Introduction

Background. Nonthermal irreversible electroporation (NTIRE) is a biophysical modality that uses high, microsecond long electric field pulses delivered across cells to produce a phenomenon known as irreversible electroporation, i.e., irreversible permeation of the cell membrane. The idea of using NTIRE for tissue ablation was first introduced in [1], where a mathematical model was used to demonstrate that electric fields can induce irreversible electroporation and cell ablation without causing thermal injury. Subsequent studies have confirmed the efficacy of NTIRE in some experimental models. For example, Miller et al. [2] reported that the application of an electric field at an intensity of 1500 V/cm with a pulse duration of 300 microseconds can induce cell ablation. Edel et al. [3] reported the effect of IRE on rat liver in vivo. According to their mathematical simulation, the field strength in the affected area was about 900–1100 V/cm and the predicted temperature rise was only 2–3°C, except for a small annular zone in which the temperature exceeded 50°C, probably causing thermal ablation. This is consistent with a previous study [4] which reported a threshold of 637 V/cm (8 pulses of 1 Hz, for a duration of 100 microseconds) to induce irreversible electroporation and necrosis in a rabbit liver. The authors concluded that the morphological changes observed after the treatment could be attributed to membrane disruption of hepatocytes. There are other reports of in vivo use of irreversible electroporation in vascular endothelial cells, cardiac conducting cells, and other tissues [5–8].

The Joule heating caused by the dissipation of an electric field can cause a rise in temperature and thermal injury [9]. A series of mathematical modeling papers [10–13] studied the heat transfer problem and the thermal damage when applying electroporation. Unlike NTIRE ablation which primarily affects the cell membrane, thermal damage affects all tissue molecules, including connective tissue, blood vessels, nerves, [5,6,8,14]. The molecular selectivity of NTIRE treatment is thus critical to sparing noncellular structures which are important for regeneration and healing processes. Theoretical studies as well as animal experiments have shown that NTIRE did not affect various anatomical extracellular structures, such as blood vessels and extra cellular conduits.

The application of NTIRE to ocular tissue was reported by our group [15]. Uveal melanoma is the most common primary intraocular malignancy in adults and is characterized by a high mortality rate due to extraocular metastasis. Metastatic disease is reported in up to 50% of patients followed for 10–15 years after primary diagnosis. Brachytherapy is the most common globe sparing treatment modality for uveal melanoma and is delivered with a radioactive plaque (such as iodine-125 or ruthenium-106). One to two weeks after the surgical insertion of the plaque, it is removed during a second operation. Complications of brachytherapy include visual loss, retinal detachment and tears, optic nerve neuropathy, cataracts, vitreous hemorrhage, and in some patients there is a need for secondary enucleation [16]. Other treatment modalities are less popular and include proton beam radiotherapy, stereotactic radiotherapy, trans-scleral local resection, enodere- cion [17], enucleation or no treatment [18].

This paper describes efforts to develop NTIRE as a new minimally invasive treatment modality for uveal melanoma, the most common primary intraocular malignancy in adults, and other ocular malignancies. The paper deals with a 3D mathematical simulation model of the eye that employs the simultaneous solution to the electric field equation and to the Pennes bioheat equation to predict the electric field in the eye as well as the rise in eye temperature in response to the application of a high power electric pulse. Treatment efficacy was defined as the fraction of tumor volume in which the electric field exceeded a predefined target field and treatment safety was calculated by the ratio of the electric field in the tumor to the electric field in the vitreous humor or in the macula. Results show that treatment efficacy and safety are criteria that can be used to optimize the NTIRE treatment protocol. [DOI: 10.1115/1.4005203]

Keywords: irreversible electroporation, uveal melanoma, heat transfer, eye
advanced model of heat transfer in the eye has been recently published by Shafahi and Vafai [19]. We believe that in the future, combining more advanced models with a similarly detailed electric field of the eye model and with the methodology developed in this paper will produce a simulation tool that can enhance treatment safety and efficacy by enabling the physician to optimize electrode position, pulse amplitude, duration, and frequency.

**Methods**

**Geometric Model.** The eye was modeled in 3D, based on anatomical dimensions published in the literature [20,21]. A 5 mm high uveal melanoma tumor with a base diameter of 10 mm (these dimensions correspond to a size medium uveal melanoma tumor) was added to the eye at the posterior pole (Fig. 1). We simulated a treatment plan of electric pulses to the eye while changing the electrode configurations as depicted in Fig. 2.

Configuration #1 was comprised of an internal (intravitreal) spherical surface electrode which fully covered the intraocular surface of the tumor and an external 2 mm disk electrode located on the outer surface of the sclera, opposite the sclera facing part of the tumor. Configuration #2 was comprised of an internal (intravitreal) 2 mm disk-shaped electrode centrally located on the tumor surface and a similar external electrode located on the outer sclera. Configuration #3 was comprised of two large spherical electrodes: one internal electrode covering the inner surface of the intraocular tumor, and the external scleral electrode covering the outer sclera opposite the tumor base. Configuration #4 was comprised of an external (scleral) 5 mm radius ring electrode and an external 1 mm radius disk electrode located in the center of the ring electrode. Configuration #5 was comprised of an internal (intravitreal) disk electrode located on the inner tumor surface and an external ring electrode positioned on the sclera opposing tumor margins (Fig. 2). The electrode configurations were chosen based on surgical applicability and similarity to the brachytherapy method for uveal melanoma [18].

**Electrical Model.** The electrical potential and electric field for each spatial point in the eye was calculated by the solution to the electric field equation (Eq. (1)),

\[
\nabla(\sigma \nabla \phi) = 0
\]

where \(\sigma\) is the electrical conductivity and \(\phi\) is the potential at a specific location. Because of the capacitive charging time is expected to be short in the eye tissue (which has a high water content), the non-Ohmic response of the tissue was neglected, similar to other studies modeling electroporation (e.g., [22,23]).

**Bioheat Model.** After solving the field equation, the Joule heating (\(p\)) rate per unit volume (W/m\(^3\)) caused by the electric field can be calculated by

\[
p = \sigma |\nabla \phi|^2
\]

The Joule heat generated during the electroporation treatment can then be added to the Pennes bioheat equation [24],

\[
\rho c_p \frac{\partial T}{\partial t} = \nabla (k \nabla T) + w_b c_b(T_a - T) + q'' + p
\]

where \(k\) is the thermal conductivity of the tissue, \(T\) is the temperature, \(w_b\) is the blood perfusion, \(c_b\) is the heat capacity of the blood, \(T_a\) is the arterial temperature, \(q''\) is the metabolic heat generation, \(p\) is the electric heat generation, \(\rho\) is the tissue density, and \(c_p\) is the heat capacity of the tissue. Some of the eye tissues are avascular (e.g., cornea, lens) while in the back of the eye, the retina and the sclera have complex blood systems. Modeling heat transfer in the eye is usually based on empirical and numerical models reported by several authors [25–27] in which the blood convection coefficient in the back of the eye (sclera and retina) was found to be 65 W m\(^{-2}\) K\(^{-1}\) (Eq. (4)) while in the anterior part of the eye (cornea) there is heat loss through convection, radiation, and tear evaporation (Eq. (5)). In the present model the bioheat boundary conditions were based on Scott [27] with some modifications. The boundary conditions on the sclera are

\[
-k \frac{\partial T}{\partial n} = h_s(T - T_h)
\]

The boundary conditions on the corneal surface are

\[
-k \frac{\partial T}{\partial n} = E + h_c(T - T_{amb}) + \alpha (T^4 - T_{amb}^4)
\]

where \(T\) is the temperature to be solved (K), \(k\) is the thermal conductivity (W/mK), \(c\) is specific heat capacity (J/kg K), \(p\) is density (kg/m\(^3\)), \(t\) is time (s), \(E\) is evaporation rate = 40 (W/m\(^2\)) (W/m\(^2\)), \(T_{amb}\) is ambient temperature = 298 (K), \(T_{hit}\) is blood
The various eye structures (cornea, aqueous humor, vitreous, lens, sclera, melanoma tumor, and retina) were assumed to be isotropic in all directions. Tear film electrical properties were neglected. Since there are no reported measures of the electrical characteristics of uveal melanoma, we conducted an exploratory parametric study to evaluate the effect of these parameters on treatment efficiency, in which the electrical conductivity of the tumor was set as 0.332 S/m and was factorized by 0.25, 0.5, 1, 1.5, 2 (e.g., for a pulse of 10 μs, the time steps were t = 0, 1, 2, 3, …, 10 μs). We tested the convergence of the numerical solution by decreasing the voxel dimension successively until we reached a convergence of 0.1%. Validation of the electric model was done by decreasing the voxel dimension successively until we reached a convergence of 0.1%. Validation of the electric model was done by decreasing the voxel dimension successively until we reached a convergence of 0.1%. Validation of the electric model was done by decreasing the voxel dimension successively until we reached a convergence of 0.1%.
Results

Initial Temperature Distribution of the Eye. The initial temperature distribution of the eye (T0) was calculated according to boundary conditions with blood temperature of 37.0°C (Fig. 3). As can be seen, there is a significant temperature gradient between the exterior ocular surface (cornea) and the inner ocular surface (the retina). The results are consistent with previous model analyses [27] as well as experimental data [37,38], thus this simulation can serve as a partial validation of the present heat transfer model of the eye.

Electric Field. Figure 4 depicts a typical solution of the electrical problem when applying pulse potential of 1000 V. The area of the tumor and eye tissue where electric field exceeds 1000 V/cm is marked in white. It can be seen that in electrode configuration #3 all of the tumor is within the target electric field, while in the other configuration, only part of the tumor exceeds the target.

Because of the geometry caused complexity of the electric field distribution we decided to use the average electric field in the tumor as one measure of the effectiveness of the various electrode configurations. Using the average electric field as a measure is...
meaningful because of the linearity of the problem. The highest average intratumor electric fields were found for configurations #3 and #5. Average vitreous electric field was highest in electrode configuration #5, of moderate amplitude in configurations #2 and #3, and significantly lower in configurations #4 and #1. The calculated safety factors (average tumor electric field divided by average vitreous electric field) were 1247, 307.5, 179.2, 45.3, and 21.4 for electrode configurations #1, #3, #4, #2, and #5, respectively.

The fraction of tumor volume within the electric fields of 500, 800, and 1000 V/cm for the various pulse potentials is depicted in Fig. 5. The fraction of the tumor within the various target fields was dependent on the pulse potential and electrode configuration. For a specific pulse potential, electrode configuration #3 was associated with the largest tumor coverage followed by configuration #5, whereas configuration #4 was associated with the smallest tumor coverage.

However, because of the significant effect of the electrode configuration on the vitreous electric fields and its importance for safety considerations, the relation between tumor volume affected by the electric field and the vitreous volume affected by the electric field was calculated and is depicted in Fig. 6.

The results show that electrode configurations #2 and #5 produce a larger potential collateral damage in the vitreous area than

**Fig. 4** The white area represents tumor area in which the electric field exceeds 1000 V/cm in five electrode configurations. Pulse potential was 1000 V/cm, tumor conductivity was 0.17 S/m.

**Fig. 5** Fraction of tumor within electric field targets (500, 800, 1000 V/cm) are depicted against the pulse potential for five electrode configurations. Triangles, open diamonds, and asterisks represent field targets of 500, 800, and 1000 V/cm, respectively.

**Fig. 6** The fraction of tumor within the target field of 1000 V/cm is depicted against vitreous electric field for five electrode configurations.
configurations #4, #3, and #1. Configuration #1 was found to be particularly effective in minimizing the damage in the vitreous area. For this reason, further analyses are reported for the latter three, “safer” electrode configurations.

Figure 7 depicts the effect of tumor conductivity on treatment efficiency. Figure 7(a) depicts the fraction of tumor volume in which the electric field is larger than the target field of 1000 V/cm versus the pulse potential for five tumor conductivities. As expected, tumor conductivity was found to be inversely proportional to the treatment efficiency. Figure 7(b) depicts the tumor fraction in which the electric field is larger than 1000 V/cm versus the tumor conductivity factor, for a pulse potential of 1500 V. Configuration #1 was not found to be sensitive to tumor conductivity, whereas treatment efficiency is affected by tumor conductivity in configurations #3 and #4. This result further demonstrates the importance of electrode configuration design analysis for developing a NTIRE treatment protocol for the eye.

Effect of Heating by Electrical Pulses. The heating effect of the electric pulse was simulated for pulse potentials of 1500, 500, and 2000 V and electrode configurations #1, #3, and #4, respectively. Electric pulses with pulse duration of $1 \times 10^{-2}$, $1 \times 10^{-3}$, and $1 \times 10^{-6}$ s were simulated at pulse frequencies of 0.1–10 Hz. Figure 8 depicts a typical case of maximal and average variation in temperature in response to two electrical pulses in the case of electrode configuration #4 (which had the highest scleral temperature increase). In this specific pulse setting there are large variations in temperature during and between the pulses in the retina, sclera, and tumor as compared to the relatively stable temperature in other ocular domains. The temperature increase which is related to the pulsed Joule heating is followed by temperature decrease, which is caused by heat convection and radiation from the eye (see Methods). It can be seen that the second temperature peak is slightly higher than the first temperature peak.

Figure 9 depicts the maximal and the average temperatures as a function of time, in response to 90 electric pulses with pulse repetition frequency of 1 Hz in the retina, sclera, and tumor. The
temperature increases as a function of the number of pulses in both the maximal as well as the average temperature. The combined effect of pulse duration and pulse repetition frequency on maximal scleral temperature after 90 pulses in the three analyzed electrode configurations is depicted in Fig. 10. Increased scleral temperature was associated with increased pulse duration and increased pulse repetition frequency. Pulse duration of 100 microseconds was associated with scleral temperatures higher than 70°C in electrode configurations #1 and #4 in all pulse frequencies while the temperature rise in configuration #3 was dependent
on pulse repetition frequency. In contrast, a pulse duration of 1 microsecond was not associated with significant increase in scleral temperature in all pulse frequencies setting. In general, maximal scleral temperature was higher in electrode configuration #4 followed by configurations #3 and #1.

### Discussion

This mathematical simulation study suggests that NTIRE can, theoretically, be safely applied to the treatment of intraocular tumors. The simulation shows that the maximal electric field is near the electrodes, while the average electric field outside the area of interest was significantly lower. The simulation of NTIRE treatment using electrode configuration #1 shows that the electric field in the tumor is more than three orders of magnitude higher as compared to the electric field outside the tumor. This is a consequence of the proximity between the electrode and the tumor and the heterogeneity of the tissue electrical properties. Interestingly, the safety factor was lower in configuration #3, which is similar to electrode configuration #1, except for the smaller external electrode. The safety factor of configuration #4 was found to be relatively high, which suggest that it might be possible to use this external only electrode configuration for intraocular tumor ablation. This particular configuration has great advantage over intraocular electrode configurations associated with insertion of intraocular electrodes. The insertion of intraocular electrodes might be associated with intraocular complications, such as infection, retinal detachment, similar to what is reported for intraocular injection of drugs [39-40].

The fraction of tumor volume within or above a target electric field was found to be dependent on electrode configuration, pulse potential, as well as tumor conductivity. Though the fraction of the tumor within the target field was highest in electrode configuration #3, when safety considerations are applied, it might be desirable to use electrode configurations #1 or #4. Increased tumor conductivity was associated with decreased intratumor electric field. This effect was largest in configuration #1 as compared to configuration #4 while in configuration #3 it was negligible (Fig. 7(b)).

The thermal effect of NTIRE was found to be dependent on electrode configuration and pulse potential, duration, and repetition frequency. As expected, maximal temperature rise was found in the sclera, because of the electrode proximity and electric field magnitude. The combined effect of pulse duration and repetition frequency demonstrated that 1 microsecond pulse was not associated with increased temperature, while pulse duration of 10 microseconds was associated with significantly increased scleral temperature when pulse repetition frequency was higher than 1 Hz. Pulse duration of 100 microseconds (which is the commonly reported pulse duration [41,42]) was associated with increased scleral temperature in all pulse repetition frequencies in electrode configurations #1 and #4 and for most frequencies in #3. The results suggest that application of 100 microsecond pulses on the eye sclera should be done with low pulse repetition frequency, or should be associated with a cooling device, similar to RF ablation [43].

It should be emphasized that this is a first order model, whose primary goal is to introduce the problem and to illustrate the nature of the solutions. First, for the sake of simplicity, electrodes were modeled as boundaries and not as 3D objects. This is similar to previous papers [14,41,43]. However, in reality the metallic electrodes can serve as a heat sink, thus reducing the temperature rise in tissue. Thus our analysis can be regarded as a worse case scenario for evaluation of temperature increase. Second, recent studies reported changes in electric conductivity of tissues during electroporation. For example, Ivorra et al. [44] reported an increase of up to 180% in tumor electrical conductivity post pulsing and suggested using the change in conductivity as a parameter to monitor treatment efficiency. Local changes in conductivity in the electroporated region can have an effect on electric fields and energy dissipation. Increased conductivity can reduce the intratumor electric field and treatment efficiency (Fig. 7), similar to what was reported in some experimental and simulation studies [44–46]. Furthermore, the changes in electric field and electric current could increase the production of heat (Eq. (2)), although the effect is not linear. However, because of the complexity of our model and the many unsolved issues (such as target field, threshold for damaged tissue, and more) we have not incorporated these changes into our model. In our model, we adopted the heterogeneity of the tissue conductivity in our model. Third, both the electric field as well as the temperature analysis employs relatively simplistic models that lack the fine details in such models as those reported by Shafahi [19].

In conclusion, this theoretical study suggests that optimization of electrode configuration and pulse parameters are important for the NTIRE treatment planning in the eye. While this first order model is valuable as an indication of the relevant issues in treatment of uveal melanoma with NTIRE, more advanced models will be needed to fine tune the clinical applications. Currently, our group is involved in animal as well as in vitro human research on NTIRE treatment of ocular tumors using theoretical analysis as guidelines. It is hoped that combining data from experiments with further advances in mathematical modeling should eventually produce a clinical NTIRE cure to uveal melanoma.

### References


