Image-based modeling of tumor shrinkage in head and neck radiation therapy^{a)}

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Purpose: Understanding the kinetics of tumor growth/shrinkage represents a critical step in quantitative assessment of therapeutics and realization of adaptive radiation therapy. This article presents a novel framework for image-based modeling of tumor change and demonstrates its performance with synthetic images and clinical cases.

Methods: Due to significant tumor tissue content changes, similarity-based models are not suitable for describing the process of tumor volume changes. Under the hypothesis that tissue features in a tumor volume or at the boundary region are partially preserved, the kinetic change was modeled in two steps: (1) Autodetection of homologous tissue features shared by two input images using the scale invariance feature transformation (SIFT) method; and (2) establishment of a voxel-to-voxel correspondence between the images for the remaining spatial points by interpolation. The correctness of the tissue feature correspondence was assured by a bidirectional association procedure, where SIFT features were mapped from template to target images and reversely. A series of digital phantom experiments and five head and neck clinical cases were used to assess the performance of the proposed technique.

Results: The proposed technique can faithfully identify the known changes introduced when constructing the digital phantoms. The subsequent feature-guided thin plate spline calculation reproduced the “ground truth” with accuracy better than 1.5 mm. For the clinical cases, the new algorithm worked reliably for a volume change as large as 30%.

Conclusions: An image-based tumor kinetic algorithm was developed to model the tumor response to radiation therapy. The technique provides a practical framework for future application in adaptive radiation therapy. © 2010 American Association of Physicists in Medicine.

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I. INTRODUCTION

A large fraction of head and neck (HN) cancer patients experience tumor or nodal volume changes during the course of radiotherapy or concurrent chemoradiotherapy.^{1–7} A clinically acceptable treatment plan developed at the beginning of treatment may degrade significantly during a multiweek course of fractionated radiotherapy. To better understand the therapeutic response and compute accumulative dose distributions for future adaptive radiotherapy,^{8–14} it is critical to model tissue kinetics. Volumetric images acquired prior to treatment for patient setup^{15–19} are valuable to assess ana-

tomical changes and their dosimetric implications^{10,20–22} and can therefore be used as data for kinetic modeling.

In general, the tissue mass is not conserved during tumor shrinkage/growth and voxel-to-voxel correspondence between these images may not exist exactly. The conventional similarity-based deformable models, therefore, cannot be applied directly to describe the process.²³ The underlying hypothesis of this work is that, while the tumor volume changes during growth or shrinkage, some of the tissue features in the target volume or at the tumor boundary region are preserved. If these feature points in the two input images can be correctly identified and linked, the association between the

FIG. 1. Flow chart of the calculation process.

points in the space between the feature points can be estimated by interpolation. Development and evaluation of such an image feature-based algorithm to model the tumor growth/shrinkage is the main purpose of this work.

II. METHODS AND MATERIALS

II.A. Software platform

The image-based HN tumor shrinkage modeling algorithm was implemented using the NLM Insight Toolkit (ITK) and the Visualization Toolkit (VTK), which are open source cross-platform C++ software toolkits and are freely available for research purposes [http://www.itk.org for ITK (Ref. 24) and http://public.kitware.com/VTK/ for VTK (Ref. 25)]. ITK provides various kinds of basic algorithms for performing registration and segmentation for medical images and VTK is primarily used for image visualization.

II.B. Overall modeling procedure

The inputs for the calculation include volumetric images of a patient acquired at different time points. The proposed model focuses first on autodetecting the homologous tissue features shared by the two images. The correspondence of the remaining points was then estimated by a thin plate spline (TPS) method.

The tissue feature at a point of interest of an image is characterized by using the scale invariance feature transformation (SIFT) method,^{26,27} which includes scale-space extrema detection, control point localization, orientation assignment, and control point descriptor. If a feature in the template image is mapped correctly to the target image, it will necessarily be mapped back to the original point in the template image when the inverse mapping is applied to the corresponding region in the target image. The bidirectional mapping procedure is included in our algorithm to increase the reliability of tissue feature correspondence.

Before mapping, the two input images are first aligned through a rigid registration. This initialization is not necessary but facilitates the calculation. Figure 1 shows the flow-chart of the proposed two-step calculation process: Autodetection of the homologous tissue features shared by the two input images using SIFT method and voxel-to-voxel association of the rest of points by TPS.²⁸ The details of SIFT and TPS methods are outlined below.

FIG. 2. (a) Schematic diagram of a voxel of interest and its surrounding 26 voxels. (b) The eight-bin histogram of the gradient vector with first bin representing the number of pixels whose gradients fall between 0° and 45°, and so forth.

II.C. SIFT-based feature detection

To determine whether a voxel can serve as a feature point, the image intensity gradients of the voxel and the surrounding 26 voxels are computed [Fig. 2(a)]. The gradient vectors of the voxels can be represented by a 3×27 gradient matrix

$$A = \begin{pmatrix} G_x^1 & G_x^2 & \dots & G_x^{27} \\ G_y^1 & G_y^2 & \dots & G_y^{27} \\ G_z^1 & G_z^2 & \dots & G_z^{27} \end{pmatrix}. \quad (1)$$

G_x^i is calculated as the x component of the image gradient for the i th voxel, and y and z components are computed in a similar way. Next, a 3×3 matrix S is constructed by making a product of the matrix A in Eq. (1) and its transpose, $S = AA^T$. Matrix S is a real symmetric matrix. To search for a feature point based on the image gradient, the matrix is diagonalized and its eigenvalues are then calculated. The eigenvalues serve as quantitative tissue feature descriptors in the region surrounded by 26 voxels. To select a sufficient number of feature points, the eigenvalues are required to be larger than a threshold value which is empirical and is around 0.1–10 (normalized by the nominal CT number of bone). This procedure of identifying a potential feature point is repeated for all voxels on both the template and the target images. In this study, about 10 000 control points were identified on each image.

A useful quantity in the SIFT method is the orientation histogram of a selected feature point. In the orientation histogram calculation of a feature point, $8 \times 8 \times 8$ voxels around it are included. To reduce adverse effects of homogeneous image contents, two neighboring voxels are merged into one voxel, the gradient vector of each merged voxel is computed. The magnitude of the vector is placed in an eight-bin orientation histogram (with 45° interval) [Fig. 2(b) shows an example of eight-bin histogram]. Furthermore, the gradient components in three orthogonal directions (x , y , and z axes) are separated. Thus, a $4 \times 4 \times 4 \times 8 \times 3 = 1536$ bin orientation histogram called the SIFT descriptor is obtained. In the orientation histogram, the number of entries for each bin represents the frequency of the same gradient orientation. To find

FIG. 3. (a) Feature points detected on the template image and (b) the target image based on the SIFT-based approach. Bright points (CT numbers set to 5000) are the matched feature points.

the correspondence of a feature point n on the template image, a least-squares difference between the orientation histograms of this point and that of a potential association n' on the target image is calculated according to

$$S_{n,n'} = \sqrt{\sum_{\alpha=1}^k |(\nabla I_n)_\alpha (\nabla I_{n'})_\alpha|^2}, \quad (2)$$

where $(\nabla I_n)_\alpha$ and $(\nabla I_{n'})_\alpha$ are orientation histograms of the two input images and α is the bin index of the SIFT orientation histogram and it runs from 1 to 1536. After $S_{n,n'}$ is calculated for all points n' on the target image, two points n'_1 and n'_2 that are closest from n in $S_{n,n'}$ domain are identified. If the ratio of these two $S_{n,n'}$ values is less than 80%, the point having the lowest S value is chosen tentatively as the correspondence of point n . Otherwise, no association is made for the point. To further increase the accuracy of feature point association, a bidirectional mapping strategy is applied to any association based on the fact that if a point is mapped to a point in the target image, it should be mapped back to the original point when an inverse association is applied to the corresponding point. Figure 3 shows an example of matched feature points after the bidirectional association on the target image (left) and template image (right) of a head and neck case.

II.D. Thin plate spline method

The associated feature points are employed as the control points for the TPS based interpolation to estimate the mapping of an arbitrary voxel on the template image. A detailed description of the TPS transformation can be found in Refs. 28–30. Here is a brief introduction of this tool.

TPS is a basis function for representing coordinate mappings from R^2 to R^2 based on two equally sized sets of landmark points (feature points in this study). Given n pairs of control points represented by (x_i, y_i) on the template image and the (u_i, v_i) on the target image, respectively, TPS model interpolates those points by minimizing the regularizing functional or “bending” energy

$$E[f(u, v)] = \int_{R^2} \int_{R^2} (f_{uu}^2 + 2f_{uv}^2 + f_{vv}^2) dudv. \quad (3)$$

The function $f(u, v)$ transforms a pixel coordinate to a new coordinate given by

FIG. 4. Generation of a digital phantom. (a) Original CT image and manual delineation; (b) image after randomly throwing away 20% of the contents; and (c) image after further deformation. The original contour and ground truth contour are also superimposed on CT image as shown.

$$f(u, v) = a_1 + a_u u + a_v v + \sum_{i=0}^n w_i U(|P_i - (u, v)|), \quad (4)$$

where P is the matrix of the control points coordinates from the template image and a_1 , a_u , and a_v define the affine part of the transformation and w_i are weighting factors providing additional nonlinear deformation. U is a TPS radial basis function $U(r) = r^2 \log(r)$. In order for $f(u, v)$ in Eq. (4) to have square integrable second derivatives, it is required that

$$\begin{aligned} \sum_{i=1}^n w_i &= 0, \\ \sum_{i=1}^n w_i u_i &= \sum_{i=1}^n w_i v_i = 0. \end{aligned} \quad (5)$$

Together with the interpolation conditions $f(u_i, v_i) = f_i$, this yields a linear system to determine the coefficients w_i and a_i

$$(K + nI)w + Pa = f,$$

$$P^T w = 0, \quad (6)$$

where $K_{ij} = U(|(u_i, v_i) - (u, v)|)$ and I is an identity matrix.

II.E. Assessment of algorithm performance

The proposed algorithm was evaluated with a series of synthetic image (digital phantom) experiments and five HN clinical cases. In the phantom study, the target image was first constructed by randomly throwing away a certain amount of voxels in a planning CT image (template image) taken from a HN case to simulate tissue shrinkage. The number of voxels thrown away was increased in steps of 10% from 10% to 80% in order to test the algorithm over a range of tumor changes. The image was further warped with a B-spline model to accommodate the tissue deformation to mimic clinical cases. B-spline grids of $10 \times 10 \times 10$ were employed in the phantom study. The deformation magnitude of three Cartesian components at each B-spline grid point was created with a random number generator following a Gaussian distribution with the mean of 0 mm and variance of 5 mm. This process and the resulting images are illustrated in Fig. 4. The “ground truth” in the image content change is known in this case, facilitating the quantitative evaluation of the proposed model.

In the patient study, planning CT and CBCT images of five head and neck patients were chosen to be the template and target images, respectively. The planning CT scans were

TABLE I. Summary of planning CT and CBCT image data set for the head and neck patients enrolled in the study. The numbers in the parentheses are the time intervals (in days) between planning computed tomography and the subsequent cone beam computed tomography.

	Planning CT	CBCT#1	CBCT#2	CBCT#3
Patient 1	512×512×156 (0)	512×512×144 (+14)	...	...
Patient 2	512×512×137 (0)	512×512×67 (+46)	...	...
Patient 3	512×512×145 (0)	512×512×61 (+23)	512×512×61 (+41)	512×512×61 (+58)
Patient 4	512×512×164 (0)	512×512×55 (+20)	512×512×55 (+27)	512×512×55 (+50)
Patient 5	512×512×162 (0)	512×512×143 (+20)	512×512×143 (+34)	512×512×143 (+54)

acquired with a GE Discovery-ST CT scanner (GE Medical System, Milwaukee, WI) with a 1.25 mm slice thickness for all patients. The CBCT images were acquired prior to each treatment using a Varian Trilogy™ system (Varian Medical Systems, Palo Alto, CA), with 90 mA tube current, 120 kV voltage, and 2.5 mm slice thickness. For the first two patients (patients 1 and 2), only one CBCT image set was used, whereas for the last three patients (patients 3–5), three subsequent CBCT image sets were employed in the study. Both planning CT and CBCT images had image dimensions of 512×512 pixels per slice. Table I lists the relevant information of the image data sets for the five cases. The time intervals (in days) between planning CT and subsequent CBCTs are also noted. All CT images were transferred through DICOM to a high-performance personal computer with Xeon (3.6 GHz) processor for the calculations described above.

To quantitatively assess the performance of the proposed technique, an index referred to as the volume overlap, which is defined as the ratio (in percentage) of the intersection volume to the union volume of two volumes, is introduced. The volume sets are formed by the manually segmented contours and the calculated contours on the target images.

III. RESULTS

III.A. Digital phantom study

CT images after synthetic modification using the method described earlier is shown in Fig. 4. The SIFT-based algorithm is applied to the synthetic images to model changes in tumor shape and size. Figure 5 represents the results of the study with 20% random removal of the original image contents. A direct overlay of the two sets of contours after a rigid registration would lead to a significant discrepancy due to the five missing tissue and “tumor shrinkage.” The maximum and mean residual errors which were calculated as the distances between the calculated contour and the ground truth

FIG. 5. Digital phantom results obtained using the proposed approach along with the ground truth contour. (a)–(c) show the results on different axial slices.

one were found to be 5.1 and 2.4 mm, respectively. The mapped tumor boundary and the ground truth contour are shown on three transverse slices of the target images. The difference between the two sets of contours is rather small as indicated by visual inspection. A quantitative calculation reveals that the mean and maximum residual errors of the mapped contour are found to be less than 1.3 and 3.0 mm, respectively. In a more systematic study where the image voxel contents were randomly thrown away and followed by additional tissue deformation, the residual error as a function of the removal percentage is illustrated in Fig. 6. The mean residual errors were found less than 1.5 mm in the cases of 50% or less of the original image contents being removed. However, when more image contents (>50%) were thrown away, larger residual errors were observed, indicating that the algorithm started to perform poorly in these cases. The maximum residual errors increased nearly monotonously with increasing image content removal.

To better illustrate the calculation process, the orientation histograms for a matched pair of feature points are plotted in Fig. 7. The left and right panels show the histograms of the matched feature points on the template and target images, respectively. For a given feature point n on the input image, the histogram include 1536 bins. Note that some bins have

FIG. 6. The residual errors between the mapped contours and the ground truth contours obtained from the known deformation matrices. Both mean and maximum errors are shown.

FIG. 7. The 1536 component vector histograms for a matched pair of feature points on planning CT (template image; left) and CBCT (target image; right).

zero entries. The least-squares difference $S_{n,n'}$ with regard to a number of potential points n' , on the target image is plotted in Fig. 8. The voxel n' that led to the least $S_{n,n'}$ is associated to the point n .

III.B. Clinical case studies

The proposed technique was applied to five HN cases to demonstrate the performance of the proposed method. To examine the overall functionality and performance of the system, a simple case (patient 1) was selected in the first study (Fig. 9). The upper and lower rows of Fig. 9 show the planning CT and CBCT images on three different axial slices with the delineated tumor target volumes. The time interval between planning CT and CBCT scans for this patient was two weeks, but the tumor volume did not change much. After the rigid alignment, the tumor target almost overlaps with that delineated by the same physician on the CBCT images. The target volumes before and after the two-week treatment are 212 and 203 cc ($\sim 4\%$ reduction in volume), respectively.

FIG. 8. Least-square difference for a fixed feature point on planning CT as a function of possible association points on CBCT.

While this case is simple, the case study does show that the algorithm is capable of producing intuitive results.

The next study (patient 2) modeled a HN case with a significant change in tumor target volume (Fig. 10). The upper row of Fig. 10 shows the planning CT images in axial, coronal, and sagittal views together with the manually delineated tumor volume (green contours). The bottom row shows the CBCT after 22 treatment fractions together with our calculation results (in red). The results were examined by the same physician. The CBCT image used in this study was acquired before the 23rd fraction of treatment. The target volume change for this case was found to be around 19% (from 253 cc before first treatment to 205 cc after 22 fractions of therapy). The results obtained using the new technique were comparable to the physician's manual segmentation. The mean and maximum displacements of the mapped target contour from the physician delineated contour on CBCT were 1.48 and 4.56 mm, respectively, and the volume overlap was calculated to be 93.2%.

For the rest three clinical cases, each had three CBCT image sets acquired every two weeks. Figure 11 shows the manually segmented GTV boundary contours and computed contours which encompass slightly larger volumes on three CBCT images [Fig. 11(b)–11(d)] for patient 5. Table II pre-

FIG. 9. Planning CT with tumor target boundary (upper row) and the modeling results overlaid on CBCT images (bottom row) in axial, coronal, and sagittal views for patient 1.

FIG. 10. Planning CT and tumor target boundary (upper row) and the modeling results overlaid on CBCT images (bottom row) in axial, coronal, and sagittal views for patient 2.

sents a quantitative comparison between the contours manually delineated by the physicians and computed using the proposed method. Overall, the mean residual errors between the two sets of are less than 2 mm, except the ones on CBCT#3 of patients 4 and 5, where tumor volumes experienced significant changes, partly due to the large time span (four weeks) from the first fraction. The volume overlap index was found to be greater than 90% except in CBCT#3 of patient 5.

IV. DISCUSSIONS

During the course of radiation treatment, many patients develop significant anatomic changes due to multiple factors, including shrinkage of the tumor and/or nodal masses, weight loss, and resolution of postoperative changes. These changes can cause uncertainties in tumor target localization and patient dosimetry. These effects can be compensated by adaptively modifying the treatment plan along the treatment course. In a recent study of 13 patients with tumors or lymph nodes measuring ≥ 4 cm in diameter, the gross tumor volume decreased throughout the course of radiotherapy at a median rate of 1.7%–1.8% per treatment day, and the parotid glands also decreased in volume at a median rate of 0.6% per treatment day.⁵ Moreover, the volume loss of these structures was frequently asymmetric. Modeling of tissue kinetic changes is an important step to better understand the therapeutic response process and to compute the cumulative doses for offline/online image-guided radiation therapy. In this work, we have proposed a SIFT-based model to model the problem of tumor shrinkage/growth.

FIG. 11. CT images and GTV boundary contours for patient 5. (a) Planning CT and GTV; (b) CBCT1; (c) CBCT2; and (d) CBCT3. On CBCT's physician's manual delineations of GTV are superimposed on the calculated contours.

Image-based modeling of tumor shrinkage/growth is essentially a registration problem. However, due to the change in the image contents, there are no exact one-to-one correspondences between two input images. Therefore, the traditional elastic or similarity-based registration models could not be applied directly to simulate the process. By autodelecting the homologous tissue features in two input images and then establishing a voxel-to-voxel correspondence, the proposed approach allows the estimation of the volumetric change from consecutive imaging data in the presence of missing, additional, and deformed tissue. As can be seen in Table II, when the target volume experienced significant change, to achieve high modeling accuracy, the time span between two sets of images should not be too large.

It is challenging to objectively assess the accuracy of deformable image registration due to the lack of the ground truth. In this study we introduced a series of digital phantom experiments to evaluate the algorithm. For the clinical cases, a commonly used approach is to compare the calculated outcome to the physician's manual segmentation. Two indices including a residual error and a volume overlap ratio are introduced to quantify the differences between the automatic procedure and the manual delineation. A direct and benchmarking assessment could be in principle achieved with a

TABLE II. The mean and maximal (in parentheses) residual errors in millimeters and the volume overlap index between the manually segmented contours and calculated contours on the CBCTs for the last three head and neck patients.

	Patient 3		Patient 4		Patient 5	
	Residual error	Volume overlap (%)	Residual error	Volume overlap (%)	Residual error	Volume overlap (%)
CBCT#1	1.73 (3.89)	93.3	1.51 (4.96)	91.7	1.56 (3.32)	90.6
CBCT#2	1.25 (4.14)	94.1	1.73 (3.69)	92.5	2.09 (3.48)	92.2
CBCT#3	1.43 (5.75)	90.2	2.56 (5.38)	92.9	2.72 (4.32)	89.8

physical phantom allowing geometrical changes. However, development of a deformable phantom and the use of such a physical phantom are themselves investigational subjects and are thus beyond the scope of the current work.

There are two issues worth of discussion. First, the modeling accuracy may depend on the quality of CBCT images. Paquin *et al.*³¹ quantitatively studied the influence of different types of noises on image registration and found that the accuracy of calculation is degraded only when the noise level exceeds a certain threshold value. Murphy *et al.*¹⁸ carried out similar studies and showed that noise level in currently available CBCT images does not reduce the accuracy of image registration, even though it may affect the precision of manual contouring. Recently, significant progress has been made in scatter correction of CBCT imaging^{19,32} and it is anticipated that the quality of CBCT will be continuously improved as various scatter removal techniques becomes more mature. Second, we note that the dosimetric change caused by tumor shrinkage can be compensated through adaptive replanning.^{6,33} With the development of an accurate tumor kinetic model, one can track the accumulated dose on a regional level.

V. CONCLUSIONS

Tumor volume changes due to loss of mass, growth, and deformation can be modeled through consecutive imaging studies and the use of the SIFT-based registration method presented in this paper. This technique will be valuable in the study of tumor response to radiation therapy (and other concurrent therapies). In the context of adaptive radiation therapy, the SIFT-based method can be used to compute the cumulative dose distribution during a course of radiation therapy by assisting physicians in delineating the tumor volume after changes due to response to therapy.

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