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Microwave-acoustic phasoscopy for tissue characterization

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In this letter, we present a method named microwave-acoustic phasoscopy (MAPC) by collecting both scattered microwave energy and microwave-induced thermoacoustic wave energy for tissue characterization. Different from conventional amplitude and spectrum analysis, we propose to evaluate the microwave-acoustic phase for tissue characterization. Theoretical analysis and experiment verification are performed to show a good agreement. Four different biological tissues are well differentiated in phase region using the proposed MAPC. This attempt of exploring intrinsic relationship between scattered microwave and induced thermoacoustic signals simultaneously provides phase contrast for tissue characterization, showing significant potential in developing phase-contrast imaging prototype based on MAPC theory. © 2012 American Institute of Physics. [<http://dx.doi.org/10.1063/1.4739493>]

Photoacoustic (PA) effect refers to the acoustic generation caused by the absorption of electromagnetic (EM) energy and thermo-elastic expansion after pulsed laser illumination.^{1–3} After first reported by Bell in 1880,⁴ photoacoustic effect has found many applications in recent years, ranging from PA tomography, PA microscopy, functional imaging, and spectroscopy to molecular imaging using contrast agents.^{5–9} Similar with optical illumination, acoustic generation induced by pulsed microwave is usually called thermoacoustic (TA) effect, which has been applied in breast and kidney imaging etc.^{10,11} Apart from microwave energy absorption, microwave scattering also exists due to dielectric constant mismatch, which is widely explored in microwave imaging for breast cancer detection.^{12,13} Generated from the same microwave source and interacting with same biological tissue, the induced thermoacoustic wave and scattered microwave are supposed to follow intrinsic relationship of strong correlation.

In this letter, we theoretically show the relationship between microwave-induced thermoacoustic wave and scattered microwave based on energy conservation analysis. Then we propose the MAPC for tissue characterization and imaging, followed by experimental verification designed to collect both scattered microwave and induced thermoacoustic signals at the same time. Energy conservation relationship for the two signals is verified, and four different tissues are well characterized using MAPC in the experiment, which can be applied to the general cases.

Shown in Fig. 1(a), the interactions between microwave and biological tissue include microwave scattering at the interface due to dielectric property difference, and microwave energy absorption in the lossy tissue with high electrical conductivity leading to thermal expansion and acoustic wave generation. For the sake of simplicity, the following analysis is based on the plane wave model, propagating in one direction, and assuming that tissue is a block of materials with thickness d_0 and cross-sectional area A , shown in Fig. 1(b). It has specific complex permittivity $\epsilon_r = \epsilon' - j\epsilon''$, where ϵ' and ϵ'' are the real and imaginary parts of the com-

plex permittivity. The total scattered microwave signal is represented by the transmitted microwave signal in the simplified planar model. Starting from Maxwell equation, the wave equation to be solved is¹⁴

$$\nabla^2 E + \gamma^2 E = 0, \quad (1)$$

E is electrical field and

$$\gamma^2 = \omega^2 \mu \epsilon' (1 - j \tan \theta), \quad (2)$$

where ω is the angular frequency, μ is permeability, and $\tan \theta$ is loss tangent expressed as $\tan \theta = \sigma / \omega \epsilon'$ with conductivity σ . A solution to Eq. (1) is $E = E_0 e^{-j\gamma z}$ with input electrical intensity E_0 . Assuming the complex parameter $\gamma = \beta - j\alpha$ where $\alpha = \omega \sqrt{\mu \epsilon'} \sqrt{\frac{1 - \cos \theta}{2 \cos \theta}}$ and $\beta = \omega \sqrt{\mu \epsilon'} \sqrt{\frac{1 + \cos \theta}{2 \cos \theta}}$, the electrical field can be expressed as

$$E = E_0 e^{-\alpha z} e^{-j\beta z}, \quad (3)$$

and the magnetic field can be found from $\nabla \times E = -j\omega \mu H$

$$H = \frac{\beta - j\alpha}{\omega \mu} E_0 e^{-\alpha z} e^{-j\beta z}. \quad (4)$$

Then the existing and absorbed microwave power could be expressed as

$$P_e = \frac{1}{2} \iint_S (E \times H^*) \cdot ds = \frac{1}{2} \iint_S E_0^2 \frac{\beta + j\alpha}{\omega \mu} e^{-2\alpha z} \cdot ds, \quad (5)$$

$$P_{\text{absorb}} = \frac{1}{2} \iiint_V \sigma |E|^2 dv = \frac{1}{2} \iiint_V \sigma E_0^2 e^{-2\alpha z} dv. \quad (6)$$

Thus, the input microwave power (real) is the existing power at $z = 0$

$$P_{in} = \text{Re}[P_e|_{z=0}] = \frac{A}{2} E_0^2 \frac{\beta}{\omega \mu}. \quad (7)$$

FIG. 1. (a) Physical principle of microwave scattering and absorption interaction with biological tissue and (b) simplified planar model for analysis.

The scattered (transmitted) microwave power (real) is the existing power at $z = d_0$

$$P_{scat} = \text{Re}[P_e|_{z=d_0}] = \frac{A}{2} E_0^2 \frac{\beta}{\omega\mu} e^{-2\alpha d_0}. \quad (8)$$

and the power absorbed by the tissue is

$$P_{absorb} = \frac{1}{2} \iiint_V \sigma E_0^2 e^{-2\alpha z} dv = \frac{A}{4\alpha} \sigma E_0^2 (1 - e^{-2\alpha d_0}). \quad (9)$$

Then, energy conservation is verified and shown below represented by averaged powers

$$\begin{aligned} \frac{P_{in} - P_{scat}}{P_{absorb}} &= \frac{\frac{A}{2} E_0^2 \frac{\beta}{\omega\mu} - \frac{A}{2} E_0^2 \frac{\beta}{\omega\mu} e^{-2\alpha d_0}}{\frac{A}{4\alpha} \sigma E_0^2 (1 - e^{-2\alpha d_0})} \\ &= \frac{\frac{A}{2} E_0^2 \frac{\beta}{\omega\mu} (1 - e^{-2\alpha d_0})}{\frac{A}{4\alpha} \sigma E_0^2 (1 - e^{-2\alpha d_0})} = \frac{2\alpha\beta}{\sigma\omega\mu} \\ &= \frac{2\omega^2 \mu \epsilon' \frac{\sqrt{1 - \cos^2 \theta}}{2 \cos \theta}}{\sigma\omega\mu} = \frac{\omega \epsilon' \tan \theta}{\sigma} = 1, \\ \therefore \bar{P}_{in} &= \bar{P}_{scat} + \bar{P}_{absorb}, \end{aligned} \quad (10)$$

indicating that the summation of averaged scattered and absorbed microwave power equals to the constant input microwave power, where $\bar{P}$ represents the averaged power. Furthermore, acoustic signal could be induced through microwave energy absorption of the tissue, following localized heating and thermo-elastic expansion. When heating time is treated as a delta function $\delta(t)$, the initial acoustic pressure of the homogeneous tissue could be expressed as¹⁵

$$p_0(t) = \Gamma \frac{\bar{P}_{absorb}}{A \cdot d_0} \delta(t), \quad (11)$$

where $\Gamma = bc^2/C_P$ is the Gruneisen coefficient, b is the isobaric volume expansion coefficient, C_P is the specific heat, and c is acoustic velocity in biological tissue. The acoustic signal propagates outwards in all directions and only one portion of the acoustic energy is detected by the ultrasound transducer. Considering all the factors including finite TA conversion efficiency, incomplete acoustic detection, and transducer response, we use $p(0 < p < 1)$ as the conversion coefficient, representing the averaged power conversion ratio of the detected acoustic power (simply expressed as $\bar{p}^2_{acoustic}$) from the absorbed microwave power $\bar{P}_{absorb}$. Similarly, because only part of the scattered microwave signal could be collected by the receiver antenna, the ratio between the averaged received scattering microwave power expressed as $\bar{p}^2_{scat}$ and the total averaged scattered microwave power $\bar{P}_{scat}$ is represented as $q(0 < q < 1)$. Then we have $\bar{p}^2_{acoustic} = p\bar{P}_{absorb}$ and $\bar{p}^2_{scat} = q\bar{P}_{scat}$. Substitute above parameters to energy conservation equation (10), we have

$$\frac{\bar{p}^2_{acoustic}}{p\bar{P}_{in}} + \frac{\bar{p}^2_{scat}}{q\bar{P}_{in}} = 1. \quad (12)$$

It is predicted that for a specific tissue, the detected acoustic signal and microwave signal by the ultrasound transducer and receiver antenna, respectively, are supposed to follow an ellipse equation with acoustic and microwave semi-axes $\sqrt{p\bar{P}_{in}}$ and $\sqrt{q\bar{P}_{in}}$.

According to Eq. (9), tissues with different conductivity σ will have different microwave absorption P_{absorb} and detected acoustic power, meanwhile $\bar{p}^2_{scat} = q\bar{P}_{scat}$ will vary in opposite direction based on Eq. (10). Therefore, tissues with different conductivity σ will fall on different locations of the ellipse. Drawing the ellipse with three tissues in Fig. 2, it is clearly shown that phase information ($\theta_1, \theta_2, \theta_3$) is capable of differentiating tissues by correlating both acoustic and microwave signals, rather than conventional methods evaluating either one of them. The phase contrast of the MAPC can be derived as

FIG. 2. Microwave-acoustic phasoscopy for three tissues with different conductivity, horizontal axis represents microwave signal, and vertical axis represents acoustic signal.

$$\begin{aligned}
1 + \frac{\Delta\theta}{\theta} &= \frac{\arctan\left(\frac{\bar{p}_{acoustic} + \Delta\bar{p}_{acoustic}}{\bar{p}_{scat} - \Delta\bar{p}_{scat}}\right)}{\arctan\left(\frac{\bar{p}_{acoustic}}{\bar{p}_{scat}}\right)} \\
&\approx \frac{\left(\frac{\bar{p}_{acoustic} + \Delta\bar{p}_{acoustic}}{\bar{p}_{scat} - \Delta\bar{p}_{scat}}\right)}{\left(\frac{\bar{p}_{acoustic}}{\bar{p}_{scat}}\right)} (1 - \varphi) \approx \left(\frac{1 + \frac{\Delta\bar{p}_{acoustic}}{\bar{p}_{acoustic}}}{1 - \frac{\Delta\bar{p}_{scat}}{\bar{p}_{scat}}}\right) \\
&\approx \left(1 + \frac{\Delta\bar{p}_{acoustic}}{\bar{p}_{acoustic}}\right) \left(1 + \frac{\Delta\bar{p}_{scat}}{\bar{p}_{scat}}\right), \quad (13)
\end{aligned}$$

where φ is infinitesimal of higher order after Taylor expansion. According to Eq. (13), correlated phase contrast is clearly enhanced by multiplication of microwave contrast $(1 + \Delta\bar{p}_{scat}/\bar{p}_{scat})$ and acoustic contrast $(1 + \Delta\bar{p}_{acoustic}/\bar{p}_{acoustic})$, which is a kind of non-linear amplification. Therefore, the proposed MAPC method is potentially powerful in tissue characterization with higher sensitivity and robustness.

The experimental setup for MAPC is shown in Fig. 3. A microwave generator (SMBV100A, Rohde & Schwarz) is used to provide 440 MHz continuous microwave, which is mixed with a pulse signal having 2 μ s pulse duration and 100 Hz repetition rate coming from function generator (33250 A, Agilent) by frequency mixer (ZX05-1HW-S+, Mini-Circuits). Through a microwave power amplifier (ZHL-100 W-GAN+, Mini-Circuits), the pulse-modulated microwave signal is amplified up to 100 W peak power and fed into a custom-designed helical antenna operating at 440 MHz. Scattered microwave signal is received by another helical antenna placed at the other side. Meanwhile, the thermoacoustic signal due to the microwave absorption is also collected by a wideband ultrasound transducer (V323-SU, Olympus) with 2.25 MHz central frequency, which is sensitive enough to detect acoustic wave with frequencies ranging from several hundred kHz to 5 MHz, followed by an ultrasound preamplifier (Model 5662, Olympus). Both scattered microwave signal and thermoacoustic signal are recorded with a digital oscilloscope (WaveMaster 8000 A, Lecroy) at 5 G samples/s rate. In the water tank, both microwave antennas and ultrasound transducer are immersed in the de-ionized water. Tissue sample is placed near the end of transmit helical antenna for maximum microwave illumination.

In order to generate and verify the proposed MAPC principle, three kinds of porcine tissues (kidney, liver, fat) with different conductivity at 440 MHz are prepared.

TABLE I. Conductivity of three different tissues at 440 MHz (S/m).

Fat	Liver	Kidney
0.0418	0.6704	1.1209

According to previous literatures,^{16–18} the conductivity values of above biological tissues are listed in Table I. Made in small round shape with 5 mm diameter and wrapped by ultra-thin polyethylene film, the biological tissue is placed close to both antennas and transducer. Due to fast propagation speed of electromagnetic wave in water and lossy small size tissue sample, scattered microwave signal is received immediately after illumination, ignoring the much weaker multi-scattering microwave. Incident microwave source is shown in Fig. 4(a), a microwave signal used for calibration is first recorded with no tissue sample placed, and subtracted by the recorded microwave signal with tissue sample to decouple the interference of direct-link microwave from transmitted antenna and reflected microwave by surrounding environment such as water tank wall, sample holder, etc. After envelope extraction and low-pass filtering, calibrated microwave signals for these three kinds of tissues are shown in Fig. 4(b). Averaged 300 times by the oscilloscope and subtraction of background noise, the recorded acoustic signal triggered by transmitted microwave pulse propagates through water media, which last about 30 μ s, are shown in Fig. 4(c). It is obvious to see that the amplitude (energy) of the received microwave envelope and acoustic signal are varying in opposite trend, i.e., the more microwave energy absorbed to induce acoustic signal, the less microwave energy scattered by the tissue.

In order to reduce the errors caused by system variation, six sets are prepared for each kind of tissue and averaged to minimize system error. Microwave and acoustic parameter M_i and A_i represent root mean square (RMS) value of the amplitude of microwave and acoustic signal in time domain, respectively. Due to different magnitude scale of microwave and acoustic signals, normalization is needed before establishing MAPC to maximize the sensing range of MAPC for tissue characterization. After obtaining (M_i, A_i) for all tissues shown in Table II, the following normalization scheme is implemented:

- (1) Set the intercept value at microwave axis to be $D_m = \max[M_i] - \min[M_i]$; set the intercept value at

FIG. 3. Experimental setup for microwave-acoustic phasoscopy.

FIG. 4. (a) Incident microwave source, (b) microwave signal detected by receive antenna, and (c) thermoacoustic signal detected by ultrasound transducer.

acoustic axis to be $D_a = \max[A_i] - \min[A_i]$. Then the ellipse equation is fixed by Eq. (14)

$$\frac{M_i^2}{D_m^2} + \frac{A_i^2}{D_a^2} = 1 \quad (14)$$

- (2) If tissue parameters are within $\min[M_i] < M_i < \max[M_i]$ and $\min[A_i] < A_i < \max[A_i]$ (first quadrant of ellipse). They are normalized by $M_{i_nom} = M_i - \min[M_i]$, and $A_{i_nom} = A_i - \min[A_i]$.
- (3) If tissue parameters are within $M_i < \min[M_i]$ and $A_i > \max[A_i]$ (second quadrant of ellipse), the acoustic parameter should be normalized by $A_{i_nom} = D_a - (A_i - \max[A_i])$ to confine it on the ellipse.

TABLE II. Extracted microwave and acoustic parameters of three kinds of tissues.

	Fat	Liver	Kidney
Microwave parameter M_i	2.0867	2.0049	1.9283
Acoustic parameter A_i	0.0014	0.0021	0.0024

FIG. 5. (a) Established MAPC and (b) tissues with different absorption rate are characterized on the MAPC.

- (4) If tissue parameters are within $M_i > \max[M_i]$ and $A_i < \min[A_i]$ (fourth quadrant of ellipse), the microwave parameter should be normalized by $M_{i_nom} = D_m - (M_i - \max[M_i])$ to confine it on the ellipse.

By applying the normalization scheme (steps 1, 2) to the extracted microwave and acoustic parameters, we have $D_m = 0.1584$, $D_a = 0.0010$ to build the MAPC ellipse in Fig. 5(a), normalized parameters of the three tissues are calculated and marked on the MAPC ellipse. Three tissues with different conductivity are well separated in the phase domain on the MAPC. The Fat and Kidney tissue are normalized to be $\theta_{fat} = 0^\circ$ and $\theta_{kidney} = 90^\circ$. Liver tissue is characterized by the phase of $\theta_{liver} = 42.42^\circ$, marked on the ellipse with negligible deviation due to the experimental variation.

In the next step, porcine muscle tissue is also characterized using the proposed MAPC. Shown in Fig. 5(b), it is with phase $\theta_{muscle} = 21.16^\circ$, revealing that its microwave absorption rate is between fat and liver, and well differentiated on the MAPC, and similar conclusion is drawn by other methods.¹⁷ Based on these experiments, we can estimate the phase sensitivity with regard to tissue's conductivity is averagely 8.34° per 0.1 S/m. In addition, applying the MAPC normalization scheme (steps 3, 4), tissues with microwave absorption rate larger than kidney or smaller than fat can also be characterized by different phase in second and fourth quadrants, respectively (the third quadrant remains blank based on the current normalization scheme). Proved by Eq. (10) and verified by the experiment, we can conclude the

proposed MAPC can characterize all the biological tissues by its microwave-acoustic phase.

Compared with current thermoacoustic characterization by tissue's EM absorption,¹⁹ the proposed MAPC evaluates both scattered microwave signal and induced thermoacoustic signal simultaneously. Phase information is extracted for different tissues rather than conventional amplitude or spectrum evaluation only.^{19,20} Such multi-mode acquisition (EM and acoustic wave) is able to provide coherent enhancement related to EM absorption and scattering of the same tissue only, as well as suppression of variation and noise due to non-coherence characteristics of their EM and acoustic waves. Therefore, the MAPC is supposed to be more sensitive and robust for tissue characterization.

In this paper, small-size homogeneous tissue samples are prepared, and MAPC is verified experimentally. To calibrate the variations of tissues' size, structure, surrounding measurement environment and status of tissue samples (freshly sacrificed/de-frozen), conversion coefficients p and q are adjustable to ensure that different types of tissues are well differentiated on the calibrated ellipse by their microwave-acoustic phases. Since the physical basis of MAPC is the dielectric property (permittivity, conductivity) of biological tissues that mainly determines the scattering and absorption of microwave, variations mentioned above will slightly influence the measurement accuracy, but will not invalidate the MAPC theory. For tissue samples or whole organs up to 5–10 cm, we would like to consider it as imaging rather than small-size tissue characterization. Correlated microwave acoustic imaging (CMAI) prototype will be built to scan the large tissue point by point, where each point is small and homogeneous enough to implement the MAPC proposed in this paper, to achieve phase contrast image. Furthermore, the tissue angiogenesis (excessive vascularisation) associated with the cancerous tissue's rapid growth leads to significant increment of ionic and dipole molecules such as free and bound water, protein, etc., which greatly increase the dielectric constant of cancerous tissue. Therefore, CMAI is intrinsically a functional imaging modality rather than anatomical imaging.

In conclusion, we propose a method named MAPC for tissue characterization collecting correlated microwave and acoustic signals. MAPC is well analyzed in theory and verified by the experiment of four different tissue characterization. This technique provides phase-contrast enhancement and will be explored to implement the CMAI prototype for clinical trials in the future.

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