Calculations of Cell Transmembrane Voltage Induced by Time-Varying Magnetic Fields

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***Abstract*— Electric pulses can create pores and/or render cell membranes permeable, and this effect has been studied for decades. Applications include cell membrane permeabilization for gene electrotransfer, drug delivery, and related electrochemotherapy, as well as tissue ablation. Here, we probe the use of time-varying magnetic fields to modulate the transmembrane voltage (TMV) across cell membranes through numerical simulations. This could be a contactless, noninvasive technique. Results show that the induced TMV values exceeding the 1 V threshold for electroporation could be achieved for short duration pulsing with fast rise and fall times. The strongest response is then predicted to occur when the lateral distance between a cell and the center of a current carrying coil equals the coil radius. The induced TMV is shown to peak when the gradient in the magnetic potential is the largest. However, with the more realistic but longer microsecond pulse stimulation systems, the induced TMV is much smaller. Hence, developing shorter pulses or fast rise times is critical for achieving membrane poration based on time-varying magnetic fields. Other effects could also focus on the use of nanoparticles (including magnetic materials) for possible heating for synergistic enhancements of transport through tumor cell membranes.**

***Index Terms*— Cellular poration, magnetic stimulation, modeling, time-varying fields, transmembrane potential.**

I. Introduction

ELECTRIC pulses can create pores in biological membranes which enhances material transport across affected cells. This effect termed "electroporation," dates back about two hundred years [1]. Much later, Neumann *et al.* [2] used pulsed electric fields to temporarily permeabilize cell membranes to deliver deoxyribonucleic acid (DNA) into cells, and coined the term "electroporation." More recent applications include gene electrotransfer [3]–[6], electrochemotherapy [7], [8], drug delivery [9], [10], and controlled immunotherapy [11]–[13]. Progress in the past ten years has led to the use of high-intensity (∼50–100 kV/cm) nanosecond duration pulsed electric fields [14]–[16]. Using electric pulsing, the following processes have been demonstrated: 1) the release of intracellular calcium which is an important messenger [17] for calcium internalization through electroporation for novel electrochemotherapy [18], [19]; 2) the shrinkage of tumors in rats [20], [21]; 3) temporary blockage of action potential in nerves [22]; 4) activation of platelets for wound healing [23]; and 5) neuronal action potential triggering [24]. Furthermore, the application of nanosecond duration and high-field pulses prevents (or reduces) heating, though not necessarily for the longer microsecond durations. The nanosecond pulsed electric fields could circumvent issues such as muscle contraction and possible burns when applied *in vivo* and allow for treatments in close proximity to critical structures and/or large vessels [25]. More progress in this field, based on irreversible electroporation and longer pulse durations, has been demonstrated by the Davalos group [26], [27].

However, exposure of biological cells and tissues to magnetic fields has not been studied much. Most of the research studies till date have focused on pulsed electric field treatment relying on electrode contact. An even newer modality that holds promise is based on the interactions of magnetic fields with living cells and tissues. Progress in experimental techniques has resulted in the burgeoning development of new approaches to target and observe the effects of magnetic fields at the intracellular and molecular levels [28]–[30]. The first successful stimulation of nerves using magnetic fields was by Polson *et al.* [31] in 1982. Since then, pulsed magnetic fields have been used in transcranial magnetic stimulation (TMS), which has been effective in the treatment of depression [32], seizures [33], Parkinson's disease [34], and in diagnostics [35].

When exposed to a time-varying magnetic field, neural tissue can be stimulated by an induced electric current, which creates/imposes a voltage across cell membranes and could trigger an action potential. As a possible application, one can anticipate the manipulation of mitochondrial potential. Mitochondria, an important cellular organelle, has been involved in a large range of physiological processes such as supplying cellular energy, signaling, cell differentiation, and even cell death [36]. Their large negative membrane potential (about −180 mV) is the main driving force in the regulatory processes [37] and has been associated with cell death in aging and in many neurological disorders [38], [39].

Consequently, analysis of magnetic field effects is of significance in understanding bio-functional changes, potential

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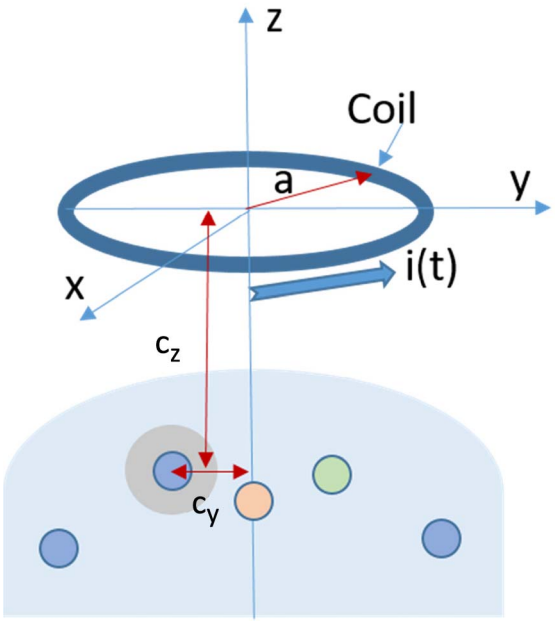

Fig. 1. Schematic of a current carrying coil above biological cells.

treatment possibilities for neurological diseases, and to ascertain the dose dependencies and potential threshold limits. Also, while medical applications based on electroporation require the application of electric pulses via electrodes inserted into tissue, pulsed magnetic fields would allow treatment without the use of invasive electrodes. *This advantage could lead to an expansion of bioelectric treatments by allowing clinicians to affect any target within the body in anoninvasivemanner.* Since time-varying currents can induce magnetic fields and give rise to ac electric fields based on Lenz's law and Maxwell's equations, it becomes germane to probe magnetic stimulation in the context of cell function manipulation.

In this article, an analysis of the time-dependent development of electric fields at cell membranes due to an externally applied magnetic field is presented based on numerical simulations. The parameter space for the magnetic stimulation for bringing about membrane poration is discussed. Our results focus on the time-dependent magnetic vector potential and the resulting induced transmembrane voltage (TMV). It thus constitutes a feasibility study for the possibility of generating suitable TMVs for cell membrane poration via Faraday induction for a contactless approach.

II. Model Details

Fig. 1 shows the basic geometry used in this modeling effort. A ring of radius "a" is shown to carry an ac current $I(t)$, with the coordinate system (x, y, z) having its origin at the center of the ring. This current carrying ring shown in Fig. 1 is displaced by distances of c_y and c_z (along the y- and z-axes) from the center of a spherical cell. For concreteness, the induced electric field (E_{ind}) and TMV at this chosen cell are assumed to be of focal interest to the present calculations. Calculations of these quantities here involved the following sequence. First, the magnetic vector potential produced by the ac current is calculated. The expressions are well-known, especially in the reference frame centered at the current carrying ring. In spherical coordinates, $A_r = A_\theta = 0$, while the third component takes the form [40]

$$A_\varphi = \frac{\mu_0 N I(t) a}{4\pi} \int_0^{2\pi} \frac{\cos(\varphi) d\varphi}{\sqrt{r^2 + a^2 - 2aR\sin(\theta)\cos(\varphi)}} \tag{1a}$$

where N represents the number of turns of the circular coil and R the radial distance between a field point and a differential element on the ring. Equation (1) can alternatively be cast in terms of the complete elliptic integrals of the first and second kind ($K(m)$ and $E(m)$, respectively) as

$$A_\varphi = \frac{\mu_0 N I(t) a}{\pi\sqrt{a^2 + x^2 + y^2 + z^2 + 2a\sqrt{x^2 + y^2}}} \times \frac{(2-m)K(m) - 2E(m)}{m} \tag{2}$$

where $m = (4a(x^2 + y^2)^{1/2}a^2 + x^2 + y^2 + z^2 + 2a(x^2 + y^2)^{1/2})$. Next, expressions for the magnetic vector potential are obtained in a reference frame at the center of the spherical cell. This is done by converting $\boldsymbol{A}$ to a Cartesian frame centered at the ring, and then, using a translation to the cell center. Thus, the components of $\boldsymbol{A}$ in the Cartesian frame become

$$A_x = -\sin(\varphi)A_\varphi = -[y/(x^2 + y^2)^{1/2}]A_\varphi \tag{3a}$$
$$A_y = \cos(\varphi)A_\varphi = [x/(x^2 + y^2)^{1/2}]A_\varphi \tag{3b}$$
$$\text{and, } A_z = 0. \tag{3c}$$

Upon translation to a new rectangular system centered at the cell, the components become

$$A_{x'} = -[(y' - c_y)/(x'^2 + (y' - c_y)^2)^{1/2}]A_\varphi \tag{4a}$$
$$A_{y'} = [x'/(x'^2 + (y' - c_y)^2)^{1/2}]A_\varphi \tag{4b}$$
$$\text{and, } A_{z'} = 0. \tag{4c}$$

Finally, converting the co-ordinates back to the spherical system centered at the cell, one obtains the following expressions for the magnetic vector potential:

$$A_{r'} = A_{X'}\sin(\theta')\cos(\varphi') + A_{Y'}\sin(\theta')\sin(\varphi') \tag{5a}$$
$$A_{\theta'} = A_{X'}\cos(\theta')\cos(\varphi') + A_{Y'}\cos(\theta')\sin(\varphi') \tag{5b}$$
$$\text{and, } A_{\varphi'} = -A_{X'}\sin(\varphi') + A_{Y'}\cos(\varphi'). \tag{5c}$$

The radial component of the total electric field induced (E) is then given by $E_r = -j\omega A_{r'} - \nabla V$. The scalar potential V appears due to charge accumulation that appears from the application of a time-varying magnetic field [41]. Expressions for the scalar potential are known and, for spherical geometry, can be expressed as

$$V(r, \theta, \varphi) = D_0 r^2 \sin(\theta)\cos(\varphi), \quad \text{for } R_+ < r < \infty \tag{6a}$$
$$V(r, \theta, \varphi) = (C_1 + D_1/r^2)\sin(\theta)\cos(\varphi), \quad \text{for } R_- < r < R_+ \tag{6b}$$
$$\text{and, } V(r, \theta, \varphi) = C_2 \sin(\theta)\cos(\varphi), \quad \text{for } 0 < r < R_- \tag{6c}$$

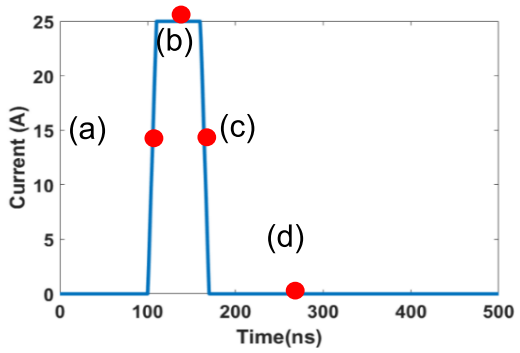

Fig. 2. Current waveform is taken to excite the 25-turn coils of radius "a" to create the time-dependent magnetic field. The four time instants "a," "b," "c," and "d" shown correspond to 105, 130, 165, and 180 ns.

where D_0, D_1, C_1, and C_2 are constants that can be determined from the continuity in potential and current density, while R_- and R_+ are the inner and outer radii of the cell membrane. The condition on potentials at the two interfaces ($r = R_-$ and $r = R_+$, with membrane thickness $d = R_+ - R_-$) yields

$$D_0/R_+^2 = C_1 R_+^2 + D_1/R_+^2 \tag{7a}$$

$$\text{and} \quad C_2 R_- = C_1 R_- + D_1/R_-^2. \tag{7b}$$

Similarly, continuity between the normal component of the current density across either sides of the two interfaces yields

$$S_0[-j\omega B_0 C/2 + 2D_0/R_+^3] = S_1[-j\omega B_0 C/2 + 2D_1/R_+^3 - C_1] \tag{8a}$$

$$S_1[-j\omega B_0 C/2 + 2D_1/R_-^3 - C_1] = S_2[-j\omega B_0 C/2 - -C_2] \tag{8b}$$

where $S_0 = \sigma_{0U} + j\omega\varepsilon_{\mathrm{OU}}$, $S_1 = \sigma_m + j\omega\varepsilon_m$ and $S_2 = \sigma_i + j\omega\varepsilon_i$. Hence, based on (7) and (8), the scalar potential in all the regions (i.e., intracellular, membrane and extracellular) can be uniquely determined. Using the magnetic vector potential from (5), the entire induced electric field at the membrane is then known.

III. Simulation Results

The input excitation current waveform that was assumed to feed a bundle of 25 turns of coil of radius "a" is shown in Fig. 2. It consisted of a narrow trapezoidal pulse having a 50-ns ON time, and 10-ns rise and fall times. Practically, it is difficult to achieve such short pulses with rapid nanosecond rise and fall times due to the coil inductances. However, this presents the best case scenario and is used as an initial numerical test.

The results obtained from the present simulations are given and discussed next. Details of the various parameters used for the modeling are provided in Table I. Simulation results for the dependence of the magnetic vector potential on the separation between the coil and the cell (parameters c_y and c_z) are discussed next. Figs. 3 and 4 show the results for A_r for different values of the parameters. The value of A_r is seen to exhibit maxima when the separation parameter (c_y) equaled the coil radius (a), as seen in Fig. 3. Furthermore,

TABLE I
List of Parameters Used in the Simulations

Parameter	Value
Radius of coil ("a")	0.15 m
Number of turns in the coil	25
Cell radius ["R= (R_++R_-)/2)"]	10 microns
Membrane thickness ("d")	5 nm
Coil axis-cell distance ("c_y")	0.05 m
Coil center to the cell plane ("c_z")	0.08 m
Membrane permittivity ("ε_m")	7 ε_0
Medium permittivity ("σ_{0U}")	80 ε_0
Cytoplasm permittivity ("ε_i")	80 ε_0
Membrane conductivity ("σ_m")	10^{-7} S/m
Medium conductivity ("σ_{OU}")	0.2 S/m
Cytoplasm conductivity ("σ_i")	0.02 S/m
Pulse ON time	50 ns
Pulse rise time	10 ns
Pulse fall time	10 ns
Time step	1 ps
Simulation time	500 ns
Pulse peak value	500 A
Sampling frequency	1 THz

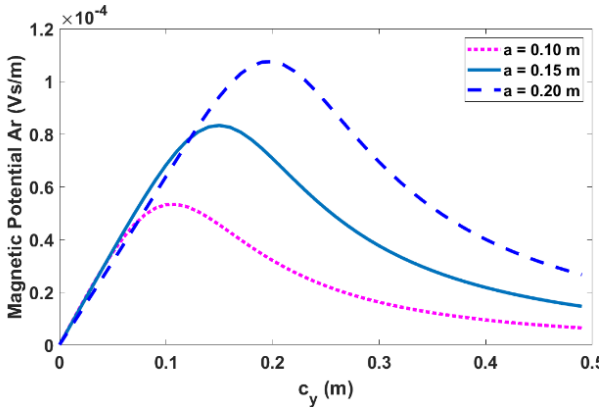

Fig. 3. Magnetic vector potential variation with separation (c_y) between the centers of the cell and coil for different coil radii.

the magnetic vector potential A_r is predicted to reduce (Fig. 4), as the distance of the coil center from the cell increases.

Ultimately, the success of applying a magnetic field (or the driven source current in the coils) depends on the ability to porate cell membranes. The threshold for such poration is often taken to be about 1 V, though in principle, at lower voltages the process could occur though over a longer time. Hence, it is germane to quantify the TMV predictions for such magnetic stimulation. The results for the TMV as a function of azimuthal angle across the surface (φ) and time

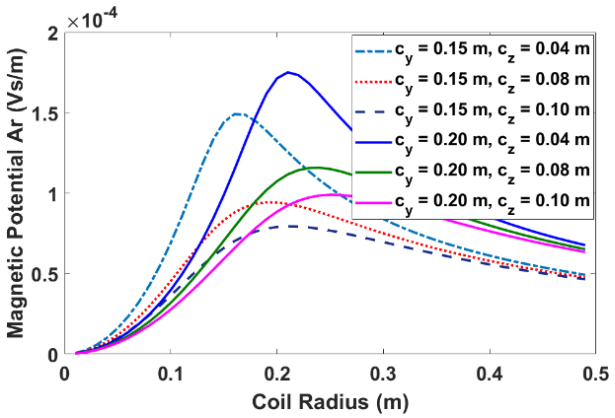

Fig. 4. Magnetic vector potential variation with coil radius for different c_y and c_z distances.

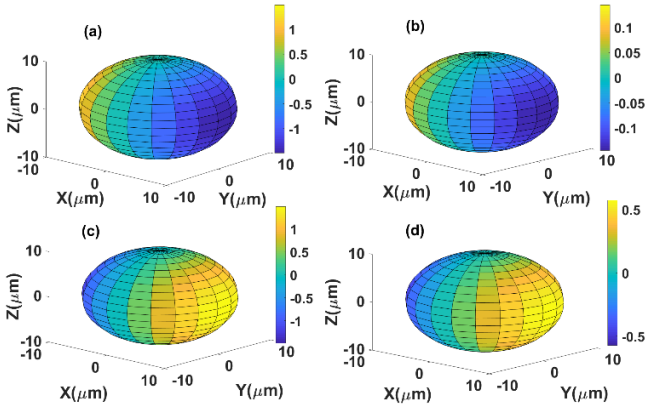

Fig. 6. TMV across the cell surface at four different time instants of: (a) 105 ns, (b) 130 ns, (c) 165 ns, and (d) 180 ns.

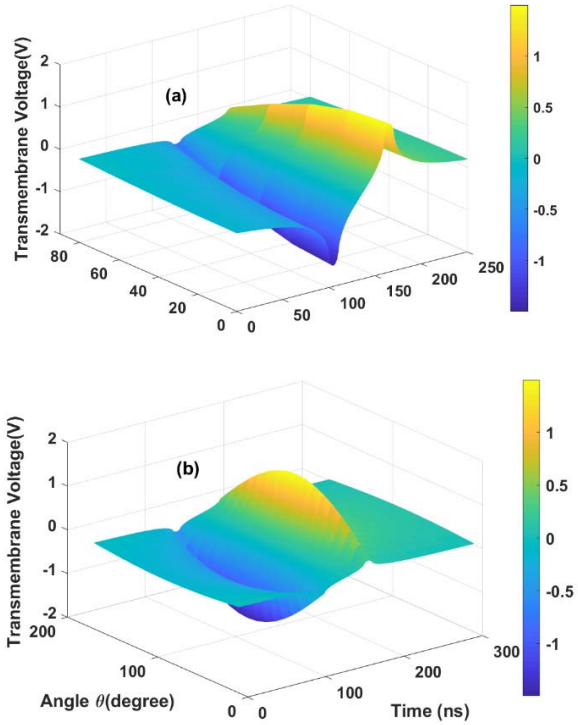

Fig. 5. TMV variation with angular displacement and time for an as spherical cell at different times. (a) Profile with azimuthal angle φ. (b) Variation with polar angle θ.

are shown in Fig. 5(a). Due to the oscillating nature of the applied waveform, both positive and negative TMV values are predicted. Furthermore, the peak magnitudes can be seen to exceed the 1 V threshold, implying there is potential for successful poration by such magnetic stimulation. The TMV as a function of polar angle across the surface (θ) and time are shown in Fig. 5(b). The peak values, as expected, are predicted to be at 90°.

The development of the TMV can perhaps be better understood by looking at the potential profiles. Such a result is shown in Fig. 6 at four different times. These were at 105 ns (when the input pulse reaches the halfway of the rising edge), then at the 130 ns instant (during the input pulse on time), a snapshot after 165 ns (when the input pulse reached the halfway of the falling edge), and a potential surface at 180 ns (10 ns after the input pulse was zero). The induced voltage depends on the rate of change of flux reversal (i.e., the flip in the flux direction) and, hence, is guided by the rising or falling edge of the current pulse. This aspect was emphasized and shown in Fig. 2. As a result, the induced TMV values are predicted to be different at various times. The highest values occur when the rate of change of current is high.

For completeness, a few different values of the biological parameters were also used to probe the dependencies of TMV outcomes on conductivity and/or permittivity. For example, larger values for the membrane-, as well as the intra and extracellular media conductivities, have been reported [42], [43]. For example, the conductivity of blood can also be higher in the ∼0.6–1.0 S/m range. So for completeness, the role of these parameters was also probed next.

The role of conductivity variations was first gauged by choosing a different combination of values. The permittivities of the extra- and intracellular media were fixed at 80 ε_0 and 60ε_0, respectively, while the membrane permittivity was at 9.8ε_0. Results obtained for the time-dependent TMV are shown in Fig. 7. The same input excitation shown in Fig. 2 was used. Based on the plots, lower conductivities (leading to smaller time-varying currents) are predicted to yield smaller membrane voltage buildup. In all cases, the values of ∼1 V or higher could be reached.

The membrane conductivity was not seen to be important in influencing the TMV, as long as the value remained at a low level. For example, changing the conductivity of membrane from 10^{-7} to 10^{-5} S/m did not change the TMV; and so, this is not shown in the figure. Fig. 8 shows the simulation results obtained with changes in the membrane permittivity. The conductivities of the intracellular medium (σ_i), medium (σ_o), and membrane (σ_m) were at 0.8, 1.2, and 10^{-6} S/m, respectively. As might be expected, the lowest permittivity (which would then result in the highest electric field at a given displacement vector) gave rise to the highest TMV. But in any event, TMV values above the electroporation

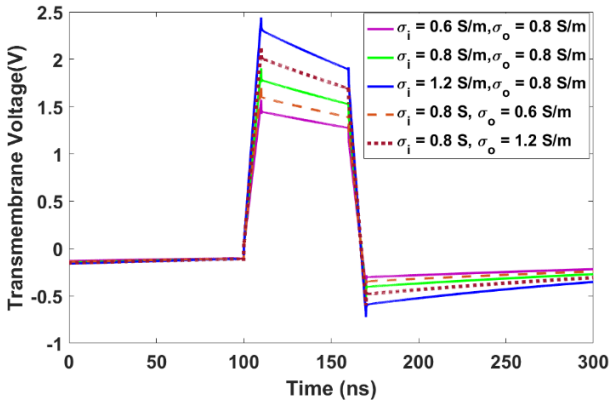

Fig. 7. Time-dependent TMV predicted for the current excitation shown in Fig. 2. Different value combinations of conductivities were used.

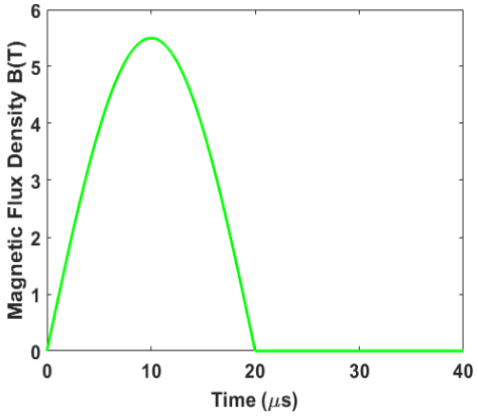

Fig. 9. Magnetic flux density B(t) waveform used for the simulations and similar to that reported by Novickij *et al.* [44].

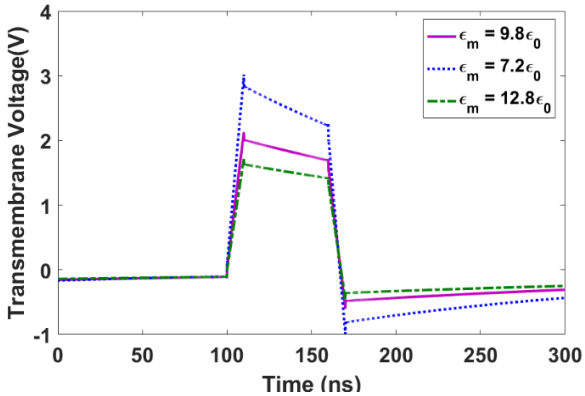

Fig. 8. Simulation results for the time-dependent TMV obtained for different membrane permittivity values.

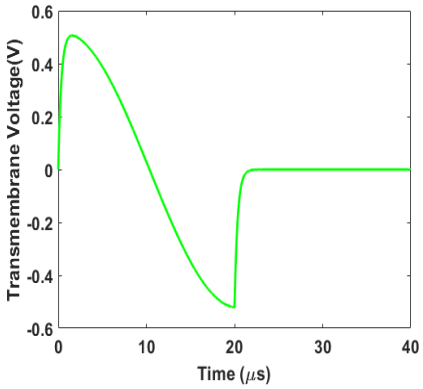

Fig. 10. Simulation results for the TMV for the magnetic waveform shown in Fig. 9 and cell location at the center of the coil stack and radially next to the innermost set of coils.

threshold of ∼1 V could be attained for such short waveforms assumed.

A recent report [44] demonstrated increased transport into cells based on the magnetic stimulation using microsecond pulses. For comparison, a waveform similar to (but not exactly the same as) that used by Novickij *et al.* [44] and shown in Fig. 9 was used to model TMV development. The biological cell was assumed to lie in the region surrounded by 66 wound coils consisting of 11 windings stacked in six layers, with a cylindrical hole at the core. In the simulations, the average radius of the coils from the axial center was 3.75 mm. The biological cell was taken to be at the center of the coil stack ($c_z = 0$) and radially near the innermost set of coils. Results shown in Fig. 10 for the above microsecond stimulation indicate a fairly robust TMV response. A peak value of ∼0.5 V is predicted.

IV. Discussion

Electric current pulses, which can produce time-varying magnetic fields, were shown to be capable of inducing electric potential at cell membranes. The transmembrane potential generation was based on Maxwell's principle of voltage induction from time-varying magnetic fields. The advantage of such stimulation is that it presents the possibility of contactless operation by relying on "action at a distance." The main objective was to obtain quantitative assessments of the TMV values based on such a modality.

The strongest response was predicted when the lateral distance between cells and the coil center would equal the coil radius. Also, in the present modality, the TMV peaks were shown to depend on the gradient in A_r, which would be at locations different from the gradients in the electric potential. The next natural step for such evaluations would then be to couple the induced TMV for obtaining the poration dynamics. The latter could be analyzed based on the Smoluchowski approaches [9], [45], [46].

The response from time-dependent magnetic fields of longer time durations indicated a much lower TMV generation. The presence of inductances associated with the current-carrying coils in practical systems is a natural impediment in causing delays and slowing the rate of magnetic field build-up. Such constraints would make it difficult to achieve short-duration pulses or fast-rising waveforms in the submicrosecond time scales. However, this practical difficulty could conceivably be offset by attempting to induce localized heating of cell membranes by the external excitation and promoting synergistic effects. As is well known, the temperature increase (as well as temperature gradients) can aid bioeffects, promote

electropermeabilization, and aid transport across membranes [47], [48]. A possibility in this connection might be to use magnetic nanoparticles (MNPs) to enhance local fields and concentrate the energy absorption in selected areas. Simple simulations have demonstrated that such MNPs could be positioned very close to the membrane, or even possibly enter the cell [49] because of their small size. If so, the combined use of magnetic stimulation, with MNPs that can attach to cells (or even tumor masses) via specific binding agents, could facilitate localized heating, or even hyperthermia-based killing with minimal collateral damage. A recent and useful development in this regard has been the development of cobalt- and manganese-doped, iron oxide magnetic nanoparticles (CoMn-IONP) encapsulated in biocompatible PEG–PCL (poly(ethylene glycol)-*b*-poly(ε-caprolactone))-based nanocarriers. These can form nanoclusters with a high heating capacity [50].

Finally, for completeness, it may be mentioned that even ordinary (and easily available) gold nanoparticles (NPs) could play a useful role in overcoming weaknesses of the magnetic (or electromagnetic) stimulation modality. For example, very recent experiments conducted on Chinese Hamster Ovary cells and *Escherichia coli* suggest that Au NPs can act as *distributed nanoelectrodes* and enhance high-intensity pulsed electromagnetic field effects at plasma membranes [51]. So then, apart from any heating benefits that could be garnered, the local electric field enhancements based on the local nanoelectrode concept could also work to build higher TMV magnitudes. These are all possibilities that merit further study.

V. Summarizing Conclusion

Ultrashort ($\sim$50 ns) and high electric fields ($\sim$100 kV/cm) have been proposed and subsequently used over the past two decades for biomedical applications using contacted techniques. The advantages of low-energy deposition for this modality include a low probability for collateral damage to neighboring tissues. The ability to affect internal organelles is another feature of the shorter electrical pulses. However, this technique has the disadvantage of being invasive and requires electrical contacts. On the other hand, electric fields can be generated through electromagnetic induction based on time-varying currents at a distance by creating alternating magnetic fields. Up until now, pulsed magnetic fields have already been used in applications such as TMS, in treatment of depression, seizures, and for Parkinson's disease. Being a noncontacted technique, this modality could be used to treat any part of the body.

In this contribution, the possibility of generating transmembrane potentials (TMVs) across a cell membrane from such an externally placed set of current carrying coils was assessed. The results for short-duration current pulsing showed that TMV values exceeding the 1 V threshold for electroporation [52], [53] could be achieved at manageable current magnitudes. Furthermore, it was demonstrated that the strongest response would occur when the lateral distance between a cell and the coil center equaled the coil radius. A lower magnetic vector potential was predicted for higher separation between centers of the coil and the cell. However, with the more realistic but longer microsecond pulse stimulation, the induced TMV was predicted to be smaller. A value of $\sim$0.5 V was obtained, which is still fairly robust. It is possible though that the cellular transport of drugs, calcium, or other ions for therapeutic applications with such longer magnetic pulses might be slower and not very efficient. The delays for transport with lower induced TMV is well known [54]. In this regard, multiple pulsing could be attempted to boost bioeffects. Another useful strategy would be to develop shorter pulses at relatively high currents or fast rise times. Future work could also focus on possible local field enhancements based on NPs or the use of magnetic NPs with longer pulses for concentrated energy absorption in the vicinity of tumor cells for aiding transport, or destruction by hyperthermia.

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References

[1] J. A. Nollet, *Recherches sur les Causes Particulieres des phénoménes électriques*. France, Paris: Guerin and Delatour, 1754.

[2] E. Neumann, M. Schaefer-Ridder, Y. Wang, and P. H. Hofschneider, "Gene transfer into mouse lyoma cells by electroporation in high electric fields," *EMBO J.*, vol. 1, no. 7, pp. 841–845, Jul. 1982.

[3] A. I. Daud, R. C. DeConti, S. Andrews, P. Urbas, A. I. Riker, V. K. Sondak, P. N. Munster, D. M. Sullivan, K. E. Ugen, J. L. Messina, and R. Heller, "Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma," *J. Clin. Oncol.*, vol. 26, pp. 5896–5903, Nov. 2008.

[4] A. V. Titomirov, S. Sukharev, and E. Kistanova, "*In vivo* electroporation and stable transformation of skin cells of newborn mice by plasmid DNA," *Biochimica et Biophysica Acta Gene Struct. Expression*, vol. 1088, no. 1, pp. 131–134, Jan. 1991.

[5] F. M. André *et al.*, "Efficiency of high- and low-voltage pulse combinations for gene electrotransfer in muscle, liver, tumor, and skin," *Hum. Gene Therapy*, vol. 19, no. 11, pp. 1261–1272, Nov. 2008.

[6] C. Rosazza, S. H. Meglic, A. Zumbusch, M.-P. Rols, and D. Miklavčič, "Gene electrotransfer: A mechanistic perspective," *Current Gene Therapy*, vol. 16, no. 2, pp. 98–129, Apr. 2016.

[7] L. M. Mir *et al.*, "Electrochemotherapy, a new antitumor treatment: First clinical trial," *Comptes Rendus de l'Academie des Sci. III, Sci. de la vie*, vol. 313, no. 13, pp. 613–618, 1991.

[8] D. Miklavčič, B. Mali, B. Kos, R. Heller, and G. Serša, "Electrochemotherapy: From the drawing board into medical practice," *BioMed. Eng. OnLine*, vol. 13, no. 1, p. 29, 2014.

[9] M. R. Prausnitz, V. G. Bose, R. Langer, and J. C. Weaver, "Electroporation of mammalian skin: A mechanism to enhance transdermal drug delivery," *Proc. Nat. Acad. Sci. USA*, vol. 90, no. 22, pp. 10504–10508, 1993.

[10] M. L. Yarmush, A. Golberg, G. Serša, T. Kotnik, and D. Miklavčič, "Electroporation-based technologies for medicine: Principles, applications, and challenges," *Annu. Rev. Biomed. Eng.*, vol. 16, no. 1, pp. 295–320, Jul. 2014.

[11] R. Nuccitelli, J. C. Berridge, Z. Mallon, M. Kreis, B. Athos, and P. Nuccitelli, "Nanoelectroablation of murine tumors triggers a CD8-dependent inhibition of secondary tumor growth," *PLoS ONE*, vol. 10, no. 7, Jul. 2015, Art. no. e0134364.

[12] C. Y. Calvet and L. M. Mir, "The promising alliance of anti-cancer electrochemotherapy with immunotherapy," *Cancer Metastasis Rev.*, vol. 35, no. 2, pp. 165–177, Mar. 2016.

[13] G. Sersa *et al.*, "Electrochemotherapy of tumors as *in situ* vaccination boosted by immunogene electrotransfer," *Cancer Immunol., Immunotherapy*, vol. 64, no. 10, pp. 1315–1327, Jun. 2015.

[14] T. B. Napotnik, M. Rebersek, P. T. Vernier, B. Mali, and D. Miklavčič, "Effects of high voltage nanosecond electric pulses on eukaryotic cells *(in vitro)*: A systematic review," *Bioelectrochemistry*, vol. 110, pp. 1–12, Aug. 2016.

[15] K. H. Schoenbach *et al.*, "Ultrashort electrical pulses open a new gateway into biological cells," *Proc. IEEE*, vol. 92, no. 7, pp. 1122–1137, Jul. 2004.

[16] R. P. Joshi and K. H. Schoenbach, "Bioelectric effects of intense, ultrashort electric pulses," *Crit. Rev. Bio-Med. Eng.*, vol. 38, no. 3, pp. 255–304, 2010.

[17] S. J. Beebe, P. F. Blackmore, J. White, R. P. Joshi, and K. H. Schoenbach, "Nanosecond pulsed electric fields modulate cell function through intracellular signal transduction mechanisms," *Physiol. Meas.*, vol. 25, no. 4, pp. 1077–1093, Jul. 2004.

[18] K. L. Hoejholt *et al.*, "Calcium electroporation and electrochemotherapy for cancer treatment: Importance of cell membrane composition investigated by lipidomics, calorimetry and *in vitro* efficacy," *Sci. Rep.*, vol. 9, no. 1, pp. 1–12, Mar. 2019.

[19] S. K. Frandsen, H. Gissel, P. Hojman, T. Tramm, J. Eriksen, and J. Gehl, "Direct therapeutic applications of calcium electroporation to effectively induce tumor necrosis," *Cancer Res.*, vol. 72, no. 6, pp. 1336–1341, Jan. 2012.

[20] N. Jourabchi, K. Beroukhim, B. A. Tafti, S. T. Kee, and E. W. Lee, "Irreversible electroporation (NanoKnife) in cancer treatment," *Gastrointestinal Intervent.*, vol. 3, no. 1, pp. 8–18, Jun. 2014.

[21] A. G. Pakhomov, *Advanced Electroporation Techniques in Biology and Medicine*, A. G. Pakhomov, D. Miklavcic, and M. S. Markov, Eds. Boca Raton, FL, USA: CRC Press, 2010.

[22] R. P. Joshi, A. Mishra, J. Song, A. G. Pakhomov, and K. H. Schoenbach, "Simulation studies of ultrashort, high-intensity electric pulse induced action potential block in whole-animal nerves," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 4, pp. 1391–1398, Apr. 2008.

[23] K. H. Schoenbach *et al.*, "Bioelectric effects of intense nanosecond pulses," *IEEE Trans. Dielectr. Electr. Insul.*, vol. 14, no. 5, pp. 1088–1109, Oct. 2007.

[24] A. G. Pakhomov, I. Semenov, M. Casciola, and S. Xiao, "Neuronal excitation and permeabilization by 200-ns pulsed electric field: An optical membrane potential study with FluoVolt dye," *Biochimica et Biophysica Acta Biomembranes*, vol. 1859, no. 7, pp. 1273–1281, Jul. 2017.

[25] M. Ahmed, C. L. Brace, F. T. Lee, and S. N. Goldberg, "Principles of and advances in percutaneous ablation," *Radiology*, vol. 258, no. 2, pp. 351–369, Feb. 2011.

[26] E. L. Latouche, C. B. Arena, J. W. Ivey, P. A. Garcia, T. E. Pancotto, N. Pavlisko, S. S. Verbridge, R. V. Davalos, and J. H. Rossmeisl, "High-frequency irreversible electroporation for intracranial meningioma: A feasibility study in a spontaneous canine tumor model," *Technol. Cancer Res. Treat.*, vol. 17, pp. 1–10, Aug. 2018.

[27] J. F. Edd, L. Horowitz, R. V. Davalos, L. M. Mir, and B. Rubinsky, "*In vivo* results of a new focal tissue ablation technique: Irreversible electroporation," *IEEE Trans. Biomed. Eng.*, vol. 53, no. 7, pp. 1409–1415, Jul. 2006.

[28] M. H. Cho *et al.*, "A magnetic switch for the control of cell death signalling in *in vitro* and *in vivo* systems," *Nature Mater.*, vol. 11, no. 12, pp. 1038–1043, Oct. 2012.

[29] S. Qin *et al.*, "A magnetic protein biocompass," *Nature Mater.*, vol. 15, no. 2, pp. 217–226, Nov. 2015.

[30] J. Dobson, "Remote control of cellular behaviour with magnetic nanoparticles," *Nature Nanotechnol.*, vol. 3, no. 3, pp. 139–143, Mar. 2008.

[31] M. J. R. Polson, A. T. Barker, and I. L. Freeston, "Stimulation of nerve trunks with time-varying magnetic fields," *Med. Biol. Eng. Comput.*, vol. 20, no. 2, pp. 243–244, Mar. 1982.

[32] C. M. Epstein and K. R. Davey, "Iron-core coils for transcranial magnetic stimulation," *J. Clin. Neurophysiol.*, vol. 19, no. 4, pp. 376–381, Aug. 2002.

[33] P. A. Anninos, N. Tsagas, J. I. Jacobson, and A. Kotini, "The biological effects of magnetic stimulation in epileptic patients," *Panminerva Med.*, vol. 41, pp. 207–215, Sep. 1999.

[34] M. Cotelli, R. Manenti, S. F. Cappa, O. Zanetti, and C. Miniussi, "Transcranial magnetic stimulation improves naming in alzheimer disease patients at different stages of cognitive decline," *Eur. J. Neurol.*, vol. 15, no. 12, pp. 1286–1292, Dec. 2008.

[35] P. M. Rossini and S. Rossi, "Transcranial magnetic stimulation: Diagnostic, therapeutic, and research potential," *Neurology*, vol. 68, no. 7, pp. 484–488, Feb. 2007.

[36] H. M. McBride, M. Neuspiel, and S. Wasiak, "Mitochondria: More than just a powerhouse," *Current Biol.*, vol. 16, no. 14, pp. R551–R560, Jul. 2006.

[37] J. Berg, J. Tymoczko, and L. Stryer, *Biochemistry*. San Francisco, CA, USA: Freeman, 2002.

[38] M. F. Beal, "Mitochondrial dysfunction in neurodegenerative diseases," *Biochim. Biophys. Acta*, vol. 1366, pp. 211–223, Aug. 1998.

[39] A. H. Schapira *et al.*, "Mitochondria in the etiology and pathogenesis of Parkinson's disease," *Ann. Neurol.*, vol. 44, pp. S89–S98, Sep. 1998.

[40] J. Simpson, J. Lane, C. Immer, and R. Youngquis, "Simple analytic expressions for the magnetic field of a circular current loop," NASA, Washington, DC, USA, Tech. Rep. NASA/TM-2013-217919, Feb. 2001.

[41] J. A. Stratton, *Electromagnetic Theory*. New York, NY, USA: McGraw-Hill, 1941.

[42] Y. Feldman, I. Ermolina, and Y. Hayashi, "Time domain dielectric spectroscopy study of biological systems," *IEEE Trans. Dielectrics Electr. Insul.*, vol. 10, no. 5, pp. 728–753, Oct. 2003.

[43] T. Kotnik and D. Miklavčič, "Theoretical evaluation of voltage inducement on internal membranes of biological cells exposed to electric fields," *Biophysical J.*, vol. 90, no. 2, pp. 480–491, Jan. 2006.

[44] V. Novickij, J. Dermol, A. Grainys, M. Kranjc, and D. Miklavčič, "Membrane permeabilization of mammalian cells using bursts of high magnetic field pulses," *PeerJ*, vol. 5, p. e3267, Apr. 2017, doi: 10.7717/peerj.3267.

[45] J. C. Neu and W. Krassowska, "Asymptotic model of electroporation," *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Top.*, vol. 59, no. 3, pp. 3471–3482, Mar. 1999.

[46] T. Kotnik, P. Kramar, G. Pucihar, D. Miklavcic, and M. Tarek, "Cell membrane electroporation—Part 1: The phenomenon," *IEEE Electr. Insul. Mag.*, vol. 28, no. 5, pp. 14–23, Sep./Oct. 2012.

[47] J. Song, R. P. Joshi, and K. H. Schoenbach, "Synergistic effects of local temperature enhancements on cellular responses in the context of high-intensity, ultrashort electric pulses," *Med. Biol. Eng. Comput.*, vol. 49, no. 6, pp. 713–718, Feb. 2011.

[48] J. Song, A. L. Garner, and R. P. Joshi, "Molecular dynamics assessment of the role of thermal gradients created by electromagnetic fields on cell membrane electroporation," *Phys. Rev. A, Gen. Phys.*, vol. 7, no. 2, pp. 024003-1–024003-7, Feb. 2017.

[49] K. Yang and Y.-Q. Ma, "Computer simulation of the translocation of nanoparticles with different shapes across a lipid bilayer," *Nature Nanotechnol.*, vol. 5, no. 8, pp. 579–583, Jul. 2010.

[50] H. A. Albarqi *et al.*, "Biocompatible nanoclusters with high heating efficiency for systemically delivered magnetic hyperthermia?" *ACS Nano*, vol. 13, pp. 6383–6395, May 2019.

[51] D. Miklavcic *et al.*, "Contactless electroporation induced by high intensity pulsed electromagnetic fields via distributed nanoelectrodes," *Bioelectrochemistry*, vol. 132, Apr. 2020, Art. no. 107440, doi: 10.1016/j.bioelechem.2019.107440.

[52] Q. Hu and R. P. Joshi, "Analysis of intense, subnanosecond electrical pulse-induced transmembrane voltage in spheroidal cells with arbitrary orientation," *IEEE Trans. Biomed. Eng.*, vol. 56, no. 6, pp. 1617–1626, Jun. 2009.

[53] Q. Hu and R. P. Joshi, "Comparative evaluation of electroporative cellular flows due to monopolar and bipolar nanosecond, high-Intensity pulses," *J. Appl. Phys.*, vol. 122, Jul. 2017, Art. no. 034701.

[54] J. C. Weaver, "Electroporation of cells and tissues," *IEEE Trans. Plasma Sci.*, vol. 28, no. 1, pp. 24–33, Feb. 2000.

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