Investigation on DNA sequencing array using 180nm technology

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***Abstract*— This paper addresses the design of a DNA sequencing array from 180nm VLSI (Very Large-Scale Integration) technology to enhance DNA sequencing as faster. cost-effective, and accurate genomic analysis. Based on the Human Genome Project (HGP) the work demonstrates how CMOS fabrication techniques have evolved into integrated biosensor systems with improved sensitivity and scalability. Experimental results from the designed circuits are simulated on Cadence, showing the possibility of efficient bio-signal detection with low noise performance. Integrating VLSI technology and biotechnology accelerates genomic research and lays the groundwork for portable, point-of-care diagnostic tools and personalized medicine. This paper also shows the improvement of DNA sequencing processes and aims to address the limitations through efficient circuit design and simulation-based validation.**

Keywords*— *DNA sequencing, CMOS sensor, 180nm technology, bioelectronics, DNA microarray. biosensors

1. INTRODUCTION

The Human Genome Project (HGP) was launched in 1990, to identify, map, and sequence all the genes in the human genome [1]. It aimed to determine the complete sequence of base pairs that constitute human DNA and to analyze the genome The project was completed in 2003, laying the groundwork for advances in genomics, biotechnology, and personalized medicine [1]. HGP paved the way for Next Generation sequencing which enabled the sequencing of thousands to millions of DNA molecules simultaneously [2].

Current Biological research and Biotechnology are based on DNA sequencing, which measures the unique arrangement of nucleotides (adenine, thymine, cytosine, and guanine) within a DNA molecule. It is crucial for a large number of applications, including forensic identification, personalized medicine, evolutionary biology, genetic disease diagnostics, and plant and animal improvement. When the Human Genome Project was completed in 2003 and the first human genome was sequenced, genomics entered a new era. Since then, studies in biomedicine and clinical diagnostics have been fundamentally transformed by the ability to read out genetic information swiftly and precisely.

Despite significant advancements, challenges remain in achieving faster, more affordable, and user-friendly DNA sequencing—particularly for point-of-care diagnostics and applications in resource-limited settings. Traditional sequencing methods, including Sanger sequencing and even advanced Next-Generation Sequencing (NGS) platforms, still rely on bulky, expensive equipment, substantial reagent consumption, and labor-intensive workflows. These limitations have driven the development of lightweight, energy-efficient, and scalable sequencing systems capable of delivering real-time results with high sensitivity and low noise.

An apparatus for detecting a transient electrical signal in a sample is offered. Systems subject apparatus also are that incorporate the presented. The subject apparatus and systems have utility in several applications, more specifically in the characterization of a sample, most specifically in the characterization of molecular entities in the sample The subject methods will shortly command and render DNA sequencing an everyday aspect of genetic research [7].

It also outlines a bioluminescence detection lab-on-chip with an immobilized luminescent reporters/probes fiber-optic faceplate directly coupled to an optical detection and processing CMOS system-on-chip (SoC) in a 0.18-/spl mu/m process [9].

In this regard, the integrated DNA sequencing functionality into electronic devices using CMOS technology offers an effective and scalable solution. CMOS-based biosensors provide several advantages, including high integration density, low power consumption, and cost-effective mass production. When implemented using 180nm technology, CMOS biosensors demonstrate strong performance while minimizing area and maintaining design simplicity. Furthermore, these circuits allow for co-fabrication with signal processing and control electronics, enabling the realization of fully integrated lab-on-chip systems.

In this paper, we examine a new technology for DNA sequencing array on 180nm CMOS technology which promises high throughput low noise, and low cost. The design comprises the sequencing arrangements of major circuit blocks like NAND logic gates, differential amplifiers, current

sources, pulse generators, and dynamics. The method is based on the principle of sequencing-by-synthesis (SBS), Simulation and verification are accomplished with the Cadence Virtuoso design environment for providing transient analysis and performance.

The content of this paper is organized as follows. Section 2 presents the Literature survey. Section 3, examines how VLSI-enabled integrated circuits address DNA on 180 nm technology. Section 4, provides the results and discussions. Section 5, highlights the pros and cons of the existing systems and followed by the conclusion and future challenges which are presented in Section 6.

2. LITERATURE SURVEY

2.1. R. Singh, D. Ho, A. Nilchi, G. Gulak, P. Yau and R. Genov, "A CMOS/thin-Film fluorescence Contact Imaging Microsystem for DNA Analysis," TCAS-I, Vol 57, No. 5, pp. 1029-1038, May 2010

In this journal, authors have developed a compact imaging system that combines a CMOS with a special thin-film optical filter to detect fluorescence signals like those used in DNA testing. The system includes a 128×128-pixel sensor made with standard manufacturing methods and a filter that blocks out unwanted light from a green laser (532 nm) very effectively [8]. The investigated microsystem's performance is validated experimentally by imaging spots of Cyanine-3 fluorophore. Finally, a human DNA microarray has been imaged with the sensor prototype.

2.2. B. Jang, P. Cao, A. Chevalier, A. Ellington, A.Hassibi, "A CMOS fluorescence-based Biosensor Microarray," ISSCC, pp. 436-437, Feb 2009.

Currently, in the field of biotechnology, one of the most important analytical tools is Biosensors. The detection systems help to identify and detect different analytes such as toxins, hormones, DNA strands, proteins, bacteria, etc by taking advantage of the selective interaction and binding of certain biological molecules. The advantage of array-based biosensors compensates for the signal-to-noise ratio and detection in the dynamic range. The capability of the array-based biosensors to detect multiple analytes simultaneously. Nowadays, bulk array sensors are in use termed as micro arrays[10].

2.3. E.R. Mardis, "Next-Generation DNA Sequencing Methods," Annual Review of Genomics and Human Genetics, pp. 387-402, Jun 2008.

New scientific discoveries from the results of the application of next-generation DNA sequencing technologies focus the massive parallel platforms on genetics [1]. Developments in sequencing technologies have allowed for comprehensive analysis of DNA and RNA at a single-base level, including complete cDNA, SAGE, and the identification of noncoding RNAs. Next-generation sequencing has further advanced investigations of ancient DNA and environmental metagenomics, presenting significant opportunities for genetic and biological research [1].

2.4. .D.R. Bentley, Whole-genome re-sequencing, Curro Opin. Genet. Dev. 16 (2006),pp. 545-552

DNA sequencing helps scientists learn about genes, genetic differences, and how genes work—important for biology and medicine. As more reference genomes become available, researchers will start re-sequencing whole genomes more often, but to do this on a large scale, sequencing needs to become much cheaper and faster. New technologies are being developed to produce huge amounts of DNA data quickly, which can then be compared to known reference sequences. The big challenge is to keep the high accuracy and quality of earlier genome projects. Soon, these new methods are expected to take over and make DNA sequencing a regular part of genetic research [6].

2.5. Margulies et. al., "Genome sequencing in microfabricated high density picolitre reactors," Nature, pp. 376-380, Sep 2005. 454

Scientists have developed a new, faster, and cheaper way to read DNA. Instead of using older, slower techniques, this system can read 25 million DNA letters in just four hours and gets it accurate 99% of the time. It works using tiny wells on a special slide and a method that copies DNA in small droplets. They tested it by reading the DNA of a small bacteria called *Mycoplasma genitalium* and managed to cover almost all of it with super high accuracy — all in just one run in the machine [2]. This is a significant advancement for DNA research, making it faster and easier to study genes.

2.6. Ronaghi et. al., "DNA Sequencing: A Sequencing Method Based on Real-Time Pyrophosphate," Science, pp. 363-365, Jul 1998.

This technique reads DNA by detecting pyrophosphate (a molecule released when DNA is built) in real time when new bases are added. When a base is correctly added to the growing DNA strand, pyrophosphate is released. This pyrophosphate triggers a series of chemical reactions that produce light. The amount of light tells us which base (A, T, C, or G) was added. By repeating this process, the DNA sequence can be determined quickly and accurately [5].

2.7. F. Sanger et. al, "DNA Sequencing with chain-terminating inhibitors," PNAS, vol. 74, no. 12, pp. 5463-5467, Dec 1997.

Here a new method is described for determining nucleotide sequences in DNA [3]. It is the same as "the plus and minus" method by Sanger, F. & Coulson, A. R. (1975) J. Mol. Biol. 94, 441-448. But to achieve specific chain-terminating inhibitors of DNA polymerase in this method it was used 2',3'-dideoxy and arabino nucleoside analogs of the normal deoxy nucleoside triphosphates. The technique was tested on the DNA of bacteriophage varphiX174 and is faster and more accurate than the earlier method.

2.8. ED. Hyman, "A new method of sequencing DNA," Analytical Biochemistry, vol. 174, issue 2, pp. 423-436, Nov 1988.

DNA is sequenced through a chemical process that breaks the DNA molecule at a particular base guanine, adenine, cytosine (alone or paired with thymine). The DNA is tagged at one end, and when the DNA is sliced, the resulting fragment lengths indicate where base appears. Scientists separate the each fragments by size by passing them through a gel and then read the DNA sequence from the radioactive band pattern. This process enables the reading of at least 100 bases from the label end[4].

3. METHODOLOGY

3.1. Overview

This study employs a sequencing-by-synthesis (SBS) technique utilizing stepwise nucleotide incorporation as the digital signals from the NAND gate at the stage 1 sensor interface circuit stage. The methodology focuses on determining a DNA sequence by detecting pyrophosphate release upon successful nucleotide addition.

3.2. Sequencing Procedure

Sequencing was performed in cycles, with each cycle consisting of the following steps:

- Nucleotide Addition - A single deoxynucleotide triphosphate (dNTP) was introduced per cycle (A, T, C, or G) using a sensor Interface circuit.
- Signal Generation - If the generated dNTP was producing the output signal as, releasing pyrophosphate (ppi).
- Detection - Signal intensity was measured using a CMOS-based sensor array.

3.3. Signal Analysis

The digital signal was performed based on the cascading networks and plotted in bar graph format, with peaks corresponding to nucleotide incorporation events. The height of each bar indicated the number of identical bases incorporated as A, G, C, and T. This signal was aligned against the known cycle order of the sensor interface circuit to reconstruct the DNA sequence.

3.4. Sequence Reconstruction

The resulting signal profile was interpreted to yield the nucleotide sequence –

AGCTTTTTATGCGCGG
{AGCTTTTTATGCGCGG}AGCTTTTTATGCGCGG

The sequence was verified by comparison with the known reference, demonstrating the accuracy of this method.

3.5. Overall Architecture

The proposed analog front-end system was developed for high-precision photodetection in DNA sequencing applications. It consists of three core subsystems -

- **Pulse Generation Block** to model photodiode current responses.
- **Comparator and Clocked Sampling Unit** for signal digitization.
- The conceptual architecture was first formulated in block-diagram form and later translated into a transistor-level schematic using Cadence Virtuoso.

3.6. Transistor-Level Design

The circuit schematic was developed using 180nm CMOS technology, focusing on low power, high gain, and area-efficient design. The major design elements include -

- **Biasing Transistors** and current mirrors to ensure stable.
- A two-stage **capacitive integrator** to collect photogenerated charge.
- An **operational amplifier (op-amp)** for amplification with a 3.3V supply.
- A **clocked dynamic comparator** running at 1.8V for digital conversion.

Each transistor was sized to optimize gain-bandwidth trade-offs and minimize noise contributions. Custom-designed bias circuits ensured robustness against process-voltage-temperature (PVT) variations.

3.7. Simulation Setup and Validation

Simulations were conducted using the Spectre simulator within the Cadence ADE environment. Key setup components included -

- Input Source Modelling - A current pulse generator simulated photodiode responses under nucleotide incorporation events.
- Transient Analysis - Conducted over multiple clock cycles to verify amplification, integration, and comparator switching.
- Output Waveform Analysis - Nodes A, and B, were monitored, and signal transitions validated.

4. PROPOSED ARCHITECTURE

The proposed CMOS-based DNA sequencing circuit is designed using 180nm VLSI technology and it consists of three main functional blocks: the sensor-interface circuit stage, signal conditioning and amplification stage, and the output driver interface stage. The schematic is fully implemented and simulated in Cadence Virtuoso, verifying functionality and performance under existing operating conditions.

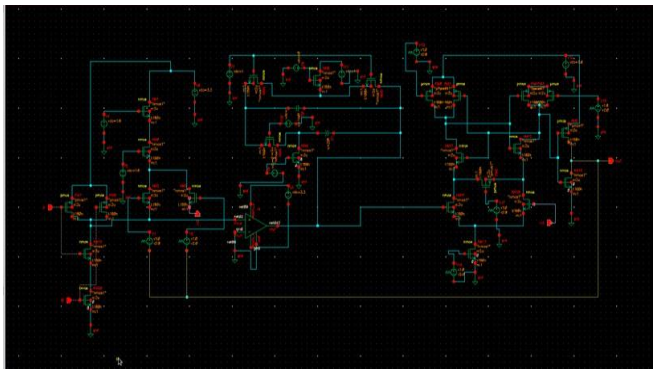

Fig.1. Transistor level schematic for the DNA Sequencing array by SBS method

4.1. Sensor Interface circuit stage

The main interface between the electrical readout circuitry and the biological environment is the sensor interface circuit termed as biosensing front-end. This block is in charge of converting biological processes into electrical signals that can be amplified and processed further on, such as DNA, ion concentration changes, etc.

The circuit's leftmost section incorporates a voltage-mode or current-mode transducer that simulates the electrical response of ion-sensitive field-effect transistor (ISFET) structures or DNA hybridization. Biochemical interactions are converted into electrical impulses by this front end. The design consists of PMOS and NMOS differential pairs to ensure high input sensitivity and minimize signal loss at the sensing interface.

Here, a CMOS NAND gate is used as a sensor interface circuit by taking advantage of the sensitivity of its input transistors to environmental or biochemical variation. This is the easiest method and the advantage is its simplicity and compactness of digital logic gates which enables the detection of biological phenomena through electrical parameter changes. NAND gate acts as a sensing PIXEL in the design.

4.2. Signal Conditioning and Amplification stage

The main section of the schematic features a series of cascaded gain stages along with an operational transconductance amplifier (OTA), which amplifies the weak biosignal to an appropriate voltage level for subsequent processing. The OTA is designed with a folded cascade topology to provide high gain while maintaining low power consumption. Stability and low noise performance are ensured by the Miller compensation capacitors and tail current sources. Furthermore, both passive and active filtering components are included to eliminate common-mode noise and external disturbances.

The amplified signal from the biosensing front end is directed into a low-noise analog amplification stage that comprises a differential-input operational transconductance amplifier (OTA). This OTA is biased with cascaded current mirrors to maintain linear operation, achieve high common-mode rejection, and ensure thermal stability. Additionally, capacitive components may be incorporated to filter out high-frequency noise, thereby making the output appropriate for analog-to-digital conversion or threshold detection.

4.3. Output Driver Interface stage

The right section of the schematic contains level shifters and output drivers that buffer and adjust the amplified signal for digital conversion or external display. The output node is designed for compatibility with ADCs or wireless transmission modules in portable diagnostic systems. Special attention is given to ensuring linearity, drive strength, and low leakage at the output stage.

The final stage of the sequencing circuit is the output driver, which buffers and conditions the amplified biosignal for external interfacing. This phase features a CMOS inverter designed to ensure fast switching, low output impedance, and sufficient driver strength for off-chip data acquisition systems. In applications requiring digital handoff, the driver converts the analog signal to logic-compatible levels. Furthermore, the driver may include level shifters to align with varying system voltages, thereby enabling integration with ADCs, microcontrollers, or wireless transmitters for portable diagnostics.

4.4. Layout and Integration Considerations

The design feature comprises a minimal silicon area integrated with digital control circuitry. The use of standard 180nm CMOS technology enables scalable manufacturing and compatibility with system-on-chip (SoC) architectures. The layout is optimized to ensure proper matching of essential analog transistors, symmetrical routing for differential signals, and reduction of parasitic capacitances.

5. RESULTS AND DISCUSSIONS

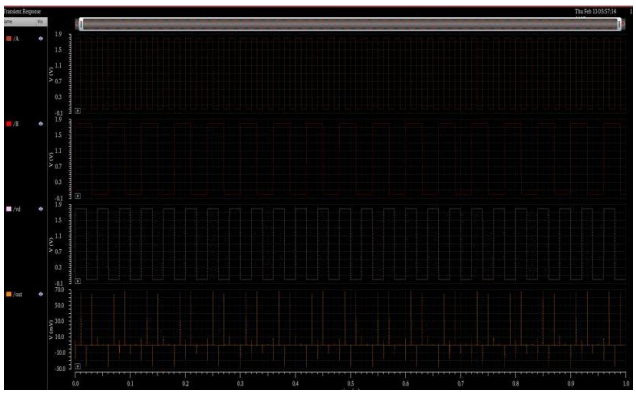

Fig.2. Simulation for DNA Sequencing array by SBS Method

5.1. Waveform Interpretations

In the Sensor Interface circuit stage, the A and B signals are the input signals that are square waves. These signals are toggling between 0 and 1.8V for the 180nm CMOS technology. These signals represent digital control pulses for the biosensing array. Use test patterns to stimulate the front end, such as DNA hybridization events and logic encoding for base detection. The duty cycle is 50%, representing the standard clock or pulse train.

The Vref Signal serves as a reference voltage and is characterized by its flat and constant nature. This signal can used to –

- Provide bias for input stages
- Establish a comparison threshold for the amplifier or comparator stage

Out Signal exhibits non-uniform, high-frequency spikes and appears analog, with multiple peaks at certain intervals. These spikes indicate –

- Bio-recognition events, during which a change in current or voltage is noted due to DNA binding or charge accumulation from the A and B Input signals.
- Time-domain representation of amplified bio signals.
- The spikes observed in the output signals suggest that the biosensing front-end i.e. the sensor Interface circuit stage and amplifier effectively converts bio-events into electrical signals. The timing of these spikes corresponds with the transitions in A and B, implying that the circuit is responsive to those stimuli (for instance, the activation of the biosensor).

Thus, the results from the transient simulation show that the designed VLSI front-end accurately detects input transitions from the biosensor array or the sensor interface circuit stage and converts them into electrical responses. The resulting output waveform displays sharp voltage transitions that align with input patterns, demonstrating proper signal amplification and responsiveness. The existence of a reference voltage and consistent timing behaviour supports the potential of this architecture for real-time DNA sequence detection applications.

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