ULTRASOUND
Sound Energy that can See and Treat

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RYERSON UNIVERSITY

Outline

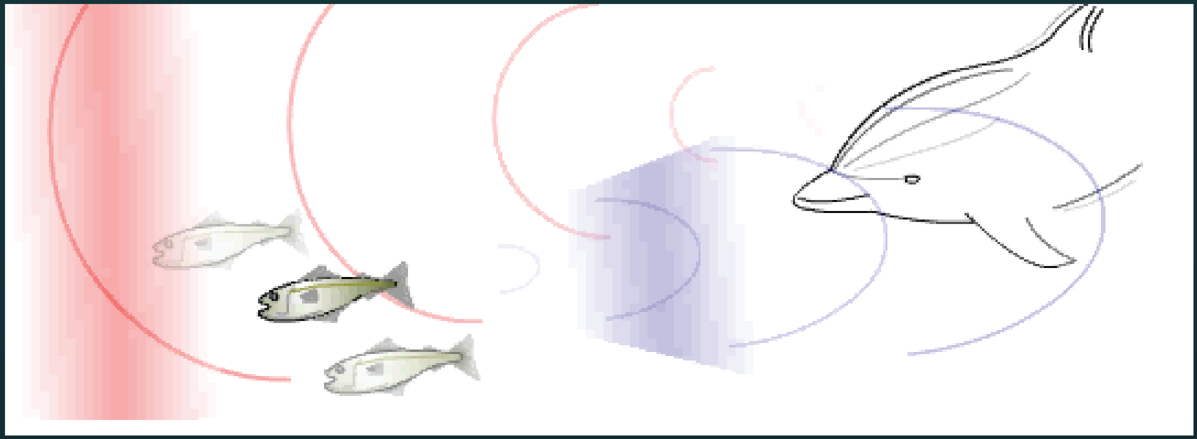
- **Introduction**
- **Diagnostic Ultrasound in Oncology**
  High-frequency Ultrasound Quantitative Imaging
- **Therapeutic Ultrasound in Oncology**
  High Intensity Focused Ultrasound (HIFU)

Ultrasound

Ultrasound is a sound energy with frequencies above human hearing threshold

f_0 > 20,000 Hz

In Nature

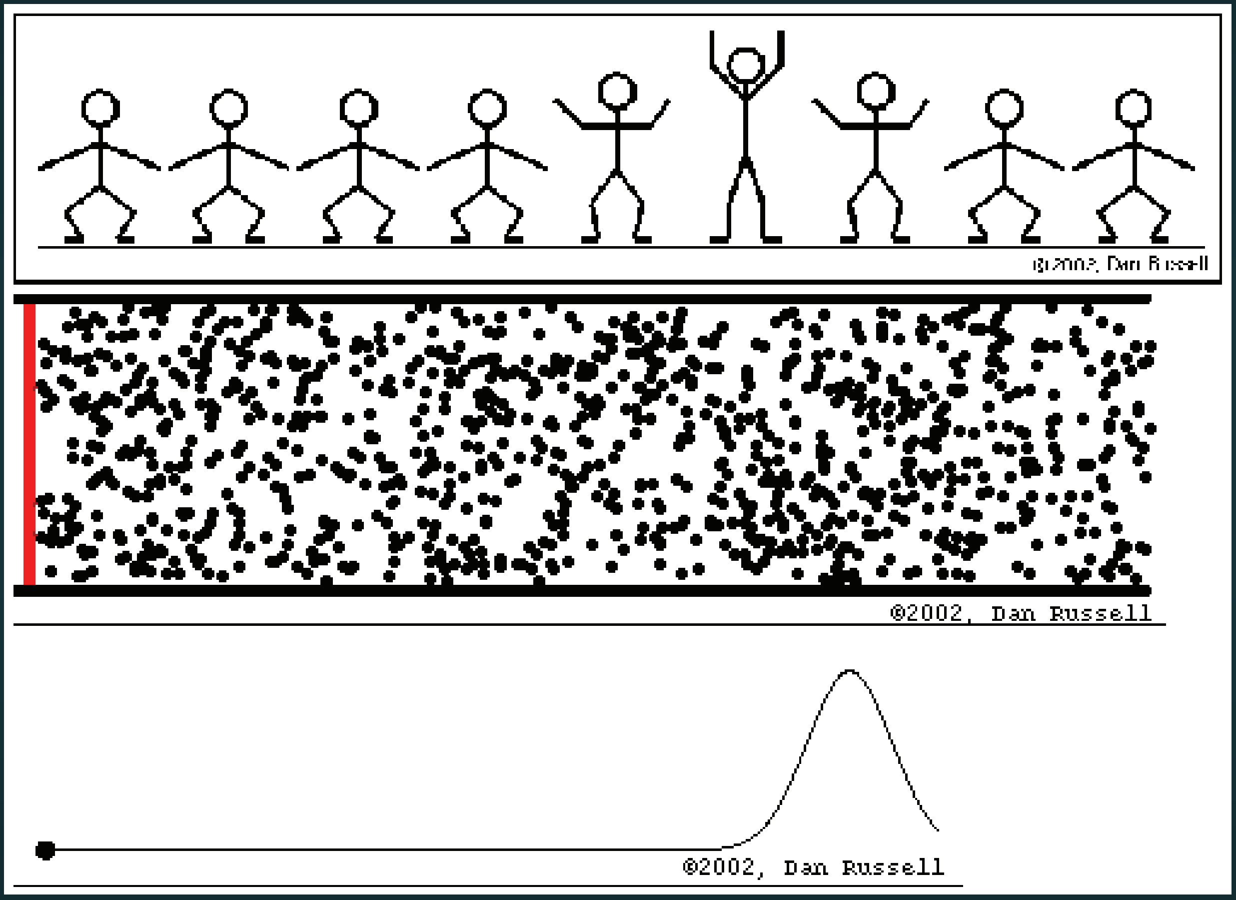


Dolphin Echolocation

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

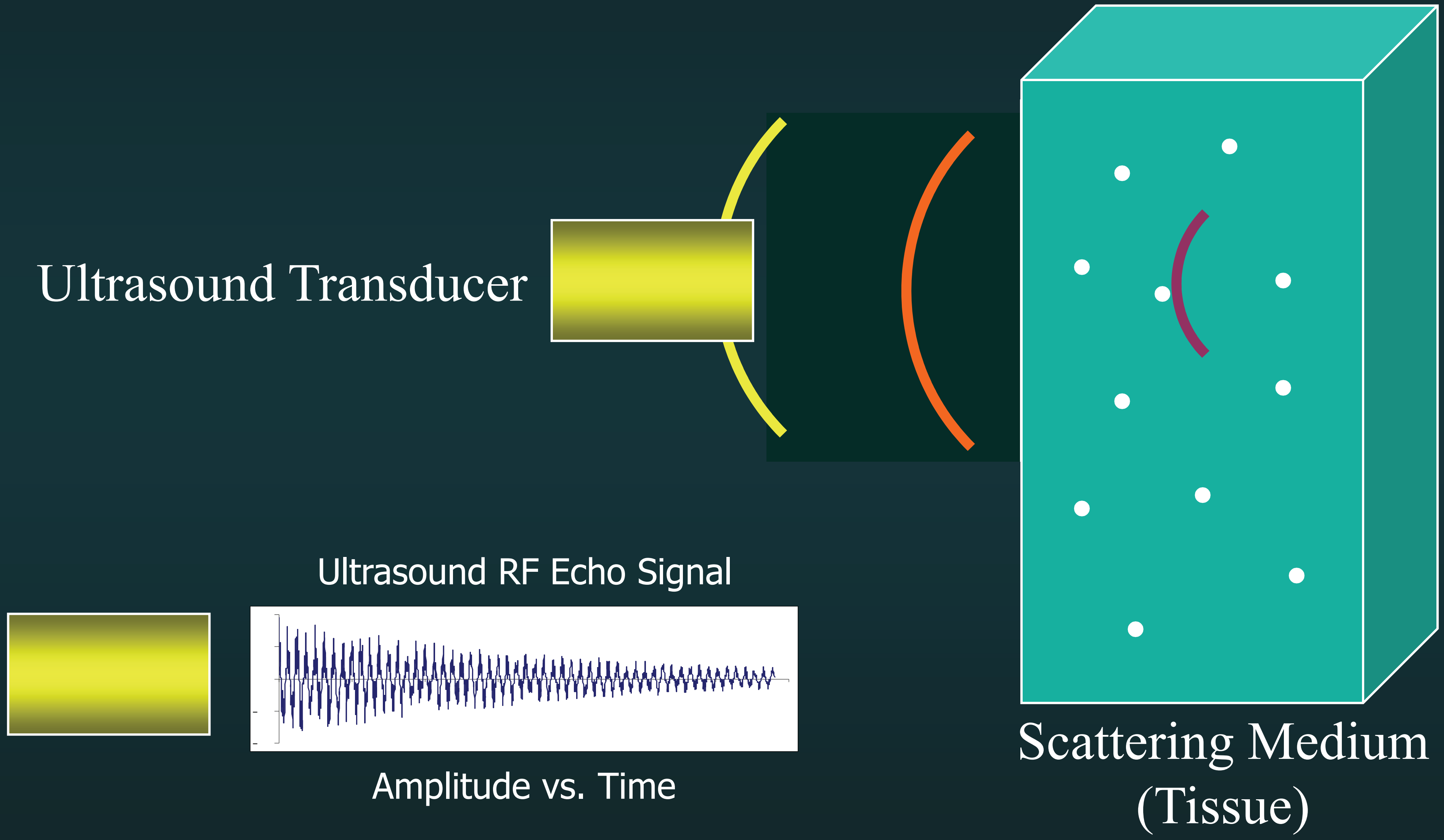
Non-ionizing, inexpensive, real-time

Ultrasound Scanners

Medium Frequency
3 – 15 MHz

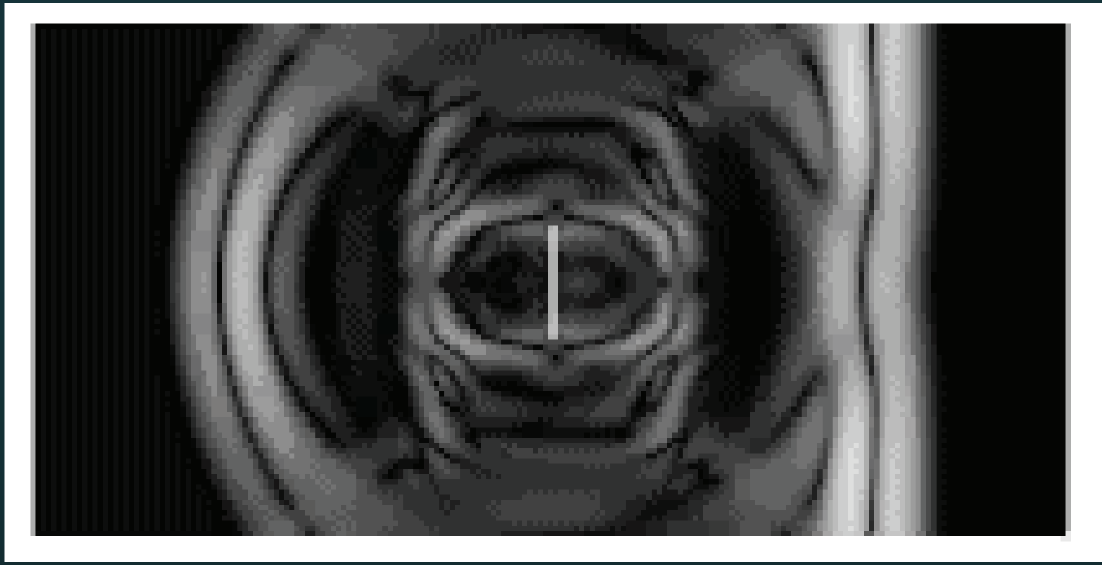
High Frequency
>20 MHz

Ultrasound Pulse-Echo Imaging
Scattering



Ultrasound Scattering

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

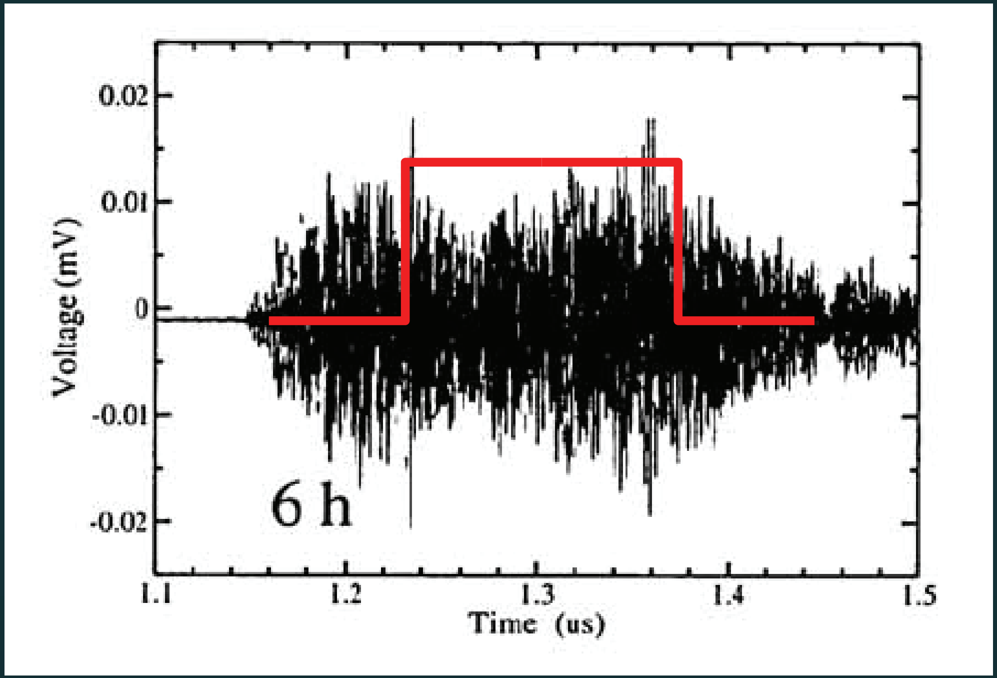


Wave3000®
CyberLogic Inc., New York, NY

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



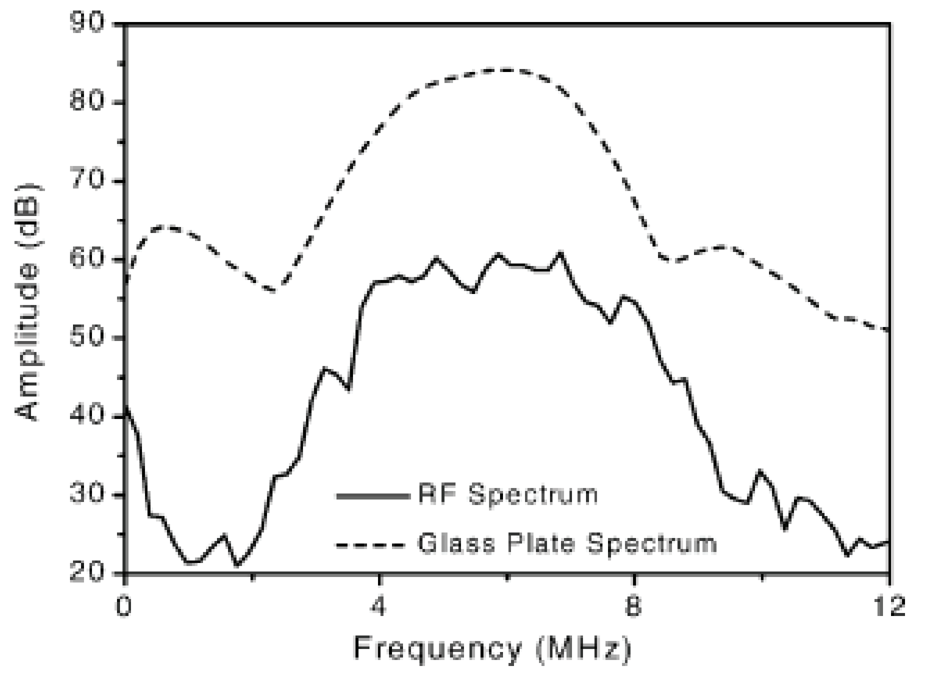


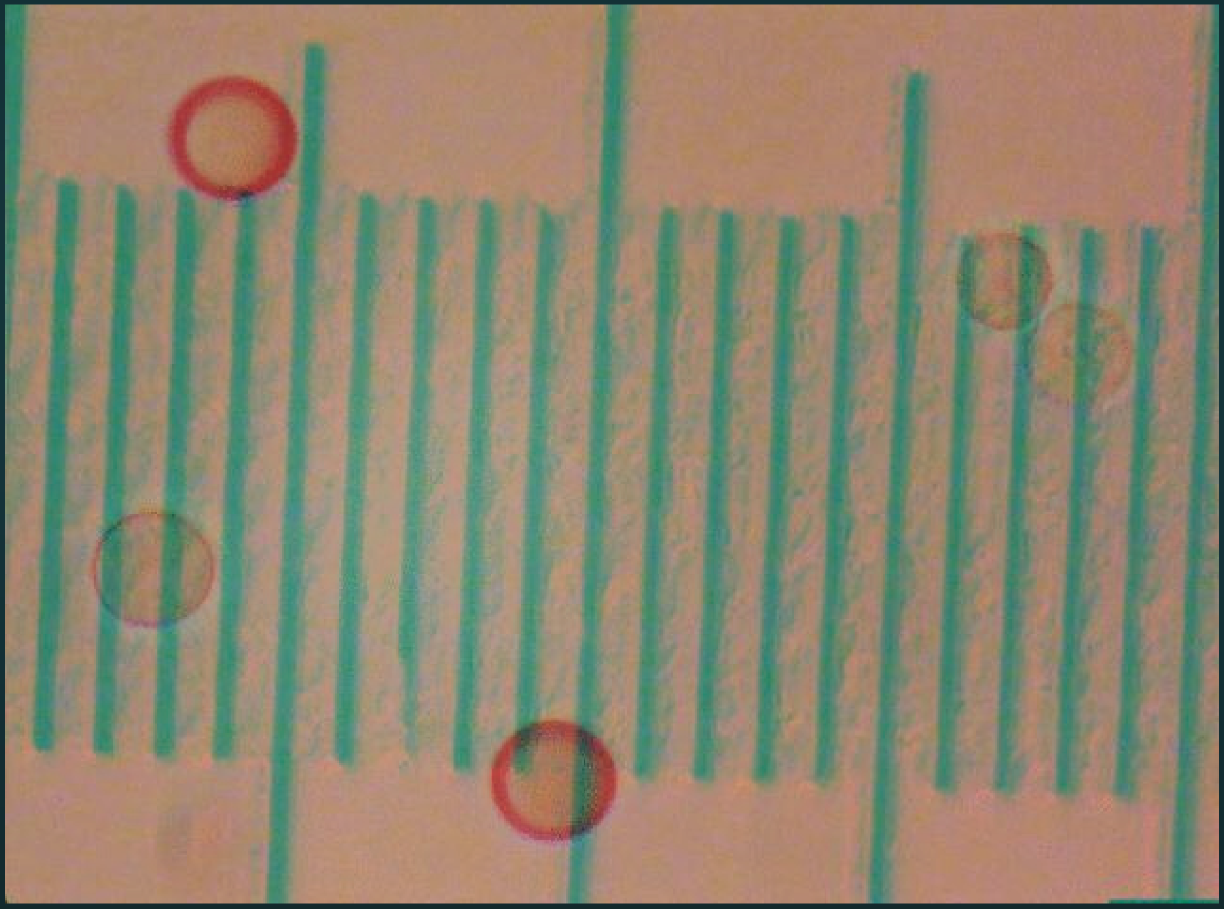
Fig. 3. RF tissue spectrum and calibration spectrum.

Quantitative Imaging!

Pattern Recognition Letters 24 (2003) 637–658

Experimental Scattering Model

- Polystyrene beads
- Diameter ~20 μm

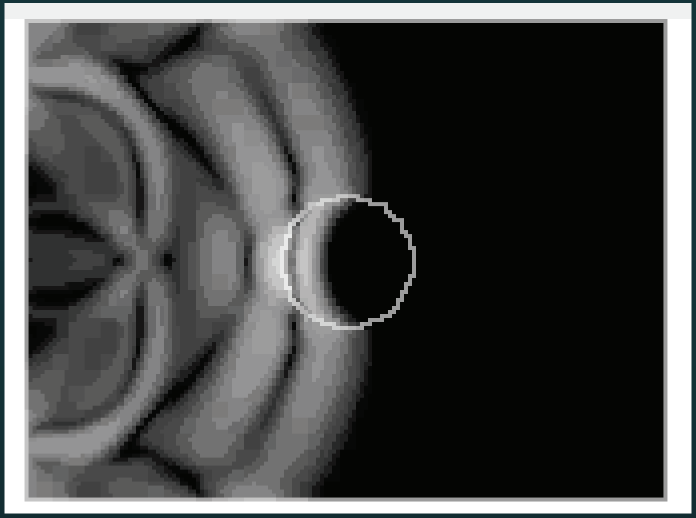


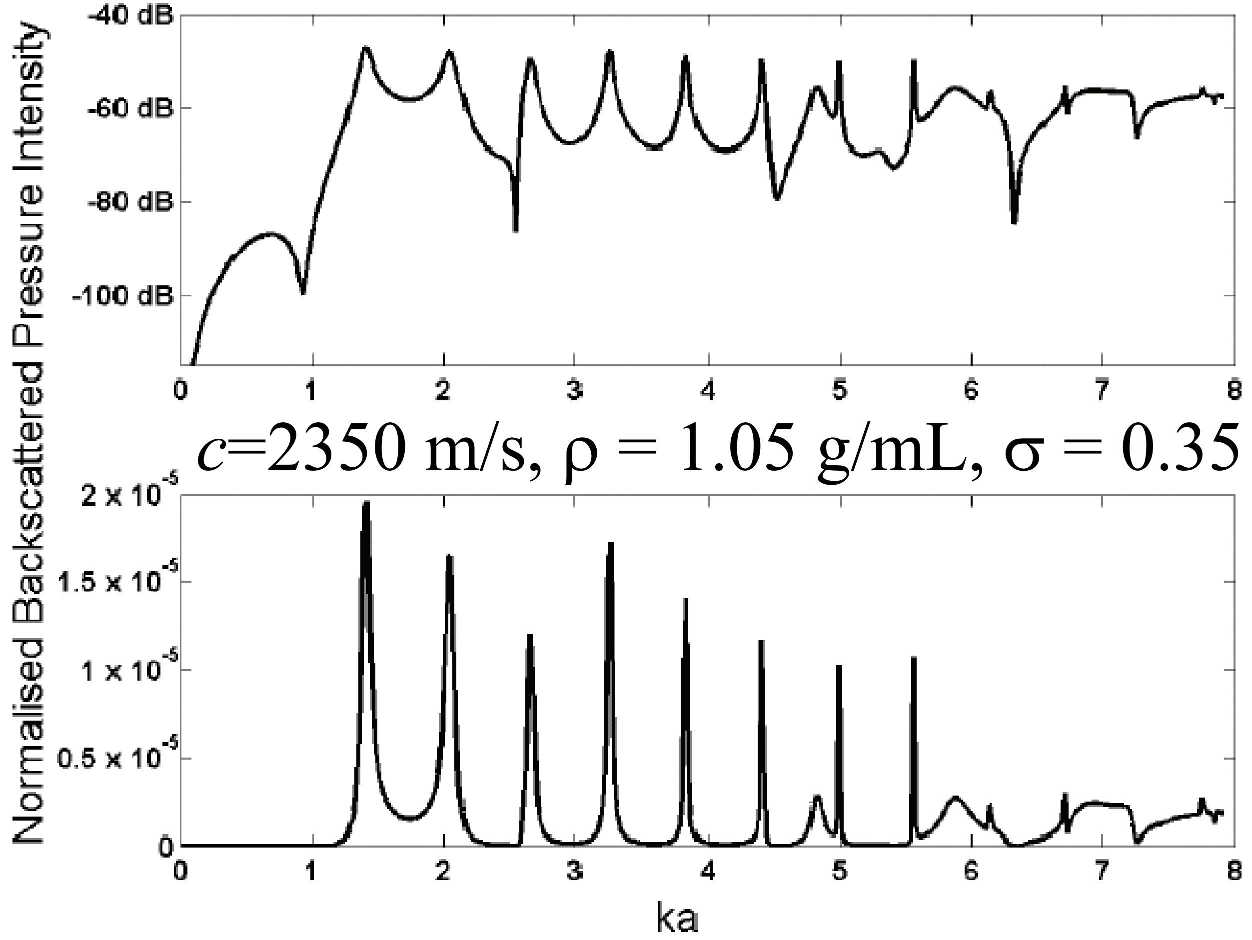
Baddour et. al. JASA (2005) 117(2), 934-943

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.)

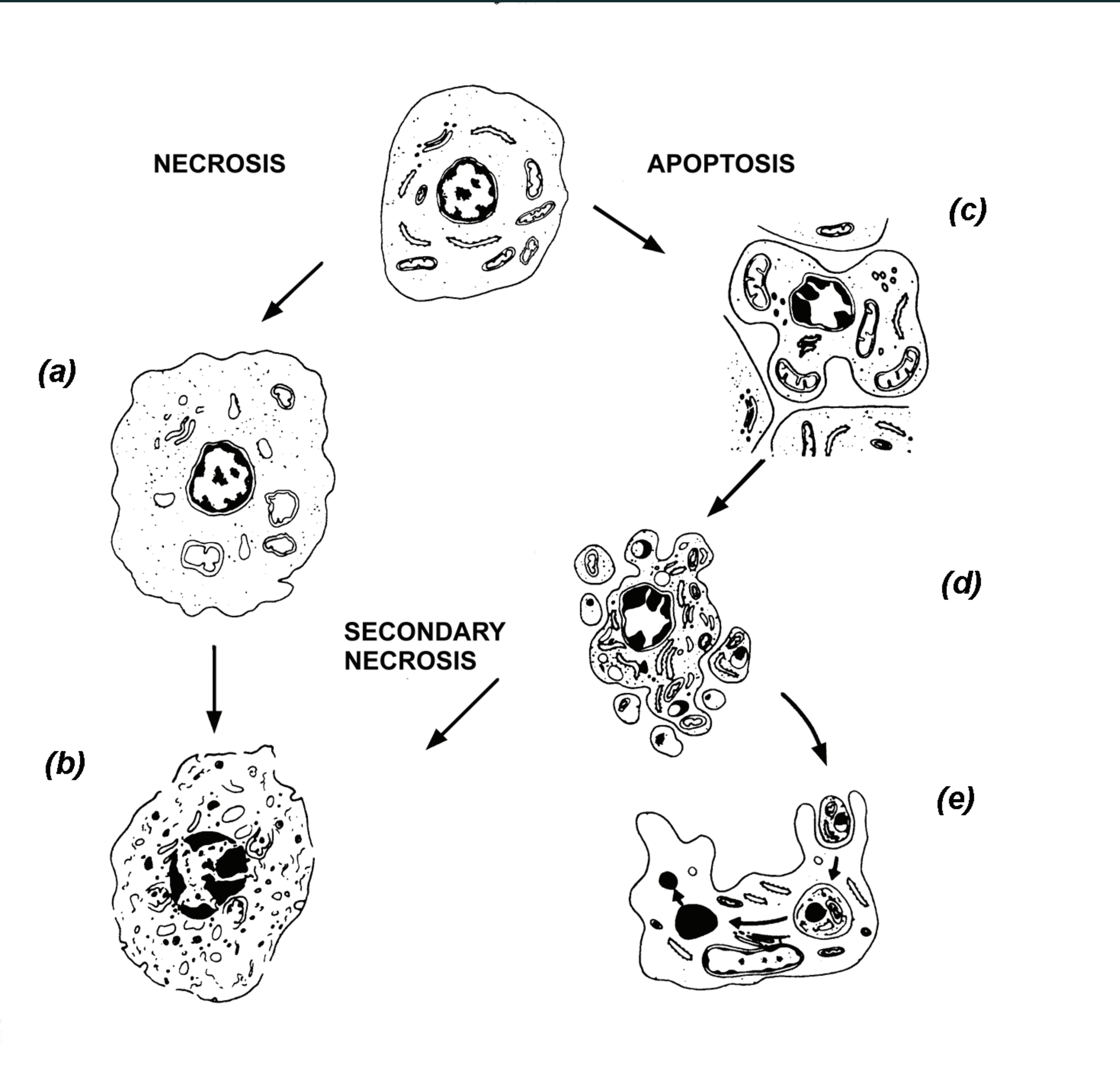
- Cell death is due to a combination of ***necrosis*** and ***apoptosis***

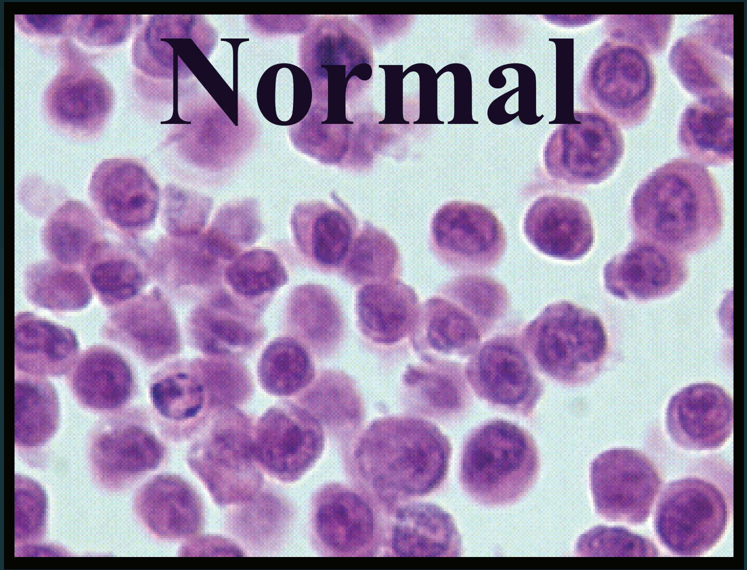
- Necrosis: Uncontrolled cell death
- Apoptosis: Programmed cell death

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



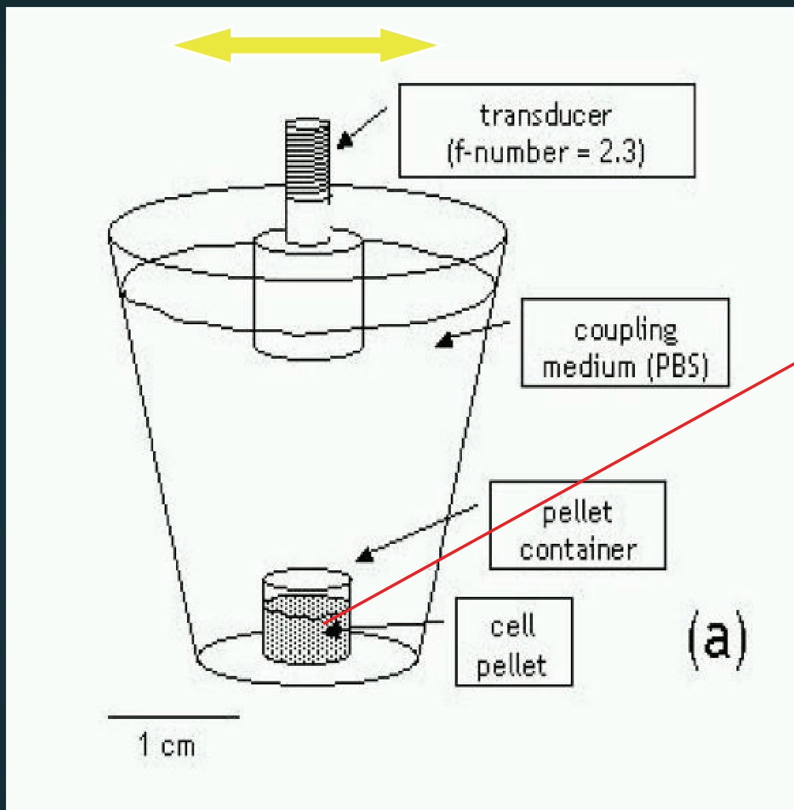


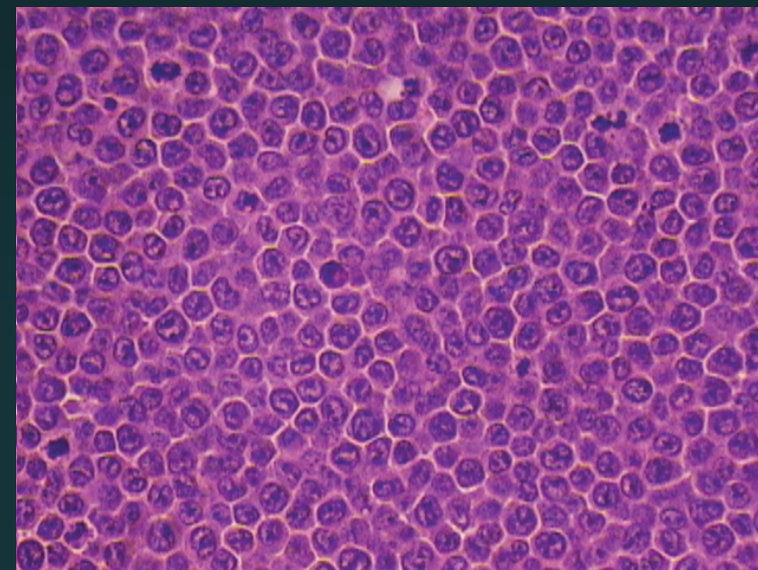
Why Would Ultrasound Backscatter be Sensitive to Cell Death?

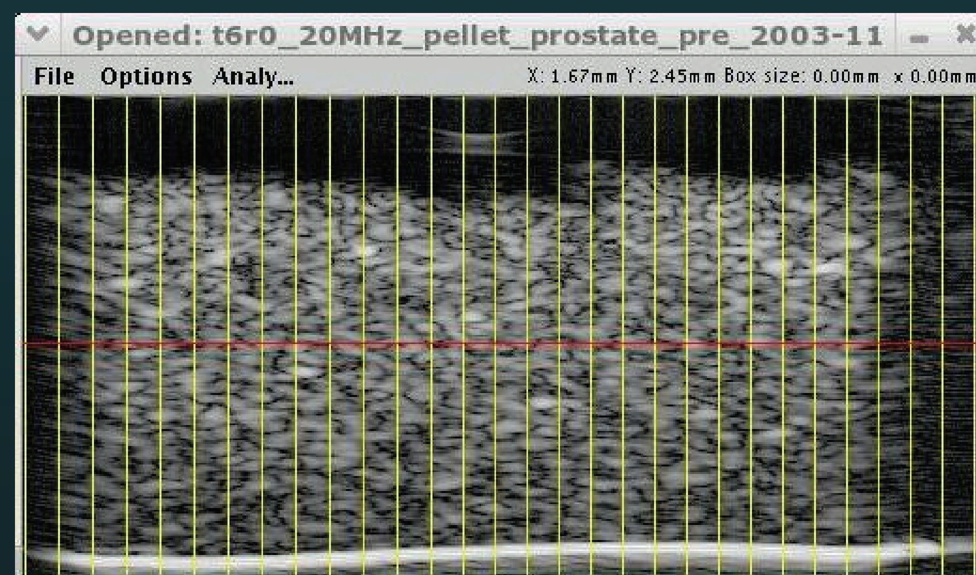
- Backscattering depends on scatterer size, physical attributes (density, compressibility), and spatial organization

- All of the above likely change during cell necrosis/apoptosis

High Frequency Ultrasound Imaging - Experimental Setup



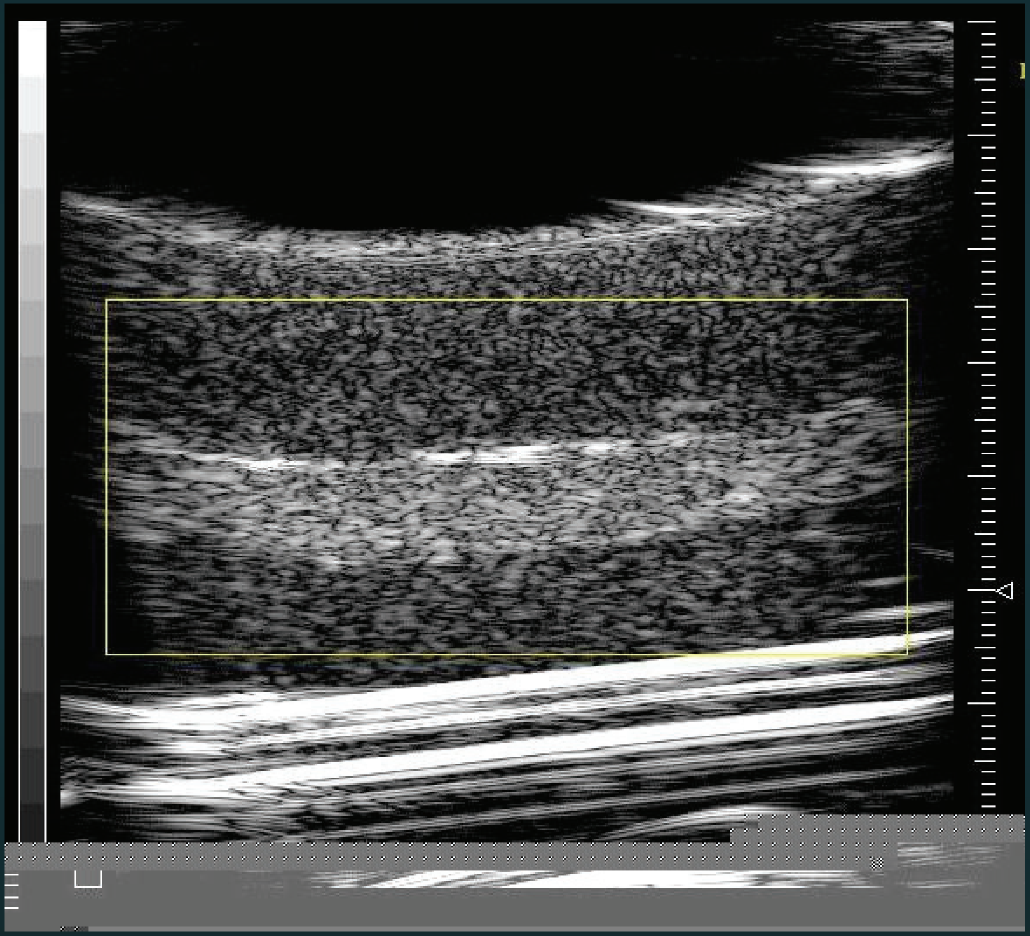




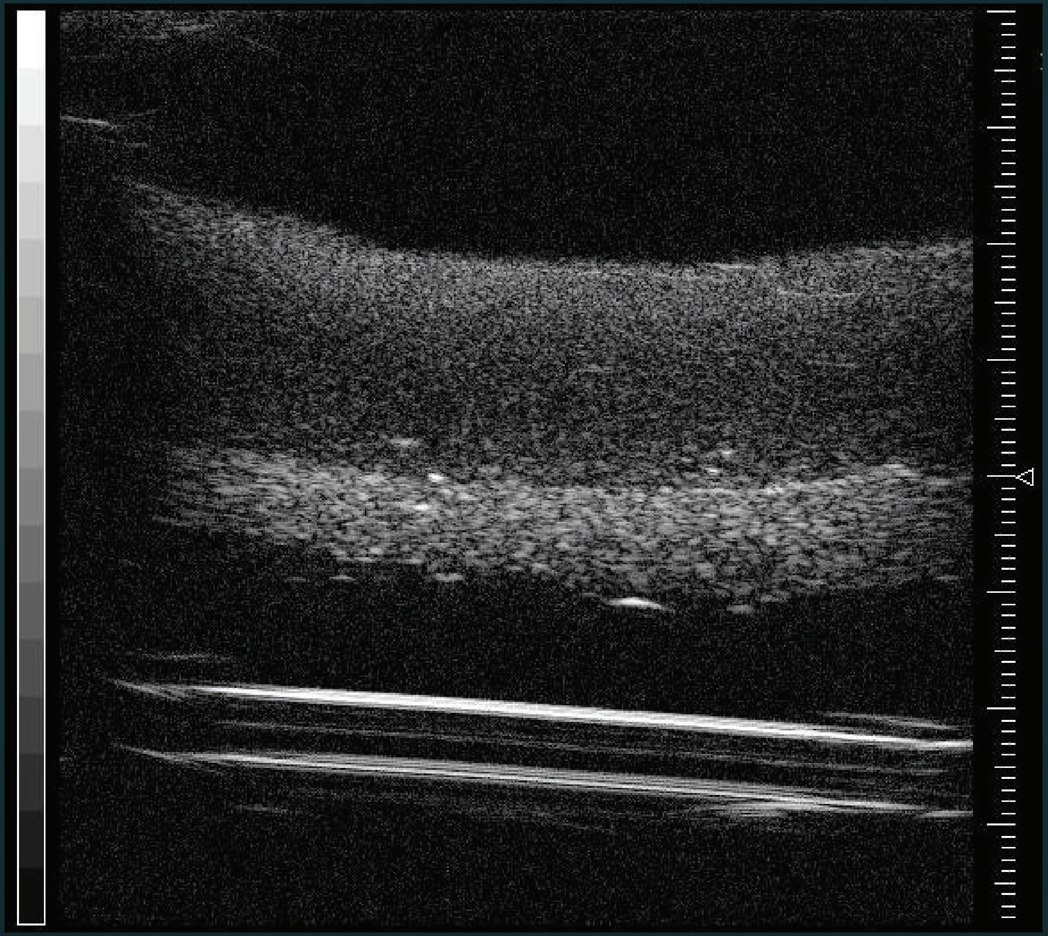
Acute Myeloid Leukemia (AML) Cancer Cells

Monitoring Cell Death

20 MHz data

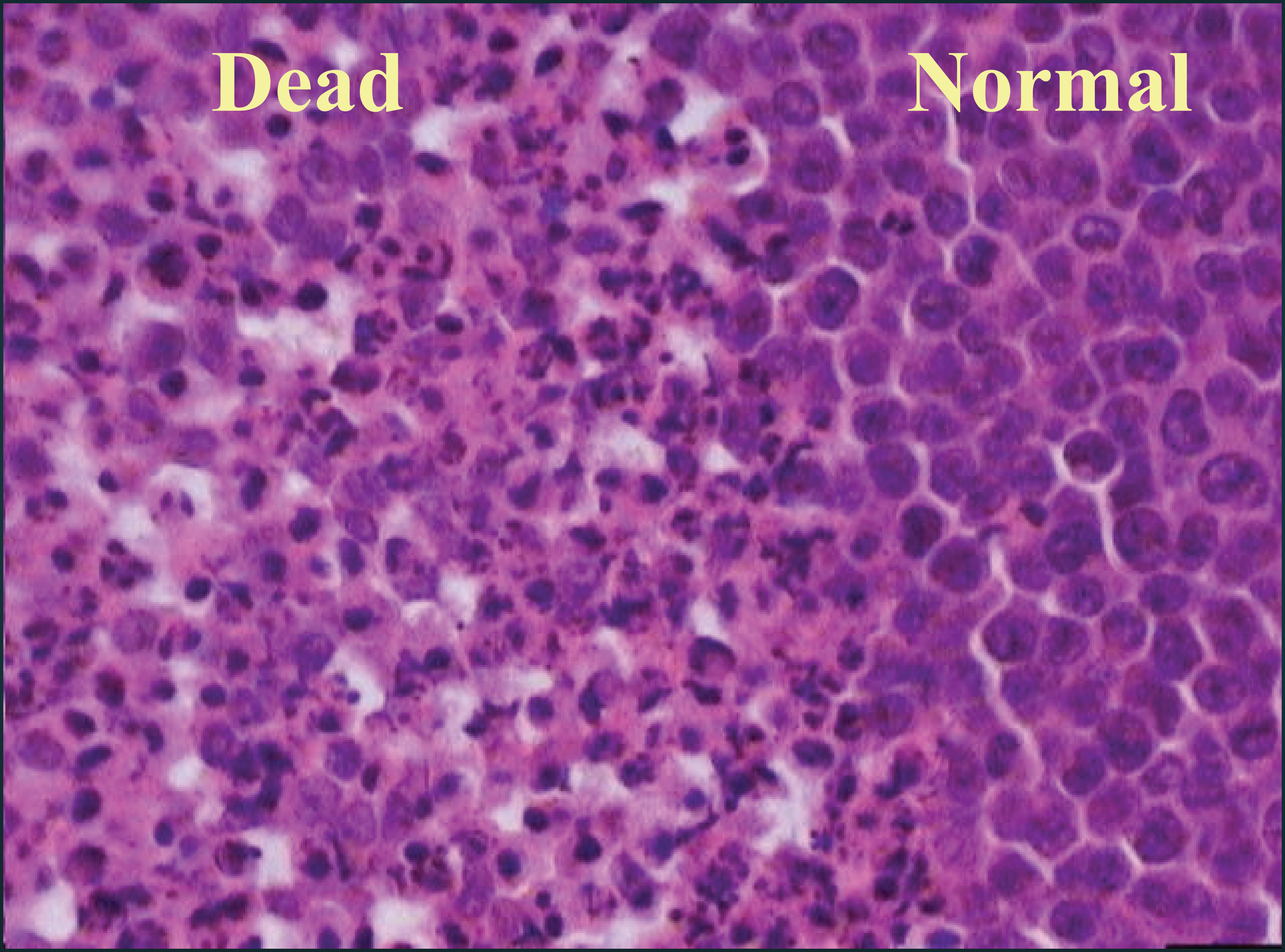


40 MHz data



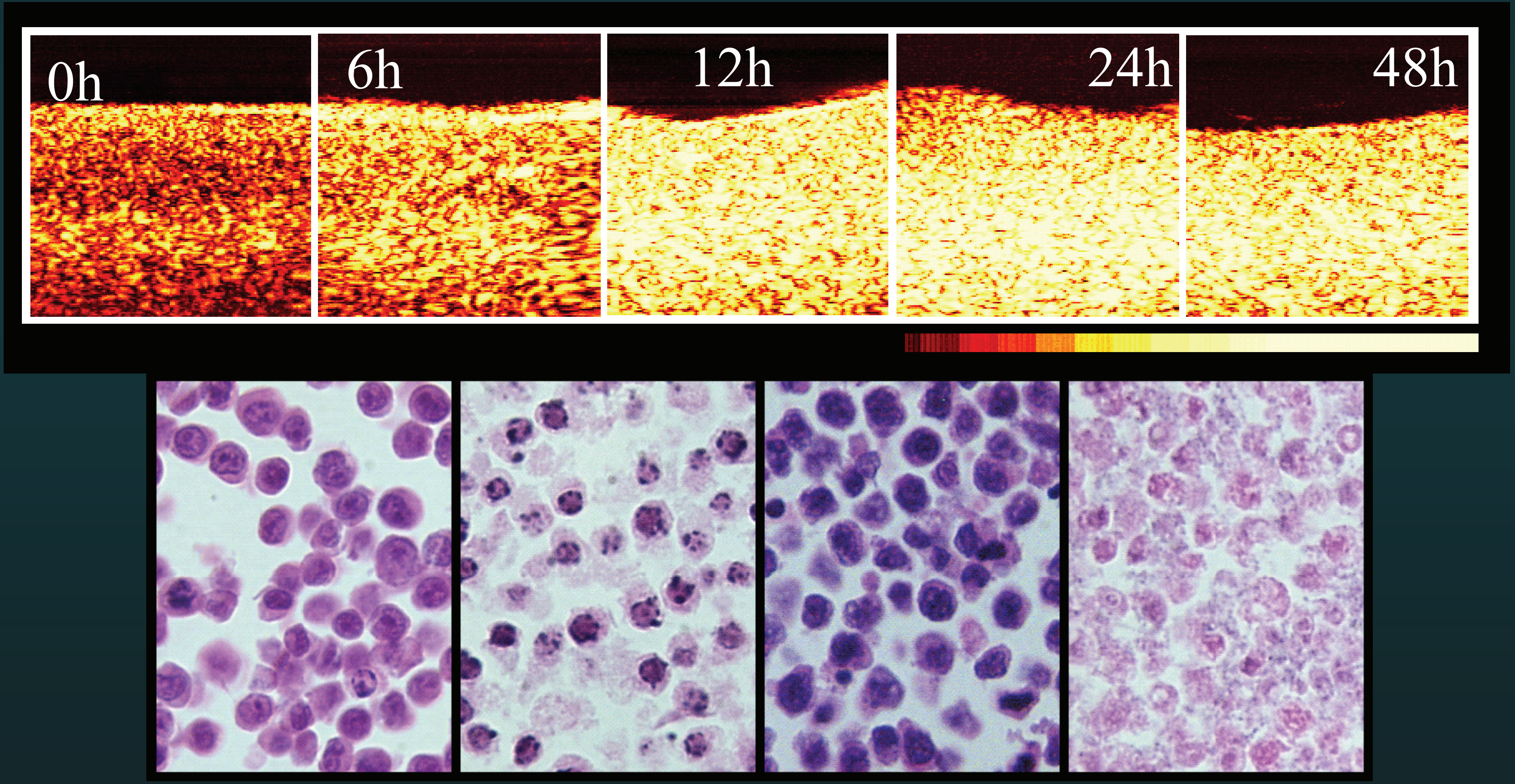
Layers: Non exposed (top) - exposed to 16h Cisplatin - non exposed (bottom)

Boundary Between Layers

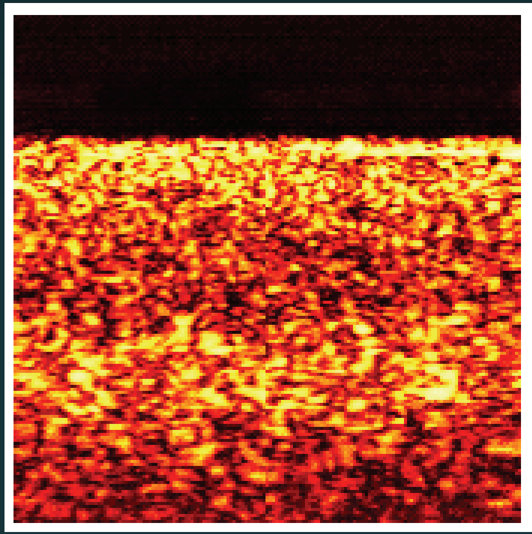


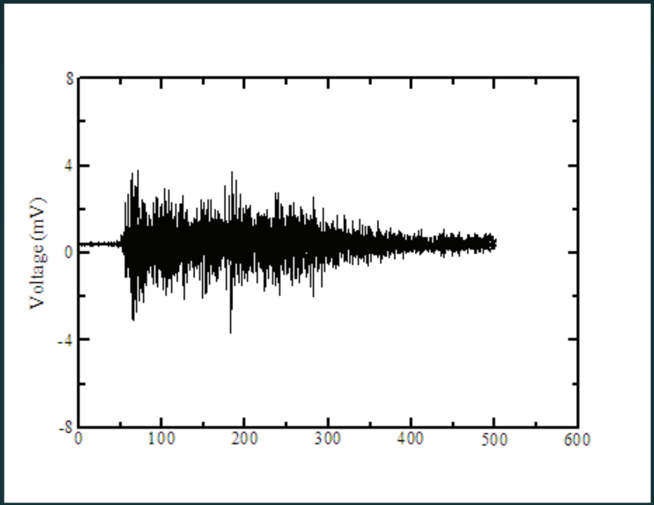
Results: Apoptosis in Cells Pellets

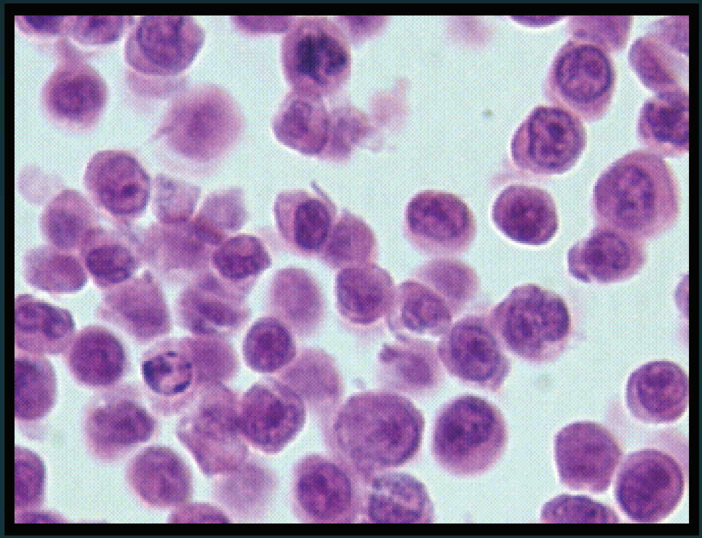
- AML cell pellets exposed to Cisplatin

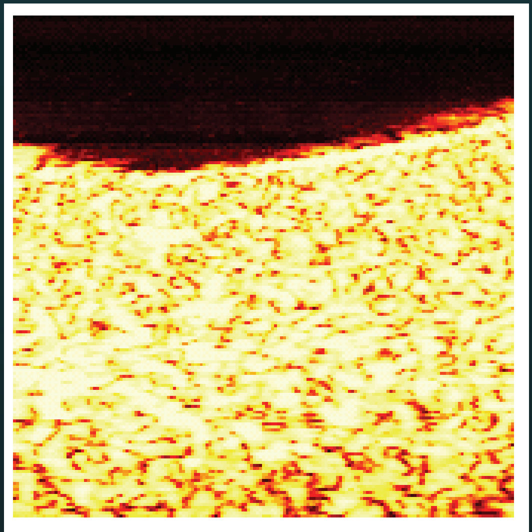


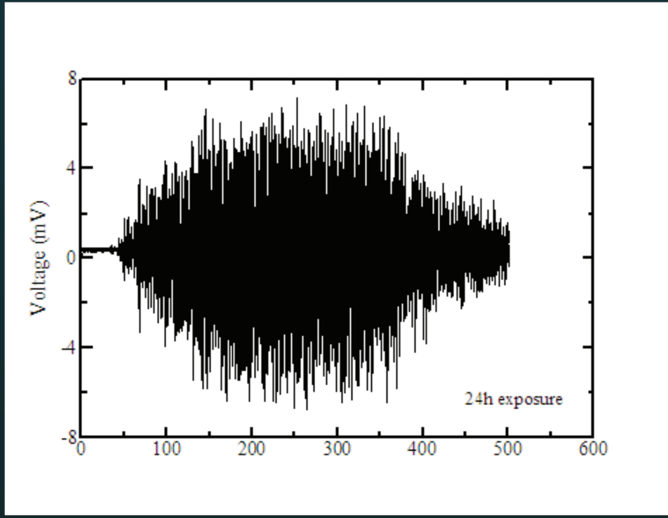
Results: Normal vs. Apoptotic Cell RF Data

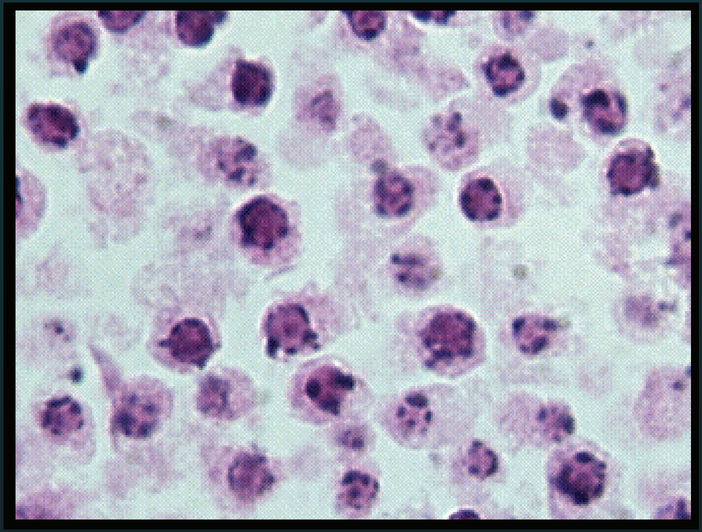






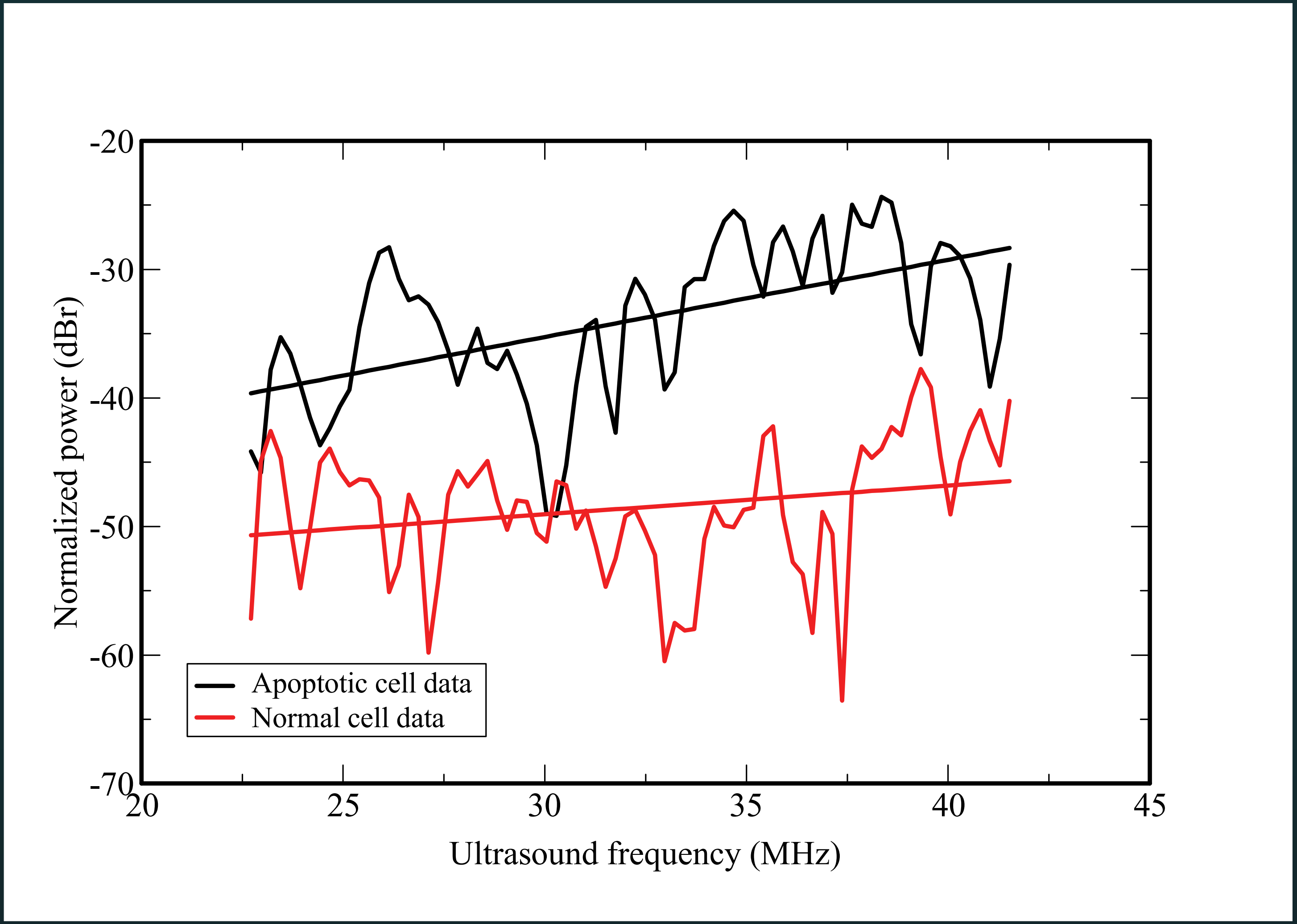






Results: Spectrum Analysis

- 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

IEEE

UFFC

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%

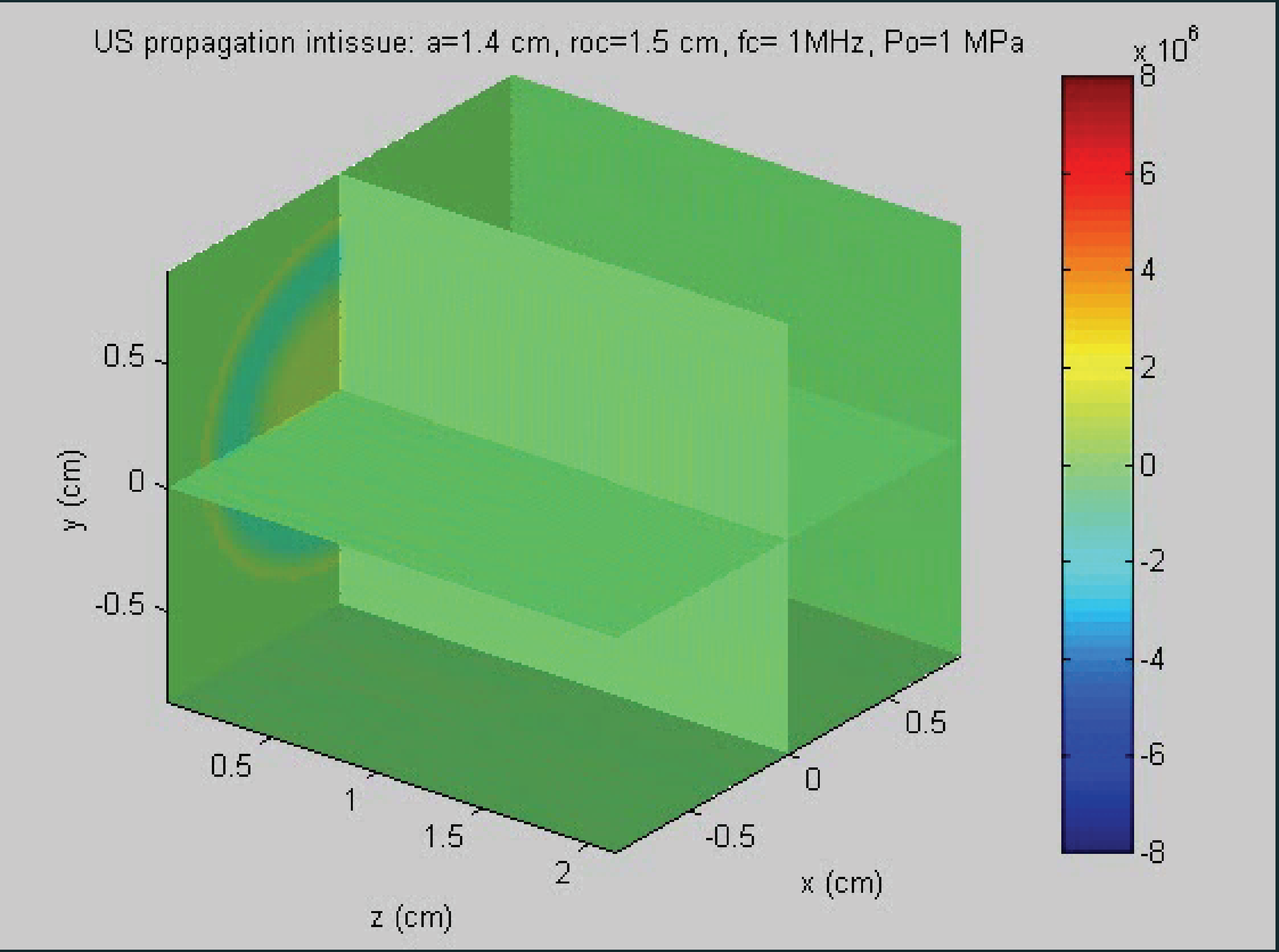
High Intensity Focused Ultrasound (HIFU)

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



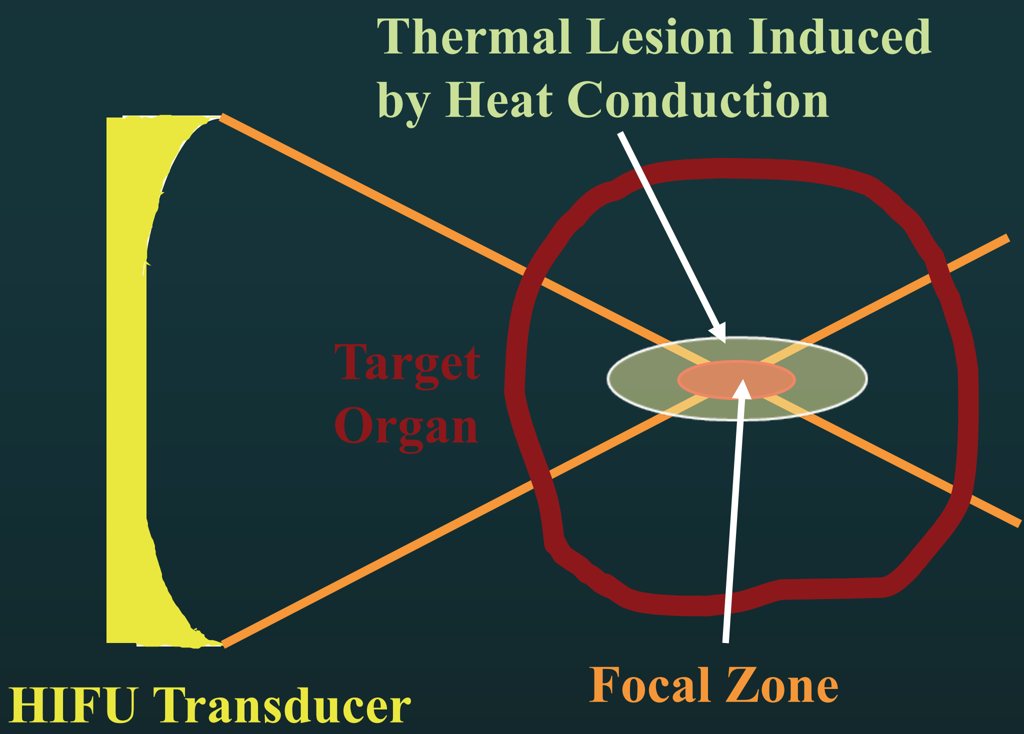
HIFU

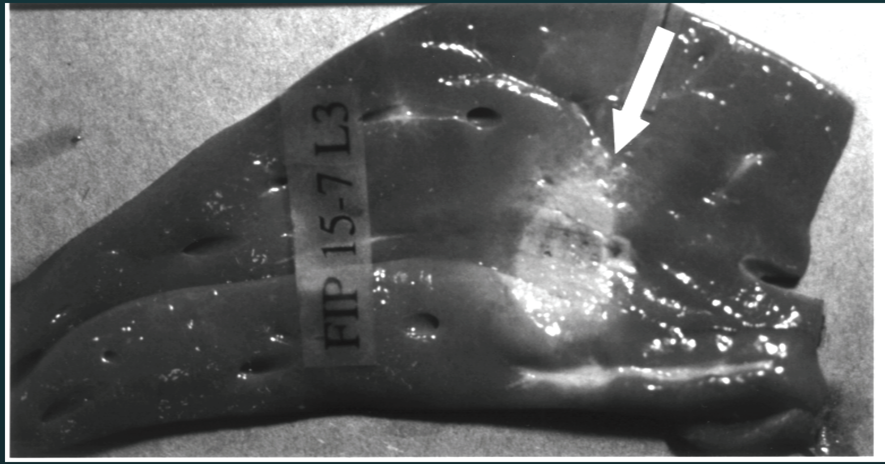
Main Features

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

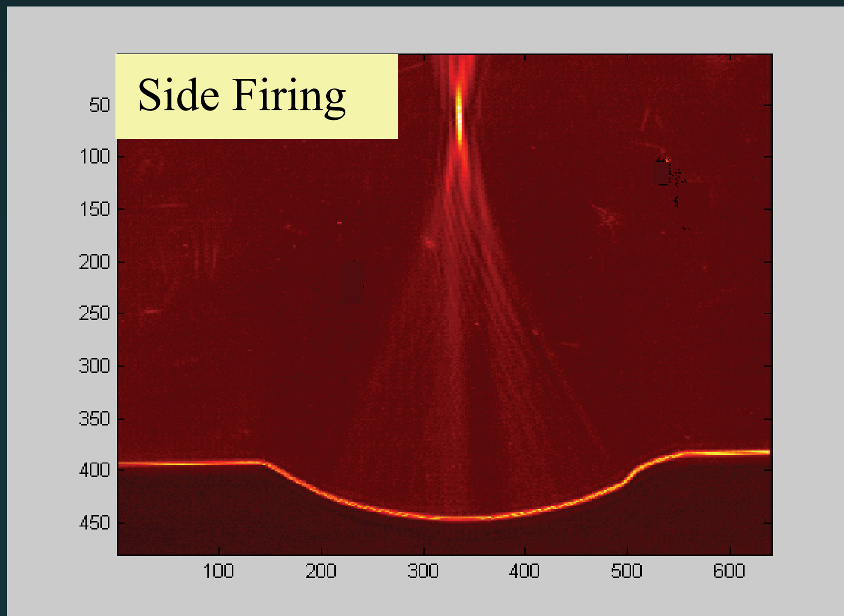


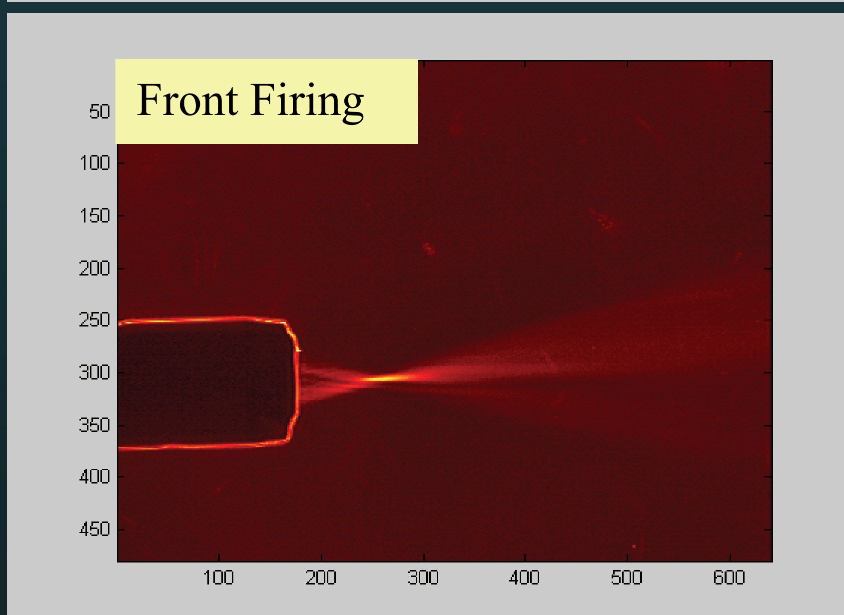


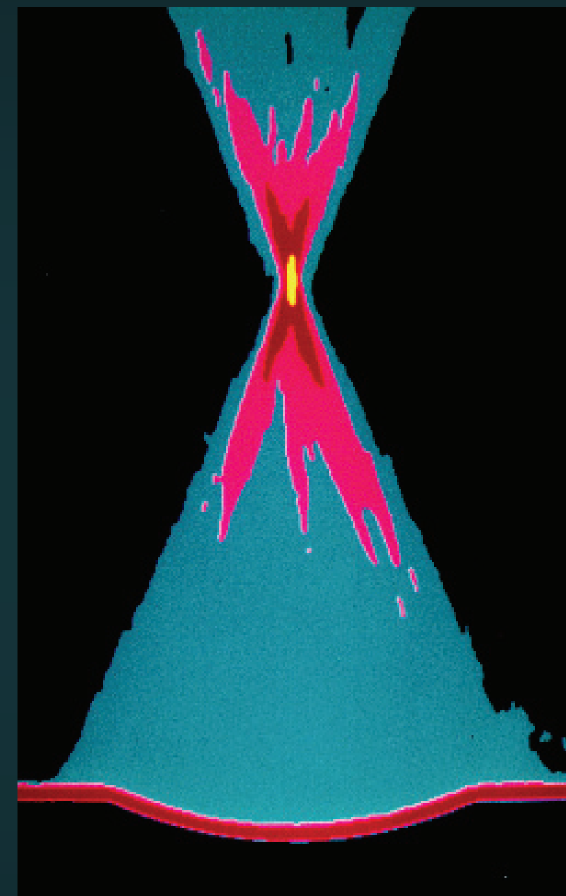
A HIFU lesion in pig’s liver

HIFU Field

Schlieren Images







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:

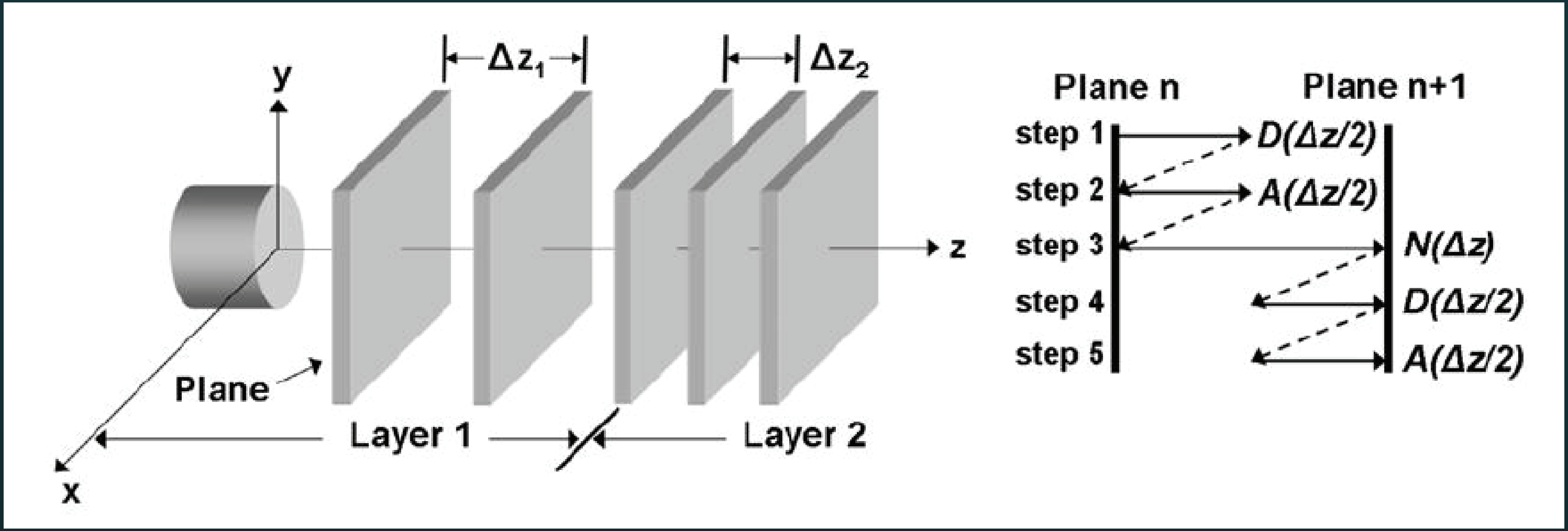
- Enhancing host antitumor immunity through expression of the tumor cells antigens (immunotherapy)

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:

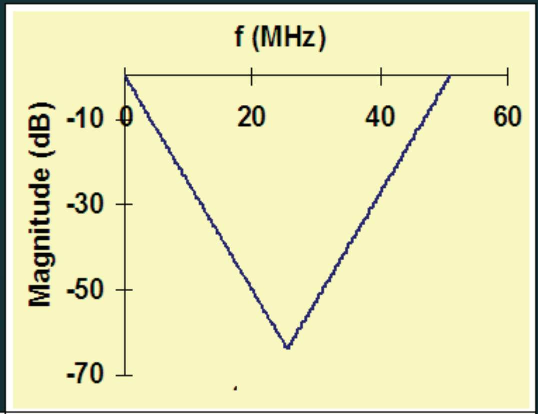
$$\left|G\left(e^{i\Omega}\right)\right| = \frac{1}{T}\exp\left[-\alpha(\Omega/T)\Delta z\right]$$

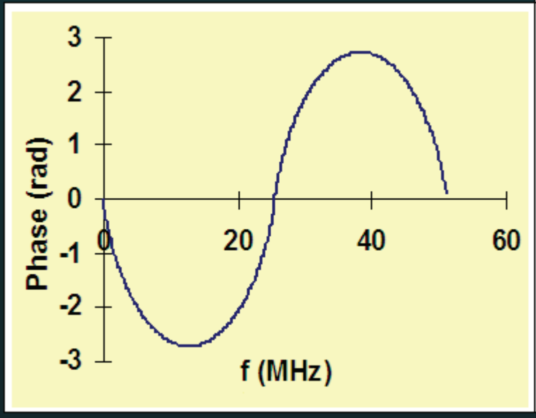
$$\arg\left[G\left(e^{i\Omega}\right)\right] = \frac{1}{2\pi} P\int_{-\pi}^{\pi} \ln\left|G\left(e^{i\theta}\right)\right| \mathrm{cotg}\left(\frac{\theta-\Omega}{2}\right) d\theta$$

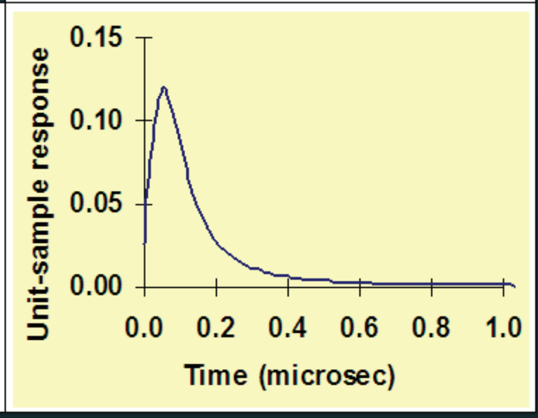
Medium = Liver

$$\alpha = 0.5\ dB / cm.MHz$$

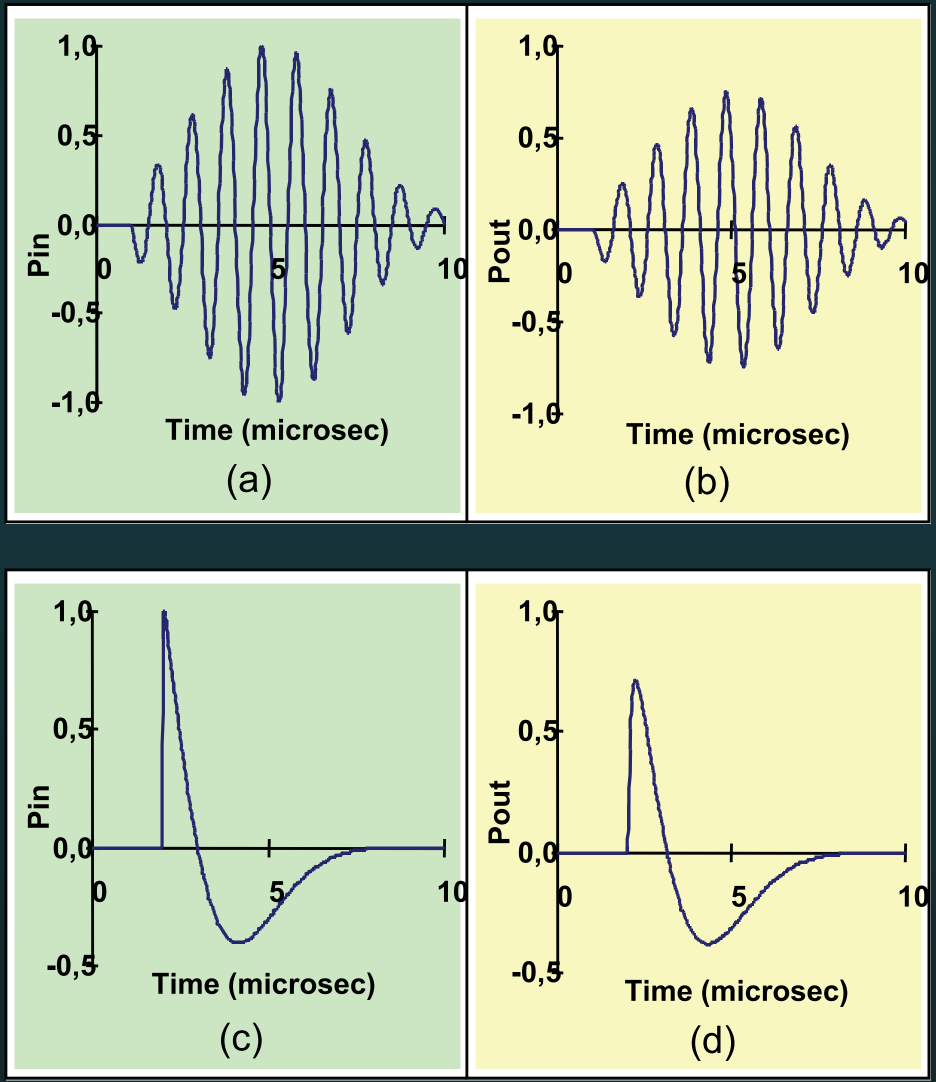
$$\Delta z = 5\ cm$$







Examples of application of the attenuator filter



Nonlinearity

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

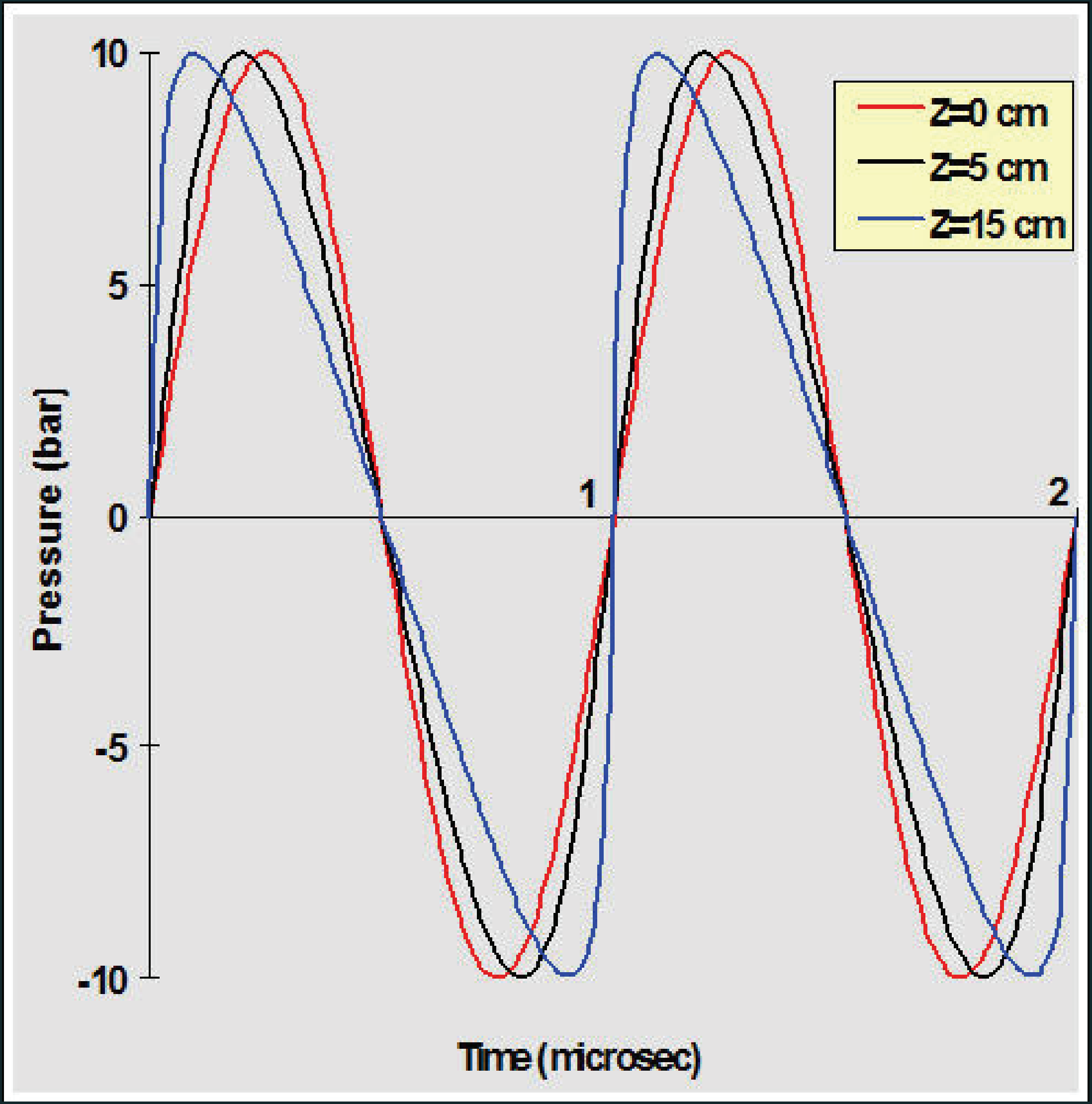
$$\frac{\partial v}{\partial z} = \frac{\beta}{c_0^2} v \frac{\partial v}{\partial \tau} \equiv \hat{L}_N v$$

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



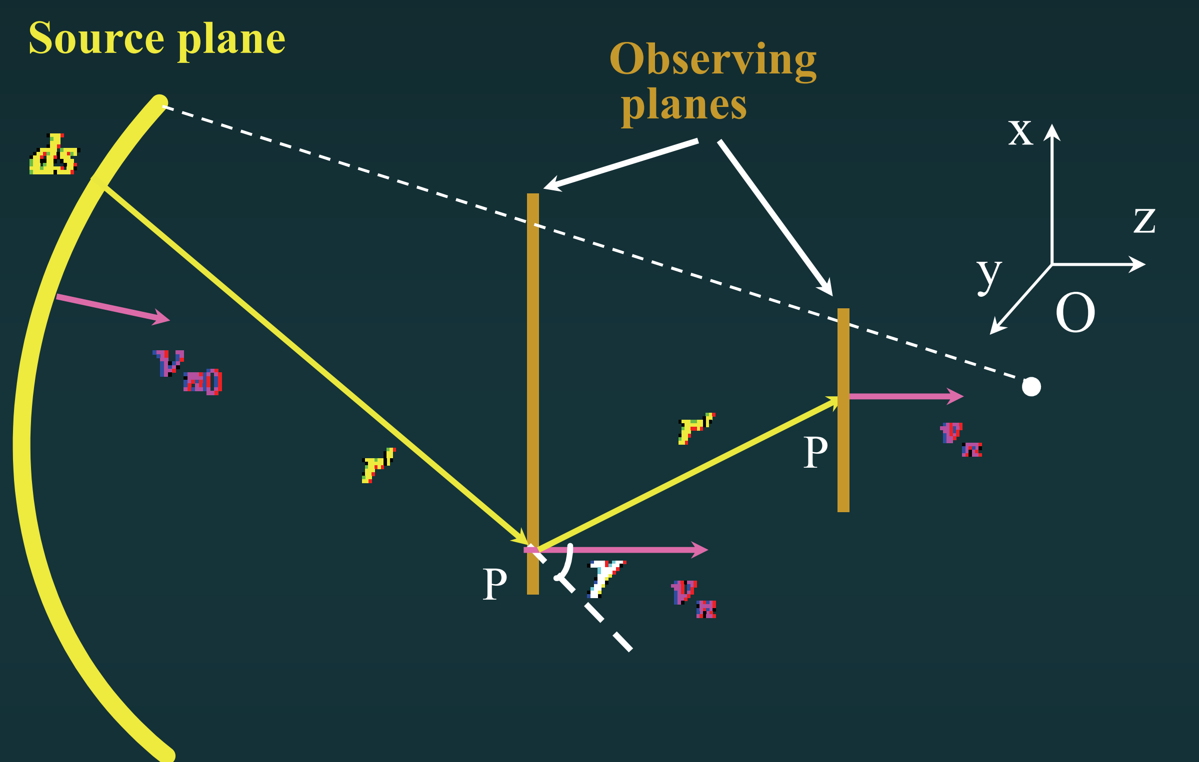
Diffraction

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

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

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

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



ρ = Equilibrium density of the medium,

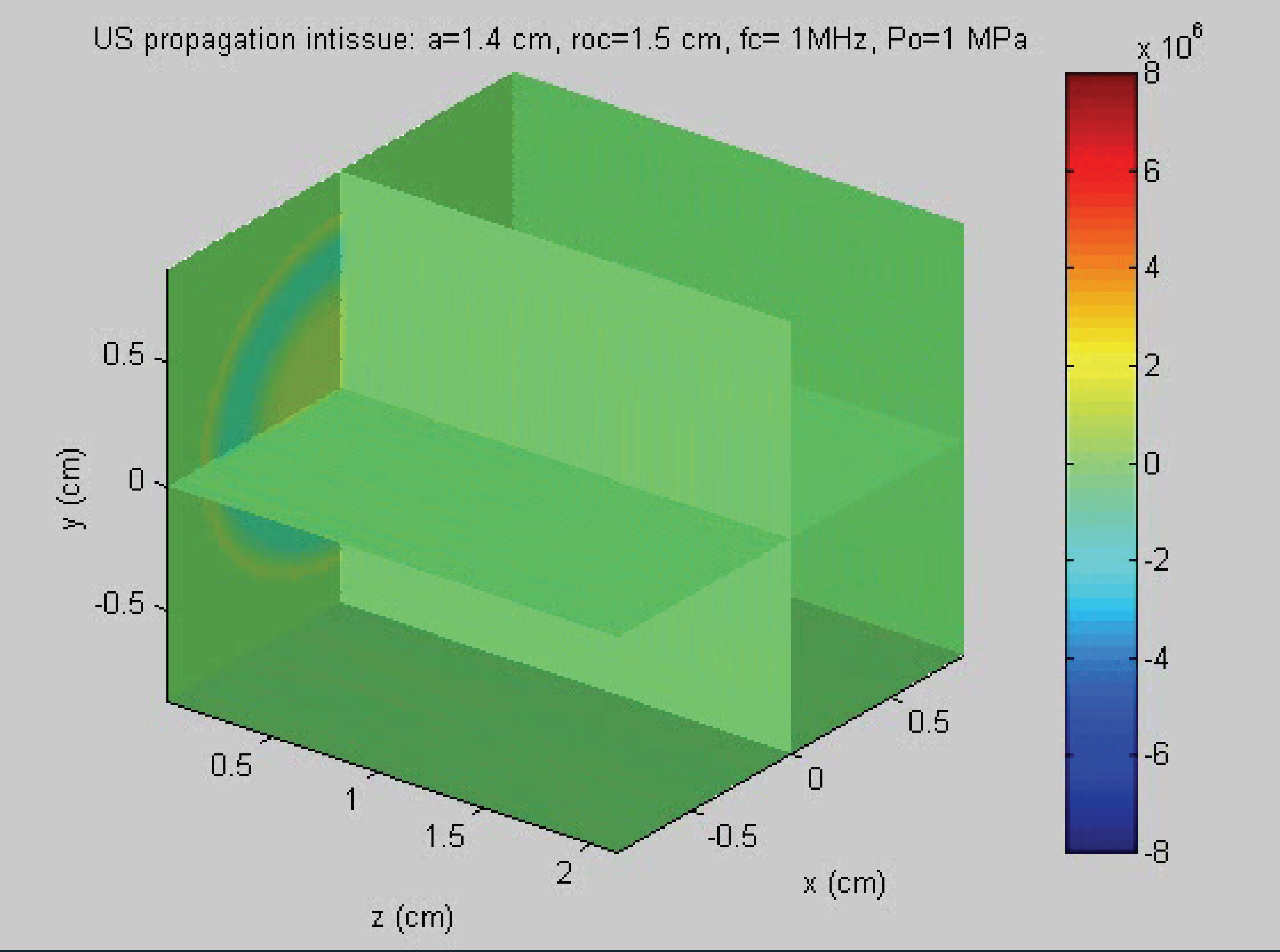
$\vec{\nabla}$ = Gradient operator,

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

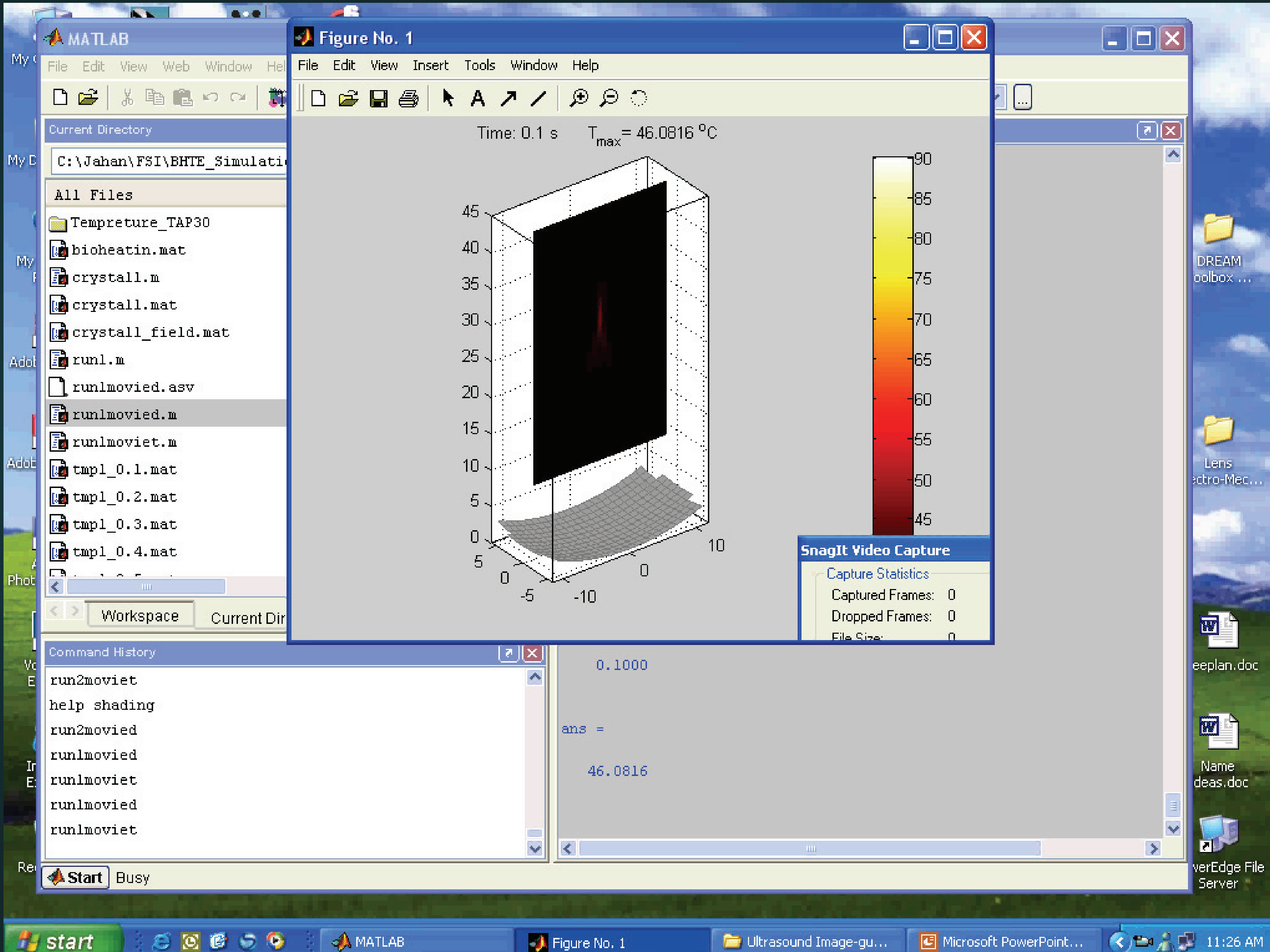
$v_n(t)$ = Instantaneous normal particle velocity,

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

Simulations – Acoustic Pressure and Intensity

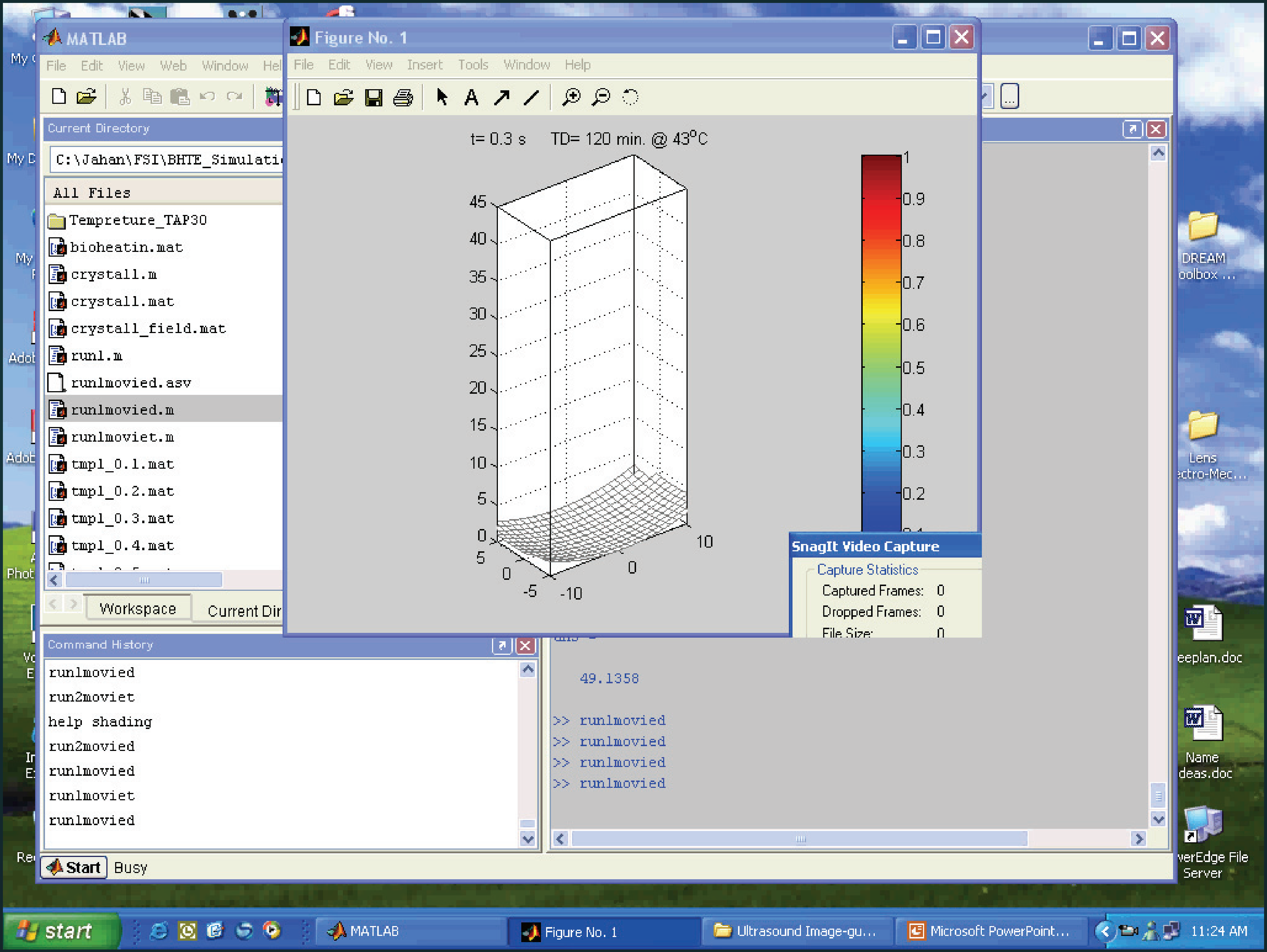


Simulations – Temperature



Simulations – Thermal Dose

TD = 120 min @ 43°C



Simulations

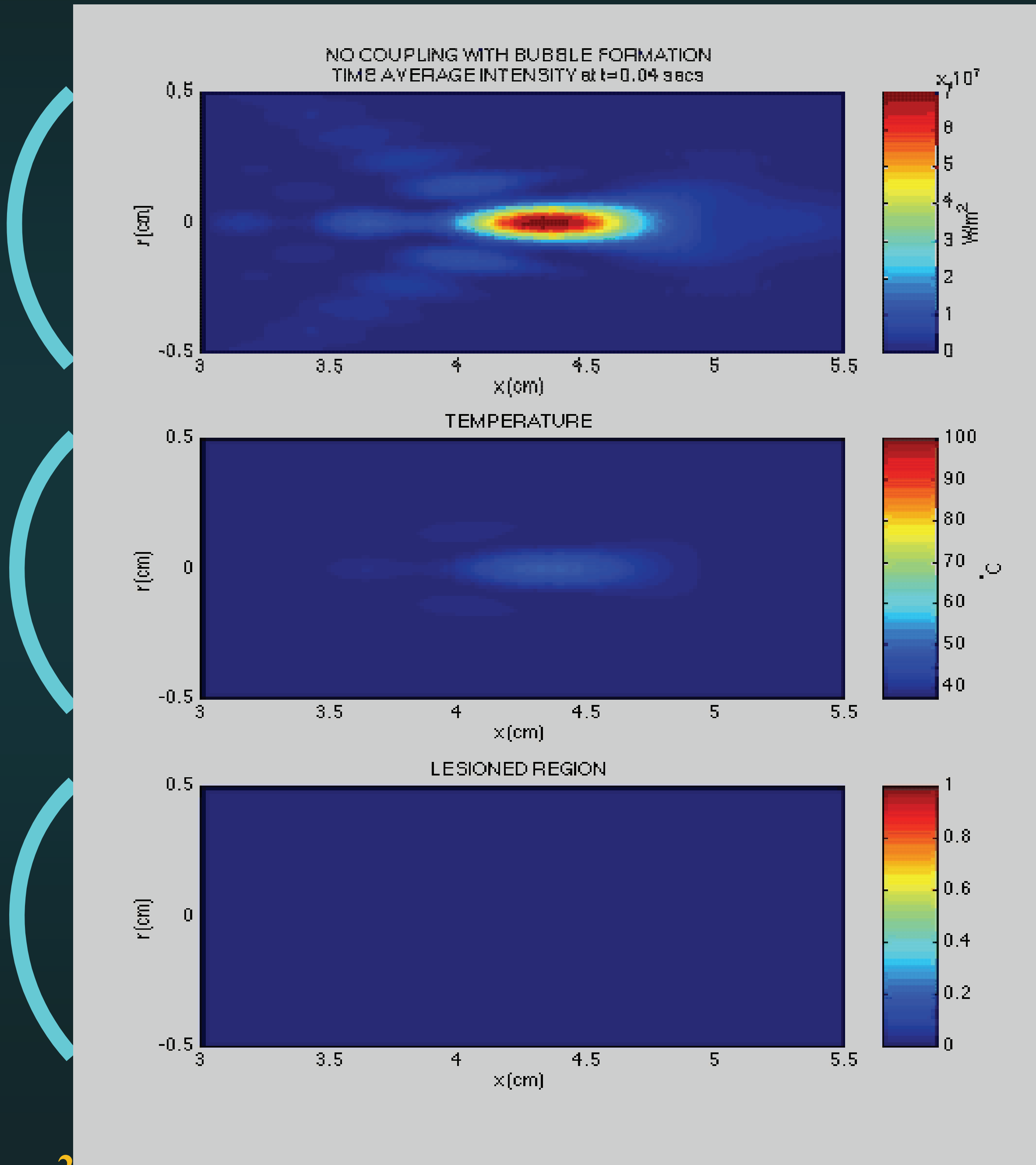
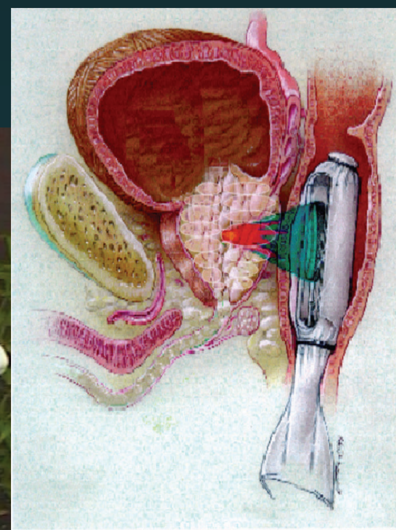


Image-guided HIFU Surgery

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

Sonatherm® 600
Misonix Inc., Farmingdale, NY



Sonablate® 500
Focus Surgery Inc., Indianapolis, IN

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

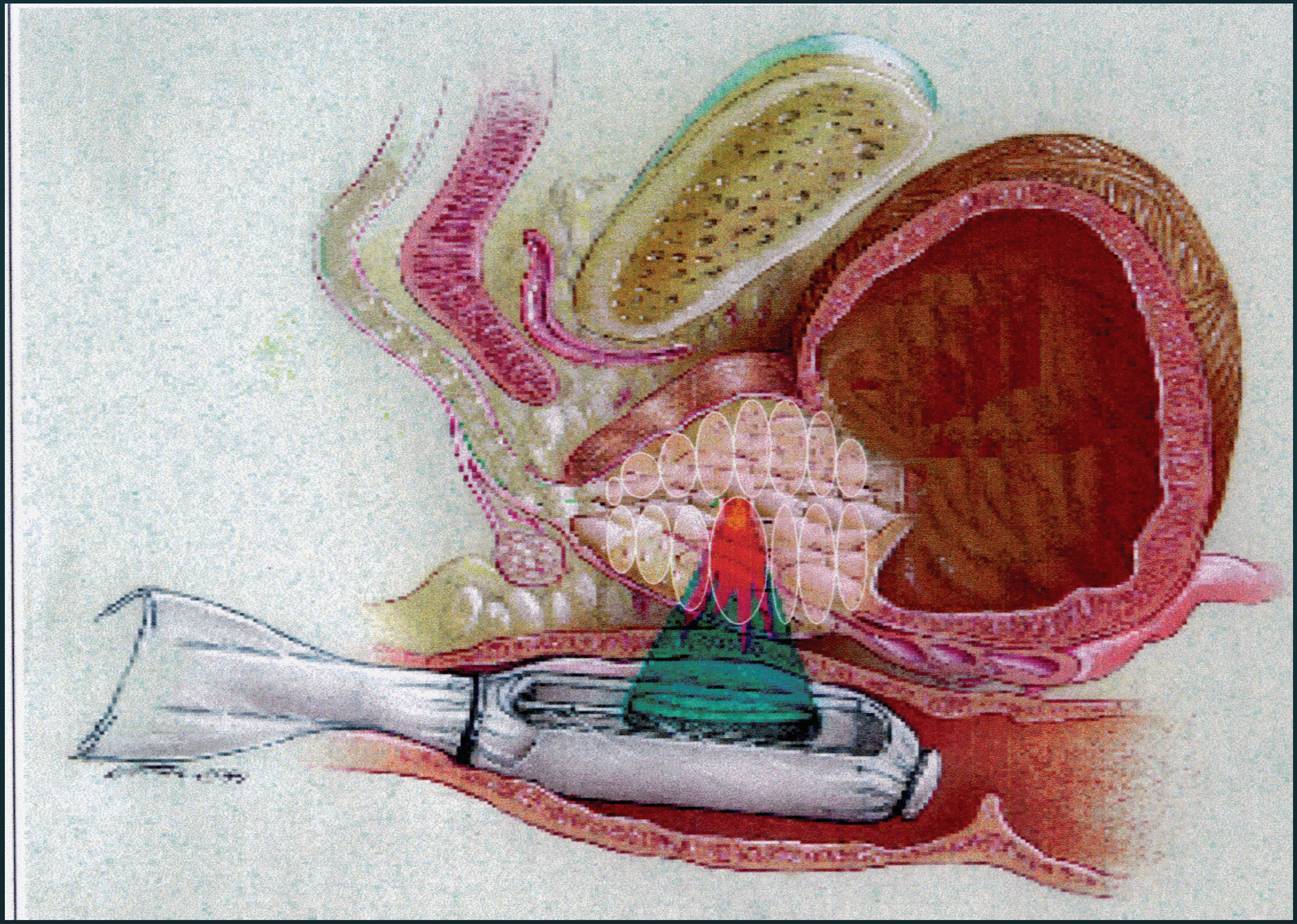
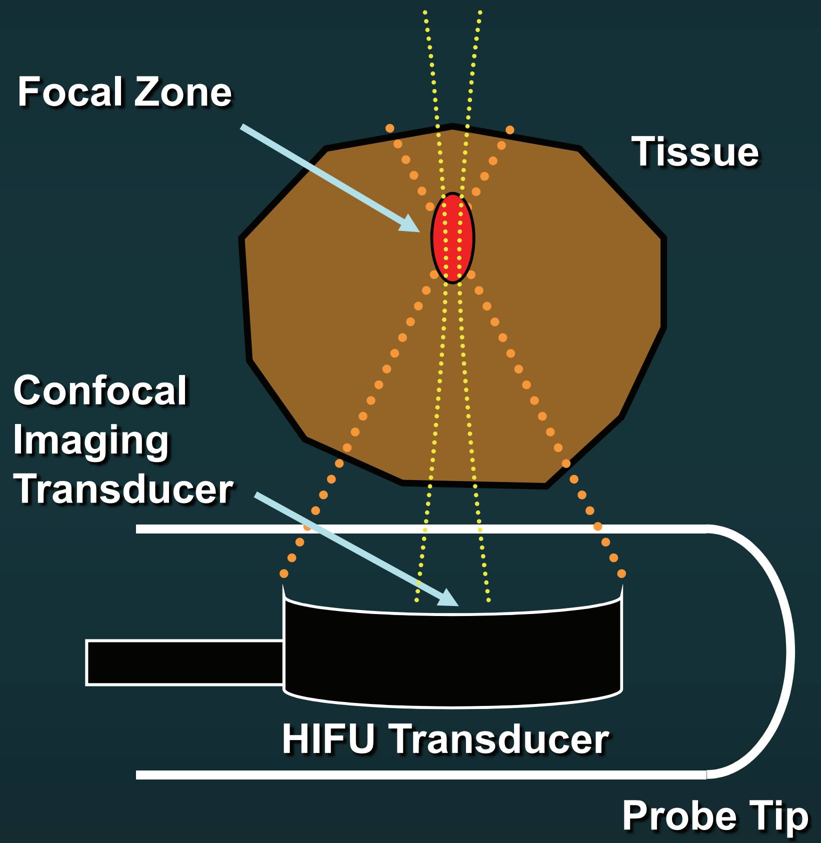


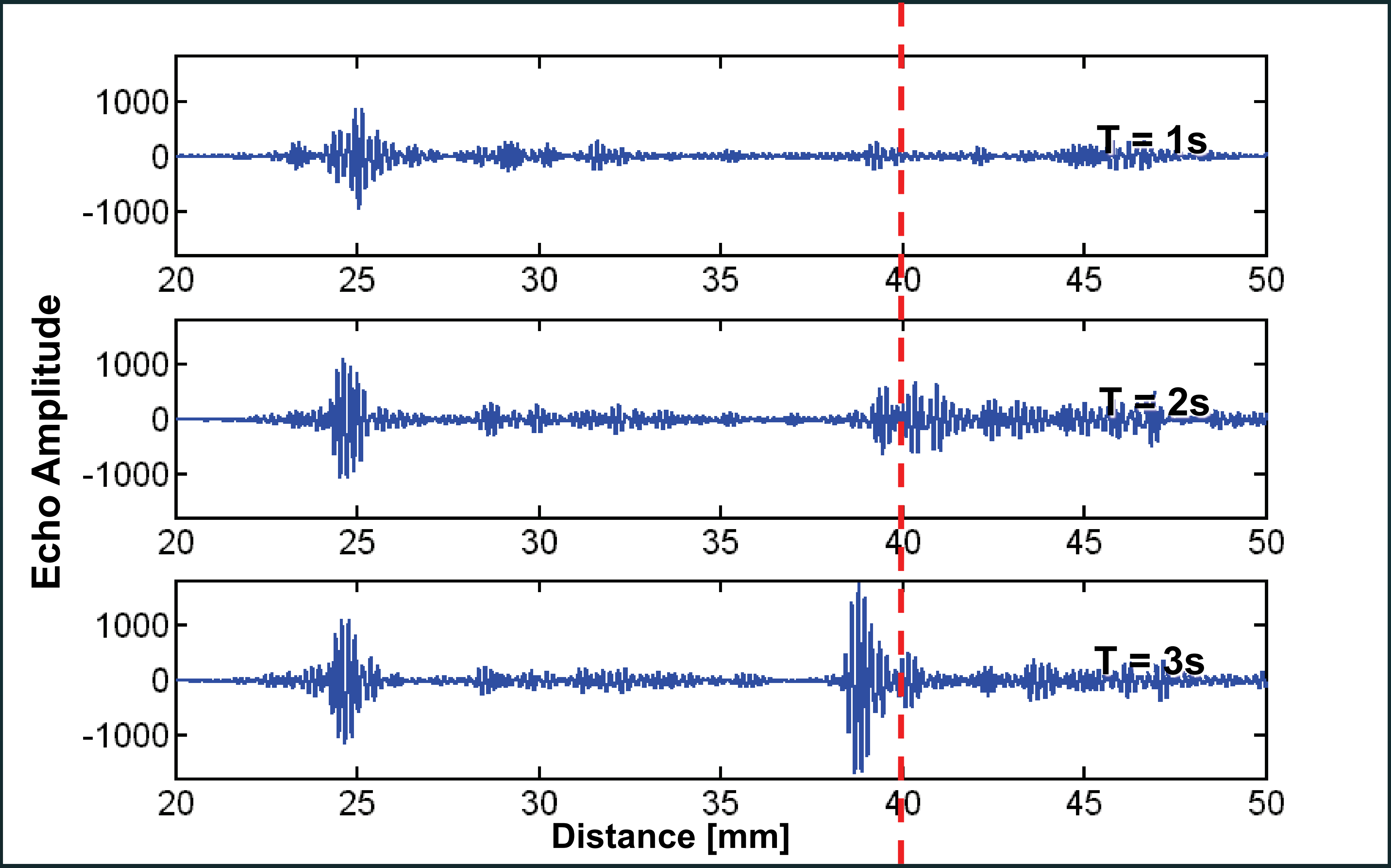
Image-guided HIFU Treatment of Prostate



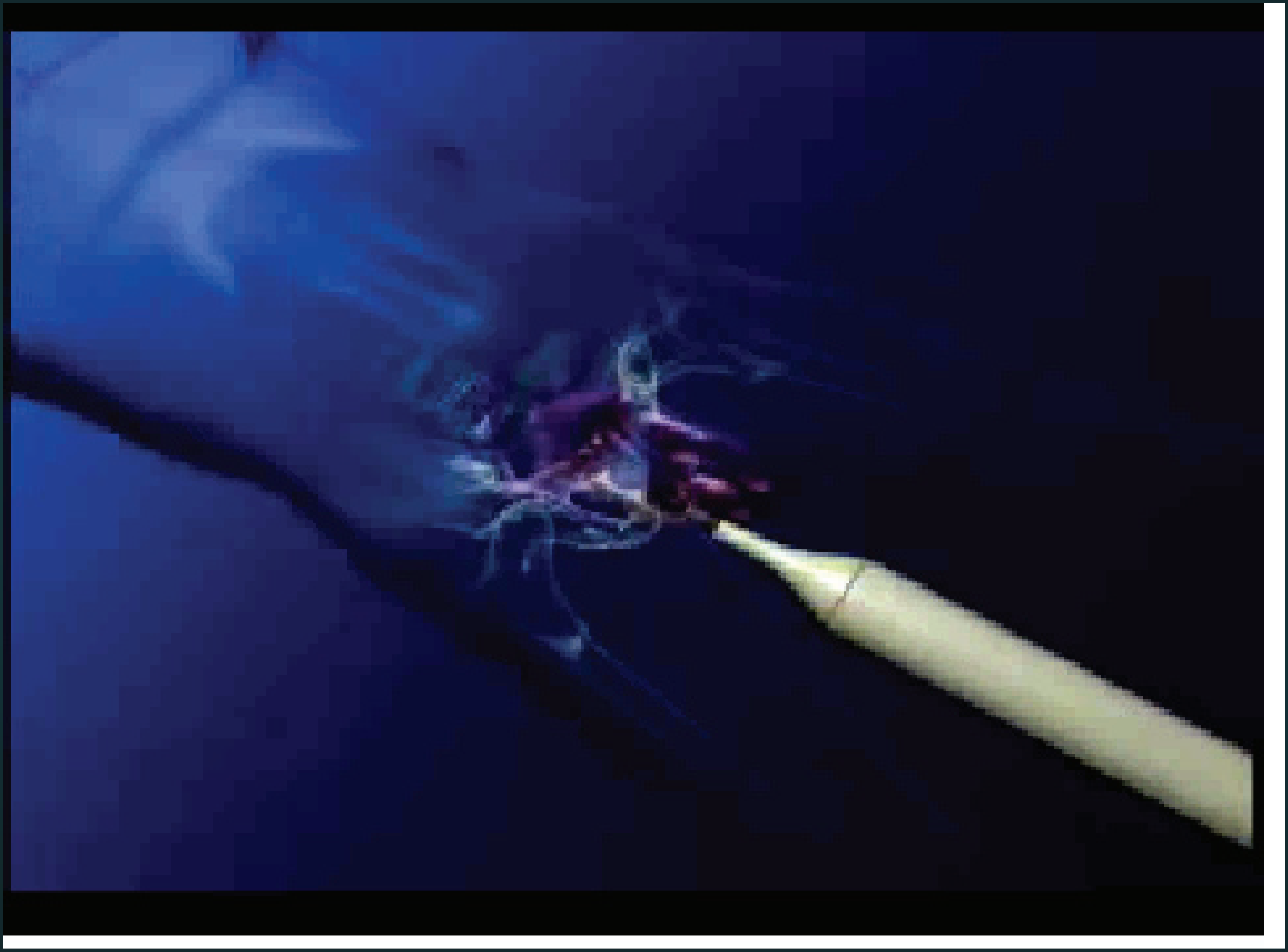
Sonablate® Therapy

Sonablate® Real-time Imaging

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