Modeling and Analysis of Monitored vs. Self-reported Postsurgical Acute Pain in a Clinical Trial [★]

Mihaela Ghita [*,**] **Negin Jalilian** [*] **Dana Copot** [*,**]
Clara M. Ionescu [*,**,***] **Martine Neckebroek** [****]

[*] *Research group of Dynamical Systems and Control, Ghent University,*
9000 Ghent, Belgium (e-mail: negin.jalilian@ugent.be,
mihaela.ghita@ugent.be, dana.copot@ugent.be,
claramihaela.ionescu@ugent.be)
[**] *EEDT Decision and Control, Flanders Make, 9000 Ghent, Belgium.*
[***] *Department of Automation, Technical University of Cluj-Napoca,*
400114 Cluj-Napoca, Romania
[****] *Department of Anesthesiology and Perioperative Medicine, Ghent*
University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium
(martine.neckebroek@ugent.be)

Abstract: This work aims to study postsurgical trauma modeling to characterize the physiological process in postoperative pain assessment in an observational trial. The skin impedance data is proposed to be fitted by derived-Cole models, i.e., single and double dispersion models and a distributed model with an inductive term related to sweat glands. These models are motivated by the biological characteristics of the skin, its physiological stratification and the current intra- and extra-cellular pathways. The correlation between the identified parameters with the patient's pain reported using the numerical rating scale (NRS) is analyzed for one patient for all three models. Following the trial, a statistically significant positive linear relationship was observed between the Anspec-Pro index and NRS ($r^2 = 0.16$, p=0.00), driving the further study of the relationship between the estimated dielectric parameters. The paper focuses to analyze the changes of the coefficients related to the particular clinical data, successfully identified using the non-linear least square procedure. The clinical significance of the results may be related to the individual model parameters for postoperative pain detection, validated on patients.

Keywords: fractional order impedance model, Cole model, non-invasive pain monitor, bioimpedance, postoperative pain

1. INTRODUCTION

More than 80% of the patients suffer from postoperative pain in postanesthesia care units (PACU) (Rawal, 2016). The persistent postsurgical pain prevalence reaches 30-50%, originating from unsatisfactory acute pain management (Luo and Min, 2017). Therefore, pain management, especially after surgical procedures, is essential as it prevents the progression from acute to chronic pain or long-lasting disabilities (Lavand'homme, 2011).

One way to achieve better pain management is by integrating pain monitors in clinical practice, which provides both clinicians with the opportunity to objectively assess pain and opioid delivery and patients to have a better experience from less pain after surgery (Lavand'homme, 2011). To date, several commercialized monitors have been indicated for objective pain assessment in PACU or analgesia levels for perioperative use (Ghita et al., 2020b). The principle of most of these tools is based on changes in

the autonomic nervous system in response to stimuli or surgical tissue trauma. The devices monitor corresponding modifications in biomarkers such as electrodermal activity, pupil reflexes, heart rate, and blood pressure (Ledowski, 2019). Even if biomarkers that indicate the biological and pharmacological process can be subjectively measured (Cowen et al., 2015), monitors that combine these biomarkers with biopotential outputs are considered assuring. However, seeking one fundamental physiological parameter change is not reliable due to the overlap between the autonomic nervous system and nociceptive signaling pathways (Cowen et al., 2015; Tracey et al., 2019). Additionally, what these biological signals lack is the analysis in both the time and frequency domain.

A basic understanding of nociceptive response is vital to good pain assessment, so modeling enables to characterize the underlying physiological process that pain promotes (i.e., palmar sweating, stress hormones releasing, and a complex series of electrochemical events generated at cells level). In this work, we propose various models describing anomalous diffusion and dielectric properties of skin tissue, based on the complex bioimpedance explored in its full potential: 2D to 3D time-frequency analysis. The

frequency response data acquired in postoperative patients is therefore used for parametric identification.

On the other hand, behavioral observation scales such as the numerical rating scale (NRS) are available in PACU to identify the intensity of pain after surgery. NRS is the most straightforward, commonly used and standard scale in daily clinical procedures for patients to describe their pain intensity, with 0 having no pain and 10 having the maximum imaginary pain. Hereby, the assessment of pain mainly relies on the self-evaluation report. Although these scores are fruitful, they are impossible to obtain in unconscious patients or not reliable in cognitively compromised patients who cannot verbalize or quantify pain (Lazaridou et al., 2018). Therefore, the investigation of developing reliable devices and methods for assessing pain objectively remains a challenge.

The recently developed device for pain assessment, namely Anspec-Pro, has enabled the acquisition of skin impedance for the data-driven modeling proposed in this paper (Ghita et al., 2020a). The monitor has been successfully validated on awake healthy volunteers undergoing induced pain and patients in PACU for detecting the perception of pain (Ghita et al., 2019; Neckebroek et al., 2020). The device and its related methodology detect active nociceptive stimulation and evoked-pain of post-surgical trauma by analyzing the frequency-modulated bioimpedance measured in the hand palm. The availability of the complex skin impedance frequency response triggered the application of data-driven electrical models in the present and previous works (Copot and Ionescu, 2018). This paper brings innovation through the mathematical modeling of time-frequency changes in skin impedance values specifically for post-trauma-related pain. These electro-chemical variations reflect alterations throughout the pain signaling pathway, as a response to the multi-frequency excitation signal applied by Anspec-Pro.

Consequently, this paper proposes three electrical models to characterize the physiological changes in skin impedance with mathematical tools. The potential of single- and double-dispersion Cole models and distributed inductive Cole model are investigated. The working hypothesis is that the identified parametric models are correlated with the NRS value reported by the patient for evaluation of its postoperative pain every 7th minute. The bioimpedance data was collected from patients included in an observational study during the PACU period, initially reported in Neckebroek et al. (2020).

The methodology of the trial and the electrical models followed by statistical analysis are presented in section 2. Next, in section 3, the obtained results from both pain monitors and the comparison between the three models are indicated and discussed. Finally, the work is concluded in section 4.

2. MATERIALS AND METHODS

2.1 Postoperative clinical data

Participants. The trial was a cohort study performed at Ghent University Hospital, Belgium (identifier on clinicaltrials.gov: NCT03832764; principal investigator: Martine Neckebroek), approved by the Ethics Committee (protocol code: EC/2017/1517). Patients who needed potent analgesia during surgery were selected from a list of the patients who planned to have a surgical operation.

Patients between the age of 18 to 75 years old that could understand and sign the written informed consent document for participation were included. Exclusion criteria were related to patients (i) having epidural analgesia infused by a pain pump, (ii) having chronic pain or getting medication used for chronic pain, (iii) having participated in a clinical trial within the past 30 days, (iv) having the operation planned at one of the upper limbs (so that placing together the blood pressure cuff and the electrodes of the pain monitor at the same upper limb would not be possible), (v) staying in daily hospital or Intensive Care Unit and (vi) pregnant women.

Patient selection was based on a randomized list assigned to two pain monitoring devices, namely Anspec-Pro and Medstorm. Therefore, the cohort study was conducted with 26 patients, 13 patients allocated to Medstorm and 13 patients to Anspec-Pro. However, for Anspec-Pro, one patient was excluded as the data acquired from the patient was incomplete. Hence, the total number of 25 patients was fully considered for this work.

Data collection. The study design consisted of two periods of monitoring: preoperative and postoperative. In the preoperative period, in the waiting room, the pain was assessed by NRS and by the pain monitor for 14 minutes. After this step, the surgery was performed according to the standard clinical procedures while the pain device did not monitor the patient's pain. In the postoperative period, in PACU, the pain was also measured by NRS (self-report or nurse evaluation at every 7 minutes) and by the pain monitor, continuously for 140 minutes. For patients who were still unresponsive, the nurses assessed the NRS value. It should be noted that the time interval of 7 minutes has been selected together with the clinical investigator as an optimal interval for pain assessment. During the monitoring periods, the patients' heart rate (HR) and mean arterial pressure (MAP) were also registered for further statistical analysis. Biometric data such as age, weight, height, and body mass index (BMI) were noted before the trial.

The used pain monitor devices in the trial were Anspec-Pro (Ghent University, Ghent, Belgium - only for research use), and Medstorm (Med-Storm Innovation, AS, Oslo, Norway). Both devices non-invasively measure the nociception level by placing three electrodes at the palm hand. The palm is considered a suitable place for detecting tissue dynamics due to changes in electrical permeability. Medstorm principle is based on measuring the number of fluctuations of skin conductance (NFSC) after inducing a single-frequency current as an input. In contrast, Anspec-Pro measures the bioimpedance response of the skin after multiple-frequency current input, allowing the characterization in the frequency domain. This is valuable because any biological tissue is frequency-dependent when excited by an alternating current, generating broader information.

2.2 Electrical modeling of skin impedance

Human skin is a complex tissue whose impedance properties change with different frequencies (Laycock and Bantel, 2016), deeper skin layers being captured by higher frequencies (Grimnes and Martinsen, 2015). Skin impedance depends on several criteria such as thickness, skin water content, and sweat glands. Electrical modeling of the skin is essential to understand and characterize the nociceptive
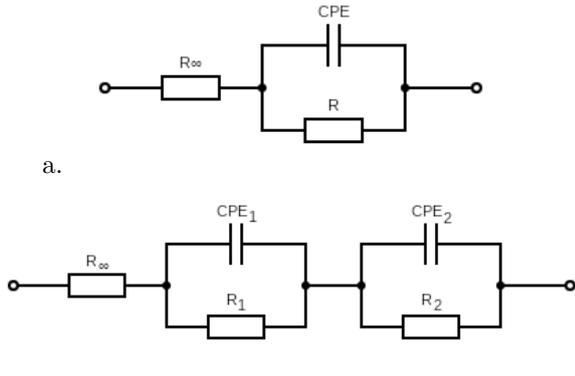
Fig. 1. Electrical bioimpedance Cole models with a. single dispersion and b. two dispersions.

and applied current pathways. Several models have been reported for skin impedance estimation with experimental data (Bora and Dasgupta, 2020). This work proposes the application of derived Cole models for fitting the clinical data of postoperative bioimpedance.

Single-dispersion Cole model. The most used model applied to different measurement techniques of impedance is the Cole model (Fu and Freeborn, 2020). Single-dispersion Cole model deals both with conductive and dielectric properties. It is composed of three electrical components, each assuming to represent a structure of the human skin. In Fig. 1a, the general Cole 1-dispersion model is depicted with a high-frequency resistor R_∞ representing the deeper tissue, the lower frequency resistor R, and a constant-phase element (CPE). CPE is a fractional capacitor that can be expressed as $Z_{CPE} = \frac{1}{Cs^\alpha}$ where $\alpha \in (0,1]$, C is the capacitance, and $s = j\omega$. The following term gives the single dispersion Cole model in Laplace domain:

$$Z_{est} = R_\infty + \frac{R}{1 + RCs^\alpha} \qquad (1)$$

Double-dispersion Cole model. Cole with double dispersion is an extension of the single-dispersion model, utilizing two Cole cells. This model demonstrates the impedance over a deeper layer of the skin and a larger frequency. In biological media, three main dispersion regions can be distinguished in the frequency spectrum, i.e., α: 10 Hz-10 KHz, characteristic for diffusion detection of the ionic species (extracellular fluid level), β: 10 kHz-10 MHz for a dielectric property measurement of the cell membrane, and $\gamma > 10$ MHz for content measurement of the biological species (intracellular fluid level) (Neckebroek et al., 2020). For modeling, only α and β will be considered, so only two Cole cells are included in the model. The permittivity decreases over increased frequency and is directly correlated with the capacitance. This model with a parallel resistor (R_2) and CPE_2 in series with single dispersion Cole model is shown in Fig. 1b, given by:

$$Z_{est} = R_\infty + \frac{R_1}{1 + R_1 C_1 s^\alpha} + \frac{R_2}{1 + R_2 C_2 s^\beta} \qquad (2)$$

with α and β dimensionless fractional numbers.

Distributed Inductive Cole model (DIC). Grimnes and Martinsen (2015) proposed a skin model, which version without electrode polarisation is depicted in Fig. 2a. In our work, we propose a distributed fractional dielectric model with Cole 1-dispersion and inductive components.
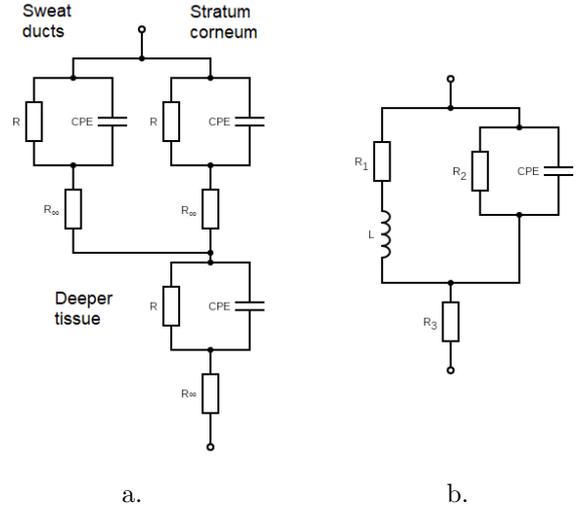
Fig. 2. Skin impedance models based on a. multiple Cole systems [14] and b. modified distributed inductive Cole model (DIC).

In this modified Grimnes model, we include the modeling of sweat ducts based on RL circuit analogy. Consider the assembly of an inductor (L) in series with a resistor (R_1), representing the sweat ducts, in parallel with the Cole 1-dispersion model, given in Fig. 2b. The corresponding impedance function for this electrical model in the Laplace domain is:

$$Z_{est} = \frac{R_2(R_1 + Ls)}{R_2 + (R_1 + Ls)(1 + R_2 C s^\alpha)} + R_3 \qquad (3)$$

It should be noted that the units of electrical components R, C, L are Ω, F, and H, respectively. $\omega = 2\pi f$ is the angular frequency in rad/s, with f the frequency in Hz and $j = \sqrt{-1}$ the unit imaginary number.

2.3 Statistical analysis

The statistical analysis was performed using MATLAB (2020b) and Minitab (2019). The acquired data from the clinical trial was analyzed for all the patients, while the identified electrical models were given for one patient in this work. However, the modeling may be further done per patient, for a personalized approach.

To demonstrate the correlation between two variables, linear regression models and correlation and covariance coefficients were calculated. The linear regression model was used to investigate if one variable can be predicted from another variable using the determination coefficient r^2 that indicates the relationship between the independent variables with the dependent ones. The correlation and covariance coefficients were obtained to demonstrate how much two variables vary relative to each other by considering the range from -1 to 1. To assess intra- and inter-variability between outcomes, t-test, ANOVA, and Tukey post hoc test were performed.

As the sample size was small for the identification of the electrical models, indicating a not-normal distribution, the Kunis-Wallis test was performed to observe the statistical significance. Statistical significance was accepted for $p \leq 0.05$. Additionally, the number of patients (n), mean (Standard Deviation - SD), median, and confidence intervals were presented.

3. RESULTS

Patients characteristics are tabled in Table 1. Biometric data was not significantly different between Anspec-Pro and Medstorm groups ($p \geq 0.09$).

Table 1. Biometric data

	Anspec-Pro (n=12)	Medstorm (n=13)	p-value
Age (y)	36.66(13.35)	40.30(18.08)	0.28
Height (cm)	167.75(9.68)	173.07(11.68)	0.11
Weight (kg)	71.58(14.29)	75.69(16.92)	0.25
BMI (kg/cm^2)	25.37 (4.27)	24.87 (3.60)	0.37

BMI—Body Mass Index

Postoperative variables were registered in PACU. It should be noted that the pain index measured by each device has undergone a different method of calculation. For Medstorm it was registered the outcome number of the monitor, i.e., the skin fluctuations per second. For Anspec-Pro, non-parametric identification based on spectral correlation was used for calculating the complex impedance from the applied multisine input and measured skin output (Ghita et al., 2020a). The resulted frequency response function (FRF) of the dynamical system is then a measure of the modulus and phase of the output signal as a function of an input frequency, relative to the applied signal. Therefore, the FRF allows modeling the unknown process, i.e. electrical changes originating from pain. For the Anspec-Pro index extracted in this paper, the complex impedance is normalized to the BMI of patients.

In Table 2, values are presented in median, the acquired clinical data consisting of outliers. NRS and pain indices in Anspec-Pro group were significantly higher than the same variables from Medstorm group ($p<0.001$), while the other two outcomes (MAP and HR) were significantly lower than Medstorm group ($p<0.001$).

Table 2. Outcome variables measured in PACU

Variables	Anspec-Pro group (n=12)	Medstorm group (n=13)	p-value
NRS	3 (0-8)	2 (0-10)	9.40E-16
HR (bpm)	68 (40-98)	75 (46-114)	1.64E-10
MAP (mmHg)	85.33 (63-113)	91.66 (72.33-116.67)	0
Pain index	1.42 (0.71-38.48)	0.07 (0-0.73)	3.68E-18

NRS—Numerical rating scale, HR—Heart rate, MAP—Mean arterial pressure

Statistical evaluation. The linear regression model in Fig. 3a indicated a statistically positive linear relationship between Anspec-Pro index and NRS ($r^2 = 0.16, p = 0$), while no significant relationship was observed between Medstorm index and NRS for the whole group of patients ($r^2 = 0.4, p = 0.32$) in Fig. 3b. Hence, the resulted correlation motivates the aim of this work to further correlate the estimated electrical parameters with NRS.

The variability among individuals has been analyzed for Anspec-Pro index. The results by means of boxplot are depicted in Fig. 4. There was no significant difference among the monitored pain, except in one individual. Anspec-Pro

a.

b.
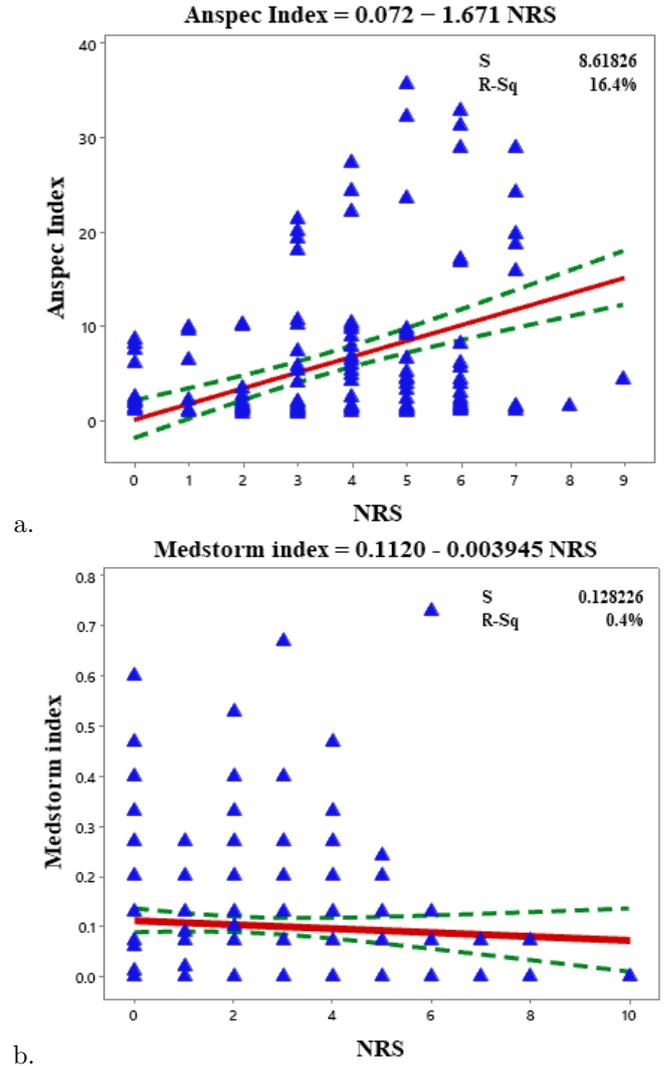
Fig. 3. Linear data fitting between a. Anspec-Pro index and NRS with statistically positive linear relationship, and b. Medstorm index and NRS with no significant relationship. The red line shows the regression line, and the green line limits the 95% confidence interval.

demonstrated a significant negative relationship between BMI and pain index ($Anspec - Pro\ index = 31.01 - 0.98 * BMI$, $r^2 = 18.6\%$, $p = 0.00$), and height and pain index ($Anspec - Pro\ index = 59.77 - 0.31 * height$, $r^2 = 10\%$, $p = 0.00$). We may consider that the individual with a low BMI and shorter height has a different liquid dispersion in the whole body that might affect the impedance values.

Model fitting. The impedance data obtained as the FRF was utilized for the identification of the three proposed models: single- and double-dispersion Cole and the distributed Cole DIC. Owing to modern fast calculating software such as MATLAB, parameter estimations are feasible by non-linear least-square fittings with the iterative algorithm *lsqnonlin*. The estimated and measured impedance is then evaluated every minute against frequency for all patients. In Fig. 5 it is illustrated the frequency response in complex form (real and imaginary parts) for one minute extracted from one patient out of the 12 to exemplify the model fitting.
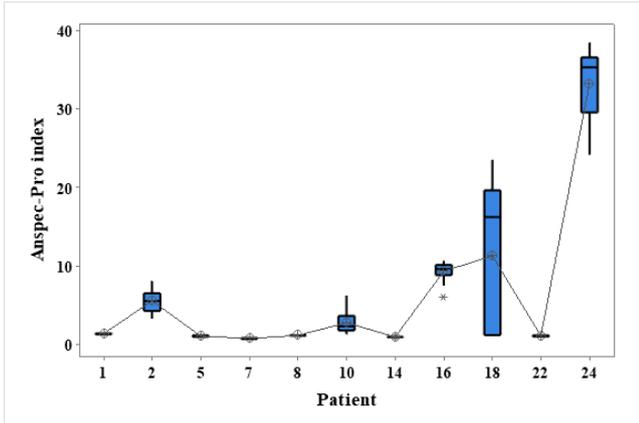
Fig. 4. Box plot analysis of inter-patient variability of Anspec-Pro pain index in all individuals.
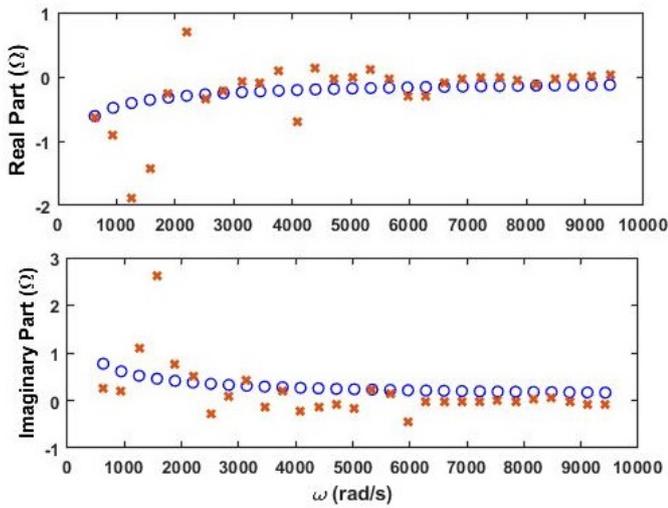
Fig. 5. Impedance data fitting with the single-dispersion Cole model exemplified for one minute of one patient, with the estimated (red) and measured (blue) values.

To statistically investigate the correlation between the estimated impedance by the three proposed models, the mean of impedance values over 7 minutes was calculated in order to obtain a comparable number of values with the self-reported NRS every 7th minute. The result was an absolute value of the impedance. Kunis-Wallis test for the individual indicated a significant difference between the estimated impedance values by the three mathematical models ($p<0.005$). In the interval graph (Fig. 6), it can be observed that the extended lines of confidence intervals of the Cole1 model and the others do not overlap, meaning that the groups are significantly different.

The correlation of the estimated impedance with NRS was performed to study if there is a significant statistical relationship with the self-reported NRS. Hence, the clinical significance may be more important than the accuracy of the model. For an individual patient, the correlation and covariance coefficients are shown in Table 3. Upon this table, the estimated impedance obtained from the Cole model with a single dispersion indicated a more robust relationship ($r = -0.57, p = 0.008$) than two other models.

The correlation of models' parameters to the self-reported NRS was further performed to explain the phys-
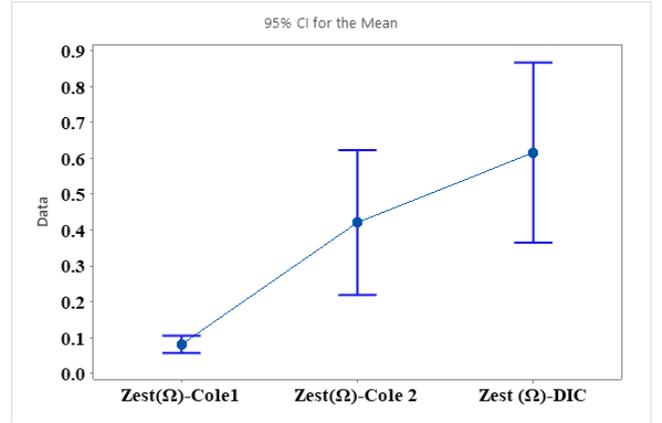
Fig. 6. Statistical analysis of estimated impedance for single-dispersion (Cole1), double-dispersion (Cole2), and distributed inductive (DIC) Cole models. The Cole1 corresponding confidence interval (CI) does not overlap with the others, having the differences in means statistically significant.

Table 3. Correlation and covariance coefficients of the estimated impedance Z_{est} and NRS

	Z_{est} Cole 1-dispersion	Z_{est} Cole 2-dispersion	Z_{est} DIC
NRS	Cov=-0.1 Corr=-0.57 p-value=0.008	Cov=0.16 Corr=0.09 p-value=0.7	Cov=0.42 Corr=0.1 p-value=0.4

Corr—Correlation coeff.; Cov—Covariance coeff.

iological electrical changes normally assumed to happen when pain occurs. For Cole1 model, the resistances for one patient showed a significant negative linear relationship with NRS ($r^2 = 41.5$ for R_∞ and $r^2 = 45.9$ for R), while capacitance term C obtained a non-significant correlation ($p = 0.09$). The coefficients of determination r^2 express that almost half of the variation in the models' parameters can be explained by NRS values, but in the inverse direction. This negative relationship may be caused by the fact that the resistance within skin layers is decreasing when signaling occurs along the sensitization pathway, related to the self-reported NRS.

Another direction of this research was to investigate the inductance term of the modified multiple-Cole model. The addition of the term L is motivated by the hypothesis that sweat ducts are better characterized by an RL circuit. By the electrical analogy of flow in vessels, the electrical inductance L is similar to the fluid inertia, related to flow rates. The inertance I impedes the rate of change of flow rate, being characterized by the formula $\Delta p = I * dq/dt$, where Δp denotes the pressure difference analog to voltage and dq the flow rate analog to current in the formulation of L. Based on these theoretical aspects, the correlation analysis between NRS and the electrical components of the proposed distributed inductive Cole model was executed. Figure 7 depicts a significant negative relationship ($r^2 = 0.33, p = 0.008$) between the electrical inductance (L) and NRS. When sweat flow increases originating from high pain, the volumetric flow rate is directly proportional to it, but the inductance decreases.

$$L\,(H) = 100.5 - 1.979\ NRS$$
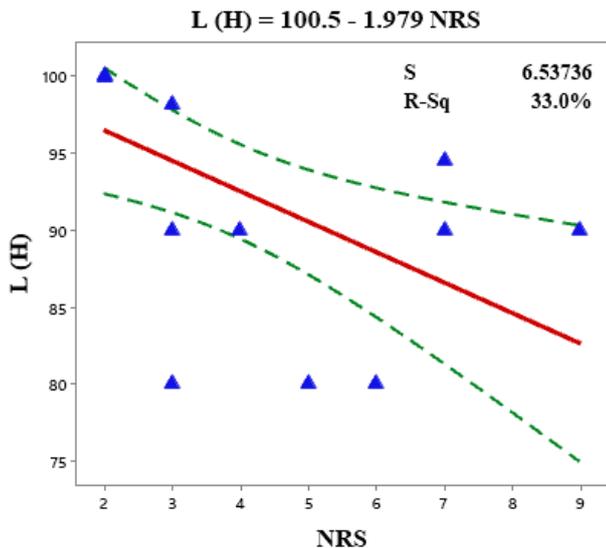
Fig. 7. Regression analysis between the identified inductance (L) and self-reported NRS for the distributed inductive Cole model in one patient.

4. DISCUSSION AND CONCLUSION

The clinical data from 25 patients within a cohort study was analyzed. The data acquired with Anspec-Pro pain sensor was estimated using electrical models due to its capability to detect pain (i.e., better correlation analysis with the self-reported NRS) and to the availability of the frequency response of the noxious effects. The innovation of this approach is that Cole models have not yet been studied for the nociception pathway. Cole models with fractional-order capacitance were selected for fitting the bioimpedance dataset, as fractional tools have previously proven to model biological phenomena (e.g., diffusion of substances in the human body, the generation of action potentials, lung dynamics) (Ionescu et al., 2017; Ghita et al., 2021; Copot et al., 2017).

The present research is limited in the number of individuals studied, and factors such as postoperative cofounders (i.e., anxiety) may influence skin electrical properties in awake subjects. Additionally, our results may not be extrapolated to any category of patients (i.e., different analgesic drugs have been used in PACU). However, the developed models are uniquely defined for one individual, and the initialization of model identification utilizing available methods such as genetic algorithms is recommended.

In conclusion, derived Cole models are applied and identified for skin frequency-dependent impedance response to analyze postsurgical acute pain. The proposed mathematical tools indicate a meaningful clinical potential of the use of dielectric parameters in the direction of characterizing the underlying physiological process, based on correlations with reported pain. Moreover, a personalized identified model per patient may be able to predict changes in such a personal experience: pain.

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