Simulating 200 KHz AC Tumor-Killing Fields With COMSOL Multiphysics®

K. W. Carlson[1], N. Paudel[2], S. Dokos[3], J. A. Tuszynski[4]
[1]Beth Israel Deaconess Medical Center - Harvard Medical School, Boston, MA, USA, [2]IEEE, Greenville, NC, USA, [3]University of New South Wales, Sydney, NSW, Australia, [4]University of Alberta, Edmonton, AB, Canada

INTRODUCTION: Alternating current 200 kHz ~2 V/cm electric fields (Tumor Treating Fields, 'TTFields') kill cancer cells by disrupting the delicate orchestration of chromosome spindle formation, but the exact mechanism of action is unknown. Conductivity of polymerized tubulin — microtubules (MTs) — was measured to be 20 S/m, over 20 times higher than that of the ambient cytosol (0.9 S/m). Thus when TTFields penetrate the cytosol, they may induce electric currents along MTs that are strong enough to disrupt key cellular functions.

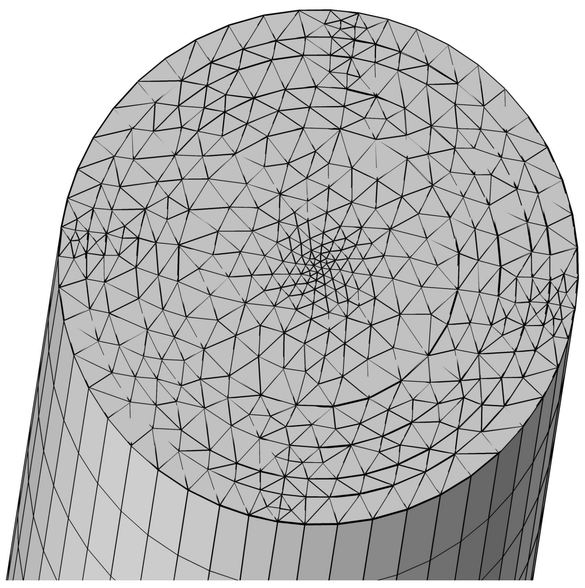

Figure 1. Multi-layered microtubule cylinder, swept mesh. Diameter: 57 nm. Each layer is assigned a different electrical conductivity.

COMPUTATIONAL METHODS: We modeled the MT as a layered cylindrical structure with conductivities for each layer as reported in the literature. Innermost is the lumen (15 nm in diameter), surrounded by 13 strands of alpha-beta tubulin dimers linked in a helix (4.5 nm thick). C-termini extend out from the helix with a thickness of 3.5 nm. MTs carry net negative charge, thus they are surrounded by a counter-ion layer (2 nm), and an outer non-conductive Bjerrum layer (3 nm). An electric field strength of 2 V/cm, representing the TTFields' field strength within the cell, was imposed in the ambient domain around the microtubule. The Electric Currents interface solves for electric potential and current density within the microtubule's layers in the frequency domain at 200 kHz.

$$-\nabla \cdot ((\sigma + j\omega\epsilon_0))\nabla V - (\mathbf{J}_e + j\omega\mathbf{P})) = Q_j$$

RESULTS: Our model shows that MTs act as electrical 'shunts' that conduct electric current within them. The highest current flows through the counter-ion layer surrounding the C-termini. The current density in this layer exceeds the level likely to disrupt the motor protein kinesin 'walk' along the C-termini. Current density is highest when both the field and the MTs are aligned with the cell axis, in accord with *in vitro* experiments.

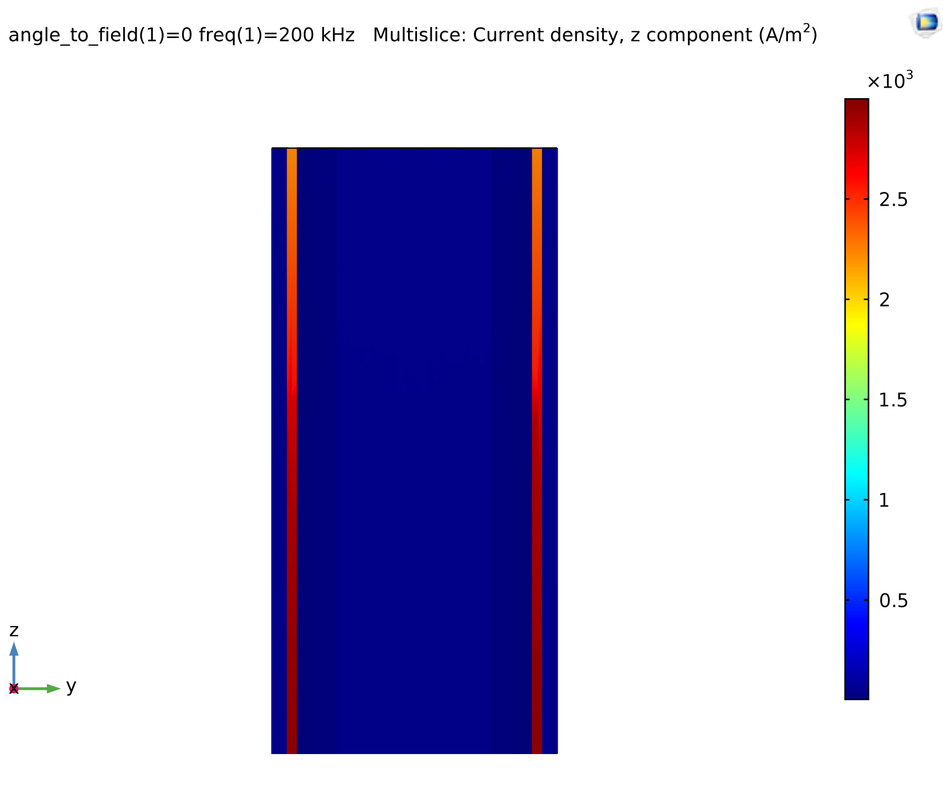

Figure 2. Electric current density when TTFields are aligned with the microtubule. Highest density corresponds to the highest conductivity (red) counter-ion layer.

CONCLUSIONS: Our results support the hypothesis that when cells are exposed to TTFields, MTs act as cables carrying high-density electric currents strong enough to disrupt the function of certain molecular motors, ultimately disrupting mitosis. Future modeling will test which motors are likely disrupted and tie predicted downstream effects to *in vitro* empirical tests.

REFERENCES:

Tuszynski JA et al. An overview of sub-cellular mechanisms involved in the action of TTFields. Int J Environ Res Public Health. 2016.
Santelices IB et al. Response to alternating electric fields of tubulin dimers and microtubule ensembles in electrolytic solutions. Sci Rep. 2017.
Kirson ED et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A. 2007.

Excerpt from the Proceedings of the 2018 COMSOL Conference in Boston