Computerized segmentation of pulmonary nodules depicted in CT examinations using freehand sketches

Yongqian Qiang, Qiuping Wang, Guiping Xu, Hongxia Ma, Lei Deng, and Lei Zhang
Department of Radiology, The First Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an City, Shaanxi Province 710061, People's Republic of China

Jiantao Pu^{a)}
Departments of Radiology and Bioengineering, University of Pittsburgh, 3362 Fifth Ave, Pittsburgh, Pennsylvania 15213

Youmin Guo^{b)}
Department of Radiology, The First Affiliated Hospital of Medical School, Xi'an Jiaotong University, Xi'an City, Shaanxi Province 710061, People's Republic of China

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Purpose: To aid a consistent segmentation of pulmonary nodules, the authors describe a novel computerized scheme that utilizes a freehand sketching technique and an improved break-and-repair strategy.

Methods: This developed scheme consists of two primary parts. The first part is freehand sketch analysis, where the freehand sketching not only serves a natural way of specifying the location of a nodule, but also provides a mechanism for inferring adaptive information (e.g., the mass center, the density, and the size) in regard to the nodule. The second part is an improved break-and-repair strategy. The improvement avoids the time-consuming ray-triangle intersections using spherical bins and replaces the original global implicit surface reconstruction with a local implicit surface fitting and blending scheme. The performance of this scheme, including accuracy and consistence, was assessed using 50 CT examinations in the Lung Image Database Consortium (LIDC). For each of these examinations, a single nodule was selected under the aid of a publically available tool to assure these nodules were diverse in size, location, and density. Two radiologists were asked to use the developed tool to segment these nodules twice at different times (at least three months apart). A Hausdorff distance based method was used to assess the discrepancies (agreements) between the computerized results and the results by the four radiologists in the LIDC as well as the inter- and intrareader agreements in freehand sketching.

Results: The maximum and mean discrepancies in boundary outlines between the computerized scheme and the radiologists were 2.73 ± 1.32 mm and 1.01 ± 0.47 mm, respectively. When the nodules were classified (binned) into different size ranges, the maximum errors ranged from 1.91 to 4.13 mm; but smaller nodules had larger percentage discrepancies in term of size. Under the aid of the developed scheme, the inter- and intrareader variability in averaged maximum discrepancy across all types of pulmonary nodules were consistently smaller than 0.15 ± 0.07 mm. The computational cost in time of segmenting a pulmonary nodule ranged from 0.4 to 2.3 s with an average of 1.1 s for a typical desktop computer.

Conclusions: The experiments showed that this scheme could achieve a reasonable performance in nodule segmentation and demonstrated the merits of incorporating freehand sketching into pulmonary nodule segmentation. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4869265>]

Key words: lung nodule, segmentation, computer-aided diagnosis, shape analysis, freehand sketches

1. INTRODUCTION

Pulmonary nodules as visualized in chest computed tomography (CT) examinations represent potential depictions of lung cancer.¹ In clinical practice, measuring volumetric changes (growth) of suspicious nodules/regions, if any, on sequential CT images has been recognized as an efficacious way of assessing its malignancy likelihood.²⁻⁵ However, manual delineation of the three-dimensional (3D) boundary of a nodule in a slice-by-slice manner is time-consuming and associated

with large inter- and intrareader variability.^{6,7} Hence, it is desirable to developing computer schemes to aid in a consistent and accurate segmentation of pulmonary nodules. The primary challenge in developing such a tool stems from the wide variety of pulmonary nodules in terms of size, location, density, and shape, as well as the varying background patterns surrounding the nodules and their frequent attachment to other structures with similar densities (e.g., blood vessels).^{8,9}

In the past, there have been a number of computerized schemes developed in an attempt to robustly segment

FIG. 1. Schematic diagram of the proposed pulmonary nodule segmentation scheme.

pulmonary nodules. Many of these utilized region growing and/or morphological operations.^{9–12} The region growing is to exploit the relatively high contrast between pulmonary nodules and surrounding structures (e.g., parenchyma), while the morphological operation is to detach the nodules from neighboring soft tissues after a thresholding procedure. In implementation, the region growing operation requires the selection of a threshold, and the morphological operation requires the selection of a structural element. Given the variety of pulmonary nodules in density, size, and shape, it is not easy to optimally determine these parameters and adaptive solutions are preferred.¹³ In practice, multiple features or strategies are typically combined to achieve a better performance. For example, Zhao *et al.*^{14,15} incorporated several criteria, such as density, gradient strength, and shape compactness, into the delineation of the nodule boundaries; Diciotti *et al.*¹⁶ applied a fusion-segregation criteria in the region growing and refined the results using a combination of a 3D geodesic distance map and a local shape analysis,⁹ and Dehmshki *et al.*¹⁷ explored the connectivity via a fuzzy map in addition to the density contrast. Unlike previous methods that performed the region growing on a threshold image, Kubota *et al.*¹⁸ performed the region growing on the Euclidean distance map of a region and identified the nodule boundary by analyzing the patterns of the region growing. Chen *et al.*¹⁹ described two filters to enhance linear structures and bloblike structures, respectively; thereafter, a front surface propagation procedure was used to segment nodules. Similar enhancement filters for nodule segmentation were described in Refs. 20 and 21. Other approaches include the active contour method,^{8,22} the shape analysis method,^{23–25} the energy-minimization method,²⁶ and the model-based method.²⁷ Despite significant efforts, it remains a challenge to segment pulmonary nodules in a consistent way regardless of its appearance and locations. For example, Ashraf *et al.*²⁸ found that the reproducibility of available computer algorithms in segmenting nodules was poor and they often failed to correctly segment nodules. In an independent comparison study involving six software systems, de Hoop *et al.*²⁹ also observed that these systems had relatively large variation in segmenting the same set of solid nodules. Even though, Biancardi *et al.*³⁰ concluded in their study that a computerized scheme was an efficient tool in assisting radiologists in nodule volumetric measurement with smaller inter- and intrareader variability as compared to human experts.

In this study, we describe a novel computerized scheme enhanced by freehand sketching to aid a consistent nodule segmentation. This segmentation-by-sketch strategy leverages the fact that pulmonary nodule segmentation is typically an interactive procedure, where a seed often needs to be specified manually by a users. Instead of providing a single

seed (i.e., a point), this scheme enables a more flexible way of specifying the region-of-interest (i.e., a nodule) using freehand sketches. In nature, the strategy is analogous to repeating the segmentation multiple times using different multiple seeds. In particular, this sketch-based interaction offers an implicit incorporation of the cognition ability of a user toward suspicious regions depicted on images into the computerized segmentation procedure. A detailed description of this scheme as well as its performance (e.g., accuracy and consistence) assessment follows.

2. METHODS

2.A. Scheme overview

The developed pulmonary nodule segmentation scheme consists of two parts (Fig. 1): (1) freehand sketch analysis and (2) an automated segmentation. The first part is designed to analyze the freehand sketches from a user and infer adaptive information, including an adaptive region-of-interest that fully enclose a nodule, an adaptive threshold that indicates the boundary of a nodule, and adaptive determination of whether a Gaussian smoothing operation should be applied. The second part is to automatically segment a nodule using an improved shape “break-and-repair” strategy (SBRT).²⁴ Their detailed implementations are presented in Secs. 2.B–2.C.

2.B. Freehand sketch analysis

Computerized pulmonary nodule segmentation is typically an interactive procedure, where a seed is needed to indicate the location of a nodule. As a natural and efficient way of communicating ideas with a computer, freehand sketches have been widely regarded as an informal representation of humans’ visual cognition.³¹ In this study, instead of using a single seed as described in many previous methods,^{9,11,12,16–18} we propose to use freehand sketching to specify a nodule. No special constraints are imposed on the way of sketching. A user can make multiple strokes on a single or multiple image slices. Examples are presented in Fig. 2 to demonstrate the flexibility of making freehand sketches. Given the discrete characteristic of an image, these strokes are formed by a set of contiguous points $\{p_i\}$, $i \in [1, N]$. We proposed to infer the following useful information from the freehand sketches to aid the segmentation of pulmonary nodules:

2.B.1. Adaptive threshold indicating the boundary density of a nodule

The reason that human eyes can perceive a nodule depicted on CT images is the existence of an intensity

FIG. 2. Examples demonstrating the flexibility of freehand sketching when specifying a nodule. The sketches are display in the overlay of the CT images.

contrast between the nodule and its surrounding parenchyma background. The region-growing approaches^{9–17} actually took advantage of this contrast-related characteristic to segment nodules. Here we propose to explore this property from a different perspective to adaptively estimate the threshold from freehand sketches. Given a point on the freehand sketches, namely p_i , a number of rays starting from this point are shot out. These rays are uniformly distributed along the polar angle θ ($\theta \in [0, 2\pi]$) and the azimuthal angle φ ($\varphi \in [0, \pi]$) in the 3D spherical coordinate system. In our implementation, the interval along the polar angle and the azimuthal angle is simply set at 15° ; hence, there will be 288 rays for each point forming the freehand sketches. Along each ray, we search for the two neighboring voxels with the largest absolute gradient magnitude but with a negative sign (i.e., the minimum gradient), because a nodule always has a higher density than its surrounding parenchyma. The gradient along a ray r is calculated using a forward first-order finite difference:

$$\nabla v = \frac{\partial r}{\partial d} \approx \frac{r_{i+1} - r_i}{\Delta d}, \quad (1)$$

where v_j denotes the intensity of the i th voxel starting from the origin, and Δd is the Euclidean distance of the neighboring voxels. When a ray is shot out from a point within a nodule, the above gradient at the nodule boundary will be negative; otherwise, the gradient will be positive. This property can be used to remove the points on the sketches that are located outside a nodule, namely, the points with the largest positive gradient magnitude. Considering that a nodule typically has limited size (e.g., <30 mm), we conservatively set the length of a ray at 50 mm in our implementation. This length

constraint is also designed to avoid the intersection of the rays with other nonlung tissues in case of juxtapleural nodules. For this situation, the rays will not contribute to the adaptive parameter computation because there is no intersection between the rays and the surrounding structures. Application of the above analysis to each point on the sketches that are located inside a nodule will lead to the identification of a number of point pairs with the minimum gradients. For each point pair, we simply use their mean A as the estimated intensity of the nodule boundary. The averaged density of these point pairs is used as the threshold t indicating the boundary density of a nodule

$$t = \frac{\sum_{i=1}^n \sum_{j=1}^m A_j}{nm}, \quad (2)$$

where n is the number of the points forming the sketches that are inside a nodule, m is the number of rays for each point ($m = 288$ in our implementation), and A_j is the mean of the identified neighboring voxels along the j th ray. t will be used as the iso-value for the geometric surface modeling operation in Sec. 2.C.

2.B.2. Adaptive determination of the subvolume that fully encloses a nodule

Whereas the identified point pairs are located across the boundary of a nodule, their locations can be used to adaptively determine the cubic subvolume that fully encloses this nodule. The mass center C of the cubic subvolume is estimated as the centroid of these boundary points. The size of the cubic

subvolume is estimated as the twice of the longest distance from the points p_i on the freehand sketches to the boundary points q_i :

$$S = 2 \times \max\{s_{ij} = \|p_i - q_j\|, i \in [1, n], j \in [1, m]\}. \quad (3)$$

Given S and C , a subvolume that encloses the nodule in question can be determined. Although S generally overestimates the size of a nodule, the size of the subvolume is empirically scaled with a coefficient (e.g., 1.5) in our implementation to guarantee a full enclosure of the nodule.

2.B.3. Adaptive determination of whether a Gaussian smoothing is needed

Given the above identified point pairs, the points with a higher density can be roughly regarded as the inner boundary of a nodule. Hence, analyzing the density of the inner boundary may infer the overall density of a nodule. For a solid nodule, this density is typically high because of the “sharp” boundary or the high contrast. For a nonsolid nodule, this density is typically low because of the relatively low contrast between the nodule and the parenchyma. When the density of a nodule (e.g., nonsolid nodule) is relatively low, the impact of image noise may be amplified somewhat because of the low contrast. As shown by the examples in Figs. 4(e) and 4(f), a nonsolid nodule typically has a relatively nonuniform density distribution; hence, a 3D Gaussian filter is applied to the identified cubic subvolume to alleviate this “unevenness.” In implementation, we empirically used -600 Hounsfield unit (HU) as the threshold for determining whether a Gaussian smoothing should be applied. When the density of the “inner” boundary is lower than -600 HU, a Gaussian smoothing will be applied. Because the density of the nodule boundary may be changed after the Gaussian smoothing, the above procedure is applied again to the smoothed subvolume to recompute the threshold indicating the boundary of the nonsolid nodule. In our implementation, the kernel size of the Gaussian smoothing was empirically selected as 3 mm and the σ was empirically set at 1.0 mm.

2.C. An improved shape “break-and-repair” strategy for pulmonary nodule segmentation

Previously, Pu *et al.*²⁴ developed a shape “break-and-repair” strategy (SBRS) for segmenting anatomical structures depicted on volumetric images. The underlying idea is to identify regions with high fidelity as key points for a smooth surface fitting and use the resulting watertight surface as an estimation or approximation of the 3D boundary of the anatomical structure in question. Its feasibility and generality were tested by segmenting human lungs and pulmonary nodules on a dataset of more than 200 CT examinations. When segmenting a nodule, as illustrated in Fig. 3, the SBRS combined a principal curvature analysis and a visibility test to identify the regions of the nodules by removing the tubular structures (i.e., the “break” operation) and invisible regions. Whereas the second derivatives, the principal curvatures are

FIG. 3. Illustration of the original implementation of the shape break-and-repair strategy for nodule segmentation (Ref. 24). Given a seed C , a set of rays are shot out in a 3D space. The first intersection points between the rays and the geometric surface, e.g., p_1 , p_2 , and p_3 , are identified as visible to the seed; while the following intersection points such as p_4 is identified as occluded or invisible. At the same time, a curvature analysis procedure is used to remove the points located on cylindrical regions (e.g., p_3). The remaining points are used for implicit surface fitting to obtain a watertight surface as the 3D boundary of the nodule. We note that p_4 is incorrectly removed because of its invisibility to the seed. This incorrect removal may lead to the missing or improper estimation of the surface where the removed points are located, as demonstrated by the example in Figs. 4(c) and 4(d).

sensitive to noises, Pu *et al.*²⁴ combined the principal directions and the principal curvatures along with a visibility test to improve the performance of pulmonary nodule segmentation. Due to the introduction of the principal directions, this combination improves the robustness in identifying regions with regular shape, such as planar surfaces (e.g., fissures) and tubular surfaces (e.g., vessels). As a result, given a juxtavascular nodule, the regions with bloblike shape, which are typically nodules in CT examinations, are kept, while the vascular regions are discarded after the application of this procedure. Detailed explanation of the SBRS can be found in Ref. 24. Given the “bloblike” shape of a nodule, this approach may work well because the majority of the nodule boundary are visible to a seed and the reconstruction operation could estimate the missed regions. However, this approach may fail to accurately delineate the boundary of nodules with complex shapes, locations, and densities (see the examples in Fig. 4). These segmentation issues are largely caused by the fact that the SBRS used a single seed and a fixed threshold (i.e., -600 HU). Here, we still follow the “break-and-repair” strategy, which consists of three steps, namely, geometric surface modeling, surface “break,” and surface “reconstruction.” However, we improved this strategy with the incorporation of the above described freehand sketch analysis and a multiple seed strategy.

2.C.1. Geometric surface modeling

Similar to SBRS²⁴ the Marching Cubes Algorithm (MCA)³² is used in this study for geometric surface modeling of the anatomical structures in the (smoothed) cubic subvolume that encloses a nodule. The adaptive density t in Eq. (2) is used as the isovalue when applying the MCA to a scalar field. The resulting surface appears as a triangle mesh.

FIG. 4. Examples showing the segmentation results by the SBRS. (a)–(b) The segmentation results of two juxtapleural nodules. (c)–(d) The segmentation results when the seeds were at different locations. (e)–(f) The segmentation results for partial solid nodules.

The example in Fig. 5(b) is the 3D surface model of the sub-volume in Fig. 5(a). The details of the MCA has been described in Ref. 32.

2.C.2. Surface “break” based on multiple seeds

Given the relative higher density of lung vessels and pulmonary nodules as compared with their surrounding parenchyma background, the surface model obtained from a cubic subvolume, as shown in Fig. 5(b), contains pulmonary nodules, lung vessels, and lung boundary surface. Hence, the “break” operation was actually designed to remove the “tubular” vessels and the “planar” lung surface. Similar to the original SBRS in Ref. 24, we still used the principal curvature analysis and the visibility test but with multiple seeds instead of a single seed. Every point on the freehand sketches from a user is treated as a seed. The usage of multiple seeds avoids the incorrect removal of the points such as p_4 in Fig. 3. In the original implementation of the SBRS, Pu *et al.*²⁴ used the ray-triangle intersection to perform the visibility test. Given the large number of rays and triangles in the surface model, the ray-triangle intersection is very time-consuming. For example, assume there are 5000 triangles in the model and 10 seed points, there will be $5000 \times 288 \times 10$ times of ray-triangle intersections. Hence, we improved this using a spherical bin by dividing a sphere into a number of bins along the polar angle

θ ($\theta \in [0, 2\pi]$) and the azimuthal angle φ ($\varphi \in [0, \pi]$) in the 3D spherical coordinate system. The azimuthal angle and the polar angle are determined in a way so that the size of a bin is smaller than that of a triangle in the surface model. Given a surface model, each of its triangles is assigned to the bin in which its normal vector falls. In each bin, only the triangle with the shortest distance to the origin of a ray is kept. In this way, the computational cost is reduced significantly with a computational complexity of $O(n)$, where n is the number of the triangles forming the surface model. This strategy avoids the intersection computation between the rays and every triangle, thereby significantly improving the computational efficiency.

2.C.3. Local implicit surface reconstruction and blending

The strength of an implicit function $f(\mathbf{x}) = 0$ lies in its capability of reconstructing a watertight surface (zero level set) regardless of its topological complexity because of its intrinsic smooth interpolation and extrapolation properties. Mathematically, a radial basis function (RBF) based implicit function $f(\mathbf{x})$ appears as

$$f(\mathbf{x}) = \sum_{i=0}^n w_i \phi(\mathbf{x} - \alpha_i) + P(\mathbf{x}), \quad (4)$$

FIG. 5. An example illustrating the steps of the improved “break-repair” procedure: (a) a juxtapleural nodule depicted on CT images, (b)–(c) the 3D surface modeling of the structures in (a) viewed from different perspectives, (d)–(e) the remaining surface after the “break” operation when viewed from different perspectives, (f) the 3D convex hull of the model in (d)/(e); (g)–(h) the identified boundary of the nodule in (a) without the convex constraint in (f) on the model in (d)/(e); and (i)–(j) the 3D boundary of the nodule in (a) with the convex constraint in (f) on the model in (d)/(e).

where $\phi(\mathbf{x})$ is a radial basis function, α_i is the location of the i th constraint points, w_i is the weight, and $P(\mathbf{x})$ is a degree one polynomial. It can be inferred from Eq. (4) that the efficiency in solving of the linear system formed by the RBF is determined by the number of the constraint points. For a large irregular nodule, the computational cost will be high in both memory and time, which may be unacceptable for nodule segmentation. For example, fitting a surface with 5000 vertices means solving a symmetric matrix with a size of $15\,000 \times 15\,000$. This required a large memory (i.e., around 1 GB) and an intensive computational cost. For efficiency purpose, we propose to use the RBF to fit small subsets of the data instead of fitting the entire dataset as an implicit function. The subsets were selected adaptively on the basis of an octree-based subdivision. Each subset contains a certain number of vertices. For example, Ohtake *et al.*³³ used 15 vertices as a subset. In this study, we define the subset as Ohtake *et al.* did. Thereafter, these local implicit functions $Q_i(\mathbf{x})$ are “blended” together using partitions of unity³³ as

$$f(\mathbf{x}) \approx \sum_{i=1}^N \varphi_i(\mathbf{x}) Q_i(\mathbf{x}), \quad (5)$$

where $\{\varphi_i(\mathbf{x})\}$ are partition-of-unity functions as blending weights. In implementation, an adaptive octree-based subdivision of the axis-aligned bounding box of an object is performed until the error of each implicit surface fitting using Eq. (5) is within a predefined small fitting error. In our implementation, we simply set the fitting error at 0.1 mm, which is sufficient in accuracy for our purpose. A detailed description of this implementation can be found in Ref. 33.

Given an implicit function $f(\mathbf{x})$, the surface of an object is the regions where $f(\mathbf{x}) = 0$. Due to the interpolation and extrapolation property of an implicit function, the final fitted surface of a juxtapleural nodule will appear as those in

Figs. 5(g) and 5(h) with an obvious oversegmentation. Although a proper lung volume segmentation scheme may fix this problem, it needs a presegmentation of the lung volume in advance. Otherwise, significant computational time is needed for this purpose. Because the existence of a pleural nodule typically forms a concave region on the lung boundary, we simply apply a convex hull to the regions after the “break” operation. Only the regions inside the convex hull are checked against $f(\mathbf{x})$. An example is shown in Figs. 5(i) and 5(j).

2.D. Testing CT dataset

To assess the performance of the developed scheme, we selected 50 chest CT examinations from a public database named Lung Image Database Consortium (LIDC).^{34,35} The depicted nodules in these examinations were manually delineated by four experienced radiologists. In order to establish a diverse dataset for our quantitative assessment, we used the computer tool developed by Tan *et al.*³⁶ to facilitate this selection. A total of 50 CT examinations were randomly selected. This publically available tool (http://online.medphys.org/mphya6/v37/i7/p3802_s1) can classify the nodules in the LIDC dataset into different categories. From each of these CT examinations, a single nodule was randomly identified. Their distributions in terms of size, density, and location, which were determined by computing the averaged measurements from the four radiologists in the LIDC, are listed in Table I. In particular, there are two masses (nodules) with a size larger than 30 mm. These CT examinations were acquired under x-ray tube current ranging from 40 to 260 mA and tube voltage at either 120 or 140 kVp, and were reconstructed with a slice thickness ranging from 0.5 to 2.5 mm and a in-plane pixel resolution ranging from

TABLE I. Distributions of the lung nodules in the collected 50 CT examinations.

Features	Value range	Number of nodules
Principal axis length (mm)	3–6 mm	14
	6–10 mm	17
	> 10 mm	19
Density	Solid	33
	Partial solid	10
	Nonsolid	7
Locations	Isolated	12
	Juxtavascular	22
	Juxtapleural	16

0.54 to 0.74 mm. A detailed description of the acquisition protocol can be found in Refs. 34–35.

2.E. Performance assessment

We assessed the performance of the developed scheme quantitatively from the following aspects:

(1) **Accuracy:** Due to the lack of the “ground truth” in a strict sense, the accuracy of the scheme was assessed by the averaged discrepancy between the computerized results and the results (outlines) manually delineated by each of the four radiologists in the LIDC. The Hausdorff distance or metric³⁷ was used to quantify the discrepancy between two outlines in 3D space. Given two objects A and B , the Hausdorff distance is defined as Eq. (6) to measure the mutual proximity between these two objects, namely, the largest Euclidean distance between any point of one object to the other [Fig. 6(a)]. We denoted the averaged Hausdorff distance here as the maximum discrepancy. However, as shown in Fig. 6(b), the Hausdorff metric is not sensitive to the local perturbation and may overestimate the discrepancy. To avoid this issue, we also computed the mean discrepancy $M(A, B)$ between two objects, which is defined as Eq. (7) and denoted as the averaged discrepancy in this study. In addition, the averaged percentage discrepancy with respect to the size of a nodule was assessed to reflect the impact of the nodule size on the magnitude of the discrepancies. These measures were computed for different categories of nodules in terms of size, density, and locations.

$$H(A, B)$$

$$= \max \left\{ \max_{a \in A} \left\{ \min_{b \in B} \{h(a, b)\} \right\}, \max_{b \in B} \left\{ \min_{a \in A} \{h(a, b)\} \right\} \right\}, \quad (6)$$

$$M(A, B) = \frac{1}{2} \left(\frac{1}{n} \sum_{i=1}^n \min \{h(a_i, b)\} + \frac{1}{m} \sum_{i=1}^m \min \{h(a, b_i)\} \right), a \in A, b \in B. \quad (7)$$

(2) **Consistence (reproducibility):** We assessed the consistence of this scheme by analyzing the inter- and intrareader variability under the aid of the computerized scheme. The above explained discrepancy measures were used for this

FIG. 6. Illustration of the Hausdorff distance (a). However, this metric is nonsensitive to local small perturbation as shown in (b) and thus may ignore the global agreement of A and B .

quantitative analysis. Two radiologists were asked to segment the nodules using freehand sketches at different time points (at least three months apart). One radiologist has an experience of 9-years, and the other has an experience of more than 30 years. No special constraints/instructions were imposed on the way of sketching. Similar to accuracy assessment, the inter- and intravariability were computed for each category of the nodules. In particular, we computed the inter- and intraobserver variability in freehand sketching. Since two radiologists were asked to perform the freehand sketching twice on 50 nodules, a total of 200 sketches were resulted. As a way of studying the sensitivity of the scheme toward to free-hand sketching, we analyzed the variability of these sketches as well as their corresponding segmentation results. In addition, a Bland-Altman plot (95% limit of agreement) was presented to demonstrate the agreement of the segmentations between the two radiologists when using freehand sketching to segment nodules. Given two segmentation results, namely A and B , the x-axis denotes their union (i.e., $A \cup B$) and the y-axis denotes their difference in volume [i.e., $(A \cup B) - (A \cap B)$] in the Bland-Altman plot.

(3) **Efficiency:** We reported the efficiency of segmenting a nodule using two separated measures. The first one is the average time cost of the two radiologists in sketching, and the second one is the average time cost of the computerized scheme in segmenting the nodules. The efficiency of the developed scheme in computer memory was also presented.

(4) **Reliability of the freehand sketch analysis procedure:** To quantify the reliability of the freehand sketch analysis in inferring adaptive information, we measured the averaged discrepancies of the inferred measures, including the threshold (isovalue) for surface modeling, the cubic sub-volume size, and the mass center of the nodule, from free-hand sketches and those computed from the final nodule segmentations. Mean discrepancies and standard deviations were calculated. The Euclidean distance was used to characterize the discrepancies. We note that the scale coefficient (1.5) is not applied when computing these measures. We also summarized the accuracy of the scheme in identifying nonsolid nodules. In particular, each individual point in the sketch was used as a single seed point for nodule segmentation and their averaged discrepancy as compared with the LIDC were

TABLE II. The averaged absolute (unit: mm)/percentage (unit: %) discrepancies between the computerized results and those in the LIDC.

Category		Maximum discrepancy (mm/%)	Mean discrepancy (mm/%)
Size	3–6 mm	$1.91 \pm 1.28/40.0 \pm 32.1$	$0.90 \pm 0.51/17.2 \pm 11.0$
	6–10 mm	$2.58 \pm 1.31/31.6 \pm 15.5$	$1.03 \pm 0.44/13.1 \pm 5.7$
	≥ 10 mm	$4.13 \pm 1.25/20.7 \pm 6.3$	$1.14 \pm 0.52/5.8 \pm 2.6$
Density	Solid	$2.25 \pm 1.12/13.5 \pm 6.7$	$0.87 \pm 0.57/5.5 \pm 4.8$
	Partial solid	$2.96 \pm 1.59/21.4 \pm 19.2$	$1.57 \pm 1.09/16.0 \pm 10.2$
	Nonsolid	$3.83 \pm 2.10/33.3 \pm 20.6$	$2.20 \pm 1.72/22.3 \pm 14.3$
Location	Isolated	$2.37 \pm 0.95/14.7 \pm 7.1$	$1.16 \pm 0.49/7.7 \pm 4.2$
	Juxtapleural	$2.91 \pm 1.35/26.1 \pm 17.9$	$1.39 \pm 0.73/14.1 \pm 7.8$
	Juxtavascular	$2.71 \pm 1.34/14.4 \pm 7.8$	$1.44 \pm 0.74/9.4 \pm 4.1$
All nodules		$2.73 \pm 1.32/20.7 \pm 12.9$	$1.31 \pm 0.57/11.1 \pm 6.2$

compared with those obtained by freehand sketches to demonstrate the advantage of the multiple seed characteristic of freehand sketches.

3. EXPERIMENT AND RESULTS

3.A. Accuracy

The discrepancies between the results obtained by the computer algorithm and the outlines in the LIDC are summarized in Table II, where the nodules were classified (binned) into different categories, namely, size, density, and locations. Larger nodules typically have larger absolute discrepancies but relatively smaller percentage discrepancies. The nonsolid nodules have both the largest absolute and percentage discrepancies. There is no obvious discrepancy when the nodules were classified into different types in terms of location. On the whole, the averaged maximum absolute and percentage discrepancies are 2.73 ± 1.32 mm and $20.7\% \pm 12.9\%$, respectively; and the averaged mean absolute and percentage discrepancies are 1.31 ± 0.57 mm and $11.1\% \pm 6.2\%$, respectively.

3.B. Consistence (reproducibility)

For the two radiologists who used freehand sketching for segmentation, the inter- and intrareader variability in averaged maximum discrepancy across all types of pulmonary nodules (Table III) was consistently smaller than 0.15 ± 0.07 mm. Although there existed an obviously large inter- and intrareader variability in freehand sketches, the discrepancy of the computerized segmentation results was small as demonstrated by

both the Hausdorff distance and the Bland-Altman plot in Fig. 7.

3.C. Efficiency

The time cost for the two radiologist to perform sketching ranges from 0.8 to 5.4 s. The average time is 1.7 s. When segmenting a pulmonary nodule after the sketching, the time cost ranges from 0.4 to 2.3 s with an average of 1.1 s for a desktop PC computer installed with an AMD Athlon™ 64 × 2 Dual 2.93 GHz central processor and 8 GB RAM) and Windows 7 operating system, depending on the size of a nodule. A larger nodule is generally associated with a higher computational cost because a large linear matrix needs to be resolved. In addition to the memory occupied by a single CT examination, which typically ranges from 60 to 250 MB depending on how many images are contained in the examination, the computer memory requirement is largely spent on solving the linear system in Eq. (4). Our experiments showed that the memory requirement for this procedure ranged from 1 to 95 MB, depending on the size of a nodule.

3.D. Reliability of the freehand sketch analysis procedure

The averaged errors in estimating the adaptive parameters (e.g., nodule size, nodule mass center) are summarized in Table IV. It is notable that the estimated measures are consistently larger than the actual measures computed from the segmented nodules. The average absolute and percentage error in estimating the mass center of a nodule are 1.31 ± 0.57 mm and $13.3\% \pm 7.6\%$, respectively. When determining the

TABLE III. The averaged discrepancies (unit: mm) in freehand sketching and in computerized segmentation results between the two radiologists.

Category	Freehand sketches		Computer results		LIDC results	
	Maximum discrepancy	Mean discrepancy	Maximum discrepancy	Mean discrepancy	Maximum discrepancy	Mean discrepancy
Inter-reader	6.53 ± 3.52	4.14 ± 2.28	0.15 ± 0.07	0.002 ± 0.01	2.99 ± 2.01	1.42 ± 1.20
Intrareader	4.82 ± 2.19	3.39 ± 1.74	0.13 ± 0.09	0.002 ± 0.01	–	–

FIG. 7. The Bland-Altman plot illustrating the agreement between the two radiologists when using freehand sketches. Given two segmentations, namely, A and B, the x-axis denotes their union (i.e., $A \cup B$) and the y-axis denotes their difference in volume [i.e., $(A \cup B) - (A \cap B)$].

density of a nodule, the accuracies for the solid nodules and the nonsolid nodules are 100%; however, three of the ten partial-solid nodules are incorrectly regarded as solid nodules, corresponding to an accuracy of 70%. When every single point on the sketches used a seed, the averaged discrepancies between the computerized results and those in the LIDC were shown in Table V.

4. DISCUSSION

We described a computer-aided nodule segmentation scheme. Its most distinctive characteristics include (1) the incorporation of freehand sketching into the segmentation procedure and (2) the segmentation of pulmonary nodules by removing nonnodule regions (i.e., vessels) in geometric space. In implementation, the freehand sketching is performed in 2D imaging slices, while all other procedures, including the sketch analysis and segmentation, are performed completely in 3D space. The performance of this scheme was assessed quantitatively on 50 nodules identified from 50 chest CT examinations in the LIDC. The freehand sketch based user interface enables a natural utilization of multiple seeds instead

of a single seed and adaptive inferring of a set of parameters for pulmonary nodule segmentation. The multiple seed based strategy improves the visibility test procedure originally proposed in the original break-and-repair solution²⁴ and thus makes it more reliable to segment nodules with complex appearance. As our experiments demonstrated, the freehand sketch analysis is capable of reliably and adaptively inferring some useful parameters and the developed scheme has a reasonable accuracy and consistence. Some segmentation examples are shown in Fig. 8 to demonstrate this. Another characteristic of this scheme is an efficient improvement of the original shape break-and-repair strategy. As explained in Ref. 24, the original break-and-repair strategy took around 0.6–7.4 s with an average 4.6 s to segment a nodule, while our scheme is capable of segmenting any nodule with an average of around 1 s. In particular, the memory requirement for solving the linear system [Eq. (4)] was lowered significantly. These improvements are attributed to the employment of a spherical bin solution and a local reconstruction and blending strategy. The octree-based local reconstruction avoids the solving of a very large linear system, which requires a heavy computational resource in both memory and time. In addition, as explained in Fig. 5, the original break-and-repair strategy cannot correctly segment juxtaleural nodules without a proper lung volume segmentation in advance. Finally, although human-computer interaction is a very important research area in computer science, it is largely ignored in the community of the medical image analysis, where most applications are actually interactive in nature. This study shows that a proper incorporation of human-computer interaction techniques (e.g., freehand sketching) may change the way of designing an algorithm for specific segmentation task and ultimately significantly improve the ultimate segmentation performance as well as the usability.

When assessing the performance of the developed scheme, we proposed a Hausdorff distance (metric) to quantitatively assess the performance of a segmentation [Eqs. (6) and (7)]. This method is capable of depicting the discrepancy (agreement) between two 2D/3D outlines and has been used recently by a number of investigations.^{38–42} Although the Bland-Altman plot⁴³ is widely used to analyze the agreement

TABLE IV. The averaged absolute/percentage errors in estimating the sizes and the centers of the pulmonary nodules from freehand sketches.

Category		Averaged error (mm)	
		Nodule size	Nodule mass center
Size	3–6 mm	$1.12 \pm 0.34/18.1 \pm 11.7$	$0.71 \pm 0.44/14.1 \pm 8.0$
	6–10 mm	$1.91 \pm 0.77/26.1 \pm 15.5$	$0.91 \pm 0.52/24.4 \pm 15.5$
	≥ 10 mm	$3.33 \pm 1.01/19.2 \pm 8.3$	$1.33 \pm 0.94/6.9 \pm 3.3$
Density	Solid	$1.82 \pm 1.12/11.3 \pm 6.2$	$0.57 \pm 0.35/2.6 \pm 1.4$
	Partial solid	$1.99 \pm 1.35/21.4 \pm 19.2$	$0.91 \pm 0.79/10.6 \pm 9.2$
	Nonsolid	$2.63 \pm 1.44/21.3 \pm 17.6$	$1.82 \pm 0.87/10.3 \pm 9.4$
Location	Isolated	$1.97 \pm 0.99/12.4 \pm 6.9$	$1.01 \pm 0.54/5.7 \pm 4.3$
	Juxtaleural	$2.11 \pm 1.26/26.1 \pm 17.9$	$1.13 \pm 0.66/15.1 \pm 8.6$
	Juxtavascular	$2.32 \pm 1.23/16.1 \pm 7.6$	$1.14 \pm 0.70/9.6 \pm 5.3$
All nodules		$2.47 \pm 1.32/19.9 \pm 11.1$	$1.31 \pm 0.57/13.3 \pm 7.6$

TABLE V. The averaged absolute (unit: mm)/percentage (unit: %) discrepancies between the computerized results and those in the LIDC when every single point on the sketches was used a seed.

Category		Maximum discrepancy (mm/%)	Mean discrepancy (mm/%)
Size	3–6 mm	$1.99 \pm 1.91/50.1 \pm 37.7$	$0.94 \pm 0.65/18.1 \pm 17.3$
	6–10 mm	$3.18 \pm 2.21/37.7 \pm 18.6$	$1.29 \pm 0.93/18.4 \pm 10.5$
	≥ 10 mm	$6.11 \pm 4.74/33.6 \pm 13.2$	$1.64 \pm 0.77/6.6 \pm 4.2$
Density	Solid	$2.47 \pm 1.31/15.2 \pm 9.7$	$0.86 \pm 0.69/5.9 \pm 5.0$
	Partial solid	$3.96 \pm 3.65/37.1 \pm 28.3$	$2.38 \pm 1.32/31.6 \pm 21.7$
	Nonsolid	$4.31 \pm 2.99/40.3 \pm 29.4$	$2.52 \pm 1.89/29.2 \pm 20.4$
Location	Isolated	$2.84 \pm 1.13/17.9 \pm 8.2$	$1.99 \pm 0.83/13.6 \pm 10.2$
	Juxtapleural	$3.55 \pm 2.67/44.2 \pm 22.7$	$1.93 \pm 0.91 / 18.4 \pm 9.4$
	Juxtavascular	$5.71 \pm 3.13/30.8 \pm 15.6$	$2.76 \pm 1.43/18.3 \pm 11.4$
All nodules		$4.24 \pm 2.71/39.3 \pm 23.6$	$2.39 \pm 1.05/22.0 \pm 10.3$

between two measures, it is not suitable for this study. The Bland-Altman is designed to visualize the relationship between two one-dimensional measures (assays), where the mean of the two measurements is used as the abscissa (x-axis) value, and the difference between the same two measurements is used as the ordinate (y-axis) value. In order to present the Bland-Altman plots, we first have to identify a one-dimensional measure to quantify a nodule. Since the results in the LIDC are 2D outlines provided by radiologists in a slice-by-slice manner, they appear as a set of points in space. It is difficult to identify a one-dimensional measure to adequately quantify the 3D outlines of a nodule that are marked separately in 2D image slices (not continuous in 3D space).

Hence, we used the Hausdorff metric to assess the discrepancy (agreement) between two segmentations.

The Bland-Altman plot in Fig. 7 showed a drastic decrease in agreement for large nodules. This does not mean that the developed scheme is not reliable for segmenting large nodules. For large nodules, even a small variation in size may correspond to an obvious absolute volume change as compared to small nodules because of the underlying cubic relationship between the size (e.g., radius/diameter) and the volume. Hence, we presented percentage discrepancies in addition to absolute discrepancies to show the agreement between the computer results and the radiologists' outlines. As presented in Table II, large nodules typically have smaller

FIG. 8. Examples showing the manual results by the four radiologists in the LIDC [(a)–(d)] and the results obtained by our two radiologists [(e)–(f)] when using our computerized schemes. The results in row (g) show the 3D models of the segmented nodules by our scheme.

FIG. 9. The determined thresholds (b) for the nodule in (a) when using 50 different single seeds and 50 different freehand sketches.

percentage discrepancies, albeit their absolute discrepancies are typically larger as compared to small nodules.

The freehand sketch analysis is associated with several parameters. The first one is the adaptive threshold aiming to segment nodules with a variety of densities. Previously, some investigators^{9,11,12,16–18} proposed to infer the threshold adaptively by analyzing the local density distribution around the “click point” or the single seed. These approaches required a seed point inside the nodule; otherwise, the adaptive threshold may not be appropriate. In contrast, our freehand sketch based multiple seed strategy is relatively insensitive to the location of the “click point.” As a simple way to demonstrate the reliability of using multiple seeds in inferring adaptive threshold, an experiment was performed, where a single seed was randomly selected within a nodule for 50 times, and meanwhile 50 different sketches were tested. The results in Fig. 9 showed that there was a much larger variation among the determined thresholds when a single seed was used as compared to free-

hand sketches. In nature, the multiple seed strategy is a combination of the results obtained from individual seeds. Second, we are fully aware that it is very difficult in practice to use a fixed threshold to determine whether a nodule is solid or non-solid. To properly segment nonsolid nodules, which typically have low densities, we used a threshold of -600 HU to determine whether a Gaussian smoothing operation was needed to alleviate the potential impact of image noise or artifacts. As our experiments showed, this threshold was reliable in identifying all solid and nonsolid nodules but incorrectly treated three partial solid nodules as solid, suggesting that a threshold of -600 HU is proper. In the future, additional effort may be needed to determine an optimal threshold for this smoothing procedure. In particular, the Gaussian smoothing filter is applied to the nonsolid nodules to reduce the variety of the nodules in density. The examples in Fig. 10 demonstrate the impact of this smoothing operation. The reason that we did not apply this smoothing operation to all types of nodules

FIG. 10. Examples illustrating the impacts of the Gaussian smoothing on the segmentation of nonsolid nodules: (a) two nonsolid nodules, (b) segmentation results without Gaussian filtering, and (c) segmentation results with Gaussian filtering.

is to delineate the boundary of a nodule as faithfully as visualized on CT images, because the smoothing may lead to somewhat blurring of the boundary. We have to note that an optimal smoothing operation depends on an accurate quantification of the noise level of the image, which is a very challenging issue. Here, we only empirically set the parameters for the Gaussian filter. Third, when estimating the size of a nodule, we used a scale factor of 1.5. Although our experiment showed that our approach typically overestimated the size of a nodule as expected, this scale factor is used only to guarantee that a nodule is fully closed in a cubic subvolume. In fact, the size of the subvolume does not affect the segmentation result because the shot-out rays typically stop at the nodule boundaries. However, a larger subvolume will result in more triangles when performing the three-dimensional surface modeling using the Marching Cubes algorithm, and this will lead to more computational costs in curvature analysis and visibility test. Given the linear computational complexity ($O(n)$) of the Marching Cubes algorithm, curvature analysis, and spherical bin based visibility test, the computation cost could be ignored.

We are aware of some limitations associated with this study. First, the developed schemes may unavoidably miss small spiculated regions. This is caused by the smoothing characteristic of the implicit surface fitting. Because it is very challenging to human experts to manually mark these details, quantifying the performance of the developed scheme in this regard becomes extremely difficult. Second, different scanning and reconstruction parameters (e.g., dosages, slice thicknesses, reconstruction kernels, and scanning devices) may be associated with different noise/image artifact levels and thereby lead to different nodule segmentation and volumetric quantification. In this study, we do not investigate this potential impact, which might need a different study. Third, when quantifying the accuracy of the developed scheme in segmenting nodules, we used the outlines marked by four radiologists in the LIDC as reference standard, which are not “ground truth” in a strict sense. Finally, we did not perform a quantitative comparison with other approaches. This is caused by the usage of different testing datasets and discrepancy metrics in available investigations.^{8–22} Reeves *et al.*¹ and Dehmeshki *et al.*¹⁷ explained this underlying challenge in their studies. For example, Keshani *et al.*⁸ used four databases from different sources for their evaluation and the segmentation accuracy was based on the count of nodule windows (labels); Dehmeshki *et al.*¹⁷ and Diciotti *et al.*⁹ asked a radiologist to visually inspect the segmentation results and used the percentage of correct segmentations as an index to assess the performance of their scheme; Chen *et al.*¹⁹ did not provide any quantitative assessment of the accuracy in nodule segmentation but simply indicated whether a nodule was segmented or not; Reeves *et al.*¹ and Kuhnigk *et al.*⁴⁴ used phantom nodules for performance assessment; Wang *et al.*⁴⁵ used the volume overlap with radiologists’ results to quantify the accuracy and the consistence of their method. However, the LIDC datasets that these investigators used only provided the outlines of the nodules marked by radiologists in a slice-by-slice manner. Given the gaps between the out-

lines in neighboring slices, it may not be proper to use the volume overlap for performance assessment. Although one of the primary objectives of the LIDC was designed to assess the performance of nodule segmentation, available approaches actually used different examinations because of the continuous growth of the LIDC in the past years. For example, Chen *et al.*¹⁹ selected 20 CT examinations randomly from LIDC for performance assessment; Diciotti *et al.*⁹ used 86 CT examinations in the LIDC for assessment; and Wang *et al.*⁴⁵ used 109 CT examinations for their performance assessment. All these make it challenge to perform an objective and reasonable comparison of the available methods in performance.

5. CONCLUSION

A computerized scheme was presented in this study to aid an objective and consistent segmentation of pulmonary nodules. Its distinctive characteristic is the introduction of freehand sketching into the segmentation process and the inferring of useful information from the sketches. Testing against a number of nodule with different shapes, sizes, locations, and densities demonstrated that this scheme could achieve a reasonable performance in nodule segmentation.

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^{a)}Electronic mail: puj@Upmc.edu

^{b)}Author to whom correspondence should be addressed. Electronic mail: cjr.guoyoumin@vip.163.com

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