Model Of An Interdigitated Electrodes System For Cell Counting Based On Impedance Spectroscopy

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Abstract: A model of a cell counter sensor based on Impedance Spectroscopy (IS) has been implemented in COMSOL Multiphysics.
The cell counter is a silicon-based microdevice consisting in 3D electrodes placed in a wide microchannel: cells flow in the microchannel through the electrodes to be detected.
The model allows to evaluate the functionality of the device depending on geometrical parameters and material properties, cutting down experimental time. Two and three electrodes configurations have been tested, focusing on the variation of impedance due to the presence or absence of particles (polystyrene beads or cells).
The resulting signal variation allows us to verify and quantify the efficiency of the device.

Keywords: Impedance Spectroscopy, cell counter, microdevice, 3D vertical electrodes

1. Introduction

A cell counter sensor based on impedance spectroscopy has been modeled by means of Comsol Multyphisics 4.2a. The cell counter consists of a system of vertical interdigitated electrodes, built on a silicon wafer by means of microfabrication technologies (Fig.1). In order to overcome the critical limiting low throughput factor, characterizing the existing cell counters, this device aims at enabling parallel measurements to detect cells flowing through parallel- plate flow-chambers, with large width-height ratio.

Impedance Spectroscopy (IS) is a powerful method for characterizing many of the electrical properties of materials and their interfaces [1]: it allows real-time detection, non-invasive sensing, label-free analyses and easiness of integration in high-throughput screening devices.

2. Materials and Methods

Impedance Spectroscopy is a kind of electrical measurement. The approach is to apply a known AC voltage to the electrodes and to observe the resulting response in current, assuming that the properties of the electrodes and of the system do not change with time [2].

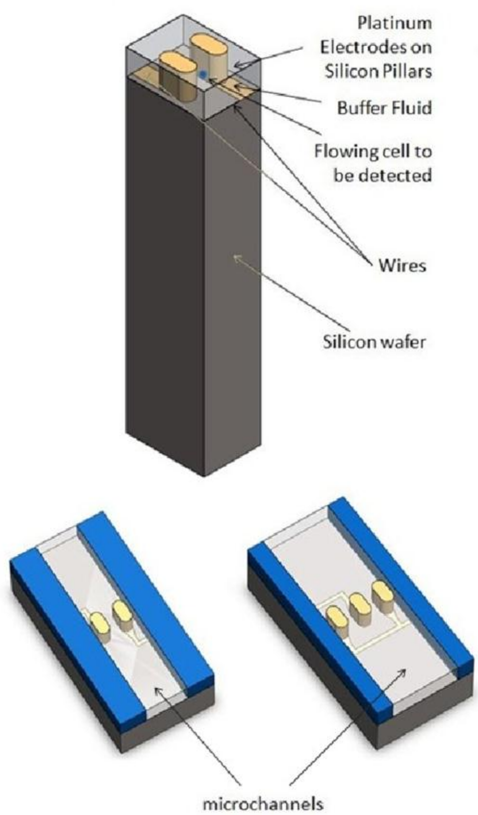

Figure 1. Model of the platinum electrodes (yellow) connected to wires, on the top of a silicon base (dark grey), placed in a microchannel (light grey). On the bottom the two configurations of electrodes are shown, 2-pillars on the left and 3-pillars on the right.

Sweeping over a wide frequency range f =10^{-5} - 10^{9} [Hz] with a small-amplitude (50 mV) single-frequency voltage, impedance amplitude Z [Ω] and the phase shift ϑ [rad], or the real and the imaginary parts of the resulting signal are measured. Our system has been characterized by employing polystyrene beads that, in the frequency range of interest, show similar insulating behavior to cells. Further simulations have been performed to detect cells. The detection of a bead or a cell between the electrodes has been identified as a variation of Z value, observable in a restricted range of electrical frequency. The system can be approximated with the equivalent circuit shown in Fig.2.

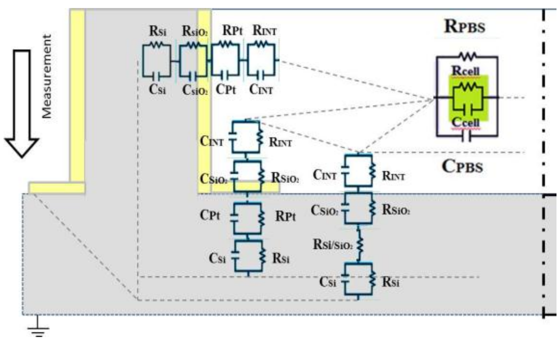

Fig.2. Sketch of the equivalent electric circuit that describes the dielectric behavior of the system. All the elements are defined by both resistive and dielectric behavior. Si=silicon, SiO_2=silicon oxide, Pt=Platinum, Int=electrochemical interface, PBs=buffer solution, Cell= cells or bead

3. Use of COMSOL Multiphysics

The model has been solved by the electric current module: electrodes' boundaries, where the voltage is applied, are defined as Terminals and the resulting value of impedance Z [Ω] is calculated as the inverse of the admittance (ec.Y11), that is expressed as the combination of a real and a complex term.

The simulation involves the equations of electrical conduction (Eq.1):

$$\boldsymbol{J} = (\sigma + j\omega\epsilon_0\epsilon_r)\boldsymbol{E} + \boldsymbol{J_e} \qquad \text{(Eq.1)}$$

where σ is the conductivity [S/m], ω is the angular frequency, ε_0 is the vacuum permittivity [8.84 10^{-12}], ε_r the relative permittivity of the material, V the potential [V] and J_e is an external generated current density [A/m^2]. Eq.2 can be defined as a complex conductivity, included in Eq.1.

$$\sigma_c = \sigma + j\omega\epsilon_0\epsilon_r \qquad \text{(Eq.2)}$$

The electric properties of the materials (silicon, platinum, buffer fluid, cell/bead) have been assigned in terms of ohmic conductivity σ [S/m] and permittivity ε [-] (Tab.1).

Material	σ [S/m]	ε [-]	Reference
Silicon	100	11.7	[3] [4]
Platinum	9.90 E+06	0	[4]
PBS 1X*	1.50	78	[5]
PBS 0.1X*	0.15	78	-
Bead	1.00 E-16	2.6	[6]
Cell	0.7	130	[7]
SiO_2	1.00 E-08	4.5	[8]
Cell membrane	1.00 E-08	5.6	[7] [9]

*PBS - Phosphate Buffered Saline

Tab 1. Dielectric properties of materials defined in the model.

Bead or cell are included in the model as a sphere of 10 μm in in diameter between the electrodes (Fig.6).

To define the behavior of elements like cell membrane or silicon dioxide passivation layer, we introduced critical thin structures/layers or contact impedances. These boundary conditions allow to assign electrical properties defined by conductivity σ [S/m], permittivity ε_r [-] and thickness d_s [m] to a surface (no geometrical thickness) (Eq.3). This approach has shown to be crucial in order to reduce the number of elements of the grid.

$$\boldsymbol{n} \cdot \boldsymbol{J} = d\frac{1}{d_s}(\sigma + j\omega\epsilon_0\epsilon_r)(V_1 - V_2) \qquad \text{Eq.3}$$

V_1 and V_2 are the potentials generated at the opposite sides of the surface.

Moreover we considered the interface between the silicon dioxide layer and the buffer fluid, including a further resistive effect of passivation layer. The contribution of this interface is taken into account by defining a purely resistive behavior in series with the already defined resistive/dielectric behavior of the silicon dioxide. The simulations are performed in absence of fluid flow but modeling the presence of a buffer solution that fills the volume of the microchannel.

4. Results

The sensitive portion of the electrode system has been modeled. Dependence of the impedance spectrum Z(f) from the dimensions, number and configuration of the electrodes has been studied (Fig.3) and compared to IS experimental measurements.
Three different geometrical configurations were tested: these configurations differ for the dimensions of the pillars and the distance between them (Tab.2).

Configuration	Width [mm]	Distance [mm]
A	30	30
B	40	40
C	50	50

Tab 2. Dimensions of the pillars and distance between them in the three different analyzed geometries.

Influence of buffer fluid conductivity on the efficiency of bead or cell detection has been investigated, in order to guide the experimental characterization of the electrodes system (Fig.3).
The system has been characterized in presence of PBS, with two different concentrations 1X and 0.1X. The conductivity of this buffer increases with the saline concentration: this difference shows up in the impedance plot as a shift of the resistive plateau over 10^4 [Hz].
The variation of the impedance signal Z in presence of a bead or a cell between the couple of electrodes is shown respectively in Fig.4 and Fig.5. To reproduce the experimental conditions bead detection is performed in PBS 0.1X and detection values reach the 272 Ω in the A configuration. Cell detection has been set in PBS 1X and detection values reach the 26 Ω, still in the A configuration. Referring to the electric circuits of Fig.2 the electrical elements modeling the bead/cell behavior act in parallel to the ones of the buffer solutions.

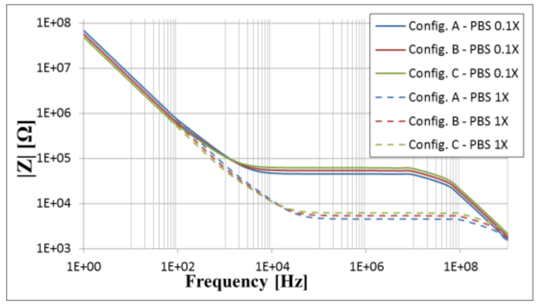

Fig. 3 Impedance Z as function of the electrical frequency for the three geometrical configurations, in presence of two different buffer concentrations: PBS 1X and 0.1X

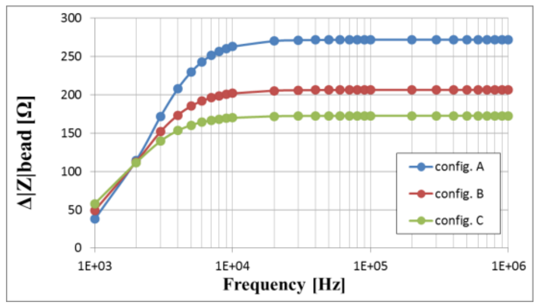

Fig. 4. Detection of a bead in PBS 0.1X. Variation of impedance module due to the presence of the bead between the electrodes

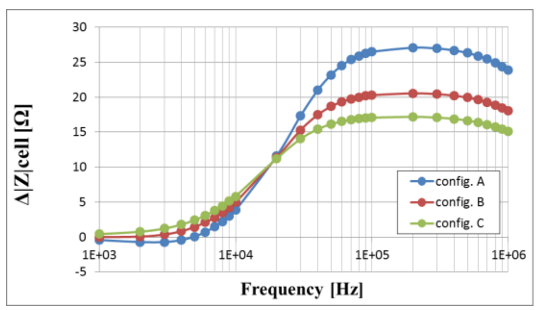

Fig. 5. Detection of a cell in PBS 1X. Variation of impedance module due to the presence of a cell between the electrodes.

Beads an cells show a similar electrical behavior at frequencies around 10^5 [Hz] so that the order of magnitude between their detection values can be explained as related to the difference of an order of magnitude from the PBS 1X and PBS 0.1X conductivities.

In Fig.6 the trend of the electrical potential in a plane parallel to the basis of the channel is plotted.
In order to preserve the counting efficiency an optimal frequency value has to be selected to perform impedance measurements on the electrodes system at only one frequency point. The use of a singular frequency allows the set of a higher sampling rate and leads to an increase of counting efficiency.
The 80 KHz frequency was then selected: it showed to be optimal both in computational and experimental results [10].

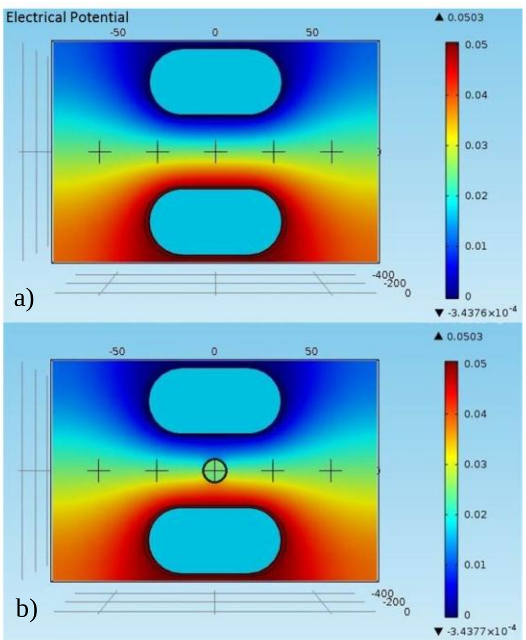

Fig. 6. View from the top: color map of electrical potential [V] at 80 kHz in a plane parallel to the basis of the channel. (a) absence (b) presence of cell.

Configuration A has also been tested in a three pillars configuration. Results of these tests are showed in Fig. 7. Signal variation is proportional to the number of beads among the pillars.

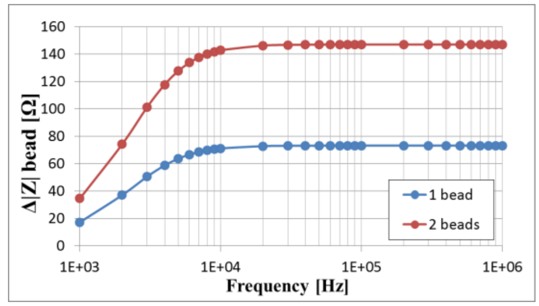

Fig. 7. Impedance variation due to the presence of beads in three-pillars device (Config. A).

5. Conclusions

The results of the impedance simulation of the electrodes system models have given results consistent with the electrical equivalent model and with the experimental characterization of the device. A come out limitation of the simulations is the representation of the device limited to the sensitive area: parasitic effects related to the presence of connection wires cannot be appreciated by means these models.

6. References

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