# A Novel Approach to Optimize Sensitivity in Ultrasound Molecular Imaging

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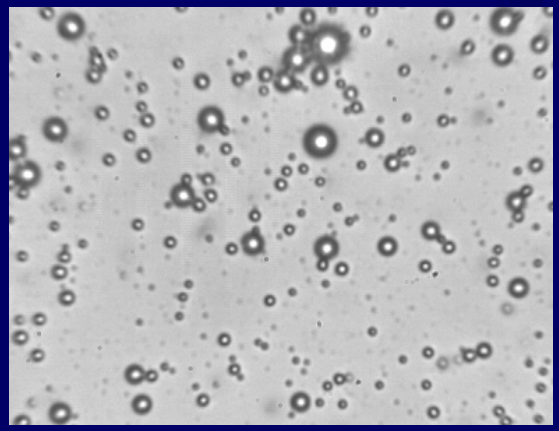
# Background

- Ultrasonic Molecular Imaging
  - Uses targeted contrast agents
  - Attachment of specific ligands
    - Antibodies
    - Peptides
    - Polysaccharides
  - Bind to cellular receptors
  - Recognize disease antigens
  - Targeted Pathologies
    - Tumors
    - Inflammation
    - Thrombus

# Targeted Ultrasound Contrast Agents

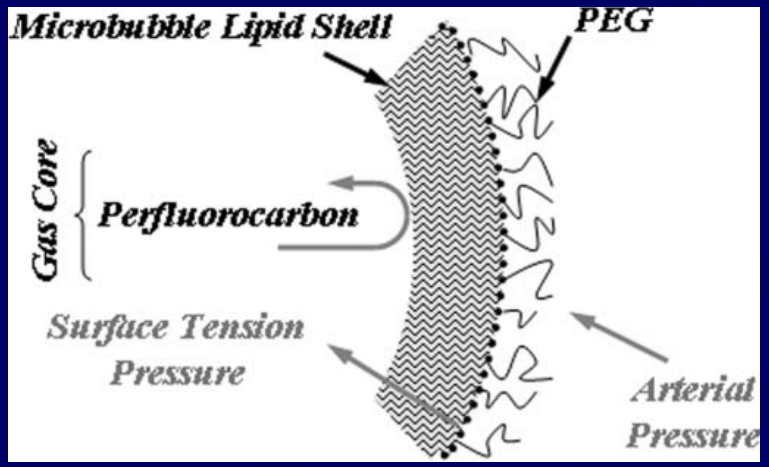
- Blood doesn't scatter US well
- Microbubble: A contrast agent
- Filled with gas: High echogenicity compared to liquid based particles or blood cells
- Diameters of the order of 1 to 5 μm
- Smaller than Red Blood Cells (6-8 μm)
- Improve the sensitivity of 2-D and 3-D ultrasound imaging



Hettiarachchi et al., Lab Chip, 2007

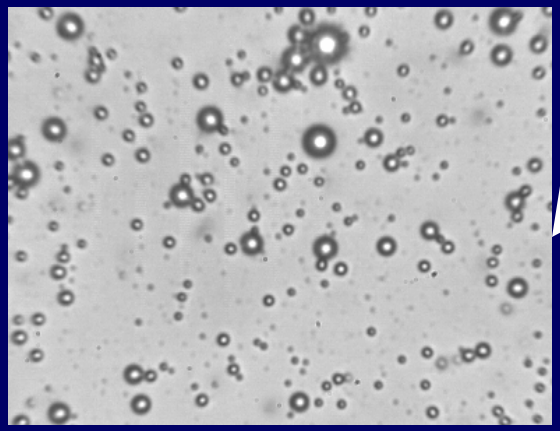
# Structure of Microbubbles

- A monolayer amphiphilic phospholipid shell
- The water insoluble hydrocarbons
- Charged phosphate head groups
- Use of PEG:
  - Coalescence
  - Phagocytosis
  - Physical barrier to enzymatic agents, adsorption of blood proteins



# Current Contrast Agent Production

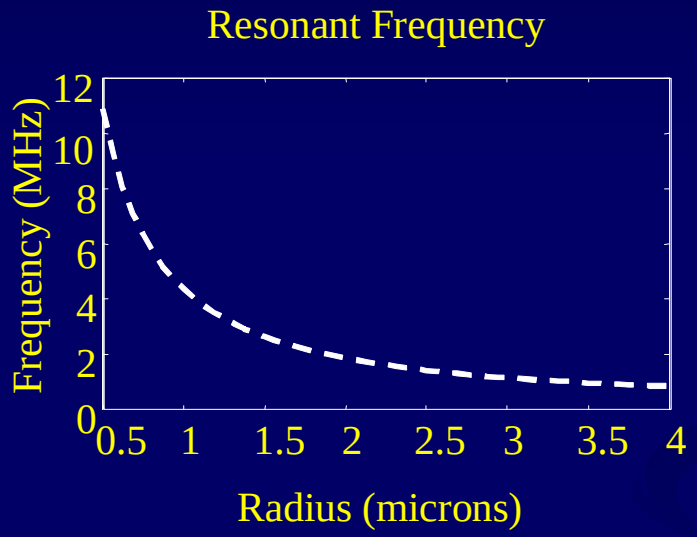
- produced by mechanical agitation of lipid solution
- polydisperse size distribution



Large Size Variance:

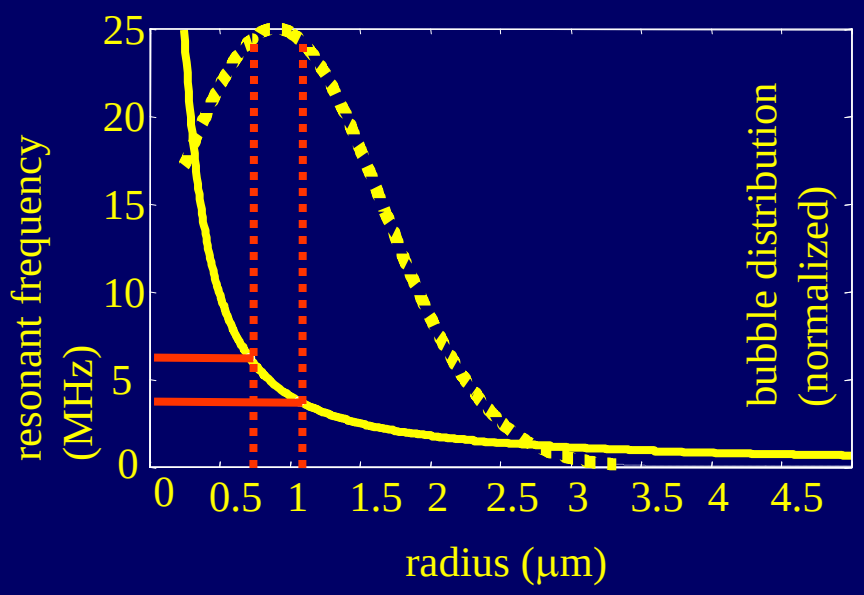
# Problems with Current Contrast Agents & Ultrasound Systems for Molecular Imaging

- Size distribution
- The resonant frequency




- Limited frequency bandwidth
- Only a small percentage of the contrast agents have diameters which result in resonant frequencies optimized for the limited bandwidth
- Fewer contrast agents retained
- Filtering does not work on lipid-shelled bubbles

## The Problem

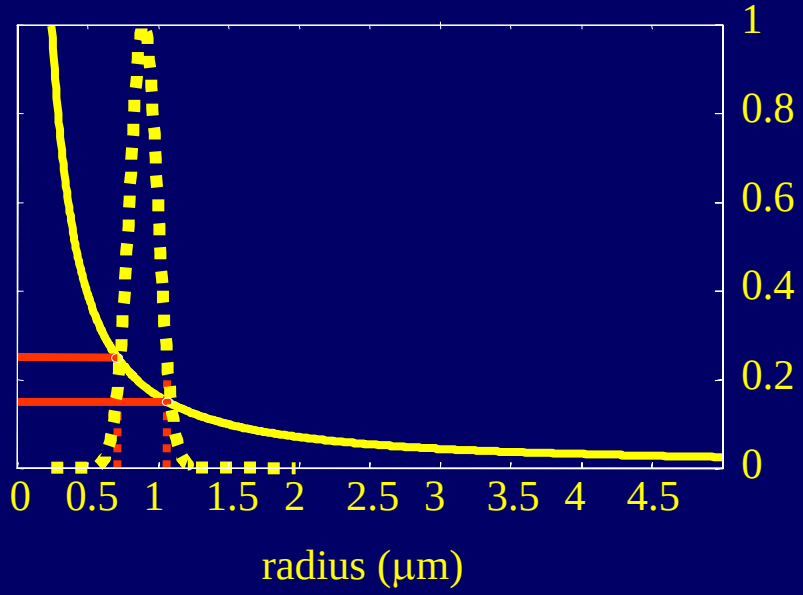



bubble size=1.8±1.5 microns

$F^{\text{receiver}}_{\text{bandwidth}}$=5.0 +/- 1.5 MHz

**detectable bubbles: 18%**

## A Solution



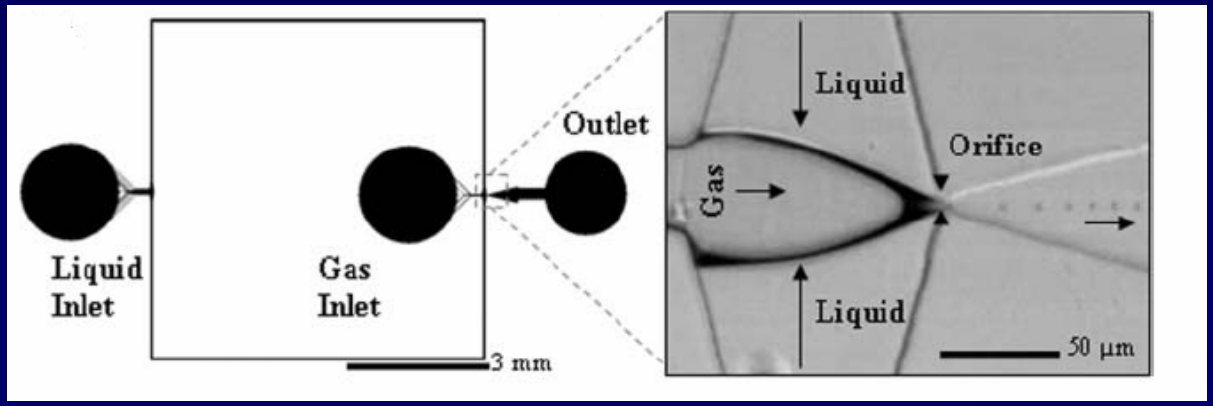

bubble size=1.8±0.2 microns

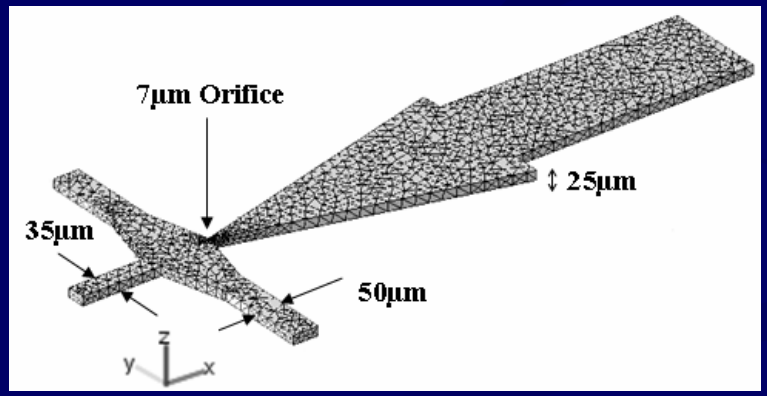
$F^{\text{receiver}}_{\text{bandwidth}}$=5.0 +/- 1.5 MHz

**detectable bubbles: 92%**

# Monodisperse Microbubble Production

- Use of Microfluidic Flow Focusing Device

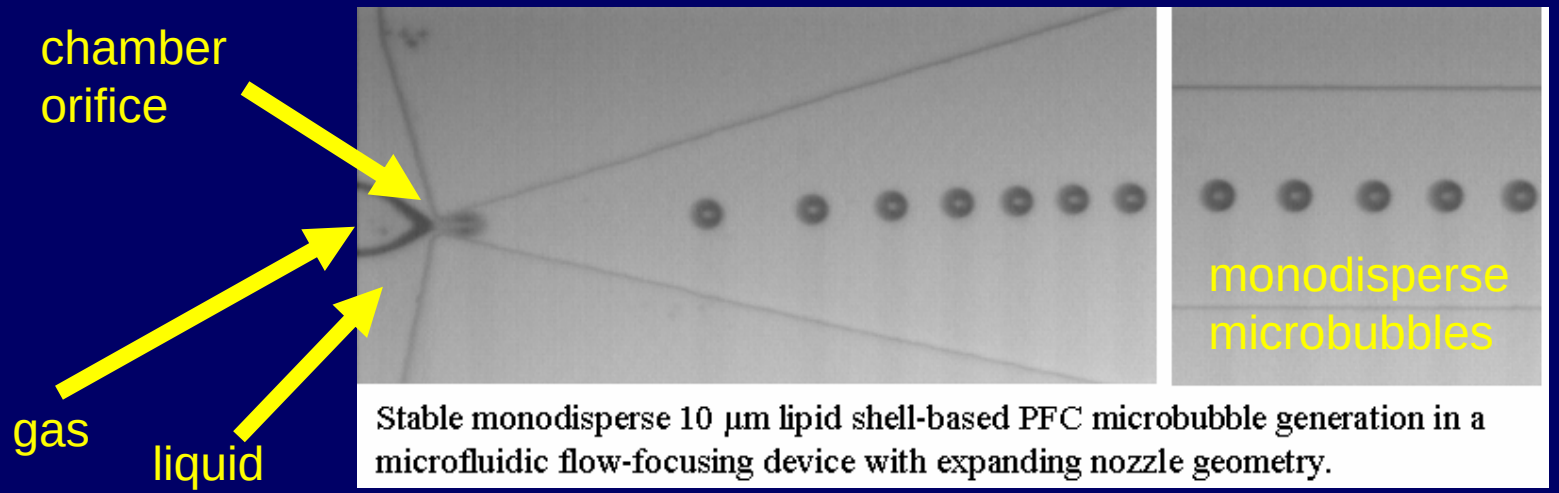


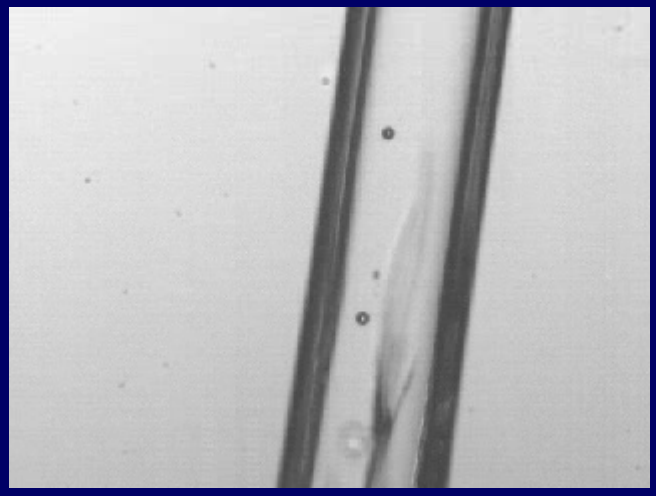

Talu, et al., *Langmuir,* 2006
Hettiarachchi et al., Lab Chip, 2007

# Why use a Microfluidic System?

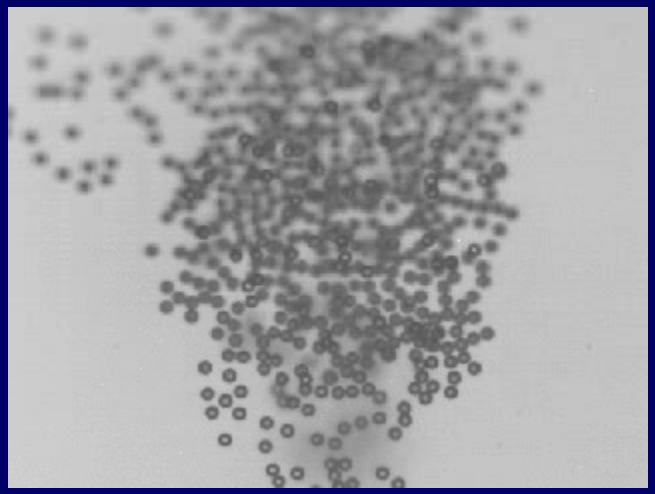
- Relatively cheap, simple, and easy to multiplex




Stable monodisperse 10 μm lipid shell-based PFC microbubble generation in a microfluidic flow-focusing device with expanding nozzle geometry.



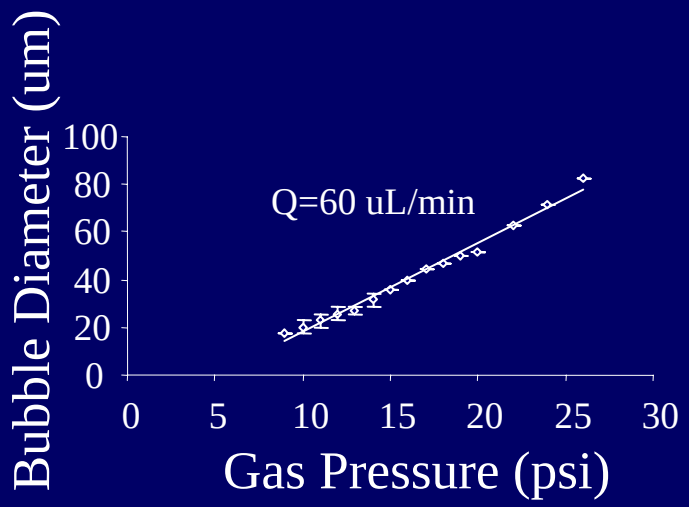
**(video playback at 1/100 speed)**

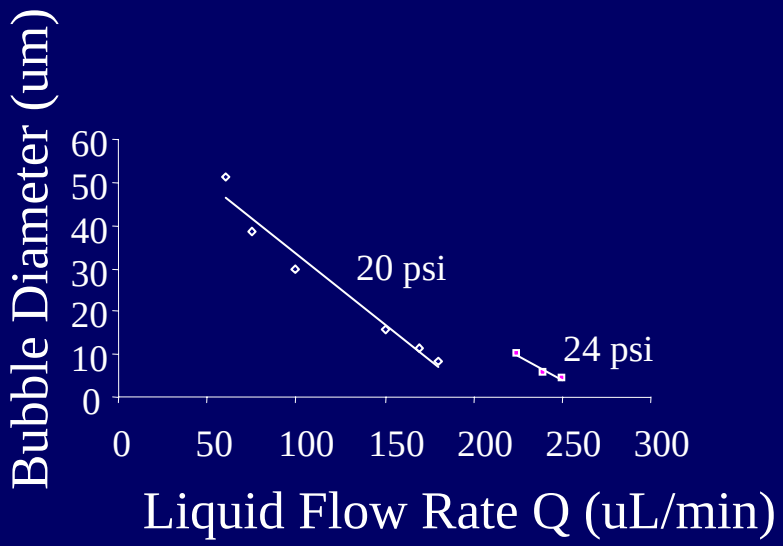


**50 μm**

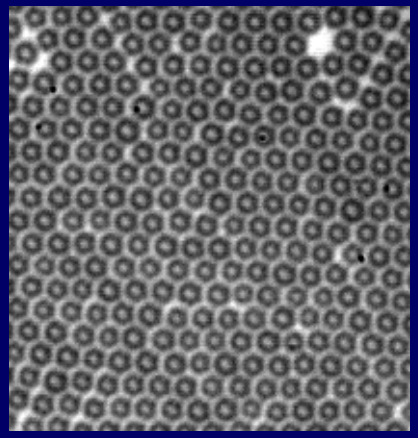
Hettiarachchi et al. *Lab on a Chip, 2007*

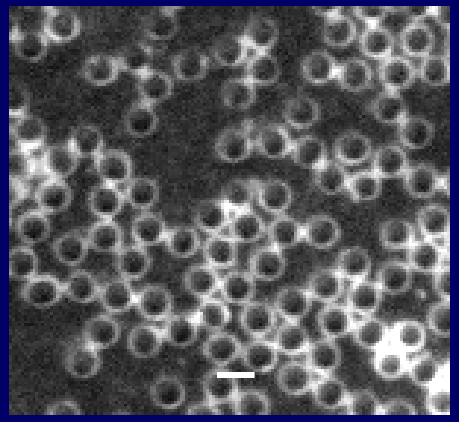
# Tailoring the Size Distribution Microbubbles



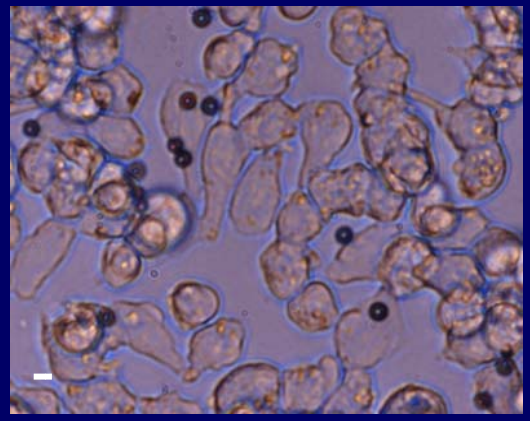




## Lipid Encapsulation for Stability



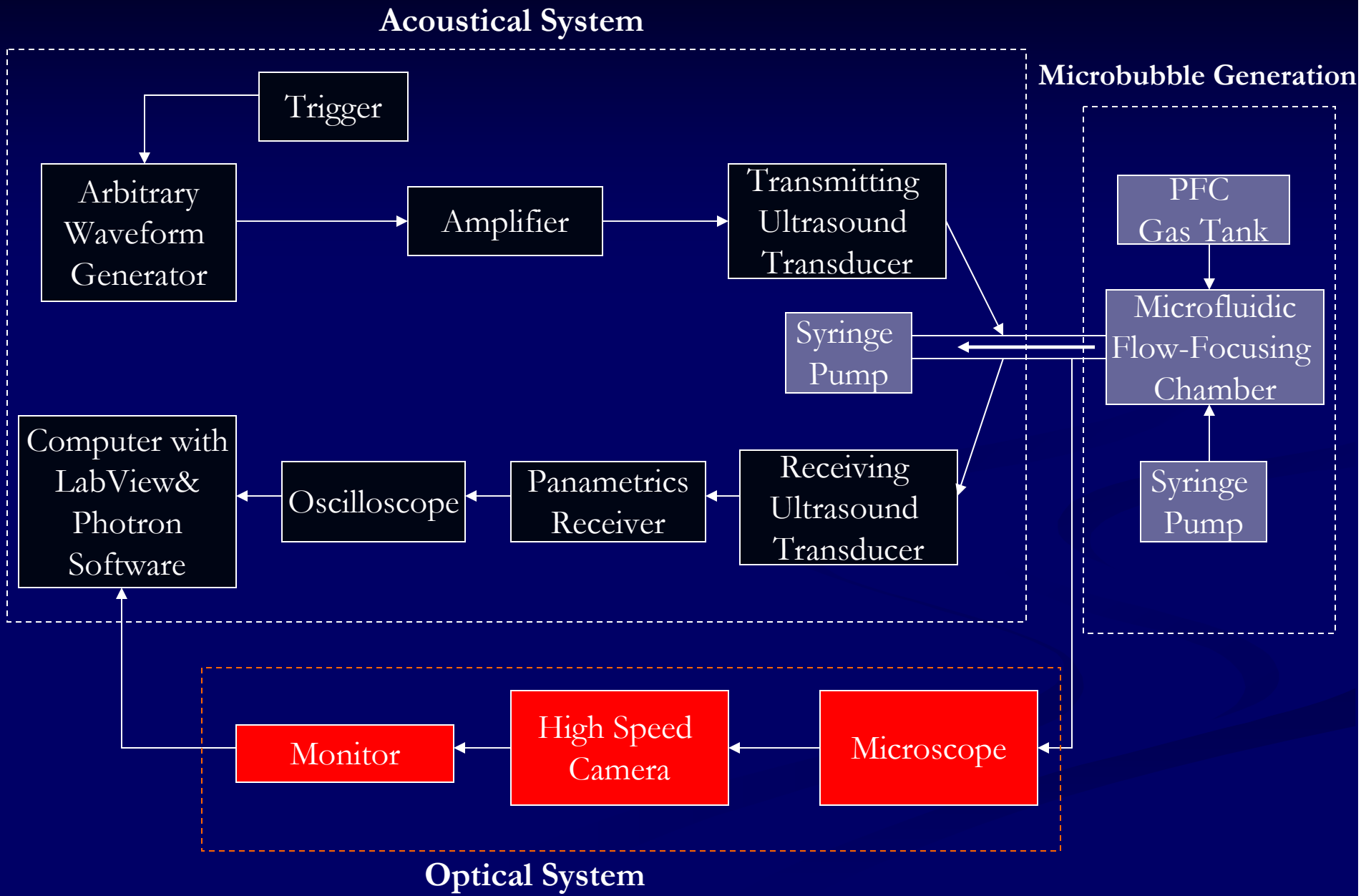


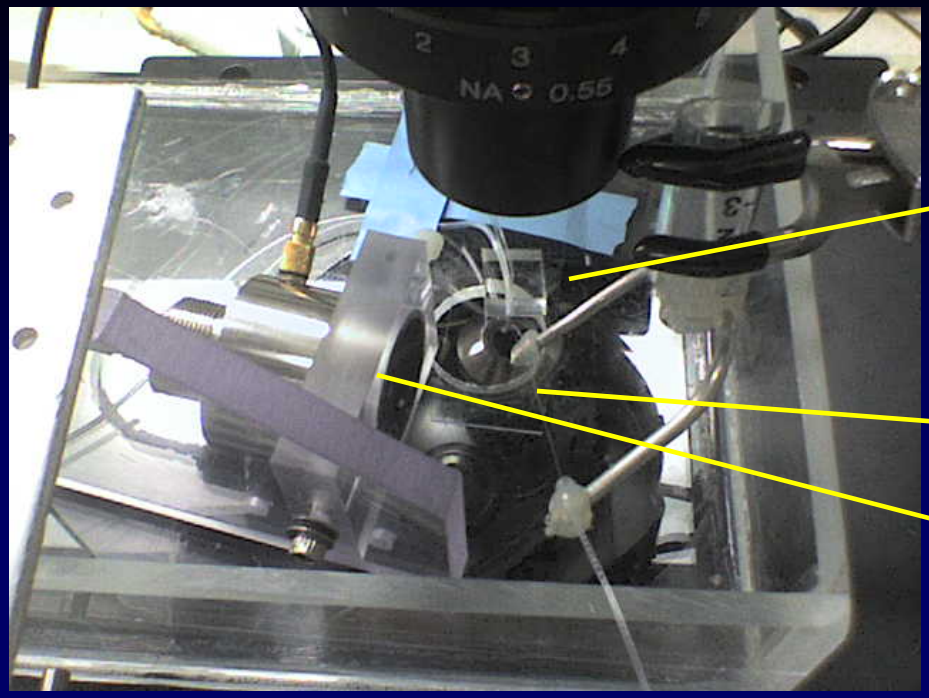
## Cell Targeting

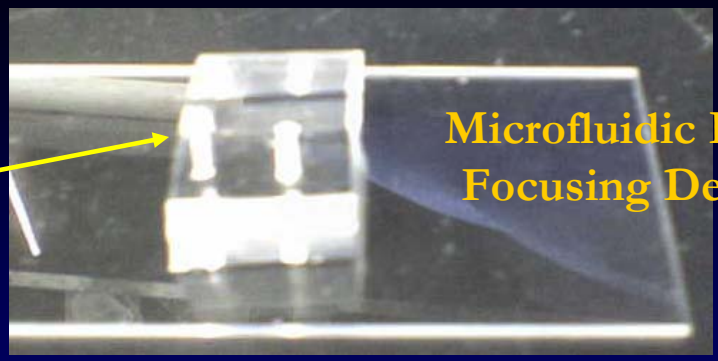


## Incorporate Targeting Ligand

# Ultrasound Imaging System





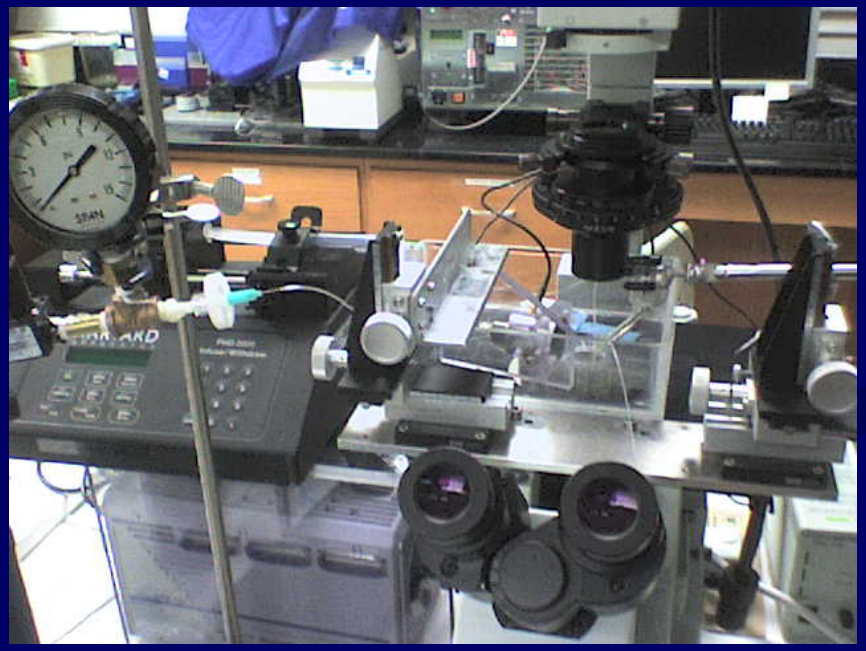



Microfluidic Flow Focusing Device

Microtube

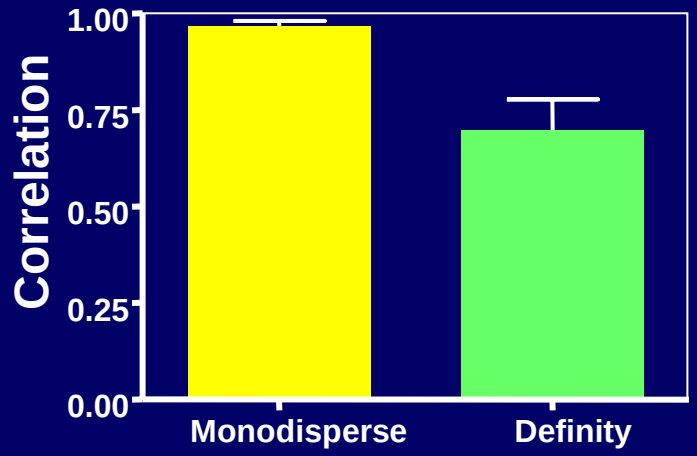
US Transducers

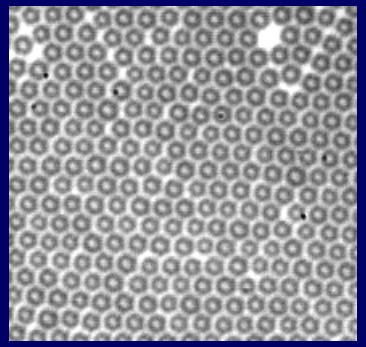
- Ultrasound Transducers
- Transmitter 2.5 MHZ /Receiver 5 MHz
- Liquid flow rate: 35 ul/min
- PFC flow rate: ~2-4 psi

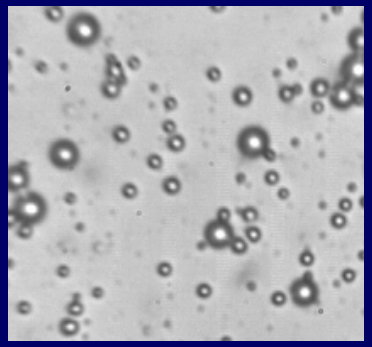


# Acoustic Studies of Monodisperse Contrast Agents

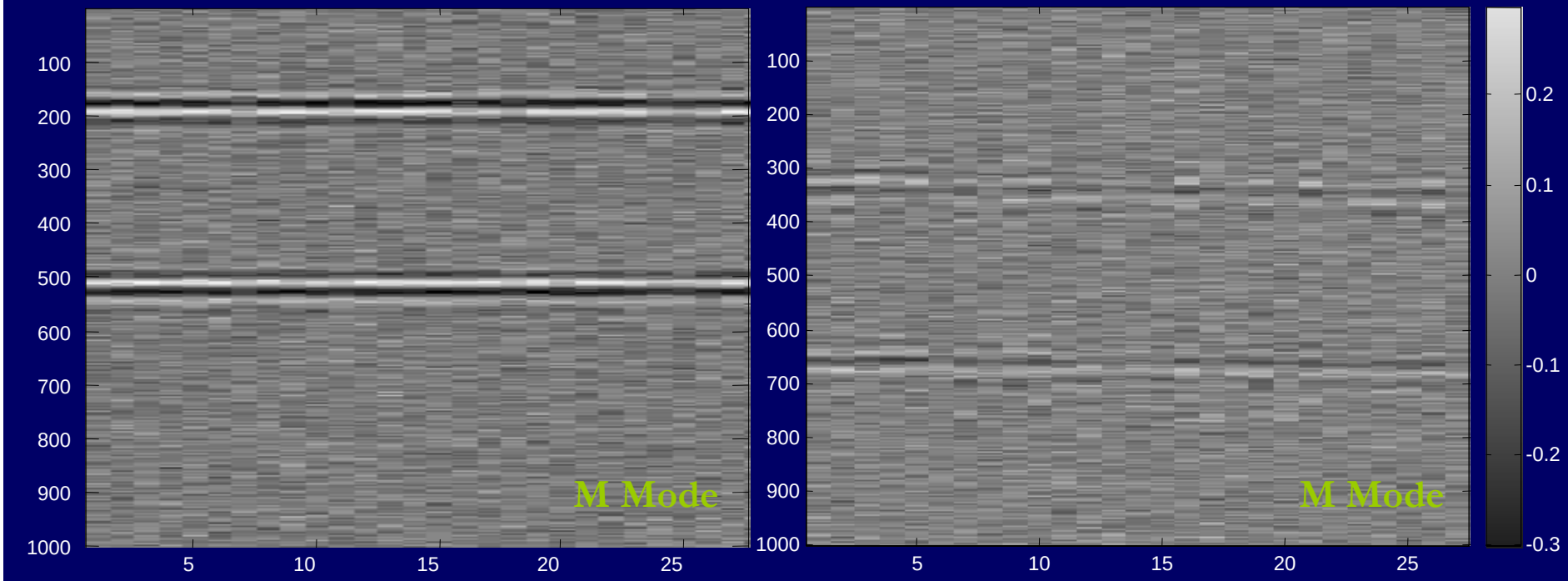
- Standard deviation of echo amplitude is smaller
- Correlation coefficient 0.95 vs. 0.70
- Improved Signal Response of Monodisperse Contrast Agents



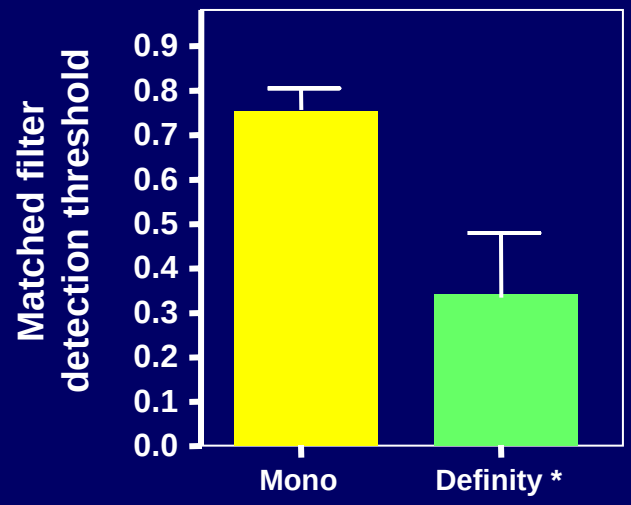


# Detection of Monodisperse Agents




Monodisperse

Polydisperse



# Summary & Conclusions

- Successful production of monodisperse contrast agents
- Monodisperse microbubble contrast agents have the potential to increase sensitivity in ultrasound molecular imaging
- More sensitive detection of monodisperse contrast agents compared to polydisperse agents
- Production rate of contrast agents is one of the challenges (in comparison to ~$10^{10}$ µl with polydisperse)

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