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# Statistical analysis of trial-to-trial variability for biophysiological recurrence plots

Tamara Tošić, Kristin K. Sellers, Flavio Fröhlich Mariia Fedotenkova, Peter beim Graben and Axel Hutt

## Abstract

Transients, metastable states (MS) and their temporal recurrences encode fundamental information of biophysiological system dynamics. To understand the system’s temporal dynamics, it is important to detect such events. In neural experimental data, it is challenging to extract these features due to the large trial-to-trial variability. A proposed detection methodology extracts recurrent MS in time series (TS). It comprises a time-frequency embedding of TS and a novel statistical inference analysis for recurrence plots (RP). To this end, we propose to transform TS into their time-frequency representations and compute RPs based on the instantaneous spectral power values in various frequency bands. Additionally, we introduce a new statistical test that compares trial RPs with corresponding surrogate RPs and obtains statistically significant information within RPs. The combination of methods is validated by applying it on two artificial datasets, commonly used in low-level brain dynamics modelling. In a final study of visually-evoked Local Field Potentials, the methodology is able to reveal recurrence structures of neural responses in recordings with a trial-to-trial variability. Focusing on different frequency bands, the  $\delta$ -band activity is much less recurrent than  $\alpha$ -band activity in partially anesthetized ferrets. Moreover,  $\alpha$ -activity is susceptible to pre-stimuli, while  $\delta$ -activity is much less sensitive to pre-stimuli.

## Keywords

*Trial-to-trial variability, Time-frequency analysis, Local Field Potentials, Recurrence plot analysis, Statistical inference, Surrogate data*

## I. INTRODUCTION

The identification of metastable states in complex dynamical systems has become increasingly important in recent time. Its significance ranges from spin glasses [1] over molecular configurations [2] to geoscientific applications [3]. In neurosciences, the related concept of sequential metastable attractors has received increasing attention in the last years [4]–[9]. Primarily, works are motivated by the experimental observation of time-transient signal features [10]–[13].

Usually the concept of metastability refers to slow transient relaxation dynamics in statistical physics [1], [14]. In a much wider sense, this notion is nowadays used for regions in the phase space of a dynamical system with relatively large dwell that are connected by transients [4], [5], [9]. Paradigmatic examples for those metastable states are *almost invariant sets* [15] and *recurrence domains* [16], such as the “wings” of the Lorenz attractor centered around its unstable foci [17], or saddles connected by heteroclinic trajectories [18].

In neuroscience, metastability assumed increasing experimental evidence over recent years. [19], [20] observed sequences of metastable electroencephalogram (EEG) topographies, which they called *brain microstates*. [10], [11], [21] argued that components of the event-related brain potentials (ERPs) reflecting perceptual and cognitive processes could be identified with metastable brain states. Mazor and Laurent, e.g., reported sequences of metastable states in a reconstructed activation space of the locust’s neural odor circuit [12]. [13] were able to detect metastable states in epileptic EEG time series through spectral clustering methods, and most recently, [6] revealed metastable transition networks in the recovery from anesthesia. Consequently, to understand underlying neural mechanisms much better, it is necessary to develop advanced techniques to detect these recurrence structures in experimental time series.

For the identification of metastability in time series, their characteristic slow time scales must be separated from the fast dynamics of phase space trajectories. The method known as *Perron clustering* [2], starts with

an *ad hoc* partitioning of the system’s phase space that leads to an approximate Markov chain description [1], [2], [13], [15], [22]. Applying spectral clustering methods to the resulting transition matrix yields the time scales of the process, while their corresponding (left-)eigenvectors allow the unification of cells into a partition of metastable states [13], [22]. Another approach by [10] utilizes the slowing-down of the system’s trajectory in the vicinity of saddles by means of phase space clustering. Most recently, beim Graben and Hutt suggested to combine recurrence plot techniques and symbolic dynamics in order to partition a system’s phase space into its recurrence domains [16], [21]. The application of the latter method to experimental event-related potentials has identified metastable attractors to so-called ERP-components, known to reflect cognitive processing stages in neural information processing.

Developing novel analysis tools for representation and tracking of nonlinear transient patterns faces numerous challenges, such as reducing the signal dimensionality while preserving the information significant for the detection task or building methods robust to acquisition noise. Recurrence analysis has been used for identifying transient patterns in experimental EEG [23], for classifying patients based on EEG time series [24] and for prediction of responses during anaesthesia [25]. A key feature of recurrence analysis is to identify sequential states in a multi-dimensional signal space. If the experimental data under study is multi-dimensional, e.g., a multi-channel EEG, the data serves directly as the input to the recurrence analysis. In the case of univariate time series, it is necessary to transform the univariate signal to a multivariate signal. Typically this is done by delay-embedding techniques [26], [27]. In neuroscience, certain frequency bands play distinct roles in neural information processing and hence the present work proposes a novel embedding technique based on time-frequency representations of univariate signals. This approach permits to analyse recurrent structures in specific frequency bands.

In this work we propose a new metastable states detection method for a set of neural signals. To obtain a statistically significant evidence of recurrence structures in signals, we conduct a statistical test over the set of novel, frequency-selective recurrence plots (RP). Below we describe methodologies for building such frequency-selective RPs and performing statistical inference tests. These tests indicate how stable the recurrence plots are with respect to trial-to-trial variability. This novel statistical evaluation is necessary in the analysis of neurophysiological data, since trial-to-trial variability is a well-known experimental finding in such signals. In our work we analyse synthetic transient oscillations involving acquisition noise to validate the methodology. Finally, the study of experimental Local Field Potentials obtained in ferrets (*Mustela putorius furo*) during a visual stimulus experiment allows to extract new insights into neural information processing. For instance, we show that temporal recurrence occurs in the  $\alpha$ -frequency band but not in the  $\delta$ -frequency band.

## II. MATERIAL & METHODS

In this section we introduce the novel method for studying temporal recurrences common in recurrence plots of different trials. Section II-A introduces classical recurrence plots and describes corresponding parameters. Then, we provide a novel method to compute recurrence plots from their time-frequency representations. In Sec. II-B we propose the statistical test method that analyses the similarity of RPs and finds their statistically significant parts. Finally, in Sec. II-C we describe the datasets used in this work.

### A. Recurrence plots and novel time-frequency representations

Recurrence is the fundamental property of dynamical systems which characterises the behaviour of the system in phase space [28]. A recurrent signal instant is a moment in time when the trajectory returns to a neighborhood of a location in phase space it has already visited previously.

Deterministic dynamical systems are described by its trajectory. A trajectory  $\underline{x}(t) \in \mathbb{R}^n$ ,  $t \in \mathbb{R}$  is sampled at times  $t = i\Delta t$ ,  $i \in \{1, 2, \dots, N\}$ , where  $\Delta t$  is the sampling time and  $N$  is the total number of samples. For the notation simplicity, in this paper we denote the signal sample  $\underline{x}(i\Delta t)$  by  $\underline{x}(i)$ . Then, a recurrence plot (RP) is defined as the  $N \times N$  matrix  $\mathbf{R}$ , whose elements  $r_{i,j}$  take values  $r_{i,j} = 1$  when two trajectory

samples lay within the open ball  $\mathcal{B}(\epsilon)$  of radius  $\epsilon$

$$r_{i,j} = \begin{cases} 1, & \text{if } d(\underline{\mathbf{x}}(i), \underline{\mathbf{x}}(j)) < \epsilon, \\ 0, & \text{otherwise,} \end{cases} \quad (1)$$

where  $d(\cdot, \cdot)$  is a distance function and  $i, j \in \{1, \dots, N\}$ . Hence, recurrence plots are two-dimensional matrices obtained by distance based thresholding and its elements take values  $r_{i,j} \in \{0, 1\}$ . In this work, pixels in RPs will be color-coded white for values  $r_{i,j} = 0$  and black otherwise.

For an arbitrary chosen  $\epsilon$  value we can not guarantee that some of the significant dynamics features are not discarded by thresholding. To minimise such a thresholding error, we compute the optimal threshold value  $\epsilon^*$  which maximises the symbolic entropy for a given distance function, as proposed in [16]. In more detail, under the assumption that recurrence states are uniformly distributed for a given recurrence plot, the method constructs disjunct and transitive symbolic matrices and maximises the entropy

$$H(\epsilon) = -\frac{1}{S_{k,\epsilon}} \sum_{k=1}^{S_{k,\epsilon}} p_k \log(p_k), \quad (2)$$

for a range of  $\epsilon$  values. Here,  $S_{k,\epsilon}$  is the number of states for a given  $\epsilon$  and  $p_k$  is the probability of the occurrence of the state  $k$ , calculated as the number of the occurrences of the symbol  $k$  divided by the total number of occurrences of all symbols. Then the optimal value

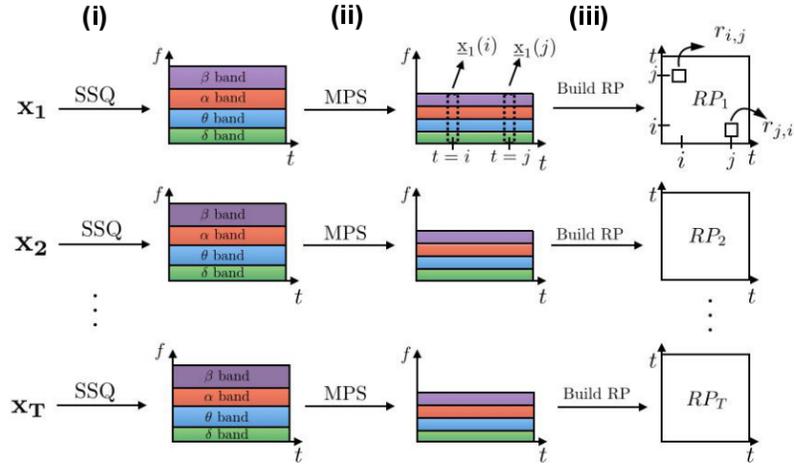
$$\epsilon^* = \arg \max_{\epsilon} H(\epsilon)$$

maximizes the entropy of the system.

After defining conventional RPs and computation of the optimal parameter  $\epsilon$ , the remaining part of this section focusses on how to build frequency-selective recurrence plots. Many biophysiological signals have characteristic frequency signatures. For example, the human heart beats about 60 times per minute in average, i.e., at the frequency of 1Hz. Another example are eye blinks that induce signal changes in the  $\alpha$ -frequency band (frequencies in the interval 8Hz-12Hz) in EEG recordings. To take into account the distinct signatures of spectral bands present in neural signals, we propose a novel concept for building recurrence plots from time-frequency signal representations, instead of building them directly from univariate data or constructing them by employing delay-embedding techniques. Such representations, in general adapted for nonstationary signal analysis, give insights into frequency bands of importance and provide additional flexibility to recurrence plot analysis that is not present in time-domain, for e.g., the possibility to weight the importance of some frequency bands. In the literature there are several ways to choose values of the frequency bands. We use the following frequency interval definitions: the  $\delta$ -frequency band denotes the interval [0.5Hz; 4Hz], the  $\theta$ -frequency band the interval [4Hz; 8Hz],  $\alpha$ -band [8Hz; 12Hz],  $\beta$ -band [12Hz; 20Hz] and the  $\gamma$ -band denotes the interval [20Hz; 40Hz].

We build novel recurrence plots in three steps, as shown in Fig. 1: (i) firstly, we expand the set of  $T$  univariate trials  $\{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_T\}$  to their corresponding time-frequency domains; (ii) secondly, we compute the mean power of the spectrum for certain sets of frequencies; (iii) finally, we compute recurrence plots by computing distances between vectors  $\underline{\mathbf{x}}(i)$  and  $\underline{\mathbf{x}}(j)$ ,  $i, j \in \{1, \dots, N\}$  as in Eq. (1). In the following paragraphs we describe these blocks in more detail.

The first block in Fig. 1 provides a time-frequency representation of the signal. In classical spectrogram calculations, the stronger (weaker) is the localisation of signals in time, the larger (smaller) are their localisation windows in frequency. This effect is called the uncertainty principle implied in the Fourier transform. A synchrosqueezing (SSQ) transform overcomes this deficiency by performing wavelet-based filtering and signal power reassignment to the appropriate frequencies. In addition, Meignen:12,Auger:13 show that SSQ is superior for processing neural signals when compared to conventional spectral analysis methods, such as continuous wavelet transform or spectrogram. Hence, we use the SSQ transform as the processing block (i) in Fig. 1.



**Figure 1.** Building frequency-selective recurrence plots from  $T$  time series. Processing blocks are represented by arrows: (i) SSQ is a synchrosqueezing transform block used to obtain time-frequency representations of signals; (ii) the MPS block computes mean values of the power spectrum for each of the chosen frequency bands, which reduces the signal dimensionality; (iii) This signal is the basis for the recurrence analysis leading to recurrence plots  $\{RP_k\}_{k=1}^T$ .

The second block in Fig. 1 computes the mean value of the power spectrum (MPS) for sets of frequencies. This is one of the basic features for studying neural signals. We assume that the dynamics of the neural system encoded in frequencies is proportional to the power spectrum in sets of frequencies. This analysis step provides multi-variate time series whose dimension is equal to the resulting vector of averaged power in frequency bands.

Finally, in the third processing block in the figure we compute recurrence plots from the obtained time-frequency dataset as in Eq. (1). If we do not explicitly mention otherwise, we use features from all the frequency bands to compute recurrence plots. In the experimental ferret dataset, additionally we present cases when recurrence plots are calculated from the single frequency band features such as  $\delta$ - or  $\alpha$ -frequency bands, since these bands play an important role in the loss of consciousness under anesthesia.

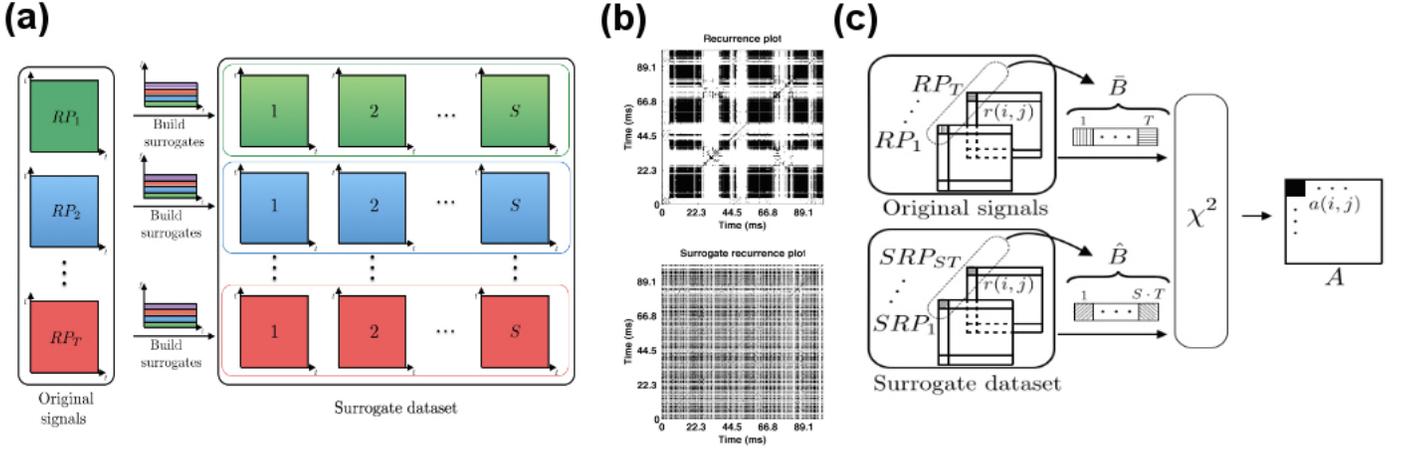
To summarize, the proposed method for building recurrence plots from time-frequency representations grasps band-related features and allows flexibility in the analysis of particular frequency bands, which is not possible in the classical RP analysis. Our approach however requires additional computations of the synchrosqueezing transform and mean power of the spectrum.

## B. Statistical analysis

We study statistical properties of frequency-selective RPs obtained from time-frequency trial representations. By virtue of noise effects and an expected trial-to-trial variability, transients of signal dynamics encoded in recurrence plot structures are expected to vary from trial to trial. To evaluate the gained recurrence plots statistically, we perform a statistical inference analysis based on a classical chi-squared test [29]. To this end, we construct surrogate recurrence plots and employ an inference test.

Classically, surrogate sets of univariate signals [30] preserve some of the important features of the original time series, for example the spectrum magnitude, while they replace the phase values by a random sequence of values. The reasoning behind this randomisation is that time domain reshaping destroys non-stationarities, so the local spectral components will vary while the global spectrum remains the same. As a consequence, the mean and variance of the signal do not change Richard:10,Borgnat:10.

In this work, we build the surrogate dataset with the same power spectrum as present in the original data, where the information component encoded in time is randomized, Fig. 2(a). For each time index of the signal we randomly select a novel index value, such that all the index values are chosen exactly once



**Figure 2.** (a) Surrogate set construction: for each of  $T$  time-frequency signal representations used for computing the original set of RPs, one computes  $S$  surrogate RPs. The resulting  $S$  surrogate recurrence plots have the same energy in time-frequency domain. In total, there are  $S \cdot T$  surrogates. (b) Examples of the RP (top) and the surrogate RP (bottom) for the transient oscillations dataset. (c) Illustration of the pixel-wise  $\chi^2$  statistical test, more details in the text.

(permutations without repetition). Then, we rearrange the time-frequency representation of trials according to the chosen index values and repeat the steps (ii) and (iii) in Fig. 1. This procedure is repeated  $S$  times per trial. Figure 2(a) illustrates how to obtain the surrogate set from  $T$  trials. Examples of an original RP and a corresponding surrogate RP are provided in Fig. 2(b).

We compare pixel-related statistical measures between the set of the original recurrence plots from different trials and their surrogates to determine whether original RPs preserve the common underlying signal dynamics in statistically significant way. This comparison is illustrated in Fig. 2 (c). In detail, we denote the set of  $T$  recurrence plots obtained from the original trial data by  $\{RP_k\}_{k=1}^T$  and its surrogate set by  $\{SRP_k\}_{k=1}^{S \cdot T}$ . In our simulations, there are  $T = 10$  trials in total, where the number of surrogates generated per trial is  $S = 100$ . The full set of surrogates counts  $S \cdot T = 1000$  surrogate RPs. We perform *pixel-wise* statistical analysis tests between the corresponding pixels of the original and the surrogate recurrence plots. Let  $\vec{B} = \{r_{i,j}^{[k]}\}_{k=1}^T$  be the vector that consists of the set of pixels with same coordinates in the original RPs and  $\hat{B} = \{r_{i,j}^{[k]}\}_{k=1}^{S \cdot T}$  is the corresponding vector of pixel values for surrogates. Vectors  $\vec{B}$  and  $\hat{B}$  consist of values from the set  $\{0, 1\}$ , since RP elements  $r_{i,j}$  by definition also take binary values, Eq. (1). To perform a chi-square test for categorical data, we build a two-by-two table whose rows take values from the classes of the original and surrogate recurrence plots and columns mark the number of  $r_{i,j} = 1$  and  $r_{i,j} = 0$  elements, respectively. The elements of this table (two rows and two columns) have the coordinates  $(l, m)$ ,  $l, m \in \{1, 2\}$ . Then, the chi-square statistics for the pixel  $(i, j)$ ,  $i, j \in \{1, \dots, N\}$  is computed by

$$\chi^2(i, j) = \sum_{l \in \{1, 2\}} \sum_{m \in \{1, 2\}} \frac{(f_o^{(i,j)}(l, m) - f_e^{(i,j)}(l, m))^2}{f_e^{(i,j)}(l, m)}.$$

Here,  $f_o^{(i,j)}(l, m)$  is the observed table value at the coordinate  $(l, m)$  for the pixel  $(i, j)$  and  $f_e^{(i,j)}(l, m)$  is its expected frequency. The latter value is computed as  $f_e^{(i,j)}(l, m) = n_r(l)n_c(m)/q$ , where  $n_r(l)$  is the total number of elements in the row  $l$ ,  $n_c(m)$  is the number of elements in the column  $m$  and  $q$  is the total number of elements in the two-by-two table. The calculated chi-square value is compared with the result in the chi-square table for predefined values of the degree of freedom  $df = 1$  and the significance level  $\alpha_s = 0.05$ . If the calculated chi-square value is larger than the value in the table, the hypothesis that signals share the same distribution is rejected, see [29] for more details. In this work, the outcomes of chi-square

tests are visually represented as matrices  $A = [a_{i,j}]$ ,  $i, j \in \{1, \dots, N\}$  whose elements take values

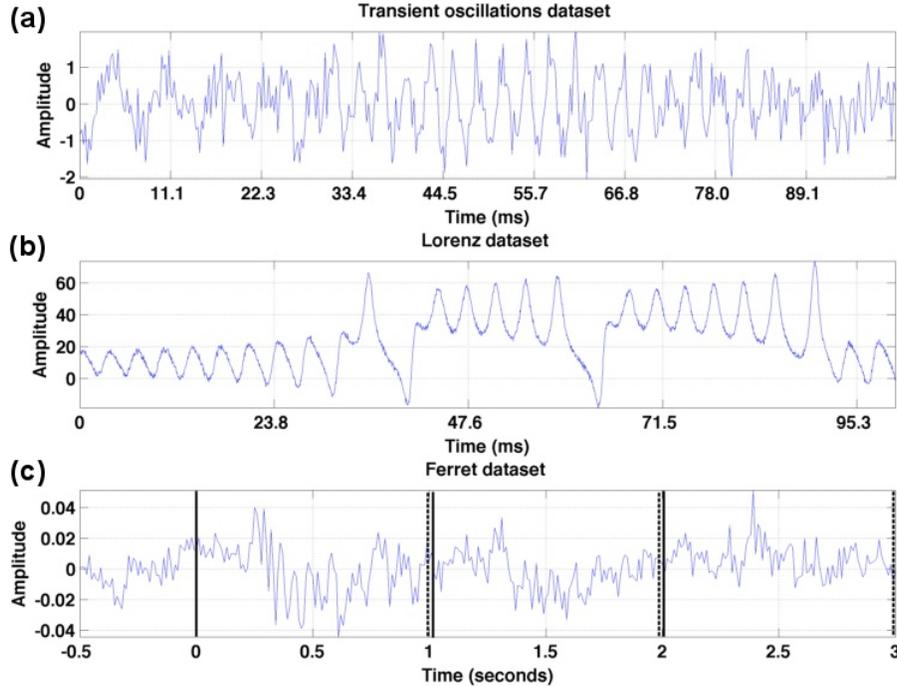
$$a_{i,j} = \begin{cases} 1, & \text{if distributions of trial and surrogate sets are different,} \\ 0, & \text{otherwise.} \end{cases} \quad (3)$$

In this work all the figures follow the same colour code as for illustrating recurrence plots, i.e., white pixels denote values  $a_{i,j} = 0$  and black pixels stand for  $a_{i,j} = 1$ .

Since single elements in RPs may be correlated to neighbouring elements, the underlying assumption of independent recurrence matrix elements may not hold and corrections of the significance test should be applied, such as the Bonferroni correction. Although we are aware of this problem, we refrain from applying the statistical correction here for simplicity since this additional feature would exceed the major aim of the present work.

### C. Datasets

To illustrate different analysis steps and to validate the power of the proposed method, we first apply the proposed algorithm to two artificial datasets. Then, the methodology is applied to experimental datasets. Single trials of these datasets are illustrated in Fig. 3 and their origin is described in detail below.

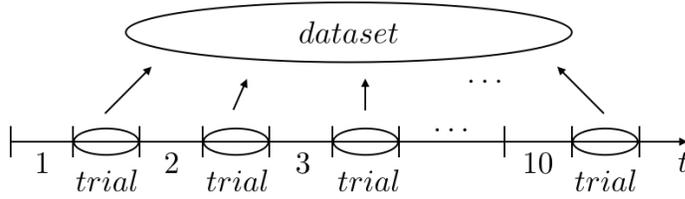


**Figure 3.** Illustration of the first trial in each of the three time series under study. (a) Transient oscillations (b) Lorenz attractor (c) Ferret dataset: trial from the set *session one* is recorded at a granular layer electrode. The vertical solid lines denote the stimulus onsets and the set of dashed lines mark the stimulus offsets.

1) *Transient oscillations*: A modified Lotka-Volterra model with  $n = 3$  interactive elements

$$\frac{dx_i(t)}{dt} = x_i(t) \left( \sigma_i - \sum_{j=1}^n \rho_{i,j} x_j(t) \right), \quad (4)$$

serves as an abstract model of event-related brain potentials [21]. Here  $x_i(t) \geq 0$ ,  $i \in \{1, 2, 3\}$  is the activity rate of the element  $i$ ,  $\sigma_n$  is the gain function and  $\rho_i$  define interactions between elements. In our setup,  $\sigma_1 = 1$ ,  $\sigma_2 = 1.2$  and  $\sigma_3 = 1.6$ ,  $\rho_{ii} = 1$ ,  $\rho_{12} = 1.33$ ,  $\rho_{13} = 1.125$ ,  $\rho_{21} = 0.7$ ,  $\rho_{23} = 1.25$ ,  $\rho_{31} = 2.1$ , and  $\rho_{32} = 0.83$ .



**Figure 4.** Experimental paradigm of the ferret experiment. In the original recording protocol [31]–[33], 10 visual stimuli are interleaved by several types of different stimuli, represented by numbers in the figure. Our dataset consists of responses to sine-wave luminance gratings only. Other types of stimuli are the black screen (intervals marked by  $\{4, 6, 9\}$ ), checkerboard noise for  $\{2, 7\}$  or fox images stimuli. The latter set consists of the weakly spatially filtered image of foxes in the intervals marked by  $\{3, 5\}$  and strongly spatially filtered image of foxes in the interval set  $\{1, 5, 10\}$ .

The output signal  $s(t)$  is a linear superposition of transient oscillations with frequencies  $\nu_1 = 170$  Hz,  $\nu_2 = 20$ Hz,  $\nu_3 = 75$ Hz, where at one time instance, only one of these three components is dominant. The activity rate  $x_i$  defines the amplitude of the component with frequency  $n_i$  and the output signal obeys

$$s(t) = \sum_{i=1}^3 a_i(t) \sin(2\pi\nu_i t) + \xi(t) \quad , \quad a_i(t) = e^{-(x_i - x_i^0)^2 / 2\eta_i^2} \quad (5)$$

with  $x_1^0 = 1.0$ ,  $x_2^0 = 1.2$ ,  $x_3^0 = 1.5$  and  $\eta_1 = 0.5$ ,  $\eta_2 = 0.33$ ,  $\eta_3 = 0.4$ . The variable  $\xi(t)$  represents measurement noise and its random values are i.i.d. Gaussian noise with zero mean and variance 0.5. The sampling rate is 450Hz. We generate 10 trials which are time-jittered by shifting the trials by 1 sample to later instances. A single trial is given in Fig. 3(a).

2) *Lorenz dataset:* The Lorenz attractor is a well-studied three-dimensional system showing non-trivial transient dynamics and their wings represent metastable states [16]. We consider the model studied by [16] and sum up the three amplitude time series to gain a univariate time series. This linear superposition may represent a macroscopic measured signal, such as EEG, capturing activity from different metastable sources. The sampling rate is equal to 2100Hz. We generate ten signal trials time-jittered by shifting the signal by 1 sample to later instances and add i.i.d. zero mean Gaussian noise with unity variance to the signals. A single trial is given in Fig. 3(b).

3) *Ferret dataset:* The experimental dataset consists of local field potential (LFP) measurements collected according to methods previously described in [31]–[33]. Briefly, female ferrets were anesthetized, intubated, and underwent surgery to gain access to primary visual cortex (V1,  $\sim 3$ mm anterior to lambda and 9mm lateral to the midline). Anesthesia induction was achieved with an intramuscular injection of ketamine (30mg/kg) and xylazine (1 – 2mg/kg), and anesthesia maintenance was achieved with 1.0% isoflurane (10 – 11cc, 50bpm, 100% medical grade oxygen), with continuous IV infusion of xylazine (1.5 mg/kg/hr xylazine with 4.25 mL/hr 5% dextrose lactated ringer’s). Animals were head-fixed in front of the presentation screen and a 32-channel depth probe was acutely inserted into cortex (50 microns contact spacing along the z-axis, NeuroNexus, Ann Arbor, MI) and was positioned to cover all cortical layers. The reference electrode was located on the same shank (0.5mm above the top recording site) and was positioned in 4% agar in saline above the brain. The full-field visual stimulus was presented on a  $52 \times 29$  cm monitor with 120Hz refresh rate and full high-definition resolution ( $1920 \times 1080$  pixels,  $GD235$ Hz, Acer Inc, New Taipei City, Taiwan) at 47 cm distance from the animal. Each trial was 30 seconds long and consisted of three parts: (i) recording interval  $[0 - 10]$ s is a baseline (screen is black); (ii)  $t_s \in [10 - 20]$ s is the presentation of the sine-wave luminance gratings; (iii)  $[20 - 30]$ s is ‘post-baseline’ (screen is again black). Visual stimuli were interleaved with other types of stimuli (all in randomized order), for instance with a black screen or with a strongly spatially filtered image of foxes (foxes are natural enemies of ferrets), see Fig. 4. The sine-wave luminance grating was presented at a rate of 1Hz for 10 seconds (during each 1s period, progressive frames

transitioned from black to white to black and all the screen pixels had the same color for any given frame). In the subsequent analysis, we consider a subset of recordings. The dataset under study starts 0.5s before stimulus onset and lasts until 3s at the end of the third stimulus cycle. This stimulus is a black screen at  $t = 0s$ ,  $t = 2s$  and  $t = 3s$  with luminance maxima at  $t = 0.5s$ ,  $t = 1.5s$  and  $t = 2.5s$ . A single trial is illustrated in Fig. 3(c).

Electrophysiological recordings were conducted during stimulus presentation. Unfiltered signals were first amplified with MPA8I head-stages with gain 10 (Multichannel Systems, Reutlingen, Germany), then further amplified with gain 500 (Model 3500, A-M Systems, Carlsborg, WA), digitized at 20kHz (Power 1401, Cambridge Electronic Design, Cambridge, UK), downsampled to  $1kHz$  afterwards, and digitally stored using Spike2 software (Cambridge Electronic Design). In total, 20 trials across two sessions conducted on different days were analysed, the session sets of 10 trials are called *session one* and *session two* in the following. Datasets are downsampled to the sampling rate equal to 100Hz.

All procedures were approved by the University of North Carolina-Chapel Hill Institutional Animal Care and Use Committee (UNC-CH IACUC) and exceed guidelines set forth by the National Institutes of Health and U.S. Department of Agriculture.

### III. RESULTS

In this section, we first apply the proposed method to two artificial datasets to verify if it reveals dynamics given the noisy set of trials. After validation of the method, we apply it on the experimental dataset and study if it extracts well the dynamics from recorded trials.

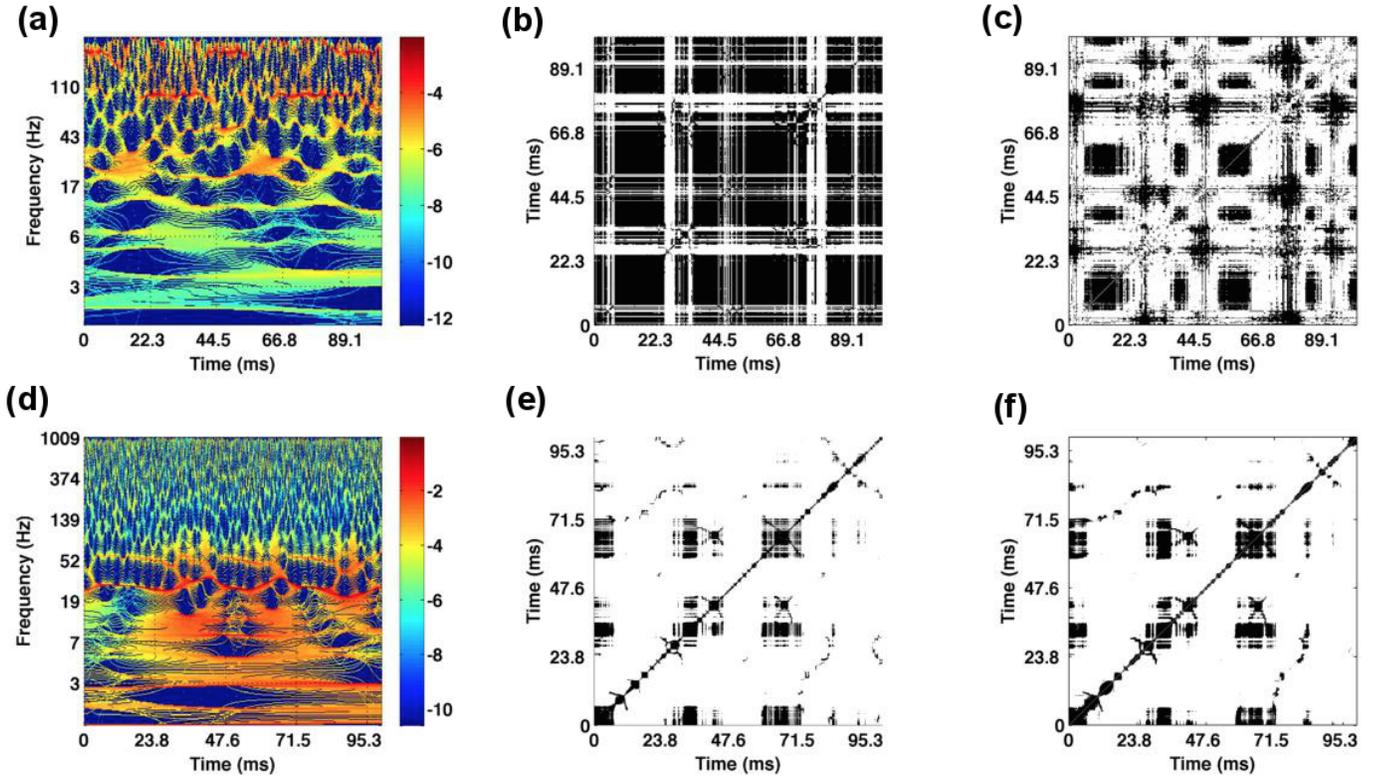
To understand the results, we first shortly describe recurrence plots for several simple test signals. As previously mentioned, black pixels denote recurrence events and white ones its absence. All recurrence plots have a black diagonal line, by definition (see Eq. 1). Signals without any recurrence have a white square RP with a black diagonal line. Random noise signals have random distribution of black pixels in the plot, with the exception of the black diagonal line. A simple periodic signal has a recurrence plot that consists of the black diagonal line and other black lines that are parallel to the diagonal, where the distance between them will reveal the period of the signal. More complex signals that have recurrent states may show different structures in RPs, for e.g., the chess-like patterns. These black colored fields can take different sizes and shapes. For two artificial datasets we expect to observe repetitive black patterns that correspond to repetitive states within signal components, introduced by construction. For the experimental dataset, we expect to observe recurrence patterns that are directed by the onset of the visual stimulus.

#### A. Artificial datasets

We illustrate our methodology in Fig. 5, which shows the analysis steps for the examples of transient oscillations (Fig. 5(a-c)) and the Lorenz attractor (Fig. 5(d-f)).

The time-frequency representation of one transient oscillation trial is shown in Fig. 5(a). As previously mentioned in Sec. II-C1, the corresponding signal exhibits three periodic components. We visually inspect the figure and observe high power spectrum values around the following time windows: (i)  $\{(0, 11), (42, 54), (85, 97)\}$  ms around  $\nu_1 = 170$  Hz; (ii)  $\{(19, 26), (64, 72)\}$  ms around  $\nu_2 = 20$  Hz; (iii)  $\{(24, 38), (74, 87)\}$  ms around  $\nu_3 = 75$  Hz. Note that for other trials these values may fluctuate because the frequency and time window of the current active component vary due to noise that models trial-to-trial variability.

The time-frequency representation of one Lorenz attractor trial is given in Fig. 5(d). The approximate time intervals during which the system stays in each of the two wings are visually inspected from the power spectrum values. The contrast between wing components in the power spectrum is not as distinct as for the transient oscillation dataset. For the component present around 20 Hz the power difference is distinguishable between the time intervals  $\{(0, 21), (90, 100)\}$  ms and  $(21, 90)$  ms. Similarly, for the component around 15 Hz, similar effect is observed for the set  $\{(24, 36), (60, 72)\}$  ms and the remaining part of the signal. Note



**Figure 5.** Illustration of time-frequency (a,d), optimal recurrence plot (b,e) for the trials of two artificial datasets shown in Fig. 3(a,b) and statistically significant recurrence plots (c,f) based on 10 trials. (a-c) transient oscillations; (d-f) Lorenz attractor.

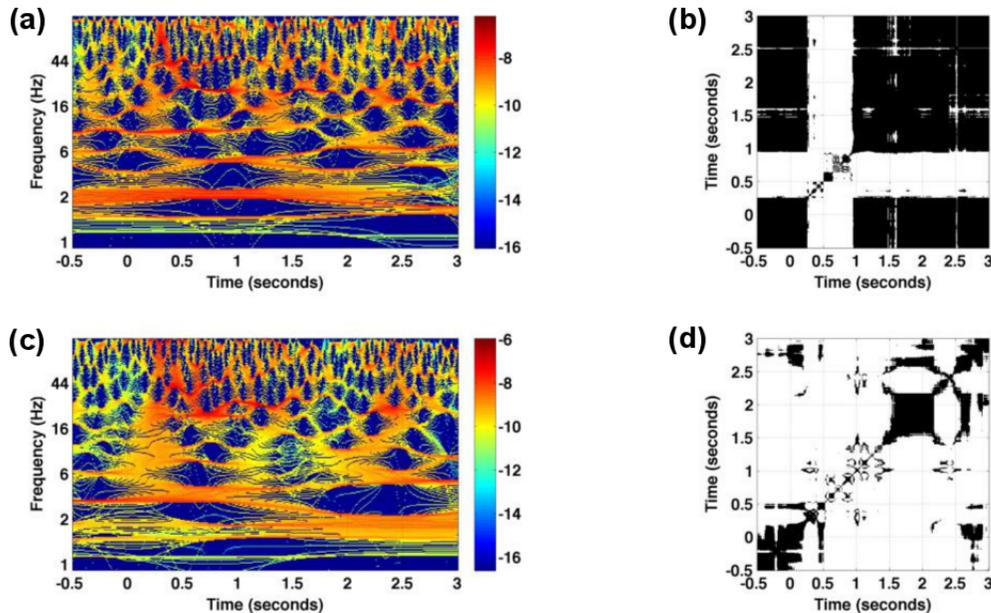
that for other trials these values may be different, because dominant frequencies and their time windows may change due to the construction of varying trials in the set.

Time-frequency plots are the basis for the recurrence analysis leading to recurrence plots given in Fig. 5(b,e) for the respective datasets. These plots show the metastable dynamics of the transient oscillations in the corresponding time windows as recurrent structures. The recurrent, i.e., repetitive, structure is visible in the illustrated trial of the transient oscillation data (b) as well in the Lorenz dataset (e). Now, considering several trials these recurrent structures may vary due to the trial-to-trial variability. Nevertheless, to study the recurrent structure *common* to all trials, we employ the statistical inference method and extract statistically significant areas of recurrence plots, as shown in Fig. 5(c,f). The recurrent structure is obvious in both plots reflecting the underlying recurrence structure in the artificial signals. In addition, these results demonstrate that the methodology extracts recurrence structures common in several trials, although the recurrent structure is less obvious in single trials, Fig. 5(b,c).

### B. Experimental data

After studying artificially generated trials and verifying that the proposed method extracts well the dynamics features given by repetitive black structures, we now investigate whether such structures can be found in the experimental data as well.

Figure 6 provides the time-frequency representations of two single trials of the same session (a,c) and the corresponding recurrence plots (b,d). We observe a high trial-to-trial variability, e.g., a strong  $\delta$ -,  $\theta$ - and  $\beta$ -activity in the first trial (a) resulting to a weak recurrent structure after stimulation, i.e.,  $t \geq 0$ s (b). In detail, there is no resemblance between the response pattern and the periodic visual stimulus of frequency 1Hz. Conversely, the time-frequency representation of the other trial (c) exhibits similar features as in the first trial whereas the recurrent structure is more prominent (d). Figure 6(d) reveals that the baseline



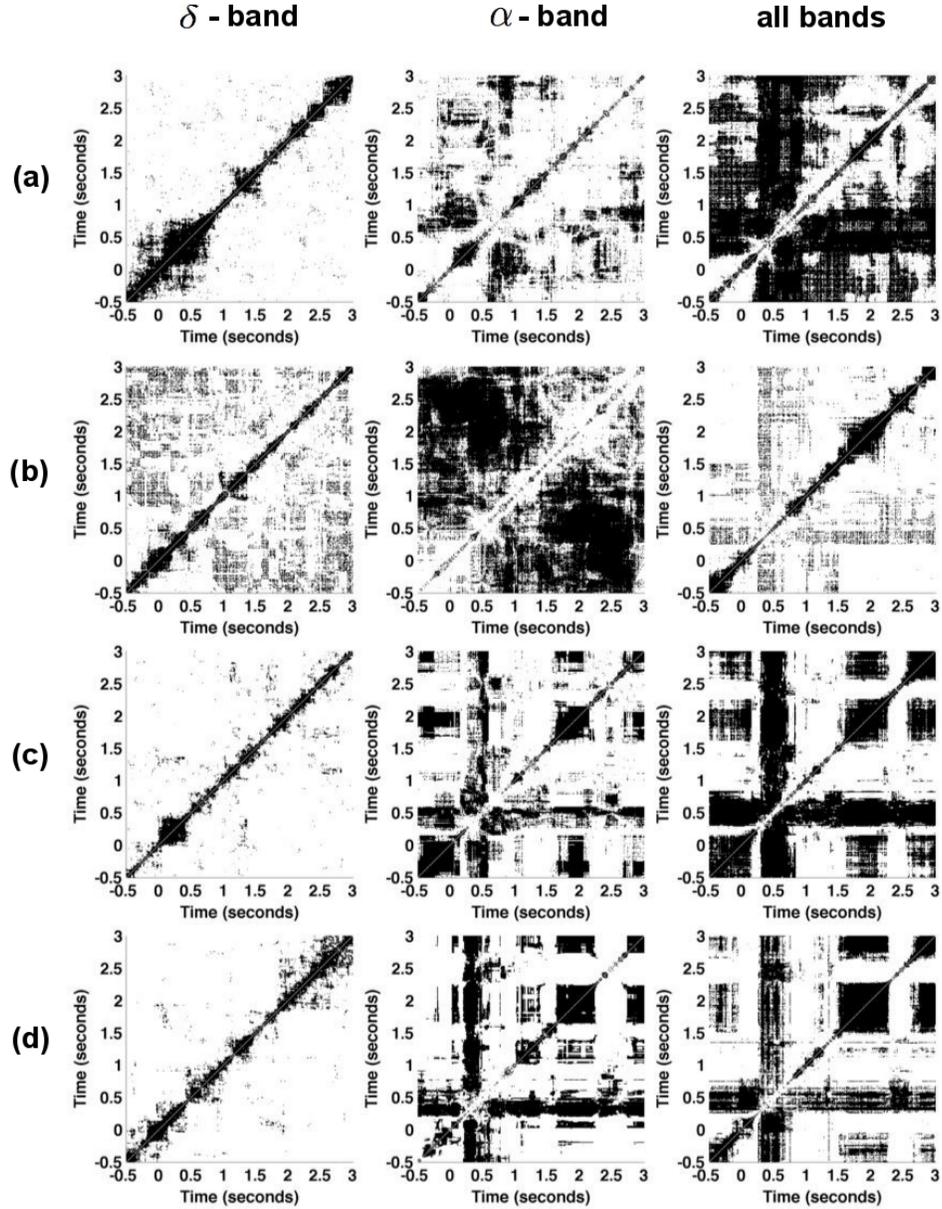
**Figure 6.** Illustration of trial variability for the experimental dataset *session one*. (a,c) the logarithm values of the power spectrum for two trials measured at a granular electrode; (b,d) the corresponding recurrence plots. Non-zero values of recurrence plots are black-coded.

activity in the time interval  $[-0.5s; 0s]$  returns in the interval  $[2.5s; 3s]$ . In addition, the signal at about  $t = 2s$  resembles activity just after  $t = 2.5s$ . This result is surprising since the experimental presentation of the visual stimulus is well-controlled and the stimulus is simple enough to expect almost identical neural responses.

To reveal the recurrent structure that is common in all trials, now we study the trial-to-trial variability of recurrence plots and aim to reveal whether the signal trials preserve the same dynamical behaviour, cf. Fig. 7. Applying the statistical method, we investigate the similarities of the results obtained from ten trials measured by a single granular sensor and from the set of ten averaged signal trials, where the average is taken over 8 granular layer sensors. This analysis is done for both ferret datasets. Moreover, we detail the analysis considering particular frequency bands which are of interest for anaesthesia. To this end, we compute recurrence plots using the values of the power spectrum coefficients in the corresponding frequency bands as illustrated in Fig. 1.

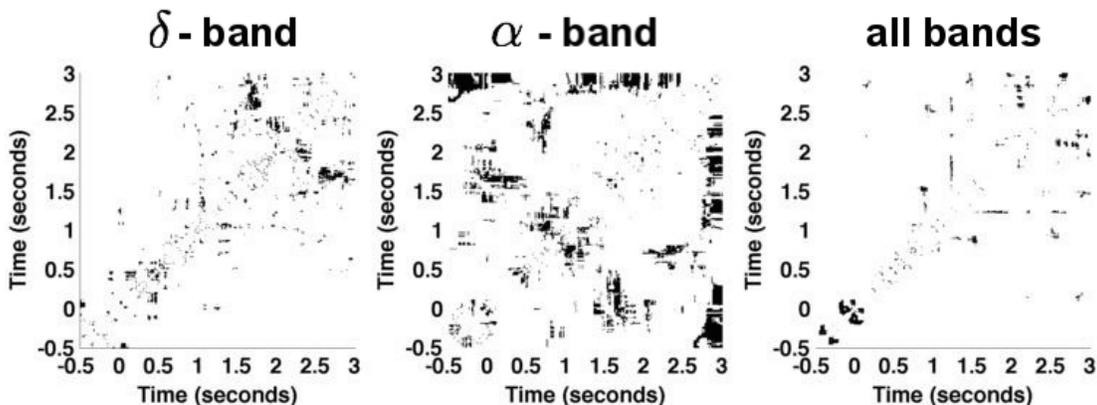
Figure 7 shows the statistically significant parts of the recurrence plots for the  $\delta$ - and the  $\alpha$ -frequency band and for all frequencies. The figure reveals that there is no statistically significant recurrent structure in the  $\delta$  frequency band in signals under study. Conversely, the  $\alpha$ -frequency band exhibits significant recurrent structures in the single granular electrode in both datasets, cf. Fig. 7(a,b). For instance, in *session one* the first response to the stimulus at  $t = 0s$  returns at  $t = 1s$  and  $t = 2s$ . Moreover, the average over granular electrodes in *session two* (Fig. 7(d)) also reveals recurrent structures, while averages over *session one* show less prominent recurrences (Fig. 7(c)). Considering all frequency bands does not reveal additional recurrences and the corresponding recurrence plots seem to reflect primarily the recurrent structure observed in the  $\alpha$  frequency band. Essentially comparing the datasets *session one* and *session two*, the latter exhibits a much clearer recurrent structure than *session one* following much closer the external stimulus.

The experimental paradigm includes visual presentations of stimulus types in a randomised order. The previous paragraphs show neurophysiological responses to the sine-wave stimulus only. To gain further insight into the trial-to-trial variability subject to various pre-stimuli, we have selected two subsets of sine-



**Figure 7.** Statistically significant parts of recurrence plots for different ferret datasets. (a) Results from a dataset of *session one* that consists of 10 trial recordings of the single granular sensor  $s_{10}$ . (b) Same as in (a) for the dataset *session two*. (c) Results are calculated based on 10 averaged trials in dataset *session one*, where each trial is averaged over 8 granular layer time series. (d) Same as in (c) for dataset *session two*.

wave trials that have two different preceding stimuli, namely the 'black screen' subset denoted by *subset one* and the subset of 'strongly spatially filtered version of foxes' denoted by *subset two*. *Subset one* includes the trials  $\{4, 6, 9\}$ , while *subset two* is composed of trials  $\{1, 5, 10\}$  of datasets *session one* and *session two*. The comparison of various pre-stimuli data is done by the chi-squared difference measure based on recurrence plots of both subsets. Figure 8 shows the statistically significant recurrences that are common in stimulus responses on both types of pre-stimuli. The diagonal lines are absent from figures, which suggests that at each time instance two comparison signals differ. Poor but visible recurrent structures in  $\delta$ -band are grouped into two distinct blocks which distinguish the activity before the stimuli (around  $t = 0$ s) and



**Figure 8.** Illustration of the influence of different visual pre-stimuli on resulting plots in experimental dataset. Statistically significant areas of recurrence plots are obtained by pixel-wise chi-square tests between trials with pre-stimulus *black screen* and those whose pre-stimulus is *fox image*. The data is taken from a single granular layer electrode in datasets *session one* and *session two* together. Both the pre-stimulus *black screen* and *fox image* have occurred three times among the 10 trials in each dataset. Significantly different values are coded as white pixels, statistically similar values are coded as black pixels.

during the stimuli, for  $t \in (1, 3)$ s. In  $\alpha$ -band, the figure shows more prominent recurrences, such as the patterns around  $t = 1.5$ s and  $t = 2.7$ s. We point out that recurrences within  $\delta$ - and  $\alpha$ -bands do not overlap, except in the pre-stimuli period, for  $t \in \{-0.5, 0\}$ s. Finally, considering all the frequency bands together does not reveal significant similarities of two pre-stimuli.

#### IV. DISCUSSION

The present work introduces a new recurrence analysis methodology for univariate time series. The first new element is the transformation to a time-frequency representation leading to a multivariate time series of spectral power. This new embedding technique permits to compute recurrence plots for specific frequency bands. The second new element is the statistical analysis of recurrence plots that takes into account spurious recurrence structures and allows to suppress them. The combination of the two methods allows to extract temporal recurrence structures in data which may reflect underlying transient dynamics in a certain range of frequencies that would have been hidden in conventional methods. To our best knowledge these two techniques have not been considered before.

The first results for two artificial datasets illustrate the methodology and indicate that method detects recurrences in a variable dataset (noise-induced trial variability) by the statistical analysis as seen in Fig. 5. These results on artificial datasets prove that the method reveals underlying recurrences in a set of trials if they are present in these trials. The subsequent analysis of single Local Field Potentials measured experimentally in ferret visual cortex reveals a high trial-to-trial variability, cf. Fig. 6. The trial-to-trial variability is surprising due to the well-controlled experiment revealing an intrinsic ongoing activity [34]. This result demonstrates that it is mandatory to take into account recurrence variability in several trials. This is done by the methodology proposed. Detailed recurrence analysis of specific frequency bands in Fig. 7 reveals missing recurrences in the  $\delta$  band whereas  $\alpha$ -activity exhibits statistically significant temporal recurrence. This important finding reflects a fundamental difference of the nature of  $\delta$ - and  $\alpha$ -activity which has been shown in previous experimental studies on the neural origin of both signal features [35]–[37].

The effects of pre-stimuli have been hypothesized [38], [39], we have investigated the effect of pre-stimuli. The performed analysis is based on a rather small set of trials reflecting the responses to identical stimuli. To have sufficiently large dataset for tests, we merged trials coming from two recording sessions.

We note that trials coming from two sessions may not be independent, which may introduce errors. We found negligible effects in the  $\delta$  frequency bands but differences in the temporal recurrence structure in the  $\alpha$  frequency band. This result indicates that  $\alpha$ -activity is more sensitive to pre-stimuli than  $\delta$ -activity in the experimental setup under study. This finding is in full line with previous theoretical [38] and experimental [40] studies on the importance of phase and power of prestimulus  $\alpha$ -activity. In addition, we notice the absence of the diagonal line and other strong recurrence patterns visible in Fig. 7. This may be the result of merging trials from different sessions, which was necessary to obtain larger test set for the analysis.

The present work shows that trial-to-trial variability in neurophysiological data occurs in spite of well-controlled and simple response-driven experimental conditions and demonstrate how to extract recurrent structures nevertheless. The methodology proposed makes it necessary to choose a well-adapted technique to transform the univariate times series to a multivariate time frequency signal. In addition to our current choice of a spectral reassignment technique, we have employed a conventional wavelet technique using complex Morlet mother wavelets and performed the same recurrence analysis (results are not shown). It turns out that this conventional method does not provide high-quality extraction of transient recurrent structures, given by the reassignment method. This may result from the worse time-frequency resolution of conventional Morlet wavelets. Future work will further investigate the best choice of multi-resolution time-frequency methods. Moreover, the methodology considers surrogate data generated by a temporal random shuffling of data and hence destructing all temporal structure. Future work may include the destruction of the recurrence structure by phase randomisation in certain frequency bands [41].

## V. CONCLUSION

To conclude, in this work we propose a novel analysis method for trial-to-trial variability of recurrence plots applying a novel statistical analysis technique. This extension of recurrence analysis by a statistical technique is motivated by the fact that many physiological datasets have a limited number of trials but possess the intrinsic recurrence property of patterns of interest. Inspired by the fact that particular physiological patterns very often occur in specific frequency bands, we first build novel recurrence plots from a time-frequency signal representation. A low dimensional time-frequency signal that is built by the band median filter is then used to obtain original trial recurrence plots. Next, we use a chi-squared statistics to obtain statistically important areas of recurrence plots. The work reveals a strong trial-to-trial variability of recurrences in experimental data in spite of the well-controlled experimental paradigm. Moreover, it turns out that recurrences occur in the  $\alpha$ -frequency band, whereas activity in the  $\delta$ -frequency band does not exhibit a temporal recurrent structure. This distinction is also present comparing datasets obtained after different pre-stimuli.

## VI. DATA SHARING

We provide the time-series of the transient oscillation dataset and Lorenz dataset on the webpage of the corresponding author.

### DISCLOSURE/CONFLICT-OF-INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### AUTHOR CONTRIBUTIONS

The majority of the analysis steps and the implementations have been performed by TT, KKS and FF have provided the experimental data and neurophysiological insights, MF has contributed additional time-frequency analysis results and PbG and AH have conceived the study. All authors wrote the manuscript together.

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