A CMOS blood cancer detection sensor based on frequency deviation detection.

R. Nagulapalli, K. Hayatleh, S. Barker, S.Raparthy and F J Lidgey

This paper proposes a technique to detect Leukaemia (blood cancer) based on the frequency modulation of a relaxation oscillator by changes in the dielectric constant of blood cells. A novel 16-bit frequency detector with a digital output has been proposed to detect the frequency difference between two oscillators based on healthy blood and Leukaemic blood. A circuit has been designed, to operate on a 1.2V supply, post layout simulations shows 0.35mA current consumption. The chip Area including pads~0.6mm∗0.45mm.

Introduction: Recently, there has been a lot of interest generated in IC design in the Bio-medical domain, particularly in disease detection techniques, for example, the detection of cancer cells in blood. The fundamental principle behind the sensor is that any material subjected to change (could be density change or contaminated by another material) leads to a change it its die-electric constant [1]. By detecting the dielectric constant variation due to cellular changes, we can quantitatively measure how much the cellular material is contaminated. For example, pure blood will have a certain dielectric constant, but cancerous blood will experience dielectric constant changes due to the presence of cancer cells. The quantitative treatment of biological cell dielectric constant variation has been studied [2][3] in the literature, where it has been demonstrated that biological cell suspensions show three noted dielectric dispersions over the frequency range of 1 Hz to 100 GHz, namely α, β and γ dispersion [2] .The α and β dispersions are relatively low frequency phenomena up to few hundreds of MHz, arising mainly because of electrode polarization and Maxwell Wagner polarization mechanism respectively. The frequency used in this work is 1GHz, hence γ dispersion is the only considered dispersion. An approximate effective dielectric constant of a cell suspension is given by the Debye equation [2],

$$\epsilon_{blood\_cancer} = \epsilon_{blood\_pure} + \frac{\delta\epsilon}{1+\left(\frac{f}{f_c}\right)^2}$$

$$\text{Where } \delta\epsilon(\text{cel parameter}) = \frac{9PrC_m}{\epsilon_0}$$

where r is the radius of the cell and Cm is the membrane capacitance. P is the volume fraction of the cells, which is dependent on the concentration of cells. From the above equation it is clearly evident that any substance dielectric constant depends on the concentration of the cell. A simple way to detect dielectric constant is to form a capacitor where the insulator (dielectric) is replaced by the material under consideration, hence any capacitance changes can be detected electrically. Generally, capacitance can be easily measured by incorporating the capacitance in an oscillator and measuring the frequency change. Few publications have dielectric constant detection by a single oscillator. Guha Demonstrated a dielectric change detection of the material by using an LC-oscillator [4], but there is no frequency detector to measure the change other than passing the sample by through a spectrum analyser, which is only suitable in the lab environment and not for integrated applications. Other researchers [5][6] have demonstrated frequency modulation by use of an LC-Oscillator, and frequency change detection with a PLL by measuring the control/error voltage deviation and converting this voltage into digital format with an ADC. However, this detection method occupies a large silicon area for the PLL loop filter, and consumes more power due to ADC and axillary circuitry. All the above mentioned works which are based on an LC oscillator, are not low power, and cannot reliably produce oscillations when a wide range of frequencies is expected due to a wide variation in the material properties [7]. A low power integrated design presented here is based on a relaxation oscillator and 16-bit digital frequency detector, which will overcome these disadvantages.

Sensor description: The present proposal is based on the fundamental principle that due to the increment in cancer cells based on cancer progression, the capacitance detected by the system will increase. On comparing the capacitance with a reference sensor which contains pure blood with that of which contains cancerous blood, we can detect the

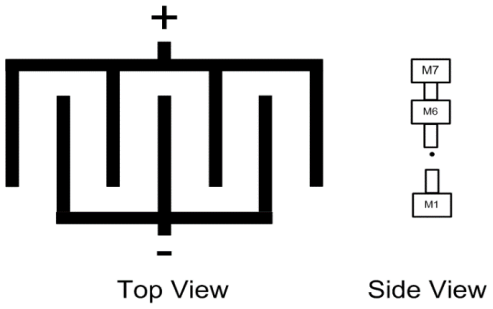

Fig. 1 *Sensor architecture (top view and side view)*

concentration of cancer cells. The interdigitated capacitance based sensor shown in Fig:1 has been chosen due to ease of its implementation and modelling [3]. This sensor has been implemented in CMOS 45nm technology, and metal layers used are from Metal-8 to Metal-1 (Fig. 1 side view shows the metal stack and via stack). Sensor size is ~ 95u*95u (shown in the layout) with 18fF intrinsic capacitance, with pure blood (dielectric constant-58) its capacitance will be ~1pF (in the current design an ideal material with K=58 instead of blood has been used). Since blood needs will be placed onto the sensor, it needs a top layer opening as well as passive opening similar to what we do for the pads. One sensor will have healthy blood and another will have cancerous blood. The sensor carrying cancerous blood will have higher capacitance due to higher dielectric constant.

Detection principle: The easy of detecting a capacitance change is to form an oscillator which is relying on sensor capacitance, such that the change in the capacitance will cause a frequency change which can easily be measured. As shown in Fig. 2, a Reference Oscillator is utilised by sensor-1 (containing pure blood) oscillating at ~1GHz whilst the Sensing Oscillator based utilising sensor-2 (containing cancerous blood) will oscillate at a lower frequency. Hence by detecting the frequency difference we can estimate the capacitance change, and hence, the relative volume of cancerous cells. Often, frequency detectors output narrow pulses, but in this paper a new frequency divider based counter has been implemented, which outputs 16-bit digital words, making it suitable for digital processing. Since this method relies on the difference of the frequencies between two very similar oscillators, any temperature drift or process variation (typically any CMOS technology will have transistors parameters variation) will be exactly same for the both of the oscillators and cancelled, as the variations will affect both oscillators.

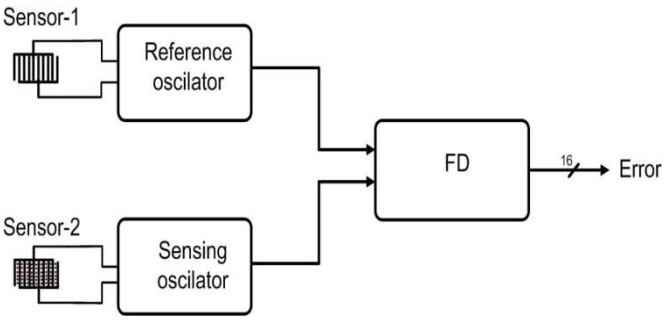

Fig. 2 *capacitance change detection concept*

In principle there are three types of oscillators: Ring, LC, and relaxation type oscillators. Due to the need for two exactly matched

oscillators, LC is not appropriate because the two inductors can influence each other [3] through substrate coupling or electromagnetic coupling. To solve this coupling issue, inductors are often separated by 2 to 3 times of their size (~300um), hence a comparatively large area will be needed for these oscillators. Additionally, LC oscillators are sensitive to power supply noise, meaning the frequency is affected by supply voltage variations. A multi-stage Ring oscillator needs multiple sensing capacitors, which is not a good option from the integration point of view, and the frequency of a ring oscillator is not only a function of capacitance, but also of transistor resistance. Sensitivity of a sensor is defined as change in frequency (or digital o/p) for a given change in sensor parameters (capacitance in the current scenario). In the case of LC oscillators, frequency depends on $C^{-0.5}$, means a 10% change in the sensor capacitance will give a 5% change in the frequency, whereas for a relaxation oscillator, the frequency depends on C^{-1}, means a 10% change in the capacitance will give a corresponding 10% change in the frequency, thus the relation oscillator has a higher sensitivity. For all the reasons above, a relaxation oscillator would be the best approach. Additionally, the frequency is relatively unaffected by changes in the supply voltage and only depends on sensor capacitance. Fig. 3 shows the relaxation oscillator circuit [8], which is based on the series charging and discharging of an RC network. Voltage across sensor capacitance varies from vcc/3 to 2Vcc/3 as shown in Fig. 3, which oscillates according to the following expression.

$$F_{osc}=\frac{0.5}{R_t C_t \ln 2}$$

Where Rt is the filter resistance and Ct is the Sensor capacitance with pure blood Ct+δC (δC is change in capacitance due to cancer)

Reference frequency $(Fr) = \frac{1}{2RtC_t \ln 2}$ (1)

Sensing Frequency= $Fs=\frac{1}{2Rt(C_t+\delta C)\ln 2}$ (2)

From the equations (1) & (2) we can derive change in the capacitance as

$$\delta C=\frac{F_r-F_s}{F_r}C_t \quad (3)$$

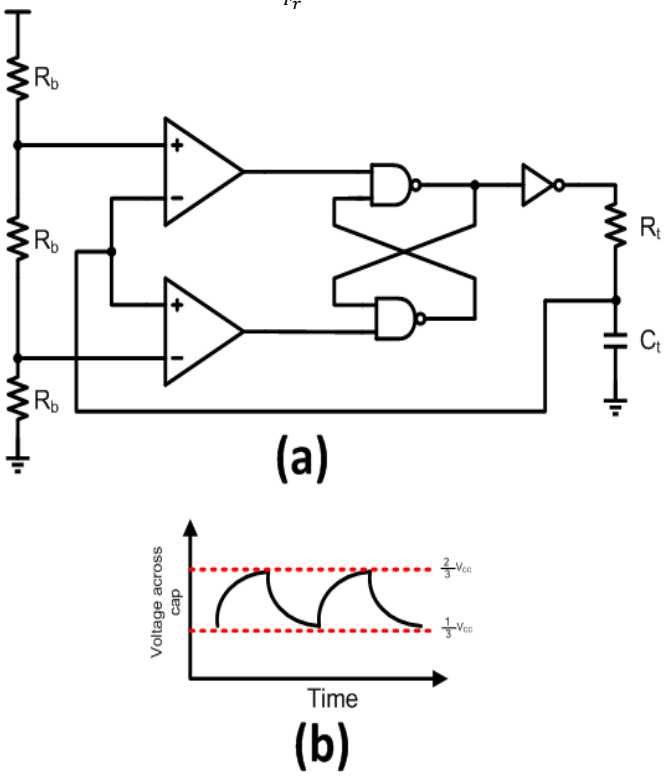

Fig. 3 (a) *Conventional Relaxation oscillator (b) voltage across sensor*

Proposed Frequency detector(FD): The Frequency detector receives signals from both the reference oscillator and sensing oscillator. The function of this detector is to sense the frequency difference, and output this difference in a digital format, which can then be read by a microprocessor. Fig. 4 shows a load-able flip flop, which consists of a multiplexer and flip-flop. When the Multiplexer Control Signal (S) is high, the flip-flops' complimentary output will be fed to the data input, hence it behaves as a (1/2) frequency divider. When S is low, it remains in 'freeze' state, which means it acts as memory and ceases any flip-flop action. Fig. 5 shows the complete circuit diagram of the frequency detector. It consists of reference and sense frequency counters which are driven by reference and sense frequency signals generated by the oscillators. Each counter is designed using loadable flip-flop (Fig. 4).

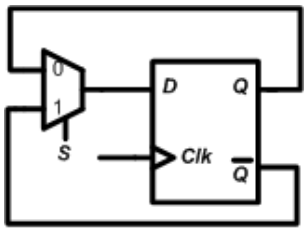

Fig. 4 Loadable flip-flop.

Asynchronous counters were chosen instead of synchronous due to their lower complexity and low power consumption. However, this can come at the cost of a glitch-problem during majority code transition, which fortunately is not an issue in this application. This is because the principle of detection relies on the final output of the counter, and does not depend on the intermediate output. When the reference frequency (1GHz) is applied to the 16-bit reference frequency counter, it counts to 2^{16} cycles. Once it reaches the max limit, the 16-input NAND generates a freeze signal. This freeze signal is fed to the sense reference counter, whose counting speed is slower because its input signal is driven by a lower frequency than the reference frequency. As soon as the freeze signal goes low, the sensor counter also freezes at some intermediate state (depending on the frequency difference). The states of the sense frequency counter flip-flops indicate the frequency difference between the two input signals, as explained below. The reference frequency counter counts for 2^N cycles at F_{ref} frequency.

Freezing time= $\frac{2^N}{F_{ref}}$ (4)

Assuming the Counter counts up to K during this time, then the counting time= $\frac{K}{F_{sense}}$ (5)

Since both counters stop at the same time we can equate equations (4)&(5), Hence $F_{sense}=\frac{K}{2^N}F_{ref}$ (6)

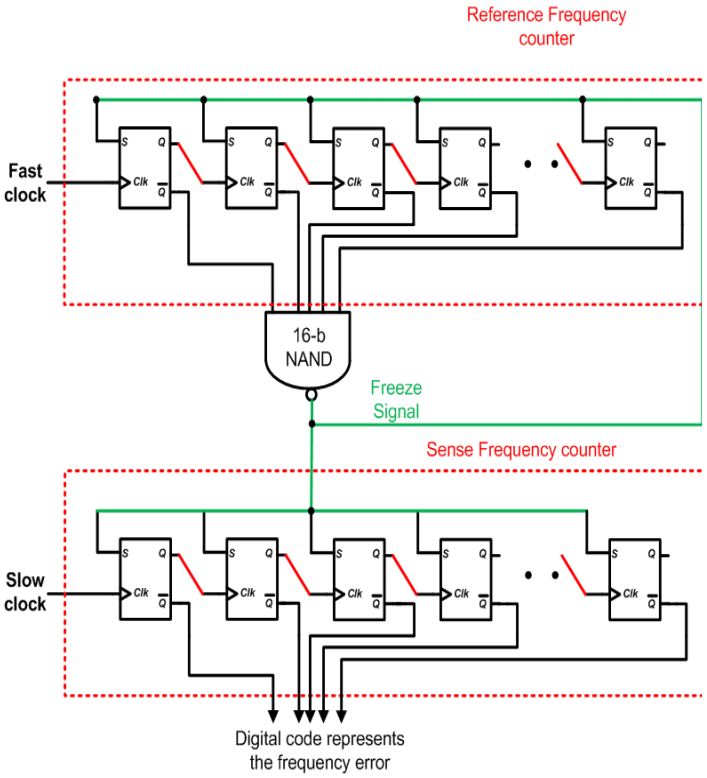

Fig. 5 *Frequency detector Architecture.*

Results: A Transistor level circuit has been implemented as per the principle explained above, and extensive simulations on the layout have been undertaken. Senor 1 was loaded with 1pF and 1.273pF capacitors in the simulations, and according to equation (1), they oscillated at 1GHz and 785MHz respectively. A high frequency oscillator will present higher sensitivity and a more compact sensor size (the lesser the frequency, the lesser the capacitor requirement from equation (1), but the frequency detector will take more power. Considering this, from simulations we found 1GHz is optimal in terms of power consumption and sensitivity. In Fig. 6 the top waveform is actually a staircase waveform, but in lower resolution it looks like straight line and shows some glitches due the asynchronous counter implementation. It represents the reference clock number of cycles and as expected the counter was frozen in 2^{16} cycles. The bottom curve shows the sense frequency counter number of cycles and it is freezing at 49281 binary code, and is clearly lagging behind the reference clock. According to equation (6) the sensing oscillation frequency can be estimated around ~752MHz. Clearly, this change in frequency can be calculated by how far is the frozen code is from all '1s' case (decimal:2^{16}). If the deviation is less, it means capacitance is very close to the reference capacitance, hence can be stated that no dielectric change (cancer) is detected.

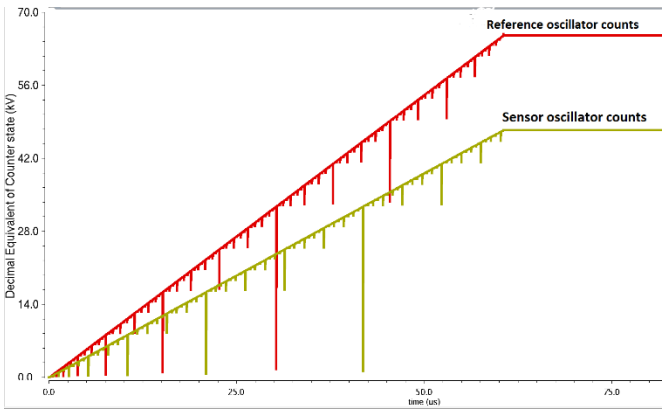

Fig. 6 *Simulation results (Y-axis represents counter state in Decimal and X-axis represents time)*

For final verification of the concept, the sensor capacitance was swept from 1.1pF to 2.9pF and the frozen code in decimal was analysed using estimated frequency versus capacitance, according to equation (6) in Fig. 7. The simulated frequency and estimated frequency was correct to within 0.16MHz. Fig. 5 shows the layout of the complete architecture, it is a pad limited layout due to 16 bit read out.

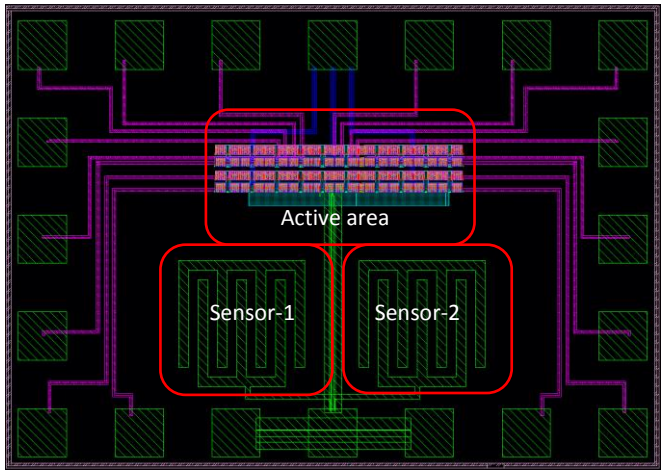

Fig. 7 *layout snapshot.*

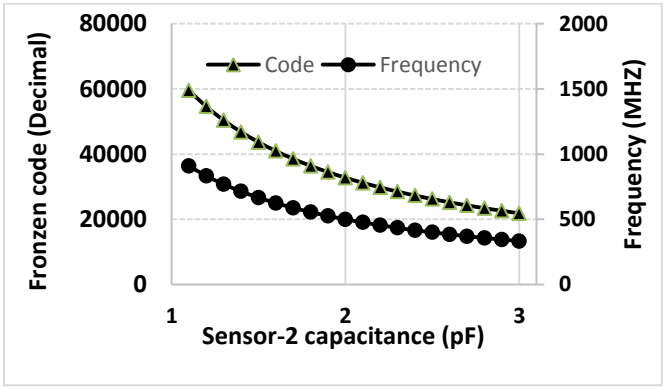

Fig. 7 *Frequency and frozen code VS capacitance value*

Conclusion: A concept has been proposed to detect blood cancer using frequency deviation detection with a digital readout and fine 15kHz resolution using a relatively simple low power device. A transistor level simulation with the layout shown and results have been generated by sweeping the capacitance of the substance rather a real blood.

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