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Tumor boundary estimation through time domain peaks monitoring: Numerical predictions and experimental results in tissue mimicking phantoms

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Abstract

A method to estimate the boundary of a tumor using an interstitial microwave probe is evaluated in numerical and phantom models. This method utilizes time-domain signal reflection from the tumor/liver interface to provide information about tumor boundary in both radial and axial directions. Using computational experiments, tumors with radial diameters up to 25 mm were estimated with less than 1 mm error. Axial diameters were estimated with at most 5 mm error. Accuracy seemed to increase with radial diameter, but decrease with axial diameter. Phantom experiments confirmed the computational results. These early results indicate that the proposed method may be used to estimate tumor boundary in both radial and axial dimensions without imaging. The technique may also be applicable in other situations that contain dielectric contrast between a volume of tissue and its background, such as monitoring tumor ablation growth. Additional work is needed to validate and optimize this method in tumor models.

I. Introduction

Thermal ablation is gaining acceptance as a method to treat hepatic tumors in patients who cannot be treated by surgery. While radiofrequency (RF) energy is the current clinical standard in high-temperature ablation, microwaves offer several additional benefits for tissue heating, including the ability to penetrate through charred or desiccated tissue; faster temperature elevation and higher internal temperatures leading to larger and more consistent zones of ablation; improved multiple-applicator support; and no ground pads [1–3]. However, as addressed in [4] two technical issues with current microwave ablation need to be improved, particularly for surgical applications. The first is applicator placement accuracy. In ablative procedures the goal is to ablate the tumor plus a 5 to 10 mm ablative margin. Poor placement can result in undertreatment, local recurrence or undesired damage to surrounding tissue [5]. The most common method for guiding applicator placement is anatomic imaging. Ultrasound can be used with both percutaneous and surgical (open or laparoscopic) approaches, but is often not available at surgery. More troublesome is the fact that many tumors are not visible on ultrasound without contrast-enhancement, which is not approved by the United States Food and Drug Administration (FDA). Computed tomography (CT) and fluoroscopic-CT can also be used for targeting and guidance, but use ionizing radiation and often require iodinated contrast to make the tumors conspicuous.

Monitoring evolution of the ablation zone during treatment is also critical to treatment success. A number of imaging technologies are now used to attempt to monitor ablation zone growth. Ultrasound provides real-time visualization, low cost and portability for easy access [6]; however, ablation monitoring is hampered by hyperechoic microbubbles that form in and around the ablation zone, which obscure the ultrasound image.

Both CT and magnetic resonance imaging (MRI) can also be used to monitor ablation progress [7,8]. However, CT requires ionizing radiation and usually requires contrast injections to

achieve adequate contrast between treated and untreated tissues. MRI is an attractive option because it can include temperature information, but MRI-compatible ablation equipment and interventional MRI systems are fairly uncommon and MRI is associated with significant monetary cost. Therefore, the goal of this work was to develop a feedback strategy that exploits the dielectric boundary between two domains (eg, tumor or ablation zone and normal tissue) of tissue using the same applicator used for ablative treatment.

A method was recently proposed to estimate tumor diameter by launching an ultrawideband (UWB) signal via a microwave ablation antenna and detecting reflections from the tumor–liver interface [4]. This method is reviewed briefly in section II of this manuscript. An improved and extended method is then proposed to estimate the tumor boundary in two directions. An experiment model is presented for validation. Simulation and experimental results are provided and analyzed in section III which prove the viability of this method and show the potential of this technique for clinical use. Finally, the results will be discussed in section IV.

II. Methodology

A. Review on Ultrawideband Peak Detection

The coaxial-fed dipole antenna is a basic type of microwave ablation applicator suitable for interstitial treatment [9]. Figure 1 shows the structure used in this study where $\hat{\epsilon}_2$ and $\hat{\epsilon}_4$ represent the complex permittivity of the dielectric layer and ambient medium respectively. The ambient medium can be tumor or normal liver tissue. Converse *et al.* [4] first proposed a method to estimate tumor size by launching a UWB signal from the ablation antenna, then detecting any signal reflected from the tumor–liver interface. Based on signal peak delay time the distance from the antenna feed point to the tumor/liver interface can be estimated. A brief synopsis of this method follows.

A differentiated Gaussian signal, $dg(t)$, is chosen as the UWB pulse,

$$dg(t) = A(t_0 - t)e^{-\frac{(t-t_0)^2}{B^2}} \quad (1)$$

where A adjusts the height of the peaks, B makes the signal sharp or blunt and t_0 is the signal center in time.

To allow numerical simulations and experiments with available equipment the response of the UWB signal from the antenna is analyzed by measuring the reflection coefficient, S_{11} , of the antenna structure. Then an estimated reflection $ref(t)$ can be achieved from Eq. (2):

$$ref(t) = F^{-1}[DG(f) \cdot S_{11}(f)] \quad (2)$$

where $DG(f) = F[dg(t)]$, $F[\cdot]$ and $F^{-1}[\cdot]$ are Fourier and inverse Fourier transform.

In this study the B value in Eq. (1) was chosen as 0.045 ns and t_0 as 0.5 ns. The spectrum of the differentiated Gaussian extends to 10 GHz.

When measuring the response from the tumor embedded in liver, this signal contains reflections from the antenna–tissue interface and the tumor–liver interface, which can be denoted as total reflection $ref_T(t)$. From simulation or phantom experiments a hypothetical reflection ref_H can be produced from the antenna inserted into an all-tumor homogeneous medium. Then the interface response can be acquired by subtracting the two signals:

$$\text{ref}_I(t) = \text{ref}_T(t) - \text{ref}_H(t) \quad (3)$$

Then the tumor radius in radial direction, r_{radial} in Figure 8, can be calculated based on the time at which the observation plane sees the maximum peak in the response.

B. Feasibility of Two Directional Boundary Detection

Analysis in [4] shows that the tumor–liver interface signal contains reflections from two waves: one propagates radially outward from the antenna and the other axially along the feed line. Therefore this method has the potential to monitor the tumor size not only in the radial direction but also in the axial direction. In addition, the axial distance from the antenna feed point to the proximal tumor boundary can provide important information about insertion depth into the tumor, not just the visible tissue surface.

The velocity of the differentiated Gaussian wave is approximated to the phase velocity of a harmonic wave whose frequency is most prominent in the differentiated Gaussian. Figure 2 shows that the wave numbers or wave lengths are different in different directions for a harmonic wave. Whereas the wave propagating in the radial direction can be assumed to have a plane wave velocity, the wave propagating in the axial direction needs to be studied.

The wave number along the conductor k_L can be determined by solving $\zeta = k_L$ of the following equation [10],[11]:

$$(k_2^2/\xi_2)H_0^{(2)}(c\xi_4)[H_0^{(2)}(b\xi_2)J_1(c\xi_2) - J_0(b\xi_2)H_1^{(2)}(c\xi_2)] - (k_4^2/\xi_4)H_1^{(2)}(c\xi_4)[H_0^{(2)}(b\xi_2)J_0(c\xi_2) - J_0(b\xi_2)H_0^{(2)}(c\xi_2)] = 0 \quad (4)$$

where b and c are the inner and outer radii of the coaxial cable dielectric (Figure 1), k_2 and k_4 are wave numbers of the coaxial dielectric and the ambient tissue medium, respectively,

$\xi_2 = (k_2^2 - \zeta^2)^{1/2}$ and $\xi_4 = (k_4^2 - \zeta^2)^{1/2}$, $H_p^{(2)}(\cdot)$ is the Hankel function of the second kind, and $J_p(\cdot)$ is the Bessel function of the first kind.

Eq. (4) can then be solved numerically to provide the wave number of the wave propagating in the axial direction. Then the wave velocity of the differentiated Gaussian is approximated by:

$$v_{\text{axial}} = \frac{2\pi f_p}{\text{real}(k_L)} \quad (5)$$

where f_p is frequency component at which the differentiated Gaussian shows the peak in the frequency domain.

The wave velocity in the radial direction is approximated by the plane wave velocity:

$$v_{\text{radial}} = \frac{c}{\sqrt{\text{real}(\hat{\epsilon}_{\text{tumor}, f_p})}} \quad (6)$$

where $\hat{\epsilon}_{\text{tumor}, f_p}$ is complex relative permittivity of the tumor at f_p .

By monitoring the peaks delay time, the tumor size in the radial and axial directions can be estimated. Calculation from Eq. (5) and (6) also shows that the axial velocity is faster than

radial velocity so the first wave detected corresponds to the reflection from the axial direction. In King's theory [12] the electric field of an insulated antenna in the radial direction has a 90° phase shift to the excitation. Assume the same phase shift exists in the detected response to the interface reflection and it would cause the radial peak inversion. The field propagating in the axial direction follows transmission line theory and the phase shift is negligible. Note that in the current setting the tumor impedance is lower than normal liver impedance so that the signal does not change sign when reflected from the boundary. Figure 3 shows the whole peaks selection scheme for accurate estimation. The distances in the radial and axial directions are calculated from:

$$r_{\text{radial}} = (T_{\text{radial}} - T_{\text{tef}}) \cdot v_{\text{radial}} / 2 + r_a \quad (7)$$

$$r_{\text{axial}} = (T_{\text{axial}} - T_{\text{tef}}) \cdot v_{\text{axial}} / 2 + r_a \quad (8)$$

where T_{tef} is the propagation time of the wave through the coaxial dielectric and r_a is the antenna radius which is used to compensate the antenna thickness.

III. Model Evaluations

A. Tissue-Mimicking Phantom Fabrication and Testing

Both numerical simulations and phantom experiments were performed to evaluate the proposed tumor size estimation method. First, phantoms were created to mimic spherical tumors of varying diameters (22, 31, 37 and 45 mm), each tumor being embedded in a medium with properties similar to normal liver (Figure 6). The liver phantom construction is based on the description in [13] with reduced viscosity. Tumor phantoms consist of 5% agar so that solid molding is possible. Phantom compositions were produced to achieve about 10% dielectric contrast between normal and tumor regions, according to published data (Table 1) [13–15]. The dielectric properties of each phantom material were then measured using an microwave network analyzer. The exact compositions (Table 1) of tumor and liver phantoms were determined to achieve different levels of dielectric contrast. The dielectric properties of each phantom material were then measured using a microwave network analyzer (PNA E8364A, Agilent Technologies, Santa Clara, CA) with an open-ended coaxial probe based on the method described in [14]. Figure 5 shows measured relative permittivity and conductivity of each phantom and the data from a Cole–Cole model. The Cole–Cole model described later is based on *ex-vivo* tissue measurement and it can be seen that the properties of the phantoms fall in the range of actual human liver. These measurements served as the basis for our numerical phantom model in validation experiments.

B. Phantom Experiments and Simulations

Figure 6 shows the experimental setup. A microwave network analyzer (PNA E8364A) was used to measure the reflection coefficient (S_{11}) of an antenna inserted into the center of each tissue-mimicking phantom described above. This geometry was chosen to avoid reflection interference from the beaker and the surface of phantom. Reflection coefficients were measured over the frequency range from 0.05 to 20 GHz, in steps of 50 MHz. Two sets of measurements were taken for each experiment. One was taken from the homogeneous tumor phantom and the other was from the tumor sphere within the liver phantom. Then the time domain signals were calculated from Eq. (2) and the interface response was acquired from Eq. (3). The geometry was then calculated from Eq. (7) and (8).

Each of the experiments carried out was accompanied by numerical simulation to validate the experimental results obtained. Finite element method (FEM) simulations were carried out using commercial software (Comsol Multiphysics v 3.3a; Burlington, MA).

All simulations were performed using an axisymmetric model of a dipole antenna inserted into a spherical tumor embedded in the liver. The simulation domain matched the experimental environment where the liver has boundaries to the beaker and the surface of air (Figure 7). The dielectric properties of tumor and liver phantoms were incorporated by the actual measured values plotted in Figure 5. The proximal end of the antenna was identified as with a 10 W coaxial input port boundary condition. A mesh consisting of 4000 triangular elements was constructed and the maximum element size was 3 mm. Convergence of numerical simulations was checked by solving the problem with mesh refinement and noting a minimal error between solutions. The simulated frequency range was chosen to be the same as in experiments: 0.05 to 20 GHz in steps of 50 MHz. S_{11} was solved at each frequency and the geometry was calculated from the same procedure as in experiments.

C. Human Liver/Tumor Simulations

To further study the clinical potential of this method, simulations were carried out assuming properties of human liver and tumor tissues. In these simulations we had easier control of various conditions such as ellipsoidal tumors and axial offset in antenna placement. Liver and tumor tissue properties were numerically defined using a multipole Cole–Cole dispersion model [16]:

$$\widehat{\varepsilon}_{\text{liver}}(\omega) = \varepsilon_{\infty} + \sum_n \frac{\Delta \varepsilon_n}{1 + (j\omega\tau_n)^{(1-\alpha_n)}} + \frac{\sigma}{j\omega\varepsilon_0} \quad (9)$$

where τ_n is a time constant to characterize the polarization in a relaxation region, ε_{∞} is the permittivity at field frequencies where $\omega\tau \gg 1$, $\Delta\varepsilon$ is the magnitude of dispersion, α is a measure of the broadening of the dispersion and σ is the static ionic conductivity. Gabriel *et al.* obtained these parameters by fitting this model to *ex-vivo* measurement to human liver [16]. Table 2 shows the parameters for the four-pole configuration.

The dielectric properties of liver and tumor are similarly frequency dependent so, for the purpose of this study, the complex permittivity of tumor was assumed to be a scalar ratio (R) of the permittivity of normal liver:

$$\widehat{\varepsilon}_{\text{tumor}}(f) = R \cdot \widehat{\varepsilon}_{\text{liver}}(f) \quad (10)$$

which simplifies the analysis of different contrast ratios. The tested values of R were chosen as 1.02, 1.10 and 1.30 respectively. The radial and axial diameters of the embedded tumor ranged from 10 to 50 mm. An axial symmetry boundary was applied at $r = 0$, with matched conditions used on the other boundaries to minimize signal reflection from these boundaries in Figure 8.

IV. Results

A. Phantom Experiment and Simulation Results

Experiments were carried out with two tumor phantoms, “Agar-60” and “Agar-75”, in spheres with 4 sizes of diameters: 22 mm, 31 mm, 37 mm and 45 mm. Sample detected signals were plotted in solid lines and accompanied by the corresponding simulated curves in dashed lines in Figure 9. Note that the critical peaks for radius calculation have shown good coincidence in

time between simulated and measured data, demonstrating that the simulation model used is a valid predictor of experimental performance.

Table 3 lists the axial and radial radii measured from phantom models. Measured data were in good agreement with actual dimensions, demonstrating less than 3 mm error in most cases tested. Global errors in radius measurements could be caused by systematic error in dielectric measurement. Note that the performance variability is not available since recursive measurements were not carried out for each case.

B. Human Liver/Tumor Simulation Results

Results presented in this section were obtained under the idealized simulations described in Section III.C. Table 4 and Table 5 list tumor size estimations for spherical and elliptical tumors with multiple dielectric contrast ratios R (Eq. (10)). Radial and axial sizes are estimated from multiple peaks as shown in Figure 3. From these simulated data, we can conclude that measurements of both radial and axial tumor dimensions are feasible. Estimations in the radial direction were accurate for all tumor sizes and shapes considered.

Calculation from Eq. (5) and (6) indicates that the wave velocity in the axial direction is approximately 2.5 times that in the radial direction at the frequency of the peak spectrum of the differentiated Gaussian. In some cases when the axial radius is much larger than radial radius or both dimensions are too small the axial peak either merges into the radial peak or is distorted greatly and is not identifiable (Figure 4). For such a situation only radial radius is measured and the axial radius is listed as “fail” in Table 4 and Table 5. Based on these results Figure 10 summarizes a “working” domain for axial detection.

The estimation of axial distance to the tumor boundary can be used to monitor the insertion of the applicator if the actual size of the tumor has been determined before the procedure. Table 6 shows the offset, which is difference between estimated and actual measured distances to the tumor radius. Positive numbers denote over-insertions for which the antenna feed point is beyond the center of the tumor and vice-versa for negative numbers. Although the percent errors in the absolute distances detected were relatively high for large offsets, the measurements reflect the over or under insertion correctly. Note that the highest measurement accuracy is when the antenna is actually on-center. Therefore, finding the center of the tumor can be accomplished through this method.

V. Conclusion and Discussion

The feasibility of using a UWB signal to estimate tumor size in radial and axial directions was investigated. Idealized simulations using a numerical liver and tumor model show that the errors in estimation were less than 1 mm for all the studied sizes in the radial direction and for radius less than 2 mm in the axial direction. The same method can be used to monitor antenna insertion depth accuracy by noting over- or underinsertion of the antenna. The simulation technique used to predict clinical performance was also validated by data collected in a phantom model, which demonstrated good agreement with numerical predictions.

The studies described in this paper utilized either numerical simulations or phantom experiments in a well-controlled, idealized environment. Many factors in clinical applications can affect the quality of this technique: irregular tumor shapes, erratic or transient dielectric boundaries or dielectric heterogeneity within measurement region caused by vessels or local variation in tissue. The dielectric contrast ratio between normal tissue and tumor in this study was as low as 1.02, to predict technique performance under worst-case conditions. Our numerical results show that the proposed boundary estimation technique is capable of discerning boundaries even with low dielectric contrast. However, we note that the lowest

dielectric contrast ratios noted in previous reports are 1.05–1.10, well above the lower threshold tested in this study [13–15]. More testing is required to determine whether similar sensitivity is achievable in a more realistic model.

This study was also limited by an assumed prior knowledge of, and homogeneity in, tumor dielectric properties. Additional measurements are needed to determine the validity of these assumptions. Alternatively, as described previously, a series of responses corresponding to a range of possible tumor properties can be simulated and the optimal reference signal chosen based upon the early uprising segment of the potential interface signals [4]. The viability of this technique needs additional verification in tissue.

Much of the value in this study lies in the possibility that this technique can be extended to monitoring the evolution of ablation zone. During ablation the dielectric properties of tissue are inhomogeneous and affected by temperature, cellular makeup and water content distribution [17–19]. Recently, temperature-dependent dielectric properties in the microwave frequency range were measured during RF ablation. Based on these data, an empirical tissue model for numerical simulations was produced that demonstrates a relatively large dielectric contrast ratio between ablated and normal tissue. We are currently evaluating the feasibility of ablation zone monitoring using the time-domain boundary estimation technique.

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Figure 1.
Scheme of the coaxial-fed dipole antenna used in this study.

Figure 2.
Phase plot of magnetic field in coaxial dipole simulation at 3 GHz.

Figure 3.
Input and response signal from simulation. $r_{\text{radial}} = r_{\text{axial}} = 1.5$ cm.

Figure 4. Distorted peaks in response signal from simulation. $r_{radial} = 1.5$ cm, $r_{axial} = 2.5$ cm.

Figure 5.
Dielectric properties of human liver and liver phantoms.

Figure 6.
Phantom experiment system for tumor size estimation.

Figure 7.
Simulation domain for phantom experiments validation.

Figure 8.
Simulation model for human liver/tumor.

(a) Agar-60 tumor with 15.5 mm radius

(b) Agar-75 tumor with 15.5 mm radius

Figure 9.
Detected signal in experiment compared with simulation.

Figure 10.
“Working” domain for tumor boundary estimation in axial direction.

Table 1

Weight percentage of normal liver and tumor phantoms.

	Normal Liver	Tumor-60	Tumor-75
Water	51.02	60	75
Sugar	46.01	33.9	18.9
NaCl	0.82	1.0	1.0
Dowcicil	0.1	0.1	0.1
Agar	n/a	5.0	5.0
HEC 5000	2.05	n/a	n/a

Table 2

Parameters from Gabriel [16] to determine dielectric properties of liver.

<i>n</i>	ϵ_{∞}	$\Delta\epsilon_n$	τ_n	a_n	σ
1	4.0	39.0	8.84 [ps]	0.10	0.02
2		6000	530.52 [ns]	0.20	
3		5.0×10^4	22.74 [μ s]	0.20	
4		3.0×10^7	15.915 [ms]	0.05	

Table 3

Experiment results of tumor radius estimation (mm).

Direction	Tumor radius	Detected radius			Error (mm)/error (%)		
		Agar-60	Agar-75	Agar-60	Agar-60	Agar-75	Agar-75
Radial	11.0	13.1	12.9	2.1/19.1	1.9/17.3		
Axial	11.0	13.4	13.6	2.4/21.8	2.6/23.6		
Radial	15.5	17.4	17.5	1.9/12.3	2.0/12.9		
Axial	15.5	17.8	19.4	2.3/14.8	3.9/25.2		
Radial	18.5	19.8	20.2	1.3/7.0	1.7/9.2		
Axial	18.5	20.9	21.4	2.4/13.0	2.9/15.7		
Radial	22.5	24.0	24.0	1.5/6.7	1.5/6.7		
Axial	22.5	23.9	25.0	1.4/6.2	2.5/11.1		

Table 4

Detected tumor radius of spherical tumor in simulation (mm).

Actual radius of spherical tumor	R = 1.02		R = 1.10		R = 1.30	
	Radial	Axial	Radial	Axial	Radial	Axial
5	5.7	fail	5.6	fail	5.5	fail
10	10.5	fail	10.4	fail	10.0	10.3
15	15.4	15.8	15.4	15.1	15.4	15.3
20	20.3	20.8	20.3	20.8	20.2	20.7
25	25.0	27.4	25.0	28.4	25.0	30.3

Table 5

Detected tumor radius of elliptical tumor in simulation (mm).

Actual radius of elliptical tumor		$R = 1.10$	
Radial	Axial	Radial	Axial
10	5	9.9	3.1
10	15	11.0	fail
15	5	15.6	3.0
15	10	15.4	11.1
15	20	15.9	19.4
15	25	16.5	fail
20	10	19.9	11.1
20	15	20.0	15.7
20	25	20.8	27.9
25	10	25.0	11.0
25	15	24.8	15.4
25	20	24.7	21.3

Table 6

Simulation results of antenna placement monitoring (mm). Tumor radius = 20 mm

Antenna vertical offset	Detected offset
+4	+3.3
+2	+1.0
-2	-2.3
-4	-8.6