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

COMSOL Conference 2018

K. W. Carlson[1], N. Paudel[2], S. Dokos[3], T. Dreeben[4], J. A. Tuszynski[5]

[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]APS, ASME, Lynn, MA, USA

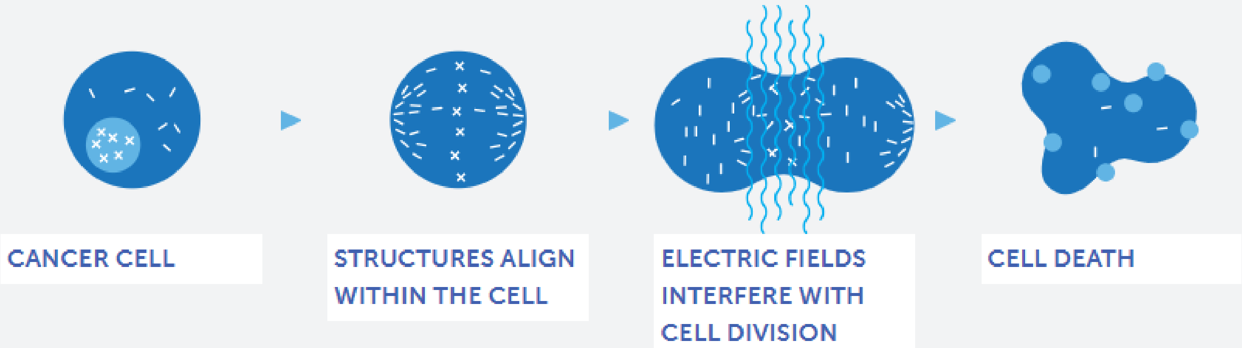
[5]University of Alberta, Edmonton, AB, Canada

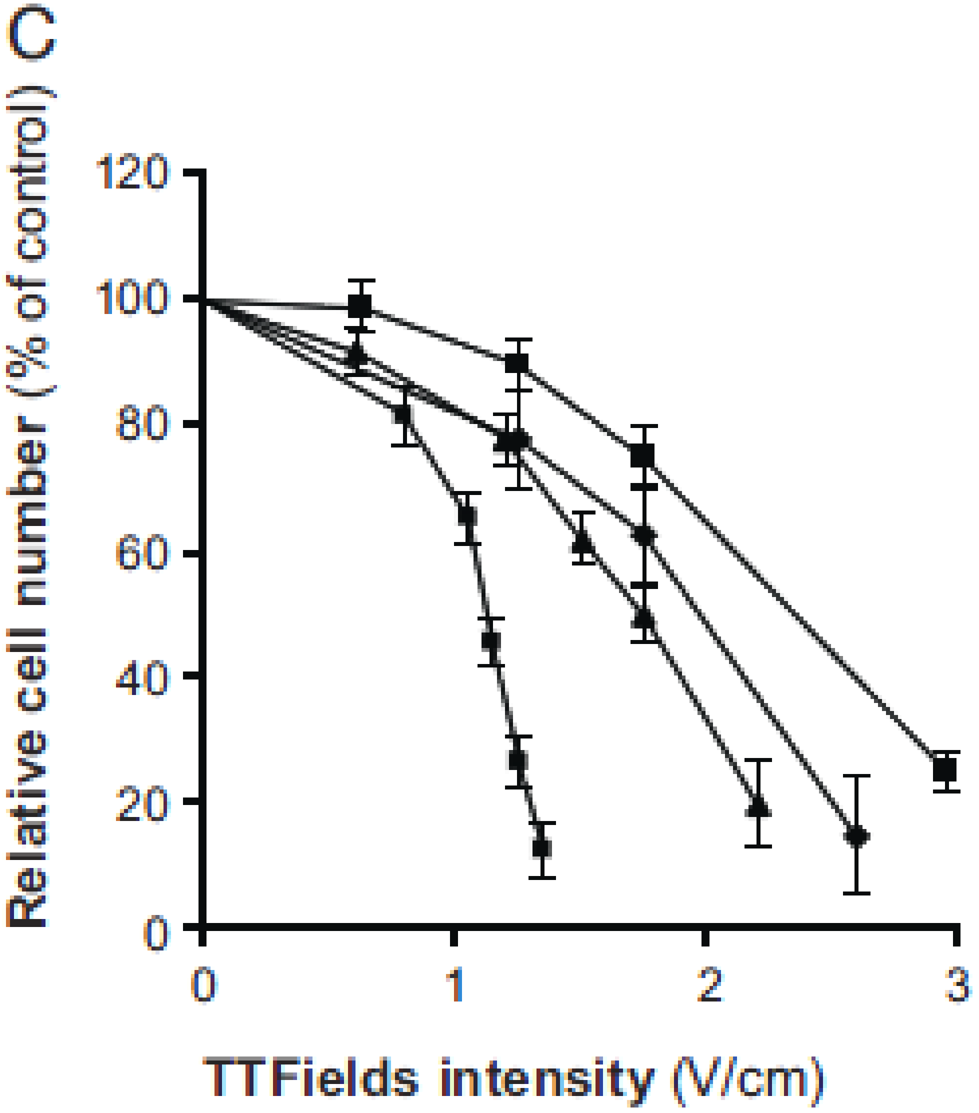
What are Tumor-Treating Fields (TTFields)?

- 200 KHz alternating current fields with target field strength of ~2 V/cm
- Approved by FDA for brain cancer (glioblastoma) in 2011
- ~1000 glioblastoma patients treated, survival extended to 19 vs 16 months
- Clinical trials for lung, stomach, pancreatic, liver, ovarian cancer and metastasis

mechanism of action

Tumor Treating Fields, or TTFields, are low intensity, alternating electric fields that disrupt cell division through physical interactions with key molecules during mitosis in solid tumor cancers.



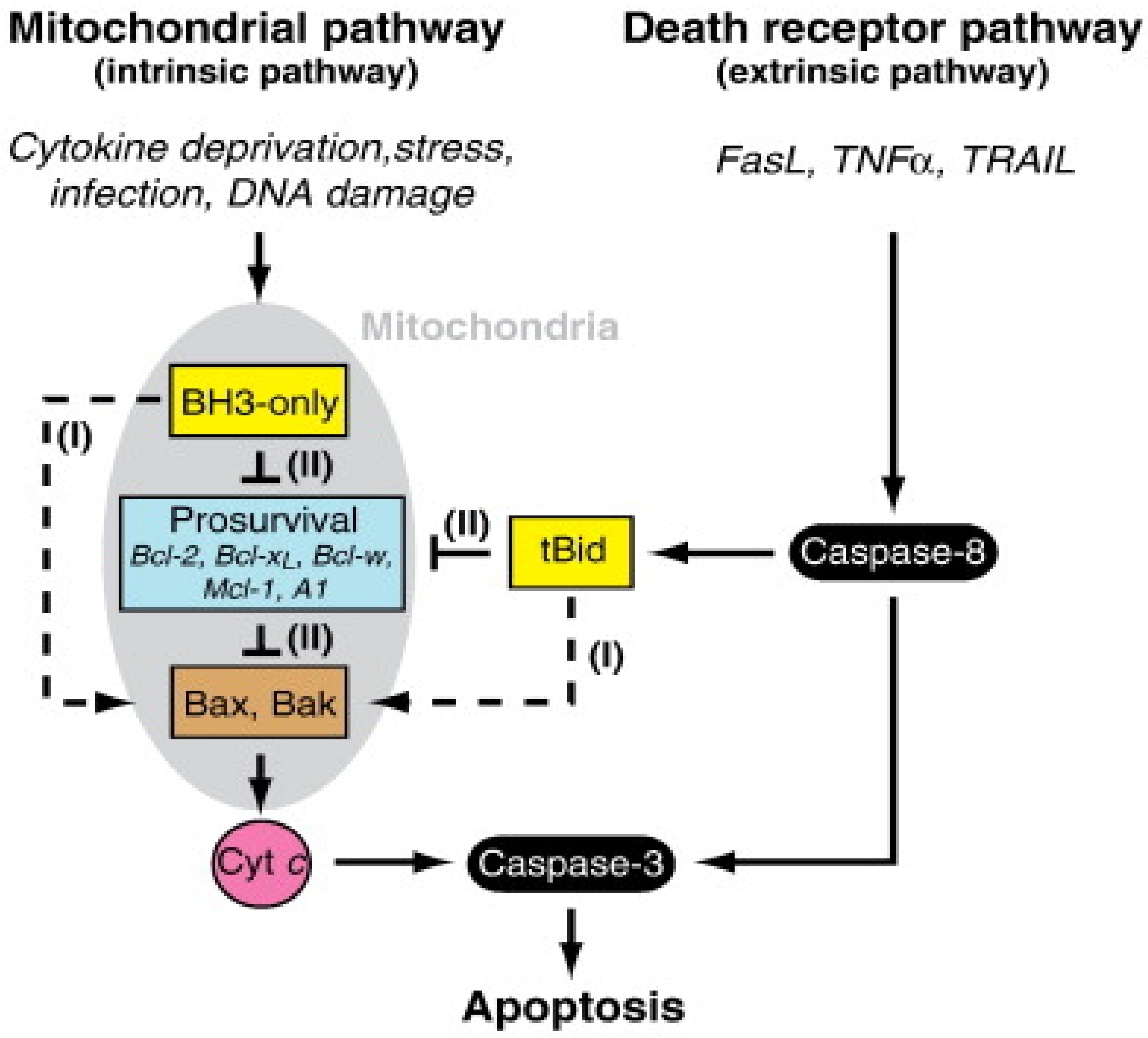


Approaches 100% efficacy *in vitro* and some *in vivo* preparations

Doesn't affect non-cancerous cells

Kirson E.D., Dbaly V., Tovarys F., Vymazal J., Soustiel J.F., Itzhaki A., et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A 2007;* ***104: 10152-7.***

Intrinsic and extrinsic apoptotic pathways



Why do we need modeling?

- TTFields kill all tumor cells in vitro
- Need to uncover the mechanism to transfer *in vitro* results to *in vivo*
- Cell studies measure outcomes
    - They don’t get at low-level intra-cellular mechanisms
- Modeling is an excellent tool for those analyses
    - Cheap and quick
- Can parameterize a model and run many scenarios

Clues to the Mechanisms
= Constraints on the Models

- Approaches 100% efficacy *in vitro* and some *in vivo* preparations
- 1 – 3 V/cm electric field strength
- Frequency-sensitive: 100 – 300 kHz = ~3 - 10 µs
- Field orientation-sensitive: 2 directional effects: 0^o and 90^o = 20% greater efficacy
- Doesn't affect non-cancer cells
- Longer exposure = greater efficacy i.e. after 1^{st} interphase
- Strongest correlation with TTFields applied in prophase
  - Rosette formation
- Increase free vs polymerized tubulin (10 – 20%)
- Aberrant spindle formation
- Cell blebbing
- Aneuploidy
- Chromosome mis-segregation
- Multiple nucleation
- Decreased septin concentration at midline in mitosis
- Multiple cell pathways – apoptosis during interphase, mitotic arrest and death, normal progression to next cycle
- Immune system effects

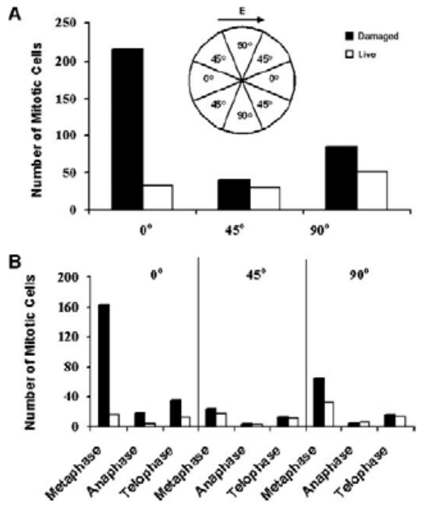
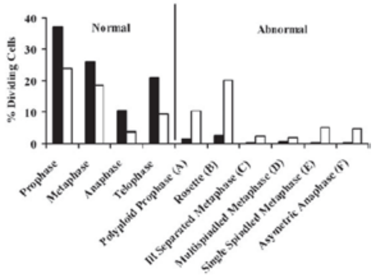
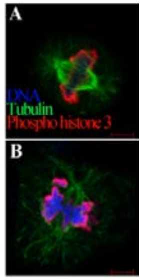
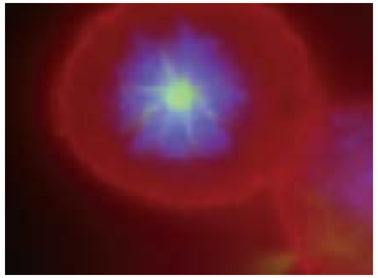
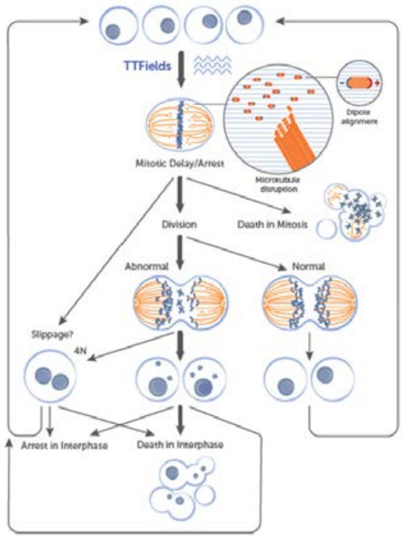


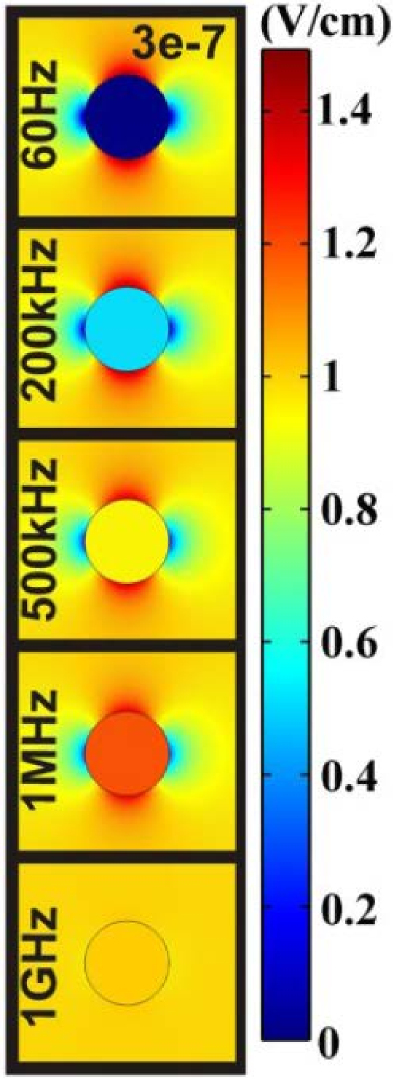
Fig. 4. Dependency of TTFields-induced cellular damage on the orientation axis of cell division relative to field direction. *Ordinate* represents the number of mitotic cells counted in four TTField-treated malignant melanoma cultures (100 kHz). *A*, total number of damaged (■) and live (□) mitotic cells in each of three sectors of different angles relative to the field direction (*inset*). The number of damaged cells is more than 5-fold larger than the corresponding number of live cells when division is aligned at or close to 0° relative to the electric field direction. In sectors of other angles, the number of damaged cells only slightly exceeds the live ones. Note that because the 45° area is double that of each of the other two sectors, the number of cells presented in this orientation was halved. *B*, dividing cell sensitivity to fields of different orientation at different stages of mitosis. When cell division axis is aligned at 0° to the electric field, the number of damaged cells (■) is significantly larger than that of intact cells (□) at all three phases of mitosis. However, the highest number of damaged cells in this orientation is seen at metaphase (8-fold more than intact cells).









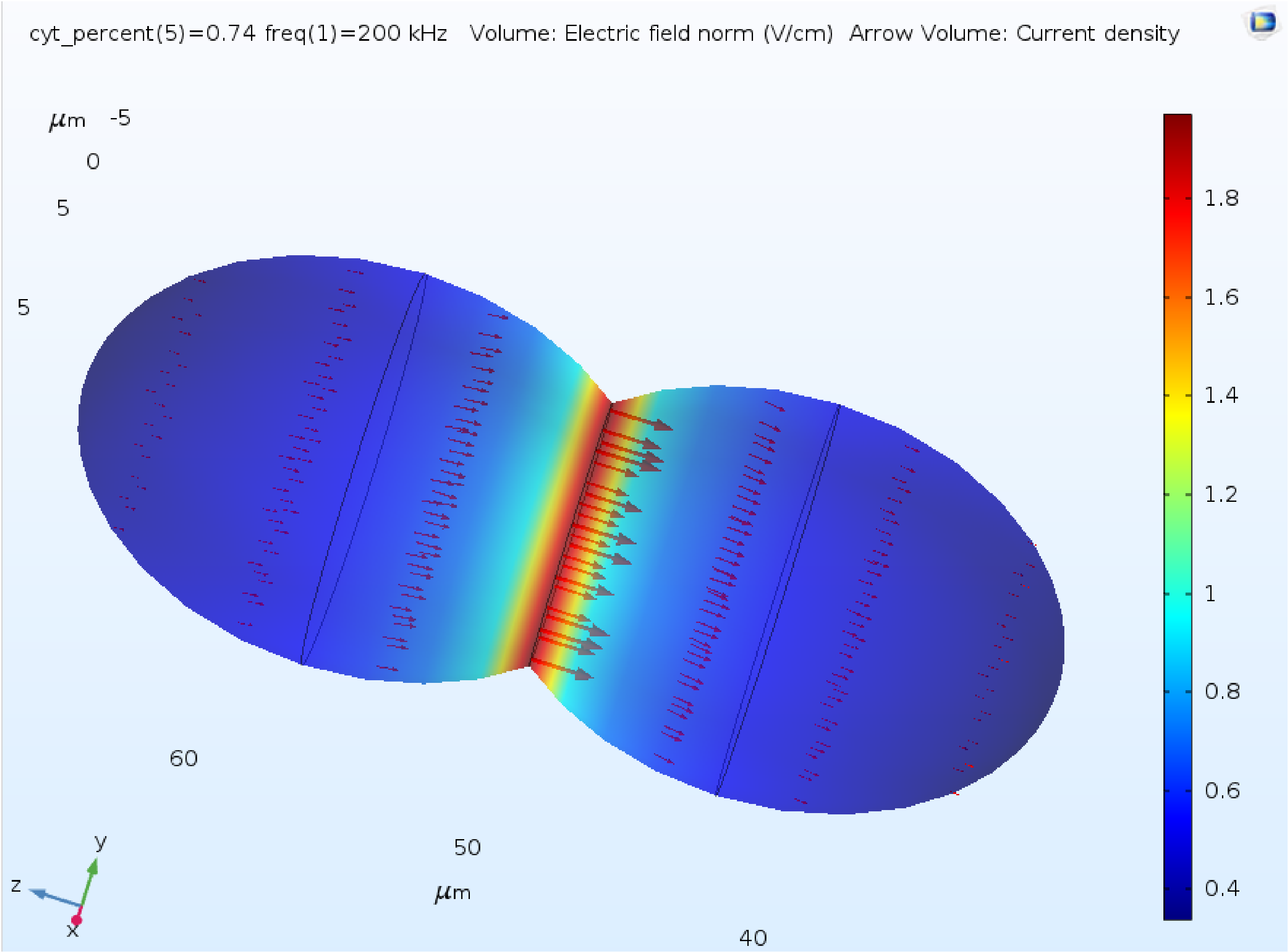


100 - 300 kHz frequency
= 3 - 5 μs period

Sufficient to penetrate cell membrance and deliver ~2 V/cm

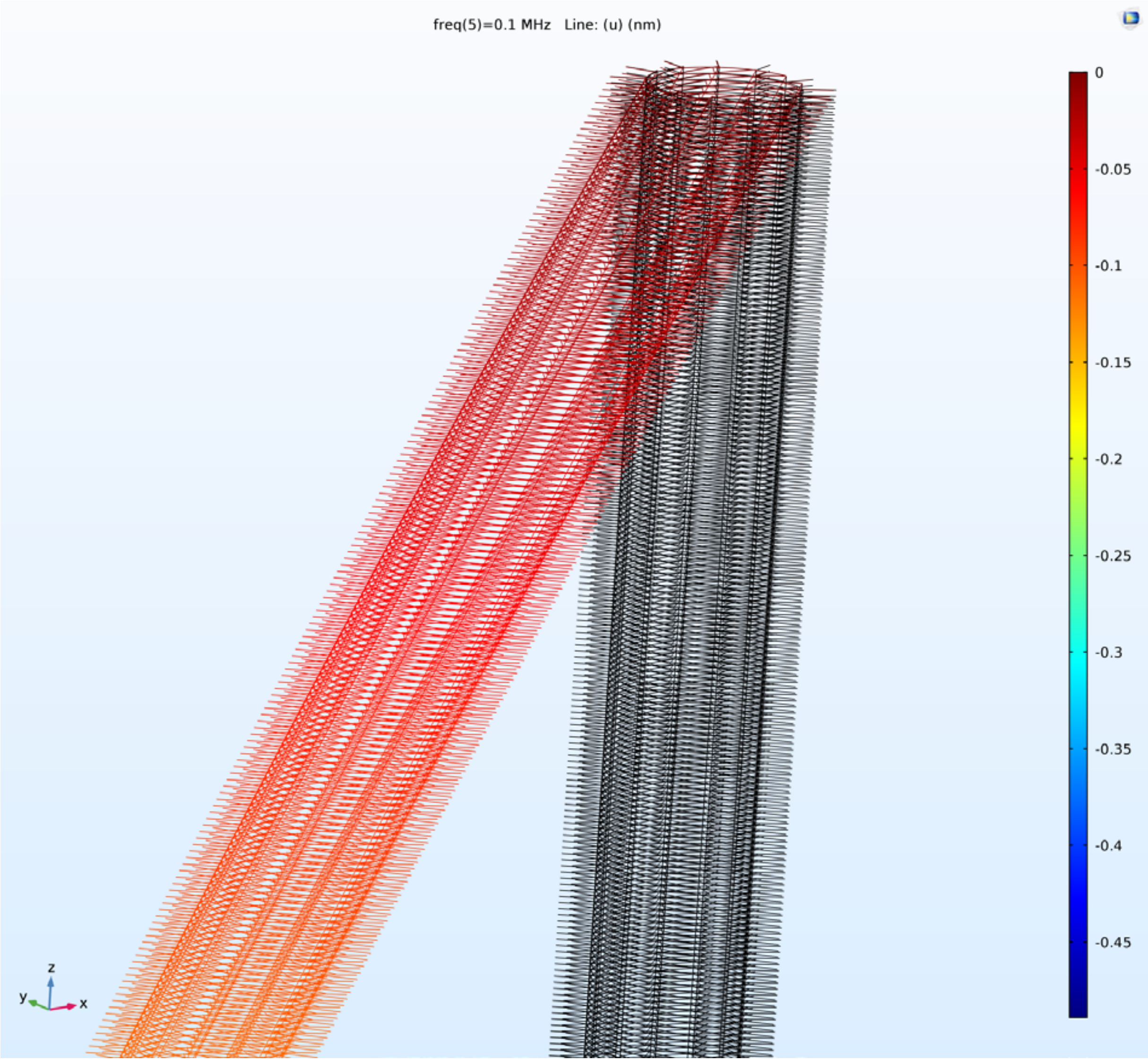
Wenger C., Giladi M., Bomzon Z., Salvador R., Basser P.J., and Miranda P.C. Modeling Tumor Treating Fields (TTFields) application in single cells during metaphase and telophase. *Conf Proc IEEE Eng Med Biol Soc 2015;* ***2015: 6892-5.***

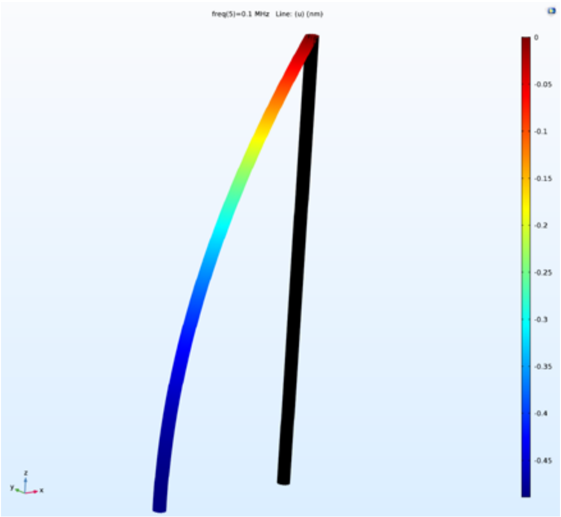
Wenger model showing current density concentration at cell furrow

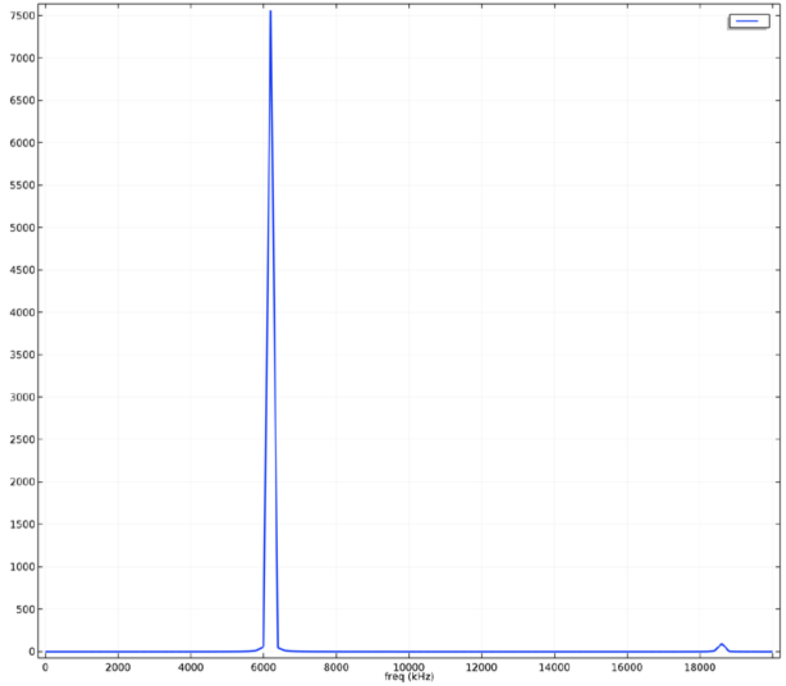


Electromechanical model

Structural mechanics + electromagnetics



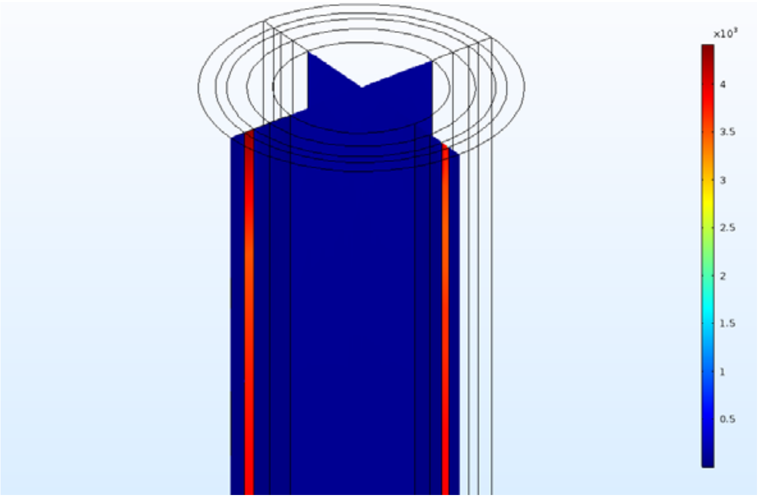




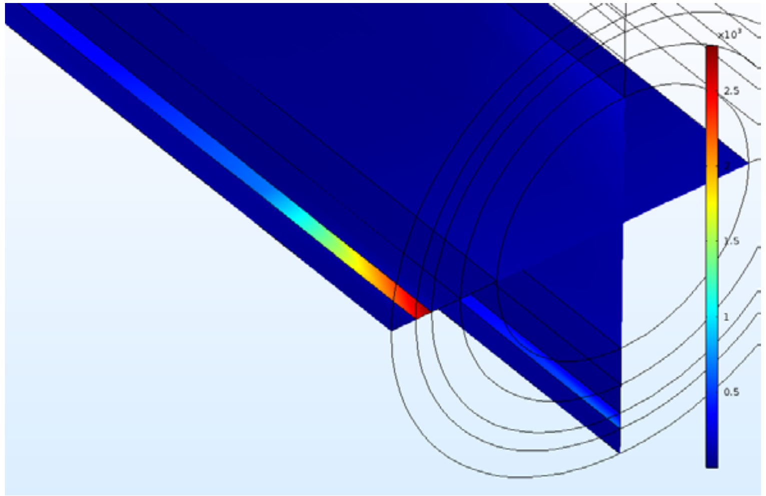
Microtubule-as-coax model

- Model a microtubule as a layered cylinder
  - lumen, helix/protofilaments, C-termini, counter-ions, Bjerrum (insulation), hydration layer
- Counter-ion layer conductivity is 20x cytosol (Tuszynski lab)
- X elementary charges ‘flowing’ per second per square nanometer
  - How to interpret and validate the results?

Aligned

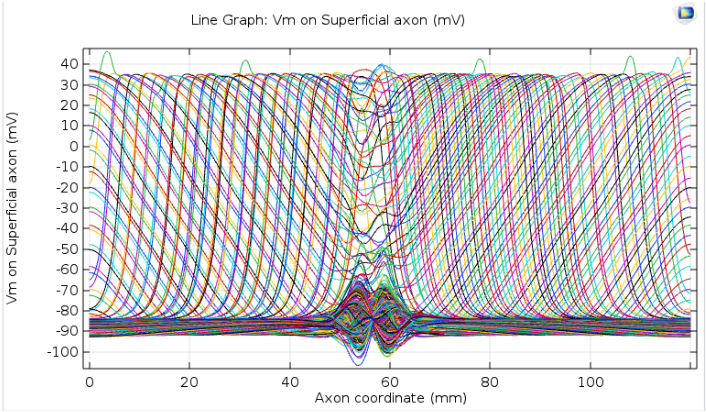


Perpendicular



Disruption metrics derive from signal-to-noise ratio

- Analogy: Background noise level against which nervous system evolved



- In the cell:
  1. Background thermal energy: k_BT = 4.2 J-nm
  2. Cellular free energy = -54 - 101 x 10^{-21} J-nm = ~25 kT

Two minimal energy disruption hypotheses

- C-termini state transitions
- Kinesin walk

Figure 6 depicts the interaction energy for several elevation cuts (angles are given in the figure) at azimuth angles, whereas Fig. 7 shows a full surface plot. It transpires that the 'up-state' has the lowest energy. (It corresponds to the C-terminus being perpendicular to the tubulin's surface). However, the cone-angle created by the constraint $E - E_0 < 50$ meV (where $E_0 = E$ ($\phi = 90°$)) is about 40°. This means that the C-termini can move readily within this cone due to thermal fluctuations ($k_B T$ is approximately 25 meV at physiological temperatures). But an important result is the existence of

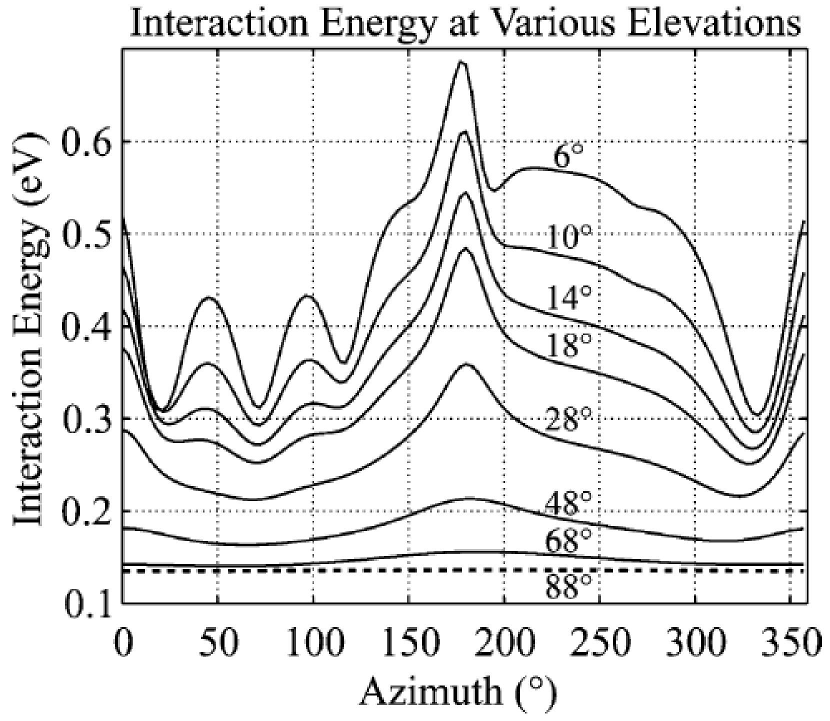
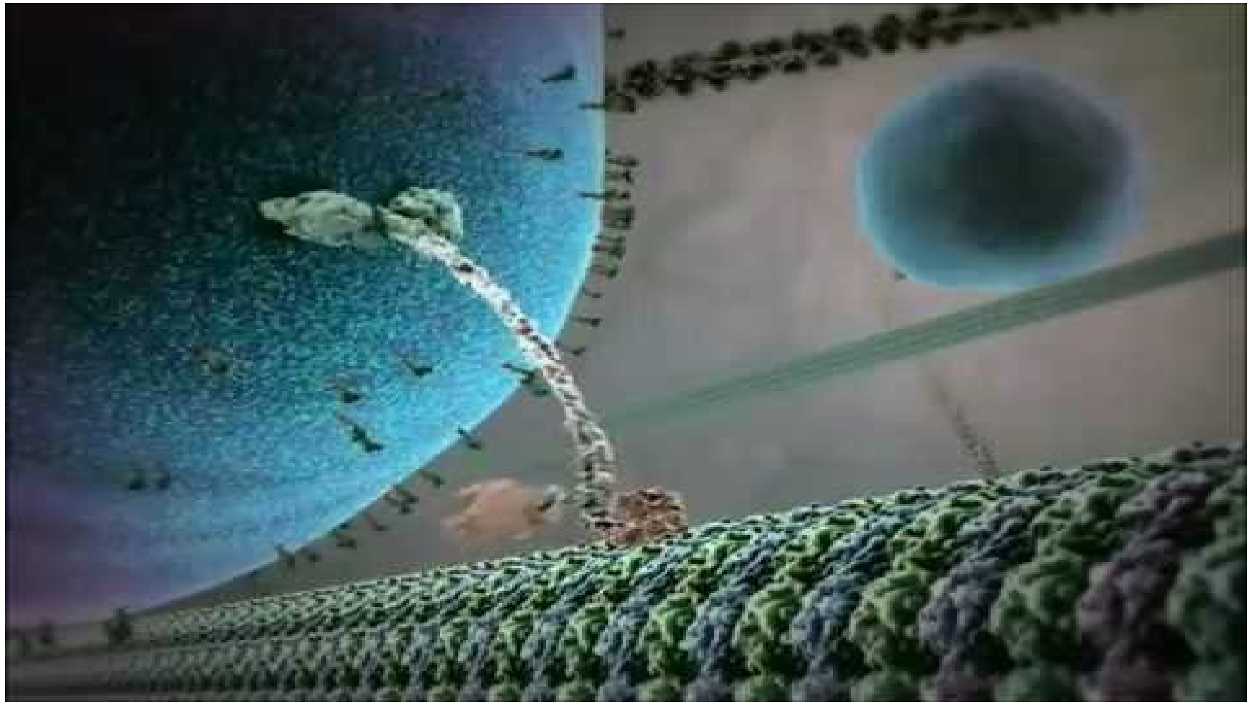
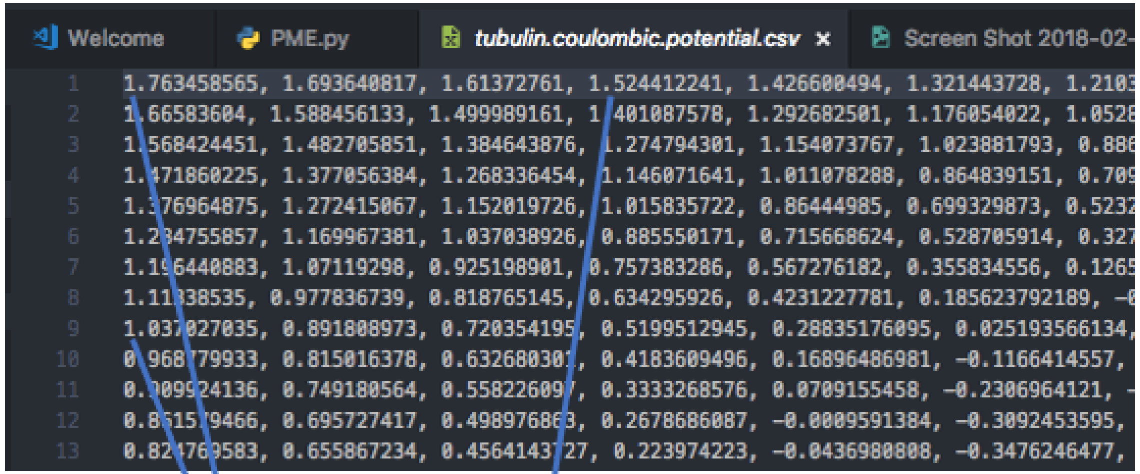


Fig. 6 Evaluation of (1) for the interaction energy between a test C-terminus and the environment vs. the azimuthal angle; each line in the figure describes an elevation cut; values are given



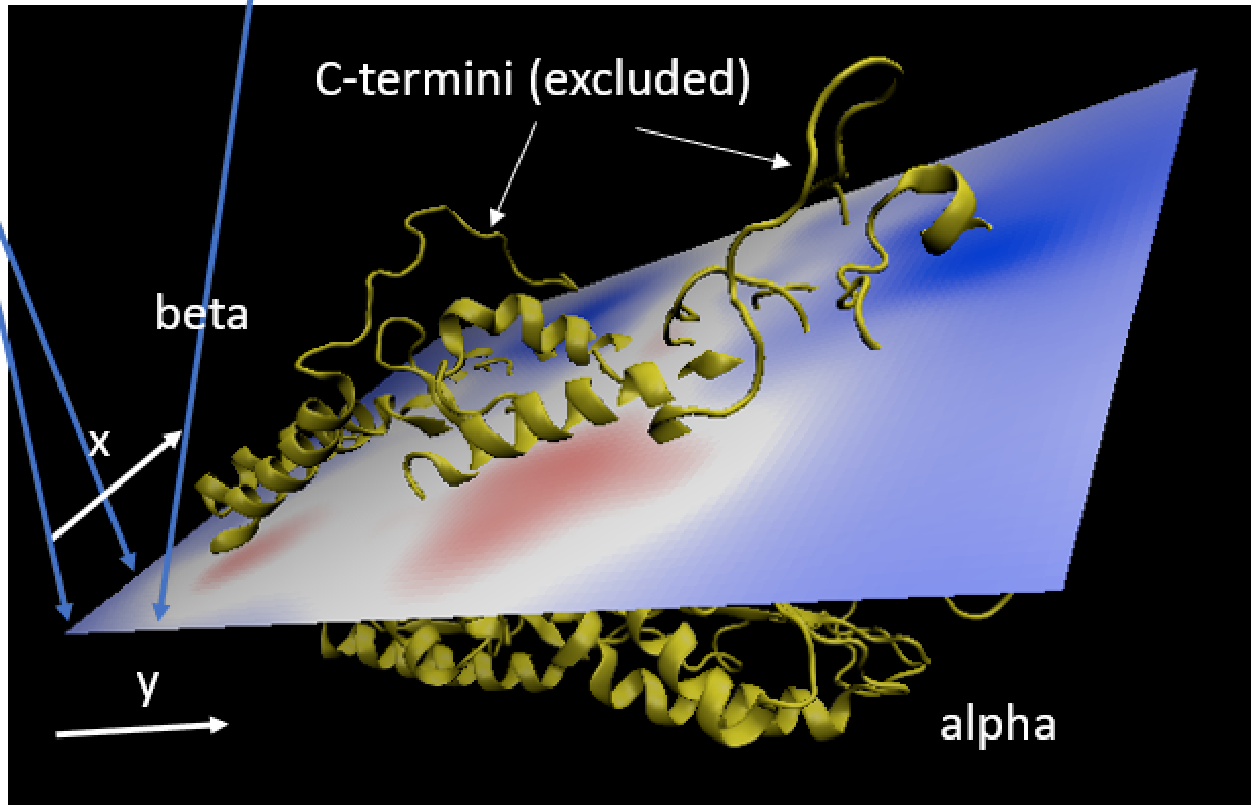
- https://www.youtube.com/watch?v=y-uuk4Pr2i8

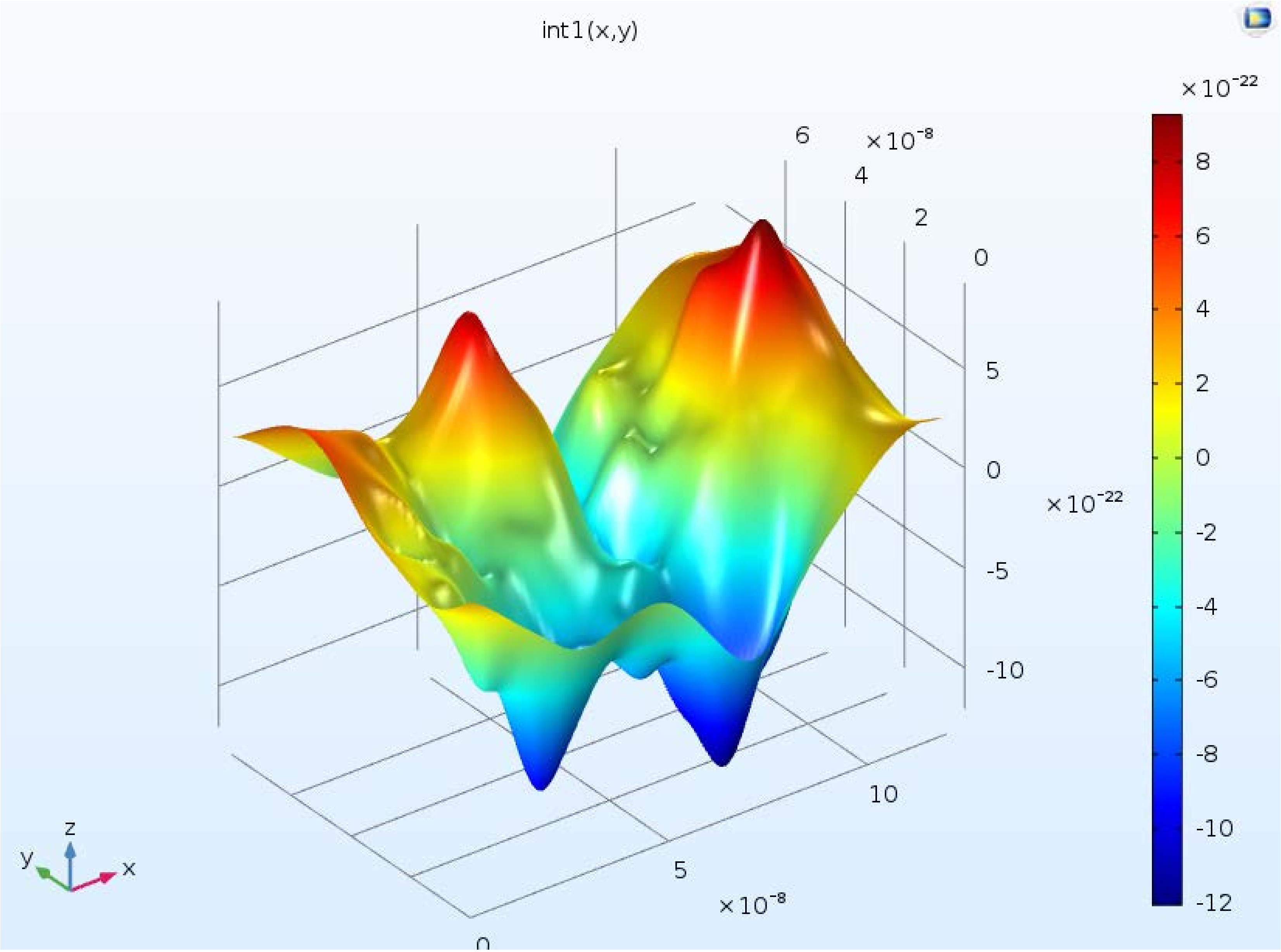
Axiomatize underlying systems level


Welcome | PME.py | tubulin.coulombic.potential.csv | Screen Shot 2018-02-

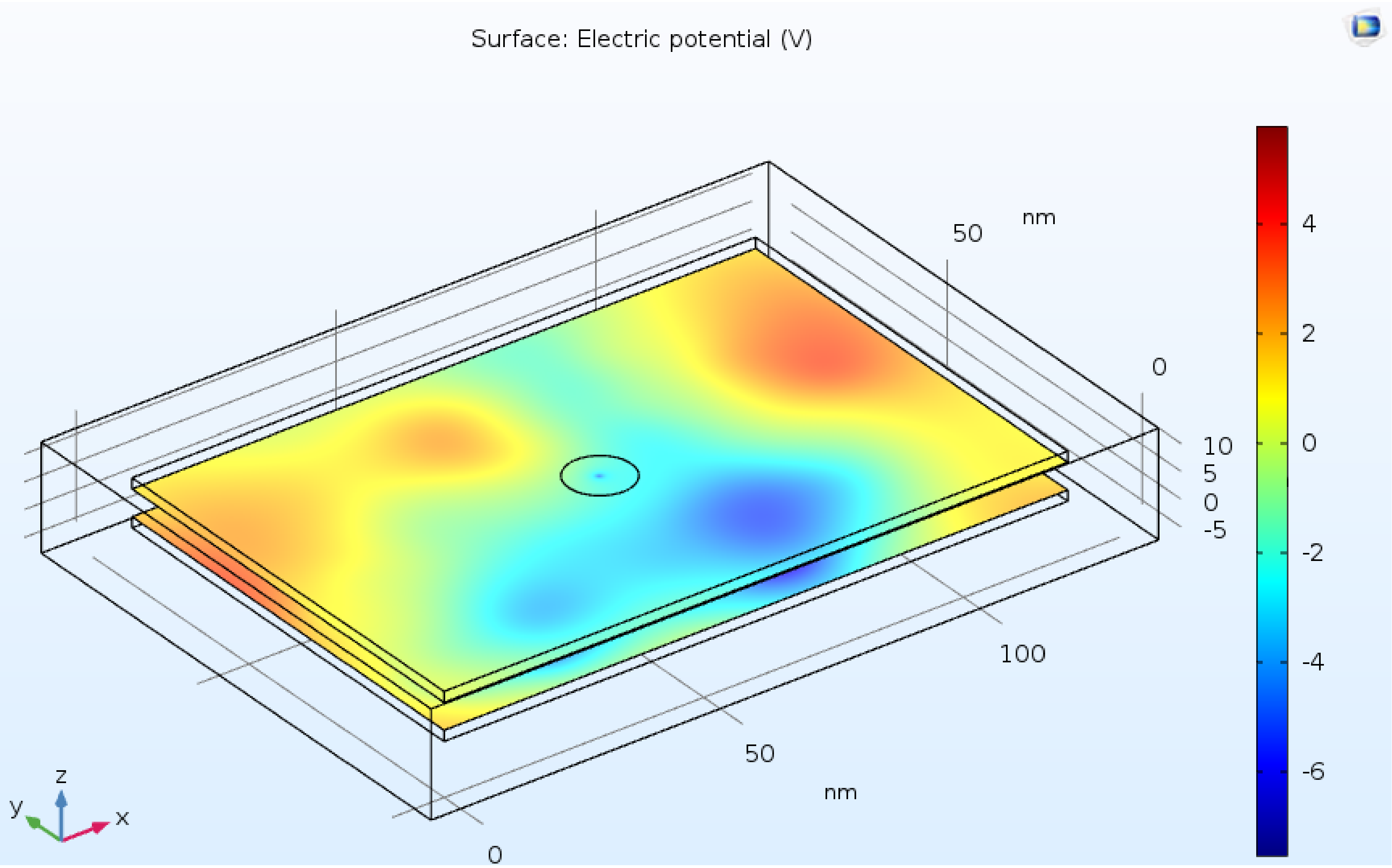
```
1.763458565, 1.693640817, 1.61372761, 1.524412241, 1.426600494, 1.321443728, 1.2103
1.66583604, 1.588456133, 1.499989161, 1.401087578, 1.292682501, 1.176054022, 1.0528
1.568424451, 1.482705851, 1.384643876, 1.274794301, 1.154073767, 1.023881793, 0.886
1.471860225, 1.377056384, 1.268336454, 1.146071641, 1.011078288, 0.864839151, 0.709
1.376964875, 1.272415067, 1.152019726, 1.015835722, 0.86444985, 0.699329873, 0.5232
1.284755857, 1.169967381, 1.037038926, 0.885550171, 0.715668624, 0.528705914, 0.327
1.196440883, 1.07119298, 0.925198901, 0.757383286, 0.567276182, 0.355834556, 0.1265
1.11338535, 0.977836739, 0.818765145, 0.634295926, 0.4231227781, 0.185623792189, -0
1.037027035, 0.891808973, 0.720354195, 0.5199512945, 0.28835176095, 0.025193566134,
0.968779933, 0.815016378, 0.632680301, 0.4183609496, 0.16896486981, -0.1166414557,
0.909924136, 0.749180564, 0.558226097, 0.3333268576, 0.0709155458, -0.2306964121, -
0.861579466, 0.695727417, 0.498976863, 0.2678686087, -0.0009591384, -0.3092453595,
0.824769583, 0.655867234, 0.4564143727, 0.223974223, -0.0436980808, -0.3476246477,
```

csv potential grid (in Volts) starts at x_0, y_0 in top left (bottom left of plane in figure). Each row in the CSV is a single row along the y direction of the plane. There are 120 values in y direction and 80 in x direction

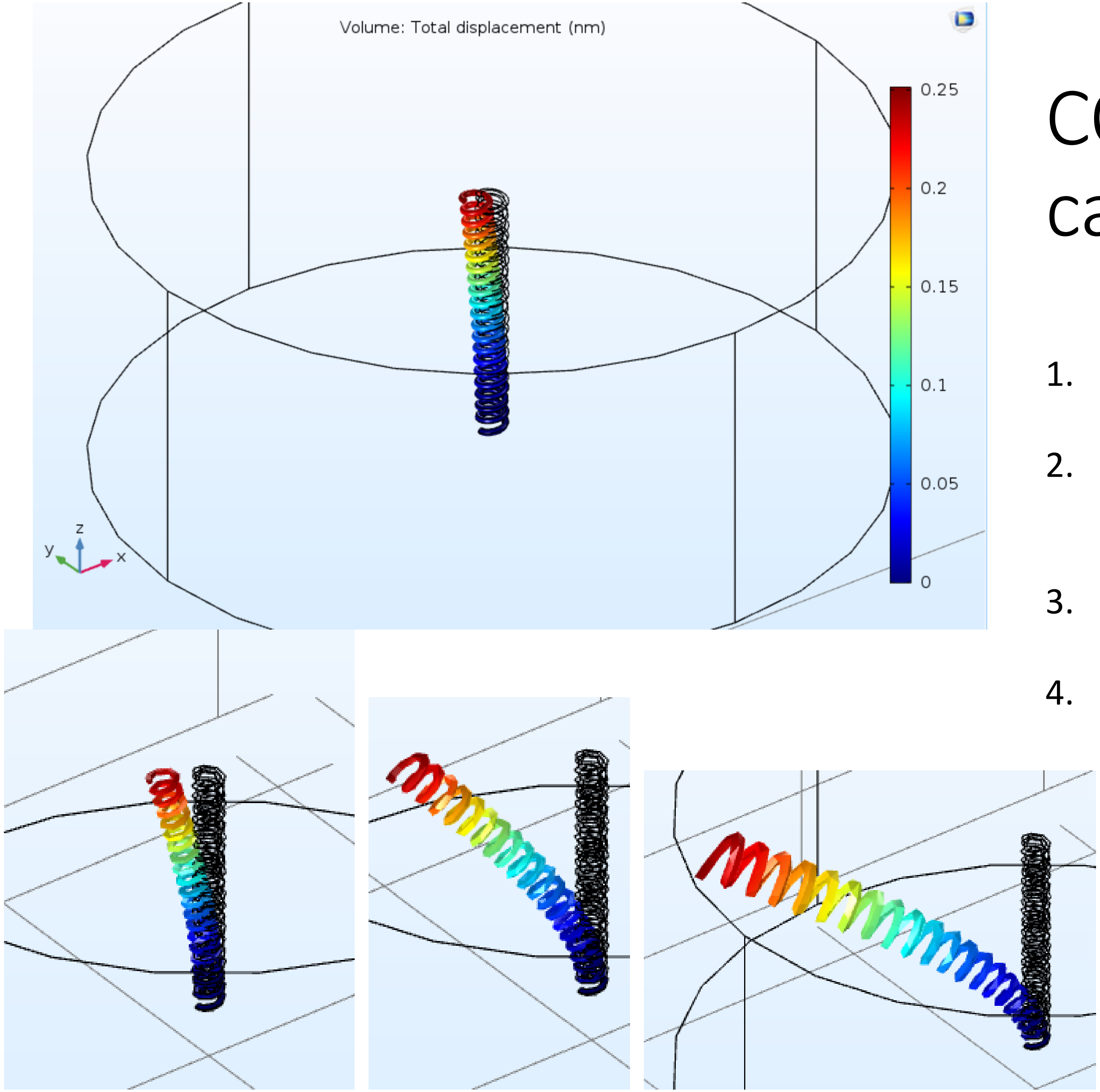




int1(x,y)
× 10^-22
8
6
4
2
0
-2
-4
-6
-8
-10
-12
6
× 10^-8
4
2
0
5
0
-5
-10
× 10^-22
10
5
× 10^-8
0
z
y
x



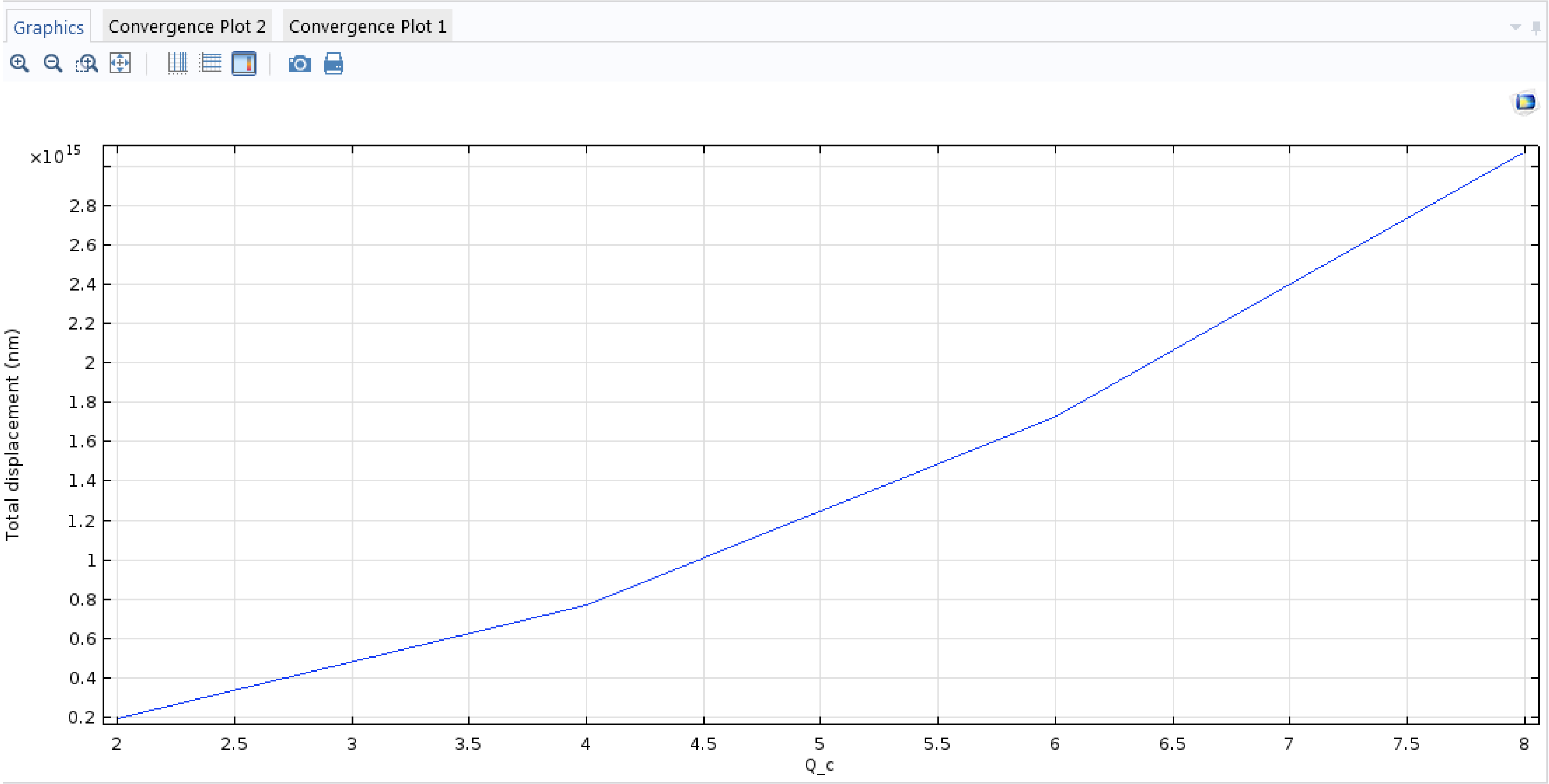
Surface: Electric potential (V)
nm
50
0
10
5
0
-5
100
50
nm
0
4
2
0
-2
-4
-6
z
y
x



COMSOL Model calibration

1. Start with Young's modulus at 2 Gpa. Adjust to achieve the following constraints:
2. kT (25 meV) calibration: A force of 4 pN acting through ~1 nm should jostle the C-terminus tip around like thermal energy
3. 50 meV calibration: A force of 8 pN should displace the C-terminus tip by ~40º (2.4 nm).
4. 120 meV calibration: A force of 16 pN should displace the C-terminus tip by ~80º (4.9 nm).

Error in model



Acknowledgments

- Ze’ev Bomzon
- Cornelia Wenger
- Novocure Ltd
- Eric Wong
- Ken Swanson
- Jeffrey E. Arle
- Thomas Dreeben
- Josh Timmons
- Rohit Ketkar

Contact: kwcarlso@bidmc.harvard.edu