Pulmonary nodule registration: Rigid or nonrigid?

Suicheng Gu

Department of Radiology, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, Pennsylvania 15213

David Wilson

Department of Medicine, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Jun Tan

Department of Radiology, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Jiantao Pu^{a)}

Department of Radiology, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, Pennsylvania 15213 and

Department of Bioengineering, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, Pennsylvania 15213

(Received 28 February 2011; revised 2 June 2011; accepted for publication 2 June 2011; published 30 June 2011)

Purpose: The primary aim of this study is to investigate the performance difference of rigid and nonrigid registration schemes in matching corresponding pulmonary nodules depicted on sequential chest computed tomography (CT) examinations.

Methods: A gradient descent based rigid registration algorithm with scaling was developed and it handled the involved geometric transformations (i.e., translation, rescaling, shearing, and rotation) separately instead of optimizing them in a single pass. Given two lung CT examinations, the scaling and translation parameters were simply estimated from the lung volume dimensions (e.g., size and mass center), while the rotation parameters were optimized progressively using gradient descent. To investigate the performance difference of rigid and nonrigid schemes in pulmonary nodule registration, the well-known nonrigid Demons algorithm was implemented and tested along with the developed schemes against 60 diverse low-dose clinical lung CT examinations with average 2-yr follow-up scans. A verified cancer and its correspondence in the follow-up scan as well as their spatial locations (mass center) were identified in each examination. In addition to the computational efficiency, the accuracy of these registration procedures was assessed by computing the Euclidean distances between the corresponding nodules after the registration. To demonstrate the advantage of the developed algorithm, the authors also implemented a fast iterative closest point (ICP) based rigid algorithm and compared their performance.

Results: Our experiments on the collected chest CT examinations showed that the nodule registration errors in 3D Euclidean distance for the developed rigid affine approach, the traditional ICP algorithm, and the refining nonrigid Demons algorithm were 9.6, 9.8, and 10.0 mm, respectively, and the corresponding computational costs in time were 5, 300, and 55 s, respectively.

Conclusions: A rigid solution may be preferred in practice for the pulmonary nodule registration in longitudinal studies because of its relatively high efficiency and sufficient accuracy for the clinical need. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3602457]

Key words: pulmonary nodule, rigid/nonrigid registration, Demons algorithm, follow-up study

I. INTRODUCTION

Radiologists frequently follow-up pulmonary nodules depicted on sequential computed tomography (CT) examinations for assessing their likelihood of being benign or malignant. It is desirable to have a tool that can aid a radiologist to locate the corresponding nodules depicted in the follow-up CT examinations in real-time because of the involvement of a large number of CT images in a single examination.¹ In the past decade, a number of automated registration schemes have been developed for this purpose, and they can be largely divided into two categories: (1) rigid method and (2) nonrigid method.

The rigid methods are typically characterized by three translation (i.e., x , y , and z) and three rotation (i.e., θ_1 , θ_2 , and θ_3) parameters, and affine methods have additional three scaling and three shearing parameters. The underlying idea

is to register images by aligning three dimensional (3D) anatomical landmarks of the human lungs. For example, Betke *et al.*² used the anatomical landmarks such as the sternum, vertebrae, and tracheal centroids for initial global registration followed by an iterative closest point (ICP) process to refine the registration results. Shi *et al.*³ developed an approach from a different perspective by aligning the center-lines of each of the three rib pairs in the initial and follow-up CT volumes. Obviously, the performance of these methods largely depended on the accuracy of the involved landmark and the surface identification, and they typically could not achieve a real-time performance due to the relatively high computational cost. Hong *et al.*^{4,5} proposed to generate a 3D distance map using narrow-band distance propagation and aligned the surfaces in a step-by-step hierarchical manner. Like previous approaches,² this hierarchical method used the

ICP procedure as well and required an accurate lung surface identification. The most distinctive characteristic of the available affine registration methods is that the optimization of the transformation parameters is performed in a single pass, while the specific characteristics of each sub-transformation are ignored, and this may lead to a relatively higher computational cost due to the complexity in optimization.

As an alternative approach for pulmonary nodule registration, the nonrigid method is typically based on either a dense nonparametric model or a parameterized function model. Most of them were a refinement of either the Demons algorithm⁶ or the B-spline method.⁷ To improve the performance of the nonrigid registration, Wang *et al.*⁸ accelerated the Demons algorithm by introducing an active force that utilized the gradient information of the source image. Some others utilized the Jacobian of the deformable transformation to achieve volume preservation.^{9,10} Blaffert and Wiemker¹¹ and Zheng *et al.*¹² used the B-spline approach to register pulmonary nodules in follow-up scans. In particular, Zheng *et al.* found that the nonrigid registration method was better than the rigid method in accuracy. However, their conclusion was only supported by an experiment on three pairs of chest CT examinations. As compared with the rigid (affine) approach, the nonrigid methods involved a much heavier computational costs in registration.

In this study, we investigate the performance of the rigid and nonrigid schemes in aiding the identification of the corresponding nodules depicted on different examinations that are acquired from the same subject. The aim is to clarify whether it is necessary to have a sophisticated nonrigid approach for follow-up pulmonary nodule registration in clinical practice. For this purpose, we developed a simple and efficient rigid affine registration method for pulmonary

nodule registration from a different perspective by dividing the affine transformation into four subtransformations and performing each subtransformation separately. The performances of the developed method and the well-known Demons algorithm as well as that of the traditional ICP-based rigid registration algorithm were tested and compared using 60 low-dose clinical lung CT examinations with average 2-yr follow-up scans. The detailed description of these developed methods as well as the experimental results follow.

II. METHODS AND MATERIALS

The basic procedures of the pulmonary nodule registration scheme developed in this study are illustrated by the flowchart in Fig. 1. Given a pair of lung CT examinations acquired at different time points, the lung volumes were first identified using a simple adaptive thresholding method described in Ref. 13. Then, an initial rigid registration is obtained. Thereafter, a nonrigid registration, namely the Demons algorithm, is applied to refine the rigid registration. Finally, we evaluate the performance of the rigid registration scheme and the refined nonrigid registration.

II.A. Gradient descent based rigid affine registration

Generally, a rigid transformation can be characterized by three translation and three rotation parameters. For an affine transformation, there are additional three scaling and shearing parameters. An affine registration procedure is to identify the optimal translation, rotation, scaling, and shearing parameters in regard to an objective function in mathematics. As mentioned above, most available approaches used the ICP algorithm to minimize the distance between the lung surfaces acquired from two examinations; thus, the spatial

FIG. 1. Scheme diagram of the developed rigid registration scheme. The arrows indicate the locations of the nodules.

locations of the points forming the lung surfaces have a direct impact on the optimization result, and the minimization process typically has a high computational complexity. Considering that the registration procedure here is performed on the examinations acquired on the same subjects and the lungs depicted in these examinations typically have no significant changes in shape (except for cases with severe diseases that may affect the lung significantly), we propose to treat the lung volume as a rigid body in this study to simplify and thus accelerate the registration process. Hence, the moving image is translated and reconstructed in a way such that it has the same volume center and the resolution as the fixed image. Now the registration is simplified as a problem of only optimizing the rotation transformation parameter. As compared with previous methods that used lung surfaces for optimization purpose, the lung volume is relatively nonsensitive to the existence of image noise or artifacts due to the

involved huge number of voxels. Hence, maximizing the overlap of the two lung volumes would be more robust than minimizing the distance of two lung surface. However, a much higher computational cost is generally associated with this procedure because of the calculation of the distances between two large sets of points. In this study, we use the surface-volume distance to reduce the computational complexity. A volume point (voxel) is regarded as a surface point if one of its six-connected neighbors is not a volume point (voxel); otherwise, the point (voxel) is defined as a point inside the volume.

In Euclidean space, the rotation of a point $p = (x, y, z)^T$ around a center $c = (x_0, y_0, z_0)^T$ can be expressed as

$$p_{\text{new}} = R(\theta, c) \circ p = A_\theta(p - c) + c, \quad (1)$$

where $R(\theta, c)$ is a rotation operator and its corresponding rotation matrix A_θ is a 3×3 orthogonal matrix [i.e., Eq. (2)].

$$\begin{pmatrix} \cos(\theta_2) \cos(\theta_3) & \sin(\theta_1) \sin(\theta_2) \cos(\theta_3) - \cos(\theta_1) \sin(\theta_3) & \cos(\theta_1) \sin(\theta_2) \cos(\theta_3) + \sin(\theta_1) \sin(\theta_3) \\ \cos(\theta_2) \sin(\theta_3) & \sin(\theta_1) \sin(\theta_2) \sin(\theta_3) + \cos(\theta_1) \cos(\theta_3) & \cos(\theta_1) \sin(\theta_2) \sin(\theta_3) - \sin(\theta_1) \cos(\theta_3) \\ -\sin(\theta_2) & \sin(\theta_1) \cos(\theta_2) & \cos(\theta_1) \cos(\theta_2) \end{pmatrix}, \quad (2)$$

where $\theta = (\theta_1, \theta_2, \theta_3)$, θ_1 , θ_2 , and θ_3 are the rotation angles around the three axes perpendicular to the sagittal plane, the coronal plane, and the axial plane, respectively. The lung surface or volume is treated as a point set. The rotation of a surface $S = \{p_i\}$ or a volume $V = \{p_j\}$ is achieved by rotating each point p that belongs to S or V . The distance between point p and volume V is defined as

$$d(p, V) = \min_{p_i \in V} d(p, p_i) \quad (3)$$

where $d(p, p_i)$ is the Euclidean distance between points p and p_i . For the sake of computational efficiency and outlier reduction, the point-volume distance was regularized by

$$d(p, V) = \min(d_0, \min_{p_i \in V} d(p, p_i)) \quad (4)$$

In this study, we empirically set $d_0 = 3$ mm. The distance between surface S and volume V is defined as

$$d(S, V) = \sum_{p_i \in S} d(p_i, V) \quad (5)$$

The rotation parameters $\theta = (\theta_1, \theta_2, \theta_3)$ are estimated by minimizing distance between the rotated lung surface of the moving image $R(\theta, c) \circ S_m$ and the lung volume of the fixed image V_f , namely solving the following optimization problem

$$\theta_{\text{opt}} = \arg \min_{\theta} d(R(\theta, c) \circ S_m, V_f), \quad (6)$$

The above optimization problem does not have a least square solution. Whereas the human lungs depicted in different examinations typically have a similar posture, the distance function $d(R(\theta, c) \circ S_f, V_f)$ is monotone increasing with respect to $|\theta|$ when angle $|\theta| = (|\theta_1|, |\theta_2|, |\theta_3|)$ is very small, where S_f be the boundary of volume V_f . Thus, the optimal θ is computed progressively using gradient descent method.

To solve the above optimization problem, θ is initiated with $(0, 0, 0)$ and updated by

$$\theta^{t+1} = \theta^t - \varepsilon \frac{\nabla D(\theta^t)}{\|\nabla D(\theta^t)\|}, \quad (7)$$

where the step size $\varepsilon > 0$ is a small scalar. The iteration stops when $(D(\theta^t) - D(\theta^{t+1}))/D(\theta^t) < \sigma = 0.001$ or $\theta \notin \Omega$, where $\Omega = \{\theta \mid |\theta_1| \leq 0.05, |\theta_2| \leq 0.05, |\theta_3| \leq 0.15\}$ is to constrain the angle θ within a small interval. Gradient of D at θ was computed using Eq. (8).

$$\begin{aligned} \nabla D(\theta) &= \left(\frac{\partial D}{\partial \theta_1}, \frac{\partial D}{\partial \theta_2}, \frac{\partial D}{\partial \theta_3} \right) \\ &= \left(\frac{D(\theta_1 + \varepsilon, \theta_2, \theta_3) - D(\theta)}{\varepsilon}, \right. \\ &\quad \times \frac{D(\theta_1, \theta_2 + \varepsilon, \theta_3) - D(\theta)}{\varepsilon}, \\ &\quad \left. \times \frac{D(\theta_1, \theta_2, \theta_3 + \varepsilon) - D(\theta)}{\varepsilon} \right) \end{aligned} \quad (8)$$

For the purpose of efficiency, a distance map (similar as in Refs. 14 and 15) is generated for the fixed volume before the optimization procedure [Eq. (4)] as shown in Fig. 2. With the availability of this distance map, the distance of any point from the rotated moving surface to the fixed volume can be directly inquired. A trilinear interpolation is used to compute the distances of noninteger points.

In each pair of examinations, we use the one with larger section thickness as the fixed image and the other one as the moving image. Because the primary computational cost is associated with the generation of a distance map for the lung volume, we compute the distance map in the scan with larger section thickness for efficiency consideration. The lung

FIG. 2. A diagram of distance map. The distances of the points in the fixed lung volume are zero. The distances of the outlier points (in white) with a distance larger than 3 mm to the lung volume are 3 mm. The distances of the left points are computed using Eq. (3).

surface is obtained from the examination with smaller section thickness due to its relatively higher accuracy in describing the lung surface; otherwise, the average registration error in Euclidean distance would increase from 9.6 to 10.0 mm and the average computational time would increase significantly as well (e.g., from 5 to 12 s).

Generally, the distance between a nodule and the mass center of the lung volume should be less than a certain distance (e.g., 100 mm). Thus, the error caused by the discretization of ε is less than $100 \cdot \sin(\varepsilon)/2 \approx 0.25$ mm, which is small enough for use. According to ε and Ω mentioned above, the procedure converges in about $\sqrt{0.15^2 + 0.05^2 + 0.05^2}/0.005 \approx 35$ steps. The computational complexity for the optimization of rotation parameters is $O\{N_v + N_s \times (N_n + N_i)\}$, where N_v , N_s , N_n , and N_i are number of volume points, surface points, neighbors of a point [determined by d_0 in Eq. (4)], and iterations, respectively. An example of the affine registration is shown in Fig. 3, where the nodule center of registration is on the same slice image with the marked nodule center.

FIG. 3. An example of the registration result using the proposed affine method.

II.B. Demons algorithm for nonrigid registration

The motivation of implementing a nonrigid registration was to study whether and how much the results of the rigid affine registration could be improved by using an additional flexible transformation model. In this study, we used the Demons algorithm⁶ with an acceleration parameter.⁸ For a given point P , let f be the intensity in fixed image F and m the intensity of the moving image M . The estimated displacement $u = \{u_x, u_y, u_z\}$ between point P and its corresponding point in M is given by

$$u = \frac{(m - f)\nabla f}{\|\nabla f\|^2 + \alpha^2(m - f)^2}, \quad (9)$$

where ∇f is the gradient of the fixed image and the acceleration parameter α is fixed to 0.5 in this study.

To improve efficiency and to reduce the possibility of being trapped in a local minima, the multiresolution scheme was used to perform the Demons registration in three stages: $64 \times 64 \times \frac{N}{8}$, $128 \times 128 \times \frac{N}{4}$, and $256 \times 256 \times \frac{N}{2}$, $N = \max(N_f, N_m)$, where N_f and N_m are the numbers of slices of fixed image and moving image, respectively. The image gradient was computed using the 3D Sobel operator¹⁶ in this study. Trilinear interpolation was used to compute image intensity at noninteger point. The Gaussian filter is applied to the whole field of the displacement in each iteration, where $\sigma = 2.0$ mm and the kernel size is $3 \times 3 \times 3$.

II.C. Testing cases and performance assessment

One hundred and twenty low-dose screening CT examinations of 60 patients, acquired from 2002 to 2009, were specifically selected from a database as a result of the University of Pittsburgh Lung Cancer Specialized Program of Research Excellence (SPOR) for the performance of pulmonary nodule registration. Those selected in this study are all pathologically verified lung cancer cases. These examinations were acquired using LightSpeed Plus 4-MDCT or LightSpeed Ultra 8-MDCT scanners GE Healthcare. The low-dose CT acquisition protocol varied slightly depending on patient size. Exposure settings ranged from 120 to 140 kVp, 29.7 ± 10.7 mAs, with section reconstruction interval ranged from 0.625 to 5 mm, and in-plane pixel size from 0.50 to 0.98 mm. Images were reconstructed with 512×512 pixel matrices using the GE Healthcare “lung” reconstruction kernel. Each patient had two scans with a time interval from 4 to 68 months (mean = 22 months). In each scan, a lung nodule was identified by a radiologist.¹⁷ Figure 4 shows section thickness of initial and follow-up scans of all the 60 cases.

To evaluate the algorithms, the error in Euclidean distance (E) between the mass centers of the corresponding nodules after registration is computed using Eq. (10)

$$E(i) = \|T \circ C_{IN}(i) - C_{FU}(i)\|, \quad (10)$$

where i is patient index, $C_{IN}(i)$ and $C_{FU}(i)$ are nodule centroids of patient i in initial and follow-up scans, respectively. The mass centers were estimated using an automated nodule segmentation scheme.¹⁸ The average, standard deviation,

FIG. 4. Section thickness of all the 60 cases.

maximum and minimum of the registration errors in 1D and 3D Euclidean distance as well as the computational costs were computed after application of the developed rigid registration scheme, the fast ICP-based rigid registration algorithm, and the nonrigid Demons algorithm to the collected examinations.

Finally, in order to demonstrate the advantage of the developed rigid registration scheme, where the parameters were optimized separately instead of in a single pass, we also implemented a fast ICP-based rigid registration algorithm described in Ref. 2. In this scheme, the rotation parameters and the translation parameters are optimized using a single objective function as Eq. (11).

$$(q_{\text{opt}}, t_{\text{opt}}) = \arg \min_{(q,t)} d^2(T(t) \circ R(q) \circ S_m, S_f), \quad (11)$$

where vector $t = (t_1, t_2, t_3)$ denotes the three translation parameters and $q = (q_1, q_2, q_3, q_4)$ is a unit vector that determines the rotation matrix. The detailed description of this fast ICP algorithm has been reported in Ref. 2. In the initiali-

zation of the ICP algorithm, the moving image was translated and reconstructed in a way such that it has the same volume center and the same image resolution with the fixed image.

III. RESULTS

The performance of the developed rigid registration scheme, the fast ICP-based rigid registration, and the Demons algorithm on the selected 60 pairs of lung CT examinations in registration accuracy (error) measured in 3D Euclidean distance were summarized in Fig. 5. The nonrigid Demons algorithm yielded the minimal registration error of 1.4 mm. As compared with our developed rigid scheme, although the Demons algorithm reduced the largest error from 37.7 to 37.1 mm, its average registration error is 0.4 mm greater. The number of cases with registration errors in 3D Euclidean distance smaller than a given distance were listed in Table I. It can be seen that the performance of our developed rigid method was slightly better than that of the

FIG. 5. Performances of our developed rigid method, the fast ICP method, and the nonrigid Demons algorithm in registration accuracy when applying them to the 60 pairs of chest CT examinations collected in this study.

TABLE I. Number of cases with registration errors smaller than given values.

Method	<5 mm	<10 mm	<15 mm	<20 mm	<Nodule radius	<Nodule diameter
Rigid	16	38	51	56	42	56
Nonrigid	12	37	50	56	42	56

nonrigid Demons algorithm; however, their performance were comparable because both methods yielded an error smaller than the mean nodule diameter (i.e., the average diameter of the initial scan and the follow-up scan) on 56/60 of the collected cases, implying that the registered nodules have somewhat spatial overlap with their correspondences depicted on different examinations. In addition, the registration errors along the three orthogonal views (i.e., axial, coronal, and sagittal) were summarized in Table II. For the axial views, the average errors of both the Demons algorithm and our developed method were around 5 mm. Whereas the average section thickness is 2.5 mm, this error actually corresponds to about 2 voxels.

We also investigated the impact of the lung volume changes between the collected chest CT examinations and their follow-up scans on the registration errors and the results were summarized in Table III. The three algorithms were comparable in performance with different lung volume changes. It can be seen that the cases with larger volume change result in larger registration error. But when the volume change is smaller than 20%, the performance difference is not insignificant. A total of 37 and 56 of the 60 cases changed less than 10% (mean = 4.7%) and 20% (mean = 7.7%) in volume, respectively. Only four of the 60 cases changed more than 20% in volume. One of the four cases with a registration error of 37.7 mm is shown in Fig. 6. For this case, the reconstruction resolution of the initial and the follow-up examinations are $0.7 \times 0.7 \times 2.5$ and $1.0 \times 1.0 \times 3.3$ (mm³), respectively. The volume of the nodule grew from 4471 to 7515 mm³. The registration errors on axial (z), coronal (y), and sagittal (x) views are 29.1, 10.3, and 20.6 mm, respectively. As shown in Fig. 6, there is a significant change of the lung volumes acquired from the two examinations, which may lead to the spatial change of the relative positions of the nodules. Specifically, there is a significant contraction of the superior segment of the right lower lobe from Figs. 6(c) to 6(d). This is because the initial small nodule in (c) that is sitting on bullae has grown in (d)

TABLE II. Average and standard deviation (STD) distance errors of the 60 cases on three axes.

Axis	Method	Average (mm)	STD (mm)	Max (mm)	Min (mm)
Sagittal (x)	Rigid	4.3	4.8	29.3	0.1
	Nonrigid	4.5	5.0	29.1	0.0
Coronal (y)	Rigid	4.5	5.7	14.5	0.1
	Nonrigid	4.7	5.2	15.1	0.1
Axial (z)	Rigid	5.2	6.3	33.2	0.1
	Nonrigid	5.2	5.9	31.3	0.2

TABLE III. Average errors in Euclidean distance of cases with different volume change rates for the three methods.

Volume change range	Number of cases (percent)	Average volume change	Mean registration error (mm)		
			Rigid	ICP	Nonrigid
[0, 0.1]	37 (61.7%)	4.7%	8.1	7.8	8.8
[0.1, 0.2]	19 (31.7%)	13.7%	8.6	9.8	9.0
[0.2, -]	4 (6.7%)	38.5%	27.8	27.7	26.0
Overall	60 (100%)	9.8%	9.6	9.8	10.0

and collapsing the bullae caused the volume loss and remodeling.

In efficiency, the average computational costs in time of the developed rigid registration scheme, the fast ICP-based registration algorithm, and the nonrigid Demons algorithm were around 5, 300, and 55 s, respectively. The experiments were performed on an Intel Core i3 PC with a 3.2 GHz CPU and 6.0 GB of RAM.

IV. DISCUSSION

In this study, we investigated the performance differences of rigid and nonrigid schemes in pulmonary nodule registration. Specifically, we developed a simple and efficient rigid registration scheme and compared its performance with the well-known nonrigid Demons algorithm and a fast ICP-based rigid registration algorithm using 60 lung CT examinations with follow-up scans. The proposed method divided the affine transformation into four independent transformations, namely, translation, rescaling, shearing, and rotation. Only the three rotation parameter was optimized progressively using gradient descent. This scheme achieved a reasonable accuracy (i.e., an average registration error of 9.6 mm in Euclidean distance) and a relatively high efficiency (i.e., around 5 s per registration) despite its simplicity. In accuracy, the method developed by Shi *et al.*,³ which used high-level landmarks (e.g., rib centerlines), had an average error of 9.7 mm; Blaffert and Wiemker's method¹¹ had an average error of 4.2 mm for examinations with a section thickness of 1 mm, and Betke *et al.*'s² method had an average error of 8 mm. Hence, the performance of our method is comparable to these in registration accuracy. For a straightforward comparison, we listed the performances of the available relevant investigations and their characteristics in methods in Table IV. In efficiency, our method only took around 5 s for registering two examinations. In contrast, an affine registration¹¹ based on image intensity and using a Gauss-Newton optimization¹⁹ and a multiresolution scheme took an average processing time of 15 s. Another method⁴ based on narrow-band distance propagation and multiresolution scheme took an average processing time of 37 s. Hence, this scheme has an obvious advantage in efficiency as compared with the available methods. We note that the purpose of this study is not to develop a completely novel and efficient algorithm for pulmonary nodule registration but to demonstrate that the matching of pulmonary nodules depicted on sequential examinations may not need a

FIG. 6. The case with distance error of 37.7 mm. The arrows indicate the position of the marked nodule centers in the initial scan and follow-up scan.

sophisticated nonrigid algorithm due to its relatively high computational cost in time.

In this study, we set the regularization parameter d_0 in Eq. (4) empirically at 3.0 mm based on an experiment, where the registration errors and the computation cost in time were computed when different values were assigned to d_0 (as shown in Table V). It can be seen that the registration performance of our developed scheme was not sensitive to d_0 , while the computational complexity in time increased as d_0 grew.

We note specifically here that the 4D-CT registration^{20–23} and the follow-up registration are two different tasks. The chest CT examinations involved in the 4D-CT registration typically have many similar characteristics (e.g., time gap in scanning, dose, image quality, reconstruction resolution, and scanning pose) and their major difference lies in the lung shape as a result of different respiratory states.^{20–23} Also, the examinations in 4D-CT registration are typically acquired throughout a respiratory cycle. In contrast, the chest CT examinations involved in the follow-up registration may vary significantly in the above mentioned aspects, and they

TABLE V. Registration errors in Euclidean distance and computational cost in time of our developed rigid registration scheme when set d_0 in Eq. (4) at different values.

d_0 (mm)	2.0	3.0	4.0	5.0	6.0	7.0	10.0	∞
Registration error (mm)	9.7	9.6	9.6	9.6	9.5	9.6	9.6	9.6
Registration efficiency (s)	5	5	6	7	9	12	31	300

are typically acquired with a long time gap. In particular, due to the impact of disease progress over a relatively long time, the lung shapes depicted on the CT images and image intensities may change significantly as well (the example in Fig. 6). In this study, the examinations for testing purpose are all verified lung cancer cases and have low doses, and the time gap between the initial scans and their follow-up scans are 2 yr on average. All these factors imposed a great challenge on the follow-up registration of the lung CT examinations.

Generally, a sophisticated nonrigid registration method is believed to have a higher accuracy in performance than a rigid one due to the involved higher degree of optimizations. However, it typically requires more computational cost in time and it is more liable to suffer from the over-fitting problem or the trap at a local minimum. Therefore, it is not always desirable to have a sophisticated registration scheme without considering the background of a specific application, and a balance among the accuracy, robustness, and computational complexity has to be considered. As our study demonstrated, the fast ICP algorithm and the nonrigid Demons algorithm have no obvious advantage in accuracy but a much higher computational cost as compared with our developed rigid method. In each iteration, the ICP algorithm is convex and has a close-form solution. However, the closed points of the fixed and the moving images are not always the true corresponding pairs, and the performance of the ICP algorithm heavily depends on the model initialization.² The nonrigid Demons algorithm typically assumes that the intensity functions of the fixed and moving images are continuous in space, and the intensity and inside lung structures of the moving images are nearly the same as that of the fixed images, but these assumptions are usually not true especially in the cases with severe lung diseases. Hence it is an extremely challenging task to assure the convergence to the global optimal solution for a nonrigid model. Therefore, we conclude in this study that the rigid registration scheme is preferred for the registration of pulmonary nodules depicted

TABLE IV. Summarization of available pulmonary nodule registration schemes and their performances.

Studies	Section thickness (mm)	Time gap (month)	Patient number	Methodology	Average error (mm)
Betke <i>et al.</i> ²	1.25–5	3 (1–7)	10	Rigid: LSR	8.0
Shi <i>et al.</i> ³	1.25	>2	20	Rigid: rib alignment	9.7
Hong <i>et al.</i> ⁴	2–8	–	10	Rigid: ICP	5.6 voxel
Blaffert and Wiemker ¹¹	1.0	–	6	Rigid: intensity correlation	4.2
				Nonrigid: B-spline	5.1
Our method	2.5 (0.625–5)	22 (4–68)	60	Rigid: surf-volume distance	9.6
				Nonrigid: Demons algorithm	10.0

on follow-up examinations due to its reasonable efficiency and accuracy as compared with the nonrigid ones. Actually, this study further verified the conclusion reached by Blaffert and Wiemker¹¹ in their study. However, they tested their method on only ten examinations acquired on six patients. In particular, although the Demons algorithm has been successfully applied to a number of nonrigid registration problems, it does not necessarily mean that the Demons algorithm for the nonrigid registration would definitely has a better performance than that for the rigid registration in the follow-up nodule registration. Whereas the nonrigid models can describe much more flexible deformation, the optimization might stop far from the optimal solution, because the Demons algorithm heavily depends on the local gradient information. This may explain why an affine registration is typically used as an initialization procedure for the nonrigid models in 4D-CT registration.²⁰ The nonrigid model may work well only if they can robustly avoid being trapped in local minima.

We recognized that there were limitations with this study. First, we assumed that the human lungs depicted on CT examinations were rigid bodies and their postures did not vary significantly. The motivation of this assumption is to simplify the optimization problem as a single rotation optimization and thus significantly improve the efficiency. We are aware that this assumption is not true in a strict sense, but our experiments showed that this approximation/simplification resulted in a comparable accuracy and a relatively high efficiency in regard to other available schemes. In this study, 56 of the 60 cases changed less than 20% (mean = 7.7%) in volume and the average registration error for these cases was 8.3 mm. Betke *et al.*² reported that the change in lung volume was 8.1% on average based on ten pairs of clinical examinations. Hong *et al.*⁵ reported that the change in lung volume was 6.5% on average based on 20 pairs of examinations. We note that when the lung shapes from two examinations have very large variations, this method may result in a large error for pulmonary nodule registration (the example in Fig. 6). Second, in this study, since the objection function [Eq. (6)] is not convex, our method may not theoretically avoid a local minima. To the best of our knowledge, there is no registration model available nowadays that is theoretically convex in nature. Our effort here is to use $d(R(\theta, c) \circ S_m, V_f)$ to approximate the monotone distance function $d(R(\theta, c) \circ S_f, V_f)$ in order to largely reduce the possibility of being trapped in a local minima. In addition, the step size ε in Eq. (7) can be properly set to reduce the possibility of being trapped in a local minima. When ε is small, it is relatively easy to be trapped in a local minima; when ε is large, there may be a large registration error. In this study, we empirically set $\varepsilon = 0.005$ with consideration of the specific application. Third, we have to note that the parameters for the Demons algorithm may not be optimal for the longitudinal registration study here because the Demons algorithm heavily depends on the local gradient information. The registration performance may be further improved, given the optimal parameters. Fourth, we only identified a single nodule for each of the 60 selected cancerous examinations for performance assessment,

albeit these examinations may contain multiple nodules. Whereas these identified nodules worked as the landmarks for a “rigid” lung volume, we believe that they may reflect the accuracy of registration scheme for other nodules as well.

V. CONCLUSIONS

We have developed a simple rigid affine registration for efficiently matching the lung nodules depicted on different examinations. The affine transformation was divided into four independent transformations and only three rotation parameters were optimized for efficiency purpose. A nonrigid registration model, namely the Demons algorithm, was implemented to refine the initial affine registration. The experiment results of nodule registration on 60 pairs of lung CT examinations showed that the proposed rigid affine registration yielded an average error of 9.6 mm in Euclidean distance with an average computational cost of 5 s in time, while the refining nonrigid Demons algorithm had an average error of 10.0 mm in Euclidean distance with an average computational cost of 55 s in time. Considering the characteristics of pulmonary nodule registration and its real-time requirement in clinical practice, we conclude that rigid affine solution may be preferred due to its obvious computational efficiency and reasonable accuracy.

ACKNOWLEDGMENTS

This work was supported in part by grants R01 HL096613, P50 CA090440 (the University of Pittsburgh Lung Cancer SPORE), and P50 HL084948 from National Institutes of Health, to the University of Pittsburgh and the SPORE in Lung Cancer Career Development Program.

^aAuthor to whom correspondence should be addressed. Electronic mail: puj@upmc.edu; Telephone: (412)-641-2571; Fax: (412)-641-2582.

¹F. Girvin and J. P. Ko, “Pulmonary nodules: Detection, assessment, and CAD,” *Am. J. Roentgenol.* **191**, 1057–1069 (2008).

²M. Betke, H. Hong, D. Thomas, C. Prince, and J. P. Ko, “Landmark detection in the chest and registration of lung surfaces with an application to nodule registration,” *Med. Image Anal.* **7**, 265–281 (2003).

³J. Shi, B. Sahiner, H. P. Chan, L. Hadjiiski, C. Zhou, P. N. Cascade, N. Bogot, E. A. Kazerooni, Y. Wu, and J. Wei, “Pulmonary nodule registration in serial CT scans based on rib anatomy and nodule template matching,” *Med. Phys.* **34**, 1336–1347 (2007).

⁴H. Hong, J. Lee, Y. Yim, and Y. G. Shin, “Automatic segmentation and registration of lung surfaces in temporal chest CT scans,” J. S. Marques *et al.* (Eds.): IbPRIA 2005, LNCS **3523**, 463–470 (2005).

⁵H. Hong, J. Lee, and Y. Yim, “Automatic lung nodule matching on sequential CT images,” *Comput. Biol. Med.* **38**, 623–634 (2008).

⁶J. P. Thirion, “Image matching as a diffusion process: An analogy with Maxwell’s demons,” *Med. Image Anal.* **2**(3), 243–260 (1998).

⁷R. Szeliski and J. Coughlan, “Spline-based image registration,” *Tech. Rep.* **94**(1), 94 (1994).

⁸H. Wang, L. Dong, J. O’Daniel, R. Mohan, A. S. Garden, K. K. Ang, D. A. Kuban, M. Bonnen, J. Y. Chang, and R. Cheung, “Validation of an accelerated demons algorithm for deformable image registration in radiation therapy,” *Phys. Med. Biol.* **50**, 887–905 (2005).

⁹Y. Yin, E. A. Hoffman, and C. L. Lin, “Mass preserving nonrigid registration of CT lung images using cubic B-spline,” *Med. Phys.* **36**(9), 4213–4222 (2009).

¹⁰K. Cao, G. E. Christensen, K. Ding, and J. M. Reinhardt, “Intensity-and-landmark-driven, inverse consistent, B-spline registration and analysis for lung imagery,” *Proceedings of the 12th International Conference on*

- Medical Imaging Computing and Computer-Assisted Intervention (MICCAI)* (2009), pp. 137–148.
- ¹¹T. Blaffert and R. Wiemker, “Comparison of different follow-up lung registration methods with and without segmentation,” *Proc. SPIE* **5370** 1701–1708 (2004).
 - ¹²Y. Zheng, K. Steiner, T. Bauer, J. Yu, and D. Shen, “Lung nodule growth analysis from 3D CT data with a coupled segmentation and registration framework,” *ICCV*, 1–8 (2007).
 - ¹³S. G. Armato III, M. I. Giger, C. J. Moran, J. T. Blackburn, K. Doi, and H. MacMabon, “Computerized detection of pulmonary nodules on CT scans,” *Radiographics* **19**, 1303–1311 (1999).
 - ¹⁴G. Borgefors, “Distance transformations in digital images,” *Comput. Vis. Graph. Image Process.* **34**(3), 344–371 (1986).
 - ¹⁵B. Fang, W. Hsu, and M. L. Lee, “Techniques for temporal registration of retinal images,” *Proceedings of the International Conference on Image Processing (ICIP)* (IEEE, Singapore, 2004), pp. 1089–1092.
 - ¹⁶I. Sobel and G. Feldman, “A 3×3 isotropic gradient operator for image processing,” talk presented at the Stanford Artificial Project (1968).
 - ¹⁷D. O. Wilson, J. L. Weissfeld, C. R. Fuhrman, S. N. Fisher, P. Balogh, R. J. Landreneau, J. D. Luketich, and J. M. Siegfried, “The Pittsburgh Lung Screening Study (PLuSS). Outcomes within 3 years of a first computed tomography scan,” *Am. J. Respir. Crit. Care Med.* **178**, 956–961 (2008).
 - ¹⁸J. Pu *et al.*, “Shape break-and-repair strategy and its application to computerized medical image segmentation,” *IEEE Trans. Vis. Comput. Graph.* **17**(1), 115–124 (2011).
 - ¹⁹T. Netsch, P. Rsch, A. van Muiswinkel, and J. Weese, “Towards real-time multi-modality 3D medical image registration,” *Proceedings of the Eighth International Conference on Computer Vision* (Vancouver, BC, 2001), Vol. **1**, pp. 718–725.
 - ²⁰Y. Yim, H. Hong, and Y. G. Shin, “Deformable lung registration between exhale and inhale CT scans using active cells in a combined gradient force approach,” *Med. Phys.* **37**(8), 4307–4317 (2010).
 - ²¹E. Rietzel and G. T. Y. Chen, “Deformable registration of 4D computed tomography data,” *Med. Phys.* **33**(11), 4423–4430 (2006).
 - ²²R. Kashani, M. Hub, J. M. Balte, M. L. Kessler, L. Dong, L. Zhang, L. Xing, Y. Xie, D. Hawkes, J. A. Schnabel, J. McClelland, S. Joshi, Q. Chen, and W. Lu, “Objective assessment of deformable image registration in radiotherapy: A multi-institution study,” *Med. Phys.* **35**(12), 5944–5953 (2008).
 - ²³K. K. Brock, “Results of a multi-institution deformable registration accuracy study (MIDRAS),” *Int. J. Radiat. Oncol. Biol. Phys.* **76**(2), 583–596 (2010).