A COMBINED FEATURE ENSEMBLE BASED MUTUAL INFORMATION SCHEME FOR ROBUST INTER-MODAL, INTER-PROTOCOL IMAGE REGISTRATION

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ABSTRACT

In this paper we present a new robust method for medical image registration called combined feature ensemble mutual information (COFEMI). While mutual information (MI) has become arguably the most popular similarity metric for image registration, intensity based MI schemes have been found wanting in inter-modal and inter-protocol image registration, especially when (1) significant image differences across modalities (e.g. pathological and radiological studies) exist, and (2) when imaging artifacts have significantly altered the characteristics of one or both of the images to be registered. Intensity-based MI registration methods operate by maximization of MI between two images *A* and *B*. The COFEMI scheme extracts over 450 feature representations of image *B* that provide additional information about *A* not conveyed by image *B* alone and are more robust to the artifacts affecting original intensity image *B*. COFEMI registration operates by maximization of combined mutual information (CMI) of the image *A* with the feature ensemble associated with *B*. The combination of information from several feature images provides a more robust similarity metric compared to the use of a single feature image or the original intensity image alone. We also present a computer-assisted scheme for determining an optimal set of maximally informative features for use with our CMI formulation. We quantitatively and qualitatively demonstrate the improvement in registration accuracy by using our COFEMI scheme over the traditional intensity based-MI scheme in registering (1) prostate whole mount histological sections with corresponding magnetic resonance imaging (MRI) slices; and (2) phantom brain T1 and T2 MRI studies, which were adversely affected by imaging artifacts.

1. INTRODUCTION

Registration of medical images is critical for several image analysis applications including computer-aided diagnosis (CAD) [1], interactive cancer treatment planning, and monitoring of therapy progress. Mutual information (MI) is a popular image similarity metric for inter-modal and inter-protocol registration [2]. Most MI-based registration techniques are based on the assumption that a consistent statistical relationship exists between the intensities of the images A and B being registered. Image intensity information alone however is often insufficient for robust registration. Hence if A and B belong to different modalities (e.g. magnetic resonance imaging (MRI) and histology) or if B is degraded by imaging artifacts (e.g. background inhomogeneity in MRI or post-acoustic shadowing in ultrasound) then A and B may not share sufficient information with each other to facilitate registration by maximization of MI. Additional information not provided by image intensities required. This may be obtained by transformation of the image B from intensity space to other feature spaces representations, $B'_1, B'_2, ..., B'_n$, that are not prone to intensity artifacts of B and further explain structural details of A, which intensity information alone fails to provide. Figure 1(c) demonstrates a scenario where an intensity based MI similarity metric results in imperfect alignment in registering a MRI section (1(b)) to the corresponding prostate histological section (1(a)). Conventional MI also results in misalignment (Fig 1(f)) of a T2 MRI brain slice (1(d)) with a T1 MRI brain slice (1(e)) with simulated affine deformation and background inhomogeneity added. In this paper, we present a new registration method called combined feature ensemble mutual information (COFEMI) that maximizes the combined mutual information (CMI) shared by template intensity image A and multiple representations of the target intensity image B in feature spaces $B'_1, B'_2, \ldots, B'_n$ that are less sensitive to the presence of artifacts and more robust to multimodal image differences.

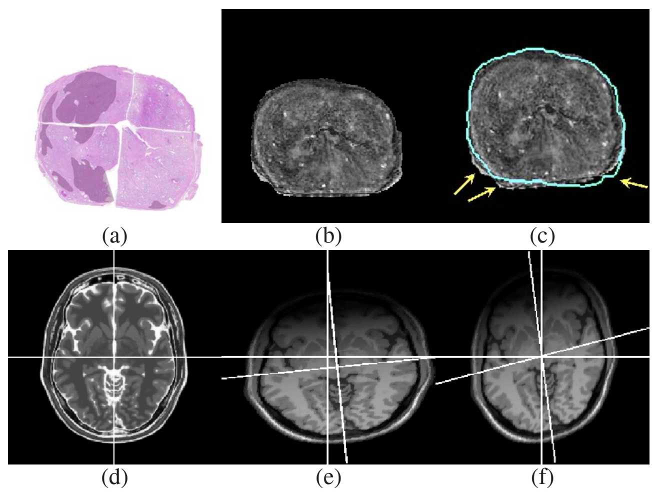


Fig. 1. Registration of a (a) whole mount histological section of the prostate with the corresponding (b) MRI section via conventional intensity-based MI (c) results in significant mis-registration (as indicated by arrows). Similar mis-registration errors (f) occur when intensity-based MI is applied to aligning (d) T2 with (e) T1 MRI images with image intensity artifacts (background inhomogeneity) and affine deformation added. Note the misalignment of the X,Y axes.

Incorporating additional information to complement the MI metric for improved registration has been investigated by others [2]. Image gradients [3, 4], cooccurrence matrices [5], color channels [6], and connected component labels [7] have been considered for incorporation by use of weighted sums of MI of multiple image pairs, higher-order joint distributions and MI, and reformulations of MI. The utility of these techniques is constrained by (1) the limited information contained in a single arbitrarily chosen feature to complement image intensity and (2) the *ad hoc* formulations by which the information is incorporated into a similarity metric. The motivation behind the COFEMI method is the use of an optimal set of multiple image features to complement image intensity information and thus provide a more complete description of the images to be registered. This is analogous to pattern recognition methods in which combining multiple features via classifier ensemble (Decisions Trees, Support Vector Machines) often results in greater classification accuracy than can be achieved by a single feature.

In order to register image B to A, the new COFEMI scheme first involves computing multiple feature images from an intensity image B using first and second order statistical and gradient calculations. A subsequent feature selection step is used to obtain a set of uniquely informative features which are then combined using a novel MI formulation to drive the registration. The novel aspects of our COFEMI registration scheme are:

- The use of multiple image features derived from the original image to complement image intensity information and overcome the limitations of conventional intensity-based MI schemes;
- The use of a novel MI formulation which represents the combined (union) information that a set of implicitly registered images $(B, B'_1, B'_2, ..., B'_n)$ contains about another image A.

We demonstrate that the CMI formulation employed in this paper is more intuitively appropriate for combination of feature space information compared with previous MI formulations [4, 6]. We also quantitatively and qualitatively demonstrate the efficacy of COFEMI on a multimodal prostate study comprising both MRI and histology and a set of multiprotocol brain phantom images from the Brainweb database [8]. For both studies the COFEMI method delivered superior performance compared to the traditional intensity-based MI scheme.

The rest of this paper is organized as follows. In Section 2, we review the conventional formulation of MI as a similarity metric. In Section 3 we describe the COFEMI registration technique. Qualitative and quantitative results are presented in Section 4 and concluding remarks in Section 5.

2. THEORY

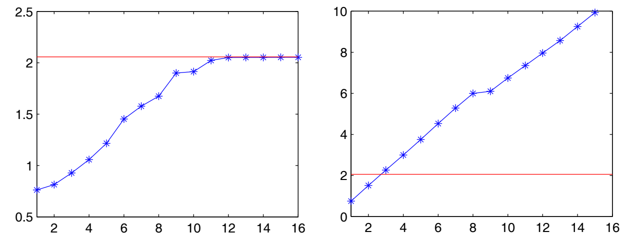
MI is often defined in terms of Shannon entropy [2], a measure of information content of a random variable. Equation 1 gives the marginal entropy, $S(A)$, of image A in terms of its graylevel probability distribution $p(a)$, estimated by normalization of the gray level histogram of A,

$$S(A) = -\sum_{a} p(a) \log p(a), \tag{1}$$

where a represents the different gray levels in A. While marginal entropy of a single image describes the image's information content, the joint entropy $S(AB)$ of two images A and B (Equation 2) describes the information gained by combined knowledge of both images.

$$S(AB) = -\sum_{a,b} p(a,b) \log p(a,b), \tag{2}$$

Thus, when image A best explains image B, joint entropy is minimized to $\max\{S(A), S(B)\}$. Equation 3 is a formulation of MI in terms of the marginal and joint entropies wherein the MI of a pair of images or random variables, $I_2(A, B)$, is maximized by minimizing



(a) CMI, $I_2(A, BB'_1 ... B'_n)$ (b) SMI, $\sum_{i=1}^{n} I_2(A, B'_i)$

Fig. 2. (a) A plot of CMI for inclusion of n feature images (a) demonstrates that CMI is bounded by $S(A)$ (horizontal line), the information content of A. (b) Plot of SMI of A and n features combines redundant information about A and is unbounded. The upper bound on the value of CMI (a) suggests that it is a more intuitive formulation for combining MI from n sources compared to SMI (b).

joint entropy $S(AB)$ and maintaining the marginal entropies $S(A)$ and $S(B)$. AB represents simultaneous knowledge of both images.

$$I_2(A, B) = S(A) + S(B) - S(AB) \tag{3}$$

Hence $I_2(A, B)$ describes the interdependence of multiple variables, or graylevels of a set of images [2]. Thus, when $I_2(A, B)$ increases, the uncertainty about A given B decreases. As such, it is assumed that the global MI maximum will occur at the point of precise registration, when maximal uncertainty about A is explained by B. Generalized (higher-order) MI [9], which calculates the intersecting information of multiple variables, is neither a measure of the union of information nor a nonnegative quantity with a clear interpretation. Surprisingly, the formulation has still been used in feature driven registration tasks [6].

3. METHODS

3.1. New Combined Mutual Information (CMI) Formulation

The combined mutual information (CMI) that a set of two semi-independent images, B and B', contain about a third image, A, is defined by the equation $I_2(A, BB') = S(A) + S(BB') - S(ABB')$. This formulation allows the incorporation of unique (non-redundant) information provided by an additional image, B', about A. Hence, the generalized form of CMI is,

$$\begin{aligned} I_2(A, BB'_1B'_2 \cdots B'_n) = S(A) + S(BB'_1B'_2 \cdots B'_n) \\ -S(ABB'_1B'_2 \cdots B'_n). \end{aligned} \tag{4}$$

$BB'_1B'_2 \cdots B'_n$ is referred to as an ensemble [9]. CMI incorporates only the unique information of additional images, thus enhancing but not overweighting the similarity metric with redundant information. Therefore, it will always be the case that $I_2(A, B\ B'_1 \cdots B'_n) \leq S(A) = I_2(A, A)$. The intuition behind using CMI is that one or more of the feature images $B'_1, B'_2, ..., B'_n$ of intensity image B will not be plagued to the same extent by intensity artifacts as B and will provide additional structural description of A. Figure 2 illustrates the properties of CMI in comparison to summation of MI (SMI) of image pairs $(A, B'_1), \ldots, (A, B'_n)$. As $B'_1, B'_2, ..., B'_n$ are introduced, CMI approaches an asymptote (Fig. 2a) equal to $S(A)$, the total information content of A. On the other hand, SMI (Fig. 2b) increased in an unbounded fashion as intersecting information between the image pairs is recounted. Despite the ambiguous meaning of the quantity measured by SMI, weighted summation of MI and related quantities (entropy correlation coefficient) is still used in feature-enhanced registration studies [4]. The plots in Figure 2 strongly suggest that CMI is a more appropriate measure of information gained from a set of implicitly registered images than weighted SMI or higher order MI.

3.2. Feature Extraction

For a template image, A, to which another image, B, is to be registered, we calculate nearly 500 feature images from B. As described in [1], these feature images $B'_1, B'_2, ..., B'_n$ comprise (i) gradient, (ii) first order statistical, and (iii) second order statistical features. Feature image B'_i where $i \in \{1, \ldots, n\}$ is generated by calculating the feature value corresponding to feature Φ_i from the local neighborhood around each pixel in B. An optimal set of features represent higher-order structural representations of the source intensity image B, some of which are not prone to the artifacts of B and most of which contain additional MI with A.

From n feature images, an ensemble of k images is defined as $\pi^{k,l} = B'_{\alpha_1} B'_{\alpha_2} \cdots B_{\alpha_k}$ for $\{\alpha_1, \alpha_2, \ldots, \alpha_k\} \in \{1, \ldots, n\}$ where $l \in \{1, \ldots, \binom{n}{k}\}$. Note that a total of $\binom{n}{k}$ ensembles of size k can be determined from $B'_1, B'_2, ..., B'_n$. It is desirable that the feature ensemble chosen for CMI based registration provide maximal additional information from B to describe A. Thus, the optimal ensemble determined by $\text{argmax}_{k,l}\{S(B\pi^{k,l})\}$ corresponds to $\pi^{n,1}$, the ensemble of all n features. Since it is not practical to to estimate the joint graylevel distribution for n images, $\pi^{k,l}$ must be considered for $k < n$. However even for $k = 5$, a brute force approach to determining optimal $\pi^{k,l}$ would not be practical. Consequently we propose the following algorithm to select the optimal feature ensemble, which we refer to as π^k. In practice, since using more than 5 features causes the gray level histogram to become too dispersed to provide a meaningful joint entropy estimate, we constrain $k = 5$. Even second order entropy calculations can be overestimated [2]. With this in mind, we use a bin size of 16 for higher order histograms so that our joint entropy estimates remain informative in the similarity metric.

Algorithm $CMIfeatures$
Input: $B, k, B'_1, ..., B'_n$.
Output: π^k.
begin
0. Initialize π^k, Ω as empty ques;
1. *for* $u = 1$ to k *do*
2. *for* $v = 1$ to n *do*
3. *if* B'_v is present *then*
3. Insert B'_v into π^k; $\Omega[v] = S(B\pi^k)$;
4. Remove B'_v from π^k;
5. *endif*;
5. *endfor*;
6. $m = \text{argmax}_v\, \Omega[v]$; Insert B'_m into π^k;
7. *endfor*;
end

3.3. COFEMI-Based Image Registration

After determining the optimal feature ensemble associated with B, π^k is used to register intensity images A and B via the CMI similarity metric (Equation 4). Correct alignment is achieved by optimizing an affine transformation by maximization of CMI of A with π^k and B, $I_2(A, B\,\pi^k)$. The registered target image, B^r, is calculated by transforming B with the determined affine deformation. A Nedler-Mead simplex algorithm is used to optimize affine transformation parameters for rotation, translation and scaling. For evaluation purposes, intensity-based MI registration is implemented using both nearest neighbor (*NN*) and linear (*LI*) interpolation and 128 graylevel bins. CMI-based registration uses *NN* interpolation.

4. RESULTS AND DISCUSSION

For purposes of evaluation, a multimodal prostate data set [1] and a synthetic multiprotocol brain data set [8] were used. The prostate data set is composed of 17 corresponding 4 Tesla *ex vivo* MR and digitized histology images, of which the MR slice is chosen as the target (B) for the alignment transformations and the histology as the template (A) to which the target is aligned. The dimension of the MR prostate volume is $256 \times 256 \times 64$ with voxel size of 0.16mm $\times$ 0.16mm $\times$ 0.8mm. The MR images have been previously corrected for background inhomogeneity [1]. Slicing and sectioning of the prostate specimen to generate the histology results in deformations and tissue loss, which can be seen in Fig 3(a) where the slice was cut into quarters for imaging. The Brainweb data comprised corresponding T1 and T2 MR brain volumes of dimensions $181 \times 217 \times 181$ with voxel size of 1mm^3. Inhomogeneity artifact on the T1 brain MR data is simulated with a cubic intensity weighting function. A known affine transformation comprising rotation in the x-y plane ($\widehat{\theta} = 5.73$ degrees), translation ($\widehat{\Delta x} = -8$ pixels, $\widehat{\Delta y} = -15$ pixels) and scaling ($\widehat{\psi_x} = .770$, $\widehat{\psi_y} = 1.124$) was applied to the T1 images.

4.1. Qualitative Evaluation

The conventional MI metric results in clear misalignment for registration of prostate MR with histology, as can be seen on the slice in Fig. 3(c) by the overlaid histology boundary in green that cuts through the top of the gland instead of along the MR prostate boundary in red. Our COFEMI registration (Fig. 3(f)) results in a more accurate alignment of the prostate MR to histology using an ensemble of four features ($k = 4$) including Haralick correlation (3(d)) and gradient magnitude (3(e)). Registration of the T1 and T2 brain phantoms (Fig. 3(h) and (g)) using intensity-based MI also results in misregistration (Fig. 3(i)) as a result of the simulated inhomogeneity and known affine transformation applied to the original T1 image (not shown). Incorporating an ensemble of T1 feature images including correlation (Fig. 3(j)) and inverse difference moment (3(k)) using COFEMI, registration is greatly improved (3(l)). A high order joint histogram with at most 32 graylevels is necessary to provide a minimally dispersed histogram appropriate for registration.

4.2. Quantitative Evaluation

Quantitative evaluation of COFEMI registration on the brain phantom MRI images (Figure 3) was performed. The T1 registration result, B^r, using COFEMI was evaluated by calculating the residual relative percent errors ($\varepsilon_\theta, \varepsilon_{\Delta x}, \varepsilon_{\Delta y}, \varepsilon_{\psi_x}, \varepsilon_{\psi_y}$) in correcting for the known deformation ($\widehat{\theta}, \widehat{\Delta x}, \widehat{\Delta y}, \widehat{\psi_x}, \widehat{\psi_y}$). In Table 1 we report the relative percentage errors in each parameter using conventional MI with *NN* (MI^{NN}) and *LI* (MI^{LI}) interpolation, and CMI using each a random ensemble (CMI^{rand}) and gradient only (CMI^{grad}), gradient having been previously used in MI studies [4, 3]. COFEMI is reported for 4 different ensembles ($\pi(1)$-$\pi(4)$) comprising between 2 to 4 features ($k \in \{2, 3, 4\}$) taken from the π^k as selected by $CMIfeatures$ (correlation, inverse difference moment, gradient, mean, sum average, median). Each value of ε_θ, $\varepsilon_{\Delta x}$, $\varepsilon_{\Delta y}$, ε_{ψ_x} and ε_{ψ_y} for $COFEMI^{\pi(1)}$-$COFEMI^{\pi(4)}$ is smaller than corresponding results obtained via MI^{NN}, MI^{LI}, CMI^{rand} and CMI^{grad}.

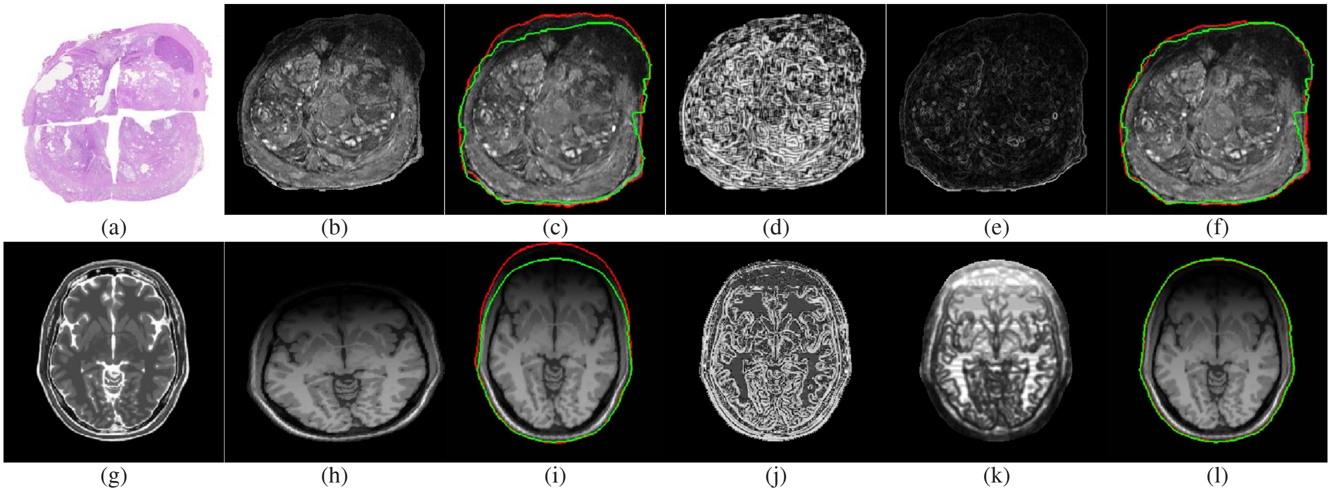


Fig. 3. Prostate MRI slice shown in (b) is registered to (a), the corresponding histological section, using intensity-based MI (shown in (c)) and COFEMI (shown in (f)) with (d) correlation and (e) gradient magnitude features. A T1 MR brain image (h) is registered to the corresponding T2 MRI (g) using MI (i) and COFEMI (l) with (j) correlation and (k) inverse difference moment features. Green contours in (c), (i), (f), (l) represent the boundary of the prostate histology and T2 brain MRI overlaid onto the registered target. Red outlines accentuate the boundaries in the registration result. COFEMI improves registration of (f) multimodal and (l) multiprotocol images compared to original MI scheme.

Metric	ε_θ	$\varepsilon_{\Delta x}$	$\varepsilon_{\Delta y}$	ε_{ψ_x}	ε_{ψ_y}
MI^{NN}	181	18.15	9.36	1.55	0.09
MI^{LI}	25.85	6.70	68.40	2.45	9.50
$COFEMI^{\pi(1)}$	4.28	8.89	1.73	0.22	0.56
$COFEMI^{\pi(2)}$	0.29	0.26	0.13	0.13	0.03
$COFEMI^{\pi(3)}$	0.06	0.37	0.33	0.07	0.08
$COFEMI^{\pi(4)}$	0.18	0.16	0.31	0.08	0.07
CMI^{rand}	215.1	49.7	39.1	2.13	6.35
CMI^{grad}	246.7	41.2	10.2	1.26	0.40

Table 1. Affine transformation parameter percent errors for registration of synthetic brain MRI are presented for MI (*NN* and *LI* interpolation), CMI (gradient and random ensembles), and COFEMI (feature ensembles $\pi(1)$,$\pi(2)$,$\pi(3)$,$\pi(4)$).

5. CONCLUDING REMARKS

In this paper we presented a new MI based registration scheme called COFEMI that exploits the combined descriptive power of multiple feature images for both inter-modal and inter-protocol image registration. An ensemble of feature images derived from the source intensity image is used for the construction of a similarity metric that is robust to non-ideal registration tasks. The COFEMI scheme is in some ways analogous to multiple classifier systems such as decision trees and AdaBoost where individual base learners are combined to form a strong learner with greater classification accuracy. By using multiple feature representations of the original image, COFEMI is able to overcome the limitations of using conventional intensity-based MI registration by providing additional information regarding the images to be registered, these feature representations being less susceptible to intensity artifacts and to structural differences across modalities.. We also present a novel method to optimally select a subset of informative features for use with COFEMI which makes limited assumptions about the formulation of the features. While one may argue that inhomogeneity correction and filtering methods may help overcome limitations of using intensity based MI techniques, it should be noted that these only offer partial solutions and conventional MI often cannot address vast structural differences between different modalities and protocols. In fact the prostate MR images considered in this paper had been previously corrected for inhomogeneity[1] and yet conventional MI was only marginal successful. The COFEMI registration technique was shown to qualitatively and quantitatively improve registration accuracy over intensity-based MI on multimodal prostate histology-MR and multiprotocol synthetic brain MR data sets. While this technique is presented in the context of affine registration, COFEMI can be used as a precursor to more sophisticated elastic registration schemes. Future work will entail evaluating our scheme on a larger number of studies and on images corresponding to different body regions and protocols.

6. REFERENCES

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