Excerpt from the Proceedings of the 2011 COMSOL Conference in Stuttgart

Comparison of Computational Methods for the Estimation of the Dielectrophoretic Force Acting on Biological Cells and Aggregates in Silicon Lab-on-Chip Devices

Sarah Burgarella[*,1], Federica Maggioni[2] and Giovanni Naldi[2]
[1]STMicroelectronics, Agrate Brianza, Milan, Italy,
[2]Department of Mathematics, University of Milan, Italy
*Corresponding author: Via C. Olivetti 2, Pal. Fiordaliso, 20041 Agrate Brianza, Milan, Italy,
email: sarah.burgarella@st.com

Abstract: Dielectrophoresis (DEP) is a promising method for particles manipulation without physical contact in silicon lab-on-chip devices. It exploits the dielectric properties of cells and aggregates suspended in a microfluidic sample under the action of high-gradient electric fields. The force is approximated by a truncation of a multipole expansion which, for single cell, reduces to the first order contribution. When the cells aggregate is "big" further terms should be considered involving higher order field derivatives. Here, we compare different force approximations, depending on the aggregate's dimension and on the non-uniformity of the electric field. Numerical modeling has been performed by using COMSOL Multiphysics to compute the electric field, to quantify the DEP forces and to simulate the particles tracings that have been compared with experimental results developed in several settings.

Keywords: Dielectrophoresis, Multipole approximation, MEMS, cell aggregates, lab-on-chip.

1. Introduction

Dielectrophoresis (DEP) is a promising method for the automated separation of biological cells suspended in a microfluidic sample. By using the dielectric properties of the cells and the ones of the surrounding medium, it is possible do design suitable devices which allow to manipulate, separate or cage cells without having any physical contact with them and avoiding more expensive marking process. When an electric potential is provided to the microelectrodes in the device, the cells experience the DEP force and, depending on their characteristics, they are attracted to or repelled from the electrodes edges [1]. Therefore, it is possible to move and separate cells of different types whose properties are different enough. The same happens if we consider bigger cellular aggregates instead of single cells.

Isolated cells have been designed using single or double shell models. They consider the main physical cell structure: the presence of the cytoplasm and the presence or absence of the cell membrane and wall. Aggregate's properties have been instead computed taking into account the reciprocal disposition of the single cells and the external microfluidic environment characteristics.

In this work we have developed, studied, and compared different numerical methods in order to compute DEP force depending on the electrical field non-uniformity factor and on the dimensions of the cellular aggregate. Furthermore, we show a comparison between experimental and simulated results for some particular cell types and electrodes configurations.

Numerical modeling has been performed with COMSOL Multiphysics® version 3.5 to compute the underlying quasi-static electric field, the aggregate's dielectric properties and the particles' trajectories.

2. Governing Equations

2.1 Point wise approximations

When a dielectric particle is subjected to an external variable electric field, the positive and negative charges centers of mass separate and it polarized. The polarizability of the cell and medium is dependent on the frequency of the electric field, and it is possible for a particle to experience either positive or negative dielectrophoresis according to the frequency of the applied electric field.

It is possible to virtually substitute the cell with an electrical dipole and, the smaller the particle is, the better is the approximation; the dipole DEP force approximation is. In case of time constant electric field it is, by considering the cell as a dipole we obtain

$$F_{DEP,dip} = 2\pi\varepsilon_m r^3 F_{CM}^{(1)} \nabla E_0^2$$

where ε_m is the medium permittivity, r is the particle radius, E_0 is the external electric field strength (the root mean square magnitude of the electric field), and $F^{(1)}_{CM}$ is the Clausius-Mossotti factor. This last factor models the cell and its behavior taking into account that also the external medium is a dielectric and, therefore, polarizes. It is defined as

$$F_{CM}^{(1)} = \frac{\varepsilon_p - \varepsilon_m}{\varepsilon_p + 2\varepsilon_m}$$

where ε_p is the particle permittivity and it assumes positive sign if $\varepsilon_p > \varepsilon_m$ meaning that the particle polarizes with the field.

We point out that, if the aggregate dimensions are too big in comparison with the field non-uniformity, the dipole DEP force approximation could be not enough and further terms in the multipole expansion should be considered [2]. Adopting the Einstein notation, the quadrupole (or second order) term in the approximation can be written as

$$F_{DEP,quad,i} = \frac{4}{3}\pi\varepsilon_m r^5 F_{CM}^{(2)} \frac{\partial E_k}{\partial x_j} \frac{\partial^2 E_i}{\partial x_k \partial x_j}$$

where x_i, x_j, x_k are the coordinate variables, and

$$F_{CM}^{(2)} = \frac{\varepsilon_p - \varepsilon_m}{2\varepsilon_p + 3\varepsilon_m}$$

Is the new Clausis-Mossotti factor. In both previous approximations, cells and aggregates are replaced with points and the values of E_0 and its derivatives are considered just in their centers of mass. This is what happens in case of time constant electric fields but, in this case, the cells assume a permanent polarization: this is the reason why, in dielectrophoresis experiments, sinusoidal time varying electric fields are applied. Under these conditions the permittivity is replaced by the complex permittivity defined as

$$\varepsilon = \varepsilon + \frac{\sigma}{j\omega}$$

where σ is the conductivity, ω is the field frequency and j is the imaginary unit. The Clausius-Mossotti factor is straightforward defined and it can take complex values. Substituting in the previous formulas and keeping an average over a time much longer than a period, we get the DEP force in case of AC electric fields, we obtain the following time-averaged force value,

$$\langle F_{DEP,dip}\rangle_i = 4\pi\varepsilon_m r^3 Re[F_{CM}^{(1)}(\overline{E}_i \frac{\partial \overline{E}_i^*}{\partial x_i} + \overline{E}_j \frac{\partial \overline{E}_i^*}{\partial x_j} + \overline{E}_k \frac{\partial \overline{E}_i^*}{\partial x_k})]$$

$$\langle F_{DEP,quad}\rangle_i = \frac{4}{3}\pi\varepsilon_m r^5 Re[F_{CM}^{(2)} \frac{\partial \overline{E}_k}{\partial x_j} \frac{\partial^2 \overline{E}_i}{\partial x_k \partial x_j}]$$

where φ is the field phase, $E_x^2 = E_x^2/2$, and E^* is the complex conjugate of the electric field value.

2.2 Discrete force

When the quadrupole approximation is not sufficiently accurate, additional multipole terms must be considered in the force calculation. Then, higher order electric field derivatives are introduced with a related numerical approximation problems. This is why another method is proposed here in order to compute the DEP force, we have called our approach the discrete method.

In general, in continuum area, the force can be seen as $\int_\Omega d\mathbf{f} d\Omega$ where $d\mathbf{f}$ is the infinitesimal force acting on the infinitesimal volume $d\Omega$. Discretizing this integral we get that the force could be approximate as $\sum_{i=1}^{N} d\mathbf{F}_i$ where $d\mathbf{F}_i$ is the force acting on the i-th "elementary" volume, small but finite (see Figure 1).

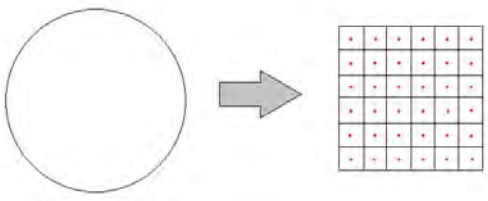

Figure 1: The discretization process.

In the continuum case we have a spherical cell, for simplicity it is virtually transformed into an iso-volumetric cube that is subsequently divided into smaller cubes. The dipole DEP force approximation is, then, computed in the center of mass of each small cube and all the contributes are finally summed up to give the total force. In this way the aggregates are no more considered as points, just first order field derivatives are computed and the value of **E** is considered in more places.

2.3 Drag force

When the cells move inside a microfluidic medium they experience a drag force. For the dimensions and velocity that appears in our dielectrophoretic experiments [3], it *could* be approximates with the Stokes's law,

$$F_{drag} = -6\pi\eta r v$$

where η is the fluid viscosity, $\boldsymbol{v}$ is the particle velocity, and r is the radius of the cell considered as a spherical particle.

3. Use of COMSOL Multiphysics

3.1Aggregate model

The cells/aggregates are represented in the DEP formula by the Clausius-Mossotti factor: their permittivity and conductivity are needed. The value for the single cell can be found in the literature while the ones for the aggregates should be computed taking into account the reciprocal disposition of the cells, their dielectric properties and the ones of the surrounding medium. One model has been built for pancreatic Langerhans islets and, as Pethig asserts in [4], the dielectric properties of a cell can be approximated by the ones of its membrane while the ones of the extracellular matrix with the values of the surrounding medium.

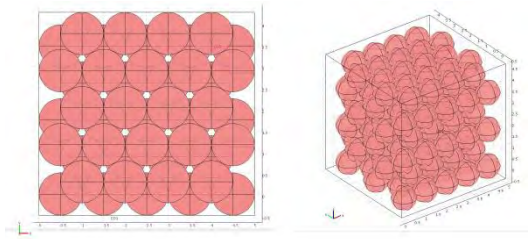

Figure 2: Aggregate's geometrical model.

Concerning the reciprocal cells disposition, the hexagonal close packing has been chosen. The geometrical model has been built using the COMSOL Multiphysics AC/DC module, quasi-static electric field: by using the suitable post-processing option, the overall permittivity and conductivity have been calculated (Figure 2).

3.2 Electric field computation

In the force comparison the chip geometry has been chosen to be constituted by eight parallel electrodes; since they are long (1.5 mm) relative to their width (50 μm), the problem can be considered two dimensional and their height is neglected. Two subsequent electrodes are filled with a 180° phase shift. Insulating boundary conditions are imposed on all the boundaries except for the ones representing electrodes where Dirichlet's conditions are used. The generated electric field and its derivatives are computed using the AC/DC module (see Figure 3). The results for the dipole force approximation are shown in Figure 4.

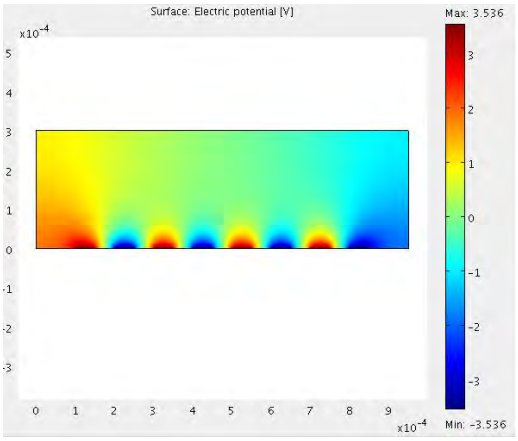

Figure 3: Computed voltage.

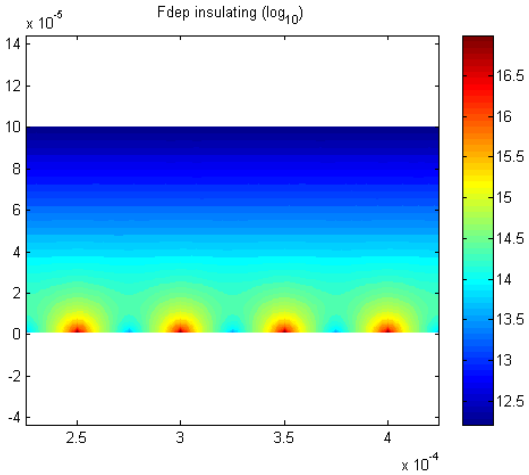

Figure 4: Dipole force approximation for 4 electrodes (log scale).

To compute the quadrupole approximation of the force, the second order field derivatives are needed. To satisfy this aim, a subdomain weak form equation in COMSOL Multiphysics PDE modes has been added to the existing model. More precisely, starting from the Green's first identity,

$$\int_{\Omega} w\Delta\varphi = \int_{\Omega} \nabla w \cdot \nabla\varphi + \int_{\partial\Omega} w \frac{\partial\varphi}{\partial n}$$

where Ω is the domain, $\partial\Omega$ is its boundary and $\boldsymbol{n}$ the outgoing unit normal; setting a new variable representing $\partial E_x / \partial x$, substituting the function w in the Green's formula with E_x, φ with the test function. By dividing the equation in the part acting on the whole domain and the one just on the boundary it is possible to get the second order partial derivatives of the field (for the other derivatives the proceed is straightforward).

3.3 Discrete Force Computation

While to compute the DEP dipole and quadrupole force approximation it is enough to know them in the cell center of mass point, to get the discrete one in the case of aggregate, their values are needed in more points and, to get the total force, it's necessary to sum them up. To this aim the connection with Matlab® has been exploited creating a routine that computes the force value in the interested points and afterwards the total force. Obviously, needing more points to be computed, this method is computationally more expensive.

3.4 Particle Tracing

To compare the experimental results with the COMSOL simulated ones, the software post-processing particle tracing option has been used. Cells' trajectories have been computed at different time points considering both the DEP and the drag force.

4. Results

4.1 Force computation comparison

Since that our aim is to understand which computational method should be used depending on the field non-uniformity and particle's dimension, we started by comparing the dipole and the quadrupole force approximations letting parameters vary. The force is computed at a height from the channel bottom equal to the aggregate's radius that has been varied between 5 and 50 µm (a typical single cell radius is equal to 5 µm, while Langerhans islets aggregates can be much bigger) while the field non-uniformity has been varied changing the electrodes width between 50 and 150 µm. To compare the dipole and quadrupole approximations, the relative contribution of the quadrupole term has been computed as

$$e = \frac{|F_{quad}|}{|F_{dip}| + |F_{quad}|}$$

for different values of the parameters and for both the x and y component. The result for F_x is shown in Figure 5: the bigger is the field non-uniformity with respect to the aggregate's radius, more important is the second order term in the multipole approximation.

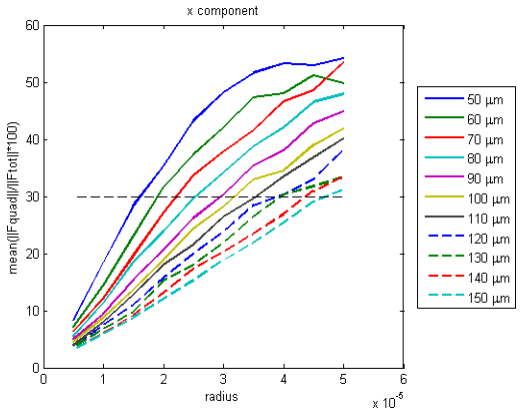

Figure 5: *e* values for the x component of the force for different electrodes widths.

Fixing a threshold value (chosen, in this case at 20%) it is possible to identify for each field non-uniformity value an aggregate's dimension (*critical radius*) above which the quadrupole approximation should be used. This should be done both for the x and the y field component and the more accurate formula is used if at least one of them is above the threshold value.

In the second step we compare the quadrupole and the discrete approximation. This has been done behaving almost the same: the only difference was in the chosen of the comparing function. A suitable one has been picked up such that the specific differences are highlighting. It is a distance function and if we indicate with f and g the quadrupole and discrete force it is defined as

$$d = \sum_{i=2}^{N} |\,(f-g)(x_i) - (f-g)(x_{i-1})\,| + |\,\overline{f} - \overline{g}\,|$$

where $\{x_i\}$ is a set of points in which the forces are computed and $\overline{g}$ is the average of the g values. Imposing a suitable threshold value a plot as in the Figure 5 can be found and the corresponding values at which the computation method should be changed

depending on the two parameters. Computing an estimation of the field non-uniformity as

$$\sqrt{\left(\frac{\partial E_x}{\partial x}+\frac{\partial E_x}{\partial y}+\frac{\partial E_y}{\partial x}+\frac{\partial E_y}{\partial y}\right)\Big/4}$$

A summary plot can be evaluated in which, giving the particular experimental setting, allows to select the method most convenient to use (Figure 6).

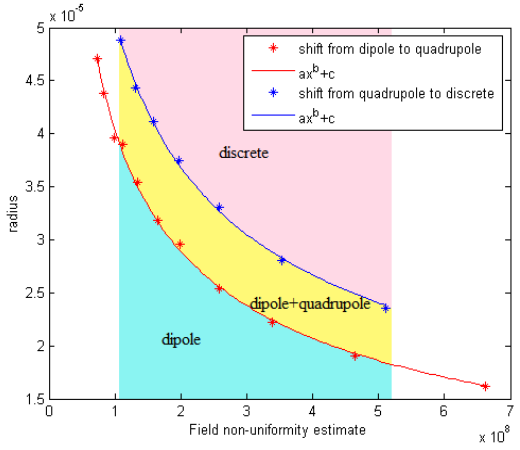

Figure 6: Resuming plot for the computation methods to be used depending on the field non-uniformity and the aggregate's radius.

4.2 Experimental-simulation comparison

By adopting the COMSOL particle tracing option, the experimental and the simulated velocity and trajectories have been compared for different experimental settings.

A first study has been made using *Saccharomyces cerevisiae* yeast cells applying a peak to peak voltage of 20 V and a frequency of 1MHz: the corresponding Clausius-Mossotti factor is such that the cells are attracted to the electrodes edges. By using image analysis techniques and looking at the particle tracing at different times step the circled particle's position has been identified both in the experimental video and in the numerical simulation.

On the bottom of the Figure 7 the comparison is shown: on the *abscissa* axis there is the time while on the *y* axis the displacement with respect to the original position. In red the data achieved from COMSOL simulation while in blue the experimental ones. The green line is obtained from the simulated analysis supposing that a friction force more than the drag one acts at the beginning of the process delaying its motion start. As we can see, within these hypothesis, the agreement is very good.

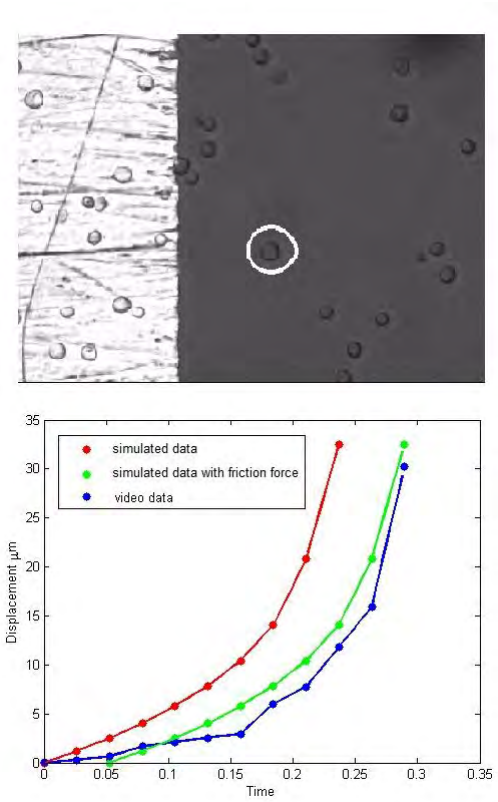

Figure 7: Comparison between the experimental and simulated results.

Another comparison has been made using Langerhans islands and a quadrupole configuration with a 1MHz field frequency and 50 V peak to peak voltage (cf. Figure 8). In this case, computing the field non uniformity and the aggregate radius, it turns out that the dipole approximation is sufficient. The field has been computed in a three dimensional model but the particle motion has been considered just on an horizontal plane. This is because, the *z* component of the force results to be really low and there isn't any information about the aggregate position along this direction neither at the beginning nor during the experiment. Choosing a suitable height (between 300 and 380 µm from the channel bottom) and introducing also in this case the extra friction force, the comparison between experiments and simulation is quite good especially between the two arrows (Figure 9). They represent the points in which the friction force stops to act and in which the second islet in the video hits the studied one modifying its motion.

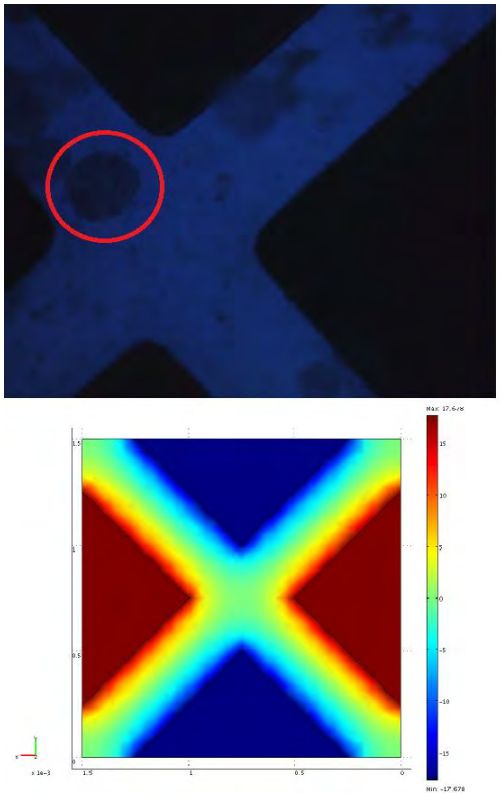

Figure 8: Video image and COMSOL voltage computation.

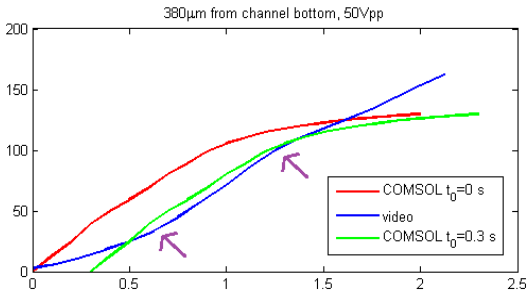

Figure 9: Experimental and simulated result comparison for the islets video.

5. Conclusions

Different computational methods for the DEP force approximation have been tested depending on the electrical field non-uniformity factor and the aggregates' dimension. Two functions have been found that indicate the threshold conditions for the method choice. For small non uniformity and small cells' radii it is enough to consider the dipole approximation, when they grow, anyway, the quadrupole should be used before coming to the discrete one.

The experimental-simulation comparison is quite good once we consider a further friction force that delays the simulated motion. This force could be, for example, a dry friction force due to the presence of the channel floor or some other kind.

6. References

1. S Burgarella, S Merlo, B Dell'Anna, G Zarola, and M Bianchessi, A modular micro-fluidic platform for cell handling by dielectrophoresis, *Microelectronic Engineering*, **87**, 2124-2133 (2010)

2. T B Jones, basic Theory of Dielectrophoresis and Electrorotation, *IEEE Engineering in medicine and Biology Magazine*, November/December 2003

3. L Fu, G Lee, Y Lin, and R Yang, Minipulation of Microparticles Using New Modes of Travelling Wave_Dielectrophoresis Forces: Numerical simulation and Experiments, *IEEE/ASME Transaction on Mechatronics*, **9 (2),** (2004)

4. R Pethig,L M Jakubek, R H Sanger, E Heart, E D Corson, and P J S Smith. Electro-kinetic Measurements of Membrane Capacit-ance and Conductance for Pancreatic B-cells. *IEEE/ASME Nanobiotechnology*, **152 (6),** 189-193 (2005)