ATTENUATION CORRECTION IN ULTRASOUND
CONTRAST AGENT IMAGING: ELEMENTARY THEORY AND
PRELIMINARY EXPERIMENTAL EVALUATION

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Abstract - Progress in imaging and quantification of tissue perfusion using ultrasound (US) and microbubble contrast agents has been undermined by the lack of an effective automatic attenuation correction technique. In this paper, an elementary model of the US attenuation processes for microbubble contrast enhanced imaging is developed. In the model, factors such as nonlinear bubble scattering, nonlinear attenuation, attenuation to both fundamental and harmonic, and US beam profile are considered. Methods are proposed for fast formation of images with automatic attenuation correction based on the model. In the proposed method, linear tissue echoes are extracted and filtered, and then used to compensate for the attenuation in nonlinear bubble echoes at the same location to produce quantities that are a truer representation of bubble concentration. The technique does not require additional measurements and can be implemented in real time. Preliminary experiments on laboratory phantoms consisting of bubbles and tissue-mimicking materials are presented and the effectiveness of the proposed method is supported by improvements in image quality compared with unprocessed data. This development is an important step towards real-time quantitative contrast US imaging. (E-mail: mengxing.tang@imperial.ac.uk)

Key Words: *Contrast agents, Attenuation correction, Perfusion quantification.*

INTRODUCTION

Tissue perfusion is a crucial indicator in clinical assessment of a wide range of clinical conditions such as heart disease and cancer. Consequently, there is a pressing need for an accurate and convenient means of quantifying perfusion in diagnostic imaging applications and for monitoring of therapeutic procedures. Ultrasound (US) offers many advantages as an imaging modality in terms of its real-time acquisition, flexibility, patient safety and cost. Furthermore, the development of microbubble contrast agents provides a means for enhancing the sensitivity of US to blood flow, and shows great potential for quantitative perfusion imaging (Wei et al 1998, Becher and Burns 2000, Foster et al 2000, Bauer et al 2002). A unique aspect of this technique is that the contrast agents can be disrupted in a controlled way to facilitate imaging the wash-in of the tissues.

Typical US contrast agents are micrometre-sized bubbles consisting of a gas core stabilised by a flexible shell. When injected into a vein, they circulate systemically and strongly increase the US echoes, brightening up the image of tissue containing them. In traditional B-mode imaging, both tissue and bubbles are shown together in the images but current techniques such as pulse inversion (PI) are used to suppress signals from tissue and to extract signals only related to microbubbles and, thus, to perfusion. Specifically, these techniques make multiple measurements of the imaged region and based on these measurements quantities related to the microbubble concentration can be derived (Eckersley et al 2005), leading to quantification of tissue perfusion.

The US echo from a target is affected by attenuation due to overlaying tissues, for which correction or compensation must be applied to obtain a more accurate measure of the echogenicity of the target. In most commercial scanners there is a process known as “time gain compensation” (TGC) which uses preset values to correct for attenuation according to

the distance between transducer and target. This usually requires manual adjustments by the operator. The same overall gain function is then applied to all scan lines in the image. As a result the correction is crude and consistency and reliability of any quantification are compromised.

A number of studies have been done to address the problem of appropriate compensation of attenuation. For example, O'Donnell (1983) and Melton and Skorton (1983) developed methods which separated attenuation into 2 or 3 levels based on the statistics of the image intensities. Hewlett Packard introduced "lateral gain compensation" for cardiac scanning - a method that allowed for global variation in attenuation when imaging through myocardium as compared with cardiac chambers. However, a key deficiency of these methods is their inability to compensate dynamically for changing patterns of attenuation coefficient.

Techniques for automatic attenuation correction in B-mode imaging have been reported in a number of studies. For example, McDicken et al. (1974) described an approach in which the signal from the receiver is integrated, inverted and fed back to control the gain. Pye et al. (1992) proposed an algorithm which calculates a variable gain function through smoothing the factor required to bring the mean echo amplitude at a specific depth to a mid-range grey level. Hughes and Duck (1997) presented a model which describes echoes in terms of attenuation and backscatter coefficients, and developed an algorithm based on this model to correct for attenuation. In their method, the assumption was that the attenuation increased as the backscatter increased. Although image processing techniques such as histogram equalisation (see, for example, Cheng and Shi 2004) can be used as an alternative for attenuation compensation to improve perceived image visualisation, quantification of image intensity based on this kind of approach is generally not plausibly justified.

While the above-mentioned techniques have shown improvement over preset and manual TGC, they were developed for standard B-mode images. As introduced previously, new imaging modes such as pulse inversion have been developed which can distinguish bubbles based on their nonlinear behaviour under US excitation. This, however, brings complications to the above-mentioned automatic attenuation correction techniques. For example, the nonlinear bubble behaviour generates higher harmonics, which are attenuated more than the fundamental frequency. Furthermore, bubble clouds can introduce significant nonlinear attenuation (Tang et al 2005). The lack of an accurate automatic attenuation compensation technique is one of the major hurdles for quantification of tissue perfusion using US and contrast agents.

Asanuma et al. (2002) proposed the use of a harmonic-to-fundamental ratio (HFR), derived from the echo data, to quantify tissue perfusion. The authors postulated that this new index was much less affected by attenuation and they validated this claim with experimental measurements. Although the results in their paper and those in the more recent study by Yoshifuku et al. (2007) seem promising, there is a lack of theoretical foundation for this technique and therefore the interpretation of the results is limited. A mathematical model has been proposed by Chen et al. (2004) to explain why HFR works; however, their model neglected a number of important variables including tissue scattering, bubble concentration, nonlinear bubble scattering, beam geometry and nonlinear attenuation due to bubbles. Consequently, the ability of this model for interpreting measured quantities remains limited. Furthermore, the proposed methods require analysis of the echo spectrum and separation of the fundamental from second harmonic components by curve fitting. This is time consuming, decreases the spatial resolution and is difficult to implement for real-time application. In another study (Simpson et al 1999) a formula closely related to this study has been proposed which can be approximated as HFR and does not require spectral analysis.

However, the formula proposed in that paper is applied with respect to detecting and characterising bubbles rather than attenuation correction.

In this paper, a mathematical description of the formation of US echoes in US contrast agent imaging is developed, from which new methods are proposed for fast image formation with automatic correction of attenuation.

THEORY AND METHODS

In this section, a model of US echo formation with attenuation is firstly described. The model contains a number of unknown parameters including, among others, the spatial distribution of bubble concentration and attenuation of US transmission due to both tissue and bubbles, and the scattering from tissue and bubbles. Most of these parameters are difficult to deduce directly, even when multiple echo measurements are available from sequences of transmitted pulses of various amplitudes and phases. New methods are then proposed in the second part of this section to use available multiple measurements to reduce the number of unknown parameters, especially those relating to attenuation, so that a better representation of bubble concentration can be extracted.

Echo formation

As shown in Fig. 1, when an US pulse of amplitude H_I (and frequency ω_0) travels through a region of tissue, the amplitude is changed to $\sigma_T A H_I$ due to: 1) forward attenuation A , which is a product of linear attenuation A_I and nonlinear attenuation A_n , $A = A_I(x) \cdot A_n(x)$; and 2) the beam profile $\sigma_T(x)$ due to transducer geometry and transmission beam-forming. It should be noted that the linear attenuation $A_I(x)$ is a function of spatial distribution of both linear scatterers and nonlinear bubbles between the transducer and x , while nonlinear

attenuation $A_n(x)$ is a function of spatial distribution of bubbles alone and is both pressure- and frequency-dependent (Tang and Eckersley 2005 and 2007). Attenuation $A(x)$ is defined as follows:

$$A(x) = A_l(x) \cdot A_n(x) = \exp\left(-\int_0^x \{a_l(x) + a_n(x)\} dx\right) \quad (1)$$

where $a_l(x)$ includes the linear attenuation coefficient due to tissue attenuation and linear part of bubble attenuation, while $a_n(x)$ is the nonlinear attenuation coefficient due to nonlinear bubble attenuation. $A_l(x)$ and $A_n(x)$ are the resulting linear and nonlinear attenuations, respectively. The scattering coefficient of the tissue at frequency ω_0 can be denoted by a function $b(x)$. The scattering from bubbles is nonlinear and can be denoted by a polynomial function of the incident pulse (Eckersley et al 2005). Although an arbitrary order polynomial can be used, for the purpose of illustration and considering the limited transducer bandwidth, a second order polynomial is used here. The scattering can then be denoted as:

$$Scat = bH_1' + c(x) \cdot (k_1 H_1' + k_2 H_1'^2) = b\sigma_T A_l A_n H_1 + c(x) \cdot (k_1 \sigma_T A_l A_n H_1 + k_2 \sigma_T^2 A_l^2 A_n^2 H_1^2) \quad (2)$$

where $c(x)$ is the concentration of bubbles and H_1' is the amplitude of the attenuated US pulse. k_1 and k_2 denote the first and second order coefficients of the polynomial and are assumed to be constant. While the first term in the bracket in eqn (1) is still of the fundamental frequency ω_0 , the second term corresponds to the second harmonic with frequency of $2\omega_0$. The reader should note that, for the sake of brevity in the above and subsequent equations, the depth dependence is no longer explicitly stated.

The scattered signals are attenuated when they travel back to the transducer. Since the amplitude of the scattered signals is very small compared with that of the transmission pulse, the bubbles will oscillate largely within the linear regime and therefore only linear attenuation A_I of the backscattered pulse is considered. The attenuation is frequency-dependent. At the fundamental frequency, the attenuation is A_I as before but, for the second harmonic, the attenuation is different and is denoted as A_2 . Furthermore, in a more realistic situation noise is present in the echoes. If we consider the additive electronic noise at the receive portion of the detection process, N which is amplified by system gain G , the echo of the pulse can finally be written as:

$$Echo(H_1) = bG\sigma_T\sigma_RA_1^2A_nH_1 + ck_1G\sigma_T\sigma_RA_1^2A_nH_1 + ck_2G\sigma_T^2\sigma_RA_1^2A_n^2H_1^2A_2 + GN \quad (3)$$

Here, G denotes the gain in scanner post processing, including any default TGC after the echoes have been received. σ_R denotes the receive sensitivity profile due to receive focusing. The noise, N , is assumed to be a Gaussian distribution noise of zero mean and variance V .

Attenuation correction

To compensate for the attenuation, multiple pulse-echo measurements are required in order to parameterise the model. Specifically, for tissue perfusion imaging where the target volume consists of tissue containing bubbles, a solution is to use tissue echoes to compensate the attenuation of bubble echoes, since the tissue and the bubbles are at the same location and are exposed to the same forward attenuation.

The bubble echoes can be readily separated from the total echoes by techniques such as PI, amplitude modulation (AM) or a combination of the two (Eckersley et al. 2005). In the

following, PI is used as an example, although the deduction can be readily extended to AM. From eqn (3),

$$E_b = Echo(H_1) + Echo(-H_1) = 2ck_2 G \sigma_T^2 \sigma_R A_1^2 A_n^2 H_1^2 A_2 + GN_1 \quad (4)$$

Here N_I is the summation of the noise from two received data sets; each has the same distribution: mean of zero and variance of V . Therefore N_I still has a zero mean but its variance is doubled to $2*V$. Equation (4) represents the PI image and, in this case, is actually the second harmonic of the echoes plus the noise. As can be seen from this equation, the nonlinear echo generated by PI is proportional to bubble concentration c , but is at the same time influenced by a number of quantities such as attenuation A_I and A_2 and the beam profiles. The aim of this study is to reduce these confounding factors and extract quantities that are proportional to bubble concentration.

The tissue signal is extracted from the reflected signal by using the opposite operation to that demonstrated in eqn (4), i.e., subtraction is used instead of addition to extract the tissue signal:

$$E_t = Echo(H_1) - Echo(-H_1) = 2bG \sigma_T \sigma_R A_1^2 A_n H_1 + 2ck_1 G \sigma_T \sigma_R A_1^2 A_n H_1 + GN_1 \quad (5)$$

It can be seen that, by doing this subtraction, the nonlinear term generated by the bubbles is suppressed and the result is effectively the echo at the fundamental frequency. Although the linear term of bubble scattering still exists, the bubble scattering is suppressed and linear scattering by tissue is doubled. Two significant advantages of this method are: 1) it makes use of exactly the same data as are required to extract the bubble echoes, so no additional acquisition is required; and 2) it only requires simple arithmetic combination and can be done in real time. Here, assuming that the noise can be treated as random and independent, the noise after the subtraction is still N_I , i.e. mean of zero and variance of $2*V$.

Similarly for AM, $Echo(H_1) - 2 * Echo(\frac{H_1}{2})$ can be used for extracting bubble echoes and $Echo(H_1) + 2 * Echo(\frac{H_1}{2})$ for extracting tissue echoes.

If for the moment we assume good SNR and ignoring the noise, dividing E_b by E_t gives:

$$\frac{E_b}{E_t} = \frac{Echo(H_1) + Echo(-H_1)}{Echo(H_1) - Echo(-H_1)} = \frac{2ck_2G\sigma_T^2\sigma_R A_1^2 A_n^2 H_1^2 A_2}{2bG\sigma_T\sigma_R A_1^2 A_n H_1 + 2ck_1G\sigma_T\sigma_R A_1^2 A_n H_1} = \frac{ck_2\sigma_T H_1 A_n A_2}{b + ck_1} \quad (6)$$

It can be seen from eqn (6) that, through this operation, a number of confounding parameters in the numerator are cancelled out by those in the denominator and a much simplified expression is obtained.

Depending on the relative significance of the two terms in the denominator, eqn (6) can be further simplified. If the target is a region of tissue containing bubbles in microvessels where a low bubble concentration can be assumed, the second term in eqn (5) and the denominator term $c.k_1$ in eqn (6) can be ignored. Equation (6) becomes:

$$\frac{E_b}{E_t} = c \cdot \frac{k_2\sigma_T H_1 A_n A_2}{b} \quad (7)$$

which presents a quantity that is proportional to bubble concentration c , but which is still affected by tissue scattering coefficient b , transmission beam profile σ_T , nonlinear attenuation A_n and backward attenuation for the second harmonic A_2 . Comparing σ_T to A_2 and A_n , it should be noted that they vary in the opposite directions; σ_T increases with depth until the focus while A_2 and A_n decrease with depth. Therefore they oppose one another to some degree in regions before the focus. If there is no significant bubble cloud between transducer

and the target, the nonlinear attenuation will be insignificant and the term A_n can simply be treated as unity. It should be noted that in this analysis the transmission profile σ_T is treated independently from the receive profile σ_R . Since it can be assumed that, in a typical clinical scanner, the receive profile σ_R is dominated by the dynamic focusing (for dynamic focusing please refer to Manes et al. 1988), effects of the different fundamental and second harmonic frequencies on σ_R have been ignored. The problem merits deeper consideration but this is beyond the scope of this paper. The tissue scattering coefficient b cannot be treated as a constant if the region contains different types of tissues. Furthermore, it should be noted that this proposed model does not take speckle formation into account. Formation of speckle introduces variation in the tissue echoes in the denominator and this also affects the estimation of bubble concentration.

In order to reduce the variation of the denominator E_t due to tissue scattering, some prior information about attenuation is used to modify the denominator. As can be seen in eqn (1), the attenuations to be corrected are effectively integrals of the attenuation coefficients along the transmission path. Therefore, attenuation can be deemed to be a smooth signal with gradual spatial variation. The scattering, on the other hand, shows variations over relatively small spatial scales.

In order to reduce this scattering-related spatial variation in E_t , a 2D spatial median filter was applied to E_t . The advantage of a median filter is that, rather than averaging the signal, it removes any large magnitude spatial variation in the signal with no affect on the rest of the signal. The size of the median filter kernel determines the spatial size of the variations that can be removed.

Choosing the size of the median filter to be much smaller than the variation in σ_T , A and G , then eqn (6) can be rewritten as:

$$\begin{aligned} \frac{E_b}{\text{MedianFilt}(E_t)} &= \frac{2ck_2G\sigma_T^2\sigma_R A_1^2 A_n^2 H_1^2 A_2}{\text{MedianFilt}(2bG\sigma_T\sigma_R A_1^2 A_n H_1 + 2ck_1G\sigma_T\sigma_R A_1^2 A_n H_1)} \\ &= \frac{ck_2\sigma_T H_1 A_n A_2}{\text{MedianFilt}(b + ck_1)} \end{aligned} \quad (8)$$

Since ck_1 in the denominator may be neglected, median filtering E_t removes the local variations in b and the remaining quantity represents a better approximation to the bubble concentration c .

Alternatively, if the target is dominated by a bubble cloud, e.g., in heart chambers or large vessels, the term b in eqn (8) can be neglected and the equation becomes:

$$\frac{E_b}{\text{MedianFilt}(E_t)} = \frac{ck_2\sigma_T H_1 A_n A_2}{\text{MedianFilt}(c) \cdot k_1} \quad (9)$$

Since the filtered concentration $\text{MedianFilt}(c(x))$ in the denominator acts to normalise $c(x)$ in the numerator, the ratio is now a quantity that is not related to local bubble concentration but which is still affected by beam profile σ_T and backward attenuation for the second harmonic A_2 and nonlinear attenuation A_n . Again, if these factors cancel out, the ratio becomes a constant, provided that H_1 , k_2 and k_1 remain the same. In this case, this quantity cannot be used for quantification of bubble concentration. However, quantifications in heart chambers or large vessels are of less interest clinically and definition of blood-chamber or blood-vessel wall interfaces are often more important. Through application of eqn (9), a more homogeneous image can be obtained in regions full of bubbles and this may facilitate improved boundary definition.

In cases of poor SNR, e.g. when signal attenuation is significant or the target consists of neither bubbles nor tissue, the denominator will be affected by noise and the ratio becomes less meaningful or even unstable if the denominator goes to zero. To avoid this instability a quantity was added to the denominator as a regulariser. The value of the regulariser can be optimised if prior knowledge of the system signal to noise ratio is available. So, finally, attenuation-corrected contrast images can be obtained by the following formula:

$$\begin{aligned} \frac{E_b}{\text{MedianFilt}(E_t) + \text{regulariser}} &= \frac{\text{Echo}(H_1) + \text{Echo}(-H_1)}{\text{MedianFilt}(\text{Echo}(H_1) - \text{Echo}(-H_1)) + \text{regulariser}} \\ &= \frac{A + GN_1}{B + GN_2 + \text{regulariser}} \end{aligned} \quad (10)$$

where A represents the noise-free even harmonics and B represents the smoothed noise-free odd harmonics. The noise in the denominator is different from that in the numerator because of the filtering process in the denominator. After the smoothing N_2 should have a much smaller variance than N_1 .

In order to optimise the regulariser, the following cost function was defined:

$$\text{Err} = \left(\frac{A + GN_1}{B + GN_2 + \text{regulariser}} - \frac{A}{B} \right)^2$$

Differentiating this with respect to the regulariser and equating to zero yields:

$$\text{regulariser} = \frac{\frac{B}{GN_2} - \frac{A}{GN_1}}{\frac{A}{GN_1 GN_2}}$$

It should be noted that the two terms in the numerator represent the SNR of the E_b and filtered E_t respectively. Therefore, if prior information about the frequency spectra of the signals A and B and the noise GN_1 is known (GN_2 can be calculated from GN_1 given the filter properties), then the regulariser can be set optimally in the sense that it minimises the squared

errors between the regularised noisy ratio and the ideal noise-free ratio. Since most quantities in the equation are spatially variant, so is this optimised regulariser. It should also be noted that the noise level and hence the optimised regulariser would be different if a different bubble imaging technique such as AM is used.

By observing that in the above ratio in eqn(8) the numerator is a second order term and the denominator is a first order term, an alternative ratio can be obtained by using the squared first order term as denominator, as in Chen (2004). If the tissue echo is dominant at the target and the bubble term in the denominator can be ignored, then:

$$\frac{E_b}{\text{MedianFilt}(E_t^2)} = \frac{2ck_2G\sigma_T^2\sigma_R A_1^2 A_n^2 H_1^2 A_2}{\text{MedianFilt}(4b^2G^2\sigma_T^2\sigma_R^2 A_1^4 A_n^2 H_1^2)} \approx \frac{ck_2 A_2}{\text{MedianFilt}(2b^2G\sigma_R A_1^2)} \quad (11)$$

By assuming that the attenuation is mainly caused by tissue and that the tissue attenuation is doubled when frequency is doubled, A_2 is actually equal to A_1 squared and the above formula can be further reduced to:

$$\frac{E_b}{\text{MedianFilt}(E_t^2)} \approx \frac{ck_2}{\text{MedianFilt}(2b^2G\sigma_R)} \quad (12)$$

It can be seen that the quantity is still affected by the scanner TGC G and receive sensitivity profile σ_R . Again, a regulariser should be added to the denominator and it can be optimised in a similar way.

Phantoms

In order to validate the attenuation correction method developed in the previous section, two phantoms were built, consisting of tissue-mimicking materials (TMM) and SonoVue™ microbubbles. Figure 2 illustrates the phantoms. The first phantom, as shown in Fig. 2(a),

consists of blocks of TMM which are submerged in a suspension of microbubbles. In this phantom, the TMM is made of gelatine and does not allow bubbles to perfuse into it. The suspension was gently stirred so that the bubbles were well mixed. This type of phantom was used to test whether the proposed method could better compensate for the attenuation for both bubble suspension and TMM and improve definition of boundaries. For the second phantom, a piece of sponge was cut into small bits (typical dimensions of 2 mm in each dimension) and put into a beaker of water. The sponge bits and water were then degassed before adding SonoVueTM bubbles. The suspension was again gently stirred so that the bubbles were well mixed. This phantom was designed to create a model of uniformly perfused tissue. Finally, one thin slice of cardboard was inserted into this phantom to create some artificial attenuation in the image. The concentration of the microbubble suspension in each of the phantoms was 90 $\mu\text{L/L}$.

Scanners

Two programmable US scanners were used to scan the phantoms and to generate raw RF data. One was an AN2300 digital US engine (Analogic Corporation, Peabody, MA, USA) and the other was an UltrasonixRP system (Ultrasonix, Richmond, BC, Canada). Both of the scanners were set to scan the phantoms with PI. It should be noted that, due to restriction of the scanners, there was a delay between the acquisition of the two echoes from the first pulse and the second pulse with reversed phase. The delay was about 2 s for the AN2300 and about 20 s for the UltrasonixRP. In order to minimise any movement during the delay, the phantoms were left to settle down for a few minutes before the acquisition began. The scan parameters for the two phantoms were slightly different and are shown in the captions of the resulting images in the next section. The central frequency of the excitation pulses for the two scanners ranged between 2~3 MHz and care was taken to use low pressure pulses to minimise bubble disruption and stirring due to radiation force. The lateral focus of the probe

was set at 12.5cm and 15cm away from the transducer surface for the UltrasonixRP and AN2300 respectively. The elevation focus of the probe was 6cm and 7cm for the UltrasonixRP and AN2300 respectively. Each phantom was scanned using one of the two scanners and raw data were recorded.

Postprocessing and data presentation

Four types of images were constructed: 1) a traditional B-mode image generated with echoes of one of the PI pulse pair; 2) a PI image from both echoes of the pulse pair; 3) an attenuation-corrected image via eqn (10); and 4) an attenuation-corrected image generated using eqn (11). Both the B-mode and PI images used the default TGC of the respective scanner for attenuation correction. The median filter used in the proposed methods had an axial size of 8 mm and a lateral size between 0.6 mm and 6 mm. The variation of the filter size in lateral direction is because the probe is a fan-beam phased array probe whose line density varies with depth.

Besides displaying the four types of images, image intensity profile across a vertical line in each image is also displayed for better comparison. In order to obtain some global quantification of the image quality, image intensity histograms are also plotted. For the second phantom which is approximately an uniform phantom, the following homogeneity index (HI) based on the histogram data is calculated:

$$HI = \frac{\max(histogram)}{FWHM}$$

Here the numerator is the peak in the histogram, while the denominator is the full width at half maximum (FWHM) of the corresponding histogram peak. For a nearly uniform image, the histogram should feature a narrow single spike and *HI* should be a large value.

RESULTS

The sets of images obtained with phantoms 1 and 2 are shown in Figs. 3 and 6, respectively. Figures 4 and 7 show the image intensities corresponding to selected lines in these images. Figures 5 and 8 show the histograms for the PI image and the compensated PI image.

Phantom 1

The results from phantom 1 show that the default TGC overcompensated the image distal to the probe and the intensity gradually increases towards the bottom of the image in both Figs. 3 (a) and (b). This overcompensation can also be seen in the intensity profiles in Figs. 4 (a) and (b).

For the corrected image in Fig. 3(c) using eqn (10), the overcompensation has been largely removed, which can also be seen in the image intensity profile in Fig. 4(c). After compensation regions of tissue or bubbles appear as more homogeneous regions. At the same time, the bubble-to- tissue contrast has been enhanced. Figure 3(d) and the red curve in Fig. 4(c) show the results using eqn (11), which seem to be overcompensated near to the probe. This is probably because that the default TGC is much smaller in the region near to the probe and therefore, through use of eqn (11), the image intensity in this region is relatively more amplified.

It can also be seen in Fig. 4 (c) that the three peaks corresponding to bubble suspension in phantom 1 are not equal. This seems to indicate that the attenuation compensation is not working as well as expected. However, from careful inspection of the two valleys in Figs. 4 (b) and (c), all corresponding to tissue-mimicking jelly, it can be seen that image intensities are at a much more constant level after correction using eqn (10),

suggesting that the compensation is actually working well. The variation of intensity profile for the bubble regions is likely due to some differences in bubble concentration among the three bubble regions. Given that the bubbles were introduced into the bottom of the phantom before stirring, the bottom chamber may have more bubbles than the top chamber. Furthermore, there could be nonlinear imaging errors, as discussed in Tang et al. (2006). Such nonlinear errors are not due to attenuation but are due to nonlinear propagation contaminating nonlinear bubble scattering.

Since there are two types of materials in this phantom, bubble and TMM, ideally there should be two narrow peaks in the histogram if attenuation is correctly compensated. It can be seen from Fig. 5(a) that there are more than two peaks for the PI image with the default TGC. The first peak near zero intensity corresponds to the black background of the image and should be ignored. There are still three significant peaks at approximately intensities of 60, 100 and 160. While bubbles correspond to the third peak of high intensity, the TMM corresponds to the first two peaks. The same material (TMM) generating two histogram peaks is due to the inappropriate attenuation correction in the PI image. For the compensated PI image using the proposed method, the histogram in Fig5(b) shows a single peak as expected,

Phantom 2

The results for phantom 2 show that the cardboard in the upper middle part of the phantom created attenuation shadows in the lower part of the B-mode image (Fig. 6(a)) and the PI image (Fig. 6(b)). This attenuation can also be seen in the intensity profile in Figs. 7(a) and (b), and is seen as a gradual decay in the signals with depth between position 100 and 200 in the x axis.

For the corrected image in Fig. 6(c) using eqn (10), the attenuation has been largely corrected and this can also be seen in the image intensity profile in Fig. 7(c). The images after correction better present the whole region, with more homogeneous intensity. Figure 6(d) and Fig. 7(d) show the results using eqn (11), which show good correction in the middle part of the image but some artefacts on both sides. The artefacts are likely due to the inhomogeneous distribution of the sponge bits in the phantom on both sides of the phantom. The inhomogeneity of the phantom can be seen in the B-mode image in Fig. 6(a). The results suggest that the ratio approach by eqn (11) may be more affected by inhomogeneous distribution of scatterers than that by eqn (10). Moreover, in the middle of the phantom where the distribution looks more homogeneous, eqn (11) has produced better- corrected results, as shown in Fig. 6(d) and Fig. 7(d).

Since this phantom can be approximated as uniformly distributed, ideally there should be a single narrow peak in the histogram if attenuation is correctly compensated. It can be seen from Fig8 (a) and (b) that there is indeed a single peak between intensity 50 and 150 for both the PI image with scanner default attenuation compensation and that with the proposed compensation. However the peak with the new method (Fig. 8(b)) is better defined. This can also be seen from the index HI defined previously. The HI for the PI image and the compensated PI image is 39 and 130, respectively; i.e. the image by the proposed method has an HI which is three times better than the PI image with scanner default attenuation compensation.

DISCUSSION

In this study, we have initially demonstrated through theoretical analysis and preliminary experimental results the potential of the proposed methods for improved quantification of tissue perfusion using ultrasound and microbubble contrast agents. Further studies based on

more realistic phantoms and human subjects are required fully to evaluate the methods and demonstrate their value in clinical applications.

It can be seen that although neither of the ratio formula can provide a total correction of the image, most attenuation and other confounding factors such as system gain and beam profiles as a result of the lateral transmission focusing, elevation focusing and dynamic receive focusing, can be automatically removed from the echoes so that a truer representation of bubble concentration can be obtained. Furthermore, the ratio-based correction do not require any additional data other than those already available in a typical contrast-specific imaging technique(e.g. PI or AM) and it can be implemented in real time. An additional advantage over manual adjustment of the TGC is that it is operator-independent and therefore more objective and time efficient.

It should be noted that the ratio formula proposed should be differentiated from the Contrast to Tissue Ratio (CTR) commonly used. For example in Pulse Inversion, CTR refers to the ratio of bubble signal to tissue signal at only even harmonics, while the ratio formula proposed here, in case of PI, is the ratio of bubble signal at even harmonics to tissue signal at fundamental and odd harmonics.

In the proposed ratios in eqns (10) and (11), the filtered denominator can only be approximated as a constant if the imaging plane consists of homogeneous tissue, which may often be satisfied when scanning, e.g., part of a liver. Scanning a heart is more complicated, since there are chambers and the proposed attenuation correction for myocardium and chambers would be different. Nevertheless, this should not be a problem, since the myocardium is of primary interest and there is little need to quantify bubble concentration in the chamber. Furthermore, by processing data from the cardiac chamber using the proposed

formula, a more homogeneous image of the chamber can be created and thus the myocardium can possibly be better delineated. However, a further complication for scanning a heart is the fibre orientation of myocardium. Studies show variations of echogenicity due to fibre orientation of myocardium (Holland et al 1998). Although the proposed filtering reduces this problem to a certain extent, the interpretation of compensated images should take this into account and this is a subject for future work. Furthermore, if the imaging plane contains multiple types of tissues of significant sizes, b will vary accordingly and this also complicates the quantification process, although variation of b in small spatial scale can be removed by the filter. The results show that the proposed method by eqn (12) is more affected by this variation in tissue type than that by eqn (10).

In this study, the time delay (2 s for the Analogic and 20 s for the Ultrasonix systems) during the acquisition of echoes from both positive and negative pulses in PI may introduce errors to the corrected images because the residual after linear cancellation may still contain linear but uncorrelated signals. Although the phantoms had been left to settle down for a while before the acquisition to minimise these errors, this might still influence the final images and further studies with fast PI acquisition are needed to illustrate the effectiveness of the proposed methods.

This study does not take into account any nonlinear propagation of ultrasound (Humphrey 2007, Duck 2002). This is potentially justified under the conditions that low acoustic power is used. However, our previous study (Tang et al. 2007) suggested that even at low acoustic pressure, nonlinear propagation may still occur and affect imaging results if there is a high concentration of bubbles on the acoustic path. This is a problem common to all imaging techniques such as PI and AM where bubble detection is based on nonlinear bubble behaviour.

It should be noted that, interestingly, a previous paper by Simpson et al (1999) has already described a very similar formula to that in this paper, i.e., dividing the sum of echoes by the difference of echoes in PI. However, the fundamental difference between that paper and this one is that this paper is proposing a framework to use the signals from tissue to correct for signals from bubbles contained in the tissue and the framework works with any nonlinear imaging mode, such as AM or PIAM. The Simpson paper, on the other hand, was looking at the different problem of detecting and characterising bubbles and their proposed formulae specifically apply to PI.

CONCLUSIONS

Automatic correction of attenuation and other confounding factors is vital to reliable and objective quantification of tissue perfusion using US and microbubble contrast agents. In this paper, a model for the US attenuation process during echo formation in US contrast agent imaging has been developed. The model contains a number of unknown parameters, most of which are generally difficult to deduce directly, even when multiple echo measurements are available. Based on this model, new methods were developed to manipulate the multiple measurements so that some unknown model parameters, especially those related to attenuation, can be largely removed and quantities that are truer representation of bubble concentration can be extracted.

Specifically, in our methods, linear echoes are extracted, median filtered and used to compensate for attenuation in bubble echoes from the same location. The methods are operator-independent, do not require any additional measurements and can be implemented in real time. Initial experiments on laboratory phantoms consisting of bubbles and tissue-mimicking materials have demonstrated the potential of the method for improved

quantification of tissue perfusion. Further studies are planned to fully demonstrate the value of the method in clinical conditions. This development is an important step towards real-time quantitative contrast US imaging.

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Fig. 1. Diagram of US echo formation.

Fig. 2. Illustration of the two phantoms.

Fig. 3. Imaging results for phantom 1.

transmit central frequency: 3 MHz;	peak negative pressure: ~286 kPa;
transmit focus: 15 cm;	phantom height: 15cm

Fig. 4. Image intensity profile on a single vertical line in the images shown in Fig. 3. For each graph x-axis shows indices of pixels along the vertical line and y-axis shows image intensity ranging from 0 to 255.

For (d), the blue line corresponds to Fig. 3(d) and the red line corresponds to Fig. 3(c).

Fig. 5. Histograms for phantom 1. (a) Histogram for the PI image in Fig. 3(b); (b) Histogram for the PI compensated image in Fig. 3(c).

Fig. 6. Imaging results for phantom 2.

transmit central frequency: 2 MHz;	peak negative pressure: < 552 kPa;
transmit focus: 12.5 cm;	Phantom height: 15cm

Fig. 7. Image intensity profile on a single vertical line in the images shown in Fig. 5. For each graph x-axis shows indices of pixels along the vertical line and y-axis shows image intensity ranging from 0 to 255.

For (d), the blue line corresponds to Fig. 5(d) and the red line corresponds to Fig. 5(c).

Fig. 8. Histograms for phantom 2. (a) Histogram for the PI image in Fig. 6(b), HI =39; (b) Histogram for the PI compensated image in Fig. 6(c), HI =130.

FIGURES

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8