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Quantitative contrast-enhanced mammography for contrast medium kinetics studies

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Abstract
Quantitative contrast-enhanced mammography, based on a dual-energy approach, aims to extract quantitative and temporal information of the tumour enhancement after administration of iodinated vascular contrast media. Simulations using analytical expressions and optimization of critical parameters essential for the development of quantitative contrast-enhanced mammography are presented. The procedure has been experimentally evaluated using a tissue-equivalent phantom and an amorphous silicon active matrix flat panel imager. The x-ray beams were produced by a tungsten target tube and spectrally shaped using readily available materials. Measurement of iodine projected thickness in mg cm\(^{-2}\) has been performed. The effect of beam hardening does not introduce nonlinearities in the measurement of iodine projected thickness for values of thicknesses found in clinical investigations. However, scattered radiation introduces significant deviations from slope equal to unity when compared with the actual iodine projected thickness. Scatter correction before the analysis of the dual-energy images provides accurate iodine projected thickness measurements. At 10% of the exposure used in clinical mammography, signal-to-noise ratios in excess of 5 were achieved for iodine projected thicknesses less than 3 mg cm\(^{-2}\) within a 4 cm thick phantom. For the extraction of temporal information, a limited number of low-dose images were used with the phantom incorporating a flow of iodinated contrast medium. The results suggest that spatial and temporal information of iodinated contrast media can be used to indirectly measure the tumour microvessel density and determine its uptake and washout from breast tumours. The proposed method can significantly improve tumour detection in dense breasts. Its application to perform in situ x-ray biopsy and assessment of the oncolytic effect of anticancer agents is foreseeable.
1. Introduction

In the past few decades conventional screen film combinations (Sabel and Aichinger 1996) and more recently digital mammography (Lewin et al 2002) have been utilized for the detection of breast tumours. Although mammography has better performance than other modalities (US, MRI, etc) for detecting lesions such as microcalcifications, its performance is limited when tumour size is small (<4 mm) (Yaffe 2000) and in investigations involving dense breasts (Nunes et al 2002). Additionally, it does not provide adequate information for tissue characterization such as differentiation between benign and malignant tumours resulting in an increased number of false biopsies (Sabel and Aichinger 1996). There is anticipation that some of these limitations of mammography can be compensated for with the introduction of new digital detectors with improved signal and noise transfer properties (Arvanitis et al 2007).

However, the small differences in the attenuation coefficients of tumours, glandular tissue and adipose tissue (Johns and Yaffe 1987) set a fundamental limit on the visualization of small tumours. Thus, new imaging approaches are necessary in order to enhance the visibility of tumours in the cluttered background of normal breast tissue.

Some of the approaches proposed so far include dual-energy imaging for microcalcification detection (Kappadath and Show 2003), breast tomosynthesis (Wu et al 2003) and breast CT (Boone et al 2001, Chen and Ning 2002). All these approaches attempt to overcome the small differences in attenuation coefficients mentioned above. Another promising, re-emerging approach which has demonstrated encouraging results in the detection of breast tumours is contrast-enhanced mammography (Lewin et al 2003, Jong et al 2003, Dromain et al 2006). Contrast-enhanced mammography can be used to visualize breast tumour angiogenesis, i.e. the formation of new blood vessels within tumours as a result of genetic mutations within the tumour cell (Folkman and Klagsbrun 1987, Folkman et al 1989).

Breast tumour microvessel density (on average 80 microvessels mm$^{-2}$) (Dromain et al 2006) is directly related to blood flow or perfusion within the tissue (Omar et al 1997). Thus, using a vascular contrast agent, the formation of new microvessels can be monitored by the strength of contrast enhancement in the image. Thus spatial and temporal measurements of the vascular contrast agent can overcome some of the limitations of conventional mammography.

In MRI assessment of the maximum intensity of the enhancement, the grade of uptake and washout of gadolinium-based contrast agents (Gd-DTPA) have been used to differentiate between benign and malignant tumours (Kuhl et al 2000). A rapid uptake and washout of the contrast agent is considered to be a strong indicator of malignancy. ‘Rim-like’ enhancement and morphological features within the tumour are employed to reduce false negative decisions (Boets et al 1994, Kuhl et al 2000) and high sensitivity has been achieved (Pediconi et al 2007). In x-ray breast imaging, early studies using computed tomography (Chang et al 1982) and digital subtraction angiography (Watt et al 1985) systems showed similar results but at the cost of high patient dose. The improved detection quantum efficiency (DQE) of currently available full field digital mammography systems (Pisano and Yaffe 2005) has led to renewed interest in performing iodine-based contrast-enhanced investigations. Recent studies employing temporal subtraction (Jong et al 2003, Dromain et al 2006) and dual-energy techniques (Lewin et al 2003) have shown ~83% specificity. This is well above the ~74% currently available from conventional screen film mammography (Pisano et al 2005).

Both MR and x-ray breast imaging have advantages and limitations and it is still unclear which of the above modalities will be able to perform contrast-enhanced measurements most efficiently. The main advantages of MR breast imaging are the lack of ionizing radiation and the three-dimensional (3D) information. The latter facilitates assessment of tumour enhancement without being obscured by super-imposed breast tissue structures. However, the high cost and
the limited access are important limitations for its widespread use. In addition, the compromise that must be made between spatial and temporal resolution means that repeated examinations maybe required when a less than optimum choice is made in the initial examination. On the other hand, in x-ray breast imaging, currently available flat panel imagers can provide high resolution with high frame rates. Assessment of tumour enhancement can be performed by projecting the 3D distribution of iodine onto the 2D detector plane. Although the temporal subtraction approach can, in principle, be used with the same efficacy (Skarpathiotakis et al 2002), high patient motion artefacts during the examination make it very difficult to effectively isolate the iodine from the cluttered breast background and hence to assess the contrast medium kinetics. This need not be a limitation in a dual-energy approach since the acquisition in rapid sequence of the low- and high-energy images, while the breast is compressed, can be used for the isolation of iodine and measurement of its projected thickness, making this approach more robust to patient motion artefacts. As each dual-energy pair of images is processed to form a single image incorporating only the iodinated regions, the time sequence of images will be much easier to quantify compared to a sequence of images derived from a simple temporal subtraction approach. Thus, the temporal variation in the iodine projected thickness can be quantified more effectively and used to measure the contrast agent kinetics in breast tumours.

We anticipate that measurements with high spatial and temporal resolution of the vascular contrast agent offered by quantitative contrast-enhanced mammography can help to increase the accuracy of diagnosis of breast cancer and also eliminate false biopsies. In addition, the quantitative information provided can be used for the selection of optimum cancer treatment (Karathanasis et al 2009) and monitor its therapeutic effect.

In the present work the evaluation of the clinical potential of quantitative contrast-enhanced mammography with high spatio-temporal accuracy is discussed. Theoretical analysis is used to select optimum parameters for undertaking measurements. These parameters include optimum spectral pair, and the trade-off between the dose and the effectiveness of the contrast medium isolation. An experimental phantom is used to verify the theoretical analysis and perform contrast medium kinetics measurements. The measurements are performed using an a:Si AMFPIs and a tungsten target tube.

2. Material and methods

2.1. Dual-energy contrast-enhanced mammography

Dual-energy imaging, where separate low- and high-energy images permit formation of material selective images, has been used in the past in digital radiography. The principles of dual-energy imaging have been extensively discussed in the literature (Alvarez and Mascovski 1976, Brody et al 1981, Lehman et al 1981, Johns and Jaffe 1985, Boone et al 1990, Lehman et al 2002) along with its practical aspects (Ergun et al 1990, Brettle and Cowen 1994, Kappadath and Show 2005). Studies using synchrotron radiation sources that provide a monochromatic beam with ideal energy separation and no spectral superposition have also been presented providing significant information regarding the minimum detectable iodine signals (Baldelli et al 2006, Sarnelli et al 2006, 2007, Prino et al 2008). In mammography dual-energy imaging has been primarily used for the isolation of microcalcifications. Estimation of vascular iodinated contrast medium thickness can be achieved in a similar way with two beams whose effective energies straddle the iodine k-edge. The k-edge approach is preferable to non-k-edge iodine imaging as it provides a higher resultant iodine contrast (Riederer et al 1981).
Consider two different energy beams: one with low (below the \( k \)-edge of iodine) and one with high (above the \( k \)-edge of iodine) effective energy incident on the breast. The low \( T_l \) and high \( T_h \) energy image signals per energy fluence absorbed by a detector when the two beams are transmitted through a breast composed of adipose tissue with thickness \( t_a \), glandular tissue with thickness \( t_g \) and iodine with thickness \( t_i \) can be expressed as

\[
T_j^b = \int \left( \frac{\Phi_j^b(E)}{dE} \cdot E \cdot \alpha_{pix}^2 \cdot e^{-(\mu_j^a t_a + \mu_j^g t_g + \mu_j^i t_i)} \cdot \eta_D(E) \cdot G_D(E) \right) dE \quad (j = l, h),
\]

where \( \Phi_j^b(E) \) is the photon fluence spectrum (photons/mm\(^2\) keV), \( E \) is the x-ray photon energy (keV), \( j = l, h \) denotes the low- and high-energy beams respectively, \( \alpha_{pix} \) is the pixel size assuming 100% fill factor (expressed in mm), \( \eta_D(E) \) is the detector quantum efficiency and \( G_D(E) \) is the detector mean gain and represents the signal in electrons generated per unit of deposited energy in the detector. The mass attenuation coefficients of adipose tissue, glandular tissue and iodine respectively expressed in cm\(^2\)/mg are given by \( \mu_a \), \( \mu_g \) and \( \mu_i \). \( t_a \), \( t_g \), and \( t_i \) is the adipose tissue, glandular tissue and iodine thicknesses in mg cm\(^{-2}\).

In the above expression, the image signal was expressed as a function of the absorbed energy fluence explicitly describing the signal formation of the image for energy integrating detectors. A spatially invariant detector, and no scatter radiation reaching the detector, is also assumed.

### 2.2. Average energy beam approximation

If the total breast tissue thickness incorporating iodine is \( t_b = t_a + t_g + t_i \), the line integral \( L_j \) of the attenuation along each beam path weighted by the detector response for the low- and high-energy beams can be estimated as follows:

\[
L_j = \ln \left( \frac{T_j^a}{T_j^b} \right) = \ln \left( \frac{\int \frac{\Phi_j^a(E)}{dE} \cdot E \cdot \alpha_{pix}^2 \cdot e^{-(\mu_j^a t_a + \mu_j^g t_g + \mu_j^i t_i)} \cdot \eta_D(E) \cdot G_D(E) dE}{\int \frac{\Phi_j^b(E)}{dE} \cdot E \cdot \alpha_{pix}^2 \cdot e^{-(\mu_j^a t_a + \mu_j^g t_g + \mu_j^i t_i)} \cdot \eta_D(E) \cdot G_D(E) dE} \right) \quad (j = l, h).
\]

The use of the image signals attenuated by 100% adipose tissue for the low and high energy beams, respectively, reduces the problem of three material compositions to two material compositions (Lemacks et al. 2002). This can be expressed as follows:

\[
I_{ja}^j(t_i, t_g) = \frac{L_j}{L_b} = \ln \left( \frac{\int \frac{\Phi_j^a(E)}{dE} \cdot E \cdot \alpha_{pix}^2 \cdot e^{-((\mu_j^a t_a + \mu_j^g t_g + \mu_j^i t_i))} \cdot \eta_D(E) \cdot G_D(E) dE}{\int \frac{\Phi_j^b(E)}{dE} \cdot E \cdot \alpha_{pix}^2 \cdot e^{-(\mu_j^a t_a + \mu_j^g t_g + \mu_j^i t_i)} \cdot \eta_D(E) \cdot G_D(E) dE} \right) \quad (j = l, h)
\]

Taking into account the energy variance of the polychromatic spectra, it has also been shown that a linear combination of high- and low-energy images enables the iodine thickness to be estimated as follows:

\[
t_i = (\mu_i^{eff})^{-1} \cdot \Delta I_a,
\]

where \( \mu_i^{eff} = -\left( \frac{\Delta \mu_i}{\Delta \mu_i} \right) \) is defined as the effective mass attenuation coefficient of iodine, \( \Delta I_a = T_a^h - \beta_g T_a^l, \beta_g = \frac{\mu_g}{\mu_i} \) is the weighting factor related to the effective suppression
of the glandular tissue, and $\Delta \mu_g(E) = \mu_g(E) - \mu_a(E)$ and $\Delta \mu_i(E) = \mu_i(E) - \mu_a(E)$ denote the residue mass attenuation coefficients of glandular tissue and iodine respectively. The above equation demonstrates that the measurement of the iodine thickness can be achieved irrespective of breast composition and detector material when the thickness of the breast and the signal attenuated by 100% adipose tissues are known.

2.3. Effective mass attenuation coefficients

The optimal weighting factors and effective mass attenuation coefficients for different breast thicknesses used in equation (4) are determined using the average attenuation coefficients of iodine, adipose and glandular tissue from the following expression:

$$\mu_j = \int \frac{\Phi_j(E)}{\mu(E)} E \mu(E) e^{-\mu_j a(E) t_b} \eta_D(E) dE$$

$$\int \frac{\Phi_j(E)}{\mu(E)} E e^{-\mu_j a(E) t_b} \eta_D(E) dE$$

$$j = l, h).$$

(5)

In the above expression the average mass attenuation coefficients are weighted by the detector response to account for its absorption efficiency and based on the present formulation are referenced to the beam attenuated by 100% adipose tissue.

2.4. Scatter in dual-energy imaging

In full field imaging scatter radiation in the low- and high-energy images will be present and will provide erroneous measurement of the x-ray attenuation from the imaged materials, limiting the accuracy in the projected thickness measurement (Ergun et al 1990, Kappadath and Show 2005, Shaw and Plewes 1987, Wagner et al 1988, Molloi and Mistretta 1998). The scatter radiation will have spatial (especially at the breast periphery) and energy dependence. However, scatter radiation to a good approximation can be expressed as a function of the scatter-to-primary ratio $(S/P)$ and using equation (4) will give the iodine projected thickness in the presence of scatter radiation as

$$t'_i = t_i + \ln \left( \frac{1 + S / P_a}{1 + S / P_b} \right)$$

$$\eta_D(E)$$

$$\frac{\eta_D(E)}{\mu(E)}$$

(6)

where $t_i$ is the real iodine thickness and $t'_i$ is the measured iodine thickness in the presence of scatter. $(S/P_a)$ and $(S/P_b)$ are the scatter-to-primary ratio beneath the adipose tissue only and breast respectively. From equation (6) it is evident that scatter radiation will introduce nonlinearities in the estimation of iodine projected thickness that will depend on the scatter-to-primary ratio $(S/P)$ of the detected photons beneath the iodine.

2.5. Signal-to-noise ratio in dual-energy imaging

Assuming that the scattered radiation can be effectively removed, then the uncertainty in the measurement of the iodine projected thickness in the final image will be

$$\sigma_{\Delta t \L} = \sqrt{\alpha_{L,h}^2 + \beta_t^2 \sigma_{L,t}^2 + (1 + \beta_t^2) \sigma_{add}^2 + \sigma_{Res}^2}$$

(7)

where $\sigma_{\Delta t \L}$ is the total rms. noise in the iodine-only image, $\alpha_L$ is the noise in the logarithmic transformed image, $\sigma_{add}$ is the total additive electronic noise of the detector and $\sigma_{Res}$ is the residual background noise and is related to the uncertainty in the estimation of the glandular composition of the breast due to linear subtraction. It is interesting to note that the quantum noise due to the presence of the scattered signal $(\sqrt{S} = \sqrt{(S/P) \times T})$ in the raw low-
high-energy images will be still present even if the scattered signal in the low- and high-energy images can be estimated with good accuracy and thus removed from the images (Kappadath and Show 2005). In equation (7), \( L' \) describes the line integral of the attenuation along each beam path in the presence of scatter. Elimination of the scattered signal from the raw images will result in substantial reduction of the residual noise.

The variance in the logarithmic transformed image can be measured from the image pair as follows:

\[
\sigma_L^2 = \sigma_T^2 \left( \frac{\partial L'}{\partial T} \right) + \sigma_{T_0}^2 \left( \frac{\partial L'}{\partial T_0} \right) \approx \left( \frac{\sigma_T}{T (1 + S/P)} \right)^2 + \left( \frac{\sigma_{T_0}}{T_0 (1 + S/P_0)} \right)^2, \tag{8}
\]

where \( \sigma_T \) and \( \sigma_{T_0} \) are the rms noise of the attenuated and unattenuated signals generated in the detector in the presence of scatter radiation respectively. In the images, the detector additive electronic noise \( \sigma_{\text{add}} \) will also be present. It is evident from the above expressions that the dual-energy image will be noisier than the single-energy images. However, it is interesting to note that the main benefit of generating an iodine only image apart from suppressing the cluttered background is to derive enhancement thresholds and provide accurate kinetics measurements of iodinated vascular contrast agents from the breast tumours, irrespective of breast composition and thickness.

Based on the above expressions, the signal-to-noise ratio (SNR) of an iodinated region of the breast can be used to estimate the theoretical limit in the detection of iodine. In the material selective imaging, assuming that the \( S/P \) ratios can be estimated with good accuracy, the SNR can be expressed as

\[
\text{SNR} = \frac{t_i}{\sqrt{\sigma_{L,i,h}^2 + \beta_k^2 \sigma_{L,i,l}^2 + (1 + \beta_k^2) \sigma_{\text{add}}^2 + \sigma_{\text{res},i}^2}}. \tag{9}
\]

The SNR suggests that the smallest iodine projected thickness can be detected when the background structure has been completely suppressed for a given photon flux, while the total additive electronic noise is small as compared with other noise sources.

2.6. System modelling

In dual-energy imaging, due to the use of two spectra the possible combinations of system parameters are large, so simulation is possibly the only way to either select the best parameters or at least to rule out the majority of the cases. The present study develops a 2D image simulation.

Spectra were generated using \texttt{xcomp5r} (Nowotny and Hvfer 1985, Meyer et al 2004). The inherent filtration of 0.8 mm Al plus added filters of I\(_2\) and Cu was used to form low- and high-energy beams respectively. The photon fluence per unit energy, provided by the program, was used to produce energy spectra for various tube settings expressed in photons/mm\(^2\)/mA. The mean breast entrance air Kerma (mGy mA\(^{-1}\)) \( D^j \) of the filtered spectra were calculated (Johns and Cunningham 1983). Using these values and the entrance photon fluence, the mean glandular dose per mA \( D_g^j \) can be estimated (Boone 2002). Division of a reference mean glandular dose (mGy) with the mean glandular dose per mA for a given spectrum fluence (quanta/mm\(^2\)/mA) provides a mean glandular dose-dependent scaling of the spectrum as follows:

\[
F^j = \frac{D_g^{j,\text{ref}}}{D_g}, \quad (j = l, h), \tag{10}
\]

where \( D_g^{j,\text{ref}} \) is a reference mean glandular dose used to weight the photon flux of the spectrum and \( j = l, h \) is the low- and high-energy beams respectively.
The photon fluence was scaled to the pixel area and then passed through adipose, glandular and combinations of adipose and glandular tissues for 4 cm and 8 cm breast thicknesses (Robinson and Kotre 2008). The choice of these breast thicknesses was indicated by thicknesses found in clinical practice. The first is close to the average breast thicknesses and the latter close to the thickest of breasts examined with x-radiology. For the combinations, different fractions of adipose to glandular tissue ranging from 100% to 0% were used as well as a range of iodine thicknesses. The iodine thickness was chosen to provide the projected thicknesses (see table 1) that comply with the values reported by other researchers (Chang et al 1982, Skarpathiotakis et al 2002).

In order to study the effects of the scatter and the scatter correction scheme, scattered radiation was estimated using the scatter-to-primary ($S/P$) ratios found in mammography. For a 4 cm thick compressed breast composed of 50% glandular and 50% adipose tissue, the $S/P$ ratio is 0.45. Although ($S/P$) ratios found in mammography have a very small variation for the energy range used in this study (Boone et al 2000), more accurate estimation should be used in order to take into account the periphery of the breast where thickness variations will cause significant deviations. For the polyenergetic beams used, the scatter spectrum was obtained by the averaged attenuated spectrum from the adipose and glandular tissue. This was performed in order to take into consideration the cases where adipose and glandular tissue are superimposed and the polyenergetic beam is attenuated by the arbitrary adipose-to-glandular ratio. Using this approach, the scatter intensity and energy distribution was uniform irrespective of beam path, although the $S/P$ ratios varied through the different beam paths. In the energy range around the iodine $k$-edge the ($S/P$) ratios are similar (Boone et al 2000) and the scatter radiation from the low- and high-energy beams has been scaled equivalently. The scatter contribution was then added to the transmitted primary intensity. It has been assumed that the presence of a small amount (< 10 mg cm$^{-2}$) of iodine in the beam does not significantly alter the $S/P$ ratio.

The integrated signal from the detector is determined by the absorption ratio ($\eta_D$) of the scintillator under study and the pixel size. A 45 mg cm$^{-2}$ (100 \(\mu\)m) thick CsI:TI and a 48.1 mg cm$^{-2}$ (65 \(\mu\)m) thick Gd$_2$O$_2$S:Tb scintillators have been used in the simulation. The choice of the above thicknesses was indicated from the scintillator thicknesses used in current clinical practice.

The geometry of the simulated images was such that the two materials (adipose and gladular) formed a ramp in order to incorporate all possible compositions of breast (see figure 1). This geometry was chosen in order to optimize the spectral pairs and assess the dose efficacy and the iodine isolation irrespective of breast composition. Only a small region of the image that incorporated different fractions of adipose to glandular tissue ranging from 100% to 0% was iodinated. For the present simulations a parallel x-ray beam has been
assumed and structural or spatial noise could be added to simulate quantum mottle and detector effects.

In order to compare the simulation with the experimentally determined SNRs the conversion efficiency of the phosphor was also incorporated in the mean system gain ($G_D$). The phosphors are assumed be linear in response. Thus, the electron charge read by the detector is expressed as electrons per keV deposited in the phosphor. The variance of the individual gains of the system can be assumed negligible; thus, the mean system gain is their linear combination.

The Poisson noise in the images was approximated using a Gaussian distribution as the number of detected photons was reasonably large and signal and noise spatial correlations were not considered (Rabbani et al 1987). A uniform scatter distribution has been incorporated in the images and the total detected photons (primary and scattered) were used to determine the Poisson noise in the low- and high-energy images. Detector additive electronic noise was expressed in rms electrons and spatial variation in the detector response or fixed pattern noise (FPN) was modelled as a sinusoid (Williams et al 1999) with its amplitude scaled linearly to the integrated signal from the detector.

Tumour angiogenesis starts when the tumour size is larger than 2 mm, so with a pixel pitch of 127 μm, frequency-dependent blurring effects are not considered in the simulation. This is also true for the NPS characteristics since the correlated components are reduced by the square of the modulation transfer function (Cunningham 2000). Thus, even for subtle lesions that do not uptake much contrast it should be unnecessary to consider the complete NPS characteristics to determine the SNR. It should be noted that this is true as long as the iodinated area is much larger than the detector spatial correlations. In addition, the minimum pixel signal should always be above signal levels where the performance of the detector is affected by the detector electronic noise. For the exposures considered in this study, the electronic noise was not significant. Table 1 summarizes the model parameters used to simulate the dual-energy images.

### 2.7. Optimal operational points

The iodine signal-to-noise ratio of the iodine selective image has been used to determine the optimal spectral pair. Thus, the spectra are scaled to provide the predetermined value of the
mean glandular dose irrespective of the tube kVp used. The thickness of the filtration was
selected so as to achieve currents within the heat capacity of the tube. The method is iterative
and aims to maximize the SNR of the iodine in the iodine selective image at different tube
kVp for a given mean glandular dose and filter combination. The low- and high-energy beams
are optimized sequentially.

The assessment of low- and high-energy spectral fluxes has been performed by studying
the SNR versus dose fraction allocated by the high-energy beam expressed as the ratio of
the mean glandular dose of the high-energy beam \( (mGd^h) \) to the total mean glandular dose
\( (mGd_{Tot}) \) (Carton et al. 2007). This ratio will provide the optimum distribution of the
mean glandular dose in the two images thus maximizing the dose efficiency during image
acquisition.

For estimation of the SNR, the mean and the standard deviation of the iodinated region of
the iodine selective image were used. This region in the low- and high-energy images appears
as a ramp since it includes the different fractions of adipose and glandular tissue. However,
in the iodine selective image the background is uniform as tissue cancellation is achieved.
Assuming that the noise in the images is uncorrelated the Rose criterion can be adopted (Rose
1953) to determine the minimum SNR for effective detection. Although noise correlation is
hard to avoid in real detector systems, in the present study it is assumed negligible and an
SNR equal to 5 is adopted as the detectability threshold. For the selection of optimal operation
points using the simulation, where the comparison of the different parameters is of interest,
an SNR equal to 3 provided adequate indicator.

2.8. Experimental dual-energy imaging and contrast medium kinetics measurements

The experimental setup incorporated a tungsten target tube (Varian NDI 160-22 using an AGO
125 generator) with a stepper motor attached to its exit window for remote and reproducible
interchange of the filters. A flat panel imager (PaxScan 4030R, Varian Medical Systems) and
an experimental breast-equivalent phantom that incorporates flow (see figure 1) have been
constructed in order to validate the theoretical predictions, and perform quantitative contrast
medium kinetics measurements (Arvanitis et al. 2007). An antiscatter grid was not used. The
phantom is composed of glandular and adipose breast-equivalent plastics (014A, Ciris Tissue
Simulation Tech.). Phantom thicknesses equivalent to 4 cm and 8 cm thick compressed breast
were used. A 7 mm PMMA slab containing a circular bath 2 mm deep and 6 mm in diameter
was placed on top of the breast-equivalent plastic. The centre of the bath was positioned at
the mid-point of the ramp, ‘A’ (see figure 1). This geometry provides a way of estimating
the degree of iodine isolation under all possible combinations of adipose and glandular tissue
in the breast. The bath, which represents a tumour, contained different concentrations of
iodinated contrast medium solution to simulate projected thicknesses of 0, 0.5, 1, 2, 3, 4, 6
and 8 mg cm\(^{-2}\). A depth of 2 mm in the PMMA was chosen to match minimum tumours sizes
that develop angiogenesis (Miles 2003).

Simulation of contrast medium kinetics of the breast is a very complex task. Our aim
was to perform contrast medium kinetics measurements based on our experimental phantom,
in order to investigate whether the temporal differences in iodine projected thickness can be
effectively detected. The flow of contrast medium in the phantom was simulated using a stable
flow peristaltic pump (Peristaltic Pump 3200, Welch Vacuum).

The contrast medium kinetics was measured by acquiring the low- and high-energy images
in two separate experiments performed under identical conditions. The two experiments were
the use of (i) an open flow circulation and (ii) a closed flow circulation. In the first, the
contrast medium after its first passage was disposed of and, in the latter, the contrast medium
after its injection was circulated in the flow circuit. By choosing these two different flow configurations we could simulate two out of the three contrast media kinetics curves found in clinical conditions (Kuhl et al. 2000). The flow rate was adjusted so as to provide flow rates similar to those found in breast examinations and at the same time provide a good mixing of the contrast medium with the circulated water before the contrast medium reached the bath that simulated the tumour. To create a clinical examination scenario a small amount (1 ml) of contrast medium was injected remotely using a 4 cc syringe. The flow was measured by volume sampling and found to be 20.4 ml min$^{-1}$.

The pulsatile flow created by the heart was not simulated. A phantom of different geometries incorporating a pulsatile pump to simulate the human physiology has been developed by Nock et al. (2007). However, for the purposes of the present work a non-pulsatile pump was felt to be sufficient to demonstrate that the temporal variation in the iodine projected thickness can be effectively used to measure the kinetics of contrast agent.

3. Results and discussion

3.1. Optimal operation parameters

The formation of the energy spectral pair is the most demanding practical aspect of dual-energy imaging (Kappadath and Show 2005, Kelcz et al. 1977, Chakraborty and Barnes 1989). The appropriate filter material and thickness for finding the optimal spectral pair is a complex compromise involving x-ray tube heat loading, total mean glandular dose, breast thickness, iodine signal and noise. In the present work mean glandular doses from the spectral pair expressed in mGy mA$^{-1}$ were used to control the spectrum fluence in order to achieve a dose efficient scheme. During the spectral pair optimization only the quantum efficiency of the phosphors has been considered.

A tungsten target tube was used throughout this work due to its tube loading capability combined with high photon fluxes, even at significant levels of filtration (Ullman et al. 2005). The formation of quasi-mono-energetic beams can be achieved by using the $k$-edge of high atomic number materials. However, there are some practical aspects that restrict the selection of the appropriate filter material. Among these are the toxicity, uniformity, availability and the cost of the material. With these in mind, filtering the low-energy spectrum with iodine in the form of contrast agent provides a good compromise. For the high-energy beam copper has been chosen as it fulfils all the above practical aspects (Skarpathiotakis et al. 2002) despite its lack of a $k$-edge in the energy range of interest (above 33.2 keV).

In figure 2 the SNR of the iodinated region versus Cu and I$_2$ filter thicknesses is shown. In order to obtain these data an iterative method has been adopted, first the spectrum of the high-energy beam has been fixed so as to have the mean energy above the iodine $k$-edge (50 kVp, 3 mm Cu filtration) and then the filtration of the low beam has been varied using 45 kVp tube load. Then the filter thickness that gave the maximum SNR for the low beam has been used and the filtration for the high beam has been varied. This process has been performed for different filtration thicknesses and kVp combinations. The trends shown in figure 2 are representative. In particular, for the iodine filtered spectrum (low energy) the SNR of the iodinated region decreases as a function of the filtration thickness whereas the Cu filtered beam behaves in the opposite way. It is evident that low iodine filter thicknesses and high copper filter thicknesses are more beneficial for high SNRs in iodinated regions in contrast-enhanced mammography. Thus for the low-energy beam, a 0.2 mm filter of iodine provides the lower tube loadings and the highest SNRs. Therefore, the low-energy beam was filtered with 3.25 mm of contrast agent (Iohexol, with 350 mg of iodine per milliliter) resulting in an
equivalent iodine thickness of 0.245 mm. For the high-energy beam a compromise between tube loading and the SNR of the iodinated area is required. Within the load capabilities of the x-ray tube in use, the thicker the Cu filter for the high-energy beam the better. Hence 0.3 mm of copper (Cu) has been used as this could be tolerated by the x-ray source used for these experiments. The methodology developed in the present study provides a way to select the optimum beams of a particular tube based on its heat loading characteristics.

Figure 3 shows the iodine image signal-to-noise ratio (SNR) as a function of tube kVp for the two beams. It can be seen that up to a tube voltage of approximately 48 kVp the SNR increases. This increase is because the high-energy beam filtration is not based on k-edge filtration, which causes the effective energy to vary strongly with kVp. The higher the kVp used the less the fraction of the beam below the k-edge is. This is not the case for the low energy, which is the k-edge filtered beam. At low kVp where a high proportion of the spectrum is below the iodine k-edge, the SNR is high. At higher kVp the mean energy of the spectrum is moving further away from the iodine k-edge and hence the SNR for the low-energy beam decreases proportionally with the increase of the low-energy beam component above the k-edge. In order to keep the kVp separation as small as possible (Ducote et al 2007) for the low-energy beam 44 kVp was selected as optimum and 48 kVp for the high-energy beam. It is worth noting that the point at which the two curves shown in figure 3 cross could provide a spectra pair with the same tube kVp. This might be beneficial under clinical conditions, as it would not require switching the tube voltage. However, as in all cases the tube currents have to be adjusted. In table 2 the simulation parameters of the two beams are shown and figure 4 shows the simulated optimum spectra pair normalized to unity.

Figure 5 plots the iodine SNR as a function of the ratio of the high-energy beam mean glandular dose to the total mean glandular dose \( \frac{mGd}{mGd^{tot}} \) for the CsI and Gd\(_2\)O\(_2\)S phosphors. It can be seen that the SNR changes little for \( mGd/mGd^{tot} \) between 0.4 and 0.7. The optimal \( mGd/mGd^{tot} \) ratio, as determined from fits of the simulated data for a 4 cm
breast, was 0.60 for both CsI and Gd₂O₂S. \( \frac{mGdh}{mGdtot} \) equal to 0.6 was used throughout this work if not indicated otherwise. For a given iodine SNR the optimum \( \frac{mGdh}{mGdtot} \) is independent of breast thickness and composition. However, at constant \( mGdtot \), thicker breasts show an optimal ratio of 0.55 for both x-ray converters (see figure 6). For a given set of conditions both phosphors show similar SNRs.

3.2. Weighting factors

The optimal weighting factors (see \( \beta \), section 2.3) and effective iodine mass attenuation coefficients for different breast thicknesses for the two different phosphors studied are given in table 3. The values in the table are for the selected spectral pair and do not change with breast composition. To measure the attenuation coefficients, only the thickness of the breast is important as it affects the degree of attenuation by the 100% adipose tissue. Due to the higher absorption efficiency of CsI above the iodine k-edge, the weighting factor (\( \beta_i \)) is smaller for the CsI phosphor. As a result the iodine effective mass attenuation coefficient (\( \mu_{eff}^i \)) is higher when the CsI phosphor is employed.

3.3. SNR versus breast thickness

Figure 6 shows the iodine SNR as a function of the ratio of the high-energy beam mean glandular dose to the total mean glandular dose (\( \frac{mGdh}{mGdtot} \)) for different breast
thicknesses. It can be seen that the distribution of the mean glandular dose between the low- and high-energy beams is shifted from approximately 0.7 for a 2 cm thick breast to approximately 0.55 for the 8 cm thick breast. Increasing the exposure to thicker breasts shifts the $mGd^h/mGd^\text{tot}$ ratio back to approximately 0.7. The SNR decreases by approximately 0.05 for every cm increase in the breast thickness.
Figure 6. The SNR for different breast thicknesses as a function of the ratio of the mean glandular dose of the high-energy beam to the total mean glandular dose $mGd^h/mGd^{tot}$. The phosphor used was CsI with 100 $\mu$m thickness. The projected thickness of iodine was 3 mg cm$^{-2}$ and the total mean glandular dose was 0.4 mGy. The fits to the simulated data points are also presented.

Table 3. Optimal weighting factors and effective iodine mass attenuation coefficients.

<table>
<thead>
<tr>
<th>Breast thickness (cm)</th>
<th>$\beta_g$</th>
<th>$\mu_{eff}^G$ (cm$^{-1}$)</th>
<th>$\beta_g$</th>
<th>$\mu_{eff}^CsI$ (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.54</td>
<td>-64.39</td>
<td>0.49</td>
<td>-72.26</td>
</tr>
<tr>
<td>4</td>
<td>0.56</td>
<td>-66.00</td>
<td>0.51</td>
<td>-72.81</td>
</tr>
<tr>
<td>6</td>
<td>0.57</td>
<td>-67.38</td>
<td>0.53</td>
<td>-73.12</td>
</tr>
<tr>
<td>8</td>
<td>0.58</td>
<td>-68.54</td>
<td>0.54</td>
<td>-73.21</td>
</tr>
</tbody>
</table>

3.4. Effect of pixel size and mean glandular dose on the SNR

The signal-to-noise ratio (SNR) can be used as an efficient estimator of the minimum detectable iodine signal and provides a means to quantify the effect of pixel size and mean glandular dose in the measurement of the projected iodine signal. Figure 7 shows the SNR as a function of pixel size and total mean glandular dose. At constant mean glandular dose the SNR scales linearly with the pixel size. This is because in the material selective image, the signal will be constant and the SNR or the noise is inversely proportional to the pixel size. It can be seen that the $SNR^2$ scales linearly with the total mean glandular dose. Thus, the higher the mean glandular dose the smaller the uncertainty in the iodine thickness measurements will be.

3.5. Experimental iodine selective image

Figure 8 shows the low-, the high-energy and the iodine selective images of the breast-equivalent phantoms. The iodine projected thickness was 3 mg cm$^{-2}$ and the mean glandular dose was $\sim$0.1 mGy. To the left of each image is the adipose tissue-equivalent plastic and to the right of each image is the glandular tissue-equivalent plastic. As can be seen in the iodine...
selective image (figure 8(c)), the iodine signal is not affected by the ramp, which formed the background breast structure incorporating all possible compositions of adipose and glandular tissue. In the image there is some remnant fixed pattern noise (phosphor nonuniformities) that has not been corrected through flat fielding. This is possibly because the effectiveness of flat fielding was limited due to the EMI noise. The nature of this noise component is non-stationary and alters the amplitude of the phosphor fixed pattern noise from frame to frame, limiting the effectiveness of flat field image averaging. However, the contrast in the image is very good and iodinated area can be clearly identified.

3.6. Iodine projected thickness measurements

The aim of quantitative contrast-enhanced mammography is to determine the magnitude of the iodine signal and its rate of enhancement in physical units. This can be obtained from the
Figure 9. The experimental iodine thickness measured with the PaxScan 4030R detector. The measured thickness from the simulated phantom incorporating scatter radiation and the same data after the scatter fraction has been removed as a function of the actual iodine thickness is also shown. The breast thickness was 4 cm and the total mean glandular was ∼0.1 mGy. For both plots the linear fits had $R^2 = 0.99$.

measurement of the projected thickness of the iodinated vascular contrast agent expressed in mg cm$^{-2}$.

Figure 9 shows the experimentally determined iodine projected thicknesses as a function of the true thickness. The total mean glandular dose was equal to 0.1 mGy and as indicated by the detector response, the acquired intensities across the images are well within its linear region. The same plot shows the simulated thickness with scatter, and also the experimental and simulated data with scatter removed. Scatter has been incorporated in the simulated images, as discussed in section 2.6. The simulated data in the absence of scatter are not included as they overlap the data when the scatter has been removed. This signifies that the linear subtraction of log-transformed images using the formulation presented provides accurate measurements of the iodine projected thickness. However, some small positive offsets appearing in the simulated data are related to the errors associated with the linear subtraction and are independent of exposure. It is expected that nonlinear subtraction could further suppress this value. However, these offsets are from 0.04 mg cm$^{-2}$ for a 2 cm thick breast up to 0.32 mg cm$^{-2}$ for an 8 cm thick breast and are not considered significant in the present study.

It is interesting to note that in the absence of iodine, its predicted thickness in the experimental data was not zero but equal to −0.65 mg cm$^{-2}$. This negative residual was because, in the absence of iodine in the experimental phantom, the circular bath representing the tumour was filled with water. In the simulation the contrast medium was simulated with iodine only and not with iodine diluted in water. Thus in the experimental data, the adipose and glandular tissue are effectively suppressed but not the water which, in fact, is considered to be iodine. In order to quantify this, the iodine selective image was converted to a water selective image. After the conversion, a projected thickness equal to 0.13 mg cm$^{-2}$ was measured. By taking into account the error due to the linear subtraction and the presence of PMMA is very
close to the real value \((0.2 \text{ mg cm}^{-2})\). Although it was shown that the error introduced is within the experimental accuracy of dual-energy imaging, in future work the diluted iodine contrast medium can be incorporated in the simulation.

In the simulations without scatter, the nonlinear response due to beam hardening becomes apparent at high concentrations of iodine (around \(40 \text{ mg cm}^{-2}\)). However, under clinical conditions the dilution of the contrast agent is of the order of 1:40 of the injected agent, leading to a concentration less than \(10 \text{ mg m}^{-1}\) for contrast media with \(350 \text{ mg of iodine per milliliter} (\text{Sarnelli et al. 2007})\). Thus, there is no reason to study iodine projected thicknesses above \(10 \text{ mg cm}^{-2}\) and therefore at iodine projected thicknesses relevant to clinical values, beam hardening does not introduce significant deviation from slope equal to unity when compared with actual iodine projected thickness.

The significant deviation from slope equal to unity in the experimentally determined iodine projected thicknesses (figure 9) is due to the presence of scatter and has the same degree of deviation as the simulated data. This is based on the assumption that in a small region (\(\sim 3 \text{ cm}\)) that surrounds the iodinated cavity the spatial distribution of scatter in the experimental data was uniform. As the simulation was based on the same geometry with the experimental phantom, the \(S/P\) ratios causing the same deviations from slope equal to unity should be approximately the same. Considering the approximations used, the agreement between the current \(S/P\) ratios and those of Boone et al (2000) using the same breast composition (50% glandular and 50% adipose) and thickness (4 cm thick) is very good. The trends in deviation from slope equal to unity are also similar to those found by other investigators in the field of angiography (Shaw and Plewes 1987).

From figure 9 it is apparent that scatter removal restores the iodine thickness, within experimental precision, to its true value in both experimental and simulated data. The deviations from slope equal to unity depend on the \(S/P\) ratios and not on the actual scatter fraction in the images as can be seen from the smaller deviations for low iodine concentrations. Thus, the greater the iodine thickness the larger the error in its measurement will be. The same holds for thick breasts and in regions of the breast with high glandular-to-adipose ratios. A special case is when the \(S/P\) ratios of the breast and adipose tissue are equal, then the scatter contribution is cancelled and \(t'_i = t_i\). This can be the case only for very low iodine concentrations and when the breast is composed of adipose tissue only. It is interesting to note that even in the case of equal intensity beams the \(S/P\) ratios cannot be considered as equal since the attenuation of the iodine differs significantly at the two different beam energies. Thus, the detected \(S/P\) ratio will be different despite the fact that over the energy range of interest the \(S/P\) ratios in the breast do not change significantly Boone et al (2000).

The results demonstrate that the scatter removal can provide a viable and dose-effective alternative for the development of quantitative contrast-enhanced mammography. The use of an antiscatter grid will only remove part of the scatter and the above corrections using scatter removal techniques will still be needed. Additionally, the use of an antiscatter grid will increase the mean glandular dose per acquisition. Further investigation to assess the significance of the antiscatter grid in the isolation of iodine is required. A combination of scatter rejection and scatter correction schemes might be appropriate.

3.7. Comparison of the experimental and modelled SNR

Figure 10 shows the experimental SNR as a function of iodine projected thickness for 4 cm and 8 cm breast thicknesses. The simulated SNRs are also shown. The scatter radiation for the 4 and 8 cm breast thicknesses was 45% and 90% of the primary beam respectively and has been incorporated in the data presented. Scatter corrections using either equation (6) or
by removing the scattered fraction from the image signal have been applied to both simulated and experimental data. The system gain, the total additive electronic noise and fixed pattern noise were incorporated in the simulation in order to compare SNRs between the experiment and the simulation. The total additive electronic noise was set equal to 1000 electrons, and its contribution to the total noise was marginal. The fixed pattern noise magnitude was set equal to 0.8% of the total signal integrated by the detector. The system gain was set equal to 0.4 electrons per keV deposited on the sensor resulting in approximately 12 electrons per 30 keV x-ray photon. As can be seen from figure 10 the simulated and experimental data have similar values. Iodine projected thicknesses less than 3 mg cm\(^{-2}\) can be effectively detected, i.e., with the SNR > 5, in the case of a 4 cm thick breast. For an 8 cm thick breast at double the dose (0.2 mGy), 3 mg cm\(^{-2}\) of iodine can be estimated with an SNR of 4. Although, iodine of 2 mg cm\(^{-2}\) can be detected with an SNR of 3, higher levels of exposure should be used in order to achieve SNRs above 5 for iodine projected thickness lower than 4 mg cm\(^{-2}\).

Skarpathiotakis et al (2002) using temporal subtraction achieved high SNR values even for 1 mg cm\(^{-2}\); however, the change in the slope by changing the exposure and the significant motion artefacts of temporal subtraction limits this approach. In work presented by Baldelli et al (2006) for single exposure dual-energy imaging, using clinical system, visualization of iodine concentrations of 4.13 mg ml\(^{-1}\) and 5.75 mg ml\(^{-1}\) for cavities 5 mm and 8 mm respectively has been reported, which is three times lower than the concentration of the present work but the exposure was five times higher (2 mGy). In work presented by Sarnelli et al (2007) energy separation (~4 KeV) proved to be slightly significant and only at the more attenuating part of the phantom. This resulted in smaller SNRs, indicating that energy separation is significant only at very thick breasts. More work in this area is needed.

This also suggests that spectra superposition is significant in order to achieve very high SNRs. However, apart from the beams provided by synchrotron radiation (Baldelli et al 2006), for x-ray tubes found in clinical practice this is unavoidable and the methodology provided at the present study provides a way to achieve optimum trade-offs in order to maximize the iodine SNR. A slight improvement for the iodine SNR is anticipated if the high-energy beam
Quantitative contrast-enhanced mammography for contrast medium kinetics studies

3.8. Contrast medium kinetics measurements

The contrast medium kinetics measurements made using the experimental phantom are presented in figures 11 and 12 for the two different circulation configurations. It is evident that temporal differences in iodine concentration can be effectively measured. Open circulation (figure 11) was used for contrast media uptake measurement, as the flow rate could be measured with high accuracy through volume sampling. The closed circulation (figure 12) was used to measure the maximum iodine projected thickness, as the amount of circulating water and the volume of injected contrast media could be measured with high accuracy. Although the closed circulation could also be used for uptake measurement, with the current setup it was not possible to confirm that the flow rate was constant. The kinetics plots shown in figures 11 and 12 that have been extracted using the two different types of circulation have also been chosen in order to study the possibility of experimentally measuring uptake and clearance similar to those reported in clinical studies (Kuhl et al 2000). The rapid uptake and washout of the contrast agent (figure 11) is considered to be a strong indicator of malignancy and the gradual increasing enhancement (figure 12) is usually seen in benign tumours.

The only corrections that were applied to the data were the water offset (see section 3.6) and scatter removal. It is important to note that the iodine projected thickness measurements (figure 9) were only used for the scatter fraction estimates at the initial part of the study and

![Graph](image)

Figure 11. Open circulation contrast medium kinetics measurements based on the experimental phantom (4 cm thick) using the PaxScan 4030R detector. Approximately one image every 7 s was acquired.

is also filtered with \( k \)-edge filter; however, materials with \( k \)-edges at the required energies (\( \sim 50 \) kev) are relatively toxic and might impose health and safety concerns that will hinder the clinical utility of the proposed approach.

The SNRs provided at the present work could be further enhanced by the development of methods to correct for phosphor and x-ray field nonuniformities. In addition, new detector technologies (Arvanitis et al 2007) and approaches (Bornefalk et al 2007, Schlomka et al 2008) can be used to further enhance both the performance and the applicability of the proposed approach.
not for the measurements shown in the kinetics plots. A precondition for the algorithm to operate under clinical conditions is an accurate knowledge of breast thickness, which is readily available on many mammographic units. Also knowledge of image intensity after attenuation by 100% adipose is required. This can be obtained by imaging an adipose-equivalent phantom of the appropriate thickness alongside the patient. Estimation of scatter intensity is also important; however, as demonstrated, Monte Carlo estimates provide adequate results.

As can be seen in figure 11, the very sharp increase and then more gradual decrease of the iodinated signal maps the passage of the injected bolus of the contrast medium from the simulated tumour. In the plot data without scatter removal are also shown. Using the first passage, the flow rate was measured to be 0.27 ml s^{-1}, \sim 18\% error compared with actual flow rate (0.33 ml s^{-1}). It is interesting to note that without the scatter correction the error in the flow rate measurement is as high as \sim 45\%. This indicates the importance of the scatter correction in measuring the contrast medium kinetics. The same holds for the measurement of the maximum iodine projected thickness that was underestimated by 33\% if the scatter was not removed.

In the kinetics measurements using the close circulation (figure 12), without the scatter correction, the measured iodine projected thickness is also underestimated. After the scatter correction has been applied the expected maximum iodine projected thickness, as measured 10 min after the contrast medium administration, was 2.4 mg cm^{-2}. At that time the curve reaches a plateau indicating that the contrast media has been uniformly diluted with the circulating water. The maximum actual iodine projected thickness after uniform dilution is 2.6 mg cm^{-2}.

Based on our current experimental setup five or six data points can provide adequate information regarding the contrast media kinetics. This is particularly relevant to clinical conditions as six image pairs will deliver a total mean glandular dose less than 1.8 mGy which is equivalent to the average glandular dose used in conventional digital mammography. It should be noted that in the present study our aim is to demonstrate that six image pairs could
be acquired at dose levels equal to those found in conventional mammography and not to
derive an optimal imaging protocol. Such a protocol should be derived from clinical studies
that will help to determine how many image pairs are needed and when acquisitions should
be acquired. In addition, when scatter corrections are applied, enhancement measurements
can be expressed in absolute units. It also demonstrates that contrast-enhanced measurements
expressed in physical units can be provided independently of calibration data at any point in
the time domain, without the need for an image mask. The elimination of a mask image makes
the beginning of image acquisition for the assessment of the vascular contrast agent uptake
less restricted; however, for the determination of uptake at least one measurement before the
maximum enhancement has been reached must be acquired.

Clinical assessment of tumour angiogenesis could be erroneous if iodine is present in
under- or over-lying tissues. In this case the enhanced signal will not be directly proportional to
tumour neovascularization but will be inflated due to the iodine in under- or over-lying tissues.
In order to compensate for this, dual-energy tomosynthesis has recently been proposed (Carton
et al 2007). However, the incorporation of tomosynthesis automatically limits the examination
to static imaging (ideally at maximum enhancement) as the dose will be considerably higher if
contrast media kinetics information is needed. This problem could be addressed by acquiring
just two image pairs at 90° with respect to each other to be used for the kinetics measurement.
This would provide adequate information on whether or not the iodine projected thickness has
been inflated by over- or under-lying iodinated areas, while keeping the dose to acceptable
levels. It could also allow for estimation of the iodinated volume if it is assumed that the
def ormation of iodinated areas in the breast due to breast compression is either negligible or
can be estimated. Adopting this approach, measurement of blood flow per unit volume of
tissue could be performed and direct link between enhanced areas and tumour microvessel
density or perfusion could be established.

The quantitative information provided could also assist intradepartmental comparisons of
the procedures used by different hospitals and could help to extract enhancement thresholds.
It could also investigate the relevance of these measurements to tumour formation when
diagnosis is considered with potential to perform in situ x-ray biopsy. It can also help on the
rapid assessment of the oncolytic effect of anticancer agents when therapy is monitored or
help to predict the outcome of chemotherapy (Karathanasis et al 2009) and chose appropriate
treatment.

4. Conclusions

The theoretical and experimental analysis of dual-energy contrast-enhanced mammography
has been presented. The results suggest that quantitative and temporal information from the
enhanced tumour can be extracted to indirectly measure the tumour microvessel density and
blood flow.

Optimization of critical parameters resulted in
(i) effective isolation of the iodinated contrast medium from breast background clutter,
(ii) optimization of the energy pair,
(iii) the ability to assess the low- and high-energy beam dose efficiency,
(iv) contrast medium kinetics measurements,
(v) measurement of iodine projected thickness expressed in mg cm$^{-2}$,
(vi) evaluation of the effect of beam hardening and scatter radiation.

The dose per view was restricted so that the total mean glandular dose from the series
of images was equivalent to or less than that from conventional mammography. Quantitative
contrast-enhanced measurements independent of calibration data at any point in the time domain can be provided using the dual-energy approach.

The systematic analysis and optimization of quantitative contrast-enhanced measurements in the breast may help with

(i) improving tumour detection in dense breasts,
(ii) tissue characterization,
(iii) the reduction of false biopsies,
(iv) clearer delineation of tumours,
(v) monitoring and predicting the oncolytic effect of anticancer agents and protocols.

Comparison with breast MR studies will reveal the clinical potential of the quantitative contrast-enhanced mammography. However, quantitative contrast-enhanced mammography has a significant advantage due to its wide spread availability, measurement of enhancement and kinetics measurements in physical units, and low cost.

Acknowledgments

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