Numerical Evaluation of the Polarizability Tensors of Stem Cells with Realistic 3D Shapes

Somen Baidya*(1), Ahmed M. Hassan(1), Beatriz Pazmino(2), Jack F. Douglas(2), Edward J. Garboczi(3)

(1) Computer Science Electrical Engineering Department, University of Missouri-Kansas City, Kansas City, MO 64110
(2) Materials Science and Engineering Division, National Institute of Standards and Technology, Gaithersburg, MD 20899
(3) Applied Chemicals and Materials Division, National Institute of Standards and Technology, Boulder, CO 80305

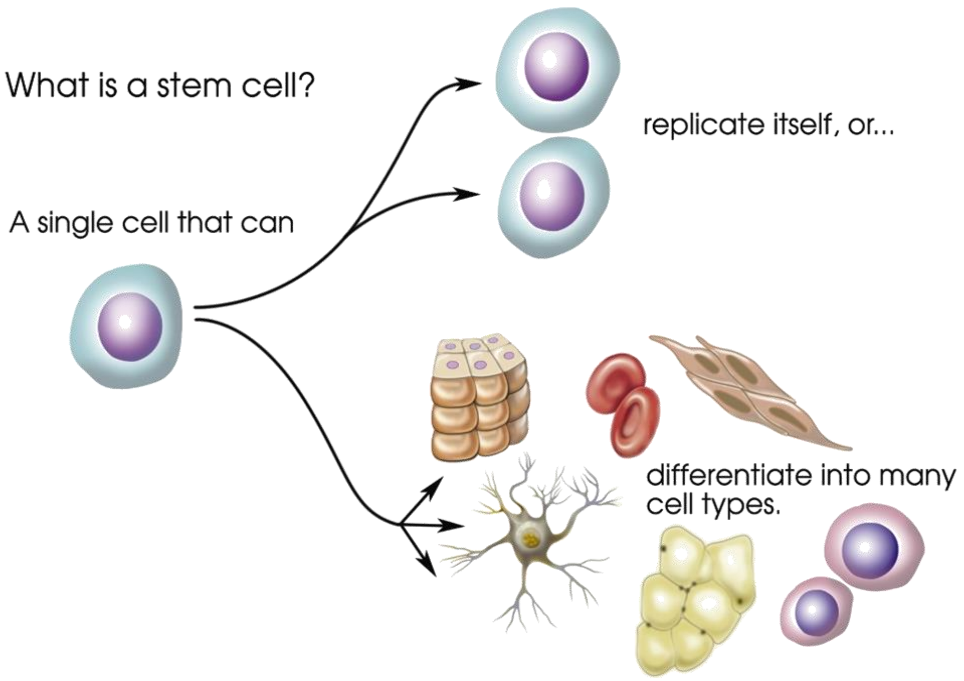
NIST National Institute of Standards and Technology U.S. Department of Commerce

UMKC

Introduction

Stem Cells differentiate into cells with different shape and functionality

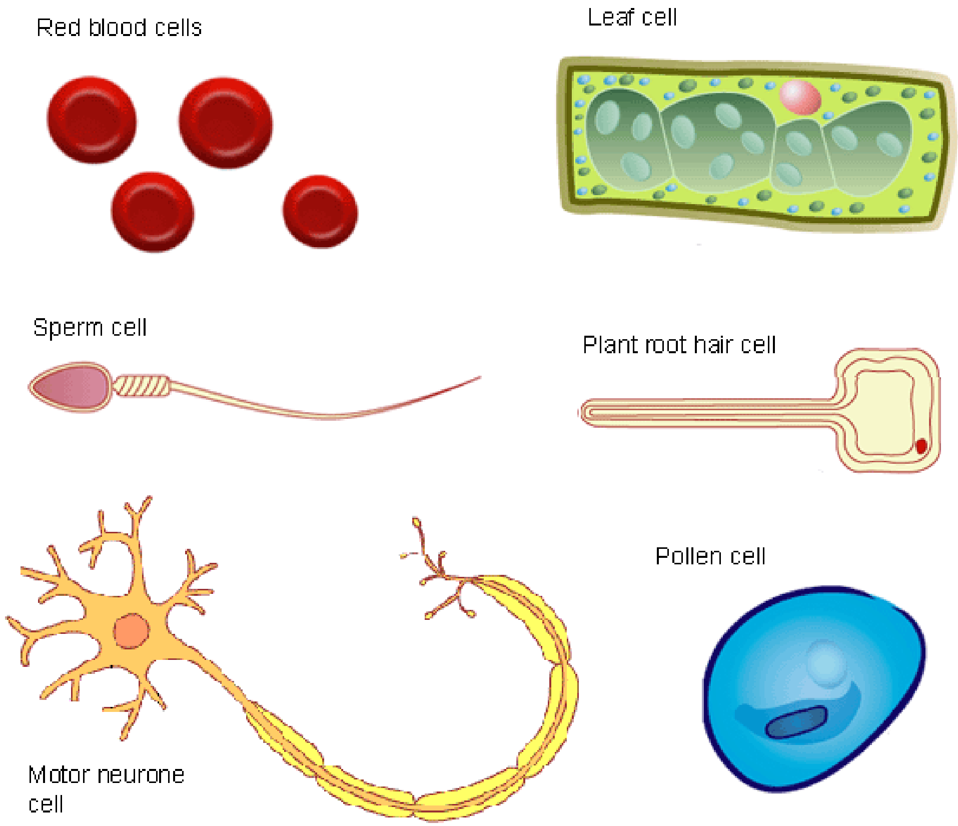
Stem Cells



Specialized cell

Stem Cell [1]

Variation in cell shape or morphology is analyzed in cell classification and cancer diagnosis study

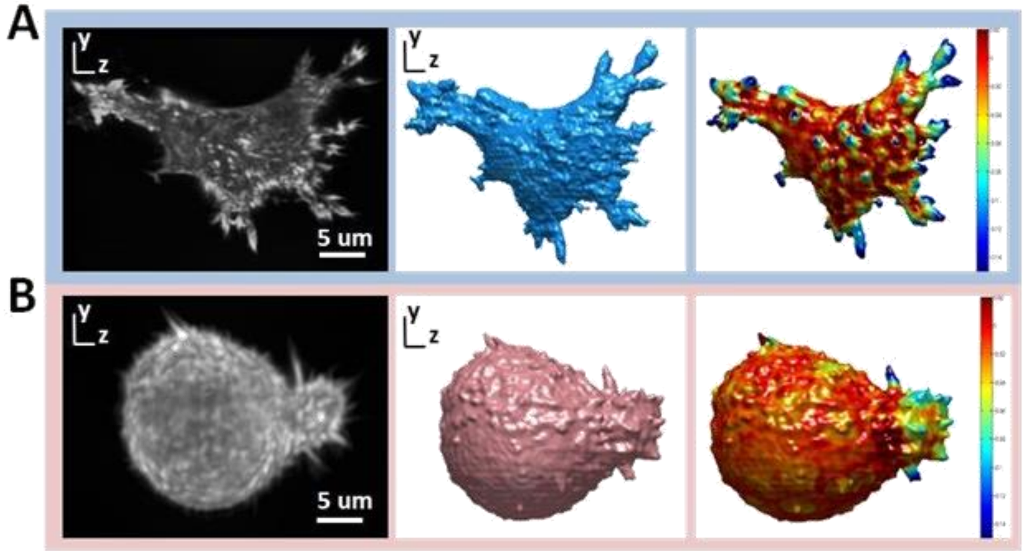


Cell Classification [2]

[1] Catherine Twomey; Understanding Stem cells: An Overview of the Science and Issues from the National Academies, http://www.nationalacademies.org/stemcells
[2] Haleo.co.uk. (2017). http://haleo.co.uk/the-body/cells/

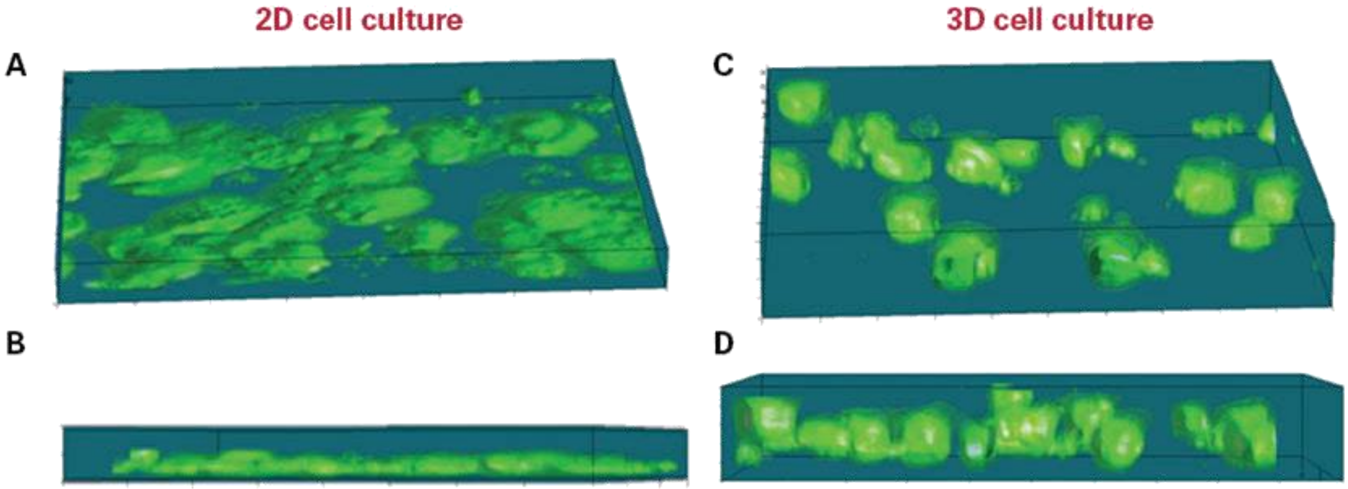
Imaging of 3D Cell Shapes

- Accurately capture the geometric parameters such as: 3D shape, volume and surface area
- Overcomes the dependency on orientation and focal plane of the image
- Helps determine the exact location of nuclei



3D Morphology of two biological cells [1]

- Growth of cells in a 2D environment during imaging can lead the cells to acquire an artificial flattened shape that does not reflect the true 3D shape of the cell in its natural environment

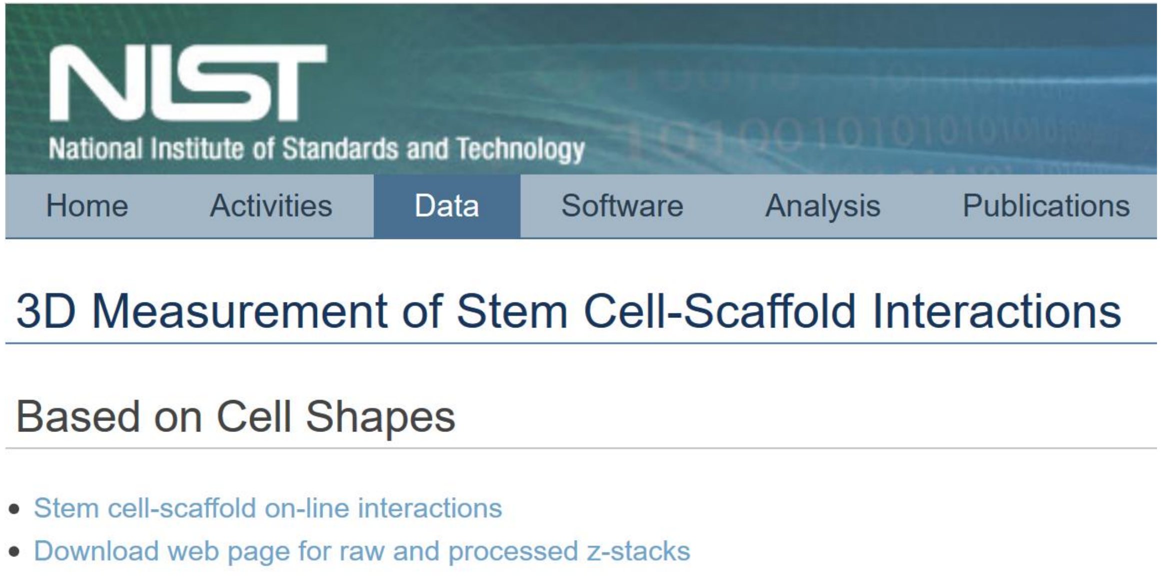


Cell Growth in 3D & 2D substrate[2]

[1] Utsouthwestern.edu. (2017). Who We Are: Danuser Lab - UT Southwestern, Dallas, Texas. http://www.utsouthwestern.edu/labs/danuser/who-we-are/
[2] Reinnervate.com. (2017). What is Alvetex? • ReproCELL Europe. http://reinnervate.com/alvetex/about-alvetex/what-is-alvetex/

NIST 3D Stem Cells Database

- NIST studied different scaffold systems to provide a 3D microenvironment that enables cells to behave more physiologically
- 3D confocal microscopy and 3D image analyses were used to reconstruct the 3D shapes of the cells
- 10 different environments (Scaffolds or planar substrates) with at least 100 cells per environment



https://isg.nist.gov/deepzoomweb/data/stemcellmaterialinteractions

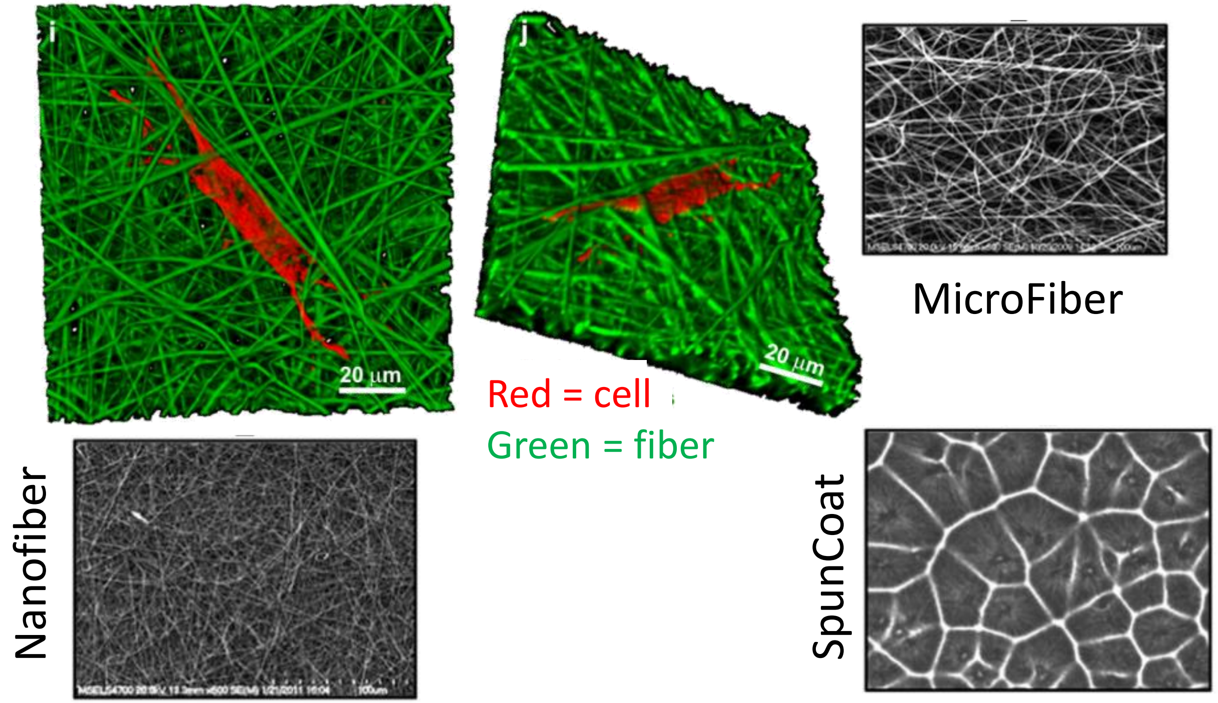


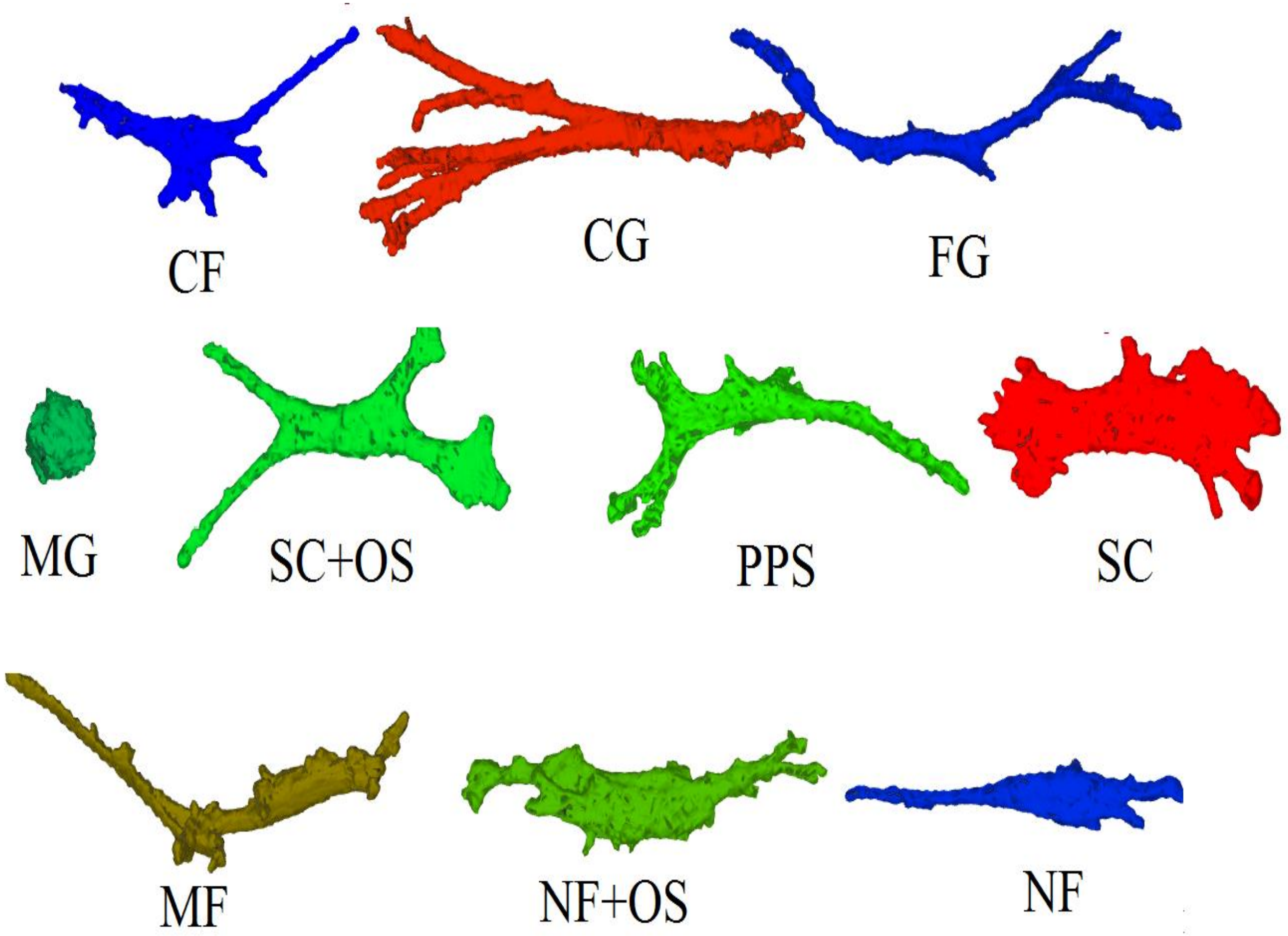
Fig: Cell Growth in Nanofiber scaffold and 3 different scaffold [1,2]

[1] T. M. Farooque, C. H. Camp, C. K. Tison, G. Kumar, S. H. Parekh, and C. G. Simon, "Measuring stem cell dimensionality in tissue scaffolds," *Biomaterials*, vol. 35, no. 9, pp. 2558–2567, Mar. 2014.

[2] Kumar, Girish, et al. "The determination of stem cell fate by 3D scaffold structures through the control of cell shape." Biomaterials 32.35 (2011): 9188-9196.

NIST 3D Stem Cells Database

- 3 families used a polymer based microenvironment: SpunCoat (SC), Nanofibers (NF), Microfibers (MF)
- 3 families used hydrogels from different sources: Matri-Gel (MG), Fibrin Gel (FG), and Collagen Gel (CG)
- Two families prepared from collagen: Collagen Gel (CG), Collagen Fibrils (CF)
- Osteogenic supplements (OS) were added to two existing cultures (NF+OS,SC+OS) to assess effect of chemical composition
- Cell shapes are strongly influenced by scaffold properties, scaffolds could drive cells into complex 1D, 2D or 3D shapes



Goal of this work is to study the electric properties of these cells with realistic 3D shapes

Static Electric Polarizability

- The static polarizability tensor describes the capability of a certain body to experience charge separation, forming a dipole moment, in response to an incident electric field

$$p = \alpha E$$

$$\begin{bmatrix} P_x \\ P_y \\ P_z \end{bmatrix} = \begin{bmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{zx} & \alpha_{zy} & \alpha_{zz} \end{bmatrix} \begin{bmatrix} E_x \\ E_y \\ E_z \end{bmatrix}$$

- Non-uniform cell geometry requires the **Numerical** solution of the following Laplace's Equation to calculate the polarizability tensors

$$\nabla^2 V(r) = 0$$

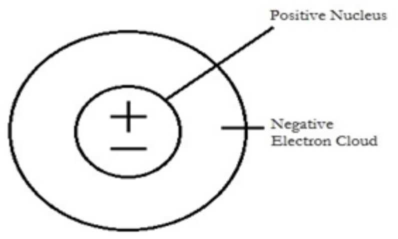


Fig. 3.12A: Atom before being placed in Electric Field

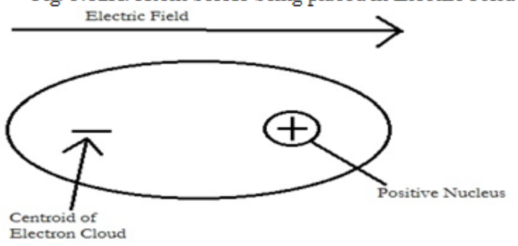
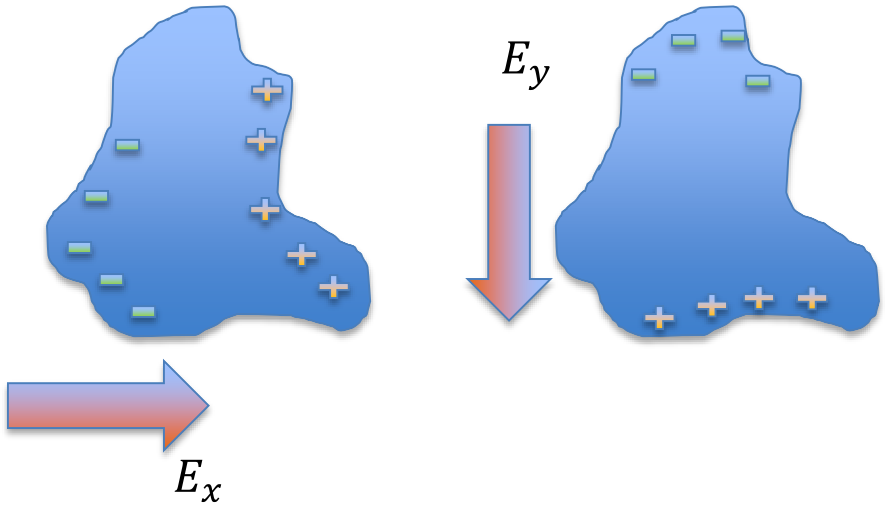


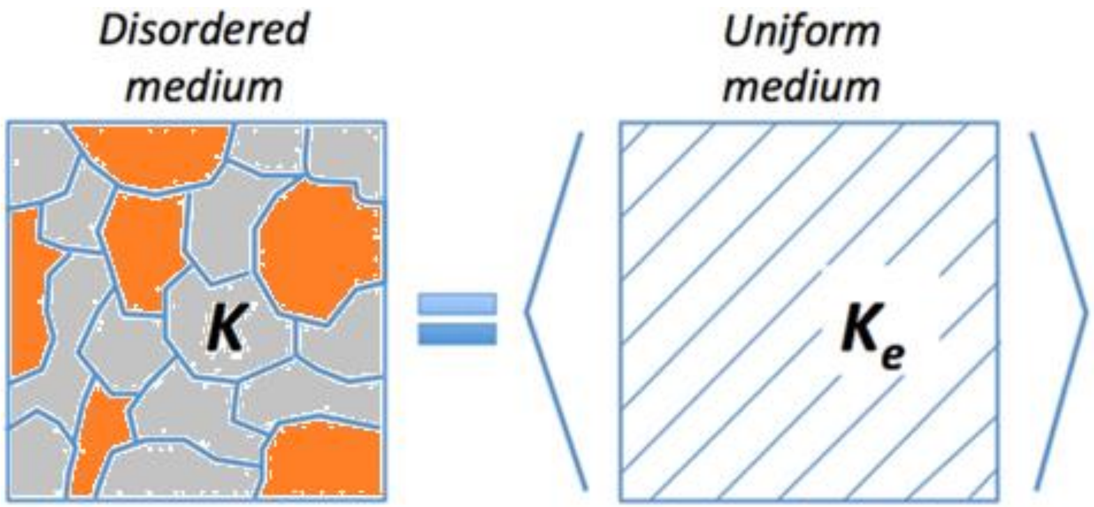
Fig. 3.12B: Atom placed in Electric Field



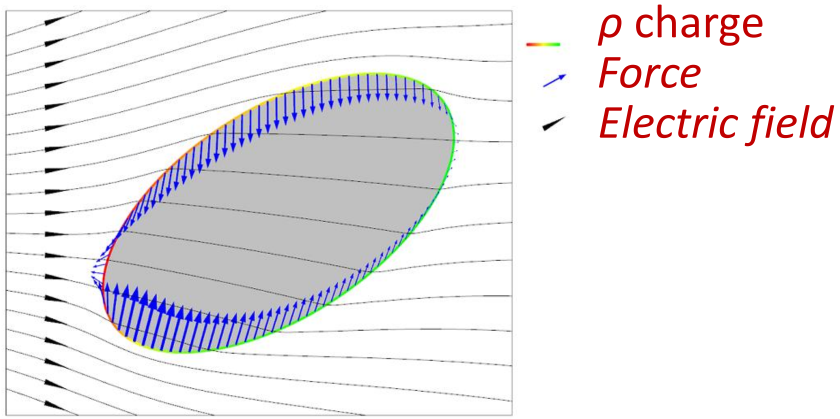
$$\alpha = \begin{bmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{zx} & \alpha_{zy} & \alpha_{zz} \end{bmatrix} \xrightarrow{\quad Diagonalization \quad} \hat{\alpha} = \begin{bmatrix} \hat{\alpha}_1 & 0 & 0 \\ 0 & \hat{\alpha}_2 & 0 \\ 0 & 0 & \hat{\alpha}_3 \end{bmatrix}$$

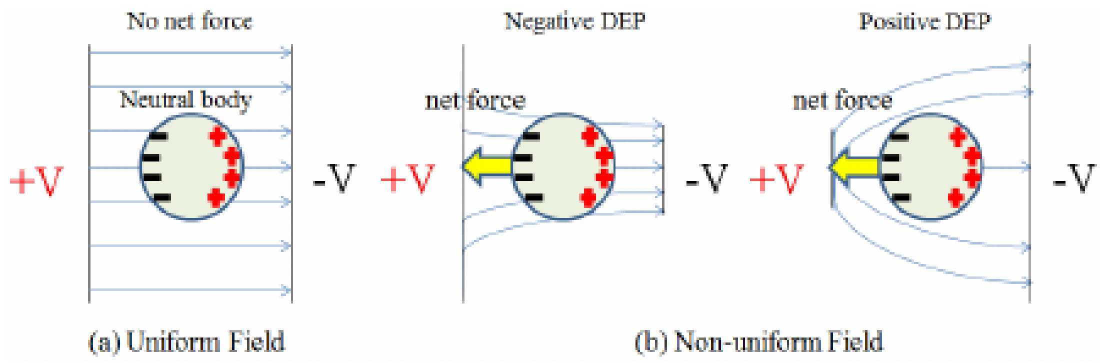
Application of Polarizability Tensor

- The effective electrical properties of composite materials i.e. tissue



- Dielectrophoresis: Motion of a cell due to an incident inhomogeneous electric field



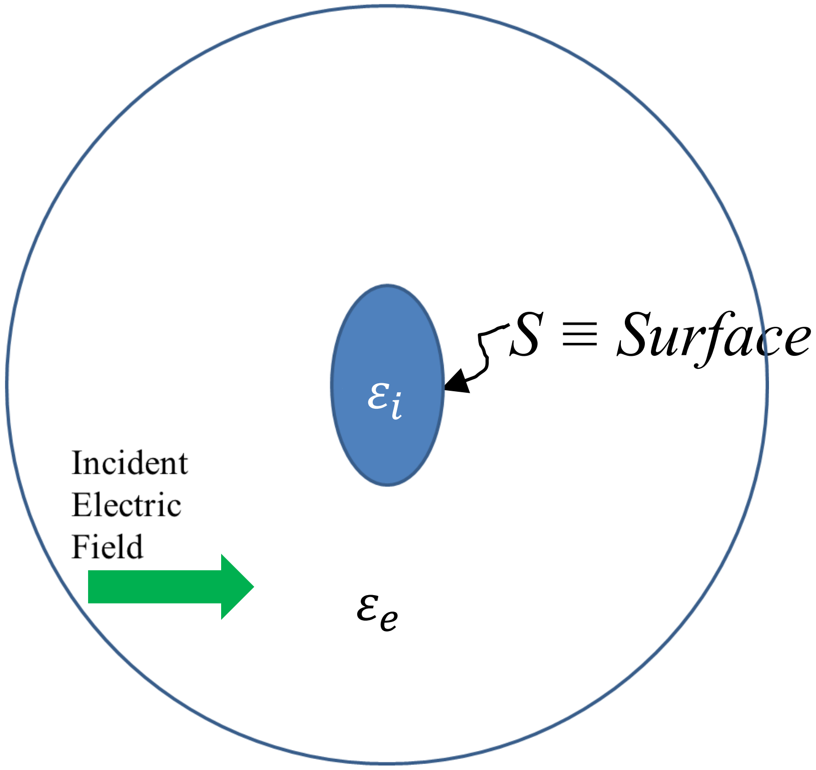


Dielectrophoretic Force, $\overrightarrow{F_{DEP}} = \frac{1}{2}\alpha V(\nabla E^2)$

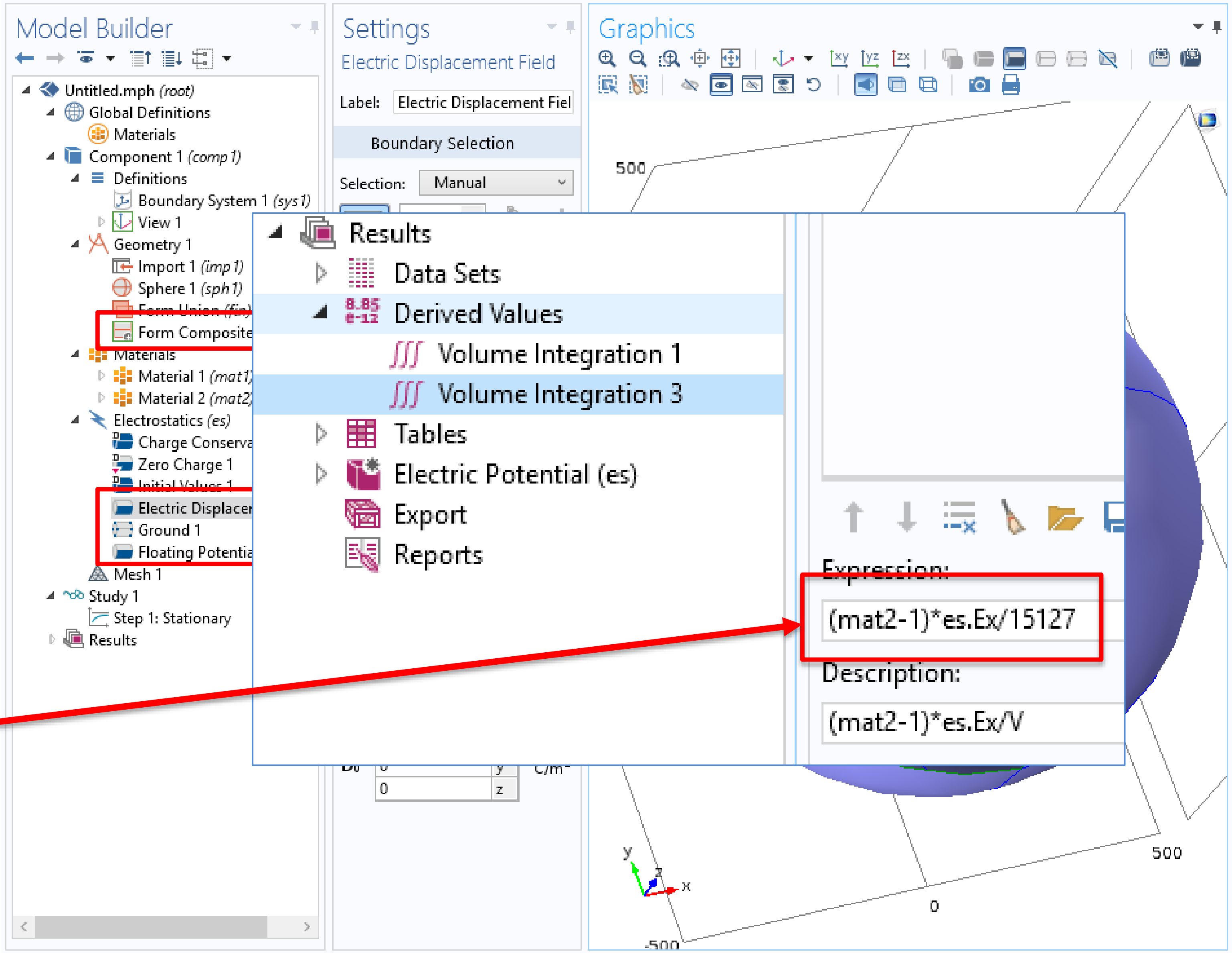
[1] Ghanbarian, Behzad, and Hugh Daigle. "Permeability in two-component porous media: Effective-medium approximation compared with lattice-Boltzmann simulations." Vadose Zone Journal 15.2 (2016).
[2] Kim, Dong, et al. "Effect of array and shape of insulating posts on proteins focusing by direct current dielectrophoresis." Journal of Mechanical Science and Technology 28.7 (2014): 2629.

Calculation of the Polarizability Tensors

Electric Polarizability Tensor (α_E)



$$p = \int_V P dV = (\varepsilon_i - \varepsilon_e) \iiint E_i dV$$



Sihvola, Ari, et al. "Polarizabilities of platonic solids." *IEEE transactions on antennas and propagation* 52.9 (2004): 2226-2233.

Electrostatic Solvers

- To validate our results for these complex cell shapes, the following independent solvers were employed:

  1. COMSOL: Commercial Finite Element Package

     (Tetrahedral discretization)

  2. SCUFF-EM: Open Source Method of Moments

     (Surface triangular mesh)

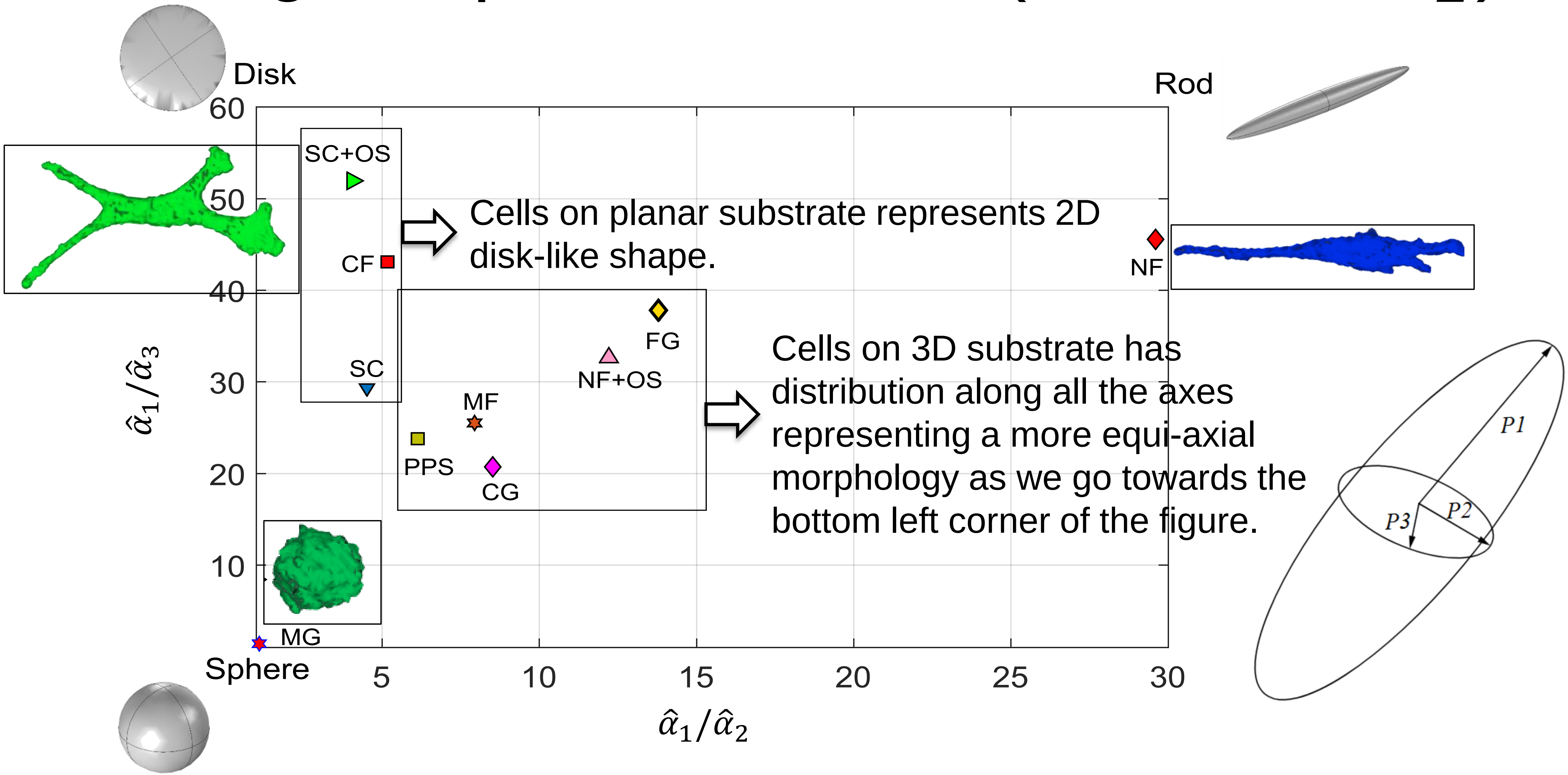
Cell Family	α_e	Scuff-EM	COMSOL	Percentage Uncertainty
PPS	$\hat{\alpha}_1$	86.4257	84.4609	2.27%
	$\hat{\alpha}_2$	14.3076	13.6767	4.41%
	$\hat{\alpha}_3$	3.3438	3.2124	3.93%
Collagen Fibrils	$\hat{\alpha}_1$	85.726	80.2635	6.37%
	$\hat{\alpha}_2$	17.0776	16.0936	5.76%
	$\hat{\alpha}_3$	1.7764	1.7029	4.14%
Microfibers	$\hat{\alpha}_1$	99.2096	92.6334	6.63%
	$\hat{\alpha}_2$	12.8925	12.2077	5.31%
	$\hat{\alpha}_3$	3.8979	3.7389	4.08%

$$\%\ \text{Uncertainty} = \frac{|\alpha_{SCUFF\_EM} - \alpha_{COMSOL}|}{\alpha_{SCUFF\_EM}} * 100$$

Maximum percentage uncertainty for the case of sampling is *6.63%*

S. Baidya, A. M. Hassan, B. A. P. Betancourt, J. F. Douglas and E. J. Garboczi, "Analysis of Different Computational Techniques for Calculating the Polarizability Tensors of Stem Cells with Realistic Three-Dimensional Morphologies," IEEE Transactions on Biomedical Engineering, Under Review

Encoding Shape Information (Based on $\boldsymbol{\alpha_E}$)



Cells on planar substrate represents 2D disk-like shape.

Cells on 3D substrate has distribution along all the axes representing a more equi-axial morphology as we go towards the bottom left corner of the figure.

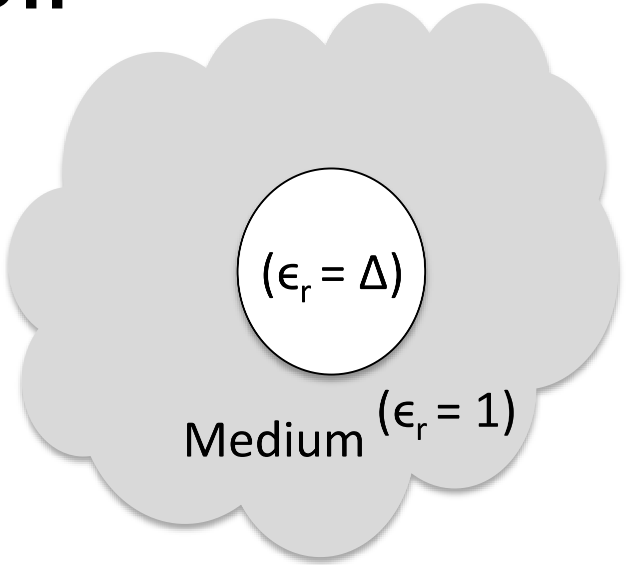
S. Baidya, A. M. Hassan, B. A. P. Betancourt, J. F. Douglas and E. J. Garboczi, "Analysis of Different Computational Techniques for Calculating the Polarizability Tensors of Stem Cells with Realistic Three-Dimensional Morphologies," IEEE Transactions on Biomedical Engineering, Under Review

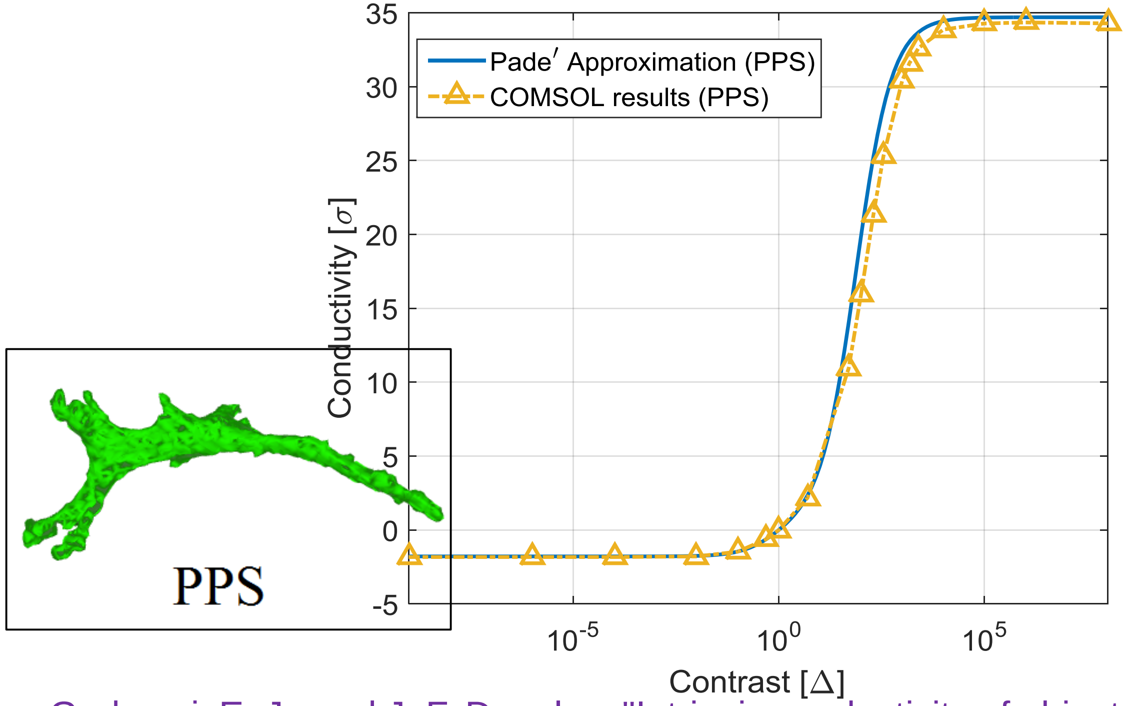
Variable Contrast for cell

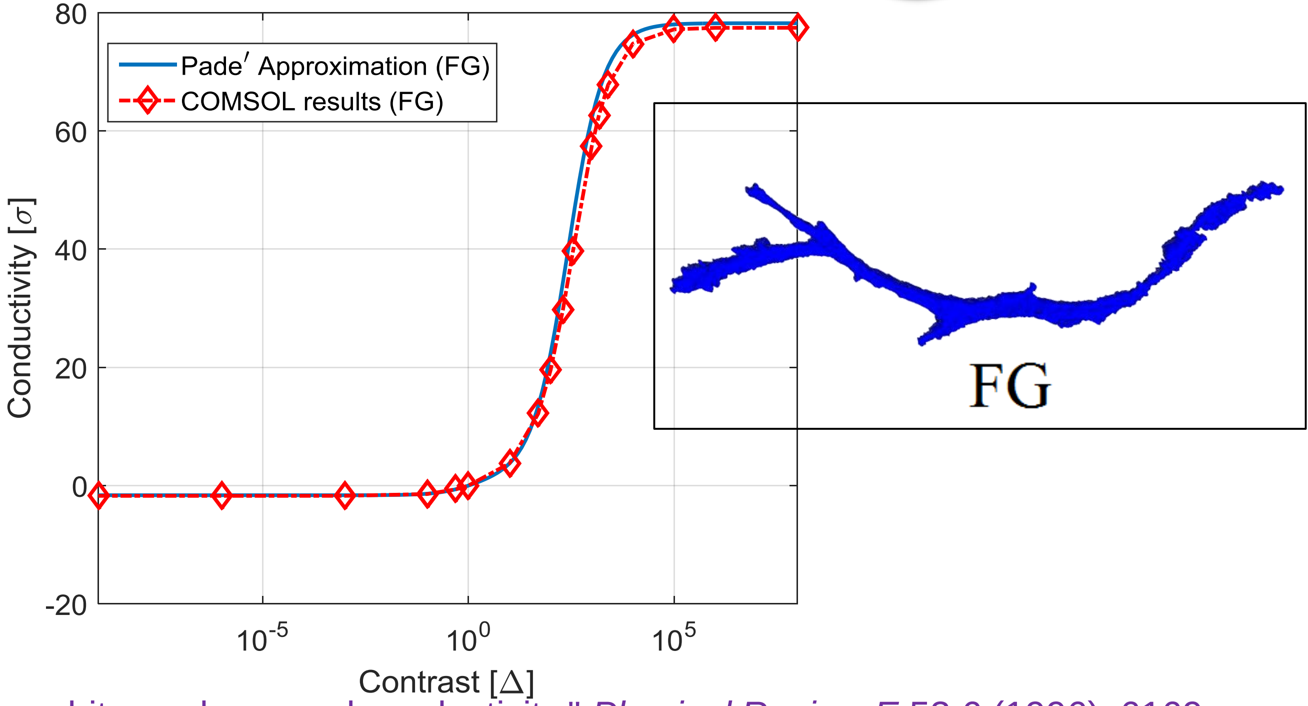
Padé approximation $$[\sigma(\Delta)] = \frac{[\sigma]_\infty(\Delta-1)^2 + a(\Delta-1)}{(\Delta-1)^2 + ([\sigma]_\infty + a/d)(\Delta-1) + a}$$

Particle shape dependent constant $$a = \frac{[\sigma]_\infty - [\sigma]_0 + [\sigma]_\infty[\sigma]_0}{1 + (1 - 1/d)[\sigma]_0}.$$

$$[\sigma]_\infty = \frac{1}{3}\mathrm{Tr}(\boldsymbol{\alpha}_\mathbf{e}) \quad [\sigma]_0 = \frac{1}{3}\mathrm{Tr}(\boldsymbol{\alpha}_\mathbf{m}) \quad [\sigma(\Delta)] = \frac{1}{3}\mathrm{Tr}(\boldsymbol{\alpha})$$







Garboczi, E. J., and J. F. Douglas. "Intrinsic conductivity of objects having arbitrary shape and conductivity." *Physical Review E* 53.6 (1996): 6169

Conclusions

- Stem cells electrical properties, such as polarizability, is affected by the culturing environment and are significantly different from those of a sphere or ellipsoid
- The electrostatic characteristics can be used as a 3D cell shape classifier
- The Padé approximation provides an accurate and a computationally inexpensive way to calculate the polarizability at any contrast

References

- S. W. Chan, K. Leung and W. Felix Wong, "An expert system for the detection of cervical cancer cells using knowledge-based image analyzer," *Artificial Intelligence in Medicine,* vol. 8, no. 1, pp. 67-90, 1996.
- T. Xie, M. Zeidel and Y. Pan, "Detection of tumorigenesis in urinary bladder with optical coherence tomography: optical characterization of morphological changes," Optics Express, vol. 10, no. 24, p. 1431, 2002.
- K. A. Giuliano, "Dissecting the individuality of cancer cells: The morphological and molecular dynamics of single human glioma cells," Cell Motility and the Cytoskeleton, vol. 35, no. 3, pp. 237-253, 1996.
- M. Minsky, "Memoir on inventing the confocal scanning microscope," Scanning, vol. 10, no. 4, pp. 128-138, 1988.
- M. G. Meyer, M. Fauver, J. R. Rahn, T. Neumann, F. W. Patten, E. J. Seibel and A. C. Nelson, "Automated cell analysis in 2D and 3D: A comparative study," *Pattern Recognition,* vol. 42, no. 1, pp. 141-146, 2009.
- E. Knight and S. Przyborski, "Advances in 3D cell culture technologies enabling tissue-like structures to be created in vitro," *Journal of Anatomy,* vol. 227, no. 6, pp. 746-756, 2014.
- G. Pucihar, T. Kotnik, B. Valič and D. Miklavčič, "Numerical Determination of Transmembrane Voltage Induced on Irregularly Shaped Cells," *Annals of Biomedical Engineering,* vol. 34, no. 4, pp. 642-652, 2006.
- P. a. S. M. Bajcsy, S. Florczyk, C. Simon, D. Juba and M. Brady, "A method for the evaluation of thousands of automated 3D stem cell segmentations," *Journal of microscopy,* vol. 260, no. 3, pp. 363-376, 2015.
- M. L. Mansfield, J. F. Douglas and E. J. Garboczi, "Intrinsic viscosity and the electrical polarizability of arbitrarily shaped objects," *Physical Review E,* vol. 64, no. 6, p. 061401, 2001.
- D. J. Audus, A. M. Hassan, E. J. Garboczi and J. F. Douglas, "Interplay of particle shape and suspension properties: a study of cube-like particles," *Soft Matter,* vol. 11, no. 17, pp. 3360-3366, 2015.
- A. Sihvola, P. Yla-Oijala, S. Jarvenpaa and J. Avelin, "Polarizabilities of platonic solids," *IEEE Transactions on Antennas and Propagation,* vol. 52, no. 9, pp. 2226-2233, 2004.
- . Vargas Lara, A. M. a. Hassan, E. J. Garboczi and J. F. Douglas, "Intrinsic conductivity of carbon nanotubes and graphene sheets having a realistic geometry," *The Journal of chemical physics,* vol. 143, no. 20, p. 204902, 2015.
- M. H. Reid and S. G. Johnson, "Efficient Computation of Power, Force, and Torque in BEM Scattering Calculations," *IEEE Transactions on Antennas and Propagation,* vol. 63, no. 8, pp. 3588-3598, 2015
- N. Moshtagh, "Minimum volume enclosing ellipsoid," *Convex Optimization,* vol. 111, p. 112, 2005.
- S. Baidya, A. M. Hassan, B. A. P. Betancourt, J. F. Douglas and E. J. Garboczi, "Analysis of Different Computational Techniques for Calculating the Polarizability Tensors of Stem Cells with Realistic Three-Dimensional Morphologies," *IEEE Transactions on Biomedical Engineering,* Under Review

Minimum Enclosing Ellipse (α_E clustering)

The general form of an ellipsoid in center form

$$\mathcal{E} = \{x \in \mathbb{R}^n \mid (x-c)^T A (x-c) = 1\}$$

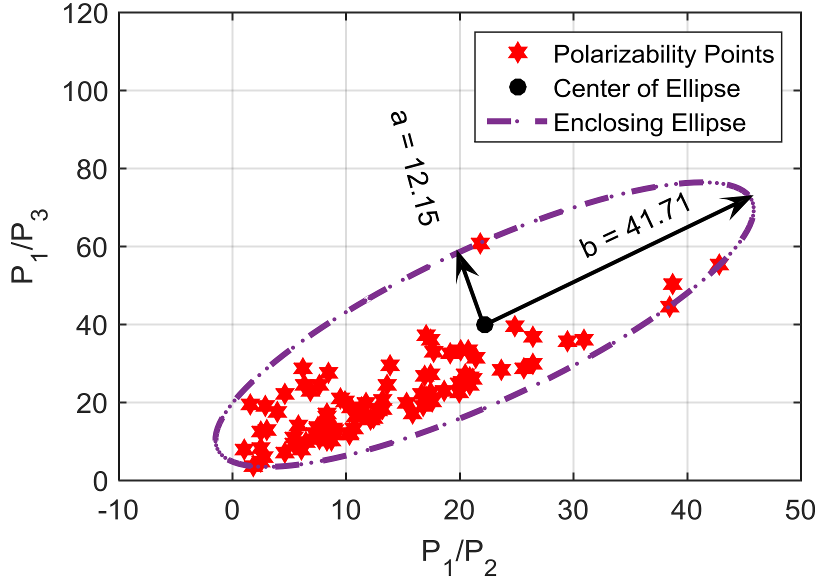
The volume of the ellipsoid

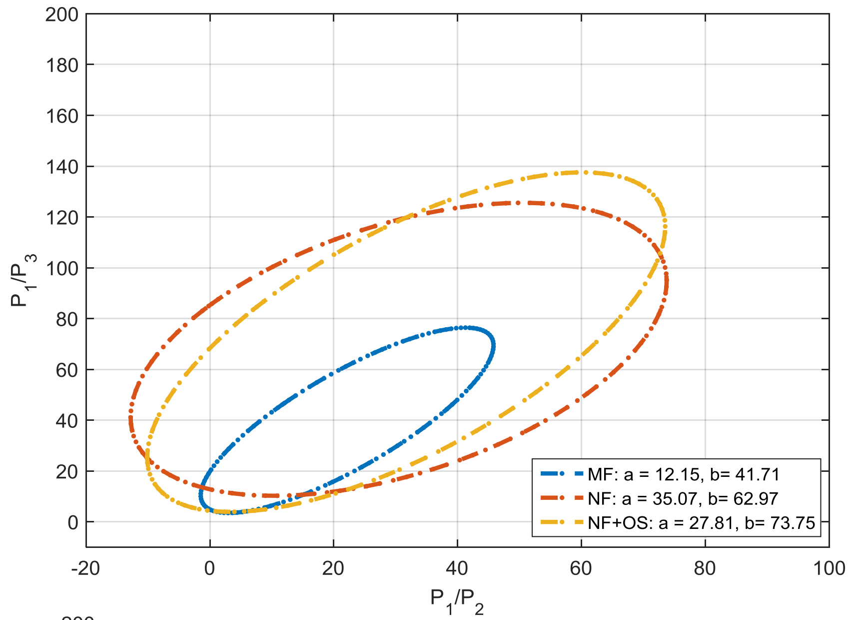
$$Vol(\mathcal{E}) = \frac{v_o}{\sqrt{\det(A)}} = v_0 \det(A^{-1})^{\frac{1}{2}}$$

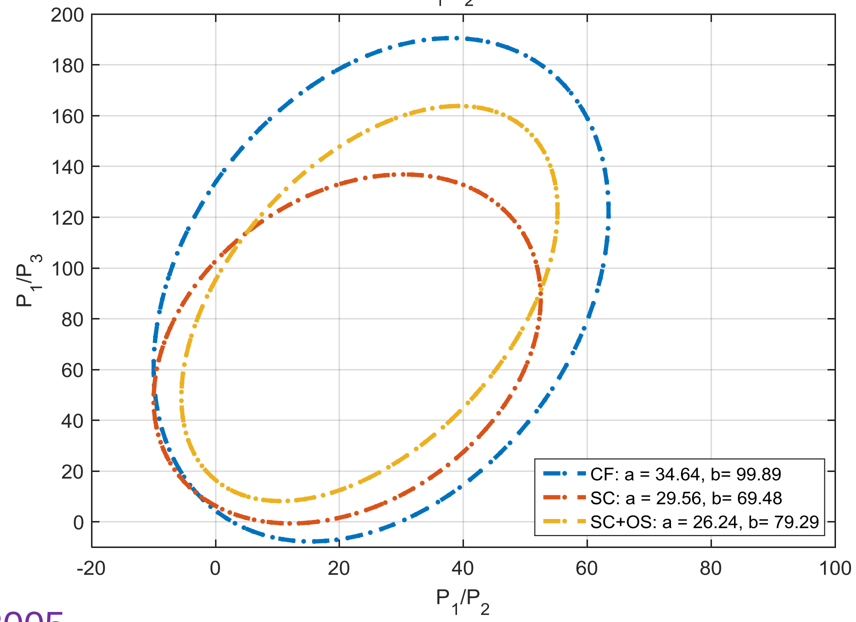
The optimization problem

Under the constraint

$$\begin{aligned} &minimize \quad \det(E^{-1}) \\ &(f_i - c)^T A (f_i - c) \le 1 \qquad i = 1,2 \ldots m \end{aligned}$$







N. Moshtagh, "Minimum volume enclosing ellipsoid," Convex Optimization, vol. 111, p. 112, 2005

Polarizability Comparison

Diagonal elements of Electric Polarizability Comparison (α_E)

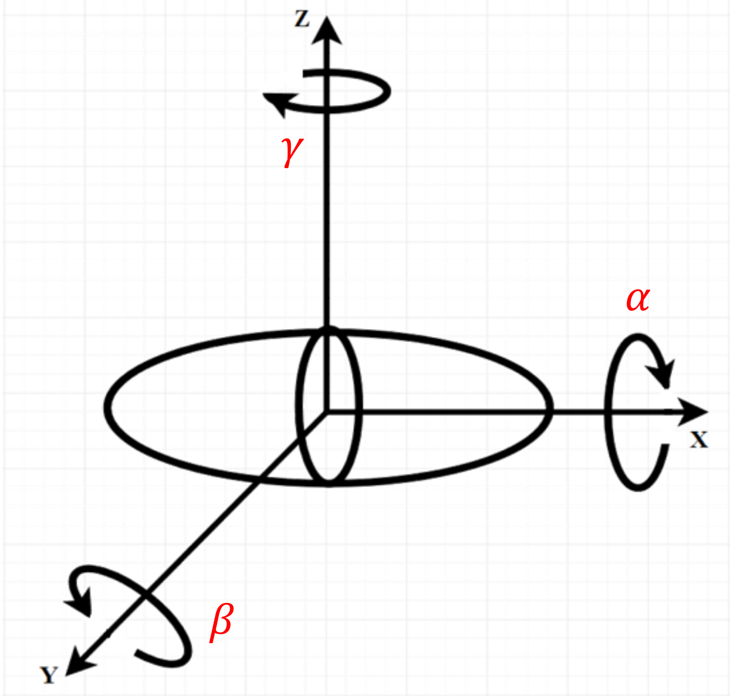
Cell Family	α_e	Scuff-EM (Down 4)	COMSOL (Down 4)	Percentage Uncertainty
PPS	P_1	86.4257	84.4609	2.27%
	P_2	14.3076	13.6767	4.41%
	P_3	3.3438	3.2124	3.93%
Collagen Fibrils	P_1	85.726	80.2635	6.37%
	P_2	17.0776	16.0936	5.76%
	P_3	1.7764	1.7029	4.14%
Microfibers	P_1	99.2096	92.6334	6.63%
	P_2	12.8925	12.2077	5.31%
	P_3	3.8979	3.7389	4.08%

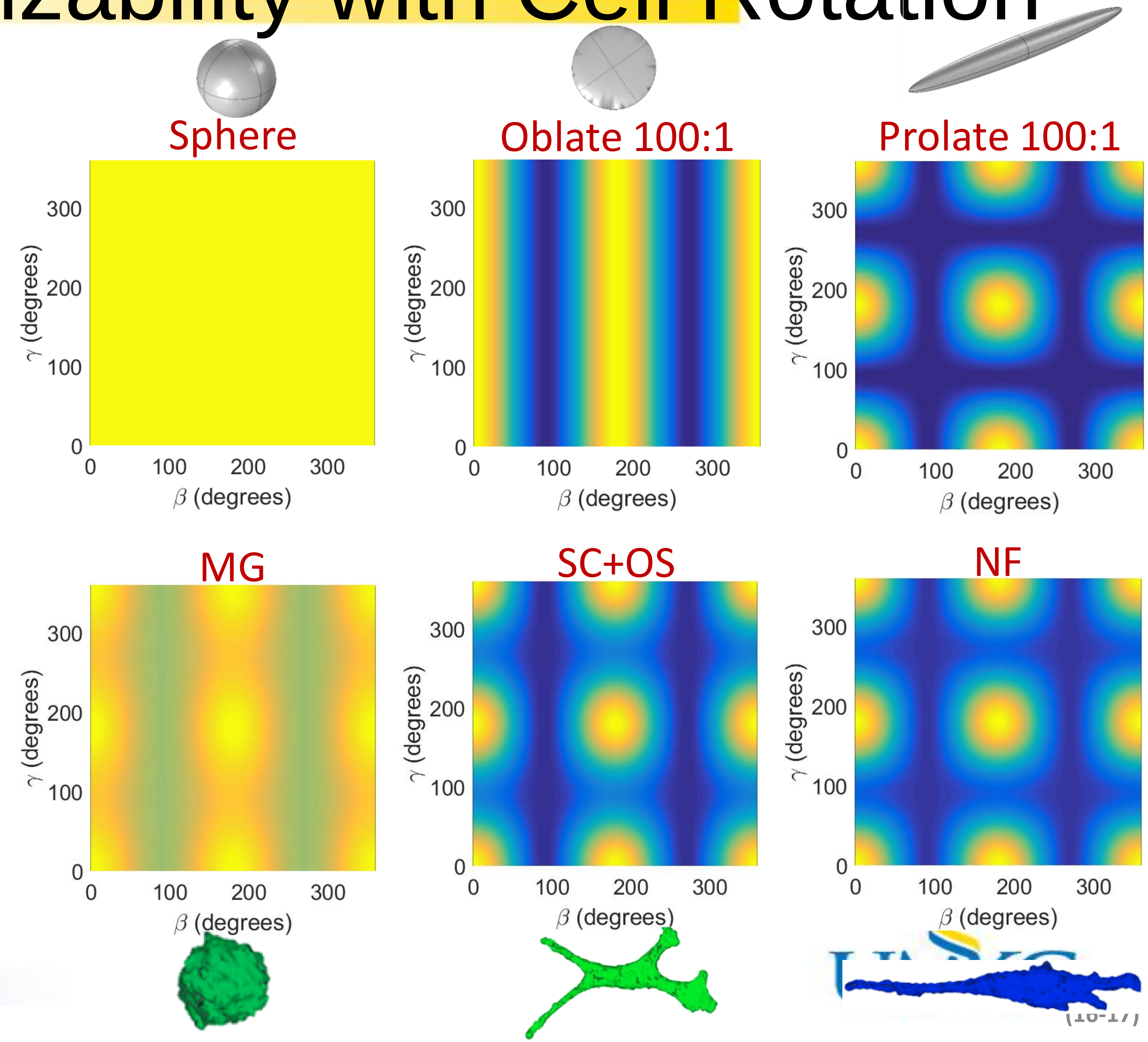
Cell Family	α_e	Voxel	Scuff-EM (Down 1)	Percentage Uncertainty
Matrigel	P_1	4.3171	4.5036	4.14%
	P_2	3.9992	3.9062	2.38%
	P_3	3.0494	2.9465	3.49%
NF+OS	P_1	92.648	85.06	8.92%
	P_2	7.4425	6.8821	8.14%
	P_3	2.405	2.5791	6.75%
Microfibers	P_1	136.9432	129.8975	5.42%
	P_2	17.3376	16.3612	5.97%
	P_3	5.0318	5.0886	1.12%

$$\%\ \text{Uncertainty} = \frac{|\alpha_{SCUFF\_EM} - \alpha_{COMSOL}|}{\alpha_{SCUFF\_EM}} * 100$$

Maximum percentage uncertainty for the case of *Down 4* sampling is 6.63%
Maximum percentage uncertainty in case of *Down 1* sampling is 8.92% .

Variation of Polarizability with Cell Rotation





- Plots show variations in α_{Exx} as the cells are rotated around the y-axis and z-axis
- Matrigel (MG) showing very small variation in α_{Exx} showing it is behaving electrically similar too a sphere
- The behavior of SC+OS is closer to an oblate ellipsoid whereas NF is closer to a prolate ellipsoid.

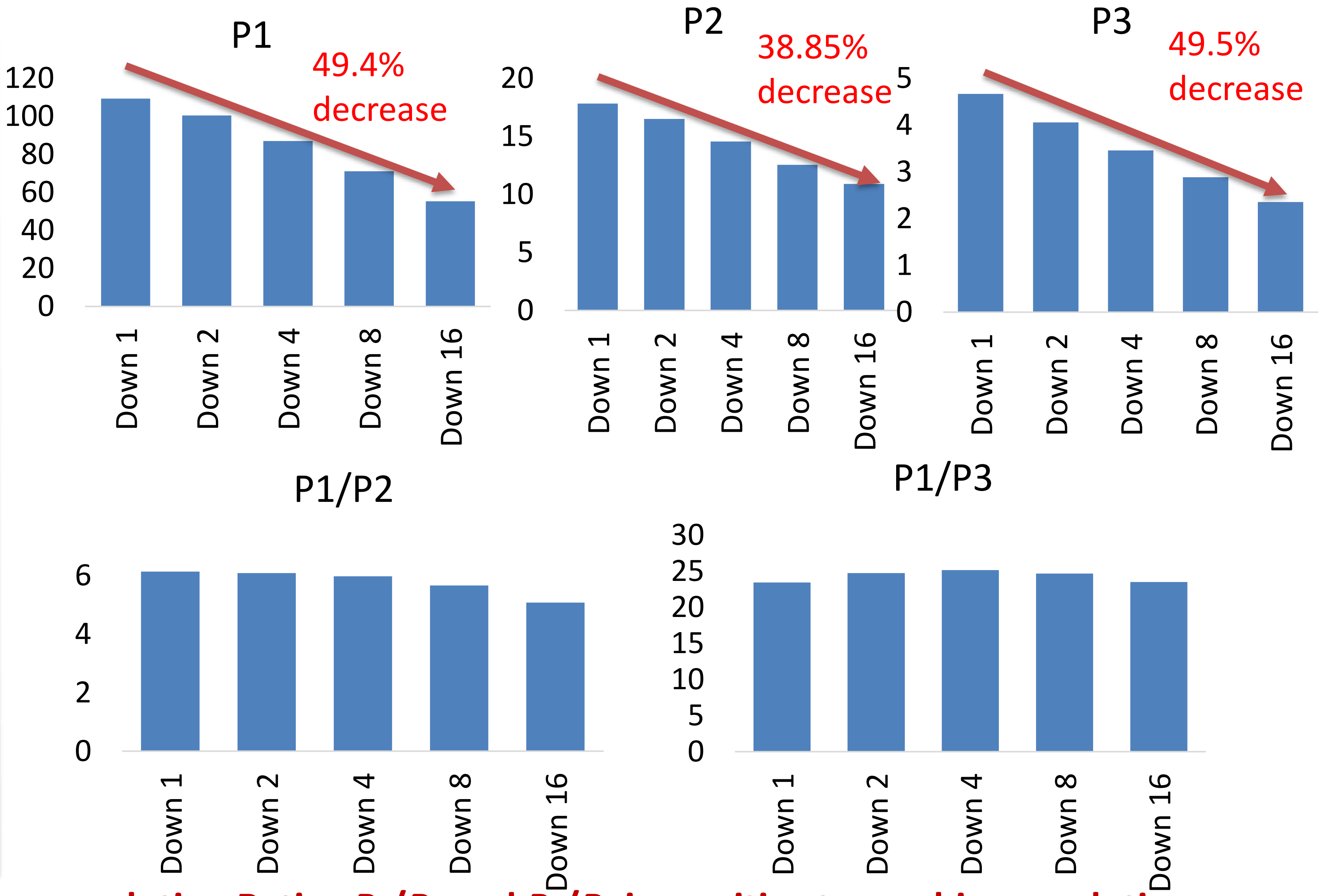
Polarizability VS Meshing Resolution (PPS)

- In general, polarizability matrix $\boldsymbol{\alpha}_\mathbf{E}$ has 9 nonzero elements (6 independent elements)
- Polarizability matrix can be diagonalized such that

$$\boldsymbol{\alpha}_\mathbf{E} = \begin{bmatrix} \alpha_{Exx} & \alpha_{Exy} & \alpha_{Exz} \\ \alpha_{Eyx} & \alpha_{Eyy} & \alpha_{Eyz} \\ \alpha_{Ezx} & \alpha_{Ezy} & \alpha_{Ezz} \end{bmatrix}$$

$$\text{Diagonalized } \boldsymbol{\alpha}_\mathbf{E} = \begin{bmatrix} P_1 & 0 & 0 \\ 0 & P_2 & 0 \\ 0 & 0 & P_3 \end{bmatrix}$$

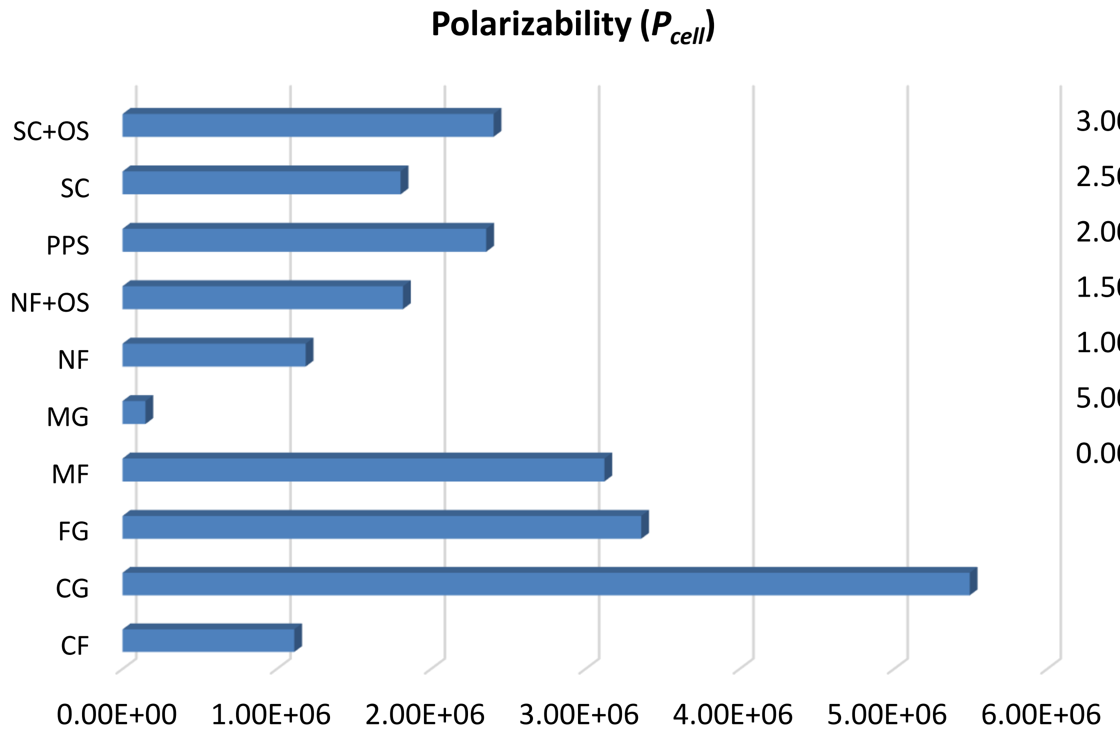
$$P_1 \geq P_2 \geq P_3$$

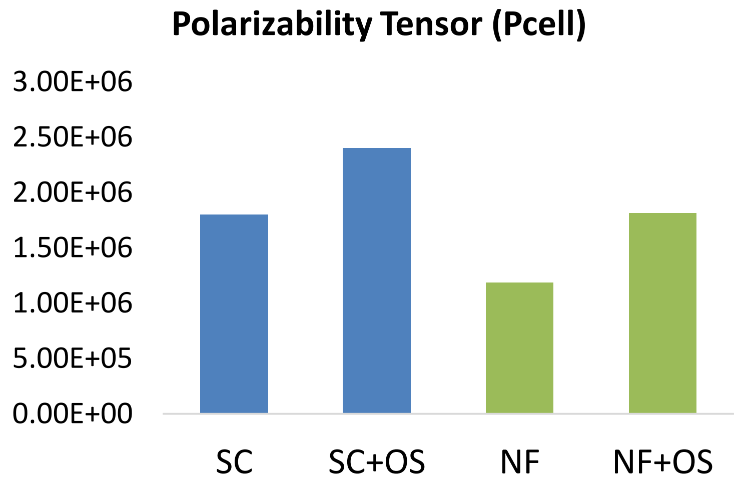


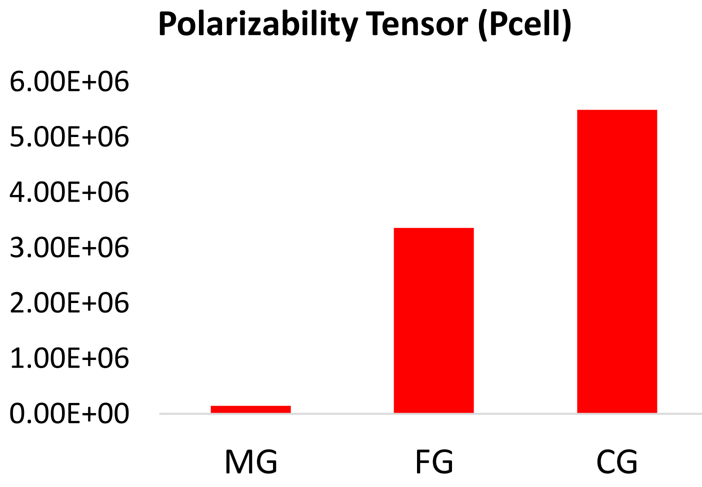
P_1, P_2, P_3 highly sensitive to meshing resolution Ratios P_1/P_3 and P_1/P_2 insensitive to meshing resolution

Observation based on the P_{cell}

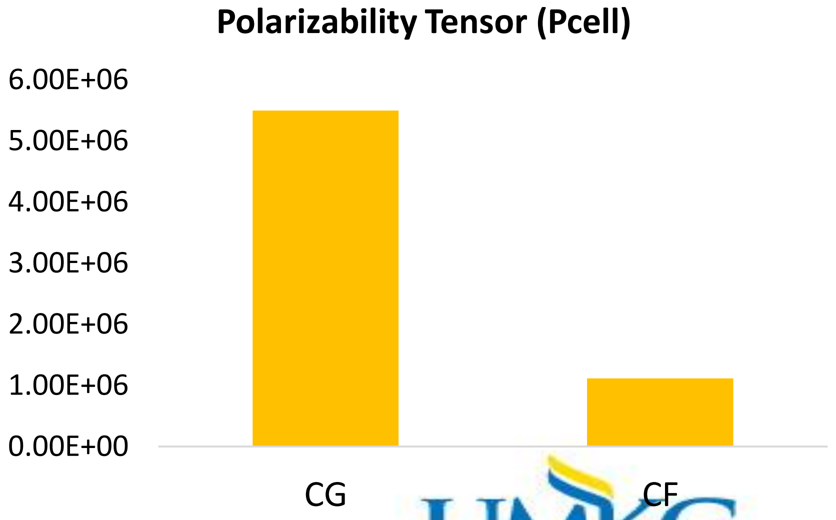
$P_{cell} = P_1 + P_2 + P_3$







- The addition of OS (osteogenic supplements) caused a significant increase in P_{cell} implying increased exposure to external excitation.
- MG, FG & CG were made from natural hydrogel but still depicting different sensitivity to electrical signals → geometry of the microenvironment has an effect on its electrical properties
- Culturing cell on Collagen Fibrils(CF) instead of Collagen Gel (CG) may improve sensitivity to electrical signals (CG).



UMKC

Polarizability Comparison (Down 4)

Diagonal elements of Electric Polarizability Comparison (α_E)

Cell Family	α_e	Scuff-EM	COMSOL	Percentage Uncertainty
PPS	P_1	86.4257	84.4609	2.27%
	P_2	14.3076	13.6767	4.41%
	P_3	3.3438	3.2124	3.93%
Collagen Fibrils	P_1	85.726	80.2635	6.37%
	P_2	17.0776	16.0936	5.76%
	P_3	1.7764	1.7029	4.14%
Microfibers	P_1	99.2096	92.6334	6.63%
	P_2	12.8925	12.2077	5.31%
	P_3	3.8979	3.7389	4.08%

Magnetic Polarizability Comparison (α_M)

Cell Family	α_M	Scuff-EM	COMSOL	Percentage Uncertainty
PPS	P_1	-2.4135	-2.4364	0.95%
	P_2	-1.7328	-1.7364	0.21%
	P_3	-1.2249	-1.2514	2.16%
Collagen Fibrils	P_1	-2.7481	-2.7811	1.20%
	P_2	-1.4856	-1.4656	1.35%
	P_3	-1.1768	-1.1674	0.80%
Microfibers	P_1	-1.9967	1.9916	0.26%
	P_2	-1.7402	-1.7626	1.29%
	P_3	-1.3312	-1.377	3.44%

$$\% \text{ Uncertainty} = \frac{|\alpha_{SCUFF\_EM} - \alpha_{COMSOL}|}{\alpha_{SCUFF\_EM}} * 100$$

Maximum percentage uncertainty for the case of α_E is 6.37%
Maximum percentage uncertainty in case of α_M is 3.44% .

UMKC

Polarizability Comparison (Down 1)

Diagonal elements of Electric Polarizability Comparison (α_E)

Cell Family	α_e	Voxel	Scuff-EM	Percentage Uncertainty
Matrigel	P_1	4.3171	4.5036	4.14%
	P_2	3.9992	3.9062	2.38%
	P_3	3.0494	2.9465	3.49%
NF+OS	P_1	92.648	85.06	8.92%
	P_2	7.4425	6.8821	8.14%
	P_3	2.405	2.5791	6.75%
Microfibers	P_1	136.9432	129.8975	5.42%
	P_2	17.3376	16.3612	5.97%
	P_3	5.0318	5.0886	1.12%

Magnetic Polarizability Comparison (α_M)

Cell Family	α_M	Voxel	Scuff-EM	Percentage Uncertainty
Matrigel	P_1	-1.8174	-1.7597	3.28%
	P_2	-1.5781	-1.5293	3.19%
	P_3	-1.4794	-1.4289	3.53%
NF+OS	P_1	-3.246	-2.981	8.89%
	P_2	-1.6968	-1.6521	2.71%
	P_3	-1.2262	-1.2308	0.37%
Microfibers	P_1	-2.2754	-2.2205	2.47%
	P_2	-1.7542	-1.6648	5.37%
	P_3	-1.5092	-1.439	4.88%

$$\% \text{ Uncertainty} = \frac{|\alpha_{SCUFF\_EM} - \alpha_{Voxel}|}{\alpha_{SCUFF\_EM}} * 100$$

Maximum percentage uncertainty for the case of α_E is 8.92%
Maximum percentage uncertainty in case of α_M is 8.89% .

UMKC

Magnetic Polarizability