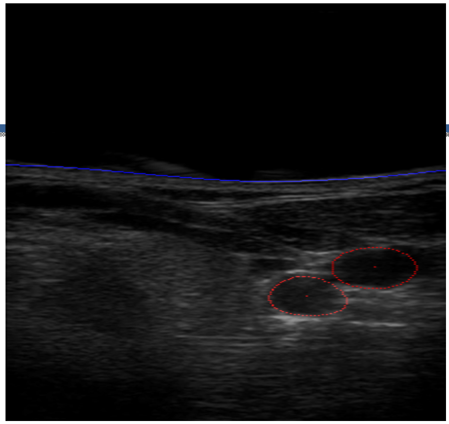

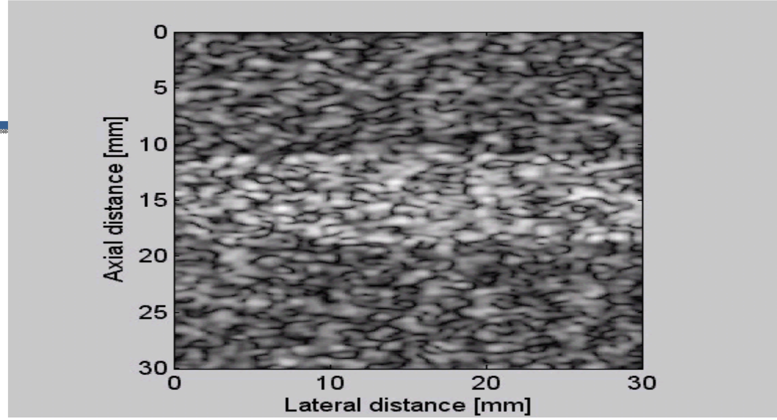

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The advances in multipulses and nonlinear ultrasound imaging modalities

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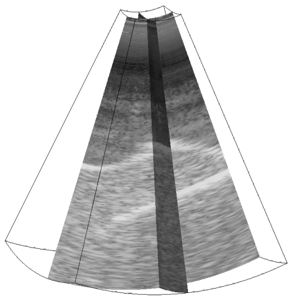

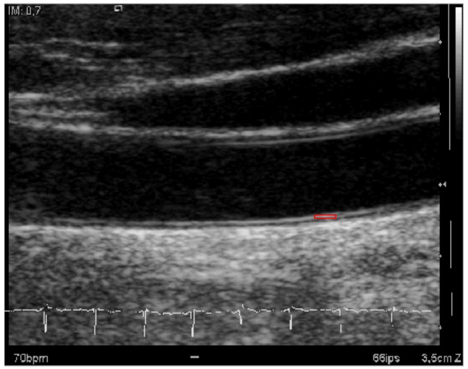

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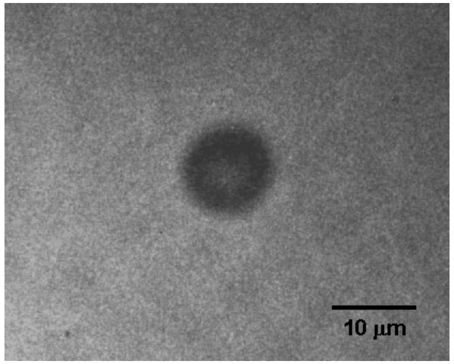
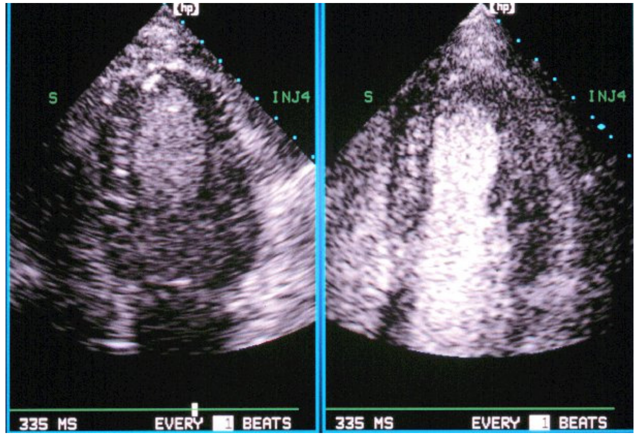
The advances in multipulses and nonlinear ultrasound imaging modalities

- **Advanced in** (Nonlinear) **Ultrasound**
  - Ultrasound Contrast Agent
  - Nonlinear ultrasound
  - **Improvement of ultrasound imaging or Nonlinear imaging**
  - Harmonic imaging
  - Multipulses imaging or Contrast (nonlinear) imaging
  - Generalization of multi-pulse techniques
  - Influence of scatterer motion to phased multipulses method

Introduction and generalities



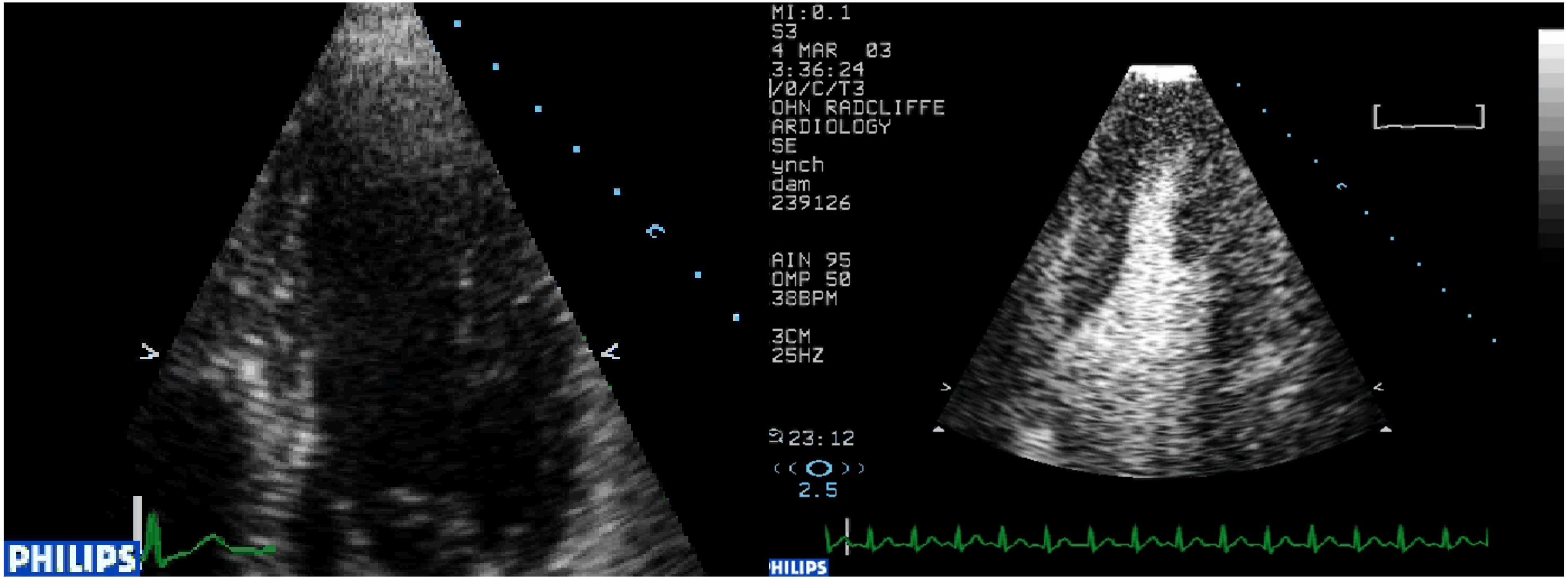


- Contrast agents are useful in all imaging modalities (X ray, MRI, PET, ...)
- Ultrasound scan is **low cost, safety,** … many benefits compared to other modality
- Ultrasound scans are the most performed worldwide,
- The additional diagnostic information obtained by using a contrast agent could potentially benefit a significant numbers of these scans.

Introduction and generalities

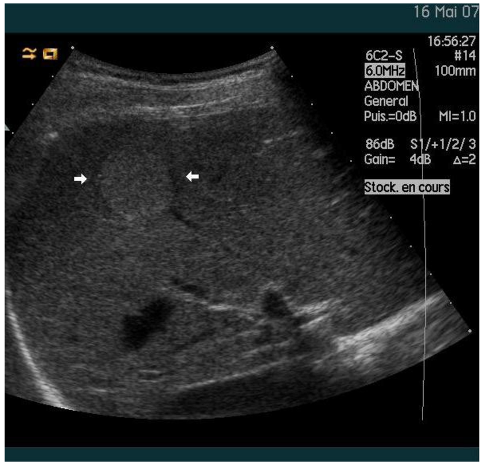
- Ultrasound imaging depends **on acoustic wave backscattered toward the probe by scatterers**
- **Increasing the amount of (strong) scatterers** should increase the number of echoes and therefore, improve the image
- First work were turned on development of new particles.
- Now, the ultrasound imaging systems are being adapted to contrast agent properties.

- No contrast agent
- contrast agent

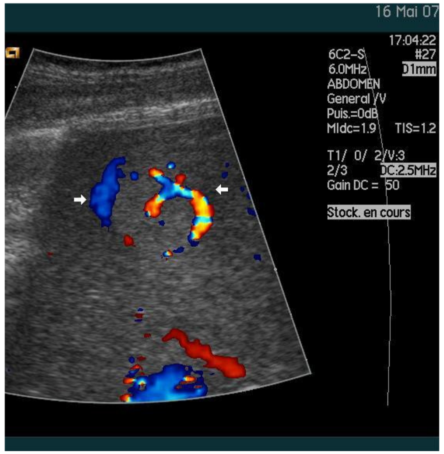


Why do we need Ultrasound contrast agents?

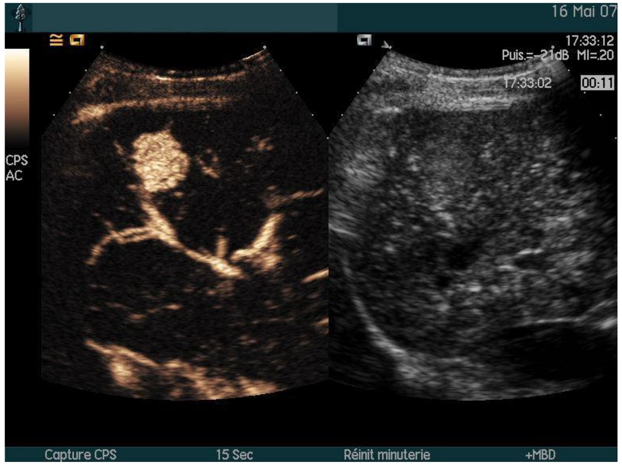
Anatomical information



Functional information (big vessels)



Functional information (microvasculature)



Historic

In 1968, Gramiak and Shah (GRAM 68) published the first work about Ultrasound Contrast Agents (USCA)

About thirty years later the first USCA are commercialized

(Albunex, Echovist, Levovist), Optison, Sonovue

Many contrast agents solutions were tested

hand shaken solutions

solids, liquids or gaseous particles

Specific imaging

Harmonic imaging,

Pulse inversion imaging, Amplitude modulation, Contrast Pulse Sequencing

Intermittent imaging, Loss of correlation imaging

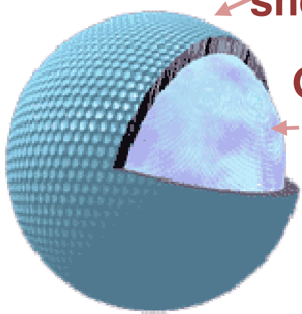
…

Principle

- **From an acoustic point of view, blood and biological tissues are equivalent to liquids (ultrasound velocity, acoustic impedance, ...).**
- **In blood, the acoustic wave is scattered by red blood cells**
- **The contrast agent injected in the blood flow (bolus or perfusion) increased the number of scatterers.**
- **In contrast echography, blood is used to vehicle contrast agent.**
- **Imaging of blood vessels and perfused tissues is improved.**
- **The maximum efficiency is obtained with gaseous particles (resonant).**

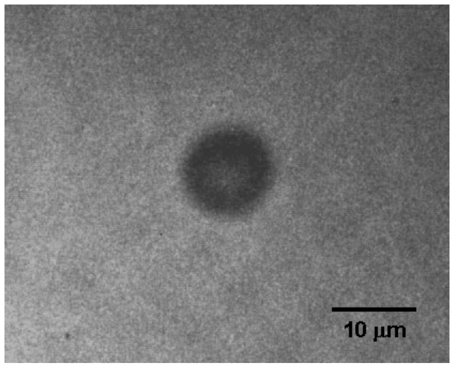
ULTRASOUND CONTRAST AGENTS (UCA)

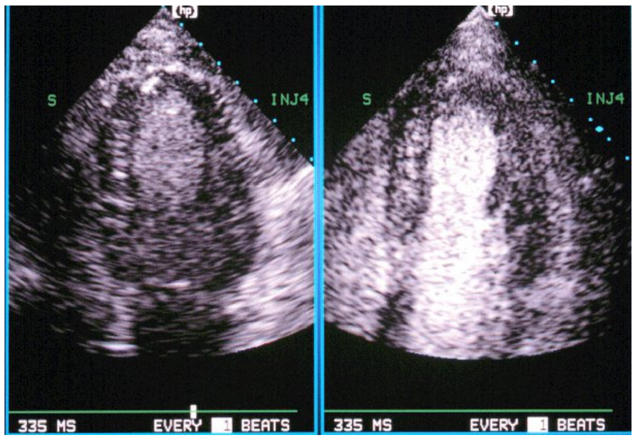
- Suspensions of **gas microbubbles** for intravenous injection
- "Boost" image quality and enhance diagnostic confidence
- Enhance **perfused tissue: UCA are transported by the blood**



Diameter 1–10 µm

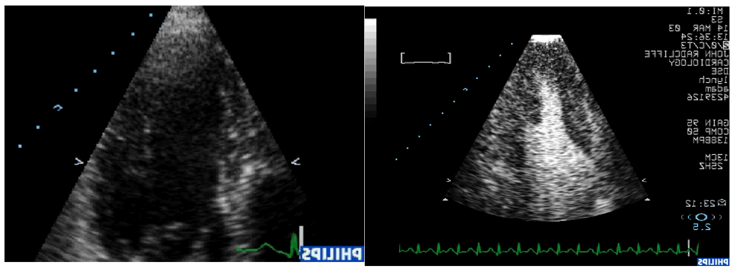
- Clinical applications
  - Estimation of myocardial perfusion
  - Detection and characterization of tumors
  - Amplification of Doppler signal





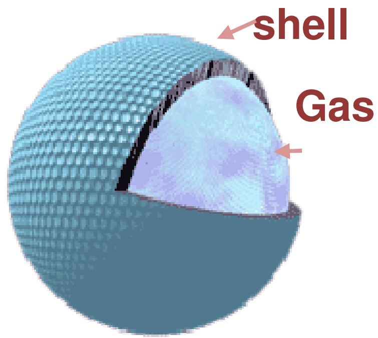
No contrast agent

contrast agent



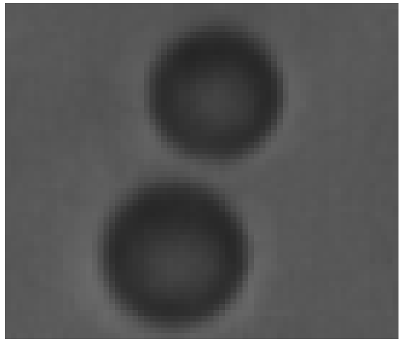
Characteristics of UCA in an acoustic field

- **Gas**
  - Air
  - High molecular weight gas with low diffusivity (perfluorocarbon, dodecofluoropentane, ...)



- **Diameter: 1-10 µm**

- **Shell**
  - Albumin, galactose, phospholipid, polymer
  - **Thickness 20-200 nm**

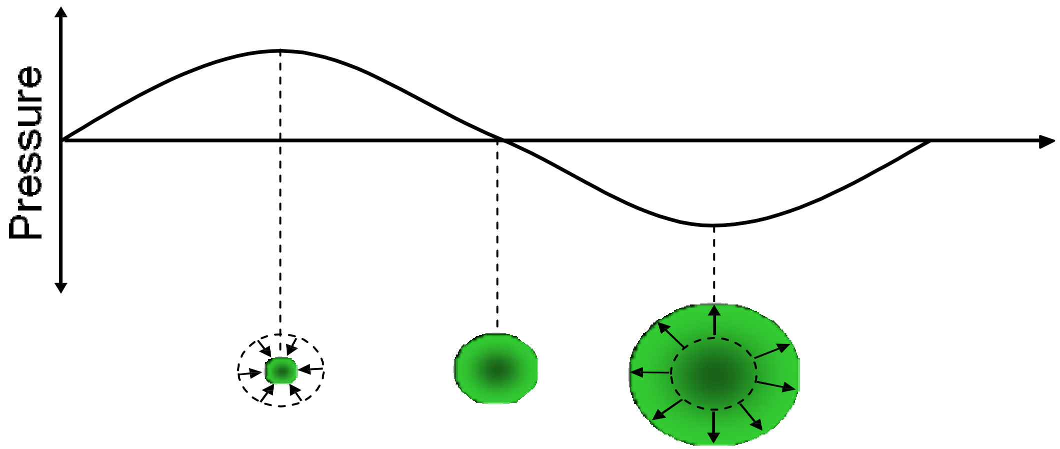


- **Resonance frequencies: 2-10 MHz**

- **Concentration before injection: 10^8 to 10^9 microparticles/ml**

- **Gas volume ≈ 1 %** (1 to 5 cm^3 of solution is intravenously injected)

Acoustic bubble properties: volume pulsation



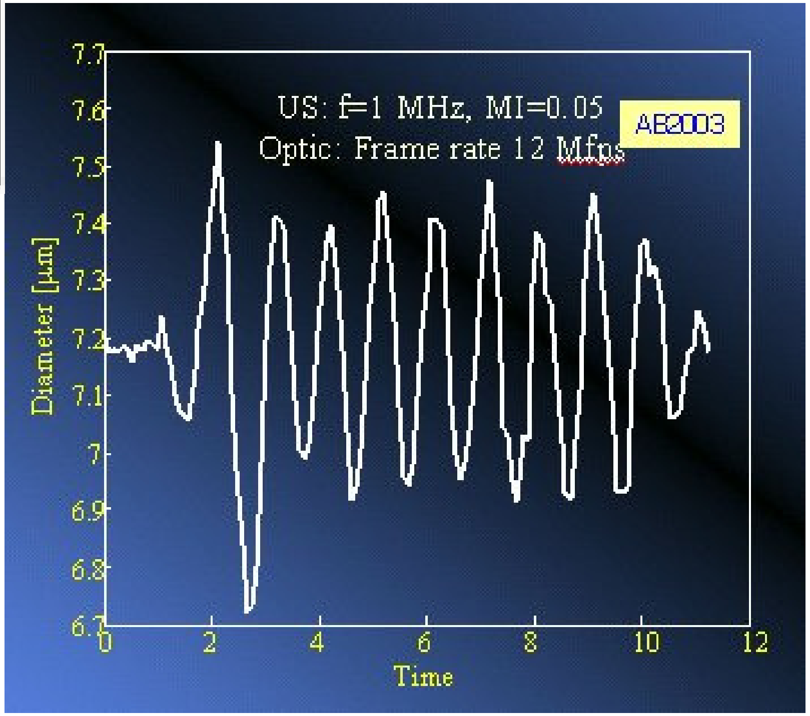
Gaseous microbubbles are highly compressible and oscillate in response to the incoming ultrasound wave.

Radius change

Thorax Center Rotterdam
with the courtesy of Nico de Jong

US: 1MHz, MI=0.05

Brandaris camera: 12 MHz



Bubble diameter – time curve

Diameter: 7.2 ±0.2

$\Delta R/R \approx 3$ %

Characteristics of UCA in an acoustic field

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$$\lambda = c / f$$

Echographic frequencies → Acoustic wavelength

$1 \text{ MHz} < f < 12 \text{ MHz}$ — $1.5 \text{ mm} > \lambda > 0.125 \text{ mm}$

Contrast agents size

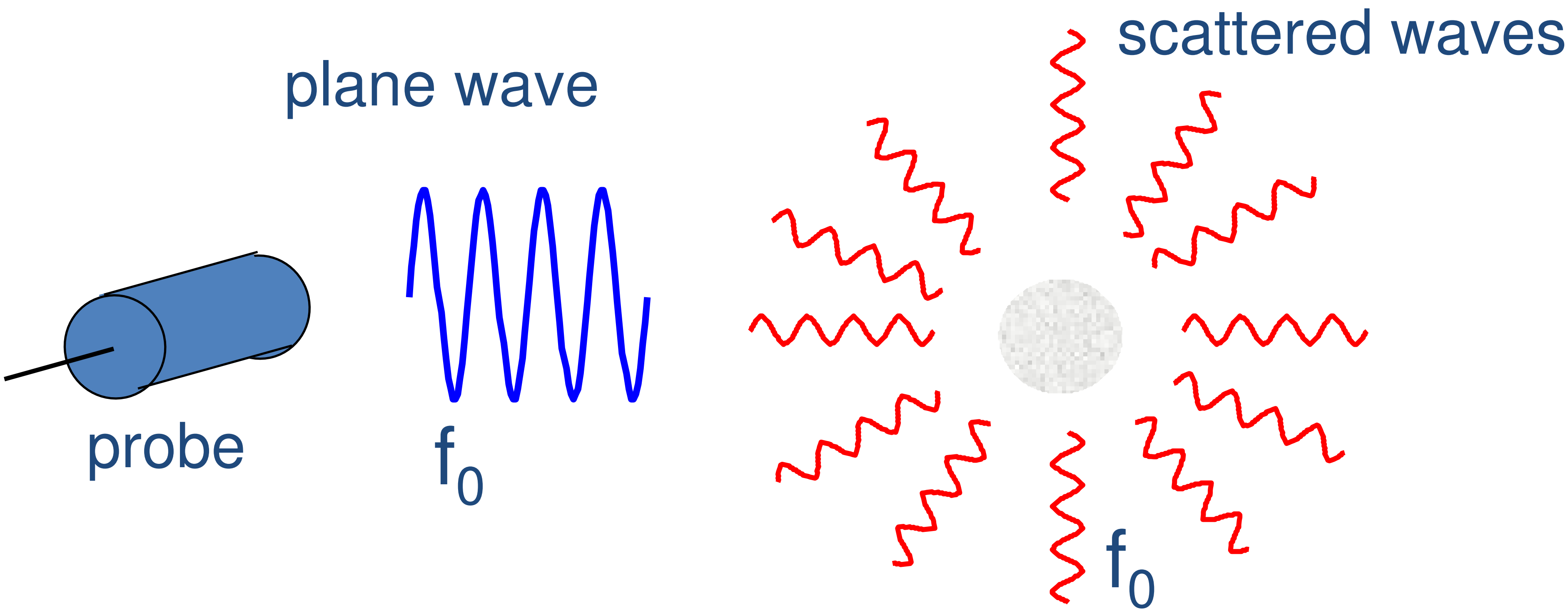
$1\ \mu m < D < 10\ \mu m$

- **The size of the particles is much smaller than the wavelength of the acoustic field (Rayleigh diffusion):**

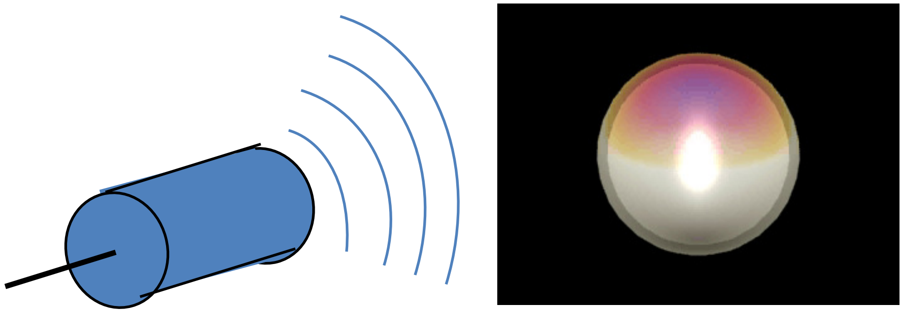
  $$D \ll \lambda$$

- **Echographic frequencies are in accordance with the resonance frequencies of bubbles.**

Linear scattering of a bubble



Linear scattering of a bubble: resonance frequency



$$R = R_o + \xi$$

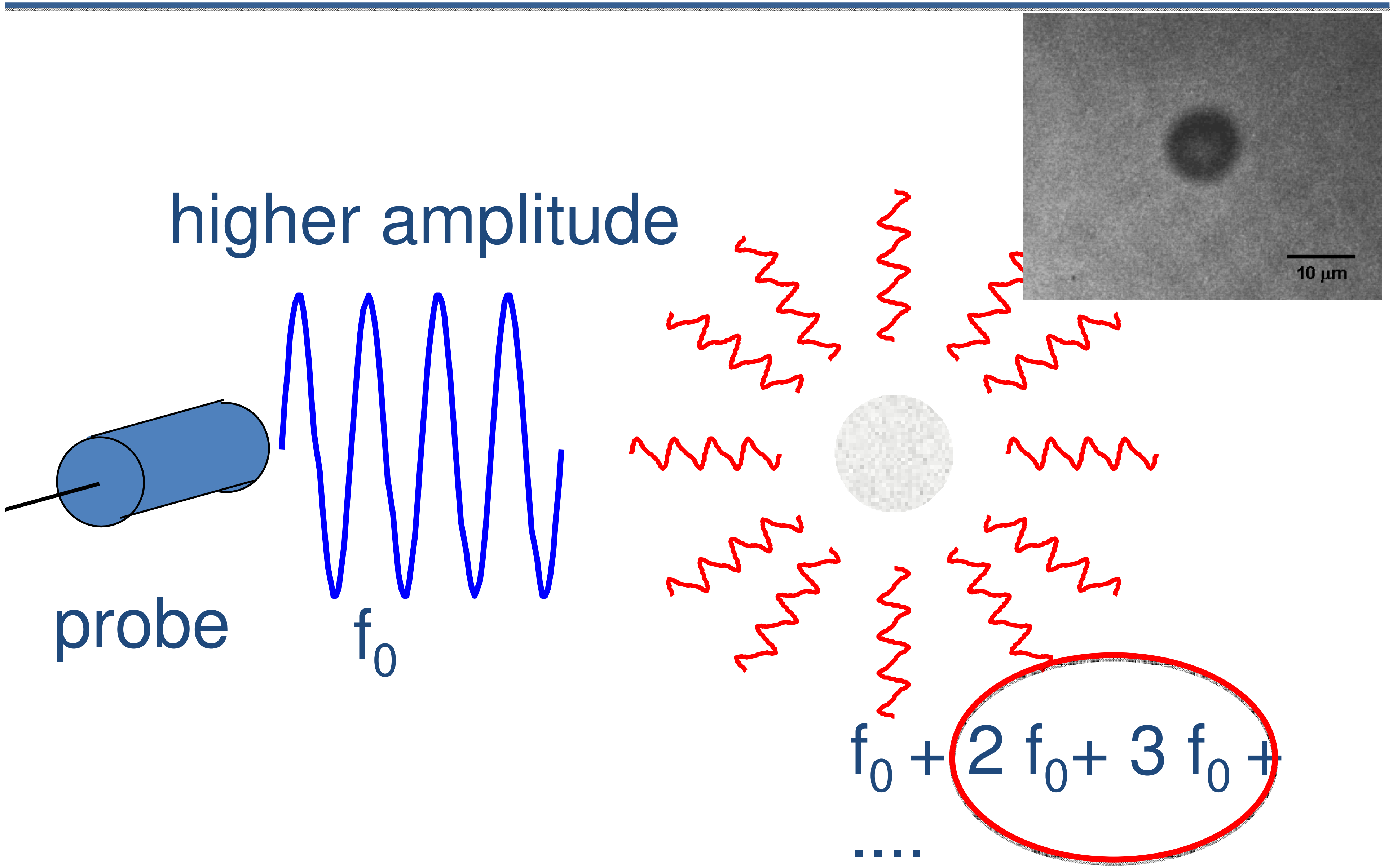
$$\xi << R_o$$

$$f_r = \frac{1}{2\pi R_o}\sqrt{\frac{3\gamma P_o}{\rho}}$$

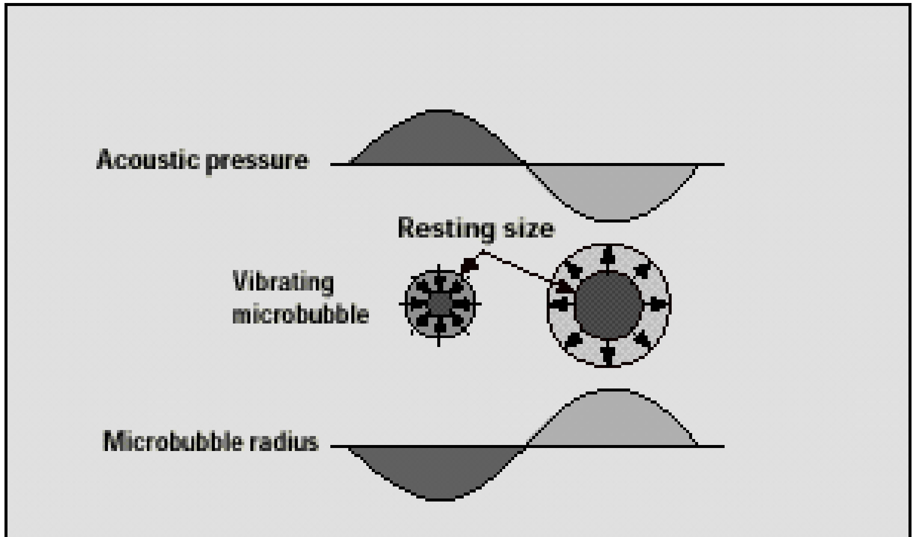
Air bubble in water $\quad f_r\, R_0 \approx 3.3\,\mathrm{MHz}\,\mu\mathrm{m}$

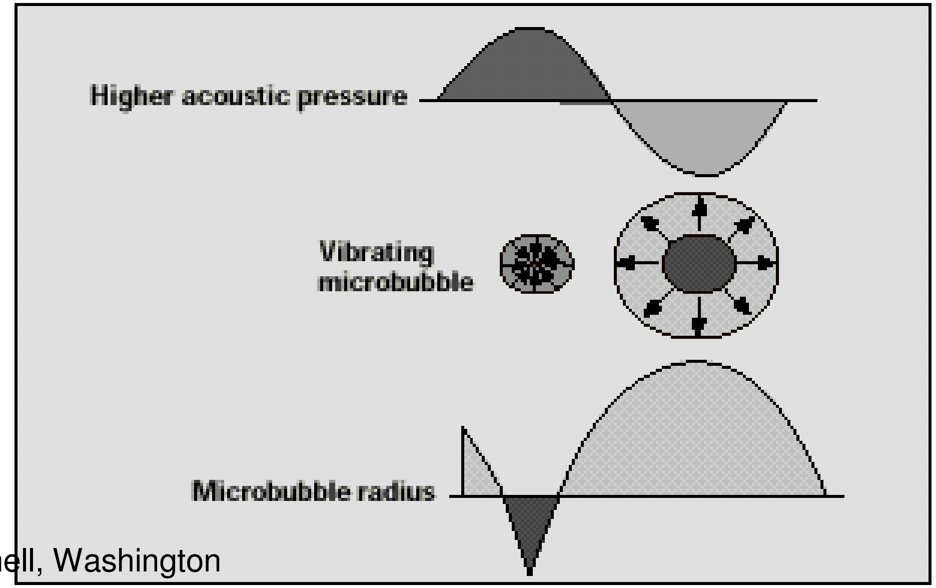
Diameter (µm)	1	2	4	6	8
Resonance frequency (MHz)	6.6	3.3	1.6	1.1	0.8

Non linear scattering of a bubble



Non linear scattering of a bubble





ATL Ultrasound, Bothell, Washington

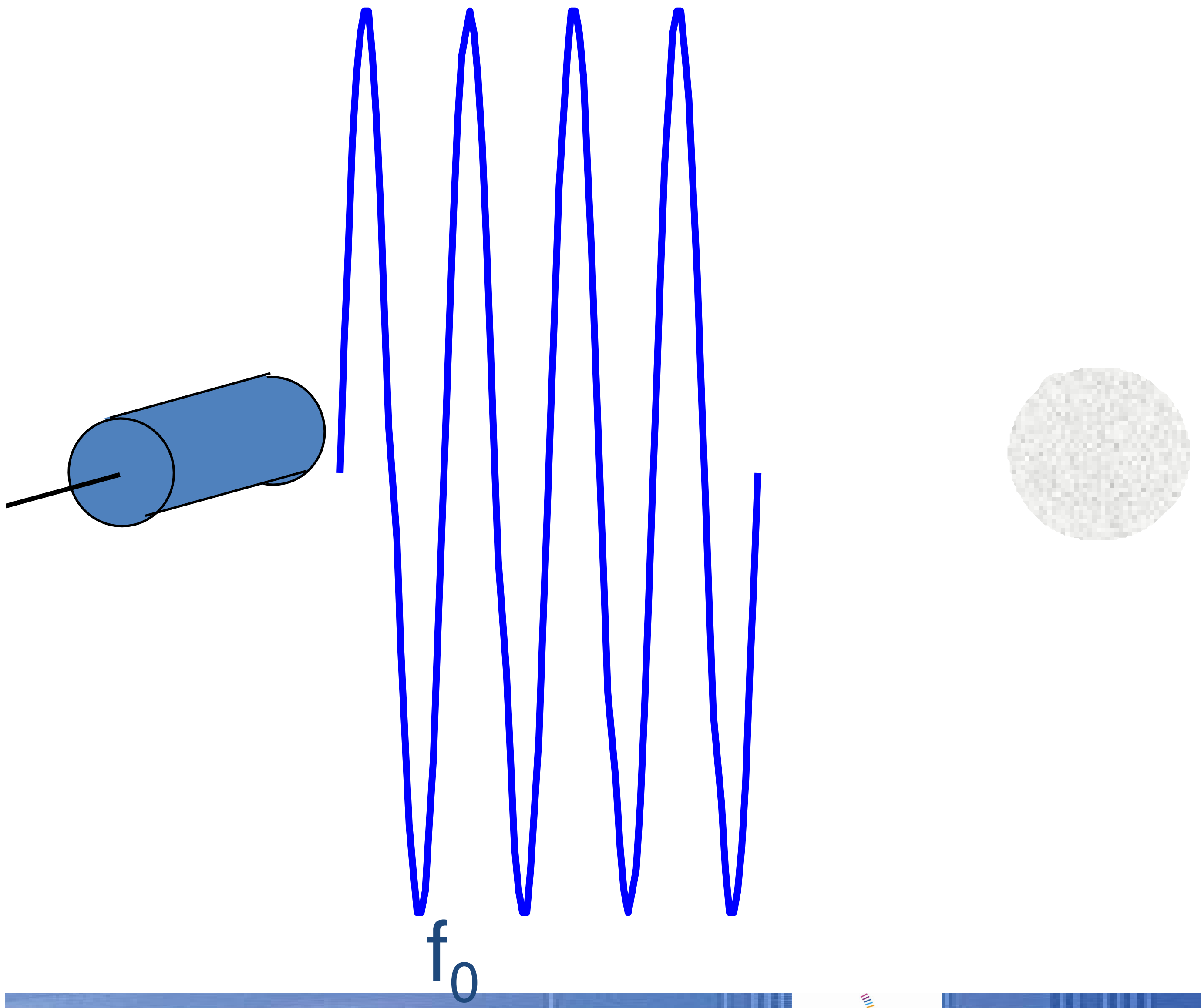
Linear scattering:
microbubble response to low amplitude acoustic wave.
The vibration is symmetric

Non linear scattering:
microbubble response to a higher amplitude acoustic wave.
The vibration is asymmetric

f_0

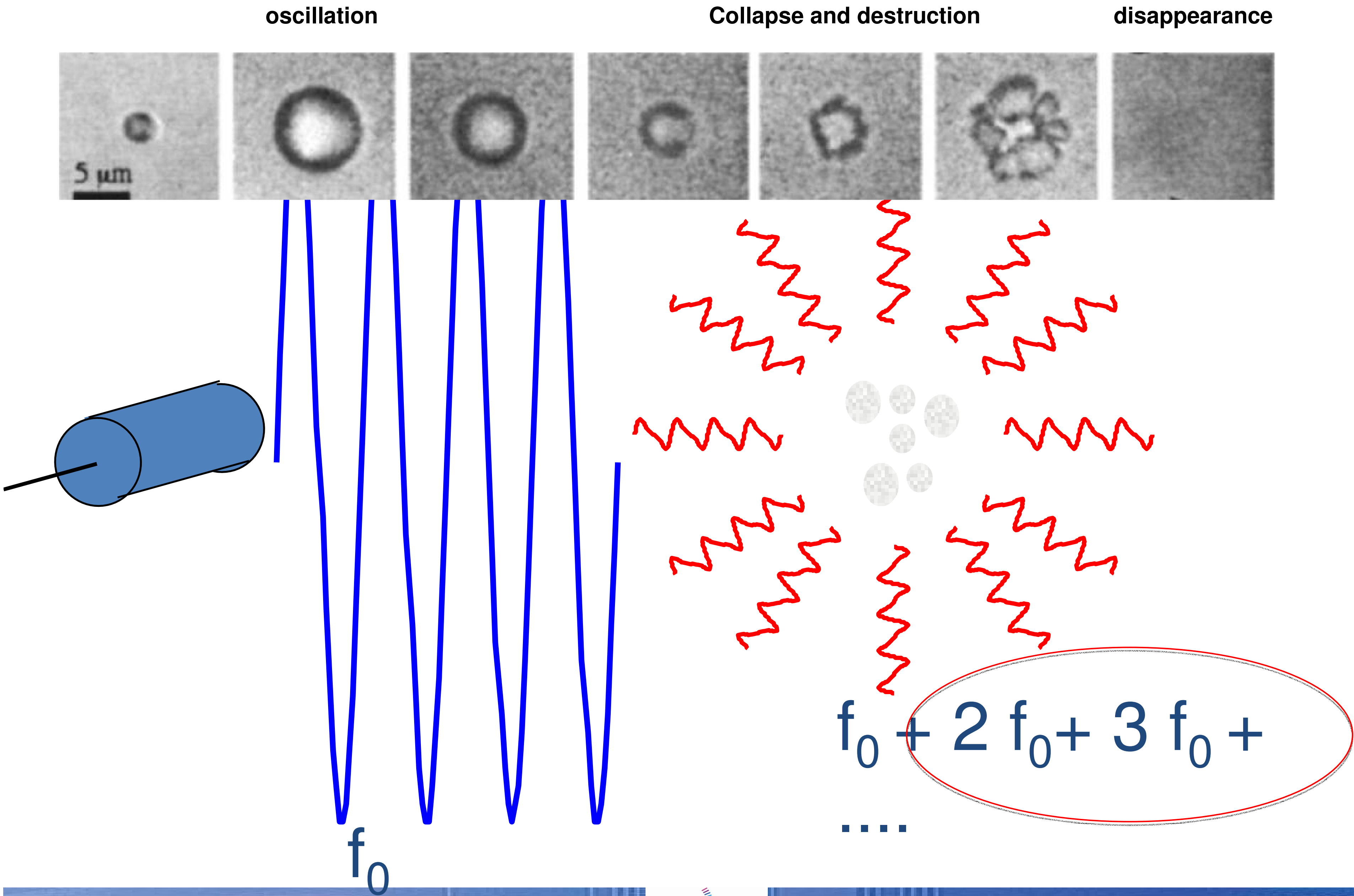
$f_0 + 2\ f_0 + 3\ f_0 + \ldots.$

Non linear (transient) scattering of a bubble



Non linear (transient) scattering of a bubble

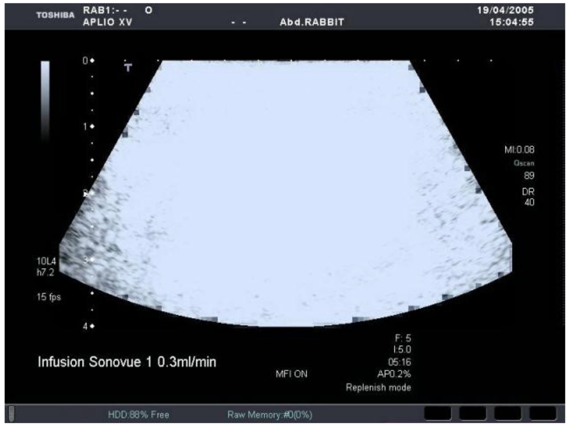
Creatis



Bubble destruction

Before destruction

Destruction (high MI)

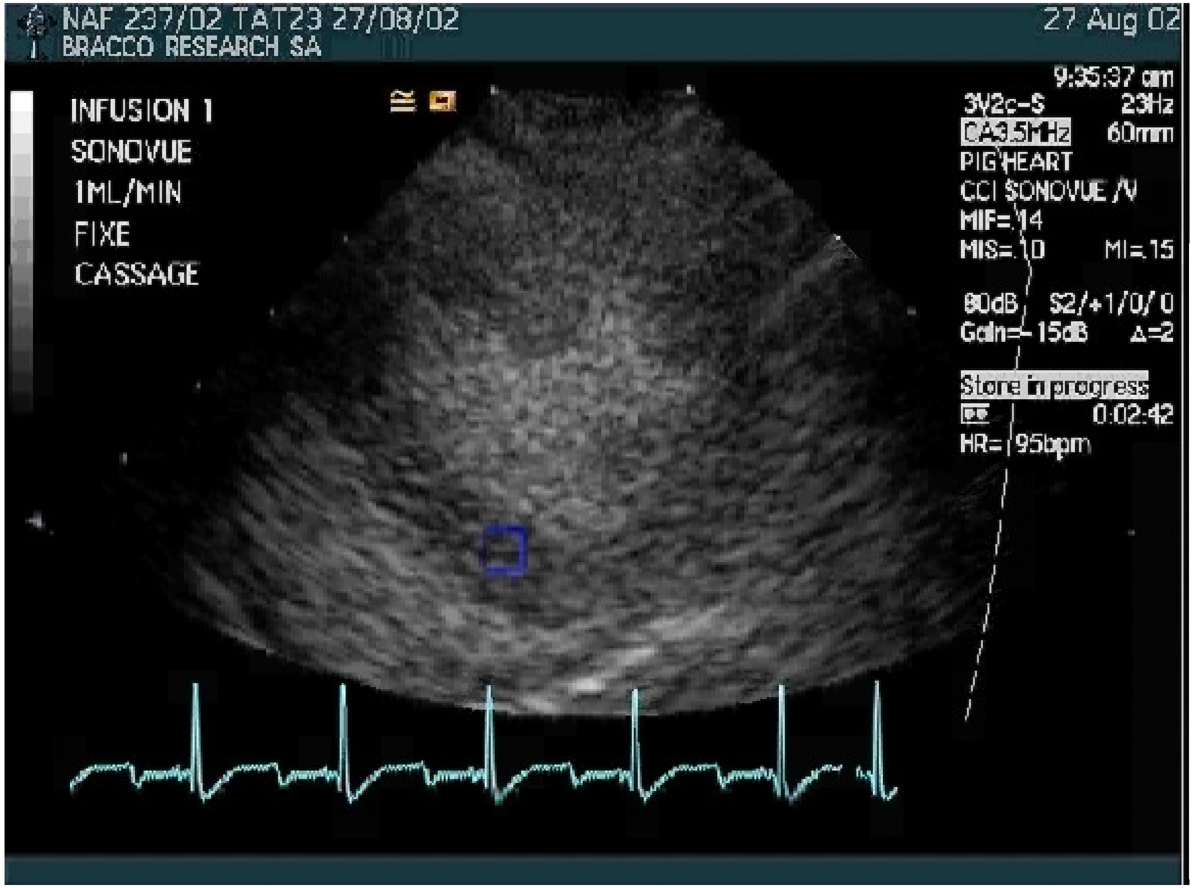


After destruction

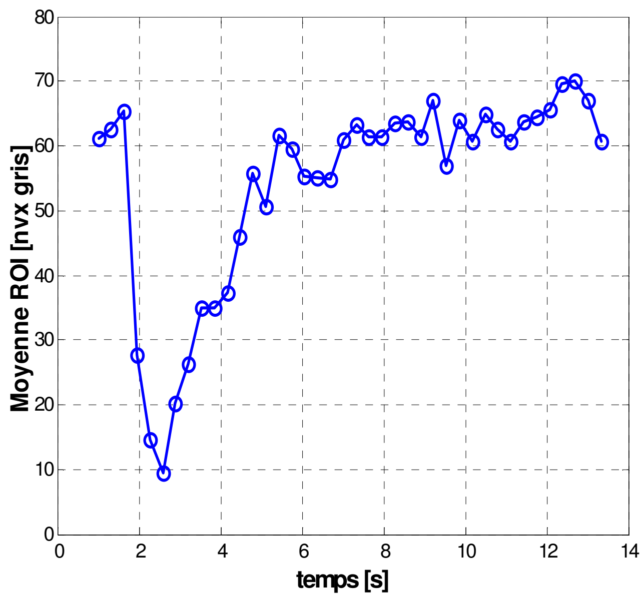
Replenishment phase during infusion of contrast agent

Bubble destruction in combination with low-MI real-time contrast imaging can be used for perfusion quantification.

Destruction and reperfusion mode

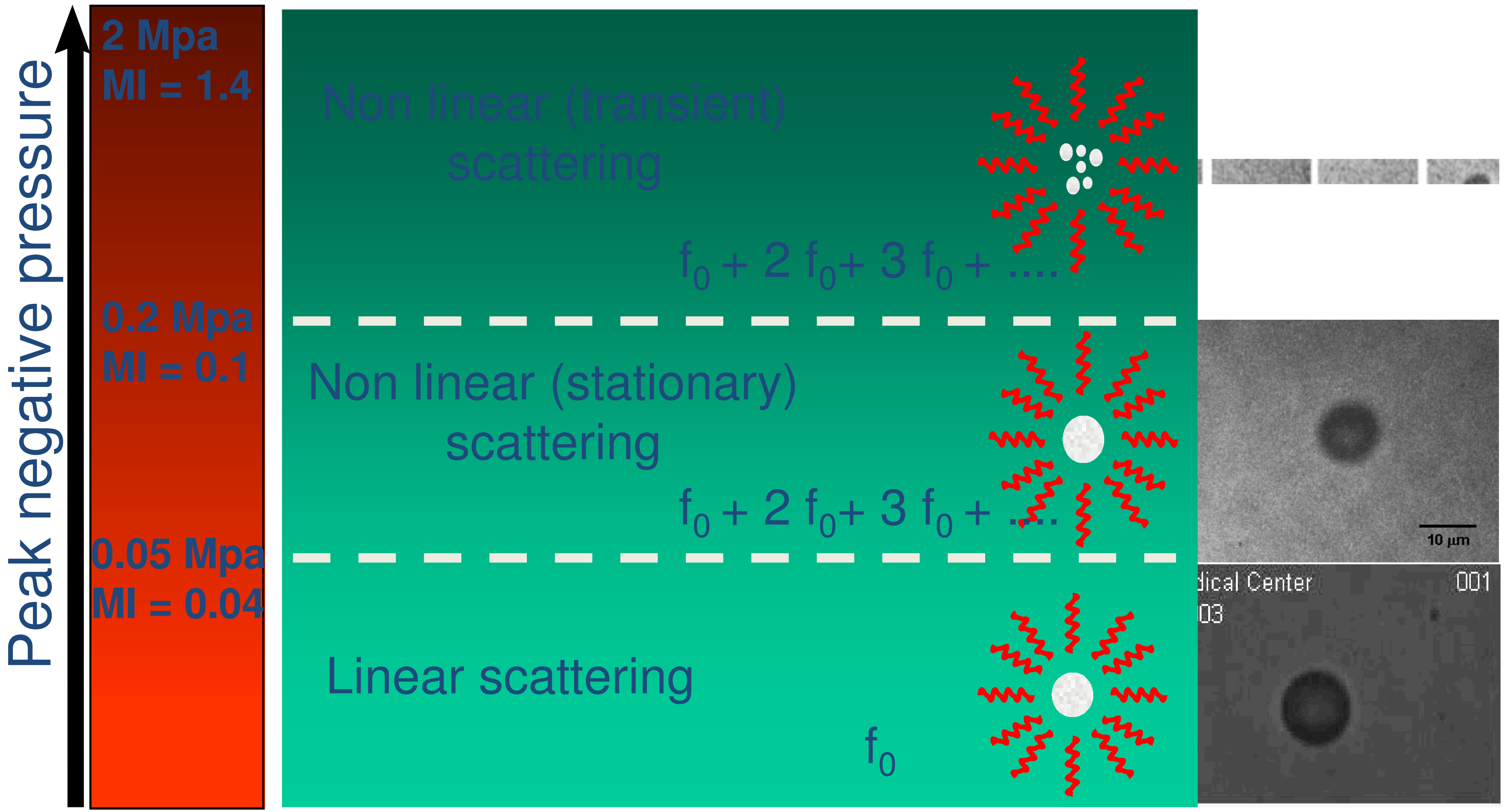


Quantification of perfusion



One shot at high intensity to destroy the contrast agent

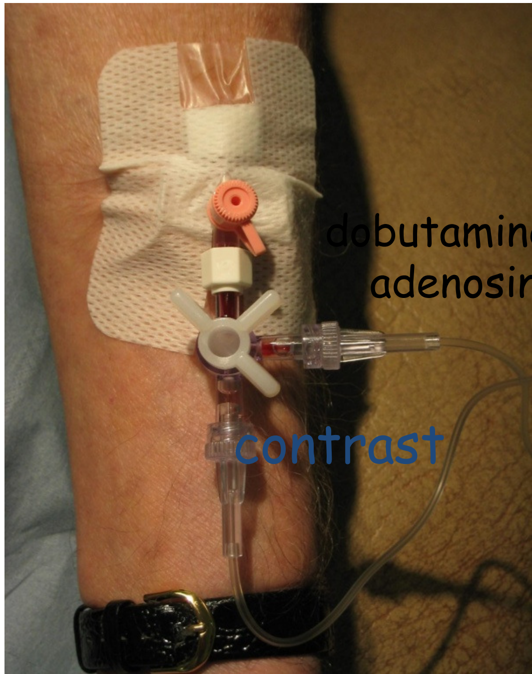
Influence of acoustic pressure



f = 2 MHz

Sonovue (Bracco)

65 € (the sample)



Acoustic bubble properties: shadowing

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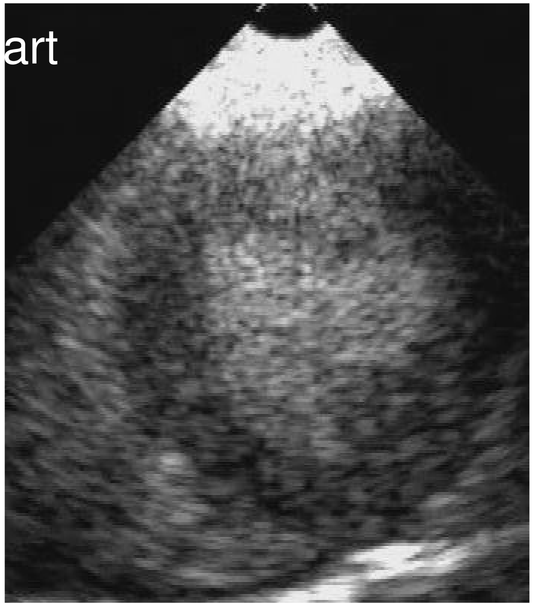
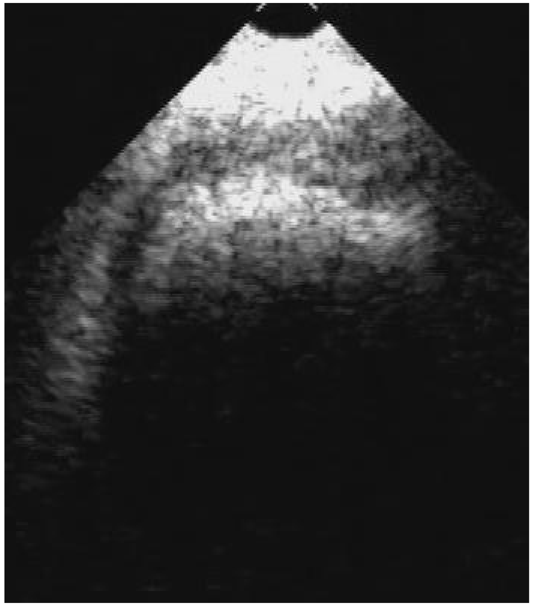
**Bubbles attenuate the ultrasound wave =>
shadowing of underlying structures**

low concentration high concentration



no shadowing



strong shadowing

Can we optimally exploit the acoustic properties of contrast-agent microbubbles?

Imaging dedicated to contrast agent

Creatis

wave scattered
by contrast agent

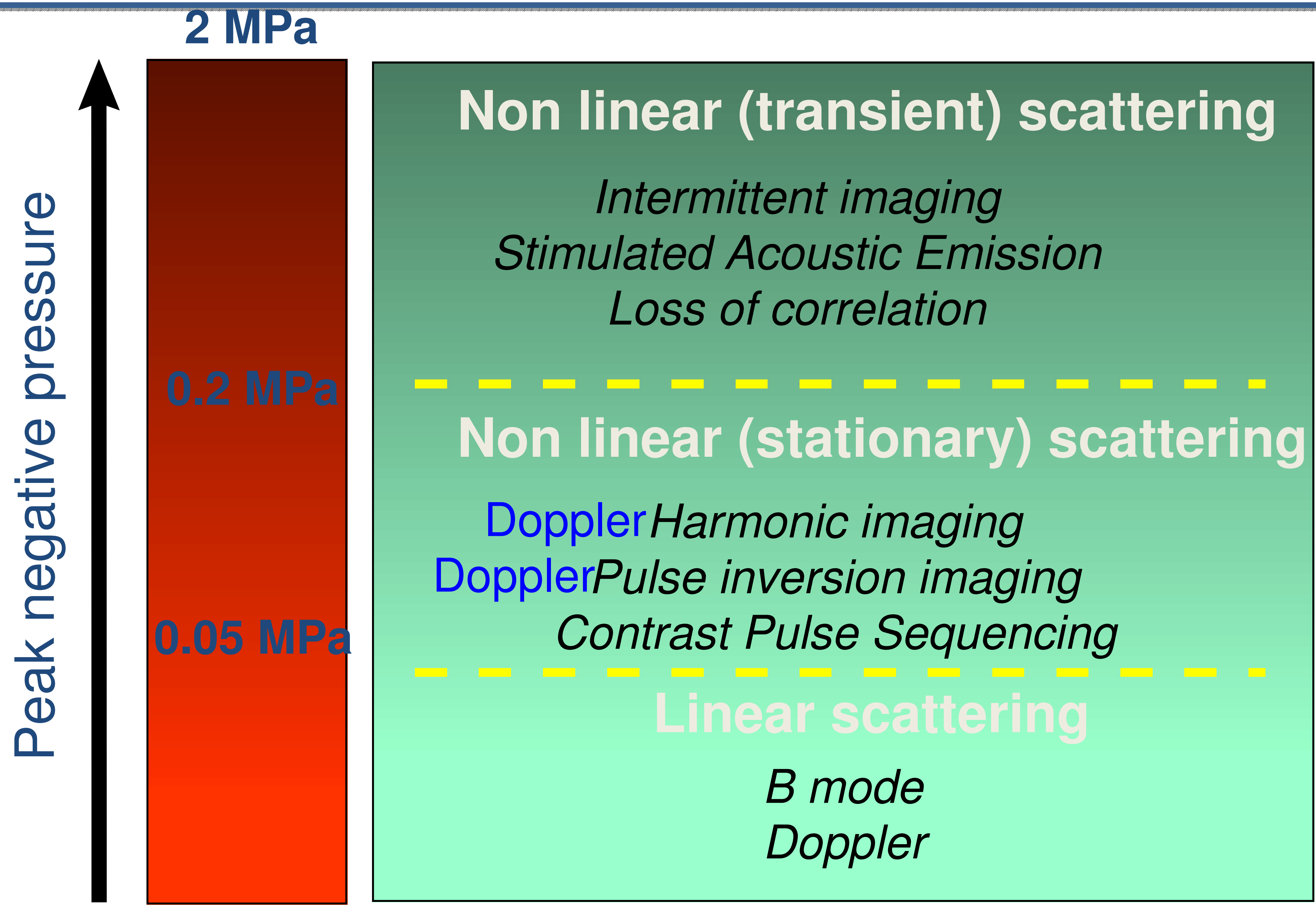
higher $\frac{\text{signal}}{\text{noise}}$

wave scattered by tissue

One scan

Two or more scans

Transmitted pulses and signal processing



2 MPa
Peak negative pressure
0.2 MPa
0.05 MPa
Non linear (transient) scattering
Intermittent imaging
Stimulated Acoustic Emission
Loss of correlation
Non linear (stationary) scattering
Doppler Harmonic imaging
Doppler Pulse inversion imaging
Contrast Pulse Sequencing
Linear scattering
B mode
Doppler

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Why Imaging is performing with contrast agent?

Strong (resonant) scatterers are increased in the perfused tissue

Why Harmonic Imaging is performing with contrast agent?

Strong (resonant) scatterers are increased in the perfused tissue

The non linearity is higher for contrast agent than the tissue one

Why Pulse Inversion Harmonic Imaging is performing with contrast agent?

Strong (resonant) scatterers are increased in the perfused tissue

The non linearity is higher for contrast agent than the tissue one

Pulse inversion increase the signal to noise ratio

Why Pulse Inversion Harmonic Doppler Imaging is performing with contrast agent?

Strong (resonant) scatterers are increased in the perfused tissue

The non linearity is higher for contrast agent than the tissue one

Pulse inversion increase the signal to noise ratio

The Doppler technique images the decorrelation of ultrasound signals

- contrast agent is moving with the blood flow
- contrast agent distribution is changing (time life)
- contrast agent spatial distribution is modified by the ultrasound field (radiation force)

Benefits and drawbacks

- **Contrast agent enhance the echos and so, the gray level of cavity and perfused tissues**
- **Ultrasound contrast imaging is**
  - contrast particle dependent
  - injection mode dependent (bolus or perfusion)
  - frequency dependent
  - imaging modality dependent
  - operator dependent
- **The protocol have to be adapted to the organ**
- **Drugs delivery?**

The advances in multipulses and nonlinear ultrasound imaging modalities

- **Advanced in** (Nonlinear) **Ultrasound**
  - Ultrasound Contrast Agent
  - Nonlinear ultrasound
  - **Improvement of ultrasound imaging or Nonlinear imaging**
  - Harmonic imaging
  - Multipulses imaging or Contrast (nonlinear) imaging
  - Generalization of multi-pulse techniques
  - Influence of scatterer motion to phased multipulses method
- **CREANUIS: Simulation of nonlinear ultrasound images**

Nonlinear propagation

Nonlinear propagation

The motion equation

$$\rho \frac{\partial \vec{u}}{\partial t} + \nabla p = 0$$

The pressure is expanded using the Taylor series

$$p = p_0 + \frac{A}{1!}\left(\frac{\rho - \rho_0}{\rho_0}\right) + \frac{B}{2!}\left(\frac{\rho - \rho_0}{\rho_0}\right)^2 + \frac{C}{3!}\left(\frac{\rho - \rho_0}{\rho_0}\right)^3 + \dots$$

linear

The celerity

$$c = c_0\left(1 + \frac{B}{2A}\frac{u}{c_0}\right)^{\frac{2A}{B}+1} \approx c_0 + \left(1 + \frac{B}{2A}\right)u = c_0 + \beta u$$

$$\beta = 1 + \frac{B}{2A}$$

Nonlinear coefficient

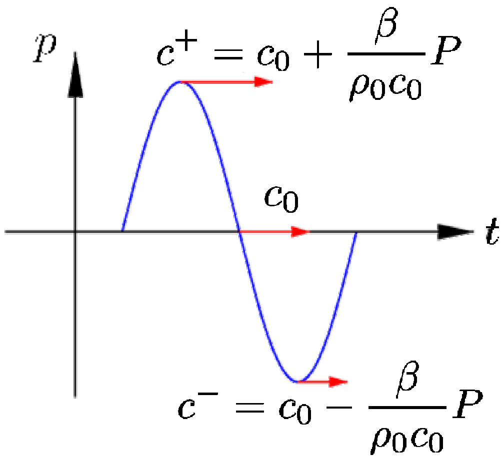
Nonlinear parameter

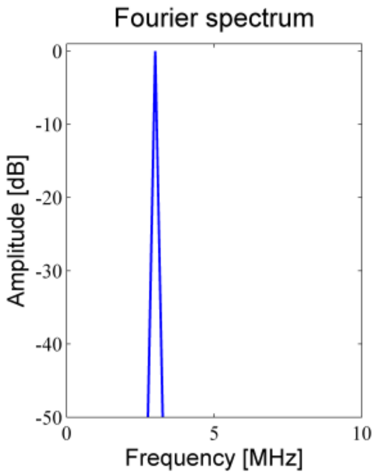
Nonlinear propagation: celerity

$$c = c_0\left(1+\frac{B}{2A}\frac{u}{c_0}\right)^{\frac{2A}{B}+1} \approx c_0 + \left(1+\frac{B}{2A}\right)u = c_0 + \beta u$$

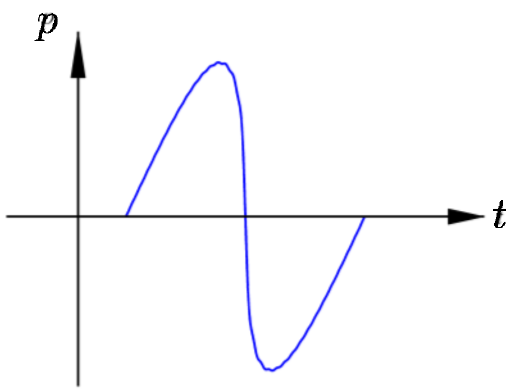
$$\beta = 1 + \frac{B}{2A}$$

Nonlinear coefficient — Nonlinear parameter

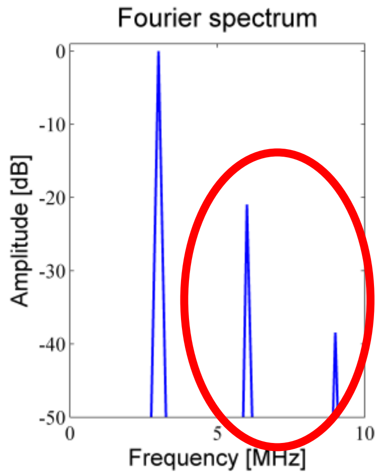




f_0

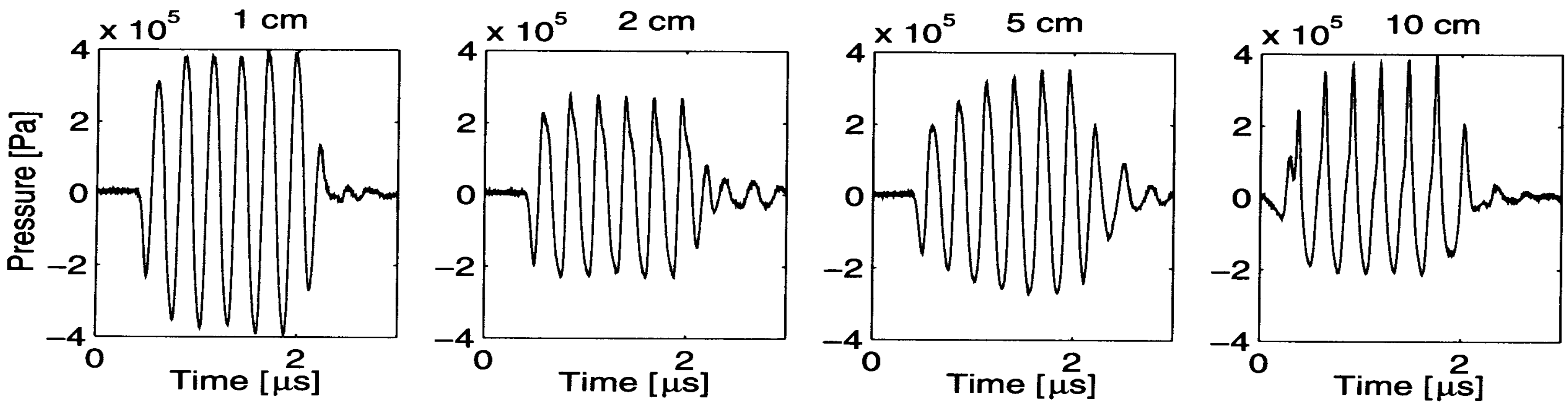


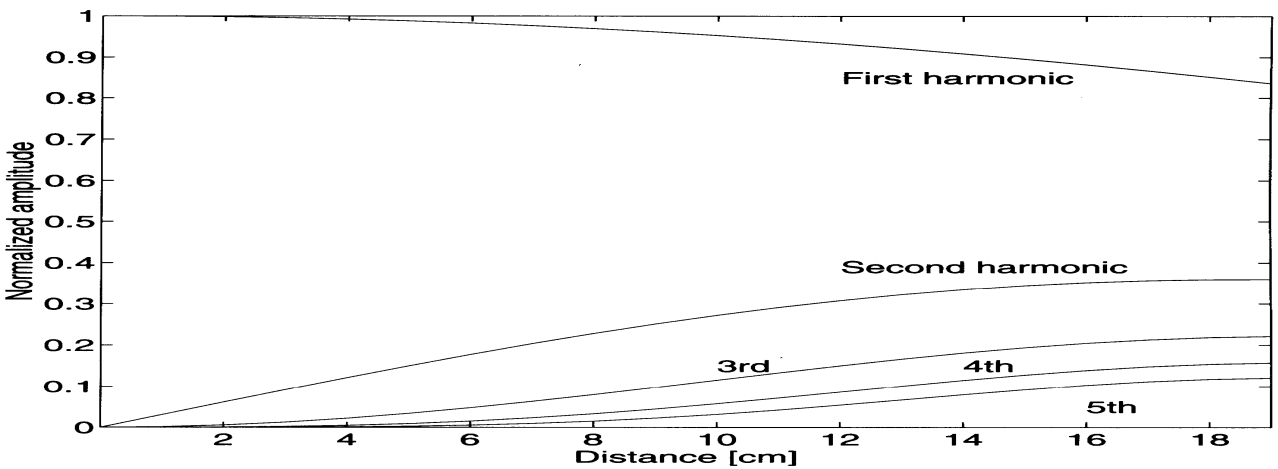
After propagation



$f_0 + 2\,f_0 + 3\,f_0 + \ldots.$

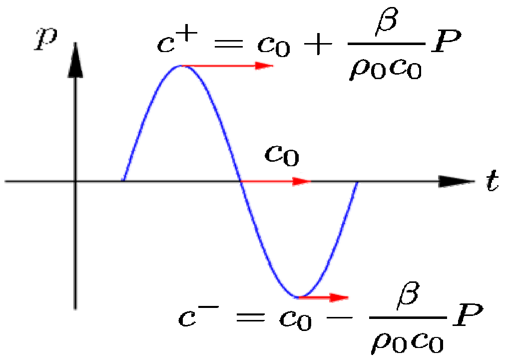
Nonlinear Propagation

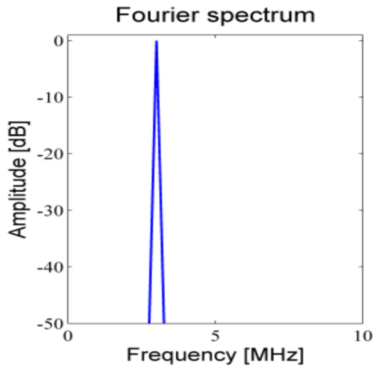




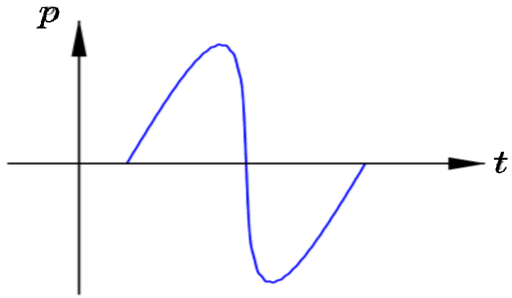
Nonlinearity: tissue and contrast agent

- **Tissue**

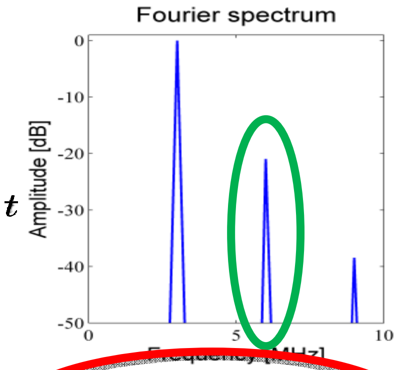




f_0

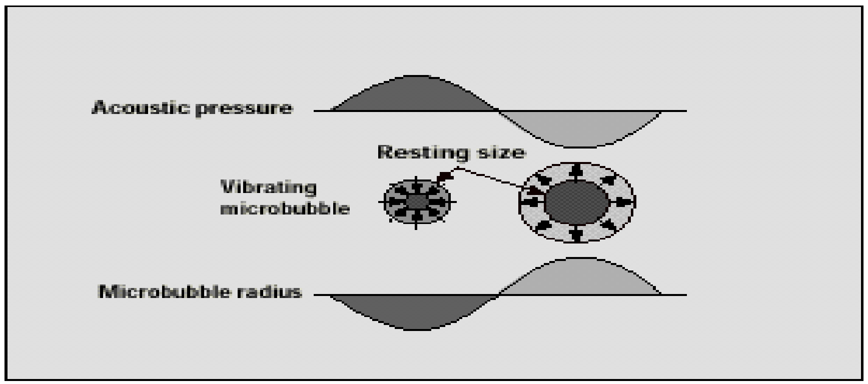


After propagation



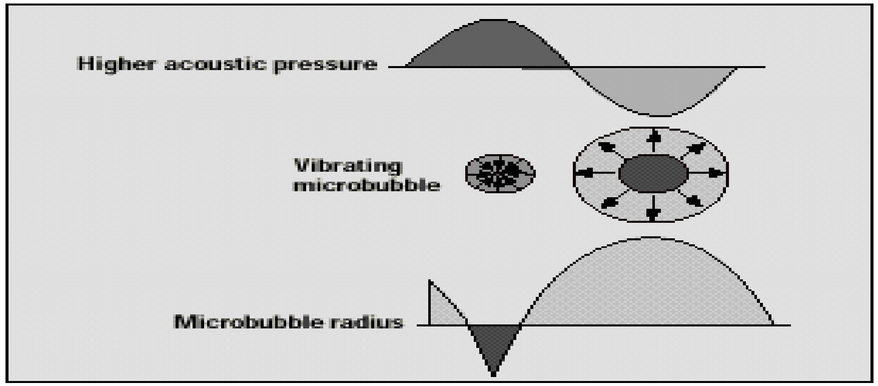
$f_0 + 2 f_0 + 3 f_0 + ...$

- **Contrast agent**



Linear scattering: The vibration is symmetric

f_0



Non linear scattering: The vibration is asymmetric

$f_0 + 2 f_0 + 3 f_0 + ...$

Imaging dedicated to contrast agent

it is a signal processing problem: higher SNR

wave scattered by contrast agent

higher $\frac{\text{signal}}{\text{noise}}$

$\mathbf{f_0 + 2\, f_0 + 3\, f_0 + ...}$

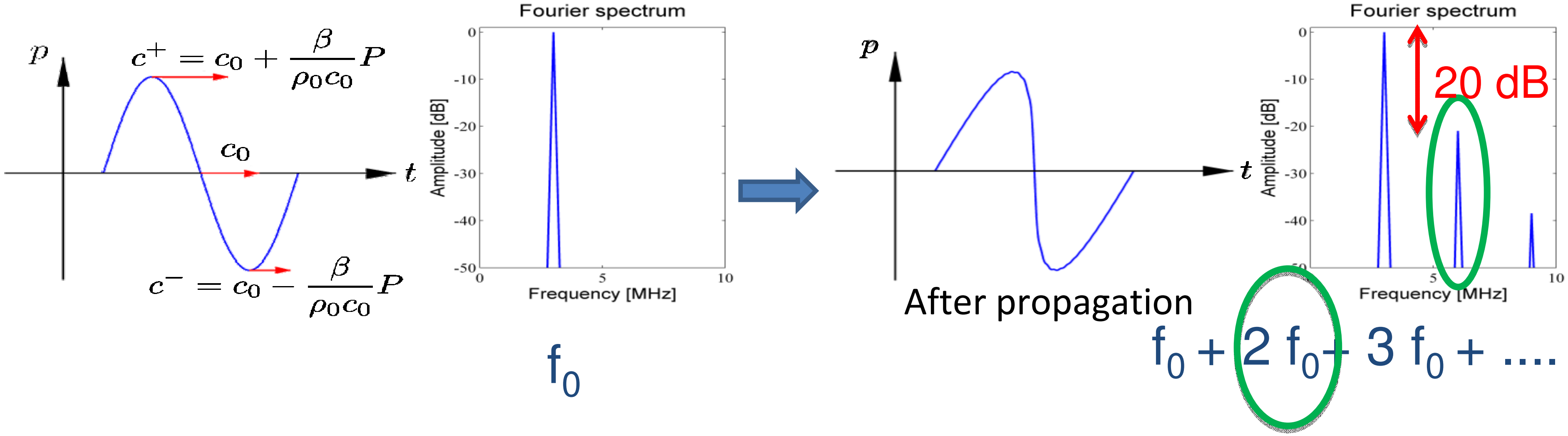
wave scattered by tissue

- **Basic of ultrasound and medical ultrasound imaging**
- **Advanced in Ultrasound**
  - Ultrasound Contrast Agent
  - Nonlinear ultrasound
  - **Improvement of ultrasound imaging or Nonlinear imaging**
  - Harmonic imaging
  - Multipulses imaging or Contrast (nonlinear) imaging
    - Pulse inversion (PI)
    - Second Harmonic Inversion (SHI)
    - Amplitude modulation (AM)
    - Pulse inversion amplitude modulation (PIAM)
    - Phase coded sequences (PCS)
    - Contrast pulse sequence (CPS)

Harmonic Imaging (without UCA)

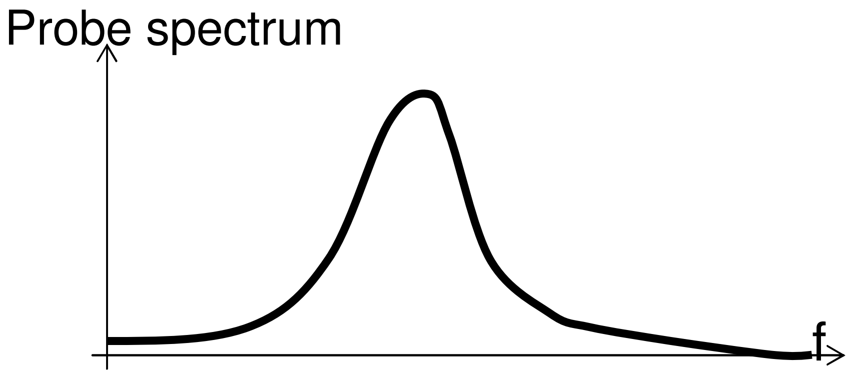
- Harmonic or Tissue Harmonic Imaging
  (without Ultrasound Contrast Agent)
  ✓ Imaging of the second harmonic backscattered to the probe (non-linear propagation in tissue)

- **Tissue**



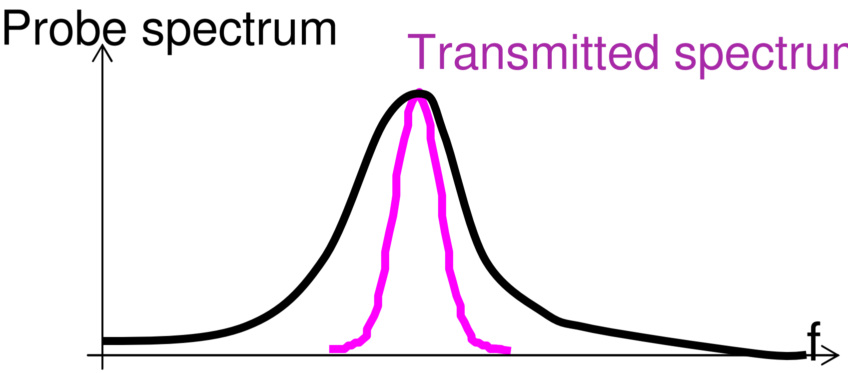
- A high pass filter at 2 f_0

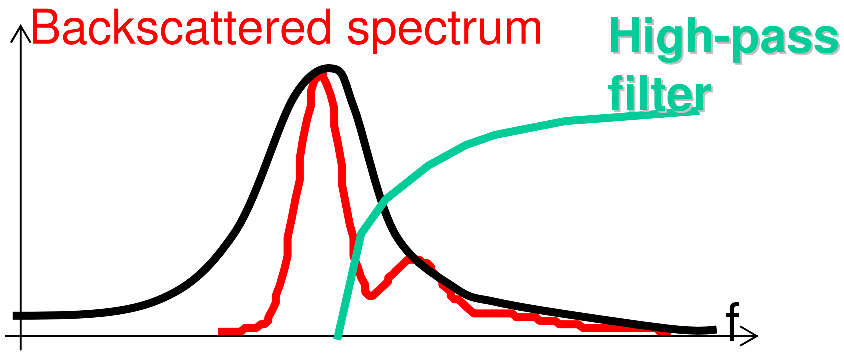
How to image the second harmonic?



- An ultrasound probe is a passband filter

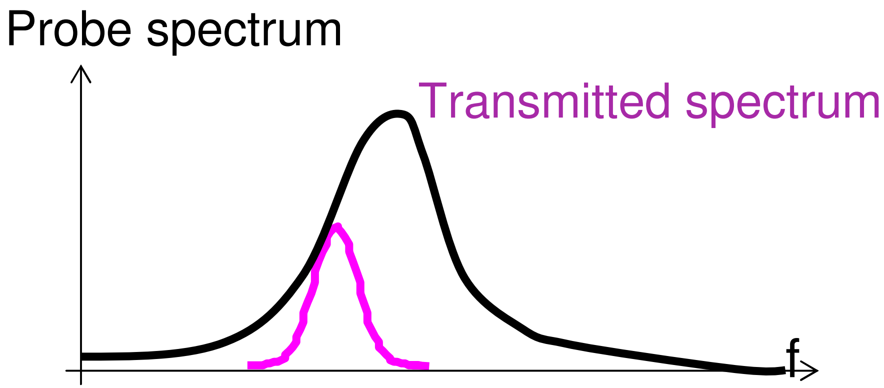
➢ Narrowband transmitted signal

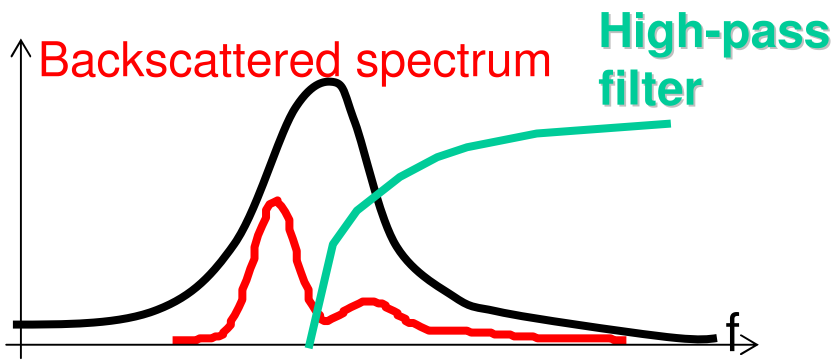




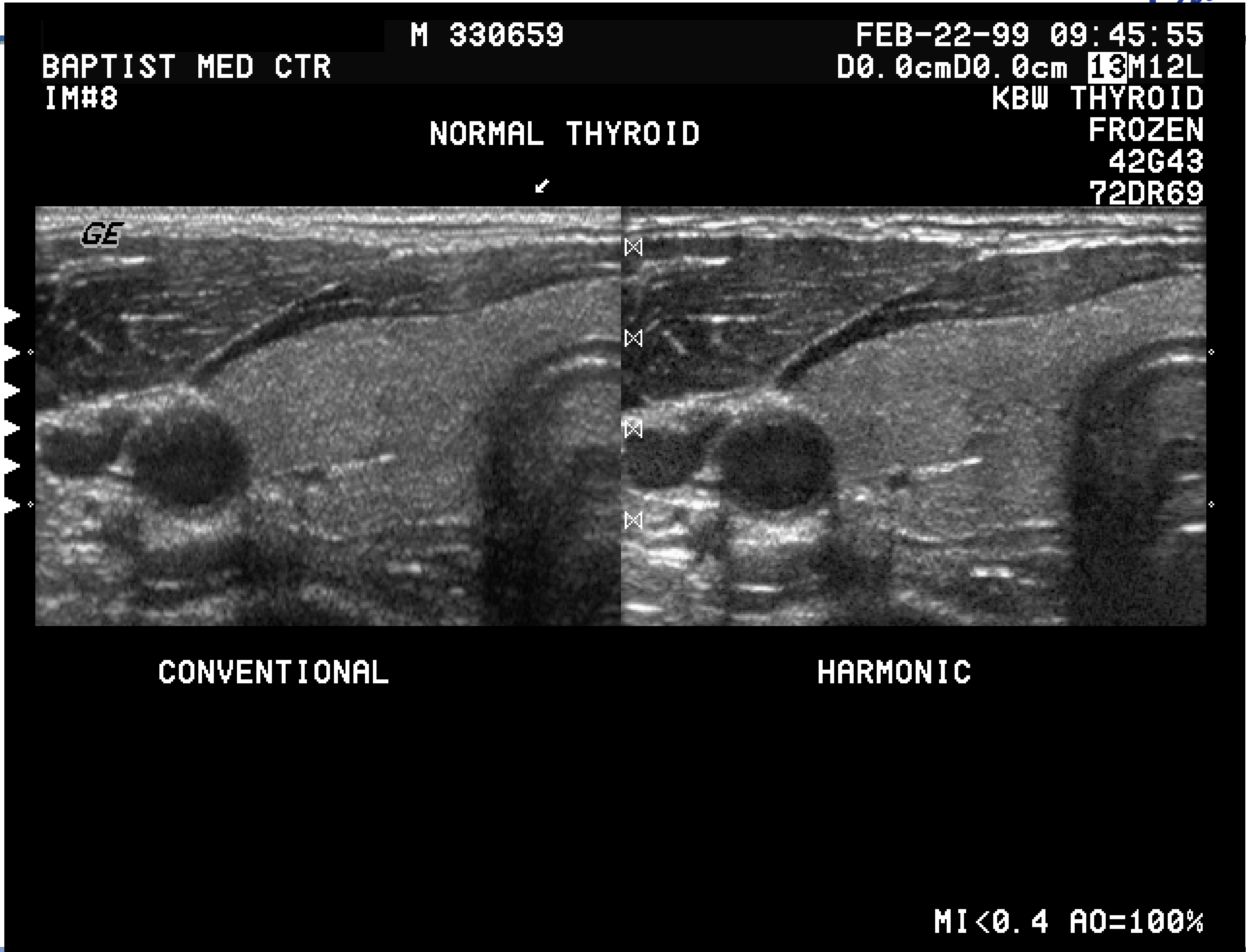
Resolution is decrease

➢ Transmitted signal in low part of transducer bandpass

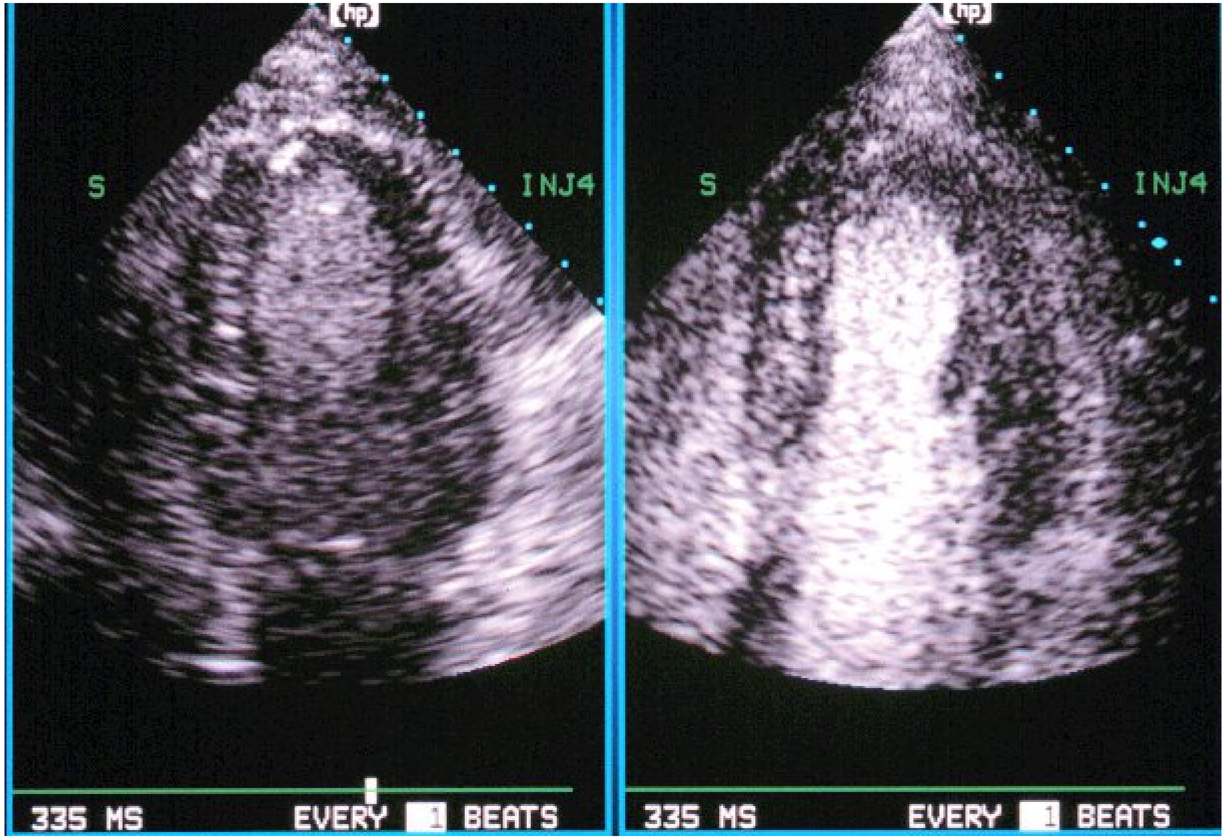




Dynamic is less


M 330659
FEB-22-99 09:45:55
BAPTIST MED CTR
D0.0cmD0.0cm 13M12L
IM#8
KBW THYROID
NORMAL THYROID
FROZEN
42G43
72DR69
GE
CONVENTIONAL
HARMONIC
MI<0.4 AO=100%

Harmonic imaging



fundamental second harmonic

Outline

- **Basic of** (Linear) **ultrasound and medical ultrasound imaging**
- **Advanced in** (Nonlinear) **Ultrasound**
  - Ultrasound Contrast Agent
  - Nonlinear ultrasound
  - **Improvement of ultrasound imaging or Nonlinear imaging**
  - Harmonic imaging
  - Multipulses imaging or Contrast (nonlinear) imaging
    - Pulse inversion (PI)
    - Second Harmonic Inversion (SHI)
  - Generalization of multi-pulse techniques
  - Influence of scatterer motion to phased multipulses method
- **CREANUIS: Simulation of nonlinear ultrasound images**

- **Multi-pulse techniques in ultrasound contrast imaging:**

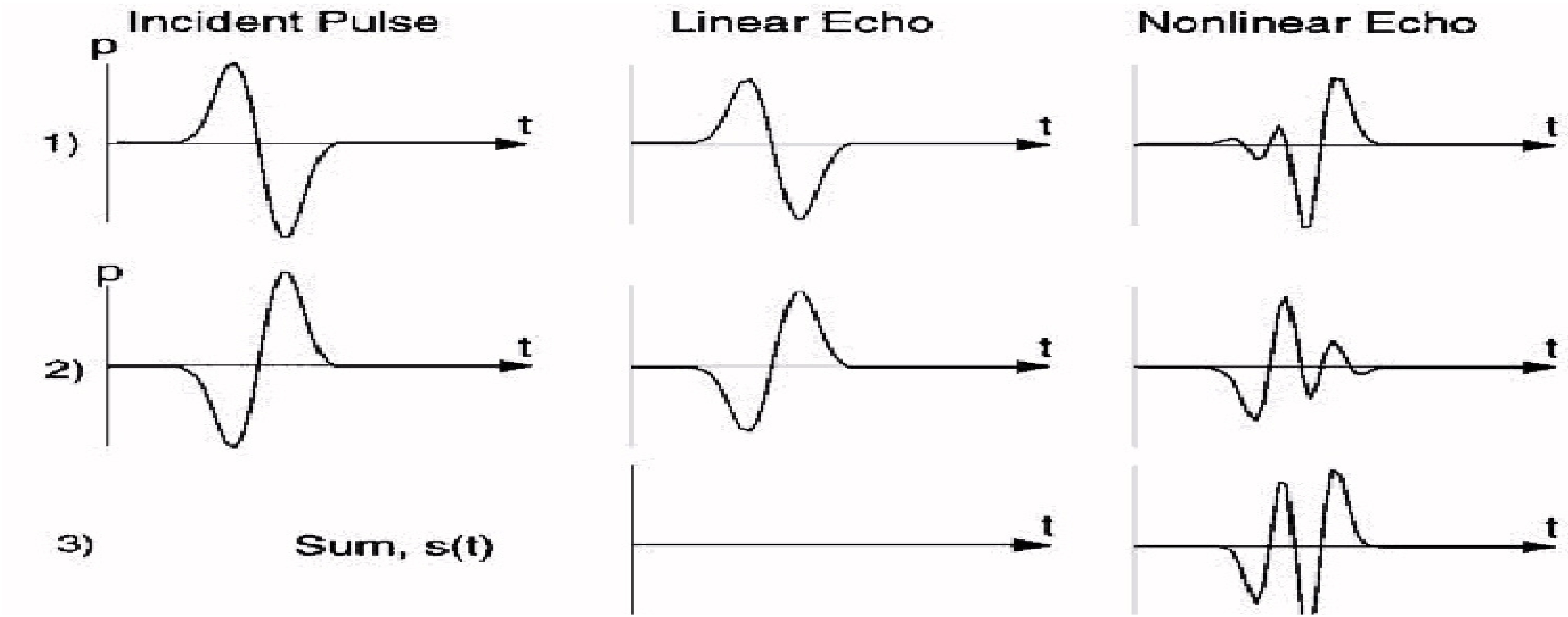
  - Amplitude modulation (AM), Brock-Fisher *et al,* 1996
  - Pulse inversion (PI), Simpson *et al.,* 1999
  - Phase coded sequences (PCS), Wilkening *et al.,* 2001
  - Contrast pulse sequence (CPS), Phillips, 2001
  - Pulse inversion amplitude modulation (PIAM), Eckersley *et al.,* 2005

    ⋮

  - Second harmonic inversion (SHI), Pasovic *et al.,* 2011

Pulse inversion imaging

- 2 incident pulses whith a phase shift $\varphi = 180^{\circ}$



Simpson, IEEE TUFFC, vol. 46, no. 2, march 1999

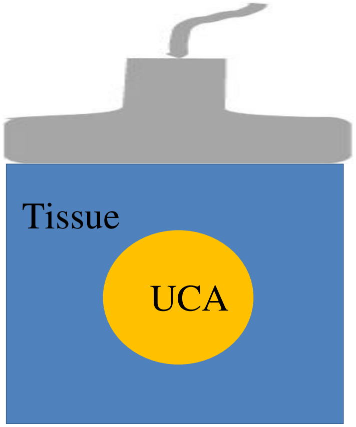
Conventional US imaging

Harmonic Doppler imaging

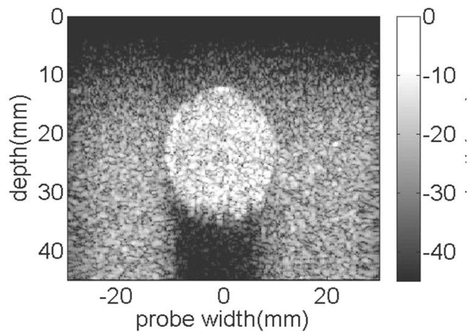
Pulse inversion Doppler imaging

With the courtesy of Piero Tortoli (Firenze University, Italy)

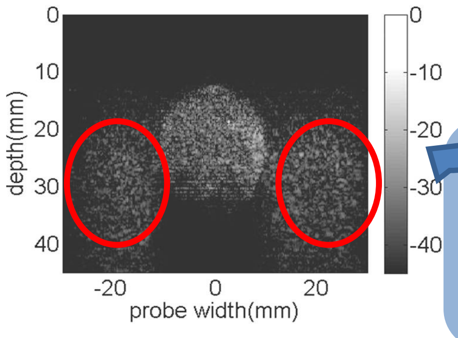
SHI: Second Harmonic Inversion



B Mode Image



Second Harmonic Image



- Tissue was previously regarded as linear (only f_0 signal exists)
- However, tissue also generates harmonic signals during the propagation: $f_0+2f_0+\ldots$
- Discrimination between UCA and tissue is reduced.

Undesired effect

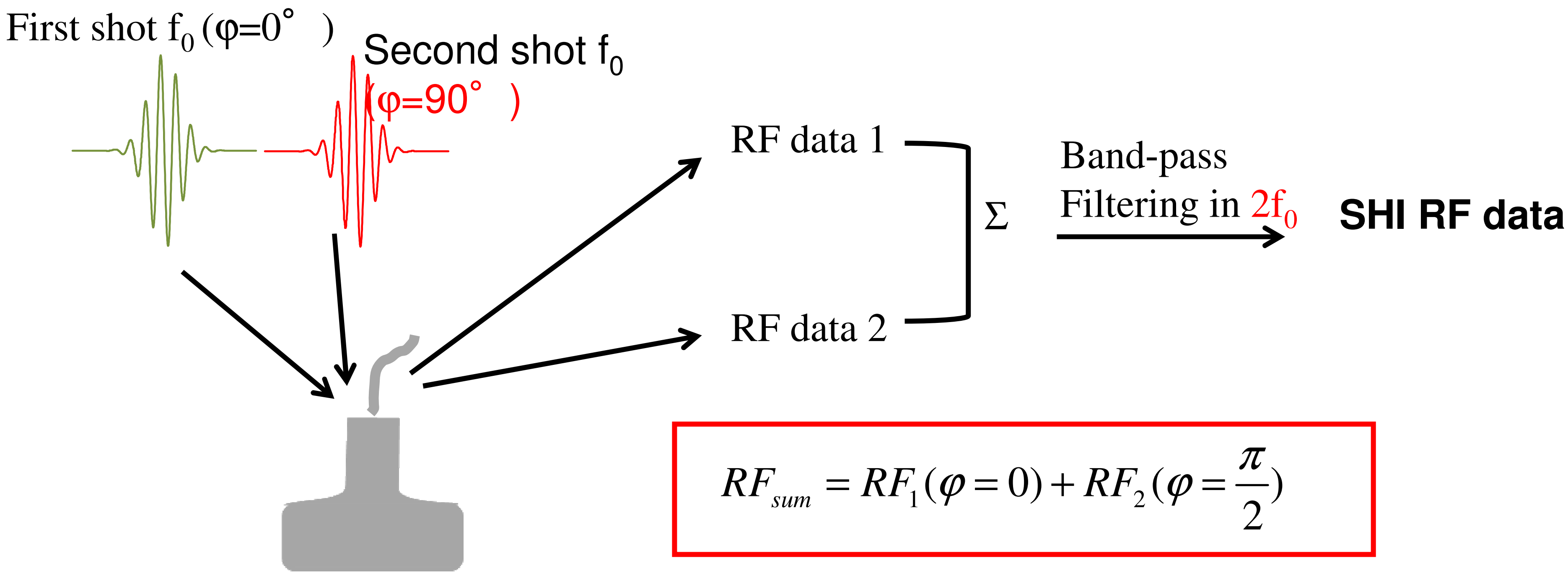
SHI objectives:

- ❖ **Decrease the second harmonic generated in tissue**
- ❖ Increase the discrimination between UCA and tissue (CTR)

SHI: Second Harmonic Inversion

Method

- As PI, 2 incident pulses but the phase shift is φ = 90°



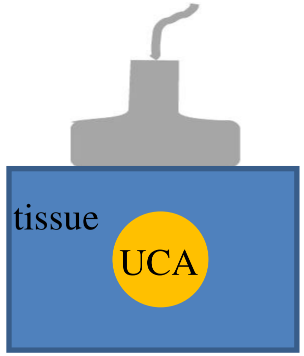
$$RF_{sum} = RF_1(\varphi = 0) + RF_2(\varphi = \frac{\pi}{2})$$

Pasovic, *Physics in Medicine and Biology*, 2011

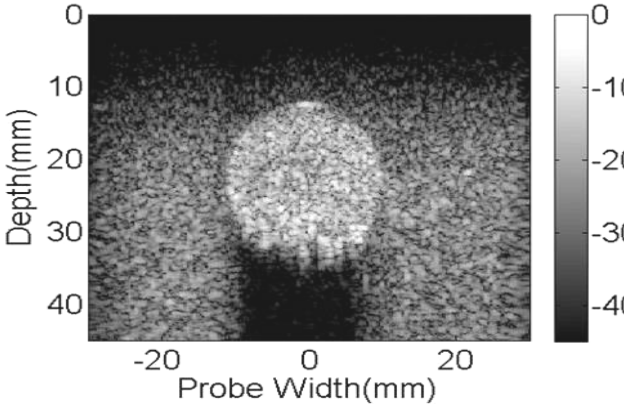
SHI: Second Harmonic Inversion

Experimental evaluation of SHI

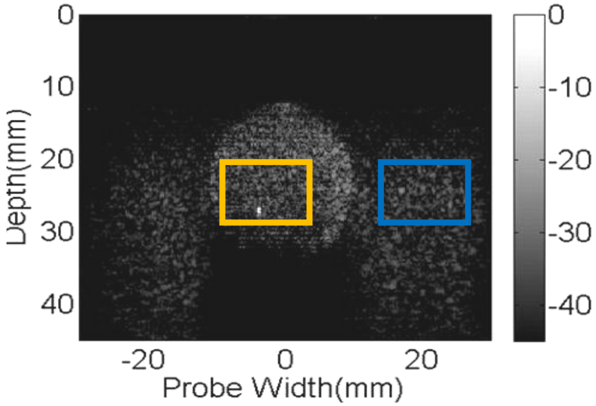
- A tissue mimicking phantom (5% agar; 1% silice)
- UCA (SHU 508A)
- Transmitted frequency: 5 MHz



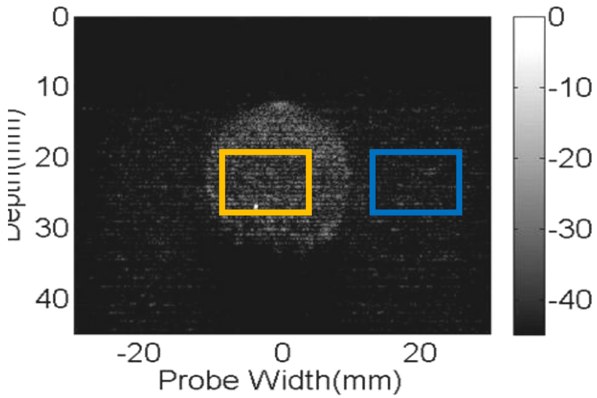
B mode



Second harmonic



SHI



$$CTR = 20 \log \frac{P_2^{UCA}}{P_2^{tissue}}$$

$CTR_{SHI} - CTR_{Har} = 4.5dB$

F. Lin *et al.*, *IEEE IUS*, 2011

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Influence of bubbles motion

However, during the experimental evaluation to SHI technique, the reduction of second-harmonic amplitude of bubbles response was sometimes observed.

Is the preservation of bubbles second harmonic related to bubbles motions?

$$RF_{sum} = RF_1(\varphi = 0) + RF_2(\varphi = \frac{\pi}{2} + \frac{4\pi\Delta z}{\lambda})$$

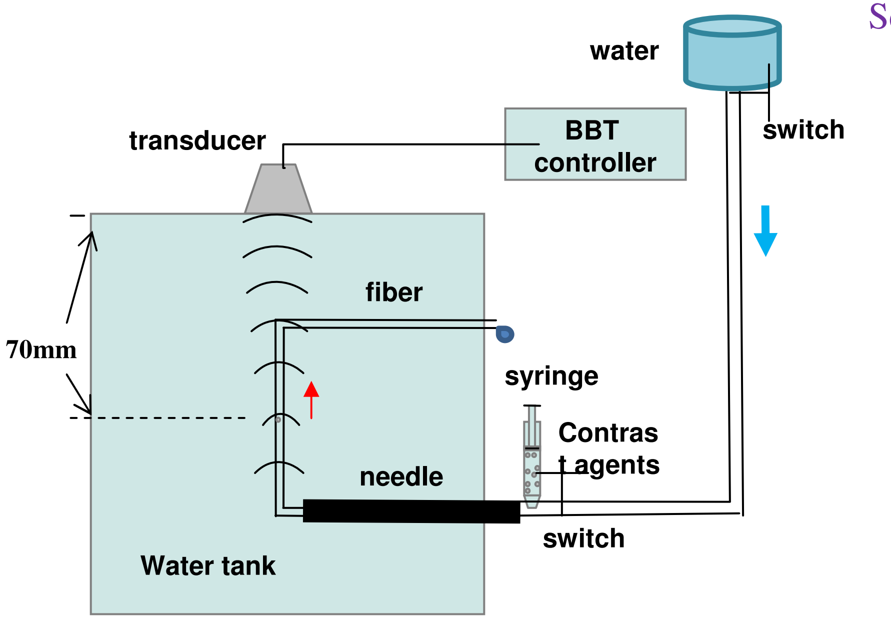
Δz: axial bubbles motion
λ: transmitted wavelength

Influence of scatterer motion to phased multipulses method

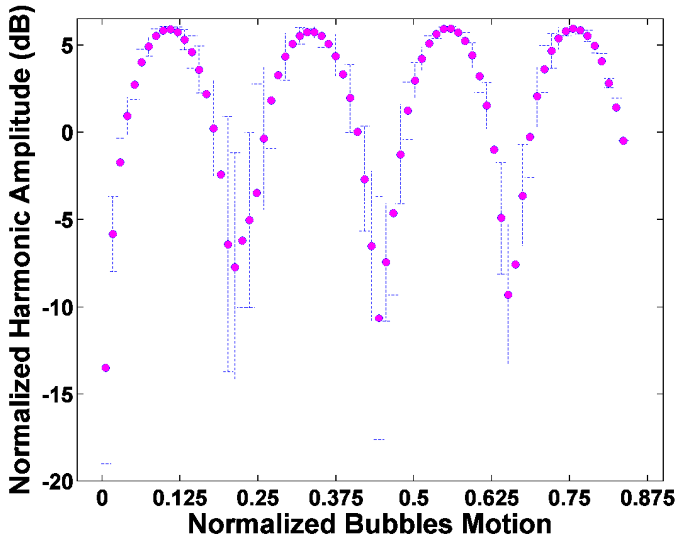
Creatis

Influence of bubbles motion

***In-vitro* experimental results**



Second harmonic amplitude of SHI versus bubbles motion



Bubbles motion is normalized to transmitted wavelength

$$RF_{sum} = RF_1(\varphi = 0) + RF_2(\varphi = \frac{\pi}{2} + \frac{4\pi\Delta z}{\lambda})$$

Δz: axial bubbles motion
λ: transmitted wavelength

Maximum at: $\Delta z = (2i+1)\lambda/8 \quad and \quad \varphi = \pi \Rightarrow PI$

Minimum at: $\Delta z = 2i\,\lambda/4 \quad and \quad \varphi = \pi/2 \Rightarrow SHI$

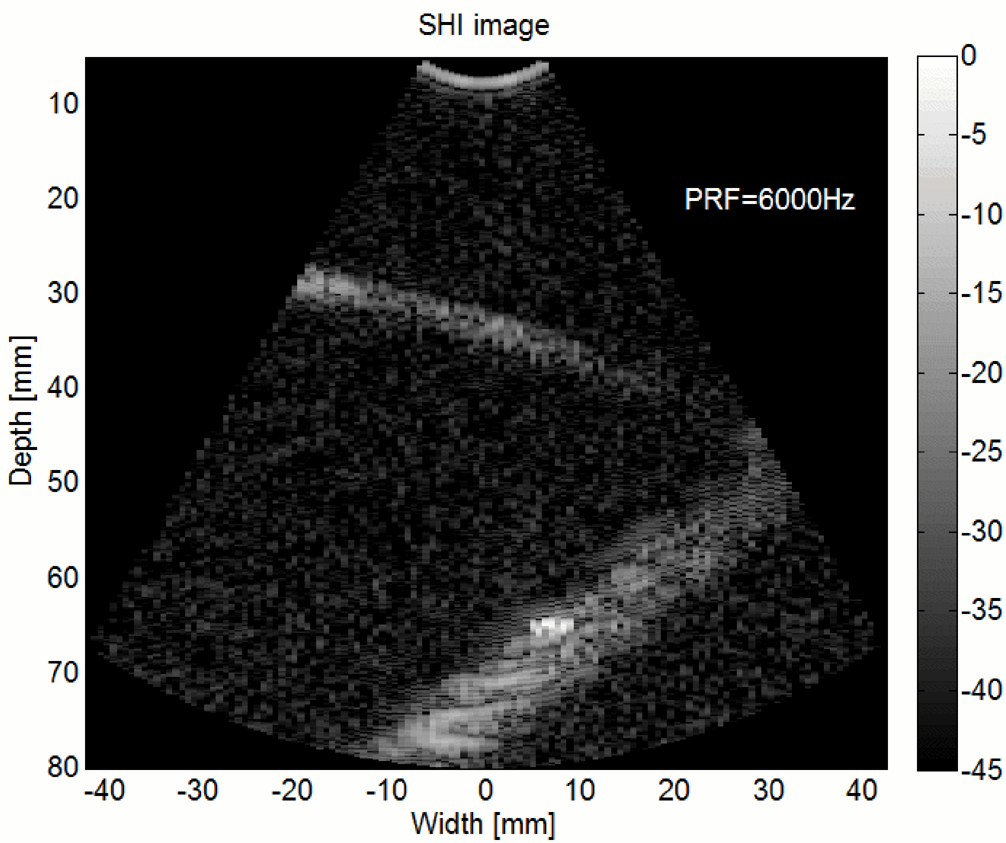
F. Lin *et al.*, *IEEE UFFC*, 2013

Influence of scatterer motion to phased multipulses method

Creatis

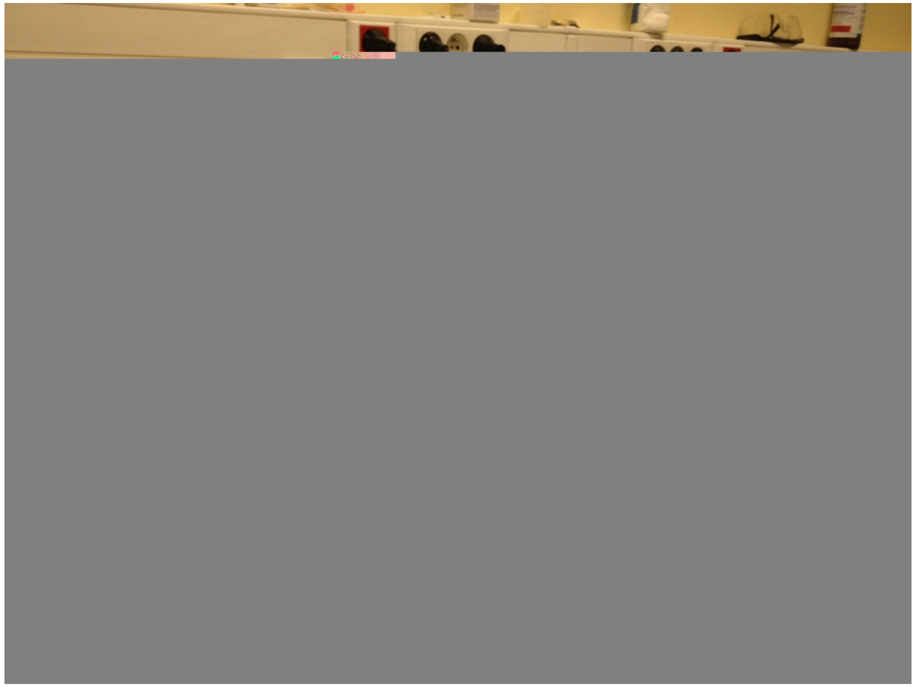
Optimization of SHI

Update PRF according to CTR until the optimal PRF is found



In-vivo **experiments**

Set up

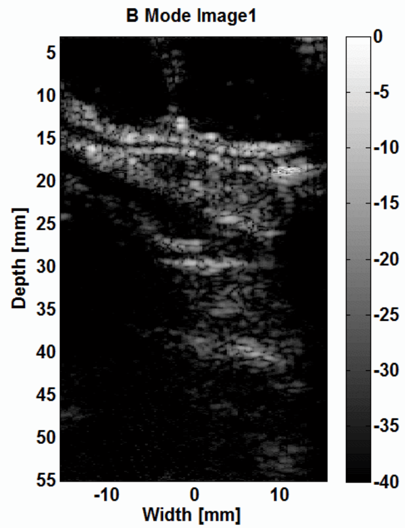


Animal: Rats
Contrast agents: Sonovue
Ultrasound platform: UlaOp
Probe: LA523 (linear)
Transmit frequency: 5 MHz

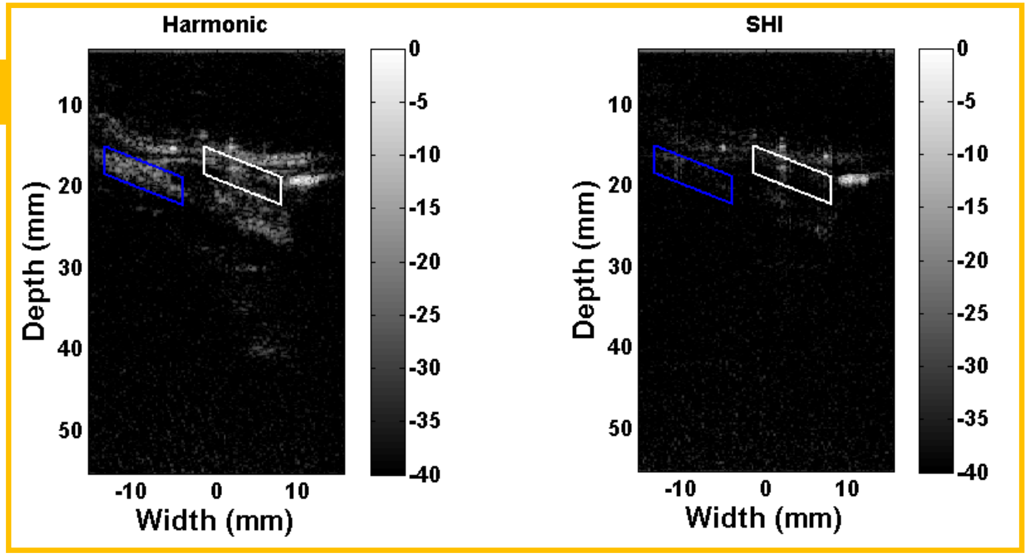
Influence of scatterer motion to phased multipulses method

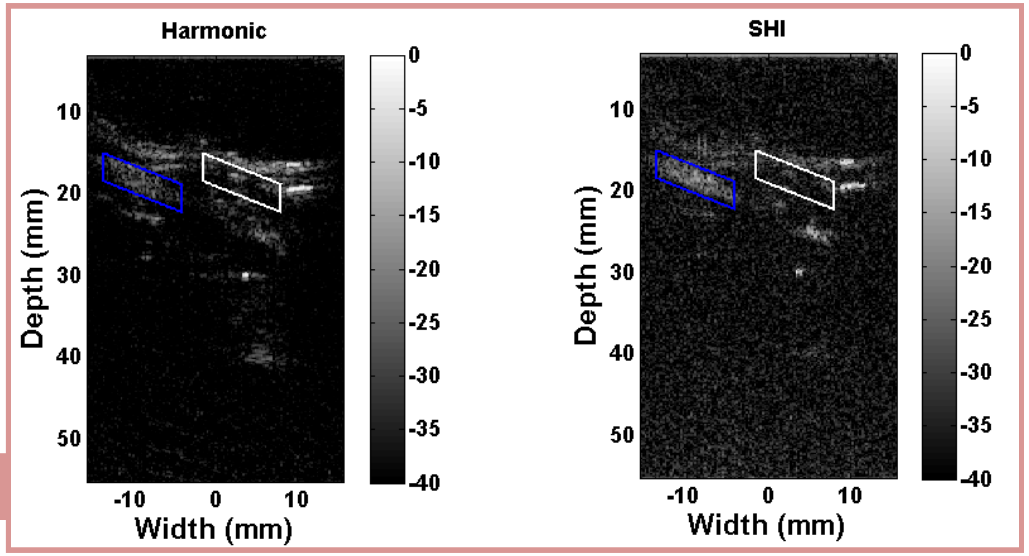
***In-vivo* experiments**

Rat 1, Vessel 1



PRF = 6000Hz





PRF = 592Hz

- blood vessel with UCA
- tissue

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Lyon, France, city of lights
December 8th