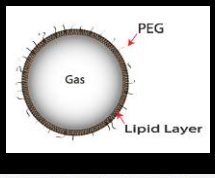
New Imaging Contrast Agents and Imaging Protocols in Contrast-Enhanced Background-Free Ultrasound and Photoacoustic Imaging

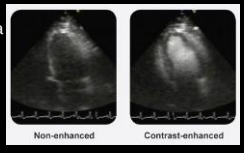
Brooks Lindsey
Stanislav Emelianov

Georgia Tech
Wallace H. Coulter Department of Biomedical Engineering
Georgia Tech College of Engineering and Emory School of Medicine
EMORY UNIVERSITY

Microbubble contrast agent imaging and considerations

- Gas core
  - C_3F_8 (Octafluoropropane)
  - C_4F_{10} (Decafluorobutane)
  - C_5F_{12} (Perfluoropentane)
  - C_6F_{14} (Perfluorohexane)
- Shell (typically lipid)
- Mechanical index
  - What is the peak negative acoustic pressure resulting in cavitation for a microbubble at resonance?
  - $\mathrm{MI} = \frac{p_-}{\sqrt{f_0}}$
  - FDA limit: 1.9 for non-contrast
  - 0.8 for Definity



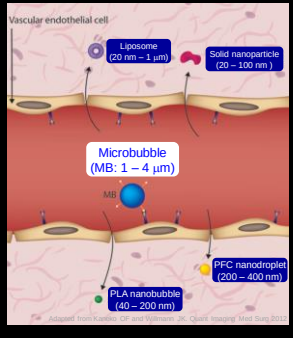


Molecular ultrasound imaging and extravascular delivery

Microbubbles
- Commonly used clinically
- Too large to reach extravascular targets

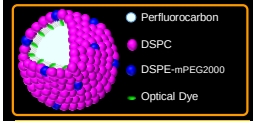
Solid nanoparticles
- Too small to respond to acoustic field

Ideal contrast agent for **contrast-enhanced molecular ultrasound**
- **Small** (sub-micrometer) to penetrate endothelium and escape vascular compartments
- **Large** acoustic cross-section to respond to ultrasound field



Molecular ultrasound imaging and extravascular delivery

US or laser-triggered perfluorocarbon nanodroplets (PFCnD)



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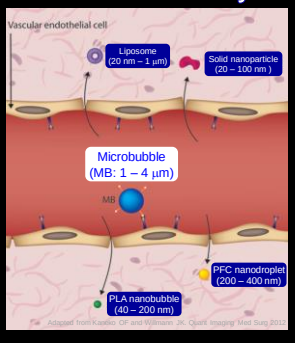
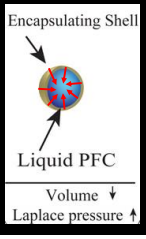


Boiling point of encapsulated nanodroplets

Boiling points

Bulk gas	200 nm droplet
C_3F_8: -36.7° C	37° C
C_4F_{10}: -1.7 ° C	79° C
C_5F_{12}: 29° C	119° C
C_6F_{14}: 57° C	150° C

Core gas in nanoscale droplets experiences several atmospheres of pressure → increased boiling point



Imaging encapsulated nanodroplets

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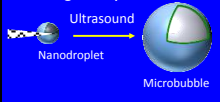
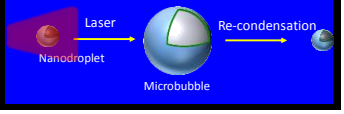
Two approaches for imaging:

1. Single vaporization



2. Temporary vaporization followed by re-condensation



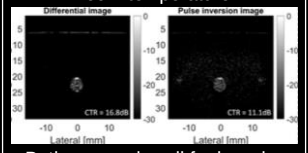
1. Imaging localized ultrasound-activation of phase change nanodroplets

Localized ultrasound activation and imaging

- Goal: Image spatial distribution of nanoscale agent
- Requires activation beam and imaging before/after activation

Approaches:
- Pulse inversion imaging of resulting microbubbles
- Differential imaging before/after activation

No motion, C_3F_8 core, 10^8/ml, room temperature

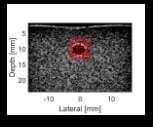


Both can work well for broad activation of high concentration agent, little motion

Localized ultrasound activation and imaging

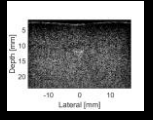
Challenges:
- Sensitivity to low concentration in regions of localized activation (molecular imaging, delivery)
- Physiological motion

No motion, C_4F_{10} core, 10^6/ml, 37° C

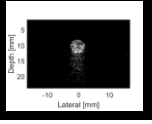


Pre-activation B-mode image

Pulse inversion



Differential



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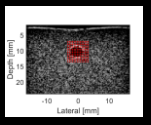
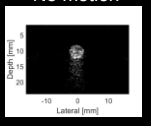
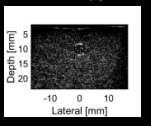


Pre-activation B-mode image

No motion

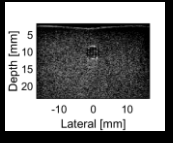


1 mm/s

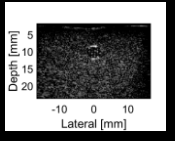


High rate physiological motion

C_4F_{10} core, 10^6/ml, 37° C
Pulse inversion, 20 mm/s

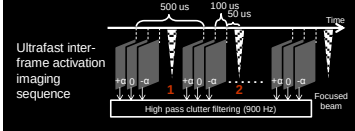


Differential, 20 mm/s



A new imaging approach

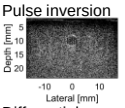
What if we image at high frame rate and activate between imaging pulses?



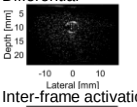
Acquisition rate: 2000 Hz

20 mm/s motion

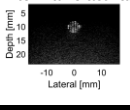
Pulse inversion



Differential

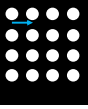


Inter-frame activation



In vivo imaging

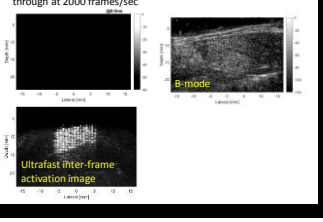
Proof of concept: Activate by steering focused beam to desired location in 6 x 6 mm grid



Rat liver

Activation beam sweeping through at 2000 frames/sec

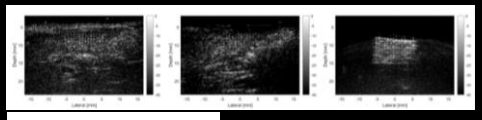
Post-activation image

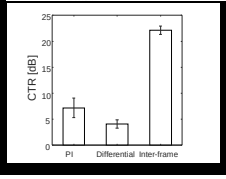


Imaging activation in the presence of physiological motion

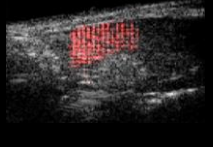
Conventional techniques

Pulse inversion | Differential | Inter-frame



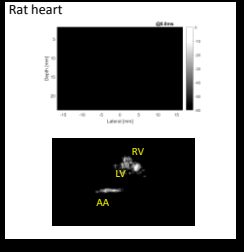


Visualizing locations of activation



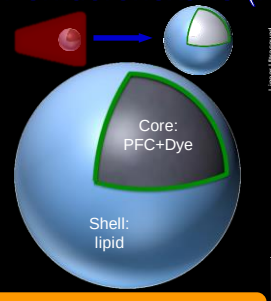
Imaging in the heart

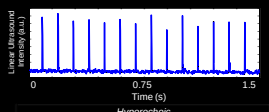
Rat heart

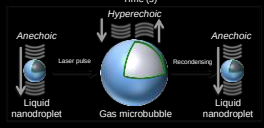


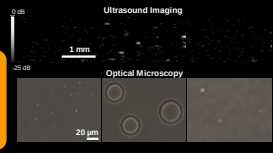
2. Laser-activated phase change contrast agents

Perfluorohexane (PFH) NanoDroplets



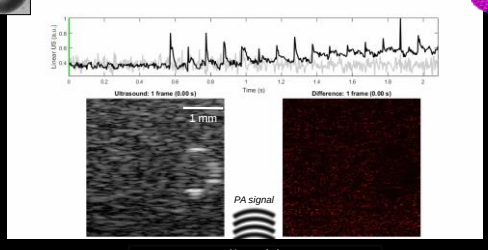


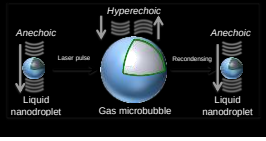




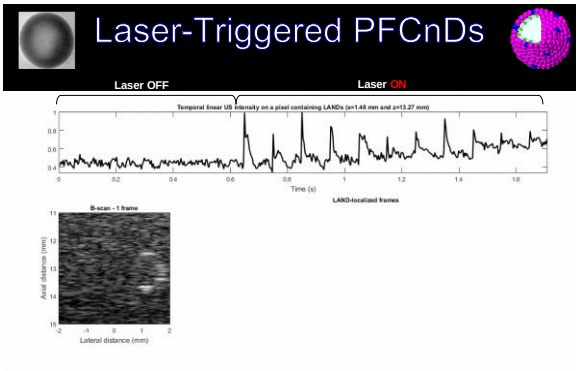
Laser-activated PFH (boiling point: **57°C**) nanoDroplets produce time-varying US (PA) contrast

Laser-Triggered PFCnDs





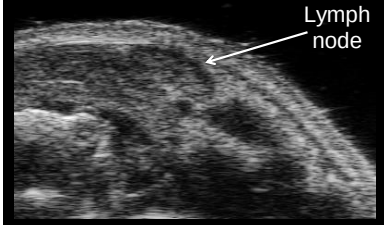
Laser-Triggered PFCnDs

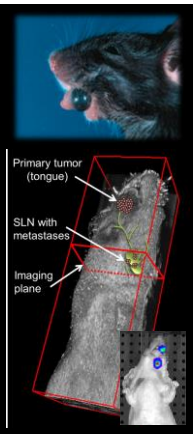


Laser-activated PFPnDs produce time-varying contrast in US imaging

Tumor Metastases in Sentinel Lymph Node

- Mouse model of oral cancer
- Metastatic foci are formed in sentinel lymph node(s) within 2-3 weeks

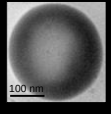


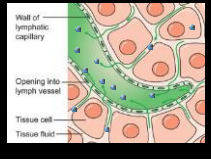


Contrast Enhanced, Laser-Assisted Ultrasound Imaging

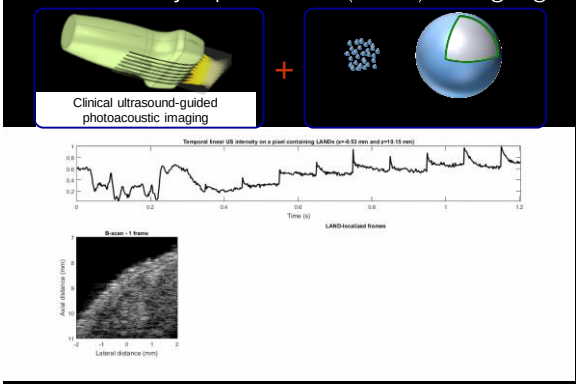
- Imaging protocol
  - Injection of perfluorocarbon (PFC) nanodroplets
  - 30 min wait
  - Ultrasound imaging of laser-activated PFCnDs

PFCnD

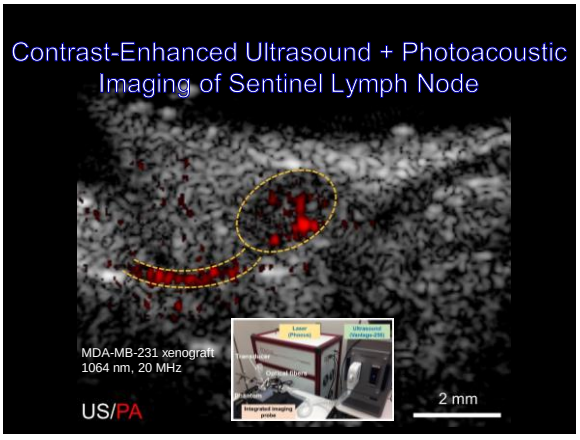




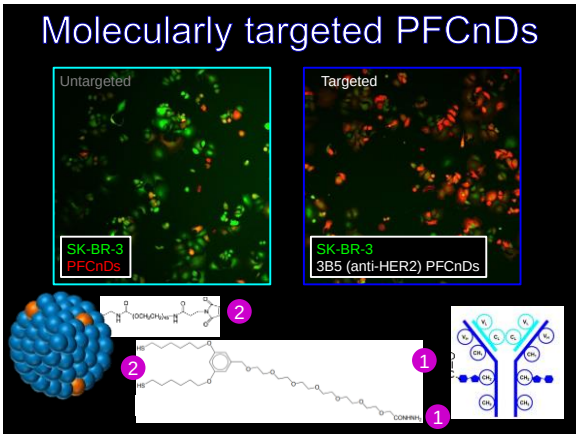
Sentinel Lymph Node (SLN) Imaging



Contrast-Enhanced Ultrasound + Photoacoustic Imaging of Sentinel Lymph Node

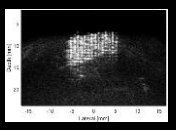


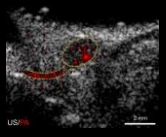
Molecularly targeted PFCnDs



Summary

- Nanoscale PFC contrast agents enable extravascular imaging
- Ultrasound or laser activation can provide high contrast images with high frame rate ultrasound imaging techniques
- Potential for lymphatic imaging and non-invasive image-guided therapy





Thank you

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Steve Yarmoska
Daniela Santiesteban
Diego Dumani
Heechul Yoon

Collaborators:
Tim Slesnick, M.D.
Mike Davis, Ph.D.
Milton Brown