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## Experimental ultrasound characterization of tissue-mimicking phantoms with high scatterer volume fractions

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Quantitative ultrasound technique is based on a frequency-based analysis of the signals backscattered from biological tissues. This technique aims to estimate the size and concentration of scatterers in order to diagnose and monitor diseases, such as cancer. The Gaussian Model (GM) and Fluid-Filled Sphere Model (FFSM) have been used for many years but are limited to dilute scattering medium, whereas the scatterers can be densely packed (for example the cells in cancer). A model adapted to dense medium is the Structure Factor model (SFM) used in blood characterization. However, the most often used SFM version is the Percus Yevick model (PYM) using the low frequency limit of the structure factor called the Percus Yevick packing factor. The aim of this work is to compare the aforementioned scattering models with measured backscatter coefficients (BSCs) on tissue-mimicking phantoms.

## 1 Introduction

Quantitative ultrasound technique is based on a frequency-based analysis of the signals backscattered from biological tissues in order to differentiate diseased versus healthy tissue and to detect cancer. This technique relies on a theoretical scattering model in order to fit the spectrum of the backscattered echoes from biological tissues to an estimated spectrum by an appropriate model. The most often theoretical scattering model is the Gaussian model developed by Lizzi [1] [2] that has been used to extract two tissue properties: the average scatterer size and the acoustic concentration (i.e., the product of the scatterer concentration times the square of the relative impedance difference between scatterers and the surrounding medium). This approach has been successfully used for the characterization of the eye [3], the prostate [4] and the breast [5] [6]. Other theoretical scattering models such that the fluid-filled sphere model [5] [6] or the solid sphere model [7] (called here the Faran model - FM) were also used to predict average scatterer sizes by modeling the tissues by an ensemble of fluid or solid spheres. The aforementioned models (Gaussian model, fluid-filled sphere model and Faran model) assumed a random distribution of scatterers (i.e. a low density of scatterers) and no multiple scattering (Born approximation). Under these hypotheses, the power of the backscattered signal increases linearly with the scatterer concentration and is affected by the size and acoustic properties of tissue scattering structures. This linear relationship has been exploited to monitor the scatterer size and concentration. However, the assumption of randomly distributed scatterers may not hold in tumors with densely packed cells [8]. A model adapted to dense medium is the Structure Factor model (SFM) used in blood characterization [9] [10]. The most often used SFM version is the Percus Yevick model (PYM) using the low frequency limit of the structure factor called the Percus Yevick packing factor [11].

The aim of this work is to compare three theoretical scattering models, namely the FM, PYM and SFM, with measured backscatter coefficients (BSCs) on tissue-mimicking phantoms. The tissue-mimicking phantoms consisted of polyamide microspheres (mean radius  $6 \mu\text{m}$ ) in water suspension mimicking densely packed cell nuclei in tumors. The phantoms had identical scatterer sizes with an impedance contrast of 58% (versus 42% in cell nuclei) but have different scatterer volume fractions ranging from 1 to 25%. Ultrasonic backscatter measurements were made for frequencies from 6 MHz to 22 MHz.

## 2 The scattering models

Three models were used to study the scattering from the tissue-mimicking phantoms: the Faran model (FM), the mod-

ified Percus Yevick model (PYM) and the modified Structure Factor model (SFM). For all three models, the formulations were written for monodisperse spheres, and we assumed no multiple scattering among the scatterers.

### 2.1 The Faran model

The original theory of Faran [12] provides an exact solution for the scattering of sound by a solid sphere in a surrounding fluid medium and thus includes shear waves in addition to compressional waves. The sphere is assumed to be insonified by a harmonic plane wave and far from the point at which the scattered pressure field is observed. The differential backscattering cross section at  $180^\circ$   $\sigma_b$  was computed for a sphere of radius  $a$  using the theory of Faran. By considering an ensemble of monodisperse solid spheres of radius  $a$ , the theoretical BSC can be written as:

$$BSC_{FM}(k) = m\sigma_b(k), \quad (1)$$

where  $k$  is the wave number and  $m$  the number of spheres per unit of volume.

### 2.2 The Structure Factor model

The SFM [9] is based on the assumption that at a high particle concentration the interference effects are mainly caused by the correlation in the disposition of individual scatterers. The SFM was generally applied to an ensemble of monodisperse fluid spheres for modeling red blood cells in blood [9] [10]. Herein, the modified SFM is written for an ensemble of solid spheres. In comparison with the Faran model described in Eq. 1, the SFM considers the interference effects relatively easily by replacing the single-particle backscattering contribution  $\sigma_b$  by the product  $\sigma_b S$ , as it was performed previously in the field of optics with the interference approximation [13]. By considering an ensemble of monodisperse solid spheres of radius  $a$ , the theoretical BSC can be written as:

$$BSC_{SFM}(k) = m\sigma_b(k)S(k), \quad (2)$$

where the differential backscattering cross section  $\sigma_b$  was calculated using the theory of Faran. The structure factor  $S$  describes the correlation in positions between particle centers. The structure factor is related to the spatial positioning of particles, according to:

$$S(\mathbf{k}) = E \left[ \frac{1}{N} \left| \sum_{i=1}^N e^{-i2\mathbf{k}\mathbf{r}_i} \right|^2 \right] \quad (3)$$

where  $\mathbf{k}$  is the wave vector,  $E$  the expected value of a random variable,  $N$  the number of particles and  $\mathbf{r}_i$  the position vectors defining the center of the  $i$ th scatterer in space. Since the medium is isotropic, the structure factor depends on  $k$ .

Table 1: Summary of the parameters used in the theoretical BSC response calculations for the polyamide microsphere. Comparison with parameters for cell nuclei (human acute myeloid leukemia cell OCI-AML-5 and human prostate cancer cell PC-3) used in [14].

	Polyamide micro-sphere	OCI nucleus	PC-3 nucleus
Radius $a$ ( $\mu$ m)	6	4.55	8.95
Sound speed $c$ (m/s)	2300	1503	1493
Density $\rho$ (kg/m <sup>3</sup> )	1030	1430	1430
Impedance $z$ (MRayl)	2.37	2.15	2.13
Poisson's ratio	0.42	0.42	0.42

### 2.3 The Percus Yevick model

In the low frequency limit, the structure factor tends towards a constant value  $S(k) \rightarrow S(0) = W$  called the packing factor [11]. The most often used packing factor expression is based on the Percus-Yevick pair-correlation function for identical, hard and radially symmetric particles. The Percus-Yevick packing factor  $W_{PY}$  is related with the particle concentration  $\phi$  as follows [11]:

$$W_{PY} = \frac{(1 - \phi)^4}{(1 + 2\phi)^2}. \quad (4)$$

For an ensemble of monodisperse solid spheres, in comparison with the SFM described in Eq. (2), the theoretical BSC for the PYM is thus obtained by replacing the structure factor  $S$  by the Percus-Yevick packing factor  $W_{PY}$  as follows:

$$BSC_{PYM}(k) = m \frac{(1 - \phi)^4}{(1 + 2\phi)^2} \sigma_b(k). \quad (5)$$

## 3 Methods

### 3.1 Tissue mimicking phantoms

The tissue-mimicking phantoms consisted of polyamide microspheres of radius  $6 \mu\text{m}$  (orgasol 2001 EXD NAT1, Arkema, France) gently stirred in water. The tissue-mimicking phantoms consists usually in microspheres in agar-agar phantom. Herein, a suspension of microspheres in water was chosen because of the difficulty to degas the agar-agar phantom with polyamide microspheres at high scatterer volume concentration ( $>15\%$ ). The phantoms had identical scatterer sizes but have different scatterer volume fractions ranging from 1 to 25%. The density acoustic parameters (sound speed, density, impedance and Poisson's ratio) of the polyamide microspheres are given in Table I. Since the aim of the study was to mimic cell nuclei, also given in Table I are the parameters of some cell nuclei used in [14].

### 3.2 Experimental setup

Two broadband focused transducers with center frequencies of 10 MHz and 17.5 MHz (and with respectively 14.2 mm and 13.8 mm focuses) were used in these experiments. The pulse-echo acquisition system was composed of an Olympus model 5072 PR pulser-receiver and a Gagescope model

8500CS oscilloscope. The transducer was put in an agar-agar gel, i.e. a solidified mixture of distilled water and 2% (w/w) agar powder (A9799, Sigma Aldrich, France), such that the distance between the transducer and the suspension was equal to 13.2 mm for the 10 MHz experiment (and equal to 12.8 mm for the 17.5 MHz experiment). The transducer focus was thus positioned below the agar-agar/suspension interface at a distance of 1 mm. The suspension was stirred in a beaker with a magnetic agitator to avoid sedimentation. Sixty RF lines were acquired and stored. Echoes were selected in the focal zone with a rectangular window of length 1 mm. The power spectra of the backscattered RF echoes were then averaged to provide  $\overline{P_{meas}}$ . This protocol was repeated two times with the two transducers for each scatterer concentration.

### 3.3 BSC estimation

The measured BSC reported in this study was computed as

$$BSC_{meas}(k) = BSC_{ref}(k) \frac{\overline{P_{meas}(k)}}{\overline{P_{ref}(k)}}. \quad (6)$$

In Eq. (6), the mean backscattered power spectrum  $\overline{P_{ref}}$  was obtained from a reference sample of polyamide microspheres of radius  $2.5 \mu\text{m}$  (orgasol 2001 UD NAT1, Arkema, France) at a low volume concentration of 0.5% gently stirred in water. Echoes from the reference sample were windowed as for the tissue-mimicking phantoms at the same depth and sixty echoes were also averaged to obtain  $\overline{P_{ref}}$ . The BSC of this reference sample  $BSC_{ref}$  was estimated using the Faran model, which theoretical value is given by Eq. (2). Indeed, for very low scatterer concentration, the three models FM, PYM and SFM are assumed to be equivalent. This reference sample was used to compensate the backscattered power spectrum  $\overline{P_{meas}}$  for the electromechanical system response, and the depth-dependent diffraction and focusing effects caused by the US beam.

## 4 Results and Discussion

Figure 1 presents the measured BSC versus frequency for four different scatterer concentrations 1, 5, 10 and 25%. The black line represents the 10-MHz center frequency transducer that allows to measure the BSC from 6 to 15 MHz, and the grey line the 17.5-MHz center frequency transducer that allows to measure the BSC from 10 to 22 MHz. Measured BSCs with both transducers in the 10-15 MHz frequency bandwidth are similar. It means that the results were not influenced by system transfer functions. Also shown in Fig. 1 are the three theoretical model BSCs the FM, PYM and SFM in green, blue and red colors respectively. Good agreement was shown between the measured frequency dependent BSCs and those predicted with the SFM for all scatterer concentrations. Whereas the FM was only satisfactory for the 1% scatterer concentration and the PYM was satisfactory for the 1, 5 and 10% scatterer concentrations.

Figure 2 shows the measured BSC amplitude averaged in the frequency bandwidth from 6 to 15 MHz versus the scatterer concentration. Also plotted are the theoretical BSC amplitude computed with the FM, PYM and SFM. Good agreement was obtained at a low volume fraction of 1% and 2.5%

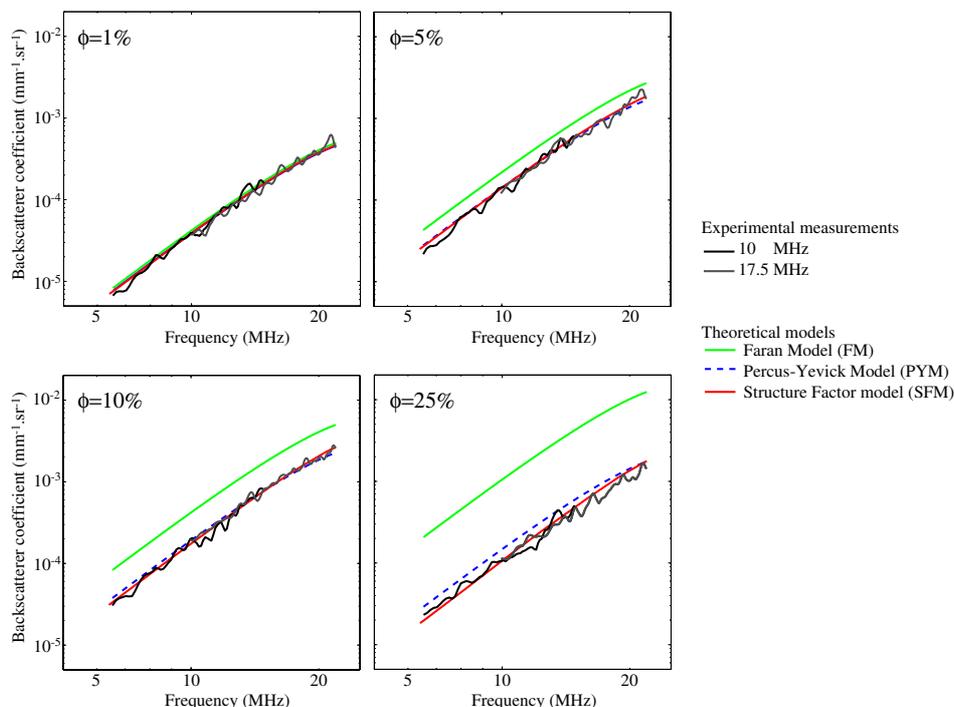


Figure 1: Measured BSC results with both transducers at center frequencies of 10 MHz and 17.5 MHz and corresponding BSC theoretical curves.

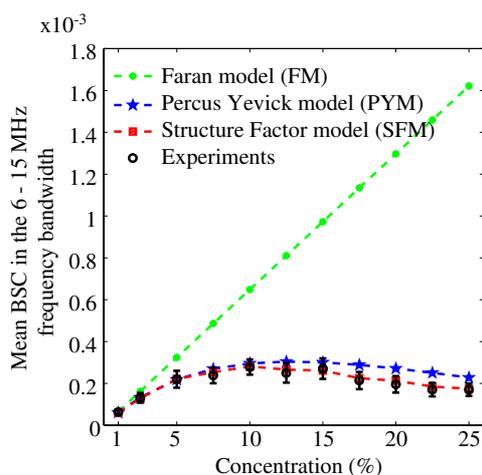


Figure 2: Comparison of the measured and theoretical mean BSC versus the scatterer concentration in the frequency bandwidth from 6 to 15 MHz.

for all models. The FM (and the PYM, respectively) overestimated the BSC amplitude for volume fraction  $>5\%$  (and for larger volume fraction  $>12.5\%$ ). The SFM was the model that better matched the experiments.

Future works are to extend the study into higher frequencies and estimate the scatterer concentration and size with the SFM.

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