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Review paper

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.

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[1]".

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. 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[2] 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

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[1] 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.

[2] Evaluation of Methods for Pulmonary Image Registration 2010, http://empire10.isi.uu.nl/

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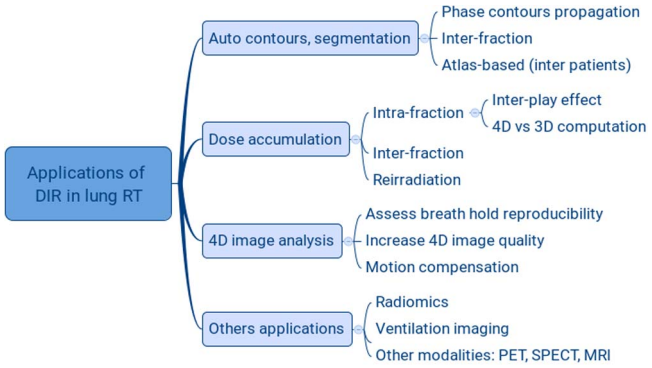

Fig. 1. Simplified classification of DIR applications in lung RT.

landmarks or segmented delineated structures, other authors have proposed to automatically estimate local DIR uncertainty [6–8]. 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 (Fig. 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.

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 a 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 distributions 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