Ultrasound contrast agents

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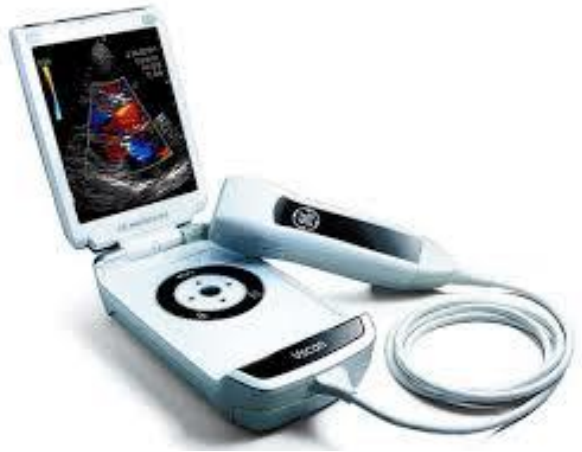

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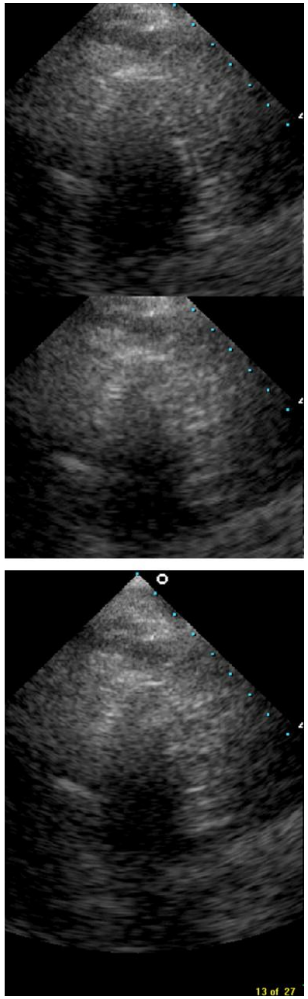
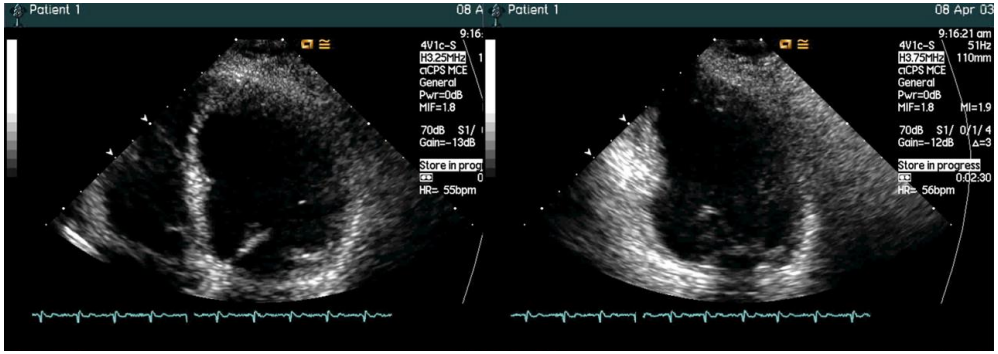
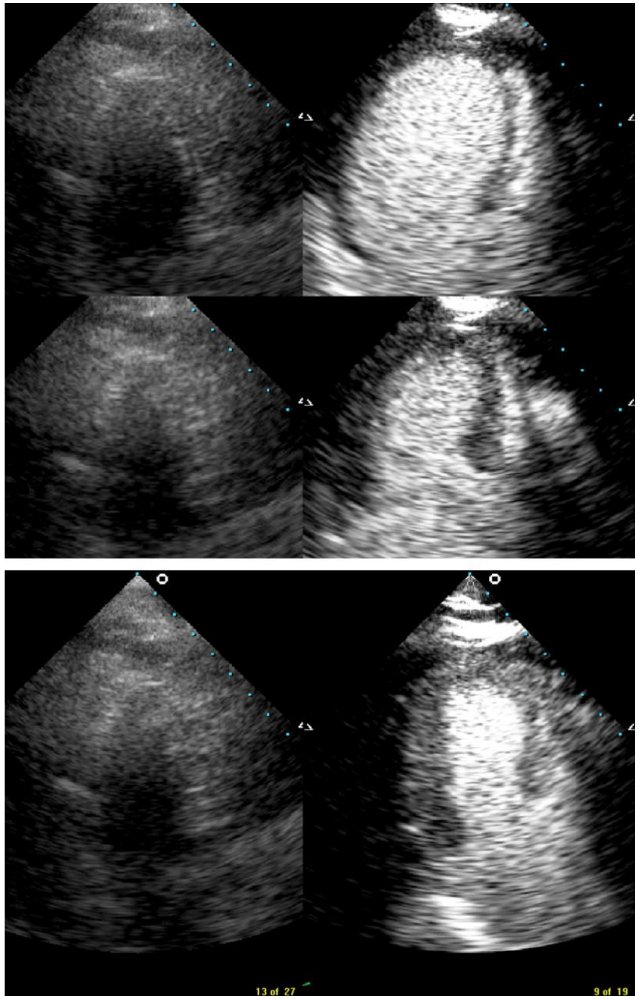
Where innovation starts

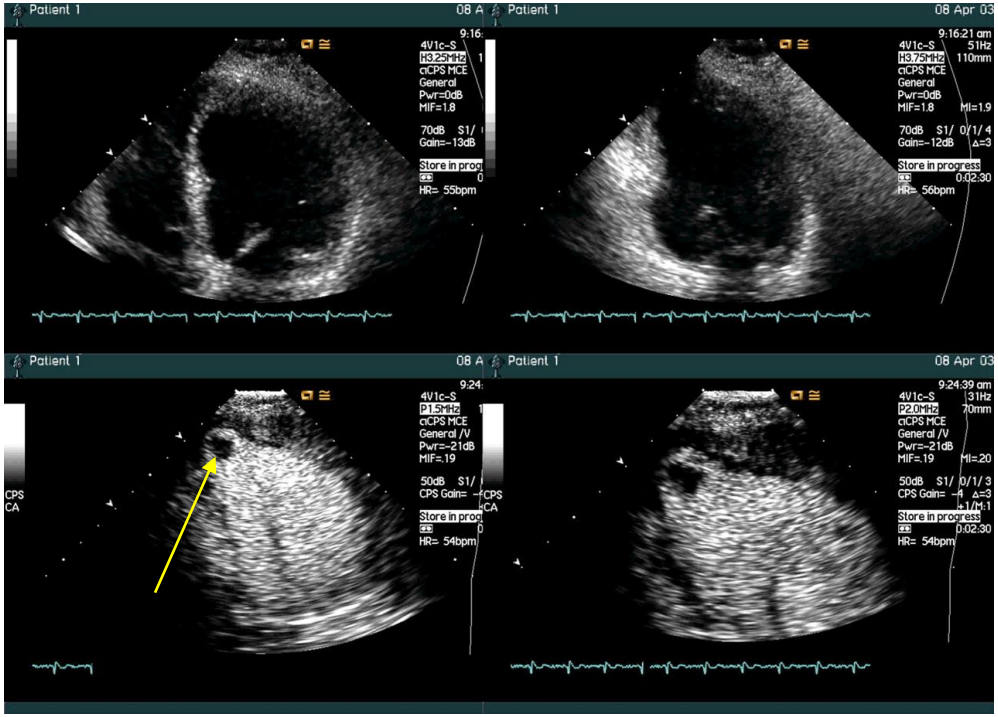
Why contrast?





Why contrast?

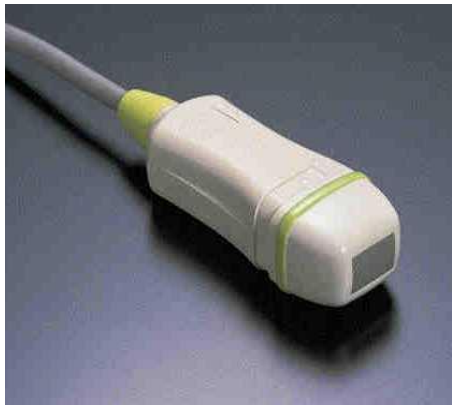




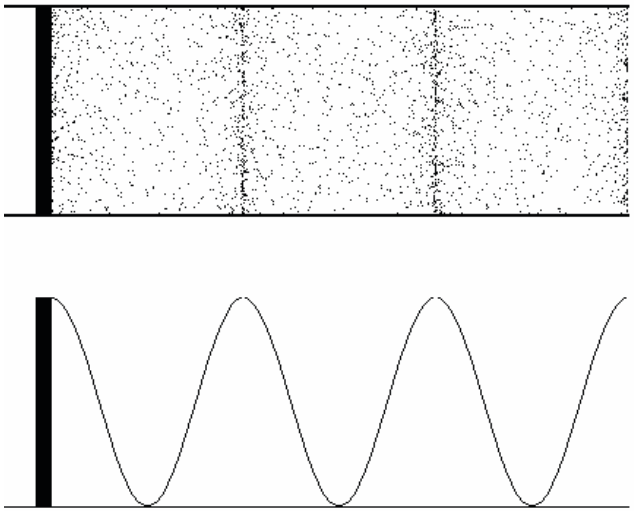
[Olszewski et al. *Eur Heart J* 2007]

Dynamic contrast-enhanced ultrasound

Ultrasound transducer



Pressure waves



Microbubbles

Applications

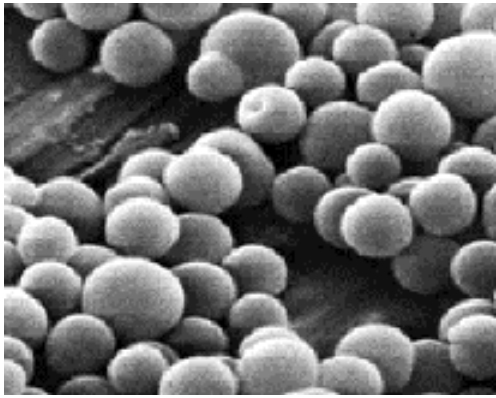
- **Detection of intracardiac shunts**
- **Intrapulmonary shunt**
- **Left ventricular opacification/endocardial border definition**
- **Assessment of myocardial perfusion**
- **Cancer diagnostics (angiogenesis)**
- **Atherosclerotic plaque characterization**

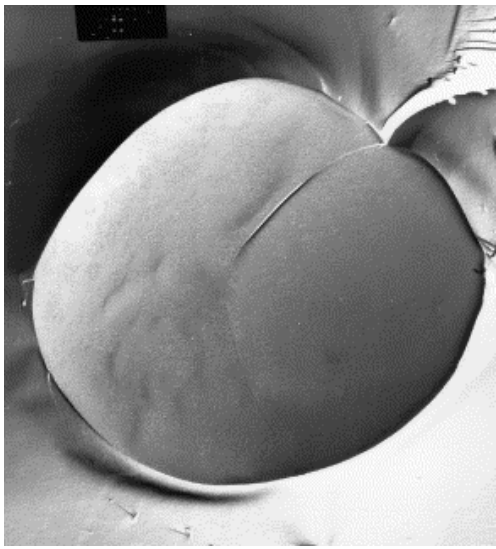
Mechanical index

- Microbubbles are deformed by higher ultrasound power to point of destruction.
- Mechanical Index (MI) = Acoustic Power [kPa] / $\sqrt{f_0}$[MHz]. It defines the mechanical interaction US/bubbles
- Low mechanical index (up to 0.3) is typically used for imaging (bubble detection).
- MI > 0.7 is associated with bubble destruction and cavitation fenomena.

Ultrasound contrast agents

- UCA are microbubbles with a diameter 1-10 μm
- They are made of an inert gas enclosed in a phospholipidic, albumin, or polymer shell.
- When invested by ultrasound waves they start oscillating and scattering energy with a non-linear behavior





Electron microscopy
13500×

Ultrasound contrast agents

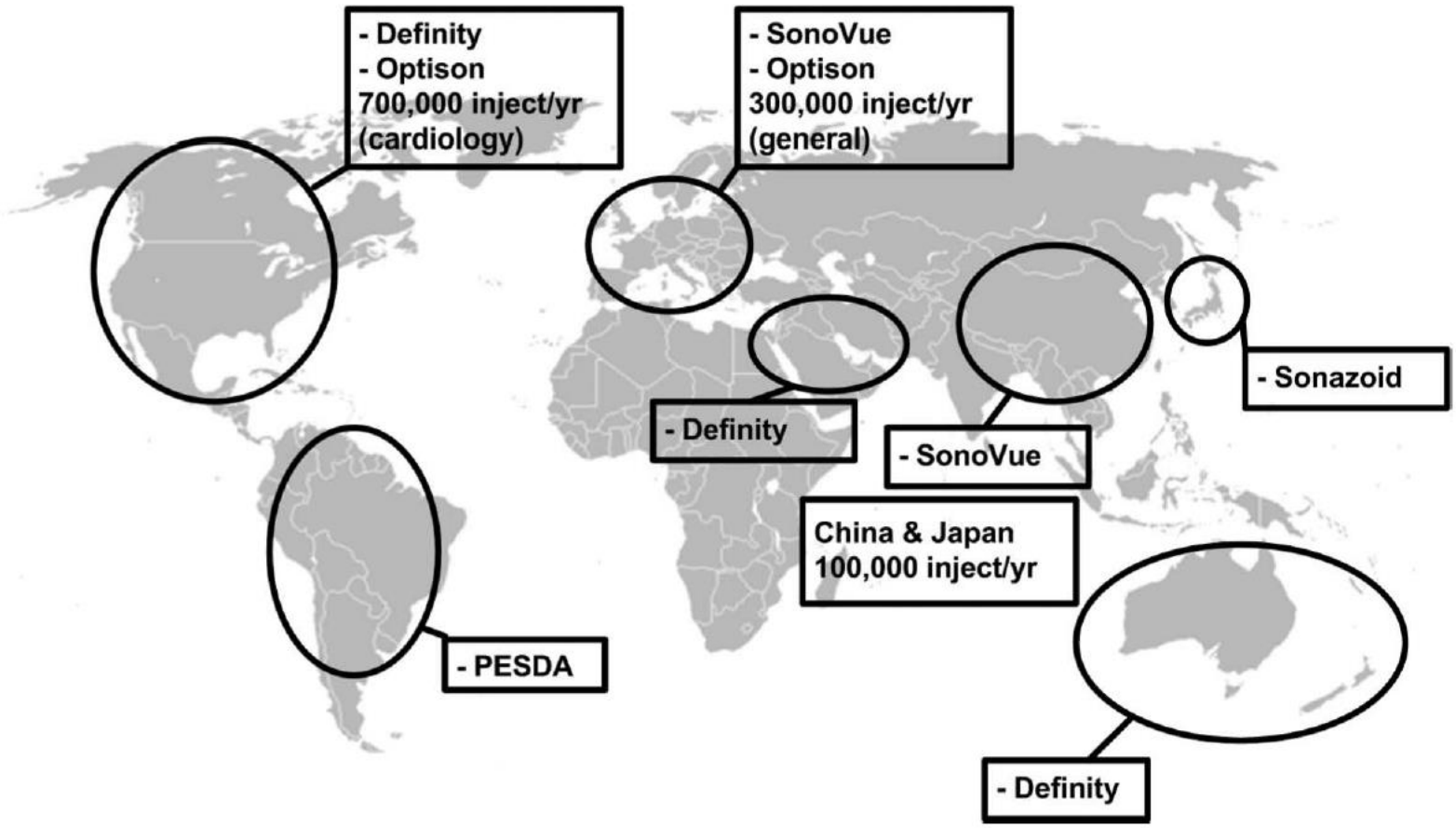
TABLE I. Commercially Available Ultrasound Contrast Agents.

Name	Manufacturer	Year	Gas	Coating	Approved	Available
Echovist	Bayer Schering Pharma AG	1991	air	galactose	EU, Japan, Canada	—
Albunex	Molecular Biosystems	1994	air	human albumin	EU, USA, Canada	—
Levovist	Bayer Schering Pharma AG	1996	air	galactose, trace palmitin	Worldwide[1]	—[2]
Optison	GE Healthcare AS	1997	C_3F_8	human albumin	EU, USA	EU, USA[3]
Definity	Lantheus Medical Imaging	2001	C_3F_8	phospholipids	Worldwide[4]	Worldwide
SonoVue	Bracco SpA	2001	SF_6	phospholipids	Europe, China, S Korea, India, Hong Kong, Singapore	Europe, China, S Korea, India, Hong Kong, Singapore
Imagent	Alliance Pharmaceutical Corp.	2002	C_6F_{14}	phospholipids	USA	—
Sonazoid	Amersham Health	2006	C_4F_{10}	phospholipids	Japan	Japan
BR38[5]	Bracco SpA	—	C_4F_{10}/N_2	phospholipids	—	—

[1]Approved in 65 countries, but not in the United States.
[2]Expected to finish in 2010.
[3]Temporarily unavailable 2006–2010.
[4]Approved in United States, Canada, Mexico, Israel, Europe, India, Australia, Koria, Singapore, UAE, and New Zealand.
[5]In clinical development.

[Faes et al, *IEEE TUFFC* 2013]

Ultrasound contrast agents



Free-bubble dynamics

Navier Stokes Equation

Fluid viscosity

Fluid pressure

$$\rho\left(\frac{\partial v}{\partial t}+\nabla\frac{v^2}{2}\right)+\mu_f(\nabla\times\nabla\times v)-\frac{4}{3}\mu_f\nabla(\nabla\cdot v)=-\nabla P$$

Fluid density

Fluid velocity

Newtonian incopressible fluid: $\nabla\cdot v=0$

Negligible vorticity (irrotational velocity field): $\nabla\times v=0$

Potential Ψ: $\nabla\Psi = v$

$$\rho\nabla\left(\frac{\partial\Psi}{\partial t}+\frac{v^2}{2}\right)=-\nabla P.$$

Bernoulli Equation

Integration for

- Radial symmetry: $v(r,t)=\dot{R}$
- $\Psi = 0$ for $r \rightarrow \infty$
- Pressure field for $r \rightarrow \infty$ is $P_\infty = P_0 + p(t)$

$$P(R)-P_\infty=\rho R\ddot{R}+\frac{3}{2}\rho\dot{R}^2$$

Internal pressure

Surface tension (N/m)

Vapor pressure

$$P(R)=P_i-\frac{2\sigma}{R}+P_v$$

$$P_i=\left(P_0-P_v+\frac{2\sigma}{R_0}\right)\left(\frac{R_0}{R}\right)^{3k}$$

Polytropic exponent

PV^k = const

k = 1: isothermal

k = γ: adiabatic

Encapsulated-bubble dynamics

Rayleigh Plesset Equation

$$\rho R\ddot{R} + \frac{3}{2}\rho\dot{R}^2 = \left(\frac{2\sigma}{R_0} + P_0 - P_v\right)\left[\left(\frac{R_0}{R}\right)^{3k} - 1\right] - P(t)$$

Modified Rayleigh Plesset Nolting Neppiras Poritsky (RPNNP) Equation

$$\rho R\ddot{R} + \tfrac{3}{2}\rho\dot{R}^2 = \left(\tfrac{2\sigma}{R_0} + P_0 - P_v\right)\cdot\left[\left(\tfrac{R_0}{R}\right)^{3k} - 1\right] + 4\tfrac{\mu_f\dot{R}}{R} - P(t)$$

Pressure drop by viscous damping due to fluid viscosity μ_f

Model for shell encapsulated bubbles (de Jong, 1991)

$$\rho R\ddot{R} + \tfrac{3}{2}\rho\dot{R}^2 = \left(\tfrac{2\sigma}{R_0} + P_0 - P_v\right)\cdot\left[\left(\tfrac{R_0}{R}\right)^{3k} - 1\right] + S_p\left(\tfrac{1}{R} - \tfrac{1}{R_0}\right) - \omega\delta_t\rho R\dot{R} - P(t)$$

Shell elasticity parameter (N/m)

Total damping factor = $b/2\pi f_n m$

damping coeff

natural frequency

mass

Damping factor

$$\delta_{\mathrm{t}} = \delta_{\mathrm{rad}} + \delta_{\mathrm{vis}} + \delta_{\mathrm{th}} + \delta_{\mathrm{f}}$$

Re-radiation damping $\delta_{\mathrm{rad}} = \dfrac{2\pi f_{\mathrm{n}}}{c} R_0,$

Fluid viscosity damping $\delta_{\mathrm{vis}} = \dfrac{2\mu_{\mathrm{f}}}{\pi f_{\mathrm{n}} \rho R_0^2},$

Thermal damping $\delta_{\mathrm{th}} = B(f, R_0)\dfrac{f_{\mathrm{n}}^2}{f^2},$

Shell friction damping $\delta_{\mathrm{f}} = \dfrac{6\mu_s T_s}{\pi f_{\mathrm{n}} \rho R_0^3}.$

[T.G. Leighton, *The acoustic bubble*, Oxford University Press, 1995]

Small oscillations for encapsulated bubbles

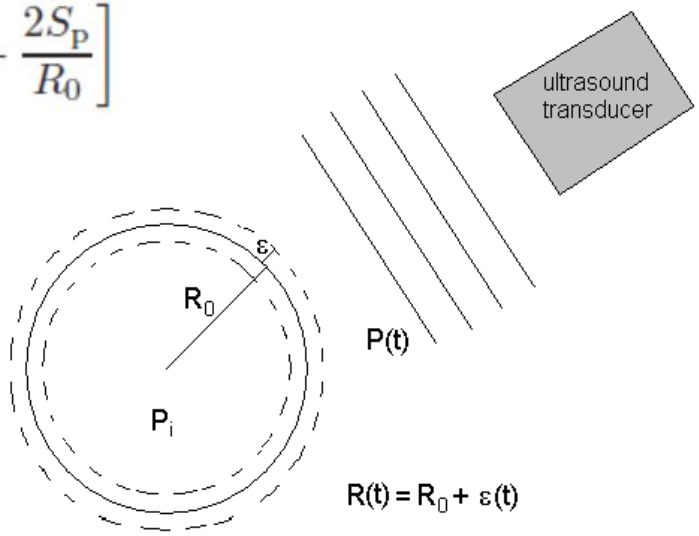
$$m\ddot{\epsilon} + b\dot{\epsilon} + s\epsilon = -4\pi R_0^2 P(t),$$

mass $m = 4\pi\rho R_0^3$,

damping coeff $b = 2\pi f m \delta_t$,

stiffness $s = 4\pi R_0 \left[3k\left(P_0 - P_v + \frac{2\sigma}{R_0}\right) - \frac{2\sigma}{R_0} + p_v + \frac{2S_p}{R_0}\right]$

1st order Taylor approximation



$$\frac{|\varepsilon(f)|}{|P(f)|} = \frac{1}{R_0\rho\sqrt{\left(f_n^2 - f^2\right)^2 + \left(f\, f_n \delta_t\right)^2}}$$

$$f_n = \frac{1}{2\pi}\sqrt{\frac{s}{m}} = \frac{1}{2\pi\sqrt{\rho}R_0}\sqrt{3k\left(P_0 - P_v + \frac{2\sigma}{R_0}\right) - \frac{2\sigma}{R_0} + P_v + \frac{2S_p}{R_0}}$$

$$f_0 = f_n\sqrt{1 - \left(\frac{\delta_t}{2}\right)^2}$$

Natural frequency for free bubbles

$$f_n = \frac{1}{2\pi}\sqrt{\frac{s}{m}} = \frac{1}{2\pi\sqrt{\rho}R_0}\sqrt{3k\left(P_0 - P_v + \frac{2\sigma}{R_0}\right) - \frac{2\sigma}{R_0} + P_v + \frac{2S_p}{R_0}}$$

Minnaert resonance:

$$f_n = \frac{1}{2\pi R_0}\sqrt{\frac{3\kappa P_0}{\rho}}$$

Backscatter coefficient

The ultrasound backscatter is defined by the *backscatter coefficient β*, which is the *scattering cross-section* (cm^2) per unit volume (cm^3) and per scattering angle (sr).

The scattering cross-section of a bubble is the ratio between the power scattered in all directions, *W* (average power over a period *T*=1/*f*), and acoustic intensity I_i.

$$\epsilon(t) = \epsilon_0 \cos(2\pi f t)$$

$$b_{rad} = 2\pi f m \delta_{rad} = \frac{16\pi^3 \rho R_0^4 f^2}{c}$$

$$W = \frac{1}{T}\int_0^T (F \cdot \dot{\epsilon}(t))dt = \frac{1}{T}\int_0^T (\dot{\epsilon}(t) b \cdot \dot{\epsilon}(t))dt = \frac{1}{2} 4\pi^2 f^2 \epsilon_0^2 b$$

Force to compensate damping

Scattering cross-section

$$\Sigma(R_0, f) = \frac{W}{I_i} = \frac{\frac{1}{2}4\pi^2 f^2 \epsilon_0^2 b}{P_i^2 (2Z)^{-1}} = \frac{4\pi R_0^2}{\left[(f_n(R_0)/f)^2 - 1\right]^2 + \delta_t^2(R_0, f)}$$

$$Z = \rho c$$

Which is the scattering cross-section if $f >> f_n$?

Backscatter coefficient

$$\Sigma_{\mathrm{tot}}(f) = \int_{R_{\mathrm{min}}}^{R_{\mathrm{max}}} n(R)\Sigma(R,f)dR$$

Total scattering cross-section accounts for interaction forces depending on normalized radius distribution *n*(*R*).

Backscatter coefficient [cm^{-1} sr^{-1}]: $\beta(f) = \dfrac{\rho_{\mathrm{n}}\Sigma_{\mathrm{tot}}(f)}{4\pi}$,

with ρ_n number of bubbles per unit volume.

Intensity received by the transducer: $I = \dfrac{dV}{z^2}\beta(f)I_{\mathrm{i}} = \dfrac{dV}{z^2}\dfrac{\rho_{\mathrm{n}}\Sigma_{\mathrm{tot}}(f)}{4\pi}I_{\mathrm{i}}$

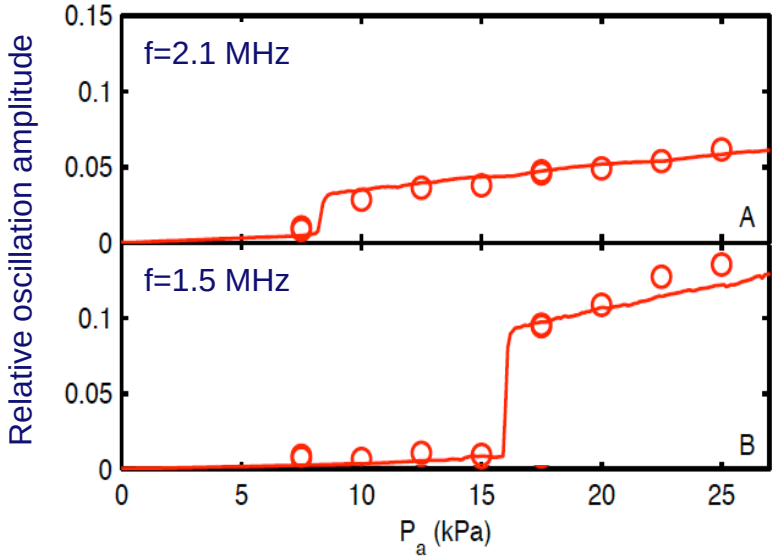
sample volume

distance from the transducer

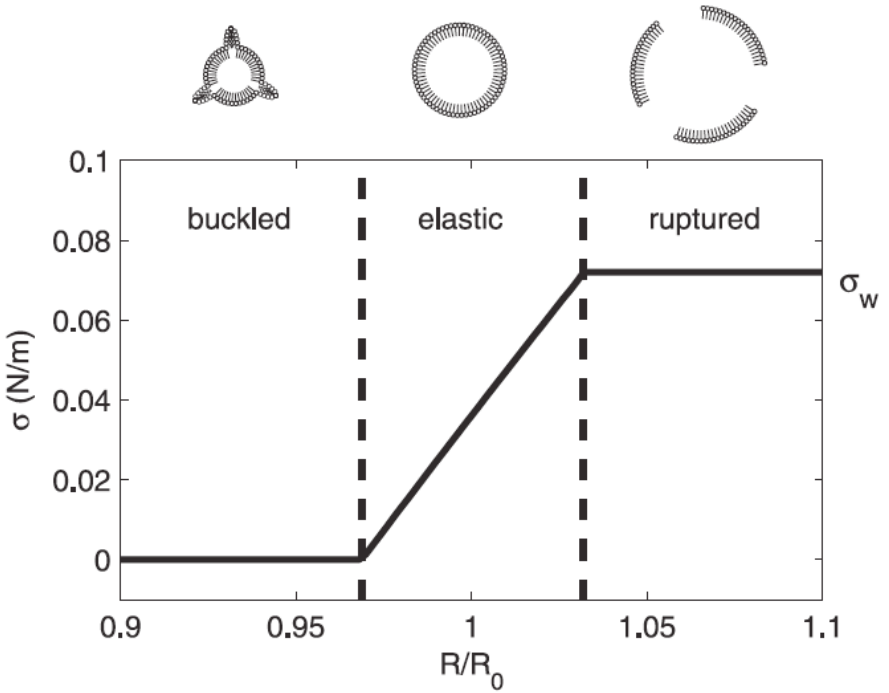
The average β(f) over the spectrum is the Integrated backscatter coefficient (IBI).

Thresholding and buckling

Thresholding



Buckling



The tension as a function of the bubble radius (R_0=2 μm) for Marmottant model in elastic regime, buckling, and rupture of the shell.

Notice the compression only behavior…

Attenuation

Extinction cross-section (similar to backscatter but for power loss)

Due to scattering

$$\Sigma_e = \left(\frac{\delta_t}{\delta_{rad}}\right)\Sigma \qquad \Sigma_{e_{tot}} = \int_{R_{max}}^{R_{min}} n(R)\Sigma_e(R,f)dR$$

Due to all damping factors

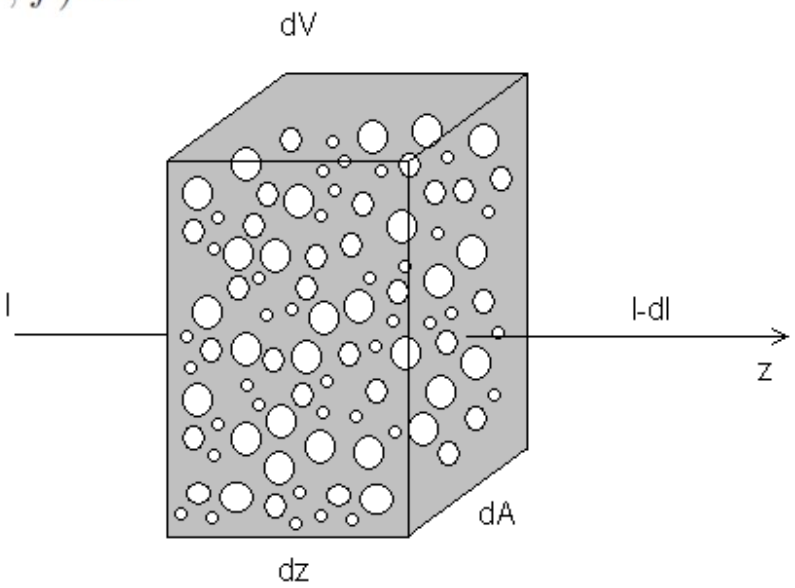
$$dW_{loss} = I\rho_n\Sigma_{e_{tot}}dV = I\rho_n\Sigma_{e_{tot}}dAdz$$

$$dI = I\rho_n\Sigma_{e_{tot}}dz$$

Loss of intensity

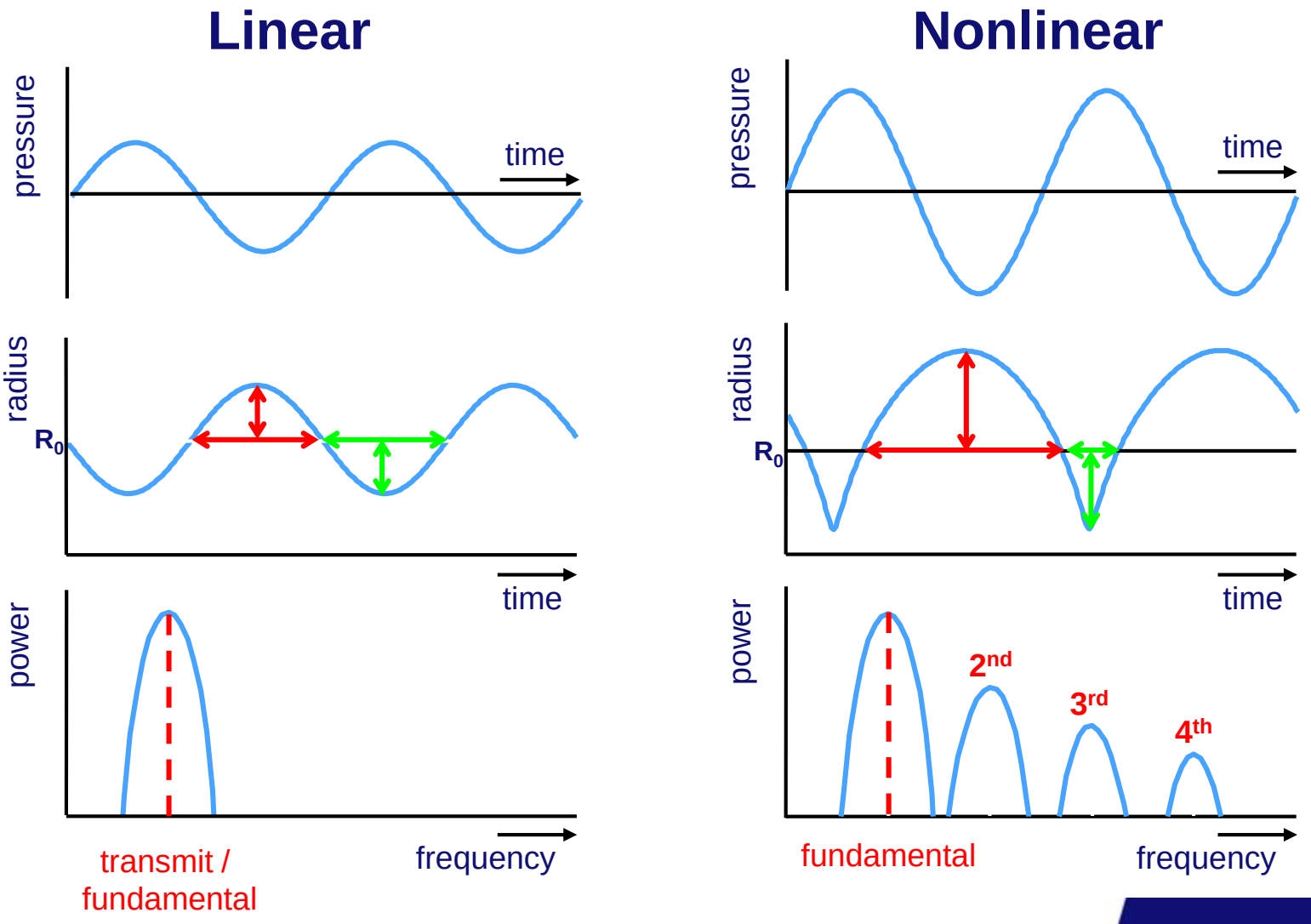
$$I(z) = I_i e^{-\rho_n\Sigma_{e_{tot}}z}$$

2 x extinction coeff a_e

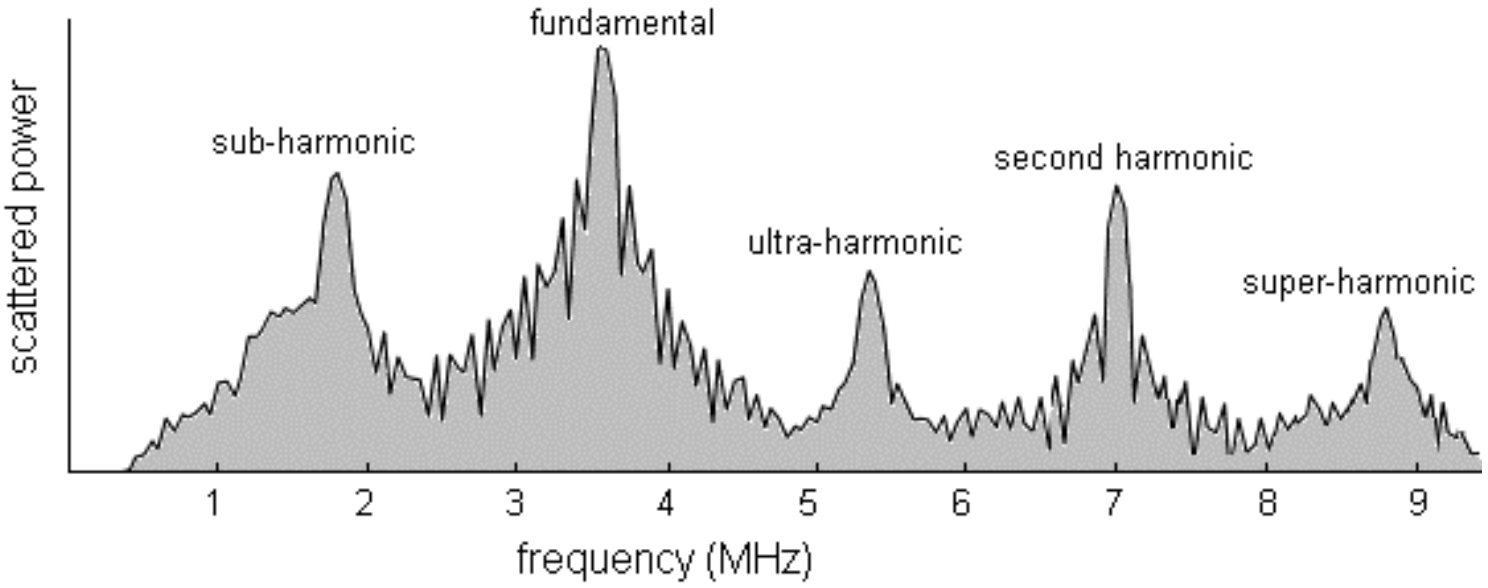


a_e depends on scattering in all directions and damping.
A term a_d can also be considered to account for chemical decay (dissolution).

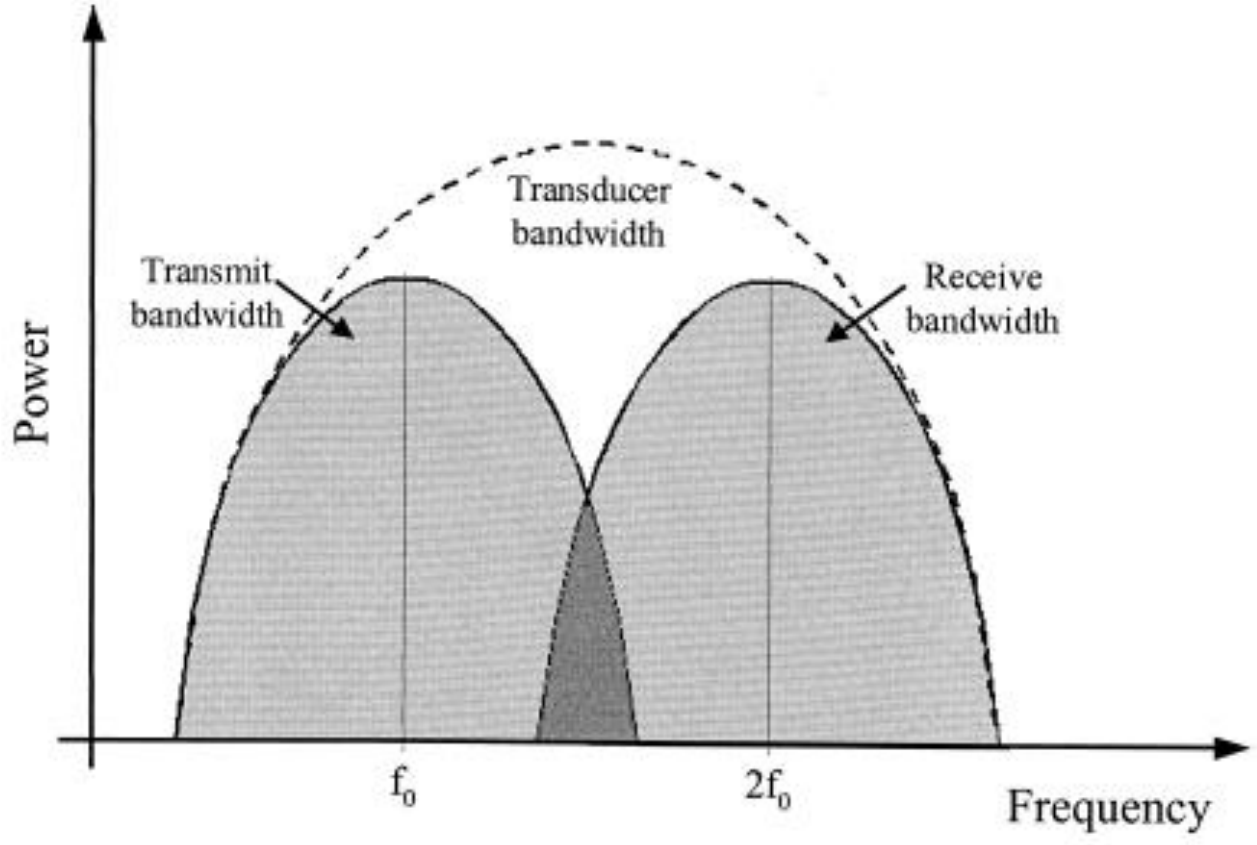
Nonlinear behavior



Backscatter spectrum



2nd harmonic imaging



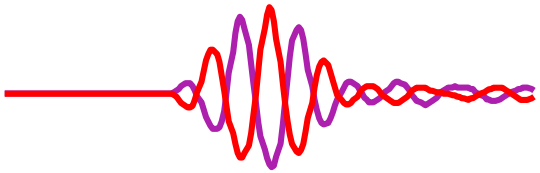
Frinking et al, *Ultras Med Biol*, 2000:26(6):965-975.

Pulse inversion

Tx: transmitting two pulses p_1 and p_2 , where: $p_2 = -p_1$

Rx: summing the two echoes: $e_{pi} = e_1 + e_2$

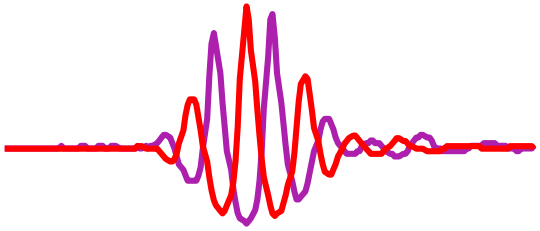
Linear:



$e_2 = - e_1$

$e_{pi} = 0$

Non-Linear:



$e_2 \neq - e_1$

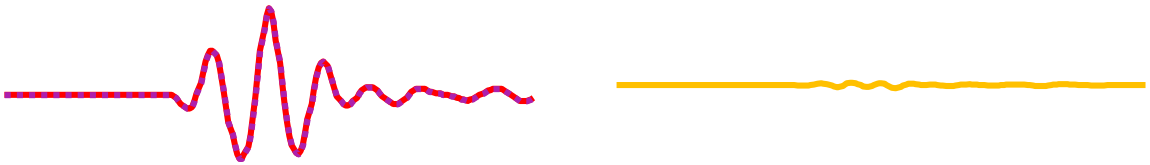
$e_{pi} \neq 0$

Power modulation

Tx: transmitting two pulses p_1 and p_2 , where: $p_2 = \alpha p_1$

Rx: scaling and subtracting the two echoes: $e_{pm} = e_1 - e_2 / \alpha$

Linear:



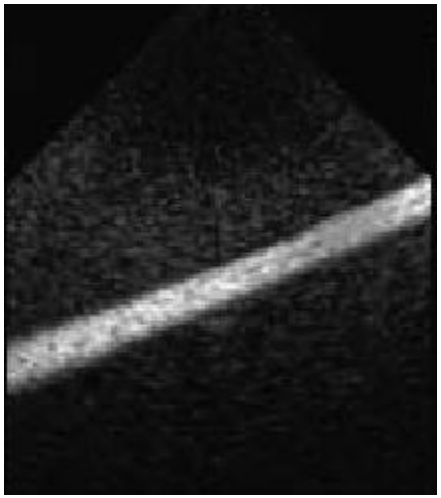
$e_2 = \alpha e_1$ $e_{pm} = 0$

Non-Linear:

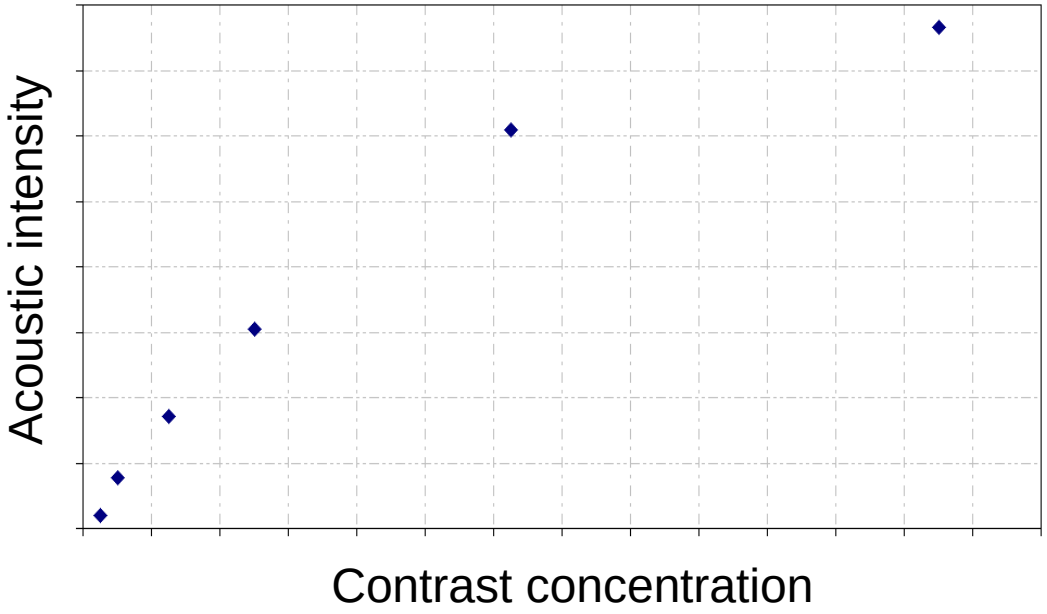
$e_2 \neq \alpha e_1$ $e_{pm} \neq 0$

Contrast-specific imaging

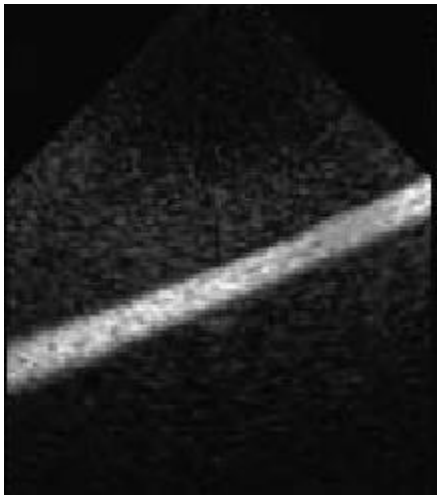
Power modulation

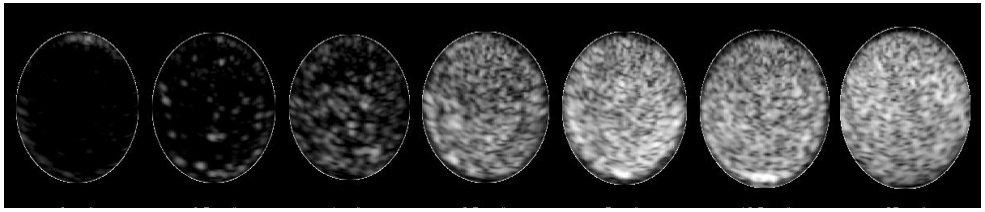


Contrast-specific imaging

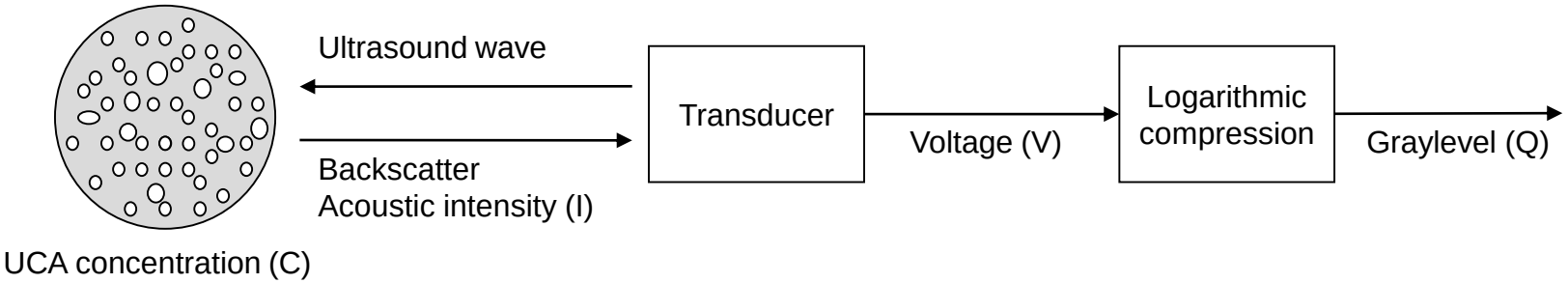


Power modulation





Data calibration / linearization



Video density:

- **Low UCA concentrations:** $I \propto C$
- **Dynamic-range compression:** $Q \propto \log(I)$

$$Q(C) = a_0 \ln(a_1 C + 1) + a_2$$

- **Dynamic-range parameter a_0**
- ***I*(*C*) regression-line angle a_1**
- **Baseline a_2**

Data calibration / linearization

If we inject a dose ***m*** in a compartment of unknown volume ***V,***

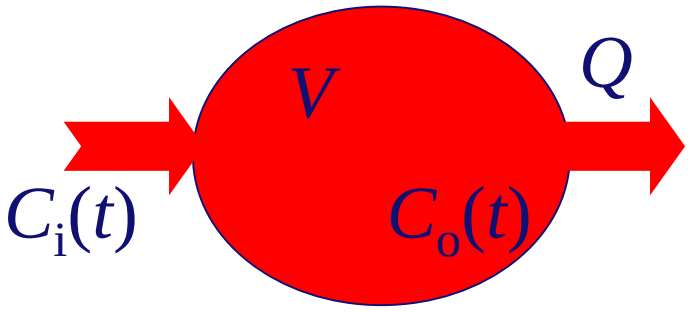
we can estimate ***V*** by measuring ***C*** :

$$V = \frac{m}{C}$$

What are ***m*** and ***C*** in contrast-enhanced ultrasound (CEUS)?

- Based on the adopted calibration, ***C*** is the concentration corresponding to the measured signal (acoustic intensity or gray levels), usually expressed in volume fraction.
- Therefore, ***m*** is the volume of injected contrast agent.

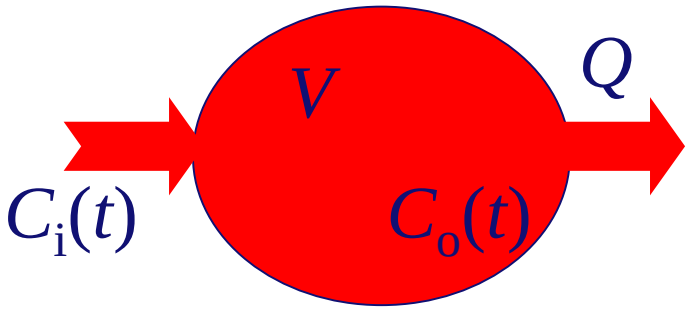
Mono-compartment model



$$\frac{dC_0(t)}{dt}V = \left(C_i(t) - C_0(t)\right)Q$$

- $C_i(t)$ = input concentration
- $C_o(t)$ = output concentration (or concentration in the compartment)
- V = volume of the compartment
- Q = flow through the compartment

Mono-compartment model



$$\frac{dC_0(t)}{dt}V = \left(C_i(t) - C_0(t)\right)Q$$

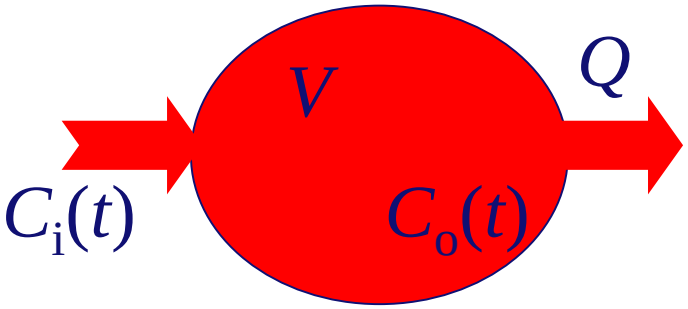
Laplace transform $L[.]$

$$\tau \frac{dC_0(t)}{dt} + C_0(t) = C_i(t) \quad \Longleftrightarrow \quad \frac{C_0(s)}{C_i(s)} = \frac{1}{\tau s + 1}$$

with

τ = system *time constant* = V/Q

Dilution impulse response of a compartment



convolution

Impulse response

$$C_o(t) = C_i(t) * h(t)$$

$$C_o(s) = C_i(s)H(s)$$

$$H(s) = L[h(t)]$$

$$h(t) = L^{-1}\left[\frac{1}{\tau s + 1}\right] = \frac{1}{\tau} e^{-\frac{t}{\tau}}$$

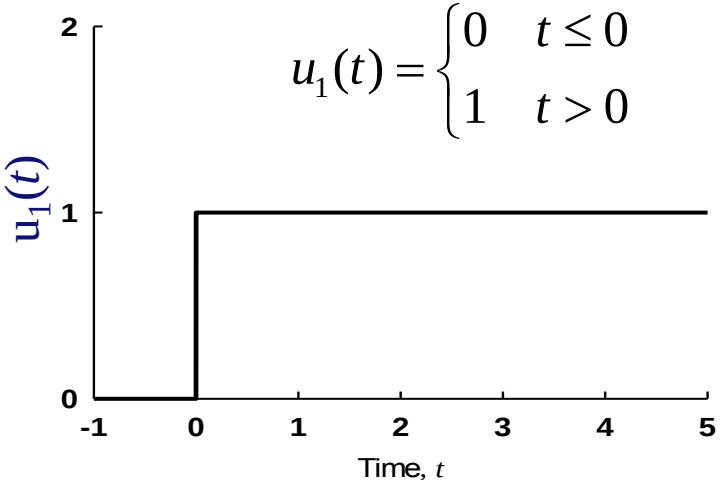
- $C_i(t)$ = input concentration
- $C_o(t)$ = output concentration
- V = volume of the compartment
- Q = flow through the compartment
- τ = system *time constant* = V/Q

Mono-compartment step response

Assume for $t \leq 0$, $C_0 = 0$, and at time $t = 0$ the input quantity, C_i, increases instantly by an amount A, i.e.,

$$C_i(t) = Au_1(t).$$

$$u_1(t) = \begin{cases} 0 & t \leq 0 \\ 1 & t > 0 \end{cases}$$



$$C_0(t) = h(t) * C_i(t) = h(t) * A \cdot u_1(t)$$

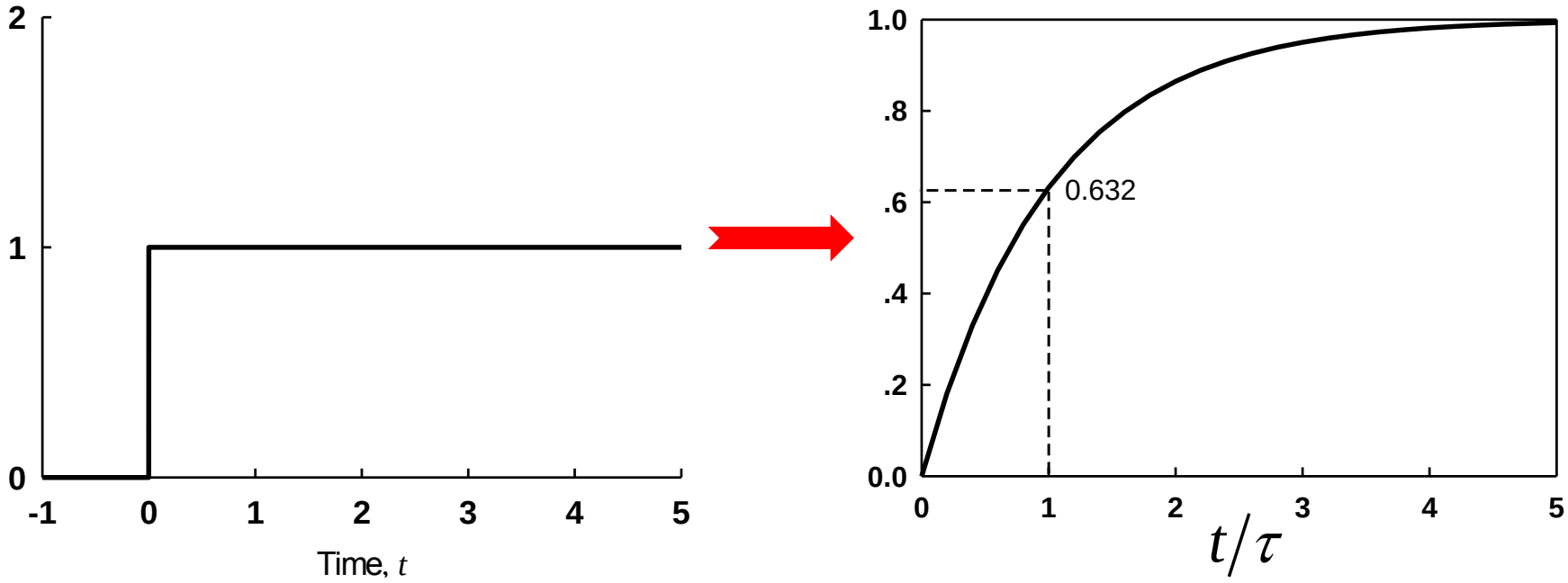
$$C_0(s) = H(s) \cdot A \cdot L\left[u_1(t)\right] = H(s) \cdot A \cdot \frac{1}{s}$$

$$C_0(s) = \frac{A}{(\tau s + 1)s} = A\left(\frac{1}{s} - \frac{\tau}{\tau s + 1}\right) \Rightarrow C_0(t) = A\left(1 - e^{-\frac{t}{\tau}}\right)$$

Mono-compartment step response

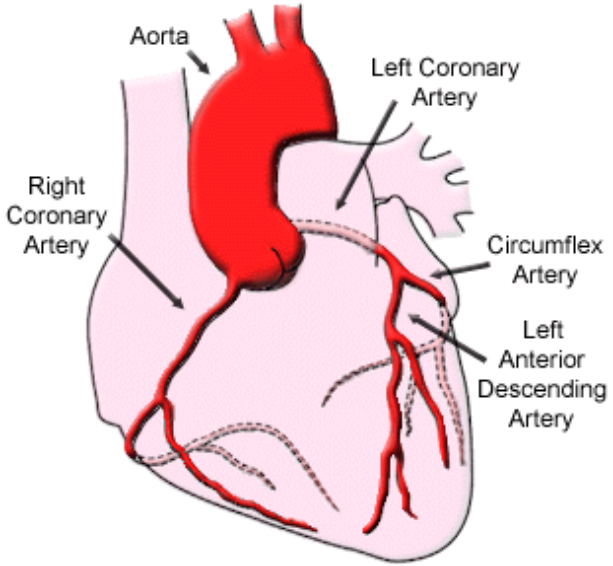
$$\text{for } A = 1$$

$$y(t) = 1 - e^{-t/\tau}$$



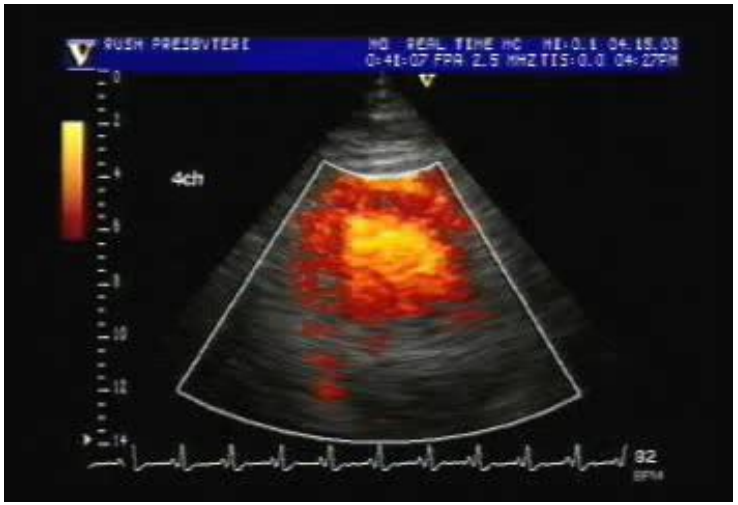
Myocardial perfusion

- MP indicates the blood flow in the myocardium [flow/unit tissue volume], which is the heart muscle.
- The major vessels in the myocardium are the coronary arteries, which draw oxygenated blood from the root of the aorta, and the coronary veins, which carry de-oxygenated blood to the right atrium (RA).
- A lack of perfusion is known as ischemia, which leads to reduced wall thickening/motion (ipokinesis) and dyssinchrony of the ventricular contraction.



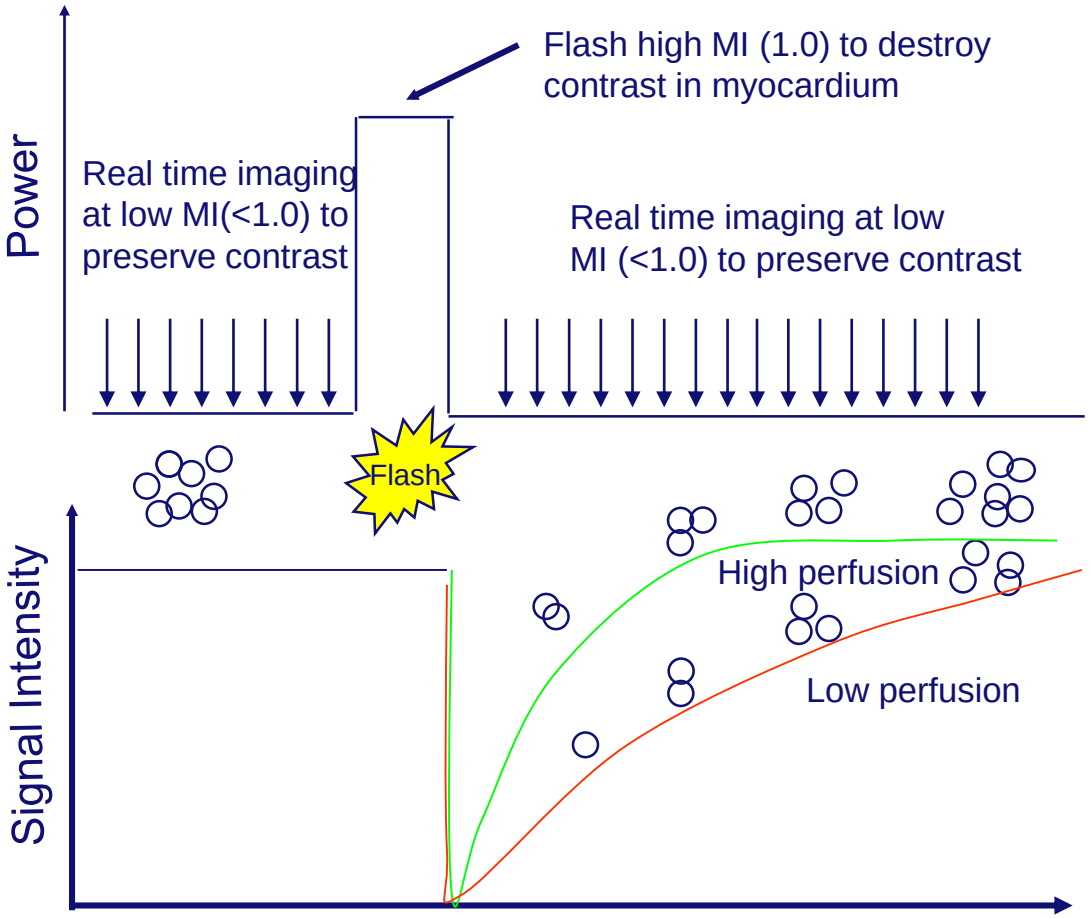
Myocardial perfusion

Destruction (flash) replenishment method



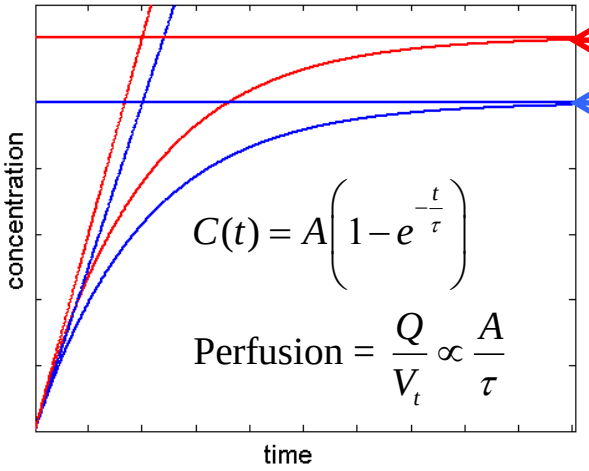
$$C_0(t) = A\left(1 - e^{-\frac{t}{\tau}}\right)$$

$$\text{Perfusion} \propto A/\tau$$



Wei et al, *Circulation*, 1998.

Myocardial perfusion



high flow

low flow

$V_v =$ vascular volume

$V_t =$ tissue volume

$Q =$ flow

$A =$ plateau concentration (vascular fraction)

$$A \propto \frac{V_v}{V_t} \Rightarrow \frac{A}{\tau} \propto \frac{V_v}{V_t} \cdot \frac{1}{\tau} = \frac{V_v}{V_t} \cdot \frac{Q}{V_v} = \frac{Q}{V_t}$$

Myocardial perfusion

Stress echo is a well known procedure in clinical practice to look at wall motion and MP. The echocardiographic investigation is made at about 85% of maximal PR.

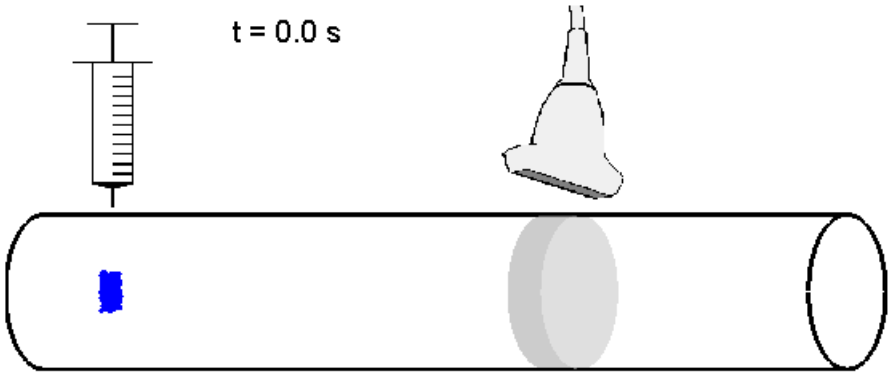
In young patients exercise is the preferred option.

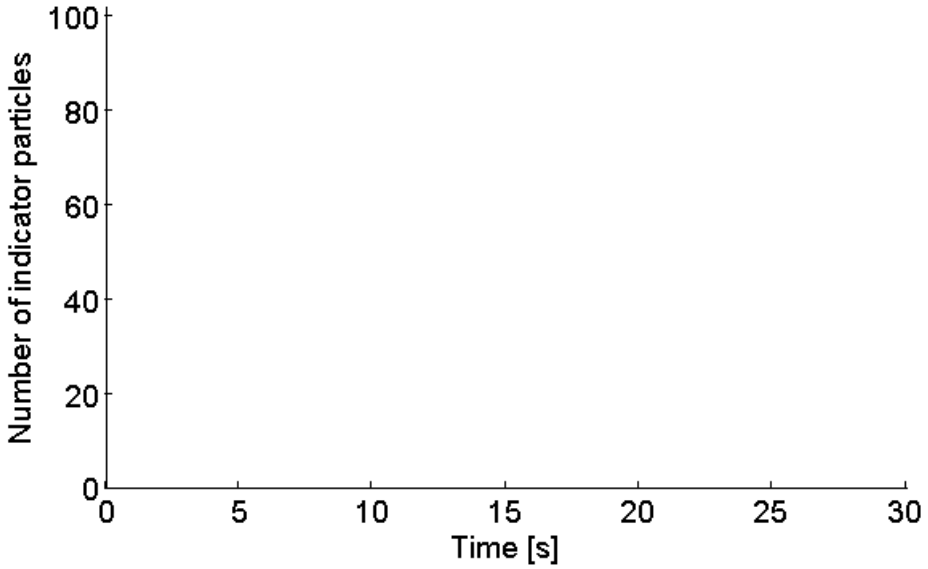
Only when exercise is not possible:

- Injection of vasodilators (more to look at MP, increase PR of ~10%)
  - Adenosine (faster effect)
  - Dipyridamole (slower effect, 10-15 min side effects, but more time for imaging…)
- Injection of dobutamine (more for wall motion)

Indicator dilution curve / time intensity curve

Evolution over time of the contrast concentration after a contrast bolus injection

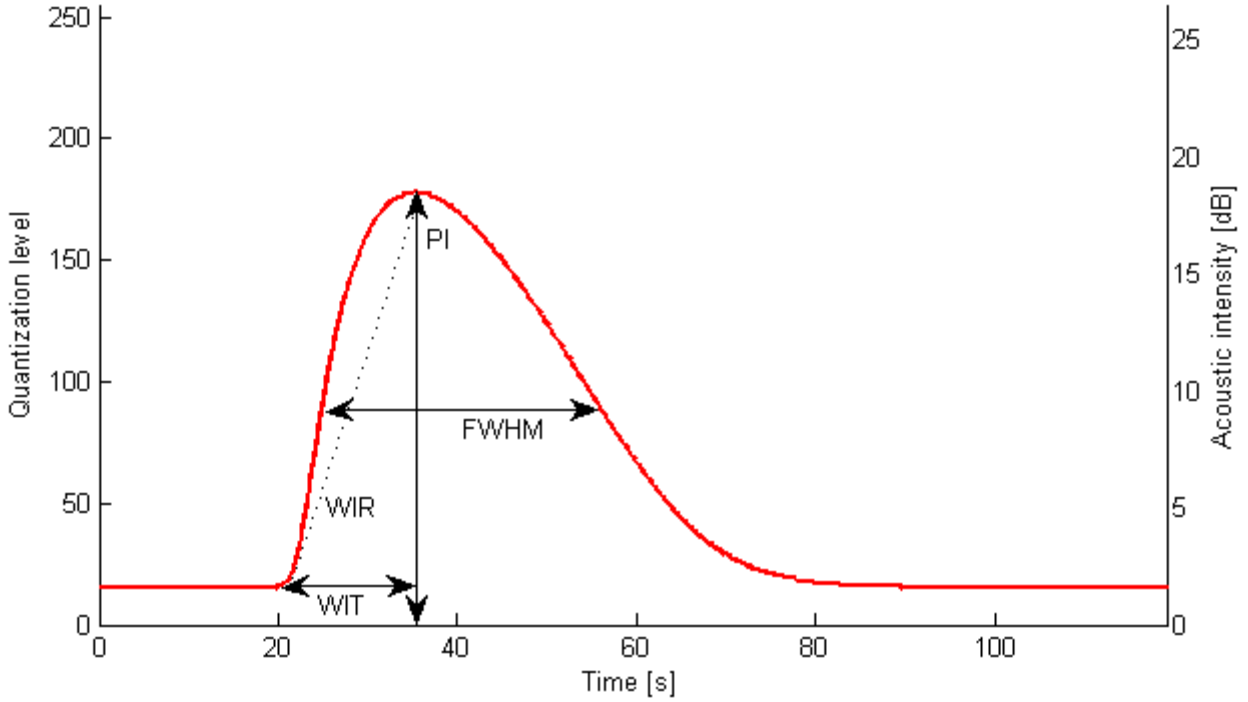




Heuristic features

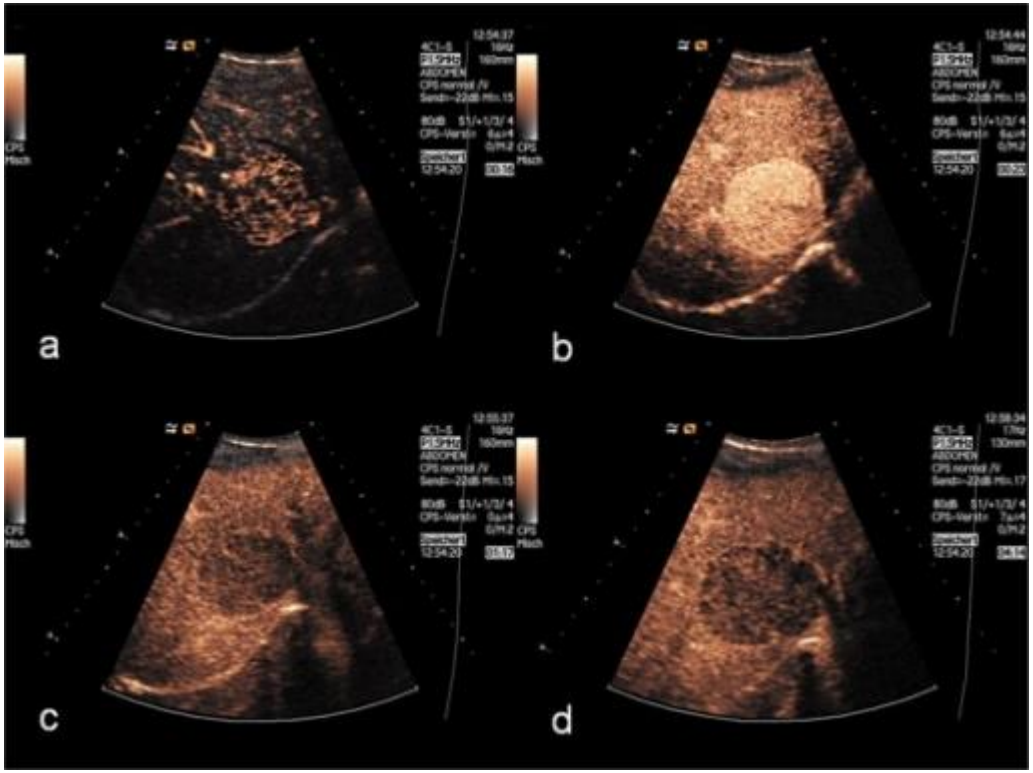
Features used for semi-quantitative interpretation of the IDC:

- Peak Intensity (PI)
- Area Under the Curve (AUC)
- Wash-in Time (WIT)
- Wash-in Rate (WIR)



Qualitative cancer diagnostics by CEUS

Qualitative diagnosis of liver lesions by early wash-in (arterial phase) and wash-out (portal phase).



Mass conservation

$$\frac{dm}{dt} = \frac{dV}{dt}\frac{dm}{dV} = Q(t)C(t)$$

We are interested in the integral of the mass-conservation equation, i.e., the *Stewart-Hamilton* equation:

$$\int_0^\infty dm = \int_0^\infty Q(t)C(t)dt \rightarrow m = Q\int_0^\infty C(t)dt.$$

Therefore, $$Q = \frac{m}{\int_0^\infty C(t)dt}$$

with

Q = constant

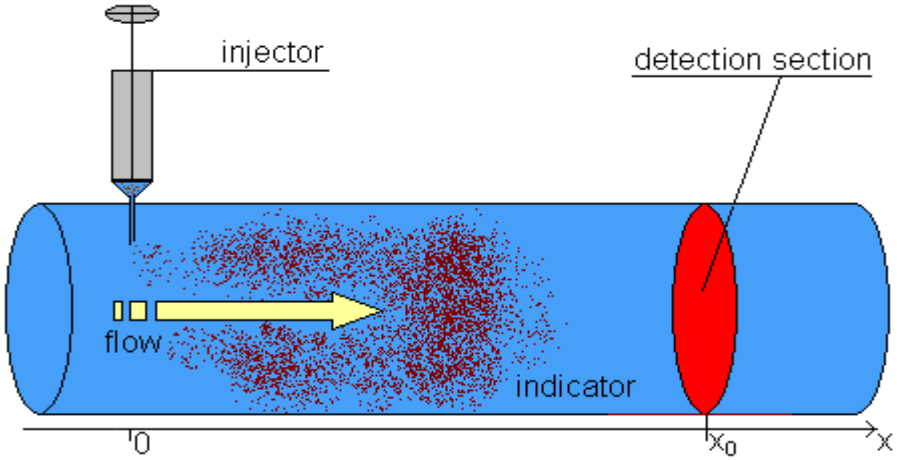
m = injected dose

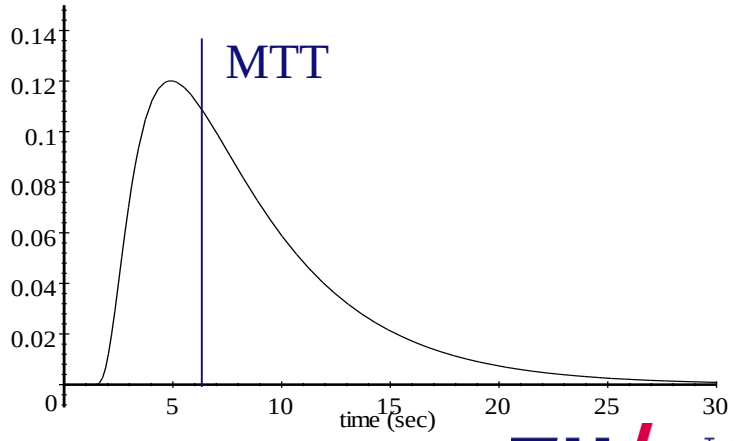
Mean transit time (MTT) and volume (V)

$$MTT = \frac{\int_0^\infty t \cdot C(t)\, dt}{\int_0^\infty C(t)\, dt}$$

$$V = MTT \cdot Q$$

$$V = \frac{m \int_0^\infty t \cdot C(t)\, dt}{\left(\int_0^\infty C(t)\, dt \right)^2}$$





Mean transit time and volume

$$\mathrm{MTT} = \frac{\int_0^\infty t \cdot C(t)\, dt}{\int_0^\infty C(t)\, dt}$$

$$V = \mathrm{MTT} \cdot Q$$

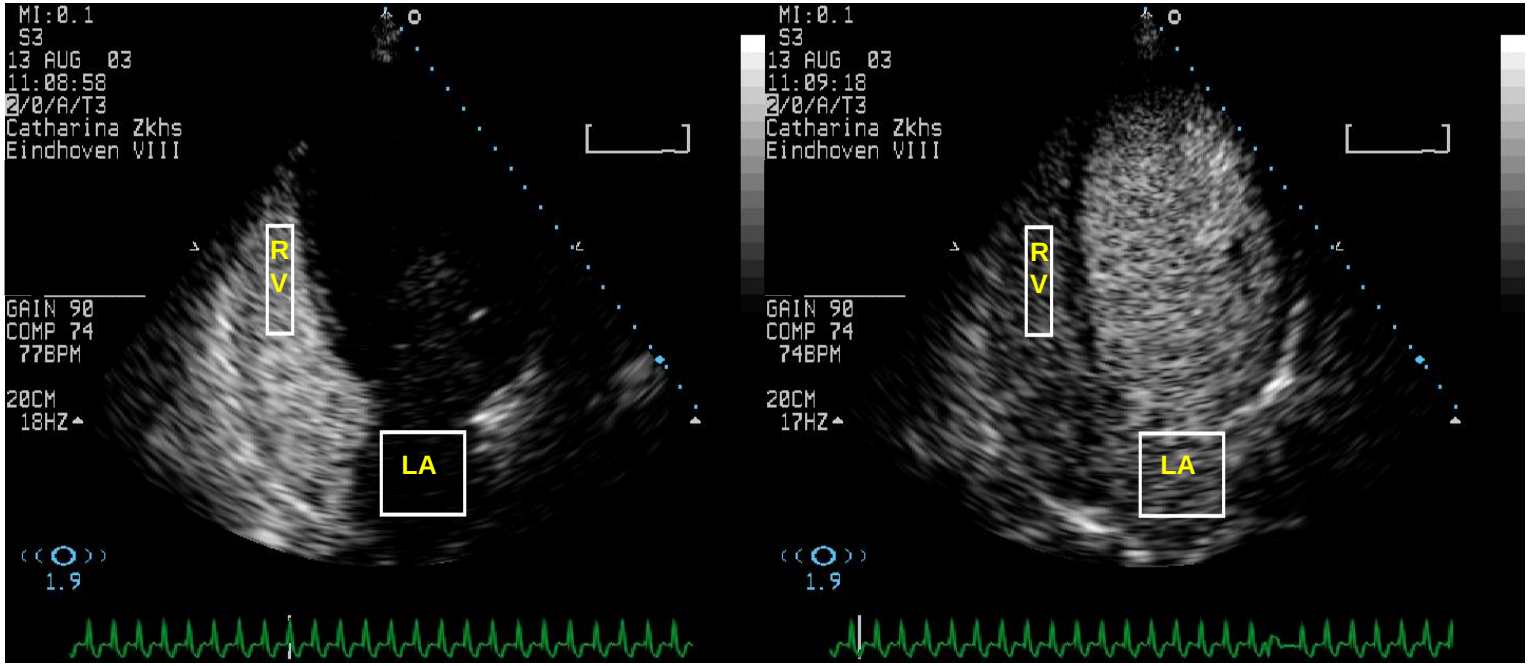
$$V = \frac{m \int_0^\infty t \cdot C(t)\, dt}{\left(\int_0^\infty C(t)\, dt \right)^2}$$

Requirements

Linear relationship concentration vs. measured quantity

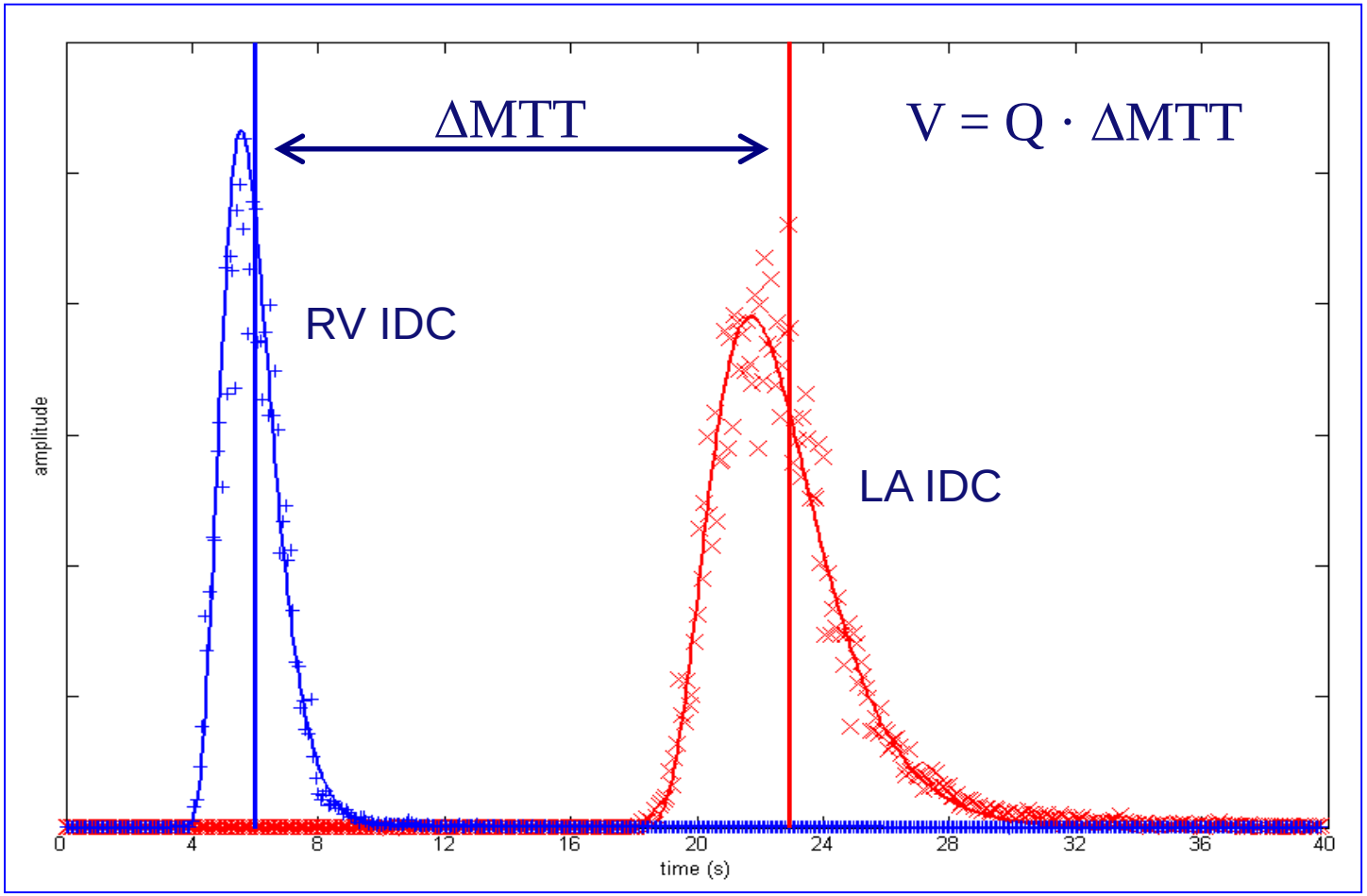
Fully determined relationship concentration vs. measured quantity

Pulmonary blood volume

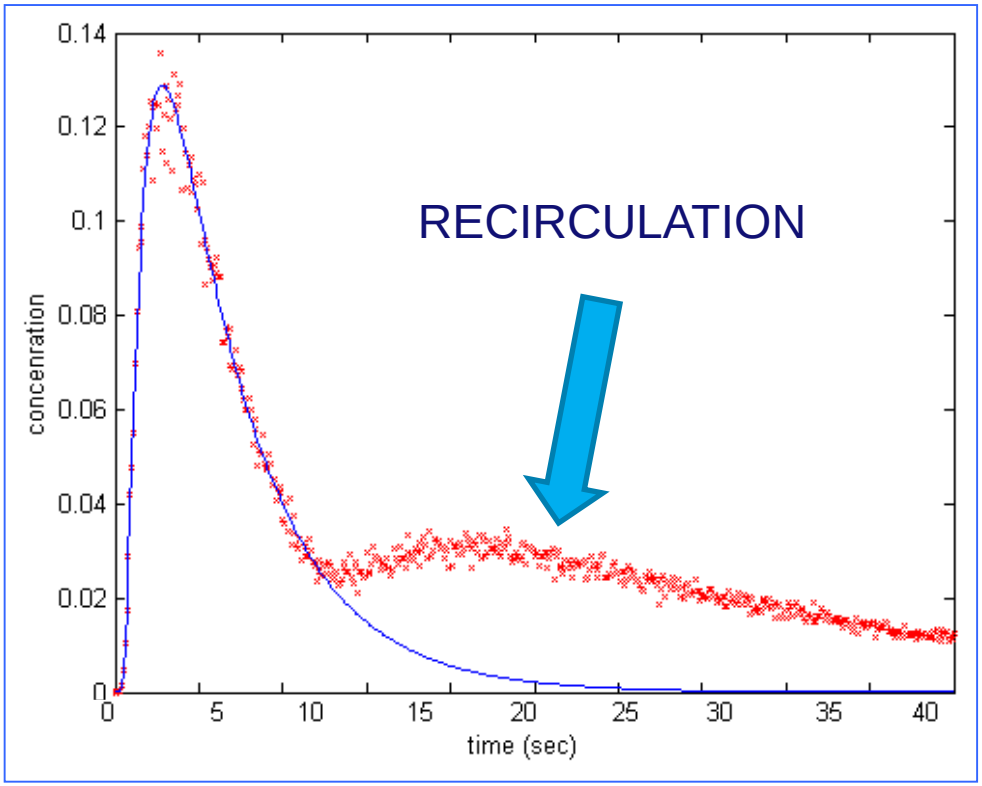


[Mischi et al, *IEEE TUFFC* 2004]

Pulmonary blood volume

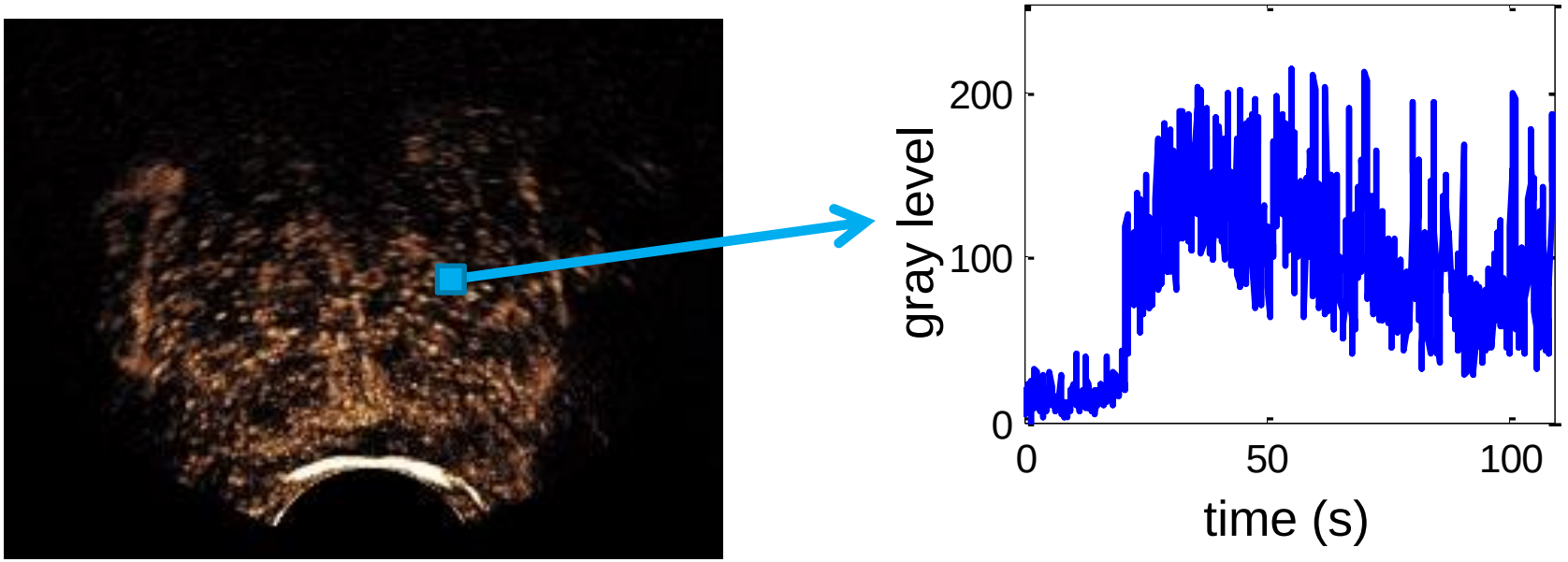


Recirculation problem

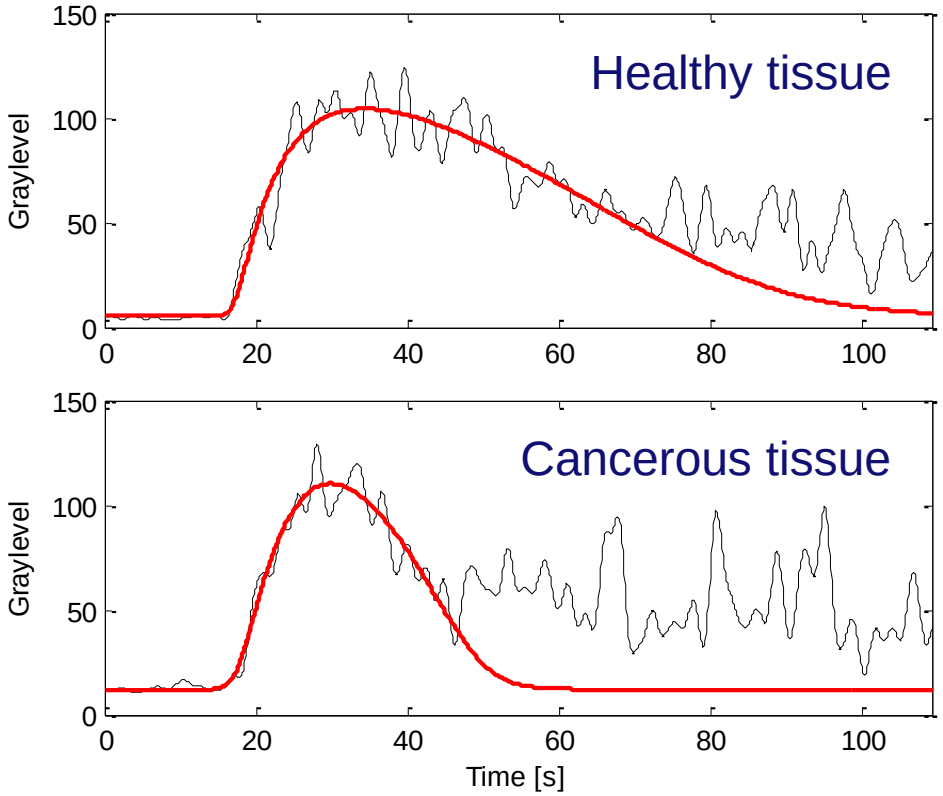


Poor signal-to-noise ratio

IDC measured from single pixels in the prostate…



Need for model fitting



Better interpretation by:

- Extraction of relevant data
- Parameter estimation

Quantitative analysis

(main) IDC distributed models

Lognormal

$$C(t) = \left(\frac{m}{Q}\right)\frac{1}{\sqrt{2\pi}\sigma t}e^{\frac{-(\ln(t)-\mu)^2}{2\sigma^2}}$$

$$MTT = e^{\mu+\frac{\sigma^2}{2}}$$

[Qian & Bassingthwaighte J Theoretical Biology 2000]

Local Density Random Walk (LDRW)

$$C(t) = \left(\frac{m}{Q}\right)\sqrt{\frac{\lambda}{2\pi\mu t}}e^{\lambda-\frac{\lambda}{2}\left(\frac{t}{\mu}+\frac{\mu}{t}\right)}$$

$$MTT = \mu$$

$$MRT \text{ (mean resident time)} = \mu\left(1+\frac{1}{\lambda}\right)$$

[Sheppard and Savage *Phys. Rev.* 1951]
[Mischi *et al*. ERASIP J Appl Signal Processing 2003]
[Kuenen *et al.* IEEE T-MI 2011]

Gamma

$$C(t) = \left(\frac{m}{Q}\right)\frac{\beta^{\alpha}}{\Gamma(\alpha)}t^{\alpha-1}e^{-t\beta}$$

shape factor

rate factor

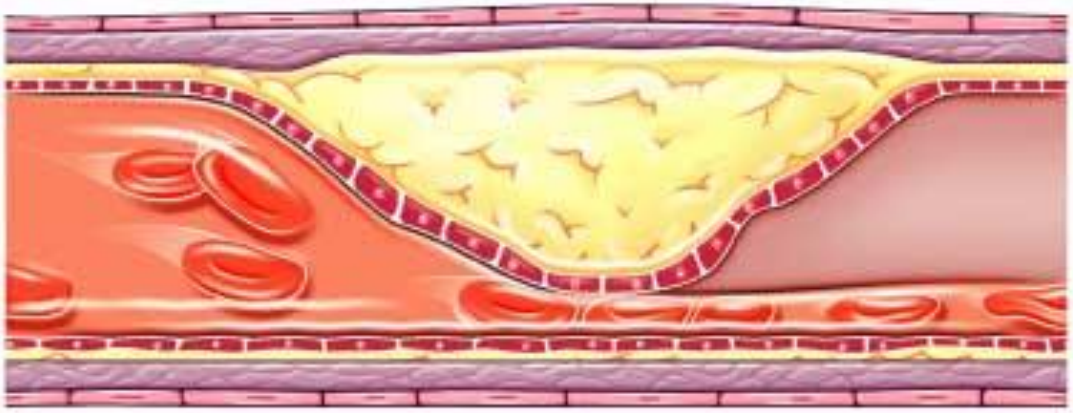
Gamma operator

$$MTT = \alpha\beta$$

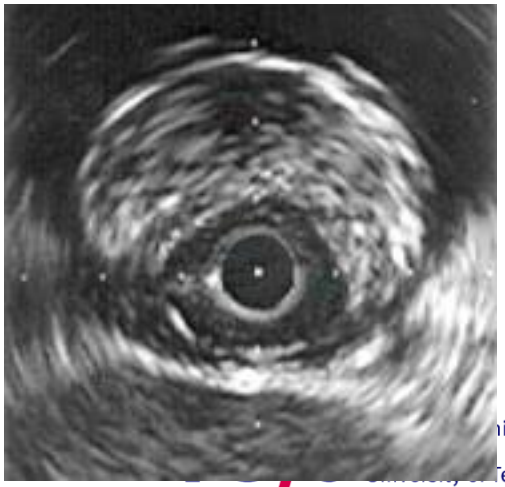
$$\Gamma(\alpha) = \int_0^{\infty} x^{\alpha-1}e^{-x}dx$$

[Thompson *et al.* Circ Res 1964]
[Mischi *et al*. Physiol Meas 2008]

Atherosclerotic plaque



Intravascular echography



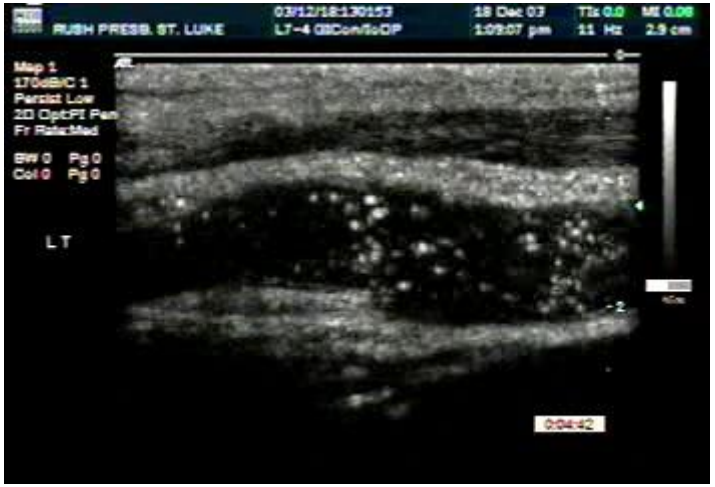
Imaging plaque perfusion

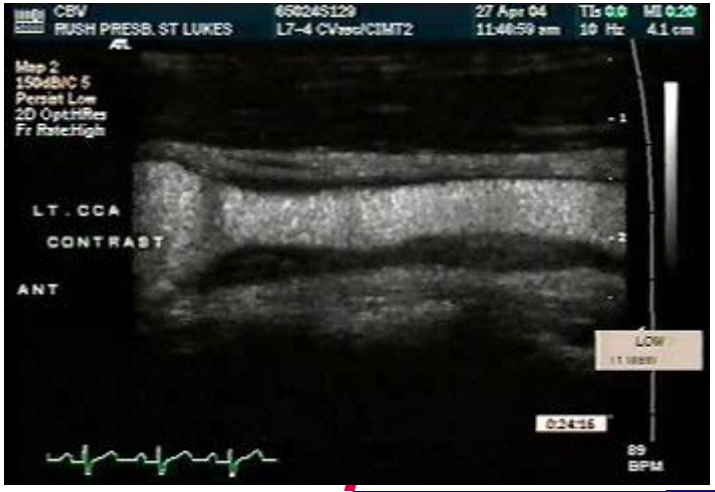
Plaque angiogenesis related to plaque instability and reduced by statin therapy [Circulation 2002;105(4):415-418].

Plaques may be considered tumors, and specific drugs (angiogenesis inhibitors) could be carried and locally delivered by targeted microbubbles [Circulation 1999, 99:1726-1732].

Plaque vascularization imaging by CEUS [SB Feinstein, JACC 2006, 48(2):236-43].

Instability and risk assessment?



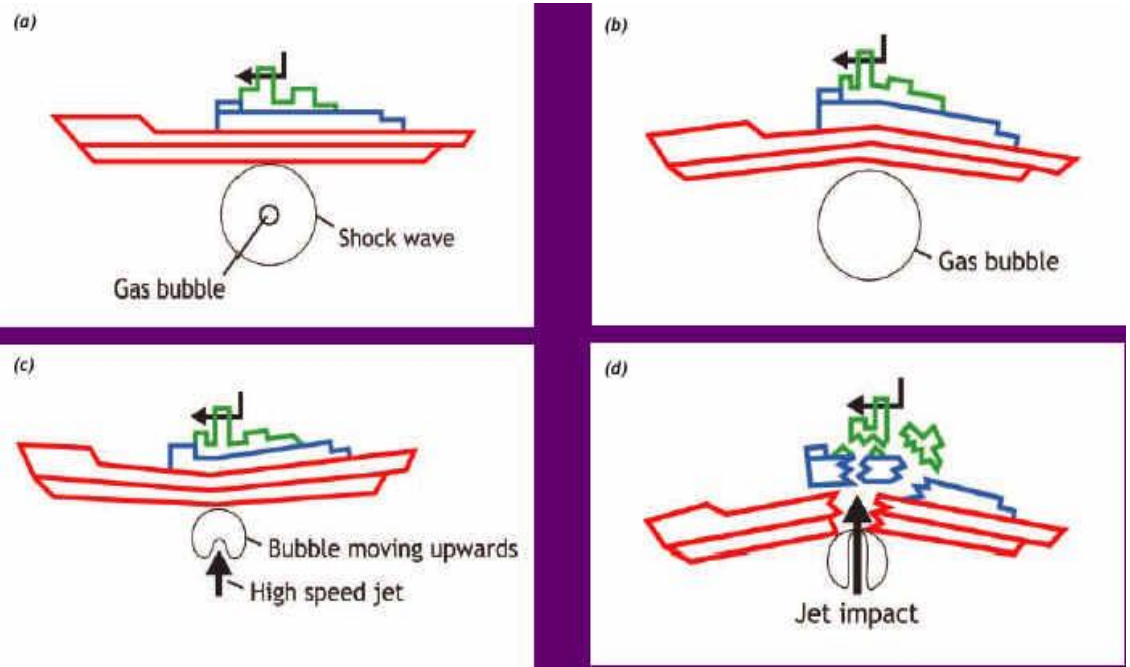


Courtesy of Prof. S.B. Feinstein

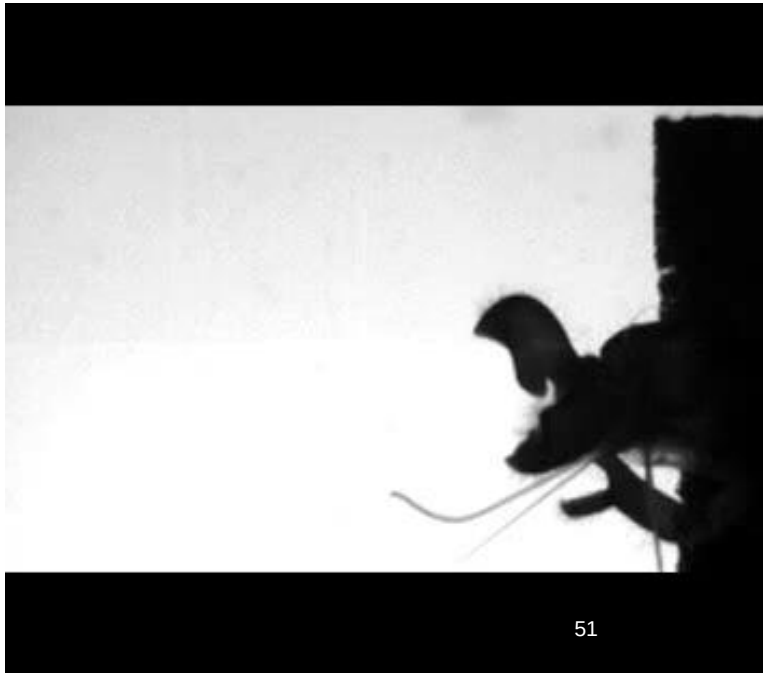
Bubbles for medical treatment

The most destructive shock is due to cavitation

Ultrasound in Med. and Biol. 21(1),97-107,1995

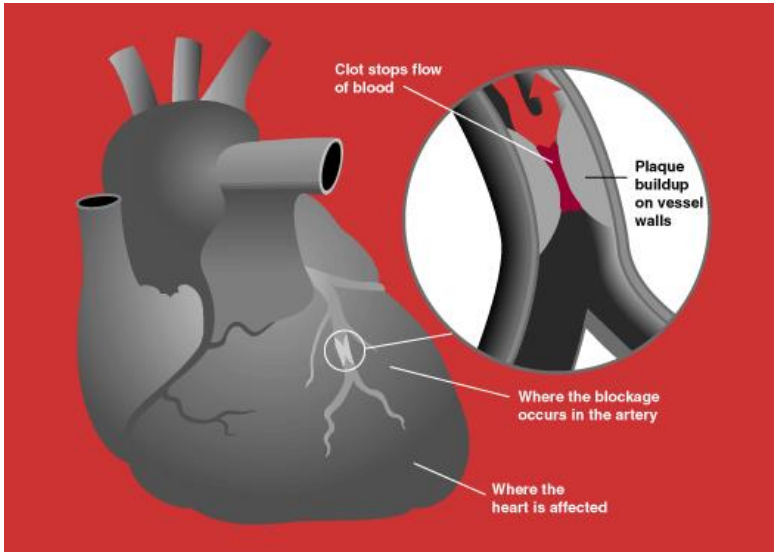


Claw jet



Thrombosis

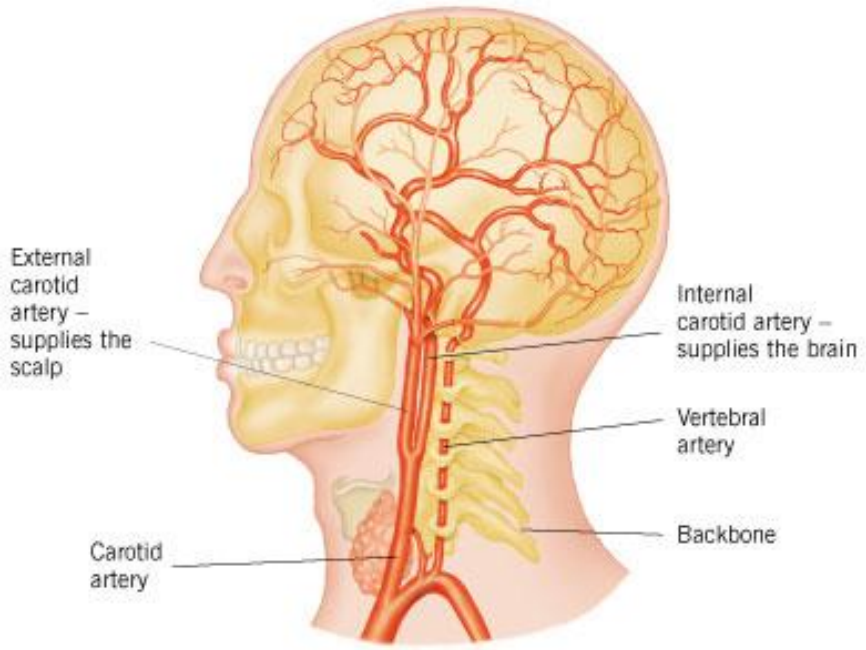
Myocardial Infarction (1,000,000 cases/year in the USA)

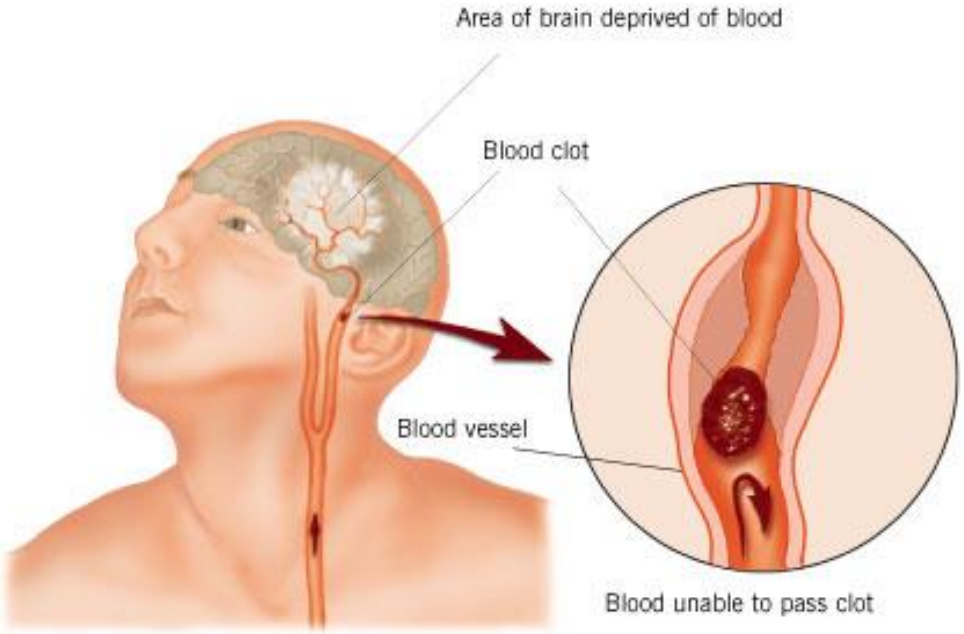


A clot, which may consist of a blood coagulation or a plaque fragment, obstructs a coronary artery and interrupts the blood flow to a specific area of the myocardium. The consequence is a myocardial infarction.

Thrombosis

Ischemic stroke (500,000 cases/year in the USA)



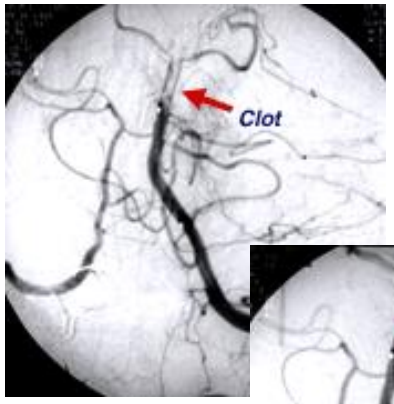


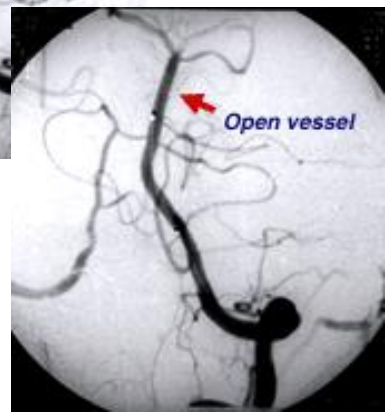
A clot, which may consist of a blood coagulation as well as a plaque fragment, interrupts the blood flow to a specific area of the brain, which stops functioning and is damaged due to anoxia.

Thrombolysis

1 - Surgical intervention

- Bypass
- Thrombectomy catheters (angioplasty)





2 - Non-invasive intervention

- Infusion (~ 0.9 mg/kg) of thrombolytic drugs such as t-PA (tissue-plasminogen activators), Urokinase, etc.
- Sonolysis with low frequency (24 kHz – 1 MHz) and high intensity (>1W/cm^2) ultrasound (high MI).

Bubble thrombolysis

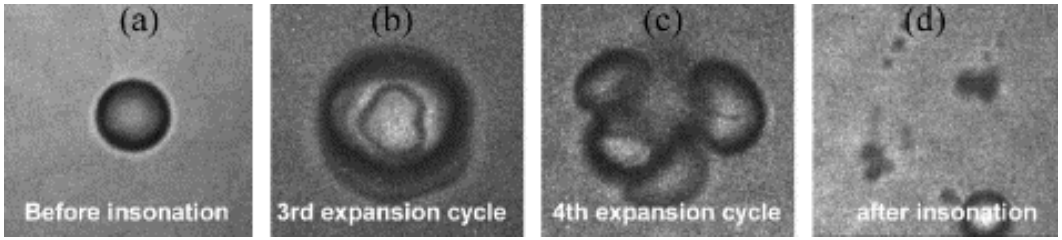
Sonolysis

It is far more efficient when combined with infusion of microbubbles. In this process, sub-micron bubbles are the most effective.

Possible explanations:

- The presence of microbubbles lowers the cavitation threshold shortening the thrombolysis time.

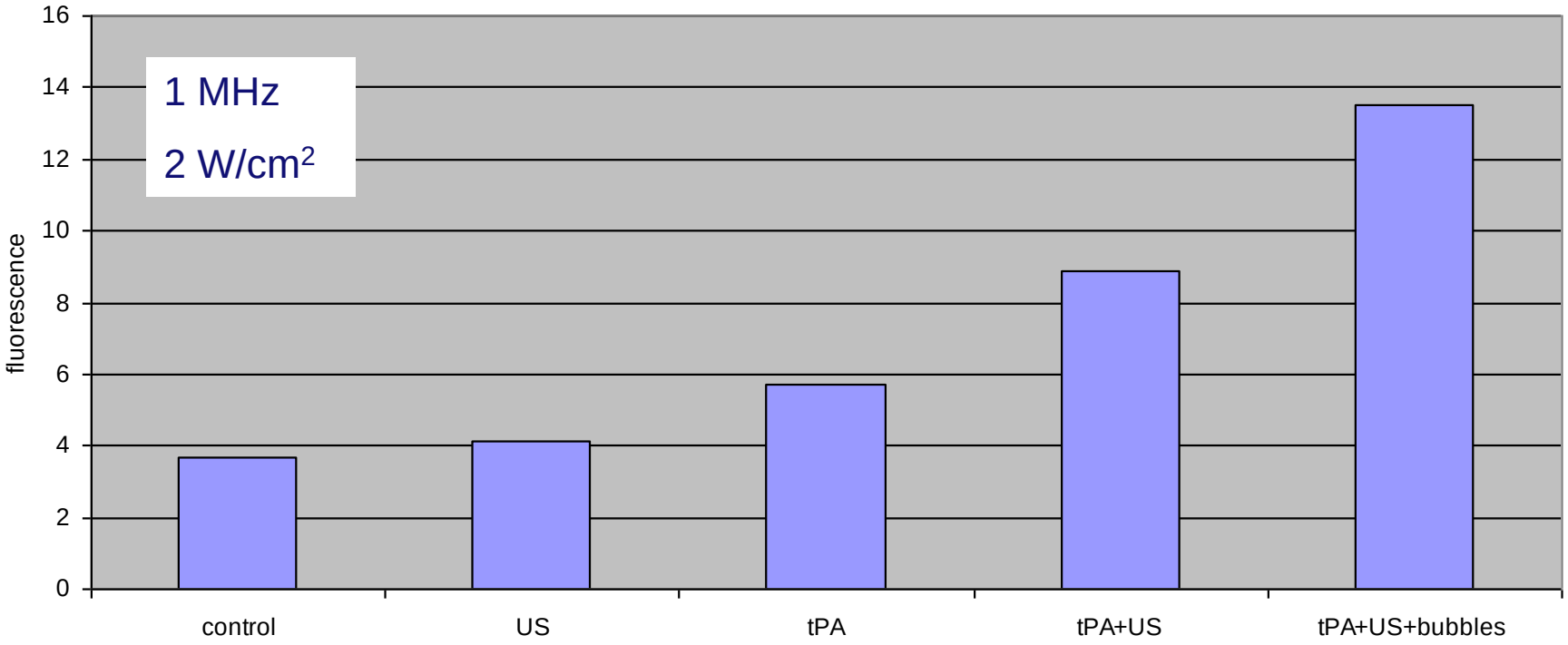
- Increased permeation of thrombolytic agent into clots.



Bubble sonoporation

Bubble thrombolysis

Sonolysis

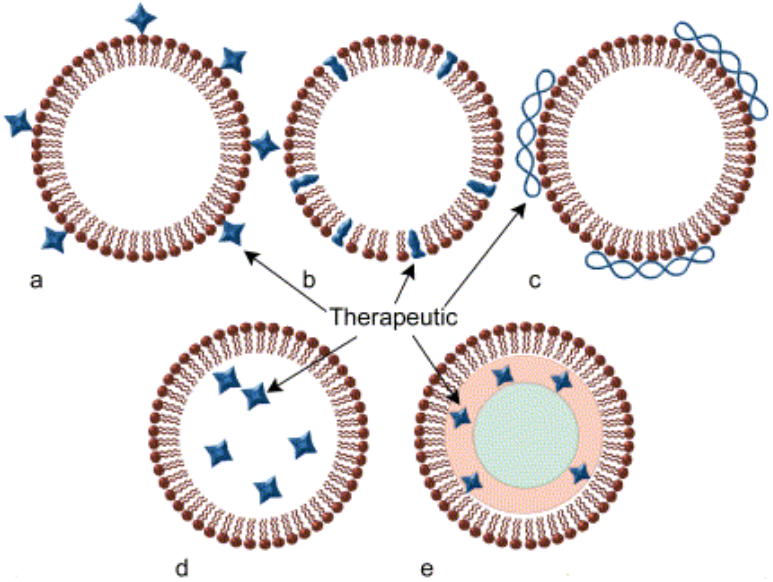


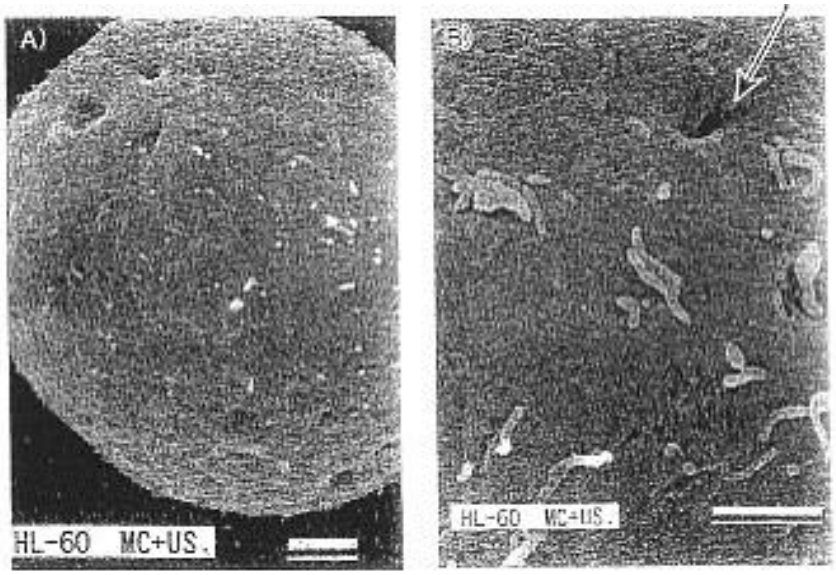
[E.C. Unger, T. Porter W. Culp, et al., Advanced Drug Delivery Reviews, vol. 56, pp. 1291-1314, 2004]

Targeted bubbles for drug delivery

Cavitation also induces a temporary increase of membrane permeability that leads to increased uptake of genes and drugs. Most efficient frequency around 1 MHz.

Microbubbles can therefore be loaded with genes or drugs and destroyed by high power ultrasound bursts for targeted drug release.





[J. Chomas, P. Dayton, D. May, K. Ferrara, Journal of Biomedical Optics, 6(2):141-150, 2001]

Targeted bubbles for drug delivery

1. Natural binding of leukocytes to bubble phospholipidic shells (enhanced by shell inclusion of phosphatidylserine) makes bubbles stick to inflamed areas, such as unstable atherosclerotic plaques, which contain macrophages, i.e., foam cells.

2. Targeted microbubbles can also be obtained by conjugating specific ligands to the shell. The main applications are:

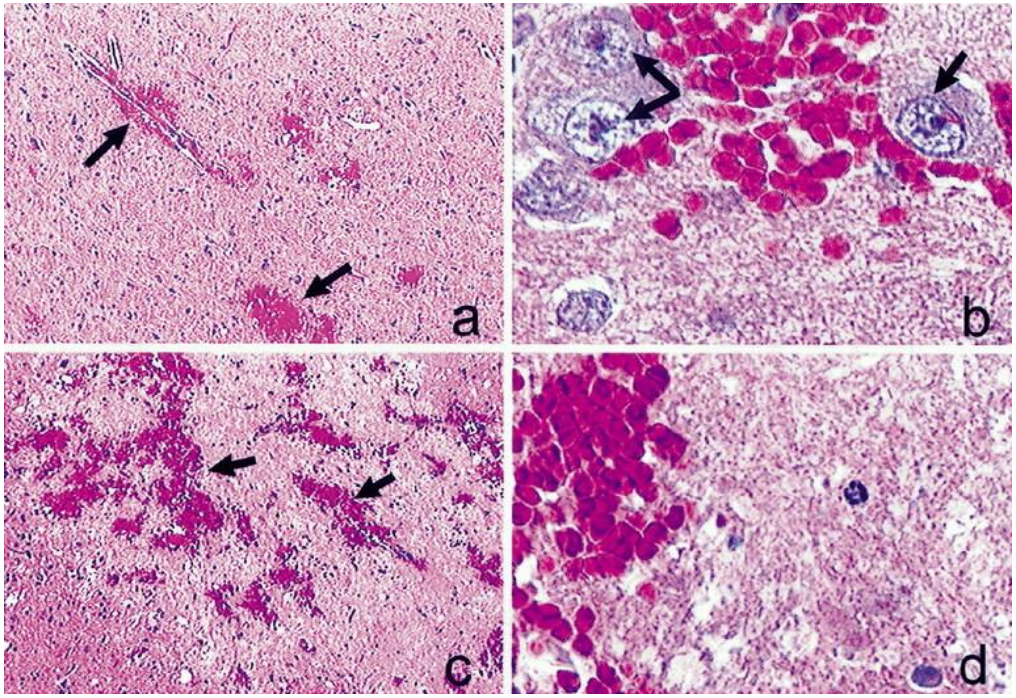
    - Bubbles targeted to attach to fibrin and integrin for thrombosis detection, adenosine delivery (myocardial reflow), and clot-lysis.
    - Bubbles targeted to α_v-integrins or vascular endothelial growth factor (VEGF) expressed in neo-vessels for early tumor and atherosclerosis detection.

Blood Brain Barrier (BBB) opening for brain medical treatment

The BBB prevents delivery of therapeutic agents to the brain

Probably due to cavitation, microbubbles with high intensity ultrasound open the BBB, as confirmed by histology and Gd MRI studies.

This techniques might allow efficient chemotherapy treatment of brain tumor metastases. Brain neurodegenerative diseases, such as Alzheimer, might be treated too.



K. Hynynen, N. McDonald, N. Vykhodtseva, F.A. Jolesz, Radiology, vol. 220, pp. 640-646, 2001

Thank you!

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