Investigation of Inertial Cavitation of Sonosensitive and Biocompatible Nanoparticles in Flow - Through Tissue-Mimicking Phantoms Employing Focused Ultrasound

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Motivation – Efficient chemotherapy

Systemic chemotherapy

- Small amount of cytostatic drug (CD) can be accumulated inside tumour
- Dosage is limited due to side effects

➔ **Drug-Delivery concepts**

- Reduce side effects
- Increase dosage of CD inside the tumorous tissue

I. Department Chemie und Pharmazie

II. IMTEK

I. Development of sonosensitive and biocompatible nanoparticles
   - Carrier of the CD
   - Initiation of drug release via focused ultrasound ➔ **Inertial Cavitation**

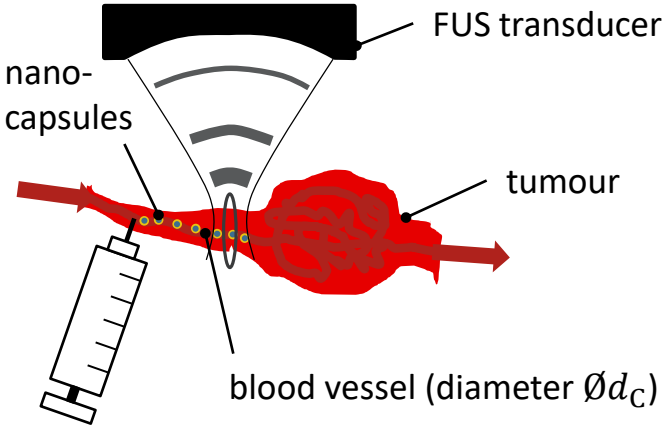
II. Investigation of suited ultrasound signals
   - Consideration of diagnostic limit value (Mechanical Index *MI*)

$$MI = \frac{\hat{p}_{\mathrm{neg}} / \mathrm{MPa}}{\sqrt{f / \mathrm{MHz}}} \leq 1.9$$

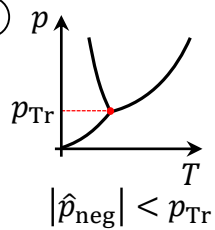
   - Setup for measurements

Motivation – Drug release

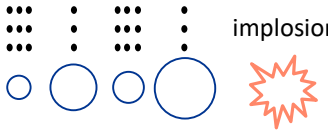
Sphere: Polymer + CD
~110 nm
Capsule: Polymer + Oil + CD
~200 – 250 nm



Drug release - Cavitation

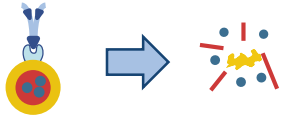
1 

2 Longitudinal wave – Bubble dynamics



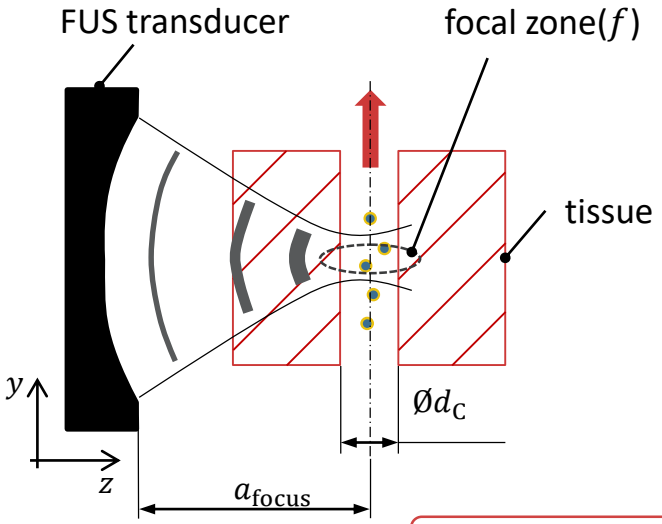
3 Bubble collapse - Implosion

Fluid jet close to surface of nanocarrier



Drug release and destruction of nanocarrier

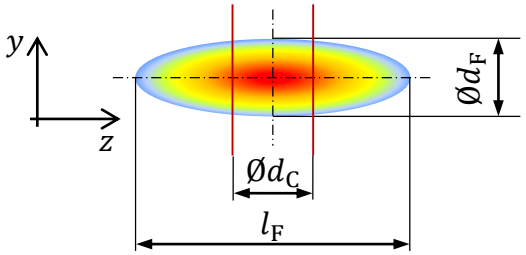
Motivation – Challenge

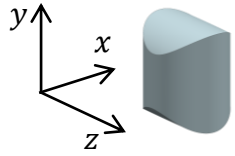


Blood vessels

$\varnothing d_C$ = 0,6 mm – 2,4 mm

Focal zone / Focal volume $V_F(f)$





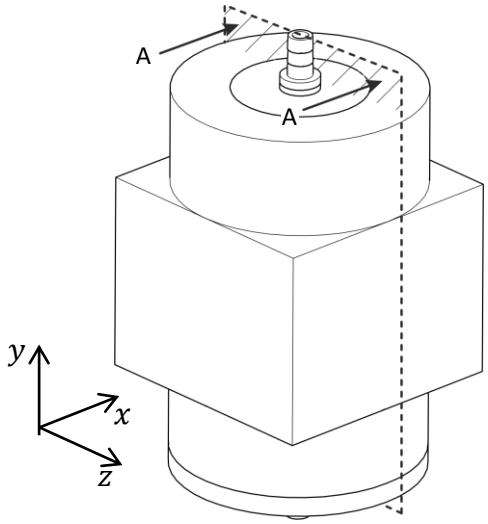
$f \uparrow \rightarrow V_F(f) \downarrow$

Sound field parameters

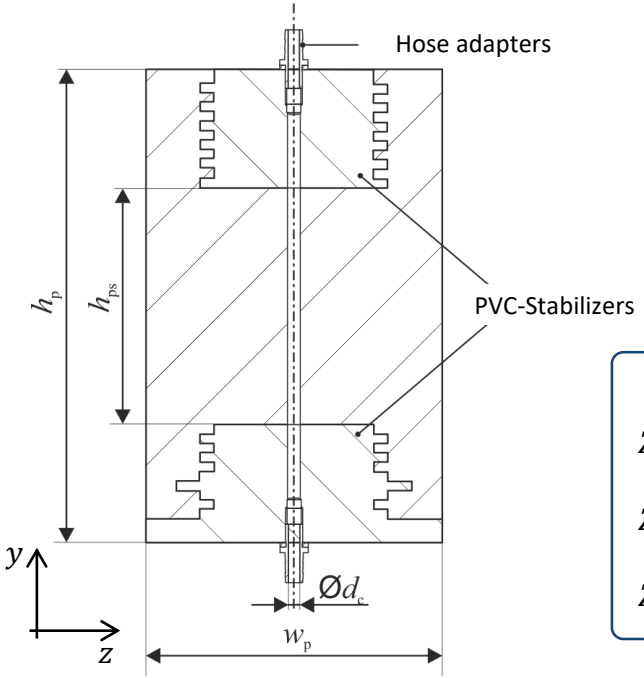
- Sound pressure $\hat{p}_{PRFPmax} = 1.85$ MPa
- Sound intensity $I_{max} \approx 1.23 \frac{W}{m^2}$
- Focal diameter $\varnothing d_{F\ -1dB} \approx 1$ mm

Experimental – PVA-Phantom

3D-View



Section A-A



Dimensions

$h_p = 100$ mm
$h_{ps} = 50$ mm
$w_p = 61$ - 63 mm
$\varnothing d_c = 1 - 3$ mm

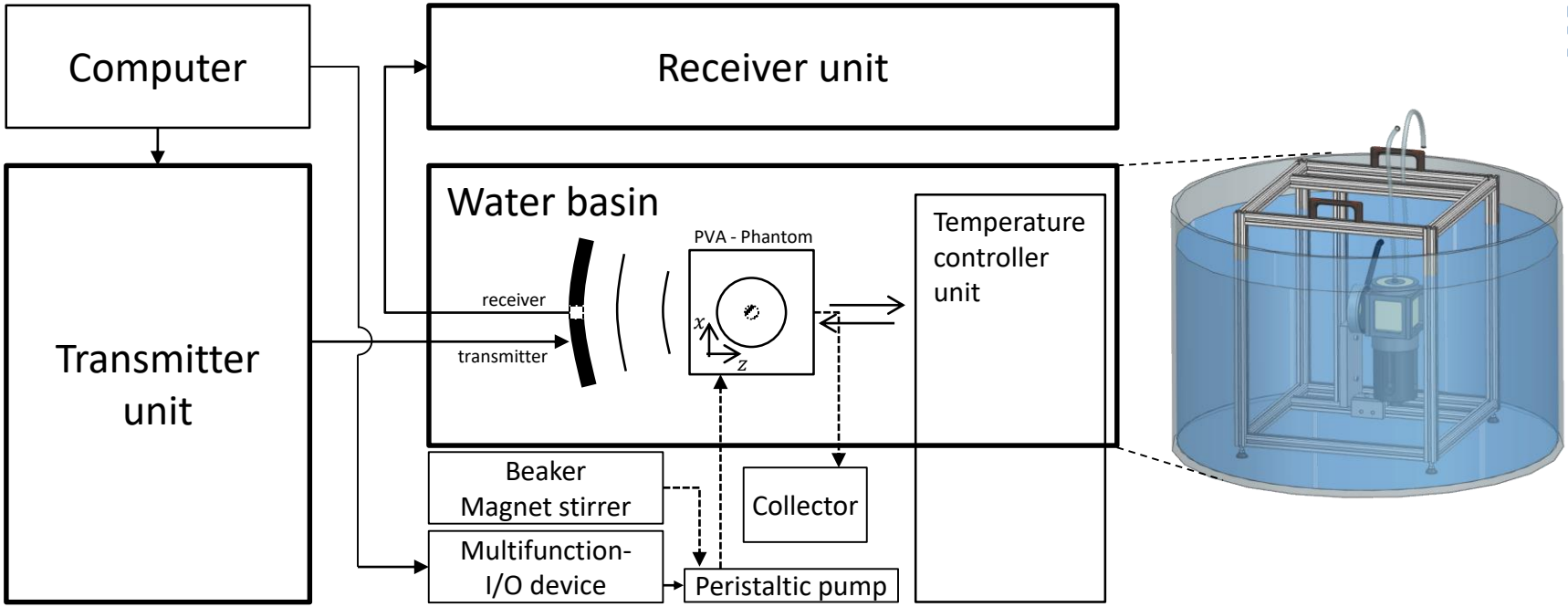
Sound impedance

$Z_{PVA} \approx 1.60 - 1.65 \cdot 10^6\ kgm^{-2}s^{-1}$

$Z_{blood} \approx 1.68 \cdot 10^6\ kgm^{-2}s^{-1}$

$Z_{muscle} \approx 1.65 \cdot 10^6\ kgm^{-2}s^{-1}$

Experimental – Setup



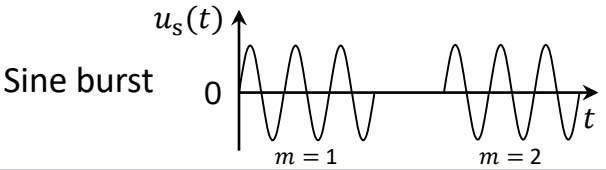
Experimental - Settings

Ultrasound signal

- Burst signal m
- $f = 550$ - 950 kHz
- $\hat{p}_{\mathrm{PRFP}}(MI = 1.4; f) \approx 1.04 - 1.36$ MPa
- $T_{\mathrm{B}} = 0.6$ ms
- $T_{\mathrm{P}} = 2$ s
- $m = 1, \ldots, M$
- $M = 50$

Additional parameters

- Water temperature $T = 30$ °C
- Flow velocity
  $v_{\mathrm{f}}(\emptyset d_{\mathrm{C}} = 1\ \mathrm{mm}) = 50$ mm/s



Cavitation → Noise

Broadband signal $u_{\mathrm{B}m}(t)$

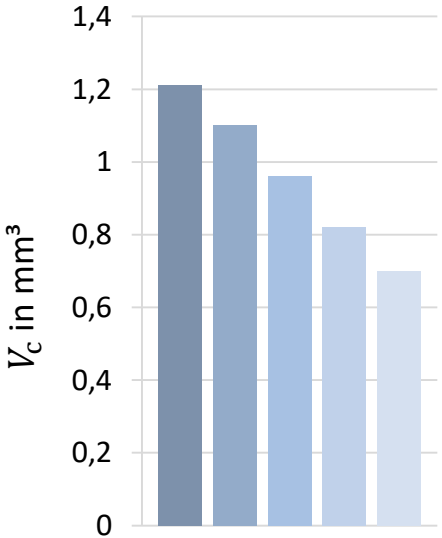
$u_{\mathrm{B}m}(t)$ ○—● $U_m(i)$

$$S_{rm} = \sqrt{\sum_{i=i_{\mathrm{S}}}^{i_{\mathrm{E}}} U_m(i)^2 / B}$$

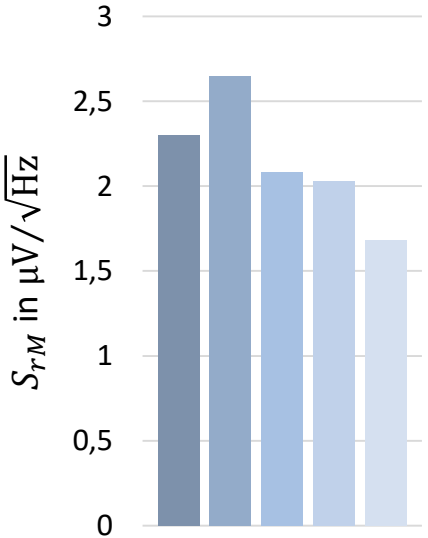
$$S_{rM} = \frac{1}{M} \sum_{m=1}^{M} S_{rm}$$

Results – Nanocapsules; $\varnothing d_C$ = 1 mm; *MI* = 1.4

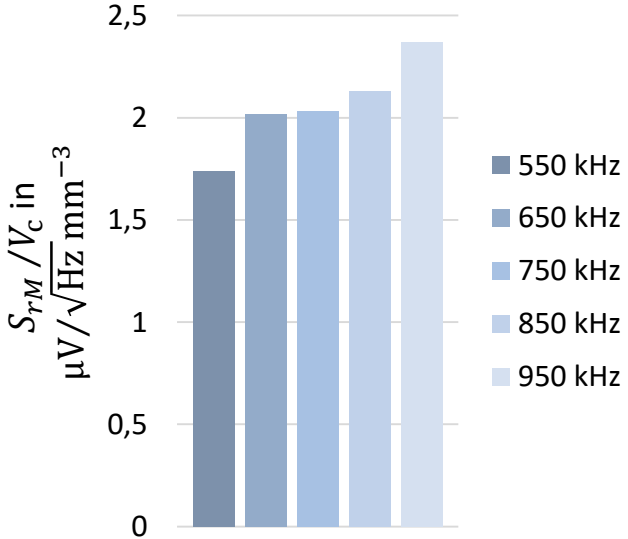
Focal volume V_c



Voltage spectral density



Voltage spectral density/V_c

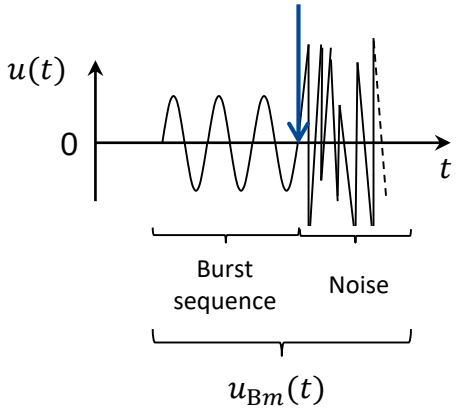


Results – Nanocapsules – Inertial cavitation

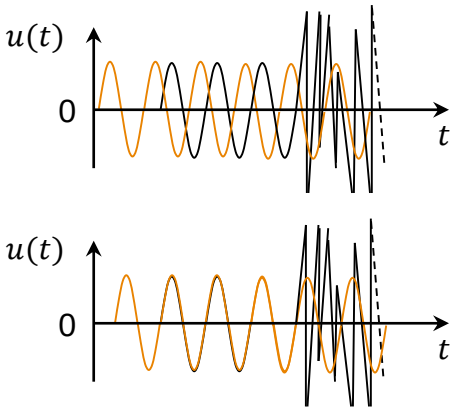
Inertial cavitation is a necessary effect for drug release

Indicator: Implosion of bubbles during positiv pressure phase (PPP) → Noise energy in PPP > Noise energy in NPP

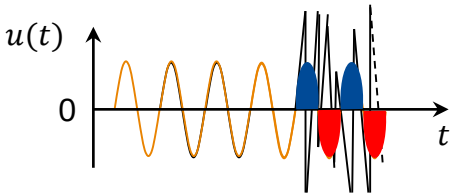
1 Determine t_{IC}



2 Model and shift signal $u_M(t)$



3 Calculate energy E_{pos} & E_{neg} of $u_{Bm}(t)$ in pressure phases



$$E_{PPP,\,NPP}(MI) = \sum_{m=1}^{M} \int_{t_{IC}}^{t_{IC}+T_B} |u_{Bm}(t)|^2 \mathrm{d}t$$

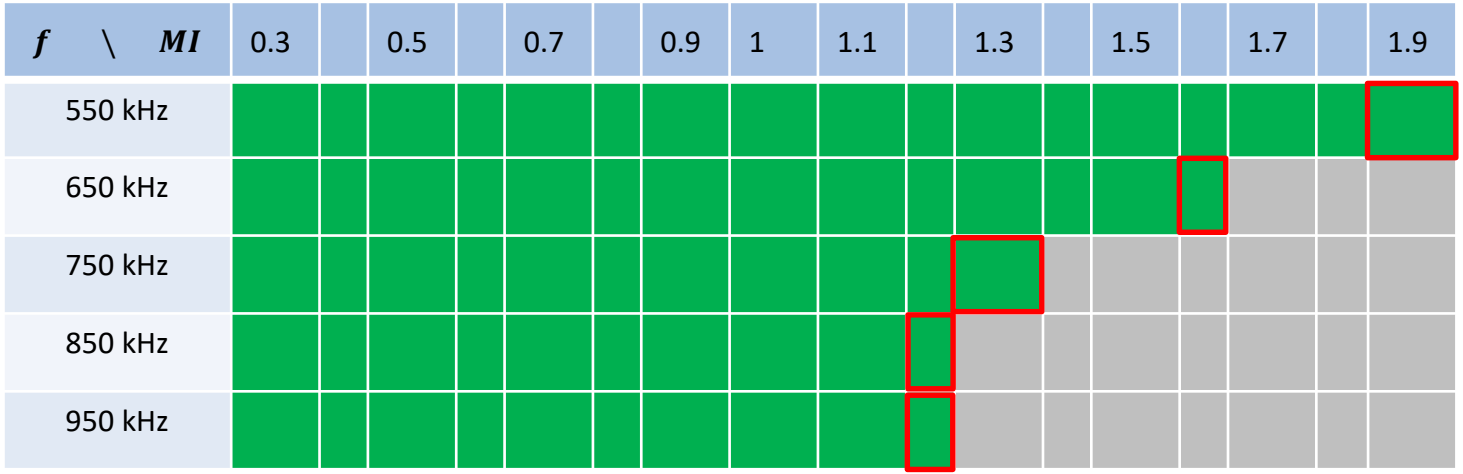
Results – Nanocapsules – Inertial cavitation

f \ MI	0.3		0.5		0.7		0.9	1	1.1		1.3		1.5		1.7		1.9
550 kHz																	
650 kHz																	
750 kHz																	
850 kHz																	
950 kHz																	

IC vanishes with an increasing frequency as well as an increasing MI (pressure)

$E_{\mathrm{PPP}} > E_{\mathrm{NPP}}$

Results – Nanocapsules – Inertial cavitation



IC vanishes with an increasing frequency as well as an increasing MI (pressure)

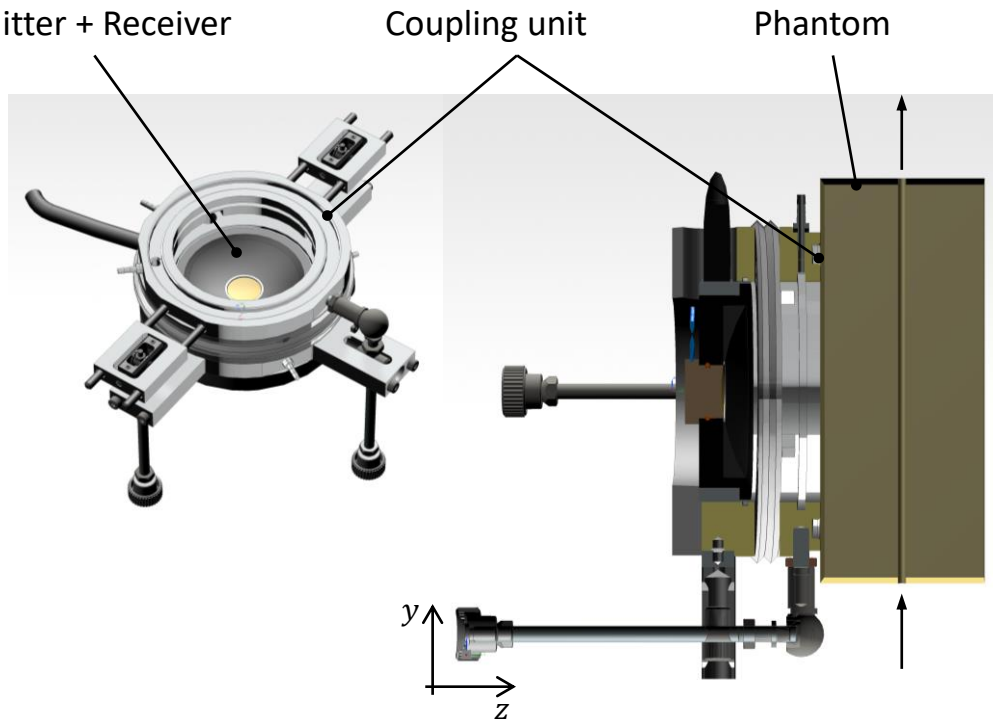
$E_{\mathrm{PPP}} > E_{\mathrm{NPP}}$

Conclusion

- Investigation of IC of the nanocapsules under realistic conditions
- By calculating the voltage spectral density, the focal volume should be considered
- Calculation of the energy of the noise signal gives a hint, if cavitation is either stable or inertial

Outlook

- PVA-Phantom employing a more complex vascularisation
- Coupling unit to investigate clinical application



Thank you for your attention

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Department Chemie und Pharmazie

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