A Hierarchical Brain Parcellation Method Based on Discrete Morse Theory for High-Resolution Resting-State Functional MRI Data

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Abstract

The subdivision of the brain into functionally distinct regions is a crucial step towards a deeper understanding of its functional architecture. Resting-state functional magnetic resonance imaging (rs-fMRI) based methods have been used to produce brain parcellations with functional significance and high intra-subject reproducibility. Recent developments in fMRI acquisition technology at ultra-high field (7T) allow whole-brain fMRI with unprecedented spatial and temporal resolution. A novel functional parcellation approach that uses methods from computational topology related to discrete Morse theory and persistent homology is presented in this work. It provides a unifying framework that is capable of efficiently deriving subject-specific parcellations from high-resolution data at multiple levels of detail, through a theoretically meaningful measure of scale, as well as the ability to match parcellations from multiple datasets of the same subject.

The novel method is applied to rs-fMRI data collected from 9 subjects on a 7T system, using ultra-high spatial resolution covering the whole-brain. We show its capability to produce parcellations with up to 80k parcels, with high functional homogeneity and high within-subject reproducibility, while remaining sensitive to differences in the data. In conclusion, these results indicate that the method proposed and implemented in this Thesis may provide an adequate tool for the functional parcellation of the brain with extremely fine detail based on rs-fMRI data, with potentially important implications to the study of human brain networks.

Keywords

Brain parcellation; resting-state functional magnetic resonance imaging (rs-fMRI); ultra-high resolution; discrete Morse theory; persistent homology
Resumo

A subdivisão do cérebro em regiões de funcionalidade distinta é um passo crucial para uma compreensão aprofundada da arquitetura funcional do mesmo. Métodos de parcelamento do cérebro que utilizam imagens de ressonância magnética funcional obtidas em repouso (rs-fMRI) são capazes de extrair regiões funcionais com boa reprodutibilidade entre dados do mesmo sujeito. Desenvolvimentos recentes em técnicas de aquisição através de campos ultra-elevados (7T) permitem obter dados de fMRI de todo o cérebro com detalhe espacial e temporal sem precedentes. Neste trabalho, é proposta uma nova técnica de parcelamento funcional baseada em métodos da topologia computacional relacionados com a teoria de Morse discreta e a homologia persistente. Esta abordagem une a capacidade de obter parcelamentos de cada sujeito com grande eficiência computacional para múltiplos níveis de detalhe, através de uma medida de escala informada do ponto de vista teórico, com a capacidade de obter correspondências entre regiões de parcelamentos de diferentes dados do mesmo sujeito.

Este método foi aplicado em dados de rs-fMRI adquiridos para 9 sujeitos num sistem 7T, utilizando alta resolução e cobrindo todo o cérebro. É demonstrada a sua capacidade de produzir parcelamentos de até 80 mil parcelas, com elevada homogeneidade funcional e elevada reprodutibilidade entre dados do mesmo sujeito, mas sensível a diferenças nos dados. Em conclusão, estes resultados indicam que o método apresentado e implementado nesta Tese possa ser uma ferramenta adequada para um parcelamento funcional do cérebro extremamente detalhado com dados de rs-fMRI, e com potenciais implicações no estudo de redes no cérebro humano.

Palavras Chave

Parcelamento do cérebro; ressonância magnética funcional em repouso (rs-fMRI); resolução ultra-elevada; teoria de Morse discreta; homologia persistente
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Abbreviations

AAL  Automated Anatomical Labeling
BOLD  blood oxygen level dependent
CBF  cerebral blood flow
CFFF  combinatorial feature flow fields
CSF  cerebral spinal fluid
DMN  default-mode network
dMRI  diffusion MRI
DOF  degrees of freedom
EEG  electroencephalography
EVI  echo volume imaging
FC  functional connectivity
fCNR  functional contrast-to-noise ratio
FID  free induction decay
FLIRT  FMRIB's linear image registration tool
fMRI  Functional MRI
FNIRT  FMRIB's non-linear image registration tool
FSL  FMRIB Software Library
ICA  independent component analysis
MEG  magnetoencephalography
MRI  magnetic resonance imaging
NMR  nuclear magnetic resonance
PCA  principal component analysis
PET  positron emission tomography

RETROICOR  retrospective image correction

ROI  region of interest

rs-FC  resting-state functional connectivity

rs-fMRI  resting-state fMRI

RSN  resting-state networks

SMS  simultaneous multi-slice

SNR  signal-to-noise ratio

SPECT  single photon emission computed tomography

SPM  Statistical Parametric Mapping

TE  echo time
1 Introduction

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This chapter is aimed at introducing the main aspects related to brain functional parcellations. It includes a motivation for this work, a brief review of the principles of magnetic resonance imaging (MRI) with a special emphasis on resting-state fMRI (rs-fMRI), a review of the state-of-the-art in brain parcellation, a summary of the contributions of this work and, finally, an outline of the structure of the remaining chapters.

1.1 Motivation

Functional segregation and functional integration are defining aspects of the functional architecture of the brain [1]. These principles represent the specialisation of different regions of the brain that is present at multiple spatial scales, from small groups of neurons specialised for specific types of stimuli to large brain regions participating in specific cognitive tasks, and their spatial-temporal modes of interaction. These properties emerge from the necessity of fast and adaptive behaviour in response to stimuli in a unified and coherent experience [2].

This view is consistent with a small-world model [3] of brain organization where a hierarchy of densely intra-connected neighbouring regions is integrated in networks of high global efficiency [4]. These features reflect a balance between the physical cost of the connections in a network and the adaptability of its topology to different stimuli, variable cognitive demands and, possibly, different stages of brain development [5]. Thus, understanding these network topological properties, as well as the location, shape and size of their constituent individual functional units across different scales, is an essential part of characterising brain function.

Functional MRI (fMRI) is a non-invasive technique that determines neural activation by measuring changes in the content of oxygen in the blood associated to local brain metabolism [6]. This blood oxygen level dependent (BOLD) signal can be used to study interactions between different regions in the brain. This interactions between segregated areas provide a way to assess functional integration, and are usually understood in terms of functional connectivity (FC), which can be inferred using measures of statistical dependencies among the time-series of fMRI data [7].

Spontaneous fluctuations in the BOLD signal can be observed in the resting brain and are viewed as a manifestation of spontaneous neuronal activity [8]. Resting-state functional connectivity reveals patterns of spatial and temporal coherence that presumably reflect the dynamics on anatomical connectivity structures [7]. This suggests that rs-fMRI data provides the required information to measure functional homogeneity across the whole brain.

Apart from its importance to mapping functional segregation, an accurate delineation of functionality distinct regions in the brain is imperative to modelling meaningful networks in brain connectivity studies [9]. Several methods exist for obtaining rs-fMRI based parcellations but only recently these have shown a high intra-subject reproducibility and borders that reflect the changes in functional connectivity at various scales [10].

Recent advances in MRI acquisition technology, such as the development of fast acquisition sequences at ultra-high-fields (7T), have made possible to obtain whole-brain fMRI data with high spatial
and temporal resolution [11]. However, the benefits of additional structure in these data come at the cost of adapting existing methods to efficiently handle the higher amount of information, both computationally and in terms of seizing its most important aspects.

1.2 A Brief Review of Functional Magnetic Resonance Imaging (fMRI)

This section introduces the basic concepts related to [fMRI]. This treatment follows [12] and [13] for an introduction to NMR and MRI, and [14] for aspects related to quantum-mechanics.

1.2.1 Principles of Nuclear Magnetic Resonance (NMR)

The phenomenon of nuclear magnetic resonance (NMR) is associated with the behaviour of atomic nuclei of non-zero spin under a uniform external magnetic field. These atoms have an odd number of neutrons or protons and so their spins do not cancel each other out. Quantum mechanics establishes that for a nucleus of spin number \( I \), only \( 2I + 1 \) energy states are allowed. Orientations that correspond to extremal energy states have a magnetic moment \( \mu \) that is either aligned parallel (lowest energy) or aligned anti-parallel (highest energy) to the field. In the case of hydrogen-1, which has \( I = \frac{1}{2} \), these are the only allowed states and transitions may occur between the two with either an absorption or an emission of a photon. The energy of these photons, and hence their frequency, is related to the strength of the uniform field \( B_0 \) by the Larmor equation

\[
\omega_0 = \gamma B_0,
\]

where \( \gamma \) is the gyromagnetic ratio and \( \omega_0 \) is the Larmor frequency. In a classical perspective, this means that \( B_0 \) applies a torque on \( \mu \) so that it aligns with the magnetic field and precesses about it, with frequency \( \omega_0 \), due to its angular momentum.

The presence of thermal energy from ambient non-zero temperature \( T \) means that not all of the nuclei will be in the lower energy state but there is a proportion between the two states with a preponderance of lower energy states. This proportion is given by the Boltzmann factor

\[
\frac{n_-}{n_+} = e^{-\frac{\gamma \hbar \omega_0}{2k_B T}},
\]

where \( k_B \) is the Boltzmann constant. This preponderance of lower energy states appears as spin excess that can be represented as a magnetization vector \( M \), while all other spins cancel out and are thus invisible. Precession is not observable when \( M \) is aligned parallel to \( B_0 \) as, in this case, \( M \) has no transverse component that can be detected by induction. An oscillating magnetic field \( B_1 \) in resonance with the nuclei and perpendicular to \( B_0 \), applies a torque that is orthogonal to the torque of \( B_0 \) and rotates the magnetization vector about its axis, out of equilibrium into the transverse plane (perpendicular to \( B_0 \)). Equivalently, in terms of quantum mechanics, \( B_1 \) transmits energy with frequency \( \omega_0 \), thus stimulating (observable) transitions between the two states. The signal is picked up by a coil as induced voltage and, terminated the application of \( B_1 \), gradually decays with time as the
spins come back to thermal equilibrium. This constitutes what is called the free induction decay (FID) and the time it takes to re-establish equilibrium is determined by two relaxation mechanisms, spin-lattice and spin-spin relaxation, characterised by time constants T1 and T2, respectively.

The amount of time during which $B_1$ is applied determines the angle between $\mathbf{M}$ and the $z$-axis. A $90^\circ$ pulse induces the largest possible transverse component while an $180^\circ$ pulse does not induce a transverse component. A different behaviour occurs when an $180^\circ$ pulse is applied after a $90^\circ$ pulse at time $\tau$. In this case, $\mathbf{M}$ is flipped through the origin i.e. $\phi(\tau^+) = -\phi(\tau^-)$ where $\phi$ is the accrued phase from free precession, relative to the $x$-axis, such that $\phi$ will be zero again at time $2\tau$. This effect is referred to as the spin echo and $\text{TE} = 2\tau$ is called the echo time.

Three relaxation times are of primary interest to MRI. T1 or spin-lattice relaxation, is related to energy exchange processes with the thermal reservoir (the thermal energy of the molecules) and to a recovery of the longitudinal component of the magnetization vector $\mathbf{M}$ following a perturbation from a $90^\circ$ pulse. T2 or spin-spin relaxation, is related to energy exchange processes between the spins as they get out of phase with each other causing a decay of the transverse magnetization. These two exponential processes are defined phenomenologically by the following Bloch equations

$$\frac{dM_z}{dt} = \frac{M_z - M_0}{T1},$$
$$\frac{dM_{x,y}}{dt} = \frac{M_{x,y}}{T2},$$

and their corresponding solutions

$$M_z(t) = M_0(1 - e^{-\frac{t}{T1}}),$$
$$M_{x,y}(t) = M_0 e^{-\frac{t}{T2}},$$

where T1 and T2 are the time constants associated with these processes. The T2* relaxation results from large-scale variations in the static magnetic field related to the geometry and composition of the sample and inhomogeneity in $B_0$. It is related to T2 by the following equation

$$\frac{1}{T2^*} = \frac{1}{T2} + \gamma \pi \Delta B_0,$$

where $\Delta B_0$ is the static field variation in the sample or voxel. Contrarily to a T2 relaxation, the T2* processes can be refocused using an $180^\circ$ spin echo sequence as these do not come from random events at the molecular level.

### 1.2.2 Magnetic Resonance Imaging

The spatial specificity that is at the core of MRI comes from the relationship between frequency and position in a spatially varying magnetic field. In the simplest case, the field varies linearly with position. This relationship is given, for a set of gradient coils (in $n$ orthogonal directions) of gradient $\mathbf{G}$, by

$$\omega(\mathbf{r}, t) = \gamma B_0 + \gamma \mathbf{G} \cdot \mathbf{r},$$

where $\mathbf{r} \in \mathbb{R}^n$ is position.
There are two additional concepts that are fundamental to common volumetric imaging methods in MRI: slice selection and Fourier imaging.

The selection of a single slice from a three dimensional object is done using a slice selective excitation pulse. This pulse excites only those spins whose Larmor frequencies lie within its spectrum, thus exploiting the fact that their precession frequency depends on position in the presence of a field gradient.

The phase of the magnetization vector in the precession can be described as

\[ \phi(r, t) = \int_0^t \omega(r, \tau) \, d\tau = \gamma B_0 t + \gamma \mathbf{G} \cdot \mathbf{r}. \]  

(1.9)

By removing the carrier frequency factor \( \exp(-i\omega_0 t) \) through demodulation, the signal obtained in the coil is a summation of the contribution from every location in the sample, as

\[ S(t) = \int \rho(r)e^{-i\phi(r, t)} \, dr = \int \rho(r)e^{-i\gamma \mathbf{G} \cdot \mathbf{r} t} \, dr, \]  

(1.10)

where \( \rho(r) \) is the number density of spins. Making the substitution \( k = \gamma \mathbf{G} t \), where \( k \) is a spatial-frequency variable, (1.10) becomes

\[ S(k) = \int \rho(r)e^{-ik \cdot r} \, dr. \]  

(1.11)

From (1.11) it becomes clear that \( S \) and \( \rho(r) \) are a Fourier pair so that

\[ \rho(r) = \int S(k)e^{ik \cdot r} \, dk. \]  

(1.12)

This means that at any time \( t \), \( S(t) \) is the value of the Fourier transform of \( \rho(r) \) at some spatial frequency \( k \) and that it is possible, in principle, to reconstruct \( \rho(r) \) in the whole spatial domain by performing a 2D (or 3D) inverse Fourier transform.

1.2.3 Functional MRI

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique that extends the framework of MRI to provide detection of activated brain regions. Unlike other functional neuroimaging methods such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), it is totally noninvasive and offers, in principle, higher spatial and temporal resolution. Electromagnetic techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) provide a much higher temporal resolution (on the order of milliseconds rather than seconds) but because measurements are mostly performed using surface sensors in the scalp, spatial information is limited by the source localization problem that arises from the geometry of their placement; whereas fMRI can provide whole brain coverage. This technique relies on measuring blood oxygenation throughout the brain to make inferences about neuronal activation.

1.2.3.A BOLD contrast mechanism

The blood oxygen level dependent (BOLD) signal is related to localized variations in the concentration of deoxyhemoglobin in the brain. Hemoglobin can have two forms: one saturated with
oxygen molecules and one desaturated, and these are named oxyhemoglobin and deoxyhemoglobin, respectively. When oxyhemoglobin releases its oxygen through the capillaries and turns into deoxyhemoglobin, it changes from being diamagnetic to being paramagnetic. This difference in magnetic susceptibility causes a distribution of shifts in the resonance frequencies of the water molecules in the blood and its surrounding tissue [15]. This effect is particularly strong on T2* relaxation that due to its sensitivity to field inhomogeneities decreases with increasing deoxyhemoglobin [16]. However, following neural activation, there is an increase in cerebral blood flow (CBF) that overcompensates for the decrease in oxygen and delivers an oversupply of oxygenated blood that results in increased BOLD contrast [16]. This type of increase in local CBF can be associated to neuronal activation because it can, in turn, be associated to glucose metabolism resulting from neuronal activity [17].

1.2.3.B Resting-state fMRI

The most widely disseminated approach to study brain function with fMRI has been to measure the changes in the BOLD signal that can be attributable to the alternation between a given task or stimulus and rest (experimental paradigm) and to map to their corresponding function, the regions of the brain for which these variations are statistically significant. This is known as task-based fMRI. In these studies, any spontaneous fluctuations in the BOLD signal that cannot be attributed to the experimental paradigm can be modelled as noise and lose importance with increasing statistical power.

The conclusion that this spontaneous fluctuations are not random noise but exhibit a high degree of temporal correlation and patterns of spatial organization [18] paved the way for a wide range of studies of spontaneous BOLD activity in the brain at rest. This technique for studying brain region interactions in the absence of specific inputs or outputs is known as resting-state fMRI (rs-fMRI). Regions with correlated BOLD activity during rest have been found to show similar functionality in task-activation studies, meaning that they reflect functional topography [8]. This property of rs-fMRI data makes it particularly appropriate for studying functional connectivity (FC). The most common techniques to study FC with rs-fMRI are: seed analysis, where the time-course from a region of interest is extracted and its temporal correlation with all other voxels is estimated; clustering algorithms that determine a partition of the voxels based on a similarity measure between their time-courses; and data-driven approaches such as independent component analysis (ICA) or principal component analysis (PCA), which decompose the data into different components by assuming orthogonality or independence between activation and other signal variations [8].

Sources of non-neural origin, such as head motion, cardiac pulsation, respiration or cerebral spinal fluid (CSF) flow constitute a considerable fraction of the variance of spontaneous BOLD activity, but regressing out this physiological and motion induced fluctuations using heart beat, respiration recordings, and estimates of subject motion or data-driven nuisance regression techniques can help to minimize their influence [19].

There are sets of co-activating regions, known as resting-state networks (RSN), that have been shown to delineate anatomically and functionally plausible networks, which are robust across subjects [20]. These include the default-mode network (DMN), which remains active during rest but exhibits
consistent task-related deactivations [21][22], where this behaviour should be related to functional incompatibility and suppression in sensory areas [23]. These networks should characterise intrinsic properties of the brain functional architecture [8].

1.2.3. C fMRI at ultra-high fields

In fMRI signal-to-noise ratio (SNR) increases linearly with increasing magnetic field strength, which can be used for higher spatial resolution [24]. At ultra-high fields (most commonly 7T), this effect is compounded by an improvement of functional contrast-to-noise ratio (fCNR) and together they provide a much greater spatial specificity, allowing to determine functional segregation down to the level of cortical columns [25]. This increase in field strength, however, poses significant technical difficulties as it becomes harder to complete k-space encoding for the whole-brain within the T2* decay time and because physiological noise scales with it [11]. Thus, improved acquisition hardware that provides better gradient performance, parallel imaging through highly parallel array coils, higher-order shimming and parallel transmit through multiple excitation coils, as well as advanced acquisition techniques such as echo volume imaging (EVI) and simultaneous multi-slice (SMS) EPI acquisition, and improved modelling of nuisance signals are required to take advantage of ultra-high fields for fMRI [11].

1.3 State-of-the-art on Brain Parcellation

The subdivision of the brain into functionally separable regions has been an active subject of research in the functional neuroimaging community. In addition to its manifest importance for brain mapping, these parcellations provide a meaningful and, to some extent, interpretable definition of network nodes for brain connectivity studies. While analyses using voxels as network nodes may provide a greater spatial localization ability [26], these define an arbitrary spatial resolution that is dependent on the acquisition technique and does not represent a primary neural unit [27][28], and often carry redundant information that may result in local spatial correlations manifesting as edges in the absence of direct functional connectivity [26]. On the other hand, region-based analyses should avoid these problems, as well as provide a better model for regions of activity as they can be characterized in fMRI data [27], higher signal to noise ratio [28], and much lower computational cost. However, an inaccurate delineation of these regions may introduce voxels with substantially different time-courses that add noise without contributing any signal [28] and significantly alter network estimation [9].

1.3.1 Anatomically-defined parcellation

A common practice in region-based functional connectivity analyses is to use atlases based on anatomically-defined regions of interest, such as those provided by software packages such as the Automated Anatomical Labeling (AAL) toolbox, FMRIB Software Library (FSL) (Harvard-Oxford) or FreeSurfer. These atlases are typically derived from manual segmentation and averaging individual labels normalized to stereotaxic space [29-32]. Other methods such as cytoarchitectonic mapping,
diffusion MRI (dMRI) or myelin content studies also produce anatomical parcellations [10]. The brain of each subject is then normalized to standard space in order to obtain each individual parcellation. This dependence on a spatial normalization procedure makes this approach particularly sensitive to misregistrations, either artifactual or from individual anatomic variability and differences in functional organization [27].

1.3.2 rs-fMRI-based parcellation

As discussed above, resting-state fMRI data should provide the required information to measure functional homogeneity and functional connectivity, thus functional areas could be determined using either one [33] or the other [34].

So far, there is only limited literature on rs-fMRI based parcellation methods but these range from unsupervised learning methods and methods from computer vision (such as region-growing and watershed segmentation) to graphical model approaches that rely either on continuous parametric distributions or on Markov Random Fields; see [35, 36]. The majority of those methods, however, does not enforce spatial contiguity of the regions which is an essential property when the distinction between network nodes and functional networks is desired [37, 38]. State-of-the-art methods impose some sort of spatial constraint in their clustering algorithms, in order to satisfy this requirement [10, 36, 37].

A spectral clustering approach for clustering whole-brain rs-fMRI data was proposed in [37]. This approach represents the data as a graph whose nodes are the voxels in the brain and whose edges represent the similarity between their time-courses. Only the similarity between neighbouring voxels is nonzero so that the clustering algorithm produces contiguous regions. The normalized cuts algorithm [39] is used to compute a partition of the graph because it maximizes the similarity within clusters while minimizing the similarity between clusters. Unfortunately, while this creates regions of uniform size in cases of ambiguity, it also tends to strongly bias the overall distribution of region sizes [10, 37].

A region-growing approach for obtaining individual brain parcellations was proposed in [10], which grows a set of stable seeds into an initial detailed parcellation that is further clustered using a hierarchical approach that enforces spatial contiguity of the parcels. The initial seeds are obtained by computing a stability map that evaluates the suitability of every time-course in the image to be representative of its neighbourhood, applying a surface-based Gaussian kernel smoother and finding its local minima. These minima are then grown into non-overlapping regions that form an initial parcellation. This growing process is regulated by an aggregation criterion. Parcellations from a range of scales are then obtained by using a hierarchical clustering algorithm to merge neighbouring regions based on the similarity between their representative time-courses. This ensures the spatial contiguity of the regions. This method was shown [10] to have a high scan-to-scan reproducibility, borders that follow changes in the functional connectivity profile and a high overlap to clusters derived from task fMRI data. This approach performs a Gaussian kernel smoothing of the stability map as a pre-processing step to remove spurious features, which has the effect of attenuating the high frequency components in the data, thus preventing parcellations at finer scales, which makes it inadequate to explore the high spatial resolution of ultra-high field fMRI. In addition, the region growing process that
builds the initial parcellation trades performance for computational speed with an empirically tuned aggregation criterion.

1.4 Goals and Approach

The main goal of this thesis is to develop a novel functional parcellation approach for high resolution rs-fMRI data recorded at ultra-high field (7 Tesla), which is based on the principles underlying the method in [10], described in [1.3.2]. Therefore, the specific aims of this thesis were to:

• Capture the much higher detail provided by the improved spatial resolution of MRI at ultra-high fields.
• Control the level of detail of the parcellation to enable the exploration of the multi-scale structure of the functional organization of the brain.
• Preserve and improve on the reproducibility and accuracy of previous methods.
• Provide a way to match the parcels from parcellations from different datasets of the same subject.

These aims are accomplished with a substitution of the region growing process by a generalisation of the watershed transform to greyscale images modelled by cubical complexes [40]. This partition operation assigns each voxel of the image to a stable basin surrounding a local minimum using discrete Morse theory. This method in [40] also provides a simplification procedure that explores this theory's connection to persistent homology and allows us to deal with the stability information directly, without any preprocessing steps, and to derive parcellations where every region has a relative stability above a certain value. Moreover, it avoids artificial constraints on region shape and size, without any sacrifices in computational efficiency.

Taking advantage of the gradient vector field construction used in the parcellation scheme described above, a procedure to match the parcels from parcellations of the same subject from different datasets, based on combinatorial feature flow fields [41], is also proposed.

The work described in this thesis was done in the scope of the project HIFI-MRI with high resolution resting-state MRI data obtained on a 7T scanner through a collaboration with the Martinos Center at Massachusetts General Hospital.

1.5 Thesis Outline

The remaining chapters of this thesis are structured as follows:

• Chapter 2 begins with a description of the proposed hierarchical brain parcellation and intra-subject region matching approaches, while giving brief introductions to discrete Morse theory and persistent homology. A description of the experimental data, preprocessing and the co-registration process are given at the end of this chapter.
• Chapter 3 presents the experimental results used to validate our approach. These include: properties that characterise the obtained parcellations, as well as the individual regions and a reproducibility study.

• Chapter 4 concludes this thesis and presents some problems and ideas for future work.

1.6 Publications arising from this Thesis


2 Methods

Contents

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This chapter elaborates on the methods used throughout this work. A description of the reasoning behind their application in this context, their main steps and the necessary background is given.

2.1 Brain Parcellation Methods

This section presents the pipeline of the proposed hierarchical brain parcellation approach. It begins with the definition of the stability map introduced in [10], which is used for measuring functional homogeneity from rs-fMRI data. Some relevant concepts on cubical complexes and gradient vector fields from discrete Morse theory are then presented, followed by their application in the context of a generalised watershed transform [40]. This is used in this work to segment the stability map. The concept of persistent homology and its role in revealing a hierarchy of functional segregation is also presented. An intra-subject parcel matching algorithm that is also based on discrete Morse theory is introduced. Finally, the implementation details for these procedures, foreseeing their application to the high-dimensionality rs-fMRI data analysed in this Thesis, are presented.

2.1.1 Measuring functional homogeneity

The first step in estimating regions that are functionally homogeneous is to measure the similarity between the time-courses in the functional data. The requirement for spatial contiguity of functional brain parcels allows for this similarity measure to be calculated only for neighbouring voxels. The stability map proposed in [10] is used as the time-course similarity measure in this work because the resulting image provides a global picture of local functional homogeneity. This is supported by the observation that the gradient of the stability map encodes the required affinity information between neighbouring voxels, in the sense that we obtain the representative stable seed of each voxel by following the path of steepest ascent from that voxel. This is the same notion behind the watershed transform that is widely used in image segmentation.

The stability map evaluates the suitability of every time-course in the image to be representative of its neighbourhood. The necessary calculations are performed in image space, and the resulting map is therefore obtained in the image space. This enables fast parallel computations as there is no data dependency between voxel stability calculations (see Equation 2.1), and the application of advanced image processing techniques such as the one described over the following sections. The stability map is computed as follows: for every voxel $x$ in the image, we calculate

$$s(x) = \sqrt{\frac{1}{\# R_x \times n_t} \sum_{i \in R_x} \| Y(i) - \langle Y \rangle_{R_x} \|^2},$$

(2.1)

where $R_x$ is the set of voxels 6-adjacent to $x$, $Y(x)$ its corresponding time-course, $\langle Y \rangle_{R_x}$ is the spatial mean time-course in $R_x$ and $n_t$ is the number of frames.

The Gaussian kernel smoothing that is applied to the final image in a previous functional parcellation method also based on the stability map [10] is not used, as it attenuates the high frequency components in the data and prevents the exploration of structure at finer scales.
2.1.2 Cubical complex model of the stability map

The application of discrete Morse theory requires the stability map image to be modelled as a cubical complex $K$. The following definition of a cubical complex follows the treatment in [42].

A $p$-cell $\alpha^{(p)}$ is an elementary cube defined as the product

$$\alpha^{(p)} = I_1 \times I_2 \times \cdots \times I_n,$$

(2.2)

where $I_j \subset \mathbb{R}$ is either $\{k_j\}$ (a degenerate interval) or the closed interval $[k_j, k_j + 1]$, for $k_j \in \mathbb{Z}$, and the dimension $p$ of $\alpha$ is the number of nondegenerate intervals in (2.2). Let $\alpha^{(p)}$ and $\beta^{(q)}$ be two cells such that $p < q$ and $\alpha \subseteq \beta$, then $\alpha$ is a face of $\beta$ and has $\beta$ as a coface. The relationship is denoted with $\alpha < \beta$ and $\beta > \alpha$. If $\alpha^{(p)} \prec \beta^{(q)}$ with $q = p + 1$, then $\alpha$ is a facet of $\beta$ and $\beta$ a is cofacet of $\alpha$.

A cubical complex $K$ in $\mathbb{R}^n$ is a collection of $p$-cells where $0 \leq p \leq n$, such that every face of a cell in $K$ is also in $K$, and any two cells of $K$ are either disjoint or have a common face. The image can be extended to $K$ by assigning to each 0-cell (vertex of $K$) the value of its corresponding voxel and assigning to every higher dimensional cell, the maximal value assigned to one of its vertices. A subcomplex of $K$ is a subset of its $p$-cells that is also closed under the face relation.

2.1.3 Discrete gradient vector field

In Forman’s discrete Morse theory, as described in [43] [44], a collection of pairs $V = \{\alpha^{(p)} < \beta^{(p+1)}\}$ of cells of $K$ such that each cell is in at most one pair of $V$ is called a discrete vector field. A
V-path is a sequence of cells
\[ \alpha_0^{(p)}, \beta_0^{(p+1)}, \alpha_1^{(p)}, \beta_1^{(p+1)}, \ldots, \beta_r^{(p+1)}, \alpha_r^{(p)}, \alpha_{r+1}^{(p)} \]  \hspace{1cm} (2.3)
such that for each \( i = 0, \ldots, r \), \( \{\alpha_i^{(p)} < \beta_i^{(p+1)}\} \in V \) and \( \beta_i > \alpha_{i+1} \neq \alpha_i \). It is a non-trivial closed path if \( r \geq 0 \) and \( \alpha_0 = \alpha_{r+1} \). A discrete Morse function i.e. a function \( f: K \mapsto \mathbb{R} \) satisfying both
\[ \#\{\beta^{(p+1)} > \alpha \mid f(\beta) \leq f(\alpha)\} \leq 1 \]  \hspace{1cm} (2.4)
and
\[ \#\{\gamma^{(p-1)} < \alpha \mid f(\gamma) \geq f(\alpha)\} \leq 1, \] \hspace{1cm} (2.5)
defines a discrete vector field by pairing cells \( \alpha^{(p)} < \beta^{(p+1)} \) if \( f(\beta) \leq f(\alpha) \); where unpaired cells are critical ones. Moreover, its V-paths have the property that
\[ f(\alpha_0) \geq f(\beta_0) > f(\alpha_1) \geq f(\beta_1) \geq \cdots \geq f(\beta_r) > f(\alpha_{r+1}). \] \hspace{1cm} (2.6)
This means that if a discrete vector field of \( f \) does not contain any non-trivial closed V-paths then it is a gradient vector field, and its V-paths (gradient paths of \( f \)) are the paths of cells for which the
values of $f$ decrease consecutively. The algorithm $\text{ProcessLowerStar}$ [45] computes a gradient vector field $V$ from the function $g$, which constitutes the extension of the image to the cubical complex $\mathcal{K}$, by growing the lower star of each vertex $x$

$$L(x) = \{ \alpha \in \mathcal{K} \mid x \in \alpha \text{ and } g(\alpha) = g(x) \}, \quad (2.7)$$

with simple homotopy expansions wherever possible i.e. by adding the pairs $\alpha^{(p-1)} < \beta^{(p)}$ such that $\alpha$ has no other cofacets. Otherwise, it adds a critical cell. The critical cells of the resulting gradient vector field $V$ fully characterize the topological changes in the level subcomplexes of $\mathcal{K}$ induced by $g$

$$\mathcal{K}_g(c) := \{ \alpha \mid \alpha \leq \beta, \text{ for } g(\beta) \leq c \}. \quad (2.8)$$

In the case of 3-dimensional images, the critical cells of dimensions 0, 1, 2 and 3 correspond to minima, 1-saddles, 2-saddles and maxima, respectively, in the scalar field.

### 2.1.4 Parcellation of the image

The construction of the gradient vector field of the stability map $V_{sm}$ immediately permits us to identify the critical 0-cells that correspond to its local minima. Just as in [10], these are locally stable seeds whose time-course in the functional image is representative of its neighbouring voxels. Additionally, $V_{sm}$ allow us to identify other types of critical cells which do not have such a straightforward correspondence to points in a 3-dimensional image [46]. The set of critical points along with the V-paths that connect them to each other (the separatrices) define what is known as the Morse chain complex $\mathcal{M}$ [44, 45], that compactly represents the same topological information as $\mathcal{K}$ [45].

$\mathcal{M}$ is a generalization of the watershed, likewise, the stable set is the analogous of the catchment basin. The stable set of a cell $\alpha$ is composed of the cells in the V-paths that end at $\alpha$ [40]. A parcellation of the functional data corresponds to the partitioning of the set of vertices of the complex $\mathcal{K}$ that models the stability map. The existence of such a partition is made clear by Lemma 5 of [40], which states that every vertex of $\mathcal{K}$ is in the stable set of exactly one local minimum.

### 2.1.5 Persistent homology of stability

Homology is a branch of algebraic topology whose main motivation is the classification of shapes by associating them with a sequence of abelian groups or modules. These groups represent the topological properties of the shape, which are properties that are invariant under homeomorphisms. Informally, an homeomorphism represents the continuous deformation of a geometric object into a new shape and the topological invariants are the holes of all dimensions in that shape. For 3-dimensional objects, the $p$-th homology groups describe connected components, handles and enclosed voids, for $p = 0, 1$ and 2, respectively. Elements of these groups are called homology classes. See [47, Chapter 4] for an introduction directed at computational topology and [48] for a more comprehensive introduction to the field of algebraic topology.

Persistent homology is concerned with the lifetime of these topological invariants in a filtration [49]. A filtration of the complex $\mathcal{K}$ is a nested sequence of subcomplexes of $\mathcal{K}$ that begins with an empty
Figure 2.4: A 1-D discrete function, a), modelled by a cubical complex (depicted as bold dots and lines along the x-axis, representing 0 and 1-cells, respectively); and b), its discrete gradient vector field along with c), its corresponding parcellation. Arrows represent pairings and crosses represent critical cells.
Figure 2.5: Level subcomplexes (depicted as bold dots and lines along the x-axis, representing 0 and 1-cells, respectively) with respect to a 1-dimensional discrete function $h$. 

b) A connected component is added to the complex at $t = h(4)$.

c),d) Two connected components merge at $t = h(2)$, so that the component created at a later time is destroyed and the other becomes the representative of the union. Persistence is given by this birth-death pairing and is defined as $h(2) - h(1)$.

The procedure discussed in the previous section assumes that the regions associated to every local minimum in the stability map all play an equivalent role in regard to functional segregation. However, as discussed in Chapter 1, this is not true due to the presence of noise and, more importantly, due to the multi-scale structure of brain organization. The notion of persistence allows us to differentiate these regions based on the length of the interval of stability values for which they endure, in other words, it is a measure of how stable that segregation is in the global picture and of how these regions are locally integrated. Moreover, this notion is different in nature to the concept of a scale space in that it is not concerned with the spatial extent of features in the data.
2.1.5.A Simplification

Discrete Morse theory provides a method for cancelling pairs of critical cells. This is possible when there is a single V-path between them so that, by reversing it, the pair is eliminated, and the resulting vector field is still a gradient vector field [44]. However, this cancellation must be done in an informed way as to retain the intended level of detail by preserving the most important structural features of the image.

A method to remove cancellable close pairs of critical cells with persistence up to a given threshold, \( \tau \), has been proposed in [40]. These pairs \((\alpha^{(p)}, \beta^{(p+1)})\) are identified by the boundary operator \(\partial_M\) which reconstructs the homology of the Morse chain complex \(M\), which in turn calculates the homology of \(K\), by recording the incidences between critical cells that are connected in \(V\); see [45]. Moreover, there must be a single V-path from the boundary of \(\beta\) to \(\alpha\), \(\alpha\) must be the closest boundary cell of \(\beta\) and \(\beta\) the closest coboundary cell of \(\alpha\).
2.1.6 Matching subject-specific parcels across datasets

Obtaining a correspondence between parcels from parcellations from different datasets of the same subject is essential to perform region of interest (ROI) based analyses with data from multiple trials and to study the within-subject (test-retest) reproducibility of the parcellation method. The gradient vector field construction used in the parcellation procedure proves useful in this task. Because the parcels are uniquely identified by the minima in $V$, the problem of matching parcels across parcellations becomes a problem of tracking minima across the gradients of those parcellations.

The algorithm proposed in [41] tracks critical points of time-dependent scalar fields. This method is based on the idea, described in [51], of extending the discrete gradient vector fields $V_i$, built from each scalar field at time $i$, to a higher dimensional discrete gradient vector field that encompasses all time instants. These fields are defined so that their corresponding Morse functions decrease with time $i$ resulting in paths flowing from $V_i$ to $V_{i+1}$. Alternatively, this field can be defined with a Morse function that decreases in time so that paths flow in the opposite direction. These are called the forward and backward tracking fields, respectively, or, more broadly, combinatorial feature flow fields (CFFF) [41]. Critical cells in either $V_i$ or $V_{i+1}$ are said to be strongly connected if there is a path connecting them both in the forward and backward tracking fields [51] i.e. there are critical lines connecting critical cells in $V_i$ and $V_{i+1}$. The approach presented in [41] provides an efficient procedure to compute these critical lines, which does not require the construction of the higher dimensional fields.

While this procedure allows tracking critical cells of all dimensions of $V$, the problem described above only requires tracking minima, where different instants of time naturally correspond to different datasets of the same subject. Following the procedure described in [41], the correspondence between two minima of different discrete gradient vector fields of two datasets is found by:

- Considering a critical 0-cell (minimum) $\alpha$ in $V_i$, one follows the single 1-dimensional V-path from its corresponding 0-cell in $V_{i+1}$ that ends in a critical 0-cell $\beta$ of $V_{i+1}$. This is equivalent to tracking $\alpha$ in the forward tracking field.

- Next, $\beta$ is tracked in the backward tracking field by following the single 1-dimensional V-path from the 0-cell in $V_i$ that corresponds to $\beta$. If this V-path leads to $\alpha$ then these minima are strongly connected which means that their associated parcels are matched.

This procedure is repeated for every critical 0-cell (minimum) in $V_i$ so that we obtain all pairs of corresponding parcels. Note that this procedure only pairs parcels whose associated minimum in $V_i$ is strongly connected to one minimum in $V_{i+1}$.

2.1.7 Implementation

The hierarchical brain parcellation procedure described in this chapter can be summarized in the following steps.

1. A stability value is computed for all voxels lying inside a chosen grey-matter mask from the rs-fMRI data of a single subject dataset.
2. A discrete gradient vector field $V_{sm}$ of the stability map is built by running the algorithm $ProcessLowerStars$ for all non-zero voxels inside the mask.

3. $V_{sm}$ goes through an iterative simplification process for a given persistence threshold that will determine the number of critical vertices left.

4. The voxels of the stability map are then assigned to their corresponding region by following the V-paths in the reverse discrete gradient vector field $V_{sm}^{-1}$, starting from each critical vertex, as this corresponds to searching their stable set.

The reason for only including non-zero voxels inside a mask is that functional connectivity is expected only between grey matter regions of the brain (and not white matter or CSF). This also has the practical advantage that only these much fewer voxels are actually processed.

The periodic structure of the cubical complex allows the representation of the gradient vector field as an array of integers. This implies that every cell is identified by a unique integer value. If for every vertex $\alpha$, its cofaces whose vertices have only coordinate values higher or equal than $\alpha$ come after it in the array, so that there exists 8 elements (1 vertex, 3 edges, 3 faces, and 1 cube) in the array for every vertex, then each cell is identified by its position in the array and we can easily determine face/coface relations, as well as their dimension and orientation by computing their indices modulo 8. In this sense, the pairing occurs between a cell identified by array position and the cell identified by its associated value. As the size of the complex is 8 times the number of voxels in the image, this means that this representation grows linearly with the number of non-zero voxels inside the mask.

The simplification routine in step 3) removes cancellable close pairs by: 1) introducing all pairs returned by the $morseBoundary$ routine \[40\] in a priority queue, ordered by persistence value; and 2) popping each pair from the queue and reversing the V-path of those pairs that did not appear in a pair with higher persistence and whose incidence value is one. This step defines the level of detail of the parcellation. The remaining minima play the role of the locally stable seeds introduced in \[10\]. The assignment in step 4) is performed by calling $traverseFlow$ \[40\] on $V_{sm}^{-1}$ for every critical vertex.

### 2.2 Experimental data

#### 2.2.1 Data acquisition

Nine healthy subjects were studied on a 7T whole-body scanner with a 32-channel receive RF coil. Two datasets of 5 min each of rs-fMRI data were collected using a GE-EPI sequence with TE = 32 ms, TR = 2.5 s, FA = 75°, GRAPPA factor = 3, simultaneous-multi-slice factor = 3, nominal echo spacing = 0.82 ms, whole-brain coverage by 123 sagittal slices and 1.1 mm isotropic resolution. A T1-weighted structural image was also acquired using multi-echo MPRAGE, with 1 mm isotropic resolution \[52\].

#### 2.2.2 Data pre-processing

Data analysis was carried out using Matlab, FSL (\[www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/\]) and Statistical Parametric Mapping (SPM) tools (\[www.fil.ion.ucl.ac.uk/spm/\]). The two datasets from
Figure 2.7: Registration pipeline. Motion correction is performed by aligning the frames in the fMRI time series with a reference frame (usually, the middle frame). The reference frame is then co-registered to the structural image which, in turn, is normalized to standard space.

each subject were concatenated and pre-processing steps included: motion correction performed using MCFLIRT from FSL; slice time correction; physiological noise modelling and removal using an extended retrospective image correction RETROICOR based on simultaneously acquired cardiac and respiratory data [53]; motion parameters regression (6 parameters from MCFLIRT); and tissue segmentation of structural images using SPM.

2.2.3 Image co-registration

An important requirement in most fMRI analyses is that the images to be studied must have voxels in the same position representing the same parts of the brain. However, subject motion inside the scanner, motion induced by physiological processes (e.g. CSF), geometric distortion resulting from magnetic field inhomogeneities and inter-subject anatomical variability all contribute to the violation of this assumption. This results in artefactual signal changes, inaccurate localisation of the activity of interest as well as loss in statistical power. Thus different types of spatial transformations are required to compensate for some of these effects.

The first of these spatial transformations, the one that accounts for subject head motion, is realignment. The usual route is to treat this as a rigid-body process, ignoring other sources of deformation (e.g. physiological, slice-time). This allows for efficient alignment of the hundreds of volumes of a typical fMRI session [54].

In order to be able to identify and compare spatial locations in the brains of different subjects, one essential step is to transform the images to a standard coordinate system, taking anatomical variability
into account. This process is called spatial normalization. There are two main steps involved in this:

- Co-registration between the functional (T2*) and structural (T1) images of the same subject. This not only allows to identify spatial locations of activity of a single subject by looking at his anatomy but also simplifies the next step significantly. A linear transformation is estimated with a volume-based registration method that can use a similarity function that is able to handle inter-modal image pairs such as these (e.g. normalized mutual information).

- Registration of the subject structural image to the template image that is in a standard coordinate system. The most widely used template image is the ICBM-152 (MNI). The methods with the best performance compute a nonlinear transformation, such as a diffeomorphism. These can be described as vector fields, whose vectors represent the movement between voxels from one image to the other. While these have a high number of degrees of freedom (DOF), regularisation ensures that they still preserve the topology of brain structures. Because of this, they are usually preceded by a linear transformation. Contrarily to the first step, this is an intra-modal registration and as such, simpler similarity functions (e.g. mean squared difference) may be used.

The issues arising from a bad performance on any of these registration procedures are amplified when using high resolution images as even small registration errors induce great uncertainty at the voxel-level while the requirement for specificity increases. Therefore, special care must be taken to ensure that the performance of these procedures is up to these expectations of higher specificity.

Co-registration of functional and structural images was done using FMRIB’s linear image registration tool (FLIRT) with the BBR cost function, where BBR stands for boundary-based registration, which is a specialised cost function for inter-modal registration that focuses on the contrast across a tissue boundary. A tissue segmentation is extracted from the reference image (structural image) and the gradient of the input image (functional image) intensity is maximized across the tissue boundary. 

Figure 2.8: Co-registration performance between the functional and structural images, depicted in MNI standard space, for one representative subject.

Figure 2.9: Co-registration performance between the structural image and the MNI template, depicted in MNI standard space, for one representative subject.
Tissue segmentation was performed using SPM. A 6 DOF transformation was estimated. Registration to standard space was performed using FMRIB’s non-linear image registration tool (FNIRT). Finally, functional data was resampled into 1 mm MNI152 space using spline interpolation. The accuracy of these registrations can be assessed in Figures 2.8 and 2.9 for one representative subject.

2.2.4 Outcomes measures

Evaluating the performance of functional parcellation methods is a challenging task as there is no "golden standard" available for comparison with the obtained results. There are, however, a few metrics available in the literature that permit to assert if the results have the desired properties.

As discussed in the previous chapter, the parcels should depict areas of functional segregation. More importantly, the choice of scale, determined by the choice of persistent threshold, should result in parcels that are comparable in terms of their functional homogeneity. Moreover, one wishes to know if these parcellations are stable over different datasets of the same subject.

2.2.4.A Average parcel volume

The granularity of the parcellation may be characterized by the number of parcels and their volume. Because the method does not produce parcels of similar size, this last property must be properly studied, and so the average number of voxels in a parcel over all parcels and its corresponding standard deviation are computed.

2.2.4.B Average Functional Coherence

The functional homogeneity of a parcel can be studied by measuring the variability among the time-courses of its voxels. The Average Functional Coherence (AFC) is one such measure and is obtained by computing the average of the fisher z-transformed correlation ratios between the voxel time-courses of a parcel and the mean time-course of that parcel for each parcel, and then, averaging these values across all parcels. The Pearson’s correlation coefficient \( r \) is given for two time-courses \( x \) and \( y \) of length \( L \) with a mean value of \( \bar{x} \) and \( \bar{y} \), and standard deviations \( \sigma_x \) and \( \sigma_y \), respectively, by

\[
    r(x, y) = \frac{(x - \bar{x})^T(y - \bar{y})}{(L - 1)\sigma_x\sigma_y},
\]

and the Fisher’s z-transformation of \( r \) is given by

\[
    z(r) = \frac{1}{2} \log \left( \frac{1 + r}{1 - r} \right).
\]

2.2.4.C Dice coefficient (Overlap)

The strong relationship between resting-state functional connectivity (rs-FC) and structural connectivity [56] suggests that parcellations across different datasets of the same subject should, to some extent, be stable, although some variability is to be expected as rs-FC is also known to fluctuate over time; a phenomenon best known as dynamic functional connectivity [57].
Figure 2.10: Mask used to delimit the parcellation shown for 3 different slices on the sagittal, coronal and axial planes, respectively.

study is performed in order to assess this property by computing the Dice coefficient of two parcels $X$ and $Y$, given by [58]

$$
dice = \frac{2|X \cap Y|}{|X| + |Y|},
$$

between every pair of corresponding parcels from two different dataset as given by the proposed parcel matching approach (see Section 2.1.6) and computing the mean of these values.

Stability values were only computed for the voxels inside a gray matter mask including cortex, deep gray matter, brainstem and cerebellum. This mask was created from the combination of the AAL atlas [30] with a brainstem mask from the HarvardOxford atlas from FSL. Figure shows this mask for 3 different slices.

For the test-retest reproducibility study, the computation of the stability map and subsequent parcellation steps were performed for each dataset separately. For this study, another version of the data was also considered, which was not subjected to physiological noise correction. This was done with the purpose of assessing the sensitivity of the achieved parcellations to the removal of spurious connectivity.
3 Results

Contents

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3.3 Parcellation Test-Retest Reproducibility .......................... 32
This chapter presents the main results obtained by the application of the proposed hierarchical functional brain parcellation method to the high spatial resolution rs-fMRI data collected from 9 subject at 7T. Properties that characterise the obtained parcellations and their relation to the choice of scale are shown. In particular, the test-retest within-subject reproducibility study that assesses the stability of these parcellations at different scales across datasets of the same subject is presented.

### 3.1 Parcellations at Multiple Scales

Parcellations of the rs-fMRI data from all 9 subjects were computed with this method for 14 different scales. The range of scales (determined by the choice of persistence thresholds $\sigma$) and the corresponding number of parcels for all parcellations are shown in Table 3.1. Figure 3.1 shows 12 representative slices (columns) of the parcellations obtained for all levels of detail (rows) of one representative subject. Figures of the parcellations obtained for the remaining subjects are available in Appendix A.1. A close inspection of Figure 3.1 shows that:

- The parcellation is indeed hierarchical, i.e. the parcels at smaller scales (higher persistence thresholds, towards the bottom rows of the figure) are composed of (full) parcels present at larger scales. This property is inherent to the simplification procedure and can be observed in the highlighted parcels (in slices (columns) 7,8; arrows coloured according to the parcels being pointed out), for instance.

- Another interesting point is that these (highlighted) relatively large regions appear early on in the hierarchy (persistence threshold $\sigma$ (row 5), slices (columns) 7,8) and remain untouched in the remaining scales. This means that all but one local minima (seeds), which originate the smaller scale parcels and merge to create one of these larger parcels, have a relatively low associated persistence value and that exactly one local minimum has a relatively high persistence value. This demonstrates that this measure of scale is only indirectly related to parcel volume and suggests that, either the seed is fairly representative of the functional specialisation of that region across the majority of scales, or that the algorithm simply cannot remove this feature, as in three-dimensional complexes some persistence pairs cannot be removed [40, 59, 60].

- While there are no explicit constraints to enforce the parcels to a single hemisphere or distinct anatomical regions (the chosen mask allows these regions to connect, as shown in Figure 2.10), these results show that the proposed method produces parcellations that are generally consistent with the underlying brain anatomy. For example, parcels exhibit some degree of symmetry between hemispheres (also see Figure 3.2) but are not shared between these two and present differences in their exact shape as expected due to the existence of known functional asymmetries. In general, parcel boundaries also respect boundaries between distinctive anatomical regions such as the cerebellum and the brainstem. An example showing a good match between the boundaries of the cerebellum and derived parcels, is depicted in Figure 3.3 for sagittal, coronal and axial slices of a representative subject.
Figure 3.1: Parcellations of a representative subject at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes. Parcels that reveal properties discussed in Section 3.1 are highlighted by arrows.
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<th>Subject 5</th>
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</table>

Table 3.1: Number of parcels obtained for all studied scales (persistence thresholds) and for all 9 subjects.

Figure 3.2: Symmetry and functional laterisation. Arrows highlighting examples of parcels that show left-right symmetry, to some extent.

Figure 3.3: Example showing a good match between the boundaries of the cerebellum and derived parcels, for sagittal, coronal and axial slices of a representative subject.
The relationship between the choice of persistence threshold $\sigma$ for the simplification procedure and the number of parcels obtained with this method is shown in Figure 3.4. The average number of parcels, which was calculated over the 9 subjects, decays exponentially from approximately 80K to 2K parcels. The highest level of detail has an average number of parcels that is still higher than the number of nodes in most whole-brain voxel-based graph analytic studies which reached no more than 20,898 voxels [26, 61, 62].

3.2 Parcellation Characterisation

3.2.1 Functional Homogeneity

The level of functional homogeneity of the parcels obtained with this method is assessed, for each level of detail, by measuring the Average Functional Coherence. These results are shown in Figure 3.5. The AFC begins by decreasing exponentially from $\sigma = 0$ to $\sigma = 0.005$ but this relation becomes linear up to approximately $\sigma = 0.1$, and stabilizes from this point onwards. Parcels begin to converge to the same level of functional homogeneity as standard deviation progressively decreases with decreasing level of detail from $\sigma = 0.01$ to $\sigma = 0.045$ and begins to increase from this point.
3.2.2 Volume

Figure 3.7 shows the average number of voxels in a parcel as a function of the persistence threshold $\sigma$. The average volume increases with increasing threshold, as expected, but the coefficient of variation of the average parcel volume depicted in Figure 3.8 shows that up to $\sigma = 0.05$ the standard deviation also increases, which means that the difference in sizes is much larger for smaller scales and indicates that the proposed method for selection of scale does not impose a strict size on the parcels, as intended. In fact, it is not expected that functional brain regions have equal sizes, and this has been the limitation of some functional parcellation methods [37]. The first and second largest scales have an average volume of 18.0875 and 21.4122 voxels (and mm$^3$ as our voxels have a volume of 1 mm$^3$), respectively, which is still below the standard 27 mm$^3$ voxel volume from typical 3T rs-fMRI data.
Figure 3.6: Coefficient of variation of the Average Functional Coherence as a function of persistent threshold $\sigma$.

Figure 3.7: Average number of voxels in a parcel as a function of persistent threshold $\sigma$. Values are averages across subjects and error bars represent the respective standard deviation. The lower panel shows a zoom into the top panel for persistence threshold between 0 and 0.1. The numbers on the top indicate the corresponding average number of parcels across subjects.
3.3 Parcellation Test-Retest Reproducibility

The within-subject consistency of the resulting parcellations is measured by performing a test-retest reproducibility study. This test consists in performing parcellations for the two fMRI datasets collected from the same subject and computing the overlap between their corresponding parcels. This is done for the same levels of detail as before. This correspondence is first determined by tracking their minima across their corresponding gradient vector fields, as discussed in the previous chapter. Figure 3.10 shows sagittal, coronal and axial slices of a representative subject (as different columns) of the parcel correspondence from the two datasets (consecutive rows) for persistence threshold values \( \sigma = 0.0, 0.005, 0.02 \) and 0.5 (every two rows). This figure confirms that the method described in Section 2.1.6 finds correspondences for most parcels (but not all, as can be seen by the absence of some regions) reflecting both the performance of the algorithm and the stability of the parcellations between datasets, even at larger scales. Figures of the remaining subjects are available in Appendix A.2.

The Dice coefficient is used as the overlap measure and it is computed and averaged across all pairs of corresponding parcels, for each subject. Finally, the group average of the mean Dice coefficient is used to evaluate the reproducibility of the method. In order to assess the sensitivity of the parcel consistency to the presence of spurious correlations in the data, tests were performed using rs-fMRI data before and after the preprocessing step of removal of physiological noise. It should be noted that all results presented here are, otherwise, obtained for physiological noise corrected data. These results can be seen in Figure 3.9. Curves for corrected and non-corrected datasets are significantly different, which indicates that the parcellation method is sensitive to the presence of meaningful correlations in the data. Most importantly, the reproducibility is higher for the physiological noise corrected data than for the non-corrected. Moreover, the peaks of maximum reproducibility are achieved for different levels of detail in the two cases, slightly higher for physiological noise corrected data \( \sigma \) between 0.015 and 0.02 than for non-corrected data \( \sigma \) between 0.035 and 0.04.
Figure 3.9: Intra-subject reproducibility of parcellations at different levels of detail, measured as the group mean dice coefficient (error bars represent standard deviation) for all 9 subjects before (red) and after (blue) physiological noise correction as a function of persistent threshold $\sigma$. Values are averages across subjects and error bars represent the respective standard deviation. The lower panel shows a zoom into the top panel for persistence threshold between 0 and 0.1. The numbers on the top indicate the corresponding average number of parcels across subjects.
Figure 3.10: Parcel correspondence for sagittal, coronal and axial slices of a representative subject (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Conclusions

Contents

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In this chapter, the work that has been presented is summarized, motivating the discussion of the main results, their implications and some ideas for future work.

4.1 Summary

In this work, a new method to obtain a hierarchy of subdivisions of the brain that attempts to capture the functional segregation and functional integration principles of brain organization from rs-fMRI images, was proposed. It builds upon the proposal of [10] to use a state-of-the-art segmentation procedure from the field of topological data analysis that provides both greater computational efficiency and a more theoretically meaningful scale information.

A procedure based on the combinatorial feature flow fields proposed in [41] that uses the same computational framework was proposed to find correspondences between parcels of the same subject from parcellations of images from different datasets.

Derived parcellations at multiple scales were obtained from high resolution resting-state fMRI data obtained from experimental 7T acquisitions.

Characterising properties of these parcellations such as the number of parcels, the average parcel volume and functional homogeneity were obtained.

A parcellation test-retest reproducibility study was performed to assess the stability of the parcellations derived using this method for different datasets within subject.

Experimental results confirm the suitability of the proposed method to satisfy the above requirements.

4.2 Discussion

The proposed method produced brain parcellations of whole-brain, ultra-high-resolution 7T rs-fMRI data at levels of detail of up to 80K parcels. This value represents about 5% of the number of voxels inside the chosen grey-matter mask (1,511,711 voxels). At this level of detail, the average parcel volume is 18.0875 (±7.1262), which means the parcels are very close in size. Additionally, this is still less than the standard 27 mm³ voxel volume from typical 3T rs-fMRI data. This makes it a good candidate for fulfilling the role of voxels in analyses where great specificity is required with the advantages of non-arbitrary localisation, dimensionality reduction and reduced spatial autocorrelation.

A persistence threshold chosen as a fraction of the range of stability values for each image has the advantages of not depending on the amplitude of the values in each image and of having a common maximum value of 1.0, corresponding to the extreme case of a persistence value from a pairing of a global maximum and a global minimum.

A reduction in the number of parcels necessarily leads to an increase in the average volume of the parcels, because the volume within the chosen mask remains constant. This fact can be observed in Figure [3.7]. This inevitably leads to parcels that, on average, are less functionally homogeneous (Figure [3.5]). On the other hand, these results show that the standard deviation of average parcel volume increases with increasing number of parcels, which means that these get progressively more
disparate sizes; and that the standard deviation of the reported measure of functional homogeneity actually decreases. These results confirm that these method treats scale as a matter of parcel overall functional coherence rather than a matter of spatial resolution.

The reproducibility study shows that these parcellations have excellent reproducibility across different datasets of the same subject as conveyed by the mean Dice coefficients computed at the various levels of detail (see Figure 3.9). The significant difference between the results obtained with and without physiological noise correction shows that this method is indeed sensitive to changes in functional connectivity, indicating the absence of some inherent bias. Moreover, it shows that correctly modelling and removing these signal fluctuations of non-neural origin is of utmost importance to functional connectivity studies and that the resulting connectivity patterns become significantly more stable. As opposed to similar analyses performed with state-of-the-art methods [10, 37], this study shows a peak of maximum reproducibility for a $\sigma$ between 0.015 and 0.02 corresponding to an average number of parcels of 14 854 and 10 240 respectively, for the case where physiological noise correction is performed. This indicates that this scale may be particularly suited to describe patterns of interest present in this data. Also of note is that data without physiological noise correction shows an even more pronounced peak situated between $\sigma = 0.035$ and $\sigma = 0.04$ that corresponds to an average number of parcels of 4978 and 4333 respectively, which indicates that these underlying physiological processes should be more prominent at this particular scale.

4.3 Future Work

These results open up several possibilities for future research.

Perhaps the most pressing question is that of how this method performs in comparison to state-of-the-art approaches. Several issues arise when attempting to do this comparison:

- Experimental results available in the literature that evaluate these methods are limited to images from 3T rs-fMRI scans with standard spatial resolutions of 3 mm cubic, which precludes a direct comparison with the results obtained in the present work.

- Aside from using images with lower detail, these analysis are usually confined to the cortical surface, which also precludes a direct comparison.

- The available implementations or in some cases, even the complexity of these algorithms is not up to the task of handling images with millions of voxels, like the ones used in this work, especially when obtaining highly detailed parcellations.

In summary, evaluating these approaches against the proposed method, in the cases where it would be possible, would require new implementations of those algorithms that were sufficiently optimized for high-resolution data.

The stability map, while it has proven to be successful at providing a great level of detail that is also very reproducible across different sessions, could be tested against other similarity measures avail-
able for rs-fMRI data. It should be noted, however, that common metrics, such as cross-correlation, are much less computationally efficient.

One of the main motivations for obtaining a functional parcellation is related to its potential benefits to complex network analysis of functional connectivity. Therefore, one possible line of research would be to evaluate and explore those benefits. [63] investigated the effects of scale on graph analytic studies using a random parcellation scheme to subdivide regions of the AAL atlas in parcels of the same size and by comparing frequently used graph analytic measures to study the resulting topology of brain connectivity networks. A similar study could be performed to evaluate the influence that choosing persistence as the measure of scale has on these network properties.

The proposed parcel matching procedure has shown to be very effective in finding correspondences between parcellations of the same subject. However, this problem becomes much harder when it comes to match parcels between parcellations from different subjects due to the presence of inter-subject anatomical variability. Optimizing this method to give consistent correspondences between parcels in a group of subjects would allow to perform group level analysis using these parcellations and should provide a better understanding of the functional organization in the brain.
Bibliography


A.1 Parcellations at Multiple Scales
Figure A.1: Parcellations of subject 1 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.2: Parcellations of subject 2 at 14 different scales determined by persistence threshold \( \sigma \) (see Table 3.1 for details). Rows represent values of \( \sigma \) ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.3: Parcellations of subject 3 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.4: Parcellations of subject 4 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.5: Parcellations of subject 5 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.6: Parcellations of subject 6 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.7: Parcellations of subject 7 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
Figure A.8: Parcellations of subject 8 at 14 different scales determined by persistence threshold $\sigma$ (see Table 3.1 for details). Rows represent values of $\sigma$ ranging from 0 (top row) to 0.5 (bottom row). Columns represent different slices on sagittal, coronal and axial planes.
A.2 Correspondence of Parcels Between Two Datasets
Figure A.9: Parcel correspondence for sagittal, coronal and axial slices of subject 1 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.10: Parcel correspondence for sagittal, coronal and axial slices of subject 2 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.11: Parcel correspondence for sagittal, coronal and axial slices of subject 3 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.12: Parcel correspondence for sagittal, coronal and axial slices of subject 4 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.13: Parcel correspondence for sagittal, coronal and axial slices of subject 5 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.14: Parcel correspondence for sagittal, coronal and axial slices of subject 6 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.15: Parcel correspondence for sagittal, coronal and axial slices of subject 7 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).
Figure A.16: Parcel correspondence for sagittal, coronal and axial slices of subject 8 (as different columns) from the two datasets (consecutive rows) for persistence threshold values $\sigma = 0.0, 0.005, 0.02, 0.5$ (every two rows).