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A Review of Lab-on-a-PCB Technology

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ABSTRACT
The early detection of diseases within a patient can often help to dramatically improve morbidity and mortality rates. These infectious diseases produce biomarkers within the patient that can be detected using biosensors. In recent years, the concept of a lab-on-a-PCB has been developed, which uses the advances in biosensing technology combined with a PCBs cheap and highly integrable format to produce devices that can speed up testing and detection of biomarkers, and potentially act as a point of care prognosis tool for medical professionals. This paper assesses the existing modern lab-on-a-PCB technologies, in particular label-free sensing, compared to conventional methods. It was found that the technology has great promise, with time-to-results as low as minutes, but large proportions of the devices still lack comparable sensitivity, accuracy and limits of detection. While this still provides for useful first contact testing on a patient, for full integration into the medical system these parameters must be pushed further. There are already examples of comparable or better accuracy devices being developed proving that in the next few decades, these goals may be achieved.

KEYWORDS: Lab-on-a-PCB; Biosensors; Electrodes; Immunoassay

I. INTRODUCTION
The human body is in an incredibly complex biochemical system, with mechanisms that scientists and researchers are still only beginning to fully understand. Monitoring key bodily function has always been at the heart of medicine, allowing the prognosis of changes in these key biological mechanisms in order to give a patient the best suited care in order to promote a short and full recovery, or to analyse patterns in order to maximise the training and development of an individual for athletic or sporting purposes.

In the past, detection of biological or biochemical changes would have been carried out by professionals in a laboratory setting, costing valuable time and effort of highly skilled, specialised individuals. The aim of lab-on-a-PCB (LoPCB) technology is to develop designs based on the PCB format that are capable of detection biomarkers in a sample and returning results in a shorter timeframe and with less required skills or knowledge than a traditional laboratory could produce. The first concept was proposed in 1996 by Lammerink *et al.* and paved the way for the use of a PCB's format to provide deep integration between sample manipulation and biosensing technology [1]. Since 2015, research in the area has been growing year on year (Fig.1) and has been showing promise for the commercialisation and widespread use of the developed designs [2].

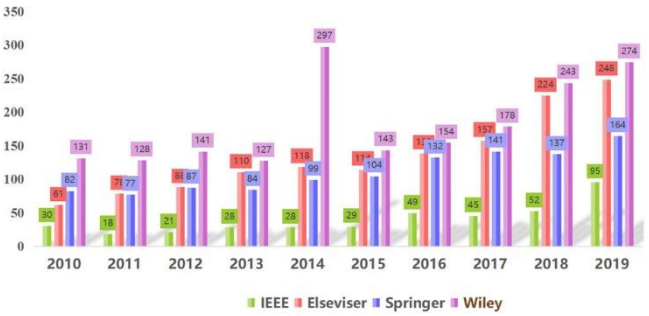

FIGURE 1. Quantity of research related to LoPCB technology, 2010-2019 from four key international databases

The PCB format lends itself incredibly well to the application of biosensing for multiple reasons. PCB technology has existed since the early 20th century [3] providing a strong industrial foundation for rapid and high-quality fabrication. The PCBs themselves also can integrate microfluidic channels and components such as electrodes can be nested within the PCB structure itself, acting as a substrate for the samples. This removes the need for external or disposable substrates required for sibling technologies such as lab-on-a-chip, which struggled to penetrate commercial markets due to complicated integration requirements.

II. OPERATION AND REVIEW
Most LoPCBs can be broken down into three distinct sections: microfluidics, biosensing and electronics. There is a wide variety of development taking place in each of these three areas, however most LoPCBs are categorised by the method of biosensing used. The current methods used for the

biosensing element of most modern LoPCBs are as follows: amperometric, potentiometric, impedimetric, optical and acoustic. The three biomechanical methods: amperometric, potentiometric and impedimetric, the focus of this report, are generally label free methods of detection. This means that they rely on the addition of a 'label' to the test samples, saving labour and required training for operation.

A. IMPEDIMETRIC CYTOMETRY FOR CERVICAL CANCER DETECTION

While in theory cervical cancer is a preventable disease, it still ranks second in most common cancers affecting women worldwide [4]. Early detection and intervention can dramatically change patient mortality rates by altering prescribed treatment. There are specific cells that, if detected, are a key pointer towards the patient likely having a form of cervical cancer. These 'circulating tumour cells (CTCs)' are only present in extremely low concentrations in a patient's blood and accurate concentration data is invaluable information for medical professionals [5].

Guo *et al*. proposed a method based on cytometry to offer a better form of early cervical cancer detection [6]. A sample suspected of containing CTCs is passed through an aperture between two electrodes. Specific cells passing through the aperture will increase the impedance between the two electrodes due to the Coulter principle [7]. This method resulted in an extremely cheap (US$2.00) to reproduce design that could offer rapid, high sensitivity results. Fig.2 shows a simplified schematic of the design

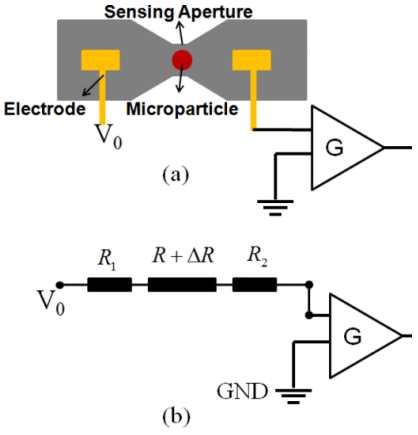

FIGURE 2. Simplified diagram explaining the impedimetric system used to detect CTCs

The design was tested against a commercially available cytometer with four concentrations of CTCs ($1x10^3$ mL^{-1}, $4x10^3$ mL^{-1}, $6x10^3$ mL^{-1} and $1.4x10^4$ mL^{-1}). The resulting comparison between the proposed device and commercial device showed an R^2 correlation of 0.996, an incredibly high result proving the viability of the design compared to other cytometers. The publication lacks a comparison to conventional methods however and fails to provide a limit of detection leaving the effectiveness for early cervical cancer detection an unknown.

B. POTENTIOMETRIC SENSING FOR DETECTION OF ANASTOMOTIC LEAKAGE

The management of electrolyte concentration within the human body is essential to the correct function of many biomechanisms. Therefore, detection of a change in the levels of specific electrolytes such as H^+, K^+ and Na^+ can be an incredibly useful marker of the health of groups of cells or organs.

After surgery, about 5% to 10% of surgical patients develop a surgical site infection, an example of this being colorectal anastomotic leakage (CAL) [8]. Early diagnosis and intervention of this problem can dramatically impact patient mortality and morbidity; however, they are hampered by current diagnostic methods and clinical practices [9]. This device uses the concept of a pH change signifying Tissue ischemia as well as concertation changes in K^+ and Na^+ signifying key cell function failure to detect an anastomotic leak.

Anastasova *et al*. produced four variants of the same design to be constructed and tested (Fig.3) [10]. while all 4 designs use an array of ion selective electrodes (ISEs), the first three differ from the last through implementation. They are designed with a larger array (34 electrodes) that is intended for folding into a ring to be inserted into the intestinal lumen. The final design, platform 4 uses a much smaller 'tab' design with fewer electrodes. These arrays use potentiometric sensing with ISEs to detect ion concentrations while inside a patient, allowing more frequent, more accurate data to be recorded which can be used to monitor cell well being around a surgical, allowing a medical professional to make more informed decisions.

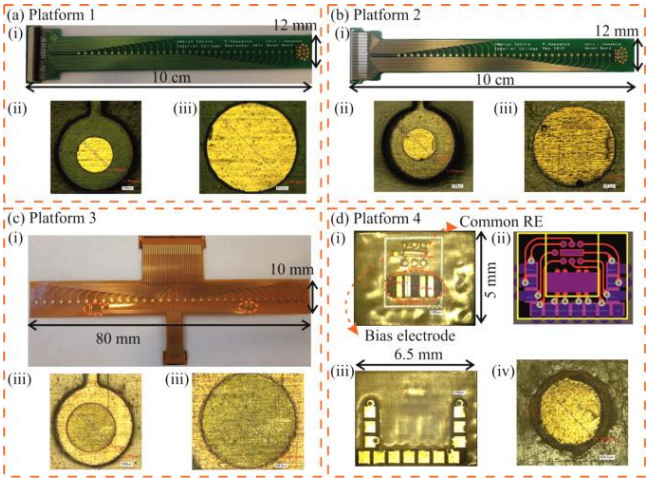

FIGURE 3. Four implementations of electrode arrays for the detection of electrolyte changes near surgical sites to identify potential infection

The resulting tests on concentrations of the three electrolytes is shown below in Table I and show high enough sensitivity to detect potential anastomotic leakage, which can be detected by a pH drop below 7.28 [11]. The use of surface contact electrodes separates this design from the aperture design seen previously, where analytes directly contact the

electrodes rather than indirect measurement. This reduces the need for fluidic components and simplifies the use, however, its desired end location of the intestinal lumen compared to sample testing does dramatically increase the complexity of application. The low cost and high accuracy offer a strong baseline for the technology to be implemented, however, external factors such as communication and insertion into the patient are yet to be discussed, leaving the technology with a high potential but uncertain future.

TABLE I

pH selective electrode				
Platform	**Sensitivity (mV/log [H^+])**	**Response time (s)**	**LOD**	**Drift mV/24 h**
Platform 1	−25.6 ± 1.6	150	3.5 units	26.5
Platform 2	−59 ± 1.8	50	2.6 units	20
Platform 3	−69.8 ± 0.8	30	3.5 units	10
Platform 4	−73.4 ± 0.6	10	2.4 units	4.2

C. AMPEROMETRIC GLUCOSE SENSING

Arguably the most successful biosensor commercially available is the blood glucose sensor. Using a paper substrate and a finger prick to provide a blood sample, the device can provide rapid results with little training required.

Developing a system that can detect glucose non intrusively could build on this achievement through the further improvement of patient quality of life. It is for this reason Kassanos *et al.* developed the PCB based amperometric glucose sensor [12]. Using an array of reference electrodes (REs), working electrodes (WEs) and counter electrodes (CEs), shown in Fig.4, an amperometric reading of the sample is taken. The current level corresponds to a concentration of glucose, shown in Fig.5.

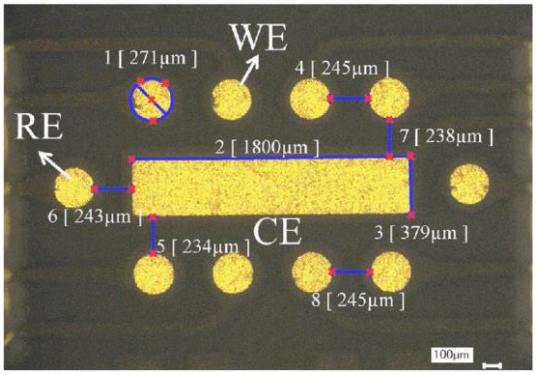

FIGURE 4. **Layout of the three-electrode typed for optimal amperometric sensing**

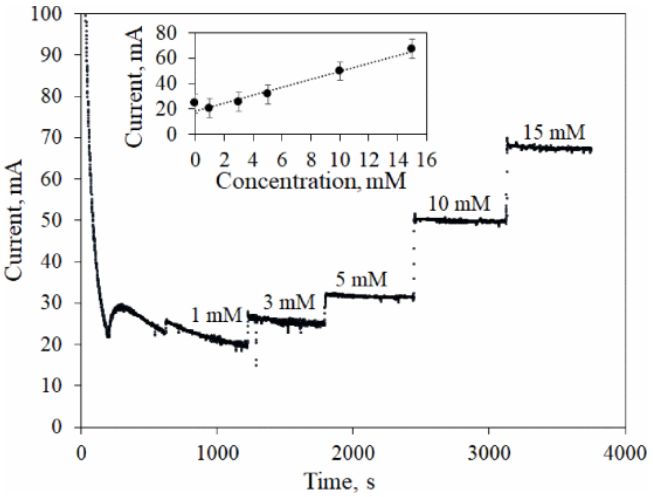

FIGURE 5. **Current readings mapped to varying concentrations of glucose added to a sample solution.**

This design offers a sensitivity of 3.13µAcm^{-2}mM^{-1} and a limit of detection of 0.8 mg/dL. For glucose concentration in sweat, which ranges from 0.1-50 mg/dL, this device may not fulfil the required demands due to lack of sensitivity. For other applications such as detection in urine, the device proposed is more than capable as any sign of glucose in a urine sample can signify worsening diabetes. This device shares many similarities with the potentiometric sensing of anastomotic leakages in design and function. Both use an array of reference and sensing electrodes and rely on surface detection on the electrode to measure change in analyte concentrations while in contact with an organ. The glucose sensor however shows much more promise as it lacks issues with respect to locating the sensor on the patient, as well as worries about the location of electronic hardware within a patient. This LoPCB is fit for use in some medical applications but still struggles to reach required sensitivities in its target function. The cost of this device and similar glucose measurement devices is extremely cheap however its alternative, using a dipstick, is also extremely cheap with one hundred tests costing as little as £5.45 [13].

D. IMPEDANCE SPECTROSCOPY FOR DETECTION OF CARDIAC MARKERS THOUGH IMMUNOASSAY

Myocardial infarction (MI) is a medical emergency in which blood supply to the heart is cut off. This is obviously a serious problem, the detection of which can be vital for medical professionals to administer correct and early treatment [14]. MI is typically detected through three key cardiac markers: Creatine-Kinase (CK-MB), Cardiac Troponin and Myoglobin [15]. The strongest correlation between a MI specifically is the detection of Cardiac Troponin, as it is only released when irreversible damage is done to the heart. It has been found that the volume of Troponin released is also proportional to the damage done, so, any device that can accurately measure low concentrations in a short timeframe can offer medical professionals vital information.

One of the most accurate detection methods available to LoPCB technology is impedance spectroscopy, which is used by Jacobs *et al.* alongside immunoassay for incredibly sensitive Troponin detection [16]. Immunoassay is the utilisation of highly specific antibody-antigen bonds to detect analytes. In this design, the sensor is coated with immobilised antibodies that capture the Troponin molecules and bind them to the substrate (Fig.6). An impedance measurement across the substrate is taken before and after the sample is added and the impedance of the two is compared to produce a measurement of Troponin concentration.

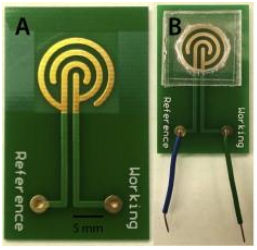

FIGURE 6. PCB used for detection of Troponin. The film shown in A and B over the electrode contains ZnO columns used to confine molecules to enhance biosensing.

A sensitivity of 10fg/mL was achieved comfortably which could reduce the time till detection from conventional methods (12 hours) dramatically and improve patient mortality rates [17]. The use of immunoassay differentiates this design from the previous examples but is an incredibly common method of bio-detection and has large benefits i.e., reducing rates of false positives. It shows a similar basis, however, with the use of a gold electrode for surface-based detection, a common theme among impedimetric, potentiometric and amperometric sensing.

IV. CONCLUSION

Overall, LoPCB technology fit a gap in the market for rapid testing for the prognosis and diagnosis of specific medical conditions. The format of a PCB offers a cheap scalable solution allowing complex designs to be mass produced with ease keeping end costs low and commercial viability high.

The size and speed of the devices often make for a powerful point of care tool but can lack the sensitivity or accuracy of full lab testing or other conventional methods. This could be a biproduct of the field's infancy. Table II shows a comparison of the devices assessed in this review.

TABLE II
COMAPRISON OF DISCUSSED DEVICES

Device/ Technology	Detection	Limit of Detection (LoD)	Sensitivity
A	Impedimetric	$1x10^3$ mL^{-1}	-
B	Potentiometric	10^{-5} [Na^+], 10^{-5}[K^+], 2.4 units pH	73.4 mV/pH, 56.3 mV/log [Na+], 57.4 mV/log [K+]
C	Amperometric	0.8 mg/dL	3.13μAcm−2mM−1
D	Impedance spectroscopy	-	10 fg/mL

Device/ Technology	Complexity compared to conventional methods	Cost	Potential (Rated from 0-10)
A	Lower	$2	4
B	Lower	'Low'	6
C	Higher	'Low'	3
D	-	'Low'	8

In the coming decades, as more research and funding is attached to the concept of LoPCB, it could become a powerful tool for the decentralisation of healthcare in low-income areas, or rapid detection of disease or illness in order to improve medical care and reduce morbidity and mortality across the economic landscape.

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APPENDIX

Appendices, if needed, appear at the end of the document.