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● *Original Contribution*

INFLUENCE OF SHELL COMPOSITION ON THE RESONANCE FREQUENCY OF MICROBUBBLE CONTRAST AGENTS

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Abstract—The effect of variations in microbubble shell composition on microbubble resonance frequency is revealed through experiment. These variations are achieved by altering the mole fraction and molecular weight of functionalized polyethylene glycol (PEG) in the microbubble phospholipid monolayer shell and measuring the microbubble resonance frequency. The resonance frequency is measured *via* a chirp pulse and identified as the frequency at which the pressure amplitude loss of the ultrasound wave is the greatest as a result of passing through a population of microbubbles. For the shell compositions used herein, we find that PEG molecular weight has little to no influence on resonance frequency at an overall PEG mole fraction (0.01) corresponding to a mushroom regime and influences the resonance frequency markedly at overall PEG mole fractions (0.050–0.100) corresponding to a brush regime. Specifically, the measured resonance frequency was found to be 8.4, 4.9, 3.3 and 1.4 MHz at PEG molecular weights of 1000, 2000, 3000 and 5000 g/mol, respectively, at an overall PEG mole fraction of 0.075. At an overall PEG mole fraction of just 0.01, on the other hand, resonance frequency exhibited no systematic variation, with values ranging from 5.7 to 4.9 MHz. Experimental results were analyzed using the Sarkar bubble dynamics model. With the dilatational viscosity held constant (10^{-8} N·s/m) and the elastic modulus used as a fitting parameter, model fits to the pressure amplitude loss data resulted in elastic modulus values of 2.2, 2.4, 1.6 and 1.8 N/m for PEG molecular weights of 1000, 2000, 3000 and 5000 g/mol, respectively, at an overall PEG mole fraction of 0.010 and 4.2, 1.4, 0.5 and 0.0 N/m, respectively, at an overall PEG mole fraction of 0.075. These results are consistent with theory, which predicts that the elastic modulus is constant in the mushroom regime and decreases with PEG molecular weight to the inverse 3/5 power in the brush regime. Additionally, these results are consistent with inertial cavitation studies, which revealed that increasing PEG molecular weight has little to no effect on inethe rtial cavitation threshold in the mushroom regime, but that increasing PEG molecular weight decreases inertial cavitation markedly in the brush regime. We conclude that the design and synthesis of microbubbles with a prescribed resonance frequency is attainable by tuning PEG composition and molecular weight.
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Key Words: **Resonance frequency, Inertial cavitation, Polyethylene gycol brush, Mushroom, Microbubble.**

INTRODUCTION

Because of their functionality as ultrasound contrast agents and drug delivery vehicles, shelled microbubbles have garnered significant interest over the past 20 y (Church 1995; de Jong et al. 1992; Hoff et al. 2000). Microbubbles, which are effective in contrast and drug delivery modalities, are typically characterized by a thin shell—often a monolayer—that coats and stabilizes a gas core. For ultrasound contrast applications, microbubbles rely on their ability to reflect and backscatter sound waves, which can be detected and interpreted by a clinical ultrasound imager. For this reason, microbubble stability is of importance to commercial manufacturers. Typical formulations produce populations of microbubbles ranging from 1 to 10 μm in diameter and comprising a polymer, phospholipid or protein shell that encapsulates a fluorinated, heavy gas (Bloch et al. 2004; Postema and Schmitz 2006; Szabo 2004). The microbubbles are often further stabilized by the addition of a covalently linked polymer, such as polyethylene glycol (PEG), to prevent, *via* steric hindrance, both microbubble coalescence and uptake *in vivo* (Drummond et al. 1999; Kenworthy et al. 1995b; Lozano and Longo 2009).

Another phenomenon relating to microbubble stability is that of inertial cavitation. Microbubbles in

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an ultrasound field respond to the positive and negative pressure portions of the pressure wave by radial oscillations (Iida et al. 2000). The oscillation period is determined by the driving frequency of the ultrasound, whereas the magnitude of the oscillations is driven mainly by the amplitude of the sound pressure. At relatively low pressures, below a so-called inertial cavitation threshold, microbubbles exhibit sustained oscillations (also called *stable cavitation*). However, above this threshold—heuristically, considered to occur when the microbubble expands to at least twice its initial radius—the microbubble undergoes a violent collapse and implosion, termed *inertial cavitation* (Ammi et al. 2006; Holland and Apfel 1989). Inertial cavitation is an undesirable outcome for a clinician (and patient) for two reasons, one being the destruction or fragmentation of the contrast agents themselves and another being the potential for the subsequent shock wave to damage nearby cells (Hensel et al. 2009; Schlicher et al. 2006). In previous work, we reported that the inertial cavitation threshold depends on microbubble shell composition, namely, the mole fraction and molecular weight of functionalized PEG. In particular, we found that PEG molecular weight exerts little influence on the inertial cavitation threshold at relatively low (approximately ≤0.025) PEG mole fractions corresponding to a dilute, so-called mushroom regime and that increasing PEG molecular weight significantly decreases the inertial cavitation threshold at relatively high (≥0.050) PEG mole fractions corresponding to a concentrated, so-called brush regime. We believe the influence of PEG on inertial cavitation relates not to changes in chemistry *per se,* but rather to changes in shell material properties. That is, we believe that increasing PEG molecular weight within the brush regime decreases microbubble shell stiffness, thereby increasing the magnitude of microbubble oscillations at a given ultrasound intensity so as to decrease the peak negative pressure required for inertial cavitaion.

If it is true that increasing PEG molecular weight within the brush regime decreases microbubble shell stiffness, then increasing PEG molecular weight within the brush regime should necessarily also decrease microbubble natural (or resonance) frequency. Accordingly, herein we examine the influence of PEG composition and molecular weight on microbubble resonance frequency by measuring the pressure amplitude loss that occurs when an ultrasound beam traverses populations of microbubbles. Previous studies (Church 1995; de Jong et al. 1992; Hoff et al. 2000) have examined the dynamics of commercially available contrast agents, for which the chemistry is fixed. We work here with homemade microbubble populations, which allow us to measure the resonance frequency systematically as a function of PEG composition and molecular weight.

In addition to the experiments, we employ a well-defined microbubble dynamics equation to model the microbubble oscillations and calculate resonance frequencies owing to changes in monolayer stiffness. To describe a dynamic microbubble system as a function of shell properties, a modification of the Rayleigh-Plesset equation is employed. In previous works, Church (1995) and de Jong et al. (1992) proposed models taking into account the effects of a shell on bubble dynamics Other equations, such as a modification of Church's equation made by Hoff et al. (2000), characterize the shell using bulk material properties in conjunction with shell thickness. We employ a model derived by Sarkar et al. (2005), which incorporates surface tension and characterizes the shell *via* rigorously defined membrane material properties, namely dilatational viscosity (κ^S) and area expansion modulus (E^S).

The Sarkar model is given as

$$R\ddot{R}+\frac{3}{2}\dot{R}^2=\frac{1}{\rho}\left\{\left(P_o+\frac{2\sigma}{R}\right)\left(\frac{R}{R_o}\right)^{3\gamma}-\frac{2\sigma}{R}-\frac{4\eta\dot{R}}{R}-\frac{4\kappa^s\dot{R}}{R^2}-\frac{2E^s\left(R^2-R_o^2\right)}{RR_o^2}-P_o+P(t)\right\} \tag{1}$$

where R = microbubble radius; R_o = microbubble resting radius; ρ = density of the liquid surrounding the microbubble; σ = surface tension; γ = polytropic index; η = viscosity of the liquid surrounding the microbubble; κ^s = dilatational viscosity of the microbubble shell; E^s = expansion modulus of the microbubble shell; P_o = ambient, hydrostatic pressure; and $p(t)$ = applied acoustic pressure as a function of time, t. As is customary, when small-amplitude oscillations are under consideration, one can linearize eqn (1) by writing $R = R_o + r(t)$, finding the Taylor series expansion of all terms involving R and its time derivatives and keeping terms to the first order in r. The result of linearization is

$$\ddot{r}+\left(\frac{1}{\rho R_o^2}\right)\left[4\eta+\frac{4\kappa^s}{R_o}\right]\dot{r}+\left(\frac{1}{\rho R_o^2}\right)\left[\left(P_o+\frac{2\sigma}{R_o}\right)3\gamma-\frac{2\sigma}{R_o}+\frac{4E^s}{R_o}\right]r=\frac{1}{\rho R_o}P(t) \tag{2}$$

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