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Analysis of the Peak Resistance Frequency Method

Boshuo Wang [Member, IEEE] and

Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90089, USA

James D. Weiland* [Senior Member, IEEE]

Department of Ophthalmology, Keck School of Medicine, and Department of Biomedical Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90033 and 90089, USA

Boshuo Wang: boshuowang@gmail.com

Abstract

Objective—This study analyzes the peak resistance frequency (PRF) method described by Mercanzini *et al.*, a method that can easily extract the tissue resistance from impedance spectroscopy for many neural engineering applications but has no analytical description thus far.

Methods—Mathematical analyses and computer simulations were used to explore underlying principles, accuracy, and limitations of the PRF method.

Results—The mathematical analyses demonstrated that the PRF method has an inherent but correctable deviation dependent on the idealness of the electrode-tissue interface, which is validated by simulations. Further simulations show that both frequency sampling and noise affect the accuracy of the PRF method, and in general, it performs less accurately than least squares methods. However, the PRF method trades off in simplicity and measurement and computation time.

Conclusion—From the qualitative results, the PRF method can work with reasonable precision and simplicity, although its limitation and the idealness of the electrode-tissue interface involved should be taken into consideration.

Significance—This work provides a mathematical foundation for the PRF method and its practical implementation.

Index Terms

Biomedical electrodes; electrode-tissue interface; neural engineering; impedance spectroscopy; tissue resistance

I. Introduction

Neuroscience and neural engineering applications rely heavily on electrodes and electrode arrays. Cuff-electrodes, microelectrodes, and multi-electrode arrays (MEA) have been utilized to study neural pathways, neural activity patterns, and neural response to outside stimuli [1]. Several types of medical devices, such as deep brain stimulators, cochlear implants, and retinal prostheses etc., have been developed to treat neurological and neural degenerative diseases using electrodes to stimulate specific targets within the nervous system [2]–[4].

The electrode-tissue interface is critical to the proper functioning of electrodes in many of these aforementioned situations, and the tissue resistance plays an important role in this interface. As this resistance could change over time due to tissue encapsulation and inflammation [5]–[7] or electrode repositioning [8] etc., monitoring the tissue impedance is prudent in many applications. An increase in tissue resistance due to encapsulation could attenuate the recorded signal amplitude, and/or increases noise levels [9]; in stimulation, it affects the shape and magnitude of the electric field, and therefore neuronal activation thresholds [6]. Decreases in tissue impedance could indicate electrode movement away from the target, which increases stimulation thresholds [8], [10], and could reduce recording sensitivity [11].

Whereas bioimpedance measurement has become a complex study on its own [12] and involves sophisticated methods such as optimal experiment design [13]–[16], impedance measurement in the field of neural engineering are often evaluated only at fixed single frequency. Many devices are only set at 1 kHz for impedance monitoring [8], [17], and electrode impedances are consequently often reported at this frequency [8], [18]. This is because the spectrum of action potentials and many stimulation pulses are centered roughly at 1 kHz. For most electrodes, however, the impedance at this frequency reflects the capacitive component of the electrode, whereas the tissue/electrolyte resistance dominates the impedance at higher frequency [10], [19]. For example, impedance at 100 kHz was correlated with proximity to the retina [10] and showed higher sensitivity compared to measurements at lower frequency (1 kHz)[8].

Ideally, impedance will represent tissue resistance when measured at high frequency, where the double layer capacitance acts like a short circuit. However, parasitic capacitance in the system introduces a non-negligible factor that could change the ideal behavior [5], [20], therefore rendering the fixed frequency approach unreliable. Nonlinear least squares fitting is a viable approach to extract parameters from impedance spectrum that exhibits arbitrarily complex behavior by adding more model elements. However, it relies on post-processing of complete measurements covering a sufficient frequency range to be accurate.

Mercanzini *et al.* described a method that utilizes a variable frequency point to estimate tissue resistance [5]. This method has been named the peak resistance frequency (PRF) method, as it chooses the frequency at which the complex impedance is the most resistive, i.e. where the phase angle is closest to zero, to evaluate the impedance magnitude. They

reported high accuracy of the PRF method, whereas fixed frequencies resulted in large deviation from the “true” value.

Several interesting issues remain unresolved though. First, the principles of the PRF method have not been explained and there are no analytical validations in the literature so far. Also, Mercanzini *et al.* discussed the double layer capacitance in terms of a constant phase element (CPE), however, used the interfacial capacitance to approximate the “admittance” of the CPE [5]. Whereas this approximation is acceptable when the exponent of the CPE is very close to 1, corrections and conversion between the double layer capacitance and the CPE are necessary when this condition is not met [21]. Last, the CPE is not an independent component of the electrode-tissue interface model, but is related to other components [22]. This complicates the discussion of how the PRF method should be interpreted when the impedance spectroscopy shows a double layer with non-ideal behavior.

In this paper, we present mathematical analysis and simulations on the PRF method, and also explored both representations (capacitance or CPE) of modeling the double layer. The results demonstrate the validity of the PRF method, while also pointing out its inherent limitation in accuracy when the electrode-tissue interface behaves non-ideally and results in noticeable deviation. Though it is less accurate when compared with more sophisticated methods, it achieves reasonable precision given sufficient frequency sampling and low noise. Therefore the PRF method is a simple and effective method to measure tissue resistance.

II. Methods

A. The Electrode-Tissue Interface Model

There has been extensive modeling of the electrode-tissue interface that well characterizes the equivalent components of this interface [19], [23]–[25]. We include the following elements (Fig. 1): the tissue resistance, the electrode double layer, the charge transfer resistance, and the parasitic capacitance. Adhering to the original method, the Warburg impedance was excluded and the tissue was modeled as a simple resistance [5]. The Warburg impedance is negligible in the frequency range of interest (100 Hz to 1 MHz) [24]. Tissue can be described using the Cole–Cole model or Fricke model [26], [27], which takes the cell membrane capacitance and extra- versus intracellular electrolyte into account. The capacitance of the tissue is shown to slightly affect neural stimulation [28]. These models are not adopted, however, because of the dependence on the specific tissue types and unnecessary complication of the interface model.

1) Tissue resistance—The tissue resistance R_s is in series with the electrode interface. Given the small dimension of microelectrodes used, this resistance could be related to the resistivity ρ of the surrounding tissue/electrolyte by

$$R_s = k \cdot \rho, \quad (1)$$

where k is the cell constant of the electrode [29]. This linear relationship assumes that the resistivity changes gradually in space, and the resistance is dominated by the environment in

close vicinity of the electrode site [23]. It is also frequency-independent in the frequency range of interest [30]. The cell constant can be used to calculate local tissue resistivity after tissue resistance has been extracted with the PRF method.

2) Charge transfer resistance—The charge transfer resistance R_{CT} arises from the electron charge transfer due to the Faradaic redox reactions at the electrode-electrolyte interface [25]. The charge transfer is a non-linear phenomenon described by the Butler–Volmer equation, and both small signal and large signal approximations for this resistance are available. For electrode characterization and tissue impedance measurement using electrochemical impedance spectroscopy (EIS), small voltages are usually applied (e.g. 10–25 mV) and the small signal approximation should be used [24]. For biomedical electrodes which in general avoid Faradaic reactions for biocompatibility considerations, R_{CT} is much larger compared to R_S for voltages and frequencies practical in neural engineering applications [31]. A dimensionless ratio of the two resistances of the interface is given as

$$x_R = \frac{R_S}{R_{CT}} \approx 10^{-3} - 10^{-6}. \quad (2)$$

3) Electrode double layer—Charge separation occurs when a metal comes into contact with electrolyte [25] and is modeled as an interfacial capacitance C_{DL} which is in parallel with the charge transfer resistance. However, the double layer often deviates from purely capacitive behavior and is better described as a constant phase element (CPE), whose frequency dependence is

$$Z_{CPE}(\omega) = \frac{1}{(j\omega)^n Y}, \quad (3)$$

where the exponent n describes the constant phase angle $\theta_{CPE} = -n\pi/2$, and Y is the “admittance” of the CPE. It should be noticed that Y and C_{DL} have different units: the former is $s^n \cdot \Omega^{-1}$, whereas the latter is $F = s \cdot \Omega^{-1}$ [21]. Therefore correction is needed when relating these two quantities. Brug *et al.* described the following relationship in electrochemical applications [22, p. 283]

$$C_{DL} = \sqrt[n]{(R_S^{-1} + R_{CT}^{-1})^{n-1} Y}, \quad (4)$$

which indicates that the CPE is coupled to both R_S and R_{CT} . However, under the condition (2) where $R_{CT} \gg R_S$ the relationship becomes

$$\begin{cases} C_{DL} \approx (R_S^{(1-n)} Y)^{1/n} \\ Y \approx C_{DL}^n R_S^{n-1} \end{cases}. \quad (5)$$

4) Parasitic capacitance—The parasitic capacitance C_P is an undesired capacitance of the system in parallel with the electrode-tissue model, due to the dielectric linkage between the leads and the environment especially when long wires or cables are used. A second dimensionless quantity x_C is introduced to quantify the ratio between C_P and C_{DL} :

$$x_C = \frac{C_P}{C_{DL}} \approx 10^{-1} - 10^{-4}. \quad (6)$$

B. Analysis of the PRF Method

The mathematical analysis to find the PRF starts with the complex impedance of the electrode-tissue interface model, which is given as

$$Z(\omega) = (Z_{DL}(\omega) \parallel R_{CT} + R_S) \parallel Z_P(\omega), \quad (7)$$

in which the symbol $\parallel$ denotes parallel connection of two impedance. The phase angle is the principle argument of the impedance

$$\varphi(\omega) = \arg(Z(\omega)), \quad (8)$$

and is in the range of $[-\pi/2, 0]$ for the electrode-tissue interface model. The PRF is the maxima of the phase in the high frequency range, and is the root (or the larger of the roots) of the condition

$$d\varphi(\omega)/d\omega = 0. \quad (9)$$

The magnitude of the impedance is then determined at this frequency ω_{PRF} which is a good approximation of the tissue impedance:

$$|Z_{PRF}| = |Z(\omega_{PRF})| \approx R_S. \quad (10)$$

Two models are explored. The first uses a regular capacitance for the double layer and includes R_{CT} . The second uses a CPE for the double layer and excludes R_{CT} as the first model shows that it is negligible in the frequency range covering PRF.

C. Electrode Parameters for Simulation

For simulation of the PRF method, the parameters of concentric bipolar microelectrodes with pencil-like tips (FHC Inc. Bowdoin, ME, USA) were used. This type of electrodes was used for resistivity mapping of retinal tissue [32] and consists of an inner pole of Pt-Ir alloy concentric with and insulated from the stainless steel outer pole. The configuration and dimensions of the electrodes are shown in Fig. 2.

A total of six electrodes were analyzed in phosphate buffered saline (PBS, Sigma-Aldrich, St. Louis, MO, USA) by EIS (1 MHz to 100 Hz) using a potentiostat (Reference600 and Interface 1000, Gamry Instruments, Warminster, PA, USA) with a Ag/AgCl reference electrode. A thick platinum wire was used as return electrode for monopolar modes and the outer pole served as the return electrode for bipolar mode. The frequency sampling was 10 points per decade. The impedance spectra were averaged, and the electrode parameters were extracted or calculated from least squares (LS) fitting of the interface model with a CPE. Table I shows the mean and standard error of the parameters, in which the parameters in bold were directly fitted.

The conductivity of the PBS was measured as $15.6 \pm 0.1 \text{ mS} \cdot \text{cm}^{-1}$ by a conductivity meter (VWR, Radnor, PA, USA), and used to calculate k of the electrode using (1). The equivalent C_{DL} was calculated using (5). The exponent n is not as close to 1 as some platinum electrodes ($n \approx 0.9$) [33], however its value around 0.8 is consistent with other biomedical electrode systems [24]. The R_{CT} was in the megaohm to gigaohm range, but could not be reliably extracted from the EIS data even when frequency reached as low as 0.1 Hz. Its variance between electrodes was also very large, and therefore R_{CT} is not included in the table.

D. Simulation of PRF Method

Impedance spectra were simulated using the electrode-tissue interface model as described in Fig. 1 and the bipolar parameters of the microelectrode from Table I. The simulation and data analysis were performed in Matlab (Mathworks, Natick, MA, USA). The tissue/electrolyte resistance was varied and calculated with (1) using resistivity values that covered 0.5 to 32 Ω -logarithmically (see Fig. 3), spanning the range of neural tissue from low resistivity (cerebral spinal fluid) to high resistivity (dura mater or epidural fat) [34]. The frequency range of the simulation is 1 MHz to 100 Hz. The PRF and $|Z_{PRF}|$ were extracted from the simulated spectra and compared to the theoretical values from the calculation. For simulation, all frequencies are given in units of Hertz.

Three models were simulated. The first uses C_{DL} for the double layer. In this case, R_{CT} was included in the model to show its influence in the low frequency region (50 M Ω , from EIS data). The other two simulations use a CPE and R_{CT} does not affect PRF. One model used a dependent CPE assuming that Y is a parametric fit and not a real physical quantity. Hence for different R_S , the interfacial capacitance should be used to calculate the corresponding Y using (5). The other was an independent CPE model which assumed that Y is a real parameter that does not change as R_S changes. These two situations gave different simulation results, which should be verified against experimental data.

E. Analysis on Sampling Density and Noise

To further explore the PRF method under noisy experimental conditions, the grid density of frequency sampling and the influence of noise were studied with a total of 100 simulation trials run in Matlab. First, a tissue resistivity was randomly generated for each trial in the range of 0.5 to 32 Ω -m. The corresponding tissue resistance was calculated using (1), and with the other bipolar parameters of the microelectrode from Table I, impedance spectra

were generated in the range of 1 MHz to 100 Hz with frequency sampling densities of 5, 10, and 20 points per decade. Then, a complex Gaussian noise was added to the spectra at each sampling point, with standard deviations of 1%, 5%, and 10% of the impedance magnitude at each point. This approach overestimates the noise as previous studies have shown that noise from electrode-tissue interface is proportional to only the real part of the impedance [35]. For each three by four combination of sampling density and noise level (including zero noise), the PRF method was applied to the spectrum and $|Z_{\text{PRF}}|$ was extracted. The corresponding tissue resistivity ρ_{PRF} was extracted using (1), and the percentage error compared to the “true” value was calculated. The error was averaged for each condition over all trials, and the standard deviation for the error is also calculated.

F. Comparison with Least Squares Method

Another commonly used method to extract the tissue resistance from impedance spectroscopy is using least squares (LS) fitting. Particularly, the complex nonlinear least squares (CNLS) method applied to relative errors is used in consideration of the nonlinear nature of the interface model and the orders-of-magnitude difference of the impedance across the spectrum:

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \sum_i \left| \frac{Z(\theta, \omega_i) - Z_{\text{Meas}}(\omega_i)}{Z(\theta, \omega_i)} \right|^2, \quad (11)$$

where θ is the vector of parameters of the model (e.g. $\theta = [R_S, C_{\text{DL}}, R_{\text{CT}}, R_P]^T$ for the first model), and i is the index of frequency points of the sampled spectrum. To compare the PRF method with LS methods, the relative error version of the CNLS method was applied to the same simulation data in the previous section, and the same statistics were obtained.

III. Results

A. Analytical Calculation

1) Model with C_{DL} and R_{CT} —The complex impedance of the first model is

$$Z(\omega) = \frac{R_{\text{CT}} + R_S + j\omega R_{\text{CT}} R_S C_{\text{DL}}}{1 - \omega^2 R_{\text{CT}} R_S C_{\text{DL}} C_P + j\omega (R_{\text{CT}} C_P + R_{\text{CT}} C_{\text{DL}} + R_S C_P)}. \quad (12)$$

Solving the corresponding condition of (9) gives a quartic equation and yields two positive roots:

$$\omega_{1,2} = \frac{\sqrt{x_C^{-1} + 1 - (x_R + x_R^2)} \pm \sqrt{\Delta}}{\sqrt{2} R_S C_{\text{DL}}}, \quad (13)$$

where $\Delta = (x_C^{-1} + 1 + x_R)(x_C^{-1} + 1 - 7x_R - 8x_R^2)$.

Using Taylor expansion and neglecting second and higher order terms of x_R , the larger root can be given as

$$\omega_{\text{PRF}} \approx \frac{\sqrt{1+x_C^{-1}-2x_R+O(x_R^2)}}{R_S C_{\text{DL}}}. \quad (14)$$

Considering (2) and (6), (14) simplifies and yields

$$\omega_{\text{PRF}} \approx \frac{\sqrt{1+x_C^{-1}+O(x_R)}}{R_S C_{\text{DL}}}. \quad (15)$$

The relative error from the approximation steps in (14)–(15) is $\sqrt{O(x_R)/(1+x_C^{-1})}$, which would be at most 1% according to (2) and (6). Further calculation using (15) then shows that under this condition

$$\begin{cases} |Z_{\text{PRF}}| = \frac{R_S}{1+x_C} \approx R_S \\ \varphi_{\text{PRF}} = -\arctan\left(\frac{2(1+x_C)}{\sqrt{1+x_C^{-1}}}\right) \end{cases}. \quad (16)$$

Thus far, the mathematical foundation of the PRF method is clearly established. Equations (15)–(16) explicitly explain that: (1) The PRF is inversely proportional to R_S and their relationship on a log–log plot has a slope of -1 ; (2) $|Z_{\text{PRF}}|$ is linearly proportional to R_S , with a ratio slightly smaller than 1. A good approximation is obtained only when $x_C \ll 1$. Otherwise it is necessary to scale the impedance magnitude by $(1+x_C)$ to find the real tissue resistance. This could be achieved by either calculating x_C with parameters extracted from EIS, or calibrating the measurement system using electrolyte of known resistivity; (3) φ_{PRF} is constant and independent of R_S , which could be used for experimental validation of this model.

2) Models with CPE—The complex impedance of the model using CPE is

$$Z(\omega) = \frac{1+(j\omega)^n Y R_S}{(j\omega)^n Y + (j\omega)^{n+1} Y R_S C_P + j\omega C_P}. \quad (17)$$

Using Euler's formula to separate the real and imaginary components of $(j\omega)^n$ the corresponding condition of (9) yields

$$\begin{aligned} & \cos\left(\frac{n\pi}{2}\right) (1-n) + R_S Y \omega^n \left[1 - 2n + 2\cos^2\left(\frac{n\pi}{2}\right)\right] \\ & + R_S^2 Y^2 \omega^{2n} (3-n) \cos\left(\frac{n\pi}{2}\right) + R_S^3 Y^3 \omega^{3n} \\ & = R_S^2 Y^2 \omega^{2n} n \sin\left(\frac{n\pi}{2}\right) / (\omega R_S C_P). \end{aligned} \quad (18)$$

This pseudo-cubic equation contains the n^{th} , $2n^{\text{th}}$, $3n^{\text{th}}$ and $(2n-1)^{\text{th}}$ order terms of, ω which is impossible to solve analytically. However, as C_{DL} and CPE describe the double layer's behavior very similarly, the PRF of one model approximates that of the other. Therefore using (15) from the first model to approximate ω in the denominator on the right side of (18), a cubic equation with an approximate solution can be obtained:

$$X^3 + \left[(3-n) \cos\left(\frac{n\pi}{2}\right) - \frac{n \sin\left(\frac{n\pi}{2}\right)}{\sqrt{x_C}} \right] X^2 + [1 - 2n + 2\cos^2\left(\frac{n\pi}{2}\right)] X + \cos\left(\frac{n\pi}{2}\right) (1-n) = 0, \quad (19)$$

in which $X = R_S Y \omega^n$ is dimensionless variable.

Given the condition that n is close to 1 and $x_C \ll 1$, an analysis of the roots shows that this equation has one real root which is approximately equal to the only coefficient term that is significantly different than zero:

$$X_{\text{PRF}} \approx n \sin\left(\frac{n\pi}{2}\right) / \sqrt{x_C}. \quad (20)$$

And the PRF is therefore given as

$$\omega_{\text{PRF}} = N R_S^{-\frac{1}{n}} Y^{-\frac{1}{n}} x_C^{-\frac{1}{2n}}, \quad (21)$$

where $N = (n \sin(n\pi))^{\frac{1}{n}}$.

Due to the approximation steps, this equation contains both representations of the double layer (Y, and C_{DL} in the form of x_C). Therefore (5) is used to substitute one for another and two expressions of the PRF were obtained:

$$\omega_{\text{PRF}} = \begin{cases} N C_P^{-\frac{1}{2n}} Y^{\frac{1-2n}{2n^2}} R_S^{\frac{1-3n}{2n^2}} \\ N C_P^{-\frac{1}{2n}} C_{\text{DL}}^{\frac{1-2n}{2n}} R_S^{-1} \end{cases}. \quad (22)$$

Using the CPE or capacitance for calculating ω_{PRF} raises a discrepancy on the dependence ω_{PRF} versus R_S show slightly different slopes on a log-log plot. The issue arises from whether to assume that the CPE is an element independent from R_S . Both cases are simulated and further discussion is given in the next section.

Using similar techniques in approximation, $|Z_{\text{PRF}}|$ can be obtained as

$$\frac{|Z_{\text{PRF}}|}{R_S} \approx 1 + \frac{\cot\left(\frac{n\pi}{2}\right)}{n} x_C^{\frac{1}{2}} - \frac{N^2}{2} x_C^{2-\frac{1}{n}} - \frac{N}{n} x_C^{\frac{3}{2}-\frac{1}{2n}} + O(x_C), \quad (23)$$

with all terms of x_C with orders equal or higher than 1 neglected. This gives an upper bound of error at 10% according to (6); however because the neglected terms do not all have the same signs, the real error would be smaller as these terms partially cancel out. Again, R_S is approximated accurately when $x_C \ll 1$ and $n \approx 1$. When this condition is not quite met, whether $|Z_{PRF}|$ over- or underestimates R_S is not apparent from simple observation as is the case with C_{DL} , and further calculation is needed. Calibration using an electrolyte of known resistivity would be the simplest way to correct the results if needed.

B. Simulation

1) Model with C_{DL} and R_{CT} —The impedance spectra simulated with different tissue resistance are shown in Fig. 3. For the PRF extracted from the phase plot, the simulation and calculation agree with each other within 0.05%. The $|Z_{PRF}|$ from the magnitude plot shows an approximately -7.6% difference from the “true” resistance used for simulation and ϕ_{PRF} stays constant, confirming the results in (16). The log-log plots of PRF versus resistance (not shown, but see Fig. 6 for similar results of models with CPE) has a slope of -1 ($R^2 > 1 - 10^{-7}$), further validating the calculation.

The -7.6% difference is relatively large, and reveals that the PRF method has an inherent deviation when electrode parameters are non-ideal, i.e. when either $x_C \ll 1$ or n being close to 1 is not satisfied. However, due to the constant relative error regardless of actual tissue resistance value, calibration could be easily done either using (16) or measuring saline of known resistivity.

2) Models with CPE—Two situations were simulated, both with R_{CT} ignored. The first assumes that the CPE admittance is not a real element, and the interfacial capacitance should be used with the varying R_S to calculate the equivalent CPE. The second assumes the opposite: that the CPE is an independent element and does not change with the tissue/electrolyte environment. The simulated impedance plots under the two situations are shown in Fig. 4 and Fig. 5, respectively.

There are distinctive characteristics that can be used to identify one model from another. The dependent CPE shows a fixed ϕ_{PRF} , similar to the model with C_{DL} , whereas the independent CPE has a ϕ_{PRF} moving closer to zero as tissue resistance increases. For the dependent CPE, the impedance magnitude diverges at low frequencies, due to dependency of the CPE’s “admittance” on the tissue resistance. On the other hand, an independent CPE shows spectra without this behavior. These characteristic might be used to experimentally identify which model is more accurate.

The validity of the CPE models is shown by the relative errors comparing calculation to simulation. For PRF, the analytical approximation has a stable relative error of 12.4% in the dependent CPE model, not varying with tissue resistance; The independent CPE model exhibits a calculation error in a similar range of 12.1% to 17.4%, increasing with the resistance. For $|Z_{PRF}|$ the dependent CPE model has a constant relative error of 8.0% for simulation and 0.3% for calculation versus “true” resistance; the independent CPE model has an estimation error in the range of 8.1% to 6.1% for simulation, and -0.1% to 2.5% for calculation. The smaller errors for the calculation are due to the approximation steps (19),

(20), and (23). The log–log plots of PRF versus tissue resistance/resistivity are shown in Fig. 6. According to (22), the dependent CPE model has a slope of -1 , whereas the independent model has a slope of $(1 - 3n)/(2n^2)$ which is steeper when $n \in (0.5, 1)$. The results again show very good agreement.

The simulation results show that the PRF method has a positive deviation for the non-ideal double layer, opposite from that of the ideal capacitive double layer. The error is constant (dependent CPE) or relatively stable (independent CPE) for different resistance values. Therefore calibration can be similarly implemented.

C. Frequency Sampling and Noise Analysis

The calculation and simulation so far have shown that the PRF method has an inherent deviation which needs correction when parasitic capacitance exists. Limited frequency sampling and measurement noise might further increase the error. Therefore simulations with such conditions were performed, and the relative errors from 100 simulated impedance spectra are shown in Fig. 7. The mean and standard deviation of the relative errors are plotted against noise level and grouped according to models and grid density of frequencies.

The mean relative errors stay relatively stable for each of the three models regardless of measurement condition, and are also in agreement with the errors from the previous simulation under ideal conditions (-7.6% , 8.0% , and 8.1% to 6.1% respectively for the three models). Therefore statistically speaking, realistic limitations do not add additional error to the PRF method on average. However, the standard deviation of errors increases with higher noise level and decreases with higher grid density of the measurement frequencies. This indicates that any individual measurement is prone to higher error with noise and sparse sampling. Ten points per decade is a reasonable minimum, and higher sampling of the spectrum is desired. The measurement noise level should be minimized and kept close to 1% , so that the results could be corrected from the inherent deviation as shown by the analysis.

D. Comparison with CNLS

The CNLS method was applied to each condition of the same 100 simulation trials and the results are shown in Fig. 8. The mean relative error is close to zero for all models and combinations of condition. As expected, the CNLS method has no inherent bias in estimating the resistivity and does not require calibration like the PRF method. The standard deviation of errors show similar trend as the noise and sampling changes, but have smaller values compared to the PRF method. The CNLS method is more tolerant against noise, at the cost of increased measurement time and computation.

IV. Discussion

This paper provides comprehensive analysis of the PRF method for extracting tissue resistance from impedance spectroscopy. Mathematical solutions validated the PRF method and revealed that the PRF method has deviations when electrodes have non-ideal behaviors. Simulations show that frequency sampling and noise do not limit the practical use of the PRF method.

A. Analytical Solution

Given the equivalent model of the electrode-tissue interface, the analytical calculation established the mathematical principle behind the PRF method. However, the equation could only be solved explicitly for the ideal double layer capacitance. Nevertheless, this model provided important insight and results that became useful later for the non-ideal model.

For example, the ideal model includes R_{CT} , complicated the analysis. Due to its non-linearity, R_{CT} varies depending on the applied stimulation. When larger voltages are used during stimulation, a large signal approximation should be used, giving different R_{CT} values. However, this does not change its relationship with the tissue resistance, which is smaller by orders of magnitudes. Therefore R_{CT} only influences the EIS in low frequency ranges, and plays an insignificant role in determining the PRF. The mathematical calculation validates this conclusion, justifying the exclusion of R_{CT} in the other models.

The model in which the double layer is represented by a CPE is very complex, and becomes impossible to solve with the irregularities in the exponents. The PRF derived for the ideal double layer model provides an approximation for the solution, which can be used to eliminate the irregularity and yield a cubic equation. However, the complexity of an exact solution to the cubic equation would not reveal useful information, and a simple solution capturing the principal interaction between tissue resistance and the double layer was derived via further approximations. The simulation data then showed that these approximation steps resulted in a fairly accurate description of the CPE model, despite that the electrode parameters used for simulations have, $x_C \approx 0.082$ and $n = 0.77$, which can be argued as not quite being “ $x_C \ll 1$ and n close to”: (1) The log-log slope of PRF versus tissue resistance/resistivity shows high accuracy (within 1%) for calculation versus simulation (Fig. 6); (2) The calculated PRF shows a non-negligible difference (12% to 18%) when compared to the simulation results; (3) $|Z_{PRF}|$ shows small discrepancy between calculation and simulation, with calculation giving results closer to the “true” value.

B. Idealness of Electrode-tissue Interface

The electrode parameters used in this work revealed the limitation of the PRF method for non-ideal electrodes. Although the calculation and simulation of $|Z_{PRF}|$ agree, they both show a significant deviation from the “true” resistance for all three models. This type of behavior was not shown by Mercanzini *et al.*, mainly because their electrode’s parameters ($x_C \approx 0.009$ and $n = 0.9$) were too close to ideal. Using their parameters (detailed results not shown), the relative error for $|Z_{PRF}|$ is only on the order of 0.1% for the double layer capacitance model, and around 1% for either case of the CPE model; also, the PRF method performs closer to the CNLS method for their parameters, confirming that the idealness of the electrode is also an important consideration for accuracy. Our results provide means to correct the impedance extracted with the PRF method using either (16) or (23) electrolyte of known resistivity is also a quick way to obtain the correction factor for a given electrode. Nevertheless, the consistency in the deviation compared to “true” resistance over a wide range indicates that the PRF method is especially applicable when the relative changes in resistance are important but their absolute values are not.

Overall, it is generally desirable to have electrodes with ideal behavior ($x_C \ll 1$ and close to 1) in order to use the PRF method without the concerns discussed above. The first condition relates to the parasitic capacitance, which is usually very small and can go unidentified or be attributed to other reasons [32, Fig. 2]. Electronics design and device fabrication should aim to limit this shunt capacitance or its influence using methods such as on-chip compensation, buffering, or signal processing. However, as smaller (less than 30 μm in diameter) micro-electrodes have been fabricated [36], the decrease of the surface area of the interface could result in double layer capacitance of similar magnitude compared to the parasitic capacitance. The second condition relates to the double layer interface, which depends on the surface inhomogeneity of electrode materials [22]. To achieve higher charge injection capacity in neural stimulation, many electrode materials [37] with rough surfaces have been developed to increase the real microscopic area of the electrode interface without increasing the geometric area of the electrode. These rough electrodes typically have non-ideal behavior of CPEs.

C. Dependence of CPE on Tissue Resistance

For the two CPE models, it remains unknown which one describes the interaction of CPE and tissue impedance more accurately. The characteristic behaviors of these two models could be easily observed from simulation results, as the simulation covered a very wide range of tissue resistivity for demonstration purpose. However it might be difficult to test this experimentally. In real devices, the change in resistance electrodes face is typically much smaller. For example, neural tissue has resistivity of 2 to 10 $\Omega\cdot\text{m}$ [29], [38], [39], with some variation due to the anisotropy of nerve fibers. Body fluids such as cerebral spinal fluid or vitreous humor have resistivity in the range of, 0.5 to 1 $\Omega\cdot\text{m}$, [40]. This change of only one order of magnitude could result in impedance spectra too close to distinguish the aforementioned characteristics, considering that the measurements are also prone to noise in recording, especially when performed *in vivo*.

D. Considerations for Implementation

For application of the PRF method, the grid density and frequency distribution of the spectrum affects the accuracy of the measurement. For most devices, a reasonably dense frequency sampling (more than 10 points per decade) could be specified. If the approximate location of the PRF is unclear initially, the overall shape of the spectrum could be obtained from a first scan with lower sampling. After identifying the region containing the PRF, subsequent routine measurements just focusing on this region could achieve sufficient accuracy by reducing the frequency range and increasing the sampling. Overall, this becomes less of a concern if electrodes with ideal behavior are used, as they have wider and flatter impedance magnitude and phase curves at frequencies near the PRF, which reduces the sensitivity requirement in obtaining a very accurate PRF, allowing the measurement with less frequency points and faster measurement speed.

The PRF method allows rapid measurement, as data acquisition can be terminated as soon as the PRF is identified. From the simulations, the PRF is mostly located within the range between 5 kHz to 500 kHz for the specific electrode parameters, and therefore a frequency sweep only needs to cover one decade or two. For interfaces of other applications, this range

is expected to be similar or even smaller as resistance changes over time or due to electrode location are limited. On the other hand, the CNLS method needs data from a full spectrum for post-processing, resulting in longer time for measurement. Also, the CNLS fitting process itself is time-consuming and computationally expensive, whereas the calibration for the PRF method is only a multiplication. The CNLS method requires some knowledge of the models to be used, whereas our analyses show that the PRF method works intuitively regardless of which of the three models is used. Therefore, the PRF method has advantages in terms of simplicity, measurement speed, and easy data reading, with trade-off in accuracy for non-ideal electrode interfaces in terms of standard deviation of error.

V. Conclusions

The validity of the PRF method to extract tissue resistance through impedance spectroscopy has been established via mathematical analysis, and the deviation resulting from non-ideal electrode interfaces has been demonstrated. The analytical results provide means to correct the tissue resistance extracted by the PRF method, if the non-ideal electrode-tissue interface results in noticeable deviation. Comparison between models of regular capacitance and CPE for the double layer shows that specific consideration should be taken if the impedance spectroscopy shows a double layer with CPE behavior. Although less accurate than least squares methods, simulations show that the PRF method work with reasonable precision when considering realistic frequency sampling and noise. Additional work should be performed to better quantify the PRF method from a statistical view point, which could further improve the understanding of the PRF method and better compare it with other sophisticated methods for parameter estimation. Experimentation should also be performed to identify whether the independent or dependent model of the CPE is a more accurate description of electrode-tissue interfaces when tissue impedance varies over time or with electrode location.

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Biographies

Boshuo Wang (S'13–M'15) received his B.Eng. degree in electrical engineering from Tsinghua University, Beijing, China, in 2010. He has obtained degrees in biomedical engineering (M.S., 2013; Ph.D., to be conferred in 2016) from the University of Southern California, Los Angeles.

He joined the Bioelectronic Research Lab at the University of Southern California as a Research Assistant in summer 2011. At the same time, he joined the inaugural class of Health, Technology and Engineering (HTE@USC), a new interdisciplinary educational program for medical and engineering students which promotes collaboration and innovation in healthcare technology. He will be joining the Brain Stimulation Engineering Lab at Duke University as a Postdoctoral Associate in spring 2016. His research interest include neural prostheses, neural engineering, and modulation, and related computational modeling, electrophysiology, and interface technology.

Dr. Wang is a member of the IEEE EMBS and the Honor Society of Phi Kappa Phi.

James D. Weiland (M'91–SM'08) received his B.S. from the University of Michigan in 1988. After 4 years in industry with Pratt & Whitney Aircraft Engines, he returned to Michigan for graduate school, earning degrees in biomedical engineering (M.S. 1993, Ph.D. 1997) and electrical engineering (M.S. 1995).

He joined the Wilmer Ophthalmological Institute at Johns Hopkins University in 1997 as a Postdoctoral Fellow and, in 1999, was appointed an Assistant Professor of ophthalmology at Johns Hopkins. Dr. Weiland was appointed Assistant Professor at the Doheny Eye Institute, University of Southern California in 2001. Currently, Dr. Weiland is a Professor of Ophthalmology and Biomedical Engineering, University of Southern California. He is Deputy Director of the Biomimetic Microelectronic Systems Engineering Research Center. His research interests include retinal prostheses, neural prostheses, electrode technology, visual evoked responses, implantable electrical systems, and wearable visual aids for the blind.

Dr. Weiland is a Fellow of the American Institute of Medical and Biological Engineering and a Senior Member of the IEEE. He is a member of EMBS, Sigma Xi, and the Association for Research in Vision and Ophthalmology.

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Fig. 1.
The electrode-tissue interface model with parasitic capacitance from the leads and other components in the system.

Fig. 2. The configuration of the microelectrodes. The inner pole consists of 80/20 Pt-Ir alloy, and the outer pole is stainless steel.

Fig. 3. Simulated impedance spectra for the double layer capacitance model with varying tissue resistivity ($\rho = 0.5, 1, 2, 4, 8, 16$, and $32 \Omega\cdot\text{m}$; arrow indicates increasing resistivity). $|Z_{\text{PRF}}|$ and ϕ_{PRF} are marked with asterisks.

Fig. 4.

Simulated impedance spectra for the dependent double layer CPE model with varying tissue resistivity (same as Fig. 3). The PRF and $|Z_{\text{PRF}}|$ are given for both simulation and calculation (upper panel, squares and circles with center dots, respectively), and only the simulated ϕ_{PRF} is shown (lower panel, asterisks). ϕ_{PRF} is independent of the tissue resistance; the impedance magnitude shows dispersion at low frequency.

Fig. 5. Simulated impedance spectra for the independent double layer CPE model with varying tissue resistivity (same as Fig. 3). Markers are the same as Fig. 4. ϕ_{PRF} increases with tissue resistance; impedance magnitude at low frequency is independent of tissue resistivity.

Fig. 6.

Log-log plots of PRF versus resistivity for the CPE models. R^2 values for the log-log fitting are larger 0.99999.

Fig. 7. Relative errors (mean and standard deviation) of the resistivity extracted using the PRF method from 100 simulated impedance spectra with different frequency sampling density and noise levels. The curves were slightly shifted in the horizontal direction to avoid overlap of the error bars.

Fig. 8.

Relative errors (mean and standard deviation) of the resistivity extracted using the least squares method from the same 100 simulated impedance spectra as in Fig. 7.

Table I

Electrode Parameters Extracted from EIS in PBS (Mean and Standard Error of the Mean).

	Bipolar Mode	Monopolar Mode – Inner Pole	Monopolar Mode – Outer Pole
R_s (k Ω)	5.14 (0.15)	5.37(0.12)	0.96 (0.05)
k (cm ⁻¹)	78.8 (2.2)	82.4 (1.8)	14.7 (0.7)
Y (n Ω ·s ^{-n})	6.9 (0.3)	6.3 (0.3)	21.7 (3.2)
n	0.77 (0.02)	0.76 (0.02)	0.84 (0.01)
C_{DL} (pF)	323.4 (31.0)	313.3 (52.3)	2765.4 (491.8)
C_P (pF)	26.6 (2.1)	16.6 (0.3)	177.7 (9.8)