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● *Original Contribution*

INVESTIGATING THE NONLINEAR MICROBUBBLE RESPONSE TO CHIRP ENCODED, MULTIPULSE SEQUENCES

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Abstract—A modified Rayleigh-Plesset model was used to investigate the nonlinear acoustic response of ultrasound contrast microbubbles to multipulse phase and amplitude modulated, chirp encoded sequences. Trade-offs between the signal-to-noise ratio (SNR) and axial resolution were quantified for differing chirp time-bandwidth products and methods for minimising the artifacts formed in the postprocessing stages were developed. It was found that the chirp length can be increased and bandwidth reduced to improve SNR, though resolution is sacrificed. Results from the simulated chirp, pulse inverted, amplitude modulated (chirp PIAM) sequences were also compared with equivalent short pulse PIAM sequences and it was found that the chirp sequences preserve their extra energy after scattering, which translates to an improved SNR after processing. Compression artifacts were reduced by using chirps with a centre frequency and bandwidth tuned to the frequency response of the microbubble and reversing the frequency sweep of one chirp in the sequence. (E-mail: r.eckersley@imperial.ac.uk) **© 2006 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Contrast microbubbles, Multipulse sequences, Coded excitation, Chirp.**

INTRODUCTION

Microbubbles play a major role as contrast agents in diagnostic ultrasound (US) and are becoming increasingly important in therapeutic applications. They show potential for imaging microvascular perfusion by enabling improvements in the sensitivity of the US system for detection of the slow moving blood in the smallest vessels (Burns and Becher 2000). This is of critical clinical significance as many diseases either arise from insufficient perfusion, or cause changes in the microcirculation.

Microbubbles typically consist of an inert gas encapsulated within a protein, lipid or polymer shell for stabilisation. Their mean diameters are ~ 5 μm so that they are able to traverse the entire capillary network after IV injection. Due to the large differences in compressibility between the encapsulated gas microbubbles and blood, they are extremely effective at enhancing the blood echo. Furthermore, at frequencies corresponding to those used clinically, the microbubbles act as resonators causing them to scatter US extremely efficiently. It should be noted that, although the encapsulating shell stabilises the microbubbles increasing their lifetime in the blood pool, its damping effect greatly influences their acoustic properties (Frinking and de Jong 1998).

For microbubbles, the relationship between the incident pressure and their response is nontrivial; in a low pressure US field ($<$100 kPa), microbubbles radiate US radially by contracting and expanding about their equilibrium radius in response to pressure variations in the compression and rarefaction phases of the US beam; as the peak pressure of the insonating pulse increases, the expansion and compression of the bubbles become nonlinear, resulting in the emission of harmonics (MacDonald et al. 2004). Detecting these nonlinear harmonic "signatures" from microbubbles and differentiating them from the echoes that result from nonlinear propagation of US in tissue forms the basis of research into contrast specific imaging.

Multipulse imaging sequences such as pulse inversion (PI) and amplitude modulation (AM) have been shown to yield high sensitivity in nonlinear imaging (Hwang and Hope Simpson 1999; Hope Simpson et al. 1999). Phillips (2001) and Eckersley et al. (2005) combined these methods and showed that multipulse PIAM can increase the detection sensitivity of US to micro-

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bubbles as nonlinear components in their response manifest throughout the band pass of the transducer system and higher order nonlinearities are further preserved after processing.

The fragile nature of microbubbles means that, at pressures within the diagnostic range (as low as 150 kPa peak negative pressure), microbubble destruction can occur. This destruction limits the ability to detect blood in the microvasculature. To avoid destruction, lower insonating pressures must be used, which reduce the sensitivity and specificity of the microbubble detection modes (Burns and Becher 2000). To overcome this problem and to increase sensitivity at low pressures, the work described in this paper modifies the transmitted sound pulses by exploiting encoding methods.

Pulse encoding techniques used in US imaging aim to maintain axial resolution whilst allowing a useful increase in SNR (Rao 1994), without surpassing peak power limitations. There exist numerous types of encoding techniques such as M-sequences, binary Golay and Barker and frequency modulated (FM) codes (Misaridis and Jensen 2005) that are used in fields such as radar and mobile communication systems, though not all of these methods are well suited to US imaging, due to the extra limitations introduced from imaging large numbers of distributed scatterers and the frequency dependent attenuation of US in tissue (Rao 1994). A signal encoded with a changing instantaneous frequency is known as a chirp and it has been found that the linear FM chirp signal is the most favourable for US imaging, as it is robust to the frequency shifts introduced by the attenuating media (Misaridis and Jensen 2005). Compared with typical imaging pulses, chirps are long in duration, so are able to carry more energy without increasing the peak amplitude, while still maintaining a wide bandwidth. After transmission, the received backscattered signal is compressed *via* a cross-correlation with its excitation chirp, which recovers the axial resolution and improves sensitivity. Due to the bandwidth of the excitation chirp, compression also acts as a bandpass filter so may suppress harmonics generated in the response. Additionally, in this processing stage, compression sidelobe artifacts can be introduced which correspond to ghost or blooming artifacts in an US B-mode image, although these can be reduced through appropriate apodisation of the insonating chirp (Takeuchi 1995). An added benefit of using chirps is that the generation of unwanted tissue harmonics due to nonlinear propagation is dependent on peak amplitude or mechanical index (MI) of the ultrasound pulse (Averkiou 2001).

Previously, Borsboom et al. (2003, 2004, 2005) investigated the use of chirp encoding in combination with harmonic filtering for microbubble detection. In this paper, simulation methods are used to investigate the sensitivity of US to microbubbles when combining chirped excitation with PIAM multipulse sequences.

THEORETICAL MODEL

A modified Rayleigh-Plesset equation (Hoff 2000) was used to simulate the acoustic response of microbubbles to chirp PIAM sequences. The model assumes a thin, viscoelastic, incompressible encapsulating shell (Church 1995) and takes into account acoustic radiation damping. The spherically symmetric radial oscillation of an individual microbubble is given by the following equation of motion

$$\ddot{R}R + \frac{3}{2}\dot{R}^2 + \frac{P_0 + P_i(t) - P_l}{\rho_l} - \frac{R}{\rho_l c}\dot{P}_l = 0 \qquad (1)$$

where $R(t)$ is the microbubble radius at time t, P_0 is the ambient pressure, P_i is the time dependent amplitude, c is the speed of sound and ρ_l is the density of the liquid. P_l is the pressure at the surface of the bubble given by

$$P_l = -4\eta_l\frac{\dot{R}}{R} - \Delta T_s + P_0\left(\frac{R_e}{R}\right)^{3\kappa} \qquad (2)$$

where η_l is the viscosity of the surrounding liquid, R_e is the equilibrium bubble radius, κ is the polytropic exponent of the gas and ΔT_s is the radial stress across the shell given by

$$\Delta T_s = \frac{12 d_{se}}{R_e}\left(\frac{1}{1+x}\right)^4 (G_s x + \eta_s \dot{x}) \qquad (3)$$

where d_{se} is the shell thickness, $x = R/R_e - 1$, G_S is the shell shear modulus and η_S is the shell viscosity. The last two terms were determined from the attenuation spectra of Sonazoid® (Hoff 2001) and have the values 50 MPa and 0.8 N s m^{-2}, respectively. After defining the excitation pressure, eqn 1 was solved using the *ode*45 function in MATLAB® which uses the explicit Runge-Kutta method with a variable step size. The scattered pressure at a given distance from the microbubble was then calculated from the radius and velocity of the bubble surface for each time point (Leighton 1994).

METHODS

Four series of experiments were designed to characterise the chirp PIAM sequence, to compare the sequence with a conventional PIAM sequence and to identify potential artifacts.

The first series simulated microbubble oscillations of known resonant properties to chirp PIAM sequences with centre frequencies tuned and untuned to the microbubbles' resonant frequencies. Series two examined the effects of manipulating the time-bandwidth product of