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A comparative analysis of integrating visual information in local neuronal ensembles

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Abstract

Spike directivity, a new measure that quantifies the transient charge density dynamics within action potentials provides better results in discriminating different categories of visual object recognition. Specifically, intracranial recordings from medial temporal lobe (MTL) of epileptic patients have been analyzed using firing rate, interspike intervals and spike directivity. A comparative statistical analysis of the same spikes from *a local ensemble of four selected neurons* shows that electrical patterns in these neurons display higher separability to input images compared to spike timing features. If the observation vector includes data from all four neurons then the comparative analysis shows a highly significant separation between categories for spike directivity ($p = 0.0023$) and does not display separability for interspike interval ($p = 0.3768$) and firing rate ($p = 0.5492$). Since electrical patterns in neuronal spikes provide information regarding different presented objects this result shows that related information is intracellularly processed in neurons and carried out within a millisecond-level time domain of action potential occurrence. This significant statistical outcome obtained from a local ensemble of four neurons suggests that meaningful information can be electrically inferred at the network level to generate a better discrimination of presented images.

Keywords

Biological neuron; Information processing; Spike directivity; Neural code; Nanoneuroscience; Neuroelectrodynamics

1. Introduction

One important function of the brain is to represent, transform and integrate information received from sensory inputs. Large populations of neurons are commonly involved in information processing in the nervous system. How is this information processed by every cell in the network and how is information integrated in the brain remained unexplained.

Traditional approaches to neural coding hypothesize that information is represented in the spike rate of neurons (Shadlen and Newsome, 1994) or precise timing of individual spikes (Bialek et al., 1991). More recently besides firing frequency data, inter-spike interval (ISI) has been assumed to characterize stimuli inputs and provide an accurate representation of distributed neural code (Gerstner and Kistler, 2002). The classical coding model highlights the importance of temporal patterns in large-scale brain networks (Shadlen and Newsome, 1994; Abbott et al., 1997; Honey et al., 2007; Felleman and Van Essen, 1991; Softky and

Koch, 1993). Therefore, the main idea of recordings and current analyses in neuroscience is to analyze and decode temporal patterns.

The neuronal activity in the temporal lobe is related to visual recognition of different objects (Liu et al., 2009). In particular these neurons can show selective, invariant, and explicit responses to a set of images. We know from Kreiman et al. (2000) that the same neurons are activated during vision and visual imagery and that firing rate is able to separate between various categories. Quiroga et al. (2005) showed that single MTL neurons fire selectively in response to a particular face, animal, object or scene since single neurons may encode features of particular objects. Almost always responses in single units outlast stimulus presentation and can be associated with conscious recognition (Quiroga et al., 2005).

However, these analyses have raised many new questions. How are categories identified, classified and remembered in these neurons? Are specific neurons or network modules dedicated to face perception? What is the relationship between temporal patterns (firing rate, ISI) and memory formation?

In this paper we try to provide some answers using ‘spike directivity’, a new measure that captures electrical features during action potential (AP) propagation. Contrary to common belief action potentials are not uniform (stereotyped) pulses of electricity. The digital-like uniformity of action potentials is not validated by experimental data (Quirk et al., 2001; Aur et al., 2005; Aur and Jog, 2006, 2007, 2010; Sasaki et al., 2011). Simple computational techniques can be used to extract information from small changes in APs waveforms (Aur et al., 2005; Aur and Jog, 2006). For every recorded spike, a new measure spike directivity (SD) can be computed using extracellular recordings. Multiple monopoles can describe the current source density of a spike and provide information regarding spatial distribution of electrical processes developed in the cell. If a reference in space is considered (e.g. one tip of tetrodes) then changes in transient charge density that occur intracellularly during action potential (AP) propagation can be represented and monitored (Aur et al., 2005).

Indeed, various characteristics can be used to analyze neuronal activity however, here only three hypotheses are considered. The first hypothesis assumes that firing rate characteristics can provide accurate measures of information processed by neurons during object presentation. The second hypothesis is that interspike interval distributions can provide accurate measures of information processed by neurons during object presentation and the third hypothesis states that spike directivity characteristics provide accurate measures of information processed by neurons during object presentation. Therefore, the main idea is to test statistical significance of these hypotheses in providing information regarding object category. In order to test above hypotheses, the activity of a relatively small subset of neurons from MTL that responded to series of presented images is analyzed. Only three categories of images are analyzed, images of faces, images of animals and images of landscapes. Each category includes five presented images.

2. Data collection materials and methods

The data was previously recorded from patients with pharmacologically intractable epilepsy that have been implanted as described in Kreiman et al. (2000) with depth electrodes to detect the area of seizure onset. The placement of the depth electrodes in the MTL followed limited clinical requirements. Images of faces, animals, and landscapes were presented for 1 s, with 1 s pause after each presentation, in pseudo-random order on a laptop computer in multiple recording sessions, six times each. During all sessions patients were asked to indicate whether a human face was presented. All patients were able to identify human faces with the error rate less than 1%. Majority of these neurons responded to several presented images. Spike detection and sorting were performed and applied to recorded data using well

established algorithms. Three main categories of presented images are considered for analysis. The firing rate characteristics, interspike interval distributions and spike directivity characteristics are computed.

The raw cross-correlations of recorded data indicate the presence of similar APs recorded from at least four implanted electrodes. Therefore, the same APs were detected in at least four electrodes that can be considered to form a ‘tetrode’ framework. An automated unsupervised classification of multidimensional data in the tetrode setup was used (KlustaKwik, Harris et al., Rutgers University). The default values of KlustaKwik from Mclust along with energy features are used to cluster the recordings. Pre-clustered spikes with similar means were merged together and from 17 clusters and only 9 clusters were further considered, about 2000 spikes. The selection of neurons was determined by the requirements to compute spike directivity from recorded AP shapes. Since spike directivity analysis requires extracting information from the variability of AP shapes, action potentials (APs) from neurons that generate smaller amplitudes are not included. Therefore, neurons that generate small AP amplitudes (max values <0.1 mV) were not considered and also one cluster with very high amplitudes was not further included. Four neurons represent the maximum number of neurons that have amplitudes >0.1 mV and can be well separated using the same group of electrodes. This procedure was followed by a manual selection of spikes. The final result shows four well separated clusters with signal amplitudes >0.1 mV which provided four neurons (N_1 – N_4) with their APs that were further analyzed (Fig. 1). For each category and for all four analyzed neurons the peristimulus time histogram (PSTH) with equal bin size (20 ms) shows the times at which the neurons fire APs. The response in these neurons did not disappear with stimulus offset and continued up to 2 s after stimulus offset. Therefore, the entire period between 200 ms and 2000 ms after stimulus onset is considered in these analyses. The presence of a refractory period in single units has been checked (less 1% spikes within <3-ms ISI). The maximum values of the means of APs amplitudes provide the difference between four channels in a tetrode configuration where about 550 spikes are generated by 4 neurons (Fig. 1 and Table 1). Without performing complex cell membrane recordings or intracellular recordings the extracellularly recorded potentials can be used to estimate changes in charge density that occur inside neurons using the charge movement model (Aur et al., 2005). Multiple monopoles can describe the current source density of a spike (Aur and Jog, 2006, 2010; Gold et al., 2006). The monopole technique was experimentally tested (Lee et al., 2011). For each clustered spike we computed spike directivity using the algorithm presented in Aur et al. (2005). To maintain a correct search direction, a test for positive definiteness of J matrix is required and corrections are introduced if necessary (Dennis and Schnabel, 1983) using plausible convergence criteria to stop the algorithm (Isaacson and Keller, 1994; Mittelhammer et al., 2000). Since the sample size is similar ($n > 40$) and the same spikes are used, then statistical methods can well capture the difference between different methods of analysis.

2.1. Image presentation and hypotheses

The set of images includes five faces with corresponding features $f^{FACES} = \{f^{Face1}, f^{Face2}, f^{Jennifer}, f^{Ander}, f^{Drew}\}$, five animals with features $f^{ANIM} = \{f^{Monkey}, f^{Horse}, f^{Eleph}, f^{Spider}, f^{Tiger}\}$ and five landscapes $f^{LAND} = \{f^{Out10}, f^{Out12}, f^{Out20}, f^{Out26}, f^{Out28}\}$ where $f^{FACES} \in F^{FACES}$, $f^{ANIM} \in F^{ANIM}$ and $f^{OUT} \in F^{OUT}$. The presentation of each image category generates neural activity which is the response considered to be the ‘output space’ with corresponding characteristics for faces $h^{FACES} = \{h^{Face1}, h^{Face2}, h^{Jennifer}, h^{Ander}, h^{Drew}\}$, animals $h^{ANIM} = \{h^{Monkey}, h^{Horse}, h^{Eleph}, h^{Spider}, h^{Tiger}\}$ and landscapes $h^{LAND} = \{h^{Out10}, h^{Out12}, h^{Out20}, h^{Out26}, h^{Out28}\}$ where $h^{FACES} \in H^{FACES}$, $h^{ANIM} \in H^{ANIM}$ and $h^{OUT} \in H^{OUT}$. The set of features f_i varies from image to image, however objects from a certain category have to share specific features. This set of features that characterize presented images

contains relevant attributes which may include semantic aspects or other particular characteristics. The neural response can be measured by estimating the firing rate. Given a set of features $f_i \in F$ the neuron transforms (maps) the set of input features in series of action potentials (APs) in such way that $h_{firing_i} \in H_F$ represents the image feature f_i :

$$F \xrightarrow{T_F} H_F \quad (1)$$

where T_F is the transformation from image feature to firing characteristics. Since images are repeatedly presented, then the estimation of firing rate can be obtained if this value is averaged. The mean firing rate response to a picture is computed as the median number of spikes across trials between 200 and 2000 ms after stimulus onset. The probability density of ISI can be also considered a measure of neural activity which embeds information. Therefore, given the same set of features $f_i \in F$ the neuron transforms (maps) this set of features in interspike interval characteristics $h_{ISI_i} \in H_{ISI}$

$$F \xrightarrow{T_{ISI}} H_{ISI} \quad (2)$$

where T_{ISI} is the transformation from image feature to ISI data. The probability density of ISI is obtained using a kernel density estimator that generates the characteristics h_{ISI}^{FACES} for faces, h_{ISI}^{ANIM} for animals and h_{ISI}^{LAND} for landscapes.

The existence of patterns of activation (micro-maps) determined by different spatial charge densities has been recently evidenced in APs (Aur et al., 2005; Aur and Jog, 2006). Since APs are spatially modulated in a meaningful way (Aur and Jog, 2010) then it is expected that electrical patterns within spikes contain information from presented images. Therefore, given a set of features f_i the neuron transforms (maps) these features in electrical patterns and spike directivity characteristics $f_i \in F$

$$F \xrightarrow{T_{SD}} H_{SD} \quad (3)$$

where $h(x_i, y_i, z_i)$ represents the distribution of electrical charges in Cartesian coordinates (x_i, y_i, z_i) and T_{SD} is the transformation from object feature into a distribution of electric patterns within spikes. Since spike directivity characterizes the transient density of electrical charges, then the third hypothesis is that the relationship between object presentation and the presence of electrical patterns (micro-maps) is not random and can be captured by an analysis of spike directivity. Since every spike directivity vector points on a sphere surface (Fig. 2a) the corresponding output features $h_{SD_i} \in H_{SD}$ are determined by estimating spike directivity and corresponding representation as distinct points on the unit sphere (Fig. 2b):

$$S^2 = \{r \in R^3: \|r\| = 1\} \quad (4)$$

In order to analyze the resulting distribution of the head of arrows on the unit sphere all three-dimensional Cartesian coordinates (x_i, y_i, z_i) are mapped into spherical coordinates θ_i and ϕ_i where:

$$\theta_i = \arctan \left(\frac{y_i}{x_i} \right) \quad (5)$$

and

$$\phi_i = a \tan \left(\frac{z_i}{\sqrt{x_i^2 + y_i^2}} \right) \quad (6)$$

The density of mapped features (only θ_i angle is considered) can be estimated using a kernel density estimator:

$$\hat{h}(\theta) = \frac{1}{ns} \sum_{i=1}^n \left(\frac{K(\theta - \theta_i)}{s} \right) \quad (7)$$

where K is a Gaussian kernel and s is the smoothing parameter Terrell and Scott (1992).

These electric patterns represented on the unit sphere map specific features of faces h_{SD}^{FACES} , animals h_{SD}^{ANIM} or landscapes h_{SD}^{LAND} .

3. Results

All four analyzed neurons responded primarily to all different images. Two different spikes recorded from the same neuron can display different spike directivities (Fig. 3). The electrical activity appears mirrored (Aur et al., 2005). Since the entire device is asymmetric, the representation of spike directivity on the north hemisphere provides a better resolution and displays in an explicit topographic manner the relationship with encoded categories (Fig. 4). Assuming normality of data, one way ANOVA statistics can be used to determine if these characteristics of faces, animals and landscapes are well separated. A similar analysis is performed for firing rate and ISI probability densities and then compared.

The estimated F -ratio and p -values summarize the result of comparative statistical analysis (see Table 2). Larger values of F -ratio show that the variation among group means do not occur by chance. In the first two neurons one way ANOVA statistics of firing rate characteristics does not provide any separation between categories (p -values > 0.1) N_1 : $p = 0.678$, N_2 : $p = 0.248$). However, the observed difference is significant ($p < 0.05$) in the neuron N_4 : $p = 0.0261$ and marginally significant ($p < 0.1$) in the neuron N_3 : $p = 0.09$. Similar analysis carried on using probability density of ISI displays highly significant category separability ($p < 0.001$) in two neurons (N_2 : $p = 0.0008$; N_3 : $p = 9.9749e-007$) and does not provide any separation in the other two neurons (N_1 : $p = 0.3196$; N_4 : $p = 0.1723$). Interestingly, the neuron where the firing rate shows high separability between ISI characteristics (N_2 : $p = 0.0008$) is the one where firing rate does not provide any separation (N_2 : $p = 0.248$). Additionally, for firing rate the difference is significant in N_4 (N_4 : $p = 0.0261$) and does not display separability if ISI is analyzed in N_4 (N_4 : $p = 0.1723$). However, one way ANOVA statistics of probability density function of the θ angle shows that electric characteristics generated during AP propagation in these neurons significantly separate these categories with p -values: N_1 : $p = 0.028$, N_2 : $p = 0.0012$; N_4 : $p = 0.011$ and the difference is marginally significant in one neuron (N_3 : $p = 0.065 < 0.1$).

If the observation vector includes data from all 4 neurons, then the comparative analysis shows a highly significant separation between categories for spike directivity ($F = 6.09$, $p = 0.0023$) and does not display separability for ISI ($F = 0.98$, $p = 0.3768$) and firing rate ($F = 0.61$, $p = 0.5492$). The normality of data is not an issue and does not change the significant difference between firing rate, ISI and spike directivity. The application of Kruskal–Wallis method shows similar significant differences between temporal coding (firing rate, ISI) and spike directivity (Table 3). In addition, the Kruskal–Wallis method does not require the assumption of a normal distribution. If the observation vector includes data from all 4

neurons, the comparative analysis with Kruskal–Wallis displays even a higher separation between categories than ANOVA ($p_{KW} = 2.629 \times 10^{-7}$). Also, in this small local network, the Kruskal–Wallis test does not display separability for ISI ($p_{KW} = 0.8904$) or firing rate ($p_{KW} = 0.4888$). A post hoc pairwise comparison shows that the difference between animals and other groups (faces and landscapes) is relevant. The firing rate and ISI analysis do not provide a significant difference between the groups (Fig. 6).

4. Discussion

In these four selected neurons spike directivity analysis outperforms firing rate and ISI outcome in relating neuronal activity with category presentation. Statistical analysis shows that spatial distribution of electrical patterns is not random, it carries information regarding presented images and their categories (Fig. 5). The change in electrical patterns follows the anatomical model of the cell, the geometry and topology of active regions involved in spike generation (Fig. 2). The comparative analysis of spike directivity data from all four neurons together provides a highly significant separation between categories in both tests (ANOVA: $F = 6.09$, $p = 0.0023$; Kruskal–Wallis, $p_{KW} = 2.629 \times 10^{-7}$) while firing rate and interspike interval data recorded from the same group of neurons do not display statistical significant separability. The occurrence of electrical patterns and spatial modulation of action potential is determined by presented objects and shaped by specific morphological characteristics of neurons (Figs. 2 and 4). Since all four neurons respond to analyzed categories and provide highly significant separation between categories in both tests, these results suggest that information regarding presented images is intracellularly processed in many neurons and electrically inferred during AP generation. Within a millisecond-level time domain of AP generation the transient charge density dynamics provides meaningful information regarding object category representation. These neurons behave as ‘weak learners’ that attend to preferred spatial directions in the probably approximately correct sense (Aur and Jog, 2007).

Indeed, statistical analysis of electrical patterns in neuronal ensemble can tell more about the image class than using a separate analysis in single cells. A different spatial propagation of action potentials can determine a change in synaptic connectivity which may alter the communication of information in the network. Therefore, a different spatial propagation will target different synapses, change proximity interactions and ephaptic coupling (Anastassiou et al., 2011). A spatial modulation of AP propagation can alter the synaptic function via Ca^{2+} signaling that may increase the release of neurotransmitters with direct effects on ion channels in the post-synaptic neuron. The selection of neurons with APs (max values >0.1 mV) is solely required to accurately estimate spike directivity and does not limit the generality of results.

This fundamental approach in perceiving information in electrical patterns within spikes connects changes in electrical patterns with molecular machinery (Wang et al., 1998; LaFerla, 2002; Woolf et al., 2009; Guan et al., 2009; Aur, 2011; Aur et al., 2011) and complex electrochemical processes that spatially modulate AP propagation (Sasaki et al., 2011). If only few neurons are analyzed (e.g. four), firing rate and ISI do not always display statistical significant relationship with presented objects categories (Fig. 6). In addition, the analysis of temporal patterns (ISI, firing rate) shows that the local ensemble does not seem to perform significantly better than individual neurons ($p_{KW} = 0.8904$, $p_{KW} = 0.4888$). Therefore, the fundamental aspects of information processing, communication and computation may be hidden to temporal analysis (firing rate, ISI).

Indeed, the roots of intelligent action seem to lie deep in information processing performed by single cells (Ford, 2009, 2010). These simple cells have evolved to carry electric signals ‘became’ neurons in order to electrically integrate various information in the brain. Earlier

theoretical models have revealed complex intracellular phenomena where molecular structures are directly involved in information processing (Barlow, 1996; Hameroff et al., 2002, 2010; Pidaparti et al., 2007; Woolf et al., 2009; Craddock et al., 2010). All of them have suggested the existence of sub-cellular platforms for information processing which preferentially regulate protein signaling pathways required to store fragments of information at the level of individual proteins.

5. Conclusion

The response of a local ensemble of four neurons to different presented images is captured by temporal coding features (firing rate, ISI) and spike directivity. Importantly, this small subset of neurons recorded by the same group of electrodes form together a local ensemble. If information from electrical patterns is considered the ensemble shows a better outcome in category recognition than any separate neuron. This property cannot be extended to temporal coding features. In fact, these experimental results confirm the existence of an important sub-cellular level for information processing. In this small local network, estimated electrical patterns provide enhanced discrimination of presented images. Meaningful changes in electrical patterns reveal that information regarding presented objects is processed within cells and electrically integrated in the brain. This outcome highlights a neuroelectrodynamics model of computation by interaction which brings back the strength of physical laws to explain the complexity of information processing in the brain (Aur, 2011; Aur and Jog, 2010; Aur et al., 2011). In addition the interaction between neurons including connectivity seems to be influenced by intracellular processes which can spatially modulate the propagation of APs. The all or none AP allows a fast interaction inside the cell when information stored within molecular structure (e.g. proteins) is carried out and integrated within the generated electric flux. Overall, this fast process (action potential-1 ms) is more energy efficient than a graded response since it provides stronger interaction with less energy. With adequate computational methods (e.g. spike directivity) this meaningful information that occurs during AP generation can be directly extracted from spikes. Spike directivity is a vector that quantifies changes in transient charge density during action potential propagation and reflects the interaction between charge densities embedded within molecular structures (e.g. proteins) and the transient developed flow of electrical charges. The presence of information regarding presented objects in the extracellular space suggests that various informations can be electrically integrated in the brain. These phenomena that occur within APs may provide a step forward in understanding the fundamental gap between molecular description, information processing, memory, neuronal function and actual framework in cognitive computation.

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Fig. 1.
The mean amplitudes of waveforms recorded from four selected neurons (A) N₁, (B) N₂, (C) N₃ and (D) N₄.

Fig. 2.

(A) The representation of spike directivity as a vector in red color when electrical patterns occur simultaneously in two axonal branches (adapted from Aur and Jog (2010)). X and Y represent the coordinates in microns of 2D-view of recorded spike. (B) A schematic representation of scaled neuron in the unit sphere. The spike directivity is represented in red color. The arrow head points on the 2-sphere surface. In a spherical coordinate system the angles θ and ϕ characterize the orientation of spike directivity vector (θ values range from 0 to 2π while ϕ values range from 0 to π). (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

Fig. 3. Two different spikes from the same neuron recorded by four electrodes represented in blue, red, green and yellow display two different spike directivities. The panels C and D are estimates from panels A and B. The differences of recorded voltages within these two spikes represented in A and B are mapped into corresponding changes of spike directivity in C and D. The head of the arrow points on a sphere with radius one ($\|t\| = 1$). (A) Four recorded waveforms and their corresponding spike directivity represented on the north hemisphere (C). (B) Four recorded waveforms and their corresponding spike directivity represented on the South hemisphere (D).

Fig. 4. The representation of spike directivity features is mapped on the north hemisphere of four neurons. The corresponding probability density estimate of spike directivity (θ_i angles) of faces in red color, animals in blue color and landscapes are represented in yellow color. (A) The representation of spike directivity head arrows on the unit sphere; (B) The probability density estimates of spike directivity (θ_i angles) display clustering effects in all four neurons (faces in red color, animals in blue color, landscapes in blue color). (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

Fig. 5.

The electrical activity of selected neuron (N_1) displays a direct relationship to encoded categories in a topographic manner. The two dimensional probability density estimate of arrowhead positions of spike directivities on the north hemisphere across θ and ϕ angles for (A) faces, (B) animals and (C) landscapes.

Fig. 6.

A post hoc pairwise comparison shows differences between SD, firing rate and ISI analyses in four selected neurons (A) If spike directivity is considered then a significant difference occurs between animals and the other two categories (faces and landscapes). (B) There is no significant difference between categories if firing rate is considered. (C) There is no significant difference between categories if ISI is considered.

Table 1

The maximum values for the means of amplitudes for all 4 selected neurons.

	Channel 1 [μ V]	Channel 2 [μ V]	Channel 3 [μ V]	Channel 4 [μ V]
N ₁	130.2	125.0	177.7	161.3
N ₂	161.6	122.8	149.1	161.3
N ₃	154.2	140.7	116.1	147.7
N ₄	126.4	143.7	148.4	121.5

Table 2

A comparative analysis one way ANOVA test.

	<u>Firing rate</u>		<u>ISI</u>		<u>SD</u>	
	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>
N ₁	0.678	0.4	0.3196	1.15	0.028	3.62
N ₂	0.248	1.57	0.0008	7.3	0.0012	6.87
N ₃	0.09	2.95	9.9749e-007	14.48	0.065	2.75
N ₄	0.0261	5.01	0.1723	1.77	0.011	4.57

Table 3

Both tests ANOVA and Kruskal–Wallis show similar differences.

<i>p</i>	<u>Firing rate</u>		<u>ISI</u>		<u>SD</u>	
	<i>p</i>	<i>p_{KW}</i>	<i>p_{ANOVA}</i>	<i>p_{KW}</i>	<i>p_{ANOVA}</i>	<i>p_{KW}</i>
N ₁	0.678	0.5398	0.3196	0.2116	0.028	0.0439
N ₂	0.248	0.2350	0.0008	0.0347	0.0012	0.0068
N ₃	0.09	0.0743	9.9749×10^{-7}	0.2099	0.065	4.692×10^{-9}
N ₄	0.0261	0.0331	0.1723	0.2358	0.011	1.26×10^{-5}