Intracranial Tumor Treating Fields Model

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***Abstract* — Tumor Treating Fields (TTF) are a relatively new modality for addressing cancer. The primary target of the treatment is glioblastoma in the brain. By placing electrodes on the scalp, AC electric fields are generated to pull apart the molecules in the tumor during mitosis. Recent research indicates that increasing the field strength would improve the treatment efficacy. The limitation in current models is the thermal capacity of the material (resistivity in scalp, skull) between the electrodes and the brain. Studies have shown that removing parts of the skull yielded better results. As such, in order to increase the field strength, an intracranial model will be developed to circumvent the skull entirely. The placement of the electrodes within the brain will be modeled in COMSOL Multiphysics 6.0 software. Machine learning can be applied to optimize for system constraints such as specific absorption rate (SAR), electric field strength, and electric field directionality.**

Keywords—tumor treating field, glioblastoma, intracranial

I. INTRODUCTION

Tumor treating fields are electric fields (AC) generated by transducer arrays placed on the scalp. At least two fields are generated by running alternating current across the skull between these arrays. They are placed perpendicular to each other in order to ensure that the different directionalities of the dipoles in the tumor are addressed. The tumor treating fields are characterized by their electric field strengths and their frequencies, which can be controlled by the current volume and frequency. The optimal frequency ranges for particular tumors have been determined [1]. In the case of glioblastoma, the typical frequency ranges between 100-300 kHz, while the field strength is between 2-4 V/m.

Fig. 1. Current TTF Setup [3]

These fields have been shown to break down tumor cells during mitosis, although the details of the underlying mechanisms in that process require further research [1]. The primary mechanism is that the electric field pulls apart the molecules with dipole moments during mitosis [6].

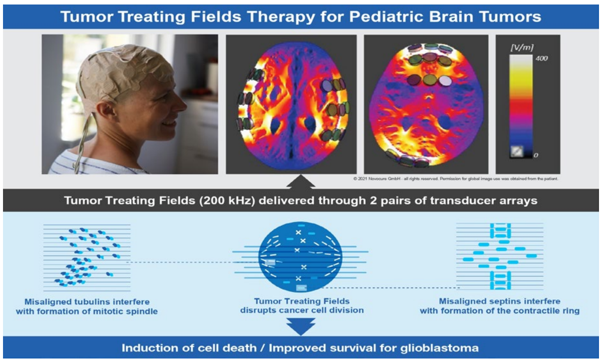


Fig. 2. TTF Mechanism Visualization [7]

Data from recent studies indicate that stronger electric fields yield better results because they achieve higher success at interacting with the dipole moments in the cells [3]. The problem with increasing the field strength is that the thermal effect on the scalp and skull can cause pain and possible damage to the patient receiving treatment. Clinical skull remodeling surgeries assisted in removing this barrier and the results were clearly positive in relation to treatment success. Compared to patients receiving normal oncological treatment with an average overall survival (OS) of nine months, the patients that also received tumor treating field treatment had an OS of approximately 15.5 months [3]. These positive results indicate that further exploration and enhancement of this system is warranted.

While increasing the field strength and altering the electrode orientations are a clear starting point for invasive systems, it is important to track the thermal effects on internal tissue as well. The World Health Organization has established safety standards for electromagnetic fields emitted by technology [2]. When transmitted over tissue, these fields deposit certain quantities of energy over particular amounts of mass. This is measured as specific absorption rate (SAR) and clearly applies to tumor treating field systems. The "occupational exposure" limit is defined as 10 W/kg. Previous models by Lok indicate that electric field orientation impacts the SAR levels spatially, but the values safely ranged between 0 and 7.5 W/kg [6].

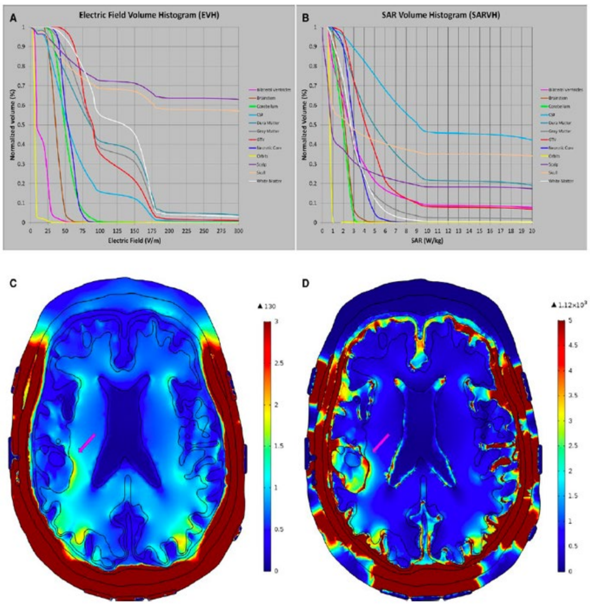


Fig. 3. TTF Mechanism Visualization [6]

The above figure depicts the relationship between the electric field distribution and the SAR levels for a specific electrode array. While the physical properties of the tissues cause variance, there is a strong correlation between both measurements. As such, thermal effects should be accounted for while designing newer models because new electrode locations may yield unique results based on organ tissue and electric field strength.

II. SYSTEM MODEL

The aforementioned skull remodeling results, while encouraging, were acquired through real application on patients with glioblastoma. The objective of this effort was to design an intracranial implementation of this system by using specific metrics. Prior to testing electrode placement in animals through surgery, the physical properties of the electric field and the brain were modeled in software. In order to simulate the effects of placing the electrodes inside the brain, COMSOL Multiphysics simulation software was used. In other tumor treating field studies, the head model developed in COMSOL is often rendered by aligning medical images of real tumors in patients with a theoretical model [6]. This model is generated as a finite-element mesh that can adopt specific physical properties in three dimensions.

For initial research into field modeling, the native SAR head model in COMSOL was used in order to experiment with transducer array location modeling. While this model is typically used to model external transmissions from technology such as cell phones, it allowed for a visualization of SAR value distribution over different materials. As stated previously, the electrode locations can impact critical variables (such as SAR) that are metrics of the efficacy of the system. These locations were altered to optimize the minimum field strengths, the field directionalities, and the maximum SAR values at any location in the brain.

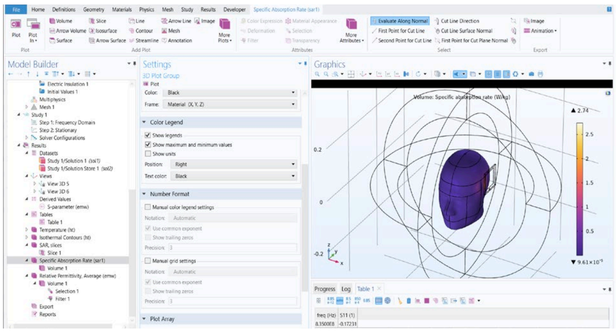
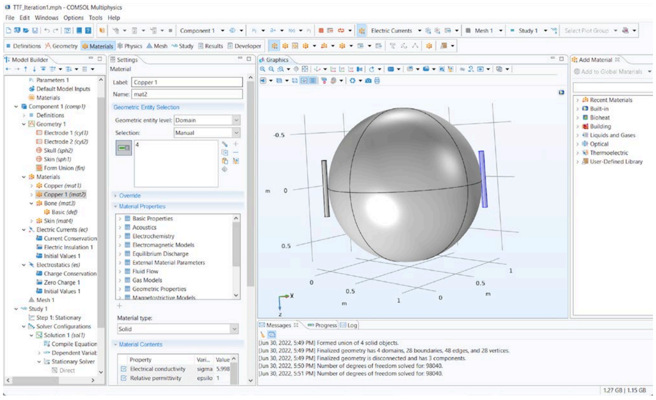


Fig. 4. Initial Native SAR COMSOL Modeling

This model allowed for experimentation with field generation and SAR value representation. Once this was achieved with, a more precise brain model was implemented with the appropriate material values provided by Lok in [5]. This was necessary due to the observation in Figure 3: the tissue properties and geometry alter the concentration of current and the field strength. Since the current will run through the ventricles inside the brain, they are a primary concern in relation to current concentration.



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[Jun 30, 2022, 5:49 PM] Formed union of 4 solid objects.
[Jun 30, 2022, 5:49 PM] Finalized geometry has 4 domains, 28 boundaries, 48 edges, and 28 vertices.
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Fig. 5.

To begin the process of modeling with realistic tissue values, the standard tumor treating field model was replicated with the basic parameters for the scalp, skull, dura, and electrodes. A triangular structure representing a ventricle was added as well, but it was not anatomically accurate. It functioned as a placeholder to study the impact of angular geometry on current flow and thermal effects on tissue at higher current concentrations.

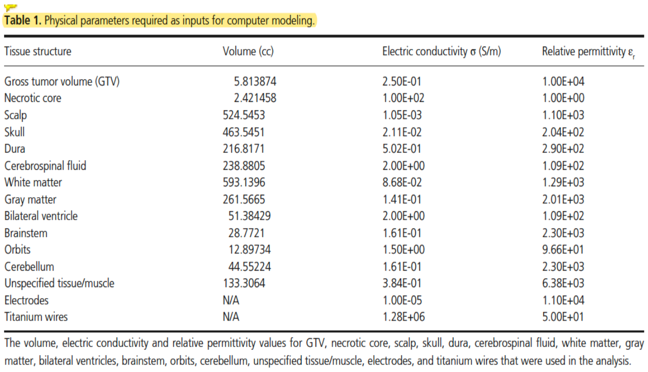


Table 1. Physical parameters required as inputs for computer modeling.

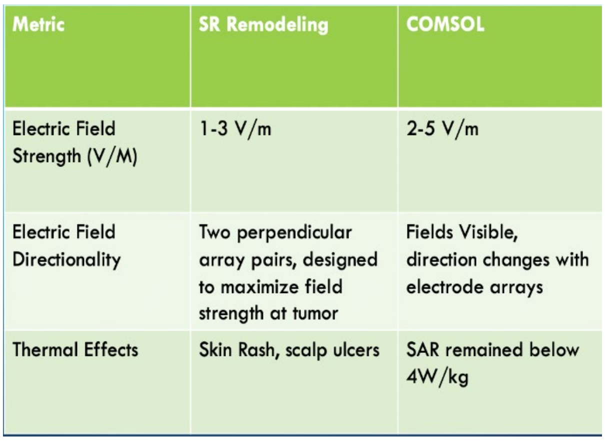
Tissue structure	Volume (cc)	Electric conductivity σ (S/m)	Relative permittivity ε_r
Gross tumor volume (GTV)	5.813874	2.50E-01	1.00E+04
Necrotic core	2.421458	1.00E+02	1.00E+00
Scalp	524.5453	1.05E-03	1.10E+03
Skull	463.5451	2.11E-02	2.04E+02
Dura	216.8171	5.02E-01	2.90E+02
Cerebrospinal fluid	238.8805	2.00E+00	1.09E+02
White matter	593.1396	8.68E-02	1.29E+03
Gray matter	261.5665	1.41E-01	2.01E+03
Bilateral ventricle	51.38429	2.00E+00	1.09E+02
Brainstem	28.7721	1.61E-01	2.30E+03
Orbits	12.89734	1.50E+00	9.66E+01
Cerebellum	44.55224	1.61E-01	2.30E+03
Unspecified tissue/muscle	133.3064	3.84E-01	6.38E+03
Electrodes	N/A	1.00E-05	1.10E+04
Titanium wires	N/A	1.28E+06	5.00E+01

The volume, electric conductivity and relative permittivity values for GTV, necrotic core, scalp, skull, dura, cerebrospinal fluid, white matter, gray matter, bilateral ventricles, brainstem, orbits, cerebellum, unspecified tissue/muscle, electrodes, and titanium wires that were used in the analysis.

Fig. 5. Physics Values for Tissue Structures [6]

III. Results and Analysis

In order to evaluate the utility of the model, the primary metrics of field strength, directionality, and SAR were compared to the findings from the skull remodeling studies.



Metric	SR Remodeling	COMSOL
Electric Field Strength (V/M)	1-3 V/m	2-5 V/m
Electric Field Directionality	Two perpendicular array pairs, designed to maximize field strength at tumor	Fields Visible, direction changes with electrode arrays
Thermal Effects	Skin Rash, scalp ulcers	SAR remained below 4W/kg

Fig. 6. Comparative Results for Key Metrics

The electric field strength is a variable that can be altered based on the thermal effects of the current on the tissue. As such, the primary focus was on the SAR values and the malleability of the electrode array locations. While the tissue structure accuracy requires improvement, the SAR values remained below the occupational exposure safety limit and were comparable to the results in Lok [6]. Moreover, the directionality of the fields was visible and could be changed based on electrode placement, which will allow for further design experimentation.

IV. Future Research

Since the results were positive in relation to the model's physical metrics, there are three steps for improvement that should be taken. As stated, the model developed thus far is not a comprehensive representation of the human head's anatomy. There are several options for importing accurate meshes into COMSOL for further simulation. To this end, the process of assigning physics values to tissue and observing the metrics will be an enhanced version of the presented model.

Once a more rigorous simulation is developed, researchers can proceed with animal surgery to test electrode array orientations. These results will inform the accuracy of the COMSOL model by informing the design and properties of the three-dimensional meshes.

If the COMSOL software can be integrated with Python scripts, then the optimization process for electrode placement can be automated. The electric field strength can be increased through a range of values in relation to the electrode placement in order to test the limits of the intracranial system. With enough data, a machine learning model can be developed around the stated critical parameters such that the fields are generated in a manner specific to a patient's tumor.

V. Conclusion

This research effort demonstrated the potential viability of an intracranial tumor treating field system. While this modality of treating tumors is relatively new, this research builds on encouraging results from studies with realistic implementations that relate to the objective of circumventing the skin and skull. An important outcome of this effort was the demonstration that COMSOL can be used to observe key metrics that dictate the efficacy and safety of transducer array technology. The primary focus of current and future research should be related to increasing the accuracy of the simulation results through both animal surgery and the inclusion of more sophisticated tissue meshes. Once a refined model is produced, then the incorporation of Python scripts can allow for the exploration of different array designs because the data will accurately reflect the impact of the electric current and field on the brain.

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