Information−theoretic characterization of concurrent activity of neural spike trains

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***Abstract*—The analysis of massively parallel spike train recordings facilitates investigation of communications and synchronization in neural networks. In this work we develop and evaluate a measure of concurrent neural activity, which is based on intrinsic firing properties of the recorded neural units. An overall single neuron activity is unfolded in time and decomposed into working and non-firing state, providing a coarse, binary representation of the neurons functional state. We propose a modified measure of mutual information to reflect the degree of simultaneous activation and concurrency in neural firing patterns. The measure is shown to be sensitive to both correlations and anti-correlations, and it is normalized to attain a fixed bounded index which makes it interpretable. Finally, the measure is compared with widely used indexes of spike train correlation. The estimate of all measures is carried out in controlled experiments with synthetic Poisson spike trains and their corresponding surrogate datasets to asses its statistical significance.**

***Index Terms*—spike trains, neural synchrony, concurrent activity, firing patterns, mutual information.**

I. INTRODUCTION

Estimators of spike train synchrony attempt to quantify the level of (dis)similarity between two (or more) spike trains, resulting in diverse synchrony measures relaying on different approaches. These measures have been shown as a very useful tool in better understanding of communication and synchronization in neural networks. Quantification of neural synchrony is of relevance for the time coding paradigm, considering that information is carried by precise spike timings [1]. Under this coding scheme, synchronized neural activity can be found in many experimental tasks, where population of neurons coordinate their activity at the single spike level. Some of them include analysis of movement direction from synchronous activity in motor cortical neurons [2], task-dependent modulation in spikes synchrony during a precision grip task [3] and stable propagation of synchronous activity in cortical neural networks [4]. The studies also encompass computation of the information transfer between synaptically coupled neurons, [5], estimation of the reliability of neural responses upon many trials triggered by the same stimulus in neocortical neurons [6], or the role of neural synchrony in the development of retinotopic maps [7]. Recently there has been also evidence on the relevance of synchronous activity for obtaining a synchrony code, although other features operating at the single unit level are important for a complete encoding of time-dependent signals [8]. All these works provide better understanding of link between correlated activity and the representation of sensory information, and bring insight into the characterization of neural multiple interactions [9].

The review paper [10] provides a systematic overview of thirty-six pairwise measures of spike train synchrony. Various indexes based on different approaches are described, including measures which calculate the distance between spikes trains, measures using cost functions to transform one spike train from another, then measures derived from cross-correlograms or information theory, and measures treating spike trains as shot-noise processes or marked point processes. Aiming to fairly quantify the level of synchrony between two spike trains, all measures are tested with respect to the defined necessary and desirable properties formalized in [10]. The necessary properties include: symmetry, robustness to recording duration and firing rate (FR), and presence of well defined upper and down limits that enable a clear differentiation between anti-correlation, correlation or absence of correlation. The desirable properties include: minimal number of input parameters, minimal assumption of structure's distribution and exclusion of periods when neurons are inactive.

The comprehensive analysis of all measures as regards both the necessary and the desirable properties − provided in [10] has resulted in the identification of three measures exhibiting all properties: the Spike Count Correlation Coefficient (SCCC) [11] and its improved version denoted as Kerschensteiner and Wong correlation (KWC) [12], and the Spike Time Tilling Coefficient (STTC) [10]. Guided by the evaluation protocol proposed in [10], a new approach for the quantification of the concurrent firing activity between two spike trains, denoted as Concurrent Firing Index (CFI), was proposed in [13]. This approach is based on fragmenting the overall spiking activity into three functional states (bursting, moderate firing and non-firing [14]), where the degree of concomitant activation is quantified as the fraction of overlap between the working states (bursting and moderate firing) of two spike trains [13].

Building on the same concept, based on the decomposition

This research has been supported by the Ministry of Education, Science and Technological Development through the project no. 451-03-68/2020-14/200156: "Innovative scientific and artistic research from the FTS (activity) domain".

of the spiking activity into working and non-firing states unfolded in time, in this paper we propose a novel information-theoretic approach to quantify the degree of concurrency in neural firing patterns. With this approach, starting from the binary representation of the spiking activity (working-1, non-firing-0) in two trains, we derive a pairwise measure based on a modified form of mutual information. This measure, denoted as CFI_{MI} index, is assumption-free, symmetric and bounded between -1 and 1. Moreover, it has a clear interpretation in terms of correlation, anti-correlation and absence of correlation. Like CFI, the measure requires the estimation of periods of neuron's silence as the only input parameter. In this work, we assess the behavior of CFI_{MI}, in comparison with STTC and KWC, using simulations of independent Poisson spike trains and of correlated and anti-correlated coupled spike trains, also assessing statistical significance through the generation of surrogate event series.

II. Materials and Methods

A. Coarse model of firing pattern decomposition

Statistically, a spike train can be modeled as a realization of a temporal point process with periods of intense and moderate activity, interleaved with periods of quiescence [15]. As a consequence, intervals between consecutive spikes (inter-spike intervals, ISIs) can be differentiated as very short, moderate or long. Spikes which delimit short, moderate or long ISIs are associated with different firing patterns: bursting, moderate firing or sparse spiking activity, respectively [14]. Exploiting this concept, we use the coarse model of firing decomposition proposed in [14]. In brief, the model partitions the whole ISIs stream (**ISI**) of a given spiking activity into three functional states: burst (**B**), idle (**I**) and firing state (**F**), as determined by the corresponding bursting and idle ISI thresholds, respectively [14].

The bursting threshold $thr_{\mathbf{B}}$ determines the entrance into the bursting pattern (state) encompassing all the ISIs for which ISI $\leq thr_{\mathbf{B}}$. It is a specific physiological constant depending on the type of neural cells which are modeled, usually in the range of [2, 10] ms depending on a brain region. The idle threshold, denoted as $thr_{\mathbf{I}}$, reflects the attenuated firing activity of specific neural cells. It is estimated for each neuron, with respect to its intrinsic firing properties as $thr_{\mathbf{I}} = b{\cdot}mean(\mathbf{ISI})$, where *mean*(**ISI**) is the average ISI duration and b is an adaptive parameter for the identification of periods of quiescence, typically set according to the prescriptions given in [14]. The analysis of the idle threshold selection, and the firing decomposition procedure on simulated and real data is provided in [14].

In this work, in order to achieve a binary representation of the spiking activity, the firing and burst states (**F** and **B**) are merged to form a single working state (**W** or state '1'), as opposed to the idle state (**I** or state '0'), which exhibits considerably attenuated neural activity. In this way, the whole spiking activity unfolded in time is fragmented into two functional states: firing (1) and non-firing (0). An illustration of the decomposition of the firing patterns into the three functional states **F**, **I** and **B** is given in Fig. 1a) for two exemplary spike trains, while the corresponding binary profiles are reported in Fig. 1b).

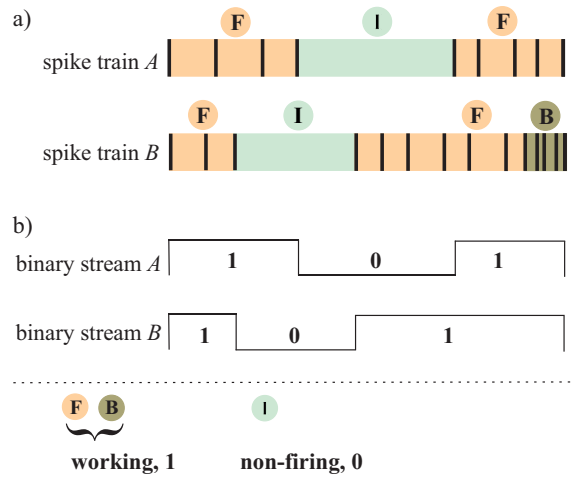

Fig. 1. a) Spiking activity decomposition into the three states (**F**, **I**, **B**); b) Binary profiles of the corresponding spike trains, obtained by merging **F** and **B** states into working (**1**) state, while **I** represents non-firing (**0**) state.

B. Concurrent firing index based on mutual information

Mutual information (MI) is a well-known symmetric measure from information theory, which quantifies the information shared between two random variables intended as the amount of uncertainty about one of the two variables that is explained by the knowledge of the other [16]. In this work, MI is applied to the binary streams of the spiking activities (an illustration is in Fig. 1b). Specifically, we consider two binary random variables A and B, for which the probability of the states '0' and '1' are obtained from the model representation described in Sect. II A. For a given two binary streams, the joint probability distribution $P_{AB}(a,b)$ is quantified, computing the relative duration of the working and non-firing states for the two trains as $P_{AB}(a,b) = T_{ab}/T$, where T_{ab} is the time during which the train A is in state a and the train B is in state b ($a, b \in \{0, 1\}$), and T is the total duration of the streams; similarly, the marginal probabilities are quantified as $P_A(a) = T_a/T$ and $P_B(b) = T_b/T$. Then, MI is computed using its standard definition [16]:

$$I(A,B) = \sum_{a,b\in\{0,1\}} P_{AB}(a,b) log_2 \frac{P_{AB}(a,b)}{P_A(a)P_B(b)}. \quad (1)$$

We modify this measure in order to be normalized and to reflect both, correlated and anti-correlated activity. Normalization is achieved considering that MI is bounded between zero (corresponding to independent variables) and the minimum of entropy of the two variables, $H_{min} = min\{H(A), H(B)\}$ (corresponding to fully dependent variables) [17]. The distinction between correlation and anti-correlation is obtained by defining two probabilities p_c and p_{ac}, to be estimated from the two analyzed trains, such that their comparison allows to set the sign of the proposed synchrony measure. Here, p_c is

computed as the average conditional probability of train A to be in one state given that train B is in the same state, while p_{ac} is computed as the average conditional probability of train A to be in one state given that train B is in the other state:

$$p_c = \frac{1}{2}\left(\frac{P_{AB}(1,1)}{P_B(1)} + \frac{P_{AB}(0,0)}{P_B(0)}\right),$$
$$p_{ac} = \frac{1}{2}\left(\frac{P_{AB}(0,1)}{P_B(1)} + \frac{P_{AB}(1,0)}{P_B(0)}\right). \quad (2)$$

With these settings, the proposed concurrent firing index based on mutual information − CFI_{MI} index, is defined as:

$$CFI_{MI} = \begin{cases} I(A,B)/H_{min} & \text{if } p_c > p_{ac}, \\ -I(A,B)/H_{min} & \text{if } p_c < p_{ac}, \\ 0 & \text{if } p_{ac} = p_c. \end{cases} \quad (3)$$

The CFI_{MI} definition assures that the index ranges from -1, corresponding to fully anti-correlated activation patterns (mutually exclusive firing periods), to 1, corresponding to fully correlated patterns (simultaneous firing periods). Moreover, the index is designed to be exactly zero when the two spiking activities are independent.

C. Simulations

The ability of the proposed CFI_{MI} index to detect uncorrelated, anti-correlated and positively correlated spiking activity was tested, in comparison with well-established synchrony measures (i.e., KWC and STTC), in simulations reproducing independent or coupled Poisson spike trains. The analysis was performed generating 100 realizations per simulation, each characterized by recording time of 300 s and firing rate equal to 3 spikes per second (except for the case where these parameters were tested). In all simulations, the CFI_{MI} index was computed after setting the recommended values $thr_{\mathbf{B}}$ = 5 ms and $b = 3$, for the parameters of the firing pattern decomposition model [14]. For estimation of KWC and STTC, the window of synchrony was set to Δt = 0.1 [10].

1) Scenario of independent Poisson spike trains: Pairs of independent Poisson spike trains were generated in order to assess the dependence of the synchrony measures on FR and recording duration. To test the dependence on the firing rate, one spike train was simulated with a FR of 1 spike/s and the other one varying the FR in the range [1, 20] spikes/s with a unit step. To test the dependence on the duration of recordings, spike trains were generated with fixed FR = 3 spikes/s and varying recording time in the range [30, 50, 100, 200, 300, 500, 1000] seconds.

2) Scenario of dependent Poisson spike trains: The second simulation scenario should enable the design of specific spike trains which can exhibit both correlations and anti-correlations. To achieve this, an empirical approach was followed, whereby the firing rate of a spike train was modulated locally in time, depending on the other spike train current activity mode. More precisely, firstly a Poisson spike train A was generated with the fixed firing rate = 3 spikes/s in the total duration of T. The number N of spikes contained in the period T was counted, and the average duration of the ISIs in the train, $\overline{ISI}$, was calculated together with the total duration of 'short' and 'long' ISIs: T_1 and T_2, intervals shorter or longer than the limit threshold $T_L = 3 \cdot \overline{ISI}$ (an illustration of all parameters is given in Fig. 2a). Using the train A as a reference, spikes were randomly put in the second train B within time intervals synchronized with each ISI of the train A, in a number modulated by the parameter γ: if the ISI had duration $T_{ISI} < T_L$, a number of spikes equal to $\gamma \cdot N \cdot T_{ISI}/T_1$ was put within the ISI; if its duration was $T_{ISI} > T_L$, a number of spikes equal to $(1-\gamma) \cdot N \cdot T_{ISI}/T_2$ was put within the ISI. In this way, the train B contained the same number of spikes as the train A, distributed in a way such that working periods in the train A were fully overlapped with non-working periods in the train B when $\gamma = 0$ (Fig. 2b), and with working periods in the train B when $\gamma = 1$ (Fig. 2c). During the simulation, the parameter γ was varied in the range [0, 1] in steps of 0.05.

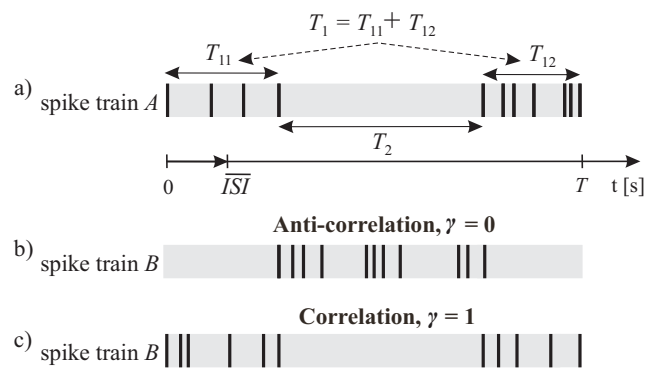

Fig. 2. a) An exemplary spike train A; b) spike train B fully anti-correlated with A, γ = 0; c) spike train B fully correlated with A, γ = 1.

D. Assessment of statistical significance

The statistical significance of the proposed CFI_{MI} index, and of the KWC and STTC measures, was assessed by means of a surrogate data test. The test allows to detect the absence of correlated firing activity for independent spike trains, and the presence of anti-correlated or correlated activity for coupled spike trains. Surrogate time series were generated by the JOint DIstribution of successive inter-event intervals (JODI) method [18]. JODI is an accurate and efficient algorithm, specifically designed for point processes, to produce surrogate event time series which share the same amplitude distribution and approximate the auto-correlation of the inter-event intervals in the original event series. Here, JODI was exploited to generate 100 pairs of independent surrogate trains for each pair of spike trains simulated as in Sect. II C2, with an assigned value of the parameter γ. The value of the analyzed measure (CFI_{MI}, KWC or STTC) obtained for the original spike trains was compared with the distribution of this measure assessed over the 100 surrogate pairs. The measure was deemed to detect

anti-correlation, absence of correlation, or positive correlation when the original value was lower than the 2.5^{th} percentile, included between the 2.5^{th} and 97.5^{th} percentiles, or higher than the 97.5^{th} percentile of the surrogate distribution, respectively.

III. RESULTS AND DISCUSSION

Fig. 3 presents the synchrony estimates between two independent Poisson spike trains generated with different firing rate ratios, as explained in Sect. II, C1. The proposed CFI_{MI} index and the KWC index display very stable estimates around zero, while STTC is stable only for small FR ratios ($\leq$ 5 spikes/s). This indicates that CFI_{MI} and KWC are independent on FR, while STTC requires fine-tuning of its input parameter Δt to sustain the FR independence property.

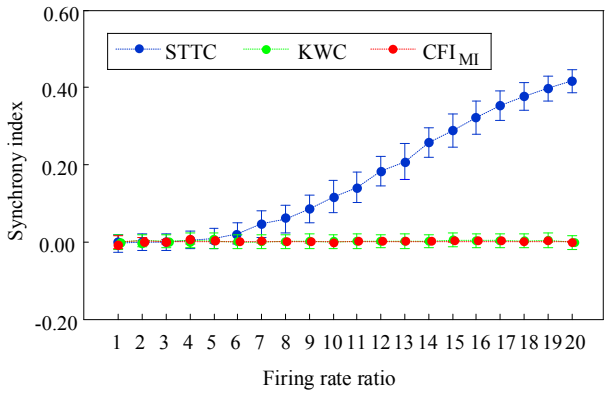

Fig. 3. Distributions of the three synchrony measures (mean and standard deviation across 100 realizations of independent Poisson spike trains) computed as a function of the firing rate ratio.

Fig. 4 reports the dependence of the synchrony measures on the duration of the recording, assessed within the simulation scenario explained in Sect. II, C1.

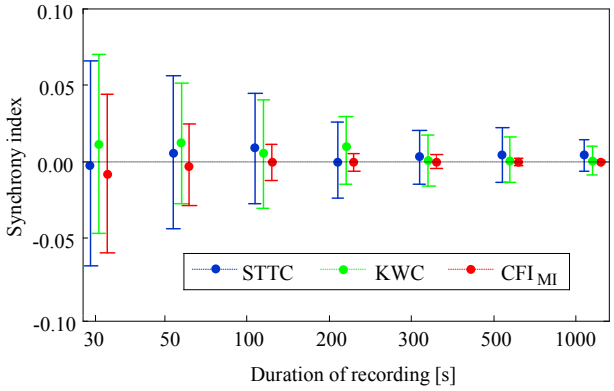

Fig. 4. Distributions of the three synchrony measures (mean and standard deviation across 100 realizations of independent Poisson spike trains) computed as a function of the duration of recording.

As independent Poisson trains were generated, all measures display values distributed around zero; as expected, estimates are more stable for longer recordings. The variance of CFI_{MI} estimates is smaller than that of the STTC and KWC measures, suggesting a higher precision for the proposed measure.

The upper panels of Fig. 5. report the behavior of the three synchrony measures estimated over 100 realizations of coupled spike trains for each value of the parameter γ, in the range [0, 1] corresponding to anti-correlation and correlation, respectively.

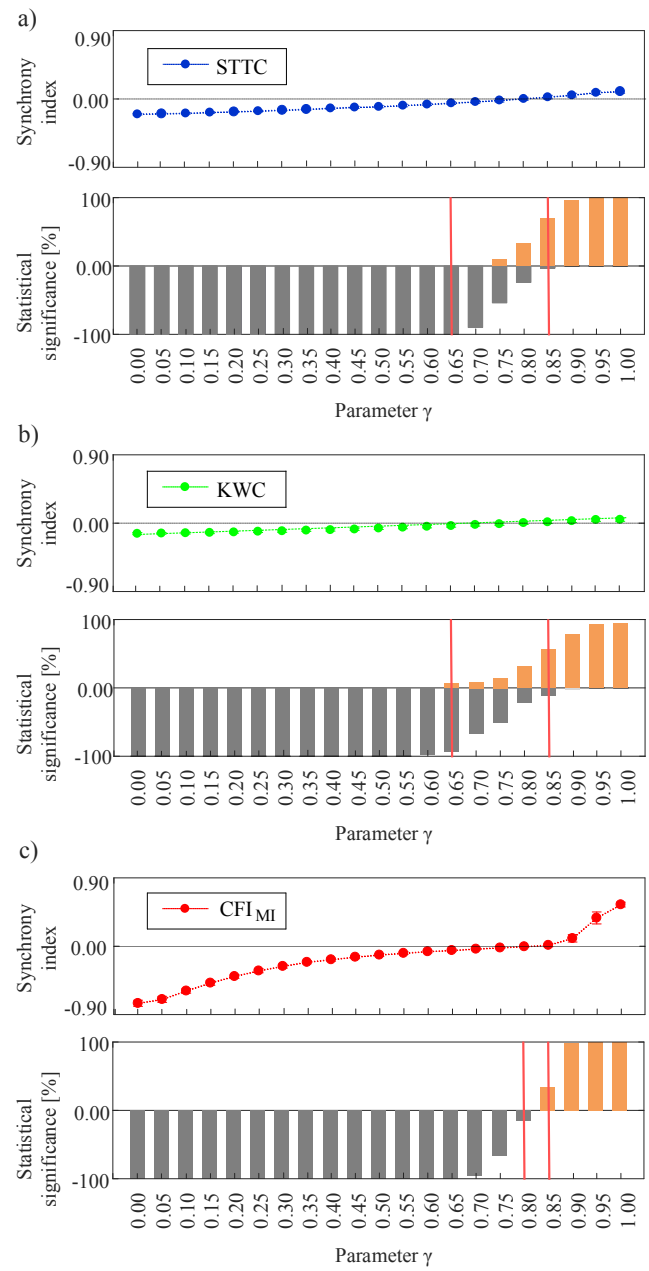

Fig. 5. Distribution across 100 realizations of coupled spike trains (upper panels) and corresponding percentage of realizations detected as significantly correlated (orange bars) or anti-correlated (gray bars; lower panels) for the three synchrony measures a:) STTC; b) KWC; c) CFI_{MI} as a function of the coupling parameter γ.

It can be noticed that in all three measures their sign clearly indicates positive and negative correlation. The bottom panels in Fig. 5. present the results of the exhaustive evaluation of the

synchrony measures on surrogate data, whereby 100 surrogate pairs were generated for each pair of coupled spike trains. For each value of the parameter γ, the bars on the graphs present the percentage of significantly anti-correlated (gray color) and significantly correlated (orange color) spike train pairs based on the measure distribution estimated over their surrogate data, as described in Sect. II, D. For γ in the range [0.65, 0.85] transition between negative and positive correlation occurs, and generated spike trains dominantly exhibit absence of correlation. In this range, STTC and KWC measures simultaneously detect non-negligible percentage of both positively and negatively correlated surrogate pairs. Whereas, the proposed CFI_{MI} index provides clear transition from negative to positive correlation over the values of γ characterized by the absence of correlation (γ = 0.80, 0.85).

IV. CONCLUSION

In this paper we propose a novel, mutual information based, approach for the quantification of the concurrent firing activity between two spike trains. Utilization of this information-theoretic metric is straightforward thanks to the binary representation of the overall firing activity into working and non-firing states [13]. The way a criterion to distinguish simultaneous from mutually exclusive firing periods is implemented, leads to a measure which possesses the necessary properties. Most prominent of those properties is a fix bound between -1 and 1 which makes the measure interpretable. Moreover, the measure is found to capture different levels of anti-correlated and correlated concurrent activity. Those properties were made possible thanks to the normalization by the minimum entropy of the two binary streams.

The proposed measure is more robust to changes in the firing rate and in the duration of the analyzed spike trains, and exhibits smaller variance in the detection of uncoupled firing activities when compared to the well-established measures in literature [10], [12]. It also exhibits higher sensitivity to coupling variations and clear transition from anti-correlation to correlation in the presence of anti-correlated and correlated activities.

Future work should include a refinement of the measure to make it able to distinguish moderate firing and bursting, its extension to the detection of multivariate interactions in networks of several interacting neurons, and the evaluation of its performance on experimental data.

ACKNOWLEDGMENT

The authors express gratitude to Leonardo Ricci and Alessio Perinelli for providing Matlab code for JODI method [18].

REFERENCES

[1] M. N. Shadlen and W. T. Newsome, "Noise, neural codes and cortical organization", Current opinion in neurobiology, Vol. 4, pp. 569–579, 1994.

[2] N. G. Hatsopoulos, C. L. Ojakangas, L. Paninski and JP. Donoghue, "Information about movement direction obtained from synchronous activity of motor cortical neurons", Proceedings of the National Academy of Sciences, Vol. 95, pp. 15706–15711, 1998.

[3] S. N. Baker, R. Spinks, A. Jackson and RN. Lemon,"Synchronization in monkey motor cortex during a precision grip task. I. Task-dependent modulation in single-unit synchrony", Journal of Neurophysiology, Vol. 85, pp. 869–885, 2001.

[4] M. Diesmann, M. O. Gewaltig and A. Aertsen, A, "Stable propagation of synchronous spiking in cortical neural networks", Nature, Vol. 402, pp. 529-533, 1999.

[5] Z. Mainen, T. J. Sejnowski, "Reliability of spike timing in neocortical neurons", Science, Vol. 268, pp. 1503–1506, 1995.

[6] A. D. Reyes, "Synchrony-dependent propagation of firing rate in iteratively constructed networks in vitro", Nature Neuroscience, Vol. 6, pp. 593-599, 2003.

[7] B. K. Stafford, A. Sher , A. M. Litke, D.A. Feldheim, "Spatial-temporal patterns of retinal waves underlying activity-dependent refinement of retinofugal projections", Neuron Vol, 64, pp. 200–212, 2009.

[8] J. Grewe et al, "Synchronous spikes are necessary but not sufficient for a synchrony code in populations of spiking neurons", Proceedings of the National Academy of Sciences Vol. 114, pp. 1977–1985, 2017.

[9] E. Brown, R. Kass, and P. Mitra, "Multiple neural spike train data analysis: state-of-the-art and future challenges", Nature neuroscience, Vol. 7, pp.456–461, 2004.

[10] C. S. Cutts and J. E. Stephen, "Detecting pairwise correlations in spike trains: an objective comparison of methods and application to the study of retinal waves", Journal of Neuroscience, vol.34, pp.14288–14303, 2014.

[11] J. J. Eggermont, "Pair-correlation in the time and frequency domain", Analysis of parallel spike trains, Springer, pp. 77-102, 2010.

[12] D. Kerschensteiner and R. O. Wong, "A precisely timed asynchronous pattern of ON and OFF retinal ganglion cell activity during propagation of retinal waves", Neuron, Vol. 58, pp. 851–858, 2008.

[13] G. Mijatovic, T. Loncar-Turukalo and N.Bozanic, "Investigating Neural Correlations − an Approach to Measure Concurrent Firing Activity, he 11th conference of the European Study Group on Cardiovascular Oscillations, Pisa, Italy, April 27th-29th, 2020, accepted paper.

[14] G. Mijatović, T. Lončar-Turukalo, E. Procyk and D. Bajić, "A novel approach to probabilistic characterisation of neural firing patterns", Journal of Neuroscience Methods, Vol. 305, pp. 67–81, 2018.

[15] E. N. Brown, R. Barbieri, V. Ventura, R. E. Kass, and L. M. Frank, "The time-rescaling theorem and its application to neural spike train data analysis" Neural computation, Vol. 14, pp.325–346, 2002.

[16] C. E. Shannon and W. Weaver, "The mathematical theory of communication", Urbana, IL, 1949.

[17] R. M. Gray, C. P. Shields, "The maximum mutual information between two random processes," Information and Control, Vol 33, pp. 273–280, 1977.

[18] L. Ricci, M. Castelluzzo, L. Minati and A. Perinelli, "Generation of surrogate event sequences via joint distribution of successive inter-event intervals" Chaos: An Interdisciplinary Journal of Nonlinear Science, Vol. 29, pp. 121102.1-12, 2019.