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ISFET for Epigenetic Reaction Monitoring

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***Abstract*—Genetic disorders are increasing from generation to generation and they are difficult to detect. De-oxy ribose nucleic acid, DNA is the basic building block that determines the genetic characteristics of all organisms including human beings. DNA methylation is the process by which methyl (CH_3) groups are added to the DNA molecule. Some diseases like cancer will change the methylation rate. By knowing the methylation rate such genetic disorders can be identified and treated in the most suitable manner. The traditional methods for DNA methylation detection require specialized laboratory equipments and relatively large quantities of DNA sample. To overcome these disadvantages CMOS-ISFET (Complementary Metal Oxide Semiconductor-Ion Sensitive Field Effect Transistor) sensors can be used. CMOS based ISFET is the recently developed active device that is apt for DNA methylation detection since it is highly sensitive, cost effective and consumes lesser area. The proposed work includes the software simulation of the CMOS ISFET sensor for effective DNA methylation detection.**

Keywords— DNA methylation; ISFET; pH; Op-amp.

I. INTRODUCTION

Genetic disorder is any disorder that is caused by an abnormality in an individual's DNA. The basic physical unit of inheritance in DNA carries instructions to make proteins. Certain changes that does not involves any change in DNA nucleotide sequence termed as epigenetic reactions can cause cells to evade normal growth controls and becomes cancer [1]. Genetic changes that promote cancer may be inherited from parents to child that means even though the parents are not directly infected by cancer they may be carriers. In such cases the early detection becomes nearly impossible since they are not aware about it.

Awareness is not a solution to this problem. The cancer detection techniques used at present are not convenient to the common people since they requires larger quantities of DNA sample, are not cost effective and consumes larger area. Also they demands a specialized person and bulky equipments. To overcome the drawbacks of the existing methods we can use a CMOS ISFET based techniques. By using this system we can replace the bulky instruments with a handheld device. ISFET based methods make use of DNA methylation rate as criterion to detect cancer [2].

II. DNA : THE GENETIC MATERIAL

DNA (De-oxy ribose nucleic acid) is the genetic material of almost all the living organisms including human and is a thread like structure carrying the genetic information.

A. DNA Bascis

DNA is the basic building block that determines the genetic characteristics of all organisms including human beings, which is having three building blocks. They are pentose sugar, phosphate group and nucleotides. DNA is formed by the repetition of these building blocks [3]. The four basic nitrogenous bases in nucleotides are Adenine (A), Thymine (T), Guanine (G) and Cytosine(C). The location of DNA is shown in Fig. 1.

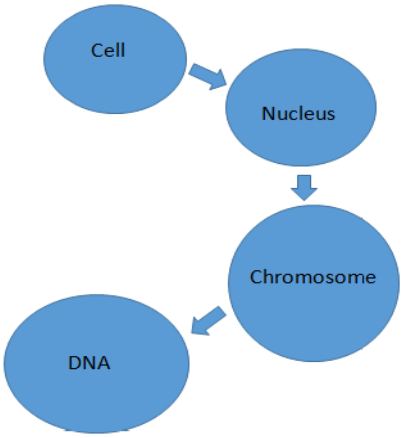

Fig. 1 The location of DNA.

The biochemical information needed for DNA methylation to be detected by the ISFETs is obtained as a result of DNA amplification of the methylated region of the DNA sample taking place. This would be based on a DNA chain extension or elongation reaction [4].

B. DNA Methylation

DNA methylation is the process by which methyl (CH3) groups are added to the DNA molecule. Some genetic diseases like cancer will change the methylation rate. Thus by detecting the rate of methylation such diseases can be detected more easily. Fig. 2 shows the process of DNA methylation [5].

Certain disruptions that are the consequence of aberrancies in the methylation levels of some areas may significantly influence the mechanisms behind the initiation as well as the progression or recurrence of cancer or they may affect whether or not certain drugs are effective as parts of a therapy scheme on an individual patient [6].

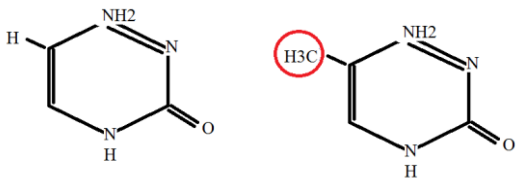

Fig. 2 DNA methylation process

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III. EXISTING TECHNIQUES FOR DNA METHYLATION DETECTION

The samples used for analysis of DNA methylation biomarkers usually contain high concentrations of background DNA from the tumour. However, tumour-derived DNA is difficult to be detected because it is often present in very low concentrations and can be contaminated substantially with the DNA from the healthy cells. Moreover, DNA methylation is not evenly distributed across the genome. Thus, methods with sensitive detection capabilities are often needed to identify aberrantly methylated tumour-derived DNA in body fluids [7]. As has been summarised by [8], the combination of different types of pre-treatment of sample DNA, followed by different analytical steps, has resulted in a plethora of techniques available for determining DNA methylation patterns and profiles at a genome-wide level.

The techniques used at present have some drawbacks to overcome and is the reason by which we are looking for a new system [9]. The existing techniques are:

A. HPLC-UV

The technique of HPLC-UV (high performance liquid chromatography-ultraviolet) is still used because it is considered to be a standard technique. However, the utility of this method is significantly limited by the need for specialized laboratory equipment and the requirement of relatively large quantities of the DNA sample to be analysed.

B. LC-MS

Liquid chromatography coupled with tandem mass spectrometry (LC-MS) is an alternative high-sensitivity approach to HPLC-UV, which requires much smaller quantities of the DNA sample. The necessary expertise and equipments are not wide spread and thus is not a commonly used technique.

C. ELISA -Based Methods

There are several commercially available kits, all enzyme-linked immunosorbent assay (ELISA) based, that enable the quick assessment of DNA methylation status. But they are prone to high variability and suitable only for the identification of large change

D. AFLP and RFLP Based

Detection of fragments that are differentially methylated could be achieved by traditional PCR-based Amplification Fragment Length Polymorphism (AFLP) Restriction Fragment Length Polymorphism (RFLP) or protocols that employ a combination of both. The disadvantage is that it has only poor resolution.

IV. CMOS ISFET

CMOS ISFETs or CMOS based Ion Sensitive Field Effect Transistors are developed to measure the pH changes. It converts the pH value at the input and the output voltage represents that pH in voltage format. The voltage obtained at the output of ISFET is an indication of methylation at the input DNA and thus we can detect the disease easily. CMOS technology can be incorporated with ISFET and there by large scale arrays can be implemented [10].

A. Capacitance dependent ISFET model

The gate electrode of the ISFET is removed and is modified to a floating gate structure. A layer made up of Si_3N_4 is used as a passivation layer to act as an ion sensitive layer [11]. Ag/AgCl electrode in the electrolyte solution acts as the remote gate. The basic structure and capacitance model is shown in Fig.3. The V_{chem} is a function of the pH variation due the methylation process.

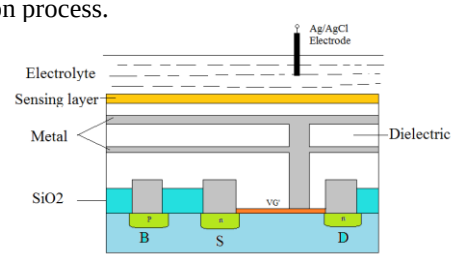

Fig. 3 Basic structure of ISFET

The definition of the ISFET as a pH sensing device without a metal gate, in contact with an electrolyte and a reference electrode, can be expanded to an ion-sensitive gate whose threshold voltage can be modulated by changes in the ionic concentration or the pH of the solution. The threshold voltage of the ISFET exhibits a dependence on the pH variations in solution [12].

B. The Readout Scheme

A simple ISFET pixel is shown in Fig .4. Each pixel has three transistors MN_0, MN_1 and MN_2 and are used as ISFET device, row select device and reset device. This is similar to the DCVS logic. It has a precharge phase and pH sensing phase. During precharge phase the node N_1 is charged to the supply voltage, V_{DD}. The charge stored will discharge to the ground potential. The discharge time depends on the pH value at the input. In other words, discharge time is a function of the drain current of the ISFET. Thus pH change is converted to the corresponding time variation. By turning off the switch S_0 this time variation can be converted to the corresponding output voltages [13]. Thus the conversion becomes complete.

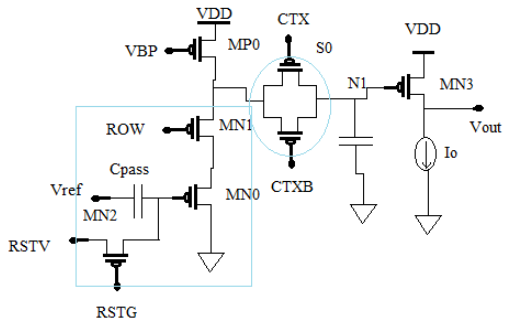

Fig. 4 pH to Time to Voltage Readout Scheme

V. PH-BASED DNA METHYLATION DETECTION SYSTEM

Operational amplifiers are the electronic circuit elements which are capable of doing many operations in different configurations. One of the functions that is important to us is to compare two values [14]. The output of ISFET is a voltage proportional to the methylation rate. An opamp can be

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used here to compare this voltage level with a standard reference value. The proposed system is shown in Fig. 5.

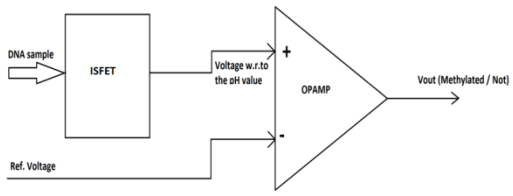

Fig. 5 pH-based DNA methylation detection system

The output of the system will be a logic high or a logic low representing methylated or unmethylated DNA at the input. If we are not bothered about the operating speed and we need a stable output then we can go for pH-based DNA methylation detection system.

VI. RESULTS AND DISCUSSION

The schematic diagram of the proposed system is shown in Fig. 6. The system is simulated using Cadence IC6.1.6. The output waveform is shown in Fig. 7. The layout of the system is shown in Fig. 8.

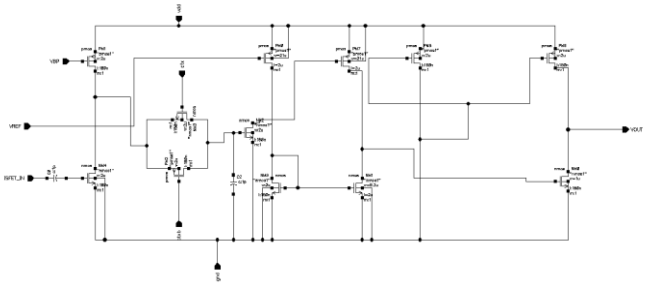

Fig. 6 Schematic diagram of pH-based DNA methylation detection system.

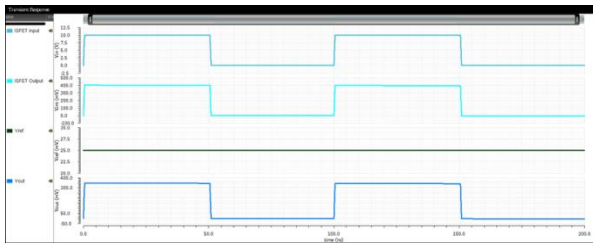

Fig. 7 Output waveform of pH-based DNA methylation detection system

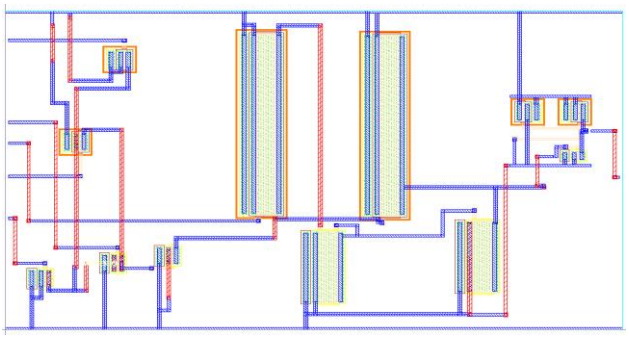

Fig.8. Layout of pH-based DNA Methylation Detection System

VII. CONCLUSION

CMOS ISFET has great potential for methylation detection. It has the advantages of high sensitivity, cost effectiveness and consumes lesser area. But, the proposed system is not capable of calculating the amount of methylation and thus the probability of being infected by the disease like cancer. The system can be upgraded in future by including the provision for that. Also, future works may include the hardware simulation and clinical testing of the CMOS ISFET sensor for effective methylation detection.

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