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Analytical and numerical calculations of optimum design frequency for focused ultrasound therapy and acoustic radiation force

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ABSTRACT

Focused ultrasound therapy relies on acoustic power absorption by tissue. The stronger the absorption the higher the temperature increase is. However, strong acoustic absorption also means faster attenuation and limited penetration depth. Hence, there is a trade-off between heat generation efficacy and penetration depth. In this paper, we formulated the acoustic power absorption as a function of frequency and attenuation coefficient, and defined two figures of merit to measure the power absorption: spatial peak of the acoustic power absorption density, and the acoustic power absorbed within the focal area. Then, we derived "rule of thumb" expressions for the optimum frequencies that maximized these figures of merit given the target depth and homogeneous tissue type. We also formulated a method to calculate the optimum frequency for inhomogeneous tissue given the tissue composition for situations where the tissue structure can be assumed to be made of parallel layers of homogeneous tissue. We checked the validity of the rules using linear acoustic field simulations. For a one-dimensional array of 4 cm acoustic aperture, and for a two-dimensional array of $4 \times 4\ \mathrm{cm}^2$ acoustic aperture, we found that the power absorbed within the focal area is maximized at 0.86 MHz, and 0.79 MHz, respectively, when the target depth is 4 cm in muscle tissue. The rules on the other hand predicted the optimum frequencies for acoustic power absorption as 0.9 MHz and 0.86 MHz, respectively for the 1D and 2D array case, which are within 6% and 9% of the field simulation results. Because radiation force generated by an acoustic wave in a lossy propagation medium is approximately proportional to the acoustic power absorption, these rules can be used to maximize acoustic radiation force generated in tissue as well.

1. Introduction

High intensity focused ultrasound (HIFU) has a number of current and potential applications that are of critical importance in health care which are summarized in [1–4]: focused ultrasound (FUS) surgery, ultrasound assisted hemeostasis, thrombolysis and targeted drug/gene delivery. Among these, perhaps the most appealing of the potential uses is cancer treatment [5–8]. Either by ablating the cancerous tissue [9] (by taking advantage of the lower temperature stability of cancerous tissue compared to normal tissue), blocking blood flow to tumors, or by assisting anticancer drugs to specific locations [10] (which allows considerably higher doses of chemotherapy to be delivered to a specific location without systemic exposure), HIFU certainly promises an effective non-invasive cancer treatment methodology. All of these are enabled by the localized heat generated by the HIFU beam. Based on the acoustic intensity requirements, focused ultrasound therapy is typically divided into two categories: high-intensity ($\sim 5 - 10^4\ \mathrm{W/cm}^2$), and low-intensity ($<\sim 5\ \mathrm{W/cm}^2$), where high-intensity refers to permanent tissue damage and low-intensity refers to temporary heating that promotes another process (like healing after injury, or drug/gene release) [4].

There are three main challenges in HIFU: (1) The frequency and penetration depth are limited with ultrasound absorption, (2) self-heating of the HIFU probe (and related IEC standard 601-1) limit the power delivered to the target, and (3) image guidance to assist HIFU. Image guidance is very critical in target visualization, therapy planning, dosimetry and confirming the results. It also provides feedback during therapy by measuring the changes in tissue properties. Especially, changes in propagation and absorption properties of tissue require changes in the therapy procedure in real time. However, issues related to image guidance are beyond the scope of this study. This paper will focus on minimizing the effects of the former two challenges by optimizing the HIFU frequency for maximum power deposition. Using suboptimal frequency in HIFU reduces efficacy, penetration depth, and increases self-heating of the probe (while trying to deliver a prescribed amount of power to the target). Hence, frequency optimization will help us alleviate the limitations mentioned in the former two challenges. Although it is widely accepted that HIFU should be

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done at low-MHz frequency range (<3 MHz), which is because of the exponential increase in acoustic attenuation with frequency, a mathematical relationship between acoustic power absorption, target depth, tissue type (or phantom type for phantom studies) and frequency has not been established. To achieve our goal, we will establish these mathematical relationships, and derive expressions for optimum frequencies that maximize acoustic power absorption at a given depth for a given tissue type, which in return can be used as a guide in designing/choosing the therapy transducer for a specific application. Finally, we will verify the validity of the optimum frequency expressions we have derived using linear acoustic field simulations.

The required dose of acoustic power to achieve therapeutic effects is usually quoted in terms of spatial peak – pulse average acoustic intensity (I_{SPPA}) and duration. Mathematically, acoustic intensity alone is not a measure of HIFU dose unless it is combined with the absorption coefficient, which is a strong function of frequency. For example, an acoustic intensity requirement of $I_{SPPA} = 1000\ \mathrm{W/cm^2}$ at the focus is ambiguous in the sense that without the knowledge of the absorption coefficient (or frequency), the amount of the acoustic power that is absorbed is unknown. Therefore, it is better to use the acoustic power absorption rather than the acoustic intensity for frequency considerations. One of the two acoustic absorption metrics we will use is the acoustic power absorption density in Watts per cm^3 at a given point, which is the product of acoustic intensity and the power absorption coefficient at that point [11, pp. 495] as shown in the following equation.

$$P_{ac1} = a \cdot 2\alpha f^m I \tag{1}$$

Here, $I = p^2/Z_0$ is the acoustic intensity (or acoustic power flux density), p is the rms pressure, Z_0 is the acoustic impedance of the medium, α is the frequency independent attenuation coefficient, f is the frequency, m is the frequency dependence parameter of attenuation, and a is a proportionality constant that accounts for the relationship between attenuation and absorbed power [12]. Attenuation of ultrasound in tissue can be attributed to absorption and scattering, and only the absorbed portion of the ultrasound energy is converted into heat. The proportionality constant a, although determinant in the amount of heat generated, does not affect the frequency dependence of absorption. For the purpose of this study, we expressed the frequency dependence explicitly in Eq. (1) and defined α as the frequency independent attenuation coefficient (as opposed to [11] where frequency dependence is included in α).

The metric defined by Eq. (1) however, is somewhat misleading. The reason is the relationship between frequency, width of the focal spot and the focusing gain (defined as the ratio of the intensity at the focus to the intensity at the surface) of the transducer. For a fixed transducer aperture, the width of the focal spot decreases and the focusing gain increases as frequency is increased. In an attenuating medium, attenuation works against the focusing gain of the transducer, and beyond a critical frequency which we will determine, dominates the focusing gain. P_{ac1} is a point-wise measure (spatial peak) of the absorbed power density, and since the focusing gain increases with increasing frequency, P_{ac1} at the focal point tends to increase with frequency as well. That is, until before attenuation takes over. However, in almost all applications, the total power absorbed within the beam, which is the integral of P_{ac1} over the focal area, is a more useful metric (Eq. (2)). The reason is that, in most HIFU applications, the target volume is typically larger than the focal spot, and the temperature rise is driven by the total power deposited at the target site rather than the spatial peak of the power absorption density.

$$P_{ac2} = \int_{A_{beam}} P_{ac1}\, dA \tag{2}$$

Here, A_{beam} – the cross-sectional area of the beam – is also a function of frequency. Maximizing P_{ac2} maximizes the total acoustic power absorbed inside the focal spot. However, for sake of mathematical completeness and for possible applications that require frequency optimization using the metric defined by Eq. (1), we will develop our mathematical formulation for both metrics.

In some situations maximizing neither of these two metrics is a desired strategy. In HIFU applications, there is always a risk of collateral damage. In almost all situations, the highest risk of collateral damage is at the surface of the transducer because, next to the focal spot, the power density is highest at or very near the transducer surface. Typically, a circulating water stand-off is used in front of the transducer to avoid excessive heating at the transducer surface. When a cooling method is not used, it is better to maximize the ratio of the power absorbed at the focus to the power absorbed at the surface, which is actually equal to the power focusing gain of the transducer times the ratio of the acoustic absorption coefficients at the focus and at the surface. However, the power focusing gain itself is not a good measure of the ratio of the temperatures at these locations. The analysis of such a problem requires finite element simulations since the heat source at the surface is distributed. Such cases does not present simple solutions and are beyond the scope of this work.

One of the important aspects of ultrasound is harmonic frequency generation caused by nonlinearity. Harmonic generation forms the basis for the harmonic imaging modality, and has been studied extensively in diagnostic ultrasound [11, pp. 381]. Nonlinearity plays an important role in therapeutic ultrasound as well. Nonlinearity is an amplitude-dependent process, and produces harmonic content proportional to the higher orders of the fundamental field. Hence, for focused ultrasound beams, the most notable harmonic generation occurs at the focal region where the acoustic pressure is highest. Because of the dependence of acoustic absorption on frequency, harmonic frequency components of the ultrasound field will be absorbed more quickly than the fundamental component as the wave propagates in tissue. This has two important effects: the absorption of the harmonics will enhance the heat generation at the focus [13,14], and the effect of the harmonics will not extend much beyond the focal region. It was also pointed out by Bacon and Carstensen [13] that the overall effect of nonlinearity and harmonic generation on tissue heating is not important unless the ultrasound beam travels to focal region without notable attenuation (for example through a water column like amniotic fluid or urine). Duck and Perkins [15] also concluded that tissue losses inhibit the generation of harmonics, and so control the extent of amplitude-dependent losses. Nevertheless, we will limit our analytical and numerical analysis to linear ultrasound fields. Linear ultrasound field propagation is only an approximation to the finite amplitude wave phenomenon, but is the only way to derive analytical relationships and come up with transducer design guides for HIFU, which is the purpose of this study. Tissue nonlinearity will present a limitation for our results which will be discussed later in the Discussion Section.

Another phenomenon that might have a profound effect on ultrasound therapy is cavitation. It was shown that for highly focused ultrasound beams the acoustic intensity values at the focus might exceed cavitation threshold [16]. Cavitation produces powerful shock waves and causes tissue damage mechanically. When controlled, cavitation is a powerful tool for tissue ablation. However, it cannot be explained with simple analytical relationships, and therefore excluded from the scope of this work.

The formulations we will derive in this paper and then use to optimize the frequency for the power absorption metrics we have just defined is relevant to acoustic radiation force imaging (ARFI) as well. Acoustic radiation force is generated by momentum transfer from an acoustic wave to a lossy propagation medium,