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Correcting spatial distortion in histological images

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Abstract

We described an interactive method for correcting spatial distortion in histology samples, applied them to a large set of image data, and quantitatively evaluated the quality of the corrections. We demonstrated registration of histology samples to photographs of macroscopic tissue samples and to MR images. We first described methods for obtaining corresponding fiducial and anatomical points, including a new technique for determining boundary correspondence points. We then describe experimental methods for tissue preparation, including a technique for adding color-coded internal and boundary ink marks that are used to validate the method by measuring the registration error.

We applied four different transformations with internal and boundary correspondence points, and measured the distance error between other internal ink fiducials. A large number of boundary points, typically 20–30, and at least two internal points were required for accurate warping registration. Interior errors with the transformation methods were ordered: thin plate spline (TPS) ≈ non-warping ≪ triangle warping < polynomial warping. Although non-warping surprisingly gave the lowest interior distance error (0.5 ± 0.3 mm), TPS was more robust, gave an insignificantly greater error (0.6 ± 0.3 mm) and much better results near boundaries where distortion was more evident, and allowed us to correct torn histology samples, a common problem. Using the method to evaluate RF thermal ablation, we found good zonal correlation between MR images and corrected histology samples. The method can be practically applied to this and other emerging applications such as in vivo molecular imaging.

Keywords: Medical image processing; Image registration; Tissue typing; Interventional magnetic resonance imaging; Thermal ablation; Histology

1. Introduction

We are developing methods to enable the comparison of medical image data to corresponding histological data [1,2]. This paper describes a critical aspect: the correction of distortion caused by histological processing. There are many instances where one wants to relate medical image data to the cellular response, as determined from histological samples, and we will describe some examples from our institution. First, there is much experience in radiofrequency (RF) ablation of tissue, typically cancerous tumors, under interventional magnetic resonance imaging (iMRI) guidance [3–7]. With regard to RF ablation, magnetic resonance imaging (MRI) can intermittently acquire temperature images during heating and structural lesion images during and after heating. Our goal is to quantitatively relate MR image measurements to tissue damage as seen histologically [1]. Second, we are attempting to correlate single positron emission computed tomography (SPECT) images using a monoclonal antibody imaging agent with tumor in the prostate by correlating the medical images with histology [8]. Third, we are using medical images to characterize in vivo drug release from a new device for localized, controlled drug release [9]. Future experiments in drug response will require histological correlation. There are many other potential applications. Notably, as medical imaging techniques are used to study in vivo molecular biology using new agents [10,11], histological validation will be critical.

As an example application, we will review the application where MR images of thermal ablation are compared to tissue response [4,5,12–15]. Only one report uses registration, and it is a two-dimensional (2D) method [14]. Others simply measure thermal lesion diameters or

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lengths in 2D MR and tissue images [4,5,12,15]. Such methods are limited by ones ability to accurately determine corresponding image slices and by the applicability of simple length measures to capture what might be a complicated three-dimensional (3D) geometry, especially in the event of multiple ablation sites. Recognizing these limitations, we are developing a 3D method consisting of a 3D rigid body registration of MR to macroscopic tissue photographs using needle fiducials followed by a 2D warp of histological sections to the macroscopic tissue photographs to correct deformation that occurs during tissue processing [1,2]. This method allows us to compare MR thermal ablation images to the corresponding histology, and hence compare MR measurements to cell death and damage. Correction of spatial distortion in histological processing is a critical step in this process.

There are methods in the literature that attempt to correct spatial distortion found in histology images. A multi-resolution, mutual information approach with thin plate spline (TPS) warping was used by Likar and Pernus [16] to align pairs of high magnification histology slides having different stains in order to classify skeletal muscle fibers. Another mutual information-based approach with TPS warp was used for correcting spatial distortions in rat brain autoradiographs [17]. This technique corrected autoradiographs to the corresponding block face image obtained during cryosectioning. Locations of six control point pairs in the 2D images were optimized for a mutual information similarity measure, and the final control point locations were used for a TPS warp. Jacobs et al. [18] used a surface-based, 'head in hat,' 3D method to register rat brain histology and MR images. To correct for spatial distortion in the histological images, they warped 2D MR images to the histological samples. Radial correspondence from a center of mass was assumed to obtain corresponding points for the TPS transformation. As part of the human brain-mapping project, cellular histology data from human brains have been mapped to medical images. As reviewed by Toga et al. [19], histology images were warped to match 2D block face images from cryosectioned brain volumes, which in turn were matched to medical images and/or atlases. Several warping methods have been applied including elastic surface and viscous fluid-based deformations [20]. Others have applied similar methods for brain mapping [21,22].

Although the above methods would probably work for some of our data, we desired a more flexible approach suitable for a wide variety of tissues, spatial distortions, missing image data due to tissue tearing, and a variety of image pairs, including MR to histology. Some methods use relatively few control points, and we require many, especially at edges, in order to correct the spatial distortions found there. This is particularly an issue because thermal ablations are often applied near the surface of an organ. Although radial correspondence is reasonable to apply in the brain, it is not generally applicable. Gray-scale matching methods such as mutual information require at least somewhat similar features, and the brain data used by many have an abundance of such features. MR images, especially those of rabbit thigh muscle, have very few features suitable for matching to histology, and the most prominent feature in histology, the edges, often do not exist in the MR image counterparts. Moreover, our goal is to determine if lesions seen in MR match those in histology. A method that warps an image to match the lesion would invalidate the experiment. Finally, we often find histology samples with missing sections due to tearing, probably because ablations can change the consistency of the tissue sample and a histology section of a tissue such as muscle can contain anatomical boundaries that separate during processing. For these and other reasons, we developed a new 2D method, which can be used interactively in a wide variety of preparations.

Relatively little validation work has been done to show that histological images are correctly transformed. Visual methods such as contour overlays and difference images are most often employed [16,19,21,22]. Image gray level measures such as mutual information can be examined [17]. Jacobs et al. [18] show that stroke lesion areas from MR and histology correlate better with warping than without warping. In those cases where point anatomical landmarks are visible in both image pairs, one could estimate error, but this has not been widely reported.

In this paper, we describe interactive methods for correcting spatial distortion in histology samples, apply them to a large set of image data, and quantitatively evaluate the quality of the corrections. We first describe methods for obtaining correspondence points, including a new technique for determining boundary correspondence points. Four different warping transformations are described. We then describe experimental methods for tissue preparation, including a technique for adding color-coded internal and boundary ink marks that are used to validate the method by measuring the transformation error. In Section 4, from a variety of experiments including ones with practical problems like incomplete boundaries and torn tissue sections, we determine the best algorithm and its accuracy. Finally, we apply the method to an example RF thermal ablation experiment.

2. Warping registration method

We now give a brief overview of our method for transforming a spatially distorted, 2D histology image to spatially match a reference image. Most often, the reference image is a photograph of a macroscopic tissue image prior to histological preparation, but it can also be a 2D MR or computed tomography (CT) image. The method works by matching corresponding points between the two images as obtained from manual entry or automatic processing of the border. Given a set of corresponding points, we then apply one of a variety of transformation methods to match