Hybrid Spline-Based Multimodal Registration Using Local Measures for Joint Entropy and Mutual Information

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Abstract. We introduce a new hybrid approach for spline-based elastic registration of multimodal medical images. The approach uses point landmarks as well as intensity information based on local analytic measures for joint entropy and mutual information. The information-theoretic similarity measures are computationally efficient and can be optimized independently for each voxel. We have applied our approach to synthetic images, brain phantom images, as well as clinically relevant multimodal medical images. We also compared our measures with previous measures.

1 Introduction

Image registration is an important technique for medical diagnosis, surgical planning, and treatment control. A challenge is to cope with the broad range of applications as well as the large spectrum of imaging modalities. Previous approaches for image registration can be classified according to the transformation model (e.g., rigid or elastic) and the used image information (e.g., landmarks or intensities). *Landmark-based* approaches are computationally efficient and allow coping with large geometric differences, while *intensity-based* approaches use more image information and do not require segmentation. Concerning *intensity-based* approaches, it is important to distinguish between monomodal and multimodal registration problems, since different types of similarity metrics are required. *Monomodal* registration can be achieved by, e.g., using the sum of squared intensity differences (SSD). Registration of images of different modalities, however, requires *multimodal* similarity metrics such as joint entropy (JE) or mutual information (MI). In general, registration using such *information-theoretic* intensity similarity metrics is robust and accurate, however, these metrics are computationally expensive since they require the estimation of probability density functions based on joint histograms (e.g., [1,2,3]).

In recent years, increased attention has been paid to *hybrid* registration approaches that integrate both landmark and intensity information (e.g., [4,5,6,7,8,9,10,11]). Hybrid approaches can be classified into two classes. The first

class of approaches uses the two types of information subsequently. Typically, one type of information is used to perform an affine preregistration to decrease computation time in the following elastic registration step (e.g., [4,5,6,7,8]). The second class of hybrid approaches couples both types of information directly (e.g., [9,10,11]). However, only few hybrid approaches have been designed for *multimodal* images (e.g., [9,5,7]) and, even if information-theoretic similarity measures are employed, often only application to monomodal images is reported. In addition, previous *spline-based* hybrid approaches typically use coarse physical deformation models such as B-splines (e.g., [9,7]) or thin-plate splines (e.g., [5,8]), and incorporate intensity information using *global*, computationally expensive information-theoretic measures. *Local* information theoretic measures exists (e.g., [12,13]), however, they have not been used in hybrid registration schemes.

In this contribution, we present a new *hybrid* approach for *spline-based* elastic registration of *multimodal* medical images. Our approach is formulated as an energy-minimizing functional that incorporates point landmarks and intensity information as well as a regularization using physically-based splines. The intensity information is evaluated *locally* based on analytic measures for joint entropy and mutual information. We suggest new information-theoretic measures that are modifications of the measures in [13], but which are more robust w.r.t. noise as well as more similar to the original information-theoretic formulations. In contrast to [13], where the measures are evaluated globally, we here evaluate and optimize the measures *locally*, i.e., independently for each voxel, and integrate them within a *hybrid* spline-based registration scheme.

2 Multimodal Hybrid Elastic Registration

2.1 Hybrid Energy Minimizing Functional

Our hybrid approach for elastic registration of *multimodal* images is based on an energy minimizing functional J_{Hybrid} that incorporates both landmark and intensity information and a regularization term:

$$J_{Hybrid}(\mathbf{u}) = J_{Data,I}(g_1, g_2, \mathbf{u}^I) + \lambda_I J_I(\mathbf{u}, \mathbf{u}^I) + \lambda_L J_{Data,L}(\mathbf{u}) + \lambda_E J_{El}(\mathbf{u}) \quad (1)$$

The first term $J_{Data,I}$ describes the intensity-based similarity measure between the source and target image, g_1 and g_2 , respectively. With the second term J_I the intensity-based deformation field $\mathbf{u}^I$ is coupled with the final deformation field $\mathbf{u}$ using a weighted Euclidean distance. The term $J_{Data,L}$ incorporates the landmark information based on approximating Gaussian Elastic Body Splines (GEBS). In contrast to other splines, an advantage of GEBS is that cross-effects can be handled [14], i.e., transversal contractions lead to longitudinal dilations according to properties of elastic tissue. The fourth term J_{El} represents the regularization of the deformation field according to the Navier equation of linear elasticity, which constrains the deformation field to physically realistic deformations. The overall functional J_{Hybrid} is minimized alternately w.r.t. $\mathbf{u}^I$ and $\mathbf{u}$.

In previous work [11], $J_{Data,I}$ was defined based on the sum-of-squared intensity differences, thus the approach was only applicable to *monomodal* registration. Here, we present two new formulations of $J_{Data,I}$ for *multimodal* registration as well as new schemes for minimizing J_{Hybrid} w.r.t. $\mathbf{u}^I$.

2.2 Multimodal Registration Using Analytic Measures for Joint Entropy and Mutual Information

For the intensity-based similarity measure $J_{Data,I}$ in (1) we suggest to use *local* analytic measures for joint entropy and mutual information. Let g be an image of dimension d over the continuous domain $\Omega \subset \mathbb{R}^d$, and $N_R(\mathbf{x})$ be the neighborhood of radius R around a point $\mathbf{x} \in \Omega$. For R being sufficiently small, the first order Taylor approximation $T_g(\mathbf{x}) \simeq \nabla g(\mathbf{x})^T \cdot \mathbf{x} + g_0(\mathbf{x})$ can be used as an approximation of $g(\mathbf{x})$ in the neighborhood of $\mathbf{x}$, where ∇g denotes the image gradient. The intensities $g(\mathbf{x})$ in the neighborhood $N_R(\mathbf{x})$ can be characterized by a random variable $\mathbf{g}$, which can be described by a probability density function. In [13] it was shown that for two images g_1 and g_2 the joint entropy $JE(\mathbf{x})$ and the mutual information $MI(\mathbf{x})$ can then be approximated by

$$JE_{orig}(\mathbf{x}) : \{c_d + \log_2(\|\nabla g_1(\mathbf{x})\| \|\nabla g_2(\mathbf{x})\| |\sin(\theta)|)\} \rightarrow \min, \quad (2)$$

$$MI_{orig}(\mathbf{x}) : \{c_d - \log_2(|\sin \theta|)\} \rightarrow \max, \quad (3)$$

where θ represents the angle between $\nabla g_1(\mathbf{x})$ and $\nabla g_2(\mathbf{x})$, c_d is a constant that depends on the dimension d , and $\|\cdot\|$ denotes the Euclidean norm. However, due to properties of the logarithm, $JE_{orig}(\mathbf{x})$ and $MI_{orig}(\mathbf{x})$ yield very large absolute values if the argument $\|\nabla g_1(\mathbf{x})\| \|\nabla g_2(\mathbf{x})\| |\sin(\theta)|$ or $|\sin \theta|$ is close to zero which leads to unstable results. In [13], $JE_{orig}(\mathbf{x})$ and $MI_{orig}(\mathbf{x})$ were evaluated *globally*, i.e., the similarity for each voxel is integrated over the whole image. If, however, at a *single* voxel the argument of the logarithm is zero or close to zero, the global measure yields a very large value, since adding logarithmic terms is equivalent to the logarithm of the product of the arguments ($\sum_i \log_2 s_i = \log_2 \prod_i s_i$). Due to the singularity of the logarithm, the value at a single voxel can render the result of the metric useless. To circumvent this problem, in [13] simplified metrics have been used which omit the logarithm:

$$JE_{simp}(\mathbf{x}) : \left\{ \left(\nabla g_1^T(\mathbf{x}) \nabla g_2(\mathbf{x}) \right)^2 \right\} \rightarrow \max \quad (4)$$

$$MI_{simp}(\mathbf{x}) : \{\cos^2 \theta\} \rightarrow \max \quad (5)$$

A disadvantage of these measures is that they differ largely from the original measures in (2) and (3). Instead, we here propose alternative formulations for JE and MI that do not have a singularity and that are more similar to the original measures.

Joint Entropy Measure. For JE , we suggest an alternative measure to (2), where the logarithm is still included. To illustrate and motivate this modification, we have generated synthetic images simulating a multimodal registration

Fig. 1. Registration problem: Source and target images

problem (light circle on a dark background and dark square on a light background, Fig. 1). By registration, the circle has to be stretched to the size and shape of the square. For each point in the source image, we have computed the similarity values w.r.t. the marked reference point (black cross) in the target image and have visualized them as 3D plots in Fig. 2. In each of the plots, the *intended* optimum is marked with a black arrow and circle. In (a), the result for $JE_{orig}(\mathbf{x})$ is shown. Since $JE_{orig}(\mathbf{x})$ needs to be minimized, the optimum can be found at the saddle point between the two elevated semi-circles. Obviously, this minimum is difficult to identify since it has a similar value as the background, which is very noisy. To reduce the sensitivity to noise, we introduce a constant $\epsilon > 0$, which is added to the argument. This leads to the result in (b). Now, the background noise is reduced significantly, but the optimum is still located at the saddle point between the two semi-circles, which is difficult to identify. To facilitate optimization, we replace $|\sin(\theta)|$ in (2) with $|\cos(\theta)|$, which leads to:

$$JE_{new}(\mathbf{x}) : \{\log_2 (\epsilon + \|\nabla g_1(\mathbf{x})\| \|\nabla g_2(\mathbf{x})\| |\cos(\theta)|)\} \rightarrow \max \quad (6)$$

Now, the measure has to be maximized, which is much easier (see (c)) than finding the saddle point in (b).

Mutual Information Measure. For MI , we suggest a similar modification where the logarithm is still included and a constant $\epsilon > 0$ is introduced. Here, the introduction of ϵ also improves the robustness of the metric:

$$MI_{new}(\mathbf{x}) : \{\log_2 |\epsilon + \sin \theta|\} \rightarrow \min \quad (7)$$

Fig. 2. Results for different metrics for JE for registration of the images in Fig. 1: (a) $JE_{orig}(\mathbf{x})$, (b) $JE_{orig}(\mathbf{x})$ after introducing a constant ϵ , (c) using $JE_{new}(\mathbf{x})$

Fig. 3. Registration of a sphere with a cube. (a) Original source and target images, (b) after landmark-based registration, (c) after intensity-based registration using JE_{new} , (d) after intensity-based registration using MI_{new} , (e) after hybrid registration using JE_{new} , and (f) after hybrid registration using MI_{new} .

In our registration approach, the measures are integrated as $J_{Data,I}$ in (1). Optimization of J_{Hybrid} is performed alternately w.r.t. $\mathbf{u}^I$ and $\mathbf{u}$. For minimization w.r.t. $\mathbf{u}^I$, $J_{Data,I} + \lambda_I J_I$ has to be minimized. To this end we have derived analytic expressions for the partial derivatives of the different measures. Note that in contrast to [13], in our approach MI and JE are evaluated *locally*, i.e., optimization of $\mathbf{u}^I$ is computed independently for each voxel, which improves the efficiency. In comparison to [11], we here use a minimization scheme based on steepest gradient since the analytic information-theoretic measures cannot be formulated by squared differences and thus the method of Levenberg-Marquardt cannot be used.

3 Experimental Results

We have applied our registration approach to 3D synthetic images, 3D brain phantom images, and clinically relevant 3D medical images. In a first experiment, we have applied our approach to the 3D synthetic sphere and cube shown in Fig. 3a. The images have a size of $128 \times 128 \times 128$ voxels and inverted contrast to simulate a multimodal registration problem. Thus, a monomodal similarity measure (e.g., SSD) would fail. Note that registration is difficult since the volume of the cube is nearly two times larger than the volume of the sphere. Eight landmarks were defined at the corners of the cube, and the registration result is computed based on the different metrics. Fig. 3 shows the results for landmark-based registration (b), for intensity-based registration based on JE_{new} (c) and MI_{new} (d), as well as for hybrid registration based on JE_{new} (e) and MI_{new} (f). It can be seen that JE_{new} and MI_{new} yield similar results. For landmark-based registration, only the corners of the cube are aligned. Using intensity-based registration, the faces of the sphere are aligned, but not the corners. The best result is obtained using the new hybrid approach, since both the faces as well as the corners are aligned.

To compare the results using our new measures with those in [13], we evaluated the registration accuracy for intensity-based registration of multimodal phantom images (MRI-PD and MRI-T1) from the BrainWeb database [15] for different levels of Gaussian noise ($\sigma_n = 0, 5, 9$; see Fig. 4a,b for the case of $\sigma_n = 5$). Here, we present results for the comparison of MI_{new} and MI_{simp} . We have generated

Fig. 4. Comparison of MI_{simp} and MI_{new} : (a) Source and (b) target image for $\sigma_n = 5$. Registration result and edge overlay of the target image for (c) MI_{simp} and (d) MI_{new} .

a deformation field $\mathbf{u}_o$ based on eight landmarks using GEBS, which is applied to the different MRI-T1 images to obtain three target images with known elastic deformations and different levels of noise. After registration, we compared the computed deformation $\mathbf{u}$ with the original deformation $\mathbf{u}_o$ and quantified the registration accuracy by the mean geometric error $\bar{\epsilon}_g = \frac{\|\mathbf{u}_o - \mathbf{u}\|}{N}$. Note that in this experiment we did not use landmarks. Without registration, we have $\bar{\epsilon}_g = 3.40$ pixels. For $\sigma_n = 0$, registration using MI_{simp} and MI_{new} yields $\bar{\epsilon}_g = 1.44$ and $\bar{\epsilon}_g = 1.08$ pixels, respectively. With increasing level of noise, our new measure consistently yields more accurate results than the previous measure. Fig. 4, for example, shows the registration results for $\sigma_n = 5$ for MI_{simp} (c) and MI_{new} (d). It can be seen that registration is more accurate in the neighborhood of the ventricles when using MI_{new} . The visual result agrees with the quantitative values: $\bar{\epsilon}_g = 1.85$ for MI_{simp} , and $\bar{\epsilon}_g = 1.55$ for MI_{new} . For $\sigma_n = 9$, MI_{simp} yields $\bar{\epsilon}_g = 2.30$, while MI_{new} yields $\bar{\epsilon}_g = 1.78$. Thus, our new measure MI_{new} is more robust w.r.t. noise than MI_{simp} . We also investigated the effect of ϵ on the registration result of MI_{new} . We found that the choice of ϵ is not critical, however, best results were obtained for $0.5 \leq \epsilon \leq 1.5$.

Furthermore, we quantified the registration accuracy of our approach using real, clinically relevant 3D multimodal medical images. We used five pairs of 3D PET transmission ($170 \times 128 \times 128$ voxels) and 3D CT ($320 \times 400 \times 400$ voxels) images of the human chest. Fig. 5, for example, shows two orthogonal slices of a 3D PET (a) and 3D CT (b) image before registration, as well as overlay images of the PET image with computed edges of the CT image before (c), after landmark-based (d), after intensity-based (e), and after hybrid registration (f) using MI_{new} . It can be seen that both the landmark-based and intensity-based registration schemes improve the alignment significantly, however, the best result

Table 1. Registration of 3D PET and CT images: Mean geometric error $\bar{\epsilon}_g$ (in voxel) for different metrics using different types of image information

			Intensities				Hybrid			
	Unreg.	LM	JE_{simp}	JE_{new}	MI_{simp}	MI_{new}	JE_{simp}	JE_{new}	MI_{simp}	MI_{new}
$\bar{\epsilon}_g$	7.36	5.32	5.60	5.76	6.70	5.60	5.17	5.05	5.28	4.83

Fig. 5. Orthogonal slices of original (a) 3D PET transmission and (b) CT images. Source image with edge overlay of the target image (c) before, (d) after landmark-based, (e) after intensity-based, and (f) after hybrid registration using MI_{new}

Fig. 6. Transversal and sagittal slices of original (a) 3D fMRI and (b) MRI-T1 images. Section of the source image with edge overlay of the target image (c) before, (d) after landmark-based, (e) after intensity-based, and after (f) hybrid registration using MI_{new} .

is obtained when using the new hybrid scheme. This was also confirmed quantitatively. For this purpose, we identified ten pairs of corresponding anatomical point landmarks in each source and target image and computed the mean geometric registration error $\bar{\epsilon}_g$ (see Tab. 1). Before registration, we have $\bar{\epsilon}_g = 7.36$ voxels. Using landmarks only, we have $\bar{\epsilon}_g = 5.32$ voxels, which is a relative improvement of 27.7%. Using intensity information only, we obtain $\bar{\epsilon}_g = 5.60$ (23.8%) and $\bar{\epsilon}_g = 5.76$ (21.7%) voxels for JE_{simp} and JE_{new} , respectively. For MI_{simp} and MI_{new} we obtain $\bar{\epsilon}_g = 6.70$ (9.0%) and $\bar{\epsilon}_g = 5.60$ (24.0%) voxels. When using the hybrid approach, we obtain $\bar{\epsilon}_g = 5.17$ (29.7%) for JE_{simp} and $\bar{\epsilon}_g = 5.05$ (31.4%) for JE_{new} as well as $\bar{\epsilon}_g = 5.28$ (28.2%) for MI_{simp} and $\bar{\epsilon}_g = 4.83$ (34.3%) for MI_{new} . Thus, in all cases, the hybrid approach is more accurate than the intensity-based and the landmark-based approaches. Furthermore, the

new intensity similarity measures JE_{new} and MI_{new} yield more accurate results for the hybrid approach than the previous measures JE_{simp} and MI_{simp} . Overall, MI_{new} yields the best results.

We also applied our approach to register 3D MRI-T1 and functional MRI (fMRI) images ($144 \times 256 \times 256$ voxels). Fig. 6 shows a transversal and sagittal view of 3D fMRI (a) and MRI-T1 (b) images. Before registration (c), a significant misalignment between source and target image is visible. After landmark-based registration using seven landmarks, a slight improvement is visible in the neighborhood of the ventricles (d). After intensity-based registration using MI_{new} (e), the global alignment is improved significantly, although local misalignments still exist. The best result is obtained when using our new hybrid approach (f), since both the global as well as the local alignment is improved.

4 Discussion

We introduced a new hybrid spline-based approach for elastic registration of multimodal images. The approach incorporates point landmarks, intensity information, as well as a physically-based regularization. Since the approach uses new local analytic measures for mutual information and joint entropy, the required derivatives can be calculated analytically, and optimization can be performed independently for each voxel. We have demonstrated the applicability of our approach using 3D synthetic images, 3D phantom images, and different types of real 3D medical images. It turned out that our new similarity measures yield a more accurate registration result than previously proposed measures. We also found that the hybrid approach improves the results compared to a pure intensity-based and a pure landmark-based scheme.

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