Simulation of CMOS compatible sensor structures for dielectrophoretic biomolecule immobilization

Honeyeh Matbaechi Ettehad*, Subhajit Guha, Christian Wenger
IHP, Im Technologiepark 25, 15236 Frankfurt (Oder), Germany
*Corresponding author: matbaechi@ihp-microelectronics.com

Abstract: This work presents the simulation of planar electrode structures, for dielectrophoretic immobilization of biomolecules. Interdigitated electrodes (IDEs) were chosen for the simulation of the dielectrophoretic immobilization. The same IDE structure can be used for CMOS compatible near field RF sensing of the immobilized biomolecules. Keeping the applied AC voltage within CMOS circuit compatible ranges, the impact of AC frequencies and fluid flow velocities on the dielectrophoretic immobilization were studied for biomolecules with different sizes. In order to achieve effective immobilization of the particles on the IDEs, the external parameters like AC frequency and flow velocity have to be optimized.

Keywords: lab-on-chip; CMOS biosensor; microfluidics; biological cells; dielectrophoretic immobilization

1. Introduction

Today dielectrophoresis (DEP) techniques combined with microfluidic biochips are widely used for many biological applications [1]–[5]. However, using the same electrode structure for dielectrophoretic immobilization and sensing has not been explored so far. In this work, interdigitated electrodes (IDE) geometry was used for immobilization and sensing. In a previous work H. Li et al. showed that IDEs are convenient for dielectrophoretic trapping [1]. The IDE is modeled to be placed in a microfluidic channel. The medium consisting of the biomolecules when pumped through the channel brings the biomolecules on top of the electrodes. The AC source is applied across the electrode to generate a non-uniform electric field which leads to dipole moments in the biomolecules. The interactive force between the induced dipoles and the non-uniform electric field is called DEP. This particles can move towards the highest electric field gradient as a result of the positive DEP (pDEP) or in reverse due to negative DEP (nDEP) depending on the relative permittivity of the medium and particles [6].

In order to optimize the capability of the sensor to immobilize biomolecules of different sizes, DEP, numerical simulations were done to study the effect of electric potential, geometrical parameters of IDEs and fluid flow velocity on particle tracing. Different geometrical parameters of electrodes such as width and space between adjacent fingers of IDEs were modelled. The applied AC voltage was kept within CMOS compatible values, while the influence of fluid flow velocities were studied.

2. Use of COMSOL Multiphysics

In this work a 2D and a 3D model was developed based on the COMSOL Multiphysics tool. In order to simulate the dielectrophoretic immobilization of biomolecules suspended in an aqueous solution, the fluid flow was considered through a microfluidic channel with a single inlet and a single outlet. Arrays of IDEs are utilized to create a non-uniform electric field that impacts the trajectory of biomolecules due to dielectrophoretic forces. The aim of this work was to optimize the immobilization of the biomolecules of different sizes on the electrode surface. The DEP force was optimized with respect to different geometrical parameters of electrodes, size of the particle and flow velocity. The IDE geometry has been adopted from the previous works done at IHP [7][8]. IDEs with 6 fingers were used as the test structure for the simulations. Figure 1(A) illustrates the device design in 3D geometry, while the simulation studies were all done in 2D in order to reduce the computational time as illustrated in figure 1(B). In this simulation, different geometrical parameters of electrodes like width and spacing between adjacent IDEs were studied. The simulated aqueous medium for the suspension of the biomolecules is considered to be blood. Due to the non-Newtonian nature of blood, a creeping flow model was considered. The Electric Current (ec) module and Particle Tracing for Fluid Flow (fpt) in conjugation with Drag and Dielectrophoretic Forces modules were used as the physics interfaces.

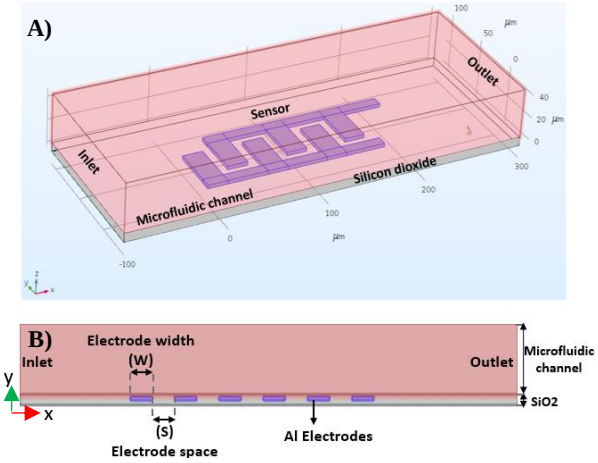


Figure 1. (A) 3D-geometry and (B) 2D-geometry of the model device used to study the dielectrophoretic forces on particle tracing.

2.1 Governing Equations

Different equations were used to simulate the flow path of the biomolecules suspended in the medium fluid and subsequently trapping them on the electrodes by DEP. Due to the non-Newtonian nature of the blood, the Creeping Flow (spf) module is used to model the fluid flow through the channel. Fluid velocity within the channel is determined based on Navier-Stokes equation.

$$0 = \nabla \cdot \left[-pI + \mu(\nabla u + (\nabla u)T) - \frac{2}{3}\mu(\nabla \cdot u)I\right] + F \qquad (1)$$

$$\nabla \cdot (\rho u) = 0$$

Here, p is the pressure, u is the velocity vector, μ is the dynamic viscosity and F is the volume force vector that is acting on the fluid.

When a particle is suspended in the fluid, it is affected by several forces. One of these forces, is called the drag force, and is caused by the fluid flow and has the same direction as the flow. The drag force is calculated based on Stokes drags law which is also applicable for creeping flows (Re_r « 1), as shown in equation (2) and (3).

$$F_{Drag} = \left(\frac{1}{T_p}\right) \cdot m_p(u - v) \qquad (2)$$

$$\tau_p = \rho_p \cdot \frac{{d_p}^2}{18\mu} \qquad (3)$$

Where τ_p is the velocity response time of particles, m_p is the particle mass, v velocity of the particles, u fluid velocity, μ fluid viscosity, ρ_p particle density and d_p particle diameter.

Furthermore, to attract and trap the molecules, the dielectrophoretic force (F_{DEP}) is required. The particles are subjected to a non-uniform AC electric field.

$$F_{DEP} = 2\pi {r_p}^3 \varepsilon_f \, real(\varepsilon^*{}_f) \, real(K) \, \nabla |E|^2 \qquad (4)$$

$$K = \frac{(\varepsilon_p{}^* - \varepsilon_f{}^*)}{(\varepsilon_p{}^* + 2\varepsilon_f{}^*)} \qquad (5)$$

$$\varepsilon_f^* = \varepsilon_r - \left(\frac{i\sigma}{\omega}\right) \qquad (6)$$

Here, r_p is the particle radius, ε_f relative permittivity of the medium, ε_f^* and ε_p^* are the complex permittivities of the fluid and particles respectively. E is the root mean square of electric field strength. Permittivity is a complex quantity which is a function of electric field's angular frequency (ω) and conductivity (σ).

The electric field E, based on the electric potential (V) which applied to the electrodes, is simulated by the Electric Currents (ec) module and is calculated based on equation (7).

$$E = -\nabla V \qquad (7)$$

The fluid flow (fpt) module together with the particle tracing contains the equations governing the motion and trajectory of particles in the fluid under the influence of a DEP force and drag force. By ignoring the gravity force, buoyancy and Brownian motion forces, the relevant equation can be written as below.

$$m_p \frac{dv}{dt} = F_{DEP} - F_{Drag} = F_T \qquad (8)$$

Where, m_p is the mass of particles, v is the velocity of the fluid and F_T is the total force acting on the particle.

Table 1, represents the fluid and particle properties which are used as parameters for the simulations. In this work, it was assumed that biomolecules are homogeneous spheres. To study the influence of the

particle size, the same dielectric properties were assumed for large and small particles.

Table 1: Initial fluid and particle parameters

fluid	viscosity	0.001 kg/(s·m)
	density	1000 kg/m^3
	permittivity	80
	conductivity	55 mS/m
Large particle	diameter	3.5 µm
	density	1000 kg/m^3
	permittivity	50
	conductivity	25 S/m
Small particle	diameter	500 nm
	density	1000 kg/m^3
	permittivity	50
	conductivity	25 S/m

2.2 Initial and boundary conditions

An electrically insulated boundary condition was applied to the fluidic boundary and the insulator in between the electrodes. Electric potential of zero Volt was then applied to the electrodes as further initial condition. Above the sensor array, the fluid flows through the channel along the x-axis, as illustrated in Figure 1. The wall conditions were imposed without slip and bounce. The condition without slipping (u = 0) is used to model solid walls and bounce for modeling the tracing of microscopic particles in the fluid. The position of the inlet and the outlet is perpendicular to the device structure. At the inlet, the initial fluid flow velocity (v_0) was set to 50 µm/s. This value was then varied between 2 and 20 µm/s to study its impact on the immobilization of particles. To establish a fluid pressure gradient in the channel, an initial fluid velocity was applied at the inlet and the outlet was kept to zero fluid velocity. For tracing the motion of particles, the freeze wall condition was selected at the outlet. In this case, the velocity and position of particles remain frozen at the point where they leave the channel outlet boundary.

2.3 Computational methods

The particle tracing with applied dielectrophoretic force field which forces the particles motion in the medium was simulated. The analysis was done in 3 steps. The electric current module simulates the electrical potential field, as shown in Figure 3. A stationary analysis was performed to simulate the velocity through the channel, as illustrated in Figure 4.

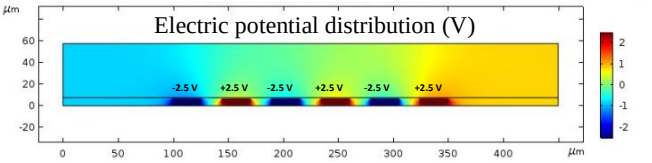


Figure 3. Electric potential distribution in the microfluidic channel at V = 5 V=V_{pp} at given frequency of 10MHz.

As can be seen in Fig. 3, the same negative and positive polarity voltage peak values of 2.5 V and -2.5 V were applied to the electrodes. Therefore, the total electric potential applied was equal to 5 V peak to peak voltage (V = 5 V = V_{pp}).

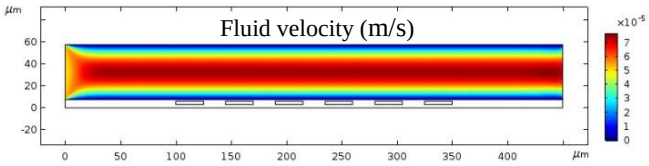


Figure 4. Velocity field across the microfluidic channel.

Figure 4 illustrates the constant fluid flow velocity in the middle part of the channel, therefore pressure is almost constant in the channel.

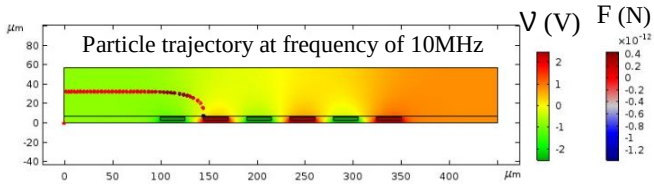


Figure 5. Particle trajectories with respect to the applied electric potential and the force acting on the particles leading to the immobilization of the biomolecules at the electrode.

For particle tracing a time dependent solution was performed using the values obtained from the frequency domain analysis, as shown in Figure 5. Since the objective of this study is to immobilize the particles on the electrodes, simulations were performed systematically to optimize the electrode geometry and to find suitable electric field frequency ranges and fluid velocities to attract the micron-beads with diameter of 3.5 µm and also the nano-beads with diameter of 500 nm.

3. Simulation Results and Discussion

Figure 6 illustrates the variation of the electric field potential and the frequency for particles with sizes of 3.5 µm and 500 nm. These results are consistent with dielectrophoretic theory. By increasing the voltage, at

a given frequency, the DEP force increases and the particles get attracted to the electrodes, Figure 6(A). However due to the use of the low voltage CMOS technology which has a voltage constraint below 5 Volts, larger electrical potential could destroy the CMOS transistors of future integrated circuits. Therefore, the objective is to balance the dielectric force, as well as optimizing the geometrical parameters of IDEs, as illustrated in Figure 7. The reduction of the particle radius decreases the DEP force. Therefore, larger electrical potentials are required to increase the DEP force. Similar simulations as illustrated in Figure 6 were applied for biomolecules with a diameter of 500 nm.

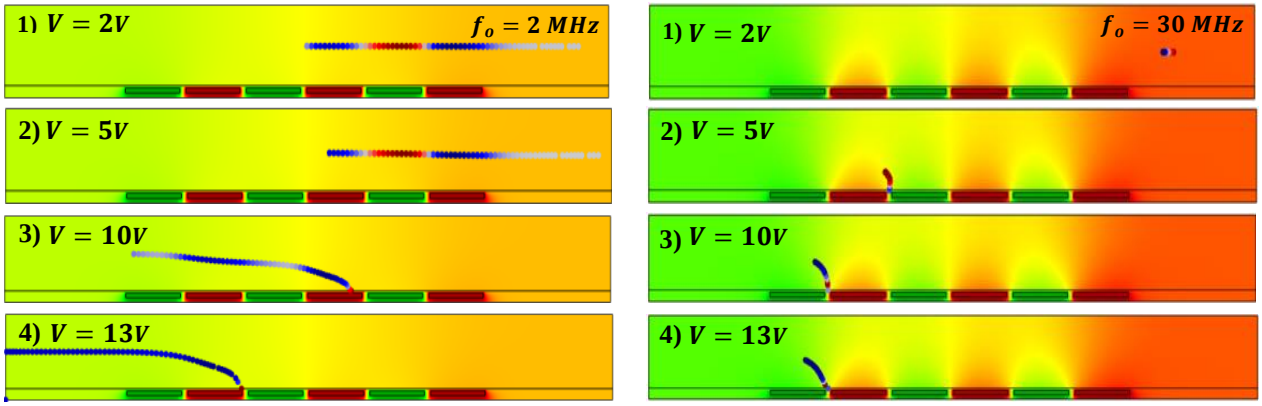
It was evaluated, that the geometry variation and the increasing of the electric potential up to 10 V, did not trap the molecules on top of the electrodes. However, by reducing the fluid flow velocity down to 2 µm/s, the molecules were attracted by DEP with almost the same trend as for the larger particles, as shown in Figure 6 (B). Furthermore, different electrode geometries of IDEs, as listed in table 2, were used with the aim to optimize the geometrical parameters that could be used for different biomolecule sizes without exceeding the CMOS compatible voltage ranges.

Table 2: Different width and spacing of IDEs for geometry optimization

Electrode width (µm)	Electrode spacing (µm)
5-10-15-20-25-30-35-40-45	5-10-15-20-25-30-35-40-45

Figure 7 shows the simulation results of DEP characterization for different IDE geometries. Figure 7 (A-B) represents the influence of the electrode widths with constant electrode spacing and vice versa.

The results demonstrate that by increasing the electrode width and spacing between adjacent electrodes, the immobilization of particles can be optimized. This is due to the improved gradient of the electric field which leads to increased DEP forces. It was evaluated that for devices with electrode spacing of 15-20 µm and widths larger than 30 µm the F_{DEP} is increased. Using electrode spacing of 5 – 10 µm requires larger widths of electrodes (> 35 µm) for immobilization of particles. Therefore, for an optimized DEP force, device geometry with smaller electrode spacing requires wider electrode widths.



(A) Particle size: 3.5 µm **(B) Particle size: 500 nm**

Figure 6. Impact of dielectrophoretic force on the trajectory of biomolecules with diameter sizes of 3.5 µm (A) and 500 nm (B) with respect to variation of the electrical potential. All the devices has the same geometrical parameters (45 µm electrodes width and 5 µm spacing between adjacent electrodes). The fluid velocity was kept constant (50 µm/s) for all the simulations with 3.5 µm biomolecule size. In order to trap the particles with smaller diameter of 500 nm onto the electrodes, the fluid velocity was reduced to 2 µm/s. The relative permittivity and the electrical conductivity of biomolecules were assumed to be 50 and 25 S/m, respectively. For the fluid these parameters were assumed to be 80 and 55 mS/m, respectively. (A) Voltage variation at constant frequency of 1.74 MHz for 3.5 µm diameter biomolecules. (C) Voltage variation at constant frequency of 30 MHz for 500 nm size particles. In all simulations, the first image represents the situation in which the DEP force is too small to attract the particles towards the electrodes. The following images illustrate the successful particle immobilization by DEP.

Results for decreasing the medium flow velocity from 50 to 20 µm/s by keeping the voltage and frequency constant showed attraction and immobilization of particles even with smaller electrode widths. As shown in Figure 7, the particles are attracted to the edges of the electrodes caused by the maximum gradient of the electric field. When particles in the medium flow across the electrode array, they will be forced by a positive or a negative dielectrophoresis, dependent from the electric constant of the particles in relation to the fluid [6][1]. When electrical permittivity of the particle is larger than the permittivity of the fluid, the particle will be impacted by the positive DEP [1]. This is the case in our simulation where the particles are trapped at the electrode edges. For the sensor design based on the results achieved from several simulations, variation of 5 to 20 µm was selected for spacing between the electrodes and variation of 15 to 45 µm were selected for electrode width, as it is shown in table 3.

Table 3: Selected electrode geometries based on simulation results for applied electric potential of 5V

El-S (µm)	El-W (µm)	Particle-d (µm)	*u* (µm/s)
20	15	3.5	50
20	20	3.5	50
20	30	3.5	50
15	35	3.5	20
10	40	0.5	2
5	45	0.5	5

For 500 nm particles variation of 5 to 10 µm for

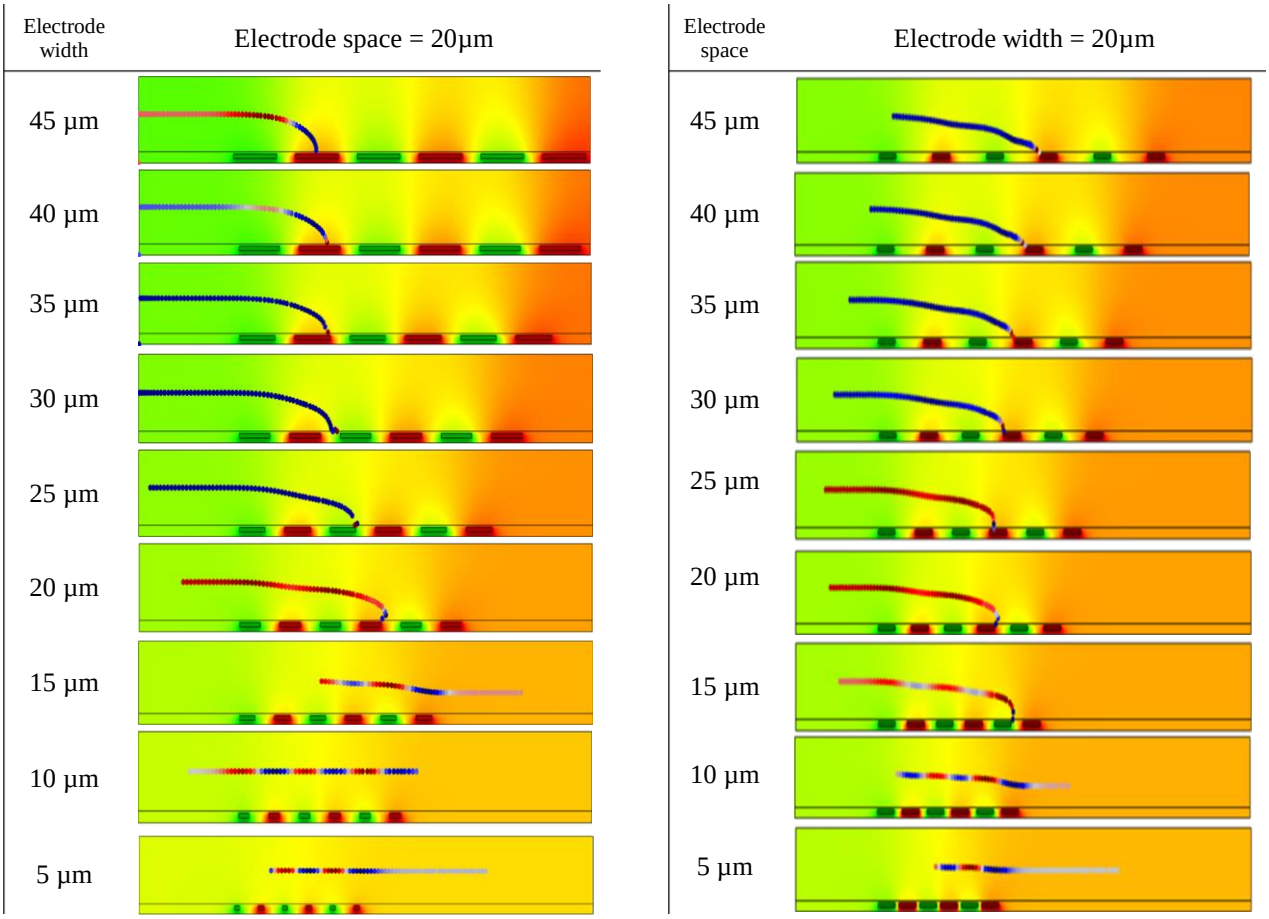


Figure 7. Dielectrophoretic force effect on biomolecules based on varying the geometrical electrode parameters. (A) Constant electrode space of 20 µm with varied electrode width; (B) Constant electrode width of 20 µm with varied spacing, at the constant electric potential of 5 V and a frequency of 10 MHz The particle diameter is 3.5µm with relative permittivity and electrical conductivity of 50 and 25 S/m, respectively. For the fluid these parameters were assumed to be 80 and 55mS/m, respectively. In both simulations, the fluid flow velocity is 50 µm/s.

electrode spacing and 40 to 45 µm for electrode width were selected with respect to flow velocity and applied frequency. It is intuitive that by keeping all the properties of the particles the same, this geometry can attract particles of 3.5 µm as well.

4. Conclusions

In order to optimize the sensor which is capable for DEP immobilization of biomolecules of different sizes, numerical simulations were done to study the effect of geometrical parameters of the IDEs, the electric potential and fluid flow velocity on particle tracing. Therefore, different geometrical parameters of the electrodes such as width and space between adjacent fingers of the IDEs were modelled. The applied AC voltages were kept within CMOS compatible ranges, while the impact of fluid flow velocity were studied. The results demonstrate that immobilization of very small particles can be optimized by reducing the flow velocity. The systematic simulation of the geometrical electrode parameters demonstrates that smaller spacing between adjacent electrodes is required for the trapping of particles on electrodes. If we want to use a platform which could be used for both particle sizes, asymmetric geometries are better than symmetric geometries which have equal sizes of electrode width and spacing. Furthermore, bigger electrode widths and smaller spacings leads to generate higher non uniform electric field which is effective for particle tracing. Accordingly, for the geometrical sensor design variation of 5 to 20 µm and 15 to 45 µm were selected for electrode spacing and width, respectively.

5. References

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