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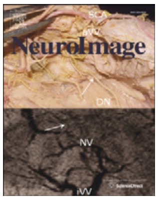

Multi-contrast multi-scale surface registration for improved alignment of cortical areas

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ABSTRACT

The position of cortical areas can be approximately predicted from cortical surface folding patterns. However, there is extensive inter-subject variability in cortical folding patterns, prohibiting a one-to-one mapping of cortical folds in certain areas. In addition, the relationship between cortical area boundaries and the shape of the cortex is variable, and weaker for higher-order cortical areas. Current surface registration techniques align cortical folding patterns using sulcal landmarks or cortical curvature, for instance. The alignment of cortical areas by these techniques is thus inherently limited by the sole use of geometric similarity metrics. Magnetic resonance imaging T1 maps show intra-cortical contrast that reflects myelin content, and thus can be used to improve the alignment of cortical areas. In this article, we present a new symmetric diffeomorphic multi-contrast multi-scale surface registration (MMSR) technique that works with partially inflated surfaces in the level-set framework. MMSR generates a more precise alignment of cortical surface curvature in comparison to two widely recognized surface registration algorithms. The resulting overlap in gyrus labels is comparable to FreeSurfer. Most importantly, MMSR improves the alignment of cortical areas further by including T1 maps. As a first application, we present a group average T1 map at a uniquely high-resolution and multiple cortical depths, which reflects the myeloarchitecture of the cortex. MMSR can also be applied to other MR contrasts, such as functional and connectivity data.

Introduction

Image registration is crucial for brain mapping studies, such as comparative morphometry and group analysis of functional data, in order to compensate for differences in position, size and shape of brain structures across individuals. Many fully automated non-linear volume registration algorithms have been developed to align brain structures, and produce very good results even for strong differences due to pathology (see Klein et al. (2009) for a review). Although these algorithms perform well for deep brain structures, they fail to accurately align the cerebral cortex, a thin sheet that is highly convoluted and variable. In magnetic resonance imaging (MRI) studies, surface registration, which aligns 2D manifolds based on their shape, is often preferred over volume registration to align cortical areas between subjects or with an atlas. The pioneering work of Brodmann (1909) and more recent histological studies (Fischl et al., 2008; Hinds et al., 2008) have shown that cortical folding patterns can be used to approximately predict the location of cortical areas, with the highest accuracy for primary cortical areas. Surface registration driven by cortical folding patterns also improves the statistical power and spatial specificity of group functional MRI analysis (Frost and Goebel, 2012; van Atteveldt et al., 2004) due to improved alignment of functional areas.

In spite of this significant improvement in cortical alignment, folding-based surface registration is inherently limited in two ways. There are regions of high inter-subject folding variability, defined in Ono's *Atlas of the Cerebral Sulci* (Ono et al., 1990), where the number of folds may differ and a one-to-one mapping of folds is not possible. Furthermore, the boundaries between functional cortical areas have a complex and variable relationship with the cortical folding pattern, in particular for higher cognitive and association cortex. Inter-subject variability in size and shape of the primary visual cortex in relation to sulcal folds has been shown in histology studies (Amunts et al., 2000; Hinds et al., 2008). More significant variability has been shown for non-primary areas including the motion sensitive visual complex MT+/V5 and Broca's area using histology (Fischl et al., 2008), task-based fMRI (Frost and Goebel, 2012), as well as T1-weighted/“T2-weighted” images (Glasser and Van Essen, 2011). Due to this complex relationship, the alignment of cortical areas is improved but is also inherently limited

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by the use of geometric information to drive the surface registration. Assuming a perfect alignment of the geometric similarity metric, such as curvature or sulcal landmarks, is achieved, there will remain a residual error in the alignment of cortical areas between subjects.

Cortical micro-architectonic features, such as the density, size, orientation and shape of cells and myelin sheaths, are more strongly related to cortical function than cortical folding patterns (Amunts et al., 2007). Structural MR images show myelin contrast that reflects the architectonic boundaries of cortical areas (Geyer et al., 2011). Very high-resolution T1 maps show exquisite intra-cortical contrast that varies as a function of cortical depth (Geyer et al., 2011; Lutti et al., 2014a; Tardif et al., 2013). Recent studies have mapped individual and group average T1 maps (Bazin et al., 2014; Sereno et al., 2013; Weiss et al., 2010), T2* maps (Cohen-Adad et al., 2012) and T1-weighted/"T2-weighted" images (Glasser and Van Essen, 2011) onto the cortical surface. Primary areas and extrastriate visual areas, which are densely myelinated, are clearly discernible on the inflated surfaces. These "myelin maps" have been shown to truly reflect the location of functionally specialized areas of the cortex using topological mapping fMRI (Bridge et al., 2005; Dick et al., 2012; Sereno et al., 2013), as well as task and resting-state fMRI (Van Essen and Glasser, 2014). We propose to use T1 maps, a quantitative index of primarily myelin content (Geyer et al., 2011; Stüber et al., 2014), to improve the surface-based alignment of cortical areas.

In this paper, we present a novel automated multi-contrast multi-scale surface-based registration technique (MMSR) for precise surface registration, with key improvements over current methods. MMSR applies a non-linear volume-based registration algorithm to surface information represented in volume space, rather than computing a deformation restricted to a spherical manifold. It can therefore be applied to surfaces with non-spherical topology, and the computed deformation is meaningful for statistical shape analysis (Miller, 2004). MMSR registers the level-set representation of the cortical surfaces and two curvature metrics (curvedness and shape index). We developed a multi-scale approach that is applied to a hierarchy of partially inflated level set surfaces with a shrinking narrowband. The final transformation is a direct symmetric diffeomorphic mapping between the original surfaces in volume space. MMSR was first introduced in a recent conference paper (Tardif et al., 2013). Here, we describe our improved implementation in detail.

For validation, we quantitatively compare MMSR to two widely accepted surface registration algorithms: FreeSurfer and Spherical Demons. Firstly, we build geometric group templates and calculate the group average and standard deviation of the registration metric, i.e. curvature, to compare the precision of the alignment. Secondly, we perform pairwise registration experiments of surfaces from the Mindboggle-101 dataset that have been manually labeled. The overlap of the labels after alignment is an indication of registration accuracy, i.e. whether the corresponding gyri have been aligned or the algorithm is sensitive to local minima.

MMSR can also include other contrasts instead of, or in addition to, the curvature metrics to drive the registration. We demonstrate this feature by including intra-cortical T1 contrast with the objective to improve the alignment of cortical areas. We present a unique high-resolution (0.5 mm isotropic) group-average T1 map of the cortical surface at four cortical depths.

Multi-contrast surface registration

The level-set framework

The MMSR algorithm applies non-linear volume registration to surface information represented in Cartesian space using a level-set framework. The level-set representation $\varphi(v)$ of a surface is a signed distance function, i.e. the value at voxel v is equal to the distance of voxel v from the surface, positive outside the surface and negative inside (Osher and Sethian, 1988). The level-set is often only defined within a maximum distance from the surface, a narrowband, to enhance computation efficiency. An example of a level-set volume image and the corresponding mesh of a cortical surface are shown in Fig. 1. Distance transforms and the level-set function have been exploited previously in rigid-body (Kozinska et al., 1997) and non-linear image registration (Vemuri et al., 2003), in particular to represent arbitrary shapes and their local variations (Hansen et al., 2007; Paragios et al., 2003). A recent article by Albrecht et al., which expands on previous work (Dedner et al., 2007; Lüthi et al., 2007), uses distance functions and other surface features, including curvature, to align surface renderings of human skulls and femurs (Albrecht et al., 2013). The advantage of the level-set framework is that numerical computations, such as surface curvature and normals, can be easily evaluated in the Cartesian grid without having to parameterize the surface. This implicit surface representation also prevents self-intersections and distortions during surface deformations. Topological changes, such as breaking and merging, are well defined and can be allowed or prevented (Han et al., 2002).

Multi-contrast approach

In addition to the level-set definition of the surface, additional surface or texture features can be used to drive the registration (Litke et al., 2005), such as surface curvature (Albrecht et al., 2013; Dedner et al., 2007). In our implementation, we use a total of four contrasts: a level-set representation of the cortical surface, two curvature metrics (curvedness and shape index) and, optionally, T1.

The level-set φ is modulated using the sigmoid function in Eq. (1), where the slope is steepest at the intersection with the surface. The modulated level-set $\widetilde{\varphi}$ spans the range [0, 1] within the narrow band specified by distance d. An example image is shown in Fig. 2.

$$\widetilde{\varphi}(v) = \frac{1}{1+e^{2\varphi(v)/d}} \tag{1}$$

In addition to this contrast, which is radial to the cortical surface, we use the surface curvature to drive the registration in the tangential plane, as in Dedner et al. (2007). Our objective is to align folds that are similar in shape and size. The principal curvatures ($\kappa_{\downarrow}1$ and $\kappa_{\downarrow}2$), as well as the Gaussian and mean curvatures (K and H), both depend on the size and shape of the folds. Furthermore, they fail to distinguish certain geometries. We chose to use the following two curvature metrics: the curvedness, representing the size of the cortical folds, and the shape index, representing the local shape of the folds (Koenderink and van Doorn, 1992). These two complementary metrics are ideal for

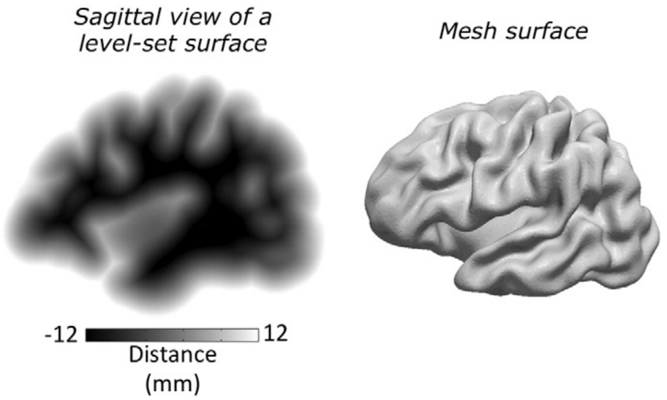

Fig. 1. Level-set representation of a cortical surface. To the left is a sagittal view of a 3D volume level-set representation of a cortical surface. The voxel values correspond to the signed distance from the cortical surface defined within a narrowband of ±12 mm. The corresponding 2D mesh representation is shown to the right.