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● *Original Contribution*

VARIATIONS IN TEMPERATURE DISTRIBUTION AND TISSUE LESION FORMATION INDUCED BY TISSUE INHOMOGENEITY FOR THERAPEUTIC ULTRASOUND

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Abstract—Tissue inhomogeneity might have an important effect on the treatment accuracy of therapeutic ultrasound. Both computer simulation and measurement were performed to study the influence of tissue inhomogeneity on the temperature distribution and tissue lesion formation induced by focused ultrasound. The inhomogeneous tissue is considered a combination of a homogeneous medium and a phase aberration screen in this article. Temperature distributions and lesion dimensions were predicted using the combination of acoustic non-linear and bio-heat transfer equations. To verify the theoretical predictions, polyethylene plates with phase distributions of different correlation lengths and standard deviations were made to mimic inhomogeneous tissues such as human abdominal tissue, and a series of experiments were performed, including acoustic and thermal measurements. The results indicate that the tissue inhomogeneity caused phase aberration of the ultrasound beam. With increasing standard deviation and correlation length of phase aberration, the scattering level of the acoustic field increased, while ultrasound-induced peak temperature and lesion size decreased. This study provides a theoretical and experimental basis for future development of accurate treatment plans for high-intensity focused ultrasound. (E-mail: juantu@nju.edu.cn or dzhang@nju.edu.cn)

Key Words: **Tissue inhomogeneity, Temperature field, High-intensity focused ultrasound, Phase aberration.**

INTRODUCTION

High-intensity focused ultrasound (HIFU) is an attractive and non-invasive method of tissue thermal therapy, and has drawn much attention in medical therapy for decades (Kennedy 2005; Mitragotri 2005; ter Haar and Coussios 2007a). Exposure to HIFU can rapidly raise the temperature higher than 70°C at the focus, permitting ablation of tumors within seconds without damage to surrounding tissues (ter Haar 1995; ter Haar and Coussios 2007b). HIFU devices are currently under investigation as effective treatment modalities for ablating solid tumors of the prostate, liver, breast, kidney and brain (Illing et al. 2005; Leslie and Kennedy 2006; Roberts 2005; Wu et al. 2004). Because HIFU energy must pass through different tissues and interfaces to reach its focus, accurate prediction of the acoustic field distribution and heat deposition in the focal region is critical to ensuring successful treatment. Most numerical modeling of non-linear wave propagation and heating within tissues has used limited sets of parameters for specific tissue models (Filonenko and Khokhlova 2001; Liu et al. 2009). Few studies have considered the variability in propagation path or physical properties of tissues (Hinkelman et al. 1994). However, scattering and phase aberration resulting from the inhomogeneity of tissues have significant effects on the accurate prediction of heat deposition at the target tissue. Inhomogeneities of the body wall are a main source of phase aberration (Douglas et al. 1998; Hinkelman et al. 1994). For example, the abdominal layer consisting of skin, entangled fat, muscle and connective tissue, as well as septa within subcutaneous fat, deteriorates the focusing of ultrasound beam in the treatment of liver tumors as a result phase aberration. Additionally, large variation in the acoustic velocity within the abdominal wall can significantly affect acoustic energy deposition in the body. Compared with that in the body wall, the

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inhomogeneity within the viscera is relatively small and only locally affects the energy deposition in that organ (Flax and O'Donnell 1988). Hence, phase aberration is considered to originate mainly from the inhomogeneity of the abdominal wall rather than the inhomogeneous viscera (Flax and O'Donnell 1988).

A sinusoidal phase screen can be used to model phase aberration, as it represents a single spatial frequency component in isolation from the continuous distribution associated with a random phase distribution. Various studies based on the phase screen model have been performed to characterize the phase aberration induced by abdominal wall. Hinkelman et al. (1994) suggested that a significant portion of the time-shift aberration caused by the abdominal wall can be described by using single- or multi-phase screen models. Huang and Tsao (2002) proposed a multi-layer phase screen model to explain the phase aberration in a linear field. Furthermore, Christopher (1997) studied a non-linear field for characterizing phase aberrations introduced by the abdominal wall. Varslot et al. (2007) subsequently used multiple random phase screens to approximate an extended heterogeneous region in a numerical investigation of tissue harmonic imaging. More recently, it has been pointed out that as the thickness of a typical abdominal wall is on the order of the correlation length, the phase aberration introduced by the abdominal wall can be simplified to a single phase screen model that is characterized by the correlation length and standard deviation of the heterogeneity (Yan and Hamilton 2011). However, all of these studies are related to the fields of diagnostic ultrasound.

The present study was aimed at addressing the influence of tissue inhomogeneity on the propagation and energy deposition of therapeutic ultrasound, through characterization of the variance in temperature distribution and lesion formation. The inhomogeneous tissue is considered a combination of a homogeneous medium and a phase aberration screen. Temperature distribution and lesion formation are predicted using the non-linear acoustic Khokhlov-Zabolotskaya-Kuznetsov equation (Zabolotskaya and Khokhlov 1969; Kuznetsov 1970) and the bio-heat transfer equation (Pennes 1948). Simulated results are discussed with respect to the variance in tissue heterogeneity. To examine the validity of numerical simulations, a tissue-mimicking phantom composed of six phase aberration plates made by a 3-D computer-controlled engraving machine was placed in the transducer propagation path to mimic the inhomogeneity introduced by tissue. The acoustic field, HIFU-induced temperature distributions and lesion dimensions in the tissue-mimicking phantom were measured and compared with the numerical simulations.

THEORY

Acoustic model

The extended Khokhlov-Zabolotskaya-Kuznetsov equation for an arbitrary power of absorption in tissue is used to describe t non-linear ultrasound propagation in tissues, which is written in non-dimensional form (Filonenko and Khokhlova 2001) as

$$\frac{\partial}{\partial T}\left(\frac{\partial P}{\partial Z}-NP\frac{\partial P}{\partial T}-A\frac{\partial^2 P}{\partial T^2}\right)=\frac{1}{4G}\Delta'_\perp P \qquad (1)$$

where $p = p/p_0$ is the normalized tgqcure; p is sound pressure, and p_0 is sound pressure at the surface of the transmitter. $\Delta'_\perp$ $\Delta'_\perp = \partial^2/\partial X^2 + \partial^2/\partial Y^2$ is the non-dimensional transverse Laplace operator with respect to X and Y. $X = x/a$, $Y = y/a$ and $Z = z/D$ are the normalized coordinates, where a is the radius of the transmitter, and D is the geometric focal distance. $T = \omega\tau$, where $\tau = t–z/c_0$ is the retarded time, and ω is the angular frequency. $N = D/Z_n$, where $Z_n = \rho_0 c_0{}^3/\omega_0\beta p_0$ is the shock wave formation distance of a plane wave, c_0 is the sound speed, ρ_0 is the density and β is the acoustic non-linear coefficient. $A = \alpha D$, where $\alpha = \omega_0{}^2 b/2\rho_0 c_0{}^3$ is the absorption coefficient, and b is the dissipative parameter of sound. $G = z_d/D$, where $z_d = \omega a^2/2c_0$ is the Rayleigh distance.

Equation (1) is solved in the frequency domain by using a finite difference algorithm (Filonenko and Khokhlova 2001). In the frequency domain, the sound pressure is represented as the Fourier series expansion

$$P=\sum_{n=-\infty}^{\infty} C_n(X,Y,Z)\exp(jn\tau) \qquad (2)$$

where $C_n(X,Y,Z)$ is the complex amplitude of pressure of the nth harmonic component at a point (X,Y,Z). Through substitution of eqn (2) in eqn (1), a set of coupled differential equations is derived and calculated numerically using the method of fractional steps with an operator splitting procedure (Filonenko and Khokhlova 2001). First, the non-linear term is solved by employing a fourth-order Runge-Kutta method. Then, the absorption term is solved as $C_n(X,Y,Z + dz) = C_n(X,Y,Z) \exp(dzA\text{-}L_{abs}(n))$. $L_{abs}(n) = –n^2$ for water, and $L_{abs}(n) = –n^{\mu}–j2n(1–n^{\mu-1})/\pi/(\mu–1)$ for the phantom (Filonenko and Khokhlova 2001), where the linear operator L_{abs} describes the absorption of a wave in compliance with the power law characteristic of biological tissues, and the constant parameter $\mu = 1.266$ is set for a tissue type of liver. Finally, the diffraction term is solved by using the finite-difference implicit backward algorithm for each harmonic.

An inhomogeneous layered tissue with small but finite thickness Δz is considered a combination of a