# Evaluation of a Symmetric Diffeomorphic Registration Algorithm for Analyzing Neurodegenerative Disease

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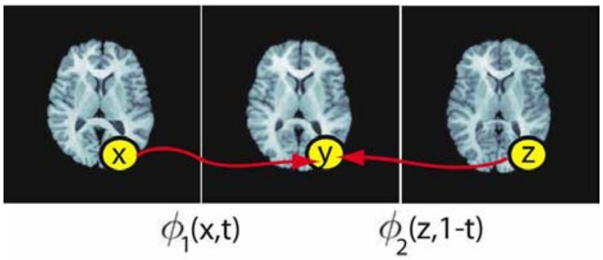
**Introduction**: One of the most challenging problems in modern neuroimaging is detailed characterization of neurodegeneration. Quantifying spatial and longitudinal atrophy patterns is an important component of this process. These spatiotemporal signals will aid in discriminating between related diseases, such as frontotemporal dementia (FTD) and Alzheimer's disease (AD), which are manifest in the same at-risk population. We evaluate a novel symmetric diffeomorphic image registration method for automatically providing detailed anatomical measurement over the aged and neurodegenerative brain. Our evaluation will compare gold standard, human segmentation with our method's atlas-based segmentation of the brain volume, the cerebral cortex and the left and right hippocampi. The new method compares favorably with Demons.

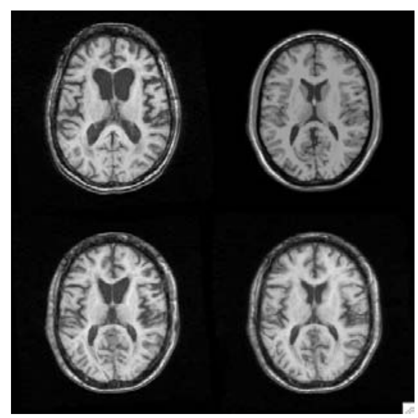
**Methods**: *Demons.* Dawant et al. used a standard method, the Demons deformable registration algorithm, for segmenting the caudate nucleus, the brain and the cerebellum for a morphometric comparison of normal and chronic alcoholic individuals [1]. Their evaluation of the algorithm found reasonable agreement between automated and manual labeling. They also showed results on the automated labeling of hippocampus but did not evaluate performance.

*Symmetric Diffeomorphisms*: A diffeomorphism is a smooth, one-to-one, onto, invertible map. Shortest paths between elements in this space are termed *geodesic*. Diffeomorphic methods were introduced into medical computer vision [2] for the purpose of providing a group theoretical, large deformation space-time image registration framework. We recently developed a symmetric formulation for estimating the geodesic connecting two images, *I* and *J,* in the space of diffeomorphic transformations. Our formulation accounts for the natural symmetry in the problem: both images move along the shape (diffeomorphism) manifold as shown in figure 1 at left. Symmetric diffeomorphisms guarantee two properties that are intrinsic to the notion of a geodesic path: the path from *I* to *J* is the same as it is when computed from *J* to *I*, regardless of similarity metric or optimization parameters. This allows us to generate reliable distance estimates and makes results independent of arbitrary decisions about which image is ``fixed" or ``moving." This novel method provides a uniquely formal and robust basis for medical image analysis. Our method is also unique in that it guarantees sub-pixel accurate, invertible transformations in the discrete domain [3] [4] as well as the ability to use landmark similarity with mutual information or other probabilistic similarity measures. Our evaluation shows the algorithm delivers what it promises: high performance on large deformation datasets, as encountered when studying elderly populations.




*Dataset.* We use a database of 20 T1 MRI images (0.85 x 0.85 x 1 mm, GE Horizon Echospeed 1.5 T scanner) from 10 normal elderly and 10 frontotemporal dementia patients. Each of the 20 images, along with the BrainWeb atlas, was manually labeled with a standard brain labeling protocol [4]. This protocol was shown to be highly reproducible for both small and large structures via six-month intra-rater reliability and inter-rater reliability measurements. Left hippocampus labeling, for example, showed a 0.92 intra-rater overlap ratio and 0.83 average for inter-rater variability. As the hippocampus is relatively small, these values are reasonable.

**Results**: We compare the performance of the SDR algorithm to the Demons algorithm for automatically labeling this dataset. Both Demons and SDR were used to automatically segment the whole brain, cerebellum and hippocampi by registering the labeled whole head MRI atlas to each individual whole head MRI. The atlas labelings are then warped by the same transformation into the space of the patient image. We then compute overlap ratios between the manual and automatic structural segmentations for each structure. An example comparison of the two methods is in figure 2 at right. The original subject image is upper left, the atlas slice is upper right, the SDR normalization is lower right, and Demons normalization is lower left.



Both algorithms produced segmentation results above the minimum threshold of 0.8 for all structures. SDR had an average overlap ratio of 0.932 for cerebrum wheras the Demons value was 0.919; for hippocampus, SDR mean = 0.901 while Demons = 0.882; for cerebellum, SDR mean = 0.883 while Demons = 0.861. We computed Student's T-test to evaluate whether SDR outperforms Demons for labeling these structures. SDR produces statistically significant better ($T > 2.5$) results over the whole dataset for each of these structures: hippocampus ($P < 0.03$), cerebellum ($P < 0.04$) and cerebrum ($P < 0.016$). The gap in performance on hippocampus ($P < 0.018$) and cerebrum ($P < 0.003$) increases when we focus only on the FTD results. This separation is caused by the presence of larger deformation in the FTD subjects some of which may not be captured by Demons. Note that, in the past, similar evaluations have shown Demons to outperform other methods.

Finally, we tested the two algorithms' ability to reproduce the statistically significant result gained from the manual labeling: the hippocampus in FTD subjects is smaller than in elderly controls after normalizing for head size. The Demons segmentation failed to produce statistically significant results. The SDR algorithm, however, *does show* significant differences in hippocampal size. Significance was evaluated with permutation testing.

**Conclusion**: This preliminary comparison shows the distinct advantage of SDR for segmenting elderly and neurodegenerative cerebrum, cerebellum and hippocampi. Note that, in addition to better performance, SDR provides a dense space-time map and transformation inverses. While the differences in performance are not huge, they are consistent, statistically significant and have a major impact on study outcome. One can extrapolate even larger differences between SDR and algorithms with lower dimensionality than either Demons or SDR. For this reason, along with the theoretical advantages that translate into practical benefits, we promote symmetric diffeomorphic algorithms in neuroimaging research, in particular when studying non-standard datasets, such as FTD and AD.

**References**: **[1]** B. Dawant, S. Hartmann, J. P. Thirion, F. Maes, D. Vandermeulen, and P. Demaerel, "Automatic 3-D segmentation of internal structures of the head in MR images using a combination of similarity and freeform transformations, part II: methodology and validation on severely atrophied brains," *IEEE Trans Med Imaging*, vol. 18, pp. 971–926, 1999. **[2]** M. Miller, A. Trouve, and L. Younes, "On the metrics and Euler-Lagrange equations of computational anatomy," *Annu. Rev. Biomed. Eng.*, pp. 375–405, 2002. **[3]** B. Avants, P. T. Schoenemann, and J. C. Gee, "Landmark and intensity-driven lagrangian frame diffeomorphic image registration: Application to structurally and functionally based inter-species comparison," *Medical Image Analysis,* in press, 2005. **[4]** B. Avants, C. L. Epstein, and J. C. Gee, "Geodesic image interpolation: Parameterizing and interpolating spatiotemporal images," in *ICCV Workshop on Variational and Level Set Methods*, 2005, in press. **[5]** B. Sparks, et al., "Brain structural abnormalities in young children with autism spectrum disorder," *Neurology*, vol. 59, pp. 184–92, 2002.