ULTRASOUND CONTRAST AGENTS BASIC PRINCIPLES AND APPLICATIONS

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UNC NCSU BME Biomedical Engineering

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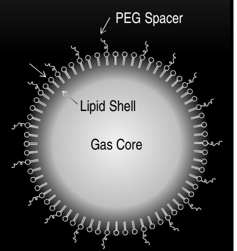
DISCUSSION POINTS

- Part I
  - Microbubble Basics
  - Fundamentals in Contrast Imaging
  - Basic Imaging Applications
- Part II
  - Advanced Imaging Applications
  - Bioeffects and Therapeutic Applications
  - Safety

PART I

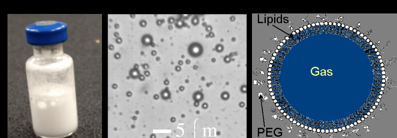
MICROBUBBLE INTRODUCTION

- What are Microbubble Contrast Agents?
  - Gas: Air, Perfluorocarbon, Sulfur Hexafluoride, etc…
  - Shell: Polymer, Lipid, Albumin, etc…
  - Size: Typically < 8 µm (Size of RBC)
  - Confined to the Vascular Space



MICROBUBBLE INTRODUCTION

- Examples



WHY MICROBUBBLES?

- Microbubbles and Ultrasound
  - **Highly Echogenic**

MICROBUBBLE PROPERTIES

- Microbubbles and Ultrasound
  - **Highly Echogenic**

Dependent On Acoustic Impedance Differences

Acoustic Impedance = Density * SoS

Water: 1.50 Mrayls
Brain: 1.56 MRayls
Bone: 1.4 MRayls
Muscle: 1.6 Mrayls
Fat: 1.33 Mrays

Tissue: 1.54 Mrayls

Orders of Magnitude Difference

Air: 0.0004 Mrayls

MICROBUBBLE PROPERTIES

- Microbubbles in an Ultrasound Field
  - Highly Echogenic
  - **Oscillate**

Oscillation Governed By…
1) Frequency
2) Pressure Amplitude
3) Pulse Repetition Frequency
4) Type of Gas Core
5) Damping Coefficients
6) Shell Properties

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MICROBUBBLE PROPERTIES

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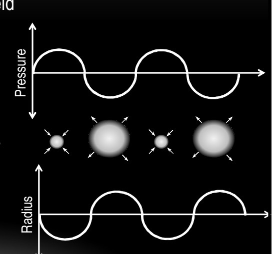
Stable Oscillatory Behavior at Low Pressures



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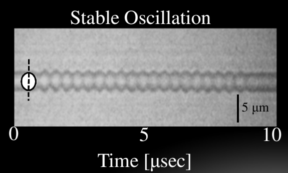

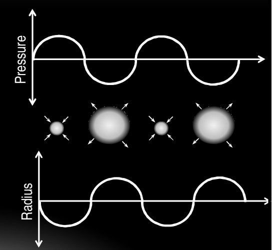

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MICROBUBBLE PROPERTIES

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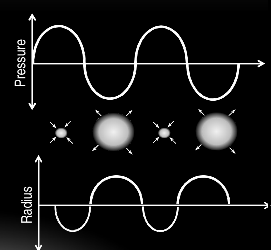
Unstable Oscillatory Behavior at High Pressures



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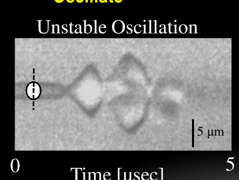

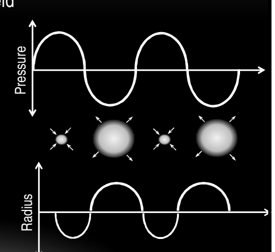

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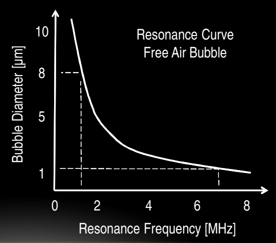

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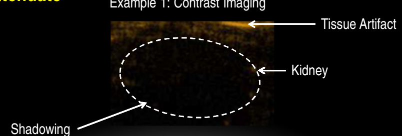
MICROBUBBLE PROPERTIES

- Microbubbles in an Ultrasound Field
  - Highly Echogenic
  - Oscillate
  - **Attenuate**

Concentration ↑
Attenuation ↑

Example 1: Contrast Imaging



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MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - **Rayleigh - Plesset** $\rho R R^{\bullet\bullet} + \frac{3}{2}\rho R^{\bullet 2} = p_L - p_o \rho R^{\bullet 2} = p_L - p_\infty$

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ρ = Density of Medium
R = Microbubble Radius
$R^{\bullet}$ = 1st Time Derivative of Radius
$R^{\bullet\bullet}$ = 2nd Time Derivative of Radius
p_L = Liquid Pressure at Wall
p_∞ = Liquid Pressure Away From Wall

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MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset
  - **Including Shell Properties**
    - Viscosity of the Shell
    - Elasticity of the Shell

$$\rho R R^{\bullet\bullet} + \frac{3}{2}\rho R^{\bullet 2} = p_{go}\left(\frac{R_o}{R}\right)^{3\Gamma} - \frac{2S_T}{R} - \frac{4\eta R^{\bullet}}{R} - p_o + P_{(t)}\sin(wt)$$

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S = Surface Tension
η = Liquid Shear Viscosity

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MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset
  - Including Shell Properties
    - Viscosity of the Shell
    - Elasticity of the Shell
  - **Complex Equation ⇨ Difficult to model and simulate**

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MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset
  - Including Shell Properties
    - Viscosity of the Shell
    - Elasticity of the Shell
  - Complex Equation ⇨ Difficult to model and simulate
    - **Concentration and Size Distributions Exacerbate Complexity!**

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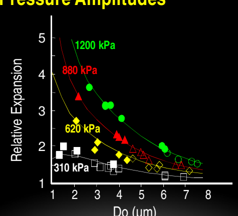
MICROBUBBLE PROPERTIES

- Microbubble Destruction Increases for…
  - **High Pressure Amplitudes**



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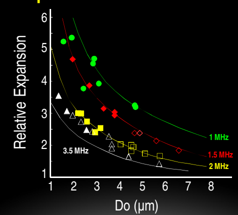
MICROBUBBLE PROPERTIES

- Microbubble Destruction Increases for…
  - **Low Frequencies**



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  - High Pressure Amplitudes
  - Low Frequencies
  - **Long Ultrasound Pulse Lengths**

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MICROBUBBLE PROPERTIES

- Microbubble Destruction Increases for…
  - High Pressure Amplitudes
  - Low Frequencies
  - Long Ultrasound Pulse Lengths
- **Most Important: High Pressure Amplitude, Low Frequency**

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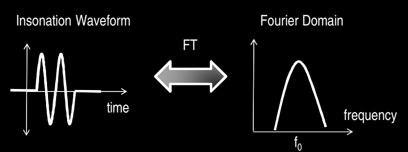
BASIC CONTRAST IMAGING TECHNIQUES

IMAGING MICROBUBBLES

- **Microbubble Response Related to Insonation Frequency**



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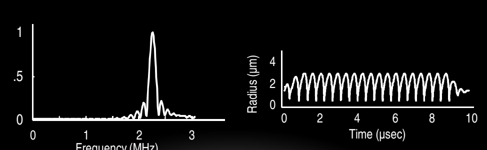
IMAGING MICROBUBBLES

- **Microbubble Response Related to Insonation Frequency**

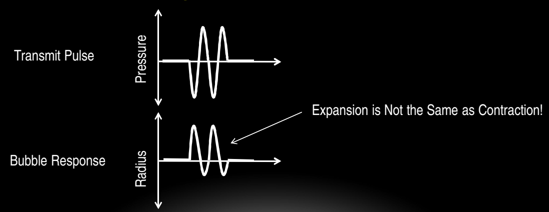
Insonation Parameters: 20 Cycle, 2.25 MHz



Chomas J, et al... Nondestructive Subharmonic Imaging. IEEE Trans. Ultrasonics 49(7), pg. 883-892, 2002

IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- **Microbubble Response is Non-Linear**



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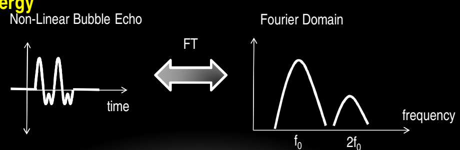
IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear
- **Microbubbles Generate Harmonic and Sub Harmonic Energy**



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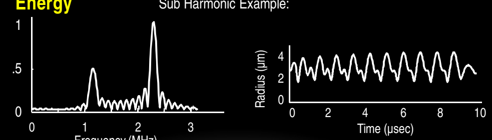
Sub Harmonic Example:



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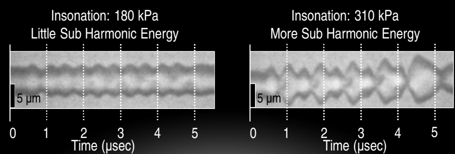

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- **Imaging Techniques Take Advantage of Microbubble Properties**

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IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear
- Microbubbles Generate Harmonic and Sub Harmonic Energy
- Imaging Techniques Take Advantage of Microbubble Properties
- **Goal: Separate Microbubble Signal From Tissue**

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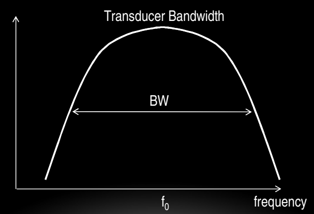
HARMONIC IMAGING

- **Transducer has Finite Bandwidth**



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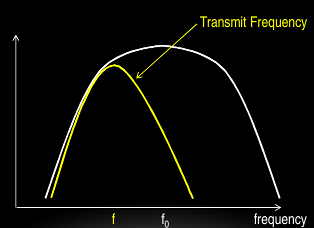
HARMONIC IMAGING

- **Insonify Microbubbles at Frequency f**



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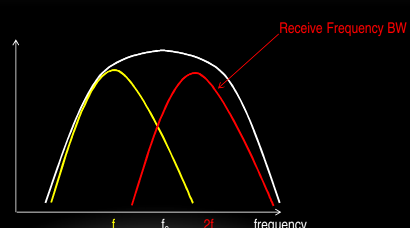
HARMONIC IMAGING

- **Receive Echo at Frequency 2f**



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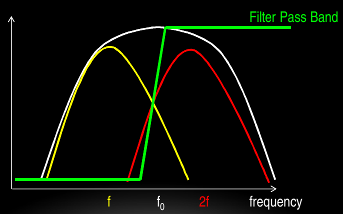
HARMONIC IMAGING

- High Pass Filter Received Signal



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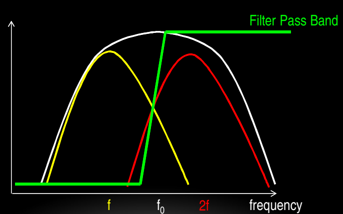
HARMONIC IMAGING

- Strong Tissue Signal Can Overpower Weak Harmonic!



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SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies

Frinking P, et al... Ultrasound Contrast Imaging: Current and New Potential Methods. UMB 26 (6), pg. 965-975, 2000.

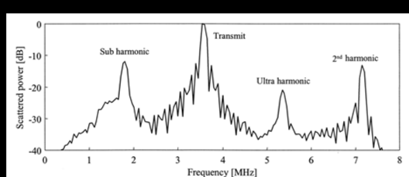
SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- **Occur at ~1/2 of the Transmitted Frequency**

Frinking P, et al... Ultrasound Contrast Imaging: Current and New Potential Methods. UMB 26 (6), pg. 965-975, 2000.

SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- **Response at ~1/2 of the Transmitted Frequency**



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SUBHARMONIC IMAGING

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- Response at ~1/2 of the Transmitted Frequency
- **Tissue Does Not Generate Sub Harmonic Energy**

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SUB HARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- Response at ~1/2 of the Transmitted Frequency
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- **Sub Harmonic Imaging**

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SUB HARMONIC IMAGING

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- Response at ~1/2 of the Transmitted Frequency
- Tissue Does Not Generate Sub Harmonic Energy
- Sub Harmonic Imaging
  - **Easy Separation from Tissue**

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- Sub Harmonic Imaging
  - Easy Separation from Tissue
  - **Lower Frequencies Mean Less Attenuation**

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  - **Low Frequency Trade-off with Resolution**

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PULSE INVERSION TECHNIQUES

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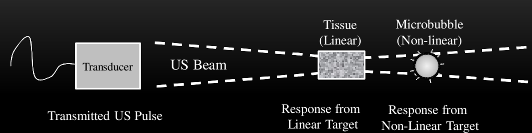
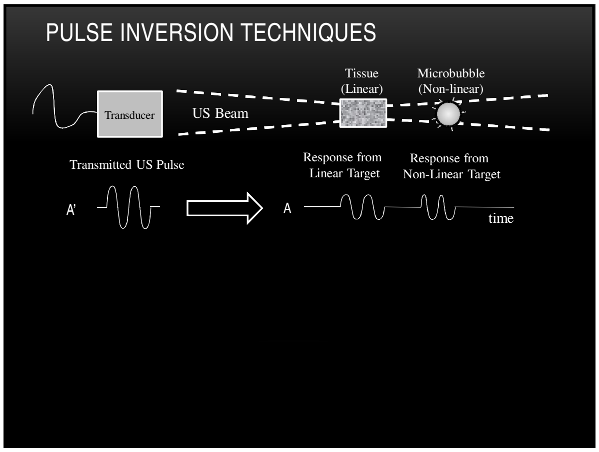
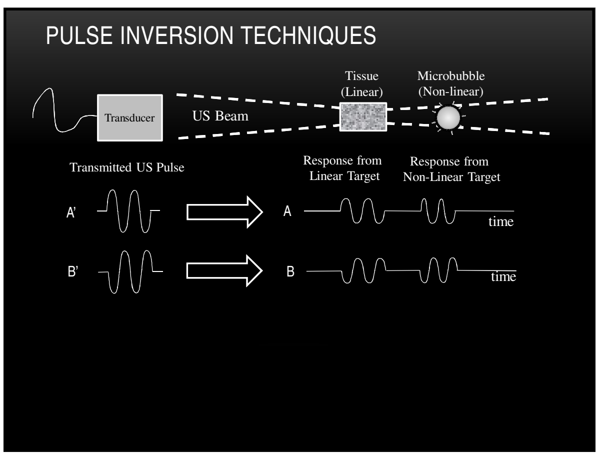



PULSE INVERSION TECHNIQUES
Tissue (Linear)
Microbubble (Non-linear)
Transducer
US Beam
Transmitted US Pulse
Response from Linear Target
Response from Non-Linear Target
A'
A
time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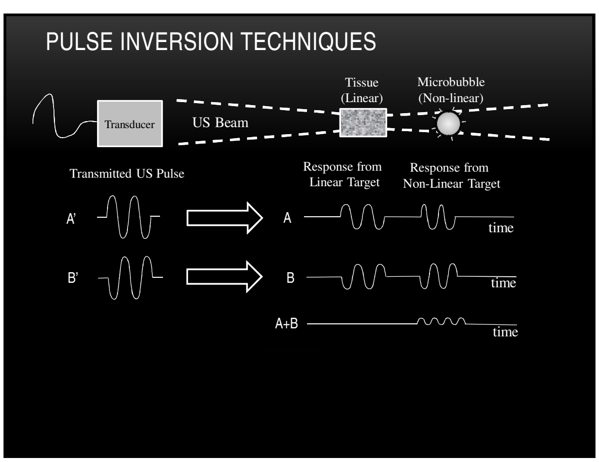
A'
A
time
B'
B
time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US Beam
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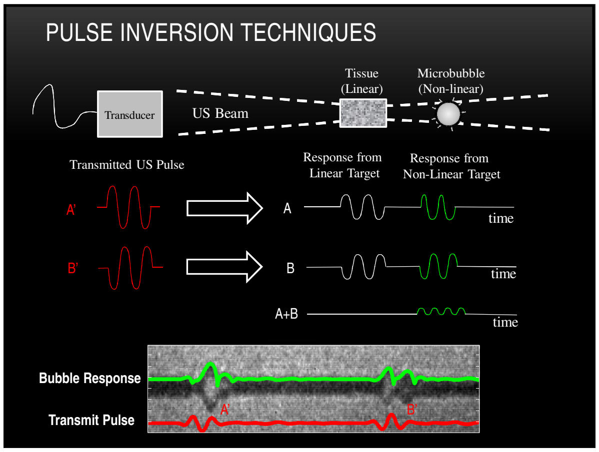
Response from Linear Target
Response from Non-Linear Target
A'
A
time
B'
B
time
A+B
time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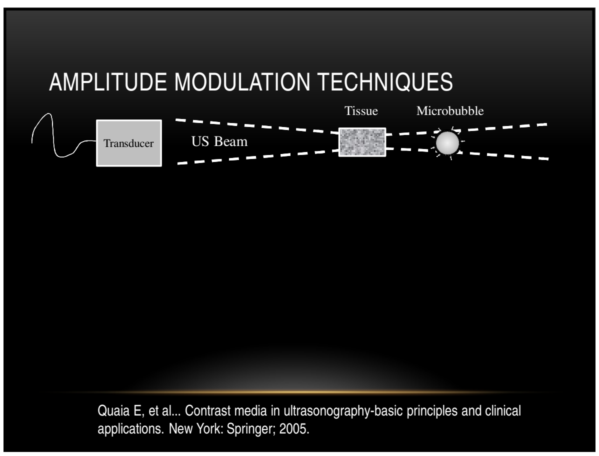
US Beam
Transmitted US Pulse
Response from Linear Target
Response from Non-Linear Target
A'
A
time
B'
B
time
A+B
time
Bubble Response
Transmit Pulse
A'
B'


AMPLITUDE MODULATION TECHNIQUES
Tissue
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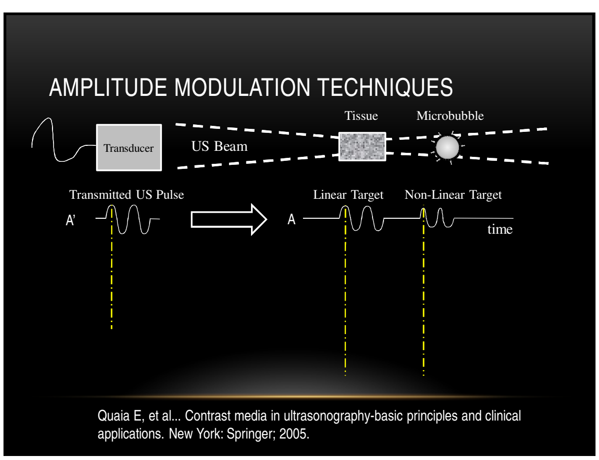
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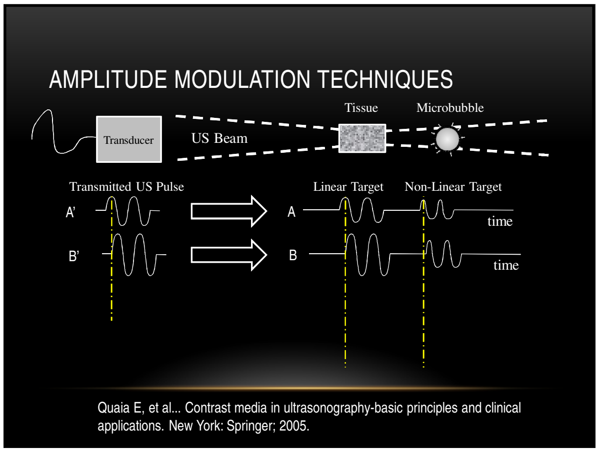
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A'
B'
A
B
time
time
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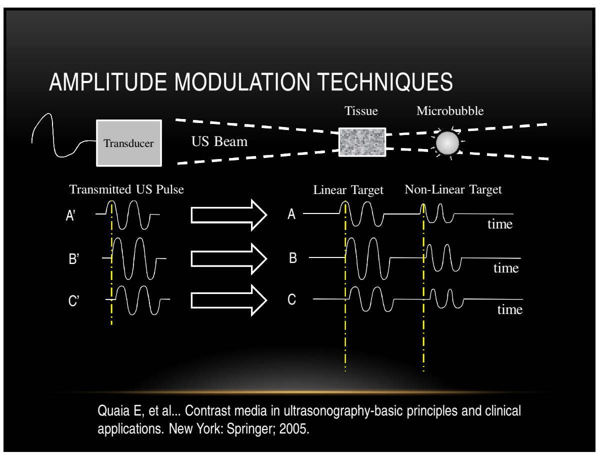
AMPLITUDE MODULATION TECHNIQUES
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Microbubble
Transducer
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Linear Target
Non-Linear Target
A'
B'
C'
A
B
C
time
time
time
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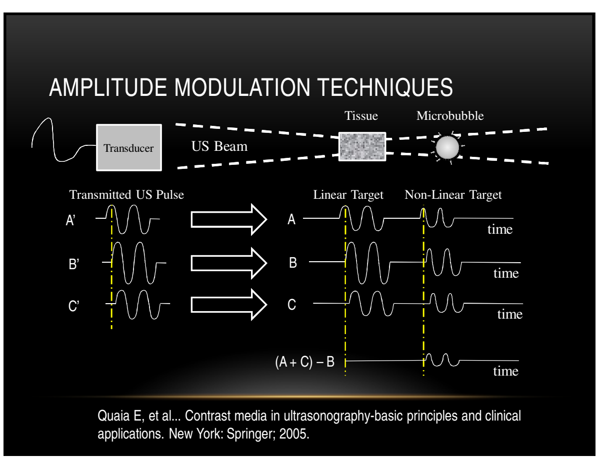
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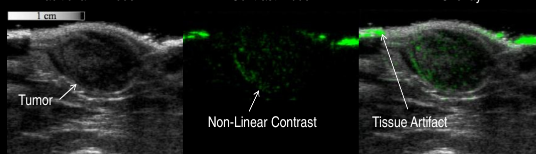
Transducer
US Beam
Transmitted US Pulse
Linear Target
Non-Linear Target
A'
B'
C'
A
B
C
(A + C) – B
time
time
time
time
Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

COMBINING TECHNIQUES

Example:
Siemens Sequoia – 15L8 Linear Array Transducer
Cadence Pulse Sequencing Mode (Contrast Imaging)
Amplitude Modulation and Pulse Inversion

Traditional B-Mode | Contrast Mode | Overlay



Streeter - Unpublished Data.

IMAGING TECHNIQUES SUMMARY

- Single Pulse Strategies
  - Harmonic Imaging
    - Disadvantage: Interference with Tissue Signal
  - Sub Harmonic Imaging
    - Disadvantage: Low Frequency = Poor Resolution
- Post-Processing Strategies
  - Pulse Inversion
    - Disadvantage: Lower Frame Rate, Sensitive to Tissue Motion
  - Amplitude Modulation
    - Disadvantage: Lower Frame Rate, Sensitive to Tissue Motion
- Most Systems Today Incorporate Some Combination!

BASIC IMAGING APPLICATIONS

CONTRAST-ENHANCED ULTRASOUND

- **Blood is a Weak Scatterer**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- **Microbubbles Help Delineate Tissue From Blood**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - **Provides Clearer Picture For Clinicians**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- **Ability to Quantify Tissue Perfusion**

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CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- Ability to Quantify Tissue Perfusion
  - **Transit Time Measurements**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- Ability to Quantify Tissue Perfusion
  - Transit Time Measurements
  - **Evaluation of Blood Volume**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- Ability to Quantify Tissue Perfusion
  - Transit Time Measurements
  - Evaluation of Blood Volume
  - **Replenishment Kinetics**

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

CONTRAST ECHOCARDIOGRAPHY

- **Assessment of Left Ventricular Cavity**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - **Requires Endocardial Border Visualization**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - Requires Endocardial Border Visualization
  - **Adequate Visualization Not Possible in 15% of Patients**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - Requires Endocardial Border Visualization
  - Adequate Visualization Not Possible in 15% of Patients
- **Left Ventricular Opacification**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - Requires Endocardial Border Visualization
  - Adequate Visualization Not Possible in 15% of Patients
- Left Ventricular Opacification
  - **Microbubbles Improve Visualization**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - Requires Endocardial Border Visualization
  - Adequate Visualization Not Possible in 15% of Patients
- Left Ventricular Opacification
  - Microbubbles Improve Visualization
  - **Produces Homogenous Opacification**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

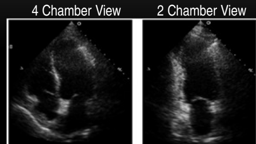
CONTRAST ECHOCARDIOGRAPHY

- Assessment of Left Ventricular Cavity
  - Requires Endocardial Border Visualization
  - Adequate Visualization Not Possible in 15% of Patients
- Left Ventricular Opacification
  - Microbubbles Improve Visualization
  - Produces Homogenous Opacification
  - **Improves Reader Accuracy and Confidence**

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

4 Chamber View   2 Chamber View

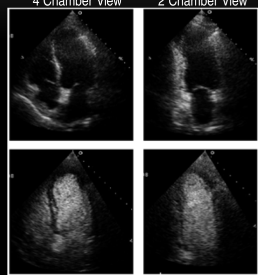


Poor Endocardial Definition

Kaufmann E, et al... Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

CONTRAST ECHOCARDIOGRAPHY

4 Chamber View 2 Chamber View



Poor Endocardial Definition

Improved Definition Due to Contrast

Kaufmann E, et al… Contrast Echocardiography. Curr Probl Cardiol; 32 (2), pg 51-96, 2005.

TIME INTENSITY CURVE

- **Contrast-Enhanced Monitoring Over Time**

Quaia E, et al… Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- **Select a Region of Interest**

Quaia E, et al… Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- **Evaluate the Intensity of the Microbubbles**

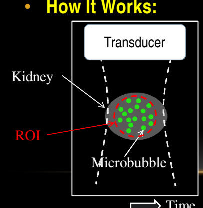
Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- **How It Works:**

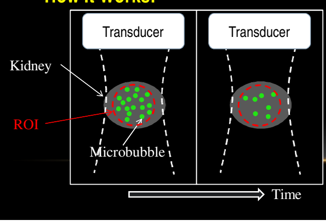
TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- **How It Works:**



TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- **How It Works:**



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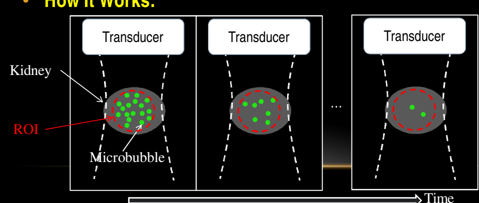

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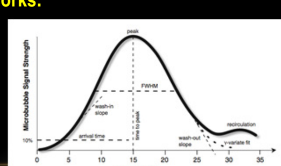
- Evaluate the Intensity of the Microbubbles
- **How It Works:**



Cosgrove D, et al... Imaging of Perfusion Using Ultrasound. Eur J Nucl Mol Imaging: 37 (Suppl 1); 2010.

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- **Example:**

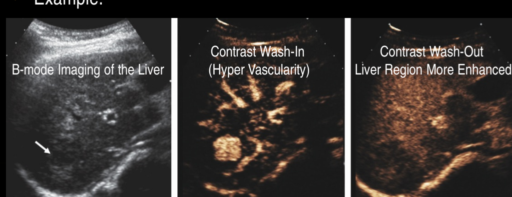
TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- Example:
  - Evaluation of Liver Lesions

Wilson S, et al... Microbubble-enhanced US in body imaging: What Role? Radiology: 257(1); 2010.

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- Example:



Wilson S, et al... Microbubble-enhanced US in body imaging: What Role? Radiology: 257(1); 2010.

DESTRUCTION-REPERFUSION

- **Perfusion Quantification Helps Understand Diseased Tissue**

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- **Microbubbles are Continuously Infused**

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Microbubbles are Continuously Infused
  - **Steady State Clearance Equals the Inflow**

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Microbubbles are Continuously Infused
  - Steady State Clearance Equals the Inflow
- **Microbubble Destruction in a Single Plane**

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

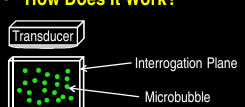
DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Microbubbles are Continuously Infused
  - Steady State Clearance Equals the Inflow
- Microbubble Destruction in a Single Plane
- **Monitoring Microbubble Refill Rate**

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- **How Does It Work?**



DESTRUCTION-REPERFUSION

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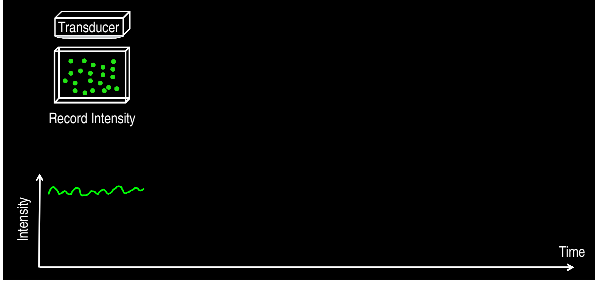
- **How Does It Work?**



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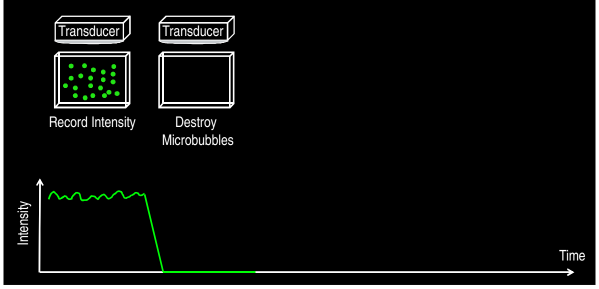

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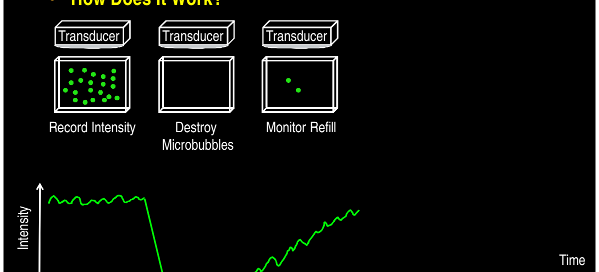

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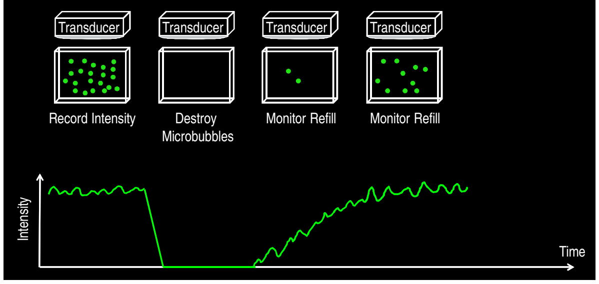
- **How Does It Work?**



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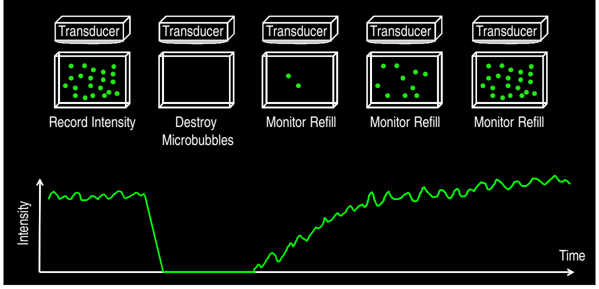


DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- **How Does It Work?**

Pollard RE, Dayton PA, Watson KD, Hu X, Guracar IM, Ferrara KW.
Motion corrected cadence CPS ultrasound for quantifying response to vasoactive drugs in a rat kidney model. Urology. 2009 Sep;74(3):675-81.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- **What Information Do We Get?**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - **Time To Peak Intensity**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - **Blood Flow Velocity (Slope)**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - Blood Flow Velocity (Slope)
  - **Fractional Blood Volume (Max Amplitude)**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - Blood Flow Velocity (Slope)
  - Fractional Blood Volume (Max Amplitude)
  - **Blood Volume (Area Under the Curve)**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - Blood Flow Velocity (Slope)
  - Fractional Blood Volume (Max Amplitude)
  - Blood Volume (Area Under the Curve)
  - **Mean Transit Time**

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
- **Destruction-Reperfusion at Pixel Level**

Streeter J, et al... A Comparative Evaluation of Ultrasound Perfusion Imaging, Molecular imaging, and Volume Measurements in Evaluating the Response to Therapy. Unpublished Data. 2012.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
- Destruction-Reperfusion at Pixel Level
- **Monitoring Time to 20% (Max Intensity)**

Streeter J, et al... A Comparative Evaluation of Ultrasound Perfusion Imaging, Molecular imaging, and Volume Measurements in Evaluating the Response to Therapy. Unpublished Data. 2012.

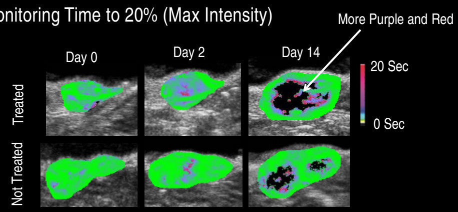
DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
- Destruction-Reperfusion at Pixel Level
- Monitoring Time to 20% (Max Intensity)
- **Tumor Perfusion Monitoring During Therapy**

Streeter J, et al... A Comparative Evaluation of Ultrasound Perfusion Imaging, Molecular imaging, and Volume Measurements in Evaluating the Response to Therapy. Unpublished Data. 2012.

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
- Destruction-Reperfusion at Pixel Level
- Monitoring Time to 20% (Max Intensity)



DESTRUCTION-REPERFUSION

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- Example:
- Destruction-Reperfusion at Pixel Level
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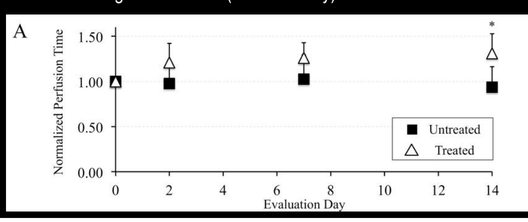


PART II

ADVANCED IMAGING APPLICATIONS

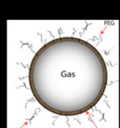
MOLECULAR IMAGING

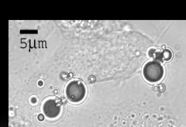
- Functional technique to evaluate changes on a molecular level
- Knowledge of molecular signature of pathology
  - Integrins, selectins etc…expressed on endothelial cells
  - VEGF, $\alpha_v\beta_3$, etc…

Dayton P, et al... Targeted Imaging Using Ultrasound. J Magn Reson Imaging; 16 (4); 2002.

MOLECULAR IMAGING

- Targeted microbubble contrast agents
  - Shell material fitted with adhesion ligand
  - **Example: $\alpha_v\beta_3$ Ligand → Cyclic RGD Peptide**

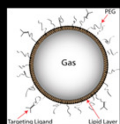


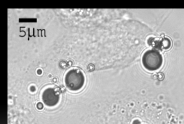


Dayton et al., Mol Imaging. 2004 Apr;3(2):125-34.

MOLECULAR IMAGING

- Targeted contrast agents injected intravascularly
- Collect at site of desired molecular marker expression
- Determine the presence or absence of a molecular change
- Assess disease or pathology prior to anatomical changes appear





Dayton et al., Mol Imaging. 2004 Apr;3(2):125-34.

MI & RESPONSE TO THERAPY

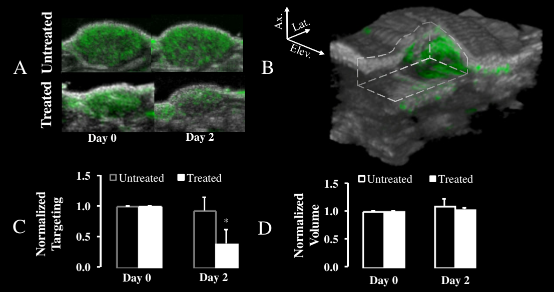
- Traditional methods for quantifying tumor progression – volume
  - *RECIST* (Response Evaluation Criteria In Solid Tumors)
- Size measurements provide delayed feedback
- Molecular imaging assesses molecular changes often before tumor size is affected

MI & RESPONSE TO THERAPY

- Example:
  - Cancer Type: Human Pancreatic Adenocarcinoma
  - Animal Model: Mouse
  - Therapy: Experimental Aurora-A Kinase Inhibitor
  - Imaging target: $\alpha_v\beta_3$

Streeter J, et al... A Comparative Evaluation of Ultrasound Perfusion Imaging, Molecular imaging, and Volume Measurements in Evaluating the Response to Therapy. Unpublished Data. 2012.

Molecular imaging of therapeutic response



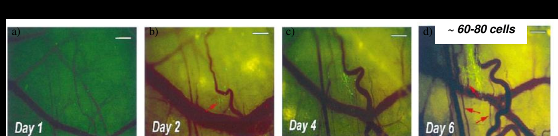
Streeter, Herrera-Loeza, Neel, Yeh, Dayton "A Comparative Evaluation of Ultrasound Perfusion Imaging, Molecular imaging, and Volume Measurements in Evaluating the Response to Therapy, In Review

Status of MI

- Mainly pre-clinical use
- Clinical Trials in Europe
  - Bracco, VEGFR2 targeted imaging in human prostate

Acoustic Angiography

- Goal:
  - Image microvasculature structure
  - Microvascular abnormalities/angiogenesis associated with malignancy

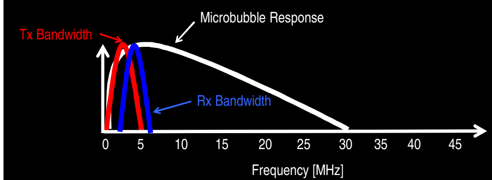


Li CY, Shan S, Huang Q, Braun RD, Lanzen J, Hu K, Lin P, Dewhirst MW., "Initial stages of tumor cell-induced angiogenesis: evaluation via skin window chambers in rodent models", J Natl Cancer Inst. 2000 Jan 19;92(2):143-7.

ACOUSTIC ANGIOGRAPHY

Requires:
- High resolution
- Tissue background suppression
- "Very-high-harmonic imaging"

Standard Clinical-Frequency Contrast Imaging

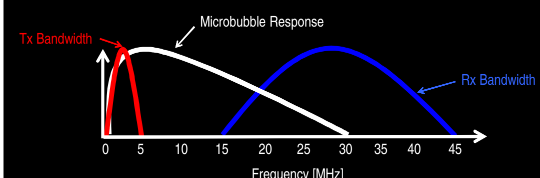


Kruse and Ferrara, IEEE Trans Ultrason Ferroelectr Freq Control. 2005 Aug;52(8):1320-9

ACOUSTIC ANGIOGRAPHY

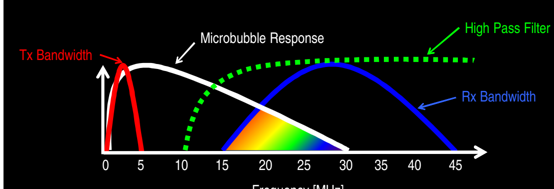
- "Very High Harmonic Contrast Imaging"

High Frequency Contrast Imaging



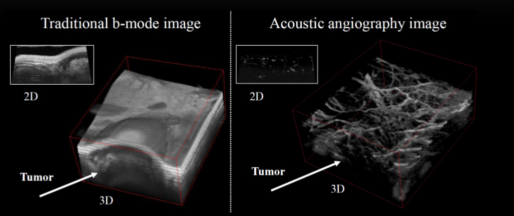
Kruse and Ferrara, IEEE Trans Ultrason Ferroelectr Freq Control. 2005 Aug;52(8):1320-9

ACOUSTIC ANGIOGRAPHY



Kruse and Ferrara, IEEE Trans Ultrason Ferroelectr Freq Control. 2005 Aug;52(8):1320-9

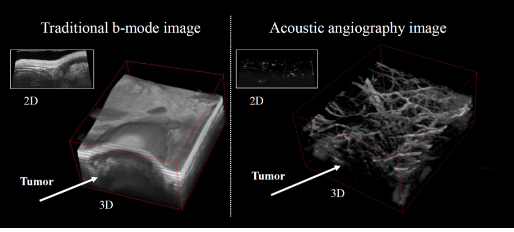
ACOUSTIC ANGIOGRAPHY



ACOUSTIC ANGIOGRAPHY

Advantages

- High Frequency - High Resolution
- Attenuation in One Direction
- Eliminates Low Frequency Tissue Signal
- Less Sensitive to Breathing Artifacts



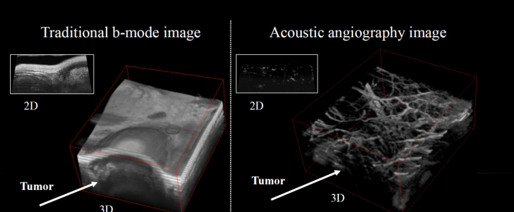
ACOUSTIC ANGIOGRAPHY

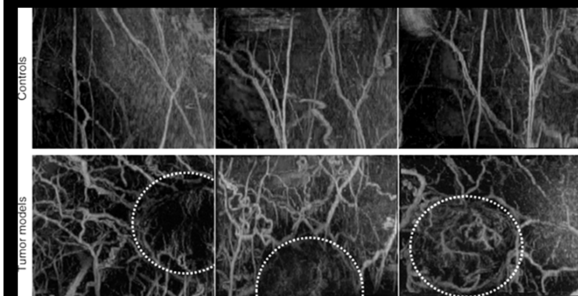
Advantages

- High Frequency - High Resolution
- Attenuation in One Direction
- Eliminates Low Frequency Tissue Signal
- Less Sensitive to Breathing Artifacts

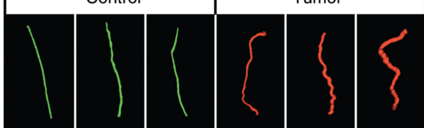
Disadvantages

- Transducers not yet commercial
- High attenuation (shallow depth imaging)
- Not a low-MI imaging technique





Gessner R, Aylward, S, Dayton PA., *Radiology, 2012.*



	Control			Tumor		
DM	1.03	1.06	1.05	1.34	1.30	1.30
SOAM	6.59	14.64	7.57	19.07	29.74	20.85

Gessner R, Aylward, S, Dayton PA., *Radiology, 2012.*

Table 2

Summary of the *P* Values for the Statistical Tests Used to Assess Interanimal and Intrapopulation Variability in Vessel Tortuosity

	DM		SOAM	
Group and Animal	Pooled Control Population	Pooled Tumors	Pooled Control Population	Pooled Tumors
Control animals				
1	.62	<.000147*†	.75	<.000147*†
2	.66	<.000147*†	.47	.0010*
3	.025	<.000147*†	.41	<.000147*†
4	.63	<.000147*†	.19	<.000147*†
5	.09	<.000147*†	.18	.002
6	.61	<.000147*†	.95	<.000147*†
7	.09	<.000147*†	.99	<.000147*†
Tumor-bearing animals				
1	<.000147*†	.89	<.000147*†	.007
2	.0002*	.41	<.000147*†	.79
3	.0002*	.004	<.000147*†	.79
4	<.000147*†	.91	<.000147*†	.47
5	.0006*	.76	.0016	.28
6	<.000147*†	.94	<.000147*†	.85
7	.0005*	.81	.0004*	.38
8	.0006*	.78	.0002*	.046
9	.0056	.16	.0014*	.11
10	<.000147*†	.14	<.000147*†	.86

Note.—Each cell indicates a comparison between the ensemble of vessel tortuosities for the animal in each row and the pooled population in each column.

* *P* values are less than the Bonferroni-corrected *P* value of .00147.

† *P* values more than 10 times smaller than the Bonferroni-corrected *P* value of .00147.

Gessner R, Aylward, S, Dayton PA., *Radiology, 2012.*

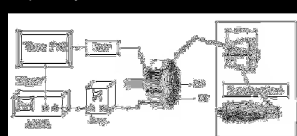
HOW ULTRASOUND ANGIOGRAPHY CAN BE USED IN ONCOLOGY RESEARCH:

- Blood vessel structure, density, and pattern can be assessed non-invasively
- Microvascular tortuosity abnormalities are an indicator of tumor development
- Prior studies have shown that vessel morphological characteristics are related to tumor malignancy and response to treatment (Bullitt)

Bullitt E, Ewend M, Vredenburgh J, et al, Neuroimage, 2009, Aug;47 Suppl 2:T143-51

Acoustic Angiography

- Traditional Ultrasound Transducer
  - Transmit and Receive (x1 Frequency Bandwidth)
- Dual Frequency Imaging
  - Transmit Using Low Frequency Bandwidth
  - Receive Using High Frequency Bandwidth



Gessner R, et al... High-resolution, high-contrast ultrasound imaging using a prototype dual-frequency transducer: In vitro and in vivo studies. IEEE Trans Ultrason Ferroelectr Freq Control. 2010.

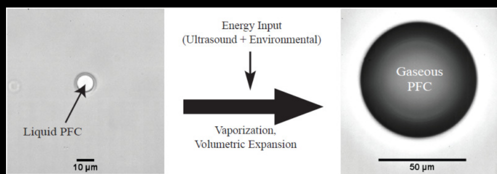
SUMMARY: DIAGNOSTIC IMAGING WITH MICROBUBBLES

- perfusion imaging **
- quantitative dynamic perfusion imaging
- molecular imaging
- acoustic angiography

** only perfusion imaging is currently used clinically in the US

ULTRASONIC ACTIVATABLE CONTRAST AGENTS

- Liquid Perfluorocarbon Core
- Lipid or Polymer Shell
- Tipped to Gaseous State by Ultrasound



Sheeran P, et al... Formulation and acoustic studies of a new phase-shift agent for diagnostic and therapeutic ultrasound. Langmuir; 27. 2011.

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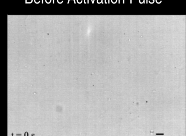
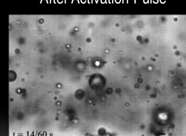
Before Activation Pulse



After Activation Pulse



Sheeran P, et al... Formulation and acoustic studies of a new phase-shift agent for diagnostic and therapeutic ultrasound. Langmuir; 27. 2011.

ULTRASONIC ACTIVATABLE CONTRAST AGENTS

- Applications
  - Vascular Occlusion
  - Extravascular Diagnostics
  - Other microbubble applications

Sheeran P, et al... Formulation and acoustic studies of a new phase-shift agent for diagnostic and therapeutic ultrasound. Langmuir; 27. 2011.

ULTRASONIC ACTIVATABLE NANOPARTICLES

- Liquid Perfluorocarbon Core
- Lipid or Polymer Shell
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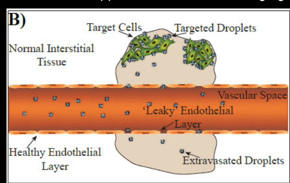
- **Example:**

A Nanoscale Approach to Molecular Imaging



Sheeran P, et al... Phase-change nanoagents for extravascular ultrasound molecular imaging: an in-vitro proof of principle. In Review. 2011.

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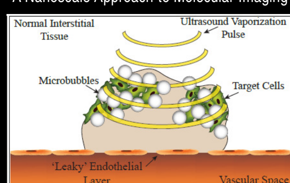

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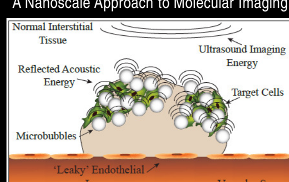

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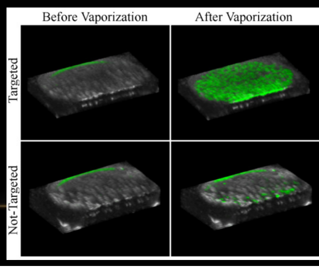
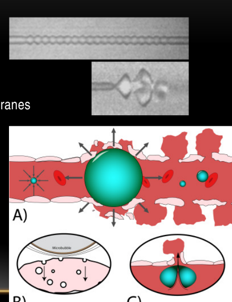


ULTRASOUND BIOEFFECTS AND THERAPY

BIOLOGICAL EFFECTS –
INTERACTION BETWEEN ULTRASOUND AND MICROBUBBLES

- Increased thermal energy conversion
- Physical effects from bubbles themselves
  - Microstreaming
  - Mechanical stimulation of biological membranes
- Cavitation (violent expand/collapse)
  - Shock Waves
  - Microbubble Jetting
  - High Pressures and Temperatures
  - Free Radical Formation



BIOLOGICAL EFFECTS

Mild

- Reversible Capillary Permeability Changes
- Reversible Cell Membrane Permeability
- Small temperature changes

Strong

- Capillary Rupture
- Tissue ablation
- Cell death

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

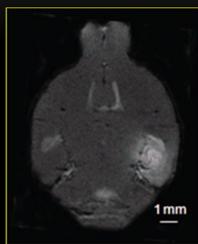
BIOLOGICAL EFFECTS

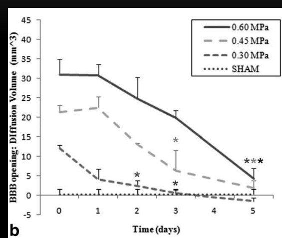
- Occur at low frequencies (~1 MHz) below that typically used for clinical imaging
- Occur at ultrasound intensity levels greater than that typically used for clinical imaging

BIOEFFECTS USED THERAPEUTICALLY

- Drug delivery – can be achieved LOCALLY with focused ultrasound and microbubbles
- Enhanced blood brain barrier permeability
- Enhanced capillary permeability
- Increased cellular delivery through cell membrane permeability
- Have been shown to significantly enhance local drug and gene delivery, and corresponding therapeutic response
- Improved thermal ablation (requires less delivered power with microbubbles – reduces thermal damage to healthy tissues)

EXAMPLE: TRANSIENT BLOOD BRAIN BARRIER OPENING





Samiotaki G, Vlachos F, Tung YS, Konofagou EE, Magn Reson Med. 2012 Mar;67(3):769-77

SAFETY

MICROBUBBLE CLEARANCE

- Microbubbles are vascular agents
- Phagocytosis in Liver and Spleen
- Gas is expelled through the lungs
- Shell content is eliminated by kidney and liver
- Phospholipids enter normal metabolism

- Typical circulation half life ~ 5-15 minutes

Quaia E, et al... Contrast media in ultrasonography-basic principles and clinical applications. New York: Springer; 2005.

SAFETY CONCERNS

- 1994 Albunex (albumin shell – air core)
- 1997 Optison (albumin shell – perfluorocarbon core)
- 2001 Definity (lipid shell – perfluorocarbon core)

INDICATIONS

Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Do not administer DEFINITY® to patients with known or suspected right-to-left, bi-directional or transient right-to-left cardiac shunts, by intra-arterial injection, or to patients with known hypersensitivity to perflutren.

Lantheus Medical Imaging

SAFETY CONCERNS

- Following reports of 11 deaths and 199 serious cardiopulmonary reactions after the administration of such agents in echocardiography.
- **2007: Black box Warning**

October 2007

Class label changes for ultrasound contrast agents:
- Contraindications for patients with serious cardiopulmonary conditions
- Boxed **WARNING**
- Mandatory physiologic monitoring

Lantheus Medical Imaging

May 2008

Class label changes for ultrasound contrast agents, based on review of new data from Lantheus and the academic community, as well as strident advocacy from physicians and ultrasound societies:
- October 2007 contraindications were removed
- Physiologic monitoring required for patients with pulmonary hypertension and unstable cardiopulmonary syndromes

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (see CONTRAINDICATIONS).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration (see WARNINGS).
- Always have resuscitation equipment and trained personnel readily available.

SAFETY CONCERNS

- Extensive Investigative Studies
  - > 5 million administered doses
    - Most frequent adverse reactions are mild
      - Headache: 5%, Nausea 4%, Flushing 4%, Dizziness 3%.
    - arrythmias, hyper/hypotension, neurologic and anaphylactoid reactions - rare

Procedure	Severe adverse effects	Risk
Contrast Echo	Death Anaphylactoid reaction	1:500,000 1: 15,000
Myocardial scintigraphy	Fatal malignancy	1:1000- 1:10,000
Exercise ECG	MI/death	1:2,500
Dobutamine stress test	MI/VF	1:2000
Coronary angiography	Death	1:1,000
Iodine (CT) contrast exam	Life-threatening reaction	1:500 – 1:5000

Table Modified from Main et al JACC 2007;50:2434-7 and from www.ICUS-society.org

FDA Revised Contrast Agents Labeling in Oct 2011

October 2011

DEFINITY® label changes:

- The following disclaimer was deleted from the Indications & Usage section: "The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established."
- The following monitoring information was deleted from the boxed **WARNING:** "In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration."
- The following statement was added to the boxed **WARNING:** "Most serious reactions occur within 30 minutes of administration."

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5.1). Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (4).
- Always have resuscitation equipment and trained personnel readily available.

http://www.fda.gov

SAFETY OF ULTRASOUND CONTRAST AGENTS: SUMMARY

- ultrasound contrast agents are very safe with a low incidence of side effects
- They are not nephrotoxic or cardiotoxic
- incidence of hypersensitivity or allergic events appears much lower than current X-ray or MR contrast agents
- As in all clinical procedures, physicians should balance potential clinical benefit against the theoretical possibility of associated adverse bioeffects in humans
- New accreditation standards (ICAEL) for the first time require US echocardiography laboratories to use ultrasound contrast agents to improve suboptimal echocardiograms, unless an alternative imaging plan is in place
- Cardiologists and radiologists throughout Europe, Canada, Asia and Latin America routinely and safely use CEUS to image and diagnose abnormalities throughout the body as well as tumors of the liver, ovaries, breast, testicles, lymph nodes, etc.

QUESTIONS?