Validation of Cooper’s Ligament Thickness in Software Breast Phantoms

Adam J. Kuperavage*a, Abdullah-Al-Zubaer Imranb, Predrag R. Bakicb, Andrew Maidmentb, David D. Pokrajaca

aDelaware State University, 1200 North DuPont Highway, Dover, DE, 19901, bUniversity of Pennsylvania, Philadelphia, PA, 19104

ABSTRACT

Anthropomorphic breast phantoms are important tools for a wide range of tasks including pre-clinical validation of novel imaging techniques. In order to improve the realism in the phantoms, assessment of simulated anatomical structures is crucial. Thickness of simulated Cooper’s ligaments influences the percentage of dense tissue, as well as qualitative and quantitative properties of simulated images.

We introduce three methods (2-dimensional watershed, 3-dimensional watershed, and facet counting) to assess the thickness of the simulated Cooper’s ligaments in the breast phantoms. For the validation of simulated phantoms, the thickness of ligaments has been measured and compared with the input thickness values. These included a total of 64 phantoms with nominal ligament thicknesses of 200, 400, 600, and 800 μm.

The 2-dimensional and 3-dimensional watershed transformations were performed to obtain the median skeleton of the ligaments. In the 2-dimensional watershed, the median skeleton was found cross-section by cross-section, while the skeleton was found for the entire 3-dimensional space in the 3-dimensional watershed. The thickness was calculated by taking the ratio of the total volume of ligaments and the volume of median skeleton. In the facet counting method, the ligament thickness was estimated as a ratio between estimated ligaments’ volume and average ligaments’ surface area.

We demonstrated that the 2-dimensional watershed technique overestimates the ligament thickness. Good agreement was found between the facet counting technique and the 3-dimensional watershed for assessing thickness. The proposed techniques are applicable for ligaments’ thickness estimation on clinical breast images, provided segmentation of Cooper’s ligaments has been performed.

Keywords: Anthropomorphic breast phantoms, phantom validation, digital mammography, Cooper’s ligaments, breast imaging, computational geometry.

Summary:

Anthropomorphic breast phantoms are important tools for pre-clinical validation of novel imaging techniques. We present three methods (2-dimensional watershed, 3-dimensional watershed, and facet counting) to assess the thickness of the simulated Cooper’s ligaments in the phantoms. For the validation of simulated phantoms, the thickness of phantom ligaments has been measured and compared with the nominal values. We demonstrated that the 2-dimensional watershed technique overestimates the ligament thickness. The facet counting technique is comparable to the 3-dimensional watershed. The proposed techniques are applicable for segmentation of clinical 3-dimensional reconstructed images, provided segmentation of Cooper’s ligaments has been performed.

*akuperavage@desu.edu; phone: 1 302 857-7688
1. INTRODUCTION

The development of efficient clinical breast imaging systems is essential for improving the prognosis in breast cancer patients. Preclinical validation of these systems using real breast images includes serious risks due to the exposure to ionizing radiation and can be costly and time consuming. For example, The ACRIN DMIST trial took 5 years, approximately 50,000 patients, and $26M to demonstrate that digital mammography is practically equivalent to screen-film imaging. A preclinical alternative, Virtual Clinical Trials (VCT), is based upon the simulation of human anatomy, image acquisition, and image analysis through mathematical observer models. As an integral part of the VCT, high resolution anthropomorphic software phantoms have been developed at Delaware State University and the University of Pennsylvania, simulating the breast outline covered by a skin layer, and the breast interior by compartments filled with adipose or fibro-glandular (dense) tissue separated by Cooper’s ligaments.

The recent development of octree-based recursive partitioning algorithms provides a fast, efficient method for simulating software breast phantoms. This development opens the possibility for large scale VCT with specified phantom tissue characteristics. The algorithm contains mechanisms to control for the thickness of the Cooper’s ligaments, and the size and orientation of the tissue compartments. The ability to control for tissue properties is crucial to achieving realistic simulated phantoms. Specifically, the thickness of simulated Cooper’s ligaments influences the percentage of dense tissue and therefore the qualitative and quantitative properties of simulated images. Validation of the thickness control mechanism in the algorithm is necessary for further refinements of the phantoms. Additionally, the need to control for septa thickness is necessary in applications such as mesoscale simulation of breast tissue and simulation of tissue repair and regeneration.

The purpose of this study is to present three methods (2-dimensional watershed (2DW), 3-dimensional watershed (3DW), and facet counting (FC)) to test if the nominal thickness control of the Cooper’s ligament in anthropomorphic breast phantoms has been achieved. The three methods were applied on a series of phantoms of varying tissue characteristics. The results were compared to the nominal thickness inputted to the algorithm.

2. METHODS

2.1 Anthropomorphic Breast Phantoms

For the validation of simulated phantoms, the measured thickness of phantom ligaments was compared with the nominal values selected in prior. These included a total of 64 anthropomorphic octree phantoms with nominal ligament thicknesses of 200, 400, 600, and 800 μm, see Fig. 1. The chosen range covers an estimated thickness of Cooper’s ligaments from histological data (289 μm). We used phantoms with linear dimension Δ=100 μm and size of 500*1000*1700 voxels, corresponding to 450 cm³ (approximately a B-cup size). The simulated phantoms had skin thickness of 1.5 mm. We varied the following factors: nominal ligament thickness (4 values: 0.2, 0.4, 0.6 and 0.8 mm); number of compartments (2 values: 167 and 333) and combinations of minimal and maximal speeds (2 combinations: (1,1) and (0.01,100)) and minimal and maximal ratios (2 combinations: (1,1) and (0.25,4)). For each of 32 combinations of parameter values, we simulated 2 phantoms with different random number generator seeds. For each phantom geometry, exact and non-exact computation of the distance between a boundary voxels and the ligament medians were computed. Three values of parameter p regulating thickness control were utilized. This resulted in the total of 384 (4*2*2*2*2*3*2) simulated phantoms.

Fig. 1 shows details of the phantoms with same geometry (specified by the phantom parameters) but varied nominal thickness. From Figs 1(a)-1(d) it is clear that the thickness of ligaments increases with the value of nominal thickness. Also, for larger values of the nominal thickness (e.g., 800 μm, Fig. 1(d)), the “dents” are observable, which influence the observed (and measured) difference between the nominal and actual thickness.
2.2 2DW and 3DW
In the watershed transformation, the image is visualized as a topographic map with pixel intensity corresponding to elevation. Points can be considered as three types: a) those that belong to a local minimum; b) points at which, if water droplets were placed on them, the droplet would migrate towards a certain local minimum; and (c) points where droplets would be equally likely to migrate to two or more local minima \(^4\). The third type of points forms the median skeleton. In both the 2DW and the 3DW methods the estimated average thickness was calculated by finding a median skeleton through the ligaments (See Fig. 2), then dividing the total volume of the ligaments by the total volume of skeleton. For the 2DW, the median skeleton was determined for each cross-section of the phantom individually using 8-point connectivity, while in the 3DW median skeleton was calculated for the entire 3-dimensional ligaments’ system using 26-point connectivity.

2.3 FC
The FC method is based on principles from stereology \(^5\). Consider ligament voxels \(v_i\), \(i=1,...,N\) that belong to the segmented Cooper’s ligaments. For each voxel \(v_i\) we determine the number \(n_i\) of compartmental voxels in its 6-neighborhood \(^6\), see Fig. 3. This number is equal to the number of voxel’s facets facing a compartmental tissue. The total volume of the ligaments is equal to:

\[
V = N \Delta^3.
\]

The average surface of the ligaments is:
\[ S = \frac{1}{2} \sum_{i=1}^{N} n_i \Delta^2. \]  

(2) 

Hence, the estimated average ligament thickness is:

\[ d_{FC} = \frac{2N \Delta^3}{\sum_{i=1}^{N} n_i \Delta^2} = \frac{2N}{\sum_{i=1}^{N} n_i} \Delta. \] 

(3) 

Figure 3. Illustration of voxels on one of the surfaces of a ligament. Numbers indicate the number of voxel facets adjacent to the simulated Cooper’s ligament tissue (bounding the ligament voxels from above).

2.4 Statistical Analysis

The following parameters of the phantom were varied: nominal thickness (four levels, 0.2, 0.4, 0.6 and 0.8 mm), number of compartments (167 and 333), minimal and maximal ratio ((1,1) and (0.25,4)) and minimal and maximal speed ((1,1) and (0.01,100) [1]). We generated phantoms with approximate (E=1)\(^7\) and exact computation (E=2) of distances between ligament voxel vertices and the ligament median. We calculated phantoms with thickness control parameter \(p \in \{1,2,3\}\). Note that \(p=1\) corresponds to the original algorithm (no improved thickness control). The effect of nominal thickness, number of compartments, minimal ratio, minimal speed, approximate or exact computation on the measured thickness were assessed utilizing multifactorial ANOVA for the measured thickness of 3DW and FC, followed by multiple comparison tests by Tukey\(^{18}\). Alpha=0.05 was the significance level.

3. RESULTS

Fig. 4 shows the relationship between nominal ligament thickness and measured thickness using the three methods (2DW, 3DW and FC) for the phantoms. Also shown are regression lines. The linear model for dependency of measured vs. nominal thickness for all three methods was significant (The \(R^2\) values were larger than 0.99 with p-values smaller than 0.0001). The 3DW and FC display remarkably similar results, although the FC appears slightly higher for 400 \(\mu\)m, 600 \(\mu\)m, and 800 \(\mu\)m. The measured 3DW and FC values are above the nominal thickness at 200 \(\mu\)m, while their measured values are below the nominal thickness for 400 \(\mu\)m, 600 \(\mu\)m, and 800 \(\mu\)m.
By looking at Fig. 4 we can see that the measured thickness increases with the nominal thickness, which confirms that the thickness control was achieved. 2DW resulted in consistently larger measured thickness than 3DW or FC. This can be explained by non-orthogonality of 2DW cross-sectional planes and median surfaces of ligaments, see Fig. 5.

**Figure 4.** Measured thickness for phantoms with different nominal thickness, obtained using 2D watershed (blue), 3D watershed (red), FC (green). Regression lines for dependency of measured vs. nominal thickness for the methods are also shown.

**Figure 5.** 2DW overestimated the thickness of ligaments not orthogonal to the cross-sectional planes.
Figs. 2 and 6 show an example of the three methods execution. By comparing Figs. 2(a) and 2(b), it is evident that 3DW results in a thicker skeleton than 2DW, and as a consequence, in smaller estimated ligament thickness. Figs. 6 (a)-(b) indicate that the number of compartmental voxels that neighbor ligament borders is 1 (dark blue) when the voxels are on the surface of the ligaments. The number of neighboring voxels increases to 2 (light blue) for voxels on the edges, and increases to 3 or 4 for voxels on the vertices (yellow or red, respectively).

Table 1. ANOVA table of simulation parameters for FC measured thickness. * Indicates significance at alpha < 0.05.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>d.f.</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob&gt;F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal Thickness</td>
<td>0.10042</td>
<td>3</td>
<td>0.03347</td>
<td>46104.27</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td># of Compartments</td>
<td>0.00006</td>
<td>1</td>
<td>0.00006</td>
<td>88.22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>E</td>
<td>0.01109</td>
<td>1</td>
<td>0.01109</td>
<td>15267.49</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MinRatio</td>
<td>0.00003</td>
<td>1</td>
<td>0.00003</td>
<td>39.97</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MinSpeed</td>
<td>0.00000</td>
<td>1</td>
<td>0.00000</td>
<td>0.24</td>
<td>0.6223</td>
</tr>
<tr>
<td>p</td>
<td>0.00047</td>
<td>2</td>
<td>0.00024</td>
<td>324.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Error</td>
<td>0.00027</td>
<td>374</td>
<td>0.00000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.11234</td>
<td>383</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results of ANOVA, Table 1 and 2, indicate that the measured thickness significantly depends on nominal thickness, number of compartments, minimal ratio, as well as on the choice of the distance measurement (exact vs. approximate) and the thickness control parameter P. Minimal speed (indicating the compartment sizes) was not statistically significant.
Table 2. ANOVA table of simulation parameters for 3DW measured thickness. * Indicates significance at alpha <0.05.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum Sq.</th>
<th>d.f.</th>
<th>Mean Sq.</th>
<th>F</th>
<th>Prob&gt;F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal Thickness</td>
<td>0.07319</td>
<td>3</td>
<td>0.02440</td>
<td>57127.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td># of Compartments</td>
<td>0.00002</td>
<td>1</td>
<td>0.00002</td>
<td>47.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>E</td>
<td>0.00806</td>
<td>1</td>
<td>0.00806</td>
<td>18868.05</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MinRatio</td>
<td>0.00010</td>
<td>1</td>
<td>0.00001</td>
<td>238.59</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MinSpeed</td>
<td>0.00000</td>
<td>1</td>
<td>0.00000</td>
<td>3.07</td>
<td>0.0805</td>
</tr>
<tr>
<td>p</td>
<td>0.00017</td>
<td>2</td>
<td>0.00009</td>
<td>202.54</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Error</td>
<td>0.00016</td>
<td>374</td>
<td>0.00000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.08170</td>
<td>383</td>
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</table>

Tukey’s test yielded significant differences between all groups within nominal thickness, number of compartments, E, and minimal ratio for both FC and 3DW. For P, P=1 (the level corresponding to the original algorithm) was significantly different from P=2, and P=3, but P=2 and P=3 for not significantly different from each other for FC and 3DW.

4. DISCUSSION

The experimental results indicate that thickness control of the septated tissue is achieved. Increase of the nominal thickness leads to an approximately linear increase of the measured thickness for all the methods. 2DW leads to an overestimation of thickness, if the image plane is not perpendicular to the ligament boundaries. FC and 3DW have comparable results in that they both seem to underestimate thickness at nominal thicknesses of 400 μm and higher. However, the current simulation leaves “dents” in the ligaments, hence achieved thickness is less than nominal. The proposed methods can provide the upper and the lower bound to the actual thickness.

The multiple comparison confirms that we are capable of thickness control (the measured thickness increases of the nominal). The introduction of the exact method to compute the distance between vertices and the ligament median resulted in the significant increase of the measured thickness (approximately 0.1mm). We believe this can be attributed to the reduction of dents. The use of a method for improved thickness control (P>1) resulted in larger measured thickness. The change of the parameter P from 2 to 3 did not significantly increase the measured thickness. The measured thickness significantly changed with the number of compartments but the change was small. The larger spread of ratios (0.25,4) resulted in slightly higher measured thickness.

Our future work will include a thorough evaluation of the anthropomorphic phantoms in order to determine whether ligament thickness depends on spatial coordinates. This can be done e.g., by splitting the phantom into smaller regions of interest (i.e., 4 quadrants). Also, we will measure average thickness for each ligament. We will evaluate the effects of new strategies for dent reduction on measured ligament thickness. We will assess the influence of ligament thickness on the percentage of dense tissue and quantitative properties of simulated images. A work in progress includes the application of these proposed techniques for ligament thickness estimation from segmented clinical 3-dimensional reconstructed images. As is evident on Fig. 1 (a-d), increasingly prominent “dents” emerge with increasing nominal thickness. Recently developed improvements in the algorithm greatly reduce the appearance of dents. Future research will also be directed towards the effect of dent reduction on nominal thickness.
Disclosure: The presented work has not been submitted for publication anywhere else.

REFERENCES