Segmentation of Polycystic Kidneys from MR images

Dimitri Racimora\textsuperscript{a}, Pierre-Hughes Viviel\textsuperscript{b}, Hersh Chandarana\textsuperscript{a}, Henry Rusinek\textsuperscript{a}

\textsuperscript{a}Department of Radiology, New York University Medical Center, New York, NY
\textsuperscript{b}Department of Radiology, Univ. of Rouen School of Med. & Pharmacy, 22 blvd Gambetta, F-76183 Rouen, France

ABSTRACT

Polycystic kidney disease (PKD) is a disorder characterized by the growth of numerous fluid filled cysts in the kidneys. Measuring cystic kidney volume is thus crucial to monitoring the evolution of the disease. While T2-weighted MRI delineates the organ, automatic segmentation is very difficult due to highly variable shape and image contrast. The interactive stereology methods used currently involve a compromise between segmentation accuracy and time. We have investigated semi-automated methods: active contours and a sub-voxel morphology based algorithm. Coronal T2-weighted images of 17 patients were acquired in one breath-hold using the HASTE sequence on a 1.5 Tesla MRI unit. The segmentation results were compared to ground truth kidney masks obtained as a consensus of experts. Automatic active contour algorithm yielded an average 22\% ± 8.6\% volume error. A recently developed method (Bridge Burner) based on thresholding and constrained morphology failed to separate PKD from the spleen, yielding 37.4\% ± 8.7\% volume error. Manual post-editing reduced the volume error to 3.2\% ± 0.8\% for active contours and 3.2\% ± 0.6\% for Bridge Burner. The total time (automated algorithm plus editing) was 15 min ± 5 min for active contours and 19 min ± 11 min for Bridge Burner. The average volume errors for stereology method were 5.9\%, 6.2\%, 5.4\% for mesh size 6.6, 11, 16.5 mm. The average processing times were 17, 7, 4 min. These results show that nearly two-fold improvement in PKD segmentation accuracy over stereology technique can be achieved with a combination of active contours and post-editing.

Keywords: image analysis, image segmentation, Polycystic Kidney Disease, active contours, stereology, MR imaging

1. INTRODUCTION

Polycystic kidney disease (PKD) is a genetic disorder with prevalence of about 600,000 in the United States. The incidence of PKD is approximately 1 in 20,000–40,000 live births and it is the fourth leading cause of kidney failure. It is characterized by the growth of numerous fluid-filled cysts in the kidneys\textsuperscript{1}. The cysts enlarge the kidney resulting in replacement and compression of the normal renal parenchyma. This results in reduced kidney function and eventual progression to end stage renal failure in many cases. By the age of 60, 45\% of PKD patients undergo renal transplantation\textsuperscript{2}. However, the progression rate of PKD is highly variable and the reason of renal failure is not well understood.

The size of the kidneys (cysts included) is predictive of not only severity of the renal functional impairment but also prognostic of disease progression, with larger volume associated with poorer renal function and higher likelihood of disease progression\textsuperscript{3}. Technical developments in radiologic imaging have the potential to quantify morphologic changes associated with PKD with accuracy. These morphological measures could inform the physician about PKD progression in individual patient and facilitate early, effective interventions and help with monitoring therapeutic efficacy of drugs which are currently under investigation. Measuring cystic kidney volume is thus crucial to monitoring the evolution of the disease. Quantitative renal imaging analysis of PKD patients is performed in research setting is now also being performed with increasing frequency in clinical management of these patients. Volumetric analysis helps to monitor treatment efficiency and to predict the need for dialysis or kidney transplantation.

Both CT and MRI can be used to monitor structural changes associated with PKD. For best separation of renal parenchyma and cysts from the background tissue, CT imaging is often combined with iodinated contrast agent. However, iodinated contrast medium may cause renal failure, especially in patients with impaired renal function at
baseline. For these reasons MRI is a preferred modality in monitoring PKD. MRI has been increasingly used for volumetric measurements because it provides high resolution images with excellent tissue contrast and no need for ionizing radiation or iodinated contrast medium. Even though MRI has better tissue contrast, compared to CT, the image acquisition is significantly slower, resulting in images that are affected by respiratory motion artifacts, signal non-uniformity, ghosting artifacts, wrap-arounds, and low signal/noise.

Bae et al\(^7\) have validated a simple three-dimensional stereology technique for measuring renal cysts and parenchyma using T2-weighted MRI. This technique is the most widely used method for PKD volumetry\(^3,5\) in research setting. Stereology consists of distributing a uniform, dense grid of points over the entire field of view of the image, including the object of interest (here it is cystic kidney). The user interacts with the grid by “counting” or marking on the display monitor the number of grid points that overlay the kidney. A two-dimensional variant of such stereology technique has been widely used in histopathology imaging\(^5,6\). Stereology technique requires a training process for an operator to be able to distinguish the renal cysts from the parenchyma. Supervision by a radiologist, such as inspecting the processed images, is highly desirable for quality control or for images with complex cysts that are less discernible than simple cysts from the background renal tissue. The accuracy and reliability of the stereology technique are also affected by the grid size and display window setting. The density of the grid is a key parameter in stereology approach; with sparse grid, the interactive marking process takes less time but results in lower segmentation accuracy. With denser grid there is improved accuracy but at the cost of longer processing time. If the grid density is equal to the voxel size, stereology technique becomes equivalent to completely manual electronic painting of the entire object of interest.

The accuracy of stereology method for PKD volumetry was investigated with phantoms, ranging in volume from 5 to 423 cm\(^3\)\(^7\). PKD phantoms were made from agarose gel, grapes, and water-filled balloons. The true volume of the phantoms was measured using fluid displacement (Archimedes principle). The average accuracy of phantom volume was 2.8%, range 2-5%. However, stereology grid density was not reported, and the influence of grid density on measurement error has not been examined.

The first objective of our study was therefore to assess the effect of grid density on error in volume measurements in patient with polycystic kidney disease imaged in vivo. Patients were imaged with T2-weighted coronal 1.5 T MRI using the HASTE sequence (CRISP study). The consensus of manual PKD segmentations by two expert radiologists was considered the reference standard.

The second objective of this study was to evaluate several automated segmentation methods for measurement of kidney volume in patients with PKD: the methods include active contours and a “thresholding with morphology” algorithm. We compared the segmentation results obtained with the different methods against expert-derived masks to determine the accuracy of each automated technique.

The third objective of this study was to evaluate the performance of a hybrid approach, in which the initial volume was obtained using automated segmentation, followed by manual editing of the results by human observer. We have analyzed both the accuracy and the efficiency of such hybrid segmentation schemes, where human observer is editing the results of automatically obtained kidney masks.

2. MATERIALS AND METHODS

2.1 Patients
Total of 17 patients with PKD were imaged. There were 2 males and 15 females with mean age of 44 years (range 22-58 years). Serum creatinine ranged from 0.7 to 2.1 mg/dL (mean: 1.0 mg/dL). Volume was measure for all 34 kidneys. Renal volumes ranged from 149 ml to 1980 ml with mean of 710 ml. 13 kidneys had volume less than 500 ml, 15 kidneys had volume which measured between 500 and 1000 ml, and 6 kidneys had volume greater than 1000 ml (Fig.1). From these images 12 kidneys were chosen at random, constrained to represent 6 right, 6 left, 4 with volume less than 500 ml, 4 with volume between 500 and 1000 ml, and 4 with volume greater than 1000 ml.
2.2 MRI acquisition
Coronal T2-weighted abdominal images were acquired on a 1.5 Tesla Siemens Avanto MRI using half-Fourier acquisition single-shot turbo spin-echo (HASTE) pulse sequence. Acquisition parameters were: TR=1000 ms, TE=94 ms, 90° flip angle, pixel bandwidth 780 Hz, NEX=1. Abdominal field of view was set to 35 cm (left-right) x 35 cm (canio-caudal) x 10 cm (a-p direction). The acquisition matrix was 320 x 256 with 80% sampling in the left-right direction. Slice thickness was 3mm. Interpolation to 320 x 320 coronal views yielded voxel size of approximately 1.1 x 1.1 x 3.3 mm.

Total acquisition time was 60 seconds, with images acquired in 4 breath-holds.

Images in DICOM format were transferred to CD-ROM media and analyzed on a standard personal computer running Microsoft Windows XP. All locally developed software was written in C++ using Visual Studio compiler.

2.3 Segmentation
2.3.1 Ground truth – segmentation by experts
Each case was manually segmented by two experienced radiologists (P-HV, HC) and one researcher (HR), each having 5+ years experience in renal anatomy and renal MRI. Cystic kidney masks \( M_i \) included renal cortex, renal medulla, and cysts. Pelvis and collecting spaces were excluded unless occupied by cysts (Fig. 1, right). Also excluded were large blood vessels and renal fat. Each slice containing kidney and adjacent cysts was segmented. The consensus masks \( M \) were then generated: a voxel \( v \) belongs in \( M \) if it was marked as part of the kidney tissue by a majority (2/3 or 3/3) of human experts.

2.3.2 Stereology
Stereology segmentation technique consists in super-imposing over an image a 3D mesh of regularly distributed markers (Fig.2). Mesh density, i.e., the separation between markers, denoted as \( M_X, M_Y, \) and \( M_Z \), expressed in mm, are the key parameters of the stereology method. Each marker can be considered as the center of a 3D box of dimensions \( M_X, M_Y, \) and \( M_Z \) and volume \( M_v = M_X \cdot M_Y \cdot M_Z \). These virtual boxes are non-overlapping and span the entire field of view of the image.7. The user interacts with the image using a software that allows quick mouse-driven erasing of markers that overlay the object of interest. At the end of interactive 3D editing session (Fig.2), the software estimates object’s volume by multiplying the number of erased markers by \( M_v \).

We have developed a stereology segmentation software that generates any prescribed mesh density. For this study we limited mesh density to satisfy \( M_X = M_Y \), to be a multiple of voxel dimension, and we kept \( M_Z \) equal to inter-slice distance. Markers were displayed as yellow crosses composed of five pixels. Single markers can be erased with a mouse click, and multiple markers are erased by quickly dragging the mouse over them. A recently implemented feature (not used in this study) provides an interactive control of the width of the eraser by responding to the mouse wheel.

We have tested three values of mesh sizes: (a) dense, \( M_X = M_Y = 6.6 \) mm, (b) medium, \( M_X = M_Y = 11 \) mm, and (c) sparse \( M_X = M_Y = 16.5 \) mm (Fig.3).
2.3.3 Active contours

Active contour segmentation and its implementation using level set methods is a well-established theoretical approach that becomes increasingly popular in medical image analysis. An open source application called ITK-SNAP was recently developed specifically for 3D segmentation tasks and validated for biomedical tasks. The software makes level set segmentation accessible to a wide range of users, including those with limited mathematical background. SNAP includes a full set of editing tools and a graphical user interface (Fig.4) to provide quick feedback to facilitate appropriate selection of level-set parameters.

ITK-SNAP implements two well-known 3D active contour segmentation methods: Geodesic Active Contours and Region Competition. In both methods, the evolving estimate of the structure of interest is represented by one or more contours. An evolving contour is a closed surface $C(u,v;t)$ parameterized by space variables $u,v$ and by the time variable $t$. 

Figure 3. The same image of a polycystic kidney analyzed using stereology method and (left) dense (6.6 mm) mesh; (right) sparse (16.5 mm) mesh. Note that renal pelvis is not included in cystic kidney mask.

Figure 4. Graphical user interface in ITK-SNAP application. Left: screenshot taken after loading the image, showing three orthogonal projections and interactive tools. Right: a portion of the display showing the background region in blue and the foreground region in white, for selected threshold.
The contour evolves according to:

$$\frac{\partial C}{\partial t} = (F_i + F_e) \ N$$  \hspace{1cm} (1)$$

where $N$ is the unit normal to the contour, and $F_i, F_e$ represent the internal and the external forces that act on the contour in the normal direction. The internal forces are derived from the contour’s curvature. They are typically used to impose smoothness constraints on the evolving contour. The external forces represent information derived from the image being segmented. After initial experimentation, we have selected the variant based on the algorithm\textsuperscript{10} that derives $F_e$ from voxel probability maps. Specifically, the probability that a voxel belongs to PKD and the probability that it belongs to the background is estimated from user-specified signal intensity thresholds (Fig. 4), subjected to local smoothing. The contour evolution equation is solved using the level set method\textsuperscript{11}. This elegant approach ensures numerical stability and it allows the contour to change topology.

### 2.3.4 Thresholding with morphology – Bridge Burner

The Bridge Burner algorithm is another semi-automatic three-dimensional segmentation method tested for PKD segmentation. Bridge Burner combines thresholding, morphologic thinning and connectivity constraints. Bridge Burner follows the “thresholding-with-morphology” approach. Variants of this approach have in the past been implemented in several laboratories\textsuperscript{13,14,15}. Conventional implementations use unconstrained growth thus introducing errors due to boundary smoothing. The algorithm has been validated for T1-weighted brain applications\textsuperscript{12}. The process originates with placement of a seed region $S$ (Fig. 5). The average signal intensity $S$ of $S$ is used to define the initial, overinclusive volume $V_0$ that is presumed to include the object to be segmented:

$$V_0 = \{ v: S_{t_{\text{min}}} < I(v) < S_{t_{\text{max}}} \}. \hspace{1cm} (2)$$

In the above equation $I(v)$ is the signal intensity of voxel $v$ and $t_{\text{min}}, t_{\text{max}}$ are the lower and upper thresholds relative to $S$. In the next step we generate the set of voxels:

$$E = \{ v: |G(v)| > S_{t_{\text{grad}}} \}, \hspace{1cm} (3)$$

characterized by strong image gradients $G(v)$. At these voxels the magnitude of Canny edges exceeds the threshold value $t_{\text{grad}}$, also normalized to the seed signal $S$. Next, $S_0$, the set of surface voxels in $V_0$ is combined with $E$ to yield the set $T$:

$$T = S_0 \cup (E \cap V_0). \hspace{1cm} (4)$$

The algorithm then identifies the set $P$, called “the peel layer” of $V_0$. $P$ is a set of all voxels that terminate a path of total length $< p$. The path is required to begin at a voxel in $T$ and to be contained entirely in $V_0$. The length of the path is the sum of the Euclidean distances between its consecutive voxels. The upper limit on length $p$ is another parameter of the algorithm. We then construct an interior set $V_1 = V_0 - P$ by removing the peel layer from $V_0$. To be effective, the parameter $p$ should be greater than the maximum width of all “bridges” that connect the desired volume to other structures in $V_0$ (for example, connections between the kidney with the spleen or the liver).

The set $V_1$ may consist of several connected components. The software proceeds by retaining $V_C$, the largest of these components. Finally, Bridge Burner algorithm applies a morphological growth operator on $V_C$, subject to the constraint that added voxels must belong to $V_0$. This operator, characterized by the parameter $g$, reverses the effect of peel layer removal (Fig. 5).

### 2.4 Assessment of segmentation accuracy and computational efficiency

The simplest measure of segmentation accuracy is the volumetric overlap of the brain masks considered as sets. If $A$ is a mask constructed by the segmentation algorithm and $G$ the ground truth mask, we can compute the relative oversegmentation error OSE as $v(A - G) / v(G)$, where $v$ is the volume or the number of voxels in the set. Similarly, the relative undersegmentation error USE is computed as $v(G - A) / v(G)$. The overall segmentation error $E$ is:

$$E = \frac{v(A - G) + v(G - A)}{v(G)}. \hspace{1cm} (5)$$

$E = 0.0$ implies perfect accuracy, i.e. full volumetric agreement with the ground truth. All steps of this project were done on a standard personal computer based on dual core 2.2 GHz processor and 2 Gb SDRAM, running Microsoft Win-XP.
2.5 Post-segmentation editing

The masks resulting from ITK-SNAP and Bridge Burner segmentation algorithms were saved as files for assessment of under- and over-segmentation error. We then proceeded to manually edit these masks. Locally developed image analysis software FireVoxel was used to carry out post-processing on each of the 24 3D masks (2 methods x 12 kidneys) obtained in this study. Editing employed variable size electronic paintbrush to fill up under-segmented areas and an electronic eraser to delete over-segmented areas on each coronal slice. A single observer performed all post-segmentation editing and the editing time was recorded for each PKD set and each method. Since we are interested in measuring editing time rather the expertise of the human observer, the operator was not blinded to gold standard kidney obtained as a consensus by radiology experts. This is thus approximating the editing by “omniscient” observer.

3. RESULTS

3.1 Stereology

The performance of stereology segmentation technique with dense, medium, and sparse grids is shown in Table 1 and figures 6 and 7. Table 1 lists the mean value and the standard deviation of execution time and corresponding volume error. The two figures use box and whiskers plots to present the distribution (median, range, and 1st, 3rd quartile) of execution times (Fig.6) and volumetric error (Fig.7).

<table>
<thead>
<tr>
<th>Mesh size (mm)</th>
<th>Volume error (%)</th>
<th>Execution time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense (6.6)</td>
<td>5.9 ± 2.7</td>
<td>17 ± 13</td>
</tr>
<tr>
<td>Medium (11.0)</td>
<td>6.2 ± 3.0</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Sparse (16.5)</td>
<td>5.4 ± 2.9</td>
<td>4 ± 3</td>
</tr>
</tbody>
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Figure 5. BridgeBurner segmentation begins by loading the volume and specifying the seed region (green box on the left screenshot). The algorithm applies thresholding, morphologic thinning, and connectivity constraints to generate the output mask shown in red on the right panel.
Figure 6. Distribution of execution times for interactive stereology method across the three mesh sizes. Note a wide range of execution times. Overall, the execution time appears to decrease approximately quadratically with mesh size.

Figure 7. Distribution of volume errors (%) for interactive stereology method and three mesh sizes. For mesh densities tested, there seems to be no improvement in accuracy with finer mesh.

3.2 Preprocessing stage

A minimal effort is required before launching the two semi-automatic tools. With ITK-SNAP algorithm based on thresholding (the variant found to be more appropriate to PKD segmentation than edge-based variant) the user must initialize the lower signal threshold. The user also sets up initial seeds (“bubbles”). A single seed placement on a central slice was found to be appropriate for PKD segmentation task. Specification of the threshold and the seed location and size could be accomplished in less than 1 minute.

An even less extensive preprocessing effort is needed to launch Bridge Burner (see Fig.5). We have used fixed values for Bridge Burner parameters: lower threshold = 0.4, upper threshold = infinity, peel parameter \( p = 2.9 \), and growth parameter 6.4.
3.3 Execution time

Both semi-automated programs produce results very quickly, requiring no more than ten seconds in all PKD cases tested in this study.

3.4 Segmentation errors

Over-segmentation error with Bridge Burner averaged 18.5% of the true volume, compared to an average 8.9% for the Active Contours technique. Bridge Burner under-segmentation error was also higher, 18.9% compared to 13.1%. The overall error was 37.4% ± 8.7% (average ± standard deviation) for Bridge Burner and 22.0% ± 8.6% for Active Contours method (Fig. 8). The differences between the accuracy for these two methods were statistically significant. The accuracy for both semi-automated methods was significantly worse than the accuracy of manual segmentation based on stereology.

![Pre-editing volume error (\%)](image)

Figure 8. Distribution of volume errors for the two semi-automatic methods.

The proximity of the spleen was found to be the predominant source of large segmentation error for both automated methods (Fig. 9). The spleen signal can be hard to differentiate from the kidney signal. Both Active Contours and Bridge Burner methods depend to a large degree on thresholding, which fails in cases like those shown in Fig. 9.

![Figure 9. Examples of gross segmentation errors (yellow arrow) caused by the presence of adjacent spleen. Top row: Bridge Burner. Bottom row: Active Contours method. Note an extensive boundary that is shared by the cystic kidney and the spleen. The size of this boundary precludes successful application of morphological peeling to separate the two organs.](image)
3.5 Post-processing effort and error

Manual post-processing of Bridge Burner masks required 19 ± 11 min editing time, whereas Active Contours required 15 ± 5 min editing time (Fig. 10). After manual editing, the overall volume errors were reduced to 3.2% ± 0.6% for Bridge Burner and to 3.2% ± 0.8% for Active Contours method (Fig. 11).

![Figure 10. Distribution of post-processing editing time for the two semi-automatic methods.](image)

![Figure 11. Distribution of post-editing errors for two semi-automatic methods.](image)

4. DISCUSSION

PKD is characterized by the progressive enlargement of kidneys due to expanding fluid-filled cysts. Assessment of PKD volume is recognized as an important marker of disease progression. Magnetic resonance imaging is increasingly used to monitor changes in patients with PKD. Acquisition of high quality abdominal MRI presents a significant challenge, as we must resolve the tradeoffs between contradictory aims of high spatial and high temporal resolution. High spatial resolution (i.e., small voxel size and thin slice) is needed for high volumetric accuracy, but it entails longer acquisition time, and problems associated with respiratory motion. A reasonable compromise, adopted in this study, is to acquire the abdominal MRI volume in several discrete breath-holds. Our protocol employed HASTE with a moderate...
undersampling, yielding slice thickness of 3.3 mm, and 1.1 mm voxels, and total acquisition time was 60 seconds. We also chose a set of cystic kidneys that is representative of clinical diversity of sizes, shapes, and cyst distribution.

While the resulting images represent the state-of-the-art in abdominal MRI, segmentation of cystic kidney is very challenging. The shape and size of PKD are highly variable, the signal within the renal structure is inhomogeneous, and the boundaries are devoid of consistent edges. Our study demonstrates that the ultimate accuracy of MRI-based volume estimates is approximately 3.4% (mean=3.2%). We could achieve this range of accuracy by applying semi-automated three-dimensional segmentation tools, followed by manual post-editing. A typical range of post-editing time was 12-20 min. Better image acquisition is probably needed to improve the limit of 3.2% average volume error. However, it is highly likely that improved interactive software can be developed to significantly reduce post-editing time to manual erasing performance.

The use of stereology method yields lower accuracy, 4.7% but faster (about 5 min) editing time. Stereology method involves a tradeoff between the time spent marking PKD region on the MRI versus the accuracy of the volume estimates. Denser grid implies a greater amount of time spent erasing the marks, with expectation of higher accuracy of the measurement. Our results show that execution time indeed increased when mesh size was reduced. For a 16.5 mm mesh, most of the kidneys were segmented within 5 min.

Unexpectedly, however, we didn’t observe reduction of volume error for denser grid. For example, several error measures for 16.5 mm mesh size, including the mean and the median volume error, are lower than for a 6.6 mm mesh size (these difference were not statistically significant). It appears that the mesh sizes used in our study already correspond to the ultimate lower limit of accuracy of the stereology method. The median volume error is approximately 6%, and the maximum volume error was approximately 11%, regardless of the grid size.

High variability of kidney shapes is most likely responsible for the large variability (as measured with standard deviations) of both execution time and volume error.

Without post-editing, the Active contours method was found to be more accurate than the method based on thresholding and morphology. Both methods suffered from significant over-segmentation error, because the surrounding organs often included regions with signal intensity of the same range as PKD values. Since Bridge Burner algorithm was dedicated to brain segmentation, it is not surprising that it handled poorly the challenges related to PKD, including wide border shared with the liver and spleen, wide range of signal values (bright and dark cysts). The level sets algorithm appears to be less sensitive to those challenging features. Moreover, Bridge Burner algorithm uses a rigid exclusion of regions with signal below user-specified lower threshold value. This often led to undersegmentation of tissue located in PKD regions but having low signal value.

Consistently with its more accurate segmentation performance, Active Contours method leads to faster post-editing times. Not only the average time, but also the lower standard deviation argue in favor of Active Contours method. Low standard deviation of editing times is of high practical consequence, as it avoids possibly very long (up to 48 min with Bridge Burner) editing session. Highly variable segmentation results are due to wide range of biological diversity of PKD shapes.

Both automated programs, but especially Bridge Burner, exhibited tendency to oversegment PKD by including adjacent spleen or liver structures. The fact that it takes longer to erase oversegmented areas than filling up undersegmented “holes” most likely explains significantly longer and highly dispersed distribution of editing times for Bridge Burner.

In order to apply our findings to disease monitoring, it would be of interest to optimize the time period between serial imaging acquisitions within a patient. To accomplish this, our data on accuracy of volume measurement will need to be combined with existing data on expected PKD volume growth. Such a study is essential to assure effectively measurement of volume growth rate and to avoid needless MRI exams.

5. CONCLUSION

We conclude that Active Contours method combined manual editing gives ultimate measurement accuracy and a consistent and reasonably short total processing and can be chosen over Bridge Burner algorithm for PKD segmentation. Stereology method proved to be efficient, requiring in most cases only 5 min when using the sparse 16.5 mm mesh. Stereology however precludes us from achieving high segmentation accuracy, limiting median error to about 6%.
6. REFERENCES