Brain Network Analysis: a Data Mining Perspective

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ABSTRACT

Following the recent advances in neuroimaging technology, the research on brain network analysis becomes an emerging area in data mining community. Brain network data pose many unique challenges for data mining research. For example, in brain networks, the nodes (i.e., the brain regions) and edges (i.e., relationships between brain regions) are usually not given, but should be derived from the neuroimaging data. The network structure can be very noisy and uncertain. Therefore, innovative methods are required for brain network analysis. Many research efforts have been devoted to this area. They have achieved great success in various applications, such as brain network extraction, graph mining , neuroimaging data analysis. In this paper, we review some recent data mining methods which are used in the literature for mining brain network data.

Keywords

Brain networks, Graph mining, Functional magnetic resonance imaging, Subgraph Patterns

1. INTRODUCTION

Recent advances in neuroimaging technology has unleashed a torrent of neuroscience data. The data give us an unprecedented opportunity to look into the activity and connectivity of the human brain non-invasively and in vivo. Brain tissue is generally described according to the broad classes of gray matter and white matter. This distinction has a historical basis in the appearance at dissection, reflecting the preponderance of cell bodies and dendrites (gray matter, e.g. cortex) and of myelinated axons, which have a fatty, whitish appearance (white matter, e.g. corpus callosum) [29]. The activity of the brain, however, is organized according to vast and complex patterns of connectivity involving multifocal distributed neural networks and white matter pathways that are considered critical to an understanding of higher order cognitive function and dysfunction [42].

The last several decades have witnessed explosive expansion in knowledge concerning the structure and function of the human brain. This can be attributed in part to advances in Magnetic Resonance (MR) imaging capabilities. Techniques such as diffusion tensor imaging (DTI), for example, that can be used for in vivo interrogation of the brain at levels that approximate cellular dimensions, have enabled tractography of the vast network of white matter fiber pathways, yielding fundamental insights into structural connectivity [5; 8; 27; 28; 2]. Functional magnetic resonance imaging (fMRI) has been used to identify localized patterns of brain activation on the basis of cerebral blood flow and the BOLD response [30; 31; 6]. Strategies, such as resting state fMRI (rs-fMRI) have been used to map functional connectivity – networks defined on the basis of correlated activity in low frequency oscillations between gray matter regions [6; 17; 33].

Brain networks have been studied extensively in recent years [36; 11], because of potential application to detection of a wide variety of brain diseases [43]. A detailed book on this topic may be found in [35]. Conventional research on brain networks focuses on connectivity derived from various neuroimaging modalities, such as electroencephalography (EEG), fMRI and DTI. These approaches emphasize creating a network among brain regions (or ROIs) and detecting changes in connectivity related to brain diseases. Conventional strategies often use either equally sized regions or anatomical landmarks (e.g., gyral and sulcal-based regions) as nodes of the network with unclear relationship to the underlying functional and structural organization of the brain. The links among these regions (e.g., functional connections or structural connections) are extracted based on neuroimaging data to form a network.

Data mining has already made significant impacts in many real-world applications in industry and science, such as social network analysis, web mining. However, brain network data pose many unique challenges for data mining community. For example, in conventional network analysis, the nodes (e.g., webpages) and edges (e.g., hyperlinks) are usually clearly defined. In brain networks, however, the nodes (i.e., the brain regions) and edges (i.e., relationships between brain regions) are not given, but need to be derived from the neuroimaging data. Different parcellation of the brain regions can result in significantly different network structures. The edges of brain networks are also highly uncertain due to the noise in imaging signals. Conventional data mining methods can seldom be directly applied to brain network data. A wide variety of new questions can also be asked in context of the brain network analysis.

In this paper, we focus on reviewing some recent data mining methods for (1) direct mining of neuroimaging data; (2) extracting brain networks from neuroimaging data; (3) mining subgraph patterns from brain networks.

Imaging-based Approaches: Neuroimaging data can naturally represented as tensor data [47; 14; 18], which gen-

Table 1: Properties of Data Mining Methods for Neuroimaging Data.

Publication	Target Disease	Imaging Data	Mining Task	Information Sources
KDD'08 [47]	Alzheimer's	MRI, CSF	Data Fusion	Neuroimage, CSF, Blood Markers
KDD'09 [37]	Alzheimer's	FDG-PET	Region Connectivity	Neuroimage
NIPS'09 [19]	Alzheimer's	PET	Region Connectivity	Neuroimage
KDD'11 [20]	Alzheimer's	FDG-PET	Effective Connectivity	Neuroimage
NIPS'11 [22]	Alzheimer's	PET, MRI	Region Identification	Neuroimage
SDM'13 [24]	AD, ADHD, HIV	fMRI	Subgraph Patterns Mining	Functional Brain Network
KDD'13a [14]	Alzheimer's	fMRI	Network Discovery	Neuroimage
KDD'13b [45]	Alzheimer's	MRI, PET, CSF	Multi-source Learning	Neuroimage, CSF, Proteomics
SDM'14 [18]	AD, ADHD, HIV	fMRI	Supervised Tensor Learning	Neuroimage

eralize the conventional vector/matrix data models. An MRI sample corresponds a 3D-array, or three-mode tensor. An fMRI sample can be represented as (3D $\times$ time) a 4-dimensional array, or four-mode tensor. Other imaging data, such as DTI, can be represented as tenors with even higher modes. Ideal data mining methods for neuroimaging data should be able to handle the extremely high dimensionality within the data, while preserving the tensor structure in the model [18].

Brain Network Extraction: Another important challenge in brain network analysis is that the network structure is very difficult to extract. In order to extract a meaningful brain network, the nodes and the edges of the networks should both be carefully extracted from neuroimaging data. Many research efforts are devoted to mining important brain regions [22; 14] and connection estimation [37; 19; 20].

Brain Network Analysis: Once the brain networks are constructed from the neuroimaging data, the next step is to analyze the networks. The challenges are that conventional network measures are optimally suited for binary/certain networks and are less well suited for weighted, uncertain, signed networks. Ideal data mining methods for brain network analysis should be able to take the unique properties on the edges (e.g., uncertainty, weights) into consideration. In some applications, we need to extract important connectivity patterns from brain networks. For example, in the classification task of brain networks, we need to extract discriminative subgraphs from the brain networks to figure out the differences among different groups of subjects: Alzheimer's patient (AD) and normal controls (NC). These subgraphs are expected to be most discriminative and reliable in the uncertain brain networks.

To summarize, we create a table of the different methods, and the different properties such as target disease, mining tasks or what type of information sources were used. This is provided in Table 1.

The rest of the paper is organized as follows. We review tensor-based neuroimaging analysis in Section 2. The network extraction is presented in Section 3. We discuss brain network analysis in Section 4. Finally, we conclude the paper in Section 5.

2. IMAGING-BASED APPROACHES

2.1 Tensor-based Modeling

Neuroimaging data can naturally represented as tensor data [47; 14; 18]. A *tensor* is a high order generalization of a vector (first-order tensor) and a matrix (second-order tensor), which is also known as multidimensional array. An m-th order tensor can be represented as $\mathcal{A} = (a_{i_1,i_2,\cdots,i_m}) \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_m}$. I_i is the dimension of $\mathcal{A}$ along the i-th mode. In the context of neuroimaging data, each fMRI sample can be represented as (3D $\times$ time) a 4-dimensional array, or four-mode tensor. An MRI sample corresponds a 3D-array, or three-mode tensor. Other imaging data, such as DTI, can be represented as tenors with even higher modes.

Based on the above definition, inner product, tensor norm, and tensor product can be defined as follows:

Inner product: the inner product of two same-sized tensors $\mathcal{A}, \mathcal{B} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_m}$ is

$$\langle \mathcal{A}, \mathcal{B} \rangle = \sum_{i_1=1}^{I_1} \sum_{i_2=1}^{I_2} \cdots \sum_{i_m=1}^{I_m} a_{i_1,i_2,\ldots,i_m} b_{i_1,i_2,\ldots,i_m}.$$

Tensor norm: the norm of a tensor $\mathcal{A}$ is

$$\|\mathcal{A}\|_F = \sqrt{\langle \mathcal{A}, \mathcal{A} \rangle} = \sqrt{\sum_{i_1=1}^{I_1} \sum_{i_2=1}^{I_2} \cdots \sum_{i_m=1}^{I_m} a_{i_1,i_2,\ldots,i_m}^2}.$$

The norm of a tensor is a generalization of the *Frobenius norm* for matrices and of the l_2 *norm* for vectors.

Tensor product: the tensor product $\mathcal{A} \otimes \mathcal{B}$ of tensors $\mathcal{A} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$ and $\mathcal{B} \in \mathbb{R}^{I'_1 \times I'_2 \times \cdots \times I'_M}$ is another tensor, where each element is

$$(\mathcal{A} \otimes \mathcal{B})_{i_1,i_2,\ldots,i_N,i'_1,i'_2,\ldots,i'_M} = a_{i_1,i_2,\cdots,i_N} b_{i'_1,i'_2,\cdots,i'_M}$$

A mth-order tensor is a rank-one tensor if it can be defined as the tensor product of m vectors: $\mathcal{A} = \mathbf{a}^{(1)} \otimes \mathbf{a}^{(2)} \otimes \cdots \otimes \mathbf{a}^{(m)}$. For rank-one tensors $\mathcal{A} = \mathbf{a}^{(1)} \otimes \mathbf{a}^{(2)} \otimes \cdots \otimes \mathbf{a}^{(m)}$ and $\mathcal{B} = \mathbf{b}^{(1)} \otimes \mathbf{b}^{(2)} \otimes \cdots \otimes \mathbf{b}^{(m)}$, we have

$$\langle \mathcal{A}, \mathcal{B} \rangle = \left\langle \mathbf{a}^{(1)}, \mathbf{b}^{(1)} \right\rangle \left\langle \mathbf{a}^{(2)}, \mathbf{b}^{(2)} \right\rangle \cdots \left\langle \mathbf{a}^{(m)}, \mathbf{b}^{(m)} \right\rangle.$$

CP factorization: given a tensor $\mathcal{A} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_m}$ and an integer R, if it can be expressed as

$$\mathcal{A} = \sum_{r=1}^{R} \mathbf{a}_r^{(1)} \otimes \mathbf{a}_r^{(2)} \otimes \cdots \otimes \mathbf{a}_r^{(m)} = \sum_{r=1}^{R} \prod_{i=1}^{m} \otimes \mathbf{a}_r^{(i)}$$

We call it a CP factorization of $\mathcal{A}$.

Major Challenges: Different from conventional data in vector space, the major research challenges of mining tensor data are as follows:

High dimension: In neuroimaging tensor data, each sample is usually represented as a high-dimensional multi-mode (also known as multi-way) array. One straightforward solution to tensor data mining is to reshape the tensors into vectors. However, the number of features will be extremely

high. For example, a typical MRI image of size $256 \times 256 \times 256$ voxels contains $16,777,216$ features [49]. This makes traditional data mining methods prone to critical issues, such as overfitting, especially with a small or moderate-sized dataset.

Tensor structure: Different from conventional vector data, tensor data can preserve the structural information of the high-dimensional space, such as the spatial relationships among different voxels in a 3-D image. These structural information can be very important in neuroimaging applications. For example, in MRI data, the values of adjacent voxels are usually correlated with each other. When converting tensors into vectors, such structural information will be lost.

2.2 Supervised Tensor Learning

Suppose we have a training set of n pairs of samples $\{(\mathcal{X}_i, y_i)\}_{i=1}^n$ for binary tensor classification problem. $\mathcal{X}_i \in \mathbb{R}^{I_1 \times \cdots \times I_m}$ is the input of the neuroimaging sample, which is represented as a tensor of m-mode. $y_i \in \{-1, +1\}$ is the corresponding class labels of $\mathcal{X}_i$. For example, if the i-th subject has Alzheimer's disease, the subject is associated with a positive label, *i.e.*, $y_i = +1$. Otherwise, if the subject is in the control group, *i.e.* the normal people, the subject is associated with a negative label, *i.e.*, $y_i = -1$.

Brain image classification tasks can be defined as a supervised tensor learning problem [18]. The optimization problem of supervised tensor learning is

$$\begin{aligned} \min_{\mathcal{W},b,\xi} \frac{1}{2} \|\mathcal{W}\|_F^2 + C \sum_{i=1}^n \xi_i \\ \text{s.t. } y_i \left(\langle \mathcal{W}, \mathcal{X}_i \rangle + b \right) \geq 1 - \xi_i, \\ \xi_i \geq 0, \forall i = 1, \cdots, n. \end{aligned}$$

where $\mathcal{W}$ is the weight tensor of the separating hyperplane. $b \in \mathbb{R}$ is the bias. C is the trade-off between the classification margin and misclassification error. The above optimization problem is a generalization of the standard SVM from vector data to tensor data.

Nonlinear separability: In many neuroimaging applications, the data is usually not linearly separable in the input space. Conventional supervised tensor learning methods which can preserve tensor structures are often based upon linear models. Thus these methods cannot efficiently solve nonlinear learning problems on tensor data.

In the work [18], He et. al. studied the problem of supervised tensor learning with nonlinear kernels which can preserve the structure of the tensor data.

Given a tensor $\mathcal{X} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_m}$, and a mapping function into a Hilbert space

$$\phi : \mathcal{X} \to \phi(\mathcal{X}) \in \mathbb{R}^{H_1 \times H_2 \times \cdots \times H_P}.$$

The optimization problem becomes

$$\begin{aligned} \max_{\alpha_1, \alpha_2, \cdots, \alpha_n} \sum_{i=1}^n \alpha_i - \frac{1}{2} \sum_{i,j=1}^n \alpha_i \alpha_j y_i y_j \langle \phi(\mathcal{X}_i), \phi(\mathcal{X}_j) \rangle \\ \text{s.t.} \sum_{i=1}^n \alpha_i y_i = 0, \\ 0 \leq \alpha_i \leq C, \forall i = 1, \cdots, n, \end{aligned}$$

where α_i are the Lagrangian multipliers and $\langle \phi(\mathcal{X}_i), \phi(\mathcal{X}_j) \rangle$ are the inner product between the mapped tensors of $\mathcal{X}_i$ and $\mathcal{X}_j$ in the Hilbert space. Based on a suitable tensor kernel function $\kappa(\mathcal{X}_i, \mathcal{X}_j)$, the decision function can be written as

$$f(\mathcal{X}) = sign \left(\sum_{i=1}^n \alpha_i y_i \kappa(\mathcal{X}_i, \mathcal{X}) + b \right).$$

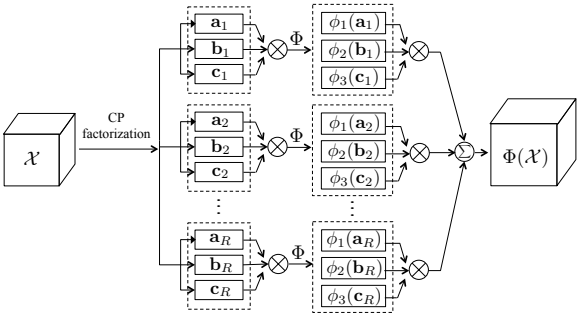


Figure 1: Dual-tensorial mapping [18]

Dual Tensor Kernel (DuSK): In order to preserve the tensor structure in both original space and feature space, we can use CP factorizations to define the tensor kernels. Similar to other kernel functions in vector space, the feature space of tensor data is a high-dimensional tensor space. We can factorize tensor data directly in both the feature space and the original space, which is equivalent to performing the following mapping:

$$\phi : \sum_{r=1}^R \prod_{i=1}^m \otimes \mathbf{x}_r^{(n)} \to \sum_{r=1}^R \prod_{i=1}^m \otimes \phi \left(\mathbf{x}_r^{(i)} \right).$$

The function can be considered as the operation of mapping the original data into tensor feature space and then conducting the CP factorization in the feature space. It is called the dual-tensorial mapping function (see Figure 1).

Suppose we have the CP factorization of $\mathcal{X}, \mathcal{Y} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_m}$ as $\mathcal{X} = \sum_{r=1}^R \prod_{i=1}^m \otimes \mathbf{x}_r^{(i)}$ and $\mathcal{Y} = \sum_{r=1}^R \prod_{i=1}^m \otimes \mathbf{y}_r^{(i)}$ respectively. Then the CP factorization of the data can be mapped into the tensor product feature space,

$$\begin{aligned} \kappa \left(\sum_{r=1}^R \prod_{i=1}^m \otimes \mathbf{x}_r^{(i)} \ , \ \sum_{r=1}^R \prod_{i=1}^m \otimes \mathbf{y}_r^{(i)} \right) \\ = \sum_{i=1}^R \sum_{j=1}^R \prod_{k=1}^m \kappa \left(\mathbf{x}_i^{(k)}, \mathbf{y}_j^{(k)} \right) \end{aligned}$$

The DuSK is an extension of the kernels in the vector space to tensor space. Thus DuSK kernel can be applied to any kernel-based learning methods to solve supervised tensor learning problems.

3. BRAIN NETWORK EXTRACTION

Brain networks are very different from conventional networks, such as social networks or Web, where the nodes and edges of the networks are predefined, e.g., the users/friendship or the webpages/hyperlinks. In brain networks, either the nodes or the edges are defined beforehand, but derived from neuroimaging data.

For the nodes of brain networks, it is essential to parcellate cerebral cortex into a set of disjoint regions and to use these brain regions as the nodes. Depending on the scale-levels, the specific brain regions represented by nodes can

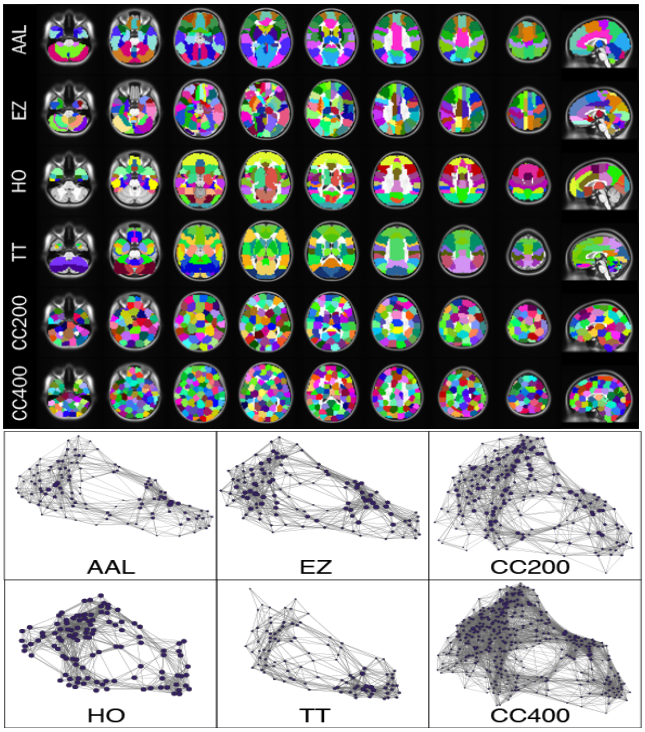


Figure 2: Different brain parcellation methods and their functional networks [13]. (a) AAL (automated anatomical labeling) [41]. (b) Harvard Oxford (HO) derived from anatomical landmarks (sulci and gyral) [15]. (c) EZ (Eickhoff-Zilles) [16]. (d) TT (Talariach Daemon) [26]. (e) CC200 and CC400 are derived from functional parcellations [12]. The functional networks were derived from all pairwise correlations between ROIs.

range from the small patches of cortex contained in individual MRI voxels to larger brain areas (e.g., dorsolateral prefrontal cortex). The structures of brain networks depend greatly on how the nodes are defined. Different parcellation methods will result in different network structures. For example, in Figure 2, we show six existing methods for brain parcellation, where the brain regions are partitioned differently according to different criteria. We can see that the structures of brain networks are also quite different when different parcellation methods are used.

For the edges of brain networks, it is essential to estimate different relationships among the brain regions [7; 35]. Examples include functional connectivity [44; 14], structural connectivity, effective connectivity [21], *etc.* Different types of connectivity will result in totally different networks, and can capture different types of relationships among brain regions.

3.1 Defining Nodes

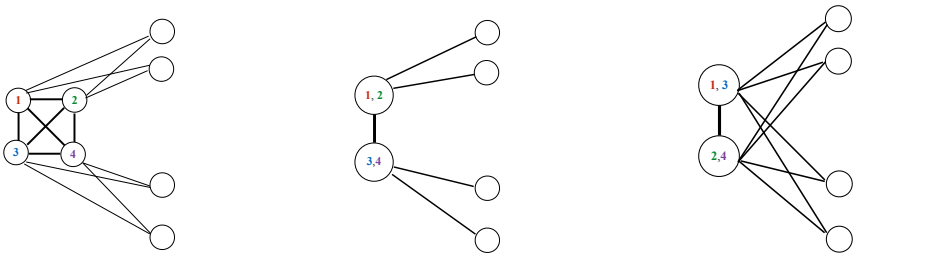
Early work in brain parcellation focused on anatomical atlases. Although much has been learned from these anatomical atlases, no functional or structural connectivity information was used to construct them. Thus an anatomically parcellated region (e.g., the anterior cingulate cortex) can contain subregions that are each characterized by dramatically different functional and structural connectivity patterns. These can significantly limit the utility of the constructed networks. The reasons are as follows: when we construct a brain network based upon a brain parcellation, we need to integrate (e.g., average) the data (e.g., functional activities) within individual regions in order to reduce the noises. We also need to integrate the connections between each pair of regions in order to reduce the uncertainty of connections. Ideally, each of the brain regions should contain subregions of homogeneous connectivity patterns, in order to preserve the utility of the network. For example, in Figure 3(a), we show the connectivity patterns of four subregions, represented as nodes ①-④. We can see that nodes ① and ② share similar connectivity patterns, which are very different from those of nodes ③ and ④. If we merge subregions with similar connectivity patterns into a larger region, as in Figure 3(b), the connectivity patterns are well preserved, because the network constructed can accurately represent the connectivity patterns of the subregions. However, if we merge subregions of different connectivity patterns into a larger region, as in Figure 3(c), the connectivity patterns can be distorted, because different patterns are integrated in the process of network construction.

Defining the nodes for brain networks, which corresponds to the community detection problem of network data, is a challenging task. The reasons are as follows:

- One key challenge comes from the noise and uncertainty of the data in the subregions. Ideally, all the subregions of a cortical region should share similar neurobiological properties, such that by aggregating these subregions into a large region, the noise and uncertainty can be reduced and the neurobiological properties of the subregions can be preserved in the large region. On the other hand, merging subregions with different properties can substantially reduce the utility of the brain network. There are trade-offs between reducing noise and preserving utility in brain parcellation.

- The second key challenge of defining nodes lies in the multiple domains of neurobiological properties, corresponding to multi-domain connectivity. These domains include spatial contiguity, functional connectivity, structural connectivity, etc. Different domains of connectivity correspond to different similarity measures among the subregions and will result in different nodes being defined during brain parcellation. There is lack of agreement on which is the best domain to define the cortical regions, because each domain can provide a unique view of the data. The domain of spatial-contiguity can improve the interpretability of the parcellated regions. The domain of functional-connectivity can help identify subregions with similar functions and connectivity patterns. The domain of structural-connectivity can help identify subregions with similar structural-connectivity patterns.

In this direction, Huang et. al. [22] studied the problem of identifying brain regions that are related to Alzheimer's disease from multi-modality neuroimaging data. Specially, MRI and PET are used to jointly identify disease related regions. MRI images can capture the structure information of the brain, while PET can capture the functional information of the brain. Both types are images can compensate each other. A sparse composite linear discriminant analysis



(a) connectivity of subregions (b) connectivity-based parcellation (c) alternative parcellation

Figure 3: An example of the network parcellation based upon connectivity. The nodes ①-④ represent four subregions of the cortex. In subfigures (b) and (c), the subregions are grouped into larger regions based upon different strategies.

model was proposed to identify brain regions from multiple types of imaging data.

Several works exist for parcellating the brain into a set of brain regions for connectivity analysis. Early efforts on brain parcellation use anatomical atlases [38] through postmortem architectonic measurements, e.g., cell morphology. Such atlases may contain subregions of heterogeneous functional or structural connectivity patterns. For resting-state functional connectivity analyses, different criteria have been used for evaluating the quality of a set of regions. (1) Functionally homogeneity: the regions should be functionally homogeneous [39]. The regionss voxels should have similar time courses [48] or produce similar functional connectivity patterns [10]. (2) Spatial contiguity: the regions should be spatially contiguous to preserve the interpretability of the parcellated regions [4; 33]. Spatial contiguity can also help identifying anatomically homogeneous regions, and hence preserve the interpretability of the connectivity results [39].

3.2 Estimating Edges

There are idiosyncratic differences among different types of edges that can be extracted from neuroimaging data.

Graph Representation: Functional brain networks are typically undirected and weighted [34]. The edge weights can be positive or negative [32]. Effective connections are directed, from source region to target region. Structural networks can be unweighted (binary tractography [1]) or weighted (in probabilistic tractography [3]) and are strictly nonnegative.

Interpretation: Structural networks can be thought of as the physical pathways along which the information flows. But functional connections cannot be interpreted in the same way, but can be thought of as the pair of regions that need to work together in order to perform a certain function. While effective connections corresponds to the causal relationships between the activities of different brain regions.

Functional connections: For functional connections, many of the research efforts focus on using sparse learning methods to derive a sparse network from functional neuroimaging data [37; 19]. In the work [37], the nodes of the brain network are given, which correspond to a set of brain regions. Then the functional activities within each region are aggregated by averaging the signals. In this way, the functional activity within the brain regions can be modeled as follows: Suppose we have n samples which are drawn from a multivariate Gaussian distribution independently, $\boldsymbol{x}_1, \cdots, \boldsymbol{x}_n \sim \mathcal{N}(\boldsymbol{\mu}, \Sigma)$. The n samples correspond to the n time frames in functional imaging data, such as fMRI or PET. These n samples are assumed to be independent from each other, though this assumption may not always hold in neuroimaging data with high temporal resolutions. But for fMRI, this assumption usually hold pretty well in practice. Assume $\boldsymbol{\mu} \in \mathbb{R}^p$, where we have p different brain regions. $\Sigma \in \mathbb{R}^{p \times p}$ is the covariance matrix to be estimated. In order to induce sparsity in the inverse covariance matrix $\Theta = \Sigma^{-1}$, l_1 norm regularization was used in the estimation process.

$$\max_{\Theta \succ 0} \log \det \Theta - \mathrm{tr}(S\Theta) - \lambda \|\mathrm{vec}(\Theta)\|_1$$

where S is the empirical covariance matrix, and λ is a regularization parameter. This was solved using a block coordinate descent method.

Effective connections: For effective connections, many of the research works focus on using structure learning method for Bayesian Networks to derive a directed network from functional neuroimaging data. In the work [20], effective connections among brain regions are modeled as a Bayesian Network (BN). The nodes of the BN corresponds to the brain regions, while the directed arcs between two nodes corresponds to the effective connections. The brain network extraction problem in this scenario becomes the structure learning problem for BN. Similar to functional connections, l_1 norm was also used to induce the sparsity within the network.

4. BRAIN NETWORK ANALYSIS

Once the brain networks are constructed from the neuroimaging data, the next step is to analyze the networks. The challenges are that conventional network measures are optimally suited for binary networks and are less well suited for weighted and signed networks. This often necessitates the conversion of weighted and signed networks to binary and unsigned networks. Such conversions are made by limiting the scope of studies to only positively weighted edges and defining a weight threshold to convert weighted networks into binary networks. These binarizing and simplifying manipulations are associated with great loss of information.

(1) The threshold is often arbitrarily made.

(2) Positively and negatively weighted edges are quite different in functions and closely related to each other in brain networks.

An ideal method for brain network analysis should be able to overcome the above methodological problems by gener-

alizing the network edges to positive and negative weighted cases.

Conventional pattern mining research on brain networks can be divided into two schemes.

(1) The first scheme is usually called a bag of edges, where the graphs are treated as a collection/bag of edges. Statistical analysis is performed on each edge at a time, or a bag of independent edges through multivariate regression/classification methods. In these analyses, the connectivity structures of the networks are blinded.

(2) The second scheme is usually call graph invariants developed from graph theory. Topological measures, such as centrality and modularity, are used to capture global patterns in connectivity. But these approaches are less sensitive to local changes in connection (e.g., changes in only a few edges) as the first scheme.

In brain network analysis, the ideal patterns we want to mine from the data should combine the two schemes together. On the one hand, the pattern should be able to model the network connectivity patterns around the nodes, just like graph invariants methods. On the other hand, the pattern should be able to capture the changes in local areas, just like bag-of-edges methods. *Subgraph patterns* are more suitable for brain networks, which satisfy both of the above requirements.

4.1 Subgraph Pattern Mining on Uncertain Graphs

To determine whether a brain network functions normally or not, we can view the brain network derived from fMRI/PET data or DTI data as a graph and apply graph classification techniques which have been used in various applications, including drug discovery, i.e., predicting the effectiveness of chemical compounds on diseases [25]. Each graph object corresponds to the brain network of a subject in the study, which is associated with a label based upon certain properties of the subject. For example, if a subject has Alzheimer's disease, the graph object corresponding to the subject can be associated with a positive label. Otherwise, if the subject is in the control group, *i.e.* the normal people, the graph object is associated with a negative label.

Mining discriminative subgraph patterns for graph objects has attracted much attention in data mining community due to its important role in selecting features for graph classifications, generating graph indices, etc. [46; 23; 9; 25; 40]. Much of the past research in discriminative subgraph feature mining has focused on certain graphs, where the structure of the graph objects are certain, and the binary edges represent the "presence" of linkages between the nodes. However, in brain network data, there is inherent uncertainty about the graph linkage structure. Such uncertainty information will be lost if we directly transform uncertain graphs into certain graphs.

Specially, in the work [24], the brain networks are modeled as uncertain graphs, where the edges are assigned with an probability of existence. Suppose we are given an uncertain graph dataset $\widetilde{\mathcal{D}} = \{\widetilde{G}_1, \cdots, \widetilde{G}_n\}$ that consists of n uncertain graphs. $\mathbf{y} = [y_1, \cdots, y_n]^\top$ corresponds to their class labels, where $y_i \in \{+1, -1\}$ is the class label of $\widetilde{G}_i$.

Definition 1 (Certain Graph). *A certain graph is an undirected and deterministic graph represented as $G = (V, E)$. $V = \{v_1, \cdots, v_{n_v}\}$ is the set of vertices. $E \subseteq V \times V$ is the set of deterministic edges.*

Definition 2 (Uncertain Graph). *An uncertain graph is an undirected and nondeterministic graph represented as $\widetilde{G} = (V, E, p)$. $V = \{v_1, \cdots, v_{n_v}\}$ is the set of vertices. $E \subseteq V \times V$ is the set of nondeterministic edges. $p : E \to (0, 1]$ is a function that assigns a probability of existence to each edge in E. $p(e)$ denotes the existence probability of edge $e \in E$.*

Consider an uncertain graph $\widetilde{G}(V, E, p) \in \widetilde{\mathcal{D}}$, where each edge $e \in E$ is associated with a probability $p(e)$ of being present. As in other works [51; 50], it is assumed that the uncertainty variables of different edges in an uncertain graph are independent from each other. All uncertain graphs in a dataset $\widetilde{\mathcal{D}}$ share a given set of nodes V, which corresponds to a parcellation of the brain regions.

Each possible outcome of an uncertain graph $\widetilde{G}$ corresponds to an implied certain graph G. Here G is *implied* from uncertain graph $\widetilde{G}$ (denoted as $\widetilde{G} \Rightarrow G$), iff all edges in $E(G)$ are sampled from $E(\widetilde{G})$ according to their probabilities of existence in $p(e)$ and $E(G) \subseteq E(\widetilde{G})$. We have

$$\Pr\Big[\widetilde{G} \Rightarrow G\Big] = \prod_{e \in E(G)} \Pr_{\widetilde{G}}(e) \prod_{e \in E(\widetilde{G}) - E(G)} \big(\, 1 - \Pr_{\widetilde{G}}(e) \,\big)$$

The possible instantiations of an uncertain graph dataset $\widetilde{\mathcal{D}} = \{\widetilde{G}_1, \cdots, \widetilde{G}_n\}$ are referred to as *worlds* of $\widetilde{\mathcal{D}}$, where each world corresponds to an implied certain graph dataset $\mathcal{D} = \{G_1, \cdots, G_n\}$. A certain graph dataset $\mathcal{D}$ is called as being *implied* from uncertain graph dataset $\widetilde{\mathcal{D}}$ (denoted as $\widetilde{\mathcal{D}} \Rightarrow \mathcal{D}$), iff $|\mathcal{D}| = |\widetilde{\mathcal{D}}|$ and $\forall i \in \{1, \cdots, |\mathcal{D}|\}$, $\widetilde{G}_i \Rightarrow G_i$. There are $\prod_{i=1}^{|\widetilde{\mathcal{D}}|} 2^{|E(\widetilde{G}_i)|}$ possible worlds for uncertain graph dataset $\widetilde{\mathcal{D}}$, denoted as $\mathcal{W}(\widetilde{\mathcal{D}}) = \{\mathcal{D} \mid \widetilde{\mathcal{D}} \Rightarrow \mathcal{D}\}$. An uncertain graph dataset $\widetilde{\mathcal{D}}$ corresponds to a probability distribution over $\mathcal{W}(\widetilde{\mathcal{D}})$. The probability of each certain graph dataset $\mathcal{D} \in \mathcal{W}(\widetilde{\mathcal{D}})$ being implied by $\widetilde{\mathcal{D}}$ is $\Pr(\widetilde{\mathcal{D}} \Rightarrow \mathcal{D})$. By assuming that different uncertain graphs are independent from each other, we have

$$\Pr\Big[\widetilde{\mathcal{D}} \Rightarrow \mathcal{D}\Big] = \prod_{i=1}^{|\widetilde{\mathcal{D}}|} \Pr[\widetilde{G}_i \Rightarrow G_i]$$

The concept of *subgraph* is then defined based upon certain graphs.

Definition 3 (Subgraph). *Let $g = (V', E')$ and $G = (V, E)$ be two certain graphs. g is a subgraph of G (denoted as $g \subseteq G$) iff $V' \subseteq V$ and $E' \subseteq E$. We use $g \subseteq G$ to denote that graph g is a subgraph of G. We also say that G contains subgraph g.*

For an uncertain graph $\widetilde{G}$, the probability of $\widetilde{G}$ containing a subgraph feature g is defined as follows:

$$\begin{aligned}\Pr(g \subseteq \widetilde{G}) &= \sum_{G \in \mathcal{W}(\widetilde{G})} \Pr(\widetilde{G} \Rightarrow G) \cdot I(g \subseteq G) \\ &= \begin{cases} \prod_{e \in E(g)} p(e) & \text{if } E(g) \subseteq E(\widetilde{G}) \\ 0 & \text{otherwise} \end{cases}\end{aligned}$$

which corresponds to the probability that a certain graph G implied by $\widetilde{G}$ contains subgraph g.

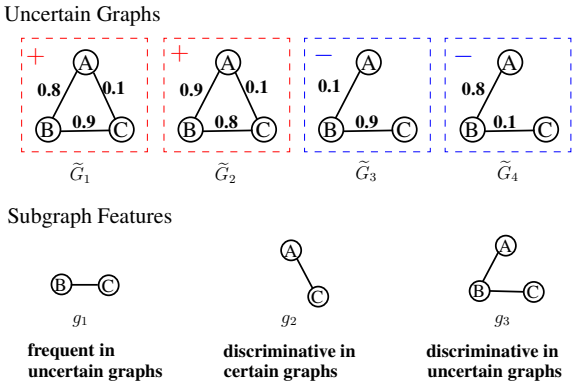


Figure 4: A toy example of uncertain brain networks, and different types of subgraph features [24].

The key issues of discriminative subgraph mining for uncertain graphs can be described as follows: The evaluation of discrimination scores for subgraph features in uncertain graphs is different from conventional subgraph mining problems. For example, in Figure 4, we show an uncertain graph dataset containing 4 uncertain graphs $\widetilde{G}_1, \cdots, \widetilde{G}_4$ with their class labels, $+$ or $-$. Subgraph g_1 is a frequent pattern among the uncertain graphs, but it may not relate to the class labels of the graphs. Subgraph g_2 is a discriminative subgraph features when we ignore the edge uncertainties. However, if such uncertainties are considered, we will find that g_2 can rarely be observed within the uncertain graph dataset, and thus will not be useful in graph classification. Accordingly, g_3 is the best subgraph feature for uncertain graph classification.

The work in [24] proposed a method based on dynamic programming to compute the probability distribution of the discrimination scores for each subgraph feature within an uncertain graph database. Then each of these probability distributions is aggregated to form a certain score based upon different statistical measures, including expectation, median, mode and φ-probability, to select discriminative subgraphs.

5. CONCLUSION

This paper provides an overview of the emerging area of brain network analysis, which has seen increasing attention in data mining communities in the recently years. Many research works on mining brain network data in the literature are not recognized as such in a formal way. This paper provides an understanding of how these works related to different data mining problems and methods. We provided different ways to categorize the data mining problems involved, such as subgraph pattern mining, supervised tensor learning and network extraction. We discussed the issue of mining brain regions that are relevant to certain diseases and the connectivities among these regions.

While brain networks are very challenging for data mining analysis, the problems are not unsurmountable. Many recent research efforts have been devoted to this area, which result in significant improvements in various dimensions. Data mining on brain networks seems to be an emerging area, which can be a fruitful research direction.

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