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Mapping registration sensitivity in MR mouse brain images

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ABSTRACT

Nonlinear registration algorithms provide a way to estimate structural (brain) differences based on magnetic resonance images. Their ability to align images of different individuals and across modalities has been well-researched, but the bounds of their sensitivity with respect to the recovery of salient morphological differences between groups are unclear. Here we develop a novel approach to simulate deformations on MR brain images to evaluate the ability of two registration algorithms to extract structural differences corresponding to biologically plausible atrophy and expansion. We show that at a neuroanatomical level registration accuracy is influenced by the size and compactness of structures, but do so differently depending on how much change is simulated. The size of structures has a small influence on the recovered accuracy. There is a trend for larger structures to be recovered more accurately, which becomes only significant as the amount of simulated change is large. More compact structures can be recovered more accurately regardless of the amount of simulated change. Both tested algorithms underestimate the full extent of the simulated atrophy and expansion. Finally we show that when multiple comparisons are corrected for at a voxelwise level, a very low rate of false positives is obtained. More interesting is that true positive rates average around 40%, indicating that the simulated changes are not fully recovered. Simulation experiments were run using two fundamentally different registration algorithms and we identified the same results, suggesting that our findings are generalizable across different classes of nonlinear registration algorithms.

Introduction

The structure and shape of the brain and its parts have been shown to be related to its function. Magnetic Resonance Imaging (MRI) allows the measurement of the intact brain's structural properties with high precision (Henkelman, 2010; Nieman et al., 2011). One MRI-based technique for probing shape differences in the brain, predominant in the study of animal models, is image registration (Badea et al., 2007; Chen et al., 2006; Lerch et al., 2008; Pitiot et al., 2007). Neuroanatomical differences between groups of subjects can then be estimated using deformation based morphometry (DBM) (Ashburner et al., 1998). Briefly, DBM works as follows. First, the MR images are aligned to a common registration target/template or one of the input images using affine transformations. Then a nonlinear registration is used for increasingly precise alignment to the target. This final registration yields the deformation fields which are then input into statistical analysis. The linear components of the deformation fields can be removed to account for overall differences in size and position. The Jacobian determinant of the deformation fields is often of interest as it summarizes the shape differences as expansions and contractions.

The lissencephalic mouse brain is homologous between individual mice, making DBM a particularly well suited method to capture differences in mouse brains. For example, Mercer et al. (2009) examined brain differences related to the *Magel2* gene, a gene that plays a role in cell differentiation and cell death. Several brain structures, such as the amygdala, the dentate gyrus and the nucleus accumbens were found to be 4–5% smaller in the mutants. The GSK-3α null mutants in Kaidanovich-Beilin et al. (2009) were shown to have the arbor vita enlarged by 9% and the pons by 5% as compared to their wild types litter mates. The gene products of GSK-3 are essential for cerebellar development and foliation. Mansouri et al. (2012) studied the effects of deficiencies in purine nucleoside phosphorylase (PNP) on the brain. Inherited defects in PNP in humans cause progressive neurological dysfunction. In their study regions in the cerebellum were shown to be about 15% smaller in PNP-knockout mice compared to wild type litter mates. In Spring et al. (2010) asymmetries in the mouse brain were investigated using DBM, which among others revealed an area in the cortex with a 15.5% difference between the left and right hemisphere.

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In the human brain with its complex and idiosyncratically folded cortex only subcortical structures may be homologous between subjects, however, DBM has been applied extensively on human MR data as well and is especially useful for longitudinal data (Brambati, 2009; Hyde et al., 2009; Kim, 2008; Tao, 2009).

Several studies have shown the superior effectiveness of MRI combined with automated image registration in comparison to stereology or manual segmentations in mice (Lau et al., 2008; Lerch et al., 2008; Spring et al., 2007). Other research, focused on human brain imaging, has compared the performance of multiple image registration packages based on a set of gold standard labels (Allen et al., 2008; Andreasen et al., 1996; Babalola et al., 2009; Bai et al., 2012; Christensen et al., 2006; Crum et al., 2004; Fischl et al., 2002; Heckemann et al., 2006; Hellier et al., 2003; Iosifescu et al., 1997; Klein et al., 2009; Ma et al., 2005; Quarantelli et al., 2002; Yassa and Stark, 2009). Calculating how accurately registration algorithms can reproduce gold standard segmentations, however, does not provide a direct estimation of their sensitivity to detecting changes in neuroanatomy, because overlap measures of labels cannot make inferences about the accuracy of registrations within those regions. To address that, Karacali and Davatzikos (2006) and Camara et al. (2006) have proposed methods to simulate atrophy on medical images. Their methods provide means to evaluating the sensitivity and accuracy of image registration techniques by simulating atrophy in a brain structure and subsequently trying to recover it.

Given the widespread use of DBM to investigate volumetric neuroanatomical differences in human and animal studies, we set out to assess its accuracy. Here we introduce a novel method to simulate atrophy and expansion in arbitrary areas in MR images and utilize this method to perform simulation experiments. The following seven points are addressed: 1) We evaluated how reliably image registration can recover change in the mouse brain by simulating atrophy in anatomical brain structures of a mouse brain atlas (Dorr et al., 2008). 2) Next we looked at how accurately the amount of simulated atrophy can be determined in the brain structures and how this depends on the size/shape/contrast at the boundaries of the structures. 3) We evaluated the influence that inherent variability in inbred mouse strains has on the recovery of simulated atrophy in brain structures, and 4) whether we systematically over- or underestimate simulated atrophy and expansion. 5) The simulation experiments were performed using two nonlinear registration methods to address the generality of our results. 6) Multiple comparison corrections were performed at a voxel level to determine the number of true and false positives. 7) Lastly, a small focal amount of atrophy was simulated in one half of a brain slice to investigate the impact of image features on the performance of image registration. The results demonstrate that three pieces of information influence the accuracy of registration on whole anatomical regions (size, compactness and inherent variability), and that while the accuracy of registration based measures of anatomy is impressive, not all simulated changes can be fully recovered.

Methods

Image acquisition

In this paper the simulation experiments used MRI scans acquired from 20 C57/bl6 male mice of young adult ages of 8–10 weeks [specimen preparation as in (Cahill et al., 2012)]. A multi-channel 7.0 T, 40 cm diameter bore magnet (Varian Inc. Palo Alto, CA) was used to acquire the anatomical images. A custom-built 16-coil solenoid array was used to image 16 samples concurrently (Lerch et al., 2011a). Parameters used in the scans were optimized for gray–white matter contrast: a T2-weighted 3D fast spin-echo sequence, with TR = 2000 ms, echo train length = 6, TE_{eff} = 42 ms, field-of-view (FOV) = 25 × 28 × 14 mm and matrix size = 450 × 504 × 250, giving an image with 56-micron isotropic voxels and an optimal signal to noise ratio (SNR) in the order of 40 (Kale et al., 2008). Total imaging time was 11.7 h. Scans were corrected for geometric distortions generated by the image acquisition process based on images of precision machined phantoms.

Creating an artificial deformation field

Atrophy and expansion were simulated by applying an artificial deformation field that produced the desired levels of volumetric loss and expansion (inspired by (Karacali and Davatzikos, 2006), see Fig. 1). First, a desired Jacobian determinant was generated for a region of interest (ROI). The Jacobian determinant of a deformation field specifies whether the change in each voxel is due to atrophy or expansion (Davatzikos et al., 1996). Voxels belonging to the ROI received either a reduced determinant (less than 1; atrophy), or an increased determinant (greater than 1; expansion). The remaining brain voxels received a determinant of 1 (no change). Next, a zero-vector deformation field was initialized. In an iterative procedure, the Jacobian determinant was calculated from the artificial deformation field and the vectors of each voxel's six nearest neighbors were adjusted to yield the approximate input determinant. To keep intracranial space constant, we created a tolerance map comprising the ventricles and the space between brain and skull (subarachnoid space) and allowed these areas to deform. To preserve topology, the volume change in these areas was limited to 50% of their original size.

The twenty mouse brain MRI scans were divided into two groups (mutants and controls) that minimized the structural differences between the groups. We simulated volume changes on two spatial scales; whole anatomical regions and focal spots.

First we induced three levels of atrophy (5, 10 and 20%) in 59 out of the 62 structures defined in Dorr et al. (2008). The 3 ventricle areas were left out and used as tolerance space. Two levels of expansion (5 and 10%) were induced in 14 randomly chosen structures with a size of at least 1 mm^3. Controls remain unchanged. Registrations at 5% atrophy were run using two registration algorithms, resulting in 236 registrations on simulated atrophy. 28 registrations were run on simulated expansion, totalling 264 registrations. A single registration took approximately 100 CPU hours, resulting in a total of about 26,400 h in single CPU time. This is equivalent to several weeks of processing on a mid-sized cluster of about 10 machines with an 8-core processor each.

Secondly, we induced focal atrophy in the mutants, the center of the simulated atrophy located at each voxel in one half of an axial brain slice (see Fig. 8). This change consisted of a 90% volume decrease in a discrete octahedron (radius of 3.5 voxels, volume of 63 voxels) translating into a 0.08 mm^3 volume loss. For computational efficiency, the data were resampled to 112-micron isotropic voxels. The entire axial brain slice contained 7640 brain voxels. We ran simulations in the left hemisphere of that slice, resulting in 3820 registrations. To ensure that our results displayed symmetry between the left and right hemisphere, we ran an additional 220 simulations in a rectangle in the right hemisphere. In total we ran 4040 registrations. Each registration at this coarser resolution took about 25 h of CPU time, totalling about 101,000 h of single CPU time for all registrations. This is equivalent to several months of processing on a mid-sized cluster. All processing was significantly sped up by using the GPC supercomputer at the SciNet HPC Consortium (Loken et al., 2010).

Image registration procedure

A multi-step image registration process was used to align the brains and create a consensus average (Kovačević et al., 2005). First, all brains were rigidly registered towards a pre-existing mouse brain average image. Then all possible pairwise 12-parameter registrations were carried out to create a linear average model of the entire data set. This linear average was the initial target for the final part of the registration. Here the scans were locally deformed through a mutli-scale nonlinear