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Inter-individual registration and dose mapping for voxel-wise population analysis of rectal toxicity in prostate cancer radiotherapy

Gaël Dréan^{1,2}, Oscar Acosta^{1,2,*}, Caroline Lafond^{1,2,3}, Antoine Simon^{1,2}, Renaud de Crevoisier^{1,2,3} and Pascal Haigron^{1,2}

1 INSERM, U1099, Rennes, F-35000, France

2 Université de Rennes 1, LTSI, Rennes, F-35000, France

3 Center Eugène Marquis, Département de radiothérapie, Rennes, F-35000, France

Abstract

Purpose: Recent studies revealed a trend towards voxel-wise population analysis in order to understand the local dose/toxicity relationships in prostate cancer radiotherapy. Such approaches require, however, an accurate inter-individual mapping of the anatomies and 3D dose distributions towards a common coordinate system. This step is challenging due to the high inter-individual variability. In this paper, we propose a method designed for inter-individual non-rigid registration of the rectum and dose mapping for population analysis.

Methods: The method is based on the computation of a normalized structural description of the rectum using a Laplacian-based model. This description takes advantage of the tubular structure of the rectum embedded in a non-rigid registration-based scheme. The performances of the method were evaluated on 30 individuals treated for prostate cancer in a leave-one-out cross validation.

Results: Performance was measured using classical metrics (Dice score and Hausdorff distance), along with new metrics devised to better assess dose mapping in relation with structural deformation (dose-organ overlap). Considering these scores, the proposed method outperforms intensity-based and distance maps-based registration methods.

Conclusion: the proposed method allows for accurately mapping inter-individual 3D dose distributions towards a single anatomical template, opening the way for further voxel-wise statistical analysis.

I. Introduction

Several studies have shown that increasing the dose to the prostate leads to improved local cancer control (1,2). However, such dose increases are limited by treatment-related toxicity involving the organs at risk (3,4). Understanding dose/toxicity relationship in prostate cancer radiotherapy proves to be crucial for improving treatment reliability from the planning stage onward. Normal tissue complication probability (NTCP) toxicity prediction models like the Lyman-Kutcher-Burman model (5,6) have been developed in order to predict toxicity events using dosimetric data. The main observations considered are dose-volume histograms (DVHs), which provide an overall representation of dose distribution based on the dose delivered per percentage of organ volume. In particular, these models have rendered it possible to establish dose-volume constraints during treatment planning so as to limit the occurrence of unwanted events (7). Nevertheless, these models display limitations (8,9), for instance those relating to the use of DVHs that result in a loss of anatomical spatial information like the organ shape and 3D dose distribution.

The strong correlation that may exist between different dose parameters of a DVH makes it difficult to extract the dose measurement that is the closest correlated with toxicity events. Furthermore, the models do not provide any understanding of local relationships between dose and effect at a suborgan level. Based on the hypothesis that certain regions of healthy organs may be more sensitive than others, new models aiming at spatially analyzing the relationship between dose and toxicity have been suggested. Some models have sought to geometrically describe spatial dose distribution on the rectal wall and correlate this description with the occurrence of rectal toxicity events (10–13). However, the parametric description of dose was approximative, and only the dose to the organ surface was taken into account.

More recently, approaches with in-depth analysis of 3D dose distribution using voxel-wise population analysis techniques have been proposed (14–16). These techniques aim to analyze the dose-effect relationship in each voxel across a population with the objective of identifying anatomical regions that may be responsible for the toxicity event occurrence. They necessitate several steps: (i) the mapping of a population of individuals in terms of their anatomy by non-rigid registration onto an anatomical template; (ii) propagation of dose distributions according to the anatomical transformation thus obtained; (iii) a local statistical analysis of dose-effect relationship. The performance of such an approach depends, however, on the accuracy of the anatomical mapping. This step may be performed with the computed tomography (CT) images used for computing the 3D dose distribution.

Interindividual mapping of the pelvic region using computed tomography (CT) planning images has been the subject of very little research in the literature. It appears complex, particularly given the very high interindividual anatomical variability (organ volume, presence or absence of gas in the rectum, etc.) and low contrast of soft tissues (17,18).

In the setting of radiotherapy, research into the anatomical registration of CT images has mainly concentrated on intraindividual images, *i.e.*, per-treatment cone beam CT and planning CT for dose accumulation purposes (19–21). Algorithms have been based on intensity for the most part (19,22–24). However, given the low contrast between soft tissues and due to the high anatomical variation observed even in the inpatient setting, methods seeking to combine image intensity information with organ segmentation have been proposed (21,25,26), using, for example, distinctive anatomical points such as calcifications, salient points, markers or distance map combined with organs meshes to guide image matching (20,27–31).

In the interindividual setting, conventional registration methods based solely on the grayscale of CT images do not enable sufficiently accurate mapping (17,18). Adding other information like anatomical features to guide the image matching process may render it possible to improve mapping accuracy in population analysis applications. Such methods are yet to be explored in settings where anatomical differences are greater and where greater deformations are being considered. See supplementary material at [URL will be inserted by AIP] in Figure 7 (electronic version), which depicts delineations and planning dose distributions for two different individuals. Employing structural descriptor maps that exploit the rectum's pseudocylindrical nature may allow the rectums of different individuals to be described in a comparable manner, rather than using tissue intensity as displayed by CT images. Note should also be taken of the steep dose gradient within the rectum, which introduces an additional difficulty as a small matching error may result in a very large dosimetric error.

The main contribution of our paper is to propose an anatomical mapping method for the rectum that employs non-rigid image registration based on a 3D structural model of the rectum constructed using delineations that were made on treatment planning CT scans during routine clinical practice. This model makes use of the pseudocylindrical nature of the

organ at risk of interest. It is founded on the solution of Laplace's equation (32), as estimated between the centerline and surface of the rectum. What is more, mapping accuracy was assessed from not only an anatomical view point but also a dosimetric one, using two new metrics that assess rectal centerline dispersion during the registration process and organ overlap relative to dose distribution.

We then present the construction method for a structural description based on the Laplacian operator in section II.1 followed by the method of registration and dose propagation into the common reference system in sections II.2 and II.3. We deal with the assessment metrics in section II.4. Results are presented and discussed in sections III and IV.

II. Methods

The principle of the method proposed for registering the rectum R_i and propagating the dose d_i of the individual i to the rectum of the anatomical template R_{AT} is described in Figure 1. Step 1 involved calculating a 3D structural model Φ_i and Φ_{AT} of R_i and R_{AT} , respectively, using the centerline and Laplacian field u . Next (step 2), following a rigid registration that optimized the sum of squared differences (SSD) and served as an initialization, a Demons nonrigid transformation aligned the individual's rectal model Φ_i with the anatomical template rectal model Φ_{AT} . Once the nonrigid transformation $\vec{T} = \vec{DF} \circ T_{rigid}$ had been obtained, where $\vec{DF}$ represented the deformation field resulting from nonrigid registration, two propagation processes were implemented (step 3); one concerned the rectum R_i , and the other concerned dose distribution d_i . Thus in the end the dose d_i of the individual was mapped onto the anatomical template reference system.

Figure 1: Proposed method for mapping the rectum and 3D dose distribution of an individual to the common anatomical template (AT).

We will first describe the structural descriptors for the rectum. We will then move on to the interindividual mapping process before finishing with an assessment of the proposed method's performance.

III.1 Construction of a 3D structural model of the rectum

To structurally describe a number of rectums of a population, it is essential that the same portion of the rectum be delineated according to a single clinical protocol. Here, organs were delineated by a specialist according to the same radiotherapy planning protocol, namely limiting the rectum to 2cm above and below the prostate and seminal vesicles. Like a cylinder, which can be entirely described by its radius and generatrix, the rectum, a pseudocylindrical tubular structure, may be described structurally based on the organ's surface and centerline.

a. Centerline γ_i

Numerous methods exist in the literature for calculating the centerline of a structure, including skeletonization (33,34), minimal-path (35,36) and flux-driven techniques (37). We chose the skeletonization method proposed by (34), which preserves the structure's topology and involves homotopically thinning a structure by iteratively deleting points in ascending order of distance map value as calculated within the object. This method was

used to calculate the centerlines γ of rectums following image smoothing using a Gaussian filter, which blurs irregularities arising from interslice manual segmentation.

b. Structural descriptor map: Laplacian field u and distance map δ

The structural descriptors planned for registering the rectum were: (i) Laplacian field as estimated between the rectal boundary F_{Ext} and centerline γ in order to describe the inside of the organ (32,38) and (ii) the map of Euclidean distances to the rectal boundary δ in order to describe the outside of the organ (39). The method is detailed below, where it is abbreviated to DMLA for Distance Map/Laplacian.

Solving Laplace's equation in a discrete domain has led to several possibilities for characterizing various structures in medical imaging. For example, the determination of organ thickness proposed by Jones (32,38) was used to accurately calculate thickness (40,41).

In this paper, the scalar field u solution of Laplace's equation as calculated within the rectum between the centerline and the surface (42,43) enables the rectum's cylindrical structure to be described in a similar fashion. Thus, registration can be driven by direct point-to-point correspondences within each individual's rectum.

Laplace's equation is a second-order partial differential equation u on a domain $\mathcal{R}$ demarcated by an external boundary F_{Ext} , here the rectal surface, and an internal boundary, here the rectal centerline γ . Its mathematical form is:

$$\Delta u(x, y, z) = \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} = 0 \quad (1)$$

with the Dirichlet boundary conditions: $u(x, y, z) = u_{Ext}$ if $(x, y, z) \in F_{Ext}$ and $u(x, y, z) = u_\gamma$ if $(x, y, z) \in \gamma$, where $\{u_{Ext}, u_\gamma\} \in \mathbb{R}$.

The solution of Laplace's equation on a domain divides that domain into a number of isopotential surfaces that form a smooth transition between F_{Ext} and γ and respect the domain's geometry.

In a discrete domain, the equation (1) may be solved using finite differences, as in (40,44). To avoid resampling anisotropic images, Laplace's equation was iteratively solved on the domain $R \setminus \{F_{Ext}, \gamma\}$ as initially proposed by Diep et al. in (45):

$$u_{it+1}(x, y, z) = \frac{1}{2(s_y^2 s_z^2 + s_x^2 s_z^2 + s_x^2 s_y^2)} (s_y^2 s_z^2 [u_{it}(x + s_x, y, z) + u_{it}(x - s_x, y, z)] + s_x^2 s_z^2 [u_{it}(x, y + s_y, z) + u_{it}(x, y - s_y, z)] + s_x^2 s_y^2 [u_{it}(x, y, z + s_z) + u_{it}(x, y, z - s_z)]) \quad (2)$$

with spacing s_x, s_y and s_z respectively; u_{it} the solution, i.e. the potential, calculated on the it^{th} iteration.

In our implementation, the Dirichlet conditions on F_{Ext} and γ were set at 0 on the centerline and 10 000 on the rectal boundary to limit errors arising from calculation approximations, while intensities on $R \setminus \{F_{Ext}, \gamma\}$ were set at 5000, i.e., the mean, as proposed in previous implementations (43). See supplementary material at [URL will be inserted by AIP], Figure 8 (a,b) (electronic version) which depicts the estimation of Laplace field in two rectums is illustrated in

Dose-effect relationships will not be analyzed outside the rectum, as the issue being dealt with here is local dose relationships within the organ as well as rectal side-effects. However, a comparable description of the outside of each individual's rectum is needed in order to guide transformation during registration. The outside of the rectum was here described using an Euclidean distance map δ to the rectal surface (39).

Thus, taking an anatomical template AT and an individual i to be mapped, descriptor maps $(\Phi_k, k \in \{i, MAR\})$ were constructed according to the equation:

$$\Phi_k(v) = \begin{cases} u_k(v), & \text{if } v \in R_k \\ \delta_k(v) & \text{otherwise} \end{cases}, \forall k \in \{i, AT\} \quad (3)$$

with u_k and δ_k the solution field of Laplace's equation and the distance map as calculated for the individual $k \in \{i, AT\}$.

III.2 Mapping rectal structural models using registration

To calculate the transformation DF pulling the individual's rectal structural model onto the anatomical template's rectal structural model, we used the accelerated Demons iterative algorithm of (24). The Demons algorithm offers the advantage of being easily configurable and has shown good performance in the inpatient registration of CT/relatively well-contrasted CT images (19,22–24). The algorithm is based on a calculation of forces from optical flow. Registration comprises an energy function minimization problem between the rectal structural model of the anatomical template Φ_{AT} and that of the individual Φ_i . This energy function is a trade-off between deformation regularity as effected by applying a Gaussian filter and image similarity, usually defined by the SSD:

$$DF = \arg \min_T \{SSD(DF(\Phi_i), \Phi_{AT})\} \quad (4)$$

Transformation is calculated using forces based on the gradient of the images:

$$F_e(x) = \frac{(DF(\Phi_i)(x) - \Phi_{AT}(x))\vec{\nabla}\Phi_{AT}}{|\vec{\nabla}\Phi_{AT}|^2 + (DF(\Phi_i)(x) - \Phi_{AT}(x))^2} \quad (5)$$

$$F_i(x) = -\frac{(DF(\Phi_i)(x) - \Phi_{AT}(x))\vec{\nabla}T(\Phi_i)}{|\vec{\nabla}DF(\Phi_i)|^2 + (DF(\Phi_i)(x) - \Phi_{AT}(x))^2} \quad (6)$$

where F_e represents an external force as calculated in a voxel x and where F_i represents an internal force that deforms the fixed image into the floating image by bringing into play the floating image's gradient. Given that the maps of the descriptors Φ_i and Φ_{AT} were constructed via the Laplace field, the values of $DF(\Phi_i)(x)$ and $\Phi_{AT}(x)$ were comparable, thus permitting cost function convergence based on the SSD.

In our implementation, and in the interest of speed, the algorithm was repeated four times in a coarse-to-fine multiresolution scheme so as to initially estimate the major deformations found in an interindividual setting. The images were then undersampled by a factor of two between each level following Gaussian kernel smoothing, the standard deviation of which was set at the size of a voxel. Figure 2 depicts an example of the registration as a deformation field and resulting jacobian determinant map. This map represents how each voxel deformed in term of its volumetric change, greater than one in case of volume expansion and less than one for volume contraction.

Figure 2. a) Individual structural model being non-rigidly registered to an anatomical template (b). c) obtained deformation field and d) Jacobian Determinant map illustrating regions of volumetric changes (expansion of contraction).

III.3 Propagation of dose

Once the deformation field DF was calculated by non-rigid registration, binary images of the rectums R_i derived from manual delineations were propagated into the anatomical template space using the calculated transformation $T = DF \circ T_{Rigid}$ and nearest-neighbor interpolation in order to preserve the image's binary nature. Similarly, dose distribution was propagated using trilinear interpolation (46). The utility of trilinear propagation is that it represents the dose of several individuals in a single anatomical landmark.

III.4 Assessment metrics of interindividual mapping

In the area of dose mapping, evaluating the accuracy of interindividual mapping is particularly complex because of the nonexistence of ground truth. In the literature, different measures have been proposed to estimate anatomical mapping accuracy and transformation validity (19,47–51). One of the most commonly used assessment methods involves measuring overlap between the reference structure of the anatomical template and the one registered (52). Dice score and Hausdorff distance are among the most commonly used evaluation metrics. However, caution should be exercised when interpreting such measures, which only reflect overall geometric overlap between transformed structures and do not show local mapping errors within the structure. It has been demonstrated that they are not very reliable for locally assessing mapping accuracy, given that a high overlap score does not necessarily imply good point-to-point mapping (53).

In the setting of population analysis, a mapping error may lead to very different results in statistical analysis. Differences in regions of homogeneous dose are of no consequence for statistical analysis. Conversely, small differences in a region with a steep dose gradient may result in large differences in dose on the reference rectum. Such a situation is described in Figure 3 illustrating two scenarios ① and ②. Let R be a patient's rectum and $T_s(R)$ its image after transformation T_s , $s \in \{1, 2\}$. The two transformations result in the same difference in alignment dx but in two opposite directions. However, the dose to the anatomical template rectum R_{AT} differs across the two scenarios: in the first scenario, the mapping error leads to a map with higher doses (scenario 1), and in the second, to a map with lower doses.

Figure 3: Two mapping processes leading to a different map of the dose (isodose curves d_i Gy) to the anatomical template rectum.

In addition to the metrics conventionally used to assess registration, we propose here a metric based on distribution that enables in-depth evaluation. The dice score was used (54) expressed as:

$$Dice(V_F, V_M) = 2 \cdot \frac{|V_F \cap V_M|}{|V_F| + |V_M|} \quad (7)$$

with V_F as the anatomical template volume, V_M the registered volume and $|\cdot| = card(\cdot)$, that is, number of voxels of the volume. Another assessment metric is the Hausdorff distance HD (55) which measures the maximum distance between these structures according to:

$$HD(V_F, V_M) = \max\{h(V_F, V_M), h(V_M, V_F)\}, \quad (8)$$

with:

$$h(V_F, V_M) = \max_{f \in V_F} \min_{m \in V_M} \|V_F - V_M\| \quad (9)$$

The behavior of the inside of the rectum was also analyzed by measuring rectal centerline dispersion γ_i after registration. In practice, mean centerline dispersion (MCD) is a measure of dispersion between the rectal centerline of the anatomical template γ_{AT} and the registered rectal centerline of the individual $T(\gamma_i)$, which are described using B-splines, and then discretized into N equidistant points (here, $N = 30$). MCD is then expressed as the mean of the Euclidean distances between corresponding points according the equation:

$$MCD(\gamma_{AT}, T(\gamma_i)) = \frac{1}{N} \sum_{k=1}^N \|\gamma_{AT}^k - T(\gamma_i)^k\|, \quad (10)$$

with γ^k being the k^{th} point of the centerline. By convention, the points were discretized from the lowest slice to the highest slice of the rectum, which were delineated according to the clinical protocol already explained.

Anatomical mapping scores do not, however, allow to fully assess dose mapping accuracy, as illustrated in Figure 3. We propose a dosimetric assessment metric of registration based on dose distribution: dose-organ overlap (DOO). This metric measures the ratio between dose distribution $T(Dose)$ on the intersection and union of $T(R)$ and R_{AT} thus:

$$DOO(T(Dose), T(R), R_{AT}) = \frac{\sum_{T(R) \cap R_{AT}} T(Dose)(v)}{\sum_{T(R) \cup R_{AT}} T(Dose)(v)}. \quad (11)$$

Where v represents a voxel.

DOO is a value between 0, when structures have no voxels in common, and 1, when the dose to the structures is identical. In practical terms, the score penalizes anatomical difference by taking into account the dose that would be mapped onto the reference structure.

III.6 Experiments

The proposed method was assessed with real data and its performance was compared with that of two other methods in which transformation is calculated using the Demons algorithm.

A total of 30 patients treated with external radiotherapy for localized prostate cancer were considered for this study. For each of them we had at our disposal treatment planning data obtained according to the same clinical protocol: planning CT, organ delineation (prostate, bladder and rectum), and 3D dose distribution. Each CT image comprised slices of 512 x 512 pixels (1mm x 1mm) in the axial plane, with an interslice distance of 2mm. See supplementary material at [URL will be inserted by AIP] for an example of delineations and planning dose distributions (Figure 7 electronic version).

Using a leave-one-out cross-validation procedure, each of the 30 patients was iteratively chosen as the anatomical template in accordance with the process presented in Figure 1. The same procedure was followed in order to map individuals according to the three other methods being used for comparison purposes. Mapping accuracy was evaluated by means of the dice score, Hausdorff distance, MCD, as well as DOO. In addition, some dosimetric parameters (Dose max, Mean Dose and V72) according to the guidelines for target volume definition in radiotherapy for prostate cancer used in the GETUG06 randomized trial (Beckendorf et al., 2011) were compared before and after dose mapping.

The first comparative method involved nonrigid registration based on tissue density of the pelvic region as displayed by CT images. We will abbreviate this method to CT-Demons from now on.

As for the proposed DMLA method, two other methods involved Euclidean distance to the organ boundary and/or to the organ centerline (56) were included. The first method will be abbreviated to DMDM from now on. In the DMDM method, the distance map came in two forms: (i) the external organ, in the form of Euclidean distance to the organ boundary, and (ii) internal organ, in the form of a normalized distance map relating to the anatomical template's structure to be registered. Normalization was required so that the maps of very different individuals, particularly in terms of rectal volume, might be compared. Thus, considering an individual i and the anatomical template AT , the descriptor maps $\Phi_{k,l}$ of this method were:

$$\Phi_{k,l}(v) = \begin{cases} \tilde{\delta}_{|internal}^{k,l}(v), & \text{if } v \in \text{Rectum} \\ \delta^k(v) & \text{otherwise} \end{cases} \quad (12)$$

with: $k \in \{i, AT\}$, l the complement of k in $\{i, AT\}$, v a voxel of the image, δ^k the Euclidean distance map to the boundary of the individual's rectum k , and $\delta_{|internal}^{k,l} = \max \{\delta_{|internal}^l\} \times \delta_{|internal}^k$.

The second method will be abbreviated as CLDMDM from now on. In the CLDMDM method, the distance map came in two forms: (i) the external organ, in the form of Euclidean distance to the organ boundary, and (ii) internal organ, in the form of Euclidean distance from the organ centerline. Thus, considering an individual i and the anatomical template AT , the descriptor maps $CD_{k,l}$ of this method were:

$$\Phi_k(v) = \begin{cases} -\delta_{Centerline}^k(v), & \text{if } v \in Rectum \\ \delta_{Rectum}^k(v) & \text{otherwise} \end{cases} \quad (12)$$

with: $k \in \{i, AT\}$, v a voxel of the image, δ^k the Euclidean distance map to the centreline or to the boundary of the individual's rectum k .

III. Results & Discussion

Figure 4 illustrates the results of registration between a patient and an anatomical template. The results of the evaluation of the CT-Demons, DMDM and DMLA registration methods are detailed in Figure 5.

Figure 4: An example of registration results for 29 individuals to the anatomical template: probability maps of the rectum (a,b,c) and representations of centerlines (d,e,f) according to the various compared mapping methods.

The illustration in Figure 4 depicts the probability map of the rectums of 29 individuals using the CT-Demons method shows very approximative organ mapping (Figure 4a). In contrast, rectal mapping using the DMDM method (Figure 4b), the CLDMDM method (Figure 4c) or the proposed DMLA method (Figure 4d) appears to be superior. This is confirmed by the dice scores and Hausdorff distances calculated in the 29 x 30 registrations and illustrated in Figure 5 (a–b). It can be seen that mapping using the CT-Demons method showed little accuracy since mean dice score was 0.7 and Hausdorff distance was more than 20mm. The other metrics proposed reinforce this observation. MCD was nearly 18mm, suggesting an approximative mapping of the inside of the rectum. Similarly, the mean DOO of 0.58 indicates that the dose to the registered organ differed greatly from the dose to the anatomical template organ.

The DMDM, CLDMDM and DMLA methods performed better regardless of the assessment metric taken into consideration. This may be due to the fact that these methods use the same structures (delineation, rectal centerline) that are also used for assessment. Therefore, in order to obtain accurate mapping, it would appear to be wise to use the anatomical information available as much as possible in the registration process, in this case organ delineations.

The results also suggest that the DMLA method yielded significantly more accurate mapping of the rectal structure (Mann-Whitney, $p < 0.05$) than did the DMDM or CLDMDM methods each metric used. The DMLA and the CLDMDM methods lowered MCD to a mean of less than 6mm or 7mm respectively as against 12.3mm for the DMDM method. This may be due to several factors: (i) First, given how the descriptor maps of the DMDM are constructed, the registration process tends to give precedence to correspondence between the maximum values in the organs. Mapping using the points with the highest values is debatable in pseudocylindrical structures like the rectum. As can be seen in supplementary material at [URL will be inserted by AIP] (Figure 9 electronic), the rectum is a complex pseudo-tubular structure, and the highest value of a distance map of two different rectums

may not be at the same anatomical location. Matching these points will lead to a biased dose distribution alignment. (ii) Second, rectal centerline is used in order to construct the DMLA and the CLDMDM. This again underlines the importance of assessing mapping accuracy. Whereas the dice score and Hausdorff distance appear to be close (although significantly different) for the DMDM and DMLA methods, a closer evaluation reveals a very different standard of centerline mapping via MCD. On the contrary, whereas MCD appear to be close for the CLDMDM and DMLA methods, the other metrics revealed high differences, suggesting that the contours of the rectum was not as well as mapped than with the DMLA method. This could be explained by the way the descriptors map of the CLDMDM was computed: because the high interindividual variability of the rectum across a population, the distance map from the centerline inside the rectum may present also high variability. Thus, as opposed to the DMDM and CLDMDM methods, the proposed DMLA method enables to compute a normalized structural descriptors map which considers simultaneously both the contours and the centerline of the organ. For instance, with a Demons registration, the relationships between dice score and, respectively, MCD and DOO are shown in Figure 5. No relationship was observed between dice score and MCD. For example, it was possible for a single dice score of around 0.8 to correspond to a relatively low (<7mm) or very high (>30mm) MCD. Conversely, there seemed to exist a relationship between DOO and dice score. However, DOO appears to penalize inaccurate registration more. Between dice score and DOO there was a drop of 16% with CT-Demons, as against 5%, 9% and 4% with the DMDM, CLDMDM and DMLA methods respectively.

In light of these results, DMLA would appear to be better indicated for in-depth analysis of dose distribution within the rectum than the other methods tested. This method could also be applied in ellipsoidal organs such as the prostate and bladder by using the organ's center of gravity rather than the centerline, as with the rectum.

Table 1 shows the averaged differences in Dose Max, V72 and Mean Dose before and after non-rigid registration on a population of 29 pts registered to a single template. The lower differences appear with the proposed DMLA method.

(a) Dice score

(b) Hausdorff distance (mm)

(c) Mean centerline dispersion (mm)

(d) Dose-organ overlap

Figure 5: Summarized results for each metric (mean ± standard deviation, ** significant difference on Mann-Whitney test) for CT-Demons, DMDM and DMLA. A) Dice score (biggest close to 1 is the best); b) Hausdorff distance (smallest close to zero is the best); c) MCD (smallest is the best); d) DOO (biggest close to 1 is the best)

Differences	CT Demons	DMDM	CLDMDM	DMLA
Dose Max (Gy)	7.149	1.011	0.971	0.812
V ₇₂	3.484	1.953	1.974	1.882
Dose Mean (Gy)	4.023	2.819	2.802	2.783

Table 1. Averaged differences in Dose max, V₇₂ and Dose Mean, computed before and after registration over a population of 29 individuals being treated with the same RT clinical protocol. The proposed DMLA is the method that better preserves the DVH dosimetric parameters.

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IV.3 Perspective: towards a voxel-wise population analysis

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The approach that we propose aims at an in-depth analysis of the local dose-effect relationship (14–16) as made possible by accurate interindividual mapping using the DMLA registration method presented in this paper. The assessment of this method suggests that rectal mapping using the DMLA method enables an entire population of rectums to be mapped in a sufficiently accurate fashion so that dose distribution may be statistically compared voxel by voxel. We thereby ensured that the results of population analysis would be anatomically meaningful. Under these assumptions, it would be then possible to calculate for example the mean in each voxel by group in patients with and without any toxicity outcome. Future research will undertake more in-depth this issue of voxel-wise statistical analysis so as to identify the rectal subregions correlating with the occurrence of side-effects.

As an example of voxel-wise operations, Figure 6 depicts the averaged 3D dose distribution of 29 patients after being mapped to a single template using three different registration methods. It has to be noticed that registration may impact voxel-wise computation as the dose may be differently mapped.

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Figure 6. Sagittal view of mean 3D dose distribution in the rectum from a cohort of 29 individuals after being mapped to a single anatomical template. The voxel-wise mean was computed following three different registration methods: a) Intensity-based Demons, b) DMDM, c) CLDMDM and d) the proposed DMLA.

In this paper, we address the problem of interindividual rectal mapping so as to analyze voxel by voxel the relationship between the occurrence of a toxicity event and planned dose within the rectum. Voxel-wise analysis may be applied to any of the organs at risk in order to study toxicity events. The rectum was chosen here over the bladder for two reasons: First, because dose-effect

relationships have been established for this organ and rectal toxicity in particular has been studied in the literature (57–61). Second, the rectum deforms less from one session to the next during treatment than the bladder does. The utility of a study based on planned dose would therefore be more debatable in the bladder. Furthermore, the decision to study dose within the rectum rather than at the organ's surface was made because dose/volume constraints during planning apply to the organ in its entirety (7).

The proposed method can also be applied for registration of any tubular structures, relying on the central path and whole organ description. In case of intra-individual rectum registration, for instance, the method can be also be used for computation of cumulative dose in an image guided radiotherapy setup. The laplacian field, provides a way to map doses inside a hollow organ such as the rectum, where the gradient of dose may be important and the DVH although informative, does not provide a description of the 3D dose distribution. The main contribution brought by the Laplacien field is the computation of a normalized structural description which is comparable across individuals, as opposed to classical distance maps.

Although From a macroscopic point of view, D_{max} , Dose moy, V_{72} may be equivalent, the 3D distribution might not be equivalent thereby potentially leading to quite considerable different results when performing analysis of local dose. The proposed scores allows the computation of the error within the structure, penalizing mismatching in regions with an important gradient of dose

IV. Conclusion

In our paper, we have proposed a novel interindividual mapping method for the rectum. The main contribution of our research is the creation of a 3D structural model of the rectum based simultaneously on the centerline and the contours and Laplacian field, which provides a normalized descriptor so as to make the most of the rectum's tubular shape. The proposed method makes it possible to map both the rectum's contours and its centerline. Our results indicate that using anatomical/geometrical information during the registration process significantly improves mapping accuracy.

This paper paves the way for voxel-wise population comparisons of dose distribution and may enable local dose-effect relationships to be analyzed in depth. This may make it possible to identify at-risk regions that need to be avoided during radiotherapy treatment planning, thereby improve radiotherapy's reliability.

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Bibliography

460 See supplementary material at [URL will be inserted by AIP] for an example of planning dose
461 distribution, laplacian construction and distance maps for different individuals.

462 *Author to whom correspondence should be addressed. Electronic mail:

463 Oscar.Acosta@univ-rennes1.fr

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Supplementary material

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647 **Figure 7: Example CTs of two different anatomies (a-b), organ segmentations (prostate [black], bladder**
648 **[blue], rectum [orange]) and 3D dose distributions of two patients.**

649

Figure 8: Example calculations of the 3D structural models obtained for two different rectums (a and f): Centerlines γ (b-g); Laplace fields u based on the centerline (c-h); Distance maps δ (d and i); and 3D structural models Φ (e-j).

658

659 **Figure 9: Example of normalized distance maps of two rectums (in millimeters). The anatomical locations**
660 **within the rectum of distance map maximum values (identified with orange Xs) differ.**

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