FENG Distinguished Lecture
Department of Biomedical Engineering
Hong Kong PolyU
24th June, 2019

Nanoparticle-mediated tissue imaging and therapy at the intersection of light and sound

Ronald A. Roy

Department of Engineering Science

The University of Oxford

Part 1: Light-enhanced HIFU Therapy

- **High-intensity focused ultrasound (HIFU) is helpful in therapeutic medical procedures**
- **Primary bioeffect is tissue heating from ultrasound absorption**
- **Acoustic cavitation can enhance HIFU efficacy by accelerating heating and promoting mechanical damage**

What is Acoustic Cavitation?

Acoustic Cavitation

A Recipe…

Start with a preferential site for liquid rupture

- Imperfectly wetted solid, preexisting gas cavity, super-heated nanodroplet, etc.

Apply an acoustic stress strong enough to overcome…

- Surface tension, inertia, viscous drag

A microbubble is formed that pulsates radially in response to periodic acoustic forcing

- Acoustic Cavitation

The Nonlinear Response of a Single Bubble

Force balance across a bubble wall

- $\Delta F = ma$
- Internal: gas pressure vapor pressure
- External: hydrostatic pressure, surface tension

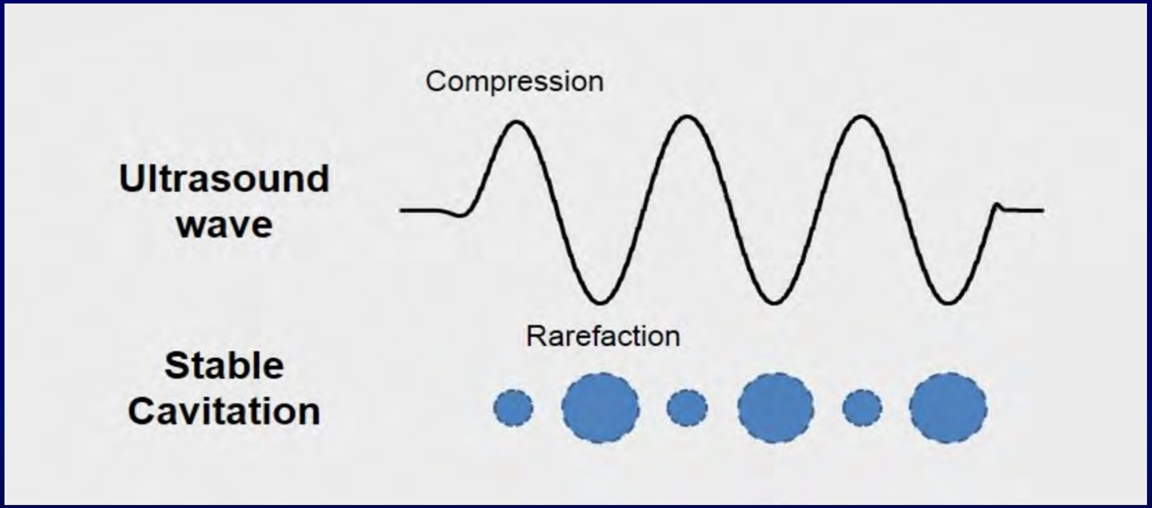
Rayleigh Plesset Equation

- 1-D radial motion, Newtonian incompressible fluid

$$\underbrace{\rho_o\left(R\ddot{R}+\frac{3}{2}\dot{R}^2\right)}_{\text{Inertial Terms}}=\underbrace{\left[\left(P_o-P_v+\frac{2\sigma}{R_o}\right)\left(\frac{R_o}{R}\right)^{3\kappa}+P_v\right]}_{\text{Total Internal Pressure}}\underbrace{-\frac{2\sigma}{R}-\frac{4\mu\dot{R}}{R}-\left(P_o+P_a\sin\omega t\right)}_{\text{Total External Pressure}}$$

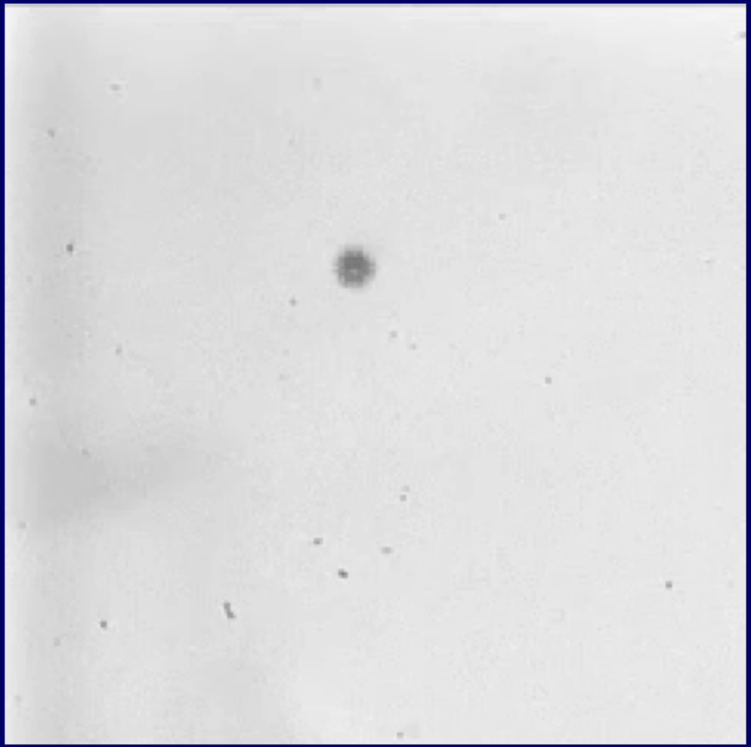
"Stable Cavitation"

- Repetitive pulsations about equilibrium radius
- Dominated by gas compressibility
- Larger bubbles and lower acoustic pressures
  - acoustic scattering and radiation pressure
  - acoustic emissions
  - micro-streaming, microjets, rectified diffusion



“Inertial Cavitation”

- Unstable growth -- violent collapse
- Dominated by liquid inertia
- Smaller bubbles, higher pressure
  - acoustic emissions
  - microstreaming
  - collapse jets, shock waves
  - Extreme conditions in the cavity (sonochemistry)



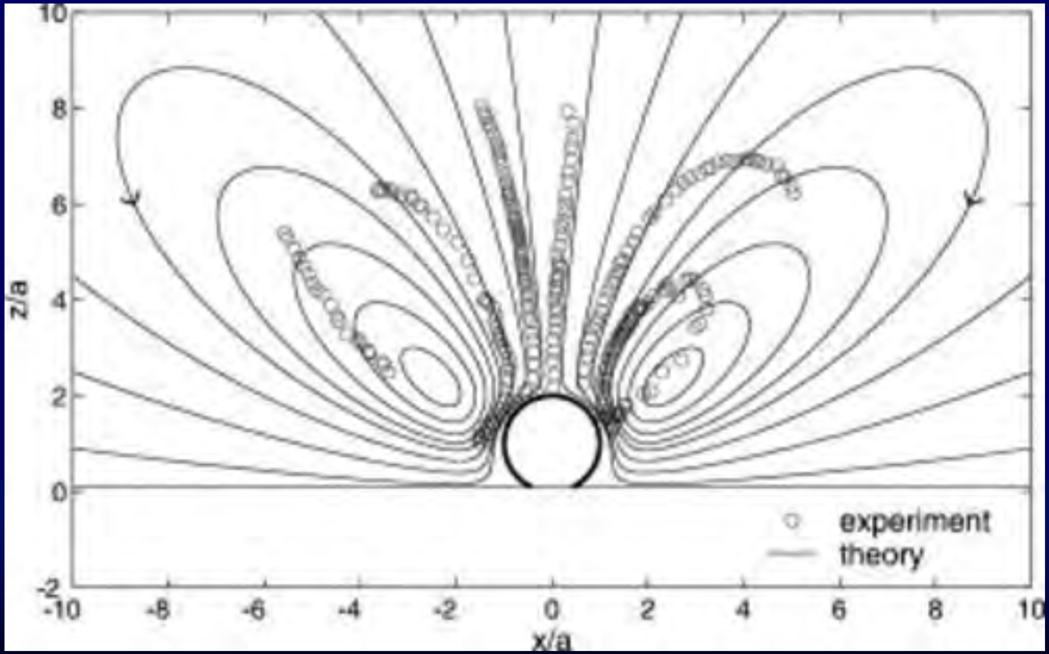
Physical Effects

Radiation Stress

$$\vec{F} = -\left\langle V(t)\vec{\nabla}P \right\rangle$$

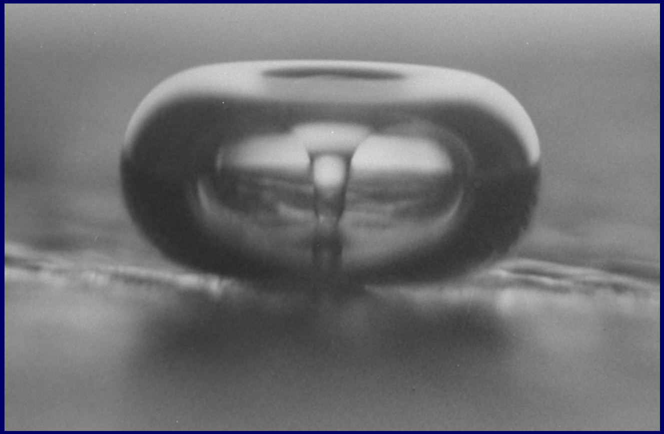
Physical Effects

Cavitation Micro-streaming



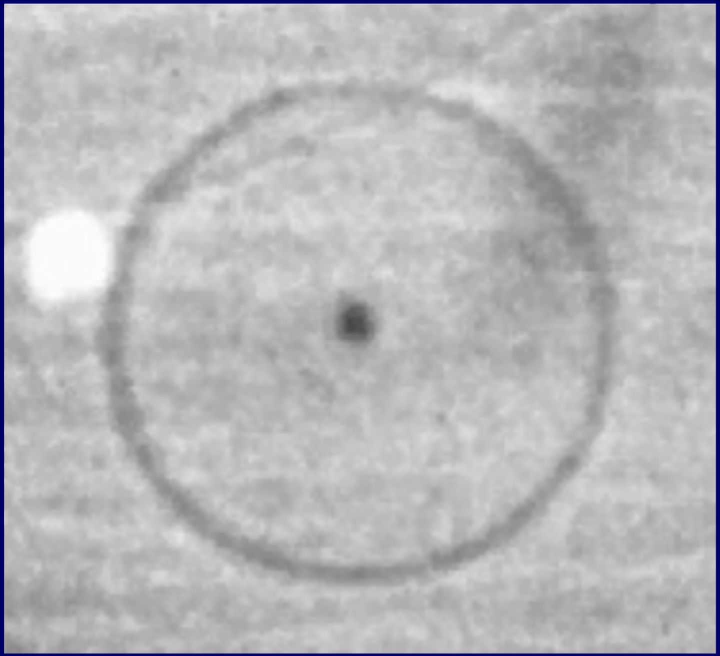
Physical Effects

Collapse Micro-jets

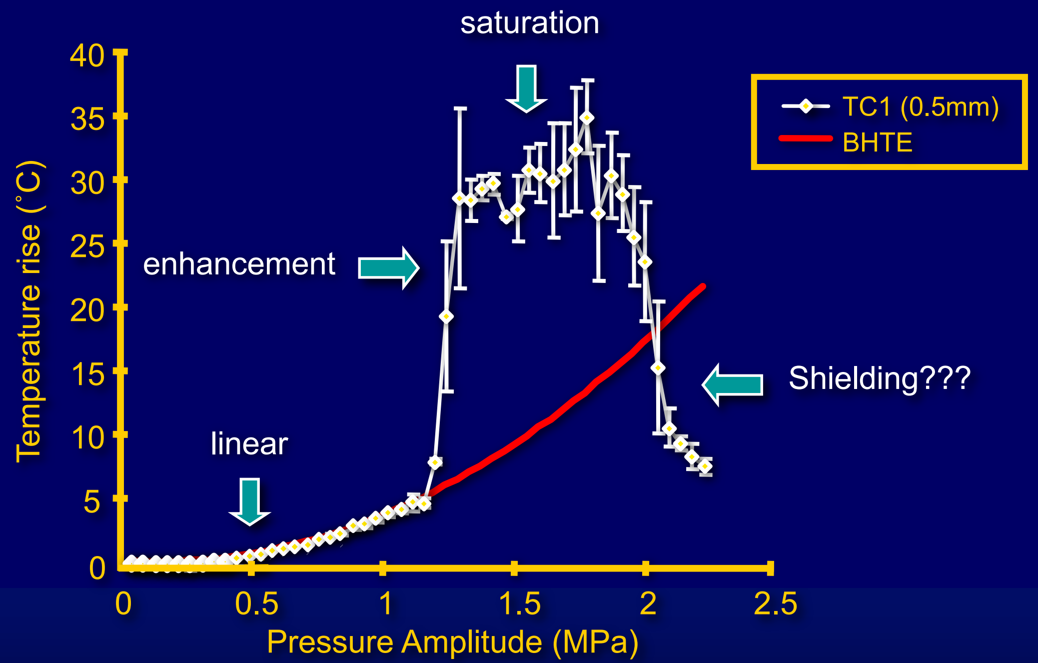


Physical Effects

Radiated Shock Waves



Physical Effects



Enhanced Heating

The Nucleation Threshold Pressure

- The “nucleation threshold” is the minimum acoustic stress required to form the bubble

- *In vivo* cavitation nucleation thresholds are high (5-7 MPa)
  - Lack of naturally occurring nuclei
  - Cavitation field difficult to control – too much damage

- Lowering the nucleation threshold makes it easier to sustain and control cavitation
  - Contrast agents
  - Superheated droplets
  - Imperfectly wetted solid microparticles

A Role for Light?

- Pulsed laser light can cavitate water.
  - Poor spatial specificity (tissue optically diffusive)
- Light absorbing nanoparticles serve as preferential site for vapor cavity formation
  - Used as contrast agents for photoacoustic imaging
- Can laser-illuminated nanoparticles serve as cavitation nucleation sites???

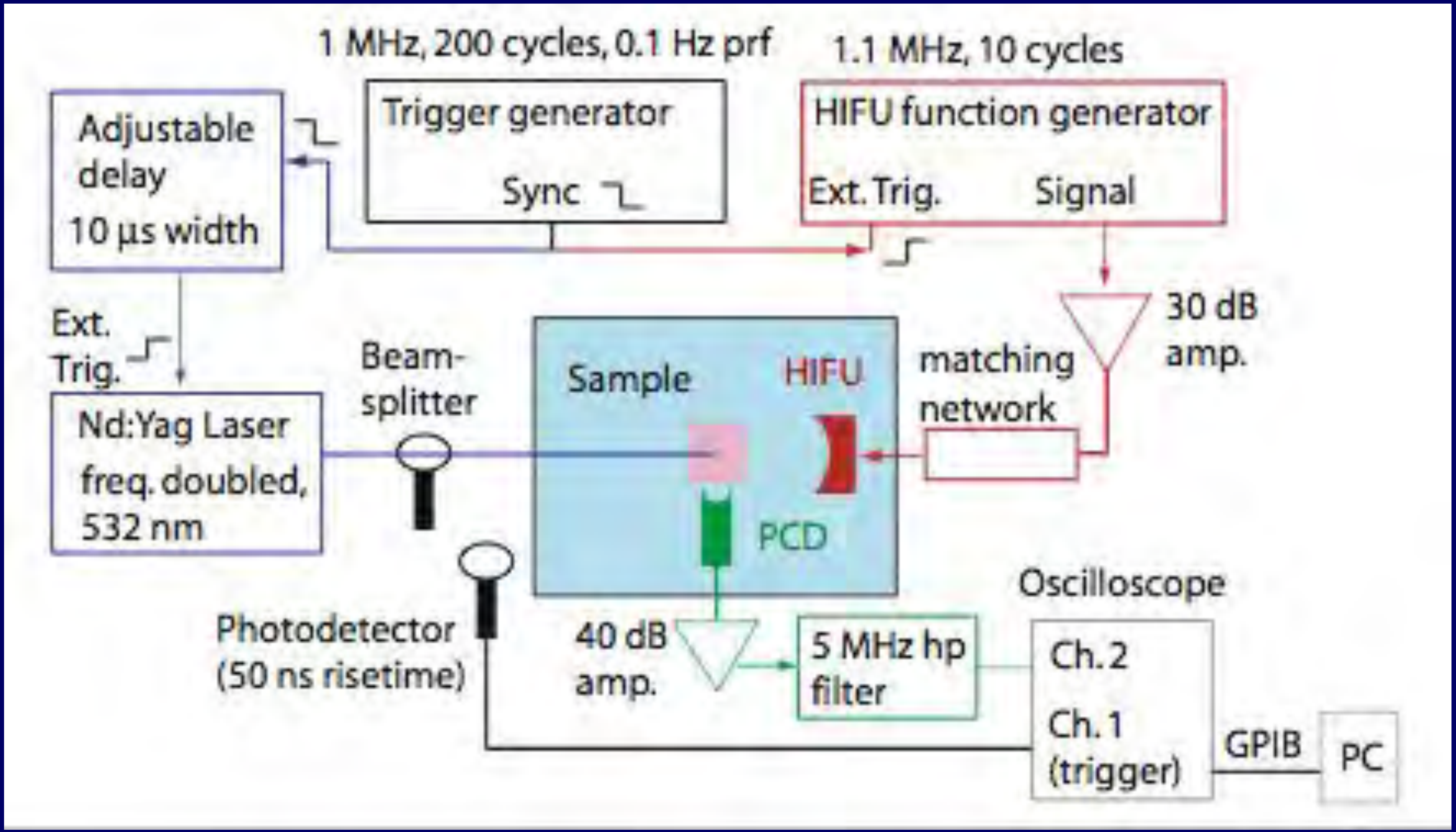
Nanoparticle Mediated Inertial Cavitation

Cavitation on Demand

”Seed” tissue phantom with 40 nm gold nano-particles:

- Irradiate with pulsed laser *and* HIFU
- Time laser to coincide with rarefaction phase of HIFU
- Measure nucleation threshold pressure…
  - With and without laser illumination
  - As a function of laser energy

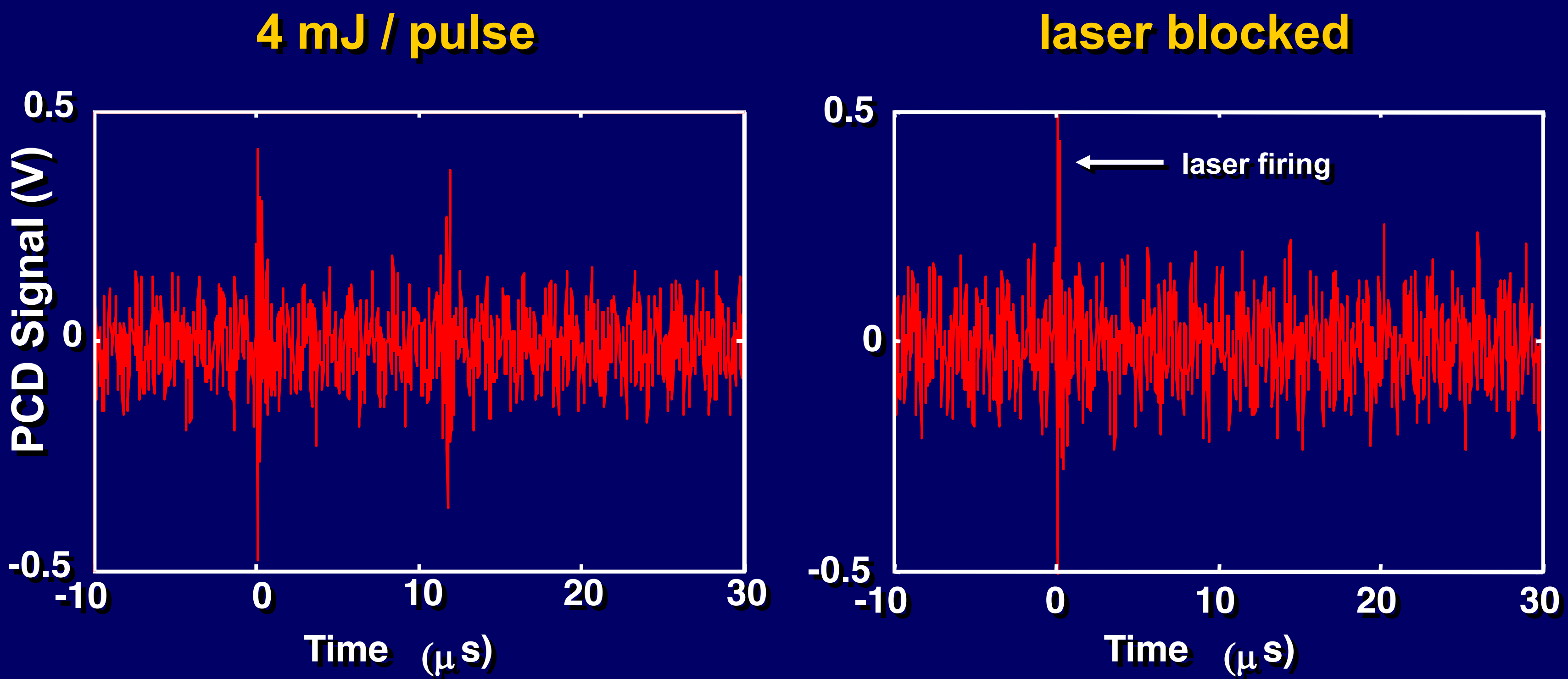
Nanoparticle Mediated Inertial Cavitation



acrylimide gel phantom
15 MHz PCD (15 mm FL)

Nd:YAG laser, 532 nm (5 ns pulse)
1.1 MHz pulsed HIFU (10 cycles)

Light Only (No HIFU)



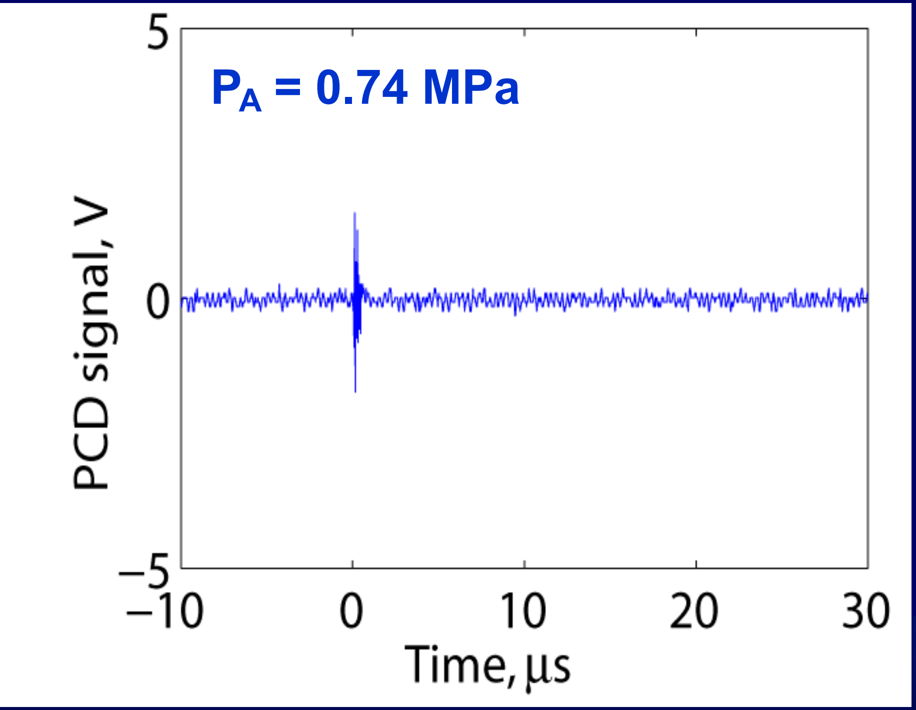
Laser nucleation threshold (no sound) ≈ 1.8 mJ/pulse

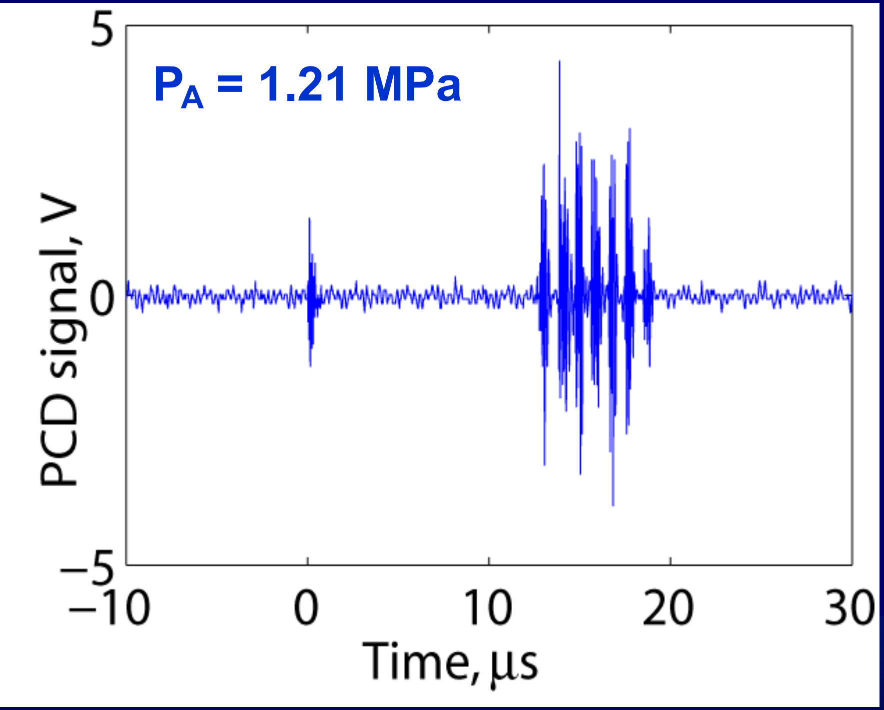
HIFU nucleation threshold (no light) ≈ 4.5 MPa

Light + Sound

0.1 mJ/pulse (3 mJ/cm²)

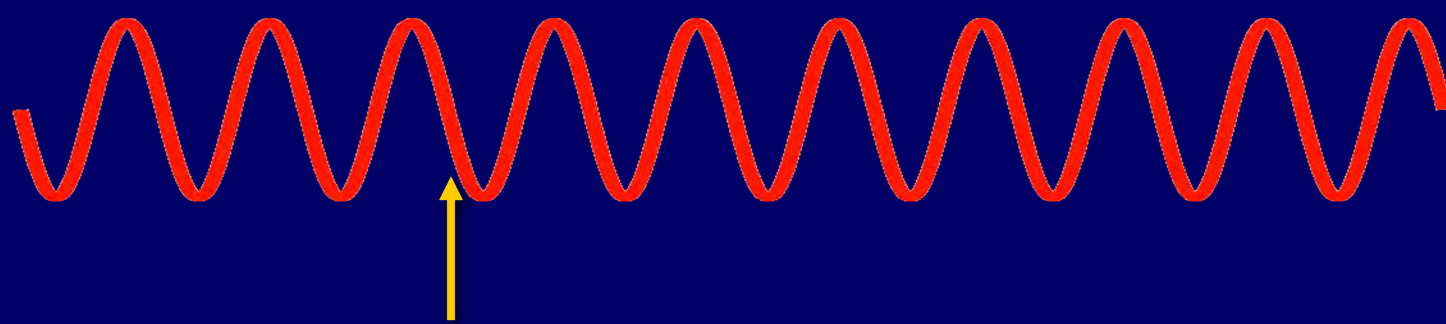
10 cycle acoustic pulse

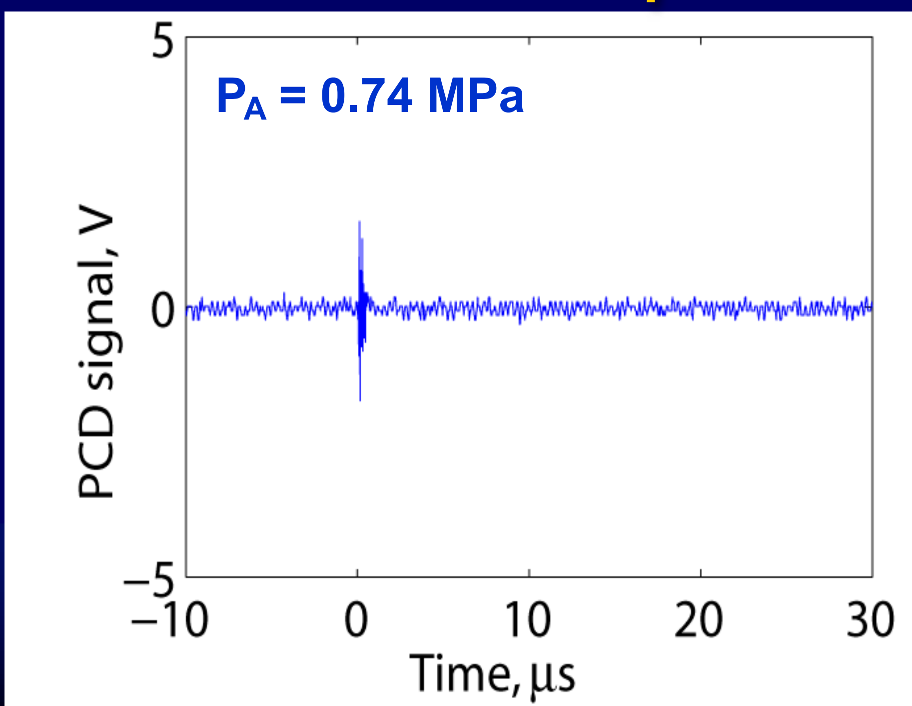


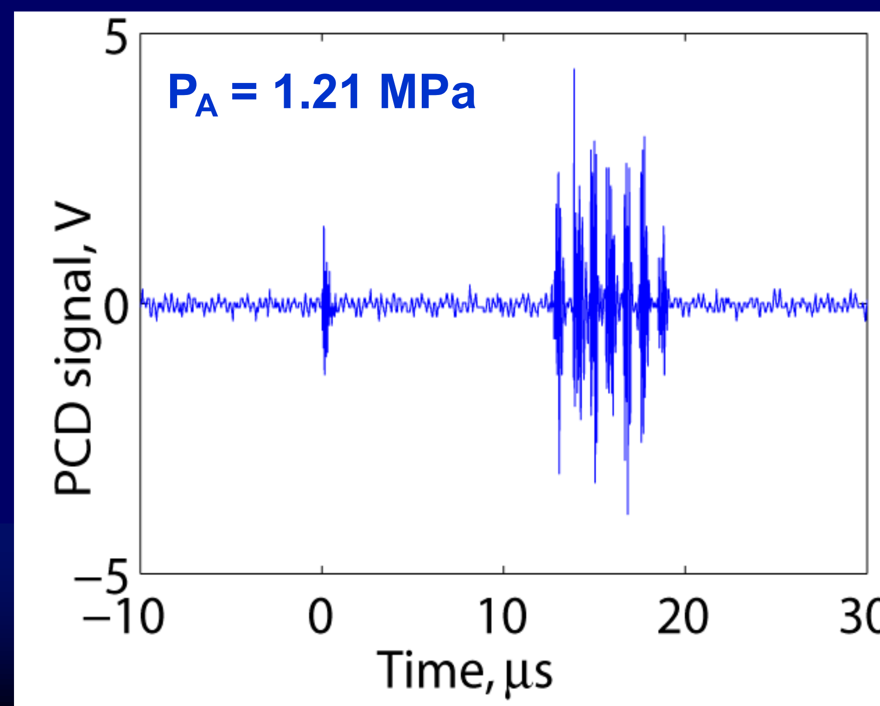


Light + Sound

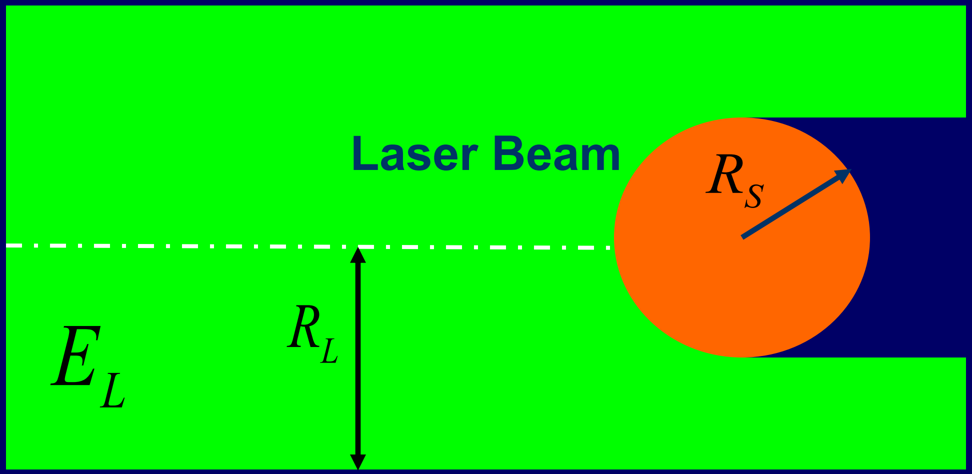
Acoustic Cavitation "On Demand"







How Does it work?
Energy Budget



Absorbed energy Q is roughly proportional to the laser energy E_L and the geometric cross section

$$Q = \beta \bullet E_L \bullet \left(\frac{R_s}{R_L}\right)^2$$

Q : absorbed energy

$\beta = \beta(\lambda_L, R_S)$: absorption efficiency

E_L : laser pulse energy

R_S : particle radius

R_L : laser beam radius

$E_L = 0.1\,\mathrm{mJ}$

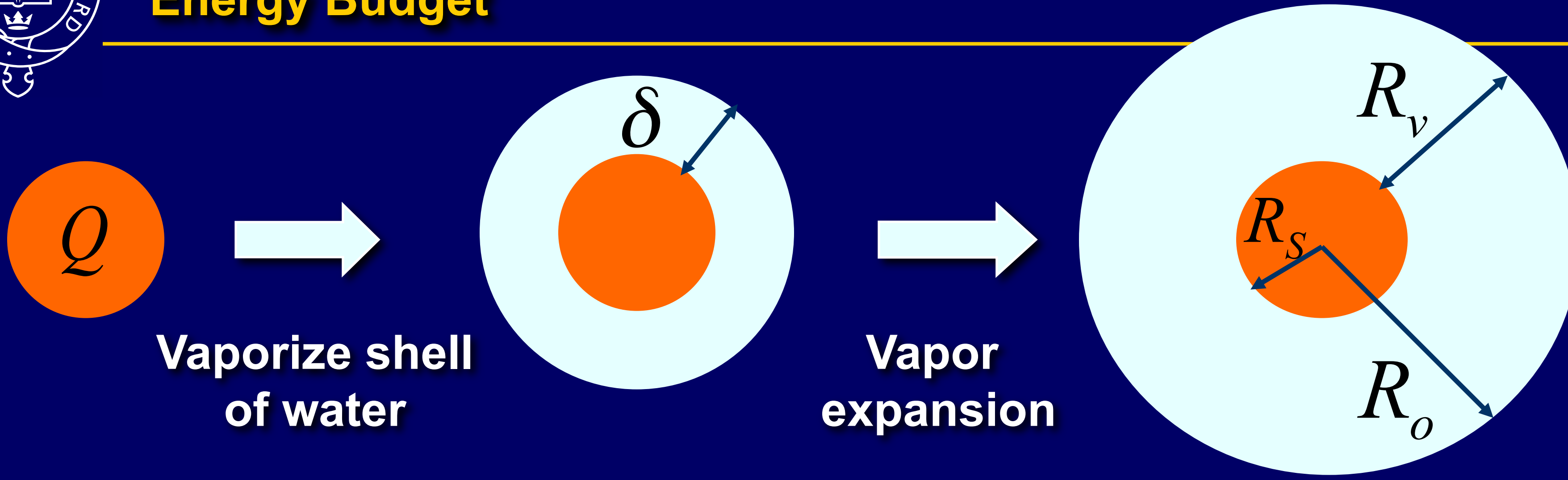
$\beta = 3.3$

$R_L = 0.8\,\mathrm{mm}$

$R_S = 40\,\mathrm{nm}$

$\rightarrow$ $Q = 0.87\,\mathrm{pJ}$

How Does it work?
Energy Budget



All absorbed energy Q is converted to heat and vaporizes a thin shell of water surrounding the particle.

$$Q = m_\delta c_v \Delta T + m_\delta h_{fg}$$

m_δ : mass of water shell, c_v : heat capacity

$\Delta T = T_{sat} - T_o$ $\quad h_{fg}$: latent heat

Vaporization expands the shell into a larger vapor nucleus:

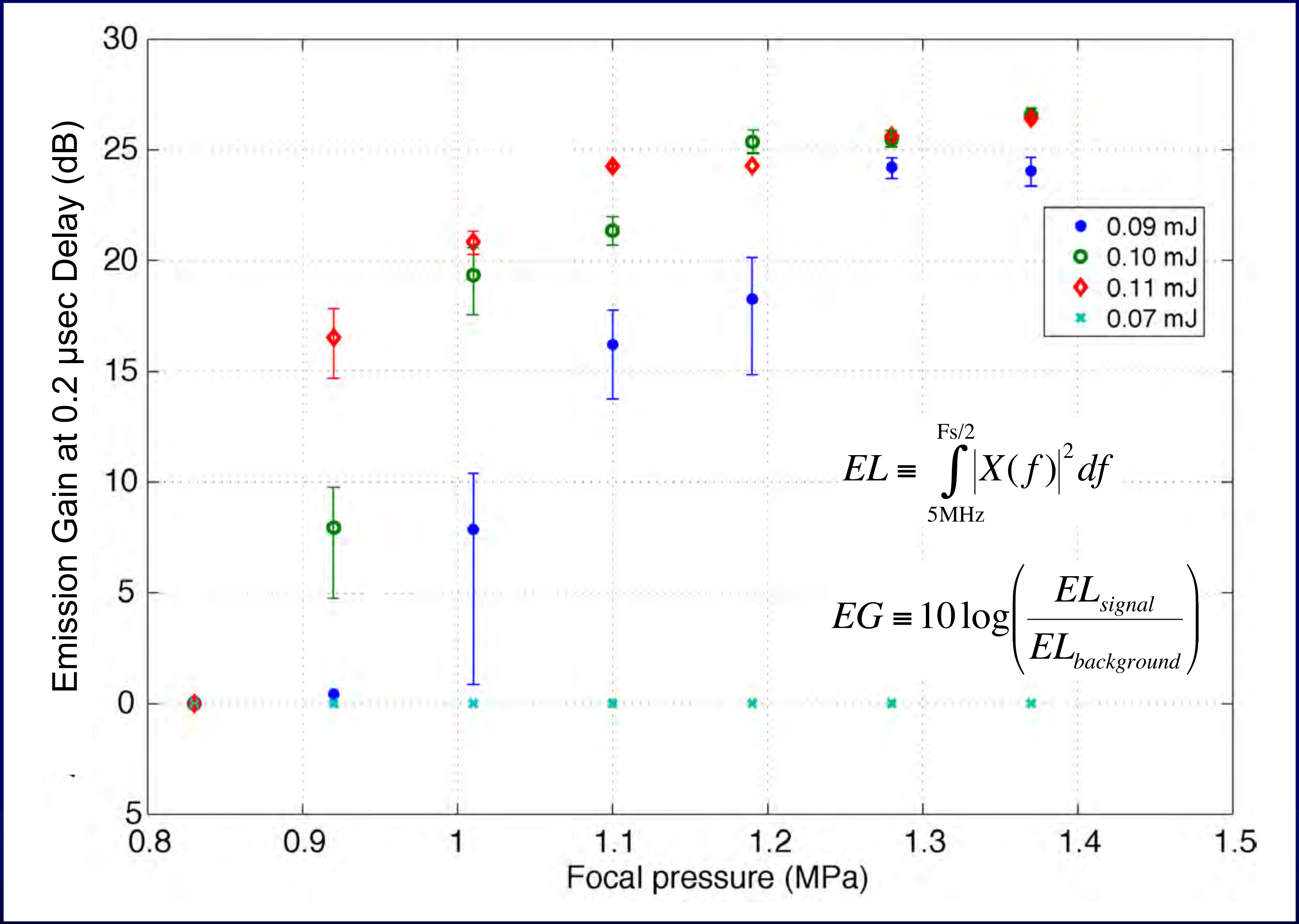
$\delta \rightarrow R_v$ (vapor shell thickness)

R_o : vapor nucleus radius

$$R_o = R_S + R_v$$

Q = 0.87 pJ → δ = 14.3 nm → R_o = 105 nm

Parameter Study

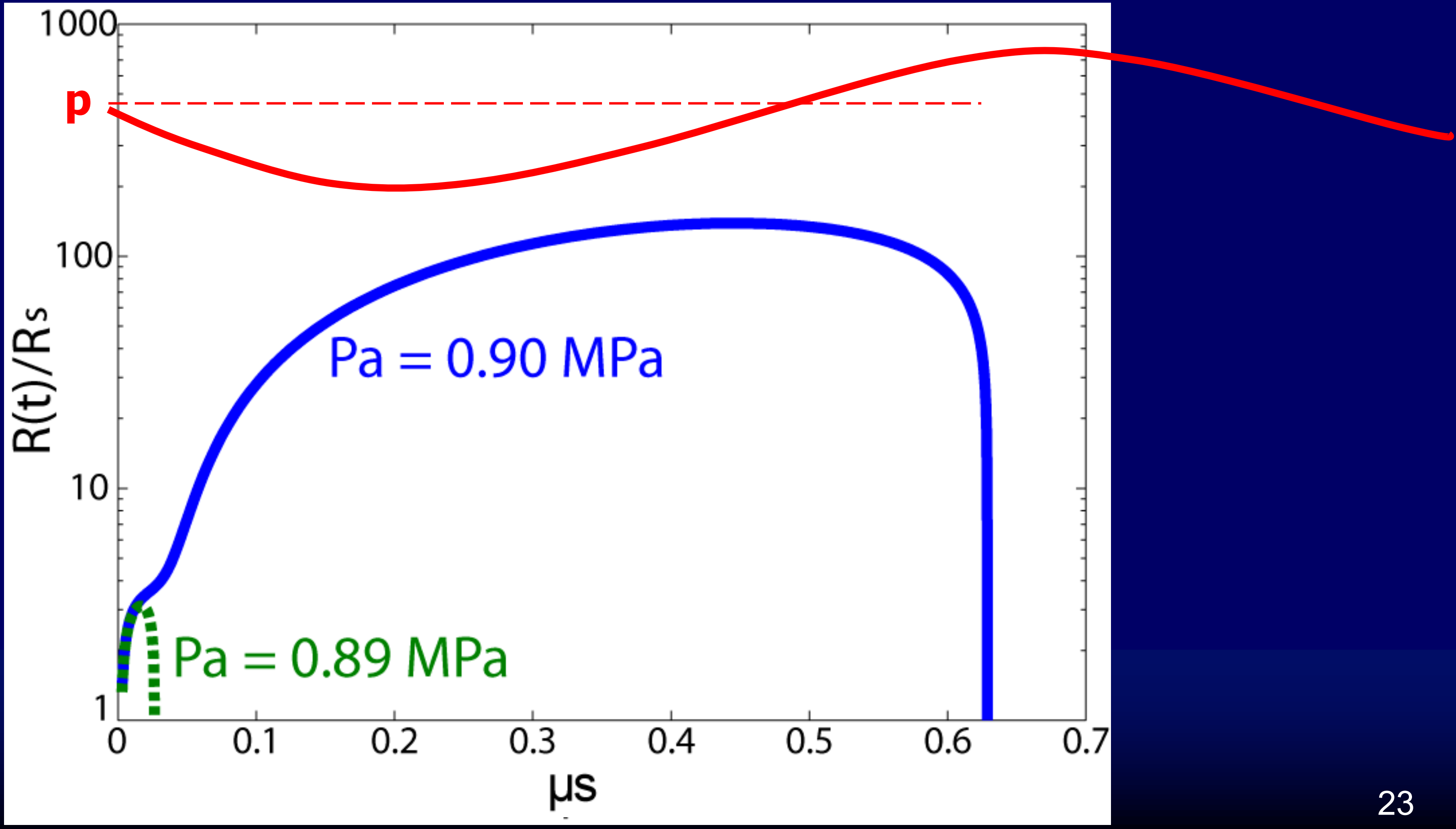


Modeling Result

Laser: 0.1 mJ/pulse (3mJ/cm²)

HIFU: 1.1MHz

Nano-Particle: Gold, 40nm in radius



Nanoparticle Mediated Inertial Cavitation

Threshold acoustic pressure reduced from 4.5 to 1 MPa

Threshold laser energy reduced from 1.8 mJ to 0.1 mJ

Effect well described by theory

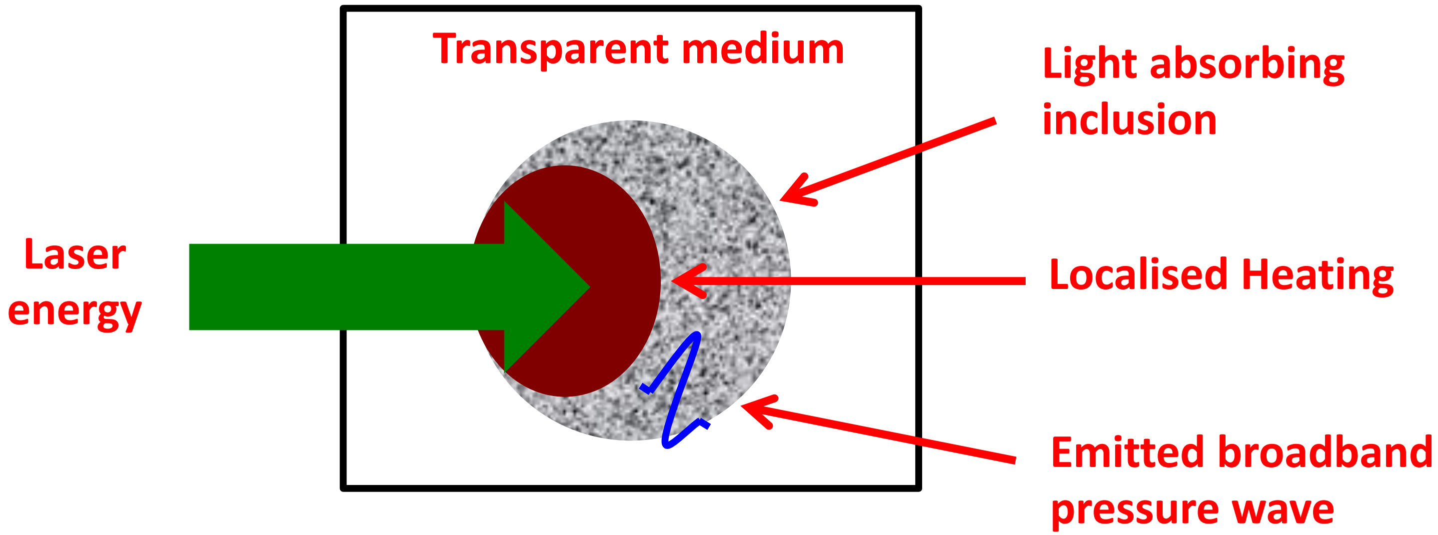
Nanoparticles can be targeted to tissue types

Nanoparticles are persistent nuclei

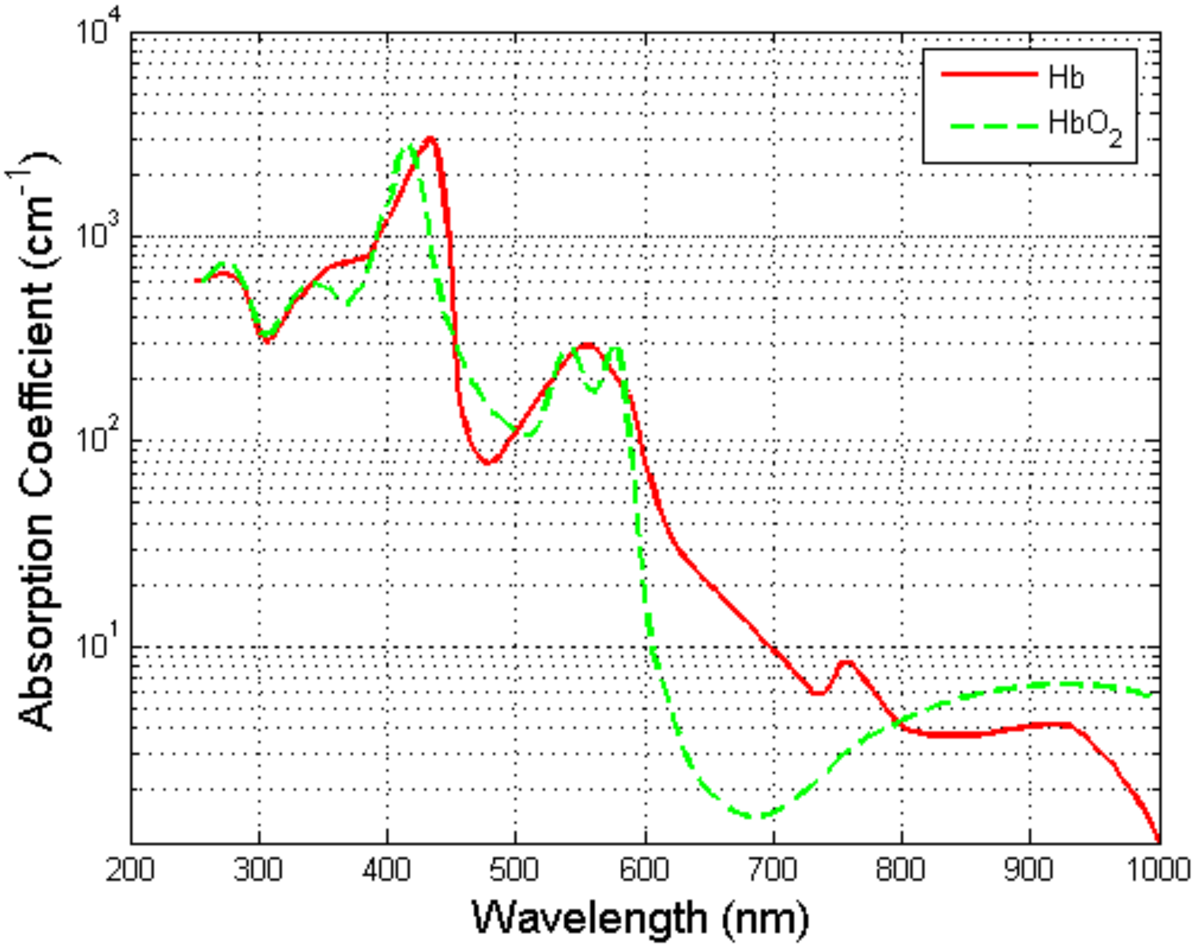
Enables cavitation nucleation "on demand"

Part 2: Ultrasound Enhanced Photoacoustic Imaging

- **Broadband acoustic emissions from thermoelastic expansion of a light absorbing medium**



Multispectral Imaging
It's About the Hemoglobin



Blood primarily impacts local absorption

Absorption measurements yield local blood concentration

Multi-spectral absorption measurements yield oxygen saturation levels

Both are key physiological functional parameters

Prahl, Oregon Medical Laser Center, *Optical absorption of Hemoglobin* (*http://omlc.ogi.edu/spectra/hemoglobin/index.html*), 1999.

But There is a Problem…

Deep tissue PA imaging requires that you get sufficient light "at depth" to excite a measureable response.

Real tissues have a lot of scattering and absorption. You can't go very deep.

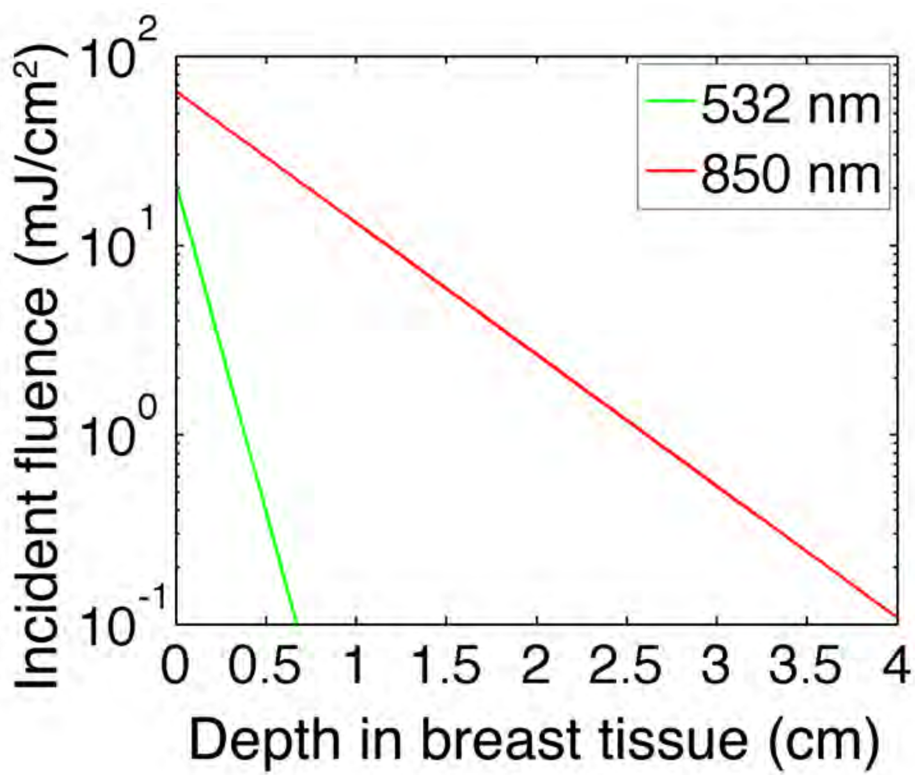
Max Permissible Exposure (MPE) for 1-100 nsec pulsed laser light*:

20mJ/cm^2 @ 532 nm

60mJ/cm^2 @ 900 nm

100mJ/cm^2 @ 1064 nm

***American National Standard**



Enhancing Photoacoustic Emissions

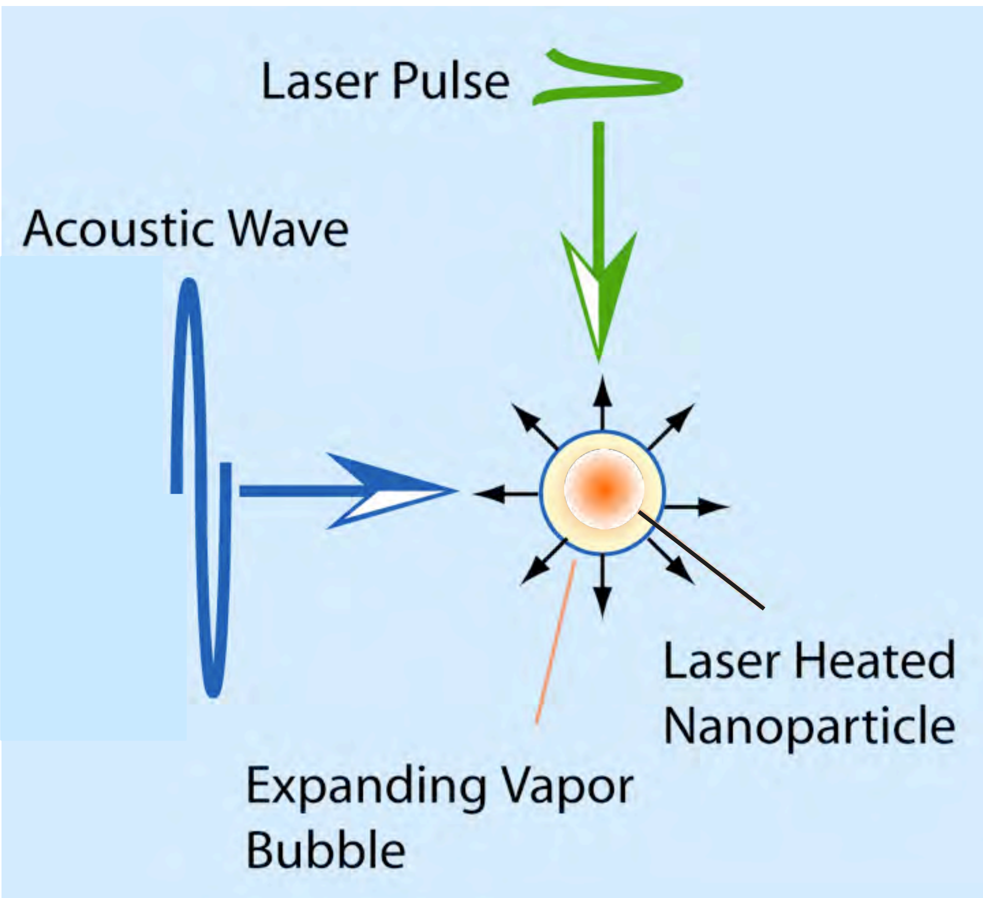
Gold Nano-particles

- **Plasmon resonant gold nano-particles are very efficient absorbers of laser energy.**
- **Used to enhance photoacoustic imaging techniques.**
- **Functionalized to targeted to specific cell populations.**
- **So….**

*720 mJ/cm^2 for a 30 nm nano-particle at 532nm and 0.5 ns pulse length Lapotko, D., Opt. Express **17**(4), 2538-2556 (2009)

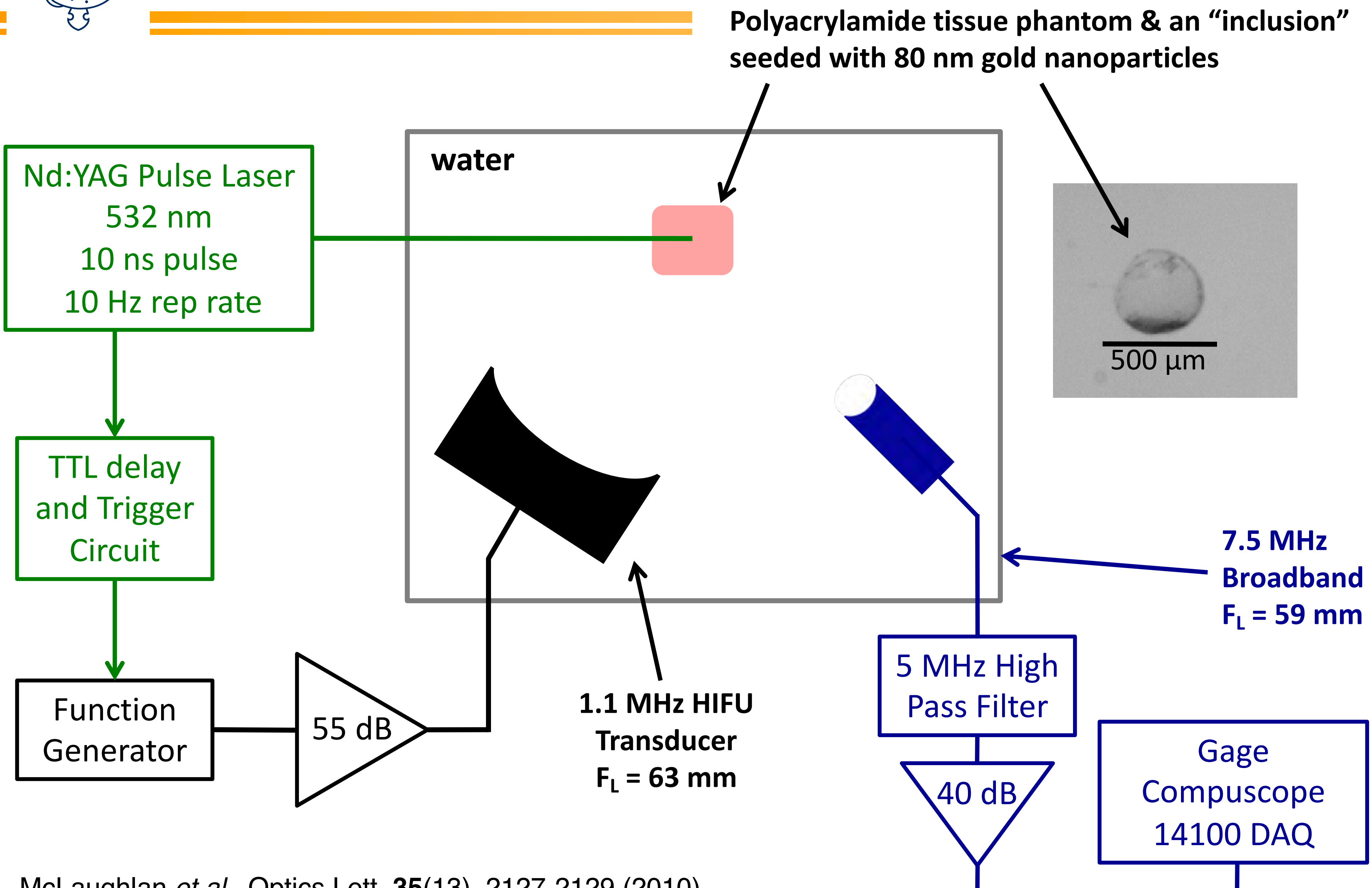
Ultrasound-enhanced Photoacoustic Emissions

Gold nanoparticle imbedded in target



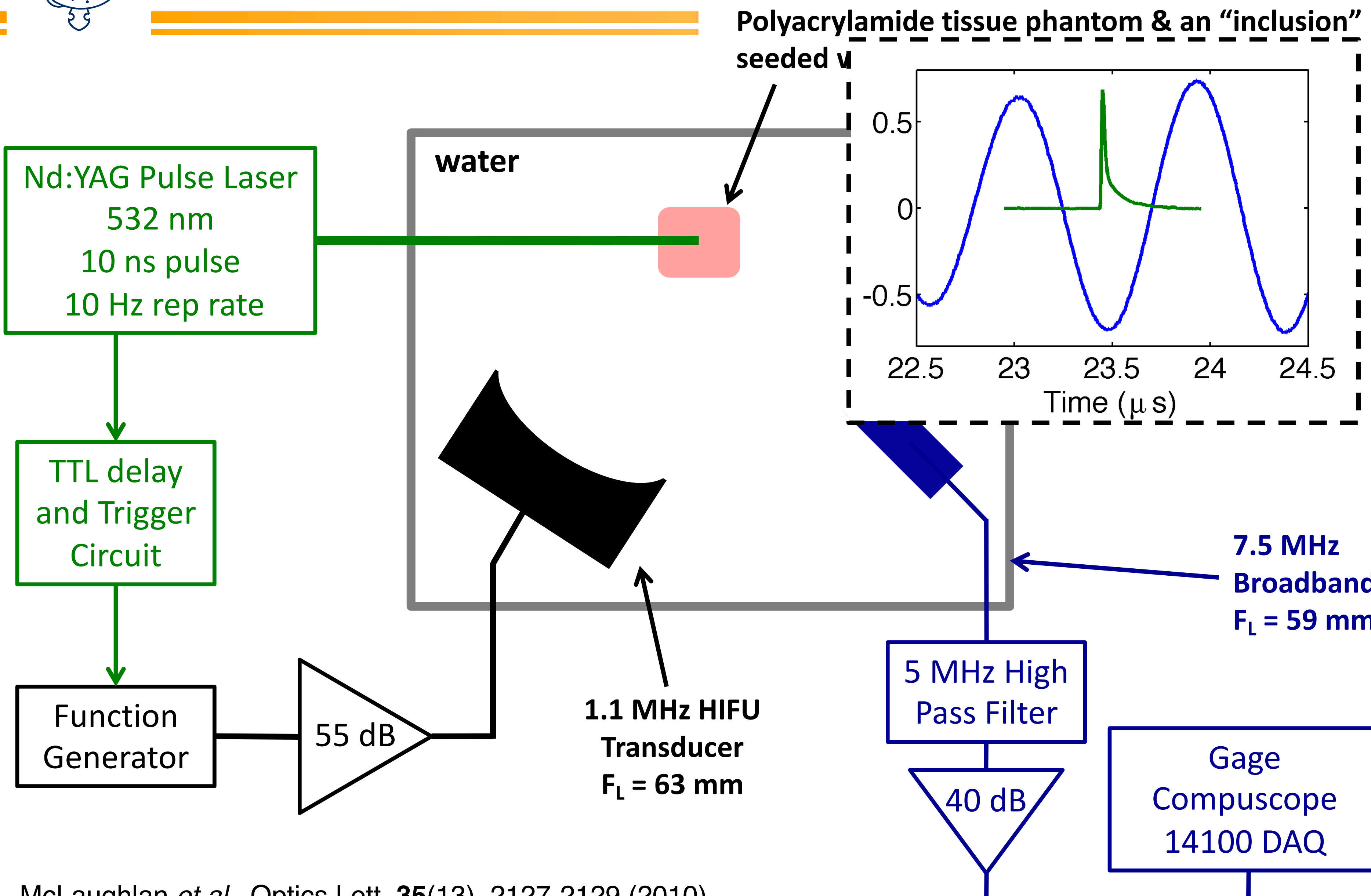
- **Introduce short laser pulse**
- **Photoacoustic emission from direct particle heating**
- **Introduce short US pulse**
- **Rarefaction causes small vapor "blanket" to rapidly expand and collapse**
- **Greatly enhances broad band emissions**

US Enhanced PA Imaging



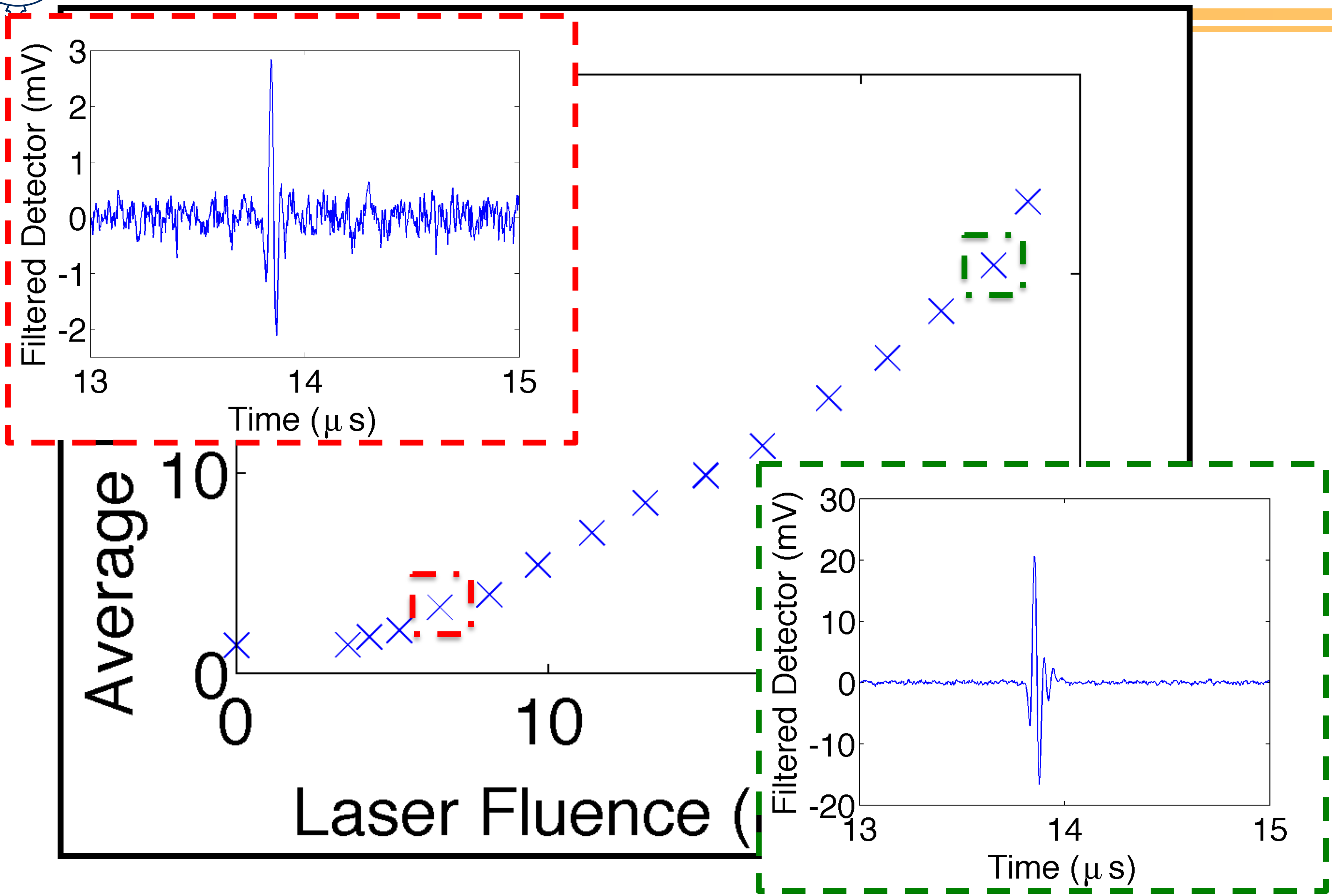
McLaughlan *et al.*, Optics Lett. **35**(13), 2127-2129 (2010).

US Enhanced PA Imaging



McLaughlan *et al.*, Optics Lett. **35**(13), 2127-2129 (2010).

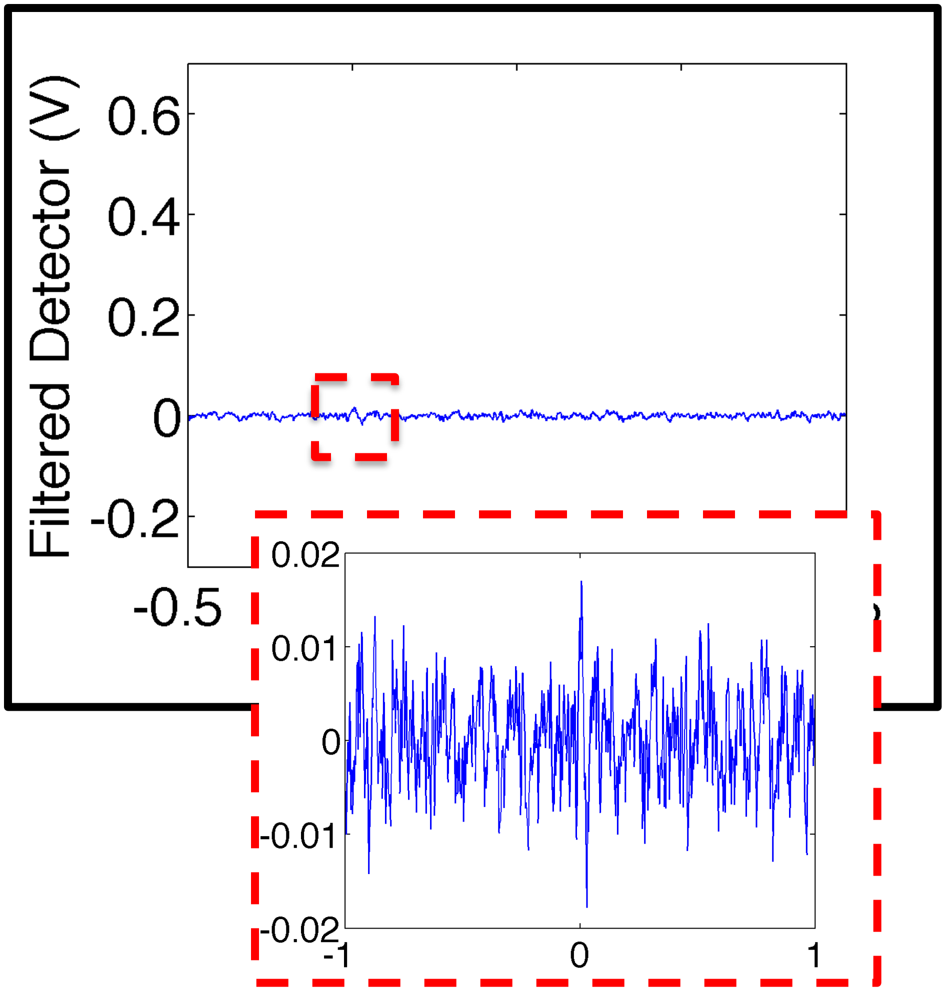
Nanoparticles + Light (no HIFU); n = 50



Nanoparticles + Light + HIFU; n = 1

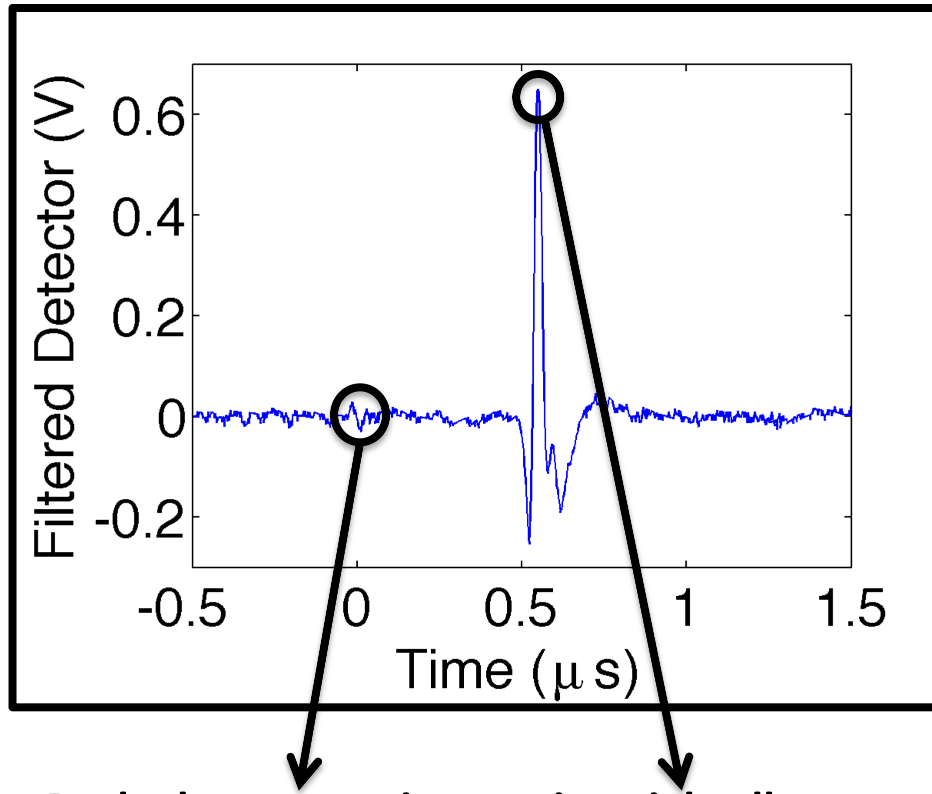
Without HIFU

Single Shot (no averaging) at 20.8 mJ/cm²



With HIFU

Single Shot with inertial collapse (1.5 MPa)



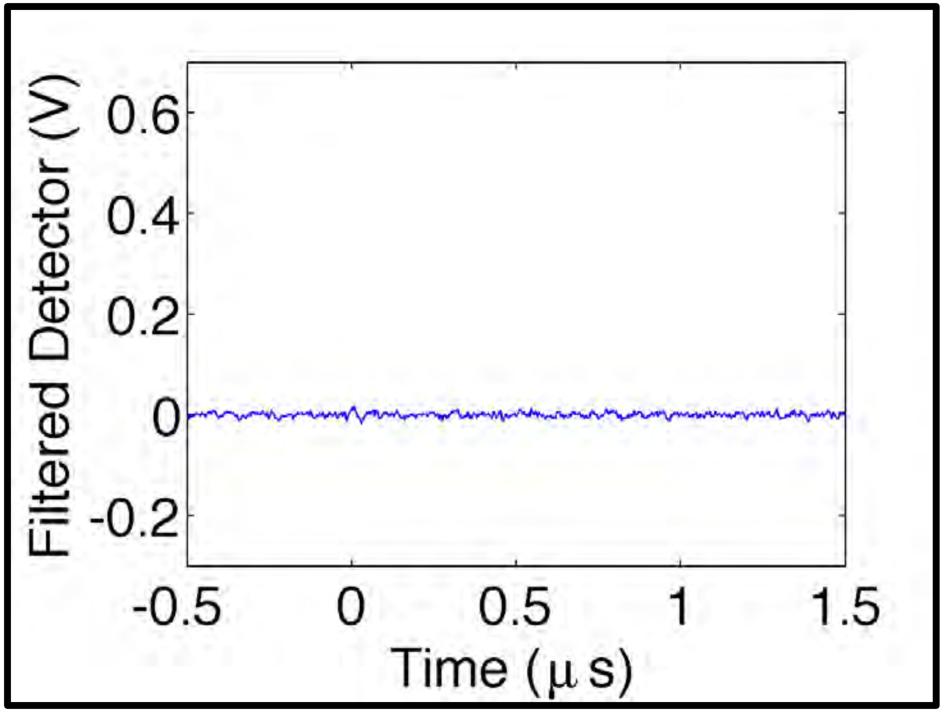
Peak photoacoustic **inertial collapse**

IC ≈ 35 times greater

Nanoparticles + Light + HIFU; n = 1

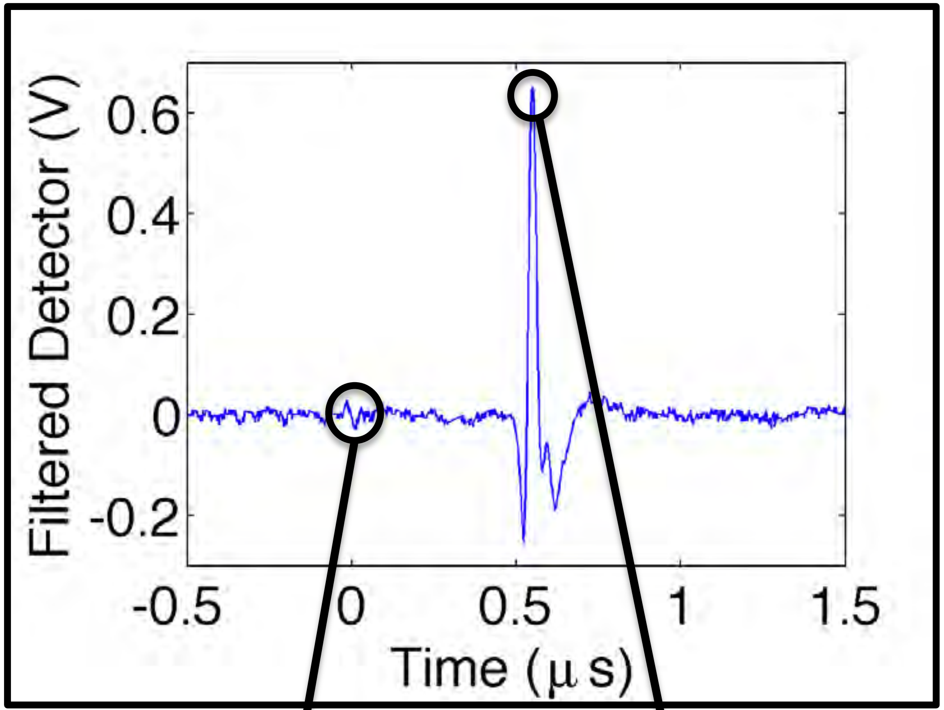
Without HIFU

Single Shot (no averaging) at 20.8 mJ/cm²



With HIFU

Single Shot with inertial collapse (1.5 MPa)



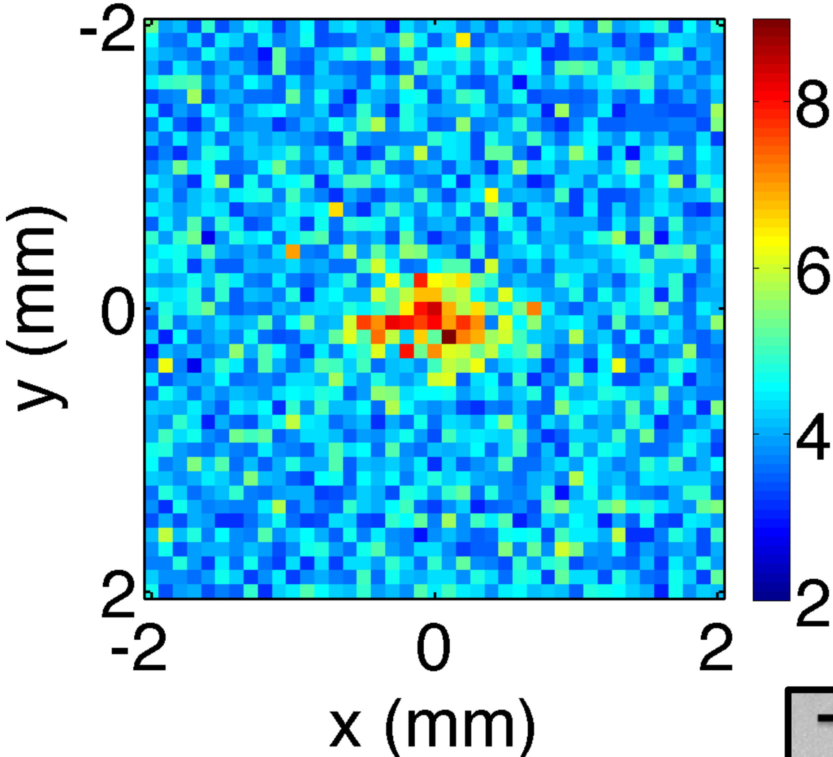
Peak photoacoustic **inertial collapse**

By exploiting the IC emission we can greatly increase photoacoustic imaging depth

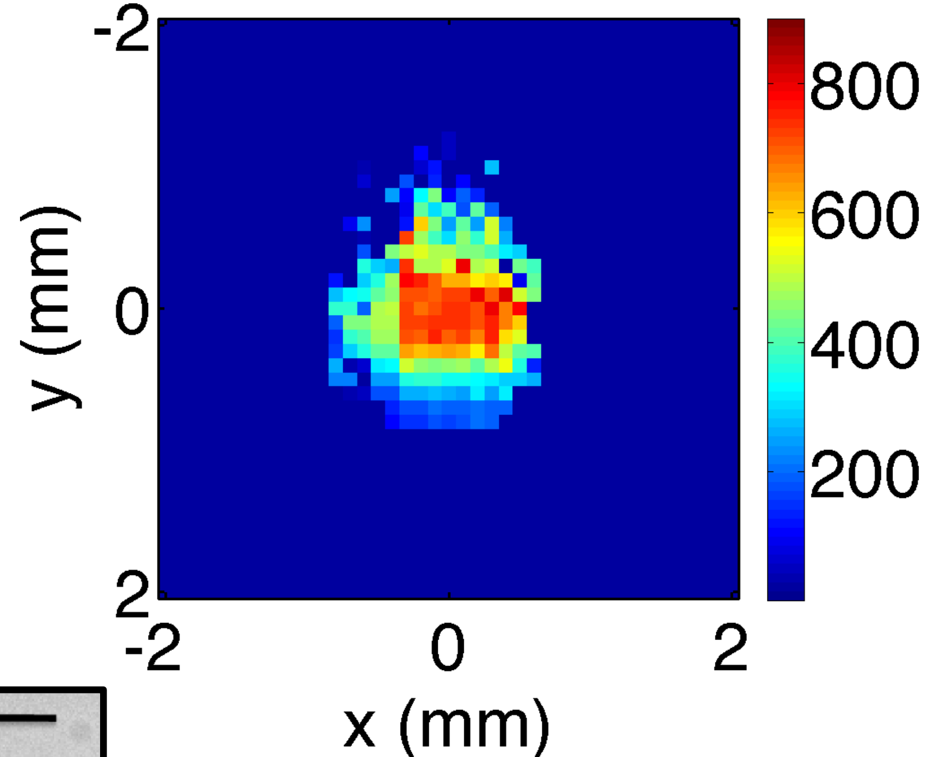
IC ≈ 35 times greater

Imaging by Inertial Collapse

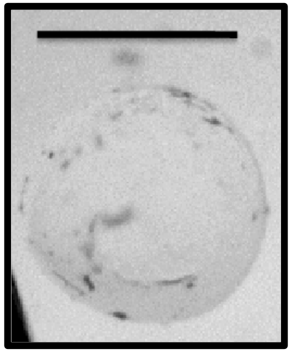
Averaged (n=10) PA Image



IC Image for a 1.5 MPa HIFU



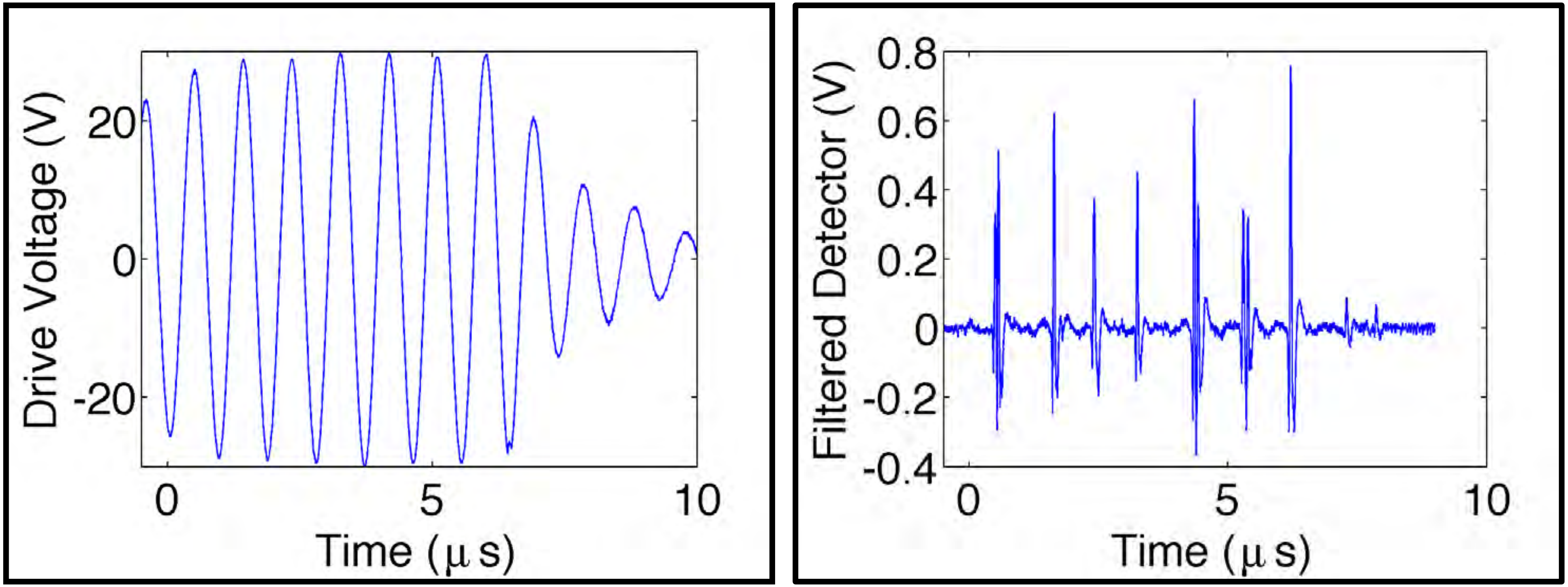
Fluence: 11.4 mJ/cm²



≈ 500 µm diameter

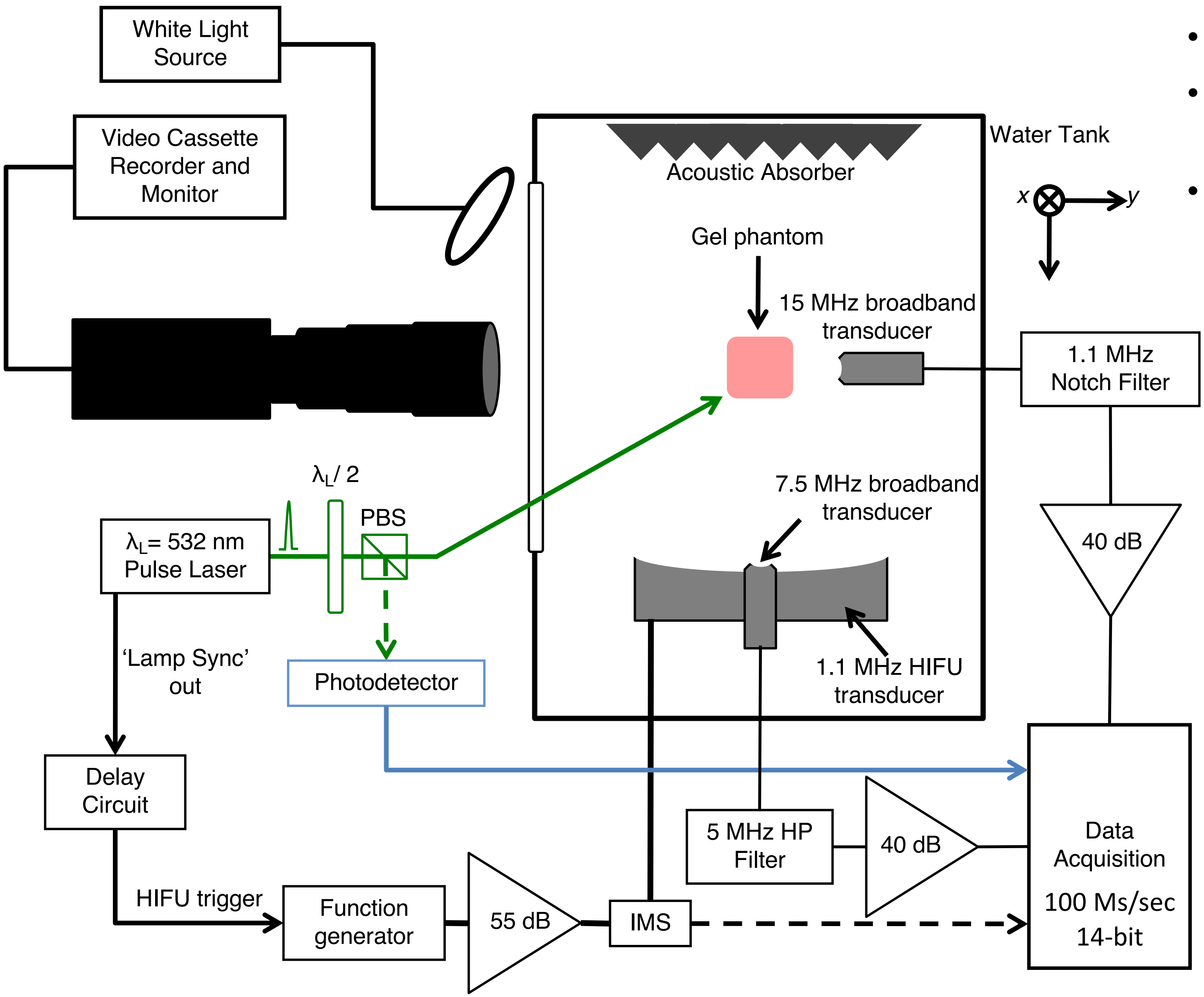
Part 3: Increase the HIFU Pulse Duration
Imaging to Therapy

•A 10 cycle, 1.5 MPa HIFU pulse, with a fluence of 11.4 mJ/cm^2



An inertial collapse detected for approximately each acoustic cycle

Concept 2: Light-enhanced HIFU Heating

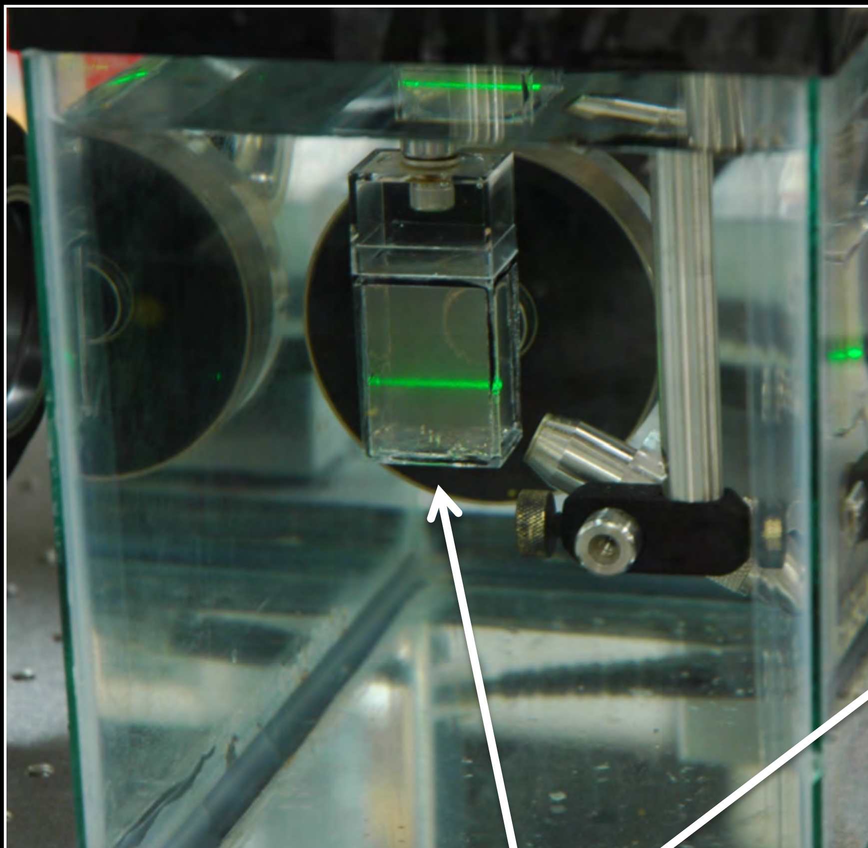


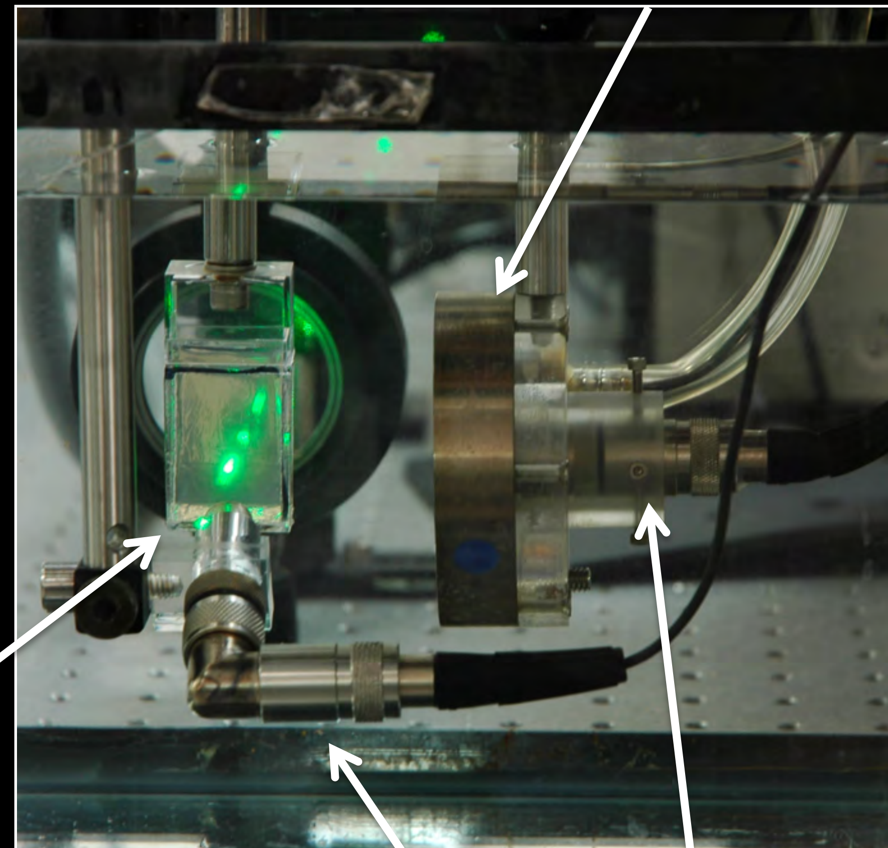
- Gel phantom (40x20x20 mm)
- Polyacrylamide with bovine serum albumin (BSA)
- Doped with 10^8 particles/ml

34 mm

Experimental Arrangement

1.1 MHz HIFU transducer





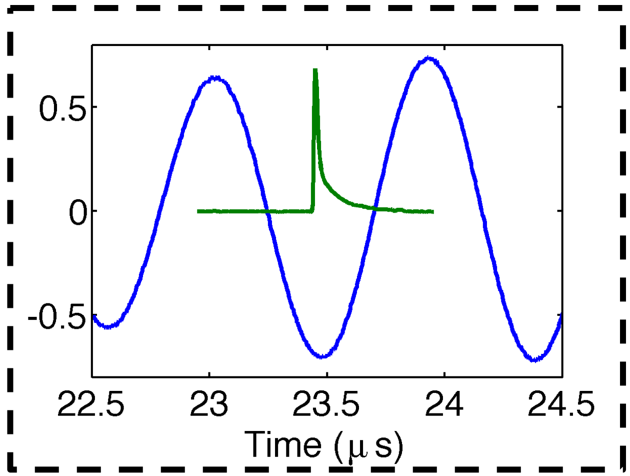
7.5 MHz PCD

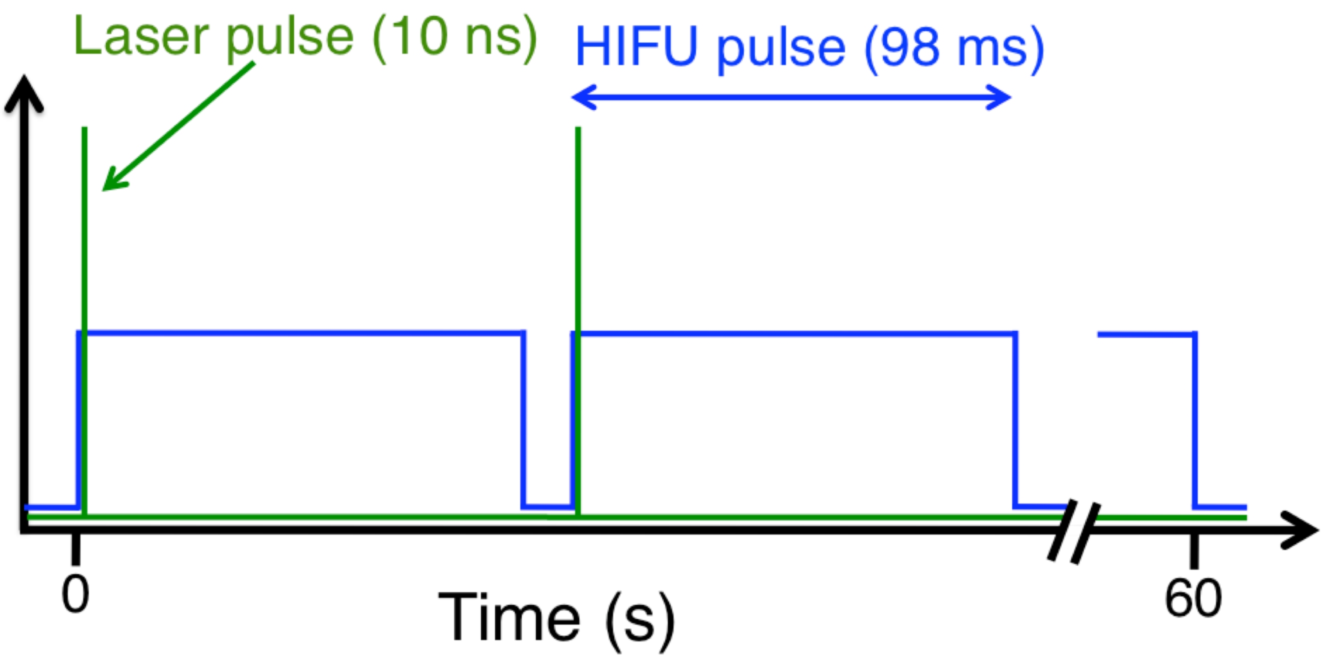
15 MHz PCD

30x30x50 mm Polyacrylamide phantom containing bovine serum albumin (BSA) and gold nanoparticles (80 nm)

Experimental Protocol

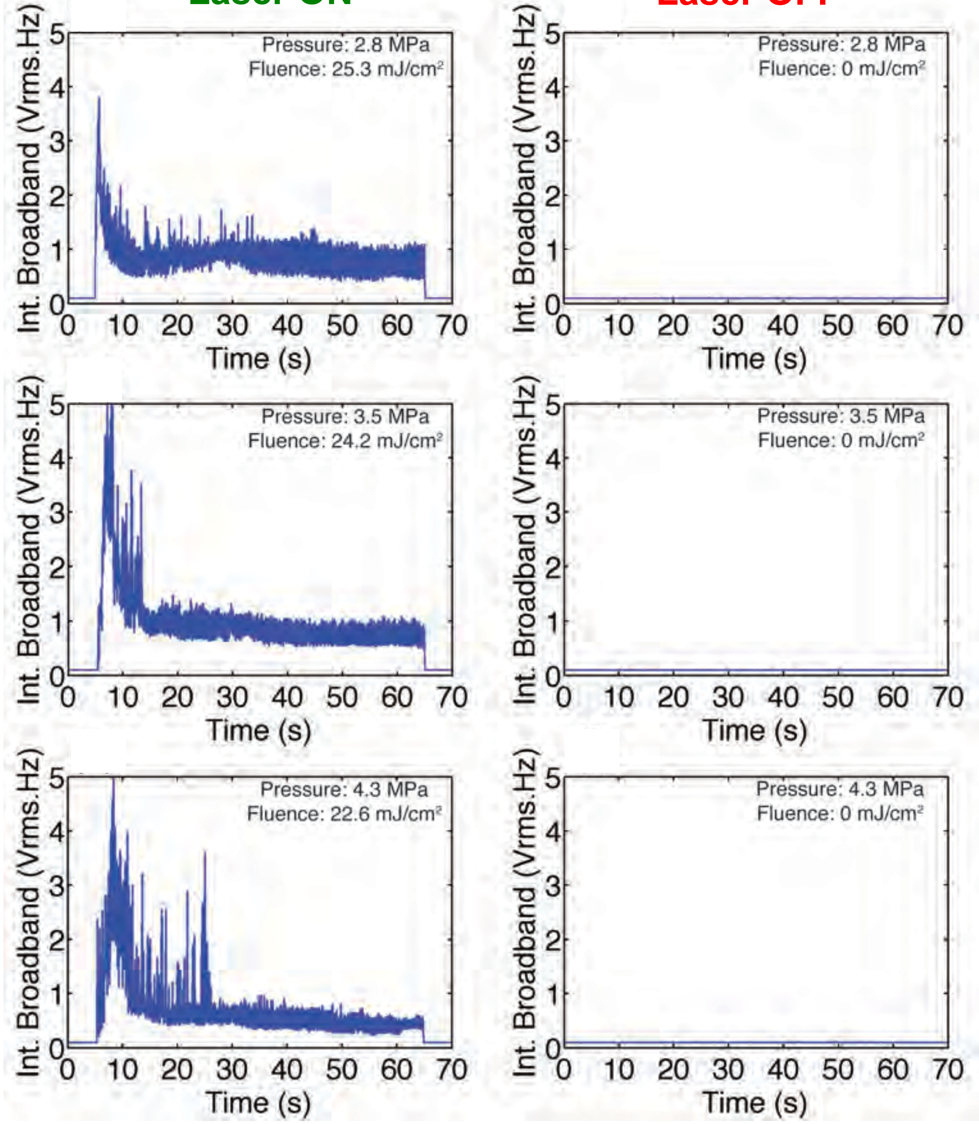
- **Laser: 10 Hz PRF, 10 nsec pulse length**
- **HIFU: Burst mode -- 1 burst per laser flash**
- **Burst length variable: 127 μsec – 98 msec**
- **60 sec exposures: P_+ ranged from 0 - 6 MPa**
- **Duty cycle varied between 0.13% & 98%**





Quasi CW Exposures: Pressure Dependence

Laser ON | Laser OFF

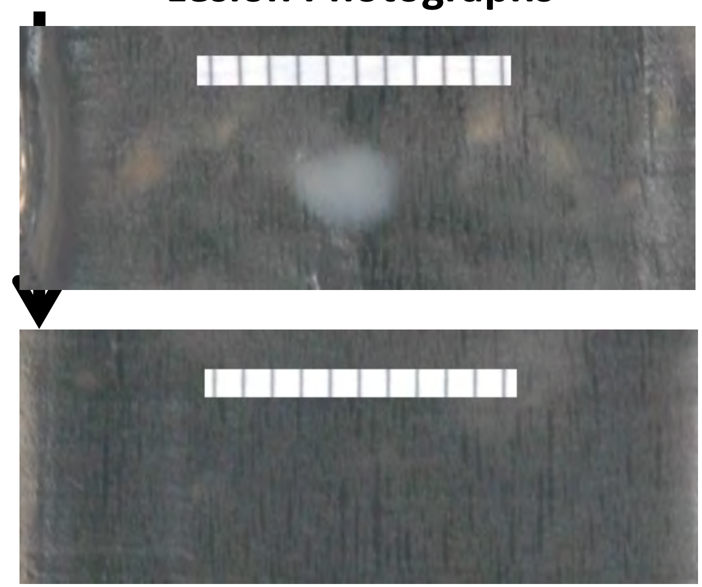


60 sec exposures

DC = 98%

7.5 MHz PCD

Lesion Photographs

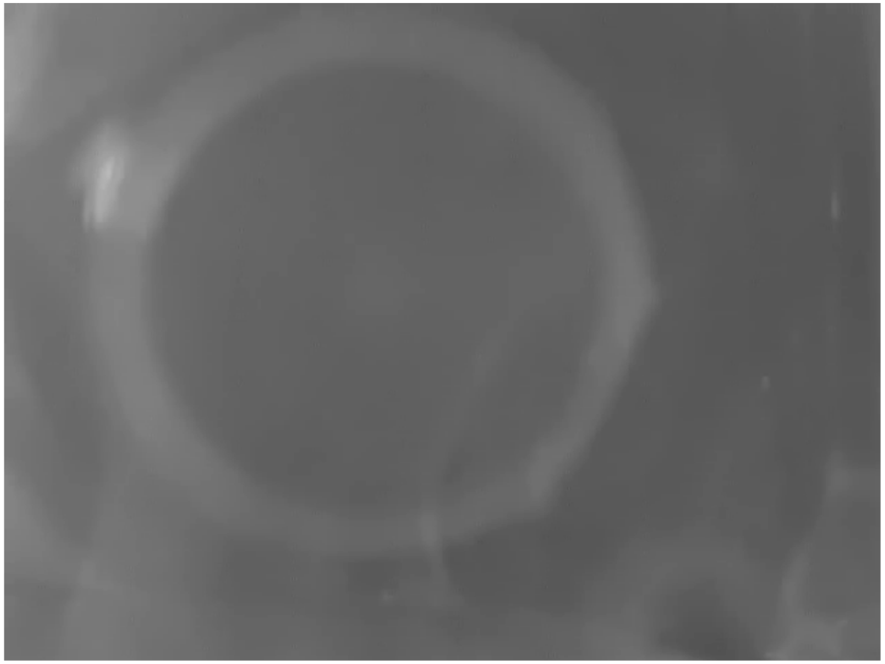


ON

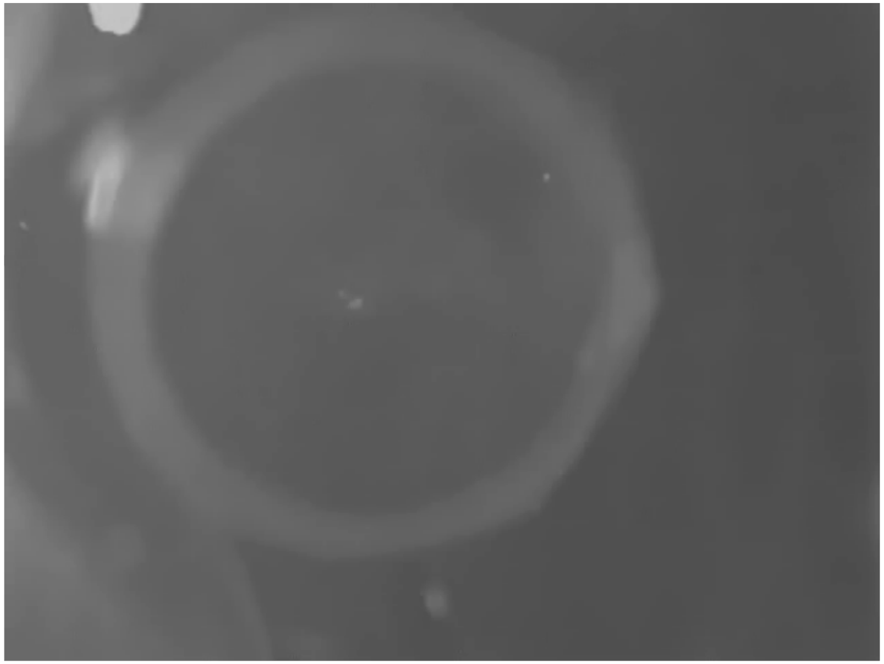
OFF

Lesion Formation

LASER OFF



LASER ON



Two videos of single 60 s HIFU exposures with and without the laser with HIFU propagating from right to left.

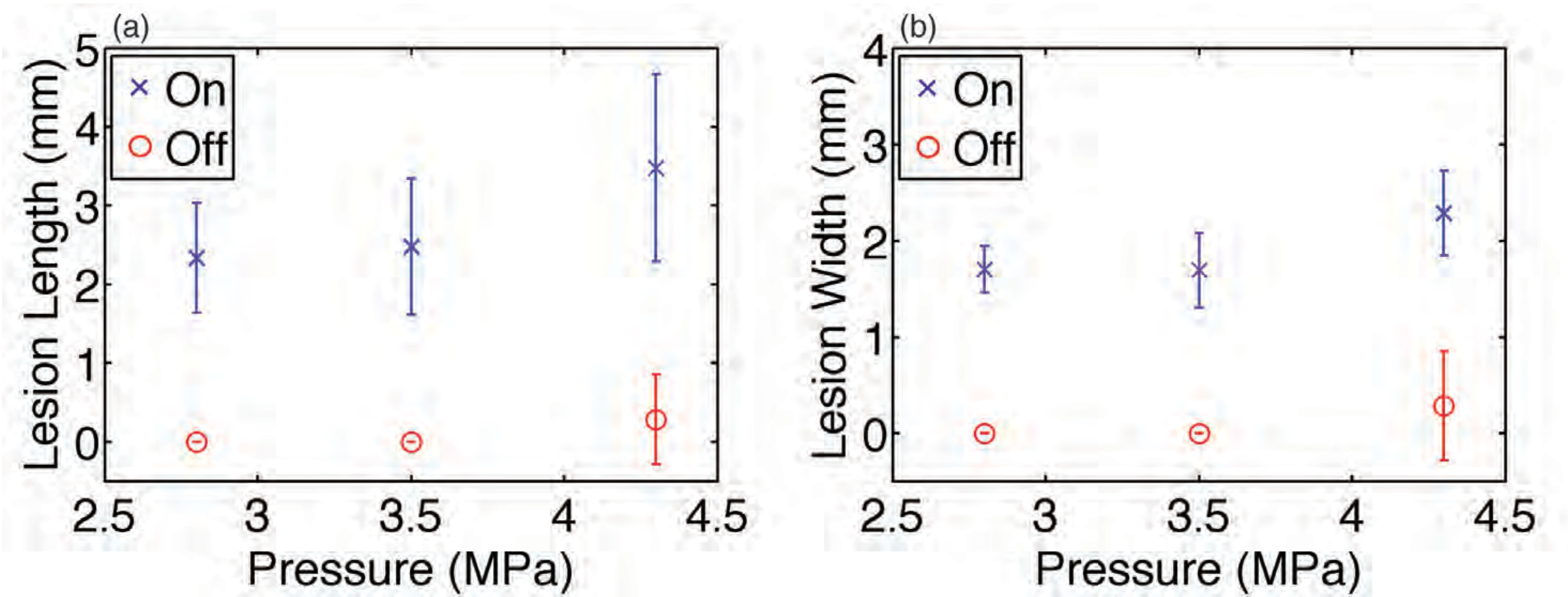
P_{neg} = 4.3 MPa

DC = 98%

Fluence = 22.6 mJ/cm^2

Lesion Dimensions

Laser Fluence = 22.6 mJ/cm² ; DC = 98%

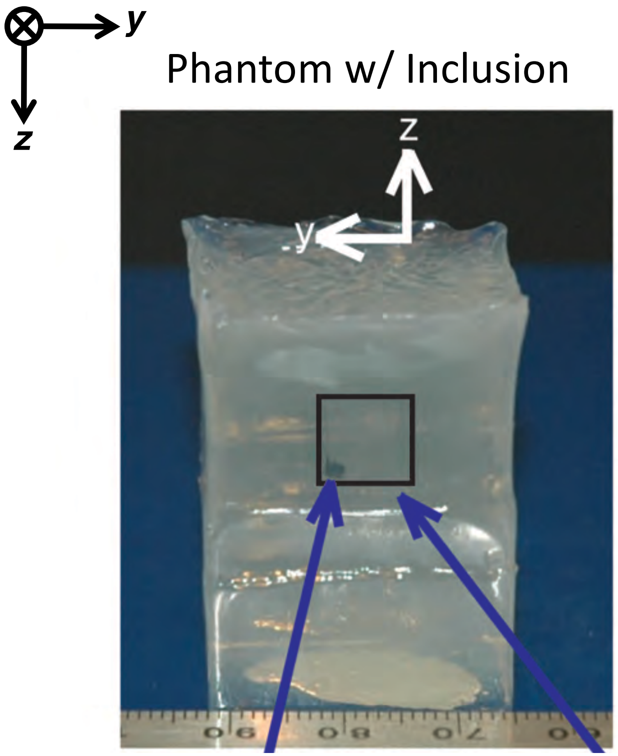


Nanoparticle-nucleated inertial cavitation enhances energy deposition
Larger lesions result from equivalent exposure conditions

Combining US Enhanced PA Imaging and Light Enhanced HIFU Therapy

- Gel/BSA phantom
- 5x5x5 mm gel/BSA Inclusion doped with gold nano-particles
- Use US-enhanced PA to image the inclusion via raster scan
- 9 separate 60s light-enhanced HIFU exposures within the imaged inclusion
- Simulate poor HIFU targeting by making 3 exposures outside of inclusion (z=6)
- P = 2.8 MPa ; Fluence = 22.6 mJ/cm^2

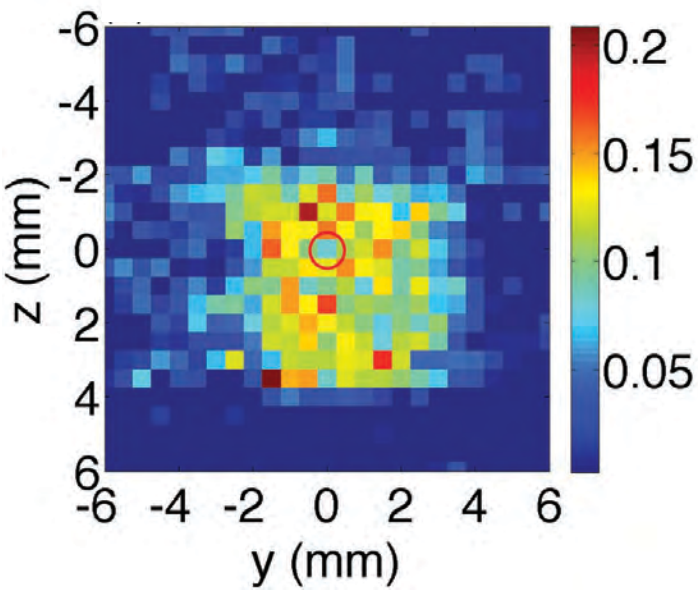
Phantom w/ Inclusion



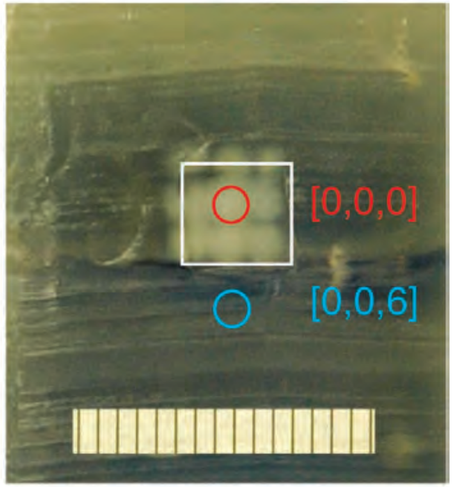
Ink on corner of inclusion

Box depicts inclusion

PA Raster Scan



Cut Away Cross Sectional Photo

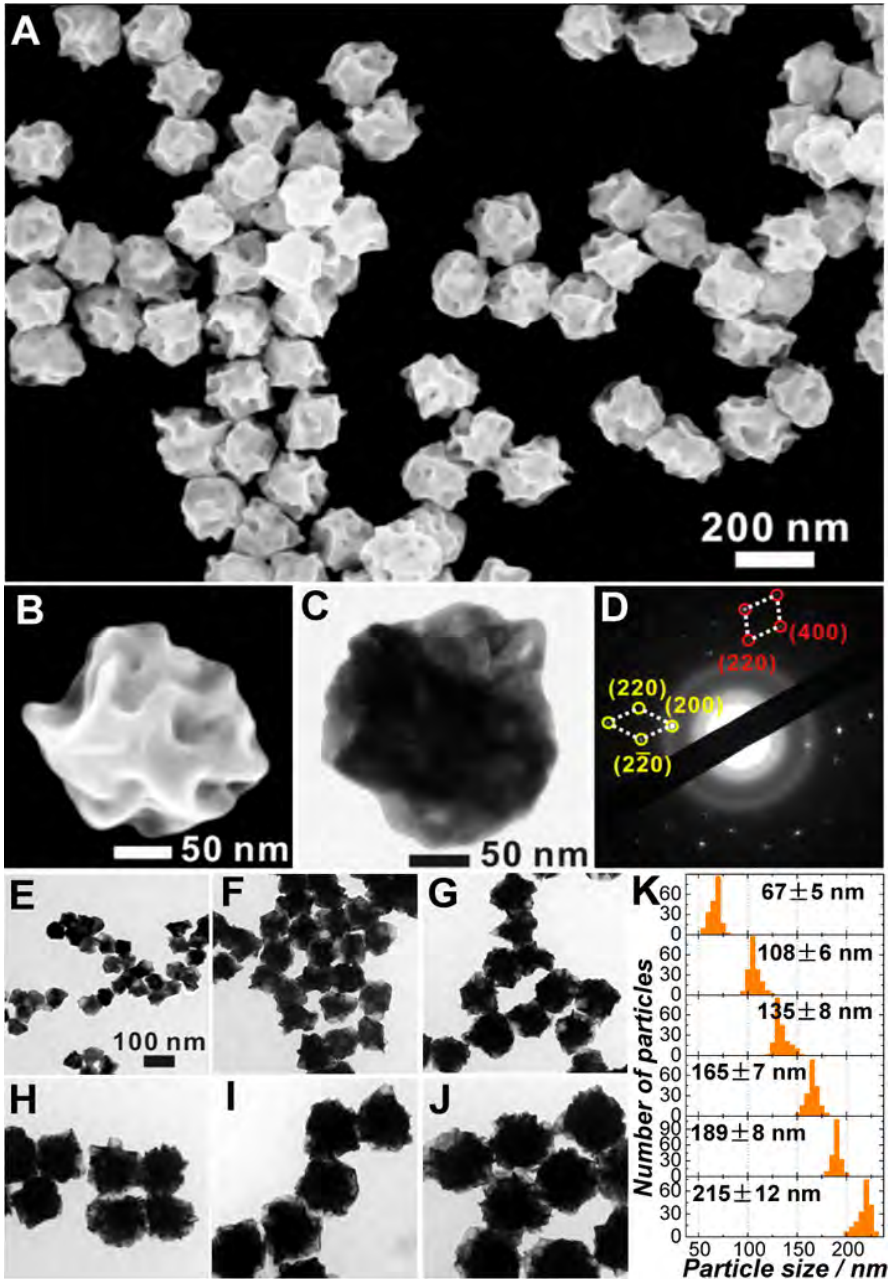


Conclusions & Extrapolations

- **Pulsed ultrasound enables photoacoustic imaging in the presence of absorbing nanoparticles**
  - x35 enhancement in PA emissions = *imaging at greater depth*
- **Pulsed laser light enables controlled HIFU cavitation in the presence of absorbing nanoparticles**
  - Cavitation *on demand* for enhanced HIFU therapy
- **Lesions form *only when and where* light & sound & particles coexist**
  - Functional particles target the tissue for both imaging *and* therapy
  - Relaxes the requirement for a precise, tightly focused acoustic beam
  - No optical targeting or alignment required (diffuse light)
- **Could lead to targeted and controlled lesion formation in optically accessible organs**
  - Breast, brain, prostate, skin
  - Catheter-based laser ablation surgery and sonothrombolysis
- **An externally activated nanoparticle for targeted drug delivery?**

Photoacoustically Active Nano-delivery Systems

- **Porous gold nano-partlces**
- **Nano tubes**
- **Light absorbing encapsulated nano-drops**



Qingfeng Zhang; Nicolas Large; Peter Nordlander; Hui Wang; *J. Phys. Chem. Lett.* **2014,** 5, 370-374.

DOI: 10.1021/jz402795x

Thank You!

Students:

Caleb Farny
Tianming Wu
Puxiang Lai
Henji Ju

Postdocs:

Jim Mclaughlan

Collaborators:

Todd Murray (Univ. of Colorado)
Chuck DiMarzio (Northeastern Univ.)
Robin Cleveland (Univ. of Oxford)
R. Glynn Holt (Boston Univ.)