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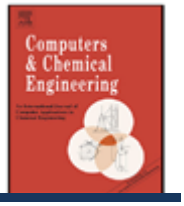

A modeling tool for the personalization of pharmacokinetic predictions

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ABSTRACT: A method to apply pharmacokinetic models to assist physicians in therapeutic drug monitoring is proposed. The practice of therapeutic drug monitoring is required for drugs characterized by a narrow therapeutic index, which consequently present toxicity concerns. The proposed method employs a physiologically based pharmacokinetic (PBPK) model to determine an initial assessment of the pharmacokinetics (PK) of a specific patient. To further increase the precision of this prediction, the method uses two experimental datasets: (i) the PK data from a group of reference subjects, and (ii) limited drug blood concentration measures of the specific patient under study.
By combining the available information, it is possible to assess the precision of the initial model prediction and determine a correction factor to improve it. The resulting patient-specific PBPK model produces encouraging results as there is a concrete reduction in prediction errors of the individualized PK with respect to experimental data.

KEYWORDS: PBPK modeling; Personalized medicine; Individualized treatment; Therapeutic drug monitoring; Pharmacokinetics.

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1 Introduction

The pharmacological treatment of patients requires the convergence of different know-hows to ensure both successful therapies and patient safety. Pharmacokinetics (PK) describes the different effects that the human body produces on drugs. After administration, drug molecules go through a number of processes known as ADME (*i.e.*, Absorption, Distribution, Metabolism, and Excretion). Their combined effect determines the drug concentration dynamics in the whole body. PK studies are a fundamental part of clinical trials and allow the assessment of safety constraints, feasible formulations, delivery strategies, and dosage regimens.

To determine the PK concentration-versus-time curve, physicians conduct experimental campaigns on a number of volunteers/patients by drawing blood samples that match an assigned time schedule. By doing so, it is possible to determine the most important PK parameters, such as AUC (*i.e.*, Area Under the drug-concentration-vs-time Curve), C_{MAX} (*i.e.*, maximum drug concentration), t_{MAX} (*i.e.*, time corresponding to C_{MAX}), and $t_{1/2}$ (*i.e.*, drug elimination half-life) (Bauer, 2008; Rowland & Tozer, 1980).

Besides the experimental study of pharmacokinetics, mathematical models can assist physicians and pharmacologists, in gaining further insight into the properties of a drug. In particular, PK models allow the prediction of the drug concentration dynamics in the blood. As drug concentration is linked to pharmacological effects, a robust and precise PK model can find a number of applications in both drug development and clinical treatment. The original and simplest way to develop a PK model is through the compartmental approach (Fan & De Lannoy, 2014). The human body is treated as a homogeneous volume and a dynamic mass balance of the drug determines the PK (Wagner, 1993). Available experimental data allow a suitable regression procedure to estimate the model parameters. Classic compartmental models can also account for a higher number of compartments (usually no more than three), which has little to do with the human anatomy/physiology but are devised to mathematically describe the ADME pathways.

The main drawback of classic compartmental models is the high specificity introduced by the regression procedure. By carrying out the parameter fitting with respect to the concentration experimental data, the parameter values are valid only to simulate the same experimental conditions as the utilized reference data. Therefore, the model is valid only in a narrow range of conditions (*e.g.*, same drug, formulation, administration route, and subject characteristics). To overcome this limitation and to devise models for PK predictive purposes, it is necessary to use a mechanistic approach when developing a model (*i.e.*, anatomically and physiologically based). By recognizing the main anatomical and physiological aspects responsible for the ADME processes, we can turn the classic compartmental structure into a physiologically based pharmacokinetic (PBPK) model. A PBPK model preserves the compartmental structure, but the compartments are assigned to specific organs or tissues and their connections are anatomically/physiologically consistent. There is a large body of scientific literature describing various PK models. For instance Laínez-Aguirre et al. (2014) developed a software that automatically tests a number of alternative compartmental models to determine the one that provides the best fit to experimental data. By investigating a similar concept, but focusing more on the actual physiology of the body, Heitzig et al. (2014) finalized a framework to determine a feasible structure for a PBPK model applied to the administration of cyclosporin A in rats. Heitzig et al. (2014) determined the drug pharmacokinetic profiles, and scaled them to humans. In addition, the use of PBPK models is appreciated by regulatory agencies, as discussed in Bouzom et al. (2012) and Rowland et al. (2015).

One of the biggest challenges of PK modeling is how to deal with inter-patient variability. In general, two patients who receive the same administration produce different drug concentration-time profiles (as shown in Figure 1).

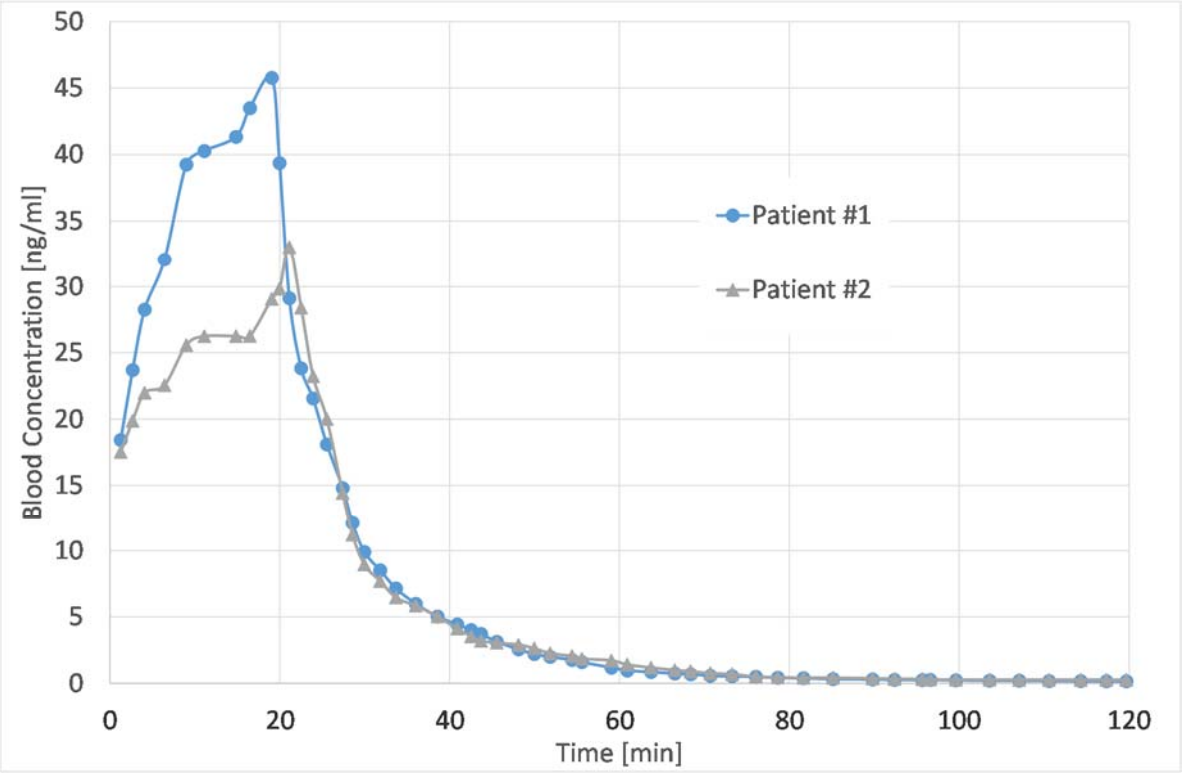


Figure 1: Example of the PK inter-individual variability according to the experimental data of Egan et al. (1993). Patients #1 and #2 were selected among a homogeneous group of subjects (American Society of Anesthesiology physical status 1, age between 18 and 40 years, within 15% of their ideal body mass, and with no important past/current diseases) and received the same administration (continuous remifentanil endovenous infusion of 20 min at 2 µg/kg/min). Even so, the two C_{MAX} values differ of about 45%. This is a rather important issue, as an excessive drug concentration peak may produce toxic effects.

This is due to several reasons, including macroscopic features such as gender, body mass, age, and race, and more implicit issues such as organ impairment, medical history, stress condition, and fasting. Further, different life habits may produce differentiation such as being a smoker or alcoholic. Finally, genotypic and phenotypic variability plays an important role (Birkett, 1997).

Theoretically, the realization of an accurate personalized PK prediction requires the availability of a large amount of data about the patient’s biological, anatomical, and physiological features. Unfortunately, such data is not easily accessible and would require a number of invasive procedures. Even if these data were available, not enough is known to translate the information into a consistent and validated model. This is due to the present state of the art of PBPK models, which are based on the approximations of the compartmental approach.

The inter-individual variability of PK can be significant and this is a critical aspect of all the drugs that produce the pharmacological effect in a narrow range of blood concentrations. Indeed, in order to produce positive pharmacological effects and limit potential toxicities, the drug concentration should remain within a specific range of values (*i.e.*, the therapeutic window). The therapeutic index, defined as TD_{50}/ED_{50} (where TD_{50} is the toxic dose and ED_{50} the effective dose for 50% of administered patients), is a clear indicator of the safety of a specific drug. Some drugs have a narrow therapeutic index, for example, phenytoin an anticonvulsant (Nation et al., 1990; Perucca, 2000), digoxin a drug used in digitalis therapy (Currie et al., 2011), theophylline used in therapy for respiratory diseases (Zeidman et al., 1997), and active principles for cancer treatment (Bardin et al., 2014). Table 1 reports common examples of drugs requiring more extensive monitoring to avoid toxicity. It is important to note that the therapeutic range is not the same as the therapeutic index as it refers to the boundaries of the target blood.

Table 1 - Therapeutic range for some drugs requiring therapeutic drug monitoring (Birkett, 1997). The therapeutic window is the range of values where the drug-blood concentration should be maintained. This may result quite challenging due to the inter-individual PK variability.

Drug	Therapeutic range [mg/L]
Amiodarone	1.0 - 2.5
Digoxin	0.5 - 2.1 [μg/L]
Phenytoin	10 - 20
Quinidine	2.0 - 5.0
Theophylline	10 - 20

To guarantee a safe therapy, it is common practice to conduct therapeutic drug monitoring (TDM). TDM is necessary whenever toxic effects may be of concern. It involves measuring blood drug concentration to verify the individual PK response in relation to toxic thresholds. In general, this measure is necessary but not sufficient as further interpretation of data by experts is required (Gross, 1998). This leads to the necessity of contextualizing the patient’s status and requires information, such as, the sampling times when the concentration measurements must be performed in relation to dosage dynamics, treatment duration with respect to a specific dose, dosing schedule, the patient’s age and gender, health state, and concomitant therapies (Birkett, 1997). Within this context, a model-assisted PK simulation can play an important role, as discussed in Gross (1998, 2001).

Available TDM procedures are classified as: (i) *a priori*, (ii) test-dose, and (iii) *a posteriori* methods. Those are alternative procedures as discussed in Rousseau and Marquet (2002). Despite the need for modeling tools in the TDM field, a real advancement towards PK individualization is still missing. At this end, PBPK models are suitable for individualization purposes as their mechanistic nature allows evaluation of the model parameters that have anatomical/physiological meaning.

We propose a method to carry out a personalized PK prediction. This method requires basic and non-invasive macroscopic patient data (*e.g.*, body mass, height, gender, and race), together with limited (*e.g.*, two/three) blood drug concentration measurements, which are commonly available from TDM. This information, together with a PBPK model (*e.g.*, Abbiati et al. (2015a); Abbiati et al. (2015b)) produce a personalized PK prediction of a specific patient.

Section 2 describes the method, while Section 3 presents a case study to predict personalized PK for TDM applications.

2 Method

The individualization method is meant to correct pharmacokinetic models prediction. In this paper we apply the PBPK model of Abbiati et al. (2016), which is a compartmental model based on the mammalian anatomy/physiology (see Figure 2). The general advantage of PBPK models is that they allow the computation of drug concentrations at multiple sites within the body. The present work focuses on blood drug concentration, as this is the common reference site for PK analysis and due to the ease with which this data is obtained.

The schematic structure of Figure 2 is translated into a system of ordinary differential equations, whose numerical solution provides the drug concentration profiles in the distribution sites (see Appendix A for further details). This model requires a number of inputs: (i) patient demographic features, (ii) drug characteristics, (iii) administration route. These data allow determining the initial conditions of drug concentrations and calculating the adaptive parameters of the PBPK model.

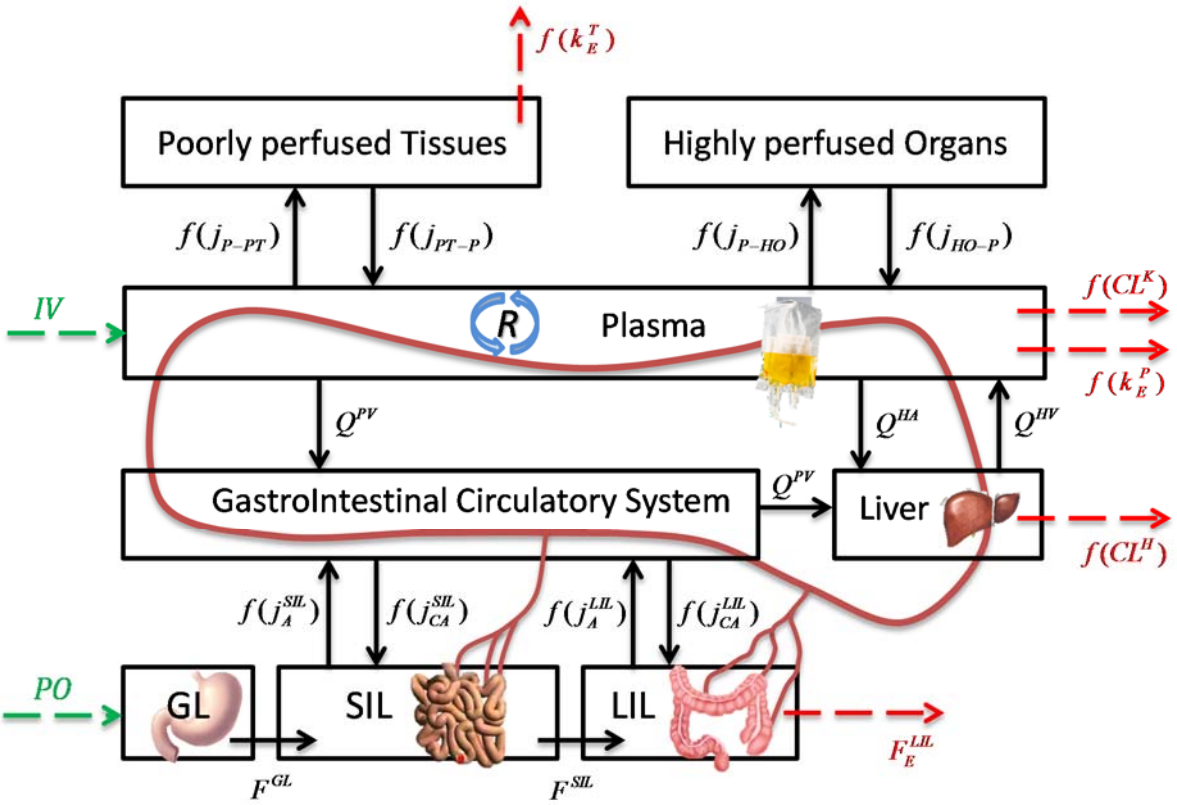


Figure 2: Compartmental structure of the physiologically based pharmacokinetic model. The boxes represent either single organs or groups of organs/tissues, black arrows symbolize the connections between compartments and are drug-distribution pathways. The green dashed arrows are just two possible administration routes (*i.e.*, endovenous (IV) and oral (PO)). Finally, the red dashed arrows are drug excretion routes. A detailed description of the model is provided in Abbiati et al. (2016).

Some of the model parameters can be evaluated for a specific patient if certain demographic data are available. However, not all the parameters can be determined by means of explicit formulas. Indeed, some parameters are unknown and are calculated by a non-linear regression procedure with respect to the experimental PK values of a reference population. As a consequence, this PK prediction is partially individualized, as it includes some demographic information coming from the involved patient, but it still cannot determine with adequate precision the blood concentration profile when the intra-patient variability of PK response is high. Abbiati et al. (2016) provide a detailed explanation of the model parameters assignment.

To reduce the model-predicted PK errors, we propose a methodology to determine a correction factor (ζ) that compensates for the difference between the model-predicted and experimentally-measured drug concentrations in the blood. Figure 3 shows a schematic representation of the methodology.

To calculate the correction factor, ζ, the proposed method requires as input data (i) the averaged PK of the population (these data exist as part of the mandatory clinical trials that describe the drug features after a number of experimental tests on a set of volunteers) and (ii) few blood samples (*e.g.*, two, three) of the specific patient (blood-sample withdrawal is a common practice in current TDM and is fast and cheap). The higher the number of blood withdrawals for the specific patient, the better the PK prediction. Of course too many measurements would reduce the efficacy of the methodology (based on a low-impact approach) and would be invasive for the specific patient.

To reduce invasiveness, enhance efficacy, and preserve economy, two blood withdrawals are a fair compromise between limited sampling and improved precision. A second aspect is the timing of these withdrawals (see Section 3.1).

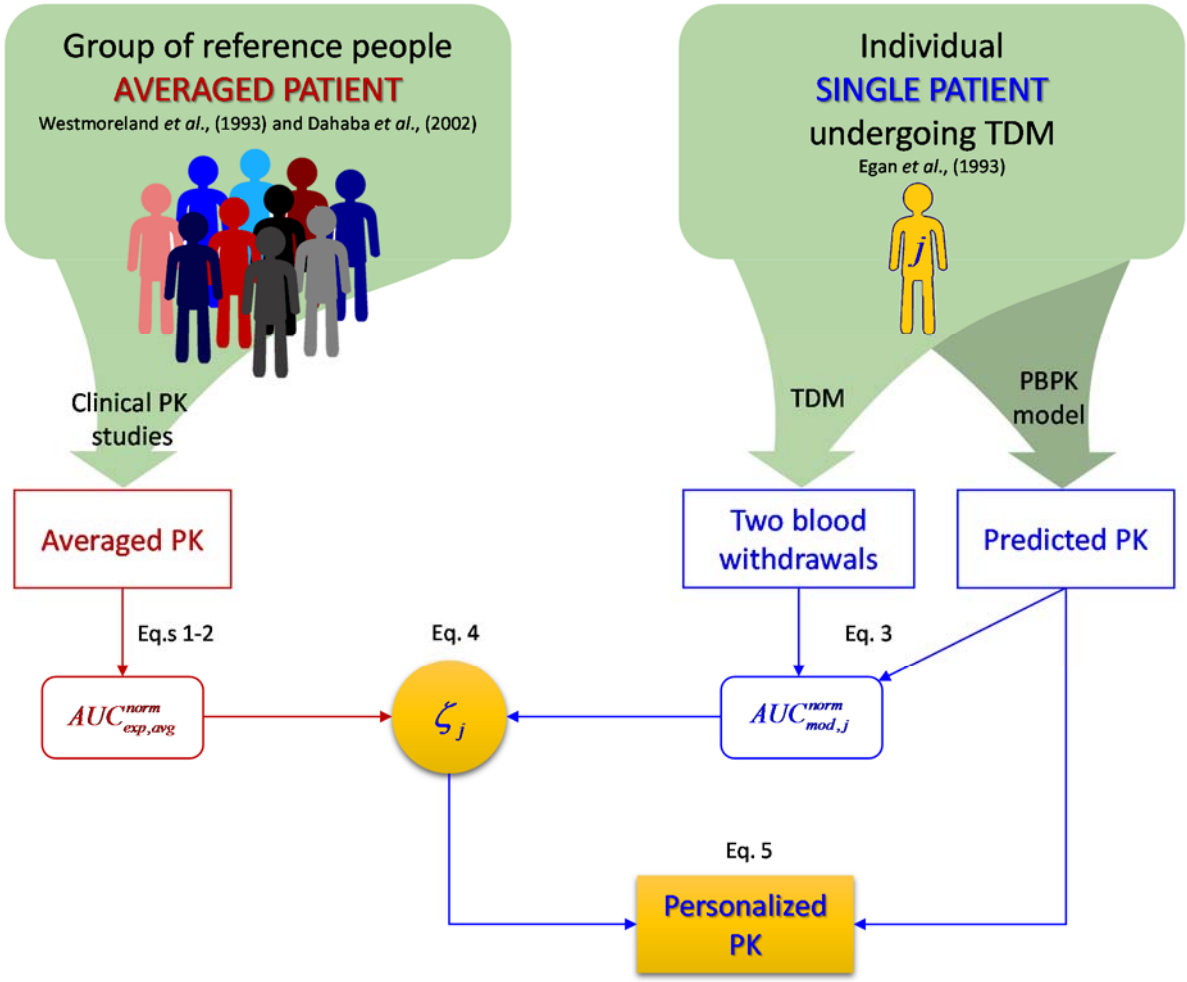


Figure 3: Sequential structure of the methodology for the evaluation of the correction factor (ζ_j), for the deployment of a personalized PK prediction. A number of patients (left top group) go through a PK study that allows determining an averaged (*i.e.*, lumped) pharmacokinetic profile (*i.e.*, AVERAGED PATIENT). When a new patient (*i.e.*, SINGLE PATIENT-j, right top block) undergoes a TDM, their personal PK is first determined by applying the PBPK model (Abbiati et al., 2016), then after an initial administration, just two blood samples are withdrawn and the corresponding drug concentrations are measured. These data allow us to determine ζ_j and eventually simulate the personalized PK.

The rationale for the proposed method is the application of ζ to customize the model PK to each patient. This is an important issue as the available literature models are not able to address the inter-individual PK variability. The key aspect is the exploitation of the existing relationship between the single concentration measurements of drug in blood and the AUC value. This link is intrinsic since the experimental AUC is nothing more than the integral of the drug concentration-time curve. By recognizing this relation, the rationale consists of making the model prediction coherent with this dependence. This is achieved by exploiting few experimental data available for the specific patient (*i.e.*, the two drug-blood concentration measures obtained during the TDM activity). The relation between the blood withdrawals and AUC is quantified for a large group of reference patients (Equations 1-2). Then, by focusing on each patient who undergoes the TDM, a similar relation is assessed (Equation 3). However, this time the relation is between

the specific patient’s drug concentration in the two samples and the AUC calculated from the PBPK model (Abbiati et al., 2016). The mismatch between these data allows us to calculate the individualized ζ_j (Equation 4). Finally, this value, multiplied by the initial model prediction, allows us to correct for the errors produced by the averaged PK model (Equation 5). Section 2.1 details this procedure and provides the quantitative equations.

2.1 Equations definition

Since the only input data are the two patient’s blood withdrawals and the population averaged PK concentrations, we propose to correlate these data. Equation 1 applies to each k^{th} volunteer who participated to the clinical trials. Here AUC is divided (*i.e.*, normalized) by the sum of the two sampled drug concentrations (these are withdrawn at optimal times, as detailed in Section 3.1).

$$AUC_{exp,k}^{norm} = \frac{AUC_{exp,k}}{\sum_{i=1}^{NS} C_{i,k}} \qquad k = 1,\ldots,NP \tag{1}$$

Where $AUC_{exp,k}^{norm}$ is the integral of the concentration-time curve of the k^{th} volunteer/patient (belonging to the group of reference people in the left top block of Figure 3), and $C_{i,k}$ are the drug-blood concentrations measured at the i^{th} sampling time.

By applying Equation (1) to the entirety of the NP reference patients, it is eventually possible to obtain an averaged value:

$$AUC_{exp,avg}^{norm} = \frac{\sum_{k=1}^{NP} AUC_{exp,k}^{norm}}{NP} \tag{2}$$

This term quantifies the numerical relation existing between AUC and two of its constituting concentration measurements applied to the reference population (*i.e.*, averaged patient in the left top block of Figure 3).

Similarly, the $AUC_{mod,j}^{norm}$ value of each single patient undergoing the TDM (as shown in the right top block of Figure 3) is:

$$AUC_{mod,j}^{norm} = \frac{AUC_{mod,j}}{\sum_{i=1}^{NS} C_{i,j}} \tag{3}$$

Where $AUC_{mod,j}$ is calculated from the PBPK model applied to the j^{th} patient undergoing the TDM, and $C_{i,j}$ are the i^{th} concentrations measured for that patient at the NS optimal times of TDM. Equation (3) assesses the same quantitative variable evaluated by Equation (2) for the experimental data, with the difference being that in Equation (3) that quantity is determined from the simulated AUC. As a result, $AUC_{mod,j}$ quantifies whether the PK predicted by the model for the single j^{th} patient differs from the experimental AUC as far as the single $C_{i,j}$ are concerned.

ζ_j is calculated by comparing $AUC_{exp,avg}^{norm}$ with $AUC_{mod,j}^{norm}$. If the “single patient” pharmacokinetics behaves as the “averaged patient” (Figure 3), then $AUC_{mod,j}^{norm}$ is close to $AUC_{exp,avg}^{norm}$, otherwise Equation (4) quantifies the correction coefficient (ζ_j) as the ratio of those terms:

$$\zeta_j = \frac{AUC_{exp,avg}^{norm}}{AUC_{mod,j}^{norm}} \tag{4}$$

In order to correct the averaged PK prediction applied to the j^{th} patient, it is sufficient to multiply the concentration vector $\mathbf{C}_{mod,j}$ by ζ_j:

$$\mathbf{C}_{personal,j} = \zeta_j \cdot \mathbf{C}_{mod,j} \quad (5)$$

Equation (5) determines the personalized PK. The goal of ζ is to keep things as simple as possible and preserve the efficacy of PBPK predictions. Indeed, the sum of concentrations (*i.e.*, the denominator term of Equation (3)) compared with $AUC_{mod,j}$ allows quantifying whether the single patient's PK is globally higher, lower, or in line with the averaged patient's pharmacokinetics measured in clinical trials. The correction factor (ζ), quantifies how much the PK of a specific patient differs from the expected averaged behavior and exploits this difference to correct the model prediction and carry out a personalized PK model.

3 Case Study

This Section presents an application of the personalization method. With the purpose of preserving the continuity with the original paper of Abbiati et al. (2015b), we refer to the experimental studies of Dahaba et al. (2002), Egan et al. (1993), and Westmoreland et al. (1993). These experimental PK studies provide individual concentration measurements of remifentanil in blood. Remifentanil is an analgesic drug that belongs to the fentanyl family. Remifentanil is widely used as an anesthetic during surgeries because of its extremely short half-life in the organism, which promotes a fast recovery after intervention and optimal control of the sedation (Duthie, 1998; Pitsiu et al., 2004). It is worth underlining that even if analgesic administration is always critical and requires constant supervision by expert anesthetists, remifentanil does not expressly require TDM. Nonetheless, for the sake of validating the proposed method, we refer to the previously cited data for a number of reasons: (i) previous works (*e.g.*, Abbiati *et al.* (2015a,b)) on PBPK model definition and individualization refer to such active principles; (ii) Egan et al. (1993) experimental data cover a sufficiently large set of patients and drug-dosage ranges; (iii) it was not possible to find in the literature a sufficient amount of experimental data on PK for drugs requiring TDM.

Before proceeding with the ζ calculation, it is necessary to evaluate the single patient's PK with the PBPK model. For this purpose, as explained in detail in Abbiati et al. (2016), it is necessary to assign/determine the model equation parameters. In particular, some of them are unknown and are calculated via a non-linear regression procedure with respect to some experimental PK data. It is first necessary to solve the PBPK model to obtain a global PK prediction. This requires input data, such as the patients' features, the drug molecule properties, and the population experimental drug-blood concentration to identify the unknown parameters of the model. The PBPK model comprises a set of ordinary differential equations (ODEs), whose number depends on the administration route. In case of intravenous administration, it is possible to neglect the gastro-intestinal compartments. Consequently, the number of equations collapses to five (see also Equations A.1-A.5 in Appendix A.1). For what concerns the model identification, this reduced model features 18 adaptive parameters, of which 6 are evaluated with a non-linear regression routine that minimizes the distance between the PK experimental data and the corresponding model predictions (see also Appendix A.2).

The data used for identification purposes are those published by Westmoreland et al. (1993) and Dahaba et al. (2002). These articles discuss the results of experimental studies on the remifentanil pharmacokinetics. In particular, Westmoreland et al. (1993) carried out a study on 24 patients who were administered four different dosages of remifentanil (2, 5, 15, 30 µg/kg as bolus infusions), while Dahaba et al. (2002) treated 13 patients who received a 20 min infusion of remifentanil at a 0.1 µg/kg/min rate.

These papers were selected because the PK studies comprised of a reasonable number of subjects (both males and females), and different intravenous routes (*i.e.*, instantaneous bolus and continuous infusion).
The PK curves reported in the abovementioned papers were used as experimental values to identify the unknown parameters of the population (*i.e.,* the “averaged patient” of Figure 3), which means that the vector of adaptive parameters of the PBPK model described the averaged anatomical/physiological features of the patients involved in the clinical trials. This set of parameters also allowed validation of the PBPK model (Appendix A reports the model equations, parameter values, and PK diagrams).
The data published by Egan et al. (1993) were used to determine the correction factor, ζ, which is characteristic of the personalized model tailored on the features of every involved patient (*i.e.*, the “single patient” of Figure 3).
The experimental study of Egan et al. (1993) reported the PK curves of remifentanil in blood for ten patients. The patients were studied in couples (*i.e.*, five couples) and received a 20 min infusion at five different doses (1, 1.5, 2, 4, and 8 μg/kg/min). As explained in Section 2, in order to determine ζ, it is necessary to measure some experimental blood concentrations of the drug for every “single” patient. The first step consists of determining the optimal times for blood withdrawals in order to extract the most significant content from the same amount of information. For this purpose, five out of ten patients of Egan’s study were used to evaluate both the reference $AUC_{exp,avg}^{norm}$ value and the optimal time points for blood withdrawals, while the remaining five patients were used to calculate ζ and validate the proposed method.

3.1 Assessment of the optimal withdrawal times

Egan et al. (1993) reported a detailed sequence of sampling times for the measurement of drug-blood concentrations and applied this sequence to a group of ten patients. To determine the optimal withdrawal times for blood sampling (used by the ζ method for TDM purposes), we considered all the possible pairwise permutations of Egan’s sampling times. Then we employed the experimental points from Egan et al. (1993) of the first five patients and applied the ζ method as many times as there were pairwise permutations. For each pair of points, we calculated the distance between the experimental AUC and simulated the predictions from the personalized model (*i.e.*, the model output corrected with ζ). The points that produced the smallest difference (*i.e.*, the personalized PK curve that was the closest to the experimental data) were selected as the optimal points and the corresponding withdrawal times as the ones to be used for TDM and personalized medicine (see right top block of Figure 3) tailored on the “single patient”.

4 Results

We considered Egan’s sampling times to determine the optimal times points for blood withdrawals. In that study, remifentanil was administered as a continuous 20 min intravenous infusion and blood samples were withdrawn according to the schedule reported in Table 2.
The Egan et al. (1993) withdrawal schedule produces a total of 52 drug-blood concentration measures for each patient. The optimal withdrawal times for the deployment of the individualized “single patient” model were found to be 12 and 22 min. These values are a consequence of the aforementioned 52 sampling times, so it was not possible to identify other intermediate optimal times.

Table 2 - Egan et al. (1993) sampling times for blood withdrawals.

Time elapsed [min]	Schedule
0 – 5	every 30 s
6 – 10	every 1 min
12 – 20	every 2 min
20.5 – 25	every 30 s
26 – 30	every 1 min
32 – 40	every 2 min
from 40 min on	at 45, 50, 55, 60, 65, 70, 80, 90, 100, 110, 120, 140 min

Nonetheless, it is reasonable to assume that the optimal withdrawal times for the 20 min remifentanil intravenous infusion should be close to these times (as reported in Table 3) as they are likely the most representative of the clinical trials conducted on the investigated patients (as shown in Figure 4).
The quantitative identification of the optimal times, when the two withdrawals are to be performed, calls for a performance indicator (PI) capable of assessing a ranking among the pairwise permutations. PI is arbitrarily chosen as one could consider different ranking measures (*e.g.*, the C_{MAX} or t_{MAX} distances). In this study, we focused on the AUC of Equation (6), as, usually, this is the most important index for pharmacologists in PK bioequivalence studies.

$$PI = \left| \frac{AUC_{exp} - AUC_{mod}}{AUC_{exp}} \right| \tag{6}$$

For the sake of mathematical detail, the pairwise permutations of the 52 sampling times for blood withdrawals (Egan et al. (1993)) are 2652 as per the combinatorial formula $\frac{n!}{(n-z)!}$, where n is the sample size (*i.e.*, 52) and z the number of coupling elements (*i.e.*, 2). However, the 2652 pairwise combinations can be halved (*i.e.*, 1326) since there are not any constraints on the sequence of coupled elements (indeed, optimal withdrawal times #5 and #12 are the same as times #12 and #5).
Once applied to Egan et al. (1993) data, the ranking criterion of Equation (6) allowed us to find the optimal withdrawal times (12 and 22 min). Table 3 reports the first three couples' withdrawal times.

Table 3 - Optimal pairwise sampling times for blood withdrawals.

Rank	Time of experimental withdrawals [min]		PI
1st	12	22	0.0035
2nd	10	21.5	0.0074
3rd	9	21.5	0.0098

For the sake of clarity, the optimal withdrawal times (*i.e.*, 12 and 22 min) should be referred and restricted to the specific administration of the experimental study (*i.e.*, 20 min continuous intravenous infusion of remifentanil). Accordingly, it is not possible to define a general rule for the optimal withdrawals as the features of the PK curve depend on both the administration route and the drug properties.
Figure 4 shows the comparison between the original PBPK model, based on a lumped approach (*i.e.*, averaged patient) to experimental measures, and the personalized model (*i.e.*, single patient) deduced from the original one and corrected by the ζ factor that is tailored to each patient.
In order to validate the improvements in the individual PK predictability, we focused on the remaining five patients of Egan's study (as the first half was used to determine the optimal sampling times). For these patients we assumed to know only two individual blood samples at 12 and 22 min, then the ζ for each

patient was calculated and eventually the original averaged model was corrected to obtain a personalized single-patient PK prediction.

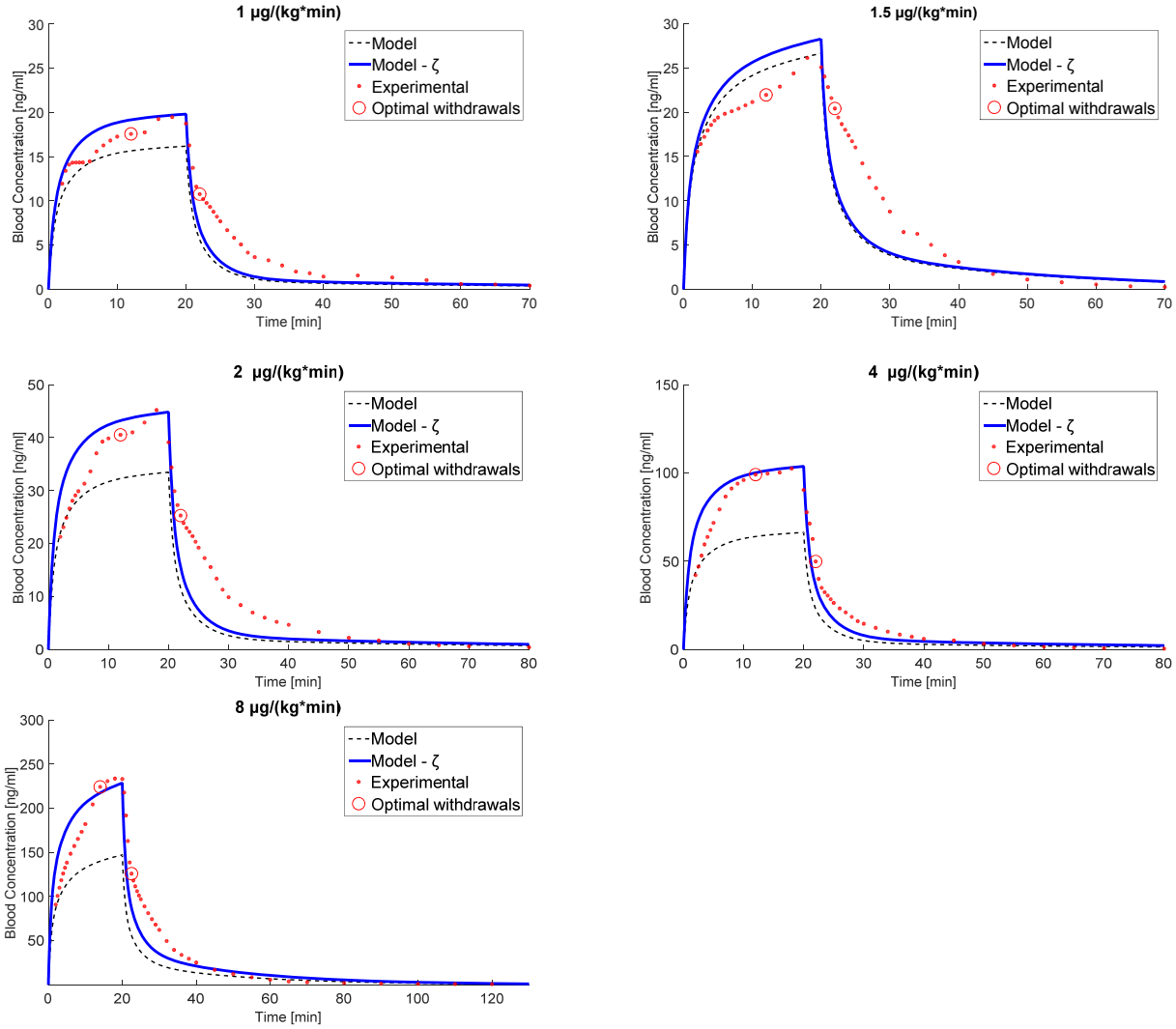


Figure 4: Comparison between model-predicted and measured concentrations. Experimental data (red points) are compared with the original model (dashed black line) and the ζ corrected model (solid blue line). The highlighted experimental points (big red circles) are the two experimental measures used to calculate ζ, while the remaining measures are just shown for the sake of comparison.

As shown in Figure 4, the ζ method confirms a concrete improvement of the PK prediction in particular when high doses of remifentanil are administered. It is worth underlining the improvement reached also in the C_{MAX} assessment as this is the critical value when toxicity is a major concern. This is a beneficial consequence of the ζ method.

In addition, C_{MAX} is an important indicator of the model quality as, contrary to AUC, it does not benefit from possible compensations in the Cxt shape. Indeed, ΔAUC may be compensated by the presence of asymmetric positive/negative areas, which may mutually suppress their relative contributions.

Table 4 - Absolute and relative error in C_{MAX} assessment with the PBPK model and the corrected one, respect to experimental values.

Patients	Absolute ΔC_{MAX} [ng/ml]		Relative ΔC_{MAX} [%]	
	Original model	ζ corrected model	Original model	ζ corrected model
#1	3.28	0.34	16.8	1.7
#2	2.1	3.74	8	14.3
#3	11.74	0.38	25.9	0.8
#4	36.19	1.28	35.3	1.2
#5	100.97	15.25	43.1	6.5

4.1 Numerical statistics

The numerical simulation was performed on a Windows 64 bit PC featuring an Intel Core i7-3770 CPU at 3.4 GHz and 8 GB of RAM. The ODE system (whose details are provided in Appendix A.4) is moderately stiff and was solved in Matlab® by the `ode15s` routine. Likewise, the `fmincon` routine solved the nonlinear regression problem for the identification of the unknown parameters. The regression procedure required a total of 160 calls of the objective function and took 272 s of CPU time. It is worth observing that the total CPU time depends on the initial guess assigned to the unknown parameters.

5 Discussion

The proposed ζ method was conceived for applications in therapeutic drug monitoring, with the purpose of assisting physicians in medical practice. In general, drugs requiring TDM have a narrow therapeutic index. Therefore, toxicity is a real concern due to the unpredictable PK variability among patients and the reduced window allowed for drug concentration fluctuations. The present study proposed a preliminary contribution to computer-assisted monitoring of drug administration and outlined a methodology to address the personalized PK theme.

The main contribution of this paper is the use of individual blood samples to determine a personalized correction factor, which quantifies the distance between the averaged PK behavior and the single-patient response. We believe that the current medical knowledge does not allow deploying an *a priori* personalized PK prediction for single patients. Such a method would require an extremely detailed screening of the patient features, ranging from macroscopic ones (*e.g.*, race, gender, body mass), to the hindered ones (*e.g.*, metabolic activity, organs impairment, concomitant therapeutic effects). The assessment of these data would be extremely complex, costly, time consuming, invasive, and would require experienced physicians to interpret the analysis results.

Given this perspective, the use of a limited number of drug-blood concentration samples (*e.g.*, two or three) is reasonable in that it limits the patients' suffering and provides important information. These blood samples are a surrogate of the detailed knowledge of the biological and physiological pathways, as they are an ADME consequence and encompass the anatomical/physiological features of the "single patient" in the outcomes.

The most evident limits of the ζ method are that it can only adjust the numerical values of the predicted PK curve by either increasing or decreasing it by a constant factor. This means that the shape (*e.g.*, curvature) and t_{MAX} of the PK curve cannot be optimally corrected. We recognize a further limitation of the ζ method, which is a general weakness of TDM, as the proposed correction depends on few

measurements that could be affected by experimental errors, and consequently produce unexpected results (*e.g.*, outliers, gross-errors). Finally, since patients requiring TDM are usually subjected to chronic treatments, their ζ factor should be reevaluated periodically as PK variations may occur, due to the continuous body adaptation and organ activity.

Despite these limitations, which we plan to overcome in a forthcoming publication (see also Section 6), the proposed ζ method has the advantage of being simple and fast, while providing a rather good improvement in the PK predictions (see also Table 4). In addition, it can be applied to any type of pharmacokinetic models available in the literature as it does not require modifying the model constitutive equations, but instead provides a correction to the pre-calculated PK curves.

The results are encouraging since the improvement in the PK assessment is evident (see Figure 4 and Sections 3-4). Starting from these results, it will be necessary to study the flexibility of the ζ method with respect to different active principles and consider administrations at different dose levels.

6 Conclusions

This article introduced a methodology for the individualization of pharmacokinetic predictions from PBPK models. To achieve a reduction of model errors, due to the unpredictable inter-individual variability in pharmacokinetic response to drug administration, a correction factor was applied to adjust the initial model prediction for the patient undergoing TDM. We tested the proposed ζ method on a set of experimental data of remifentanil pharmacokinetics (Egan et al., 1993). The main results of this study were: (i) the identification of the optimal times for individual blood withdrawals, and (ii) the validation of the ζ method.

The obtained results are encouraging and justify further study and investigation of this method. It is worth observing that patients, who require monitoring of their pharmacological therapy, are generally affected by chronic diseases that require periodic adjustment of their dosing regimens. As a consequence, simulation programs based on pharmacokinetic models can play an important role and support the physicians in decision making.

To guarantee a more flexible approach, a possible improvement to the current ζ method is under study. This new method will be tightly linked to a previous work on PBPK modeling (Abbiati et al., 2016), which proposed to classify the model parameters into three classes: (i) individualized parameters according to the patient’s features, (ii) assigned parameters from available literature studies, and (iii) unknown parameters that are calculated by a nonlinear regression procedure with respect to PK experimental data. The future approach, which further pushes the current concept of a static correction factor (ζ), is intended to identify the unknown model parameters for the single patient from the available experimental measurements. This point, if proved feasible and consistent, will make the model capable of predicting the PK concentrations in a wider dosage range and adjust the PK curve with higher precision.

From a general perspective, these practices can be classified as model-assisted PK personalization. We believe that these practices will better address the new challenges of personalized medicine in PBPK model applications for TDM.

Appendix A

This Section lists the PBPK model equations (Section A.1) and the parameter values (Section A.2) used for the PK simulation. Section A.3 shows the simulated PK curves in comparison with the experimental data of Westmoreland et al. (1993) and Dahaba et al. (2002), which were both used to identify the unknown parameters of the PBPK averaged model. Section A.4 provides details on the PBPK model.

A.1 Model equations

Equations A.1-A.5 characterize the PBPK model, and refer respectively to Plasma (A.1), GastroIntestinal Circulatory System (A.2), Liver (A.3), Highly perfused Organs (A.4), and Poorly perfused Tissues (A.5) compartments (Abbiati et al., 2016).

$$\frac{dC^{P}(t)}{dt} = -C^{P}(t)\left(j_{P-PT}(1-R) + j_{P-HO}(1-R) + \frac{Q^{HA}}{V^{P}} + \frac{Q^{PV}}{V^{P}} \right) + C^{PT}(t)\, j_{PT-P}\frac{V^{PT}}{V^{P}} + \\ + C^{L}(t)\frac{Q^{HV}}{V^{P}} + C^{HO}(t)\, j_{HO-P}\frac{V^{HO}}{V^{P}} - C^{P}(t)k_{E}^{P}(1-R) - C^{P}(t)\frac{CL^{K}}{V^{P}} + \frac{IV(t)}{V^{P}} \tag{A.1}$$

$$\frac{dC^{GICS}(t)}{dt} = -C^{GICS}(t)\left(\frac{Q^{PV}}{V^{GICS}} + j_{CA}^{SIL}(1-R) + j_{CA}^{LIL}(1-R) \right) + C^{SIL}(t)\, j_{A}^{SIL}\frac{V^{SIL}}{V^{GICS}} + \\ + C^{LIL}(t)\, j_{A}^{LIL}\frac{V^{LIL}}{V^{GICS}} + C^{P}(t)\frac{Q^{PV}}{V^{GICS}} \tag{A.2}$$

$$\frac{dC^{L}(t)}{dt} = -C^{L}(t)\left(\frac{Q^{HV}}{V^{L}} + \frac{CL^{H}}{V^{L}} \right) + C^{P}(t)\frac{Q^{HA}}{V^{L}} + C^{GICS}(t)\frac{Q^{PV}}{V^{L}} \tag{A.3}$$

$$\frac{dC^{HO}(t)}{dt} = -C^{HO}(t)\, j_{HO-P} + C^{P}(t)\, j_{P-HO}(1-R)\frac{V^{P}}{V^{HO}} \tag{A.4}$$

$$\frac{dC^{PT}(t)}{dt} = -C^{PT}(t)\left(j_{PT-P} + k_{E}^{T} \right) + C^{P}(t)(1-R)\, j_{P-PT}\frac{V^{P}}{V^{PT}} \tag{A.5}$$

A.2 Model parameters

Table A.1 lists the individualized parameters of the PBPK model. Literature correlations/formula allow to calculate these parameters (see Abbiati et al. (2016) for further details).

Table A.1 - Individualized parameters.

Parameters	Westmoreland et al. (1993)				Dahaba et al. (2002)	Units
	Group 1 [2 µg/kg]	Group 2 [5 µg/kg]	Group 3 [15 µg/kg]	Group 4 [30 µg/kg]	20 min at [0.1 µg/(kg*min)]	
V^{PT}	60059.5	58726.5	56764	59356	51098.7	cm^3
V^{HO}	1899.3	1857.1	1795.1	1877	1615.9	cm^3
V^{P}	3263.9	3191.5	3084.8	3225.7	2776.9	ml
V^{L}	2108.6	2061.8	1992.9	2083.9	1794	cm^3
V^{GICS}	14.3	14	13.5	14.2	12.2	cm^3
Q^{PV}	735.7	719.4	695.4	727.1	625.9	ml/min
Q^{HA}	220.7	215.8	208.6	218.1	1877.9	ml/min
Q^{HV}	956.4	935.3	904	945.2	813.7	ml/min

Q^K	662.2	647.5	625.8	654.4	563.3	ml/min

Remaining parameters can be either assigned from remifentanil pharmacokinetic reports or regressed from experimental data (see Table A.2).

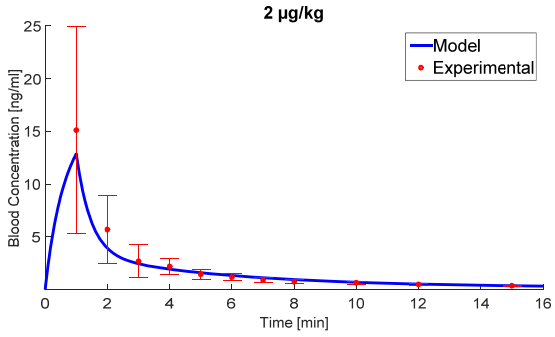
Table A.2 - Assigned and unknown parameters.

Symbol	Value	Units	Description	Type
R	3.33	-	Drug fraction bound to plasma proteins	Assigned
Eff^H	0.14	-	Hepatic efficiency of elimination	Assigned from Abbiati et al. (2016)
Eff^K	0.39	-	Kidneys efficiency of elimination	Assigned from Abbiati et al. (2016)
k_E^P	1.65	min^{-1}	Plasma Elimination kinetic rate constant	Unknown parameter
k_E^T	0.1	min^{-1}	Tissues Elimination kinetic rate constant	Unknown parameter
j_{HO-P}	0.02	min^{-1}	Highly perfused Organs to Plasma mass transfer coefficient	Unknown parameter
j_{P-HO}	0.47	min^{-1}	Plasma to Highly perfused Organs mass transfer coefficient	Unknown parameter
j_{P-PT}	0.46	min^{-1}	Plasma to Poorly perfused Tissues mass transfer coefficient	Unknown parameter
j_{PT-P}	0.29	min^{-1}	Poorly perfused Tissues to Plasma mass transfer coefficient	Unknown parameter
j_A^{LIL}	0	min^{-1}	LIL to $GICS$ mass transfer coefficient	Neglected (IV Administration)
j_A^{SIL}	0	min^{-1}	SIL to $GICS$ mass transfer coefficient	Neglected (IV Administration)
j_{CA}^{LIL}	0	min^{-1}	$GICS$ to LIL mass transfer coefficient	Neglected (IV Administration)
j_{CA}^{SIL}	0	min^{-1}	$GICS$ to SIL mass transfer coefficient	Neglected (IV Administration)

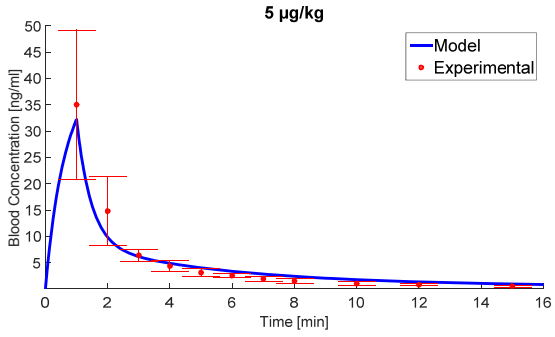
A.3 PBPK model output

Figure A.1 shows the PBPK averaged model simulation with the optimal values of the unknown parameters.

a



b



c

d

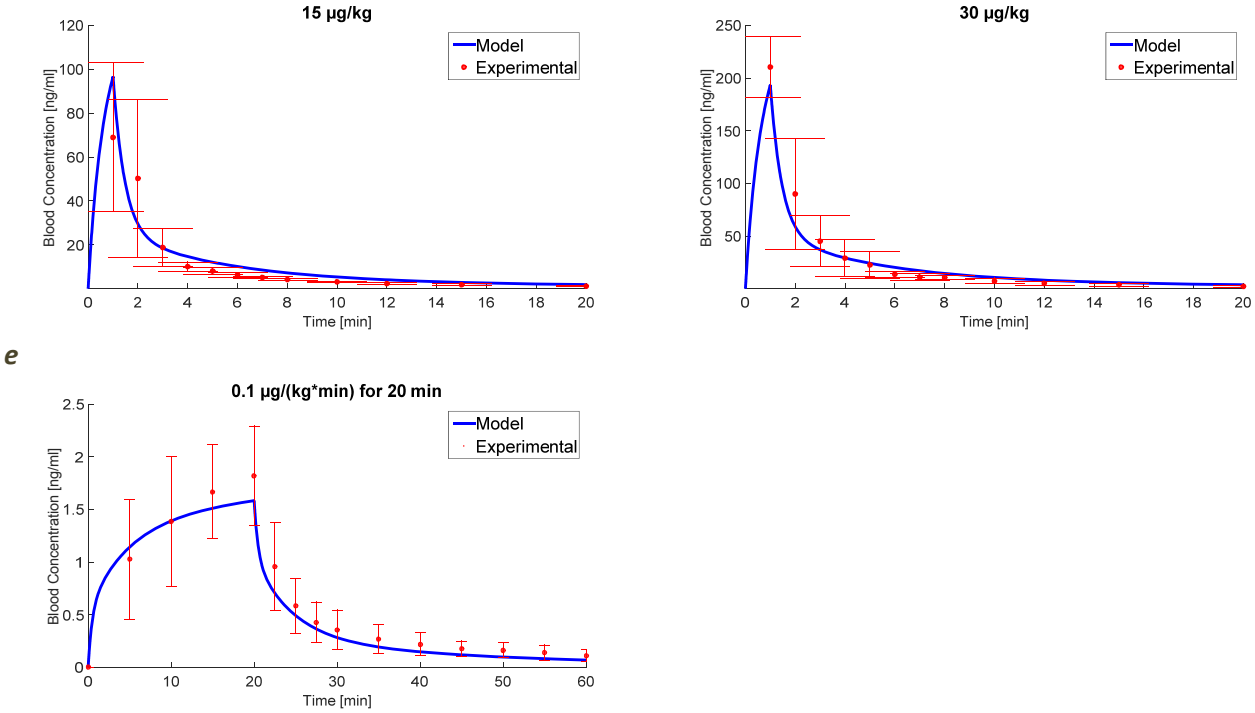


Figure A.1: Pharmacokinetic model predictions (blue solid line) for patients involved in the experimental study (red points and SD bars) of Westmoreland et al. (1993) (*a*, *b*, *c*, *d* diagrams) and Dahaba et al. (2002) (*e* diagram). These experimental data were used to identify the unknown parameters by means of a nonlinear regression procedure.

A.4 PBPK model details

Table A.3 provides some details on the numerical model features in case of IV administration:

Table A.3 - PBPK model equations and parameters detail.

Model detail		Number	Reference
PBPK compartments		5	Figure 2 (GastroIntestinal region excluded)
Equations number		5	Equations A.1-A.5
Integration variables		5	Equations A.1-A.5
Model parameters		18	Equations A.1-A.5
Type:	Individualized	9	Table A.1
	Assigned	3	Table A.2
	Unknown	6	Table A.2

Notation

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area Under the Curve (drug concentration vs time curve)
AVG	Averaged
EXP	Experimental
GICS	Gastrointestinal Circulatory System
GL	Gastric Lumen
LIL	Large Intestinal Lumen

MOD	Model
NORM	Normalized
PBPK	Physiologically Based PharmacoKinetics
PK	Pharmacokinetic
SD	Standard Deviation
SIL	Small Intestinal Lumen

Symbols

C	Drug concentration	ng/ml
CL	Clearance	ml/min
Eff	Efficiency	
IV	Intravenous	ng/min
j	Mass transfer coefficient	min^{-1}
k	Reaction rate constant (metabolism)	min^{-1}
M	Mass	ng
NP	Number of Patients	
NS	Number of pharmacokinetic Samples	
PO	Drug orally administered (*Per Os*)	ng/min
Q	Plasma flow to different organs	ml/min
R	Drug bound to protein (expressed as fraction)	
t	Time	min
V	Volume	cm^3 or ml

Subscripts

$½$	Terminal plasma half-life
A	Absorption
CA	Counter Absorption
E	Elimination
$HO-P$	From Highly perfused Organs to Plasma
MAX	Value of the drug peak concentration
$P-HO$	From Plasma to Highly perfused Organs
$P-PT$	From Plasma to Poorly perfused Tissues
$PT-P$	From Poorly perfused Tissues to Plasma

Superscripts

$GICS$	Gastrointestinal circulatory system
GL	Gastric lumen
H	Hepatic
HA	Hepatic artery
HO	Highly perfused Organs
HV	Hepatic vein
K	Kidneys
L	Liver
LIL	Large intestinal lumen
P	Plasma
PT	Poorly perfused Tissues

PV	Portal vein
SIL	Small intestinal lumen

Greek letters

ζ	Correction factor
Δ	Difference

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