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Techniques for virtual lung nodule insertion: volumetric and morphometric comparison of projection-based and image-based methods for quantitative CT

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Abstract

Virtual nodule insertion paves the way towards the development of standardized databases of hybrid CT images with known lesions. The purpose of this study was to assess three methods (an established and two newly developed techniques) for inserting virtual lung nodules into CT images. Assessment was done by comparing virtual nodule volume and shape to the CT-derived volume and shape of synthetic nodules. 24 synthetic nodules (three sizes, four morphologies, two repeats) were physically inserted into the lung cavity of an anthropomorphic chest phantom (KYOTO KAGAKU). The phantom was imaged with and without nodules on a commercial CT scanner (SOMATOM Definition Flash, Siemens) using a standard thoracic CT protocol at two dose levels (1.4 and 22 mGy CTDI_{vol}). Raw projection data were saved and reconstructed with filtered back-projection and sinogram affirmed iterative reconstruction (SAFIRE, strength 5) at 0.6 mm slice thickness. Corresponding 3D idealized, virtual nodule models were co-registered with the CT images to determine each nodule's location and orientation. Virtual nodules were voxelized, partial volume corrected, and inserted into nodule-free CT data (accounting for system imaging physics) using two methods: projection-based Technique A, and image-based Technique

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B. Also a third Technique C based on cropping a region of interest from the acquired image of the real nodule and blending it into the nodule-free image was tested. Nodule volumes were measured using a commercial segmentation tool (iNtuition, TeraRecon, Inc.) and deformation was assessed using the Hausdorff distance. Nodule volumes and deformations were compared between the idealized, CT-derived and virtual nodules using a linear mixed effects regression model which utilized the mean, standard deviation, and coefficient of variation (Mean_{RHD} , and STD_{RHD} CV_{RHD}) of the regional Hausdorff distance. Overall, there was a close concordance between the volumes of the CT-derived and virtual nodules. Percent differences between them were less than 3% for all insertion techniques and were not statistically significant in most cases. Correlation coefficient values were greater than 0.97. The deformation according to the Hausdorff distance was also similar between the CT-derived and virtual nodules with minimal statistical significance in the (CV_{RHD}) for Techniques A, B, and C. This study shows that both projection-based and image-based nodule insertion techniques yield realistic nodule renderings with statistical similarity to the synthetic nodules with respect to nodule volume and deformation. These techniques could be used to create a database of hybrid CT images containing nodules of known size, location and morphology.

Keywords

lung nodule volume quantification; virtual insertion; MTF; accuracy; Hausdorff distance

1. Introduction

Computed tomography (CT) is a prominent imaging modality that provides superb image quality and spatial detail and can lend itself to be used as a quantitative tool. Nodule sizes in CT exams are important biomarkers for patient diagnosis in cancer staging (lung cancer and/or pulmonary metastases) and are useful for gauging therapy response for patients undergoing treatment. Standardized pulmonary nodule size estimations are currently done one-dimensionally according to the response evaluation criteria in solid tumors (RECIST), and two-dimensionally according to the newly adopted American College of Radiology LUNG-RADS™ and the World Health Organization (WHO) reporting methods (WHO 1979, Therasse *et al* 2000, American College of Radiology 2014). Although these methods are widely employed clinically, tumors typically do not grow or shrink symmetrically. Volume estimation may provide a more accurate approximation of actual tumor size. Thus, it is suggested that a more robust metric for assessing tumor staging, growth, or shrinkage should be based on three-dimensional (3D) volume estimates.

The precision and accuracy of volume measurements from CT data is jointly dependent on scan settings, segmentation software, lesion characteristics, and perhaps other factors (Gavrielides *et al* 2009, Chen *et al* 2013). Quantifying the impact of these factors on volume measurement accuracy is critical. In this regard, a number of groups have investigated this measurement uncertainty through clinical studies, phantom studies, and/or simulations (de Hoop *et al* 2009, Chen *et al* 2013, Young *et al* 2015). Clinical studies based on patient images provide more relevant clinical data. However, ground truth in terms of true nodule size and shape are often difficult to obtain, if at all possible. For clinical studies, this

drawback is further compounded by the issue of exposing patients to ionizing radiation (de Hoop *et al* 2009, Zhao *et al* 2009).

Another approach to assessing volume measurement accuracy involves phantoms. Inherent to this type of study is the ability to establish the true nodule size, and eliminate patient safety concerns (Xie *et al* 2013b). Phantom studies have provided a means for a number of groups to evaluate the factors that impact volume measurements in lung nodules including dose level, slice thickness, reconstruction algorithms and kernels (Chen *et al* 2012, Chen *et al* 2013, Xie *et al* 2013a, Xie *et al* 2014). Although providing many advantages, phantoms are limited in their complexity. They do not supply all the potential nodule and tissue variation compared to real clinical images and synthetic nodules are simplified and unrealistic.

Alternatively, computer simulation studies can provide a degree of clinical realism at a low cost, with no exposure to patients. For example, Young *et al* evaluated the effects of dose reduction and reconstruction methods on lung nodule volumetry through simulations (Young *et al* 2015), and Li *et al* used simulations to evaluate volume estimation in low contrast conditions (Li *et al* 2015). Along this same line, it is possible to use computer simulations to fuse real patient CT data with simulated data, resulting in so-called 'hybrid' CT images. Li *et al* and Solomon *et al* both generated hybrid images by inserting virtual lesion models into reconstructed CT images (Li *et al* 2009, Solomon and Samei 2014). Although those image based insertion methods produced realistic results they may not be valid to properly assess the impact of reconstruction on nodule volumes. This is especially true when nonlinear iterative reconstruction algorithms are used. For such needs, inserting virtual nodules into projection data, could prove advantageous (Chen *et al* 2015b, Xu *et al* 2015). Both image-based and projection-based insertion techniques are potentially valuable for assessing lung nodule volume accuracy because they provide the essential ground truth information that is lacking from clinical data.

The purpose of this study was to develop and validate methods of inserting virtual lung nodules in terms of those attributes; thereby enabling the development of standardized databases of hybrid CT images where 'ground truth' is known (i.e. nodules with known volume and morphology). A total of two insertion techniques were developed and evaluated; they included Technique A, and Technique B, a projection-based and an image-based insertion of idealized (theoretical) virtual lesion models. Technique C used an image-based blending method where cropped CT ROIs can be extracted from a source image and blended into a target image. Technique C was previously developed and is included as a benchmark for the new techniques. The three methods were evaluated with respect to nodule volumetry and morphology.

2. Materials and methods

Section 2.1 gives an overview of the key physical components of the phantom, synthetic nodules, and CT image acquisition parameters that were used to produce CT-derived lesion volume and morphology. These were accompanied by the corresponding computer-aided design (CAD) virtual nodules that were instrumental in simulating the imaging system's

rendering of the synthetic nodules. A general description of MTF-informed virtual lesion insertion is also provided. Section 2.2 defines the various sub-components of MTF blurring in CT, and the process by which they were obtained. These MTF subcomponents were applied to CAD lesion models in sections 2.3 and 2.4 to simulate the CT-derived lesion volume and morphology. Sections 2.3–2.5, describe virtual lesion insertion techniques evaluated in this paper. Section 2.6 presents the nodule volume quantification metric, while sections 2.7 and 2.8 describe morphology measurement and quantification analysis.

2.1. Phantom and data acquisition

The study used a series of synthetic nodules independently manufactured by Computerized Imaging Reference Systems (CIRS, Norfolk, VA.) of three sizes (8 mm, 9 mm and 10 mm), four morphologies (spherical, elliptical, lobular and spiculated) and with a single radiodensity of 100 HU (Li *et al* 2015). The nodules were physically inserted into the lung section of an anthropomorphic chest phantom (LUNGMAN, Kyoto Kagaku, Kyoto, Japan) (figure 1). There were 12 unique nodules with each nodule having an identical copy, resulting in 24 total nodules (table 1). All nodules were solid and had known shapes, weights, volumes, and radiodensities. They were individually wrapped in low density Styrofoam to reduce the potential for vessel and pleura attachment in the phantom. This was done in order to exclude any confounding factors that might affect the estimation of nodule volume using the segmentation algorithm. The nodules were randomly distributed throughout the lung. The actual nodule volumes were measured by CIRS.

The phantom was imaged repeatedly with and without nodules at multiple dose settings using a standard thoracic CT protocol with a commercial CT scanner (SOMATOM Definition Flash; Siemens, Healthcare GmbH, Forchheim, Germany). This was done to allow for technique dependence assessment under a multiplicity of conditions. Images were acquired with a flying focal spot at 120 kV, 1.0 pitch, 1.4 mGy CTDI_{vol} and 22 mGy CTDI_{vol}. Raw image data were saved to enable projection-based insertion of virtual nodules (i.e. Technique A).

Phantom images were reconstructed at 0.6 mm slice thickness with 0.6 mm increment and 400 mm reconstructed field of view using the vendor-provided weighted filtered back-projection (WFBP) and an iterative reconstruction algorithm (SAFIRE-Sinogram Affirmed Iterative Reconstruction at strength 5, Siemens Healthcare, Forchheim, Germany) hereinafter referred to as IR. An overview of the scan and reconstruction protocols are shown in table 2.

To register the 3D CAD lesion models with the corresponding synthetic nodules, an interactive 3D volume rendering software package (Avizo, FEI Visualization Science Group) was used. First a rough estimate of each nodule's location was made by visually examining the CT data. Next, using a consistent threshold value of -750 Hounsfield Units, an isosurface representation of the nodule was generated. Finally, the 3D CAD models of the nodules were imported and manually co-registered with the synthetic nodules isosurfaces by adjusting the model's location and orientation (figure 2(a)). The registered 3D CAD models were then exported and saved into new files. The purpose of registering the 3D CAD models was simply to allow them to assume a similar orientation and location as their synthetic counterparts. Such a process has no impact on lesion volumes.

The registered 3D CAD masks were voxelized (figure 2(b)) to match the voxel size of the native CT data (x : 0.78 mm, y : 0.78 mm, z : 0.6 mm). Partial volume effects were accounted for by first voxelizing the CAD model at a super-sampled voxel size (10X the target CT voxel size), filtering the image volume with an averaging kernel, and then downsampling to the native CT voxel size. Please note that this averaging kernel was only applied to account for partial volume effects. This is not to be confused with the MTF which simulates the systematic blurring (i.e. finite focal spot size, detector size, and reconstruction). These partial-volume corrected nodule images served as the input to the nodule insertion Techniques A and B, described in sections 2.3 and 2.4.

2.2. Empirical determination of system blurring

In linear system's theory, medical imaging systems are modeled as a cascade of linear shift invariant subsystems. Consequently, in the frequency domain, the acquired image blur can be modeled as the multiplication of the input object with the modulation transfer function (MTF) of the interacting subsystem(s). Following this framework, the total system MTF, MTF_s , was assumed to be the product of a geometrical or pre-reconstruction MTF, MTF_g , and a reconstruction MTF, MTF_r (figure 3). Only MTF_g is needed for insertion Technique A since it models the pre-reconstruction blur imposed on the image of the input object. Technique B required both MTF_g and MTF_r since it describes the blur of a post reconstructed image of the input object.

In this study, all MTFs were empirically determined based on image data from a custom phantom with cylindrical inserts (Mercury v2.0, Duke University, Durham, NC) (Wilson *et al* 2013). First, MTF_s representative of the total imaging system's optics (focal spot blur and detector size blur) and reconstruction (algorithm and kernel blur), was measured using the physical phantom's contrast inserts (Solomon *et al* 2015). MTF_r was further determined by virtually inserting a non-blurred cylinder into the Mercury v2.0 phantom projection data. The reconstructed images of this data thus included real cylinders that were subjected to blurring from all subsystems (i.e. MTF_s), and virtually inserted cylinders that were only subject to reconstruction blurring effects (i.e. MTF_r). Using these data, MTF_s and MTF_r were measured and combined to derive the pre-reconstruction MTF_g (figure 3). For insertion Techniques A (projection-based) and B (image-based), an accurate model of CT system blurring was needed (figure 2(c)) as each technique incorporates the unique MTF that the CT system would apply to an input object.

2.3. Projection domain nodule insertion

The projection-based method (Technique A) of virtually inserting nodules simulates the forward projection process of the CT imaging system (figure 4(a)). First the nodule-free phantom images were examined to ensure optimal lesion insertion in the pre-defined locations for each nodule. These locations were chosen to match the corresponding synthetic nodule locations from the nodule-filled phantom images. By applying MTF_g to the voxelized and partial volume corrected 3D nodule model, a pre-reconstruction nodule image volume was formed. This virtual nodule was inserted into a forward projection routine using the correct geometrical configuration of the CT system. However, the forward projector did not explicitly model the CT system optics (i.e. it used an idealized source-detector model),

which is why the nodule models were blurred with MTF_g prior to forward projection (Joseph 1982). Finally, this simulated nodule projection data was combined with the raw CT projection data from the nodule-free phantom scans and then reconstructed with FBP and IR (figure 4(b)).

2.4. Image domain nodule insertion

In nodule insertion Technique B, the voxelized and partial volume corrected 3D nodule models were first blurred with MTF_s to simulate blurring from the entire imaging system. The blurred models were then added directly to the target CT data. The insertion locations used were identical to those from Technique A (figures 5(a) and (b)).

2.5. Image blending nodule insertion

In nodule insertion Technique C, the entire volume containing each nodule was cropped from the source image and fused into the nodule-free target image using a custom blending technique (figures 6(a) and (b)). This method was investigated in this study because previous work demonstrated its effectiveness by comparing the detectability of the inserted and native lesions, and by investigating whether experienced radiologists can differentiate between inserted and native lesions (Pezeshk *et al* 2015). This method is based on Poisson image editing (Pérez *et al* 2003), which performs an inward interpolation of the boundary values of the desired blending area within the nodule-free image on a slice-by-slice basis. The interpolation is guided by the gradient field of the source image, so that the nodule is seamlessly inserted into the interior of the desired blending area by solving a series of differential equations with Dirichlet boundary conditions. The algorithm was designed to minimize the magnitude of the gradient difference between the blended and source images within a region defined by a boundary containing the lesion. This was subject to the condition that on the boundary, the blended image is equal to the target image. The boundary condition facilitated the seamless appearance of the insertion, while the minimization effectively inserted the grayscale variation of the source within the boundary, and thus the lesion, into the target. To blend a nodule into a new location, the user only had to draw a casual boundary encompassing the nodule, and select the center of a nodule-free insertion area within another image.

2.6. Quantification of nodule volume

The nodule insertion techniques were validated by comparing the volumes of CT-derived nodules to the virtually inserted nodules for each insertion Technique (A–C). A clinical analysis software package (iNtuition, TeraRecon, Inc) was then used to obtain an estimate of the nodule volume from the reconstructed CT images. Nodule volume quantification was achieved through a semi-automated process. The user marked the center of the nodule and an automatic segmentation was performed on the image without any further user input. The nodule boundaries were estimated by the software. Upon executing the segmentation algorithm, the software reports the calculated volume (figure 7). The user also has the option to manually select an ROI and either add or remove a region that they feel does or does not accurately represent the nodule. Manual modifications were seldom performed in this study as it was only necessary when the software incorrectly identified nearby tissue as being nodule material or excluding parts of the nodule due to a perceived air gap. There was one

challenging case involving a synthetic nodule that had an air pocket in its center. This case was conveniently corrected using the manual ROI. Since all of the nodules were solid, clear nodule boundaries could be readily identified by the segmentation software.

2.7. Quantification of nodule morphology

Apart from volume estimation accuracy, an analysis was done to assess the difference in nodule shape between the idealized nodules and the nodules as they appeared in the CT images. Nodule morphology was examined based on the Hausdorff distance (HD) which is a measure of the distance between two subsets of a metric space (Huttenlocher and Rucklidge 1992, Aspert *et al* 2002). In the context of this study, the subsets being compared represent points in 3D Euclidean space from both an idealized CAD surface representation of the nodule and from an isosurface of the nodule as it appeared in the CT images. The CAD surfaces used were the same as described in section 2.1. Since the segmentation algorithm (iNtution) did not allow for the segmentation masks to be exported, the isosurface function was used to extract lesion volumes. The 3D isosurfaces were generated for each nodule, dose level, reconstruction algorithm, and insertion technique (including the CT-derived nodules). Volumes were extracted using an empirically chosen threshold -750 HU which corresponded with measured volumes from the segmentation algorithm. Vessels were also segmented and removed prior to isosurface rendering. The isosurface function in Matlab R2015a was used to define nodule surfaces. Subsequently, nodule surfaces were converted to polygon mesh surfaces composed of faces and vertices. A figure of merit based on the HD between the isosurface of the inserted nodule image (CT-derived and virtual) and the CAD surface of the nodule was extracted for each case as follows.

Assuming P represents the set of all vertices on the theoretical nodule surface and Q represents the set of vertices of the isosurface of a nodule image. Two 3D Cartesian grids of voxels were defined that spanned the minimum and maximum points in each 3D direction of P and Q , respectively. Note that these voxels are different from, and in general smaller in size than the voxels in the reconstructed CT images. 25 voxels were used for each grid in each direction with i , j , and k denoting indices of the voxel grids in the x , y , and z direction, respectively (i.e. $P_{i,j,k}$ and $Q_{i,j,k}$). Supposing $P_{i,j,k}$ contains N vertices and $Q_{i,j,k}$ contains M vertices, the $M \times N$ distance matrix, $D_{i,j,k}$, for a given voxel can be defined by the Euclidean distance between all elements of $P_{i,j,k}$ and $Q_{i,j,k}$. Correspondingly, each column of $D_{i,j,k}$ gives all distances between the m th vertex in $Q_{i,j,k}$ and all vertices in $P_{i,j,k}$. The regional Hausdorff distance ($RHD_{i,j,k}$) for a given voxel can thus be calculated by first finding the minimum of each column of $D_{i,j,k}$ and then taking the maximum value of the resulting vector. Only voxels in which $P_{i,j,k}$ and $Q_{i,j,k}$ were non-empty were used for further processing. The figures of merit used were the mean, standard deviation and coefficient of variation of RHD, denoted $Mean_{RHD}$, STD_{RHD} , and CV_{RHD} respectively. Note that large $Mean_{RHD}$ indicates that the nodule is larger in size with respect to the CAD surface; while large STD_{RHD} or CV_{RHD} implies that the shapes of the two surfaces are different (i.e. the image isosurface is deformed relative to the idealized surface). Also note that the CV_{RHD} figure of merit is insensitive to the size scaling of two surfaces. Thus if the isosurface is simply a larger replicate of the CAD surface but with the same shape, CV_{RHD} would be zero, while $Mean_{RHD}$ would be non-zero. $Mean_{RHD}$, STD_{RHD} and CV_{RHD} were calculated

for all nodules, dose levels, reconstruction algorithms, and insertion techniques with the goal of comparing the values from the CT-derived nodules, with those of the virtually inserted as described in the proceeding section. This measurement process is illustrated in figure 8.

2.8. Statistical analysis

In accordance with recommendations from the Quantitative Imaging Biomarkers Alliance (QIBA) Metrology Working Group, several statistical analyses were performed. For the volumetric analysis, the first was to compare the volume bias between the gold-standard (i.e. CIRS-based volumes). and the virtual and CT-derived nodule volumes. Second, a difference comparison was made between the CT-derived nodule volumes and those of the virtual nodules from each insertion technique (Bland and Altman 1999, Kessler *et al* 2015, Raunig *et al* 2015). The volume bias between the synthetic nodules and CT-derived nodules is termed the percent bias (PB). The volume difference between the CT-derived nodules and nodules from each virtual insertion technique is termed the percent difference (PD). It is important to note that the PD measure between virtual lesions from all techniques with respect to the CT-derived lesion volumes is the central focus of this study. Both PB and PD were evaluated with percent error (PE), averaged over all nodules as

$$PE_{bc} = \frac{1}{n} \sum_{a=1}^n PB_{abc} \quad PE_{abc} = \frac{V_{abc} - V_t}{V_t} \times 100, \quad (1)$$

where V_{abc} ($a = 1, \dots, n$, $b = 1, \dots, B$, $c = 1, \dots, C$) is the measured volume of the nodule for the a th nodule, b th dose, and c th reconstruction ($n = 24$, $B = 2$, $C = 2$). In the first volume analysis scenario, V_t represents the reference gold-standard volume obtained through CIRS. However, in the second scenario, V_t represents the CT-derived volume measured with iNtuition. The standard deviation was also computed. Small PE values indicate a more accurate measurement. For example, this implies that the virtual insertion techniques properly simulated the nodule rendering. To directly compare the CT-derived and virtual nodules, paired t -tests were performed (significance threshold of 0.05). Also linear regression analysis was used with the coefficient of determination (R^2) taken as a figure of merit describing the linearity between the CT-derived and virtual nodule volumes.

From the morphological analysis, the figures of merit $Mean_{RHD}$, STD_{RHD} and CV_{RHD} , were generated from comparing the CAD drawings to the images of CT-derived nodules and the images of the virtual nodules. They were applied to the linear mixed effects model

$$\log(RHD_{abcd}) = \mu + \tau_a + \alpha_{size,a} + \alpha_{shape,a} + \beta_b + \gamma_c + \delta_d + \varepsilon_{a,b,c,d} \quad (2)$$

where RHD_{abcd} is the observed value for the $Mean_{RHD}$, STD_{RHD} or CV_{RHD} for the a th nodule ($a = 1, \dots, 24$), measured at the b th dose ($b = \text{low or high}$) using the c th reconstruction method ($c = \text{FBP or IR}$) and the d th insertion type ($d = \text{CT-derived, Technique A, Technique B or Technique C}$). Equation (2) explains variations in the RHD figure of merit in terms of a baseline value μ , which represents an 8 mm CT-derived spherical nodule, that was measured at low dose with FBP reconstruction. The other terms in the model are a nodule specific

random effect τ_a , which is assumed to have a zero mean Gaussian distribution with a standard deviation σ_b as well as the fixed effects of size $\alpha_{\text{size},a}$, shape $\alpha_{\text{shape},a}$, dose β_b , reconstruction method γ_c and insertion method δ_d (i.e. Technique A, B or C). Finally, $e_{a,b,c,d}$ is measurement error, assumed to have a zero mean Gaussian distribution with a standard deviation independent of the subject specific effect τ_a . Model (2) is fit using the method of restricted maximum likelihood (REML) to the observed data with the non-linear mixed effect (nlme) package in the statistical software (R, www.r-project.org). Note that the log transformation was used to achieve an approximately Gaussian distribution for the error term. This was done to determine if the process of virtually inserting the nodules affected the nodule shape in a similar fashion as with the synthetic nodules that went through the standard imaging process.

3. Results

3.1. Nodule volume

All nodules were inserted using Techniques A and B and were segmented successfully. For Technique C, four nodules were excluded due to their close proximity to vasculature resulting in 80 out of 96 insertions (4 nodules $\times$ 2 doses $\times$ 2 reconstructions = 16 missing insertions). Table 3 gives the percent bias of the CT-derived and virtual nodule volumes relative to the CIRS reference gold-standard volumes of the synthetic lesions. The results show that CT-derived nodule volume estimates deviate from the ground truth by 13–16%. All insertion techniques exhibit similar deviation. Similarly, table 4 shows PD, R^2 , and p -values (paired t -test) of the virtual nodule volumes relative to the CT-derived nodule volumes. In essence, table 4 indicates how the MTF-blurred virtual nodules are interpreted by the volume estimation software with respect to the CT-derived nodules. Using Technique C as a benchmark, volume measurements made of its cropped nodule images have very small differences from the original nodule images. Comparisons of results from Techniques A and B compared to that of Technique C shows that Technique B tends to work better than Technique C for FBP images, but the reverse trend seems to hold in IR images. On the other hand, Technique A underestimates nodule volumes by $<1\%$ relative to Technique C. However, the magnitude of the differences for all techniques are small which suggest that Techniques A, B, and C all closely model the effect of the imaging system on nodule size rendering. A positive PD indicates that the volume measured from the virtual nodule images was greater than the volume measured from the CT-derived nodule images. Linearity plots shown in figure 9 summarizes the measured volume comparison of simulated lesions with respect to CT-derived volume measurements of physical lesions. Additionally, lesion grouped by size and specified by shape in each sub-plot. Data points are partitioned in terms of CTDI levels, and FBP or IR reconstruction. The goodness of fit (R^2) for each plot was greater than 0.97.

3.2. Nodule morphology

The estimated effects confirm higher values of Mean_{RHD} for larger size nodules, with significantly higher results for 9 mm (p -value = 0.03) and marginally so for 10 mm (p -value = 0.08) as seen in table 5. The analysis also shows significantly higher Mean_{RHD} values for elliptical and particularly spiculated shapes relative to spherical. Mean_{RHD} was significantly

lower for Technique C (p -value = 0.002). For the two reconstruction algorithms and doses used, there was no significant effect of reconstruction method or dose on the nodule morphology when the virtual nodules were compared to the CT-derived nodules.

Analysis also shows higher STD_{RHD} values for other shapes relative to spherical, especially for spiculated (p -value < 0.0001, table 5). This suggests a greater degree of difference between the idealized and the segmented morphology for other nodules compared to that for spherical nodules. A significantly lower STD_{RHD} for Technique C (p -value = 0.01) was observed. The effect of dose was relatively small but significant (p -value = 0.003) in the analysis of STD_{RHD} . In the analysis of CV_{RHD} , results show higher CV_{RHD} values for other shapes relative to spherical, especially spiculated lesions. Most importantly, there were significantly higher effects for all other insertion types relative to CT-derived nodules (p -value < 0.02) where estimated effects confirm higher values of CV_{RHD} for Techniques A, B and C. Using the two reconstruction methods, there was no significant effect of reconstruction method on any of the measurement parameters.

4. Discussion

Developing an insertion method that accurately reflects the true imaging system and its influence on nodule volumetry can improve the quality of nodule quantification. It provides a platform for advanced image quality and perception assessment. In this work, two simulation methods (Technique A and B) were developed to add nodules of known properties in a manner that bears the physics (i.e. MTF) of the imaging system and its reconstruction parameters. Also, a third method, Technique C, was implemented based on the extraction of non-juxtapleural nodules from one CT image into the same or similar CT image dataset. We then examined the impact of these insertion methods on nodule volumetry using volume quantification measurements for two dose levels and two reconstruction algorithms, across multiple nodules of various shapes and sizes.

From a theoretical standpoint, Technique A (projection-based) should provide the most accurate results and be the most robust method across a wide range of reconstruction settings. As such, one may argue why other insertion methods would be of utility. In this study, each of these Techniques were included for specific reasons. Technique A is the most complicated to implement and requires detailed knowledge of the imaging system geometry, and therefore, it is not a foregone conclusion that Technique A can be successfully implemented. Thus validation against synthetic nodules was clearly needed. Alternatively, there are many instances in which Technique A is impossible to apply (e.g. no access to raw projection data or no information about the system geometry). For this reason, Technique B (image-based) was developed as a practical alternative to Technique A. Additionally, Technique C (image blending) was further included to provide benchmarking for Technique A/B results against a prior established technique. While Technique C gives similar results to Techniques A and B, unlike Technique C, A and B allow for evaluation of the impact of various reconstruction algorithms via lesion modeling.

The proper blurring of the lesion masks through the MTF is an important component in achieving realistic virtual nodule insertions for Techniques A and B. In a separate analysis

done to examine the relevance of MTF-blurring, the percent error between the CT-derived nodule volumes and virtual nodule volumes more than doubled ($>6\%$) when the blurring was not applied. Incorporating appropriate MTF blurring corresponding to the imaging system from which the patient data are obtained enables nodule renditions that better reflect imaging system's rendering of synthetic lesions. Utilizing the MTF, our studies show that realistic nodules can be simulated with a high degree of volumetric accuracy (Projection-based: 1.01% – 2.24% ; Image-based: -2.28% to 0.28%) when compared to CT-derived nodules. This shows that either technique can be a viable replacement for the presence of synthetic lesions.

One group (Chen *et al* 2015a) has demonstrated development of a framework to perform projection domain lesion insertions, meanwhile another (Ma *et al* 2016) performed projection domain lesion insertions for observer detection tasks. Similarly, another group (Solomon and Samei 2014) performed image domain virtual lesion insertion for evaluation of observer performance. They reported an AUC of 0.55 for the task of discerning between real and virtual lesions. Additionally, image domain virtual lesion insertion has been applied in radiology to evaluate the effectiveness of radiologist's image reading processes (Rubin *et al* 2014) and in computer aided detection (CAD) algorithm training (Pezeshk *et al* 2016). The previous studies were useful for qualitative, observer-based assessments. However, beyond qualitative lesion modeling, the MTF based methods used in this study allow for quantitative lesion assessment in terms of lesion size and shape characteristics. Since the MTF is a conventional image quality metric and can reflect a wide range of CT technologies, its use can serve as a powerful platform for generic lesion insertion via both pre and post-reconstruction methods. This enables both projection and image domain insertions.

The measured similarity between the CT-derived and virtual nodule volume was expected to be maximum for projection-based insertions than image-based insertion. However, the results show that both types of insertion techniques generate similar levels of volume accuracy. Nevertheless, the benefits of having a projection-based insertion technique outweighs that of the image-based since there is a greater degree of flexibility for generating and testing a wide array of imaging conditions prior to reconstruction. On the other hand, the limiting factor for image-based insertion is that nodules can best be inserted into CT datasets that were acquired and reconstructed with the exact imaging conditions and parameters under which the nodule was imaged. Otherwise, without an exact match, there will be incongruence between the two in terms of accurate volume and morphology representation. While evaluation of other quantitative properties can be useful, all nodules used in this study had identical radiodensity, material composition, and internal homogeneity. This limited the scope of the present work to appropriately focus on lesion size and shape as the relevant properties of interest in determining how the nodules would be impacted by the various insertion techniques. Future work will benefit from assessment of contrast, CT number, and lesion heterogeneities to address these factors in nodule simulation.

The goal of this study was to ascertain lesion volumetry results for two novel lesion insertion techniques with respect to an established technique using select clinically relevant protocols. The protocols employed approach the upper and lower bounds of clinically realistic dose

values. Also, the acquisition was derived from the suggested AAPM Quality CT Protocol for lung cancer screening with the Siemens Flash scanner. While the study is not extensive in terms of having a broad set of varying acquisitions and reconstruction parameters, due to practical considerations, it offers relevant assessment of nodule volume and shape rendering under a variety of conditions. By emulating low dose thoracic scan conditions, we expected to find that nodule volume accuracy would deteriorate as a result of increased noise or decreased dose. However, other work showed that bias did not change monotonically with dose (Young *et al* 2015). In this study, similar results were observed as there was no clear trend relating change in volumetric estimation to dose. This was particularly noticeable since the average PB results for low dose scans (table 3) showed less deviation from the ground truth in the case of the CT-derived nodule volume measurements.

For morphological measurements, the figures of merit (Mean_{RHD} , STD_{RHD} and CV_{RHD}) served as a means to quantify the morphological change resulting from the imaging system's influence on the object's shape. For (Mean_{RHD} and STD_{RHD} , there was a statistically significant effect of nodule size (see table 5). As nodule size increased, so did the variability in lesion morphology. However, that effect diminished when we normalized it by the mean value (i.e. CV_{RHD}). Therefore, for quantifying changes in shape independent of size scaling, CV_{RHD} is the recommended figure of merit. When considering CV_{RHD} for insertion techniques, there were minimal statistically significant differences between the HD measurements and the baseline (8 mm spherical, CT-derived, low dose, FBP). Overall, these results indicate that the expected morphological changes due to the CT system were modeled similarly by the virtual insertion techniques. As expected, a greater degree of morphological changes was observed with spiculated nodules when compared to other nodule types. Generally, while there is no significant effect of reconstruction method, the effect of dose is statistically significant, but its estimate is very small in magnitude.

Since segmentation can be influenced by the presence of tissue surrounding the nodule, this potential for error was minimized by surrounding the synthetic nodules with low density Styrofoam, thus producing an apparent empty space between the nodule and the lung parenchyma. Also, low density Styrofoam pieces were placed in strategic locations of the phantom lung insert during the nodule-free phantom acquisitions to ensure adequate locations for virtual nodule insertions. In the case of projection and image domain insertion in real clinical cases, it is desired that lung tissue be completely replaced with the new nodule and adjacent environment. However, in our current framework, nodule data were superimposed onto the native CT data. We are currently investigating different strategies to replace the native tissue.

We acknowledge that a limitation to our study is that it was based on a phantom. As previously stated, phantoms are limited in their complexity. They do not supply all the potential nodule to tissue variation that are present in real clinical images. However, in our study, an anthropomorphic phantom with a realistic lung insert containing lung vasculature models was used to mimic reality. Currently, phantom based approaches are the only way that truth about the synthetic nodule characteristics can be foreknown and appropriately assessed in the manner we demonstrated. Since having access to ground truth is crucial to gauging the validity of these techniques, this study is fundamentally limited to phantoms.

Another constraint is that synthetic nodules tend to be too simplistic in that they are generally solid and do not span the wide variety of clinical nodule shapes and heterogeneity. While this has been a long standing challenge in phantom based studies, it underscores the need for more advanced synthetic nodules that incorporate heterogeneity, and softly-tapered edge profiles. Additionally, registration between the isosurface of the image of the synthetic nodules and the 3D CAD drawings was performed manually. A more rigorous approach would minimize any inaccuracies in registration. While our empirical MTF method is being used for the first time in this work, we acknowledge that further development is needed to most accurately account for lesion blurring from the imaging system. In particular, the small systematic bias in projection domain lesion volumes may be attributed to a possible over-blurring. Further, more work in assessing the impact of reconstruction settings on the insertion quality is an active area of investigation for future work.

In summary, we have compared projection and image based nodule insertion techniques in a volume and morphology estimation study which was performed using a combined phantom and simulation approach. We have taken an important step towards defining novel projection and image based lesion insertion methods that generate volume estimates with accuracy similar to a commonly used image-based technique. Future work will focus on further testing of projection domain versus image domain insertion by using a wider range of dose and reconstruction settings and 3D smoothing processes. While our projection domain insertion technique provides close agreement with the CT-derived lesion rendering, improvement of this technique is expected to correct the observed small systematic bias. In addition, it will be useful to investigate how volume estimation in projection and image based insertion methods are influenced by other segmentation software. Determining the inter-dependencies between these insertion techniques and imaging parameters will enable better volume quantification for reliable virtual insertion of nodules in CT images. In turn, an optimized virtual insertion method could be applied to a range of areas such as segmentation algorithm performance testing and machine learning applications.

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Figure 1.

(a) The anthropomorphic chest phantom with lung insert containing realistic pulmonary vessels. (b) Synthetic nodules of various sizes and shapes were attached to the lung insert to simulate pulmonary nodules. (c) Virtual 3D CAD mesh models of the synthetic nodules.

Figure 2. Schematic showing the steps to virtual nodule insertion for Techniques A and B. (a) Co-registration, (b) voxelization, (c) acquire system MTF, (d) blurred lesion model, (e) lesion insertion.

Figure 3.
 (a) Theoretic description of an imaging system's MTF sub-components. (b) MTF sub-component plots.

Figure 4.

Technique A: (a) projection domain nodule insertion workflow. (b) Image of nodule inserted via projection-based insertion.

Figure 5.
Technique B: (a) image domain nodule insertion workflow. (b) Image of nodule inserted via image-based insertion.

Figure 6.

Technique C: (a) image domain nodule insertion workflow. (b) Image of nodule inserted via image-based insertion.

Figure 7. (a) Coronal maximum intensity projection view of nodule of interest in a clinical software package (iNtuition, TeraRecon, Inc). (b) Semi-automatically segmented nodule in units of cm³. (c) 3D rendering of lower right lung showing nodules and major vascular structures. (d) 3D rendering of segmented nodule.

Figure 8.

Flow chart of the regional Hausdorff distance (RHD) measurement process.

Figure 9.

CT volumetry comparison CT-derived nodules and virtually inserted nodule volumes from (A) Technique A (B) Technique B, and (C) Technique C. Nodules are partitioned by size and shape across two doses and reconstruction algorithms. For Technique C, each plot contains 20 out of 24 nodules as indicated in section 3.1.

Table 1

List of nodule characteristics.

Nominal diameter (mm)	Shape	CIRS volume (mm ³)
8, 9, 10	Spherical	280, 380, 520
8, 9, 10	Elliptical	280, 380, 530
8, 9, 10	Lobular	270, 380, 530
8, 9, 10	Spiculated	270, 390, 530

Table 2

Scan and reconstruction parameters.

Scanner	Siemens Somatom definition flash
CTDI _{vol} (mGy)	1.4, 22
kVp	120
Pitch	1
Collimation (mm)	128 × 0.6
Rotation time (sec)	0.5
Reconstruction thickness (mm)	0.6
Reconstruction kernel	B31f, I31f

Table 3

Inserted nodules: average PB (with standard deviation) of CT-derived and virtual nodule measured volumes relative to the synthetic lesion (CIRS volumes).

	CT-derived nodules	Projection domain Technique A	Image domain Technique B	Image domain Technique C
FBP: CTDI 1.4 mGy	-13.37 (3.62)	-15.33 (4.42)	-13.68 (3.62)	-13.92 (3.86)
FBP: CTDI 22 mGy	-14.04 (3.58)	-15.00 (3.59)	-13.84 (3.64)	-13.62 (3.34)
IR: CTDI 1.4 mGy	-15.28 (3.61)	-16.18 (3.65)	-14.86 (3.57)	-15.70 (3.32)
IR: CTDI 22 mGy	-15.81 (3.62)	-16.89 (4.13)	-13.85 (3.83)	-15.48 (3.94)

Table 4

Inserted nodules: average PD (with standard deviation), R^2 , and p -value of measured volumes of the virtual nodules versus the CT-derived nodules.

Protocol	Projection domain			Technique A			Image domain			Technique B			Image domain			Technique C		
	Avg. percent diff.	R^2	p -value	Avg. percent diff.	R^2	p -value	Avg. percent diff.	R^2	p -value	Avg. percent diff.	R^2	p -value	Avg. percent diff.	R^2	p -value	Avg. percent diff.	R^2	p -value
FBP: CTDI 1.4 mGy	-2.24 (4.07)	0.99	<0.05	-0.28 (4.03)	0.99	>0.05	-0.33 (2.15)	0.99	>0.05	-0.33 (2.15)	0.99	>0.05	-0.33 (2.15)	0.99	>0.05	-0.33 (2.15)	0.99	>0.05
FBP: CTDI 22 mGy	-1.03 (4.28)	0.98	>0.05	0.34 (4.67)	0.98	>0.05	0.95 (2.97)	0.98	>0.05	0.95 (2.97)	0.99	>0.05	0.95 (2.97)	0.99	>0.05	0.95 (2.97)	0.99	>0.05
IR: CTDI 1.4 mGy	-1.01 (4.03)	0.98	>0.05	0.57 (4.41)	0.98	>0.05	-0.26 (1.15)	0.98	>0.05	-0.26 (1.15)	0.99	>0.05	-0.26 (1.15)	0.99	>0.05	-0.26 (1.15)	0.99	>0.05
IR: CTDI 22 mGy	-1.69 (4.12)	0.99	>0.05	-2.28 (3.69)	0.98	<0.05	0.87 (3.19)	0.98	<0.05	0.87 (3.19)	0.99	>0.05	0.87 (3.19)	0.99	>0.05	0.87 (3.19)	0.99	>0.05

Table 5

Results of the morphological statistical analysis using Mean_{RHD} , STD_{RHD} and CV_{RHD} as a figure of merit. Techniques A, B and C have 24, 24 and 20 nodules per dataset respectively. Quantities were log transformed before statistical analysis.

Term	Mean_{RHD}		STD_{RHD}		CV_{RHD}	
	Effect	p-value	Effect	p-value	Effect	p-value
Baseline	-2.29		-3.03		-0.74	
Size (9 mm)	0.47	0.03	0.51	0.01	0.04	0.58
Size (10 mm)	0.37	0.08	0.39	0.05	0.02	0.76
Ellipse	0.8	0.003	1.1	0.0001	0.3	0.003
Lobular	0.19	0.41	0.46	0.05	0.27	0.007
Spiculated	2.65	<0.0001	3.1	<0.0001	0.45	0.0001
IR	-0.06	0.07	-0.03	0.17	0.02	0.14
Dose	0	0.29	-0.003	0.003	-0.002	0.03
Technique A	-0.03	0.44	0.03	0.34	0.06	0.01
Technique B	-0.04	0.31	0.01	0.76	0.05	0.02
Technique C	-0.14	0.002	-0.09	0.01	0.05	0.02