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Geodesic regression on orientation distribution functions with its application to an aging study

Jia Du [a], Alvina Goh [b], Sergey Kushnarev [a], Anqi Qiu [a,c,d,*]

[a] Department of Biomedical Engineering, National University of Singapore, Singapore
[b] Department of Mathematics, National University of Singapore, Singapore
[c] Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore
[d] Clinical Imaging Research Centre, National University of Singapore, Singapore

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ABSTRACT

In this paper, we treat orientation distribution functions (ODFs) derived from high angular resolution diffusion imaging (HARDI) as elements of a Riemannian manifold and present a method for geodesic regression on this manifold. In order to find the optimal regression model, we pose this as a least-squares problem involving the sum-of-squared geodesic distances between observed ODFs and their model fitted data. We derive the appropriate gradient terms and employ gradient descent to find the minimizer of this least-squares optimization problem. In addition, we show how to perform statistical testing for determining the significance of the relationship between the manifold-valued regressors and the real-valued regressands. Experiments on both synthetic and real human data are presented. In particular, we examine aging effects on HARDI via geodesic regression of ODFs in normal adults aged 22 years old and above.

Introduction

High angular resolution diffusion imaging (HARDI) is a recent advanced magnetic resonance imaging (MRI) technique that allows us to visualize the three-dimensional architecture of neural fiber pathways in the human brain. It measures diffusion along n uniformly distributed directions on the sphere and can characterize more complex neural fiber geometries when compared to diffusion tensor imaging (DTI). One way to characterize diffusion in the brain white matter based on the HARDI signals is Q-ball imaging, which uses the Funk–Radon transform to reconstruct an orientation distribution function (ODF). The model-free ODF is the angular profile of the diffusion probability density function of water molecules (Aganj et al., 2010b; Descoteaux et al., 2007; Frank, 2002; Goh et al., 2009; Hess et al., 2006; Özarslan and Mareci, 2003). By quantitatively comparing fiber orientations retrieved from ODFs against histological measurements, Leergaard et al. (2010) show that accurate fiber estimates can be obtained from HARDI data. However, HARDI is not widely used by clinicians and neuroscientists partially due to its relatively long acquisition time. Moreover, there is a lack of fundamental statistical tools that can fully utilize the information of complex neural fiber orientations characterized by the ODF.

There has been great emphasis on deriving scalar-based metrics from ODFs so that fundamental statistical tools, such as linear regression, can be easily employed. One of the earliest scalar measures is the generalized fractional anisotropy (GFA) proposed by Tuch (2004). GFA is defined as the ratio of standard deviation of the ODF to its root mean square. Similar to fractional anisotropy (FA) derived from DTI, GFA takes a value between zero and one and describes the degree of anisotropy of a diffusion process. GFA has thus far been used in studies on subcortical ischemic stroke (Tang et al., 2010), impulsivity (Liu et al., 2010), and genetic influence on the brain white matter (Chiang et al., 2008a, 2008b), yielding promising results. In addition to GFA, other scalar measures have also been proposed. Rao et al. (2012) propose a scalar measure known as peak geodesic concentration (GC), which is defined as the concentration relative to the peak fiber orientation identified from ODF and thus reflects the degree of directionally coherent diffusion. Rao et al. (2012) claim that GC is sensitive to the presence of single or multiple fiber populations within a voxel and therefore, is a unique scalar measure that can be used for the evaluation of pathology. Ghosh and Deriche (2011) use a polynomial approach to extract geometric characteristics from ODFs and define peak fractional anisotropy (PFA) and total-PFA at the fiber orientation with the extrema and principal curvatures. Finally, Assemlal et al. (2011) propose and compute the apparent intravoxel fiber population dispersion (FPD). It conveys the manner in which distinct fiber populations are partitioned within the same voxel and is more effective in revealing regions with crossing tracts than FA. Despite the ease of statistical analysis on the aforementioned scalar measures, they discard the complete information that is inherent in ODF and is of interest in detecting underlying axonal organization.

* Corresponding author at: Department of Biomedical Engineering, National University of Singapore, 9 Engineering Drive 1, Block EA 03-12, Singapore 117576, Singapore. Fax: +65 6872 3069.
E-mail address: bieqa@nus.edu.sg (A. Qiu).

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Recently, multivariate statistical analysis has been directly applied to ODFs (e.g. Cheng et al., 2009; Goh et al., 2011; Lepore et al., 2010). For example, Lepore et al. (2010) perform a multivariate group-wise genetic analysis of white matter integrity by adapting the multivariate intraclass correlation value (ICC) to ODFs. The ICC is obtained from the coefficients of the spherical harmonics of ODFs at each voxel. Lepore et al. (2010) show that the ICC increases the detection power in finding genetic influence on the white matter architecture when compared to statistics derived from GFA. Instead of working with ODFs in the Euclidean space, several recent works have proposed a Riemannian framework for analyzing ODFs. Goh et al. (2011) use the square-root representation for the ODF Riemannian manifold. Under this representation, Riemannian operations, such as the geodesics, exponential and logarithm maps, are available in closed form. Goh et al. (2011) develop principal geodesic analysis on tangent vectors of ODFs on the manifold and generalize the Hotelling's T-squared statistic for the comparison of ODFs between two populations. Cheng et al. (2009) approximate the square root of the ODF as a linear combination of orthonormal basis functions. Since the coefficients of this expansion live in a finite-dimensional sphere, processing operations can be performed in the space of coefficients with reduced computational complexity.

Since the Riemannian framework facilitates the utilization of the full information of ODFs, the natural question is whether fundamental statistical tools, such as regression, can be adapted from the Euclidean space to the manifold setting. Regression analysis is a fundamental statistical tool to determine how a measured variable is related to one or more independent variables. The most widely used regression model is linear regression because of its simplicity, ease of interpretation, and ability to model many phenomena. However, if the response variable takes values in a nonlinear manifold, a linear model is not applicable. Such manifold-valued measurements arise in many applications, including those that involve directional data, transformations, tensors, and shapes and in our case, ODFs.

Indeed, researchers have recently paid great attention to the regression problem on manifolds (e.g. Davis et al., 2010; Fletcher, 2011, 2012; Hinkle et al., 2012). Hinkle et al. (2012) develop the theory of parametric polynomial regression in Riemannian manifolds and Lie groups and show the application of Riemannian polynomial regression to shape analysis in Kendall shape space. Davis et al. (2010) study regression analysis on the group of diffeomorphisms for detecting longitudinal anatomical shape changes. Fletcher (2012) develops a generalization of linear regression to manifolds. More precisely, Fletcher (2012) proposes a regression method that models the relationship between a manifold-valued random variable and real-valued independent variables using a geodesic curve.

In this paper, we adapt the framework of geodesic regression, proposed in Fletcher (2012), to the HARDI data. To this end, we derive the algorithm for the geodesic regression on the Riemannian manifold of ODFs. Similar to Fletcher (2012), we define a least-squares problem that minimizes the sum-of-squared geodesic distances between observed ODFs and their model fitted data in order to find the optimal regression model. We derive the appropriate gradient terms later in this paper and use the gradient descent to seek the minimizer of this least-squares problem. In addition, we show how to perform statistical testing for determining the significance of the relationship between the manifold-valued regressors and the real-valued regressands. We apply the ODF regression algorithm and statistical testing to synthetic and real human data. We examine aging effects on brain white matter via geodesic regression of ODFs in normal adults aged 22 years old and above.

Methods

Geodesic regression for the ODF

In statistics, the *simple linear regression* is an approach to modeling the relationship between a scalar dependent variable Y and a non-random scalar variable denoted as X. A linear regression model of this relationship can be given as

$$Y = \beta_0 + \beta_1 X + \epsilon, \tag{1}$$

where β_0 is an unknown intercept parameter, β_1 is an unknown slope parameter, and ϵ is an unknown random variable representing the error drawn from distributions with zero mean and finite variance. Given n observations, i.e., x_i, y_i, for $i = 1, 2\ldots,n$, the least square estimates, $\hat{\beta}_0$ and $\hat{\beta}_1$, for the intercept and slope can be computed by minimizing the square errors

$$\left(\hat{\beta}_0, \hat{\beta}_1\right) = \underset{\left(\hat{\beta}_0, \hat{\beta}_1\right)}{\arg\min} \sum_{i=1}^{n} \| y_i - \beta_0 - \beta_1 x_i \|^2. \tag{2}$$

This minimization problem can be analytically solved. The observations, y_i can be approximated as

$$\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i, \quad i = 1, 2, \ldots, n.$$

We will now extend the above simple linear regression to the one modeling the relationship of the ODF and one non-random scalar variable, X, by adopting the general framework of geodesic regression in Fletcher, 2011, 2012.

ODF manifold

From existing literature (Aganj et al., 2010b; Descoteaux et al., 2007; Tuch, 2002), we know that at a specific spatial location, $x \in \mathbf{\Omega}$, HARDI measurements can be used to reconstruct the ODF, the diffusion angular profile of water molecules. The ODF is actually a probability density function defined on a unit sphere $\mathbb{S}^2$ and is denoted as $p(\mathbf{s}), \mathbf{s} \in \mathbb{S}^2$. In our study, we choose the square-root representation, which was used recently in ODF processing, registration and atlas generation (Cheng et al., 2009; Du et al., 2012, submitted for publication; Goh et al., 2011). The *square-root ODF* $\left(\sqrt{\text{ODF}}\right)$ is defined as $\boldsymbol{\psi}(s) = \sqrt{p(s)}$, where $\boldsymbol{\psi}(s)$ is assumed to be non-negative to ensure uniqueness. The space of such functions is defined as

$$\mathbf{\Psi} = \left\{\boldsymbol{\psi} : \mathbb{S}^2 \rightarrow \mathbb{R}^+ \forall s \in \mathbb{S}^2, \boldsymbol{\psi}(s) \geq 0; \ \int_{s \in \mathbb{S}^2} \boldsymbol{\psi}^2(s) ds = 1\right\}.$$

From information geometry (Amari, 1985), the functions $\boldsymbol{\psi}$ lies on the positive orthant of a unit Hilbert sphere, a well-studied Riemannian manifold. It can be shown (Srivastava et al., 2007) that the Fisher–Rao metric is simply the $\mathbb{L}^2$ metric, given as

$$\left\langle \boldsymbol{\xi}_j, \boldsymbol{\xi}_k \right\rangle_{\boldsymbol{\psi}_i} = \int_{\mathbf{s} \in \mathbb{S}^2} \boldsymbol{\xi}_j(s) \boldsymbol{\xi}_k(s) ds,$$

where $\boldsymbol{\xi}_j, \boldsymbol{\xi}_k \in T_{\boldsymbol{\psi}_i} \mathbf{\Psi}$ are tangent vectors at $\boldsymbol{\psi}_i$. The geodesic distance between any two functions $\boldsymbol{\psi}_i$, $\boldsymbol{\psi}_j \in \boldsymbol{\psi}$ on a unit Hilbert sphere is the angle

$$\begin{aligned} \text{dist}\left(\boldsymbol{\psi}_i, \boldsymbol{\psi}_j\right) &= \left\| log_{\boldsymbol{\psi}_i}\left(\boldsymbol{\psi}_j\right) \right\|_{\boldsymbol{\psi}_i} = cos^{-1}\left\langle \boldsymbol{\psi}_i, \boldsymbol{\psi}_j \right\rangle \\ &= cos^{-1}\left(\int_{\mathbf{s} \in \mathbb{S}^2} \boldsymbol{\psi}_i(s) \boldsymbol{\psi}_j(s) ds\right), \end{aligned} \tag{3}$$

where $\langle \cdot, \cdot \rangle$ is the $\mathbb{L}^2$ dot product on the sphere $\mathbb{S}^2$. Note that the geodesic distance is not rotation invariant. $log_{\boldsymbol{\psi}_i}\left(\boldsymbol{\psi}_j\right)$ is the *logarithm map* from $\boldsymbol{\psi}_i$ to $\boldsymbol{\psi}_j$ with the closed-form formula

$$\overrightarrow{\boldsymbol{\psi}_i \boldsymbol{\psi}_j} = log_{\boldsymbol{\psi}_i}\left(\boldsymbol{\psi}_j\right) = \frac{\boldsymbol{\psi}_j - \left\langle \boldsymbol{\psi}_i, \boldsymbol{\psi}_j \right\rangle \boldsymbol{\psi}_i}{\sqrt{1 - \left\langle \boldsymbol{\psi}_i, \boldsymbol{\psi}_j \right\rangle^2}} cos^{-1}\left\langle \boldsymbol{\psi}_i, \boldsymbol{\psi}_j \right\rangle. \tag{4}$$