CHAPTER 2

Literature Reviews

This chapter described the fundamental of megavoltage computed tomography on a Tomotherapy system in terms of the physical interactions and the theory of contrast resolution on MVCT when compared with the kVCT images. Then proposed the principle of the deformable images registration (DIR) process in various models to find the best estimated deformation vector field (DVF). Use of DIR for radiotherapy application and explained the function and general workflow of deformable image registration and adaptive radiotherapy software in cases of image deformation and dose processing for adaptive application. Finally, described the validation techniques for deformable image registration assessment.

2.1 Megavoltage computed tomography on a Tomotherapy system

Helical tomotherapy (HT) is a unique Intensity Modulated Radiation Therapy (IMRT) modality that combines elements of diagnostic radiology and radiation therapy in a single unit. The TomoTherapy system is capable of producing megavoltage computed tomography images (Figure 2.1) using the same beam line components that are used for treatment procedures by using the 6 MV Accelerator (tuned to 3.5 MV for MVCT).

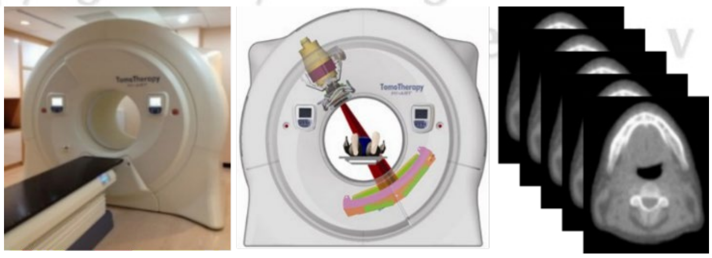

Figure 2.1 TomoTherapy MVCT Images acquisition
Source: Tomotherapy Inc., Madison, Wisconsin, USA

Physical interactions with soft tissues in term of MVCT is actually very similar to standard kVCT. In both cases, the incident photon beam is attenuated primarily by Compton scattering (Ruchala *et al*., 1999). For significantly higher-Z materials there will be an inherently better contrast per photon at the kV energies due to the increased amount of photoelectric interaction, yet these materials (e.g. bone) generally have sufficiently high contrast at MV energies because of their density.

Tomotherapy system is able to produce MVCT image quality that are useful for patient position verification in a reasonable time using an acceptable dose (Ruchala *et al*., 1999). Therefore, daily MVCT image is the standard guidance for patient set-up verification. However, the theory of contrast resolution in MVCT, the ability to resolve soft-tissue contrast differences is fundamentally limited by the number of photons used to create the image (Keller *et al*., 2002) due to the use of MV photons results in a greater absolute dose deposition per photon. In order to maintain comparable doses for MV and kV tomography, the number of MV photons must be significantly reduced. Unfortunately, this reduction decreases the signal-to-noise ratio (SNR) and thus impairs soft tissue contrast detectability (Ruchala *et al*., 1999). It is generally understood that deformable image registration will work best with feature-rich images where there is little or no ambiguity between corresponding points in source and target images. The “goodness of fit” will likely be qualitatively assessed via inspection of these visible features, which are also the primary drivers of the calculation and so are naturally the best matched locations. Yeo *et al*. (2013) assess the accuracy of 12 DIR algorithms and quantitatively examine, in particular, low-contrast regions. As might be expected, the deformation is estimated less accurately for low-contrast regions than for high-contrast features. Ramadaan *et al*. (2013) demonstrated that deformable image registration on kVCT images can yield clinically acceptable results and time-saving benefits in contouring that improve clinical workflow.

2.2 Deformable Image Registration (DIR)

Deformable image registration is a process to find the best estimated deformation vector field (DVF), which forms the voxel correspondence between 2 different images set (Zitova *et al*., 2003). The most exciting and challenging research on image registration involves the development of deformable registration algorithms (Goshtasby *et al*., 2003).

Deformable registration is an ill-posed problem because there is generally no unique solution to a registration problem. Usually image registration is formulated as an optimization problem (Zitova *et al*., 2003).

Image registration can be defined as finding the function h and g in following equation 2.1 for mapping between two 3D images I_1 and I_2: where I_1 is called the *"source or moving image"* and I_2 is called the "*target or fix image"*.

$$I_2(x, y, z) = g(I_1(h(x, y, z))) \tag{2.1}$$

The function g is called an "*objective function"* this term as matching criteria, (dis) similarity criterion or distance measure. The optimization problem consists of either maximizing or minimizing the objective function depending on how the matching term is chosen (Sotiras *et al*., 2013). This function accounts for a difference in image intensities of the same object in I_1 and I_2 (Zitova *et al*., 2003).

The function h is the "*deformation model"*, used to describe geometric differences. It is a spatial 3D transformation that describes the mapping homologous locations from the target physiology to the source physiology. The result of the registration algorithm naturally depends on the deformation model and the objective function (Sotiras *et al*., 2013).

An image registration algorithm involves three main components:

1) Deformation model,
2) Objective function or matching criteria
3) Optimization method.

2.2.1 Deformation models

The choice of deformation model is of great importance for the registration process as it entails an important compromise between computational efficiency and richness of description (Sotiras *et al*., 2013). It also reflects the class of transformations that are desirable or acceptable, and therefore limits the solution to a large extent. Furthermore, the choice of the deformation model implies an assumption regarding the nature of the deformation to be recovered.

Deformable image registration finds a matrix that represents how individual voxels of one image are ‘‘deformed’’ (moved, etc.), so they optimally line up with corresponding voxels from another image (Haksoo *et al*., 2014). The transformation defines where any voxel of the target image 'comes from' in the source image, but it does not define where any voxel of the source image 'goes to' in the target image (Lourengo *et al*., 2013). The choice of deformation models depends on the mapping directions, transformation frameworks and deformation algorithms;

1) Forward and backward mapping

For two images *I* and *J*, while *I* is the moving image and *J* is the fixed image, deformable image registration is to be computed the deformation vector field *V*. (Yang *et al*, 2010): Regarding the definition of the deformation vector field, ***V*** is defined on the coordinates on *J*. It is the “*pull-back*” vector field (*backward mapping*), has the same array dimension as *J*. Each element of *V* is a 3D vector, associated with a voxel in *J*, The direction of the 3D vector is from the point in *I* to the matching point in *J*.

However, the *“pull-back”* motion field is the *“push-forward”* motion field (*forward mapping*) if the image registration direction is inverted (the two images are interchanged).

If the moving image and the fixed image have been determined for a registration computation as illustrate in Figure 2.2., the most important difference between the two motion fields is that:

The pull-back motion field is defined on the voxels in the fixed image,

The push-forward motion field is defined on the voxels in the moving image.

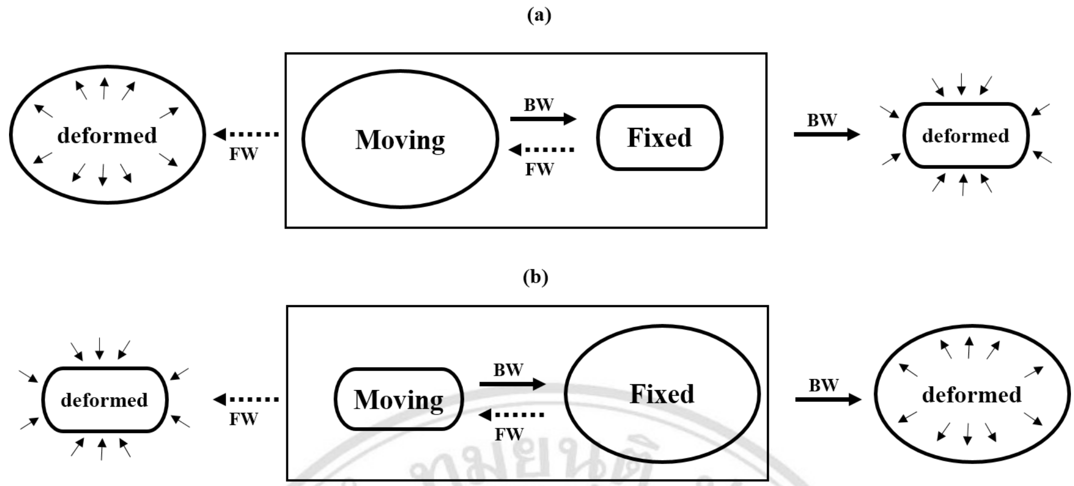

Figure 2.2 Schematization of a deformable registration, (a) the pull-back motion field (BW) is defined on the voxels in the fixed image and the push-forward motion field (FW) is defined on the voxels in the moving image. (b) the pull-back and push-forward motion field when the moving and fixed images were interchanged.

2) Asymmetric and Symmetric transformations

Asymmetric transformation is the majority of the existing registration algorithms. As a consequence, when interchanging the order of input images, the registration algorithm does not estimate the inverse transformation. The statistical analysis that follows registration is biased on the choice of the target domain.

To minimize this problem, Christensen and Johnson first proposed the inverse consistency by formulating the registration in both directions into an overall energy function in the optimization. This ensures the consistency of registration in two directions (Kristy *et al*., 2013).

Symmetric transformation uses the method by simultaneously estimating both the forward and the backward transformation. The data matching term quantifies how well the images are aligned when one image is deformed by the forward transformation, and the other image of the backward transformation. In theory, symmetric registration results are not biased towards the transformation direction which means that results should be the same when registration is performed the source image to target image or interchanging the order of input images. The final mapping from one image to another is calculated by inverting one transformation function and composing it with the other.

Lourengo *et al*. (2013) demonstrated the inverse methods gave the most robust results in terms of inverse-consistency between the composition of forward and inverse transformations.

3) Deformation Algorithms

Parametric algorithms: The parametric transformation models that are often described by a set of basic functions. In parametric, non-rigid medical image registration, the basis function is a spline (Kristy *et al*., 2013). Parametric image registration can be categorized by the spatial arrangement of landmarks or control points and characterized a quite limited number of parameters.

Non-parametric algorithms: based on a vector per voxel describing the displacement and attempt to model the deformation of the anatomy in terms of well-studied models of fluid flow or the deformation of a viscoelastic material (Kristy *et al*., 2013).

3.1) *Horn and Schunck Optical flow algorithm*: A special kind of method is optical flow, which is used to find small deformations in temporal sequences of images. At a given point *P*, let *s* be the intensity function in *S* and *m* the intensity in *M* (see Figure 2.3). The basic hypothesis of optical flow is to consider that the intensity of a moving object is constant with time, which gives, for small displacements (Thirion *et al*., 1998). These vectors can be thought of as 'optical velocity' vectors showing the direction of image intensity flow (Kristy *et al*., 2013).

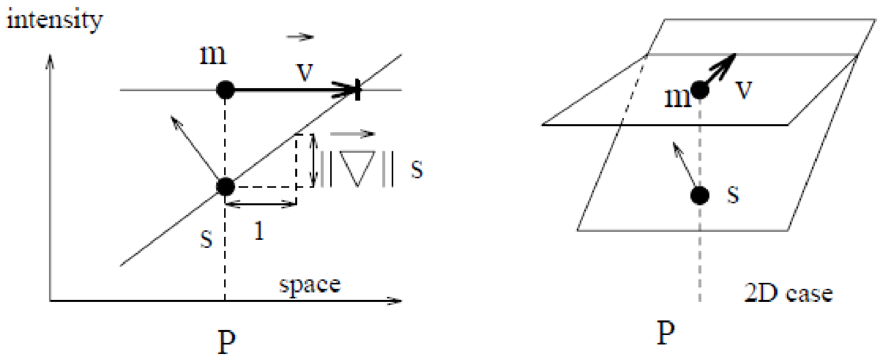

Figure 2.3. Instantaneous velocity from image M to image S.

Source: Thirion *et al*. (1998)

3.2) *Original Demons algorithms*: The concept of the Demons algorithm is that the voxels in the static or target image S act as local forces that move the voxels in the moving or source image. The moving image is iteratively deformed by applying a displacement vector u as in equation 2.2.

$$u^{i+1} = \frac{(M^i - S)\nabla S}{(\nabla S)^2 + (M^i - S)^2}, \tag{2.2}$$

where u^{i+1} is the displacement at $i + 1$ iteration, S is the static image, M^i is the moving image at the i^{th} iteration, and ∇S is the gradient of the static image S. There are two forces in the equation (i) the internal image gradient-based force ∇S and (ii) external force ($M_i - S$). The internal force does not change during the iterations, whereas the external force changes after each iteration. The term $(M_i - S)^2$ is added to make the deformation field computation more stable. Before the next iteration, the displacement is convolved with a Gaussian kernel, as the Gaussian convolution removes noise and improves geometric continuity (Kristy *et al*., 2013).

Varadhan *et al*. (2013) demonstrated the DIR results in a daily clinical environment might be very variable and affected by various factors such as patient anatomy, image quality, and registration parameters of the particular algorithm. Yeo *et al*. (2013) demonstrated the model studied, optical flow algorithms performed better than demons algorithms, with the *original Horn and Schunck* performing best. The degree of error is influenced more by the magnitude of displacement than the geometric complexity of the deformation. However, Ramadaan *et al*. (2013) demonstrated the deformable image registration using a Modified Demons algorithm yields clinically acceptable results and time-saving benefits in contouring that improve clinical workflow.

2.2.2 Matching Criteria

Matching criteria can be distinguished three groups of registration methods according to how they exploit the available information to drive the matching process: *Geometric Methods, Iconic methods* and *Hybrid methods* combine both types of information. Geometric methods aim to register two images by minimizing a criterion that takes into account landmark information. However, Interpolation results in a decrease in accuracy as the distance from the landmarks increases. Nevertheless, geometric methods constitute a reliable approach for specific applications. Geometric registration has also important applications in image-guided interventions (Sotiras *et al*., 2013).

Iconic methods, often referred to as either voxel-based or intensity-based methods, quantify the alignment of the images by evaluating an intensity-based criterion over the whole image domain. When compared to the geometric methods, this approach has the potential to better quantify and represent the accuracy of the estimated dense deformation field. In iconic methods, the matching term integrates the evaluation of a dissimilarity criterion that takes into account the intensity information of the image elements. Two cases should be distinguished regarding the iconic: 1) *the mono-modal case*, involving images from one modality, and 2) *the multi-modal one*, involving images from multiple modalities.

1) Mono-Modal Registration: In the mono-modal case, the same imaging device is used to capture the same type of information for both volumes.

Intensity-Differences methods*:* As in equation 2.3, image A be the reference static image and image B be the moving image to be transformed to match with image A. $A(\vec{x})$ and $B(\vec{x})$ are the intensity values at the locations with spatial coordinates *x* in images A and B, respectively. The symbol *T* will be used to represent a registration transformation. The simplest pixel similarity metrics are based on the difference in image intensities at corresponding points between two images. The most commonly used metric is *the mean squared difference MSD* (*A*, *B*), which is minimized during registration (Kristy *et al*., 2013).

$$\mathrm{MSD}(A,B)=\frac{1}{N}\sum_{\vec{x}}[A(\vec{x})-T(B(\vec{x}))]^2, \tag{2.3}$$

Correlation-Based Methods*:* Cross-correlation is a basic statistical criterion to measure similarity in signal and image processing. The cross-correlation metric has the disadvantage of being sensitive to changes in image amplitude of *A* and *B*. An approach frequently used to overcome this difficulty is to perform matching via *the correlation coefficient (CC)* metric, or the normalized cross-correlation (NCC) as in equation 2.4.

$$\mathrm{CC}=\frac{\sum_{\vec{x}}(A(\vec{x})-\bar{A})(T(B(\vec{x}))-\bar{B})}{\sqrt{\sum_{\vec{x}}(A(\vec{x})-\bar{A})^2\sum_{\vec{x}}(T(B(\vec{x}))-\bar{B})^2}}, \tag{2.4}$$

where $\bar{A}$ is the mean pixel value in image A in the overlapping region and $\bar{B}$ is the mean pixel value of image B in the overlapping region.

2) Multi-Modal Registration: multi-modal registration is more challenging as the choice of an appropriate matching criterion is a harder task.

Information-Based Methods: Information theory is based on probability theory and statistics. The most important quantities of information are entropy, the information in a random variable, and mutual information (MI), the amount of information in common between two random variables. MI does not entirely solve the overlapping problem. In particular, changes in the overlap of very low intensity regions of the image (especially noise around the patient) can disproportionately contribute to the MI. *The normalized mutual information (NMI)* is the alternative normalizations of the joint entropy have been proposed to overcome this problem as in equation 2 5.

$$NMI(A,B) = \frac{H(A) + H(B)}{H(A,B)} \tag{2.5}$$

H(A) and H(B) are the marginal entropies of image A and B, respectively, and H(A,B) the joint entropy. NMI can range between 0 and 2 and values of NMI>1 typically represent a good match between images.

2.2.3 Optimization methods;

After constructing a cost function and selecting the transformation model (which may require regularization) appropriate for the image registration problem, the final step is to obtain the transformation parameters that yield the best or optimal registration. Mathematically, this problem can be stated as follows: given a cost function f and unknown transformation parameters, find the optimal set of parameters that maximize (or minimize) the cost function. Optimization strategies, which seek to determine the parameters of the transformation model to maximize or minimize the cost function, are selected based on accuracy, computational efficiency, and robustness. A termination condition is often used in conjunction with a computational method because, in practice, the extremum is not precisely known and must be estimated. Due to the empirical nature of the termination condition, a simple optimization method, which yields a similar but not necessarily the best parameters compared with a more complex method, is usually preferred in radiation therapy applications due to the practical limits of registration accuracy in clinical implementation. Unlike the rigid or affine transformation, the nonrigid transformation is normally a local free-form mapping. Due to the degeneracy of deformation, it is impossible to perform realistic transformation without proper regularization (Kristy *et al*., 2013).

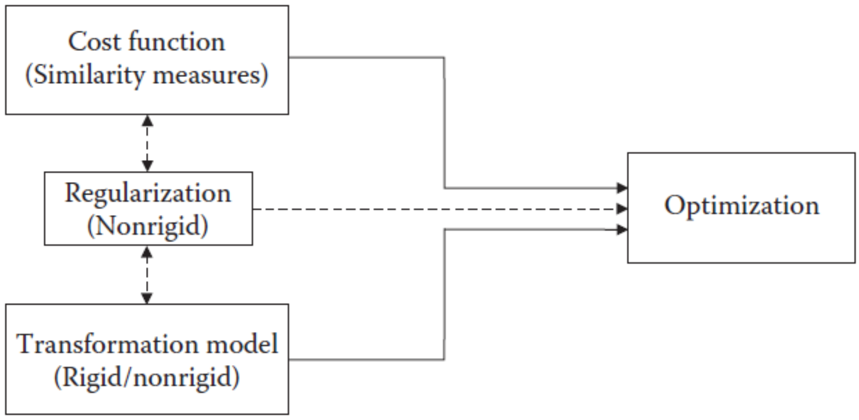

Figure 2.4 Component diagram of image registration
Source: Kristy *et al*. (2013)

In Figure 2.4 illustrated the component diagram of image registration. Solid lines represent required input/output, whereas broken lines represent optional input/output depending on the registration problem.

2.3 Use of deformable image registration for radiotherapy applications

Deformable Image Registration has become commercially available in the field of radiotherapy. DIR is an exciting and interesting technology for multi-modality image fusion, anatomic image segmentation, Four-dimensional (4D) dose accumulation and lung functional (ventilation) imaging. Furthermore, DIR is playing an important role in modern radiotherapy included Image-Guided Radiotherapy (IGRT) and Adaptive Radiotherapy (ART). DIR is essential to link the anatomy at one time to another while maintaining the desirable one-to-one geographic mapping (Jingu *et al*., 2013).

2.3.1 Dose accumulation with deformable image registration

The schematic diagram of creating dose accumulation with dose warping is shown in Figure 2.5. First, DIR is performed between CT1 (moving image) and

CT2 (reference image) to create a transformation, T1. Then, Resultant transformation was applied to dose 1 to create dose 1´, which is warped dose distribution according to reference CT image. Finally, we added the two dose distributions (dose 1 and dose 1´) to create dose accumulation.

This dose warping technique is expected to be useful for evaluation of dose accumulation between previous plan and current plan for re-irradiated patient, and interfraction dose. Arai et al evaluated the differences between cumulative dose in the spinal cord using rigid registration and that using DIR for two-step adaptive IMRT for head and neck cancer and showed the difference between the two registrations was 1.6 Gy and demonstrated that the difference might depend on the accuracy of the registration (Arial et al.,2013). Furthermore, Modern radiotherapy can use multimodality treatments to evaluate the irradiated dose for tumor and other organ at risks accurately, dose accumulation between different treatments is required.

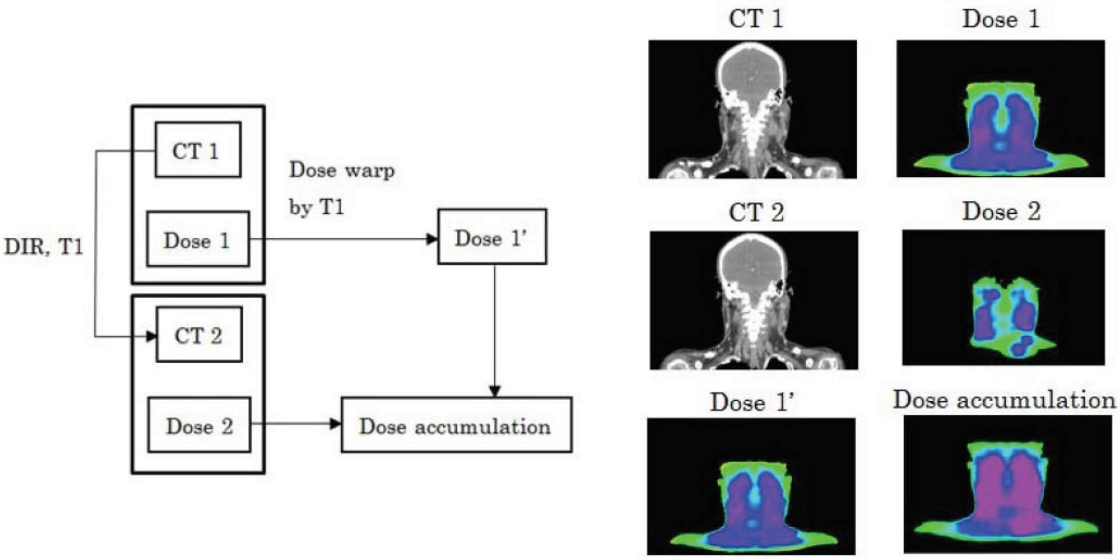

Figure 2.5 Schematic diagram for dose accumulation with deformable image registration (DIR). DIR was perfumed between CT1 and CT2 to create transformation, T1. Then, T1 was applied to Dose 1 to make Dose 1´. Finally, the Dose 1´ added to Dose 2 to create dose accumulation. Source: Jingu *et al*. (2014)

Nowadays, many the open source toolkits software for deformable registrations were developed such as the ITK/VTK/MITK software. However, they are large software toolkits and not only for radiation oncology, but for the entire image-processing community (Yang *et al*., 2011). In 2010 the software suite call deformable image registration and adaptive radiotherapy (DIRART) was developed by Yang (Yang *et al*., 2011). DIRART is the open source software toolkits which more focused on medical imaging, radiation oncology, and ART, and could be more natural to start with for users from these focused fields.

2.3.2 Deformable Image Registration and Adaptive Radiotherapy (DIRART) software

DIRART software suite for deformable image registration (DIR) plus adaptive radiotherapy (ART). DIRART has undergone several major revisions and currently consists of 450+ MATLAB program files with 40,000+ lines of code. It contains DIR algorithms, common ART functions.

Design of DIRART**:** As illustrated in Figure 2.6, DIRART is designed around the concepts of RT objects, including images, structures, doses, and DVFs. These RT objects (in ovals) interact via different DIR and ART tasks (in rectangles). The dashed arrows emphasize how DVFs or voxel mapping are applied to remap structures and doses. The dotted arrows emphasize that DIRART calls external Computational Environment for Radiotherapy Research (CERR) functions to do dose metric operations (DVHs, etc.) (Yang *et al*., 2011).

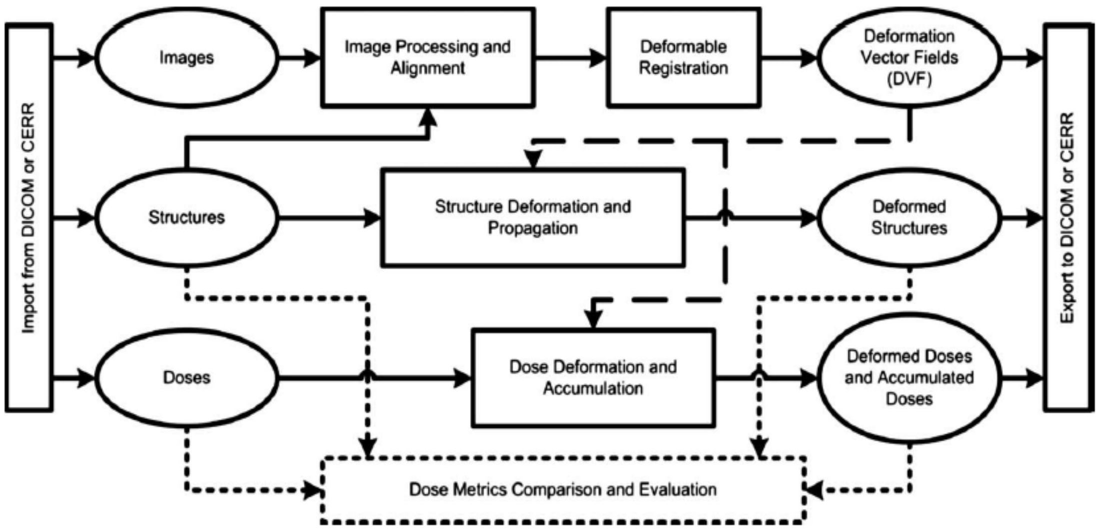

Figure 2.6 General workflow of DIRART software

Source: Yang *et al*. (2011)

DIRART implemented two common DIR frameworks, the asymmetric registration framework and the inverse consistency registration framework. Both frameworks support multi-resolution approach and multiple pass approach. An ART toolkit which is able to perform dose and structure remapping, dose accumulation and analysis using the DIR results, with a complimentary package to CERR to provide additional DIR and ART functions. Moreover, by exchanging DICOM-RT data, it could be used an external interface to the commercial treatment planning system (Yang *et al*., 2011).

DIRART software can provide many functions for ART, especially on the following tasks: 1) automatic contour propagation between treatment planning CT and daily CT, 2) remap data between planning CT and daily CT either way for evaluation purpose, 3) register all daily dose (to planning dose grid), to accumulate them for evaluation. Figure 2.7 illustrated the offline ART workflow in DIRART software when DIRART is able to perform the few tasks in the general working flow: 1) structure contour propagation, 2) dose deformation; 3) dose accumulation.

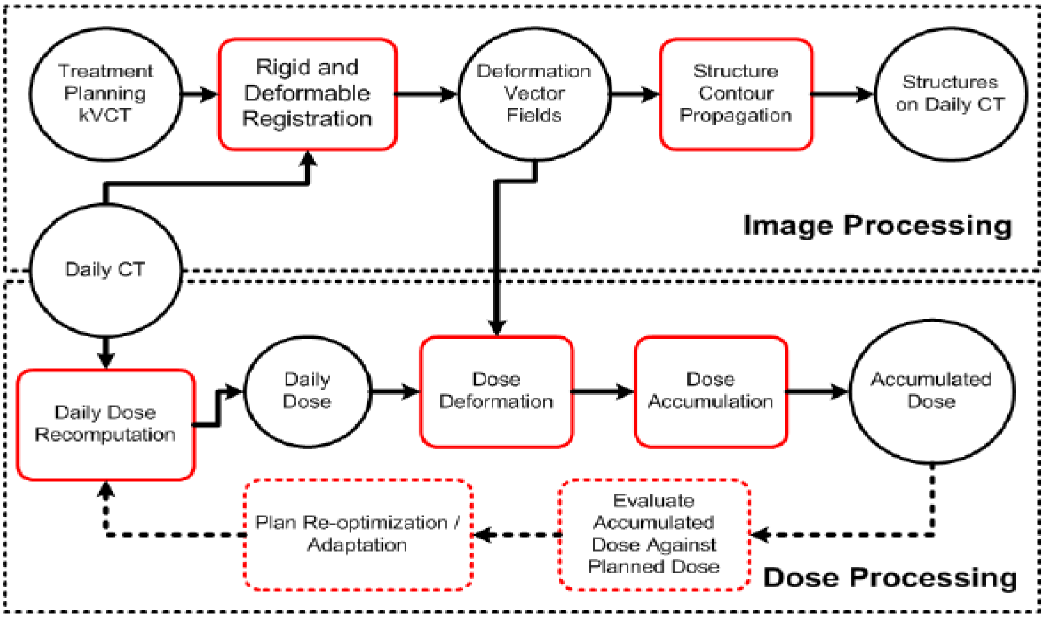

Figure 2.7 Offline ART workflow in DIRART software

Source: Yang *et al*. (2011)

Different operational parameters, used by the same algorithm, can also affect the registration accuracy. This implies that using automated, standard, or default settings may not give estimates with the greatest accuracy, suggesting a need for parameter optimization. Yeo *et al*. (2013) performed DIR with DIRART software, the greatest accuracy was exhibited by the *original Horn and Schunck* optical flow algorithm. Some algorithms failed to reproduce the geometry at all, while others accurately deformed high contrast features but not low contrast regions.

2.4 Validation techniques of deformable Image Registration

Validation of image registration is a challenging task. The goal of image registration is to find the correspondence of each voxel between image A and image B. Unlike the goal of autosegmentation, where the algorithm only needs to find the boundary of the organ, image registration has the additional burden of needing to find the correspondence of voxels within the organs as well. This becomes particularly important for advanced applications of deformable registration, such as dose accumulation, adaptive radiotherapy, and response assessment (Kristy *et al*., 2013).

There are several different methods to validate image registration. They can be broadly categorized into the following groups.

2.4.1 Volume-based criterion: propagation of region of interest (ROI) contours between registered images

Every image contains some number of ROIs, including tumors, organs, or other identifiable substructures. Once an expert user has contoured these ROIs, they can be used to validate the image registration algorithm. In an ideal situation, the expert user would perfectly contour the ROIs on each image. (contours A on image A and contours B on image B) and the image registration algorithm would propagate the contours on image A onto image B (resulting in contours A′). The differences between contours A′ and contours B would be due to uncertainties in the image registration algorithm. The most common overlap metric is the Dice similarity coefficient (DSC): The metric computes the number of pixels that overlap between the two volumes as in equation 2.6, which is defined as two times the overlap of A′ and B, divided by the sum of the volume of A′ and B as shown below.

$$DSC = 2(A' \cap B)/(A' + B) \tag{2.6}$$

If A′ and B have no overlap, then the DSC is 0, and as the contours become identical, the DSC approaches a value of 1 (Kristy *et al*., 2013). Goldberg–Zimring *et al.* (2005) suggested that satisfactory volume matching should be 70% or more for adaptive radiotherapy applications.

Ramadaan *et al*. (2013) evaluates the performance and accuracy of a commercial DIR system with Demons-based algorithm by using the standard radiotherapy phantoms and one in-house built phantom. The algorithm performance was assessed quantitatively, using volume analysis and the DSC, and also assessed for 5 head and neck cancer patients using clinical CT images. Phantom investigations gave varying results with average DSC scores ranging from 0.69 to 0.93, with an overall average of 0.86 ± 0.08. Clinical results were generally better with a DSC range of 0.75-0.99 and an overall average of 0.89 ± 0.05, DIR reduced the time required by physicians to contour the images of head and neck cancer patients by ~47%.

2.4.2 Image matching Quality: Evaluating the intensity correlation

Similarity measure is a quantitative measure which tells us the degree of similarity between two images. The most popular metrics include the sum of the squared intensity difference (SSD), correlation coefficient (CC), and mutual information (MI). The intensity difference-based metrics are computationally attractive, but they require that the two objects have intensity values in the same range; the correlation coefficient requires that the intensities of the two images are related by a linear transformation, whereas MI is the metric of choice when images from different modalities need to be registered (Kristy *et al*., 2013).

Mean square difference (MSD) will be zero when the images are correctly aligned and will increase with misregistration (registration error). These measures are normalized so that they are not affected by the number N to solve the problem when use the sum square difference.

Correlation coefficient can take values between -1 and +1 where +1 represents a maximum of correlation between images. The CC method assumes a linear relationship between the intensity values in the images; therefore, it can deal with differences in image contrast and brightness (Kristy *et al*., 2013).

NMI method is the alternative normalizations of the joint entropy, which proposed to overcome the overlap problem in mutual information (Kristy *et al*., 2013). NMI can range between 0 and 2 and values of NMI >1 typically represent a good match between images (Penney *et al*., 1998)

Varadhan *et al*. (2013) demonstrated the evaluation based on anatomical correspondence, physical characteristics of deformation field, and image characteristics can facilitate DIR verification with the ultimate goal of implementing adaptive radiotherapy. Rigaud *et al*. (2013) compared the performance of multiple deformable image registration methods. The two most effective DIR methods were the demons and the free form deformation (FFD), with both the mutual information (MI) metric and the filtered CTs.

2.4.3 Deformation fields analysis

The analysis of deformation fields enables to ensure that the deformations are physically plausible and that forward and backward transformations are inverse-consistent.

1) Inverse consistency error (ICE): The inverse consistent error measures the degree of consistency between forward and backward transformation. The forward transformation, T_{FW} maps the point i to j the backward transformation, T_{BW} maps the point j to i′. The distance between i and i′ consists on the inverse consistent error (Figure 2.8): IC = $\|I - i'\|$. The optimal transformation is found minimizing d distance.

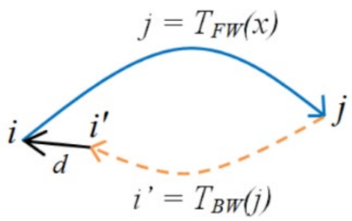

Figure 2.8 Schematization of the inverse consistent error: d = IC error = $\|I - i'\|$

Source: Lourengo *et al*. (2013)

2) Jacobian analysis: The Jacobian matrix contains 9 values (for a 3D transformation) and describes how the transformation changes in each of the 3 directions. The determinant of the Jacobian matrix gives the local volume change and both can be calculated at any point in the transformation and describe the local properties of the transform at that point.

To ensure that no folding had occurred during registration the transformation must be invertible, i.e., it has an inverse. The Jacobian is an indicator of the invertibility of the transformation and it is given by the following equation (Lourengo *et al*., 2013):

$$J_T(x) = \begin{vmatrix} \frac{\partial T_x(x)}{dx} & \frac{\partial T_x(x)}{dy} & \frac{\partial T_x(x)}{dz} \\ \frac{\partial T_y(x)}{dx} & \frac{\partial T_y(x)}{dy} & \frac{\partial T_y(x)}{dz} \\ \frac{\partial T_z(x)}{dx} & \frac{\partial T_z(x)}{dy} & \frac{\partial T_z(x)}{dz} \end{vmatrix}$$

J_T (x) = 1 if the volume at x remains the same after the transformation, J_T (x) > 1 if there is volume expansion and J_T (x) <1 if there is volume shrinkage. J_T (x) ≤ 0 means that folding had occurred which is physically impossible and mathematically not invertible (Lourengo *et al*., 2013).

Varadhan *et al*. (2013) assessed the DIR on the head and neck case, the ICE was much larger for the demons algorithm (6.5 mm) as compared to B-spline (0.7 mm). The MSD was comparable for both algorithms. The minimum Jacobian was used to assess the registration algorithms in forward and inverse directions for all three anatomical sites. Lourenco *et al*. (2013) evaluated the DIR performance based on visual inspection of registration results and computation of similarity measures to ensure image matching quality, deformation field analysis and calculation of the inverse consistent error to ensure that the transformations are physically plausible. The inverse methods gave the most robust results in terms of inverse-consistency between the composition of forward and inverse transformations with a median mean ICE of 0.009 mm.