Simulations of insonated contrast agents: Saturation and transient break-up

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Under insonation contrast agents are known to perform nonlinear pulsations and deform statically, in the form of buckling, or dynamically via parametric mode excitation, and often exhibit jetting and break-up like bubbles without coating. Boundary element simulations are performed in the context of axisymmetry in order to establish the nonlinear evolution of these patterns. The viscoelastic stresses that develop on the coating form the dominant force balance tangentially to the shell-liquid interface, whereas the dynamic overpressure across the shell balances viscoelastic stresses in the normal direction. Strain softening and strain hardening behavior is studied in the presence of shape instabilities for various initial conditions. Simulations recover the pattern of static buckling, subharmonic/harmonic excitation, and dynamic buckling predicted by linear stability. Preferential mode excitation during compression is obtained supercritically for strain softening phospholipid shells while the shell regains its sphericity at expansion. It is a result of energy transfer between the emerging unstable modes and the radial mode, eventually leading to saturated oscillations of shape modes accompanied by asymmetric radial pulsations in favor of compression. Strain softening shells are more prone to sustain saturated pulsations due to the mechanical behavior of the shell. As the sound amplitude increases and before the onset of dynamic buckling, both types of shells exhibit transient break-up via unbalanced growth of a number of unstable shape modes. The effect of pre-stress in lowering the amplitude threshold for shape mode excitation is captured numerically and compared against the predictions of linear stability analysis. The amplitude interval for which sustained shape oscillations are obtained is extended, in the presence of pre-stress, by switching from a strain softening constitutive law to a strain hardening one once the shell curvature increases beyond a certain level. This type of mechanical behavior models the formation of lipid bilayer structures on the shell beyond a certain level of bending, as a result of a lipid monolayer folding transition. In this context a compression only type behavior is obtained in the simulations, which is accompanied by preferential shape deformation during compression at relatively small sound amplitudes in a manner that bears significance on the interpretation of available experimental observations exhibiting similar dynamic behavior. © 2013 American Institute of Physics. [http://dx.doi.org/10.1063/1.4794289]

I. INTRODUCTION

Thus far, analysis of the available experimental observations and numerical simulations of contrast agents are performed based on the assumption of radial symmetry for pulsations ranging from linear1–3 to very large nonlinear4–6 excursions of the microbubble response. Emphasis is placed on the effect of nonlinear shell material behavior in the dynamics of the microbubble and more specifically in the quantitative characteristics of the backscattered signal, i.e., harmonic content and...
scattering cross section, and the radial time series, i.e., resonance frequency and radial excursion from equilibrium as a function of amplitude or phase of the oscillation. In this fashion, a number of dynamic phenomena that were reported experimentally in association with pulsating contrast agents have been studied, such as the nonlinear reduction of resonance frequency and the abrupt onset of radial vibrations as the sound amplitude increases, the compression only and expansion only effects, and the rich harmonic content of certain contrast agents at large amplitudes.

All the above effects can be recovered within the scope of radial symmetry, with the exception of compression only behavior that is most likely associated with a deformed bubble interface, and the harmonic content that is enriched in the presence of shape modes buckling and break-up. It is known that axisymmetric pulsations may arise as a result of parametric mode excitation for the appropriate amplitude and size range. Static buckling and wrinkling of the interface can occur as a consequence of gas diffusion out of the shell and the subsequent development of large compressive stresses on the interface. Alternatively, the presence of a nearby boundary, or another contrast agent, may accelerate growth of interfacial instabilities and instigate phenomena like jet formation and, finally, splitting and break-up of the microbubble. In almost all of the above cases eigenmodes dominating the post-buckling behavior are expected to be axisymmetric, especially in the presence of a standing pressure wave as indicated by the available experimental observations. Even when static buckling is observed, in the absence of sonication, axisymmetric modes are expected to prevail in the post buckling regime, unless there are significant imperfections in the base state manifested as deviations from sphericity, in which case nonaxisymmetric modes dominate when buckling occurs. When shell deformation arises as a result of gas diffusing out of the microbubble non-axisymmetric modes are reported experimentally, however they prevail after the onset of the first axisymmetric buckling mode has taken place in which case subsequent unstable modes evolve on a highly distorted microbubble. In general, and certainly when an acoustic wave is present, the assumption of axisymmetry is applicable and is adopted throughout the present study.

In view of the above it is of interest to ascertain the range of validity of spherical symmetry assumption in the presence of axisymmetric disturbances. In particular, the onset of static buckling when the overpressure across the microbubble shell is increased needs to be studied in order to investigate the parameter range over which steady deformed shapes appear, the super or subcritical nature of the bifurcation, and how such shapes affect parametric mode stability when acoustic disturbances are imposed. Linear stability analysis and optical observations of pulsating contrast agents indicate the possibility for parametric excitation of axisymmetric modes. In the latter study nonlinear saturation of the emerging modes was reported. It is important to establish a parameter range for mode saturation vs break-up in the presence of acoustic disturbances, in order to facilitate optimal control of procedures involving a cycle of low amplitude pulsing for imaging purposes, followed by a destructive acoustic signal that will allow for drug delivery to selected nearby tissues or simply microbubble replenishment for perfusion measurements. In addition, certain dynamic patterns, such as jetting and explosive break-up via growth of unstable modes that have been experimentally observed with pulsating contrast agents, are very important in establishing the localized effects that contrast agents have on nearby surfaces, cells or tissue. Such patterns have been extensively charted numerically in the case of free bubbles but the study of coated microbubbles is lagging in this aspect. It is also important to investigate the response of contrast agents surrounded by different types of shell material, e.g. strain softening or strain hardening shells, in the regime of nonlinear disturbances.

The constitutive law seems to be of central importance in understanding the mechanism behind the onset of “compression only” and “expansion only” behavior of contrast agents. The above two response patterns are associated with predominantly negative/positive excursions of the microbubble radial motion with respect to the equilibrium radius. In a recent study of radial pulsations it was seen that the former behavior is associated with strain hardening shells whereas strain softening shells exhibit “expansion only” behavior. The Marmottant model is essentially a hybrid of the above two models and associates “compression only” behavior with buckling of the shell at the moment that compressive stresses start to develop on it, i.e., it prescribes negligible bending resistance. Nevertheless, optical observations of pulsating contrast agents capture compression only behavior at very low amplitudes while a shift to expansion only behavior is observed as the amplitude of
sound increases. Nonlinear simulations of axisymmetrically deformed contrast agents may offer an alternative explanation as to the mechanism behind shape deformation at low amplitudes and its association with buckling and the constitutive law.

Available axisymmetric or 3d simulations of contrast agents treat the coating either as a thick liquid layer or as a very thin free surface characterized by surface tension. The microbubble is immersed in a Newtonian liquid or a viscoelastic fluid while emphasis is placed on the effect of nearby compliant walls or on the interaction of the contrast agent with a surrounding microvessel. In the latter study an effort is made to establish a lumped model combining the compliance of the microvessel liquid with that of the surrounding tissue. The importance of wall elasticity in the microbubble response is pointed out in all cases along with the effect of confinement on the microbubble pulsation. In the present study emphasis is placed on shell viscoelastic behavior including membrane and bending elasticities as well as shell viscosity. Interaction with acoustic disturbances of varying sound amplitude is investigated while the effect of nearby boundaries is neglected and is left for a future study. In this context, the microbubble dynamic behavior, as this manifests itself in the linear and nonlinear phenomena discussed in the previous paragraphs, is thoroughly studied as a problem of flow structure interaction.

The problem formulation is discussed in Sec. II, where the viscoelastic model for the shell surrounding the microbubble and the inviscid formulation for the host fluid are presented and justified in the context of contrast agent dynamics. Next in Sec. III the boundary element method is presented for studying axisymmetric oscillations and specific test runs are performed in order to validate the numerical methodology vs previous stability results. Finally, in Sec. IV selected numerical results are presented and discussed in the context of outstanding issues in the literature of contrast agent dynamics, as outlined in the presentation provided in the previous paragraphs and, lastly, in Sec. V conclusions are drawn and directions for future research are proposed.

II. PROBLEM FORMULATION

We consider axisymmetric pulsations of an encapsulated microbubble subject to acoustic disturbances. Large deviations from radial pulsations are allowed in order to capture nonlinear dynamic phenomena such as microbubble deformation/buckling, jetting, and break-up. The formulation of shell mechanics and surrounding medium behavior follows closely the analysis presented in Refs.4 and 14, but in the present study emphasis is placed in the nonlinear regime of axisymmetric disturbances. A brief outline of the model adopted for the numerical study that is performed, is provided in the following.

A. Mechanical equilibrium on the shell

The contrast agent is treated as a microbubble surrounded by a thin shell that behaves as an axisymmetric viscoelastic solid. The shell is initially at equilibrium with elastic forces balancing a possible external overpressure, in which case the shell is at a state of pre-stress and its shape may deviate from a sphere, Fig. 1, depending on whether the overpressure exceeds the buckling threshold corresponding to its stretching, \( G_s \), and bending, \( k_B \), modulus:

\[
P_G (t = 0) - P_{St} = 2h \sigma + \Delta F_n (t = 0),
\]

\[
\Delta F_n (t = 0) = 0, \quad 2h = \nabla_s \cdot \vec{n}.
\]

Here \( \sigma \), \( h \), denote surface tension and mean curvature whereas \( \nabla_s \), \( \vec{n} \), are the surface gradient operator and outwards pointing normal vector with respect to the coated microbubble. The effect of surface tension, \( \sigma \), is only included for completeness since its importance is negligible for the type of shell, and the overall physical conditions, considered here that operates mostly in the solid condensed phase. Consequently, unless a significant amount of the enclosed gas has escaped into the host fluid, thus generating a certain amount of pre-stress on the shell in which case \( \Delta F_n (t = 0) \neq 0 \), the internal pressure is equal to the exterior one. In the absence of any overpressure the external
Pressure is equal to the ambient pressure, $P_{St} = P_a$. Alternatively, deviations from radial pulsations may arise as a result of disturbances in the external pressure field along the azimuthal direction, $P_{St} = P_{St}(\theta)$, arising, perhaps, due to the influence of nearby boundaries or other microbubbles. $P_{St} = P_\infty$ is the static pressure field that is determined by the far field conditions in the surrounding fluid. In the absence of any overpressure no elastic forces are developed on the shell which acquires its stress free radius, $R(t_0) = R_{SF}$, $\hbar = 1/R_{SF}$. It should also be stressed that viscous forces on the liquid side of the interface are neglected in comparison with the viscoelastic stresses that develop on the shell. More details on this assumption are provided in the next section, Sec. II B. The initial gas pressure inside the microbubble is the same as the ambient pressure $P_a$ in the absence of any external overpressure whereas it is determined via the interfacial force balance ((1a) and (1b)) when pre-stress is present along with the adiabatic condition:

$$P_G(t_0) V_G = \gamma = \frac{4}{3} \pi R_{SF}^3,$$

(2)

$R(t_0) = R_{Eq}$ denotes an initial spherical shape that includes the possibility of pre-stress. In the absence of pre-stress $R_{SF} = R_{Eq}$ and $P_G(t_0) = P_a$. The force balance described by Eqs. (1) and (2) is perturbed by the application of an acoustic disturbance in the far field:

$$P_\infty (t_0) = P_a (1 + \varepsilon \cos \omega t),$$

(3)

with $\varepsilon$ and $\omega_f$ denoting the amplitude and forcing frequency of the disturbance. The elastic stresses that develop correspond to stretching and bending of the shell in response to the external forcing.

The stresses that develop on the shell as a result of the external overpressure are due to stretching and bending, i.e., elastic stresses, and to the rate of area dilatation and shear, i.e., viscous stresses. The dilatational and shear viscosities of the shell are taken to be equal to $\mu_s$, an assumption that is often used in the context of capsule dynamics where coatings of similar nature are involved. When static equilibrium prevails viscous stresses on the shell vanish but they have to be considered when the dynamic behavior of the microbubble is of interest. In this context the viscoelastic forces on the shell read

$$\Delta F = \Delta F_n \dot{n} + \Delta F_\varepsilon \dot{\varepsilon} = -\nabla_s \cdot \overline{T},$$

(4)

with $\nabla_s$, $\overline{T}$ denoting the surface divergence and viscoelastic stress tensor on the shell, respectively. The latter consists of the straining, bending, and rate of strain or viscous tensions,

$$\overline{T} = \tau_x + \tau_y = \tau + \tilde{q} \varepsilon + \tau_s,$$

(5a)

$$\tau = \tau_s \varepsilon \varepsilon_s + \tau_y \varepsilon_y \varepsilon_y,$$

(5b)

$$\tilde{q} = q \dot{n},$$

(5c)
with \( s \) denoting the arc-length along a meridian, \( \varphi \) the meridional angle, \( \mathbf{n} \) the outwards pointing unit normal vector with respect to the microbubble, \( \mathbf{q} \) the transverse shear force resultant that develops within the shell cross-section and generates a bending moment and \( D_s \) the rate of biaxial deformation tensor. The transverse shear is associated with the principal components, \( m_s, m_\varphi \), of the bending moment tensor via a torque balance on the shell

\[
\mathbf{q} = \frac{1}{r_0} \frac{\partial r_0}{\partial s} \left[ \frac{\partial}{\partial r_0} (r_0 m_s) - m_\varphi \right],
\]

where as the elastic strain and bending tensions are associated with the principal extension ratios of the shell, \( \lambda_i \), via the strain, \( w \), and bending, \( w_B \), energy. In the same fashion the dependence of the rate of strain tensions on the principal extension ratios can be recovered.

More details on this approach are provided in Refs. 30–33. Based on this approach and following the analysis presented in Refs. 4 and 14, in the present study we employ three different forms of the strain energy corresponding to a shell obeying Hooke’s law, the Mooney-Rivlin (MR) and the Skalak (SK) law, Fig. 2,

\[
\tau_s^H = \frac{G_S}{1 - \nu_s} \left[ \lambda_s^2 - 1 + \nu_s \left( \lambda_s^2 - 1 \right) \right], \quad K = \frac{G_S (1 + \nu_s)}{1 - \nu_s},
\]

\[
\tau_s^{MR} = \frac{G_{MR}}{\lambda_s \lambda_\varphi} \left[ \frac{1}{(\lambda_s \lambda_\varphi)^2} \left[ 1 + b \left( \lambda_\varphi^2 - 1 \right) \right] \right], \quad K = 3G_{MR},
\]

\[
\tau_s^{SK} = \frac{G_{SK}}{\lambda_s \lambda_\varphi} \left[ \lambda_s^2 \left( \lambda_s^2 - 1 \right) + C \left( \lambda_s \lambda_\varphi \right)^2 \left( \left( \lambda_s \lambda_\varphi \right)^2 - 1 \right) \right], \quad K = G_{SK}(1 + 2C),
\]

and similarly for \( \tau_\varphi \). As can be gleaned from Fig. 2 the above three constitutive laws, respectively, describe a linear stress strain relationship with a constant slope representing the area dilatation modulus, \( \gamma \), or a nonlinear stress strain relationship with a decreasing/increasing slope as the magnitude of stress increases, thus signifying a varying area dilatation modulus. It has been shown in the literature and will be discussed herein also that these features play central role in the response pattern exhibited by different types of contrast agents. In the above \( G, K \) denote the shear and area dilatation moduli, \( \nu \) is the Poisson ratio of the shell while \( b \) and \( C \) are parameters measuring...
the degree of softness or area incompressibility of the MR and SK shells, respectively.\textsuperscript{33} It should be stressed that the last two constitutive laws prescribe a nonlinear relationship between the elastic tensions that develop on the shell and the level of deformation that is observed, whereas viscous tensions are taken to depend linearly on the rate of strain tensor,

\begin{equation}
\frac{ds}{dt} = \frac{2\mu_s}{\kappa_s} \frac{d\lambda_s}{dt},
\end{equation}

\(\mu_s\) denotes the 2d shell dilatational viscosity, while the 3d dilatational viscosity is defined as \(\kappa_s = 3\delta \mu_s\) with \(\delta\) denoting the shell thickness. In an axisymmetric geometry the principal extension ratios assume the form

\begin{equation}
\lambda_s = \frac{ds}{ds} = \frac{S_0(t)}{S_0(0)}, \quad \lambda_{\phi} = \frac{r_0(t)}{r_0(0)}, \quad r_0 = r \sin \theta,
\end{equation}

where \(S\) denotes the arc-length along the generating curve of the axisymmetric shell, \(\xi\) is a Lagrangian variable identifying a particle on the shell as it deforms, \(r_0\) is the radial coordinate in cylindrical coordinates and \(r, \theta, \phi\), denote spherical coordinates. In Eq. (11) it is assumed that the shell is in its unstressed state at \(t = 0\). Finally, the bending moments are obtained via the bending measures of strain, \(K_s, K_{\phi}\), that relate the deviation of the two principal curvatures, \(k_s, k_{\phi}\), from their reference value in the absence of bending:

\begin{equation}
m_s = \frac{k_B}{\kappa_s} (K_s + vK_{\phi}), \quad m_{\phi} = \frac{k_B}{\kappa_s} (K_{\phi} + vK_s), \quad K_s \equiv \lambda_s k_s - k_R, \quad K_{\phi} \equiv \lambda_{\phi} k_{\phi} - k_{\phi}.
\end{equation}

In the present study and due to the inherent anisotropy of the shell coatings of contrast agents, e.g., surfactant monolayers, the bending elasticity \(k_B\) is not related to the shear modulus \(G_s\) and is therefore an independent parameter of the shell along with \(G_s\), or area dilatation \(K\), and the constitutive law parameters \(b\) or \(C\) for MR or SK shells.

B. Coupling with the surrounding fluid flow

We want to study the dynamic response of a microbubble that is initially at mechanical equilibrium, as described in the previous section, Sec. II A, subject to an acoustic disturbance in the far field as per Eq. (3). The inertia of the coating is negligible and consequently it instantaneously assumes the appropriate equilibrium shape in response to pressure changes in the surrounding fluid. Thus, the force balance described in Eqs. (1a) and (1b), remains valid in the context of the dynamic response, with the addition of viscous stresses in the liquid side of the interface as well as the shell and the static pressure \(P_s\) substituted by the dynamic pressure in the liquid \(P_t(t)\). At

\begin{equation}
r = r_s, \quad \left[-\rho l \frac{\partial}{\partial t} + \mu_l \left( \nabla \mathbf{u} + \nabla \mathbf{u}^T \right) \right] \cdot \mathbf{n} + P_s \mathbf{n} = \sigma \left( \tilde{\mathbf{N}} \cdot \mathbf{n} \right) \mathbf{n} + \Delta \mathbf{F},
\end{equation}

\(r_s\) denotes the radial position vector of the interface. Viscous dissipation is considered as the only damping mechanism due to the very small size of the microbubble.\textsuperscript{34} Upon obtaining order of magnitude estimates for the different components of the above force balance, viscous stresses in the liquid scale like \(\mu_l \omega\) whereas viscous stress resultants on the shell scale like \(\mu_l \omega R_0\). Substituting indicative values for the involved physical properties, i.e., \(\mu_l \sim 10^{-3}\) Kg/(m s) for water as the surrounding fluid and \(\mu_s \sim 10^{-8}\) Kg/s for shell viscosity,\textsuperscript{35} it turns out that shell viscosity dominates for very small microbubbles, e.g., when \(R_0 \sim 1\) \(\mu\)m viscous stresses on the shell are larger by an order of magnitude. Thus, for the type of applications envisioned for such microbubbles, it is not necessary to calculate the normal and shear stresses on the shell due to the liquid motion and dropping the viscous forces in the limit of large \(R_0 \equiv (R_0^2 / \omega \mu_l) / \mu_l\) does not generate a singularity in the solution, i.e., introduction of a boundary layer is not needed for capturing the flow characteristics near the interface. The dominant force balance on the normal and tangential direction of the shell interface is defined by the equilibrium between pressure, elastic, due to shell stretching and bending, and viscous forces due to the rate of shell stretching. Consequently, evaluating the pressure on the liquid side of the shell at each time instant constitutes the sole influence of the surrounding fluid on the pulsating microbubble. The assumption of negligible viscous stresses on the liquid side has been
employed in previous studies on the dynamic behavior of red blood cells\textsuperscript{30} or capsules, where it was shown that extracellular viscous effects are negligible in comparison with shell viscosity and were neglected in membrane relaxation studies via a micropipette. In a more recent numerical study on free pulsations of encapsulated and gas microbubbles, using a boundary fitted control volume approach\textsuperscript{36} with a Navier-Stokes solver while focusing on low amplitude phenomena, it was shown that viscous correction is necessary for obtaining shape mode eigenfrequencies of pulsating gas bubbles within acceptable accuracy. This result is in accordance with previous asymptotic solutions\textsuperscript{37} that account for the viscous boundary layer attached to the free surface surrounding the bubble. On the contrary, simulations with encapsulated microbubbles\textsuperscript{36} recover eigenfrequencies of natural shape modes as predicted by stability analysis\textsuperscript{14} using inviscid theory for the surrounding liquid, thus attesting to the validity of the assumption of negligible viscous forces on the liquid side of the interface employed in the present study.

At this point we introduce dimensionless variables by setting the initial bubble radius, $R_0 \equiv R(t = 0)$ with $R' \equiv \bar{r}/R_0$, as the characteristic length scale and the inverse forcing frequency, $1/\omega t$ with $t' \equiv \omega t$, as characteristic time. $G_s$ denotes the shear modulus of the shell, $\rho$ the density of the surrounding liquid and $\bar{r}$ position vector; dimensionless variables are denoted with primes. Consequently, $\omega t R_0$ emerges as the characteristic velocity, $\rho \omega^2 R_0^3$ as characteristic pressure and $\rho \omega^2 R_0^3 \Re_s$ as characteristic interfacial tension of the problem,

$$\tau'_s = \frac{\tau_s}{\rho \omega^2 R_0^3} = \frac{G_s}{\rho \omega^2 R_0^3} \sigma_s = G \sigma_s, \quad \tau'_v = \frac{\tau_v}{\rho \omega^2 R_0^3} = \frac{\mu_s \omega}{\rho \omega^2 R_0^3} \sigma_v = \frac{1}{\Re_s} \sigma_v,$$

$$q' = \frac{q}{\rho \omega^2 R_0^3} = \frac{k_B}{\rho \omega^2 R_0^3} Q = K_B Q, \quad k_i' = \frac{k_s}{1/R_0}.$$

Substituting in Eq. (13), neglecting surface tension and viscous forces on the liquid side and dropping primes from dimensionless variables for simplicity, the normal and tangential force balances on the interface read

$$P_G - P_i = k_s \left( G \sigma_s + \frac{1}{\Re_s} \sigma_s^v \right) + k_v \left( G \sigma_v + \frac{1}{\Re_s} \sigma_v^s \right) - \frac{K_B}{r_0} \frac{\partial}{\partial s} (r_0 Q) = \Delta F_n,$$  

$$\Delta F_i = \left( \frac{\partial}{\partial s} \left( G \sigma_s + \frac{1}{\Re_s} \sigma_v^s \right) \right) + \frac{1}{r_0} \frac{\partial r_0}{\partial s} \left[ G \left( \sigma_s - \sigma_v^s \right) + \frac{1}{\Re_s} \left( \sigma_v^v - \sigma_v^s \right) \right] + K_B k_s Q = 0.$$  

In the above $G, K_B$ are dimensionless quantities determining the relative importance of elastic forces due to stretching or bending and the acoustic disturbance, while $\Re_s$ signifies the relative strength of viscous forces on the shell and the acoustic disturbance.

Assuming negligible viscous and acoustic damping the pressure exerted on the surrounding fluid is calculated by employing inviscid theory. Consequently the dynamic version of Bernoulli’s law can be applied in order to associate liquid pressure on the shell with that in the far field,

$$\frac{\partial \Phi}{\partial t} + \frac{1}{2} \left| \nabla \Phi \right|^2 + P_i = P_\infty,$$  

$$P_\infty = P_0 (1 + \varepsilon \cos t).$$

The left-hand side in Eq. (16) is evaluated on the shell/liquid interface and $\Phi$ signifies the velocity potential that can be defined in the liquid, provided there are no sources of vorticity in the flow field in the vicinity of the microbubble, e.g., nearby bounding surfaces. Introducing Lagrangian derivatives along with the normal force balance we obtain the dynamic boundary condition on the shell

$$\frac{D \Phi}{D t} = \frac{\partial \Phi}{\partial t} + \bar{u} \cdot \nabla \Phi = \frac{\partial \Phi}{\partial t} + \left| \nabla \Phi \right|^2 = \frac{1}{2} \left| \nabla \Phi \right|^2 + P_\infty - P_G + \Delta F_n, \quad \bar{u} = \nabla \Phi,$$

$$\bar{u} \cdot \nabla \Phi = 0.$$
subscript \( s \) denotes quantities defined on the interface. When irrotationality and continuity of the flow field hold, the velocity potential satisfies the Laplacian. The latter can be recast in an integral form that relates velocity potential, \( \Phi \), to the normal velocity of interfacial particles, \( \partial \Phi / \partial n \), and involves quantities defined on the microbubble/liquid interface:

\[
\nabla^2 \Phi = 0 \rightarrow -\Phi(\hat{r}, \hat{\theta}, t) + \frac{1}{r^2} \Phi(\hat{r}, \hat{\theta}, t) - \Phi(\hat{r}, \hat{\theta}, t) \frac{\partial G(\hat{r}, \hat{\theta}, r, \theta)}{\partial n} r \sin \theta \left(r_0^2 + r^2 \theta_0^2\right)^{1/2} \xi = \int_0^1 \frac{\partial \Phi}{\partial n} (r, \theta, t) G(\hat{r}, \hat{\theta}, r, \theta) r \sin \theta \left(r_0^2 + r^2 \theta_0^2\right)^{1/2} d\xi.
\]

In the above equation, \( G \) and \( \partial G / \partial n \) denote the axisymmetric free space kernel of the Laplacian and its normal derivative on the interface, respectively. \( r, \theta \) and \( \hat{r}, \hat{\theta} \) are spherical coordinates representing source and field points on the generating curve of the axisymmetric shell/liquid interface, Fig. 1, whereas \( \xi \) and \( \hat{\xi} \) are Lagrangian markers. They are introduced as a means to identify interfacial particles as well as their velocity via the kinematic interfacial condition:

\[
\frac{dr_0}{dt} = \hat{r}_0 \xi, \quad u_0 = \hat{\nabla} \Phi|_{s} \rightarrow \frac{dr}{dt} \bigg|_{r_0, \theta_0} = \frac{\Phi_{\xi} r_0 + \frac{\partial \Phi}{\partial n} r_0 \frac{\sqrt{r_0^2 + r^2 \theta_0^2}}{r_0^2 + r^2 \theta_0^2}}{r_0^2 + r^2 \theta_0^2},
\]

subscript \( \xi \) denotes partial differentiation along the interface while \( r, \theta \), and \( r_0, \theta_0 \) denote current and initial spherical coordinates of Lagrangian particles occupying the interface. Since the interface is not a free surface the tangential part of the kinematic condition is not used and the azimuthal coordinate of the particles is updated via the tangential force balance. Due to axisymmetry, derivatives with respect to the arc length along the interface satisfy the following conditions:

\[
\frac{\partial r}{\partial \xi} = \frac{\partial \Phi}{\partial \xi} = \frac{\partial^2 \Phi}{\partial \xi \partial n} = \frac{\partial^2 \theta}{\partial \xi^2} = 0, \quad \text{at } \xi = 0, 1
\]

(20)

corresponding to the two poles of the coordinate system. Equations (2) and (3) defining the pressure in the microbubble and the far field, after they are recast in their dimensionless form, along with interfacial force balances ((15a) and (15b)) and Eqs. (17)–(20) determining the flow problem in the surrounding fluid, constitute the formulation of nonlinear pulsations of an encapsulated microbubble. Finally, upon integrating the governing equations throughout the flow domain and incorporating the interfacial conditions we obtain the energy balance relating variations in the kinetic energy of the microbubble with (a) pressure changes inside it with respect to the far field, (b) the elastic energy that is stored in the shell in the form of stretching and bending and (c) viscous dissipation as a result of the dilatation rate. The latter two effects arise due to shell viscoelasticity,

\[
\frac{1}{2} \frac{d}{dt} \iint_A \Phi \frac{\partial \Phi}{\partial n} dA + \iint_A \frac{\partial \Phi}{\partial n} (P_G - P_{\infty} - \Delta F_n) dA = 0.
\]

III. NUMERICAL SOLUTION

Due to the assumption of irrotationality in the surrounding liquid a combination of the boundary and finite element method is used for the spatial discretization of the problem formulation. The Runge-Kutta time integrator is then employed in order to update the location of the interface, via the \( r, \theta \) coordinates, as well as the velocity potential, \( \Phi \), at each time step. The numerical methodology that is used in the present study is similar to that presented in previous numerical studies of pulsating gas bubbles with the exception of the treatment of the tangential component of the kinematic condition. When the motion of a free surface is investigated, as is the case with gas bubbles, the normal component of the kinematic condition is used in order to update the location of the interface. The tangential component is introduced as a means to establish a mapping between the old position of Lagrangian particles in the interface and their new location on the updated interface. When an encapsulation is present emphasis is placed on the flow structure interaction aspect of the problem.
while the viscosity of the surrounding fluid is neglected. The tangential force balance is used instead in order to provide the displacement of the interfacial particles in the azimuthal direction as a function of their radial displacement which is provided by the normal component of the kinematic condition, Eq. (19).

Consequently, the interface consists of a group of Lagrangian particles characterized by a \( \xi \) coordinate ranging between 0 and 1. This coordinate remains constant in time identifying a certain interfacial particle throughout its trajectory in the flow domain. Thus at any time instant, when the location of a particle on the interface is known, \( r(\xi, t), \theta(\xi, t) \), as well as the velocity potential, \( \Phi(\xi, t) \), the viscoelastic stresses on the interface, and the pressure inside the microbubble can be evaluated via the dimensionless version of Eqs. (2) and (6)–(12). Next, the normal derivative of the potential on the interface for the same time instant is provided by solving Eq. (18), which completes calculation of the problem variables at time \( t \). Subsequently, the radial position and velocity potential of the particles are updated by time integrating the dynamic and kinematic boundary conditions, Eqs. (17) and (19). The time derivative of the azimuthal position of interfacial particles, \( d\theta/dt \), is solved for via the tangential force balance (15b):

\[
\int_0^1 \left( \frac{2r^2 \partial \xi \partial \xi}{Re_s s_t^2} - \frac{2 \theta \cos \theta}{Re_s \sin \theta} \right) r_0 \xi B_\xi d\xi - \int_0^1 \frac{2r^2 \partial \xi \partial \xi}{Re_s s_t^2} \left( r_0 B_{\xi \xi} + r_0 \xi B_\xi \right) d\xi
\]

\[
= \int_0^1 r_0 K_B m_\xi \left( k_{\xi \xi} B_\xi + k_{\xi \xi} B_{\xi \xi} \right) d\xi
\]

\[
+ \int_0^1 k_{\xi \xi} m_\xi r_{0 \xi \xi} B_\xi d\xi + \int_0^1 G \sigma_\xi \left( r_0 B_{\xi \xi} + r_0 \xi B_\xi \right) d\xi - \int_0^1 G \left( \sigma_\xi - \sigma_\xi \right) r_{0 \xi \xi} B_\xi d\xi +
\]

\[
\int_0^1 \left( \frac{2 \theta r_{\xi \xi} + 2 \theta r_{\xi \xi}}{Re_s s_t^2} \right) \left( r_0 B_{\xi \xi} + r_0 \xi B_\xi \right) d\xi - \int_0^1 \left( \frac{2 \theta r_{\xi \xi} + 2 \theta r_{\xi \xi}}{Re_s s_t^2} \right) \left( r_0 B_{\xi \xi} + r_0 \xi B_\xi \right) d\xi,
\]

(22)

where \( B_\xi \) is the B-cubic spline test function.

It should also be stressed that calculation of bending stresses in Eq. (17) involves discretization of the fourth order derivative of the shell radial position. This is not an appropriate operation since B-cubic splines are only continuous up to the second derivative. In order to circumvent this issue integration by parts which brings down the order of differentiation while introducing a third order derivative in the integral formulation of the dynamic boundary condition. Evaluation of the third derivative is acceptable with the cubic splines as basis functions since the weak formulation in the finite element methodology requires square integrable functions.

Finally, the location of the interface and velocity potential are advanced in time by applying the Runge-Kutta time integrator in Eqs. (17), (19), and (22). The pressure disturbance in the far field enters the algorithm at this stage via the contribution of \( P_\infty(t) \) to the right-hand side of Eq. (17). This process is then continued until the microbubble achieves saturated pulsations or transient break-up takes place. The latter situation is identified by exceedingly large amplitudes, \( a_n \), of the emerging shape modes, e.g., \( a_n \sim R_0 \), or by the appearance on the interface of regions of very small radius of curvature. A similar approach is adopted when a step change in the far field pressure is applied, or an acoustic disturbance of sufficiently low forcing frequency.

Spatial discretization via the boundary and finite element methodology as well as time integration proceed as described in Refs. 39 and 38. It should also be stressed that, owing to axisymmetry, only the generating curve of the axisymmetric microbubble interface need be discretized. A certain complication arises due to the appearance of third order derivatives with respect to the arc-length of the interface in the normal and tangential force balances, Eqs. (15a) and (15b), in the process of discretizing terms pertaining to bending tensions; Eqs. (15a) and (15b) contain a fourth order derivative which is reduced to third order upon integrating by parts their finite element representation. Since B-cubic splines, which are the basis functions that we use for the finite and boundary element representation of the unknown functions, only guarantee continuity up to and including the second derivative of the interpolating function, we anticipate growth of spurious short wave modes as the simulation proceeds in time, whose wavelength is always comparable to the minimum element size.
Indeed, this is observed in the numerical simulations that were performed, especially in regions of interface where large change of curvature takes place. In order to circumvent this restriction, a limited number of Legendre modes are retained in the Fourier expansion of the numerically calculated values of the radial position, the velocity potential and the normal velocity, $\partial \Phi / \partial n$. The number of the modes in the expansion varied from $N/3$ to $N/5$, with $N$ denoting the number of elements, while at the same time monitoring the conservation of total energy, Eq. (21). The time step was fixed depending on the number of elements as well as the velocity of the interface. In fact, the time step varied from $10^{-4}$ till $5 \times 10^{-7}$ in all the simulations that are presented in the following sections. Typically, 150-600 elements are used for the discretization of the interface in the region $0 \leq \theta \leq \pi$.

As the number of elements and consequently the size of the system matrix increase construction of the latter, which is fully populated as is normally the case with the boundary integral methodology, becomes the most time consuming part of the computation. More specifically, construction of the system matrix takes up more than 80% of the CPU time with the rest of the CPU time dedicated mainly to matrix inversion. In order to optimize computational speed we resort to parallel strategies. In particular, the system matrix is constructed in a parallel fashion with different processors dedicated to different rows of the matrix. The above numerical implementation is validated against mesh refinement and by monitoring the variation of the total energy of the system, Eq. (21). Finally, comparison with results of linear theory pertaining to the stability of radial pulsations with respect to axisymmetric disturbances, constitutes an additional check for our calculations and is discussed in the next section, Sec. III A.

A. Code validation

In order to validate the numerical methodology outlined above we perform a series of numerical simulations trying to recover the stability threshold for harmonic or subharmonic resonance to take place. The parameter range is selected in such a way as to recover certain aspects of experimentally reported contrast agent behavior such as resonance frequency, sound amplitude threshold for the onset of parametric shape mode excitation, and the amplitude of the excited shape mode. Based on optical measurements of nonspherical shape modes that grow on microbubbles coated by a phospholipid monolayer and manipulated via laser tweezers in order to be moved to the desirable location off the nearest boundary, axisymmetric perturbations exhibit maximal growth for microbubbles with resonant rest radius, i.e., $R_0 = R_{SF} \approx 2.5 \mu m$ when $v_t \approx 1.7$ MHz. Consequently and assuming strain softening shell behavior with $b = 0$ and shell thickness $\delta \approx 1$ nm the shear modulus $G_{ij}$ is on the order of 80 MPa. Furthermore, upon requiring the amplitude threshold for the onset of four lobed shape modes of a microbubble with $R_{SF} = 3.6 \mu m$ to be $\varepsilon < 2$, so that parametric mode excitation takes place within a relatively small number of cycles, we obtain an estimate for the shell bending resistance $k_B = 3.0d-14$ N$m$ by performing linear stability analysis for parametric excitation of $P_4$. Finally shell viscosity is estimated to be $\mu_s = 20$ Pa*s, by requiring that the maximum amplitude of the radial pulsations be as close as possible to the experimental results, when a microbubble of rest radius $R_{SF} = 2.3 \mu m$ is insonated at a sound amplitude of $\varepsilon = 4$. For the above parameter range linear stability analysis predicts $\varepsilon \approx 1.7$ as the stability threshold. Fig. 3(a) illustrates the growth of unstable shape modes as predicted by Floquet analysis when $\varepsilon = 2$, with the fourth Legendre eigenmode, $P_4$, dominating via harmonic resonance. Numerical simulations of a microbubble with the above physical properties, pulsating in response to an external acoustic disturbance, recover the stability threshold for the onset of $P_4$ pulsations predicted by linear analysis, i.e. $\varepsilon = 1.7$. As the amplitude of the forcing is raised to 2 relatively rapid growth of $P_4$ is detected, Fig. 3(b), that is first registered over a time scale of, roughly, 30 periods of the forcing in agreement with linear analysis, see also Fig. 3(a), until mode saturation sets in. Both $P_4$ and $P_6$ pulsate at harmonic resonance, Fig. 3(b), with the forcing. In particular, the emerging shape modes achieve their maximum amplitude just when the radial position assumes its minimum value during compression. This coordination is clearly illustrated in Fig. 3(c) that focuses on the time interval within which the microbubble has achieved steady pulsation. The microbubble interface during this time frame is characterized by four lobed shapes during compression and almost radial symmetry.
during expansion, Fig. 4(a) illustrates the spherical shape and the four-lobed shape at maximum and minimum radial displacement during saturation, with $x$ being the axis of symmetry. Finally, the kinetic, elastic, and total energy of the microbubble as well as viscous dissipation are registered at each time step, Fig. 4(b), illustrating energy conservation throughout the simulation. The time step of the simulation varies between $10^{-4}$ and $10^{-5}$, the latter value is appropriate during the growth phase of the unstable eigenmode, with $2\pi$ denoting a period of the forcing. The number of elements varies from 150 to 250 in order to capture areas of large curvature as shape deformation takes place.

As an additional test, free pulsations of a coated microbubble were studied numerically by imposing a disturbance on the radial coordinate of the shell. The same set of natural parameters is employed as in the above simulations with the difference that now the shape of the shell is disturbed
initially, rather than the far field pressure, assuming the form

\[ r_s(\theta, t = 0) = R_{SF} + \varepsilon_s P_4(\theta). \]  

(23)

The microbubble is initially at equilibrium with the shell at a stress free state and \( \varepsilon_s = 0.4 \). As expected the microbubble exhibits volume pulsations and shape oscillations dominated by \( P_0 \) and \( P_4 \), Figs. 5(a) and 5(b). They are both eventually damped out with the bubble returning to the original spherical shape at rest radius. Fourier analysis of the time series pertaining to the two dominant modes reveals their respective frequencies, \( \nu_0 \approx 0.8, \nu_2 \approx 0.56 \) and \( \nu_4 \approx 1.66 \), all in agreement with linear analysis for volume pulsations, see also Ref. 4 as well as stability analysis for axisymmetric shape oscillations for the corresponding parameter range; \( b = 0, G_{3D} = G_s/\delta \), etc.
FIG. 5. (a) Shape mode evolution and (b) shapes of the same microbubble as in Figs. 3 and 4, undergoing free pulsations subject to an initial shape perturbation in the form of $P_4$ with amplitude $\varepsilon_s = 0.4$. The predictions for the characteristic eigenfrequencies of the microbubble based on linear theory are accurately recovered by the numerics.

In this particular simulation time has been made dimensionless via the balance between elastic forces and inertia, $\hat{t} = \frac{t}{\sqrt{\frac{\rho R^2}{G\delta}}}$. It is related to the original dimensionless time as $\hat{t} = t\sqrt{G}$; $G \approx \frac{G_s}{(\rho R_0^3/\omega^2)} \approx 0.015$. Hats are dropped from the x coordinate labels of Fig. 5 corresponding to time, for convenience.

IV. RESULTS AND DISCUSSION

In this section a detailed account of the numerical simulations that were performed is presented, aiming at identifying the different patterns in the nonlinear response of individual contrast agents.
subject to step changes, Sec. IV A, or acoustic disturbances, Sec. IV B, in the far field pressure. In the former case disturbances in the initial shape are also investigated. The possibility for deviation from sphericity at static conditions and saturated pulsations of shape modes are investigated, corresponding to the above two disturbance types for shells obeying the Mooney-Rivlin or the Skalak constitutive laws. Finally, the effect of pre-stress in the initial configuration is examined on the onset of shape oscillations, depending on the constitutive law, and directions for future research are pointed out.

FIG. 6. Dynamic simulations until break-up for a step change in pressure, $\Delta P = 2P_s$ beyond the buckling threshold. Parameters are those provided in Fig 1 of Ref. 42. Evolution of (a) and (b) shape modes and (c) bubble shapes is provided; $R_0 = 1.0 \, \mu m$, $\mu_s = 7 \, Pa*ms$, $G_{3D} = 88 \, MPa$, $k_B = 3.616d-16 \, N*m$, $\varepsilon = 2.0$, $b = 0$ (MR shell), $\gamma = 1.07$, $\nu = 0.5$, $P_{st} = 101325 \, Pa$, $\mu_1 = 0$, $\delta = 23.1 \, nm$. 
A. Investigation of static deformations

The response of a coated microbubble subject to a step change in the far field pressure or to an initial disturbance of its shape is examined and the possibility for steady deformed shapes to eventually appear is investigated. Based on the energy minimization principle the spherical shape first becomes unstable subject to axisymmetric disturbances when the external pressure exceeds a certain threshold. This was verified in the context of linear stability analysis of contrast agents. Recent studies on static deformation of spherical shells subject to an external pressure load indicate that the above instability is a transcritical bifurcation that extends towards smaller overpressures beyond a critical threshold.

\[ \Delta P_{Cr} = P_{Ext} - P_G = \frac{2}{3(1+\nu)^{1/2}} \frac{3G_{3D}\delta^2}{R_0^2}, \quad P_{Ext} = P_{St} = P_a(1+\varepsilon), \quad R_0 = R_{SF} \] (24)

with \( \delta \) denoting the shell thickness, \( G_{3D} \) the 3d shear modulus and \( \nu \) the Poisson ratio. The above analytic formula is valid for very small static deformations, \( (R-R_0)/R_0 \), at the compressed state. The buckling resistance of contrast agents subject to axisymmetric and three dimensional disturbances was also studied via a finite element methodology coupled with an energy minimization principle. The predominance of axisymmetric disturbances at the onset of shell buckling leading to an asymmetric shape that exhibits a progressively stronger indentation on one of the two poles, was thus verified in agreement with the previous study. Furthermore, it was shown that three-dimensional wrinkled shapes around the indented pole arise beyond a certain lower threshold of the shell volume. Nevertheless, the latter study did not provide evidence on the stability of the different solution branches. Adopting the parameter range employed in Ref. static stability analysis was performed for a contrast agent coated by a strain softening shell with a relatively large dilatation modulus; \( R_0 = R_{SF} = 1 \mu m, G_{3D} = 88 \text{ MPa}, \delta/R_0 = 0.0231, \) and \( k_B = 3G_{3D}\delta^3/\left[12(1-\nu^2)\right]. \) Thus \( \varepsilon \approx 1.92 \) was obtained, see also Ref. as the critical overpressure for buckling to occur with the 11th Legendre mode as the dominant eigenmode. Performing dynamic simulations in the context of the present study for a contrast agent with the above properties at equilibrium and an initial far field pressure disturbance \( P_a \), without any pre-stress or initial shape deformation, illustrates this behavior in the form of a constantly increasing \( P_{11} \), Fig. 6(b), until shell rupture. The shell initially responds by acquiring a compressed spherical shape as a result of the external overpressure. This is illustrated by the long plateau in the time series of \( P_0 \) in Fig. 6(a) almost immediately after imposition of the disturbance. However, because the initial disturbance lies above the threshold pressure for static buckling to occur, steady compression is not sustained. Rather, the shell buckles in a fashion predicted by linear stability analysis with \( P_0 \) subsiding, long time behavior in Fig. 6(a), in favor of \( P_{11} \) that emerges as the dominant eigenmode, Fig. 6(b), hence the asymmetry in the shape. As the shape deformation increases nonlinear effects start playing a significant role by transferring energy from the most unstable mode \( P_{11} \) to neighboring modes, e.g., to \( P_{10}, P_3, P_4 \) as shown in Fig. 6(b). This is a recurring theme that appears when nonlinear effects enter the microbubble dynamics. In the absence of any robust break-up criteria we terminate the simulation when the amplitude of the emerging eigenmodes matches that of the radial pulsation. Snap-shots of microbubble shape during the simulations reveal a sequence of highly indented shapes near one of the two poles, similar to those obtained in the static deformation computations provided in Refs. 41 and 42 albeit with constantly increasing indentation depth as time elapses, as clearly illustrated in Fig. 6(c). This behavior conforms with the finding of static stability pertaining to the nature of the bifurcating branch of asymmetric shapes, namely that it extends to overpressures that are lower than the critical. As far as the original family of spherical shapes is concerned, the fact that it loses stability for overpressures that are larger than the above critical value is ascertained by the above simulations. It should be stressed that the above behavior was obtained in Ref. 41 neglecting compressibility of the gas enclosed by the shell. The results of the present study suggest that this behavior persists when gas compressibility effects is included in the model. A more systematic search of the bifurcation diagram accounting for gas compressibility was not pursued herein and is left for a future study.
As a last test simulations and stability analysis was performed based on experimental reports regarding pulsations of polymer-based-shell contrast agents and destruction subject to acoustic disturbances. Simulations relevant to the above measurements were also performed in Ref. 42 employing an improved version of the shell buckling model, originally proposed in Ref. 10 that allows the shell to sustain a certain amount of compression before buckling occurs. However, this is done in a fashion that introduces buckling in the shell constitutive law and this can generate inconsistencies. For example, in their effort to recover experimental observations regarding transient break-up of contrast agents the authors of Ref. 42 propose a buckling tension \( \Delta P_m R_0/2 = \sigma_m \text{buckling} = -1\, \text{N/m} \) which, when combined with the 2d compression modulus \( \chi = 10\, \text{N/m} \) and the prediction for the critical overpressure for buckling to occur \( \sigma_m = -2/3 \chi (\delta/R_0) \), provides a rather unrealistic prediction for the shell thickness \( \delta/R \approx 0.15 \).

In the present study an alternative approach is adopted. Namely, the shear modulus and shell thickness were estimated, \( G_{3D} \approx 300\, \text{MPa} \) and \( \delta \approx 50\, \text{nm} \), so that the experimentally obtained critical overpressure, \( \Delta P_m \approx 1.57\, \text{MPa} \), was recovered when \( R_0 = 1.5\, \mu m \). In order to account for finite deviations from the initial stress-free state and test the validity of formula (24), numerical calculation of the unstable eigenvalues was also performed via stability analysis that was carried out in the manner described in Ref. 14. Furthermore, several combinations of \( G_{3D} \), \( \delta \) values are eligible in order to recover the experimentally reported critical overpressure. However, the above values were selected, corresponding to a \( 2d \) area dilatation modulus \( \chi = 45\, \text{N/m} \), after a trial and error approach aiming at recovering the static buckling overpressure as well as the amplitude threshold for the onset of dynamic buckling after a small number of radial pulsations leading to transient break-up of the microbubble, Fig. 7(a). In the dynamic simulations bending resistance \( k_B \) was estimated based on the classic formula \( k_B = 3G s^2 / (2(1-\nu^2)) \approx 1.25 \times 10^{-14} \, \text{Nm} \) while shell viscosity was set to \( \kappa_s = 7.2d-9\, \text{N/m*s} = 3\delta \mu_s \) as proposed in Ref. 43. Figure 7 illustrates this process. In particular, panels of Figs. 7(b) and 7(c) provide amplitude time series of shape modes of a contrast agent pulsating in response to an acoustic disturbance with amplitude \( \varepsilon = 15.5 \) and frequency \( \nu_f = 1.7\, \text{MHz} \), as predicted by stability analysis and numerical simulation, respectively. Clearly shape modes start growing within the first period of oscillations after the imposition of the acoustic disturbance while strictly emerging during the compression phase of the pulsation, as expected for the case of dynamic buckling. The shape of the interface progressively becomes more and more distorted in an asymmetric fashion since \( \chi \) is the dominant among the unstable modes. Eventually, the microbubble breaks up due to excessive growth of the unstable modes with a shape sequence resembling those presented in Fig. 6(c). Both aspects of the dynamic response of the microbubble agree well with the experimental observations as far as the amplitude threshold and the mode of break-up are concerned. The Mooney-Rivlin constitutive law was employed for the shell behavior, however \( B \equiv k_B (\chi/3)/R_0^3 \approx 3.7 \times 10^{-4} \) and consequently, as shown in Ref. 14, the static buckling limit is virtually indistinguishable from the one obtained via Hooke’s law. Repeating the simulation with a slightly smaller amplitude, \( \varepsilon = 15 \), we obtain a pattern of damped pulsations without any shape mode excitation. Overall, we should point out that, for the parameter range employed in the above simulation, \( \chi = 45\, \text{N/m} \), \( R_0 = 1.5\, \mu m \), \( k_B = 1.25 \times 10^{-14} \, \text{Nm} \), and \( \kappa_s = 7.2d-9\, \text{N/m*s} \), the resonance frequency for volume pulsations \( \nu_0 \approx 20\, \text{MHz} \gg \nu_f = 1.7\, \text{MHz} \) in which case the critical overpressure for static and dynamic buckling almost coincide as pointed out in Ref. 14. Furthermore, the same methodology was employed in order to recover the critical overpressure reported in Ref. 42 when \( R_0 = 2.5\, \mu m \). Using the same parameters for the shell, i.e., \( \chi = 45\, \text{N/m} \), \( \kappa_s = 7.2d-9\, \text{N/m*s} \), and \( B = 3.7 \times 10^{-4} \), the same critical overpressure and unstable mode were obtained for static and dynamic buckling, i.e., \( \varepsilon \approx 9 \), as in the experimental observations reported in Ref. 42. The same type of instability with \( P_0 \) being the dominant unstable mode, as in Figs. 7(b) and 7(c), was observed for the entire range of initial radii that was examined, thus corroborating the validity of the above described mechanism of dynamic buckling pertaining to the overall picture of contrast agent behavior leading to break-up. In Fig. 7(a) the stability threshold for varying initial radius \( R_0 = R_{SF} \) is shown for the above shell parameters as predicted by the static (squares) and dynamic stability (triangles) analysis, respectively. For comparison it is juxtaposed to the model and experimental results of Ref. 42. Clearly, the static and dynamic buckling thresholds are very close to each other, in agreement with experiments, due to the very large resonance frequency of the polymer based shell.
FIG. 7. (a) Threshold of dynamic buckling is used to interpret experiments on transient break-up reported in Figure 7 from Ref. 42 for different bubble sizes; P, R stand for εPa and R0 in the context of the present study. Estimates of χ and δ/R are obtained in the text. Triangles indicate the threshold for dynamic buckling14 with forcing frequency 1.7 MHz based on stability analysis and simulations; Pf is the unstable mode for all cases shown. Squares indicate the threshold for static buckling to occur based on stability analysis.14 The crosses and the first dotted line correspond to the static buckling threshold as calculated in Ref. 42. The upper dotted line corresponds to the static criterion for shell rupture. The circles correspond to dynamic simulations of pulsating coated bubbles based on the revised Marmottant model proposed in Ref. 42. Finally, the lower and upper staircase patterns correspond to experimental findings in Ref. 42 pertaining to the onset of transient or immediate bubble break-up, respectively. Explosive shape mode growth captured by (b) stability and (c) numerical analysis indicating dynamic buckling, for the case with R0 = 1.5 μm, μs = 0.048 Pa*s, G3D = 300 MPa, k3 = 1.25d-14 N*m, ε = 15.5, b = 0 (MR shell), γ = 1.07, ν = 0.5, Pst = 101325Pa, μs = 0, δ = 50 nm, νf = 1.7 MHz.
When dynamic buckling takes place the time scale of events is much smaller and requires a larger amplitude, as also implied by the findings reported in Ref. 42. Consequently, the scaling of the line that is predicted herein by dynamic stability analysis and numerical simulations is closer to that of the experimental results. Furthermore, the model adopted in the present study captures the dynamics of the microbubble without having to introduce the effect of buckling in the shell constitutive law and does not imply an unrealistically large value of the shell thickness.

B. Mode saturation and transient break-up

A central issue in the dynamics of pulsating contrast agents pertains to the threshold beyond which the microbubble cannot sustain steady pulsations and breaks-up as a result of transient growth of shape modes. Such behavior is of great importance in biomedical imaging applications via contrast agents as it determines the mechanical index threshold for obtaining acoustic signal from pulsating microbubbles and allows for establishing controlled destruction and replenishment procedures in order to observe and quantify perfusion of vital organs. In the following we present an extensive parametric investigation of microbubble dynamics aiming at clarifying this aspect of their response to acoustic disturbances as the sound amplitude varies but also for two different shell types, namely, strain softening and strain hardening shells. The parameter range investigated pertains mainly to lipid shells which tend to exhibit a lower area dilatation modulus in comparison with polymer shells. The case of an initially stress-free shell is first examined followed by an investigation on the effect of pre-stress.

1. Simulations near the threshold of parametric instability

This subsection focuses in the nonlinear evolution of instabilities in the regime of the phase diagram that covers the region beyond the threshold of parametric instability. First, the situation portrayed in Fig. 3 is revisited and it is seen that shape modes start to grow on a time scale that is on the order of that predicted by stability analysis, Fig. 3(a). Furthermore, it is seen that as the dominant unstable eigenmode, P₄, performs saturated pulsations the radial mode, P₀, switches from the steady pulsations predicted for nonlinear radial pulsations to a different steady pulsation mode whereby the radial excursion from the stress free state during compression is slightly but definitely larger than the one obtained during the expansion phase of the pulsation, Figs. 3(b) and 3(c). This was a recurring theme in the present study for the cases for which saturated pulsations were reached by the emerging shape mode. As illustrated in Fig. 3 P₄, i.e., the dominant shape mode according to linear theory for this parameter range, mainly grows during the compressive phase of the radial pulsation of the microbubble. This can be cross-checked by direct examination of the graphs illustrating the time evolution of P₄ and P₀ according to the prediction of linear theory, Fig. 3(a), and based on the nonlinear simulations, Figs. 3(b) and 3(c). In particular, Fig. 3(c) that focuses on the steady pulsation regime in the time series of the dominant shape modes, clearly depicts the coordination of the maxima in the amplitude of P₄ with the minima of P₀. In the context of nonlinear pulsations this is accompanied by energy exchange between P₄ and P₀. Due to harmonic resonance, growth of P₄ occurs mainly during the compression phase that lasts half the period of the forcing. Within this time frame energy is exchanged with the radial mode and this affords saturation of P₄, since the latter does not have the time to absorb more of the available elastic energy and has to share it with P₀. The latter mode exhibits additional compression in order to accommodate the transferred energy, hence the apparent asymmetry in the oscillation of the radial mode.

As the amplitude of the acoustic disturbance was increased the onset of shape oscillations was accelerated as well as the establishment of saturated pulsations by the emerging shape mode and the concomitant additional excursion from equilibrium during compression. Both effects become more intense as the sound amplitude increases. Eventually, as the sound amplitude approached the threshold for dynamic buckling, growth of additional shape modes was observed that could not be controlled by energy exchange thus leading to transient break-up of the microbubble, Fig. 8. As illustrated by Fig. 8(a) presenting the time series of the amplitudes of the dominant modes predicted by linear stability for this parameter set and \( \varepsilon = 3 \), the threshold for dynamic buckling has not yet
been reached; for this type of shell, in order to achieve significant growth of unstable modes within 4-5 periods of the forcing $\varepsilon_{Cr}$ for dynamic buckling is on the order of 4. Rather, growth of P7 and other modes during compression is too fast for nonlinear energy transfer to achieve saturation thus accelerating transient break-up.

When shape modes grow as a result of subharmonic resonance the pattern of saturated pulsations persists when the amplitude exceeds the threshold predicted by parametric stability analysis whereas the extrema in the time evolution of the amplitudes of the emerging shape modes concur with the minima in the amplitude of the radial mode. This is clearly shown by Figs. 9(a)–9(c) illustrating the amplitudes of the shape modes predicted by linear stability and nonlinear oscillations, as well as the shapes acquired by the microbubble in the process of reaching saturation. The shell material is similar to that employed in the simulations presented in Figs. 3–5 and 8, while the forcing frequency is changed to 3.4 MHz. Consequently, the unstable modes have twice as much time to grow in comparison with the situation pertaining to harmonic resonance and attainment of saturation is not as common. However, when saturation is achieved nonlinear energy transfer results in asymmetry in the radial pulsations of the microbubble that is in favor of compression, as is the case with harmonic resonance. Further increase in the sound amplitude results in faster growth of unstable shape modes, the prevailing type of resonance reverts to harmonic in this parameter range, until transient break-up occurs, Fig. 10, long before the onset of dynamic buckling; for this type of shell, in order to achieve significant growth of unstable modes within 4-5 periods of the forcing, $\varepsilon_{Cr}$ for dynamic buckling is predicted by stability analysis to be on the order of 14.

When the coating consists of a strain hardening material, e.g., a lipid bilayer described by the Skalak constitutive law, steady pulsations were not observed in the parameter range examined herein. In this case also, the unstable shape modes arise mainly during the compressive phase of the radial pulsation as illustrated in Fig. 11 for the case of harmonic resonance. Figures 11(a) and 11(b) demonstrate the time evolution of the dominant shape modes as well as the type of resonance recovered both via linear stability, Fig. 11(a), and nonlinear simulations, Fig. 11(b). A slow but sustained growth of the dominant eigenmode is observed leading towards the establishment of steady pulsations albeit very slowly. In the case portrayed in Fig. 11 the sound amplitude is in the supercritical range, but very near the threshold of parametric stability, the growth rate of the emerging modes is slow and the onset of steady pulsation is possible. At the same time the amplitude of the radial pulsation exhibits a slight excursion in favor of compression in the manner described before for strain softening shells. As the sound amplitude is increased well beyond the stability threshold, growth of unstable modes cannot be controlled via energy transfer and the microbubble breaks-up. As can also be gleaned from the shape sequences shown in Fig. 11(d) deviations from sphericity occur mainly during the compression phase of the pulsation, a situation also observed with strain softening shells. However, strain hardening shells become softer during compression and this facilitates deformation and growth of shape modes. This aspect of the shell mechanical behavior explains the difficulty in establishing steady pulsations by microbubbles coated by a strain hardening shell in the range of parametric shape excitation. Consequently, microbubbles of this type tend to exhibit break-up beyond an amplitude threshold that is much smaller than the one signifying the onset of dynamic buckling, via harmonic or subharmonic resonance.

2. Dynamic buckling instability

Experimental observations, Fig. 12(a), reported in Ref. 15 of an MP1950 contrast agent that is coated with a phospholipid membrane at an equilibrium radius $R_0 = R_{SF} = 1.5 \mu m$, insonated with a two-cycle sinusoid with peak negative pressure of 1.2 MPa and a center forcing frequency $\nu_f = 2.4$ MHz, reveal that the microbubble contracts initially, then expands to a triple radius relative to the equilibrium one and subsequently contracts again until near the minimum radius the membrane breaks up producing 5 smaller free bubbles. Inviscid numerical simulations considering the membrane as a free bubble with an adjusted surface tension such that the maximum expansion radius is recovered, show no shape distortion on a time scale that is relevant to the above experiments, thus indicating a different collapse mechanism of the contrast agent with respect to that of a free bubble.
FIG. 8. Shape mode growth indicating transient break-up by (a) linear and (b) numerical analysis; (c) shapes of the shell; $\varepsilon = 3.0$ while the rest of the parameters remain the same as in Fig. 3.
FIG. 9. Case of saturated pulsations via subharmonic resonance. Shape mode growth by (a) linear and (b), (c) numerical analysis; (d) shapes of the shell: $\varepsilon = 5.1, v_1 = 3.4$ MHz while the rest of the parameters remain the same as in Fig. 3.
FIG. 10. Case of transient break-up. Shape mode growth by (a) linear and (b) numerical analysis; (c) shapes of the shell; \( \varepsilon = 7.0 \), while the rest of the parameters remain the same as in Fig. 9.
FIG. 11. Tendency for saturated pulsations via harmonic resonance of a strain hardening shell. Shape mode growth by (a) linear and (b), (c) numerical analysis; (d) shapes of the shell; $R_0 = 3 \mu m$, $\epsilon = 2.9$, $C = 1$ (SK shell), $\nu_1 = 1.7$ MHz while the rest of the parameters remain the same as in Fig. 3.
FIG. 12. Dynamic buckling of a lipid shell. (a) Experimental optical frame images and evolution of the diameter of the oscillation and fragmentation of a contrast agent microbubble (MP1950); all the frames are adapted from Ref. 15. Shape mode growth via (b) linear stability and (c) numerical analysis within the time frame of the experiment; (d) shapes of the microbubble during collapse using progressively finer meshes; \( R_0 = 1.5 \mu m, \mu_s = 1.32 \text{ Pa*s}, G_{3D} = 590 \text{ MPa}, \sigma = 0.051 \text{ N/m}, k_B = 3.45d-13 \text{ N*m}, \varepsilon = 12, b = 0 \) (MR shell), \( v_f = 2.4 \text{ MHz}, \gamma = 1.07, \nu = 0.5, P_{st} = 101325 \text{ Pa}, \mu_l = 0, \delta = 1 \text{ nm}. \)

When the microbubble interface is treated as a shell obeying the Mooney-Rivlin constitutive law with, \( b = 0 \), an adjusted surface elasticity of \( \chi = 1.77 \text{ N/m} \) in order to recover the maximum expansion radius, and \( k_s = 3.96d-9 \text{ N/m*s} \) as predicted by experimental results for this kind of microbubble,\(^{44}\) then in order to capture numerically the shape sequence shown in Fig. 12(a) within the correct time scale, the bending modulus \( k_B \) is set to \( 3.45 \times 10^{-13} \text{ N*m} \), see also Figs. 12(b)
This numerical result is corroborated via both stability analysis, in the manner shown in Ref. 14 and mesh refinement, Fig. 12(d). The dynamic buckling instability appears near the minimum of the bubble radius and depends on the value of the bending modulus, $k_B$. When $k_B$ is increased to $5 \times 10^{-13}$ Nm no shape distortion appears in this time scale and the contrast agent executes spherical oscillations.

It should also be pointed out that for large sound amplitudes, and before the onset of shape modes, strain softening shells exhibit an expansion only type behavior as a result of the shell becoming softer at expansion, see also the time series of $P_0$ in Figs. 12(a)–12(c). This effect is obscured by the onset of shape modes or break-up.

3. Effect of pre-stress

When the protective shell is pre-stressed at the time instant at which the acoustic disturbance is imposed, the dynamic behavior of the microbubble can be significantly altered since the stability thresholds for the onset of parametric excitation or dynamic buckling will be affected. Pre-stress may arise as a result of diffusion of the enclosed gas through the shell into the host fluid after repeated insonations or due to excessive area concentration of the surfactant constituting the shell. In such cases the initial energy content of the microbubble is increased, for fixed initial radius, due to the strain energy of the compressed shell as well as the internal overpressure. In fact, it can be seen by extending linear stability analysis to account for pre-stress as a result of a certain amount of internal pressure loss due to previous isothermal gas diffusion through the shell, that the amplitude threshold for parametric mode excitation and dynamic buckling is decreased with increasing initial pressure loss or, equivalently, increasing amount of pre-stress. This is clearly illustrated by performing stability analysis and numerical simulations for the situations depicted in Figs. 3, 4, and 9, pertaining to harmonic and subharmonic resonance of a lipid monolayer shell, respectively, with the same parameter values as in the above figures while allowing for in plane compressive stresses on the shell. The unstressed equilibrium radius is taken to be $R_{SF} = 4.0 \mu m$ whereas the initial bubble radius is set to $R_0 = R_{Eq} = 3.6 \mu m$ corresponding to an almost 50% pressure loss with respect to the unstressed state where the internal pressure is, roughly, $P_a = 1$ atm. The initial radius is obtained upon application of the normal force balance in the absence of an acoustic disturbance while imposing a pressure difference of $0.5P_a = P_{St} - P_G(t = 0)$ on Eqs. (1a) and (1b); in this case $P_{St} = P_a$. A spherical initial configuration is adopted assuming that the initial compression is below the threshold required for the onset of static buckling. In this fashion linear stability and simulations, Fig. 13, verify the reduction in the parametric stability threshold with respect to the case shown in Figs. 3 and 4. Assuming an initial pressure loss of 50% shape mode pulsations are obtained for sound amplitude as low as $\varepsilon = 0.9$, Figs. 13(a)–13(c); the amplitude threshold for parametric excitation in the absence of pre-stress was estimated to be 1.7 via Floquet analysis and nonlinear simulations. The shape mode which initially dominates via harmonic resonance is $P_3$, as can also be gleaned by monitoring the microbubble shape within a period of the forcing, Fig. 13(d). However, additional shape modes become unstable due to non linear interaction and their presence is manifested in the eigenmode analysis of shape variations, Fig. 13(e). Steady pulsations eventually prevail via a similar energy transfer process as the one described in Figs. 3 and 4, as well as via nonlinear interaction between neighboring unstable modes. As the sound amplitude increases transient break-up is observed as in the case without pre-stress, owing to the increased growth rate of the unstable shape modes. It should be noted that in the presence of pre-stress the boundary between parametric mode excitation and dynamic buckling becomes blurred as instability sets in much faster for both cases triggering a larger number of unstable modes, while very large overpressures are observed that are comparable with the value required for static buckling to occur. Therefore, establishing a steady pulsation is more difficult in this context since energy transfer occurs among a larger number of unstable shape modes that are liable to overthrow the stability of the microbubble.

A similar behavior is recovered by the stability analysis and simulations shown in Fig. 14 regarding the reduction in the amplitude threshold for subharmonic mode excitation in comparison with Fig. 9 where no pre-stress is initially present, $\varepsilon = 3.5$ vs 5.1 in Fig. 9. Mode saturation is
FIG. 13. Parametric stability threshold and saturated pulsations at reduced sound amplitude, for a prestressed MR shell in harmonic resonance. Shape mode growth by (a) linear and (b), (c) numerical analysis; (d) shapes of the shell; $R_{eq} = 4.0 \mu m$, $R_0 = 3.6 \mu m$, $\varepsilon = 0.9$, while the rest of the parameters remain the same as in Fig. 3.
FIG. 14. Parametric stability threshold and saturated pulsations at reduced sound amplitude, for a prestressed MR shell in subharmonic resonance. Shape mode growth by (a) linear, (b), (c) numerical analysis and (d) shapes of the shell; $R_{SF} = 4 \mu m, R_0 = 3.6 \mu m, \varepsilon = 3.5$, while the rest of the parameters remain the same as in Fig. 9.
observed here also, within the time frame of the numerical simulation, characterized by the energy transfer process accompanied by additional excursion from equilibrium during the compressive phase of the pulsation. As the sound amplitude is further increased transient break-up prevails due to rapid growth of a number of unstable eigenmodes.

When the response of a pre-stressed shell that obeys a strain hardening constitutive law is simulated, the pattern of earlier destabilization of the microbubble is recovered leading to parametric excitation of a number of unstable modes and transient break-up without any tendency for mode saturation. This is a similar situation with the simulations in the absence of pre-stress with the difference that now growth of unstable modes is accentuated. They all participate in the nonlinear energy transfer between modes thus disallowing mode saturation to take place.

Overall, nonlinear simulations reveal a tendency of the microbubble to undergo transient break-up over a relatively wider amplitude range than expected by linear analysis. In the latter case break-up is predicted as the amplitude threshold for dynamic buckling to occur is exceeded. Nevertheless, experiments indicate significant shape mode excitation leading to saturation even at relatively low amplitudes after repeated sound pulses. In most of the above cases the microbubble also exhibits compression only behavior with the compression phase being significantly favored over the expansion phase. Furthermore, it is during the compression phase of the pulsation that the microbubble exhibits any significant deviation from the spherical configuration. The simulations presented so far capture the onset of saturated pulsations followed by transient break-up as the sound amplitude increases and predict the asymmetry as regards shape deviations from spherosymmetry in favor of compression reported in experiments. Furthermore, they recover the onset of axisymmetric shape oscillations for relatively low sound amplitudes, also reported in experiments, by introducing the effect of pre-stress that lowers the stability threshold. The above findings seem to corroborate the validity of the strain softening shell model, especially for lipid shells, which in conjunction with bending stiffness can predict shape oscillations, saturated pulsations and transient break-up. The only outstanding issue pertaining to the dynamic response of lipid shells is associated with the “compression only” behavior, Fig. 15, that cannot be reconciled with the mechanical behavior exhibited by strain softening type shells; see also simulations of radial pulsations of microbubbles coated by strain softening and strain hardening shells presented in Ref. 4. In fact, Fig. 15 exhibits an interesting shift between the two types of behavior with increasing sound amplitude, captured by optical measurements of a pulsating coated microbubble. The simulations presented in this section can account for a certain level of compression only behavior during saturation but it is not proportionate with the extent observed in experiments. This type of pattern requires a constitutive law of the strain hardening type that makes the shell softer at compression.

In an effort to accommodate such a breadth of effects over a relevant parameter range, and motivated by recent studies that highlight the presence of folding instabilities in lipid monolayers...
subject to compressive stresses, we investigate the effect of dynamically changing the constitutive law that characterizes the mechanical behavior of the shell on the microbubble dynamics. The appearance of bilayer or even multilayer structures is reported in the latter study with a wavelength on the order of micrometers. As is known from studies on the mechanical behavior of red blood cells, the protective membrane that surrounds the cytoplasm is a lipid bilayer that is more difficult to stretch as it expands while the opposite happens at compression, i.e., it exhibits strain hardening behavior. Consequently, we proceed to assume that the shell is originally strain softening, i.e., it becomes softer upon expansion and harder upon compression, as expected for a lipid monolayer whose lipid molecules are pushed farther apart with decreasing external pressure whereas they are more tightly arranged when subjected to external overpressure. However, beyond a certain level of deformation, determined in an ad hoc fashion in the present study when the local radius of curvature

FIG. 16. Compression only behavior by switching from an MR to an SK shell type beyond a cut-off amplitude in the emerging shape modes. (a) Evolution of $P_0$ and $P_4$ shape modes as the cut-off amplitude that is introduced for switching from the MR to the SK constitutive law decreases from 0.06 and 0.01; $b = 0$ for the MR shell, $C = 1$ for the SK shell, while the rest of the parameters remain the same as in Fig. 14. The case without changing the constitutive law (CL) is also presented. (b) A zoom-in is also provided for the saturation phase.
drops below a preset value, the lipid molecules locally get close enough to form bilayer structures that alter the mechanical behavior of the shell rendering it strain hardening. There are several indications in the literature of lipid monolayers pointing towards this direction,\textsuperscript{45, 47, 48} hence we tested the consequences of such a phase transition instigated by the dynamics of coated microbubbles.

To this end we repeated the simulations for a pre-stressed shell shown in Fig. 14 allowing for a change in the constitutive law as the amplitude of any shape mode exceeded a fixed threshold. The amplitudes of the shape modes were obtained by performing Fourier decomposition of the shape in the form of Legendre polynomials; they constitute the appropriate eigenfunctions for axisymmetric problems in spherical geometry, see also Ref. 14. Figure 16 illustrates the stabilizing effect that such a phase transition can have on the dynamics of the bubble as a function of the cut-off amplitude. As the cut-off amplitude is set to 0.06 shell behavior switches to strain hardening at the time instant for
which the amplitude of the dominant shape mode, $P_4$, reaches this value and a significant reduction in the amplitude of all the emerging modes is achieved in comparison with the pre-stressed shell shown in Fig. 14. Further reduction of the cut-off amplitude to 0.01 mitigates, the onset of shape modes, as shown in Fig. 16(a), and extends the transient time before a state of steady shape oscillations sets in, a zoom in on the phase of saturated pulsations is provided in Fig. 16(b). Furthermore, compression only behavior in the radial time series is accentuated. At first glance this may sound counter-intuitive since, as shown throughout this section, shells obeying the Skalak law right from the onset of the pulsating motion rarely reach saturation. The reason for this drastic change illustrated in Fig. 16 lies in the fact that when pre-stress is present the thresholds for parametric mode excitation and dynamic buckling approach each other. Shape modes arise mainly during compression and strain hardening shells can acquire very small radii during compression since they become softer during this phase of their pulsation. As a result viscous stresses can grow significantly on the shell thus preventing any further growth of shape modes. This is also the reason why shells obeying the Skalak law exhibit a very large amplitude threshold for the onset of dynamic buckling. In this context, our simulations indicate that mode saturation, or sustained pulsation without break-up, is possible for sound amplitude as large as $\varepsilon = 5.0$ and the same amount of pre-stress, Figs. 17(a) and 17(c), whereas without the change in the constitutive law the microbubble exhibits transient break-up, Figs. 17(b) and 17(d).

V. CONCLUSIONS

Nonlinear stability of pulsating contrast agents was examined using the method of boundary elements accounting for inertia effects and pressure changes in the host fluid, coupled with stretching and bending elastic forces on the shell that coats the microbubble. Owing to the small size of the microbubble and the large shell viscosity relatively to that of the host fluid, shell viscosity is the only damping mechanism introduced.

The threshold for static buckling and the nature of the emerging eigenmodes were recovered when a step change in the external pressure was imposed. Similarly, the concurrence of static and dynamic buckling thresholds for contrast agents pulsating at large amplitudes and forcing frequencies that are much lower than their resonance frequency was ascertained by comparison with available experimental and theoretical studies. In this fashion, the applicability of the model proposed in the present study for the description of the acoustic response of polymer based shells, which are characterized by a very large area dilatation modulus, is verified.

In the context of the acoustic response of contrast agents coated with lipid shells, they are characterized by a smaller area dilatation modulus, to disturbances in the ultrasonic range linear stability results pertaining to the onset of parametric mode excitation and dynamic buckling were recovered and extended to investigate the distinction between saturated pulsations and transient break-up. When the sound amplitude is slightly above the threshold for parametric mode excitation mode saturation is eventually achieved by the dominant eigenmode predicted by linear stability. This is afforded via exchange of elastic energy with the radial mode, mainly during compression which is when most of the growth of unstable modes takes place,that generates additional compression of the bubble volume while stabilizing the emerging shape mode. Pulsations at harmonic resonance are more amenable to this dynamic behavior since unstable modes have more time to grow when subharmonic resonance takes place. Shells exhibiting strain hardening behavior rarely exhibit saturated pulsations in this fashion because, as soon as parametric mode excitation takes place, further growth of shape modes occurs quite fast during the compression phase due to the fact that such shells become softer at compression. As the sound amplitude further increases and before the threshold for dynamic buckling is reached both types of microbubbles, i.e., coated by strain hardening or strain softening shells, exhibit transient break-up due to simultaneous growth of several unstable modes that exchange and absorb the available energy. As the sound amplitude is further increased break-up as a result of dynamic buckling is captured numerically and validated against experimental data. This type of behavior captures most aspects of the dynamic response of lipid shells by treating the coating as a strain softening material. Identifying the threshold between steady pulsations and transient break-up is very useful for the design of future generations.
of contrast agents since it is critical in determining the mechanical index of the applied ultrasound pulse for obtaining acoustic response and subsequently destroying the microbubbles in order to study and, possibly, quantify perfusion of vital organs. However, the amplitude threshold for the onset of saturated shape pulsations is relatively large when compared against experimental reports.\textsuperscript{7}

The presence of pre-stress reduces the amplitude threshold for the onset of parametric mode excitation and dynamic buckling, in agreement with experimental observations. However, it also reduces the gap in the amplitude thresholds pertaining to these two instability mechanisms. Growth of shape modes occurs much faster while a large number of shape modes become unstable within the same parameter range. As a result the window for sustained shape mode oscillations and mode saturation is significantly restricted. In addition, compression only behavior is not captured to the extent that is reported in the literature.\textsuperscript{7,10} Nevertheless, based on the results obtained in this study as well as the available literature the conjecture regarding the mechanical behavior of lipid shells as strain softening is corroborated. In other words, their elasticity increases as the area concentration of the monolayer increases, i.e., at compression, and this facilitates the interpretation of almost all the recorded behavior of such bioparticles.\textsuperscript{4,7,9,13–15}

Switching from a strain softening to a strain hardening mechanical behavior, as regions of reduced radius of curvature dynamically appear on the shell, signifies a phase transition of the shell material corresponding to a folding instability leading to formation of lipid bilayer structures in such regions. Consequently, additional compression of the microbubble is achieved that damps the growth rate of shape modes due to shell viscosity, and extends the parameter range over which sustained shape pulsations and mode saturation takes place. This pattern can be observed even at low amplitudes, especially when the shell is pre-stressed, and, depending on the extent of the stabilization affected by this transition, it persists over a relatively wide range of sound amplitudes. Furthermore, compression only type behavior is obtained in the simulations within the time interval over which the shell is described by a strain hardening constitutive law. In this fashion, available experimental observations indicating that sustained shape oscillations exhibiting compression only behavior can be achieved by contrast agents coated with lipid mono-layers for sound amplitudes that are too small based on linear stability analysis,\textsuperscript{7} can be accommodated by assuming a certain amount of pre-stress and allowing for a phase transition from strain softening to strain hardening behavior. The latter transition is imposed in an \textit{ad hoc} fashion in the present study and further research is required to properly describe the shell elastic energy so that it captures folding instabilities that generate bi or even multilayer structures as stretching and bending of the shell take place.

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\textsuperscript{7} M. Overvelde, “Ultrasound contrast agents-dynamics of coated microbubbles,” Ph.D. dissertation (University of Twente, 2009).


