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

Sarah Burgarella

STMicroelectronics, Agrate Brianza, Milan, Italy

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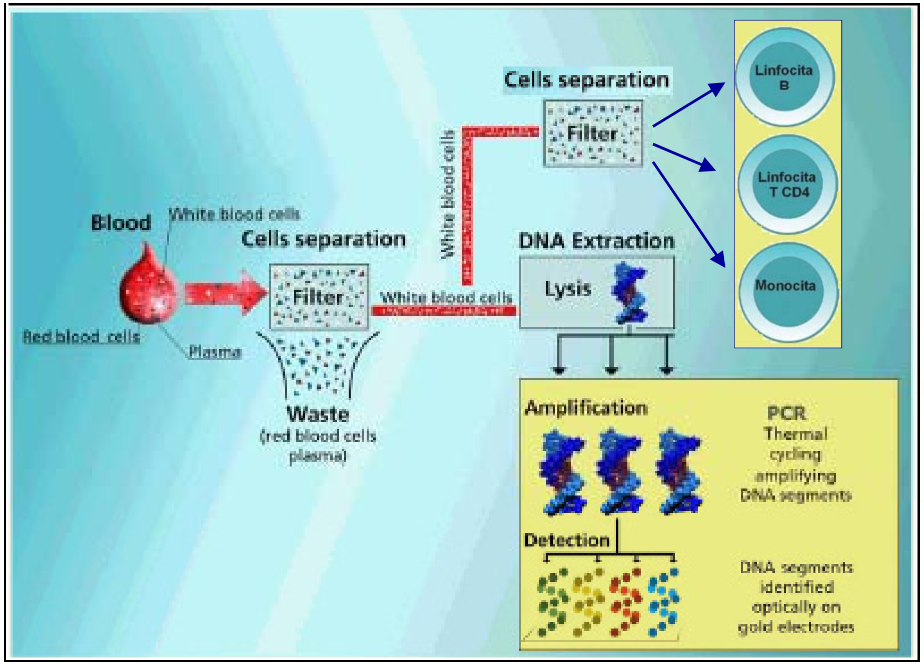
STMicroelectronics and bioMEMS

<u>A mature product</u>:

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

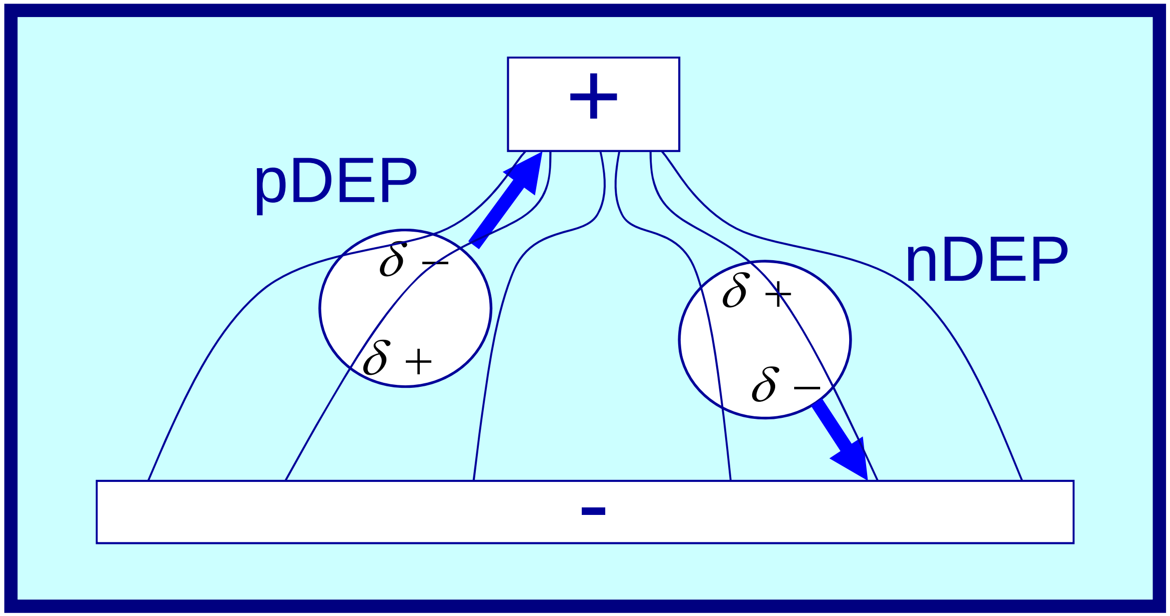
<u>Research</u>:

on-chip solutions for cell analysis (microcytometry, cell sorting and cell counting applications)



Dielectrophoresis

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.



$$\overline{F} = \left(\overline{m}\cdot\nabla\right)\overline{E} \qquad \overline{m} = 4\pi\varepsilon_m F_{CM} R^3 \overline{E}$$

Dielectrophoresis

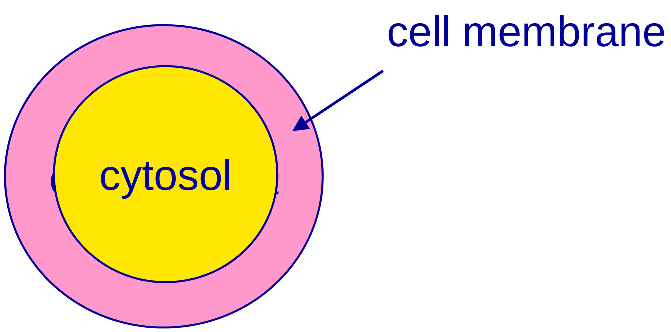
Clausius-Mosotti factor

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

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

Suspending medium

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

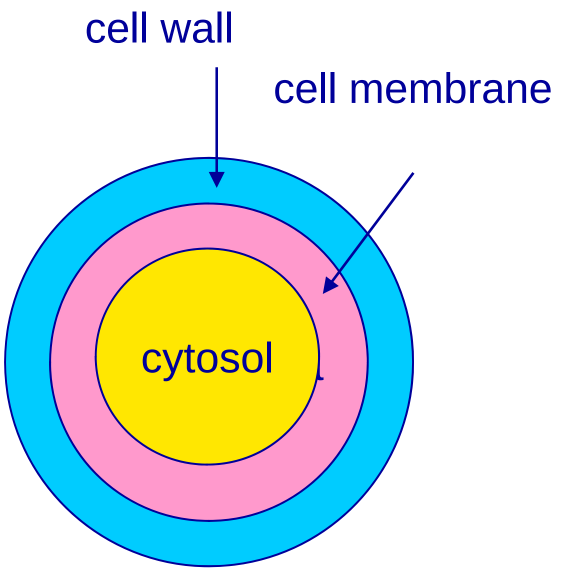


Cell with single membrane

(human B-lymphocytes)

Dielectrophoresis

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



Cells with double shell model

(Saccharomyces Cerevisiae yeast cells with membrane and wall)

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

Dielectrophoresis

- Time-averaged dielectrophoretic force

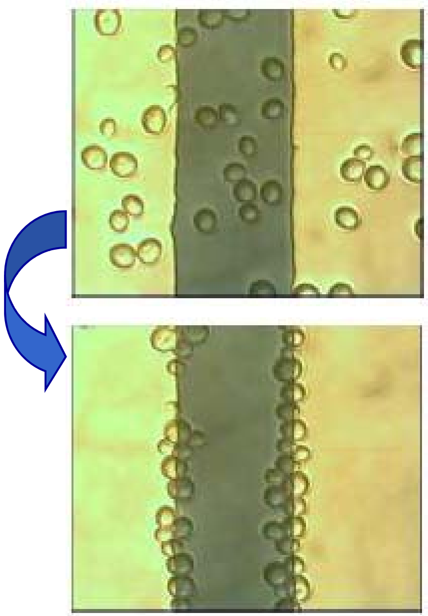
$$\langle \overline{F}(\overline{r})\rangle = 2\pi\varepsilon_m R^3 \left[\frac{1}{2}\mathrm{Re}(F_{CM})\nabla\left(E_{x0}^2+E_{y0}^2+E_{z0}^2\right)+\mathrm{Im}(F_{CM})\left(E_{x0}^2\nabla\varphi_x+E_{y0}^2\nabla\varphi_y+E_{z0}^2\nabla\varphi_z\right)\right]=$$

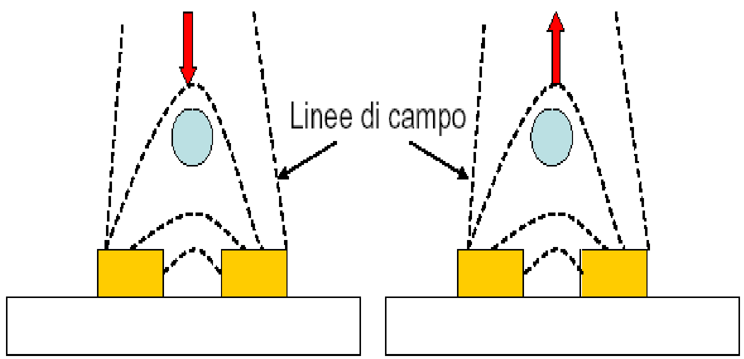
$$=2\pi\varepsilon_m R^3\left[\mathrm{Re}(F_{CM})\nabla E_{rms}^2+\mathrm{Im}(F_{CM})\left(E_{x0}^2\nabla\varphi_x+E_{y0}^2\nabla\varphi_y+E_{z0}^2\nabla\varphi_z\right)\right]$$

$$\Rightarrow \quad \langle \overline{F}_{DEP}(\overline{r})\rangle = 2\pi\varepsilon_m R^3\,\mathrm{Re}(F_{CM})\nabla E_{rms}^2$$

Standing wave DEP

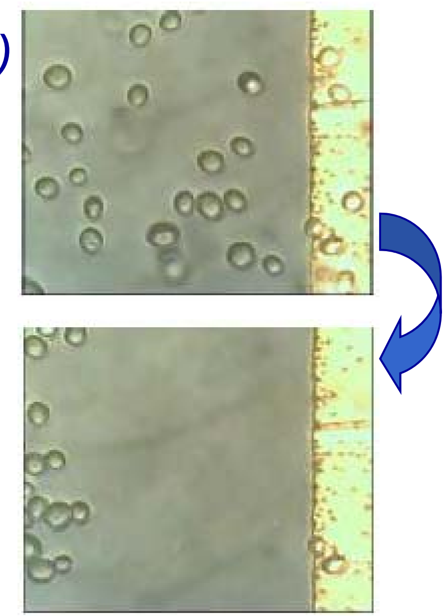
(Saccharomyces Cerevisiae yeast cells)





pDEP
$\mathrm{Re}(F_{CM})>0$

nDEP
$\mathrm{Re}(F_{CM})<0$

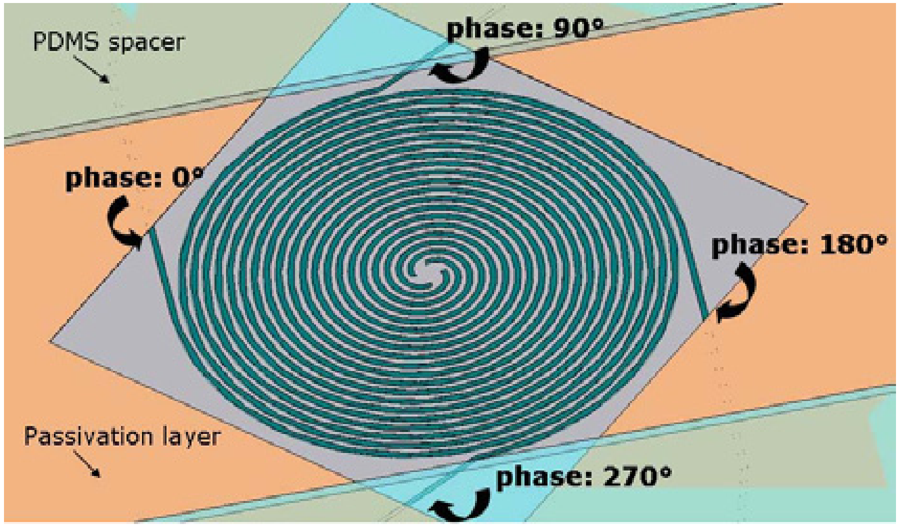


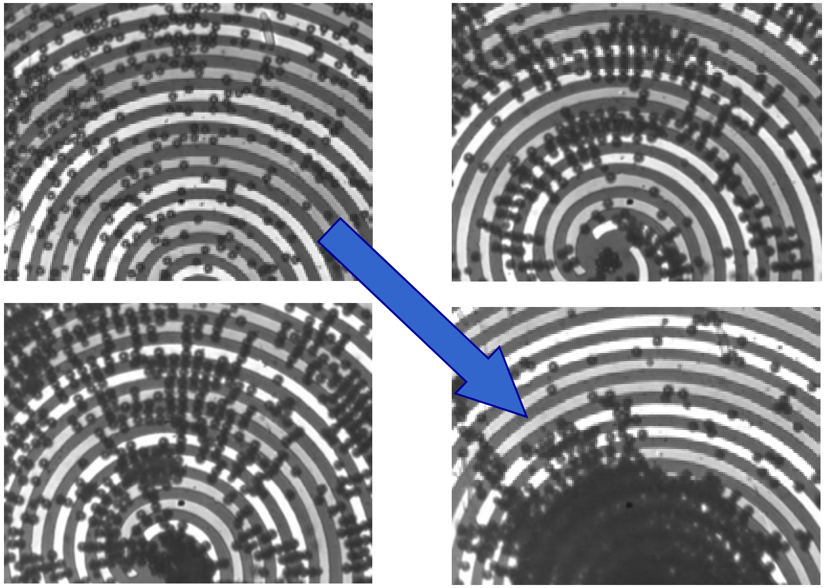
Dielectrophoresis

$$\left\langle \overline{F}_{TWD}\left(\overline{r}\right)\right\rangle = 2\pi\varepsilon_m R^3 \,\mathrm{Im}\left(F_{CM}\right)\left(E_{x0}^2\nabla\varphi_x + E_{y0}^2\nabla\varphi_y + E_{z0}^2\nabla\varphi_z\right)$$

Travelling wave DEP

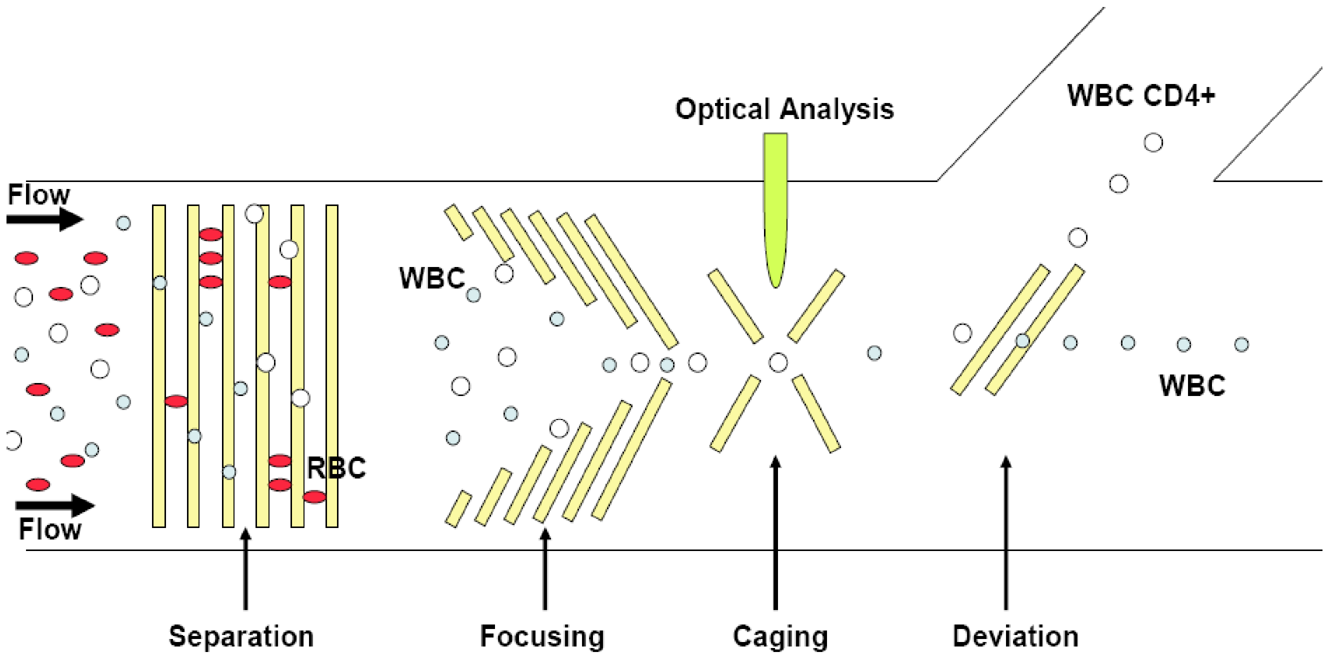
(polystyrene beads, 10 µm in diameter)





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).

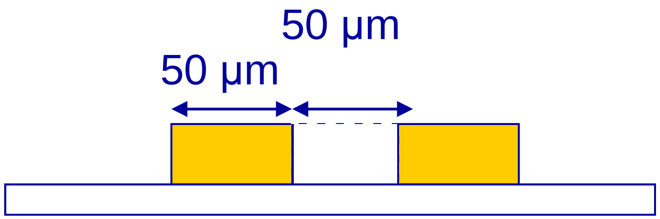


- Numerical and parametrical modelling has been performed to simulate the electric field distribution and to quantify the consequent pico-Newton DEP forces acting at the microscale, in order to optimize the geometry of each functional module.

DEP characterization module

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

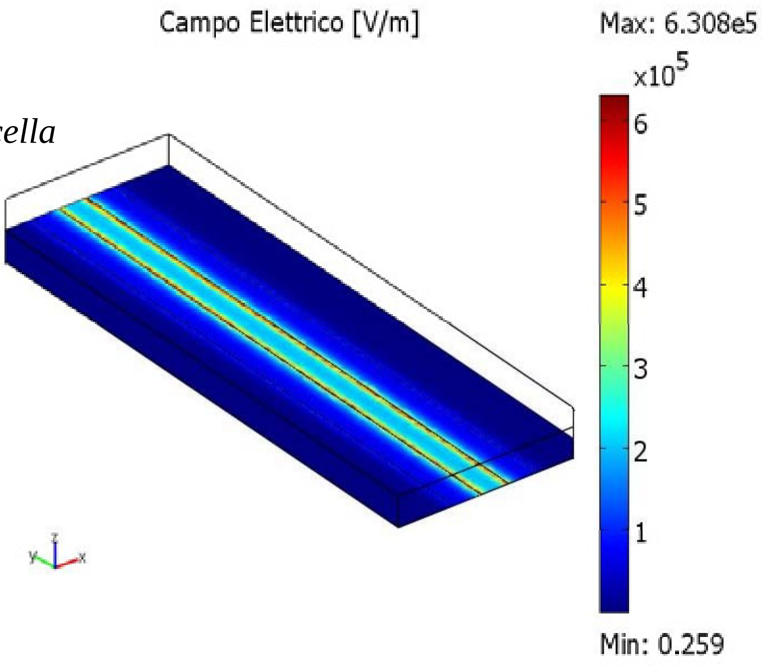
- Measurement of the traslational velocity in a double bar electrode array
- Relation of the real component of F_{CM} with cell velocity of attraction or repulsion (pDEP or nDEP, respectively)

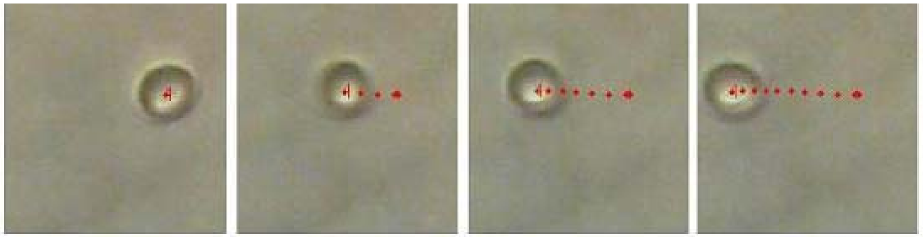


(opposite sine signals, 20 Vpp)

$$\overline{F}_{DEP} = 2\pi\varepsilon_m r^3 \operatorname{Re}(F_{CM})\nabla E_{rms}^2 = 6\pi\eta\, rU_{particella}$$

$$\operatorname{Re}(F_{CM}) = \frac{3\eta U_{particella}}{\varepsilon_m r^2 \nabla E_{rms}^2}$$

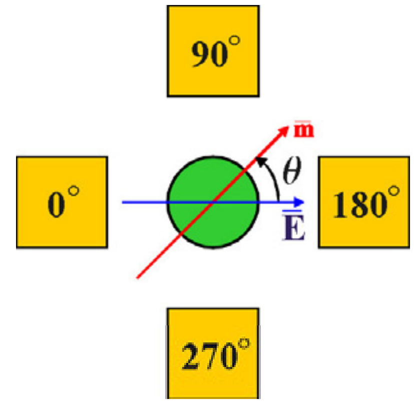




Dielectric properties determination

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

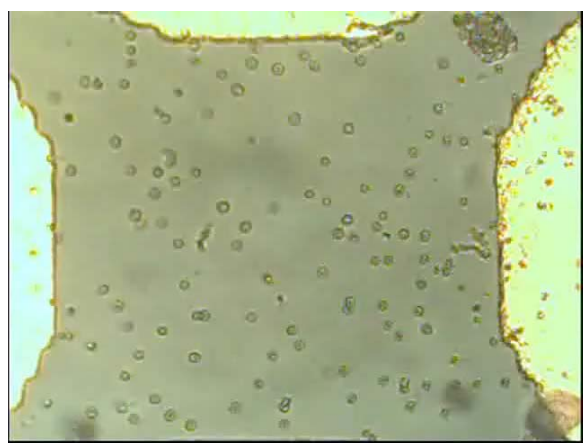
- Measurement of the rotational velocity of cells in the quadrupole configuration
- Relation between the imaginary component of F_{CM} and the rotational velocity of cells

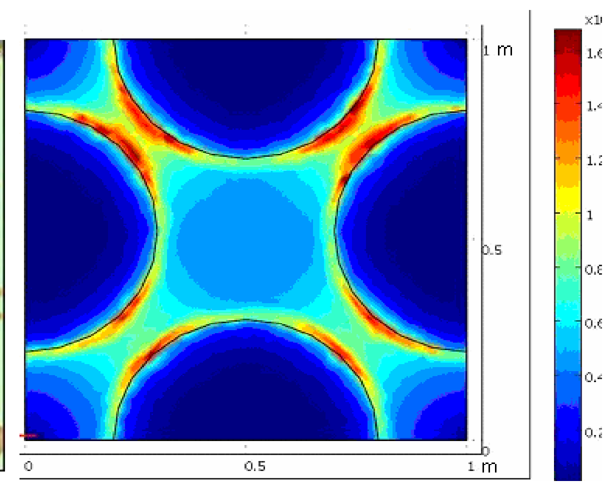


(sine signals in quadrature, 20 Vpp)

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

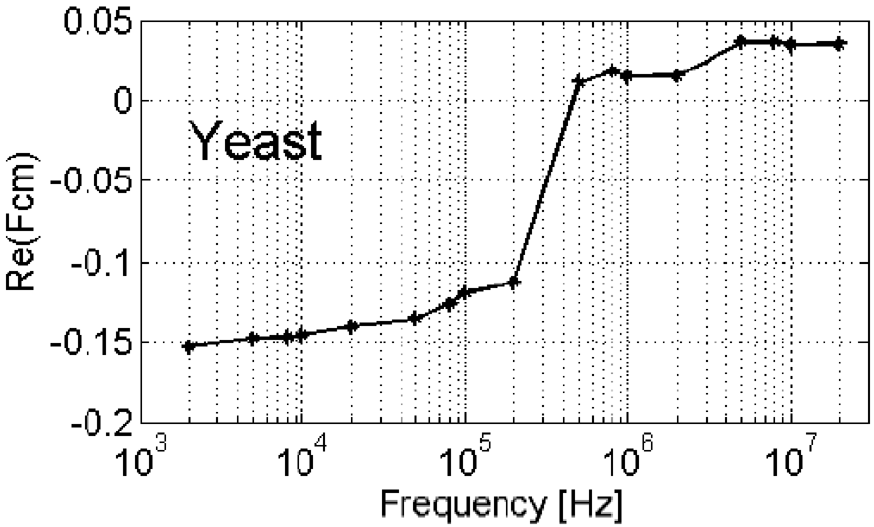
$$\operatorname{Im}(F_{CM}) = -\frac{\Omega(f) \cdot 2\eta}{\varepsilon_m E_0^2}$$

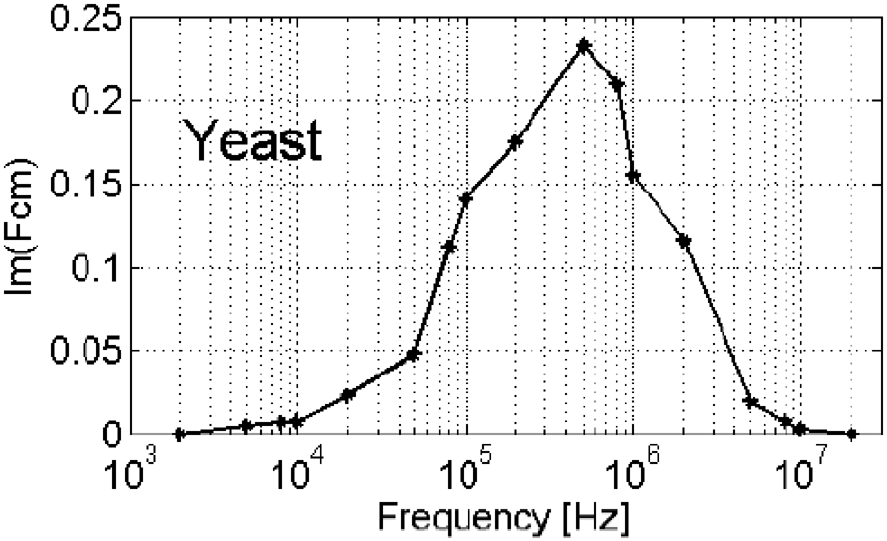




Dielectric properties determination

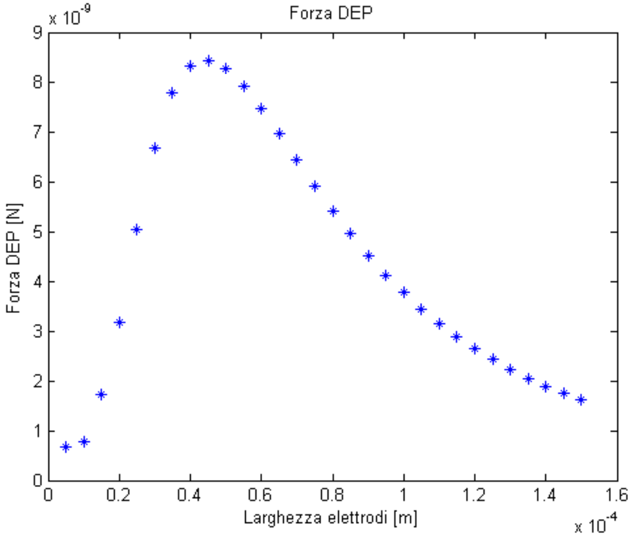
Real and imaginary component of the Clausius Mosotti factor as a function of the frequency of the applied electric field - *Saccharomyces Cerevisiae* yeast cells in a suspension with conductivity σ_m= 435 μS/cm

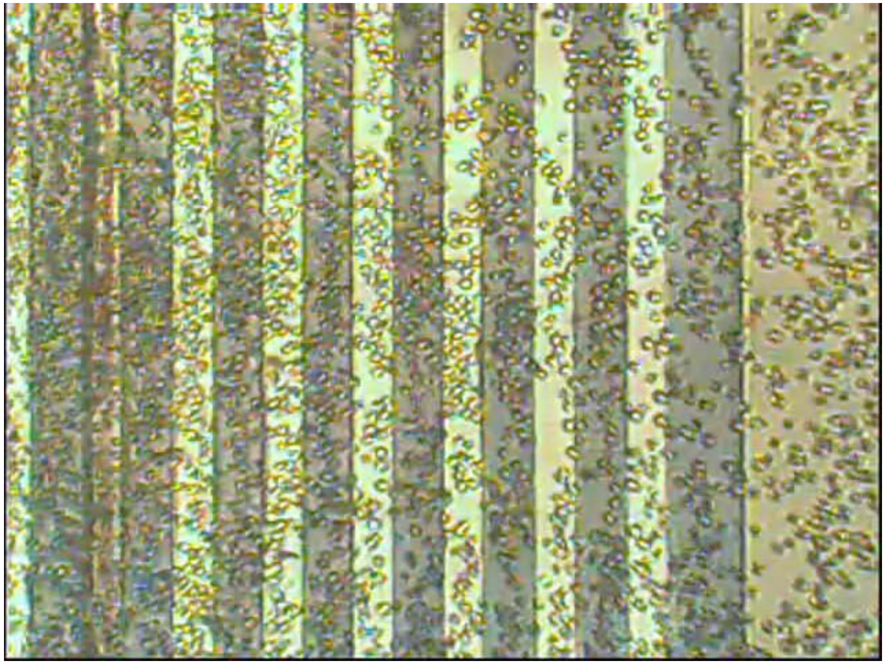




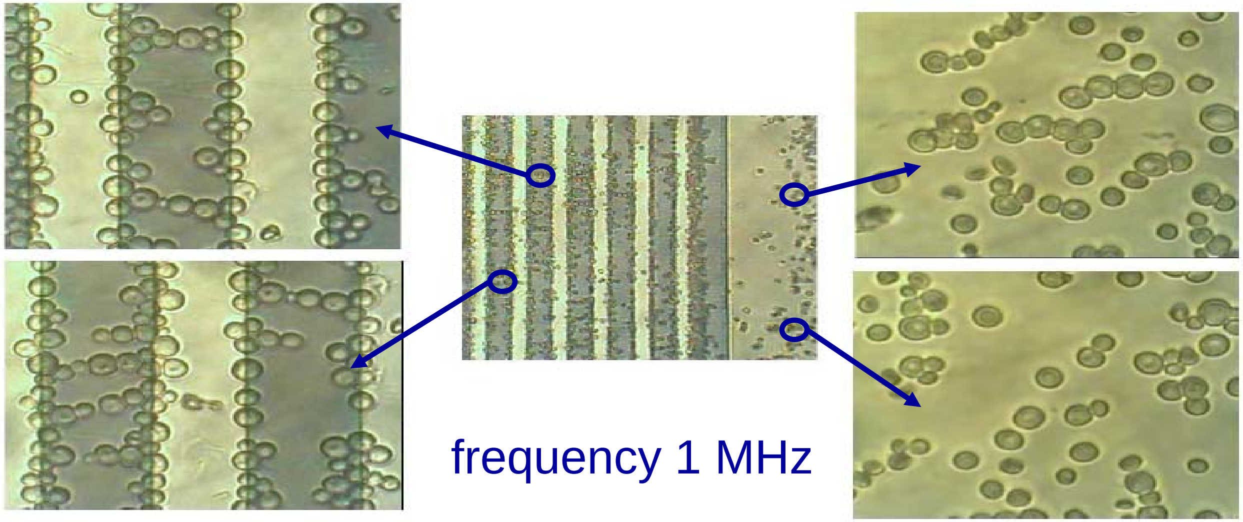
Multi-bar array filter for cell separation

Parametrical modelling maximizing the DEP force





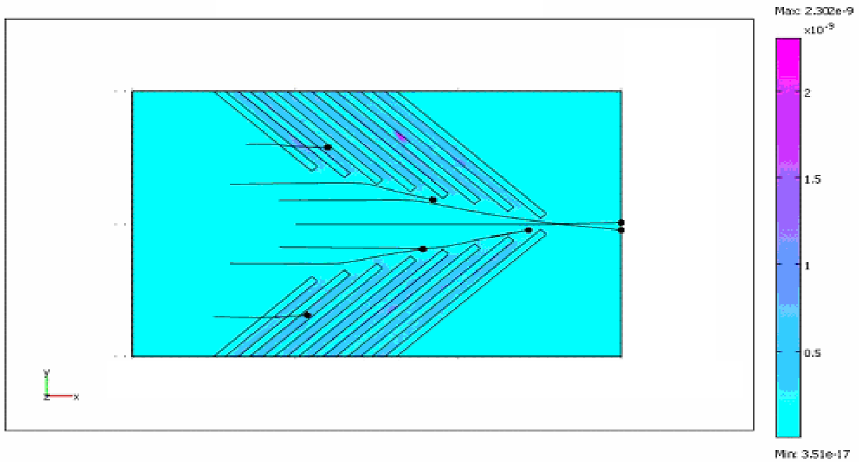
Separation of *Saccharomyces Cerevisiae* yeast cells and sheep Red Blood Cells (RBC)

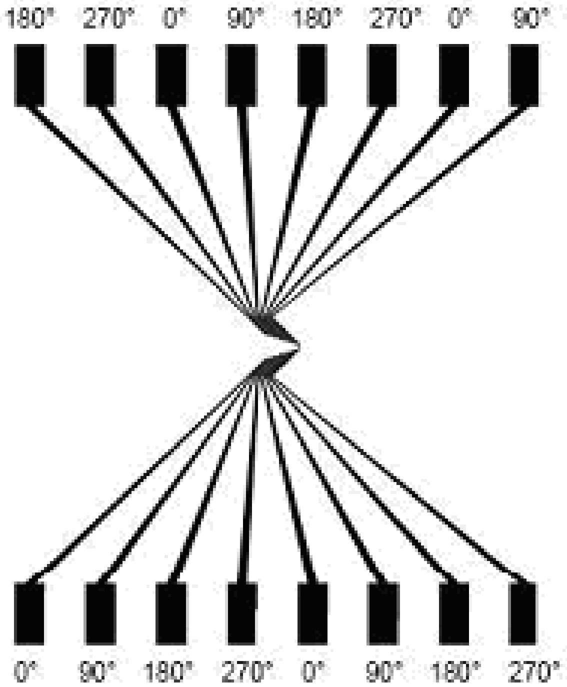


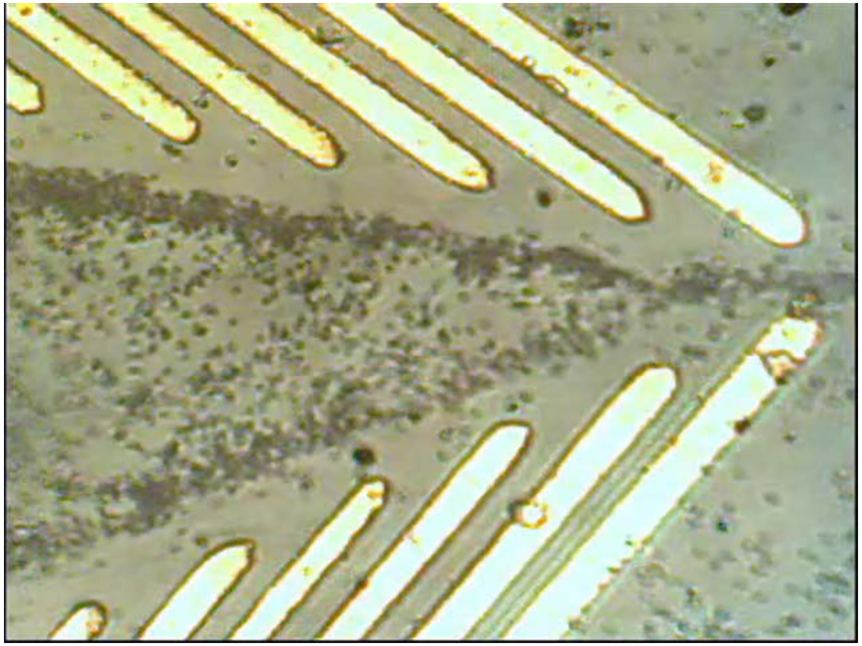
frequency 1 MHz

Fishbone-like module for cells focusing

Focusing module:
Saccharomyces Cerevisiae yeast cells suspension, conductivity 435 μS/cm and cell concentration $1.8 \cdot 10^6$ cells/ml

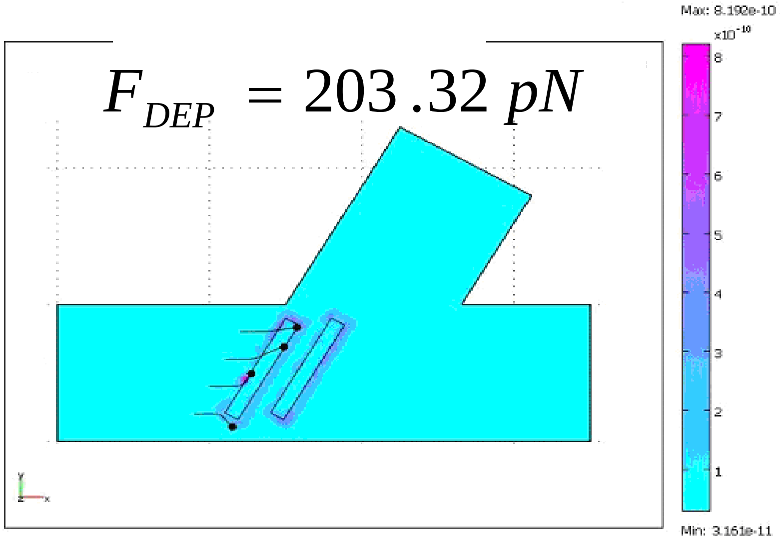


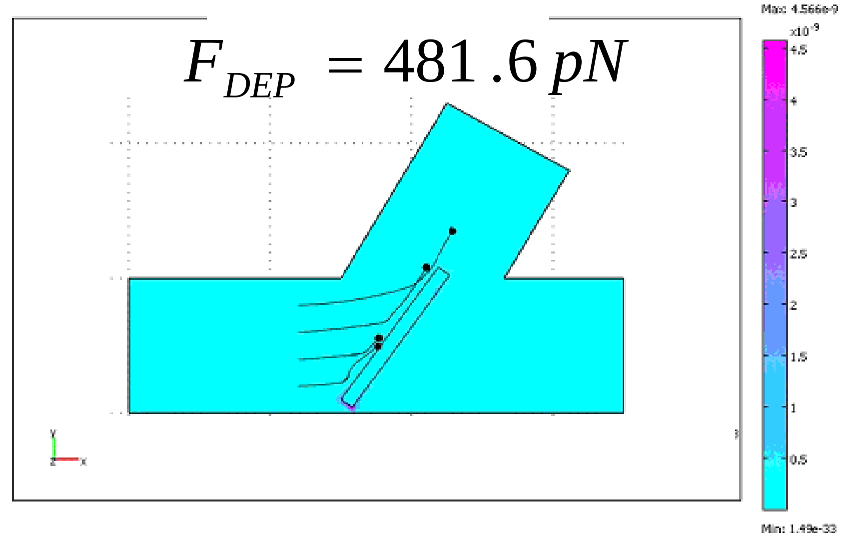




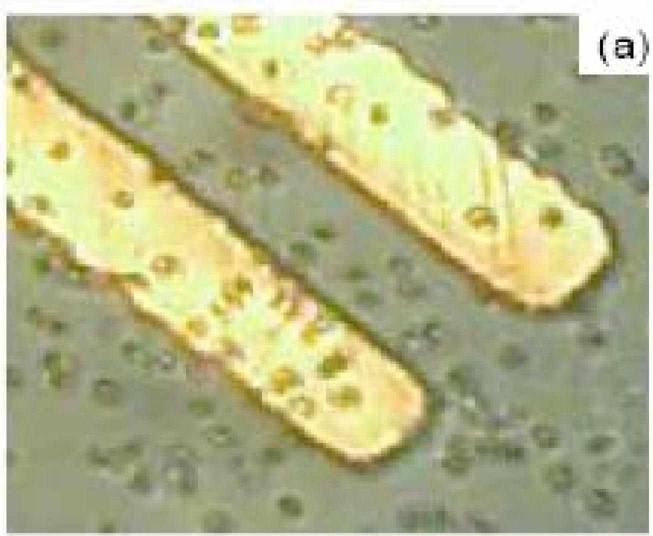
frequency 100 kHz

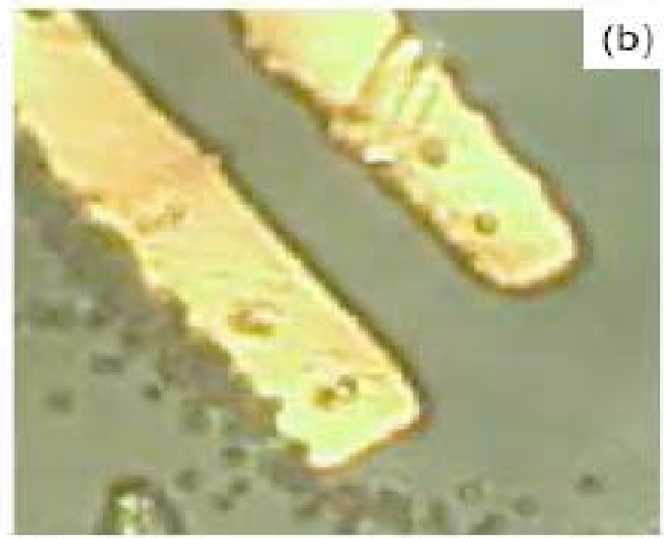
Deviation module





DEP off

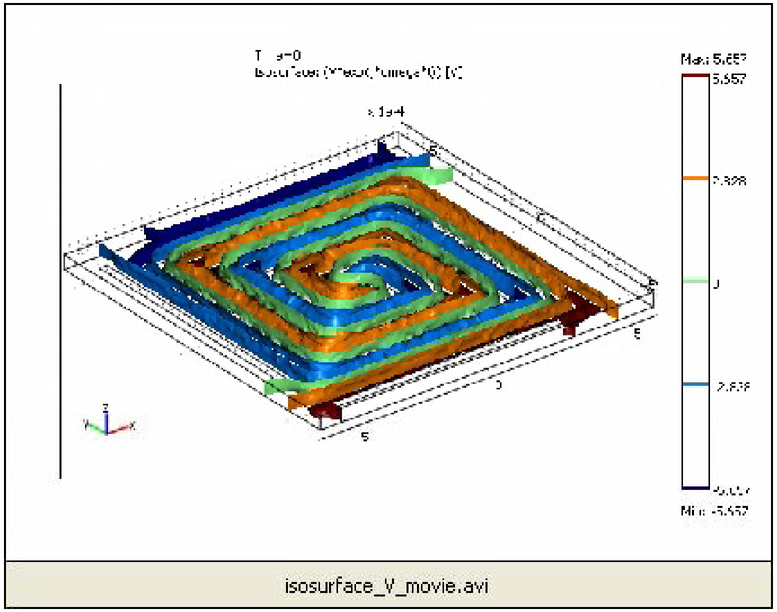


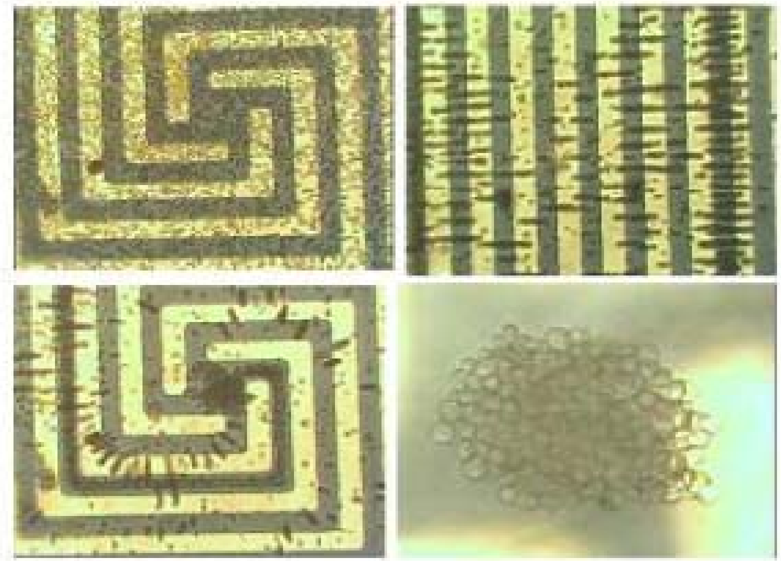


DEP on

frequency 200 kHz

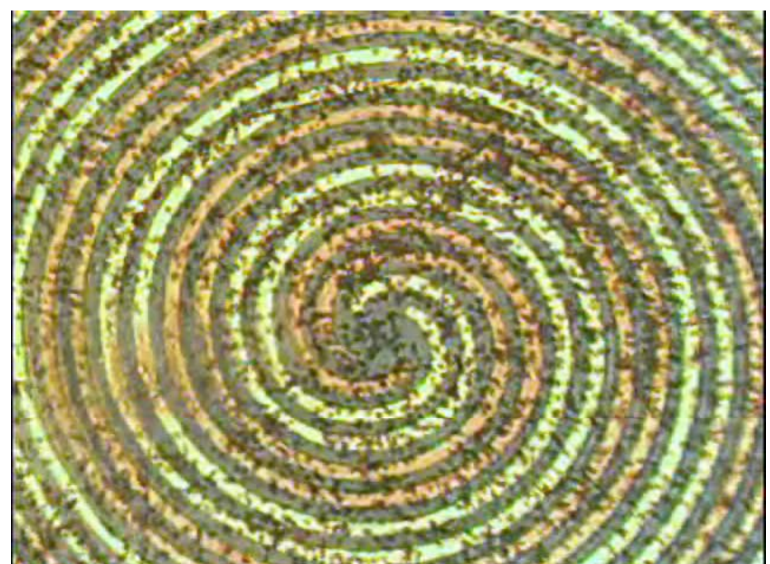
Cells concentration module





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.

Contacts:

Sarah Burgarella

STMicroelectronics

AST – e-Health Group, Agrate B.za (Milan), Italy

sarah.burgarella@st.com

tel: +39 039-6036130