bound it from below (along with other applications). Furthermore, its calculation is straightforward, as we see next.

The formal definition of Lempel–Ziv complexity is recursive. Given the word x_1^n, a *block* of length l $(1 \leqslant l \leqslant n)$ is just a segment of x_1^n of length l, i.e. a subsequence of l consecutive letters, say $x_{i+1}^{i+l} := x_{i+1} x_{i+2} \cdots x_{i+l}$ $(0 \leqslant i \leqslant n - l)$. In particular, letters are blocks of length 1 and blocks of higher length are obtained by juxtaposition of blocks of lower length. Set $B_1 = x_1^1 = x_1$ and suppose that

$$B_1 B_2 \cdots B_k = x_1^{n_k}$$

where $B_1 B_2 \cdots B_k$ denotes the juxtaposition of the blocks B_1, $B_2 = x_2^{n_2}, \ldots, B_k = x_{n_{k-1}+1}^{n_k}$ and $n_{k-1} + 1 \leqslant n_k < n$ (with $n_0 = 0$ and $n_1 = 1$). Define

$$B_{k+1} := x_{n_k+1}^{n_{k+1}} \qquad (n_k + 1 \leqslant n_{k+1} \leqslant n),$$

to be the block of minimal length such that it does not occur in the sequence $x_1^{n_{k+1}-1}$. Proceeding in this way, we obtain a *decomposition* of x_1^n in 'minimal' blocks, say

$$x_1^n = B_1 B_2 \cdots B_p \tag{2}$$

in which only the last block B_p can occasionally coincide with one of the foregoing blocks $B_1, \ldots, B_{p-1}$. The *complexity* $C_\alpha(x_1^n)$ of x_1^n is then defined as the number of blocks in the (clearly unique) decomposition (2):

$$C_\alpha(x_1^n) := p = p(\alpha).$$

Intuitively speaking, the complexity of a word counts the number of different patterns that it contains. As explained above formally, the first symbol on the left of the word defines the first block. From there one moves rightward letter by letter, until the string of symbols beginning just after the previous block and ending at the current position happens not to have appeared before. At this point, a new block is defined. The procedure is illustrated by the following example. The decomposition of the binary word $x_1^{19} = 01011010001101110010$ into minimal blocks of new patterns is

$$0|1|011|0100|011011|1001|0$$

where the vertical lines separate the blocks. Therefore, the complexity of x_1^{19} is 7.

The generation rate of new patterns along x_1^n, a word of length n with letters from an alphabet of size α, is measured by the *normalized complexity* $c_\alpha(x_1^n)$, which is defined by

$$c_\alpha(x_1^n) = \frac{C_\alpha(x_1^n)}{n/\log_\alpha n} = \frac{p(\alpha)}{n} \log_\alpha n.$$

Sequences which are not 'complex' (e.g. periodic or quasi-periodic) have a very small normalized complexity. At the opposite end are the random sequences. Although the normalized complexity can take values higher than one, the normalized probability of random sequences is about one with very high probability.

Normalized complexity is connected with several important concepts of information theory such as entropy, compression ratio for information of lossless sources (Ziv 1978), optimal encoding (Ziv and Lempel 1978) and randomness (Leung and Tavares 1985). Further applications concerning the number of internal states of the neuronal sources are addressed in Amigó *et al* (2003). Here we will pursue only its relation to entropy.

5. Complexity and entropy

To explain the relation between $c_\alpha(x_1^n)$ and the entropy $H_\alpha(S)$ of the source S which has produced x_1^n, some definitions are needed. S is said to be *stationary* if

$$p(x_1^\infty : x_{i_1} = \alpha_{i_1}, \ldots, x_{i_k} = \alpha_{i_k}) = p(x_1^\infty : x_{i_1+j} = \alpha_{i_1}, \ldots, x_{i_k+j} = \alpha_{i_k})$$

for every $j, k, \alpha_{i_1}, \ldots, \alpha_{i_k}$, which means that the statistical properties of the (in principle, arbitrarily long) words do not change if the origin of time is shifted. Since, in general, the entropy fails to exist for non-stationary sources, we dispense with them henceforth. A stationary source is called *ergodic* if sample averages and time averages coincide almost surely, i.e. one can calculate expected values over the word ensemble using the relative frequencies of the letters in a 'typical' word. As a consequence, all the sequences produced by a ergodic source have the same statistical properties (except maybe for a set of probability zero).

One can prove (Ziv 1978) that (i) if S is stationary, then

$$\limsup_{n\to\infty} c_\alpha(x_1^n) \leqslant H_\alpha(S) \qquad \text{on average} \tag{3}$$

and, moreover, (ii) if S is ergodic, then

$$\lim_{n\to\infty} \sup c_\alpha(x_1^n) = H_\alpha(S) \qquad \text{almost surely.} \tag{4}$$

For the practitioner, this second inequality boils down to the following: the normalized complexity of a sufficiently long word is, with high probability, a close estimate of the source entropy (with the proviso that S is ergodic). Numerical simulations with Markov processes suggest that for, say, 1000-bit-long sequences (such as those that we consider below) the entropy estimation via Lempel–Ziv complexity is less than 2% off the true value, which is very satisfactory. In the general case (S stationary), the normalized complexity provides on average lower bounds to the source entropy. In either case, the higher the normalized complexity of a typical word, the higher the corresponding source entropy.

As a rule, stationarity is an assumption which cannot be taken for granted in biological systems and should be checked on a case-by-case basis. Indeed, phenomena such as adaptation, synaptic plasticity etc amount to a sizable time variability in the statistical properties of the performances. As regards ergodicity, it can be tested in practical cases by sampling typical trajectories; every such time series $x_1x_2\cdots$ should produce the same time average for any observable f of the data, $\lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^{n} f(x_i)$. Ergodicity is a kind of efficiency principle which is very often encountered in Nature for stationary processes.

In practice, when estimating the entropy of stationary sources one way or the other, one always faces the problem of undersampling. It is therefore very important to know about the convergence rate of the estimator used. Eventually, one can resort to numerical simulation to get the necessary insight. This issue has been addressed in the context of pattern matching by Farach *et al* (1995), Kontoyiannis *et al* (1998) and Wyner *et al* (1998). In any case, it should be clear that, for our present purposes, the role of the normalized complexity as an entropy estimator is of secondary importance since we are primarily interested in using it to distinguish neuronal sources under different conditions. This means that we can (and will) use it even when the existence of the entropy is dubious because of non-stationarity.

6. Experimental work

We have studied experimentally the complexity of neuron responses to different stimuli under controlled conditions. The data was obtained from primary cortex recordings both *in vivo* and in brain slice preparations (*in vitro*). Intracellular recordings *in vivo* were obtained from anaesthetized adult cats (see Sanchez-Vives *et al* 2000a for details). For the preparation of slices, 2–4-month-old ferrets of either sex were used (see Sanchez-Vives *et al* 2000b for details). Action potentials were detected with a window discriminator and the time of their occurrence was collected with a 10 μs resolution. All the recordings included in this study corresponded to stable recordings from neurons with a membrane potential of at least -60 mV and overshooting action potentials. The resulting time series were used to analyse the neuron spiking. As regards the stimuli, they were of three kinds:

(1) *Periodic current*. Intracellular sinusoidal currents were injected *in vivo* and *in vitro*. The frequency of the waveform was 2 Hz and the intensity ranged between 0.2 and 1.5 nA.
(2) *Periodic visual stimulation*. The visual stimulus consisted of a sinusoidal drifting grating presented in a circular patch of 3°–5° diameter, centred on the receptive field centre (*in vivo*). Only simple cells (classified as shown by Skottun *et al* 1991) were included in this study.
(3) *Random current*. Random currents with different degrees of correlations were injected during the intracellular recordings from cortical brain slices (*in vitro*).

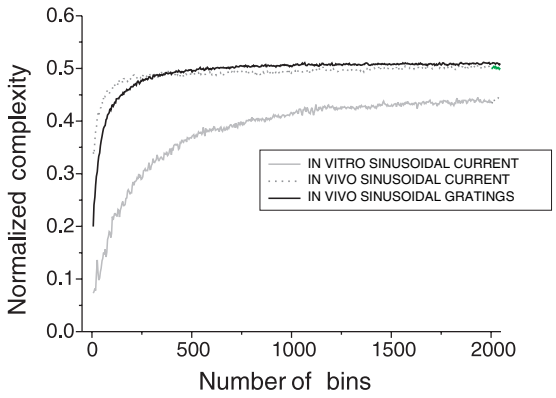

Figure 4. Interspike time coding and periodic stimuli. The curves show the normalized complexity versus number of bins for periodic stimuli (visual stimulation and current injection) both *in vivo* and *in vitro*. The curves saturate as the number of bins increases. This behaviour is typical for the interspike time coding.

All in all we have four ensembles of stimuli with well-defined properties. The sample counts are as follows:

(1) Periodic current injection *in vivo*: 8 samples (spike train lengths between 15.56 and 47.64 s).
(2) Periodic current injection *in vitro*: 8 samples (spike train lengths between 15.87 and 23.62 s).
(3) Periodic visual stimulation: 8 samples (spike train lengths between 36.74 and 81.81 s).
(4) Random current injection *in vitro*: 20 samples (spike train lengths between 16.32 and 35.47 s). For details, see Wang *et al* (2003).

For convenience, the corresponding SNE sources will be referred to as *in vivo*, *in vivo* periodic current etc. We will verify experimentally in the next section that it is safe to assume these sources to be stationary.

7. Results

Let x_1^n be the result of encoding a spike train recorded in any of the above four experimental settings. In order to gain more insight into the complexity of neuronal responses, we have graphically represented $c_\alpha(x_1^n)$ as a function of the number of letters α (for interspike time coding) and also as a function of the word length n (for bin coding). This graphical analysis was repeated with spike trains covering all cases. Remember that n is fixed (and equal to the number of spikes) for the interspike time coding and $\alpha = 2$ for the binary bin coding while, for the general bin coding, there is a weak dependence of α on n which shows up in the graphs as instabilities. For this reason we limit the discussion of the complexity curves to the interspike time coding and the binary bin coding. The results obtained can be summarized as follows.

(1) For *interspike time coding* (see figures 4 and 5), the curves $c_\alpha(x_1^n)$ versus α are convex $\cap$, converging sharply with increasing α to flat horizontal profiles. We call these stationary values *saturation levels* and they are about the same for periodic stimuli (*in vivo* and *in vitro*). The saturation levels corresponding to random inputs are more scattered due to their manifold autocorrelation functions but, as one expects, they do not overlap with

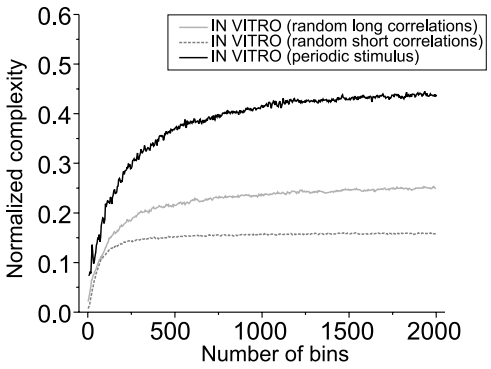

Figure 5. Interspike time coding and random stimuli. Two of the curves show the saturation levels for *in vitro* random stimuli with short and long correlations. The third curve (corresponding to periodic current injection) is shown for comparison.

the non-random ones. The non-parametric bootstrap 95% confidence intervals for the saturation levels are the following:

(i) *Periodic current injection in vivo*: the complexity curve increases sharply to its horizontal saturation level with small fluctuations. Saturation levels lie in the interval [0.4379, 0.5390].

(ii) *Periodic visual stimulation in vivo*: saturation occurs typically at a level c_α in [0.4793, 0.5307].

(iii) *Periodic current injection in vitro*: saturation sets in around $\alpha = 600$ at a level c_α in [0.3948, 0.4072].

(iv) *Random current injection in vitro*: the saturation level changes with the input signal, which hints at a relation between the asymptotic complexity values and the rate of decay of the autocorrelation function of the corresponding stimulus. The confidence interval for long correlations is [0.1961, 0.2440] and for short correlations it is [0.0986, 0.1339].

(2) For *binary bin coding* (see figure 6), the curves $c_2(x_1^n)$ versus n are not as smooth as with the previous coding. This means that the transfer of information is very sensitive to the changes in the number of intervals used in the encoding process. In this case, the complexity curves do not display plateaus. Rather, from $n \approx 2500$–3500 time bins on, they decay (figure 7) in a convex $\cup$ way following the classical formula of MacKay and McCulloch for the entropy (Rieke *et al* 1998, formula (3.22)):

$$H(S) \approx \frac{\overline{r}T}{n} \log_2\left(\frac{ne}{\overline{r}T}\right) = \frac{\overline{r}T}{n \ln 2} \ln\left(\frac{ne}{\overline{r}T}\right) \tag{5}$$

where T is the duration of the spike train and $\overline{r}$ the mean firing rate. Inserting in (5) the average experimental value $\overline{r}T = 199$ obtained from periodic current injection *in vivo*, it can be checked in figure 7 that the normalized complexity and MacKay–McCulloch entropy curves fit very well along the tail and that, in fact, the normalized complexity bounds from below the entropy.

Similarly to the previous case, the complexity curves for the binary bin coding also permit one to discriminate what kind of stimulus was applied in each case (figure 6).

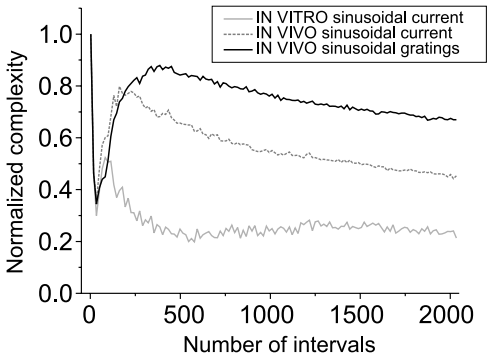

Figure 6. Binary bin coding. Normalized complexity versus number of intervals for periodic stimuli.

(3) Suppose c_0 is the saturation level of the curve $c_\alpha(x_1^n)$ versus α for a given spike train encoded by the *interspike time technique*. Then, from

$$c_\alpha(x_1^n) = \frac{C_\alpha(x_1^n)}{n/\log_\alpha n} = c_0$$

it follows that

$$C_\alpha(x_1^n) = \frac{c_0 n}{\log_\alpha n} = \frac{c_0 n}{\log_2 n}\log_2 \alpha.$$

Recall that the factor $\log_2 \alpha$ is the entropy in bits s^{-1} of a memoryless symmetric source with α letters. Moreover, if the source can be assumed to be ergodic, then, according to (4) and (1), we have

$$c_0 \approx H_\alpha(S) = \frac{H(S)}{\log_2 \alpha}$$

for α in the saturation region. Thus, (i) the complexity grows logarithmically when α varies in the saturation region and (ii) the ratio between the informations generated by an ergodic SNE source and the memoryless symmetric source with α letters (both in bits s^{-1}) is constant and equal to c_0. This means that the efficiency of the ergodic SNE sources stabilizes when the number of letters increases.

(4) The spike train is encoded by the binary bin method, so holds $c_2(x_1^n) \approx H(S)$. It follows that the entropy of the ergodic SNE sources ('E' meaning binary bin coding) can be directly read in bits s^{-1} from the normalized complexity curves.

(5) For non-ergodic sources, the above '$\approx$' must be replaced by '$\lesssim$', the resulting inequalities holding now on average. In this way, some bounds for the entropy can be easily derived. Another possible way to circumvent non-ergodicity consists of decomposing the stationary source in ergodic components. But then one needs to estimate the size of the components.

8. Discussion

The general picture that one gets from the previous results is that the complexity curves (and, in particular, saturation levels) are able to distinguish some neuronal responses from others according to the stimulus features. Interestingly enough, the saturation levels are also invariant in the sense that the neuronal responses to the same stimulus have about the same value. We elaborate further on these and other relevant considerations in the following points.

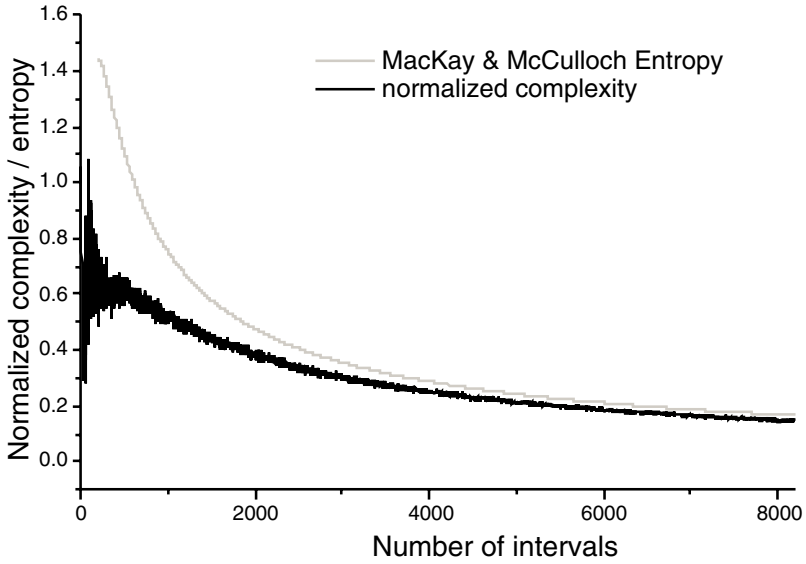

Figure 7. Comparison of the MacKay and McCulloch entropy with the normalized complexity for periodic current injection *in vivo*. The parameter value $\overline{r}T = 199$ (see equation (5)) has been obtained from the experimental spike trains by averaging.

(1) The saturation levels obtained with the interspike time coding clearly distinguish *in vivo* from the two *in vitro* sources, but do not discriminate between the two *in vivo* sources. This drawback does not arise if the bin coding is used. Hence, the two codings together do differentiate all four experimental cases.

(2) If α (interspike time coding) is so high that every spike gets a different letter, then a further increase in α only changes the names but not the number of different letters of the encoded spike train x_1^n. Hence, the complexity $C_\alpha(x_1^n)$ remains the same. Likewise, if n (bin coding) is so high that there is at most one spike per bin, then a further increase in n only adds more zeros to the encoded spike train, without practically changing its complexity $C_\alpha(x_1^n)$. In both cases, the refinement of the respective gauge has no effect on the complexity value. In other words, spike trains have a threshold scale (corresponding to the maximal firing rate of the neurons) beyond which no further structure can be resolved because there is none. Upon division of $C_\alpha(x_1^n)$ by the ever increasing factor $n/\log_\alpha n$, the resulting $c_\alpha(x_1^n)$ tends to zero both with α and n, i.e. the tails of the normalized complexity curves in both codings go down to zero.

(3) In order to check the stationarity of our experimental data series, we have also calculated the normalized complexity of encoded spike trains within a window sliding along the responses to *periodic* stimuli, i.e. the normalized complexity of a block x_i^{i+l-1} with fixed length l and variable starting position i in the encoded response. Figures 8 and 9 represent $c_\alpha(x_i^{i+l-1})$ versus i with $l = 0.6L$ (L = total length of the spike train) for interspike time coding and binary bin coding, respectively, showing that, in our case, stationarity is certainly an acceptable assumption. This also implies that the repetition of the same stimulus produces outputs of comparable complexity. We have separately checked this point in figure 10, where the normalized complexity of neural responses (discretized with interspike time coding) to periodic visual stimulation *in vivo* is seen to be about the same when the stimulus is repeated. Hence, although responses to the same stimulus

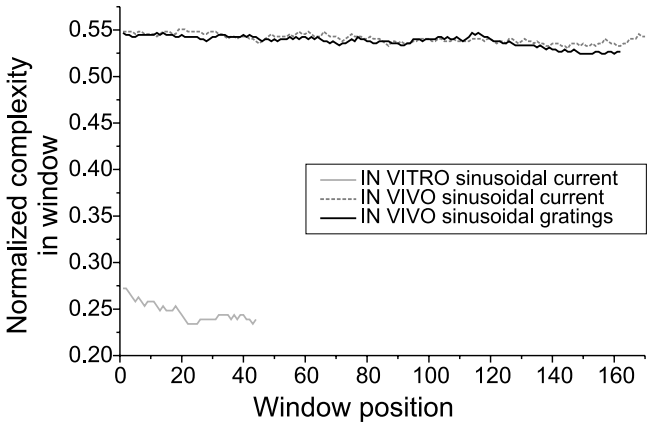

Figure 8. Calculation of the normalized complexity with sliding windows—interspike time coding (128 bins used for encoding). The window length is 60% of the train length. The position of the left end of the window is given by the abscissa.

change, their complexity remains approximately constant. This invariance property of the normalized complexity was observed in Amigó *et al* (2003).

(4) *In vivo* spike trains are more complex than *in vitro* spike trains in all codings considered. In the language of neuronal sources this can be reworded by saying that *in vivo* sources convey more Shannon information than *in vitro* sources. We suggest that this fact might be due to a higher synaptic noise *in vivo*. Neurons *in vitro* are embedded in a network that is silent and, therefore, there is no ongoing synaptic activity. On the other hand, neurons recorded *in vivo* are highly connected in a network that is active and they have access to more information sources, which enhances the information content of their responses. A similar result for a measure of variability which compares adjacent interspike intervals was obtained by Holt *et al* (1996).

(5) As already mentioned, the complexity of encoded spike trains depends on the coding method used. In particular, neuronal signals can be binary coded in such a way that the normalized complexity is about 1 and, therefore, they are completely random. This provides a biometric technique for generating random binary sequences.

9. Conclusions

The main and most general conclusion we can draw from our results is that Lempel–Ziv complexity allows one to characterize the spike trains, albeit in a coding-dependent way, according to the experimental setting that they come from. The simplest characterization occurs for the interspike time coding. The complexity curves exhibit then long saturation levels, which are about the same for stimuli belonging to the same experimental case. For the (binary) bin coding, the complexity curves have long tails whose decay rates are related to the mean firing rates obtained from the corresponding spike trains. We conclude that saturation levels and mean firing rates must describe some common features of those stimuli. From these facts we conjecture that different properties of the stimuli are transmitted by means of different codes, so the communication in the nervous system would be based rather on multiple neural codes.

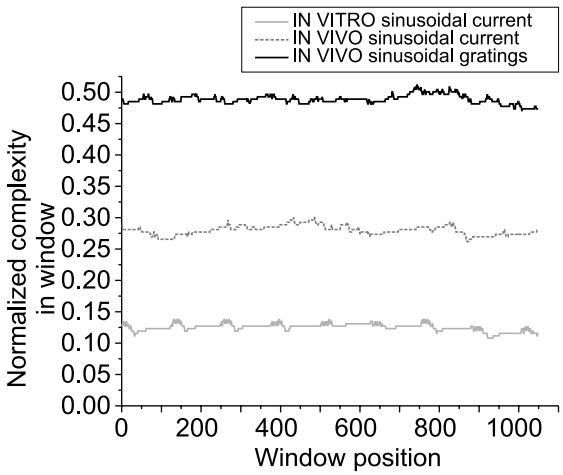

Figure 9. Calculation of normalized complexity with sliding windows—binary bin coding (2048 intervals used for encoding). The window length is 60% of the train length. The position of the left end of the window is given by the abscissa.

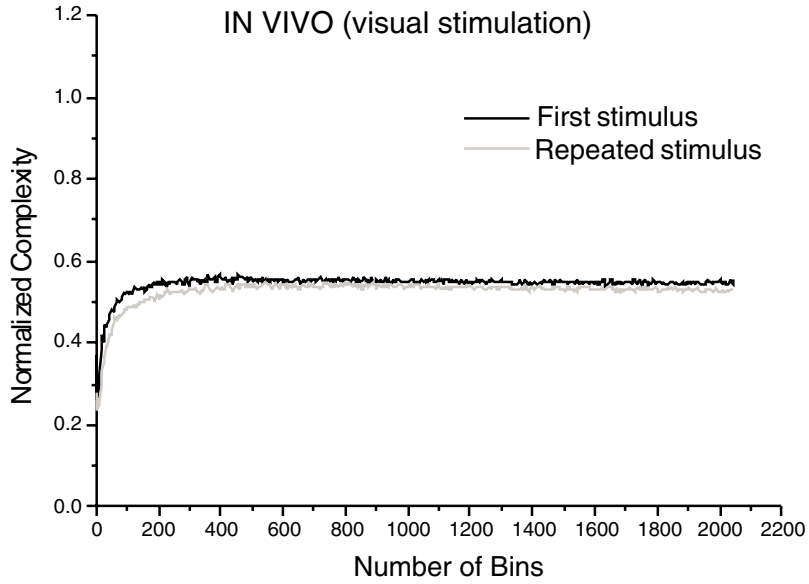

Figure 10. Interspike time coding. This figure shows the complexity curve of the neural response to a repeated application of the same stimulus (sinusoidal visual stimulation).

The reason for choosing Lempel–Ziv complexity is its conceptual and computational simplicity, together with its independence from the source properties since it refers to individual sequences. Moreover, the normalized complexity is related in a mathematically sound way to several information-theoretical properties, the most prominent being the source entropy, which permits in turn the study of the information-theoretical aspects of our model whenever feasible.

Returning to the general dependence of the complexity on the encoding technique, let us stress that complexity values obtained with different codings refer, of course, to different SNE

sources, so there is no formal objection to that dependence. Along these lines, remember, for example, that the interspike time coding does not discriminate between the two *in vivo* cases (visual stimulation and random current injection), whereas the binary bin coding does. But, more significantly, the complexity is higher *in vivo* than *in vitro* in any coding that we have considered so far, which hints at some basic difference regarding the Shannon information being transferred.

To sum up, we believe that complexity theory is a valuable tool in the quest to understand the nervous system from the point of view of information theory. We have shown in this paper how neural responses can be singled out in various ways and their information content estimated by means of the (normalized) complexity. In doing so we have modelled the neuron as an information source and discussed our quantitative results in the light of this approach. Eventual practical applications thereof will include the assessment of the spike train entropy in an alternative way and the study of epilepsy (Rapp *et al* 1994) as well as the decorrelation effects of neurons. Further applications of complexity (also in other approaches) are the subject of current investigation.

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