Principles and Mechanisms of Ultrasonic Contrast

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Educational Objectives

1. Identify the role of contrast agents in enhancing ultrasound image quality
2. Describe implemented imaging techniques of current ultrasound scanners
3. Explain the physics of contrast agents to demonstrate their optimal clinical use

Clinical background

- Ultrasound scans p.a.: 135 million [a]
- 0.5 per cent use contrast enhancing products [a]
- Better diagnosis of myocardial perfusion
- Relatively inexpensive imaging technique better diagnostic information.
- **No** FDA approved contrast agent for **radiological** applications

Sources: (a) Amersham Health Inc. owned by GE Healthcare

Source: Fuminori Moriyasu, M.D., Ph.D., Department of Gastroenterology & Hepatology, Tokyo Medical University, Japan

Table of Contents

From B-mode to X-mode

- Classical Applications
  - B-mode and M-mode
  - Spectral Doppler, Color Flow, and Power Doppler
- New Modes
  - Harmonic imaging
  - Pulse inversion (with harmonic or power mode)
  - Microvascular imaging
  - Flash contrast imaging

Enhancing Contrast

- Definition of contrast:

$$C = \frac{I_2 - I_1}{I_1}$$

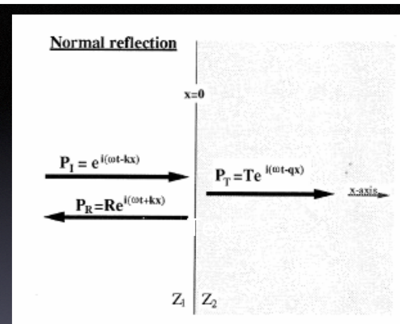
- Role of Ultrasonic Contrast Agents

- Physical principals of Tx, system, and Rx
  - backscatter amplitude ↑
  - creation of none transmit frequencies
  - ... more

Physical Principals

- Acoustic transmission
  - B-mode, Doppler
- Acoustic bubble response
  - amplitude, phase, frequency, ...
- Frequency - Size relationship
  - Minnaert Frequency: 3 μm gas bubble - 1.1 MHz res freq.

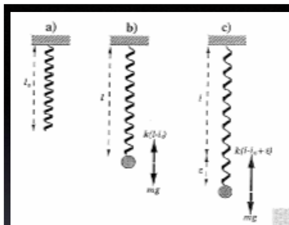
$$f = \frac{1}{2\pi}\,\frac{1}{R0}\sqrt{\frac{3 \times P_0}{\rho_L}}$$

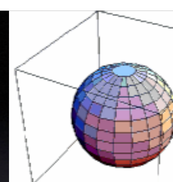


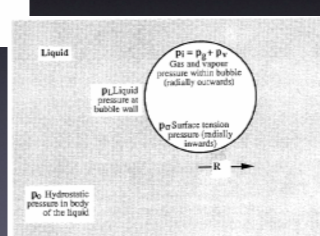
Impedance (Z) : Z = ρ • c

Reflection due to mismatch: $R = \frac{Z_2 - Z_1}{Z_2 + Z_1}$

Water : 1.5 MRayl, Air : 0.3 MRayl







- Harmonic oscillation
  F = k x
- Equilibrium of imposed pressures

Rayleigh scatterer

$$\sigma_s = 4\pi a^2 (ka)^4 \left[\left(\frac{K - K_0}{3K}\right)^2 + \frac{1}{3}\left(\frac{\rho - \rho_0}{2\rho + \rho_0}\right)^2\right]$$

Material	Bulk modulus K [MPa]	Density r [kg/m^3]	Monopole	Dipole
Water	2250	1000	0	0
Air	0.14	1.14	2.9 10^7	0.33

Sonoluminescence

Sonoluminescence is the emission of light by bubbles in a liquid excited by sound. It was first discovered by scientists at the University of Cologne in 1934, but was not considered very interesting at the time. [1]

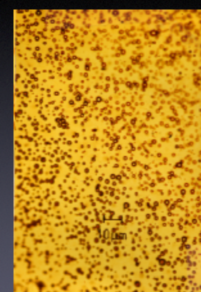
At least 10,000 degrees Celsius, and possibly a temperature in excess of one million degrees Celsius. [2]

Sources:

1. H. Frenzel and H. Schultes, Z. Phys. Chem. B27, 421 (1934)
2. D. F. Gaitan, L. A. Crum, R. A. Roy, and C. C. Church, J. Acoust. Soc. Am. 91, 3166 (1992)

Modern Contrast Agents

- ‘Gas bubbles’
- Sophisticated shell
  - prevent coalescense, reduce diffusion albumin, lipid, plus receptors, ...
- Complex interior gas
  - low diffusion, low solubility Dodecafluoropentane, others ...



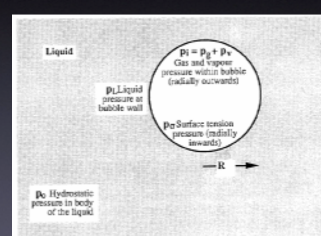
Modern Contrast Agents

Manufacturer	Trade name	Code name	Interior gas	Shell material	Status*
Acusphere	.	(AI-700)	perfluorocarbon	copolymers	Phase II
Alliance Pharma.	Imavist	(AFO-150)	perfluorohexane	surfactant	Phase II
Andaris Ltd.	Myomap	(AIP 201)	albumin	air	suspended
.	Quantison	.	‘’	‘’	suspended
Bracco Diagno.	SonoVue	(BR1, BR14)	perfluorobutane	phospholipid	Phase II, (I+)
Byk Gulden	.	(BY963)	-	phospholipid	Phase III(E), II
Cavitation Ctrl Tech.	Filmix	.	-	lipid	PreClinic(US) I(E)
ImaRx Pharma.	SonoRx	.	-	cellulose	market(US), appr(E)
.	Definity	(MRX-115)	perfluoropropane	lipid bilayer	Phase II/III
.	.	(DMP-115)	air	‘’	‘’
.	.	(YM 454)	-	-	Phase III(J)
.	.	(MRX-408, MRX-CSI)	perfluoropropane	-	preclinical
Mallinckrodt	.	(MP1550)	perfluorobutane	lipid	preclinical(?)
.	.	(MP2211)	‘’	‘	‘’
Molecular Biosys.	Oralex	.	air	dextrose	Phase II+
.	Optison	(FS069)	perfluorobutane	albumin	market, Phase II
Nycomed	Sonazoid	(NC100100)	perfluorobutane	lipid	Phase II/III
POINT Biomedical	biSphere	(PB127)	air	gelatine-polymer	Phase II
Schering AG	Levovist	(SHU508A)	-	galactose	market(E),III+(US/J)
.	Sonavist	(SHU563A, SHU616A)	air	cyanoacrylate	Phase II
Sonus Pharma.	EchoGen	(QW3600)	dodecafluoropentane	albumin	market(E), II/III(US)
.	SonoGen	(QW7437)	‘’	charged surfactant	Phase I

* Status depends on the proposed application

Mathematical and Physical Modelling

- Equation of motion
- Harmonic response



Physics of Bubbles

- Energy Balance
  - kinetic and potential energy, Lagrange formalism
  - -> Rayleigh-Plesset equation
  - Ideal gas law, vapor pressure, surface tension (Laplace pressure), viscosity, static pressure, *sound pressure*

$$\partial_t \partial_t R(t) == \frac{1}{R(t)} \left(-\frac{3}{2} (\partial_t R(t))^2 + \frac{1}{\rho_L} \left(\left(P_0 + \frac{2\sigma}{R_0} - P_d \right) \left(\frac{R_0}{R(t)} \right)^{3\kappa} + P_d - \frac{2\sigma}{R(t)} - \frac{4\eta_L \partial_t R(t)}{R(t)} - P_0 - P_\infty(t) \right) \right)$$

Physics of Bubbles

- Energy Balance
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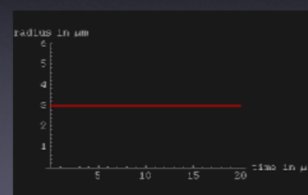
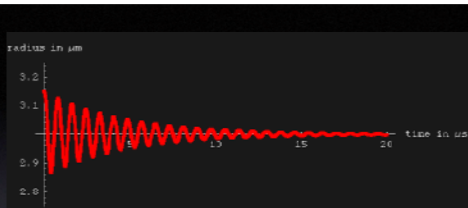
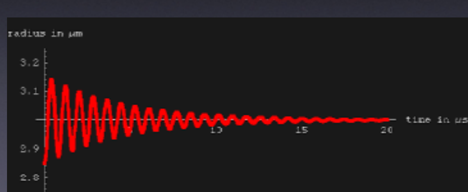
  - Ideal gas law, vapor pressure, surface tension (Laplace pressure), viscosity, static pressure, *sound pressure*

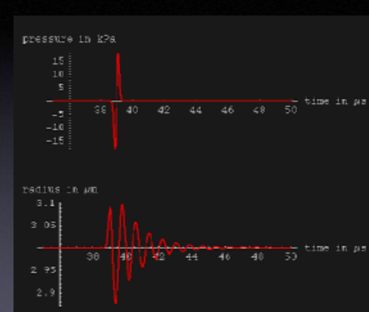






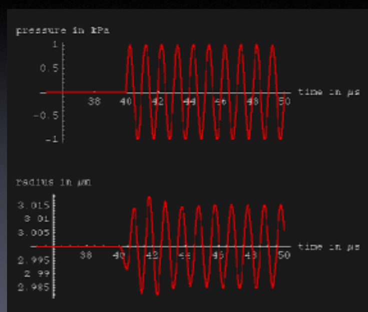
Acoustic Excitation

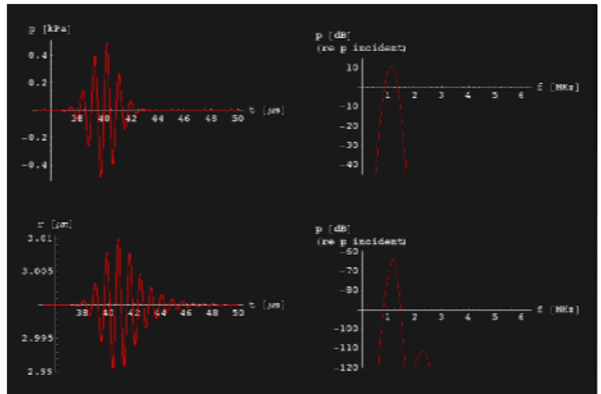
- Single Pulse
  - one cycle
  - increased viscosity
  - ring down at resonance frequency of bubble



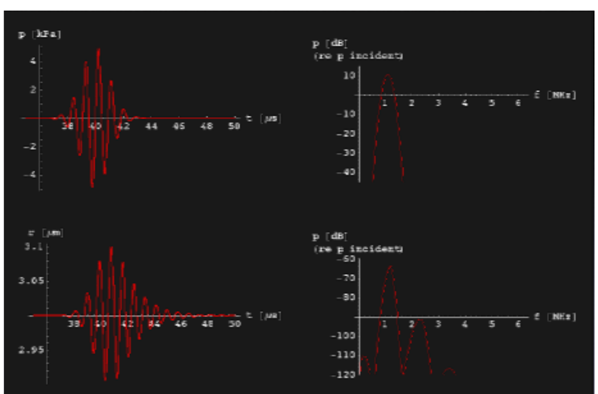
Acoustic Excitation

- Continuous
- Wave Excitation
  - ring-up time
  - for 4 cycles
  - very low pressure
  - linear oscillations

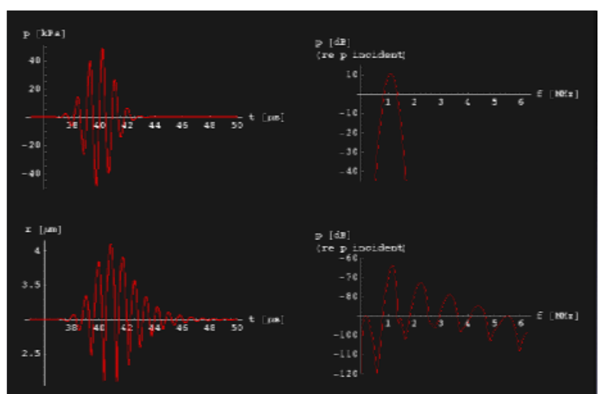




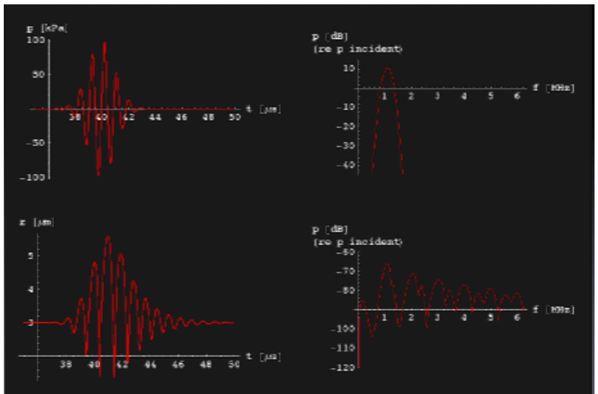
0.5 kPa excitation



5 kPa excitation



50 kPa excitation

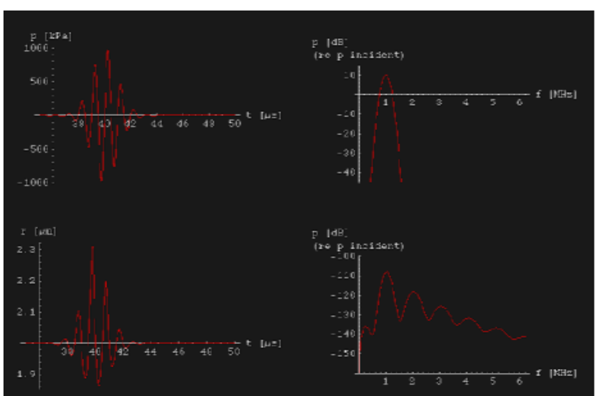


100 kPa excitation

The Shelled Bubble

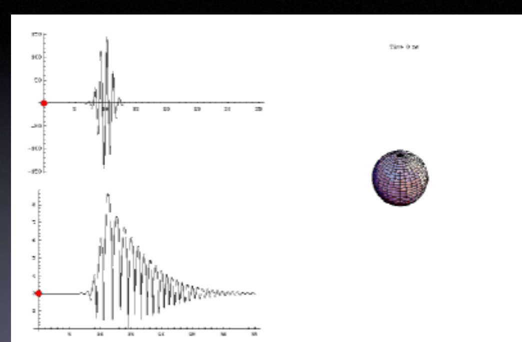
- Elastic Layer based model
  - additional parameters:
  - mass density of shell material, second surface tension term,
  - second viscosity term, elastic modulus of shell material

$$R_1[t]\,\partial_t U_1[t]\left(1+\left(\frac{\rho_L-\rho_S}{\rho_S}\right)\frac{R_1[t]}{R_2[t]}\right)+ (U_1[t])^2\left(\frac{3}{2}+\left(\frac{\rho_L-\rho_S}{\rho_S}\right)\left(\frac{4(R_2[t])^3-(R_1[t])^3}{2(R_2[t])^3}\right)\frac{R_1[t]}{R_2[t]}\right) == \frac{1}{\rho_S}\left(P_{GC}\left(\frac{R_{O1}}{R_1[t]}\right)^{3\kappa}-P_\infty[t,\phi]-\frac{2\sigma_1}{R_1[t]}-\frac{2\sigma_2}{R_2[t]}- 4\frac{U_1[t]}{R_1[t]}\left(\frac{V_S\mu_S+(R_1[t])^3\mu_L}{(R_2[t])^3}\right)-4\frac{V_S G_S}{(R_2[t])^3}\left(1-\frac{R_{e1}}{R_1[t]}\right)\right)$$

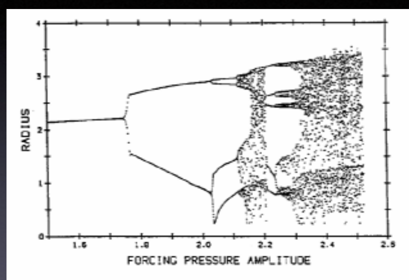


1 MPa excitation

Bubble oscillation under p_∞ of 150 kPa



Chaotic oscillation



Source: V Kamath and A Prosperetti, ''Numerical integration methods in gas bubble dynamics,'' J. Acoust. Soc. Am. 85, 1538–1548 (1989)

Imaging Modes

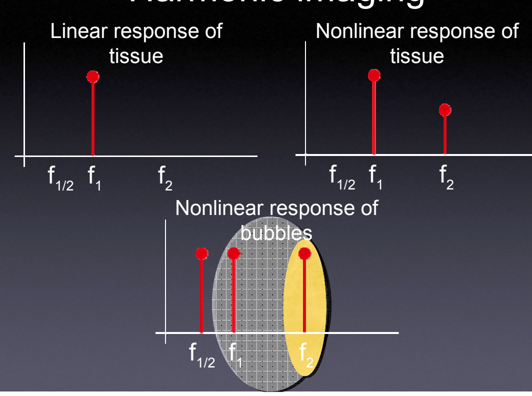
- Harmonic imaging
- (Harmonic) Coded Excitation
- Pulse inversion & Power pulse inversion
- Flash contrast imaging
- Microvascular imaging
- Agent detection imaging

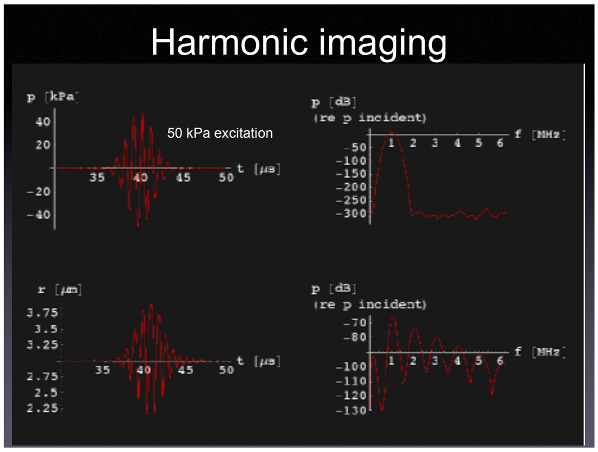
Mechanical Index

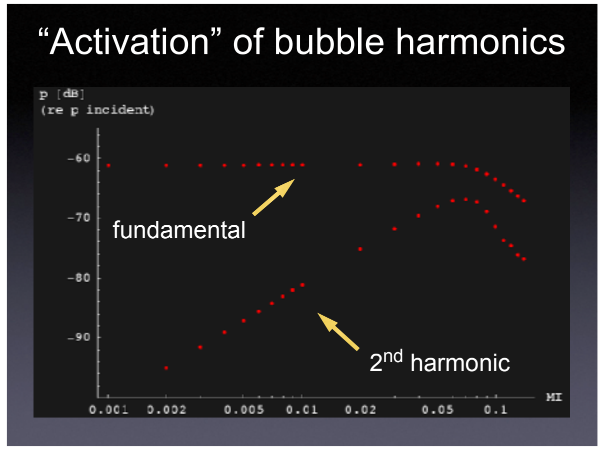
$$MI = \frac{P_{-}\,[MPa]}{\sqrt{f\,[MHz]}}$$

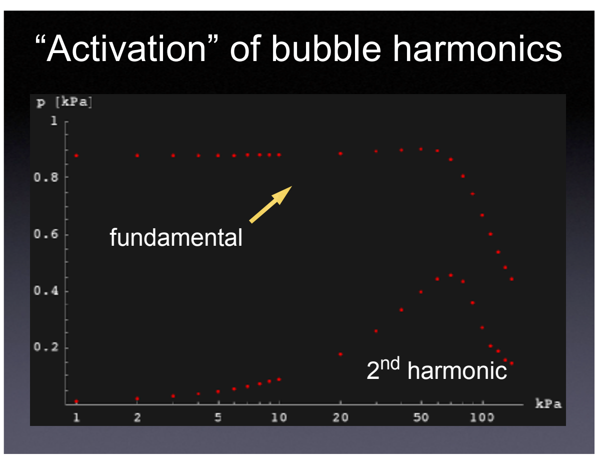
Source: CX Deng, Q Xu, RE Apfel, CK Holland "Inertial cavitation produced by pulsed ultrasound in controlled host media", JASA 100 (2) 1199-1208 (1996)

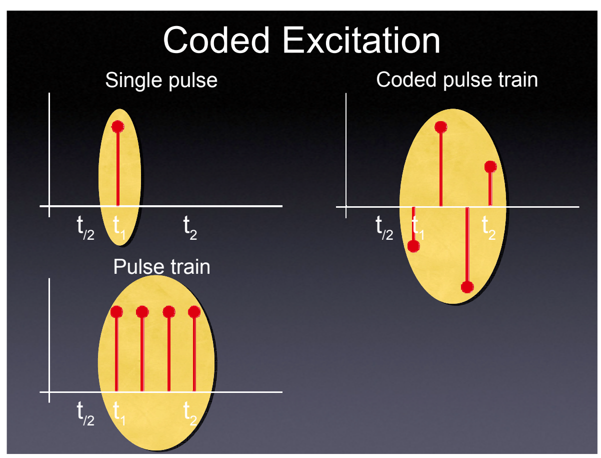
Harmonic imaging

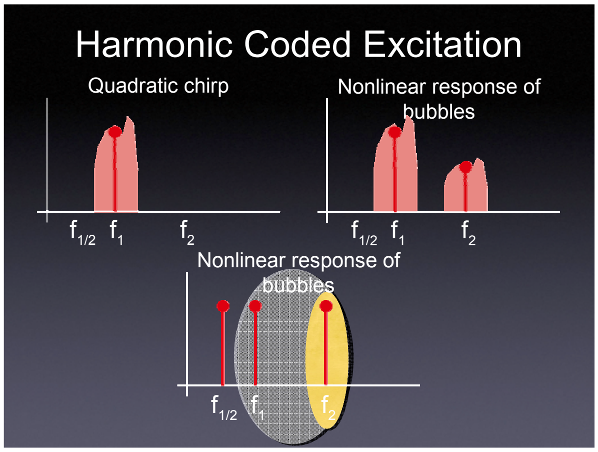


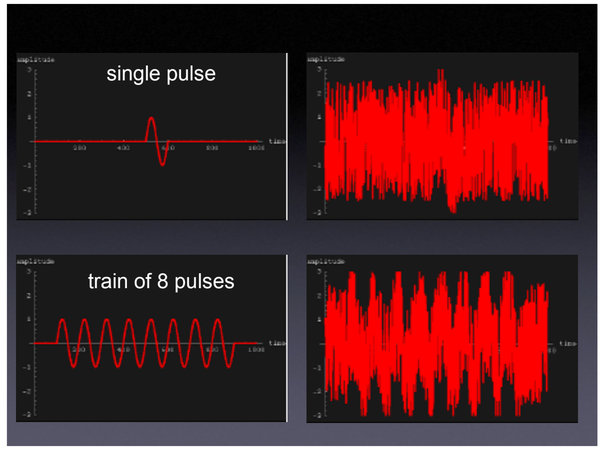

Harmonic imaging
p [kPa]
50 kPa excitation
t [μs]
r [μm]
p [dB]
(re p incident)
f [MHz]

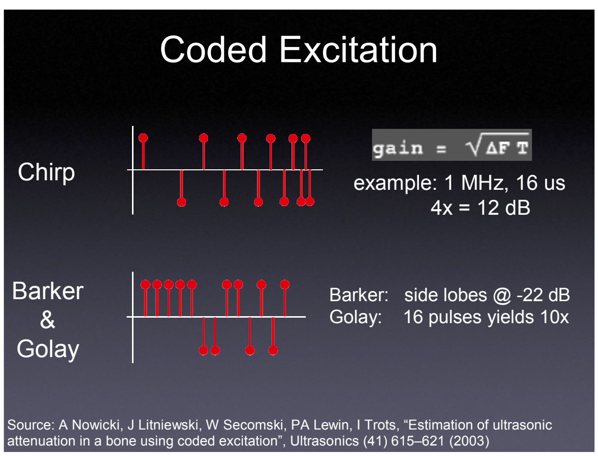

"Activation" of bubble harmonics
p [dB]
(re p incident)
fundamental
2nd harmonic
MI

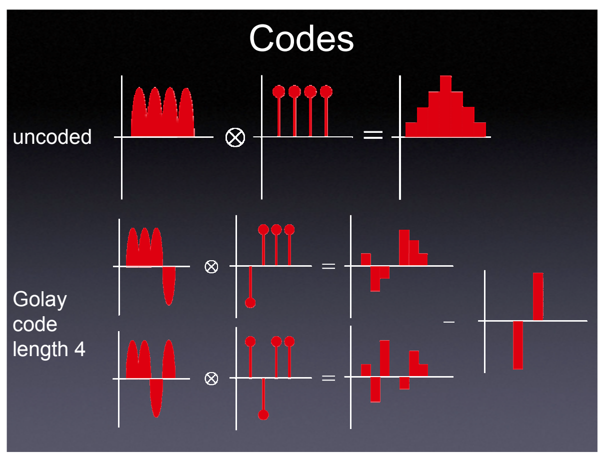

"Activation" of bubble harmonics
p [kPa]
fundamental
2nd harmonic
kPa

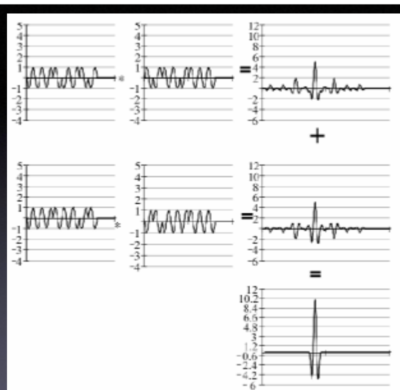

Coded Excitation
Single pulse
Coded pulse train
Pulse train


Harmonic Coded Excitation
Quadratic chirp
Nonlinear response of bubbles
f1/2 f1 f2
f1/2 f1 f2
Nonlinear response of bubbles
f1/2 f1 f2


single pulse
train of 8 pulses


Coded Excitation
Chirp
gain = √ΔF T
example: 1 MHz, 16 us
4x = 12 dB
Barker & Golay
Barker: side lobes @ -22 dB
Golay: 16 pulses yields 10x
Source: A Nowicki, J Litniewski, W Secomski, PA Lewin, I Trots, "Estimation of ultrasonic attenuation in a bone using coded excitation", Ultrasonics (41) 615–621 (2003)


Codes
uncoded
Golay code length 4



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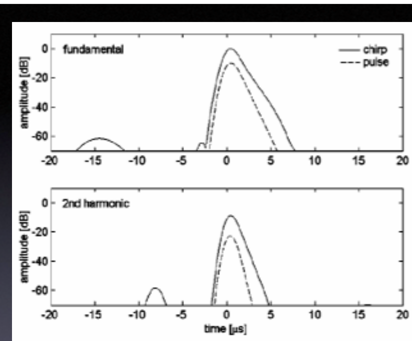
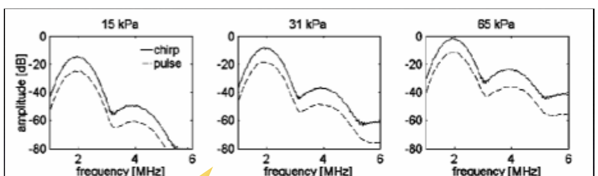


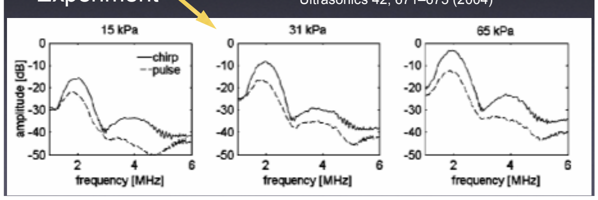
Source: J Borsboom, CT Chin, N de Jong “Experimental evaluation of a non-linear coded excitation method for contrast imaging” Ultrasonics 42, 671–675 (2004)

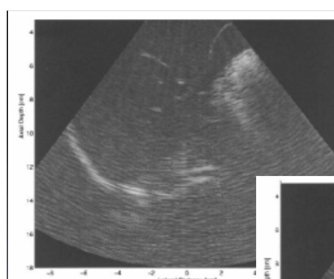


Simulation

Experiment

Source: J Borsboom, CT Chin, N de Jong “Experimental evaluation of a non-linear coded excitation method for contrast imaging” Ultrasonics 42, 671–675 (2004)



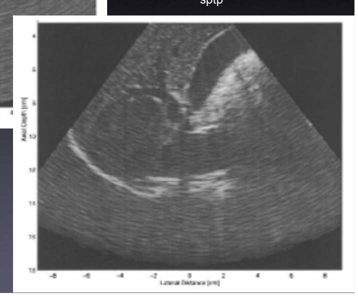


Gall bladder

gain in penetration

same I_{sptp} at focus

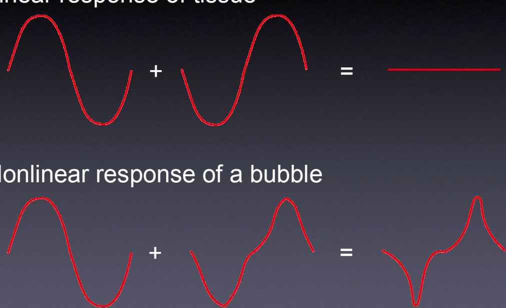
Source: TX Misaridis, K Gammelmark, CH Jørgensen, N Lindberg, AH Thomsen, MH Pedersen, JA Jensen, “Potential of coded excitation in medical ultrasound imaging” Ultrasonics 38, 183–189 (2000)



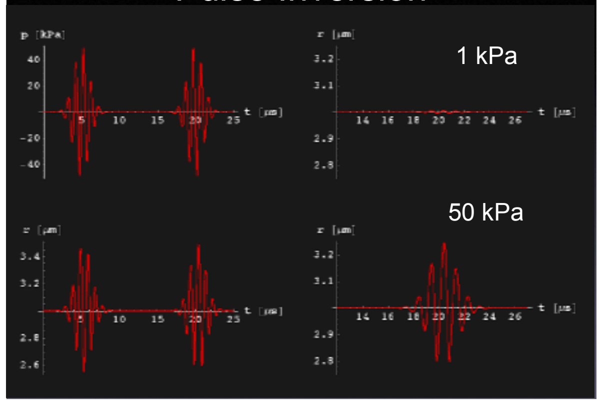
Pulse Inversion

Linear response of tissue

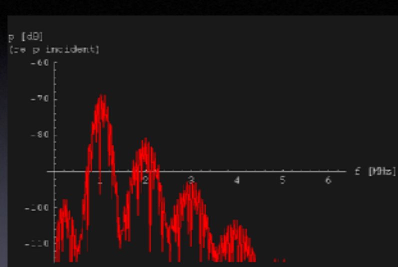
Nonlinear response of a bubble

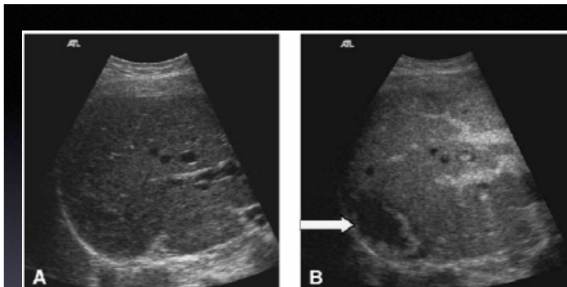


Pulse Inversion



Pulse Inversion





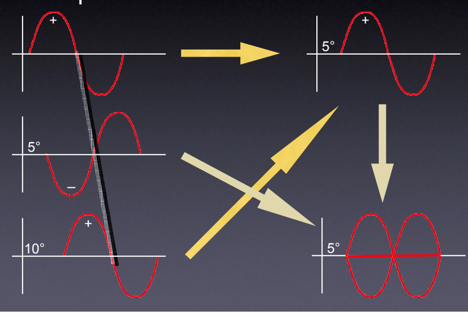
- Hemangioma. Both images with ultrasound contrast agent. (A) conventional imaging (B) Pulse inversion imaging [a]

Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

Power Pulse Inversion

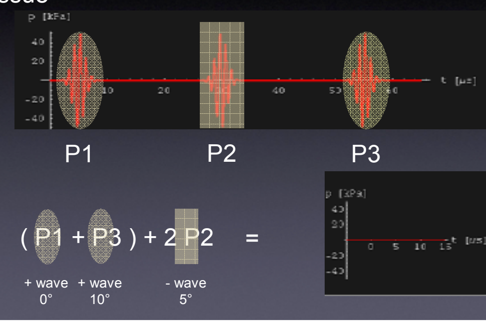
assume breathing motion of 2 cm/s
this is: 20 um per firing, ie. 4.8° phase shift @ 1 MHz

Linear response of tissue



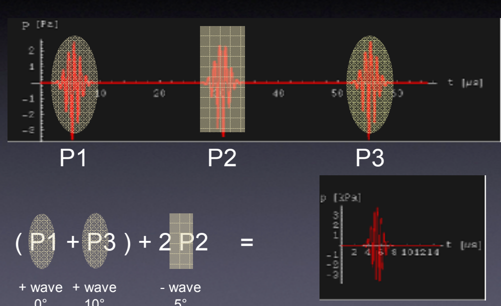
Power Pulse Inversion

Linear response of (moving) tissue



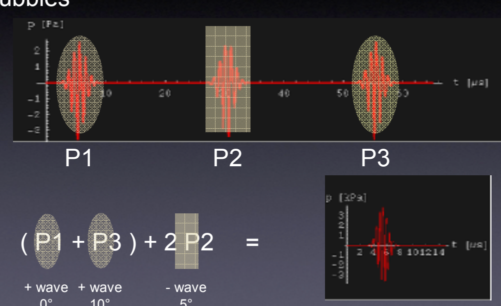
Power Pulse Inversion

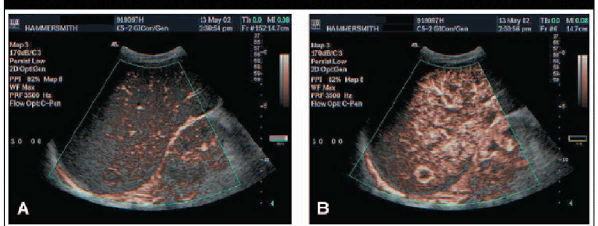
Nonlinear response of bubbles



Power Pulse Inversion

Nonlinear response of moving bubbles



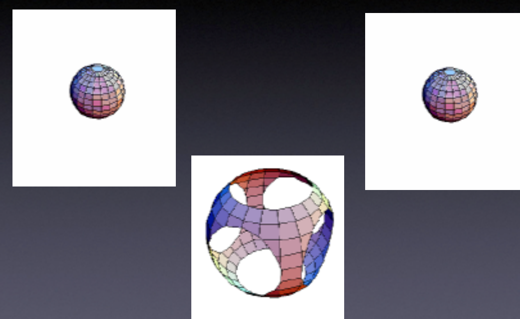


- Splenic hemangioma. Both images with ultrasound contrast agent and Power Pulse Inversion. (A) Initial bubbles arrival (B) peripheral filling [a]

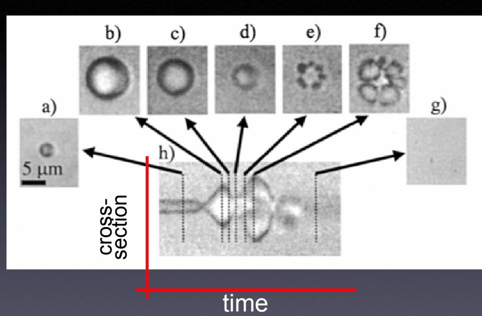
Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

Flash Echo Imaging

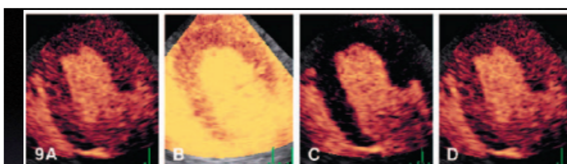
Destruction of contrast agents



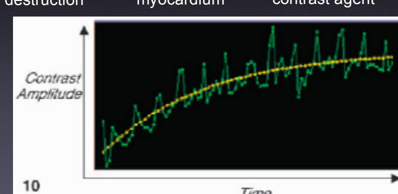
Flash Echo Imaging



Source: Chomas JE , et al "Optical observation of contrast agent destruction." Appl. Phys. Lett., Vol. 77, No. 7 (2000)



stable perfusion of the myocardium | high MI USCA destruction | no agent in myocardium | refill of ultrasound contrast agent



Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

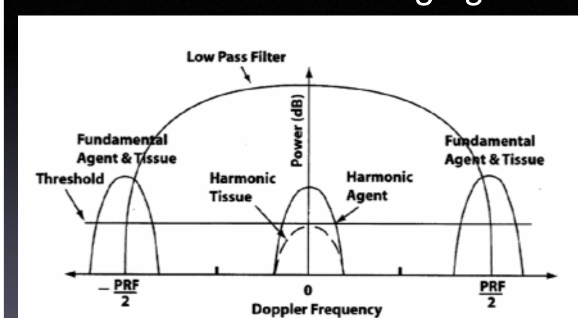
Flash Contrast Imaging

Microvascular Imaging

- Problem
  - slow velocities
  - few bubbles
  - large tissue scatter
- Solution
  - Doppler
  - Harmonic
  - Threshold

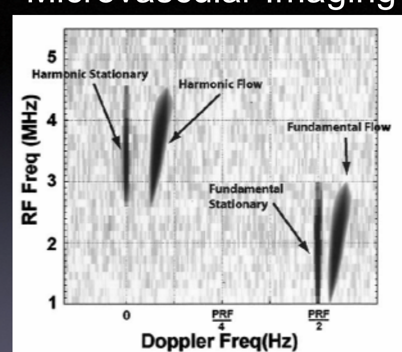
Phase wrap to zero

Microvascular Imaging



Source: M Bruce, M Averkiou, K Tiemann, S Lohmaier, J Powers, K Beach "Vascular flow and perfusion imaging with ultrasound contrast agents" Ultrasound in Med. & Biol., Vol. 30, No. 6, pp. 735–743, 2004

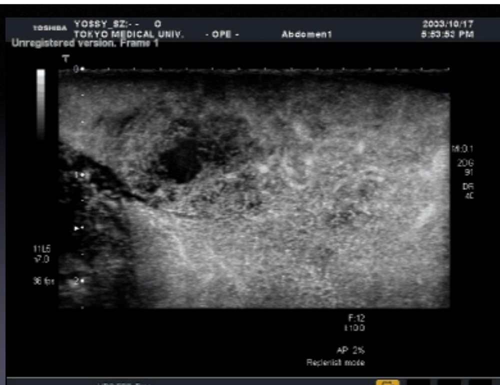
Microvascular Imaging



Source: M Bruce, M Averkiou, K Tiemann, S Lohmaier, J Powers, K Beach "Vascular flow and perfusion imaging with ultrasound contrast agents" Ultrasound in Med. & Biol., Vol. 30, No. 6, pp. 735–743, 2004

In vivo Examples

Source: Dr. Fuminori Moriyasu (Department of Gastroenterology & Hepatology, Tokyo Medical University, Japan)



Source: Dr. Fuminori Moriyasu (Department of Gastroenterology & Hepatology, Tokyo Medical University, Japan)

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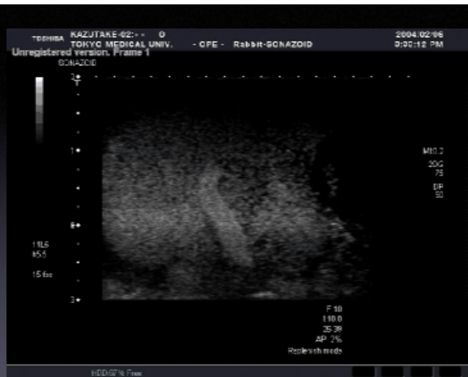
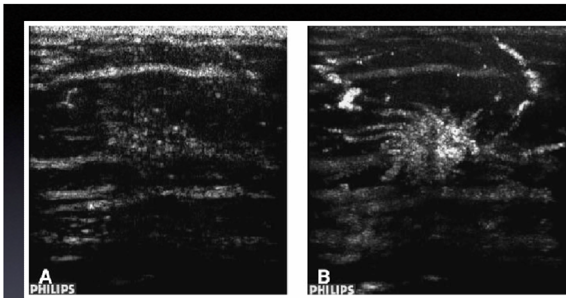
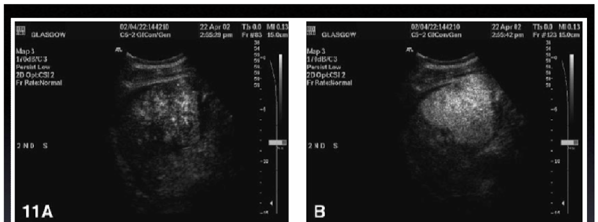


Source: Dr. Fuminori Moriyasu (Department of Gastroenterology & Hepatology, Tokyo Medical University, Japan)



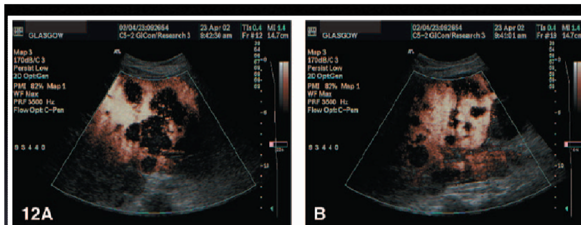
- Breast ductal carcinoma. Both images with ultrasound contrast agent. (A) Single image of a cine-loop (B) microvascular imaging to capture tracks of bubbles (a)

Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)



- Hepatocellular carcinoma. Low mechanical index scanning using SonoVue (Bracco). (A) Early phase arterial blood supply. (B) Complete filling of hepatocellular carcinoma before portal venous enhancement of normal liver [(a)]

Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

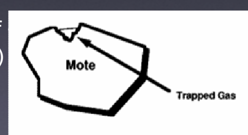


- Agent detection imaging: Levovist (Schering AG)
- Black holes in the images indicate metastases.

Source: (a) Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

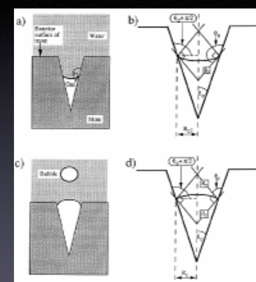
Bioeffects

- Cavitation
  - inertial = transient cavitation
    bubble collapse (compression phase)
  - theoretical tensile strenght: 100 MPa (1.44 nm bubble)
  - experimental values of
    (hydrophobic particles)
  - .
- Contrast agent
  Levovist



Mote model

- Levovist
  - suspension of galactose microparticles (99.9%) and
  - palmitic acid (0.1%)



Collapsing bubble

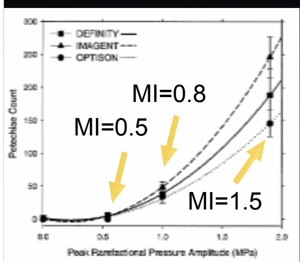
Source: Lawrence Crum JASA

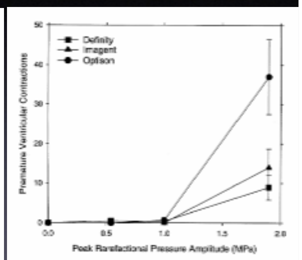
In vivo Bioeffects

- Observation of:
  - microvascular permeabilization
  - petechial hemorrhage
  - premature ventricular contractions
  - .
- Contrast agents:
  - Optison (Mallinckrodt Inc., St. Louis, MO)
  - Definity (Bristol-Myers Squibb Medical Imaging, Inc. N. Billerica, MA)
  - Imagent (Alliance Pharmaceutical Corp., San Diego, CA)

Source: P Li, WF Armstrong and DL Miller, “Impact of myocardial contrast echocardiography on vascular permeability: comparison of three different contrast agents” Ultrasound in Med. & Biol., Vol. 30, No. 1, pp. 83–91 (2004)

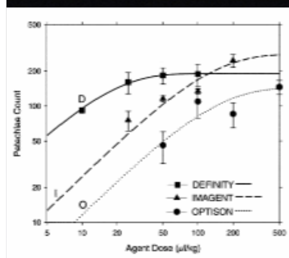
Acoustic pressure

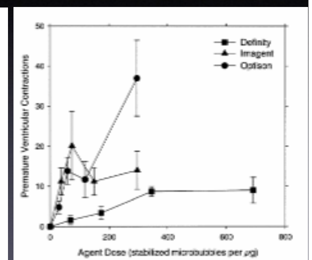




recommended MI: <1 Imagent®, <0.8 Definity®

Agent Dose





10 to 100 uL/kg Optison®, 6.25 uL/kg Imagent®, 10 to 20 uL/kg Definity®,

Acknowledgments and References

- *In vivo* movies from Dr. Fuminori Moriyasu
  (Department of Gastroenterology & Hepatology, Tokyo Medical University, Japan)
- Illustration movie by ImaRx Therapeutics
  (ImaRx Therapeutics, Inc., Tucson, AZ)
- Some images and illustrations from

  Averkiou M., Powers J., Skyba D., Bruce M., and Jensen S. "Ultrasound Contrast Imaging Research." Ultrasound Quarterly Vol. 19, No. 1, pp. 27-37 (2003)

  Bruce M., Averkiou M., Tiemann K., Lohmaier S., Powers J., and Beach K. "Vascular Flow and Perfusion Imaging with Ultrasound Contrast Agents." Ultrasound in Med. & Biol., Vol. 30, No. 6, pp. 735–743 (2004)

  T.G. Leighton, The Acoustic Bubble, Academic Press (1994)

  Chomas JE et al, "Optical observation of contrast agent destruction." Appl. Phys. Lett., Vol. 77, No. 7 (2000)