Mini-Symposia Title:

The Evolving Science and Engineering of Tumor Treating Fields:-Part II

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Theme:

- ○ 01. Biomedical Signal Processing
- ○ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/ Nano-bioengineering; Cellular/ Tissue Engineering &
- ○ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ○ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ◉ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

Mini-Symposia Synopsis— Max 2000 Characters

Tumor Treating Fields (TTFields) is a therapy utilizing alternating electric fields to inhibit cancer cell division. TTFields are aprpoved for the treatment of Glioblastoma Multiforme and Mesothelioma. Ongoing clinical trials are testing the efficacy and safety of TTFields for treating other malignancies including non small cell lung, pancreatic ovarian and hepatocellular cancer. We are planning two symposia in which experts in the field of TTFields will discuss recent scientific and engineering developments.The sessions will include talks discussing recent studies on the mechanism of action of TTFields, simulation-based studies on TTFields therapy and clinical research regarding imaging of response to TTFields and combination of TTFields with radiation therapy. The sessions will also include a talk from a patient, who is currently being treated with TTFields, thereby providing a unique perspective on how the journey cancer patients go through, and how they integrate TTFields into their lives.We believe this session will stimulate new opportunities for collaboration and increase involvement of the biomedical engineering community in this new and exciting field.

Electric Field Simulations for Transcranial Brain Stimulation using Boundary Element Fast Multipole Method: An Efficient Algorithm Implementation

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Abstract:
Accurate high resolution modeling of electric fields within the subject-specific gyral pattern and white matter pathways may improve transcranial stimulation targeting and focality, and potentially lead to new treatment opportunities. The objective is to describe the corresponding algorithms and modeling software with detailed human head models using the boundary element fast multipole method and to apply this software to study TMS, TES, and DBS focality. The corresponding TMS software toolkit is available online for evaluation.

Radiation Therapy Dose Distribution Comparisons for Glioblastoma with and without Concurrent TTFields *

Jimm Grimm, Khadija Sheikh, Rachel Grimm, Greg Stachelek, Kenneth Forster, Carla Scofield, Ian Butterwick, Kristin J. Redmond, Lawrence R. Kleinberg, Michel Lacroix and Anand Mahadevan

***Abstract*— The standard quality assurance (QA) gamma criteria for intensity modulated radiation therapy (IMRT) that a reference plan is not excessively different from the treatment actually to be delivered, is that for 95% of points there must be a dose that differed by no more that 3% within 3mm of the expected location. We applied this same 3%/3mm gamma criteria to radiation therapy plans on an anthropomorphic phantom with and without a TTFields array to assess the effect on dose distribution, and 30 of 30 plans passed the QA criteria.**

I. INTRODUCTION

Compatibility of concurrent tumor treating fields (TTFields) with radiation therapy is investigated, since each has been proven effective for newly-diagnosed and recurrent glioblastoma (GBM) (1-3). The radiation beams would pass through the TTFields ceramic array before entering the patient, thus the effects on dose distribution must be studied.

II. METHODS

The effects on a single radiation beam from several types of bolus material were compared to that of a single 1mm thick 19mm diameter TTFields ceramic disc as in Fig. 1A. A TTFields array consists of four 150mm by 100mm sheets of 9 discs each, which is affixed to various regions of a patient's head. The radiation therapy treatment plans for 10 consecutive GBM patients were recalculated on an anthropomorphic head phantom, each for 3 distinct positions of the TTFields array, as well as without the array. For each of the 10 cases, the dose calculation without the array was used as the reference, and a 3%/3mm gamma criteria was applied with Mapcheck software (Sun Nuclear, Inc, Melbourne, Fl, USA) to compare the calculated dose distributions with each of the 3 array positions.

III. RESULTS

Changes to the radiation were largest at the surface as seen in Fig. 1A. Likewise, compared to the reference dose distribution in Fig. 1B, the few mismatching points in Fig. 1C were near the surface and close to the ceramic discs; more than 95% of points passed the 3%/3mm gamma criteria.

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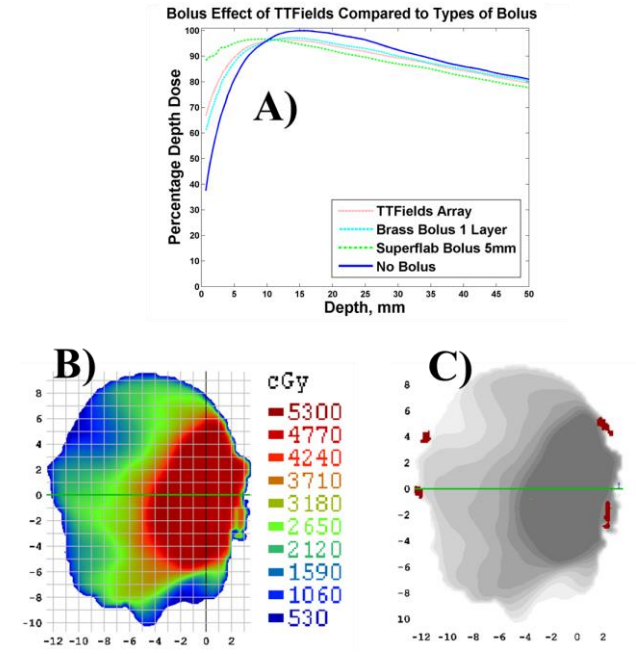

Figure 1. A) Radiation depth dose curve through various types of bolus, showing differences primarily near the surface. B) Axial slice of sample radiation therapy plan without TTFields array on a head phantom. C) results of 3%/3mm gamma criteria comparison with the TTFields array; the red points failed the criteria but more than 95% of points passed for all 30 plans.

IV. DISCUSSION & CONCLUSION

Since dose recalculations for all 3 array positions passed the 3%/3mm gamma criteria for all 10 cases, it is not likely that this additional test is necessary for each patient. Nevertheless, close monitoring of outcomes for patients undergoing concurrent therapy is needed.

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In-Vitro Exposure Setup for Tumor Treating Fields

Saba Harke, Lukas Berkelmann, Anaclet Ngezahayo and Dirk Manteuffel

***Abstract*—We present an in-vitro electromagnetic exposure setup allowing the irradiation of cell cultures for investigations of mechanisms of action of so called *Tumor Treating Fields*. The setup features a set of electrodes enabling four polarization directions and a quiet homogeneous field distribution within the cell cultivation area. We hypothesize that the setup should increase the efficiency of in-vitro TTFields application, which will be evaluated in further cell culture experiments. Subsequently, mechanism of action can be investigated and discussed in a conclusive manner.**

I. INTRODUCTION

So called Tumor Treating Fields (TTFields) is a relatively new treatment of recurrent tumors such as glioblastoma. While the therapeutic effect has been shown in clinical studies [1], the exact mechanism of action is yet unclear. Different in-vitro application setups have been developed for the exploration of possible effects on cells [2, 3]. The electric field strength applied is typically in the range of a few hundreds of volts per meter with a frequency range of $100 \leq f\ [\mathrm{kHz}] \leq 500$. Experiments conducted in [1, 2] suggest that TTFields are most effective, when polarized parallel to the division axis of tumor cells. Obviously, in the culture dish the orientation of the cells in cytokinesis is randomly distributed. Therefore, an efficient exposure setup should enable multiple adjustable polarizations while maintaining a homogeneous field distribution in the cultivation area of the cells.

II. METHODS

Compared to the setup in [2] having four electrodes the new design presented here features eight electrodes (Fig. 1, left). In order to change the polarization of the field while maintaining a largely homogeneous distribution in the cell cultivation area six electrodes (two facing pairs of three electrodes) are excited at the same time. By switching the electrodes in a circular manner, different polarization directions of the electric field can be achieved. Fig. 1 (right) shows a computation of the electric field within the cell culture medium conducted with the low frequency solver of Sim4Life. The excitation is chosen to generate an electric field strength of around $E = 100\ \mathrm{V_{RMS}/m}$ at the center of the dish

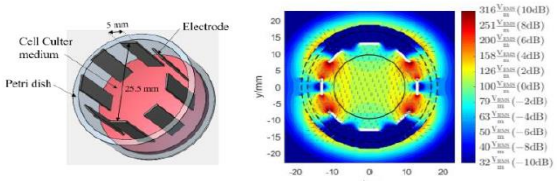

Fig. 2: Schematic view on the in-vitro irradiation setup (left) and Electric field distribution within the setup (right). The circle at the center marks the area where cells can be cultivated. Excitation frequency: $f = 100$ kHz.

III. RESULTS

Table 1 compares the relative standard deviation (RSD) and the maximum relative deviation (MRD) of the electric field strength of the setup in [2] and the setup presented in this paper. The maximum diameters d_{max} were chosen where the RSD is under 10 % and the MRD is under 30 %. The comparison verifies a bigger area of homogeneity of the electric field within the cell culture region for the new setup.

	d_{max}/ mm	RSD/ %	MRD/ %
4 Electrodes	13.2	9.81	25.01
8 Electrodes	18.4	9.77	27.33

Table 1: Comparison with a previous application setup

IV. DISCUSSION & CONCLUSION

The presented modified TTFields in-vitro exposure setup enables adjustable polarization by switching sets of multiple electrodes. Compared to a setup presented in [2] it also enables better homogeneity of the field distribution in the cell culture area. Subsequently, the efficacy of in-vitro TTFields application will be evaluated. Based thereon the mechanisms of action can be investigated and discussed conclusively.

V. REFERENCES

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Automatic evaluation of the quality of realistic computational head models

Reuven Shamir, Novocure ltd., Haifa, Israel

Abstract— **A major challenge associated with simulating delivery of electrotherapeutics in a patient-specific manner is the creation of accurate patient head models. A key step to achieve this goal is to correctly segment the head into tissues of similar electrical properties. Visual inspection of segmentation quality is invaluable but time-consuming. Automatic quality assessment can assist in automatic refinement of the segmentation parameters, suggest flaw points to the user and indicate if the segmented method is of sufficient accuracy for TTFields simulation. Here we utilize demonstrate an algorithmic approach aimed at automatic assessment of head model quality.**

I. INTRODUCTION

A major challenge associated with simulating delivery of electrotherapeutics in a patient-specific manner is the creation of accurate patient head models. A key step to achieve this goal is to correctly segment the head into tissues of similar electrical properties. Automatic segmentation of the brain from MRI images is challenging, particularly when malignancies are present in the brain. Hence, the creation of head accurate head models can be time-consuming and labor-intensive. Even the task of examining a model visually and determining whether or not refinement of the segmentation is required, can require significant amounts of times when a large number of models are being created. Therefore , algorithms that evaluate segmentation quality automatically are highly desired. Here we demonstrate a novel approach aimed to assess segmentation quality when creating realistic head models from MRIs.

II METHODS

The purpose of this study was to evaluate the quality of head models created using atlas-based segmentation approaches. To measure the quality of a new segmentation method, the Dice coefficient was measured between new segmentations and validated- head segmentations of a training set (n=20). Next, four categories of features that seemed relevant for atlas based segmentation methods were examined 1) quality of global (affine) registration between atlas and MRI; 2) quality of local (deformable) registration; 3) input image properties, such as signal to noise (SNR) and; 4) geometrical properties of the segmented tissues. The features were incorporated in a decision tree regressor. We applied a leave-one-out approach on the 20 TTFields patients' head MR-T1 images, their validated segmentations and their automatically generated counterparts. We compared the measured Dice coefficients between the sets to the Dice coefficients' predictions.

III. RESULTS

Dice coefficients for intra-cranial tissues were significantly ($p < 0.05$) correlated with the registration (global and local) quality features and the shortest axis length of the tissue (geometrical parameter). In contrast, dice coefficients of extra-cranial structures such as the scalp and skull were significantly ($p < 0.05$) correlated with image quality and geometrical features characterizing the tissue. The model created with the decision tree regressor predicted dice coefficient , which were highly correlated with the actual measured dice coefficients (average absolute difference 3% (SD = 3%); $r = 0.92$, $p < 0.001$).

IV. CONCLUSIONS

These results show that automated evaluation of segmentation quality estimation is feasible by incorporating a machine learning approaches and features that are relevant to the segmentation. To fully exploit this approach it is important to investigate how model imperfections influence the accuracy of simulation results. Combining an understanding on the interplay between model accuracy and simulation accuracy with methods for automatically quantifying model quality, and (perhaps even specific defects within the model) is expected to reduce the time required to inspect segmentations and determine whether or not they are suitable for high-quality simulation-based studies.of electro-therapeutics.

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Modeling TTFields Effects on Intracellular Structures to Reveal its Mechanism of Action

Kristen W. Carlson, Nirmal Paudel, Socrates Dokos, Thomas Dreeben, Ze'ev Bomzon

We show the results of testing hypotheses via numerical modeling and analysis of Tumor Treating Fields' (TTFields) effects on sub-cellular structures critical to mitosis in tumor cells. Likely targets include microtubules, C-termini, kinesin, septin, and mitochondrial membranes. We discuss the connection of each sub-cellular effect to hypotheses about TTFields' mechanism of action. Model and empirical results indicate that among its principal effects, TTFields may activate intrinsic apoptosis, a built-in cell death cycle.