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A time-dependent model for improved biogalvanic tissue characterisation

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ABSTRACT

Measurement of the passive electrical resistance of biological tissues through biogalvanic characterisation has been proposed as a simple means of distinguishing healthy from diseased tissue. This method has the potential to provide valuable real-time information when integrated into surgical tools. Characterised tissue resistance values have been shown to be particularly sensitive to external load switching direction and rate, bringing into question the stability and efficacy of the technique. These errors are due to transient variations observed in measurement data that are not accounted for in current electrical models. The presented research proposes the addition of a time-dependent element to the characterisation model to account for losses associated with this transient behaviour. Influence of switching rate has been examined, with the inclusion of transient elements improving the repeatability of the characterised tissue resistance. Application of this model to repeat biogalvanic measurements on a single ex vivo human colon tissue sample with healthy and cancerous (adenocarcinoma) regions showed a statistically significant difference ($p < 0.05$) between tissue types. In contrast, an insignificant difference ($p > 0.05$) between tissue types was found when measurements were subjected to the current model, suggesting that the proposed model may allow for improved biogalvanic tissue characterisation.

1. Introduction

Evidence suggests that the surgical resection of cancer may benefit from being personalised [1,2]. Integration of such a treatment model requires more detailed data regarding tissue health than is currently available through standard preoperative imaging techniques. Therefore, the development of improved intraoperative assessment techniques is crucial. Intraoperative sensing has seen much focused research, through imaging using passive and active agents [3,4] and through direct measurement of mechanical [5] and electrical properties [6].

Measurement of the passive electrical resistance of biological tissues using a biogalvanic power source has been proposed as a simple means of distinguishing tissue type, or healthy from diseased tissue [7,8]. When integrated into surgical tools, this method has the potential to relay real-time information regarding tissue health. Success of the technique requires improved understanding of the electrochemistry of the galvanic cell as well as the electrical properties of tissues under direct current. The potential difference across a biogalvanic cell, established by placing two differing metal electrodes across a target tissue, can drive a measureable cell current. Modulation of cell current is achieved through sequential switching across a range of external resistive loads. With the assumption of a constant open circuit voltage (OCV), Golberg et al. [7] related the measured cell current, I for a specific external load, R_{EXT} to the internal resistance of the galvanic cell, R_{INT} using Eq. (1). Chandler et al. [9] proposed fitting the vector of voltages, $\boldsymbol{V}$ measured across the corresponding external resistances, $\boldsymbol{R_{EXT}}$ to an electrical model of the cell in accordance with Eq. (2). Fitting in this way was developed as a means of improving the accuracy and precision of the determined internal resistance and to avoid the assumption of a fixed OCV. However, results still showed significant hysteresis within the characterised internal resistance between increasing and decreasing external load switching directions [9].

$$\frac{1}{I} = \frac{R_{EXT}}{OCV} + \frac{R_{INT}}{OCV} \tag{1}$$

$$\boldsymbol{V} = \frac{OCV}{(\boldsymbol{R_{EXT}} + R_{INT})}\boldsymbol{R_{EXT}} \tag{2}$$

The hysteresis shown is due to transient behaviour noted between external load switching points [10]. Two possible sources of this phenomenon are: (1) the diffusion of ions at the electrode–tissue

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1350-4533/

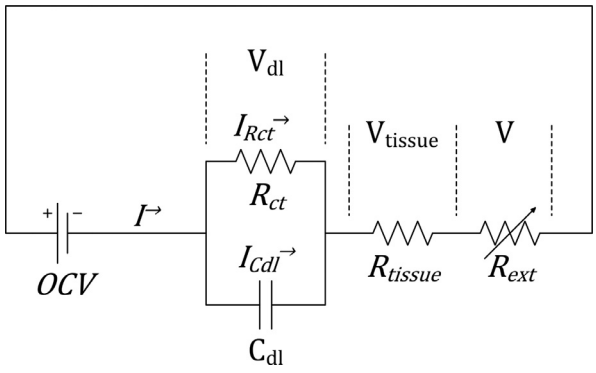

Fig. 1. Electronic equivalent model of the biogalvanic cell including time-dependent electrode interface parameters.

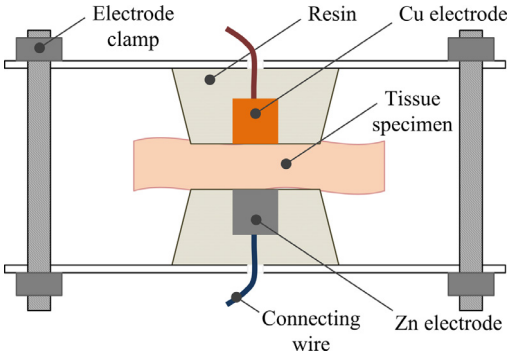

Fig. 2. Testing configuration for axially aligned biogalvanic characterisation cell.

interface, and (2) electrical losses caused by resistive and capacitive nature of the electrode–tissue interface.

Under certain conditions the current within electrochemical (galvanic) systems can be controlled by the rate of reaction at either the cathode or anode [11]. This may be determined by the rate of charge transfer or the mass transport of active species to/from the reaction interface. For a mass-transport limited system the diffusion of active species can lead to significant time varying currents within measured data [11]. Alternatively, transient currents may be associated with the electrical properties of the electrode interface. Specifically, the electrical resistance associated with charge transfer and the capacitive properties of the electrochemical double layer (EDL) may act in combination to produce transients with specific time constants [11]. Measurement and characterisation of these properties is a goal of techniques such as electrochemical impedance spectroscopy (EIS) [12], and transient based DC techniques [13]. This paper reports on adaptation of the biogalvanic characterisation model (Eq. (2)) to account for transient behaviour associated with electrical losses at the tissue–electrode interface. The study compares the influence of external load switching rates on the determined internal resistance of ex vivo porcine colon tissue using the two characterisation methods. Application of the transient model has also been extended to measurements taken from ex vivo healthy and cancerous human colon tissue. The efficacy of the technique is discussed in the context of application within surgical sensing.

2. Time-dependent model

The established fitting method [9] utilises a single resistance in series with the galvanic power source and external load, expressed in Eq. (2). Inclusion of time-dependent electrode interference can be achieved through a more comprehensive model, where aspects of the electrode impedance are included. Fig. 1 shows the developed model, where potential losses across the electrode (V_{dl}) are accounted for through a parallel resistance (R_{CT}) and capacitance (C_{DL}) associated with the charge transfer resistance and EDL capacitance respectively.

The cell can be considered as discrete voltage losses across the EDL (V_{dl}), tissue resistance (V_{tissue}) and external resistance (V) in accordance with Eq. (3). The voltage drop across the EDL forms the most complex aspect of the model, with the response given by Eq. (4), with the time-constant (τ) being the product of the charge transfer resistance and EDL capacitance. The steady-state current for a particular external load R^i_{ext} can be calculated using Eq. (5). The current step for subsequent loads (ΔI) is therefore determined as the difference in steady-state currents for sequential external loads. Eq. (6) gives the voltage response across a specific external resistance. Individual voltage responses for a set of external loads can be summed to give the full voltage–time response. A Levenburg–Marquardt algorithm [14] was implemented in software (LabVIEW, National Instruments) to optimise OCV, R_{ct}, C_{dl}, and R_{tissue} parameters to the measured voltage–time data based on known external loads and switching rate.

$$OCV = V_{dl} + V_{tissue} + V \tag{3}$$

$$V_{dl} = IR_{ct}\left(1 - e^{\frac{-t}{\tau}}\right) \tag{4}$$

$$I^i = \frac{OCV}{\left(R_{ct} + R_{tissue} + R^i_{ext}\right)} \tag{5}$$

$$V^i_{(t)} = OCV - \Delta IR_{ct}\left(1 - e^{\frac{-t}{\tau}}\right) + \Delta IR_{tissue} \tag{6}$$

3. Methods

Measurements were conducted on a single piece of ex vivo porcine tissue taken from the mid-colonic spiral and tested under laboratory conditions (20 °C) within 4 h of slaughter. The animal used was bred and sacrificed in accordance with UK Home Office regulations (Animals (Scientific Procedures) Act 1986). Test electrodes (12 mm diameter Zn & Cu) were set in non-conducting resin, wet ground (1200 grit) and clamped in axial alignment (separation 5.2 mm) under minimal strain onto the colon tissue, as illustrated in Fig. 2. A potentiostat (CompactStat, Ivium Technologies) was connected to the electrode and programmed to control the external load on the cell across 10 logarithmically spaced resistance values ranging from 1 MΩ to 336 Ω. A preliminary investigation was performed to assess the influence of time on the characterised resistance, associated with the drying of the tissue. Although an influence was shown, its effects were on a larger time scale than the presented studies. This factor was therefore assumed to not be influential within the presented data. The rate of external load switching was varied from 1 to 0.02 Hz in a random test order with the voltage–time response of each recorded at 100 Hz. Each voltage response was characterised using the models of Eqs. (2) and (6) and the representative tissue resistance values of R_{INT} and R_{tissue} determined respectively.

Freshly excised human colon tissue was obtained in accordance with NHS and Leeds University Teaching Hospital Trust ethics procedures. The tissue specimen was removed as part of a right hemicolectomy, with subsequent histopathology being performed after testing. Five repeats were taken within a healthy tissue region and five from the location of the tumour (identified by the surgeon). The electrode configuration was arranged as shown in Fig. 2. Testing was performed using the same external resistor range as with porcine testing, with switching rate fixed at 0.1 Hz. The time-dependent response from each test was analysed using the developed transient model and compared to characterisation using a single fixed internal resistance. For each model an independent samples t-test was conducted to compare the resistance of healthy and cancerous tissue.