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NONLINEAR PROPAGATION MODELS IN ULTRASOUND HYPERTHERMIA

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INTRODUCTION

One of the most promising recent applications of ultrasound in medicine is hyperthermia treatment. Ultrasound has been employed as therapeutic agent for over four decades, especially because of its ability to selectively increase temperature of a volume of tissue. It is now known that this selective heating is due to the differing acoustic absorption properties of tissue [1] and the collagen content [2]. The attention which ultrasound hyperthermia has gained as a prospective treatment modality for cancer is reflected in the number of recently published papers on the topic. A rather comprehensive review of current knowledge in ultrasound hyperthermia is given in the Special Issue on hyperthermia and cancer therapy in the IEEE Transactions on Biomedical Engineering, [3] and the Special Issue on ultrasound hyperthermia in the IEEE Transactions on Sonics and Ultrasonics [4]. In addition, another review has been completed [5], and several papers were presented at the recent IEEE Ultrasonics Symposium [6].

At deep tumour sites, due to the absorption characteristics of tissue, focused ultrasound in 0.5 - 3 MHz frequency range is most appropriate for inducing hyperthermia. However, in the case of cutaneous or subcutaneous tumours, an unfocused sound wave can be used. Regardless of whether focused or unfocused ultrasound is employed, it is desirable to have a model for the precise and reliable prediction of the temperature increase at the insonified tissue volume. Several models have already been developed; they allow estimation of the termal distribution in irradiated tissue volumes [7] and account for influence of varying parameters such as sound velocity, density of the medium and object size [8]. However, most of the current models have been developed under the assumption that acoustic wave propagation is linear in the considered medium. Consequently, although those models do account for the geometry of the treated volume and the shape of the acoustic radiator [9], the attenuation of the medium [10], the rate of delivery of acoustic energy [11], and the blood flow or perfusion [12], they are not fully adequate to predict the temperature elevation because they negelect the effects of finite amplitude ultrasound propagating in the medium (tissue).

It is known that the attenuation in nonlinear media depends upon the local acoustic pressure amplitude for a given fundamental frequency. It is also known that such anomalous effects can occur in biomedical applications [13,14,15].

The work presented here represents a further refinement of the preliminary work presented by Haran and Lewin [16], and discusses the development of a nonlinear layered model of energy deposition in hyperthermia applications under plane wave irradiation conditions. It is a one dimensional model based on Burger's Equation [17,18,19]. The model allows the evaluation of heating patterns produced by ultrasound treatment in selected tissue volumes and concurrently it facilitates assessment of the dependence of temperature elevation on tissue nonlinearity. The model makes use of a series algorithm [19] and facilitates study the propagation of finite amplitude waves through multiple layered media similar to the situations encountered in hyperthermia treatment.

Only very recently has a theoretical study of the absorbed power generated by a focussed ultrasound beam been published which takes into account nonlinear propagation phenomena [20]. His theoretical work has been partially confirmed by in vivo experiments in dog thighs [21].

THEORETICAL BACKGROUND

A convenient analytical description of the nonlinear propagation can be obtained making use of Burgers' equation [17].

For a plane wave traveling in the x direction the incremental change of particle velocity U can be approximated by a truncated power of series of the form:

$$U(x + \Delta x,t) = U(x,t) + (\partial U/\partial x)\Delta x \tag{1}$$

where t denotes time and higher order terms have been neglected. To obtain the differential change of particle velocity with respect to x, one can employ the following version of Burgers' equation [22,23].

$$\partial U/\partial x = \beta U(\partial U/\partial \tau) + \Gamma(\partial^2 U/\partial \tau^2) \qquad (2)$$

$$\tau = \omega_0 t - kx$$

$$\beta = \omega_0(1 + B/2A) / c_0^2$$

where c_0 is the infinitesimal bulk wave velocity (dispersion is neglected).

B/A is the first term in the pressure density relation [17], ω is the angular frequency and k is the wave number. Γ is a constant related to the dissipation in the medium [22]. The continuous plane wave can be represented by a Fourier series and combined with the two equations above. The result is shown in the following expression for the incremental change of the particle velocity for the nth harmonic:

$$U_n(x+\Delta x) = U_n(x) - \{i\beta(\sum_{l=1}^{n-1} lU_lU_{n-l} + \sum_{l=n}^{\infty} nU_lU^*_{l-n}) + \alpha_0 n^b U_n\}\Delta x \qquad (3)$$

where α_0 is the attenuation coefficient for the fundamental frequency and b is the exponent of the power law behaviour of attenuation with frequency. Details of this derivation are given elsewhere [18,19]. There are two terms within the curly brackets of the last equation. The first term involves two summations and these represent the accretion and depletion of harmonics as the wave propagates over the incremental distance. The second term represents loss due to attenuation. In general, when the latter term dominates the effects of finite amplitude distortion are negligible. It has been shown that this is frequently the case in most soft tissues [19]. Given the knowledge of U(x) (eq.3), the calculation of the intensity, which is proportional to the square of the particle velocity, can be carried out. Subsequently, the rate of loss of acoustic energy to the propagating medium can be related to temperature rise.

Model of the tissue medium

In this work, tissue has been modelled as layered medium. Variations of attenuation were assumed to occur in the z-direction (depth) only, and the attenuation has been considered constant within each tissue layer. Although the overall attenuation is frequency dependent, the calculations have been performed at a single discrete frequency using a single value of attenuation for each layer, in order to simplify the computational requirements. The values of attenuation coefficient required in computation have been taken from published data [24]. Since absorption is perhaps the most dominant tissue property, the simulation did not include diffraction, scattering, refraction and dispersion effects. The influence of those parameters has been evaluated experimentally by determining the difference between the calculated and measured results (see Experimental).

Since a water path stand-off or delay is common in the application of therapeutic ultrasound and hyperthermia treatment, the model includes a layer of water path; this is followed by a layer of muscle and a layer of soft tissue.

In summary, the one dimensional model used in the present work consisted of three propagation layers. In addition the model allowed variation of the following parameters: i) length of the propagation layer, ii) initial source intensity, iii) fundamental frequency , and iv) the physical properties of the layers such as absorption, sound velocity, and second order nonlinearity parameter B/A. To simplify accounting for interface losses, the model assumed that plane continuous or quasi-CW waves were normally incident on plane boundaries.

EXPERIMENTAL

The experimental program has been carried out to verify validity of the computer model and to test the influence of neglecting the field parameters mentioned above. In particular, the influence of refraction effects was determined by using test cells filled with liquids such as Dow Corning Silicon Oil type 710 and SAE 30 motor oil. Those liquids were selected because they exhibit acoustic impedances close to that of water, yet their sound speeds differ from the sound speed of water. This minimised reflections of the sound beam due to the impedance mismatch. The refractive test cells were placed at the different axial distances from the source and the simulated and measured acoustic fields were compared.

Prior to the experiments, a careful calibration of the measurement system, comprised of an acoustic source, a wideband PVDF polymer hydrophone for sensing ultrasonic fields, an oscilloscope for monitoring temporal waveforms and a spectrum analyser, was performed. This initial calibration was carried out in a homogeneous nonattenuating medium (distilled, degassed water). The subsequent measurements were aimed at the verification of the validity of the theoretical model/computer simulations. These measurements were carried out in an attenuative medium (castor oil). The castor oil has been selected as the attenuative medium because castor oil acoustical properties are well documented.

A three layer model was constructed using the nonlinear equation (Eq. 3). The first layer represented water, and the path length was varied from 0 to 20 cm. The second layer represented muscle with a 3 cm thickness, and the third layer represented soft tissue (liver parenchema) 2 cm thick. Interface losses were computed assuming plane continuous waves normally incident on plane boundaries.

RESULTS

As the high intensity ultrasound wave travels through water, it is distorted, causing the generation of many higher frequency harmonics. These higher harmonics are more quickly attenuated upon entering a more dissipative medium like a soft tissue. The result would be less energy arriving at the target than linear theory would predict and not as much of temperature rise as might be expected or desired. Typical results are shown in Figure 1, where normalized intensity (normalized intensity is defined as a quotient of the intensity calculated according to the nonlinear propagation theory and the initial intensity at the face of the transducer) is plotted against range (propagation distance), correspond to a water path of only 2 cm long. The solid curve represents calculations based on the linear theory while the data points are based on the nonlinear model described above. There is little difference between those curves; however, as the propagation distance is increased to 10 and 15 cm (Figures 2 and 3, respectively) the differences become more significant.

The initial intensity is also a factor in this effect. This situation is depicted in Figures 4, 5 and 6. For a 20 cm water path, variation of the initial intensity from 10 to 30 to 60 W/sq.cm. results in significant changes in the energy delivered at the tumour site. It can be seen that the energy is being lost to the intervening layers of tissue through which the sound wave travels.

Figure 7 is perhaps a more straightforward presentation of these data. Here is plotted the intensity at the source versus the intensity after passing through three layers. The parameter being varied is the water path length. The solid line represents values calculated using the linear theory and the dashed lines are calculated using the nonlinear model applied to water path lengths of 5 to 20 cm.

CONCLUSIONS

The key to hyperthermia treatment using ultrasound is the delivery of a known amount of energy to the tumour site in order to raise its temperature a prescribed amount. It has been shown that the use of water path stand-offs or delays can lead to distortion of the wave and significantly reduce the amount of energy arriving at the tumour. Thus it is clear that nonlinear effects cannot be disregarded in the design of ultrasound hyperthermia treatment. While energy loss is predicted here for plane transducers, [20,21] has suggested a technique to increase the efficiency of hyperthermia treatment by exploiting the nonlinearity of tissue using focused transducers.

It has to be stressed that the model discussed here is only an approximation of the complex in vivo conditions existing during clinical ultrasound hyperthermia treatment and, as already mentioned, will need to be further refined. Also, the conditions simulated in the model may not cover all treatment regimes. However, the model is capable of demonstrating the significant factors to be considered in the design, application and calibration of hyperthermia devices. Thus the model may lead to optimisation of ultrasound hyperthermia and therapeutic procedures through: i) selection of frequency, transducer geometry and the length of water stand-off length, ii) reduction of the temperature rise of intervening (healthy) tissue layers, and iii) increased safety.

Another effect arising from the nonlinearity of the medium is the phenomena of acoustic saturation [17] which is characterized by a fixed amount of energy arriving at the tumour regardless of the source strength. The model discussed above can also be used to predict combinations of ultrasound frequency and water path length which may result in saturation at the tumour site.

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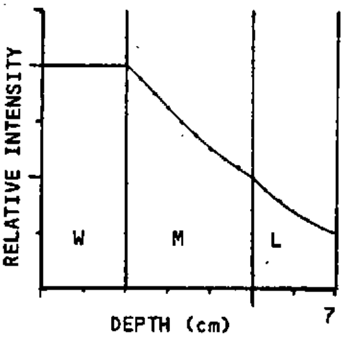


FIGURE 1.

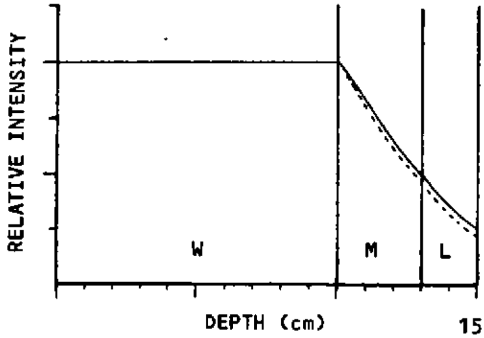


FIGURE 2.

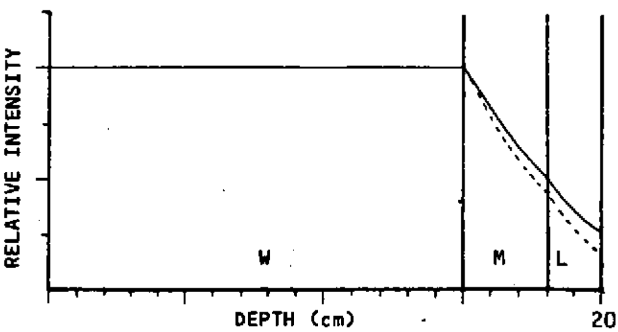
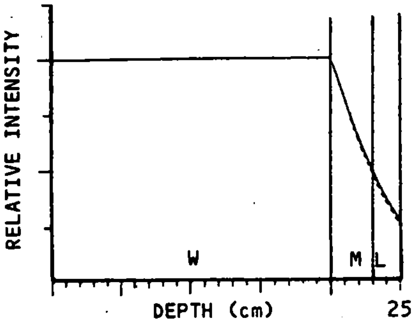


FIGURE 3.

NONLINEAR PROPAGATION MODELS IN ULTRASOUND HYPERTHERMIA



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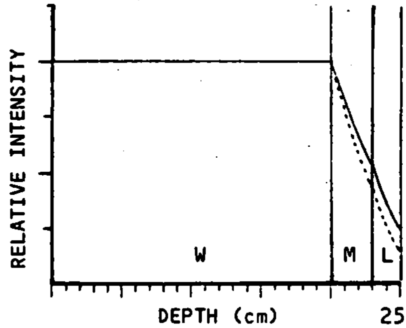

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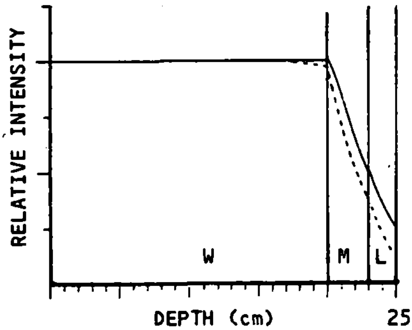

FIGURE 6.

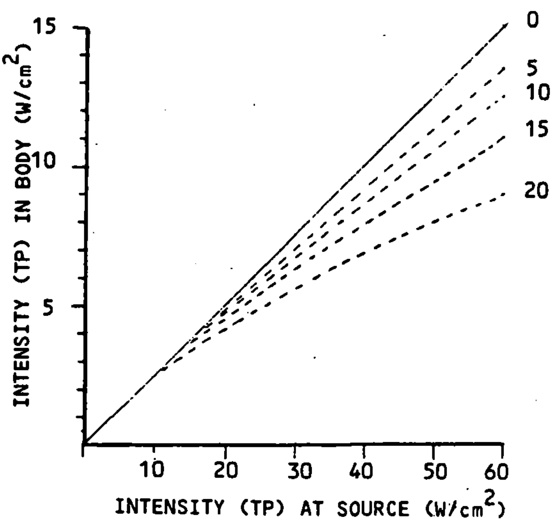

FIGURE 7.