NEWS

Research Profile: Bringing dielectrophoresis to the masses . . . of cells

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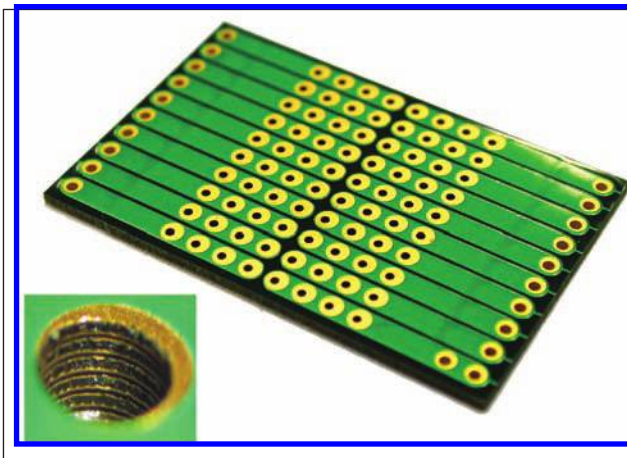
Bringing dielectrophoresis to the masses . . . of cells

Dielectrophoresis—the induced motion of particles in a nonuniform electric field—can serve as a sensitive indicator of subtle changes in the inner workings of a cell, but the technique's cumbersome, one-off nature has relegated it to the sidelines as a useful tool for cell biology or drug discovery. In a paper published in *AC* (**2008**, *80*, 2063–2068), collaborators Kai Hoettges and Michael Hughes and their colleagues at the University of Surrey (U.K.) describe their version of a multiwell plate format that turns dielectrophoresis into a rapid assay designed for use in high-throughput screening applications. "From start to finish, we can run an entire series of dielectrophoresis measurements on 20 groups of 4 sets of cells in about 30 minutes using a stamp-sized device and a commercial [microwell] plate and fluid-handling systems," says Hughes.



A spectra-chip dielectrophoresis device with 20 sets of 4 wells. The close-up of an actual well (inset) shows the alternating layers of gold-coated copper electrodes and polyimide insulating layers.

In a typical dielectrophoresis experiment, cells are placed on a glass slide fitted with electrodes. When an alternating current is applied to the electrodes, the cells move toward either the positive or negative electrode, depending on factors such as membrane surface charge, membrane capacitance, and conductivity of the cytoplasm. By varying the frequency of the alternating current and counting the number of cells attracted to one pole or the other, researchers can create a dielectrophoresis spectrum that characterizes a given cell state. Perturbing the cells in any way, such as by adding a drug, changes the spectrum.

Hoettges, a clinical chemist, and Hughes, a dielectrophoresis expert, took this system and essentially rolled it into a tube, creating dielectrophoretic wells. They start by building a conductor–composite laminate comprising 12 layers of 17-μm-thick copper interleaved with 75-μm-thick polyimide. They then drill 1 mm holes spaced 2.25 mm apart on-center through the composite, bond the laminate to a 1-mm-thick polyimide sheet to form the base of the wells, and coat the exposed copper with gold to ensure biocompatibility. Finally, they wire alternate layers of conducting material to opposing phases of an ac generator. The wells are wired together in clusters of four, with each cluster connected to its own ac generator. This configuration allows the researchers to measure an entire frequency spectrum in parallel by subjecting each set of four wells to a unique ac frequency.

This multilayer, tubular electrode configuration increases dramatically the electric field strength within a given volume of fluid compared with a planar system, raising the dielectrophoretic force operating on the cells, explains Hughes. Depending on the characteristics of a given cell population, the cells move toward either the center or the outer edges of the well. And because the well base is transparent, cell movements within each well can be measured by recording the light transmitted through it with a video camera. To reduce noise in the system, the researchers analyze signal intensity only in the outer 30% of the radius of each well, a region that contains 64% of the total volume.

In addition to the smaller "spectra-chip" setup, which measures 23.5 × 34 mm, the researchers are using the same methods to build a larger "spectra-plate" device that has 1536 wells arranged in clusters of 16, 32, and 64 in different regions of the plate. The 86 × 127 mm spectra-plate is bonded to the empty frame of a 96-well plate with an eye toward eventual use in commercial 1536-well systems.

Using the spectra chip, the researchers could distinguish between viable and dead yeast cells, a standard assessment measure for dielectrophoresis. Moreover, using curve-fitting software on the measured frequency spectra, they could determine the percentage of viable versus nonviable cells with an accuracy of 1%. The ability to do this suggests that array-based dielectrophoresis should be useful for conducting IC_{50} assays.

Next, they tested the effects of three different ion channel blockers on a human leukemia cell line. The cells showed distinct spectral changes after exposure to each of the three agents. The data also showed that two of the agents, 5-nitro-2-(3-phenylpropylamino)benzoic acid and verapamil, decreased cytoplasmic conductance, whereas treatment with quinine increased it. In each case, the amount by which the cytoplasmic conductance changed was as expected, given the known mechanisms of action for the drug. "We're convinced that these multiwell systems will finally help dielectrophoresis realize its potential in cell-based studies," says Hughes. ■

—Joe Alper