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Citation: Medical Physics **42**, 40 (2015); doi: 10.1118/1.4894702 View online: http://dx.doi.org/10.1118/1.4894702 View Table of Contents: http://scitation.aip.org/content/aapm/journal/medphys/42/1?ver=pdfcov Published by the American Association of Physicists in Medicine

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The ANACONDA algorithm for deformable image registration in radiotherapy

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(Received 9 October 2013; revised 23 June 2014; accepted for publication 13 August 2014; published 16 December 2014)

Purpose: The purpose of this work was to describe a versatile algorithm for deformable image registration with applications in radiotherapy and to validate it on thoracic 4DCT data as well as CT/cone beam CT (CBCT) data.

Methods: ANAtomically CONstrained Deformation Algorithm (ANACONDA) combines image information (i.e., intensities) with anatomical information as provided by contoured image sets. The registration problem is formulated as a nonlinear optimization problem and solved with an in-house developed solver, tailored to this problem. The objective function, which is minimized during optimization, is a linear combination of four nonlinear terms: 1. image similarity term; 2. grid regularization term, which aims at keeping the deformed image grid smooth and invertible; 3. a shape based regularization term which works to keep the deformation anatomically reasonable when regions of interest are present in the reference image; and 4. a penalty term which is added to the optimization problem when controlling structures are used, aimed at deforming the selected structure in the reference image.

Results: To validate ANACONDA, the authors have used 16 publically available thoracic 4DCT data sets for which target registration errors from several algorithms have been reported in the literature. On average for the 16 data sets, the target registration error is 1.17 ± 0.87 mm, Dice similarity coefficient is 0.98 for the two lungs, and image similarity, measured by the correlation coefficient, is 0.95. The authors have also validated ANACONDA using two pelvic cases and one head and neck case with planning CT and daily acquired CBCT. Each image has been contoured by a physician (radiation oncologist) or experienced radiation therapist. The results are an improvement with respect to rigid registration. However, for the head and neck case, the sample set is too small to show statistical significance.

Conclusions: ANACONDA performs well in comparison with other algorithms. By including CT/CBCT data in the validation, the various aspects of the algorithm such as its ability to handle different modalities, large deformations, and air pockets are shown. © 2015 American Association of *Physicists in Medicine*. [http://dx.doi.org/10.1118/1.4894702]

Key words: deformable image registration, validation, adaptive radiotherapy, thoracic 4DCT data, cone beam CT

1. INTRODUCTION

For accurate and efficient treatment planning, deformable image registration (DIR) plays an important role. DIR has been used in medical applications for many years and several surveys of the field as well as large-scale studies have been published.¹⁻⁶ Through DIR, we can propagate contours from one image set to another image set and map dose defined on one image set to another as described already by Kessler.⁷ Contour propagation is of importance for an efficient work flow, i.e., avoiding tedious manual contouring.⁸ Dose mapping is used in treatment evaluation by dose accumulation during the treatment course through daily cone beam CTs (CBCTs) or CT-on-rails as is illustrated, e.g., by Schwartz et al.;⁹ in dose response evaluation during the treatment course based on daily CBCTs;¹⁰ and in 4D dose accumulation to study interplay effect.¹¹ Another example where DIR is used is for mapping densities between planning CT and CBCT in order to compute dose on the daily CBCT.¹²

To compute a DIR, we need a measure of similarity, acting as a driving force for the registration computation. The similarity measure can be based on geometrical structures or image intensities. DIR algorithms using a similarity measure based on geometrical structures are described by, e.g., Brock *et al.*¹³ and Eom *et al.*¹⁴ For intensity based we have, among others, the well known Demon's algorithm.¹⁵ Klein *et al.*¹⁶ describe a DIR toolbox called elastix, which includes several intensity based algorithms.

For the geometric approach, we need landmarks, such as surfaces, curves, or points, marking out relevant structures defined in the two image sets. The first and crucial step of a DIR algorithm using the geometric approach is the, possibly manual, extraction of landmarks. Once that is done, the landmarks are registered according to some criterion and the result is extrapolated to the full volume. By sophisticated selection of landmarks, which can be tedious and time consuming, we can obtain a deformation vector field which is anatomically reasonably close to the landmarks without



FIG. 1. Illustration of the adaptive regularization weight β for a 2D transversal slice during CT/CBCT DIR with ANACONDA. The green colorwash highlights regions where β is increased to achieve deformation vector field invertibility— β range from 1000 (transparent) to 10000 (bright green). Arrows (yellow) are pointing to regions requiring the highest β values.

being dependent on the underlying image data. This makes it robust to noise or choice of image modality. However, we have no information of the movements in regions where no landmarks have been selected and cannot guarantee a reasonable deformation vector field in such regions. This drawback can be compensated for by using biomechanical modeling, see, e.g., the work by Brock *et al.*¹³ In the work by Glocker et al.,¹⁷ a discussion on advantages and disadvantages with a geometric approach is given.

For the intensity based approach, intensities are matched voxel- or patch-wise using some mathematical or statistical criterion. In this case, all voxels or at least patches of voxels take part in driving the DIR algorithm. On the other hand, we have no guarantee that the deformation is anatomically reasonable. In homogeneous regions, many positions can give the same image similarity measure and we can end up with an irregular deformation vector field.⁶ It has been shown that using only intensities is not enough in low contrast regions.^{18,19} An intensity based DIR algorithm is more difficult to develop for multimodality applications and can be more sensitive to unexpected contrast variations such as surgery and air cavities if based on image similarity in terms of, e.g., sum of squared differences only.¹⁷ Several attempts to avoid this type of problems have been presented in the literature, for instance, by creating intermediate images through neighborhood descriptors²⁰ or Gabor features,²¹ and use them in the subsequent intensity based DIR. Myronenko and Song²² present a novel similarity measure which accounts for spatially varying intensity distortions. To measure image similarity in CT/CBCT DIR, various approaches have been suggested such as histogram matching for normalization of the intensities in the CBCT image prior to DIR (Ref. 23) or performing intensity correction incorporated in the DIR process.^{24,25}

Using a hybrid solution, like ANAtomically CONstrained Deformation Algorithm (ANACONDA) presented in this paper, can have the benefit of both the geometric approach and the intensity based approach while avoiding their previously noted drawbacks. Most commercial systems are, to our knowledge, either geometric or intensity based. Hybrid solutions have been proposed already in 2001 by Christensen et al.²⁶ and the interest in such solutions in the field of radiotherapy has increased in recent years due to limitations of pure image intensity based algorithms.^{17,19,27-30} Godley et al.²⁷ present an algorithm where masks are created for bladder and rectum and subsequently incorporated in a demon-based algorithm for DIR in the pelvic region. In the work by Kim et al.,¹⁹ difficulties in performing CT/CBCT DIR for the pelvic region are pin pointed for a commercially available intensity based system. They instead propose to use a combination of contours and intensities. Image similarity is measured through mutual information in order to handle intensity range differences between CT and CBCT images. A



Fig. 2. The absolute value of the signed distance map of the ROI Bladder in the target image, ranging from small to high distances with increasing brightness. Controlling ROI Bladder before and after ANACONDA has been applied is shown overlayed in dark gray and white, respectively.

Case	Dimensions	Voxel size (mm ³)	Number of landmarks	Displacement mean (SD) (mm)
1	$256 \times 256 \times 94$	$0.97 \times 0.97 \times 2.5$	300	4.01 (2.91)
2	$256 \times 256 \times 112$	$1.16 \times 1.16 \times 2.5$	300	4.65 (4.09)
3	$256 \times 256 \times 104$	$1.15 \times 1.15 \times 2.5$	300	6.73 (4.21)
4	$256 \times 256 \times 99$	$1.13 \times 1.13 \times 2.5$	300	9.42 (4.81)
5	$256 \times 256 \times 106$	$1.10 \times 1.10 \times 2.5$	300	7.10 (5.14)
6	$512 \times 512 \times 128$	$0.97 \times 0.97 \times 2.5$	300	11.10 (6.98)
7	$512 \times 512 \times 136$	$0.97 \times 0.97 \times 2.5$	300	11.59 (7.87)
8	$512 \times 512 \times 128$	$0.97 \times 0.97 \times 2.5$	300	15.16 (9.11)
9	$512 \times 512 \times 128$	$0.97 \times 0.97 \times 2.5$	300	7.82 (3.99)
10	$512 \times 512 \times 120$	$0.97 \times 0.97 \times 2.5$	300	7.63 (6.54)

TABLE I. Properties of the DIR-LAB data sets.

framework for DIR built on a Markov random field formulation and a discrete optimization is presented by Glocker *et al.*¹⁷ It is applied to combinations of intensity information and landmarks. Image similarity measure is selected depending on the application. The Demon's algorithm, in which the sum of squared differences is used as image similarity measure, can be combined with information from contoured image sets as described by Gu *et al.*²⁹ Starting from a finite element model approach for geometric alignment, combinations with image similarity measures internally have been proposed.^{28,30}

In this work, we present ANACONDA for DIR. It is available in the commercial treatment planning system RayStation (RaySearch Laboratories AB, Stockholm, Sweden). The algorithm is general as it can be used for many body sites and is well suited for more difficult registration problems where image intensities alone cannot solve the problem. It combines image information (i.e., intensities) with anatomical information as provided by contoured image sets. The registration problem is formulated as a nonlinear optimization problem and solved with an in-house developed solver, tailored to this problem. The DIR algorithm as described here, using a correlation coefficient to measure image similarity, can be applied to image sets of modality CT or CBCT and is validated using thoracic 4DCT data as well as CT/CBCT data. Validation of the algorithm and resulting deformation vector field is a crucial question. It can be done using real patient data or phantom data and the measurements used can be based on contour propagation accuracy, landmark tracking, or image similarity. Rohlfing³¹ showed that high scores on image similarity and contour propagation overlap can be achieved even for obviously unsound DIR. A validation therefore needs to include landmark tracking. This is confirmed in the study by Kirby et al.⁶ For thoracic 4DCT DIR validation, we use the publically available data described by Vandemeulebroucke et al.³² and Castillo et al.³³ Both data sets have landmarks marked in a reference and a target phase, thus allowing for, among other types of comparison, computation of target registration errors. For CT/CBCT DIR validation, we use two pelvic cases with planning CT and a total of seven daily CBCTs as well as one head and neck case with planning CT and three daily CBCTs made available through a collaboration with Princess Margaret Cancer Centre, Toronto, Canada. Planning CTs and daily CBCTs have been contoured by a physician or experienced radiation therapist thus allowing for validation based on contour propagation accuracy.

The way contours are incorporated in the ANACONDA objective function is inspired by chamfer matching (originally described for 2D images by Barrow *et al.*³⁴). For rigid image registration, chamfer matching has proved useful in



Fig. 3. The reference phase of DIR-LAB 1. To the left, a volume rendering with the landmarks in 3D and to the right, a 2D coronal slice through the 3D volume.

TABLE II. Properties of the POPI data sets.

Case	Dimensions	Voxel size (mm ³)	Number of landmarks
1	$512 \times 512 \times 141$	$0.98 \times 0.98 \times 2.0$	100
2	$512 \times 512 \times 169$	$0.98 \times 0.98 \times 2.0$	100
3	$512 \times 512 \times 170$	$0.88 \times 0.88 \times 2.0$	100
4	$512 \times 512 \times 187$	$0.78 \times 0.78 \times 2.0$	100
6	$512 \times 512 \times 161$	$1.17 \times 1.17 \times 2.0$	100
ICCR	$512 \times 512 \times 141$	$0.98 \times 0.98 \times 2.0$	40

medical applications^{35,36} but so far, to our knowledge, not commonly used for hybrid DIR . In the work by Liu,³⁷ a chamfer matching approach is taken to DIR but using only geometric information and developed for 2D images. Collins *et al.*³⁸ use chamfer distances from automatically extracted cortical sulci to guide DIR. However, it is not clear how the information is incorporated into the objective function. Furthermore, the weighting between image information and contoured image sets is not explicitly stated.

The algorithms, of the above referred, we have found to be most similar to ANACONDA are described by Kim *et al.*¹⁹ and Gu *et al.*²⁹ For those we point out the following differences: In the algorithm by Kim *et al.*,¹⁹ a separate step is required for handling rigid bone registration as well as manual interaction to identify regions such as rectum gas and motion artifacts. These regions are then excluded from image similarity measurements. Image similarity is measured using mutual information in comparison with correlation coefficient for ANACONDA. In comparison with the algorithm by Gu *et al.*,²⁹ ANACONDA has the advantage of being

TABLE III. PI	roperties of (СТ/СВСТ	data.
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applicable to CT/CBCT DIR. Furthermore, ANACONDA, as mentioned above, uses a novel approach for how contours are incorporated in the objective function. Glocker *et al.*¹⁷ make a distinction between coupled and hybrid registration using two separate steps—one geometric step followed by one intensity based step—is being made. We remark that ANACONDA is a coupled registration solution as the objective function includes both the geometric and the intensity information.

2. METHOD AND MATERIALS

2.A. The ANACONDA deformable registration algorithm

Denote the reference image R, the target image T, and the rigid transformation aligning the images $M : \mathbb{R}^3 \to \mathbb{R}^3$. Let the deformation grid be a set of gridpoints arranged in a regular manner on a lattice dividing space into boxshaped elements (voxels). The DIR algorithm computes a vector field defined on the grid. This vector field is called a *deformation vector field*. The deformation vector at gridpoint $x_i \in \mathbb{R}^3$ is denoted $v_i \in \mathbb{R}^3$. The registration problem is formulated as a nonlinear optimization problem with objective function $f : \mathbb{R}^n \to \mathbb{R}$

$$f(v) = \alpha C(v) + (\beta H(v) + \gamma S(v)) + \delta D(v), \tag{1}$$

where $\alpha, \gamma, \delta \in \mathbf{R}$ are non-negative weights, *n* is the number of variables, and $\beta : \mathbf{R}^3 \to \mathbf{R}$ is a non-negative, real valued weight function. The value of *n* equals three times the number of gridpoints in the deformation grid. The terms C(v), H(v), S(v), and D(v) are briefly introduced in the following and then described in more detail in the subsequent sections.

Prostate 1					
Modality	СТ	CBCT	[CBCT	CBCT
Name	PlanCT	"Gas above E	Bladder" "Gas	and Full Rectum"	Small Bladder
Voxel size (mm ³)	$0.95 \times 0.95 \times 2.0$		1.0	$\times 1.0 \times 2.0$	
Dimensions	$512\times512\times166$		410	$\times 410 \times 60$	
Bladder vol (mm ³)	218.44×10^{3}	$163.53 \times$	10 ³	231.71×10^3	150.70×10^3
"Rectum" vol (mm ³)	53.75×10^{3}	$55.04 \times$	10^{3}	115.41×10^{3}	47.30×10^3
Prostate 2					
Modality	СТ	CBCT	CBCT	CBCT	CBCT
Name	PlanCT	Small	"Gas"	"Full Bladder	"Normal"
		Bladder		and Rectum"	
Voxel size (mm ³)	$0.89 \times 0.89 \times 2.0$		1.0:	$\times 1.0 \times 2.0$	
Dimensions	$512\times512\times155$		$410 \times 410 \times 60$		
Bladder vol (mm ³)	456.66×10^{3}	102.66×10^{3}	129.69×10^{3}	253.95×10^{3}	167.83×10^{3}
Rectum vol (mm ³)	(mm ³) 32.88×10^3		52.63×10^{3}	53.42×10^{3}	35.07×10^3
Head and Neck					
Modality	С	Т	CBCT	CBCT	CBCT
Name	Plai	nCT	"CBCT 5"	"CBCT 10"	"CBCT 15"
Voxel size (mm ³)	0.98×0.00	$.98 \times 2.0$		$1.0\times1.0\times2.0$	
Dimensions	512 × 51	2×193	$410 \times 410 \times 132$		
"Parotid (right)" vol (m	1m ³) 28.91	$\times 10^3$	25.14×10^3	24.26×10^{3}	20.70×10^{3}
"Parotid (left)" vol (mr	n ³) 25.69	$\times 10^{3}$	19.20×10^{3}	20.22×10^3	16.40×10^{3}



Fig. 4. Prostate 2 with PlanCT volume rendered to the left and rigidly fused with Small Bladder to the right. ROIs Bladder (yellow), "Prostate" (red), and Rectum (light blue) as solid lines in PlanCT and dashed lines in Small Bladder.

The image similarity is measured by the correlation coefficient C(v).

The regularization of the deformation grid is controlled by the term $\beta H(v) + \gamma S(v)$. The first part of the regularization term, $\beta H(v)$, which encourages the coordinate functions to become approximate minimizers of the Dirichlet energy, determines the smoothness and invertibility of the deformation vector field. The local smoothness and invertibility of the deformation vector field is controlled by the non-negative, real valued weight function $\beta : \mathbf{R}^3 \to \mathbf{R}$ which is defined on the deformation grid. If β is large, the deformation vector field will become invertible. To prevent generating inverted elements, the algorithm implements a restart strategy to increase β when needed. After convergence of the optimization algorithm, the determinant of the Jacobian matrix is computed at all gridpoints and if any negative values are detected, β is locally increased in that region of the deformation vector field. The second part of the regularization term, $\gamma S(v)$, penalizes large shape deviations of regions of interest (ROIs) defined in *R*.

If the user includes ROIs or points of interest (POIs) to guide the deformation algorithm, this *a priori* information which is incorporated into D(v). The minimization of f(v)is computed by a nonlinear limited memory solver.³⁹ It can be noted that C(v) and D(v) involve gradient calculations on image data using finite differences and trilinear interpolation while gradients of H(v) and S(v) can be computed using analytical expressions. To reduce the influence of image



Fig. 5. Head and Neck with PlanCT and CBCT 15 are shown rigidly fused. ROIs Parotid (left) (green) and Parotid (right) (blue) as solid lines in PlanCT and dashed lines in CBCT 15.

Fig. 6. Segmentation of the left (pink) and right (green) lungs for DIR-LAB 1. To the left, volume rendered and the lungs as wireframes and to the right, a 2D slice through the volume.

artifacts, the images *R* and *T* are filtered using a Gaussian filter with $\sigma = 1/3$ voxel. The optimization problem is solved on three resolution levels, 10, 5, and 2.5 mm, and the resulting deformation vector field is used as initial solution to the next resolution level.

2.A.1. Image similarity measure

Looked upon as functions, the images describe mappings $R, T : \mathbf{R}^3 \to \mathbf{R}$ which are computed using trilinear interpolation. The deformation vector field acts on *R* and the similarity between the deformed image and *T* is measured by the correlation coefficient

$$C(v) = \frac{\sum_{i} (R(x_{i}) - \bar{R}) (T(M(x_{i}) + v_{i}) - \bar{T})}{\sqrt{\sum_{i} (R(x_{i}) - \bar{R})^{2}} \sqrt{\sum_{i} (T(M(x_{i}) + v_{i}) - \bar{T})^{2}}}.$$
 (2)

The sums are computed over an index set which can be the whole of R or any subset. \overline{R} and \overline{T} are the mean intensity computed over the gridpoints which are contained in the index set and are mapped into T. Typical index sets are the patient external ROI or some focus region(s) in R. It is well known that C is invariant to linear transformations of the image intensities. This is an advantage when using ANACONDA for CT/CBCT DIR. Methods using for instance sum of squared intensity differences as image similarity measure will require a special step to handle the differences in intensity range between CT and CBCT. See, e.g., the work by Hou *et al.*,²³ where histogram matching is used.

2.A.2. Regularization

A regularization of the deformation vector field is obtained by minimizing the Dirichlet energy for the coordinate functions of the deformation vector field. Since minimizers of the Dirichlet energy are harmonic maps, H(v) is designed to penalize deviation from the mean value property. Another motivation for this approach is the fact that harmonic mappings of triangular meshes are invertible under reasonable assumptions.⁴⁰ This follows from the maximum principle for harmonic functions. The voxel containing v_i is box shaped and the six face connected gridpoints are denoted N_i . We then define

$$H(v) = \sum_{i} \|v_{i} - \frac{1}{n_{i}} \sum_{j \in N_{i}} v_{j}\|^{2},$$
(3)

which is a quadratic expression in the optimization variables with the required properties. When the optimizer has converged, the determinant of the Jacobian of the deformation field is computed to detect inverted elements. If such elements are detected, the weighting function β is modified in the following way: the values of β in a 1 cm neighborhood around the inverted grid voxels are multiplied by 2.0 and the resulting weight image is filtered by a Gaussian filter with $\sigma = 3.0$ to achieve a smooth varying weight function. This strategy is illustrated in Fig. 1. Decreasing the size of the neighborhood will result in a larger number of restarts, but a more local influence.

The second part of the regularization term is called *shape* based regularization. Assume there is a triangular mesh representing an anatomical region defined in R. We would like the deformation algorithm to deform the mesh in a reasonable manner. For example, although smooth and invertible, a deformation vector field could potentially deform structures in a nonintuitive way, if the driving similarity measure is not reliable. This could happen for very noisy images with severe artifacts or erroneous landmarks. The aim of the shape based regularization term is to add robustness to protect against erroneous image data.

46 O. Weistrand and S. Svensson: ANACONDA for DIR

Deformation of the shape is measured by the function

$$S(v) = \sum_{k} \sum_{i,j} \|(M(q_i^k) - M(q_j^k)) - (M(q_i^k) + v_i) - (M(q_j^k) + v_j))\|^2 = \sum_{k} \sum_{i,j} \|v_i - v_j\|^2,$$
(4)

where q_i^k are the mesh vertices for shape constraining ROI k expressed as mean value coordinates⁴¹ in the variables and the sum is computed over every pair (i,j) which defines an edge of the mesh. The deformation vectors v_i and v_j are also expressed in terms of mean value coordinates since vertices of the triangle meshes do not in general correspond to voxel centra in the deformation grid. We remark that S(v) is invariant to global translations and rotations as it only depends on differences between deformation vectors.

2.A.3. Controlling structures

The user can choose to include controlling ROIs and controlling POIs to guide the deformation algorithm. The resulting objective function is defined as

$$D(v) = \sum_{k} \sum_{i} d_{k}^{2} (M(q_{i}^{k}) + v_{i}) + \sum_{j} ||M(q_{j}^{k}) + v_{j} - q_{j}^{t}||^{2},$$
(5)

where $d_k : \mathbf{R}^3 \to \mathbf{R}$ is the approximate Euclidean distance to controlling ROI k and q_i^k is a vertex of the triangular mesh k, representing the controlling ROI expressed in terms of mean value coordinates of the eight gridpoints defining the smallest box which contains the vertex on the reference image. The idea here is to extend the chamfer matching technique originally introduced by Barrow et al.³⁴ By computing a signed distance map, using the fast marching method described by Sethian,⁴² which approximates the distance from a point in space to the surface of the controlling ROI defined in the target image, the expression above can be efficiently computed. The gradient is computed using finite differences. The chamfer matching technique was chosen because it introduces a large capture range allowing fast convergence even for ROIs with large differences in size. This situation often occurs for bladders with different filling conditions. The need for controlling structures in the pelvic region is discussed in Sec. 3.B and illustrated by Foskey et al.⁴³ and Kim et al.¹⁹ Controlling structures are illustrated by Fig. 2. There, the absolute values in the signed distance map of the ROI "Bladder" in the target image are shown. The Bladder from the reference image rigidly mapped to the target image is shown overlayed in dark gray and the Bladder mapped according to ANACONDA using Bladder as controlling structure in white.

The last sum in Eq. (5) penalizes controlling POIs where the target point for $q_j \in R$ is denoted $q_j^t \in T$. Since, in this case, a known one-to-one mapping exists, there is no need for a distance map. However, the POI defined in the reference image must be contained in the deformation field.

FIG. 7. Fusion views for the reference phase and the target phase before (top) and after (bottom) ANACONDA with focus region applied. Lungs have been contoured but are not used as controlling ROIs in ANACONDA. Solid line shows the ROIs in the reference phase and dashed line the ROIs in the target phase deformed to the reference phase.

2.B. Materials

In this Subsection, we describe the data sets which we have used to validate ANACONDA.

2.B.1. Thoracic 4DCT data

We want to benchmark ANACONDA with respect to other algorithms and for this purpose, use the publically available data described in the following.

2.B.1.a. Deformable image registration laboratory (DIR-LAB). The DIR-LAB, the Department of Radiation Physics

Data set	Focus	3D	RL	AP	SI
DIR-LAB 1	Lungs	1.07 (0.50)	0.38 (0.30)	0.42 (0.33)	0.78 (0.50)
		1.63 (1.07)	0.44 (0.35)	0.51 (0.41)	1.34 (1.11)
DIR-LAB 2	Lungs	1.05 (0.52)	0.43 (0.33)	0.43 (0.35)	0.70 (0.53)
	_	2.38 (2.55)	0.54 (0.46)	0.61 (0.63)	2.03 (2.61)
DIR-LAB 3	Lungs	1.17 (0.62)	0.46 (0.39)	0.50 (0.43)	0.80 (0.57)
	_	3.93 (3.20)	0.83 (0.75)	1.12 (1.14)	3.40 (3.22)
DIR-LAB 4	Lungs	1.48 (0.96)	0.63 (0.68)	0.65 (0.52)	0.92 (0.86)
	_	2.38 (2.28)	0.73 (0.77)	0.81 (0.86)	1.85 (2.22)
DIR-LAB 5	Lungs	1.41 (1.24)	0.60 (0.71)	0.60 (0.78)	0.91 (0.94)
	_	3.34 (3.34)	0.75 (0.82)	1.16 (1.61)	2.67 (3.17)
DIR-LAB 6	Lungs	1.51 (1.00)	0.55 (0.47)	0.65 (0.71)	1.03 (0.87)
	_	2.65 (2.86)	0.65 (0.66)	0.73 (0.67)	2.25 (2.87)
DIR-LAB 7	Lungs	1.24 (0.77)	0.49 (0.52)	0.54 (0.49)	0.80 (0.66)
		6.80 (6.16)	1.35 (1.22)	1.96 (2.25)	5.95 (6.05)
DIR-LAB 8	Lungs	1.72 (2.46)	0.53 (0.67)	0.71 (1.20)	1.29 (2.17)
	_	9.89 (9.56)	1.21 (1.13)	2.90 (3.08)	8.90 (9.45)
DIR-LAB 9	Lungs	1.20 (0.66)	0.51 (0.43)	0.54 (0.47)	0.75 (0.60)
	_	3.25 (2.87)	0.83 (0.76)	1.48 (1.42)	2.43 (2.72)
DIR-LAB 10	Lungs	1.21 (0.69)	0.40 (0.33)	0.53 (0.43)	0.87 (0.69)
	_	2.72 (3.50)	0.47 (0.45)	0.82 (0.92)	2.30 (3.52)
POPI 1	Lungs	0.82 (0.38)	0.32 (0.24)	0.34 (0.29)	0.57 (0.37)
	_	1.10 (0.94)	0.40 (0.36)	0.48 (0.71)	0.78 (0.68)
POPI 2	Lungs	1.20 (1.02)	0.53 (0.62)	0.49 (0.53)	0.77 (0.85)
	_	3.52 (4.95)	0.91 (1.00)	1.07 (1.59)	2.90 (4.80)
POPI 3	Lungs	0.82 (0.54)	0.33 (0.31)	0.33 (0.26)	0.54 (0.54)
	_	1.52 (2.10)	0.55 (0.72)	0.41 (0.40)	1.23 (2.02)
POPI 4	Lungs	0.88 (1.43)	0.31 (0.31)	0.26 (0.19)	0.68 (1.43)
	_	2.26 (3.47)	0.48 (0.61)	0.51 (0.75)	2.00 (3.43)
POPI 6	Lungs	0.85 (0.49)	0.34 (0.31)	0.41 (0.35)	0.53 (0.40)
	_	1.25 (1.54)	0.39 (0.33)	0.44 (0.44)	0.96 (1.54)
POPI ICCR	Lungs	1.07 (0.62)	0.47 (0.53)	0.46 (0.37)	0.64 (0.53)
	_	1.20 (1.24)	0.48 (0.31)	0.46 (0.44)	0.77 (1.28)
Average DIR-LAB	Lungs	1.31 (0.94)	0.50 (0.48)	0.55 (0.57)	0.88 (0.84)
Average DIR-LAB		3.90 (3.74)	0.78 (0.74)	1.21 (1.30)	3.31 (3.70)
Average POPI	Lungs	0.94 (0.73)	0.38 (0.38)	0.38 (0.33)	0.62 (0.67)
Average POPI	_	1.81 (2.37)	0.54 (0.55)	0.56 (0.72)	1.44 (2.29)
Average	Lungs	1.17 (0.87)	0.46 (0.45)	0.49 (0.48)	0.79 (0.78)
	—	3.11 (3.23)	0.69 (0.67)	0.97 (1.08)	2.61 (3.17)

at University of Texas M. D. Anderson Cancer Center, is behind an initiative of making validation data publically available from http//www.dir-lab.com. Currently, it is possible to download ten thoracic 4DCT images, each with ten phases, with 300 landmarks marked in the reference (maximum inhalation) phase and their corresponding positions in the target (maximum exhalation) phase.

For detailed description of the data sets, we refer to Castillo *et al.*^{33,44} and Table I. One example from the DIR-LAB data sets with landmarks is shown in Fig. 3, volume rendered to the left and a 2D slice to the right. Twenty-one algorithms have been benchmarked against the DIR-LAB data as reported on the webpage (accessed June 11, 2014). The algorithms range from a comparison between different implementations of the Demon's algorithm (orig-

inally described for DIR by Thirion¹⁵) on GPU to being tailored for thoracic 4DCT data by using trajectory modeling.

2.B.1.b. POPI. The Léon Bérard Cancer Center & CRE-ATIS Laboratory, Lyon, France, is behind another initiative on making validation data publically available from http://www. creatis.insa-lyon.fr/rio/popi-model/. The data are referred to as the point-validated pixel-based breathing thorax model (POPI model). Currently it is possible to download the original POPI model consisting of one thoracic 4DCT image with 40 landmarks marked in the reference and the target phase; and six thoracic 4DCT images, each with ten phases, with 100 landmarks marked in the reference and the target phase.

For a detailed description of the data sets, we refer to Vandemeulebroucke *et al.*,^{32,45} where not only the data sets but also algorithmic benchmarkings are presented, and Table II.

FIG. 8. Target registration error mean for ANACONDA in comparison with rigid registration as well as the worst and best published results.

POPI 5 has been excluded as we had problems with importing the data available on the POPI web page for that specific patient and thus, could not include it in the benchmarking.

2.B.2. CT/CBCT data

Through a collaboration with Princess Margaret Cancer Centre, Toronto, Canada, we have access to planning CT and daily CBCT images for two pelvic cases and one head and neck case, in the following referred to as "Prostate 1," "Prostate 2," and "Head and Neck," respectively. All CBCTs have been acquired using Elekta XVI. The CBCTs were rigidly registered to their respective planning CT using the intensity based rigid registration available in RayStation. The rigid registration algorithm uses the correlation coefficient as image similarity measure and the measure is evaluated over all voxels in the patient external ROI on the floating image.

2.B.2.a. Pelvic. For Prostate 1 and Prostate 2, three and four, respectively, daily CBCT data sets were chosen for which the difference with respect to the planning geometry differed a lot as summarized in Table III. Bladder, prostate, and rectum were contoured by a physician or experienced radiation therapist on both the planning CT and the daily CBCTs. In addition to that, bone was segmented using the automatic bone segmentation available in RayStation. We use these data sets to show the impact of the controlling ROIs which allows us to handle cases with large deformations in low contrast regions as well as occurrences of air pockets and gas. In Fig. 4, "Plan CT" and "Small Bladder" are shown for Prostate 2. We remark that for both Prostate 1 and Prostate 2, the bladder is full and extends outside the field-of-view if rigidly propagated to any of the daily CBCTs.

2.B.2.b. Head and neck. For Head and Neck, the left and right parotid were contoured by a physician or experienced radiation therapist on both the planning CT and the daily CBCTs. Fraction 5, 10, and 15 were chosen to show the performance on CT/CBCT DIR in cases where controlling

ROIs are not necessary to use. See Table III for details. In Fig. 5, PlanCT and "CBCT 15" are shown.

2.B.3. Validation metrics

We have validated ANACONDA based on landmark tracking (when applicable), contour propagation accuracy, and image similarity. In addition to that, we have for the pelvic data measured the mean of the Jacobian determinant for bone to validate that bone is not deformed by ANACONDA. We have also computed the number of inverted elements in the deformation vector fields.

Landmark tracking was done for the thoracic 4DCT data using the landmarks described above. We measured the difference between the position obtained by propagating a point in the reference image to the target image with the corresponding position in the target image, the *target registration error*. Mean and standard deviation were measured in 3D as well as superior–inferior (SI), anterior–posterior (AP), and right–left (RL) directions.

For contour propagation accuracy, for the CT/CBCT data, we used the provided contours. For the thoracic 4DCT data, we contoured the left and the right lung in the reference phase and the target phase using model based segmentation as provided by RayStation. The procedure was performed in an automatic way. We visually verified that the resulting contours reasonably outlined the two lungs. One example of a contoured image set can be seen in Fig. 6. For each structure on the reference phase, we propagated it to the target phase and compared it with the corresponding structure contoured on the target image. There are many available metrics for measuring spatial overlap. We have used Dice similarity coefficient (DSC), first described by Dice⁴⁶ as it is a commonly used metric in medical imaging. DSC ranges between 0, for no overlap, and 1, for complete overlap.

For image similarity, we used C(v), see Eq. (2), i.e., the same measure as during the optimization process.

TABLE V. DSC for propagated contours in comparison with original contours, image similarity, and number o
invertible elements for ANACONDA. As additional information to the number of inverted element, the smalles
Jacobian determinant (Jac. Det.) is listed. Rigid registration results are listed in parenthesis for comparison.

Data set	Focus	DCS lung (left)	DCS lung (right)	Image similarity	Number of inverted elements	Minimum Jac. Det.
	Lunge	0.08(0.04)	0.00 (0.05)	0.07 (0.81)	0	0.31
DIR-LAB 1	Lungs	0.98(0.94)	0.99(0.95)	0.97 (0.81)	0	0.51
DIR-LAB 1	Lunge	0.99(0.94)	0.99(0.95)	0.99(0.94)	0	0.33
DIR-LAB 2	Lungs	0.99(0.95)	0.99(0.95)	0.90(0.79)	0	0.22
DIR-LAB 2	Lunge	0.99(0.93)	0.99(0.93)	0.95 (0.54)	0	0.20
DIR-LAB 3	Lungs	0.99(0.94)	0.99(0.93)	0.90(0.08)	0	0.34
DIR-LAB J	Lunge	0.99(0.94)	0.99(0.93)	0.99(0.91)	0	0.44
DIR LAB 4	Lungs	0.90(0.91)	0.90(0.92)	0.90(0.71)	0	0.01
DIR-LAB 5	Lunge	0.99(0.91)	0.99(0.92)	0.96 (0.76)	0	0.01
DIR-LAB 5	Lungs	0.98(0.95)	0.99(0.93)	0.90(0.70)	0	0.11
DIR-LAB 5	Lunge	0.95(0.95)	0.98 (0.86)	0.99(0.92)	0	0.12
DIR-LAB 6	Lungs	0.97 (0.85)	0.98 (0.86)	0.07(0.31)	0	0.02
DIR-LAB 0	Lungs	0.98 (0.89)	0.97 (0.90)	0.97(0.64)	0	0.05
DIR-LAB 7	Lungs	0.98 (0.89)	0.97 (0.90)	0.95 (0.03)	0	0.04
DIR-LAB /	Lunge	0.98 (0.89)	0.97 (0.90)	0.97(0.87)	0	0.03
DIR-LAD 8	Lungs	0.99 (0.90)	0.99(0.89)	0.94(0.43) 0.98(0.83)	0	0.01
DIR-LAD 0	Lunge	0.99(0.90)	0.99(0.89)	0.98(0.83)	0	0.00
DIR-LAB 9	Lungs	0.98(0.91)	0.98(0.92)	0.94 (0.38)	0	0.20
DIR-LAB 9	Lunge	0.98(0.91)	0.98(0.92)	0.98 (0.80)	0	0.01
DIR-LAB 10	Lungs	0.98(0.90)	0.98(0.91)	0.93(0.00)	0	0.03
DIR-LAD IU		0.98(0.90)	0.99(0.91)	0.98(0.87)	0	0.01
POPI 1	Lungs	0.98(0.93)	0.99(0.94)	0.90(0.01)	0	0.04
		0.99(0.93)	0.99(0.94)	0.99(0.92)	0	0.09
POPL2	Lungs	0.98(0.92)	0.98(0.91)	0.93(0.34)	0	0.20
POPL 2		0.98(0.92)	0.98(0.91)	0.97 (0.80)	0	0.01
POPL 2	Lungs	0.98(0.94)	0.98 (0.90)	0.90(0.30)	0	0.23
POPL 4		0.98(0.94)	0.99(0.90)	0.98(0.87)	0	0.00
POPI 4	Lungs	0.99(0.93)	0.99(0.93)	0.94(0.02)	0	0.00
POPL 6		0.99 (0.93)	0.99(0.93)	0.98(0.89)	0	0.15
POPI 6	Lungs	0.99(0.93)	0.99(0.93)	0.97(0.71)	0	0.40
POPI 0		0.99(0.93)	0.99(0.93)	0.98(0.91)	0	0.55
POPI ICCR	Lungs	0.98 (0.94)	0.99 (0.93)	0.99 (0.98)	0	0.04
Average	Lungs	0.98 (0.92)	0.99 (0.92)	0.95 (0.64)	0	0.15
Average	_	0.98 (0.92)	0.99 (0.92)	0.98 (0.89)	0	0.15

3. RESULTS

3.A. Thoracic 4DCT data

In the following, we have used the default settings for ANACONDA provided in RayStation 4.5 for CT/CT DIR, which means that the real valued weights are $\alpha = 1.0$, $\gamma = 0.5$, and $\delta = 0.5$. $\beta(v_i) = 400$.

Most algorithms listed on the DIR-LAB webpage evaluate the objective function only inside the lung region. We therefore decided to segment the lung region, using the region growing algorithm available in RayStation, and include results for ANACONDA with and without focus region. Neither shape constraint nor controlling structures were used. In Fig. 7, DIR-LAB 1 is shown as example. The reference phase is fused with the target phase before (top) and after (bottom) ANACONDA with focus region applied.

In Table IV, the target registration errors when using ANACONDA are listed. When using focus region, we have

an average error which is 1.17 mm in 3D in comparison with 8.33 mm before ANACONDA was applied. The errors are, as expected, highest in the superior–inferior as that is where the largest movements are.

In Fig. 8, the target registration errors are compared with published results. We have included the best and the worst results listed on the DIR-LAB webpage (by June 11, 2014) and by Vandemeulebroucke *et al.*^{32,45} For DIR-LAB 1, 2, and 5, results for the 21 algorithms have been reported, for DIR-LAB 3 and 4 seventeen, and for DIR-LAB 6–10, nine algorithms. For POPI 1–6, results from four algorithms have been reported and for POPI ICCR, five algorithms. We remark that for the DIR-LAB data sets, we have used the 300 landmarks possible to download, while some of the algorithms in Fig. 8 have used the complete set of landmarks as reported on the DIR-LAB webpage. We can conclude that ANACONDA performs well in comparison, especially when using focus region. Without focus region, we note that two cases are

50 O. Weistrand and S. Svensson: ANACONDA for DIR

TABLE VI. Results for the pelvic data using rigid registration, ANACONDA without controlling ROIs, ANA-CONDA with Bladder, Prostate, and Rectum as controlling ROIs. Metrics included are DSC for the different ROIs, image similarity, mean of the Jacobian determinant of the deformation vector field, and number of inverted elements.

Prostate 1				
	Gas above Bladder		Gas and Full Rectum	Small Bladder
DSC Bladder				
Rigid	0.83		0.75	0.79
No controlling	0.81		0.82	0.73
Controlling	0.99		0.99	0.98
DSC Prostate				
Rigid	0.89		0.87	0.94
No controlling	0.94		0.89	0.96
Controlling	0.98		0.95	0.98
DSC Rectum				
Rigid	0.77		0.51	0.74
No controlling	0.85		0.60	0.69
Controlling	0.97		0.93	0.96
Image similarity				
Rigid	0.47		0.47	0.50
No controlling	0.82		0.91	0.83
Controlling	0.81		0.79	0.80
Mean Jacobian deter	minant			
No controlling	0.92		0.91	0.92
Controlling	0.93		0.98	0.95
Number of inverted e	elements			
No controlling	0		0	0
Controlling	0		0	0
Prostate 2				
	Small Bladder	Gas	Full Bladder and Rectum	Normal
DSC Bladder				
Rigid	0.36	0.46	0.73	0.55
No controlling	0.38	0.47	0.75	0.56
Controlling	0.98	0.93	0.96	0.96
DSC Prostate				
Rigid	0.72	0.70	0.57	0.69
No controlling	0.72	0.73	0.55	0.68
Controlling	0.97	0.95	0.98	0.97
DSC Rectum				
Rigid	0.58	0.47	0.55	0.49
No controlling	0.60	0.63	0.60	0.48
Controlling	0.97	0.92	0.93	0.90
Image similarity				
Rigid	0.64	0.73	0.70	0.68
No controlling	0.90	0.90	0.89	0.90
Controlling	0.84	0.85	0.89	0.87
Mean Jacobian deter	minant			
No controlling	0.99	1.00	1.01	1.01
Controlling	0.99	1.00	1.02	1.01
Number of inverted e	elements			
No controlling	0	0	0	0
Controlling	0	0	0	0

especially problematic, DIR-LAB 7 and 8. Those are further discussed in Sec. 4.

In Table V, DSC for propagated contours is listed together with the correlation coefficient, i.e., a measure on image similarity, and the number of inverted elements. In this case we cannot compare to the results for other algorithms, but can conclude that the figures are close to 1 which shows that ANACONDA performs well both with respect to contour propagation and image similarity. Furthermore, that the resulting deformation vector fields contain no inverted elements. Rigid registration results are listed for comparison.

The average computation time to run ANACONDA for the DIR-LAB and POPI data sets was 17 s on a machine running Windows 7 (64-bit) operating system with 24 GB installed memory and Intel Xeon W3580 (4 cores) CPU. The GPU was a NVIDIA GTX 760.

3.B. CT/CBCT data

In the following, we have used the default settings for ANACONDA provided in RayStation 4.5 for CT/CBCT DIR, which means that the real valued weights are $\alpha = 1.0$, $\gamma = 0.5$, and $\delta = 0.5$. $\beta(v_i) = 1000$.

The results for the CT/CBCT data are summarized by Table VI (Prostate 1 and Prostate 2) and Table VII (Head and Neck). From Table VI, it is evident that image information alone is not enough for CT/CBCT DIR in the pelvic region for large deformations; image similarity increases significantly compared with rigid registration (p < 0.001), while DCS remains on a rather low level. This is pointed out by several authors, e.g., Kim *et al.*¹⁹ Using Bladder, Prostate, and Rectum as controlling ROIs, we can achieve a DIR with both high values for DCS (p = 0.0078 for Bladder, Prostate, and Rectum being significantly better than rigid registration) and for image similarity. At the same time bone is kept rigid, which is shown by a mean Jacobian determinant being close to 1.0. The controlling ROIs were not used as shape constraints. We remark that image quality is better for the daily

TABLE VII. Results for Head and Neck using rigid registration and ANA-CONDA (without controlling ROIs). Metrics included are DSC for the different ROIs, image similarity, and number of inverted elements.

	CBCT 5	CBCT 10	CBCT 15
DSC Parotid (left)			
Rigid	0.65	0.67	0.63
No controlling	0.78	0.81	0.81
DSC Parotid (right)			
Rigid	0.84	0.77	0.74
No controlling	0.88	0.82	0.85
Image similarity			
Rigid	0.63	0.63	0.59
No controlling	0.76	0.76	0.73
Number of inverted	elements		
No controlling	0	0	0

CBCT in Prostate 2 than in Prostate 1 which explains the slightly better results.

It is of interest to investigate the performance of ANA-CONDA when using a subset of the ROIs as controlling ROIs to see the affect on the alignment of noncontrolling ROIs. For this purpose, we have ran ANACONDA using only Bladder and Rectum as controlling ROIs. For Prostate 1, the results are similar to what is presented in Table VI except for DCS Prostate which remains on a level equivalent to using no controlling ROIs. For Prostate 2, where the image quality is better, mean DCS Prostate is 0.86, in comparison with 0.69 for no controlling ROIs and 0.97 for Bladder, Prostate, and Rectum as controlling ROIs. This indicates that the controlling ROIs have influence of the alignment of noncontrolling ROIs in cases when the image quality is good enough.

From Table VII, we can conclude that ANACONDA handles CT/CBCT DIR well. DSC for Parotid (left) and Parotid (right) as well as image similarity has values closer to 1 than if rigid registration only was used. In this case, the sample set is too small to show statistical significance (p = 0.125). We remark that for Head and Neck, we ran ANACONDA using no controlling ROIs. Moreover that the CBCT data suffer from dental filling artifacts which affects the image similarity measure. Finally, the volume of parotid is small which means that discretization effects are high.

The average computation time to run ANACONDA for Prostate 1 and Prostate 2 was 18 s with and 10 s without controlling structures on a machine running Windows 7 (64-bit) operating system with 24 GB installed memory and Intel Xeon W3580 (4 cores) CPU. The GPU was a NVIDIA GTX 760.

4. DISCUSSION AND CONCLUSIONS

We have presented a deformable image registration algorithm for applications in radiotherapy, ANACONDA. The algorithm is commercially available through the treatment planning system RayStation (RaySearch Laboratories AB, Stockholm, Sweden). The aim of this work was to describe the algorithm in order to avoid users needing to work with "a black box" as well as to make validation of the algorithm public. ANACONDA was benchmarked for thoracic 4DCT data and CT/CBCT data of the pelvic and the head and neck region. For the thoracic 4DCT data, it was compared with results from other published algorithms and proven to perform well in comparison. For CT/CBCT data, contoured data sets were used and it was shown that ANACONDA can handle both large deformations and multimodality, in terms of CT/CBCT, data. To summarize, ANACONDA is a versatile algorithm due to the combination of using image similarity as well as, if wanted, anatomical information. It can be precise in cases such as bifurcation tracking in 4DCT of the thorax region and at the same time handle low contrast regions found in CT/CBCT registrations of the pelvic region.

ANACONDA is formulated as a nonlinear optimization problem with an objective function consisting of a weighted linear combination of different terms. The weights have been experimentally determined by evaluating the algorithm on data sets provided to us through research collaborations as well as through cooperation with clinics using the RayStation treatment planning system. The weights are not tailored to the data sets used for validation in this paper. Since the pelvic region is a body region where controlling structures are more likely required, the weight for the controlling structures, δ , has been given a numerical value high enough to handle large, but reasonable, anatomical changes found in this region due to differences in bladder and rectum filling. If δ is too large, e.g., 10 times larger than the chosen value, the influence from the image similarity term is not enough to give a satisfactory registration in regions not covered by controlling structures. If δ is given small numerical value, e.g., 10 times lower than the chosen value, the term in the objective function handling controlling structures will not have a significant influence of the objective function. To study in detail the weight for β , we recomputed the results for the thoracic 4DCT data when varying β by 10%. For β = 440.0, the mean target registration error was 1.15 ± 0.82 mm and for $\beta = 360.0, 1.17 \pm 0.86$ mm. This can be compared with the reported value 1.17 ± 0.87 mm (β = 400.0). Hence, ANACONDA is stable with respect to β . One often mentioned difficulty with DIR is to keep bone rigid even when large deformations occur close to the bone regions. As shown for the pelvic data, ANACONDA performs well on this aspect. However, we remark that shape based regularization can be used for this purpose if further emphasize is required, hence, by creating a bone ROI, include it as shape constraint and possibly increase γ . The exact numerical values of the weights α , β , γ , and δ are found in Sec. 3.

ANACONDA differs from other hybrid DIR solutions on various aspects. The novel way of incorporating contour information through a chamfer matching inspired approach and by using an adaptive regularization of the grid in order to avoid inverted elements are the two most interesting.

The performance of ANACONDA without focus region on DIR-LAB 7 and DIR-LAB 8 is not satisfactory. The anatomical changes in these data sets are large, which is evident from the mean target registration error when no DIR is used. The optimizer, which finds local minima in the objective function and not a global minimum, does not succeed in finding a solution where both the internal structures of the lungs are well registered and the surroundings of the lungs in this case. DIR-LAB 7 and DIR-LAB 8 are typical cases which would benefit if the algorithm modeled a sliding interface between lung and lung cage. Further developments of ANACONDA involves the implementation of site specific features such as sliding interfaces, e.g., the mentioned lung and the lung cage interface, as well as other biomechanical properties. See, e.g., the initiatives by Risser et al.⁴⁷ and Delmon et al.⁴⁸ Another improvement is to implement mutual information as image similarity measure to deal with CT/MR DIR. Additional benchmarking by participating in EMPIRE10 for thoracic 4DCT data,⁵ as well as submitting results for the head and neck region initiative described by Pukala et al.,49 is planned. Another aspect of DIR validation is its accuracy in dose deformation where validations can be done using deformable gels.^{50,51} In this work, we have focused on accuracy of image deformation but it is of interest to investigate the performance on dose deformation in the future.

ANACONDA in its present form (RayStation 4.5) is GPU accelerated, thus facilitates fast contour propagation and can, once validated for dose deformation, be used in online adaptive replanning.

ACKNOWLEDGMENTS

The CT/CBCT data were made available by University of Health Network (UHN), Toronto, Canada, through REB study 11-0250-CE. Michael Sharpe, Patricia Lindsay, Joanne Moseley, Vickie Kong, and Biu Chan, at Princess Margaret Cancer Centre, UHN, are gratefully acknowledged for helping to collect, contour, and transfer the data. This research was supported by EU FP7 funding through project ART-FORCE No. 030-103.

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