

In a rut
People make such a big thing of living and it really isn't that important... You go to bed at night and you fall asleep and it's all over. Then you wake up the next day and you have to start all over again.

Andy Warhol



Serhat Altunc

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SPECIAL ARTICLE

Subnanosecond Pulsed-Power Generated Electric Fields for Cancer Treatment

Serhat Altunc, Ph.D.

Abstract—This article summarizes ongoing research on the use of pulsed power-generated electric fields as a delicate tool for skin cancer treatment. A prolate-spheroidal impulse radiating antenna is used as a noninvasive technique for generating an electromagnetic implosion to kill melanoma cells.

Index Terms—Pulsed-power generated electric field, Impulse radiating antennas, Cancer treatment

INTRODUCTION

HIGH-intensity nanosecond pulsed power-generated electric fields have been used in a variety of biological applications and have initiated the establishment of a brand new research area called bioelectrics. Bioelectrics combines two distinct disciplines: pulsed high voltage engineering and cell biology [1-4].

Millions of people around the world are dying each year because of cancer. Even though considerable progress has been made in treating several forms of this disease, we need to develop safer, cheaper, more effective, and less invasive treatment methods.

The effects of intense electrical pulses on biological cells provide a new tool for therapeutic applications such as cancer treatments and gene therapy. Needle arrays have been used for treating melanoma tumors using pulsed electric fields. This, however, is an invasive approach, resulting in discomfort to the patient. Impulse radiating antennas (IRA) are now being investigated as a noninvasive pulsed electric field delivery system for skin cancer treatment. IRAs can deliver a subnanosecond pulse into tissue with a spatial resolution in the centimeter range and even in the millimeter range with the use of a focusing electromagnetic lens [5]. In addition, IRAs can deliver subnanosecond electric fields to melanoma tissues that are not easily accessible with needles. Most recently it has been shown that such pulsed electric fields cause shrinkage and even complete elimination of melanoma tu-

mors [1-4]. A prolate-spheroidal IRA (psIRA) can be used to obtain electromagnetic focusing on the target to reduce the damage to the tissue layers surrounding the target and skin [5-9].

BACKGROUND AND MOTIVATION

Intense nanosecond electric pulses (nEPs) provide a new tool for cancer treatment, gene therapy, etc. For example, nEP can induce apoptosis in mammalian cells. One promising result is the discovery, by the Frank Reidy Center for Bioelectrics at Old Dominion University (<http://www.odu.edu/engr/bioelectrics/>), that nEPs can destroy tumors in mice [1-3].

Pulsed electric fields of 10's kV amplitude delivered in nanoseconds or shorter timescale are an exciting new development in the biomedical field. nEPs have shown the potential to kill skin cancer cells and also allow the insertion of new genes into living cells with the aim of correcting genetic defects. The initial method of applying such electric fields, through implantable electrodes, is a limiting factor with respect to practical applications. A psIRA can be used as a noninvasive cancer treatment tool, opening up the subnanosecond pulse regime, which is thought to offer greater treatment advantages [1-2].

A cell can be modeled as an electrical circuit as in Fig. 1 [4]. One can model the various cell membranes by their capacitances. The cytoplasm and organelles can be modeled by their resistances. The cytoplasm is conductive,

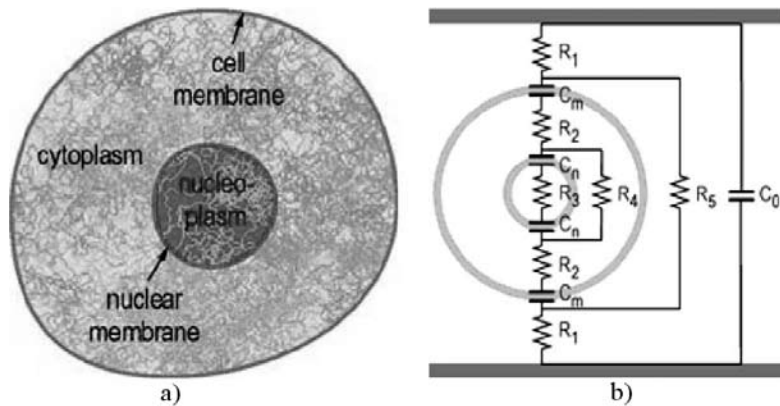


Figure 1. (a) Structure of a biological cell (as would be seen with a light microscope). (b) Double-shell model of a biological cell and superimposed equivalent circuit of the cell [4].

whereas the membranes have low conductivity. Therefore, one can model the cell as a conductor surrounded by an ideally insulating envelope. Embedded proteins in the membrane serve as valves or channels for ions.

While investigating the effect of the electrical pulses on the biological tissues, one should consider four important characteristics that determine their precise effects on the cells. These characteristics are pulse rise time, pulse duration, the number of pulses, and the amplitude of the electric field pulses. Most pulsed electric field effects act on the plasma membrane. The plasma membrane charging time, 100 ns, constitutes a significant division in addressing pulsed electric field effects on biological cells. A subnanosecond duration electric pulse (sEP) will pass through the membrane into the cytoplasm because the sEP has a faster rise time than most mammalian plasma membrane charging time. If we apply long duration pulses compared to the charging time of the capacitor formed by the outer membrane, just the outer membrane will be charged and the electric field between subcellular membranes will be zero for a fully insulating outer membrane. However, in practice, we will also have potential differences between subcellular membranes. This effect will be significant if the pulse rise time is shorter. If the sEP has a sufficiently large amplitude it can have significant effects on organelles [1,2].

When the amplitude of the pulsed electric field is increased beyond the threshold required for voltage-gating effects, but with a pulse duration that is shorter than the charging time of the plasma membrane, an effect at the cell membrane called electroporation occurs [3]. It is believed that this effect creates openings in the cell membrane, allowing for the transfer

of large molecules across the cell membrane. Electroporation is generally reversible and even useful, unless the pulse amplitude is too large and/or its duration too long. The electroporation effect can be used for chemotherapy and gene insertion. Electroporation might allow delivery of certain drugs or nanoparticles into the cell without strongly affecting the viability of the cells. Retention of the pores in the membrane wall, however, can lead to cell death (apoptosis).

If we have a pulsed electric field rising faster than 10 ns, the ions in the cytoplasm have insufficient time to migrate to the plasma membrane and the applied electric field is able to transit the plasma membrane and affect the intracellular structures. Electroporation can now occur at the subcellular membranes and we can manipulate intracellular structures. This can be used to kill cancer cells and insert gene-modified DNA [1,2].

A PROLATE-SPHEROIDAL IMPULSE RADIATING ANTENNA FOR NONINVASIVE CANCER TREATMENT

Research on nEPs is yielding promising results for cancer treatment and gene insertion [1-3]. However, in earlier studies the electric field was invasively delivered to the tumor using implanted electrodes and this treatment has some disadvantages, including discomfort. Current research has been initiated into using psIRAs to noninvasively deliver the sEP to the melanoma cells [5-9].

For sPE applications the dielectric properties of the tissue play a key role in determining the electric field distribution compared with the resistive characteristics of the media. First, for sEPs the conductance of the membranes are as-

Licence to err
You can break every grammatical and syntactical rule consciously when, and only when, you have rendered yourself incapable of breaking them unconsciously.

Bernard Levin

What counts
Throughout all written history the killing of people was never limited by the ability to kill people but always by the amount of intention to kill people.

Edward Teller

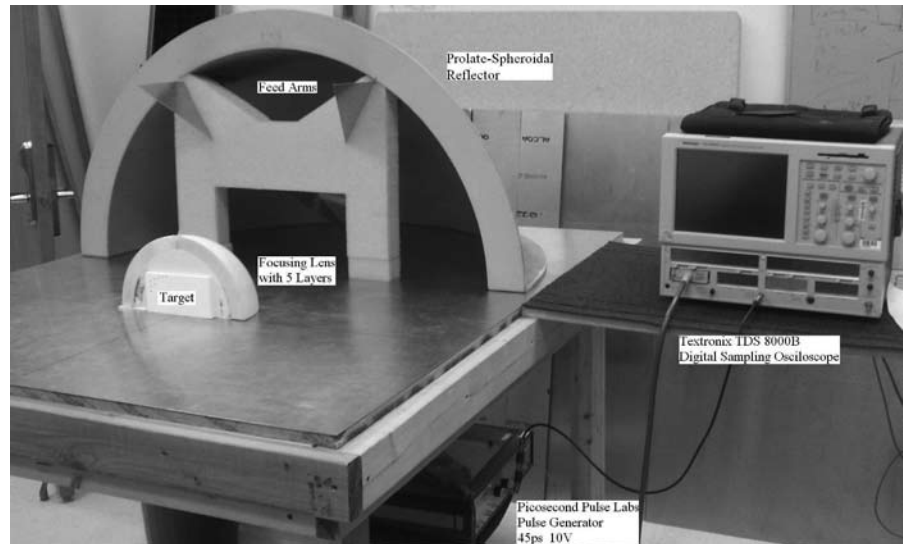


Figure 2. Experimental setup of psIRA and focusing lens geometry for cancer treatment

sumed to be zero and the capacitive components of cytoplasm and nucleoplasm are neglected. Second, subnanosecond regime is giving promising results for electric field-cell interactions. psIRAs may be able to induce apoptosis in tissue instead of needles [1,6].

Using electrodes embedded in the tissue limits the cancer treatment efficacy of the pulsed electric field since the tumor is close to the skin or surface of the body. psIRAs allow one to apply such electric fields to tissues more directly compared with using needles. The psIRA will also reduce the damage to the tissue layers surrounding the target and the skin. The spatial resolution of an electric field generated in tissue depends on the pulse duration and the permittivity of the tissue. Even though IRAs have been mainly designed for far-field applications, for bioelectric applications one needs to operate in the near-field.

A psIRA is used to launch an inhomoge-

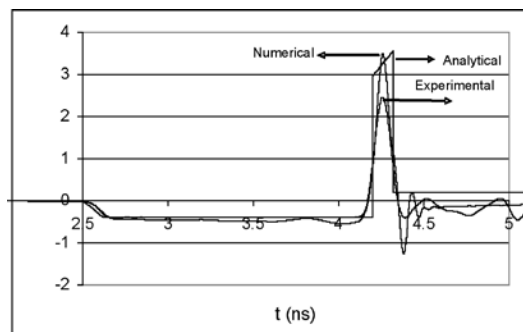


Figure 3. Analytical, numerical and experimental focal waveforms for two-arm psIRA without focusing lens.

neous plane wave from one focal point and reflect it toward a second focal point where the melanoma tissue is located. We choose a special case of the psIRA's geometric parameters (as in [6]) where the geometric parameters are $z_p = 0$, $b = \Psi_0 = .5m$, $a = .625m$, $z_0 = .375m$ (1) where z_p is the z-coordinate of the truncation plane, a and b are the two radii for the prolate-spheroid, and z_0 is the focal distance.

The experimental set-up that is being investigated and would be suitable for cancer treatment uses basically four components: a two feed arm psIRA, a sampling-oscilloscope, a pulse generator, and a focusing lens and target. (It should be noted that only a two feed arm is required in this proof-of-principle experiment since a conducting ground plane is used. In future actual experiments with patients a four feed arm full IRA will be used.) As seen in Fig. 2, we use a Tektronix TDS 8000B Digital Sampling-Oscilloscope with a Tektronix 80E04 sampling head to measure the waveform at the second focal point. In addition, we use a Picosecond Pulse Labs pulser with a PSQL 4050 RPH fast pulser head generator for pulse excitation. The output of the step generator is a 45-ps rise time with a 10 V amplitude.

We have investigated a new manifestation of an IRA in which we use a prolate spheroid as a reflector instead of a parabolic reflector and focus in the near-field region instead of the far-field region. This technique minimizes skin damage associated with inserting electrodes near the tumor. Analytical calculations, numerical simulations, and experimental data is used to find the focal waveform characteristics and spot sizes. Figure 3 presents analytical, numeri-

Layers	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
r (cm)	15	12	9.7	7.8	6.2	5	4	3.2	2.6	2.1
ϵ_r	1.6	2.4	3.7	5.8	9	14	21.7	33.6	52.2	81

Table 1. Radii and ϵ_r values for each layer in an optimized 10-layer graded permittivity dielectric focusing lens.

cal and experimental focal waveforms for a two arm psIRA without a focusing lens. This work has been completed and reported.

For our final experiments, we will be using a focusing lens at the second focal point of the psIRA. Our motivations for using a lens before the second focal point are to eliminate impedance mismatch between the dielectric constant of air and the dielectric constant of the target, $\epsilon_{r\text{target}}$ and to obtain better focusing. The lens

provides $\epsilon_{r\text{target}}^{1/4}$ times greater field amplitude and a $\epsilon_{r\text{target}}^{1/2}$ reduction in the spot size.

In order to eliminate the impedance mismatch between the target (which is typically close to the dielectric constant of water, $\epsilon_{r\text{water}} = 81$) we have designed a graded-permittivity dielectric lens. A lens design procedure, with constant wavelength-to-cross-section ratio as (dielectric constant) increases from unity to $\epsilon_{r\text{target}}$, is used to obtain better focusing at the second focal point of a psIRA. Our analytical calculations and numerical simulations show that the lens should comprise at least 10 layers and have a 15 cm radius to achieve the desired focusing [5]. (Table 1 presents the calculated radii and ϵ_r values for different adjacent 10 layers.)

For our initial experiments, however, in order to simplify construction, we have designed and fabricated a 5-layer lens and the relative dielectric constant of the 5th layer is $\epsilon_{r\text{target}} = 9$.

CONCLUSIONS

Subnanosecond pulsed electric fields are an exciting new development in the biomedical field for cancer treatment and gene therapy. sPEs may kill melanoma and allow for the insertion of new genes into living cells with the aim of correcting genetic defects. The invasive method of delivering these fields, through implantable electrodes, is a limiting factor with respect to practical applications. The noninvasive delivery technology using a psIRA that we described in this article may also be developed for application to target cells deep within the human body. Given the tightly focused wavebeam spot, this would also result in significantly reduced dam-

age to adjacent healthy tissue. This ongoing research project will speed the development and use of pulsed electric fields as a new medical therapy.

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Dilemma

The coexistence of an insatiable appetite for more knowledge and an intense suspicion of its further development is a paradox of Western culture today.

Frank Furedi

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