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Regional flux analysis for discovering and quantifying anatomical changes: An application to the brain morphometry in Alzheimer's disease

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ABSTRACT

In this study we introduce the *regional flux analysis*, a novel approach to deformation based morphometry based on the Helmholtz decomposition of deformations parameterized by stationary velocity fields. We use the scalar pressure map associated to the irrotational component of the deformation to *discover* the critical regions of volume change. These regions are used to consistently *quantify* the associated measure of volume change by the probabilistic integration of the flux of the longitudinal deformations across the boundaries. The presented framework unifies voxel-based and regional approaches, and robustly describes the volume changes at both group-wise and subject-specific level as a spatial process governed by consistently defined regions. Our experiments on the large cohorts of the ADNI dataset show that the regional flux analysis is a powerful and flexible instrument for the study of Alzheimer's disease in a wide range of scenarios: cross-sectional deformation based morphometry, longitudinal discovery and quantification of group-wise volume changes, and statistically powered and robust quantification of hippocampal and ventricular atrophy.

1. Introduction

Deformation based morphometry is a fundamental instrument for *discovering* and *quantifying* the dynamics of biological processes, for instance growth, or pathological changes. We can broadly identify two main paradigms for the analysis of volume changes in T1 magnetic resonance (MR) images: *hypothesis-free* and *regional* analysis. In the first case, the volume changes are modeled at finer scales in the whole brain such as in the voxel/tensor based morphometry and in the cortical thickness analysis (Fox et al., 2001; Thompson et al., 2003).

On the one hand these methods are useful for exploratory purposes at the population level, but usually lack robustness for a reliable quantification of the changes at the subject level. On the other hand, regional analyses are focused on the detection of significant changes in regions which are identified thanks to a preliminary segmentation. For instance, the boundary shift integral measures the longitudinal atrophy as a function of the displacement of segmented boundaries (Freeborough and Fox, 1997). These approaches can provide robust assessment of longitudinal atrophy (Leung et al., 2010b), but are limited to previously defined regions of interest. Therefore they might fail to detect the complex and spread pattern of changes which is likely to characterize the biological variation. For example the failure in the recent trials on AD to show significant treatment effects on the hippocampal volume changes led to question whether a more general but still powered analysis would be able to detect possible improvements (Raschetti et al., 2007).

1.1. Unifying regional and hypothesis free-approaches

Providing a measure of volume change which can at the same time *consistently identify* and *reliably quantify* the volume changes is crucial for understanding the dynamics of the pathological evolution and for providing stable measures for the clinical setting.

Non-linear registration encodes the morphological changes between pairs of longitudinal MRIs as deformation fields. It was employed both for the whole brain exploratory analysis and for the regional quantification, for instance through the Jacobian determinant analysis (Boyes et al., 2006). However, the identification of atrophy regions through group-wise voxel-by-voxel analysis of Jacobian determinant maps, like in tensor based morphometry (TBM) (Riddle et al., 2004), is prone to statistical issues such as multiple comparisons problems. Moreover, the robustness of the regional quantification of the Jacobian is inherently dependent on the accuracy of the underlying anatomical segmentation, and is highly sensitive to numerical biases introduced by the

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spatial derivatives. For these reasons, tools like TBM are mainly employed in research and found limited applications in the practical clinical routine.

The above limitations might be overcome by noticing that the topology of deformation fields implicitly encode the spatial location of relevant atrophy processes, and thus we might not really require the explicit definition of anatomical regions for the Jacobian determinant analysis (Davatzikos et al., 2009). The aim of this paper is indeed to develop novel analysis techniques to simultaneously extract and analyze these regional features encoded by the deformations.

1.2. Helmholtz decomposition of anatomical deformations

It was proposed in Hansen et al. (2009) to parametrize the deformations by irrotational and divergence-free components, according to the Helmholtz decomposition of vector fields. If we assume that atrophy is described by the change of volume associated with the deformation, then it is completely identified by the irrotational part of the deformation, while the divergence-free part only accounts for volume preserving ("locally rigid") processes which can be interpreted as tissue reorganization. With such a decomposition, the locations of the maximum/minimum irrotational potential define the centers of expanding and contracting regions (Lefevre et al., 2009). These extrema may represent a promising feature for localizing brain atrophy.

A different measure of volume change associated to the deformation field is the flux across surfaces (Chung et al., 2001), which may be seen as the infinitesimal formulation of the boundary shift. However flux-based analysis has been seldom used in morphometric studies, due to the complexity of reliably integrating vector normals on segmentations of the regional boundaries.

Expanding on the conference article (Lorenzi et al., 2012) we propose to merge these approaches, leading to the *regional flux analysis of deformations*, a novel method for reliably *discovering* and robustly *quantifying* volume changes based on the Helmholtz decomposition.

In Section 2 we introduce the Helmholtz theorem, and the relationship between pressure and flux of deformations. These measures are used in Section 3 to provide a probabilistic formulation for the definition of the group-wise regions involved in the atrophy process. We then apply the proposed framework to the study of Alzheimer's disease (AD), to identify and quantify the brain atrophy in three different scenarios: explorative group-wise morphological comparison (Section 4), discovery and quantification of group-wise longitudinal atrophy (Section 5), and robust and statistically powered quantification of hippocampal and ventricular atrophy (Section 6). All the experiments are performed on large cohorts of the ADNI dataset (for details on the experimental data please refer to Appendix A).

2. Helmholtz decomposition for stationary velocity fields

The present work is based on the image registration framework parameterized by stationary velocity fields (SVF), which has been already applied for the longitudinal analysis of deformations (Lorenzi et al., 2011), and for which an implementation of the LCC-logDemons algorithm is available (Lorenzi et al., 2013a).

2.1. Stationary velocity field parameterization of deformations

In the registration setting parameterized by SVFs the diffeomorphic transformation ϕ which maximizes the similarity between a given pair of images belongs to the subset of diffeomorphisms generated by the flow of a tangent SVF v (Arsigny et al., 2006). Such a deformation is parametrized through the Lie group exponential of v, denoted $\exp(v)$, defined by the solution of the ODE: $\frac{\partial \phi(x,t)}{\partial t} = v(\phi(x,t))$, with initial condition $\phi(x,0) = id(x)$, where $id(x)$ is the identity transformation. This ODE defines a one parameter subgroup, $\phi_t(x) = \phi(x,t)$ since $\phi_{s+t}(x) = \phi(x,s) \circ \phi(x,t) = \phi(x,s+t)$. The transformation is obtained at the parameter value $t = 1$, i.e. $\phi(x) = \phi(x,1)$.

The advantage of the SVF parameterization lies in the simplification of mathematical operations on diffeomorphic transformations, for instance for inverse computing and composition (Arsigny et al., 2006). More generally, the tangent nature of SVF simplifies the definition of statistical quantities, like the group-wise barycenter (Pennec and Arsigny, 2012) or local principal components analysis of variations (Seiler et al., 2011).

In the following sections we show how the SVF framework can be used to define a consistent statistical setting for the group-wise analysis of longitudinal anatomical volume changes.

2.2. Pressure potential and flux through a region

The Helmholtz theorem states that a vector field v (which in our case is a SVF) which vanishes at infinity can be uniquely factored as the sum of an irrotational and a divergence free component, $v = \nabla \mathbf{p} + \nabla \times \mathbf{A}$ (Fig. 1) (Arfken and Weber, 1995).

The irrotational component ∇p is the gradient of a *scalar* pressure (potential) field $\mathbf{p}$, while the divergence-free component is the curl of the vector potential $\mathbf{A}$. Since $\nabla \times \nabla \mathbf{p} = 0$, the scalar pressure component encodes the information concerning all the volume change.

Please note that the diffeomorphic transformation $\phi(x, t) = exp(\nabla(t\mathbf{p}))(x)$ is the flow of an irrotational velocity field $\nabla \mathbf{p}(x) = d\phi(x, t)/dt$, for every t. On the other hand the divergence-free component is by definition such that $\nabla \cdot \nabla \times \mathbf{A} = 0$ and therefore it describes the incompressible part of the deformation.

Finally, the flux of a stationary velocity field across a given surface ∂V is given by the Divergence (or Ostrogradsky's) theorem, and can be rewritten as $\oint_{\partial V} v \cdot \mathbf{n} dS = \int_V \nabla \cdot v dV$.

Recently the Helmholtz decomposition was introduced in the Demons registration in order to estimate incompressible deformations (Mansi et al.). Here we propose to use it for the analysis of the compressible part, which encodes the observed matter loss as a smooth compression/expansion process. In such a model, the associated divergence quantifies the apparent anatomical changes as the flux of the estimated SVF across surfaces.

2.2.1. Topology of pressure fields

Theoretically, given the irrotational field $\nabla \mathbf{p}$ one could partition the whole space into *critical regions* of positive and negative divergence $\nabla \cdot \nabla \mathbf{p}$, each of them containing a critical point of local maximal/minimal pressure $\mathbf{p}$ (Fig. 2). From the divergence theorem, the flux across the boundaries of these regions is flowing either inward or outward. The saddle points for the pressure are on the boundaries of those regions, and identify a change in the flow.

The analysis of the critical points of a pressure map can be addressed by the *Morse–Smale* theory as a topological problem, leading to the representation of incompressible fields as a geometrical complex of regions, boundaries, edges and vertices (Morse, 1934). Although intriguing, the application of such concepts to medical imaging is still difficult, due to the missing statistical version (and implementation) of the Morse theory. In order to obtain a tractable approach to the problem, we propose in this study to focus on the statistical definition of a consistent *subset* of critical regions in a sample of observed pressure maps. This way we can robustly describe group-wise irrotational fields as a spatial process governed by key critical regions. In the following section we provide a framework for the statistical definition of these critical regions, and for the quantitative analysis of the associated scalar flux, in order to provide a robust measure of volume changes in anatomical studies.

3. Probabilistic group-wise definition of the critical regions

The aim of this section is to provide a statistical definition of the group-wise pressure field associated to a set of observed pressure

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