Electric and magnetic properties of contrast agents for thermoacoustic imaging

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ABSTRACT

The endogenous contrast in thermoacoustic imaging is due to the water and ionic content in tissue. This results in poor tissue specificity between high water content tissues. As a result, exogenous contrast agents have been employed to improve tissue specificity and also increase the SNR. An investigation into the sources of contrast produced by several exogenous contrast agents is described. These include three gadolinium based MRI contrast agents, iron oxide particles, single wall carbon nanotubes, saline and sucrose solutions. Both the dielectric and magnetic properties of contrast agents at 3GHz have been measured using microwave resonant cavities. The DC conductivity of the contrast agents were also measured. It is shown that the measured increase in dielectric contrast, relative to water, is due to dipole rotational loss of polar non electrolytes, ionic loss of electrolytes or a combination of both. It is shown that for the same dielectric contrast, electrolytes make better thermoacoustic contrast agents than non-electrolytes, for thermoacoustic imaging.

Keywords: Thermoacoustic imaging, Contrast agents, Conductivity, Permittivity,

1. INTRODUCTION

Thermoacoustic imaging is an imaging technique based on the absorption of short pulses of electromagnetic radiation, typically at microwave frequencies, by tissue. The absorbed energy gives rise to a localised pressure increase which in turn produces propagating ultrasound waves. By recording the ultrasound waves at different positions around the tissue surface, an image of the tissue can be reconstructed. The initial pressure distribution p_0 due to the absorbed electromagnetic (EM) energy can be written as

$$p_0 = \Gamma H \tag{1}$$

where Γ is known as the Gruneisen coefficient, a dimensionless thermodynamic constant that gives an indication of how efficiently the energy absorbed in the volume is converted to pressure, while H is the absorbed energy density. The absorbed energy is often considered in term of absorbed power at microwave frequencies, and the absorbed power density (P_d) and can be obtained from Poynting relation,[1] as (2)

$$P_d = -\frac{\omega}{2}\int_V (\mu_0 \mu_r^{''} \mathbf{H}\cdot\mathbf{H}^* + \epsilon_0 \epsilon_r^{''} \mathbf{E}\cdot\mathbf{E}^*)dv - \frac{1}{2}\int_V (\sigma_c \mathbf{E}\cdot\mathbf{E}^*)dv \tag{2}$$

$\mathbf{E}, \mathbf{H}$ represent the electric field intensity (V/m), magnetic field intensity (A/m), in a linear, isotropic, source free tissue having complex permittivity ($\epsilon^* = \epsilon_0[\epsilon_r^{'} - j\epsilon_r^{''}]$), complex permeability ($\mu^* = \mu_0[\mu_r^{'} - j\mu_r^{''}]$) and conductivity ($\sigma_c$) respectively. The first, second and third terms on the RHS of (2) represents the time averaged power loss inside the tissue volume due to magnetic loss, dielectric polarisation loss and joule heating respectively. It is typical to replace the dielectric polarisation loss term $\omega\epsilon_0\epsilon_r^{''}$ with an equivalent conductivity (σ_d), so that eqn. (2) becomes:

$$P_d = -\frac{\omega}{2}\int_V \mu_0 \mu_r^{''} \mathbf{H}\cdot\mathbf{H}^* - \frac{1}{2}\int_V \sigma_t \mathbf{E}\cdot\mathbf{E}^* dv \tag{3}$$

where $\sigma_t = \sigma_d + \sigma_c$ is the total conductivity measured in the tissue. The contribution of σ_c is regarded to be a frequency independent contribution, while σ_d depends on frequency. In tissue, the loss contribution from σ_c

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is due to the ionic content of tissue while σ_d is due to dipole rotational loss of polar molecules such as water and proteins. Due to their relatively large size, proteins have relaxation frequencies at KHz - MHz frequencies, whereas smaller water molecules relax in the GHz range.[2] Thus at microwave frequencies, the water content dominates the dielectric properties of tissue. As a result, specificity between high water content tissue, is limited in thermoacoustic imaging. The use of exogenous contrast agents to selectively increase the contrast of high water content tissues, is therefore very appealing.

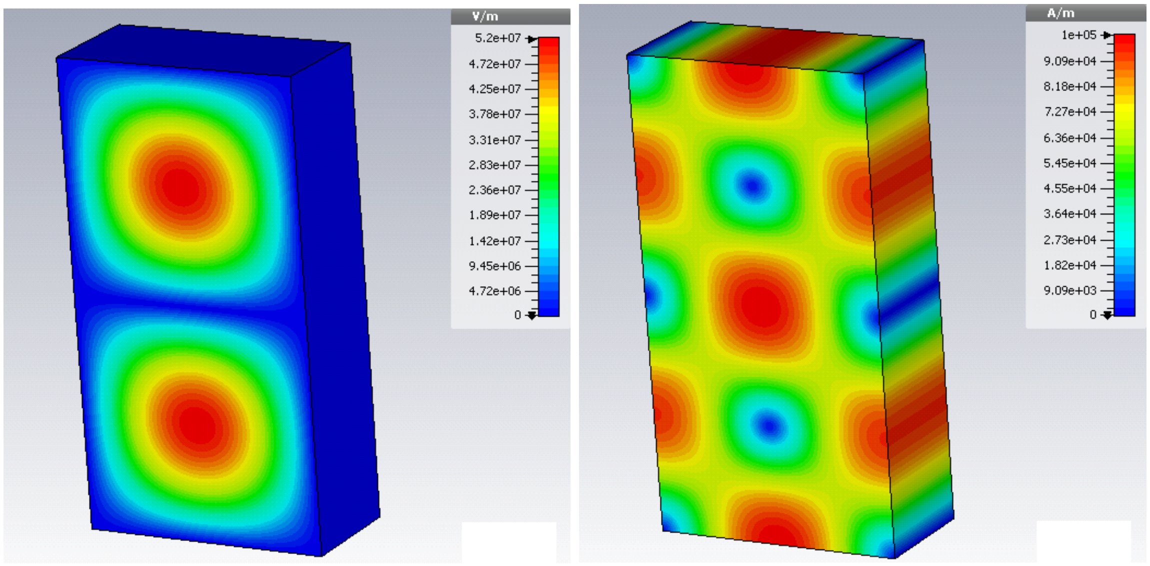
A number of exogenous contrast agents have been suggested for use as thermoacoustic contrast agents. These include iron oxide particles,[3] carbon nanotubes[4,5] and Magnevist[6]®(a gadolinium based MRI contrast agent). Because a detailed electrical and magnetic characterisation of the properties of these contrast agents at microwave frequencies, was not carried out in these previous studies, there is uncertainty about the source(s) of contrast. The aim of this work is to address this limitation by measuring the electric and magnetic properties of these contrast agents at 3GHz, using waveguide resonant cavities. 3GHz is a frequency commonly used for thermoacoustic imaging because high peak power pulsed sources are readily available at this frequency, and also, the dimensions of the antenna required, which is a function of wavelength, are much smaller than that required at MHz frequencies. § 2 discusses the cavity resonator technique for characterising the electric and magnetic properties of contrast agents while the experimental results are presented in § 3 before a discussion of the sources of contrast in § 4.

2. COMPLEX PERMITTIVITY AND COMPLEX PERMEABILITY MEASUREMENTS

The dielectric and magnetic properties of the contrast agents were measured using two rectangular waveguide cavities designed to resonate at 3GHz. A standing wave is set up inside the cavity when energy is coupled into it, through any of the two coaxial ports connected to the cavity. The resonant frequency and quality factor (Q-factor) of the cavity can be determined from the measured transmission coefficient between the two coaxial ports. The transmission coefficient of the cavity was measured using a network analyser (Rhode and Schwarz FS8). When the cavity is perturbed by inserting an small absorber into the location of the electric field maxima, the change in resonant frequency and Q-factor (relative to the empty cavity) can be used to determine the dielectric properties of the absorber. Similarly, by inserting an absorber into the position of magnetic field maxima, corresponding to a position of electric field minima inside the cavity, the magnetic properties of the absorber can be determined. To avoid having to move the absorber between positions of electric field maxima and magnetic field maxima in a cavity, two rectangular waveguide cavities were designed, supporting a TE_{101} resonant mode or TE_{102} resonant mode. The electric field has its maxima at the centre of the TE_{101} cavity, while the magnetic field has a maxima at the centre of the TE_{102} mode cavity. Figure 1 shows the simulated E and H field distribution in the TE_{102} cavity used to measure the magnetic properties of the contrast agents. The resonant cavity perturbation method has an advantage of offering high sensitivity, at a single frequency, compared to other non resonant methods, such the the open ended coaxial probe technique. Additionally the coaxial probe is unable to measure the magnetic properties of the absorber, as the technique is based on the assumption that the sample is non-magnetic.[7] Figure 2, shows the measured transmission coefficient for the TE_{101} cavity for different absorbers. The cavities measure either the total electric loss or total magnetic loss at 3GHz. But as shown in (2), the total electric loss term σ_t is made up of σ_d and σ_c. An independent measurement of σ_c of the contrast agents was therefore made using a DC conductivity meter (HI 99300, Hannah instruments). The contribution of the dielectric polarisation loss term can then be obtained from the difference between σ_t and σ_c

3. RESULTS AND DISCUSSION

The measurements of the electric and magnetic properties of the contrast agents are presented in Table 1 for Magnevist (a clinical gadolinium MRI contrast agent), SWCNT and iron oxide particles (EM1301, approved clinically for sentinel lymph node detection), which have previously been used as thermoacoustic contrast agents.[3–6] In addition, two other clinical gadolinium based MRI contrast agents (Dotarem and Prohance), which contain different gadolinium compounds to Magnevist,[8] were measured. Also characterised were solutions of two solutes:



(a) (b)

Figure 1. (a) |E| distribution (b) |H| distribution, in the TE_{102} mode cavity showing minimum |E| (maximum |H|) field at the centre of the cavity where the absorber would be located

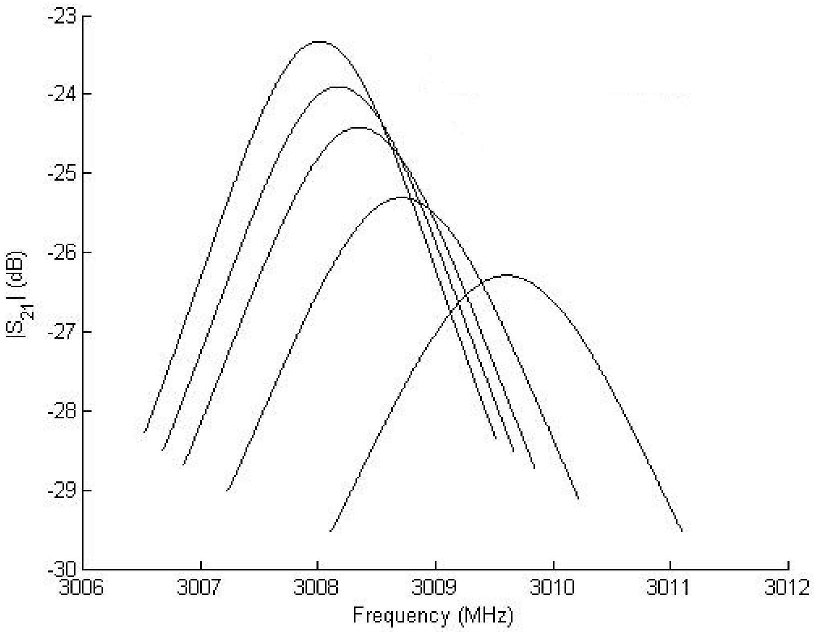


Figure 2. Measured transmission coefficient of the TE_{101} mode cavity containing different concentrations of sucrose solution

sodium chloride and sucrose, whose chemical behaviour in solution are well known. The concentration of Magnevist, Dotarem, Prohance and EMC1301, was 0.5M, as administered clinically. The concentration of sucrose was also 0.5M, while the saline concentration was 0.154M as used in clinical intravenous infusions.

Table 1. Complex permittivity and complex permeability of clinical 0.5M contrast agents.

Contrast agent	$\epsilon_r^{'}$	$\sigma_t \mid_{3GHz}$ (S/m)	σ_c (S/m)	$\sigma_d \mid_{3GHz}$ (S/m)	$\mu_r^{'}$	$\mu_r^{''} \times 10^{-2}$
Water	77.76	2.098	0.0002	2.098	1.087	-0.01
Saline[†]	75.25	3.456	1.4100	2.046	*	*
Sucrose	71.93	2.487	0.0021	2.485	*	*
Magnevist (Gd based)	49.75	3.320	0.568	2.752	1.474	0.88
Dotarem (Gd based)	56.65	3.402	0.435	2.967	1.276	0.29
Prohance (Gd based)	60.54	2.857	0.0504	2.807	1.690	2.00
EM1301 (Fe based)	74.70	2.281	0.0097	2.271	1.886	4.40
SWCNT[‡]	78.78	2.092	*	*	*	*

[*] no measurements available

[‡] 1.117mg/ml (≈ 3.3uM)

[†] physiological saline containing 9g/L (0.154M) NaCl

3.1 Electric loss

From Table 1, it can be seen that the increase in σ_t (relative to water) for saline is due to the increase in σ_c, while that of sucrose, is due to the increase in σ_d. This is because when sodium chloride (NaCl) is introduced into water, the Na^+ and Cl^- ions dissociate and become surrounded by water molecules. This solvation process leads to the existence of mobile ions in the water. It is this presence of ions in solution that gives rise to an increase in the σ_c of the electrolyte relative to water. Because NaCl complete dissociates into mobile Na^+ and Cl^- ions, it is termed a strong electrolyte. Some other substances only partially dissociate into ions when in solution, with some molecules of the solute remaining intact as aqueous molecules. These are known as weak electrolytes. Sucrose on the other hand is neither a strong electrolyte or a weak electrolyte. This is because, when sucrose molecules undergoes solvation they do not dissociate but remain wholly intact as aqueous sucrose molecules, and do not release ions into the solution. However, because sucrose is a polar molecule just like water, an increase in σ_d is observed as the number of rotating dipoles per unit volume increases.

Of the three 0.5M gadolinium contrast agents in Table 1, σ_c of Magnevist and Dotarem is almost two orders of magnitude higher than that of Prohance. This is because the active gadolinium compounds in Magnevist ($[\text{Gd-DTPA}]^{2-}$) and Dotarem ($[\text{Gd-DOTA}]^{-}$) are known to be anionic while that in Prohance ([Gd-HP-(DO3A]) is a neutral compound.[8] It is the negative charge on the chelate, not the charge on Gd^{3+}, that is responsible for the measured σ_c in Magnevist and Dotarem. The small increase in σ_c of Prohance can be attributed to the small amounts of excipients that accompany the contrast agent. All three gadolinium contrast agents show an increase in σ_d, relative to water, suggesting that similar to sucrose, they contain polar solutes. While Magnevist and Dotarem appear to be weak electrolytes (due to increase in both σ_c and σ_d), Prohance is a non-electrolyte (only σ_d increases significantly).

The iron oxide particles show only moderate increase in σ_t relative to water, the increase being predominatly due to σ_d. The increase in σ_d is because the iron oxide particles have a polar carboxydextran coating, in order to form stable suspensions of the particles. Because the σ_c of the solution is negligible, it suggests that the iron oxide particles by themselves have negligible conducting properties. The SWCNT gave no measurable increase in contrast, as carbon nanotubes are in general non conducting and non polar.

3.2 Magnetic loss

It has been suggested,[6] that the magnetic properties of Magnevist (because it is used as an MRI contrast agent) could result in contrast for thermoacoustic imaging. This is unlikely at microwave frequencies, because the measured magnetic loss term $\mu^{''}$, as shown in Table 1 at 3GHz, is several orders of magnitude less than σ_t. This is because most magnetic loss mechanisms (Hysteresis, Neil relaxation, Brownian relaxation) are low frequency processes (in the order of KHz - MHz). Additionally, because σ_d of water increases with frequency (a rise from 0.0024 S/m at 100MHz to 0.243 S/m at 1GHz), the electric loss of the contrast agent solutions is expected to be much greater than the magnetic loss at microwave frequencies.[9]

3.3 Permittivity

It can be observed from Table 1 that, in addition to the differences in σ_t between contrast agents, there is also a difference in the real part of the complex permittivity ($\epsilon_r^{'}$) of the contrast agents. The concentration of solute in the solution of contrast agent has a direct effect on how $\epsilon_r^{'}$ changes from that of water. For example, the 0.5M solutions of Magnevist, Dotarem, Prohance and Sucrose in Table 1 contain 469g, 376.8g, 279.4g, 171.4g of solute respectively, while the 0.154M saline solution contains 9g of solute. Of these contrast agents, the Magnevist solution has the smallest $\epsilon_r^{'}$, while saline has the highest. This is because in the Magnevist solution (which contains the largest concentration of solute) more water molecules (which have high $\epsilon_r^{'}$ due to a large dipole moment per unit volume) are displaced, than in the saline solution. Although $\epsilon_r^{'}$ does not explicitly appear in the expression for the absorbed power density (3), its effect is implicit, because the EM field distribution inside the absorber depends on $\epsilon_r^{'}$ of the absorber. Since $\epsilon_r^{'}$ represents an energy storage term, two contrast agents having the same σ_t but different $\epsilon_r^{'}$, would result in different values of absorbed power density (P_d).

4. CONCLUSION

The electric and magnetic properties of thermoacoustic contrast agents have been measured at 3GHz, using waveguide resonant cavities. Using a DC conductivity meter, an additional measurement of the ionic conductivity of the contrast agents allowed the quantification of the individual loss terms. It has been shown that the contrast is almost exclusively electric in nature as the magnetic loss term is several orders of magnitude smaller than the electric loss term. It has also been shown that the contrast provided by the gadolinium based agents is due to the chemical structure of the gadolinium chelate they contain, which makes them behave either as electrolytes or non-electrolytes, and not from the gadolinium itself. For iron oxide particles, it has been shown that the modest contrast provided is due to the polar coating on the particles, not the iron oxide itself. For single wall carbon nanotubes, there was no measurable contrast at all. Of all the substances measured, saline provided the highest ratio of dielectric contrast to solute concentration, suggesting strong electrolytes may make the best contrast agents for microwave thermoacoustic imaging.

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