

# Deformable image registration applied to lung SBRT: usefulness and limitations

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## Abstract

Radiation therapy (RT) of the lung requires deformation analysis. Deformable Image Registration (DIR) is the fundamental method to quantify deformations for various applications: motion compensation, contour propagation, dose accumulation, etc. DIR is therefore unavoidable in lung RT. DIR algorithms have been studied for decades and are now available both within commercial and academic packages. However, they are complex and have limitations that every user must be aware of before clinical implementation. In this paper, the main applications of DIR for lung RT with their associated uncertainties and their limitations are reviewed.

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## 1. Introduction

Deformable image registration (DIR) has been studied for more than 20 years and it has a long history with research in radiation therapy (RT). Indeed, the clinical interest is large with numerous applications: motion compensation, auto-contouring, dose accumulation etc. Since the early years of DIR, important progresses have been made: algorithms are faster, more precise and more accessible than ever. However, several challenges and limitations remain such as validation, tissue appearance/disappearance and robustness. This review focuses on applications of DIR in lung cancer and CT images, but DIR can be used in many other sites (head and neck, prostate etc) and with other image

modalities (MRI, PET, SPECT, US), every situation having specific challenges. General practical recommendations in RT may be found in the recent AAPM TG report [1].

*DIR in a nutshell.* First, the main concepts at the core of most DIR algorithms are briefly summarized below. For more details, several excellent reviews are available which cover in depth biomedical image registration methods [2, 3]. DIR is an ill-posed problem formalized as the optimization of a function balancing the similarity between images and the plausibility of the deformation. This tradeoff is at the heart of all DIR algorithms. The three main components are 1) the measurement of image similarity, 2) the parameterization of the deformation and 3) the optimization method. Image similarity can be estimated via numerous approaches, e.g. the popular Mutual Information metric, or metric mixing voxel-based and geometrical extracted features. Deformation vector fields (DVF) may be directly estimated or they may be parameterized with fewer unknowns, e.g. using the popular B-spline basis functions. The cost function is composed of an image similarity term and a transformation plausibility term. It may be optimized via gradient-based continuous methods or discrete approaches (graph-based). This is a very active field of research - around 150 publications per year in PubMed in the last few years - applied to a wide range of applications. In RT, usage of DIR has significantly progressed [3], particularly for thorax images. However, ten years after our review optimistically presenting the potential of DIR in IGRT [4], it can be observed that clinical use of DIR is “like sex for teenagers: everyone talks about it, nobody really knows how to do it, everyone thinks everyone else is doing it, so everyone claims they are doing it too<sup>1</sup>”.

*Evaluation.* Like other key components, such as the dose computation engine in a TPS, it is necessary to evaluate DIR. However, a ground truth is generally not available. Indeed, the accuracy is often measured via anatomical landmarks, e.g.

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<sup>1</sup>The authors could not retrieve the original author of this quote heard at a conference, but it mainly refers to “big data” in Internet references.

bifurcation of airways, using Target Registration Error (TRE) criteria averaging the distances between landmarks. Additionally, other anatomical structures, e.g. lines corresponding to vessels or organ contours can be used. Several open databases of thoracic images with their corresponding evaluation data are available (see table 1) and they have proved to be very useful as demonstrated by their high number of citations. For example, the EMPIRE10<sup>2</sup> challenge [5] compared more than 40 algorithms with a database of 30 pairs of thoracic CT images: the first 10 methods depicted TRE lower than 0.9 mm. Instead of relying on manually defined landmarks or segmented delineated structures, other authors have proposed to automatically estimate local DIR uncertainty [6, 7, 8]. More detailed analysis on DIR evaluation may be found in [9, 10].

## 2. Applications of DIR in lung RT

This article splits the applications of DIR in lung SBRT in four parts: contouring, dose accumulation, 4D image analysis and other applications (Figure 1). Most of the bibliographic references are listed in tables in the supplementary materials (most of the bibliography is arbitrarily limited to the last 5 years). Note that the computational time of the methods was not studied here.

### 2.1. DIR for contouring

It seems that DIR was first used in lung RT to perform automatic segmentation or auto-contouring. The principle is to use DIR between an already contoured reference image and an image to be contoured. Once the DVF is obtained, it is used to propagate the contours from one image to the other. The algorithms that perform auto-contouring may be separated into three groups: 1) methods to propagate contours between respiratory phases (intra session, 4D CT), 2) methods for inter-session contouring, 3) initial contouring, mostly with inter-patient atlas approaches. Table 2 lists some bibliographic references.

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<sup>2</sup>Evaluation of Methods for Pulmonary Image Registration 2010, <http://empire10.isi.uu.nl/>

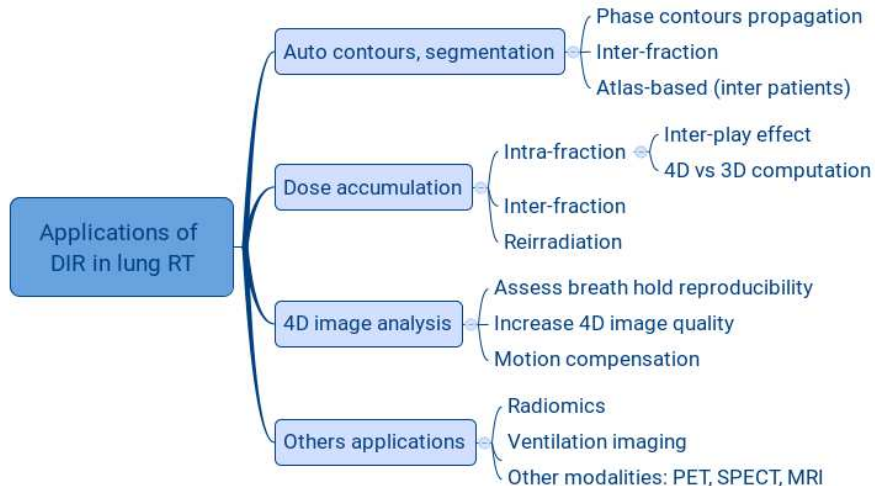


Figure 1: Simplified classification of DIR applications in lung RT.

Phase-to-phase auto-contouring propagates lung, tumor or lymph node contours from one phase to the other breathing phases of a 4D CT image. A specific uncertainty lies in the “sliding issue”. Indeed, the lung and the liver slide on the opposite side of the pleura and the wall, generating discontinuities in the motion field. However, DIR generally relies on the assumption that the sought transformation is smooth, preventing correct estimation of those discontinuities. If not specifically taken into account, the deformation near sliding areas will be underestimated in the lungs and overestimated along the pleura, e.g. in the thoracic wall. Several proposals have been made mostly based on separated DIR regularizations according to segmented regions that are supposed to slide along each other. Regions may be as simple as lungs segmentation or more refined as the so-called *motion-mask* following intra and extra pleural regions [11]. It is not clear, however, if commercial solutions provide sliding correction yet (it is mentioned as future work in [12]). It is relatively easy to detect if sliding is taken into account by looking at specific sliding regions, around lungs boundaries near the diaphragm and the liver. Apart from sliding, another limitation also is image 4D CT artifacts that may prevent reliable contouring (see section 2.3).

Several studies have evaluated the accuracy and usefulness of 4D CT contour propagation with very good results in terms of accuracy, contour reproducibility and delineation time [13]. Expected precision is generally better than 2 mm, in particular for the alignment of lungs boundaries, e.g. in the EMPIRE10 challenge [5] the majority of algorithms were very well adapted.

Propagating contours made on the planning CT onto images acquired during other treatment sessions (CT or CBCT) is also a classical use of DIR in the progression towards adaptive treatment planning. However, DIR contour propagation for inter-fraction delineation is particularly difficult in the lungs because the breathing motion is combined to inter-fraction motion. Moreover, tissue changes such as atelectasis or emphysema in the course of the treatment may introduce wrong results. Near multimodal registration between CT and CBCT requires specific attention as the image intensity ranges are different and CBCT contains more noise and potentially reconstruction artifacts such as streaks or cupping. Image intensities have to be pre-processed by some kind of histogram equalization before using mono-modal similarity measures (SSD), or multi-modal similarity measure should be used, e.g. the correlation coefficient or the Mutual Information.

Finally, initial contours on the planning CT may be performed automatically via atlas segmentation methods using DIR to deform the image to be segmented with an atlas containing one or several images with associated validated contours (and statistical properties). This approach has also been proposed for the segmentation of fine lung structures such as lobes or airways. However, only a few studies are dedicated to lung SBRT. DIR uncertainty should be compared to inter-observer uncertainty of contouring itself, which could be large, particularly for target volumes [14]. It should be emphasized that, like any automated algorithm, auto-contouring based on DIR will never lead to perfect results and will provide incorrect results in some situations (image artifacts, large atelectasis or emphysema, etc). Hence, results must be visually validated after each use and may require manual adjustment that may be time consuming. Future developments, such as better visualization and interaction tools, will probably

come from the industry.

## *2.2. DIR for dose accumulation*

DIR is used to perform dose accumulation (DA) between dose distributions computed on different anatomical states. DA accumulates dose quantities once the dose distribution have been mapped from one image to the other. Two main situations can be considered separately: intra-fraction motion (breathing motion) and inter-fraction changes (session-to-session or re-irradiation).

### *2.2.1. Methods for dose mapping*

Computing DA consists of warping with DIR then summing two dose distributions to the same reference coordinates system. Different mapping methods have been proposed because multiple source dose voxels (dosel) may merge into a single destination dosel, or conversely a source dosel may split into several destination dosels. Li et al.[15] summarized and compared the two main proposed methods: direct dose mapping (DDM) and energy/mass transfer (EMT) mapping. DDM interpolates dose values from one dose grid to the other, while EMT counts the total energy and mass transferred to each voxel by taking into account the dosel volume change (thanks to the Jacobian of the deformation), before computing the dose by dividing energy by mass. Mean differences between the two approaches appear small for 4D breathing dose accumulation but larger differences could appear near sharp dose gradient regions and could reach 11%. It is recommended to use EMT because it is based on a “more theoretically sound physics principle”, taking into account the repartition of energy based on volume changes rather than an interpolation.

### *2.2.2. Intra-fraction dose accumulation*

In general, treatment planning systems only compute dose in static anatomies, even though the lungs move due to breathing. The impact of respiratory motion on the dose distribution has been studied with 4D dose computation: from a 4D CT composed of 8 to 10 phases, dose distributions are computed for every phase and accumulated thanks to DIR performed with each phase relative to a

reference phase. This process has been studied for various situations: 4D dose compared to average 3D CT, or compared to free breathing CT, or compared to average intensity projection (AIP), all those methods with different margin strategies (Table 3). For example, Ohira et al.[16] showed that AIP can predict the target 4D dose coverage with less than 3 % dose difference in target volumes and 1 Gy for Organs At Risk (OAR), but with large differences (up to 10 Gy) for large respiratory motion, e.g. near the liver. Valdes et al.[17] observed marginal differences between 3D and 4D dose calculations, lower than DIR uncertainty, and concluded that 4D dose calculations are not necessary for most cases treated with SBRT. However, for OAR, large motion or GTV with highly irregular shapes, 4D computation should be preferred.

For modulated beam delivery, the interplay effect, i.e. the concurrent motion of the patient and the irradiation system (multi-leaf collimator, MLC, and gantry), may potentially result in over- or under-dosage. Note that heart motion is generally not taken into account [18]. The evaluation of dosimetric impact has been performed by measurements with dynamic setups or with simulations involving DIR. Most studies converge towards clinically acceptable dose differences due to interplay effects (below 4%), with the differences increasing as motion increases (Table 3). As an example, Rao et al. [19] concluded that 3D dose computation provides clinically acceptable 4D dose approximations for both GTV and critical structures. Differences between 3D and 4D dose distributions seem to be patient dependent; no clear population trends were observed between dose differences and tumor extend [20]. Most of the studies investigate IMRT on a conventional linac (VMAT, RapidArc, DMLC), the specificity of other devices (e.g. Cyberknife, Tomotherapy) devices should be evaluated independently.

The consequences of irregular breathing cycles have been less studied. As an example, for delivery strategies based on tumor tracking with dynamic MLC, Yang et al [21] found that dose increases in the target and OARs when there is a difference of 10% between anticipated and actual breathing speeds. Finally, it should be emphasized that these studies concern photon beams only: ion beam

treatments, with proton or carbon, could lead to very different results, with large differences between 3D and 4D dose computation [22].

### *2.2.3. Inter-fraction dose accumulation*

DIR is also used to perform DA in inter-fraction situations, typically for adaptive radiotherapy (ART) or for re-irradiation (Table 3). One first limitation comes from the tissue appearance or disappearance (TAD) that may occur between the two images to be registered. Examples include: tumor volume expansion [23], fibrosis, emphysema, atelectasis, and radiation-induced normal tissue changes [24]. Indeed, deformation models used in DIR algorithms do *not* explicitly take TAD into account: the underlying assumptions generally used to model the deformations between images may consider smoothness, continuity or diffeomorphism, which is not the case with TAD. The resulting displacement field in the vicinity of TAD is distorted, e.g. stretching or collapsing tissues, and provides unreliable DA. Even if some attempts have been proposed, such as in [25] for lung, in [26] for brain or in [27] to include excision, to our knowledge, it is still an open problem. Besides those limitations, DIR has however been shown to be almost always more accurate than rigid registration [28, 29]. Finally, it is also not clear what the consequences are of accumulating doses separated by several months but this is more of a radiobiology question than a DIR problem. Indeed, the radiobiological rationale for tissue repair when large delays occurred between irradiation is largely unknown.

### *2.2.4. Conclusion for dose accumulation*

The reliability of DA has been and still is the subject of rich and interesting debates (Table 3). In summary, DIR is generally considered reliable for intra-fraction situations, provided that sliding motion is taken into account. Even if the impact of DIR uncertainties on the DA could be not significant [30], there is an interplay between DIR uncertainties and dose gradient that can result in large DA errors in areas of steep dose gradients [31]. For inter-fraction applications, even if DIR is considered more precise than simple rigid registration,



there are still inherent limitations due to TAD, and radiobiology uncertainties associated to distant time dose accumulation. It is recommended to identify situations of TAD both from images inspection and analysis of the DVF, looking for suspicious Jacobian extrema values and other metrics [6]. Note that this article focuses on photon beams, but similar studies have been proposed in hadrontherapy, both for proton and carbon ion beams (see last row of Table 3).

### 2.3. DIR for 4D image analysis

4D CT and CBCT images are invaluable sources of information when studying patient-specific breathing motion. As shown in table 4, they can be used to track target motion, both for principal tumors and lymph nodes, and to assess the reproducibility and uncertainty associated with breath-hold approaches. One principal limitation of 4D CT images is related to the potential presence of image artifacts, mostly caused by irregular breathing: 4D acquisitions rely on the assumption of constant breathing motion. Those artifacts lead to distorted or blurred structures [32] that may locally impact the accuracy of DIR results in the vicinity of the artifacts. It is thus recommended to identify areas that contain artifacts, potentially automatically [33, 6]. DIR has also been used to enhance the quality of CT images. For example, some artifacts may be reduced with repeated fast helical acquisitions combined with 4D motion modeling based on DIR [34]. Alternatively, 4D DIR may smooth-out some artifacts [35] thanks to temporal regularization. Image noise may be reduced by combining the phases of a 4D CT that have been deformed to the same reference state via DIR [36, 37], thus providing a *motion compensated* image. This, in particular, can be used to compute an image representing the time-averaged position of the patient, called the *mid-position* [38]. Similarly, 4D CT and associated motion models computed with DIR may be exploited during CBCT reconstruction to provide motion-compensated images and potentially improve the temporal resolution of 4D-CBCT. Image quality enhancement via DIR is limited by the initial image quality; it is unlikely that any method will improve images if the artifacts are too large. Moreover, those methods are inherently limited by the underlying

ing assumption of smooth deformation of which the artifacts are considered a violation.

#### *2.4. DIR for other topics*

DIR in lung RT may also be used for other purposes. For example, it has been suggested that DIR could be used to provide functional ventilation images (Computed Tomography Ventilation Imaging, CTVI) to visualize and quantify the spatial distribution of air-volume changes on a voxel-per-voxel basis [39]. Also, DIR could be used to find imaging biomarkers with radiomics approaches that correlate image features with tissue density changes observed after irradiation [24]. Also, the data mining of large sets of images to automatically detect sensitive regions [40] also requires DIR methods to first align images in a common reference frame. Finally, DIR is also employed in lung SBRT with other modalities than CT, in particular with MR, SPECT or PET images (table 5). The same limitations as described before occur.

### **3. Conclusion and recommendations**

Radiation therapy of lung tumors requires the analysis of various deformations and DIR is the fundamental method of quantifying image deformation, so DIR is unavoidable in lung RT. However, it is still relatively complex, it has some limitations and, just like any dose computation algorithm, it should be commissioned and regularly evaluated.

Evaluation may be divided into two parts, “offline” (commissioning) and “online” (daily practice). First, the commissioning of a new software should be performed as an end-to-end test on a database of cases where a ground truth is available. Several metrics (TRE, regions overlap etc) can be used to evaluate the achievable accuracy of the proposed algorithm, helping to determine the best parameters. As most algorithms may require parameter adjustment to provide the best performances, it is recommended to use algorithms that allow for altering those parameters. Different commissioning should be performed for

every type of localization and use-case. Second, in daily clinical use of DIR, for which no reference is available in a reasonable time, every patient-specific results should be reviewed via a pre-determined set of visual criteria. Criteria include: potential TAD and image artifacts, comparison between reference image and deformed image with color-overlaid images, special care around sliding regions, etc. As a practical example, mid-position lung treatment planning was setup in our institution with the following procedure. First, the chosen DIR algorithm [41, 11] used to compute the mid-position image was commissioned on open databases [42, 43] considering TRE criteria. Then, for every patient included in the study, DIR result is validated by the clinical team by a visual protocol that includes 1) evaluation of 4D CT image artifacts, 2) 4D movie of all breathing phases warped to the reference phase (results should ideally be almost identical with very few density modification), 3) color overlay of mid-position image over the 4D CT, 4) visual inspection of mid-position image alone. At the end of the process, image is validated and the treatment may continue. If a problem is detected, a backup plan not using DIR is used.

Recently, the AAPM report of the TG-132 [1] gathered extensive and comprehensive information on the general use of DIR in radiation therapy. We refer to this publication for practical advices and procedures. Table 6 recapitulates the main limitations or points of attention. It should be emphasized that DIR is not an end but an intermediate step in a process for a given objective that may have additional issues as well. For example, besides DIR difficulties, dose accumulation for re-irradiation raises the challenges of the accumulation of radiobiological effects.

With decades of development, DIR appears to be sufficiently advanced and evaluated to be used in clinical environments provided that users are properly trained, aware of underlying assumptions and limitations of the algorithms, and software commissioning is properly performed based on the knowledge of these limitations. DIR algorithms are now widely available, with both commercial software and academic packages (Table 7). We again refer to TG-132 [1] for a list of vendor recommendations that may also be useful to help the choice of a

particular software. As most algorithms may require parameter adjustment to provide the best performances, it is recommended to use algorithms that allow for changing those parameters during commissioning. The field is still evolving and future trends include increased speed, better user interaction and validation, and increased robustness. We also envisioned progresses in the automated detection of regions of potential issues, e.g. TAD in particular, and, with the advance of large databases of cases, progresses in automated contouring reliability. From a theoretical point of view, efforts should be directed towards deformations and similarity measures able to deal with TAD and robustness to noise and artifacts. Additionally, generic lung motion models and lung function analysis will bring new insights. The near future of MR-linac devices is also opening new usages and concerns about DIR in lung RT.

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### **Tables in supplementary materials**

Table 1: Bibliographic references for the validation of DIR in lung. [See supplementary material]

Table 2: Bibliographic references for auto contouring based on DIR. [See supplementary material]

Table 3: Bibliographic references for dose accumulation in lung RT. [See supplementary material]

Table 4: Bibliographic references for 4D image analysis. [See supplementary material]

Table 5: Bibliographic references for use of DIR in radiomics or with other modalities than CT. [See supplementary material]

General	Need QA (end-to-end test) Warning to setup material (masks, bolus)
Intra-fraction (4D CT)	Sliding tissues (solutions exist) Inaccurate estimation close to 4D artefacts Effects of irregular breathing cycles Effects of heart motion
Inter-fraction	Current algorithms cannot deal with tissue (dis)appearance Uncertainties in homogeneous intensity region Uncertainties of physical dose accumulation
Inter-patient (contours, atlas)	The deformation type is barely constrained Can require manual contours cleaning Not applicable yet for target volumes
Re-irradiation	Current algorithms cannot deal with tissue (dis)appearance Unknown biological dose accumulation

Table 6: Main limitations of DIR applications

Table 7: Some software for DIR. [See supplementary material]

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We arbitrarily limit most of the bibliography to last 5 years (2011 and after).

Ref	Comments
[1]	DIR evaluation review
[2]	Empire database
[3]	MIDRAS database
[4]	Dir-Lab database
[5]	Popi-model database
[6, 7, 8, 9, 10, 11]	Compare performances of DIR methods
[12, 13, 14, 15, 16, 17]	Evaluation assessments
[18, 19, 20, 21, 22]	Some deformable phantoms
[23, 24, 25, 26, 27]	Sliding issue

Table 1: Bibliographic references for the validation of DIR in lung

Ref	Comments
[28, 29, 30, 31, 32, 14, 33, 34, 35, 36]	Phase to phase contouring (Lung 4D)
[37, 36]	Fraction to fraction contouring
[38, 39, 40, 41, 42]	Atlas-based contouring
[43, 39, 40, 41, 44, 45, 30, 46, 42, 47, 48]	Fine lung structures (lobes, airways) segmentation

Table 2: Bibliographic references for auto contouring based on DIR

Ref	Comments
[49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61]	Dose accumulation methodology
[62, 53, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74]	Intra-fraction accumulation
[75, 76, 77, 78, 70, 79, 80, 81, 82, 83, 84, 85, 86, 87, 83, 88, 89, 90]	Interplay effect
[66, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100]	Inter-fraction accumulation
[101, 102, 103]	Re-irradiation
[104, 105, 106, 107, 103]	Reliability
[108, 109, 110, 99]	Impact of DIR uncertainty
[111]	Tissue disappearance and appearance
[105, 112, 7, 113, 114]	Phantom studies
[115, 116, 87, 117, 118, 119, 120, 121]	Hadrontherapy

Table 3: Bibliographic references for dose accumulation in lung RT

Ref	Comments
[122, 123, 124, 125, 126, 120]	Target tracking
[127, 128, 129, 130]	Breath-hold reproducibility
[131, 24, 132, 133, 134, 135, 136, 137, 138, 17]	Enhance 4D CT quality
[139, 140, 141, 142, 143, 144, 145, 146]	Enhance 4D CBCT quality
[147, 148, 149, 150]	Motion compensation
[151, 152, 153, 128, 154, 155, 156, 157, 158, 159, 160, 161]	Computed Tomography Ventilation Imaging

Table 4: Bibliographic references for 4D image analysis

Ref	Comments
[162, 163, 164, 165, 166]	Radiomics, data-mining
[167, 168, 169, 170]	MRI
[171, 172, 173, 174, 175, 176]	PET

Table 5: Bibliographic references for use of DIR in radiomics or with other modalities than CT.

Table 6: Main limitations of DIR applications. [See main text]

Software	Reference
ANT (Advanced Normalization Tools)	(web) [177]
NiftyReg	(web) [178]
Elastix	(web) [179]
MIRTK	(web)
ITK	(web)
Plastimach	(web) [180]
DIRART	(web) [181]
VV	(web) [182]
MEVIS	(commercial) (web)
Anaconda	(commercial) (web) [183]
SmartAdapt Varian	(commercial) (web) [184]
Mirada	(commercial) (web)
Dosisoft	(commercial) (web)

Table 7: Some software helpful for DIR

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