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A bio-impedance probe to assess liver steatosis during transplant surgery

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Abstract—
This work addresses the design of a bioimpedance probe to assess steatosis on the exposed liver in the donor during liver transplant surgery. Whereas typically bioimpedance uses needle probes to avoid surface effects, for clinical reasons a non-penetrative probe is required. In addition the need to ensure that the measurement is representative of the bulk tissue suggests a larger probe than is normally used to ensure a sufficiently large measurement volume. Using a simple model, simulations and tests on bovine liver, this paper investigates the relationship between probe dimensions and depth of measurement penetration and investigates the accuracy which might be expected in a configuration suitable for use in the operating theatre on intact but exposed livers. A probe using ECG electrodes is proposed and investigated.

I. Introduction

Increased demand and a shortage of organs for transplant means that there is increasing use of steatotic livers – liver cells with excess intra-cellular fat content. These are more susceptible to injuries during ischaemia and reperfusion, and have lower tolerance to hypoxia [1]. Visual inspection prior to removal from the donor provides an indication of the liver's utility but a method to quantify the degree of steatosis at this stage would be a valuable tool in assessing the likely success of a transplant. Analysis of biopsy samples is not always appropriate because of the time taken to assess the sample and the feasibility of having one done at short notice. Currently livers are assessed histopathologically into three groups within the range of fat content between 0-100%; a target is to provide discrimination into bands of 10-15%.

Bioimpedance is a sensitive measure of tissue characteristics [2]. Parramon et al. showed correlation with steatosis in rat livers [3], with an increase in impedance of 50% for high fat (33%) livers over a control group (<5%). Haemmerich et al. [4] measured differences in conductivity of four between healthy liver tissues and metastatic tumours after ablation; Laufer et al. [5] showed a difference with cirrhotic liver. Bahti et al. [1] demonstrated correlation with steatosis in human livers tested in the donor during surgery.

The impedance of cells is normally modeled as A first order low pass response (e.g. the Cole-Cole mode [3]). The low frequency resistance is expected to be particularly sensitive to fat content [3] but rather than relying on spot frequency impedance measurements, a more robust approach is to use phase or, preferably, swept frequency measurements to estimate roll off (transition) frequency. Simple analysis of uniform current flow in a volume with rectangular cross section suggests that phase is a better measure of fundamental properties (conductivity, permittivity) than the magnitude of impedance, which depends strongly on sample dimensions.

Tetrapolar needle probes with collinear or small square electrode configuration and needle spacing 1-2mm, sampling a region of several cubic millimetres [2,3,4,5], are well established in the literature for single and multi-frequency measurements on samples of excised tissue. However the application in transplant surgery addresses new challenges. Measurements must be taken without penetrating the liver; hence the probe must be as robust as possible to surface effects and structure (e.g. bile ducts, veins) beneath the surface; this suggests a larger measurement volume (cm^3 rather than mm^3). Precision in placing the probe is not possible in the operating theatre - the donor liver is exposed with blood supply intact – and measurements have to be made following exposure of the liver at the donor procedure. Bahti's results [1], from a probe with potentially very large measurement volume to overcome the problem of inheterogeneity, were affected by variability in positioning and liver size.

In this paper, the relation between measurement volume and size of a collinear probe is presented. The model shows that current distribution is related primarily to the separation of the feed electrodes in a uniform medium, and this allows probes of different sizes to be investigated for robustness to organ structure and surface effects.

II. Background

In transplant surgery, the anterior aspect of both left and right lobes are initially exposed. Liver dimensions are donor dependant, the right lobe being larger. It is wedge shaped, with vertical height varying from about 3cm - 7cm over its depth of about 18cm [6]. The upper (diaphragmatic) surface of this lobe is the target measurement site.

Normal liver consists largely of cellular tissue, organised in a hexagonal structure, surrounded by a connective layer, the Glisson's capsule, between 70 and 90μm thick [10]. Fat

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is usually contained as discrete globules within the cytosol of liver cells. The tissue may be considered uniform at typical scales of bioimpedance measurement.

However, at the macroscopic scale, the lobe is non-uniform. Bile ducts, arteries and veins, typically several mm in diameter, constitute around 5% of liver volume [8]. Both blood and bile have significant larger conductivities (relative conductivity to excised liver tissue liver, 6-12 [2,4]), or possibly 3-6 times larger than perfused liver [9]. It is desirable to ensure that the measurement volume is significantly larger than duct or vein size to avoid over sensitivity to position. This suggests that large probes are better. The larger depth penetration of bigger probes also improves robustness to surface effects, such as Glisson's capsule (significant in surface elastography [7]) and possibly blood flow. However the downside of a larger measurement volume is that if it extends close to the boundary of the sample, the sample dimensions affect the current distribution and so the measurements (see sec III).

In the next sections the relation between 3-D current density distribution (on which the measurement volume primarily depends) and probe dimensions is investigated using a simple analytical model. A finite element simulation is developed to investigate errors arising from surface and bulk artifacts for a collinear tetrapolar probe. Experiments on bovine liver, to assess reproducibility and errors from sample dimensions, are described.

III. Methodology: Modelling and Simulation

A. Simplified Analytical Model

Consider Fig 1, which shows the two current injection electrodes of a tetrapolar probe. Assume that the probes are placed in (perfect) contact with the surface of a semi-infinite homogeneous conductive medium, at A and B in the figure.

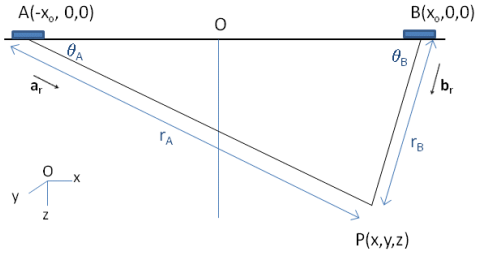

Figure 1: The geometry of the sample and two feed electrodes

Consider a constant current, *I,* injected at the electrodes. Assume that the current injection is from a point at the centre of each and flows into electrode A and out of B (at $\pm x_o$,0,0). At point P (x,y,z), at distance r_A, r_B from the electrodes' centres, the current densities from each can be assumed to flow outwards in the radial direction, $\mathbf{a}_r$,$\mathbf{b}_r$:

$$J_A = \frac{I}{2\pi}\frac{a_r}{r_A^2}; J_B = \frac{I}{2\pi}\frac{b_r}{r_B^2} \quad (1)$$

Impedance is estimated through measuring the potential difference at the measurement electrodes, assumed collinear. It can be found by integrating the electric field (**E**=σ**J**) in any direction between the electrodes. For simplicity we choose to integrate along the x-axis and so the net density current of interest is the x-component. Consider therefore just this component of the current density, J_{xo}. At point P (x,y,z) including currents from both electrodes:

$$J_x = \frac{I}{2\pi}\left(\frac{\cos\theta_A}{r_A^2} - \frac{\cos\theta_B}{r_B^2}\right) \quad (2)$$

Substituting from Fig 1:

$$J_x = \frac{I}{2\pi}\left(\frac{x+x_o}{((x+x_o)^2+y^2+z^2)^{3/2}} - \frac{x-x_o}{((x-x_o)^2+y^2+z^2)^{3/2}}\right) \quad (3)$$

To show the dependence on feed electrode position, x_o spacing, these equations can be rewritten as follows:

$$J_x = x_o\frac{I}{2\pi}\left(\frac{X+1}{((X+1)^2+Y^2+Z^2)^{3/2}} - \frac{X-1}{((X-1)^2+Y^2+Z^2)^{3/2}}\right) \quad (4)$$

and $X=x/x_o$, $Y=y/x_o$, $Z=z/x_o$.

Note the spatial distribution of current density depends only on these normalised quantities, and not x_o itself.

So far we have assumed a semi-infinite model of tissue. The finite boundary conditions can be modeled using the method of images [11]. For example to include the effect of height, h, of tissue a set of electrodes, identical to the first, is placed at z = -2h, with polarity of current chosen so there is no the current crossing the physical boundary (z = -h) in the z direction. (Note the method is not exact because of the upper boundary - but it is a useful first approximation). Again the current distribution depends only on normalised quantities, with the addition of $H=h/x_o$.

A similar analysis can be carried out for the x-and y variations. In the y-direction, the situation is identical if the electrodes are considered to be point sources. In the x-direction the image is the feed pair.

B. Finite Element Models

The measurement configuration was modeled using the FEM modeler Comsol Multiphysics 3.5. The liver was modeled as a uniform cuboid in the Electromagnetics Conductivity Media d.c. model, assuming a cross sectional area of 10x10cm and depth between 1cm and 12cm. The probe was assumed to consist of four collinear electrodes, each of 5mm radius (modelling the ECG electrodes used in the experimental work). The model (See Fig 2a) was used to confirm current distribution and errors from artifacts and not to predict values; therefore current and conductivity were normalised to a values I=1, σ=1 in the liver tissue and, from the discussion in the last section, results can be interpreted in terms of dimensions normalised to the feed electrode spacing, taken as x_o = 1cm .

At 50kHz, the frequency of the experimental measurements, the skin depth is over 1m (taking σ= 0.1Sm^{-1} [3]). Therefore the d.c. and a.c. analyses are equivalent if

results are interpreted in terms of a complex conductivity. Two aspects of the liver were modeled: a surface layer (which may represent Glisson's capsule or may be from blood flow (conductivity relative to perfused liver, $\sigma_{rL} \approx 3$ – sec II), and bile ducts or veins, (for bile $\sigma_{rL} \approx 6$) modeled by rigid cylinders. Cylinders were placed with axes in the x- or y directions, and in positions of maximum current density (worst case scenarios). It is likely that the conductivity of Glisson's capsule is higher than liver; for example tendon, another connective tissue, has σ_{rL}=2.5 [12]. Dimensions were chosen to cover the range which might be encountered in the liver (sec II).

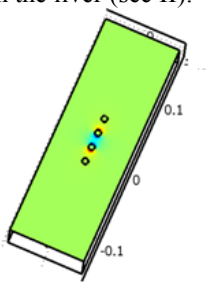

Fig 2a Geometry of FEM simulation with centre fed electrodes, x-current density shown on top surface (not to scale).

Fig2b:Probe showing trial positions for electrode insertion with ECG electrode inserted. (2cm between adjacent positions)

C. *Experiments*

To test repeatability and the probe design in operation, measurements were taken on bovine liver using the probe above and the 915 body analyser from Maltron International. The body analyser injects 0.7mA of current at 50kHz, and displays impedance and phase angle. The probe was a four electrode collinear probe, using ECG electrodes as shown in Fig 2b, but with feed and measurement ECG electrodes 5cm and 3cm from the origin respectively (i.e. x_o=5cm).

A complete ox liver was collected from a local abattoir shortly after killing and kept refrigerated until tests the same evening. Six samples were taken (two identical but with the capsule removed between them (capsule thickness estimated as 93µm [7]). All others had no capsule.

IV. Results

A. *Results and Simulation*

1) *Measurement Volume*

The probe measurement volume was assessed by examining the current density with depth. Fig 3 shows the variation in J_x with normalised depth, Z into the sample (on the z-axis).

Note the current density falls to half its surface value J_{xo} in a depth approximately equal to $z = 0.7x_0$. From the discussion at the end of section IIIA, we estimate the measurement region as approximately $0.7x_o$ in both depth and lateral directions. In the x-direction simulations show that it does not extend much outside the probe. These results support Parramon's identification of a 2mm measurement depth for the needle probe, fed from outside electrodes with x_0 = 2.7mm [3]. Note however that the change in J_{xo} with H because of height dependent current distribution leads to differences in the impedance measured with height H of the sample.

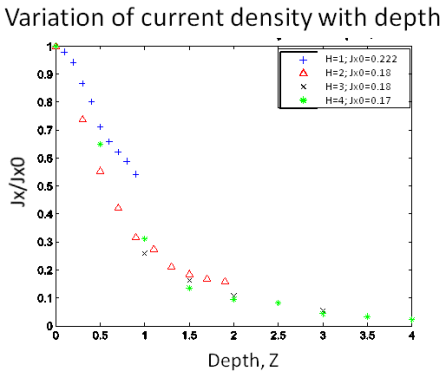

Fig 3 : Variation in horizontal current density J_x /J_{xo} crossing the z-axis with depth Z into the sample, where J_{xo} = J_x (0,0,0)

2) *Inhomogeneity: surface and bulk effects*

Fig 4 shows the effect of a surface layer, depth δ, over a range of conductivity (relative to liver tissue), σ_{rL} covering typical artifacts (sec II). For x_o = 1mm the upper line represents a layer of 100µm, such as Glisson's capsule. The error is small. However the error increases rapidly as the layer increases in depth: a layer of 200µm from, for example, blood contamination would give an error of around 10%. Errors are negligible for a larger probe ($\delta << 0.1x_o$).

Fig 5 shows results from models of small veins and ducts. The dimensions represents typical values if x_o =1cm. Errors are small. However if x_o =1mm the normalised radii would be 10 times greater, and errors very significant. Indeed for a small probe the whole measurement volume could be within a region of different σ_{rL}

3) *Bovine liver*

Fig 6 shows measurements on the bovine liver. The height of each sample varied depending on position in the liver. It was difficult to maintain the shape of the samples once the capsule was removed. Each point shows the average of three measurements taken with the probe in place; the variation in these was very low. The probe was removed and repositioned between each set of measurements.

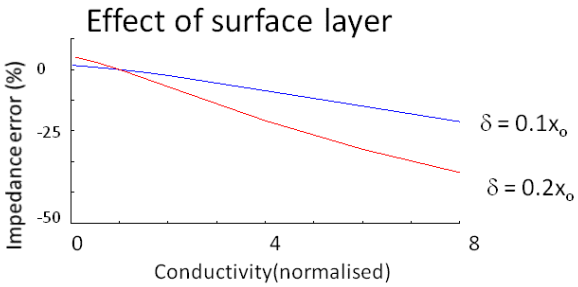

Fig 4: Impedance error (change from no layer) measured for layers of depth $0.1x_o$ and $0.2\ x_o$ on surface for different σ_{rL}.

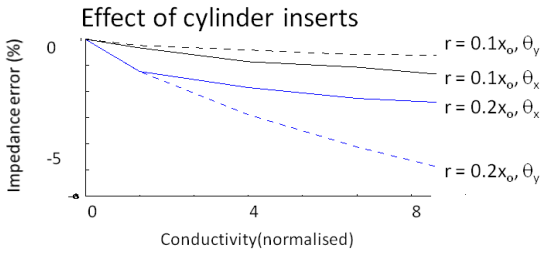

Fig 5: Error for cylinders, radius r, for different σ_{rL} . Cylinders orientated n x, y directions (θ_x , θ_y). θ_x placed directly below electrodes; θ_y below edge of feed electrode

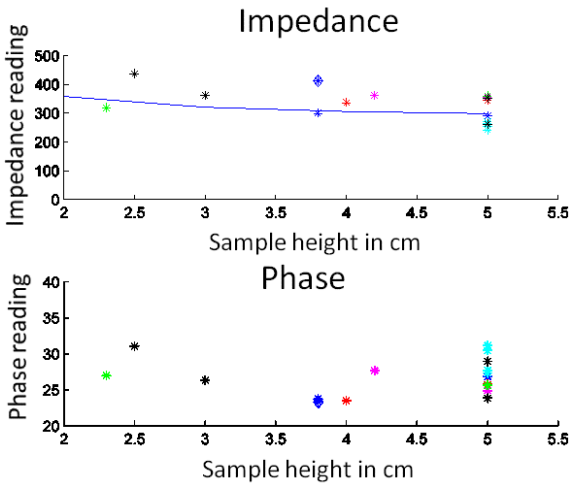

Fig 6: Measurements on six different bovine liver samples (each a single colour). Feed, measurement electrodes placed at: x= ± 5,3 cm. Solid line indicates the depth variation expected from simulation (drawn to pass through the mean impedance at 5cm.). Cyan samples with capsule; black represents the same samples with capsule removed. All samples: 12 x 7cm wide except sample circled on impedance plot: 12 x 3.8 cm wide

The capsule had no obvious effect. However sample height was significant, as predicted by the simulation (solid line in upper figure of Fig 6) for impedance; phase is robust to difference in sample dimensions. To correct for height, the solid curve in Fig 6 (top) was fitted to a third order polynomial (suggested by (4)). A correction of 1.12 (found from simulation) was also applied to the impedance measurement for the narrow sample at 3.8cm depth. Table I shows the standard deviation (normalised to mean) for phase, and for impedance with and without corrections. Phase is the more reliable measurement even after correction. Whether the impedance changes are from error or genuine liver structure remains to be investigated

TABLE I: NORMALISED STANDARD DEVIATION

Phase	Impedance	Impedance (corrected)
0.09	0.164	0.148

V. DISCUSSION

This paper has investigated the design of a probe bio-impedance to quantify steatosis in donor livers. A particular issue addressed is the reliability which might be achieved from using a surface tetrapolar probe on the right lobe of the liver in-vivo. Analysis and simulation have shown that the depth penetration of such a probe is related to the distance between its feed electrodes. A probe with feed electrode spacing of around a centimeter has sufficient penetration to avoid excessive errors resulting from structural artefacts below the surface, although blood vessels and bile ducts with radius of the order of 1mm and more may cause errors of a few percent, depending on their orientation and position. However as the depth penetration increases with feed electrode spacing, so does the sensitivity to sample dimensions. These observation, backed by measurements on sample bovine livers, suggests that, unless suitable sites can be chosen, impedance magnitude alone is not a good measure, and that phase may be a more reliable measure. Swept frequency measurements may also offer a measurement with greater robustness to changes in the size of the liver.

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