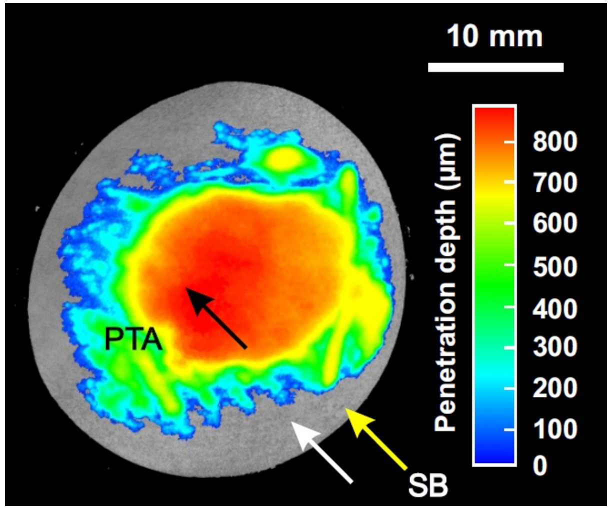
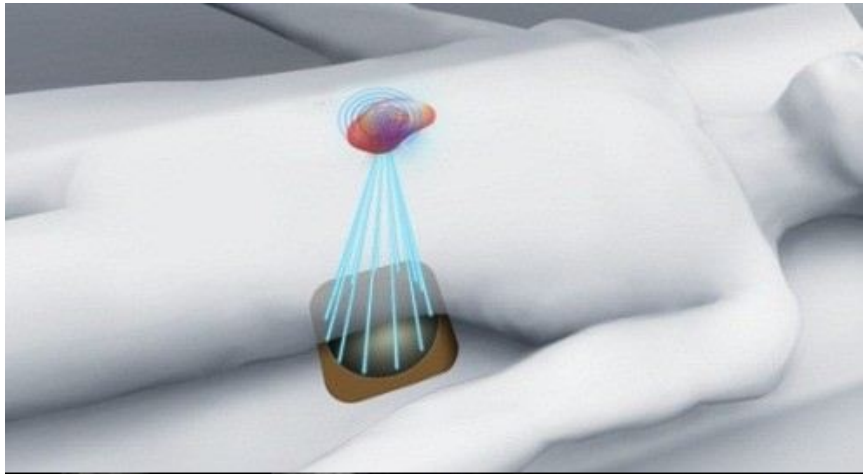
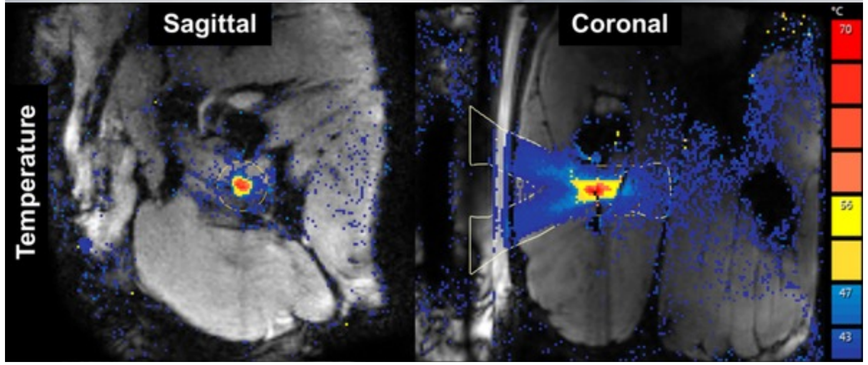
Biomedical Ultrasonics, 5 cr

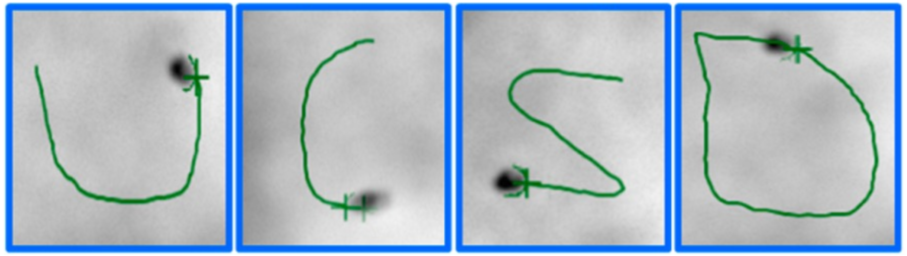
Heikki Nieminen

13.9.-16.12.2021

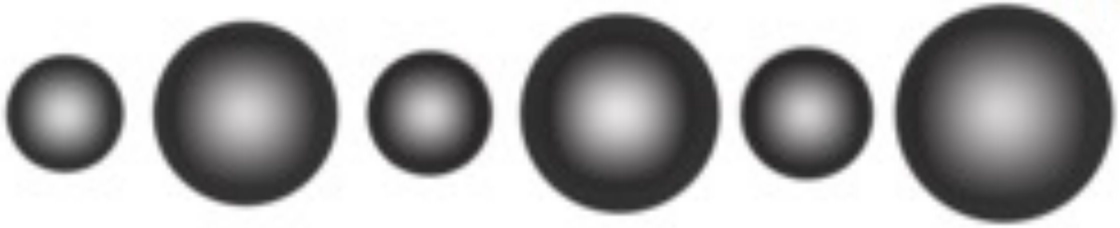






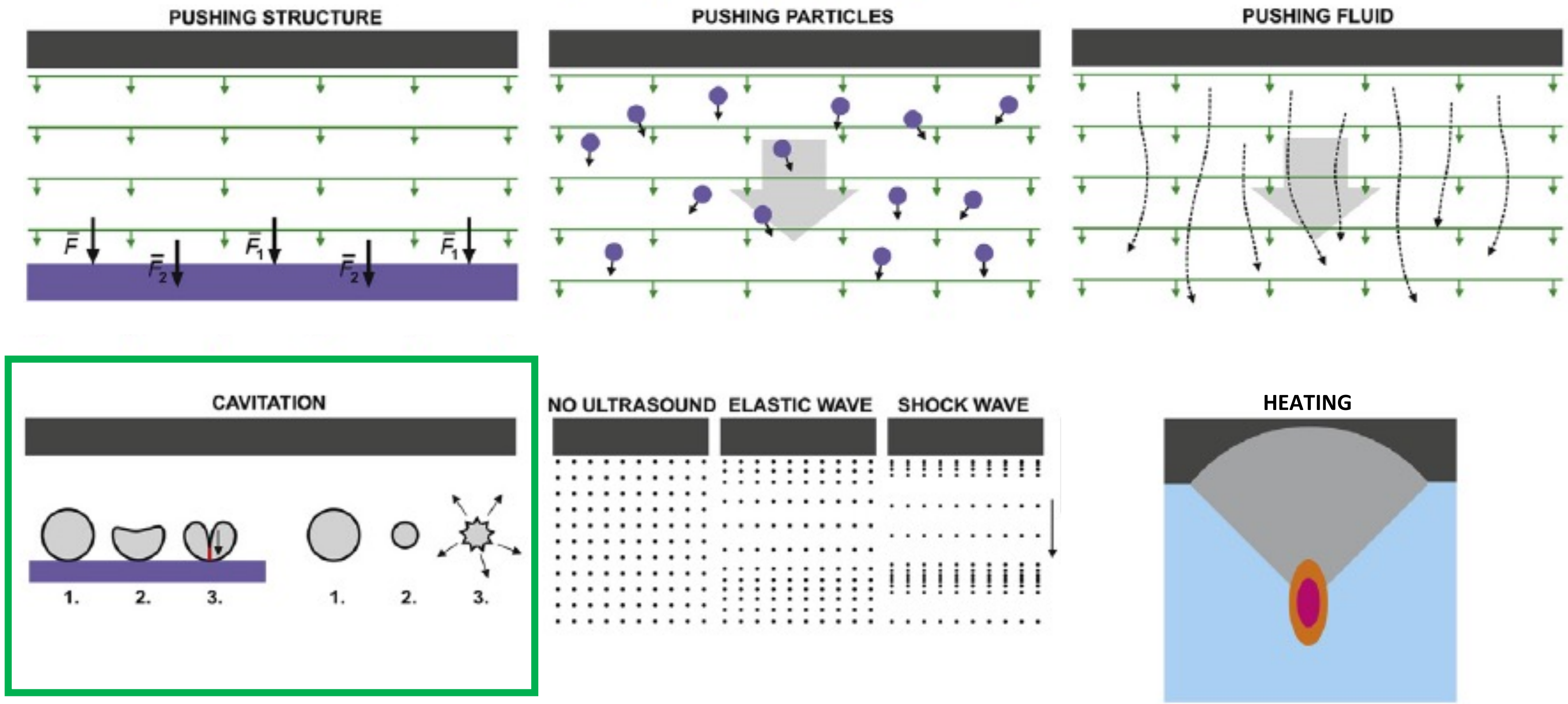


Cavitation

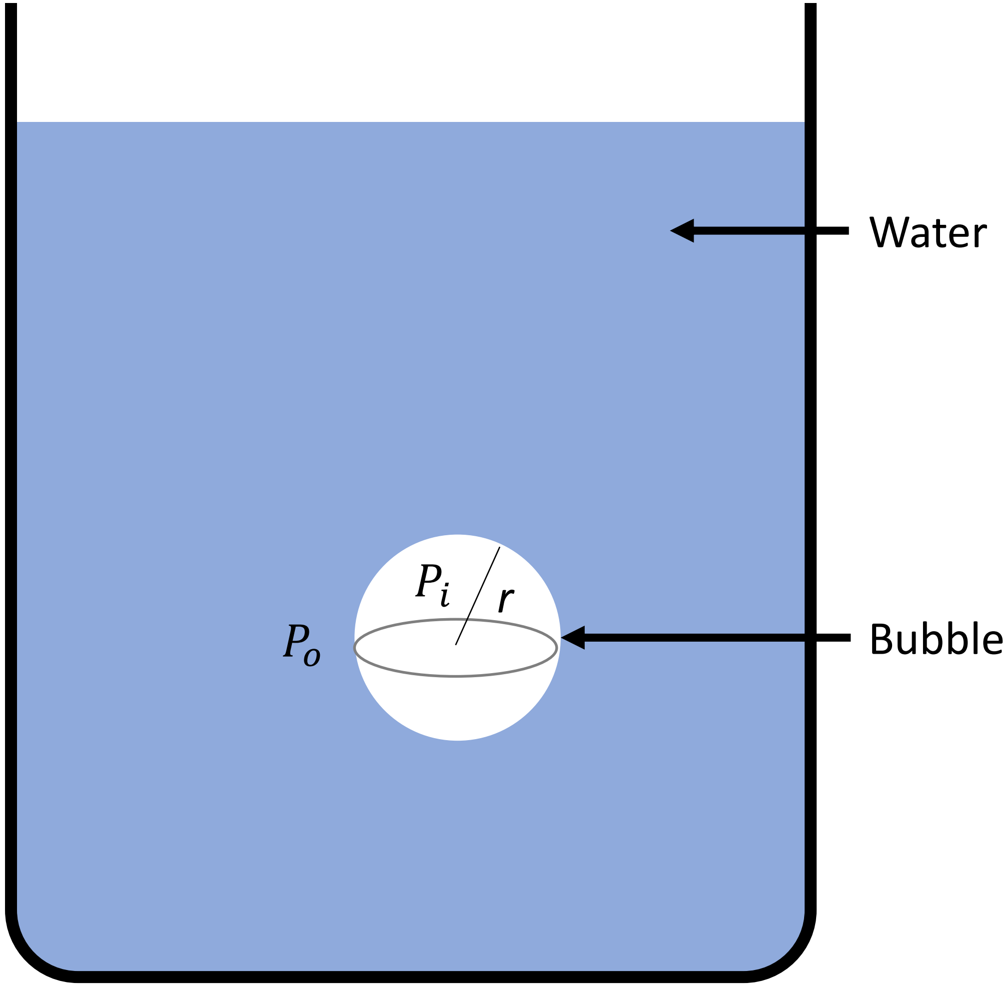


Duck et al. 1998, p. 199-223

Non-linear ultrasonics



A bubble at rest



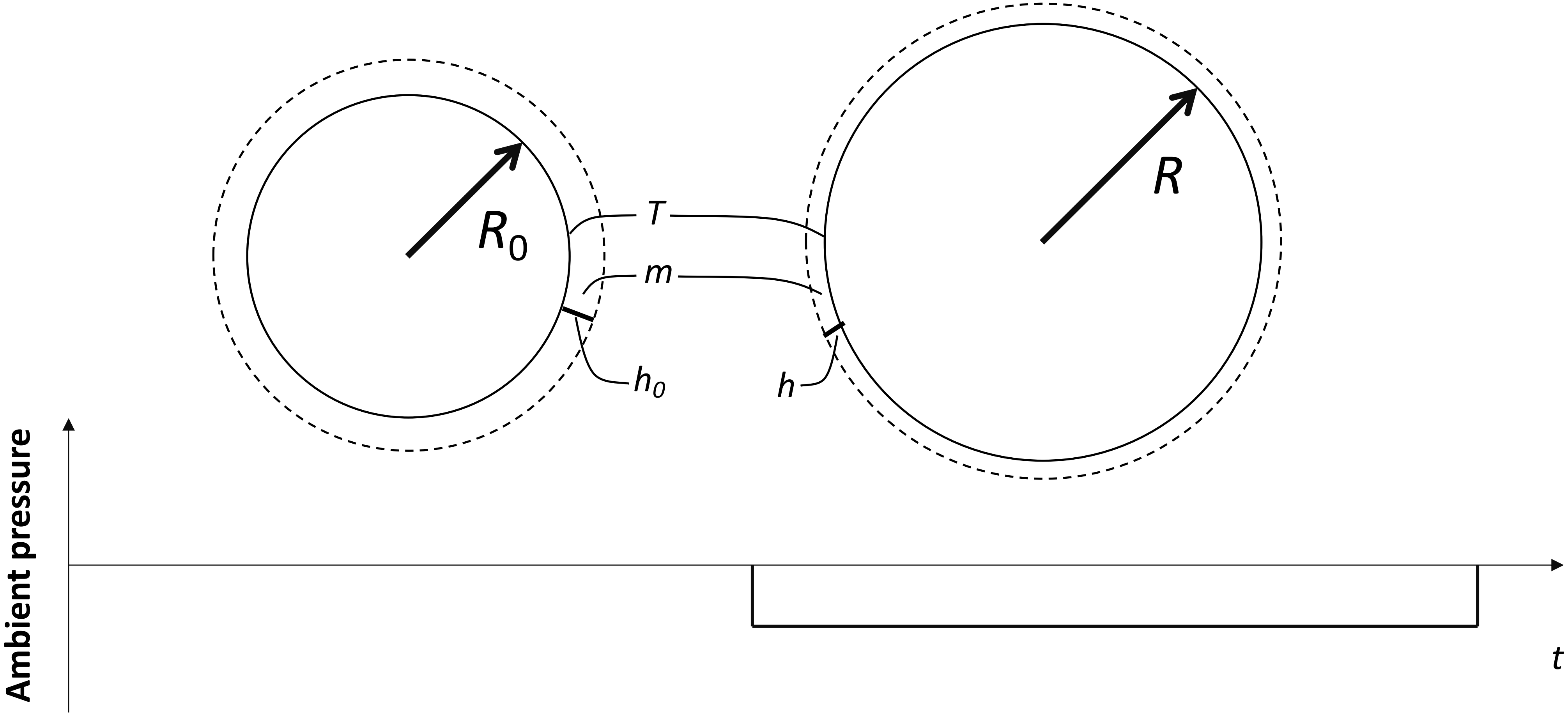
$$\Delta P = P_i - P_o = \frac{2T}{r}$$

$$\Rightarrow P_i = \frac{2T}{r} + P_o$$

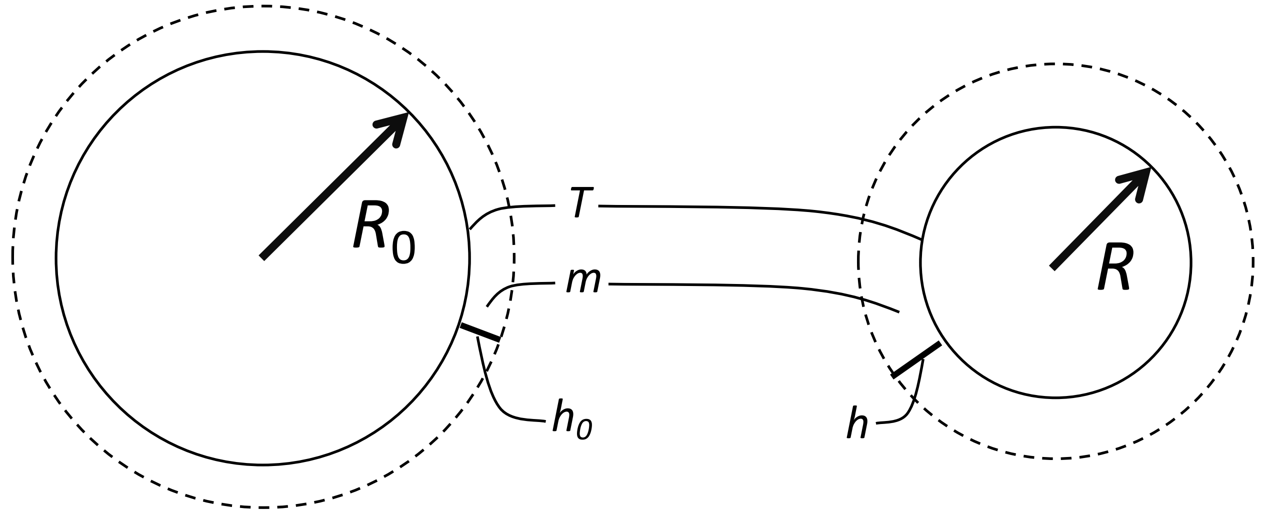
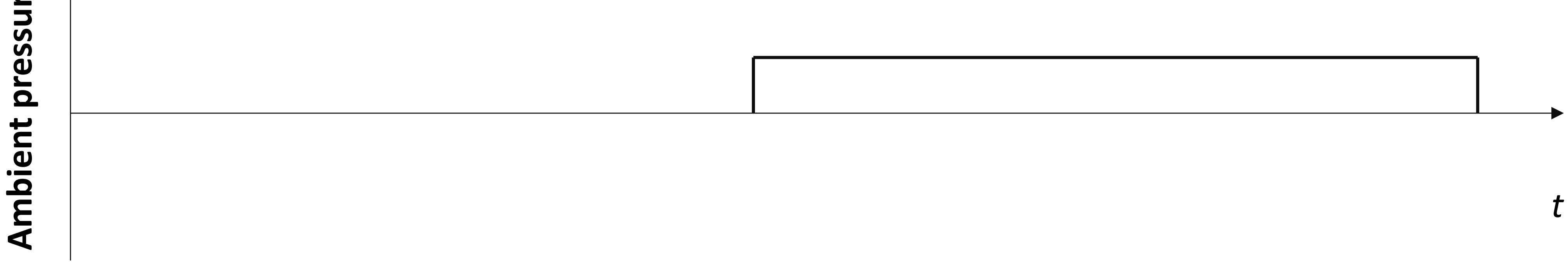
P_o = stationary pressure outside the bubble
P_i = stationary pressure inside the bubble
T = surface tension (72mN/m for water)
r = bubble radius

Surface tension tends to minimize the surface area of the bubble.

Bubble under low pressure



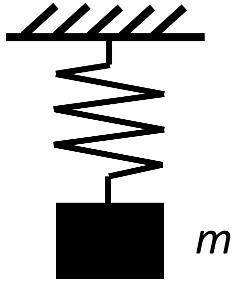
Bubble under high pressure

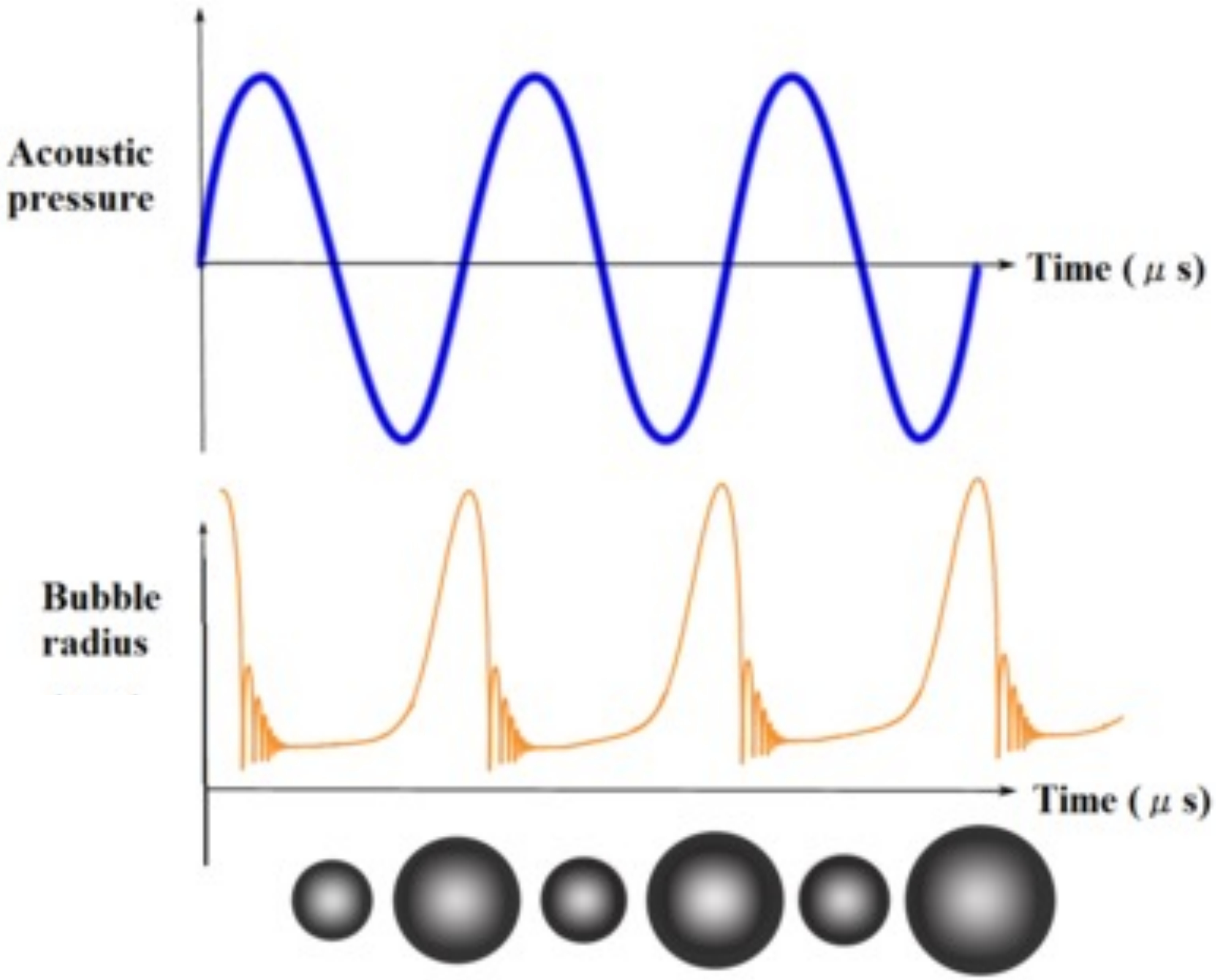
Analogy to Hooke's law

$$\boxed{F = -kx = ma}$$

F = force
k = spring constant
m = mass
a = acceleration

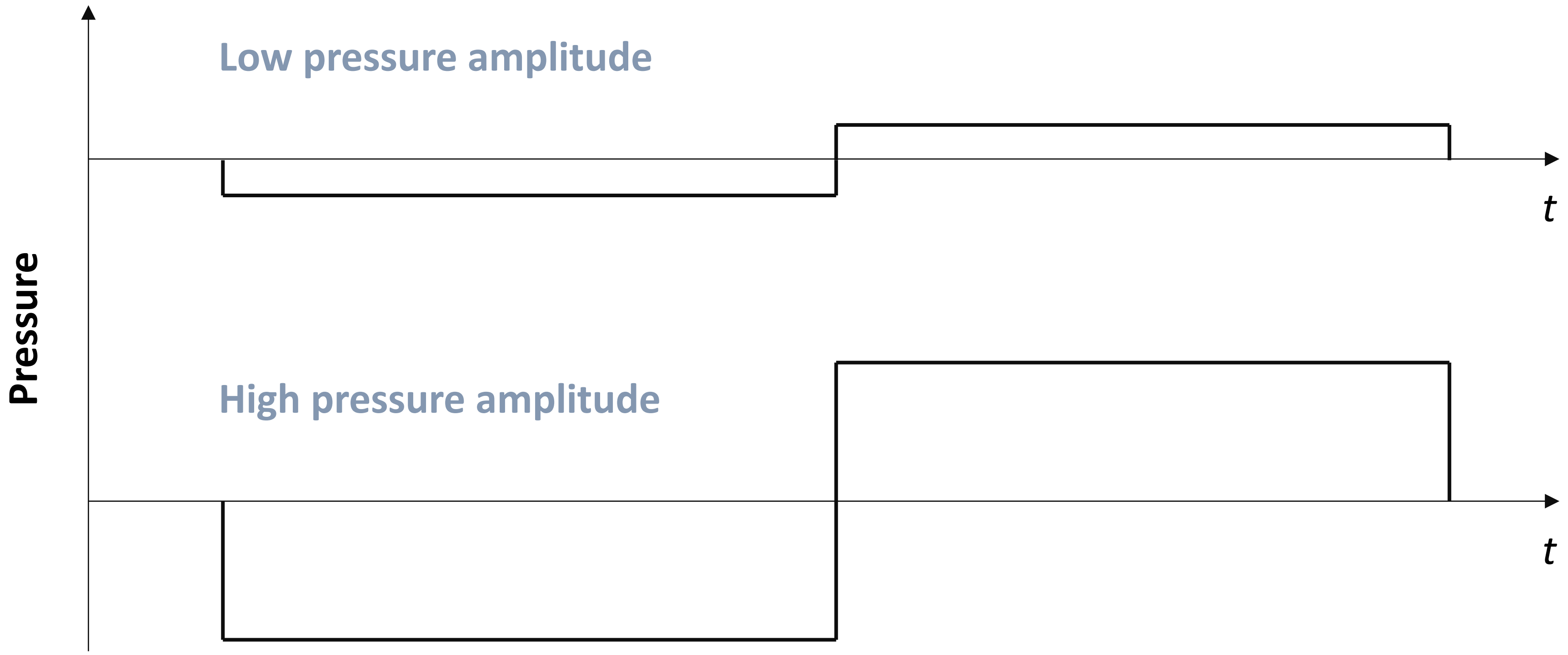


Bubble ringing



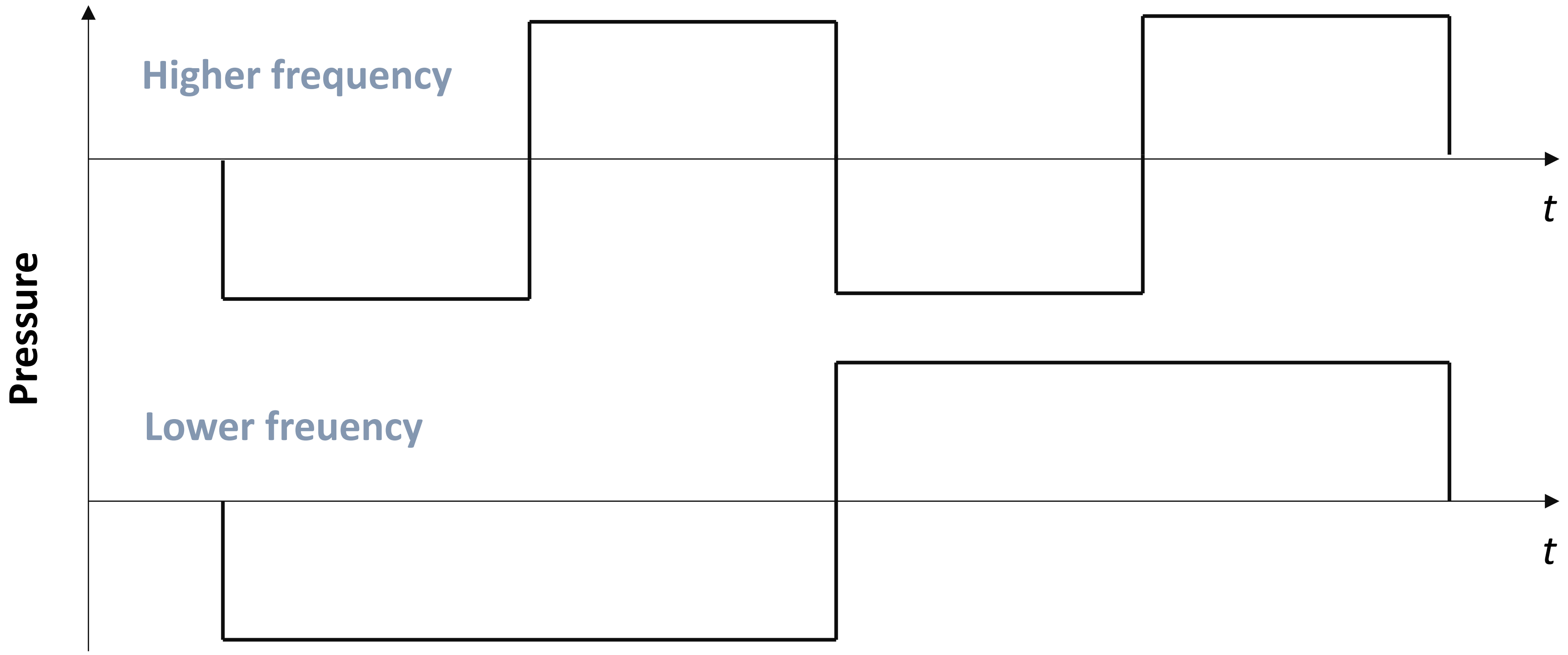
Driving the bubble with low or high pressure amplitude

- How would the bubble radius behave differently under externally induced low or high-pressure fluctuation, e.g. ultrasound?

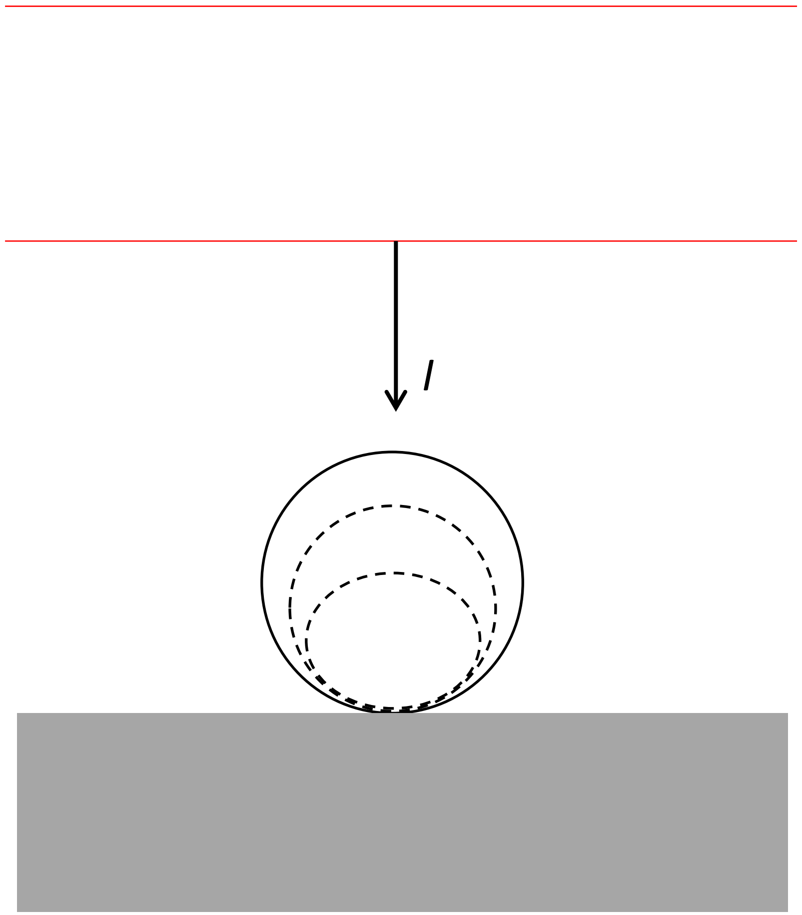


Driving the bubble with low or high pressure amplitude

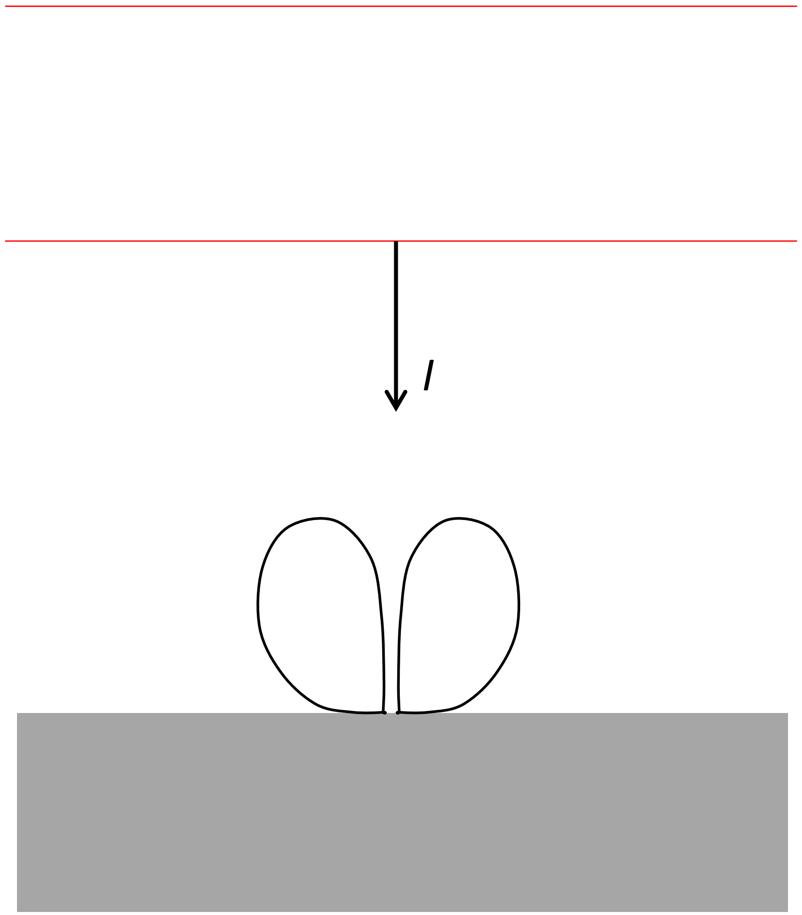
- How would the bubble radius behave differently under externally induced pressure fluctuation with low frequency vs. high frequency?



Cavitation bubble near wall

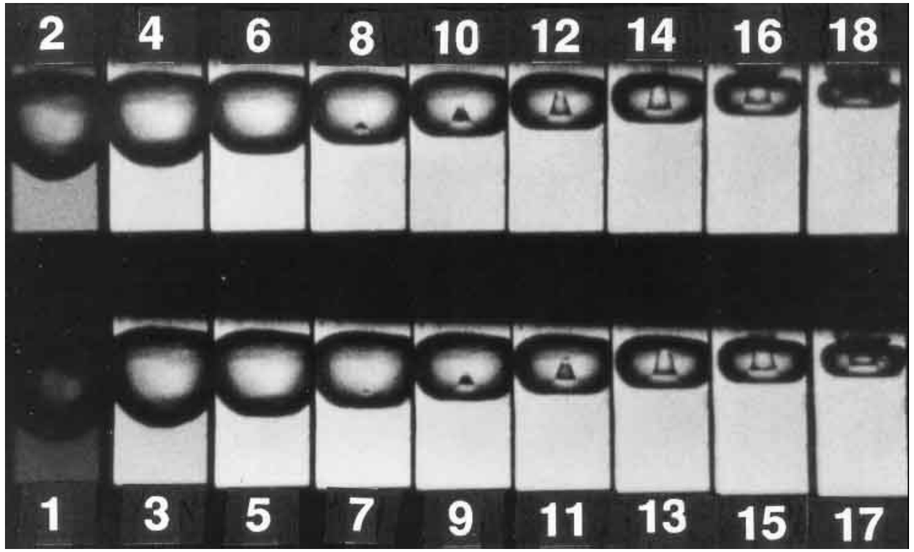


Oscillating bubble near wall



Cavitation

- Definition of cavitation: *interaction of small bubbles and pressure variations inside liquids,* e.g. due to ultrasound.
- The classical example: due to cavitation ship propellers corrode faster than expected



Time interval between frames 2µs, frame width is 1.4mm

Source: http://authors.library.caltech.edu

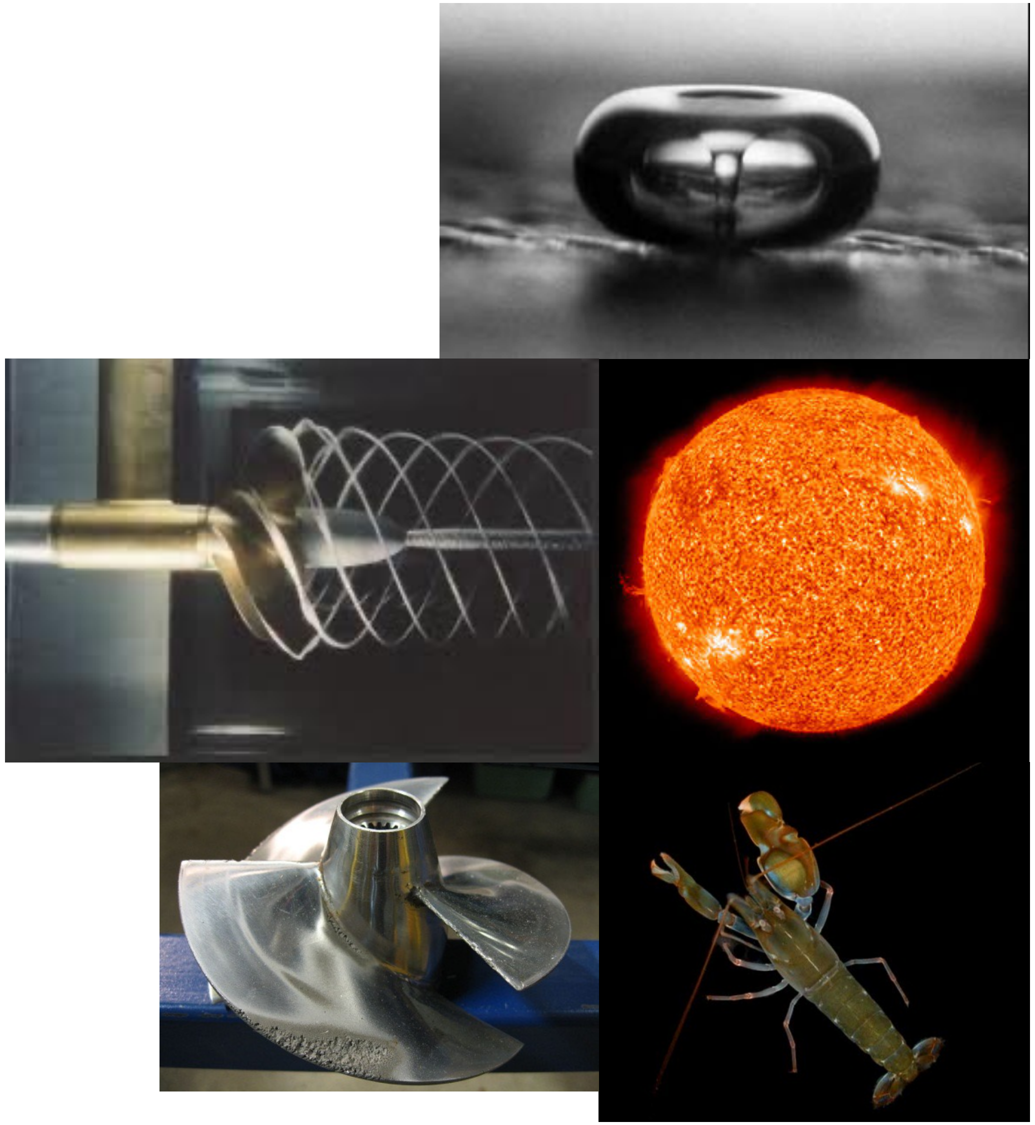
Stable and Transient cavitation

- **Two kinds of oscillations (usually radial):**
  - *Stable or non-inertial cavitation*
    - Bubble oscillates linearly or non-linearly with pressure over many cycles of an acoustic wave
  - *Transient or inertial cavitation*
    - Bubble grows or collapses more or less violently (bubble radius > 2 x bubble radius at rest)
- To simplify, bubble behavior depends on 1) bubble size compared to acoustic wavelength and 2) pressure amplitude of the driving wave.

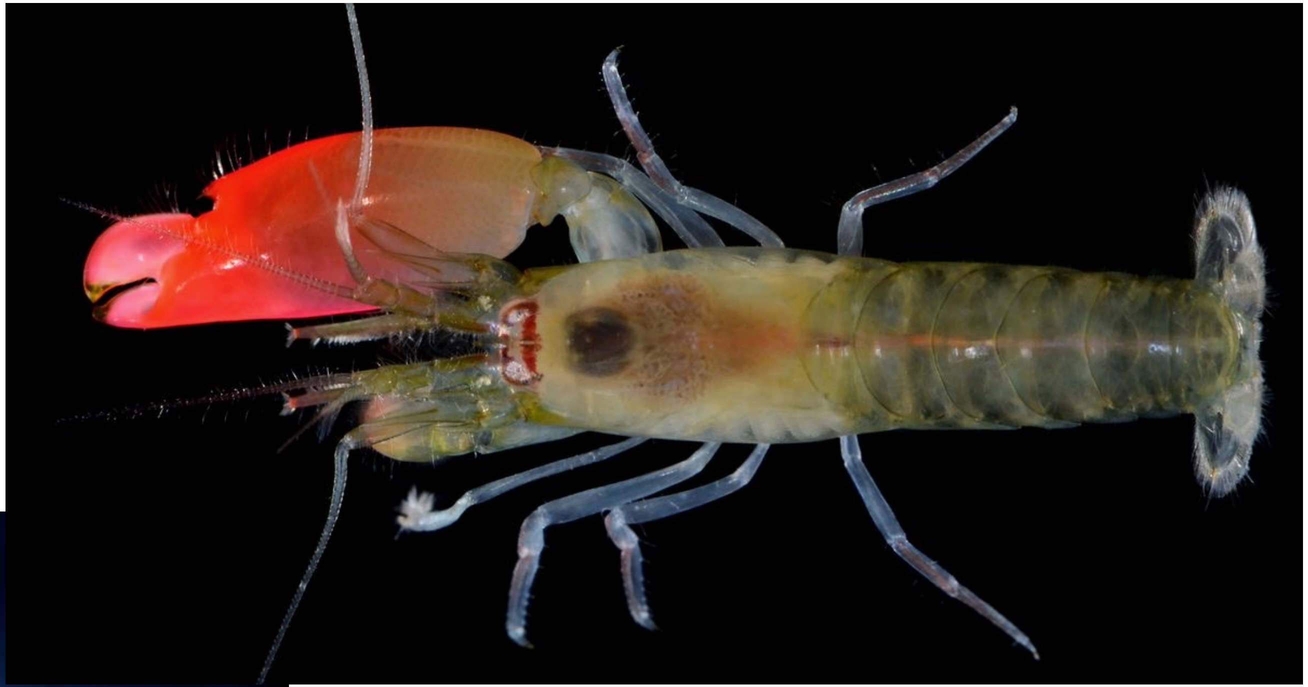
Cavitation

Cavitation generates:

1. thousands of Kelvins
2. pressures of Gpa
3. local accelerations 12 orders of magnitude higher than gravity
4. shock waves and
5. photon emission



Video: Pistol shrimp



Cavitation characteristics

- Every bubble acts as a “bell”. Every bubble has its resonance frequency.
- Cavitation is strongly a threshold phenomenon, mainly dictated by the PNP, since PNP contributes to bubble growth.
- At small small amplitudes, the oscillation is stable. Beyond a given PNP, the oscillation become chaotic and violent
  - Potentially leads to implosions and rapid liquid motion
- Relevance from biological/medical aspect:
  - The inertia and change in momentum of the liquid can induce high forces on tissue or matter

Cavitation characteristics

- Cavitation is characterized by limited predictability
  - A threshold phenomenon
  - Depends on *e.g.*
    - Driving frequency
    - Peak negative pressure
    - Size distribution of gas bubbles
    - Precence of cavitation nuclei
    - Bubble surface tension
    - Bubble history

Mechanical index

- Mechanical index: $MI = \frac{PNP}{\sqrt{f}}$

Note the non-SI units!

PNP = peak-negative pressure (MPa)

f = frequency (MHz)

FDA *MI* limitations for imaging:

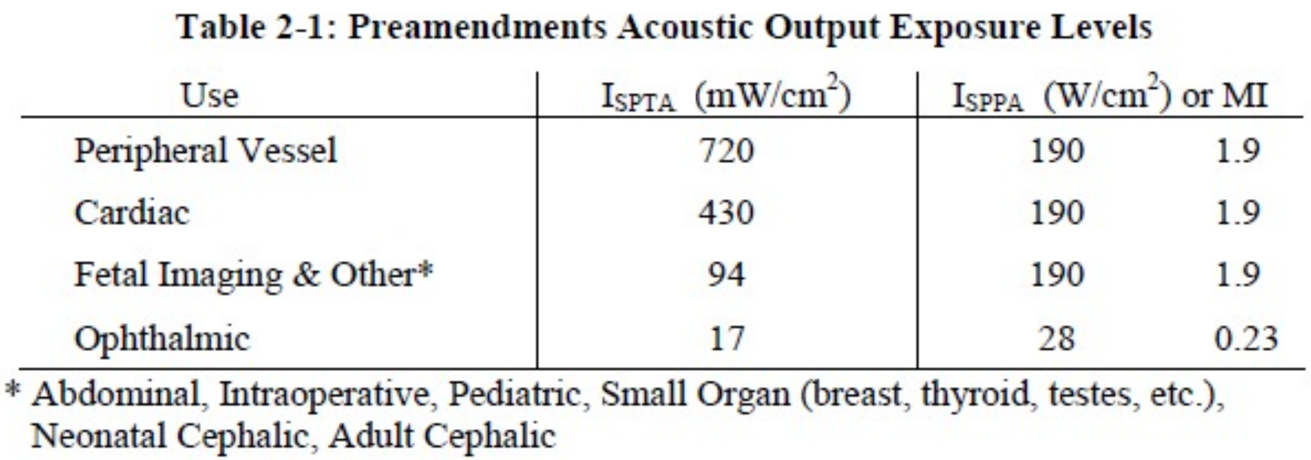


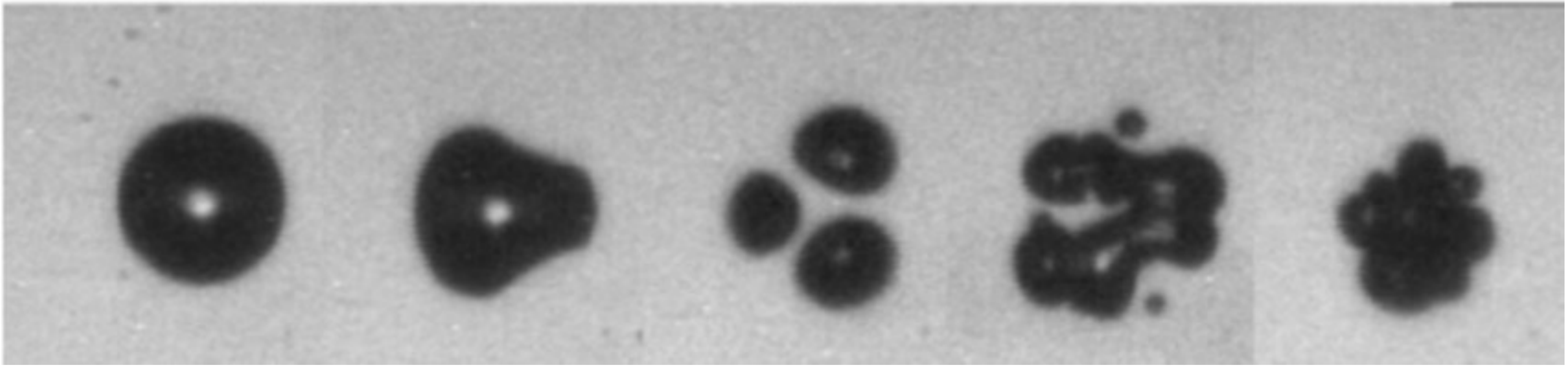
Table 2-1: Preamendments Acoustic Output Exposure Levels

Use	I_{SPTA} (mW/cm^2)	I_{SPPA} (W/cm^2) or MI	
Peripheral Vessel	720	190	1.9
Cardiac	430	190	1.9
Fetal Imaging & Other*	94	190	1.9
Ophthalmic	17	28	0.23

* Abdominal, Intraoperative, Pediatric, Small Organ (breast, thyroid, testes, etc.), Neonatal Cephalic, Adult Cephalic

FDA *MI* limitations for therapy are usually evaluated case-by-case –basis.

History-dependence of cavitation



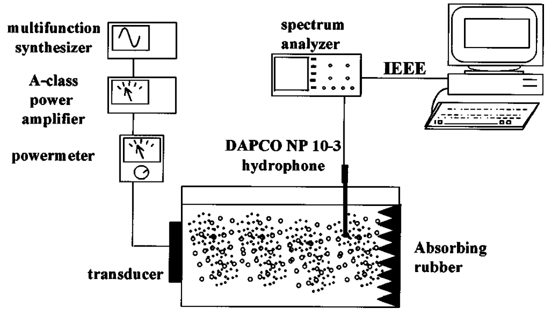
Versluis et al. Phys. Rev. E 82, 026321 2010:
https://www.researchgate.net/publication/46423457_Microbubble_shape_oscillations_excited_through_ultrasonic_parametric_driving/download

History-dependence:

What interpretations can you make from this data?

Harmonics/Resonance?
Bubble size?
Inertial or non-inertial?
Number of bubbles?

f = 1.075 MHz

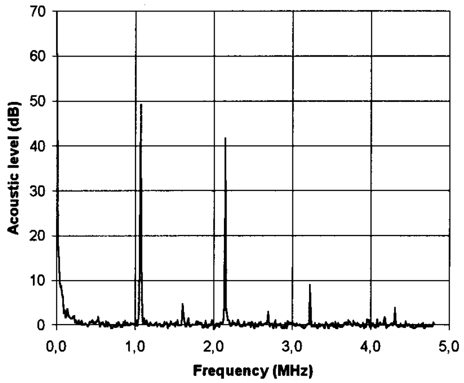


Frohly et al 2000

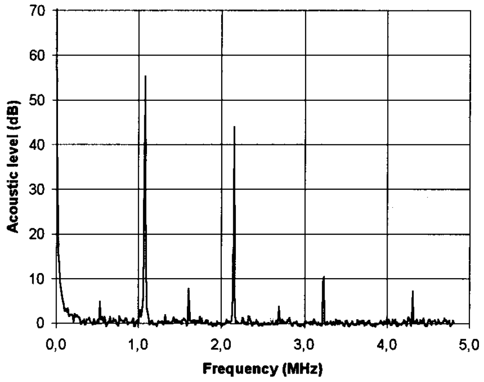
INCREASING INTNSITY

INCREASING INTENSITY

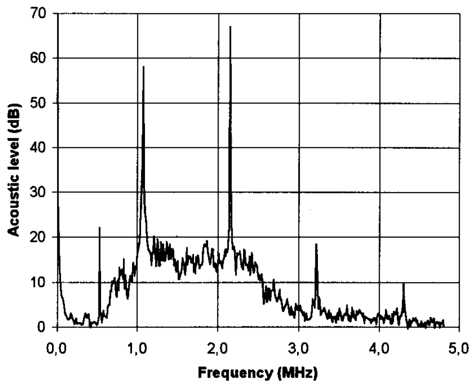
$12\ mW/cm^2$ acoustic intensity



$24\ mW/cm^2$ acoustic intensity

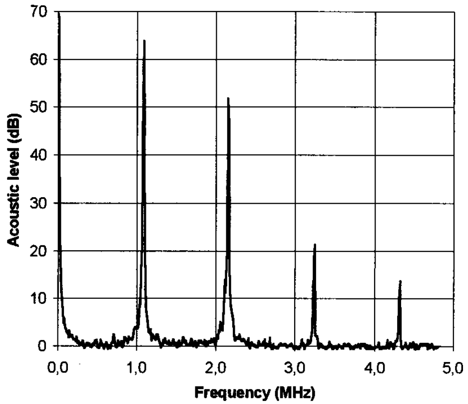


$60\ mW/cm^2$ acoustic intensity

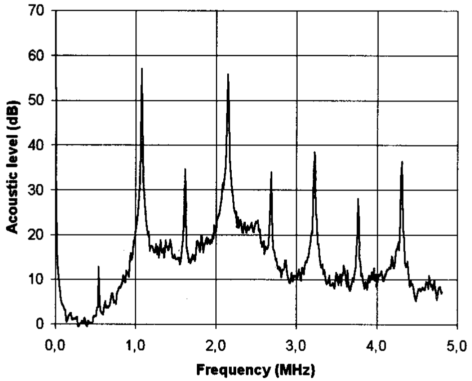


DECREASING INTENSITY

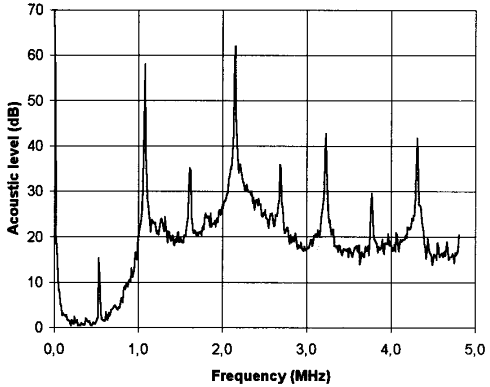
$12\ mW/cm^2$ acoustic intensity



$24\ mW/cm^2$ acoustic intensity



$60\ mW/cm^2$ acoustic intensity



DECREASING INTNSITY

Bubble resonance

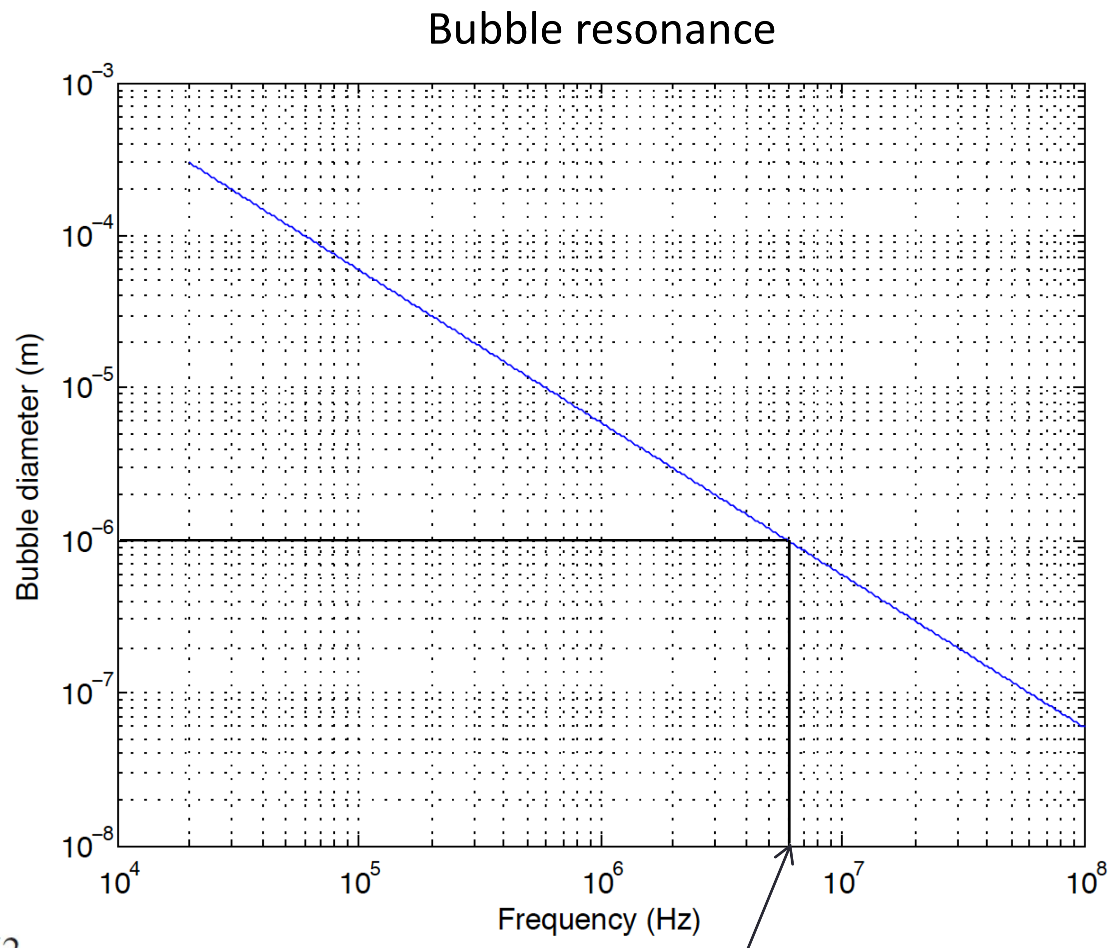
- M. Minnaert reported 1933 on ”musical air-bubbles”, which resonate at certain frequencies under external driving pressure fluctuation.
- Assuming inviscid media and and neglecting surface tension bubble resonance follows the following dependence:

$$f R_{\mathrm{res}} \approx 3 \text{ m/s}$$

for air bubbles at athmospheric pressure, where f = driving frequency and R_0 = bubble radius at rest.

$$R_{\mathrm{res}} = \frac{1}{2\pi f}\left(\frac{3p_0}{\rho}\right)^{1/2}$$

p_0 = ambient pressure, ρ = water density

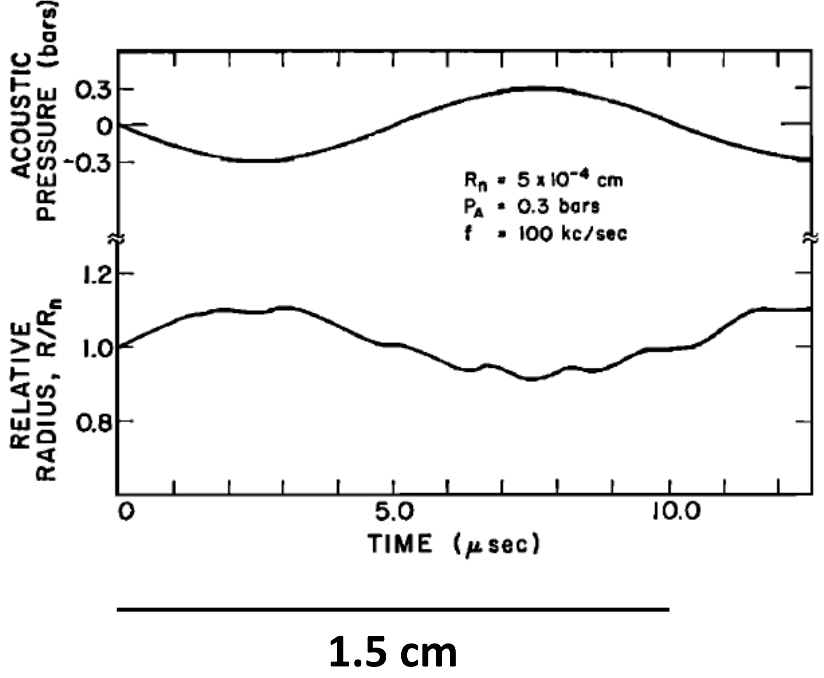


- 1 mm bubble (dia) resonance at 6 kHz
- 6 µm bubble (dia) resonance at 1 MHz
- 1 µm bubble (dia) resonance at 6 MHz

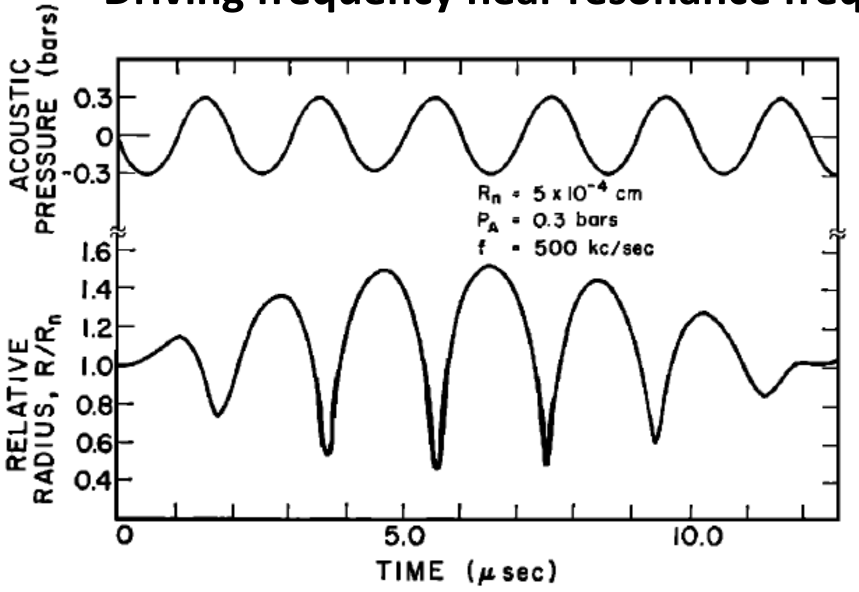
Driving frequency & bubble resonance

- Relative bubble radii modulated by ultasound

Driving pressure of resonance



Driving frequency near resonance freq.



Eller et al 1965: http://scitation.aip.org/content/asa/journal/jasa/37/3/10.1121/1.1909357

Threshold for cavitation depends on bubble resonance

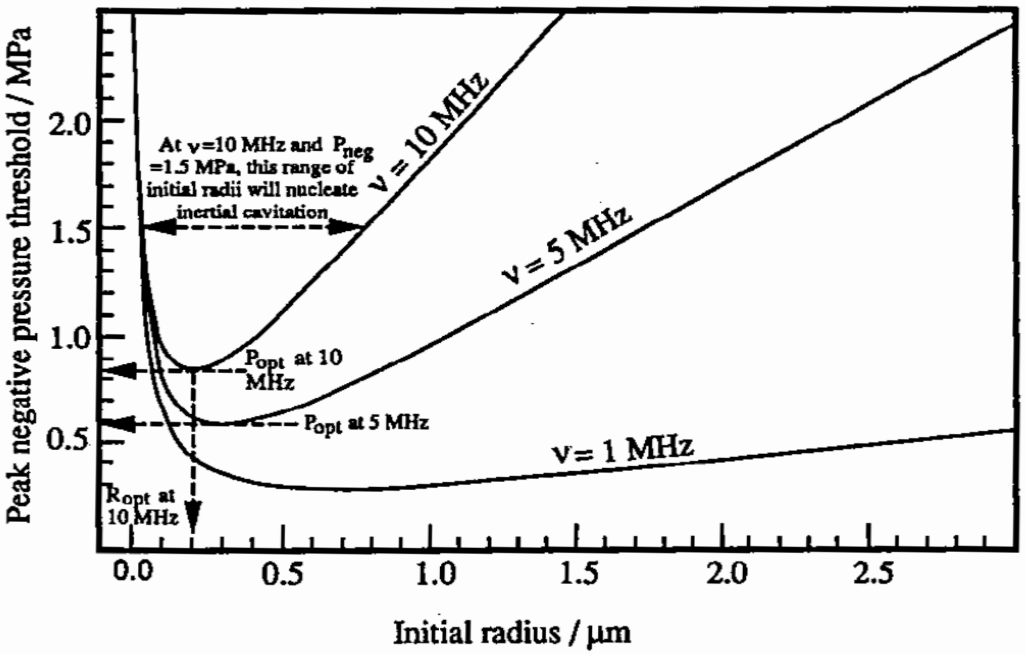


Figure 11.1. *The threshold for inertial cavitation, as predicted by the theory of Apfel and Holland. For each frequency a line can be plotted: if the conditions of peak negative pressure and of the initial bubble radius are such that the point of interest on the graph lies below the line, non-inertial cavitation will occur. If the point of interest is above the line, inertial cavitation will occur. Reprinted by permission of Elsevier Science from 'Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound' by R E Apfel and C K Holland, Ultrasound in Medicine and Biology, vol 18, pp 267–81, copyright 1991 by World Federation of Ultrasound in Medicine and Biology.*

Bubble collapse (boom & light)

Shock wave

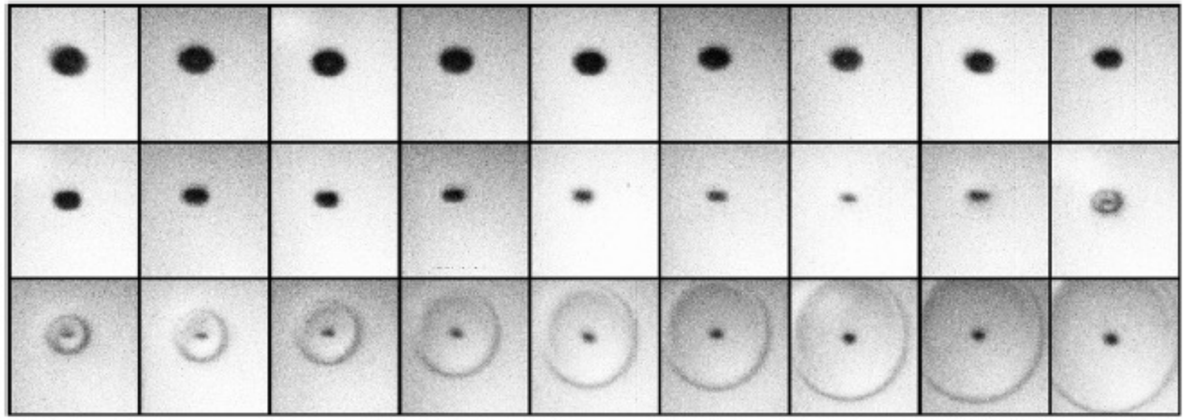


Figure 28. Photographic series of the dynamics of a laser produced bubble collapse in water, combined from several sequences taken at 20.8 milion frames per second (48 ns interframe time). The bubble reaches its maximum radius of 1.1 mm 99.5 μs before the first frame. The size of the individual frames is 1.5 × 1.8 mm^2. (Courtesy of C D Ohl.)

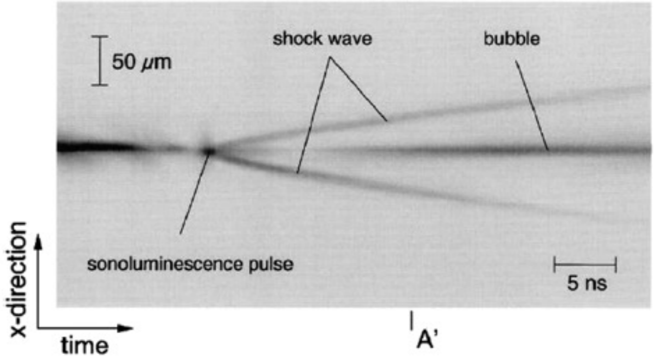


Figure 59. Streak photograph of a collapsing sonoluminescing bubble. Intensity inverted plot. (Reprinted with permission from R Pecha and B Gompf [215]. Copyright 2000 by the American Physical Society.)

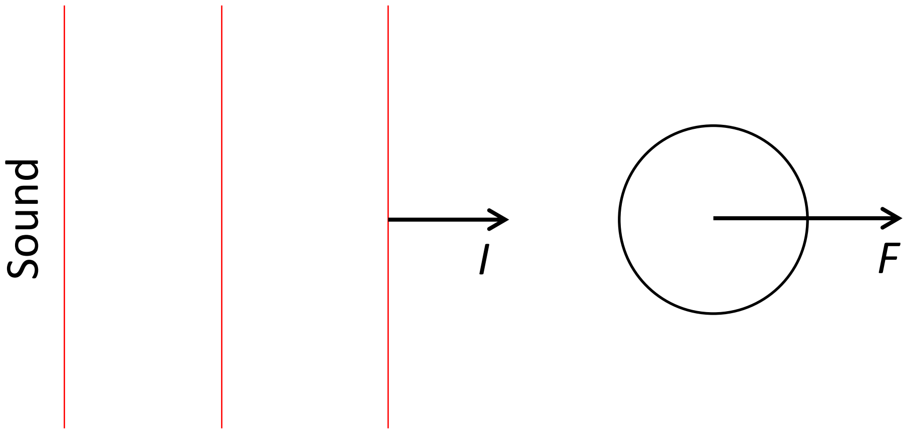
Sonoluminescence

Figure 71. Colour photograph of the light emitted by a trapped, positionally unstable bubble. Long exposure. (Courtesy of R Geisler.)

Lauterborn & Kurz 2010: http://iopscience.iop.org/0034-4885/73/10/106501/pdf/0034-4885_73_10_106501.pdf

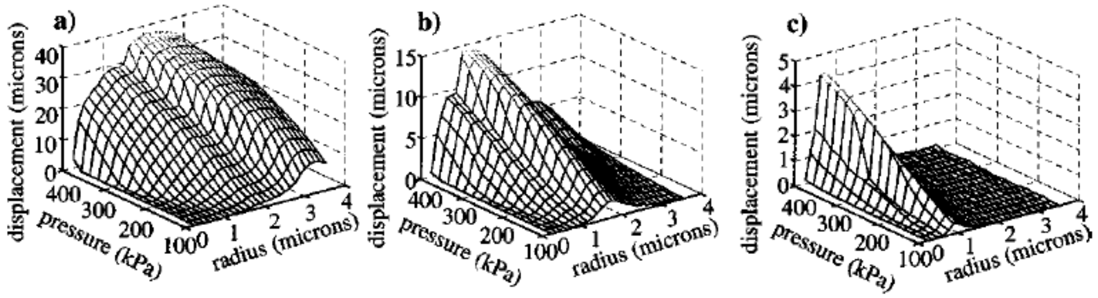
Primary Bjerknes force

- Primary Bjerknes force is the acoustic radiation force of a travelling wave that is excerted on a bubble



Radiation force on single bubbles

20 cycle pulse

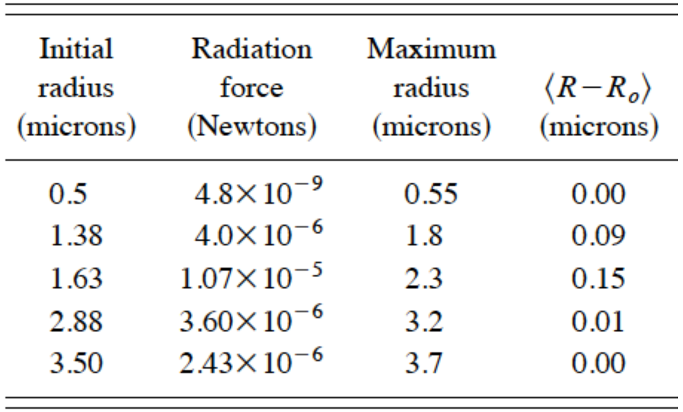


1 MHz **2.25 MHz** **5 MHz**

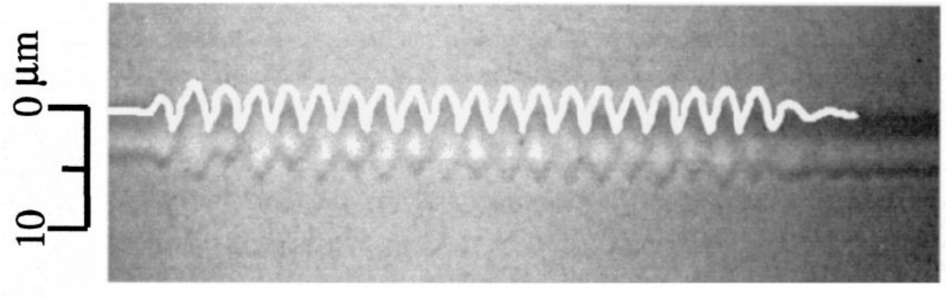
Max. translation:

- Maximized at bubble resonance

2.25 MHz, 100 kPa



Initial radius (microns)	Radiation force (Newtons)	Maximum radius (microns)	$\langle R-R_o \rangle$ (microns)
0.5	4.8×10^{-9}	0.55	0.00
1.38	4.0×10^{-6}	1.8	0.09
1.63	1.07×10^{-5}	2.3	0.15
2.88	3.60×10^{-6}	3.2	0.01
3.50	2.43×10^{-6}	3.7	0.00

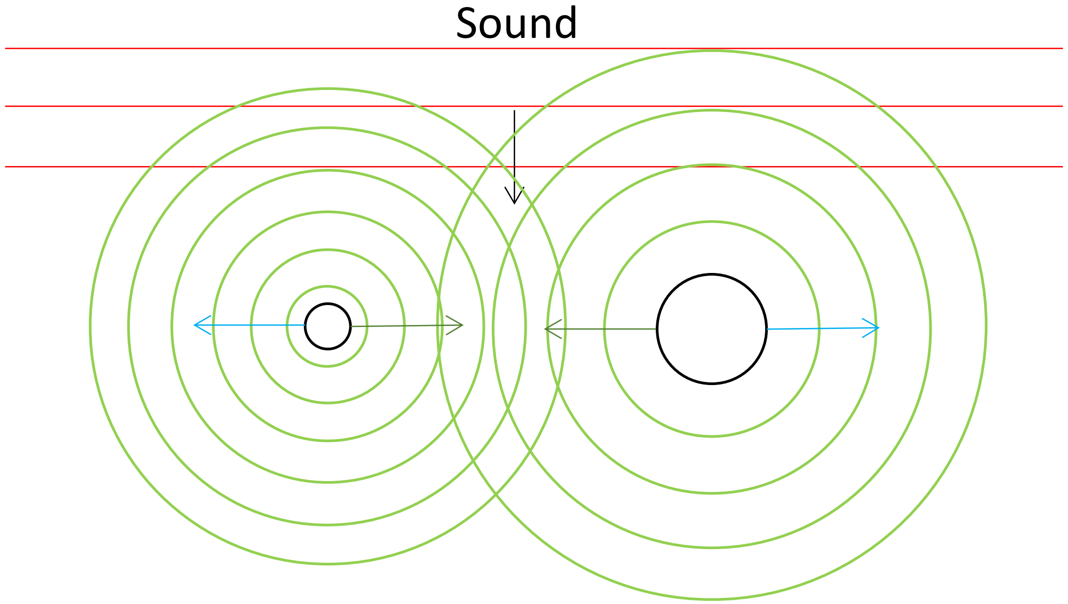


Medical ultrasound may generate micro-bubble speed as high as 0.5 m/s (5 um distance in 20 cycles of 380 kPa, 2.25 MHz ultrasound).

Dayton et al. http://www.ncbi.nlm.nih.gov/pubmed/12430830

Secondary Bjerknes force

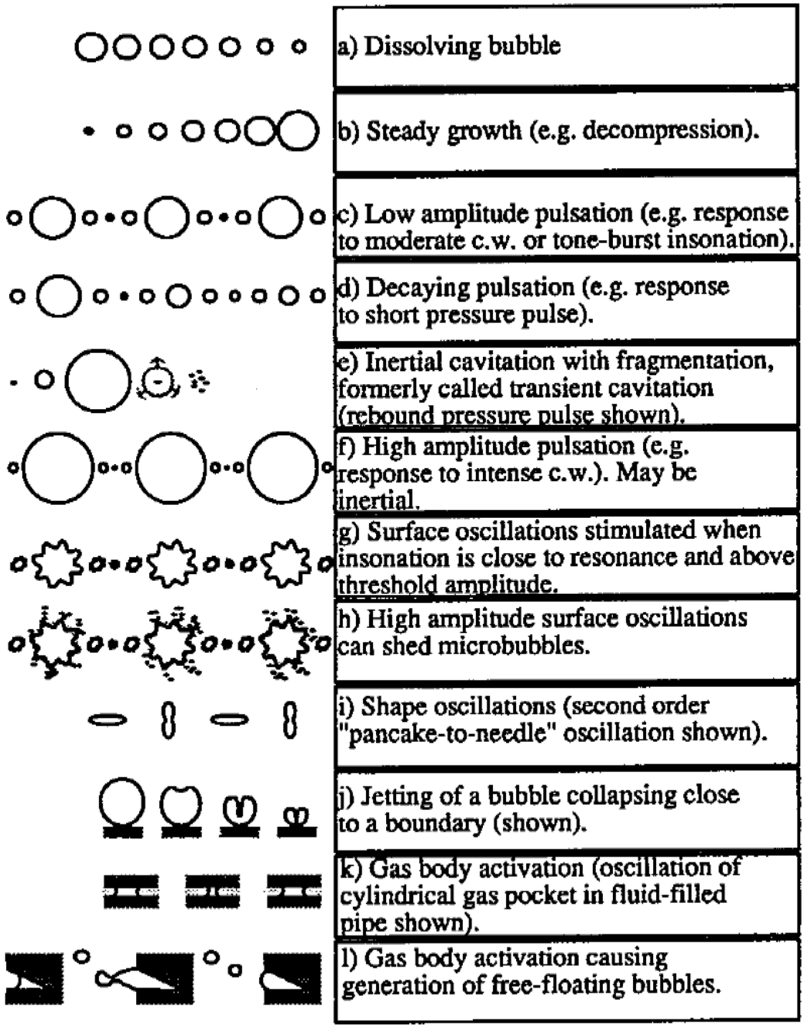
- Secondary Bjerknes forces arise from the acoustic radiation in sound field generated by oscillating bubbles (or particles)



Linear case: If $f_{\text{res, 1}} < f_{\text{drive}} < f_{\text{res, 2}}$: bubbles attract each other

else : bubbles repel each other

Different forms of cavitation



a) Dissolving bubble

b) Steady growth (e.g. decompression).

c) Low amplitude pulsation (e.g. response to moderate c.w. or tone-burst insonation).

d) Decaying pulsation (e.g. response to short pressure pulse).

e) Inertial cavitation with fragmentation, formerly called transient cavitation (rebound pressure pulse shown).

f) High amplitude pulsation (e.g. response to intense c.w.). May be inertial.

g) Surface oscillations stimulated when insonation is close to resonance and above threshold amplitude.

h) High amplitude surface oscillations can shed microbubbles.

i) Shape oscillations (second order "pancake-to-needle" oscillation shown).

j) Jetting of a bubble collapsing close to a boundary (shown).

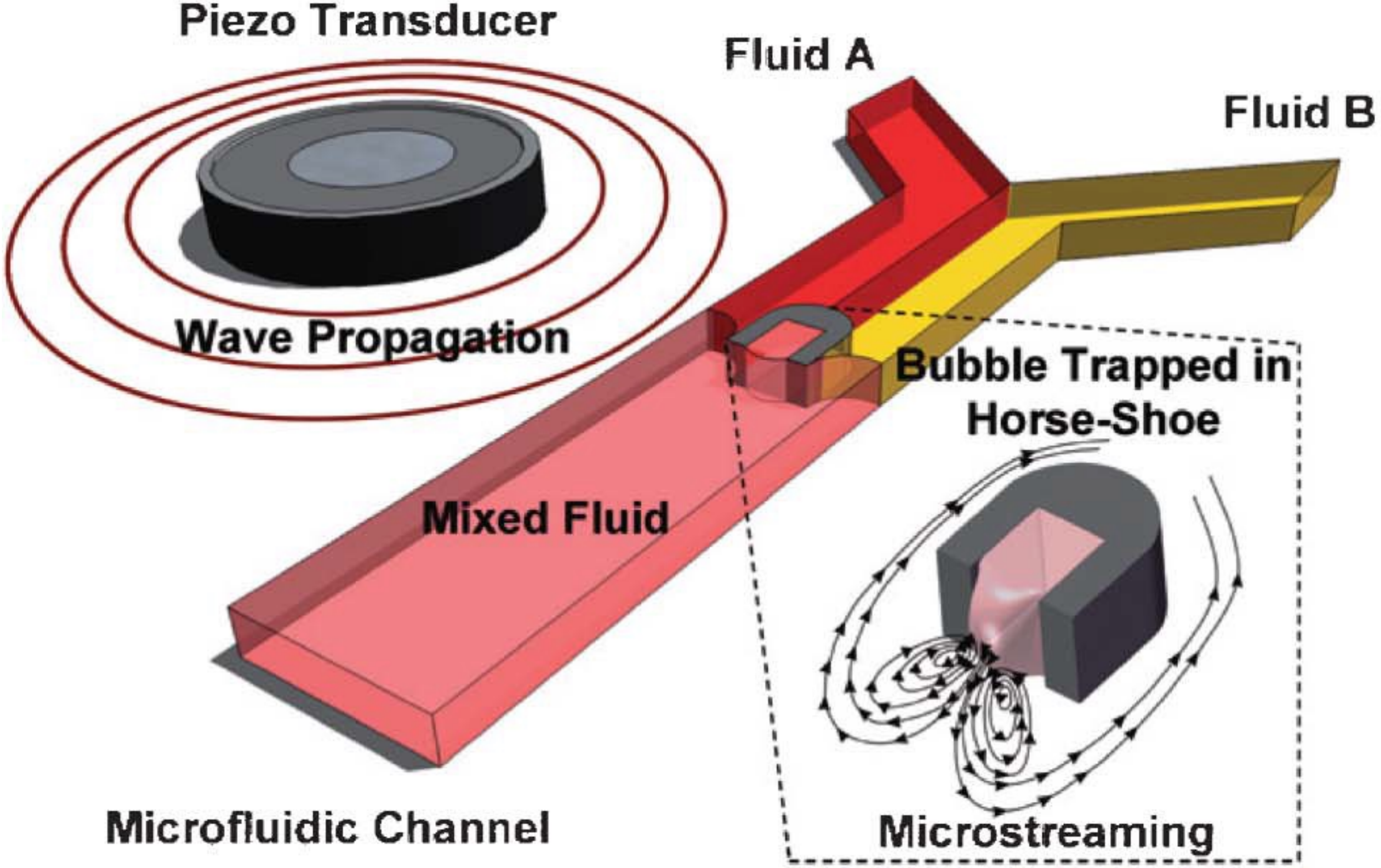
k) Gas body activation (oscillation of cylindrical gas pocket in fluid-filled pipe shown).

l) Gas body activation causing generation of free-floating bubbles.

Figure 11.2. *A schematic illustration of the range of bubble behaviour. The behaviours are described in the text. The expansion ratios drawn for these bubbles are exaggerated to illustrate the pulsations more clearly.*

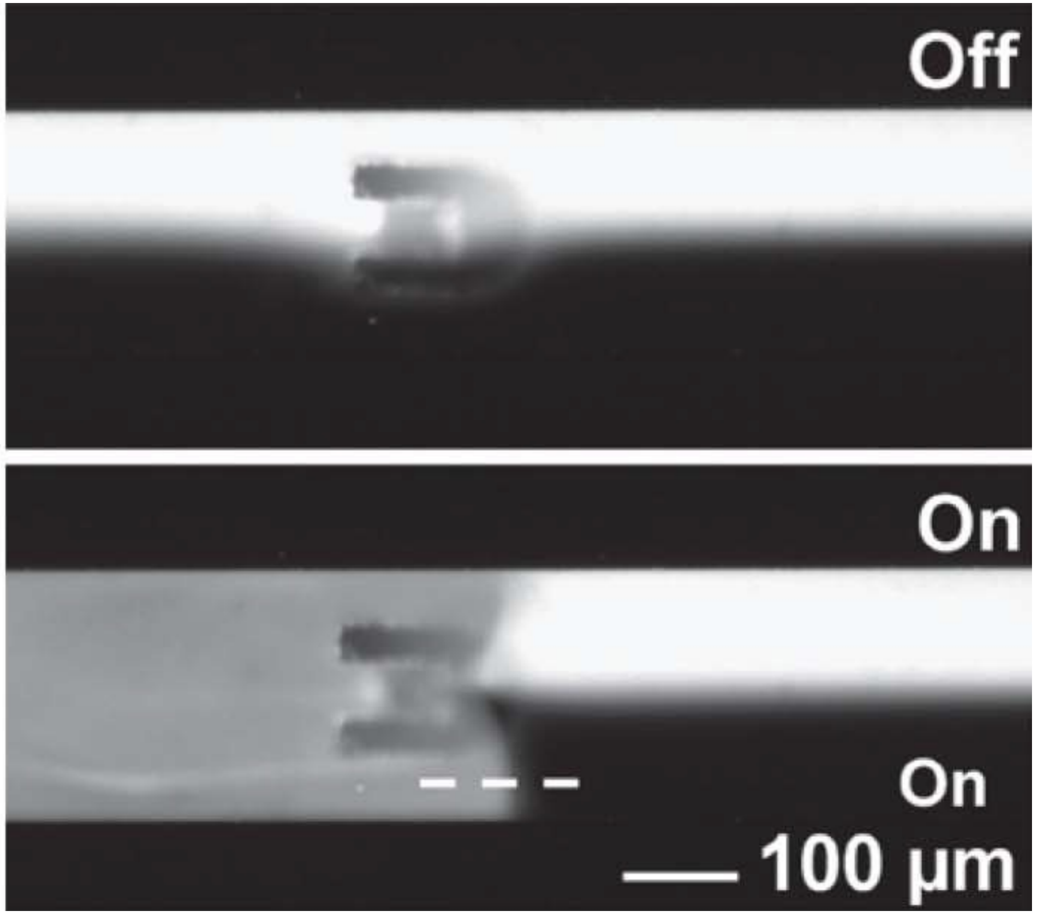
Real-life examples

Micro-bubble –enhanced micro-streaming



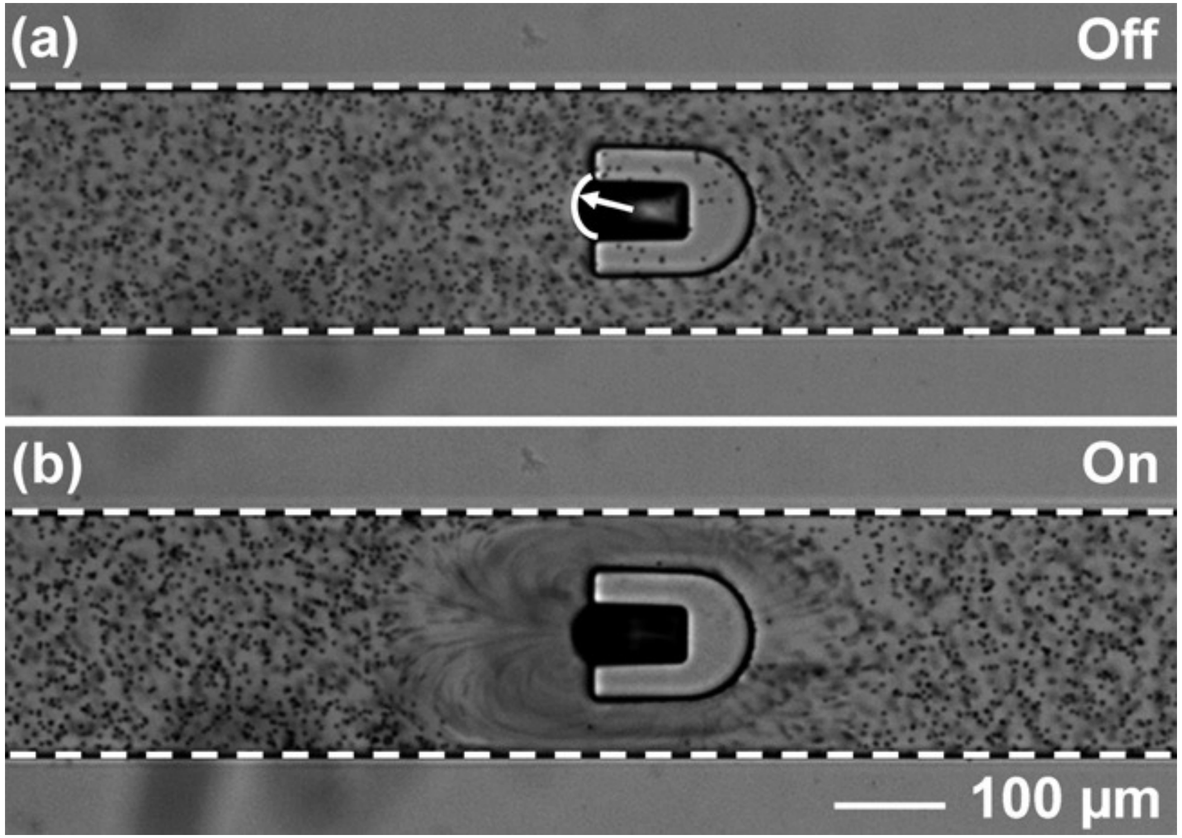
http://pubs.rsc.org/en/content/articlepdf/2012/lc/c2lc40203c

Micro-bubble –enhanced micro-streaming: fluid mixing



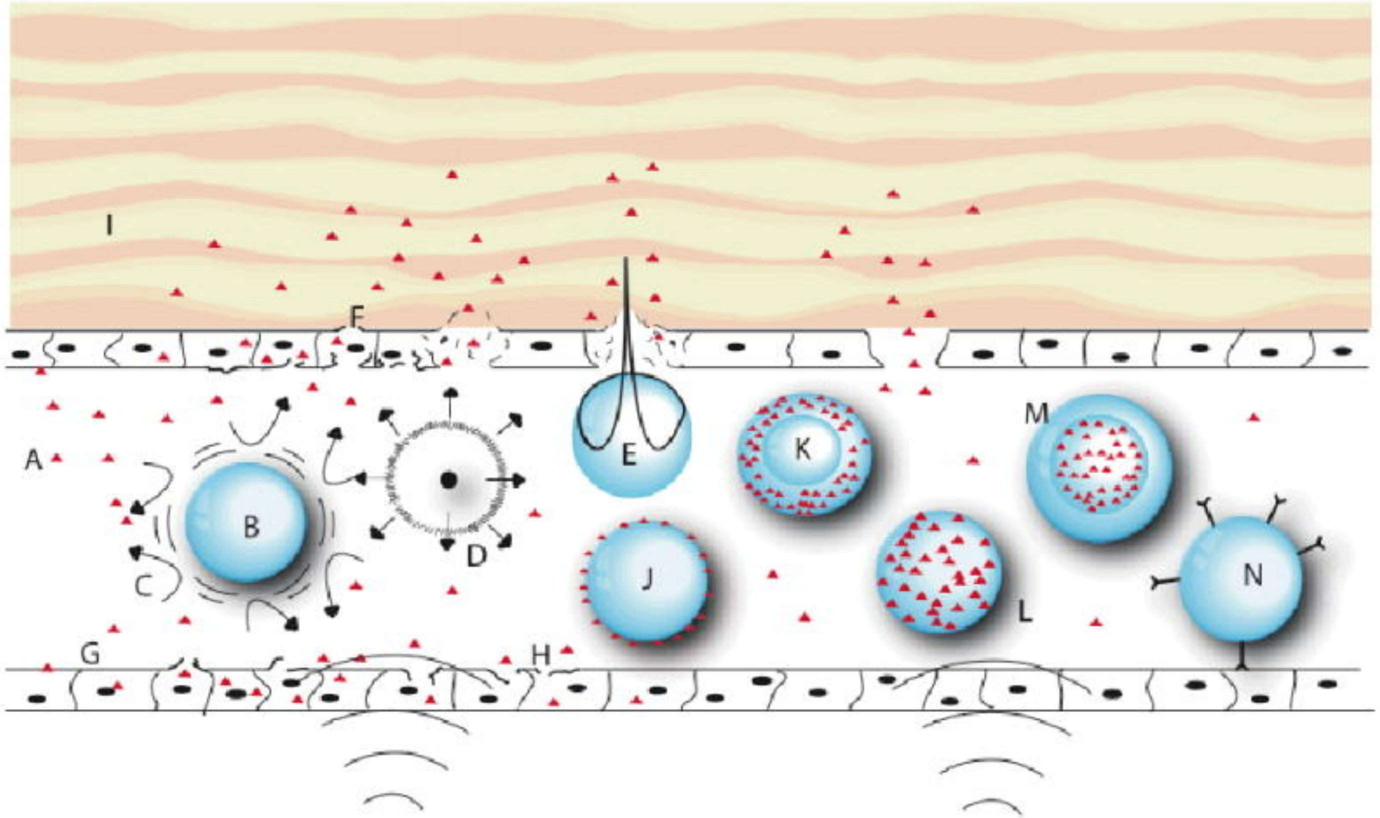
http://pubs.rsc.org/en/content/articlepdf/2012/lc/c2lc40203c

Micro-bubble –enhanced micro-streaming: mixing particles



http://pubs.rsc.org/en/content/articlepdf/2012/lc/c2lc40203c

Micro-bubble-enhanced delivery



Schematic representation of various modes by which drug delivery can be enhanced by ultrasound. A: therapeutic agent (triangles); B: gas bubble undergoing stable cavitation; C: microstreaming around cavitating bubble; D. collapse cavitation emitting a shock wave; E: asymmetrical bubble collapse producing a liquid jet that pierces the endothelial lining; F: completely pierced and ruptured cell; G: non-ruptured cells with increased membrane permeability due to insonation; H: cell with damaged membrane from microstreaming or shock wave; I: extravascular tissue; J: thin-walled microbubble decorated with agent on surface; K. thick-walled microbubble with agent in lipophilic phase; L: micelle with agent in lipophilic phase; M: liposome with agent in aqueous interior; N: vesicle decorated with targeting moieties attached to a specific target.

Pitt et al. 2006: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1361256/

Vesicle rupture induced by a single bubble

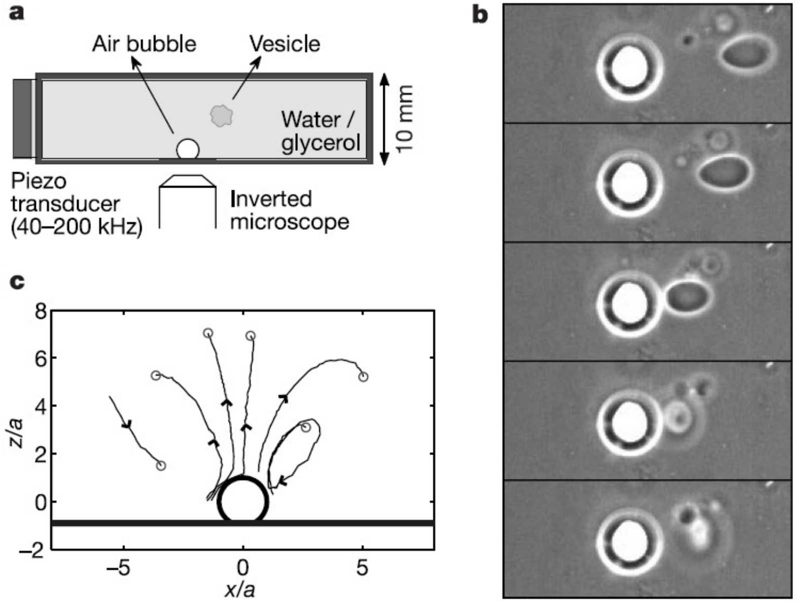
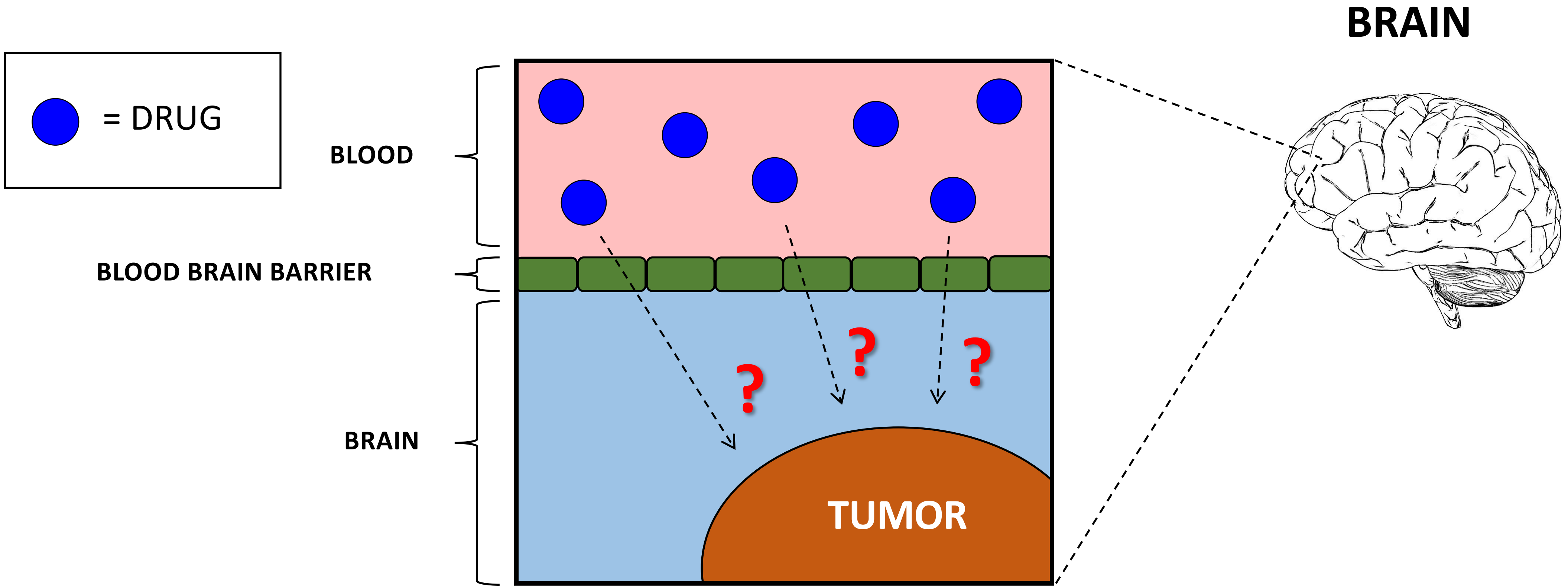


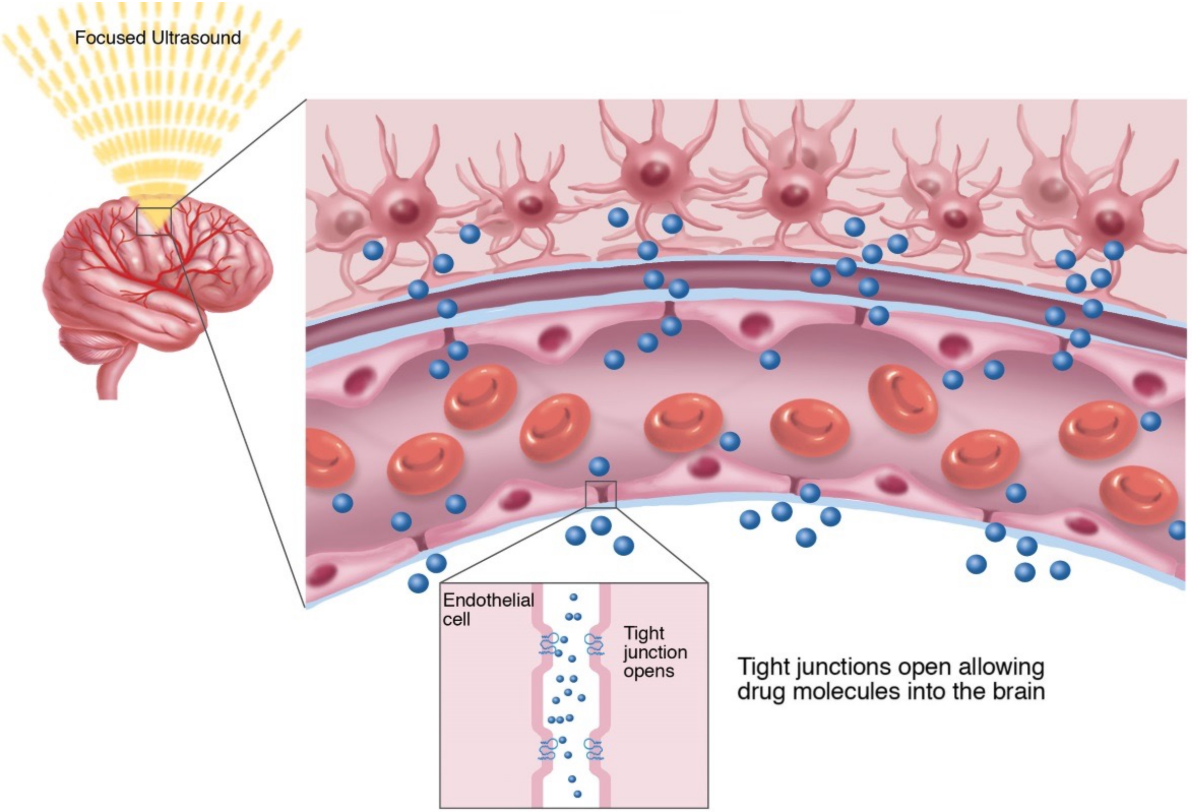
Figure 1 Vesicle motion near an oscillating bubble. **a**, Layout of the experiment. The piezoelectric transducer generates a standing ultrasound field. **b**, High-speed time series (bottom view through inverted microscope) of vesicle motion (interframe time 10 ms). The bright object is a bubble of radius $a \approx 15\ \mu m$ at the cuvette wall, whose oscillation amplitude is too small to be seen here. The dark object on the right is a lipid vesicle, whose shape far from the bubble would be spherical. Here it is severely deformed as it approaches the bubble, collides with it, and is then expelled away from the observer (upwards in the cuvette), blurring as it leaves the focal plane (see Supplementary movie 1). **c**, Experimentally observed trajectories of vesicles in a side view (z is the axis perpendicular to the cuvette wall to which the bubble is attached).

Marmottant et al. 2003 Nature, vol 423, pp: 153-155

Blood-brain barrier opening



Blood-brain barrier opening

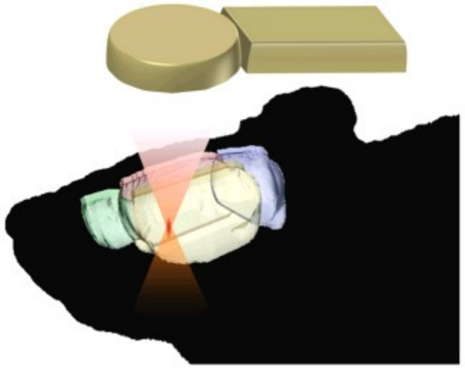


Tight junctions open allowing drug molecules into the brain

https://physicsworld.com/a/focused-ultrasound-opens-the-blood-brain-barrier-2/

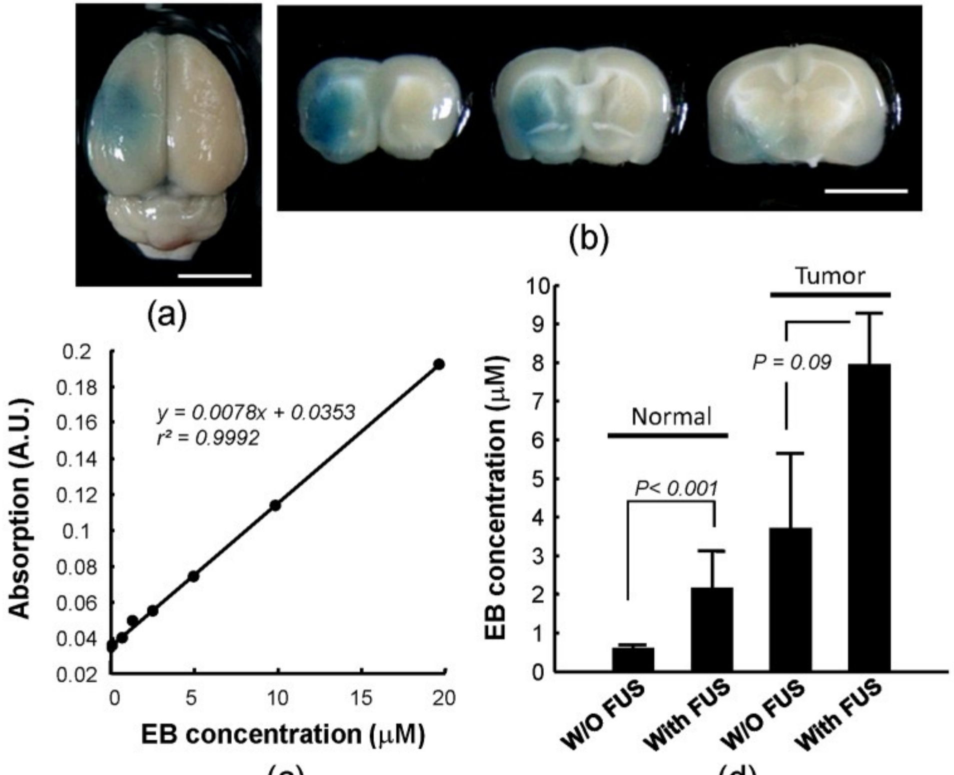
Blood brain barrier opening in rat brain

Ultrasound + introduced micro-bubbles



(a)

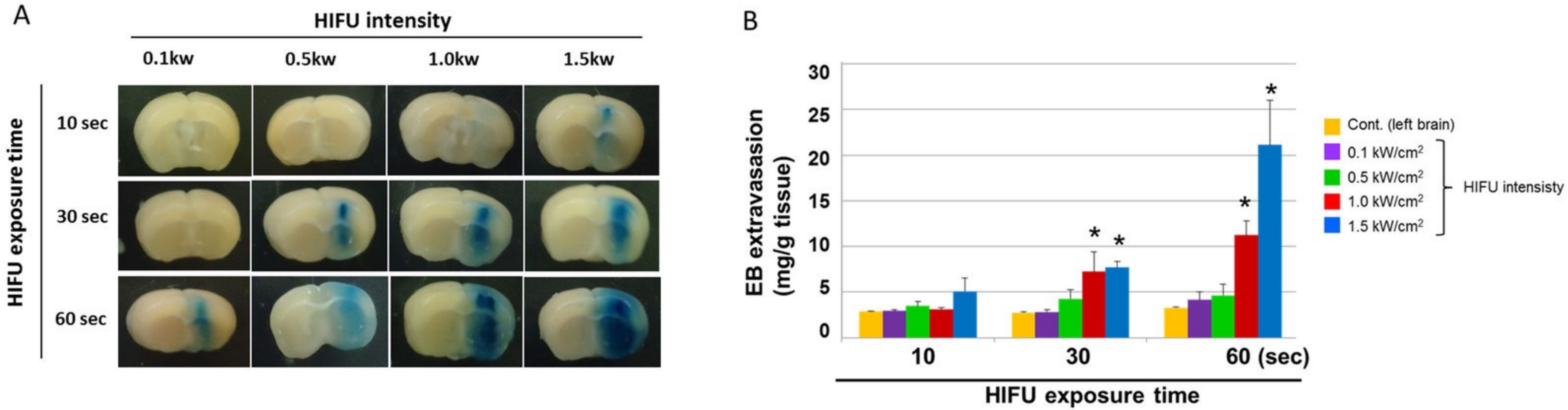
Representative Evans Blue dye stained Brain sections and calibrations after inducing FUS-BBB opening.
(a, b) brain sections viewed from the top and in corresponding brain sections. Bar = 5 mm. (c) Calibration of Evans Blue dye concentration using its correlation with ELISA light absorption ($r^2 = 0.9992$). (d) Evans Blue quantification of experimental group 1 animals. FUS-BBB opening reached a 3.8-fold increase in EB concentration in normal rats ($p<0.001$) and a 2.1-fold increase in tumor rats ($p = 0.09$).



(a) (b) (c) (d)

Wei et al. 2013 http://www.ncbi.nlm.nih.gov/pubmed/23527068

Blood-brain barrier opening

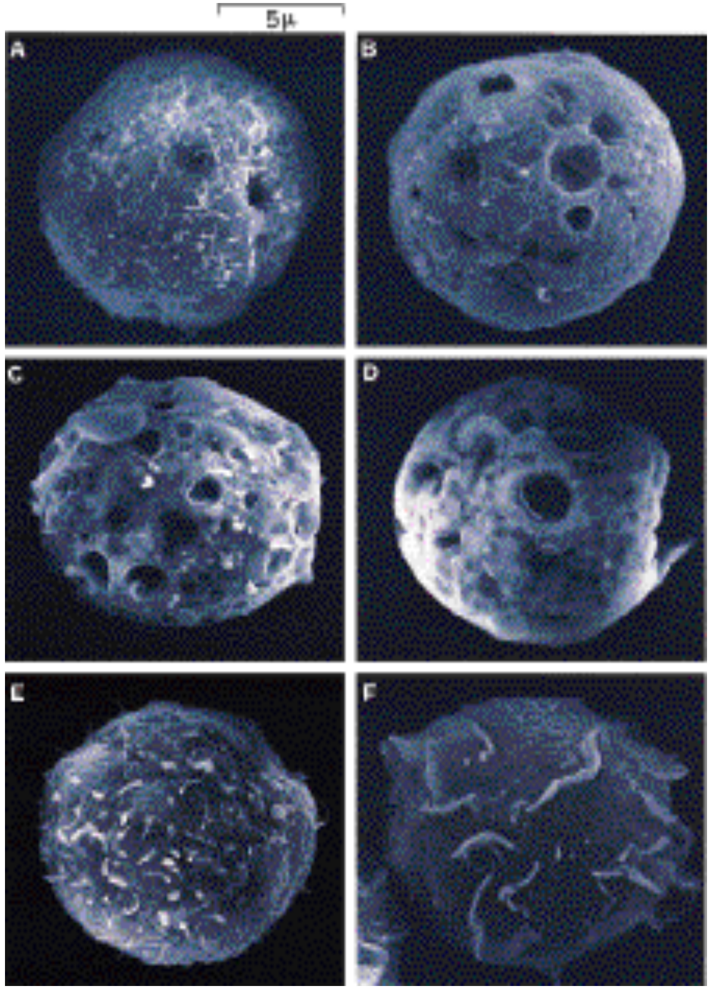


Negishi et al 2015: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588205/

EB = Evans blue

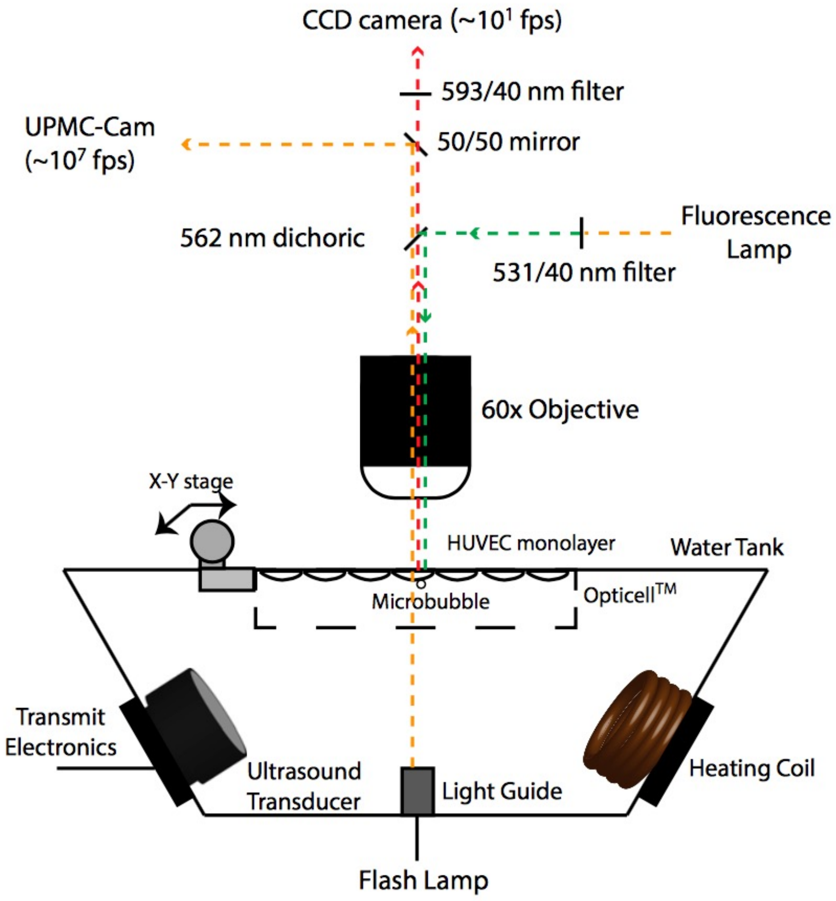
Sonoporation of cells

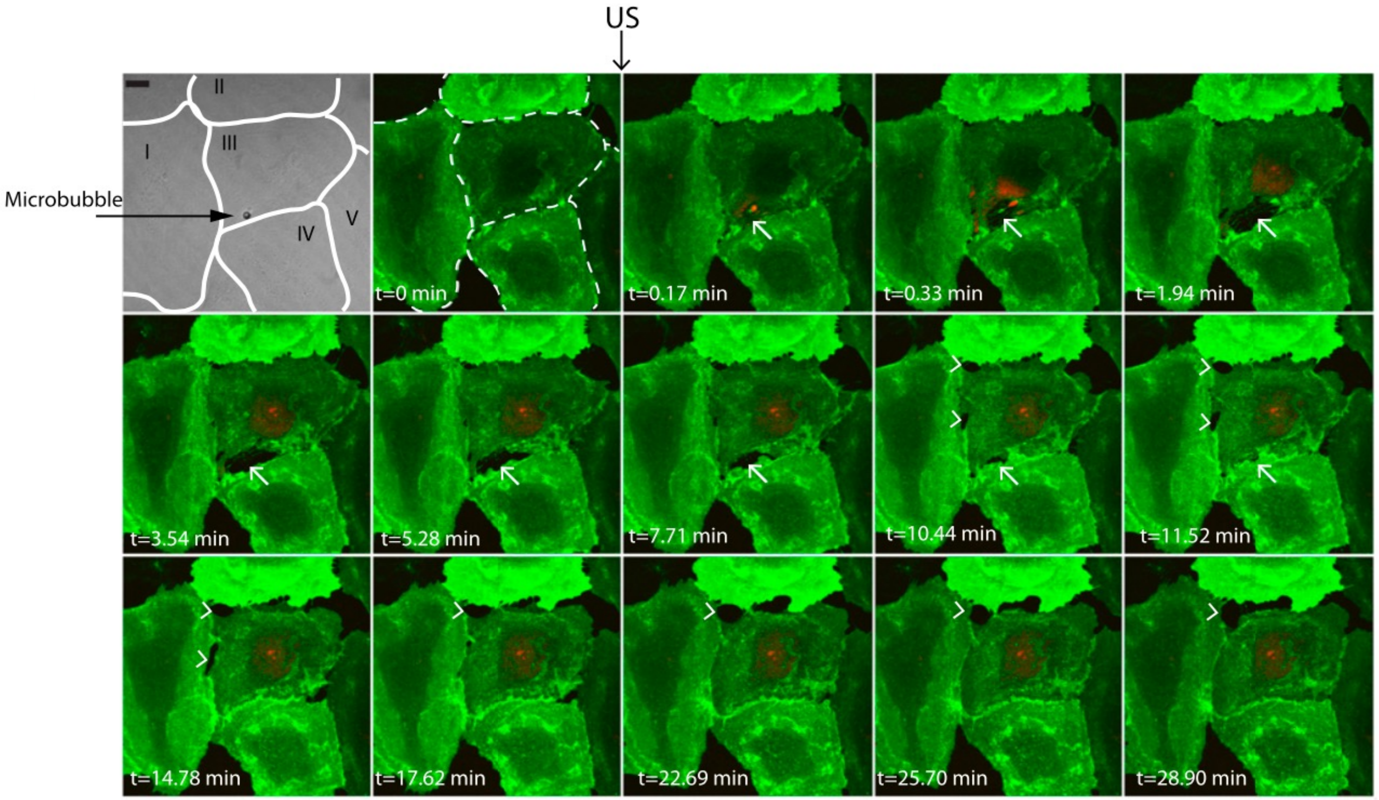
In sonoporesis cell wall permeability
to drugs and genes is enhanced
by enhancing porosity at the cell wall.



Tachnibana et al 1999, Lancet, Vol 353, pp: 1409

Sonoporation of cells

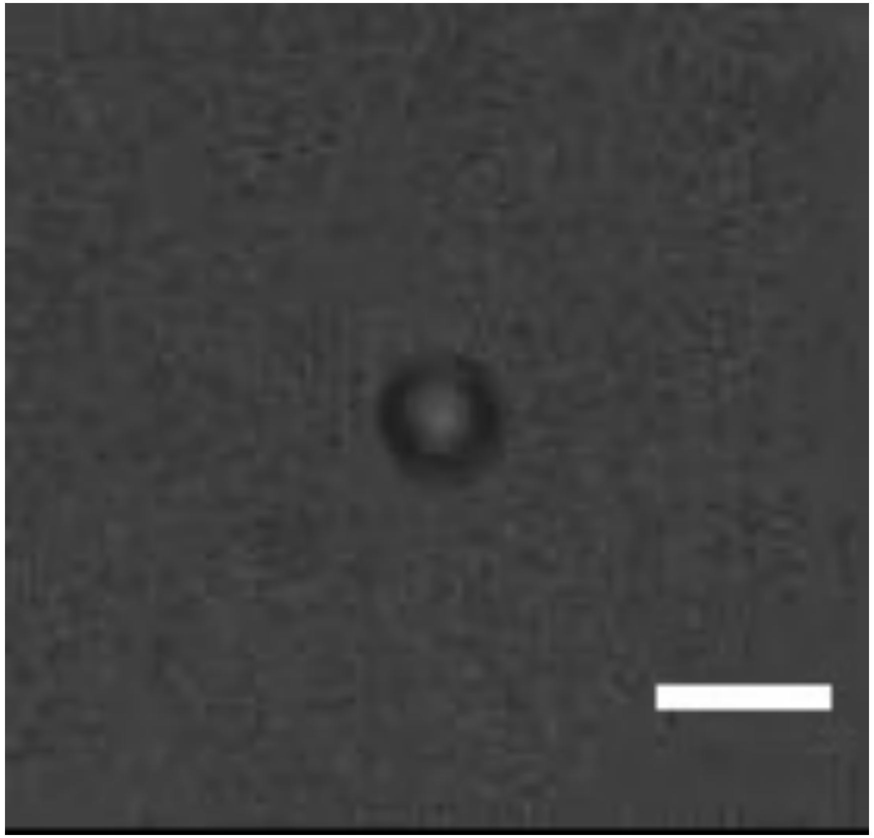




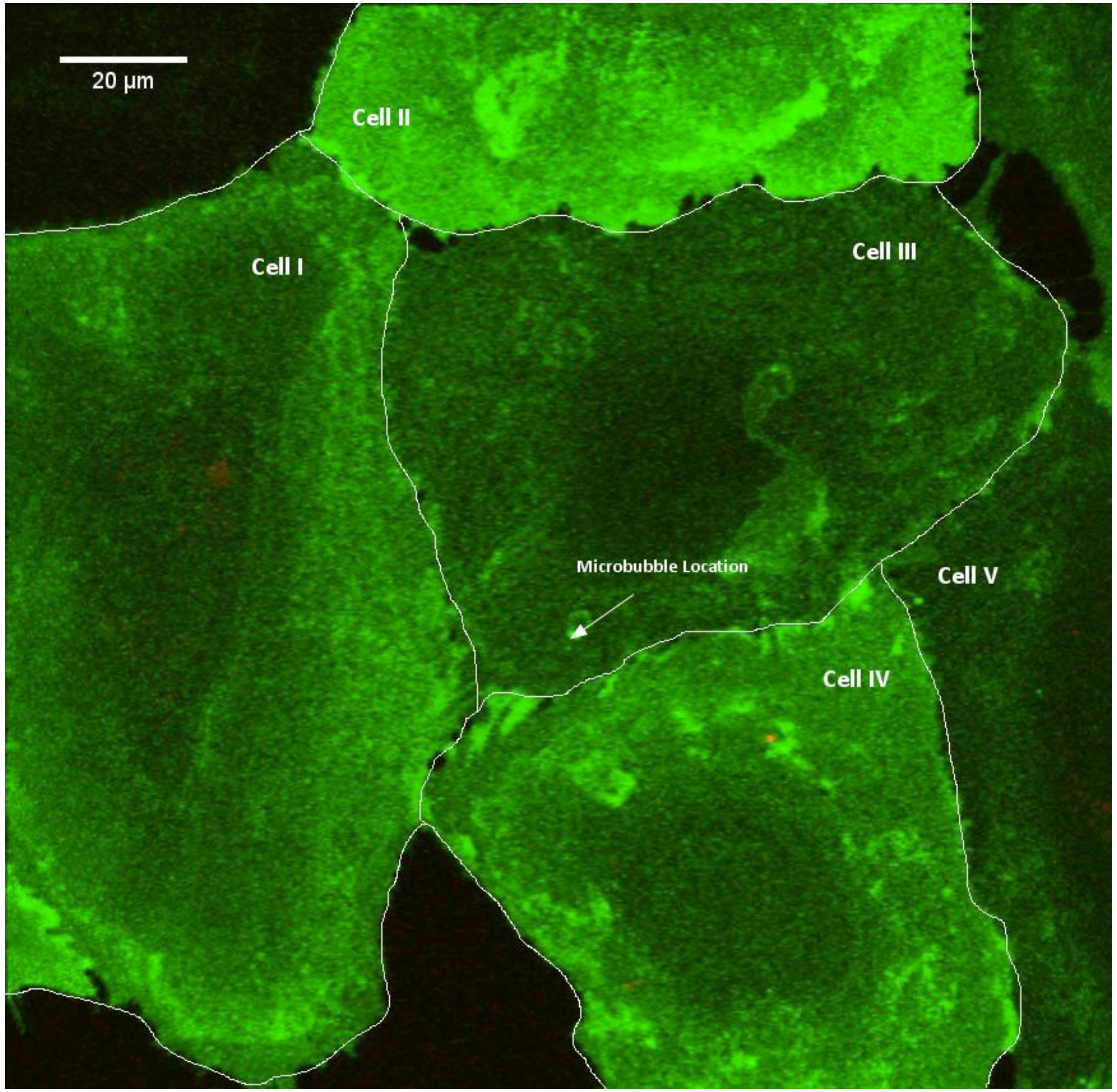
Hetfield et al. 2016: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5018802/pdf/pnas.201606915.pdf

Sonoporation of cells

Cavitation



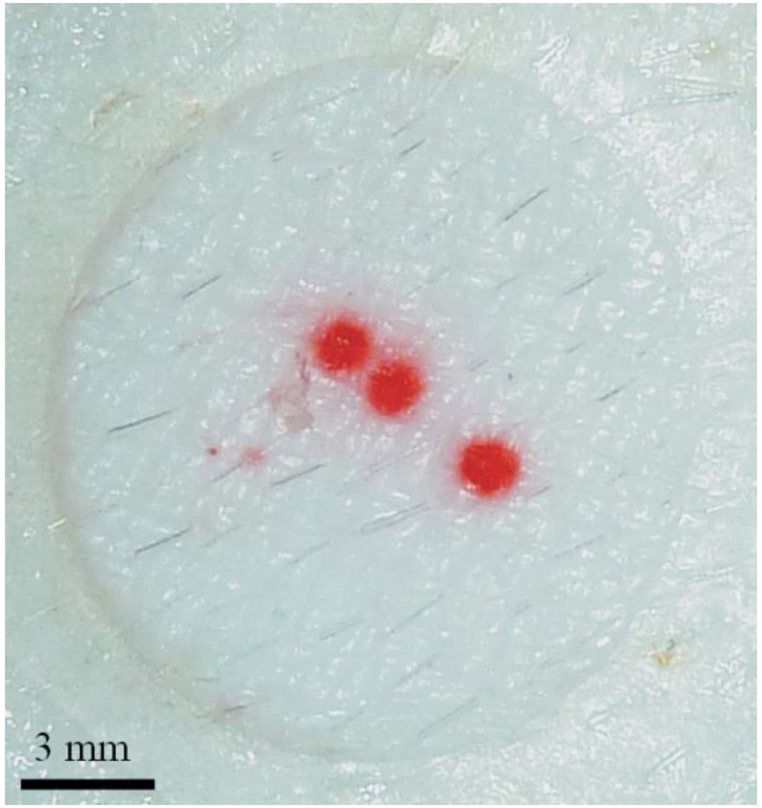
Delivery of nucleus stain



Hetfield et al. 2016: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5018802/pdf/pnas.201606915.pdf

Transdermal delivery

Cavitation-mediated agent delivery into pig skin



SonoPrep device for
transdermal drug delivery

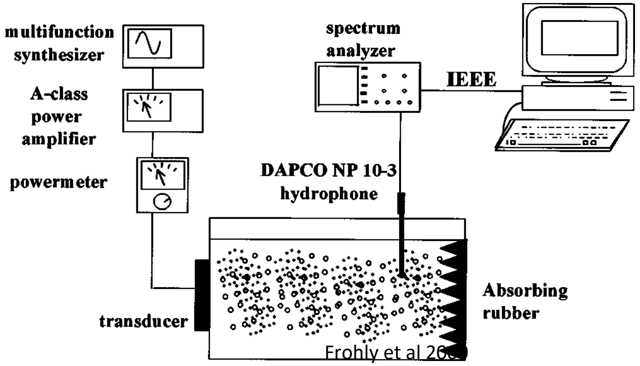
Polat et al 2010: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3050019/

Detection of cavitation

- Detection of cavitation:
  - bubble visualization is one application, but high frame rate cameras are expensive and not practical for industrial applications

    ➔ usually cavitation is detected indirectly
- Acoustic detection:
  - Non-inertial cavitation:
    - Harmonic freq: *nf*, where *n* = 1, 2, 3…
    - Subharmonic freq: *f*/2
    - Ultraharmonic freq: (2*n*+1)*f*/2,

    where *n* = 1, 2, 3… and *f* is the driving frequency
    - SH and UH oscillations result from chaotic oscillations typically occurring at higher acoustic driving amplitudes
  - Inertial cavitation:
    - broadband signal from the collapsing bubbles



Frohly et al 2000