MULTI-ATTRIBUTE COMBINED MUTUAL INFORMATION (MACMI): AN IMAGE REGISTRATION FRAMEWORK FOR LEVERAGING MULTIPLE DATA CHANNELS

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ABSTRACT
We present a novel methodological framework for leveraging multiple image sources, including different modalities, acquisition protocols or image features, in the registration of more than two images via information theoretic data fusion. The technique, referred to as multi-attribute combined mutual information (MACMI), adopts a multivariate application of mutual information (MI) to allow several coregistered images to be represented as a single high dimensional multi-attribute image. Our approach improves scenarios involving registration of multiple images as it, (1) utilizes all aligned images obtained in earlier registration steps, (2) improves alignment accuracy compared with pairwise approaches that only consider two images (and hence a fraction of the available data) at a time, and (3) avoids complex optimization problems often associated with fully-groupwise methods. For example, if two coregistered volumes such as T2-weighted and PD-weighted MRI are to be aligned with PET, it is intuitively better to use information from both MR protocols instead of choosing one for registration with PET. In the automated elastic registration of 20 corresponding multiprotocol (T1, T2, PD) synthetic MRI images of the brain with known misalignment of PD MRI, MACMI showed significant improvement in terms of deformation field error over conventional MI-based pairwise registration ($p < 0.05$). For a total of 108 corresponding whole-mount histology (WMH), T2 MRI, and DCE (T1) MRI images obtained from 17 prostate specimens with cancer, elastic registration of WMH to both MRI protocols simultaneously was performed via MACMI. Improved alignment in terms of prostate overlap and cancer localization was observed using MACMI, compared to pairwise registration of WMH to the individual T2 and DCE MR protocols.

Index Terms—image registration, MACMI, mutual information, free form deformations, multi-attribute, multivariate

1. INTRODUCTION
Multimodal registration tasks often involve aligning images with different structural attributes (e.g. CT and MRI) [1], or structural-functional attributes (e.g. T2 and DCE MRI) [2]. Since, more and more, multiple acquisition protocols (such as dynamic contrast enhancement (DCE) and diffusion weighted imaging (DWI)) are being acquired from the same modality (MRI), it is often necessary or desirable to consider multiple image channels, which may be in various degrees of misalignment. Alignment of multiple image sets from a range of modalities and protocols, and representing different structural or functional attributes is a common but formidable task. In this paper, we present a new method for registration of multiple data sets (e.g. histology, T2, and DCE MRI) that simultaneously considers several coregistered multifunctional or multiprotocol image scenes (e.g. aligned T2 and DCE MRI).

Alignment of more than two image sets representing very different structural or functional attributes of the same object is not well studied. The limitations of fully-groupwise approaches are generally two fold; they either (1) involve high degrees of freedom optimization problems arising from multiple simultaneous transformations, or (2) are limited to images with similar intensity and deformation characteristics. In the groupwise registration method by Bhatia [3], all images contribute to the same histogram used for entropy calculation, hence restricting the technique to images of the same type. On the other hand, the groupwise method of Studholme [4] utilizes a high dimensional distribution suitable for multimodal data, but the use of a dense deformation field requires a constraint that penalizes deformations that deviate from an average deformation. However, when large and different deformations must be corrected in some images, such as between ex vivo and in vivo images, this may be restrictive. Other methods require repeated refinement of individual transformations before convergence [5]. More recently, Balcı [6] performed simultaneous registration of a large number (50) of patient’s brain MRI scans using a sum of univariate (1D) entropy values (Stack Entropy) calculated at every pixel location. However, since this cost function requires many images to calculate entropy at each pixel location, it is suited only for registration of very large populations rather than just a small number of images.

Therefore, simple sequential pairwise registration steps between modalities or protocols are most commonly performed in such multimodal cases to bring all image sets into alignment. Figures 1(a) and (b) illustrate two possible approaches to pairwise registration of three images ($A$, $B$, $C$) from different modalities and protocols. In Fig. 1(a), image $A$ (histology) is treated as a reference to which $B$ (T2 MRI) and $C$ (DCE MRI) are independently registered. In Fig. 1(b), image $C$ is registered to $B$, which is then registered to $A$. In both cases, the two registration steps are independent and utilize only two images at a time. Such pairwise approaches to registration of three multimodal images have been used by Lee [1] to register CT, MR and SPECT images of the prostate, and by Chappelow [2] to register histology, T2 MR and DCE MR images of the prostate. In [1], MR was used as a reference image to which both CT and SPECT were aligned in two completely independent registration steps, as in Fig. 1(a). In [2], high resolution histology was registered to T2 MRI, followed by registration of T2 MRI to DCE MRI, as in Fig. 1(b), again using two completely independent registration steps.

While pairwise registration is a straightforward solution, in con-
Fig. 1. Registration of *ex vivo* histology (*A*), *in vivo* T2 (*B*) and *in vivo* DCE (*C*) MR images of a prostate. Pairwise registration of the three images can be achieved by (i) alignment to a single reference image (both *B* and *C* to *A*) or (ii) consecutive alignment (*C* to *B* and *B* to *A*). Alternatively, (iii) a multi-attribute image registration scheme involves initial pairwise alignment of like images (DCE and T2 MRI), followed by alignment of histology with an image ensemble comprising the registered MR images.

Considering only two images at a time, it exploits only a fraction of the available data to drive each registration step. Further, in subsequent alignment steps, it is necessary to select a single image from the already coregistered imagery. A more effective approach is to exploit the information acquired from prior alignment steps. As illustrated in Fig. 1(c), following registration of *C* to *B*, both of the newly aligned images could be considered simultaneously to perform registration with *A*. The main idea is that since *B* and *C* are in alignment, and represent different and informative image attributes, both should be considered in unison to determine the appropriate alignment with *A*. This approach is akin to previous studies that have used supplemental images in the form of textural features to improve registration by enhancing anatomical details in areas where intensity information alone may be inadequate for successful registration [7].

To define a similarity measure capable of handling several images or high dimensional data, information theoretic quantities may be employed. For example, multivariate formulations of MI have been demonstrated [8, 2] to incorporate multiple calculated texture feature images. Thus, multivariate MI may also be applied so that any and all registered multifunctional images may be simultaneously considered during registration. For example, in Fig 1(c), multivariate MI may be used to compare histology with the multi-attribute image composed of T2 and DCE MRI.

The novel contribution of this work is a formal framework for incorporating multiple modalities, protocols or even feature images, in an automated registration scheme that is facilitated by the use multivariate MI for efficient information theoretic fusion of sets of coregistered data (multi-attribute images). This framework, which we refer to as Multi-Attribute Combined MI (MACMI), is distinguished from previous groupwise approaches in that it handles images that are very different in terms of intensities (e.g. multimodal data) and deformation characteristics (e.g. *in vivo* to *ex vivo*), and it involves a simple (low degree of freedom) optimization procedure whereby individual image transformations are determined in sequence.

MACMI is evaluated in the context of a clinical problem involving multiprotocol MR imaging of the prostate, where prior to radical prostatectomy (RP) cases, *in vivo* MR images from T2 structural and DCE functional acquisition protocols are obtained. Following RP, digital scans of whole-mount histology (WMH) sections are obtained, upon which cancer may be delineated. Cancer ground truth on corresponding MRI may then be determined by registration with WMH. For this specific case and 108 corresponding sets of images from 17 prostates, the MACMI registration framework involves, (1) alignment of the T2 and DCE images using a standard image similarity measure to generate a multi-attribute MR image, followed by (2) multimodal elastic registration of WMH with the multi-attribute MRI. We also quantitatively evaluate our method on 20 corresponding slices of a synthetic brain MRI study from BrainWeb1.

2. MULTI-ATTRIBUTE IMAGE REGISTRATION BY INFORMATION THEORETIC DATA FUSION

2.1. Formulation of MACMI

Equation 1 below is a common formulation of MI of a pair of images (or random variables) $A_1, A_2$ in terms of Shannon entropy.

$$I_2(A_1, A_2) = S(A_1) + S(A_2) - S(A_1, A_2), \quad (1)$$

where $I_2(A_1, A_2)$ describes the interdependence of 2 variables, or intensity values of a pair of images [7].

The conventional MI formulation can be extended to high dimensional images, by combining multiple dimensions or attributes of each via high order joint entropy calculations. We refer to this application of MI as multi-attribute combined MI (MACMI) to distinguish it from conventional applications of MI and higher order MI, and denote it as $I_2^*$. Unlike the more familiar higher order MI ($I_n$, $n \geq 2$), the goal of MACMI is not to measure only the intersecting information of multiple images ($A_1, \ldots, A_n$), but to quantify the combined information content encoded by one multivariate observation (e.g. $A_1, \ldots, A_n$) with respect to another (e.g. $B_1, \ldots, B_n$).

In the simplest case, the MI ($I_2^*$) that a single image $A_1$ shares with an ensemble of two other images, $B_1$ and $B_2$, is,

$$I_2^*(A_1, B_1, B_2) = S(A_1) + S(B_1, B_2) - S(A_1, B_1, B_2). \quad (2)$$

By considering $B_1$ and $B_2$ as simultaneously measured semi-independent variables in the single multidimensional ensemble $B_1 B_2$, any dependence that exists between $B_1$ and $B_2$ is discounted and MI remains bounded by the smaller of $S(A_1)$ and $S(B_1)$. The generalized form of MI between the $n$ dimensional ensemble denoted $E_{m}^B = A_1 \ldots A_n$ with the $m$ dimensional ensemble $E_{m}^B = B_1 \ldots B_m$ is,

$$I_2^*(E_{n}^A, E_{m}^B) = S(E_{n}^A) + S(E_{m}^B) - S(E_{n}^A E_{m}^B). \quad (3)$$

Thus, MACMI accomplishes fusion of the multiple dimensions of a multi-attribute image, hence allowing intersecting information between two such images (e.g. $E_{n}^A$ and $E_{m}^B$) to be calculated.

1http://www.bic.mni.mcgill.ca/brainweb/
2.2. Registration of Multi-attribute Images using MACMI

Given several images to be aligned with each other, some or all of which may or may not be in alignment, MACMI proceeds as follows, using Figure 2 to illustrate.

**Step 1. Initial Pairwise Alignment (optional)** of a first pair of images using a conventional similarity measure, or skip to Step 2 if coregistered imagery exists. For example, as shown in Fig. 2(b), images \( A \) and \( C \) can be registered.

**Step 2. Generate Multi-attribute Images** as ensembles of existing coregistered images, including any obtained in Step 1. For example, \( B_1 \) and \( B_2 \) are already aligned, yielding \( E(B_1, B_2) \), while \( C \) may be aligned to \( A \) from Step 1 (Fig. 2(b)) yielding \( E(A'C') \).

**Step 3. Register Multi-attribute Images** using \( I_2^* \). For example, align \( E(B_1, B_2) \) to \( A \) or \( C \) (Fig. 2(a)), or to \( E(A'C') \) (Fig. 2(b)).

**Step 4. Combined Registered Images** into a new higher dimensional multi-attribute image. For example, if \( A \) was registered to \( E(B_1, B_2) \) in Step 3, generate \( E(A'B_1B_2) \).

**Step 5. Continue Multi-attribute Registration** with Steps 3-4 while unregistered images remain, hence considering all imagery simultaneously upon the last iteration. For example, if \( A \) was registered to \( E(B_1, B_2) \) in Step 3, continue with \( E(A'B_1B_2) \) and \( C \), then, when \( C \) is registered to \( E(A'B_1B_2) \), stop; if \( E(B_1, B_2) \) was registered to \( E(A'C') \) in Step 3, stop.

This approach yields cumulative incorporation of all images, while allowing flexibility to choose the order of multi-attribute image construction. In the absence of a predetermined order for combining images, improvement over pairwise registration would still realized with MACMI regardless of order.

Two generic examples of possible MACMI operation on 4 images \((A, B_1, B_2, C)\) are presented in Fig. 2. In this example, \( A \) and \( C \) could represent images from two dissimilar modalities such as CT and PET, and \( B_1 \) and \( B_2 \) could represent multimodal images such as T1 and PD MRI. \( B_1 \) and \( B_2 \) may be in implicit alignment through hardware configuration or previously brought into alignment. Fig. 2(a) demonstrates how the coregistered images \( B_1 \) and \( B_2 \) are combined into a multi-attribute image \( E(B_1, B_2) \), which is used as a reference to which image \( A \) and/or \( C \) are aligned. The simultaneous use of both \( B_1 \) and \( B_2 \) in \( E(B_1, B_2) \) via \( I_2^*(A, E(B_1, B_2)) \) and \( I_2^*(C, E(B_1, B_2)) \) has the following benefits, (1) avoids ambiguity in choosing \( B_1 \) or \( B_2 \), and (2) potentially provides improved alignment versus use of just \( B_1 \) or \( B_2 \) individually. In the alternative approach demonstrated in Fig. 2(b), \( C \) is first registered to \( A \) to form \( C' \) and \( E(A'C') \), and all images are then aligned using \( I_2^*(E(A'C'), E(B_1, B_2)) \) to consider all available data simultaneously.

3. EXPERIMENTAL DESIGN AND RESULTS

3.1. Synthetic Brain Registration

The multimodal data set from BrainWeb comprises 20 corresponding multiprotocol (T1, T2, and PD) MRI slices for which ground truth alignment is known. We denote the T1, T2, and PD MRI slices as \( T_1, T_2 \) and \( PD \), respectively. Since the individual slices of \( T_1, T_2 \) and \( PD \) are initially in alignment, we apply a known non-linear deformation \((T^{PD})\) to \( PD \) to generate \( PD^{D} \) with known misalignment from the other images. Registration using an elastic Free Form Deformation (FFD) model [8] is then executed to recover the initial correct alignment via a corrective deformation \((T^{PDC})\). We denote the recovered \( PD \) slice as \( PD^{DC} \). MACMI is performed in a manner similar to the scenario described in Fig. 2(a), whereby \( PD^{DC} \) is registered to the multi-attribute image comprising the coregistered sections \( T_1 \) and \( T_2 \) via the recovered transformation,

\[
T^{DC}_{MACMI} = \arg\max_T I^*_2(E(T1T2), T(PD^D)).
\]  

Conventional pairwise registration is also performed using MI for registration of \( PD^{D} \) to \( T_1 \), as well as \( PD^{D} \) to \( T_2 \), for comparison with MACMI. Two \( PD^{D} \) images are thus obtained via \( T^{PD}_{FW1} = \arg\max_T I^*_2(T1, T(PD^D)) \) for registration with \( T_1 \) and \( T^{PD}_{FW2} = \arg\max_T I^*_2(T2, T(PD^D)) \) for registration with \( T_2 \). Estimation of \( I_2^* \) was achieved using 2D and 3D probability density estimates with 128 and 40 graylevel bins, respectively, chosen empirically to provide robust estimates for both methods.

Quantitative evaluation of registration accuracy can be performed easily since the correct coordinate transformation, \( T^{op} \), is known. First, the magnitude of error in the transformation \( T^{co} \) determined by registration can be quantified in terms of mean absolute difference (MAD) \((F_{mad}(T^{co}))\) and root mean squared (RMS) error \((F_{rms}(T^{co}))\) from \( T^{op} \) over the \( N \) total image pixels \( c \),

\[
F_{mad}(T^{co}) = \frac{1}{N} \sum_c |T^{co}(c) - T^{op}(c)|,
\]

\[
F_{rms}(T^{co}) = \sqrt{\frac{1}{N} \sum_c (T^{co}(c) - T^{op}(c))^2},
\]

Further, the original \( PD \) is compared directly with the resulting \( PD^{D} \) using L2 distance \((D_{L2})\) as an unrelated similarity measure.

Table 1 presents a comparison of these evaluation measures for transformations obtained in elastic registration of the \( n = 20 \) multiprotocol MRI slices using MACMI \((T^{MACMI}_{FW,FW})\) and both pairwise registration approaches \((T^{PD}_{FW1}, T^{PD}_{FW2})\). MACMI achieves better performance in terms of each measure, with significantly lower error \((p < 0.05 \text{ for } n = 20)\) compared to one or both pairwise methods. The \( p \)-values for the paired \( t \)-tests comparing MACMI to both pairwise MI approach are given in the last two rows of Table 1.
Table 1. Comparison of elastic registration accuracy for MACMI and pairwise MI alignment of n = 20 pairs of synthetic PD MRI with coregistered T1 and T2 MRI brain images. Shown measures are, error of recovered deformation field (in mm) in terms of $F_{mad}$ and $F_{rms}$, and distance ($D_{L2}$) between the undeformed and recovered PD MRI. MACMI results are significantly more accurate than either pairwise approach ($p$-values for both tests shown).

<table>
<thead>
<tr>
<th></th>
<th>$F_{mad}$</th>
<th>$F_{rms}$</th>
<th>$D_{L2}$</th>
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</thead>
<tbody>
<tr>
<td>$T_{PW1}$ (MI, T1-PD)</td>
<td>0.9117</td>
<td>2.1407</td>
<td>1.83e+03</td>
</tr>
<tr>
<td>$T_{PW2}$ (MI, T2-PD)</td>
<td>0.9506</td>
<td>2.0248</td>
<td>2.35e+03</td>
</tr>
<tr>
<td>$T_{MACMI}$ (MACMI, MR-PD)</td>
<td><strong>0.8348</strong></td>
<td><strong>1.9307</strong></td>
<td><strong>1.71e+03</strong></td>
</tr>
<tr>
<td>$p$-value ($T_{PW1}$ vs. $T_{MACMI}$)</td>
<td>0.0817</td>
<td>0.0578</td>
<td>0.0174</td>
</tr>
<tr>
<td>$p$-value ($T_{PW2}$ vs. $T_{MACMI}$)</td>
<td>0.0013</td>
<td>0.2020</td>
<td>1.8e-10</td>
</tr>
</tbody>
</table>

3.2. Clinical Prostate Registration

The multimodal, multiprotocol prostate data set comprises a total of 108 corresponding in vivo T2 structural MRI ($S$), DCE functional MRI ($F$) and ex vivo whole-mount histology (WMH) ($H$) sections of 17 prostate cancer cases in 3 to 10 slices of each study. As previously described, the goal of this task is to register WMH to both MRI protocols in order to map cancer ground truth onto MRI, thus allowing training and evaluation of a multiprotocol computer-aided diagnosis system. Since T2 and DCE MRI are acquired in sequence and with minimal movement, the multi-attribute image representation $E(S,F)$ is generated from the registered T2 and DCE MRI, as shown in Figs. 3(b)-(d). Automatic FFD registration of WMH to the multi-attribute MR image is performed by $I_2^E (E(S,F), T(H))$, resulting in a warped WMH, as shown in Fig. 3(c). The histological cancer ground truth is then mapped onto $S$ and $F$, as shown in Figs. 1(f),(g). Qualitative examination of overlaps of $S$ and the registered $H$, as shown in Fig. 1(h), and the cancer maps on MRI suggest that MACMI outperforms pairwise MI (not shown).

4. CONCLUDING REMARKS

We have presented a registration framework for incorporating multiple image sources, including different modalities, acquisition protocols or image features, in the registration of several images. MACMI obviates the need for fully-pairwise registration approaches, works with images that are very different in terms of intensities and deformations, and is shown to improve registration accuracy. Unlike groupwise registration, the optimization problem remains simple while allowing for both highly dissimilar modalities and large deformations of variable magnitude. We demonstrate the use of MACMI for registration of 108 multimodal (histology, T2 and DCE MR) prostate image sets, and for 20 sets of synthetic T1, T2 and PD MR brain images. Statistically significant improvement in registration accuracy is observed in using MACMI to simultaneously register PD MRI to both T1 and T2 MRI, compared to pairwise registration of PD to T1 or T2 MRI. Qualitative examination of alignment between multiprotocol clinical prostate MRI and histology suggests improved performance via MACMI over pairwise MI. While we utilized histograms for density estimation, other techniques, such as entropic graphs, can be applied for larger numbers of images. It is important to note that in the absence of a predetermined order for combining images, MACMI may still be applied by combining images in a completely arbitrary order. Even in this scenario, MACMI still represents an improvement over fully-pairwise registration by utilizing all registered images. Future work will investigate the influence of the order of multi-attribute image construction on alignment accuracy.

5. REFERENCES


Fig. 3. Elastic registration of corresponding slices of (a) histology (WMH), (b) in vivo T2 and (c) DCE (single post-contrast time point) MRI of a prostate under the MACMI framework. (d) Multi-attribute images are generated from coregistered T2 and DCE MRI. (e) WMH is registered to the T2-DCE multi-attribute image using $I_2^E$ to compare all three sources. The histological cancer label is then mapped onto (f) T2 and (g) DCE MRI (shown in green, prostate segmented). (h) Overlay of T2 MRI and warped WMH demonstrate accurate alignment.