White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Leeds.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/97325/

Version: Accepted Version

Article:
Chandler, JH, Culmer, PR, Jayne, DG et al. (2015) A time-dependent model for improved biogalvanic tissue characterisation. Medical Engineering and Physics, 37 (10). pp. 956-960. ISSN: 1350-4533

https://doi.org/10.1016/j.medengphy.2015.07.005

© 2015, IPEM. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International http://creativecommons.org/licenses/by-nc-nd/4.0/

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

A time-dependent model for improved biogalvanic tissue characterisation

J.H. Chandler[1*], P.R. Culmer[1], D.G. Jayne[2], A. Neville[1]

[1]*School of Mechanical Engineering, University of Leeds*
[2]*Leeds Academic Surgical Unit, St. James's University Hospital, Leeds*

[*]*Corresponding author: Tel: ++44 113 343 2179. Fax: +44 113 242 4611 E-mail address: mn07jhc@leeds.ac.uk*

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.

Keywords: biogalvanic; tissue resistance; galvanic cell; time-dependent model; electrochemical transients; tissue sensing; surgical sensing.

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 equation (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 equation (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].

$$\frac{1}{I} = \frac{R_{EXT}}{OCV} + \frac{R_{INT}}{OCV} \qquad (1)$$

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

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 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 (equation 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.

Time-dependent model

The established fitting method [9] utilises a single resistance in series with the galvanic power source and external load, expressed in equation (2). Inclusion of time-dependent electrode interference can be achieved through a more comprehensive model, where aspects of the electrode impedance are included. Figure 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.

Here Fig. 1.

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 equation (3). The voltage drop across the EDL forms the most complex aspect of the model, with the response given by equation (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_{ext}^{i}can be calculated using equation (5). The current step for subsequent loads (ΔI) is therefore determined as the difference in steady-state currents for sequential external loads. Equation (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.

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

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

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

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

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 Figure 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 - 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 – 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 equation (2) and (6) and the representative tissue resistance values of R_{INT} and R_{tissue} determined respectively.

Here Fig. 2.

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 Figure 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.

Results

Figure 3 shows the voltage measured across the external load as a function of time for the different switching rates employed. It is evident from the data that there is significant time dependence within each rate test. Voltage profiles between external load switching show an approximate exponential decay in most cases. External load switching rate therefore shows significant impact on the voltage measured prior to transition, as used in the characterisation model of [9]. It is evident that for longer duration tests that there is more deviation from the pure exponential decay under certain load conditions.

Here Fig. 3.

Here Fig. 4.

Application of the transient model fitting method to the measured data allowed characterisation of the different rates tested in terms of the four fitting parameters. An example of the fitting result is shown for the median rate (0.1 Hz) in figure 4. The quality of the fit is not completely consistent across the full load range of the test possibly suggesting parameter variation with cell potential. In this case, the model fit parameters may be considered as an average over the data range. Of the fit parameters, the tissue resistance has been used for direct comparison to the internal resistance of equation (2). Figure 5(a) shows the characterised resistance values for the two methods as a function of external load switching rate. Variability with rate is clear in both cases but is significantly reduced through the implementation of the transient model. This is demonstrated further by the reduction in standard deviation of the mean also presented.

Here Fig.5.

Histological analysis of the human tissue specimen reported a well differentiated caecal adenocarcinoma. Figure 5(b) shows repeat characterisations of this region along with a corresponding healthy tissue region using a single internal resistance model as presented in equation (2). On average, the characterised resistance using equation (2) was lower for healthy tissue (M = 62.7, SD = 12.8 kΩ), than for cancerous tissue (M = 67.2, SD = 5.2 kΩ). This difference, -4.5 kΩ, BCa 95% CI [-15.5, 8.6], was not significant $t(8) = -0.73$, $p = 0.475$; this represented a small-sized effect, d = 0.35. With the single fixed resistance model approach (equation (2)), the overlapping responses and their high variability makes discrimination of tissue health impossible for the sample tested. In contrast, application of the transient model to the voltage-time data (figure 5(c)) shows lower tissue resistance values with reduced variability for the respective tissue conditions. The average characterised resistance using this model showed a higher resistance for healthy tissue (M = 4.5, SD = 0.5 kΩ), than for cancerous tissue (M = 0.95, SD = 0.16 kΩ). This difference, 3.56 kΩ, was highly statistically significant $t(8) = 15.2$, $p < 0.000$; this represented a large-sized effect, d = 7.1. This indicates that, for the single sample tested, only the proposed model is capable of statistically differentiating between healthy and cancerous tissue.

Discussion

The external load switching rate has a significant impact on the measured voltage-time response. Due to the complex nature of the electrochemical system this influence is not exclusively due to resistive and capacitive phenomena at the electrode interface but also due to current fluctuations as diffusion of ion species impacts on galvanic reaction rates. Diffusion related drift in the voltage response appears more clearly over larger time-scale tests, particularly prior to load switching stages in the 0.02 Hz test shown in figure 3. This inevitably reduces the accuracy of the proposed model fitting method although it is evident from figure 4 and 5 that fitting to the model of equation (6) gives a good approximation to the system and yields meaningful data in terms of tissue resistance and electrode-tissue

interface parameters. In particular, figure 5(a) shows the results from resistance characterisation using implementation of equation (2) and the proposed transient model of equation (6). Significant dependence on the switching rate is shown for the former leading to a larger error in the mean resistance across all test conditions. Implementation of the transient model reduces this variability, through removal of the electrode parameters from the system. A lower average tissue resistance is produced with much less variability with switching rate. For application within surgery the measurement system should allow optimisation through control of the external load switching rate. With the proposed model of equation (6), it is feasible that the switching rate be reduced to allow faster characterisation, without causing large errors associated with electrode phenomena within the output metrics. Additionally, this use of the time-dependent model would allow comparison between resistance values characterised using different external load switching rates.

The characterised internal resistance values in figure 5(b) show poor specificity for healthy and cancerous tissue. This may be as a direct result of the relatively large and variable influence of the electrode resistance. However, application of the time-dependent model fit allows some separation of these electrode properties from the tissue resistance of interest. Figure 5(c) shows how the application of the proposed model gives much less variability and generates a clear distinction between the healthy and cancerous tissue tested. The values of tissue resistance are also much lower than those predicted using a single fixed internal resistance. Statistical analysis (independent samples t-test) indicates no significance ($p > 0.05$) when the model of equation (2) is implemented, while a significant difference ($p < 0.05$) is present upon application of the proposed model, equation (6). This result supports the use of the proposed model for biogalvanic determination of a tissue resistance. However, further repeated measures are required for assessment of the clinical efficacy of the technique.

It was evident from previous work [9], that the biogalvanic technique is practically suitable for integration into surgical tools for transmural tissue assessment. However, the sensitivity of technique to external loading rate and direction posed limitations to its application. The presented model adaptations offer a simple means of reducing the influence of these factors and move the technique a step closer to being suitable for surgical integration.

Improvement to the proposed model could be achieved by allowing variation of the fitting parameters over the range of external loads tested. In addition, diffusion processes may be accounted for through inclusion of more complex electrical elements within the model. These adaptations may prove to increase the accuracy of the technique. However, the added complexity and a move from representative parameters would make interpretation significantly more challenging. A secondary approach could look to exploit the electrode-tissue interface, where modification of the electrode surface may produce additional tissue information. This could be extracted when separated from tissue resistance using the proposed model. In effect, this could lead to a bi-modal device without increasing the complexity of the characterisation.

Conclusion

Assessment of the voltage-time response during biogalvanic tissue characterisation shows parameter dependency, particularly in the case of external load switching rate. This variability propagates through to the characterised tissue resistance and is due to the properties of electrode-tissue interface. This paper demonstrates this phenomenon and proposes the use of a more comprehensive time-dependent model to account for and separate electrode-tissue-interface and bulk tissue parameters. Model development and fitting processes have been described and tests have shown reduced variation in characterised tissue resistance with external load switching rate. The proposed model has been demonstrated as a potential means of improving the repeatability of biogalvanic tissue resistance characterisation through isolation of a tissue specific parameter. This may allow for differences between healthy and cancerous colon tissue resistance to be statistically separated, as shown in the single case evaluated. Based on the findings presented, the adjusted biogalvanic characterisation model may allow faster measurements to be taken without influence on the determined tissue resistance. This may allow for biogalvanic tissue sensing to be practically implemented within surgical applications.

Acknowledgements

We would like acknowledge the continued support of the Leeds Cancer Research UK (CRUK) Centre who have funded this work (CRUK grant no. 483355). Testing on ex vivo human tissue was conducted with informed patient consent and in compliance with standard NHS arrangements for the collection and retention of human samples for biomedical research, as detailed in the Human Tissue Act 2004.

References

[1] Tufano RP, Kandil E. Considerations for personalized surgery in patients with papillary thyroid cancer. Thyroid. 2010;20:771-6.

[2] Tiernan JP, Ansari I, Hirst NA, Millner PA, Hughes TA, Jayne DG. Intra-operative tumour detection and staging in colorectal cancer surgery. Colorectal Dis. 2012;14:e510-e520.

[3] Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen H-J. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. The Lancet Oncology. 2006;7:392-401.

[4] van Dam GM, Themelis G, Crane LMA, Harlaar NJ, Pleijhuis RG, Kelder W, Sarantopoulos A, de Jong JS, Arts HJG, van der Zee AGJ, Bart J, Low PS, Ntziachristos V. Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: first in-human results. Nat. Med. 2011;17:1315-9.

[5] Săftoiu A, Vilmann P, Ciurea T, Popescu GL, Iordache A, Hassan H, Gorunescu F, Iordache S. Dynamic analysis of EUS used for the differentiation of benign and malignant lymph nodes. Gastrointest. Endosc. 2007;66:291-300.

[6] Halter RJ, Schned A, Heaney J, Hartov A, Paulsen KD. Electrical Properties of Prostatic Tissues: I. Single Frequency Admittivity Properties. J. Urol. 2009;182:1600-7.

[7] Golberg A, Rabinowitch HD, Rubinsky B. Galvanic apparent internal impedance: An intrinsic tissue property. Biochem. Biophys. Res. Commun. 2009;389:168-171.

[8] Golberg A, Laufer S, Rabinowitch HD, Rubinsky B. In vivo non-thermal irreversible electroporation impact on rat liver galvanic apparent internal resistance. Phys. Med. Biol. 2011;56:951-63.

[9] Chandler JH, Hood A, Culmer PR, Jayne D, Neville A. Technological assessment of the biogalvanic method for tissue characterization. Physiol. Meas. 2014;35:297.

[10] Chandler JH, Culmer PR, Jayne DG, Neville A. Assessment of electrochemical properties of a biogalvanic system for tissue characterisation. Bioelectrochemistry. 2015;101:138-145.

[11] Gileadi E. Physical Electrochemistry. Weinheim: Wiley-VCH Verlag; 2011.

[12] Moisel M, de Mele MAFL, Müller WD. Biomaterial Interface Investigated by Electrochemical Impedance Spectroscopy. Adv. Eng. Mater. 2008;10:B33-B46.

[13] Walter GW. Critical analysis of some electrochemical techniques including polarization resistance, for the study of zinc coating performance in near neutral chloride solutions. Corros. Sci. 1975;15:47-56.

[14] Moré J. The Levenberg-Marquardt algorithm: Implementation and theory. In: G.A. Watson, editors. Numerical Analysis, New York: Springer-Verlag; 1977, p. 105-116.

Legends for Figures

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.

Fig. 3: Voltage profiles from biogalvanic characterisation of porcine ex-vivo tissue for a range of external load switching rates.

Fig. 4: Example of model fitting result for 0.1 Hz external resistor switching rate, where the parameters of OCV, R_{ct}, C_{dl}, and R_{tissue} have been optimised to match to the measured data using equation (6).

Fig. 5: (a) Resistance characterisation results using a single fixed internal resistance model (equation 2) and the proposed transient model of equation (6) for ex vivo porcine colon as a function of external resistor switching rate. Biogalvanic characterisation repeat results for healthy and cancerous colon tissue using (b) the single internal resistance model, and (c) the proposed time-dependent model. The mean ±1SD is also shown.