# MULTI-MODAL DIFFEOMORPHIC DEMONS REGISTRATION BASED ON POINT-WISE MUTUAL INFORMATION

*H. Lu*[1], *M. Reyes*[1], *A. Šerifović*[2], *S. Weber*[1], *Y. Sakurai*[3], *H. Yamagata*[3], *Ph. C. Cattin*[4]

[1]Institute for Surgical Technology and Biomechanics, University of Bern, Switzerland
[2]Faculty of Electrical Engineering, University of Tuzla, Bosnia and Herzegovina
[3]Research & Development Center, TOSHIBA Medical Systems Corporation, Japan
[4]Medical Image Analysis Center, University of Basel, Switzerland

## ABSTRACT

In this paper we propose a variational approach for multi-modal image registration based on the diffeomorphic demons algorithm. Diffeomorphic demons has proven to be a robust and efficient way for intensity-based image registration. However, the main drawback is that it cannot deal with multiple modalities. We propose to replace the standard demons similarity metric (image intensity differences) by point-wise mutual information (PMI) in the energy function. By comparing the accuracy between our PMI based diffeomorphic demons and the B-Spline based free-form deformation approach (FFD) on simulated deformations, we show the proposed algorithm performs significantly better.

***Index Terms—*** Image Registration, Diffeomorphisms, Mutual Information

## 1. INTRODUCTION

Medical imaging techniques have become indispensable to examine the human anatomy from anatomical and functional viewpoints. Since different imaging principles are able to generate different information, we often need to fuse these images to have the necessary information in one single image. Therefore, accurate multi-modal registration methods play a crucial role in many clinical applications.

Many non-rigid registration methods have been proposed in the past years, among which diffeomorphic demons [1] has proven to be a robust and reliable method [2]. The main idea of the algorithm is based on the classic Demons introduced by Thirion [3], which computes the pixel velocity from the image intensity difference. Instead of performing the optimization procedure on the displacement field space as in the classic demons, diffeomorphic demons combines a recently developed Lie group framework on diffeomorphisms and optimizes for Lie groups. Thus, this method ensures a smoother invertible transformation. Nevertheless, diffeomorphic demons cannot handle multi-modal registrations due to the similarity metric it uses. Therefore, it is quite essential to have a metric which can deal with multi-modal images. Information theory based similarity metrics such as mutual information (MI) are widely used to deal with images with different imaging technologies. Such measures rely on global statistics and are difficult to use in variational registration approaches. Rogelj *et al.* [4], however, proposed a point similarity measure derived from global mutual information. This measure allows estimation of mutual information on individual image points.

In this paper we present a modification of the diffeomorphic demons algorithm to allow for multi-modal image registration. The energy function of the registration framework is replaced by a measurement of global mutual information that is maximized during the optimization procedure. In Section 2 the diffeomorphic demons algorithm for mono-modal image registration is described, followed by Section 3 describing its extension to multi-modal image registration. In Section 4, the proposed algorithm is compared against FFD using simulated deformations on several sets of T1 and T2 brain magnetic resonance (MR) images.

## 2. DIFFEOMORPHIC DEMONS MODEL

### 2.1. Demons Registration

The classic demons algorithm is based on a heuristic argument called "demons" that create forces according to local characteristics of the images in a similar way Maxwell did for solving the Gibbs paradox. The forces are inspired by the optical flow equations and the method alternates between computation of the forces and regularization by Gaussian smoothing. The registration framework is treated as an optimization problem that aims at finding the displacement of each pixel so as to get a reasonable alignment of the images. This results in a computationally efficient algorithm compared to other non-rigid registration procedures such as those based on linear elasticity.

The whole registration algorithm can be summarized by a model with an energy consisting of a similarity function, a transformation error function and a regularization term.

Given a fixed image $F$, a moving image $M$, and a transformation field $s$, the energy function with respect to the update field $\mathbf{u}$ can be described as follows:

$$E_s^{corr}(\mathbf{u}) = \|F - M \circ (s + \mathbf{u})\|^2 + \frac{\sigma_i^2}{\sigma_x^2}\|\mathbf{u}\|^2, \qquad (1)$$

where $\sigma_i^2$ and $\sigma_x^2$ accounts for noise on the image intensity and the spatial uncertainty on the correspondences respectively.

Using a first-order Taylor expansion, Equation (1) can be linearized as:

$$E_s^{corr}(\mathbf{u}) = \|F - M \circ s + J\mathbf{u}\|^2 + \frac{\sigma_i^2}{\sigma_x^2}\|\mathbf{u}\|^2, \qquad (2)$$

with $J = -(\nabla F + \nabla(M \circ s))/2$ for an efficient second-order minimization (ESM) symmetric registration.

The energy function reaches minimum when its gradient is zero, thus we can get the update field as:

$$\mathbf{u} = -\frac{F - M \circ s}{J^2 + \frac{\sigma_i^2}{\sigma_x^2}} J. \qquad (3)$$

Gaussian smoothing is used as the regularization term for the displacement $\mathbf{u}$. The registration must solved iteratively as the update field is based on local information.

### 2.2. Diffeomorphic Extension

One of the major drawbacks of the classic demons algorithm is its inability to generate an invertible output transform when compared to diffeomorphic image registration algorithms. Vercauteran *et al.* [1] proposed a diffeomorphic extension to the demons framework. The main idea was to adapt the optimization procedure to a space of diffeomorphic transformations. Given the current transformation $s$, the update is done through the exponential map on the Lie group with an update step $\mathbf{u}$:

$$s = s \circ \exp(\mathbf{u}). \qquad (4)$$

The final iterative registration algorithm can be written as follows:

- Given the current transformation $s$, compute a correspondence update field $\mathbf{u}$ by minimizing $E_{corr}(\mathbf{u})$ with respect to $\mathbf{u}$.
- For a fluid-like regularization let $\mathbf{u} \leftarrow K_{fluid} * \mathbf{u}$. The convolution kernel will typically be a Gaussian kernel.
- Let $c \leftarrow s \circ \exp(\mathbf{u})$.
- For a diffusion-like regularization let $s \leftarrow K_{diff} * c$ (else let $s \leftarrow c$). The convolution kernel will also typically be a Gaussian kernel.

## 3. MULTI-MODAL DIFFEOMORPHIC DEMONS

### 3.1. Point-wise Mutual Information

Mutual information is an information theoretic entity that measures how much information is gained about one random variable by the knowledge of another random variable. It is defined by marginal and joint entropies:

$$MI = H(A) + H(B) + H(A, B), \qquad (5)$$

and can be computed as:

$$MI = \sum_{i_F, i_M} p(i_F, i_M) \log\left(\frac{p(i_F, i_M)}{p(i_F)p(i_M)}\right), \qquad (6)$$

where $i_F$ and $i_M$ are image intensities of image $F$ and $M$.

As can be seen from Equation (5) mutual information is a global metric, giving only one similarity value for the whole image area. Rogelj *et al.* [4] introduced the idea of a point similarity measure so that the global mutual information can be computed locally. In other words, every pixel in the image has its own contribution to the global mutual information. Thus, the equation can be rewritten in the following form:

$$\begin{aligned} MI &= \frac{1}{N}\sum_x S_{MI}(x) \\ S_{MI}(x) &= \log\left(\frac{p(i_F(x), i_M(x))}{p(i_F(x))p(i_M(x))}\right), \end{aligned} \qquad (7)$$

where $x$ denotes the pixel in the image, and $N$ is the number of pixels in the overlapping area.

### 3.2. Integration into Diffeomorphic Demons

To realize multi-modal registration within diffeomorphic demons framework, we modify the external forces by replacing the mean squared error term defined in Equation (1) with point-wise mutual information. The energy function will then become:

$$E_s(\mathbf{u}) = \log\left(\frac{p(i_F, i_{M\circ(s\circ\exp(u))})}{p(i_F)p(i_{M\circ(s\circ\exp(u))})}\right). \qquad (8)$$

Since a larger mutual information value indicates better alignment, maximization of the energy function is required instead of minimization as in the classic diffeomorphic demons.

Assuming that $E$ is maximum when $\nabla E((u)) = 0$, one could simply use the gradient of the point-wise mutual information as the external force. Taking account of the consistency of the registration [5], using forward and reverse forces [6] makes the optimization more accurate and robust.

The forward force estimation $F_f$ is defined as the gradient of point-wise mutual information with respect to the fixed image. It moves the points in the fixed image to better match the moving image:

$$F_f(x) = \frac{\partial}{\partial \epsilon}\Big|_{\epsilon=0} S_{MI}(i_F(x+\epsilon), i_{M\circ s}(x)), \tag{9}$$

while the reverse force $F_r$, which tends to align the points in the moving image with respect to the fixed image, is defined as:

$$F_r(x) = \frac{\partial}{\partial \epsilon}\Big|_{\epsilon=0} S_{MI}(i_F(x), i_{M\circ s}(x+\epsilon)), \tag{10}$$

The update field can finally be defined as:

$$\mathbf{u} = k_E(F_f - F_r), \tag{11}$$

where the coefficient $k_E$ indicates the update step length which controls the optimization speed.

To accelerate the registration speed and avoid local minima, a multi-resolution approach with multiple levels is adopted in our work. Within a predefined number of iterations, the registration starts at the coarsest resolution level having the least amount of image detail, and continues with higher resolutions using the previously obtained transformation as an initialization.

## 4. EXPERIMENTS AND RESULTS

To quantitatively evaluate the accuracy of the proposed point-wise mutual information based diffeomorphic demons algorithm, we compared it to the free-form deformation (FFD) registration method, Rueckert *et al.* [7], on artificially distorted images.

To statistically analyze the benefit of the proposed method, we used the software package R (www.r-project.org). Normality of the distributions was tested with the Kolmogorof-Smirnov test. A $p$-value $< 0.05$ was considered statistically significant for all tests.

Since a purely qualitative analysis is insufficient to validate multi-modal non-rigid registration methods, our experiments base on recovering a synthetic deformation field. The synthetic deformation model we adopted consists of a regular grid with a random shift of each node, interpolated by thin plate spline [2]. There are two parameters that may be varied, the grid size and the possible extent of the random deformation that is applied on each grid point. As the choice of synthetic deformation parameters can bias the quantitative evaluation, we adopted different degrees of synthetic deformations.

To test our multi-modal registration algorithm we need a set of perfectly aligned ground truth images from multiple modalities. For this reason we used images from the BrainWeb MRI Simulated Normal Brain Database [8]. This database can provide T1 and T2 images with different noise and bias configuration. In the experiment we used MRI T1 and T2 images with an isotropic voxel size of $1 \times 1 \times 1\,\text{mm}^3$.

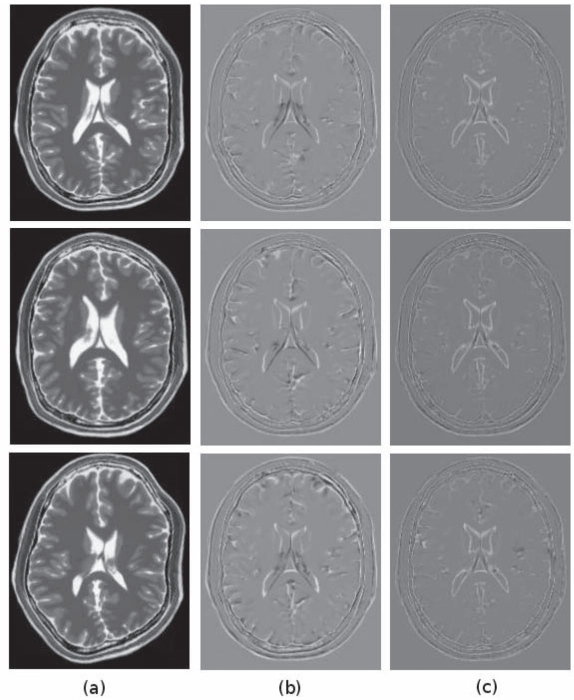

**Fig. 1**: (a) Synthetically deformed T2 image with a maximum deviation of $4\,\text{mm}$, $6\,\text{mm}$ and $8\,\text{mm}$ respectively, (b) difference of the ground truth T2 image and FFD registration, (c) difference of the ground truth T2 image and registration with our multi-modal diffeomorphic demons

For all our experiments three levels of resolution are adopted consisting of 20 iterations each. We use a Gaussian kernel with a sigma $\sigma = 3$ for the update field regularization and sigma $\sigma = 2$ for deformation field Gaussian regularization. The coefficient $k_E$ is set to 4 at the beginning of optimization and is decreased proportionally during the iterations in order to facilitate convergence. The quality of the registration is evaluated by the following criteria:

- Root-Mean-Square of Displacement Field (RMS):

$$e_{RMS} = \sqrt{\frac{1}{N_\Omega}\sum_{x\in\Omega}(\varphi_{syn}(x) - \varphi_{reg}(x))^2}, \tag{12}$$

  where $N_\Omega$ denotes the number of voxels in the overlapping domain, $\varphi_{syn}$ and $\varphi_{reg}$ are the synthetic ground truth and the computed deformation field.

- Maximum Distance Error (MDE):
  Maximal difference of all the components of the two displacement fields $\varphi_{syn}$ and $\varphi_{reg}$ .

- Global Mutual Information (MI):
  Computed with Equation (6).

We generated three sets of distorted T2 images. Each dataset consists of 20 randomly synthesized deformations. All the

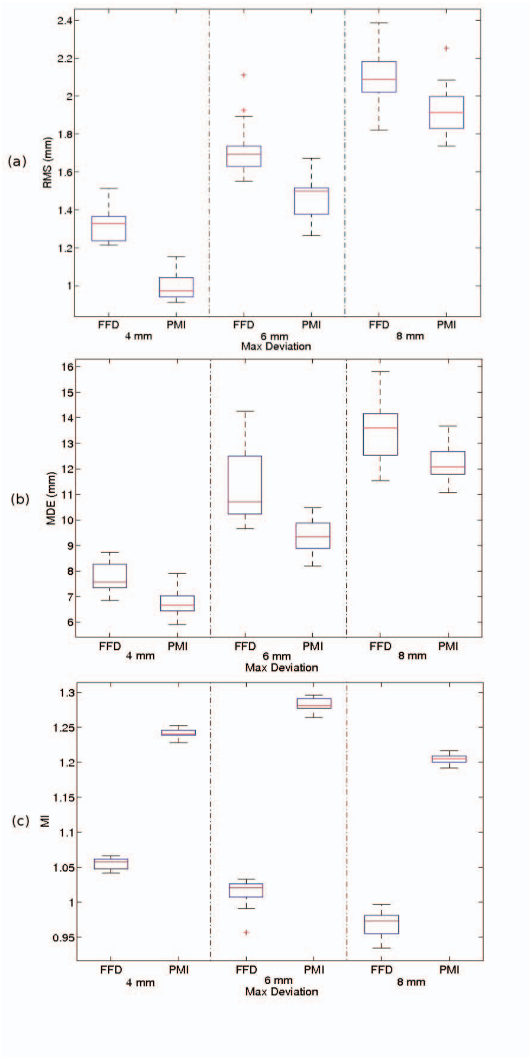


**Fig. 2**: Comparison of the results between PMI diffeomorphic demons and FFD. Each column represents different distortion levels at 4 mm, 6 mm and 8 mm, in which the left item indicates FFD and the right item indicates PMI diffeomorphic demons. (a) Boxplot of RMS (b) Boxplot of MDE (c) Boxplot of MI

deformations are generated based on a grid size of $32 \times 32$ and with maximum deviations of 4 mm, 6 mm and 8 mm.

The results of the registration are plotted in Fig. 2. We can see that our proposed multi-modal demons outperforms the FFD in all distortion levels. The displacement field is significantly closer ($p < 0.05$) to the ground truth than for FFD. Similarly, the achieved MI value for the registered images is significantly higher ($p < 0.05$) and the MDE was also significantly lower for our approach than for FFD. However, both algorithms are sensitive to the degree of distortion as the registration results for both approaches get worse with higher synthetic deformations.

## 5. CONCLUSION

This paper describes an extension to the diffeomorphic demons registration method by integrating point-wise mutual information allowing to use the sound mathematical demon framework also for multi-modal registrations. We evaluated our proposed method using simulated BrainWeb images with synthetic deformations of different degree. The registration results that we obtained are compared with the state-of-the-art B-Spline based FFD approach. We show that the proposed method consistently outperforms FFD.

Our future work will focus on the exploration of new energy terms and different regularization approaches to make the method applicable to a wider range of applications. Efforts will also be made to make the implementation available to the community.

## 6. REFERENCES

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