Robust Analysis of Non-stationary Cortical Responses: tracing Variable Frequency Gamma Oscillations and Separating Multiple Component Input Modulations

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Abstract— **Natural signals have a complex nature and most often encode information both in the frequency and time domain. Neuronal signals in particular have a very nonlinear behavior, with features of interest appearing sparsely and discontinuously. Therefore, methods that characterize and enable the visualization of these data are of great importance. Here, we present two algorithms that act on different dissociation problems in neuroscience: Firstly, the definition of trajectories in a time-frequency-power three dimensional space and secondly, the dissociation of modulatory effects of different time scales. The methods have the advantage of preserving the transient nature of neuronal features and of providing a practical computational implementation. We apply these methods on cortical response to visual stimuli where multiple parameters are manipulated. Results show that such response characteristics reveal features that are not explained by current theories of underlying mechanisms of oscillatory response.**

Keywords— **neuroscience, feature extraction, spectral pattern, time-domain decomposition.**

I. INTRODUCTION

Neuronal activity has complex dynamics, its behavior resembling that of chaotic systems, where small perturbations trigger highly a nonlinear response [**Error! Reference source not found.**]. Electrophysiological signals recorded from cortical structures reflect this by showing a high level of non-stationarity [**Error! Reference source not found.**]. Moreover, coding in the brain is achieved through time-related features, but also through spectral features such as oscillatory activity and coherence [**Error! Reference source not found.**].

The analysis and visualization of this type of data is often difficult due to the multiple relevant dimensions of the extracted information. For example, in order to analyze the neuronal response to a particular stimulus from a spectral point of view, the average power spectrum of the response period will reveal general spectral components of the response, but will hold no information about the temporal localization of the spectral feature. Also, such averaging cannot dissociate between a strong, short burst of oscillatory activity and a weak prolonged oscillation. Moreover, frequency variation within response period will appear as a broad spectrum response in a time-averaged spectrum.

For these reasons, a time-resolved analysis of spectral patterns is of interest. But in this case, the response pattern is a three dimensional component, defined by time, frequency and power. Also, multiple oscillatory modes coexist, each representing either a different underlying cortical process or a harmonic of the main response component. In order to independently isolate these three dimensions and further isolate the main response from multiple oscillatory modes, we introduce a new method to structurally define the trajectory of neuronal activity through this three dimensional space, rendering the independent analysis of each dimension possible. Further, we describe a method of dissociating modulatory effects on these individual parameters via a time-domain spectral decomposition method, without being perturbed by the non-stationary nature of the analyzed signals.

We apply these methods to analyze gamma-band oscillatory response in the visual cortex. Gamma oscillations occur in the range of 30-120 Hz and are associated with multiple processes in the brain, from perception to high level cortical processes such as attention and memory [**Error! Reference source not found.**]. In the visual cortex, this component is known to be modulated by visual input strength, such as contrast, but the nature of this modulation is not yet understood [**Error! Reference source not found.**]. Specifically, frequency and power increase with input strength. The relationship between frequency, power and input strength of gamma oscillations represent hallmarks for underlying mechanisms. For example it is hypothesized that intrinsic membrane properties of neurons within the cortical volume of interest affect the frequency stability and power of gamma [**Error! Reference source not found.**].

We implemented a series of methods that can evaluate the relationship between frequency and power in the local field potential (LFP) spectral response. We apply these methods in the study of transient oscillatory responses. Also, we look at the evolution of these parameters with respect to different stimulus characteristics to test whether they establish a codependent relationship in all circumstances.

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II. Methods

All the experiments were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC), according to the guidelines of the Society for Neuroscience and the Romanian law for the protection of animals, approved by the local ethics committee and overseen by a veterinarian.

We acquired electrical signals using silicon probes from the visual cortex of isoflurane anesthetized mice while they were presented moving orientation gratings. We had two types of stimuli, one where contrast of the gratings was fixed and the spatial and temporal frequencies were low (0.1 cycles/degree, 1.75 cycles/s) and another where contrast was following a triangular modulation and spatial and temporal frequencies were higher (0.28 cycles/degree, 5 cycles/s). The acquired signal was filtered with a low pass filter with a cutoff frequency of 300 Hz.

III. Spectral pattern detection

We defined a method capable of following an oscillatory pattern through a three-dimensional space, based on the assumption that the movement through this space happens smoothly on all axes. For this purpose, we computed a time-resolved Fourier decomposition and computed the spectral power. On this three-dimensional space, we traced the power crest of the response.

Specifically, we split our response period into windows which we multiplied with a Blackman window to minimize border effects. Then, we adjusted the length of the window with zero padding to have enough resolution in frequency. We computed the fast Fourier transform and computed the power for each time and frequency bin.

Our method makes, several assumptions:

- Response is defined by increase in power with respect to baseline conditions. Therefore, we normalized the spectrum to a baseline period, where no stimulation was provided.
- The point of maximum power is part of the response of interest.
- In two successive time bins, the closest maxima in frequency is part of the same oscillatory component.

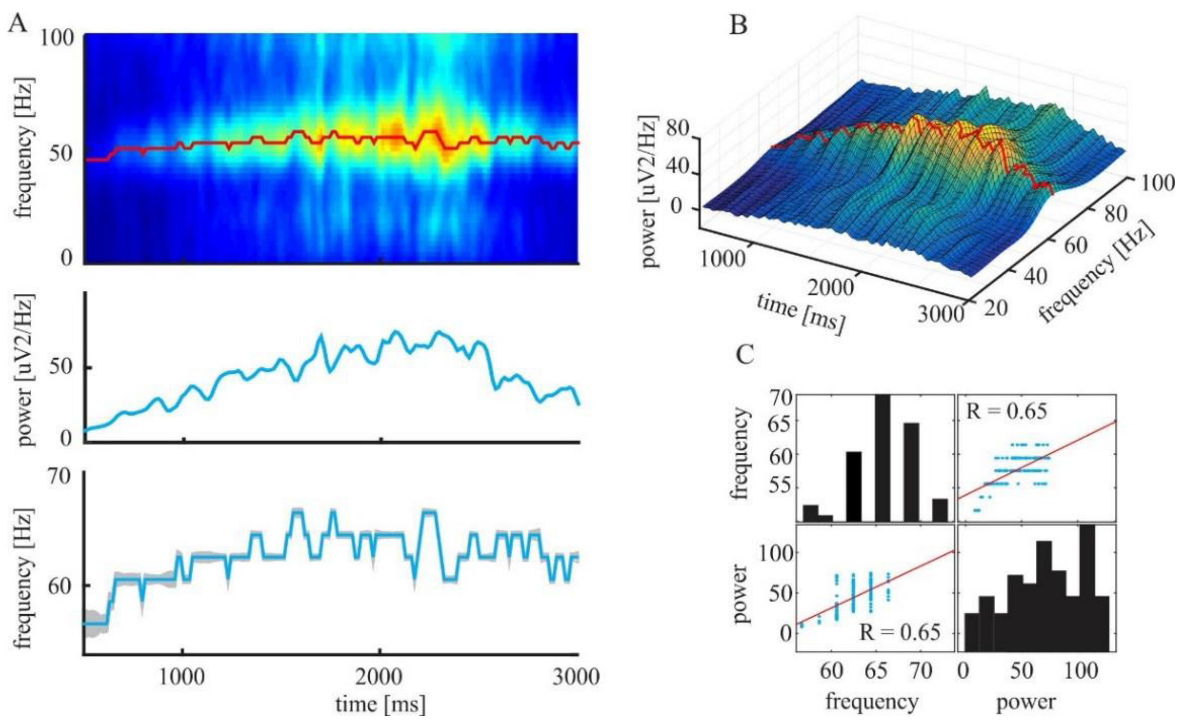

Fig. 1. Pattern analysis of the time-resolved FFT of simulation LFP: A - time-resolved FFT across response period. Red line mark the selected trajectory in peak following; below are the power and frequency of the followed peak across time; B - A three-dimensional view of the response and the crest-detection algorithm. C - Scatter plots of power versus frequency of the followed peak and histograms of each measure; Red line marks the linear correlation and the coefficient value is noted for each plot.

We mention that the time-frequency response could also be defined using other decomposition methods, such as a wavelet transform.

Therefore, the definition of spectral component is determined taking the following steps:

- The time and frequency band of interest are defined. **Note** that the presence of a response within these bands of interest is necessary for the effectiveness of the method. A good way to determine response time is through a power threshold, therefore eliminating periods of time where there is no relevant pattern to detect. Limiting the frequency band can be of interest when dissociating between multiple oscillatory components of different power ranges.
- The coordinates of the point of maximum power is detected. This will be the starting point for tracing the response trajectory.
- Through an iterative process, the closest maxima on the frequency axis is determined for each time bin while moving away from the point of origin towards the beginning and towards the end of the response period respectively.
- For each point, define the time, frequency and power.

Fig. 1shows an application of this algorithm on electrophysiological local field potentials (LFP) recorded in the primary visual cortex of anesthetized mice while they were presented a visual stimulus composed of moving gratings of variable contrast. The response pattern shows that power and frequency vary across time. From here on, the shape of each trajectory parameter can be assessed independently. In this case, the correlation between the two parameters is computed and the histogram of each is displayed.

IV. EMPIRICAL MODE DECOMPOSITION

We wanted to analyze the differential effect that stimulus features had on power and frequency of the LFP spectral pattern. We introduced two degrees of variability in our stimulus: one was a moving sinusoidal grating. The passage of the grating through the receptive field of the recorded brain area causes local luminance fluctuations, altering both power and frequency of the response. The second variable was contrast: the difference between the brightest pixel and the darkest one was modulated by a triangular carrier. Contrast varied in a slow timescale (one period = 4.5 s) while local luminance varied rapidly (200 ms). We needed a method to reliably separate the modulations induced by each factor, when we knew the timescale of each modulatory effect. We therefore needed to break down signals which were non-stationary and non-linear, with no assumptions of periodicity or sinusoidal approximation.

For this, we applied an algorithm of empirical mode decomposition, which represents an alternative to spectral decomposition methods [**Error! Reference source not found.**]. It offers the advantage of an easy implementation operating integrally in the time domain.

The basic principle is an iterative filtering and subtraction of independent mode functions (IMFs), also called the sifting process.

An IMF is defined as a function that

- Has one extreme between zero crossings and
- Has a mean value of zero.

The algorithm comprises of the following steps:

- For a signal $X(t)$, the local minima and maxima are detected. The definition of locality determines the effectiveness and calculation time of the EMD.
- The upper and lower envelopes are determined by cubic spline interpolation of the points of local maxim and minima.
- The average of the upper and lower envelopes $M_{11}(t)$ is computed and subtracted from the original signal.

$$H_{11}(t) = X(t) - M_{11}(t)$$

- The residual H_{11} is then treated as the input data in an iterative process of subtraction of mean envelopes until H_{1k} is an IMF, that is:

$$Nr(extremes) = Nr(zeros) \pm 1$$

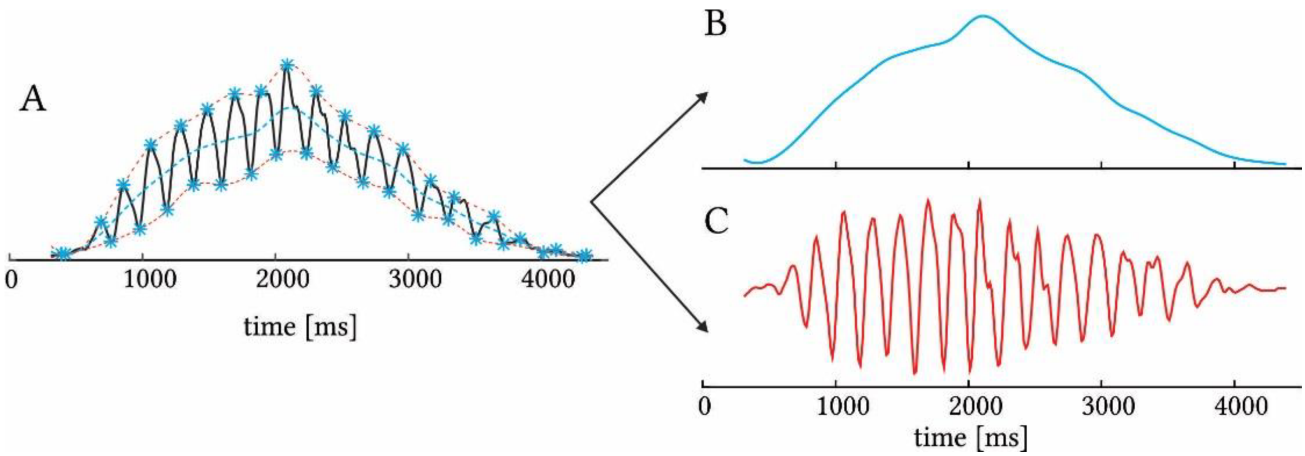

Fig. 2. Adapted variant of Empirical mode decomposition algorithm example: A – a power profile of neuronal response to moving gratings of variable contrast. Blue markers indicate the detected minima and maxima. Red dotted lines are the computed envelopes and the blue dotted line is their mean. B – the slow component of the decomposition resulted by the subtraction of the first mode from the original signal. C – the detected first mode, using a definition of locality restricting maxima and minima that are at least 100 ms apart.

- Therefore H_{1k} is the first intrinsic mode function, containing the shortest period component of the signal.

$$IMF_1 = H_{1k}$$

- This component is subtracted from the original signal:

$$R_1 = X(t) - IMF_1$$

And the same process is performed on the residual until the residual does not contain any fluctuations, that is:

$$Nr(extremes) = 0$$

The components $IMF_1 \dots IMF_n$ are the modes of the signals and create a nearly orthogonal basis of the signal.

In our experimental conditions, we wanted to separate between a fast and a slow component of the data, without making any assumption on the harmonic structure of the oscillation, its stationarity or its stability in frequency. Therefore we adapted the EMD algorithm so that we could achieve this in the fastest, simplest way.

We first limited the range of timescales of the decomposition by limiting the number of local minima and maxima detected. We therefore imposed a minimum distance in time between two maxima and minima respectively so as to ignore components that are above our frequency of interest, but still preserve the features for further analysis.

Second, we only needed to dissociate between two timescales. Therefore, we extracted the first mode as the fast modulatory effect and the first residual as our slow modulatory effect. Fig. 2 shows an example of this decomposition applied on power fluctuations in LFP in response to fast luminance (Fig. 2 C) and slow contrast (Fig. 2 B) variation.

V. Discussion

The structural detection of spectral components is relevant when each element represents a different underlying mechanism. In our case, we were interested in the isolation of an oscillatory component of neuronal responses which has a large range of frequency variation, but represents the same underlying process. To characterize this process without limiting the frequency range of its fluctuation or smearing its properties by averaging across a wide range of frequencies, we chose to structurally follow the pattern of the response within the three dimensional space of time, frequency and power. We found this algorithm useful for independent analysis of the power and frequency dimension of the oscillatory response in particular, eliminating any artefacts caused by the variation of one with respect to the other.

This algorithm was especially useful when oscillatory response was non-stationary. For example, we looked at response properties of gamma oscillations where the spatial and temporal frequency of the stimulus was low enough to elicit transient responses at each grating passage through the receptive field (Fig. 3). In this case, our algorithm successfully traced the power and frequency patterns of the response, revealing a complex trajectory. Frequency and power in this case did not follow the same pattern, as predicted by other studies.

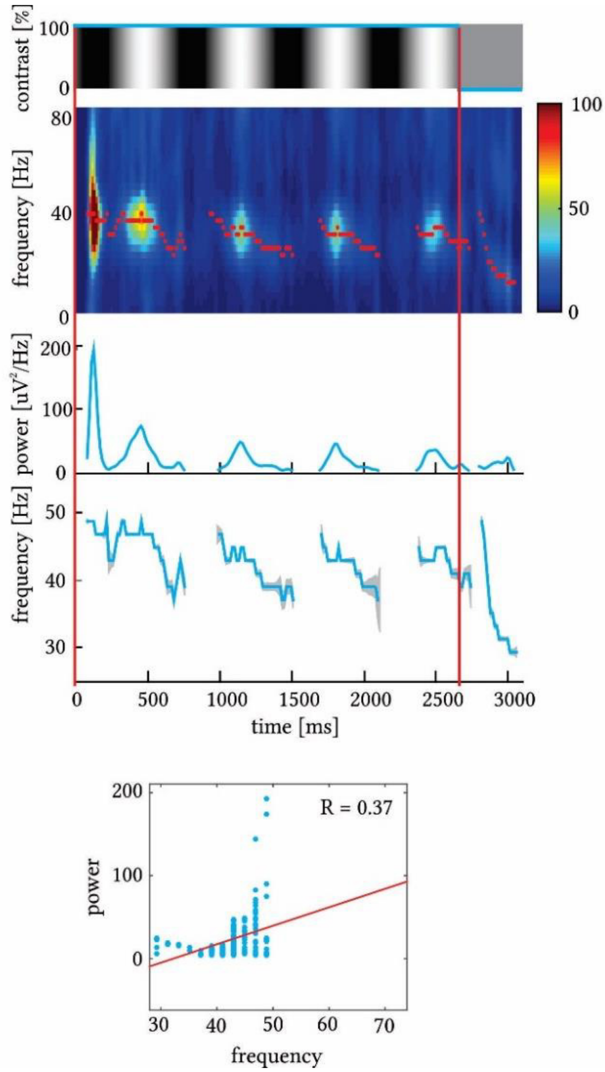

Fig. 3. Pattern analysis of transient oscillatory responses. From top to bottom: visual stimulus profile presented; time-resolved Fourier transform of the response period. Red dots mark the selected points in peak following. Note that a power threshold was selected so as only to look for patterns where there is a response; Power and frequency of the followed response pattern. Red vertical lines show start and end of visual stimulation; Scatter plot of power versus frequency of the followed oscillatory component. Red line represents the linear correlation of the two values whereas the correlation coefficient r is listed.

Further, we looked at the relationship between frequency and power when different stimulus manipulations occurred. By separating the effects induced by luminance and contrast variation using the adapted variant of empirical mode decomposition, we were able to independently test the correlation between frequency and power for each of the varied parameter.

We found that power and frequency are differently correlated as a function of local luminance and contrast level respectively. Specifically, power and frequency were highly correlated with respect to contrast, but luminance of the receptive field induced a lower correlation between the two. This fact corresponds to our observations when looking at the response pattern at lower spatial and temporal frequencies (Fig. 3), where we see a low correlation between power and frequency when only luminance is varied.

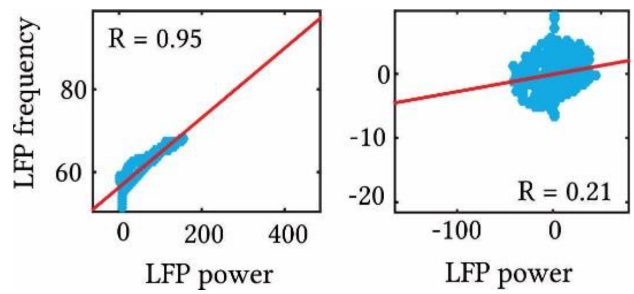

Fig. 4. Power and frequency correlations as a result of modulatory causes of different timescales. Scatter plots of frequency versus power of the response pattern in slow timescales (*Right),* corresponding to contrast modulation, and fast timescales (*Left*) corresponding to the passage of the grating through the receptive field.

These observations have important implications in the study of mechanisms underlying oscillatory behavior in the cortex. They suggest that existing theories about interactions giving rise to synchronization and increase in local field potential power within a specific frequency range fail to explain all features that are observed experimentally. In particular, the Pyramidal-INterneuron Gamma (PING) mechanism [**Error! Reference source not found.**] predicts that a stronger input is associated to a larger gamma power and a higher frequency [**Error! Reference source not found.**] [**Error! Reference source not found.**]. Our results indicate that this seems not to be the case when the activity of the cortical circuit is modulated by the local luminance fluctuation in the receptive fields of underlying cells.

VI. Conclusions

The study of oscillatory components across time and their dependence on input parameters within cortical networks is extremely important, impacting directly on our understanding of the functional role of such oscillations. Here, we proposed two methods which aim to characterize transient oscillatory responses more precisely and to disambiguate between dimensions of these responses and the various causes that lead to modulations of the response. We showed the application of these algorithms in the spectral analysis of local field potentials recorded in the visual cortex of anesthetized mice, while being presented a series of moving stimuli with variable contrast and local luminance. With the aid of these methods, we were able to determine the trajectory of the response through a three-dimensional time-frequency-power space and separate the effects of modulation of different timescales on each of these dimensions. Our results indicate that such analysis methods reveal features which are not explained by current theories about mechanisms of gamma oscillatory responses and are therefore of great relevance in the development and testing of novel theories.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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