DynaCaps2014

Dynamics of Capsules, Vesicles and Cells in Flow

UTC, Compiègne-France, July 15-18, 2014

«Static response of coated microbubbles: Modelling simulations and parameter estimation»

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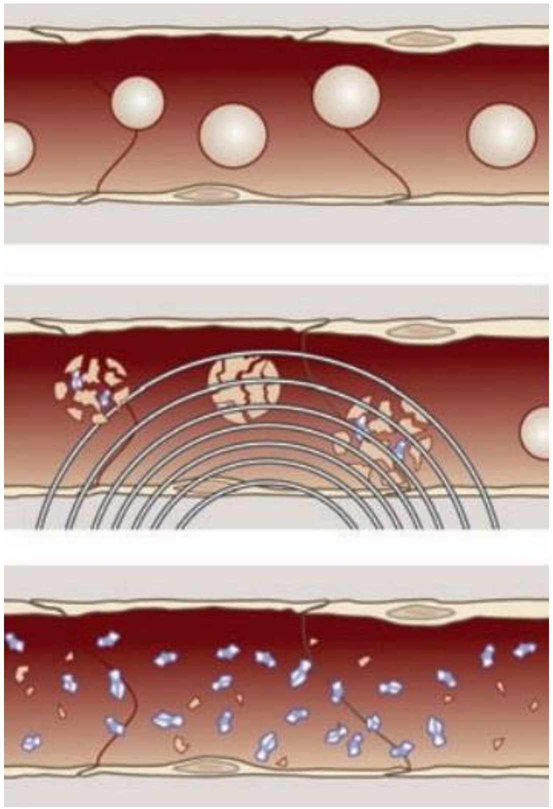
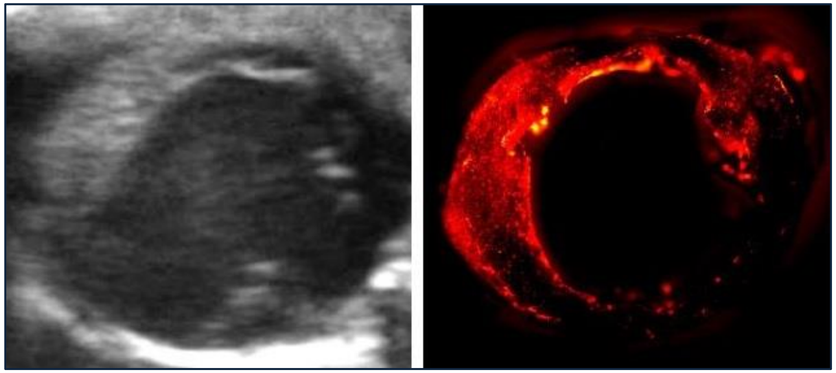
Presentation Outline

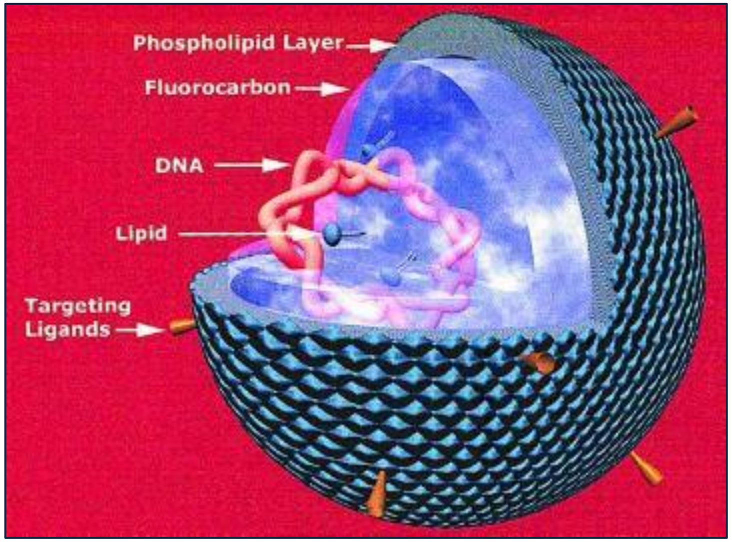
- Introduction
- Theoretical Analysis
- Numerical Solution
- Results
- Conclusions
- Current and Future Research



Applications:
Medical Imaging & Drug Delivery

- ✓ Strong Backscattered Acoustic Signal
- ✓ Biocompatibility





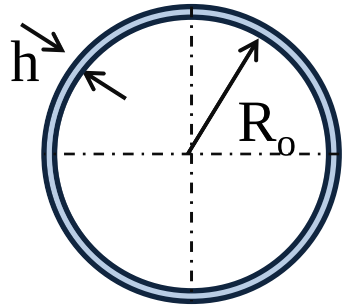
1. Ferrara, K., R. Pollard, and M. Borden, *Ultrasound Microbubble Contrast Agents: Fundamentals and Application to Gene and Drug Delivery.* Annual Review of Biomedical Engineering, 2007. 9(1): p. 415-447.
2. Kaufmann, B.A., K. Wei, and J.R. Lindner, *Contrast Echocardiography*. Current Problems in Cardiology, 2007. 32(2): p. 51-96.
3. Unger, E.C., T.O. Matsunaga, T. McCreery, et al., *Therapeutic applications of microbubbles*, European Journal of Radiology, 2002. (42) : p. 160–168

Polymeric Shells | **Lipid Shells**

Geometry

Initial Radius: R_o

Shell Thickness :h



Initial Radius: R_o

Elastic Properties

Elastic Modulus: E

Bending Modulus:

$$k_b = \frac{Eh^3}{12\left(1-\nu^2\right)}$$

Independent parameters:
E, h

Area Dilatation: x=3Eh

Bending Modulus:
k_b: Independent variable

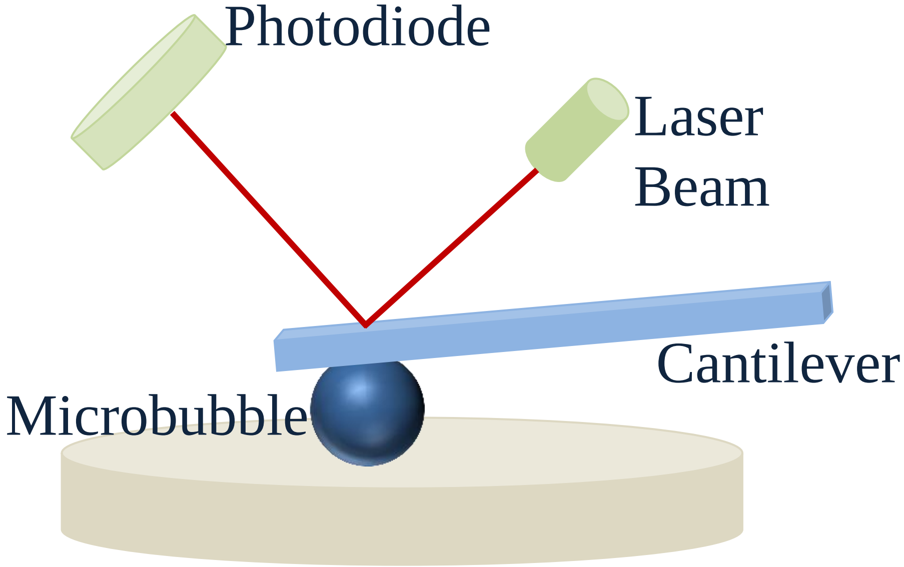
Independent parameters:
x, k_b

Experiments

Ultrasound Measurements

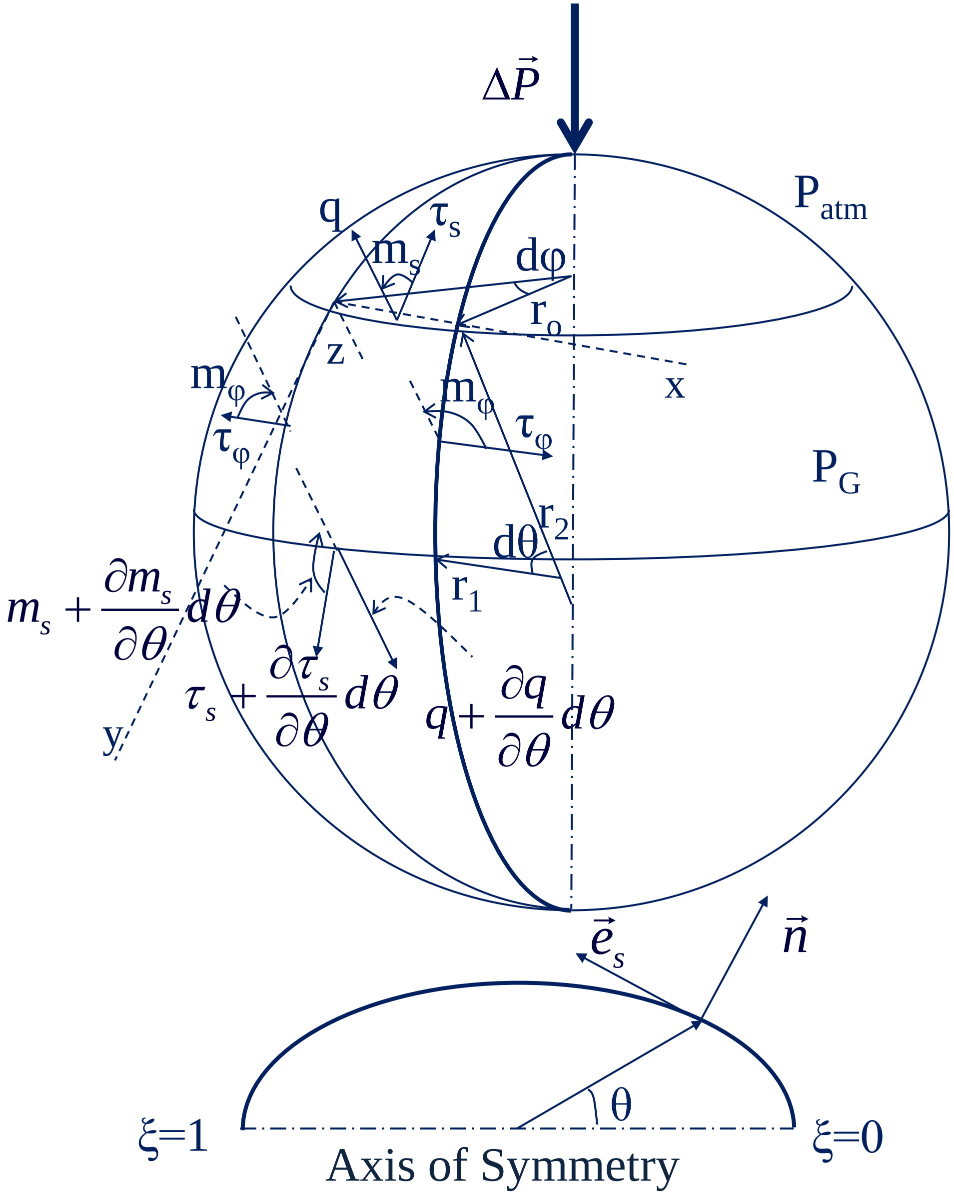
Static Measurements

Atomic Force Microscopy
(In collaboration with
Un. of Edinburgh)



Scope of this work

- Simulation of static response of microbubbles
- Comparison with experimental measurements
- Study of mechanisms that deform the shell
- Estimation of elastic properties
- Optimization of the design of bubbles



Force Balance

$$\Delta\vec{F} = \Delta\vec{P} \Rightarrow \begin{cases} \Delta\vec{F}_N = \left(P_{atm} + \Delta P - P_G\right)\vec{n} \\ \Delta\vec{F}_s = \vec{0} \end{cases}$$

Bending Moments Balance

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

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

Isothermal Compression

$$P_{G0}V_0 = P_G V$$

Neo-Hookean Constitutive Law

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

Boundary Conditions

$$\frac{\partial r}{\partial \xi} = \frac{\partial^2 \theta}{\partial \xi^2} = 0 \ \text{ at } \ \xi = 0{,}1$$

4. Timoshenko, S.P. and S., Woinowsky-Krieger, 1959 *Theory of plates and shells* Mc-Graw-Hill Int. Editions.
5. Barthes-Biesel, D., A. Diaz, and E. Dhenin, *Effect of constitutive laws for two - dimensional membranes on flow-induced capsule deformation* Journal of Fluid Mechanics, 2002. 460: p. 211 – 222
6. Tsiglifis, K., *Numerical simulation of bubble dynamics in response to acoustic disturbances*, Doctoral Dissertation, in *Dpt of Mechanical Engineering*. 2007, Un. of Thessaly: Volos.
7. Serpetsi,, S., *Numerical study of mechanical properties of microbubbles with elastic shell-application in Atomic Force Microscopy*, Master Thesis, in *Dpt of Mechanical Engineering*. 2011, Un. of Thessaly: Volos.

Dimensionless Numbers

$$\tilde{P} = \frac{P_{atm} R_o}{x} = \frac{\text{resistance due to pressure changes}}{\text{resistance due to stretching}}$$

$$\tilde{k}_b = \frac{k_b}{x R_o^2} = \frac{\text{resistance due to bending}}{\text{resistance due to stretching}}$$

Polymeric Shell

$$\tilde{P} = \frac{P_{atm} R_o}{Eh} \quad O\left(10^{-3} - 10^{-2}\right)$$

$$\tilde{k}_b = \left(\frac{h}{3R_o}\right)^2 \quad O\left(10^{-5} - 10^{-3}\right)$$

Lipid Shell

$$\tilde{P} = \frac{P_{atm} R_o}{Eh} \quad O\left(10^{-2} - 10^{0}\right)$$

$$\tilde{k}_b = \frac{k_b}{x R_o^2} \quad O\left(10^{-5} - 10^{-3}\right)$$

Finite Elements

- Method of Weighted Residuals $\underline{\underline{J}} \cdot \vec{c} = \vec{R}$ $\underline{\underline{J}} : (2N+7)\times(2N+7)$

  N number of elements

- Basis Functions:
  B-Cubic Splines

$$B_i\left(t_j\right) = \begin{cases} 4, & j=1 \\ 1, & j=i\pm 1 \\ 0, & j=i\pm 2 \end{cases}$$

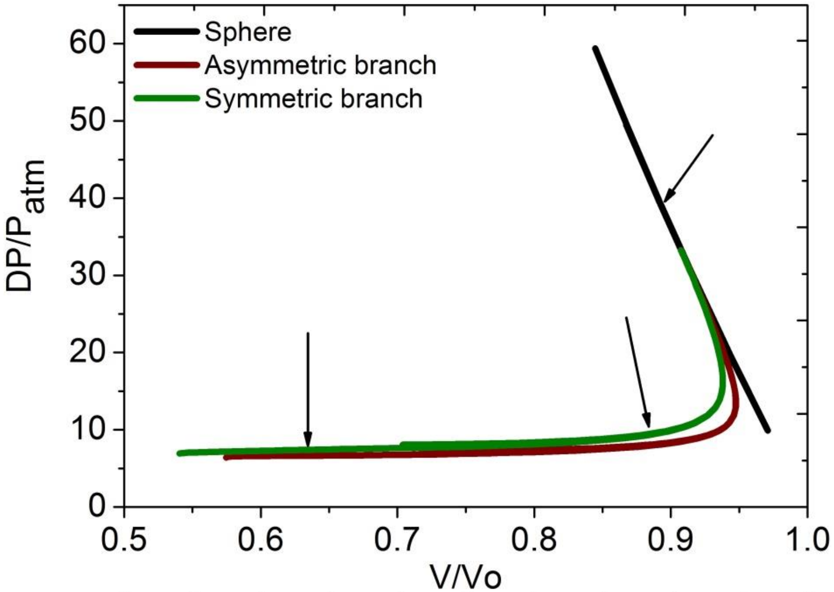
- Solution of Linear System of Equations: Newton-Raphson Iterations

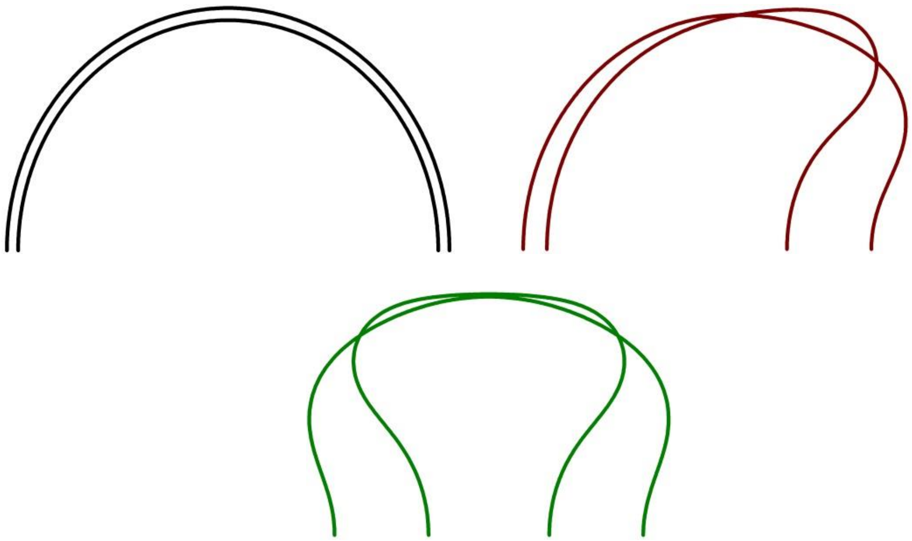
- Calculation of Integrals: 4 Points Gauss Quadrature

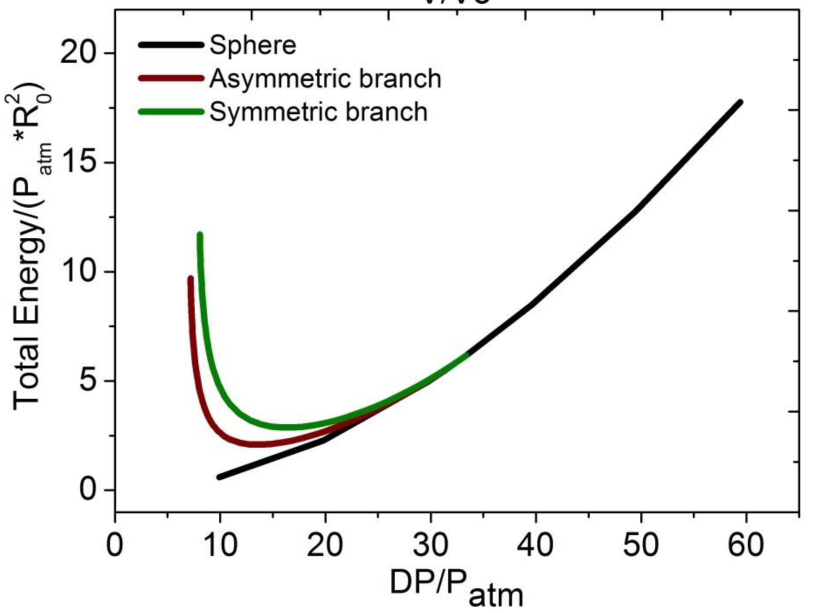
- Validation: Calculation of the critical buckling load and the volume of the microbubble

8. Pelekasis, N.A., J. A. Tsamopoulos & G. D. Manolis, *Equilibrium shapes and stability of charged and conducting drops*. Phys. Fluids , 1990. A2(8), 1328
9. Tsigklifis, K. and N.A. Pelekasis, *Parametric Stability and dynamic buckling of an encapsulated microbubble subject to acoustic disturbances*. Phys. Fluids, 2011. 23, 012102

Uniform External Overpressure (Benchmark Calculations)







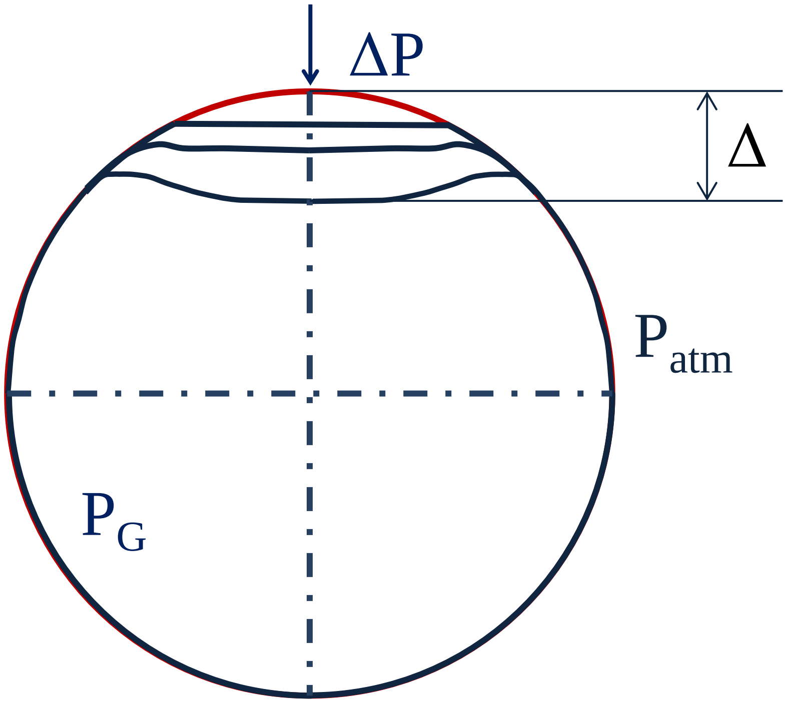
$$\tilde{P} = 4.0 \cdot 10^{-3} \qquad \tilde{k}_b = 1.0 \cdot 10^{-3}$$

$$\Delta P_{cb} = \frac{6G_s}{\sqrt{3\left(1-\nu^2\right)}}\left(\frac{h}{R_o}\right)^2$$

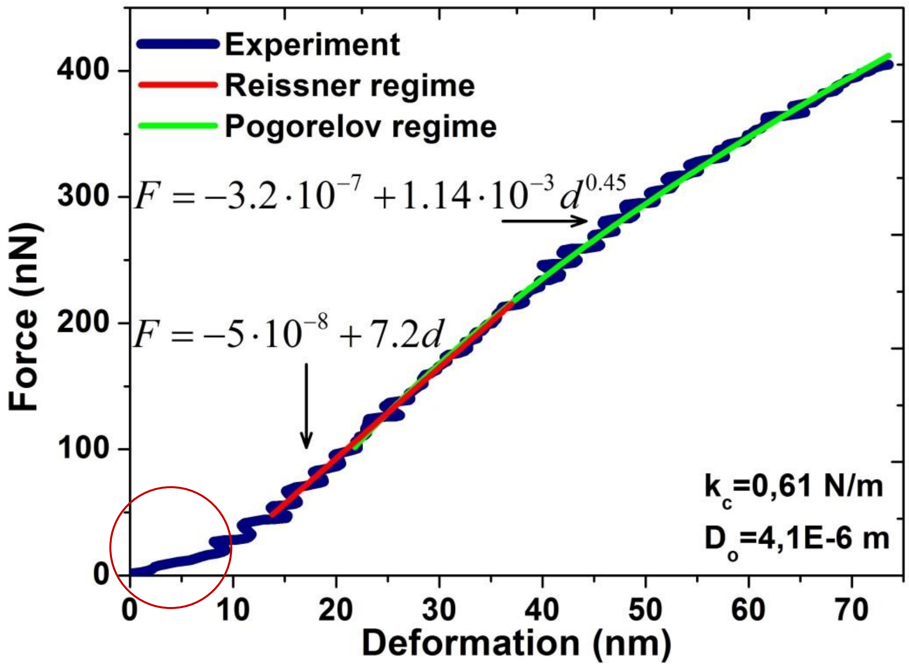
10. Knoche, S. and J. Kierfeld, *Buckling of spherical capsules.* Physical Review E, 2011. **84**(4): p. 046608

Results Outline

- Estimation of elastic properties for polymers and lipids
- Deformation of the microbubble subject to a point load



Polymeric Shell



Adhesive forces (F≤10 nN)
Elastic forces (F>>10 nN)

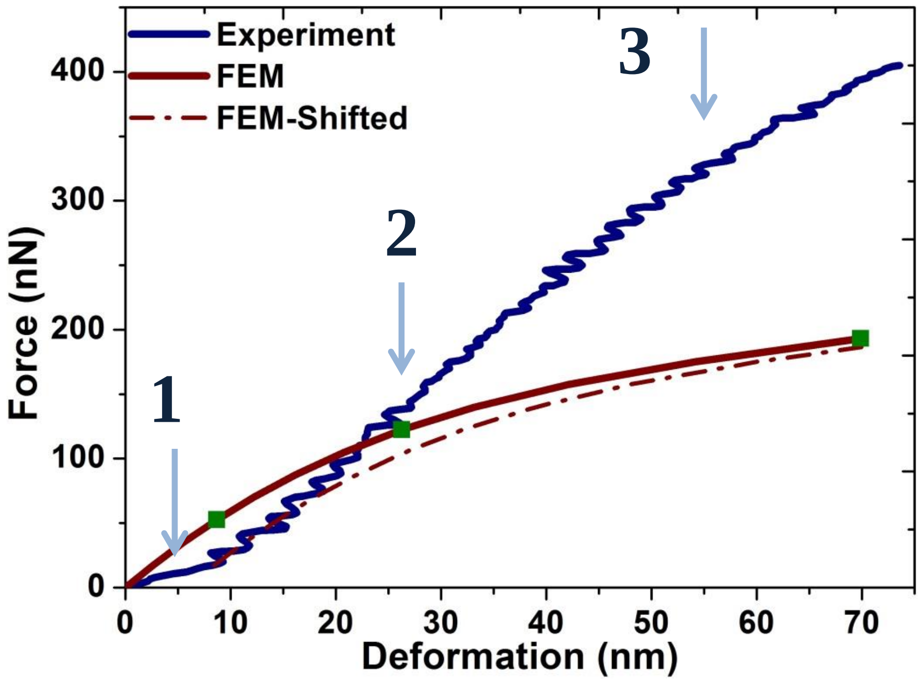
Reissner's eq. $$F = \frac{4}{\left[3\left(1-\nu^2\right)\right]^{0.5}} \frac{Eh^2}{R_o} \Delta$$

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

Young's Modulus	Thickness
Asymptotic Equations	
6 GPa	31 nm
Experiment	
5 GPa	30 nm

11. Reissner, E., *Stresses and small displacements of shallow spherical shells*: I and II, Journal of Mathematics and Physics, 1946. **25**: p. 279-300
12. Pogorelov, A.V., *Bendings of Surfaces and Stability of Shells*, American Mathematical Society, 1988
13. Glynos, E., et al., *Nanomechanics of Biocompatible Hollow Thin-Shell Polymer Microspheres*, Langmuir, 2009. **25**(13): p. 7514-7522.

Polymeric Shell-Comparison of FEM & AFM Experiment

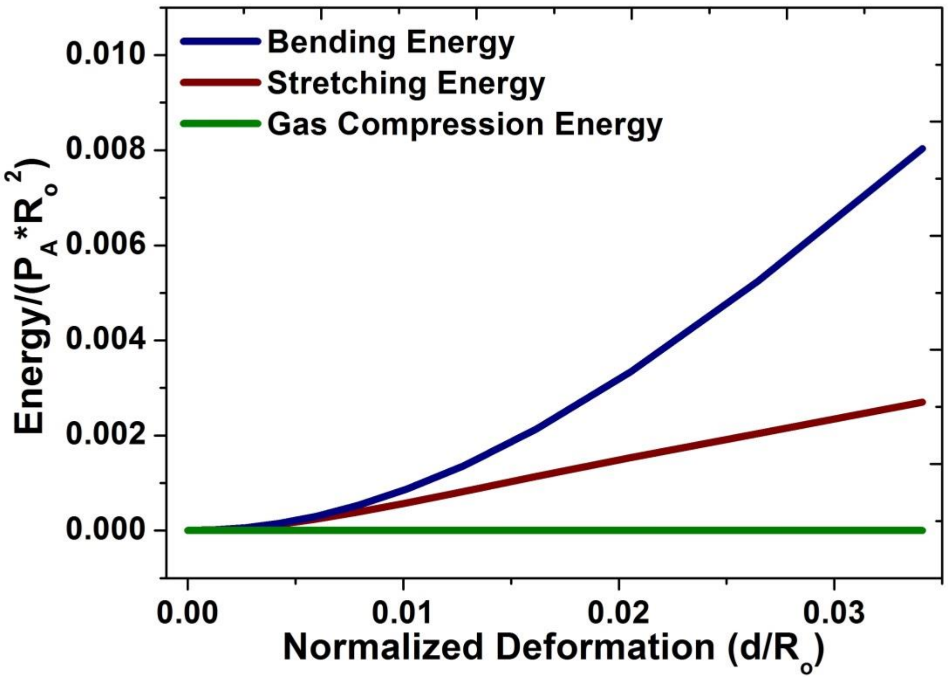


1. Non linear regime (F ≤10nN)
Probably due to adhesive forces. Not included in the fem model.

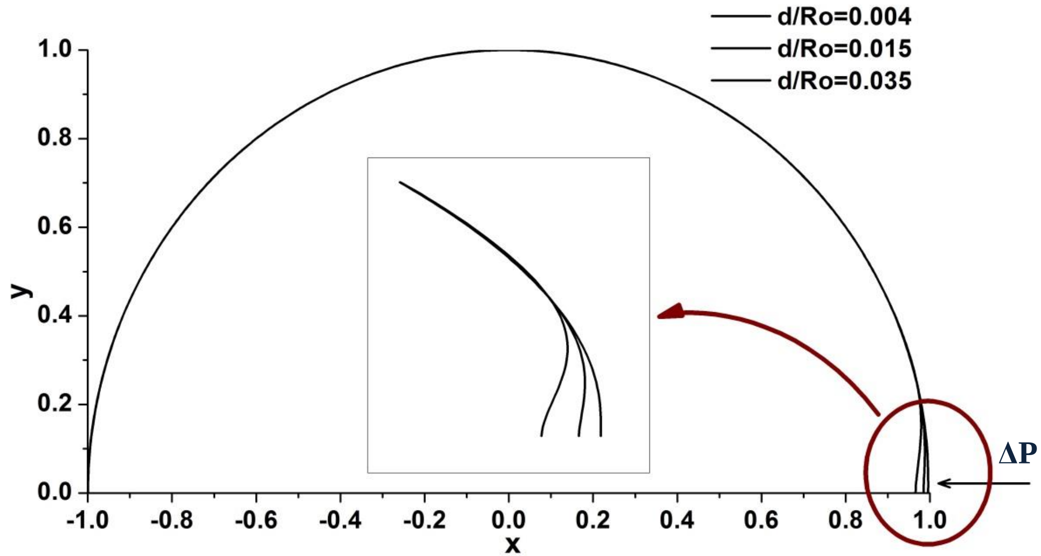
2. Linear regime
Elastic forces-flattened shape

3. Non linear regime
Elastic forces-crater formation. Discrepancies between FEM simulations and experiments probably due to 3D instabilities and load distribution. Not included in the fem model.

Polymeric Shell-Post Processing FEM Results

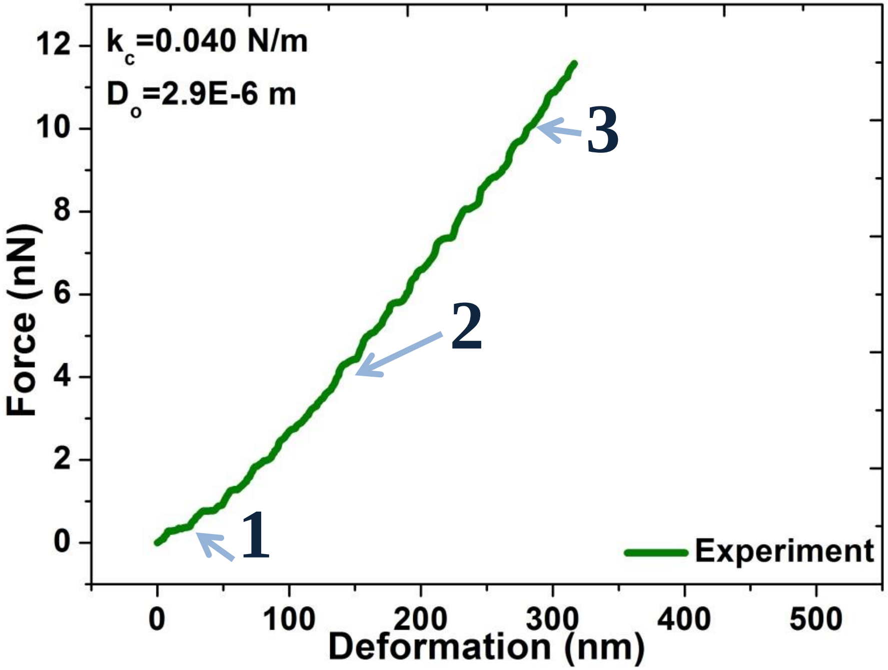


Elasticity dominates over gas compressibility



Dimple formation for increasing loading

Lipid Shell-AFM Experiment



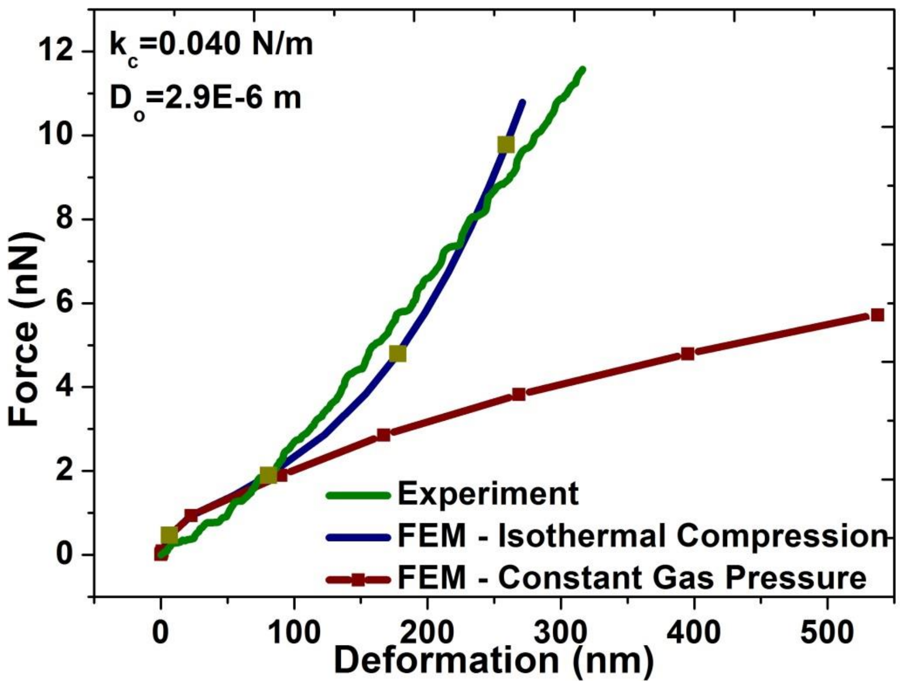
1. Non linear regime, probably due to adhesive forces (not included in the model) where capillarity balances elasticity.

2. An extensive linear regime – Capillarity stretching and bending equally important → Reissner ?

3. Non linear regime due to compressibility

14. Buchner Santos E. et al., *Nanomechanical Properties of Phospholipid Microbubbles*, Langmuir, 2012. **28** (13): p. 5753-5760.

Lipid Shell-Comparison of FEM & AFM Experiment

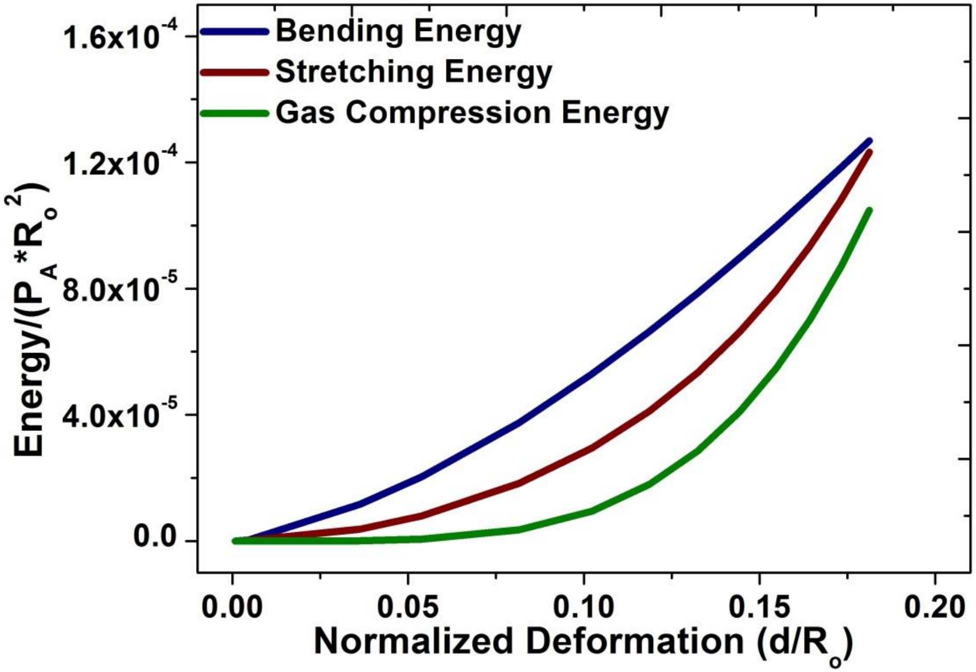


Performing a parameter sweep in the $\tilde{k}_b, \tilde{P}$ space and comparing with the experimental or simulated curve provides shell parameters

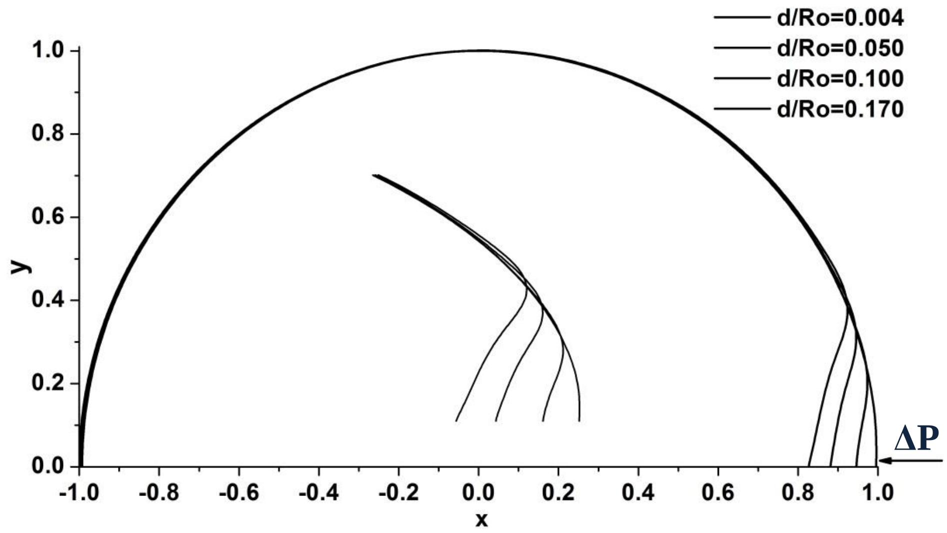
$$\left.\begin{aligned} \tilde{k}_b &= \frac{k_b}{xR_o^2} = 0.7\cdot 10^{-5} \\ \tilde{P} &= \frac{P_{atm}R_o}{x} = 3.4\cdot 10^{-1} \end{aligned}\right\} \Rightarrow \begin{gathered} x = 0.4N/m \\ \& \\ k_b = 6.2\cdot 10^{-18}\,Nm \end{gathered}$$

15. Buchner Santos E. et al., *Nanomechanical Properties of Phospholipid Microbubbles*, Langmuir, 2012. **28** (13): p. 5753-5760.

Lipid Shell-Post Processing FEM Results



Gas compressibility is comparable to elasticity



Crater formation for increasing loading

Polymeric Shell

- The experimental curves of polymeric microbubbles exhibit three different regimes.

- Adhesive forces and stretching control the first non linear regime.

- Elastic forces (stretching and bending stiffness) determine the initial linear and nonlinear regime (Reissner-Pogorelov).

- Gas compressibility controls microbubble and determines nonlinear regime at large deformations.

- Balance between above forces determines transition between Reissner and Pogorelov regimes and can be used for estimating elastic modulus (E) and shell thickness (h).

Lipid Shell

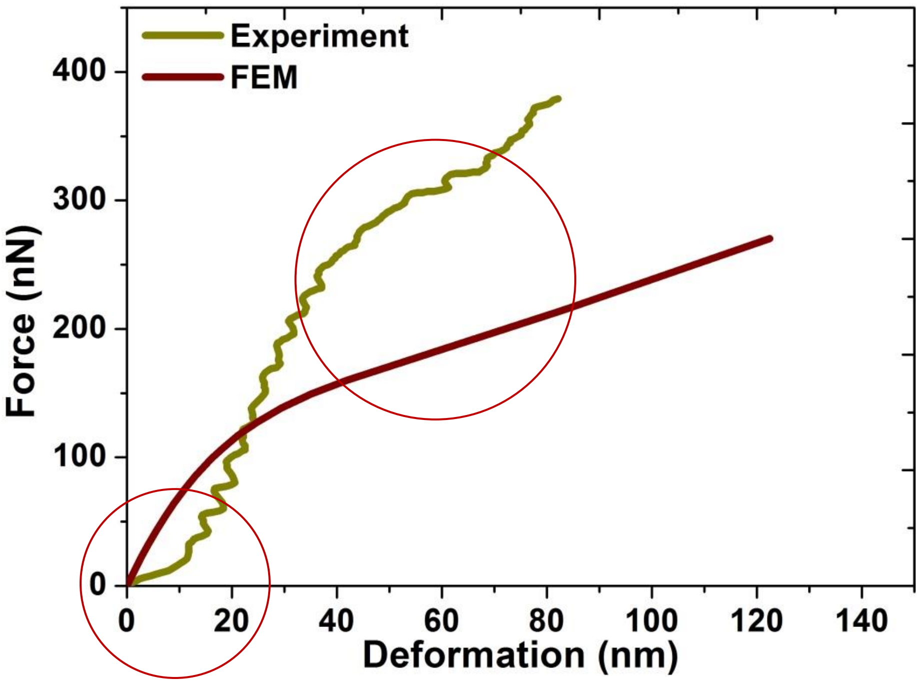
- Balance between capillarity and stretching determines the first non linear regime.

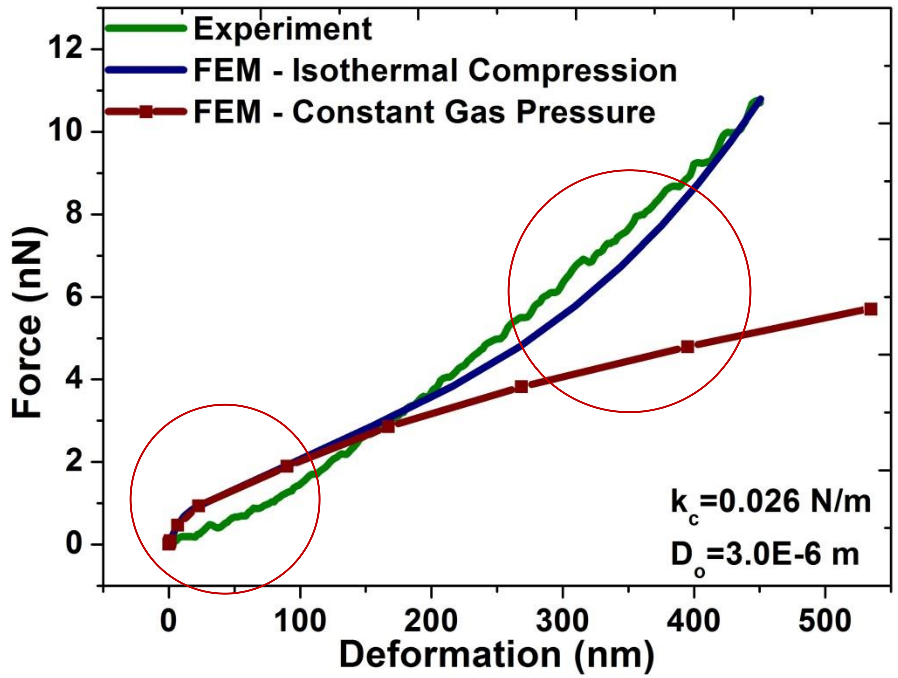
- Gas compressibility is of the same order as elastic forces at large deformations, increasing the stiffness of the bubble.

- In lipid monolayer shells adhesion forces may be of the same order as elastic forces over a longer force range
  The shell is stabilized and crater formation/transition to a Pogorelov type regime is probably delayed
  For large enough forcing, buckling of the shell takes place leading to crater formation

- Lipid monolayer shells do not necessarily obey a Reissner-Pogorelov type transition. Elastic properties may be estimated by a transition from adhesion dominated to Pogorelov regime.

Goal of current work

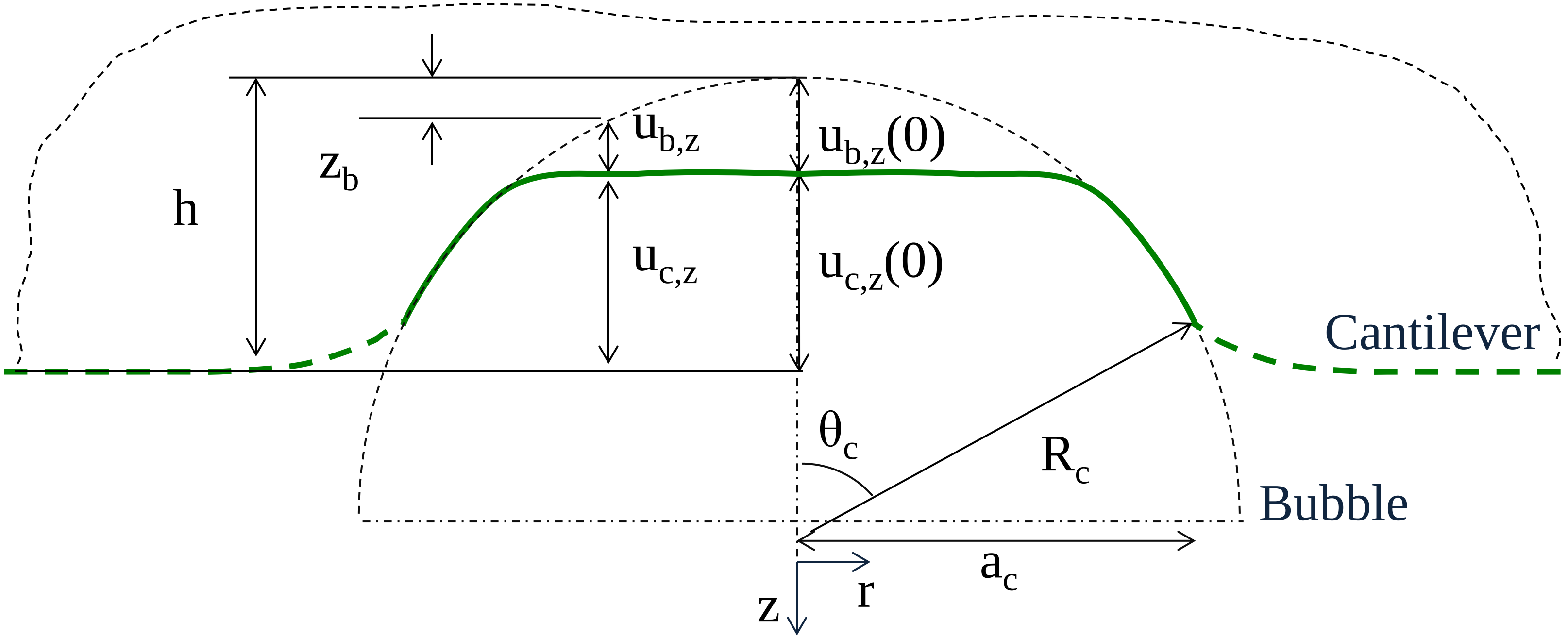




Modeling of contact between microbubble and cantilever

- Estimation of load distribution
- Estimation of deformation of the cantilever
- Account for capillary forces (validation of adhesion regime)
- Validation of adhesion to Pogorelov transition pattern

- **Modeling of the contact area between the cantilever of the AFM and microbubble (load distribution).**



- Linear elasticity for the deformation of cantilever: (BEM)

$$u_{c,z}(r') = \frac{4(1-\nu^2)}{E_c}\int_0^{a_c} P_z(r')G(r,r')r'dr'$$

$$0 \le r' \le a_c, \qquad 0 \le r \le 5a_c$$

- Kinematic condition at the interface:

$$u_{c,z}(r') + u_{b,z}(r') + z_b = cons.$$

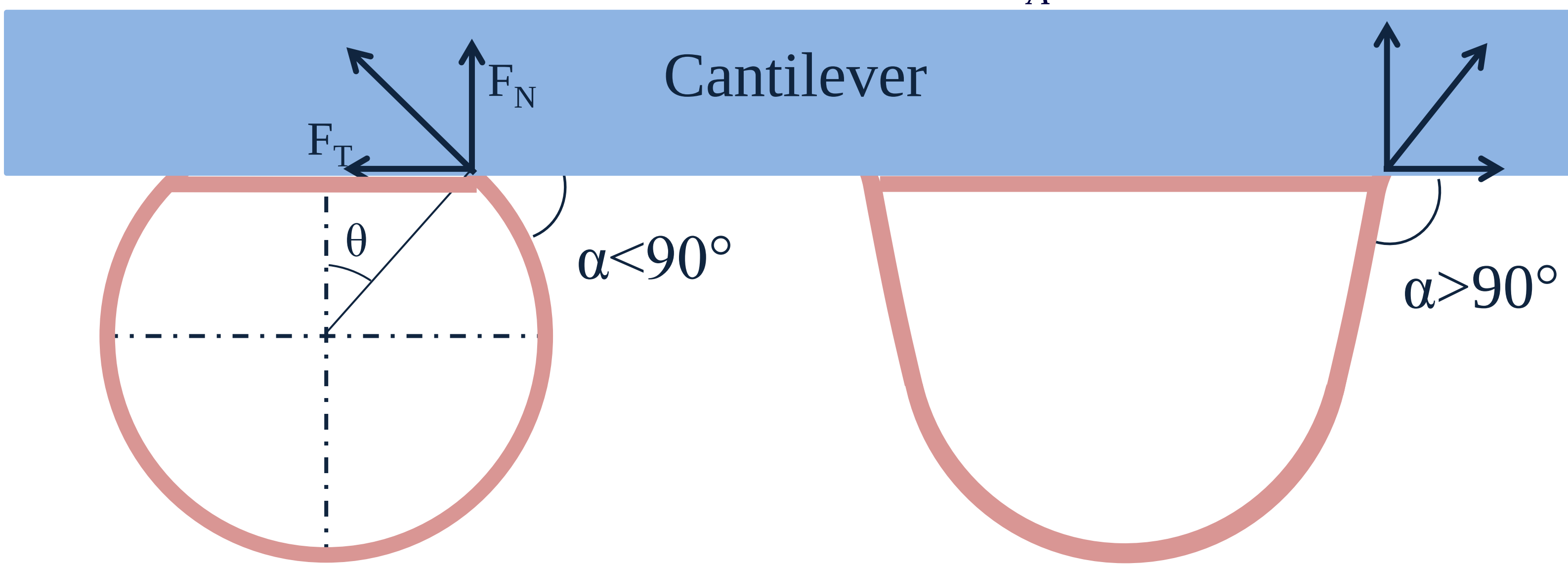
16. Landau, L.D., et al., *Theory of Elasticity* 1986: Butterworth-Heinemann.

- **Consideration of capillary forces in the contact area**

Normal load component on the bubble: $P_G - P_N - P_A = \vec{\nabla}_s \cdot \left(\underline{\underline{\tau}} + \vec{q}\vec{e}_s \right) + \sigma \vec{\nabla} \cdot \vec{n}$

Load on the cantilever: $P_z = P_N + \sigma \vec{\nabla} \cdot \vec{n}$

Total force on the bubble: $F = \oiint_A P_N \vec{n} dA$



Capillary stresses may counteract compressive elastic stresses and delay crater formation.

17. Johnson, K.L., K. Kendall and A.D. Roberts, *Surface Energy and the Contact of Elastic Solids* Proceedings of the Royal Society of London. A. Mathematical and Physical Sciences, 1971. **324**(1558): p. 301-313

- **Asymptotic Analysis**

$$F = \frac{32\pi E h \lambda^2 R_o}{1-\nu}\theta^6 + 4\pi R_o \sigma \theta^2 - 2\pi R_o \sigma$$

- Force required for zero deformation: $F = -2\pi R_o \sigma$

- When contact length is small, capillarity balances the elasticity: and determines a non linear regime in force-deformation curve.

$$4\pi R_o \sigma \theta^2 \sim \frac{32\pi E h \lambda^2 R_o}{1-\nu}\theta^6 \quad \text{as} \quad \theta \to 0$$

Deformation $\Delta / R_o \sim \theta^2 \to F \sim \left(\Delta / R_o\right)^3$ in this regime

- The above formulation is currently studied via numerical simulations.

18. Shanahan, M.E.R., *A Novel Test for the Appraisal of Solid/Solid Interfacial Interactions.* The Journal of Adhesion, 1997. **63**(1-3): p. 15-29

Future Research

3-D Modeling of the deformation of the microbubble subject to static load.

19. Vella, D., et al., *Wrinkling of Pressurized Elastic Shells* Physical Review Letters, 2011. **107**(17): p. 174301

Thank you for your attention!

Merci beaucoup pour votre attention!

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

European Union
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