A Fluidic Cell Embedded Electromagnetic Wave Sensor for Online Indication of Neurological Impairment during Surgical Procedures

R.T. Blakey¹, A. Mason and A.I. Al-Shamma’a
BEST Research Institute, School of Built Environment, Liverpool John Moores University, Liverpool, UK.

Email: r.t.blakey@2010.ljmu.ac.uk

Abstract. Lactate is known to be an indicator of neurological impairment during aortic aneurysm surgery. It is suggested that cerebrospinal fluid removed during such surgery could provide useful information in this regard. Medical professionals find the prospect of online detection of such analytes exciting, as current practice is time consuming and leads to multiple invasive procedures. Advancing from the current laboratory based analysis techniques to online methods could provide the basis for improved treatment regimes, better quality of care, and enhanced resource efficiency within hospitals. Accordingly, this article considers the use of a low power fluidic system with embedded electromagnetic wave sensor to detect varying lactate concentrations. Results are promising over the physiological range of 0 – 20 mmol/L with a calibration curve demonstrating an $R^2$ value > 0.98.

1. Introduction
It is well known that patients undergoing surgical or endovascular aneurysm repair (EVAR) of acute and chronic thoraco-abdominal aortic disease [1, 2] have an inherent risk of paraplegia. This is caused by restriction of the spinal cord blood flow and lack of oxygen during the procedures, typically referred to as spinal cord ischemia [3]. The current preventative measure practiced by surgeons is to collect cerebral spinal fluid (CSF) by inserting a spinal drain. In doing so, pressure upon the spinal cord is reduced, and thus, so too is the inherent risk of paraplegia.

The authors have been working for some time toward developing a method which could make use of the collected CSF as a marker of some underlying patient condition. At the moment any CSF collected would normally be discarded as biological waste. However, researchers at Liverpool Heart and Chest Hospital (LHCH) are particularly active in looking for ways to identify the onset of paraplegia in patients. Part of this work involves CSF analysis in the search for indicators of sub-clinical cord ischemia and compromise. This notion at that CSF might harbour such important information is supported separate research [4] which observed that lactate concentration in CSF increased with the onset of patient paraplegia. One would normally expect to see physiological levels of lactate in blood around 1 mmol/L; in pathology this may rise to 10-15 mmol/L, or higher in the case of exercise [5].

¹ r.t.blakey@2010.ljmu.ac.uk
Analysis of CSF would be most practical immediately after it has been drained from a patient, since in many cases this would allow the surgeon to take immediate corrective action in addition to improved diagnostic accuracy. Other authors have considered optical [6, 7] and magnetic resonance [8] techniques for the quantification of analytes in CSF. In many cases, the in-situ analysis of CSF could remove the need for subsequent surgical procedures, thus improving the efficiency of hospital resources and arguably improving patient care. Previous work by the authors [9-12] has considered microwave spectroscopy using a resonant microwave cavity as a potential method to analyse CSF in real-time as it is extracted from a patient during surgery.

Microwave spectroscopy has seen use for a variety of purposes, including monitoring of water quality [13, 14], filter monitoring [15] and also for use monitoring oil, gas and water concentrations [16]. It is thought that the use of microwave spectroscopy, as in the previously mentioned applications, will provide affordable and rapid diagnostics for the healthcare scenario described in this work.

This work goes a step further through the application of a novel sensor system, patented by the authors [17-19], which makes use of a planar electromagnetic structure rather than a cavity. This structure could conceivably be placed in-line with a spinal tap and, more importantly, is much cheaper to manufacture than a cavity system. Thus, it serves as a more practical option than the cavities used in previous “proof-of-concept” work.

The microwave sensing technique is robust, requiring low power and having good depth of penetration in respect of analyte materials. Also, of particular interest in medical applications is the non-ionising nature of microwave radiation; the technique used in this paper has low power output at around 1 mW (0 dBm) but has good penetration depth and equipment could be made portable for use at the bedside. These are features which practitioners see as a significant benefit over existing technologies, particularly X-ray imaging [20].

The multi-parameter nature of broadband microwave analysis can provide unique signal spectrum signatures. In this work, captured microwave signals are presented in the form of scattering parameters (commonly referred to as S-parameters), with measurement of the reflected (S$_{11}$) and transmitted (S$_{21}$) microwave signal being possible. These signals vary depending upon properties of the analyte presented to the sensing structure, such as conductivity and permittivity [21]. Conductivity is a measure of a material’s ability to conduct an electric current. Permittivity is a measure of how an electric field is affected by a dielectric medium, which is determined by the ability of a material to polarise in response to the field, and reduce the total electric field inside the material. Therefore, permittivity ($\varepsilon_r$) as defined in (1) relates to a material’s ability to transmit an electric field and is a complex value which varies with frequency, and accounts for both the energy stored by a material ($\varepsilon'$) as well as any losses of energy ($\varepsilon''$) which might occur.

$$\varepsilon_r = \varepsilon' + j\varepsilon'' $$

As a material alters in concentration or type, it is likely that its permittivity will change leading to a change in response if the material is the target of microwave radiation. By measuring this response over a range of frequencies, one can characterise materials in order to infer their properties.

2. Materials and Methods

The novel structure used in this work is based upon a co-planar design. This design was chosen in order to minimise losses and interferences which might occur from external sources. Co-planar devices are well known for exhibiting this vital property, and therefore in this application offers a great deal of control in relation to how the sensor responds to analyte materials [22]. In particular, the sensor is constructed to ensure that only a small area is sensitive to dielectric change, which enhances significantly its robustness for the aforementioned use (i.e. in-line with a spinal tap). In addition, and as demonstrated in Figure 1, the electric field created by the sensor is dissipated significantly within 2 mm of its surface.
Figure 1. Illustrating the dissipation of the sensor electric field only a short distance from the sensor surface, which is particularly beneficial in removing environmental effects and interference.

The sensor is constructed in-house using an end mill process. An FR4 epoxy substrate is used which is coated on both sides with a 35 µm copper layer. After the milling process, tin plated finish is applied to the copper, and a side mount SMA connector is attached to provide connectivity to a Vector Network Analyser (VNA), discussed later, or other appropriate hardware.

The sensor is embedded in a bespoke fluidic cell constructed of polymethylmethacrylate (PMMA), which has a high performance liquid chromatography (HPLC) compatible inlet and outlet ports in order to allow fluid to pass through the cell and come into contact with the sensor device itself. Although this system represents a laboratory environment, it is feasible that a fluidic cell such as this could be placed in-line with a spinal tap, or similar depending on the application, and thus the CSF analyte could easily be introduced to the sensor during a surgical procedure. Testing of this principle will be the aim of future work. The sensor and fluidic cell combination is shown in Figure 2.

Figure 2. The sensor and fluidic cell combination used for the experimental work.

In order to test the capability of this sensor system, the work involves the use of a synthetic CSF, comprising deionised water combined, in varying quantities, with L-(+)-Lactic acid solution (Sigma-Aldrich, 27714). In particular, the following concentrations (mmol/L) were measured: 0, 0.2, 0.4, 1, 1.6, 2, 4, 10 and 20. The experimental work was repeated 6 times and an average of the results taken. Between each repetition the fluidic cell was cleaned with deionised water in order to eliminate possible contamination. A quaternary pump (Perkin Elmer) was used to introduce samples to the fluidic cell, and this was used to mix the lactic acid and deionised water to the concentrations previously detailed. The deionised water and lactate solutions were stored in an incubator at 30 °C, and feed tubes between the solutions and fluidic cell were kept short to minimise temperature loss. Each measurement took 3 minutes; 1 minute was allowed for the system to be flooded with the analyte.
and a further 2 minutes settling time was allowed. A low (2 ml/min) pumping speed was selected to minimise the build-up of air in the fluidic cell resulting from turbulence, particularly in the area contacted by the sensor. In the real world, this speed could easily be emulated in-situ although the speed of pumping itself has been found to have little direct effect on the response of the sensor beyond issues with air build-up.

Dielectric measurements were performed using an Agilent Technologies (Hewlett Packard) 8720 ET Vector Network Analyser (VNA). The instrument was set to generate a signal between 100 MHz and 1 GHz over 1601 data points for 10 linear frequency sweeps and calculate the $S_{11}$ (reflected signal) parameters. Data was collected using bespoke LabView software and later analysed, as shown in Section 3 of this paper. The complete experimental setup is shown in Figure 3.

![Figure 3. Overview of the experimental setup, including quaternary pump, vector network analyser and sensor system.](image)

### 3. Results

The $S_{11}$ measurements taken during the experimental work were used in order to identify change which occurred due to the varying concentration of lactic acid. Two resonant peaks where noted as responding to the change in lactate concentration. When water was present in the cell, these peaks were at approximately 394 MHz and 573 MHz; the latter however was found to give more pronounced response to lactate and so results for the fundamental resonance only are presented in this paper.

In Figure 4, the response of the sensor is shown as captured from the VNA, with the shift in electromagnetic spectrum clearly demonstrated. In Figure 5, the sensor response is shown in the form of a calibration curve over the full range of concentrations tested. Deionised water is used as a background reading against which all other readings are normalised; thus the results emphasise the change in response of the sensor at the indicated frequency. The sensor shows a logarithmic response, with the greatest sensitivity shown up to concentration levels of 2 mmol/L. From Figure 5 it is clear that there is a good correlation ($R^2 > 0.98$) between the sensor response and the lactate concentration.
These results are an important step forward for this work, which has for a number of years strived to develop a method for real-time CSF analysis which would be simple to implement and not require any significant change to current surgical procedure. While previous work has shown the potential for electromagnetic wave techniques (e.g. cavities and planar structures), this shows a technique which could be applied in-line to current spinal tap procedures.

The technique uses only a small amount of power in the microwave region (approx. 1 mW). It is therefore non-destructive and, more importantly in a medical setting, non-ionising. It is important also to mention that the sensor response, after cleaning, returned to its original baseline output when flooded with deionised water which is promising in terms reliability and robustness for long term use. Longevity may not be a pressing concern in the healthcare field, as it is likely the sensor system would be single use due to potential biohazard risks. However, in other applications long term use of the sensor would certainly be preferable, and the authors are looking to apply this technique in other areas including water quality monitoring, industrial process monitoring and for biomedical screening.

One feature of note with the sensor, namely with the substrate material chosen, was the effect of water absorption. Over a period of time, the sensor substrate could be observed to absorb water, which was evident as drift in the sensor output signal. This was easily compensated however by allowing a significant pre-experimental period where the sensing system was exposed continuously to deionised water for a period > 40 hours. After this time, the change in sensor output as a result of drift during a single experiment (i.e. maximum change is 6.17×10^4 Hz) is considerably smaller than the change resulting from change of lactate concentration (i.e. 1.07×10^6 Hz). This drift could be compensated during manufacture, and would not be a feature of any sensor used for in-situ measurements. Figure 6 shows the variation of sensor output over time, with the largest change in resonant frequency apparent within the first 20 hours of operation. After this time the sensor output stabilises significantly, with small variations being accounted for by small changes (± 2 °C) in the laboratory temperature as a result of the thermostat controlled heating and ventilation system.

The variation of sensor output due to the choice of substrate is currently under investigation, and it is proposed that using alternative substrates (e.g. ceramic) will resolve current issues with sensor drift. In addition, temperature variation is likely to be resolved by using a differential measurement method. Once implemented, these remedial methods are expected to greatly improve the sensor usability.
This work has successfully proven the concept that novel electromagnetic sensor embedded into a fluidic cell is an attractive technique capable of providing real-time information on the composition of the CSF. In previous work a microwave cavity technique was used to perform offline measurements of lactate suspended in a phosphate buffered saline (PBS) solution, since this is considered more representative of blood than deionised water. Due to the added conductivity of the media, it is proposed that this is a far more challenging environment for the sensor to operate in. Therefore further work with this sensor will consider the use of both PBS and blood background media spiked with similar concentrations of lactate as demonstrated in this paper in order to determine a more realistic idea on the sensitivity of this sensor for the intended application. An important aspect however is that the purpose of this sensor is not for precise quantification of lactate in blood, but rather to determine if the level is too high. This alone would indicate if there is some underlying issue with the patient; a precise value would be of little use to a surgeon in theatre. If the sensor indicates the elevated lactate level, its exact value could later be determined using standard laboratory procedures.

Alongside this work, the response of the sensor to other analyte solution types and concentrations is being explored and a database of these microwave signature spectra is being compiled, which can later be used for online process control in a broad range of industrial applications in the wastewater industry, chemical and pharmaceutical production lines.

4. Conclusion
An electromagnetic wave sensor embedded within a fluidic cell has been reported. The system demonstrates an improvement over previous work by the authors, and is a step toward achieving the goal of a truly online system for the indication of lactate level (i.e. is it abnormally high?) in a patient under-going a procedure such as surgical or endovascular aneurysm repair. The paper demonstrated sensitivity of the sensor system to varying levels of lactic acid, in the range 0 to 20 mmol/L in a deionised water solution. The measured results (i.e. resonant peak shift) at 394 MHz from the electromagnetic wave sensor show an excellent correlation with the varying concentration. Further work will consider other background media (e.g. blood), in addition to other potential applications in the biomedical, process and water industries where real-time monitoring of various fluidic analyte materials is becoming ever more necessary.

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