2024 European Control Conference (ECC)
June 25-28, 2024. Stockholm, Sweden

A compartmental modelling framework for drug distribution in lean and obese patients in long-term general anesthesia*

Amani R. Ynineb[1], Erhan Yumuk[1,2], Hamed Farbakhsh[1], Ghada Ben Othman[1], Dana Copot[1], Isabela R. Birs[1,3], Cristina I. Muresan[3], Robin De Keyser[1], Samir Ladaci[4], Clara M. Ionescu[1,3] and Martine Neckebroek[5]

***Abstract*— In personalized medicine applications such as general anesthesia, an individualised pharmacokinetic (PK) model requires to move away from the classical assumption of homogeneous drug mixing in various tissue compartments in the body. By default, these model coefficients are pre-surgery initialized from population based models as a function of age, gender, weight, height, lean body mass and do not include at this moment specific drug diffusion patterns in the fat compartment, whereas various types of fat will induce various time constants in non-lean 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. The model is a novel advance in providing the control community with yet increasingly realistic patient models for closed loop control of anesthesia.**

I. INTRODUCTION

Anomalous diffusion is an important deal breaker in terms of controlling areas of variable diffusion coefficients and modified permeability due to material structure and properties of material cell composites [1]. In practice, it implies a careful tuning of the controller to be robust to these variations while assuming homogeneous mixing and time invariant dynamics (i.e. today's standard), irrespective of the patient individualised patterns at hand. In today's paradigm of personalised medicine, and targeted drug therapy, there is a need to move away from the assumption of homogeneity and to embrace tools which enable a polyvalent distribution of drug molecules in complex and dynamic tissue environment.

According to a March 2023 report from the World Obesity Atlas (WOA), more than half of the global population (51%, or over 4 billion people) will have obesity by 2035, which will affect all regions and continents of the world. Obesity lies at the very baseline of comorbidities challenging surgery outcomes and patient recovery times. Massive expansion and remodeling of adipose tissue during obesity differentially affects specific adipose tissue depots and significantly contributes to vascular dysfunction and cardiovascular diseases [2]. Evidence has shown that it even affects neuro-cognitive related processes in elderly [3]. As the majority of patients undergoing general anesthesia are obese, elder and suffer from cardio-vasculatory pathologies, these are challenges which need to be addressed with updates in today's existing population based models for closed loop control of anesthesia. To say that fat is just one compartment of the minimally three involved in the physiological models of general anesthesia, is clearly an understatement, but it works well in lean and overweight patients and for relatively short (less than 6 hours) time anesthesia. General anesthesia is regulated by means of multi-drug cocktails of carefully designed ratios to achieve clinical effect of hypnosis, analgesia and neuromuscular blockade while maintaining lack of awareness during surgical stimuli. Population based models assume a Gaussian distribution normal variance of homogeneous distribution of drugs within the soft tissues, muscle and fat. The only notable difference is their time constant, as the uptake and clearance rates are faster in muscle tissue than in fat tissue mainly due to the higher blood perfusion density.

In major surgery the duration of general anesthesia may take anything between 6 to 18 hours. This implies a long time that the patient stays in the horizontal position, with a slight 15 degrees angle inclination. The compartmental models for characterising the time constants of drug distribution within the body, i.e. blood, muscle and fat, are no longer valid

This work was funded in part by the European Research Council (ERC) Consolidator Grant AMICAS, grant agreement No. 101043225. Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

Cristina I. Muresan is financed by a grant of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022 – I9, grant number 760018/27.01.2023. This work was in part supported by a grant of the Romanian Ministry of Research, Innovation and Digitization, PNRR-III-C9-2022 – I8, grant number 760068/23.05.2023. I.R. Birs acknowledges the support of Flanders Research Foundation, Postdoc grant 1203224N and by a grant of the Romanian Ministry of Research, Innovation and Digitization, PN-III-P1-1.1-PD-2021-0204,within PNCDI III. D. Copot acknowledges the support of Flanders Research Foundation, Postdoc grant 12X6819N.

[1]Ghent University, Department of Electromechanics, Systems and Metal Engineering, Research Group on Dynamical Systems and Control, Tech Lane Science Park 125, Zwijnaarde 9052, Belgium amani.ynineb@ugent.be, erhan.yumuk@ugent.be, hamed.farbakhsh@ugent.be, dana.copot@ugent.be, claramihaela.ionescu @UGent.be

[2]Technical University of Istanbul, Department of Control and Automation Engineering, Maslak, 34469, Istanbul, Turkey, yumuk@itu.edu.tr

[3]Technical University of Cluj Napoca, Romania, Department of Automation, Memorandumului Street 20, Cluj, Romania, cristina.muresan@aut.utcluj.ro

[4] National Polytechnic School, Department of Automatics and Control Engineering, 10 Rue des Frères OUDEK, El Harrach, 16200, Algiers, Algeria, samir.ladaci@g.enp.edu.dz

[5]Ghent University Hospital, Department of Anesthesia, Corneel Heymanslaan 10, Ghent 9000, Belgium, Martine.Neckebroek@UGent.be

Copyright ©2024 EUCA

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 fractal dimension of tissue cell structure and fractal Brownian motion models [4]. Specifically, 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. An analogy to geological porosity and permeability models is made to illustrate a parallelism to fat cells and their various compositions and properties depending on the type of fat existing in the body.

This paper is organised as follows: we introduce the theoretical framework on which fat tissue properties vary as a function of increasing body mass index, thereby affecting dynamic exchange of absorption and clearance of drug from the compartment. We propose in third section the augmented pharmacokinetic model to include an extra fat volume where the drug molecules are trapped for longer times as a function of body mass index. In the fourth section 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.

II. Slow acting compartment model: fat volume

Fat tissue is comprised of various types of cells, dependent on the type of fat it makes and the period of time the fat has been formed. Much like different types of geology materials: clay, sand, gravel, stones, there is a degree of porosity and degree of permeability of water through these kind of substrates. We will build hereafter a theoretical framework based on such analogy between geology and fat tissue properties.

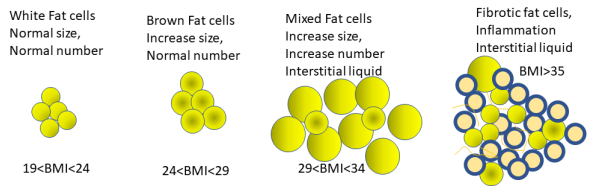

Fig. 1. Evolution of fat cells as a function of changes in body mass index.

Let us see the various stages of fat tissue and its respective properties. Assume a set of fat cells and their changes in properties as a function of body mass index (BMI), as depicted in Figure 1. In normal fat cells, i.e. brown fat, the balance of interstitial liquid and inner permeability are nominal as they 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. This is often observed in children and lean adults, with normal BMI values. Brown fat breaks down blood sugar (glucose) and fat molecules to create 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. Most of our fat, however, is white fat, which stores extra energy. Too much white fat builds up in obesity. At this point, the molecular diffusion becomes anomalous at meso- and micro-scales of various lattice matrices of fat tissue structural and their properties [5].

As fat continues to deposit, it becomes "old" and transforms into white fat cells, which tend to aggregate and stick together, growing in number and size [6]. As such, the volume increases and so does porosity as the interstitial liquid is now larger in capacity to transfer drug molecules into the tissue. However, as the volume increased, the time constant for dispersion of drug molecules may become slower. This is observed in overweight BMI values.

As the fat volume further increases, the fat cells develop inflammatory response, causing fibrosis of the cells, whereas the diffusion is much impaired [7]. This also contributes to trapped interstitial liquid causing further inflammation and reducing angiogenesis in tissue reconstruction [8]. Further evidence indicates that local and systemic roles of adipose tissue derived secreted factors and increased systemic inflammation during obesity and increase their detrimental impact on cardiovascular health [2]. In this extreme case, we have a mixed porosity pattern whereas permeability is much impaired - this is much like geological composite layers where gravel is mixed with sand and fine sediment, thereby obstructing water flow.

Following the above properties variation with BMI, we propose to model this as the nonlinear relation given in Figure 2. This corresponds to a porosity-permeability bistable equilibrium as depicted in Figure 3.

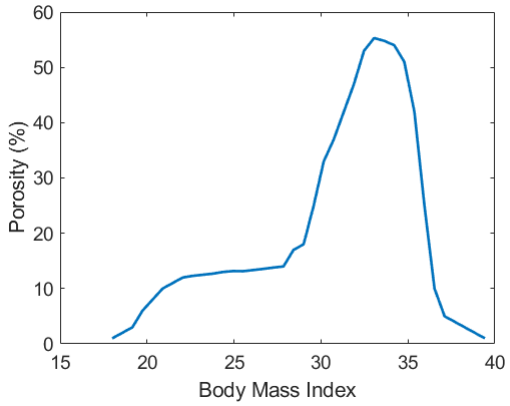

Fig. 2. Relation between porosity of fat tissue and evolution of the BMI.

There is a nonlinear correlation between the data in Figure 2 and in Figure 3. This relation is seen in Figure 4 which represents the relationship between the BMI and the relative ratio of porosity to permeability. To find a good approximation to this relation, Curve Fitter was used in Matlab, which gives the regression polynomial in (1). Increasing the numerical complexity of this latter with a higher order polynomial (above 4) did not give significant improvement. Hence 4th order was a good trade-off between accuracy and

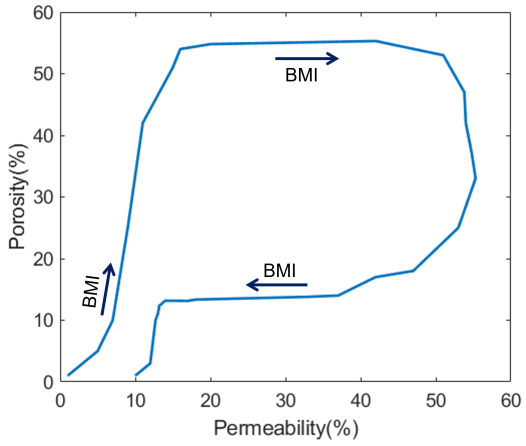

Fig. 3. Relation between porosity of fat tissue and permeability of drug molecules. Arrows indicate the evolution of BMI from normal to morbidly obese.

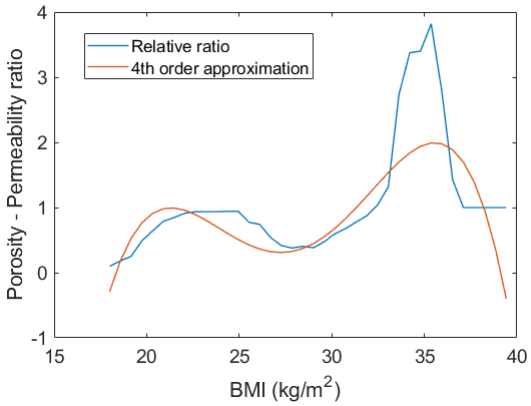

Fig. 4. Relation between relative ratio of porosity to permeability against BMI from normal to morbidly obese.

complexity. A better approximation could be made in further studies:

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

and the approximation is also illustrated in Figure 4.

III. Augmented Pharmacokinetic Model for Fat Volume

The ODEs 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 [9], for blood:

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

with $u(t)$ the input infusion rate of drug (in our case propofol), in $[mg/min]$, and V_1, in $[l]$, represent the compartmental volume of the blood.
For fast acting compartment denoting muscle volume:

$$\dot{x}_2(t) = k_{12}x_1(t) - k_{21}x_2(t) \quad (3)$$

and for slow acting compartment denoting fat volume:

$$\dot{x}_3(t) = k_{13}x_1(t) - k_{31}x_3(t) \quad (4)$$

where the parameters k_{ij} for $i \neq j$ are the drug transfer frequency from the i^{th} to the j^{th} compartment as defined in (11), and $u(t)$ $[mg/min]$ is the infusion rate of the anesthetic drug into the central compartment, i.e. the blood compartment.

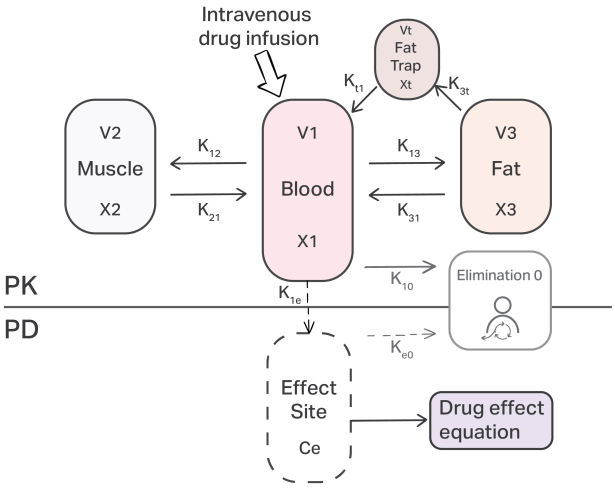

Fig. 5. Compartmental model augmented with additional volume of fat cells where drug trapping occurs for long term general anesthesia in non-lean patients.

Having relation in (1) at hand, we propose to augment the pharmacokinetic model of general anesthesia with the additional trap compartment as depicted in Figure 5:

$$\dot{x}_t(t) = k_{3t}x_3(t) - k_{t1}x_t(t) \quad (5)$$

denoting the fat compartment volume with trapped drug molecules. k_{3t} and k_{t3} represent the constants of the drug transfer rate from the fat compartment to the fat trap compartment and vice versa (12). Next, we have the hypothetical compartment for characterising effect of drug into the body x_e, which is called the effect-site concentration:

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \quad (6)$$

The parameters of the PK model depend on age, weight, height and gender and are linked to the type of drug used. This study uses Schnider model for propofol as described in [10]:

$$\begin{aligned}V_1 &= 4.27 \\ V_2 &= 18.9 - 0.391 \cdot (age - 53) \\ V_3 &= 238\end{aligned} \quad (7)$$

The volumes V_1, V_2 and V_3 , in $[l]$, represent the compartmental volume, i.e. blood, muscle and fat, respectively. We introduce here the relation for trap volume V_t as a function of BMI:

$$V_t = BMI \cdot V_3/100 \quad (8)$$

The clearance rates, in $[l/min]$, are calculated as:

$$\begin{aligned} C_{l1} &= 1.89 + 0.0456 \cdot (weight - 77) \\ &\quad -0.0681 \cdot (lbm - 59) \\ &\quad +0.0264 \cdot (height - 177) \\ C_{l2} &= 1.29 - 0.024 \cdot (age - 53) \\ C_{l3} &= 0.836 \end{aligned} \tag{9}$$

and the augmented compartment needs a clearance rate as a function of relation in (1):

$$C_{lt} = C_{l3}/Risk \tag{10}$$

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. Next, we can calculate the model coefficients, in $[min^{-1}]$, as a function of their clearances and volumes respectively:

$$\begin{aligned} &k_{10} = \tfrac{C_{l1}}{V_1}, \quad k_{12} = \tfrac{C_{l2}}{V_1}, \quad k_{13} = \tfrac{C_{l3}}{V_1} \\ &k_{21} = \tfrac{C_{l2}}{V_2}, \quad k_{31} = \tfrac{C_{l3}}{V_3}, \quad k_{e0} = k_{1e} = 0.456 \end{aligned} \tag{11}$$

and for the additional compartment of fat trap volume:

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

where lbm represent the lean body mass [11] for men :

$$lbm_m = 1.1 \cdot weight - 128 \cdot \tfrac{weight^2}{height^2} \tag{13}$$

and for women:

$$lbm_f = 1.07 \cdot weight - 148 \cdot \tfrac{weight^2}{height^2} \tag{14}$$

The relation between the effect site concentration from (6) and the measured effect in the brain, i.e. the Bispectral Index (BIS) is modeled as a nonlinear sigmoid Hill curve scaled between 0%-100%, with 100% denoting fully awake patient [12]:

$$BIS(t) = E_0 - E_{max} \frac{x_e^\gamma(t)}{x_e^\gamma(t) + C_{50}^\gamma} \tag{15}$$

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. Arguably, apart from the induction phase when the nonlinear sigmoid shape of the function from (15) is traversed, during maintenance of depth of anesthesia at constant values between 40-60%, the response can be approximated by a linear function [13]. In long term anesthesia, the function in (15) therefore can be reduced to a linear approximation as a mere gain scheduling control strategy.

IV. Results and Discussion

To illustrate the effects taking place in the new compartment we employ our open-source patient simulator that is described in detail in our previous work [14] available in Matlab/Simulink® software environment. This latter reproduces the clinical expected effects of various drugs interacting among the anesthetic and hemodynamic states [15]. In this paper, we focus only on the hypnotic part of this simulator. Table I gives the biometric and drug effect values for a set of representative patients.

TABLE I

Representative Patient Database (all males) with PK Model Biometric Values and PD Model Sensitivity Values from [14].

Index -	Age (yrs)	Height (cm)	Weight (kg)	BMI (mg/ml)	lbm -	C_{50}	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 start by detailing the results for 5 hours to see the inter-patient variability: Figure 6 depicts the evolution of the concentrations in the three compartments (blood, muscle and fat) during the first 5 hours of simulation. The time constants of drug absorption and clearance correspond to the clinical onset values for each patient from Table I. Next, Figure 7 depicts the evolution of the effect site concentration, trapped drug concentration and the level of anesthesia BIS in patients. It can be observed that the trapped drug clears at a much slower rate than the effect site compartment, therefore creating a long tail in the BIS level response at the output of the system. This explains why post-surgery, patients with BIS above 70 which are sent out to recovery units, are experiencing side effects long after the surgery. This is visible if the simulation time is increased to 72 hours, shown in Figure 8. In this figure, we simulated for patient 1, index 1 in Table I with a BMI of 32.7 kg/m^2 (obese).

Next, we simulate the full dataset from Table I for 72 hours with results, depicted in Figures 9 and 10, respectively. In Figure 10, we can see that patients with a BMI higher than 30 have a slower clearance rate in the fat trap compartment than others. This effect can be seen in detail in Figure11

The control algorithm mimicking closely the actions of the anesthesiologist for decision making process to compensate future actions altering the depth of anesthesia, is by its nature a predictive control algorithm, and our prior work reported its feasibility in both simulation [16] and in clinical trials [10].

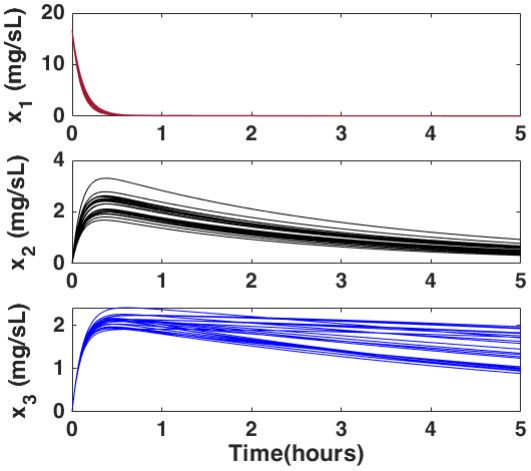

Fig. 6. Evolution of drug concentration in the first three compartments: blood (X_1), muscle (X_2), fat (X_3), as a function of time during the first 5 hours of simulation.

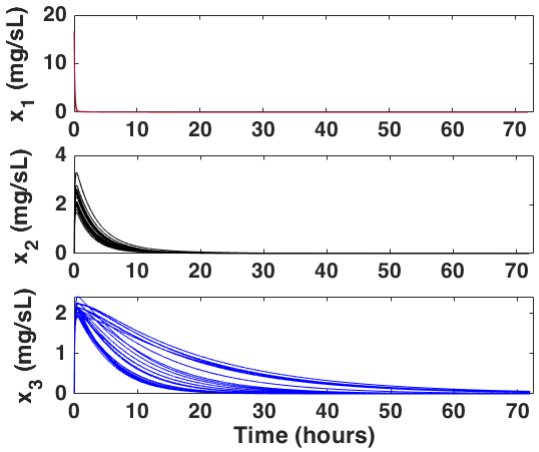

Fig. 9. All patients: evolution of drug concentration in the first three compartments: blood, muscle, fat, as a function of time during 72 hours of simulation.

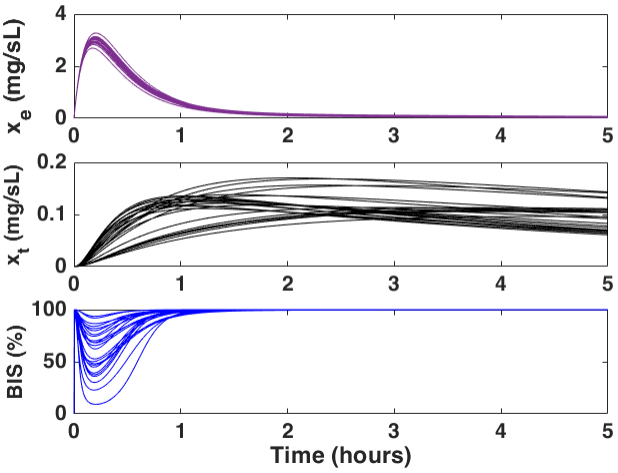

Fig. 7. Evolution of drug concentration in the adjacent compartments: effect site (C_e) and fat trap (X_t), followed by hypnosis level induced in the BIS variable, during the first 5 hours of simulation.

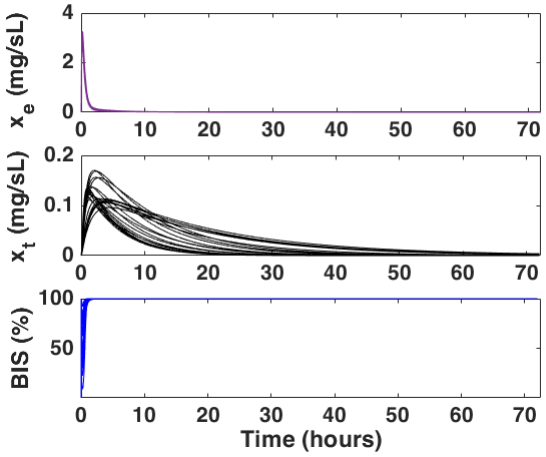

Fig. 10. All patients: evolution of drug concentration in the fat, fat trap and long tails of BIS levels in the 72 hours of simulation.

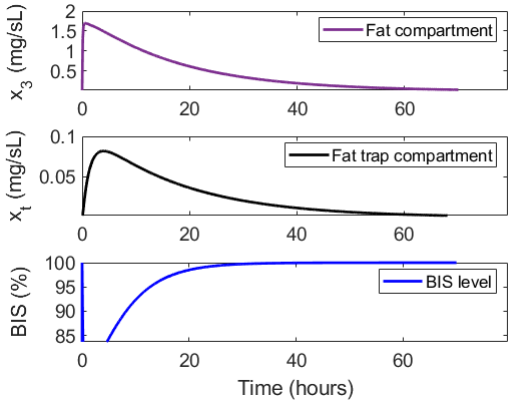

Fig. 8. Evolution of drug concentration in the fat, fat trap and long tails of BIS levels in the 72 hours of simulation.

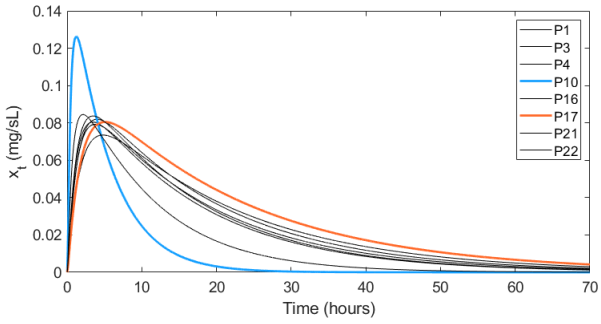

Fig. 11. Comparison of the fat trap compartment (X_t) clearance rate from patients that have high BMI (over 30, P17 with the highest:33.2) and the lowest BMI (P10 with 19.8)

Other methods such as artificial intelligence algorithms may deliver additional information on evolutions of anomalous diffusion patterns within the tissue, something which may be relevant for plastic surgery in critical traumatic surgery. However, due to long tails in the dynamic response, and furthermore long tails of fractal derivatives for anomalous diffusion [17], errors in estimations may cumulate and bias significantly the values, introducing a risk for under- or over-dosing control actions. Some recent correction mechanisms from such inferential models using artificial intelligence have been proposed in [18]. This leads us to discuss some of the limitations of this study. The augmented compartment model can well benefit from additional features such as time-varying model coefficients of absorption and clearance. This is based on the so-called sponge theory: a dry sponge absorbs faster and more water than an already wet one. Similarly, a tissue without drug will bind/release faster drug molecules of drug; as drug molecules populate tissue cells in a heterogeneous manner (i.e. trapped) the absorption and clearance vary in time, as shown in Fig 11: Patient 10 with a normal BMI absorbs/release faster and more drugs molecules than the obese patients. In addition, we could use memory based models such as those proposed in [19], to further pinpoint anomalous diffusion patterns [20]. Crowded environments tends to follows dynamics resembling social behaviour where residence times are longer as more particles populate the limited volume [21]. Another limitation of our study refers to complex additional pathophysiology of the patient, e.g. co-morbidities such as impaired renal function affect clearance rates and may well facilitate drug trapping in other compartments (blood).

V. CONCLUSIONS

This paper introduced a novel compartment in the pharmacokinetic 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. Further developments aim to provide a heterogeneous mixing to better model local adipose tissue (visceral, subcutaneous) as to better estimate drug concentrations for enabling better closed-loop control of anesthesia.

REFERENCES

[1] V. Sposini, D. Krapf, E. Marinari, R. Sunyer, F. Ritort, F. Taheri, C. Selhuber-Unkel, R. Benelli, M. Weiss, R. Metzler, *et al.*, "Towards a robust criterion of anomalous diffusion," *Communications Physics*, vol. 5, no. 1, p. 305, 2022.

[2] M. Koenen, M. A. Hill, P. Cohen, and J. R. Sowers, "Obesity, adipose tissue and vascular dysfunction," *Circulation Research*, vol. 128, no. 7, pp. 951–968, 2021.

[3] D. Sundh, R. Rudäng, M. Zoulakis, A. G. Nilsson, A. Darelid, and M. Lorentzon, "A high amount of local adipose tissue is associated with high cortical porosity and low bone material strength in older women," *Journal of Bone and Mineral Research*, vol. 31, no. 4, pp. 749–757, 2016.

[4] G. Muñoz-Gil, G. Volpe, M. A. Garcia-March, E. Aghion, A. Argun, C. B. Hong, T. Bland, S. Bo, J. A. Conejero, N. Firbas, *et al.*, "Objective comparison of methods to decode anomalous diffusion," *Nature communications*, vol. 12, no. 1, p. 6253, 2021.

[5] M. Palombo, A. Barbetta, C. Cametti, G. Favero, and S. Capuani, "Transient anomalous diffusion MRI measurement discriminates porous polymeric matrices characterized by different submicrostructures and fractal dimension," *Gels*, vol. 8, no. 2, p. 95, 2022.

[6] M. K. DeBari and R. D. Abbott, "Adipose tissue fibrosis: mechanisms, models, and importance," *International journal of molecular sciences*, vol. 21, no. 17, p. 6030, 2020.

[7] X. Huang, W. Zhou, and D. Deng, "Effective diffusion in fibrous porous media: A comparison study between lattice Boltzmann and pore network modeling methods," *Materials*, vol. 14, no. 4, p. 756, 2021.

[8] A. Samourides, L. Browning, V. Hearnden, and B. Chen, "The effect of porous structure on the cell proliferation, tissue ingrowth and angiogenic properties of poly (glycerol sebacate urethane) scaffolds," *Materials Science and Engineering: C*, vol. 108, p. 110384, 2020.

[9] S. B. Mortensen, A. H. Jónsdóttir, S. Klim, and H. Madsen, "Introduction to PK/PD modelling-with focus on PK and stochastic differential equations," 2008.

[10] M. Neckebroek, C.-M. Ionescu, K. Van Amsterdam, T. De Smet, P. De Baets, J. Decruyenaere, R. De Keyser, and M. Struys, "A comparison of propofol-to-BIS post-operative intensive care sedation by means of target controlled infusion, Bayesian-based and predictive control methods: an observational, open-label pilot study," *Journal of Clinical Monitoring and Computing*, vol. 33, pp. 675–686, 2019.

[11] L. L. Moisey, M. Mourtzakis, R. A. Kozar, C. Compher, and D. K. Heyland, "Existing equations to estimate lean body mass are not accurate in the critically ill: Results of a multicenter observational study," *Clinical nutrition*, vol. 36, no. 6, pp. 1701–1706, 2017.

[12] A. M. Araújo, H. Machado, P. G. de Pinho, P. Soares-da Silva, and A. Falcão, "Population pharmacokinetic-pharmacodynamic modeling for propofol anesthesia guided by the bispectral index (BIS)," *The Journal of Clinical Pharmacology*, vol. 60, no. 5, pp. 617–628, 2020.

[13] C. Ionescu, J. T. Machado, R. De Keyser, J. Decruyenaere, and M. M. Struys, "Nonlinear dynamics of the patient's response to drug effect during general anesthesia," *Communications in Nonlinear Science and Numerical Simulation*, vol. 20, no. 3, pp. 914–926, 2015.

[14] C. M. Ionescu, M. Neckebroek, M. Ghita, and D. Copot, "An open source patient simulator for design and evaluation of computer based multiple drug dosing control for anesthetic and hemodynamic variables," *IEEE Access*, vol. 9, pp. 8680–8694, 2021.

[15] M. Ghita, D. Copot, I. R. Birs, C. I. Muresan, R. De Keyser, M. Neckebroek, M. M. Struys, and C. M. Ionescu, "Uncertainty minimization and feasibility study for managing the complex and interacting anesthesia-hemodynamic system," in *2022 IEEE 61st Conference on Decision and Control (CDC)*. IEEE, 2022, pp. 6064–6069.

[16] C. M. Ionescu, R. De Keyser, B. C. Torrico, T. De Smet, M. M. Struys, and J. E. Normey-Rico, "Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia," *IEEE Transactions on Biomedical Engineering*, vol. 55, no. 9, pp. 2161–2170, 2008.

[17] A. Piryatinska, A. Saichev, and W. Woyczynski, "Models of anomalous diffusion: the subdiffusive case," *Physica A: Statistical Mechanics and its Applications*, vol. 349, no. 3-4, pp. 375–420, 2005.

[18] H. Seckler and R. Metzler, "Bayesian deep learning for error estimation in the analysis of anomalous diffusion," *Nature Communications*, vol. 13, no. 1, p. 6717, 2022.

[19] D. Copot and C. Ionescu, "Tailored pharmacokinetic model to predict drug trapping in long-term anesthesia," *Journal of Advanced Research*, vol. 32, pp. 27–36, 2021.

[20] R. Metzler, J.-H. Jeon, A. G. Cherstvy, and E. Barkai, "Anomalous diffusion models and their properties: non-stationarity, non-ergodicity, and ageing at the centenary of single particle tracking," *Physical Chemistry Chemical Physics*, vol. 16, no. 44, pp. 24 128–24 164, 2014.

[21] I. M. Sokolov, "Models of anomalous diffusion in crowded environments," *Soft Matter*, vol. 8, no. 35, pp. 9043–9052, 2012.