Towards Local Estimation of Emphysema Progression Using Image Registration

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ABSTRACT

Progression measurement of emphysema is required to evaluate the health condition of a patient and the effect of drugs. To locally estimate progression we use image registration, which allows for volume correction using the determinant of the Jacobian of the transformation. We introduce an adaptation of the so-called sponge model that circumvents its constant-mass assumption. Preliminary results from CT scans of a lung phantom and from CT data sets of three patients suggest that image registration may be a suitable method to locally estimate emphysema progression.

Keywords: Emphysema, image registration, disease progression measurement, sponge model, local slope model

Category: registration.

1. INTRODUCTION

Lung densitometry on chest CT images can be used as a surrogate for measuring the destruction of lung tissue in emphysema.[1] While methods to perform global quantification of lung density exist,[1] local quantification is less well studied. Emphysema can be quantified globally by computing density estimators on the lungs. Examples of these estimators are the average density of the lung, the p-th percentile point (Perc, the Hounsfield Unit (HU) at which p percent of the lung voxels have a lower value, e.g. Perc15) or relative area (RA, the percentage of lung voxels below a certain HU, e.g. RA-910) of the cumulative histogram. Comparison of the estimators between two follow-ups can be used to evaluate disease progression. Information about the location of emphysema progression may help in assessing the efficacy of drugs that are developed to treat this disease.[2] For example, with global quantification a treatment effect could go unnoticed when a drug protects the healthy part of the lungs, while the affected part cannot be saved. Therefore, localisation of density changes is required.

The major challenge for proper estimation of emphysema progression using CT is the large influence of the inspiration level on lung density, compared to the influence of emphysema. Since emphysema is a slowly progressive disorder, visual inspection of CT scans can only indicate progression in severe cases or after many years.

A possible strategy to locally estimate changes in density is to segment regions of the lung, such as lung lobes or lung segments. The density estimators can subsequently be computed per region. To obtain a more and more local analysis, increasingly smaller objects have to be identified, and the corresponding region in the follow-up scan has to be found. In this paper, we do not pursue this research direction, but instead rely on image registration to establish local correspondence between follow-up chest CT scans. This in principle enables computation of disease progression on a per-voxel basis, given sufficient quality of the registration method and a good model for the relation between density and inspiration level of the lung.

In this paper we introduce a method to evaluate local emphysema progression. This method is based on the assumption that the lung behaves as a sponge. We modified the sponge model to allow for a more flexible relation between lung volume and density.

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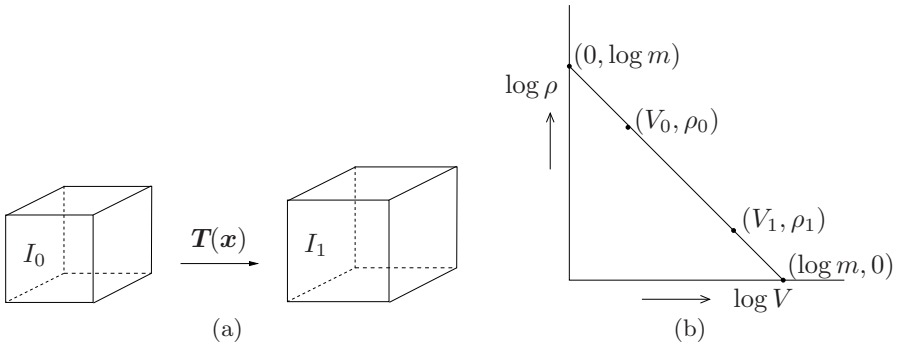


Figure 1: (a) Corresponding parts of the lung at time t_0 and t_1, related by the transformation $\boldsymbol{T}$. The larger volume at t_1 illustrates deeper inhalation. The sponge model assumes constant mass, so $m_0 = V_0\rho_0 = V_1\rho_1 = m_1$. (b) The relation between density and volume, see Equation (1), in a log-log plot, where $m = m_0 = m_1$. The slope of the line is given by $s = \frac{\log \rho_0 - \log \rho_1}{\log V_0 - \log V_0} = \frac{\log m - 0}{0 - \log m} = -1$.

2. METHODS

Our goal is to estimate emphysema progression between two time points, t_0 and t_1, given one or more CT scans for each time point. The basic relation between mass m and volume V is given by $m = V\rho$, where ρ denotes density, which can be rewritten to:

$$\log \rho = \log m - \log V. \tag{1}$$

For CT images, the density is related to the Hounsfield Unit by $\rho = \text{HU} + 1000$. The volumes of the lungs are related by: $V_1 = V_0 \det J_{\boldsymbol{T}}$, where V_t are the lung volumes at time $t \in \{0, 1\}$, $\boldsymbol{T}$ the spatial transformation relating the two lungs, and $\det J_{\boldsymbol{T}}$ the determinant of the Jacobian of this transformation.

2.1 Lung Model: Sponge

The sponge model of the lung assumes mass preservation over time and over the lung breathing cycle: $m_1 = m_0$, so $\rho_1 = \rho_0 V_0 / V_1$ (where the subscript denotes the time instance), or $\tilde{I}_1(\boldsymbol{T}(\boldsymbol{x})) + 1000 = (\tilde{I}_0(\boldsymbol{x}) + 1000)[\det J_{\boldsymbol{T}}(\boldsymbol{x})]^{-1}$, where $\tilde{I}_t$ are the CT scans at time point t. We introduce the notation $I_t(\boldsymbol{x}) = \tilde{I}_t(\boldsymbol{x}) + 1000$ and arrive at:

$$I_1(\boldsymbol{T}(\boldsymbol{x})) = I_0(\boldsymbol{x})[\det J_{\boldsymbol{T}}(\boldsymbol{x})]^{-1}. \tag{2}$$

The sponge model is illustrated in Figure 1.

2.2 Lung Model: Local Slope

In the sponge model we assumed mass preservation over time and over the breathing cycle. We know, however, that this assumption is not correct, due to variability in lung blood perfusion during breathing and CT scanner effects. This changes the measured mass of the lungs. Experimental results [3, Figure 2B and 3B] suggest to adapt the sponge model, such that the slope is not fixed to -1. The model is adapted to: $\rho_1 = \rho_0 (V_1/V_0)^s$, which can be expressed in terms of the CT images:

$$I_1(\boldsymbol{T}(\boldsymbol{x})) = I_0(\boldsymbol{x})[\det J_{\boldsymbol{T}}(\boldsymbol{x})]^{s(\boldsymbol{x})}. \tag{3}$$

A slope of $s = -1$ corresponds to the sponge model. For $s > -1$ the adapted model states that when inhaling ($V_1 > V_0$), the density decreases with a rate below the sponge model, and vice versa. In other words, when inhaling, for $s > -1$, the density decreases less than can be contributed to the increase in volume, so mass is entering the lungs.

The slope parameter s enables a more realistic model, but requires setting to a proper value. When available, CT scans taken at different inspiration levels, but at the same point in time, can be used to estimate the slope

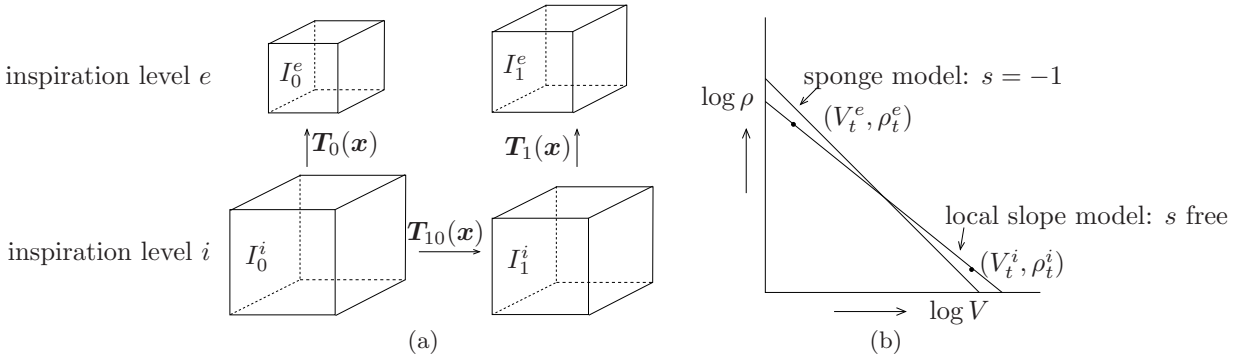


Figure 2: (a) For each point in time, we have two CT scans available: a scan at inspiration level e: I_t^e and a scan at inspiration level i: I_t^i. Scans are related by the transformations $\boldsymbol{T}_0(\boldsymbol{x})$, $\boldsymbol{T}_1(\boldsymbol{x})$ and $\boldsymbol{T}_{10}(\boldsymbol{x})$. (b) The relation between density and volume in a log-log plot for time point t, with slope s possibly different from -1 and dependent on the spatial location.

s locally, see Figure 2. At the same time point we can assume no change in emphysema, so all effects are not related to disease.

The slope is estimated from the CT scans at time t_0 at position $\boldsymbol{x}$ as follows:

$$s_0(\boldsymbol{x}) = \frac{\log \rho_0^e - \log \rho_0^i}{\log V_0^e - \log V_0^i} = \frac{\log I_0^e(\boldsymbol{T}_0(\boldsymbol{x})) - \log I_0^i(\boldsymbol{x})}{\log \det J_{\boldsymbol{T}_0}(\boldsymbol{x})}. \tag{4}$$

Estimating the slope $s_1(\boldsymbol{y})$ based on the scans at time t_1 is also possible. In that case the transformation $\boldsymbol{T}_{10}(\boldsymbol{x})$ needs to be applied to $s_1(\boldsymbol{y})$, to obtain the slope in the domain of I_0^i, so a resampling step is required. When comparing two groups of patients who did and did not receive a drug it is preferable to estimate the slope at time t_0 to avoid introducing a bias in the analysis when a drug changes the slope over time.

2.3 Progression Estimation

A naive measure of emphysema progression would simply subtract the matched images: $I_1^i(\boldsymbol{T}_{10}(\boldsymbol{x})) - I_0^i(\boldsymbol{x})$ (*subtraction* method). However, this would neglect changes in volume due to inspiration, which influence density. Therefore, we perform volume correction using $\det J_{\boldsymbol{T}_{10}}$, and arrive at:

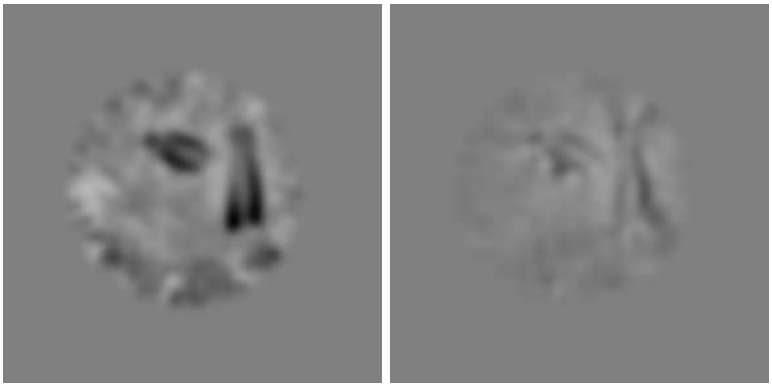
$$\text{progression}(\boldsymbol{x}) = I_1^i(\boldsymbol{T}(\boldsymbol{x})) - I_0^i(\boldsymbol{x})[\det J_{\boldsymbol{T}_{10}}(\boldsymbol{x})]^{s(\boldsymbol{x})}, \tag{5}$$

where $s(\boldsymbol{x}) = -1$ for the *sponge* method, and $s(\boldsymbol{x})$ as estimated with Equation (4) for the *local slope* method. A "progression measure" equal to zero indicates no progression, and > 0 (< 0) indicates less (more) emphysema.

The progression images obtained with Equation (5) are post-processed with an intensity windowing ($[-500, 500]$) and a Gaussian smoothing ($\sigma = 2$ voxels), to reduce artifacts from inaccurate registration near vessels.

2.4 Image Registration

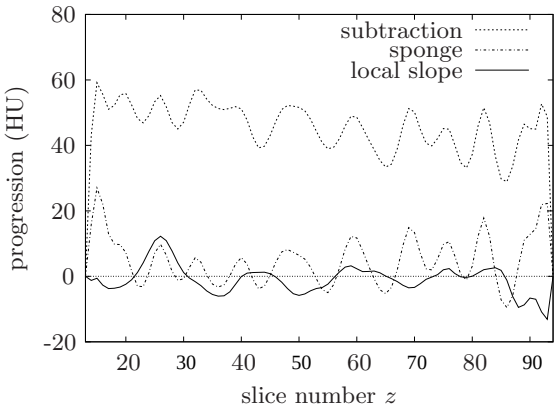
The transformations are estimated using nonrigid intensity-based image registration, using the software package `elastix` (`http://elastix.isi.uu.nl`). To obtain a course alignment an affine registration was performed prior to nonrigid registration. The nonrigid transformation was modelled by B-splines.[4] Normalised Correlation (NC) was used as a similarity measure. A multi-resolution approach for both the images and the transformation was used, with a Gaussian image pyramid and a final B-spline grid spacing of $10\times10\times10$ mm. A stochastic gradient descent method[5] was used for optimisation. The step size a_k was chosen as a decaying function of the iteration number k: $a_k = a/(A+k)^\alpha$, with $a > 0$, $A \geq 1$ and $0 < \alpha \leq 1$ user-defined constants. $A = 50$ and $\alpha = 0.6$ in this paper as suggested by Klein *et al.*[5] Masks obtained from Pulmo software (Medis Specials, Leiden, The Netherlands) are used to focus the registration on the lungs. For the clinical application lung masks are generated by means of a standard region growing algorithm based on Zagers *et al.*,[6] described in more detail by Stoel *et al.*[7]



(a) sponge model (b) local slope model

Figure 3: Phantom data. Examples of slices of the progression images for two models. The artifact from the tubes is not due to a misregistration, but related to differences in HU between V_0 and V_1. The artifact is reduced when taking the local slope into account.

(a) lung phantom



	subtraction	sponge	local slope
all	46.0 ± 6.8	4.9 ± 7.4	-0.9 ± 4.4
range	45.5 ± 6.9	3.1 ± 5.8	-0.2 ± 4.0

Figure 4: The plot (top right) shows the progression measure (Equation (5)) averaged over a CT slice. The table (lower right) shows the progression measure averaged over the entire lung (average ± standard deviation). 'all' refers to the average taken over all slices within the lung; 'range' skips the first and last 5 slices, since they contain artifacts due to misregistration.

3. EXPERIMENTS AND PRELIMINARY RESULTS

3.1 Phantom Experiment

A phantom mimicking the lung was constructed previously,[8] see Figure 4(a). It consists of a cylinder filled with material with density approximately equal to lung density, and with tubes that mimic the airways. Volume is adjusted by moving a piston inside the cylinder, while mass is retained. The phantom was scanned at several volumes. Since the mass did not change between scans, the progression measure (5) should be zero everywhere. The CT scan was reconstructed at a 512 by 512 matrix with an in-plane resolution of 0.488 mm by 0.488 mm. Each scan contained $\approx$ 100 slices, which were 5.0 mm thick, with 2.5 mm increment, according to a standard protocol optimised for lung densitometry.[7]

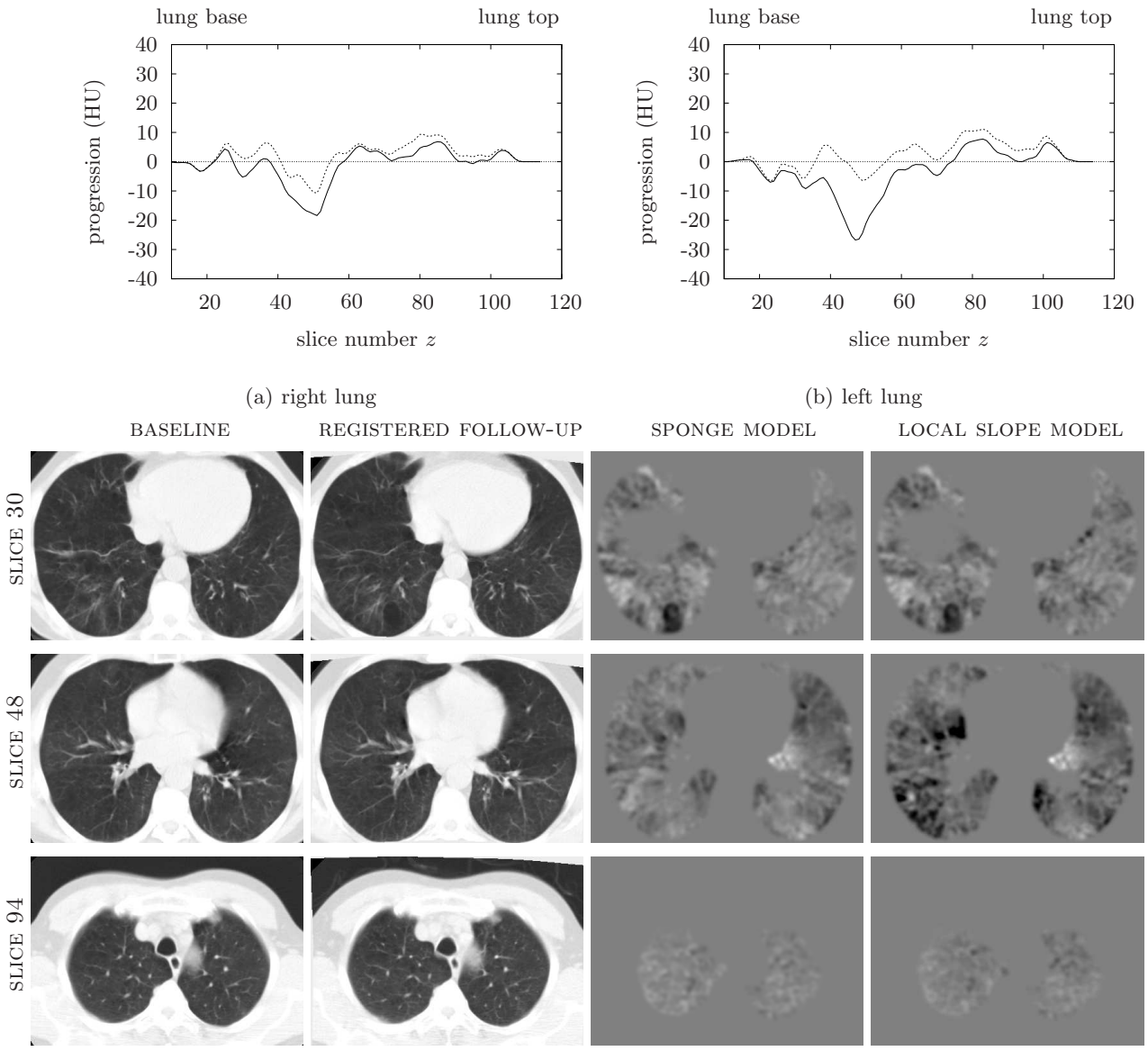


Figure 5: Patient 1. Plot (a) and (b) show the average progression per CT slice for the sponge model (dotted line) and the local slope model (solid line). The images show slices from the CT scans (two leftmost columns) and the computed progression images (two rightmost columns).

The phantom at a low volume $V_0 = 1.128\,\mathrm{l}$ was registered to a high volume $V_1 = 1.402\,\mathrm{l}$. Four resolution levels were used during registration; for each level 1000 iterations were set. a was set to 10000.

The slope was measured using a third scan with the phantom at a volume $V_2 = 1.401\,\mathrm{l}$. After registration the three measures of progression were computed. The results are given in Figure 3 and 4. When no volume correction is applied, the progression measure is larger than zero, since $V_1 > V_0$. As presented in Figure 4 both the sponge method and the local slope method show a progression around zero, as desired. The latter method has the lowest standard deviation.

3.2 CT Patient Data

The methods are applied on CT data sets of three patients suffering from pulmonary emphysema due to a $\alpha(1)$-antitrypsin deficiency.[1] Two scans acquired at different inspiration level were available for each of the two time

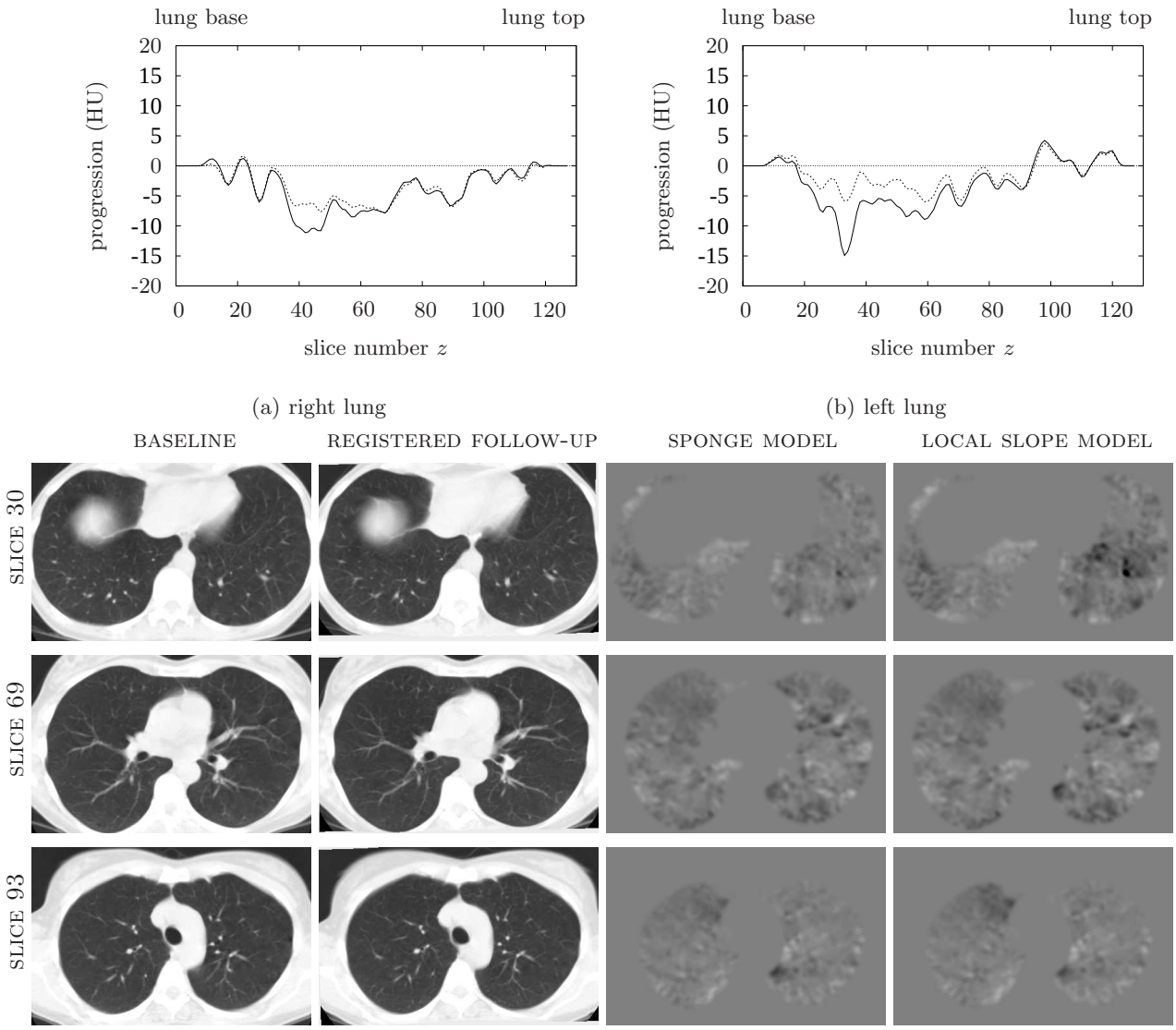


Figure 6: Patient 2. Plot (a) and (b) show the average progression per CT slice for the sponge model (dotted line) and the local slope model (solid line). The images show slices from the CT scans (two leftmost columns) and the computed progression images (two rightmost columns).

points: baseline and follow-up after 2.5 years. The CT scans were reconstructed at a 512 by 512 matrix with an in-plane resolution of around 0.7 mm by 0.7 mm. Each scan contained ≈ 140 slices, which were 5.0 mm thick, with 2.5 mm increment.

The scans were visually graded by a pulmonologist. The second baseline scan was compared to the follow-up closest in lung volume. This minimised the effect of volume differences on the assessment of the pulmonologist. The pulmonologist only had access to the original CT scans and not to the results of the automatic methods. For the first patient he assessed a slight increase in emphysema at the bottom of each lung and no change at the top. For the second patient he reported minimal progression of emphysema at the bottom half of both lungs and no change at the top. For the third patient he rated severe progression at the top of the right lung, while emphysema was unchanged elsewhere.

The follow-up scan was registered nonrigidly to baseline. Additionally, for the local slope estimation the two scans at follow-up were registered. The follow-up scans were chosen since these scans had a larger lung volume

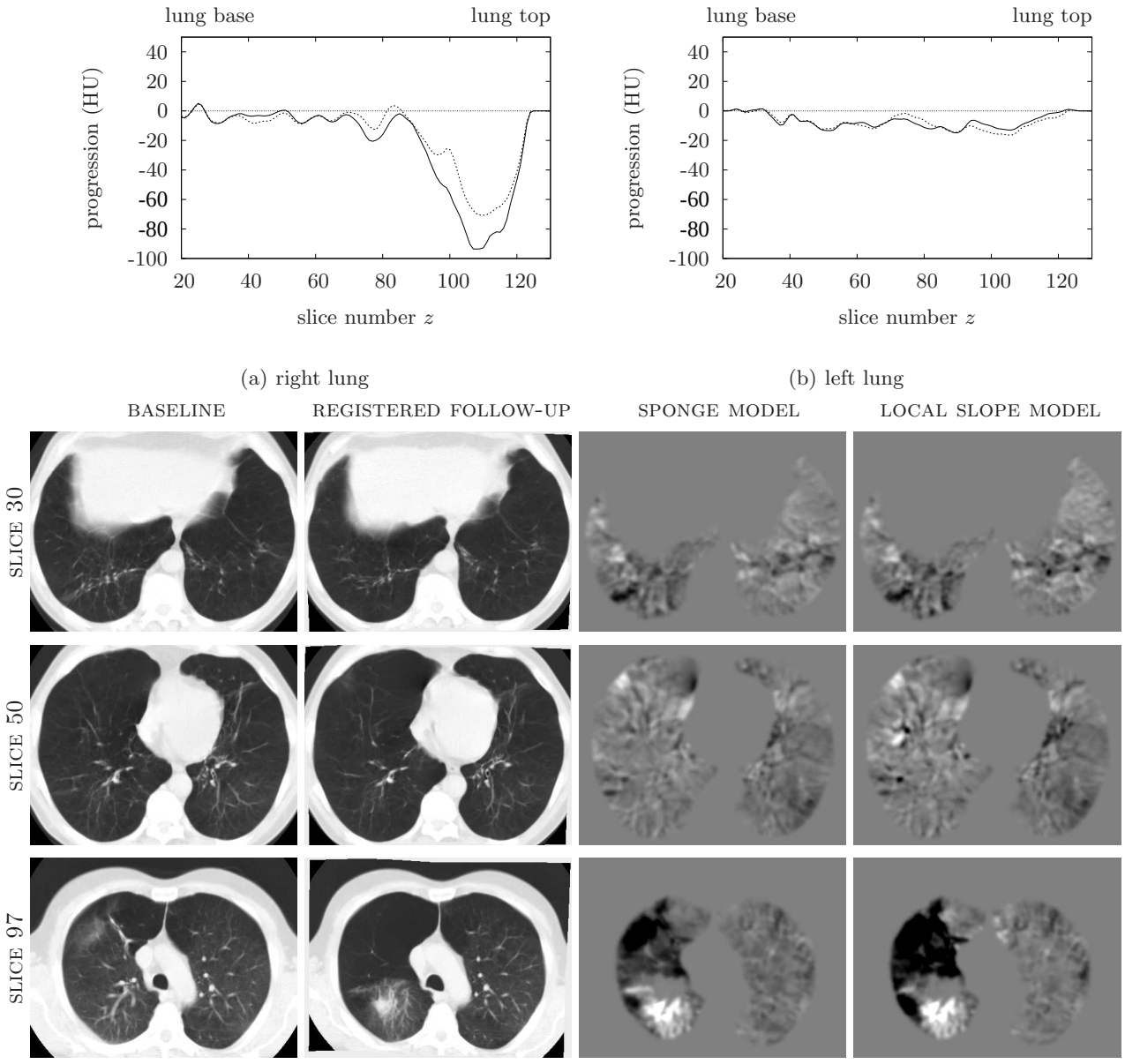


Figure 7: Patient 3. Plot (a) and (b) show the average progression per CT slice for the sponge model (dotted line) and the local slope model (solid line). The images show slices from the CT scans (two leftmost columns) and the computed progression images (two rightmost columns).

difference, which enables for a more accurate estimation of the slope, see Figure 2b: noise has less influence when the two points (V_t^e, ρ_t^e) and (V_t^i, ρ_t^i) are further apart. Five resolution levels were used during registration; for each level 1000 iterations were set. a was set to 100000, 50000, 30000, 10000 and 10000 for the five resolutions, respectively. A localised version of normalised correlation was employed, similar to the Local Mutual Information measure proposed by Klein *et al.*.[9] A cubic random sample region of $50 \times 50 \times 50$ mm was used for localisation. An affine registration using NC was performed prior to nonrigid registration for initialisation.

Figures 5 - 7 show the results of the automated methods. For patient 1 the plots of Figure 5 do not show progression of emphysema for the sponge model, and to some extent for the local slope model at the bottom of the lungs. This is due to the averaging over the entire CT slice. Closer inspection of the data reveals that progression

is very local for this patient, and is detectable from the progression images for both lung models. The bottom three rows of Figure 5 show three slices from the CT scans. From left to right: the baseline scan, the registered follow-up scan, the progression image according to the sponge model, and the progression image according to the local slope model. The first two slices are taken near the lung base and do show local progression; the last slice is taken near the lung top and does not show progression. For patient 2, see Figure 6, both lung models showed some progression, especially at the bottom half of the lung. For patient 3, see Figure 7, the left lung showed no progression by both methods. The right lung showed progression at the lung top. This corresponded with the assessment by the pulmonologist for all three patients.

4. CONCLUSIONS

The results of the phantom data show that volume correction is needed to evaluate changes in emphysema. The expected absence of mass changes in the phantom was correctly approximated by both methods that take volume correction into account. Visual inspection of progression of emphysema in three patients was not different from the results of the automated methods. Compared to previous methodology[1] the methods additionally offer local assessment. Moreover, the proposed methods are potentially more sensitive, since small localised changes cannot be found by global tools.

The sponge model does take changes in lung volume into account to estimate progression. There are other factors, however, influencing the measured lung density, such as changes in lung mass due to changes in blood perfusion, or CT scanner related differences between scans.[7] The local slope method offers additional flexibility compared to the sponge model to also take these factors into account when computing progression. Since we currently have no tools to distinguish between patient and scanner related influences, the best we can do is to handle them as one aggregated source of error. The slices from the progression images in Figure 3, illustrate that the local slope method can compensate for differences in tube appearance between scans, while the sponge model cannot.

The correct estimation of emphysema progression critically depends on the accuracy of the registration method. Mismatches around vessels could be corrected by inclusion of a vessel enhancement[10] step in the registration framework. Since the computation of Equation (5) involves the Jacobian of the transformation, the smoothness of transformation may need to be controlled by adding a bending energy penalty term to the registration cost function.[4]

Another important aspect of the proposed approach is the lung model. We have evaluated it using a phantom mimicking the lung. In the current setup only volume is changeable. An interesting improvement over this setup is to additionally adjust the mass within the phantom, preferably also locally. This way we would be able to assess if the proposed method is able to correctly predict changes in density.

Additionally, we want to evaluate the proposed methods on a large set of clinical data.[1] The challenge will be to find a reasonable standard of reference, given the inability of a human eye to perceive subtle differences in brightness between isolated areas. Correlation with lung function parameters, such as Forced Expiratory Volume in one second (FEV_1), can only evaluate the progression measures globally and not locally.

In conclusion, we proposed a method to locally estimate possibly subtle differences in lung density based on the registration of follow-up chest CT scans and postprocessing.

5. NEW OR BREAKTHROUGH WORK

This work is not submitted for publication or presentation elsewhere. The new work includes the local volume correction step, and the extension to the local slope model.

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