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OPTIMAL METHODS FOR FUNCTIONAL CONNECTIVITY ESTIMATION IN MAGNETOENCEPHALOGRAPHY.

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Actuality of the work.

From the birth of the first civilizations to the present, the questions of how consciousness and reason are organized in man and other living beings continue to be key for us. It so happened that their reflection first took place within the framework of religious and then philosophical paradigms, which in Western European tradition significantly echoed and complemented each other.

The scientific approach to cognition was formed only relatively recently within the group of disciplines that include biology, neurophysiology, cognitive psychology and electrophysiology. Within these disciplines, the key to understanding the cognitive function of humans and animals in the broadest sense is the structure of the central nervous system and, in particular, the brain.

Interestingly, the cognitive mechanisms have not always been associated with brain function, even within the framework of materialistic description. For example, Aristotle considered the heart as the source of thought, and the brain was given only the role of a radiator, cooling the blood. Nevertheless, already in the era of classical antiquity Galen has formed the idea that it is the brain that is the source of thought, and thus the tool by which knowledge is realized. Then, it took more than one and a half thousand years for the idea to take root that the study of the central nervous system and its highest department - the cortex of the large hemispheres - can offer an answer to the fundamental question"what is the human intellect". To date, there is still no satisfactory answer to this question, and it will probably not appear soon. However, in the course of a long and difficult movement towards this Ultima Thule, our understanding of more applied things revolving around neurophysiology has been incomparably enriched. From a practical point of view, it is difficult to overestimate the importance of understanding the work of the CNS for medicine, however, not limited to it alone.

Today, along with the general blurring of interdisciplinary boundaries, neurosciences are increasingly linked to more technical and engineering disciplines. For example, in 1943, inspired by the architecture of neural ensembles of the living brain, McCulloch and Pitts created the first computational model of the neural network, thus creating a class of machine learning algorithms so popular today [1]. Brain-computer interfaces, which allow to form a control command based on the electromagnetic activity of the brain directly, are becoming increasingly popular today, which opens up completely new prospects for human integration with the machine.

In this regard, the development of methods related to the study of the structure and work of the brain, as well as the decoding of the signals generated by it are of extreme interest today. At the same time, over the last hundred years, thanks to a dramatic leap in the development of electronics, physics and computer science, the set of tools in the hands of a neurophysiologist has been significantly enriched. Today, the existing methods can be divided into invasive and non-invasive from the point of view of the need for surgery to perform measurements.

The first group includes intracranial encephalography — a method in which electrical potentials are recorded directly from the cortex of the large hemispheres. Shortcomings and advantages of this approach are obvious. The former primarily refers to the need for surgery to perform measurements, which significantly limits the ability of a neurophysiologist to obtain data for the study. In practice, such measurements on a person are possible only for patients who underwent brain surgery in connection with some neurological disease, usually epilepsy. During the operation, electrodes registering electrical activity are placed on the cortex to monitor brain activity after surgery. It is clear that the number of such data, as well as the possibility of conducting any complex cognitive experiments on patients who underwent brain surgery is very limited. However, the quality of the electrical signal recorded in the immediate vicinity of its source is incomparably higher than that obtained by recording the electroencephalogram from the scalp surface.

Non-invasive methods, on the other hand, provide a much more flexible tool for human brain research due to the lack of need for surgery. Structural neuroimaging techniques such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Diffusion Tensor Imaging (DTV) are used to study the anatomical organization of the brain and as an auxiliary tool in the analysis of neural cortical population activity. They allow non-invasive acquisition of static three-dimensional images of brain tissue. To study the dynamic activity of neurons, functional neuroimaging techniques are used, namely, — functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalogy (EEG), and magnetic encephalography (MEG).

Only the last two methods measure brain electrical activity directly, while fMRI and PET measure local blood flow, which changes relatively slowly, significantly limiting the temporal resolution of these methods. Thus, for EEG and MEG, the temporal resolution is $\approx$ 1ms, and methods that measure local blood flow allow only processes with characteristic times of about one second and slower. At the same time, oscillatory electrophysiological processes generated by brain tissue have characteristic times from 0.1 seconds and faster [2]. Thus, among all the analysis tools available today, *only EEG and MEG allow non-invasive recordings of relatively fast electrophysiological activity of the brain*, which makes them an indispensable tool for studying *oscillations* and their *synchronization* in the human brain.

The ability to generate oscillations or rhythmic current activity is an essential feature of neural populations. The nature of the emerging rhythms, as well as their functional purpose, remain a subject of study today, and there is no uniform, accepted by all viewpoint on this issue. However, the hypothesis that oscillations generated by different neural populations serve as a mechanism allowing various functionally specific areas of the brain to selectively exchange information with each other is widely accepted. In other words, it is assumed that oscillations are responsible for the *functional integration* processes. According to existing conceptions, functional integration of neural ensembles is carried out by synchronization of oscillations generated by these ensembles. At the same time, areas of the cortex, where rhythmic activity is synchronized, are able to transmit information more efficiently, while desynchronized areas, on the contrary, cease to exchange signals. This idea of organizing effective channels for information transfer between neural ensembles due to synchronization was named in the literature as «communication through coherence» [3]. In brief, oscillation synchronization is the mechanism that allows for the dynamic linking of functionally specific brain regions in a network to perform a specific cognitive task. The study of such networks, which arise and decay in the process of solving certain cognitive tasks in the brain, is now one of the central topics in the study of brain activity, both in typical development and pathology [4—7], [8; 9]. From the point of view of research into such networks, the concept of *functional connectivity* is distinguished, meaning statistical regularities in simultaneous activation (in the broadest sense) of various brain regions. At the same time, the conclusion that these brain regions worked synchronously is based on the calculation of a certain metric reflecting the degree of similarity of measured (or mathematically recovered) signals in these areas. Such metrics are called *measures of connectivity*.

Much in the field of functional connectivity has been done with the use of fMRI technology, but the aforementioned limitation of fMRI in the form of poor temporal resolution makes electrophysiological methods of measurement irreplaceable in connectivity analysis. Magnetoencephalography occupies a special place, which combined with methods of signal recovery on the cortex due to the higher accuracy of the forward model compared to the EEG provides a unique combination of less than a centimeter resolution in space and millisecond resolution in time [10—12].

In general, the assessment of connectivity on the basis of non-invasive electrophysiological data is a complex engineering problem, on which the scientific community has already spent a lot of effort. Over the past few decades, many methods for estimating functional connectivity have been developed and tested from standard approaches that include measures of signal synchronization in the time and frequency domain (such as correlation and coherence), to more sophisticated, often non-linear measures of connectivity [13—29]. None of the proposed measures, with their advantages and disadvantages, is, however, universal due to the continuing technical difficulties [30; 31].

One of the most significant problems encountered when evaluating functional connectivity is the so-called *signal leakage*, which is explained by the fact that the inverse problem for the EEG/MEG is ill-posed. In practice, this means that having a limited set of measurements it is impossible to unambiguously restore the configuration of the sources that generated the signal. This, in turn, means that it is impossible to completely unmix the signals recorded by the sensors, — signals from other sources will inevitably be mixed in each of the recovered ones. Consequently, all recovered signals will be to some extent similar to each other, even if the original signals showed no sign of synchronization. Therefore, the connectivity measures, being measures of similarity of signals, will show overestimated values. As a result, there is a problem of distinguishing between true synchronization and the one that is caused by fundamental constraints of noninvasive electrophysiology.

The first attempt to solve this problem was made in 2004 in the article by G. Nolte [19], in which the authors propose to use as a measure of connectivity a value called an imaginary part of coherence. To do this, each signal must first be transformed into a frequency domain, then for each pair of signals, the coherence function must be computed, and finally the imaginary part of coherence must be taken from the obtained value. The idea behind this method of evaluating connectivity is that the imaginary part of the coherence has a non-zero value only for signals with a non-zero phase difference, while the leakage effect always manifests itself as a false synchronization with zero phase delay, thus contributing only to the real part of coherence. Indeed, this approach significantly increases the robustness of the method to signal leakage. However, since the coherence function is normalized by the estimated signal power (which, being purely real values, are subject to the influence of the signal leakage) the final estimates of connectivity on the imaginary part of the coherence also, albeit to a lesser extent, spoilt by the effect of leakage.

This detail was brought to Stam's attention in 2007 in his article [24]. Stam suggested to use the average value of the phase difference sign of the two signals instead of an imaginary part of coherence to evaluate synchronization. Such a measure is very similar to the imaginary part of coherence, but the normalization (hidden in the operation of taking the imaginary part sign) is now done only by purely imaginary values, which do not depend on the signal leakage. Stam called his measure the phase lag index (PLI).

The next step in the evolution of the chain of methods based on the idea of an imaginary part of coherence is a measure called a weighted phase lag index (wPLI). It was described by Vinck and co-authors in his 2011 article. The motivation for developing the new connectivity measure was the fact that the PLI measure proved to be too unstable with respect to noise. The main drawback of the phase lag index, as well as its advantage over the imaginary part of the coherence, lies in the operation of taking the sign. The fact is that for noise sources randomly changing phase difference sign has too great an impact on measurements. To get rid of this shortcoming, Vinck suggested weighing the phase difference sign by the amplitude of the imaginary part of the corresponding cross-spectral coefficients. Thus, the contribution from noise sources of small amplitude is small, which makes the measure more stable.

The family of connectivity measures based on the imaginary part of coherence is not limited to the three approaches outlined. A similar idea, but from a slightly different angle, was applied in the article [32]. In this article, the authors use the correlation of envelopes of two narrowband signals as a measure of synchronization. The problem of signal leakage is solved in following way: two time series are reconstructed on the cortex, then one of them is projected orthogonally to the second, after which the envelopes are calculated and the correlation coefficient between them is obtained. This approach based on orthogonalization of time series turns out to be equivalent to taking an imaginary part of the corresponding cross-spectral coefficient.

All of the outlined methods, based on the imaginary part of coherence, however, have one significant drawback, namely — all of them are not sensitive to zero phase lag synchronization. As mentioned above, taking an imaginary coherence part is equivalent to removing the zero phase lag synchronization data. Practically, this means not only that it is impossible to detect networks synchronized with zero phase delay, but also a poor signal-to-noise ratio (SNR) for networks with low phase delay. Moreover, the closer this phase delay is to zero, the worse the SNR for a single pair of sources. Conversely, the closer the phase difference between two signals to $\pi/2$, the higher the SNR value.

Clearly, this uneven distribution of the method's detector characteristics over phase delays limits the researcher's capabilities. This fact is aggravated by the fact that zero phase synchronization seems to be a widely represented phenomenon in the organization of oscillatory brain activity, [33–35], which can be explained by the presence of a common input for two nodes of the network, or by their bidirectional interactions, [36].

For this reason, non-invasive electrophysiology nowadays has an acute need for a connectivity measuring instrument that, on the one hand, will be resistant to the signal leakage effect and, on the other hand, will be able to detect networks for the entire spectrum of phase delays.

An attempt to create such method was made in 2015 in the article [37]. In this article, the authors used a fundamentally different approach to combat the effect of the signal leakage. The idea of this method is to use information about the mutual location of signal sources and sensors to construct specific spatial filters that allow us to clear one source from a signal that came from another source for subsequent measurement of any synchronous index. The authors suggested using the correlation of envelopes as such an index. The structure of the proposed method is as follows in more details. First, the signals on the sensors are used to restore the signals on the sources. Then, one of the sources is fixed on the cortex. All other sources are spatially filtered from the activity that leaked from the fixed source. Then, the correlation of envelopes between the fixed source and all other sources is measured. To get the connectivity value for each pair of sources, you need to repeat the procedure by selecting each of the remaining sources as a fixed source. Finally, since the resulting connectivity matrix is generally asymmetric, the connector values for the (i,j) and (j,i) pairs are averaged. Such heuristics has been named by the authors of the article as geometric correction scheme (GCS).

GCS method conceptually was a serious advance, as now it is possible to detect networks with small phase shifts, remaining (at least in theory) outside the influence of the signal leakage effect. In reality, however, this correction method only partially eliminates this effect, since it does not take into account leakage from third sources when assessing connectivity. As an example, we can consider a situation where there are three powerful sources, no two of which have been synchronized. In this setting, despite the lack of synchronization, the GCS method will give high Connectivity values for all three pairs of links, because although for each pair the correction will clear the signals from the leakage into each other, the signal from the third source, leaking into each source of the pair, will create a common component in the recovered sources. As a result, the connectivity we measure for source pairs that are not synchronous, after the geometric correction for the source pair, will actually reflect the degree of leakage from the third source into each signal from the pair. Clearly, if the third signal is close to the first two, the leakage effect will be quite significant. As a result, for a large number of active sources, even a cleaned signal is extremely polluted, which significantly limits the applicability of GCS to practical tasks.

Thus, *there is still no method for estimating connectivities, which allows reliable detection of networks with low phase lags and at the same time free from the signal leakage effect*.

Modern practice of using conectivity measures in neurophysiological studies in the vast majority of cases follows one of two possible schemes. The first scheme assumes studying of neurophysiological effect in *sensor space*, i.e. the measure of connectivity chosen by the researcher is applied directly to signals recorded by electrodes. The second variant assumes transition to source space — first, possible sources of recorded electrophysiological activity on the cortex are estimated, and then this or that measure of connectivity is applied to these sources.

Obviously, the first option allows you to make only a very rough assessment of the localization of nodes of the restored networks, so it is often used only as a first approximation to the result. More interesting, though more complex conceptually and more computationally intensive, is the second option, which first evaluates the signal on the sources and then considers a measure of connectivity.

Evaluation of sources in noninvasive electrophysiology is an ill-posed inverse problem [38]: its solution could not be unambiguously determined. In other words, any electrophysiological measurements made with a limited set of sensors can be explained by the infinite number of configurations of electromagnetic activity sources located on the cortex. The vast majority of such configurations would be absurd in terms of physiology. Among the infinite array of solutions, it is necessary to choose one that on the one hand explains the observations well, and on the other hand — corresponds to the existing concepts of brain physiology.

Therefore, the solution of the inverse problem in noninvasive electrophysiology always requires the introduction of additional a priori information about the solution structure into the model. Not every method of solving the inverse problem can explicitly specify the point at which an additional assumption about the solution structure is made, but most of such methods (for example, [39—42]) can be described in terms of Tikhonov regularization [43], which allows to reduce the solution search task to minimization of the two-member functional: the first one — how well the solution explains the measured signal, the second one — how well it corresponds to the class of solutions that we consider «physiological». However, formalization of the «physiological» concept can involve a wide range of different assumptions about the structure of the solution — from the natural requirement of continuity in space and time (as in MNE, [39]) to information about the anatomical structure of the brain.

Source estimation in this setting is optimal from the point of view of minimization of the selected functional, but in the synchronous oscillations search task, source estimation is not an end in itself. Optimality of this estimation does not guarantee optimal estimation of sufficient statistics of synchronicity in the source space.

The two-step procedure for assessing connectivities generally provides suboptimal results in terms of evaluating the relevant statistics.

Optimal evaluation of the synchrony statistics in source space by observations requires consideration of generative models with formulation of a priori assumptions for networks instead of those for sources. In particular, it would be desirable to find such solutions to the inverse problem that explain the measurements by *minimum set of networks*. The motivation for this approach lies in the well-known principle of the Occam Razor — the explanation of the observed data should be as simple as possible. It is known that solutions of this type, i.e. those in which the number of individual structural elements explaining the data is minimal, are implemented using sparse regularization. However, it is not quite clear how to introduce such regularization in the framework of a two-step procedure.

Having in mind all the above, it can be concluded that today the procedure for assessing connectivity on the basis of non-invasive electrophysiological data on the one hand is still poorly developed and needs improvement (it is no coincidence that new methodological articles on the topic of assessing connectivities are regularly published), and on the other hand is a key tool for modern neurophysiology, following the shift of emphasis in the study of the brain from the activation of its individual areas to the interaction between them.

The goal The purpose of this study is, therefore, to develop a method for estimating connectivity that

- allows to estimate phase synchrony in conditions of mutual signal leakage
- is sensitive to networks with low phase lags
- optimal in terms of evaluating sufficient statistics for connectivity
- is capable of taking into account a priori information on the organization of phase synchronies.
- not sensitive to network level signal leaks

as well as its validation in application to simulated MEG data.

In order to achieve the set goal it was necessary to solve the following **tasks**:

1. Develop a method of signal leakage removal.
2. Explore the properties of signal cleaning techniques for networks with small and large phase shift; compare with the techniques described in the literature.
3. Develop a methodology for optimal evaluation of sufficient statistics for phase synchronicity.

4. Implement an estimation algorithm allowing the use of sparse regularization.
5. Develop code for numerical solution of the task of non-convex optimization
6. Develop a method to visualize the found networks.
7. Develop a methodology for generating data simulating brain activity.
8. Compare the detector characteristics of the developed method on simulated data on standard metrics (AUC-ROC, AUC-Pre-Rec)

The novelty

1. For the first time, the problem of connectivity estimation was considered in the source pair space
2. For the first time it was demonstrated that it is possible to clean the signal from the leakage effect by means of orthogonal projection operation.
3. For the first time the criterion of optimal signal leakage filtering for phase synchronization evaluation was formulated.
4. For the first time, the task of evaluating the cross-spectral density matrix in the source space was solved by the global optimization method.

Theoretical and practical significance. Theoretical importance is determined by the fact that for the first time was proposed an approach to combat the problem of signal leakage through the vectorization of the generating model of the cross-spectrum, as well as through methods of optimal filtering and global optimization.

Practical significance is based on the fact that the developed set of algorithms provides a new tool in the hands of a researcher-electrophysiologist. This tool makes it possible to study interactions of cortical structures, previously available for study only by invasive methods.

Methodology and research methods. Studies are based on the theory of inverse problems, the theory of estimation, methods of digital signal processing, optimal filtration, global optimization of non-convex functions, as well as work on methods of connectivity estimation in electrophysiology.

Main provisions for the defence:

1. A method has been developed that allows detecting phase-linked sources with near-zero phase delays from non-invasive MEG records. The essence of the method is to build a spatial filter that operates in the space of vectorized matrices of cross-spectral power density, which allows you to suppress the contribution of members responsible for the signal leakage effect that masks information about the interaction with the near-zero phase.
2. The optimality of the proposed filter in terms of removing the contribution of third sources to the phase connectivity assessment for a fixed network is shown.
3. Based on the global IrMxNE optimization method and the proposed filter, a leak-resistant method was developed at the networks and sources levels. The former is provided by the sparse properties of the IrMxNE method, the latter – by the properties of the developed filter.

The reliability of the obtained results is provided by theoretical calculations, results of numerical modeling, comparison with other methods of phase connectivity estimation as well as validation of the developed method on real data.

Publications and probation of the work.

The main results of the present work were reported on:

1. International conference "Methodological problems of cortex regions functional synchronisation assessment based on MEG/EEG data",
   Тема: *Globally-optimized power and shift invariant imaging of coherent sources (GO-PSIICOS)*
   Moscow, Russia, 2015.
2. International conference "Brain Connectivity Workshop 2015",
   Title: *GO-PSIICOS (Globally-Optimized Power and Shift Invariant Imaging of Coherent Sources)*,
   San Diego, USA, 2015.
3. International conference "Biomag 2016",
   Title: *Power and shift invariant imaging of coherent sources by MEG data*,
   Seoul, South Korea, 2016.
4. International conference "Biomag 2018",
   Title: *Oblique projection for phase shift invariant imaging of coherent sources*,
   Philadelphia, USA, 2018.
5. International conference "Biomag 2018",
   Title: *NeuroPycon: A python package for efficient multi-modal brain network analysis*,
   Philadelphia, USA, 2018.

Personal contribution into the main provisions for the defense. All results presented in the dissertation were obtained personally by the author. In preparing articles and reports, the author relied on the assistance of co-authors and the scientific adviser.

Publications. The main results on the topic of the dissertation are presented in the following printed publications.

Higher-level publications

1. *Ossadtchi A.* Phase shift invariant imaging of coherent sources (PSIICOS) from MEG data / A. Ossadtchi, D. Altukhov, K. Jerbi // NeuroImage. — 2018. — т. 183.
2. NeuroPycon: An open-source python toolbox for fast multi-modal and reproducible brain connectivity pipelines / D. Meunier [и др.] // NeuroImage. — 2020. — т. 219, October 2019.
3. Visbrain: A multi-purpose GPU-accelerated open-source suite for multimodal brain data visualization / E. Combrisson [и др.] // Frontiers in Neuroinformatics. — 2019. — т. 13, March. — с. 1—14.

First chapter

In the first chapter we formulate a methodological basis for studying connectivity with the help of the MEG and EEG, based on well-known and widely used today methods of solving the inverse problem and estimating connectivity for the MEG and EEG.

We begin by describing biological mechanisms of information exchange between neuron populations and describe the hypothesis of communication through coherence, according to which for efficient interaction of neuron populations must work in the mode of coherent oscillations. Further, we introduce a formal definition of the coherence function of the two signals generated by brain sources.

Since for non-invasive methods (MEG and EEG) we do not have direct access to the signals generated by the cortex, we consider the physical mechanisms of MEG/EEG signal generation that allow us to formulate the concept of forward operator — linear mapping, between the signal generated by the cortex and the signal recorded by the sensors. The forward operator allows us to formulate a generative model for non-invasive electrophysiology data.

Further, on the basis of the generative model, we describe a group of methods for solving the inverse problem and methods for estimating connectivity in source space based on it, which form the methodological basis for our proposed method of estimating connectivity.

Second chapter

In the second chapter we again consider the generative model of the MEG/EEG signal to formulate the generative model of the cross-spectral density matrix (cross-spectrum) on its basis. The structure of the cross-spectrum generative model allows us to explicitly point to the constituents responsible for the signal leakage effect in the recorded data — the effect, which significantly complicates the evaluation of functional connectivity and masks the synchronization with low phase lags.

To remove the sources of leakage signal, we vectorize the generative model of the cross-spectrum and build an orthogonal projection operator, which allows you to suppress the contribution of undesirable additives due to the special spatial structure of the three types of compounds included in the generating model of the cross-spectrum: compounds, generating signal leakage, compounds, carrying information about the interaction of sources with small phase shifts and compounds, carrying information about the interaction of sources with phase shifts close to $\pi/2$. To describe the spatial structure of these subdivisions, we introduce the concept of 2-topography. The proposed projection operation is the basis for the group of methods presented in this dissertation.

Then we generalize the projection operation on the model with free dipolar orientation and formulate the author's method of network discovery in source space (PSIICOS).

Then we consider the proposed method from the point of view of optimal filtration by introducing a formal definition of mutual signal leakage for two network nodes in the source space. We obtain the result that the proposed projection generates spatial filters in the space of 2-topographies, which minimize the mutual signal leakage for two points of the cortex.

We study the constructed filters from the point of view of spatial bias of estimation and offer a scheme of normalization which leads to unbiased estimation. Modification of the PSIICOS method with such a normalization scheme we call PSIICOS Unbiased.

The spatial filtering method obtained in this way allows localizing existing networks, but it does not allow to cut off the situation when there are no real interactions. The reason for that is absence of normalization for the evaluated metric of source interaction strength and, consequently, impossibility to select an objective threshold. To cope with this situation, we formulate a method of normalizing the estimated cross-spectral coefficients taking into account the signal leakage effect. We call the obtained method PSIICOS Normalized.

To cope with the effect of leakage at the network level, we describe a known in the literature evaluation method with mixed norm, which generates sparse solutions, and modify it to work in the network space using the proposed projection. The resulting method we call GO-PSIICOS.

Third chapter

To validate the proposed projection method, in this chapter we compare PSIICOS with a set of algorithms widely used in the neuroscience literature on a set of experiment simulations. The numerical simulation results show superior detector characteristics of PSIICOS compared to other methods used for comparison, especially for networks with low phase lags.

Further, based on the simulation data, we investigate the properties of the PSIICOS method. In particular, we show that the detector characteristics of the algorithm indeed show evenly high quality solutions for the entire phase delay range. In addition, we investigate the effect of the projection on the 2-topographies of the imaginary and real parts of the cross-spectrum, as well as signal leakage and show that the proposed projection only slightly weakens the contribution of the real part, while seriously suppressing the 2-topographies of the signal leakage. We also study the impact of the projection rank on the ratio of suppression of power in the subspaces under consideration and based on this analysis, we formulate recommendations for the selection of the projection rank. Finally, we investigate the effect of forward model inaccuracies on the solution quality of the PSIICOS algorithm and show that the solution quality drops only slightly for noise levels close to real conditions.

Then we demonstrate the work of the PSIICOS method on real data in the task of motor imagery. We show how the method can be applied to the analysis of experimental data and how the problem of inability to select a threshold for the method can be solved using a bootstrap procedure. We analyze the networks found on real data in terms of physiological plausibility.

We then compare the PSIICOS Unbiased method with the original method, and by applying both methods to the simulation data, we show that normalizing the filters leads to a better algorithm.

In the next section we examine the PSIICOS Normalized method and show that using normalization for cross-spectrum elements allows us to cut off the found source pairs that are isolated only due to the large amplitude, but not phase synchronization.

Finally, we demonstrate the application of the GO-PSIIOCS algorithm and show that this algorithm really allows us to get rid of the effect of signal leakage at the network level, and is able to track emerging and fading networks in the dynamics.

The main results of the work are given in the **conclusion**:

1. A review of studies of changes in brain functional connectivity in various pathologies was conducted.
2. A method of cleaning EEG and MEG data from signal leakage was developed, on the basis of which a family of algorithms for phase synchrony estimation was developed, allowing to find networks with close to zero phase delays.
3. The objective of phase synchrony estimation under conditions of signal leakage was formulated and solved as a problem of optimal filtering.
4. An algorithm allowing to find networks with close to zero phase delays, optimal in the global sense and allowing to cope with the problem of false positives of the second kind caused by the signal leakage was proposed.
5. A numerical study of the properties of the proposed projection has been carried out, showing that the developed method allows to suppress the contribution of the subspace of the signal leakage into the matrix of cross-spectral power density estimated on the sensors.
6. Numerical study of the projection method properties showed that the developed method allows to find networks with close to zero phase delays under conditions of non-invasive MEG measurements, which are characterized by a significant signal leakage between sources
7. Comparison with currently available algorithms for estimating connectivity from non-invasive simulation data showed a significant advantage of the proposed network detection technique in conditions of small phase delays.
8. The application of the method of signal leakage cleaning to real data allowed to detect physiologically plausible networks, which cannot be detected by other methods.
9. A numerical study of the influence of the rank values of the proposed projection on the properties of the algorithm was carried out, which made it possible to obtain heuristics for selecting the rank.
10. Numerical study of the influence of forward model inaccuracies on the solution quality of the proposed algorithm has shown that characteristic for real recordings error ranges in the estimation of forward model have little effect on the quality of the obtained solutions.

11. A package of utilities in the MATLAB environment was created to accomplish the tasks, which includes tools for generating test data, visualizing the spatial and temporal structure of networks, and finally, software implementations of developed algorithms. PSIICOS, PSIICOS Unbiased, PSIICOS Normalized implemented in PSIICOS, GO-PSIICOS implementated separately as GO-PSIICOS, auxillary utilities and visualisation tools‘ implementation can be found at utils_psiicos
12. The developments obtained in the course of work on this dissertation were implemented in the Visbrain and Neuropycon software packages available for public use.

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