

Non Invasive Microwave Sensor for the Detection of Lactic Acid in Cerebrospinal Fluid (CSF)

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Abstract. This research involves the use of a low power microwave sensor for analysis of lactic acid in cerebrospinal fluid (CSF), an indicator of neurological impairment during aortic aneurysm surgery which could provide the basis for improved treatment regimes and better quality of care with more efficient use of resources. This paper presents initial work using standard lactate curves in water followed by lactate in “synthetic CSF”. A multi-modal spectral signature has been defined for lactate, forming the basis for subsequent development of microwave sensor platform that is able to detect concentrations of lactic acid in CSF of volumes less than 1ml.

1. Introduction

The electromagnetic waves ranging from 0.3GHz up to 300GHz can be used to analyse the cerebrospinal fluid (CSF) from the patient based on the electrical properties for chemical specification contain in the fluid. Microwave analysis has a range of advantages for biomedical applications. It is a non-ionising technique utilising low power output at around 1mW (0dBm) but has good penetration depth and equipment can be portable for use at the bedside. The multi parameter nature of broadband microwave analysis can provide unique signal spectrum signatures which is a reflected signal $|S_{11}|$ and/or a transmitted signal $|S_{21}|$ based on parameters such as conductivity and permittivity [1]. Conductivity is a measurement of a material's ability to conduct an electric current. Permittivity is a measurement 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 relates to a material's ability to transmit an electric field and is a complex value which varies with changing frequency, and accounts for both the energy stored by a material (ϵ') as well as any losses of energy (ϵ'') which might occur.

This project is work in partnership with Liverpool Heart and Chest Hospital (LHCH). LHCH has commenced with the analysis of CSF fluid. Patients who are undergoing surgical or endovascular aneurysm repair (EVAR) of acute and chronic thoraco-abdominal aortic disease [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, referred to as spinal cord ischemia [3]. The current preventative measure is to

insert a spinal drain to relieve pressure. At present this fluid is discarded as waste, but researchers at LHCH believe that analysis of the CSF can be used to indicate sub-clinical cord ischemia and compromise. If microwave analysis of CSF can be used to detect and monitor impending cord ischemia, intervention may be performed to reverse this process before irreversible ischemia and paraplegia are clinically apparent.

2. Sample Preparation

Serial dilutions of L(+)-lactic acid which were prepared to cover a range from low, physiological and supraphysiological levels (0-64 mmol/L) in distilled water and in a more complex solution prepared in-vitro containing some of the major constituents of CSF. An ultrafiltrate of plasma, CSF contains approximately 0.3% plasma proteins (15 to 40 mg/dL) of which low-molecular weight proteins predominate [4,5] "Synthetic CSF" was prepared from an ultrafiltrate of human citrated plasma [6] using Amicon Ultra-4 centrifugal filters to exclude proteins above a molecular weight of 100 kDa to mainly prealbumin, albumin and transferrin together with other low molecular weight constituents that may be found in CSF in-vivo. The plasma filtrate was diluted in Dulbecco's phosphate buffered saline (DPBS) (-CaCL₂, -MgCL₂, Ph 7.4) [7] to give approximate protein levels found in normal CSF samples. Sample concentrations were as follows: 0mM, 0.25mM 0.5mM, 1mM, 2mM, 4mM, 8mM, 16mM, 32mM, 64mM and 1M.

3. Electromagnetic Waves Fundamental and Waveguide

Electromagnetic (EM) waves [8,9] are waves of energy that travel through a vacuum at the speed of light, approximately $c=3 \times 10^8$ m/s. EM waves consist of two primary components, an electric (E) field and a magnetic (H) field. The electric field and magnetic field oscillate in phase perpendicular to each other and perpendicular to the direction of energy propagation. EM waves can be visualised as a sinusoidal wave.

3.1. Maxwell's Equations

Maxwell's equations [10] describe the relation of the electric and magnetic field to each other and to the position and motion of charged particles. Maxwell's equations relate the electric and magnetic fields to their sources, charge density and current density. The equations can be combined to show that light is an electromagnetic wave. The general four fundamental electromagnetic equations are shown in equation (1) to (4),

$$\nabla \cdot D = \rho \quad (1)$$

$$\nabla \cdot B = 0 \quad (2)$$

$$\nabla \cdot E = -\frac{\partial B}{\partial t} \quad (3)$$

$$\nabla \cdot H = J + \frac{\partial D}{\partial t} \quad (4)$$

In equations (1) to (4), E represents the electric field in volts per metre (Vm^{-1}) and H represents the magnetic field in amperes per metre (Am^{-1}). D is electric displacement field in coulombs per square metre (Cm^{-2}) and B is the magnetic flux density in tesla (T). J is the electric current density in amperes per square metre (Am^{-2}) and ρ is the electric charge density in coulombs per cubic metre (Cm^{-3}).

3.2. Waveguide

The waveguide [11] is a particular form of transmission line; it is a hollow conducting tube to contain the electromagnetic energy. The different configuration of electric field and magnetic field could exist in the waveguide and are known as transverse electromagnetic (TEM) modes. The transverse electric (TE) and transverse magnetic (TM) are the two types of mode which usually exist in the waveguide.

The electrical power is transported through a waveguide by means of electromagnetic waves, which can take several different forms (modes), depending on the frequency, the waveguide dimensions and the material properties inside. This determines how the electric and magnetic fields appear in the waveguide.

The two most important modes in the circular waveguide are known as TE_{111} and the TM_{010} modes which are shown in Figure 1. The red line in Figure 1 represents electric field and the green line represents magnetic field. These modes differ from electromagnetic waves in free space because they have to be higher than a certain minimum frequency in order to be able to propagate through the waveguide at all.

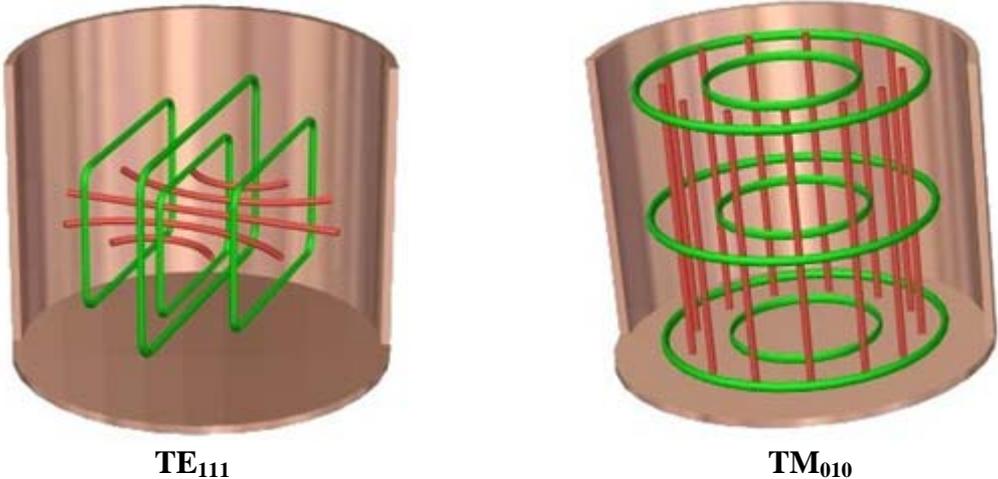


Figure 1: Electromagnetic mode patterns in a circular waveguide

4. High Frequency Structure Simulator (HFSS)

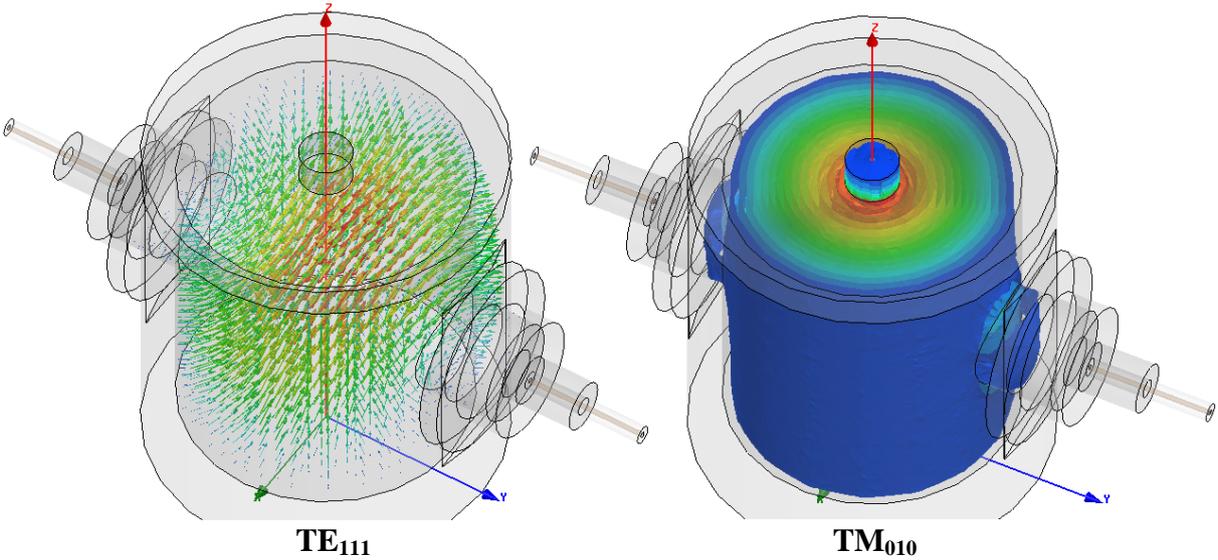


Figure 2: TE and TM modes in a cylindrical cavity

High Frequency Structure Simulator (HFSS) is a 3D full wave electromagnetic field simulation software which can be used to design RF structures [12]. HFSS can be used to design IC packages,

PCB interconnects, antennas and RF and microwave components. The outputs of HFSS include S-parameter, Full-Wave SPICE extraction and 3D electromagnetic field simulation [13].

The TE and TM modes for cylindrical cavity which was used for this project can be simulated by using HFSS. Figure 2 shows the configurations for the first two modes in a cylindrical cavity which is used for this project. Figure 2 shows the first TE_{111} modes, and the second TM_{010} modes in the cavity. The red colour region in Figure 2 represents the maximum and the blue colour region represents the minimum of the electric and magnetic field.

5. Experiment and Results

The project begins with the evaluation of microwave technology using the simplest of a number of proposed biomedical applications, lactic acid as a marker of ischemia in CSF. This is partly due to lactate being inexpensive and also CSF provides a relatively simple background that can be synthesised in-vitro.

The LHCH laboratory prepares the samples, placing lactate in water and lactate in “synthetic CSF” with varying concentrations; 10ml volumes are placed in polypropylene centrifuge tubes. A ZVL-6 Rohde and Schwarz VNA was used, and temperature variations were minimised through the use of an environmental chamber. A cylindrical cavity sensor was used for the sample measurement which is shown in Figure 3. With the cavity attached to the VNA, it is possible to measure microwave spectrum parameters. The cavity was designed to accept 15ml polypropylene centrifuge tubes, which must contain identical fluid volumes since the cavity is volume sensitive. This system facilitates empirical analysis of materials presented to the cavity and is useful for determining specific areas of interest in the microwave spectrum.

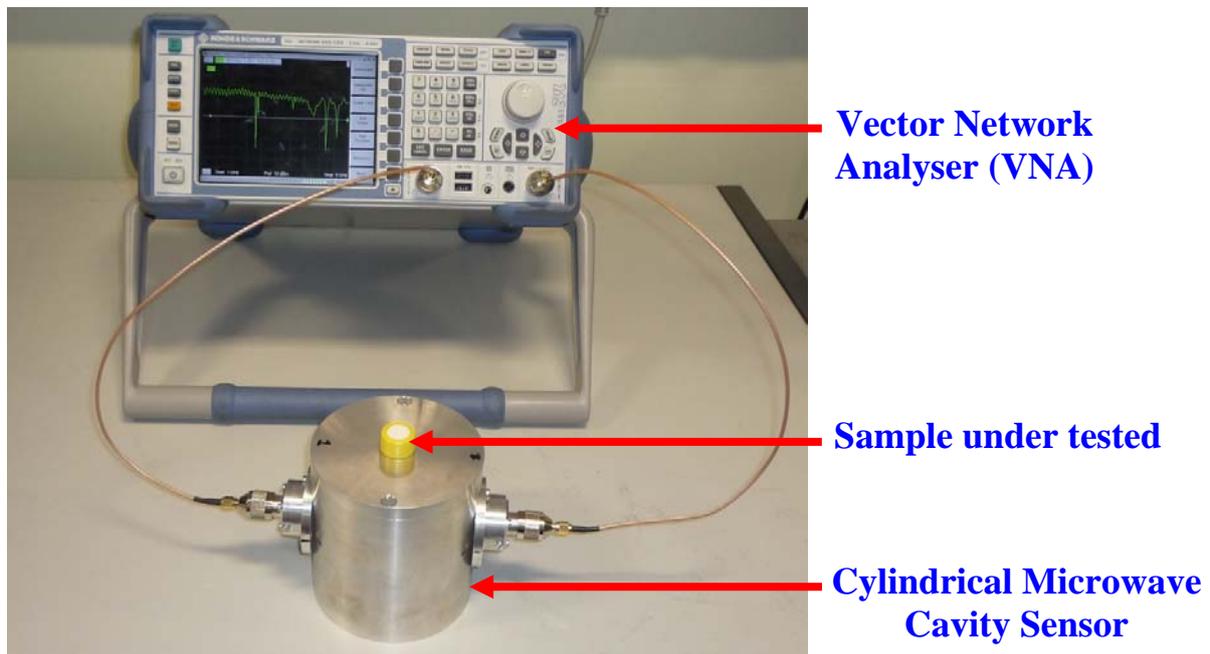


Figure 3: Experimental setup for lactate measurement

Figure 4 shows the $|S_{11}|$ for lactic acid in water. From Figure 4, one can see the level of amplitude decrease as the concentration of the lactic acid increases from 0mM (blank) to 64mM at around 1040MHz. These results also demonstrate a linear sensor response to varying concentrations of lactic acid.

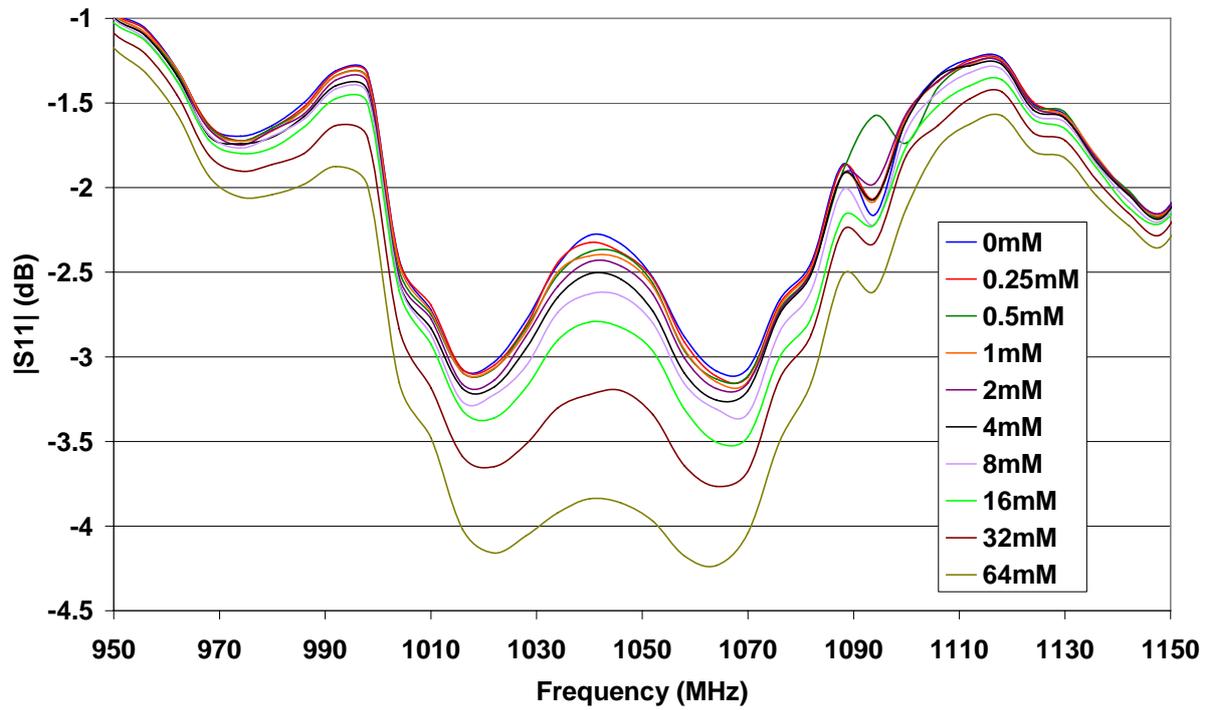


Figure 4: $|S_{11}|$ for lactic acid in water

Figure 5 shows the $|S_{11}|$ for lactic acid in “synthetic CSF”. From Figure 5, one can see the signal amplitude decrease as the concentration of the lactic acid increases from 0mM to 64mM at around 1035MHz. These results also show the linearity for the lactic acid with different concentrations.

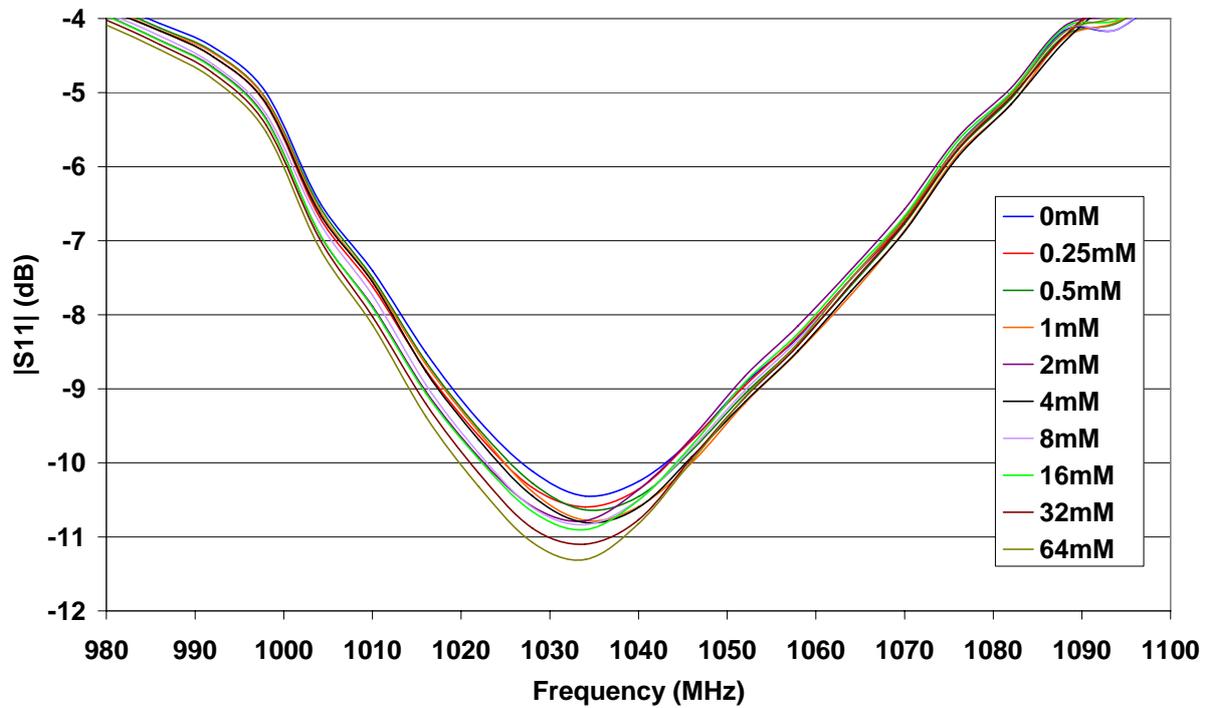


Figure 5: $|S_{11}|$ for lactic acid in “synthetic CSF”

6. Conclusion

Microwave detection in biology is an emerging new field with potential applications ranging from the non-invasive measurement of substances in blood such as glucose, alcohol and drugs, to the detection of infections and cancer. The sensor shown in this paper exhibits promising results for the lactic acid in water and “synthetic CSF”. The work here serves as a means to identify the detection limits associated with the technique before progressing in defined steps towards validating the method for measuring lactic acid in patient CSF samples and then expanding the work to include other clinically useful indicators in CSF such as albumin, glucose, lactate dehydrogenase (LDH) and other biomarkers present at lower (μM) concentrations. This research aims to work towards multi-parameter biochemical measurements in a range of more complex biological fluids and to investigations with cellular material.

7. References

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