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Modelling ultrasonic backscattering of an SPIO-MRI contrast agent

Martin P Mienkina¹, Michiel Postema¹, Christian Hansen², Georg Schmitz¹

¹Institute for Medical Engineering, Ruhr-Universität Bochum, Bochum, Germany

²Institute for High Frequency Engineering, Ruhr-Universität Bochum, Bochum, Germany

Abstract

The ultrasonic backscatter coefficient (BSC) of superparamagnetic iron oxide (SPIO) nanoparticles, which are used as a liver MRI contrast agent, was simulated using a Yagi backscattering model. The BSC of SPIO cores that are aggregated in the lysosomes of Kupffer cells is significantly higher (85 dB) than the BSC of non-aggregated SPIO cores. Considering *in vivo* concentrations, the aggregated SPIO does not elevate the BSC of the liver markedly (9×10^{-6} dB). Thus, the reported visibility of SPIO in clinical ultrasound cannot be explained by classical scattering theory. Other non-linear effects need to be taken into account.

1 Introduction

Superparamagnetic iron oxide nanoparticles, such as ferucarbotran, are conventionally used as contrast agents for magnetic resonance imaging (MRI). These agents can be used for the detection of malignant liver tumors since they aggregate in Kupffer cells, only. Kupffer cells are exclusively present in healthy liver tissue [1].

It has recently been shown *in vivo* that these agents are detectable in liver sonography, too [2]. An ultrasound study of a liver has been performed after the administration of ferucarbotran for MRI. It revealed pathologic foci within the liver that were not detectable before the injection of the contrast agent.

By investigating the acoustic scattering behaviour of these nanoscale contrast agents we aim to optimize the use of these particles as a novel contrast agent for sonography. Additionally, we study principle nanoscale backscattering phenomena that are of interest for the understanding of nanoscale ultrasound contrast agents such as liquid perfluorocarbon [3].

2 Materials and Methods

Ferucarbotran is a superparamagnetic iron oxide (SPIO) contrast agent that causes a signal decrease in T2-weighted MR images. This agent mainly accumulates in the liver (80%) and the spleen (5-10%). Several minutes after the bolus injection the agent is sequestered by phagocytic cells and decreases the MR signal of the liver and the spleen.

The SPIO cores of ferucarbotran consist of magnetite (Fe_3O_4 density: $\rho = 5150 \text{ kg/m}^3$, speed of sound (SOS): $c \approx 5000 \text{ m/s}$) and maghemite (Fe_2O_3

$\rho = 4900 \text{ kg/m}^3$, $c \approx 5000 \text{ m/s}$) and are coated by carboxydextran. The polycrystalline core comprises several monocrystals, each of 4.2 nm size. At maximum a bolus of 1.4 ml is applied comprising 756 mg ferucarbotran, which is equivalent to 39.2 mg iron. The carboxydextran coat of ferucarbotran is degraded by the phagocytic cells of the liver, the Kupffer cells, and the SPIO cores are clustered in the lysosomes of the Kupffer cells.

The human liver weights 1.3-1.5 kg in average. The Kupffer cells comprise 2 % of the total parenchymal volume of the liver [4]. They measure 12-16 μm . The lysosomes of the Kupffer cells account for 0.3 % of the total liver volume. In the further course of this work it is assumed that the Kupffer cells exhibit a spherical morphology and that the lysosomes of Kupffer cells are concentrated in a spherical structure. The insonification of a spatially varying distribution of tissue compressibility and density generates an echo signal. The echo signal can be subdivided into components that origin from macroscopic changes of the acoustical properties of tissue (coherent specular reflection) and components originating from tissue structures with wavelength (Mie scattering) and sub-wavelength size (Rayleigh scattering). If the scatterer volume fraction is high, the scatterers are not uniformly random and statistically independent distributed and one needs to take into account a correlation between the scatterers. A continuum scattering model, which uses a spatial autocorrelation function (ACF) describing the density and compressibility fluctuation of a two-component medium was presented by Yagi [5]. The characteristic length of the ACF depends on the scatterer concentration and the scatterer size.

Thus, the acoustic backscattering of the SPIO contrast agent is modelled assuming that the SPIO filled ly-

sosomes can be interpreted as scatterers in the scope of the Yagi model. The acoustical properties of these lysosomes are derived by averaging the properties of the SPIO particles and the liver tissue according to the SPIO concentration. The backscatter coefficient (BSC) is given as [5]:

$$\eta(k, H) \approx \frac{k^4 r_Y^3}{12\pi} \left(\frac{\kappa_1 - \kappa_0}{\kappa_m} - \frac{\rho_1 - \rho_0}{\rho_m} \right)^2 (1-H)^4 H \times \left[\frac{0.37}{\left[1 + 1.1k^2 r_Y^2 (1-H)^2 \right]^2} + 0.63e^{-0.85k^2 r_Y^2 (1-H)^2} \right] \quad (1)$$

where $k = \omega/c$ is the wave number, ω is the angular frequency, i.e. insonification frequency (4MHz), c is the SOS of the medium, r_Y is the characteristic radius of the scatterers, H is the volume fraction of the scatterers in the medium, κ_1 is the compressibility and ρ_1 is the density inside the scatterer and the corresponding values outside are κ_0 and ρ_0 , κ_m and ρ_m are the mean value according to H . The scatterers of the model correspond to the SPIO filled lysosomes and the medium corresponds to the liver using the values given in Section 2.

The BSC based on the Yagi model for SPIO filled lysosomes is compared to the BSC of non-aggregated SPIO cores and *in vivo* measurements of the BSC of the human liver [6]:

$$\eta(k) = 4.5 \times 10^{-5} \left(\frac{kc}{2\pi} \right)^{1.6} \text{ cm}^{-1} \text{ Sr}^{-1} \quad (2)$$

The gain of the BSC is computed according to Eq. 3:

$$g = 10 \log_{10} \left(\frac{\eta_1 + \eta_2}{\eta_2} \right) \quad (3)$$

3 Results

Figure 1 shows the simulation of the BSC gain for η_1 set to the BSC of SPIO filled lysosomes and for η_2 set to the BSC of the liver (cf. Eq. 2). The gain is depicted as a function of the effective radius of the lysosomes and the fraction of Kupffer cells that aggregate the contrast agent. The total contrast agent dose remains constant for all parameter configurations. For *in vivo* values the gain is 9×10^{-6} dB. Aggregated and non-aggregated SPIO cores exhibit congruent curves. However, the BSC of aggregated SPIO is significantly higher than the BSC of non-aggregated SPIO (gain ≈ 85 dB).

4 Discussion

We have simulated the backscatter coefficient of SPIO filled lysosomes and compared it to non-aggregated SPIO cores and the BSC of the liver. The backscattering model shows that the BSC of aggre-

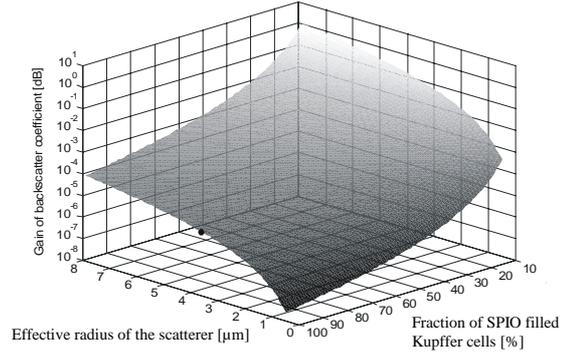


Fig. 1 Simulation of the BSC gain of the liver due to SPIO filled Kupffer cell lysosomes. The black dot denotes *in vivo* values.

gated SPIO is significantly higher than the BSC of non-aggregated SPIO. However, the effects of the aggregated SPIO are negligible compared to the BSC of the liver assuming a linear backscattering model and *in vivo* concentrations of ferucarbotran. The observations of [2] cannot be explained by classical scattering theory. Additional non-linear effects, such as cavitation, need to be considered. Further clinical studies need to be conducted in order to understand the possible visibility of SPIO contrast agents in clinical ultrasound.

5 Literature

- [1] P. Reimer, T. Balzer, "Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications," *European Radiology*, vol. 13, pp. 1266-1276, 2003.
- [2] H. Tanzer, G. Sigl, et al., "Is Iron Oxide a Tissue-specific Contrast Medium in Diagnostic Ultrasound? A Case Report," *Ultraschall in der Medizin*, vol. 25, pp. 448-449, 2004.
- [3] M. S. Hughes, J. N. Marsh, et al., "Acoustic characterization in whole blood and plasma of site-targeted nanoparticle ultrasound contrast agent for molecular imaging," *Journal of the Acoustical Society of America*, vol. 117, pp. 964-972, 2005.
- [4] A. Blouin, R. P. Bolender, et al., "Distribution of organelles and membranes between hepatocytes and nonhepatocytes in the rat liver parenchyma," *The Journal of Cell Biology*, vol. 72, pp. 441-455, 1977.
- [5] G. Schmitz, "Ultrasound in Medical Diagnosis," in *Scattering*, R. Pike and P. Sabatier, Eds. London: Academic Press, 2002, pp. 161-174.
- [6] K. A. Wear, B. S. Garra, et al., "Measurement of ultrasonic backscatter coefficient in human liver and kidney *in vivo*," *Journal of the Acoustical Society of America*, vol. 98, pp. 1852-1857, 1995.