Published in final edited form as:

Phys Med Biol. 2010 June 7; 55(11): 3027–3044. doi:10.1088/0031-9155/55/11/003.

Validation of a method for measuring the volumetric breast density from digital mammograms

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Abstract

The purpose of this study was to evaluate the performance of an algorithm used to measure the volumetric breast density (VBD) from digital mammograms. The algorithm is based on the calibration of the detector signal versus the thickness and composition of breast-equivalent phantoms. The baseline error in the density from the algorithm was found to be $1.25 \pm 2.3\%$ VBD units (PVBD) when tested against a set of calibration phantoms, of thicknesses 3–8 cm, with compositions equivalent to fibroglandular content (breast density) between 0% and 100% and under x-ray beams between 26 kVp and 32 kVp with a Rh/Rh anode/filter. The algorithm was also tested against images from a dedicated breast computed tomography (CT) scanner acquired on 26 volunteers. The CT images were segmented into regions representing adipose, fibroglandular and skin tissues, and then deformed using a finite-element algorithm to simulate the effects of compression in mammography. The mean volume, VBD and thickness of the compressed breast for these deformed images were respectively 558 cm³, 23.6% and 62 mm. The displaced CT images were then used to generate simulated digital mammograms, considering the effects of the polychromatic x-ray spectrum, the primary and scattered energy transmitted through the breast, the anti-scatter grid and the detector efficiency. The simulated mammograms were analyzed with the VBD algorithm and compared with the deformed CT volumes. With the Rh/Rh anode filter, the root mean square difference between the VBD from CT and from the algorithm was 2.6 PVBD, and a linear regression between the two gave a slope of 0.992 with an intercept of -1.4 PVBD and a correlation with $R^2 = 0.963$. The results with the Mo/Mo and Mo/Rh anode/filter were similar.

1. Introduction

Mammographic breast density (MBD) represents the appearance of the stroma and epithelial tissue (collectively referred to as fibroglandular tissue) on the mammogram. Areas containing fibroglandular tissue are distinguished from surrounding fatty tissue due to the larger x-ray attenuation coefficient of the former (Johns and Yaffe 1987). High MBD has been identified as a strong risk factor for the development of breast cancer. Wolfe (1976, 1976a) first proposed this relationship, which has been confirmed by others (Saftlas and Szklo 1987, Heine and Malhotra 2002, 2002a, Goodwin and Boyd 1988, Boyd *et al* 2007), showing a two- to fourfold increase in risk between women with low and high MBD. In addition, it is more difficult to obtain an accurate interpretation of mammograms of dense breasts; there is a greater likelihood of both missed cancers and false positive results

(Whitehead *et al* 1985, Sala *et al* 1998, van Gils *et al* 1998). The assessment of MBD is, therefore, a potentially important tool. It can be used to identify women at increased risk who could benefit from more frequent screening or the use of alternative imaging and diagnostic methods (van Gils *et al* 1999). Also, MBD is one of the strongest risk factors that can be modified through adjustment of other factors, such as diet (Tseng *et al* 2007, Takata *et al* 2007) and physical activity (Irwin *et al* 2007). A causal link between MBD and breast cancer remains to be demonstrated.

Many of the currently used tools for assessment of mammographic density rely on two-dimensional measurements and express MBD in terms of the fraction of the projected area of the breast that appears to be composed of fibroglandular tissue. It is more logical, however, that cancer risk is related to the number of fibroglandular cells, which is proportional to the volume of dense tissue in the breast and, therefore, there is an interest in the measurement of volumetric breast density (VBD). Furthermore, knowledge of breast composition is required for estimation of the radiological dose to the breast in medical imaging (Yaffe *et al* 2009) and a more accurate estimation of composition could improve the validity of dose estimation.

There have been many methods developed to estimate the volumetric radiological breast density. Frequently, the most practical way to obtain the VBD is from mammograms, as women frequently receive this examination for breast cancer screening. Highnam *et al* (1996, Highnam and Brady 1999) have developed a physics model of the complete imaging system in screen-film mammography in order to extract the thickness of fibroglandular tissue, a quantity that they refer to as h_{int} . Van Engeland *et al* (2006) described a simple physical model of full-field digital mammography to calculate the VBD and have shown good agreement with breast density measurement using magnetic resonance imaging. Pawluczyk *et al* (2003) and Kaufhold *et al* (2002) have developed methods, relating the transmitted signal measured on breast tissue-equivalent calibration objects to their known thickness and compositions, and have applied this relation to estimate VBD using mammograms of breasts. Another approach, a version of the dual-energy x-ray absorptiometry technique used for bone densitometry, modified for use in the breast (Shephard *et al* 2002), can, in principle, offer precise measurements of the VBD at very low doses but requires a dedicated and separate procedure.

A breast density algorithm, Cumulus V, was developed as a refinement of the method by Pawluczyk *et al* (2003) by adapting it to digital mammography and by using a combination of measurement and modeling to estimate the compressed breast thickness (Mawdsley *et al* 2009, Tyson *et al* 2009).

For any method that attempts to quantify the mammographic density from projection images, it is necessary to test the accuracy of that method. In this work, we use volumetric attenuation data obtained with a prototype dedicated breast computed tomography (DBCT) system developed at the University of California, Davis (Boone *et al* 2006, 2006a, 2001, Lindfors *et al* 2008) to perform such a validation on the Cumulus V algorithm.

2. Materials and methods

The approach used to validate Cumulus V is summarized in figure 1. Women were imaged on a prototype breast CT system (Boone *et al* 2006, 2006a, 2001, Lindfors *et al* 2008) and the CT image slices were segmented according to the major tissue types, fibroglandular, fat and skin. The CT data were then ‘deformed’ using finite-element analysis to simulate mechanical compression of the breast. The deformed breast volume was converted to x-ray attenuation coefficients, according to the tissue type, at energies such as those used in

mammography and simulated projection digital mammograms were created. Finally, the simulated mammograms were analyzed with Cumulus V, and the resulting VBD was compared to the VBD from the deformed CT volume.

2.1. Breast CT

The acquisition and processing of the CT image information is depicted in figure 1. During CT imaging on the prototype CT system, the patient lies prone on a table with the breast pendant through an aperture. An x-ray tube and a flat-panel detector array rotate about the breast to acquire the projection data. The cone-beam projections are acquired at 80 kV with a tungsten target and 0.3 mm copper filtration. CT images are then reconstructed from the projection data. The images are stored as a volumetric array of x-ray attenuation coefficients, each representing tissue in a volume (voxel) with dimensions between 0.21 mm and 0.41 mm in the coronal plane, and between 0.25 mm and 0.41 mm in the sagittal plane.

The CT scans were reconstructed in terms of effective attenuation coefficients. These measurements reflect the x-ray energy fluence transmitted by the breast and absorbed by the flat-panel detector. They include the effects of x-ray scattering and beam hardening. Following image reconstruction, a ‘cupping’ correction was performed to correct for scatter and hardening artifacts.

The voxels in the CT image were classified into four components: air (breast exterior), skin, adipose and fibroglandular tissue. The frequency distribution of attenuation coefficients was computed and the threshold between the breast and the air, which has low CT values, was determined. Because skin and fibroglandular tissue have similar CT values, we initially used a two-compartment Gaussian fit to segment the histogram. This allowed the determination of a threshold voxel value at the intersection of the two Gaussian distributions. To verify whether the threshold was satisfactory (in some cases the Gaussian functions were not well separated), images of central slices in the transverse, coronal and sagittal planes were displayed and the threshold was adjusted manually until the most satisfactory separation between the skin/fibroglandular tissue and the fat was obtained. To identify the voxels representing skin, the periphery of the breast was determined for each slice, and a morphological dilation operator was applied to dilate the periphery by an amount similar to the thickness of the skin (approximately 1.5 mm, Huang *et al* 2008). The voxels that were in the dilated periphery and also previously segmented in the fibroglandular class (which included the skin) were classified as skin voxels. Finally, a 3×3 integer median filter was applied to the classified slices. The segmentation reduced the noise in the image but also removed some detail in the parenchyma (see figure 2). The VBD was calculated as

$$\text{VBD}_{\text{sk}} = (V_{\text{fg}} + V_{\text{sk}}) / (V_{\text{fg}} + V_{\text{ad}} + V_{\text{sk}}), \quad (1)$$

where V_{fg} , V_{ad} and V_{sk} are respectively the volumes of fibroglandular, adipose and skin tissues. We also computed the VBD excluding the skin as

$$\text{VBD}_{\text{nsk}} = V_{\text{fg}} / (V_{\text{fg}} + V_{\text{ad}} + V_{\text{sk}}). \quad (2)$$

2.2. Deformation

2.2.1. General—A number of finite-element studies have been conducted to simulate the deformation of breast tissue to investigate the effect of material properties (Tanner *et al* 2006) and mechanical compression (Qiu *et al* 2004, Kellner *et al* 2007). These tools were

used in our study to simulate the mechanical displacements that would occur under compression of the breast in mammography.

From the segmented data obtained from the CT images of the volunteers, 3D finite-element representations of the breast were constructed, and the linear elastic material properties (Kellner *et al* 2007) as listed in table 1 were attributed correspondingly to the skin, fat and fibroglandular tissue classes.

To simulate the compression of the breast, the finite-element breast model is placed between two rigid plates with rounded corners (with 0.5 cm radius). The bottom plate is initially raised to an appropriate fixed position under the breast to provide support and the top plate moves downward to achieve the specified target thickness for the ‘compressed’ breast (see figure 3). The plates were offset toward the nipple (i.e. away from the chest wall) by approximately 2 cm to facilitate mechanical modeling of the compression. The target compression thickness was selected as a function of breast diameter at the chest wall using the relation determined by Boone *et al* (2005).

2.2.2. Boundary conditions—The surface of the breast at the chest wall plane (where it attaches to the thorax) is allowed to be displaced in the superior–inferior direction only. The breast is allowed to slide on the plates as compression is applied using a contact-surface model consisting of the external surface of the skin, and the surface of the plates facing the breast. A coefficient of friction of 0.1 is used to simulate the movement restriction of the breast in contact with plates. Similar values have been used by Pathmanathan *et al* (2008) and Yin *et al* (2004), but to the best of our knowledge, experimental coefficients of friction between the breast and compression plate are not available. Finally, in order to accommodate large deformation of the breast, nonlinear geometry is used in the analysis.

2.3. Mammogram simulation

The deformation algorithm produced a displacement vector for each point in the volume. These were used to displace the initial segmented CT volume $m_0(x, y, z)$, where m_0 represents the tissue composition, initially having the two possibilities after segmentation of $m_0 = 1$ for fibroglandular tissue and $m_0 = 0$ for adipose tissue, to the new ‘destination’ points. These were then interpolated onto a regular Cartesian grid using a three-dimensional Gaussian kernel scaled to the appropriate voxel dimensions. The result was a displaced fractional density map $m(x, y, z)$, which was converted into x-ray attenuation values μ using

$$\mu(x, y, z, E) = m(x, y, z) \cdot \mu(E)_{fg} + (1 - m(x, y, z)) \cdot \mu(E)_f, \quad (3)$$

with μ_{fg} and μ_f the attenuation of fibroglandular and fatty tissue respectively, and E the x-ray energy. Note that the interpolation allows m to assume any value between 0 and 1. The attenuation values were obtained from Byng *et al* (1998) for breast equivalent plastic. A second interpolation was performed to displace the skin voxels only, which were then converted to attenuation values for skin, obtained from Hammerstein *et al* (1979) and then merged to complete the volume. The energies corresponded to a spectrum chosen as a function of the compression thickness (see table 2). A ray-tracing algorithm adapted from Siddon (1985) was then used to model the transmission of an obliquely incident x-ray beam through the volume, so that for each ray path, a product of attenuation coefficient and thickness, $\mu(E)T$, at each energy, E , was obtained. The $\mu(E)T$ maps were then interpolated onto the simulated detector plane at a 0.25 mm detector element size. For this simulation, the lower surface of the breast was assumed to lie $d = 10$ mm above the detector plane (corresponding to the upper surface of the anti-scatter bucky), with a source to image distance (SID) of 660 mm. The source was located directly above the center of one edge of

the detector, corresponding to the chest wall of the patient, as illustrated in figure 4. The thickness of the breast, $T(x, y)$, was determined by projecting a volume of unity attenuation. The compression thickness of the breast was calculated as an average over the relatively flat portion of the thickness map.

The relative signal due to the energy from directly transmitted (primary) x-rays, $P(x, y)$, was calculated as

$$P(x, y) = \frac{\int \phi(E) \cdot e^{-\mu(E)T} \cdot \eta(E) \cdot \Gamma E \cdot dE}{\int \phi(E) \cdot \eta(E) \cdot \Gamma E \cdot dE}, \quad (4)$$

where $\eta(E) = (1 - e^{-\mu_d(E)T_d}) \cdot \mu_{den}/\mu_d$ is the fraction of x-ray photons absorbed in the detector medium of thickness T_d and of linear attenuation, and linear absorption coefficients μ_d and μ_{den} , respectively. In this expression, Γ is the number of electron-hole pairs or scintillation photons generated per unit of absorbed x-ray energy and is assumed to be constant over the x-ray spectrum. The spectrum $\phi(E)$ was obtained from Boone *et al* (1997). The detector material used was CsI:TI at a thickness of 120 μm , and the attenuation coefficients of the material were obtained from the NIST database (Hubbell and Seltzer 1996). The expression in the denominator is used to normalize the spectrum to unit area.

The relative signal due to scatter energy, $S(x, y)$, was simulated by convolution, using the scatter point-spread function (PSF) data of Boone *et al* (Boone and Cooper 2000, Boone *et al* 2000). The functions were interpolated from the 1 cm thickness intervals and 50% fractional fibroglandular tissue composition intervals provided by Boone *et al* to 2 mm thickness intervals and 10% composition intervals, respectively. The scatter was calculated for the compression thickness, T , and average composition, $\bar{m}$, of the breast and at each E . It was found that truncation of the scatter PSFs to a square region, 22 cm on a side, had a negligible effect on the scatter calculations:

$$S(x, y) = \frac{\int \phi(E) \cdot [\text{FOV}(x, y) \otimes S_{\text{PSF}}(x, y; E, T, \bar{m})] \cdot \eta(E) \Gamma \cdot dE}{\int \phi(E) \cdot \eta(E) \cdot \Gamma E \cdot dE}, \quad (5)$$

where $\text{FOV}(x, y)$ is defined as unity where the breast is present and zero elsewhere, $S_{\text{PSF}}(x, y)$ is the scatter point spread function in units of scattered energy per incident primary photon and $T(x, y)$ is the thickness of the breast.

Because the value for the gain, Γ , is unknown, the relative signals obtained in equations (4) and (5) were scaled to the response of an actual detector (GE Senographe DS) by multiplying them by an experimental flat-field image $I_0(x, y)$, expressed in analog-to-digital units (ADU). It was acquired at the same kilovoltage (kVp) as used in the simulation of P and S , and divided by its mAs exposure. This procedure also automatically corrected for the remaining small variations in the image after the flat-fielding correction, and the effect of the inverse-square law.

We also included the effects of the anti-scatter grid and of detector glare. We used a method similar to Carton *et al* (2009) to measure the grid performance parameters. The point spread function due to detector glare, G_{PSF} , was measured in a similar method to that used by Lutha and Rowlands (1990). It is obtained by measuring the signal at the center of a series of radio-opaque lead disks with different diameters. The G_{PSF} was fitted to a relation $G_{\text{PSF}} = F_1 \cdot e^{-r/r_1} + F_2 \cdot e^{-r/r_2}$ where r is the distance from the center of a pixel of interest to a point (x, y) in the detector plane. The G_{PSF} accounts for the low-frequency blurring of the

detector. No correction for the high-frequency blurring was applied because the density is evaluated at a relatively coarse spatial scale.

Thus, the simulated mammogram $I(x, y)$ in units of ADU is given by

$$I(x, y) = \left[\frac{I_0(x, y)}{T_p(0)} \cdot mAs_I \cdot \left(T_p(T) \cdot P(x, y) + \frac{T_s(T) \cdot S(x, y)}{(1 - (T(x, y) + d)/SID)^2} \right) \right] \otimes G_{\text{PSF}}(x, y), \quad (6)$$

where mAs_I is the desired exposure, and $T_p(T)$ and $T_s(T)$ are respectively the primary and scatter transmission of the anti-scatter grid as a function of the average tissue thickness T . Since I_0 is obtained in the detector plane, and S is expressed per incident primary photon, (i.e. at the entrance plane of the breast), it is necessary to scale I_0 for the scatter portion of the image using the inverse-square law. Three sets of simulated mammograms were generated, for the Rh/Rh, Mo/Rh and Mo/Mo anode/filter combinations.

To test equation (6), images of slabs of tissue-equivalent plastic of 0% density and of dimensions $10 \text{ cm} \times 12.5 \text{ cm}$, with thicknesses of 3, 5 and 7 cm, were simulated at 26, 28, 30 and 32 kVp with a Rh/Rh anode/filter and compared with the corresponding experimental images. The differences in signal $\Delta I = I_{\text{exp}} - I_{\text{simu}}$ were observed, where I_{exp} and I_{simu} are the mean signal values of the phantom images for the experiment and simulation, respectively. ΔI was also converted to its corresponding difference in VBD, $\Delta M = \Delta I \cdot D_{\text{pm}}$. The sensitivity D_{pm} was calculated as $D_{\text{pm}} = 100\% \cdot dm/dI$, where I is the image pixel value at the center of a $12.5 \times 10 \times T \text{ cm}^3$ parallelepiped calculated using equation (6), and with $\mu = \mu_{\text{fg}} \cdot m + \mu_{\text{f}} \cdot (1 - m)$ in equation (4).

2.4. Volumetric density measurement algorithm

2.4.1. Calibration—An algorithm, Cumulus V, was developed for quantification of the VBD from mammograms as a refinement of the calibration method of Pawluczyk *et al* (2003). For a given target/filter combination, breast equivalent phantoms (by CIRS, Norfolk, VA, USA) of various thicknesses T containing cylindrical ‘plugs’ 2.54 cm in diameter, nominally equivalent to a breast fat and fibroglandular tissue mixture, are imaged at different kVp settings. To keep the contribution from scatter constant, the plugs are surrounded by regions composed of 50% adipose and 50% fibroglandular equivalent material of the same thickness as illustrated in figure 5. The images are first divided by the corresponding mAs exposure, and the detector signal values for fat, $I_{\text{f}}(\text{kVp}, T)$, and fibroglandular, $I_{\text{fg}}(\text{kVp}, T)$, are obtained as an average over the projected image of the disk. At the same kVp and anode/filter combinations, the signal $I_0(\text{kVp})$ with no object in the field is obtained at the same locations as I_{f} and I_{fg} , and also divided by the mAs. The calibration is completed by computing two empirical relations: f_0 for fat and f_1 for fibroglandular tissue, obtained by fitting a two-dimensional second-degree polynomial surface to the signal values:

$$\ln \left(\frac{I_{\text{f}}(\text{kVp}, T)}{I_0(\text{kVp})} \right) = f_0(\text{kVp}, T) = \sum_{i,j=0}^2 a_{ij} \text{kVp}^i T^j \quad (7)$$

$$\ln \left(\frac{I_{\text{fg}}(\text{kVp}, T)}{I_0(\text{kVp})} \right) = f_1(\text{kVp}, T) = \sum_{i,j=0}^2 b_{ij} \text{kVp}^i T^j \quad (8)$$

where a_{ij} and b_{ij} are the coefficients of a polynomial least-squares fit. The calibration procedure is repeated for the three target/filter combinations: Mo/Mo, Mo/Rh and Rh/Rh. We note that the attenuation coefficients of the tissue-equivalent plastic materials (Byng *et al* 1998) used for the calibration are slightly different than those of actual breast tissue (Johns and Yaffe 1987). For consistency we used the plastic attenuation values in the simulated mammograms described in section 2.3. The Cumulus V algorithm contains a correction, based on equation (6), to account for the difference in attenuation coefficients between the plastic and tissue.

2.4.2. Density measurement—With the image of a breast or phantom $I(x, y)$ obtained at a given kVp and mAs, the oblique path length through the breast

$T'(x, y) = T(x, y) \cdot \sqrt{1 + (x^2 + y^2)/SID^2}$, where $T(x, y)$, the thickness perpendicular to the x, y plane, is determined from the mammography system with appropriate corrections (Mawdsley *et al* 2009, Tyson *et al* 2009) and the values $f_0(\text{kVp}, T)$, $f_1(\text{kVp}, T)$ and

$f_m(x, y) = \ln \left(\frac{I(x, y)}{mAs \cdot I_0(\text{kVp})} \right)$ are computed. The breast density $m(x, y)$ for the path through tissue corresponding to each image pixel is determined by linear interpolation between the

values f_0 and f_1 , so that $m(x, y) = \frac{f_m(x, y) - f_0}{f_1 - f_0}$. Finally, the VBD is computed as

$$VBD = \frac{\sum_{x,y} m \cdot V_c}{\sum_{x,y} V_c}$$
, where V_c is the volume of the column of tissue above the pixel at the location (x, y) . V_c is a truncated slanted pyramid, of volume $V_c = (L/SID)^2 a^2 T \cdot [1 - T/L + T^2/3 \cdot L^2]$, where a is the pixel dimension and $L = SID - d$, with $d = 10$ mm the gap between the bottom of the object and the detector due to the bucky.

The density with no skin is also estimated by subtracting the ratio V_{sk}/V_{TOT} from the VBD. The total volume is $V_{TOT} = \sum_{x,y} V_c$, while the volume of skin V_{sk} is approximated by assuming a 1.5 mm layer of skin around the breast (Huang *et al* 2008). Thus, $V_{sk} = \sum_{x,y} a^2 \cdot \delta \cdot 3 \text{ mm}$. The factor $\delta = 1.03$ accounts for the approximately 3% higher attenuation of skin compared to pure fibroglandular tissue (Hammerstein *et al* 1979), at the mean energies used in mammography.

The precise thickness $T(x, y)$ of the compressed breast in clinical mammography is not generally available. In Cumulus V, the method of Mawdsley *et al* (2009) and Tyson *et al* (2009) is used to predict the thickness of the breast at every point. However in this work, where the mammograms were simulated from CT, the thickness map $T(x, y)$ of the breast was known exactly.

3. Results

3.1. CT analysis and deformation

As a first test of the deformation procedure, we compared the volumes and VBD of the CT data (26 cases) and of the displaced volume. We found that the displacement conserved the total breast volume within an average of 1.5% of the original CT-derived value, whereas the VBD was conserved within 4.4%, on average, relative to the CT-derived absolute units of percent VBD (PVBD). The mechanical deformation procedure required offsetting the compression plates toward the nipple for the application of boundary conditions. This resulted in approximately 33% of the total breast volume, located in a region proximal to the chest wall not being fully compressed to constant thickness when the deformation was applied. For the purposes of validation of the Cumulus algorithm, the portion of the breast

for which there was not uniform compression was cropped from the dataset and the remainder of the data were used for mammogram simulation. Therefore, the absolute volumes of the deformed and cropped breast and of its dense tissue in this comparison will be substantially lower than those in the entire breast. Figure 6 illustrates the deformation and cropping processes.

For the purposes of comparison with Cumulus V, the VBD determined by CT, VBD_{CT} , was computed as the mean of the displaced fractional density volume $m(x, y, z)$, within the cropped region. The total breast volume determined by CT, V_{CT} , was also calculated on the deformed and cropped breast volume. The average VBD_{CT} , V_{CT} and compressed thickness of the 26 cases were 23.6%, 558 cm³ and 62 mm, respectively. The mean relative difference between VBD_{CT} and the un-cropped original VBD from the CT image was 9%. The difference is explained by the presence of pectoralis muscle, segmented as fibroglandular tissue, often present near the chest wall, but removed by the cropping.

3.2. Mammogram simulation

Table 3 provides a summary of the results for the grid performance as a function of thickness, for all the beam configurations. Generally, our experimental uncertainties in T_p , the primary transmission, and T_s , the scatter transmission, were respectively ± 0.01 and ± 0.02 .

In the characterization of glare, G_{PSF} , under exposure conditions of 29 kVp and a Rh/Rh anode/filter, we measured $F_1 = 0.08$, $F_2 = 0.03$, $r_1 = 3.1$ mm and $r_2 = 13.9$ mm. We found no substantial difference in the parameters for the other exposure conditions.

In the testing of the simulation versus experimental images of slabs, figure 7 shows the distribution of values (in ADU/mAs) in the simulated and experimental phantom images, for thickness 5 cm and 7 cm simulated and imaged at 28 kVp and 30 kVp respectively with a Rh/Rh anode/filter. The distributions were obtained over a central region of the phantom image, covering approximately 85% of the phantom's projected surface. Figure 8(a) shows the comparison of the means of the distributions for all the thicknesses and kVp, and figure 8(b) the corresponding difference in density ΔM between the experiment and simulation. The sensitivity D_{pm} in PVBD/(ADU/mAs) is shown in table 4.

The distributions of values between the experimental and simulated phantom images were remarkably similar. The root mean square (rms) $\text{rms}(\Delta I)$ was 0.72 ADU mAs⁻¹, which corresponds to an rms error of 2.4% in the signal. Those errors in the signal resulted in a corresponding rms difference of 2.4 PVBD between the experiment and simulation.

3.3. Cumulus V

Cumulus was tested for self-consistency by analyzing images of the calibration phantoms (from a separate exposure), which also contain plugs of intermediate density (see figure 5). Figure 9 shows a histogram of the absolute density difference between the true density of the cylindrical plug (m_{exp}) and the estimated density (m_{calc}), calculated at each pixel over the area of the plugs from phantoms of 3–8 cm thicknesses imaged at 26, 28, 30 and 32 kVp with a Rh/Rh target/filter. The mean difference $m_{exp} - m_{calc}$ was 1.25 PVBD with a standard deviation of 2.3 PVBD.

3.4. Comparison of Cumulus with simulated mammograms

The 26 CT volumes were segmented, deformed, projected and used to simulate an image using equation (6). The values for the glare functions are found in section 3.2, and the values for $T_p(T)$ and $T_s(T)$ were linearly interpolated at the compressed thickness of the breast using

the values of table 3. The images were then analyzed with Cumulus V to obtain the density VBD_{CV} (with and without skin) and the total volume V_{CV} . We restricted the computation of V_{CV} and VBD_{CV} to points where the computed VBD_{CV} was in the physically acceptable range from 0% to 100%. On average, for the 26 cases simulated with an Rh/Rh anode/filter, only 6.4% of the total number of pixels in the breast image were excluded for this reason. These pixels corresponded to only 2.3% of the breast volume on average. For the Mo/Rh and Mo/Mo sets, these pixels corresponded to 1.9% of the breast volume. The likely cause of these nonphysical results is discussed in section 4.

Excellent agreement between V_{CT} and V_{CV} was observed. A linear least-squares fit between the two gave a slope of 1.01 with an intercept of -7.2 cm^3 , and a correlation $R^2 = 0.999$. The rms difference in volume between CT and Cumulus, $\text{rms}(V_{CT} - V_{CV})$, was 11.5 cm^3 or 2.1% of the mean CT volume. Good agreement was observed between VBD_{CT} and VBD_{CV} , with and without the skin (see figures 10 and 11). Table 5 shows the results of linear regression analysis between VBD_{CT} and VBD_{CV} , and also the rms difference $\text{rms}(\Delta VBD)$, where $\Delta VBD = VBD_{CT} - VBD_{CV}$.

4. Discussion and conclusion

The purpose of this study was to investigate the performance of an algorithm that measures the VBD from digital mammograms. We observed that our algorithm agrees very well with the values obtained from breast CT, both on the total volume of the breast and on the VBD with or without including the skin, as shown in figures 10 and 11. To the best of our knowledge, only the algorithm of Van Engeland *et al* (2006) also proposed a validation by means of comparison with a 3D dataset. Van Engeland *et al* (2006) used a simple polychromatic model of primary attenuation, without considering the effects of scatter or detector efficiency. Internal calibration was achieved by finding a reference fatty pixel value in the image. The validation was done by comparison with segmented MR images of the same 22 patients for which 4 digital mammographic views (2 for each breast) were obtained. The total breast volumes from the MR images and mammograms were not compared, but a correlation of 0.97 with a relative error of 13.6% was observed between the dense tissue from MR and the average dense tissue from the four mammographic views of each patient.

Our algorithm is similar to those of Pawluczyk *et al* (2003) and Kaufhold *et al* (2002) in that it uses an empirical calibration of the detector signal as a function of thickness and composition from breast-equivalent phantoms to determine the density of a breast of known thickness, in which image was acquired under known conditions. The algorithm is susceptible to various sources of error. For the Rh/Rh anode/filter combination, the baseline error in the algorithm from a self-consistency test (section 3.3) results in a systematic underestimation of $1.25 \pm 2.3 \text{ PVBD}$. This deviation is thought to originate from noise in the calibration images, errors due to the polynomial least-square fits and variations in the gain map between the time of calibration and the test. Thus, the offset of -1.4 PVBD and the rms difference of 2.6 PVBD between the ground truth from CT and the Cumulus algorithm discussed in section 3.4 suggest that the algorithm performs well when it is applied to the simulated breast images. It is also an indication that the model used to simulate the mammograms is accurate. The simulation model and baseline error in the algorithm were only tested versus phantom images for the Rh/Rh anode/filter combinations. However, the performance of Cumulus was similar on simulated images with Mo/Rh and Mo/Mo anode/filter combinations as it was with Rh/Rh.

Another type of error occurs when the algorithm yields a PVBD outside of the acceptable range between 0% and 100% (see section 3.3). There are several factors that may be responsible for this error. First is the use of calibration phantoms that have uniform

thickness. Because the thickness of the breast varies and particularly because it decreases in the peripheral region, the scattered radiation profile will differ between the calibration exposures and actual mammograms. This can cause a discrepancy in the density determination. The points in the images that gave PVBD values less than 0 or greater than 100 had an average actual thickness of 18 mm and tended to be located mostly in the peripheral region. Moreover, the calibration curves converge to the same value at 0 thickness, and thus are close together for thin attenuators, causing the density estimation to be more sensitive to small errors in measuring or simulating the image signal at lower thickness.

Another reason for those unphysical results may arise from the assumption in the algorithm of a strictly two-compartment model for the breast. That is, the algorithm assumes that for a given tissue thickness and corresponding image signal, there is a unique combination of fat and fibroglandular tissue possible. Certainly, the presence of skin (and of blood vessels) in the breast is a departure from the two-compartment model, meaning that there is more than one combination of tissues possible that can give rise to a given signal at a given thickness. The skin has attenuation very close to that of fibroglandular tissue, and thus such errors are likely to occur only for pixels where the local density without the skin is already close to 100% or 0%, but it can occur at any thickness of tissue. We also note that the performance of Cumulus in estimating the VBD_{NSK} was not as good as for VBD_{SK} . This may be due to our assumption of a total skin thickness of 3 mm ($1.5 \text{ mm} \times 2$). In actuality, the skin thickness is likely to vary among women and possibly within the same breast.

The accuracy of the validation is also dependent on our model to simulate realistic digital mammograms. The model is based on a description of the physics of imaging the breast, considering the incident polychromatic x-ray spectrum, the primary and scattered radiation exiting the breast, the anti-scatter grid and the flat-panel detector conversion of x-ray energy into an image. It also employs experimental parameters, such as the grid transmission factors, the glare properties of the detector and a flood image to determine the gain of the detector as well as to account for the small variations in the field due to the heel effect. The performance of the model in simulating the image signal and VBD as a function of kVp and thickness is shown in figures 8(a) and (b). The errors varied approximately from -4 PVBD to 3 PVBD. We attribute the variation in error to two factors. First, although there can be a small dependence of the gain, Γ (equations (4) and (5)), on energy, this was not considered in our model. By assuming that Γ is constant, it is cancelled in equations (4) and (5), and the gain from the flood field image is assumed (equation (6)). This effect was small, and the average rms error in the signal between simulation and experiment was 2.4%. Secondly, we can see in table 4 that the sensitivity of density with respect to the image signal is larger for greater tissue thickness and for lower kVp. Thus, for some cases, small errors in the signal lead to noticeable errors in PVBD. The sensitivity was generally higher with the softer Mo/Rh or Mo/Mo anode/filter combination than that with the Rh/Rh combination. Thus, it is reasonable that a larger offset of approximately 2.5 PVBD was observed between VBD_{CT} and VBD_{CV} for the image sets using the Mo anode, compared with the -1.4 PVBD offset for the Rh anode image set.

We can analyze the errors associated both with the simulation and Cumulus in more detail by separating the image set (with the Rh/Rh anode/filter) into kVp subsets. Table 6 indicates the average $\Delta VBD = VBD_{CT} - VBD_{CV}$ and the predicted density error ΔM due to the model, linearly interpolated or extrapolated from the results of figure 8(b) at appropriate thickness. By combining ΔM with the systematic 1.25 PVBD underestimation shown in figure 9, we obtain a total expected difference between CT and Cumulus of -1.5 PVBD, 2.0 PVBD and 4.1 PVBD for the cases imaged at 28 kVp, 29 kVp and 30 kVp, respectively. The slight discrepancies between the expected VBD and the observed ΔVBD error within those

sets may arise from the fact that the signal and VBD difference shown in figure 8(b) were obtained with phantoms of 0% density, while the simulated mammograms had average densities of 32%, 26% and 17%, for the subsets imaged at 28 kVp, 29 kVp and 30 kVp, respectively. This may have occurred because of an increase in the sensitivity, D_{pm} , with increasing density and thus the errors due to our simulation model could be different for the cases studied than with the 0% phantoms. This is supported by the data in table 4 which show an increase in sensitivity with increased attenuation.

Using actual mammograms with the corresponding CT from the same volunteers for purposes of validation will remove any errors due to the simulation of images. On the other hand, there are some advantages in using simulated mammograms. This approach allows for a self-consistent comparison between CT and the Cumulus algorithm. The validation is, therefore, insensitive to potential errors in the absolute anatomical VBD due to the segmentation or the finite-element deformation since they are preserved in the simulated projection mammogram. Furthermore, we compare a breast CT volume with its direct projection with no potential discrepancy (such as would be caused by inclusion of the chest wall with pectoralis muscle in the mammogram and not in the CT) between the two. And finally, the thickness of the breast is known exactly, and therefore potential errors due to errors in thickness measurement or estimation are avoided.

Area breast density is a well-validated risk factor for breast cancer risk. Methods such as the one proposed in this work will allow investigation of the relation between risk and VBD. Logically, one might expect VBD to be a better risk predictor than areal density because it presumably represents the amount of actual tissue at risk, the parenchyma and stroma. The VBD method can also be used to investigate the relation between volume and area density, by finding a global threshold in the volume density that results in an area density well correlated to a user-determined density.

Acknowledgments

We received valuable technical assistance and helpful advice from Dr James Mainprize. We are grateful for financial support through a Program Project grant from the Terry Fox Foundation.

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Figure 1. Flowchart summary of the validation process. From top to bottom: sagittal slice from a segmented CT volume, sagittal slice from the displaced volume, negative logarithm of the simulated digital mammogram and calculated density map of the mammogram.

Figure 2. Illustration of segmentation on a coronal CT slice. Left: original slice in units of the effective linear attenuation coefficient (cm^{-1}) displayed with a narrow window; right: segmented slice.

Figure 3. Illustration of the finite-element model (FEM) deformation process. U represents the magnitude of the displacement in cm.

Figure 4.
Projection geometry. Left: side view; right, top view.

Figure 5.
Sample image of the 'plug' phantom with surrounding 'padding'.

Figure 6. Illustration of the finite-element deformation and cropping (white vertical line). Left: original segmented CT; right: displaced fractional density volume. From top to bottom, sagittal, transverse and coronal slices.

Figure 7.

Distribution of ADU/mAs values on simulated and experimental images of a breast equivalent phantom of thickness 5 cm (a) and 7 cm (b), imaged at 28 kVp (a) and 30 kVp (b), with a Rh/Rh anode/filter. The dashed line is the simulated image and the solid line is the experimental image. The distributions are computed over an area of approximately 107 cm² of the projected area of the phantom.

Figure 8.
 (a) Comparison between the means of the experimental (full lines) and simulated (dashed lines) phantom images. The open circles, squares and disk represent the 3 cm, 5 cm and 7 cm images, respectively. Marker size is representative of the error in the values. (b) Corresponding difference ΔM in PVBD between experiment and simulation.

Figure 9.
Histogram of the VBD difference between the density on the plug phantoms and the calculated density from the phantoms using Cumulus.

Figure 10.

Comparison between VBD from CT and Cumulus V for the set of images with a Rh/Rh anode/filter combination. Open circles denote the VBD with skin and crosses the VBD_{NSk} . Dashed line is the identity function.

Figure 11.

Comparison between VBD from CT and Cumulus V for the set of images with a Mo/Rh anode/filter (a) and a Mo/Mo anode/filter (b). Open circles denote the VBD with skin and crosses the VBD_{NSk}. Dashed line is the identity function.

Table 1

Elastic properties of breast tissue.

Tissue	Modulus of elasticity (kPa)	Poisson's ratio
Fat	1.0	0.49
Fibroglandular	10.0	0.49
Skin	88.0	0.49

Table 2

Correspondence between the spectrum and breast thickness.

Compression thickness (mm)	kVp (Rh/Rh)	kVp (Mo/Rh)	kVp (Mo/Mo)
30–50	28	27	26
50–70	29	28	27
70–80	30	29	28

Table 3

Grid performance parameters

anode/filter	Rh/Rh				Mo/Rh				Mo/Mo			
	28	29	30		27	28	29		26	27	28	
T_p	0 cm	0.63	0.63	0.64	0.62	0.62	0.63		0.59	0.60	0.60	
	3 cm	0.68	0.69	0.69	0.66	0.66	0.67		0.63	0.64	0.64	
	5 cm	0.69	0.70	0.70	0.67	0.66	0.68		0.65	0.66	0.66	
	7 cm	0.70	0.71	0.71	0.68	0.68	0.69		0.68	0.68	0.69	
T_s	3 cm	0.15	0.15	0.16	0.15	0.16	0.15		0.14	0.15	0.15	
	5 cm	0.15	0.14	0.14	0.15	0.16	0.16		0.15	0.14	0.15	
	7 cm	0.16	0.15	0.16	0.17	0.17	0.17		0.15	0.15	0.15	

Table 4

Sensitivity D_{pm} in PVBD/(ADU/mAs).

<i>T</i> (cm)	kVp			
	26	28	29	30
3	-4.07	-2.73	-2.30	-1.97
5	-7.61	-4.81	-4.00	-3.38
7	-15.01	-9.15	-7.48	-6.23

Table 5

Linear regression and rms analysis between VBD_{CT} and VBD_{CV}

Linear regression parameters		Slope	Intercept (PVBD)	R ² correlation	rms(Δ VBD)
Rh/Rh	VBD _{Sk}	0.992	-1.4	0.963	2.6
	VBD _{Nsk}	0.907	0	0.939	3.2
Mo/Rh	VBD _{Sk}	1.002	2.4	0.960	2.6
	VBD _{Nsk}	0.916	3.1	0.933	3.1
Mo/Mo	VBD _{Sk}	0.970	2.5	0.942	2.5
	VBD _{Nsk}	0.888	3.7	0.930	2.9

Table 6

Observed (Δ VBD) and predicted (ΔM) VBD error as a function of kVp for the Rh/Rh image set

kVp	28	29	30
Number of cases	3	14	9
Mean T (cm)	3.9	5.9	7.4
Δ VBD (PVBD)	-3.0	2.0	2.5
ΔM	-2.7	0.8	2.9