



Annese, V. F. et al. (2019) The Multicorder: A Handheld Multimodal Metabolomics-on-CMOS Sensing Platform. In: 2019 IEEE 8th International Workshop on Advances in Sensors and Interfaces (IWASI), Otranto, Italy, 13-14 Jun 2019, pp. 130-135. ISBN 9781728105574 (doi:[10.1109/IWASI.2019.8791347](https://doi.org/10.1109/IWASI.2019.8791347)).

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Deposited on: 09 December 2019

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# The Multicorder: A Handheld Multimodal Metabolomics-on-CMOS Sensing Platform

Valerio F. Annese, Chunxiao Hu, Claudio Accarino, Christos Giagkoulovits, Samadhan B. Patil, Mohammed A. Al-Rawhani, James Beeley, Boon C. Cheah, Srinivas Velugotla, James P. Grant, and David R. S. Cumming

*Electronics and Nanoscale Engineering, School of Engineering, University of Glasgow, Glasgow G12 8LT, United Kingdom*

**Abstract**—The use of CMOS platforms in medical point-of-care applications, by integrating all steps from sample to data output, has the potential to reduce the diagnostic cost and the time from days to seconds. Here we present the ‘Multicorder’ technology, a handheld versatile multimodal platform for rapid metabolites quantification. The current platform is composed of a cartridge, a reader and a graphic user interface. The sensing core of the cartridge is the CMOS chip which integrates a 16x16 array of multi-sensor elements. Each element is composed of two optical and one chemical sensor. The platform is therefore capable of performing multi-mode measurements: namely colorimetric, chemiluminescence, pH sensing and surface plasmon resonance. In addition to the reader that is employed for addressing, data digitization and transmission, a tablet computer performs data collection, visualization, analysis and storage. In this paper, we demonstrate colorimetric, chemiluminescence and pH sensing on the same platform by on-chip quantification of different metabolites in their physiological range. The platform we have developed has the potential to lead the way to a new generation of commercial devices in the footsteps of the current commercial glucometers for quick multi-metabolite quantification for both acute and chronic medicines.

**Keywords**—CMOS, Metabolomics, diagnostics, point-of-care, lab-on-chip, Photodiodes, SPAD, ISFET.

## I. INTRODUCTION

The need for portable diagnostic devices is a shared vision [1-3]. In the science-fictional Start-Trek universe, a portable multi-function analyzer, called the ‘Tricorder’, was able to instantly diagnose medical conditions in seconds. Sixty years after the show, Star Trek’s fictional device is maybe not too far from becoming a reality. In fact, metabolomics – the study of the small molecules (metabolites) produced by human cells during the metabolism - promises to succeed where proteomics and genomics strive to overcome major challenges [4, 5]. Nowadays, more than 114000 metabolites have been detected in body fluids, tissues and organs and more than 4200 in human serum only [6]. The increasing interest in metabolomics is related to its capability of describing the phenotype: while genomics describes what ‘could happen’ in the organism (genotype), the metabolome is affected by both genetic and environmental factors, providing a direct functional readout of the physiological state of the organism [7, 8]. It is not a case that the best-selling drugs act somehow on metabolic pathways [9]. Metabolomics-based point-of-care devices have already demonstrated their world-changing capabilities in a wide range of applications. Glucose monitoring handheld devices, for examples, have massively improved life quality for

people affected by diabetes [10]. Similar handheld units are also commonly employed in roadside alcohol monitoring [11]. Cholesterol and lactate meters are also getting progressively popular [12].

However, due to the huge diversity of chemical structures, to date, there is no single technology available to analyze the entire metabolome [7]. On the contrary, metabolomics devices usually employ single-modality bench-top laboratory instruments such as nuclear magnetic resonance spectroscopy, gas and liquid chromatography-mass spectrometry and spectrophotometry [9]. Each technique provides different advantages/disadvantages widely discussed in the literature [9].

The advancement of complementary metal oxide semiconductor (CMOS) technology has produced a dramatic impact on portable and low-cost biomedical sensing applications [13]. The most commonly used sensing techniques in point-of-care applications are optical and electrochemical, where CMOS technology has been successfully employed. Photodiode (PD) arrays have been employed for colorimetric [14] and fluorescence detection [15]. CMOS-based Single Photon-Avalanche Diodes (SPADs) have been successfully employed for auto-fluorescence and chemiluminescence measurements [16]. CMOS technology has also been utilized for Surface Plasmon Resonance (SPR) measurements [17] and ISFET-based DNA sequencing [18]. Also, Electrochemical microelectrode arrays have been demonstrated to be suitable for metabolites detection [19].

In the last decade, as a result of the maturity of the technology, a large interest in multimodal CMOS chip has risen. A multimodal chip is a microelectronic integrated circuit suitable for more than one sensing technique. For instance, an ISFET and PD array has been utilized for improved DNA sequencing in a dual-mode CMOS chip [20]. Also, a combination of PDs, electrodes and LEDs have been shown for neural imaging [21].

In this manuscript, we present a scalable multi-sensor platform for rapid multimodal metabolite sensing: the ‘Multicorder’. The core of the platform is a CMOS 16x16 array of multi-sensor elements. Each element integrates a PD, a SPAD and an ISFET that can be utilized independently or simultaneously. Thus, the Multicorder can be used for multi-modalities measurements. The sensors were implemented in an array format so that measurements can be averaged to reduce noise and increase accuracy. We believe this platform could enable a new generation of commercial devices in the footsteps of the current commercial glucometers for quick multi-metabolite quantification for both acute and chronic medicine.

The rest of this paper is organized as follows: in section II, the architecture of the platform is described. Section III describes the performance of the sensors. Section IV shows the capability of the platform in different modalities by quantifying different metabolite concentrations within the physiological range. Section V concludes the paper.

## II. THE MULTICORDER PLATFORM

The Multicorder platform is made of 3 sub-units: the cartridge, the reader and the Graphic User Interface (GUI) (Fig. 1). The versatility of the Multicorder resides in the possibility of functionalizing the chip-surface for the target application. At the current state, a wide range of biological tests has been developed on-chip with minimal modifications of the cartridge only. The reader is composed of a PCB and a microcontroller. The reader is employed for addressing, data digitization and data transmission to the GUI via a USB link. The GUI is a software running on a tablet computer allowing user interaction.

### A. The Cartridge

The cartridge of the development platform includes the CMOS chip with post-processing, chip packaging and biological receptors. In the final vision of the project, the cartridge will be disposable and pre-functionalized with relevant bio-receptors. However, in this work due to limited resources, the cartridges have been refurbished after use in order to be reused many times. The Multicorder chip integrates a 16 x 16 array of multi-sensor elements, each comprising a PD, SPAD and ISFET sensor, for a total of 256 elements and 768 sensors.

The chip was fabricated using a commercially available CMOS 350 nm HV 4-metal process provided by AMS. The chip size is 3.4 x 3.6 mm. The size of the multi-sensor element is 110  $\mu\text{m}$  x 110  $\mu\text{m}$ . This arrangement ensures an even distribution of each modality sensors across the active area of the chip. The chip circuitry includes addressing to allow each sensor array to be controlled and operated either independently or simultaneously (see Fig. 2). Specifically, each sensor can be addressed using two 4 – 16 decoders. PDs and ISFETs have analogue outputs. Differently, SPAD outputs are digital since the chip has embedded counters. In order to improve the performance of the ISFET sub-array, the chip was post-processed [23].

After post-processing, the CMOS chip is wire bonded and packaged into a ceramic chip carrier. Wire bonds are usually encapsulated with epoxy resin (302-3M 1LB) to provide mechanical strength and protection. A culture ring is also glued to the ceramic chip carrier and sealed with epoxy resin allowing solution assays. Micrograph pictures of the cartridge are reported in Fig. 3

The biological receptors used are related to the target analyte. In general, specific receptors are used in order to trigger a biochemical reaction with the metabolite to be quantified. The specific reaction produces a change in the biophysical properties of the sample that can be quantified by a sensor. Examples of physical changes induced by the reaction are light absorbance or pH modifications. The rate and the endpoint of the reaction are usually related to the concentration of the analyte under test. The employed biological receptors utilized in the data presented in this manuscript are reported in the results section (Section IV).

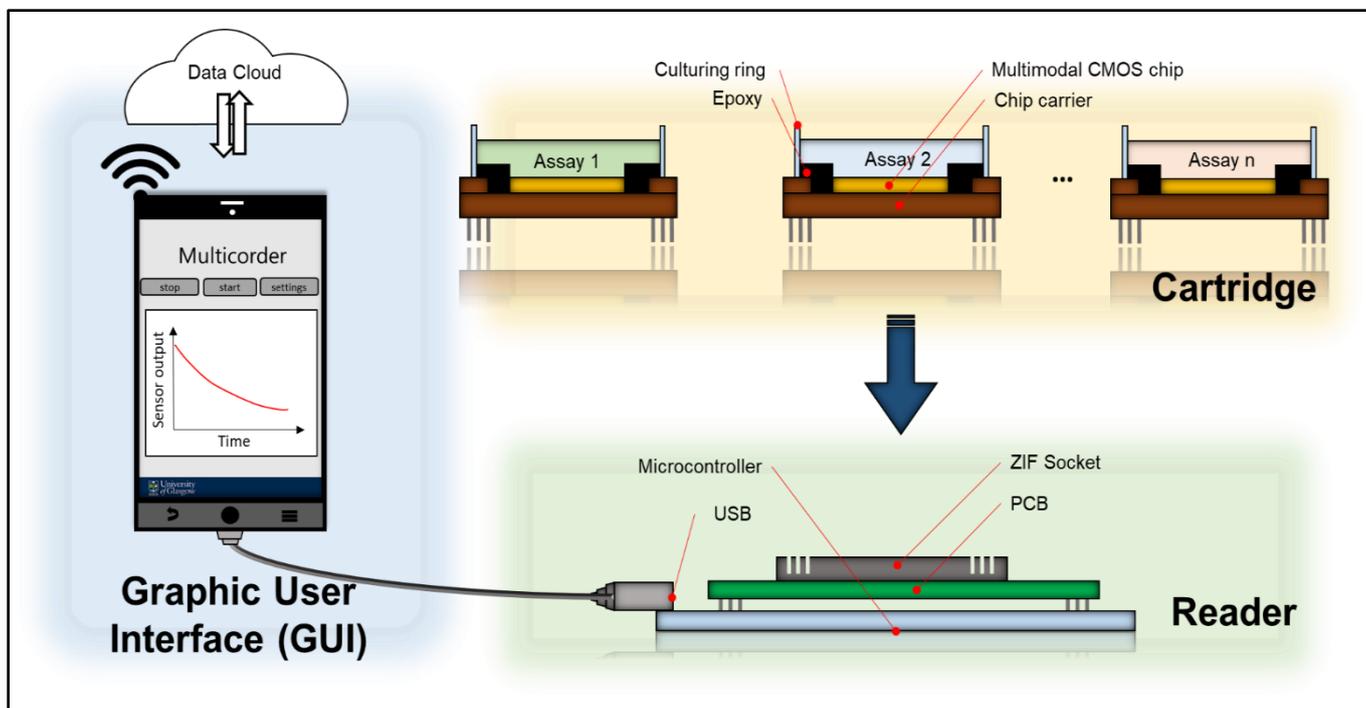


Fig.1. Architecture of the platform. The platform is made up of three sub-units: the cartridge, the reader and the GUI.

## B. The Reader and the GUI

The reader is made up by a PCB board and a microcontroller (see Fig. 4). The PCB board allows connecting the cartridge in a very user-friendly mode by employing a Zero Insertion Force (ZIF) socket. The output of the sensor is driven by the microcontroller. The microcontroller is dedicated to the addressing of the array, data digitalization and data transmission to the GUI by USB link. The USB link also provides power for the chip and the Mbed processor. The ST Nucleo F334R8 board was employed and programmed with custom firmware. In this work, PD data is digitized with a 12-bit ADC at 16 frames per second (fps). ISFET data is digitized with the same number of bit but the reading cycle is shorter and a higher frame rate is achieved (42 fps). Differently, SPAD data does not need digitization (output data is already digital).

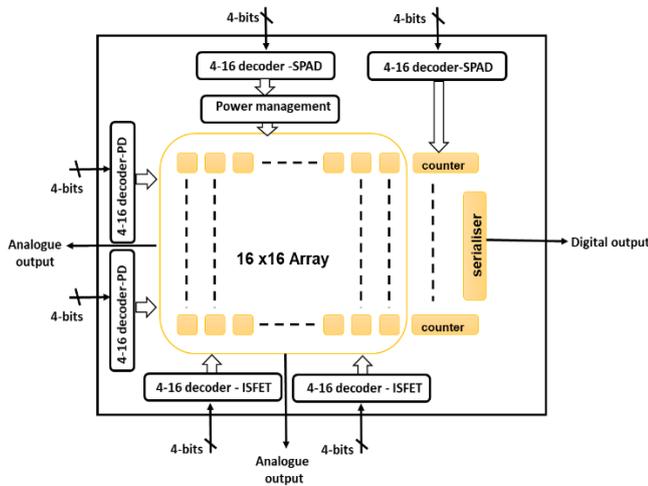


Fig. 2. Block-diagram of the CMOS chip, describing the independent addressing and read-out architecture of each sensing technique.

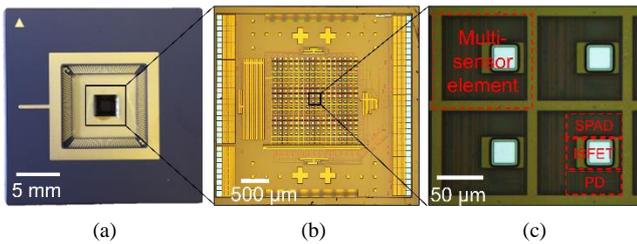


Fig. 3. Micrograph of the multimodal sensor array: (a) Cartridge after wire-bonding to the chip carrier, (b) CMOS chip, (c) Multi-sensor elements.

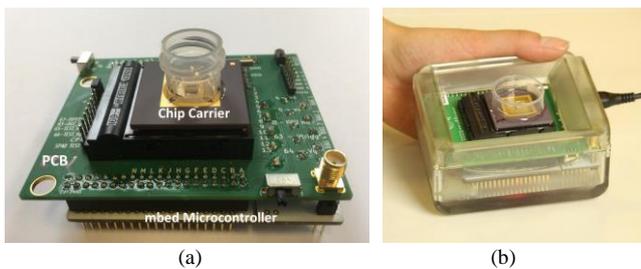


Fig. 4. Demonstrative pictures of the reader. (a) The cartridge is connected using a Zero Insertion Force socket. The cartridge package is also adapted for assays in solutions. (b) The Multicorder platform is portable and can be hand held.

The GUI is a software running on an electronic device with USB communication and graphics capabilities. In this work, we successfully used a tablet and a computer. The GUI performs data collection, visualization, analysis, storage and uploads the final test result onto a cloud via Wi-Fi.

## III. SENSORS PERFORMANCE

The sensors were independently characterized.

To test the dynamic range of the optical devices a monochromator was configured at a wavelength of 550 nm and attached to an optical integrating sphere to ensure uniform light distribution. An optical power meter (1936-R, Newport, USA) was fitted to one exit port to measure the light intensity and the CMOS chip was placed at another exit port. In dark conditions, the output of the PD was 408 mV because of the dark current. The measured dynamic range for the photodiode was 0.05 - 4.9  $\mu\text{W}/\text{cm}^2$ . Photodiode responsivity at 550 nm was 21.6 mV/ $\mu\text{W}$ . The SPAD dynamic range was measured similarly and with the same light wavelength. The SPAD array was activated and biased at 21.5 V, 3 V above its breakdown voltage. The measured dynamic range for the SPAD was 0.45 - 600 nW/ $\text{cm}^2$ . SPAD photon detection probability peak at 475 nm was 41 %. In dark conditions, the SPAD produced a dark count rate (DCR) of 10 kcps.

To evaluate the ISFET pH dynamic range and sensitivity, the chip was tested with five buffer solutions (pH 5, 6, 7, 8, 9). A silver/silver chloride (Ag/AgCl) reference electrode was used biased at  $\sim 1.3$  V with respect to the ISFET source voltage. Prior to testing the sensor, the chip was washed with DI water, dried with  $\text{N}_2$  and then tested in the pH 9 buffer to establish a baseline. The data showed a pH sensitivity of 33 mV/pH with a linear response between pH 5 and pH 9 when tested against a commercial pH probe (HI522, HANNA instruments).

The noise source in CMOS sensors array can be divided into fixed pattern noise (FPN) and temporal noise [24]. While FPN is the variation of the output among elements when the same input is applied, temporal noise introduces variability in measurements from the same sensor. In general, there are 3 different sources of temporal noise found within the sensors namely, flicker noise (also known as 1/f noise), shot noise and thermal noise. Based on the physical nature of the sensor one of these noise components dominates the others dictating the signal distribution. Flicker noise is a very low frequencies disturbance which is modelled as a function of 1/f, where f is the frequency [25]. Thermal noise is Gaussian noise with a broadband frequency spectrum which is usually restricted to the sensor spectrum. Shot noise is generated by a carrier crossing a p-n barrier and it usually results in a DC current, such as the dark current of a photodiode or the leakage current of a diode [25, 26]. Each of our sensors is affected by all three components in different ways, ISFET is primarily affected by thermal noise and flicker noise while shot noise is largely predominant in PD and SPAD. By exploiting the fact that the above-mentioned noise sources can be modelled as Gaussian distribution [27], averaging the readout of each array reduces the standard deviation and therefore produce more reliable results. The averaging process proved to effectively reduce the disturbance as a function of  $1/\sqrt{N}$ , where N is averaged population.

#### IV. MULTIMODAL BIOLOGICAL EXPERIMENTS

We performed biological experiments for metabolite quantifications in order to demonstrate the chip capability to perform different sensing modalities.

In this manuscript, we demonstrate the use of three modalities: colorimetric, chemiluminescence and pH sensing. Additionally, the platform was used also for Surface Plasmon Resonance (SPR) [28, 29]. Altogether, the chip demonstrated to be suitable for four different sensing modalities.

The developed biological assay employs reagents which react with the target analyte hence modifying the initial biophysical properties of the solution. The concentration of the target analyte can be determined by estimating the rate of the reaction using the Michaelis-Menten model [30]. Data shown in this section are averaged over the entire array and the test is concluded in minutes.

##### A. Colorimetric

A colorimetric assay utilizes specific reagents that undergo a measurable and progressive light absorbance change at a specific wavelength. In this manuscript, we report colorimetric measurement to quantify concentrations of cholesterol.

A two-step reaction chain has been implemented. First, a reaction between cholesterol and cholesterol oxidase was induced. This reaction produces hydrogen peroxide ( $H_2O_2$ ). The produced  $H_2O_2$  was used as a substrate to oxidase o-dianisidine together with peroxidase. Oxidized o-dianisidine shows higher light absorbance at 500 nm. Thus, as the reaction proceeds, the light absorbance of the reaction changes and this physical change can be detected by PDs when illuminated with constant green light from a monochromator at 500 nm. The setup for this method is shown in Fig. 5.

Before the measurement, the chip was cleaned with standard procedures (acetone, isopropyl alcohol and sonication). Afterwards, a mixture solution of triethanolamine (830  $\mu$ l 20 mM), cholesterol (40  $\mu$ l 10 mM in 10% (w/v) Triton X-100), peroxidase enzyme (50  $\mu$ l 60 U/ml) and o-dianisidine (40  $\mu$ l 7.89 mM) was placed onto the sensor surface. The pH of the solution was 8.5.

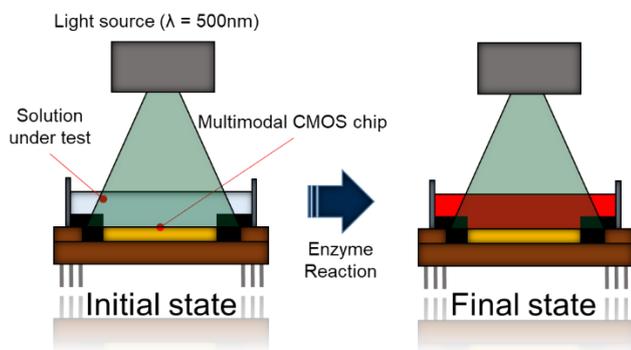


Fig 5. Setup for colorimetric mode. The light absorbance change generated by a specifically designed reaction was measured by PDs.

After a stable baseline was obtained, 40  $\mu$ l 10 U/ml cholesterol oxidase enzyme solution was added to initiate the reaction. Two concentrations of cholesterol (25  $\mu$ M and 400  $\mu$ M) were measured. This range covers the cholesterol physiological range in human blood (< 4.1 mM) [31].

Figure 6 shows the PDs output for the performed experiments. Increasing the concentration of the target analyte creates a detectable increment in the rate of the reaction w.r.t. the control.

Choline, xanthine and sarcosine have also been quantified with this technique on the same platform and reported into related works [32].

##### B. Chemiluminescence

A Chemiluminescence assay employs specific reagents to create a progressive light emission during the reaction. In this manuscript, we demonstrate chemiluminescence measurement by quantifying urate.

Similarly to colorimetric mode, a two-step reaction chain was utilized. First, the urate-uricase enzymatic reaction was used to produce  $H_2O_2$ . Next, the produced  $H_2O_2$  was used as a substrate to react with Luminol. Under the catalytic activity of peroxidase, the reaction Luminol -  $H_2O_2$  emits a small number of photons. The generated blue light was detected by SPADs. The setup of the chemiluminescence is depicted in Fig. 7.

After standard cleaning procedures, a mixture solution of 900  $\mu$ l 100  $\mu$ M urate in 50 mM triethanolamine pH 8.5, 50  $\mu$ l 60 U/ml peroxidase enzyme solution, and 50  $\mu$ l 8 mM luminol solution was placed onto the sensor surface. After a stable baseline was obtained, 50  $\mu$ l 1 U/ml Uricase enzyme solution was added to initiate the reaction.

Two concentrations of urate (100  $\mu$ M and 1 mM) and one control measurement were used to demonstrate the quantification in the physiological range (200  $\mu$ M –500  $\mu$ M) [33]. Figure 8 shows the SPADs output for the performed experiments. Confirming that, increasing the concentration of the target analyte creates a detectable increment in the rate of the reaction w.r.t. the control. It is worth noticing that the same measurement could not be performed employing PDs because the light intensity was below the PD sensitivity range

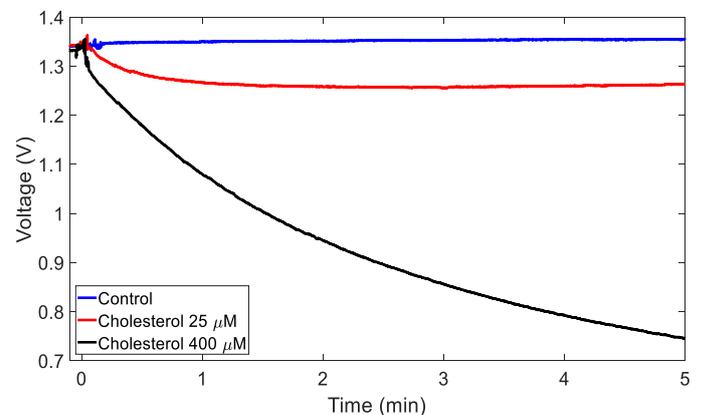


Fig 6. Cholesterol quantification using the colorimetric technique. Data is averaged over the entire array. The test is completed in minutes.

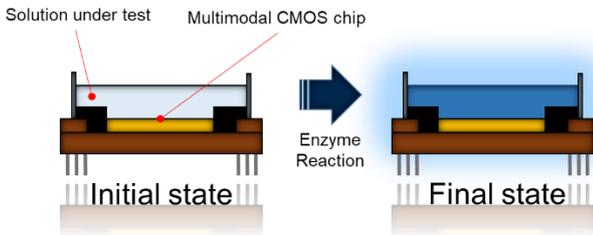


Fig 7. Setup for chemiluminescence mode. A specific reagent mix reacts with the analyte under test producing a small amount of light. The produced light was detected by SPADs.

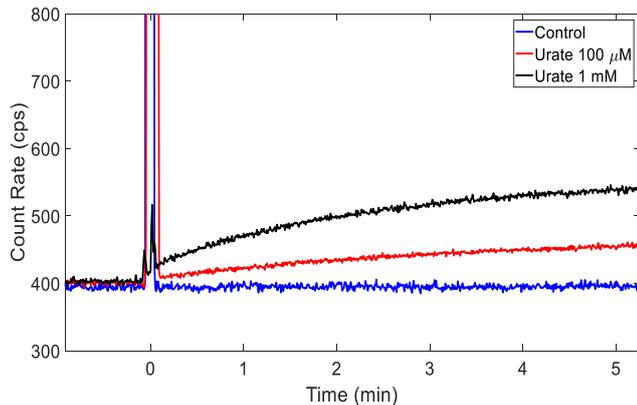


Fig 8. Urate quantification using the chemiluminescence technique. Data is averaged over the entire array. The test is completed in minutes.

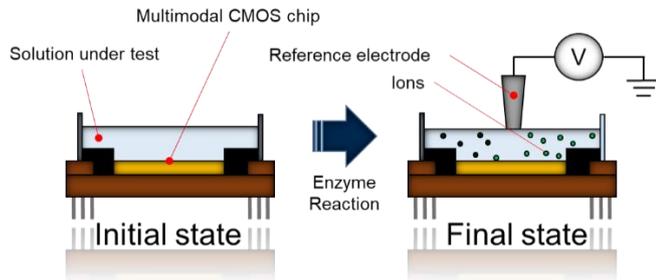


Fig 9. Setup for pH sensing. A specific reagent mix reacts with the analyte under test producing a pH change. The produced pH was measured by ISFETs.

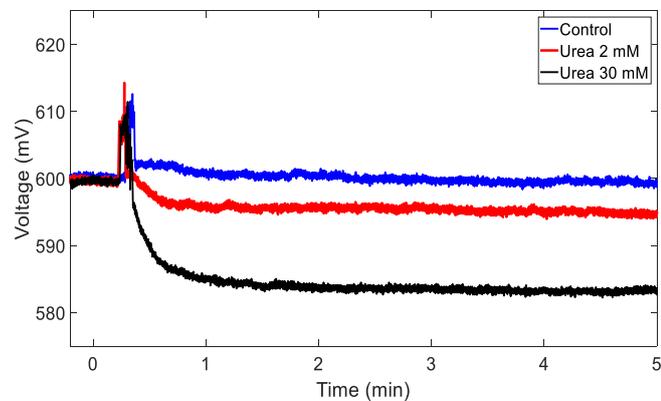


Fig 10. Urea quantification by pH sensing. Data is averaged over the entire array. The test is completed in minutes.

### C. pH sensing

The pH-based assay employs specific reagents to create a progressive pH change during the reaction. In this manuscript, we demonstrate pH sensing mode by quantifying urea.

A single step reaction was utilized in these experiments. A chemical reaction between urea and urease was started in order to produce ions (such as  $H^+$ ). The progressive production of ions creates a pH change. Urea-urease activity tends to increase the pH of its solution as it produces ammonia, which is a basic molecule. Therefore, ISFETs were employed for pH-based sensing. The setup of the performed experiments is shown in Fig. 9.

After the standard cleaning of the chip, the potential of the Ag/AgCl reference electrode was set to 0 V. To start the experiment, 950  $\mu$ l 30 mM urea in 50 mM triethanolamine pH 8.5 was firstly placed on the sensor surface. After a stable baseline was obtained, 50  $\mu$ l 80 Units/ml urease enzyme solution was added to initiate the reaction.

Two concentrations of urea (2 mM and 30 mM) and one control measurement were used to demonstrate the performance of the ISFET. A decrease in the electrical signal was detected by the ISFET and shown in Fig. 10. These values cover the physiological range of urea in human blood (2.5 mM – 7.8 mM) [34]. Glucose quantification has been also achieved using the same sensing modality [23].

### D. Simultaneous Assay

Since the sensors can be independently addressed, different modalities can be used at the same time. In [35], we demonstrated that the Multicorder platform can operate both colorimetric and pH sensing to simultaneously quantify glucose and cholesterol. In [32], we also demonstrate that physical separations fabricated on top of the sensing area enable the use of the Multicorder for simultaneous enzyme-based assays of multiple metabolites. Multiplexing immunoassays on the top of the Multicorder chip have also been demonstrated [36].

## V. CONCLUSION

We have presented a CMOS-based multimodal sensor array for metabolites quantification.

The colorimetric technique has been demonstrated by using PDs for the quantification of cholesterol in the physiological range. Chemiluminescence sensing has been demonstrated by employing SPADs for the quantification of urate in the physiological range. pH sensing performed by ISFETs also shown the suitability of the chip to quantify urea. SPR measurements have also been demonstrated on the same platform in related works [28, 29]. Multimode multiplexing and simultaneous assays have also been achieved [32, 35, 36]. Altogether, the chip demonstrated to be suitable for four different sensing techniques to be used independently or simultaneously. Future work includes the integration of additional sensing modalities into the platform [37].

We believe this platform could enable a new generation of commercial devices for low-cost, rapid and accurate diagnostics.

## ACKNOWLEDGEMENT

This work was supported by EP/K021966/1 and EP/L023652/1.

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