Atlas to Image-with-Tumor Registration based on Demons and Deformation Inpainting

Hans Lamecker, Xavier Pennec

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Hans Lamecker[1,2], Xavier Pennec[2]

[1] Zuse Institute Berlin (ZIB), Germany,
[2] Asclepios Research Project, INRIA, France

Abstract. This paper presents a method for nonlinear registration of images, where there exists no one-to-one correspondence in parts of the image. Such a situation occurs for instance in the case where an atlas of normal anatomy shall be matched to pathological data, such as tumors, resections or lesions. Our idea is to use local confidence weights and to model pathological regions with zero confidence. We integrate this concept into the efficient and publicly available diffeomorphic demons registration framework. Finally, we show that this process better captures deformations in high-confidence regions than without using the proposed modification. Furthermore, it is easy to implement and runs faster than previous approaches.

1 Introduction

Spatial registration of a 3D atlas to patient images is a fundamental approach to enhance individual patient data with valuable information, e.g. for simulating therapy effects. Such information may be a segmentation, physiological or structural data, which is not available for a given patient, as well as other clinical parameters. Reasons for the unavailability of such patient information in a clinical setting are manifold. Factors like radiation exposure, anesthesia, invasiveness of the measurement process, etc. have to be taken into account to find the correct balance patient safety, comfort and therapy benefit.

Atlas to patient registration of 3D image data faces a variety of challenges. First of all, the construction of an atlas is not trivial. Often, such a construction involves application-specific decisions, which renders the use of an atlas for other applications difficult. These decisions influence the choice of an appropriate image-to-image registration scheme, including cost functions (e.g. single or multi-modal), class of deformations (especially when dealing with large deformations), regularization, etc. More importantly, in the usual clinical setting patient data is pathological. One particularly challenging case are topological changes between the atlas (representing normal anatomy) and the patient data, e.g. because of the presence of tumors, lesions or surgical resections. Under these circumstances, the deformation of the atlas onto the patient image cannot be modeled with a smooth deformation.

A general solution for this problem seems beyond reach, hence application-specific methods are devised, which incorporate additional knowledge about the

type of pathology at hand. For instance, in atlas to tumor registration one approach is to incorporate tumor growth models and seeding strategies into the registration process [1, 2]. This is prone to errors in the initial seed placement.

An alternative approach is to endow a registration method with a local measure of confidence in the resulting deformation [3]. Then the pathological region can be modeled with low or zero confidence. This approach is more general in the sense that it decouples the registration from the specific pathology model.

The main contribution of this work is to combine the concept of zero-confidence local weights with the highly efficient log-domain diffeomorphic demons framework [4] in such a way that its efficiency is preserved. This will be accomplished through a inpainting process as an additional step in the demons scheme (see Sec. 2). In [3], the regularization step of the demons is modified over the whole image, while our approach only requires a computation on the zero-confidence region. Furthermore, our method can be implemented easily as an extension to the freely available ITK implementation of the demons [5].

We will also show in a prototypical study that this improves the segmentation of structures around pathologies both on simulated and clinical data sets, and can thus serve as a basis for further therapy planning.

2 Demons Algorithm with Deformation Inpainting

In this section we briefly summarize the demons method and motivate and explain our extension. Furthermore we compare it to related approaches.

Image registration can be formulated as a minimization problem of a cost function $E(F, M; s)$, that measures the dissimilarity between a (fixed or reference) image F and a deformed (moving or template) image $M \circ s$, where s is a spatial deformation. Usually, such a cost function consists of two terms: an intensity dissimilarity E_i and a regularization term E_r. One fundamental idea to explain the demons algorithm lies in the introduction of a hidden variable [6], called the correspondences c, as well as an additional cost E_c measuring the deviation between correspondences and deformation:coefficients

$$E(c, s) = \frac{1}{\sigma_i^2} E_i(F, M, c) + \frac{1}{\sigma_c^2} E_c(c, s) + \frac{1}{\sigma_r^2} E_r(s) \tag{1}$$

where

$$\begin{aligned} \sigma_i &= \textit{unreliability} \text{ of image intensity} \\ \sigma_c &= \textit{uncertainty} \text{ of correspondences} \\ \sigma_r &= \textit{irregularity} \text{ of the deformation} \end{aligned}$$

This idea then allows to come up with an alternate minimization scheme starting with $k = 0$ as follows:

1. **Correspondence step:** given s_k, solve

$$c_k = \underset{c}{\operatorname{argmin}} \left\{ E_1(c) := \frac{1}{\sigma_i^2} E_i(F, M, c) + \frac{1}{\sigma_c^2} E_c(c, s_k) \right\} \tag{2}$$

2. **Regularization step:** given c_k, solve

$$s_{k+1} = \underset{s}{\operatorname{argmin}} \left\{ E_2(s) := \frac{1}{\sigma_c^2} E_c(c_k, s) + \frac{1}{\sigma_r^2} E_r(s) \right\} \tag{3}$$

This type of regularization is called diffusion-like, while when s is replaced with $\partial s/\partial t$ in (3) it is called fluid-like. For suitable choices of E_i, E_c and E_r the minimization can be performed very efficiently, in particular for $E_i = \|F - M \circ s\|^2$. Choosing $E_c = \|c - s\|^2$ and E_r as a weighted sum of spatial derivatives of s leads to a Tikhonov functional, which can be solved in Fourier space. One special case are separable Gaussian kernels, which can be implemented efficiently, and are hence commonly used for regularization. For more details refer to [7]. Finally, the whole program was consistently extended to deal with diffeomorphic deformations as described in [4].

Instead of replacing the global uncertainty coefficients with local coefficients as proposed in [3], which leads to a highly non-trivial mathematical optimization problem for the regularization step, we propose an extension to the optimization scheme of (2) and (3). Let us denote the pathological region Ω in the fixed image F, and assume the atlas is given by the moving image M:

3. **Inpainting step:** Given the deformation s_{k+1} on the boundary $\partial\Omega$ of the pathological domain, overwrite the current deformation s_{k+1} inside Ω with the solution of the Laplace equation $\Delta s = 0$.

If the input image is given on a regular grid, the Laplace equation turns into a sparse linear system of equations, where at each voxel i inside Ω we have

$$v_i = \frac{1}{|N_i|} \sum_{j \in N_i} v_j \tag{4}$$

where v_i is the local deformation at voxel i, and N_i is the set of neighboring voxel to i. All v_i on the boundary $\partial\Omega$ of the domain are fixed. One option would be to solve this system once and apply the inverse matrix at each iteration of the demons. However, storing this matrix can become a prohibitive burden on computer memory even for small pathological regions. An alternative way is to use a fixed point technique such as iterated means, whose stationary point is a solution of the Laplace equation. This is easy to implement: given the values on $\partial\Omega$ iteratively compute (4) for all voxels in Ω until v_i does not change more than a given threshold.

This approach models zero confidence in the deformation within the pathological region, since no information about the image data is considered inside Ω. The inpainting step merely interpolates the deformation on the boundary of the domain into the pathological region. As before, depending on whether we apply

the step to s or the update of s we get diffusion- or fluid-like inpainting. This step also generalizes to diffeomorphic deformations by performing the inpainting in the log-domain, either on the velocity or the update field [4].

The influence of undersegmentation of the tumor is different to that of oversegmentation. The latter would correspond to a relaxation of the v_i on the tumor boundary, reflecting a 'not certain' region (as opposed to the 'certainly not' within the tumor).

The idea of inpainting was also presented in [8], but as a pre-processing step before the registration. Here the pathological regions in the patient image are inpainted directly. This may introduce a bias since arbitrary new image information is added. In [3], a diffusion equation is solved with a stiffness field that locally varies across the whole image. Their method was not designed for diffeomorphic deformations, and is implemented using a grid-based parallel infrastructure. Hence, in its sequential version their algorithm runs significantly slower than ours. Another approach was presented in [9]. It involves solving a coupled system of PDEs. Here, the generalization to diffeomorphic demons is not obvious, and no runtimes are provided. More importantly, it is not clear how to model zero-confidence in this approach.

3 Results

3.1 Simulated MR Data

As a first validation we compare the result of the *conventional* registration (steps 1 and 2 only) [5] with the modified method (including step 3) on simulated T1 weighted MR data. The system presented in [10] allows to place tumor seeds in a normal reference image (in this case a data set from the BrainWeb database [11]), and simulate their growth. The result is a simulated MR image with a tumor. However, the exact growth process is known and hence a segmentation of all structures in the tumor image, including white matter, is available.

We register the normal reference image from the BrainWeb database with the simulated tumor image (see Fig. 1a) whose segmentation around the tumor is known (Fig. 1b). Fig. 1c shows the deformation of the segmentation from the atlas image to the tumor image using the conventional registration, where there is a clear bias due to the distinct intensity in the tumor region. This bias largely disappears (Fig. 1d) when the inpainting step is switched on. Almost everywhere on the boundary of the tumor the white matter deformation is captured much more accurately, i.e. the segmentation in Fig. 1d is much more similar to Fig. 1b than Fig. 1c is to Fig. 1b. In both cases we use the same parameter settings for the demons algorithm. In particular we adopt diffusion-like regularization only. Experiments with fluid-like regularization showed inferior results.

3.2 Clinical Data

In this experiment we perform an evaluation on clinical T2 weighted images of a patient with a glioma. We use two image acquisitions of the patient at

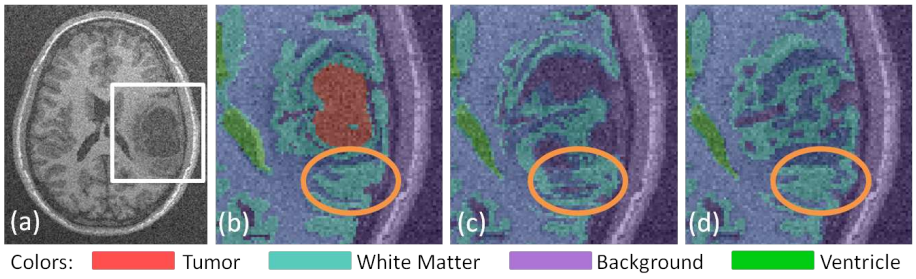

Fig. 1. (a) shows simulated tumor image. (b) shows manual segmentation of white matter (turquoise) around tumor (red), and a ROI on the tumor boundary (orange ellipse). (c) shows atlas-based segmentation without deformation inpainting (bad segmentation in ROI), (d) with inpainting (much better segmentation in ROI).

two different time-points about 5 months apart. During this time the glioma has evolved quite significantly (Fig. 2). For both images, a segmentation of the tumor is assumed to be given (in our case it was segmented in the T2 images by an expert). The atlas is a segmented T2 image of a normal subject (Fig. 3).

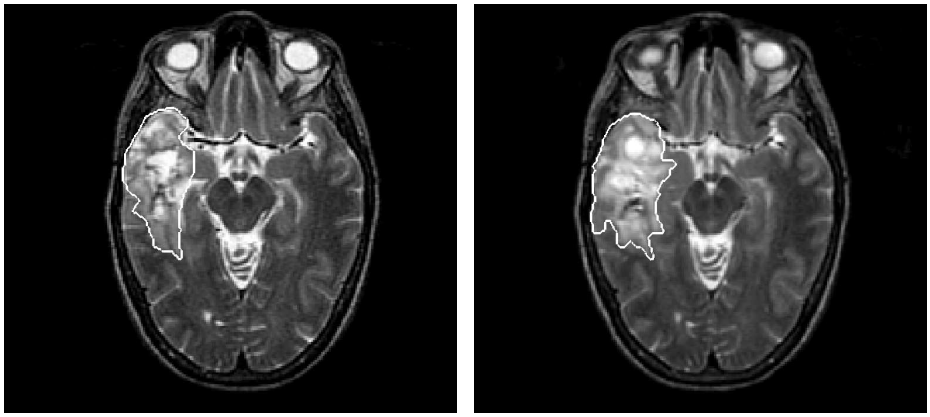

Fig. 2. T2 weighted patient images with glioma at two different time-points.

In order to compare the registration performance with and without inpainting, we perform the following experiment. Let us denote the two patient acquisitions with M and N, and the atlas image with A. First, we register M with N to obtain a deformation $T : M \to N$. This is a conventional (smooth) *reference* registration [5], since both images contain a tumor. Therefore we do not expect topological changes (no metastases). Next, we register the atlas A to both time-points to obtain $T_1 : A \to M$, and $T_2 : A \to N$. The situation is depicted in the diagram in Fig. 4.

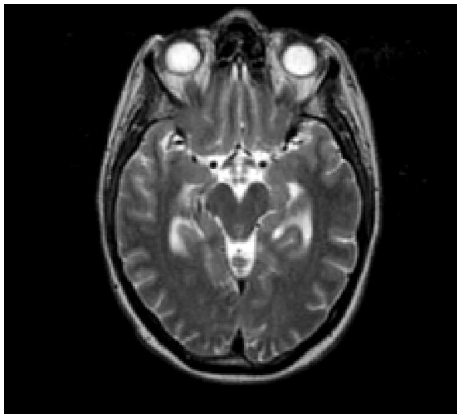

Fig. 3. Atlas: T2w MRI of normal subject

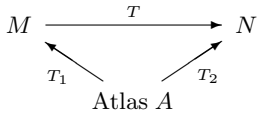

Fig. 4. Two tumor images M and N can either be registered directly via a *reference* deformation T or via concatenating two atlas registrations T_1 and T_2.

Taking the reference deformation T between M and N as ground-truth we expect to get a similar deformation by taking the detour via the atlas. Therefore we measure the norm of these difference as

$$\|T(p) - (T_2 \circ T_1^{-1})(p)\|$$

for each voxel p and both cases without and with inpainting. The result is illustrated in one axial slice through the image in Fig. 5. Blue-like colors denote small deviations while red-like colors indicate deviations above 5 mm.

We note that the deviations around the tumor boundaries reduce significantly when the inpainting step is applied as compared to the conventional registration process. This means, that there is less bias from the image intensity inside the tumor regions in the case of inpainting deformations, hence the registration becomes more consistent with the reference deformation in the critical regions along the tumor boundaries.

3.3 Performance

The method was implemented as an extension to the ITK diffeomorphic demons code [5], using iterated means to solve the inpainting problem. The clinical data sets have a resolution of $256 \times 256 \times 64$ voxels. On an Intel Xeon processor with 3 GHz the runtime for the conventional registration was about 1 min, and for the modified demons method about 9 min, where the additional time stems from the inpainting step. This time may be reduced using the inverse matrix approach on the cost of memory consumption (the glioma region consists of about 50k voxels, which would result in a matrix size of about 10 GB in single precision). For the iterated means approach, the runtime depends on the number of voxels in the pathological region and the stopping criterion for the local averaging. In our experiments, we stop when the change of the local average reaches machine accuracy everywhere. This condition may be softened to increase speed.

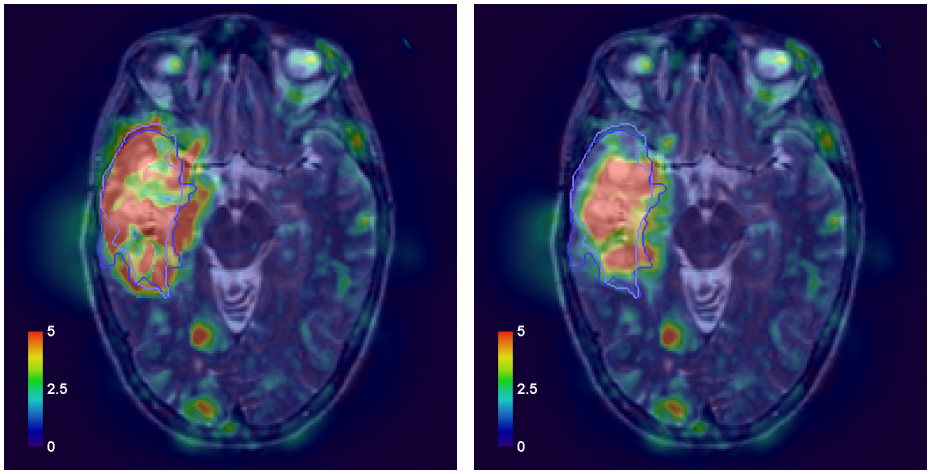

Fig. 5. Differences between reference deformation T and concatenated atlas deformations $T_2 \circ T_1$ without (left) and with (right) inpainting (color scale: blue 0 mm to red 5 mm).

4 Conclusions and Outlook

In this paper we have proposed a simple extension of the diffeomorphic demons framework with the aim of improving atlas to patient registration in the presence of pathologies in the patient image. This extension is easy to implement, as it does not modify the demons framework but constitutes a post-processing step, which can be implemented easily. This additional step can be seen as a inpainting process where the current deformation field is interpolated from the boundary of a pathological region into the region itself. The rationale behind this approach is that the correspondences and hence the deduced deformation field is not reliable in the pathological region because there is no one-to-one correspondence with a region in the atlas.

The use of the Laplacian with fixed boundary values does guarantee a linear transition from one end of the gap to the other end. However, it does not guarantee smoothness at the boundary, meaning that the resulting inpainted vector field probably isn't diffeomorphic. One avenue for future research is to find an inpainting method that will preserve the diffeomorphic properties of the original demons algorithm. Furthermore, from a theoretical perspective it is interesting to derive the full mathematical formulation of locally adaptive confidence in the demons framework. As a next step, the connection may be analyzed between this formulation and the inpainting process as a kind of limit as the confidence tends to zero.

The inpainting procedure allows for the integration of more general (geometric-like) knowledge into the registration process by using other models than the Laplace model of this work. The image inpainting literature [12] offers a rich va-

riety of ideas, e.g. for incorporating anisotropy to model structural or functional tissue properties.

Application-relevant issue are: (a) selection of the atlas, and (b) validation of the performance of the approach when transferring structural data such as DTI fiber tracks, for example. In pediatric oncology, the acquisition of DTI is prohibitive due to the acquisition time and consequential artifacts. One type of benchmark could be the evaluation of the therapy outcome based on a tumor evolution prediction.

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