The mechanism of nanoparticle-mediated enhanced energy transfer during high-intensity focused ultrasound sonication

Chandan Bera,†*a Surendra B. Devarakonda,‡b Vishal Kumar,‡a Ashok K. Ganguli‡c and Rupak K. Banerjee‡†d

In this combined experimental and theoretical research, magnetic nano-particle (mNP) mediated energy transfer due to high intensity-focused ultrasound (HIFU) sonication has been evaluated. HIFU sonications have been performed on phantoms containing three different volume percentages (0%, 0.0047%, and 0.047%) of mNPs embedded in a tissue mimicking material (TMM). A theoretical model has been developed to calculate the temperature rise in the phantoms during HIFU sonication. It is observed from theoretical calculation that the phonon layer at the interface of the mNPs and TMM dominates the attenuation for higher (0.047%) concentration. However, for a lower concentration (0.0047%) of mNPs, intrinsic absorption is the dominating mechanism. Attenuation due to the viscous drag becomes the dominating mechanism for larger size mNPs (>1000 nm). At a higher concentration (0.047%), it is observed from theoretical calculations that the temperature rise is 25% less for gold nano-particles (gNPs) when compared to mNPs. However, at lower concentrations (0.0047% and 0.002%), the difference in temperature rise for the mNPs and gNPs is less than 2%.

The effect of larger size Fe₃O₄ microcapsules coated with PLGA has shown possible enhancement in hyperthermia during an HIFU procedure.8 Here, the size of the microcapsules used are considerably larger (886 nm) and the acoustic power used is significantly high (250 W). Such higher powers are known to cause skin burns and damage to neighboring healthy cells.9,10 To measure the HIFU-induced temperature rise (ΔT), three (0%, 1%, 3%) volumetric concentrations (φ) of magnetic nano-particles (mNPs) embedded in a tissue-mimicking material (TMM) have been studied by our group.4 However, the φ used has been non-physiological and the measurements are known to have artifacts due to direct focusing of the HIFU beam on the thermocouples (TCs).

Experimental investigations have suggested attenuation to be the main cause for the rise in temperature during HIFU therapy.3–6 However, there is a lack of fundamental understanding of the physics behind HIFU attenuation and the associated increased ΔT in media such as ferrofluids or NPs embedded in a TMM. A few theoretical investigations have been conducted to compute the HIFU propagation using fluid dynamics principles such as “streaming theory” in fluids and the heat transfer mechanism in TMMs.6,11–14 However, the mechanistic principles linked to NP mediated hyperthermia during HIFU sonication have not been reported previously by other researchers. This research is innovative because it provides fundamental understanding of the mechanistic principles of HIFU attenuation and the associated enhanced temperature rise in tissue.

Introduction

Hyperthermia directed to tumor cells using high intensity focused ultrasound (HIFU) has attracted a lot of interest.1–6 The HIFU treatment (ablation) is a non-invasive alternative to conventional surgical procedures. However, one of the major problems associated with HIFU procedures is controlled therapeutic delivery of energy (heat) to the tumor site, while minimizing collateral damage to the surrounding healthy tissue. To reduce collateral damage, microcapsules and nano-particles (NPs) have been used as energy absorbers at the tumor site during HIFU sonication.4,7,8 This combined experimental and theoretical research is significant because the use of NPs has the potential to address a major unmet need in the hyperthermia field that has existed for decades and could dramatically change the procedure of ablation under clinical settings by avoiding (a) uncontrolled cavitation and (b) any potential collateral damage to normal surrounding tissues.

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rsc.li/pccp

DOI: 10.1039/c7cp03542j

Accepted 3rd July 2017
Received 25th May 2017

Published on 03 July 2017. Downloaded by UNIVERSITY OF CINCINNATI on 1/30/2019 4:03:47 AM.
mimicking materials embedded with NPs. Such findings can be extended to tissue ablation during HIFU sonication under clinical settings.

The HIFU absorption in media embedded with NPs depends on thermal processes within the viscous and phonon layers at the interface of the metal NPs as well as on the intrinsic absorption properties of the media.\textsuperscript{14–17} Fig. 1 is a schematic representation of different mechanisms during ultrasound propagation in a medium with mNPs.\textsuperscript{14} The incident HIFU wave on any medium undergoes scattering, absorption, and transmission (Fig. 1A). The intrinsic absorption attenuation coefficients in NPs and media have been calculated following Brawer et al.\textsuperscript{16} and the theory of strokes.\textsuperscript{17} Propagating HIFU waves in a medium also interact with the thermal phonons and consequently, a part of the wave is absorbed. Due to the wave absorption, there is an increase in the momentum of thermal phonons inside the medium. The rise in momentum sets up heat flow in the direction of HIFU propagation. The flow of thermal phonons generates a phonon layer surrounding the mNPs (Fig. 1B). The HIFU attenuation due to the formation of a phonon layer has been calculated using a theoretical formulation.\textsuperscript{14}

In addition, viscous drag is established around the mNP as the wave propagates (Fig. 1C), due to the density difference between the medium and the mNP. The HIFU attenuation due to the density difference at the interface between the mNPs and the medium has been calculated using a stress–strain relationship for isotropic elastic solids.\textsuperscript{15}

In this research, a theoretical model is developed to predict the $\Delta T$ in mNPs embedded in a TMM during HIFU sonication. Using the theoretical model, the intrinsic absorption, as well as phonon layer and viscous drag attenuation coefficients for mNPs embedded in a TMM have been evaluated. In addition, $\Delta T$ has been compared between gold nano-particles (gNPs) and mNPs embedded in a TMM using the theoretical model. Experiments have been performed on tissue phantoms containing a TMM with $\phi$ of 0%, 0.0047%, and 0.047% mNPs. Each tissue phantom has been embedded with four TCs and HIFU sonication has been performed in the center of the TC array using an acoustic power of 14.5 W. The temperature data during the sonication have been recorded at each embedded TC. An inverse algorithm\textsuperscript{16,19} has been used to calculate the $\Delta T$ at the focus. The combined experimental and theoretical research is unique because it elucidates the contribution of three modes of HIFU attenuation: (a) viscous and (b) phonon layers at the interface of variable sized NPs; and (c) intrinsic absorption within the tissue mimicking material, leading to enhanced temperature rise. To our knowledge, mechanistic principles for evaluating acoustic attenuation and the associated $\Delta T$ during HIFU procedures in media embedded with mNPs or gNPs have not been reported elsewhere.

**Methods**

The experimental method for the preparation of the TMM embedded with mNPs and the measurement technique of the focal temperature have been discussed. Subsequently, a theoretical model for the temperature rise in the TMM embedded with NPs during HIFU sonication has been assessed. Three mechanisms of attenuation (intrinsic absorption, phonon layer, and viscous drag) leading to the temperature rise in the TMM phantom are discussed in the theoretical model. Furthermore, the equation for the temperature rise has been derived by solving the thermal transport equation, which includes the effect of acoustic attenuation mechanisms.

**Preparation of the TMM**

Three cylindrical fixtures embedded with an array of four thin-wire TCs have been developed. The TCs (labeled T1–T4) with a diameter of 0.003 inches have been arranged in two layers (Fig. 2A). Each layer has two TCs and is separated by a distance of 4 mm. The layers are 3 mm apart in the axial direction. A 35.34 mL gelrite-based TMM has been prepared according to the protocol of King et al.\textsuperscript{20} To prepare a tissue phantom with 0% mNP concentration by volume, the 35.34 mL liquid TMM has been poured into the first fixture until the fixture is filled. The construction of phantoms with mNPs has been explained in detail by Dibaji et al.\textsuperscript{21} Utilizing this method, phantoms with 0.0047% and 0.047% mNP concentration have been fabricated. Also, the TEM imaging and XRD of the mNPs have been performed (Fig. 3). The TEM image shows monodisperse nanoparticles of size ~10 nm. The XRD pattern of the mNPs agrees well with JCPDS PDF file no. 01-071-6336 of Fe$_3$O$_4$, which demonstrates high crystallinity of the mNPs.
Sonication procedure

Fig. 2B, shows the transducer (H102, Sonic Concepts Inc., Bothell, WA) having a focal length of 6.26 cm, outer diameter of 6.4 cm, and inner diameter of 2.2 cm. An operating frequency of 1.025 MHz has been used for the transducer which is driven in a continuous-wave mode using a signal generator (33220A, Agilent Technologies). A 150 Watt amplifier (150A100B, Amplifier Research) has been used to amplify the signal. A positioning system has been used to adjust any of the coordinates (x, y, and z) in discrete 0.025 mm increments.

A period of 30 s has been used for the sonication of the transducer. The temperatures from the TCs have been recorded using an OMB-DAQ-56 (Omega Engg. Inc., Stamford, CT) data acquisition system. The temporal resolution of the temperature measurements is 0.5 s. An acoustic power of 14.45 W is used for the sonication. Three trials (n = 3) have been performed for each φ.

Focal temperature measurements

High resolution micro-CT (Inveon Multimodality System, Siemens Inc., Germany) has been used to scan the tissue phantoms. The processing and acquisition software of the CT scan are Inveon Research Workplace 4.2 and Inveon Acquisition Workplace (IAW) 2.0.2, respectively. Precise locations of the TC junctions are determined using the CT scan and are later used in the inverse algorithm to determine the location of the beam focus.18,19

Here, the coordinates of the beam focus are treated as unknowns. The location of the beam is adjusted until the difference between the computed temperature rise at the subarray nodes and experimentally measured values at those locations is minimized. The location of beam-focus is determined at the location having the minimum error. Later, the beam location is used in the exponential integral to determine the temperature variations. The temperature distribution as a function of time is

\[
T(r,t) = \frac{2\pi f_0 r_0^2}{2\kappa_f \rho_c C_f} \left[ \text{Ei} \left( \frac{-r^2}{2r_0^2} \right) - \text{Ei} \left( \frac{-r^2}{2r_0^2 + 4\kappa_f t r_0^2} \right) \right] \quad (1)
\]

where \( \text{Ei}(x) \) is the exponential integral:

\[
\text{Ei}(x) = -\int_{-x}^{\infty} \frac{e^{-s}}{s} \, ds
\]

The on-axis intensity is calculated in the plane of T1–T2 (at 1.5 mm away from the focus) using the exponential integral. Considering the HIFU beam being Gaussian near the axis where the lesion is formed, the power (on-axis intensity times beam area) is constant along the axis near the focus. The beam width at the focus is calculated by equating the power at the focus and the power in the T1–T2 plane. The calculated intensity and the beam width are further used in the exponential integral to obtain the temperature variations at the focus.

Theoretical model

Attenuation coefficients. The temperature rise in the TMM phantoms embedded with NPs is caused due to acoustic attenuation from three mechanisms: (a) intrinsic absorption, (b) phonon layer, and (c) viscous drag. The net attenuation due to the three mechanisms is obtained by

\[
\alpha_{nf} = \alpha_a + \alpha_t + \alpha_v \quad (2)
\]

The total intrinsic absorption coefficient (\( \alpha_a \)) is a combination of the intrinsic absorption coefficients of the NPs and the medium,

\[
\alpha_a = \phi \alpha_{np} + (1 - \phi) \alpha_f \quad (3)
\]
The intrinsic absorption attenuation coefficient ($\alpha_t$) for the medium is calculated using the theory of Stokes\textsuperscript{17} and is calculated by the equation below:

$$\alpha_t = \frac{2\eta \omega^3}{3\rho_0 T_r^2}$$  \(\text{(4)}\)

The intrinsic absorption attenuation coefficient ($\alpha_{np}$) for NPs is calculated using the equation\textsuperscript{16} below:

$$\alpha_{np} = 1.1 \frac{\gamma^2 \omega^3 C_{np} T_{abs}}{v_{np}^3}$$  \(\text{(5)}\)

where $\gamma^{-1} = \frac{1}{T_b} + \frac{1}{T_{np}}$.

The HIFU attenuation coefficient due to the phonon layer is calculated using the following equation:\textsuperscript{14}

$$\alpha_t = 12 \frac{\phi}{k^2 d^2} \rho_0$$  \(\text{(6)}\)

The viscous drag attenuation coefficient is calculated from the equation\textsuperscript{14} below,

$$\alpha_v = \frac{18}{4Y^4 (\frac{\rho_t}{\rho_{np}} + 2)^2 + 36Y^3 (\frac{\rho_t}{\rho_{np}} + 2)^2 + 162 (\frac{\rho_t}{\rho_{np}})^2} Y(Y + 1)$$

$$\text{where } Y = \left(\frac{\omega}{v_s}\right)^{1/2}$$

### Temperature rise in the TMM.

The equation representing the heat transfer mechanism through solid spheres suspended in a medium is presented below:\textsuperscript{14,22}

$$\frac{\partial T}{\partial t} - \frac{k}{\rho_c C_{cf}} \nabla^2 T = \frac{\rho_0 \beta P_t \nu_{ref} e_{ref}}{\rho_{cf} C_{cf}}$$  \(\text{(8)}\)

The 2nd term of the LHS in eqn (8) is neglected as the calculated temperature rise at the focus of the HIFU beam is considered to be isotropic in and around the focal region. The RHS of eqn (8) is the coupling term of HIFU pressure and temperature.\textsuperscript{22} To solve eqn (8), the pressure term ($P_t$) is replaced by power ($P_0$) of HIFU using the relationship $P_t = \frac{P_0 e^{2\pi v_{ref} t}}{A v_m}$. The heat wave parameter ($T_0$) is obtained from Allegra et al.\textsuperscript{14} Eqn (8) is solved along with the attenuation coefficients (eqn (3), (6), and (7)) to derive the temperature rise through the TMM embedded with NPs.

Furthermore, eqn (8) is integrated to give the equation for temperature rise ($\Delta T$) due to HIFU attenuation as,

$$\Delta T = \int_0^t \frac{T_0 \beta v_{ref} e_{ref} P_0}{\rho_{cf} C_{cf} A v_m} e^{2\pi v_{ref} t} \, dt$$  \(\text{(9)}\)

where $C_{nf}$ is the heat capacity, $v_{ref}$ is the sound velocity in the medium, $A$ is the area of the HIFU beam, $T_0$ is the heat wave parameter, $v_m$ is the particle velocity, and $P_0$ is the HIFU acoustic power. A beam focal radius ($r_{beam}$) of 1 mm has been considered based on the HIFU transducer used in the experiment. This theoretical formulation has been derived assuming a spherical shape for the NPs. It is also assumed that all NPs are well separated so that the phonon and viscous layer of one NP is not interacting with surrounding NPs within the TMM.

### Results

Fig. 4, shows the comparison of experimental and theoretical $\Delta T$ at the HIFU-beam focus in the TMM embedded with 10 nm size mNPs, for a frequency of 1.025 MHz. The theoretical $\Delta T$ has been calculated using eqn (9) with the TMM as the medium using the physical properties provided in Table 1. The experimental error bars represent the standard deviation over three trials ($n = 3$). For the $\phi$ of 0% and 0.0047% mNPs, the theoretical and experimental $\Delta T$ agree within 5% at all time-points, whereas for a $\phi$ of 0.047% this difference is less than 7% for the initial 10 s of sonication time. At 10 s, the experimental and theoretical $\Delta T$ values for a $\phi$ of 0.047% mNPs are 21.1°C and 19.6°C, respectively. Beyond 10 s, the theoretical $\Delta T$ plateaued earlier than the experimental $\Delta T$ and the maximum difference between the two is 23% at 30 s. There is close agreement between the experimental and theoretical $\Delta T$ for all $\phi$ during the first 10 s of sonication, which is indicative of accurate accounting of the energy source or deposition as input. The difference in $\Delta T$ after 10 s for higher $\phi$ (0.047%) may be due to the assumption of homogeneous heat diffusion in the thermal transport equation (eqn (8)) which could lead to saturation in the theoretical $\Delta T$ for longer sonication times.

![Fig. 4](image-url) Temperature rise ($\Delta T$) in the TMM for $\phi$ of 0%, 0.0047%, and 0.047% of mNPs for a power ($P$) of 14.5 W for a sonication period of 30 s. Symbols represent experimental values and lines represent values from theoretical calculations.
Table 1 List of physical properties of the TMM, mNPs, and gold nano-particles (gNPs) used in eqn (1)–(9)

<table>
<thead>
<tr>
<th>Materials</th>
<th>TMM</th>
<th>Fe3O4 (mNPs)</th>
<th>Gold (gNPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isobaric specific heat, (c_p) (J kg(^{-1}) K(^{-1}))</td>
<td>4064</td>
<td>651.26</td>
<td>129</td>
</tr>
<tr>
<td>Density, (\rho) (kg m(^{-3}))</td>
<td>1040</td>
<td>5.17 \times 10^3</td>
<td>19.3 \times 10^3</td>
</tr>
<tr>
<td>Thermal conductivity, (k) (W m(^{-1}) K(^{-1}))</td>
<td>596.0 \times 10^{-1}</td>
<td>7</td>
<td>3.17 \times 10^2</td>
</tr>
<tr>
<td>Bulk modulus, (K) (Pa)</td>
<td>2.24 \times 10^{11}</td>
<td>1.24 \times 10^{11}</td>
<td>2.20 \times 10^{11}</td>
</tr>
<tr>
<td>Gruneisen parameter, (\gamma)</td>
<td>—</td>
<td>1.33</td>
<td>3.0</td>
</tr>
<tr>
<td>Viscosity, (\eta) (Pa s)</td>
<td>1000 \times 10^{-3}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Volumetric thermal expansion coefficient, (\beta) (K(^{-1}))</td>
<td>2.748 \times 10^{-4}</td>
<td>11.8 \times 10^{-6}</td>
<td>42 \times 10^{-6}</td>
</tr>
<tr>
<td>Poissons ratio, (\nu)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Ultrasound velocity (m s(^{-1}))</td>
<td>1468</td>
<td>4897</td>
<td>3053</td>
</tr>
</tbody>
</table>

Fig. 5 reports the contribution of the intrinsic absorption, phonon layer, and viscous drag attenuation coefficients for various sizes of mNPs with \(\phi\) of (a) 0.0047% and (b) 0.047%. For the mNPs, up to the size of 11 nm and \(\phi\) of 0.0047%, the contribution of the intrinsic attenuation coefficient is greater than the phonon layer attenuation coefficient (Fig. 5A). However, for a higher \(\phi\) (0.047%) of mNPs, a similar trend is observed up to the size of only 3 nm (Fig. 5B). For the mNPs, up to the size of 60 nm and for a lower \(\phi\) (0.0047%), the contribution of the intrinsic attenuation coefficient is greater than the viscous drag attenuation coefficient (Fig. 5A). However, for a higher \(\phi\) (0.047%) of mNPs, a similar trend is observed up to the size of only 20 nm (Fig. 5B).

In the mNP size range of about 11 nm to 1000 nm, the phonon layer remains the dominating attenuation mechanism contributing to increased \(\Delta T\). HIFU attenuation in media embedded with NPs depends on the thermal and shear wave propagation in NPs and media. The thermal and shear waves produced at the boundary of the NPs lead to the formation of a phonon layer and viscous drag, respectively. Phonon layer attenuation is maximum when the thermal wavelength is equal to the particle size. It is expected that the thermal wavelength is about 1000 nm for the concentration of mNPs used in this study. 14 Therefore, a peak in HIFU attenuation due to viscous drag is observed at mNP size of about 2000 nm. Subsequently, the total attenuation reduces gradually for higher sizes (>2000 nm) of mNP. For the mNP size (10 nm) and \(\phi\) of 0.047% used in this study, attenuation through the phonon layer is the dominating mechanism compared to viscous drag and intrinsic absorption. Similarly, for the 10 nm mNPs, the contribution of phonon layer attenuation and viscous drag attenuation for a higher \(\phi\) (0.047%) is an order of magnitude greater than at a lower \(\phi\) (0.0047%). Consequently, the \(\Delta T\) is 30% more for higher (0.047%) \(\phi\) as compared to a lower (0.0047%) \(\phi\) at a fixed power of 14.5 W (Fig. 4). Thus, this research is innovative as it elucidates the principles of HIFU attenuation and the associated enhanced temperature rise in a TMM embedded with NPs.

Fig. 6, shows the variation of \(\Delta T\) with acoustic power after 30 s of sonication for the TMM embedded with mNPs. The \(\Delta T\) has been calculated using eqn (9) for the mNP size of 10 nm and for the \(\phi\) of 0%, 0.0047%, and 0.047%. At all powers, the

![Fig. 5](https://example.com/fig5.png) Different attenuation mechanisms in the TMM with mNP size. (A) For 0.0047% \(\phi\) of mNPs and (B) for 0.047% \(\phi\) of mNPs. The black line is for total attenuation, the red line is for the phonon layer, the blue line is for viscous drag, and the magenta line is for intrinsic absorption (both X and Y axes are in a logarithmic scale).
increase in $\Delta T$ is about 20% and 60% higher for the TMM with $\phi$ of 0.0047% and 0.047% mNPs, respectively, when compared to the TMM with $\phi$ of 0% mNPs.

Fig. 7, reports the theoretical $\Delta T$ variation with time in mNPs and gNPs embedded in the TMM. A size of 10 nm and three $\phi$ values (0.002%, 0.0047%, and 0.047%) are considered for the theoretical calculations. For a higher $\phi$ (0.047%), the peak $\Delta T$ after 30 s of sonication is $\sim$ 25% lower for gNPs when compared to that of mNPs. Similarly, the peak $\Delta T$ is $\sim$ 2% lower for gNPs when compared to that of mNPs for lower $\phi$ (0.0047% and 0.002%). This could be because, the lattice thermal conductivity and volumetric expansion coefficient for gNPs are very high compared to mNPs. This causes the phonon layer interface of gNPs to become relatively more isotropic within the TMM leading to lower HIFU attenuation in the phonon layer. Hence, intrinsic absorption becomes the dominating HIFU attenuation mechanism in gNPs for the size of 10 nm resulting in comparatively lower $\Delta T$.

By suitably selecting the power at a particular frequency, it is possible to optimize the $\Delta T$ during the HIFU procedure for hyperthermia application. The HIFU attenuation due to viscous drag starts to play an important role for particle sizes greater than 1000 nm. For large size ($\sim$ 1000 nm) particles, $\Delta T$ is significantly enhanced and it can induce thermal damage to neighboring healthy cells during clinical applications. A moderate $\Delta T$ can be obtained by using a NP size of $\sim$ 10 nm and an acoustic power of $\sim$ 8–15 W. In other words, at these low power levels the $\Delta T$ can be localized around the NPs in the focal zone through the phonon layer attenuation and minimize the diffusion of heat into the surrounding tissue. This may allow reduced collateral damage to surrounding normal tissues.

**Conclusions**

This research has developed a theoretical model to calculate the $\Delta T$ in a TMM embedded with NPs. HIFU experiments have been conducted on TMM phantoms with $\phi$ of 0%, 0.0047%, and 0.047% of 10 nm size mNPs and the results have been compared with the theoretical calculations. Using the theoretical model, it is possible to estimate the $\Delta T$ within 5% error for lower $\phi$ (0.0047%) and within 7% for higher $\phi$ (0.047%) for the initial (10 s) sonication period. The principal mechanisms involved in the HIFU attenuation inside the TMM and mNPs have been discussed. For a $\phi$ of 0.047%, the phonon layer at the interface of the mNPs and TMM is the dominating attenuation mechanism as compared to intrinsic absorption. Whereas, for $\phi = 0.0047$% mNPs, attenuation due to intrinsic absorption dominates as compared to the phonon layer. Attenuation due to viscous drag becomes dominant for large size particles (> 1000 nm). The contribution to $\Delta T$ by different attenuation mechanisms strongly depends on the particles size and $\phi$ of NPs. Unlike mNPs, it is also found that intrinsic absorption remains as the dominating attenuation mechanism for gNPs up to a $\phi$ of 0.047%. This combined experimental and theoretical research is unique because it discusses the contribution of HIFU attenuation mechanisms to the temperature rise.

In conclusion, the size and $\phi$ of NPs play a significant role in controlling the collateral damage to normal cells during HIFU procedures. Using the theoretical model, the suitable size and $\phi$ of NPs can be determined to achieve the required $\Delta T$ in any medium at lower acoustic powers. Therefore, this investigation can help in better planning of clinical trials of HIFU ablation procedures with or without NPs.

**Nomenclature**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>$\phi$</td>
<td>Volume fraction of nano-particles (NPs)</td>
</tr>
<tr>
<td>$\rho_{np}$</td>
<td>Density of NPs (kg m$^{-3}$)</td>
</tr>
<tr>
<td>$\rho_t$</td>
<td>Density of medium (kg m$^{-3}$)</td>
</tr>
<tr>
<td>$\rho_{nf} = \phi \rho_{np} + (1 - \phi) \rho_t$</td>
<td>Density of medium embedded with NPs (kg m$^{-3}$)</td>
</tr>
<tr>
<td>$C_{np}$</td>
<td>Heat capacity of NPs (J kg$^{-1}$ K$^{-1}$)</td>
</tr>
<tr>
<td>$C_t$</td>
<td>Heat capacity of medium (J kg$^{-1}$ K$^{-1}$)</td>
</tr>
</tbody>
</table>
$C_{nt} = \varphi C_{np} + (1 - \varphi)C_f$  Heat capacity of medium embedded with NPs (J kg$^{-1}$ K$^{-1}$)

$k$  Thermal conductivity of the medium (W m$^{-1}$ K$^{-1}$)

$P_0$  Acoustic power (W)

$\varphi_{nt}$  Total attenuation coefficient

$\varphi_t$  Intrinsic absorption attenuation coefficient of medium

$\varphi_v$  Phonon layer attenuation coefficient

$\varphi_{np}$  Intrinsic absorption attenuation coefficient of NP

$v$  Viscous drag attenuation coefficient

$A = \pi r_{beam}^2$  HIFU beam focal area (m$^2$)

$r_{beam}$  HIFU beam focal radius (m)

$v_{np}$  Speed of sound in NP (m s$^{-1}$)

$v_{t}$  Speed of sound in medium (m s$^{-1}$)

$v_{nt} = \varphi v_{np} + (1 - \varphi)v_{t}$  Speed of sound in medium embedded with NPs (m s$^{-1}$)

$m$  NP mass (kg)

$t$  Sonication time (s)

$\omega$  HIFU frequency (Hz)

$\nu_m = \sqrt{\frac{4\pi P_0}{m\omega}}$  Velocity of the NP in the medium (m s$^{-1}$)

$P_t = \frac{\rho v_{nt}^2}{A v_m}$  HIFU pressure (Pascal)

$\beta$  Volumetric thermal expansion coefficient (K$^{-1}$)

$T_{abs}$  Absolute temperature (K)

$\gamma$  Gruneisen parameter

$\tau$  Phonon relaxation time (s)

$\eta$  Viscosity of medium (Pa s)

$v_s$  Kinematic viscosity of medium (m$^2$ s$^{-1}$)

$T_0$  Heat wave parameter

$\tau_b = \frac{3k_{np}}{C_{np} \rho_{np} v_{np}^2}$  Bulk phonon relaxation time (s)

$\tau_{nt} = \frac{d}{v_{nt}}$  Relaxation time for boundary scattering (s)

$d$  Diameter of NPs (nm)

$k_s$  Wave number

$r$  Radial coordinate (m)

$r_0$  Beam radius (m)

$I_0$  Intensity on the beam axis (W m$^{-2}$)

$\kappa_f$  Diffusivity of the medium (m$^2$ s$^{-1}$)

**References**


**Funding**

This work has been partially supported (time spent by co-investigators) by the National Science Foundation (Grant No. 1403356).

**Acknowledgements**

CB and VK thank DST Nano Mission and INST for support.


