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Editorial

Advances and challenges in deformable image registration: From image fusion to complex motion modelling

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ABSTRACT

Over the past 20 years, the field of medical image registration has significantly advanced from multi-modal image fusion to highly non-linear, deformable image registration for a wide range of medical applications and imaging modalities, involving the compensation and analysis of physiological organ motion or of tissue changes due to growth or disease patterns. While the original focus of image registration has predominantly been on correcting for rigid-body motion of brain image volumes acquired at different scanning sessions, often with different modalities, the advent of dedicated longitudinal and cross-sectional brain studies soon necessitated the development of more sophisticated methods that are able to detect and measure local structural or functional changes, or group differences. Moving outside of the brain, cine imaging and dynamic imaging required the development of deformable image registration to directly measure or compensate for local tissue motion. Since then, deformable image registration has become a general enabling technology. In this work we will present our own contributions to the state-of-the-art in deformable multi-modal fusion and complex motion modelling, and then discuss remaining challenges and provide future perspectives to the field.

1. Introduction

The first issue of *Medical Image Analysis* featured one of the landmark articles in multi-modal image fusion, which introduced mutual information as an information-theoretic similarity measure to be maximised in order to obtain geometric alignment of images acquired from different imaging modalities (Wells et al., 1996). Since then, over 160 articles whose title features the term *registration* have been published just in this journal alone, with many more articles using or building on image registration; at the time of writing, close to 280 articles contained *registration* within their title, abstract, or keyword. While image registration has become an automated tool for robust, automated brain registration, its use case has quickly expanded from rigid-body alignment of images taken from the same subject at roughly the same time point, to: alignment of serial imaging of the same subject to monitor changes due to disease progression such as dementia; matching of pre-operative to intra- or post-operative images; as well as to analyzing group differences across cohorts of patients and control subjects. Initially, this was limited to displaying localized differences in image overlays for visual inspection, but a whole range of locally affine or high-dimensional deformable image registration methods has been developed over the past two decades for recovering, quantifying and analyzing local motion and deformations. For conciseness, we refer the reader to an excellent recent review of deformable medical image registration (Sotiras et al., 2013) and the references therein.

In this paper, we will give an overview in Section 2 of our contributions to the field of deformable image registration, inspired by two mainstream approaches: *Demons* (Thirion, 1998) and Free-Form Deformations using B-splines (Rueckert et al., 1999), in the context of complex sliding organ motion modelling, as well as multi-modality and dynamic registration in oncological imaging. It is important to note though that while our main clinical driver is in cancer, our methods are more widely applicable. We then focus on remaining challenges and future perspectives to the field in Section 3, where we will discuss the continued importance of image registration in medical imaging, and its need to interact with image formation on the one hand, while on the other hand pushing forward the field of learning complex motion and extracting clinically meaningful imaging parameters for knowledge discovery.

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2. Advances

In 1998, Thirion's so-called *Demons* method (Thirion, 1998) was published in this journal as an extension to the optical flow method established in computer vision (Horn and Schunck, 1981). In brief, a dense deformation field is optimized using local image forces, alternated with Gaussian smoothing of the deformation field for regularization. The method has spawned a wealth of Demons-inspired methods that can enforce diffeomorphic mappings, with some extensions to multi-modal imaging. Over the past two decades, Demons have proved to be a very flexible and highly popular framework for performing local image alignment, due to their simple yet elegant mathematical formulation. However, Demons in their standard formulation are limited by the types of deformations that can be modelled. Data-driven, locally adaptive regularization methods have increasingly been developed to overcome some of these limitations, as we discuss in Section 2.1.

A second method that has arisen at around the same time as Demons is deformable registration based on Free-Form Deformations (FFDs) using B-splines, developed by Rueckert et al. (1999). The primary advantage of B-spline FFDs over Demons or related methods that operate on dense deformation fields, is their compact representation and intrinsic regularization. This method has become exceedingly popular, and has been expanded another decade later by Glocker et al. (2008) using a discrete optimization formulation based on Markov random fields (MRFs). We discuss in Section 2.2 how such a formulation for deformable registration can be further extended to model complex motion scenarios.

Another challenging aspect of deformable registration derives from its adaptation to multi-modal imaging. Global similarity measures such as mutual information and its normalized versions have been found to be very effective for rigid-body registration; however, for deformable registration, local updates of global measures or point-wise extensions are not as effective, as they can cause localized differences to disappear by collapsing the local deformation field, which in turn necessitates regularization to prevent such physically implausible deformations. Point-wise updates are known to be sensitive to image noise, a fact which has spawned the field of non-local or patch-based methods for more robust similarity calculations. In Section 2.3 we outline our work on deriving such a patch-based, modality-independent similarity measure.

Finally, motion correction of dynamic imaging, such as DCE-MRI, is mostly limited to applying a multi-modal, global similarity measure, with the work presented by Rueckert et al. (1999) being an early example. The key parameters of interest in DCE-MRI are related to the pharmacokinetic (PK) modeling, which help to gain insight into tissue perfusion characteristics. We discuss in Section 2.4 how such modeling can be used for driving the deformable registration process.

2.1. Complex motion modelling using Demons

The conventional *Demons* algorithm (Thirion, 1998) regularizes the estimated deformations using Gaussian smoothing, which does not accord well with the complex physiology present in e.g. the thoracic cage and abdomen. To address both the sliding motion occurring at the pleural cavity boundary and the smooth motion within the lungs, we have proposed a modified *Demons* method that uses bilateral filtering for regularization (Papież et al., 2014). To this end, a set of filter kernels is assembled based on the local position, intensity and deformation similarity. In contrast to our previous work on sliding motion modelling (Risser et al., 2013), this approach does not require explicit segmentation of sliding organ surfaces. The estimation of physiologically plausible transformations using our spatially adaptive regularization model, which naturally handles complex motions at sliding interfaces, was also demonstrated by local quantification of sliding motion (see Fig. 1). More recently, we have introduced a fast image-guided filtering procedure to further improve registration accuracy in dynamic lung and liver cancer imaging (Papież et al., 2015).

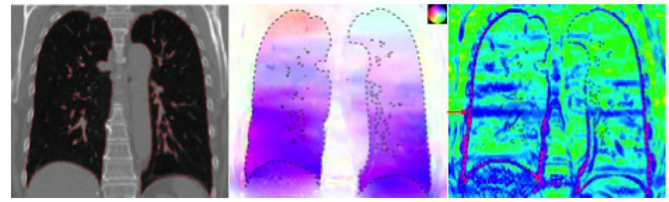

Fig. 1. Example of Demons registration using bilateral filtering for a CT lung data inhale/exhale pair. From left to right: coronal view of lung CT; colour-coded deformations; sliding motion quantification. The results demonstrate that our framework efficiently handles deformation discontinuities for estimation of complex motion. See Papież et al. (2014) for details.

2.2. Complex motion modelling using discrete optimization

The traditional B-spline FFDs method is subject to intrinsic smoothness properties which are undesirable if there are local motion discontinuities in the presence of sliding organs. This is further enhanced by its original continuous formulation, which was reformulated by Glocker et al. (2008) into a powerful discrete optimisation framework called *drop*. We have further enhanced this by introducing several new elements that allow for more complex motion modelling (Heinrich et al., 2016):

First, starting from a similar MRF-based approach as *drop*, we employ a dense displacement sampling technique (*deeds*) for potential displacements to replace the conventional continuous optimization and associated multiple iterative warps (Rueckert et al., 1999). This enables us to directly estimate discontinuous motion and avoid local minima. Second, we simplify the graphical model used by *drop* to a minimum-spanning-tree (MST), which removes the assumption of neighboring B-spline nodes undergoing similar motion, while acknowledging that discontinuities often coincide with intensity changes. Optimization using belief propagation for this MST not only improves the accuracy of the registration of thorax and abdomen, while significantly reducing the computational complexity, but also enables estimation of registration uncertainty for the displacements of every node. Third, we replaced the conventionally used uniform transformation grid with image-derived supervoxels (Heinrich et al., 2016). Using multiple layers of such sparse supervoxels, we are able to comprehensively and compactly model piece-wise smooth deformations while preserving the registration accuracy for small anatomical details. The global optimum can be estimated for each layer independently, while voxel-wise displacement vectors are obtained by combining the results of all layers on a local level.

Fig. 2 illustrates the performance of this combined approach to recover sliding lung motion. The obtained registration uncertainty was used in Heinrich et al. (2016) to enhance the accuracy of atlas-based segmentation (enabling a local fusion of segmentation labels from multiple probable transformations) and to visualise areas where the algorithm automatically detects potential registration errors (see Fig. 3).

2.3. Modality-independent deformable registration

In Heinrich et al. (2012) we developed the concept of modality-independent neighborhood descriptors (MIND) to overcome the limitations, noted above, of global image statistics, in particular for low initial overlap (as common in thoracic/abdominal scans) or when local intensities are unreliable (e.g. in ultrasound, or