CMOS based sensor for dielectric spectroscopy of biological cell suspension

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Abstract. In this work we investigate the use of microwave frequency range to measure the concentration of cells in a biological cell suspension. A theoretical model is discussed and the advantage of high frequency, which is to avoid dispersion mechanisms due to the cell parameters at lower frequencies (for example membrane capacitance), has been described. Interdigitated capacitor (IDC) has been proposed as the sensor for analysing the concentration of a cell species in the suspension. The read-out circuit is a VCO using the IDC and a pair of inductors as resonator. The capacitance of the IDC which is the function of the permittivity of the biological cell suspension determines the resonant frequency of the LC tank oscillator. Thus the concentration of cells in a solution, affecting its permittivity, is read out as the frequency of the oscillator.

1. Introduction
Dielectric spectroscopy has been effectively used for decades to characterize biomaterials, giving information about membrane capacitance of cells, intra-cellular organells, etc [1]. However characterization of concentration of a particular cell species in a suspension, based on dielectric measurements is yet to be explored in a broader aspect. In this paper we explain the proposed theory of dielectric measurement to characterize the concentration of cells in a suspension and also describe a CMOS sensor which is used for the above purpose.

A new era of biosensors has been ushered in with the establishment of solely electrical measurement based label free sensing techniques. Typical biosensors, especially based on optical principle are affinity based and require selective target analyte combination for functioning [2]. These sensors are faced with the challenge of a complex read out mechanism usually based on fluorescence detection [3]. The advantage of simple read out circuits coupled with the ease of fabrication of CMOS or BiCMOS circuits have therefore made electrical biosensors very lucrative.

In this work we propose a solely electrical measurement based biosensor to detect the concentration of cells in a biological cell suspension operating at a frequency around 12 GHz. Jarić et al performed capacitive measurements of cells at 2 GHz [4]. However it has been reported that dispersion mechanisms of biomaterials especially DNA can exist up to 5 GHz to 7 GHz [5]. Hence we selected a frequency of operation above this frequency and slightly below the characteristic frequency of water (17 GHz). Interdigitated capacitor (IDC) has been used as the sensor element. The IDC structure is coupled with inductors, to form an LC oscillator whose resonant frequency is a function of the permittivity of the solution underneath the sensor. The control circuit is a pair of cross coupled transistors, similar to a cross coupled VCO, with an output buffer stage. Thus a dielectric change in the solution due to change in concentration of cells in it is detected as the frequency change of the oscillator.
2. Dielectric Dispersion Modelling

Biological cell suspensions show three noted dielectric dispersions over the frequency range of 1 Hz to 100 GHz, namely α dispersion, β dispersion and γ dispersion respectively [5]. The α and β dispersions are principally low frequency phenomenon up to few hundred megahertz, arising mainly because of interfacial polarisation and Maxwell Wagner polarization mechanism respectively. However in this work mainly γ dispersion of the cell suspension is taken into account as the operating frequency of the sensor is centred around 12 GHz, close to the characteristic frequency of water at 17 GHz. The γ dispersion of a cell is caused by the polarization of the water molecules within it. The effective dielectric constant of the cell suspension is given by the Debye equation,

$$\varepsilon_{\text{sol}} = \varepsilon_\alpha + \frac{\Delta \varepsilon}{1 + (\frac{f}{f_c})^2}$$

where $\varepsilon_{\text{sol}}$ is the effective dielectric permittivity of the solution, $\varepsilon_\alpha$ is permittivity of the suspending medium at frequency $f$, also given by a similar Debye equation, $\Delta \varepsilon$ is the dielectric dispersion due to the presence of the cells, $f_c$ is the characteristic frequency of the dispersion process and $f$ is the measuring frequency. The static ($f=0$) permittivity change of the suspending medium is given as,

$$\varepsilon_s = \varepsilon_\alpha + \Delta \varepsilon$$

$\Delta \varepsilon$ is called the dielectric dispersion and is given by cellular parameters as,

$$\Delta \varepsilon = \frac{9\pi r P C_m}{\varepsilon_0}$$

where $r$ is the radius of the cell and $C_m$ is the membrane capacitance as shown in fig.1. $P$ is the volume fraction of the cells, which is dependent on the concentration of cells $N$. In this work we have considered a standard yeast cell of diameter 10 µm and $C_m=1\mu F/cm^2$.

$$P = \frac{4\pi r^3 N}{3V_{\text{channel}}}$$

$V_{\text{channel}}$ is the volume of the fluidic channel containing the cell suspension.

![Figure 1](image1.png)

**Figure 1.** Single shell model of yeast cell showing cell radius and membrane capacitance

It can be seen from equation (4) that the volume fraction for same number of cells $N$ can be increased by reducing the volume of the channel. Debye equation also determines the permittivity of water and is given as

$$\varepsilon_w = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + (\frac{f}{f_c})^2}$$

where $\varepsilon_s$ is the static permittivity of the water (suspending medium) and $\varepsilon_\infty$ is the high frequency permittivity. Therefore using equation (2),(3) and (4), the permittivity of the solution can be written as
The permittivity of the cell suspension with respect to the concentration of cells is shown in fig. 2. At the operating frequency, 12 GHz, the slope \( \frac{\partial \varepsilon}{\partial N} \) is approximately 2, that is, for single cell the permittivity changes by 2.

\[
\varepsilon_{\text{cell-sol}} = \varepsilon_{\infty} + \frac{\varepsilon_{\infty} - \varepsilon_{0}}{1 + \left(\frac{f}{f_0}\right)^2}
\]

3. Sensor Circuit Design

As mentioned above interdigitated capacitor is used for sensing the permittivity of biological cell suspension. The resonant frequency of the IDC coupled with two inductors \( L \) is dependent on the capacitance of the IDC with the standard relation,

\[
f = \frac{1}{2\pi(LC)^{0.5}}
\]

The ratio of the capacitance of the IDC with air as the dielectric material to the capacitance with cell suspension gives the information about the permittivity of the cell suspension,

\[
\frac{C_{\text{IDT[Air]}}}{C_{\text{IDT[sol]}}} = \frac{F(\varepsilon_{\text{air}})G(\text{geom})}{F(\varepsilon_{\text{sol}})G(\text{geom})}
\]

where \( G(\text{geom}) \) is the function of the geometry of the IDC obtained from conformal mapping techniques [6] and \( F(\varepsilon) \) is the function of permittivity. From equation (7) and equation (8), the ratio of the resonant frequencies can be obtained as,

\[
\frac{f_{\text{air}}}{f_{\text{sol}}} = \left(\frac{F(\varepsilon_{\text{sol}})}{F(\varepsilon_{\text{air}})}\right)^{0.5}
\]

The IDC is fabricated from the top metal 2 of 250nm process of IHP. The core VCO circuit is shown in fig. 3 along with the IDC. The transistors M1, M2 and M3 form the current source for the oscillator and the transistors M4 and M5 are used as the cross coupled pair for negative resistance to sustain the oscillations.

![Figure 2](image1.png)

**Figure 2** Permittivity with respect to number of cells in the biological suspension.

![Figure 3](image2.png)

**Figure 3 (a)** The core VCO control circuit for the oscillator. **(b)** Circuit layout with the IDC sensor
The sensors are often passivized using a thin layer of SiO$_2$ or Si$_3$N$_4$ of about 300 nm thickness. This influences the sensitivity of the measurement and had to be carefully taken into consideration while designing the VCO and the IDC. Fig.4 shows the FEM simulated variation of capacitance of IDC due to change of permittivity of a biological cell suspension flowing through a capillary placed on top with different passivation thickness. No major effect due to the passivation is noted from the slope of the curves up to 1µm thickness of passivation which makes this concept a good candidate for several practical applications.

![Figure 4](image)

**Figure 4 (a)** Variation of capacitance of IDE with respect to permittivity of biological suspension **(b)** Variation of resonant frequency with permittivity of solution

Fig 4 (b) shows the variation of resonant frequency with the permittivity of the solution. Approximately 130 MHz, of frequency shift is noted for a unit change of permittivity for ideal case.

### 4. Conclusion

The theory of dielectric permittivity measurement to determine the concentration of a cell species in a biological cell suspension is explored and established in this work. The frequency range around 17 GHz has been identified to be relevant to perform this measurement as it avoids the dispersions mechanisms at lower frequencies ($\alpha$ dispersion, $\beta$ dispersion). At this frequency, concentration of the cells is the dominant parameter for change in permittivity of the cell suspension. An easy and effective read out circuit based on a cross coupled VCO topology has been proposed and designed. A sensitivity of 130 MHz per unit permittivity has been obtained in simulation. Furthermore, the influence of the passivation on top of the chip has been investigated; it has been shown that no major effect is noted for a thickness up to 1µm. The Typical passivation thickness for the used process is 300nm. Hence the almost constant sensitivity up to a passivation thickness of 1µm is a highly relevant aspect for the practical applications of such a sensor and makes it a realistic solution for use in most biological environments.

### References

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