Thermal safety of ultrasound-enhanced ocular drug delivery: A modeling study

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Purpose: Delivery of sufficient amounts of therapeutic drugs into the eye for treatment of various ocular diseases is often a challenging task. Ultrasound was shown to be effective in enhancing ocular drug delivery in the authors' previous *in vitro* and *in vivo* studies.

Methods: The study reported here was designed to investigate the safety of ultrasound application and its potential thermal effects in the eye using PZFlex modeling software. The safety limit in this study was set as a temperature increase of no more than 1.5 °C based on regulatory recommendations and previous experimental safety studies. Acoustic and thermal specifications of different human eye tissues were obtained from the published literature. The tissues of particular interest in this modeling safety study were cornea, lens, and the location of optic nerve in the posterior eye. Ultrasound application was modeled at frequencies of 400 kHz–1 MHz, intensities of 0.3–1 W/cm², and exposure duration of 5 min, which were the parameters used in the authors' previous drug delivery experiments. The baseline eye temperature was 37 °C.

Results: The authors' results showed that the maximal tissue temperatures after 5 min of ultrasound application were 38, 39, 39.5, and 40 °C in the cornea, 39.5, 40, 42, and 43 °C in the center of the lens, and 37.5, 38.5, and 39 °C in the back of the eye (at the optic nerve location) at frequencies of 400, 600, 800 kHz, and 1 MHz, respectively.

Conclusions: The ocular temperatures reached at higher frequencies were considered unsafe based on current recommendations. At a frequency of 400 kHz and intensity of 0.8 W/cm² (parameters shown in the authors' previous *in vivo* studies to be optimal for ocular drug delivery), the temperature increase was small enough to be considered safe inside different ocular tissues. However, the impact of orbital bone and tissue perfusion should be included in future modeling efforts to determine the safety of this method in the whole orbit especially regarding potential adverse optic nerve heating at the location of the bone. © 2015 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4929553>]

Key words: therapeutic ultrasound, ocular drug delivery, modeling, thermal safety

1. INTRODUCTION

Rise in temperature and overheating of sensitive eye structures is a concern in the clinical application of ultrasound for drug delivery into the eye.^{1–5} The absence of blood flow in the cornea and lens, which is avascular, exacerbates potential harmful effects of increased temperature due to decreased ability for heat dissipation.^{2,6}

Ultrasound application was shown to increase the permeability of the cornea and provide enhancement in drug delivery, and has a potential to provide an effective and safe method for ocular drug delivery in the treatment of eye infections and inflammations.^{7,8} Results of our previous *in vitro* study showed that the exposure of the cornea to 880 kHz ultrasound for

5 min at intensities of 0.19, 0.34, and 0.56 W/cm² resulted in 2.1, 2.5, and 4.2 times increase of the corneal permeability for sodium fluorescein (a small hydrophilic dye), respectively, as compared to sham treatment.⁹ The permeability increase *in vivo* using the same ultrasound parameters was 2 times at 0.19 W/cm², 4 times at 0.34 W/cm², and 10.6 times at 0.56 W/cm², as compared to sham treatment.¹⁰ The results of our previous study demonstrated 2 times and 1.5 times increase in the delivery of ophthalmic steroid dexamethasone sodium phosphate *in vitro* as compared to sham treatment, with statistical significance, at intensity of 1.0 W/cm² and frequency of 400 and 600 kHz, respectively.⁷ Further, the increase in dexamethasone sodium phosphate concentration in aqueous humor samples was 2.8 times ($p < 0.05$) with

ultrasound application (0.8 W/cm^2 for 5 min) at 400 kHz and 2.4 times ($p < 0.01$) at 600 kHz as compared to sham-treated samples in our previous *in vivo* study.⁸ Similar results were also obtained in a recent study by Lamy *et al.* where ultrasound application at similar parameters (1 W/cm^2 at 880 kHz for 6 min) was shown to result in 3–3.6 times increase in riboflavin delivery into corneal stroma through intact corneal epithelium.¹¹ Further, Nuritdinov showed that application of 880 kHz ultrasound at 0.2 W/cm^2 for 5 min produced a 4.6 times increase in the corneal permeability for a hydrophilic compound, fluorescein, in an aerated solution.¹² It was also shown that ultrasound at frequencies of 470–880 kHz and intensities of $0.2\text{--}0.3 \text{ W/cm}^2$ applied for 5 min in a continuous mode produced up to 10-fold increase in the corneal permeability for a radioactive compound, ^{125}I in a rabbit model, *in vivo* with the maximal increase observed at 660 KHz.¹³ Feasibility of ultrasound-enhanced trans-scleral drug delivery has also been tested. For example, several recent studies indicated that ultrasound-mediated delivery was effective in delivering macromolecules into the posterior segment of the rabbit eye *via* trans-scleral route.^{14–16} No adverse effects were observed for up to 2 weeks after ultrasound application in the posterior segment of the eye. Another recent study by Razavi *et al.* showed that ultrasound can enhance the delivery of fluorescein sodium via the scleral route with no significant alteration observed in the eye tissues.¹⁷ In this study, inertial cavitation was shown to be the mechanism responsible for this delivery enhancement.

Palte *et al.* investigated thermal and mechanical effects of ultrasound exposure (by utilizing thermocouple temperature measurements and histological evaluations) to determine potential adverse changes in different regions of the eye.¹ In this study, the eye temperature was increased above the recommended limits (eye tissue temperature increase of greater than 1.5°C above physiological levels) as a result of 10 min of ultrasound application (using nonorbital rated diagnostic ultrasound); however, the authors failed to find any evidence of eye tissue damage.¹ The conclusion of this study was that regulatory recommendations may be too strict in the case of ocular ultrasound. In the study by Lamy *et al.*, the maximal temperature increase due to 6 min of ultrasound application (at 880 kHz and 1 W/cm^2) was 6.1°C from baseline temperature of 34°C . This temperature increase did not appear to cause any changes in biomechanical properties of the cornea.¹¹

In the study reported here, we focused on modeling of the interaction between ultrasound and eye tissues for determination of ultrasound thermal safety in drug delivery applications. Measuring the temperature increase in different eye tissues, by using thin wire thermocouples, was not possible during our previous drug delivery studies^{7,8} since it would compromise the drug delivery measurements. This modeling study developed a temperature map that gives the exact location and temperature increase in different eye tissues during ultrasound application. To the best of our knowledge, this is the first study to report these findings. The method is also applicable where tissue damage, by placing thermocouples, should be avoided, or placing thermocouples in the tissue of interests is not possible.

TABLE I. Dimensions for rabbit and human eyeball structures (Refs. 18–20). All dimensions are shown in mm.

	Rabbit	Human
Anteroposterior length	16–19	23–25
Anterior chamber depth	2.9	3.5
Diameter of cornea	13.5–14	10.6
Thickness of cornea at its center	0.3–0.4	0.5
Thickness of cornea in periphery	0.45	0.7
Thickness of lens	6.36	3.5–4.3
Thickness of sclera	0.33	0.5–1.0
Thickness of choroid	0.07	0.1–0.5
Thickness of retina	0.05	0.1–0.5

2. METHODS

2.A. Human eye model

A theoretical model of the human eye was designed based on the accurate geometrical measurements for different eye structures obtained from the published literature.^{18–20} A rabbit model was used in our previous *in vitro* and *in vivo* experimental studies, but an actual human eye was used for modeling studies since it offers results that are more relevant for eventual patient treatment. Rabbit eyes have been used as an acceptable ophthalmic research model because they are similar to the human eye.²¹ Further, acoustic and thermal properties of the rabbit eye tissues are expected to be similar to human eye tissue.²² Dimensions of human and rabbit eye structures are shown in Table I.

The eyeball model used in this study included cornea, aqueous humor, lens, vitreous humor, sclera, choroid, retina, and optic nerve. Figure 1 shows a schematic of human eye anatomy.

Acoustic and thermal specifications for different modeled eye tissues had to be known, to be able to establish all of the eye structures in the model accurately. These parameters for human eye are provided in Table II. Tissue density of 1070 kg/m^3 was used in the whole PZFlex model which is an average estimation for different eye tissues (average value for

Fig. 1. Schematic of human eye. This drawing is based on an anatomical eye appearance.

TABLE II. Acoustic and thermal characteristics of different eye structures (Refs. 22–26).

	Speed of sound (m/s)	Acoustic attenuation (dB cm ⁻¹ MHz ⁻¹)	Specific heat (J/kgK)	Thermal conductivity (W/mK)
Cornea	1586	0.78	4178	0.58
Sclera	1647	0.97	4178	0.58
Aqueous humor	1497	0.01	3997	0.59
Choroid	1527	0.95	3840	0.60
Lens	1647	1.19	3000	0.40
Vitreous humor	1532	0.01	3999	0.60
Retina	1538	1.15	3680	0.57
Optic nerve	1644	0.7	3750	0.53

density of different eye tissues is 1066 kg/m³ with the range of 1034–1088 kg/m³.²³

The perfusion was assumed to be negligible because there is no blood supply in cornea, lens, and vitreous body.²⁶ This assumption is not correct in the case of retina and choroid, and our model overestimates the temperatures achieved in these tissues. The baseline temperature for the model was set to be 37 °C, which is the normal temperature of the human eye.²⁷

2.B. Acoustic simulations

Modeling studies were conducted using a finite-element analysis software package (PZFlex, Weidlinger Associates, Mountain View, CA). This numerical program uses a finite-element and explicit time-domain approach for modeling ultrasound propagation, frequency dependent attenuation, thermal effects over time, etc. A desktop computer (Dell T5500, Round Rock, TX) with dual-core 64-bit 2.66 GHz Intel processors and 40 GB memory was used in our modeling studies. Both acoustic and thermal simulations were performed using this software to obtain quantitative information on interaction between ultrasound and eye tissues. In this model, the axis was set to be symmetric, and the boundary conditions at the sides and bottom of the model were set to be absorbing. In our modeling experiments, the maximum computation time was 30 min.

The acoustic properties of our modeling setup were similar to those present in our previously performed *in vitro* and *in vivo* drug delivery experiments.^{7,8} The modeling setup included a continuous ultrasound beam at frequencies of 400 kHz–1 MHz, intensities of 0.3–1 W/cm², and exposure duration of 5 min. The ultrasound field was modeled as an unfocused beam with uniform cross-sectional intensity. In the acoustic model, the pressure was applied to the cylindrical surface of the flat transducer to generate an ultrasound beam. The regions of the eye that were along the beam path included cornea, lens, and optic nerve in the back of the eye. The active diameter of the transducer was 15 mm. The distance from the transducer to the surface of the cornea was at near field to far field transition distance, d_{ff} , which was calculated to be 1.5, 2.25, 3.0, and 3.75 cm for 400, 600, 800 kHz, and 1 MHz, respectively. d_{ff} is the location of the furthest maximum pressure for the flat ultrasound transducer.²⁸ The material between eye and transducer was water. The drug solutions used in our previous

experimental studies^{7,8} were hydrophilic with water base properties; therefore, water was a suitable choice. The complete design of our model is shown in Fig. 2.

The main areas of interest in our modeling studies were cornea, lens, and optic nerve in the back of the eye. Thermal conductivity and specific heat capacity for each structure in the eyeball had to be known to run the model—these values were obtained from the published literature and are provided in Table II.

There are two ways to design the acoustic model, using pulsed and ultrasound continuous wave propagation. We used the continuous model to match the actual ultrasound parameters used in our previous drug delivery experiments.^{7,8} In this model, continuous sinusoidal drive of a specific frequency (400 kHz–1 MHz) and amplitude were applied until the whole system reached steady state, and after that the energy loss data were gathered. The amplitude of this sinusoidal drive was calculated using the following equation:

$$I = \frac{p_0^2}{2\rho c} \rightarrow p_0 = \sqrt{I \times 2\rho c}, \quad (1)$$

where I is intensity averaged over one or more cycles of continuous wave propagation in W/m², p_0 is the pressure amplitude

FIG. 2. Geometric model of the eye that is axisymmetric. White rectangle shows the 2D representation of the ultrasound transducer. The dotted line represents the axisymmetric model.

in $\text{kg/s}^2 \text{ m}$, ρ is density in kg/cm^3 , and c is speed of ultrasound in m/s .

2.C. Calculations of pressure intensity and heat source

The heat production rate per unit volume, as a result of ultrasound application, depends on characteristics of the medium, biological tissues in our study, and ultrasound field, and it is equal to dissipation rate for ultrasound,²⁹

$$q_v = 2\alpha I, \quad (2)$$

where α is the absorption coefficient in Np/unit length and I is the time-averaged intensity. Heat production rate, q_v , varies from one region to another as the ultrasound beam passes through the tissue.^{29,30} As shown in Eq. (3), absorption and frequency can have both a linear as well as a nonlinear relationship when the power m is not unity, and frequency can be expressed as

$$\alpha(f) = \alpha_1 f^m, \quad (3)$$

where α_1 is the absorption coefficient at 1 MHz, f is the frequency in MHz, and m is a number between 1 and 1.3.²⁹

In many applications of ultrasound where the pressures are low enough that nonlinearity effects are negligible,²⁹ the relation between medium density and pressure is assumed to be linear. The maximum pressure at the highest intensity (1.0 W/cm^2) used in our studies was 0.146 MPa . The threshold for nonlinearity is highly dependent on both the ultrasound systems used and the bioeffects of interests. At our applied ultrasound parameters, the nonlinearity effects as related to tissue heating should be negligible as shown in the work by Soneson and Myers³¹ and Curra *et al.*³²

Further assumption as related to linearity is that the plane wave traveling through the medium with pressure amplitude varies in a sinusoidal pattern over time and is characterized by single frequency. The relation between the intensity $I(z)$ of a plane wave, at specific frequency and tissue depth, with I_0 at initial location or depth is shown by^{29,30}

$$I(z) = I_0 e^{-2az}, \quad (4)$$

where I_0 is the intensity at $z = 0$ and a is the attenuation coefficient (both scattering and absorption) at frequency f . The attenuation and absorption coefficients were shown to be similar in the liver, and it is assumed that the same is true for other soft tissues.^{22,33} If the attenuation is just based on absorption, then Eq. (3) can be changed to

$$I(z) = I_0 e^{-2\alpha f z}, \quad (5)$$

where α is the absorption coefficient (Np/cm) and is a function of frequency.

The exact equations used in the PZFlex modeling approach can be found in the references by Abboud *et al.*³⁴ and Wojcik *et al.*³⁵ The PZFlex finite-element implementation for acoustic wave propagation is based on a first order system of equations. In our modeling experiments, the initial conditions were set at zero. The boundary conditions were chosen to be perfect matching layer (PML). In thermal simulations (described

below), the governing equation was the bioheat transfer equation.^{36,37} The initial condition was body temperature, and the boundary conditions were set to body temperature.

2.D. Thermal simulations

The acoustic wave propagation through the whole eye model was investigated. Then, the acoustic energy deposition due to absorption (or reflection), as a result of ultrasound wave propagation across the model, was the driving force for thermal model. Thermal and acoustic model cannot be coupled because even though energy deposition and temperature can be calculated simultaneously, the differences in time scale between thermal effects (in scale of seconds) and acoustical effects (wave propagation in scale of microseconds) would make this modeling effort inefficient. Therefore, the best approach was to run the ultrasound wave propagation model until it reaches steady state, then one cycle of wave propagation was calculated; the energy loss due to attention through the whole model was recorded and used to run the thermal model as described in our previous publications.^{38,43} Based on the software specifications, the acoustic field simulation was run with a continuous sinusoidal drive of a given frequency, with identical cycles, over the entire model. The steady state is case dependent and was observed by monitoring the time-domain trace in the field in front of the transducer until it was found to be steady. This time can be estimated as $1.5 \times \text{length of model/speed of sound in tissue}$ (as based on PZFlex manual). The steady state is typically noted in the continuous mode after 10–20 waves have passed through the point of interest. Figure 3 shows the result of acoustic simulation, which includes the pressure map of the entire model, and loss map as a result of energy attenuation.

2.E. Finite-element mesh

A dense elemental mesh, which contains greater number of elements, was utilized to achieve a constructive interface between all waves in the acoustic model. The meshing could be less dense in the thermal model as compared to the acoustic model because the variation of temperature across the model could be captured using a smaller number of elements in the system. To set the meshing for simulation, the average velocity (in this case, the average of ultrasound velocity in different parts of the eye was 1560 m/s) and frequency variables (400 kHz – 1 MHz) were defined; the wavelength was determined, and size of elements was set accordingly. The more elements the model has, the more accurate is the representation of the object. The PZFlex user manual suggests at least 12 elements per wavelength. The number of elements used for our acoustic and thermal models was 30, to ensure adequate accuracy of the model. To investigate the effect of number of elements per wavelength on the results, a distinct test was implemented. For one of the parameters (400 kHz and 0.8 W/cm^2), the model was run for different number of meshing elements (20, 30, 40, 50, 60, and 70) to determine whether our choice of 30 elements provided adequate results. Figure 4 shows the effects of different number of elements and their relation to peak

FIG. 3. Ultrasound wave propagation through an eye model. (a) Pressure map as a result of acoustic simulation. (b) Energy loss through the eye model as a result of ultrasound wave propagation.

pressure during the simulation. The results indicated that the peak pressure did not deviate when using number of elements that were equal to or greater than 30 in our simulations.

2.F. Thermal safety

In our studies, we set safety limits for temperature increase during ocular ultrasound application as up to 1.5°C above physiological temperature levels based on European Federation of Societies for Ultrasound in Medicine and Biology recommendations³⁹ and previous experimental safety studies.¹ Current US Food and Drug Administration guidance for ophthalmic ultrasound manufacturers recommends I_{SPTA} of lower than 50 mW/cm^2 and thermal index (TI) of less than 1.^{36,40} TI is the ratio of device's total acoustic power

to the power needed to increase tissue's temperature by 1°C . However, it is important to keep in mind that these are guidance documents and different ultrasound parameters can be approved by US FDA and used clinically if safety and effectiveness of the approach is justified.⁴¹ The loss of acoustic energy was used as a heat source input to observe temperature distribution in the eye. After modeling studies were performed using the following combination of ultrasound parameters, frequencies of 400, 600, 800 kHz, and 1 MHz at intensities of 0.3, 0.5, 0.8, and 1 W/cm^2 for 5 min, the peak temperature was obtained in different eye tissues. To better observe areas that were affected by heat generated from ultrasound application, a MATLAB algorithm³⁸ was used which could access the lost data from thermal simulation, draw a contour of eye structures of interest, and map the areas with different temperatures. Since the simulations were axisymmetric, just one side of the model is shown in the relevant figures in Sec. 3.

FIG. 4. Impact of meshing density on accuracy of our eye model. Increasing the meshing number above 30 used in our simulations would not have a significant effect on the modeling results.

3. RESULTS

The results for each ultrasound parameter combination are shown in Figs. 5–8. The baseline temperature was set to 37°C , and temperature changes indicated below are based on changes from this value. Our results showed (Fig. 5) that using ultrasound at a frequency of 400 kHz in drug delivery experiments had minimal effects on the eye tissues. It is worth noting that this frequency was shown in our previous experiments to lead to the highest increase in transcorneal drug delivery (at an intensity of 0.8 W/cm^2 , and exposure duration of 5 min).^{7,8}

The temperature increase at an intensity of 0.3 W/cm^2 was 0.3°C in the cornea, and was 0.5°C in the lens. The change in temperature in the lens was higher (1°C), at 0.5 W/cm^2 as compared to 0.3 W/cm^2 . At an intensity of 0.8 W/cm^2 , temperature elevation was 1.5°C in the lens and 1°C in the cornea. The maximal temperature increase of 2.5°C was observed inside the lens at the highest intensity of 1 W/cm^2 .

FIG. 5. Temperature distribution after 5 min of ultrasound application at a frequency of 400 kHz and intensities of 0.3, 0.5, 0.8, and 1 W/cm². Each subplot represents the flat ultrasound transducer located at d_{ff} from the surface of the eye and eye structures of interest including cornea, lens, and optic nerve in the posterior eye. The left side of each subplot shows temperature contours at several locations, and the right side shows the temperature pattern.

Also, ultrasound application caused an increase of 1 °C in the cornea at intensity of 1 W/cm². No temperature increase was observed in the back of the eye.

In case of ultrasound application at 600 kHz (Fig. 6), the increase in temperature was more pronounced. The temperature increase at 0.3 W/cm² was 0.5 °C in the cornea and was 1 °C in the lens. Increase in temperature in the cornea and lens was 1 and 1.5 °C, respectively, at 0.5 W/cm². At higher intensity (0.8 W/cm²), temperature elevation was 2.5 °C in the lens, and 1.5 °C in the cornea. The maximum increase of 3 °C was in the center of the lens while applying ultrasound at an intensity of 1 W/cm² for 5 min. Using the same parameters, the temperature of the cornea was increased by 2 °C. No temperature increase in the back of the eye was observed at these ultrasound parameters.

Application of ultrasound at 800 kHz (Fig. 7) caused the temperature in the back of the eye (at the optic nerve location) to increase 1.5 °C at an intensity of 1 W/cm². The temperature increase observed in the center of the lens was 4 °C at 0.8 W/cm² and 5 °C at 1 W/cm². The temperature of the cornea increased by about 2.5 °C at this frequency and at the highest intensity of 1 W/cm².

Among all the frequencies tested during thermal simulations, a frequency of 1 MHz ultrasound produced the highest temperature increase on all structures of interest, i.e., cornea, lens, and optic nerve (Fig. 8). The temperature increase observed, even at lowest tested intensity of 0.5 W/cm², was 3 °C in the center of the lens, 1.5 °C in the cornea, and 1 °C in the back of the eye. The most significant temperature elevation (6 °C in the lens, 3 °C in the cornea, and 2 °C in the back of

Fig. 6. Temperature distribution after 5 min of ultrasound application at a frequency of 600 kHz and intensities of 0.3, 0.5, 0.8, and 1 W/cm².

the eye) was observed at 1 W/cm². The summary of maximal temperatures observed in eye tissues at different ultrasound frequencies is provided in Table III.

4. DISCUSSION

Modeling methods (utilizing PZFlex software) have been used in several previously published studies to investigate the safety of ultrasound application in biological tissues. For example, a study done by Nell and Myers indicated that mathematical modeling is a good method to investigate the amount of temperature rise due to ultrasound absorption in tissues in the proximity of the bone. These authors have successfully confirmed their modeling results with experimental measurements.⁴² Further, our previous studies showed a good correlation between PZFlex modeling results and thermocouple

measurements in tissue-mimicking phantoms.⁴³ Similar results were obtained when PZFlex model was compared to thermocouple measurements done in *ex vivo* rabbit eyes.³⁸

Attenuation of ultrasound energy or loss of ultrasound wave amplitudes as the wave passes through a medium such as tissue can be caused by different mechanisms such as reflection, refraction, scattering, and most importantly absorption.²⁸ From this list, scattering and absorption cause the most of energy attenuation. If the medium is not uniform and consists of different layers, the acoustic impedance differences between layers can cause reflection and refraction. Acoustic scattering happens when the medium is inhomogeneous, and the ultrasound wave encounters structures that have the same size or are smaller than its wavelength. In the case of absorption, the acoustical energy of ultrasound, as it is absorbed by medium, converts into heat.^{4,44} As the ultrasound frequency

FIG. 7. Temperature distribution after 5 min of ultrasound application at a frequency of 800 kHz and intensities of 0.3, 0.5, 0.8, and 1 W/cm².

increases, the thermal effects become more pronounced,⁴⁵ with their relation to ultrasound intensity and duty cycle directly proportional. As frequency increased in our experiments, more acoustic energy was converted to heat, which resulted in higher energy attenuation. Because of high acoustic attenuation in the lens,²² the greater temperature increase was observed in that area of the eye.

In addition to ultrasound frequency, the intensity of the ultrasound wave plays an important role in heat generation. The greater the intensity is, the higher the heat production will be.²⁹ The graphic representation of energy loss after thermal simulation showed that the temperature of the lens increased the most as a result of ultrasound application. The temperature increase produced in the lens is higher as compared to cornea and optic nerve because of its high acoustic attenuation (see Table II).

The absence of blood flow in the cornea and lens which are avascular, results in slower cooling and more heat absorption in these tissues during ultrasound exposure.^{2,6} Overheating of the lens is a major concern since it may result in cataract formation.⁴⁶ Guy *et al.* specified that the potential risk would be generated if the temperature increases above 41 °C.⁴⁷ Cataracts have also been observed when a rabbit eye was exposed to localized, very high radiofrequency (RF) field at 2450 MHz for more than 30 min at power densities causing very high dose rates of 150 W/kg, and temperatures of 41 °C.⁴⁸ Hyperthermia levels (of 41–43 °C) were also shown to cause functional changes in the corneal epithelial cells.⁴⁹ Our modeling study showed that temperature increases obtained using ultrasound at higher frequencies may have resulted in temperatures that could cause adverse effects in the lens and cornea.

FIG. 8. Simulated temperature distribution after 5 min of ultrasound application at frequency of 1 MHz and intensities of 0.3, 0.5, 0.8, and 1 W/cm².

Previously reported experimental studies on the values of acoustic properties of eye lens resulted in a relatively large range of values. For example, a study by Huang *et al.*⁵⁰ measured attenuation of healthy porcine lens as 0.48 ± 0.2 (dB/cm)/MHz, while a study by Raitelaitiene *et al.*⁵¹ reported attenuation values for human lens of 5.88 (dB/cm)/MHz. We have based our modeling studies on the experimental

values for acoustic properties of different human eye structures including the lens reported by de Korte *et al.*²⁵ Further, a leading book reference for physical properties of different tissues by Duck²² reported human lens attenuation as 8 dB/cm at 10 MHz which would correspond to 0.8 (dB/cm)/MHz at 1 MHz since acoustic attenuation of the lens was reported to be linear with frequency.⁵² It should be noted that higher values of the lens attenuation than the ones used in our studies would lead to more concerning outcomes regarding temperature increase. This issue could be resolved by utilizing pulsed ultrasound exposures that were shown recently to be successful in achieving enhancement in ocular drug delivery,¹⁷ to minimize temperature increase inside the eye.

Ciliary body and ciliary zonules were not included in our eye model due to their small size and the lack of reported acoustic and thermal parameters for these tissues.²² However,

TABLE III. Summary of maximal temperatures in different eye tissues (°C) during ultrasound application.

	400 kHz	600 kHz	800 kHz	1 MHz
Cornea	38	39	39.5	40
Lens	39.5	40	42	43
Back of the eye (optic nerve)	37	37.5	38.5	39

the temperature values for these tissues are expected to be the same or lower than our modeled values in the sclera exposed to ultrasound in front of the eye and should not be of additional safety concern (please see temperature contours in Figs. 5–8). Ciliary body has been reported in previous studies to have the same acoustic attenuation as sclera (of $1.17 \times f^{1.57}$ Np/m where f is frequency),⁵² and ciliary zonules are fibrous tissue similar to sclera's fibrous tunic and are also expected to have similar acoustic and thermal properties as the sclera. Further, previous experimental work indicated that the mean temperatures during ultrasound exposure in *ex vivo* human and rabbit eyes were lower in the ciliary body as compared to the lens;⁶ therefore, safety limits imposed by the lens heating in our modeling studies should be sufficient to address heating of ciliary bodies as well.

Measuring the temperature of different eye tissues was not feasible in our previous *in vitro* and *in vivo* studies since thermocouple placement in different eye tissues would have compromised drug delivery measurements;^{7,8} therefore, this modeling study was needed to observe the impact of ultrasound application at our proposed parameters on potential heat generation in the lens and other eye tissues. Modeling can help with choosing the parameters that would not cause thermal damage to the eye while applying ultrasound to enhance ocular drug delivery. The ultrasound parameters used in the modeling studies were obtained from our previous *in vitro* and *in vivo* experiments.^{7,8} Combinations of ultrasound parameters were determined which did not result in a substantial temperature increase in the cornea, lens, and the back of the eye and could be considered safe. Fortunately, these same parameters were shown to be the most effective for drug delivery in our previous experimental studies. Our previous experimental thermal measurements provided the values for the cornea temperature,⁷ which were used to assess the validity of simulation results. The temperature was measured inside the donor compartment of the diffusion cell in proximity of the cornea, and maximal temperature increase was $\sim 3^\circ\text{C}$.⁷ This value is equivalent to the maximal temperature change which was observed in the cornea at the most severe case, at 1 MHz and 1 W/cm^2 , in this modeling study.

Limitations of our study included the absence of bone interfaces that are present in the orbit and not accounting for tissue perfusion. Because the normal cornea, lens, and vitreous body are avascular tissues, the perfusion effect in previously published ocular studies has been assumed to be negligible.^{26,53,54} Further, for vascularized structures inside the eye, such as ciliary body, the impact of perfusion on tissue heating during ultrasound exposure is expected to be minor⁶ due to the lack of large blood vessels inside the eye.⁵⁵

The impact of orbital bone is of safety concern.^{42,56} Depth of the orbit in human is 40–50 mm, with the eye located in front (with the depth of 25 mm).⁵⁷ The remaining orbital area (between the eye and the bony eye socket) is 15–25 mm long and filled mostly with muscle and fat tissue. However, optic nerve passes through the optic canal in the bone and potential adverse heating in this area is of concern^{56,58,59} and should be explored further by modeling heating patterns in the whole orbit. These heating patterns would depend on a number of

factors including the attenuation of ultrasound waves due to intervening tissues between the bone and ultrasound transducer located in the front of the eye (approximately 50 mm away), perfusion of surrounding tissues, and the impact of soft tissue–bone interface. If these future studies show concerning temperature values at the bone interface, utilization of pulsed ultrasound mode in ocular drug delivery may be a way to remedy this safety concern.¹⁷ Previous experimental studies that utilized ultrasound at physiotherapy levels of continuous exposure (similar to our levels) indicated that the impact of the bone can be substantial (up to 4-fold higher temperatures as compared to the same location in the tissue with no bone present) within close proximity (5–7 mm) of the bone.⁵⁶ Moros *et al.*⁵⁶ used 3 different temperature measurements techniques (fiber-optic temperature probes, infrared camera, and MRI) to determine temperature increases at the soft tissue phantom–bone interfaces exposed to planar 1 MHz transducer at acoustic powers of 5.4–30 W and exposure durations of 0.5–15 min. The findings of their studies indicated that significant heating of over 4-fold was induced at the tissue–bone interfaces in proximity (within 5 mm) from the bone (as compared to the tissues at equivalent distance with no bone present). For long exposure experiments (15 min of ultrasound exposure in continuous mode), the additional temperature increase due to the bone interface was present at 10 mm from the bone inside the soft tissue. This study indicated that the bone heating would be limited to the orbital tissues in the proximity of the bone and should not impact our results for the temperature increases inside the eye. Further, theoretical calculations that we performed indicated that potential additional heating at the bone interface would impact the soft tissues to up to 6.7 mm from the bone based on calculated diffusion length for our model after applying 5 min of ultrasound exposure in continuous mode.^{29,60} The diffusion length is calculated as $(kt)^{1/2}$ where k is thermal diffusivity coefficient of soft tissue of $0.15 \times 10^{-6}\text{ m}^2/\text{s}$ and t is exposure time in seconds. Therefore, both previous experimental studies and theoretical analysis indicated that the tissues impacted by the bone interface would be within 7 mm from the bone in our studies, and the presence of the bone should not impact the results that we have obtained for the tissues located within the eye.

5. CONCLUSIONS

In our study, modeling was used to investigate the amount of heat generated in a human eye model as a result of using continuous mode ultrasound application at different frequencies and intensities at the same parameters that were shown effective for enhancing ocular drug delivery. This modeling study provided further knowledge about heat distribution in the eye tissues and led to a better understanding of what ultrasound parameters should be used in future experiments and eventually in the clinical setting.

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