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Graph Spectral Characterization of Brain Cortical Morphology

Sevil Maghsadhagh\textsuperscript{1}, Anders Eklund\textsuperscript{2}, and Hamid Behjat\textsuperscript{3}

Abstract—The human brain cortical layer has a convoluted morphology that is unique to each individual. Characterization of the cortical morphology is necessary in longitudinal studies of structural brain change, as well as in discriminating individuals in health and disease. A method for encoding the cortical morphology in the form of a graph is presented. The design of graphs that encode the global cerebral hemisphere cortices as well as localized cortical regions is proposed. Spectral metrics derived from these graphs are then studied and proposed as descriptors of cortical morphology. As proof-of-concept of their applicability in characterizing cortical morphology, the metrics are studied in the context of hemispheric asymmetry as well as gender dependent discrimination of cortical morphology.

I. INTRODUCTION

The conventional approach for characterization of brain morphology and study of its changes is to quantify the volumes of a set of brain structures [1]. Cortical thickness measures are also popular means for characterizing morphology [2]. As volume and cortical thickness measures are incapable of capturing the full anatomical information, anatomical shape descriptors [3], [4] have been proposed to provide significant complementary informative representation of brain morphology. For example in [5], it was shown that shape descriptors of cortical and an ensemble of subcortical structures provide a powerful means to discriminate individuals based on their age, sex and neurodegenerative disorder. These shape descriptors use triangular surface mesh volumes or tetrahedral volume tessellation constructions of brain structures, and exploit eigenfunctions of the Laplace-Beltrami operator [6].

Here we build on these works in several respects. Firstly, we use voxel-based graph designs. That is, we use the volumetric voxel representation of the 3D structure of the cortical ribbon, and construct a graph with vertices associated to individual voxels, and connectivities defined based on geodesic adjacencies; designs of graphs based on a similar encoding of gray matter include, subject-specific designs of cerebral [7] and cerebellar [8] cortices and group-based template designs [9], but these graphs were leveraged for analysis of fMRI data rather than shape characterization. Secondly, we encode and exploit morphological information of an ensemble of localized cortical regions as opposed to using shape descriptors of the global cortical structure. This is done by designing graphs that encode localized cortical regions. Thirdly, we propose the use of shape descriptors across different spectral bands in contrast to using exact graph Laplacian eigenvalues.

II. METHODS

A. Graphs and Their Spectra

An undirected, unweighted graph $\mathcal{G} = (\mathcal{V}, \mathcal{E}, A)$ consists of a set $\mathcal{V}$ of $N_g := |\mathcal{V}|$ vertices, a set $\mathcal{E}$ of edges (i.e., pairs $(i, j)$ where $i, j \in \mathcal{V}$), which can be fully described by an adjacency matrix $A$ with elements $A_{i,j}$ equal to 1 if $A_{i,j} \in \mathcal{E}$, and 0, if otherwise.

Using $A$, the graph diagonal, degree matrix $D$ is defined with elements $D_{i,i} = \sum_j A_{i,j}$, and the graph’s normalized Laplacian matrix $L$ is defined as

$$L = I - D^{-1/2} A D^{-1/2}. \quad (1)$$

Since $L$ is symmetric and positive semi-definite, it can be diagonalized as $L = \Sigma \Lambda \Sigma^T$, where $\Sigma = [\chi_1 \chi_2 \cdots | \chi_{N_g}]$, is an orthonormal matrix containing a set of $N_g$ eigenvectors $\{\chi_k\}_{k=1}^{N_g}$, and $\Lambda$ is a diagonal matrix whose entries equal the associated real, non-negative eigenvalues that define the graph spectrum $\mathcal{S}$ as

$$\mathcal{S} = \text{diag}(\Lambda) = \{0 = \lambda_1 \leq \lambda_2 \leq \cdots \leq \lambda_{N_g} \leq 2\}. \quad (2)$$

Unlike classical Euclidean domain spectrum, each graph has a unique definition of spectrum, with a unique range $[0, \lambda_{N_g}]$ and a unique set of irregularly spaced eigenvalues with possibility of multiplicity greater than one.

B. Cerebral Hemisphere Cortex Graphs

1) Global Cerebral Hemisphere Cortex (GCHC) Graphs: For a given hemisphere, a graph that encodes its cortical topology is designed. Cortical ribbons extracted using the FreeSurfer software package [10] serve as the base of the design. Voxels within the cortical ribbon are treated as graph vertices. Graph edges are defined based on 26-neighborhood connectivity of voxels in 3D space. Two vertices are connected through an edge if they lie within each other’s 26-neighborhood. Due to limited voxel resolution, edges derived merely based on Euclidean adjacency may include spurious connections that are not anatomically justifiable, for instance, at touching banks of sulci. By exploiting pial surface extractions, such anatomically unjustifiable connections, i.e., graph edges, are pruned out. No weight is assigned to the edges.
2) Cortical Parcellation: A hemisphere is parcellated into a set of regions of approximately equal volume. For satisfying equality of regional volumes, the number of regions may slightly vary between hemispheres depending on the level of volumetric asymmetry. The parcellation is performed using spectral clustering [11], and graph partitioner Chaco [12] is leveraged for a computationally efficient implementation. Specifically, to parcel the left/right hemisphere in to \( P \) parcels, initially, a set of vectors are defined by sampling the first \( P \) Laplacian eigenvectors of the associated GHCH graph as
\[
y_{i} = [\chi_{1}[i], \chi_{2}[i], \ldots, \chi_{P}[i]], \quad i = 1, \ldots, N_{g}^{(i)},
\]
where \( N_{g}^{(i)} \) denotes the number of vertices of the GHCH graph. Vectors \( \{y_{i}\}_{i=1}^{P} \) are then clustered with the \( \text{k} \)-means algorithm in to \( N \) graph vertex clusters \( \{C_{j}\}_{j=1}^{n} \), where \( C_{1} \cup C_{2} \cup \cdots \cup C_{P} = \{1, \ldots, N_{g}^{(i)}\} \). Voxels associated to each vertex cluster \( C_{i} \) are then treated as a single parcel, resulting in \( N \) localized cortical parcels within the hemisphere.

It is worth noting that in the present work the number of parcels is defined based on a specified desired resolution for the parcels across hemispheres and subjects. In other words, rather than parcellating different hemispheres all in to a fixed number of parcels, we instead keep the parcel size fixed, thus allowing some variation in the number of parcels across hemispheres and subjects.

3) Localized Cerebral Hemisphere Cortex (LCHC) Graphs: A graph is designed for each cortical cluster, which we denote as localized cerebral hemisphere cortex (LCHC) graph. The vertex set of a LCHC graph associated to cluster \( i \) consists of voxels that lie within the associated vertex cluster \( C_{i} \), and the edge set is defined based on the same neighbourhood connectivity principle and pruning approach as that explained in constructing GCHC graphs; in practice, the \( A \) matrices of LCHC graphs can be extracted from the \( A \) matrix of their associated GCHC graph.

C. Spectral characterization of cortical graphs

In the following, we define a set of spectral graph metrics that quantify morphological information across the Laplacian spectra of GHCH graphs and LCHC graphs.

1) Spectral metric for GCHC graphs: Given \( N \) subjects, let \( S_{n}, \ n = 1, \ldots, N \), denote the spectrum of the GCHC graph of the left/right hemisphere of subject \( n \). At a given spectral band, denoted \( \alpha - \beta \) where \( \alpha \in [0, 2], \beta \in (0, 2] \) and \( \alpha < \beta \), a spectral metric is defined on the GCHC graph as
\[
\Theta^{\alpha-\beta}_{n} = |s^{\alpha-\beta}_{n}|,
\]
where \( |\cdot| \) denotes set cardinality and set \( s^{\alpha-\beta}_{n} \) is given as
\[
s^{\alpha-\beta}_{n} = \begin{cases} 
\{\lambda \in S_{n} | \alpha \leq \lambda \leq \beta\}, & \alpha = 0, \\
\{\lambda \in S_{n} | \alpha < \lambda \leq \beta\}, & \text{otherwise}.
\end{cases}
\]
GCHC graphs, at 1 millimeter cubic resolution as presented in this work, have approximately 300 K vertices. Direct computation of \( s^{\alpha-\beta}_{n} \) is thus computationally cumbersome as it requires deriving exact eigenvalues of the \( L \) matrix. In particular, to compute \( s^{\alpha-\beta}_{n} \) at different spectral bands spanning the entire spectrum, a full eigendecomposition of matrix \( L \) is needed, which is practically infeasible. In this work, for GCHC graphs, we compute their exact spectra within \([0, 0.1]\), i.e., lower 5% spectral tail, and use an approximation scheme to estimate the number of eigenvalues that fall within spectral bands at upper parts of the spectra.

The approximation is performed using the spectrum slicing method [13, Section 3.3], which has also been previously used in [14] for approximating graph spectra. Specifically, the number of eigenvalues of \( L \) that fall below a given \( \alpha \in [0, 2) \) can be computed as follows. Firstly, a triangular factorization of matrix \( L - \alpha I \) is performed, i.e., \( L - \alpha I = \Pi \Delta \Pi^{T} \), where \( \Pi \) is a lower triangular matrix and \( \Delta \) is a diagonal matrix. Secondly, by invoking a corollary of Sylvester’s law of inertia, it holds that the number of negative eigenvalues of \( \Delta \), denoted \( N_{\beta} \), is equal to the number of negative eigenvalues of \( L - \alpha I \), and thus equal to the number of eigenvalues of \( L \) less than \( \alpha \). Similarly, the number of eigenvalues of \( L \) that fall below a given \( \beta \in [0, 2], \beta > \alpha \), denoted \( N_{\beta}^{\alpha} \), can be estimated. An approximation of \( s^{\alpha-\beta}_{n} \) is thus given by \( N_{\beta}^{\alpha} - N_{\alpha} \).

2) Spectral metric for LCHC graphs: Assume the left/right hemisphere of subject \( n \) being parcellated, at a desired resolution, in to \( K_{n} \) parcels, thus, resulting in a set of \( K_{n} \) LCHC graphs. Let \( S_{n,k}, \ k = 1, \ldots, K_{n} \), denote the Laplacian spectrum of the \( k \)-th LCHC graph of subject \( n \). At a given spectral band, denoted \( \alpha - \beta \) where \( \alpha \in [0, 2], \beta \in (0, 2] \) and \( \alpha < \beta \), a spectral metric is defined on the set of LCHC graphs as
\[
\theta^{\alpha-\beta}_{n} = \frac{1}{K_{n}} \sum_{k=1}^{K_{n}} |s^{\alpha-\beta}_{n,k}|, \quad n = 1, \ldots, N,
\]
where set \( s^{\alpha-\beta}_{n,k} \) is given as
\[
s^{\alpha-\beta}_{n,k} = \begin{cases} 
\{\lambda \in S_{n,k} | \alpha \leq \lambda \leq \beta\}, & \alpha = 0, \\
\{\lambda \in S_{n,k} | \alpha < \lambda \leq \beta\}, & \text{otherwise}.
\end{cases}
\]
It is worth noting that \( \sum_{k=1}^{K_{n}} s^{\alpha-\beta}_{n,k} \) is generally not equal to \( s^{\alpha-\beta}_{n} \), nor is \( \{S_{n,1} \cup S_{n,2} \cup \cdots \cup S_{n,K_{n}}\} = S_{n} \), as has been empirically observed, consistently, across our analysis.

This observation provides intuition showing that the spectra of LCHC graphs can be seen as a novel decomposition of the single spectrum of the associated GCHC graph, such that the unity of the LCHC graph spectra is not equal to the single GCHC graph spectrum. Detailed theoretical analysis of this property is deferred to future work.

D. Statistical analysis of variations in cortical morphology

In the following, results from hypothesis tests on i) left-right hemisphere asymmetry and ii) hemispheric morphological differences between gender are presented. The primary objective with these tests is to study the variability of the proposed spectral metrics \( \Theta^{\alpha-\beta}_{n} \) and \( \theta^{\alpha-\beta}_{n,k} \), across various
spectral bands and parcellation resolutions. We report p-values that result from the tests as a means to study the variations. We do not attempt to attach any tag of significance to the findings, and as such, uncorrected p-values are reported.

### III. Results

The analyses were performed on a subset of subjects from the Human Connectome Project [15] database, consisting of 75 female and 75 male subjects, all within the age group of 31-35 years. The female and male subject subsets were selected objectively based on the numerical ordering of HCP subject identifiers, starting from smallest identifiers. Fig. 1 shows the right hemispheres of 6 of the subjects, where the first three subjects are females and the second three are males; cortical parcellations obtained using the scheme described in Section II-B.2 are also illustrated.

#### A. Graph spectral markers of hemispheric asymmetry

Variations in the cortical morphology between left and right hemisphere have been numerous in reported in literature, see for example [16]. Wilcoxon rank-sum test analysis was performed on the right hemispheres, implemented separately for each gender to prevent bias. The tests were performed on $\Theta_{n,k}^{\alpha-\beta}$ and $\theta_{n,k}^{\alpha-\beta}$ metrics across different spectral bands. Table I summarizes the resulting statistical p-values. P-values obtained from tests on $\Theta_{n,k}^{\alpha-\beta}$ are lower than corresponding ones obtained from test on $\theta_{n,k}^{\alpha-\beta}$, across different parcellation resolutions, excluding the first spectral band. This suggests the superiority of GCHC graphs in encoding hemispheric asymmetry over LCHC graphs.

### TABLE I: Hemispheric asymmetry. P-values from Wilcoxon rank-sum tests on sets i) $\Theta_{n,k}^{\alpha-\beta}$, for the left hemispheres of the male group, and ii) $\theta_{n,k}^{\alpha-\beta}$, for the right hemispheres of the male group, across different spectral bands and parcellation resolutions. Similarly, the last column shows p-values from Wilcoxon rank-sum tests analyses were performed on sets i) $\Theta_{n,k}^{\alpha-\beta}$, for the left hemispheres of the male group, and ii) $\theta_{n,k}^{\alpha-\beta}$, for the right hemispheres of the male group. The same tests performed on the female group led to similar results; results not presented due to limit of space.

| Spectral Band | Local Graphs | Global Graphs |
|---------------|--------------|--------------|
|               | 5K | 6K | 7K | 8K | 9K | 10K |
| 0 – 0.1       | 0.1021 | 0.1351 | 0.0600 | 0.0602 | 0.1458 | 0.1902 | 0.1479 |
| 0.1 – 0.2     | 0.0971 | 0.1356 | 0.0527 | 0.0577 | 0.1796 | 0.1960 | 0.0320 |
| 0.2 – 0.3     | 0.2057 | 0.4136 | 0.0985 | 0.1986 | 0.6165 | 0.9980 | 0.0012 |
| 0.3 – 0.4     | 0.4355 | 0.9646 | 0.3571 | 0.5058 | 0.7881 | 0.4511 | 4.8 \times 10^{-4} |
| 0.4 – 0.5     | 0.0863 | 0.5413 | 0.5627 | 0.7224 | 0.5798 | 0.0594 | 4.9 \times 10^{-4} |
| 0.5 – 0.6     | 0.0718 | 0.6903 | 0.3531 | 0.8609 | 0.0699 | 0.0943 | 7.1 \times 10^{-4} |
| 0.6 – 0.7     | 0.1527 | 0.9281 | 0.1381 | 0.4158 | 0.2936 | 0.2635 | 6.8 \times 10^{-4} |
| 0.7 – 0.8     | 0.0432 | 0.5602 | 0.0664 | 0.1600 | 0.8317 | 0.5309 | 7.1 \times 10^{-4} |
| 0.8 – 0.9     | 0.0350 | 0.3801 | 0.0610 | 0.2627 | 0.6264 | 0.3863 | 0.0014 |
| 0.9 – 1.0     | 0.0302 | 0.3920 | 0.0610 | 0.2627 | 0.6264 | 0.3863 | 0.0015 |
| 1.0 – 1.1     | 0.3297 | 0.0754 | 0.3822 | 0.3192 | 0.1044 | 0.0153 | 7.1 \times 10^{-4} |
| 1.1 – 1.2     | 0.0555 | 0.1056 | 0.0112 | 0.0360 | 0.2037 | 0.5767 | 0.0025 |
| 1.2 – 1.3     | 0.0237 | 0.1852 | 0.0104 | 0.0340 | 0.3397 | 0.9341 | 0.0017 |
| 1.3 – 1.4     | 0.1441 | 0.4163 | 0.0584 | 0.0821 | 0.2524 | 0.2926 | 0.0220 |
| 1.4 – 1.5     | 0.0397 | 0.0221 | 0.0049 | 0.0103 | 0.1390 | 0.0147 | 0.0010 |
| 1.5 – 1.6     | 2.3 \times 10^{-7} | 8.2 \times 10^{-5} | 1.2 \times 10^{-4} | 1.5 \times 10^{-5} | 1.5 \times 10^{-4} | 7.3 \times 10^{-6} | 3.8 \times 10^{-5} |
| 1.6 – 1.7     | 0.0012 | 9.6 \times 10^{-4} | 1.6 \times 10^{-4} | 0.0012 | 0.0025 | 1.4 \times 10^{-4} | 1.1 \times 10^{-2} |
| 1.7 – 1.8     | 0.0017 | 0.0124 | 0.0003 | 6.8 \times 10^{-4} | 0.0180 | 4.0 \times 10^{-4} | 1.2 \times 10^{-4} |
| 1.8 – 1.9     | 0.2075 | 0.5377 | 0.3065 | 0.3388 | 0.0324 | 0.1787 | 0.0694 |
| 1.9 – 2.0     | 0.2311 | 0.9179 | 0.1056 | 0.7198 | 0.7172 | 0.0684 | 0.4057 |

Yet, it should be noted that a large extent of the p-values would survive even a strict Bonferroni correction for the number of spectral bands studied.
Fig. 2: Eigenvectors of the GCHC graph and three LCHC graphs associated to the right hemisphere of subject S1, cf. Fig. 1, overlaid on the cortical ribbon shown in gray. Note that the eigenvectors are defined in 3D space whereas only a single axial slice of them is shown, which limits manifesting their full spatial variation. Eigenvectors of LCHC graphs better capture localized morphological variations, whereas those of the GCHC graph better capture global topological variations.

TABLE II: Same as in Table I but on a set of narrower spectral bands spanning spectral range [0, 0.1]; results on spectral band 0 – 0.1 replicated from Table I. Tests that led to p-values lower than that obtained on corresponding tests at spectral band [0, 0.1] are underlined.

| Spectral Bands | Local Graphs 5K | 6K | 7K | 8K | 9K | 10K | Global Graphs |
|----------------|-----------------|----|----|----|----|-----|---------------|
| 0 – 0.01       | 0.3229          | 0.4670 | 0.3210 | 0.5558 | 0.2290 | 0.9730 | 0.4800 |
| 0.01 – 0.02    | 0.1153          | 0.4821 | 0.1004 | 0.8312 | 0.3415 | 0.0633 | 0.4590 |
| 0.02 – 0.03    | 0.4705          | 0.0109 | 0.0429 | 0.7879 | 0.2992 | 0.1392 | 0.7420 |
| 0.03 – 0.04    | 0.0059          | 0.5388 | 0.7078 | 0.4999 | 0.2757 | 0.4774 | 0.3270 |
| 0.04 – 0.05    | 0.5526          | 0.3425 | 0.2388 | 0.2225 | 0.0586 | 0.0879 | 0.8280 |
| 0.05 – 0.06    | 0.2823          | 0.0231 | 0.2386 | 0.0173 | 0.5262 | 0.9795 | 0.9520 |
| 0.06 – 0.07    | 0.0312          | 0.3065 | 0.0337 | 0.2363 | 0.2106 | 0.0237 | 0.0770 |
| 0.07 – 0.08    | 0.7290          | 0.1080 | 0.7217 | 0.2402 | 0.1422 | 0.7795 | 0.2775 |
| 0.08 – 0.09    | 0.6384          | 0.8579 | 0.1973 | 0.0424 | 0.4844 | 0.0738 | 0.4780 |
| 0.09 – 0.1     | 0.9247          | 0.3110 | 0.0291 | 0.7437 | 0.0237 | 0.5826 | 0.3508 |

To provide better discrimination. This observation can be interpreted as that discrimination of gender is best exhibited as regional variations in cortical morphology rather than as global hemispheric variations.

With similar reasoning as that provided in Section III-A, the tests were also performed at narrow spectral bands in the lower-end of the spectra. The results are shown in Table IV. Table III, all tests led to significant p-values. In contrast to tests on hemispheric asymmetry, these tests on gender variation at narrow spectral bands in the lower end of the spectra resulted in few lower p-values than that obtained on the spectral band [0, 0.1]; see underlined values in Table IV.

IV. CONCLUSIONS

The design of cerebral cortical graphs, consisting of global hemisphere graphs and localized cortical graphs, was presented. Global hemisphere graphs encode the global topology cerebral hemisphere cortices, whereas local cortical graphs capture more subtle localized variations in cortical morphology. The set of spectra of local cortical graphs can be seen as an implicit decomposition of the single spectrum of the associated global hemisphere graph. Experimental results suggest the benefit of spectral features of cortical graphs as a powerful means for discriminative characterization of cortical morphology in relation to gender. Our future work will focus on testing the proposed cortical graph features on a larger cohort of healthy as well as patient subjects. Characterization and early detection of changes in cortical morphology that arise in various types of dementia [18], [19], in particular, Alzheimer’s disease, will be explored. The proposed cortical graphs can also be found applicable for graph spectral processing of functional MRI data, see for example [9], in particular, through exploiting novel spectral graph filter design algorithms [20] that allow adaptation to both cortical structure as well as graph spectral content [21] of cortical activity.

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TABLE III: Validation of LCHC and GCCHC graph spectral metrics for discrimination of gender. P-values from Wilcoxon rank-sum tests on \(\left(\theta_{n-1}\right)_{\alpha=1,70}\) on groups: i) the set of 75 leftfri hematical hemispheres, the male group, and ii) the set of 75 leftfri hematical hemispheres of the female group, are presented. Similarly, p-values from Wilcoxon rank-sum tests on \(\left(\theta_{n-1}\right)_{\alpha=1,70}\) on the same two groups are also presented. For both LCHC and GCCHC graphs, tests were performed across different spectral bands, and for the LCHC graphs, also across different parcellation resolutions.

TABLE IV: Same as in Table III but on a set of narrower spectral bands spanning spectral range [0, 0.1]; results on spectral band 0 - 0.1 replicated from Table III. Values lower than that on corresponding tests at spectral band 0 [0, 0.1] are underlined.