HIDDEN MARKOV MODEL-BASED MULTI-MODAL IMAGE FUSION WITH EFFICIENT TRAINING

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ABSTRACT

Automated spatial alignment of images from different modalities is an important problem, particularly in bio-medical image analysis. We propose a novel probabilistic framework, based on a variant of the 2D hidden Markov model (2D HMM), to capture the deformation between multi-modal images. Smoothness is ensured via transition probabilities of the 2D HMM and cross-modality similarity via class-conditional, modality-specific emission probabilities. The method is derived for general multi-modal settings, and its performance is demonstrated for an application in cellular microscopy. We also present an efficient algorithm for parameter estimation. Experiments on synthetic and real biological data show improvement over state-of-the-art multi-modal image fusion techniques.

Index Terms— Biological image analysis, deformable, fusion, registration, multi-modal

1. INTRODUCTION

Bio-medical image registration problems have been widely explored in recent years, resulting in reliable and accurate deformable registration techniques for images of the same modality. However, multimodal image fusion is a more challenging task due to differences in the nature of the data, and remains an active area of research. When images of different modalities are available from the same subject or region of interest, they usually provide complementary information. Advances in technology have enabled the collection of large amounts of such multi-modal data, and the sheer size of this data makes manual annotation and analysis impractical. Automated spatial alignment of these images is an important task and is essential in relating relevant information from each modality, which in turn aids diagnosis.

Mutual Information (MI) has been successfully used in a variety of rigid [1] and deformable [2] registration problems. Multimodal extensions built on the cubic B-spline framework of [2] were proposed in subsequent papers [3, 4], and use variants of MI (conditional MI and normalized MI respectively) which are more suitable for multi-modal applications. A drawback of these registration methods is that they do not offer a practical extension to the case where one or both of the modalities proffers multiple channels of information. A natural extension of MI-based approaches to include data with multiple channels (e.g., RGB data) would require estimating higher dimensional joint histograms. However, the complexity of populating such a histogram grows exponentially with the number of channels, and these methods quickly become impractical for multi-channel or multi-feature modalities. Further, inadequate population of such high dimensional histograms due to sparse availability of data could lead to inaccuracies in the inferred deformation (the "curse of dimensionality"). In [5], a graph-based implementation of α -MI is used to achieve multi-feature mutual information with feasible time complexity. While this method mitigates the above shortcoming due to registering multi-channel data, it still suffers from another issue of the MI-based techniques discussed. MI is intrinsically a global measure and its local estimation, which is performed by dividing the image into non-overlapping regions, can be unreliable. In multi-modal image datasets with considerable structural changes between modalities, this can yield inaccurate estimation of the joint histograms and compromise the performance of deformable registration.

A recent paper, [6], proposes a modality independent neighborhood descriptor (MIND) which exploits local structural similarities between multimodal image pairs. Descriptors are calculated on a defined spatial search region in each modality and sum of squared differences (SSD) is used as a measure of distance between descriptors. The final deformation is estimated using Gauss-Newton optimization. This method, however, relies on significant anatomical similarity between images of the two modalities, which may not be present if different types of information are captured by the different modalities.

To overcome deficiencies in prior approaches, we propose a framework for multi-modal non-rigid fusion. Our contributions include:

- A principled probabilistic method for multi-modal data fusion applicable to the general case of multi-channel inputs, wherein the optimal global transformation between the the two modalities is approximated by a set of local transformations. The parameters, implementing cross-modality matching costs and smoothness constraints, are embedded within a two-dimensional hidden Markov model (2D HMM) framework.
- An efficient procedure for training the system parameters, which approximates the performance of the full complexity training process at a fraction of the run time.

2. PROPOSED APPROACH

Our aim is to find the deformation that best explains how an image from one modality (the "source") can be warped to correspond as closely as possible to an image from the second modality (the "target"). The proposed approach estimates the global deformation with a set of local deformations. Consistency of local translations and optimal cross-modality matching are achieved through a 2D HMM built on a first order Markov mesh random field (MMRF). Additionally, we employ a coarse-to-fine pyramid scheme, starting at a lower resolution and performing successive refinement at finer resolutions.

The central problems associated with HMMs - learning model parameters, and inferring optimal state given observations and the

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Fig. 1: Mapping a point (x, y) (with feature vector $\mathbf{S}_{x,y}$) in the source image to a point $(x + \tau_x, y + \tau_y)$ (with feature vector $\mathbf{T}_{x+\tau_x,y+\tau_y}$) in the target image using a translation τ .

learned model - are solved using computationally efficient algorithms [7] in the conventional 1D case. However, direct extension of these to 2D is intractable in most practical applications due to exponential increase in complexity. As a result, many approximations of the full 2D-HMM have been suggested ([8, 9, 10]). The turbo hidden Markov model (T-HMM) introduced in [10] consists of horizontal and vertical 1D HMMs that are decoded separately but communicate by iteratively inducing priors on each other, in a manner similar to the decoding of turbo codes. The T-HMM framework, used in this work, offers efficient approximations for learning and inference while outperforming related approaches.

2.1. Deformation Smoothness Model

At any given level of the multi-resolution pyramid, each pixel corresponds to a node of the HMM. Each state q of the HMM corresponds to a unique translation τ (with components τ_x and τ_y and the x- and y-directions respectively) relating the source and the target. Therefore, a state with translation τ maps a point (x, y) in the source to $(x + \tau_x, y + \tau_y)$ in the target (see Fig. 1). Translations of neighboring nodes are correlated as quantified by the transition probabilities of the HMM. Assuming a stationary HMM, the transitions probabilities of the T-HMM's constituent horizontal and vertical 1D HMMs are given by $a^H(\tau, \tau') = P(q_{x,y} = \tau' | q_{x,y-1} = \tau)$ and $a^V(\tau, \tau') = P(q_{x,y} = \tau' | q_{x-1,y} = \tau)$ respectively. We make the simplifying (but removable) assumption that the horizontal and vertical HMMs have identical parameters, as biological images typically do not exhibit horizontal or vertical directionality. Further, we impose shift invariance so probability of transitioning from one state to another depends only on the difference between translations. Finally, we restrict to parametric transition probabilities to increase robustness of the training procedure. On our experiments, we use a Gaussian model with variance σ in both directions.

$$a^{H}(\tau,\tau') = a^{V}(\tau,\tau') = a(\delta\tau) \propto \exp\left\{-\frac{1}{2}\left(\frac{\delta\tau_{x}^{2} + \delta\tau_{y}^{2}}{\sigma^{2}}\right)\right\}$$
(1)
where $\delta\tau = \tau - \tau', \, \delta\tau_{x} = \tau_{x} - \tau'_{x}$ and $\delta\tau_{y} = \tau_{y} - \tau'_{y}$.

2.2. Data Similarity Measure

The cost of matching a point in the source to one in the target is captured by the HMM's emission probabilities. The emission probability $b_{x,y}^{\tau}$ represents the probability of matching the source feature vector at (x, y), given by $\mathbf{S}_{x,y}$, to the target feature vector at a translation (τ_x, τ_y) , given by $\mathbf{T}_{x',y'}$.

$$b_{x,y}^{\tau} = P(\mathbf{T}_{x',y'}|\mathbf{S}_{x,y}) \tag{2}$$

In our discussion, we consider the general multi-channel, multi-class case. The model of $P(\mathbf{T}_{x',y'}|\mathbf{S}_{x,y})$ can be specialized according to application if required.

Objects of a given class may be represented very differently in different modalities. Therefore, we assume that the relation between source and target feature vectors at specific locations is not direct, but rather, only through the underlying true object type at corresponding locations. In other words, the source feature vector, the underlying object type at the corresponding location in the source $(\omega_{x,y}^S)$, the underlying object type at the location after translation in the target $(\omega_{x',u'}^T)$ and the target feature vector form a Markov chain.

$$\mathbf{S}_{x,y} \longleftrightarrow \omega_{x,y}^{S} \longleftrightarrow \omega_{x',y'}^{T} \longleftrightarrow \mathbf{T}_{x',y'} \tag{3}$$

Applying the law of total probability to (2) under the Markov assumption (3),

$$b_{x,y}^{\tau} = \sum_{m=1}^{M} P(\omega_m | \mathbf{S}_{x,y}) P(\mathbf{T}_{x',y'} | \omega_m)$$
(4)

where M is the total number of object classes, indexed by m. In our experiments, we model $P(\mathbf{T}_{x',y'}|\omega_m)$ with a mixture of K Gaussians, noting that linear combinations of Gaussians can approximate arbitrarily shaped densities.

$$P(\mathbf{T}_{x',y'}|\omega_m) = \sum_{k=1}^{K} w_m^k P(\mathbf{T}_{x',y'}|\omega_m^k)$$
(5)

where mixture component weights must satisfy the constraint:

$$\sum_{k=1}^{K} w_m^k = 1 \ \forall m \in \{1, 2, \dots M\}$$
(6)

Each individual component density is a Gaussian having dimensionality D (equal to that of the target feature space) and mean and covariance μ_m^k and Σ_m^k respectively.

$$\frac{P(\mathbf{T}_{x',y'}|\omega_m^k) =}{\frac{\exp\{-\frac{1}{2}(\mathbf{T}_{x',y'} - \mu_m^k)^T \mathbf{\Sigma}_m^{k^{-1}}(\mathbf{T}_{x',y'} - \mu_m^k)\}}{(2\pi)^{\frac{D}{2}} |\mathbf{\Sigma}_m^k|^{\frac{1}{2}}}$$
(7)

2.3. Parameter Estimation

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2.3.1. Background: Baum-Welch Training

Parameters are estimated from source-target pairs of multi-modal images. The parameter estimation problem is usually solved using the Baum-Welch algorithm [11]. As noted in [7], this reestimation procedure can be interpreted as an implementation of the Expectation-Maximization (EM) algorithm [12] and is known to monotonically increase likelihood. Re-estimation formulas for HMM parameters are derived by maximizing Baum's auxiliary function, given by:

$$Q(\lambda'|\lambda) = \sum_{Q} P(Q|S, T, \lambda) \log P(S, Q|T, \lambda')$$
(8)

with respect to λ' , where λ denotes the current estimate of HMM parameters, λ' the model re-estimate and Q, a sequence of states $Q = \{q_{x,y}, x = 1, 2, \dots, X, y = 1, 2, \dots, Y\}$. S and T denote corresponding source and target images. During the E-step, the modified forward-backward iterations are used to estimate the occupancy probabilities of the horizontal and vertical 1D HMMs,

$$\gamma_{x,y}^{H,\tau} = P(q_{x,y}^{H} = \tau | S, T, \lambda)$$

$$\gamma_{x,y}^{V,\tau} = P(q_{x,y}^{V} = \tau | S, T, \lambda)$$

and the overall occupancy probability

$$\gamma_{x,y}^{\tau} = \frac{\gamma_{x,y}^{H,\tau} + \gamma_{x,y}^{V,\tau}}{2}$$

as well as the ancillary training variables

$$\xi_{x,y}^{H}(\tau,\tau+\delta\tau) = P(q_{x,y+1}=\tau+\delta\tau,q_{x,y}=\tau|S,T,\lambda)$$

$$\xi_{x,y}^{V}(\tau,\tau+\delta\tau) = P(q_{x+1,y}=\tau+\delta\tau,q_{x,y}=\tau|S,T,\lambda)$$

The per-component posterior probability at each node is also reestimated, as given by

$$\phi_{x,y,m}^{\tau,k} = \frac{P(\omega_m | \mathbf{S}_{x,y}) w_m^k P(\mathbf{T}_{x',y'} | \omega_m^k)}{\sum\limits_{m=1}^M P(\omega_m | \mathbf{S}_{x,y}) \sum\limits_{k=1}^K w_m^k P(\mathbf{T}_{x',y'} | \omega_m^k)}$$
(9)

where $x' = x + \tau_x$ and $y' = y + \tau_y$.

During the M-step, Baum's auxiliary function is maximized with respect to each parameter to obtain the following re-estimation formulas: $\sum e^{\tau} e^{\tau,k}$

$$\hat{w}_{m}^{k} = \frac{\sum_{x,y,\tau}^{\sum \gamma, \tau} \gamma_{x,y} \varphi_{x,y,m}}{\sum_{x,y,\tau,k} \gamma_{x,y} \phi_{x,y,m}^{\tau,k}}$$
(10)

$$\hat{\boldsymbol{\mu}}_{m}^{k} = \frac{\sum\limits_{x,y,\tau} \gamma_{x,y}^{\tau} \phi_{x,y,m}^{\tau,k} \mathbf{T}_{x',y'}}{\sum\limits_{x,y,\tau} \gamma_{x,y}^{\tau} \phi_{x,y,m}^{\tau,k}}$$
(11)

$$\hat{\boldsymbol{\Sigma}}_{m}^{k} = \frac{\sum\limits_{x,y,\tau} \gamma_{x,y}^{\tau,k} \phi_{x,y,m}^{\tau,k} (\mathbf{T}_{x',y'} - \hat{\mu}_{m}^{k}) (\mathbf{T}_{x',y'} - \hat{\mu}_{m}^{k})^{T}}{\sum\limits_{x,y,\tau} \gamma_{x,y}^{\tau,k} \phi_{x,y,m}^{\tau,k}}$$
(12)

$$\hat{\sigma^{2}} = \frac{\sum_{x,y,\tau,\delta\tau} [\xi_{x,y}^{H}(\tau,\tau') + \xi_{x,y}^{V}(\tau,\tau')] (\delta\tau)^{2}}{\sum_{x,y,\tau,\delta\tau} [\xi_{x,y}^{H}(\tau,\tau') + \xi_{x,y}^{V}(\tau,\tau')]}$$
(13)

2.3.2. Proposed Training Approach

As noted in [13], Baum-Welch training is computationally expensive. Viterbi training [14] is an approximation to Baum-Welch in which each observation is assumed (with a weight of 1) to have resulted from the overall most probable state sequence. In the restimation formulae of Sec. 2.3.1 above, $\gamma_{x,y}^{\tau}$ at each point is replaced by an indicator function which takes a value of 1 for the most probable state at that point and 0 for all other states. In addition, $\xi_{x,y}^{H}(\tau, \tau')$ and $\xi_{x,y}^{V}(\tau, \tau')$ are calculated as products of such indicator functions.

In Baum-Welch training, the assignment of observations to states is soft, that is, at a given point (x, y), the probability of each state being selected is given by $\gamma_{x,y}^{\tau}$. In Viterbi training, the assignment is hard, where the winning state is selected with weight 1. We propose a modification to Viterbi training in which the variables $\xi_{x,y}^{H}(\tau, \tau')$ are calculated as follows:

$$\xi_{x,y}^{H}(\tau,\tau') = \begin{cases} \gamma_{x,y}^{\tau} \gamma_{x,y+1}^{\tau'} & \tau = \arg\max_{t}(\gamma_{x,y}^{t}), \\ \tau' = \arg\max_{t}(\gamma_{x,y+1}^{t}) \\ 0 & \text{otherwise} \end{cases}$$

(14)

 $\xi_{x,y}^V(\tau,\tau')$ is calculated similarly. In addition, $\gamma_{x,y}^{\tau}$ is replaced by $\psi_{x,y}^{\tau}$ in re-estimation equations.

$$\psi_{x,y}^{\tau} = \begin{cases} \gamma_{x,y}^{\tau} & \tau = \arg \max_{t} (\gamma_{x,y}^{t}) \\ 0 & \text{otherwise} \end{cases}$$
(15)

The proposed approach has the same reduced complexity as Viterbi training, yet we do not entirely give up the information conveyed by $\gamma_{x,y}^{\tau}$ - high probability winning states are weighted higher than low

Training Method	Level		
	3	2	1
Baum-Welch	2.58	10.84	43.83
Proposed Method	1.36	5.55	23.10

Table 1: Average run times (in seconds) at different levels of resolution.



Fig. 2: An example pair of synthetic images used in our experiments.

probability winning states. In our experiments, the overall DSC (defined in Sec. 3) was found to be 0.8039 if Baum-Welch training was used, and 0.8037 if the proposed approach was used. Table 1 compares the average run time of each update iteration at different levels in the multi-resolution pyramid. As can be observed, the proposed approach achieves significant reduction in run time with a negligible loss in accuracy when compared to Baum-Welch training.

2.4. Inference

Inference is performed via the Viterbi decoding procedure with modified forward-backward iterations as described in [10].

3. EXPERIMENTS AND RESULTS

We present the performance of our proposed approach on a synthetic dataset as well as on data obtained from the RC1 connectome [15]. We compare our method with MIND [6] and α -MI [5]. To evaluate registration quality, we used manual segmentations of both modalities along with manually annotated object-level (celllevel) associations. We generated automated segmentations by transforming the manual segmentations of the source image to the target image domain using the transformation obtained from each method. The resulting automated segmentation (S_{trans}) was compared to the manual target segmentation (T) using the Dice similarity measure (DSC) [16] as a measure of overlap.

$$DSC = \frac{2|S_{trans} \cap T|}{|S_{trans}| + |T|}$$
(16)

where $|\bullet|$ denotes number of pixels. To check the statistical significance of improvement in results, we performed paired two-sided Wilcoxon tests [17] on DSC values obtained using the proposed approach and DSC values from each competing method. A value of p < 0.05 was considered to indicate statistical significance. Further, we measured average run time (on a dual-core 3.2 GHz Intel Core i3-550 processor) for each method.

3.1. Synthetic Data

As a proof of concept, we first performed experiments on synthetically generated bimodal data. The dataset consists of 10 pairs of 256-by-256 pixel grayscale images generated as follows: (i) Create a source cell distribution image by generating 100 randomly located and shaped ellipses and randomly assigning each cell to one of three



Fig. 3: (Best in color) Visual results on a single cell (a)-(f) CMP channels (4-aminobutyrate (GABA), Glutamate, 1-amino-4-guanidobutane(AGB), Glycine, Glutamine, Taurine respectively) of the a region in RC1 with ground truth boundary of cell of interest in red (g) ATEM image corresponding to the same region, with ground truth cell overlaid in red (h) ATEM image with result of matching using α -MI (i) using MIND (j) using the proposed approach.

Method	DSC	p-value	Run Time
α-MI [5]	0.5398 ± 0.0331	3.9×10^{-3}	1167 s
MIND [6]	0.5708 ± 0.0293	4.8×10^{-2}	219 s
Proposed	0.6016 ± 0.0202	_	758 s

Table 2: Comparison of results on synthetic data.

classes. (ii) Fill the cells by drawing the intensity of each pixel independently from a normal distribution whose parameters are classdependent, and add noise. This is the source image. (iii) Generate a random deformation field using an MRF. (iv) Use this to deform the source cell distribution image and obtain a target cell distribution image. (v) Draw the intensity of each cell pixel from a class-dependent normal distribution specific to the second modality, which is different from the distribution in first modality. Add noise. This forms the target image.

We used three resolution levels for all compared approaches. For the α -MI-based approach, we used trial-and-error to find the optimal value of parameters, which were found to be $\alpha = 0.999$ and k = 5respectively. For the proposed approach, posterior probabilities at the source are learned via Expectation Maximization [12] for Gaussian Mixture Models (EM-GMM). The feature vector for the target image is the pixel intensity. We set M = 4 and K = 1. Wilcoxon tests were performed over the 10 synthetic image pairs. Average run time for each 256×256 image is also reported. The performance of the proposed approach in comparison to related methods is shown in Table 2. We see that the proposed approach outperforms competing approaches.

3.2. Connectome Data

We tested the proposed approach on biological data from the open access connectome RC1 [18, 15]. RC1 data was collected from a 0.25 mm diameter section of the Inner Plexiform Layer (IPL) of rabbit retina, and consists of 370 slices with a total of 1132 cells of 6 major types. We focus our attention on the top 7 slices, which consist of two modalities. Computational molecular phenotyping (CMP), a form of light microscopy which gives functional information, is used to image the first 6 slices of the volume. Each slice is probed for a unique amino acid and the resulting 6-channel data provides "protein signatures" which help in cell classification, but do not provide structural information. The seventh slice is imaged using an automated electron transmission microsocope (ATEM) and is a complementary

Method	DSC	p-value	Run Time	
α-MI [5]	0.7536 ± 0.1427	1.9×10^{-4}	4644 s	
MIND [6]	0.7459 ± 0.1303	5.7×10^{-4}	998 s	
Proposed	0.8037 ± 0.1226		2996 s	
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Table 3: Comparison of results on connectome data.

source of information which clearly shows the structure of cells, but does not give any functional information. (See Fig. 3.)

In our experiments, we set CMP as the source and ATEM as the target. We used three resolution levels for all approaches. The optimal value of parameters for the α -MI cased approach were found to be $\alpha = 0.99$ and k = 7 respectively. For the proposed approach, posterior probabilities at the source are learned using EM-GMM on the protein signatures in CMP. The feature vector for the target image is the average pixel intensity in a 5×5 neighborhood. We found the optimal values of hyper-parameters to be M = 7 and K = 2. The performance of the proposed approach in comparison to related methods is shown in Table 3. We divided the data into 64 nonoverlapping regions to perform the Wilcoxon tests. We observe that the proposed approach shows statistically significant improvement over both other methods. The average run-time for these 64 regions (each of size 512×512 pixels) is also reported.

The proposed approach shows the most improvement over competing methods when there is a large deformation between modalities. One explanation for this is that we account for large deformations right in the training phase. An example of such a case is shown in Fig. 3. We notice that α -MI and MIND do not capture the cell boundary well (with a DSC of 0.6683 and 0.6070 respectively for this example) whereas the proposed approach performs considerably better, both qualitatively and quantitatively (DSC = 0.8736).

4. CONCLUSION

We have presented a novel general purpose multi-modal multichannel image fusion method, with the deformation system embedded in the probabilistic framework of a 2D HMM and solved using the T-HMM approximation. Further, we propose an efficient approximation to maximum likelihood parameter estimation. We provide test results on both synthetic data and the special case of biological data, which show significant gains over state-of-the-art multi-modal multi-channel deformable registration techniques.

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