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A fractional order impedance model for heterogeneous drug distribution in obese patients during general anesthesia ⋆

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Abstract: Personalised pharmacokinetic models imply stepping away from the classical assumption of homogeneous drug mixing in various tissue compartments in the body, with a particular impact on obese patients. In this work, the pharmacokinetic compartmental model structure is revisited to account for non-uniform distribution of uptake/clearance time constants in patients as a nonlinear function of body mass index. Simulations are confirming expected patterns of drug distribution in the body and can account for post-anesthesia side effects up to 72 hours. We apply spectroscopy to extract the complex impedance in fat tissue samples. The data is modelled by a Cole-Cole model, where parameters of the fractional order impedance model are optimized using a genetic algorithm. The findings suggest that fat tissue will exhibit anomalous diffusion when drug uptake and clearance are present.

Keywords: fractional order impedance model, Cole-Cole model, bioimpedance, compartmental modelling, general anesthesia, frequency domain, spectroscopy

1. INTRODUCTION

Obesity constitutes a primary etiological factor underlying comorbidities that challenge surgery outcomes and patient recovery times. Expansion and remodeling of adipose tissue, which differ in various regions of the body, play a significant role in disrupting vascular function and contribute markedly to the development of cardiovascular diseases. (Koenen et al. (2021)). Patients undergoing general anesthesia are lean or with varying degrees of obesity, some are elderly and some suffer from cardio-vascular pathologies; all challenges which need to be carefully addressed.

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General anesthesia is regulated by means of multi-drug cocktails of carefully designed ratios to achieve clinical effects of hypnosis, analgesia, and neuromuscular blockade while maintaining a lack of awareness during surgical stimuli. In population-based pharmacological models, it is assumed that the dispersal of drugs within soft tissues, muscle, and fat adheres to a Gaussian distribution with normal variance. The most significant distinction lies in their kinetic properties; the absorption and elimination rates in muscle tissue are faster compared to fat tissue, mainly due to the higher blood flow density.

The comorbidities require substantial changes in patient models for pharmacokinetics (PK) and pharmacodynamic (PD) effects, in order to effectively use them in computerized closed-loop control of general anesthesia. Certain surgical procedures require prolonged intervention times which may take anything between 6 to 18 hours. The compartmental models for characterizing the time constants of drug distribution within the body, are no longer valid in these extreme situations and need to take into account drug diffusion patterns which may no longer adhere to the normal distribution of population models. In fact, it may well be linked to the fractal dimension of tissue cell structure and fractal Brownian motion models (Muñoz-Gil et al. (2021)). This paper introduces the concept of anomalous diffusion in slow-acting soft tissue metabolite binding as a function of percent fat mass in the body volumetric distributions. We use fat cell exempt for experimental data on which fractional order impedance models are fitted. Complex bio-impedance measurements are performed in several devices monitoring nociception stimulation during general anesthesia, such as those reported in Ionescu et al. (2024), but also during intensive care monitoring, as reported in Ghita et al. (2023). This supports the theory that fat tissue will exhibit anomalous diffusion when drug uptake and clearance are present.

This paper is organized as follows: We introduce in the second section the theoretical framework on which fat tissue properties vary as a function of increasing body mass index, thereby affecting the dynamic exchange of absorption and clearance of drugs from the compartment. Then, we propose the augmented PK model to include an extra fat volume where the drug molecules are trapped for longer times as a function of body mass index (Copot and Ionescu (2021)). A Cole-Cole model is introduced in the third section to characterize data from real fat tissue samples using impedance spectroscopy as an experimental method. We present simulation results and discussion, along with limitations of the study. A conclusion section summarizes the novelty of the paper and proposes further developments.

2. REVISITING FAT COMPARTMENT MODEL

2.1 Fat Tissue Properties Variability

Fat tissue, or adipose tissue, is composed of specialized cells called adipocytes, or fat cells, which are responsible for storing and releasing energy. The stages of fat tissue and their properties can vary depending on body mass index (BMI), as illustrated in Figure 1. In individuals with a lower BMI, brown fat, known for its thermogenic

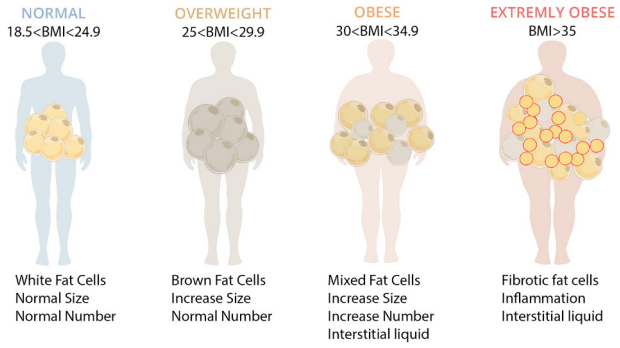

Fig. 1. Evolution of fat cells as a function of changes in body mass index.

properties, is more prevalent. In this case, the balance of interstitial liquid and inner permeability are nominal and can facilitate the molecular binding in-out of the cell, thereby abiding to a normal diffusion pattern as best described by Fick's laws of diffusion. Brown fat breaks down blood sugar (glucose) and fat molecules to generate heat and help maintain body temperature. Lower temperatures activate brown fat, which leads to various metabolic changes in the body facilitating permeability of in/out molecular transport of species. The majority of our body fat is white fat, serving as a reserve for surplus energy. In cases of obesity, there's an excessive accumulation of this white fat. During such instances, the movement of molecules becomes irregular at the meso- and micro-levels within the different lattice structures and characteristics of the fat tissue(Palombo et al. (2022)).

As fat accumulation progresses, it ages and undergoes transformation into white fat cells, which have a propensity to clump and adhere to one another. This process results in an increase in both the number and size of these cells. As a result, the volume of the fat cells expands, enhancing the porosity due to the increased capacity of interstitial fluid to transport drug molecules within the tissue. However, this increase in volume may also lead to a slowdown in the rate of drug molecule dispersion throughout the tissue, a phenomenon commonly observed in individuals with a higher BMI. Adding to this complexity, continued fat accumulation triggers an inflammatory response in the fat cells, culminating in cell fibrosis and further impaired diffusion (Huang et al., 2021). This inflammatory condition not only obstructs drug diffusion and diminishes angiogenesis in tissue reconstruction, but also contributes to the entrapment of interstitial liquid (Samourides et al., 2020). Moreover, research indicates that both local and systemic effects of secreted factors from adipose tissue intensify during obesity, exacerbating systemic inflammation and amplifying their adverse impact on cardiovascular health (Koenen et al., 2021). In such extreme cases, the tissue exhibits a mixed porosity pattern whereas permeability is much impaired.

There is a nonlinear correlation between the relative ration of porosity - permeability and the BMI values, this can be fit in a 4th order regression polynomial that represents the $Risk$ of fat trapping:

$$Risk = -0.000436 * BMI^4 + 0.0489 * BMI^3 - 2.012 * BMI^2 + 36.01 * BMI - 236; \quad (1)$$

2.2 Augmenting the Classic Patient Model

The differential equations characterizing the Propofol uptake as the PK model are given by the relations to the variation of concentrations x_i with $i = 1, 2, 3$ the respective compartments, for blood, muscle, and fat:

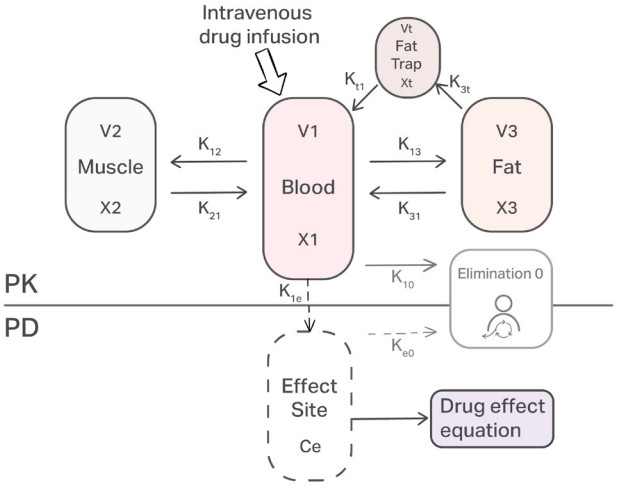

Fig. 2. Compartmental model augmented with additional volume of fat cells where drug trapping occurs for long term general anesthesia in non-lean patients.

$$\begin{aligned}\dot{x}_1(t) &= -k_{12}x_1(t) - k_{13}x_1(t) - k_{10}x_1(t)\\ &\quad +k_{t1}x_t(t) + k_{21}x_2(t) + k_{31}x_3(t)\\ &\quad +u(t)/V_1\\ \dot{x}_2(t) &= k_{12}x_1(t) - k_{21}x_2(t)\\ \dot{x}_3(t) &= k_{13}x_1(t) - k_{31}x_3(t)\end{aligned} \tag{2}$$

where the parameters k_{ij} for $i \neq j$,in $[min^{-1}]$, denoting the drug transfer frequency from the i^{th} to the j^{th} compartment and $u(t)$, in $[mg/min]$, is the input infusion rate of Propofol.

The hypothetical compartment for characterizing the effect of the drug into the body, i.e. the effect of drug in brain is called the effect-site concentration compartment and is defined by:

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \tag{3}$$

The parameters of the PK models can be calculated using the Schnider model for Propofol (Merigo et al., 2017) as follows :

$$\begin{aligned}V_1 &= 4.27\\ V_2 &= 18.9 - 0.391 \cdot (age - 53)\\ V_3 &= 2.38\end{aligned} \tag{4}$$

The volumes V_1, V_2 and V_3, in $[l]$, represent the compartmental volume, i.e. blood, muscle and fat. The clearance rates, in $[l/min]$, are calculated as:

$$\begin{aligned}C_{l1} &= 1.89 + 0.0456 \cdot (weight - 77)\\ &\quad -0.0681 \cdot (lbm - 59)\\ &\quad +0.0264 \cdot (height - 177)\\ C_{l2} &= 1.29 - 0.024 \cdot (age - 53)\\ C_{l3} &= 0.836\end{aligned} \tag{5}$$

where lbm represents the lean body mass for male:

$$lbm_m = 1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2} \tag{6}$$

and for female:

$$lbm_f = 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2} \tag{7}$$

Next, we can calculate the model coefficients as function of their clearances and volumes respectively:

$$\begin{aligned}k_{10} &= \frac{C_{l1}}{V_1}, \quad k_{12} = \frac{C_{l2}}{V_1}, \quad k_{13} = \frac{C_{l3}}{V_1}\\ k_{21} &= \frac{C_{l2}}{V_2}, \quad k_{31} = \frac{C_{l3}}{V_3}, \quad k_{e0} = k_{1e} = 0.456\end{aligned} \tag{8}$$

Having relation (1) at hand, we propose to augment the PK model of general anesthesia with the additional trap compartment as depicted in Figure 2:

$$\dot{x}_t(t) = k_{3t}x_3(t) - k_{t1}x_t(t) \tag{9}$$

denoting the fat compartment volume with trapped drug molecules, where k_{3t} and k_{t3} represent the constants of the drug transfer rate from the fat compartment to this compartment and vice versa, with its trap volume:

$$V_t = BMI \cdot V_3/100 \tag{10}$$

and its clearance rate :

$$C_{lt} = C_{l3}/Risk \tag{11}$$

where $Risk$ may be considered as the amount of risk for trapping, hence the higher the $Risk$ values (as the BMI increases), the slower the clearance from the trap volume, hence the molecules stay longer times in the fat trap tissue. and for the additional compartment of fat trap volume:

$$k_{3t} = \frac{C_{lt}}{V_t}, \quad k_{t1} = \frac{C_{lt}}{V_1} \tag{12}$$

The relation between the effect site concentration from (3) and the measured effect in the brain, i.e. the Bispectral Index (BIS) is modelled as a nonlinear sigmoid Hill curve scaled between 0%-100%, with 100% denoting fully awake patient:

$$BIS(t) = E_0 - E_{max}\frac{x_e^{\gamma}(t)}{x_e^{\gamma}(t) + C_{50}^{\gamma}} \tag{13}$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half of the maximum effect and γ describes the steepness of the dose-response curve. E_0 and E_{max} are considered equal to the value of 100. It could be argued that, with the exception of the induction phase where the function from (13) exhibits a nonlinear sigmoid shape, the response during the maintenance of depth of anesthesia at steady levels between 40-60% can be approximated using a linear function (Ionescu et al. (2015)).

3. SIMULATION RESULT

To illustrate the effects taking place in the new compartment we employ our open source patient simulator described in (Ionescu et al. (2021)) available in Matlab/Simulink software environment. Table 1 gives the biometric and drug effect values for a set of representative dataset of patients. The simulation assumes an input drug dose in form of a bolus infusion of 3.33 mg/s during 5 seconds in the central compartment, i.e. in the blood compartment. The simulation time is for 72 hours, in open loop simulation at periodical intervals every 1 second.

Table 1. Representative Patient Database (all males) with PK Model Biometric Values and PD Model Sensitivity Values

Index -	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)	lbm -	C_{50} (μ/ml)	γ -
1	74	164	88	32.7	60	2.5	3
2	67	161	69	26.6	53	4.6	2
3	75	176	101	32.6	69	5	1.6
4	69	173	97	32.4	67	1.8	2.5
5	45	171	64	21.9	52	6.8	1.78
6	57	182	80	24.2	62	2.7	2.8
7	74	155	55	22.9	44	1.7	3.5
8	71	172	78	26.4	60	7.8	2.9
9	65	176	77	24.9	60	2.9	1.88
10	72	192	73	19.8	62	3.9	3.1
11	69	168	84	29.8	60	2.3	3.1
12	60	190	92	25.5	71	4.8	2.1
13	61	177	81	25.9	62	2.5	3
14	54	173	86	28.1	62	2.5	3
15	71	172	83	28.1	62	4.3	1.9
16	53	186	114	33	77	2.7	1.6
17	72	162	87	33.2	59	4.5	2.9
18	61	182	93	28.1	69	2.7	1.78
19	70	167	77	27.6	58	6.8	3.1
20	69	168	82	29.1	60	9.8	1.6
21	69	158	81	32.4	55	3.2	2.1
22	60	165	85	31.2	60	5.1	2.51
23	70	173	69	23.1	56	3.67	3.1
24	56	186	99	28.6	73	5.8	2.3

We simulate the full database of patients from Table 1, with results depicted in Figure 3. The interpatient variability is visible in the variations of the responses as a function of each patient's characteristics. This figure shows the evolution of the effect site concentration, fat compartment concentration, trapped drug concentration, and the level of anesthesia BIS in the patient. It can be observed that the trapped drug clears at a much slower rate than the effect site compartment. Patients with a lower BMI tend to have higher absorption rates and faster clearance rates than individuals with higher BMIs. Consequently, the rate at which the BIS level decreases is slower in patients with a higher BMI. This suggests that they may need more drugs. Therefore this explains why in post-surgery, patients with BIS above 70 which are sent out to recovery units, are experiencing side effects long after the surgery.

To push this study further, an experimental model identification was made on real animal fat tissues. The aforementioned sample is then excited using the *Modulab XM* device to measure its complex impedance (Z) over a wide range of frequency in high resolution steps, as depicted in photos given in Figure 4. The test reference signal is applied through a *potentiostat* and applying *frequency response analyzer* on the measured current and voltage from the material response, an impedance is delivered by its complex variables through the Fourier transform. The device communicates via an Ethernet link to an external PC, running XM-STUDIO ECS software for control and monitoring purposes in real-time data storage and processing protocol. For the purpose of analysis of this paper, the material depicted in Figure 4 has been evaluated through the design of a test frequency range from 10^{-2} to 10^{4} Hz in 100 frequency points ($N_s = 100$). The data was recorded for further processing as real ($Re(Z)$) and imaginary ($Im(Z)$) parts of complex impedance as a function of test frequency, depicted in Figure 5.

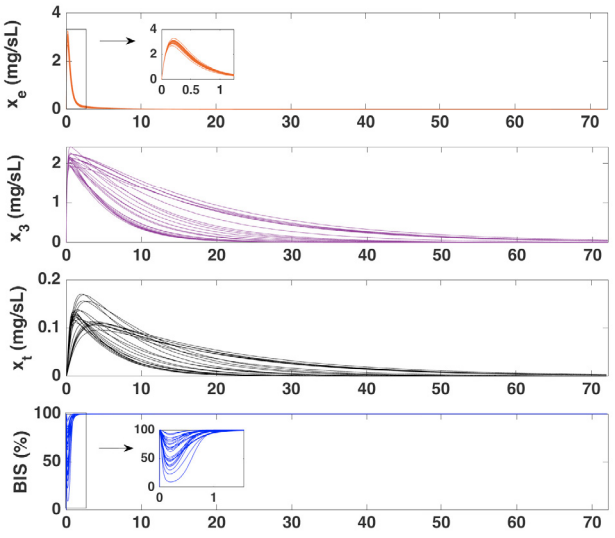

Fig. 3. All patients: evolution of drug concentration in the fat, fat trap and long tails of BIS levels in the 72 hours of simulation.

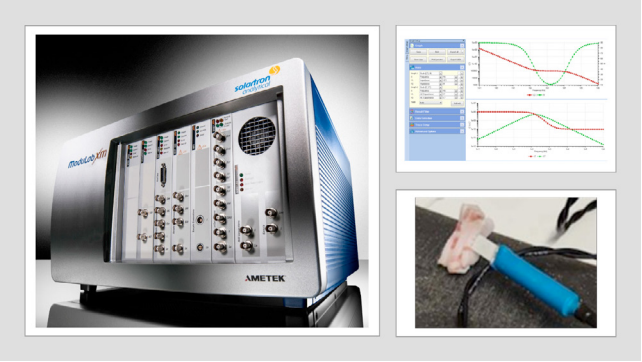

Fig. 4. Photo of the Solartron spectroscopy device (left), the graphical user interface with impedance data plotted (right-top) and the fat tissue sample in ceramic sensor connection (right-bottom).

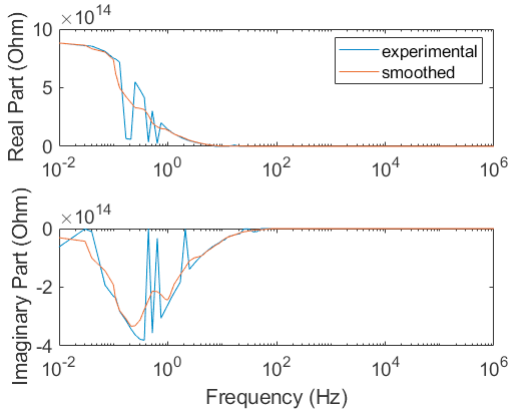

Fig. 5. Complex impedance data from fat tissue sample as a function of frequency. The data was smoothed to eliminate noise before identification step.

The Cole-Cole model is the natural model structure for characterizing biological tissue impedance data (Vosika et al. (2014); Ionescu et al. (2017)), given as a lumped fractional order impedance model (FOIM):

$$M_{FOIM}(s) = R + \frac{K}{1 + (\frac{s}{p})^{\beta}} \tag{14}$$

where R denotes the gain at infinite frequencies, K denotes the relative gain difference between low and high frequencies, $1/p^{\beta}$ denotes pseudo-capacitance of the constant phase element. β is the dispersion parameter, which ranges between 0 and 1. It describes the distribution of relaxation times in the system. A value of 1 indicates a single relaxation time (Debye behavior), and values less than 1 indicate a distribution of relaxation times. It follows that $\tau = \sqrt[\beta]{1/p}$ is the relaxation time constant by analogy to Debye materials characteristics. The relaxation time constant of the material needs to be scaled to the relative gain of the excited frequency response function, as it varies significantly from low to mid and high frequency range behaviour.

Given the nonlinearity in the parameters in the FOIM model from (14), genetic algorithm optimization has been used for searching optimality of the cost function, with the function in Matlab `ga` in MathWorks (2024). It solves stochastic global search optimization problems by repeatedly modifying a population of individual solutions. The algorithm generates a random population of the FOIM model parameters as an initial population, a fitness function calculates the difference between the measured impedances and the impedances predicted by the model for each parameter set. Through selection, crossover, and mutation, the next children generation is produced at each step by selecting individuals from the current population with parameters that better fit our data to be parents. Over successive generations of elite retention, the population of parameter sets converges towards an optimal or near-optimal solution until stopping conditions are met, giving a set of parameters for the FOIM (R^*, K^*, p^*, β^*) that best fits the experimental impedance data (i.e., the lowest error)(Davis (1991)).

$$\begin{aligned} Z_{estimated}(j\omega) &= R^* + \frac{K^*}{1 + (\frac{j\omega}{p^*})^{\beta^*}} \\ &= Re(Z_{estimated}) + jIm(Z_{estimated}) \end{aligned} \tag{15}$$

The fitness function is used to minimize the error between the actual impedance measurements and those predicted by the Cole-Cole model.

$$\begin{aligned} E_{Re} &= \frac{1}{N_s}\sqrt{\sum_{i=1}^{100}(Re(Z) - Re(Z_{estimated}))^2} \\ E_{Im} &= \frac{1}{N_s}\sqrt{\sum_{i=1}^{100}(Im(Z) - Im(Z_{estimated})^2} \\ Error &= \sqrt{E_{Re}^2 + E_{Im}^2} \end{aligned} \tag{16}$$

In order to choose the global best-fitting solution per patient, we calculated the Normalized Root Mean Square Error ($NRMSE$) of each optimal parameter vector generated after each GA iteration. The parameters set having the highest incidence were considered for the model initialization in the online procedure for the same patient, having at least the $NRMSE$ <0.1. A fit value of 0 indicates a perfect fit between the data and the estimated model outputs, giving a fitting percentage equal to $fit = 100*(1-NRMSE)$. The optimization result for one tissue sample is depicted in Figure 6 along with the corresponding best fit for model identification response.

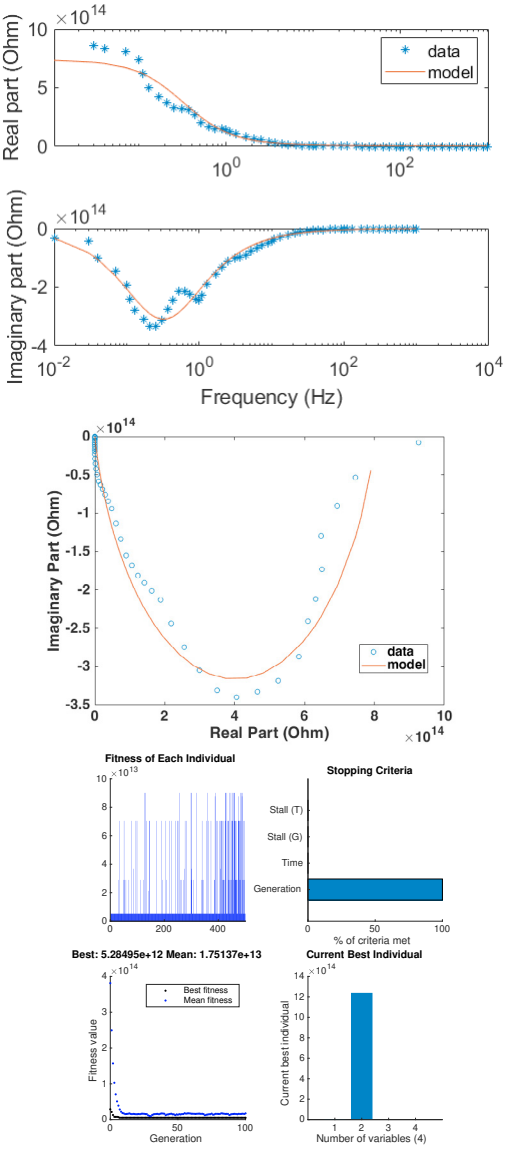

Fig. 6. An example of identification result for the real and imaginary parts of FOIM model in 4 parameters (top), the equivalent polar plot of model and data for the fat sample (middle), and its genetic algorithm optimization solver view (bottom). The identified model was $R = 4.84 \cdot 10^{12}$, $K = 7.37 \cdot 10^{14}$, $p = 0.323$, $\beta = 0.88$.

The results of the fractional order impedance model from our fat samples show a higher resistivity (R) compared to other types of tissues, this aligns with the known properties of fat tissue, indicating a low water content and a high lipid content. The strong polarization (K) suggests that fat tissue exhibits a significant polarization effect.

This is related to its ability to store energy in an electric field due to the alignment of dipolar molecules within the tissue. The low characteristic frequency (p) indicates that the polarization relaxation of fat tissue is quite slow. This slower response in fat tissue concord with the theoretical results in Figure 3. The Cole-Cole Exponent (β) is close to 1, which means the tissue has a distribution of relaxation times that is fairly narrow. This could suggest that the fat tissue has a relatively homogeneous composition. In the context of the Cole-Cole model, the term "anomalous diffusion" refers to a deviation from the simple Debye behavior, which is characterized by a single relaxation time. Anomalous diffusion can be related to the complexity of the medium through which molecules or ions move, leading to a non-uniform distribution of relaxation times. Considering the given parameter $\beta = 0.88$, we infer that the behavior is not perfectly Debye, which implies that the diffusion might not be completely normal and hints at some degree of heterogeneity in the fat tissue.

The next step in this research is to link the FOIM model from (14) to the augmented PK model from (9). Firstly, it requires to develop a method for sensing fat tissue drug distributions in local peripheral body tissue in patients. At this moment, this is not yet available, but a promising solution could be envisaged by smart textiles, and by bioimpedance measurements that can deliver the data onto which the FOIM model can be identified corresponding to the individual patient undergoing general anesthesia (Neckebroek et al. (2020)). If this is available, then the dynamic time constant extracted from the model in (14) can be used to update the uptake and clearance coefficient values in the PK equation from (9).

4. CONCLUSION

This paper introduced a novel compartment in the PK model for general anesthesia. The novel compartment indicates the property of fat tissue to locally trap drug molecules for longer times, following slower clearance rates. The simulation of the proposed augmented model indicates good agreement with long tails of drug release which can be explained by long-term post-anesthesia side effects in patients undergoing major surgery and/or long-term general anesthesia. An experimental data model has been provided to indicate the potential for anomalous diffusion dynamics in fat tissue, as it can be well represented by Cole-Cole models. Further developments aim to provide a sensing technology for capturing data in local fat tissue in each patient and thereby contributing to better patient models of local adipose tissue (visceral, subcutaneous). This in turn enables better estimates of drug concentrations for improved performance of computerized closed-loop control of anesthesia.

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