Impedance measurement system simulation for trapped cell model in various microwell geometries

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Abstract. Single cell analysis is a measurement or detection of individual cell properties and responses. The method is of significance due to stimulated responses of any individual cell are different depending on their morphology and functionality. Therefore, detected properties from a group of cells cannot be used to represent that of the individual cell. Since cells can move freely in a microfluidic system, a trap must be added to the system to fix the cell position at the detection region for long period observation and assay. One of the most popular used cell trap in the biomedical field is a microwell array. A sensitive technique for measuring single cell properties is an impedance measurement, in which small change in electrical properties of the cell and the surrounding medium between excitation and pick-up electrodes is recorded. However, the microwell placed between two electrodes acts as an electrical insulator to reduce the signal passing through the system. This paper focuses on the effect of microwell geometry parameters generated from the design of experiments (DOE) software on detected signals using finite element simulation software. The study found that the microwell wall thickness affects the detected current signal most significantly and the optimized geometry that minimally reduces measured current signal was 20 µm height, 5 µm well thickness, and 16 µm gap size.

1. Introduction

Single cell analysis has gained much attention from the biomedical science community due to the fact that individual cells from a population may behave or response differently to stimuli. Microfluidics offers advantages over traditional cell control and manipulation techniques in which many techniques could be used to both manipulate and monitor of a small volume of cell solution [1]. One of the most popular techniques used in monitoring a cell in a microfluidic device is an impedance detection in microwells. To perform single cell impedance measurement, a cell is first trapped in microwell and the AC voltage is applied to electrodes between microwell, and a slight change in impedance or current in the region between electrodes is recorded. Microwells are usually fabricated from an electrical insulator such as photosil and polydimethylsiloxane (PDMS) [2] which act as a barrier between cell and electrodes, resulting in a decrease in measured current signal. To overcome this problem, microwell geometry must be modified so that the signal could freely pass between cell and electrodes. In this study, the effect of microwell geometries on detected current were numerically investigated using COMSOL Multiphysics software with AC/DC module. The designed microwell with minimum signal deduction would be used in fabricating actual device for single HaCaT cell impedance detection.

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2. Theory

A mammalian cell structure is composed of an insulating cell membrane and a conducting cytoplasm. It could be modeled as a single shell model, in which a conducting sphere is covered by nanometer scale insulating layer [3]. As described in details by Sun [4], the single-shell cell model parameters $R$ and $C$ refer to electrical resistance and electrical capacitance of medium (m), inner or cytoplasm (i), and shell or cell membrane (sh) respectively. Without the microwell, the impedance spectrum from circuit simulation of a cell model placed between two electrodes inside the medium solution shows that different parts of the cell model respond to excitation frequency of different range [5]. The impedance of the system without the microwell can be calculated from [3]

$$Z = \frac{1}{sC_m + \frac{1}{R_m} + \frac{1}{Z_{cell}}} ,$$

where $s = j\omega$, and the impedance of cell ($Z_{cell}$) can be obtained from

$$Z_c = \frac{R_{sh}R_tC_{sh}C_i s^2 + (R_{sh}C_i + R_{sh}C_{sh} + R_tC_i)s + 1}{R_{sh}C_{sh}C_i s^2 + C_i s} .$$

When microwell was added to the system, the impedance spectrum increases due to decreasing of current signal. The total impedance becomes

$$Z = \frac{1}{sC_m + \frac{1}{R_m} + \frac{1}{Z_{cell}}} + Z_{microwell} .$$

3. Design and method

The microfluidic system comprises two planar electrodes at the bottom of a microchannel, PDMS microwell placed between two electrodes, and 20 $\mu$m diameter cell model. The inner radius of microwell was fixed at 15 $\mu$m. The medium solution is Phosphate buffer saline (PBS). The detection area is shown in figure 1. To increase the measured current signal of microfluidic system, the geometry of microwell was modified. In this study, the varied microwell dimensions are gap, height, and thickness. Since the detected signal is the result of the coupling of the geometry’s parameters, the design of experiments (DOE) (Minitab) was used to find the optimized geometry that gives out the lowest reduction of current signal when compared with impedance measurement of the cell without microwell. Ranges of parameters are gap size: 4-16 $\mu$m, microwell thickness: 5-20 $\mu$m, and height: 12-20 $\mu$m. The applied voltage is 10 V with 1 MHz frequency since cell only allows high frequency range to pass through [6]. The electrical properties of the materials used in the simulation are shown in table 1.

| material       | electrical conductivity (S/m) | dielectric constant |
|----------------|------------------------------|---------------------|
| cell membrane  | $1 \times 10^{-8}$           | 7                   |
| cytoplasm      | 0.5                          | 45                  |
| PBS            | 1                            | 80                  |
| PDMS           | $2.5 \times 10^{-14}$        | 2.3                 |
Figure 1. Model of cell and detection area in medium solution in (a) 3D view of detection area and (b) top view of detection site.

Figure 2. Top view of electric field line distribution in detection area for (a) cell without microwell (b) with microwell and (c) microwell with gaps.

4. Results and discussion
The effect of microwell geometry on electric field line distribution within the detection area is illustrated in figure 2. It can be seen that having a gap in microwell allows the electric field to penetrate through the cell, therefore sensing the cell’s interior. The reference simulated current for cell without microwell is 297 $\mu$A. From the DOE run results shown in table 2, the microfluidic system gives the minimal current reduction when the microwell geometry is 20 $\mu$m height, 5 $\mu$m well thickness, and 16 $\mu$m gap size. The Pareto chart in figure 3 indicates geometry that affects current signal most significantly is microwell.

| Height ($\mu$m) | Thickness ($\mu$m) | gap ($\mu$m) | current ($\mu$A) |
|-----------------|-------------------|-------------|-----------------|
| 12              | 5                 | 4           | 290             |
| 12              | 5                 | 16          | 291             |
| 12              | 20                | 4           | 266             |
| 12              | 20                | 16          | 277             |
| 16              | 12.5              | 10          | 280             |
| 20              | 5                 | 4           | 290             |
| 20              | 5                 | 16          | 292             |
| 20              | 20                | 4           | 246             |
| 20              | 20                | 16          | 260             |
thickness, followed by microwell height and well thickness coupling, microwell height, and microwell gap, as indicated by a vertical reference line in the graph.

![Figure 3. Pareto chart of the standardized geometry effect.](image)

5. Conclusion
In this study, COMSOL multiphysics software was successfully used in the current signal simulation for the impedance sensing in the microwell trapped cell model. The optimized microwell geometry that minimally reduces the measured current signal, as determined using DOE software, was 20 µm height, 5 µm well thickness, and 16 µm gap size. The result of this study will be applied in fabricating the actual microfluidic device for HaCaT cell impedance measurement.

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