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Kurmukov Anvar Ildarovich

Hierarchical structure of brain connectomes

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Academic Supervisor: Leonid E. Zhukov, PhD, Professor, National Research University Higher School of Economics.

Introduction

The scientific problem, based on the solution of which the dissertation research is directed, based on the almost complete absence of informative neuroimaging biomarkers of the brain (both neurodegenerative and psychiatric), which would make it possible to identify the pathological process precisely, build a predictive trajectory of the course of diseases and evaluate the effectiveness of treatment, including pharmacological effects. Such biomarkers are necessary for solving personalized diagnostics, effective treatment, and prevention of disease development. The use of non-invasive neuroimaging data when searching for such biomarkers looks quite natural [1]. The task, however, is complicated by the systemic nature of brain diseases, primarily psychiatric, when in most cases it is impossible to localize the pathological substrate clearly and unambiguously link the changes with the course of the disease. For this reason, modern research tends to analyze pathological patterns at the level of network structures of the brain, representing not only individual regions of the brain but also their structural-functional connections [14]. At this level, the construction of biomarkers of brain diseases requires work at the junction of image processing (analysis of neuroimaging data), modern predictive modeling, and analysis of graphs and network structures. In the dissertation research, algorithms were developed to analyze brain networks' modular structure [10], acting as biomarkers of pathological processes. In the future predictive models based on the developed algorithms will allow for a personalized forecast of the development of brain diseases with automated analysis of non-invasive neuroimaging data.

The relevance and importance of the research

The relevance of this study is due to the importance of the early prediction of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. According to a meta-analysis conducted by the international organization Alzheimer's Disease International (ADI), as of 2015, people living with Alzheimer's disease reach 46.8 million. Every 20 years, this number doubles; thus, it is expected that by 2050 it will reach 131.5 million people [35]. According to the same report, global costs associated with dementia reach $ 818 billion (US) in 2015 alone; in 2018, these costs amounted to $ 1 trillion (US) [36]. Recently, it is believed that the use of various biomarkers obtained from neuroimaging data, such as MRI and PET (positron emission tomography), should play an essential role in the diagnosis of dementia in general and Alzheimer's disease in particular [25]. For example, it has been shown that the use of such a simple biomarker as brain atrophy, measured by structural MRI, serves as a very accurate predictor for the early diagnosis of Alzheimer's disease [29]. For example, many works set themselves the following task: to predict whether the transition from an earlier stage of the disease to a later one will occur at a particular time interval. This formulation allows using modern machine learning methods and solving the so-called classification problem (if the time interval is fixed) [24], [40], or regression (if not). It is necessary to have a sufficient amount of labeled longitudinal data to solve this task. The markup should contain accurate information about the stage of the disease for each time observation. Note that this formulation differs from the simple task of classifying pathology from the norm (for example, Alzheimer's versus not Alzheimer's) in that the prediction is made about the patient's condition in the future and not at the moment. Thus, the solution to this problem may be advisable not only from a scientific but also from a clinical point of view. The

study of the development (disease progression) of neurodegenerative diseases plays a critical role in early diagnosis and treatment strategies [15], [32].

The purpose and objectives of the study

The task of the dissertation research is to develop algorithms for the data mining of non-invasive neuroimaging of various modalities, allowing, based on the reconstruction of anatomical and functional network structures of the brain [41], to assess their hierarchical modular organization [3] and build predictive models in the field of diagnostics and prognosis of the course of neurodegenerative and psychiatric diseases ... From a practical point of view, we are talking about the construction of clinically informative biomarkers to solve the problems of personalized diagnostics, plan therapy, and prevent brain diseases. From a scientific point of view, new results have been obtained that develop the most promising approaches to predictive modeling based on multimodal neuroimaging data. Following the generally accepted definition, by a biomarker, we mean an objectively measurable characteristic that can be considered as an indicator of normal biological processes, pathogenetic processes (in this case, brain diseases), or pharmacological responses to therapeutic interventions [31]. The attention of this work to the network structures of the brain is due to the systemic nature of disorders in the structure and functioning of the brain, which is characteristic of many pathologies, primarily in psychiatry.

For this reason, in modern research, the connectomic approach [5] is of increasing interest, within which the human brain is analyzed as an integral network with a specific structure. A connectome is a graph in which the vertices correspond to brain regions, and connections indicate either the presence of anatomical tracts between the corresponding zones or their tendency to be

jointly activated in the process of functioning. Fig. 1 shows an example of a human connectome.

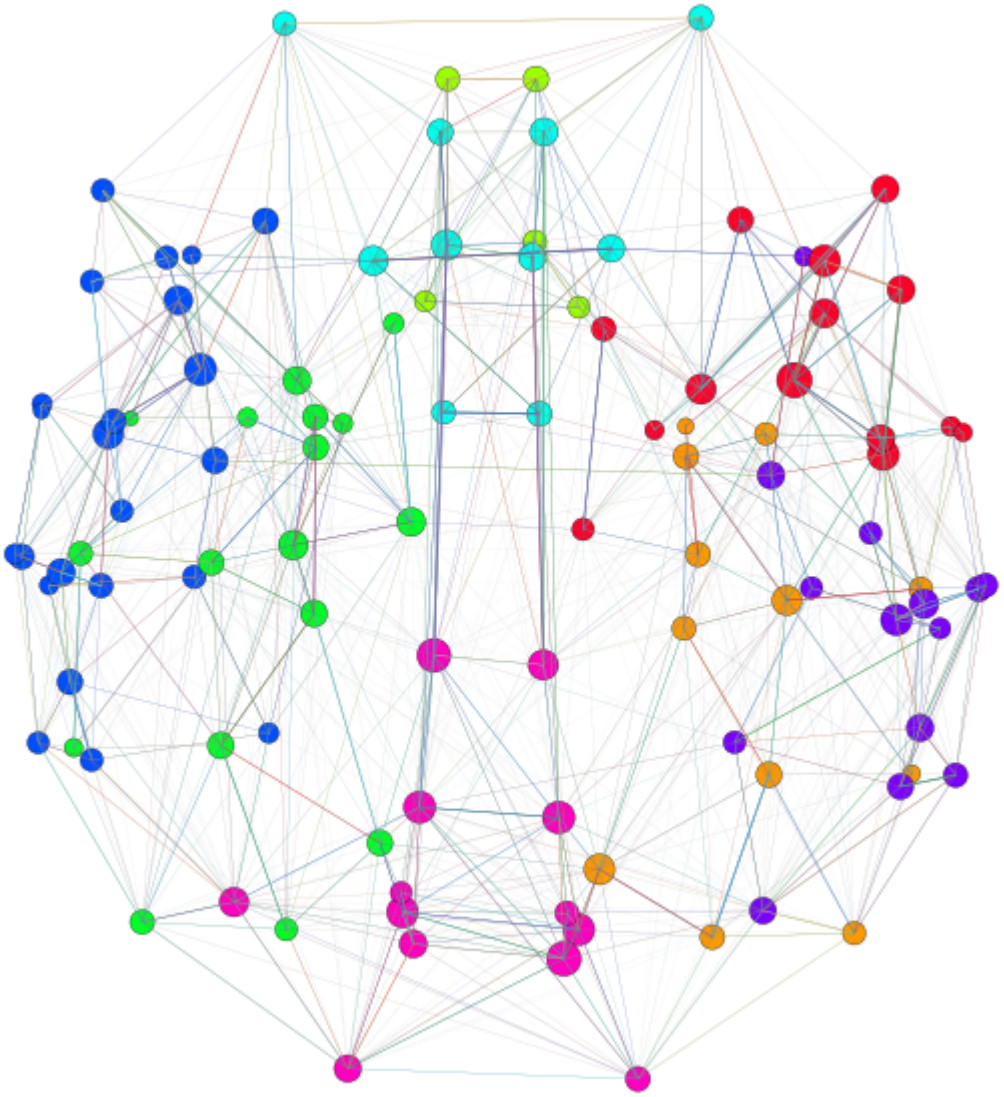

Figure 1. Graph of a human brain connectome. The regions of the Desikan atlas are used as vertices. Vertex colors correspond to communities obtained using Louvain modularity algorithm.

It is expected that the application of modern predictive modeling methods to this kind of data reconstructed based on neuroimaging will improve the accuracy of diagnostic and prognostic models of diseases associated with brain

pathologies. From a mathematical point of view, the problem of predictive modeling on the network structures of the brain is as follows. We consider a data sample a set of pairs consisting of an input graph representing the brain network reconstructed from neuroimaging data and a categorical output variable that takes a small number of different values. For example, the target variable can take values from 0 to 2, encoding three states: the subject is healthy (0), the prodromal phase of schizophrenia (1), and schizophrenia itself (2). The task is reduced to classification, that is, building a mathematical model, which for each new example of the input graph will produce the most probable value of the target variable. Standard quality metrics suitable for a specific application can be used to assess the quality of the model. Note that the specificity of the subject area determines the number of key features of the analyzed input graphs. We are talking about relatively small (about a hundred vertices) undirected graphs with a single connected component. Each vertex in such a graph is labeled uniquely according to the specific area of the brain that it represents, and the set of such labels is the same for all graphs within the applied problem being solved. Vertices have a set of attributes that specify their coordinates in three-dimensional space and the physical parameters of the corresponding zones (thickness and surface area). The graph is weighted, and in the case of multimodal data for the network structure of one brain, there can be two sets of weights, one of which includes assessments of the connectivity of brain regions through anatomical tracts, and the other indicates the intensity of joint activation of zones according to functional diagnostics data. Thus, the standard classification methods cannot be used to solve the problem in view due to the specifics of the input data having the described structure. When constructing predictive models based on such data, it is crucial to most fully preserve information about the key features of the structure of brain networks, of which the most important for us is their modular organization [26]. Modular networking means that its vertices tend to cluster into modules, or communities,

with very dense intragroup and sparse intergroup connections. Authors of [2], show for the first time that it is the modular organization of brain networks that changes in the case of systemic psychiatric diseases (topological features of functional networks in patients with a diagnosis of early childhood schizophrenia were analyzed). The results obtained within the framework of the work suggest that such an approach to the construction of predictive models based on neuroimaging data can be productive in solving the problem of classifying psychiatric diseases (in particular, autism spectrum disorders [20]) and neurodegenerative diseases (disease risk groups Alzheimer's [21]). This suggests that it is the structure of the communities of brain regions in the connectome that fully reflects the topological organization of the initial network and, thus, contains enough information to build predictive models to distinguish clinically significant diagnostic groups. Each connectome can be represented by a vector of length equal to the number of brain regions (graph vertices), in which each value encodes the belonging of the corresponding brain region to one of the communities in the optimal partition of the initial network into disjoint communities. Such a representation allows one to estimate the distances between the original graphs as the distances between the corresponding partitions and, at the next step, to construct algorithms for the classification of normal and pathological network structures using nuclear methods that take as input a matrix of such pairwise distances between the original objects.

Within the framework of the dissertation research, the following tasks were set and solved:

1. Methods for the classification of connectome graphs were proposed, allowing to take into account the overlapping structure of communities and their hierarchical organization.
2. A method was proposed for constructing a brain atlas based on diffusion MRI data using a continuous connectome model. The atlas was obtained on the basis of a data-driven approach and not on the basis of the

anatomical or functional structure of the brain. However, it successfully identifies anatomical structures as regions and, at the same time, can be adjusted to work with a specific data set.

3. A model of disease progression based on multimodal neuroimaging data was proposed. The proposed probabilistic model considers both morphometric characteristics (such as the thickness of the brain's gray matter) and structural (connections between different regions).

It is important to emphasize that the algorithms developed in the framework of the dissertation research were evaluated and compared in terms of their informativeness and usefulness in the predictive modeling of diseases associated with brain pathology. The modular organization of network structures reconstructed based on neuroimaging data was considered a potential biomarker, informative from the point of view of early diagnosis of the disease and personalized prognosis of its course.

Novelty and main results

Chapter 1 outlines the mathematical model of the structural connectome and details of the reconstruction of such graphs based on magnetic resonance imaging (MRI) data. Chapter 2 describes a list of methods used to find vertex communities, compare individual clusterings, and average them. Chapter 3 outlines existing ones and suggests some new ways to build kernels based on various characteristics of graphs. We demonstrate the effectiveness of the described kernels for solving the problems of binary classification of various phenotypes, pathologies, and norms. Chapter 4 outlines an extension of the EBM model that allows you to use connectivity data (connectomes) to generate a priori distribution for the degeneration order of brain regions. Finally, Chapter 5 explores the hierarchical organization of connectome graphs. It is shown that

groups of vertices of connectome graphs that form dense communities are often anatomically close. Finally, Chapter 6 proposes a method for constructing an anatomical atlas based on the structural (physical, through axonal connections) connectivity of regions, which surpasses existing anatomical atlases in several ways. The thesis consists of an introduction, six chapters, a conclusion, bibliography, illustrations, and tables. The total volume of the thesis is 177 pages.

The main results of the research and the provisions for the defense.

As part of the dissertation research, it was demonstrated and/or proposed:

1. A method for solving the problem of classifying objects represented in graphs defined on one set of vertices (with a different set of edges) is proposed. The method is based on comparing intersecting and non-intersecting cluster structures of such graphs, which makes it possible to reduce their feature description effectively.
2. A model of disease progression based on multimodal neuroimaging data is proposed. The proposed probabilistic model considers both morphometric characteristics (such as the thickness of the brain's gray matter) and structural (connections between different regions).
3. A method for constructing an anatomical atlas of the cerebral cortex based on structural connectivity data using a continuous connectome model is proposed.
4. Hierarchical properties of connectome graphs derived from data are studied and described. It has been demonstrated that vertex communities in connectome graphs often form anatomically close regions.

Publications

First-tier publications:

1. Kurmukov A., Mussabaeva A., Denisova Y., Moyer D., Neda J., Thompson P. M., Gutman B. A. Optimizing connectivity-driven brain parcellation using ensemble clustering // Brain Connectivity. 2020. Vol. 10. No. 4. P. 183-194.
2. Kurmukov, A., Musabaeva, A., Denisova, Y., Moyer, D. and Gutman, B., 2018, September. Connectivity-driven brain parcellation via consensus clustering. In International Workshop on Connectomics in Neuroimaging (pp. 117-126). Springer, Cham.
3. Kurmukov A., Zhao Y., Mussabaeva A., Gutman B. Constraining Disease Progression Models Using Subject Specific Connectivity Priors, in: Lecture Notes in Computer Science book series Issue 11848. Springer, 2019. P. 106-116.
4. Kurmukov, A., Ananyeva, M., Dodonova, Y., Gutman, B., Faskowitz, J., Jahanshad, N., Thompson, P. and Zhukov, L., 2017. Classifying phenotypes based on the community structure of human brain networks. In Graphs in Biomedical Image Analysis, Computational Anatomy and Imaging Genetics (pp. 3-11). Springer, Cham.

Other publications:

1. Kurmukov A., Dodonova Y., Burova M., Mussabayeva A., Petrov D., Faskowitz J., Zhukov L. E. Topological modules of human brain networks are anatomically embedded: evidence from modularity analysis at multiple scales, in: Computational Aspects and Applications in Large-Scale Networks. Springer Proceedings in Mathematics and Statistics Vol. 247. Springer, 2018., P. 299-308.
2. Kurmukov A., Dodonova Y., Zhukov L. E. Machine learning application to human brain network studies: a kernel approach, in: Models, Algorithms, and Technologies for Network Analysis. Springer Proceedings in Mathematics and Statistics / Ed. by V. A. Kalyagin, A. I. Nikolaev, P. M. Pardalos, O. Prokopyev. Vol. 197. Springer, 2017. doi P. 229-249.

3. Kurmukov A., Dodonova Y., Zhukov. Classification of normal and pathological brain networks based on similarity in graph partitions. IEEE 16th International Conference on Data Mining Workshops, ICDMW. Том 0, Pages 107 – 112, July 2016.

The organization of the thesis

Task: *"Classification of norm and pathology based on the cluster structure of human brain graphs."*

It is assumed that within connectomes, it is possible to identify in an informative way the communities of vertices that represent regions of the brain. Informativeness means for us the ability to determine, based on the resulting partitions, the distances between the graphs in such a way that expectedly similar graphs are close - for example, those belonging to people with a specific neurodegenerative disease.

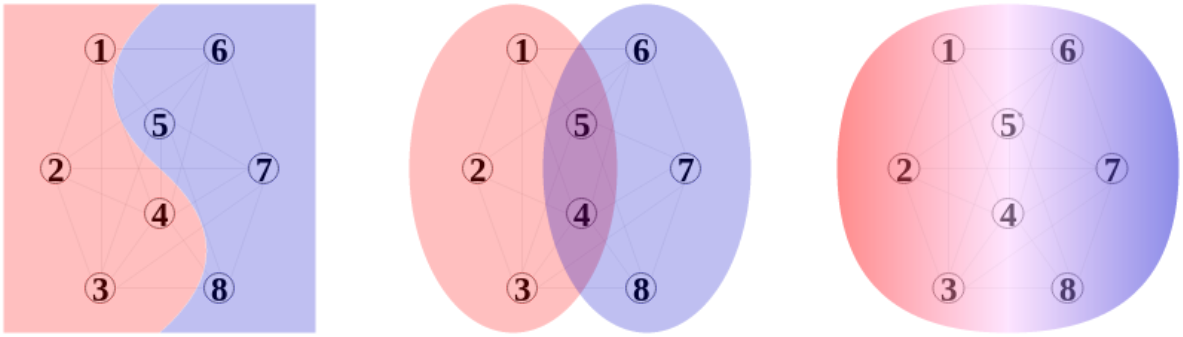

Figure 2. Different types of clustering. From left to right: non-overlapping clusters, overlapping clusters, fuzzy clusters.

Based on this idea, several problems were solved to distinguish between patients with various diseases, such as autism spectrum disorders, Parkinson's disease, and Alzheimer's disease, and people without pathology based on graphs of structural connections of the brain (connectomes). For this, various models have been proposed using information about the differences in the partitions of graphs into subgraphs, typical for connectomes of groups of norm and pathology. The proposed approaches differ in whether a vertex can simultaneously belong to several communities and whether a different degree of such membership is possible. If the partitioning of connectome graphs into disjoint communities is considered, this information can be encoded by a vector of length equal to the number of graph vertices. Each element of such a vector is

an indicator of the vertex's belonging to the community. Otherwise, if the partition of graphs into intersecting communities is considered [37], it will be encoded not by a vector but by a matrix. The membership matrix contains values that correspond to the probability of a brain region belonging to one of the communities or by a set of matrices if we are talking about different hierarchical levels of analysis. Fig. 2 shows a schematic representation of the division of the graph's vertices into communities, overlapping clusters, andfuzzy clusters. In this case, the problem arises of correctly estimating the distances between such objects to construct predictive modeling algorithms on them.

Task: *"Hierarchical structure of connectome graphs"*

Human brain communication networks exhibit modular organization: cortical regions form tightly connected clusters with relatively few intercluster connections. However, little is known about whether the modular structure of brain networks is reproducible and, most importantly, to what extent these vertex clusters are associated with anatomy. To solve these questions, we use MRI data of the same people, scanned at intervals of several weeks (longitudinal data), and reconstruct the brain's structural networks on several scales, divide them into communities, and assess the similarity obtained by clustering. We check the stability of the modular structure in two ways, firstly, we compare the cluster structures of graphs obtained from the same person and different people, and secondly, we compare the resulting graph clusters with anatomically close regions. Our results show that the modular structure of brain networks is well reproduced in the framework of repeated experiments (test-retest reliability). In addition, the results obtained confirm the theoretically substantiated hypothesis that the regions of the brain adjacent in the anatomical space also, as a rule, belong to the same network clusters of vertices. For high-resolution networks, we compared the two approaches to partitioning their vertices into communities. The first approach is based solely on the structure of the topological connections of the graph. The second approach is primarily based on anatomy because the vertices of the high-resolution graph were placed in communities, based on the fact that they were anatomically adjacent and belonged to the same region of the cortex in the anatomical atlas (and therefore to the same parent on the low-resolution network). We have demonstrated that the modularity of these latter vertex colorings was still very high and only slightly lower than the modularity estimated with respect to topologically optimal partitions. In addition, we demonstrated that the similarity between topologically optimal and anatomical colorings was very high. Topological modules largely resembled the anatomical grouping of adjacent areas of the

cortex and were hierarchically built into the structure of anatomical communities. Using multiscale analysis (graphs in different resolutions) and algorithms for partitioning networks into communities, we found new evidence to support the theoretically based hypothesis that brain regions adjacent in anatomical space also tend to belong to the same hierarchically nested topological modules Fig. 3.

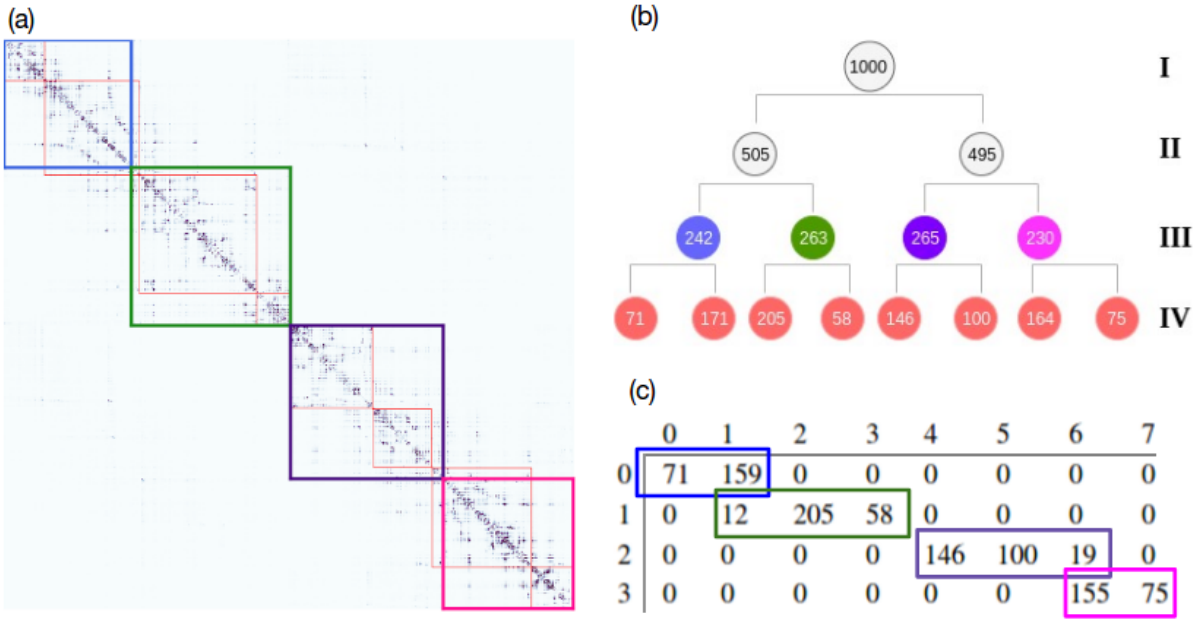

Figure 3. Three ways to demonstrate the hierarchical nesting of clusters of high-definition networks in communities formed in low-definition networks. (a) High-resolution network adjacency matrix with eight topological units with the best division into communities (light red squares) and four anatomical communities (blue, green, purple and pink squares); the first-level communities are almost strictly embedded in the second-level messages. (b) A hierarchical tree with four levels: I - the entire 1000-vertex connection, II - two hemispheres, III - four clusters inherited from the anatomically mapped low-resolution network partition, IV-eight clusters obtained by high-resolution Leuven partitioning of the network. Cross-tabulation of the co-occurrence of cluster labels in a high-resolution network (eight clusters, horizontal) and four anatomical partitioning communities (vertical).

Task: *"Building an atlas of the human brain based on diffusion MRI data and graph-theoretical models."*

A method was proposed for constructing a brain atlas based on diffusion MRI data using a continuous connectivity model [27]. Data from the Human Connectome Project [33] were used for computational experiments. The Atlas was constructed from 425 HCP participants (167 men, 258 women). The Louvain Modularity algorithm, igraph implementation [6], was used to restore individual clusters. A meta-algorithm for averaging individual parcels was proposed to construct a group atlas. A comparison was made of different approaches to averaging: using the meta-graph, using the mean graph, greedy optimization of the coloring of the vertices of the graph in such a way as to minimize the Karcher means:

$$C^{*} = \arg\min_{C} \Sigma^{N}_{i=1} d(C_i, C)^2,$$

where Ci are individual parcellations, obtained via continuous connectome clustering, C* - optimal ensemble clustering.

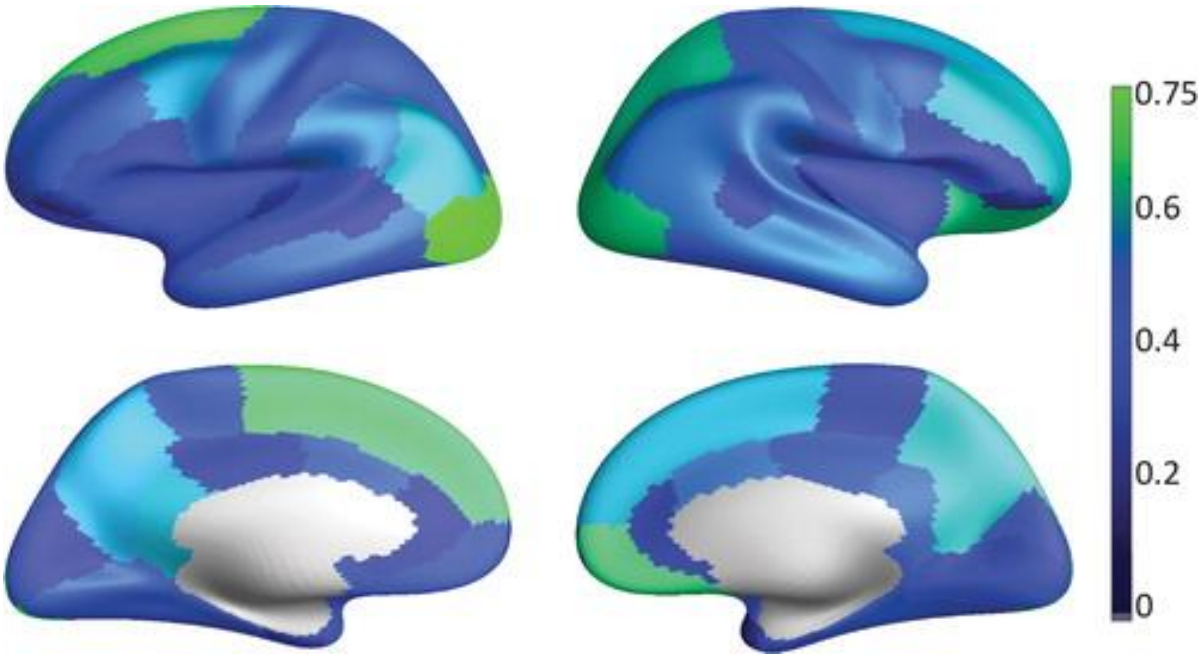

Figure 4. Intersection of an optimal connectivity-based parcellation with anatomical parcellation Desikan. Colors are according to the Dice score.

The results showed that the atlas obtained in this way can effectively describe the data on the connectivity of the regions of the brain, surpassing the existing atlases (for example [7], [8], [9]) based on anatomy in a number of parameters.

Task: *"Modeling and predicting neurodegenerative diseases without using longitudinal data."*

There are several approaches to modeling the progression of neurodegenerative diseases. For example, several studies are based on the hypothesis that the progression of biomarkers follows a sigmoidal trajectory [17] depending on the stage of progression. For example, the thickness of the cerebral cortex [11] decreases, and CDR (Clinical Dementia Rating) the marker is growing. This group of works is characterized by various methods of selection of sigmoid parameters based on real data. For example, in [18], a method was proposed for selecting individual parameters of progression using no more than four time observations, the authors use a linear model as a model of progression (depending on time), and the values of biomarkers (such as the thickness of the cortex, cognitive indicators, etc.)) follows a sigmoidal trajectory (depending on the stage of progression). Another popular approach is the so-called Event-based modeling (EBM) [12]. This generative model is based on the following hypothesis: the disease affects different parts of the brain in a specific order. Some areas are affected first, then others. Changes in areas of the brain from the end of this list correspond to the later stages of the development of the disease. If the order of the lesions of the areas can be restored, on its basis, it is possible to make predictions about the current state of the patient even without longitudinal data. In addition, in [39], it was demonstrated that to restore this order, one can do with cross-sectional data (that is, data in which only one observation corresponds to each patient). Works based on this hypothesis differ in the way they model the sequence of events.

Despite its popularity, this model has several disadvantages. For example, it is assumed that each specific biomarker follows a single trajectory in the process of disease progression for all patients. In [38], the authors tried to eliminate this

drawback by dividing patients into homogeneous groups, within which the behavior of biomarkers differs only slightly. Another significant drawback is that the number of areas considered in the original work was small: a standard atlas of the brain surface was used, dividing it into 70 regions. In [23], the authors switched from regional features to features measured at the level of the vertices of the polygonal grid of the brain surface (about hundreds of thousands of vertex features).

Moreover, the authors used the assumption of a sigmoidal trajectory of biomarker progression. Thus their work can be considered an attempt to overcome another disadvantage of the EBM approach - namely, the determinism of the sequence of the affected regions. As another drawback, we note that information about the diagnosis is used in modeling very little or not at all. Parametric unsupervised learning models are mainly used, such as the Gaussian Mixture Model (and mixtures of other parametric distributions). Therefore, in [34], the authors used a combined approach consisting in the sequential application of the classification model (this stage helps to separate the early stages from the later ones, based on the data), and then - the generative model (at this stage, the specific order of the lesions of the brain regions is deduced). The last significant drawback, which, as far as we know, was not touched upon in any of the existing works, is the ratio between the number of fit parameters M and the sample size N. The effectiveness of modern machine learning methods is mainly due to the increasing size of training samples. The fact is that the number of parameters of the predictive model usually does not depend on the sample size, so the M / N ratio tends to 0 with an increase in the training dataset. In the latest modifications of the EBM model, the selection of individual parameters is carried out. Thus the value of M grows linearly with the growth of N, which significantly limits the generalizability of this approach.

Finally, there is the last group of works in which the progression of the disease is described in terms of propagation through the "networks" of the brain -

connectomes [30], [16]. Such networks can be built on the basis of diffusion or functional MRI data. The works of this block differ from each other in the nature (law) of the spread (progression) of the disease along the brain network, as well as in the assumptions about which groups of vertices (areas) or ribs (connections between areas) are affected in the first place. For example, in [4], a model is considered according to which "hubs" are at the greatest risk, that is, network sections with the larger number of connections ("nodal stress"), the idea that the disease spreads along with bundles of neurons ("trans neuronal spread") considered in [19]. According to a recent review [28], the network approach does not yet allow predictions about the stage of the disease or the rate of progression. Therefore, it is not applicable from a clinical point of view. As part of solving this problem, a prognostic model of the progression of Alzheimer's disease was proposed [22], which takes into account the statistical parameters of the population and individual factors of development. In this case, the model can be built without using longitudinal data.

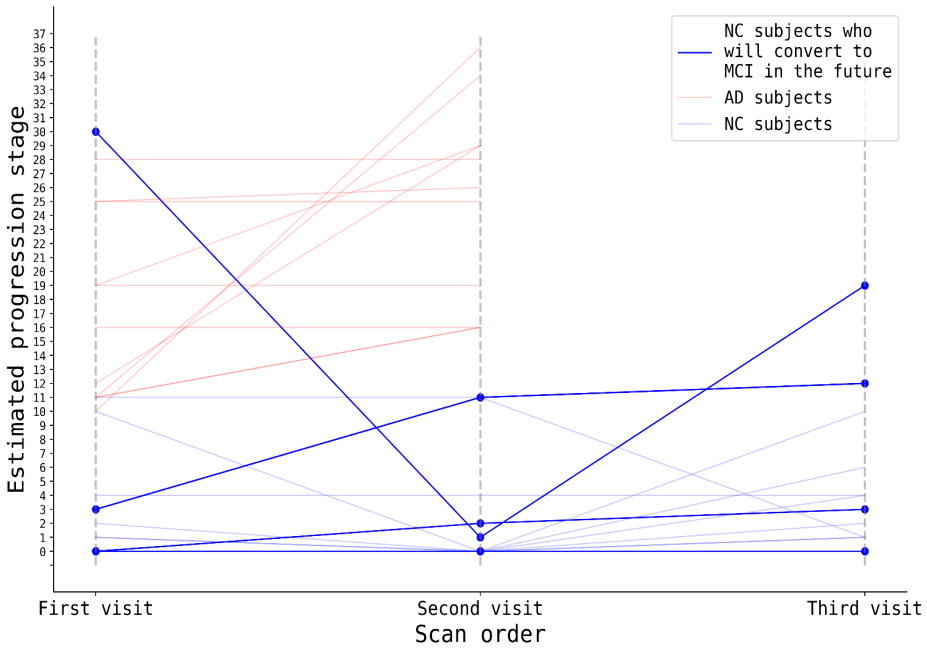

Figure 5. Several selected subjects. Disease stages are calculated using a progression model with individual connectome prior order on cross-sectional data. The image shows the stages for observations from the test dataset, each line corresponds to one patient, red lines correspond to patients with Alzhemer's disease, pale blue - healthy people, bright blue, healthy people during the first visit, for whom it is known that in the future they began to manifest themselves dementia symptoms.

Specifically, we proposed an extension of the Event-based model [13], which allows us to incorporate individual data on the connectivity of brain regions. The event-driven disease progression model uses the assumption that the degeneration of separate areas occurs sequentially (different areas can degrade at different rates), and its task is to restore this sequence. For this, a Bayesian model with an uninformative prior distribution is used. In our work, we have proposed an informative prior distribution based on the anatomical relationship of individual regions. Computational experiments have shown that the use of

diffusion MRI data (together with biomarkers derived from structural MRI) can improve prognostic indicators compared to using only structural MRI. Fig. 5 shows an example of predicting progression scores for the test portion of patients. Alzheimer's patients receive higher progression scores compared to healthy patients.

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