QUANTITATIVE IMAGING OF ULTRASOUND CONTRAST AGENTS: CURRENT CHALLENGES

M-X Tang Dep. Bioengineering, Imperial College London, London, UK
R J Eckersley Imaging Sciences Dept., Imperial College London, London, UK
E Stride Dept. Mechanical Engineering, University College London, London, UK

1 INTRODUCTION

The development of microbubble contrast agents in medical ultrasound(US) has provided new ways for imaging and quantification of tissue perfusion. Physiologically relevant parameters such as relative vascular volume, flow velocity and relative perfusion rate can be deduced based on the contrast enhanced image sequences. This has been studied in a number of clinical conditions such as diagnosis and treatment monitoring of liver tumour [1][2][3] and assessment of myocardial function [4][5][6].

As has been described in [7][8], the behaviour of the microbubbles can be highly nonlinear. While such nonlinear behaviour has created opportunities for the bubbles to be distinguished from background tissue to provide blood flow-specific information, it has also created significant challenges in imaging and image based quantitative assessment of tissue perfusion. In this paper we will describe such challenges in detail.

2 QUANTITATIVE IMAGE FORMATION

In this section the ultrasound image formation process is explained and the physical parameters that can be quantified, together with other confounding parameters, are described.

The echoes acquired by a typical US scanner contain both attenuation and scattering information from the imaged object. Since in general the imaging of tissue scattering properties is of primary clinical interest, the image formation processing in the scanner aims to remove the attenuation and other confounding factors from the final image.

The scattering coefficient is defined as the scattering cross-section per unit volume. The scattering cross-section for a certain spatial location can be calculated as the power of the scattered signals divided by the incident acoustic intensity for that location. If the volume of the resolution cell containing the scatterers is known, then the scattering coefficient can be readily obtained given the scattering cross-section.

In reality, it is difficult to accurately obtain such scattering coefficients as this requires estimation of the incident acoustic intensity within the imaging area and of the scattered signal power prior to propagation as it returns to the transdcuer and is attenuated. This estimation can only be performed if the variation of the acoustic signal due to attenuation, beam diffraction and transmit/receive focusing, can be accurately estimated. Various techniques, including manual and automatic Time Gain Compensation(TGC), have been developed [9] to correct for attenuation and recover the scattering coefficients of the imaged object, although none of them can remove the confounding factors completely. As a result the final images represent not only the desired scattering coefficients but also contain variations due to the confounding factors described above. Furthermore, the ultrasound images displayed in a typical scanner are log compressed for improved dynamic range in the display and this has to be taken into account in any intensity-based quantification method/algorithm.

The influence of attenuation and other factors during image formation to the final images means that quantification of tissue scattering properties based on image intensity would be affected. In fact some imaging artefacts due to attenuation, such as acoustic shadowing and enhancement in

traditional B-mode images, have been used to help identify soft or hard objects such as cysts or stones. In clinical practice the intensity of ultrasound images is not generally used in a quantitative way and quantification in ultrasound generally refers to geometry measurements such as the size of an embedded structure.

With the development of microbubble contrast agents, there has been an increasing need to quantify microbubble concentration, and hence tissue perfusion, based on image intensity. For microbubble contrast agent imaging, instead of forming traditional B-mode images which contain both tissue and microbubbles within the tissue, it is desirable to form microbubble-only images in order to better visualise and quantify tissue perfusion. Nonlinear imaging techniques such as pulse inversion(PI) have been developed to remove tissue echoes and produce microbubble-only images reflecting their acoustic scattering coefficient of various harmonic frequencies [10]. Again correction for attenuation and other confounding factors has to be conducted to generate images that reflect scattering coefficients and this is even more challenging, as explained in the following section.

It should be noted that there exist another type of bubble-only imaging technique called transient imaging [11], whereby a high power ultrasound pulse is used to destroy the bubbles and images are based on the decorrelation of echoes before and after the high power pulse. However this type of technique cannot produce continuous images, as time is needed for the bubbles to refill the imaged region before next image can be taken. Furthermore, high acoustic power will create significant nonlinear propagation which would make quantification more difficult, as is discussed below. In the rest of the paper we will only concentrate on low power continuous imaging where bubble destruction is minimal/limited.

3 MICROBUBBLE SCATTERING AND QUANTIFICATION

In order to quantify the scatterer concentration based on ultrasound images, it is necessary to establish a relationship between the acoustic scattering coefficient for an image resolution cell and:

a) the concentration of the scatterers within the resolution cell;
b) the acoustic parameters, such as pressure and frequency, incident upon the resolution cell.

The reason for establishing a) is obvious and ideally the relationship should be linear so that quantification of scatterer concentration can be obtained directly from quantification of the scattering coefficient. For b), it is necessary because even though the transmitter parameters of the scanner can be fixed, the incident acoustic parameters vary spatially within the imaging area due to the confounding factors such as attenuation, wave diffraction and transmission focusing. For a broadband system, the incident acoustic frequency also varies spatially and this is primarily due to frequency-dependent attenuation of the medium. To carry out quantification, ideally the scattering coefficient does not change with acoustic parameters such as pressure and frequency, otherwise the same scattering coefficient(hence the image intensity) does not necessarily mean the same scatterer concentration and further calibration will be needed.

For quantification of microbubble concentration, the relationship in both a) and b) need to be established. This does not seem to be an easy task given the highly nonlinear behaviour of microbubbles. A number of studies have been conducted in this area and the following section describes the findings from both the literature and from our studies.

3.1 Effect of concentration

There have been many studies which have demonstrated a simple linear relationship between the concentration and the scattering coefficient for microbubble suspensions. One such study is that of de Jong [12], who showed that the scattered power of Albunex® microbubbles excited with 5MHz broadband pulse has a linear relationship with the concentration of the microbubbles within a range of 6.9×10^3 ~ 2.25×10^6 bubbles/ml. Given a fixed incident acoustic intensity and scattering volume, the scattered power is proportional to scattering coefficient. A more comprehensive study by Marsh

et al. [13] showed that the linear relationship holds for Albunex® concentrations of up to $2.1x10^7$ bubble/ml, and over a wide range of frequencies from 1 to 16MHz.

If the concentration continues to increase, there will be a point where multiple scattering will start to occur. This will not only affect the simple linear relationship between concentration and scattering, but could affect neighbouring regions as the time delay due to multiple scattering is shown as spatial displacement in ultrasound images. This will certainly affect quantification. Stride and Saffari [14] have studied the multiple scattering of microbubbles and has found that multiple scattering could be discernible at moderate concentrations (10^6 microbubbles/ ml) such as may be present in vivo and this is dependent on the incident acoustic pressure and whether or not the bubbles are at resonance. For Marsh's study [13] a relatively low peak-negative pressure of 110kPa was used.

In summary, if a relatively low acoustic pressure is used and if the bubble concentration is low enough ($<10^6$ /ml), assuming a linear relationship between scattering coefficient and bubble concentration is reasonable.

3.2 Pressure dependent scattering

As is described in [7][8], microbubble behaviour is highly nonlinear with regard to the incident acoustic pressure. It has been well established that the microbubbles undergoes three regimes of behaviour as the acoustic pressure increases [15].

A number of studies have been performed to establish the relationship between microbubble scattering and acoustic pressure. Frinking et al. [16] have demonstrated experimental measurements showing the scattering coefficient of Quantison® to increase abruptly with incident acoustic pressure when the pressure goes beyond 200kPa. This is probably due to destruction of the encapsulating shell surrounding each bubble and release of the gas inside. Sboros et al [17] have shown similar experimental results where the scattering cross-section of two types of contrast agents, Quantison® and Definity®, increase with peak-negative pressure proportionally for a pressure range of 600kpa ~ 1.5MPa. Simulation results with certain bubble dynamics models, such as Herring, Gilmore and RPNNP models, have also demonstrated the dependence of scattering upon incident acoustic pressure [17]. Measurements at relatively low acoustic pressure were done in Tang[18] for acoustic pressure ranging from 50kPa to 500kPa on Sonovue® and the results show little pressure dependence of scattering. However Emmer et al has found through fast speed optical recording [19] using pressures between 20kPa and 250kPa that there is a pressure threshold above which bubbles start to oscillate and this threshold is size dependent, with smaller bubbles having higher threshold. This actually indicates that pressure-dependent scattering should happen at low acoustic pressure. A later paper of Emmer [20] resolved the discrepancies by showing that the nonlinear scattering is only measurable if the larger bubbles, which have nearly no threshold behaviour, are removed. If large bubbles are present, which is the case for Tang's study, scattering would be dominated by the large bubbles at low acoustic pressure and pressure-dependence is less detectable.

For detection purposes it is more useful to know the dependence of harmonic generation on incident acoustic pressure. As before, a nonlinear relationship is found between the scattering and incident acoustic pressure. Morgan [21] demonstrated that scattered power at 2^{nd} harmonics increases nonlinearly with transmitted acoustic intensity for Albunex®, MP1950 and Optison®, It was also found that scattering increases more sharply for Albunex® than for Optison® for transmit pressures of over 200kPa and transmit frequencies of 2.4 and 5 MHz. Shi et al [22] have investigated sub-harmonics and it was shown that for Levovist, the sub harmonic generation is highly nonlinear and undergoes 3 phases as the incident pressure increase from 0.1 to 1.3MPa: its amplitude undergoes a rapid growth in the intermediate acoustic pressure range around 0.3~0.6MPa with much slower increases at both lower and higher acoustic pressures. In another paper Shi [23] also demonstrated non-linear relationship for Optison® and showed that the

subharmonic and ultrasharmonic components updergo rapid growths in the intermediate acoustic pressure range and much slower increases at both lower and higher acoustic pressures.

In summary the scattering of microbubbles is generally demonstrated to be nonlinear with acoustic pressure. This has implications in clinical imaging. Regions of the same bubble concentration may show different brightness in the image if the incident pressures differ due to attenuation and/or diffraction, even if the attenuation and the diffraction can be perfected compensated.

3.3 Frequency dependent scattering

The dependence of the scattering coefficient upon the incident frequency for a population of bubbles is dependent on the size distribution of the population and the shell properties. Both De Jong 1993[12] and Marsh[13] have shown that scattering by Albunex® increases with frequency below a certain frequency and then is virtually constant for higher frequencies. There is a slight difference in the turning frequency reported by de Jong and Marsh1998 which is probably due to the fact that Marsh made the measurements at body temperature while de Jong used room temperature. Frinking [16] has shown a similar trend for Quantison® where there is a monotonic increase of scattering coefficient with frequency followed by a plateau. For a recent study on Sonovue® by Tang et al[18], it is demonstrated that the scattering coefficient peaked at 1.5MHz and then decreased with frequency.

Briefly, the dependence of the bubble scattering coefficient upon the incident frequency could be significant, depending on the frequency range and the type of bubbles used. This has clinical implications and microbubble concentration may be misrepresented in images. E.g. regions of the same bubble concentration may have different measured scattering coefficient because the incident frequencies are different due to frequency dependent attenuation.

3.4 Time dependent scattering

As described in [7], the properties of microbubbles change over time due to e.g. diffusion of gas. The size of bubbles can also change due to ultrasound excitation. Consequently the scattering of microbubble clouds changes with time. The change to microbubbles over time would mean that, depending on the time scale of the change, it may be problematic to compare images acquired at different times.

4 MICROBUBBLE ATTENUATION AND QUANTIFICATION

In order to accurately quantify the concentration of microbubbles, attenuation has to be estimated and corrected for. As described previously, various techniques have been developed for B-mode imaging and some degree of success has been achieved. However, the presence of microbubbles and the microbubble-specific imaging posed new challenges.

4.1 Pressure-dependent Attenuation of the total acoustic power

In terms of attenuation of the total acoustic power, tissue can be considered to have a constant attenuation coefficient at low acoustic pressure when no significant nonlinear propagation in tissue occurs. For microbubbles however, the attenuation coefficient, measured even at very low acoustic pressure, exhibit a dependence on the initial acoustic pressure. Studies in Chen 2002[24] and Tang 2005[25] have demonstrated such significant dependence of attenuation on pressure, even when the pressure is as low as 50kPa. Figure1 is an example of such pressure dependence The mechanism is not clear but possible causes include nonlinear damping of the bubbles and the threshold behaviour of bubbles at low pressures.

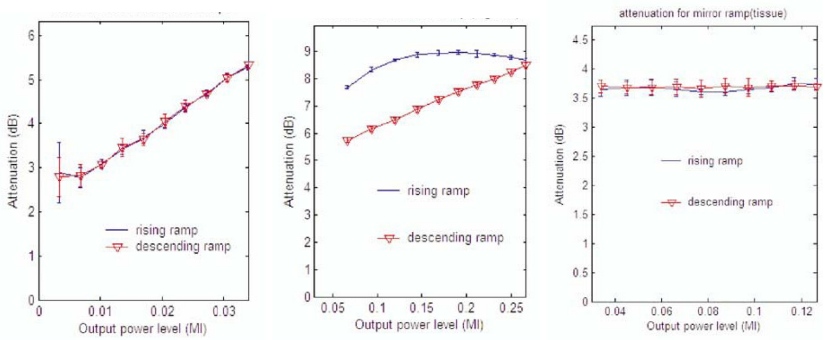

Figure1: pressure dependent attenuation for a Sonovue® microbubble suspension. The two curves in each graph represent consecutive attenuation measurements with a rising power ramped excitation followed by a descending one. The overlap of the two curves indicates that bubble destruction was minimal; In low power case(left), poor correlation between the two curves indicates bubble destruction(middle). The graph on the right hand side is the attenuation for human tissue without microbubbles, which is pressure independent.

4.2 Nonlinear propagation

The pressure-dependent attenuation of microbubbles in terms of the total acoustic power is only a part of a more general phenomenon: nonlinear propagation. In nonlinear propagation, acoustic power is transferred from fundamental frequency to harmonics. It has been long established that nonlinear propagation occurs in bubble clouds [26][27] in the ocean. An example of such nonlinear propagation is show in Fig2 where the nonlinearly propagated pulse has significant 2nd harmonic. In their study, Stride and Saffari [14] have implemented a numerical model of nonlinear propagation through a coated microbubble cloud.

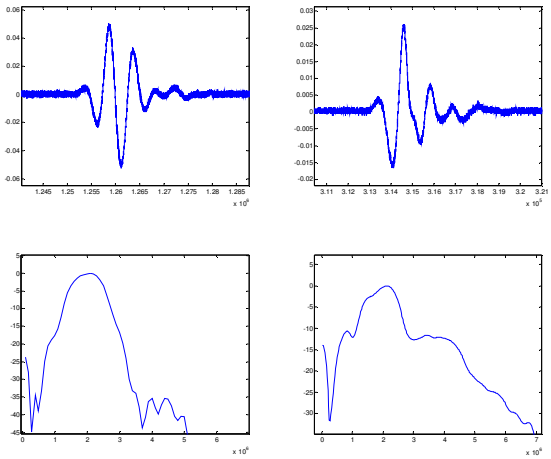

Figure2: Pulses before and after nonlinear propagation:
Top row: an initial broad band pulse(left) and the pulse after transmitting through a 6cm Sonovue® microbubble suspension with concentration of 230ul/1L (right)
Bottom row: the frequency spectra corresponding to the pulses in the top row.

A more recent study by Tang and Eckersley [28] has investigated the implications of nonlinear propagation through a microbubble cloud for clinical imaging. It has been demonstrated that two kinds of imaging artefacts exist due to nonlinear propagation. Firstly tissue will be misclassified as bubbles and secondly bubble concentration will be misrepresented. It should be noted that if the

acoustic pressure increases to a certain level, nonlinear propagation will occur even at the absence of microbubble cloud([26][29] and the same kind of imaging artefacts will be created. Thus a method for correcting such nonlinear propagation is needed.

4.3 Frequency dependent attenuation

The attenuation of microbubbles is frequency dependent too. It has been widely demonstrated that there will be a minimum value for the transmitted power through microbubble clouds, i.e. a maximum in attenuation, when measured over a range of frequencies. An example of such studies is that of de Jong 1993[12] for Albunex® microbubbles. In a study by Shi [23] it was found that the peak of the attenuation in the spectrum changes over a time of 16 minutes. Chen 2002[24] measured attenuation at different frequency for Definity® and Optison® and it was concluded that broadband technique to measure attenuation spectrum might not be appropriate due to the pressure dependent attenuation. Tang 2007[18] measured frequency dependent attenuation for Sonovue® and a peak was found around 1.75MHz.

4.4 Time dependent attenuation

Similarly, the scattering of microbubble clouds changes with time. Figure 3 shows an example of an attenuation measurement for a Sonovue® suspension measured over 30 minutes in a beaker with a stirrer. This change in microbubble response with time indicates the need for a dynamic attenuation compensation process; otherwise images acquired at different times cannot be fairly compared.

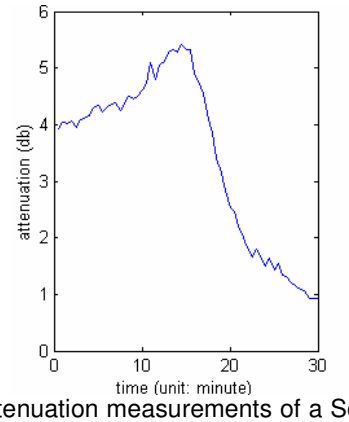

Figure3: attenuation measurements of a Sonovue® suspension measured over 30 minutes in a beaker with a stirrer

In summary, nonlinear behaviour of microbubbles, including the dependence of the microbubble acoustic behaviour on acoustic pressure, frequency, time and bubble concentration, present significant challenges in terms of performing quantitative measurements. Various imaging artefacts may occur as a result of these phenomena and the key to reliable quantitative imaging would need to rely on better modelling of the attenuation and scattering properties of microbubbles and a model-based calibration method for the measured scattered signals in order to extract quantitative information. In a recent work we have developed a model based attenuation correction technique for microbubble contrast agent imaging[30]. In the technique the scattering signals from linear tissue are extracted, filtered and then used to calibrate scattering signals from microbubbles. Since we can have two different signals that originate from the same spatial location, one can be used as a reference to effectively correct for the attenuation, including nonlinear attenuation, of the other. Initial results have shown the effectiveness of the technique on laboratory phantoms. Further in vivo studies are needed to fully demonstrate the potential of the technique.

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