

# 1 Deformable Image Registration and Validation

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## 1.1 Introduction

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As explained in Section ref!) effects of motion can have a significant impact on a radiation treatment. Therefore a proper investigation is necessary for each specific patient. There are several motion mitigation techniques available that can operate on beam delivery, patient immobilization or treatment planning level.

An important part of motion mitigation is proper and frequent imaging. While most commercial treatment planning software provide rigid registration between different images, deformable image registration (DIR) is currently rarely used. DIR can quantify anatomical and biological variations better compared to rigid registration [Sarrut, 2006] and is essential as well in photon as in ion radiotherapy, with usage in adaptive radiotherapy [Yan et al., 1997, Yan, ], 4D optimization [Trofimov et al., 2005], 4D dose calculation [Flampouri et al., 2006], contour propagation [Lu et al., 2006]. DIR usage spreads even into other categories, besides radiotherapy [Cleary and Peters, 2010, Her, 2012, Nithiananthan et al., 2011, Naini et al., 2010]. Several different DIR algorithms are available, such as B-spline [Rueckert et al., 1999], Demons [Thirion, 1998], linear elastic finite element [Venugopal et al., 2005], optical flow [Zhong et al., 2007], viscous fluid [Christensen et al., 1996], etc.

One of the reasons for the DIR is not used in commercial software is the lack of proper DIR quality assurance (DIRQA). While several different DIRQA methods exist, none of them are definitive and most of them are time consuming. It is possible to evaluate DIR with deformable phantoms, where the type and size of deformation is known [Kashani et al., 2007, Kirby et al., 2011]. However such quality assurance is time consuming and it would be hard to use it in everyday clinical work flow DIR validation can also be based on landmark positions, specifically their location before and after registration. In absence of externally planted markers, locating landmarks in patient anatomy can be take a fair amount of time and it can be difficult to identify landmarks in low-contrast regions [Varadhan et al., 2013]. Another option is to compare delineated contours with the propagated ones. It is more efficient technique than landmark checks, however it is even more time consuming and it does not address the region within the contour.

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In this chapter tools to handle DIR and DIRQA will be presented. Tools were constructed for open-source software 3D Slicer, described in Section 1.2.1. In Section 1.2.2 details on how DIR was performed will be explained. Next, Section 1.2.3 will address the DIR validation - an extensive tool was created with various functionalities to tackle DIRQA. DIR and DIRQA tools were tested on a real patient data and results will be presented in the Section 1.3. Lastly, everything will be summed up in Section 1.4.

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## 1.2 Implementation

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### 1.2.1 3D Slicer

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3D Slicer (Slicer) is a software platform for analysis and visualization of medical images [Slicer, 2016a, Fedorov et al., 2012]. Slicer is a free, open-source software (BSD-style license) available on Windows, MacOSX and Linux operating systems. It comes with a vast variety of tools, such as:

- Handling a variety of image formats, including DICOM, NRRD and MHA
- Visualization of voxel images, polygonal meshes and volume renderings
- Registration tool (rigid and non-rigid) and display of vector fields
- Automatic image segmentation
- Analysis and visualization of diffusion tensor image data
- Device tracking for image-guided procedures

The foundation of Slicer is written in C++ and it's functions can be accessed also with Python to provide rapid, iterative development. Graphical user interface is built in Qt. Visualization is based on VTK, a graphical library commonly used in scientific research.

Slicer is a research tool and as such offers tools to implement new functionalities in the form of extensions (modules). They can either be execution of external command-line program, or writing modules with new features, or automate Slicer processes in form of scripted modules. In the next sections different Slicer modules will be presented, which were all developed in the scope of this thesis. The purpose of modules is to perform DIR and provide validation of the obtained results.

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### Registration nomenclature

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To provide a clear and consistent description of methods used, an overview of the expressions is given here.

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- **Reference image** - image that serves as a reference position in registration (image that is registered to).
- **Moving image** - image that is being registered to the reference image (image that is registered from).
- **Warped image** - result of applying transformation map of registration to moving image. It should be as close to the reference image as possible.
- **True registration** - registration from moving to reference image. Similar, everything connected to true registration will use true (true vector field, true warped image, true absolute difference, true Jacobian, etc.).
- **Inverse registration** - registration from reference to moving image (opposite or inverse of true registration. As in true registration, term inverse can be used for everything connected to it (inverse vector field, inverse warped image, inverse absolute difference, inverse Jacobian, etc.).

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### 1.2.2 Registration

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A commonly used software for registration in medical research is Plastimatch [Shackleford et al., 2010]. It is free and open-source software, available as a command-line executable program. Plastimatch B-spline registration is also available in Slicer as part of an extension SlicerRT [Pinter et al., 2012]. The integration of Plastimatch in Slicer brings the advantage of a graphical user interface and hence a quick modification of parameters and display of results. However, the disadvantage comes when a large number of registrations is required, since a user presence is required. In a complete 4DCT registration there are  $2(N - 1)$  registrations required - from reference phase to each of  $N$  phases of 4DCT and vice versa, except for the reference phase itself. Typical 4DCT consist of 10 phases, therefore a automatic registration of a 4DCT is a necessity.

Automatic DIR was constructed from two parts. First, a DIR Python class was written to handle image locations, to preform DIR in the Plastimatch module, to use right naming conventions and to store all output files (vector fields and warped images). DIR Python class is shown in Appendix 1.5.

Beside DIR Python Class a patient hierarchy concept was introduced to handle loading of different phases in Slicer and track progress of DIR and DIRQA. It is explained in Section 1.2.2.

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### Patient hierarchy

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Patient hierarchy follows a subject hierarchy principle in Slicer. It was designed for a clear overview of the registration process, DIRQA and all resulting files. Another reason is to track

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DIR and DIRQA in case if they are interrupted by Slicer crash. DIR and DIRQA files can be quite large and can cause Slicer to run out of memory. With patient hierarchy Slicer is able to continue work from where it was interrupted rather than starting anew.

There are several levels in patient hierarchy. Each level also has different attributes, where details regarding each level can be written.

- Level 1: **Patient name** - separates different patients.
- Level 2: **Registration node** - separates between different registration, e.g. registration between 4DCT phases, between CT and 4DCT, MRI and CT...

*Attributes:*

- The file directory of images, vector fields and registration quality files.
  - Number of phases to be registered.
  - Reference phase
- Level 3: **Registration phase** - specific registration phase. Registration is done between all phases and the reference one. There have to be at least two phases
  - Level 4: **Node** - can be either an image, a vector field, an inverse vector field or any of DIRQA nodes (see Section 1.2.3).

*Attributes:*

- Exact file paths for specific node.
- Statistical values if node is absolute difference, Jacobian or inverse consistency (see Section 1.2.3).

Patient hierarchy can be constructed in two ways. First option is to manually crate the whole patient hierarchy, from top to bottom level, with necessary attributes. Second option is to use a automatic script to look for files on hard drive and create corresponding levels. The second option is possible only by using proper naming conventions are file names and locations.

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### 1.2.3 Registration Quality Checks

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In order to provide visual and quantitative assessment of the registration quality a **Deformable Image Registration Quality Assurance** module was created. It provides different image checks (false color, checkerboard, absolute difference, flicker, movie and landmark positions) and vector checks (Jacobian and inverse consistency error). Details on all different checks will be explained in this section. Reference image, warped image, vector and inverse vector (vector from reference to moving phase) are used as inputs for DIRQA module. Additional landmarks and region of interest (ROI) can be used as an input.

All check that use some kind of mathematical operation on or between images (absolute difference, Jacobian and inverse consistency error) were build using tools from ITK library [Yoo et al., 2002].

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### False color

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A good way to see difference between two images is to overlay them. However, since CT scans are usually displayed in grayscale color code, the differences can become indistinguishable. Especially if the images are quite similar, as reference and warped image usually are. With applying opposite color code to overlaying images two things are achieved. Firstly, regions where the registration was successful will be in grayscale. Furthermore the differences will be in color of image they belong to. In the module we used red and cyan color code for reference and warped image respectively. See Fig. 1.1 for details.

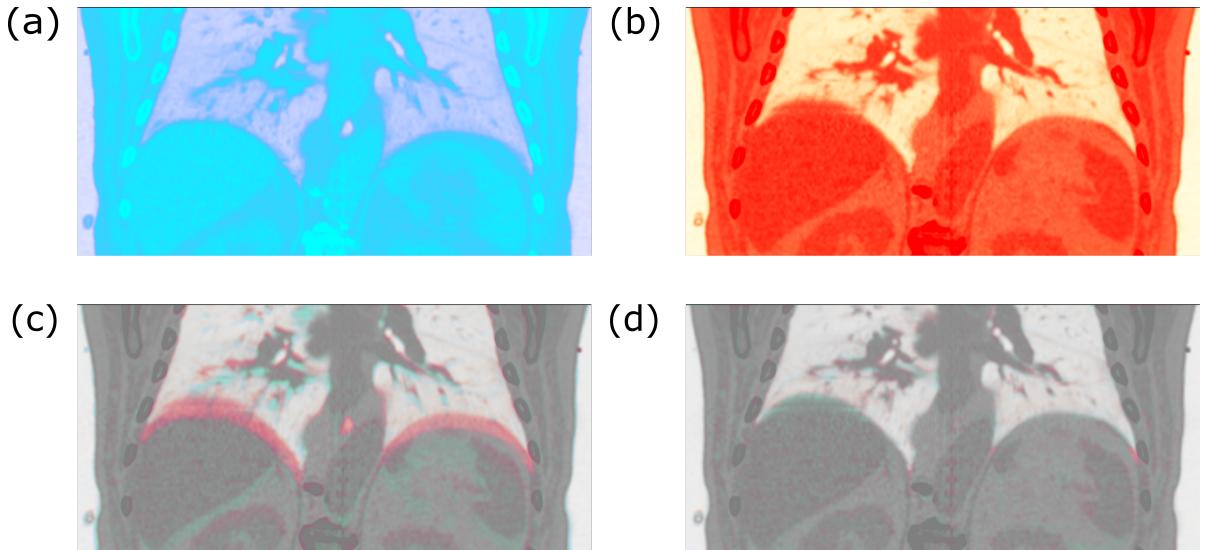


Figure 1.1: Example of false color overlay. Images (a) and (b) show red and cyan color code, respectively, for CT scan. (c) displays overlaid false colored images before and (d) after registration.

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### Checkerboard

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As the name suggests, checkerboard creates an image of tiles. Each tile alternates between reference and warped image, as shown in Fig. 1.2. The differences between two images become apparent if there is no smooth transition from one tile to the next. The number of tiles can be manually selected. While the checkerboard offers clear indication of differences, it requires user to spot them - similar to false color.

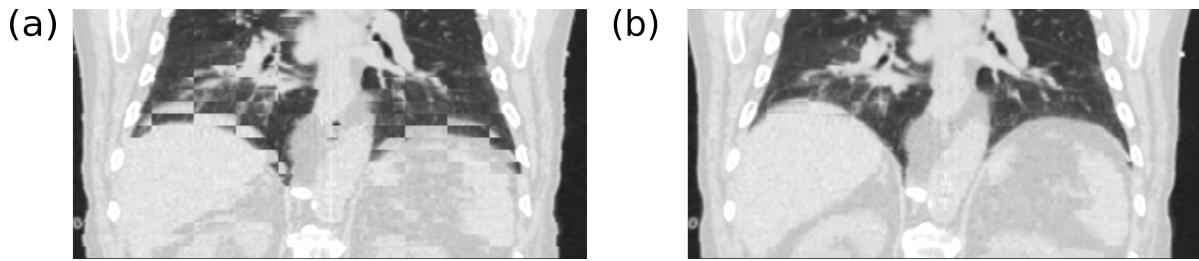


Figure 1.2: Example of checkerboard image. Image consist of tiles alternating between two images.

Tiles in image (a) alternate between scans before registration and in image (b) after registration.

### Absolute difference

To stress the difference between reference and warped image an absolute difference between voxel values is calculated and displayed. New image is generated, with voxels populated as the absolute difference between reference and warped image voxel values, as shown in Fig. 1.3. Furthermore, average, standard deviation, minimum and maximum of absolute differences are calculated for quantitative assessment of registration quality (in ideal case all values would be 0).

The absolute difference feature is similar to false color, but it displays differences clearer and it also provides quantitative values. In contrast to false color which only relies on user examination.

Absolute difference can be computed between reference and moving image, named default absolute difference, to provide initial estimate of difference between images. After the registration it can be done on true and inverse warped images (true and inverse absolute difference) to show registration results. Usually, registration works on minimizing absolute difference, so it is a direct indicator of registration success.

To spare computational time or to focus on a specific region, absolute difference can also be calculated just on a specific ROI (if used as an input). Usually ROI around patient body is selected, rather than calculating on a whole patient CT.

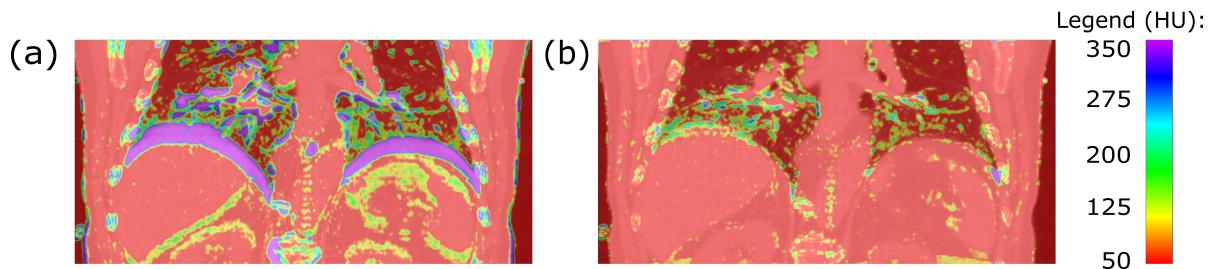


Figure 1.3: Absolute difference image before (a) and after registration (b). The mean absolute difference before registration (default absolute difference) is 62 HU and 31 HU after registration (true absolute difference).

### Movie

Medical images are usually quite large - typical CT image consist of  $512 \times 512 \times 100$  pixels, which makes inspecting image checks (false color, checkerboard, absolute difference) a time-consuming task. Movie feature allows for smoother display of different image slices. User selects, which view he would like to inspect (axial, sagittal or coronal) and presses start. Selected views then start scrolling from one limit to the other. It allows user to focus on registration details, rather than scrolling through slices.

Movie and flicker (explained below) do not offer any specific registration check, but improve the process of registration quality assurance.

### Flicker

While it is possible to display two images side by side in Slicer, it can sometimes be hard to see fine differences between the two images. Flicker alternates between reference and warped image on a single display. Flicker changes image each 0.5 s.

### Landmark positions

Landmark positions are often used to determine registration spatial accuracy [Castillo et al., 2009]. Landmark can either be a specific feature in patient anatomy, or an external marker. The position of the landmark in the warped image would ideally be at the same position as in reference image. The module measures the Euclidean norm between the landmark position in reference and warped image.

User has to manually select landmarks in reference and moving image. For landmarks based on patient anatomy a physician is required. Landmark from moving image can then be automatically transformed with transformation vector field to obtain position in warped image or it can be manually selected in warped image.

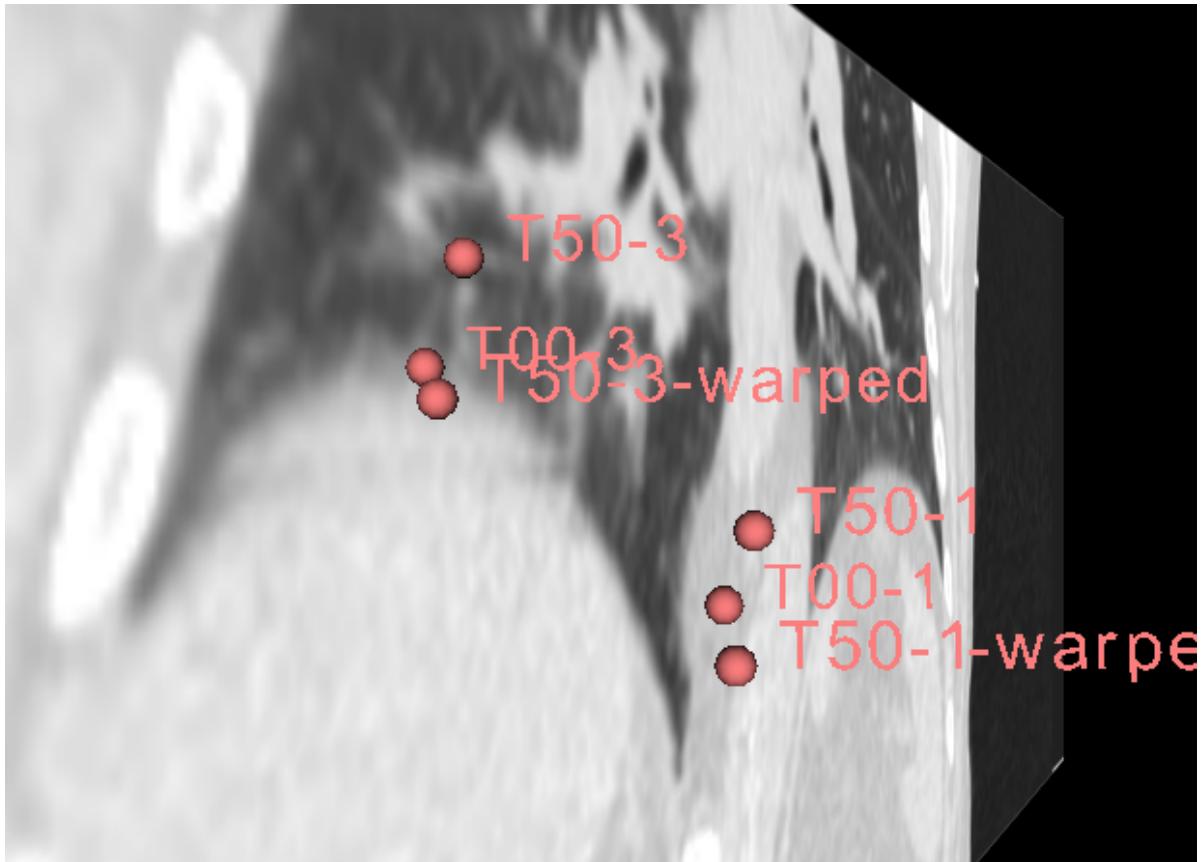


Figure 1.4: 3D display of landmarks in three phases - T00 and T50 (end-inhale and end-exhale, respectively) and T50 warped to T00 (T50-warped). Average distance of corresponding landmarks between T00 and T50 is 0.1 and between T00 and T50-warped is 0.1.

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### Jacobian

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Jacobian determinant (Jacobian) of the vector field is used to validate physical behavior of registration [Leow et al., 2007]. Jacobian of vector field should be positive, since negative Jacobian values correspond to folding, which is physically unrealistic for patient anatomy (organs can not be folded) [Chen et al., 2008, Rey et al., 2002]. Expansions and contractions around a point are indicated by Jacobian values of greater and less than 1, respectively.

DIRQA module calculates and displays the Jacobian of the vector field. Average, standard deviation, minimum and maximum values of Jacobian are also displayed. Similar to absolute difference it also has ROI feature implemented.

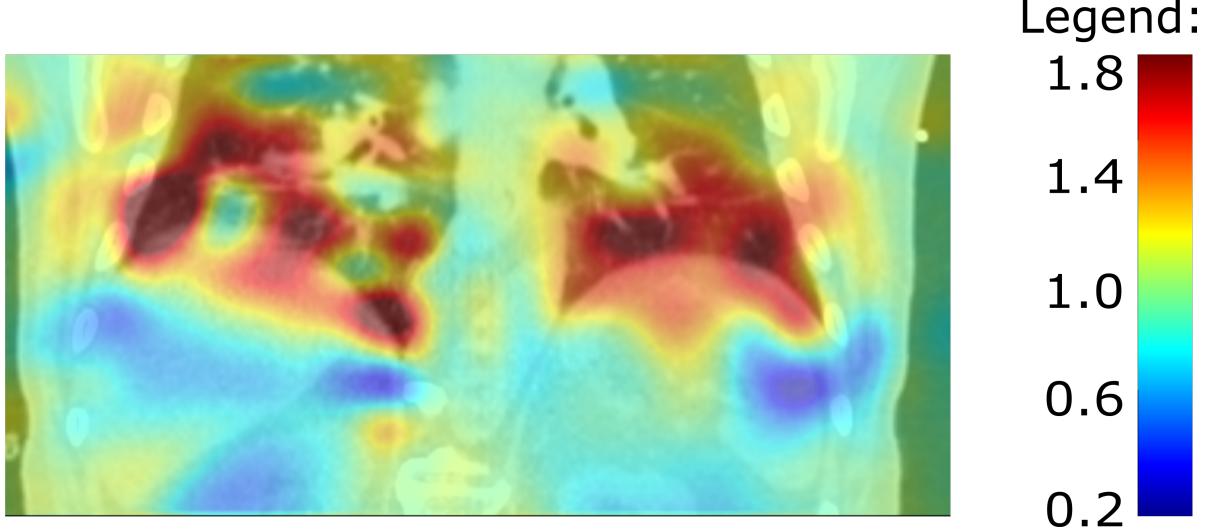


Figure 1.5: Image of Jacobian overlaid on CT scan. The average value of displayed Jacobian is 1.0 with 0.7 STD. CHECK!

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### Inverse Consistency Error

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Inverse consistency error (ICE) is consistently used in literature as one of the main vector field checks **citati**. The principle is as followed. Suppose we have two vector fields -  $u_{AB}$  obtained from registration of image A to B and  $u_{BA}$  from registration of image B to A. The two registrations should be preformed separately. In ideal scenario,  $u_{AB}$  would be a direct inverse of  $u_{BA}$ . However, deformable image registration algorithms do not yield perfectly inverse consistent vector field.

To check for ICE, an algorithm was created that first transforms point  $x$  using  $u_{AB}$ . Newly obtained point  $x'$  is then transformed with inverse vector field,  $u_{BA}$  which yields  $x''$ . The ICE is defined as Euclidean norm between  $x$  and  $x''$ :

$$ICE = x - x'' = x - u_{BA}(x') = x - u_{BA}(u_{AB}(x)) \quad (1.1)$$

Points  $x'$  and  $x''$  can have an arbitrary position in space, while vector fields  $u_{AB}$  and  $u_{BA}$  are positioned on a grid. To apply transformation  $u_{BA}(x')$  a interpolation has to be made to put  $x'$  on a  $u_{BA}$  grid. A tri-linear interpolation is used in this module.

As in Jacobian, ICE image is calculated and displayed, along with values for average, standard deviation, minimum and maximum values. ROI feature is also implemented. An example is shown in Fig. 1.6

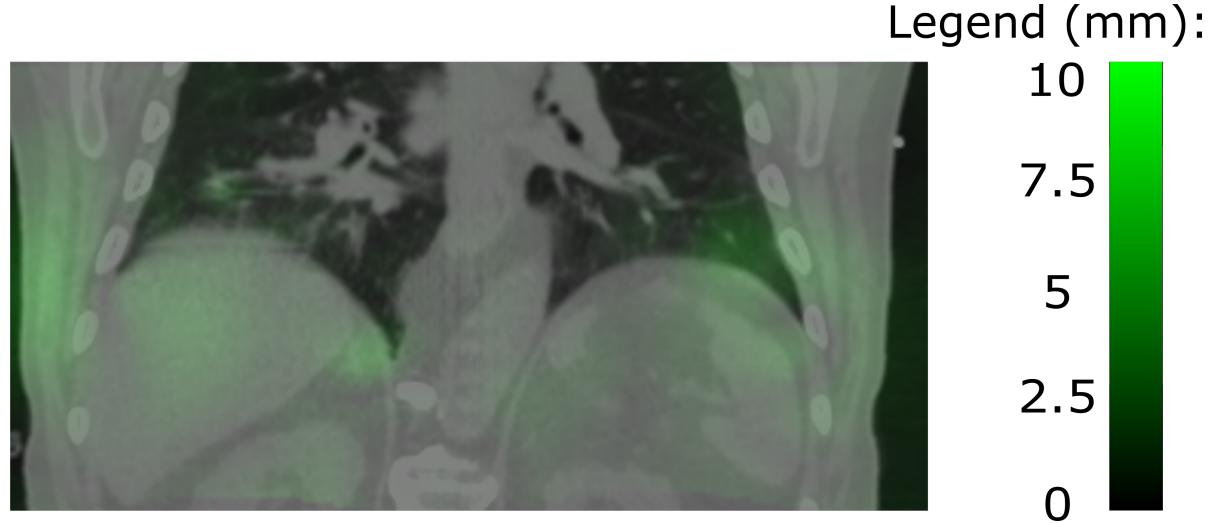


Figure 1.6: Image of inverse consistency error (ICE) overlayed on CT scan. The average value of displayed ICE is 1.0 with 0.7 STD. CHECK!

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## 1.3 Verification

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Several extensions for Slicer were created to tackle the issue of motion in treatment planning. With these extensions it is possible to perform DIR, DIR quality assurance, estimate organ motion and make midP scans. All extensions have to be checked on actual clinical data, to make future extension usage possible. Furthermore it is necessary to test if extensions could be used in a typical clinical work flow. Especially DIR validation, which is the reason for the lack of DIR in commercial treatment planning software.

DIR and DIR validation was done on lung 4DCT patient data. As part of a GSI pig-irradiation project (?) DIR and DIR validation was integrated in clinical work flow. Finally an example of midP scan on a liver cancer patient and its usage will be presented.

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### 1.3.1 Registration of lung 4DCT patient data

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Chapter **REF** and **REF** present studies on simulating active scanning carbon ion treatment (CiT) for lung cancer patient. The effects of interplay can drastically change the dose distribution for CiT and it is necessary to quantify effects of motion with DIR and transfer results into treatment planning software (TRIP4D in this case). An automatic procedure is required to perform DIR and DIR validation on a large number of patients. This was achieved with Slicer modules described in Section 1.2.

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#### Materials and Methods

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A time-resolved CT (4DCT), consisting of 10 motion phases (0% - 90%) with resolution ? was acquired for 23 patients. Phase 0% corresponds to an end-inhale phase and was chosen as a reference phase.

DIR was performed for each patient between each phase and reference phase and vice versa (true DIR and inverse DIR). For each patient 18 registrations were made, leading to 414 registrations in total.

DIRs were done with B-Spline Plastimatch module and patient hierarchy in Slicer (see Section 1.2.2 and 1.2.2). Two stages were used with details given in Table 1.1.

Table 1.1: Parameters used for Plastimatch registration. A mean squared error metric was used.

Details for each parameter can be found in [Plastimatch, 2016].

Parameter	Stage 1	Stage 2
Resolution	4,4,2	1,1,1
Grid size	50	15
Regularization lambda	0.005	0.005
Iterations	200	100

Absolute difference was computed for three image pairs: reference and moving image (default absolute difference), reference and moving warped image (true absolute difference), moving and reference warped image (inverse absolute difference). In total 621 absolute differences were calculated and a down-sampling by a factor of 2 was done on all images before calculation to save computer time. Similarly, 414 vector fields were also down-sampled by a factor of 2 before calculating Jacobian and ICE checks.

ROI around patient body was manually created to get better results - area outside of patient is roughly the same in all states (air) and does not contribute to DIR. ROI was then used in absolute difference, Jacobian and ICE.

For each patient it took around 1 h for all 20 DIR and **30 min** for complete DIRQA on all 20 DIR on Linux computer with 8 clusters and 16 GB RAM.

## Results

DIR was successfully performed on all 23 patients. An example of DIR is shown on Fig. 1.7. Vector fields resulting from all DIR were analyzed and data is shown in Table 1.2. There was no statistical difference between true and inverse vector fields. The biggest contribution to vector field magnitude was from superior-inferior direction (around 50%), next was anterior-posterior direction (around 30%) and the smallest contribution was from left-right direction (around 20%).

Table 1.2: Data of vector magnitudes. Values are presented as average (range).

	True vector field	Inverse vector field
Mean	0.38 (0.01 - 1.28)	0.38 (0.01 - 1.3)
STD	0.95 (0.04 - 3.17)	0.98 (0.04 - 3.55)
Max	9.67 (0.61 - 28.56)	10.17 (0.56 - 37.11)

Dependence of true and inverse absolute difference on default absolute difference is shown in Fig. 1.8. Fig. 1.8 also shows default absolute difference distribution across 9 phases.

Distribution of Jacobian and ICE results are shown in Fig. 1.9 and 1.10. Maximum values of true and inverse maximum and minimum Jacobian and ICE were tested against maximum vector magnitudes and fitted with linear function. Results are plotted in Fig. 1.12. Additionally, dependence of maximum true Jacobian on minimum inverse Jacobian was tested and results are displayed in Fig. 1.11. Parameters from linear fit in Fig. 1.11 were used to calculate so-called scaled Jacobian for outliers. Each voxel,  $x$ , in scaled Jacobian,  $S$  was calculated from true and inverse Jacobian,  $J_{True}$  and  $J_{Inverse}$ , as:

$$S(x) = 1.7 \ln(J_{True}(x)) + \ln(J_{Inverse}(x)) \text{content...} \quad (1.2)$$

Example of scaled Jacobian is shown in Fig. 1.11.

All linear fits used in Fig. 1.8, 1.11 and 1.12 were statistically significant ( $p < 0.05$ ).

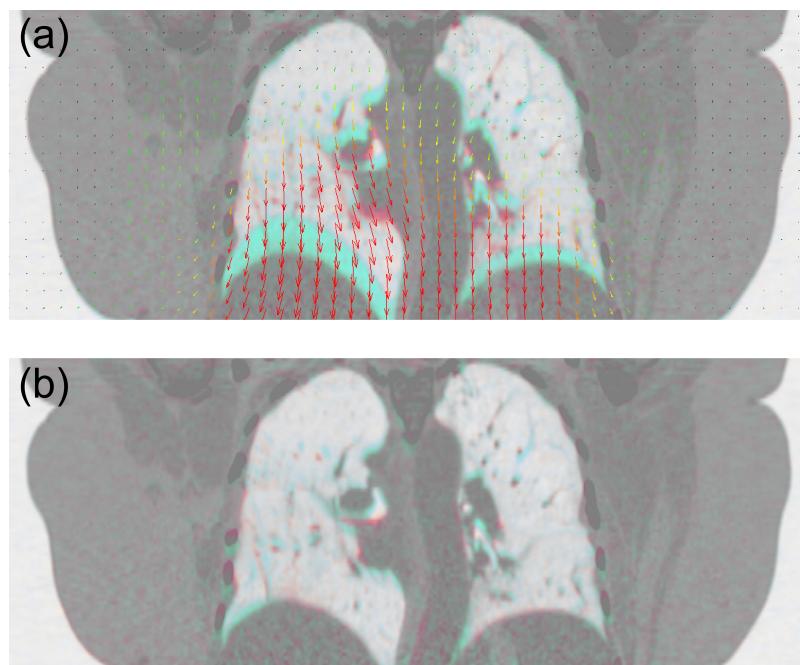


Figure 1.7: False color overlay of two phases before (a) and after (b) DIR. Vector field is displayed on image (a) as arrows.

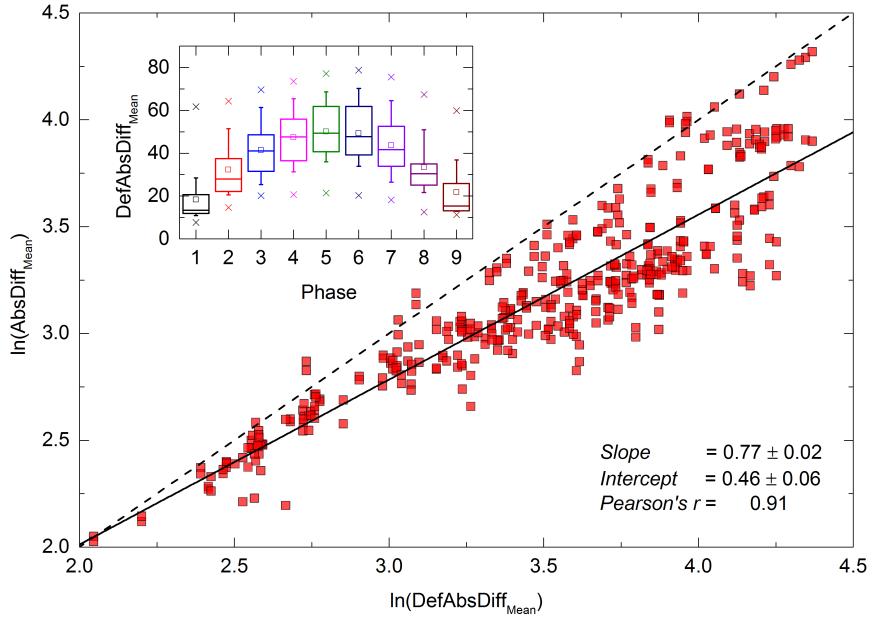


Figure 1.8: Natural logarithm of true and inverse absolute difference (AbsDiff) plotted against default absolute difference (DefAbsDiff). Solid line shows linear fit, with parameters written in corner. Dashed line shows  $y(x) = x$  plot. Inset shows box plots of mean distribution of default absolute difference across nine 4DCT phases. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

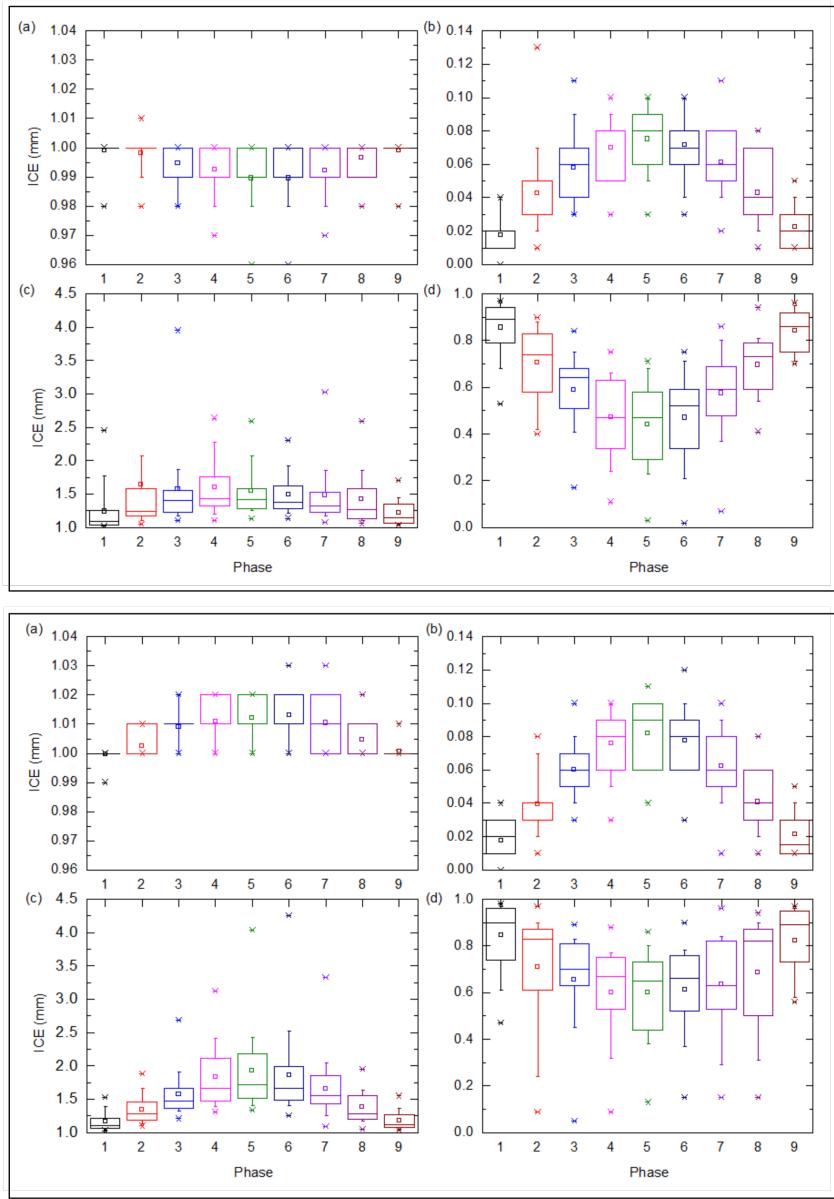


Figure 1.9: Data for Jacobian of vector fields (top) and inverse vector fields (bottom) for 9 4DCT phases (reference phase 0 is excluded) for 23 lung cancer patients. Mean, STD, maximum and minimum are represented as (a), (b), (c) and (d), respectively. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

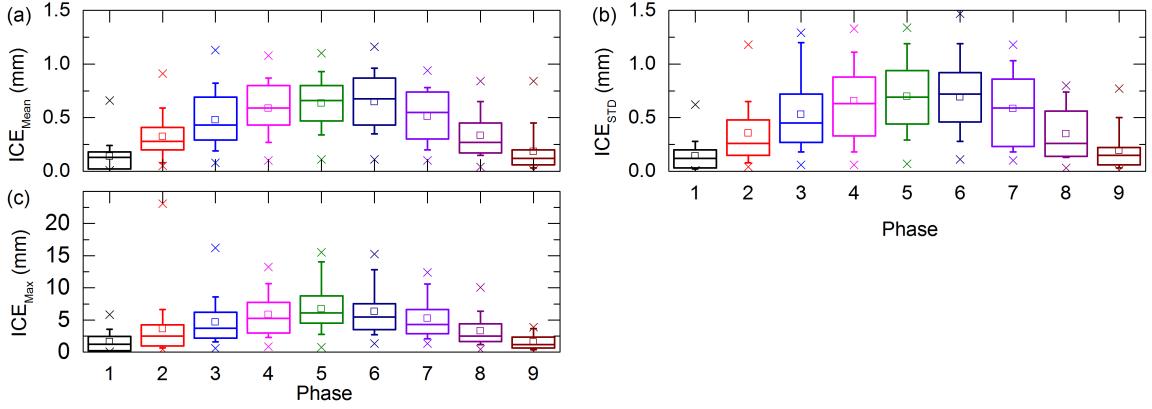


Figure 1.10: Data for ICE for 9 4DCT phases (reference phase 0 is excluded) for 23 lung cancer patients. Mean, STD, maximum are represented as (a), (b) and (c), respectively. ICE Minimum is 0 throughout all phases and patients. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

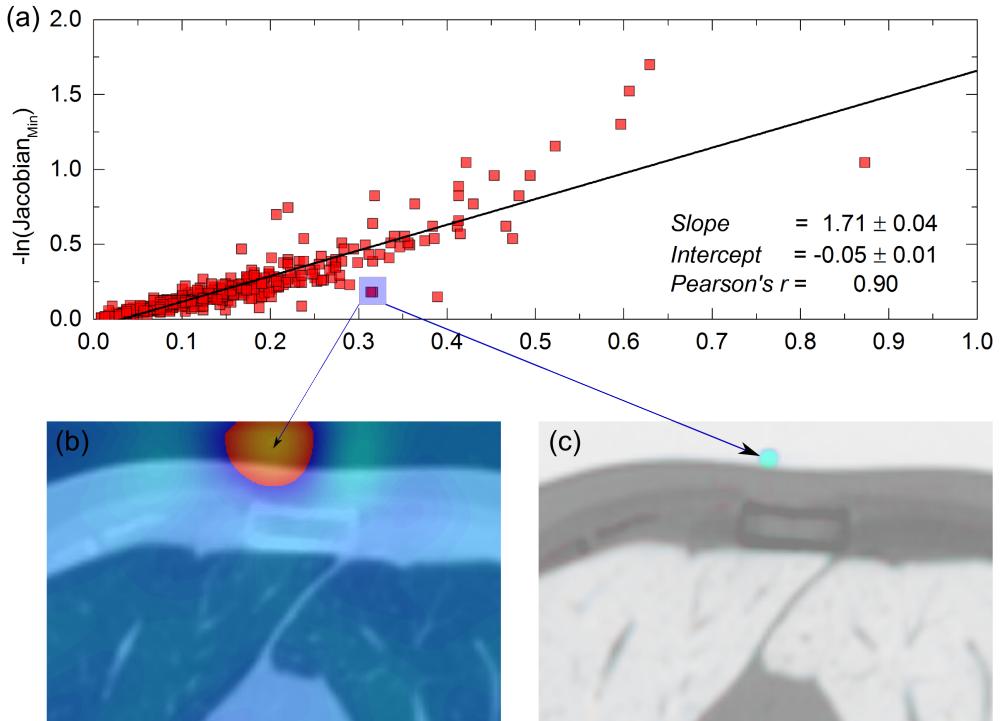


Figure 1.11: (a) Plot of negative natural logarithm of minimum Jacobian versus maximum Jacobian. Linear fit is displayed with solid line and it's parameters are given in the corner. (b) Shows part of the image of modified Jacobian (see text) overlayed on patient CT scan. (c) shows the CT scan of phases where Jacobian patient in (b) was calculated in false color.

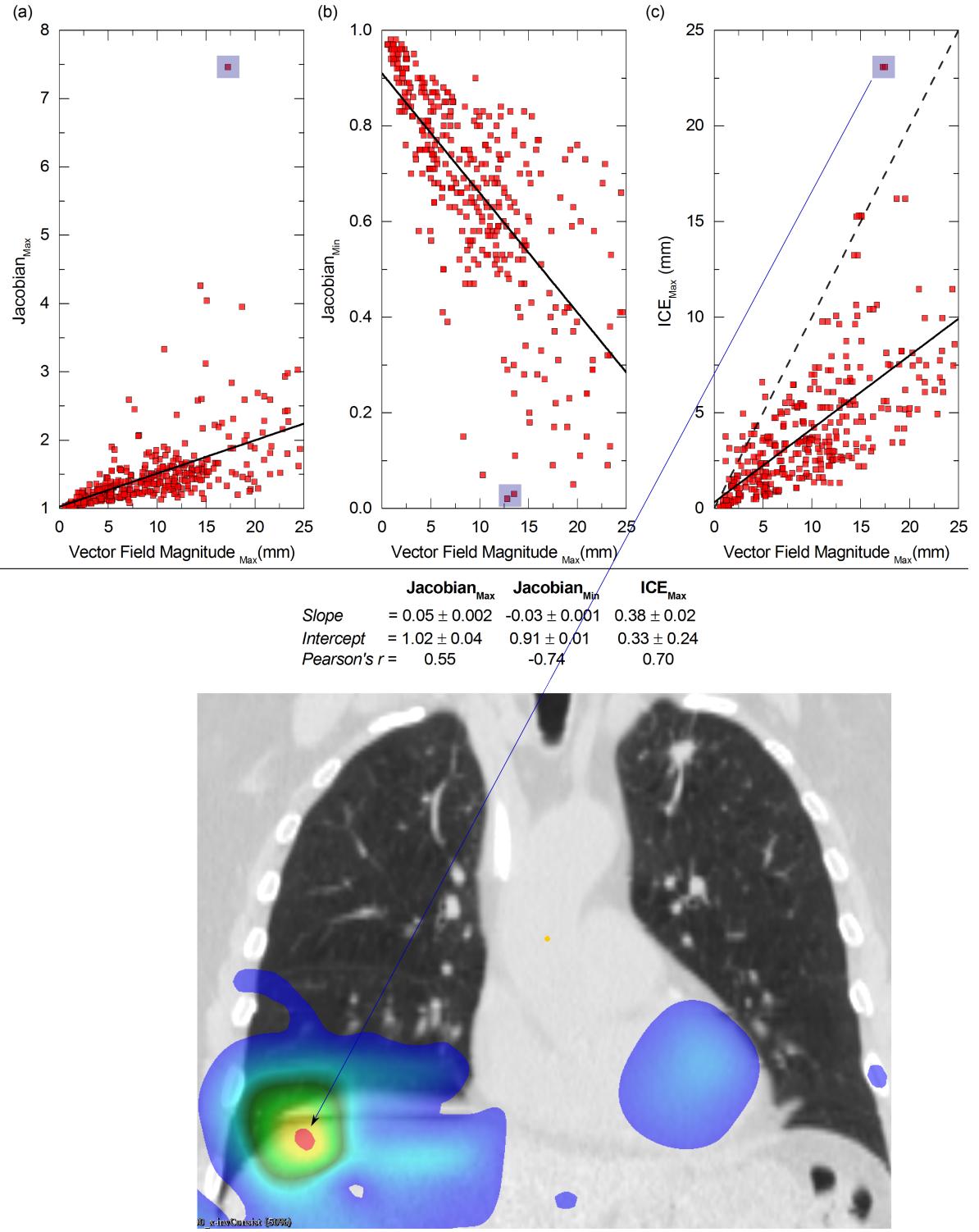


Figure 1.12: Values of maximum Jacobian (a), minimum Jacobian (b) and ICE (c) plotted against maximum vector magnitudes. Linear fit is displayed with solid line and parameters are written below the plots. Dashed line in (c) shows  $y(x) = x$  plot. Values resulting from patient on image (d) are highlighted with blue squares in (a)-(c). ICE is displayed on (d) using color table as displayed in legend.

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## Discussion

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Vector field magnitudes confirms previously published data that the biggest motion for lungs is in superior-inferior direction [Seppenwoolde et al., 2002, Britton et al., 2007, Liu et al., 2007]. The mean vector field magnitude is small (in submilimiter range), because the ROI included the whole patient body, not just the lungs where most of the motion occurs. Vectors and inverse vectors are similar, which was expected.

There was a good correlation (Pearson's  $r = 0.91$ ) between absolute difference before and after DIR. The greater the difference between reference and moving image, the better DIR can match them. Few cases have slightly higher absolute difference after DIR, which should not occur, since DIR was minimizing absolute difference metric. The reason lies in construction of warped images. Vector field is used to transform moving image to warped image. If the vector field is large on edges, an empty space will be left there in warped image. Absolute difference will therefore seem larger after DIR. A future modification of absolute difference module should handle empty spaces at edges.

Due to small mean vector field magnitudes, values for true and inverse Jacobian were close to 1 with small STD, which indicates that most of the patient body does not change during the 4DCT scan. However, patient expansions and contractions can be seen on maximum and minimum Jacobian, which were around 1.50 and 0.65 respectively. If a part of a patient body contracts from reference to moving image, then it expands in inverse direction and vice versa. The correlation was confirmed in Fig. 1.11a, with a high Pearson's  $r$  (0.90). Furthermore outliers from linear fit spot inconsistencies in DIR as shown in Fig. 1.11a and b, where a small artifact was found in one patient phase solely from the deviation from linear fit in Fig. 1.11.

Mean and STD ICE are in submilimeter range, which confirms correlation between vector field and ICE (see Eq. 1.1). The maximum ICE values can be large, with up to 2.3 cm, but still smaller as average maximum vector values.

Large vector field magnitudes will produce more errors in DIR as shown in Fig 1.12. Linear fit was used for estimation on increase (decrease) of Jacobian and ICE. Additionally, ICE should always be lower as maximum vector field values. Cases above dashed lines in Fig 1.12c all have poor DIR, confirming the hypothesis An extreme case (highlighted in Fig. 1.12a-c) had an image artifact present in one phase (shown in Fig. 1.12d) leading to inconsistencies in DIR.

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### 1.3.2 Registration of pig heart 4DCT data

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Atrial fibrillation is an unorganized atrial activity, causing a quivering motion of the heart. Heart is therefore not able to sustain a healthy pumping rhythm. Atrial fibrillation is not a deadly disease, however it worsens the patients quality of life and increases the risk of a stroke [Benjamin et al., 1998]. A common method for treating atrial fibrillation is catheter ablation [January et al., 2014], where the success rate is still limited and can even lead to major complications or even death of a patient [Cappato et al., 2005, R et al., 2010].

As an alternative treatment, a carbon-ion therapy was proposed [Bert et al., 2012] and later feasibility was shown experimentally [Lehmann et al., 2015b]. In 2014<sup>1</sup> a pilot experiment was performed at GSI using large animal model (pigs) and scanned carbon-ion to verify treatment *in vivo*.

To estimate and compensate motion of the heart during irradiation DIR of 4DCT data was required. Furthermore, because of the actual irradiation of live pigs a DIRQA had to be made, to ensure validity of DIR. Description of procedure will be here, along with the results.

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## Materials and Methods

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### Pig irradiation experiment

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A detailed description of pig irradiation experiment is given here [Lehmann et al., 2015a]. Here DIR and DIRQA used in the experiment will be presented. A cardiac gated contrast enhanced CT scans (4DCT-cardiac) were made on 15 pigs with a multidetector 64 row Siemens Somatom Definition Flash scanner (Siemens Healthcare, Forchheim, Germany) with 1 mm voxel and 1 mm slice spacing were used. There was no breathing motion present, since a breath-hold technique was used. Cardiac motion was divided into 10 sequential phases (0-10%) and a field of view of 400 mm for skin-to-skin images was used. 8 pigs had a pacemaker implemented, because the irradiation was planned to disturb heart rhythm and pacemaker should compensate. Pigs are therefore divided into two groups, with pacemaker (PM) and without one (noPM).

After CT acquisition, DIR on 4DCT-cardiac phase was made using B-Spline Plastimatch module and patient hierarchy in Slicer (see Section 1.2.2 and 1.2.2). Details on parameters can be found in Table 1.3. Phase 0% was chosen as a reference phase. All other phases were registered to reference phase with inverse registration as well. An example of checklist for users to follow the right procedure is shown in Fig. 1.13a.

Based on lung patient DIR and because of the time pressure, DIRQA was made only on DIR from one phase, phase 50%. DIRQA consisted of absolute difference<sup>1</sup>, Jacobian and ICE. DIRQA

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<sup>1</sup> Relative difference between moving and warped image absolute difference was displayed in DIRQA file rather than just absolute values.

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results were stored in a text file (example shown in Fig. 1.13b) and users checked if the values did not exceed expected ones: Absolute difference mean should be positive; Jacobian mean should be 1 with not too high extreme values; ICE mean should be smaller than 2 mm with not too high extreme values. ROI was manually created to encompass pig body and then used in all DIRQA checks.

After successful DIR and DIRQA vector fields were used in treatment planning and the resulting plans were used in pig irradiation experiment.

*For each patient it took around 1 h for all 20 DIR on Linux computer with 8 clusters and 16 GB RAM.*

Table 1.3: Parameters used for Plastimatch registration. Details for each parameter can be found here [Plastimatch, 2016].

Parameter	Stage 1	Stage 2
Resolution	4,4,2	2,2,1
Grid size	50	15
Regularization lambda	0.005	0.005
Iterations	200	100

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### Post-experiment analysis

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After pig irradiation experiment, a more detailed DIRQA was made, with all phases included in DIRQA. In addition to original checks explained in previous section, absolute difference checks were made on inverse warped image, Jacobian was made on inverse vector field and vector magnitudes were analyzed.

(a)

### Checkliste Bestrahlungsplanung

DOSE: 400 TARGET: PV SCHWEIN: Uniform

Scripts path: AlXd/user/motion/Beamtime/GSI1407/Simulations/SCRIPTS

Heartbeats during CT: N:45 bpm Final motion: Sin\_3mm\_1200ms0

Task	Script	Done?	Name	Date
Create Header		✓	AE	17.07.
Copy CT data to PatientData2		✓	AE	17.07.
Sort CTs (contrast/native)		✓	AE	"
Sort motion phased		✓	AE	"
Check # of files in each phase	CTX.sh	✓	AE	"
Check contrast and native slices	"	✓	AE	"
Create CTX	"	✓	AE	"
Create MHA	"	✓	AE	"
Check BB coordinates and write Header		✓	AE	"
Copy Contours		✓	AE	18.07.
Create VDX		✓	AE	"
Change 0 to 1 for Target (VDX)		✓	AE	"
Check voi names in VDX		✓	AE	"
FalseColorCheck contrast<->native (00)		✓	AE	18.07.
Contours native ok?				
Registration contrast -> 4DCT		✓	AE	17.07.
Registration ok?		✓	AE	17.07.

(b)

DIRQA for: Registration Node Contrast 4D

InvVector

x: 4.01

y: 3.59

z: 4.1

Vector

x: 4.53

y: 4.11

z: 4.49

AbsoluteDifference

Mean: 0.19

STD: 0.41

Max: 1446.0

Min: 0.0

Jacobian

Mean: 1.0

STD: 0.05

Max: 1.48

Min: 0.65

InverseConsistency

Mean: 0.11

STD: 0.17

Max: 1.97

Min: 0.0

Figure 1.13: (a) Part of the checklist for quality assurance during pig irradiation. DIR and DIRQA is highlighted in red and consisted of two steps. First DIR was made on 4DCT-cardiac and afterwards DIRQA was made on DIR on phase 50%. End result was presented as text shown in (b).

## Results

All DIRs were successful and during experiment all DIRQA checks were positive. An example of DIR is shown in Fig. 1.14. A vector field analysis is shown in Table 1.4. No statistical difference was observed between true and inverse vector field. However, significant difference was observed between vector field magnitudes of PM and noPM. Contributions to vector field magnitudes from three axis were equal.

Table 1.4: Data for vector magintudes. Values are presented as average (range).

	PM		noPM	
	True vector field	Inverse vector field	True vector field	Inverse vector field
Mean	0.08 (0.03 - 0.16)	0.08 (0.03 - 0.14)	0.07 (0.0 - 0.18)	0.06 (0.0 - 0.17)
STD	0.4 (0.09 - 0.78)	0.36 (0.08 - 0.68)	0.3 (0.05 - 0.77)	0.28 (0.04 - 0.71)
Max	8.24 (1.6 - 17.33)	7.98 (0.7 - 17.76)	5.9 (0.97 - 15.91)	5.38 (1.08 - 12.42)

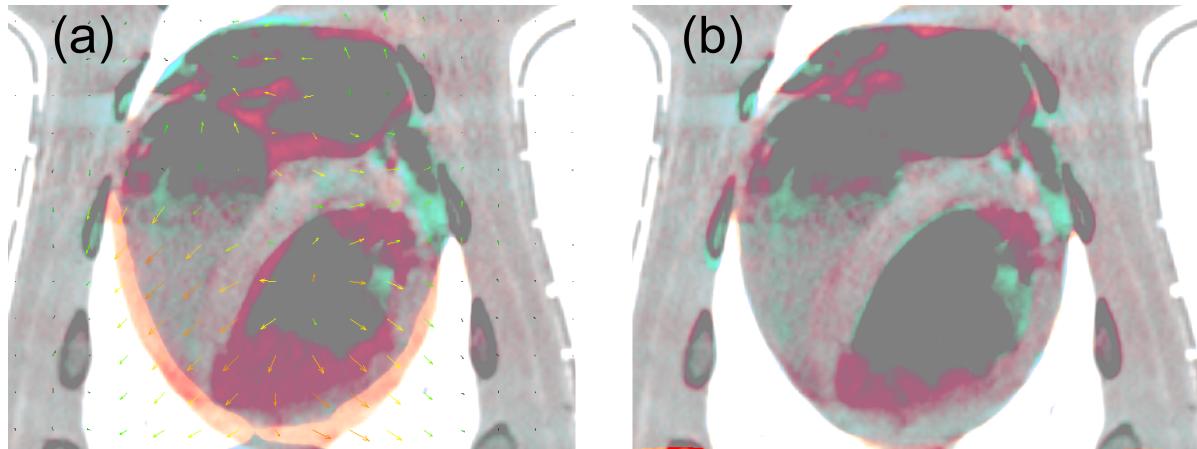


Figure 1.14: False color overlay of two phases before (a) and after (b) DIR. Vector field is displayed on image (a) as arrows.

Dependence of true and inverse absolute difference on default absolute difference with a linear fit is shown in Fig. 1.15. Default absolute difference distribution across 9 phases can be seen in inset in Fig. 1.15.

Distribution of Jacobian and ICE results are shown in Fig. 1.16 and 1.17. Maximum values of true and inverse maximum and minimum Jacobian and ICE were tested against maximum vector magnitudes and fitted with linear function. Results are plotted in Fig. 1.19. Additionally, dependence of maximum true Jacobian on minimum inverse Jacobian was tested and results are display in Fig 1.18.

All linear fits in Fig. 1.15, 1.18 and 1.19 were statistically significant ( $p < 0.05$ ).

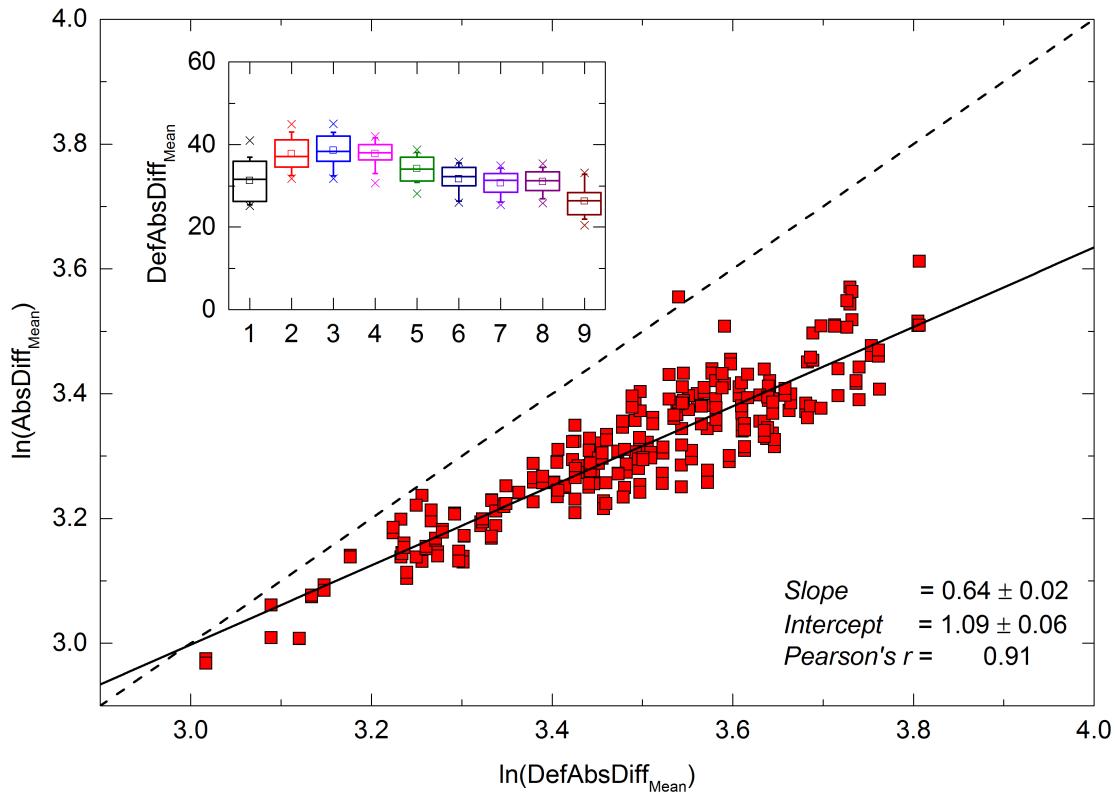


Figure 1.15: Natural logarithm of true and inverse absolute difference (AbsDiff) plotted against default absolute difference (DefAbsDiff). Solid line shows linear fit, with parameters written in corner. Dashed line shows  $y(x) = x$  plot. Inset shows box plots of mean distribution of default absolute difference across nine 4DCT phases. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

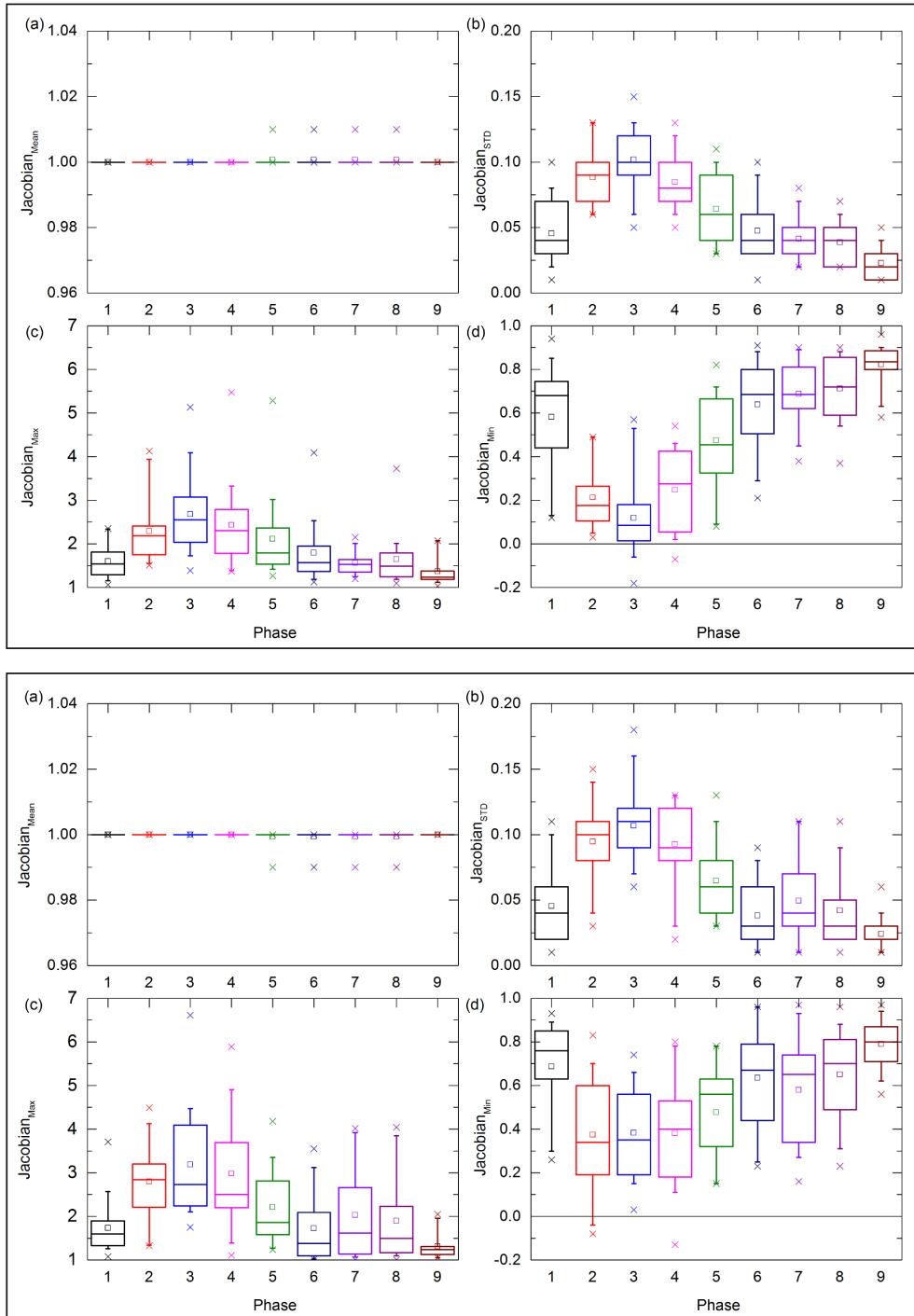


Figure 1.16: Data for Jacobian of vector fields (top) and inverse vector fields (bottom) for 9 4DCT phases (reference phase 0 is excluded) for 23 lung cancer patients. Mean, STD, maximum and minimum are represented as (a), (b), (c) and (d), respectively. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

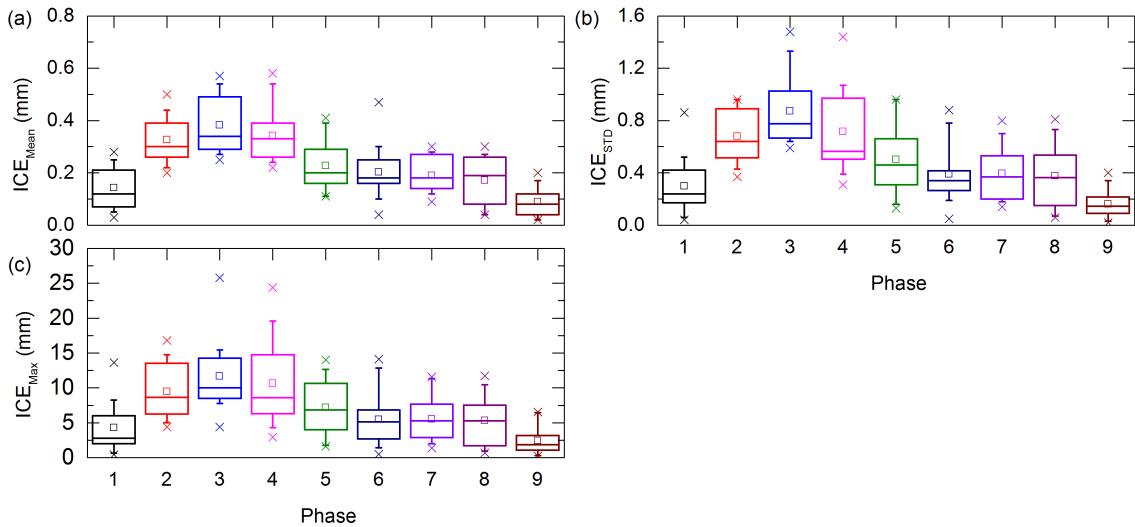


Figure 1.17: Data for ICE for 9 4DCT phases (reference phase 0 is excluded) for 23 lung cancer patients. Mean, STD, maximum are represented as (a), (b) and (c), respectively. ICE Minimum is 0 throughout all phases and patients. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

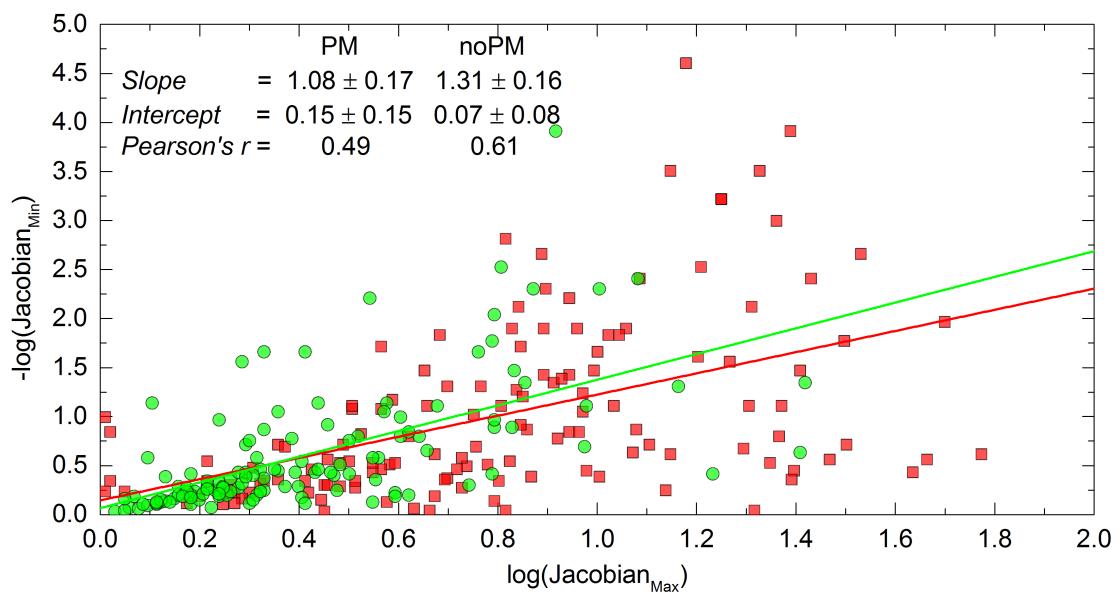


Figure 1.18: (a) Plot of negative natural logarithm of minimum Jacobian versus maximum Jacobian. Linear fit is displayed with solid line and it's parameters are given in the corner.

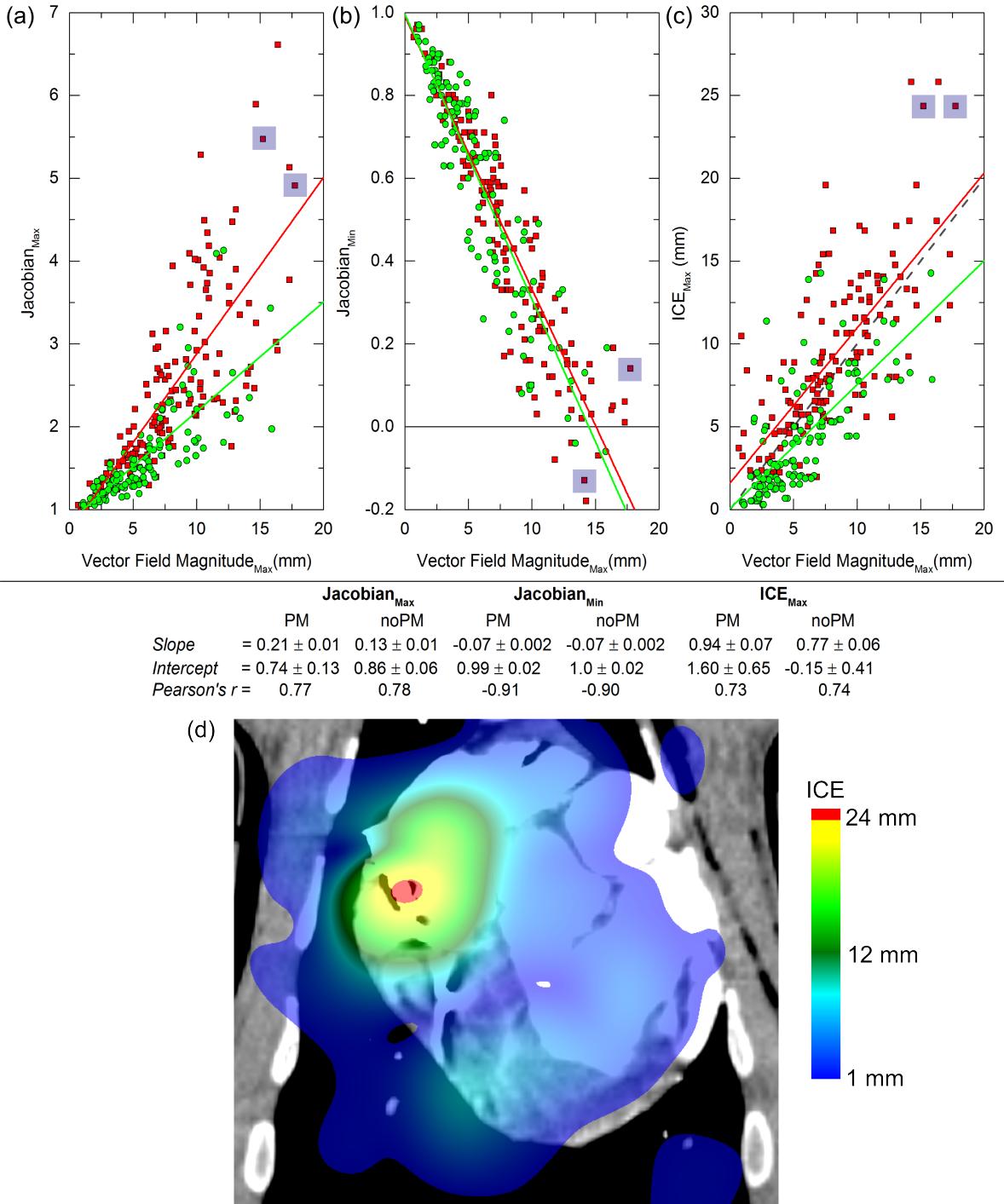


Figure 1.19: Values of maximum Jacobian (a), minimum Jacobian (b) and ICE (c) plotted against maximum vector magnitudes. Linear fit is displayed with solid line and parameters are written below the plots. Dashed line in (c) shows  $y(x) = x$  plot. Values from patient on image (d) are highlighted with blue squares in (a)-(c). ICE is displayed on (d) using color table as displayed in legend.

---

## Discussion

---

Mean vector field magnitudes were small (approx. 0.1 mm), since pigs were in a breath-hold position and the only motion was the beating of the heart. Despite the small mean vector magnitude it was still enough to observe statistical difference between the PM and noPM. Consequently, the difference between the two groups is consistent throughout the DIRQA.

The DIR did well in terms of lowering the absolute difference metric. There was a strong correlation between default versus true and inverse absolute difference. The shape of default absolute difference distribution persist then in other DIRQA check as well.

A good result in absolute difference does not necessary mean a good DIR, as can be seen from Jacobian and ICE checks. The mean Jacobian and ICE were 1 and 0, respectively, since the vector fields were small on average. However there were large deviations present in Jacobian and ICE. Most notably, there were a few cases of negative minimum Jacobian which would suggest organ folding. Since organ folding did not occur during a heart beat, negative minimum Jacobian points to inconsistencies in DIR. The inconsistencies in DIR can be also seen on Fig 1.18, with a poor correlation between minimum inverse and maximum true Jacobian. The correlation is better for noPM, however there are still cases that deviate from linear fit.

The large deviations in Jacobian and ICE can in part be explained with large maximum vector field values, as shown in Fig. 1.19. All linear fits have good correlation, with no difference between PM and noPM in the quality of the fits. The actual linear fit parameters, however, further show the inconsistencies in DIR. The clearest example of inconsistencies in DIR is with linear fit from maximum ICE PM, which lies above  $y(x) = x$  function. This basically means that there were points further away from starting point after true and inverse transformation, then by just after true transformation. The linear fit for maximum ICE showed better results in this terms, since it lied below  $y(x) = x$  function.

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## 1.4 Summary and Discussion

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Tools to preform DIR and DIRQA were presented in this chapter. Different modules were written for an open-source software Slicer, that can handle large DIR problems, such as registering whole 4DCT. In addition to DIR the modules can also make DIRQA on the same set as DIR was made with several different checks. The main objective of this work was to provide systematic approach to DIR and to give parameters on DIRQA that can estimate the quality of DIR. A first analysis of DIRQA checks was done on a large DIR database - 684 DIR were checked in total.

Most of the work was based on Slicer, which is well-established software in medical research. To date, there are more than 500 publications that have used Slicer in their research [Slicer, 2016b], with topic ranging from teaching [Pujol et al., 2016], disease staging [Liu et al., 2016, Liu et al., 2015], motion tracking [Behringer et al., 2015] to image reconstruc-

tion [Meyer et al., 2015], image registration [Li et al., 2015, Fedorov et al., 2015, ?] and others. Slicer offers a lot of different functionalities and is especially good for research, since it can be modified to specific needs. However, it is important to stress that Slicer is not a medical application and can be used only for research. Additionally, Slicer can sometimes be unstable with unexpected crashes. It is constantly under development and more and more errors are fix with each new release. New releases also bring new functionalities, but there can be problems with backtrack compatibility Even though there are some disadvantages to using Slicer, it's advantages definetelly outweigh them and make Slicer a useful tool, as was showed in this chapter.

Results shown in this chapter were obtained with DIR made by B-Spline algorithm. Several other algorithms exist, demons most commonly used alongside B-Spline [Thirion, 1998]. Varadhan et al. made comparison between B-Spline and demons DIR for lung case [Varadhan et al., 2013] and showed that B-Spline is superior to demons, especially if there is difference in contrast between images. They used mutual information metric, to account for differences in contrast. Images used in this chapter were either all without (lung case) or all with (pig case) contrast agent, therefore there was no difference in contrast between images. Mutual information metric was tested as well for DIR, however the results were much worse than mean square error metric.

The evaluation of DIR was made by DIRQA module. The main advantage of the DIRQA module is that all different techniques are gathered in a single place and can be used on a specific case. The ease of use is also essential, for DIRQA to find it's way into clinical work flow A test of using DIRQA in potential clinical work flow was done at GSI during pig experiment, where different users had to use both DIR and DIRQA modules. The experiment was also under time pressure, since there is a scheduled beam time and it cannot be shifted. There were already prepositions for frameworks for DIRQA in clinical work flow [Varadhan et al., 2013], however none were tested in an actual clinical environment

The techniques used in DIRQA can be divided into visible (false color, checkerboard) and quantitative (absolute difference, Jacobian and ICE). While the quantitative can be used to pinpoint errors in DIR, the visible can be used to actually see the error and how does it affect the end result, as shown in Fig. 1.11)c. All three quantitative checks have been used in literature as a possible DIRQA [Varadhan et al., 2013, Leow et al., 2007, Christensen and Johnson, 2001, Bender and Tomé, 2009]. They all share the same flaw, however, that they are a necessary condition for a successful DIR but not sufficient. One common DIRQA check in literature that our module is currently missing, is comparison of anatomical correspondence - comparison between reference, moving and warped contours. Ideally warped and reference contour should be the same. Two metrics are used in contour comparison - dice similarity coefficient [Varadhan et al., 2013] and Hausdorff distance [Huttenlocher et al., 1993]. Slicer already has functionalities for both contour comparison checks, so they could be used. The biggest dis-

advantage of anatomical correspondence check is that contour delineation is required in both, reference and moving phase, which is almost never done by physicians, since it takes too much time. Lack of contour in both, reference and moving phase, was also the reason the anatomical correspondence check was not used.

Studies on DIRQA so far have focused on a small number of DIR cases, whether it is phantom [Mutic et al., 2001, Moore et al., 2004] or patient studies [Wu et al., 2008, Varadhan et al., 2013]. With small number of DIR it is possible to thoroughly examine each DIR, so that DIRQA can be explained. In this chapter a different approach was used. Rather than examining each DIR individually, a large dataset was analyzed and common traits for DIR were found. Due to differences in anatomical sites, DIRQA parameters have to be found for each anatomical site individually, since they deviate can significantly, as seen by two different cases presented here.

DIR of lung 4DCT can be considered relatively easy, since the changes between phases are small and the contrast between lungs and other tissue is high. This is supported by Fig. 1.11 and 1.12. The correlation between expansion of tissue in reference phase should directly correlate to tissue contraction in moving phase. Even though Fig. 1.11a shows only plot between maximum and minimum Jacobian in two phases, the correlation is still apparent (Pearson's  $r = 0.9$ ). With calculation of difference between maximum and minimum Jacobian in each individual voxel, it is possible to pinpoint the position of outliers, as shown in Fig. 1.11, where a small artifact in one phase was responsible for deviation. In a similar fashion, deviation from linear fit in Fig. 1.12a-c, was attributed to lung artifact in one phase.

If the DIR of lung 4DCT was considered relatively easy, opposite hold true for DIR of 4DCT-cardiac. The motion of the heart during a heartbeat is complex, with muscles stretching REF and contracting in different direction. Furthermore, the volume of blood shifts from one ventricle to the other. Because blood carries a contrast agent, different phases in 4DCT-cardiac have different distribution of HU in heart. Additionally, pacemakers cause several complications in CT scan [?] as could be seen in differences between PM and noPM. This can be clearly seen in the PM linear fit of maximum ICE in Fig. 1.19, which is above  $y(x) = x$  curve. The complexity of DIR is also seen in the negative values of Jacobian, which should not occur. The errors in DIRQA checks did not happen in phase 5, which was investigated during experiment, so all DIRQA during experiment was positive. The DIR of 4DCT-cardiac is currently under careful investigation and several different solutions are being tested.

In the future DIRQA module should undergo further testing. In addition to checking DIRQA on different anatomical sites and between different modalities, it should be investigated how good is DIRQA at spotting inconsistencies in DIR, i.e. what is the number of false negatives. Furthermore, with more data analyzed, the parameters in DIRQA checks should get more precise and outliers would be easier spotted.

---

## 1.5 Appendix

---

```
class registrationParameters():
    def __init__(self ,patientName ,referenceNode ,referenceNumber ,resample = []):
        self.patientName = patientName
        self.referenceNode = referenceNode
        self.referenceNumber = referenceNumber
        self.movingNode = None
        self.movingNumber = ''
        self.movingHierarchy = None
        self.parameters = {}
        self.warpVolume = None
        self.warpDirectory = ''
        self.vectorVolume = None
        self.vectorDirectory = ''
        self.vf_F_name = ''
        self.mhaOn = False
        self.resample = resample

    def setWarpVolume(self):
        warpVolume = slicer.vtkMRMLScalarVolumeNode()
        slicer.mrmlScene.AddNode( warpVolume )
        storageNode = warpVolume.CreateDefaultStorageNode()
        slicer.mrmlScene.AddNode ( storageNode )
        warpVolume.SetAndObserveStorageNodeID( storageNode.GetID() )
        self.warpVolume = warpVolume

    def setVectorVolume(self):
        vectorVolume = slicer.vtkMRMLGridTransformNode()
        slicer.mrmlScene.AddNode( vectorVolume )
        storageNode = vectorVolume.CreateDefaultStorageNode()
        slicer.mrmlScene.AddNode ( storageNode )
        vectorVolume.SetAndObserveStorageNodeID( storageNode.GetID() )
        self.vectorVolume = vectorVolume

    def register(self):
        if not self.referenceNode or not self.movingNode:
```

```

print "Not_enough_parameters"
return

registrationName = self.patientName + "_" + self.movingNumber + "_"
if self.warpVolume:
    self.warpVolume.SetName(registrationName+"_warped")
if self.vectorVolume:
    self.vectorVolume.SetName(registrationName)
if self.mhaOn:
    self.vf_F_name = self.vectorDirectory + registrationName + "_vf.mha"

self.setParameters()
#run plastimatch registration
plmslcRegistration= slicer.modules.plastimatch_slicer_bspline
slicer.cli.run(plmslcRegistration, None, self.parameters, wait_for_completion=True)
#Resample if neccesary
#TODO: Descripton in process.
#self.resampleVolume()
#save nodes
self.saveNodes()
#Switch

registrationName = self.patientName + "_" + self.referenceNumber+ "_"
if self.warpVolume:
    self.warpVolume.SetName(registrationName+"_warped")
if self.vectorVolume:
    self.vectorVolume.SetName(registrationName)
if self.mhaOn:
    self.vf_F_name = self.vectorDirectory + registrationName + "_vf.mha"

self.setParameters()
self.switchPhase()

slicer.cli.run(plmslcRegistration, None, self.parameters, wait_for_completion=True)
#Resample if neccesary
#TODO: Descripton in process.
#self.resampleVolume()

```

```

#Save nodes
    self.saveNodes(switch = True)

def saveNodes(self ,switch = False):
    logic = RegistrationHierarchyLogic()
    if self.warpVolume:
        if not self.warpDirectory:
            print "No_directory"
            return
        if switch:
            name = NAME_INWWARP
        else:
            name = NAME_WARP
        filePath = self.warpDirectory + self.warpVolume.GetName() + ".nrrd"
        if logic.saveAndWriteNode(self.warpVolume ,self.movingHierarchy ,name ,f
            print "Saved_Warped_Image_" + self.warpVolume.GetName()

        if self.vectorVolume:
            if not self.vectorDirectory:
                print "No_directory"
                return
            if switch:
                name = NAME_VECTOR
            else:
                name = NAME_INVECTOR
            filePath = self.vectorDirectory + self.vectorVolume.GetName() + "_x.c
            if logic.saveAndWriteNode(self.vectorVolume ,self.movingHierarchy ,name ,
                print "Saved_vector_field."

def switchPhase(self):
    if not self.parameters:
        print "No_parameters"
        return

    self.parameters["plmslc_fixed_volume"] = self.movingNode.GetID()
    self.parameters["plmslc_moving_volume"] = self.referenceNode.GetID()

```

```

def setParameters(self):
    parameters = {}

    parameters["plmslc_fixed_volume"] = self.referenceNode.GetID()
    parameters["plmslc_moving_volume"] = self.movingNode.GetID()

    parameters["plmslc_fixed_fiducials"] = ''
    parameters["plmslc_moving_fiducials"] = ''

    parameters["metric"] = "MSE" #'MI

    if self.warpVolume:
        parameters["plmslc_output_warped"] = self.warpVolume
    else:
        parameters["plmslc_output_warped"] = ''
    if self.vectorVolume:
        parameters["plmslc_output_vf"] = self.vectorVolume
    else:
        parameters["plmslc_output_vf"] = ''

    if not self.vectorVolume and self.vf_F_name:
        parameters["plmslc_output_vf_f"] = self.vf_F_name
    else:
        parameters["plmslc_output_vf_f"] = self.vf_F_name

    parameters["enable_stage_0"] = False

    parameters["stage_1_resolution"] = '4,4,2'
    parameters["stage_1_grid_size"] = '50'
    parameters["stage_1_regularization"] = '0.005'
    parameters["stage_1_its"] = '200'
    parameters["plmslc_output_warped_1"] = ''

    parameters["enable_stage_2"] = True
    parameters["stage_2_resolution"] = '2,2,1'
    parameters["stage_2_grid_size"] = '15'
    parameters["stage_1_regularization"] = '0.005'

```

```

parameters["stage_2_its"] = '100'
parameters["plmslc_output_warped_2"] = ''

parameters["enable_stage_3"] = False
parameters["stage_3_resolution"] = '1,1,1'
parameters["stage_3_grid_size"] = '15'
parameters["stage_1_regularization"] = '0.005'
parameters["stage_3_its"] = '100'
parameters["plmslc_output_warped_3"] = ''
self.parameters = parameters

def resampleVolume(self):
    if not self.vectorVolume or not self.vectorVolume.IsA('vtkMRMLVectorVolu
        print "No_vector_volume_for_resampling."
        return

    if self.resample == []:
        print "No_resample_values."
        return

    if not len(self.resample) == 3:
        print "Too_many_values_for_resampling."
        return

oldVectorVolume = self.vectorVolume

#Create new vector volume
newVectorVolume = slicer.vtkMRMLVectorVolumeNode()
newVectorVolume.SetName(oldVectorVolume.GetName())
slicer.mrmlScene.AddNode(newVectorVolume)

#Create strings for resampling
spacing = ''
size = ''
for i in range(0,len(self.resample)):
    spacing += str(oldVectorVolume.GetSpacing()[i]*self.resample[i])
#extent = oldVectorVolume.GetImageData().GetExtent[2*i+1]
extent = oldVectorVolume.GetImageData().GetExtent()[2*i+1]+1

```

```
size += str(extent/self.resample[i])
if i < 2:
    spacing += ','
    size += ','

print "Resampling_" + oldVectorVolume.GetName() + "_to_new_pixel_size"

#Set parameters
parameters = {}
parameters["inputVolume"] = oldVectorVolume.GetID()
parameters["outputVolume"] = newVectorVolume.GetID()
parameters["referenceVolume"] = ''
parameters["outputImageSpacing"] = spacing
parameters["outputImageSize"] = size
```



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