Extraction of Cardiac Cell Membrane Fractional-Order Capacitance from Current Response to Voltage Step

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***Abstract*—The aim of the article is to examine the possibilities of modeling electrical properties of cardiac cell membrane using the Cole impedance model containing a fractional-order capacitor. A method is presented to determine the parameters of the model based on the current transient response to a voltage step applied to the membrane. The method is based on the numerical minimization of the least squares error between the recorded and calculated transient response of the model using the MATLAB function fminsearch. The use of a fractional-order capacitor in the membrane model is found to result in a reduction in the modeling error compared to that of the classic capacitor.**

***Index Terms*—Bioimpedance; Biological system modeling; Fractional calculus.**

I. INTRODUCTION

It is well known that current flowing through a classic capacitor is proportional to the time derivative of its terminal voltage. Similarly, the voltage drop across a classic inductor is a function of the time derivative of the current. In both these cases, the derivatives are of first order. Currently, mathematicians already have a very well-developed theory of derivatives and integrals of non-integer (fractional) order, called "fractional calculus" [1]. This branch of mathematics has gradually penetrated many disciplines, such as physics, system theory, economics, electrical engineering, bioengineering, etc., where it helps to better describe the behaviour and properties of various systems, phenomena, or processes [2], [3]. Fractional calculus also found its way into the field of analogue electronic circuits, where Fractional-Order Elements (FOE) or Fractors were defined, allowing differentiation or integration of non-integer order between cross voltage and through current [4]. The FOE admittance can be written as $Y = s^{\alpha}F$, where $s = j\omega$ is the Laplacian operator, α is the real number expressing the order, and F is the proportionality constant generally referred to as fractance. Considering $\alpha \in (0, 1)$, the element is called "Fractional-Order Capacitor" (FOC) or "capacitive fractor" and F represents its pseudo-capacitance. For $\alpha \in (-1, 0)$, the FOE is a fractional-order inductor or inductive fractor with pseudo-inductance $1/F$. Apparently, choosing the values of $\alpha = -1, 0, 1$, the classic inductor, resistor, and capacitor are obtained, respectively. FOEs with higher fractional order can also be defined for $|\alpha| > 1$ as described, e.g., in [5]. From the above admittance relation, it is apparent that the slope of its magnitude is 20α dB per frequency decade and its phase is $\alpha\pi/2$ radians or 90α degrees. As the phase is independent of frequency, this element is also called the "Constant Phase Element" (CPE).

A. Related Works on Cole Impedance Model

Circuits with FOEs are important parts of various control systems, signal filters and generators, and modeling applications [6]. Another large area of employment of FOE is modeling the electrical properties of biological tissues and biochemical materials [7]. Modeling the impedance characteristics of various samples using electronic circuits (also called "phantoms") is very important, especially in cases where it is difficult to maintain the properties of these samples over time. This is often the case with biological materials that degrade rapidly over time or are difficult to obtain. Preservation of sample properties using circuit models is also important for the development of new measurement techniques of these samples and comparison of various results reached by different researchers dealing with the same topic and using different measurement methods.

The Cole impedance model shown in Fig. 1 is commonly used to characterize bioimpedance properties [8]. It consists of a resistor R_{∞} that represents the resistance of the model at a very high frequency, a resistor R_1, and FOC with fractance F and order α which is also known as the dispersion coefficient. The resistance of the model at a very low frequency is expressed as $R_{\infty} + R_1$. Many research studies confirmed that employing FOC instead of the classic capacitor in the Cole model brings improvement in

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modeling accuracy [7] and this work attempts to validate this statement for cardiac cells.

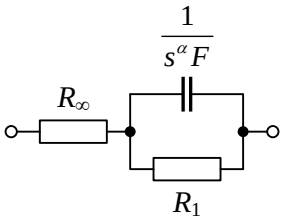

Fig. 1. Single-dispersion Cole impedance model.

To accurately characterize a particular object using the Cole model, it is necessary to determine the four parameters R_∞, R_1, α, and F from the measured data. Early methods extracted the parameters from the real-imaginary impedance plot, later numerical methods have been proposed that select the model parameters so that the analytical response of the model fits the experimental data with a minimal least squares error [7]. The utilized response may be in the frequency domain (impedance or its selected component) or in the time domain (voltage or current response to a defined waveform). The method described in this paper uses time-domain measurements with voltage excitation, whereas related techniques for extracting the Cole model parameters using the current input signal and least squares fitting can be found in [9], [10].

B. Cell Membrane Electrical Model

To the best of the authors' knowledge, the Cole model with FOC has not yet been used in modeling the electrical properties of the cardiac cell membrane. Usually, an equivalent circuit corresponding to Fig. 1 is used for this modeling, but instead of FOC, a standard capacitor is used [11], [12]. Hence, the objective and scientific novelty of this work is to determine whether the electrical impedance properties of the cell membrane show a fractional character and therefore whether it is possible to model them more accurately with the Cole circuit, where the α value is not equal to one, but is lower. For simplicity, in this initial study, we consider that the model contains only one capacitor. To be precise, the circuit should contain two separate capacitors that represent the properties of the surface and tubular membranes. However, these capacitances are usually very strongly electrically bound due to a small tubular lumen resistance between them, and therefore it is possible by conventional measurements to obtain only a total membrane capacitance equal to the sum of the above-mentioned sub-membrane capacitances [13].

It should be noted that the fractal behavior of a cell membrane is discussed in [14] where the fractal dimension D is found to be a measure of the morphological complexity of the membrane. The fractal single-shell model that describes the dielectrics of mammalian cells proposed in [14] is, in fact, based on FOC with $\alpha = 1/(D - 1)$.

This paper further contains the following parts. In Section II, the measurement technique that provides a transient response of the membrane current to the voltage step excitation is described. Then analytical relations for the impedance and current transient response of the Cole model are given. Subsequently, the minimization of the error between the measured and analytical transient response is described and the optimized values of the model elements are determined. Section III contains a discussion of the results and a comparison of approximation errors with the FOC vs. standard capacitor employed in the Cole model. Conclusions are drawn in Section IV.

II. METHODS

A. Measurement Technique

Figure 2 shows an experimental setup comprising an isolated cardiac cell (orange) connected to a glass patch microelectrode [13], [15]. For the measurements in this paper, cardiomyocytes were obtained by enzymatic isolation from the right ventricles of adult male anesthetized Wistar rats (275 ± 50 g). Single rod-shaped cardiomyocytes with well-visible striations were used for the experiments. The isolated cardiomyocytes were placed in a measuring chamber containing a Tyrode solution, which the myocytes also perfused during the measurements. Glass patch pipettes were pulled from borosilicate glass capillary tubes using a programmable horizontal puller and then heat polished. The resistance of the filled glass electrodes was kept below 1.5 MΩ to keep the resistance of cell access as low as possible. During the measurement, it is also important to choose the position of the glass patch electrode to achieve the best possible contact (gigaseal) with the cell. A typical point of contact is the center of the cell. Recordings of current have been performed using the whole-cell patch-clamp technique in the voltage-clamp mode at room temperature (23 ± 1°C) using Axopatch 200B equipment (Axon Instruments Inc., USA) and pCLAMP 10.2 software.

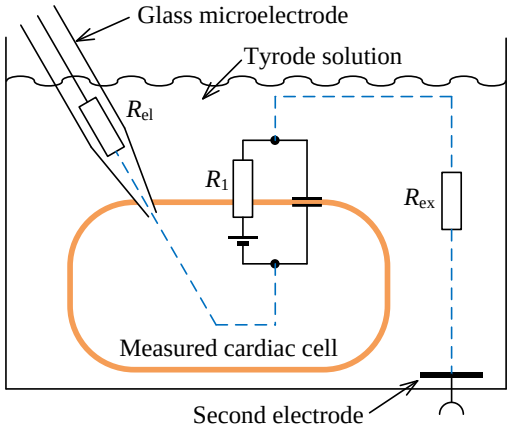

Fig. 2. Experimental setup for measuring the current step response of the cell membrane.

Apparently, the schematic symbols indicated in Fig. 2 form an electrical equivalent circuit corresponding to the Cole model in Fig. 1. The access resistance corresponding to the sum of the glass electrode resistance (R_{el}) and the resistance of the extracellular solution between the electrode and the measured cell (R_{ex}) is modelled by R_∞ in Fig. 1. The parallel resistive-capacitive circuit across the membrane can be represented in the model by the elements R_1 and FOC.

Measurement techniques used in cellular electrophysiology are based on the measurement of

membrane currents and action potential of cells. The patch-clamp technique, a specialized version of the voltage clamp, is used to measure membrane currents. This measurement method is based on evaluating current responses to changes in membrane voltage, most commonly rectangular pulses or harmonic waveforms. Small voltage pulses around the resting membrane voltage are usually used to study the electrical properties of the membrane. In the sub-threshold range of the imposed membrane voltage, the parameters of the model elements are regarded as constants [11]. Determination of the membrane parameters from the recorded responses is based on analytical formulas that describe the electrical equivalent circuit of the cell connected to the measuring device in the time or frequency domain. Measurement in the time domain using continuous rectangular wave stimulation allows for high resolution determination of membrane model parameters [12], [16] and will also be used in this work to find the parameters of the Cole model. The typical waveforms of the imposed rectangular voltage and the membrane current responses are schematically sketched in Fig. 3. Only positive pulses are depicted, as only the time interval from t_0 to t_f will be further utilized for the extraction of model parameters.

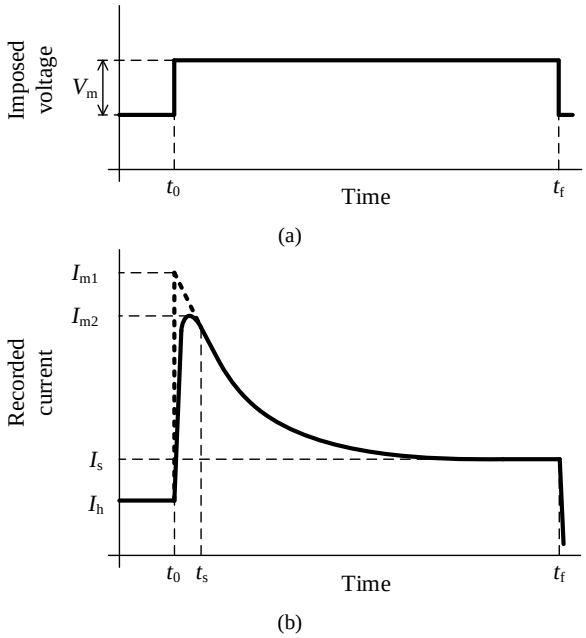

Fig. 3. Imposed voltage pulse (a) and response of the membrane current (b).

To simplify the following steps, it is convenient to shift the recorded current down by the value of the holding current I_h. Thus, the average holding current was detected and subtracted from the recorded current. This makes it possible to consider the current I_h equal to zero and the voltage oscillating between 0 V and V_m in the subsequent steps. Similarly, the time t_0 will be considered zero to shift the rising edge of the input voltage to the base position. Note the initial transient event in the current response between t_0 and t_s associated with the limited slew rate of the setup where the recorded current differs from the expected theoretical response indicated by the dashed line. The maximum current value I_{m1} cannot be determined exactly from the measured data, and only an approximate value I_{m2} is available.

B. Derivation of Analytical Formulas

The input impedance of the Cole model in Fig. 1 is given in Laplace transform by

$$Z(s) = R_\infty + \frac{R_1}{s^\alpha F R_1 + 1}. \tag{1}$$

The current through the model can be computed by Ohm's law as $I(s) = V(s)/Z(s)$, while the voltage $V(s)$ is in this case the Laplace transform of the voltage step with amplitude V_m, i.e., $V(s) = V_m/s$. After substitution, the current is

$$I(s) = \frac{V(s)}{Z(s)} = \frac{V_m}{s\left(R_\infty + \dfrac{R_1}{s^\alpha F R_1 + 1}\right)}. \tag{2}$$

After rearranging, the relation (2) becomes a format

$$I(s) = V_m \left(\frac{s^{\alpha-1}\dfrac{1}{R_\infty}}{s^\alpha + \dfrac{R_1 + R_\infty}{F R_1 R_\infty}} + \frac{s^{-1}\dfrac{1}{F R_1 R_\infty}}{s^\alpha + \dfrac{R_1 + R_\infty}{F R_1 R_\infty}} \right), \tag{3}$$

which is suitable for the inverse Laplace transform leading to analytic description of the transient response. For this purpose, the following formula is utilized [17]

$$L^{-1}\left[\frac{s^{\alpha-\beta}}{s^\alpha + \gamma}\right] = t^{\beta-1} E_{\alpha,\beta}\left(-\gamma t^\alpha\right), \tag{4}$$

where $E_{\alpha,\beta}(-\gamma t^\alpha)$ is the Mittag-Leffler function with two parameters defined as [17]

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k\alpha + \beta)}, \tag{5}$$

where $\Gamma(\cdot)$ is the Gamma function. The resulting time-domain expression of the Cole model current response due to the voltage step is

$$i(t) = V_m \left[\frac{1}{R_\infty} E_{\alpha,1}\left(-\frac{R_1 + R_\infty}{F R_1 R_\infty} t^\alpha \right) + \right.$$
$$\left. + \frac{1}{F R_1 R_\infty} t^\alpha E_{\alpha,\alpha+1}\left(-\frac{R_1 + R_\infty}{F R_1 R_\infty} t^\alpha \right) \right]. \tag{6}$$

In the case of replacing the FOC in the model by a classic capacitor with capacitance C, the relation (6) simplifies to the following form containing exponential function

$$i_{\text{int}}(t) = \frac{V_m}{R_1 + R_\infty}\left[\frac{R_1}{R_\infty} e^{-\frac{R_1 + R_\infty}{C R_1 R_\infty} t} + 1 \right]. \tag{7}$$

Relations (6) and (7) will be used to obtain the parameters

of the model by minimizing the error against the recorded current response. According to the resulting error, it will be evaluated whether FOC in the model improves the modeling of the electrical properties of the cell compared to the classic capacitor.

C. Least Squares Fitting

Non-linear least squares fitting of the recorded current decay is used to find element values of the Cole model containing either a FOE or a classic capacitor. This numerical method aims to minimize the following Least Squares Error (*LSE*)

$$LSE = \sum_{i=1}^{n} \left[i(t_i, X) - RecCur(t_i) \right]^2, \tag{8}$$

where X is the sought vector of Cole model parameters (R_∞, R_1, α, F), $i(t_i, X)$ is the time-domain response calculated by (6) using X, and $RecCur(t_i)$ is the current response recorded. A total of $n = 60$ time instants t_i are chosen from the interval between t_s and t_f. These instants are logarithmically distributed over time so that the fitting considers more data points at the beginning of the response, where the current changes faster.

The fitting was carried out using the MATLAB® function *fminsearch* with the argument given by (8). The Mittag-Leffler function was evaluated with accuracy 10^{-10} by routine [18]. The *fminsearch* function requires an initial guess of the sought parameters X. Generally, the resistance R_∞ would be determined as $R_\infty = V_m/I_{m1}$. However, as already mentioned at the end of Section II-A the maximum current value I_{m1} cannot be detected from the measured response. Anyway, the achieved maximum I_{m2} is sufficient for the initial guess of the resistances in the Cole model. Thus, the relations $R_{\infty G} = V_m/I_{m2}$ and $R_{1G} = V_m/I_s - V_m/I_{m2}$ can be used to get the initial guesses of the model resistances.

Due to the fact that the cell membrane shows a current response close to the standard exponential function, a relatively high value of α approaching one can be expected. Therefore, it is appropriate to choose $\alpha_G = 0.9$ as the initial guess. As an initial estimate of fractance F, it is possible to use a capacitance value C_G determined by a method for the extraction of the classic membrane capacitance from the exponential response, such as [19].

To minimize the probability of finding a local minimum, the function *fminsearch* is executed multiple (100) times, each time with randomly selected initial guesses from the intervals:

– R_∞ randomly selected from $0.1R_{\infty G}$ to $R_{\infty G}$ (since I_{m2} is lower than I_{m1}, the resistance R_∞ must be lower than $R_{\infty G}$),
– R_1 randomly selected from $0.1R_{1G}$ to $10R_{1G}$,
– α randomly selected from 0.6 to 1,
– F randomly selected from $0.1C_G$ to $10C_G$.

The resulting X parameters are then taken from the run with the lowest *LSE*. The pseudocode of the proposed method is presented in Algorithm 1.

Algorithm 1. Pseudocode of the parameter extraction method.

```
Input: abf datafile, C_G
Output: X_final, LSE_final, i_final
load Data from recorded abf datafile by abf2load function
RecCur ← current waveform shifted to base position, i.e., I_h = 0, t_0 = 0 and selected 60 log-spaced samples between t_s and t_f (t_s determined empirically from graph)
V_m, I_m2, I_s ← detect values from Data and RecCur
for m = 1 to 100
   Guess ← generate random initial guess of X parameters
   minimize the LSE error (8) using fminsearch function with initial Guess
   if actual LSE is lower than LSE from previous cycle
      X_final ← X
      LSE_final ← LSE
   end if
end for
i_final ← compute current response (6) using X_final
display X_final, LSE_final, i_final
```

III. RESULTS AND DISCUSSION

To verify the proposed method, records of membrane current responses in rat cardiomyocytes to voltage rectangular pulse in Tyrode solution are used [13], [15]. The measurement has been performed by the setup described in Section II-A and averaged from last 20 pulses of a batch of total 200 pulses.

Since cell capacitance measurement techniques are usually based on the application of small sub-threshold voltage steps around the resting membrane voltage of the cell, the voltage levels of the rectangular stimulus signal are chosen −80 mV and −75 mV, so the amplitude V_m is 5 mV. This limited amplitude prevents membrane depolarization and ensures constant parameters of the membrane electrical model shown in Fig. 2. If the membrane was depolarized, voltage-dependent ionic channels would be activated and the capacitance of the cell membrane could not be measured [11].

The positive pulse width (t_f−t_0) of the imposed voltage is 20 ms and the sampling time is 5 µs. The transient response of the recorded current with the initial point (t_0, I_h) shifted to zero is shown in black in Fig. 4. The circle marker on the trace indicates the sample at the time t_s = 185 µs where the initial transient event decayed and from which the response was subjected to processing. A logarithmic scale is used on the horizontal axis for better visibility of the waveforms at the time period close to the origin.

The red line in Fig. 4 represents the current response computed by the relation (6) corresponding to the Cole model with FOC and other parameters detected by the described fitting method. Very good agreement with the measured black response can be observed. Comparison of the results with the model corresponding to the Cole circuit but containing a classic capacitor is also present. The parameters of this integer-order model are extracted by two methods. The first one employs the fitting procedure presented in this paper, however, the relation (7) instead of (6) is used in the *LSE* computation for the *fminsearch* function. The response resulting from this method is shown

by the green line in Fig. 4. The second method used for comparison stems from the work in [19] where a three-point (3P) approach is proposed to detect the model parameters. The element values computed by the 3P method and substituted into (7) result in the blue response in Fig. 4. The curves in Fig. 4 differ the most from each other in the initial times, below 100 µs. However, we must recall that the fitting could be performed first in the observed steady state starting with the circled initial sample at t_s = 185 µs. For higher times (after the initial sample), the curves begin to converge, but the differences between them are still noticeable. To better assess the results in this area, the relative errors of the fitted current responses against the recorded one are plotted in Fig. 5.

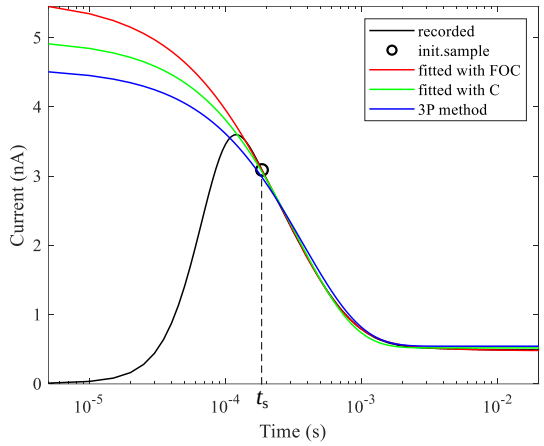

Fig. 4. Current transient responses: recorded (black), fitted with FOC (red), fitted with classic capacitor (green), and response with model parameters detected by the 3P method [19] (blue).

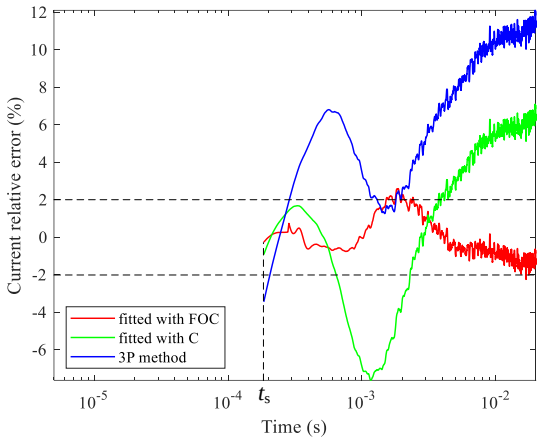

Fig. 5. Relative errors of responses fitted with FOC (red), fitted with classic capacitor (green), and model parameters detected by the 3P method [19] (blue) against the recorded response.

It is apparent from the graph that the response obtained with the Cole model with FOC and the parameters extracted by the proposed method results in the lowest relative error, mostly below ±2 %. The error of the model with the extracted classic capacitance reaches its worst-case value of −7.6 % and the model corresponding to the 3P method provides the highest error of about 12 %. Note that at times lower than t_s, it is not possible to evaluate the relative error because this interval is affected by the initial transient event. The extracted model parameters, *LSE* values and maximum absolute values of the relative errors for the three considered methods are summarized in Table I.

From Table I, it is seen that the three methods differ even more when compared in terms of the *LSE* parameter. Regarding *LSE*, the method described with FOC is again the best, followed by the same method with the classic capacitor and the 3P method.

IV. Conclusions

In this paper, a method for determining parameters of a cell membrane circuit model containing FOC based on current transient response was presented when applying voltage rectangular pulse. The results show that the Cole model containing FOC is able to better approximate the recorded current response compared to the corresponding models with the classic capacitor. The fractional-order extracted value α is 0.9363, which may appear to be close to the value of 1 of a classic capacitor, but the maximum relative approximation error of the current response is reduced approximately three times when using FOC instead of classic capacitor. The method proved to be very robust, as it is able to deal with a recorded current response where it is not possible to perform the fitting from the beginning of the rise time due to the initial parasitic transient event.

From the relatively high detected α value close to 1, it can be concluded that the membrane has a geometrically simple structure close to the arrangement of a classic capacitor. A lower α value can be expected for more morphologically complex structures. A lower α value was also observed when measuring responses of entire tissues composed of many cells, where numerous intracellular, extracellular, and cellular membrane resistances and capacitances appear. As the parameter α is also referred to as a dispersion coefficient, it can be considered as a measure of the heterogeneity of cell sizes and shapes [7].

Future research may address the relationship between the detected α value and various cell membrane properties. For example, the mentioned connections with the morphological complexity of the membrane or its various pathological phenomena can be investigated.

TABLE I. EXTRACTED PARAMETER VALUES AND ERRORS FOR THE CONSIDERED EXTRACTION METHODS.

Method	**Extracted model parameters**				***LSE* (A²)**	**Max. abs. relative error (%)**
	R_∞ **(MΩ)**	R_1 **(MΩ)**	***F* or *C***	α		
This work FOC	0.8979	9.609	582.0 pF×s$^{\alpha-1}$	0.9363	2.508×10^{-21}	2.599
This work classic cap.	1.004	8.612	366.0 pF	1	4.109×10^{-20}	7.626
3P method [19]	1.096	8.091	384.2 pF	1	2.256×10^{-19}	12.11

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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