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Mid-space-independent deformable image registration

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ABSTRACT

Aligning images in a mid-space is a common approach to ensuring that deformable image registration is symmetric – that it does not depend on the arbitrary ordering of the input images. The results are, however, generally dependent on the mathematical definition of the mid-space. In particular, the set of possible solutions is typically restricted by the constraints that are enforced on the transformations to prevent the mid-space from drifting too far from the native image spaces. The use of an implicit atlas has been proposed as an approach to mid-space image registration. In this work, we show that when the atlas is aligned to each image in the native image space, the data term of implicit-atlas-based deformable registration is inherently independent of the mid-space. In addition, we show that the regularization term can be reformulated independently of the mid-space as well. We derive a new symmetric cost function that only depends on the transformation morphing the images to each other, rather than to the atlas. This eliminates the need for anti-drift constraints, thereby expanding the space of allowable deformations. We provide an implementation scheme for the proposed framework, and validate it through diffeomorphic registration experiments on brain magnetic resonance images.

Introduction

The computation of a set of dense spatial correspondences among images – a.k.a. image registration – is a central step in most population and longitudinal imaging studies. Linear transformation is often not sufficient to account for cross-subject anatomical variation or temporal changes in an individual anatomy, thereby making deformable image registration (Sotiras et al., 2013) a necessary part of most analysis pipelines. The importance of registration accuracy in neuroimaging is evident from the literature; for instance, inaccurate alignment has been shown to lead to incorrect diagnosis (Reuter et al., 2014) and ineffective radiotherapy (Castadot et al., 2008) of tumors, and the inability to detect early effects of Alzheimer's disease (Cuingnet et al., 2011; Fischl et al., 2009).

In deformable registration, the choice of the reference space in which the images are compared affects the outcome, making the resulting deformation field dependent on this choice. Choosing the native space of one of the input images (say, the first image) as the reference breaks the symmetry of *pairwise* registration, meaning that reversing the order of the input images will produce different spatial correspondences. Such an inverse-inconsistency has been shown to be related to biased errors introduced into the estimation of Alzheimer's disease effects (Fox et al., 2011; Hua et al., 2011; Thompson and Holland, 2011; Yushkevich et al., 2010), daily dose computation (Yang et al., 2008) and auto re-contouring (Ye and Chen, 2009) in radiation therapy, the quantification of lesion evolution in multiple sclerosis (Cachier and Rey, 2000; Rey et al., 2002), and the measurement of longitudinal changes (Reuter et al., 2012). Local volume changes in the deformation field and discretization artifacts are two major contributors to registration asymmetry. Pairwise registration has been proposed to be symmetrized by minimizing the average of two cost functions, each using one input image as the reference space (Cachier and Rey, 2000; Christensen and Johnson, 2001; Tagare et al., 2009; Trouvé and Younes, 2000), which unfortunately results in the non-uniform inte-

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gration of the image mismatch measure in the native spaces of the input images (Aganj et al., 2015b).

In a different approach to achieve symmetry in pairwise registration, both images are deformed and compared in an abstract reference space chosen to be "in between" the native spaces of the images, known as the *mid-space* (Ashburner and Ridgway, 2013; Avants and Gee, 2004; Beg and Khan, 2007; Chen and Ye, 2010; Joshi et al., 2004; Lorenzen et al., 2004; Lorenzen et al., 2006; Lorenzi et al., 2013; Noblet et al., 2008, 2012; Škrinjar et al., 2008; Yang et al., 2008; Ye and Chen, 2009). Since both images are treated equally, mid-space registration is invariant with respect to the ordering of the images. Such approaches essentially minimize their cost functions with respect to *two* transformations that take the two input images to the mid-space. However, without additional constraints, this increases the degrees of freedom of the problem twofold, compared to the end result of pairwise registration that is the *one* transformation taking one input image to the other. Furthermore, if the images are compared in the mid-space, the optimization algorithm is given the liberty to update the mid-space so as to decrease the cost function without necessarily changing the resulting image-to-image transformation. For example, the algorithm can shrink the regions with mismatching image intensities to make the deformed images look more similar in the mid-space, without necessarily making them more similar in their native spaces. To alleviate these issues, additional constraints are used to prevent the mid-space from drifting away from the native spaces of the two images. These *anti-drift* constraints, which are different from those regularizing the transformations, define the mid-space. They typically either restrict the space of possible pair of transformations (resulting in fewer degrees of freedom), or penalize those values of the two transformations that move the mid-space away from the native spaces. The most common such constraints, proposed in the mid-space registration and atlas construction literature, are restrictions on the two transformations to have opposite displacement fields (Aljabar et al., 2008; Bhatia et al., 2004; Bouix et al., 2010; Fonov et al., 2011; Guimond et al., 2000; Miller et al., 1997; Noblet et al., 2012; Studholme and Cardenas, 2004; Yang et al., 2008) or velocity fields (Ashburner and Ridgway, 2013; Grenander and Miller, 1998; Lorenzi et al., 2013). In large deformation models, geodesic averaging of the deformations has also been proposed, which preserves the desired properties of the transformations (Avants and Gee, 2004; Joshi et al., 2004; Lorenzen et al., 2006). The anti-drift constraints, however, can have the side effect of restricting the final image-to-image transformation, thereby causing the exclusion of some legitimate results (see the section "*Mid-space based registration*" for examples). Furthermore, the choice of these constraints may affect the results by biasing the registration algorithm towards favoring a particular set of transformations.

Unbiased *atlas* construction techniques can constitute mid-space registration, as the images are deformed to the atlas space (Ashburner and Ridgway, 2013; Hart et al., 2009; Joshi et al., 2004). In an atlas construction approach to image registration, the desired output is the deformation field, but not the auxiliary atlas. Consequently, one can analytically solve for the atlas in the cost function, leading to an implicit-atlas cost function that is minimized with respect to the image-to-atlas transformations. To that end, it was initially proposed to compare the deformed images to the atlas in the mid-space (Geng et al., 2009; Joshi et al., 2004). A better-justified generative model, however, progresses from the atlas to the images and compares the deformed atlas to the images in the native image spaces (Allassonnière et al., 2007; Ma et al., 2008; Sabuncu et al., 2009). Taking advantage of this native-space atlas construction resolves the issue of susceptibility to shrinkage-type problems, leading to a proper implicit-atlas cost function for mid-space registration (Ashburner and Ridgway, 2013). Nevertheless, the registration still remains a function of *two* transformations taking the images to a mathematically defined mid-space.

In this work, we derive the key fact that implicit-atlas registration has a data term that is inherently independent of the mid-space, and only depends on the overall image-to-image transformation. This implies that the individual image-to-atlas transformations are redundant and unnecessary to keep, and that anti-drift constraints are indeed not needed. We also show how to analytically solve the common Tikhonov regularization terms with respect to one of the image-to-atlas transformations. These lead us to a new cost function that, in contrast to the existing mid-space approaches, can be minimized directly with respect to the image-to-image transformation, with no anti-drift constraints. The proposed cost function is general and can be used with any deformation field parameterization, such as the displacement and the velocity fields.

This article extends our preliminary conference version (Aganj et al., 2015a). In particular, we propose a new regularization term in addition to the data term (Section "*Methods*"), evaluate our method more comprehensively on 3D brain magnetic resonance images (Section "*Results and discussion*"), propose the extension of our framework to group-wise deformable registration (Appendix A), and provide further details on the derivations and the implementation of the method (Appendix B and Appendix C).

Methods

Mid-space based registration

We begin with a brief overview of mid-space based pairwise deformable registration. An extension of our framework to group-wise registration is suggested in Appendix A. Let $I_1, I_2 : \Omega \to \mathbb{R}$ be the two d-dimensional input images to be registered, where $\Omega \subseteq \mathbb{R}^d$.[1] The goal of pairwise deformable registration is to compute the regular transformation $T: \Omega \to \Omega$ that makes overlapping regions of I_1 and $I_2 \circ T$ locally correspond to each other; a task that is often accomplished by minimizing a cost function with respect to T. In one popular approach, the image-to-image transformation T is parameterized as $T = T_2 \circ T_1^{-1}$, where T_1 and T_2 deform I_1 and I_2 to a *mid-space* (see Section "*Introduction*" for references). The deformed images may be compared in the mid-space by minimizing a data term such as the common sum of squared differences (SSD) term, $\int_\Omega ((I_1 \circ T_1)(y) - (I_2 \circ T_2)(y))^2 dy$ (Geng et al., 2009; Joshi et al., 2004).[2] The mid-space data term is by definition invariant with respect to the ordering of the images; i.e., swapping I_1 and I_2 will swap T_1 and T_2 in the produced set of transformations.

With no additional constraints, the dimensionality of the mid-space registration problem (solving for T_1 and T_2) is twice as large as the standard asymmetric problem (solving for T). Another drawback of this approach is that the mid-space can drift arbitrarily far away from the native spaces of the images due to large changes in T_1 and T_2, for instance through combination with a transformation S, as $T_1 \circ S$ and $T_2 \circ S$, which decreases the mid-space cost function without changing the final $T = (T_2 \circ S) \circ (T_1 \circ S)^{-1} = T_2 \circ S \circ S^{-1} \circ T_1^{-1} = T_2 \circ T_1^{-1}$. An example of this phenomenon is the situation where the optimization algorithm updates T_1 and T_2 in order to shrink the regions where the deformed images do not match, resulting in a decrease in the mid-space cost function, without necessarily changing the end result, T. To avoid this issue, additional constraints are often employed to keep the mid-space "close" to the native image spaces. Such constraints reduce the degrees of freedom and to some extent prevent the mid-space drift, however, at the expense of limiting our ability to model all possible transformations T. Examples of such anti-drift constraints and their limitations are as follows:

[1] Multi-spectral images, $I_1, I_2: \Omega \to \mathbb{R}^p$, $p > 1$, can also be similarly incorporated in this framework.

[2] Throughout this article, we use the vectors x, y, and z to denote the space of I_1, the mid-space, and the space of I_2, respectively.

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