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Regularization of EEG and MEG inverse problem based on physiologically plausible priors

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Contents

1 Dissertation topic

1.1 EEG and MEG inverse problem

Electroencephalography (EEG) [1] and magnetoencephalography (MEG) [2] are noninvasive neuroimaging techniques with high temporal resolution of the millisecond range, unavailable to many other methods of brain activity research. Due to the high temporal resolution, EEG and MEG techniques are widely used for diagnostics of a wide range of neurological disorders, including epilepsy, without exposing the patient to additional risk.

More accurate diagnosis and detailed analysis of cognitive processes require the use of EEG/MEG inverse problem solving methods, which allow the activity of neuronal populations to be assessed from noninvasive recordings of brain electromagnetic activity. The spatial resolution of EEG is quite high, on the order of a few millimeters, especially in areas of the brain with high curvature [3]. The spatial resolution of EEG is lower than that of MEG and is on the order of a centimeter [4].

Due to fundamental physical constraints, the inverse problem is known to be ill-posed (or underdetermined) [5] and need to be regularized in order to find a unique solution [6]. Even after imposing constraints, the solution can be unstable: small errors in the recorded experimental data can lead to significant changes in the solution. Thus, the spatial resolution of EEG/MEG ultimately depends on the choice of method for solving the inverse problem.

An obligatory prerequisite for solving the inverse problem is the forward problem solution: the problem of signal recovery on sensors by known activations of dipole sources. It is known that electric field and, consequently, EEG measurements are sensitive to conductivity changes of different tissues on the way from sources to sensors: some tissues have high conductivity, such as brain, cerebrospinal fluid and scalp, but skull has low conductivity. The magnetic field is less sensitive to differences in tissue conductivity [7]. For the forward EEG problem, therefore, the best choice is the *boundary element method, BEM* [8], which realistically simulates different tissues. The *overlapping spheres* method [9] may also be suitable and less computationally expensive for MEG.

Let the recorded EEG/MEG data for each time moment t be a vector $\mathbf{x}(t)_{[M\times 1]}$, where here and further in square brackets the size of the vector (matrix) is given, and M is the number of sensors. Let the solution of the forward problem be found by one of the suitable methods and stored in the operator $\mathbf{G}_{[M\times N]}$, where N — the number of sources in the cortical model.

The regularization of the inverse problem consists in introducing additional a priori assumptions about what properties the desired source activity should have. The assumptions are implemented in the form of constraints imposed on the final solution. Depending on the regularization technique used, one can distinguish a number of approaches to the inverse problem solving.

1.2 Interictal spike analysis in patients

Most of the methods proposed in this research have been tested on data from patients with epilepsy, and in this section we provide the motivation for this particular application of our algorithms.

Epilepsy is one of the most common neurological diseases in the world, accompanied not only by the presence of seizures, but also by the risk of co-morbidities, cognitive deficits, psychological disorders and adverse social consequences. According to the World Health Organization, there are more than 50 million people worldwide with diagnosed epilepsy[1]. Despite the fact that for most patients seizures can be stopped with the right combination of antiepileptic drugs, about 30% of patients have a pharmacoresistant form of epilepsy, in which drug treatment can not control seizures [10]. In this case, the patient may have an option of neurosurgery, and in about half of the cases such surgery can completely eliminate seizures for at least 10 years, and in 85% of cases surgery leads to a significant reduction in seizure frequency and improves the patient's quality of life [11], [12].

In a common case of multifocal epilepsy, pathological activity originates in one compact part of the brain, called the epileptogenic zone, from which it subsequently spreads to other parts of the brain, often involving deep structures, and propagates to broad cortical areas, causing a seizure [13]. Localization of the epileptogenic zone is the most important step in the treatment of pharmacoresistant forms of epilepsy, and the effectiveness of surgical intervention directly depends on its quality. Neurosurgical intervention is the removal of tissue in the epileptogenic zone or dissection of neural connections to prevent the spread of pathological activity. Typically, noninvasive EEG recordings, invasive electrocorticogram (ECoG) or depth electrode recordings are used to localize the epileptogenic zone, but increasingly, and when available, noninvasive MEG [14] technique is preferred.

To identify the epileptogenic zone, various brain regions are examined for the presence of interictal spikes — short, high-amplitude events 100-200 ms in length, significantly prominent compared to background EEG/MEG activity, and usually generated by one or more focal sources. The area of the brain that generates the interictal spikes is called the irritative zone. Typically, one of the irritative zones coincides with the epileptogenic zone. To improve the accuracy of preoperative diagnosis of epilepsy, new methods and approaches for detailed analysis of interictal spikes need to be developed, and noninvasive diagnostic methods are most valuable because they involve less risk for the patient.

[1]https://www.who.int/news-room/fact-sheets/detail/epilepsy

In the paper [15], the authors analyze epileptiform activity induced by traumatic brain injury in humans and rats. The authors note that noninvasive EEG recordings were insensitive to pathological activity, whereas invasive recordings showed its presence in 86% of patients. At the same time, [16] showed that interictal MEG recordings can contain meaningful information sufficient for proper localization of the epileptogenic zone and subsequent surgical intervention. Often the problem of finding the epileptogenic zone is solved in terms of analyzing the distribution of activity between areas throughout the brain, but there is also reason to believe that epileptiform activity has a distribution at the local level, but such observations are based on invasive recordings [17], [18] or on the modeled data [19].

1.3 Research goals

Usually the choice of a priori assumptions about the nature of brain source activity for the inverse problem regularization is determined not by their physiological plausibility, but rather by technical convenience, allowing, for example, to obtain an analytical solution for the inverse operator (MNE, wMNE, LORETA), or the availability of a known numerical optimization algorithm for iterative solution search (MCE, FOCUSS). The aim of this work is to develop approaches to solve the inverse EEG and MEG problem based precisely on physiologically determined constraints. In this case, the desired solution is more reasonable, corresponds to the physiological nature of the process and allows to draw further conclusions about the phenomenon under study.

Among many methods for solving inverse EEG and MEG problems, adaptive LCMV beamformers [20], [21], [22] stand out due to their high spatial resolution, which can be achieved when the observed activity is caused by a small number of focal sources and these sources are not correlated. Beamformers are known to be prone to error when activations of sources are correlated. Given the fact that the physiology of brain functioning suggests many cases where sources are correlated, this limitation is significant for the reconstruction of source activity from real data. The aim of the first part of the work is to develop such a modification of the adaptive beamformer, which, on the one hand, will preserve its high spatial resolution, but, on the other hand, will allow to recover the synchronous activity of the brain sources.

Although it has been proven that for a number of brain processes, neural activity propagates in the form of cortical traveling waves [23], most cognitive studies, and thus methods for solving the inverse problem, rely on the assumption that brain activity can be represented as the sum of static source activations [24]. There are sufficient experimental evidence to believe that the local distribution of interictal spikes in patients with epilepsy can be described by cortical wave propagation [25], [26], [27]. In the second part of the study, our goal was to develop an algorithm for solving the inverse EEG/MEG problem that uses the physiologically plausible assumption of spatiotemporal connectivity of the reconstructed activity. The algorithm also allows to reconstruct the characteristic parameters of the wave model, namely the direction and velocity of the wave.

Analysis of MEG recordings of interictal brain activity in patients with epilepsy makes it possible to localize irritative zones noninvasively, with minimal patient discomfort, and with high accuracy and to study the spatiotemporal dynamics of the epileptogenic network. Identification of irritative zones implies search and localization of interictal spikes containing valuable diagnostic information. Usually the search for epileptiform events is performed by means of visual analysis of recordings by experts. Given that we are talking about multi-channel data with several hundred channels, and very focal events, such visual analysis is a very time-consuming procedure and the result can be biased due to the expert. Since manual processing of a large amount of data leads to expert fatigue and an increase in the probability of committing an error, the analysis usually stops at the minimum number of processed events, subjectively considered to be sufficient. The aim of the third part of the work was to develop a method of automatic search for interictal spikes and their clustering to determine the irritative zone, requiring minimal participation of the expert only at the time of the final validation of the results.

To sum up, **the goals of this research**:

1. To develop algorithms and methodology for solving the EEG/MEG inverse problem for reconstruction of synchronous source activity with high spatial resolution.

2. To study the properties of the proposed methods in numerical experiments and to apply it to the real data in the auditory paradigm. To analyze the evoked potentials in auditory tasks.

3. To develop an algorithm for solving inverse EEG/MEG problems based on the assumption of wave propagation of the activity, to study its properties and to apply the developed method to interictal recordings of patients with epilepsy.

4. To develop the algorithms for automatic interictal EEG/MEG processing to detect irritative zones in the patients with epilepsy.

5. To develop an epileptogenic zone detection methodology based on mathematical analysis of the dynamics of epileptic activity during the interictal period (algorithm from part 2) and on the analysis of a large number of automatically detected and clustered spikes (algorithm from part 3).

1.4 Key results

As a result of this study, we have developed several new techniques for solving the inverse problem of EEG and MEG, which are based precisely on physiologically plausible assumptions about neuronal activity.

In the first part of the study, we developed two new methods: ReciPSIICOS and whitened wReciPSIICOS, which are modifications of the classical adaptive LCMV beamformer and, on the one hand, preserve its high spatial resolution but, at the same time, allow to reconstruct the synchronous activity of brain sources. The properties of the two proposed algorithms were investigated first using realistically simulated data and then on real MEG data recorded in auditory paradigms. We compared the solutions obtained by the proposed methods with the classical MNE and LCMV approaches. An analysis of the properties of the algorithms on real data showed similar results to the analysis of model data. Our experiments showed that the LCMV beamformer is significantly sensitive to the presence of correlated sources in the data, the solution suffersv from the signal cancellation problem and often contains only one of the synchronous sources, and with a smeared activation map. MNE often fails to find all active sources, or finds overly biased and highly distributed activations. ReciPSIICOS and whitened wReciPSIICOS, however, show high solution quality and allow finding focal bilateral sources.

In auditory EEG experiments, we were able to show that in two consecutive sessions of a monetary incentive delay task in which monetary losses were encoded using auditory stimuli, the auditory MMN component increased significantly for those signals that predicted large monetary losses. We also showed that the FRN component was modulated by both magnitude and probability of results during the auditory MID task, whereas no such effect was found for dN200. In addition, the dN200 component, which is associated with updating information about the magnitude of the estimated gain, correlated with the standard FRN, which is associated with a negative RPE. The methods developed to reconstruct the activity of correlated sources at high resolution will allow further analysis of the observed phenomena.

In the second part of the research, we propose a methodology for the noninvasive study of the fine spatial and temporal structure of interictal spikes observed in EEG and MEG, based on the concept of traveling cortical waves. We presented the interictal spike event as a superposition of pregenerated traveling waves specified for individual anatomy. We used the LASSO method with positive coefficients to estimate the optimal velocity and directions of wave propagation. We tested the performance of the algorithm on both model data and real MEG signals and demonstrated that the propagation dynamics of spikes recorded in MEG can be measured on a spatiotemporal scale of millimeter/millisecond. Despite the presence of errors, some of the interictal spikes were successfully fitted using a traveling wave model. We observed that in all three patients whose data were analyzed, wave behavior was not typical for all interictal spikes. «Wave» spikes form the well spatially delineated clusters. Moreover, for patients in whom epileptogenic region data were available, these clusters coincide with this region. Based on these results, which are in good agreement with invasive data [17], [18], we suggest that analysis of interictal spikes recorded in MEG may help in localizing the epileptogenic zone.

In the third part, we proposed a two-stage method for automatic detection of interictal spikes and clustering them to determine the irritative zones. In the first stage, we use ICA (independent component analysis) decomposition of the data into independent components and automatically select «spike» components using heuristics. We then use the threshold in the time series of the selected components to identify the time samples that are candidates to be the peaks of the interictal spikes. In the second step, we validate the found events by the results of spatiotemporal clustering of the sensor records around the found peaks using convolutional sparse coding. We validated the results of our analysis by comparison with the irritative zones identified by visual inspection, as well as by comparison with the resection zone along with the known outcome of surgery. Automatically reconstructed irritative zones overlapped with those reconstructed by visual analysis in six of seven patients. In the remaining patient, both automatically and visually reconstructed areas did not overlap with the resection area and, for this patient, the surgical outcome corresponded to the Engel IIB classification. The advantageous difference of our method from the currently existing ones is the fully automatic analysis of the MEG record, implying the participation of an expert only at the final stage to verify the results.

1.5 Scientific novelty

It is known that while for a small number of independent sources, adaptive beamformers exhibit a quality of inverse solution that is superior to other methods, in the presence of correlated sources, the solutions turn out to be inconsistent. Several approaches to solving this problem have been presented in the literature, but most of them use the idea of zeroing out sources that are potentially correlated with the target source. Since there may be several correlated sources and the cortical model may be complex, such approaches are in practice too computationally expensive. In addition, they require the researcher to hypothesize about sources that are correlated, which may not be known for all experimental paradigms. We propose a modification of the beamformer that only requires the user to select the rank of the projection used in the method.

In addition, we have proposed for the first time an algorithm for solving the inverse EEG/MEG problem using the wave activity propagation assumption (wave priors). The currently available software FieldTrip [28], MNE Python [29], Brainstorm [30] have implemented a wide range of techniques to solve the inverse problem. Approaches that refuse to model neuronal activity using a set of current dipoles have also been proposed in the literature, for example the paper [31] considers spherical harmonics as a solution. However, despite the fact that the phenomenon of traveling cortical waves has gained popularity during the last decade and more and more studies demonstrate the diversity of their function in norm and pathology, none of the currently proposed solutions uses information about the spatiotemporal connectivity of the activations.

In the literature there are a number of approaches for automatic search for interictal spikes in EEG/MEG recordings. Despite the variety of ideas implemented, all of the currently existing methods have significant drawbacks. Methods based on morphological analysis face the problem of high variability of spike morphology even for one patient, and even more between different patients. Template search methods imply labeling of a significant amount of record by an expert. Methods of adaptive filtering turn out to be inefficient and characterized by low specificity. The closest to the approach we are developing are the methods based on the analysis of independent components, but even in this case the analysis is not automatic, because the choice of the necessary component and the interpretation of the results must be made by an expert. The advantage of the proposed approach is the full automation of the algorithm combined with the high efficiency of irritative zone reconstruction and the possibility of additional cluster analysis based on the estimated typical patterns.

1.6 Theoretical and practical significance

The algorithm for solving the inverse EEG/MEG problem using the assumption of spatiotemporal propagation of neuronal activity will make it possible to further investigate the increasingly popular phenomenon of cortical traveling waves. In addition to theoretical contribution, the developed method can be used for applied purposes, namely for functional diagnostics of the dynamics of neuronal activity in pathology: to study the interictal activity of patients with epilepsy. The development of noninvasive or minimally invasive methods to analyze the spatiotemporal distribution of interictal spikes in patients with pharmacoresistant forms of epilepsy will potentially increase the effectiveness of neurosurgical intervention and reduce postoperative risks. In the future, analysis of local patterns of interictal activity propagation may become an integral part of preoperative diagnosis. The proposed algorithm can be easily extended to analyze segments of data related to the onset of a seizure, which will become more available in the near future due to the development of new mobile MEG units with optically pumped magnetometers that the patient can wear on the head. It is important to emphasize that the developed algorithm can be applied not only to the study of epilepsy, but also to other neurophysiological studies that study brain activity, which has a spatiotemporal propagation pattern. For example, this method can be used to analyze evoked and induced responses in a paradigm with multiple presentation of stimuli. In this case, the task of finding the moment of the onset of local wave propagation is greatly facilitated.

One of the most important clinical applications of EEG and MEG is preoperative diagnostics of epilepsy, search for irritative zones and establishment of epileptogenic zone among them. The effectiveness of diagnosis directly depends on the number and quality of interictal spikes marked in the data. Since marking is usually done manually by an expert as a result of visual analysis, the number of events found is limited by the notion of a reasonable labor intensity of the marking task and is often insufficient for a complete analysis. We have demonstrated the applicability of the convolutional sparse coding method to detect interictal spikes and localize the irritative zone in patients with epilepsy. The advantage of this analysis is that it does not require the participation of an expert, and as a result localizes several clusters with characteristic activity patterns. The simplicity and accuracy of automatic detection of interictal spikes will allow further development of noninvasive methods in preoperative diagnosis. Although we were able to reproduce the results of visual analysis and provide clinically relevant information based on our results, a larger set of cases is needed to further quantify the reliability of our approach and test its application in clinical settings.

1.7 Research Methods

Methods from the following areas were used in the research: signal processing techniques, theory of inverse problem, estimation theory and machine learning, optimization theory.

1.8 The main defense points

1. Two LCMV beamformer modification methods (ReciPSIICOS, wReciPSIICOS) have been developed that allow the reconstruction of synchronous source activity from noninvasive EEG and MEG data. The superiority of the proposed algorithms over the classical MNE and LCMV beamformer on both model and real data is shown.

2. An algorithm for solving the inverse EEG/MEG problem based on the assumption of wave propagation was developed. Its properties have been investigated on model data. The results obtained for three patients demonstrate the relationship between the goodness of fit of interictal spikes with the traveling wave model and the belonging of the spikes to the epileptogenic zone.

3. We developed an algorithm for analyzing interictal MEG recordings of patients with epilepsy to search for irritative zones. The methodology includes automatic detection of interictal spikes, their localization and clustering, as well as determination of a typical activity pattern for each cluster. The methodology has been validated on seven patients.

1.9 Author's contribution to the study

1. In the first part of the study the author: worked on the development of the idea of the algorithm, which originally belongs to the supervisor A. E. Ossadchi and is complementary to the idea presented in the thesis of D. I. Altukhov; wrote code to implement all algorithms in Matlab[2]; fully calculated the results of all computational experiments to explore the properties of the algorithm; analyzed real data for Dataset 1; created visualization results; made a significant contribution to the manuscript.

2. In the second part of the study, the author: worked on the development of the method idea, which belongs to the scientific supervisor A. E. Ossadchi and in the first version was implemented by the author's colleague E. A. Kalenkovich, in the process the method was significantly changed, compared with the original version; wrote code to implement the method in Matlab and partially in Python[3]; computed results of all computational experiments; computed results on real patient data; mainly contributed to the manuscript.

3. In the third part of the study, the author: continuing the research of her supervisor A. E. Ossadchi, made a significant contribution to the development of Stage 1 of the proposed algorithm; wrote the code in Matlab for Stage 1[4]; tested the algorithm on three patients from the second part of the study.

1.10 Publications and approbation of research

Conferences

1. *International conference* «The 8-th Mismatch Negativity Conference», «A novel beamformer immune to correlated sources and forward model inaccuracies», poster, Helsinki, Finland, 2018.

2. *International conference* «The 21-st International Conference on Biomagnetism BIOMAG», «MEG-based functional microscopy using traveling wave priors», poster, Philadelphia, USA, 2018.

3. *International conference* «Tubingen Systems Neuroscience Symposium», «MEG-based epilepsy diagnostics using traveling wave priors», poster, Tubingen, Germany, 2018.

4. *International conference* «MEG UK», «Traveling wave model for SOZ localization in MEG data», oral presentation, Cardiff, UK, 2019.

[2]Code can be found in the repository https://github.com/kuznesashka/ReciPSIICOS
[3]https://github.com/kuznesashka/wave_prior_inverse
[4]https://github.com/kuznesashka/ASPIRE

5. *International conference* «Organization for Human Brain Mapping», «MEG based functional microscopy using traveling wave priors: a new technology for exploring epilepsy», poster, Rome, Italy, 2019.

6. *International conference* «BCI-Samara», «MEG based functional microscopy using traveling wave priors», best poster award, Samara, Russia, 2019.

7. *International conference* «Baltic Forum: Neuroscience, Artificial Intelligence and Complex Systems», «Local propagation of MEG interictal spikes: source reconstruction with traveling waves priors», oral presentation, Kaliningrad, Russia, 2021.

First-tier publications

1. *Kuznetsova A., Nurislamova Y., Ossadtchi A.* Modified covariance beamformer for solving MEG inverse problem in the environment with correlated sources. NeuroImage. 2021. 228. 117677. DOI: 10.1016/j.neuroimage.2020.117677.

2. *Krugliakova E., Klucharev V., Fedele T., Gorin A., Kuznetsova A., Shestakova A.* Correlation of cue-locked FRN and feedback-locked FRN in the auditory monetary incentive delay task. Experimental Brain Research. 2018. 23. 141-151.

3. *Gorin A., Krugliakova E., Nikulin V., Kuznetsova A., Moiseeva V., Klucharev V., Shestakova A.* Cortical plasticity elicited by acoustically cued monetary losses: an ERP study. Scientific Reports. 2020. 10. 21161.

Second-tier publications

1. *Кузнецова А. А., Осадчий А. Е.* Анализ локальной динамики распространения межприступных рязрядов с помощью модели бегущих волн. Журнал высшей нервной деятельности. 2022. т. 72, No 3. с. 370—386. DOI: 10.31857/S0044467722030078

2 Contents

2.1 Inverse EEG/MEG problem solving in the presence of correlated sources using a modified beamformer

The spatial resolution of EEG/MEG and the result of source activation reconstruction from recorded sensor signals critically depend on the approach used to solve the incorrectly posed inverse problem. In recent years, adaptive beamformer solutions have become increasingly popular [20], [21], [22]. In cases where a small number of uncorrelated sources are activated, the beamformer solution is optimal and provides high spatial resolution. However, it is also known that beamformers tend to make errors when activations of sources correlate with each other: as a result, the resulting time series have a low signal-to-noise ratio and cortical maps of the resulting activation distributions are often meaningless.

This limitation significantly hampers the wider use of the promising beamformer technique, especially given that the fundamental mechanisms of brain function, its inherent symmetry, and the use of experimental paradigms linking activations to stimulus presentation result in significant correlation in brain source activity. To overcome this limitation, we have developed a new approach based on a modification of the covariance matrix of the data, which allows the creation of beamformers that maintain high spatial resolution despite the presence of correlated sources in the data [32].

2.1.1 The main idea of the proposed method

We propose a new modification of the beamformer that is insensitive to the contributions of correlated sources in the data. The two proposed methods are based on a projection operation applied to the vectorized covariance matrix of the sensor space. This projection procedure is complementary to the one developed earlier by colleagues in the PSIICOS [33] method. The PSIICOS method was originally developed to analyze connectivity from MEG data, in particular, to noninvasively detect interactions between sources with near-zero phase delay. The problem PSIICOS solves is the presence of volume conduction artifacts in the MEG data. Source activations, which are in fact independent, may show up as correlated activity on the sensors. Thus, the goal of the method is to project away from the effects of volume conduction and estimate true source correlations. PSIICOS uses a projection operation that is applied to a cross-spectrum sensor space matrix represented as an element of M^2-dimensional vector space. It has been shown [33] that PSIICOS can separate the signal leakage subspace and the subspace containing the contribution of truly coupled sources quite well.

However, the presence of correlated sources is the reason for the problem solved in this paper: the interactions of the sources lead to the signal cancellation problem when solving the inverse problem with the adaptive beamformer. The solution is arranged so that in the case of correlated sources it is possible to select for them the reciprocal coefficients of the spatial filter, so as to artificially reduce the target functional. Applying a projection-based approach similar to the one described above allows us to efficiently solve the problem of estimating the time series of correlated sources using an adaptive beamformer. We use a complementary version of the PSIICOS projection for the sensor covariance matrix, so that instead of suppressing the contribution of source powers, we emphasize them, and, conversely, reduce the contribution of correlated sources. This projection does not remove the activity of the correlated sources, but rather selectively treats their contributions to the covariance matrix and creates a fairly accurate approximation of the ideal data covariance that would be hypothetically observed if these sources were independent. We called the new methods ReciPSIICOS and whitened wReciPSIICOS because the proposed algorithms solve a problem complementary to the one that PSIICOS solves.

2.1.2 Covariance matrix in the sensor space

The covariance matrix $\mathbf{C}_{x[M\times M]}$ computed in sensor space plays a key role for the adaptive beamformer and is the central object for our methods. We represent the vectorized sensor covariance matrix as the following sum:

$$vec(\mathbf{C}_x) = vec(E\{\mathbf{x}(t)\mathbf{x}^T(t)\}) = \sum_{i=1}^{R} vec(\mathbf{g}_i\mathbf{g}_i^T)c_{ii}^{ss} + \sum_{i=1}^{R}\sum_{j=i+1}^{R} vec(\mathbf{g}_i\mathbf{g}_j^T + \mathbf{g}_j\mathbf{g}_i^T)c_{ij}^{ss} + vec(\mathbf{C}_n) \quad (1)$$

where $vec(\cdot)$ – matrix vectorization operation, $(\cdot)^T$ – transpose operation, R – number of active sources, $\mathbf{g}_i$ – column of direct model matrix corresponding to i-th source (source topography), $\mathbf{C}_n$ – the noise covariance matrix and, the most key entity here, c_{ij}^{ss} – the source covariance matrix element for i and j sources.

It can be observed that the terms in the above sum are divided into two types: those containing the powers of sources c_{ii}^{ss} (the diagonal elements of the covariance matrix) and those containing the values of covariances between different sources c_{ij}^{ss} (the off-diagonal elements). The terms of the second type are the reason why the adaptive beamformer solution is invalid. The weights of the spatial beamformer filter are arranged in such a way that the target functional can be reduced artificially by suppressing the activations of correlated sources. We propose two methods for constructing a projection that allow us to tune out the contribution of the cross terms to the covariance matrix in the sensor space.

2.1.3 ReciPSIICOS technique

The first proposed approach is to project the vectorized sensor covariance matrix onto the source power subspace $\mathcal{S}_{pwr}^{K}$ of dimension K, which is given by the linear span of vectorized auto-products of source topographies $vec\left(\mathbf{g}_i\mathbf{g}_i^T\right)$, $i = [1, \ldots, N]$.

In order to build the projector, you need to perform the following sequence of steps:

1. Create a matrix $\mathbf{G}_{pwr}$: the columns are the vectorized autoproducts of the topographies for all sources from the forward model $vec\left(\mathbf{g}_i\mathbf{g}_i^T\right)$.

2. Apply singular decomposition to the obtained matrix: $\mathbf{G}_{pwr} = \mathbf{U}_{pwr}\mathbf{S}_{pwr}\left(\mathbf{V}_{pwr}\right)^T$. Get the projection matrix on the source power subspace $\mathcal{S}_{pwr}^K$: $\mathbf{P} = \mathbf{U}_{pwr}^K\left(\mathbf{U}_{pwr}^K\right)^T$, where $\mathbf{U}_{pwr}^K$ consists of the first K of the left singular vectors. The projection rank K is a configurable parameter.

3. Apply the obtained projector $\mathbf{P}$ to the vectorized sensor covariance matrix $vec\left(\mathbf{C}_x\right)$, to emphasize the contribution of source powers and reduce the contribution of correlations between them. As a result, we obtain a new covariance matrix: $\widetilde{\mathbf{C}}_x = vec^{-1}\left(\mathbf{P}\cdot vec\left(\mathbf{C}_\mathbf{x}\right)\right)$.

4. Since the projection procedure does not guarantee that the resulting matrix retains the property of positive definiteness required of the covariance matrix, we propose to replace the negative eigenvalues of the new matrix by their absolute values.

   Thus, the final covariance matrix is equal to $\widetilde{\mathbf{C}}_x^{abs} = \widetilde{\mathbf{E}}|\widetilde{\mathbf{\Lambda}}|\widetilde{\mathbf{E}}^T$, where $\widetilde{\mathbf{E}}$ и $\widetilde{\mathbf{\Lambda}}$ — matrices of eigenvectors and eigenvalues for $\widetilde{\mathbf{C}}_x$.

5. When calculating the coefficients of the spatial filter of the adaptive beamformer, we use the new covariance matrix $\widetilde{\mathbf{C}}_x^{abs}$ instead of $\mathbf{C}_x$.

2.1.4 wReciPSIICOS technique

The projection proposed in the second method allows to project the vectorized covariance matrix of the sensors onto the orthogonal complement of the K-dimensional source correlation subspace $\mathcal{S}_{cor}^K$, which is defined by the linear span of vectorized cross products of source topographies $vec\left(\mathbf{g}_i\mathbf{g}_j^T + \mathbf{g}_j\mathbf{g}_i^T\right)$, $i, j = [1, \ldots, N]$. However, in order to preserve as much as possible the contribution of the source powers, we apply this projection in the whitened space with respect to the subspace of the source powers $\mathcal{S}_{pwr}^K$.

The algorithm consists of the following steps:

1. Compose matrix $\mathbf{G}_{cor}$: use vectorized symmetric sums of external products of source topographies as columns i and j, $vec\left(\mathbf{g}_i\mathbf{g}_j^T + \mathbf{g}_j\mathbf{g}_i^T\right)$ and calculate $\mathbf{C}_{cor} = \mathbf{G}_{cor}\mathbf{G}_{cor}^T$.

2. Compose a matrix $\mathbf{G}_{pwr}$, similar to the previous method, from the vectorized autoproducts of topographies. We obtain the matrix $\mathbf{C}_{pwr} = \mathbf{G}_{pwr}\mathbf{G}_{pwr}^T$.

3. Using the spectral decomposition $\mathbf{C}_{pwr}$, calculate the whitening operator $\mathbf{W}_{pwr}$ for the subspace $\mathcal{S}_{pwr}$:

$$\mathbf{W}_{pwr} = \mathbf{E}_{pwr}\mathbf{\Lambda}_{pwr}^{-1/2}\mathbf{E}_{pwr}^T, \tag{2}$$

where $\mathbf{E}_{pwr}$ — the matrix of eigenvectors of the matrix $\mathbf{C}_{pwr}$ and the diagonal matrix $\mathbf{\Lambda}_{pwr}$ contains corresponding eigenvalues.

4. Apply the whitening transform to the matrix $\mathbf{C}_{cor}$: $\mathbf{C}_{cor}^w = \mathbf{W}_{pwr}\mathbf{C}_{cor}\mathbf{W}_{pwr}^T$.

5. Apply the spectral decomposition to the obtained matrix:

$$\mathbf{C}_{cor}^w = \mathbf{E}_{cor}^w\mathbf{\Lambda}_{cor}^w\left(\mathbf{E}_{cor}^w\right)^T \tag{3}$$

6. Obtain a projector in space orthogonal to the source correlation subspace $\mathcal{S}_{cor}$, operating in space whitened with respect to $\mathcal{S}_{pwr}$:

$$\mathbf{P} = \mathbf{W}_{pwr}^{-1}\left(\mathbf{I} - \mathbf{E}_{cor}^{wK}\left(\mathbf{E}_{cor}^{wK}\right)^T\right)\mathbf{W}_{pwr}, \tag{4}$$

where $\mathbf{I}$ — unit matrix, $\mathbf{E}_{cor}^{wK}$ — matrix of first K eigenvectors of matrix $\mathbf{C}_{cor}^w$, $\mathbf{W}_{pwr}$ — whitening matrix.

7. Apply the obtained projector $\mathbf{P}$ to the vectorized sensor covariance matrix $vec\left(\mathbf{C}_x\right)$ to project it orthogonally to the source correlation subspace:

$$\widetilde{\mathbf{C}}_x = vec^{-1}\left(\mathbf{P} \cdot vec\left(\mathbf{C}_x\right)\right) \tag{5}$$

8. Just as for the previous method, the applied projection does not guarantee that the resulting matrix $\widetilde{\mathbf{C}}_x$ will be positively determined, so we propose to replace the negative eigenvalues by their absolute values:

$$\widetilde{\mathbf{C}}_x^{abs} = \widetilde{\mathbf{E}}|\widetilde{\mathbf{\Lambda}}|\widetilde{\mathbf{E}}^T, \tag{6}$$

where $\widetilde{\mathbf{E}}$ и $\widetilde{\mathbf{\Lambda}}$ — matrices containing eigenvectors and eigenvalues $\widetilde{\mathbf{C}}_x$.

9. Use the new covariance matrix $\widetilde{\mathbf{C}}_x^{abs}$ instead of the original $\mathbf{C}_x$ to calculate the adaptive beamformer weights.

2.1.5 Key results

The properties of the two proposed algorithms, ReciPSIICOS and whitened wReciPSIICOS, were investigated first with realistically simulated data and then on real MEG data.

Simulation results

For each of the Monte Carlo simulations, we randomly selected a pair (symmetrical in different hemispheres) or a triplet (random, but no closer than 4 cm to each other) of sources and then modeled one of two cases: sources activated with strongly correlated time series, with weak correlation, or independently. We added realistically simulated noise to the target activity, which was created by activating 1000 non-target sources with a given signal-to-noise ratio. Non-target sources were randomly selected for each trial. Then, in order to compare the results of the proposed methods with the classical ones, for each of the simulations the source activity was reconstructed by each of the four methods: reciPSIICOS, whitened wReciPSIICOS, MNE, and LCMV beamformer.

Typically beamformers are applied to data under the assumption of a small number of active target sources, so the study presents the results of computational experiments with 2 and 3 sources in Monte Carlo mode, that is, with an arbitrary choice of three locations and with different degrees of source activity correlation. The method demonstrated high robustness. In addition, the noise generated by non-target sources adds additional complexity and is another indicator of the robustness of the method.

We evaluated the quality of the solution using three metrics: 1) the average distance from the maximum of the recovered activation to the generated true source (localization bias), 2) the average radius of activity spread in the space around the maximum (spreading area), and 3) the proportion of computational experiments with successful detection of all true sources (all 2 or 3 sources found, detection ratio). We evaluated the distribution of these metrics for different values of the signal-to-noise ratio in the data, as well as for different contributions of the artificial error that were added to the forward problem matrix. To make the simulation more realistic, we generated activity from a denser cortical model than reconstructed.

Two symmetrical sources

- We have plotted curves showing the dependence of the three listed quality metrics (bias, spreading area, proportion of complete detections) on the signal-to-noise and error levels in the forward model matrix for synchronous and asynchronous sources and four methods for solving the inverse problem: ReciPSIICOS, wReciPSIICOS, MNE, LCMV.
- In the case of modeling asynchronous sources, both of our proposed ReciPSIICOS and wReciPSIICOS methods retain high spatial resolution of the LCMV beamformer and show similar metrics to it: they allow us to obtain a compact solution (with a maximum radius of about 0. 5 cm) with a small bias relative to the simulated location (about 1 cm), explained by the use of a more sparse cortical model for source recovery, as well as the high proportion of experiments in which all sources were found (about 95 %).

- In the case of synchronous sources, as expected, the LCMV beamformer demonstrates the effect of signal cancellation and tends to find activation only in one hemisphere. The values of the observed metrics are significantly degraded compared to the asynchronous case: the bias is about 6 cm, the spreading area is about 2.2 cm, and the ratio of experiments in which all sources are found is about 5 %.
- At the same time, ReciPSIICOS and wReciPSIICOS are also sensitive to the appearance of correlated sources, but much less. The values of the metrics are slightly inferior to the asynchronous case: the bias is approximately 1.2 cm and the spreading area is approximately 0.7 cm. The fraction of computational experiments with successful detection of all sources differs slightly for the two methods as the signal-to-noise ratio increases: for ReciPSIICOS it reaches 80 %, and for wReciPSIICOS it is about 70 %.
- The developed ReciPSIICOS and wReciPSIICOS methods are less sensitive to errors in the forward model operator than the classical LCMV beamformer.
- Quality of source reconstruction using distributed MNE solution does not depend on the presence or absence of correlation between sources, but in all cases is inferior to other methods on all three metrics.

Three synchronous sources

- In the case of three strongly correlated sources, the whitened wReciPSIICOS shows the best recovery quality: in 60% of all computational experiments it allows to find all three sources, and in almost 100% at least two of them. The resulting source activations are very focal.
- ReciPSIICOS shows a quality similar to MNE, and inferior to wReciPSIICOS. All three sources are detected only 40% of the time, the bias and spreading area of the activation is larger than in the previous case.
- LCMV shows the same dramatic deterioration of the metrics as in the case of two correlated sources. The method is unable to detect three sources, because the resulting activation maps are too smeared.

Three moderately correlated sources

- In this case, ReciPSIICOS shows the same high quality as the whitened wReciPSIICOS. By all metrics the methods are superior to the classic MNE and LCMV.

Real data analysis results

To test the proposed algorithms on real data, we used two sets of MEG data. In each of them subjects participated in experiments with auditory stimuli. The advantage of such data for us is that the auditory system is sufficiently well-studied and we can predict what the final solution on the sources should look like.

In addition, the auditory system is involved in more complex mechanisms than just primary perception of sounds, for example, we have studied the phenomenon of neuroplasticity by presenting auditory stimuli in various tasks. Previous studies in both humans and animals have demonstrated remarkable results of cortical plasticity induced by some kind of experience. In our work [34], we studied whether the widely used monetary incentive delay task, MID alters the neural processing of stimulus signals that encode expected monetary outcomes. We used a novel auditory version of the oddball paradigm in which participants responded to acoustic cues that encoded expected monetary losses. To investigate brain plasticity induced by the task, we encoded the loss amounts as deviant auditory cues in the oddball paradigm. We conducted oddball sessions before and after two sessions of the MID task. During the oddball task, we detected a component of MMN, mismatch negativity, acting as an indicator of cortical plasticity. We found that two sessions of the MID task caused a significant increase in MMN for stimulus signals that predicted large monetary losses, especially when discrimination of monetary signals was necessary to maximize the amount of gain. Task-induced plasticity correlated with learning-related neural activity recorded during the MID task.

Reflecting the mismatch between received and predicted outcomes, reward prediction error, RPE plays an important role in learning in a dynamic environment. A number of studies have suggested that the feedback related negativity, FRN, component that is known to occur when unexpected outcomes are obtained encodes the RPE. Although FRN has been shown to be sensitive to the probability of receiving a reward, the effect of the size of the reward on FRN has yet to be clarified. In studies of the neural basis of outcome reward prediction, the MID task has proven particularly useful. In study [35], we investigated whether the FRN and dN200 components recorded during the auditory MID task were sensitive to the probability and size of rewards. The dN200 component was associated with updating information about the magnitude of the estimated outcomes. We showed that FRN was modulated by both magnitude and probability of outcomes during the auditory MID task, whereas no such effect was found for dN200. In addition, the dN200 component, which is associated with updating information about the magnitude of intended outcomes, correlated with the standard FRN, which is associated with a negative RPE.

Further analysis of the sources that are involved in the mechanisms described above requires the development of methods that can reconstruct the activity of correlated sources with high resolution.

Dataset 1

The first data set includes MEG recordings of two subjects who participated in sessions of passive listening to sounds with a frequency of 40 Hz monaural to the left ear. For each trial, we considered a latency of 250 ms after stimulus presentation as the point with the maximum amplitude of the evoked response. We expected to see bilateral activation in the primary auditory cortex: more amplitude in the contralateral right hemisphere and less amplitude in the left hemisphere.

- For both subjects, source reconstruction with ReciPSIICOS showed the result we expected: we obtained fairly focal activations located bilaterally in the primary auditory cortex, with greater amplitude in the right hemisphere.
- wReciPSIICOS results for both subjects were similar to ReciPSIICOS: bilateral activations were found, the amplitudes between hemispheres were correctly distributed, but the activations appeared more spatially distributed than the first method.
- LCMV for both subjects showed similar ipsilateral activation to ReciPSIICOS, but completely incorrect localization in the contralateral hemisphere. The amplitudes recovered with the LCMV beamformer were about 400 times lower than those recovered with ReciPSIICOS, a consequence of the signal cancellation effect.
- For the first subject, MNE reconstructed only activation in the right hemisphere. For the second subject, bilateral activations were obtained, but with a significant bias and too large a propagation area.

Dataset 2

The second set of data presents MEG recordings of one subject who listened sounds binaurally in the oddball paradigm: he was presented with a series of identical sounds with occasional inclusions of different frequency (deviant) sounds. In response to the deviant stimulus, the subject had to press a button with the index finger of his right hand. We solved the inverse problem for the MMNm component of evoked potentials [36]: the average difference between responses to deviant stimuli and responses to standard stimuli. The component found peaked at 159 ms after stimulus presentation.

- Using the example of a source from the primary auditory cortex, which for a given latency turned out to be highly active in both the ReciPSIICOS solution and the LCMV solution, we showed that the amplitude of the time series reconstructed with ReciPSIICOS is significantly higher than in the LCMV solution. We have shown that this effect cannot be explained by the difference in the norms of the obtained solution coefficients. At the same time, also the time series obtained with ReciPSIICOS shows a significantly prominent activation peak for the MMNm peak latency, while the time series reconstructed by LCMV does not have such a prominent peak.

- The activation map obtained with the LCMV beamformer highlights activity in the primary auditory cortex of the right hemisphere. Activity was also found in the left hemisphere, but weakly pronounced and significantly distributed throughout the cortex.

- ReciPSIICOS made it possible to reconstruct high amplitude activations in the primary auditory cortex bilaterally.

- Whitened wReciPSIICOS not only allowed us to reconstruct similar activity in the primary auditory cortex bilaterally, but also the activation of the left hemisphere motor cortex that we expected to see due to the motor part of the task. This result replicates the wReciPSIICOS result described above in the simulation of three synchronous sources.

- MNE reconstructed activity only in the left hemisphere, and it turned out to be too spreaded.

Based on all of the above results, we can say that the analysis of the properties of the algorithms on real data showed similar results to the analysis of model data. The LCMV beamformer is significantly sensitive to the presence of correlated sources in the data, whereas ReciPSIICOS and whitened wReciPSIICOS show high solution quality and allow finding focal bilateral sources with a much larger dynamic activation interval.

Thus, we can conclude that the methods proposed in this paper represent simple and efficient solutions that inherit the property of high spatial resolution of the beamformer, but increase its robustness to the presence of correlated sources in the data.

2.2 A traveling wave model for analyzing the local dynamics of interictal spike propagation

In this section we present a summary of [37], in which we proposed a new method for solving the inverse EEG/MEG problem, which uses the assumption of the wave nature of neuronal activity propagation as its basis. We investigated the properties of the method using realistic computational experiments. We then applied the proposed algorithm to interictal spikes in MEG recordings of patients with epilepsy. Although the following narrative is built around the application of the method specifically to epilepsy research, the proposed method can be used to study any neuronal processes that involve wave propagation.

2.2.1 Data model

In this paper we propose a methodology for a noninvasive study of the fine spatial and temporal structure of interictal spikes observed in the MEG data of patients with pharmacoresistant forms of epilepsy. We consider the interictal spike as an episode of traveling wave propagation.

We assume that the radial wave emanates from the generating source and propagates in N_d^* different directions along the cortical surface. Keeping in mind that the distance travelled by the wave depends on the speed of its propagation, we assume that the path lengths of all waves are equal to each other by the number of N_s nodes of the cortex which the wave has visited. Thus, the d-direction of propagation can be represented as a sequence of active cortical sources $\mathbf{p}_d = [\mathbf{r}_d^1, \ldots, \mathbf{r}_d^{N_s}]$, where $\mathbf{r}_i = [x_i, y_i, z_i]$ contains the coordinates of the source in three-dimensional space, $d \in [1, \ldots, N_d^*]$, and the first source is the same for all directions (the generating source).

The time series of activation sources from the set $\mathbf{p}_d$ form a matrix $\mathbf{S}^d$. To represent the propagation of the neural activity generating the discharge as a wave in space and time, we model the activation time series, which for subsequent sources are shifted in time relative to the previous ones. Having a direct operator $\mathbf{G}$ with fixed source orientation, the multichannel EEG/MEG signal, $\mathbf{X}$, can be represented as a linear combination of cortical traveling waves $\mathbf{W}_d, d \in [1, \ldots, N_d^*]$ projected into sensor space:

$$\mathbf{X} = \sum_{d=1}^{N_d^*} \alpha_d \mathbf{G}_d \mathbf{S}^d + \mathbf{E} = \sum_{d=1}^{N_d^*} \alpha_d \mathbf{W}^d + \mathbf{E}$$

The matrix $\mathbf{G}_d$ is formed from the columns of the direct operator matrix $\mathbf{G}$, corresponding to the source topographies from the path $\mathbf{p}_d$. The $\mathbf{E}$ matrix models non-related brain activity and additive sensor noise. The α_d coefficients correspond to the contribution of each propagation direction to the observed MEG activity.

2.2.2 «Basis» waves

For the data model presented above, we assume that the propagation of MEG activity can be represented as a linear combination of traveling waves in the sensor space. The basic idea of the methodology proposed in this paper is to generate patterns of traveling waves, which we call «basic» waves, and then to find their combination with the least number of terms that best fits to the MEG data.

Next, we describe the algorithm for calculating basis waves. For simplicity, we define the number of active cortical sources along each propagation pathway as equal to the number of observations made during an event: $N_s = T \cdot fs$, where T is the duration of the event in seconds, fs is the sampling frequency. In our computational experiments, we consider the case where the simulated activation time series for each of the N_s sources have a sinusoidal waveform and are shifted in time relative to their sequence from the starting point. For each direction of propagation, the source time series matrix $\mathbf{S}^d$ is formed from rows:

$$\mathbf{S}_i^d = 1 + cos\left(\frac{2\pi(t-k_i)}{N_s}\right), k_i \in [1, \dots, N_s], t = [1, \dots, N_s]$$

.

The source positions $\mathbf{p}_d = [\mathbf{r}_d^1, \dots, \mathbf{r}_d^{N_s}]$ in each case depend on the individual anatomy, the position of the source $\mathbf{v}_s = [x_s, y_s, z_s]$ and the wave speed. For each «basic»$>$ wave, we need to find a path on a graph with N vertices connected according to the adjacency matrix $\mathbf{A}$ defined by the 3-D model of the cortex. For a given initial position on the cortex with N_d nearest neighbors, we define N_d «basic» waves propagating in the directions of these nearest neighbors. For ease of analysis in practical applications, we do not add new vertices or edges to the graph corresponding to the cortical model. A limitation of this approach is the fact that the number of propagation directions depends on the density of vertices in the region under study and, in the case of adaptive meshes, on the local curvature. The latter makes sense, since the spatial resolution of the MEG correlates with the local curvature [3].

In this paper, we describe in detail the algorithm for generating propagation paths for the starting point $\mathbf{v}_s$. We generate sets of «basic» waves for different propagation velocities: from 0.3 to 1.5 m/s.

In addition to radial waves, we also considered a spherical wave propagating simultaneously in all directions and consisting of a sum of radial waves, but our tests on model and real data showed that spherical waves are not selected by the algorithm as participants in the optimal combination.

2.2.3 Optimal combination of traveling waves

Once the «basic» waves have been generated, the next stage of analysis is to find the combination that best describes the observed MEG data. Based on physiological assumptions, the desired combination should contain only a few «basic» waves corresponding to several dominant propagation directions. Therefore, we look for the most sparse solution that describes the data and corresponds to a small number of well-defined dominant propagation directions.

To find the contribution of each precomputed «basic» wave to the MEG data, we used the LASSO [38] method, with the additional restriction that the LASSO coefficients must be positive. Since we are considering a multichannel problem, we vectorized the data matrix $\mathbf{X}$ and «basic» waves on the sensors. The optimization problem is formalized in the following:

$$\min_{\alpha_0,\ldots,\alpha_{N_d}} \left\| vec(\mathbf{X}) - \sum_{d=0}^{N^d} \alpha_d \cdot vec(\mathbf{W}_d) \right\|^2 + \lambda \sum_{d=0}^{N_d} |\alpha_d|$$
$$\text{subject to } \alpha_d \geq 0, d = 0, \ldots, N_d$$

The main advantage of this method is that due to the non-smooth regularization term with a L_1 norm penalty, the selection of features is performed so that the coefficients of uninformative propagation directions are equal to zero.

This procedure is then applied to all sets of generated basis waves with two parameters: propagation velocity and wave onset timepoint. The best solution is chosen according to the R^2 metric (i.e., the percentage of explained variance).

An important issue in the generation of «basic» waves is the detection of the very first source initiating the wave propagation. We determine the region of interest (ROI) in a first approximation using the RAP-MUSIC [39] dipole fitting algorithm. To improve the accuracy of the solution, we scan the ROI, using the cortical nodes that fall there as starting points, and compare the solutions using the R^2 metric.

2.2.4 Key results

In this paper, we propose a methodology for noninvasive investigation of the fine spatiotemporal structure of interictal spikes observed in MEG data from patients with pharmacoresistant forms of epilepsy. We studied the properties of the algorithm in realistic computational experiments. We then used the developed algorithm to analyze the local distribution of interictal spikes of patients with epilepsy. Preliminary results from patient data demonstrated that spikes coming from the epileptogenic zone exhibit a higher quality of wave model fitting than discharges from other regions. We believe that information about the spatiotemporal dynamics of interictal activity propagation in the future may be useful for planning a gentler surgical intervention.

In the present work, we considered in both model and real data only the case of focal epilepsy, assuming that the interictal spikes is generated by a well localized cortical region and further spreads locally, engaging the running wave mechanism. We did not consider the case of generalized interictal spikes, which often involve deeper brain structures, because it is in the scenario of focal epilepsy that the application of the developed algorithm makes practical sense, making it possible to obtain additional information for localizing the epileptogenic zone.

Simulation results

Computational Monte Carlo experiments were calculated for three signal-to-noise levels: values 1, 2 and 3. We constructed ROC curves showing how successful the proposed algorithm is in detecting traveling waves. To construct these curves, we used 300 Monte Carlo tests in which the wave propagation was set to a randomly uniformly chosen propagation rate from the options considered, and 300 tests in which only static activity was simulated without propagation in space. The corresponding area under the curve (ROC AUC) values are 0.78, 0.95, and 0.97, which means that the proposed method successfully separates propagating and static activity at a reasonably high signal-to-noise ratio.

Next, we evaluated the quality of the simulated propagation speed reconstruction. For SNR = 1, the algorithm tends to significantly overestimate the propagation velocity compared to the true value: the reconstructed velocities do not match the true value, except for the highest propagation velocity. For SNR = 2 there are still many errors in the velocity determination, but the absolute difference between the estimated and actual values is much lower than for the previous case. For SNR = 3 the estimated value coincides with the actual velocity or with the closest to it. It is important to note that errors in the velocity estimate are unavoidable even for the high SNR values because of the error we introduce in localizing the starting point and because of the use of a more sparse cortical model to solve the inverse problem. Given that we consider the propagation time as fixed, in case the initial starting point of the wave found by the algorithm is shifted relative to the actual one towards the end point of the propagation path, the speed will naturally appear underestimated. Conversely, if the starting point is shifted in the opposite direction from the end of the path, the speed will be overestimated. The higher the SNR in the data, the smaller these errors are.

We then estimated the errors in the estimated propagation direction. The error was calculated as $1-cos(\phi)$, where ϕ is the angle between the actual and estimated principal propagation directions. The values of this metric range from zero to one. For all SNR levels, most errors are less than 0.1, and all errors tend to decrease with increasing signal-to-noise ratio.

Although the proposed method successfully finds traveling waves and reconstructs their anatomical pathways, it is still subject to errors due to (1) uncertainties in the estimation of the wave onset timepoint and (2) inaccuracies in the parameterization of the cortical surface. The errors occurring for the first reason can be reduced by selecting high-amplitude spikes for analysis. The second problem can be solved by performing a more accurate brain scan (7T MRI).

Real data results

We used real MEG data from three patients with epilepsy: 10-minute MEG recordings during sleep. For automatic detection of interictal spikes, we used the method [40], which is based on the independent component analysis (ICA). Then, for each of the events found, we selected the corresponding current dipoles using the RAP-MUSIC algorithm [39]. The localization of the sources generating the found events on the cortex allows us to assess how physiologically plausible the automatically detected events are. We used 0.97 as the threshold for the subspace correlation metric, and all events for which RAP-MUSIC found a lower correlation were removed from subsequent analysis.

The proposed algorithm was applied to each interictal spike found separately. We then applied a simple deterministic clustering algorithm based on the proximity between the retrieved points to combine all sources into dense clusters with radius no larger than 1 cm, each containing at least ten dipoles. ASPIRE parameters were found empirically and fixed for all patients. Despite the fact that the described automatic detection procedure was run separately for the gradiometers and magnetometers, the resulting clusters detected were approximately the same. We applied the proposed method to each detected interictal spike and aggregated the resulting R^2 values based on their cluster membership. Since the goal of this analysis is to find a qualitative but simple fit of the interictal spike, another important factor is the number of propagation directions in the optimal solution. Analysis of patient data revealed variability in the fit of the wave model depending on specific discharges. A wave model with a choice of only a few dominant directions is appropriate only for a fraction of the discharges analyzed. We calculated fractions of discharges with an explanation quality of at least 0.6 for each cluster found for the three patients.

In all three data sets analyzed, the clusters found differ in the percentage of discharges well explained by the traveling wave model. Interestingly, the areas with the highest percentage of well explained spikes for Patient 1 and Patient 2 coincide with epileptogenic foci that were independently identified by neurosurgeons. In the case of Patient 1, the epileptogenicity of the foci found was also confirmed by a two-year follow-up of the patient after surgery. Information about the location of the epileptogenic area in Patient 3 is not available because surgery was not performed. These results are consistent with previous observations that interictal spikes in the epileptogenic area have a stable direction of propagation [26].

2.3 Automatic detection method for irritative zones in MEG data of patients with epilepsy

This section provides a summary of [40] work. In this work, we propose a method of automatic detection and clustering of clinically significant events in the data, which requires minimal user involvement and involves the possibility of visual inspection of the resulting clusters by an expert. The analysis consists of two main steps: first, selection of potential candidates for interictal spikes and [41] dipole fitting; and second, validation of found events based on the results of spatiotemporal clustering of sensor records around the found peaks [42].

We applied the proposed algorithm to the MEG data of seven patients who were seizure free as a result of successful surgical intervention. Visual inspection of the MEG recordings by experts, as well as information about the area removed during surgery, was available for the patients. We performed the proposed analysis separately for gradiometers and magnetometers: a set of clusters was formed for each sensor type, and for each cluster a list of events associated with it. After a cluster was formed, the averaged event template was used to localize the irritated area.

2.3.1 Search for potential interictal spike events

The advantageous difference of our method from the currently existing ones is the fully automatic analysis of the MEG record, implying the participation of an expert only at the final stage to verify the results. The independent component analysis, ICA based method is supplemented by the implementation of criteria for automatic selection of the component responsible for interictal activity. To search for candidate interictal events, we first decompose the MEG data into independent components using the fastICA method. We limited the number of independent components to twenty. Among the first ten independent components, sorted by percentage of variance explained, we selected those that corresponded most to the «spike» pattern. Such components were characterized by a high coefficient of kurtosis (from 1 to 10) and also by a high degree of component fitting with the dipole model (degree of «dipolarity» of the component). For magnetometers, the threshold for the degree of explanation by the dipole model was 80%, for gradiometers 60%. If the degree of fit exceeded 95%, such component was selected regardless of the value of the kurtosis coefficient. Approximation with current dipoles was performed using the MUSIC [39] method.

Then, in the time series of selected independent components, we distinguished time samples with peak activation. For this purpose, the data were filtered in the frequency band from 20 to 90 Hz. In addition, we transformed the time series of independent components using the preprocessing.RobustScaler() method from the sklearn library, in order to bring all the series to the same amplitude. Next, the peaks were found using the signal.find_peaks() method from the scipy library. We automatically lowered the threshold for detection until at least 300 peaks were found in each patient. We allocated intervals of -20 to 30 ms around the peaks found in the data and further localized them using the MUSIC algorithm[39]. We limited the frequency of occurrence of the interictal spike so that the interictal interval was greater than 0.5 seconds. In the case of overlapping candidates at such an interval, we chose the event for which the quality of the dipole fitting was higher.

2.3.2 Detected events validation

We used the convolutional sparse coding, αCSC paradigm to validate the found events. We used a multivariate [42] model, which effectively reflects the fact that the activity of each source is reflected on a whole set of MEG sensors. A multichannel record $\mathbf{X}_{[M\times T]}$, where M is–the number of sensors and T is–the number of time samples in the record, is decomposed into a set of k patterns with a spatial pattern $u_{k[N\times k]}$ and a temporal pattern $v_{k[k\times t]}$, where t is–the number of time samples in one event. The closeness of each point to the k-pattern is determined by a sparse activation vector $z_{k[k\times T]}$, which consists of a small number of non-zero positive elements. The optimization problem for finding patterns looks like this:

$$\min_{u_k,v_k,z_k} \sum_{m=1}^{M} \frac{1}{2} \left\| \mathbf{X} - \sum_{k=1}^{K} z_k u_k v_k^T \right\|^2 + \lambda \sum_{k=1}^{K} |z_k|$$
$$\text{subject to } \|u_k\|^2 \leq 1, \|v_k\|^2 \leq 1, z_k \geq 0$$

The αCSC algorithm produces spatiotemporal patterns represented by the triplet u_k (the weight of each sensor), v_k (the temporal trend) and the activation vector z_k, which determines the proximity of each temporal point in the MEG data to the pattern. To assign an event to a template, we set the threshold to 7 median absolute deviations (*mean absolute deviations, MAD*) and then decrease it until at least 15 events fall into the template or the threshold reaches 1.5 MAD. Thus, each template is associated with a set of events with similar spatiotemporal characteristics.

The quality of the cluster built around each template was evaluated using three metrics: the quality of the spatial pattern fit u_k; the average correlation v_k with the epoch time series on the sensor with maximum u_k; and the number of events in the cluster (flag, 1 for 20 or more pieces). Each of these three metrics is scored between 0 and 1, and the average value forms the score of the pattern. Templates for which the values of the metrics exceed the threshold of mean + 1 standard deviation of the score distribution have been selected into the template library.

In order to delineate the boundaries of irritative zones, we use the minimum norm algorithm, MNE [8], implemented in the MNE-Python [29] library. For the averaged events in each cluster, we calculated the covariance matrix for the interval [-0.5, 0.5] around the peak. The activation map for each spike was binarized: we assigned a value of 1 to each point where the activation exceeds 50% of the maximum activation, and 0 otherwise. The final binary map thus contains only points that are indicated by at least half of the individual digit maps. The binary activation map was smoothed to within 10 mm to delineate the area associated with spike activity.

Spatiotemporal clusters based on αCSC templates were used to estimate the irritative zones. For each template in the library, we localized the average event from all belonging to the cluster. Templates obtained from gradiometers and magnetometers were considered independently. For each template, an activation map was calculated for two time points: PEAK, i.e., the time count of maximum discharge amplitude, and SLOPE — the time count preceding the peak point, when the activity is still above the baseline and the spatial pattern provides a clear focus. For both time samples, SLOPE and PEAK, the activation map was threshold-filtered at 50% of the maximum activation value and converted into a binary activation map. For each patient, we summarized the binary maps of all patterns. Sources that were indicated by more than half of the templates were selected and smoothed over a range of 10 mm. The resulting activation map delineated the predicted irritative zone.

2.3.3 Key results

In this paper, we proposed a method for automatic detection of interictal spikes in MEG data of patients with epilepsy, which are then used to localize irritative zones. We applied the developed method to 20-minute sleep recordings of seven patients who were seizure free as a result of neurosurgical intervention. Our algorithm involves two steps: 1) searching for potential epileptiform events and 2) clustering them using convolutional sparse coding. For each cluster combining interictal spikes, we reconstructed its characteristic spatiotemporal pattern.

For the seven patients analyzed, we identified 25 event patterns (16 by gradiometer and 9 by magnetometer). We automatically detected 549 discharges and calculated that the rate of discharge generation per minute averaged 2.41 with a scatter [0.9 - 3.6]. Each cluster included an average of 22.1 events with a spread [15.0 - 31.0].

We validated the results of our analysis by comparison with irritable areas identified by visual inspection as well as by comparison with the resection area along with the known outcome of surgery. Automatically recovered irritable areas overlapped with those recovered by visual analysis in six of seven patients. In the remaining patient, both automatically and visually restored areas did not overlap with the resection area, and for this patient, the surgical outcome matched the Engel IIB classification.

SLOPE and PEAK latencies of detected sources correspond to different spatial distribution of activity, and therefore different localization of the irritative zone. We compared the average distance from the localized irritative zones recovered by PEAK and SLOPE to the resection border and found that the irritative zone localized by SLOPE was significantly closer to the resection border (Wilcoxon test, $p = 0.01$). The distance from the resection border to the SLOPE-localized area was not significantly different from the distance to the area recovered by visual analysis (Wilcoxon test, $p = 0.31$). In all patients, the mean distance from the resection border was 8.4 ± 9.3 mm for visual analysis, 12.0 ± 12.0 mm for SLOPE, and 22.7 ± 16.4 mm for PEAK. Thus, the irritative zone recovered for both SLOPE and PEAK is relatively close to the resection border.

3 Conclusion

Due to fundamental limitations, the inverse problem of EEG and MEG is ill-posed and the search for a unique solution requires the regularization: the addition of constraints on the expected nature of the reconstructed activity. In this research, we have proposed three new methods for activation reconstruction on sources, in which regularization is chosen due to the physiological nature of the phenomena under study.

We have developed two methods that are modifications of the classical adaptive LCMV beamformer and, on the one hand, preserve its high spatial resolution but, at the same time, allow to recover synchronous activity of brain sources. The properties of the algorithms were investigated first with realistically simulated data and then on real MEG data recorded in auditory paradigms. The ReciPSIICOS and whitened wReciPSIICOS methods showed high solution quality and allowed reconstruction of focal synchronous sources, outperforming classical methods.

We also proposed a method for localizing the traveling waves and determining their parameters from noninvasive EEG/MEG recordings. We applied the proposed approach to analyze the dynamics of local propagation of interictal spikes in patients with pharmacologically resistant focal epilepsy. When MEG technology is used, paired with suitable inverse problem solving methods, we can gain insight into the anatomical pathways of the traveling waves. To regularize the inverse problem, we model interictal spikes as a superposition of traveling waves propagating in radial directions in all directions from the source. This model works reasonably well both on model MEG data and on data from patients with epilepsy, in whom wave patterns of activity propagation can be reconstructed for a portion of the interictal spikes occurring in a particular cortical region. Although the proposed method successfully finds traveling waves and reconstructs their anatomical pathways, it is still subject to errors due to (1) uncertainties in the estimation of the initial wave onset point and (2) inaccuracies in cortical surface parameterization. The errors occurring for the first reason can be reduced by selecting high-amplitude spikes for analysis. The second problem can be solved by performing a more accurate brain scan (7T MRI). However, not all spikes can be equally well explained by a wave model with few predominant propagation directions. These cases require more detailed further study.

Reliable identification of the irritative zone is a prerequisite for proper clinical assessment of patients suffering from pharmacoresistant form of epilepsy. Given the multidimensional nature of MEG data, visual analysis of epileptiform neurophysiological activity is time-consuming and can leave clinically relevant information undetected. We recorded and analyzed the interictal activity of seven patients with epilepsy (Vectorview Neuromag) who successfully underwent surgery (Engel $\geq$ II). We validated our approach by calculating the distance from the irritative area assessed with the proposed method to the border of the surgically removed area. The proposed analysis technique provides the basis for reproducible and unbiased analysis of MEG recordings in epilepsy.

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