Published in final edited form as:

Phys Med Biol. 2016 November 21; 61(22): 7864–7880. doi:10.1088/0031-9155/61/22/7864.

Automated segmentation of liver and liver cysts from bounded abdominal MR images in patients with autosomal dominant polycystic kidney disease

Youngwoo Kim¹, Sonu K. Bae¹, Tianming Cheng¹, Cheng Tao¹, Yinghui Ge¹, Arlene B. Chapman², Vincente E. Torres³, Alan S. L. Yu⁴, Michal Mrug⁵, William M. Bennett⁶, Michael F. Flessner⁷, Doug P. Landsittel⁸, and Kyongtae T. Bae^{1,†}

¹Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

²Department of Internal Medicine, Emory University School of Medicine, Atlanta, GA 30307, USA

³Department of Internal Medicine, Mayo College of Medicine, Rochester, MN 55905, USA

⁴Department of Internal Medicine, Kansas University Medical Center, Kansas City, KS 66160, USA

⁵Division of Nephrology, University of Alabama, Birmingham, AL 35487, USA

⁶Legacy Good Samaritan Hospital, Portland, OR 97210, USA

⁷National Institute of Diabetes and Digestive and Kidney Disease, National Institute of Health, Bethesda, MD 20892, USA

⁸Department of Internal Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Abstract

Liver and liver cyst volume measurements are important quantitative imaging biomarkers for assessment of disease progression in autosomal dominant polycystic kidney disease (ADPKD) and polycystic liver disease (PLD). To date, no study has presented automated segmentation and volumetric computation of liver and liver cysts in these populations. In this paper, we proposed an automated segmentation framework for liver and liver cysts from bounded abdominal MR images in patients with ADPKD. To model the shape and variations in ADPKD livers, the spatial prior probability map (SPPM) of liver location and the tissue prior probability maps (TPPMs) of liver parenchymal tissue intensity and cyst morphology were generated. Formulated within a three-dimensional level set framework, the TPPMs successfully captured liver parenchymal tissues and cysts, while the SPPM globally constrained the initial surfaces of the liver into the desired boundary. Liver cysts were extracted by combined operations of the TPPMs, thresholding, and false positive reduction based on spatial prior knowledge of kidney cysts and distance map. With cross-validation for the liver segmentation, the agreement between the radiology expert and the proposed method was 84% for shape congruence and 91% for volume measurement assessed by

[†]Present address: Department of Radiology, University of Pittsburgh School of Medicine, 3362 Fifth Avenue, Pittsburgh, PA 15213, USA

the intra-class correlation coefficient (ICC). For the liver cyst segmentation, the agreement between the reference method and the proposed method was ICC=0.91 for cyst volumes and ICC=0.94 for % cyst-to-liver volume.

Keywords

autosomal dominant kidney disease; polycystic liver disease; image segmentation; prior probability map; level set

1. Introduction

Quantitative imaging plays a crucial role for monitoring disease progression, clinical management, and targeted therapeutic trials in a number of pathologies including autosomal dominant polycystic kidney disease (ADPKD) (Bae and Grantham 2010). In particular, liver volume measured from MR images is an important imaging biomarker for the assessment of ADPKD progression (Hogan *et al* 2015, Chapman *et al* 2003, Grantham *et al* 2006). Polycystic liver disease (PLD), characterized by multiple liver cysts, occurs in patients with autosomal-dominant polycystic liver disease as well as in the vast majority of patients with ADPKD (Bae *et al* 2006). With the progression of PLD, expansion of liver cysts and an enlarged liver compress the adjacent organs, including the heart, kidneys, and spleen as well as the diaphragm, gastrointestinal tract, and vascular system. This compressive mass effect and ensuing complications may lead some patients to experience chronic debilitating conditions and be predisposed to a severely impaired quality of life. The current treatment interventions include cyst aspiration or fenestration, liver resection, and, in extreme cases, liver or combined liver-kidney transplantation (Hogan *et al* 2015).

The volumes of the liver and liver cysts are important disease biomarkers for the assessment of the severity of PLD (Hogan *et al* 2015). In typical clinical settings, liver volume from CT or MR are measured manually by a trained expert who must delineate the liver border on each image of the abdominal CT or MR; and while the segmentation and volume measurement of the liver by this manual method is straightforward, it is also laborious and time-consuming. To overcome some of the limitations of the manual method, a number of semi-automated (Afifi and Nakaguchi 2012, Beichel *et al* 2012, Peng *et al* 2015, Peng *et al* 2014b, Peng *et al* 2014a) or automated (Ruskó *et al* 2009, Zhang *et al* 2012b, Huynh *et al* 2014, Masoumi *et al* 2012, López-Mir *et al* 2014) techniques have been proposed. The methods can be categorized into two main approaches: the shape prior-based approach (Zhang *et al* 2012b, Heimann *et al* 2006, Heimann *et al* 2007, Kainmüller *et al* 2007, Seghers *et al* 2007, Zhang *et al* 2010) or the atlas-based approach (Furukawa *et al* 2007, Ling *et al* 2008, Zhou *et al* 2005, Okada *et al* 2008, Slagmolen *et al* 2007, Park *et al* 2003). Both methods were applied to the segmentation of normal livers and/or livers with tumors but maintained the normal shape of the liver, since successful segmentation by the shape-prior method requires that the liver shape remains close to normal. Similarly, the atlas-based method requires the detection of well demarcated landmarks for initial rigid registration or alignment of the atlas. Because of this requirement, the atlas-based method was usually applied to contrast-enhanced or multi-phase CT images with conspicuous edge definition.

None of the previously published methods for automated segmentation of the liver appears adequate for the segmentation of PLD livers because the liver-specific shape and anatomical constraints required by these methods would not be applicable to PLD livers that are markedly heterogeneous in shape and anatomical variation. With the progression of disease, livers become more deformed by expansion of cysts in the liver and neighboring right kidney (Gabow *et al* 1990, Everson 1993, Chauveau *et al* 2000) (Figure 1). Thus, the segmentation of PLD livers in advanced disease is highly demanding even for expert radiologists. Moreover, the segmentation and volumetric measurement of liver cysts are even more time-consuming and technically challenging than that of the liver.

Incorporating a priori knowledge and statistics into segmentation schemes is an effective way of segmenting complex structures when structural and expert domain knowledge is available. A number of studies have utilized shapes of target objects as the prior knowledge combined with a geodesic active region model (Paragios and Deriche 2002), a level set (Gloger *et al* 2012), and dictionary learning (Zhang *et al* 2012a), while Kim *et al.* (Kim *et al* 2014) employed an intensity prior statistics formulated with level set framework. Furthermore, a recent study reported a fully-automated segmentation of kidneys from MR images in patients with ADPKD by exploiting prior knowledge of spatial location of kidneys modeled as spatial prior probability map (SPPM) and propagated shape constraints (PSC) that were incorporated into the level set framework (Kim *et al* 2016, Kline *et al* 2016). To date, however, no study has published an automated segmentation of livers and liver cysts in PLD.

Thus, the purpose of our study was to develop an automated method for segmenting the liver and liver cysts in PLD using MR images with the prior statistical information of liver location, intensity distribution of liver parenchyma, and morphology of liver cysts and to evaluate and compare its performance to the conventional, manual segmentation method.

2. Materials and methods

2.1. Database

The study was approved by the institutional review board and informed consent was obtained from all subjects. The study subjects consisted of 146 patients with ADPKD: 60 men and 86 women with the mean age of 43.4 ± 9.2 (SD) ranging from 25 to 58. As part of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study, the patients underwent MRI scanning of the abdomen from three different vendors (Siemens Medical Systems, Iselin, NJ, USA; General Electric Medical Systems, Milwaukee, WI, USA; and Philips Medical Systems, Best-Leiden, The Netherlands) at four institutions (Emory University, Institution 1; University of Kansas Medical Center, Institution 2; Mayo Clinic, Institution 3; and University of Alabama at Birmingham, Institution 4). The MR images were acquired at 1.5T MR scanners using coronal T_2 -weighted single shot fast spin echo (SSFSE) sequence with fat saturation. The MRI parameters were 4–9 mm slice thickness, 0.68–1.76 mm/pixel resolution, 90/170 ip angles, and 420–1582/81–102 ms repetition time/echo time. More details in MR parameters are described in Table 1. The slice thickness and pixel resolution varied because the subjects had a wide range of liver sizes that required the adjustment of slice thickness to minimize the number of breath-holds covering

the entire liver during MR image acquisition. The details of MRI protocol of the CRISP study are described in previous publications (Chapman et al. 2003, Grantham et al. 2006).

The acquired abdominal MR images were reviewed and evaluated by a radiologist to ensure the complete coverage of key organs and appropriate image quality with no serious artifacts. Incomplete coverage and degraded image quality would seriously compromise the accuracy of volumetric measurements. During the image review process, the radiologist determined the upper and lower borders of the bounding box that encompasses the whole liver and kidneys. Furthermore, to generate the reference standard datasets for training and validation, a radiologist reviewed and manually delineated the liver boundary slice-by-slice from the bounded abdominal MR images using commercially available software (Analyze 12.0; Mayo Clinic, Rochester, MN). Following the segmentation of the liver, the radiologist adjusted the intensity threshold in each image slice to obtain a binary image that separated the cysts (bright region) from the liver parenchyma (dark region). The volumes of cysts were computed from the product of the slice thickness and areas of the bright regions.

For cross-validation of our automated segmentation method, the 146 subjects were randomly selected and split evenly into two subsets: D_1 or D_2 . Initially, D_1 served as training set and D_2 served as the test set for the segmentation method and evaluation of the segmentation performance, respectively. Then, these two datasets were swapped— D_1 became the test set and D_2 the training set—and reanalyzed for cross-validation and data analysis.

2.2. Segmentation method and implementation

Our automated segmentation method was achieved in five steps (Figure 2): preprocessing, SPPM construction, tissue prior probability map (TPPM) construction, liver segmentation, and cyst extraction. The preprocessing step included a spatial normalization of MR images that were acquired at different spatial resolutions and the total variation (TV) regularization to reduce noise (Rudin *et al* 1992). The SPPM was constructed from the spatially normalized liver masks. The TPPMs were generated by combining two different probability profiles corresponding to two separate liver tissue components: the intensity prior probabilities for liver parenchyma and the shape prior probabilities for liver cysts. The SPPM and TPPMs were applied to two individual steps: the segmentation of the whole liver including the liver parenchyma and cysts; and the extraction of the cysts from the segmented liver using the shape prior probability map.

2.2.1. Preprocessing—As mentioned in section 2.1, the slice thickness and pixel resolution of MR images varied among subjects. To eliminate this variation, the MR image dataset of each subject was normalized and interpolated by using the MR acquisition pixel spacing and slice thickness information available in the Digital Imaging and Communications in Medicine (DICOM) header. The normalization process allowed MR volume datasets to be represented with the consistent volumetric resolution of 256(H) × 256(W) × 64(D) (Thévenaz *et al* 2000). The normalization factor of each dataset was saved and used to compute volumes of the liver and cysts at the original resolution after the completion of the segmentation process. In addition, TV regularization was applied to MR volume datasets to reduce noise while allowing for piecewise constant solutions to preserve

edges. The parameters used for the TV regularization process were 0.1 for the regularization and 100 for the iteration (Rudin et al. 1992).

2.2.2. Construction of spatial prior probability map—The objective of SPPM was to exploit the spatial information of the liver within the abdomen, in consideration of varying configurations, distributions, and sizes of polycystic livers. The SPPM was constructed using a set of liver masks that were segmented manually by the radiology expert and normalized in the preprocessing step. With the liver masks (m_{rad}), SPPM (p_{SPPM}) is expressed as the following formula,

$$p_{\text{SPPM}}(\mathbf{x}) = \frac{1}{N} \sum_{n=1}^N m_{\text{rad}}^n(\mathbf{x}). \quad (1)$$

In (1), $\mathbf{x} \in \mathbb{R}^3$ is the voxel location, n is the index of masks, and N is the total number of training sets. In Figure 3, the coronal mid cross-sectional SPPM and the 3D surface rendering are illustrated.

2.2.3. Generation of tissue prior probability maps—Polycystic liver consists of two tissue compositions: the liver parenchyma and cysts. Our segmentation scheme exploited this distinct tissue property to improve the segmentation efficiency. Two separate prior probability maps were generated using the complementary imaging features: the intensity map for the liver parenchyma and the shape map for the cysts.

The intensity prior probability map was constructed by analyzing the distribution of signal intensities in MR images. A typical signal intensity histogram of T_2 -weighted abdominal MRI (Figure 4a) contained four major peaks representing air (background), liver parenchymal tissue, intraperitoneal adipose tissue, and cyst. With the guide of the SPPM directed to the high probable regions of the liver, the pixel distribution of the liver parenchyma was determined. For the input MRI volume, the region corresponding to $p_{\text{SPPM}} > 0.5$ within the SPPM was determined from the intensity histogram (solid line in Figure 4b). From this region, a probability density function, p_{RMS} , was estimated on the basis of root mean square (RMS) as follows:

$$\sigma_{\text{RMS}} = \sqrt{\frac{\sum_{i=1}^{\mu} h(i)(i - \mu)^2}{\sum_{i=1}^{\mu} h(i)}}, \quad (2)$$

$$p_{\text{RMS}}(i) = \frac{1}{\sigma_{\text{RMS}} \sqrt{2\pi}} \exp \left\{ -\frac{(i - \mu)^2}{2\sigma_{\text{RMS}}^2} \right\}, \quad (3)$$

where $h(\cdot)$ is the histogram within SPPM region, i is the voxel intensity, and μ is the first peak of $h(\cdot)$. The estimated p_{RMS} is shown in Figure 4b as the dotted line fitted to the first

mode of $h(\cdot)$. With $f(\mathbf{x}) \in \mathbb{R}^3$ for the input MRI volume, the intensity prior probability map for liver parenchyma, p_{NPT} , was computed as follows,

$$p_{\text{NPT}}(\mathbf{x}) = p_{\text{RMS}}(f(\mathbf{x})). \quad (4)$$

The liver parenchyma represented by p_{NPT} is shown as the high signal intensity regions in Figure 5b.

Following the generation of the intensity prior probability map, the shape prior probability map was built on the basis of sphere-like shape characteristics of cysts. The difference of Gaussians (DoG), that approximates the Laplacian of Gaussian (LoG) filtering, was applied to determine circle- or sphere-like shapes (Lindeberg 2015). For the MR volumetric datasets, the DoG filter was implemented with the following formula,

$$\Gamma_{K\Sigma}(\mathbf{x}) = \frac{1}{(2\pi)^{3/2} K |\Sigma|^{-1/2}} \exp \left\{ -\frac{1}{2} (\mathbf{x})^T K \Sigma^{-1} (\mathbf{x}) \right\}. \quad (5)$$

In (5), Σ is the three dimensional covariance matrix of multivariate Gaussian kernel and $K \in \mathbb{R}$ is the scale parameter for Σ . With this filter, the shape prior probability map for cysts was constructed as follows:

$$p_{\text{CYST}}(\mathbf{x}) = f(\mathbf{x}) * \Gamma_{K_1\Sigma} - f(\mathbf{x}) * \Gamma_{K_2\Sigma}, \quad (6)$$

where $K_2 > K_1$. The cysts represented by p_{CYST} are shown as the high signal intensity regions in Figure 5c.

Finally, the liver and cyst prior probability maps were combined with the following formula,

$$p_{\text{COMB}}(\mathbf{x}) = \max(p_{\text{NPT}}(\mathbf{x}), p_{\text{CYST}}(\mathbf{x})), \quad (7)$$

where p_{NPT} and p_{CYST} were normalized ranging from 0 to 1 for each case.

2.2.4. Segmentation of liver with level set framework—The constructed three prior probability maps (i.e., p_{SPPM} , p_{NPT} , and p_{CYST}) were incorporated into the level set framework for optimization to determine the boundary of the liver from surrounding structures (Osher and Sethian 1988, Chan and Vese 2001). The total energy functional combined with the maps was defined as follows,

$$E(\phi(\mathbf{x}), \mu_{\text{in}}, \mu_{\text{out}}) = E_{\text{SPPM}}(\phi(\mathbf{x}), \mu_{\text{in}}, \mu_{\text{out}}) + E_{\text{COMB}}(\phi(\mathbf{x})), \quad (8)$$

$$E_{\text{SPPM}}(\phi(\mathbf{x})) = - \int_{\Omega} \ln p_{\text{SPPM}}(\mathbf{x}) H(\phi(\mathbf{x})) d\mathbf{x} - \int_{\Omega} \ln (1 - p_{\text{SPPM}}(\mathbf{x})) (1 - H(\phi(\mathbf{x}))) d\mathbf{x}, \quad (9)$$

$$E_{\text{COMB}}(\phi(\mathbf{x})) = \eta \int_{\Omega} |\nabla H(\phi(\mathbf{x}))| d\mathbf{x} + \lambda_1 \int_{\Omega} (p_{\text{COMB}}(\mathbf{x}) - \mu_{\text{in}})^2 H(\phi(\mathbf{x})) d\mathbf{x} \\ + \lambda_2 \int_{\Omega} (p_{\text{COMB}}(\mathbf{x}) - \mu_{\text{out}})^2 (1 - H(\phi(\mathbf{x}))) d\mathbf{x}, \quad (10)$$

$$\mu_{\text{in}} = \frac{\int_{\Omega} p_{\text{COMB}}(\mathbf{x}) H(\phi(\mathbf{x})) d\mathbf{x}}{\int_{\Omega} H(\phi(\mathbf{x})) d\mathbf{x}}, \quad (11)$$

$$\mu_{\text{out}} = \frac{\int_{\Omega} p_{\text{COMB}}(\mathbf{x}) (1 - H(\phi(\mathbf{x}))) d\mathbf{x}}{\int_{\Omega} (1 - H(\phi(\mathbf{x}))) d\mathbf{x}}. \quad (12)$$

In (8)–(9), $\phi(\mathbf{x}; t) : \Omega \rightarrow \mathbb{R}$ is the monotonically increasing or decreasing signed distance function, Ω is a set of voxels in the input MRI volume, and $H(\cdot)$ is the Heaviside function

approximated as $H_{\varepsilon} = \frac{1}{2} [1 + \frac{2}{\pi} \arctan(\frac{x}{\varepsilon})]$. In our implementation, $\phi > 0$ and $\phi < 0$ were set to represent the inside and outside of surfaces, respectively, while $\phi = 0$ indicated the boundary and t is a time parameter denoting the iteration. In (10), η , λ_1 , and λ_2 are fixed parameters, in which η controls the speed of convergence while λ_1 and λ_2 balance the terms. In this study, η was set to be 0.5, and λ_1 and λ_2 were set to be 1.

Finally, the motion equation denoting the evolution of the initial surface was derived by Euler-Lagrange equation as follows:

$$\frac{\partial E(\phi(\mathbf{x}), \mu_{\text{in}}, \mu_{\text{out}})}{\partial \phi(\mathbf{x})} = - \frac{\partial \phi(\mathbf{x})}{\partial t}, \quad (13)$$

$$\frac{\partial \phi(\mathbf{x})}{\partial t} = \delta(\phi(\mathbf{x})) \left[\eta \operatorname{div} \left(\frac{\nabla \phi(\mathbf{x})}{|\nabla \phi(\mathbf{x})|} \right) - \lambda_1 (p_{\text{COMB}}(\mathbf{x}) - \mu_{\text{in}})^2 + \lambda_2 (p_{\text{COMB}}(\mathbf{x}) - \mu_{\text{out}})^2 + \ln \left(\frac{p_{\text{SPPM}}(\mathbf{x})}{1 - p_{\text{SPPM}}(\mathbf{x})} \right) \right],$$

(14)

where $\delta(\cdot)$ is the delta function detecting the spatial location of the volume. Figure 6 is an example of the level set evolution with iteration illustrating the convergence of the initial surfaces toward the boundary of the liver.

2.2.5. Extraction of cysts—Cysts were extracted in two steps: the initial extraction and revision. The initial extraction of cysts was performed on the basis of the liver and cyst prior probability maps (p_{NPT} and p_{CYST}). Thresholds were applied to the probability maps to obtain the initial cyst regions, Λ , as follows:

$$\Lambda = \{\mathbf{x} | p_{\text{CYST}} > \alpha, p_{\text{NPT}} < \beta\}. \quad (15)$$

In order to determine the constant values, α and β , we conducted experiments for all combinations of both values ranging from 0 to 1 and assessed the accuracy in terms of cyst volumes. The experimental results showed that the accuracy of the values ranged from 0.6 to 0.9 for α and 0.2 to 0.5 for β was similar (ICC=0.92–0.94), but the values $\alpha = 0.8$ and $\beta = 0.3$ showed the highest accuracy, balancing the tradeoff between false positives and negatives. The heat map in Figure 7 shows the the accuracy of all feasible combination of these parameters.

In patients with polycystic kidney disease, kidney cysts neighboring the liver might be falsely extracted as liver cysts (Figure 8a). The segmented liver boundary surrounding falsely extracted kidney cysts had a concave contour. In addition, the falsely extracted kidney cysts were located inferior to the liver area and were presented as isolated structures outside the segmented liver boundary. These observations were used as criteria for removing falsely extracted kidney cysts by means of constructing a distance map. In the map, the distance from the top of the liver mask was combined with the distance of the centroid of the mask, where the centroid was set to 1 and the bottom of the liver boundary was set to 0. The distance map forced the removal of a single isolated structure less than 0.3 in the mean distance value. Figure 8b shows a distance map and its application to remove a falsely segmented kidney cyst without affecting correctly extracted liver cysts.

2.3. Data analysis

The performance of the automated segmentation for the liver was evaluated and compared with the manual segmentation references by means of two metrics: the Dice similarity coefficient (DSC) (Dice 1945), which measures how closely two independently segmented livers match geometrically when they are superimposed onto each other, and the intra-class correlation coefficient (ICC) of the segmented liver volume measurements between the two methods. For the liver cysts, the segmentation outcome of each individual cyst could not be assessed because it was not available by the reference method. Thus, the total cyst volume measurement and the relative percent cyst over liver volume in each liver dataset between the automated and reference manual method were compared by means of ICC and corresponding confidence intervals.

For the cross-validation of the training and test sets, the data analyses and evaluations were performed twice, E_1 and E_2 . The E_1 was conducted with the D_1 dataset for the test set and

the D_2 for the training set, while the E_2 was performed with the D_2 dataset for the test set and the D_1 for the training set. In addition, Bland-Altman analysis was used to estimate the bias and limits of agreement (LoAs). The statistical analysis was performed in IBM SPSS Statistics (version 20; SPSS Inc., Chicago, IL).

3. Results

The segmentation outcomes from livers of varying size and cyst burden are shown with superimposed manual and automated boundaries in Figure 9. Compared with a normal liver, the contours of a polycystic liver are often irregular because cysts deform the normal smooth surface of the liver. Although the segmentation results by the manual and automated methods show some differences in finer boundary depiction, the overall boundaries determined with the two methods are in good agreement. Noteworthy in Figure 9 is that the boundaries of the liver were segmented distinctly from the polycystic kidneys that were very closely located to the posterior aspect of the liver. The mean $\pm$ SD of the DSCs for E_1 and E_2 were 0.84 ± 0.03 and 0.84 ± 0.04 , respectively.

The scatter plots for the volume measurements of the livers segmented by the manual versus the automated method are shown in Figure 10. The ICCs were 0.91 ($P<0.001$; CI: 0.86–0.94) for E_1 and 0.90 ($P<0.001$; CI: 0.85–0.94) for E_2 . The Bland-Altman analysis demonstrated that the LoAs were (–562.6, 294.8 ml) for E_1 and (–404.1, 411.7 ml) for E_2 . The LoAs were (–0.24, 0.14) for E_1 and (–0.21, 0.23) for E_2 with normalized values in which the volume differences were divided by the reference volume.

The automated segmentations of cysts from the same four subjects in Figure 9 are shown in Figure 11. While most of the clearly-defined cysts were extracted, some small faintly-defined cysts were not segmented. The scatter plots for the volumes of the cysts segmented by the manual versus the automated method are shown, along with the corresponding volumetric percentage of the cysts relative to the liver volume, in Figure 12. The ICCs were 0.91 ($P<0.001$; CI: 0.88–0.94) for the cyst volumes and 0.94 ($P<0.001$; CI: 0.92–0.96) for the volumetric percentage of the cysts over liver.

4. Discussion

Our study demonstrated the feasibility of automated segmentation of liver and liver cysts from bounded abdominal MR images in patients with PLD livers. Given the heterogeneity and uncertainty of ADPKD liver morphology, we designed our segmentation method not to require a fixed priori shape of the liver. Our segmentation method is highly flexible and applicable to livers with varying morphologies and sizes, not only for PLD livers but also normal livers. The algorithm of the method was based on the prior statistical information of liver location (SPPM), regional MR signal intensity distribution of liver parenchyma (intensity prior probability map), and morphology of liver cysts (shape prior probability map). The SPPM globally constrained and guided the initial surfaces of the liver into the desired boundary. On the other hand, the TPPM captured the candidate regions of liver parenchyma and cysts. The TPPM and SPPM were formulated within the 3D level set framework.

How well our method performed was assessed by the cross-validation of the training and test sets using the manual segmentation by a radiology expert as the reference standard. The cross-validation showed excellent correlations across livers of varying size and cyst burden. With the *a priori* constraint terms formulated in the level set framework, our method successfully segmented the liver regions. The agreement in segmentation between the automated method and the radiologist expert was 84% in the shape congruence and 91% in the volume measurements. Although it is difficult to directly compare our result with others because no previous studies were reported for the segmentation of polycystic livers, we may use previous studies of the automated segmentation of normal livers as the reference comparison. Previous studies reported the overlap ratios as the segmentation performance index ranged from 81% (Seghers et al. 2007) to 89.2% (Okada et al. 2008). The shape congruence of 84% in our proposed method is near the median value of the range, suggesting the robustness of our method despite the complex heterogeneous shape of PLD livers with substantial burden of liver cysts, even with the presence of abundant kidney cysts neighboring the posterior surface of the liver.

For liver cyst extraction, we exploited the principal morphological characteristics of liver cysts with the implemented shape prior probability map. Furthermore, we took advantage of the spatial prior knowledge of kidney cysts by using the distance map from the centroid of the segmented liver to eliminate kidney cysts that were falsely classified as liver cysts outside concave liver contours. While most of clearly demarcated liver cysts were successfully extracted, some small faintly-defined liver cysts were not segmented. Cysts are often heterogeneous in signal intensity and subject to partial volume averaging that affects the shape and signal conspicuity of cysts. Even for the manual segmentation, radiologists have to carefully adjust and select a threshold to balance between the over- and under-segmentation of cysts. Thus, the implementation of automated segmentation was also prone to a trade-off between false positive and false negative extraction of liver cysts.

The performance of the automated cyst segmentation method was compared with the cyst volume measurements by the radiologist's reference region-based thresholding method. Overall, the automated and reference methods showed excellent intra-class correlations in terms of total volume (ICC=0.91) and portion in the liver (ICC=0.94). However, the automated method shows slight underestimation, especially for larger total volume of cysts, compared with the reference method. This discrepancy was likely a result of the intrinsic technical differences between the two methods. In the reference region-based thresholding method, the cyst area is differentiated from the background liver parenchyma and computed by thresholding of signal intensity over the entire liver region. Hence, even a single bright pixel may be included in the computation of cyst area. Therefore, the total cyst volume measured by the automated method is expected to be smaller than that by the region-based thresholding method. We postulate that the usage of more strict thresholds in the region-based thresholding method may lead to smaller total cyst volumes matching more closely to those measured with the automated method.

In addition to the estimation of volumes, the location and size distribution of segmented liver cysts may help characterize the patterns of PLD disease progression (Bae *et al* 2013). The automated segmentation and volumetric measurements of livers could provide an efficient

way of processing and analyzing MR image datasets with reduced manual operations, particularly in a large-scale ADPKD study. Furthermore, when MR images are acquired at different time points in a longitudinal study, in addition to measuring liver volume changes, it may be possible to superimpose the automatically segmented liver boundaries over the different time points to compare and determine the regional temporal changes in liver growth and morphology. In order to substantiate the application of the automated segmentation method to a longitudinal study, additional validation studies are required.

This study has several limitations. First, only some of the key image processing parameters were tested for sensitivity in determining the performance and stability of a segmentation method. In this feasibility study, we mainly focused on the development of a new automated segmentation method and the evaluation of the measurement precision between the automated and reference manual methods. Second, the proposed method was evaluated in terms of DSC between the segmented surfaces to assess the global shape congruence rather than distance measures that may show more local differences between the automated and reference methods. Third, the box that bounded a candidate liver region was not automatically selected or determined in the current implementation. The upper and lower borders of the box were manually delineated by a radiologist. If the bounding box is not determined during the image quality assessment process, it may be automatically estimated on the basis of key anatomical landmarks such as the lung, aorta, and bladder. Fourth, microscopic cysts or grossly irregular cysts were not segmented by our method, with sphere-like shape assumption for cysts. These cysts may be extracted with the implementation of more sophisticated methods such as shape training method to model morphological variations. However, the collective volume of these microscopic or irregular cysts is quantitatively rather insignificant compared to the overall cyst size.

5. Conclusions

We have developed an automated method for the segmentation of livers and liver cysts from bounded abdominal MR images in patients with varying severity of ADPKD. The performance of our segmentation method was in good agreement with that of the manual reference segmentation method.

Acknowledgments

The CRISP study is supported by cooperative agreements from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (DK056943, DK056956, DK056957, DK056961), by the National Center for Research Resources General Clinical Research Centers at each institution (RR000039, Emory University; RR00585, Mayo College of Medicine; RR23940, Kansas University Medical Center; RR000032, University of Alabama at Birmingham), and the National Center for Research Resources Clinical and Translational Science Awards at each institution (RR025008, Emory; RR024150, Mayo College of Medicine; RR033179, Kansas University Medical Center; RR025777 and UL1TR000165, University of Alabama at Birmingham; RR024153 and UL1TR000005, University of Pittsburgh School of Medicine). The investigators are indebted to the radiologists, nephrologists, radiology technologists, imaging engineers, and study coordinators in CRISP.

References

- Afifi, A., Nakaguchi, T. Liver segmentation approach using graph cuts and iteratively estimated shape and intensity constraints; Proc. Medical Image Computing and Computer-Assisted Intervention (MICCAI); 2012. p. 395-403.

- Bae K, Park B, Sun H, Wang J, Tao C, Chapman AB, Torres VE, Grantham JJ, Mrug M, Bennett WM, et al. Segmentation of individual renal cysts from mr images in patients with autosomal dominant polycystic kidney disease. *Clinical Journal of the American Society of Nephrology*. 2013; 8(7): 1089–1097. [PubMed: 23520042]
- Bae KT, Grantham JJ. Imaging for the prognosis of autosomal dominant polycystic kidney disease. *Nature Reviews Nephrology*. 2010; 6(2):96–106. [PubMed: 20111050]
- Bae KT, Zhu F, Chapman AB, Torres VE, Grantham JJ, Guay-Woodford LM, Baumgarten DA, King BF, Wetzel LH, Kenney PJ, et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the consortium for radiologic imaging studies of polycystic kidney disease cohort. *Clinical Journal of the American Society of Nephrology*. 2006; 1(1):64–69. [PubMed: 17699192]
- Beichel R, Bornik A, Bauer C, Sorantin E. Liver segmentation in contrast enhanced ct data using graph cuts and interactive 3d segmentation refinement methods. *Medical Physics*. 2012; 39(3):1361–1373. [PubMed: 22380370]
- Chan TF, Vese LA. Active contours without edges. *IEEE transactions on Image Processing*. 2001; 10(2):266–277. [PubMed: 18249617]
- Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Bae KT, Baumgarten DA, Kenney PJ, King BF, Glockner JF, Wetzel LH, et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The consortium for radiologic imaging studies of polycystic kidney disease (CRISP) cohort. *Kidney international*. 2003; 64(3):1035–1045. [PubMed: 12911554]
- Chauveau D, Fakhouri F, Grünfeld J-P. Liver involvement in autosomal-dominant polycystic kidney disease therapeutic dilemma. *Journal of the American Society of Nephrology*. 2000; 11(9):1767–1775. [PubMed: 10966503]
- Dice LR. Measures of the amount of ecologic association between species. *Ecology*. 1945; 26(3):297–302.
- Everson GT. Hepatic cysts in autosomal dominant polycystic kidney disease. *American Journal of Kidney Diseases*. 1993; 22(4):520–525. [PubMed: 8213790]
- Furukawa, D., Shimizu, A., Kobatake, H. Automatic liver segmentation method based on maximum a posterior probability estimation and level set method; *Proc. MICCAI Workshop on 3D Segmentation in the Clinic: A Grand Challenge*; 2007. p. 117-124.
- Gabow PA, Johnson AM, Kaehny WD, Manco-Johnson ML, Duley IT, Everson GT. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. *Hepatology*. 1990; 11(6):1033–1037. [PubMed: 2365280]
- Gloger O, Tönnies KD, Liebscher V, Kugelman B, Laqua R, Völzke H. Prior shape level set segmentation on multistep generated probability maps of mr datasets for fully automatic kidney parenchyma volumetry. *IEEE Transactions on Medical Imaging*. 2012; 31(2):312–325. [PubMed: 21937343]
- Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, Wetzel LH, Baumgarten DA, Kenney PJ, Harris PC, et al. Volume progression in polycystic kidney disease. *New England Journal of Medicine*. 2006; 354(20):2122–2130. [PubMed: 16707749]
- Heimann, T., Meinzer, H-P., Wolf, I. A statistical deformable model for the segmentation of liver ct volumes; *Proc. MICCAI Workshop on 3D Segmentation in the Clinic: A Grand Challenge*; 2007. p. 161-166.
- Heimann, T., Wolf, I., Meinzer, H-P. Active shape models for a fully automated 3d segmentation of the liver-an evaluation on clinical data; *Proc. Medical Image Computing and Computer-Assisted Intervention (MICCAI)*; 2006. p. 41-48.
- Hogan MC, Abebe K, Torres VE, Chapman AB, Bae KT, Tao C, Sun H, Perrone RD, Steinman TI, Braun W, et al. Liver involvement in early autosomal-dominant polycystic kidney disease. *Clinical Gastroenterology and Hepatology*. 2015; 13(1):155–164. [PubMed: 25111236]
- Huynh HT, Karademir I, Oto A, Suzuki K. Computerized liver volumetry on mri by using 3d geodesic active contour segmentation. *American Journal of Roentgenology*. 2014; 202(1):152. [PubMed: 24370139]

- Kainmüller, D., Lange, T., Lamecker, H. Shape constrained automatic segmentation of the liver based on a heuristic intensity model; Proc. MICCAI Workshop on 3D Segmentation in the Clinic: A Grand Challenge; 2007. p. 109-116.
- Kim Y, Ge Y, Tao C, Zhu J, Chapman AB, Torres VE, Yu AS, Mrug M, Bennett WM, Flessner MF, Landsittel DP, Bae KT. Automated segmentation of kidneys from mr images in patients with autosomal dominant polycystic kidney disease. *Clinical Journal of the American Society of Nephrology*. 2016; 11(4):576–584. [PubMed: 26797708]
- Kim Y, Hong BW, Kim SJ, Kim JH. A population-based tissue probability map-driven level set method for fully automated mammographic density estimations. *Medical physics*. 2014; 41(7): 071905. [PubMed: 24989383]
- Kline TL, Korfiatis P, Edwards ME, Warner JD, Irazabal MV, King BF, Torres VE, Erickson BJ. Automatic total kidney volume measurement on follow-up magnetic resonance images to facilitate monitoring of autosomal dominant polycystic kidney disease progression. *Nephrology Dialysis Transplantation*. 2016; 31(2):241–248.
- Lindeberg T. Image matching using generalized scale-space interest points. *Journal of Mathematical Imaging and Vision*. 2015; 52(1):3–36.
- Ling, H., Zhou, SK., Zheng, Y., Georgescu, B., Suehling, M., Comaniciu, D. Hierarchical, learning-based automatic liver segmentation; Proc. IEEE Conference on Computer Vision and Pattern Recognition (CVPR); 2008. p. 1-8.
- López-Mir F, Naranjo V, Angulo J, Alcañiz M, Luna L. Liver segmentation in mri: A fully automatic method based on stochastic partitions. *Computer Methods and Programs in Biomedicine*. 2014; 114(1):11–28. [PubMed: 24529637]
- Masoumi H, Behrad A, Pourmina MA, Roosta A. Automatic liver segmentation in mri images using an iterative watershed algorithm and artificial neural network. *Biomedical Signal Processing and Control*. 2012; 7(5):429–437.
- Okada T, Shimada R, Hori M, Nakamoto M, Chen Y-W, Nakamura H, Sato Y. Automated segmentation of the liver from 3d ct images using probabilistic atlas and multilevel statistical shape model. *Academic Radiology*. 2008; 15(11):1390–1403. [PubMed: 18995190]
- Osher S, Sethian JA. Fronts propagating with curvature-dependent speed: algorithms based on hamilton-jacobi formulations. *Journal of Computational Physics*. 1988; 79(1):12–49.
- Paragios N, Deriche R. Geodesic active regions and level set methods for supervised texture segmentation. *International Journal of Computer Vision*. 2002; 46(3):223–247.
- Park H, Bland PH, Meyer CR. Construction of an abdominal probabilistic atlas and its application in segmentation. *IEEE Transactions on Medical Imaging*. 2003; 22(4):483–492. [PubMed: 12774894]
- Peng J, Dong F, Chen Y, Kong D. A region-appearance-based adaptive variational model for 3d liver segmentation. *Medical physics*. 2014a; 41(4):043502. [PubMed: 24694159]
- Peng J, Hu P, Lu F, Peng Z, Kong D, Zhang H. 3d liver segmentation using multiple region appearances and graph cuts. *Medical physics*. 2015; 42(12):6840–6852. [PubMed: 26632041]
- Peng J, Wang Y, Kong D. Liver segmentation with constrained convex variational model. *Pattern Recognition Letters*. 2014b; 43:81–88.
- Rudin LI, Osher S, Fatemi E. Nonlinear total variation based noise removal algorithms. *Physica. D. Nonlinear Phenomena*. 1992; 60(1):259–268.
- Ruskó L, Bekes G, Fidrich M. Automatic segmentation of the liver from multi-and single-phase contrast-enhanced ct images. *Medical Image Analysis*. 2009; 13(6):871–882. [PubMed: 19692288]
- Seghers, D., Slagmolen, P., Lambelin, Y., Hermans, J., Loeckx, D., Maes, F., Suetens, P. Landmark based liver segmentation using local shape and local intensity models; Proc. MICCAI Workshop on 3D Segmentation in the Clinic: A Grand Challenge; 2007. p. 135-142.
- Slagmolen, P., Elen, A., Seghers, D., Loeckx, D., Maes, F., Haustermans, K. Atlas based liver segmentation using nonrigid registration with a b-spline transformation model; Proc. MICCAI Workshop on 3D Segmentation in the Clinic: A Grand Challenge; 2007. p. 197-206.
- Thévenaz P, Blu T, Unser M. Interpolation revisited. *IEEE Transactions on Medical Imaging*. 2000; 19(7):739–758. [PubMed: 11055789]

- Zhang S, Zhan Y, Metaxas DN. Deformable segmentation via sparse representation and dictionary learning. *Medical Image Analysis*. 2012a; 16(7):1385–1396. [PubMed: 22959839]
- Zhang S, Zhan Y, Dewan M, Huang J, Metaxas DN, Zhou XS. Towards robust and effective shape modeling: Sparse shape composition. *Medical image analysis*. 2012b; 16(1):265–277. [PubMed: 21963296]
- Zhang X, Tian J, Deng K, Wu Y, Li X. Automatic liver segmentation using a statistical shape model with optimal surface detection. *IEEE Transactions on Biomedical Engineering*. 2010; 57(10): 2622–2626. [PubMed: 20615804]
- Zhou X, Kitagawa T, Okuo K, Hara T, Fujita H, Yokoyama R, Kanematsu M, Hoshi H. Construction of a probabilistic atlas for automated liver segmentation in non-contrast torso ct images. *International Congress Series*. 2005; 1281:1169–1174.

Figure 1.
MRI images of polycystic livers with a range of cystic burdens.

Figure 2.

The overview of the automated segmentation process. The segmentation was operated in five steps: preprocessing, spatial prior probability map construction, tissue prior probability map construction, liver segmentation, and cyst extraction.

Figure 3. Images of spatial prior probability map (SPPM) presenting (a) coronal mid cross-section and (b) 3D surface rendering with the SPPM value $p_{\text{SPPM}} = 0.5$.

Figure 4. Typical histogram of (a) T_2 -weighted abdominal MRI and (b) regions corresponding to SPPM probability $p_{\text{SPPM}} > 0.5$ (solid line) with fitted probability density function (dashed line) for the liver parenchyma.

Figure 5. Tissue prior probability maps: (a) original image, (b) intensity prior probability map for liver parenchyma, and (c) shape prior probability map for cyst tissue.

Figure 6.

Illustration of level set evolution in columns at (a) initial, (b) 25, (c) 50, and (d) final iterations. The zero-level sets are delineated in solid lines. The four images on the top row represent the three-dimensional rendering of the entire zero level sets over the original image. The subsequent rows from top to bottom correspond to 25%, 50%, and 75% slice location from anterior to posterior within the volume, respectively.

Figure 7.

The heat map depicting the cyst extraction accuracy in terms of all feasible combination of the parameters, α and β , in which the color bar indicates the ICCs on the right.

Figure 8.

Cyst extraction process: (a) initial extraction of liver cysts including a falsely segmented kidney cyst (yellow arrow), (b) distance map to remove falsely segmented kidney cysts, and (c) final extraction of liver cysts. The small circle in (b) represents the centroid of the liver mask.

Figure 9.

The automated segmentation boundary (red contour) of the liver superimposed with the manual reference segmentation (green contour) in four subjects representing (a) the anterior 25% cross-section; (b) the middle section; (c) the posterior 25% cross-section of the liver; and (d) the 3D surface renderings of the segmented livers.

Figure 10.

Scatter plots of liver volume measurements between the reference and automated methods at two test sets: (a) D_1 and (b) D_2 . The ICCs were (a) 0.91 ($P < 0.001$; CI: 0.86–0.94) and (b) 0.90 ($P < 0.001$; CI: 0.85–0.94). The diagonal line in the figure represents the line of identity.

Figure 11.

Extraction of liver cysts in four subjects from Figure 9. The extracted cysts are delineated in yellow contours. While most of clearly-defined cysts were extracted, some small faintly-defined cysts were not segmented.

Figure 12.

Scatter plots of (a) cyst volume measurements and (b) volumetric percentage of cysts relative to liver between the reference and automated methods. The intra-class correlation coefficients were (a) 0.91 ($P < 0.001$; CI: 0.88–0.94) and (b) 0.94 ($P < 0.001$; CI: 0.92–0.96). The diagonal line in the figure represents the line of identity.

Table 1

MRI acquisition parameters from four different institutions.

Scanner	Institution	#Cases	Pixel Spacing (mm)	Slice Thickness (mm)	Repetition Time (TR) (ms)	Echo Time (TE) (ms)
Siemens	1	50	1.4 ± 0.1	6.1 ± 0.4	685.3 ± 36.1	82.9 ± 0.3
	2	53	0.8 ± 0.1	6.1 ± 0.4	1535.1 ± 32.7	90.2 ± 1
GE	3	26	1.5 ± 0.1	5	584.5 ± 98.7	100.1 ± 1.1
	4	17	1.3	4.9 ± 0.6	806.6 ± 152.2	90
Total		146	1.2 ± 0.3	5.7 ± 0.7	989.8 ± 423	89.4 ± 5.9