43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society

Pre-Conference Workshops & Social Events:
Saturday, October 30, 2021
Conference Dates:
Monday, November 1 – Friday, November 5, 2021

Conference Chair

Emilio Sacristan, UAM | Ci3m

Program Chairs

Joaquin Azpiroz, Universidad Autonoma Metropolitana – CI3M

Roberto Lavarello, Pontificia Universidad Catolica del Peru

EMB IEEE Engineering in Medicine and Biology Society | IEEE

Indexed in PubMed® and MEDLINE®, Products of the United States National Library of Medicine

PubMed MEDLINE U.S. National Library of Medicine

2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 978-1-7281-1179-7/21/$31.00 ©2021 IEEE | DOI: 10.1109/EMBC46164.2021.9630196

High Frequential Resolution Networks: Considerations on a New Functional Brain Connectivity Framework

Víctor Rodríguez-González, Víctor Gutiérrez-de Pablo, Carlos Gómez, *IEEE Senior Member*, Yoshihito Shigihara, Hideyuki Hoshi, Roberto Hornero, *IEEE Senior Member*, Miguel A. Tola-Arribas, Mónica Cano, Jesús Poza, *IEEE Senior Member*

***Abstract*— Connectivity analyses are widely used to assess the interaction brain networks. This type of analyses is usually conducted considering the well-known classical frequency bands: delta, theta, alpha, beta, and gamma. However, this parcellation of the frequency content can bias the analyses, since it does not consider the between-subject variability or the particular idiosyncrasies of the connectivity patterns that occur within a band. In this study, we addressed these limitations by introducing the High Frequential Resolution Networks (HFRNs). HFRNs were constructed, using a narrow-bandwidth FIR bank filter of 1 Hz bandwidth, for two different connectivity metrics (Amplitude Envelope Correlation, AEC, and Phase Lag index, PLI) and for 3 different databases of MEG and EEG recordings. Results showed a noticeable similarity between the frequential evolution of PLI, AEC, and the Power Spectral Density (PSD) from MEG and EEG signals. Nonetheless, some technical remarks should be considered: (i) results at the gamma band should exclude the frequency range around 50 Hz due to abnormal connectivity patterns, consequence of the previously applied 50 Hz notch-filter; (ii) HFRNs patterns barely vary with the connection distance; and (iii) a low sampling frequency can exert a remarkable influence on HFRNs. To conclude, we proposed a new framework to perform connectivity analyses that allow to further analyze the frequency-based distribution of brain networks.**

I. Introduction

Neural signals are the result of synaptic interactions between neurons. They contain valuable information about brain function that could help to a deeper understanding of neural processes, such as brain maturation or the neural mechanisms associated with the onset and progression of diverse diseases [1]. In this regard, brain imaging techniques play an important role, as they can record brain activity in a non-invasive way. Electroencephalogram (EEG) and magnetoencephalogram (MEG) are two electrophysiological imaging techniques with a high temporal resolution [1]. EEG has a reduced cost and a high portability compared with MEG [1]. On the other hand, MEG provides a higher spatial resolution, as well as robustness against volume conduction effects [1].

EEG and MEG signals can be analyzed in different ways [2]: i) 'zero order analyses', by exploring local activation patterns at individual sources; ii) 'first order analyses', by computing the interactions between each pair of sources; and iii) 'second and higher order analyses', characterizing the higher order interactions of brain activity. Zero order metrics are widely used, but over-simplify a complex system as the brain [2]. Thereby, they are completed by first, second and higher order analyses, which provide a framework to assess the complex relationships between different brain regions [2].

Most of the methodological approaches applied to carry out 'second and higher order' analyses are based on considering the classical neurophysiological frequency bands (*i.e.*, delta, theta, alpha, beta, gamma, and high-gamma) [3], [4]. Although these frequency bands have been useful to glimpse the underlying brain organization [5], this division of the spectrum presents several limitations: it oversimplifies a complex system as the brain by limiting the ways of establishing frequency-based networks; it obscures the intricate architecture of the interactions between brain regions that occur within a band; and the between-subjects spectral variability or individual idiosyncrasy of the connectivity patterns is neglected by defining *a-priori* fixed bands. Although some connectivity measures, as Coherency or Phase Slope Index, provide frequency-dependent results, they are based on cross-spectral densities, which impacts on their frequential resolution and makes it difficult to deal with volume conduction effects.

Here, we present a new approach to analyze the functional connectivity of EEG and MEG recordings that overcomes the previous limitations by increasing the frequency resolution of the analyses, the so-called *High Frequential Resolution Networks* (HFRN). Specifically, we propose to construct the functional connectivity matrices by filtering the signals using narrow frequency bands, thus removing the frequency resolution limitation that is now present in these analyses. Nevertheless, there are many technical aspects to be considered before applying this novel methodology. Hence, in this study, we will address some relevant methodological issues that have to be considered when using HFRN.

This research was supported by 'Ministerio de Ciencia, Innovación y Universidades' and 'European Regional Development Fund' (FEDER) under project PGC2018-098214-A-I00, by 'European Commission' and 'FEDER' under project 'Análisis y correlación entre la epigenética y la actividad cerebral para evaluar el riesgo de migraña crónica y episódica en mujeres' ('Cooperation Programme Interreg V-A Spain-Portugal POCTEP 2014–2020'), and by 'CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN)' through 'Instituto de Salud Carlos III' co-funded with FEDER funds. V. Rodríguez-González was in receipt of a PIF-UVa grant from the 'University of Valladolid'.

V. Rodríguez González, V. Gutiérrez-de-Pablo, C. Gómez, R. Hornero, and J. Poza are with the Biomedical Engineering Group, University of Valladolid, Valladolid, Spain (corresponding author's e-mail: victor.rodriguez@gib.uva.es).

C. Gómez, R. Hornero, and J. Poza are with the Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN, Spain).

Y. Shigihara and H. Hoshi are with the Hokuto Hospital, Obihiro, Japan.

R. Hornero and J. Poza are with Instituto de Investigación en Matemáticas (IMUVA), University of Valladolid, Spain.

M.A. Tola-Arribas and M. Cano are with the Department of Neurology and with the Department of Clinical Neurophysiology, respectively, 'Río Hortega' University Hospital, Valladolid, Spain.

II. Materials

A. Participants and neurophysiological signals

Three different datasets were used from healthy elderly participants: (i) *HOKUTO*, with 29 MEG recordings; (ii) *POCTEP*, with 51 EEG recordings; and (iii) *HURH*, with 45 EEG recordings. In all the databases, 5 minutes of resting-state eyes-closed neurophysiological activity were recorded. Participants were required to stay still and awake during the acquisition of the signals, that were monitored in real time to avoid somnolence.

The characteristics of the recordings in each database are described below:

- *HOKUTO* (Japan) – Signals were acquired with a 160-channel axial gradiometer MEG system (MEG Vision PQ1160C, Yokogawa Electric), with a sampling frequency (fs) of 1000 Hz . This database was formed by 17 males and 12 females with an age of 69.0±5.2 years (mean±standard deviation, SD).
- *POCTEP* (Spain and Portugal) – Signals were acquired using a 19-channel EEG system (Neurofax JE 921A, Nihon Kohden), with a sampling rate of 500 Hz using 19 electrodes from the international 10-20 system (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, and O2). The database included 26 males and 25 females with an age of 80.1±7.1 years (mean±SD).
- *HURH* (Spain) – Signals were acquired with a 19-channel EEG system (XLTEK®, Natus Medical) using the international 10-20 system and the same 19 electrodes used in *POCTEP*. The fs was of 200 Hz. The database was composed by 14 males and 31 females with an age of 76.3±4.0 years (mean±SD).

All the recordings were conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Ethical Committees (Hokuto Hospital for *HOKUTO*, Porto University for POCTEP, and 'Río Hortega' University Hospital for *HURH*).

B. Preprocessing

All the signals were preprocessed using a similar pipeline [6]: i) application of a finite impulse response (FIR) filtering using a Hamming window: bandstop (49.5-50.5 Hz) to remove line noise, and bandpass (1-70 Hz) to limit noise bandwidth; ii) independent component analysis to remove artifacts; and iii) visual selection of 5-second artifact-free trials. Furthermore, due to the increased spatial resolution of the MEG signals, the SOUND algorithm was applied before the preprocessing pipeline thus having this database an additional preprocessing step that reconstruct at source level the artifactuated segments of the signals [7]. The mean number of trials per participant was: 49±8 (mean±SD) for *HOKUTO*, 44±11 (mean±SD) for *POCTEP*, and 46±7 (mean±SD) for *HURH*.

III. Methodology

A. Source localization

To ameliorate the volume conduction and field spread effects, all the analyses were carried out at source level. The inverse problem was solved using the *weighted Minimum Norm Estimation* (wMNE) algorithm, which restricts the solutions by minimizing the energy while weighting the deeper sources to ease their identification [8]. Furthermore, an anatomical template with 15000 cortical sources was used. Those sources were grouped in the 68 regions of interest (ROIs) defined by the Desikan-Killiany atlas [9]. Consequently, all the subsequent analyses will be performed at source level.

B. Estimation of the power spectral density

Power spectral density (PSD) of the signals was computed by means of the Blackman-Tuckey method, using a rectangular window of 5-second length without overlapping. Next, each PSD was normalized by its total power, thus obtaining the normalized PSD (PSDn) [6].

C. Generation of the HFRN

Many connectivity metrics have been proposed to assess the association between time series. In this study, we used two of the most widely used: the orthogonalized Amplitude Envelope Correlation (AEC), and the Phase Lag Index (PLI) [10]. We applied these two metrics because they are simple and widespread, but based on different principles: while PLI measures the relationship of two time series examining their phase changes, AEC is based on the signal amplitude [10]. Besides, PLI has the advantage of being robust against volume conduction effects [10]. Deeper insights on these connectivity measures can be found in [10]. Also, it is noteworthy that analyzing two different connectivity metrics will allow us to make our results relatively independent of the connectivity measure employed.

Typically, connectivity metrics that analyze the coupling between brain regions are computed in the well-known classical frequency bands; this yields a poor frequency resolution. Here, we aim to present a methodology that can analyze more precisely the frequential evolution of the interactions between the different brain regions. For this task, we used a narrow-bandwidth FIR bank filter of 1 Hz bandwidth, with an overlapping of 50% from 1 Hz to 70 Hz. The filter order was set to 333 (*i.e.* 1/3 of the minimum epoch length, that is the maximum allowed by MATLAB *filtfilt* function) as we wanted to keep the precision of the filter response as high as possible [11]. A Hamming window was employed to reduce the ringing effects associated to the relatively high order of the filter [11]. Signals were filtered forward and backward to avoid phase distortion [11]. Furthermore, we used the signal reflection technique to ameliorate the edge effects of the filter, as the signals were filtered before the segmentation process [11].

IV. Results and Discussion

A. Influence of the acquisition technique in HFRN

Figure 1 shows the frequency distribution of PSDn, and of connectivity strength calculated by means of PLI, and AEC for the three databases under assessment. In the three curves, the values of all the ROIs were averaged. It is noteworthy that PLI and AEC present some similarities between them, as well as with PSDn. For all the databases, it can be appreciated that PLI and AEC exhibit a peak in the alpha range, which partially corresponds with the alpha peak in PSDn, but slightly shifted

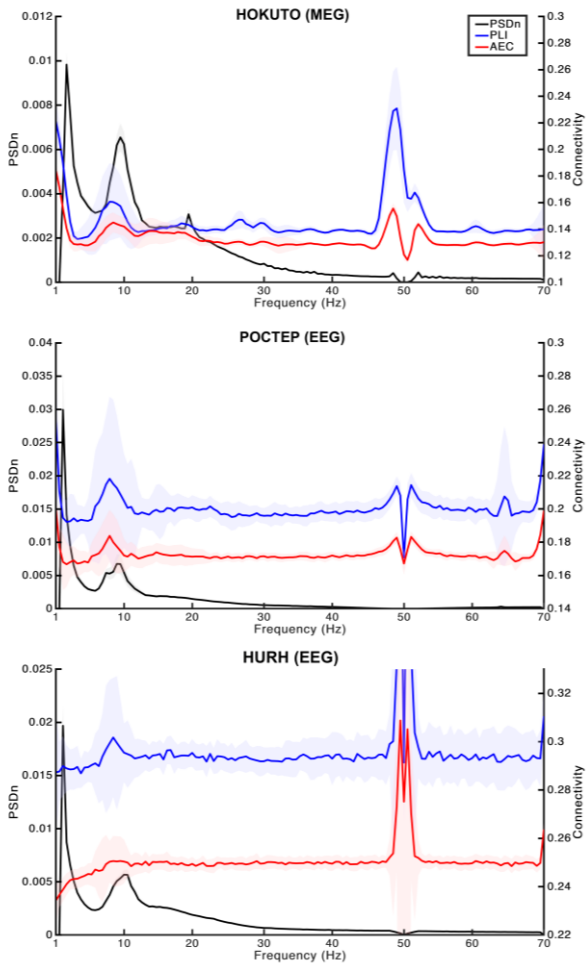

Figure 1. Frequency distribution of the PSDn (black), PLI (blue), and AEC (red). First row corresponds with HOKUTO MEG database, second with POCTEP EEG database, and the last one with HURH EEG database. The left axis reflects values of the PSDn, while the right axis reflects the connectivity values (PLI and AEC). For each measure, he dark line indicates the median value, and the shaded area corresponds to the standard deviation.

to lower frequencies. Nonetheless, the distribution of the curves presents remarkable differences between them. This supports the fact that, although PSDn and connectivity metrics contain partially overlapped information and should not be considered as completely independent, they are reflecting different properties of the neural activity: PSDn reflects local synchrony of nearby neuronal pools, while the connectivity parameters reflect long-range synchronization [2]. These findings are in line with a previous study where a significant correlation was found between different network metrics and the relative power in alpha, which can be estimated from PSD [12]. Recent research also found significant correlations between the PSD and the clustering coefficient [13]. Hence, our findings support the hypothesis that PSDn reflects not only the local activation of neuronal pools but also the synchronization of distant functional units [14]. In this regard, Figure 2 depicts the frequential evolution of PLI and AEC as a function of the connection distance, estimated from the Desikan-Killiany atlas. It could be appreciated that the distance barely influences the frequential distribution. Although the strength exhibits some differences around the

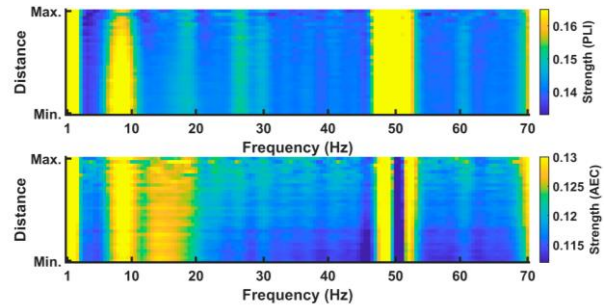

Figure 2. Connectivity strength calculated by means of PLI (first row) and AEC (second row) as a function of frequency (x-axis) and distance (y-axis) for *HOKUTO* database. Distances were grouped in 32 equally-spaced intervals. Distance values were removed as they are ambiguous due to the usage of a head template.

alpha band for higher distances, it is likely provoked by the reduced number of connections in the high-distance intervals.

For all databases it could be appreciated that the connectivity around alpha band presents the highest values (apart from the artifact around 50 Hz, which will be analyzed below). Alpha oscillations are associated with higher cognitive processes, being widely analyzed [15]. It can be hypothesized that this increased connectivity in alpha band could be linked to a "working state" in resting-state where the brain seems to be hyper-connected. Furthermore, it could also be appreciated that in alpha band the variability of the connectivity signals is very high. This issue suggests a relevant inter-participant variability that could be being a confounding factor in the studies that employs fixed frequency bands. HFRN would enable the design of personalized frequency bands, which would adapt the connectivity analyses to each subject's particular idiosyncrasies.

Of note, a prominent change in the connectivity distribution appears around 50 Hz for both, PLI and AEC. Two hypotheses could explain the presence of this artifact: (i) the partial mitigation of the interference of the power line noise, and (ii) the bandstop filter applied to remove that interference. By visually inspecting the PSDn from the different databases, it could be appreciated that the effect of the power line noise is almost fully removed, thus it is probably that this artifact is provoked not by the power line noise, but the filter itself. In line with this idea, it could also be observed for *HOKUTO* at the lower cutoff frequency (*i.e.*, 1 Hz), for *HURH* at upper cutoff frequency (*i.e.*, 70 Hz), and for *POCTEP* at both, lower and upper cutoff frequencies, that a similar artifact seems to appear; it is probably provoked by the artificial increase of connectivity due to the alteration of the signal properties due to the bandpass filtering applied to limit noise bandwidth.

B. Influence of the sampling frequency in HFRN

By comparing the results from the different databases, remarkable differences can be appreciated between them. It can be observed an increased smoothness for the results of *HOKUTO* regarding both EEG databases and for *POCTEP* when compared to *HURH*. Furthermore, the magnitude of the results also varies between iterations, with *HURH* showing higher values than *POCTEP*, and this showing higher values than *HOKUTO*. It could be hypothesized that these differences could be provoked by the sampling frequency (*Fs*), as *HOKUTO* was acquired with a *Fs* greater than *POCTEP* and

HURH by a factor of two and five, respectively. This finding is not in line with a previous study where the connectivity results were barely influenced by *Fs* [16]. Nonetheless, this discrepancy may be motivated the approach used, as Fraschini and colleagues employed only one frequency band from 1 to 20 Hz [16].

To directly evaluate the influence of the sampling frequency, the HFRN were constructed for the *HOKUTO* database downsampling the signals to different *Fs* values: 800, 600, 400 and 200 Hz (apart from the original *Fs* = 1000 Hz). Figure 3 depicts the results; it can be appreciated that the magnitude of the connectivity and the ripple increase with the decrease of the sampling frequency. This issue suggests that the higher the sampling frequency, the more defined the frequency distribution of the connectivity patterns.

C. Limitations and future lines

There are some methodological issues that should be considered for future analyses. First, only one parameter (the sampling frequency) was analyzed, while there could be more factors influencing the networks, as the epoch length that has been previously proven to have a remarkable influence in the connectivity patterns [16]. Besides, despite the fact that the filter has been carefully selected, it would be interesting to analyze in depth the influence of different filter settings in the HFRN. Also, it should be tested a central-frequency-dependent adaptative-filtering approximation. Finally, it would also be interesting analyze the influence of the source localization algorithm.

V. Conclusions

We have proposed a novel methodology that enables the study of the brain connectivity patterns with a high frequential resolution. Although the analysis pipeline is still under development, several key methodological considerations can be delineated from the present study. Firstly, HFRN allowed to glimpse an increase in the connectivity strength in the alpha band, similar to the alpha peak in the PSDn, showing a noticeable alignment between both curves. Secondly, it has been observed that the global strength of HFRNs does not depend on the distance of the assessed connection. Thirdly, it is noteworthy that the gamma band should exclude the frequency range around the power line interference, due to the distortion introduced by the power line filtering. Finally, it could be appreciated that the Fs influences the HFRN, with higher Fs values showing smoother results with lower magnitude values.

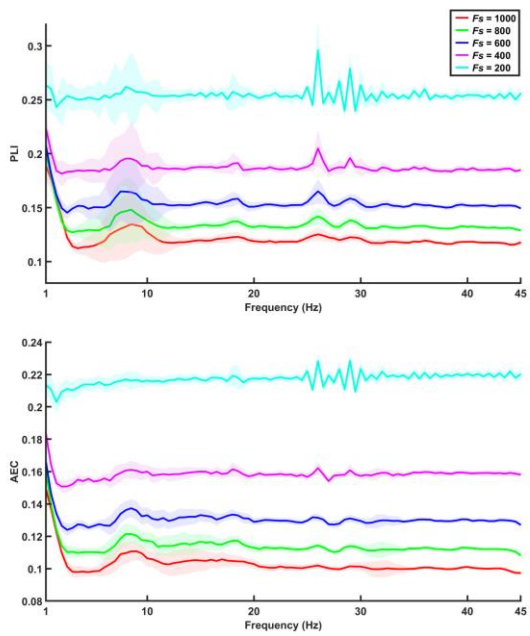

Figure 3. Influence of the sampling frequency (*Fs*) in the frequency distribution of PLI (first row) and AEC (second row) for the *HOKUTO* database. The line is the median value, and the shaded area the standard deviation. The assessed *Fs* values are: 1000 Hz (red line), 800 Hz (green line), 600 Hz (dark blue line), 400 Hz (pink line), and 200 Hz (light blue line). X-axis has been limited to 45 Hz to ease the visualization of the curves by removing the 50-Hz-artifact.

References

[1] C. Babiloni, *et al.*, "Fundamentals of Electroencefalography, Magnetoencefalography, and Functional Magnetic Resonance Imaging," *Int. Rev. Neurobiol.*, vol. 86, no. 5, pp. 67–80, 2009.

[2] C. J. Stam and E. C. W. van Straaten, "The organization of physiological brain networks," *Clin. Neurophysiol.*, vol. 123, no. 6, pp. 1067–1087, Jun. 2012.

[3] M. Hardmeier, *et al.*, "Reproducibility of Functional Connectivity and Graph Measures Based on the Phase Lag Index (PLI) and Weighted Phase Lag Index (wPLI) Derived from High Resolution EEG," *PLoS One*, vol. 9, no. 10, pp. 1–10, Oct. 2014.

[4] P. Tewarie *et al.*, "Structural degree predicts functional network connectivity: A multimodal resting-state fMRI and MEG study," *Neuroimage*, vol. 97, no. 15, pp. 296–307, Aug. 2014.

[5] W. Klimesch, "The frequency architecture of brain and brain body oscillations: an analysis," *Eur. J. Neurosci.*, vol. 48, no. 7, pp. 2431–2453, Oct. 2018.

[6] V. Rodríguez-González *et al.*, "Consistency of local activation parameters at sensor- and source-level in neural signals," *J. Neural Eng.*, vol. 17, no. 5, p. 056020, Oct. 2020.

[7] T. P. Mutanen, *et al.*, "Automatic and robust noise suppression in EEG and MEG: The SOUND algorithm," *Neuroimage*, vol. 166, pp. 135–151, Feb. 2018.

[8] F.-H. Lin, *et al.*, "Spectral spatiotemporal imaging of cortical oscillations and interactions in the human brain," *Neuroimage*, vol. 23, no. 2, pp. 582–595, Oct. 2004.

[9] R. S. Desikan *et al.*, "An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest," *Neuroimage*, vol. 31, no. 3, pp. 968–980, Jul. 2006.

[10] S. J. Ruiz-Gómez, *et al.*, "Computational modeling of the effects of EEG volume conduction on functional connectivity metrics. Application to Alzheimer's disease continuum," *J. Neural Eng.*, vol. 16, no. 6, p. 066019, Oct. 2019.

[11] M. X. Cohen, *Analyzing Neural Time Series Data: Theory and Practice*, 1st ed. London: The MIT Press, 2014.

[12] M. Demuru, *et al.*, "A comparison between power spectral density and network metrics: An EEG study," *Biomed. Signal Process. Control*, vol. 57, p. 101760, Mar. 2020.

[13] V. Rodriguez-Gonzalez *et al.*, "Estudio de la asociación entre los patrones de activación local y de sincronización global en el EEG en la enfermedad de Alzheimer," in *Libro de Actas del XXXVIII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, 2020, pp. 121–124.

[14] P. Tewarie *et al.*, "Relationships Between Neuronal Oscillatory Amplitude and Dynamic Functional Connectivity," *Cereb. Cortex*, vol. 29, no. 6, pp. 2668–2681, Jun. 2019.

[15] E. Başar and B. Güntekin, "A short review of alpha activity in cognitive processes and in cognitive impairment," *Int. J. Psychophysiol.*, vol. 86, no. 1, pp. 25–38, Oct. 2012.

[16] M. Fraschini, *et al.*, "The effect of epoch length on estimated EEG functional connectivity and brain network organisation," *J. Neural Eng.*, vol. 13, no. 3, p. 036015, Jun. 2016.