



## 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.

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## 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 sub-

jects. 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.

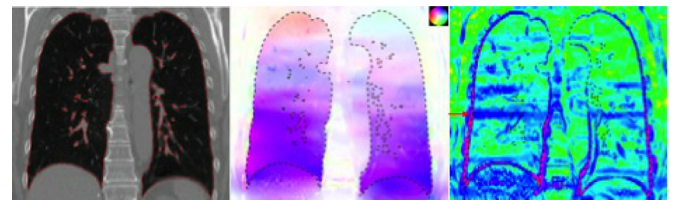
A second method that has arisen at around the same time as Demons is deformable registration based on Free-Form Deformations (FFDs) using B-splines, developed by Rueckert et al. (1999). The primary advantage of B-spline FFDs over Demons or related methods that operate on dense deformation fields, is 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



**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.

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).

### 2.2. Complex motion modelling using discrete optimization

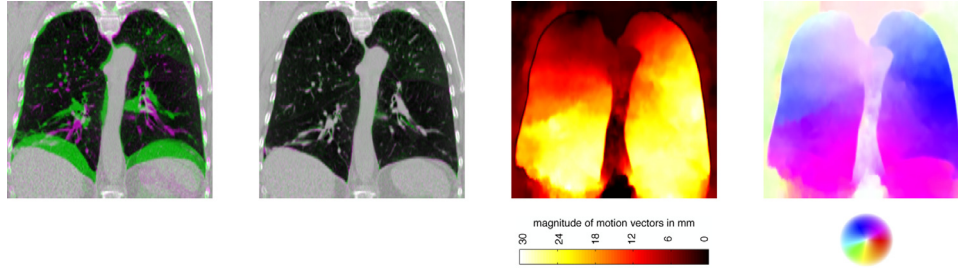
The traditional B-spline FFDs method is subject to intrinsic smoothness properties which are undesirable if there are local motion discontinuities in the presence of sliding organs. This is further enhanced by its original continuous formulation, which was reformulated by Glocker et al. (2008) into a 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



**Fig. 2.** Example deformable registration of an inhale-exhale lung CT scan pair. Overlay before/after registration in green (inhale phase) / magenta (exhale phase), motion magnitude in mm, colour-coded displacement field (using an HSV-colour representation for vector orientation) are shown for coronal planes. The displacement fields demonstrate that the sliding of the lungs is well preserved. See [Heinrich et al. \(2016\)](#) for details.



**Fig. 3.** From left to right: Exemplar coronal slice of target MRI scan; propagated segmentation labels from atlas scan; local certainty of label propagation See [Heinrich et al. \(2016\)](#) for details.

MRI with local bias fields), or otherwise insufficient for describing structural image content. MIND, which was inspired by [Buades et al. \(2005\)](#), is based on the observation that while intensities may not be directly comparable across scans, they share a spatial pattern of local self-similarities. The vector-valued descriptors are densely calculated using patch similarities within the non-local neighborhood of each voxel, standardized by a local contrast estimation.

Each MIND vector element is based on the normalized sum of squared differences (SSD)  $D_N$  over a small image patch  $\mathcal{P}$  (with a local patch coordinate  $\mathbf{p}$ ) within the current image with intensities  $I$ :

$$D_N(\mathbf{x}) = \frac{1}{V(\mathbf{x})} \sum_{\mathbf{p} \in \mathcal{P}} (I(\mathbf{x}_1 + \mathbf{p}) - I(\mathbf{x}_2 + \mathbf{p}))^2 \quad (1)$$

where  $V(\mathbf{x})$  describes a locally varying contrast estimate over the SSDs of several neighbors in  $\mathcal{N}_x$ . In our original paper,  $\mathbf{x}_1$  coincided with  $\mathbf{x}$ , but using different offsets for both compared patches was shown to improve robustness against noise and capture more local context in following work, including an efficient calculation of patch SSDs for a fixed neighborhood layout  $\mathcal{N}$  based on separated moving average filters.

Using MIND enables the use of well-known metrics (e.g. sum of squared differences) and efficient continuous or discrete optimization methods for deformable registration. It may also improve the convergence of registration methods as the descriptors capture a wider context of geometric image information. We have been able to demonstrate that MIND can improve the accuracy of deformable registration for both multi-modal scan pairs as well as scans with challenging contrast changes, such as thoracic/abdominal computed tomography (CT) and MRI.

#### 2.4. Dynamic deformable registration

Dynamic imaging, such as DCE-MRI, aims to extract clinically meaningful quantitative image information from pharmacokinetic models, based on either semi-quantitative or fully quantitative parameters. While such techniques have become established in neuroimaging, detailed voxel-wise analysis outside the brain is chal-

lenged by different kinds of physiological motion, such as respiratory, cardiac or peristaltic motions, necessitating deformable registration. To accommodate localized intensity differences due to contrast agent uptake, we have advanced the original rigid registration approach with an embedded PK model by [Buonaccorsi et al. \(2007\)](#) to deformable registration. In [Bhushan et al. \(2011\)](#) we have adopted the Demons framework for joint PK model fitting and estimation of the deformation field within a Bayesian setting, by maximising the joint posterior probability  $P$  of the deformations  $\hat{\mathbf{u}}$  applied to each dynamic time frame, and the PK parameters  $\hat{\Theta}$  that best explain the observed data:

$$[\hat{\Theta}, \hat{\mathbf{u}}] = \arg \max_{\Theta, \mathbf{u}} P(\Theta, \mathbf{u} | X_0, \mathbf{Y}, \sigma) \quad (2)$$

where  $X_0$  denotes the image before contrast agent injection,  $\mathbf{Y}$  denotes the image formation model, and  $\sigma$  is a noise parameter. We have extended our discrete registration method presented in [Section 2.2](#) to 4D, by setting up a temporal chain of MSTs across the whole dynamic sequence. For each individual tree, optimization is carried out using belief propagation. While the spatial connectivity is captured by the individual MSTs, the temporal continuity is captured by the temporal chains. We have successfully applied this approach to DCE-MRI data for colorectal cancer ([Enescu et al., 2014](#)), showing improvement over our continuous, probabilistic framework ([Bhushan et al., 2011](#)) in form of less diffuse PK maps that are the natural output of both techniques. While this 4D discrete method has been originally developed for DCE-MRI, its groupwise formulation naturally lends itself to other dynamic imaging techniques with contrast agent or tracer injections, as well as cine imaging without contrast enhancement, such as 4DCT data of the lungs, where the temporal regularization is of particular advantage.

### 3. Challenges and Perspectives

In this section, we identify a number of areas where deformable registration, in the context of complex motion modelling and beyond, requires further research efforts for successful translation into clinical practice.



*Continuous versus discrete methods:* It remains to be explored which of the two proposed concepts, *Demons* using locally adaptive regularisation, or dense displacement sampling using supervoxel belief propagation, are more suitable for complex motion modelling. The former method relies on continuous optimization methods that can be prone to local minima, but can be regularized very flexibly. The latter is of much lower computational complexity, and is attractive in its implicit sliding boundary segmentation using the supervoxel formulation, but its regularization is commonly limited by the resulting MST node connectivity within the MRF framework. It is expected that hybrid methods will emerge in the near future.

*Model-based versus model-free methods:* While embedding a PK model into dynamic image registration is a very attractive concept, as it directly results in corrected PK parameters of interest, it also is biased towards a potentially invalid PK model of choice. It may therefore be advantageous to provide flexible PK model selection (which would reflect in cancer imaging the expected tumor heterogeneity), or use a model-free approach, in order to de-bias the registration from the PK modelling. For example, in Papież et al. (2015) we have adopted *Demons* to optimize over contrast-invariant features to drive registration locally in a supervoxel image-guided filtering approach, applied to contrast-enhanced liver imaging.

*Whole-body and hybrid scanning systems:* With the advent of combined scanning systems such as PET/MR, deformable registration will continue to be an important component of joint image reconstruction and attenuation correction. Moreover, whole-body imaging sets a new level of challenge for deformable registration, from dealing with individual organs and immediate surroundings, to describing overall body motion due to patient movement and physiological motion. Fetal imaging is one of the most challenging fields here where maternal and fetal motion present particular registration challenges in the compounding of fast-shot MR image stacks or fusion of multiple ultrasound images.

*Predictive motion modelling:* Serial imaging, for monitoring normal or pathological growth, degenerative disease such as dementia, or physiological changes due to treatment response or interventions, continues to present deformable image registration with highly complex motions and tissue modelling scenarios. One use case in cancer is the embedding of mechanistic and/or stochastic models of tumor growth and therapeutic response into serial registration, which is an active area of our ongoing research.

As things stand today, there remain huge challenges for deformable image registration, which will need to move away from the simple troika of: transformation model; cost function balancing image similarity and transformation complexity; and continuous or discrete optimization method; which together currently form the major components of a generic registration method. Embedding the physics of image formation, as well as machine learning methods, in particular deep learning, will enable deformable image registration to finally move from mere motion compensation for image fusion to true information discovery, by learning and predicting tissue deformations and pathological changes. We expect

that *Medical Image Analysis* over the next two decades will witness significant advances in this field, which will continue to cross-cut to the computer vision, graphics, machine learning and computational modelling communities, while moving into the *-omics* and *big data* era.

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