Patterning Cells with the Flip of a Switch for Bioengineering Applications

Simulation aids researchers in understanding how unevenly-shaped cells rapidly form patterns under an applied electric field. This method, dielectrophoresis, is currently under development at Clemson University and Tokyo Electron for layer-by-layer material assembly.

BY JENNIFER A. SEGUI

Significant growth in biofabrication research over the past decade has been accompanied by the development of innovative patterning methods to manipulate molecules or groups of cells to create, for example, organized constructs and reactive biological systems. These engineered biomaterials can be used for a wide range of applications, including early stage drug development and testing.

Dielectrophoresis (DEP) has emerged recently as a promising method for patterning cells and for nanoscale assembly of materials for electronics, energy, and medical applications. "DEP is particularly attractive for cell or material patterning because it provides a precise and efficient technique for layer-by-layer assembly that is suitable for industry-scale mass production," explains Guigen Zhang, Professor of Bioengineering at Clemson University where he leads the Biosensors and Bioengineering Laboratory. "In DEP, a non-uniform electric field applied across a single layer of dielectric particles can be used to pattern the entire sample in mere seconds, at the flip of a switch" (see Figure 1).

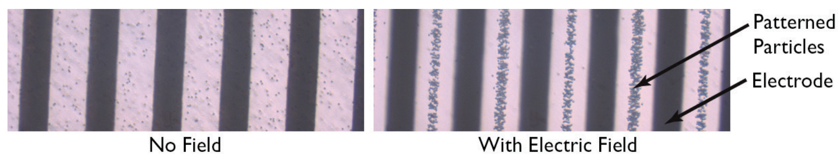


FIGURE 1. Under an applied electric field, the disordered sample of particles at left assembles into organized lines between pairs of electrodes that alternate between positive and ground potential.

Zhang is working in collaboration with researchers Jozef Brcka, Jacques Faguet, and Eric Lee from Tokyo Electron U.S. Holdings, Inc. to better understand the fundamental principles behind DEP and optimize its use for patterning[1-3]. Their investigation entails using multiphysics simulation in combination with experiment to verify new theories and equations governing the DEP force. Drawing from the investigation of DEP for complex biological systems could also produce novel bio-inspired methods for enhancing the capabilities of tools for the semiconductor industry.

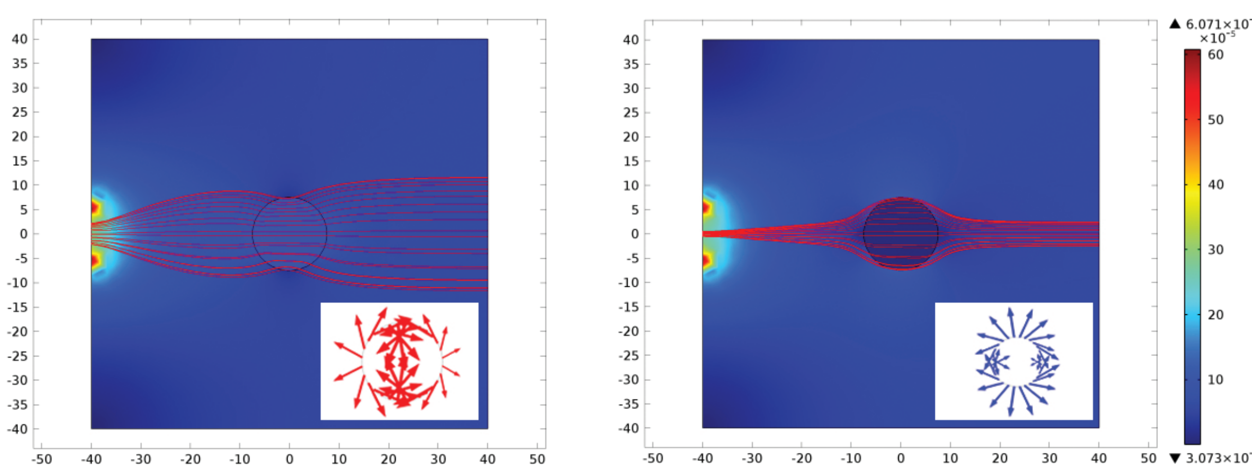


FIGURE 2. Simulation results from COMSOL Multiphysics® demonstrate surface polarization for a model of a particle suspended in a medium and subject to a non-uniform electric field. At left: Positive DEP occurs when the particle is more polarizable than the suspension medium creating a net DEP force that points left, in the direction of increasing field strength. At right: Negative DEP occurs when the particle is less polarizable than the suspension medium, causing the particle to move toward the right in the direction of decreasing electric field strength.

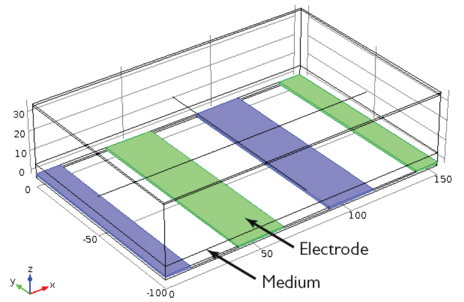


FIGURE 3. The model geometry is shown with the parallel electrodes biased with alternating potential and ground in the simulations.

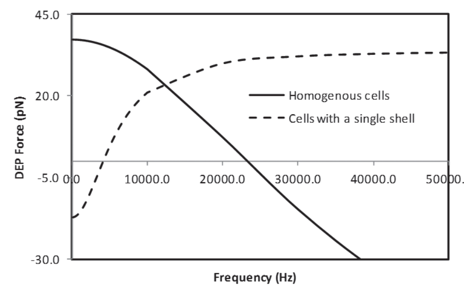


FIGURE 4. Plot of the frequency-dependent DEP force experienced by a cell when it is modeled as a homogenous body or as a nonhomogeneous body with a single shell.

MECHANISM OF DEP

In DEP, either non-uniform AC or DC electric fields are applied to dielectric particles or cells in media causing them to become polarized. The relative polarizability of the particle and media ultimately determines the dipole orientation and, consequently, the direction of movement along the field lines (see Figure 2).

Zhang and his colleagues have identified several discrepancies or limitations of the existing DEP theory to accurately explain observed behavior such as cell rotation, particle alignment, and electric field distortion. Their research aims to address these limitations and elucidate the impact of the observed behavior on pattern formation.

SIMULATING THE DEP FORCE FOR CELLS

Several 2D and 3D models have been developed by the Clemson-Tokyo Electron collaboration using the Electrostatics interface, Moving mesh interface (ALE), and the equation-based modeling capabilities in COMSOL Multiphysics®. Each model investigates the variables affecting the DEP force experienced by particles leading to the observed rotation and alignment behavior.

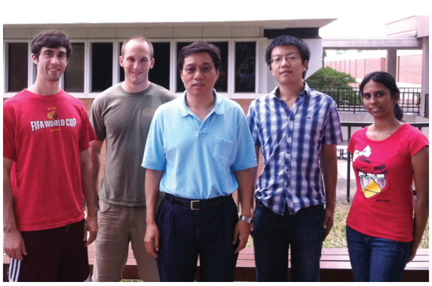
In the 3D models, the electrode setup consists of equidistant rectangular strips of gold coated with insulating aluminum oxide where alternating electrodes are positively biased and grounded (see Figure 3). Particles or cells are suspended in deionized water or other media in the models.

To illustrate the limitations in existing DEP applications, shell models that take into account the nonhomogeneous properties of cells were used to calculate the complex permittivity and then the DEP force in the simulations. Additionally, in some studies, the formation of an electric double layer and the particle size were taken into account when calculating the conductivity of the particle.

For example, the magnitude of the simulated DEP force determined using a single-shell model, which takes into account the nonhomogeneous properties of the cell membrane, appropriately shows a trend that is actually the opposite of the original theory (see Figure 4). Zhang notes that, "with COMSOL, simulation is no longer a black box approach, thus enabling us to better understand the factors affecting DEP."

Although single-shell models for cells provide a more accurate prediction, to incorporate the nonhomogeneity in other cellular components including the nucleus, Zhang and colleagues developed a volumetric approach to account for electric field distortion and to quantify the DEP forces and torques experienced by cells[3]. "Simulation results based on the new approach successfully confirm experimental observations that cells could rotate due to the noncircular shape of the cell body and off-centered nuclei," reports Zhang.

By developing and validating comprehensive multiphysics models that incorporate a multitude of factors, their work provides a wealth of information and a better understanding of how DEP can be used with great selectivity to pattern cells and other materials. Zhang believes that their "efforts will someday help realize many potential capabilities of DEP for important bioengineering applications including bioprinting, biofabrication, and biosensing for advancing drug screening and discovery, tissue engineering, and regenerative medicine." ■



At left, from left to right: Johnie Hodge, Sam Bearden, Guigen Zhang, Yu Zhao, and Vandana Pandian from Clemson University. At right, also from left to right: Jozef Brcka, Eric Lee, and Jacques Faguet from the Technology Development Center at Tokyo Electron U.S. Holdings, Inc.

References

Refer to the following online resources from the Proceedings of the COMSOL Conference 2013, accessible at **www.comsol.com/papers-presentations**:

[1] V. Pandian, et. al. *Some Commonly Neglected Issues Which Affect DEP Applications.*

[2] Y. Zhao, et. al. *Effect of Electric Field Distortion on Particle-Particle Interaction Under DEP.*

[3] Y. Zhao, et. al. *Elucidating the Mechanism Governing the Cell Rotation Behavior Under DEP.*