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Learning-based Stochastic Object Models for Characterizing Anatomical Variations

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Abstract

It is widely known that the optimization of imaging systems based on objective, task-based measures of image quality via computer-simulation requires the use of a stochastic object model (SOM). However, the development of computationally tractable SOMs that can accurately model the statistical variations in human anatomy within a specified ensemble of patients remains a challenging task. Previously reported numerical anatomic models lack the ability to accurately model inter-patient and inter-organ variations in human anatomy among a broad patient population, mainly because they are established on image data corresponding to a few of patients and individual anatomic organs. This may introduce phantom-specific bias into computer-simulation studies, where the study result is heavily dependent on which phantom is used. In certain applications, however, databases of high-quality volumetric images and organ contours are available that can facilitate this SOM development. In this work, a novel and tractable methodology for learning a SOM and generating numerical phantoms from a set of volumetric training images is developed. The proposed methodology learns geometric attribute distributions (GAD) of human anatomic organs from a broad patient population, which characterize both centroid relationships between neighboring organs and anatomic shape similarity of individual organs among patients. By randomly sampling the learned centroid and shape GADs with the constraints of the respective principal attribute variations learned from the training data, an ensemble of stochastic objects can be created. The randomness in organ shape and position reflects the learned variability of human anatomy. To demonstrate the methodology, a SOM of an adult male pelvis is computed and examples of corresponding numerical phantoms are created.

Keywords

Stochastic object models; imaging system optimization; image quality assessment; geometric attribute distributions; radiation therapy

1. INTRODUCTION

When optimizing an imaging system by use of task-based measures of image quality via computer-simulation studies, it is important to account for all sources of randomness in the measurement data.^{1–3} One important source of randomness is variability in the class of objects that are imaged. Unless object variability is incorporated, the computer-simulation studies may suffer from bias, as the study results may greatly depend on which objects are used for the study. Computational phantoms, either voxelized or mathematical, have been proposed for medical imaging simulation, aiming to provide a practical solution to characterize object variability.^{4–10} However, the development of volumetric stochastic object models (SOMs) that are both computationally tractable and are able to accurately model the statistical variations in human anatomy within a specified ensemble of patients remains a challenging task.

The majority of previously reported anatomic numerical phantoms^{4, 7–10} lack the ability to accurately model inter-patient and inter-organ variations in human anatomy, while also modeling organ shape with a high level of detail and realism. This is mainly because they are established on image data corresponding to only a few patients, at most. For example, Segars *et al.* created the cardiac-torso (NCAT) phantom¹¹ and more recently the extended cardiac-torso (XCAT) phantom⁹ by incorporating data from the *VisibleHumanProject*® to create organ models using parameterized non-uniform rational B-spline (NURBS) surfaces. Those phantoms combine the advantages of voxelized and mathematical phantoms, in which the organ generation and deformation is realized by manually manipulating the control points defining the NURBS. The *VisibleHumanProject*® data contains highly detailed anatomical organ segmentations, resulting in realistic organ shape detail in the NCAT/XCAT phantoms. However, because this data includes only one male and one female patient data set, information regarding the statistical properties of inter-patient and inter-organ variations in a specified patient population is not present. To date, numerical phantom generation methods generally do not model the statistical properties of human anatomical organs while also maintaining a high level of anatomical shape detail.

Although SOMs can be determined by use of the raw measurement data in a computed imaging system,¹² databases of high-quality volumetric images^{13–15} with clinically approved organ contours can also be considered for this purpose. Working with reconstructed volumetric images is particularly convenient when the goal is to characterize anatomic variations within a patient population via a SOM. It is possible to create realistic SOMs by capturing most of the variations in a patient population and producing instances that quantify the organ randomness and are geometrically proper, meaning that these samples preserve topology, do not have geometric singularities (e.g. discontinuities, cusps), and have little to no organ overlap. A variety of anatomical shape models have been proposed to describe both the common geometric features and the geometric variability among instances of the population in many shape analysis fields.^{16–21} While shape models have been developed for applications that include image segmentation^{18, 19} and disease detection,^{20, 21} they have not been systematically explored for constructing realistic anatomical phantoms that can facilitate systematic approaches to imaging system optimization.

The purpose of this study is to develop a tractable methodology for learning a SOM that can characterize anatomical variations within a patient population from a set of volumetric training images. The SOM is generated based on learning the geometric attribute distributions (GAD)²² of human anatomic organs. The learned SOM, constrained by respective principal attribute variations calculated from training data, can characterize the inter-organ centroid variations and the shape variations of individual organs within the patient population. Therefore, numerical representations of organs with different shapes and positions can be generated in a flexible and realistic manner by assigning random weights to the attribute distributions. In this way, an ensemble of numerical phantoms can be assembled, whose anatomic variations mimic those of the patient population utilized in generating the GADs. To demonstrate the methodology, a SOM corresponding to an adult male pelvis is computed and examples of a corresponding ensemble of numerical phantoms are created.

2. OVERVIEW OF METHODOLOGY

2.1 Overall Scheme

In this work, a SOM refers to a stochastic process associated with an ensemble of objects, which can represent the variability in organ shape and location among a patient population. Although not addressed here, the methodology presented below can also incorporate pathologies such as tumors when clinically-approved contours are available. The general workflow to develop a computational framework for learning SOMs from clinical patient images is shown in Figure 1. The workflow includes five main steps: collecting and pre-screening patient data, learning the multi-organ centroid GAD, learning individual organ shape GADs, establishing the SOM based on learned GADs, and finally generating an ensemble of numerical phantoms. A training dataset of volumetric images with segmented organ contours is utilized to learn the GADs of organs. Although a more accurate segmented input leads to more accurate GAD learning, the proposed method is expected to remain useful even when this condition is not strictly satisfied, if the segmentation uncertainty is small compared to anatomical variations.

Two types of GADs are learned in this study: one to describe inter-organ centroid distribution and the other to describe shape distributions of individual organs. The inter-organ centroid relationships of multiple organs of interest are characterized by a single *centroid GAD*. A collection of *shape GADs* is established to describe the shape variations of each individual organ. In other words, a single shape GAD is associated with each organ to describe its shape variations. Together, the shape and centroid GADs are capable of representing the statistical variations of individual organ shapes and variations in their relative locations. These statistical variations are representative of the patient population, as defined by the training data.

Based on the learned centroid and shape GADs, we can create an ensemble of stochastic objects that are constrained by the respective principal attribute variations learned from the training data. Random organ shapes and locations can be generated by stochastically sampling the generated centroid and shape GADs, and an anatomical phantom can be further assembled by positioning the sampled organ shapes according to the sampled locations in

three-dimensional (3D) space. By repeatedly sampling from the centroid and shape GADs, an ensemble of numerical phantoms can be formed. Details regarding these steps are provided below.

2.2 Step 1: Collect and pre-screen patient data

The proposed methodology assumes that a collection of 3D images with delineated structures is available corresponding to a specified subject cohort. Datasets of cancer patients treated with radiation therapy are good examples of input for this study. Radiation therapy treatments involve the delivery of high dose to the tumor while sparing organs-at-risk (OARs) to maximize tumor control while minimizing damage to surrounding OARs. Contours of OARs and tumors are routinely delineated and verified as the first step of the radiation treatment process, which is a perfect input candidate for the task in this study. The desired phantom type dictates the selected anatomical site for the training data. For example, if the aim is to generate male pelvis phantoms, patients treated with radiation therapy for prostate cancer can be selected as they will have all contoured organs relevant to the male pelvic region. In our study, a database of clinically approved organ contours delineated from CT and/or MRI images in radiation therapy is employed.

The collected patient datasets needs to be pre-screened to correct for pose differences and organ contour labeling errors. In radiation therapy, most patients are treated with their head towards the gantry and in the supine position (known as head-first-supine position). However, it is possible for patients to be imaged in other orientations. All patient images are first re-oriented retrospectively into the head-first-spine position by rotating the organ surfaces around the appropriate Cartesian coordinate axes. Then the organ labels and contours are checked to make sure all labels represent reasonable anatomical organs; inappropriately labeled datasets are excluded. For example, in the case study shown in Section 3, there were contours that were labeled as normal organs (e.g. prostate), but that actually referred to the post-operative surgical cavity. These contours do not represent actual organs and therefore should not be utilized to train the models. These kinds of contours were excluded based on manual visual inspection using in-house contour viewing software in this study.

2.3 Step 2: Learn the centroid geometric attributes of multiple organs

In this step, we characterize the GAD for the centroids of organs of interest from a patient population. Without loss of generality, we assume that the pre-screening process in Step 1 described in Section 2.2 produces M approved patient datasets, and each contains N organ surfaces. Each organ surface is represented by a collection of 3D points on the surface:

$\mathbf{S}_{m,n} = \left\{ \mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_{K_{m,n}} \right\}$, $1 \leq m \leq M$, $1 \leq n \leq N$, where $\mathbf{S}_{m,n}$ denotes the surface of the n^{th}

organ of the m^{th} patient, and $K_{m,n}$ denotes the number of representative surface points on $\mathbf{S}_{m,n}$. The centroid of the n^{th} organ of the m^{th} patient is given by the mean of $\mathbf{S}_{m,n}$:

$\mathbf{g}_{m,n}^{ori} = \text{mean}_{\mathbf{p}_i \in \mathbf{S}_{m,n}} (\mathbf{p}_i)$. Due to set-up variations when acquiring volumetric images for

different patients, the system centroid (i.e. the mean of centroids of all N organs) may vary dramatically from patient to patient. Therefore, we apply Procrustes analysis^{23, 24} to align

the centroid sets of all patient datasets so that they yield the same system centroid. This aims at reducing the effects of positioning differences on generating the organ centroid GAD. The Procrustes analysis includes steps of translation, scaling, and rotation, which are given below:

1. Translation: We denote the system centroid of the m^{th} patient as:

$$\bar{\mathbf{g}}_m = \text{mean}_{1 \leq n \leq N} (\mathbf{g}_{m,n}^{ori}). \quad (1)$$

We then choose the system centroid of the first patient dataset as a reference ($\bar{\mathbf{g}}_{ref} = \bar{\mathbf{g}}_1$), and translate the system centroid of the other patient datasets to the reference $\bar{\mathbf{g}}_{ref}$:

$$\mathbf{g}_{m,n}^{trans} = \mathbf{g}_{m,n}^{ori} - (\bar{\mathbf{g}}_m - \bar{\mathbf{g}}_{ref}). \quad (2)$$

A translated centroid vector of all organs of each patient is formulated as:

$\mathbf{G}_m^{trans} = [\mathbf{g}_{m,1}^{trans}, \mathbf{g}_{m,2}^{trans}, \dots, \mathbf{g}_{m,N}^{trans}]^T$, where $[\cdot]^T$ denotes the transpose of a matrix or vector.

2. Scaling: Each translated centroid vector $\mathbf{G}_m^{trans}$ is scaled by a weighting factor s_m :

$$s_m = \left(\sum_{n=1}^N \|\mathbf{g}_{m,n}^{trans} - \bar{\mathbf{g}}_{ref}\|^2 \right)^{-\frac{1}{2}} = \left(\sum_{n=1}^N \|\mathbf{g}_{m,n}^{ori} - \bar{\mathbf{g}}_m\|^2 \right)^{-\frac{1}{2}}, \quad (3)$$

$$\mathbf{G}_m^{scaled} = s_m \mathbf{G}_m^{trans}. \quad (4)$$

The s_m terms are calculated so that the root mean square distance from the centroid of each organ to the reference origin $\bar{\mathbf{g}}_{ref}$ equals unity; this is according to the referenced Procrustes analysis.

3. Rotation: Again, the first patient's centroid vector is chosen as a reference:

$\mathbf{G}_{ref}^{scaled} = \mathbf{G}_1^{scaled}$. The centroid vector $\mathbf{G}_m^{scaled}$ is rotated by an orthogonal 3×3 rotation matrix $\mathbf{\Omega}_m$ such that the L_2 norm between the rotated centroid vector and $\mathbf{G}_{ref}^{scaled}$ is minimized:

$$\mathbf{\Omega}_m = \underset{\mathbf{\Omega}}{\text{argmin}} \|\mathbf{\Omega} \mathbf{G}_m^{scaled} - \mathbf{G}_{ref}^{scaled}\|^2, \text{ subject to } \mathbf{\Omega}^T \mathbf{\Omega} = \mathbf{I}, \quad (5)$$

where $\mathbf{I}$ denotes the identity matrix. The solution to the problem shown in Eqn.(5) can be obtained by use of singular value decomposition.²⁵ The final aligned centroid vector of the m^{th} patient is therefore given by:

$$\mathbf{G}_m = \mathbf{\Omega}_m \mathbf{G}_m^{scaled}. \quad (6)$$

After obtaining an aligned centroid vector $\mathbf{G}_m$ for each m^{th} patient, we can construct the centroid GAD by assuming that these aligned centroids of all N organs follow a multi-variate Gaussian distribution:

$$\mathbf{G}_m \sim \mathcal{N}(\bar{\mathbf{G}}, \mathbf{\Sigma}_G), \quad (7)$$

with the empirical mean given by

$$\bar{\mathbf{G}} = \frac{1}{M} \sum_{m=1}^M \mathbf{G}_m, \quad (8)$$

and the empirical covariance matrix given by

$$\mathbf{\Sigma}_G = \frac{1}{M-1} \sum_{m=1}^M (\mathbf{G}_m - \bar{\mathbf{G}})(\mathbf{G}_m - \bar{\mathbf{G}})^T. \quad (9)$$

Performing principle component analysis (PCA) on the covariance matrix gives:

$$\mathbf{\Sigma}_G = \mathbf{E}_G \mathbf{\Lambda}_G \mathbf{E}_G^T, \quad (10)$$

where $\mathbf{E}_G = [\mathbf{e}_1^G, \mathbf{e}_2^G, \dots, \mathbf{e}_N^G]^T$ consists of all eigenvectors $\{\mathbf{e}_i^G\}$ of the covariance matrix, and $\mathbf{\Lambda}_G$ is a diagonal matrix whose i^{th} diagonal element λ_i^G is the i^{th} eigenvalue. Eqns.(7), (9), and (10) indicate that the aligned centroid vector $\mathbf{G}_m$, with its mean subtracted, follows an independent multi-variate Gaussian distribution in the eigenvector space spanned by $\{\mathbf{e}_i^G\}$:

$$\mathbf{E}_G^T(\mathbf{G}_m - \bar{\mathbf{G}}) \sim \mathcal{N}(0, \mathbf{\Lambda}). \quad (11)$$

Eqns.(7) and (11) are the generated centroid GAD from patient data.

2.4 Step 3: Learn the shape geometric attributes of individual organs

In this step, the organ shape GADs are learned from the patient population. As opposed to learning the inter-organ centroid GAD from all N organs, shape GADs are learned for each individual organ. In the collected training data, an organ is represented by a three-dimensional mathematical surface. It is challenging to directly learn shape properties from radiation therapy organ contours due to their lack of specific geometric properties and clear intensity characteristics. Therefore an implicit surface function is employed to provide approximated shape representation for landmark-less organs.²⁶ Denoting $O_{m,n}$ as the n^{th} organ of the m^{th} patient, and considering a volume V_n that contains the n^{th} organ, the implicit surface function $\psi_{m,n}(\mathbf{r})$ with respect to a voxel $\mathbf{r}$ within volume V_n is defined as:

$$\psi_{m,n}(\mathbf{r}) = \begin{cases} -dis(\mathbf{r}), & \text{if } \mathbf{r} \text{ is outside organ } O_{m,n} \\ 0, & \text{if } \mathbf{r} \text{ is on the organ surface} \\ dis(\mathbf{r}), & \text{if } \mathbf{r} \text{ is inside organ } O_{m,n} \end{cases} \quad (12)$$

where $dis(\cdot)$ is a distance function that calculates the shortest distance from $\mathbf{r}$ to the organ's surface. Applying $\psi_{m,n}$ to all voxels within V_n yields a vector $\Psi_{m,n}$ that encodes the shape attribute of $O_{m,n}$. We construct the shape GAD model for the n^{th} organ by assuming $\Psi_{m,n}$ follows a multi-variate Gaussian distribution:

$$\Psi_{m,n} \sim \mathcal{N}(\bar{\Psi}_n, \Sigma_{\Psi_n}), \quad (13)$$

with the empirical mean given by:

$$\bar{\Psi}_n = \frac{1}{M} \sum_{m=1}^M \Psi_{m,n}, \quad (14)$$

and the empirical covariance matrix given by:

$$\Sigma_{\Psi_n} = \frac{1}{M-1} \sum_{m=1}^M (\Psi_{m,n} - \bar{\Psi}_n)(\Psi_{m,n} - \bar{\Psi}_n)^T. \quad (15)$$

Similar to that shown in Section 2.3, performing PCA on Eqn.(15) yields:

$$\Sigma_{\Psi_n} = \mathbf{E}_{\Psi_n} \Lambda_{\Psi_n} \mathbf{E}_{\Psi_n}^T, \quad (16)$$

where $\mathbf{E}_{\Psi_n} = [\mathbf{e}_1^{\Psi_n}, \mathbf{e}_2^{\Psi_n}, \dots, \mathbf{e}_N^{\Psi_n}]^T$ consists of all eigenvectors $\{\mathbf{e}_i^{\Psi_n}\}$ of the covariance matrix, and $\mathbf{\Lambda}_{\Psi_n}$ is a diagonal matrix whose i^{th} diagonal element $\lambda_i^{\Psi_n}$ is the i^{th} eigenvalue. Equations 13, 15, and 16 indicate that the shape attribute vector $\Psi_{m,n}$, with its mean subtracted, follows an independent multi-variate Gaussian distribution in the eigenvector space spanned by $\{\mathbf{e}_i^{\Psi_n}\}$:

$$\mathbf{E}_{\Psi_n}^T (\Psi_{m,n} - \bar{\Psi}_n) \sim \mathcal{N}(0, \mathbf{\Lambda}_{\Psi_n}). \quad (17)$$

Eqns.(13) and (17) denote the shape GAD of the n^{th} organ's shape. The same procedure is repeated for all N organs.

2.5 Step 4: Create randomly-generated objects based on the learned GADs

After obtaining both the centroid and shape GADs, a sampling procedure can be invoked to create objects through a stochastic sampling process.

Sampling the centroid GAD: To create a stochastic realization of multi-organ centroids, we sample the centroid GAD represented in Eqn.(11) while only keeping those eigenvectors corresponding to K_G largest eigenvalues:

$$\hat{\mathbf{G}} = \bar{\mathbf{G}} + \sum_{k=1}^{K_G} \alpha_k \sqrt{\lambda_k^{\bar{\mathbf{G}}}} \mathbf{e}_k^{\bar{\mathbf{G}}}, \quad (18)$$

where K_G is a user-defined number to determine those largest eigenvalues to be used, and α_k is a random scalar sampled from a standard Gaussian distribution $\mathcal{N}(0, 1)$.

Sampling the shape GAD: For each organ, a stochastic realization of organ shapes can be obtained by sampling the shape GAD represented in Eqn.(17):

$$\hat{\Psi}_n = \bar{\Psi}_n + \sum_{k=1}^{K_{\Psi_n}} \beta_{k,n} \sqrt{\lambda_{k,n}^{\Psi_n}} \mathbf{e}_{k,n}^{\Psi_n} \quad (19)$$

where K_{Ψ_n} is a user-defined number to determine those largest eigenvalues to be included, and $\beta_{k,n}$ is a random scalar sampled from a standard Gaussian distribution.

$\hat{\Psi}_n$ implicitly represents the organ shape as a signed distance function. Therefore, a threshold of 0 is applied to convert this signed distance function $\hat{\Psi}_n$ into a 3D binary image, with positive values converted to 1 and others converted to 0. The contour points of the binary

image are exported as 3D point-cloud data. The 3D surface mesh is established from the point-cloud data by use of an open-source software application, MeshLab.²⁷ The procedure involves point-normal calculation and triangle mesh creation with Poisson surface reconstruction.²⁸ The initial created meshes might contain a large number of points, which increases the calculation time for the following image simulation process. Therefore, quadric edge collapse decimation²⁹ is applied to reduce the number of mesh points by collapsing triangle edges to minimize the quadric error. The Taubin smoothing method³⁰ is then applied to preserve the shape realism by reducing the faceted appearance of the triangular meshes. The initial meshes are thus simplified into a triangular mesh with fewer points. This process is repeated for generating each sampled organ shape.

Handling organ overlapping issues: A potential issue involved in generating SOM realizations is that some organs might overlap with each other because the samplings of centroid and shape GADs are two independent processes, especially when those organs are anatomically close to each other, e.g., the bladder, prostate, and rectum in the human pelvis site. Though this is a common problem that exists in many other published stochastic medical phantoms,^{4, 7–10} there is no well-established solution to address this issue as far as we are aware.

In this study, the overlapping issue is handled using a heuristic iterative shifting approach. The general idea is to shift the overlapped organs apart along opposite directions to eliminate the overlap, with constraints on the maximum shift distance to avoid the organ being shifted to a unrealistic position. Also, the organs are shifted according to a priority organ list, which is determined based on the importance of anatomic position of different organs. The details of this heuristic iterative shifting approach is described below:

1. Try out $N_{attempts}$ different combinations of randomly generated centroids $\widehat{\mathbf{G}}$ and randomly generated shapes $\{\widehat{\Psi}_n\}$ to see if any one combination gives a non-overlapping phantom.
2. If all of these combinations have organ overlap, choose one combination (or generate a new combination) and invoke the following procedures in the steps 3–6:
3. Position organs $\{\widehat{\Psi}_n\}$ according to $\widehat{\mathbf{G}}$ and a pre-defined organ priority list (that specifies which organ should be placed first).
4. For i from 2 to N , if the i^{th} organ overlaps with any of the already-positioned $i - 1$ organs, shift the i^{th} organ away from the overlapped organ until they are separated, and repeat this procedure until the i^{th} organ no longer overlaps with any of the $i - 1$ already-positioned organs. The shifting distance is computed from the length of the overlapped region projected onto the line passing the centroids of two overlapped organs.
5. If the shifting can be completed within N_{shift} steps, and the final shifted distance is smaller than a pre-set maximum permissible shift distance d_{shift}^i for the i^{th}

organ, proceed to the next organ; else, re-generate the i^{th} organ's shape Ψ_i according to Eqn.(19) and repeat the step 4.

6. If re-generating the i^{th} organ's shape does not yield a non-overlapping phantom after $N_{regenerate}$ times, discard the centroids and shapes, and return to Step 2 to start with a new phantom.

Note that the parameters $N_{attempts}$, N_{shift} , $N_{regenerate}$, and the organ priority list can be determined and customized based on specific SOMs. In the case study shown in Section 3, we empirically set the parameters $N_{attempts} = 5$, $N_{shift} = 10$, $N_{regenerate} = 5$, and the organ priority list to be {prostate, bladder, rectum, femoral head, and skin} in a high-to-low order.

Creating stochastic objects: Finally, each created organ shape mesh is translated to the corresponding centroid position defined in $\hat{G}$. As such, a SOM realization with multiple organs can be created.

2.6 Step 5: Generate numerical phantoms from the SOM realization

In order to create numerical phantoms from the SOM realization described in Section 2.5, we assign object property values to each organ, which can be employed to model different object properties as encountered.

First, the physical nature of these properties should be dictated by the type of phantom. For example, in order to use the phantom for X-ray CT, MRI, and ultrasound imaging, the physical properties such as linear attenuation coefficients, proton densities, or acoustic impedance, respectively, should be considered and assigned accordingly.

Second, the organ properties can also be assigned in different spatial distributions. As a simple solution, a uniform, homogeneous material can be assigned to each individual organ. As a specific example of physical property assignment in the case study shown in Section 3.2, uniform materials with linear attenuation coefficient distributions are assigned for each specific organ to all spatial locations within the organ to simulate CT images.^{31–34}

3. CASE STUDY: HUMAN PELVIS SOM

The proposed methodology can be employed to create numerical phantoms for any anatomical organs, provided a collection of segmented anatomical structures. As an example, a human pelvis SOM and corresponding numerical phantoms were generated in this study.

3.1 Create the male pelvis SOM

As an example, a total of 20 prostate X-ray CT datasets were collected from the Department of Radiation Oncology at Barnes Jewish Hospital with the approval of the Institutional Review Board. Since these patients were treated with radiation therapy for prostate cancer, clinically approved organ contours from these images were also available and could be used for learning the centroid and shape GADs. Each patient dataset includes all delineated organs relevant to prostate radiation treatments, which are the prostate, bladder, rectum, femoral heads, pelvic bone, and seminal vesicles.

The shape and centroid GADs are learned following the procedures described in Section 2.3 and Section 2.4. A SOM realization corresponding to the male pelvis region is created based on the learned GADs and following the sampling procedure described in Section 2.5. The number of principal components in Eqns.(18) and (19) during the sampling procedure are chosen to be $K_G = 3$ for the centroid model. The number of utilized components K_{ϕ_n} was organ-specific such that each shape GAD contained at least 95% of the shape variations.

Figure 2 depicts a two-dimensional slice of the mean $\bar{\Psi}_n$ of the bladder, which is represented as a signed distance function. The corresponding binary image, with the perimeter contour superimposed in blue is displayed as well. The contour points generated from this process are exported in a three-dimensional point-cloud format. A triangular mesh is created from the point-cloud data by employing the MeshLab software.²⁷ An example of a generated point cloud and triangular mesh of the bladder is shown in Figure 3.

3.2 Generate the human pelvis numerical phantoms

To create numerical pelvis phantoms suitable for X-ray CT imaging, appropriate linear attenuation coefficients μ need to be assigned to each organ within the phantom. We build a hierarchical tree structure to assign a material property to each organ. Figure 4 displays the designed hierarchical tree structure for placing the male pelvis organs in a pre-defined order. The hierarchical tree captures the parent-child relationship between each organ and the exterior of the human body. As a simple example, the interior of each organ is assigned a single, homogeneous material by use of the information provided by the NIST online database.³⁵ Using the online database, a polyenergetic spectrum of linear attenuation coefficient distributions $\mu(E)$ is assigned to each organ according to the defined material. In addition, for the bony structures such as the femoral head and pelvis bone, an interior layer is created by shrinking the contour mesh by 1.5 mm, and assigned a lower density value, to accommodate for lower-density cancellous bone.

4. RESULTS

4.1 The learned centroid and shape GADs of human pelvis organs

Figure 5 displays the results of the learned centroid GAD model using the collected prostate cancer patients described in Section 3.1. Figure 5a shows all the centroids utilized in the training dataset properly aligned via Procrustes analysis.³⁶ Figure 5b shows the mean centroid and the statistical centroid distribution for the femoral heads, prostate, and rectum. The first two principal component distributions are plotted as line segments, with the lengths determined from the eigenvalues of the PCA results. The centroid GAD is learned while utilizing the aligned centroids from individual organs, preserving the inter-structural centroid differences.

As an example of the shape GADs, Figure 6 displays the organ shape variations for the bladder. It shows various shape GAD distribution samples obtained from different values of $\beta_{k,n}$ in Eqn.(19). More specifically, the three rows show the sampled shapes by setting the weight factor $\beta_{k,n}$ of the first three principal components $\sqrt{\lambda_{k,n}^{\Psi_n}}$ of eigenvectors $\mathbf{e}_{k,n}^{\Psi_n}$ to $-2, 0,$

and +2 respectively. Figure 6 demonstrates that random sampling of the established shape GAD is capable of approximating the shape attribute in a new organ shape.

4.2 The generated numerical pelvis phantom

Figure 7 displays single-shape deformation results by applying random variations on a soft tissue organ (bladder) and a bony organ (left femur). For each organ, new shapes are generated by simply adjusting the elements of the weight vector $\beta_{k,n}$ in Eqn.(19). While for the result shown in Figure 6 the principal components were adjusted individually and manually, in Figure 7, a new organ is generated by automatically generating $\beta_{k,n}$ from a standard Gaussian distribution $\mathcal{N}(0, 1)$ for all $1 \leq k \leq K_{\phi_n}$, with its value constrained within $[-2, +2]$ (sampling 95% of the Gaussian distribution) to avoid unrealistic organ shape distortion. Although the same weight factors are applied to generate new realizations of bladder and left femur bone, there is much more inter-structural shape variations for deformable organs such as the bladder when compared to more rigid organs such as the left femur bone.

Figure 8 displays the interior organs of six different realizations of the SOM based on both centroid and shape GADs. The displayed organs include the prostate, bladder, rectum, femoral head, pelvic bone, and seminal vesicles.

4.3 The simulated CT images with the pelvis SOMs

As an example, numerical male pelvis phantoms were generated in our study, and their utility for performing a X-ray CT imaging simulation study was demonstrated as well. To generate CT images of a numerical phantom, projection images were first simulated by tracing a ray from a poly-energetic x-ray source through the numerical phantom to each detector element, and calculating the resulting intensity at each detector element using exponential attenuation. Each source ray had a total intensity of $I_0 = 1 \times 10^5$ photons, determined as an adequate amount based on the noise in the simulated projection images when compared to clinical CT projection images. These projection images were reconstructed using a filtered backprojection algorithm, with an adjustable filter being determined by the parameter α (described in Appendix). This parameter was manually selected to match the image appearance of clinical CT images. The Appendix contains a detailed description of the CT image generation process.

Figure 10 displays various CT images generated using the pelvis models shown in Figure 8 and the process described in the Appendix. The cross-sections of the CT images shown in Figure 10 are from the same z-slice as that shown in Figure 9. The simulated CT images were generated using the same acquisition and reconstruction parameters for all six different SOM realizations. As expected, when the object model deforms geometrically (i.e. shape and centroid), the related CT image deforms geometrically as well. A set of CT images of these phantoms can be simulated with varying acquisition and reconstruction parameters (see Appendix for more information). The simulated images can be used for varied applications, e.g., a task-based image quality assessment study and automatic segmentation algorithm performance study.

The calculations for the above results were obtained by implementing the numerical phantom generation methodology of Section 2 using a laptop with the Ubuntu operating system version 14.04 LTS with an Intel i7 CPU, having 8 GB of RAM. The following calculation times were recorded. The centroid modeling stage takes less than 1 minute. The shape model training is the most computationally extensive step, and is dependent on the number of voxels used for the implicit surface function. Shape model training takes approximately 20 minutes for smaller organs (e.g. left femoral head) and up to approximately 90 minutes for larger structures such as the external skin contour. The phantom generation process takes no longer than 5 minutes per phantom, including the proposed organ overlap removal strategy. Thus all calculations can be performed on a standard desktop or laptop computer.

5. DISCUSSION

In this study, a new methodology is proposed and implemented to create a SOM based on clinical approved organ structures. Unlike some other numerical phantom generation methods, the proposed method can produce a collection of phantoms that consider the inter- and intra-postural relationships of human anatomical organs. The organ stochastic properties inherited in the SOMs are based on actual patient data, which guarantee the statistical relevance of the organ variations. Below, we discuss the overall methodology strategy, organ overlapping issues, future research work, and potential applications of the study.

5.1 Overall strategy

The purpose of this study is to propose a novel and tractable methodology for learning a SOM and generating numerical phantoms from a set of volumetric training images. The realism of generated numerical phantoms can be evaluated in a theoretical sense. That is, the generated phantoms are deemed to realistically capture the patient variation since the GAD models are based on actual patient data and modeling using a statistical tool such as principal component analysis. The accuracy can also be evaluated by checking their spatial integrity within the simulated images with respect to the numerical phantoms used to generate the images.

In this proposed methodology, while not explicitly incorporated, volume was implicit in the shape modeling process as an extension of shape. Section 4.2 shows an example of establishing an adult male pelvis phantom. The patient population used in this example was relatively narrow in that only adult men were utilized. Thus, the differences in organ volume from patient-to-patient were mostly attributable to shape differences. It is possible that if a wide range of ages (i.e. children and adults) were used to train the model that volume may be a concern. However, we think that patients from a wide range of ages should be separated to groups and train different models separately for more realistic SOM generations. Therefore, volume variations are not a concern for this study since the proposed methodology is designed to model a specific patient population.

In this study, as opposed to learning the inter-organ centroid GAD from all N organs, shape GADs are learned for each individual organ based on two considerations. The first reason is theoretical and relates to the intra-structural nature of organ shapes. Human organs vary in

both the type and degree of deformations. For example, the femoral head varies mostly as rigid rotation and scaling variations among patients, while soft-tissue organs such as the bladder and prostate exhibit more shape variations among patients. Thus, each organ shape is likely to have its own statistical distribution. Considering the intrinsic differences among organs, and aiming to create realistic deformations for each organ, it is more straightforward to formulate the statistical shape model by defining a single signed-distance function for each organ separately. In this way, random samples for each specific organ can be isolated with that from other organs. Moreover, constructing a single signed-distance function vector for all shapes poses two challenges. The first is how to effectively define a single signed-distance function for a multi-organ model, and the second is how to perform random samplings from such model to formulate isolated organs.

The second reason is practical in nature and is in regards to computational memory. Accurately modeling individual shapes necessitates high-resolution distance functions, defined by Eqn.(12) in Section 2.4. Storing these high-resolution distance functions, which have thousands of floating-point numbers for each shape, in memory is itself expensive. Therefore, storing this information for all organs and all patients exceeds the memory limitations of most standard computers, making this approach not computationally feasible. This is especially true if a large number of patient datasets are utilized to train the models. Due to the theoretical and technical limitations of a multi-organ shape GAD approach, multiple single-organ shape GAD models are recommended for the proposed methodology.

Many algorithms were utilized in the proposed strategy, including Procrustes analysis, principal component analysis, and Poisson surface reconstruction, in addition to the triangular mesh simplification algorithms and the CT image simulation/reconstruction algorithms. For each step in this methodology there are other algorithms which can be potentially used instead of the ones chosen in this study. In many cases the results of other algorithm choices will produce a negligible difference in the overall modeling results and the generated phantom appearance; this is especially true of Procrustes analysis and the triangular mesh construction and simplification. We confirmed this during the design of the methodology by testing other forms of rigid registration and mesh construction.

In order to create a stochastic realization of multi-organ centroids and individual organ shapes, K_G and K_{Ψ_n} are user-defined numbers to determine those largest eigenvalues to be used in Eqns.(18) and (19). These two parameters enable a balance between model robustness and computational tractability. When using all of the components obtained from PCA, the entire variance of the data is modeled, but this is computationally expensive. Moreover, in PCA the majority of the variance is typically explained within the first few principal components, and if too many components are chosen the samples may be contaminated in the sense that they may include components from the noise subspace, which do not accurately reflect the true variations of organ shape/organ centroid locations. In our case study, we chose these parameters automatically such that at least 95% of the variance in the training data was explained by the models. This provided a suitable balance between model robustness and computational tractability.

5.2 Overlapping issue

We proposed a heuristic iterative shifting strategy to solve the organ overlapping issue, as described in Section 2.5. This heuristic iterative shifting approach was applied in Section 3 when generating a cohort of male pelvis numerical phantoms, which involved a relatively small number of deformable organs with sufficient distance between them. For this particular application, the shifting approach was adequate for generating the cohort without an excessive number of attempts. However, a phantom with a large number of organs in closer proximity (e.g. the head-and-neck anatomical region) may require a more robust approach for organ overlap removal. Moreover, even though the shift distance is upper-bounded by a maximum value, the final location of the shifted organ may still be unrealistic, under which condition the generated phantom should be discarded. We therefore explored some other strategies for solving the overlapping issue, which are detailed and analyzed below.

1. One simple strategy is to adopt a *Generate-and-Discard* approach,^{37–42} where we can repeatedly draw random samples from the GADs (Eqns.(18), (19)) until the corresponding stochastic object has no overlapped organs. This strategy is applicable when the overlapping does not happen often, so that a phantom can be obtained within a reasonable amount of time despite repeated runs.
2. A second strategy is a heuristic *Crop-and-Assign* approach, where the overlapped region can be simply assigned to one of the overlapped organs, according to a priority list. For example, stiffer structures, like bones, should be assigned a higher priority since they tend to “push away” softer, deformable tissues. This strategy is applicable when organ locations have significantly larger impact on subsequent study, compared to organ shapes.
3. A third strategy consists of imposing constraints on organ shape generation (choices of $\beta_{n,k}$) according to a fixed set of centroids. This is essentially a linear programming problem with a few unknowns (number of $\beta_{n,k}$, which is K), and many constraints (the number of pixels that are already “occupied” by other organs, which can be on the order of thousands). The linear programming problem may be quite difficult to solve, depending on the ease at which the constraints can be satisfied. Therefore this strategy is only applicable if the aforementioned linear programming problem can be solved, but will still suffer from the slow computation speed associated with solving such a problem.
4. Finally, another intuitively and possible approach would be to shift the organs along their principal components, as defined by the centroid GAD model, thereby maintaining the statistical distribution of the centroid model. However, based on our experience, no matter how the centroids are shifted their statistical properties may still have to deviate from the learned centroid GAD in order to avoid organ overlap. Moreover, shifting along the principal component direction may increase the overlap rather than help remove it in some situations. Therefore, this strategy is only applicable if the deviation from the learned centroid GAD is not critical for a specific application.

5.3 Potential clinical applications

The current study applies the centroid and shape GADs to quantify inter-patient statistical variations, both in organ shape and organ position. The SOMs can especially be used to assess many aspects of the radiation therapy treatment process, including image quality, contouring accuracy, and treatment efficacy, using simulation studies with a known ground truth. For example, the generated CT images from these phantoms could be segmented, either manually or automatically, and the segmentation results can be compared directly to the numerical phantom boundaries for ground truth assessment. In radiation therapy, treatment planning quality is commonly evaluated based on tumor prescription dose coverage, which is the most critical plan quality evaluation criterion. The realistic numerical simulations from this study allow for combination of both organ-at-risk (OAR) and tumor anatomical information with the effects of patient populations or patient-specific motion, and therefore has great potential for quality assessment of treatment planning and delivery based objectively on therapeutic tasks.

5.4 Future work

In this study, the aim was to present a general strategy for numerical phantom generation. As such, the pelvis phantom was generated as an example to show the feasibility and effectiveness of the methodology. However, different human anatomical sites (head and neck, lung, pelvis), in addition to different age groups, will yield different deformations and variations, and warrants separate investigation. Therefore further, in-depth studies should be performed using a large library of patient images acquired on various human anatomical sites. Part of our future work will be to conduct such studies, both with retrospective anonymized data and IRB-cleared prospective data.

Both centroid and shape GAD models were assumed to vary according to a multi-variate Gaussian distribution in this study. While this distribution may be suitable for centroid modeling, it is possible that more complex distributions may be more appropriate for shape modeling, for example a multi-modal distribution. Each organ might have its own optimal descriptive statistical distribution, e.g., Gaussian or multi-modal or otherwise, based on theoretical or empirically demonstrated fact. A multi-variate Gaussian distribution was chosen as a starting point for the models in this study, but certainly not as a necessary end point for every modeled organ. Future work will include empirical, organ-specific analysis of the optimal statistical distributions for shape GAD modeling. In addition, both the shape and centroid GADs can also be extended to incorporate intra-patient variations, e.g. inter- and intra-fraction patient motion, if adequate image data (e.g. daily cone-beam CT images from on-board imagers of medical linear accelerators, on-board MRI images from Viewray) can be obtained. Establishing SOMs that include patient motion will be another ongoing work for improving the generality of SOMs and exploring more clinical applications, e.g. the assessment of motion management strategies in radiation therapy.

In this study, principal component analysis was chosen as a robust tool to model statistical inter-patient and inter-organ variations, which is a suitable candidate for computational tractability and the ability to intuitively generate new samples. Considering the wide applications of emerging machine learning algorithms, such as neural networks,⁴³

developing advanced machine-learning based method and investigating the added computational burden will be explored in future work.

Organ overlapping is a challenging issue in stochastic phantom generation. The strategy we used in this study is a heuristic but practical strategy that is adequate for our application. We explored those other strategies and briefly discussed them in this study with the hope to provide a straightforward way of solving the overlapping problem, rather than giving a mathematically perfect solution in terms of maintaining the statistical properties of the generated samples. Developing and incorporating more appropriate constraints remains a focus of our future work.

The SOM for this study was demonstrated using CT images. As a specific example of physical property assignment in the case study shown in Section 3.2, uniform materials with linear attenuation coefficient distributions are assigned for each specific organ to all spatial locations within the organ to simulate CT images. Surely, the organ properties can also be assigned in different spatial distributions considering the heterogeneity within organs. Methods that incorporate texture into organ property assignment can address this intra-organ difference, with details given in related literature.^{44, 45} In any case, the choice of physical property distribution will have an important effect on the appearance of the resulting simulated images, and should be determined based on the desired use of the phantoms (e.g. organ delineation, disease diagnosis, etc.). Further investigations are needed for more realistic image simulations.

SOMs can also be utilized for simulating images from other imaging modalities, if the appropriate intrinsic physical properties are provided. For example, each organ could be assigned a proton density value in addition to an attenuation coefficient, and the transport of radio-frequency waves through tissue could be simulated to produce MRI acquisitions. Also, one additional application of the numerical phantom generation is to incorporate patient motion to create four-dimensional CT or four-dimensional MRI images for patient motion management strategy design, which is another important and challenging task. Similar simulations could also be performed for cone-beam CT and ultrasound imaging. Further investigation is needed in order to generate simulated images from other modalities. Multi-modality imaging using these numerical phantoms, and subsequent incorporation into the aforementioned task-based image quality assessment framework, is part of our on-going work.

6. CONCLUSION

A novel and tractable methodology for learning a SOM from a set of volumetric images is developed. As opposed to other reported methodologies which do not allow for the creation of a statistical ensemble of realistic patient phantoms, the proposed methodology can generate realistic numerical phantoms that encapsulate the statistical variations of a patient population based on GAD models. These models characterize the inter-structural centroid variations and the intra-structural shape variations of each individual anatomic structure, based on the assumption that these properties vary according to a multi-variate Gaussian distribution. The scalable and deformable GADs enable the creation of a series of

anatomically variable phantoms. Phantom variations are not randomly selected, but are instead based on statistical distributions from real patient data. As a demonstration, a SOM for the male pelvis and simulated CT images were created and investigated.

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APPENDIX:: Simulation of CT Image with Pelvis Numerical Phantom

As an example in this study, simulated X-ray CT images were generated from numerical male pelvis phantoms. Figure 10 displays various CT images generated using the object models shown in Figure 8 and the process described in this Appendix.

A.1. CT Projection Data Generation

In order to generate CT images of a created numerical phantom, projection images were first simulated by tracing a ray from a poly-energetic x-ray source through the numerical phantom to each detector element d . Each ray has I_0 photons, and the resulting intensity $I(d)$ at the detector element d can be calculated by using exponential attenuation:

$$I(d) = \sum_{i=1}^{N_e} I_0 \phi(E_i) e^{\left(-\sum_{s=1}^{N_s} \mu_s(E_i) l_s\right)}. \quad (20)$$

The discrete poly-energetic imaging source spectrum $\phi(E_i)$ for each i^{th} energy bin was generated by implementing the TASMIP algorithm,⁴⁶ resulting in a spectrum sampled at integer kVp intervals E_i from 1–150 kV. Thus the total number of energy bins, N_e , is equal to 150. The spectrum $\phi(E_i)$ is normalized such that its sum is unity. Thus the product $I_0 \phi(E_i)$ is the number of photons per ray for energy bin E_i . Each s^{th} organ in the phantom was assigned a specific material (e.g. air, soft tissue, bone, etc.). A C++ class was developed to load and calculate linear attenuation coefficient spectra $\mu_s(E_i)$ for each s^{th} of total N_s organs that were obtained directly from the NIST database online.³⁵ Logarithmic interpolation was utilized to obtain attenuation coefficient values for each energy of the source spectrum. Table 1 lists the utilized materials for this study and the corresponding organs for each material. Since NIST data was not available for spongy bone, cortical bone was used as a substitute, with a decreased density applied.

The calculation of each segmented pathlength l_s of a specific ray was performed using knowledge of the hierarchical tree structure as described in Section 3.2 and depicted in Figure 4. For each source ray I_0 , the intersection length for the highest level (in this case the external contour) was calculated first, then the intersection lengths for the next sub-level (e.g. prostate), and so forth. The calculated pathlengths for children organs were subtracted from the calculated parent pathlength to yield the correct segmented ray pathlength through each organ. Then the appropriate attenuation coefficient was applied into the Eqn.(20) for the given photon energy and organ material. This process was repeated for all N_s organs that

intersect with the source ray. Since the organ models were represented as triangular meshes, the ray-triangle intersections between the source ray and the organ model needed to be calculated to determine the pathlength; this was performed using the highly optimized Moller-Trumbore algorithm.⁴⁷

Prior to image reconstruction, Poisson noise was added to the projection images using the detector intensity $I(d)$ from Eqn.(20), and a pseudo-random number generator. Finally, a Gaussian blur filter was applied to the projection data to simulate the degraded spatial resolution from signal spread within CT detectors.

A third-generation CT scanner was simulated to image the object model in this study. Specifically, the physical properties of the Philips Brilliance 64-slice CT scanner used in our clinic were used for modeling. Thus the scanner diameter was set as 80 cm, and the fan detector contained 672 channels for 64 detector rows, with dimensions of 1.0 and 0.625 mm, respectively. This yielded a maximum scan field of view (FOV) of approximately 60 cm. Helically-acquired projection data was obtained by translating the source in the z-direction between projection acquisitions, with a helical pitch of 1.0.

A.2. CT Image Reconstruction

To accommodate for the multi-slice, helically-acquired projection data, a filtered interpolation approach in the z-dimension was utilized to obtain single-slice, axial projection data. The filtered interpolation approach imitates the work of Taguchi and Aradate,⁴⁸ which includes two steps of 1) resampling by linear interpolation using adjacent data points and 2) filtering the resampled data set. These axial slices were then reconstructed using a standard filtered backprojection approach for fan-beam data.⁴⁹ The variable notation below mimics that of Taguchi and Aradate;⁴⁸ the reader is referred there if further depth of content is desired.

A.2.1. Projection Z-Filtering

The aim of filtered interpolation is to sample a set of single axial slice of projection data $p_a(\beta, \gamma)$ location given the set of initial helically acquired projection data $p(\beta, \gamma, z)$ covering a certain scanning length. The interpolated axial slice of projection data $p_a(\beta, \gamma)$ is then used to reconstruct images using a traditional axial FBP technique. Here, β represents the view (i.e. rotation) angle of the CT source, γ represents the detector channel angle, and z represents the specific position of the helical projection data in the longitudinal direction (i.e. perpendicular to the axial image plane).

First, projection resampling is performed on $p(\beta, \gamma, z)$ to obtain a set of N_{interp} projection values for each β and γ at a specific z position. These values span the range of the slice thickness, determined by the user-defined filter width W_{filter} , at uniformly spaced intervals denoted by index i . The resampled projections $p_i(\beta, \gamma, i)$ were calculated via linear interpolation, weighted by the fractional distance ω from each desired calculation z -position and the adjacent z -positions of the initial projections:

$$p_r(\beta, \gamma, i) = \omega(\beta, \gamma, j(i)) \times p_i(\beta, \gamma, j(i) + 1) + (1 - \omega(\beta, \gamma, j(i))) \times p_i(\beta, \gamma, j(i)), \quad (21)$$

$$\omega(\beta, \gamma, j(i)) = \frac{z_r(i) - z_i(\beta, \gamma, j(i))}{z_i(\beta, \gamma, j(i) + 1) - z_i(\beta, \gamma, j(i))}, \quad (22)$$

$$z_r(i) = z_0 + i \times \Delta z, \quad (23)$$

$$\Delta z = \frac{W_{filter}}{2 \times N_{interp} + 1}, \quad (24)$$

where $j(i)$ is the actual helical projection data index for the i^{th} interpolation point. The desired number of interpolated points, N_{interp} , was manually selected. Both the 180° and 360° complementary projection data were incorporated for data interpolation.

Second, having the resampled set of projection values for each β and γ , singular values for each axial projection data element were calculated by applying a user-defined filter:

$$p_a(\beta, \gamma) = \frac{\sum_{i=-I}^I \omega_f(i) \times p_r(\beta, \gamma, i)}{\sum_{i=-I}^I \omega_f(i)}, \quad (25)$$

where the filter design was determined by the weights $\omega_f(i)$. As opposed to the distance weights ω , $\omega_f(i)$ weights the resampled data based on user-defined priorities. A moving average filter is utilized in this study.

A.2.2. Filtered Backprojection

The sampled axial projection data set was then reconstructed using a traditional FBP approach. Due to the fan beam acquisition, the back-projection was first weighted according to the scanner radius D and the projection channel angle γ :

$$p'(\beta, \gamma) = p_a(\beta, \gamma) \times D \times \cos(\gamma). \quad (26)$$

Projection images were then filtered with a Fourier-domain based filter that was applied prior to back-projection. An adjustable *sinc* filter was utilized in this study, given by the following equation:

$$f(\omega) = \left| \frac{2}{\alpha} \sin\left(\frac{\alpha\omega}{2}\right) \right|, \text{ for } -\pi \leq \omega \leq \pi, \quad (27)$$

where α is a user-adjusted parameter that allows for a trade-off between image sharpness and image noise, tailored according to the desired user's imaging aims. As α increases, the image noise decreases but so does the image sharpness. The filter is then applied to the weighted projection data at each source angle, denoted by $P'(\beta)$:

$$P_f(\beta) = \alpha \times \mathcal{F}^{-1}\{\mathcal{F}\{P'(\beta)\} \times f(\omega)\}, \quad (28)$$

where $\mathcal{F}$ and $\mathcal{F}^{-1}$ represent one-dimensional Fourier transform and inverse Fourier transfer, respectively.

Finally, linear interpolation was utilized to sample $P_f(\beta)$ for $-\gamma_m < \gamma' < \gamma_m$ at intervals of α to obtain $p_f(\beta, \gamma')$. γ' denotes the detector angle of the ray that passes through (r, θ) , and γ_m is the maximum γ' beyond which $p_f(\beta, \gamma') = 0$. Then, the axial CT image pixel values $f(x, y)$ at pixel (x, y) were calculated using a weighted backprojection of the filtered projection data p_f based on the following Eqns.(29), (30), and (31).

$$f(x, y) = \frac{2\pi}{M} \sum_{m=1}^M \frac{p_f(\beta_m, \gamma'(r, \theta, \beta_m))}{L^2(r, \theta, \beta_m)}, \quad (29)$$

$$L^2(r, \theta, \beta_m) = [D + r\sin(\beta_m - \theta)]^2 + [r\cos(\beta_m - \theta)]^2, \quad (30)$$

$$\gamma'(r, \theta, \beta_m) = \frac{r\cos(\beta_m - \theta)}{D + r\sin(\beta_m - \theta)}, \quad (31)$$

where M is the number of axial projections and r and θ are the polar coordinate equivalents of the pixel Cartesian coordinates x and y , with the origin located in the center of the reconstructed image space. L denotes the distance from the x-ray source to the reconstruction point (r, θ) at view angle β_m . All CT images in this study were reconstructed using the aforementioned approach, with $W_{\text{filter}} = 3\text{mm}$ and $I = 4$. A rectangular filter was employed for the z -filtering (i.e. constant ω_f for all values of i). Lookup tables for L^2 , γ' , and projection data z -positions were calculated prior to reconstruction to speed up computational time. All Fourier transform operations were executed using FFTW⁵⁰ and an optimized C++ library for fast Fourier transform calculation. After reconstruction all CT images were saved with DICOM formatting using the ITK C++ library.⁵¹

REFERENCES

- [1]. Barrett HH and Myers KJ, [Foundations of Image Science], John Wiley & Sons (2013).
- [2]. Metz CE, "Roc methodology in radiologic imaging,," *Investigative radiology* 21(9), 720–733 (1986). [PubMed: 3095258]
- [3]. Vennart W, [ICRU Report 54: Medical imaging the assessment of image quality: ISBN 0-913394-53-X. 4 1996, Maryland, USA], WB Saunders (1997).
- [4]. Xu XG, "An exponential growth of computational phantom research in radiation protection, imaging, and radiotherapy: a review of the fifty-year history," *Physics in medicine and biology* 59(18), R233 (2014). [PubMed: 25144730]
- [5]. Zankl M and Eckerman K, "The gsf voxel computational phantom family," *Handbook of Anatomical Models for Radiation Dosimetry*, 65–85 (2010).
- [6]. Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, and Evans AC, "Design and construction of a realistic digital brain phantom," *IEEE transactions on medical imaging* 17(3), 463–468 (1998). [PubMed: 9735909]
- [7]. Caon M, "Voxel-based computational models of real human anatomy: a review," *Radiation and environmental biophysics* 42(4), 229–235 (2004). [PubMed: 14730450]
- [8]. Zu XG, "The vip-man model—a digital human testbed for radiation simulations," tech. rep., SAE Technical Paper (2005).
- [9]. Segars WP, Mahesh M, Beck TJ, Frey EC, and Tsui BM, "Realistic ct simulation using the 4d xcat phantom," *Medical Physics* 35(8), 3800–3808 (2008). [PubMed: 18777939]
- [10]. Li CM, Segars WP, Tourassi GD, Boone JM, and Dobbins JT III, "Methodology for generating a 3d computerized breast phantom from empirical data," *Medical Physics* 36(7), 3122–3131 (2009). [PubMed: 19673211]
- [11]. Segars WP and Tsui BM, "Study of the efficacy of respiratory gating in myocardial spect using the new 4-d ncat phantom," *IEEE Transactions on Nuclear Science* 49(3), 675–679 (2002).
- [12]. Kupinski MA, Clarkson E, Hoppin JW, Chen L, and Barrett HH, "Experimental determination of object statistics from noisy images," *JOSA A* 20(3), 421–429 (2003). [PubMed: 12630828]
- [13]. Kotasidis FA, Tsoumpas C, Polycarpou I, and Zaidi H, "A 5d anthropomorphic numerical phantom for respiratory-gated parametric imaging simulation studies in dynamic emission tomography," in [2013 IEEE Nuclear Science Symposium and Medical Imaging Conference (2013 NSS/MIC)], 1–3, IEEE (2013).
- [14]. Aubert-Broche B, Evans AC, and Collins L, "A new improved version of the realistic digital brain phantom," *NeuroImage* 32(1), 138–145 (2006). [PubMed: 16750398]
- [15]. Erickson DW, Wells JR, Sturgeon GM, Samei E, Dobbins JT III, Segars WP, and Lo JY, "Population of 224 realistic human subject-based computational breast phantoms," *Medical physics* 43(1), 23–32 (2016). [PubMed: 26745896]
- [16]. Cootes TF, Taylor CJ, Cooper DH, and Graham J, "Active shape models-their training and application," *Computer vision and image understanding* 61(1), 38–59 (1995).
- [17]. Cootes T, Roberts M, Babalola K, and Taylor C, "Active shape and appearance models," in [Handbook of Biomedical Imaging], 105–122, Springer (2015).
- [18]. Heimann T and Meinzer H-P, "Statistical shape models for 3d medical image segmentation: a review," *Medical image analysis* 13(4), 543–563 (2009). [PubMed: 19525140]
- [19]. Ferrari V, Jurie F, and Schmid C, "From images to shape models for object detection," *International journal of computer vision* 87(3), 284–303 (2010).
- [20]. Gordillo N, Montseny E, and Sobrevilla P, "State of the art survey on mri brain tumor segmentation," *Magnetic resonance imaging* 31(8), 1426–1438 (2013). [PubMed: 23790354]
- [21]. Tomoshige S, Oost E, Shimizu A, Watanabe H, and Nawano S, "A conditional statistical shape model with integrated error estimation of the conditions; application to liver segmentation in non-contrast ct images," *Medical image analysis* 18(1), 130–143 (2014). [PubMed: 24184436]
- [22]. Chen H-C, Tan J, Dolly S, Kavanaugh J, Anastasio MA, Low DA, Li HH, Altman M, Gay H, Thorstad WL, et al., "Automated contouring error detection based on supervised geometric

- attribute distribution models for radiation therapy: A general strategy," *Medical physics* 42(2), 1048–1059 (2015). [PubMed: 25652517]
- [23]. Goodall C, "Procrustes methods in the statistical analysis of shape," *Journal of the Royal Statistical Society. Series B (Methodological)*, 285–339 (1991).
- [24]. Stegmann MB and Gomez DD, "A brief introduction to statistical shape analysis," *Informatics and mathematical modelling*, Technical University of Denmark, DTU 15(11) (2002).
- [25]. Schönemann PH, "A generalized solution of the orthogonal procrustes problem," *Psychometrika* 31(1), 1–10 (1966).
- [26]. Yang J, Staib LH, and Duncan JS, "Neighbor-constrained segmentation with level set based 3-d deformable models," *IEEE Transactions on Medical Imaging* 23(8), 940–948 (2004). [PubMed: 15338728]
- [27]. Cignoni P, "Meshlab." <http://meshlab.sourceforge.net/>. Accessed: 2016-4-5.
- [28]. Hoppe H, "Poisson surface reconstruction and its applications," in [Proceedings of the 2008 ACM symposium on Solid and physical modeling], 10–10, ACM (2008).
- [29]. Garland M and Heckbert PS, "Surface simplification using quadric error metrics," in [Proceedings of the 24th annual conference on Computer graphics and interactive techniques], 209–216, ACM Press/Addison-Wesley Publishing Co (1997).
- [30]. Taubin G, "A signal processing approach to fair surface design," in [Proceedings of the 22nd annual conference on Computer graphics and interactive techniques], 351–358, ACM (1995).
- [31]. Zhou H, Keall PJ, and Graves EE, "A bone composition model for monte carlo x-ray transport simulations," *Medical physics* 36(3), 1008–1018 (2009). [PubMed: 19378761]
- [32]. Schneider W, Bortfeld T, and Schlegel W, "Correlation between ct numbers and tissue parameters needed for monte carlo simulations of clinical dose distributions," *Physics in medicine and biology* 45(2), 459 (2000). [PubMed: 10701515]
- [33]. White DR, Booz J, Griffith RV, Spokas JJ, and Wilson IJ, "Report 44," *Journal of the International Commission on Radiation Units and Measurements* 23(1), NP (1989).
- [34]. Scott JA, "Photon, electron, proton and neutron interaction data for body tissues icru report 46. international commission on radiation units and measurements, bethesda, 1992," *Journal of Nuclear Medicine* 34(1), 171–171 (1993).
- [35]. US Department of Commerce, N., "NIST: X-Ray mass attenuation coefficients." <http://www.nist.gov/pml/data/xraycoef/index.cfm> (17 Sept. 2009). Accessed: 2016-4-1.
- [36]. Gower JC, "Generalized procrustes analysis," *Psychometrika* 40(1), 33–51 (1975).
- [37]. Cootes TF and Taylor CJ, "A mixture model for representing shape variation," *Image and Vision Computing* 17(8), 567–573 (1999).
- [38]. Cremers D and Schnörr C, "Statistical shape knowledge in variational motion segmentation," *Image and Vision Computing* 21(1), 77–86 (2003).
- [39]. Grenander U, [Lectures in pattern theory I, II and III: Pattern analysis, pattern synthesis and regular structures], Berlin: Springer-Verlag (1976).
- [40]. Hastings WK, "Monte carlo sampling methods using markov chains and their applications," *Biometrika* 57(1), 97–109 (1970).
- [41]. Metropolis N, Rosenbluth AW, Rosenbluth MN, Teller AH, and Teller E, "Equation of state calculations by fast computing machines," *The journal of chemical physics* 21(6), 1087–1092 (1953).
- [42]. Mumford D and Gidas B, "Stochastic models for generic images," *Quarterly of applied mathematics* 59(1), 85–111 (2001).
- [43]. Schmidhuber J, "Deep learning in neural networks: An overview," *Neural Networks* 61, 85–117 (2015). [PubMed: 25462637]
- [44]. Dolly S, Ehler E, Lou Y, Anastasio M, and Li H, "Th-cd-601–1: A generation methodology for numerical phantoms with statistically relevant variability of geometric and physical properties," *Medical Physics* 44(7), 3666–3666 (2017).
- [45]. Bond JD, "Expansion of the 4d xcat phantom library with anatomical texture," (2013).
- [46]. Boone JM and Seibert JA, "An accurate method for computer-generating tungsten anode x-ray spectra from 30 to 140 kv," *Medical physics* 24(11), 1661–1670 (1997). [PubMed: 9394272]

- [47]. Möller T and Trumbore B, “Fast, minimum storage ray/triangle intersection,” in [ACM SIGGRAPH 2005 Courses], 7, ACM (2005).
- [48]. Taguchi K and Aradate H, “Algorithm for image reconstruction in multi-slice helical ct,” *Medical Physics* 25(4), 550–561 (1998). [PubMed: 9571623]
- [49]. Kak AC and Slaney M, [Principles of computerized tomographic imaging], Society for industrial and applied mathematics (2001).
- [50]. Frigo M and Johnson SG, “The design and implementation of fftw3,” *Proceedings of the IEEE* 93(2), 216–231 (2005).
- [51]. Yoo TS, Ackerman MJ, Lorensen WE, Schroeder W, Chalana V, Aylward S, Metaxas D, and Whitaker R, “Engineering and algorithm design for an image processing api: a technical report on itk-the insight toolkit,” *Studies in health technology and informatics*, 586–592 (2002). [PubMed: 15458157]

Figure 1:
The proposed flowchart of the key steps in stochastic object model creation process.

Figure 2:
(a) A two-dimensional slice of the mean $\bar{\Psi}_n$ of the bladder. (b) The corresponding binary image after thresholding and perimeter determination of the bladder.

Figure 3:

An exported anatomical organ, the mean $\bar{\psi}_n$ of the bladder, depicted as a point cloud (a) and as a triangular mesh (b) after performing Poisson surface reconstruction.

Figure 4:
The hierarchical tree used to orderly assign μ for organs in pelvis.

Figure 5:

The learned inter-structural centroid GADs. The centroid training data set is pictured in panel (a), while the mean centroid and centroid distributions of these organs are displayed in panel (b). The first two principal components are visualized as line segments, whose length is the variance constrained to $\pm 2\sigma$.

Figure 6:

Various bladder shapes generated by different weighted linear combinations of the mean shape attribute and principal components of the eigenvectors of the bladder shape attribute.

Figure 7:

The shapes of organs can be deformed by varying the weighting vector $\beta_{k,n}$ in Eqn.(19). The top row displays the variations of the bladder, while the bottom row displays the variations of the left femoral head. The left column shows the mean organ shape while the two right columns show the deformed organs produced using the shape GAD model with different $\beta_{k,n}$.

Figure 8:

By varying the weighting vector α_k in Eqn.(18) and $\beta_{k,n}$ in Eqn.(19), the organ shapes and interstructural distances can be deformed. Organ models including prostate, bladder, rectum, femoral heads, pelvic bone, and seminal vesicles are displayed here, with the exception of the patient external surface for demonstration of internal organs.

(a) Shape deformation 1

(b) Centroid deformation 1

(c) Shape & centroid deformation 1

(d) Shape deformation 2

(e) Centroid deformation 2

(f) Shape & centroid deformation 2

Figure 9:

A sample of 2D cross-sections, located at a cutplane inserted in the 3D models of the phantoms shown in Figure 8.

Figure 10:

Simulated CT images corresponding to six realizations of the SOM shown in Figure 8. The slices shown here are the same z-slice as that shown in Figure 9. All images were generated using a 140 kVp source spectrum. Other parameters include: $I_0 = 1 \times 10^5$ per detector element, kVp = 140, recon filter set as a *sinc* function with $\alpha = 2$, reconstruction field of view (FOV) = 45 cm, slice thickness = 3 mm, helical pitch = 1. The details of parameters I_0 and α are described in the Appendix.

Table 1:

The NIST materials utilized for the patient object models.

Material Name	NIST Material	$\rho(g/cm^3)$	Structures
Adipose	Adipose Tissue (ICRU 44)	0.95	External
Bone (Compact)	Bone, Cortical (ICRU 44)	1.92	Femurs (Exterior)
Bone (Spongy)	Bone, Cortical (ICRU 44)	1.0	Femurs (Interior)
Soft Tissue	Tissue, Soft (ICRU Four-Component)	1.0	Bladder, Prostate, Rectum