33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Deformable registration of histological sections to brain MR images using a hybrid boundary-based slice-to-volume approach

Sergey Osechinskiy and Frithjof Kruggel

Abstract— **Registration of histology to three-dimensional (3D) magnetic resonance (MR) images is often required for the analysis of brain structure and investigation of brain pathologies. A novel algorithm for deformable registration of an individual histological section to a brain MR image is described. The cost function uses a novel hybrid intensity- and boundary surface-based measure that reflects the contrast of histological slice intensities across the boundary of the pial and inner cortical surface. The algorithm relies on implicit representation of cortical surfaces reconstructed from an anatomical MR image, and computes the cost function in a level set framework. The algorithm is evaluated on cross-modality registration of myelin-stained histological sections to a high-resolution MR image of the human brain.**

I. INTRODUCTION

Registration of histological sections with magnetic resonance (MR) images is an important step in quantitative analysis and cross-modality comparison of brain histology and MRI data [1],[2]. The registration task poses a challenging problem, because a brain sample is subjected to multiple nonuniform and nonrigid deformations in the process of preparation and histological sectioning. Global and local distortions pertinent to different stages of histological sectioning procedure are described in [3]. A brain sample undergoes global shrinking during fixation in formalin, and each slice is experiencing local uncorrelated non-linear distortions when sectioned. When data for contiguous sections are available, registration may proceed in two stages: sequential slices are 2D-aligned into a 3D histology volume, and the histology volume is further 3D-registered with an MRI or a positron emission tomography (PET) image. For example, Ourselin et al. [3] applied a block matching algorithm to align histological sections into a reconstructed volume, which is then registered to MRI data with a 3D-version of the same algorithm. If available, photos of the cryomacrotome cut view may be used as intermediate data, facilitating 2D-alignment and volume reconstruction. Mega et al. [4] utilized an elastic warping/surface matching approach to register stained sections with optical images, and applied a 3D rigid registration to align cryovolume photos with PET. Optical images may also serve as a reference in case histological sections are not contiguous (e.g., see [5]).

When histology data are sparse, and no intermediate optical data are available, co-registration with MRI is posed as a 2D-to-3D, slice-to-volume registration problem (Fig. 1), which is concerned with finding a correspondence between a deformed image and a section of a volume by a warped surface. Jacobs et al. [6] registered rodent brain histology to MRI in two steps: first by rigid alignment of a histological slice with an MR image based on a modified "head and hat" surface matching algorithm, followed by a 2D warping of a planar section of the MRI volume onto a histological image. The 2D warping step used matching landmarks automatically selected along both sets of contours. However, modeling the sectioning surface as a plane may not correctly reflect global deformations of a brain sample; such cross-section is better modeled as a warped surface. In addition, it has been found that a surface-to-surface matching can be less accurate compared to intensity-based registrations [7].

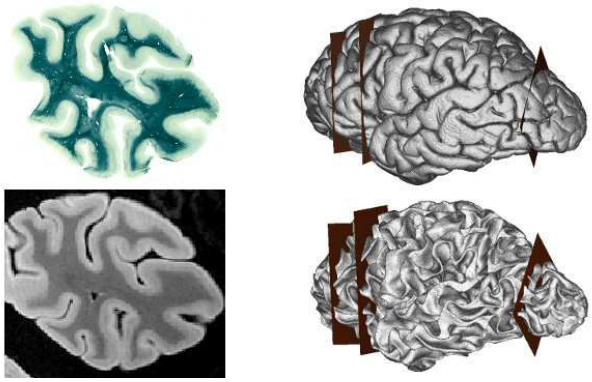

Fig. 1. Illustration of hybrid boundary-based slice-to-volume registration of a histological section to an MRI volume (left: a histological and a registered MR slice; right: rendering of three histological sections cutting through the pial (top) and the inner (bottom) cortical surface reconstructed from MRI).

We described detailed results of deformable registration of an individual histological section to a brain MR image in the intensity-based slice-to-volume registration framework in [8]. In this study, we present a novel approach with a hybrid cost function that uses a measure based on (a) intensities from histology and (b) surface boundaries derived from an MR image, a measure that reflects the contrast of histological slice intensities across the boundary of the pial and inner cortical surface. The new approach was inspired by the recent work on boundary-based rigid alignment by Greve and Fischl [9], which demonstrated good performance in intermodal rigid registration with partial field-of-view brain coverage in one of the images, even to the extent of registering single slices. We employ this idea of a hybrid intensity- and boundary-based cost function in a new application of nonrigid slice-to-volume registration, with the aim of improving the spatial overlap of a cortical ribbon in registered histology and MR

S. Osechinskiy and F. Kruggel are with the Department of Biomedical Engineering, University of California, Irvine CA 92697, USA {sosechin,fkruggel}@uci.edu

978-1-4244-4122-8/11/$26.00 ©2011 IEEE

slices. Our algorithm, contrary to [9], which is based on a surface mesh model, relies on an implicit representation of cortical surfaces reconstructed from an anatomical MR image [10], and efficiently computes the cost function in a level set framework. In addition, our algorithm can use both the pial and the inner cortical boundary, as opposed to [9], which uses the white matter surface only.

II. METHODS

We now describe our approach for the nonrigid registration. A prerequisite, the reconstruction of cortical surfaces from an anatomical 3D MR image, is described elsewhere, for example, see level set deformable model methods in [10] or [11]. Although our registration algorithm relies on implicit representation of cortical surfaces in the form of level set functions, it can be used as well in conjunction with any surface mesh based cortical reconstruction software (e.g., with FreeSurfer [12]), by means of an additional preprocessing step that computes a (signed) distance function on a surface mesh (e.g., via the *mris_volmask* tool generating a distance ribbon volume in FreeSurfer).

Our registration algorithm consists of three main parts: (1) a cost function with a similarity measure, (2) a geometric transformation with a deformation model, and (3) an optimization scheme. A slice-to-volume nonrigid registration takes as an input a 2D image (called target or floating image) and finds a corresponding warped cross-section slice (called registered image, 2D) in a 3D volume (called source or reference image). Let $I((x,y)\in\Omega)\in\mathbb{R}$ and $V((x,y,z)\in\Phi)\in\mathbb{R}$ denote the real-valued intensity function of a continuous version of a 2D histological image and a 3D MR image with domain $\Omega\subset\mathbb{R}^2$ and $\Phi\subset\mathbb{R}^3$ respectively. Continuous images are obtained from discrete images by a chosen interpolation model, for example by trilinear or spline interpolation. A geometric transformation $\mathscr{T}$ is defined as a mapping $\mathscr{T}:\Omega\mapsto\Psi,\Psi\subset\Phi$; the mapping determines the domain of a warped slice $\Psi\subset\mathbb{R}^3$. Then a registered image I_R (MR slice) is defined as the following intensity function: $I_R(V,\mathscr{T})=\{i_R=V(\vec{r}),\vec{r}\in\Psi\}$. We assume that the inner (white) and the outer (pial) cortical surfaces are represented by the level set functions $\Phi_w(x,y,z)$ and $\Phi_g(x,y,z)$. Then slices $\phi_{w,g}(\Phi_{w,g},\mathscr{T})=\{\phi_{w,g}=\Phi_{w,g}(\vec{r}),\vec{r}\in\Psi\}$ denote registered cross-sections through the level set volumes, which implicitly represent contours of the white and pial surface boundary in the registered MR slice I_R.

A. Cost function

Let $S_{sim}(I_1,I_2)$ denote an intensity-based similarity measure (a scalar) between two images I_1, I_2, such that closer similarity of images results in higher value. Two widely used examples of such a similarity measure are the correlation coefficient (CC) and the normalized mutual information (NMI) [10]. A traditional intensity-based cost function is usually defined as:

$$C(I,V,\mathscr{T})=-S_{sim}(I,I_R)+\beta E(\mathscr{T}(\Omega)), \qquad (1)$$

where $E(\mathscr{T}(\Omega))$ is the deformation energy of the geometric transformation, and β is the weight parameter at the energy penalty term. Image registration seeks the optimal transformation $\mathscr{T}=\text{argmin}(C(I,V,\mathscr{T}))$ that minimizes the cost function. Here, we propose to replace a purely intensity-based similarity measure S_{sim} in Eq. (1) with a new hybrid measure that captures the contrast of histological image intensities $I(x,y)$ across the boundary of the inner or pial cortical surface:

$$H_{w,g}=\iint_{\Omega\mapsto\Psi}\frac{\left\langle\nabla I(\vec{x}),\nabla\phi_{w,g}(\vec{x})\right\rangle}{\frac{1}{9}\sum_{\vec{x}_i\in\bar{N}_8(\vec{x})}I(\vec{x}_i)}\,\hat{\delta}(\phi_{w,g}(\vec{x}))\,d\vec{x}, \qquad (2)$$

where angle brackets denote the inner product between the intensity gradient vector ∇I and the gradient of the level set function $\nabla\phi$, $\bar{N}_8$ is the closed 8-neighborhood of a 2D-point $\vec{x}\in\Omega$. The integration is carried out over the histological image domain Ω, and implies that the one-to-one mapping $\mathscr{T}:\Omega\mapsto\Psi$ supplied by the registration' geometric transformation is used where needed (e.g. in $\phi_{w,g}(\vec{x})$). The integration uses a smeared-out approximation of a delta-function $\hat{\delta}(\phi)$ (see [13]) defined as follows:

$$\hat{\delta}(\phi)=\begin{cases}0 & \phi<-\varepsilon,\\ \frac{1}{2\varepsilon}\left(1+cos\left(\frac{\pi\phi}{\varepsilon}\right)\right) & -\varepsilon\le\phi\le\varepsilon,\\ 0 & \varepsilon<\phi,\end{cases} \qquad (3)$$

where the parameter ε determines the size of the bandwidth of numerical smearing. The hybrid measure defined in Eq. (2) represents a contour integral, written in level set representation [13], of the histological slice intensity gradient component that is normal to the cortical boundary in the slice. The sign and magnitude of this component reflect the intensity contrast across the boundary. For example, if gray matter (GM) has brighter intensities than white matter (WM), the component (for the inner cortical boundary) will have a positive sign and larger values if the cortical ribbon is well registered between the two modalities. In the integral, the normal component of the intensity gradient is weighted by the average intensity in the neighborhood in order to normalize the intensity contrast and account for local variations of intensity for a particular tissue class. The tunable parameter ε influences the capture range of the hybrid measure, and should not exceed the width of the narrow band that was used in a level set model in cortical reconstruction (see [10],[11]); we set $\varepsilon=3$ voxels in our experiments. Finally, with the new similarity measure, the hybrid boundary-based cost function is defined as:

$$C_{BB}=-\alpha_w H_w(I,\Phi_w,\mathscr{T})-\alpha_g H_g(I,\Phi_g,\mathscr{T})+\beta E(\mathscr{T}(\Omega)), \qquad (4)$$

where α_w and α_g are user-defined weights setting the relative importance of the contrast across the inner and pial cortical surface, respectively. In addition, the sign of a weight $\alpha_{w,g}$ accommodates the direction of the contrast in a particular histological modality; for example, for a histological image with GM brighter than WM and brighter than background, $\alpha_w\ge 0$ and $\alpha_g\le 0$ should be used (e.g., $\alpha_w=1,\alpha_g=-1$).

B. 2D-to-3D warping transformation based on thin-plate splines

Thin-plate splines (TPS) [14] interpolation function $T(x,y,\theta)$ is defined as an affine term and a superposition of radial basis functions (RBF):

$$T(x,y,\theta) = a_0 + a_1 x + a_2 y + \sum_{(x_i,y_i)\in\theta} w_i U(||(x_i,y_i)-(x,y)||) \quad (5)$$

where $\{a_0,a_1,a_2\}$ are affine coefficients, $\{w_i\}$ are RBF weights, and $U(r) = r^2 \log r$ are RBFs originating at control points $\theta = \{(x_i,y_i)\}$ (see [14]). Given a set of interpolation conditions $T(x_i,y_i) = t_i\{(x_i,y_i) \in \theta\}$, there exists a closed form solution for TPS coefficients [15]. TPS minimizes the bending energy:

$$E_T = \iint_{\mathbf{R}^2} (T_{xx}^2 + 2T_{xy}^2 + T_{yy}^2) dxdy. \quad (6)$$

TPS are typically used in a 2D nonrigid registration based on point-landmark matching [6], [16]: point-landmarks in a target image serve as control points, and matched landmarks in a source image define displacements (u,v) of a 2D warp, which is modeled by two independent TPS functions. Our slice-to-volume registration does not use landmarks. Instead, TPS are used in a novel way to parametrize a smooth 3D deformation of a 2D surface: control points are placed in a regular grid on the 2D image domain Ω, and a 3D warp is modeled by three independent TPS functions $u(x,y,\theta)$, $v(x,y,\theta)$, and $w(x,y,\theta)$: $\mathcal{T}_{warp} : (x,y) \mapsto (x+u, y+v, w)$. The displacements (u_i,v_i,w_i) at the control points serve as degrees of freedom (DOF) and thus "steer" the deformation; TPS coefficients are computed from these displacements. The smoothness energy of the deformation field is the sum of three individual TPS bending energies $E_{\mathcal{T}} = E_u + E_v + E_w$. For slice-to-volume registration, the warping transformation $\mathcal{T}_{warp}$ is combined with a 3D alignment $\mathcal{T}_{align}$ in the form of a rigid (6 DOFs: rotation, translation) or a Procrustes (9 DOFs: rotation, translation, scaling) transformation.

III. EXPERIMENTAL RESULTS

High-resolution MR images of an isolated left brain hemisphere fixated in formalin were acquired post mortem (3T T_1 3D-MDEFT FOV 96x192x128 mm, 256x512x512 voxel 0.375x0.375x0.25 mm, scanning time 12 h). The contrast of the MR images is inverted due to fixation in formalin (see MR slice in Fig. 1). After MRI scanning, coronal sections were cut from brain sample at 1.5 cm spacing. Slices were myelin-stained and scanned on a flat-bed scanner at 2000 dpi. The MR image was preprocessed to correct for intensity inhomogeneities, and converted to an isotropic resolution of 0.35 mm. Histological images were converted to an 8-bit gray-scale intensity range (Fig. 2), and re-sampled to match the spatial resolution of the MRI data; the bright background was suppressed by thresholding. The registration algorithm was applied to coronal histological slices from three distinct blocks of the brain sample (#1: in the prefrontal, #2: in the central, and #3: in the occipital region of the left hemisphere). The cost function was minimized by the NEWUOA algorithm [17]. For nonrigid registrations, $\beta = 0.1$ has been chosen (see [8]). Rigid registration runs in less than one minute for both CC-based and hybrid cost function. Nonrigid boundary-based registration currently takes between 0.5-1.2 hours on a 2.4 GHz Athlon CPU, depending on the number of control points.

Registration	#1 (%)	#2 (%)	#3 (%)
CC rigid	78.69	79.97	70.24
BB rigid	82.34	80.19	73.08
BB TPS ($\alpha_w = 1, \alpha_g = 0$)	81.83	84.00	75.73
BB TPS ($\alpha_w = 0, \alpha_g = -1$)	82.49	86.43	77.05
BB TPS ($\alpha_w = 1, \alpha_g = -0.5$)	83.68	88.13	78.98
BB TPS ($\alpha_w = 0.5, \alpha_g = -1$)	83.83	86.20	79.32

TABLE I

REGISTRATION RESULTS: % OVERLAP OF THE CORTICAL RIBBON PIXELS IN REGISTERED IMAGES (CC - CORRELATION COEFFICIENT INTENSITY-BASED COST FUNCTION; BB - BOUNDARY-BASED HYBRID COST FUNCTION)

Table I shows quantitative evaluation of the quality of registration results measured by the percentage of pixels in the registered cortical ribbon that have bright intensity ($I > 150$) in histology, and thus can be also classified as GM in histology, and can be counted as a match in both modalities. Results demonstrate that the boundary-based nonrigid registration consistently yields a 5-10% improvement in the overlap of the cortical ribbon compared to the intensity-based approach. Figure 2 shows contours of the cortical boundary in a registered slice overlaid on a histological image. From intensity-based registration (red contours) to boundary-based rigid and nonrigid registration (green and yellow contours), gradual improvement of a contour placement is noticeable in multiple areas of a slice (indicated by red arrows).

IV. CONCLUSION AND FUTURE WORK

The proposed algorithm has the following advantages: (i) It uses a novel hybrid intensity- and boundary-based cost function, which reflects the contrast of image slice intensities across the cortical surface boundary, and improves the registration of the cortex. (ii) It allows registration of individual, sparsely spaced histological sections. (iii) It models non-planar cross-sections by a smooth surface warped in three-dimensional space, and extends existing techniques of landmark-based TPS 2D warping to landmark-free 3D warping of a slice. (iv) It combines 3D alignment and warping in one optimization stage. The algorithm extends the existing boundary-based registration approach, which is based on a surface mesh model, to implicit representation of cortical surfaces, and efficiently computes the cost function in a level set framework. The cost function is applicable to all choices of histological staining that provide the WM/GM contrast.

Histological examination still remains the gold standard for a precise characterization of the anatomy and pathology of neural tissue. MR image contrast has a complex origin that makes exact relationships between MRI and histology

unclear; correlates of MRI findings with histology have to be studied and validated. Accurate registration of high-resolution MRI to cortical histology is essential for a quantitative comparison of trans-cortical intensity profiles. The described method has useful potential for various applications in mapping of brain histology to 3D imaging, for example, in building multi-modal 2D-3D atlases of rodent and human brains, and in comparison of histology with MRI for a better characterization of MRI-detectable or MRI-invisible pathological features. The algorithm is not limited to slice registration, but is generally applicable to rigid/nonrigid boundary-based registration of partial-brain images.

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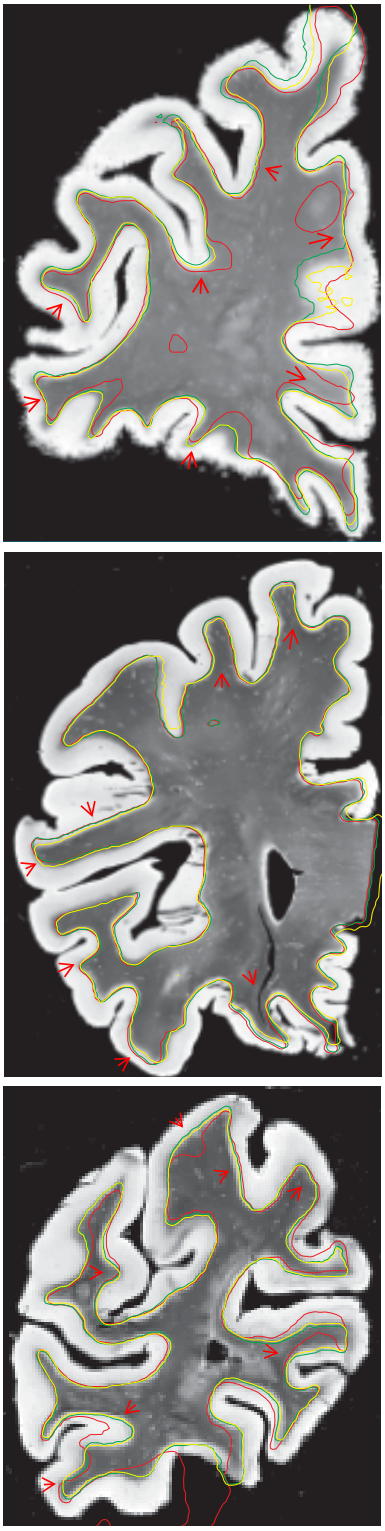

Fig. 2. Histological images (gray-scale) overlaid with contours of the inner cortical boundary from a registered MR slice (red contour: by CC rigid registration; green contour: by BB rigid registration; yellow contour: by BB nonrigid TPS registration; red arrows indicate an improvement of a contour placement; weights $\alpha_w = 1$, $\alpha_g = 0$, and $\beta = 0.1$ were used)