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A new mechanical index for gauging the human bio-effects of low frequency ultrasound

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***Abstract*— Low frequency ultrasound has a diverse set of industrial and medical applications ranging from high power industrial ultrasound equipment through to various therapeutic medical applications. In recent years, several speech interface applications have also been developed which exploit the low ultrasonic frequency region to augment human-computer interfacing. These devices tend to operate just above the threshold of human hearing where signals can be generated and detected using off-the-shelf audio hardware components. Mechanical index has long been one of the main criteria used for determining safety limits for human exposure to ultrasound, however it is known to be inaccurate below about 500 kHz. This paper revisits the mathematical and physical foundations of the mechanical index, in particular transient cavitation, and applies these to the low-frequency ultrasound region. Simulations are performed to evaluate the effects on both blood and water. From the results, a new mechanical index formulation is proposed, which extends down to significantly lower frequencies. The aim is to provide a gauge for determining bio-effects of emerging and future low frequency ultrasonic applications operating around 20 kHz to 100 kHz.**

I. INTRODUCTION

Low frequency (LF) ultrasound has many applications including transdermal drug delivery [1], dentistry, eye surgery, body contouring, the breaking of kidney stones and eliminating blood clots [2]. Sound in this region tends to obey the familiar laws of audio, is easily handled by audio circuitry, devices and systems, and yet is inaudible to humans [3]. Encouraged by these advantages, several applications of LF ultrasound are emerging. A recent example includes ultrasonic speech systems [4], [5], where LF ultrasonic reflection is used to echo-map the human vocal tract. Other examples include the use of LF ultrasound for mouth state detection [6] and systems that use LF ultrasound as an aid to augment speech processing and recognition in noisy environments. Each of these has been made possible through the extension of speech autoregressive modelling tools upwards in frequency [7]. Despite these and other forthcoming applications, there are significant gaps in the coverage of published safety standards which govern the use of low frequency (therapeutic) ultrasound – and yet each example mentioned involves significant long term human exposure to the ultrasonic signals.

It is true that industrial ultrasound standards do extend to the LF region (since this is their predominant operating range), however the applications do not involve deliberate human exposure to the signals. Thus, these existing standards tend to focus on minimizing the risks to humans from airborne exposure. At present, there is no specific standard covering ultrasonic contact exposure for industrial applications [8].

TABLE I

MECHANICAL INDEX LIMITS AS SPECIFIED BY THREE SIGNIFICANT STANDARDS RELATING TO DIAGNOSTIC ULTRASOUND.

Standard	MI	Applications
US FDA [10]	1.9	All except ophthalmology
	0.23	Ophthalmology
IEC [9]	0.3-0.7	Industrial
BMUS [11]	0.3 *Restrict exposure time for lung/intestine*	
	0.7 *Potential hazard*	

By contrast, diagnostic medical ultrasound applications are predominantly contact methods, and thus several standards apply to ensure safety for high frequency applications. Thermal and mechanical indices (TI and MI respectively) are used to quantify ultrasound effects in IEC 60601 part 2-37 [9] and other significant standards. The formulation for TI extends directly to the LF range, however the direct application of MI as it is currently defined is extremely questionable in the LF ultrasonic region. For reference, Table I summarises the safe limits of MI as defined by the most significant standards relating to diagnostic ultrasound.

This paper will revisit the existing MI formulation theory in Section II, present simulations concerning its effectiveness (especially for LF ultrasound) in Section III, before proposing and exploring a modified definition of MI in Section IV. Section V then concludes the paper.

II. MECHANICAL INDEX

Introduced by Apfel and Holland in 1991 [12], MI serves as a means of quantifying the potential for bio-effects due to transient cavitation. If P_r is the peak rarefractional pressure in vivo in MPa and f is the frequency of the beam in MHz, then MI is defined as

$$MI = P_r/\sqrt{f} \tag{1}$$

This has been applied widely within the frequency range of 0.5–15 MHz [13], but we will see that it is questionable whether the classical MI formulation is an appropriate index for frequencies below about 500 kHz.

Eqn. 1 is based upon the solution of an analytical model developed by Apfel in 1986 [14] and later extended by Holland in 1989 [15]. The model describes the motion of

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a gas bubble in a liquid medium during the propagation of sound. The theory considers a stable bubble with initial radius R_0, in a state of stable equilibrium inside a liquid medium with ambient pressure P_0, density ρ, viscosity μ, and surface tension σ, initially at temperature T_0. During the negative, rarefaction, portion of the acoustic pressure field, the bubble can lose stability and grow rapidly. This occurs when the pressure amplitude becomes lower than the Blake pressure threshold. If P_0 is the ambient pressure and $X_B = 2\sigma/R_0P_0$ relates to the surface tension and initial bubble radius [16], then Blake pressure threshold can be defined as

$$P_B = P_0\left\{1+\frac{4}{9}X_B\sqrt{\frac{3X_B}{4(1+X_B)}}\right\} \tag{2}$$

Although this describes a pressure change, it is fundamentally a static phenomena and does not adequately explain the time-varying behaviour of the bubble in a modulating acoustic field. Thus the theory of Holland and Apfel [15] extends the cavitation relationship between pressure amplitude, bubble radius, medium characteristics and frequency. This describes a bubble of initial radius R_0 experiencing transient cavitation as the result of an acoustic wave with frequency f and pressure amplitude P_r. The collapse result in a maximum temperature of T_m inside the bubble.

First define p'_b is defined as the difference between normalised acoustic pressure p ($p = P_r/P_0$) and normalised Blake threshold, so that $p'_b = p-(P_B/P_0)$ (note, P_0 again denotes ambient pressure). γ is the ratio of specific heats of the gas inside the bubble and ξ is given as:

$$\xi = 2p - p'_b - 2 + \sqrt{(p-1)p'_b} \tag{3}$$

then we can define the relationship between bubble behaviour and acoustic wave frequency f as;

$$f = \frac{\frac{1}{3\pi R_0}\sqrt{\frac{P_0\xi}{\rho}}\left\{\sqrt{\frac{(p-1)}{p}}+\sqrt{\frac{p'_b}{p}}\right\}}{\left\{\frac{T_m}{T_0(\gamma-1)(\frac{\xi}{3}+1)}\right\}^{\frac{1}{3}}-0.46+\frac{4\mu}{R_0}\sqrt{\frac{2}{\rho P_0\xi}}+\frac{2\sigma}{P_0R_0}p_b'^{\frac{2}{3}}\sqrt{\frac{\xi}{3}}} \tag{4}$$

Several theoretical assumptions can be made to assist in solving the model described by (4), with the main ones being: (a) the expansion and collapse of the bubble occur during a single acoustic cycle, (b) the bubble experiences only adiabatic expansion and (c) the maximum internal collapse temperature is 5000 K in the gas trapped inside the bubble [15]. The temperature of 5000 K is considered to be high enough to produce potentially highly destructive free radicals during the collapse.

III. Evaluation of Mechanical Index

Replacing the characteristic parameters of the liquid (4) simply describes the variation of threshold pressure P_r with frequency f, given an initial bubble radius R_0. To derive the pressure threshold in the frequency range 20–500 kHz, we solve (4) using the Newton-Raphson method, for air bubbles of R_0 in the range of 1–100μm (where γ=1.4 for air bubbles). To maintain consistency with the published work of Apfel and Holland [12], two biological fluids are considered, namely blood and water. The following values are adopted for density, surface tension, and viscosity, respectively: water: ρ=1000 kg/m^3, σ=72 nM/m, and μ=0.001 Pa. For blood: ρ=1059 kg/m^3, σ=56 nM/m, and μ=0.005 Pa. The equilibrium hydrostatic pressure for both liquids was taken to be P_0=0.101325 MPa=1 atm, initial temperature T_0=300 K and maximum collapse temperature set to T_m=5000 K. Fig. 1 plots the variation of pressure threshold with initial bubble radius for the frequency range of 20–500 kHz in water. A similar graph is possible for blood.

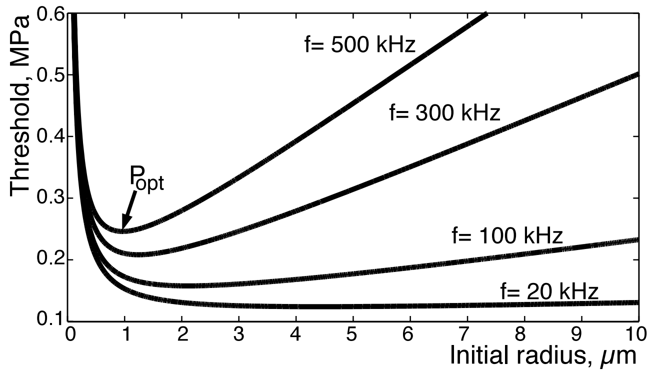


Fig. 1. Water cavitation threshold plotted as a function of initial air bubble nucleus radius for ultrasonic frequencies of 20, 100, 300 and 500 kHz. The assumptions of the calculations (following [12]) are; initial bubble temperature 300 K, growth of bubbles in a single cycle of ultrasound, and adiabatic collapse at a temperature of 5000 K.

Next, the threshold for inertial cavitation is derived as a function of frequency in a standard fashion [12], [13]. As observed in Fig. 1, for each frequency point f in the range 20–500 kHz, there exists a bubble size requiring minimum acoustic pressure to undergo transient cavitation at that frequency. The minimum acoustic pressure associated with this bubble size is the cavitation threshold P_t. Repeating this procedure for each frequency in the range, gives the variation of threshold pressure P_t with frequency. Fig. 2 demonstrates the variation of cavitation threshold for water and blood in the 20–500 kHz range.

Fitting the calculated data in Fig. 2, to a power law distribution with P_t in MPa and f in MHz gives

$$P_t = A + Bf^n \tag{5}$$

where A=0.10, B=0.216, n=0.6 for water and A=0.11, B=0.26, n=0.68 for blood with the sum of least square errors being 9×10^{-8}, 9×10^{-7} respectively. The water threshold data is also fitted to (5) since this is the basis of the definition of MI [12], but results in B=0.28, n=0.25 with the sum of least square errors being 0.0019. Fitting the data to $P_t = Bf^{1/2}$ results in B= 0.38 and the least square errors of 0.06. This means that while use of $P_t = Bf^{1/2}$ as the basis for the formulation of MI can still be considered valid in the LF range, it is less accurate in this range than at

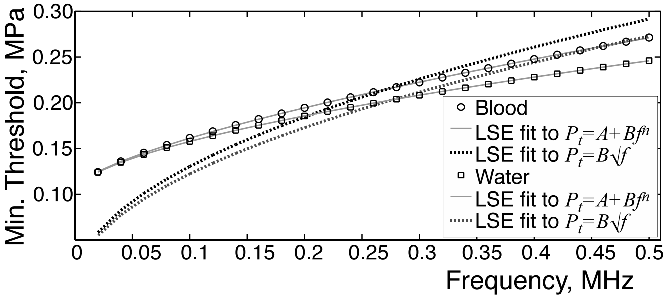
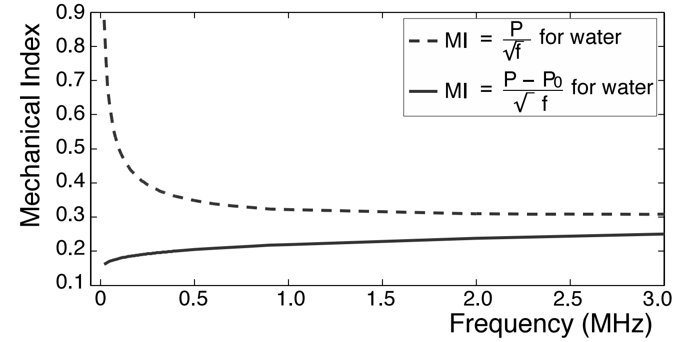
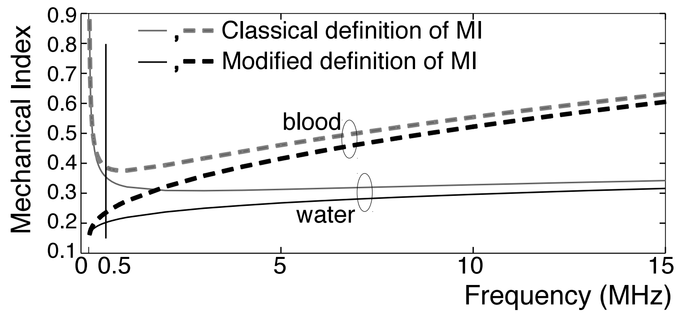


Fig. 2. Variation of minimum cavitation threshold for optimum sized bubbles in water and blood for a frequency range of 20–500 kHz. This assumes that all nuclei sizes are present [15]. The square and circle marks show the calculated values of threshold. Solid lines represent least square fit of the calculated data to a power law distribution. Dashed lines represent a least squares fit.



(a) 20 kHz to 3 MHz in water.



(b) 20 kHz to 15 MHz in both water and blood.

Fig. 3. Variation of the mechanical index based on the classic definition, and modified relationship, eqn. 6, for (a) LF and therapeutic ultrasonic range of 20 kHz to 3 MHz in water and (b) frequency range of 20 kHz–15 MHz in both water and blood.

higher frequencies. With decreasing frequency, the limit of the pressure threshold does not approach zero (as predicted by $P_t = Bf^{1/2}$) but, approaches the Blake threshold in a static under-pressure condition [16]. This is consistent with the observation of Church [13] indicating that a value of MI that is safe in terms of the likelihood of a cavitation-induced adverse bio-effect at high frequency may not be equally safe at low frequencies.

IV. Modified MI

With the decrease of frequency as the pressure threshold approaches [16], the linear resonant radius R_r increases[1] and the size of the optimal cavitation nuclei (R_0 being in the order of $R_r/3$ [17]) also increases. With increasing R_0 in (2), the Blake threshold approaches P_0. Accordingly, in fitting the calculated data to $P_t = A + Bf^n$, when f approaches zero, parameter A should have a value close to P_0. This is consistent with the best fit of $P_t = A + Bf^n$ to the calculated threshold data over the frequency range of 20–500 kHz. With mean values of A=0.105, B=0.238, n=0.64 for water and blood, parameter A can be safely replaced with P_0 (which was 0.101325 MPa in this model). Consequently, a modified index MI_{LF} can be proposed as

$$MI_{LF} = \frac{P - P_0}{\sqrt{f}} \tag{6}$$

(as previously, P and P_0 are in MPa and f is in MHz). To explore this in comparison with the classical definition of MI in (1), Fig. 3 plots both for the frequency ranges 20 kHz–3 MHz and 20 kHz–15 MHz respectively.

It is evident that the modified mechanical index provides less deviation in the LF range from observation. In addition the formulaic basis of this index ($P_t = A + Bf^n$) better describes the calculated data plotted in Fig. 2. Accordingly the formula in (6) provides a more accurate index for estimating cavitation in the frequency range of 20–500 kHz.

Thresholds for generating bio-effects of LF ultrasound have been extensively reported, but these vary with the type of cell or tissue being studied.

[1] For water under normal atmospheric pressure, the linear resonant radius R_r of spherical air bubbles which will resonate at frequency f is approximated as $R_r = 3.28/f; R_r \geq 0.01mm$ where f is in kHz and R_r in mm.

A. Supporting studies

A classic study by Hill revealed thresholds for inertial cavitation in a liquid suspension of cells to be near 1 $\mathrm{Wcm^{-2}}$ from 0.25 to 3 MHz [18]. For this range the variance in the classic index value is 6.1 times greater than the variation of the modified index. The threshold to produce observable lesions in human skin was determined by Boucaud et al. [19] to be 2.5 $\mathrm{Wcm^{-2}}$ at 20 kHz in vitro, which can be considered an extreme hazard limit for contact exposure to human skin at low frequencies. At this frequency, the classic and modified indices are evaluated as 1.94 and 1.2 respectively, both significantly below the onset of observable lesions.

B. Further tests

More human subject or human tissue experiments are, of course, necessary to derive exact safe limits of mechanical index in the LF ultrasonic region: especially as the number of low frequency ultrasonic applications grows. However it is clear that the modified index presented in this paper yields values that are more conservative, and which lie closer to the observations (for both water and blood) than the original MI.

It should be mentioned that for LF ultrasound-based human computer interface device experimentation – which may involve long term exposure to LF ultrasonic frequencies – cavitation in the coupling region near the skin surface is likely to pose the greatest bio-effect risk. At these frequencies and $110\,\mathrm{dB}_{SPL}$, $TI = 0.47$ and $MI = 4.4\times10^{-5}$, so airborne exposure need not be time-limited, however a sensible limit of no more than 200 minutes per day should probably be adopted for contact exposure [20].

V. CONCLUSION

Low frequency ultrasound has a wide range of therapeutic and industrial applications. In addition, novel emerging usages are being introduced in this range, including transdermal drug delivery [1], blood brain barrier disruption and ultrasonic speech [5] which subject the human body to this type of signal, and potentially for sustained exposure. Gaps in the existing medical and industrial standards for LF exposure, and the introduction of new research trends in this frequency range, increase the importance of adequate safety standards and associated studies of potential hazards. This paper has taken a quantitative approach to safety for LF ultrasound. It investigated the mechanical index, which is one of the main bases for current ultrasonic safety standards (primarily for high frequency ultrasound), and extended the analysis to the LF ultrasonic range. Starting with the established theory of Holland and Apfel [15], numerical simulations and analyses were conducted for ultrasonic effects on blood and water, leading to a proposed modification in the definition of mechanical index. This new index has been proposed to more accurately describe cavitation thresholds for LF ultrasound.

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