The Physical Effects of Bubbles and Cavitation in High Intensity Focused Ultrasound

Ronald A. Roy

George Eastman Visiting Professor
The University of Oxford

Boston University, Boston, MA

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Presentation Abstract

The application of ultrasound to tissue at therapeutic levels can, in some cases, result in bubble formation. These bubbles can promote mechanical disruption, accelerate tissue heating, and contribute to the formation of irregularly shaped lesions. The relevant mechanical and thermal effects depend critically on several factors, such as temporal peak and temporal average acoustic intensity, the duration of cw insonation, the duration and duty cycle of pulse insonation, the presence of cavitation nuclei, tissue temperature, and the tissue acoustic, rheological, and thermal properties. We will present a brief primer on the relevant bubble dynamics followed by a summary description of what physical effects matter, when and why. Implications for HIFU treatment monitoring through the active and passive bubble detection are discussed. [Work supported by the Dept. of the Army (award No. DAMD17-02-2-0014) and the Center for Subsurface Sensing and Imaging Systems (NSF ERC Award No. EEC-9986821).]

Medical Ultrasonics in a Nutshell

- **Diagnostic Procedures**
  - Imaging, blood flow, multi-mode, molecular, functional
- **Therapeutic Procedures**
  - Tissue healing/destruction
  - Hemostasis & thrombolysis
  - Drug delivery and much more
- **Process Control**
  - Mixing, cleaning, lysis, sonoporation, sonochemistry
- **Thermal & Mechanical Effects**

Physical Interactions

- Sound scattering from interfaces and microstructure
  - The basis for ultrasound imaging
- Sound absorption
  - Tissue heating
- Momentum transfer
  - Convective streaming & radiation stress
- Mechanical Stress
  - Tissue rupture -- acoustic cavitation

A Prominent Role for Microbubbles!

- **Bubbles promote sound scattering**
  - Ultrasound contrast agents
- **Bubbles promote tissue heating**
- **Bubbles promote tissue disruption**
  - Rupture, shock waves,
  - Collapse jets, microstreaming
- **Bubbles promote drug delivery**
  - Targeting, sonoporation, sonochemistry
- **Many other effects**
  - Opto-acoustics, laser ablation, vessel occlusion…

A Primer on Bubble Acoustics
Nonlinear Response of a single bubble

Consider force balance across a bubble wall

- **Internal: gas pressure vapor pressure**
- **External: hydrostatic pressure, surface tension**
- **Dynamics: acoustic stress, viscous stress**

Rayleigh Plesset Equation

- **1-D radial motion, Newtonian incompressible fluid**

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

Keller Miksis Equation

- **Accounts for the compressibility of the liquid**

Acoustic Cavitation
A Recipe…

Start with a preferential site for liquid rupture

- Physical impurity, preexisting gas cavity

Apply an acoustic stress strong enough to overcome…

- Surface tension, inertia, viscous drag

Bubble responds in accordance with nonlinear equation of motion

Two Classes of Bubble Response…

Geneology of Cavitation
Stable Cavitation

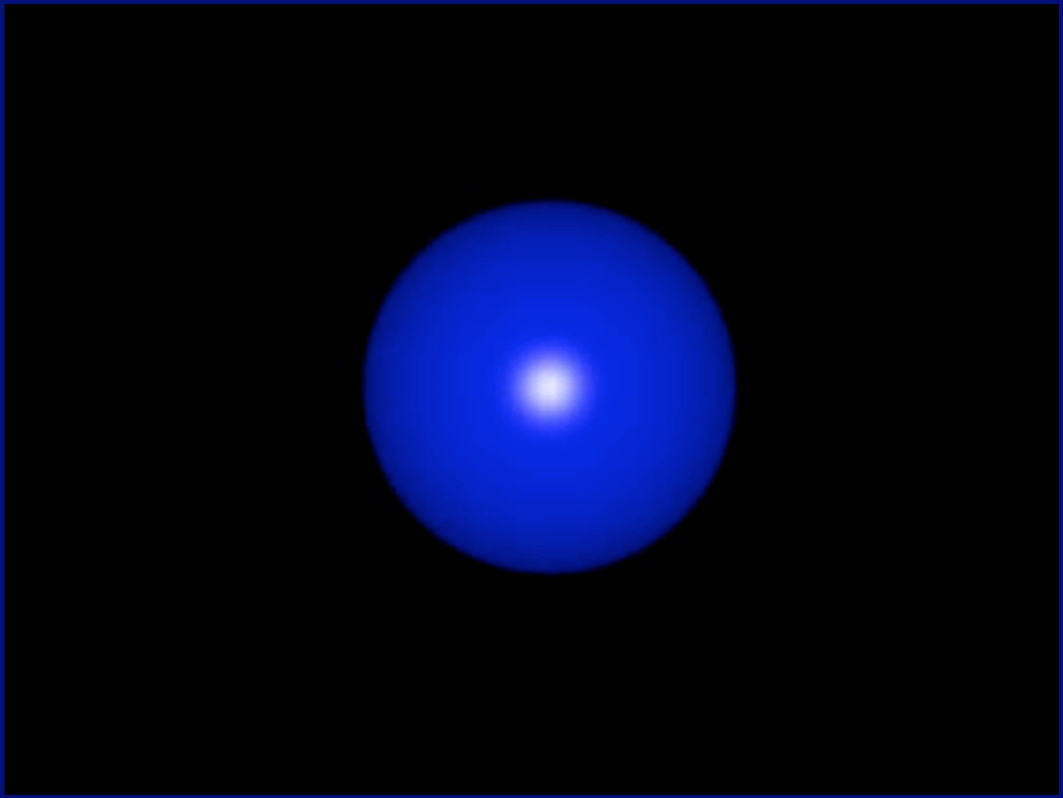
Drive bubble at low-moderate forcing pressures

- Repetitive pulsations about an equilibrium radius
- Motion dominated by the compressibility of the gas
- Pressures of order 1-5 ATM (depending on frequency and bubble size)
- Larger bubbles
- Rectified diffusion
- *Acoustic emissions*
  - *Harmonic*
  - *Subharmonic*
  - *Noise diagnostics*

F = 1 MHz

$R_{Res} \approx$ 4-5 μm

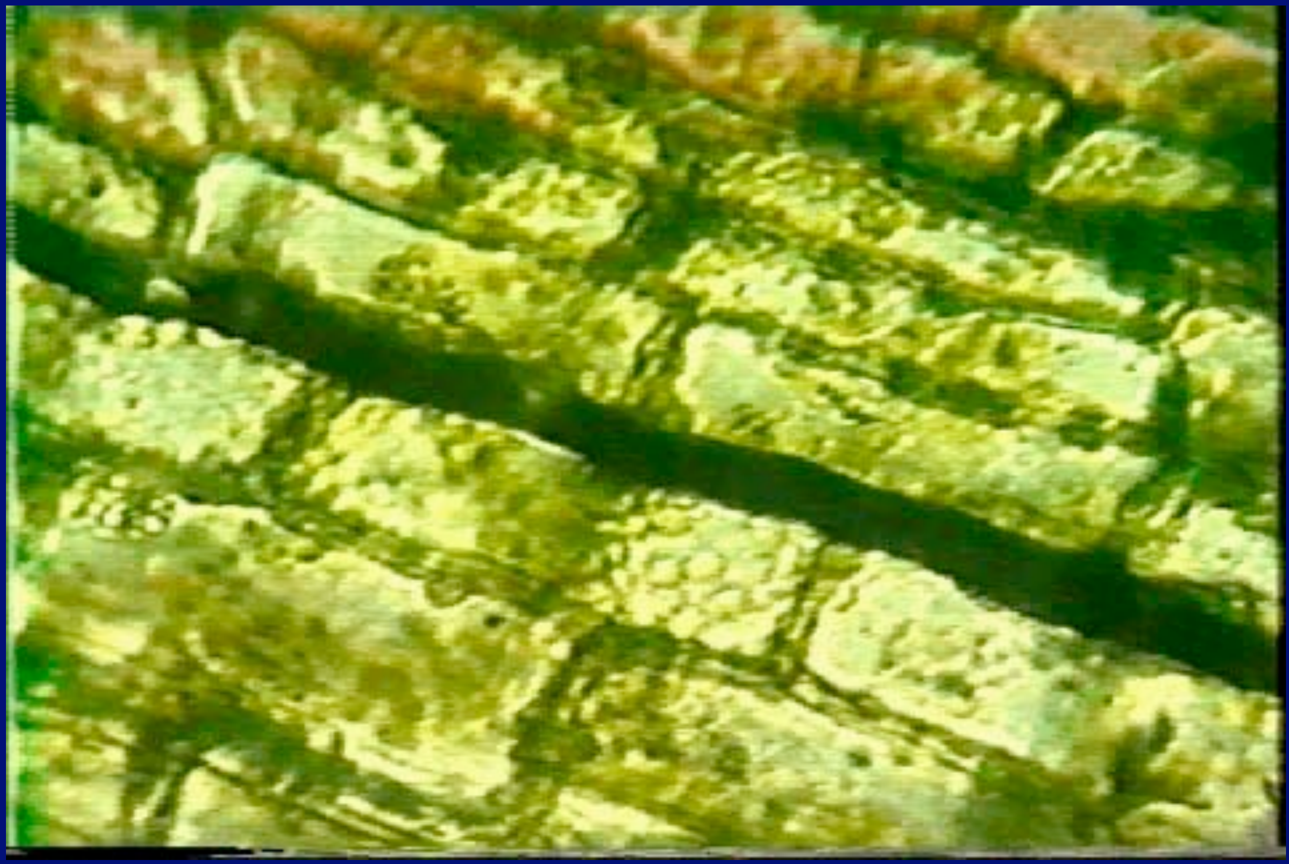
R_0 = 30 μm



Physical Effects
Stable Cavitation

Microstreaming in the fluid media

- Promotes mixing (chemical reactions, drug delivery, etc.)
- Promotes cleaning
- Promotes cell lysis



Cavitation micro-streaming in *Elodea* Leaf

Courtesy Ed Carstensen, Doug Miller and Wes Nyborg

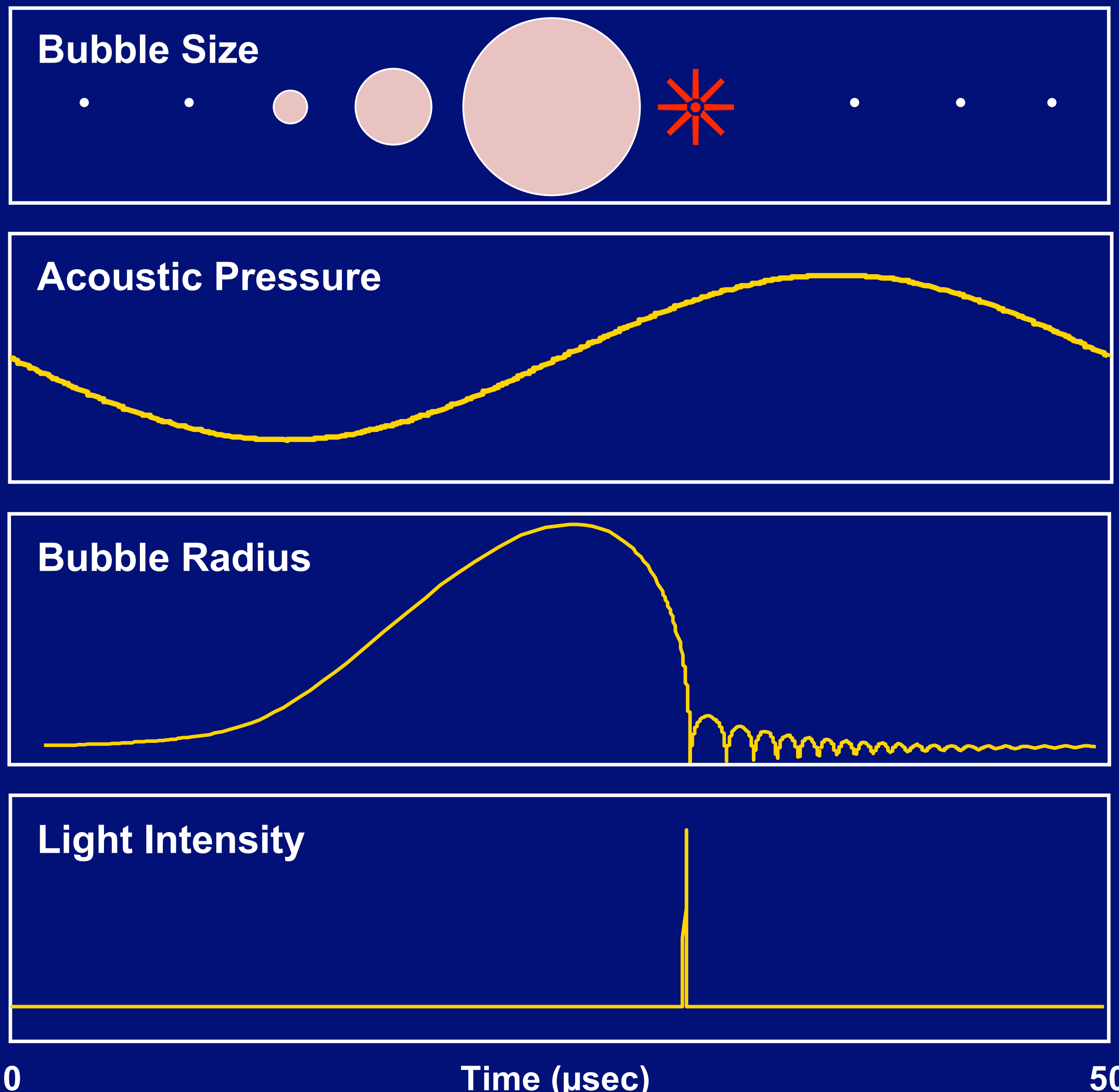
Physical Effects: *Inertial Cavitation*

Sonoluminescence
- "light from sound"

Inertial collapses of acoustically forced bubbles in liquid

Generic SL Cycle:
- Isothermal expansion
- Rapid adiabatic collapse
- Chemical dissociation

$F = 20$ kHz
$R_{Res} = 160\ \mu m$
$R_0 = 0.1\ \mu m$



Physical Effects
Inertial Cavitation

- Sonoluminescence in water exposed to a 20 kHz ultrasonic horn

Courtesy Lawrence Crum, Univ. of Washington

Physical Effects
Inertial Cavitation

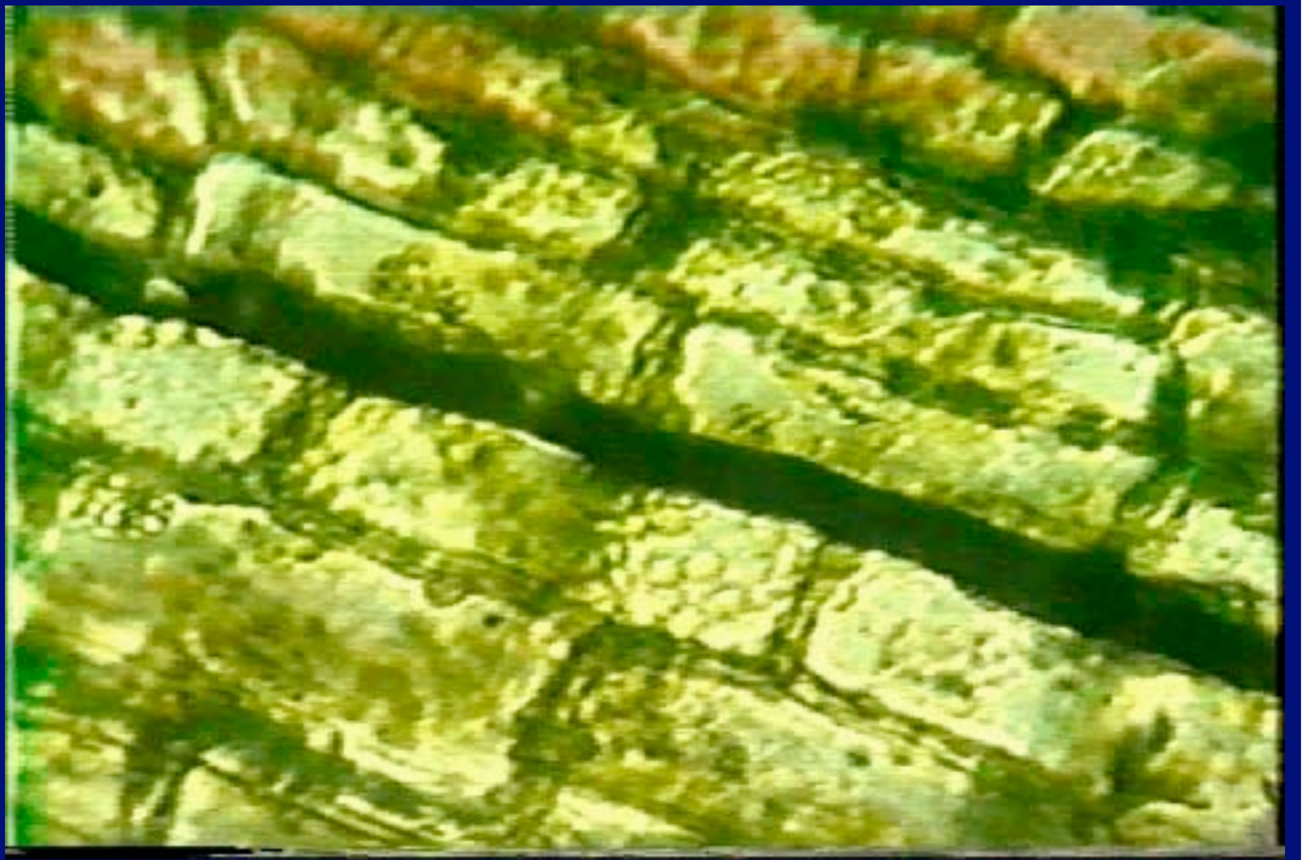
Extensive Microstreaming

- Shearing flows and tear apart tissues

Collapse microjets

Radiated shock waves

Extreme conditions Inside the collapsing bubble



Converts acoustical energy to concentrated mechanical *and* thermal energy

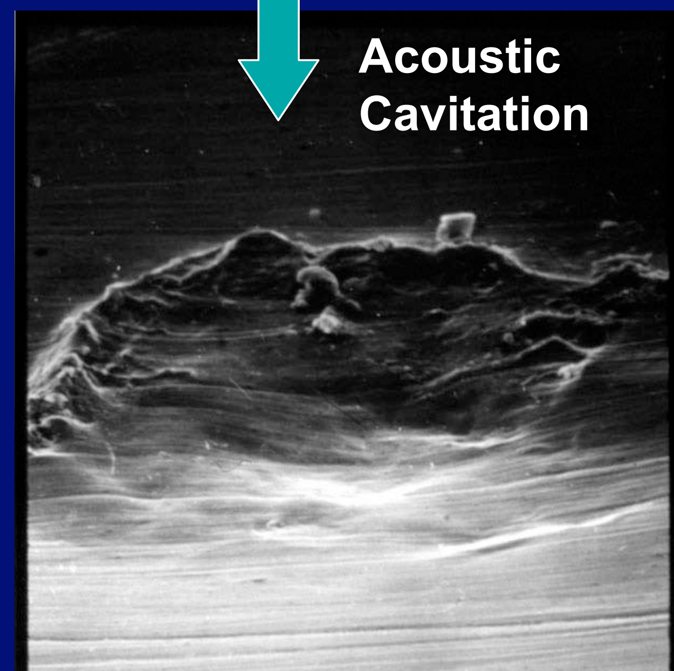
…Thermal Energy?

Physical Effects
Inertial Cavitation

- **Collapse Microjets**

Hydrodynamic Cavitation

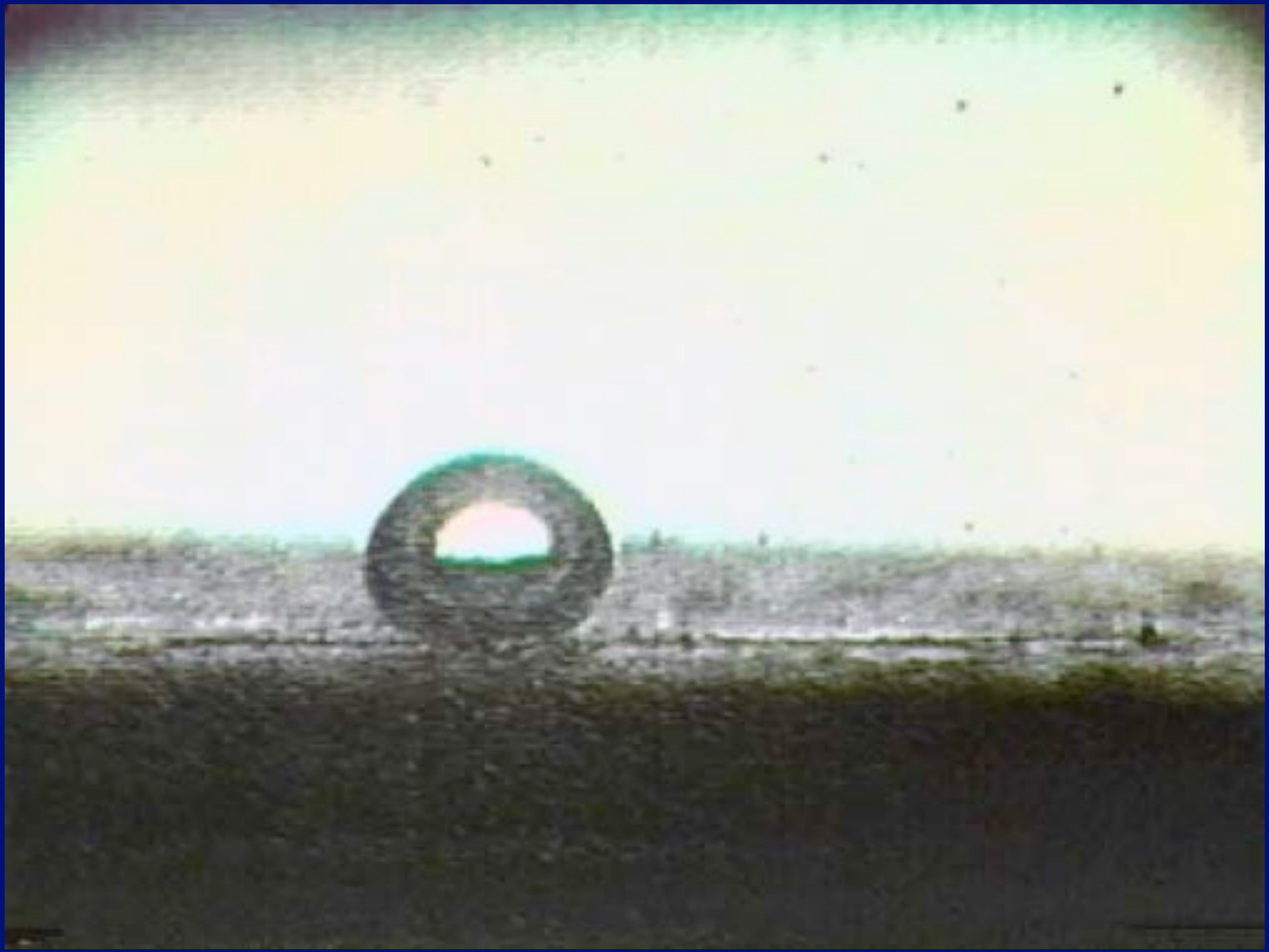
Acoustic Cavitation



Courtesy Lawrence Crum, Univ. of Washington

Physical Effects
Inertial Cavitation

Collapse Microjets
- A vapor cavity in glycerine

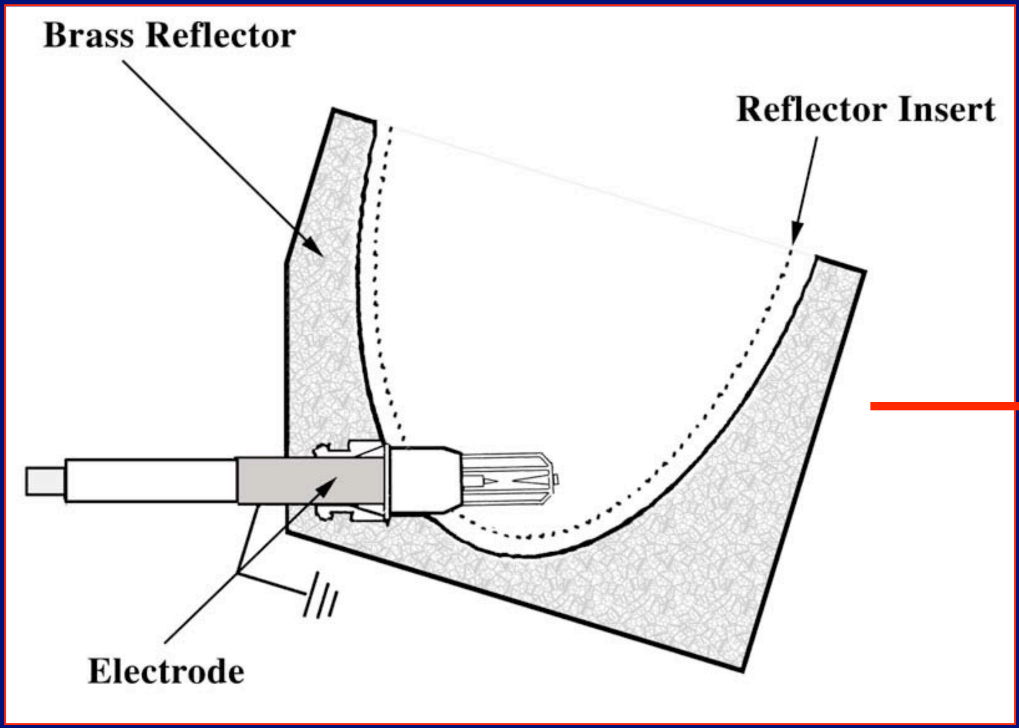


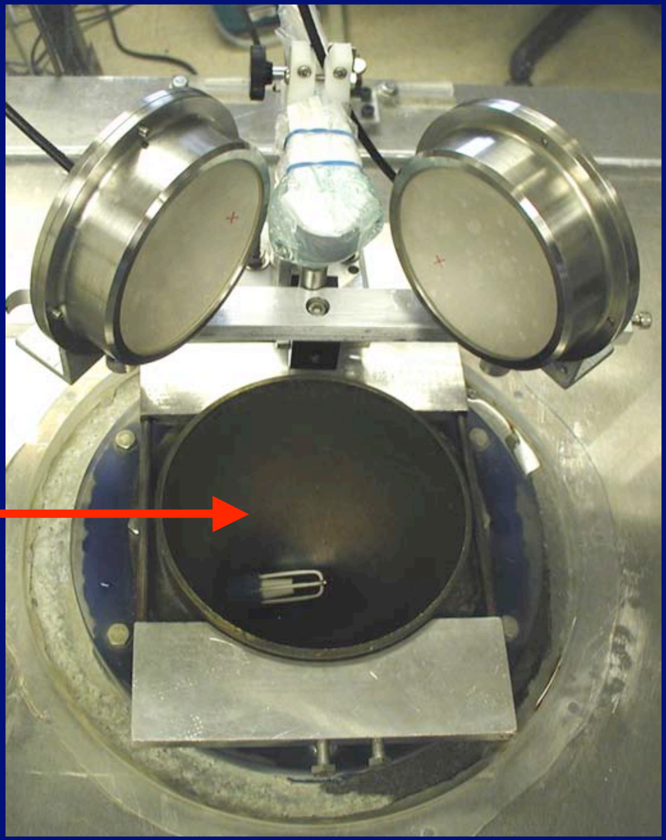
Courtesy Lawrence Crum, Univ. of Washington

Physical Effects
Collapse Jets

Extracorporeal Shock Wave Lithotripsy

- Jetting from a cavitation cloud!
- One of several physical mechanisms for kidney stone destruction

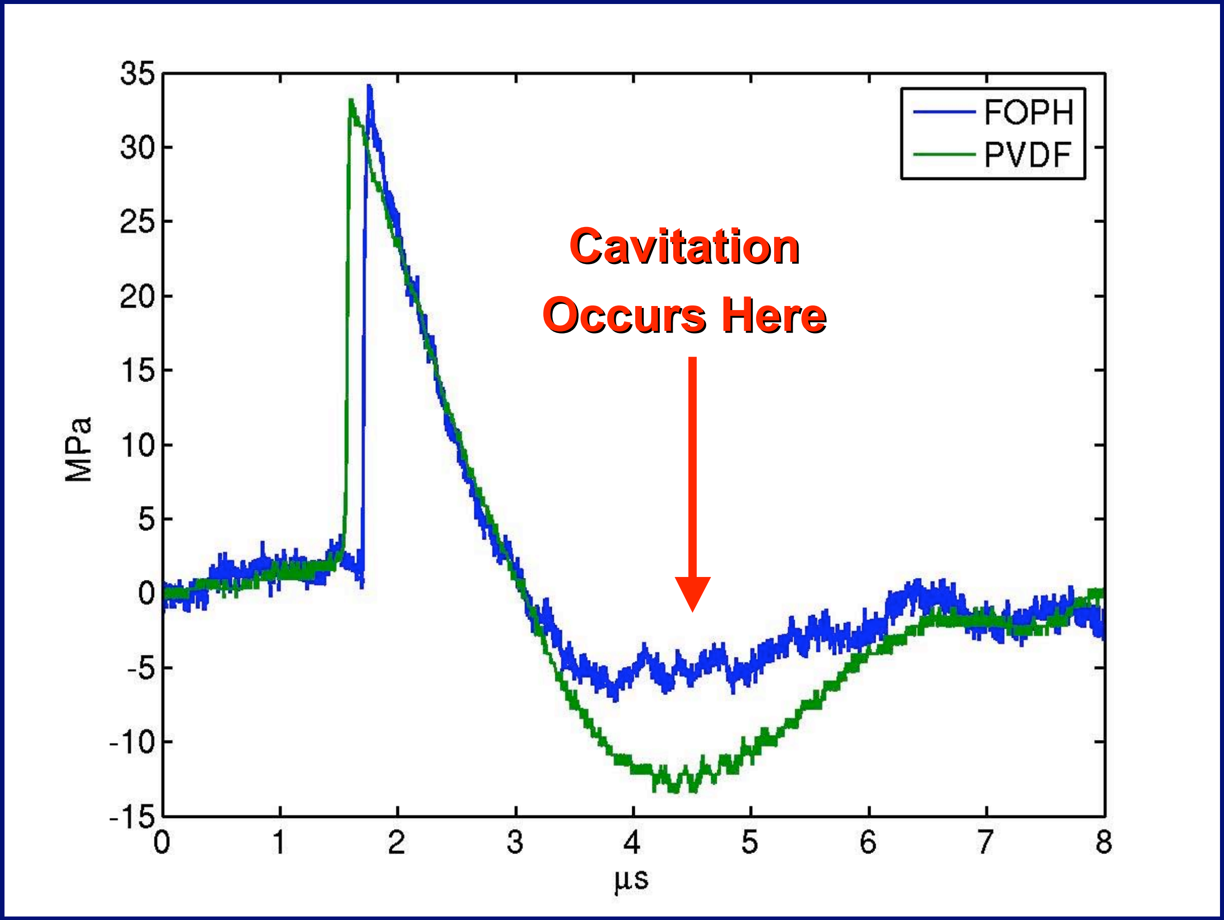




Courtesy Mike Bailey, Univ. of Washington & Robin Cleveland, Boston Univ.

Physical Effects

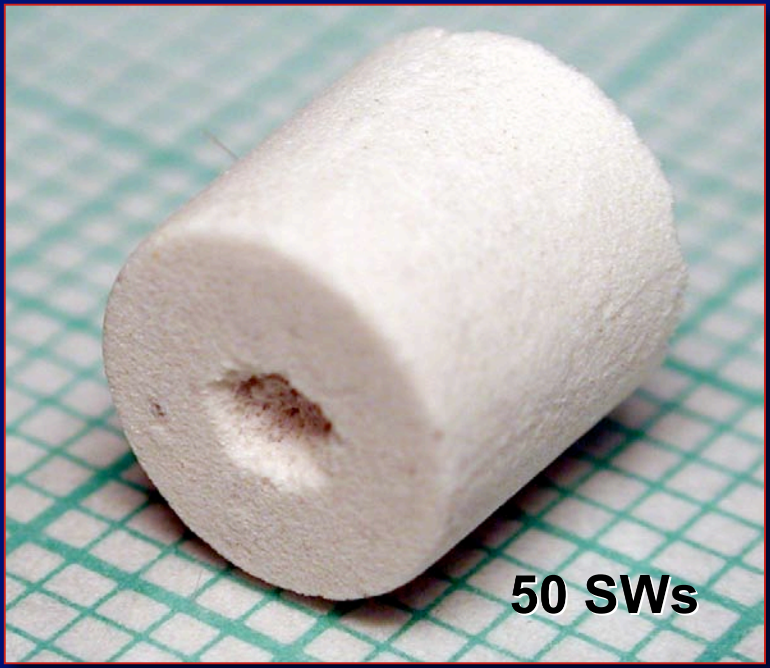
Collapse Jets



Courtesy Mike Bailey, Univ. of Washington & Robin Cleveland, Boston Univ.

Geneology of Cavitation
Cloud Collapse Dynamics

Extracorporeal Shock Wave Lithotripsy
- Eroding an "artificial" kidney stone



Courtesy Mike Bailey, Univ. of Washington & Robin Cleveland, Boston Univ.

Physical Effects

Where to go from here..

Microstreaming

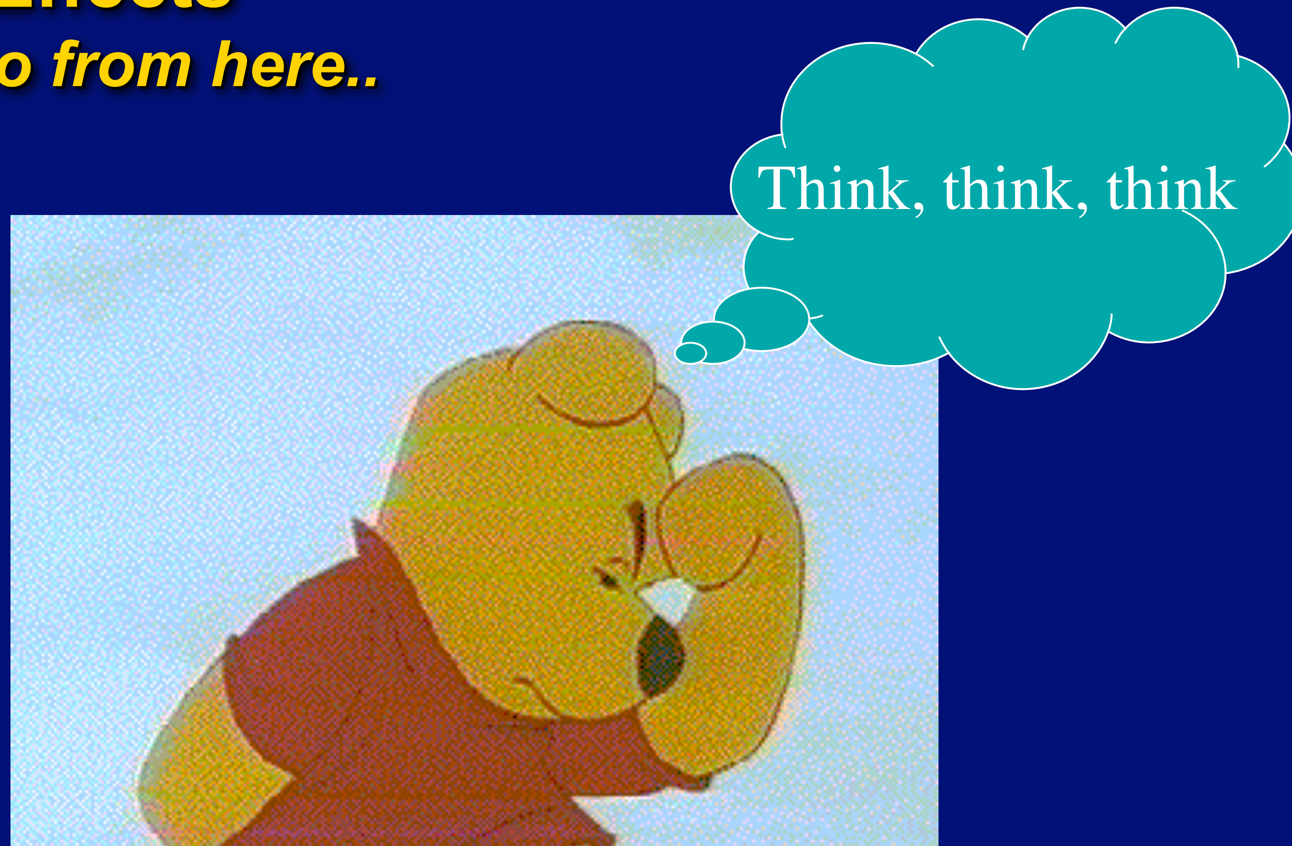
Collapse microjets

Radiated shock waves

Extreme conditions

Other effects

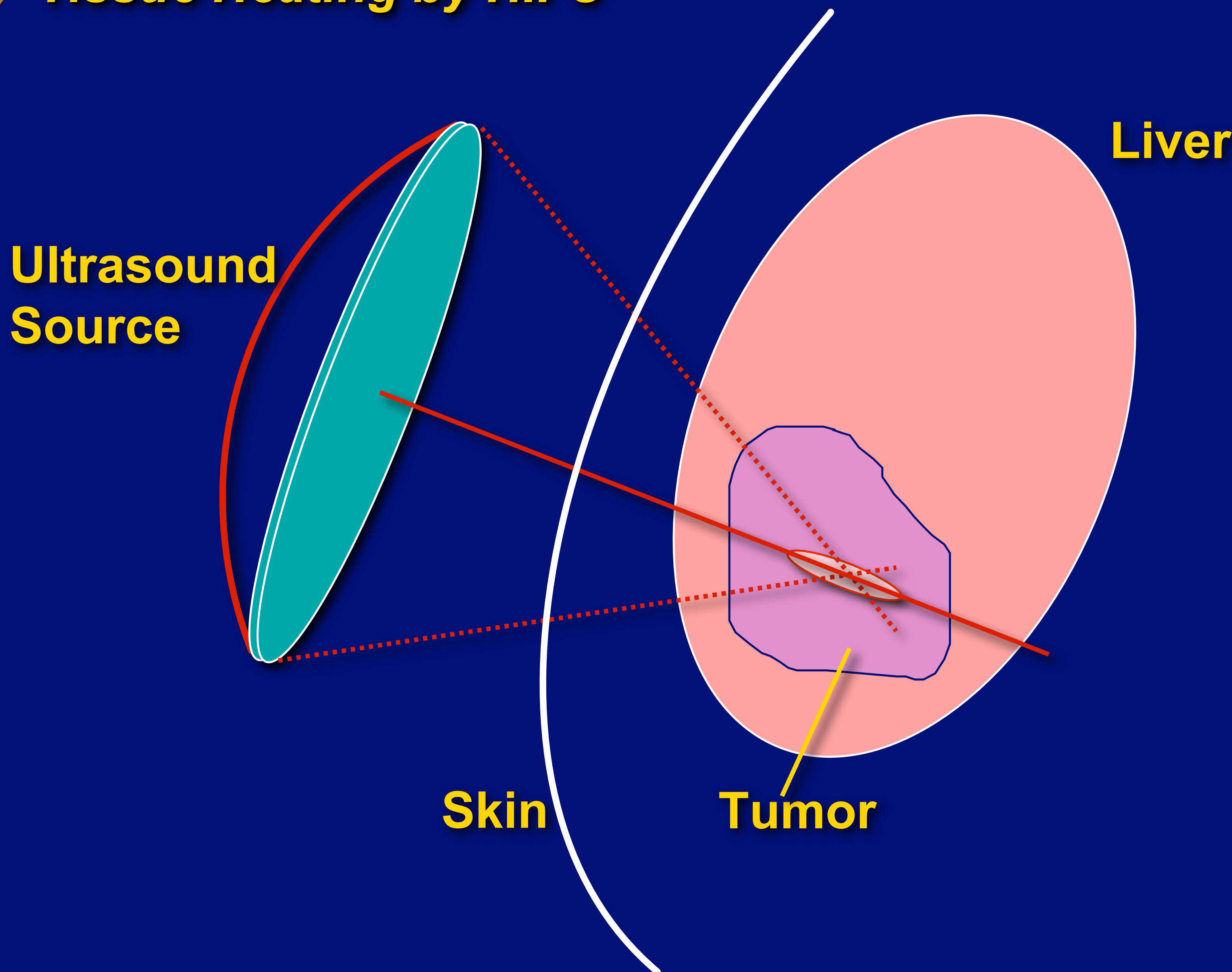
- **Too little time!**



Mechanism for converting acoustical energy to highly concentrated mechanical *and* thermal energy

…Thermal Energy???

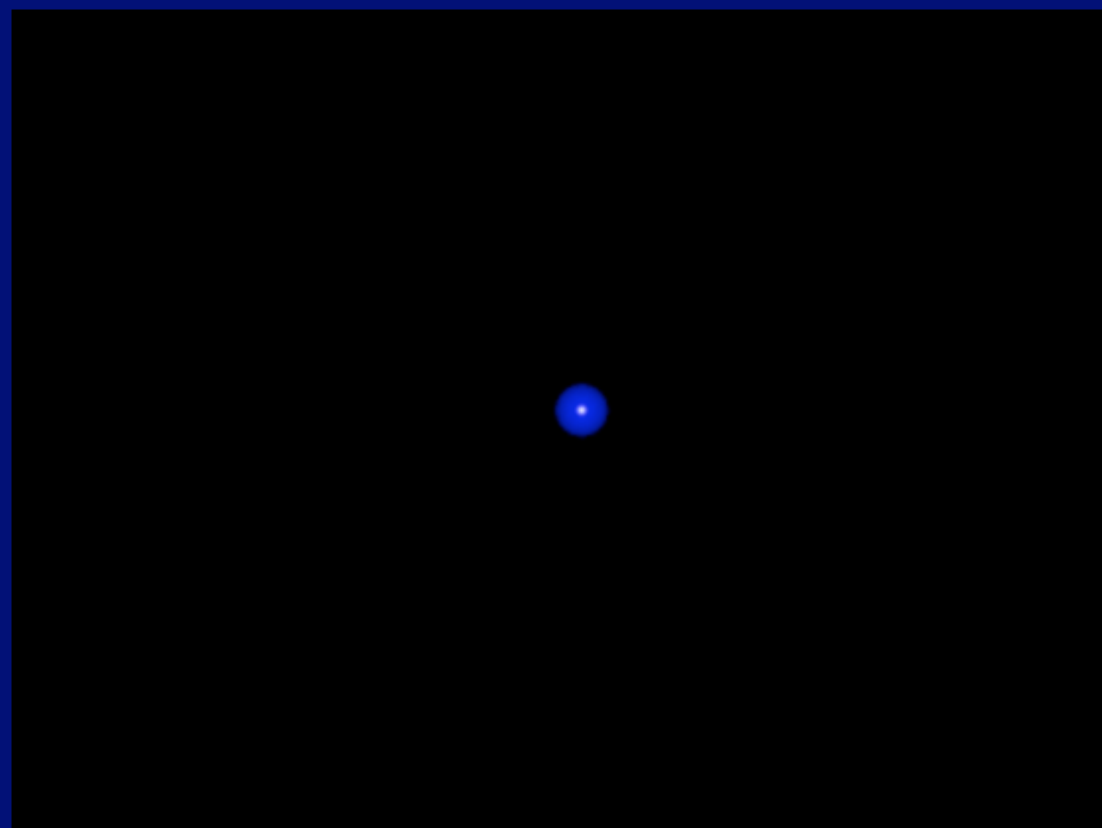
Focused Ultrasound Surgery
Tissue Heating by HIFU



Geneology of Cavitation
Inertial Cavitation

Drive bubble at higher forcing pressures

- Unstable growth followed by violent collapse
- Motion dominated by the inertial of the liquid
- Pressures > 10-15 ATM (depending on frequency)
- Subresonant bubbles
- *Acoustic emissions*
  - *Broadband*
  - *Noise Diagnostics*



F = 1 MHz

$R_{Res} \approx$ 4-5 μm

R_0 = 0.1 μm

Focused Ultrasound Surgery
Tissue Heating by HIFU

US Beam Direction

Courtesy Gail ter Haar
Institute for Cancer Research

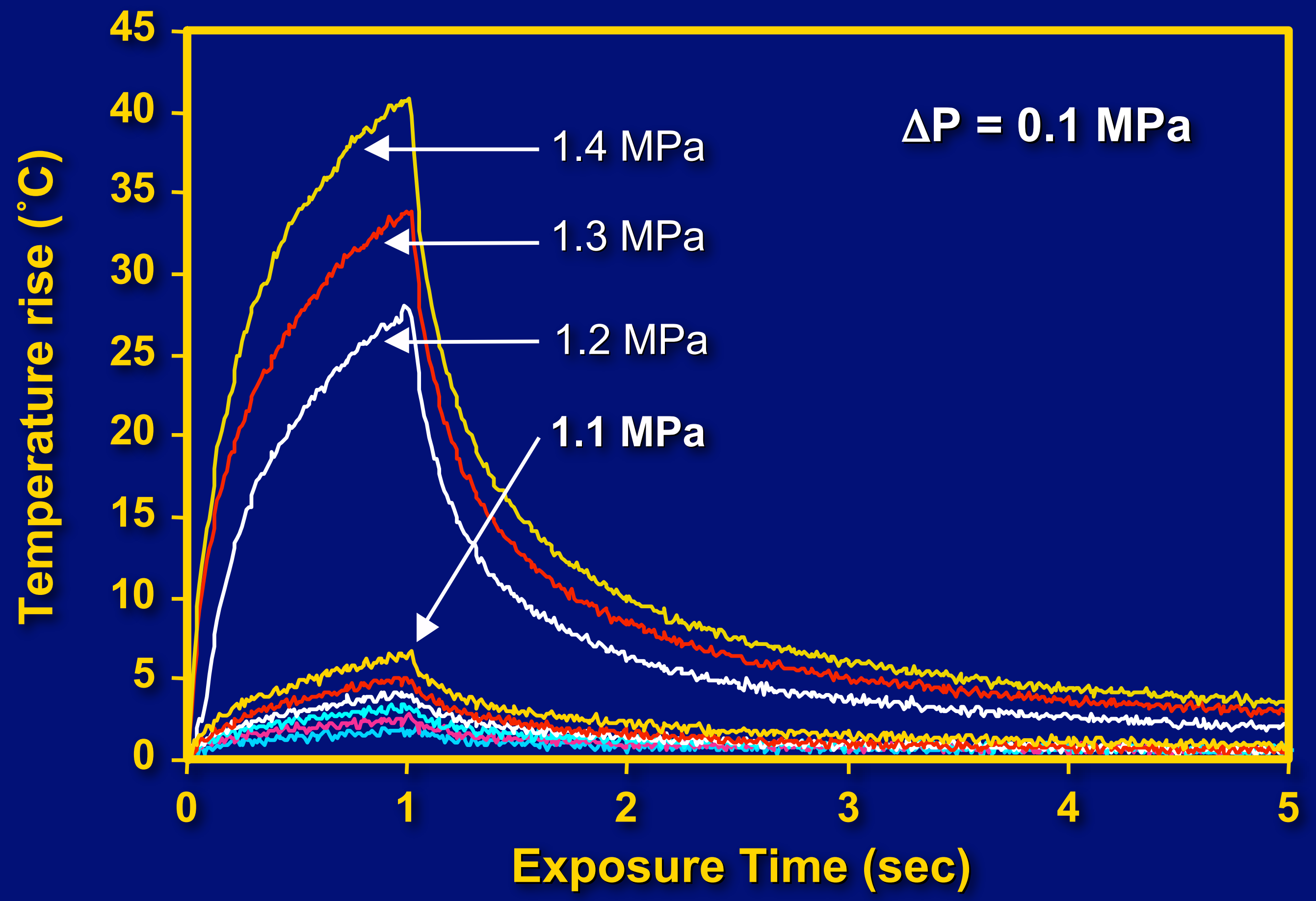
Focused Ultrasound Surgery
Tissue Heating by HIFU

- **Cancer**
  - Liver, kidney, prostate, breast, brain, skin…
- **Non Cancer**
  - Uterine fibroids, BPH, opthalmology…
- **Trauma Care**
  - Acoustic hemostasis
    - Transcutaneous
    - Intraoperative
- **Clinical Trials**
  - Columbia University
  - Univ. of Washington
  - Oxford University
  - Multiple sites in China
  - Others…

HAIFU 'JC-Tumor Therapy System'

Focused Ultrasound Surgery

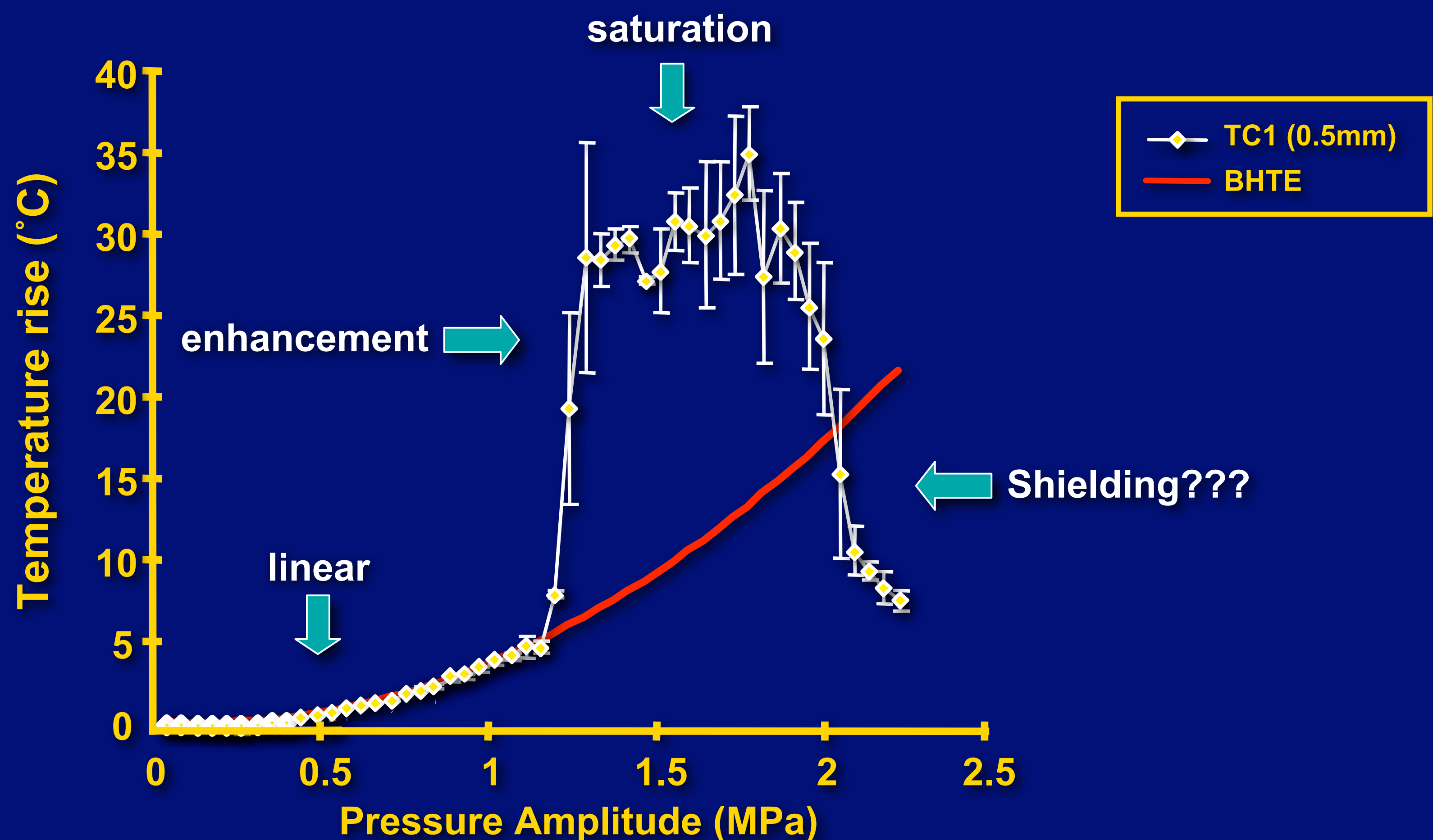
Dependence on HIFU Pressure Amplitude



Threshold suggestive of the onset of cavitation

Focused Ultrasound Surgery

Dependence on HIFU Pressure Amplitude

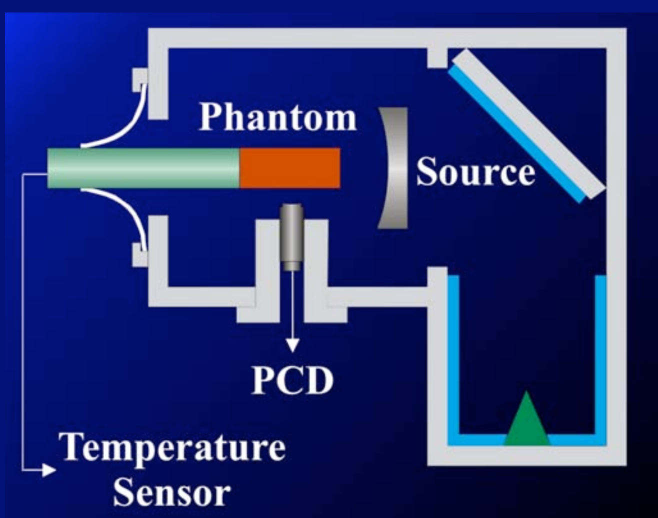


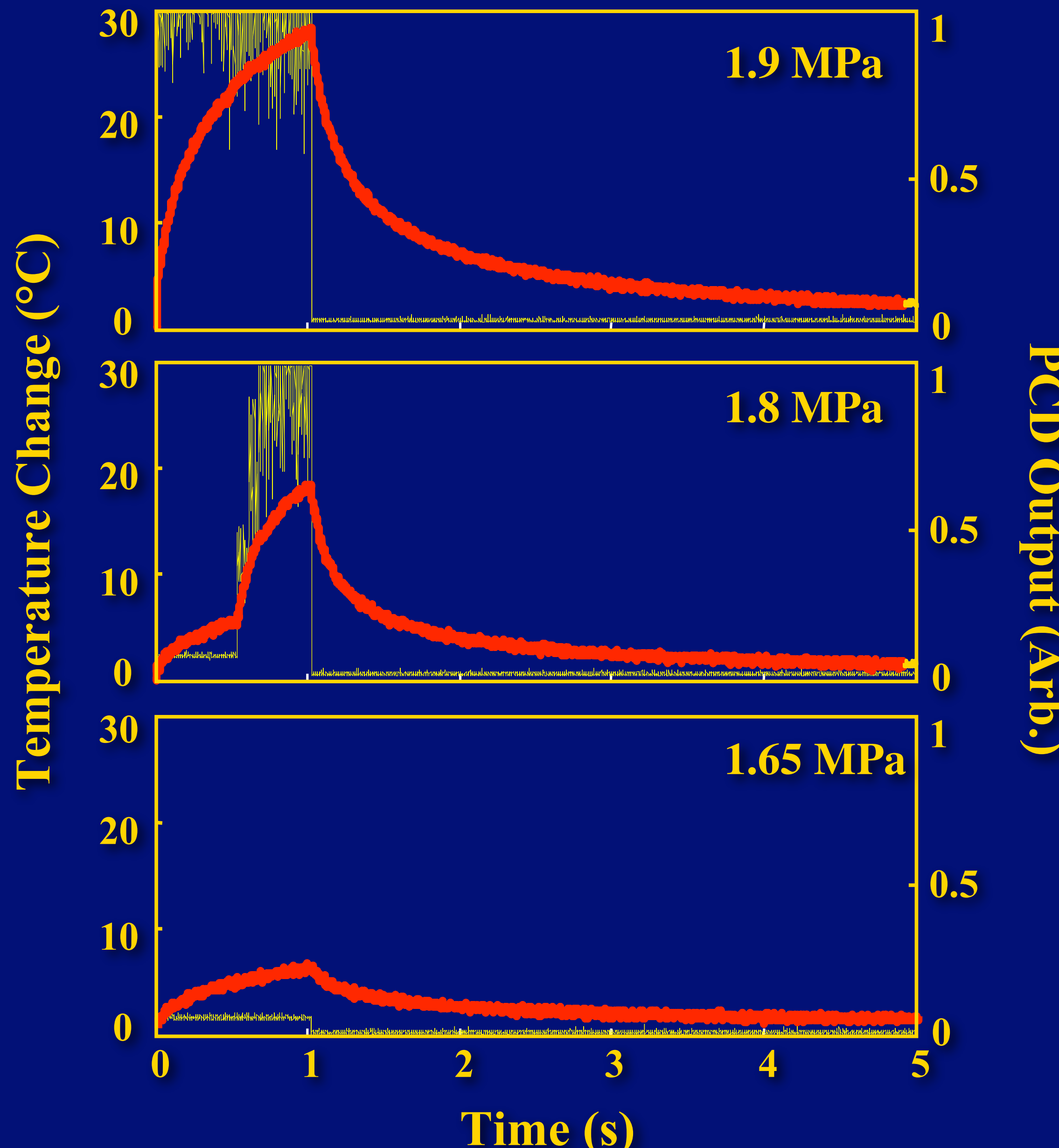
Phantom: Graphite & agar mix **Frequency = 1 MHz** **Duration = 1 second**

Sensing Accelerated Heating with Noise

Good correlation between onset of enhanced heating & onset of broadband acoustic emissions

Inertial Cavitation Matters Most





Modeling Bubble Enhanced Heating

$$\rho C \frac{\partial T}{\partial t} = \overbrace{K\nabla^2 T}^{\text{Conduction}} + \overbrace{q_{us} + q_{bubbles}}^{\text{SourceTerms}}$$

$$q_{bubbles} = q_{vis} + q_{rad}$$

$$q_{us} = \frac{2\alpha}{\omega^2 \rho c}\left(\frac{\partial p}{\partial t}\right)^2$$

Computed from FDTD solution to Westervelt Eq.

Related to product of viscous force and bubble wall velocity

----

larger bubbles

higher viscosities

Stable Cavitation is Implicated

The absorption of broad-band acoustic emissions

----

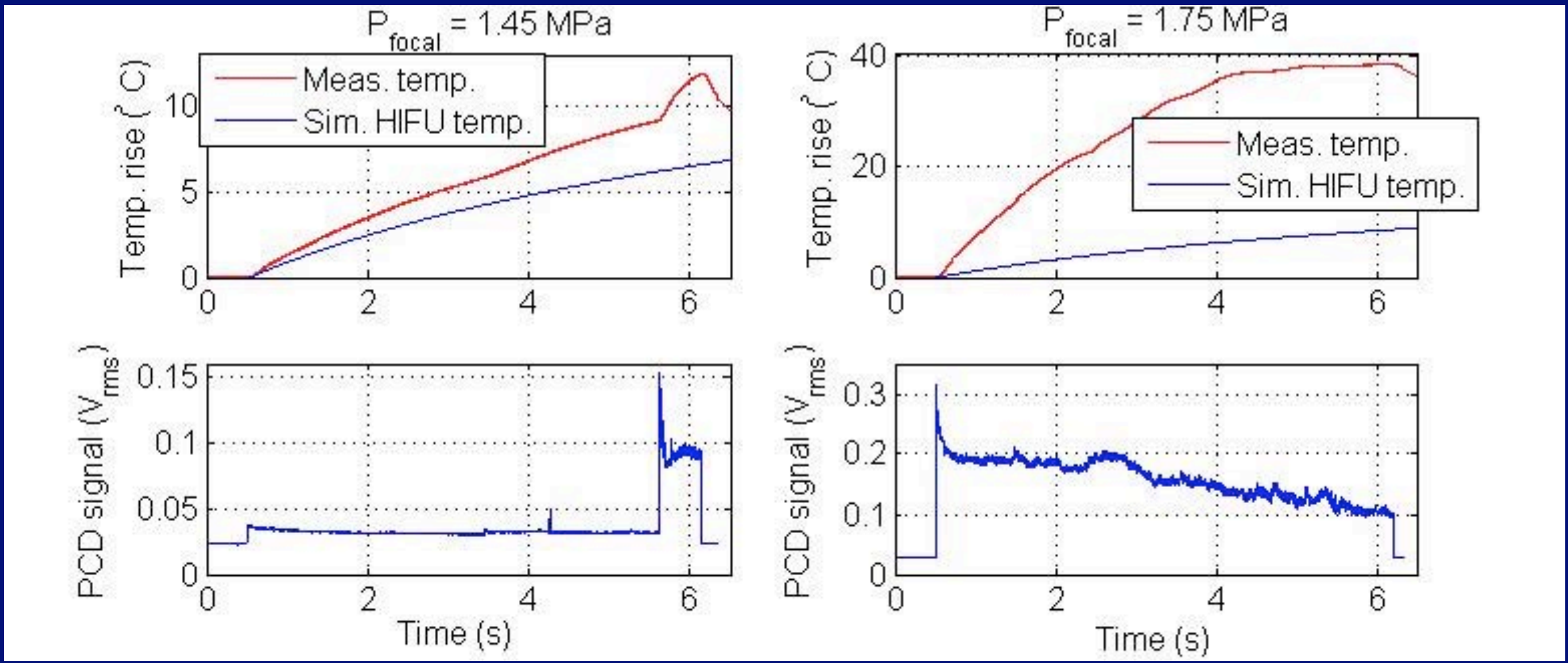
smaller bubbles

low viscosities

Inertial Cavitation is Implicated

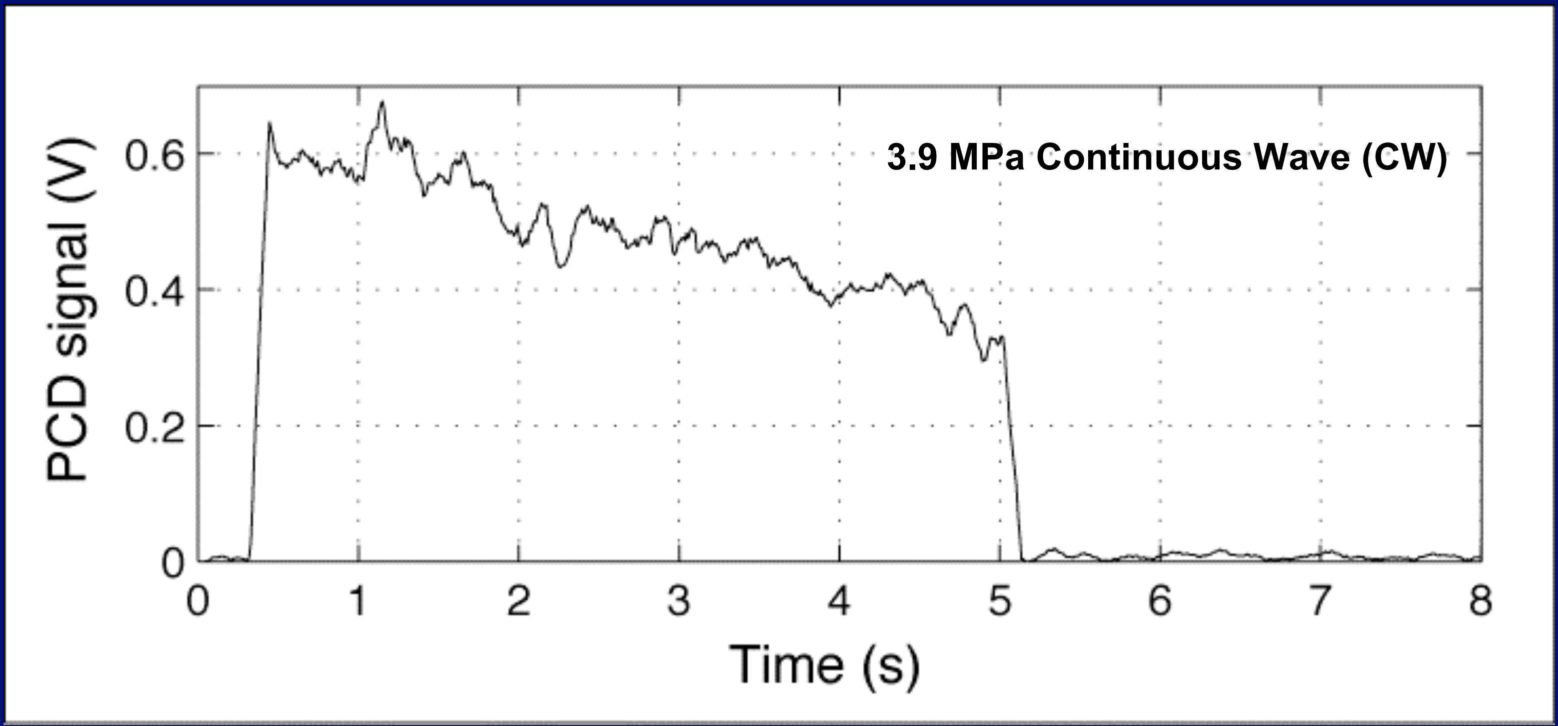
Can We Control -- or at least monitor -- this?

- **Measured vs. predicted temperature rise with bubbles present**
  - **Measured ΔT exceeds visco-thermal predictions**
  - **Deviation always occur when there is broad band noise**
  - **Use of noise diagnostics to monitor bubble enhanced heating**



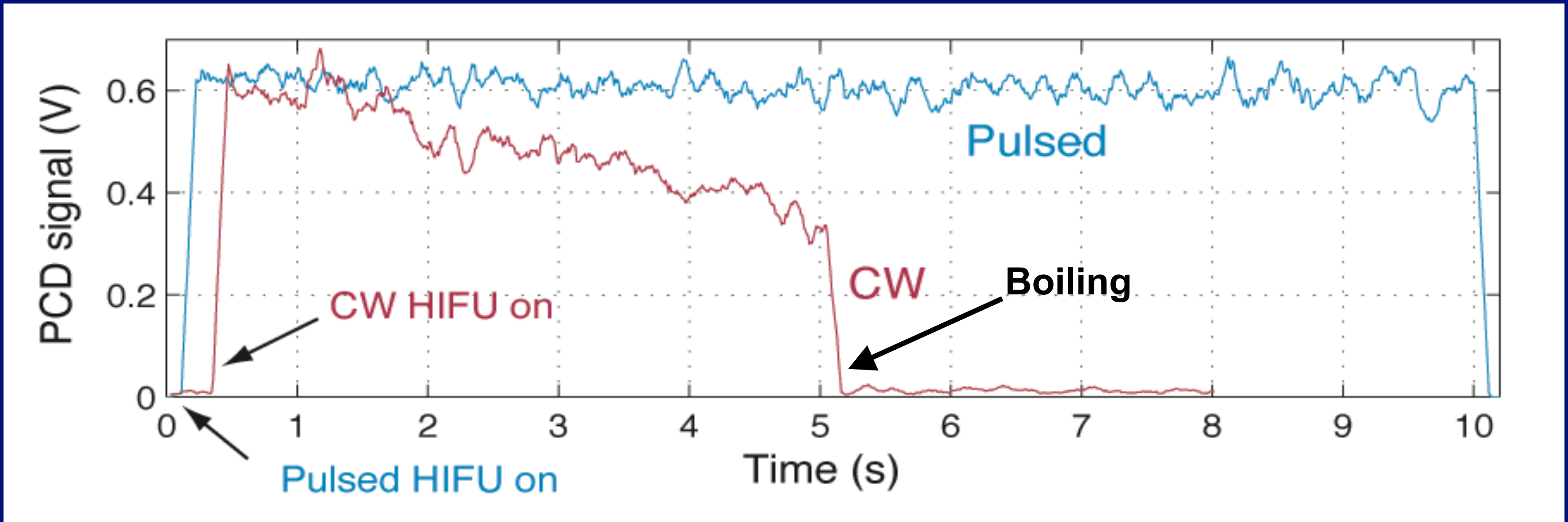
Reduction in PCD Emission With Time?

- For sufficiently high pressures, PCD focal emissions always decrease with time
  - Reduced bubble-assisted heating rates
  - Suggestive of focal shielding?
  - Inhibit cavitation field growth while still driving inertially



A Simple Cavitation Controller?

- 100-cycle burst at 2.2 kHz PRF (20% duty cycle)



- Pulsing the HIFU field serves top stabilize the PCD signal
  - Measurements indicate a lower focal temperature rise
  - Is this effect due only to prefocal heating, or is temperature implicated as well?

What Happens if the Tissue Gets Too Hot Too Quickly?

Lesion formation in a gel
- LHS: side lighting
- RHS: back lighting

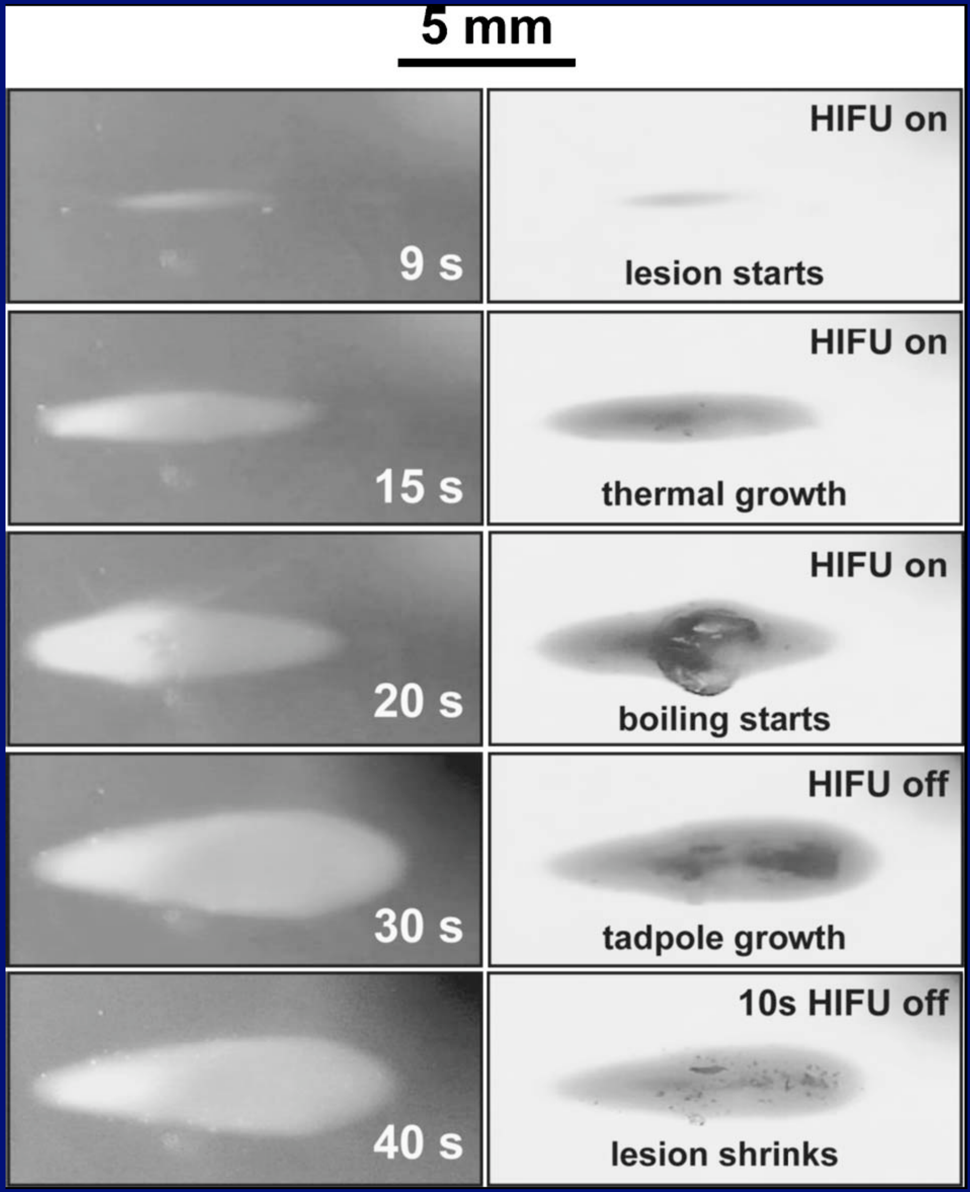
3.5 MHz, 14 kW/cm^2, 30 sec exposure

Two separate runs in a low absorbing phantom

Boiling leads to the formation of a malformed tadpole" lesion

Inertial cavitation precedes boiling, but the progression is extremely rapid (10's of msec)

Khokhlova *et al.*, *J. Acoust Soc. Am.* 119, 834-848, 2006



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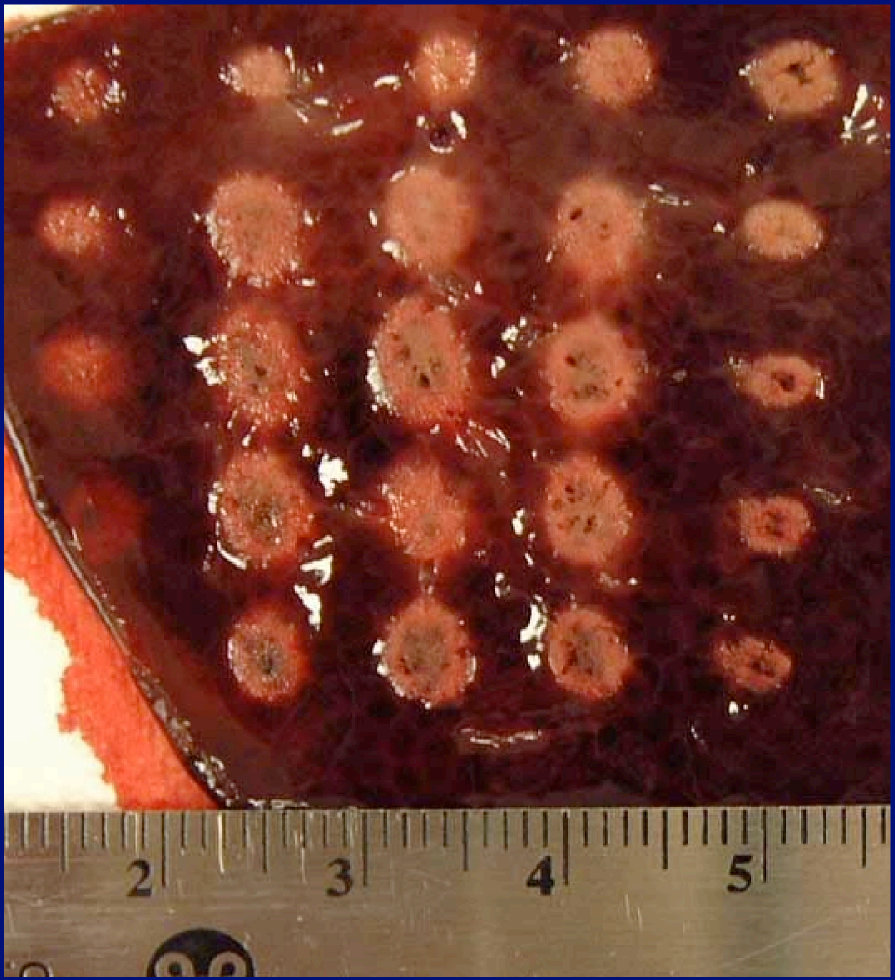

Bubbles and HIFU Lesion Formation

- Bubbles alter the acoustic properties of the medium. Subresonant size -- employ an effective medium approximation:
  - Sound speed depression and enhanced attenuation
- Shielding beyond the focus and backscattered energy pre-focally
  - Shields the "target" from incident energy
  - Causes the lesion to migrate towards the transducer
    - Greater energy = more heating
    - Problematic when forming larger lesions
- As the tissue heats, bubble collapse arrested by vapor pressure
  - Inertial cavitation "shuts down" and boiling takes over

Is sensing & controlling inertial cavitation a moot point?

Not Necessarily

- So long as you avoid boiling temperatures, controlled inertial cavitation can still offer therapeutic value
- "Gentler" heating and/or non-thermal effects may be desirable
  - Heating of sensitive regions
  - Thrombolysis, drug delivery, non-thermal tissue disruption
- Real-time feedback for tuning the bubble field
  - Control via duty cycle, pressure schedule, multiple frequencies
- Why isn't this currently be done *in vivo*?
  - There are no cavitation nuclei in tissue!
  - Nuclei are essential and may need to be introduced externally (contrast agents, etc.)

In Closing…

- Bubbles play a variety of roles in a wide range of diagnostic, therapeutic and process ultrasound procedures
  - The list is far longer that the material just presented!
- "Bubble response physics" is diverse and can be highly nonlinear
  - Linear: scattering, absorption, dispersion
  - Nonlinear: streaming, jetting, shocks, energy concentration, extreme conditions upon inertial collapse
- For years cavitation was something to avoid
  - Control via duty cycle, pressure schedule, multiple frequencies
- Cavitation is now being used to promote both diagnostic and therapeutic effects
  - For HIFU, pre-existing cavitation nuclei are essential

I Thank…

YOU, FOR YOUR KIND ATTENTION…

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