A Modular Platform for Cell Characterization, Handling and Sorting by Dielectrophoresis

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European Comsol Conference 2009 – October 14-16, Milan, Italy
A mature product:

*InCheck*, a lab-on-chip for DNA amplification by Polymerase Chain Reaction (PCR) and analysis

Research:
on-chip solutions for cell analysis (microcytometry, cell sorting and cell counting applications)
Dielectrophoresis (DEP) is a promising method for cell manipulation and separation without physical contact, exploiting the dielectric properties of cells under the action of high-gradient electric fields.

\[
\vec{F} = \left( \overline{m} \nabla \right) \vec{E}
\]

\[
\overline{m} = 4\pi\varepsilon_0 \overline{F}_{CM} R^3 \overline{E}
\]
Dielectrophoresis

Clausius-Mosotti factor

\[ F_{CM} = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \]

\[ \varepsilon_m^*(\omega) = \varepsilon_m - \frac{j\sigma_m}{\omega} \]

Suspending medium

\[ \varepsilon_p^* = \varepsilon_{mc} \left[ \left( \frac{r}{r - d} \right)^3 + 2 \left( \frac{\varepsilon_{int}^* - \varepsilon_{mc}^*}{\varepsilon_{int}^* + 2\varepsilon_{mc}^*} \right) \right] \left[ \left( \frac{r}{r - d} \right)^3 - \left( \frac{\varepsilon_{int}^* - \varepsilon_{mc}^*}{\varepsilon_{int}^* + 2\varepsilon_{mc}^*} \right) \right] \]

Cell with single membrane

(human B-lymphocytes)
Dielectrophoresis

\[ \varepsilon_p^* = \varepsilon_w^* \cdot \frac{2 \left( 1 - \left( \frac{r - d_w}{r} \right)^3 \right) \cdot \varepsilon_w^* + \left( 1 + 2 \left( \frac{r - d_w}{r} \right)^3 \right) \cdot \varepsilon_{\text{int}+mc}^*}{2 + \left( \frac{r - d_w}{r} \right)^3 \cdot \varepsilon_w^* + \left( 1 - \left( \frac{r - d_w}{r} \right)^3 \right) \cdot \varepsilon_{\text{int}+mc}^*} \]

Cells with double shell model

(Saccharomyces Cerevisiae yeast cells with membrane and wall)

\[ \varepsilon_{\text{int}+mc}^* = \varepsilon_{mc}^* \cdot \frac{2 \left( 1 - \left( 1 - \frac{d_{mc}}{r - d_w} \right)^3 \right) \cdot \varepsilon_{mc}^* + \left( 1 + 2 \left( 1 - \frac{d_{mc}}{r - d_w} \right)^3 \right) \cdot \varepsilon_{\text{int}}^*}{2 + \left( 1 - \frac{d_{mc}}{r - d_w} \right)^3 \cdot \varepsilon_{mc}^* + \left( 1 - \left( 1 - \frac{d_{mc}}{r - d_w} \right)^3 \right) \cdot \varepsilon_{\text{int}}^*} \]
Dielectrophoresis

- Time-averaged dielectrophoretic force

\[
\langle F(\vec{r}) \rangle = 2\pi \varepsilon_m R^3 \left[ \frac{1}{2} \text{Re}(F_{CM}) \nabla \left( E_{x0}^2 + E_{y0}^2 + E_{z0}^2 \right) + \text{Im}(F_{CM}) \left( E_{x0}^2 \nabla \phi_x + E_{y0}^2 \nabla \phi_y + E_{z0}^2 \nabla \phi_z \right) \right] = \\
= 2\pi \varepsilon_m R^3 \left[ \text{Re}(F_{CM}) \nabla E_{rms}^2 + \text{Im}(F_{CM}) \left( E_{x0}^2 \nabla \phi_x + E_{y0}^2 \nabla \phi_y + E_{z0}^2 \nabla \phi_z \right) \right]
\]

\[
\langle \overline{F_{DEP}}(\vec{r}) \rangle = 2\pi \varepsilon_m R^3 \text{Re}(F_{CM}) \nabla E_{rms}^2
\]

Standing wave DEP

(Saccharomyces Cerevisiae yeast cells)
Dielectrophoresis

\[
\langle \vec{F}_{TWD} (\vec{r}) \rangle = 2\pi \varepsilon_m R^3 \text{Im}(F_{CM}) \left( E_{x0}^2 \nabla \phi_x + E_{y0}^2 \nabla \phi_y + E_{z0}^2 \nabla \phi_z \right)
\]

*Travelling wave DEP*

*(polystyrene beads, 10 μm in diameter)*
The dielectrophoretic modular platform

- The dielectrophoretic platform that has been developed is composed of several functional units, organized in a first characterization module and in a series of manipulation stages that can be rearranged on a single chip, depending on the target application (ex: HIV infection level monitoring).

- Numerical and parametrical modelling has been performed to simulate the electric field distribution and to quantify the consequent pico-Newton DEP forces acting at the microscale, in order to optimize the geometry of each functional module.
How to determine the real part of the Clausius-Mosotti factor:

- Measurement of the translational velocity in a double bar electrode array
- Relation of the real component of $F_{CM}$ with cell velocity of attraction or repulsion (pDEP or nDEP, respectively)

\[
\overline{F}_{DEP} = 2\pi \varepsilon_m r^3 \Re(F_{CM}) \nabla E_{rms}^2 = 6\pi \eta r U_{\text{particella}}
\]

\[
\Re(F_{CM}) = \frac{3\eta U_{\text{particella}}}{\varepsilon_m r^2 \nabla E_{rms}^2}
\]
Dielectric properties determination

How to determine the imaginary part of the Clausius-Mosotti factor:

- Measurement of the rotational velocity of cells in the quadrupole configuration
- Relation between the imaginary component of $F_{CM}$ and the rotational velocity of cells

\[
\Omega(f) = \frac{-4\pi \varepsilon_m r^3 \text{Im}(F_{CM}) E_0^2}{6\eta V} = -\frac{\varepsilon_m E_0^2}{2\eta} \text{Im}(F_{CM})
\]

\[
\text{Im}(F_{CM}) = -\frac{\Omega(f) \cdot 2\eta}{\varepsilon_m E_0^2}
\]

(sine signals in quadrature, 20 Vpp)
Dielectric properties determination

Real and imaginary component of the Clausius Mosotti factor as a function of the frequency of the applied electric field - *Saccharomyces Cerevisiae* yeast cells in a suspension with conductivity $\sigma_m = 435 \, \mu S/cm$
Multi-bar array filter for cell separation

Parametrical modelling maximizing the DEP force

Separation of *Saccharomyces Cerevisiae* yeast cells and sheep Red Blood Cells (RBC) at frequency 1 MHz.
Fishbone-like module for cells focusing

Focusing module: *Saccharomyces Cerevisiae* yeast cells suspension, conductivity 435 $\mu$S/cm and cell concentration $1.8 \times 10^6$ cells/ml

frequency 100 kHz
Deviation module

\[ F_{DEP} = 203.32 \, pN \]

\[ F_{DEP} = 481.6 \, pN \]

DEP off

DEP on

frequency 200 kHz
Saccharomyces Cerevisiae yeast cells are concentrated at the center of the spiral array for inspection and counting: numerical simulation and experimental results.

(frequency 100 kHz)
Conclusions

• The functioning of the electrode configurations in the characterization module and in the series of manipulation stages has been demonstrated with different cells types.

• The experimental results and those from modelling are in close agreement.

• The dielectrophoretic platform represents a complete solution, allowing the dielectric characterization of the cell types of interest and their manipulation in applications in which cell handling and sorting are needed.
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