Estimation of temperature elevation generated by ultrasonic irradiation in biological tissues using the thermal wave method*

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(Received 13 June 2012; revised manuscript received 26 August 2012)

In most previous models, simulation of the temperature generation in tissue is based on the Pennes bio-heat transfer equation, which implies an instantaneous thermal energy deposition in the medium. Due to the long thermal relaxation time τ (20 s–30 s) in biological tissues, the actual temperature elevation during clinical treatments could be different from the value predicted by the Pennes bioheat equation. The thermal wave model of bio-heat transfer (TWMBT) defines a thermal relaxation time to describe the tissue heating from ultrasound exposure. In this paper, COMSOL Multiphysics 3.5a, a finite element method software package, is used to simulate the temperature response in tissues based on Pennes and TWMBT equations. We further discuss different factors in the bio-heat transfer model on the influence of the temperature rising and it is found that the temperature response in tissue under ultrasound exposure is a rising process with a declining rate. The thermal relaxation time inhibits the temperature elevation at the beginning of ultrasonic heating. Besides, thermal relaxation in TWMBT leads to lower temperature estimation than that based on Pennes equation during the same period of time. The blood flow carrying heat dominates most to the decline of temperature rising rate and the influence increases with temperature rising. On the contrary, heat diffusion, which can be described by thermal conductivity, has little effect on the temperature rising.

Keywords: thermal wave model of bioheat transfer, temperature elevation, ultrasound irradiation

PACS: 43.35.+d, 43.80.+p **DOI:** 10.1088/1674-1056/22/2/024301

1. Introduction

Hyperthermia and high intensity focused ultrasound (HIFU) have become useful techniques for the treatment of cancer and other diseases. In order to develop an ultrasound technique into an effective quantitative method, it is necessary to know the temperature distribution in biological tissues generated by ultrasound irradiation, both theoretically and experimentally, so that the temperature of the lesion in a focal area can be correctly controlled.

Traditionally, temperature elevation in biological tissues is usually predicted by the Pennes bioheat equation.[1,2] Huang *et al*.[3] developed a numerical simulation that couples models for ultrasound propagation, acoustic streaming, ultrasound heating, and blood cooling in a Newtonian viscous medium based on the Pennes model. Also, these authors carried out a series of *in vitro* experiments employing non-uniform flow-through tissue phantoms, which were designed to provide the verification of the model predictions. It is known that the Pennes bioheat transfer equation is based on Fourier's law and assumes that heat propagation occurs at an infinite speed,[4] that is to say, if a material is subjected to thermal perturbation, the heating effect will be felt instantaneously in all parts of the conducting medium without any relaxation time. This is obviously not in conformity with physical reality. Furthermore, the Pennes bioheat transfer equation may not be used to characterize the temperature oscillation phenomenon in living tissues[5] due to its first order in time differential form. To make up for the disadvantages of the theory, Liu *et al*.[6] developed a thermal wave model of bioheat transfer (TWMBT) in biological tissues. The thermal relaxation time τ is introduced in the TWMBT, which reflects the tissue response to thermal perturbation. The thermal relaxation time is expressed, here, as $\tau = \alpha/C_t^2$, where α is thermal diffusivity, and C_t is the speed of thermal wave in living tissues and often referred to as the "second sound".[7] Physically, the thermal relaxation time τ represents the time delay between the heat flux vector and the temperature gradient,[8] that is, the heat flow does not start instantaneously, but grows gradually with thermal relaxation time τ, after applying a temperature gradient. The thermal relaxation time τ ranges from 10^{-8} s to 10^{-14} s for homogeneous substances.[9] Most heating processes are far longer than this time scale, and the classical method has been successfully applied to heat conduction in these materials. However, the values of τ in biological tissues have been predicted to be 20 s–30 s[9,10] because they are composed of porous capillary bodies and cells, i.e., heterogeneous, multiphase systems. In such highly nonhomogeneous inner structures, the local heat transfer interactions take place at different levels and the time is needed for accumulating the thermal energy that is required for transferring the heat to the nearest element within the non-

*Project supported by the National Basic Research Program of China (Grant Nos. 2011CB707902 and 2012CB921504), the National Natural Science Foundation of China (Grant No. 11274166), and the State Key Laboratory of Acoustics, Chinese Academy of Sciences (Grant No. SKLA201207).

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homogeneous inner structures.[9] Also, it reflects energy interaction at the structural level rather than at the molecular or crystal lattice level as in homogeneous materials and it may take a much greater value. Mitra *et al*.[11] made experimental measurements in processed meat and obtained $\tau \approx 16$ s. Because the speed of the heat propagation in living tissue is much smaller than that in other materials such as metals and liquids, the thermal relaxation times of biological tissues are far more than those of the metal, the thermal model which has been considered to have a finite speed of heat propagation is more rational, and will reveal more of the bio-heat transfer properties. Therefore, the TWMBT model may be more suitable for describing the temperature elevation in biological tissues induced by ultrasound irradiation.

The non-homogeneous inner structure of biological tissue suggests the existence of non-Fourier heat conduction behavior, as temperature oscillation and thermal wave behavior are commonly observed. Temperature oscillation in living tissue was first observed by Richardson *et al*.[12] and later by Roemer *et al*.[5] who subjected canine thigh muscle to microwave heating at different power levels. Davydov *et al*.[13] experimentally observed that the heat transfer in tissue under strong heating exhibits anisotropy, which cannot be explained by the Fourier-based heat model. Mitra *et al*.[11] carried out four different experiments with processed meat for different boundary conditions and also observed the thermal wave behavior. Banerjee *et al*.[14] measured the thermal response of meat under laser irradiation, and found that the non-Fourier heat conduction equation is better than the classical Fourier heat conduction.

The one-dimensional TWMBT solution in skin subjected to constant surface temperature heating in a finite medium was obtained using the separation of variables to obtain the analytical solution.[6] Because of the complexity of the heating distribution, no analytical solution of the TWMBT equation for this case has been obtained up to now. Various numerical methods[15] have been proposed for solving hyperbolic diffusion problems such as the TWMBT equation. As shown by Chen and Liu,[15] the major difficulty encountered in numerically solving hyperbolic diffusion problems lies in numerical oscillations. The numerical scheme involving the Lapace transform technique and the control volume method[16–18] were used to solve this problem. It must be pointed out that the hyperbolic diffusion equation has been used by several authors to deal with relevant problems.[19,20] Recently, researchers studied further the analytical solutions of TWMBT[21–24] and used different methods including transformation method and superposition technique to acquire the numerical solutions of TWMBT.[25,26] Some new bioheat transfer models, which include the fractional heat conduction constitutive model and the dual-phase-lag model, were proposed to describe the thermal effects.[27,28] Researchers also studied the effects of bubbles and pulsed ultrasound on temperature field[29,30] and the non-invasive estimation of the temperature from the echo.[31]

In this study, our interest focuses on the transient temperature variation in biological tissues generated by ultrasound irradiation. We study the temperature elevation induced by the ultrasound using TWMBT model and discuss the influence of the thermal relaxation time, the thermal conductivity and the blood flow on ultrasound therapy treatment. The Pennes equation is now mainly used to study the temperature elevation induced by ultrasound, but as shown by the previous studies, the thermal wave effects are obviously reflected in the high-intensity, short-term source, so we discuss the difference between the Pennes and TWMBT equations and hope that it can provide some guidance for the ultrasound therapy, especially hyperthermal and HIFU treatment.

2. Theory

The heat deposition due to the absorption of ultrasound can be obtained from

$$Q = Q_0 \cdot 4 \sum_{n=1}^{N_{\max}} n^{1.1} |C_n|^2, \quad Q_0 = 2\alpha_t I_0, \tag{1}$$

where the complex amplitude of the n-th harmonic C_n is calculated from Khokhlov–Zabolotskaya–Kuznetsov (KZK) equation,[32] $N_{\max}$ is the maximum number of the calculated harmonic, α_t is the absorption coefficient of the tissue, and I_0 is the sound intensity at the surface of the source.

We use COMSOL Multiphysics 3.5a, a finite element method software package, to simulate the temperature response in biological tissues based on the Pennes and TWMBT equations. Traditionally, the temperature distribution in biological tissue can be predicted from the Pennes equation[1]

$$\rho C_t \frac{\partial T}{\partial t} = K_t \nabla^2 T - W_b C_b (T - T_b) + Q_m + Q_v, \tag{2}$$

where ρ, C_t, and K_t are the density, specific heat capacity, and thermal conductivity of the tissue respectively, T is the temperature of the biological tissue, T_b is the temperature of blood, Q_m and Q_v are the rate of heat generation per unit volume due to the metabolism and external heat source respectively, W_b and C_b are perfusion rate and specific heat capacity for blood, respectively.

In COMSOL Multiphysics 3.5a, the model to describe the heat conduction is as follows:

$$\delta_{ts} \rho C_t \frac{\partial T}{\partial t} + \nabla \cdot (-K_t \nabla T) = C_b W_b (T_b - T) + Q_m + Q_v, \tag{3}$$

where δ_{ts} is the coefficient of time scale. Before the heating, the metabolism and the initial temperature of tissue (T_0) and blood (T_b) are related by $T_0 - T_b = Q_m / W_b C_b$. When heating, the heating induced by the metabolism is very small compared with the absorption from the ultrasound, therefore, we

can think that the external is the only heat source from ultrasound while the heat from the metabolism is set to be zero. So the blood temperature is equal to the initial temperature of the tissue, that is, $T_b = T_0$. The boundary condition is that the temperature outside the computation area is constant. If we set δ_{ts}=1, equation (3) is corresponding to Eq. (2), then we can use COMSOL Multiphysics 3.5a software to solve the Pennes equation. Q_{ext} can be calculated from Eq. (1).

The TWMBT equation in biological tissues can be expressed as[6]

$$\begin{aligned}&\nabla\cdot(K_t\nabla T(x,t))+W_bC_b(T_b-T)+Q_v+Q_m\\&+\tau\left(-W_bC_b\frac{\partial T}{\partial t}+\frac{\partial Q_m}{\partial t}+\frac{\partial Q_v}{\partial t}\right)\\&=\rho C\left(\tau\frac{\partial^2T(x,t)}{\partial t^2}+\frac{\partial T(x,t)}{\partial t}\right).\end{aligned}\tag{4}$$

To simplify the problem, Q_m, K, W_b, θ_0, τ, ρ, and C are assumed to be constants.

Considering that the heat source does not change with time, Eq. (4) can be rewritten as follows:

$$\begin{aligned}&\rho C\tau\frac{\partial^2T}{\partial t^2}+(\rho C+W_bC_b\tau)\frac{\partial T}{\partial t}+\nabla\cdot(-K_t\nabla T)\\&=W_bC_b(T_b-T)+Q_m+Q_v.\end{aligned}\tag{5}$$

In COMSOL Multiphysics 3.5a, the model of partial differential equation is as follows:

$$e_a\frac{\partial^2T}{\partial t^2}+d_a\frac{\partial T}{\partial t}+\nabla\cdot\Gamma=F.\tag{6}$$

If we set $\Gamma=-K_t\nabla T, F=W_bC_b(T_b-T)+Q_m+Q_v$, $e_a=\rho C\tau$, and $d_a=\rho C+W_bC_b\tau$, the model can describe the TWMBT equation, which can be solved by the software of COMSOL Multiphysics 3.5a.

We choose liver as the medium of numerical study: the central frequency of the transducer $f_0=2$ MHz, the radius $a=6$ mm, transducer geometry focal length $D=50$ mm, density $\rho=1050$ kg/m^3, the speed of sound $c_0=1580$ m/s, attenuation coefficient $\alpha=0.7$ dB/(cm/MHz), nonlinear coefficient $\beta=4.6$, $W_b=16.7$ kg/(m^3·s), $C=C_b=3500$ J/(kg·°C), and $k_t=0.640$ W/(m·°C).[33] The sound pressure at the surface of the transducer is $p_0=1.73\times10^5$ Pa. The computation area is $Z\in[0,2]$ and $R\in[0,1]$ (the axial distance is twice the focal length of the source and the radial distance is the same as the radius of the transducer).

3. Numerical results

The two-dimensional distribution of temperature rise caused by the heat deposition predicted by the Pennes equation can be seen in Fig. 1. If τ is set to be zero, and we use COMSOL Multiphysics 3.5a to solve the TWMBT equation, the result can be seen in Fig. 2, which corresponds to Fig. 1 well. It is demonstrated that the setting in Eq. (6) to solve the TWMBT equation is correct because when τ is zero, the TWMBT equation is reduced to the Pennes equation.

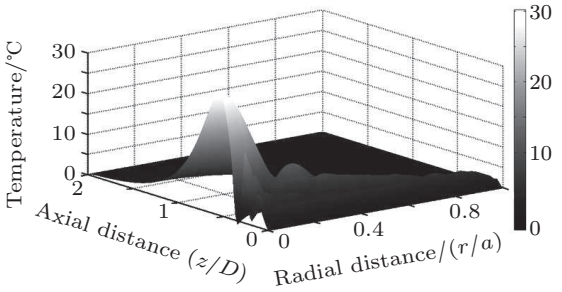


Fig. 1. Two-dimensional distribution of temperature rise caused by the heat deposition predicted by the Pennes equation.

Then we can set the different thermal relaxation times in the TWMBT equation and study its influence on temperature rise in biological tissues. Figure 2 shows that when the thermal relaxation time changes, the temperature distribution within the focus area of the tissue will not change significantly, but the maximum temperature rise changes. Figure 3 shows the temperature rise distribution along the axial direction at 90 s under different thermal relaxation times. Although the thermal relaxation times are different, the maximum temperature rises all occur at 0.53, which is 0.53 times the focal length at the axis of symmetry. Therefore the thermal relaxation time does not change the temperature distribution. When $\tau=0$ s, the maximum temperature rise is 30.33 °C; when $\tau=10$ s, the maximum temperature rise is 28.55 °C, reduced by about 1.78 °C; and when $\tau=20$ s, the maximum temperature rise is 26.18 °C, further reduced by about 2.37 °C. The maximum temperature rises in the tissue changing with time under different thermal relaxation times are shown in Fig. 4. At the beginning of ultrasound heating, the temperature rise is delayed due to the existence of the thermal process. Later on, the heat absorbed from ultrasound energy within the tissue gradually spreads evenly; the rate of the maximum temperature rise within the focus area begins to increase. Then the heat diffusion within biological tissue and blood flow of heat away begin to show their effects on temperature rise, the rate of the maximum temperature rise begins to decrease. The maximum temperature rise will eventually become stable. Therefore the effect of thermal relaxation time on the temperature rise under the focused ultrasound irradiation mainly reflects at the early stage of irradiation. It also shows that the influence of thermal relaxation time on the rate of the maximum temperature rise is of the order of τ, which intuitively gives the physical meaning of the thermal relaxation time. The greater the thermal relaxation time, the lower the maximum temperature rise is, which is very important in clinical practice. Due to thermal relaxation time, the temperature rise may be lower than that predicted from the traditional Pennes equation. Therefore

if doctors think that the temperature at the point of the tissue has reached the treatment demand while stopping ultrasound heating, they may not achieve the target of thermal ablation of target tissue due to the relaxation time.

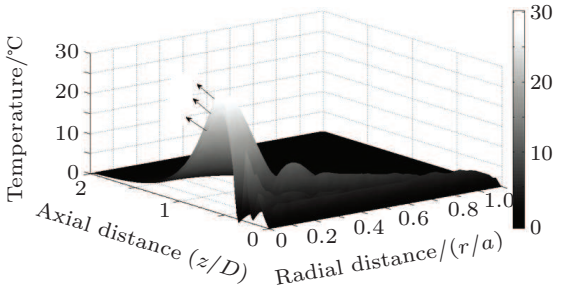


Fig. 2. Two-dimensional distributions of temperature rise caused by the heat deposition predicted by TWMBT ($\tau = 0$ s, $\tau = 10$ s, and $\tau = 20$ s).

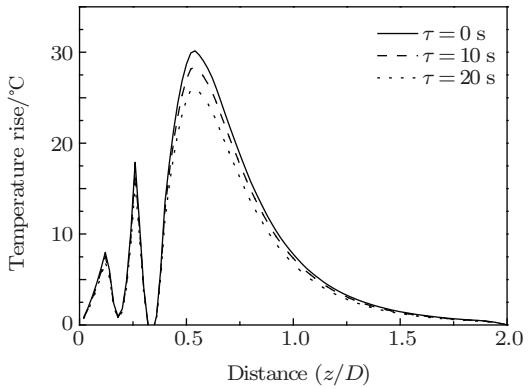


Fig. 3. Temperature rise distributions along the axial direction at 90 s under different thermal relaxation times from TWMBT equation, where the solid line is for $\tau = 0$ s, dashed line is for $\tau = 10$ s, and dotted line is for $\tau = 20$ s.

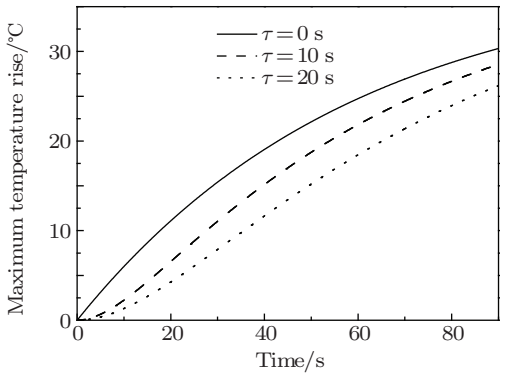


Fig. 4. Maximum temperature rises in the tissue changing with time under different thermal relaxation times from the TWMBT equation, where the solid line is for $\tau = 0$ s, the dashed line is for $\tau = 10$ s, and the dotted line is for $\tau = 20$ s.

We also consider the temperature rises under different values of thermal conductivity of the tissues. Setting the thermal relaxation time $\tau = 10$ s, Fig. 5 represents the maximum temperature rise in the tissue, changing with time under different values of thermal conductivity $K_t = 0$ W/(m·°C) and $K_t = 0.64$ W/(m·°C). Two curves are almost overlapped. The maximum temperature rise is 0.02 °C in the case of $K_t = 0$ W/(m·°C) higher than that of $K_t = 0.64$ W/(m·°C). So the effect of the energy dispersal factor on tissue temperature rise is very small. Next, we will discuss the effect of blood flow on temperature rise within the focus of the tissue under the radiation of ultrasound. Because the blood flow will take heat away, it will also affect the temperature rise within the tissue. Figure 6 shows the temperature rise changing with time in the presence and the absence of blood flow when the thermal relaxation time is $\tau = 10$ s. It shows that in the thermal wave model, although the rate of the temperature rise is suppressed at the early stage of heating due to the introduction of thermal relaxation time, with the increase of the time of the ultrasound heating, the influence of the thermal relaxation time on the temperature rise gradually disappears, the influence of blood flow on the temperature rise becomes obvious and becomes more apparent with the increase of the heating time. The maximum temperature rise in the tissue is eventually stable due to the fact that the heat is taken away by the blood flow.

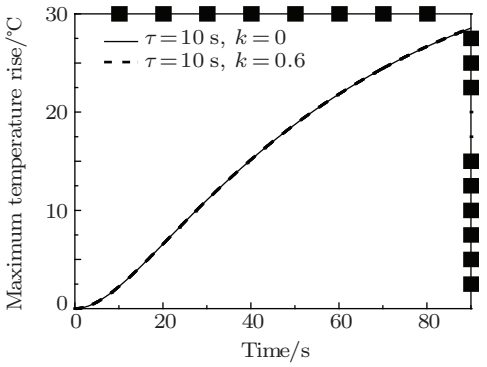


Fig. 5. Maximum temperature rises in the tissue, changing with time under different values of thermal conductivity of the tissue using thermal wave model when the thermal relaxation time $\tau = 10$ s, where the solid line is for $K_t = 0$ W/(m·°C), dashed line is for $K_t = 0.6$ W/(m·°C).

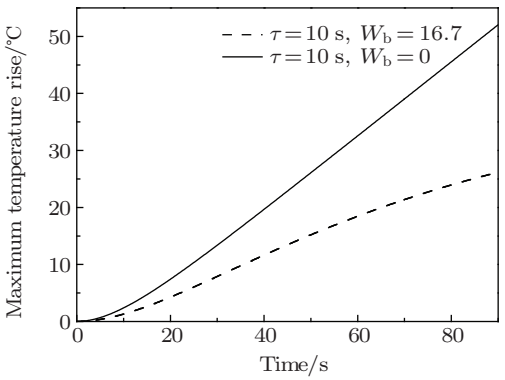


Fig. 6. Maximum temperature rises in the tissue, changing with time under different blood perfusion rates of the tissue using thermal wave equation when the thermal relaxation time $\tau = 10$ s, where the solid line is for $W_b = 0$ kg/(m^3·s), the dashed line is for $W_b = 16.7$ kg/(m^3·s).

4. Discussion

From the numerical results, we can find the following phenomena. (i) When the tissues are heated by the focused ul-

trasound, the rate of temperature rise around the focused area decreases. With the increase of the heating time, the influences of the blood perfusion and the heat diffusion on the temperature rise also gradually decrease, the temperatures of the tissues tend to be stable. (ii) The influence of the blood perfusion on the temperature rise is greater than that of the heat diffusion. (iii) Because of the thermal relaxation in thermal theory, the temperature rise delays at the beginning of the heating by ultrasound. The effect of the thermal relaxation on the temperature rise becomes weak with the increase of the heating time. Compared with calculations by the Pennes equation, the temperature rise predicted by the TWMBT equation is low under the condition of the same heating time. If we use the Pennes equation to predict the temperature elevation *in vivo* induced by ultrasound irradiation using the same parameters as those for the TWMBT equation, the actual temperature at the focus in the biological tissues under the same irradiation conditions may be too low to treat the tumor because of the thermal wave effect.

The Pennes equation predicts a temperature rise higher than that of the TWMBT at the beginning, because the Pennes equation is based on the concept of infinite heat propagation speed, while the TWMBT equation considers the heat propagation in living tissue at a finite speed, which requires a certain time for the heat to transfer to the inner tissue from the surface. Therefore there is a time delay between the heat flux vector and the temperature gradient across a material, which means that it needs more time to accumulate the heat to transfer to the nearest element of the tissue. This time lag causes longer thermal dissipation, so the temperature rise by the TWMBT equation is lower than that by the Pennes equation.

The time lagging behavior of the temperature becomes important for a rapid heating process, and the temperature decreases with thermal relaxation time increasing. If the heating duration is longer, there is no significant difference in temperature between with and without considering the effect of the thermal relaxation time. In other words, when the heating duration is relatively short, the results of the wave bioheat transfer equation are quite different from those from the Pennes bioheat transfer equation. On the other hand, under the irradiation of the source with higher intensity, there exists a larger temperature gradient inside the tissues, therefore the thermal relaxation time of the tissues becomes longer and the thermal wave effect becomes evident. In addition, reducing the overall treatment time is important and a rapid heating with high intensity scheme is therefore essential for an effective thermal therapy. Now hyperthermia and HIFU are very important for treating cancer and other diseases. Due to the high intensity and short duration of the treatment, the non-Fourier of TWMBT model may be more appropriate. During the treatment, the thermal relaxation of tissue will delay the appearance of peak temperature and reduce the thermal dose. Furthermore, damage to human tissue from thermal therapy is in the form of an exponential function of temperature,[28] so small improvement in the prediction of temperature can strongly influence the prediction of damage. Therefore, this study will exert an important influence on the therapeutic effect of the hyperthermia and HIFU.

5. Comparison

The experiments in Refs. [34]–[37] proved that the TWMBT model was feasible in evaluating the thermal performance of flame resistant fabric, where it was concluded that the TWMBT model can be more accurate than the previous model. Figure 7 shows the temperature profiles for the subsurface of the skin stimulant beneath the fabric sample. A better agreement is found between the temperature results measured by the skin simulated and those obtained from the numerical model at the value $\tau = 20$ s than that at the value $\tau = 15$ s. With the increase of the thermal relaxation time, the temperature rise decreases. The tendency is also the same as our theoretical prediction shown in Fig. 4. It is found that the measured temperatures are lower than theoretical predictions during 0 s–6 s while they are higher than the theoretical calculations during 6 s–30 s. The reason may be that the thermal properties (density, specific heat capacity, and thermal conductivity) of the sample are each a function of the temperature,[38] which leads to the thermal relaxation time changing with temperature while they are considered as constants in the theoretical analysis.

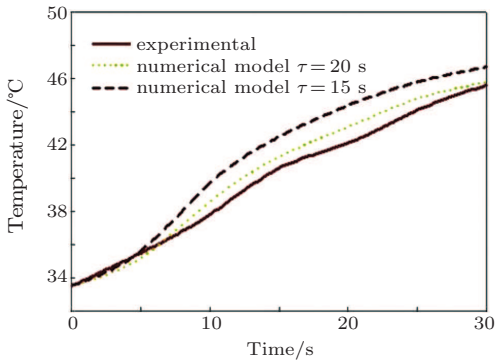


Fig. 7. (color online) Zhu's work (original figure is in Ref. [36], Fig. 6).

Jaunich *et al.*[39] conducted the bioheat transfer analysis of short pulses of laser irradiation on body tissues. They showed that the experimentally measured temperature distributions are consistent with the predictions made through the hyperbolic heat conduction model. Banerjee *et al.*[14] compared the measured temperatures with those obtained by the Fourier, as well as non-Fourier model and observed that the non-Fourier results accord with the experimental data. Further

experimental verification is necessary to measure the thermal relaxation time in living tissues and verify the theoretical predictions of the TWMBT model.

6. Conclusion

In this paper, using the commercial finite element software, we theoretically studied the temperature elevation induced by ultrasound irradiation in biological tissues. Considering the finite speed of heat propagation in biological tissues and their long thermal relaxation time, the effect of the thermal wave may not be neglected. The temperature elevations generated by ultrasonic irradiation predicted by the TWMBT equation are lower than those predicted by the Pennes equation. Due to the finite speed of wave speed of wave propagation, the temperature rise predicted by the TWMBT occurs with a time lag. The investigation of the physical mechanisms and behaviors of thermal wave propagation in biological tissues is expected to promote the development of clinical techniques such as hyperthermia and HIFU technology.

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