

ULTRASOUND

Sound Energy that can See and Treat

Michael C. Kolios, Ph.D., Associate Professor

Jahan Tavakkoli, Ph.D., Assistant Professor

Dept. of Physics, Ryerson University

May 2008

RYERSON UNIVERSITY

Outline

- **Introduction**
- **Diagnostic Ultrasound in Oncology**
High-frequency Ultrasound Quantitative Imaging
- **Therapeutic Ultrasound in Oncology**
High Intensity Focused Ultrasound (HIFU)

Ultrasound

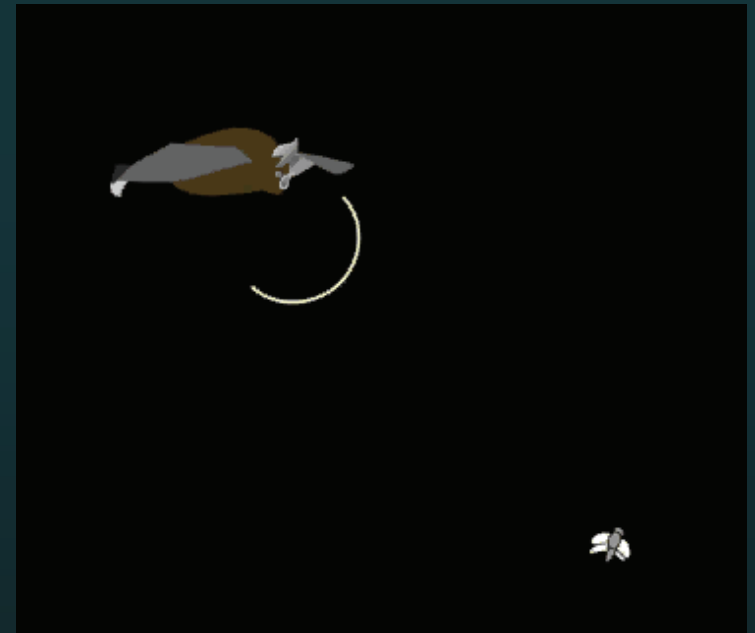
Ultrasound is a sound energy with frequencies above human hearing threshold

$$f_0 > 20,000 \text{ Hz}$$

In Nature



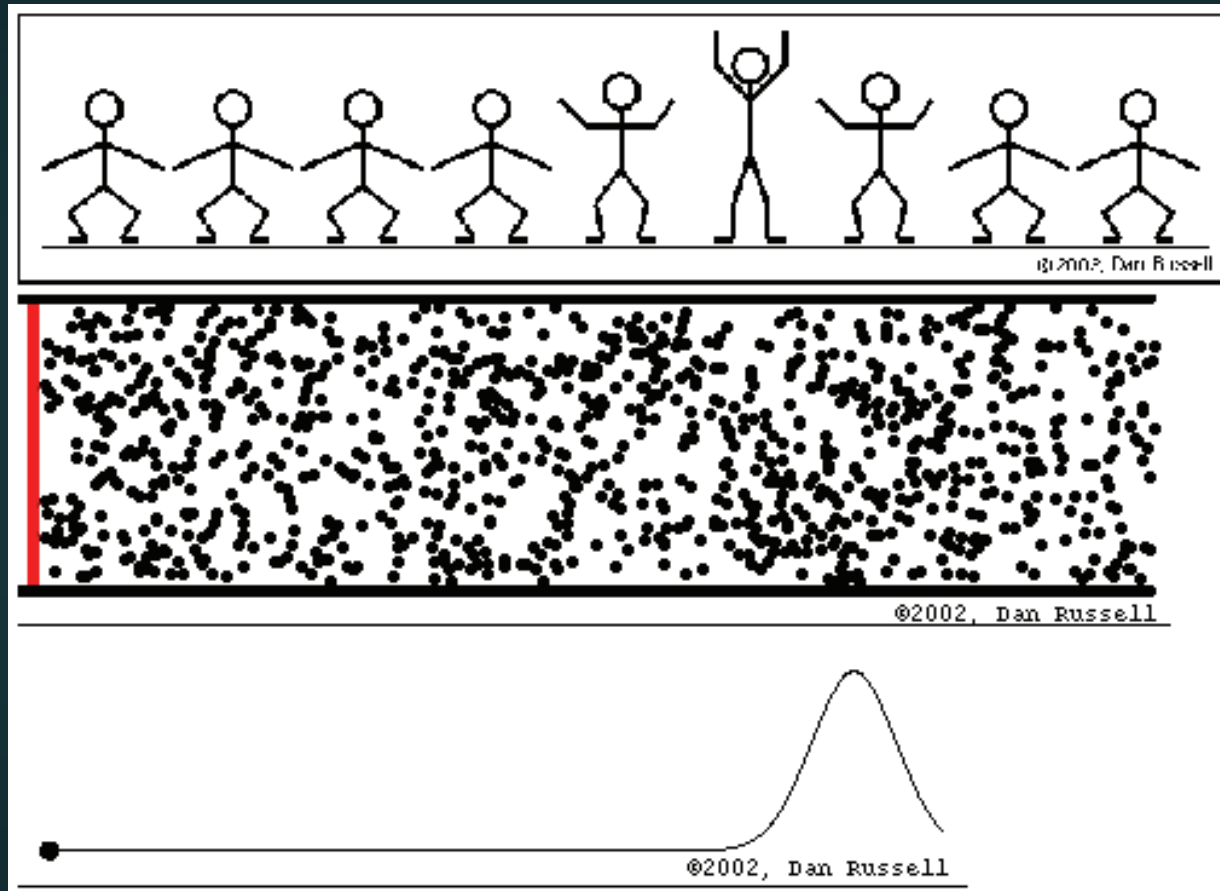
Dolphin Echolocation



Bat Echolocation

Ultrasound is a Wave Phenomenon

What is a Wave?



A wave is a disturbance or fluctuation which travels through a medium.

Wave transfers *energy* but not *matter*!

History of Ultrasound

- Discovery of *Piezoelectric Effect* by Pierre and Jacques Curie in 1880.
- First applications in underwater sonar during the World War I.
- Rapid development of military, industrial, and medical applications since 1940s.

Current Civil Applications of Ultrasound

Applications in Industry

- NDT/NDE
- Ultrasonic Cleaners
- Ultrasonic Welding
- Etc.

Application in Medicine and Biology

Diagnostic Ultrasound

- Pulse-Echo Imaging (1D, 2D, 3D, 4D)
- Doppler Imaging
- Elastography
- Etc.

Therapeutic Ultrasound

(1) Low-power Therapies

Sonophoresis, Sonoporation, Sonothrombolysis, Gene Therapy, Bone Healing, Wound Healing, Etc.

(2) High-power Therapies

Physiotherapy, Lithotripsy, and High Intensity Focused Ultrasound (HIFU)

PART 1

Diagnostic Ultrasound

High-frequency Ultrasound Quantitative Imaging

Applications in Oncology

Ultrasound Pulse-Echo Imaging

Baby - 2D Image



Baby - 3D Image

Non-ionizing, inexpensive, real-time

Ultrasound Scanners



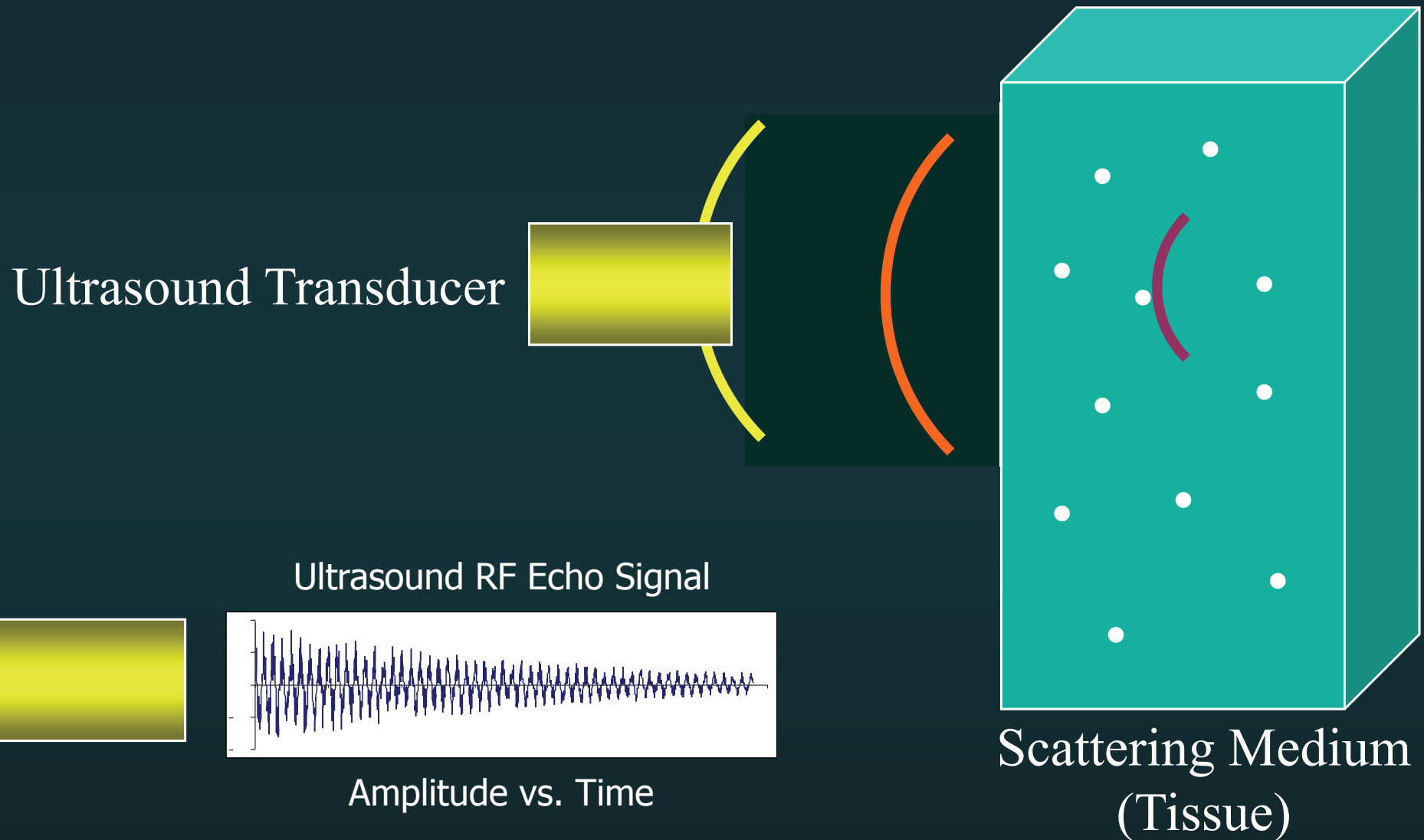
High Frequency
>20 MHz



Medium Frequency
3 – 15 MHz

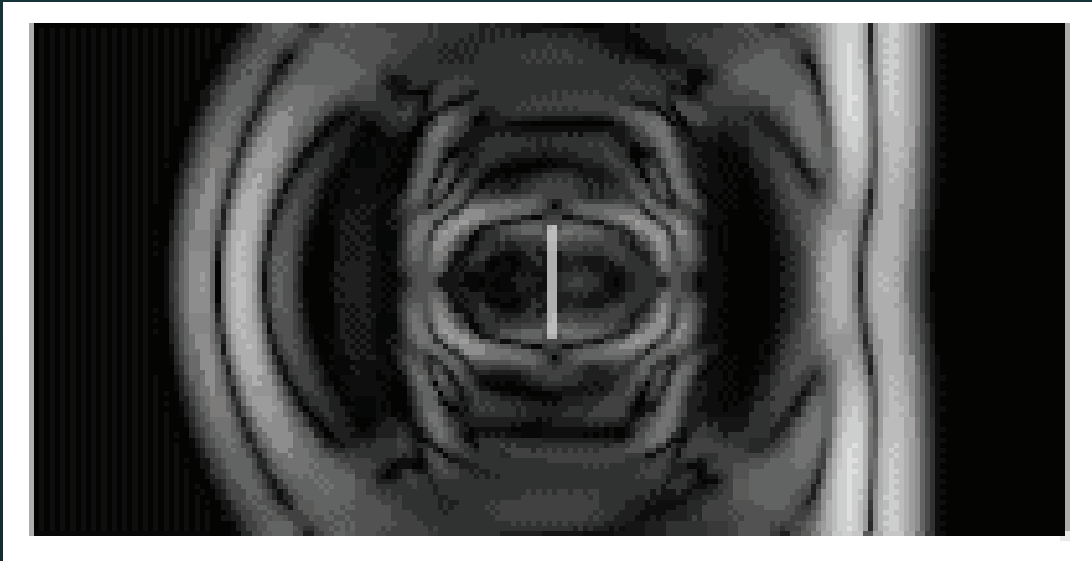


Ultrasound Pulse-Echo Imaging Scattering



Ultrasound Scattering

$$BSC \sim \frac{k_o^2 a^3}{3} \left[\frac{\kappa_1 - \kappa_o}{\kappa_o} + \frac{\rho_1 - \rho_o}{\rho_1} \cos \theta \right]$$



Wave3000®

CyberLogic Inc., New York, NY

Important Parameters:

- Incident frequency
- Size of scatterers
- Physical properties of scatterers (density and compressibility)
- Spatial distribution of scatterers

Spectral Analysis of Radio Frequency (RF) Data

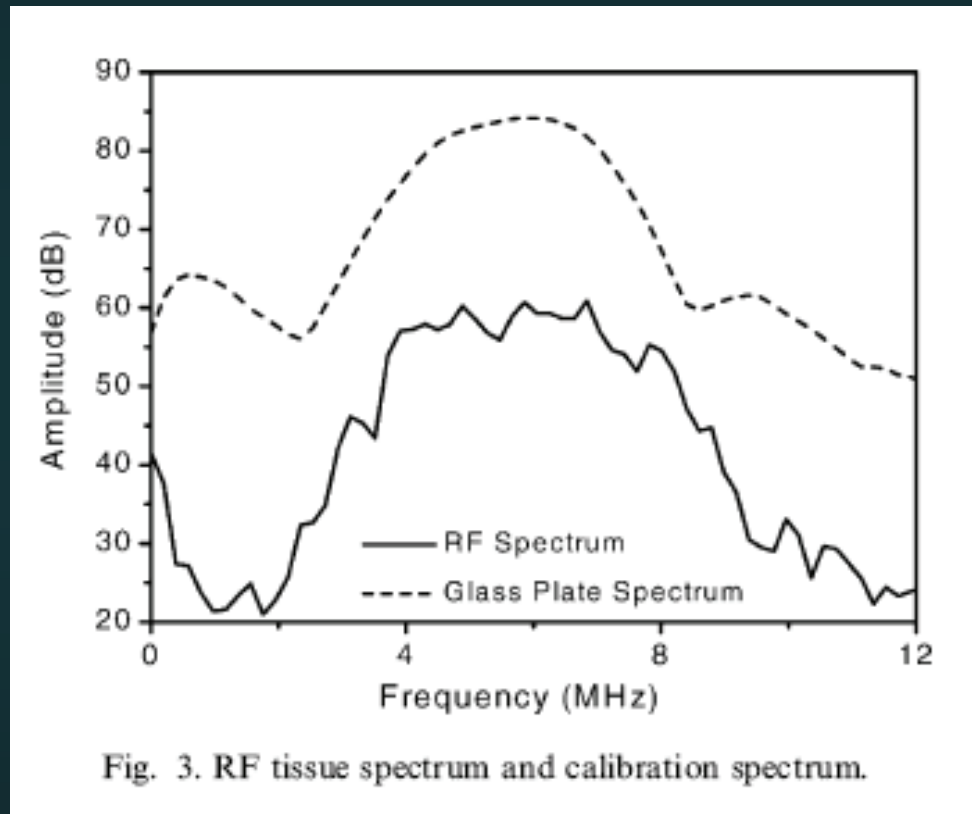
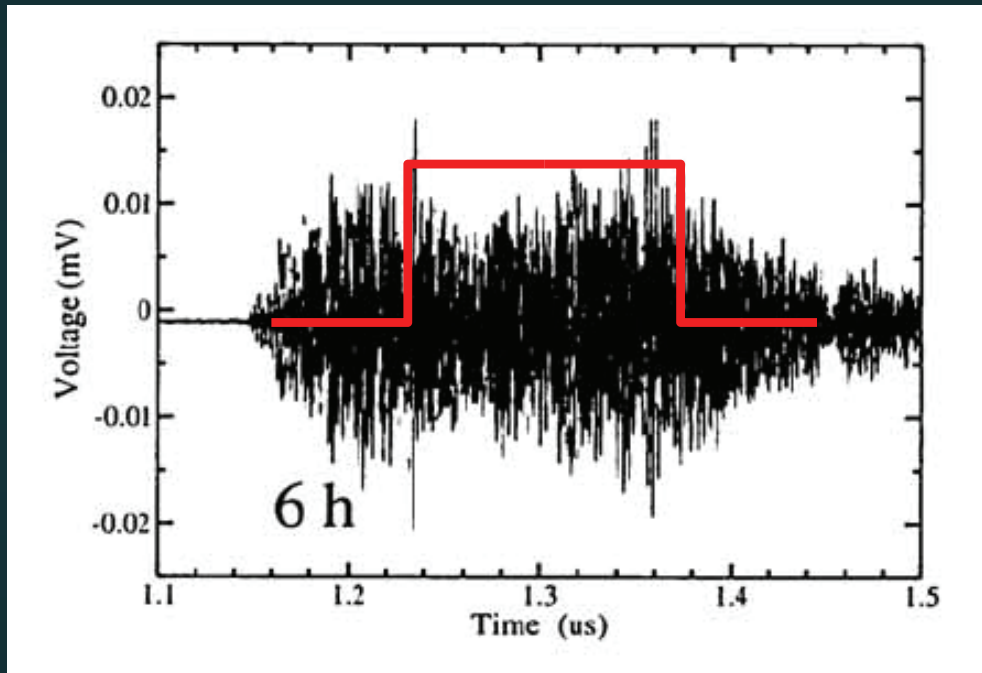


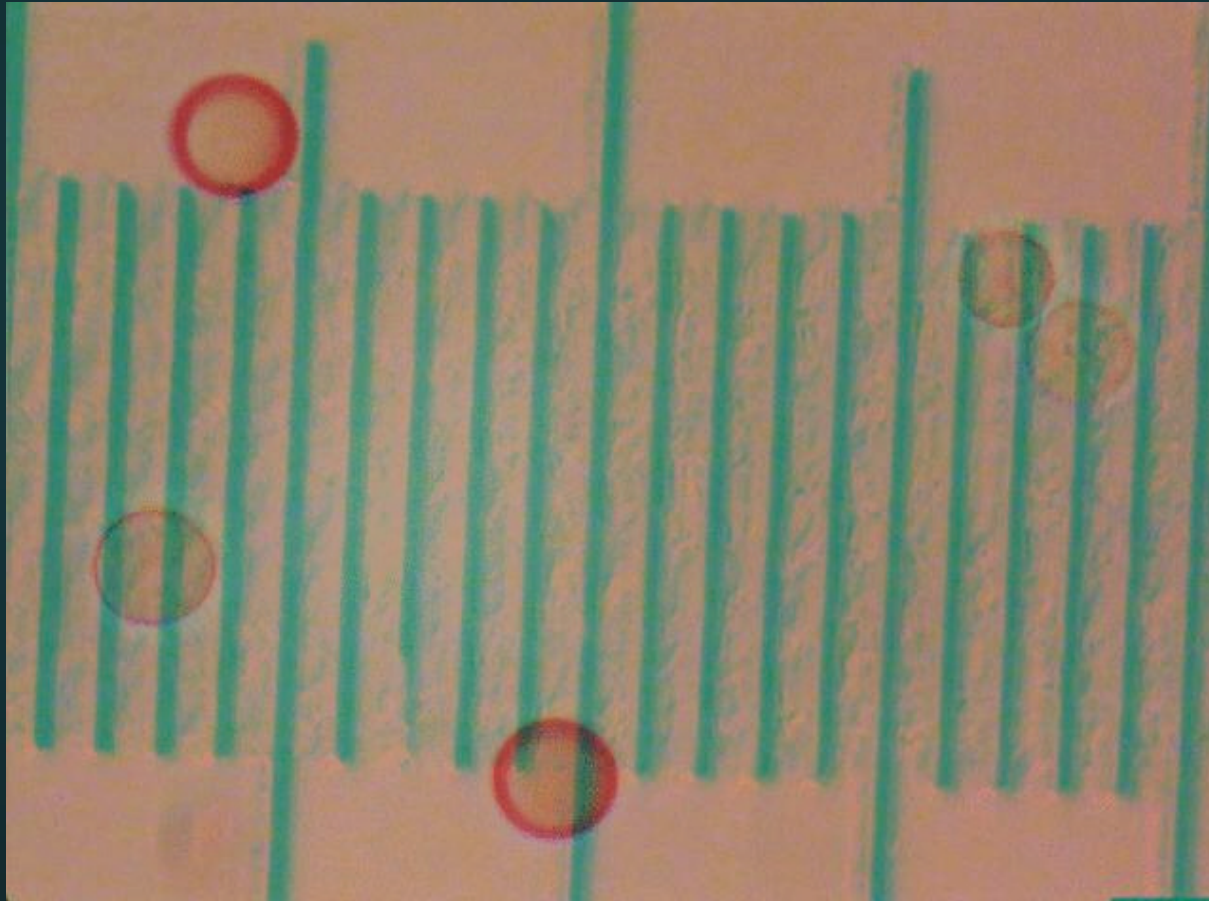
Fig. 3. RF tissue spectrum and calibration spectrum.

Quantitative Imaging!

Pattern Recognition Letters 24 (2003) 637–658

Experimental Scattering Model

- Polystyrene beads
- Diameter $\sim 20 \mu\text{m}$

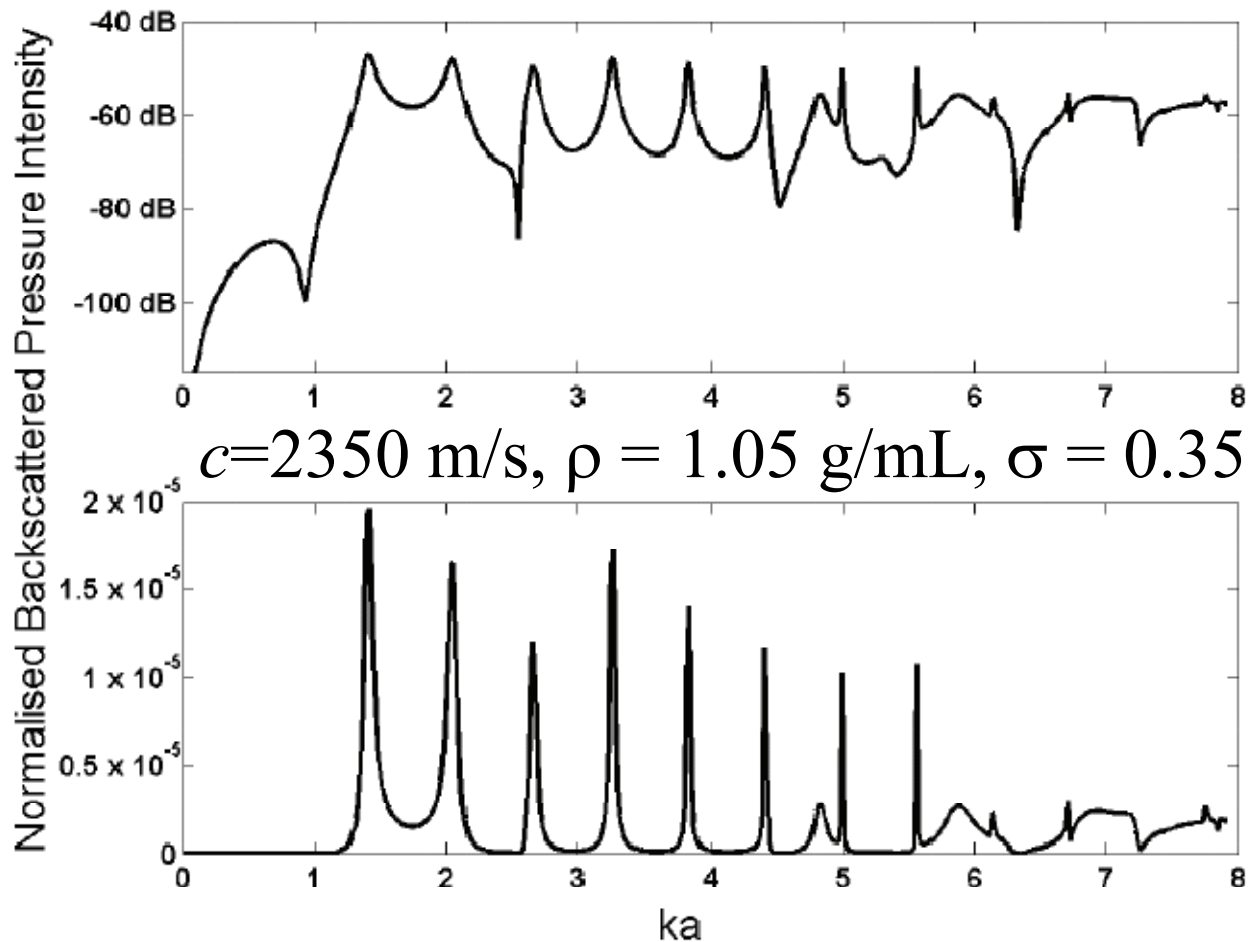
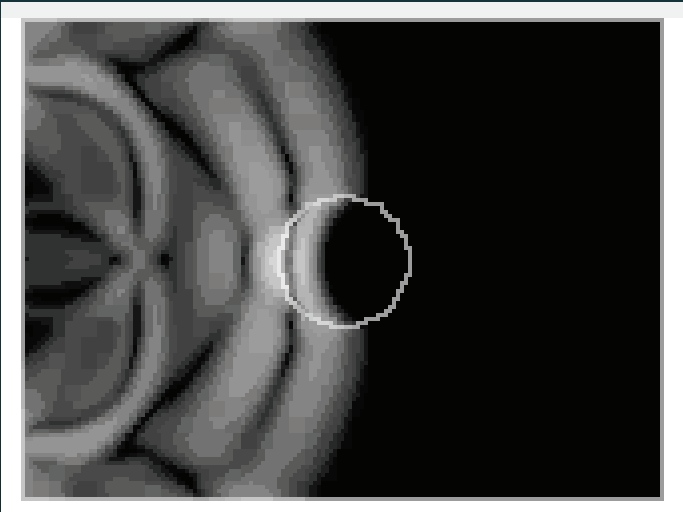


Baddour et. al. JASA (2005) 117(2), 934-943

Simulation and Measurement

Frahn's
Scattering
Model

$$p_s(t, k_3, \theta) = \frac{P_i a}{2r} \left[\frac{2}{x_3} \sum_{n=0}^{\infty} (-1)^n (2n+1) \sin \eta_n e^{-i\eta_n} P_n(\cos \theta) \right] e^{-ik_3(c_3 t - r)}$$



Cancer Treatment - Cell Death

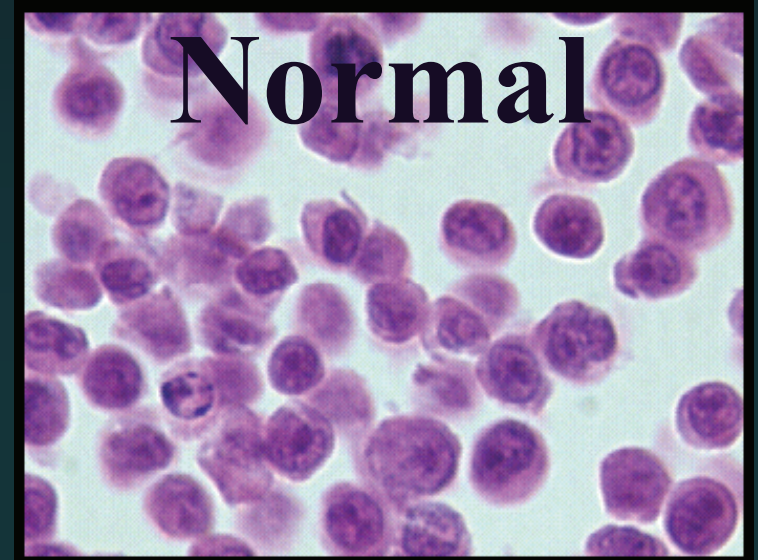
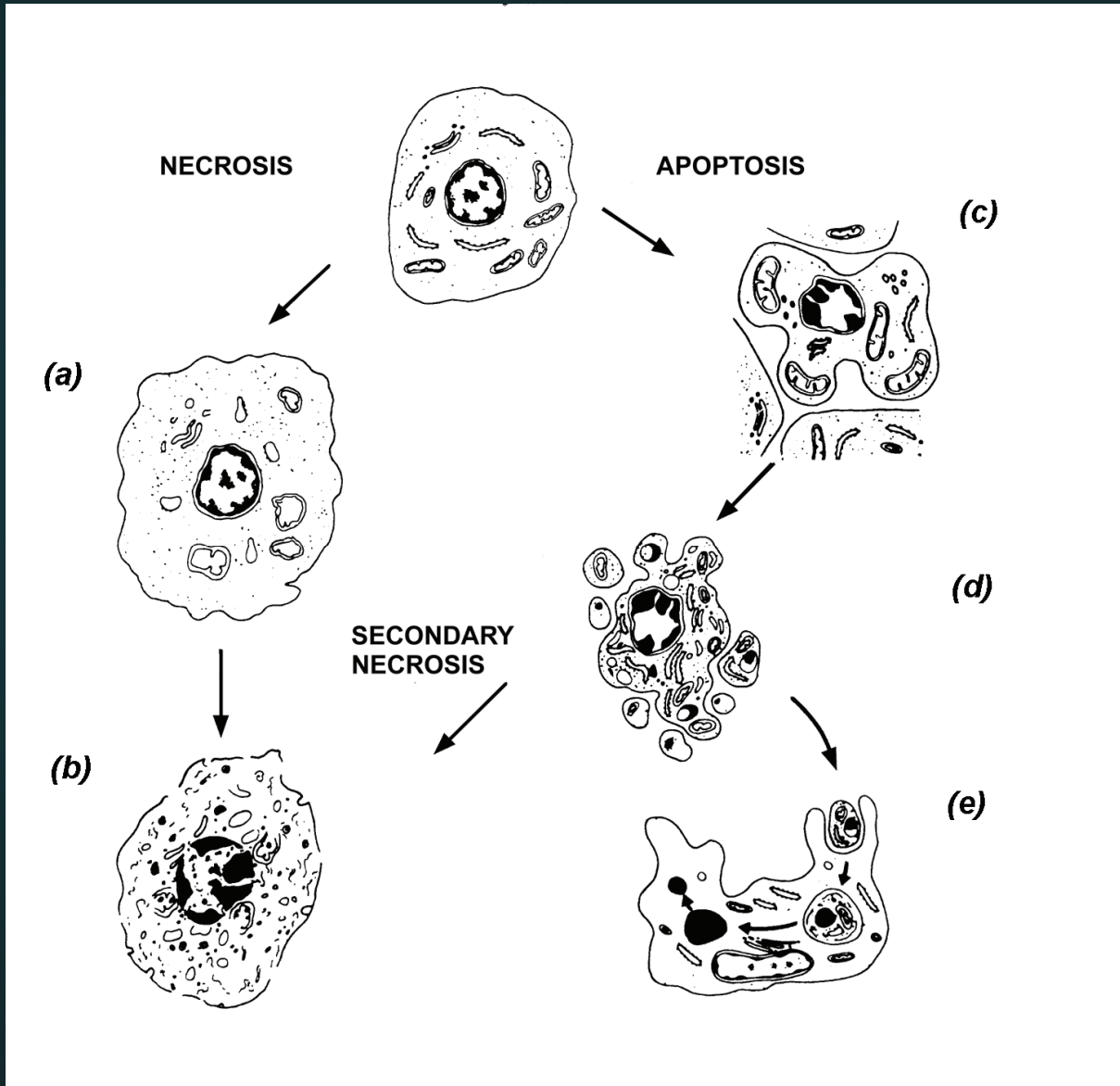
- Chemotherapy (Cisplatin, etc.)
- Energy-based Methods
 - Ionizing radiation (α and β particles, γ and x rays, etc.)
 - Heat therapy (RF, microwave, ultrasound, etc.)
- Cell death is due to a combination of necrosis and apoptosis
- Necrosis: Uncontrolled cell death
- Apoptosis: Programmed cell death

Apoptosis

- Apoptosis: programmed cell death
- Body's normal way of getting rid of unneeded or abnormal cells
- Large changes in cellular and nuclear structure
- May play role in cancer therapy along with necrosis



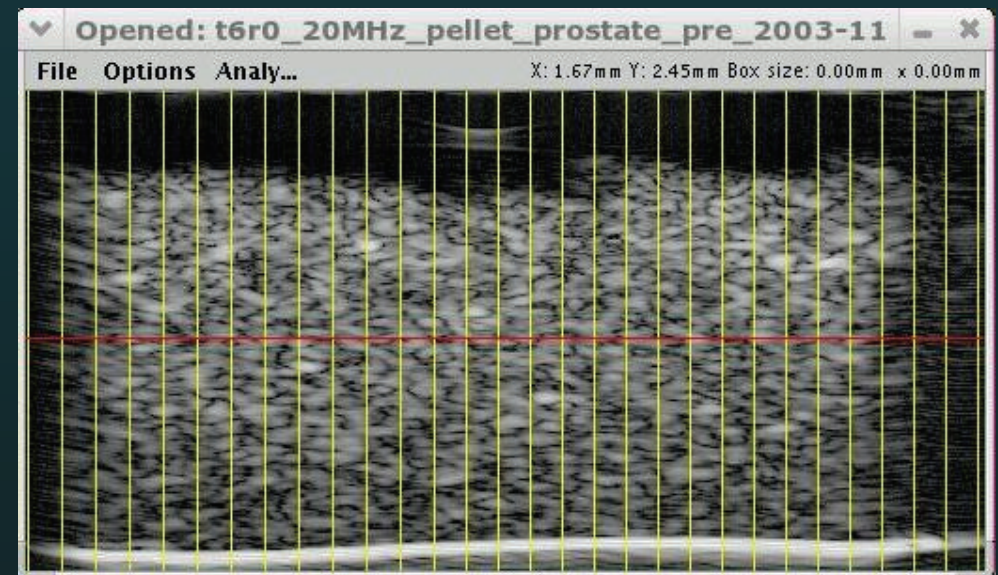
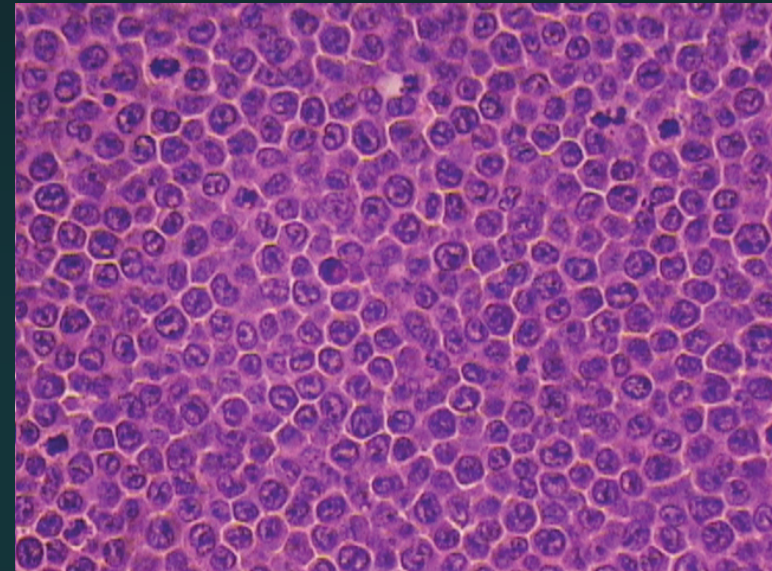
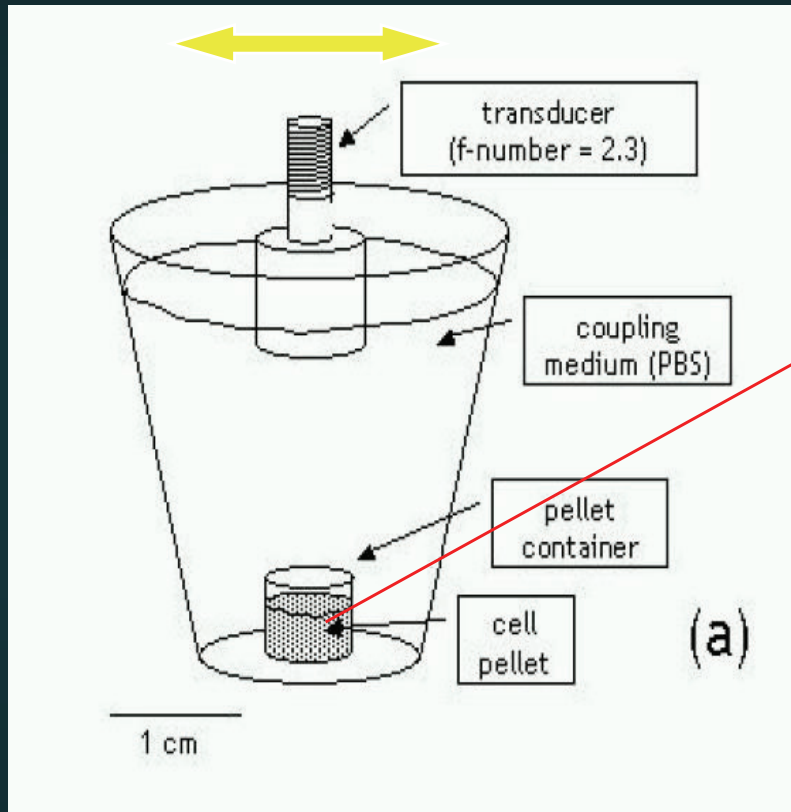
Morphological Changes in a Dying Cell



Why Would Ultrasound Backscatter be Sensitive to Cell Death?

- Backscattering depends on scatterer size, physical attributes (density, compressibility), and spatial organization
- All of the above likely change during cell necrosis/apoptosis

High Frequency Ultrasound Imaging - Experimental Setup

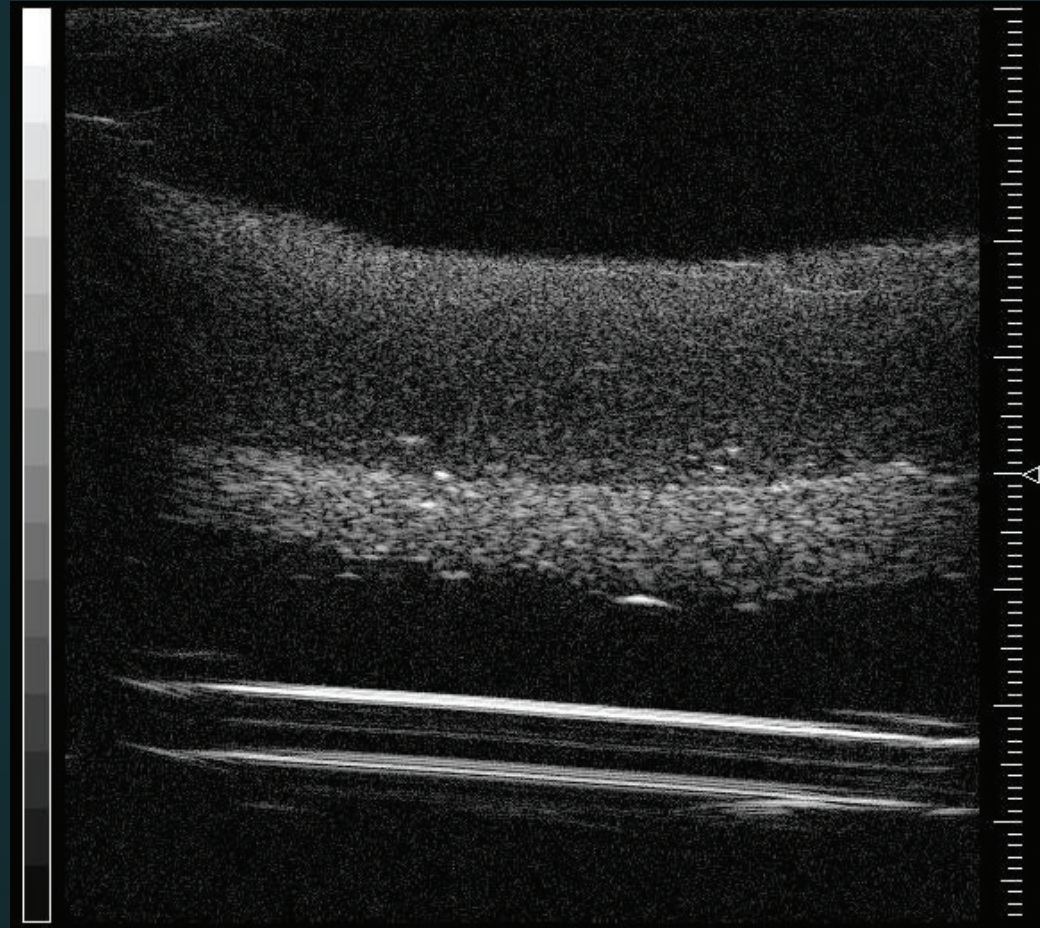
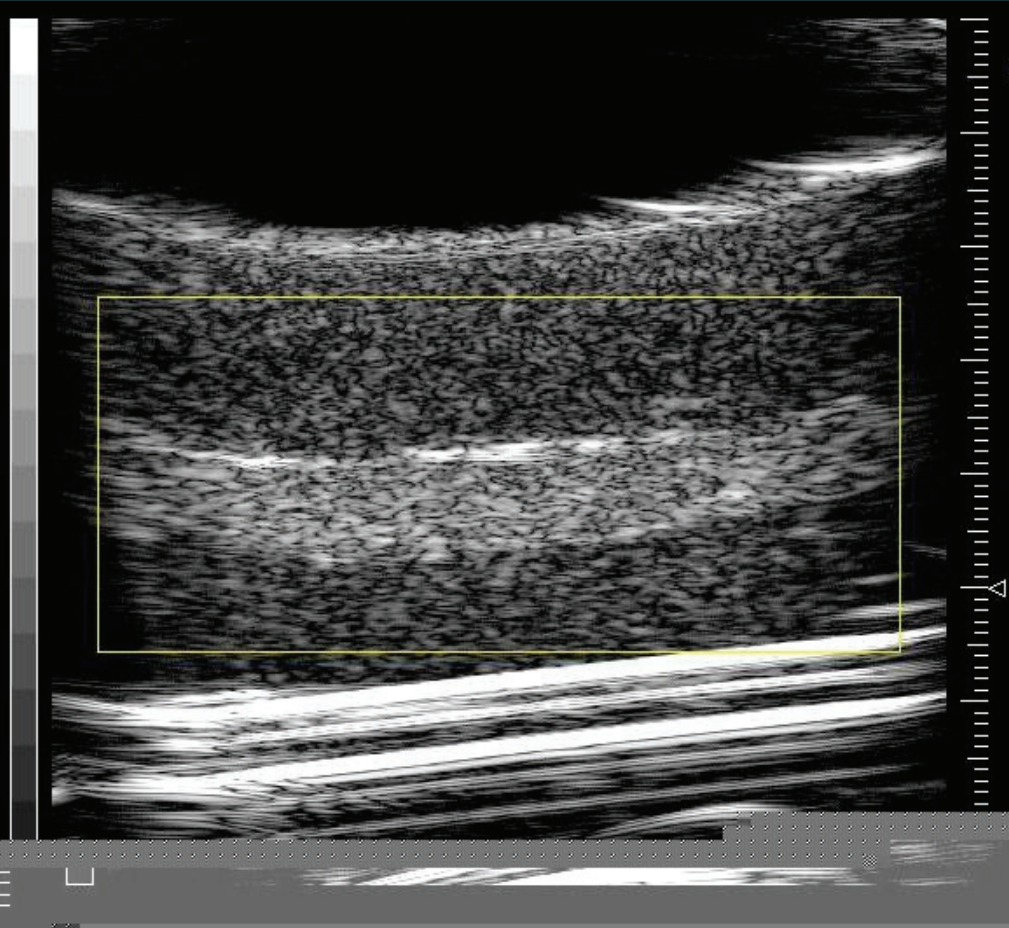


**Acute Myeloid
Leukemia (AML)
Cancer Cells**

Monitoring Cell Death

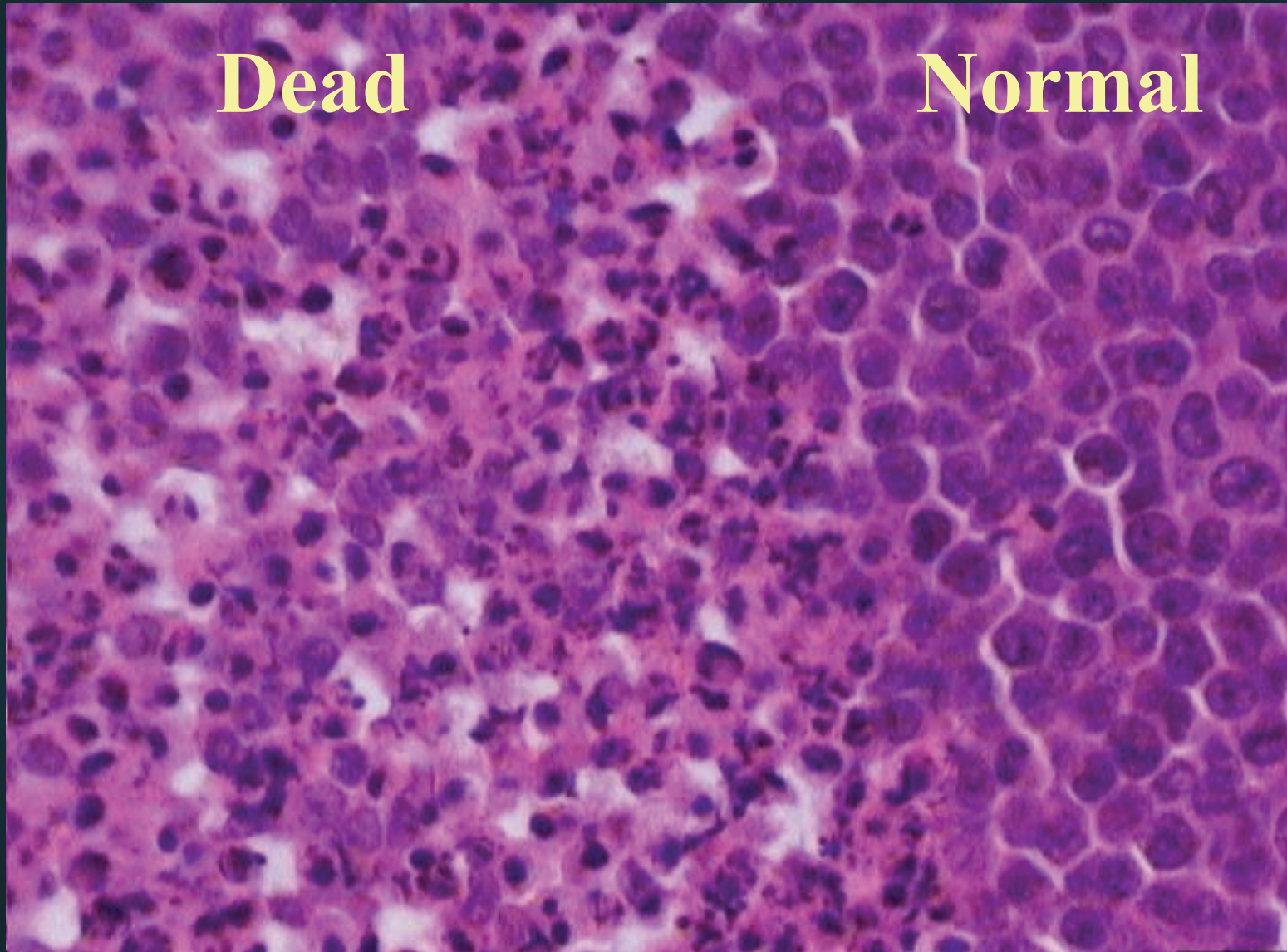
20 MHz data

40 MHz data



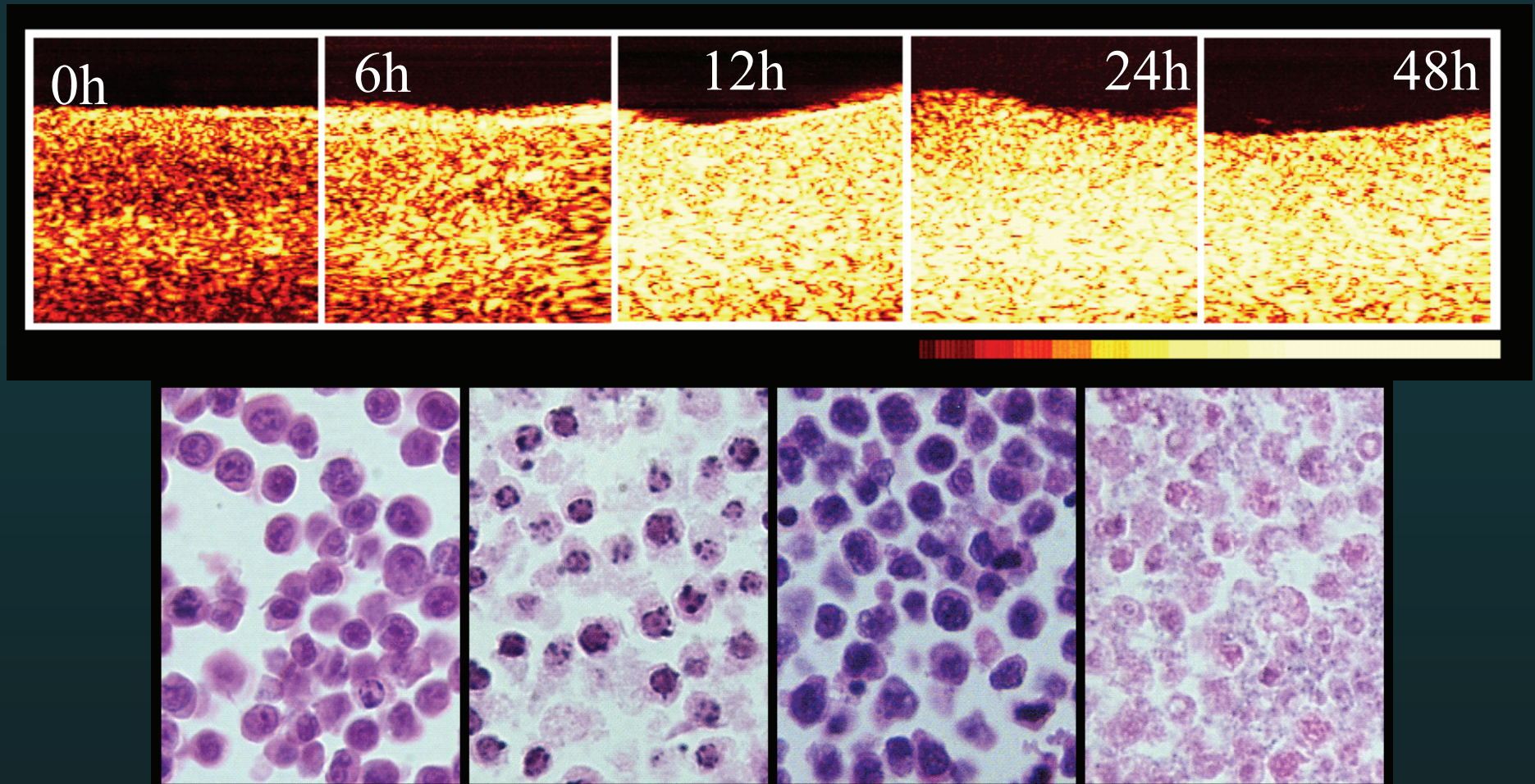
Layers: Non exposed (top) - exposed to 16h Cisplatin - non exposed (bottom)

Boundary Between Layers

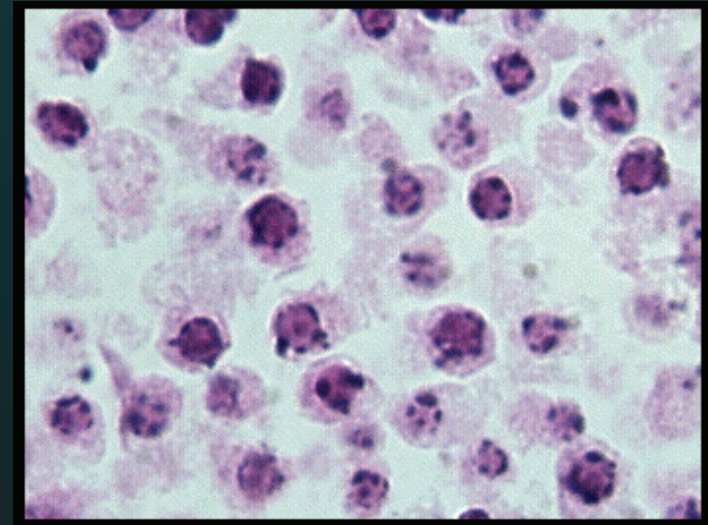
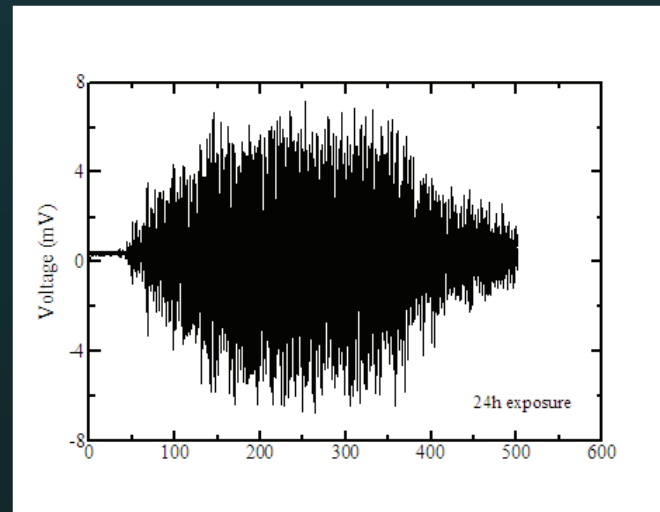
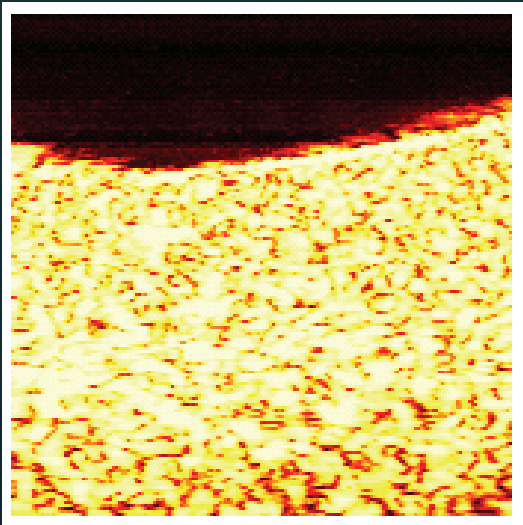
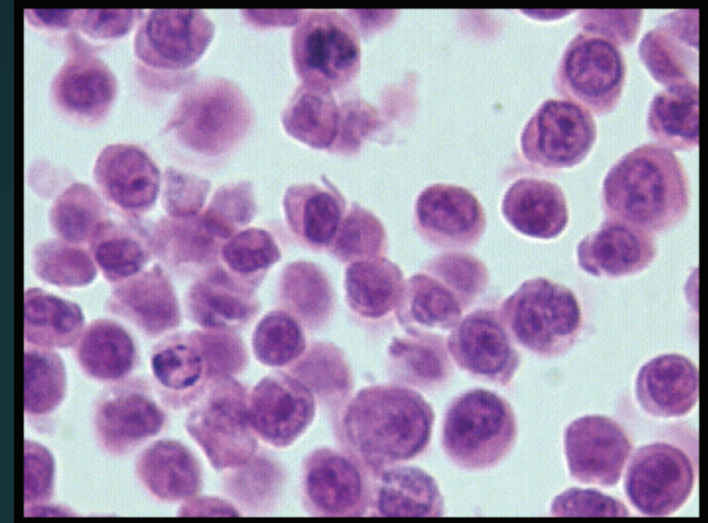
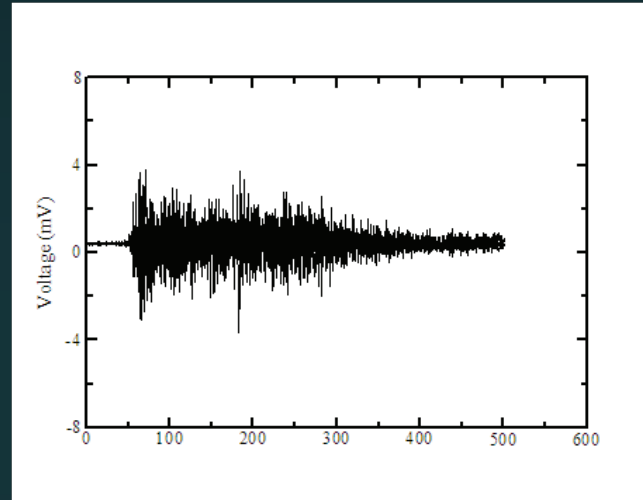
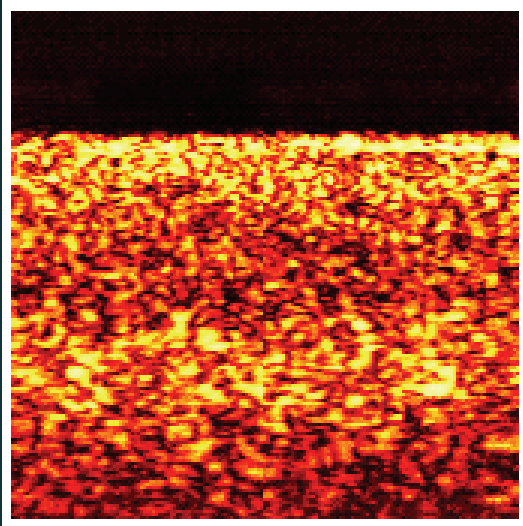


Results: Apoptosis in Cells Pellets

- AML cell pellets exposed to Cisplatin

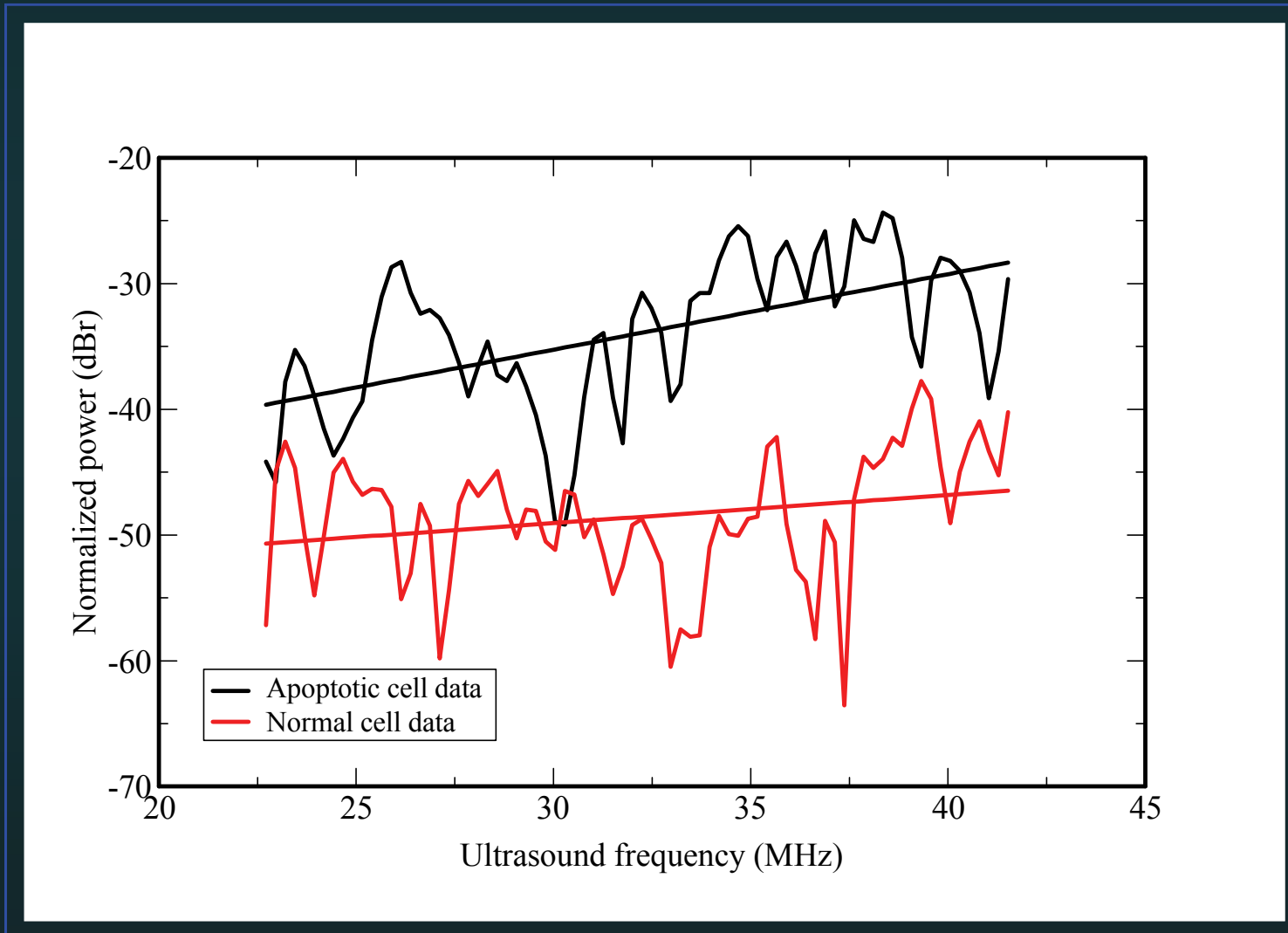


Results: Normal vs. Apoptotic Cell RF Data



Results: Spectrum Analysis

■ Apoptotic vs. Normal Cells



Conclusions

- Ultrasound is sensitive to changes in cell size, physical properties and spatial distribution
- Backscatter increases and changes in spectral slopes seen in cell death (apoptosis & necrosis) for cell lines studied
- Results were verified in animal cancer models

PART 2
Therapeutic Ultrasound

**High Intensity Focused Ultrasound
(HIFU)**

Applications in Oncology

Therapeutic Ultrasound Growth

Latest International IEEE Ultrasonics Symposium



2007 IEEE International Ultrasonics Symposium
Short Courses & Tutorials October 28-31 2007

Hilton New York, New York, NY, U.S.A.

Sponsored by the IEEE Ultrasonics, Ferroelectrics & Frequency Control Society

Total number of oral sessions in Group 1 (Medical Ultrasonics) = 31

Number of sessions in therapeutic ultrasound = 8

Therapeutic ultrasound = 26%

High Intensity Focused Ultrasound (HIFU)

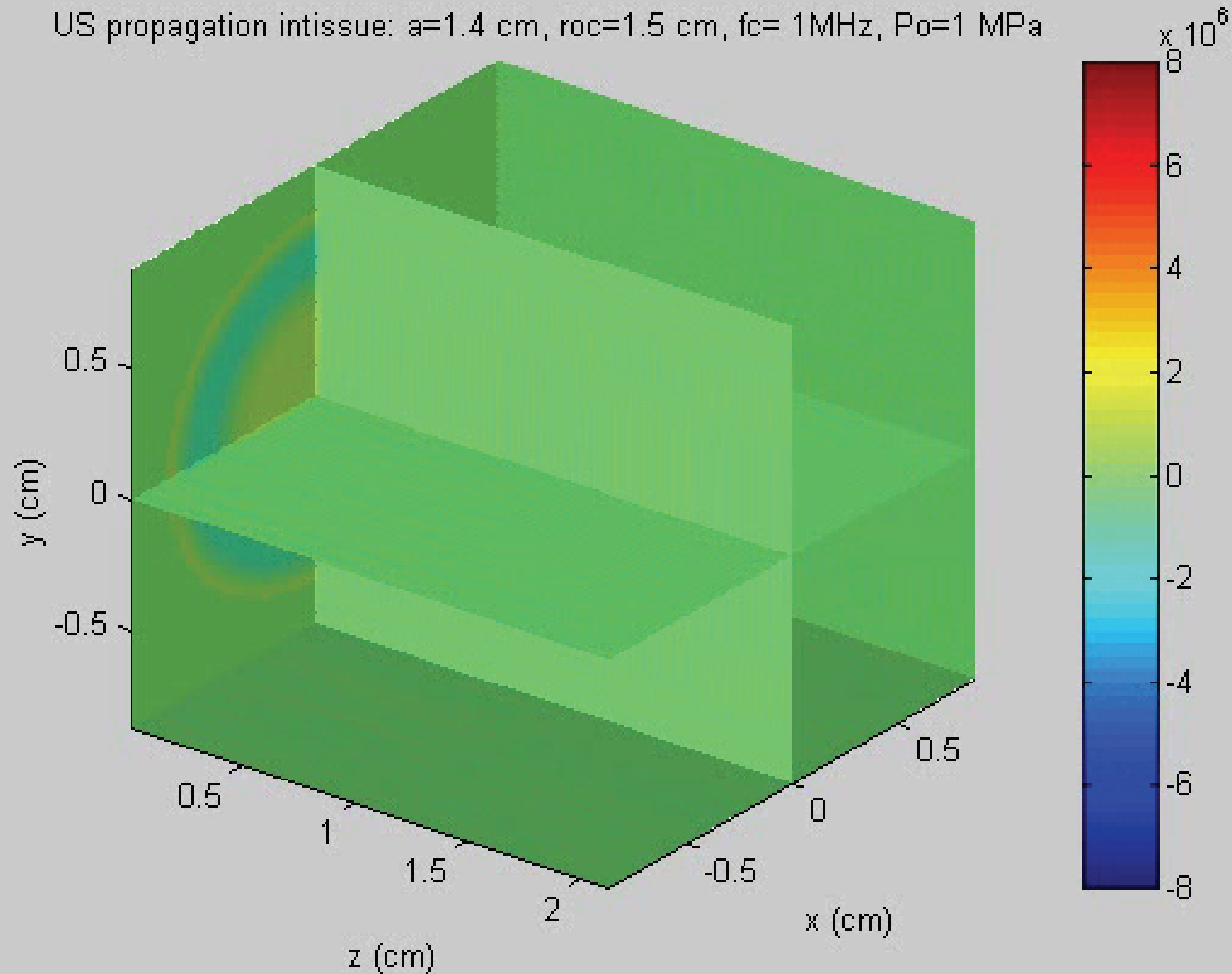
Bursts of focused ultrasound energy
~3 order of magnitude more intense
than diagnostic ultrasound used as a
noninvasive therapy option

Applications

- Benign and Malignant Solid Tumor Treatment (Prostate, Liver, Kidney, Breast, Bladder, etc.)
- Hemostasis to Control Bleeding
- Noninvasive Surgeries (Neurosurgery, Orthopedics, Cosmetic Surgery, etc.)

Focused Ultrasound

US propagation intissue: $a=1.4$ cm, $r_{oc}=1.5$ cm, $f_c=1$ MHz, $P_o=1$ MPa



HIFU

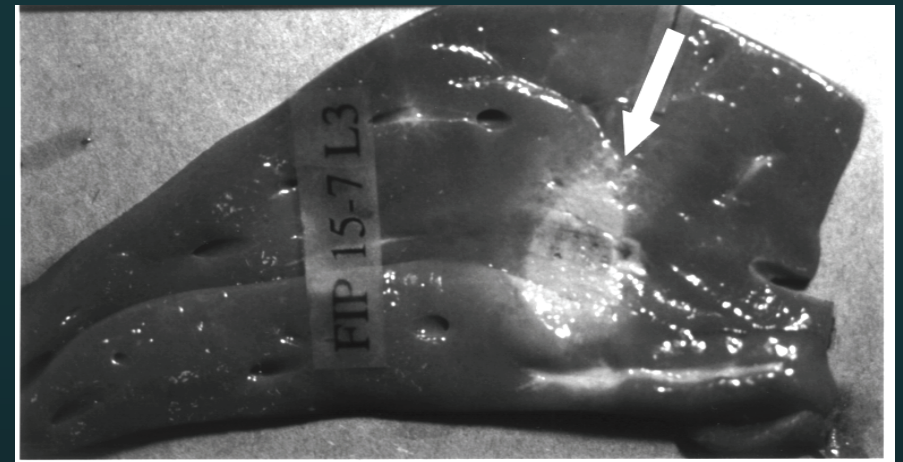
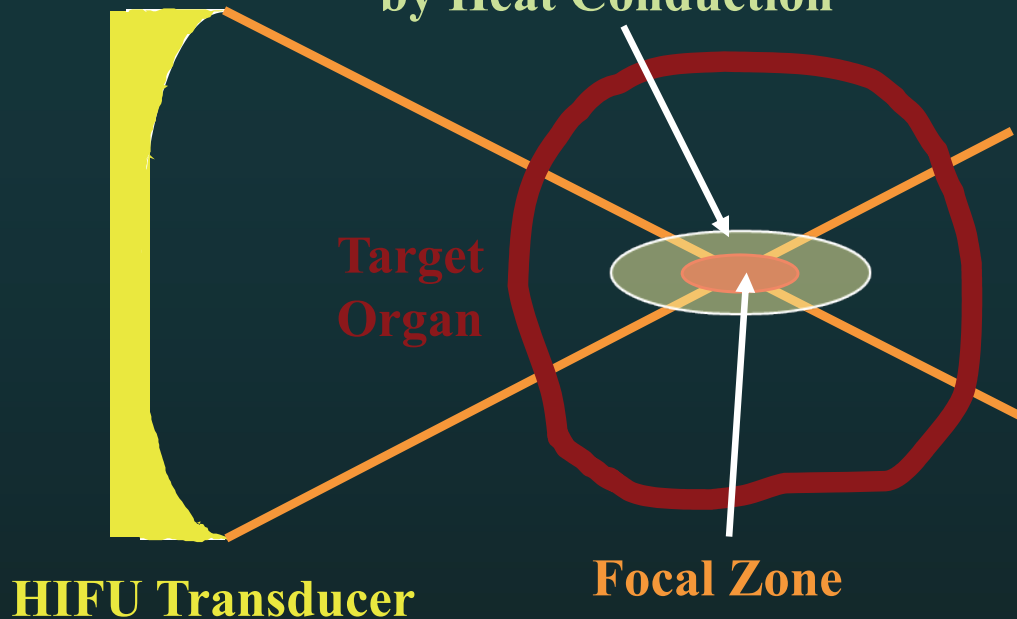
Main Features

- **Highly Intensive:** $I_{\text{focal}} \sim 500 - 10000 \text{ W/cm}^2$
- **Highly Focused:** F-no. $\sim 0.7 - 2$
- **Frequency:** $\sim 0.5 - 10 \text{ MHz}$
- **Exposure On/Off Time:** A few ms - s
- **Temperature Rise at the Focus:** $> 20 \text{ }^\circ\text{C/s}$
- **Focus Size:** $\sim 0.1\text{-}2 \text{ mm} \times 1\text{-}20 \text{ mm}$

HIFU - A Non-Invasive Surgery Tool

- Very Well-delineated Lesions
- No Damage to Intervening Tissue
- Rapid Temperature Rise → Blood Perfusion Independent
- Non-invasive Bloodless Surgery

Thermal Lesion Induced
by Heat Conduction

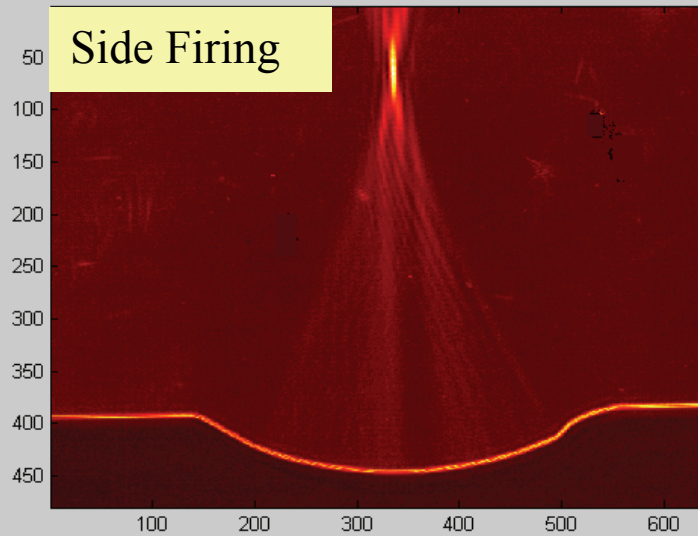


A HIFU lesion in pig's liver

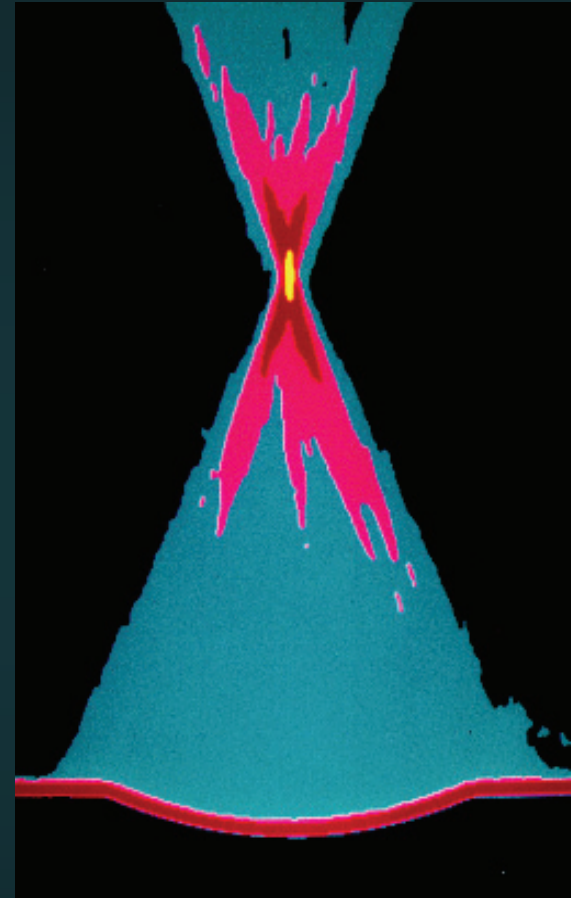
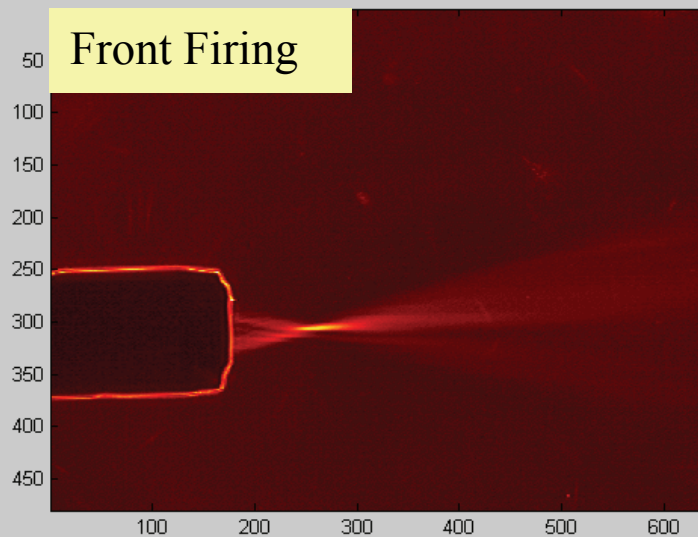
HIFU Field

Schlieren Images

Side Firing



Front Firing



Mechanisms of Interaction with Tissue

Direct Mechanisms:

(1) Thermal

- Coagulation Necrosis

Conversion of mechanical energy to heat via tissue attenuation

(2) Non-thermal

- Cavitation and/or Vapor Bubbles
- Radiation Pressure
- Acoustic Streaming

Indirect Mechanisms in Oncology:

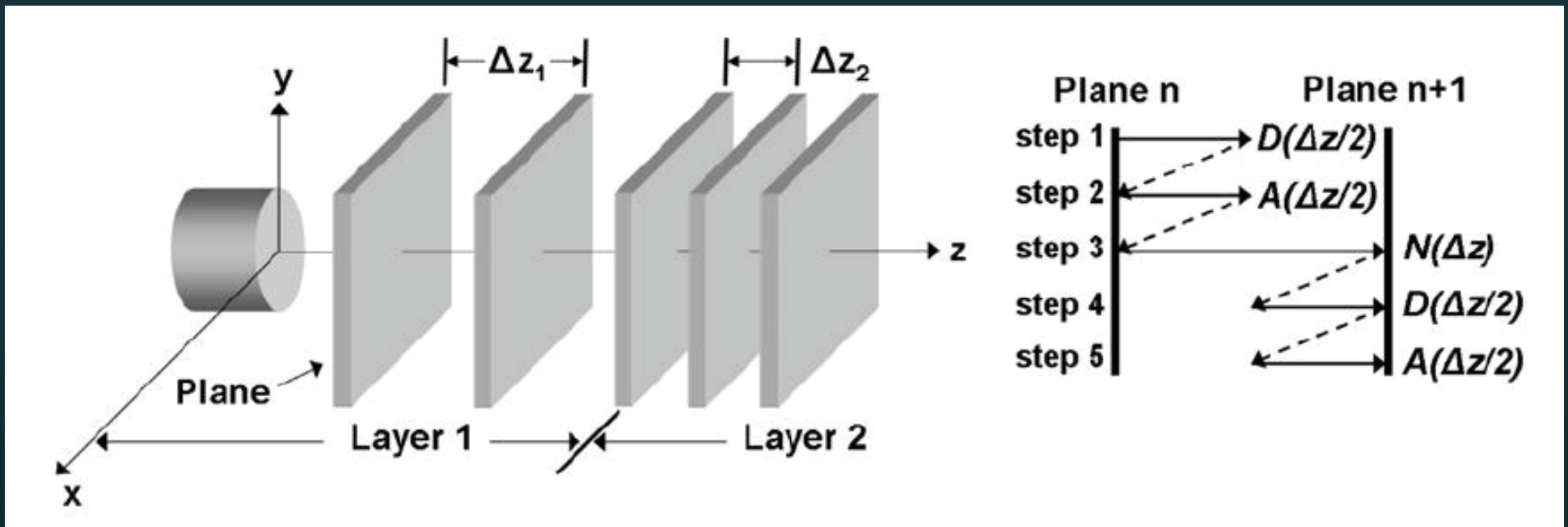
- Enhancing host antitumor immunity through expression of the tumor cells antigens (immunotherapy)

Areas of Research Interests

- **HIFU Modeling and Simulations
(Nonlinear Acoustics)**
- **Image-guided HIFU Surgery**

Nonlinear Ultrasound Modeling and Simulation

- ◆ Separate the main effects: diffraction, attenuation and nonlinearity
- ◆ Propagate these effects in a marching scheme using a novel second-order operator-splitting algorithm



D = Diffraction, A = Attenuation, N = Nonlinearity

Attenuation

Minimum-phase FIR digital attenuator and dispersive filter:

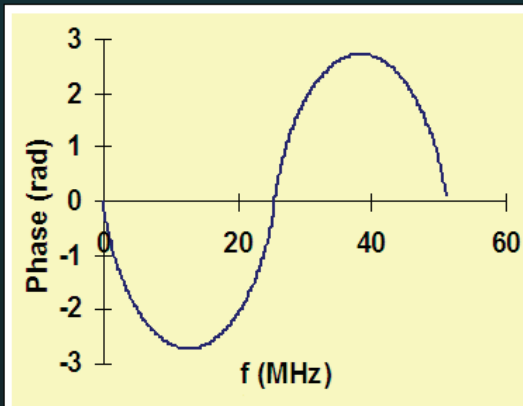
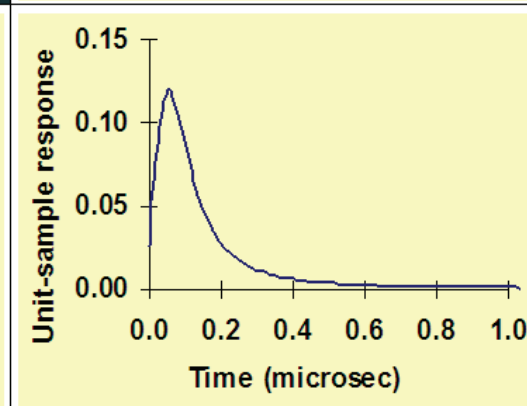
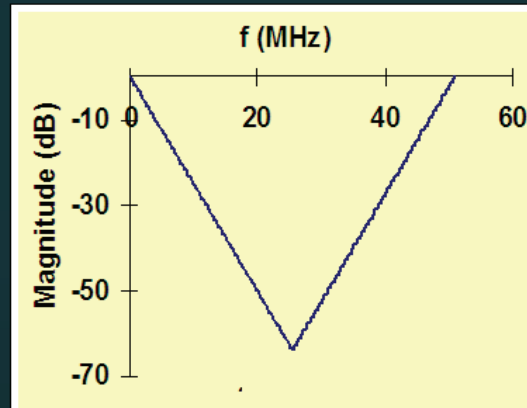
$$|G(e^{i\Omega})| = \frac{1}{T} \exp[-\alpha(\Omega/T)\Delta z]$$

$$\arg[G(e^{i\Omega})] = \frac{1}{2\pi} P \int_{-\pi}^{\pi} \ln|G(e^{i\theta})| \cotg\left(\frac{\theta - \Omega}{2}\right) d\theta$$

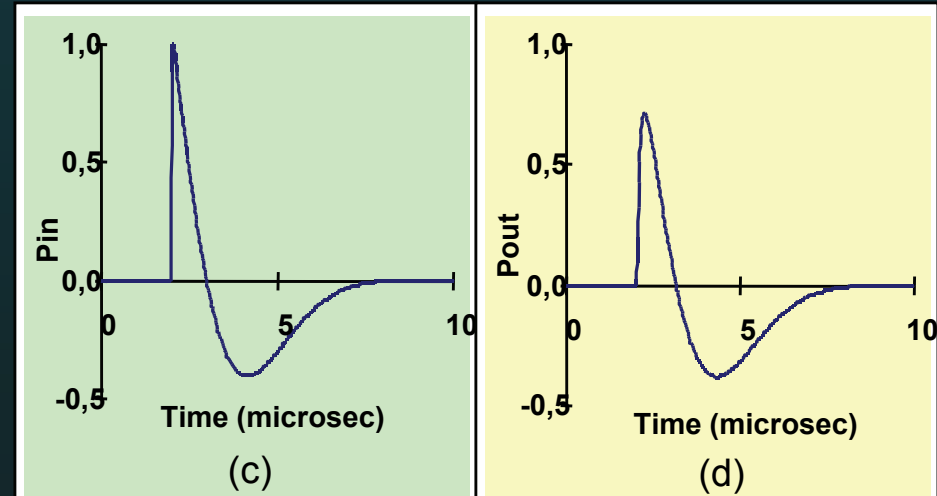
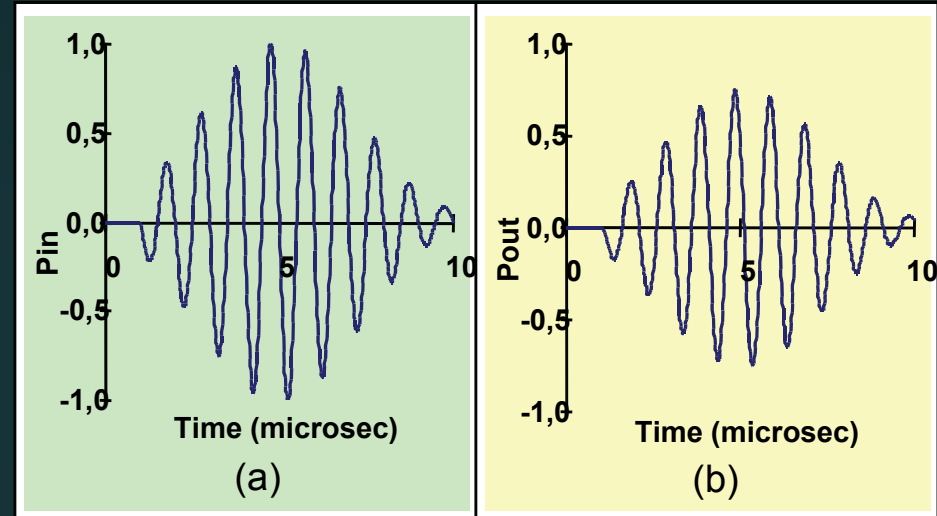
Medium = Liver

$\alpha = 0.5 \text{ dB} / \text{cm} \cdot \text{MHz}$

$\Delta z = 5 \text{ cm}$



Examples of application of the attenuator filter



Nonlinearity

Berger's equation for a plane wave propagating in a nonlinear medium:

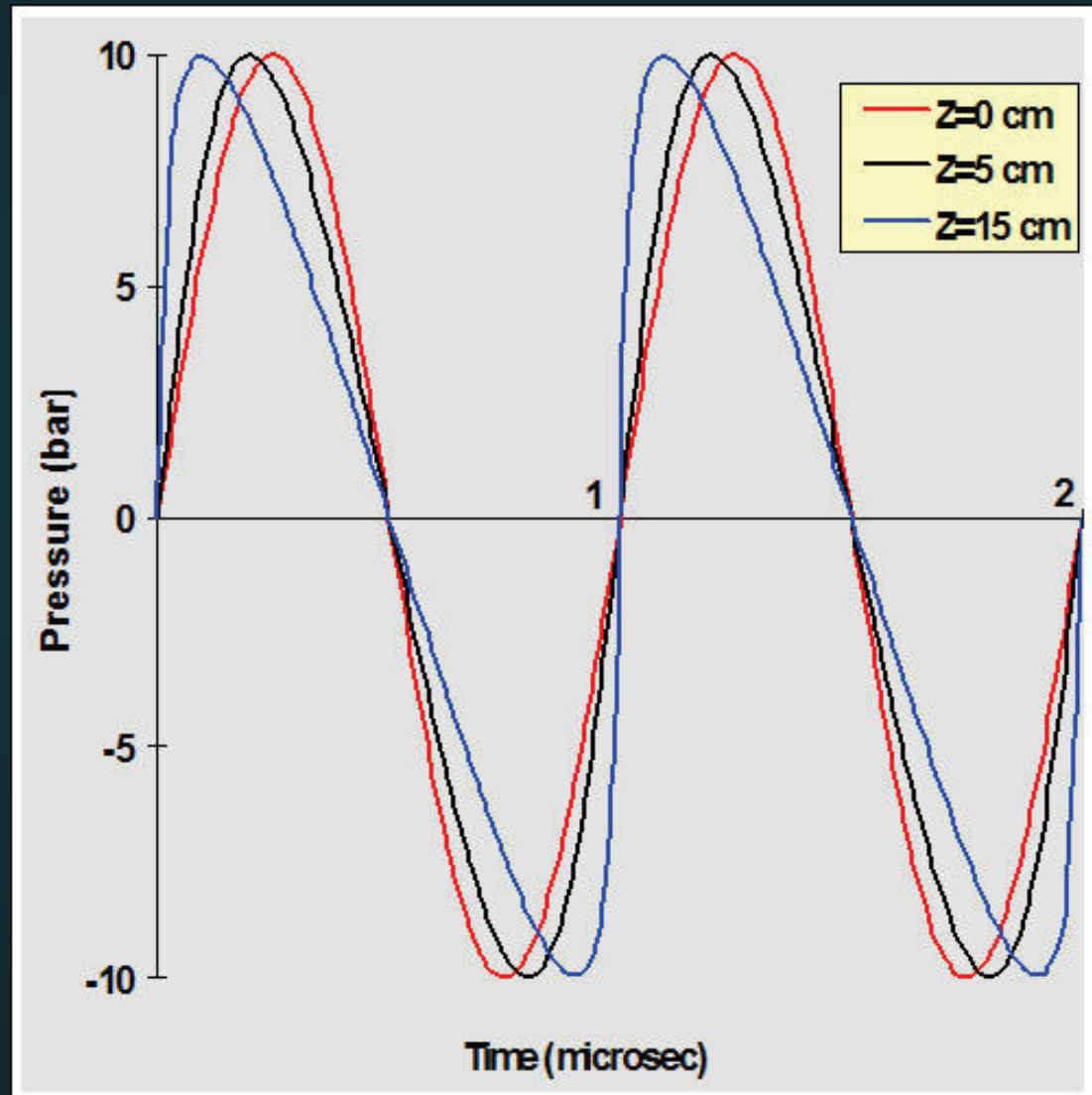
$$\frac{\partial v}{\partial z} = \frac{\beta}{c_0^2} v \frac{\partial v}{\partial \tau} \equiv \hat{L}_N v$$

where $\beta = 1 + \frac{B}{2A}$ is the nonlinear parameter of the medium.

The Poisson solution to the nonlinear Berger's wave equation:

$$v(z + \Delta z, \tau) = v \left\{ z, \tau + \frac{\beta \Delta z}{c_0^2} v(z, \tau) \right\}$$

Nonlinearly-induced wave distortion



Diffraction

From the classical theory of sound for a linear and non-dissipative medium:

$$p(\vec{r}, t) = \rho \frac{\partial \phi(\vec{r}, t)}{\partial t}$$

$$\vec{v}(\vec{r}, t) = -\vec{\nabla} \phi(\vec{r}, t)$$

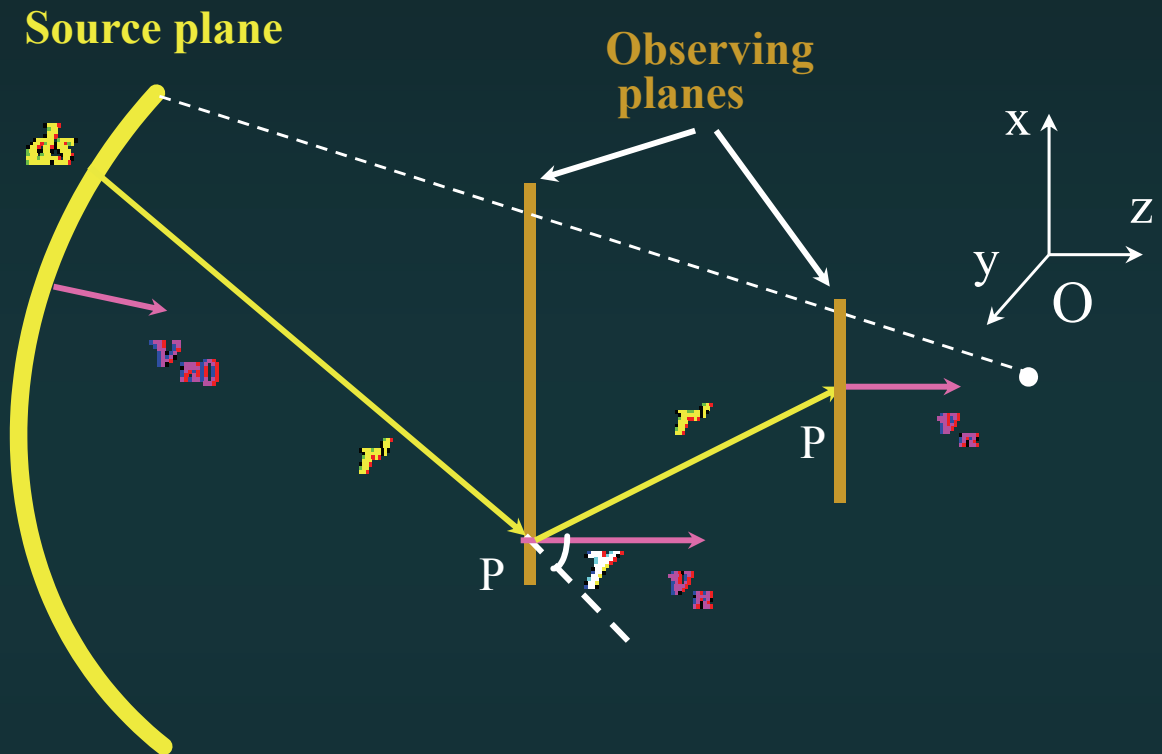
$$\phi(\vec{r}, t) = \frac{1}{2\pi} \iint_S \frac{v_n(t - r'/c_0)}{r'} ds$$

ρ = Equilibrium density of the medium,

$\vec{\nabla}$ = Gradient operator,

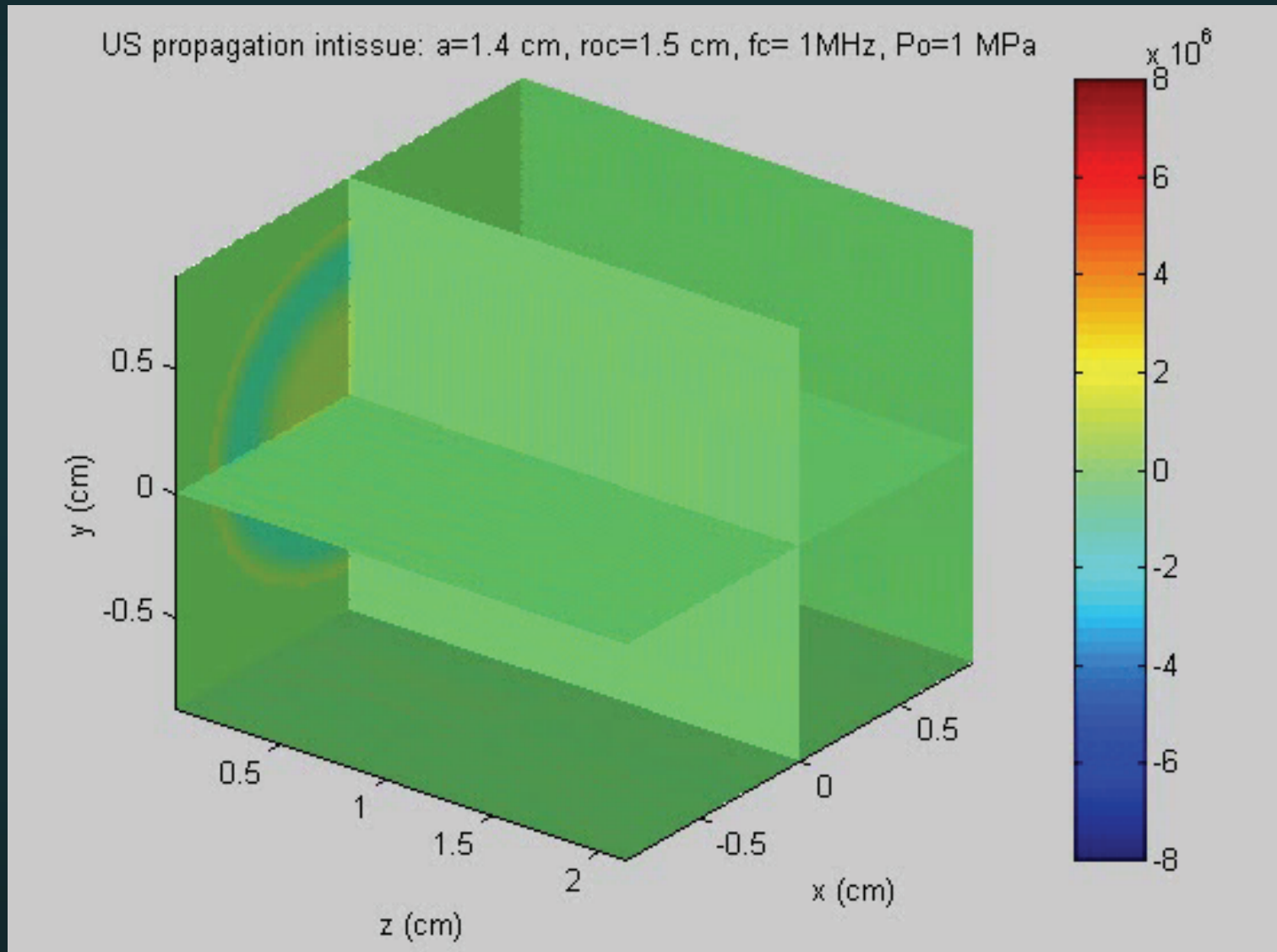
$\phi(\vec{r}, t)$ = Velocity potential,

$v_n(t)$ = Instantaneous normal particle velocity,



r' = Distance between the observation point and the surface element, ds , located at the source front surface.

Simulations – Acoustic Pressure and Intensity



Simulations – Temperature

The image displays a MATLAB simulation environment. The main window, titled "Figure No. 1", shows a 3D surface plot of temperature. The plot is a rectangular slab with a color gradient from dark red (low temperature) to yellow (high temperature). The axes are labeled with values: the vertical axis ranges from 0 to 45, the horizontal axis from -5 to 10, and the depth axis from -10 to 10. A color bar on the right indicates temperature values from 45 to 90. The plot is titled "Time: 0.1 s" and "T_{max} = 46.0816 °C".

The MATLAB Command History window shows the following commands:

```
run2moviet  
help shading  
run2movied  
runlmovied  
runlmoviet  
runlmovied  
runlmoviet
```

The Command Window shows the output:

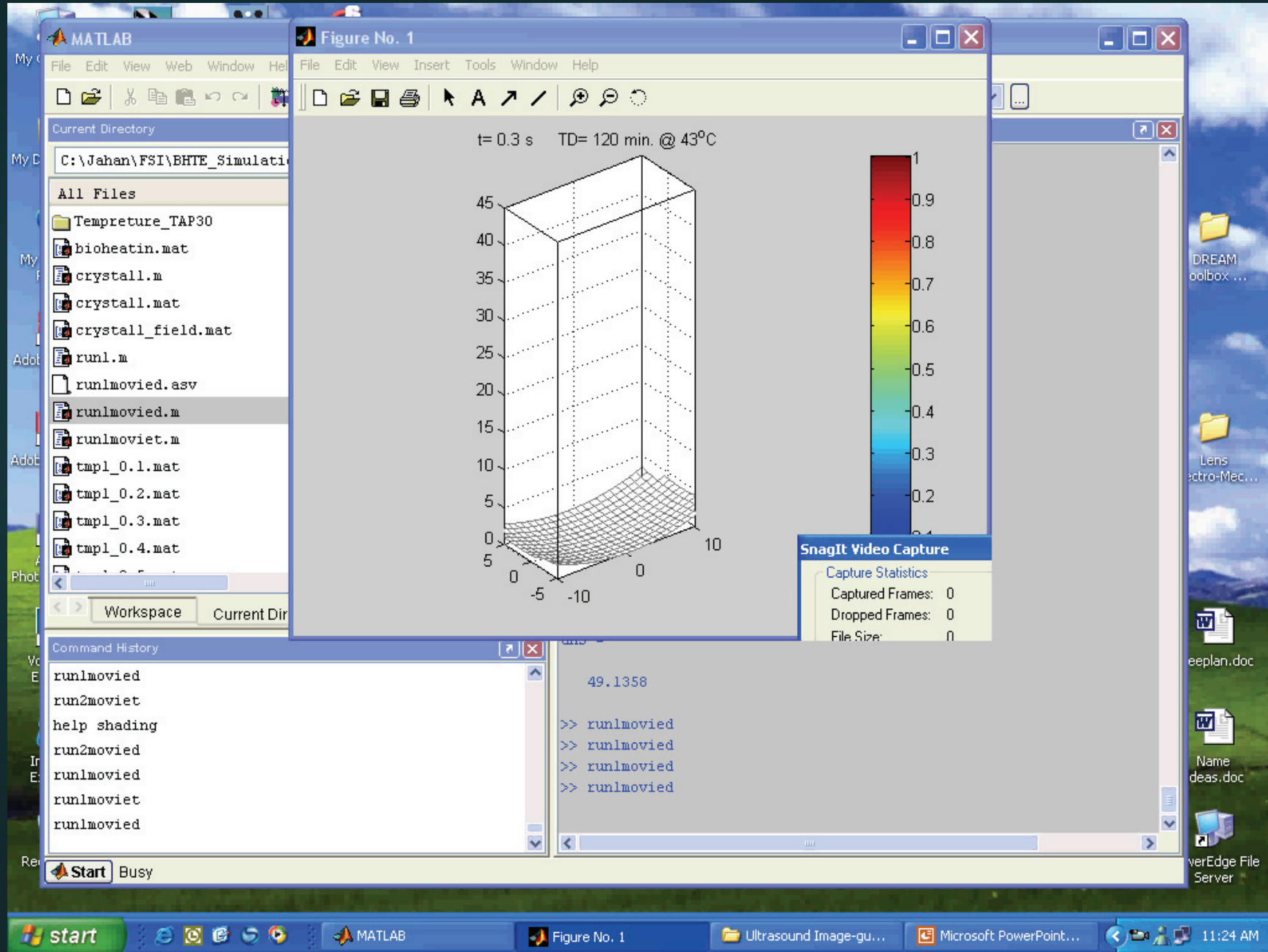
```
0.1000  
  
ans =  
  
46.0816
```

The MATLAB File Explorer shows the current directory as "C:\Jahan\FSI\BHTE_Simulati" and lists several files, including "Tempreture_TAP30" and various ".mat" and ".m" files.

The Windows taskbar at the bottom shows the Start button, several application icons, and the system tray with the time "11:26 AM".

Simulations – Thermal Dose

TD = 120 min @ 43°C



Simulations

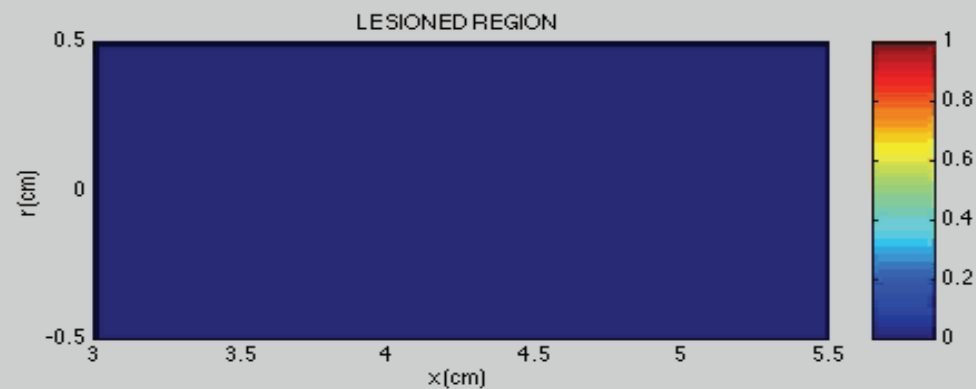
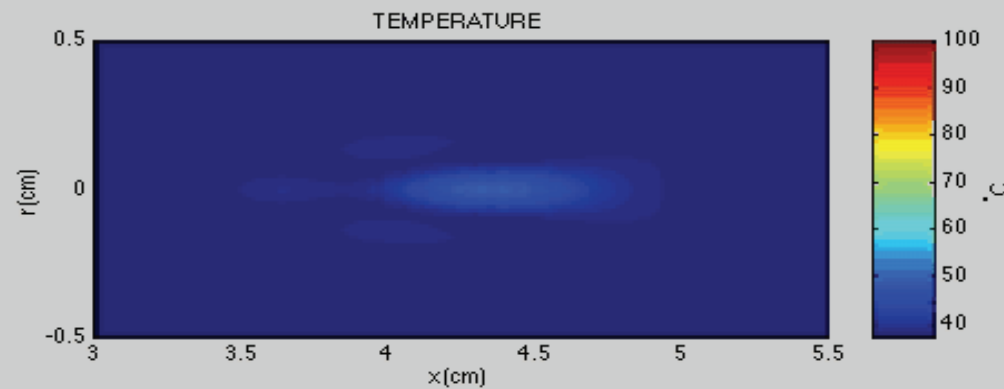
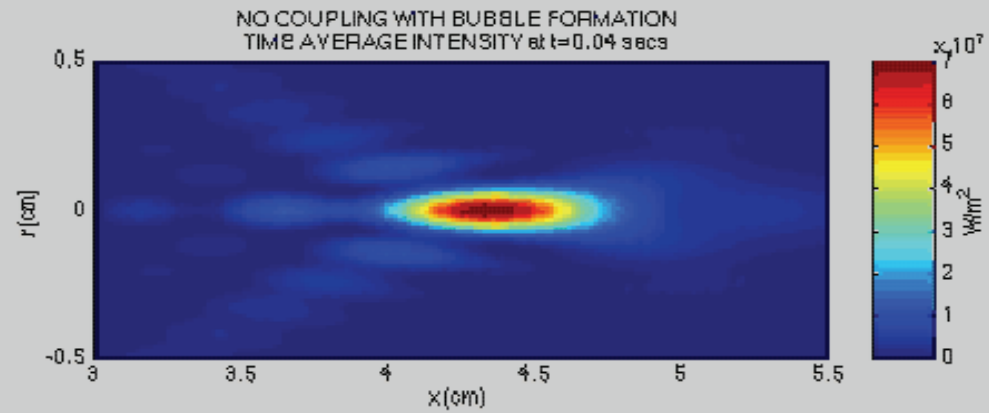
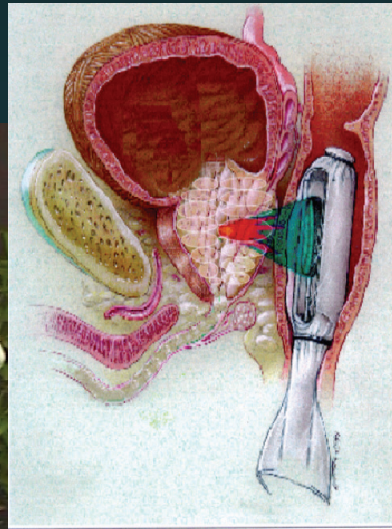


Image-guided HIFU Surgery

Target applications: oncology, cosmetic surgery, neurosurgery, and pain management



Sonatherm® 600
Misonix Inc., Farmingdale, NY



Sonablate® 500

Focus Surgery Inc., Indianapolis, IN



Xthetix®



Ultrasite GT

Guided Therapy Systems LLC, Mesa, AZ

HIFU for Prostate Cancer Treatment

Focus Surgery Inc., Indianapolis, USA



Sonablate® 500

- **Transrectal Approach (Minimally Invasive)**
- **Prostate Cancer and BPH Therapy**
- **Off-the-shelf Modules**
- **Totally Digital Platform**
- **CE and JIST Approved**
- **FDA Phase III Clinical Trials for Prostate Cancer is Undergoing**
- **More than 3000 Patients have been Treated to date Worldwide**

Prostate Cancer Treatment

Transrectal Image-guided HIFU Treatment of Prostate

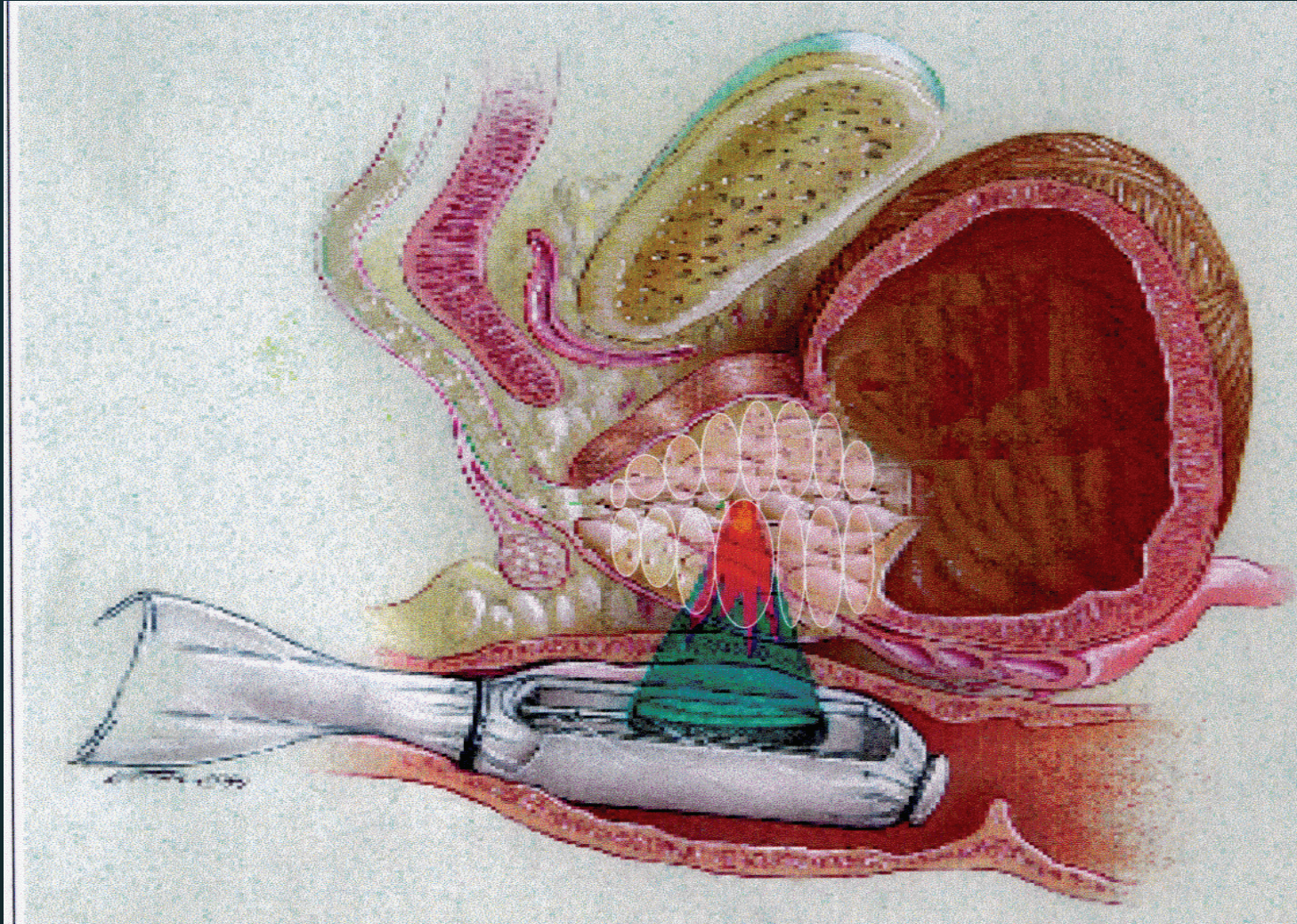
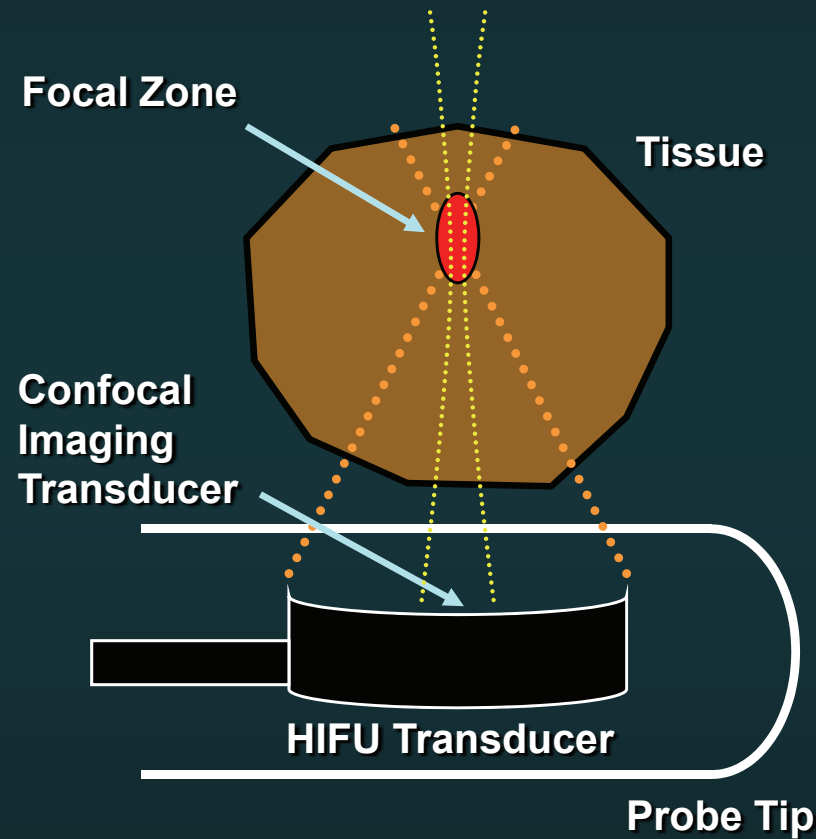


Image-guided HIFU Treatment of Prostate



Sonablate® Therapy

Sonablate 500 – HIFU Feedback Research Version 1.7FB (3.0) (c) 2000 Focus Surgery, Inc.

Site: **IU - LARC** Patient: **Dog1** Probe: **SN5001 4.0/3.0**

PREPARE IMAGE PLAN **• THERAPY** VOLUME



0:01:30



0:01:30

+2.12



0:00:00



0:00:00

+2.10

4.0

Grid Misc

Zone Zone

FB Cool

Dynamic power

30.0 watts [37.0]

STATUS

0:10:30 total
0:01:30 elapsed
0:09:00 remaining

94%

probe temperature
17.4 C
Sonablate pump chiller

reflectivity index
10

RF amplifier
0.0 [5.2-6.6] watts
2.4 seconds

Start HIFU therapy

Pause HIFU therapy

Scan Freeze Scan

Image verification **06/20/2001** Therapy verification **06/20/2001**

Status: **_AUTO_ saving screen to disk file...** May 6, 2002 10:57:43 AM

Sonablate® Real-time Imaging

Sonablate 500 -- HIFU Feedback Research Version 1.7FB [3.0] (c) 2000 Focus Surgery, Inc.

Site: IU - LARC Patient: Dog1 Probe: SN5001 4.0/3.0

PREPARE IMAGE PLAN **• THERAPY** VOLUME

4.0 A E

Grid Meas.

Zone Zone

FB Clear

0:10:30 total
0:01:48 elapsed
0:08:42 remaining

17%

probe temperature
17.2 C
SonaChill pump chiller

reflectivity index
3

RF amplifier
0.0[5.0,6.6] watts
2.9 seconds

STATUS

30.0 watts [37.0]

Image verification 06/20/2001 Therapy verification 06/20/2001

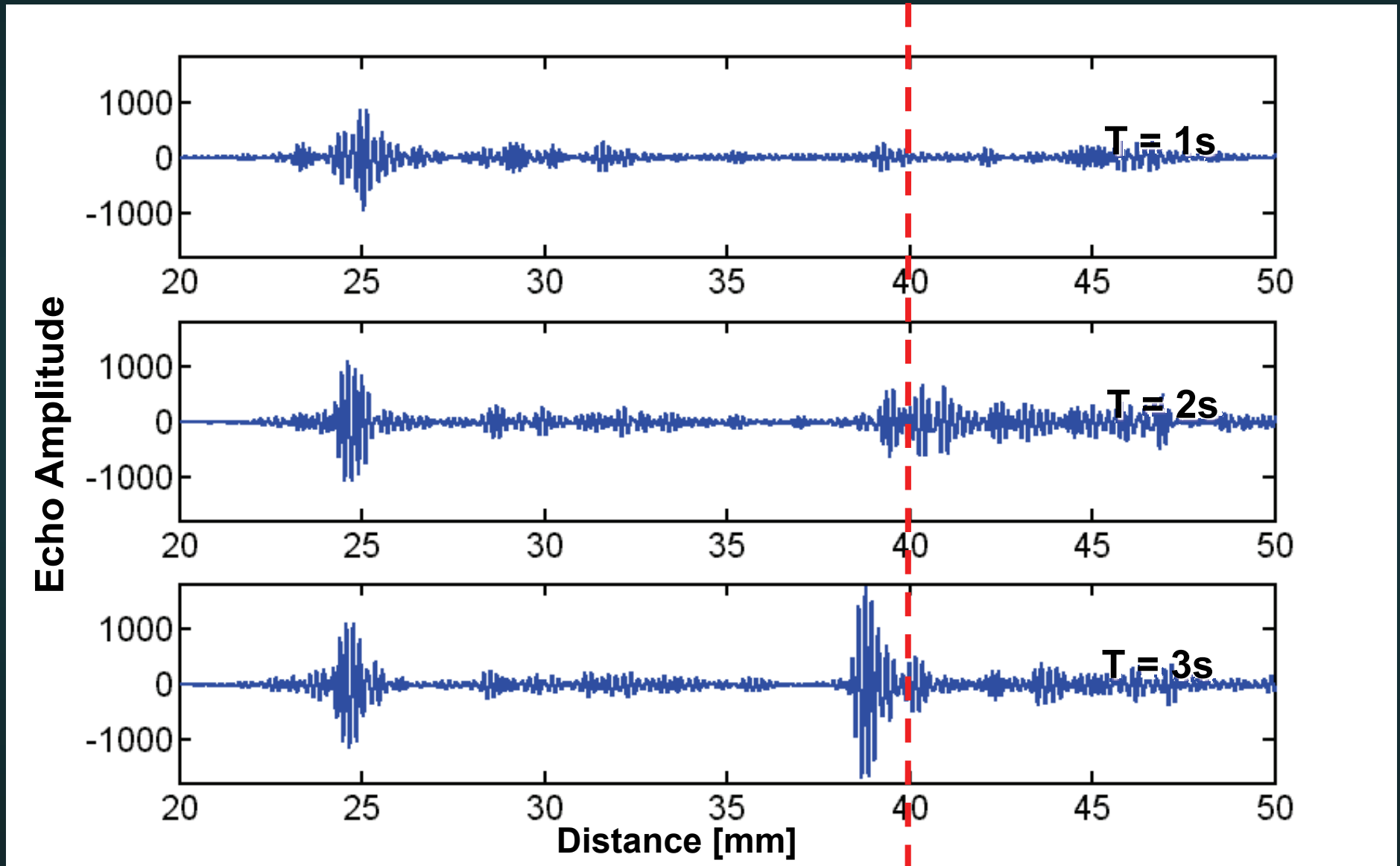
Start HIFU WWW Pause HIFU WWW

Scan Freeze Scan

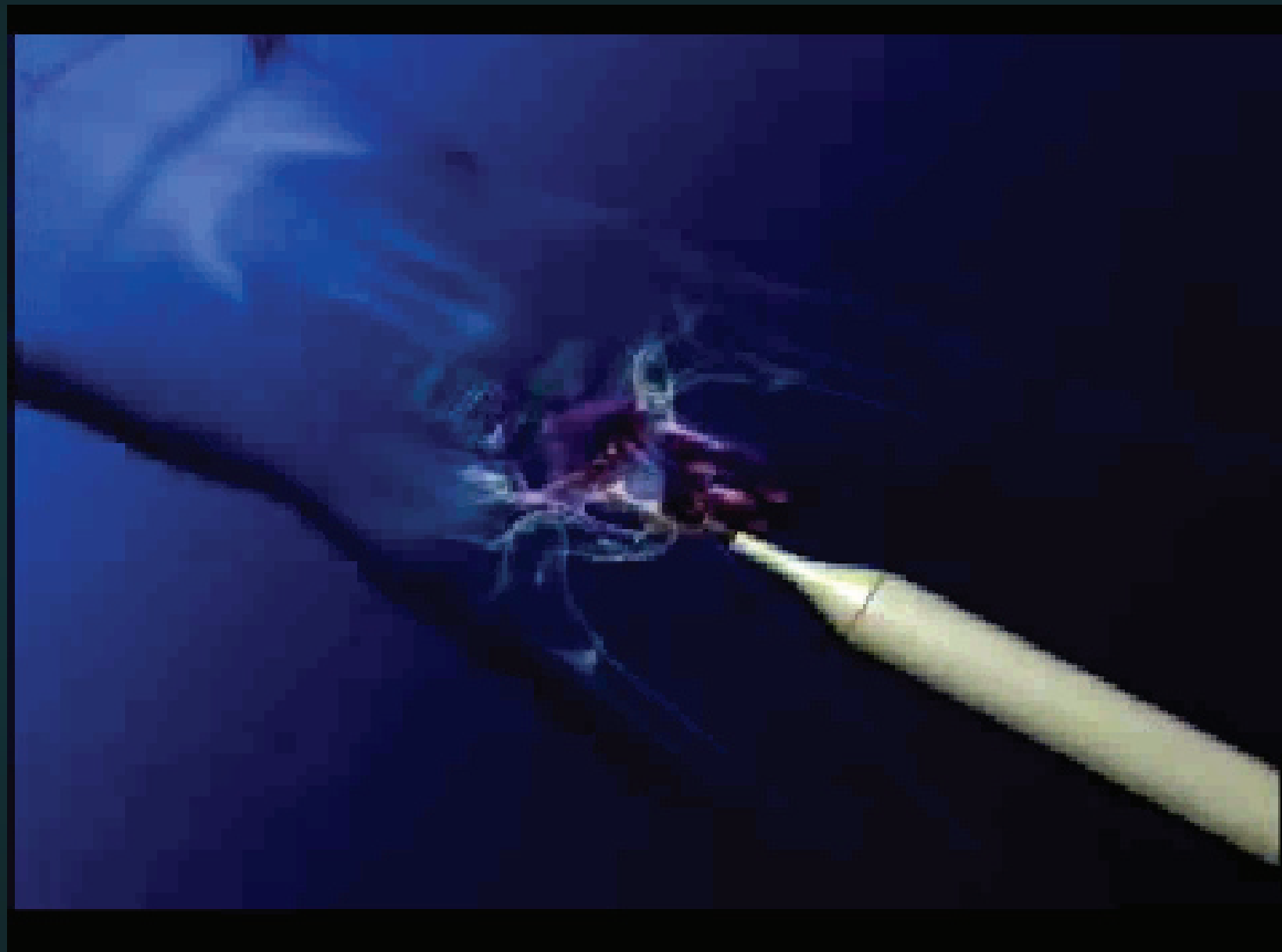
Status: _AUTO_ saving screen to disk file...

Image: May 6, 2002 10:58:01 AM

HIFU Lesion Detection – RF Data Processing



Sonablate® Treatment of Prostate Cancer



Conclusions

Ultrasound

- **Imaging**

 - Anatomical

 - Physiological

- **Therapy**

 - Bloodless Surgery

 - Non- or Minimally-invasive

 - Minimal Mortality and Morbidity

 - Cost Effective

- **An Active Area of Research and Development**

Acknowledgements



2008 Conference