

27.4 A Multichannel DNA SoC for Rapid Point-of-Care Gene Detection

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Point-of-care diagnostics for detection of genetic sequences require biosensing platforms that are sensitive to the target sequence, and are also fast, mass-manufacturable, and – ideally – disposable. Conventional lab-based methods of detecting DNA sequences rely on optical methods, typically by the addition of fluorescent tags to the target DNA that in turn latches onto a DNA probe sequence only if there is a match between the two. These techniques are cumbersome as they require upfront tagging of the DNA with expensive reagents and laboratory equipment to detect the optical signals. Recently, developments have been made in transferring these optical methods to inexpensive CMOS ICs [1], although the requirement for tagging remains. Magnetic beads offer an alternative means of tagging the DNA and their presence can be detected by the shift in resonant frequency of an on-chip LC tank [2]. There have also been attempts based on “label-free” electrochemical detection using FETs [3,4], but none of these have been implemented in unmodified standard CMOS.

We have developed a pioneering all-electrical approach that does not require tagging of DNA. The principle of label-free electrochemical DNA detection using an ion-sensitive field effect transistor (ISFET) was originally described in [5]. However, this prior art used a custom (non-CMOS) FET with an exposed Al_2O_3 gate insulator, a macroscopic reference electrode, and a heat bath with control unit to control the temperature of the reagents; furthermore, it was only able to detect a single DNA sequence, which has limited application. The SOC for DNA detection presented herein integrates the discrete laboratory apparatus of [5] into a single IC while using standard CMOS manufacturing (unlike the all-electrical approach in [6]), and moreover has scalability to the detection of multiple DNA sequences by use of multiple on-chip ISFET sensors, temperature sensors and heaters along with ADCs and digital IO. This single-chip solution can be incorporated into disposable cartridges that are interchangeable depending on the DNA sequences to be detected. The structure of the cartridge is shown in Fig. 27.4.1 and consists of the IC embedded within a microfluidic assembly in which there are microchambers with access channels for the delivery of reagents. The ISFETs are implemented as unmodified floating-gate pMOS devices [7].

When there is a match between target DNA from a sample and the on-chip DNA probes, H^+ ions are released, changing the pH of the reagents inside the microchamber in which the match took place (Fig. 27.4.1). ISFETs are sensitive to the pH of liquids on the passivation interface above their floating gates and this manifests itself as a shift in the V_t of the ISFET where V_t is the threshold voltage referred to a reference electrode that sets the potential of the electrolyte [8]. Hence, the IC can detect whether a reaction has taken place in any of the chambers by monitoring the V_t of the ISFETs beneath those chambers. There are many ways to do this, one of which is to pass the drain current through weak-inversion signal processing circuits for the optimum balance of sensitivity and dynamic range [9].

The architecture of the SOC is shown in Fig. 27.4.2. The IC consists of a bank of 40 ISFETs with associated readout circuitry that allows one of the 40 ISFETs to be used as a reference ISFET (termed a REFET). Thus all ISFET readout signals are outputted differentially as $(V_{\text{ISFET}} - V_{\text{REFET}})$: this means that all common-mode noise (including electrochemical noise in the reaction chambers, allowing a quasi-reference electrode to be used) is rejected and this, together with up-front gain, gives an input-referred noise voltage of only 25 μV over the bandwidth of interest. Floating-gate transistors have different levels of as-deposited charge which cause large variations in the output voltage: these variations are cancelled using individual 10-bit DACs as shown in Fig. 27.4.3, thus preventing saturation of the instrumentation circuitry which is designed to resolve small signals. Therefore this architecture overcomes the two common performance issues with standard CMOS ISFETs: electrochemical drift and V_t offsets due to charge [8].

Because biochemical reactions are highly sensitive to the temperature of enzymes and reagents, the system controls temperature to an accuracy of 0.5°C with an inter-chamber precision of 0.1°C. This is done with an array of 10 temperature sensors distributed across the chip outputting the differential signal

$(V_{\text{PTAT}} - V_{\text{CTAT}})$. These sensors are trimmed using individual 8-bit current-steering DACs fed from registers sitting within an OTP block. Figure 27.4.3 shows the reported temperature from the IC under isothermal conditions before and after trimming showing that the required precision is obtained.

The ISFET and temperature signals are filtered by 50 G_m -C anti-aliasing LPFs with a low $f_{3\text{dB}}$ of 8 Hz. The filtered signals are passed through 50 2nd-order $\Sigma\Delta$ Ms with a peak SNR of 80 dB. The resulting bitstreams are gathered by control logic which implements an SPI interface for full-duplex communication with an external handheld analyser which also does decimation filtering. The IC as it currently stands can detect up to 39 different genetic letters (allowing for one channel to be used for the reference chamber). Scalability is a key aspect to the design of the IC because as research into genetics advances, applications will be found that require the identification of more and more genetic letters. To that end, the IC is both scalable internally in that the architecture allows more ISFETs and temperature sensors to be easily added, and the SPI interface is implemented such that multiple ICs can be daisy-chained together. A table of key performance specifications is given in Fig. 27.4.4 in which all values are exact or typical unless otherwise stated. The sensitivity of the IC to pH of liquids in the microchambers is shown in Fig. 27.4.5; the output signal has a square-law dependence on pH and the dotted line is a 2nd-order polynomial least squares best fit. Deviations from this best fit are due to the difficulty of precisely setting the pH of buffers as shown by the error bars, and do not represent a limitation of the IC itself.

This platform can be applied to many different kinds of genetic testing. One application is the identification of single nucleotide polymorphisms (SNPs), which are a change in a single letter of the genetic code. The IC has sufficient ISFETs to be able to identify up to 19 SNPs but for demonstration purposes in this paper only one SNP was detected, utilising only 3 of the ISFETs: one as a REFET described above, and the other two beneath chambers containing reagents suitable for identifying a SNP which reveals information about a person's drug metabolism. This SNP can take the letter A or C only and so each of two chambers was loaded with a different DNA detection “probes” suitable for capturing the target region of the DNA and detecting these two letters. In this case, a reaction is deemed to have occurred when the output signal from either or both chambers crosses a preset threshold: if this happens, there is a match between the patient's DNA and the letter of interest. The time-to-result of 29 different reactions with DNA in which a match was verified to have occurred using optical lab apparatus is shown as a histogram in Fig. 27.4.6 (“Inf” refers to reactions that failed to pass the detection threshold; this occurred due to non-optimised reaction chemistry in those cases). This Figure shows the speed of this on-chip DNA detection method and good agreement with conventional optical methods.

The die is shown in Fig. 27.4.7. In a 0.35 μm process, it has an area of 26 mm^2 .

References:

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- [9] C. Toumazou, L. Shepherd, “Using Transistors to Linearise Biochemistry,” *Electronics Letters*, Vol. 43, pp. 65-67, Jan. 2007.

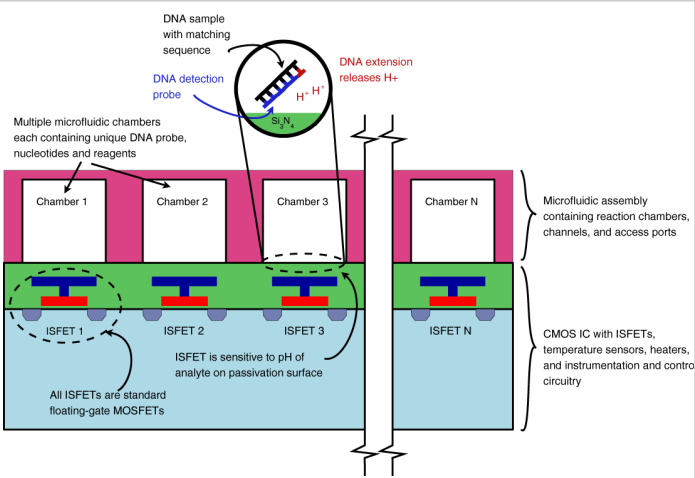


Figure 27.4.1: Cross-section through the cartridge containing the IC and the microfluidic assembly.

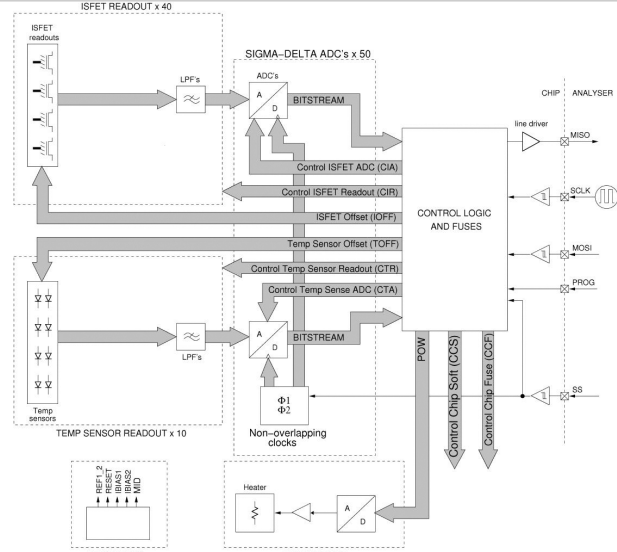


Figure 27.4.2: Architecture of the SOC.

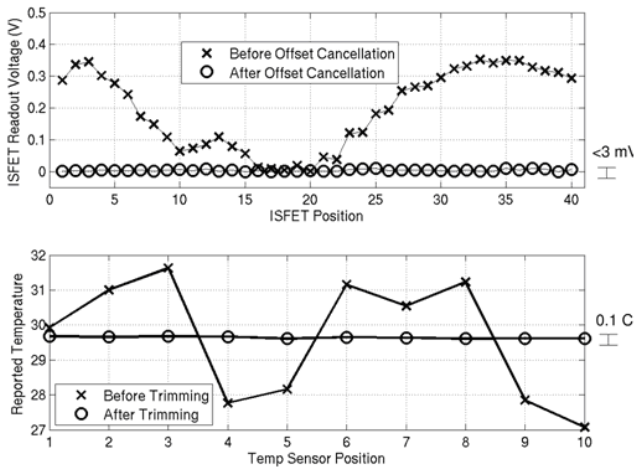


Figure 27.4.3: Cancellation of offsets in the ISFETs and trimming of the temperature sensors to a precision of 0.1°C.

Parameter	Value	Comments
Reaction chambers	40 per IC	Scalable on-chip or externally by daisy-chaining IC's
Temperature control accuracy	0.5 C	
Intra-die temp control precision	0.1 C	Individual sensor trimming via 8-bit DAC's
Max number of daisy-chained IC's	400	Electrical limit; realistic physical size places lower limit
Anti-aliasing filter f3dB	8 Hz	Gm-C using 0.1 nS transconductor
DSM OSR	1024	
Down-sampled sample rate	1 Hz	
Decimation filter	16,384-tap FIR	Implemented as software in the analyser
Min DSM SNR in ideal test conditions	> 80dB	
Peak system SNR	50 dB	Real conditions: reference electrode as input & including electrochemical noise
Input-referred noise voltage	25 uV	Referred to floating polysilicon gate of ISFET
OTP	128-bit	Poly fuse
Registers	approx 500	Controlling trimming, signal flow, heater, test, etc

Figure 27.4.4: Key performance metrics of the DNA detection system incorporating the SOC.

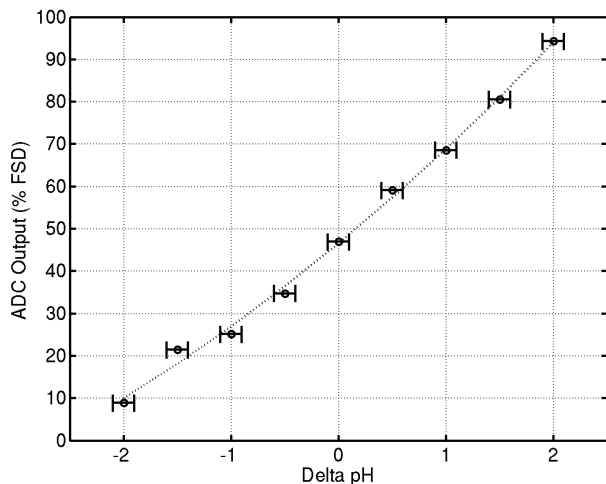


Figure 27.4.5: ADC decimation filter output as the pH of the liquid in a reaction chamber is varied.

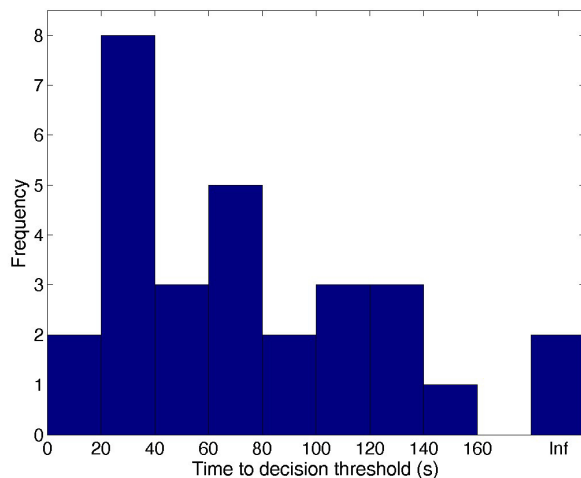


Figure 27.4.6: The time taken to identify a match between probe and target when using the SOC for SNP detection.

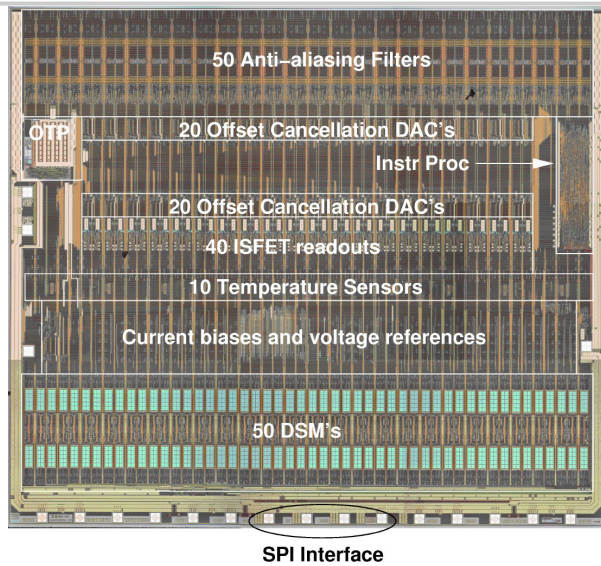


Figure 27.4.7: Micrograph of the manufactured IC. The die size is 5.5x4.7mm.