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

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Abstract

Alternating 200 kHz electric fields ~2 V/cm (Tumor Treating Fields, 'TTFields') kill cancer cells by disrupting the delicate orchestration of chromosome spindle formation, but the exact mechanism of action is unknown. The likely suspects are polarized intracellular molecules such as microtubules. Calculations and our first simulations show that TTFields-tubulin interaction energy is insufficient to disrupt function.

Recently the conductivity of microtubules (MTs) was measured to be 20 S/m, which is 400 times higher than that of the ambient cytosol (0.05 S/m) [2]. Based on studies of MTs and their micro-environment, we built a COMSOL model of the MT as a layered cylindrical structure like a coaxial cable: Innermost is the lumen (15 nm in thickness), surrounded by 13 strands of alpha-beta tubulin dimers linked in a helix (4.5 nm). 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).

We built a finite element model in COMSOL Multiphysics (tm) incorporating these layers and examined the current density induced in each layer by TTFields for MTs varying in length from 1 - 10 µm within an ambient 200 kHz AC electric field of 1 - 4 V/cm. The notable COMSOL techniques used in the model include: an interpolation function used to import the results of molecular dynamics simulations and map them onto a 2D surface, moving mesh to capture displacement due to electrostatic forces, coupled Solid Mechanics and AC/DC physics.

To test this hypothesis, we performed numerical simulations evaluating the magnitude of the electric current along MTs exposed to TTFields at 200 kHz. We found that when TTFields penetrate the cytosol, they may induce electric currents along MTs in the counter-ion layer that are strong enough to disrupt key cellular functions. Our model shows that MTs act as electrical 'shunts' that conduct electric current within them. The current density in the counter-ion layer exceeds the level likely to disrupt the motor protein kinesin 'walk' along the C-termini. The current density is highest when both the field and the MTs are aligned with the cell axis, in accord with in vitro experiments.

Homing in further on the specific mechanism, recent work reveals a highly sensitive phase of the kinesin walk. The back 'foot' of kinesin is released from its C-terminus contact by ATP (10-19 Joules). The kinesin molecule 'neck' then lurches forward over 10 ms, skipping over the intermediate C-terminus where the forward foot is attached, and placing the new forward foot near the next C-terminus. The final phase of the walk is believed to take place when thermal buffeting of the forward foot randomly positions it near enough to the C-terminus for electrostatic forces to bind it. We are examining this diffusion phase to determine if TTFields present a stall force ≥ 10-19 N preventing diffusion and disrupting the kinesin walk.
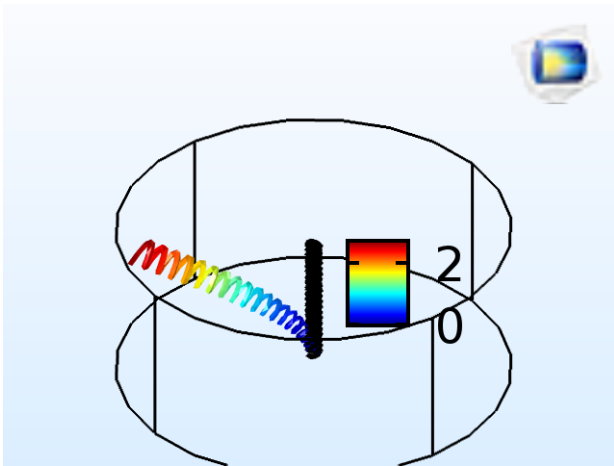
Figures used in the abstract

Figure 1: Displacement of C-terminus by 200 kHz Tumor-treating electric field.