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Study of the Static Response of a Coated Microbubble Under the AFM: Numerical & Asymptotic Analysis

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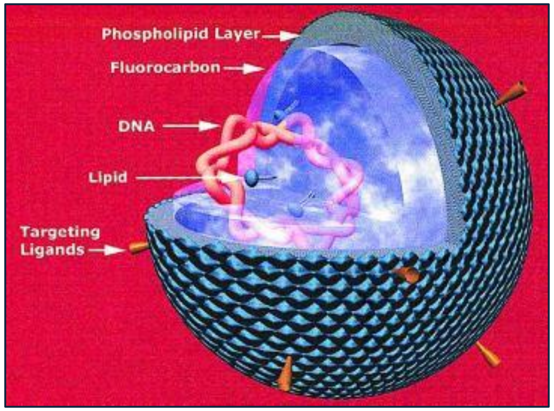
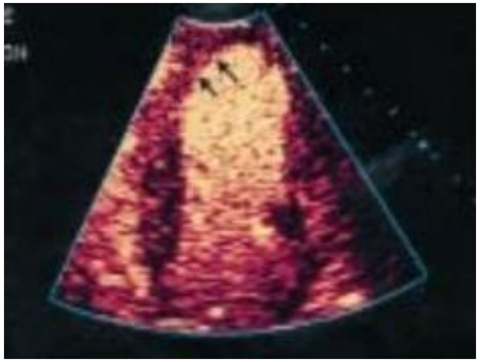
Outline

- Introduction
- Mathematical Modeling
- Numerical Analysis
- Results
- Conclusions

- Elastic coating (Polymer or Lipid)
- Initial Diameter ~ 2-5 μm
- Initial Thickness ~ 1-30 nm
- Strong Backscattered Acoustic Signal
- Biocompatibility

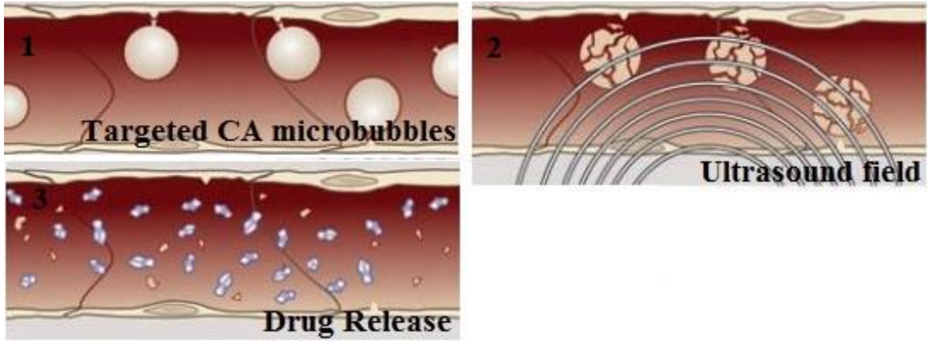


➢ Medical Imaging-Diagnostic Applications (Heart, Kidney, Liver)

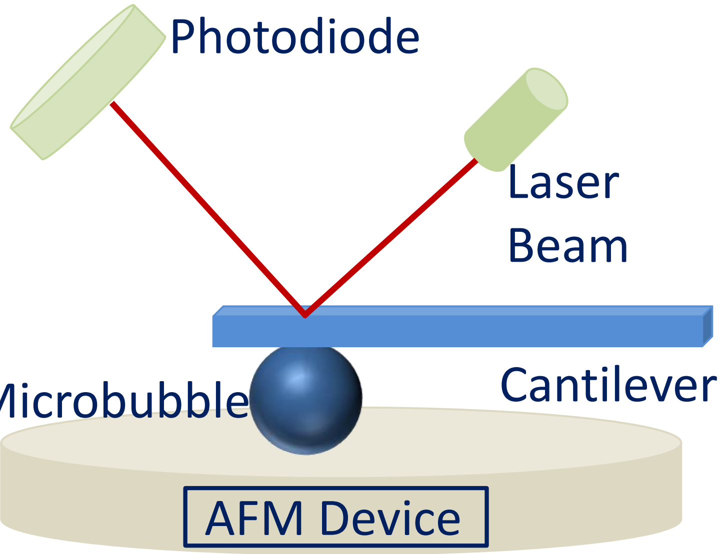


[Blomley et al., *Br. Med. J.*, 2001]

➢ Treatment with microbubbles-Drug or gene delivery

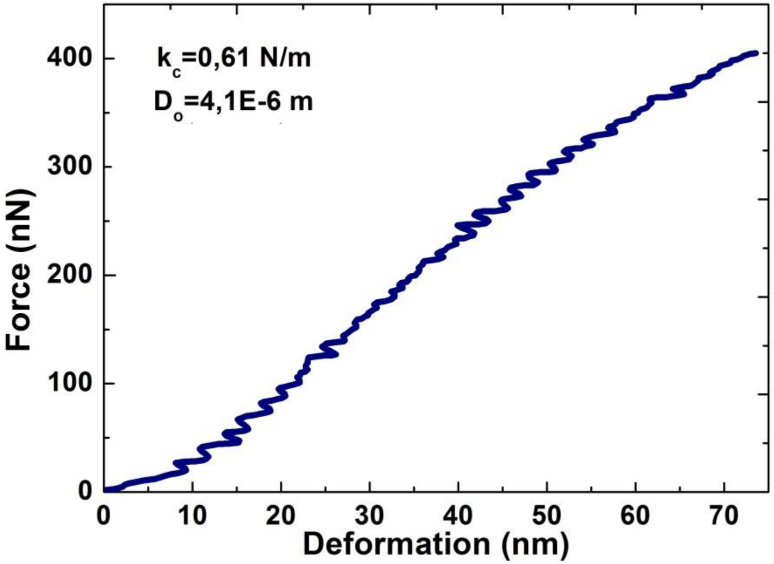


[Ferrara et al., *Annu. Rev. Biomed. Eng.*, 2007]



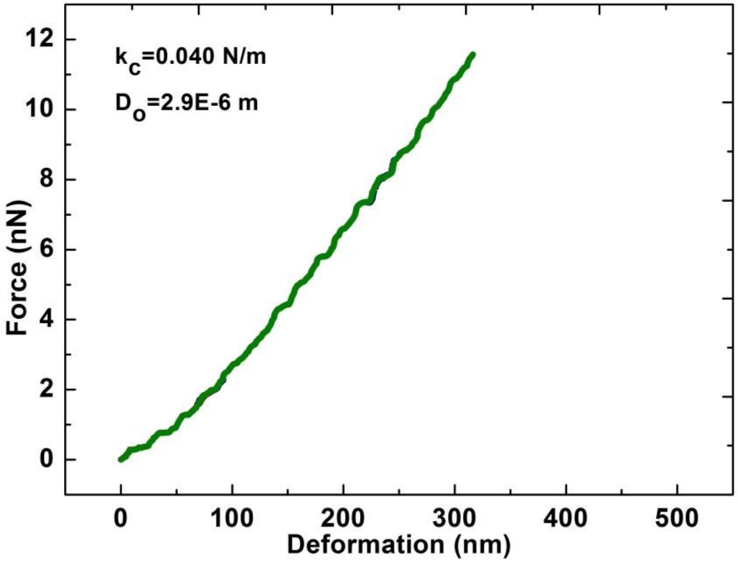
Experimental Investigation of the Mechanical Properties with the Atomic Force Microscope (AFM).

Microbubble covered with polymer



[Glynos et al., *Langmuir*, 2009]

Microbubble covered with lipid

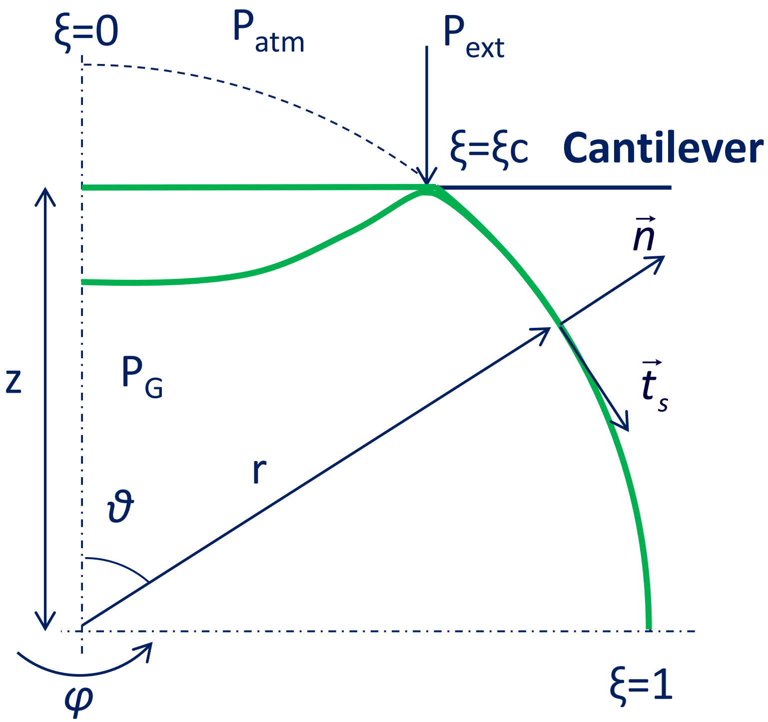


[Buchner Santos et al., *Langmuir*, 2012]

Scope of the Present Work

- Simulation of the static response of CA microbubbles.
- Comparison with AFM experimental measurements.
- Estimation of the elastic properties (Young’s & bending modulus).
- Optimization of the design of microbubbles

Classic Contact Problem (Polymeric Bubbles)



Deformation=$z(\xi_c)$

↓

Comparison against experiments

Normal and Tangential Force Balance

$$\Delta\vec{F} = \Delta\vec{P} \Rightarrow \begin{cases} \Delta\vec{F}_N = (P_G - P_{atm})\underline{\underline{I}}\cdot\vec{n} \\ \Delta\vec{F}_s = \vec{0} \end{cases}$$

$$\Delta\vec{F} = -\vec{\nabla}_s\cdot\left(\tau_{ss}\vec{t}_s\vec{t}_s + \tau_{\varphi\varphi}\vec{t}_\varphi\vec{t}_\varphi + q\vec{t}_s\vec{n}\right) + \sigma\vec{\nabla}_s\cdot\vec{n}$$

$$\vec{q} = \vec{\nabla}_s\cdot\underline{\underline{m}}\cdot\left(\underline{\underline{I}} - \vec{n}\vec{n}\right) \quad ; \quad q^+(\xi_c) + q^-(\xi_c) = P_{ext}$$

Kinematic Condition

$z_\xi = 0$ at $\xi = \xi_c$

Isothermal Gas Compression

$$P_{G0}V_0^\gamma = P_G V^\gamma$$

Constitutive Equation: Hook's Law

$$\tau = G_s\frac{1+\nu}{1-\nu}\left(\lambda^2 - 1\right)$$

$$m_i = k_b\left(K_i + \nu K_j\right)/\lambda_j, \quad K_i \equiv \lambda_i k_i - k_i^R$$

Effect of pre-stress

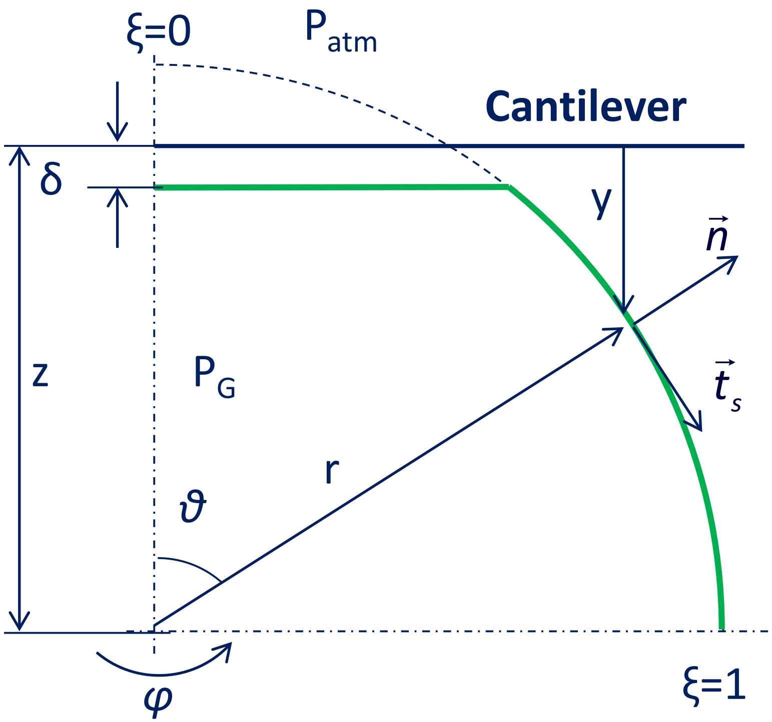
$$\lambda_i = \frac{dS}{dS^{SF}}, \text{ where } \lambda_i^0 = \frac{dS^0}{dS^{SF}} \neq 1$$

Boundary Conditions

$r_\xi = \vartheta_{\xi\xi} = 0$ at $\xi = 0$ and 1

[Pozrikidis, *J. Fluid Mech.*, 2001]
[Tsiglifis & Pelekasis, *Phys. Fluids*, 2011]
[Barthès-Biesel et al., *J. Fluid Mech.*, 2002]
[Updike & Kallins, *Trans. ASME*, 1970, 1972, 1972]

Adhesive Potential-Bubble Covered With Elastic Shell



Deformation=z(F=0)-z

↓

Comparison against experiments

Normal and Tangential Force Balance

$$\Delta\vec{F} = \Delta\vec{P} \Rightarrow \Delta\vec{F}_N = \left(P_G - P_{atm}\right)\underline{\underline{I}}\cdot\vec{n} \quad \& \quad \Delta\vec{F}_s = \vec{0}$$

$$\Delta\vec{F} = -\vec{\nabla}_s\cdot\left(\tau_{ss}\vec{t}_s\vec{t}_s + \tau_{\varphi\varphi}\vec{t}_\varphi\vec{t}_\varphi + q\vec{t}_s\vec{n}\right) + \vec{\nabla}\cdot\left[\left(W+\sigma\right)\vec{n}\vec{n}\right]$$

$$\vec{q} = \vec{\nabla}_s\cdot\underline{\underline{m}}\cdot\left(\underline{\underline{I}} - \vec{n}\vec{n}\right)$$

$$W = W\left(y\right) = W_o\left[\left(\frac{\delta_A}{y}\right)^4 - 2\left(\frac{\delta_A}{y}\right)^2\right]$$

Isothermal Gas Compression

$$P_{G0}V_0^{\gamma} = P_G V^{\gamma}$$

Constitutive Law: Mooney-Rivlin

$$\tau_{ij} = \frac{G_s}{3\lambda_i\lambda_j}\left[\lambda_i^2 - \frac{1}{\lambda_i^2\lambda_j^2}\right]\left[1 + b\left(\lambda_j^2 - 1\right)\right]$$

$$m_i = k_b\left(K_i + \nu K_j\right)/\lambda_j, \quad K_i \equiv \lambda_i k_i - k_i^R$$

Effect of pre-stress

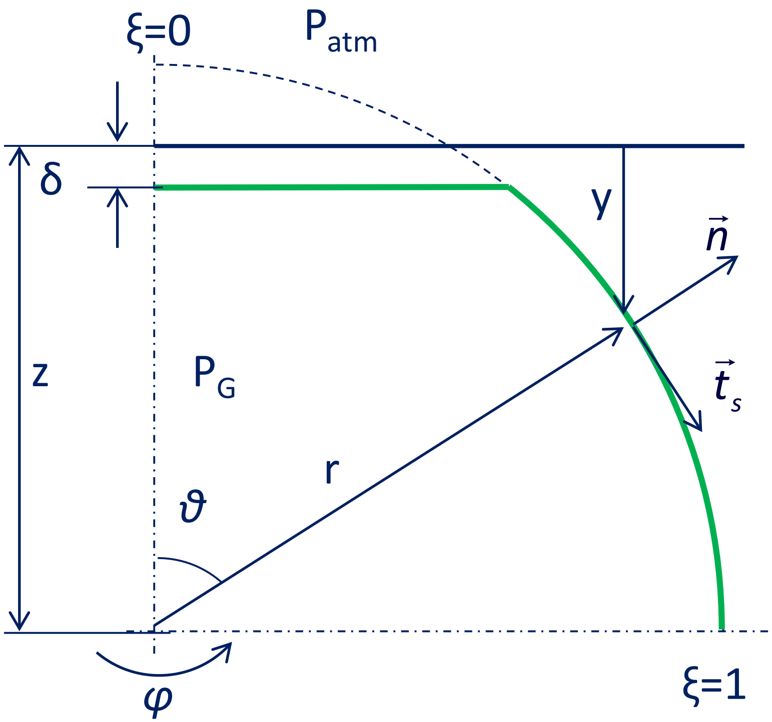
$$\lambda_i = \frac{dS}{dS^{SF}}, \ \text{where} \ \lambda_i^0 = \frac{dS^0}{dS^{SF}} \neq 1$$

Boundary Conditions

$$r_\xi = \vartheta_{\xi\xi} = 0 \ \text{at} \ \xi = 0 \ \text{and} \ 1$$

[Blount et al., *Proc. R. Soc. A*, 2013]

Adhesive Potential-Free Bubble



Deformation=z(F=0)-z

↓

Comparison against experiments

Normal Force Balance

$$P_G - P_{atm} = 2H(\sigma - W) + \frac{\partial W}{\partial n}$$

$$W = W(y) = W_o\left[\left(\frac{\delta_A}{y}\right)^4 - 2\left(\frac{\delta_A}{y}\right)^2\right]$$

Arc-Length

$$ds^2 = (rd\vartheta)^2 + dr^2$$

Isothermal Gas Compression

$$P_{G0}V_0^\gamma = P_G V^\gamma$$

Boundary Conditions

$$r_\xi = \vartheta_{\xi\xi} = 0 \text{ at } \xi = 0 \text{ and } 1$$

[Chamakos, Kavousakis & Papathanasiou, *Soft Matter*, 2013]

Finite Elements

Weak Form-Classic contact problem

$$R_1 = \int_0^1 \left[\left(k_s \tau_{ss} + k_\varphi \tau_{\varphi\varphi} + \sigma 2H + P(\xi) + P_{atm} - P_G \right) B_i r \sin\vartheta s_\xi - \frac{\sigma\left(B_{i,\xi\xi} s_\xi - B_{i,\xi} s_{\xi\xi} \right)}{s_\xi^2} - \frac{m_\varphi B_{i,\xi} \sigma_\xi}{s_\xi} \right] d\xi + M_{BT}$$

$$R_2 = \int_0^1 \left[\tau_{ss} B_{i,\xi} \sigma + B_i \sigma_\xi \tau_{\varphi\varphi} + \sigma m_s \left(k_{s,\xi} B_i + k_s B_{i,\xi} \right) + k_s m_\varphi B_i \sigma_\xi \right] d\xi + N_{BT}$$

$$R_3 = P_G V^\gamma - P_{atm} V_0^\gamma$$

where

$\xi = 0 : (\vartheta = 0) \quad M_{BT} = 0$ and $N_{BT} = 0$

$$\xi = 1 : \left(\vartheta = \frac{\pi}{2} \right) \quad M_{BT} = \frac{\sigma m_s B_{i,\xi}}{s_\xi} - \sigma q B_i \quad \textit{and}$$

$$N_{BT} = -\left[k_s m_s + \tau_{ss} \right] \sigma B_i$$

$$s_\xi = \frac{ds}{d\xi} = \sqrt{r^2 \vartheta_\xi^2 + r_\xi^2} \; ; \; \sigma = r \sin\vartheta \; ; \; \sigma_\xi = \frac{d\sigma}{d\xi} = r_\xi \sin\vartheta + r\vartheta_\xi \cos\vartheta$$

Finite Elements

Weak Form-Adhesive Potential with Elasticity

$$R_1 = \int_0^1 \left[\left(k_s \tau_{ss} + k_\varphi \tau_{\varphi\varphi} + (\sigma - W) 2H + P_{atm} - P_G \right) B_i r \sin\vartheta s_\xi - \frac{\sigma \left(B_{i,\xi\xi} s_\xi - B_{i,\xi} s_{\xi\xi} \right)}{s_\xi^2} - \frac{m_\varphi B_{i,\xi} \sigma_\xi}{s_\xi} + \frac{\partial W}{\partial n} \right] d\xi + M_{BT}$$

$$R_2 = \int_0^1 \left[\tau_{ss} B_{i,\xi} \sigma + B_i \sigma_\xi \tau_{\varphi\varphi} + \sigma m_s \left(k_{s,\xi} B_i + k_s B_{i,\xi} \right) + k_s m_\varphi B_i \sigma_\xi + \frac{\partial W}{\partial s} \right] d\xi + N_{BT}$$

$$R_3 = P_G V^\gamma - P_{atm} V_0^\gamma$$

Weak Form-Adhesive Potential for a Free Bubble

$$R_1 = \int_0^1 \left[2H(\sigma - W) + P_{atm} - P_G + \frac{\partial W}{\partial n} \right] B_i r \sin\vartheta s_\xi d\xi$$

$$R_2 = \int_0^1 \left[S_{\max} - \left(r^2 \vartheta_\xi^2 + r_\xi^2 \right)^{0.5} \right] B_i r \sin\vartheta s_\xi d\xi$$

$$R_3 = P_G V^\gamma - P_{atm} V_0^\gamma$$

Finite Elements

- **Method of Weighted Residuals:** $\underline{\underline{J}} \cdot \vec{c} = \vec{R}$
  $\underline{\underline{J}}$: Jacobian Matrix
  $\vec{c}$: Uknown coefficients
  $\vec{R}$: Residuals

- **Basis Functions:**
  B-Cubic Splines
  $$B_i\left(t_j\right) = \begin{cases} 4, & j = 1 \\ 1, & j = i \pm 1 \\ 0, & j = i \pm 2 \end{cases}$$

- **Calculation of Integrals:** 4 Points Gauss Quadrature

- **Solution of Linear System:** Newton-Raphson Iterations
  Simple or Arc-Length Continuation

- **Validation:** Calculation of the critical buckling load and comparison with previous analytical or experimental results.

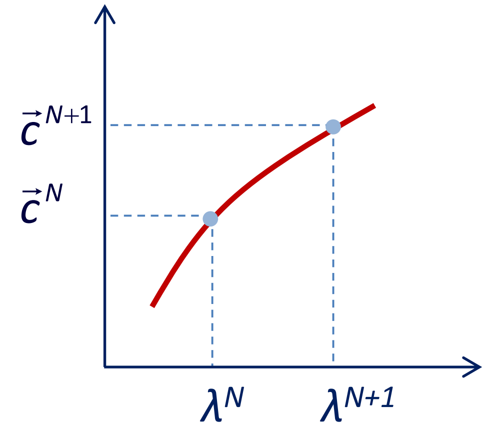
[Pelekasis, Manolis, Tsamopoulos, *Phys. Fluids,* 1990]
[Tsiglkifis & Pelekasis, *Phys. Fluids,* 2011]
[Lytra & Pelekasis, *Fluid Dyn. Res.*, 2014]

Continuation of the solution

Simple Continuation:

$$\lambda^{N+1} = \lambda^{N} + \Delta\lambda$$

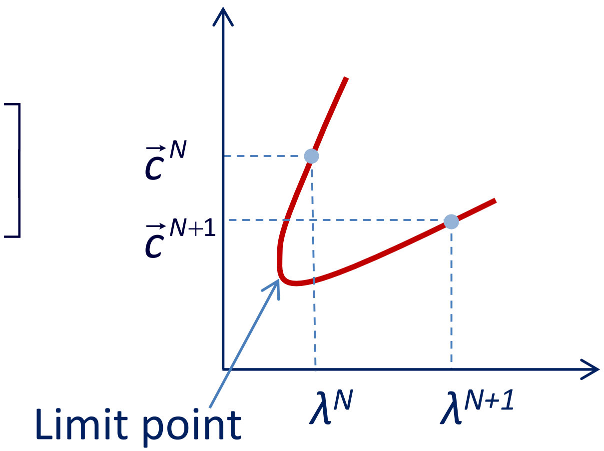
Initial guess for the new solution (N+1): $\vec{c}^{\,N+1} = \vec{c}^{\,N}$



Arc-Length Continuation:

$$\begin{bmatrix} [J] & \vec{R}_\lambda \\ \vec{N}_c & N_\lambda \end{bmatrix} \begin{bmatrix} \vec{c} \\ \lambda \end{bmatrix} = \begin{bmatrix} \vec{R} \\ N \end{bmatrix} \quad \text{and} \quad \begin{bmatrix} [J] & \vec{R}_\lambda \\ \vec{N}_c & N_\lambda \end{bmatrix} \begin{bmatrix} \partial\vec{c}/\partial s \\ \partial\lambda/\partial s \end{bmatrix} = \begin{bmatrix} \partial\vec{R}/\partial s \\ \partial N/\partial s \end{bmatrix}$$

$$N = \left(c_i^{N+1} - c_i^{N}\right)^2 + \left(\lambda^{N+1} - \lambda^{N}\right)^2 - \Delta s^2$$



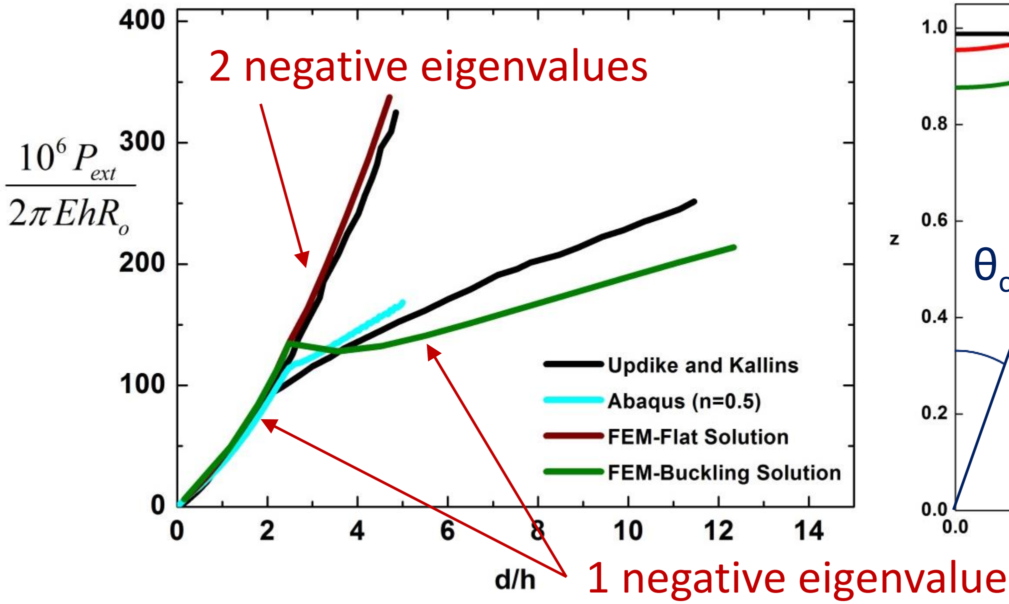
Initial guess for the new solution (N+1):

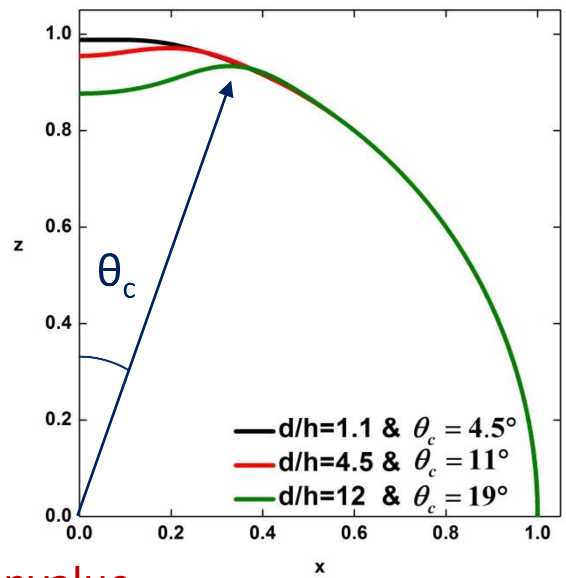
$$\vec{c}^{\,N+1} = \vec{c}^{\,N} - \frac{\partial \vec{c}^{\,N}}{\partial s}\Delta s$$

$$\lambda^{N+1} = \lambda^{N} - \frac{\partial \lambda^{N}}{\partial s}\Delta s$$

Initial Guess → Newton-Raphson Iterations → Convergence

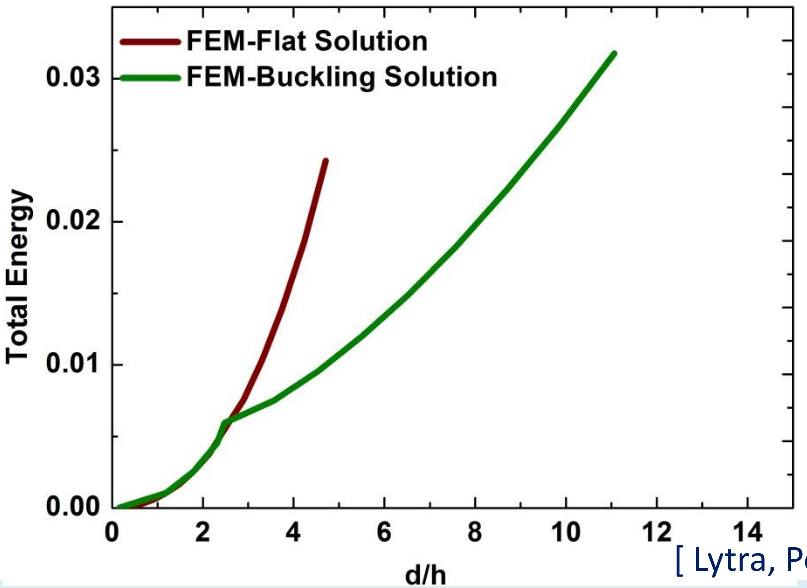
Validation of Classic Contact Modeling





$E = 10^9\ Pa$

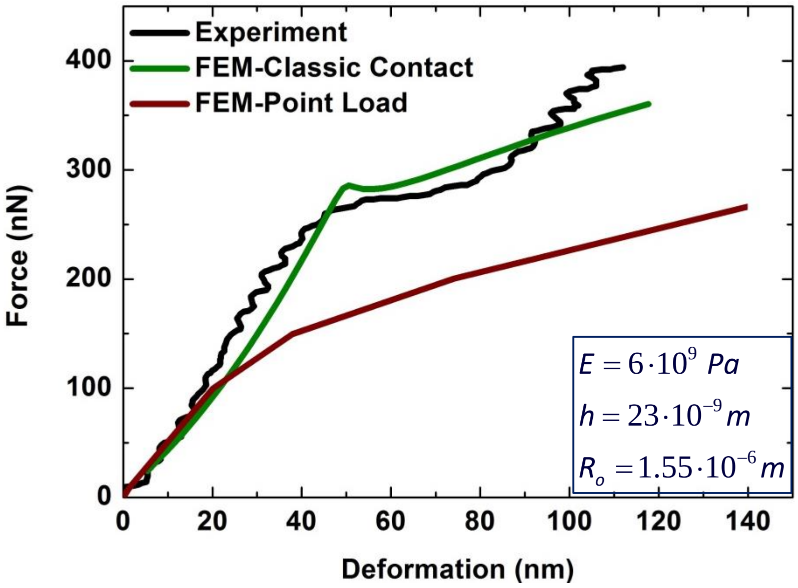
$R/h = 100$

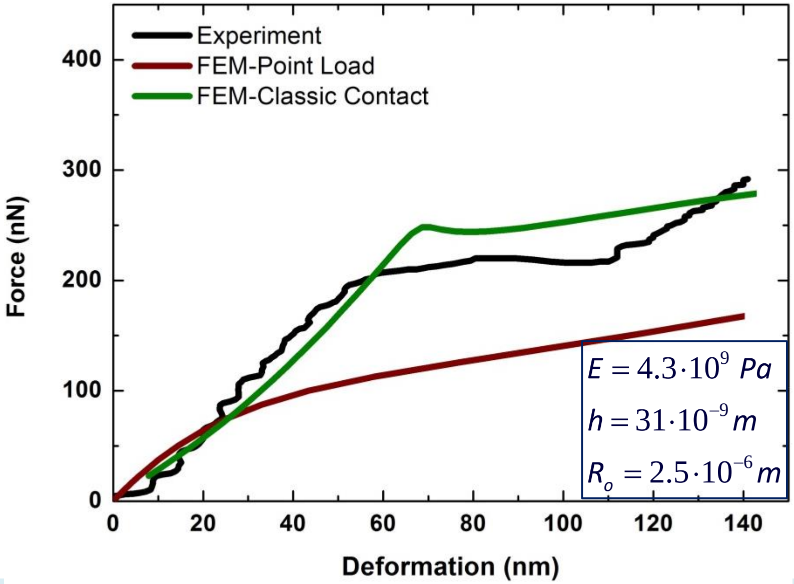


- Buckling point by FEM: (2.5, 130) & θ_c=9°
- Buckling point by U&K: (2.1,100) & θ_c=8°
- The buckling FEM curve corresponds to a solution with the same number of negative eigenvalues with the flat curve before buckling.

[Updike & Kallins, *Trans. ASME*, 1970, 1972, 1972]
[Lytra, Pelekasis, Zafiropoulou, Zisis, Giannakopoulos, *8th GRACM Full Paper*]

Classic Contact Modeling-AFM Data of Polymeric Bubbles



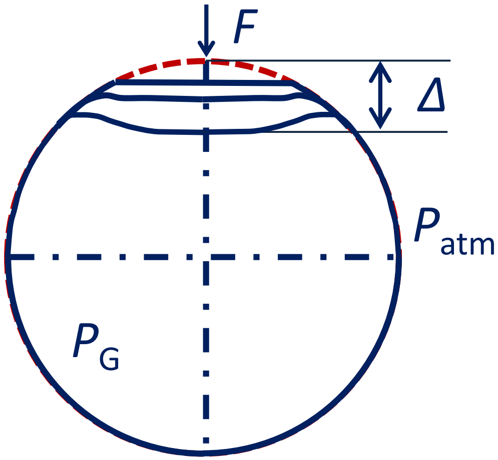


- Linear region - flat shape.
- Non-linear region - buckled-shell.
- The simulation can capture the experimental data.
- The amount of pre-stress explains the different response of experimental curves.
- The discrepancy in higher values of deformation is probably due to 3D-effects.

[Glynos et al., *Langmuir*, 2009]
[Lytra, Pelekasis, Sboros, Glynos, Koutsos, *Procedia IUTAM*, 2015]

Asymptotic Analysis for Polymeric Bubbles

Point Load



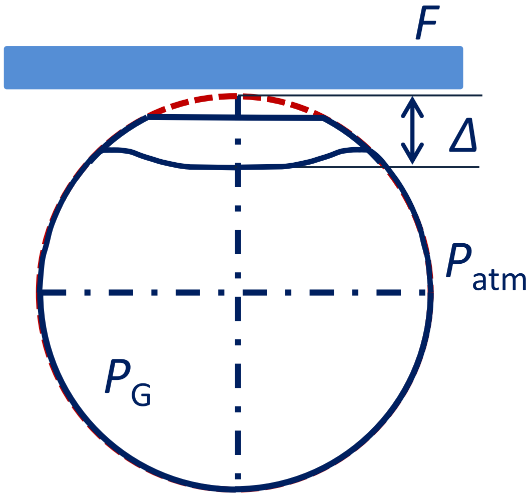
Reissner's eq. $$F = \frac{4}{\left[3\left(1-\nu^2\right)\right]^{0.5}} \frac{Eh^2}{R_o} \Delta$$

[Reissner, *J. Math. Phys.*, 1946]

Pogorelov's eq. $$F = \left[\frac{3.56E^2h^5}{\left(1-\nu^2\right)R_o^2}\Delta\right]^{0.5}$$

[Pogorelov, *Am. Math. Soc.*, 1988]

Plane Contact

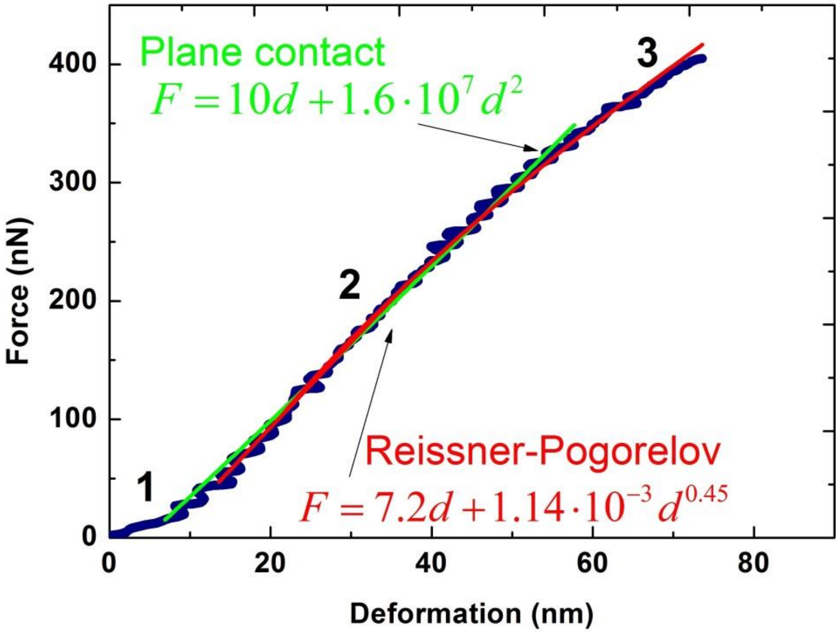


Stage I: $$F = \frac{4}{\left[3\left(1-\nu^2\right)\right]^{0.5}} \frac{Eh^2}{R_o} \Delta + 0.06543\frac{Eh}{R_o}\Delta^2$$

Stage II: $$F = 3.807\frac{Eh^3}{\left(1-\nu^2\right)R_o}\left(\frac{\Delta\sqrt{1-\nu^2}}{h}\right)^{0.5}$$

[Lytra, Pelekasis, Zafiropoulou, Zisis, Giannakopoulos, *8th GRACM Full Paper*]

Elastic Properties Estimation - Polymeric Bubbles



Reissner's eq. **Pogorelov's eq.**

$$F = \frac{4}{\left[3\left(1-v^2\right)\right]^{0.5}} \frac{Eh^2}{R_o} \Delta \; ; \; F = \left[\frac{3.56 E^2 h^5}{\left(1-v^2\right) R_o^2} \Delta \right]^{0.5}$$

Plane Contact:

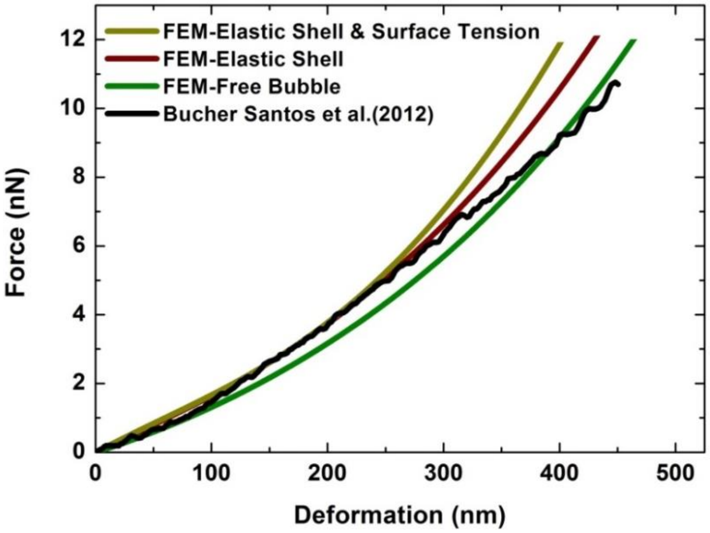
$$F = \frac{4}{\left[3\left(1-v^2\right)\right]^{0.5}} \frac{Eh^2}{R_o} \Delta + 0.06543 \frac{Eh}{R_o} \Delta^2$$

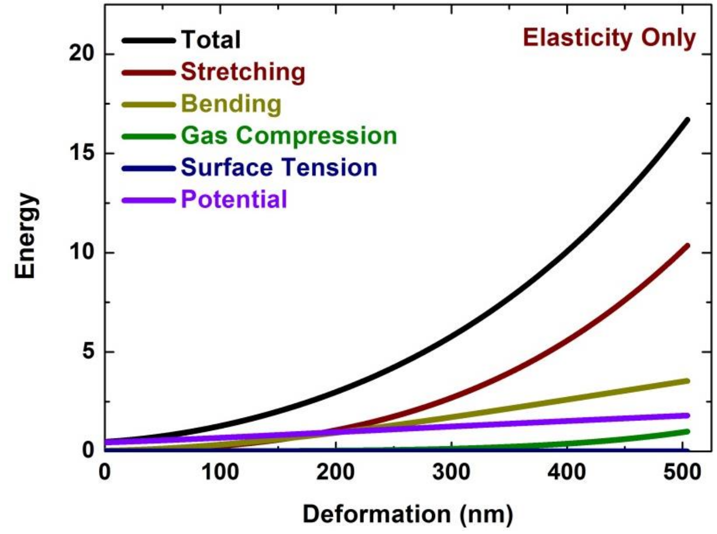
R_o=1.3 μm ; v=0.5	AFM Experiment	Reissner-Pogorelov	Plane Contact
Young's Modulus [GPa]	10-16	8.5	20
Shell Thickness [nm]	20	25	16

The elastic properties can be estimated by a single measurement, the f-d curve.

[Glynos et al., *Langmuir*, 2009]
[Lytra, Pelekasis, Sboros, Glynos, Koutsos, *Procedia IUTAM*, 2015]

Adhesive Potential-Bubble Covered With Lipid





Elasticity Only

χ=0.05 N/m

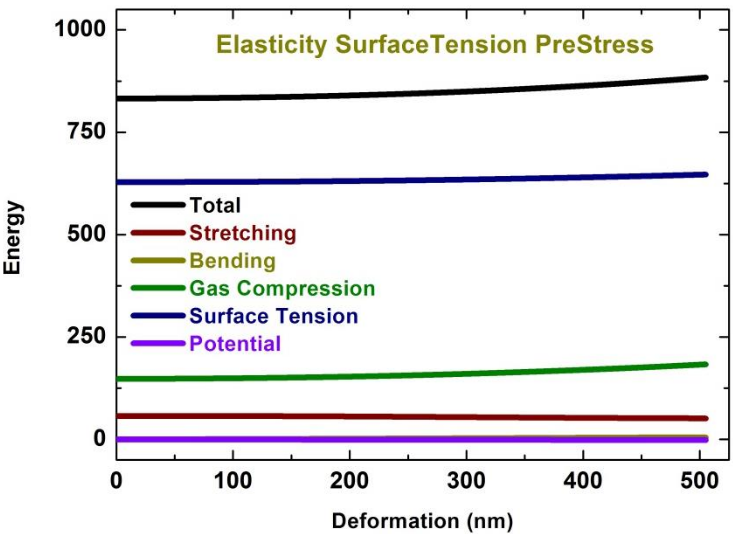
$k_b=3\cdot10^{-16}$ Nm

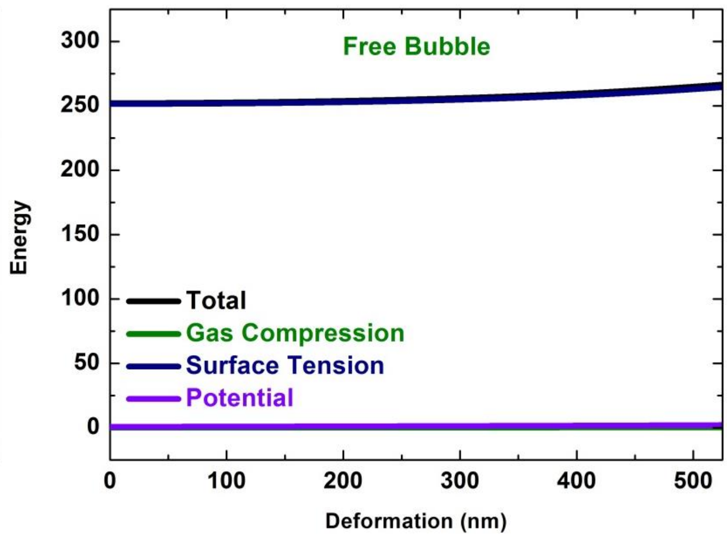
$W_o=10^{-4}$ N/m

$\delta_A=50\cdot10^{-9}$ m

γ=1.07

Mooney-Rivlin (b=1)





Elast. Surf. Tension Pre Stress

χ=0.05 N/m

$k_b=3\cdot10^{-16}$ Nm

$W_o=10^{-4}$ N/m

$\delta_A=50\cdot10^{-9}$ m

$\sigma=10^{-2}$ N/m

$V=-0.14\cdot10^{-6}$ m

γ=1.07

Mooney-Rivlin (b=1)

Free Bubble

$\sigma=4\cdot10^{-2}$ N/m

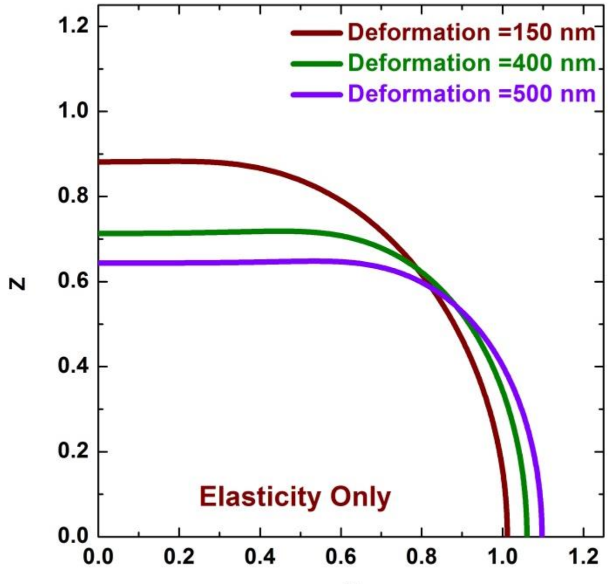
$W_o=10^{-4}$ N/m

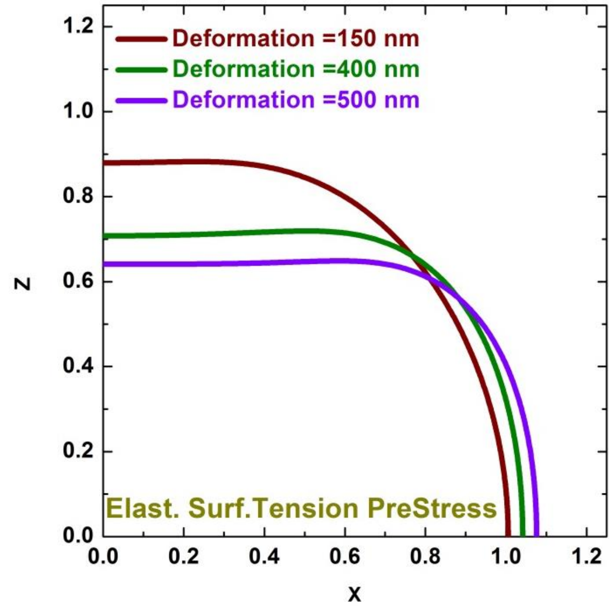
$\delta_A=50\cdot10^{-9}$ m

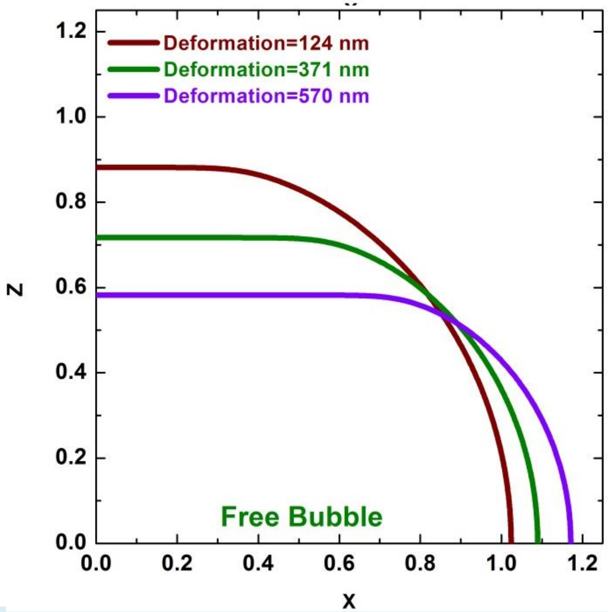
γ=1.07

[Buchner Santos et al., *Langmuir*, 2012]

Adhesive Potential-Bubble Covered With Lipid

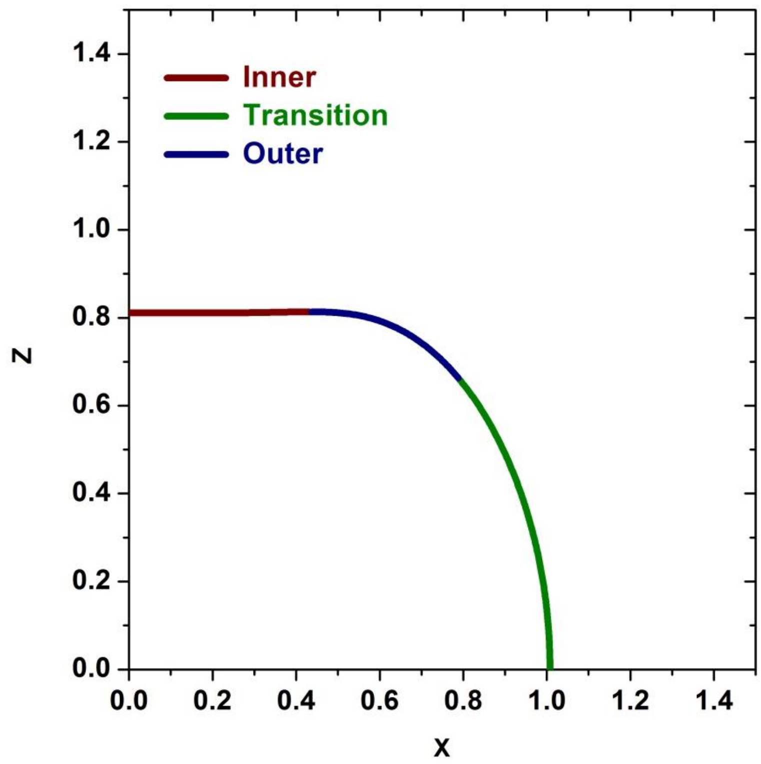






- The shell remains flattened.
- The contact angle is not constant.

Asymptotic Analysis for Lipids



Inner Region:

$$P_{in} - P_{out} \sim \frac{\partial W}{\partial n}$$

[Pressure difference ~ Disjoining Pressure]

Transition Region:

$$\frac{\partial W}{\partial n} \sim k_b$$

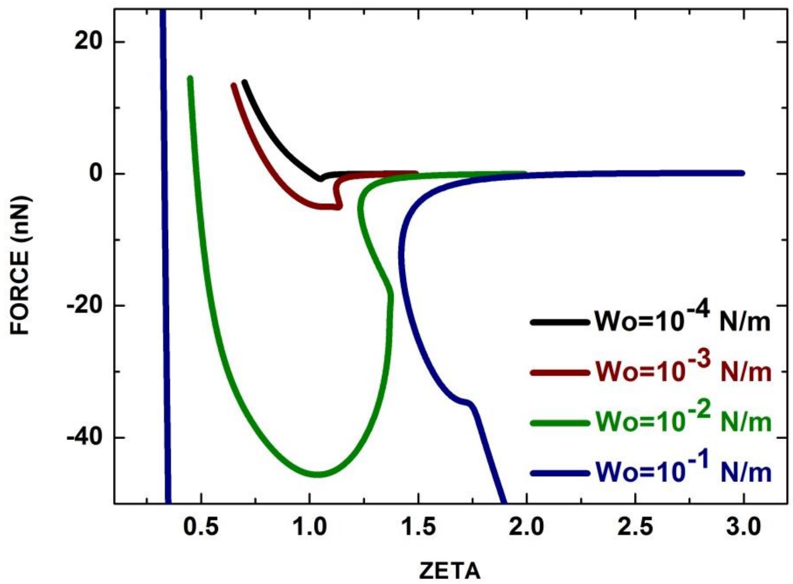
[Bending ~ Disjoining Pressure]

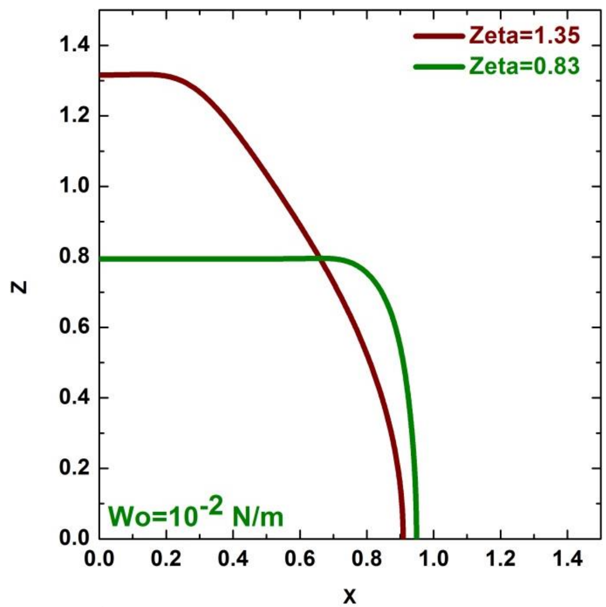
Outer Region

$$P_{in} - P_{out} \sim k_b + \chi$$

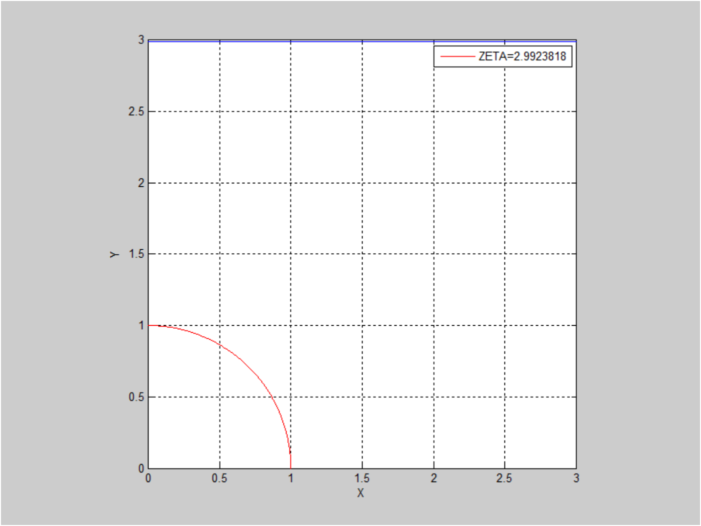
[Pressure difference ~ Bending and stretching]

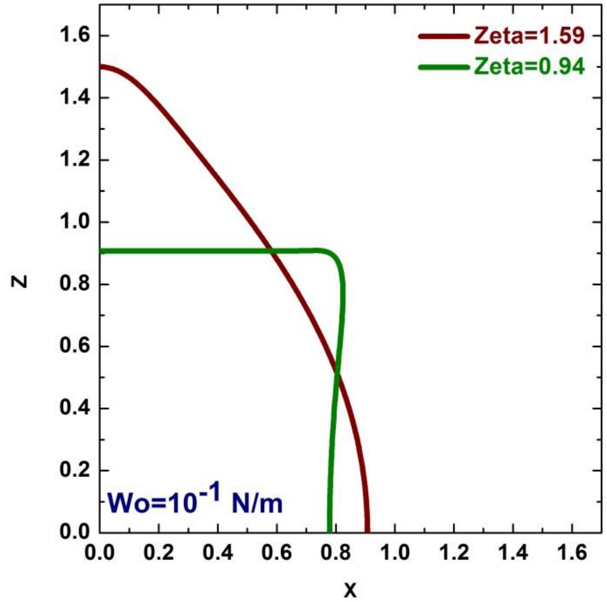
Adhesive Potential-Parametric Study (Elasticity Model)





$W_o=10^{-1}$ N/m





- The classic contact model can easily simulate the force-deformation curve of a microbubble covered with polymeric shell.
  - The linear regime followed by a non-linear is associated with a sub-critical bifurcation.
  - In the linear regime, the shell remains flattened, but in the non-linear buckling takes place.

- In cases of lipids, which are softer, the intermolecular forces must be accounted for.
  - The experimental curve is almost linear, which indicate that buckling is not taking place.
  - Three models are considered in the present work, where no buckling was observed. The change of length is preferable, than bending, due to adhesion, which attaches the shell in cantilever.
  - The elasticity only model seems to be the more suitable for the simulations of the static response of CA microbubbles, covered with lipid.
  - The estimation of the elastic properties, requires further asymptotic analysis and perhaps different experimental set-up with side view photos.

Current & Future Work

- Simulation of a drop and a microbubble resting on a flat surface (Trapped microbubbles).
- Further asymptotic analysis and estimation of the elastic properties of bubbles covered with lipids.

“This work is performed in the framework of the operational program: «Education and lifelong learning» **- «Aristeia I»** and is cofounded by the European Union (European Social Fund), national resources and the

Dep. of Mechanical Engineering-University of Thessaly.”

European Union
European Social Fund

OPERATIONAL PROGRAMME
EDUCATION AND LIFELONG LEARNING
investing in knowledge society
MINISTRY OF EDUCATION & RELIGIOUS AFFAIRS
MANAGING AUTHORITY
Co-financed by Greece and the European Union

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programme for development
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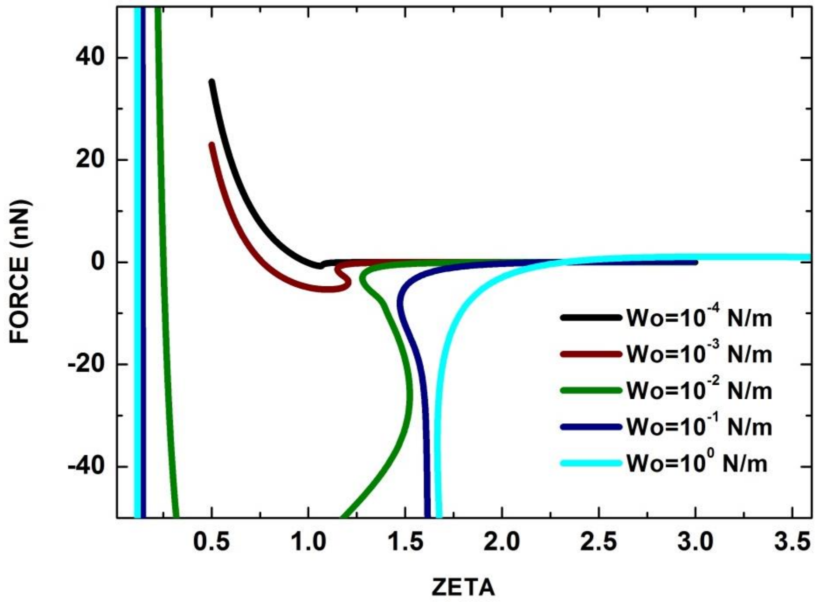
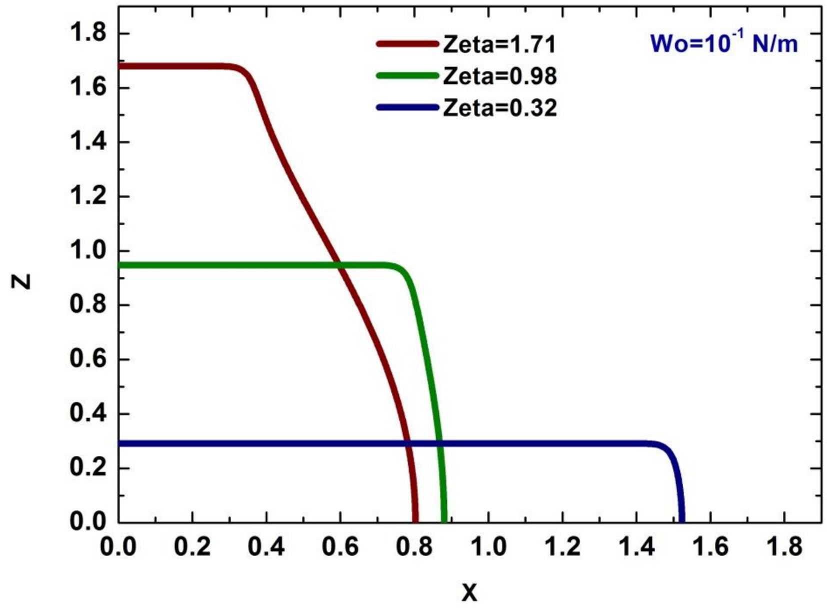
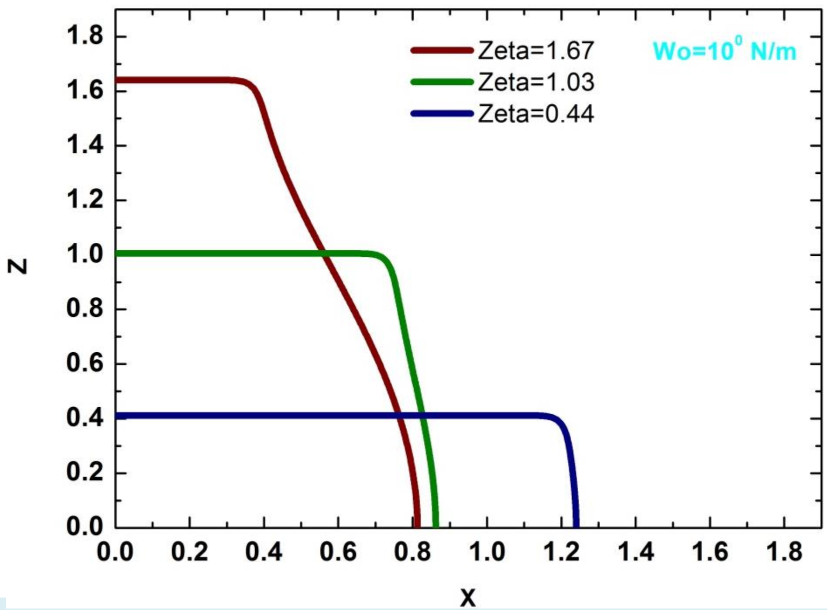
Thank you for your attention!
***Ευχαριστώ πολύ*!**

Questions?

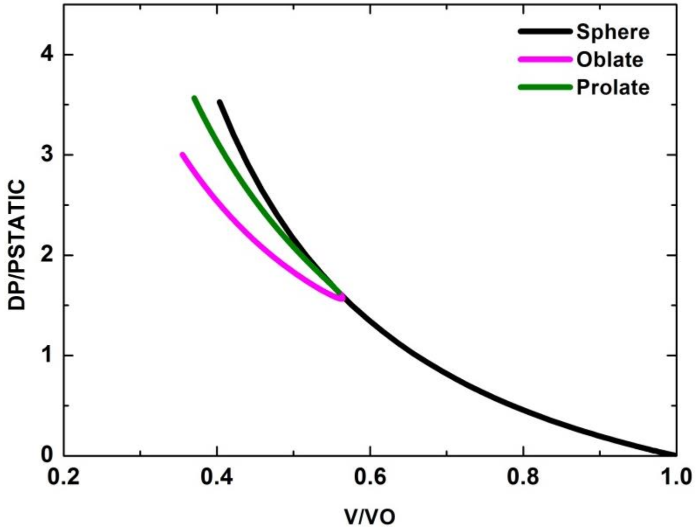
Adhesive Potential-Parametric Study (Free Bubble)

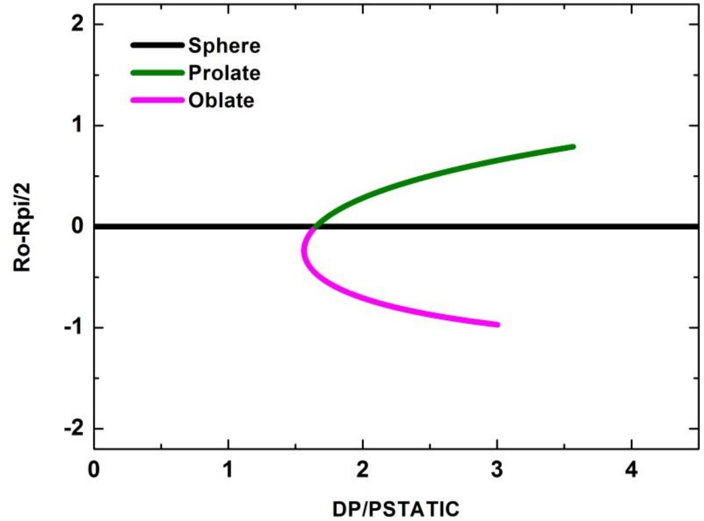




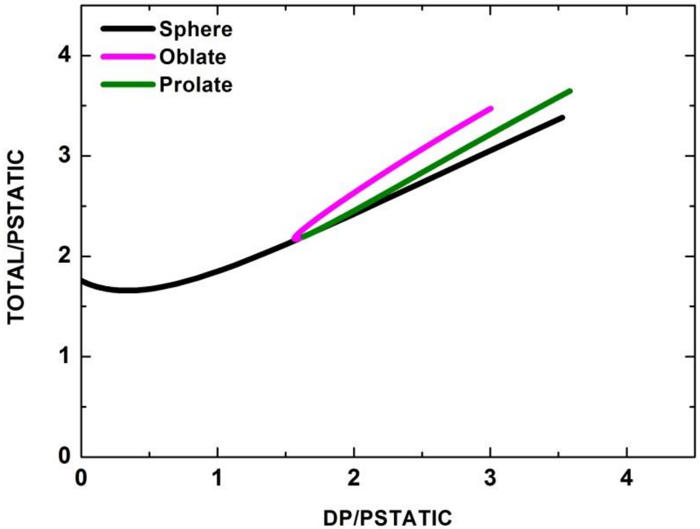


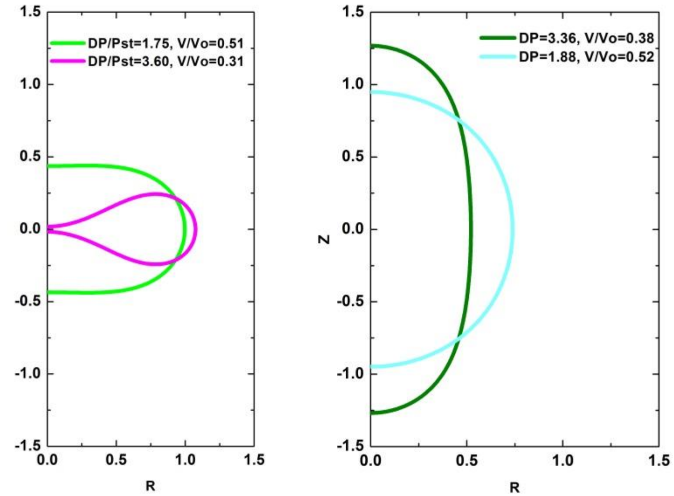
Bifurcation Diagrams





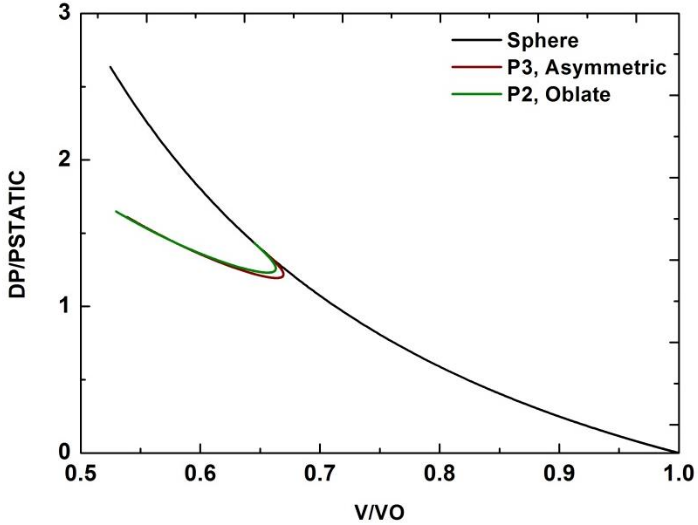
G_s=40 MPa
k_b=3·10^{-14} Nm
σ=0.051 N/m
Mooney-Rivlin

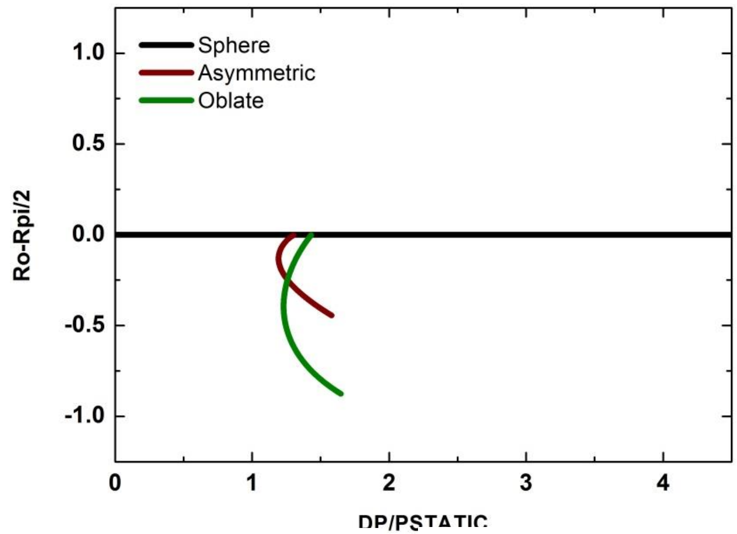




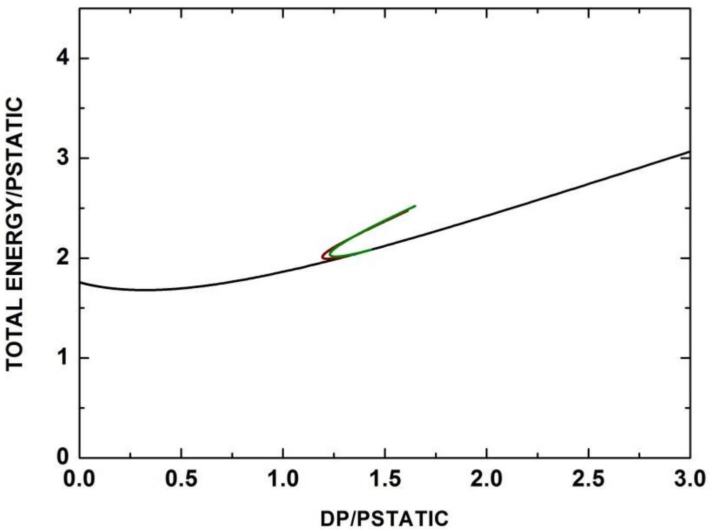
[Lytra & Pelekasis, *Fluid Dyn. Res.*, 2014]

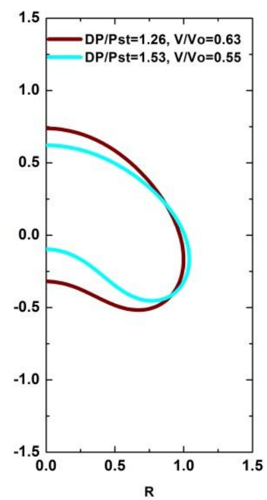
Bifurcation Diagrams

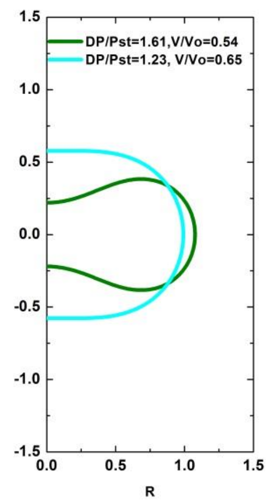




G_s=80 MPa
k_b=$3\cdot10^{-14}$ Nm
σ=0.051 N/m
Mooney-Rivlin







[Lytra & Pelekasis, *Fluid Dyn. Res.*, 2014]

- The static response of microbubbles, covered with an elastic shell, subject to a uniform pressure was investigated.
  - In this problem, the shell remains spherical for increasing the external overpressure, but its volume is decreasing.
  - When the overpressure reaches the critical load, the shell buckles into a symmetric or a non-symmetric shape. The buckling is indicated by one more negative eigenvalue. Following simple continuation, the post-buckling f-d curve is generated.
  - In every post-buckling curve a limit point was accounted and arc- length continuation was performed.
  - In the case of Gs=40 MPa, the first bifurcation point is dominated by the a *symmetric* eigenmode (P2), which leads to a oblate or prolate shapes.
  - In the case of Gs=80 MPa, the first bifurcation point is dominated by a *non-symmetric* eigenmode (P3) and non-symmetric shapes.