Title

The information transmitted by spike patterns in single neurons.

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Abstract

Spike patterns have been reported to encode sensory information in several brain areas. Here we assess the role of specific patterns in the neural code, by comparing the amount of information transmitted with different choices of the readout neural alphabet. This allows us to rank several alternative alphabets depending on the amount of information that can be extracted from them. One can thereby identify the specific patterns that constitute the most prominent ingredients of the code. We finally discuss the interplay of categorical and temporal information in the amount of synergy or redundancy in the neural code.

Keywords

neural code, sensory encoding, information theory, spike patterns, synergy.
1 The role of spike patterns in the neural code

Many studies have shown that precise spike timing plays an important role in the encoding of sensory stimuli. For example, in the cat LGN (Reinagel and Reid, 2000) the transmitted information was shown to be a rapidly increasing function of the resolution with which the timing of spikes was read out, up to the sub-millisecond regime. Similar results were observed in the rat somatosensory cortex (Panzeri et al., 2001; Arabzadeh et al., 2006), the fly H1 neuron (Strong et al., 1998), and the grasshopper auditory system (Rokem et al., 2006).

In some cases, the additional information obtained by reading out the neural responses with high temporal resolution was explained in terms of a firing-rate code whose time-dependent spiking probability exhibited sharp and rapid temporal fluctuations accurately encoded by just a few spikes (Montemurro et al., 2007). In such cases, the neural code is mainly instrumented by precisely timed single spikes. In other cases, however, extended spike patterns (comprising more than a single action potential) have been found to play an important role. This was shown, for example, in the cat LGN (Reinagel and Reid, 2000), and in the cat auditory cortex (Furukawa and Mindelbrooks, 2002), by comparing the information transmitted by the original spike train with that encoded in shuffled responses, where the within-trial correlations between subsequent spikes were eliminated, though preserving the timing precision of individual spikes. These studies concluded that specific temporal arrangements of spikes were relevant to information transmission.

Several distinct features within spike trains have been identified as possible carriers of the neural message. For example, both in the primate primary visual cortex (Reich et al., 2000) and in the electrosensory lobe of the weakly electric fish (Oswald et al., 2007) the duration of interspike intervals (ISIs) was shown to encode particular stimulus properties, i.e., ISIs of different lengths were associated to distinct stimulus features. In the salamander retina (Gollisch and Meister, 2008), a prominent coding role was assigned to the correlations between the response latencies of different cells. In the leech, the velocity of tactile stimuli was encoded by the number of spikes in each burst (Arganda et al., 2007).

The information that is encoded in structured sequences of spikes and silences is only avail-
able when the spike train is read out with extended words, that is, with temporal windows that are sufficiently long to contain several spikes. To quantify the extra information that is gained from such long read-out windows, the concepts of synergy and redundancy have been introduced. In general terms, if the information carried by a collection of variables is higher than the sum of the information carried by the individual elements, then the code is called synergistic. In the opposite situation, the code is redundant (Brenner et al., 2000; Pola et al., 2003; Schneidman et al., 2003). This means that, when assessing the amount of synergy between two variables $R_1$ and $R_2$, we need to determine whether the information $I(R_1, R_2; S)$ encoded by the joint pair $(R_1, R_2)$ about another variable $S$ is larger or smaller than the sum $I(R_1; S) + I(R_2; S)$ of the information encoded by $R_1$ and $R_2$ separately. The amount of synergy $S_{\text{syn}}$ is (Pola, 2003; Schneidman 2003)

$$S_{\text{syn}} = I(R_1, R_2; S) - I(R_1; S) - I(R_2; S).$$

(1)

When applying these ideas to neural coding, $S$ is typically the stimulus, and $R_1$ and $R_2$ are two features of the neural code. In population coding, for example, $R_1$ and $R_2$ are the responses of two different neurons (Gawne and Richmond, 1993; Petersen et al., 2001). In this paper we focus on single-neuron coding, so $R_1$ and $R_2$ represent the response of just one neuron in different time bins.

The amount of synergy between time bins in the neural code has been often estimated in order to determine whether spike patterns play a relevant role (Reinagel and Reid, 2000; Liu et al., 2001; Kumbhani et al., 2007). However, even when $S_{\text{syn}}$ was found positive, the information-bearing spike patterns were not explicitly displayed. In this paper we focus on specific spike patterns, and we provide a quantitative assessment of their relevance in the neural code. We do so by calculating the mutual information between stimuli and responses for different choices of the read-out alphabet. Each alphabet is composed of a collection of spike patterns. As we vary the alphabet, we make increasingly finer distinctions between patterns. By assessing how much information is gained by making fine discrimination between patterns, we reveal which are the informative patterns. Finally, we discuss the consequences of our analysis in the evaluation of how synergistic or redundant the neural code is.

For definiteness, we focus on bursting neurons, where the intra-burst spike count $n$ (that
is, the number of spikes within each burst) is taken as the relevant response feature encoding specific stimulus properties. Burst firing has been ubiquitously found in sensory systems (see, for example, Krahe and Gabbiani, 2004; and references therein). There are different dynamical processes that produce bursting. For example, in the mammal LGN (Sherman, 2001) burst generation is associated to a T-type calcium current, that induces slow oscillations in the membrane potential (low threshold spikes) which, in their depolarized phase, give rise to burst firing. In the weak electric fish, instead, bursting results as a consequence of the geometry of cells: the active propagation of action potential into the dendrites produces a rebound effect, that induces high-frequency repetitive firing (Mainen and Sejnowsky, 1996). In the grasshopper auditory system (Eyherabide et al., 2008) bursting is induced by specific time-dependent stimuli, that fluctuate with time scales of the order of 5-10 msec.

Several studies have demonstrated that bursts have a specific role in the encoding of sensory information. Thus, by comparing the average stimulus eliciting bursts with the one generating isolated spikes, cat LGN bursts were shown to appear in response to stimulus features having a significantly lower power spectrum (Lesica and Stanley, 2004), higher contrast (Reinagel et al., 1999; Lesica and Stanley, 2004) and comprising more natural statistical distributions (Lesica and Stanley, 2004; Denning and Reinagel, 2005) than the features associated with the generation of isolated spikes. Similarly, in the electric fish, bursting was associated with particularly low-frequency events (Oswald et al., 2004), comprising either excitatory or inhibitory stimulus deflections (Metzner et al., 1998). Moreover, the detailed properties of the burst-triggering features were shown to depend critically on the mean stimulus level (Lesica et al., 2006), thus suggesting an adaptive, dynamical role in burst coding.

In these studies, the stimulus features encoded by the event burst (as a whole) were found significantly different by those encoded by the event isolated spike. Other analyses have gone further, discriminating the features encoded by bursts containing specifically \( n \) spikes. If different \( n \) values are associated to different stimulus features, then we may speak of a non-trivial neural code, where the intra-burst spike count \( n \) carries information about the stimulus. So far, \( n \) was shown to encode the magnitude of the slope of the stimulus in bursting pyramidal neurons (Kepecs et al., 2002; Kepecs and Lisman, 2003), the velocity of tactile stimuli in leech (Ar-
ganda et al., 2007), and the amplitude of acoustic fluctuations in grasshopper auditory neurons (Eyherabide et al., 2008).

2 Methods

2.1 Estimation of mutual information rates

In order to calculate mutual information rates between stimuli and neural responses, we have adapted the Direct Method introduced by Strong et al. (1998) to estimate the information transmitted by specific spike patterns. In its original formulation, the method begins by representing the spike train as a sequence of integer numbers, where each number indicated the number of spikes falling within the corresponding time bin (see Fig. 1). For high-resolution binnings, spike

Figure 1: Representation of the spike train as a sequence of symbols. A: A given spike train (top) is represented as a binary string (top string) or as an integer string (bottom string), depending on the alphabet used to identify response patterns. In the integer string, all consecutive spikes separated by ISIs smaller than $\tau$ were grouped into the same burst. B: Three example spike trains that are mapped onto the same integer string, though corresponding to different binary strings.
trains are always represented as binary strings, since the duration of the spike itself ($\approx 1 \text{ msec}$) and of the refractory period ($\approx 2 - 3 \text{ msec}$) forestalls the occurrence of more than a single spike in a short time bin.

Here, the method was broaden to also encompass estimations of the information carried by specific spike patterns. In the first place, one must decide which are the spike patterns that are going to compose the building-blocks of the neural alphabet. For definiteness, in the top string of Fig. 1A, we show the representation of a given spike train, when the only symbols comprising the alphabet are spike (1) and no spike (0). In the bottom string, however, we use a different alphabet. In this case, each time bin represents the number of spikes that follow, whose inter-spike intervals (ISIs) are smaller than a certain prescribed value (equal to $\tau$, in the case of the figure). Hence, the neural alphabet is composed of all non-negative integers, and each symbol represents the intra-burst spike count $n$ of the burst that begins at that time bin.

Notice that once we have decided which spike patterns are going to be taken into account, the new representation of the spike train in terms of patterns can be derived from the original binary representation. As such, it constitutes a processed version of the spike train. The *Data Processing Theorem* (Cover and Thomas, 1991) precludes any manipulation of the spike train from increasing the information transmitted about the stimulus. Hence, the information encoded by the selected patterns is necessarily smaller than the originally contained in the spike train. In fact, there might be several binary sequences that are mapped onto the same integer sequence. In our example, where bursts are defined as sequences of spikes whose ISIs fall below $\tau$, the number $n$ is allocated at the time bin where the burst begins. Hence, with this representation, the information about the precise temporal location of the subsequent spikes in the burst is lost. In Fig. 1B, three example spike trains corresponding to the same integer string in A are exhibited.

Once the spike train is represented as a sequence of symbols (one symbol per pattern), the method follows the same steps as in Strong et al. (1998). That is, consecutive symbols are grouped into *words* of length $w$, and the noise entropy of the distribution of words is subtracted from the total entropy. One thus obtains the information $I_w$ carried by words of length $w$. The
analysis is repeated for different word lengths \( w \), and the mutual information rate is

\[
I = \lim_{w \to \infty} \frac{I_w}{w}.
\]

In this paper, in order to assess which patterns are relevant to information transmission, we have calculated the information rate \( I \) with different choices of the patterns conforming the neural code.

When estimating the information transmitted by the full unprocessed spike train, we have worked with time bins of 0.1 msec (for the simulated data) and 0.4 msec (for the experimental data). These numbers were selected small enough to capture the temporal precision of the responses, and at the same time, not too small as to yield severe sampling problems. Bias corrections were taken into account using the NSB method (Nemenman et al., 2004).

By taking the limit to infinite word length in Eq. (2), we are considering arbitrarily long words. In practice, the limit only needs to be taken until the window is long enough as to encompass all the correlation structure in the spike train. Even larger windows need not be considered, since once subsequent windows are independent from each another, \( I_w \) grows linearly with \( w \), so the ratio in Eq. (2) remains constant. When \( w \) is smaller than the correlation length in the spike train, however, \( I_w/w \) may bear a non-trivial dependence with \( w \).

2.2 Simulated data

In the simulations, the stimulus consists of a Poisson command signal, that has four different aspects: \( \alpha, \beta, \gamma \) or \( \delta \), as shown in Fig. 2. For definiteness, we can think of the stimulus as a sequence of brief light pulses, that can appear in four different colours. When the red light flashes, the stimulus is labelled as \( \alpha \). In the same way, blue is associated with \( \beta \), green and yellow with \( \gamma \) and \( \delta \). Each stimulus induces a response burst of \( n \) spikes, and the value of \( n \) depends on the identity of the stimulus. The temporal axis is segmented into bins of 0.1 msec, and the total duration of the stimulus is 100 sec. If \( P_0 \) represents the probability that no stimulus was shown, the stimulus probabilities in each time bin are

\[
\begin{align*}
P_0 &= 0.995314 \\
P_\alpha &= 1.7378 \times 10^{-3} \\
P_\beta &= 1.2874 \times 10^{-3} \\
P_\gamma &= 9.5373 \times 10^{-4} \\
P_\delta &= 7.0654 \times 10^{-4}
\end{align*}
\]
These probabilities were chosen so that the four stimuli were ranked in order of decreasing importance. If due to limited resources a channel cannot afford to represent the identity of all the four stimuli, their relative probabilities make it convenient to discriminate first stimulus \( \alpha \) from the other three, then (if more resources are available) stimulus \( \beta \) from the remaining two, and finally (if resources are enough), stimuli \( \gamma \) and \( \delta \). This scenario implies there is a hierarchy of possible codes, depending on the length of the code-words that we are willing to use.

The entropy rate of the stimulus is

\[
H_{\text{stim}} = -\frac{1}{\Delta t} \sum_i P_i \log(P_i),
\]

where \( i \) runs over \( 0, \alpha, \beta, \gamma, \delta \), and \( \Delta t \) is the bin size. This entropy can be decomposed into temporal entropy and categorical entropy,

\[
H_{\text{stim}} = H_{\text{temporal}} + H_{\text{categorical}}.
\]

The temporal entropy is the one that only distinguishes whether at each point in time there is a stimulus or not. Hence, if \( P_1 = P_\alpha + P_\beta + P_\gamma + P_\delta \) represents the probability that any stimulus is shown,

\[
H_{\text{temporal}} = -\frac{1}{\Delta t} [P_0 \log(P_0) + P_1 \log(P_1)].
\]

The categorical entropy quantifies the variability associated to the fact that each stimulus can appear in four different types

\[
H_{\text{categorical}} = \frac{P_1}{\Delta t} \left[ -\sum_{i=\alpha,\beta,\gamma,\delta} \frac{P_i}{P_1} \log \left( \frac{P_i}{P_1} \right) \right].
\]

In Eq. (7), the term between brackets is formally an entropy, with normalized probabilities \( P_i/P_1 \).

In our work, the true entropy rate of the stimulus is compared to the one of another random process, where only a single type of stimulus is shown, and whose apparition rate is equal to \( P' = P_\alpha + 2P_\beta + 3P_\gamma + 4P_\delta \).
2.3 Electrophysiology

Intracellular recordings were conducted in vivo on the auditory nerve of *Locusta Migratoria* (see the details in Rokem et al., 2006). The auditory stimulus was a high frequency sine tone (3 kHz) modulated with a low-pass filtered Gaussian amplitude distribution of controlled mean (44.76 dB), standard deviation (6 dB) and cut-off frequency (200 Hz). This stimulus was designed to incorporate some key features of grasshopper courtship songs, are accurately represented in the spike trains (Rokem et al., 2006) and are relevant to behaviour (Balakrishnan et al., 2001; Krahe et al., 2002). The acoustic stimulus lasted for 1 second, and was repeated 503 times, while the spike train was recorded. Between successive repetitions, a pause of 700 msec was incorporated, in order to avoid slow adaptation effects. Bursting responses were observed, and the probability of observing a burst of exactly $n$ spikes in a bin of 0.4 msec was

$$
P(n = 1) = 2.89 \times 10^{-2} \quad P(n = 2) = 6.71 \times 10^{-3}$$
$$P(n = 3) = 1.42 \times 10^{-3} \quad P(n = 4) = 2.52 \times 10^{-4}$$
$$P(n = 5) = 4.36 \times 10^{-5} \quad P(n = 6) = 2.4 \times 10^{-6}$$

3 Quantifying the information transmitted by specific spike patterns: a model study

In the simulations, the stimulus consisted of a Poisson command signal, that could take the values $\alpha, \beta, \gamma$ or $\delta$, as shown in Fig. 2. The four possible outcomes should be interpreted as four particular stimuli (or stimulus features) that pop out occasionally, and induce four different responses in a sensory cell. At any given time bin, either there is no stimulus (the null event), or stimulus $\alpha, \beta, \gamma$ or $\delta$ is presented to the subject. Assigning the label 0 to the null event, we are in the presence of a process with 5 possible outcomes, with probabilities $P_0, P_\alpha, P_\beta, P_\gamma$ and $P_\delta$. Subsequent time bins are independent from one another. In Fig. 2A, an example stimulus is depicted. The height of the vertical bars represents which of the four stimuli was shown.

We assume that the neuron encodes the identity of the different stimuli with bursts of varying spike count $n$, modelling the experimental results discussed above (Kepecs et al., 2002; Kepecs and Lisman, 2003; Arganda et al., 2007; Eyherabide et al., 2008). As illustrated in Fig. 2B,
the cell generates a single spike in response to stimulus $\alpha$, a doublet in response to stimulus $\beta$, a triplet for stimulus $\gamma$ and a quadruplet for $\delta$. Notice that, by construction, the identity of the stimulus is entirely encoded in the intra-burst spike count $n$. Hence, in order to be able to discern which stimulus was presented, a downstream neuron (or an external observer, as ourselves) should read out the activity of the cell using extended words. This neural code has two distinctive components. First, the time at which a burst is initiated encodes when a stimulus was presented. We then say that the spike train carries temporal information. Second, the number of spikes inside the burst encodes which stimulus was presented (Theunissen and Miller, 1995), that is, provides categorical information about the stimulus. As shown below, these two aspects are sometimes confused, if unappropriate readouts are employed.
For simplicity, we assume that the input/output transformation is noiseless. Or, equivalently, that spike-time jitter is always inside the size of each bin, that is, 0.1 msec. Hence, the conditional response probabilities read

\[ P(\text{burst of order } n|\alpha) = \delta^k(n, 1) \]

\[ P(\text{burst of order } n|\beta) = \delta^k(n, 2) \]

\[ P(\text{burst of order } n|\gamma) = \delta^k(n, 3) \]

\[ P(\text{burst of order } n|\delta) = \delta^k(n, 4) \quad (9) \]

where the Kronecker Delta function \( \delta^k(n, i) = 1 \) if \( n = i \), and vanishes otherwise. Our theoretical neuron, therefore, is not defined through a stochastic or a dynamical process, but rather operates as a mere transcription device, that represents stimuli in terms of spikes. In this paper, we focus on the question of how faithfully this translation can be read out, depending on the readout alphabet and word length we use.

For any coding scheme, the information \( I_w \) contained in words of length \( w \) must always be an increasing function of \( w \), simply because the longer the words we are reading out, the more we know about the stimulus. If time bins are fully independent from each other, then \( I_w \) grows linearly with \( w \) (Cover and Thomas, 1991). If time bins are correlated, then \( I_w \) may grow faster or slower than linearly, thus giving rise to interesting dependencies. In these cases, \( I_w/w \) may either be an increasing or a decreasing function of \( w \), for intermediate \( w \). If the encoding system, however, has a finite correlation time, then eventually, for sufficiently long word lengths, \( I_w \) will grow linearly with \( w \). There, \( w \) can be assumed to contain all the relevant code-words used to transmit information, and \( I = I_w/w \) can be safely considered the real information rate.

In Fig. 3 the rate \( I_w/w \) is depicted as a function of the word length \( w \). The desired information rate \( I \) is defined as the limit of this ratio when \( w \to \infty \) (see Methods, Sect. 2.1). Black circles represent the information transmitted by the whole collection of spikes with the usual binary code (1 = spike, 0 = no spike). White circles and lines represent other codes (see below). The two panels correspond to two different choices of the refractory period \( \tau \) of the intra-burst ISI. In A, \( \tau \) is equal to 1 msec, as in Fig. 2B, whereas in B, \( \tau = 0.1 \) msec.

Noiseless conditional probabilities imply that the noise entropy of the responses vanishes. Hence, in this case, the mutual information is equal to the total entropy of the responses. This entropy, in turn, should be expected to lie slightly below the entropy of the stimulus, which can be evaluated analytically (see Methods, Sect. 2.2 for the relevant parameters). In Fig. 3A,
Figure 3: Information ratio $I_w/w$ as a function of the word length $w$. Different lines and symbols correspond to different identifications of the neural alphabet. The information transmitted by the whole collection of spikes shows a dependence with the word-length, tending asymptotically to the information encoded by the whole collection of bursts. A: Refractory period: 1 msec. B: Refractory period: 0.1 msec. Grey horizontal segments on the left: analytically-calculated entropy rate of a binary Poisson stimulus, whose mean frequency is equal to the firing rate of the model neurons in A and B. Black horizontal segments on the right: analytically-calculated entropy rate of the stimulus.

we see that in the limit of long words, $I_w/w$ approaches the theoretical value of the stimulus entropy (represented by the black bar bulging outwards, at the right of the plot), though falling slightly below. This small discrepancy is due to the fact that even noiseless spike trains cannot always represent the stimulus faithfully. If, for example, two consecutive stimuli $\delta$ are drawn in two sequential time bins, the system has no time to allocate four spikes for each stimulus. Recall that each burst of 4 spikes lasts for $4\tau = 4$ msec, and each time bin lasts 0.1 msec. In our simulations, hence, if a stimulus arrives before the system has finished representing the previous stimulus, the new stimulus is ignored. In the case of Fig. A, this happens 420 times, out of 4689 stimulus presentations. As $\tau$ diminishes, the overlap probability decreases. In panel
the results of another simulation are depicted, where the refractory period $\tau$ was set to 0.1 msec. This is not a biologically realistic value, so this case should be taken as an academic exercise designed to show that whenever the number of overlaps decreases (it has now dropped to 21/4775), the asymptotic value of $I_w/w$ approaches the theoretical value (the dark bar on the right) more closely.

Let us now focus on the dependence of the information with the word length. In Fig. 3, we see that the information encoded by the whole collection of spikes is initially high. Why does this value surpass the theoretical stimulus entropy rate in about 40%? For short enough words, there is at most a single spike in each word, and spikes appear to be positioned anywhere within the word. For longer words, this apparent freedom is no longer seen, since the correlations between spikes limit the number of ways in which spikes can be located. But this limitation is not evident, for $w < \tau$. Given that in this example there is no trial-to-trial variability, all the apparent diversity in the location of the spikes has to be assigned to the stimulus: all spiking times can be assumed to be encoding something about the stimulus. In the present case, where $w$ is too short to contain complex spike patterns, each spike is taken to represent a detected stimulus - even the second, third and fourth spikes of each burst. Hence, by reading the neural activity with too short windows, what in reality is categorical information about the identity of the stimulus is interpreted as temporal information. Of course, single spikes can only encode a single type of stimulus, because a spike standing alone cannot discriminate between different kinds of stimuli. Thus, while the categorical information in the actual stimulus is lost, additional temporal information about another non-existing stimulus of higher rate is gained. In fact, the grey bars protruding outwards at the left of the plots represent the theoretical entropy rate of a binary Poisson process whose mean frequency is equal to the firing rate of the modelled cells in $A$ and $B$ (See Methods, Sect. 2.2). Notice the difference: the real stimulus has four possible categories ($\alpha, \beta, \gamma, \delta$), and an apparition rate of 46.85 Hz. The apparent stimulus, instead, has only a single category, and an apparition rate of 91.05 Hz. The tight match between the entropy of the apparent stimulus and the value of $I_w/w$ for $w < \tau$ cannot be casual. It confirms that for small time windows, the information rate appears larger than the real information, because the readout system is interpreting each spike as a new stimulus, whose frequency of occurrence is higher than the frequency of the real stimuli. In the present example, there is no trial-to-
trial variability (or equivalently, spike-time jitter is constrained to be smaller than our time bin of 0.1 msec). Consequently, the additional temporal information about the fictitious Poisson binary stimulus is significantly high. In contrast, the lost categorical information about the real stimulus is limited. The tradeoff between these two effects explains the difference between the initial and final value of $I_{w}/w$.

However, as soon as the window length $w$ reaches $\tau$ the information rate diminishes rapidly. This happens at $w = 1$ msec, in Fig. 3A, and at $w = 0.1$ msec, in B. At this point, two spikes may fall inside the same window, so the apparent freedom with which spikes had seemed to be located is no longer present: often, spikes come in close succession, separated by an interval $\tau$. There is, hence, a typical correlation time in the spike train, that reduces the number of possible words that appear. In this example, it turns out that such correlations are the crucial (and the unique) aspect of the spike train encoding the identity of the stimulus. Therefore, if the information rate diminishes as a function of $w$, it is not due to the fact that correlations provide redundant information, but rather, that for very short windows, the information was erroneously high.

What happens if we represent the spike train as a sequence of bursts, instead of a sequence of spikes? If inside the bin $t$ we indicate the number of spikes $n$ of the burst starting at $t$, the ratio $I_{w}/w$ does not depend on the word length $w$, as shown by the white dots in Fig. 3. Therefore, the information rate can be estimated equally well with $w = 1$ and $w \to \infty$. By construction, in this case an $n$-based code captures all the information contained in the spike train, and does so with 1-bin words. This example serves to emphasize that if one is able to identify the relevant patterns in the spike train, employing symbols that represent those patterns explicitly can save us an enormous amount of time and resources. Recall that the computational time required to estimate information rates with the Direct Method grows exponentially with $w$.

The importance of identifying the relevant patterns in the spike train, however, goes beyond an operational convenience. By trying out different possible encoding schemes and comparing the resulting information rates, one may actually deduce which symbols are the essential ingredients of the neural code. A code based on these symbols, thus, constitutes the minimal code preserving most of the information, and still allows us to quantifying the categorical and the
temporal information separately. In Fig. 3, this is shown by the lines. The dotted line (Alphabet 1) corresponds to a representation of the spike train where only the time at which a burst (any burst) is initiated. Thus, here we also use a binary string, but now each symbol “1” tags the time at which a burst with any number of spikes (including bursts of 1 spike, that is, isolated spikes) is generated. With such a read-out code we are not discriminating between the four different types of stimuli. All the categorical information is lost, whereas all the temporal information is preserved. By comparing the black circles with the dotted line in Fig. 3A, we see that there is a loss of information in approximately 16% (≈ 76 bits/sec). In this stimulus, hence, 84% of the information corresponds to determining the temporal location of each stimulus (a task for which alphabet 1 is well suited), and 16% to identifying which of the four stimuli was presented (something this code fails to do altogether).

We can go one step further, and distinguish one response pattern from the other three. This is equivalent to assuming that isolated spikes ($n = 1$) encode certain stimuli, and bursts ($n > 1$) encode some other stimuli, irrespective of whether $n = 2, 3$ or 4. If the stimuli associated with isolated spikes have significantly more behavioural relevance than the other stimuli, or if they appear more often, then discriminating these stimuli from the rest may be a convenient (and economic) strategy. As mentioned in Sect. 1, several experimental studies have shown examples where bursts (as a whole) encode different stimulus features than isolated spikes. In our example, hence, we define Alphabet 2 as composed of 3 symbols: “0” representing no spike, “1” for isolated spikes, and “2” for doublets, triplets and quadruplets of spikes. With this representation, we obtain the information rates depicted in dashed lines. Once again, $I_w/w$ is independent of $w$, and its numerical value accounts for 50% of all the categorical information in Fig. 3A. This means that out of the 76 bits/sec that are needed to identify which stimulus was presented, 38 of them correspond to identifying stimulus $\alpha$ from the other three. Defining Alphabet 3 as the one distinguishing between no spikes, isolated spikes, doublets, and bursts containing either 3 or 4 spikes indifferently, we get the information rates shown with the solid line. Hence, the distinction between stimulus $\beta$ from $\gamma + \delta$ takes 25 extra bits/sec. Finally, the cost of distinguishing between $\gamma$ and $\delta$ is 13 bits/sec.

The information rates obtained for read-out codes that are increasingly complex, hence,
provide a natural way of quantifying how much information is encoded by each pattern, and how much each pattern adds to the total information rate.

4 Quantifying the information transmitted by specific spike patterns: an experimental study

Grasshopper acoustic receptors fire in response to amplitude-modulated broad band signals (see Machens et al., 2001; Gollisch et al., 2002; Rokem et al., 2006; for further details). In Fig. 4A we show the modulation of a sound-wave stimulus used to drive the recorded cells. In B, 50 trials of the response of a single receptor may be seen (see Sect. 2.3 for the experimental details). A visual inspection of the raw data allows us to identify isolated spikes, as well as short sequences of 2, 3 or 4 spikes coming in succession. These patterns are reliably maintained along trials. In this cell, hence, it makes sense to ask how much information is transmitted by the collection of all spikes, and to compare it to the one encoded by the intra-burst spike count \( n \), as was done above with the simulated data.

In the simulations, all intra-burst ISIs lasted exactly the same interval \( \tau \). Hence, it sufficed to detect all sequences of spikes separated by \( \tau \) to identify bursts. In the experiment, however, burst detection becomes less straightforward, since the ISIs separating consecutive spikes form a continuum. We then need a strategy to decide which spikes belong to the same burst, and which ones correspond to different bursts. To that end, we take the ISI distribution of the cell, depicted in Fig. 4C. The first and most prominent peak corresponds to the most probable intra-burst ISI. The second peak is associated to the characteristic time of inter-burst ISIs. Hence, we take the minimum separating the two peaks as the limiting time \( \tau = 3.9 \) msec separating intra-burst and inter-bursts. We next go through the spike train, and whenever we find two spikes that are separated by an interval that is smaller than \( \tau \), we assign those two spikes to the same burst (a doublet). If yet another spike follows closely (within an interval smaller than \( \tau \)), then we add it to the previous ones, and form a triplet, and so forth. The longest burst in the spike train contained 6 spikes (in Sect. 2.3 we provide the relative frequency of bursts of different \( n \) values). With this procedure, we represented the spike train as a sequence of integer values, as
Figure 4: Recordings in a grasshopper acoustic receptor. A: Amplitude of the sound stimulus used to drive the recorded cell, in decibels. In the experiment, each trial lasted for 1 second. B: Responses to the first 50 stimulus presentations (out of a total of 503 trials). Single spikes can be seen, as well as doublets and triplets. C: ISI distribution of the recorded data. The two peaks correspond to the most probable intra-burst ISI (left) and the inter-burst ISI (right). The minimum between the two maxima is the limiting ISI $\tau$ used for classifying spikes into bursts.

In Fig. 5, the ratio $I_w/w$ is depicted as a function of the word length $w$. The black circles represent the information transmitted by the whole collection of spikes. We see that $I_w/w$ starts at a fairly low value around 100 bits/sec, and progressively grows up to almost 180 bits/sec, reaching the asymptotic value at $w \approx 5$ msec. As explained above, $\tau$ was set to 3.9 msec. Hence, it proves crucial to work with windows that are long enough to contain pairs of spikes, in order to accomplish a correct readout of the neural message. Even longer windows, incorporating triplets, quadruplets and higher-order bursts, provide only minor corrections. The
Figure 5: Information ratio $I_w/w$ as a function of the word length $w$, for the spike train generated by a grasshopper acoustic receptor. Different lines and symbols correspond to different identifications of the neural alphabet. The information transmitted by all bursts is remarkably similar to that of all spikes, implying that there is no information loss by reading out the spike train in terms of a sequence of bursts.

The quantitative value of such corrections is assessed by considering alternative codes. The white circles in Fig. 5 correspond to the integer $n$-based burst code, whereas the different lines represent the reduced alphabets 1-3, introduced in Sect. 3. We see that by completely ignoring the number of spikes within each burst (alphabet 1) the transmitted information is 25% lower. A significant improvement is made by distinguishing single spikes from the rest of the bursts (alphabet 2), and a minor refinement is accomplished by further discriminating bursts of 2 spikes. The overlap between the solid line (alphabet 3) and the white dots (all bursts) implies that no further information is gained by distinguishing between bursts of $n > 2$.

As dictated by the Data Processing Theorem (Cover and Thomas, 1991), when the word length $w$ is long enough to encompass all information-bearing correlations in the spike train, the information carried by the whole collection of spikes (black circles) must lie above all the other codes, as confirmed by Fig. 5. However, in principle nothing prevents the code based on all spikes to encode even more information than all the burst-based codes. Indeed, if the precise location of subsequent spikes inside each burst were relevant, the black circles should be expected to lie significantly above all the other curves. From Fig. 5, however, we see that all the information in the spike train is well captured by the burst-based code (white circles). Hence, the integer representation of the spike train carries all the relevant information. We
therefore conclude that the only response features that carry information are the location of the first spike in each burst, and the number of spikes per burst.

Having assigned a relevant value to the discrimination between single spikes, doublets, and higher order bursts, we may now wonder what these different symbols in the neural alphabet mean, in terms of the stimulus features that elicit them. Going back to panels A and B, we may now interpret the stimulus-response transformation, by identifying the stimulus features that precede single spikes, doublets, and higher-order bursts. Specifically, we see that doublets of spikes are generated by stimulus deflection of higher amplitude than the ones required for single spikes. Triplets, in turn, are preferentially found following stimulus excursions that are not only high, but also wide. Quantitative methods to assess the differences between the stimulus features eliciting bursts containing different number of spikes have been described in Eyherabide et al. (2008).

5 Discussion

Numerous studies have attempted to determine whether spike patterns play a relevant role in the neural code. So far, two basically different approaches have been employed. In the so-called quantitative methods, the role of spike patterns was assessed by means of information-theoretical measures. The information transmitted by the full spike train is first estimated, with as high a temporal resolution as limited-sampling problems permit (see Panzeri et al., 2007, and references therein, for a discussion of the sampling limitations of information estimation). This full-blown information is regarded as the true information content of the spike train. This information is then compared to the one obtained by an altered readout mechanism where spike patterns can no longer play a role. In some experiments, the altered readout mechanism consists in considering words containing only a single time bin (Reinagel and Reid, 2000; Furukawa and Mindelbrooks, 2002; Kumbhani et al., 2007). Obviously, single-bin words cannot account for the information encoded in spike patterns. In other cases, the altered readout mechanism is obtained by shuffling the spike train, mixing the responses obtained throughout the different trials, within a fixed time bin (Reinagel and Reid 2000, Furukawa and Middlebrooks, 2002; Osborne
et al., 2004; Montemurro et al., 2007). This procedure eliminates within-trial structured spike patterns, though preserving the correlations in the peri-stimulus time histogram. If the amount of information obtained from the full spike train is significantly higher than the one resulting from the altered readout, it has often been concluded that spike patterns play a relevant role in information transmission.

The disadvantage of the quantitative approach is that, even if it allows us to conclude that spike patterns are indeed important, it does not enable us to identify which are the relevant code-words, nor to disclose their meaning in terms of the stimulus. In this respect, this method may be tagged as **blind**. In compensation, being based on a numerical evaluation of the information loss, one may precisely assess the relevance of the spike patterns in quantitative terms. Therefore, although we still lack explicit knowledge of the relevant code-words, we are provided with a precise quantification of how much information is lost, if those patterns (whichever they might be) are ignored.

As an alternative to the quantitative methods, there are also **qualitative** ones. In the first place, we need to identify specific patterns in the spike train, whose meaning we are interested in. These patterns are picked either by visual inspection of the responses, or with more sophisticated detection procedures (see for example, 2001; Fellous et al., 2004; Eyherabide et al., 2008). Next, one identifies the average stimulus feature eliciting the chosen patterns, and performs some statistical test to assess whether these features are different from one another or not (see, for example, Reich et al., 2000; Arganda et al., 2007; Oswald et al., 2007; Eyherabide et al., 2008). This procedure allows us to read out the correspondence between specific patterns in the spike train and their associated stimulus features. However, unless a quantitative evaluation of the importance of each pattern is performed, one cannot determine whether the correspondence between spike patterns and stimulus features is a crucial ingredient of the code or not. Moreover, if not all of the relevant response features have been identified, such correspondence may remain incomplete, perhaps missing even the most important code-words employed by the cell.

Here, we combined the quantitative and qualitative methods. We chose specific spike patterns in the neural alphabet, thereby allowing an explicit description of the neural code. Once
these patterns have been identified, a qualitative analysis of their meaning in terms of the stim-
ulus can easily follow, by means of covariance analysis. At the same time, by constructing a
sequence of nested alphabets, with increasingly finer distinction between the patterns, we quan-
titatively assessed the role of each pattern in the neural code. Our goal was to discover the most
compact code compatible with preserving the available information.

In the example discussed in Sect. 3 we saw that there was a representation of the spike
train (the $n$-based alphabet) that allowed us to recover all the information in the spike train. If
this alphabet was reduced, some information was lost. We therefore conclude that the $n$-based
alphabet contained all the relevant patterns in the neural code, and no superfluous patterns.
When we applied the same procedure to the experimental analysis of Sect. 4 (where the relevant
patterns were unknown) we found that the relevant code-words were isolated spikes, doublets,
and bursts of $n > 2$. These three patterns contained all the information in the spike train, and
none of them was idle.

An important point in our procedure was to analyze the dependence of $I_{w}/w$ on the window
length $w$. Only when $I_{w}/w$ has reached its asymptotic value can one be sure that the read-out
windows are long enough to encompass all information-bearing spike patterns. By determining
the minimal word length $w_0$ for which $I_{w}/w$ is indistinguishable from its asymptotic value, we
bound the maximal length of the relevant patterns. In our work, conclusions about the nature
of the neural code are only drawn for $w \geq w_0$. In other studies, however, the very dependence
of $I_{w}/w$ on the window length $w$ was used to assess the synergistic or redundant nature of the
code. Specifically, if for long $w$, the information $I_{w}/w$ was larger than $I_{1}/1$, patterns were
assigned a synergistic role (see, for example, Brenner et al., 2000; Reinagel and Reid, 2000;
Liu et al., 2001; Kumbhani et al., 2007). In view of the results obtained in Sect. 3 we believe
that those discussions should be handled cautiously, as explained below.

**Consequences to the synergy/redundancy discussion**

In Sect. 3 readouts based on short words were shown to confound categorical information with
temporal information. In order to disentangle these two aspects, here we consider three more
extreme experiments. The first one contains categorical information alone, the second one, only temporal information, and the third one, a mixture of the two. In Fig. 6A, the response

![Diagram](image)

Figure 6: Idealized experiments, to discuss the interplay between categorical and temporal information. In A, each trial contains only a single stimulus. Here, only categorical information can be extracted from the responses. Individual time bins contain no information at all, so the code is synergistic. B: Numerous stimuli are shown in each trial, at random times. Two possible noiseless codes are depicted. In both cases, the responses identify the apparition of each stimulus, but they do not encode the stimulus category. Response 1 allocates a single spike to each stimulus, and response 2 a doublet. In response 1, different time bins are neither synergistic nor redundant, whereas in response 2, they are redundant. C: Example spike train corresponding to the code of A and the stimulation protocol in B.

properties of the categorical experiment are displayed. Each trial begins with the presentation of either stimulus $\alpha$ or $\beta$. Responses are measured in a time window locked to stimulus onset. In this case, hence, all response properties encode stimulus identity, since in all trials, the stimulus appears at time 0. Upon presentation of stimulus $\alpha$, the cell either generates a triplet, or a single spike, both options with probability 1/2. In response to stimulus $\beta$, instead, one always gets a doublet, though the precise timing of the second spike is uncertain. Using the time bins depicted in dashed lines, different time bins are synergistic: the information obtained from reading out the whole response is higher than the sum of the information obtained in each time bin. In fact, single bins contain no information at all.

Now let us consider an example where the neural responses encode temporal information alone, as depicted in Fig. 6B. There, each trial contains many stimuli, and the time of stim-
ulus apparition is a stochastic variable itself. Two possible noiseless codes are discussed. In both cases, responses are assumed to only encode stimulus apparition, with no discrimination of stimulus category. In Response 1, each stimulus is encoded with a single spike, and in Response 2, with a doublet. Time bins are taken small enough to allocate a single spike at most. If stimuli are drawn independently from one another, in response 1 different time bins are neither synergistic nor redundant. In response 2, instead, different time bins are redundant. In general terms, whenever a neural response encodes temporal information alone, spike patterns are bound to introduce redundancy, since the addition of extra spikes into the encoding patterns can add no new information. Indeed, the larger the number of spikes in each pattern, the larger the amount of redundancy. In C, we show the response that would be obtained if the code introduced in A was recorded with the time-dependent protocol of panel B. In this case, although the encoding of categorical information is synergistic, the time-dependent code is redundant. This is usually the case, since for fine temporal binnings and low jitter, categorical information is much smaller than temporal information (see Eqs. (5) and (7), where the categorical information is shown to be proportional to the apparition rate of the stimulus, which is usually much smaller than unity). In conclusion, the tradeoff between the encoding of stimulus category and the time of stimulus apparition is responsible for the redundancy between different time bins, even in neural codes where all the categorical information is encoded in spike patterns.

6 Conclusions

We have shown that by studying how the information rate depends on the choice of the neural alphabet we may decide which are the important, information-bearing patterns in the neural code. It is then possible to go back to the stimulus, and interpret those code-words in terms of specific stimulus features. Our procedure, hence, allows us to read-out the neural code, and at the same time, to quantify the additional information encoded by specific spike patterns. Our results are easily applicable to the case of bursting sensory neurons, where the number of spikes inside each burst has been reported to encode specific stimulus features.

We also discuss an example where, even though by construction all the categorical infor-
mation about the stimulus is encoded in spike patterns, the code appears to be redundant when evaluated with standard techniques. This follows from a tradeoff between the synergy associated to the encoding of categorical information and the redundancy in the representation of temporal information. We therefore claim that the results obtained from estimating the amount of synergy in the neural code need to be viewed as the combined effect of these two opposing phenomena.

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