Medical Image Analysis 38 (2017) 184–204

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

Transformation diffusion reconstruction of three-dimensional histology volumes from two-dimensional image stacks

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ARTICLE INFO

Article history:
Received 13 July 2016
Revised 15 March 2017
Accepted 21 March 2017
Available online 23 March 2017

Keywords:
Diffusion equation
Translation
Similarity
Affine
B-spline transformation
Histology reconstruction
Blockface

ABSTRACT

Traditional histology is the gold standard for tissue studies, but it is intrinsically reliant on two-dimensional (2D) images. Study of volumetric tissue samples such as whole hearts produces a stack of misaligned and distorted 2D images that need to be reconstructed to recover a congruent volume with the original sample's shape. In this paper, we develop a mathematical framework called Transformation Diffusion (TD) for stack alignment refinement as a solution to the heat diffusion equation. This general framework does not require contour segmentation, is independent of the registration method used, and is trivially parallelizable. After the first stack sweep, we also replace registration operations by operations in the space of transformations, several orders of magnitude faster and less memory-consuming. Implementing TD with operations in the space of transformations produces our Transformation Diffusion Reconstruction (TDR) algorithm, applicable to general transformations that are closed under inversion and composition. In particular, we provide formulas for translation and affine transformations. We also propose an Approximated TDR (ATDR) algorithm that extends the same principles to tensor-product B-spline transformations. Using TDR and ATDR, we reconstruct a full mouse heart at pixel size 0.92 µm × 0.92 µm, cut 10 µm thick, spaced 20 µm (84G). Our algorithms employ only local information from transformations between neighboring slices, but the TD framework allows theoretical analysis of the refinement as applying a global Gaussian low-pass filter to the unknown stack misalignments. We also show that reconstruction without an external reference produces large shape artifacts in a cardiac specimen while still optimizing slice-to-slice alignment. To overcome this problem, we use a pre-cutting blockface imaging process previously developed by our group that takes advantage of Brewster's angle and a polarizer to capture the outline of only the topmost layer of wax in the block containing embedded tissue for histological sectioning.

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1. Introduction

Traditional histology, the study of tissue microarchitecture, originated in the 17th c. with first applications of microscopy to animal-derived samples by Marcello Malpighi. It has become the gold standard for structural description of cells and tissue, serving important functions in clinical diagnosis of pathologies. Traditional histology produces two-dimensional (2D) images, resolving cellular and sub-cellular detail in slices that typically are several micrometers thick. A wide variety of chromatic stains, developed since the 18th c., enable cell labeling (e.g. Masson's Trichrome or Picro Sirius Red dyes label myocytes, collagen and endothelial cells). Although most clinical tissue samples are small, typically from biopsies, interest in imaging whole organs has grown over the last decade, in organs such as brain (Amunts and Zilles, 2015; Annese, 2012), heart (Burton et al., 2006; Magee et al., 2015; Mansoori et al., 2007) or lung (Rusu et al., 2015), for instance to inform computational models that aim to simulate brain function, cardiac contraction or respiration, to guide studies relating structure to function,

Abbreviations: ATDR, Approximated Transformation Diffusion Reconstruction; FTCS, Forward-Time Central-Space; TD, Transformation Diffusion; TDR, Transformation Diffusion Reconstruction.

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http://dx.doi.org/10.1016/j.media.2017.03.004
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or to serve as a reference for lower resolution non-invasive imaging modalities such as Magnetic Resonance Imaging (Amunts et al., 2013; Plank et al., 2009; Rusu et al., 2015).

One of the main limitations of traditional histology is the fact that the acquired 2D images cannot be directly stacked to reconstruct a consistent 3D volume with the original sample shape due to a series of tissue transformations. Cardiac tissue, for example, swells by >20% during the first half-hour of ex-vivo saline perfusion (Bub et al., 2010). Histological processing for wax-embedding reduces tissue volume by 48% compared to ex vivo MRI (Burton et al., 2014), and produces non-affine deformations. Cutting of wax-embedded tissue inherently destroys the rigid alignment between 2D slices. In addition, histology stacks tend to contain large amounts of data (e.g. a rat heart, sliced at 10 µm, produces roughly 1000 slices, which, if imaged at a resolution of 0.46 µm × 0.46 µm, require ∼1 TB hard drive space (Burton et al., 2006)). The process of recovering the sample's original 3D shape, generally referred to as *3D histology reconstruction* or *congruencing*, has received a fair amount of attention in the field since Wilhelm His' studies of human embryos in 1880, with significant mathematical and computing improvements in the last decades.

Reconstruction of histology sections typically starts with a rough rigid pre-alignment, either registering slices to an external reference (histology-reference pre-alignment) or to each other within the stack (intra-histology pre-alignment). Pre-alignment produces jagged slice-to-slice transitions, so it is followed by finer histology registration (intra-histology refinement). Coarseness of alignment and refinement is given by the degrees of freedom of the transformation used by the registration method, e.g. rigid (Ourselin et al., 2001; Rusu et al., 2015), affine (Adler et al., 2014, 2012; Xu et al., 2015), 1D piecewise linear (Ju et al., 2006), elastic spring triangular mesh (Guest and Baldock, 1995; Saalfeld et al., 2012), Discrete Smooth Interpolation (Machin and Sperber, 1996), displacement field (Burton et al., 2006; Gaffling et al., 2015; Mansoori et al., 2007; Schmitt et al., 2006; Wirtz et al., 2004), curvature flow (Cifor et al., 2011, 2009), symmetric normalization (SyN) diffeomorphism (Adler et al., 2012), diffeomorphic inverse consistent algorithm (Yushkevich et al., 2006), large deformation diffeomorphic metric mapping (LDDMM) (Ceritoglu et al., 2010), or tensor-product B-spline (Arganda-Carreras et al., 2010; Feuerstein et al., 2011; Gaffling et al., 2015; Magee et al., 2015; Müller et al., 2014; Roberts et al., 2012; Schubert et al., 2016; Song et al., 2013).

Algorithms that reconstruct the stack without an external reference of the pre-cut sample shape abound in the literature (Cifor et al., 2011; Fónyad et al., 2015; Gaffling et al., 2015; Guest and Baldock, 1995; Ju et al., 2006; Müller et al., 2014; Roberts et al., 2012; Saalfeld et al., 2012; Song et al., 2013; Wirtz et al., 2004; Xu et al., 2015) and are featured in software applications such as Voloom (microDimensions GmbH), BioVis3D, or 3DView (3DHISTECH Ltd.). Such reference-free approaches have long been known to be susceptible to a series of geometric artifacts. These include: "the straightening of curvatures (reconstructing a cucumber from a banana), false z-axis orientation (setting the tower of Pisa upright), or the conversion of asymmetric shapes into symmetric ones (reconstructing the bill of a raven into the bill of a woodpecker)" (Streicher et al., 1997). This set of geometric artifacts is informally known in the literature as the straight banana problem. In Section 2.3.1 we formalize this concept as the "maximum alignment" solution, and discuss its differences with the desired "true shape" solution. Other reference-free artifacts are wobbly boundaries (Ju et al., 2006) and drift or z-shift effect caused by the accumulation of correlated registration errors (Casero et al., 2016; Feuerstein et al., 2011; Yushkevich et al., 2006) (see example in Section 3.2.1). Nonetheless, reference-free reconstruction may be of interest if an external reference is simply not available, if faithful reconstruction of the shape is not crucial, or if maximum alignment coincides with the true shape, as it is the case for small rectangular or cylindrical samples with structures normal to the cutting plane. This is not the case for large cardiac samples, though, as preserving epicardial and endocardial shapes and complex structures such as locally-defined cleavage planes between myocardial layers, vasculature and trabeculae is necessary for computational modeling. Therefore, to avoid those artifacts our workflow includes an external reference, although the reconstruction algorithms we propose can be used with or without one.

Examples of external references in the literature are tissue markers (Ourselin et al., 2001; Streicher et al., 2000), drill holes (Streicher et al., 1997), template or atlas (Ali and Cohen, 1998; He et al., 1995; Ju et al., 2006; Timsari et al., 1999), structural probability map (Müller et al., 2014), MRI (Adler et al., 2014, 2012; Ceritoglu et al., 2010; Gibb et al., 2012; Gilbert et al., 2012; Malandain et al., 2004; Mansoori et al., 2007; Ourselin et al., 2001; Rusu et al., 2015; Schormann et al., 1995; Thompson and Toga, 1996), CT (Atkinson, 2014), micro-CT (Khimchenko et al., 2016) or 2D images of the tissue surface at the cut side of the embedded tissue, a.k.a. *blockface images* (Bardinet et al., 2002; Gefen et al., 2003; Kim et al., 1997; Mega et al., 1997; Ourselin et al., 2001; Schubert et al., 2016; Siedlecka et al., 2013a, 2013b; Toga et al., 1994). Taking a different approach, (Xu et al., 2015) use bisected nuclei in liver histology as natural fiducial markers to avoid geometric artifacts without an external reference. This requires a sufficiently uniform distribution of bisected nuclei, which is not guaranteed for cardiac tissue, in particular in areas where myocytes run orthogonal to the cutting plane. Also, nuclei visualization limits the number of dyes that can be used. Our external reference is a novel type of blockface image developed by our group (Casero et al., 2016; Gruscheski et al., 2015; Siedlecka et al., 2013a, 2013b). Our method takes advantage of light polarization when illuminating the wax top surface at Brewster's angle to produce a sharp near-binary 'negative' image of the regions where tissue protrudes. Unlike 3D images obtained prior to histological processing, such as CT or MRI, blockface images are acquired directly at the microtome and do not involve an ill-posed 2D→3D alignment problem caused by different slicing angle between histology and the 3D image, as well as 3D tissue deformations out of the slice plane, as seen in previous work by our group (Gibb et al., 2012; Mansoori et al., 2007). Furthermore, the 2D→2D alignment problem is trivially parallelizable. In common with the majority of the literature, we only use the blockface images to pre-align the histology stack. Alternatively, (Adler et al., 2014, 2012; Feuerstein et al., 2011; Mansoori et al., 2007) use the external reference during refinement. In this case, the external reference can be seen as a regularization term that also introduces registration noise, caused by its lower resolution and imaging artifacts, and interferes with the delicate local transformations necessary to align small structures. Another alternative is to first refine the histology stack and then register to an external MRI reference solving a 3D→3D alignment problem (Ceritoglu et al., 2010; Malandain et al., 2004). For the blockface external reference, this approach would need to be adapted as a regularized 2D→2D alignment to take advantage of the blockface-histology slice-by-slice correspondence, and is beyond the scope of this work.

Apart from the type of registration method and the use of an external reference, another main feature of reconstruction methods is how they sweep the stack of N histology slices $I_0, \ldots, I_{N-1}$. The prevalent approaches in the literature are sequential algorithms that register one slice at a time towards one or more neighbors, applying the resulting transformation straight away. Any slice can be used as the initial one, but to simplify the notation, let's assume that the sweep starts at I_0. Algorithms that register each slice I_i to a unilateral radius-d neighborhood $I_{i-d}, \ldots, I_{i-1}$ need only one

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