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Quantitative breast tissue characterization using grating-based x-ray phase-contrast imaging

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Abstract
X-ray phase-contrast imaging has received growing interest in recent years due to its high capability in visualizing soft tissue. Breast imaging became the focus of particular attention as it is considered the most promising candidate for a first clinical application of this contrast modality. In this study, we investigate quantitative breast tissue characterization using grating-based phase-contrast computed tomography (CT) at conventional polychromatic x-ray sources. Different breast specimens have been scanned at a laboratory phase-contrast imaging setup and were correlated to histopathology. Ascertained tumor types include phyllodes tumor, fibroadenoma and infiltrating lobular carcinoma. Identified tissue types comprising adipose, fibroglandular and tumor tissue have been analyzed in terms of phase-contrast Hounsfield units and are compared to high-quality, high-resolution data obtained with monochromatic synchrotron radiation, as well as calculated values based on tabulated tissue properties. The results give a good impression of the method’s prospects and limitations for...
potential tumor detection and the associated demands on such a phase-contrast breast CT system. Furthermore, the evaluated quantitative tissue values serve as a reference for simulations and the design of dedicated phantoms for phase-contrast mammography.

Keywords: x-ray imaging, computed tomography, phase contrast, breast imaging, tissue properties

(Some figures may appear in colour only in the online journal)

1. Introduction

Breast cancer is the most common cause of cancer death in women worldwide (Ferlay et al 2010). Although mammographic screening programmes and improved systemic therapy have continuously reduced the mortality over the past decades, the rate of missed lesions and the rate of false positives remain crucial (Berry et al 2005, Smith and Andreopoulou 2004). Many efforts are therefore made to enhance diagnostic performance especially of dose-free imaging modalities like magnetic resonance imaging or sonography (Kuhl 2007a, 2007b, Sehgal et al 2006, Athanasiou et al 2009, Le-Petross and Shetty 2011). Despite radiation risks, new developments in x-ray imaging are still motivated by benefits such as high resolution, low costs, fast acquisition and operator independence. Whereas tomosynthesis is already in a very advanced state, further activities focus on spectral and full tomographic imaging or the combination of both (Skaane et al 2013, Ding and Molloy 2012, Schmitzberger et al 2011, Prionas et al 2010, Kalender et al 2012).

Another frontier in radiology is x-ray phase-contrast imaging, which is very promising for the visualization of weakly absorbing detail such as soft tissue fine structure. Several methods have been introduced to exploit the phase shift induced to x-rays rather than their absorption within an object. A detailed overview of the different techniques and recent preclinical and biomedical results can be found in Bravin et al (2013).


Further results have been achieved by phase-contrast breast computed tomography (CT) (Bravin et al 2007, Keyriläinen et al 2008, Sztrókay et al 2012, 2013). Latest developments in this direction include synchrotron measurements at very low doses and feasibility studies in the laboratory (Zhao et al 2012, Grandl et al 2013).

In the context of tomographic phase-contrast imaging of the breast, this work addresses the question of whether quantitative tissue characterization in analogy to the well-established Hounsfield scale in conventional attenuation-based CT might be a valuable tool for future 3-D breast diagnostics. X-ray grating interferometry was chosen for the investigations as the technique allows for quantitative imaging even when employed using high-powered polychromatic x-ray sources (Weitkamp et al 2005, Pfeiffer et al 2006, Herzen et al 2009, Donath et al 2010). One specimen containing healthy breast parenchyma as well as invasive ductal carcinoma has been scanned with high resolution at the beamline ID19 of the European
Synchrotron Radiation Facility (ESRF), Grenoble, France. In addition, three excised samples comprising a benign phylloides tumor, a fibroadenoma and an invasive lobular carcinoma have been examined at a laboratory setup at the Technische Universität München, Germany. Present tissue types were specified by histopathology and the associated quantitative results were compared to values calculated based on literature.

Besides the insight into the potential advantages and limitations of phase-contrast breast CT imaging, the results are particularly interesting for simulations and the design of adequate phantoms for the optimization of phase-contrast mammography systems (Munro et al 2010, Raupach and Flohr 2012, Vedantham and Karellas 2013).

2. Methods and materials

2.1. Grating-based phase-contrast imaging

A detailed description of an x-ray grating interferometer can be found in Weitkamp et al. (2005). A phase grating acts as beam splitter and creates periodic intensity modulations at the so-called fractional Talbot distances. Differences in the phase shift that x-rays undergo when passing two adjacent paths through an object cause a local shift of this pattern. Attenuation by the object, on the other hand, results in a loss of intensity as commonly exploited in conventional x-ray imaging. Usually the detector pixel size exceeds the period of the intensity pattern, which typically is in the order of a couple of micrometers. For this reason, an analyzer grating of the same period as the interference pattern and consisting of highly absorbing structures is placed in front of the detector. This grating is translated perpendicularly to the grating lines while several images are acquired. During this stepping approach, a sinusoidal intensity oscillation is recorded in each detector pixel. Mean intensity and position of this curve can be evaluated by Fourier analysis. A comparison of data obtained with and without the sample in the beam finally provides two radiographic images: the conventional attenuation-contrast and the differential phase-contrast image. In a tomography scan, many projection images are generated from different angular directions and a 3-D volume of the object can then be reconstructed by applying the filtered backprojection algorithm. In case of phase-contrast, the filter function in the reconstruction algorithm can be replaced by an imaginary Hilbert filter to account for the differential nature of the projections (Pfeiffer et al 2007).

Taking setup-dependent factors into consideration, the distribution of the linear attenuation coefficient \( \mu(x, y, z) \) and the refractive index decrement \( \delta(x, y, z) \) within the sample can be determined from the attenuation-contrast and phase-contrast datasets, respectively (Herzen et al 2009). The method is applicable at polychromatic x-ray sources with low brilliance by adding a third grating to the imaging setup. This absorption grating is placed close to the x-ray tube and its slits serve as an array of individually coherent, but mutually incoherent sources (Pfeiffer et al 2006).

2.2. Phase-contrast Hounsfield units

In daily diagnostics, the use of Hounsfield units (HU) simplifies the differentiation of certain tissue types with x-ray CT by assigning setup-independent quantitative values to them. These units are defined by

\[
\text{HU} = \frac{\mu_{\text{tissue}} - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}} \times 1000,
\]

where \( \mu_{\text{tissue}}, \mu_{\text{water}} \) and \( \mu_{\text{air}} \) are the linear attenuation coefficients of the associated tissue, water and air. In analogy, Donath et al (2010) proposed Hounsfield units for phase-contrast imaging.
(HUp) by replacing the respective linear attenuation coefficients $\mu$ by the corresponding refractive index decrements $\delta$:

$$\text{HUp} = \frac{\delta_{\text{tissue}} - \delta_{\text{water}}}{1000}. \quad (2)$$

The refractive index decrement $\delta$ is given by

$$\delta = \frac{r_0 h^2 c^2}{2\pi E^2} \sum N_i f_i^1,$$

where $r_0$ is the classical electron radius, $h$ is the Planck constant, $c$ is the speed of light, $E$ is the x-ray energy, $N_i$ is the atomic density of type $i$ atoms (number of atoms per unit volume) and $f_i$ is the real part of their atomic scattering factor in the forward direction (Als-Nielsen and McMorrow 2008). For energies far above any absorption edges $f_i^1$ can be replaced by the element’s atomic number $Z_i$ and the sum $\sum N_i f_i^1$ equals the electron density $\rho_e$ of the material. The refractive index decrement of a tissue $\delta_{\text{tissue}}$ can then be directly derived from its electron density according to

$$\delta_{\text{tissue}} = \frac{r_0 h^2 c^2}{2\pi E^2} \rho_e,\text{tissue}. \quad (4)$$

Alternatively, the theoretical $\delta$-value of a tissue can be calculated from its mass density $\rho_{\text{tissue}}$ and elemental composition in weight fractions $w_i$:

$$\delta_{\text{tissue}} = \frac{r_0 h^2 c^2}{2\pi E^2} \sum (w_i \times N_i / A_i) \rho_{\text{tissue}},f_i^1, \quad (5)$$

with $A_i$ being the atomic mass of atom $i$ and $N_A$ being Avogadro’s number. For a comparison of measurements and literature, both equations are used later on to obtain phase-contrast Hounsfield units from tabulated data.

Combining equations (2) and (4) yields the relation

$$\text{HUp} = \frac{\rho_{e,\text{tissue}} - \rho_{e,\text{water}}}{\rho_{e,\text{water}} - \rho_{e,\text{air}}} 1000, \quad (6)$$

which reveals that phase-contrast Hounsfield units are energy independent. This is in contrast to conventional Hounsfield units, which show a strong energy dependence at low energies due to a varying contribution of photoelectric absorption and Compton scattering to the overall attenuation. In this study, air is neglected in the definition of phase-contrast Hounsfield units as the deviation from exact values is only about 0.1%. In this case, the measured HUp value can be easily converted to identify a tissue’s electron density by reversing equation (6) to

$$\rho_{e,\text{tissue}} = \left(1 + \frac{\text{HUp}}{1000}\right) \rho_{e,\text{water}}, \quad (7)$$

where $\rho_{e,\text{water}} = 3.34 \times 10^{29} e \text{ m}^{-3}$ is the electron density of water.

2.3. Breast tissues in literature

With respect to radiography, the healthy breast is composed of two major tissue types: fibroglandular and adipose tissue. Fibroglandular tissue is a mixture of fibrous connective tissue (the stroma) and the functional (or glandular) epithelial cells that line the ducts of the breast (the parenchyma) (Yaffe 2008). Adipose tissue mainly consists of lipid and has a lower linear attenuation coefficient than fibroglandular tissue. Unfortunately, the attenuation of tumor and fibroglandular tissue is very similar, posing a challenge for tumor detection especially in dense breasts (Johns and Yaffe 1987).

Hammerstein et al (1979) evaluated densities and elemental compositions of adipose and glandular tissue from fresh mastectomy samples for dose calculations in mammography.
By interpolation of the results, densities and elemental compositions for various mixed states of both tissue types can be generated to simulate breast tissue (Boone 1999). An extensive collection of human tissue compositions and densities, including adipose and glandular tissue, was published by Woodard and White (1986). They state three different properties for both tissue types to reflect the high variance of results in their analysis. The data was also partly listed in a report of the International Commission on Radiation Units and Measurements ICRU (1989) and is the basis of many theoretical considerations involving breast tissue. Further elemental compositions and densities of glandular and adipose tissue used in this study are taken from Poletti et al (2002) and were obtained by a commercial elemental analyzer.

Electron densities of breast tissues that we found in the literature have been quantified by Compton scattering methods. First results were presented by Shrimpton (1981) who examined adipose and breast tissue among others. The size of the specimens was about 3 cm and breast tissue was presumably a mixture of both—adipose and fibroglandular tissue. Another investigation concentrated solely on breast tissue samples (including tumor tissue) to determine electron densities for the design of a mammography phantom (Al-Bahri and Spyrou 1998). Later studies were performed comprising of a high number of samples to evaluate the potential of Compton scattering for the diagnosis of breast biopsies (Ryan et al 2005, Antoniassi et al 2010, 2012).

2.4. Samples and measurements

Our study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained before imaging. Indication for breast surgery followed recommendation of the interdisciplinary tumor board of the University of Munich breast center. The excised breast samples were macroscopically examined by an experienced pathologist and representative and orientable tissue parts were selected and placed in 50 ml plastic cylinders (diameter 3 cm) filled with 4% neutral-buffered formaldehyde solution. Histological work-up was performed after the measurements to correlate and identify tissue types.

In total, four different specimens were investigated. The first one contained adipose tissue, healthy fibrous breast parenchyma as well as invasive ductal carcinoma and was scanned at the beamline ID19 of the European Synchrotron Radiation Facility (ESRF), Grenoble, France. The energy of the coherent monochromatic beam was set to 23 keV. The height of the silicon phase grating with a period of 4.8 μm was matched to introduce a phase shift of π to the x-rays. The corresponding analyzer grating had a period of 2.4 μm and was positioned 48.1 cm behind the phase grating. A Frelon CCD (type e2v, 2048 × 2048 pixels), lens-coupled to a LuAG scintillator of 125 μm thickness, has been used as detector. The optics have been set to an effective pixel size of 30 μm. 1199 projections with four phase steps have been collected with an exposure time of 0.8 s per image in this 360° tomography. For further information on sample, setup and measurement, we refer to Štrókay et al (2013).

The other three specimens—including adipose tissue, fibrous tissue, phylloides tumor, fibroadenoma and invasive lobular carcinoma—were examined at a laboratory setup located at the Physics Department of the Technische Universität München. The experimental system combines a rotating molybdenum anode x-ray tube with a photon counting detector (Pilatus II, Dectris, Switzerland). The interferometer consists of three gratings of 5.4 μm period manufactured by Microworks GmbH, Karlsruhe. The source grating is placed 40 cm behind the x-ray source. The distances from this to the phase grating and from the phase to the analyzer grating are both 80 cm. Thus, the interferometer is installed in a symmetric setup configuration. The rotation stage is mounted directly in front of the nickel phase grating which
is designed to induce a phase shift of $\pi$ to incoming x-rays of 22.8 keV. The field of view is $4 \times 2$ cm$^2$ (width $\times$ height) with an effective pixel size at sample position of 0.1 mm. The CT measurements were carried out at a tube voltage and current of 40 kV and 70 mA, respectively. For each sample 1200 projections with 11 phase steps per projection were recorded over 360°. The exposure time per image was 5 s and the total scan time was about 30 h with an overall dose of approximately a few Gy applied to the sample. For comparison, the requirements on a clinical system are in the range of seconds and mGy. This shows the highly experimental state of the imaging setup which is neither speed nor dose optimized. In addition, the scan parameters in this study were primarily chosen to attain good image quality and reliable quantitative tissue values.

2.5. Quantitative analysis

All 3-D phase-contrast datasets $\text{pci}(x, y, z)$ were obtained by applying a standard filtered backprojection with a Hilbert filter. This imaginary filter function allows for a correct reconstruction of the object function from the original differential projection images (Pfeiffer et al 2007). The refractive index decrement of each voxel $\delta(x, y, z)$ can then be determined by

$$\delta(x, y, z) = \frac{\text{pci}(x, y, z) - 1}{2\pi d r},$$

where the setup-dependent factors $p_2$ and $d$ are the period of the analyzer grating and the propagation distance between phase and analyzer grating, respectively. The factor $r/l$ is only considered for data recorded at setups with fan- or cone-beam geometry, e.g. the laboratory setup employed in our study, and corrects for the reduced sensitivity of a measurement that occurs if the sample is not directly placed in front of the phase grating. Here, $r$ is the source-to-sample distance and $l$ denotes the distance from the source to the phase grating (Engelhardt et al 2007, Herzen et al 2009).

Previous phantom studies conducted at the beamline ID-19 (ESRF) demonstrated the high accuracy that can be achieved by grating interferometry in the evaluation of refractive index decrements $\delta$ using synchrotron radiation (Zanette et al 2011, Willner et al 2013). For most examined materials and substances the theoretical values are within one standard deviation of the experimental results. This suggests that systematic errors resulting from data processing and uncertainties in the knowledge of the exact propagation distance $d$ or the correct x-ray energy of the monochromator are in the same order of magnitude or even smaller than the actual image noise.

Strong differences in phase shift, e.g. between the walls of the sample cylinder and air, can cause phase wrapping artifacts and affect the ability of quantitative imaging (Zanette et al 2011). For this reason the tubes containing the breast specimens were mounted underneath the sample rotation stage at both imaging systems—synchrotron and laboratory setup—and submerged in a plastic container of about 4 cm thickness and filled with water during the measurements. In this case the final 3-D datasets obtained from equation (8) already yield the refractive index decrements relative to the surrounding water $\Delta\delta = \delta - \delta_{\text{water}}$. For the further conversion to phase-contrast Hounsfield units (HU) according to equation (2) (and without air), these numbers were finally divided by the theoretical $\delta_{\text{water}}$-value calculated for the respective energy and multiplied by 1000.

This last step is more challenging when dealing with polychromatic x-ray tubes since an effective energy needs to be assigned. Besides the spectral intensity distribution, the different contributions of the individual energies to the total interference pattern have to be taken into account as well. This makes it very complicated to calculate an effective energy in grating-based phase-contrast imaging even if source spectrum, spectral sensitivity of the detector and
Figure 1. Two exemplary tomographic phase-contrast images of healthy breast parenchyma embedded in adipose tissue (a) and (b) and the distribution of quantitative phase-contrast Hounsfield units (c) and (d) in two selected cubic regions-of-interest as shown in (b). Whereas adipose tissue yields values around $-70$ HUp, fibroglandular tissue exhibits positive values with a peak maximum at about 66 HUp.

Further parameters are known. Instead we inserted a PMMA rod as calibration material into each sample cylinder for the laboratory measurements. The experimental values obtained for the rods were then correlated to tabulated data of PMMA to select the proper effective energy. Simplified, this whole procedure can be understood as linear rescaling of the original dataset with $pci(x, y, z)$ with water (0 HUp) and PMMA (approx. 156 HUp) being the fixed points. If the data, like in our case, is recorded relative to water, the corresponding transformation is expressed by

$$HUp(x, y, z) = pci(x, y, z) \frac{156}{pci_{PMMA}}. \quad (9)$$

Obviously, systematic errors are here reduced to deviations of the surrounding background from 0 after reconstruction and density fluctuations of the employed PMMA rods. There is generally less beam hardening in phase-contrast imaging than in conventional attenuation-based CT (Chabior et al 2011). Since all samples were measured in a water bath and do not contain high absorbing structures, beam hardening effects can be assumed to play only a minor role in our data analysis.

3. Results and discussion

3.1. Synchrotron source

Phase-contrast imaging results of the specimen measured at the synchrotron are presented in figure 1. The two images display healthy breast parenchyma (bright signal) embedded in adipose tissue (dark signal). Two cubic regions of 0.5 cm side length ($170 \times 170 \times 170$
Two exemplary tomographic phase-contrast images displaying adipose tissue and an invasive ductal carcinoma containing bright circular ductal structures (a) and (b). The histograms of two cubic regions representing adipose tissue (c) and tumor tissue (d) show distinct peaks with maxima at $-68\text{ HUp}$ and $47\text{ HUp}$, respectively.

 Voxels were chosen from the 3-D dataset and their histograms are plotted in figures 1(c) and (d). Region A (marked in figure 1(b)) mainly contains adipose tissue. The associated histogram has one narrow peak with a maximum at $-68\text{ HUp}$. Region B was chosen to cover as much fibroglandular tissue as possible, but still parts of adipose tissue are enclosed within the parenchyma. Whereas the peak of adipose tissue is again located between $-65$ and $-70\text{ HUp}$ in the histogram, the fibroglandular tissue has its peak maximum at $66\text{ HUp}$. All values between both tissue types can be found within the analyzed cubic region. The small peak at about $20\text{ HUp}$ corresponds to the surrounding formalin solution.

Further imaging results of the same sample, now comprising adipose tissue and invasive ductal carcinoma, are shown in figure 2. The tumor appears as a solid area with clear boundaries (figure 2(a)). The narrowed scaling of figure 2(b) reveals bright circular structures within the tumor tissue which coincide with dilated ducts (Sztroke et al. 2013). Also in this case histograms of two cubic regions were prepared to illustrate the distribution of quantitative values. The histogram of region A with pure adipose tissue is nearly identical to figure 1(c), a narrow peak with its maximum at $-68\text{ HUp}$. Region B contains mainly tumor tissue. The peak in the corresponding histogram has a maximum at $47\text{ HUp}$ which is about $20\text{ HUp}$ lower than fibroglandular tissue. Moreover, a gentle slope towards higher $\text{HUp}$ values can be recognized, which represents the bright signal of the dilated ducts.

To cope with the different sizes of the observed tissue structures, 24 small regions-of-interest ($10 \times 10$ pixels) were chosen for each type—adipose and fibroglandular tissue, invasive tumor and ducts—to evaluate and assign quantitative $\text{HUp}$ values. The mean values of all considered pixels and the associated standard deviations are listed in table 1. The determined values for adipose, fibroglandular and tumor tissue are $-68.7 (2.7)$, $65.2 (6.0)$ and
Table 1. Phase-contrast Hounsfield units of adipose, fibroglandular, tumor tissue and ducts obtained at synchrotron measurements compared to values calculated from tissue properties found in literature.

<table>
<thead>
<tr>
<th>Tissue type: Adipose Fibro-</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>−68.7 (2.7)</td>
</tr>
<tr>
<td>Tissue composition:</td>
<td></td>
</tr>
<tr>
<td>Hammerstein (1979)</td>
<td>−71.2</td>
</tr>
<tr>
<td>W&amp;W 1 (1986)</td>
<td>−67.7</td>
</tr>
<tr>
<td>W&amp;W 2/ICRU</td>
<td>−48.8</td>
</tr>
<tr>
<td>W&amp;W 3</td>
<td>−30.4</td>
</tr>
<tr>
<td>Poletti (2002)</td>
<td>−70.8</td>
</tr>
<tr>
<td>Compton scattering:</td>
<td></td>
</tr>
<tr>
<td>Shrimpton (1981)</td>
<td>−71.9 (6.0)</td>
</tr>
<tr>
<td>Al-Bahri (1998)</td>
<td>36.8 (3.9)</td>
</tr>
<tr>
<td>Ryan (2005)</td>
<td>−29.9 (42.0)</td>
</tr>
<tr>
<td>Antoniassi (2010)</td>
<td>−29.9 (47.9)</td>
</tr>
<tr>
<td>Antoniassi (2012)</td>
<td>−38.9 (41.9)</td>
</tr>
</tbody>
</table>

47.0 (2.8) HUp, respectively, and in good agreement to the peak maxima in the histograms in figures 1 and 2. The highest value of 72.5 (5.0) HUp was found for the ducts. Image noise within a homogenous area of the surrounding formalin solution was around 2.4 HUp. The exceeding standard deviations in the analysis of fibroglandular tissue and ducts (6 and 5 HUp) suggest higher variances in the actual tissue compositions.

3.2. Comparison to literature

For a comparison to previously published breast tissue properties (see section 2.3), phase-contrast Hounsfield units were calculated from the elemental compositions and corresponding mass densities or directly from the given electron densities as described in section 2.2. All values including the experimental synchrotron results of this study are listed in table 1. Woodard and White (1986) specified three different sets of properties for each tissue which represent the mean of all data that was available (denoted as W&W 2) as well as the mean plus/minus the standard deviation (W&W 1 and 3). Overall a wide spread of values ranging from about −70 to almost 80 HUp can be noticed. The data for adipose and tumor tissue provided by the different references seems to be more consistent than for fibroglandular tissue. The measured −68.7 HUp for adipose tissue is in very good agreement to the values derived from tabulated tissue compositions. In case of the data quoted from Woodard and White (W&W) this applies to the lowest of the three values. With the exception of Shrimpton (1981), the results obtained by Compton scattering methods in comparison tend to be somewhat higher (around −40 to −30 HUp). The results of Al-Bahri and Spyrou (1998) have previously been criticized as being inaccurate due to the freeze-drying of the samples ahead of the measurements and the lack of essential corrections, e.g. for background, multi-scattering and self-attenuation (Ryan et al 2005, Antoniassi et al 2010). This might explain the large discrepancies found for adipose tissue.

The evaluated 65.2 HUp for fibroglandular tissue exceeds most reference values, but is close to the higher value obtained from the data of W&W and the HUp calculated from the electron density determined by Antoniassi (2010). The values observed for tumor tissues in our measurements are in line with the findings made by applying Compton scattering.
The most likely reason for discrepancies between our results and previous results stated in the literature is the high spatial resolution of our measurements which enables a clear distinction between certain tissue types, e.g. fibroglandular and adipose tissue. In the other studies, the results reflect the average of volumes with side lengths of a few millimeters. The histogram displayed in figure 1(d), which represents the HUp-distribution within a cubic region of 0.5 cm side length covering as much fibroglandular tissue as possible, clarifies this assumption. The mean value of this volume amounts to 10.5 HUp and is significantly lower than the value attained for ‘pure’ fibroglandular tissue due to the remaining adipose tissue. The three considerably differing phase-contrast Hounsfield units based on the tissue compositions of W&W as well as the high standard deviations stated by Ryan (2005) and Antoniassi (2010 and 2012) further indicate the great variance of values that arises from an insufficient spatial resolution and the presence of both—adipose and fibroglandular tissue—within the samples.

The tumor tissue in our measurement exhibits around 45 HUp and, thus, a lower value than observed for fibroglandular tissue. This is in contrast to the Compton scattering measurements where the highest values are obtained for tumor tissue. Once again this inconsistency might be caused by the limited spatial resolution in these experiments. Whereas fibroglandular tissue often incorporates portions of adipose tissue, these inclusions are displaced during tumor growth leading to larger and more homogeneous areas of high density.

A similar line of argument, but on a smaller length scale, can account for the lower phase-contrast Hounsfield units of tumor tissue compared to healthy parenchyma in our measurements. Fibrous tissue components, such as collagen strands, give rise to increased phase-contrast signals as observed for the dilated ducts. These components are mostly missing on a sub-pixel length scale within a tumor cell proliferation and might be responsible for the difference between tumor and fibroglandular tissue. As a side note to this point, the conventional Hounsfield units that were quantified by analyzing exactly the same regions-of-interest of the synchrotron data are 60 HU for fibroglandular tissue, 63 HU for tumor tissue and 70 HU for the ductal structures. Apparently, the absence of fibrous components in the tumor tissue is in this case outweighed by another effect, presumably by the absence of sub-pixel sized adipocytes.

3.3. Laboratory source

Histological work-up of the first sample examined at the polychromatic x-ray tube setup revealed a benign phylloides tumor surrounded by adipose tissue and healthy parenchyma. An exemplary histological slice (hematoxylin eosin staining) and two representative phase-contrast images are displayed in figures 3(a)–(c). The benign phylloides tumor is well-defined and can be clearly discriminated from adipose and fibroglandular tissue. A cubic region of 0.5 cm side length (now comprising 50 × 50 × 50 voxels) covering all three tissue types was chosen (marked in figure 3(b)) to analyze the associated phase-contrast Hounsfield units. The corresponding histogram in figure 3(d) displays three peaks with maxima at −67 HUp, 44 HUp and 66 HUp which can be attributed to adipose, tumor and fibroglandular tissue, respectively. These results are consistent with the findings at the synchrotron. Despite the varying type of tumor, again a difference of about 20 HUp between tumor and fibroglandular tissue can be observed. However, the two peaks are not completely resolved and intermediate values exist.

The phase-contrast image in figure 4(a) shows a benign fibroadenoma as confirmed by histopathology. The mean phase-contrast Hounsfield unit of the marked area (50 × 100 pixels) is 45.1 (5.2) HUp and thus in the same range as the tumor types described before. The standard deviation of 5.2 HUp is larger than the actual image noise of about 2.5 to 3.0 HUp. The reason for the higher deviation in this area are the thin bright structures that become visible
Figure 3. Histological slice in H&E-staining (a) and two correlated phase-contrast images (b) and (c) of a benign phylloides tumor surrounded by adipose and fibroglandular tissue. The three peaks in the histogram (d) of a cubic region covering all three tissue types resemble the previous results obtained at the synchrotron: adipose tissue between $-70$ and $-65$ HUp, tumor tissue around $45$ HUp and fibroglandular tissue at about $65$ HUp.

Figure 4. Phase-contrast imaging results of a benign fibroadenoma (a). A narrowed window scaling (b) reveals fine bright structures which can be assigned to fibrous strands in histology. Like the other tumor types before, fibroadenoma features quantitative values around $45$ HUp. The high values in the line plot (c) correspond to fibrous strands.

When choosing a narrowed window scaling (figure 4(b)). These features reach values of up to $65$ HUp as illustrated in the line plot in figure 4(c) and can be related to fibrous strands pervading the fibroadenoma in histology.
Figure 5. Two histological slices in H&E-staining (a) and EvG-staining (b) showing an infiltrating lobular carcinoma and correlated phase-contrast image (c). Region A contains many tumor cells while region B represents mainly fibrous tissue. The two areas can be distinguished by their mean phase-contrast Hounsfield units of 52 HUp and 68 HUp.

The third sample investigated at the laboratory setup comprises an infiltrating lobular carcinoma which is one of the most difficult breast tumors to diagnose. Histological slices thereof in two different stainings—hematoxylin eosin (H&E) and elastica van gieson (EvG)—are presented together with a correlated phase-contrast image in figure 5. Two small regions-of-interest are marked within the pictures. Region A can be assigned to lobular carcinoma, whereas region B contains none or only a few tumor cells but very fibrous tissue. The mean phase-contrast Hounsfield units of these two areas account for about 52 HUp and 68 HUp, respectively. The standard deviations are around 4.5 HUp resulting in a contrast-to-noise ratio of 3.1 for the two regions, which allows for a differentiation between the specified tissue types.

4. Conclusions

Concerning the use of tissue properties for the calculation of input parameters in simulations or the choice of suitable phantom materials, our study suggests the following conclusions: if the electron density of a certain mixture of adipose and fibroglandular tissue is needed, the values of ‘adipose tissue 1’ and ‘mammary gland 3’ published by Woodard and White (1986) should be taken for the interpolation. The actual mean values—‘adipose tissue 2’ and ‘mammary gland 2’—which are also quoted in the ICRU report 44 are seemingly not good representatives as they already comprise fractions of the respective other tissue type. The tissue compositions and densities of Hammerstein et al (1979) and Poletti et al (2002) deliver quite adequate values as well, but again the declared pure fibroglandular tissue might contain small amounts of adipose tissue in both cases as the corresponding phase-contrast Hounsfield units appear a little bit too low.

Tumor tissue has values of around 45 to 50 HUp (\(\rho_e = 3.49 - 3.51 \times 10^{29} \text{e m}^{-3}\)) according to our measurements. This is the case for all investigated tumor types—the malignant ductal and lobular carcinomas as well as the benign phylloides tumor and fibroadenoma. Whereas it is not possible to discriminate between malignant and benign tumor cells by quantitative numbers alone, the morphological information revealed by differences in fibrous and less fibrous tissue values as well as the appearance and shape of fibrous strands or dilated ducts might allow for tumor identification. However, the examination of more samples is necessary to understand the fingerprints of certain tumor types and clarify the potential diagnostic value of phase-contrast computed tomography. This should include additional healthy reference samples for the purpose of comparison as the fibroglandular tissue within the examined breast specimens might not be representative of the whole spectrum of female breast parenchyma. Moreover the effects of tissue excision and formalin fixation on quantitative tissue values
that might be caused by blood loss or tissue shrinkage should be addressed to assure the conclusions remain valid in vivo.

5. Summary

In this study, we demonstrated the feasibility of quantitative breast tissue characterization using grating-based phase-contrast computed tomography at polychromatic x-ray sources. Phase-contrast Hounsfield units for adipose tissue, fibroglandular and tumor tissue were determined with monochromatic synchrotron radiation and high spatial resolution. Three specimens, including adipose tissue, healthy parenchyma, benign phylloides tumor, fibroadenoma and lobular carcinoma, were measured at a laboratory x-ray tube setup and the resulting values are in excellent agreement with the observations at the synchrotron.

In terms of clinical value of phase-contrast Hounsfield units, further investigations are needed to come to a better understanding of how the differentiation of fibrous and less fibrous tissue or the visualization of dilated ducts might improve tumor detection. Regardless, the results acquired at this stage show that a dose-compatible phase-contrast breast CT or a phase-contrast system for the examination of biopsy samples should be able to resolve at least 15–20 HU for a potential diagnostic benefit.

In addition to clinical applications, grating-based phase-contrast computed tomography is a valuable tool for gathering combined information on tissue properties (electron densities) and breast morphology. These findings can contribute to the design of dedicated phantoms for phase-contrast mammography or to perform enhanced dose simulations for mammographic systems in general.

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