A novel model for an encapsulated microbubble based on transient network theory

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Introduction

Encapsulated microbubbles (EMBs) are widely used to enhance contrast in ultrasound sonography and are finding increasing use in biomedical therapies such as drug/gene delivery and tissue ablation. EMBs consist of a gas core surrounded by a stabilizing shell made of various materials, including polymers, lipids and proteins. We propose a novel model for a spherical EMB that utilizes a statistically-based continuum theory based on transient networks to simulate the encapsulating material. The use of transient network theory provides a general framework that allows a variety of viscoelastic shell materials to be modeled, including purely elastic solids or viscous fluids. This approach permits macroscopic continuum quantities – such as stress, elastic energy and entropy – to be calculated locally based on the network configuration at a given location. The model requires a minimum number of parameters that include the concentration of network elements, and the rates of attachment and detachment of the elements to and from the network. Using measured properties for a phospholipid bilayer, the model closely reproduces the experimentally-measured radial response of an ultrasonically-driven, lipid-coated microbubble. The model can be readily extended to large nonspherical EMB deformations, which are important in many biomedical applications.

Methods

We consider a spherical, encapsulated gas bubble of instantaneous radius, R, which is suspended in an infinite, incompressible, Newtonian liquid. Due to the encapsulation, we neglect the presence of vapor in the interior and treat it as adiabatic. We assume spherical symmetry and use spherical polar coordinates (r, θ, ϕ) to denote position. If we further assume the shell thickness, d_s, is small compared to the bubble radius (i.e., $d_s \ll R$), the gas density is negligible, and that the shell density and liquid density are comparable, then conservation of momentum in the radial direction yields [1],

$$R\ddot{R} + \frac{3}{2}\dot{R}^2 = \frac{1}{\rho_l}\left[\left(p_0 + \frac{2\sigma}{R}\right)\left(\frac{R_0}{R}\right)^{3\kappa} - p_0 - p_{ac}(t) - \frac{2\gamma}{R} - 4\mu_l\frac{\dot{R}}{R} + \frac{3d_s}{R}\sigma_{rr}(R,t)\right], \qquad (1)$$

where ρ_l is the liquid density, μ_l is the liquid viscosity, γ is the surface tension, κ is the ratio of specific heats, R_0 is the initial radius, $\dot{R}$ is the radial velocity, $\ddot{R}$ is the radial acceleration, t is time, p_0 is the hydrostatic pressure of the surrounding liquid, $p_{ac}(t)$ is the applied acoustic pressure, and σ_{rr} is the radial component of the stress tensor in the shell.

In this study, we present a new approach to model the viscoelastic mechanical properties of the bubble encapsulation by utilizing transient network theory (TNT) based on the work of Vernerey et al. [2]. The theory considers the shell material as an active network of interconnected elements that attach and detach at nodes with rates k_a and k_d, respectively, depending on the force applied. The approach here applies to any viscoelastic material and the individual elements could represent, for example, polymer chains, individual lipids, lipid domains or proteins, depending on the encapsulating material. The concentration of elements (or chains) that are attached to the network (moles per unit current volume) is represented by $c(t)$. To estimate the mechanical behavior, the density of the elements (or chains) and the average distance between elements (or chain length) are required. The TNT provides evolution equations to describe how these quantities vary in time in response to deformation and temperature fluctuations [2]. In the case of a permanent network, in which the rates of attachment and detachment are zero and the concentration is steady, the model reduces to that of an elastic solid. For the case where the kinetics of attachment and detachment are much faster than the rate of loading, a model for a viscous, incompressible fluid is recovered.

In this analysis, we make several simplifying assumptions about the EMB encapsulating material: 1) the dissociation rate coefficient, k_d, is constant; 2) the shell is incompressible; 3) the concentration of attached network elements, c, is steady; 4) the shell temperature is steady and uniform; and 5) mechanical energy dissipation is neglected. The first three assumptions yield the following constant concentration,

$$c = \frac{k_a}{k_a + k_d} c_{tot}, \tag{2}$$

where c_{tot} is the total concentration of elements, including those that are not connected to the network. Equation (2) also implies that the association rate constant, k_a, is constant due to assumptions 1) and 3). Given all of the assumptions above, it can be shown that the radial component of stress in the shell, σ_{rr}, is given by the following equation,

$$\sigma_{rr}(t) = \frac{2}{3} c k_B T \left\{ e^{-k_d t} \left[\left(\frac{R_0}{R(t)} \right)^4 - \left(\frac{R(t)}{R_0} \right)^2 \right] + \int_0^t k_d \left[\left(\frac{R(\tau)}{R(t)} \right)^4 - \left(\frac{R(t)}{R(\tau)} \right)^2 \right] e^{-k_d (t-\tau)} d\tau \right\}, \tag{3}$$

where k_B is the Boltzmann constant and T is the temperature, which is assumed here to be uniform throughout the entire domain. The last term in (3) involves an integral from the initial time $t = 0$ to the current time t, which demonstrates that the instantaneous stress in the shell depends on prior values of the radius, i.e., the shell behavior is history-dependent.

The EMB model using the TNT is represented in simplified form by equations (1)-(3) above. These include three independent parameters for the shell that may be specified as k_a, k_d and c_{tot}, in addition to the temperature, T. However, if temperature is assumed constant, as in the present work, then we can reduce the number of shell parameters to two, ck_BT and k_d, which have physical meaning as discussed below. To solve this model, we apply a 4th-order Runge-Kutta method using MATLAB to numerically solve the nonlinear ordinary differential equation (1) for the radius, $R(t)$, using the values of c and σ_{rr} given by (2) and (3), respectively. The history integral in (3) is solved via the trapezoidal method.

Results

To validate our EMB model using the TNT, we compare the results of simulations to the experimental data of van der Meer et al. [3], as presented in Tu et al. [4]. In the experiment, a lipid-shelled microubble (BR-14, Bracco Diagnositics) with an initial radius of $R_0 = 1.7$ μm was excited in water with an 8-cycle Gaussian-tapered acoustic pulse with a 2.5 MHz center frequency and 40 kPa maximum pressure amplitude, as shown in the left figure of Fig. 1. The experimental measurements of radius vs. time are shown as circles in the right figure of Fig. 1. To determine appropriate parameters for the TNT model, we derive estimates based on measured properties of lipid bilayers. The experimental data in Fig. 1 shows that the variation in radius – and, thus, the shell strain – is on the order of 10%. For small deformations and constant values of c and k_d, the TNT model degenerates to the well-known Maxwell model of viscoelasticity in which the shear modulus is given by ck_bT and the relaxation time by $1/k_d$ [2]. Based on the results of measurements of shear moduli and relaxation times for solvent-free glycerol mooleate bilayer lipid membranes by Crawford and Earshaw [5], we set $ck_BT = 0.771$ mN/m^2 and $k_d = 2.94 \times 10^4$ s^{-1}. The liquid parameters in equation (1) are set equal to those for water at standard conditions. Using these parameter values and the acoustic forcing shown in Fig. 1, the radial response predicted by the TNT model is plotted as a solid line in the right figure of Fig. 1. The fit between the simulation data and the experimental data is quite good over most of the pulse cycle, except near the end of the pulse where there is noticeable discrepancy. This discrepancy suggests there may be damping mehanisms in the EMB that are not accounted for in our model.

In Tu et al. [4], the experimental radius vs. time data shown in Fig. 1 is compared with the simulation results of three spherical EMB models by Marmottant et al. [6], Chatterjee and Sarkar [7] and Hoff [8]. The best-fit shell parameters for each model were determined iteratively by minimizing the standard deviation (STD) between the experimental and calculated radii data. The agreement between the experimental results and these three models based on the best-fit parameters are not shown here, but are similar to the results shown with the TNT model in Fig. 1. In particular, the radius computed by the Marmottant, Sarkar and Hoff models closely match the experimental data in the middle of the pulse cycle, but show noticeable deviations during the beginning and ending transient periods. Thus, the TNT model provides comparable matching to the observed radius vs. time data as the Marmottant, Sarkar and Hoff models. Similar to these models, the TNT model requires the specification of two shell parameters, which in this case are ck_BT and k_d. An important distinction, however, is that the radial response predicted by the TNT model is based on the use of experimental measurements to estimate the shell parameters, whereas the other models use iterative fitting to determine parameter values that provide a good match to the observed data. It is important to note that the use of data from [5] for a lipid bilayer is not ideal as the actual EMB is coated with a lipid monolayer. However, the close fit to the observed radius vs. time data provided by TNT through the use of measured properties, rather than fitted parameters, is encouraging.

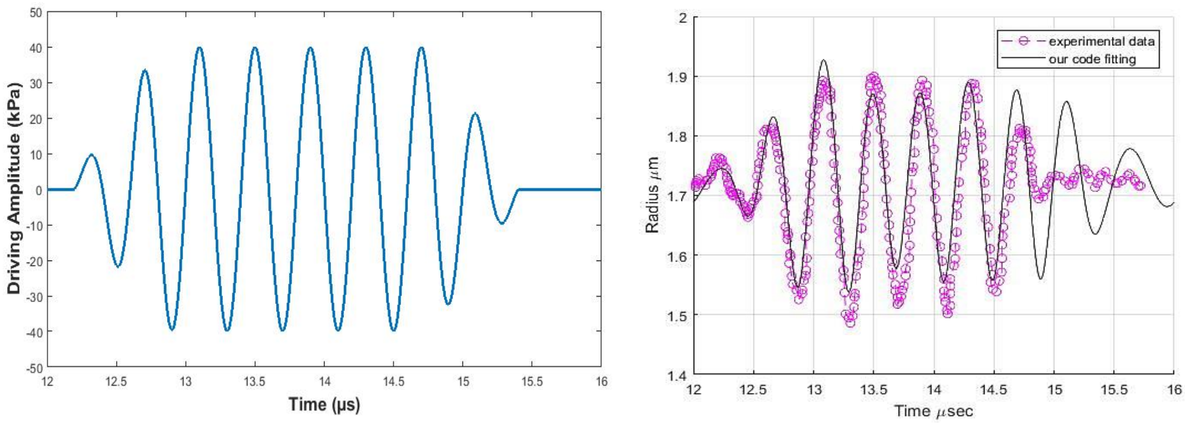

Figure 1: (Left) Gaussian-tapered acoustic pulse with 8 cycles, a 2.5 MHz center frequency and 40 kPa maximum pressure used as input forcing. (Right) Radial response of EMB for $R_0 = 1.7$ μm based on the transient network shell model (solid line) plotted against the experimental data (circles) of van der Meer et al. [3]. The parameters used in the model are $ck_BT = 0.771$ mN/m^2 and $k_d = 2.94 \times 10^4$ s^{-1}.

Conclusions

We have presented a novel model for a spherical encapsulated microubble (EMB) by using a statistically-based continuum theory known as transient network theory (TNT) to account for the shell mechanics. The TNT framework is based on a network of elements that dynamically attach and detach to each other based on specified kinetic rates. The model requires a minimum number of parameters to represent the shell behavior. By using measured values for lipid bilayers to determine these shell parameters, the model accurately simulates the experimental data of a lipid-coated EMB driven by an acoustic pulse. The use of TNT to model the encapsulation has several advantages over current approaches to modeling EMBs. For example, the TNT has the potential to model any viscoelastic material – lipids, polymers or proteins – as well as purely elastic solids or viscous fluids. In addition, microscale physics that may be important for understanding the dynamic behavior of EMBs can be incorporated into the TNT model in a natural way, unlike present continuum-level models. Furthermore, the TNT provides a means to compute shell stresses locally and account for large amplitude deformations, which allows the theory to be readily adopted into more complex models of nonspherical EMB oscillation.

References

[1]. Doinikov AA, Haac JF, Dayton PA, Modeling of nonlinear viscous stress in encapsulating shells of lipid-coated contrast agent microbubbles, Ultrasonics, 49: 269-275, 2009.

[2]. Vernerey FJ, Long R, Brighenti R, A statistically-based continuum theory for polymers with transient networks, Journal of the Mechanics and Physics of Solid, 107: 1-20, 2017.

[3]. van der Meer SM, Dollet B, Voormolen MM, Chin CT, Bouakaz A, de Jong N, Versluis M, Lohse D, Microbubble spectroscopy of ultrasound contrast agents, Journal of the Acoustical Society of America, 121: 648-656, 2007.

[4]. Tu J, Guan J, Qiu Y, Matula TJ, Estimating the shell parameters of SonoVue microbubbles using light scattering, Journal of the Acoustical Society of America, 126: 2954-2962, 2009.

[5]. Crawford GE, Earnshaw JC, Viscoelastic relaxation of bilayer lipid membranes. Frequency-dependent tension and membrane viscosity, Biophysical Journal, 52: 87-94, 1987.

[6]. Marmottant P, van der Meer S, Emmer M, Versluis M, de Jong N, Hilgenfeldt S, Lohse D, A model for large amplitude oscillations of coated bubbles accounting for buckling and rupture, Journal of the Acoustical Society of America, 118: 3499-3505, 2005.

[7]. Chatterjee D, Sarkar K, A Newtonian rheological model for the interface of microbubble contrast agents, Ultrasound in Medicine and Biology, 29: 1749-1757, 2003.

[8]. Hoff L, Acoustic Characterization of Contrast Agents for Medical Ultrasound Imaging, (Kluwer, Dordrecht), 2001.