# Analogue Realization of Fractional-Order Healthy and Cancerous Lung Cell Models for Electrical Impedance Spectroscopy

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***Abstract*—This work proposes an integrated-circuit architecture emulating healthy and cancerous lung cell behaviors, approximated by Cole models and is suitable for calibration and phantom experimental testing of electrical bioimpedance circuits and systems. The architecture is based on fractional-order elements implemented with both active and passive components, offering an accurate transfer function behavior between $10$kHz and $1$MHz. The high-level architecture includes an analog all-pass filter coupled with a current conveyor. Performance and accuracy of the proposed architecture is confirmed via Monte-Carlo simulation. The proposed circuitry has been designed in TSMC $90nm$ CMOS process and simulated using the Cadence IC suite.**

***Index Terms*——Fractional-order models, healthy lung cell, cancerous lung cell, current feedback operational amplifier**

## I. Introduction

The human tissues are characterized by specific electrical properties that reveal important information about their physical structure and function over space, time and frequency. Therefore, bioimpedance measurements, such as simple tetrapolar measurement, Electrical Impedance Tomography (EIT) and Electrical Impedance Spectroscopy (EIS) are recently becoming widespread methods that can assist the diagnostic process, avoiding invasive or continuous ionizing radiation exhibition procedures. In biompedance measuring methods, a small amplitude alternating current that meets the patient safety standards is acted via an electrode pair, attached on the patient skin surface [1].

Since bioimpedance measuring approaches are still developing both in hardware and software terms, accurate simulations and calibration experiments that include the subject electrical equivalent are immensely desired. This requirement introduces some challenges, since the electrical behavior of most human tissues is very complex and non-linear over the frequency domain. They usually follow a Cole frequency dispersion sequence. Moreover, the measurements often need to be taken at a wide frequency range, since each frequency region reveals specific tissue properties that might not be detectable at other regions [2].

Hence, high accuracy and large spectrum models are developed in order to replicate the human tissues' cells behavior. Due to their Cole nature, fractional-order models are essential to achieve the desired accuracy. Many mathematical fractional-order models have been established for biological applications. However, there is a noticeable lack of circuit modelling realization, which is necessary for the simulation of bioimpedance measuring system and the calibration with prior experiments using phantom circuitries. This absence is presented due to the fact that Cole models are impossible to be implemented using linear RC circuit equivalents.

EIT and EIS are widely utilized at the thoracic imaging, for the examination of the lung's structural and functional characteristics. Due to the lung's dynamic behavior over the time domain, thoracic tomographic images are usually obtained at frequencies between 10kHz and 1MHz [1]. Moreover, any maligant tissue regions are more detectable at higher frequencies. Therefore, fractional-order models are needed to be applied at this frequency span.

In this work, an analogue implementation of fractional-order models, emulating normal and cancerous lung tissue cells from 10kHz-1MHz, is presented. Since fractional-order models offer more degrees of freedom, in comparison with integer-order, they are more accurate and sophisticated for real-world system description [3], [4]. The implementation of the models is based on analog filters. In order to transform the voltage (filter output) to impedance, we add a voltage to current (V/I) converter. The whole architecture describes the behavior of a fractional-order element.

The remainder of this paper is organized as follows. In Section II, a brief presentation of the mathematical fractional-order model for the healthy and the cancerous lung tissue is written. In Section III, the analogue implementation is described and in Section IV, simulations performed in Cadence IC suite and the corresponding results are demonstated and discussed. Finally, in Section V, the conclusion is written.

## II. Lung Cole model

Many studies related with the lungs' electrical properties over various frequency ranges are found in the literature. Extensive studies for Cole parameter fitting at a large variety of human tissues are found in [5], [6]. General Cole modelling

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TABLE I: Normal and cancerous lung cell Cole parameters [11]

| Parameter | $R_\infty$ ($\Omega$) | $R_o$ ($\Omega$) | $a$ | $\tau$ ($\cdot 10^{-7} s$) | $C$ ($\mu F/s^{1-a}$) |
|---|---|---|---|---|---|
| Normal | $153 \pm 69$ | $1280 \pm 421$ | $0.66 \pm 0.06$ | $5.70 \pm 3.71$ | 0.067 |
| Cancerous | $76 \pm 80$ | $558 \pm 143$ | $0.64 \pm 0.08$ | $6.82 \pm 0.12$ | 0.235 |

studies targetted in EIS are also presented in [7] and [8]. Specific work on the lung tissue cell electrical behavior from 1 MHz to 20GHz is found in [9], while [10] searches an accurate correlation between the air content and the admittance. In this particular work, we implement the Cole model described in [11], since it covers the frequency spectrum of interest (10 kHz to 1MHz) for EIS applications, and separates the model behavior between benign and maligant lung tissue cells.

Each cell can be modelled using a parallel combination of a Constant Phase Element (CPE) and a resistor, in series with a shunt impedance as it is depicted in Fig. 1. The Cole equation that expresses the healthy lung cell [11] is given by:

$$z_b(\omega) = R_{\infty,b} + \frac{R_{0,b} - R_{\infty,b}}{1 + (j\omega)^{a_b} \cdot (R_{0,b} - R_{\infty,b}) C_b} \quad (1)$$

while the equation that expresses the cancerous cell [11] is given by:

$$z_m(\omega) = R_{\infty,m} + \frac{R_{0,m} - R_{\infty,m}}{1 + (j\omega)^{a_m} \cdot (R_{0,m} - R_{\infty,m}) C_m} \quad (2)$$

Where $R_{\infty,i}$ is the shunt Ohmic impedance, towards which the cell's impedance converges while frequency tends to infinity, $R_{o,i}$ is the low frequency resistor, $a_i$ is the fractional CPE order, $\omega$ is the angular frequency and $C_i$ the CPE's pseudo-capacitance. The characteristic time constant $\tau_i$ is expressed by:

$$\tau_i = \sqrt[a_i]{(R_{0,i} - R_{\infty,i}) C_i} \quad (3)$$

The CPE's impedance is computed with the following expression:

$$z_{CPE} = \frac{1}{C_i (j\omega)^{a_i}} \quad (4)$$

It is noted that $i = b, m$, where $b$ denotes a healthy lung cell and $m$ a maligant one. The Cole parameter values for both cases are demonstrated in Table I, where the CPEs' values have been estimated from (3) using the mean parameter values.

It is obvious that there is a large variation at the parameters' values, mainly due to the lung's air content. A lung can be at any state between the full inhalation (inflated state) and the full exhalation (deflated state). Nevertheless, in this work we are focusing on EIS applications for cancerous cell detection. Since between 10kHz and 1MHz the electrical conductivities and permittivities of a normal and a cancerous cell do not overlap [11], our analogue circuitry model is based on the mean parameter values.

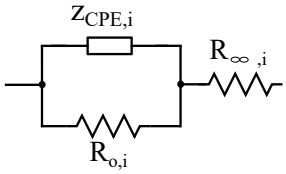


Fig. 1: Cole model for a lung cell, where $i = b, m$.

## III. Model Implementation

Implementation of the behavior of fractional-order elements is based on two types of approximation techniques due to the fact that they are not yet available for massive production. The first technique is RC-network approximation which provides easy implementation but it does not have the capability of electronic tuning on the element's characteristics (order or impedance) [12], [13].

The second one is integer order expression and the behavior of the element is approximated for example by means of the continue fraction expansion (CPE) method, round a center frequency $\omega_o = 1/\tau$. This is achieved via electronic parts such as operational transcoductance amplifies (OTAs) [14], current mirrors [15] and current feedback operation amplifiers (CFOAs) [16], [17]. A fractional-order model of lung is implemented in [14], using OTAs as active elements but the frequency range does not exceed 10Hz.

### A. RC-network approximation

A typical network for approximating the behavior of fractional-order capacitor is depicted in Fig. 2. It is consists of two correction factors $R_p$ and $C_p$ and $m$ parallel resistors and capacitors branches. The generalized expression of the RC-network impedance is given by:

$$Z_{tot}(s) = sC_p + \frac{1}{R_p} + \sum_{\kappa=1}^{m} \frac{sC_\kappa}{sR_\kappa C_\kappa + 1} \quad (5)$$

Since the practical frequency of interest is between 10 kHz and 1MHz, the center frequency is $f_o = 100\,\text{kHz}$ and the appropriate order of the RC-network is $m = 3$ (in order to achieve at least $1.5^\circ$ accuracy). Elements' values are summarized in Table II for both lung cells. The center frequency, the order $m$ of the RC-network and the values of passive elements are derived using MATLAB code [12], [13].

### B. CFE approximation

The behavior of fractional-order capacitor is described by a fractional-order differentiator connected with a double-output Current Conveyor (DO-CCII) which acts as Voltage to Current

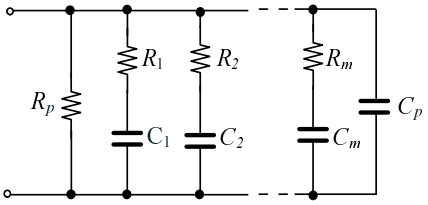


Fig. 2: Valsa-Vlach RC-network.

TABLE II: Passive element values for approximating the fractional-order capacitors of Fig. 2.

| Normal Lung | | Cancerous Lung | |
|---|---|---|---|
| Element | Value | Element | Value |
| $C_1$ | 1.0 nF | $C_1$ | 2.90 nF |
| $C_2$ | 451.40 pF | $C_2$ | 1.25 nF |
| $C_3$ | 203.48 pF | $C_3$ | 535.77 pF |
| $C_p$ | 167.02 pF | $C_p$ | 404.42 pF |
| $R_1$ | 15.9 kΩ | $R_1$ | 5.5 kΩ |
| $R_2$ | 3.4 kΩ | $R_2$ | 1.2 kΩ |
| $R_3$ | 720 Ω | $R_3$ | 274 Ω |
| $R_p$ | 58.7 kΩ | $R_p$ | 19.1 kΩ |

(V/I) converter. Fractional-order differentiator is approximated by an all-pass filter, which is implemented by utilizing Current Feedback Operational Amplifiers (CFOAs) as active elements.

The frequency range is set to be from 10kHz to 1MHz for our model and we choose $3^{rd}$-order CFE approximation round a center frequency $\omega_o = 1/\tau$ [14]–[17]. The expression of the $3^{rd}$-order CFE approximation is described by:

$$(\tau s)^{\alpha} \approx \frac{a_3 s^3 + a_2 s^2 + a_1 s + a_o}{b_3 s^3 + b_2 s^2 + b_1 s + b_o} \tag{6}$$

where:
$\alpha_3 = b_o = \alpha^3 + 6\alpha^2 + 11\alpha + 6$,
$\alpha_2 = b_1 = -3\alpha^3 - 6\alpha^2 + 27\alpha + 54$,
$\alpha_1 = b_2 = 3\alpha^3 - 6\alpha^2 - 27\alpha + 54$,
$\alpha_o = b_3 = -\alpha^3 + 6\alpha^2 - 11\alpha + 6$
and $\alpha$ is the order of the differentiator (all pass filter) [14]–[17]. The complete design of proposed architecture is depicted in Fig. 3 and parameters are summarized in Table III. In Fig. 3 the resistors' and capacitors' values can be easily calculated using the corresponding parameters based on (6). The transfer function of the fractional-order differentiator, which is based on a $3^{rd}$-order all pass filter is given by:

$$H(s) = (\tau s)^{\alpha} = \frac{a_3 s^3 + a_2 s^2 + a_1 s + a_o}{b_3 s^3 + b_2 s^2 + b_1 s + b_o} \tag{7}$$

The impedance of the fractional-order capacitor is given by:

$$Z_{cap}(s) = \frac{R_{vi}}{H(s)} \tag{8}$$

where $R_{vi}$ is the appropriate resistor of the V/I converter and $H(s)$ is the expression of the filter.

TABLE III: Parameter of the circuit in Fig. 3.

| Parameter | Value | Parameter | Value |
|---|---|---|---|
| $b_3$ | 1 | $b_2$ | $\frac{1}{R_1 C_1}$ |
| $b_1$ | $\frac{b_2}{R_2 C_2}$ | $b_o$ | $\frac{b_1}{R_3 C_3}$ |
| $\alpha_3$ | $\frac{R_6 R_8}{R_1(R_6+R_8)}$ | $\alpha_2$ | $\frac{\frac{\alpha_3}{RC} + \frac{b_2 R_8 R_6}{RC(R_6+R_8)}}{}$ |
| $\alpha_o$ | $\frac{b_1 R_8}{R_7(R_6+R_8)}$ | $\alpha_1$ | $\frac{RC\alpha_o + \frac{b_2 R_8 R_6}{RCR_5(R_6+R_8)}}{}$ |

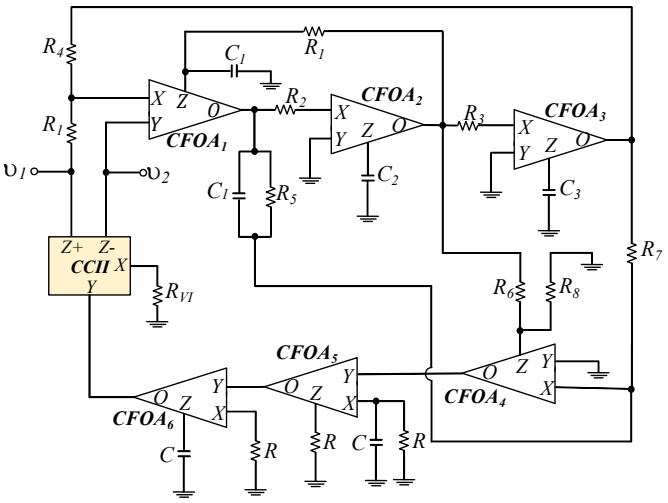


Fig. 3: Implementation of fractional-order capacitor emulator.

## IV. Simulations and Results

The proposed lung cell has been designed in TSMC 90 nm CMOS process, using the Cadence IC design suite. The schematic of the corresponding CFOA is shown in Fig. 4 and the schematic of the appropriate V/I converter is depicted in Fig. 5, according to [17]. The power supply rails are set to $V_{DD} = -V_{SS} = 0.75\,\text{V}$, $I_b = 200nA$, $I_{bias} = 3nA$ and all transistors operate in the sub-threshold region. The dimensions of the MOS transistors of the CFOA and the DO-CCII are summarized in Table IV.

The obtained magnitude and phase responses in comparison with both RC-network and theoretically predicted ones confirm the behavior of the fractional-order healthy and cancerous lung cell model as shown in Fig. 6. The results of the proposed impedance models are in fine agreement with the theoretical ones and confirm the proper operation, performance and accuracy of the proposed topology.

The sensitivity behavior has been evaluated using the Monte-Carlo analysis tool for $N = 100$ runs for impedance and phase for health lung. The mean value of the impedance and phase is $I_{mean} = 1.06\,\text{k}\Omega$ and $P_{mean} = -18.28°$ and the standard deviation is $\sigma_I = 0.07\,\text{k}\Omega$ and $\sigma_P = 1.36°$

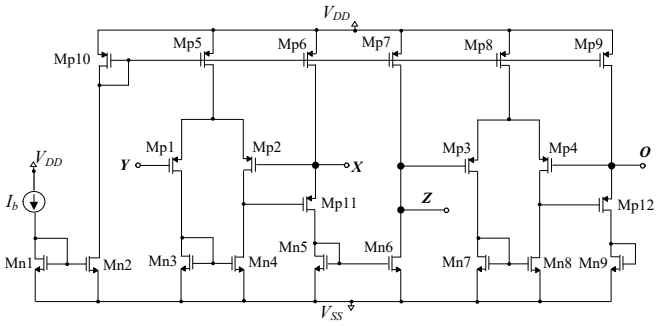


Fig. 4: Employed CFOA.

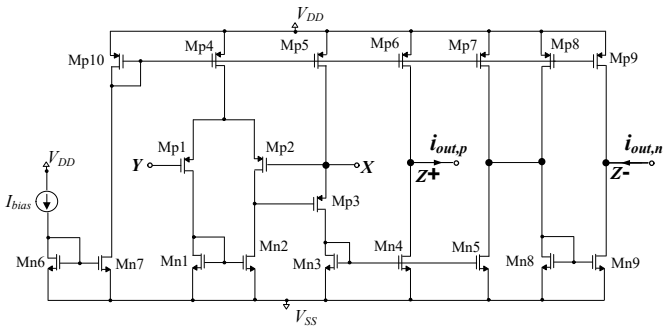


Fig. 5: Employed DO-CCII for the implementation of V/I converter.

at $f_o = 100\,\text{kHz}$, respectively. The Monte-Carlo analysis demonstrates the performance and accuracy of the proposed architecture.

TABLE IV: MOS Transistors Dimensions – CFOA & DO-CCII.

| CFOA | W/L (μm/μm) | DO-CCII | W/L (μm/μm) |
|---|---|---|---|
| $M_{n1}$-$M_{n9}$ | 13/0.5 | $M_{n1}$-$M_{n9}$ | 13/0.5 |
| $M_{p5}$-$M_{p10}$ | 50/0.5 | $M_{p4}$-$M_{p10}$ | 50/0.5 |
| $M_{p11}$,$M_{p12}$ | 100/0.5 | $M_{p3}$ | 100/0.5 |
| $M_{p1}$-$M_{p4}$ | 20/0.4 | $M_{p1}$,$M_{p2}$ | 20/0.4 |

## V. Conclusion

In this paper, we implemented the healthy and cancerous lung cells (Cole model) in fractional order integrated form using CFOAs and CCIIs as active elements. Simulations showed very low impedance and phase errors for fractional-order model and also confirming the accuracy and the performance of the proposed architecture, in system level. The ICs implemented can be used in more complex circuitry setups for calibration and phantom experimental testing, much more effectively than simple resistor or RC networks.

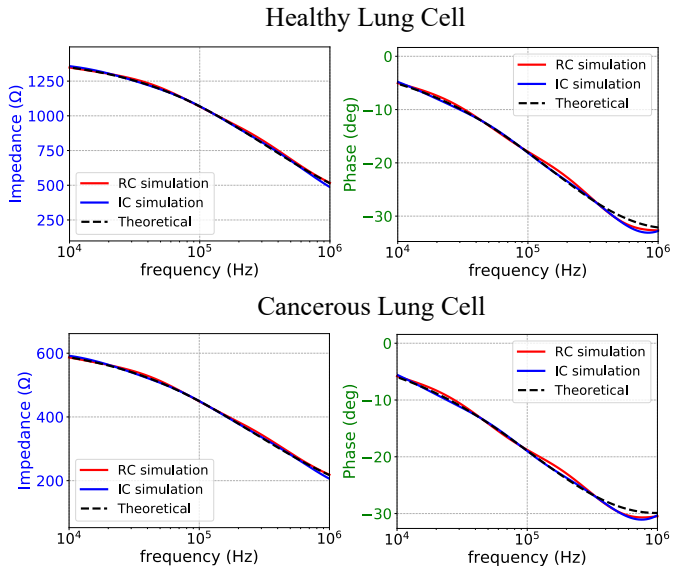


Fig. 6: Frequency responses of fractional-order lung cell model.

## Acknowledgment

This research is co-financed by Greece and the European Union (European Social Fund- ESF) through the Operational-Programme "Human Resources Development, Education and Lifelong Learning" in the context of the project "Strengthening Human Resources Research Potential via Doctorate Research" (MIS-5000432), implemented by the State Scholarships Foundation (IKY).

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