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A Computational Strategy for Dose Adaptation at the Population and Group Levels

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Abstract: *With the intention to achieve the best therapeutic outcomes, dose adaptation underpins the clinical practice by tailoring dose and time in order to maximize efficacy while minimizing toxicity. Depending on the drug properties and the clinical context, three successive levels of dose adaptation can be considered, i.e., approaches based on population, group and individual. To make a rational choice for the dose adaptation level and determine the best drug regimens, we here propose a modeling and simulation strategy based on the platform provided by the population pharmacokinetic/pharmacodynamic methodology at population and group levels. In order to compare the performance of different dose and time schedules, we introduced probabilistic conceptualized time- and concentration-based therapeutic indicators. Using carbamazepine as a drug model and a recently reported population pharmacokinetic (Pop-PK) model for the group of patients of 60 years and older, we were able to quantitatively study the performance of different group-dosing regimens in order to find the best ones. As indicated by our results, TID regimen was clearly favored among others, confirming thus suggestions in several clinical reports. Moreover, different time schedules that can reach the same therapeutic target for this group were identified through our methodology, giving thus a wider choice for the clinical practice.*

Keywords: *Dose Adaptation, Dose Individualization, Mathematical Modeling, Population Pharmacokinetics, Therapeutic Drug Monitoring.*

I. Introduction

Tailoring the drug dose and time schedule to a patient's therapeutic need is an integral part of Therapeutic Drug Monitoring (TDM) and dose adaptation. The intention is to target the best therapeutic outcomes for an individual or a specific population by maximizing the desired therapeutic effect and minimizing toxicity [1].

TDM is applied for a variety of drugs, such as antibiotics [2], anti-epileptics [3], immunosuppressants [4], etc, and involves the measurement and interpretation of drug concentrations in biological fluids rather than using clinical endpoints [5]. For anticancer drugs, it is even crucial since they generally have narrow therapeutic indices, *i.e.,* toxicity occurs at doses close to those required for the therapeutic effect, and are associated with high inter-individual variability. To achieve a therapeutic optimization, dose adaptation based on drug plasma concentrations is considered the most effective method [1]. Indeed, therapeutic outcomes are generally reported to be more correlated with certain pharmacokinetic surrogates, such as the area under the concentration-time curve, maximum concentration, or duration of plasma concentration above a threshold, rather than the dose itself. Depending on the drug properties and clinical context, three dose adaptation approaches can successively be envisaged (referred to as dose individualization in [6]). The first, known as the population dosing method, relies on the assumption of a uniform population clearance to establish a same dose for all patients [6]. The second, referred to as group dosing method, is based on the fact that patients belong to a same covariate group, in which they share similar pharmacological characteristics and a same group dose can thus be applied. However, when a specific clinical situation arises, a completely individual-based approach becomes the ultimate third choice, subsequent to the group dosing strategy [7, 8].

The population pharmacokinetic/pharmacodynamics approach (Pop–PK/PD), which is able to quantitatively describe the dose-concentration-effect-toxicity relationships for a population, is a convenient platform for the determination of the appropriate dose adaptation approach. The decision process can be undertaken by setting up objective criteria for the expected trade-off between therapeutic benefit and acceptance of risk. Three consecutive steps can be involved: first, the general population can be tested for the therapeutic outcomes using common dose and time schedules. If the therapeutic outcomes exhibit a statistically significant nonuniformity, a covariate analysis can then be performed to identify patient groups and try to determine a suitable drug regimen for each. However, it could occur that this covariate grouping step is still not sufficient with some patients being out of therapeutic scope. In this case, we have to recourse to an individual-based approach to estimate the specific individual parameters. It is clear that the latter procedure presents obvious

therapeutic advantages but with potential inconvenience for the patient and health system, which explains its use only as a means of last resort [9]. This individual-based step is out of the scope of the current work.

In this paper, based on the above philosophy, we present a rational strategy for the determination of the best drug regimen in the context of group-dosing method for dose adaptation. The methodology that we propose herein to compare the efficacy and toxicity of the considered drug regimens is in fact inspired by the idea to find those models parameters that maximize the likelihood of a specific event. For this, we introduced in probabilistic terms a set of therapeutic indicators (TI). More precisely, two types of TI, time- and concentration-based indicators, are defined in reference to the relationship of the time-concentration curves generated by a dosing regimen with the Therapeutic Window (TW) [10, 11].

As a pre-requirement of our methodology, we need to use a Pop-PK model of the studied drug and population. To illustrate our approach, the Pop-PK model of carbamazepine [12], a widely used drug for partial onset seizures, is taken as an example.

This paper is organized as follows. In the Materials and Methods Section, we detailed our methodology and introduced several TIs with their use in the evaluation of the performance of dosing regimens. In the Results Section, several graphical and numerical diagnostics of the performance are presented. Additional issues related to the applicability of our methodology are included in the Discussion Section.

II. Materials And Methods

2.1 Regimen design in terms of dose and time

A dosing regimen will be defined on a daily basis with the following notations:

$$\text{Regimen} = (\mathbf{D},\boldsymbol{\tau}) \tag{1}$$

where

$$\mathbf{D} = \{D_1, D_2, D_3, \cdots, D_k\}$$
$$\boldsymbol{\tau} = \{\tau_1, \tau_2, \tau_3, \cdots, \tau_k\}, \qquad \tau_1 < \tau_2 < \cdots < \tau_k$$

Each pair (D_i, τ_i), $i = 1, \cdots, k$, represents a dose and its corresponding dosing time; k is the number of drug administrations per day.

Thus, the total daily dose (TDD) is:

$$\text{TDD} = \sum_{i=1}^{k} D_i \tag{2}$$

2.2 Therapeutic indicators and regimens performance

The performance of a particular dosing regimen will be evaluated through its associated PK profiles in reference to TW = [TW_{min}, TW_{max}], where TW_{min} is the minimum effective concentration and TW_{max} is the minimum toxic concentration. TW is known to correlate with toxic and therapeutic effects [13, 14]. Two types of TI are proposed in the following two subsections.

2.2.1 Time-based therapeutic indicators

The first time-based TI is the effective time TI_{Eff}, which can be defined as the daily time spent by a steady-state drug concentration-time curve (PK profile) within TW. For an individual PK profile $C_i(t)$, it is given by:

$$TI_{Eff}(C_i) = \text{Length}\{t : TW_{min} \le C_i(t) \le TW_{max}\} = \int_{1\ day} \chi_{TW}\left(C_i(t)\right) dt \tag{3}$$

where $\chi_{TW}(C_i(t)) = 1$ if the value of $C_i(t)$ is within TW, and $\chi_{TW}(C_i(t)) = 0$, otherwise.

Since various PK profiles can be associated to a given drug regimen due to the inherent population variability, we can evaluate the performance of a regimen by averaging the TI_{Eff} of N simulated PK profiles of this regimen. This can be expressed as:

$$TI_{Eff}(\text{Regimen}) = \frac{1}{N}\sum_{i=1}^{N} TI_{Eff}(C_i) \tag{4}$$

The second time-based TI refers to the toxicity of a PK profile and is defined as the daily time that drug concentration spent over TW_{max}. For an individual PK profile $C_i(t)$, this toxic time TI_{Tox} is given by:

$$TI_{Tox}(C_i) = \text{Length}\{t : C_i(t) > TW_{max}\} = \int_{1\ day} \chi_{[TW_{max},+\infty)}\left(C_i(t)\right) dt \quad (5)$$

where $\chi_{[TW_{max},+\infty)}\left(C_i(t)\right) = 1$ if $C_i(t)$ is over TW_{max}, and $\chi_{[TW_{max},+\infty)}\left(C_i(t)\right) = 0$, otherwise.

Analogously to Eq.4, we can also define:

$$TI_{Tox}(\text{Regimen}) = \frac{1}{N}\sum_{i=1}^{N} TI_{Tox}\,(C_i) \quad (6)$$

2.2.2 Concentration-based therapeutic indicators

TIs can also be concentration-based. For their definition, three therapeutic zones delimited by TW are used. We refer to these zones as non-effective, effective, or toxic, whenever they are below, within, or beyond TW, respectively (Fig.1). Using these zones, six categories, denoted CAT, of individual PK profiles can be defined through their trajectories across these different zones. Thus, an individual PK profile is said to belong to the category of non-responders (NR), responders (R), or adverse-responders (A) if it is completely located in the non-effective, effective, or toxic zone, respectively. Moreover, the hybrid category of non-responders/ responders (NR/R), responders/adverse-responders (R/A), or non-responders/responders/adverse-responders (NR/R/A) can be defined for those concentration-time curves that pass through more than two corresponding zones. This partition is illustrated in Fig.1.

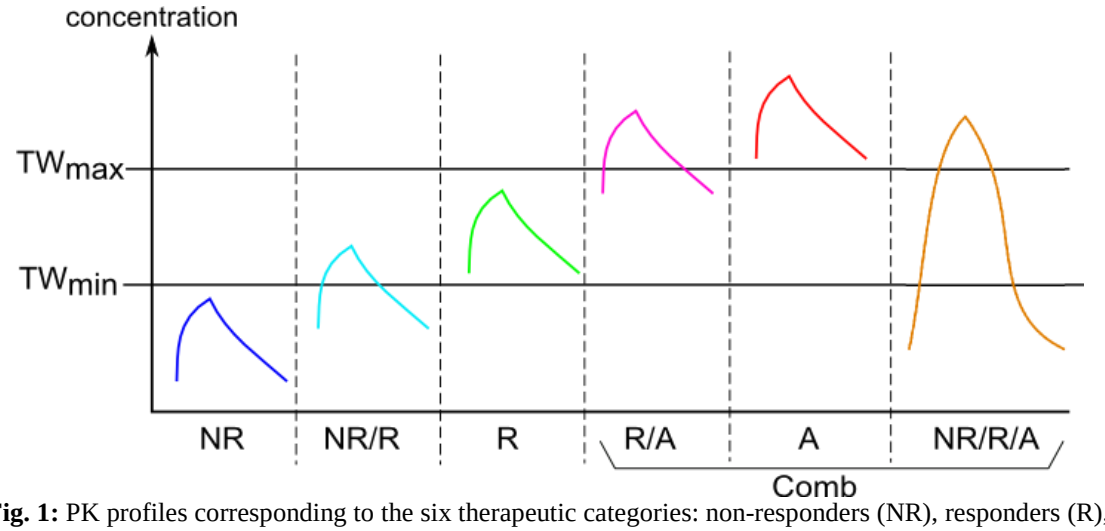

Fig. 1: PK profiles corresponding to the six therapeutic categories: non-responders (NR), responders (R), adverse-responders (A), and hybrid non-responders/responders (NR/R), responders/adverse-responders (R/A), or non-responders/responders/adverse-responders (NR/R/A). Comb = (R/A)∪A∪(NR/R/A)

Considering all PK profiles associated to a given drug regimen, we can evaluate the proportion of these PK profiles that belong to one of the above six categories. In other terms, we can use these proportions to define the probability of a given dosing regimen with respect to a category:

$$Prob_{Regimen} = \frac{1}{N} \times \text{number of PK profiles belonging to CAT} \quad (7)$$

where N is the total number of the simulated PK profiles for this regimen, and CAT can be one of NR, R, A, NR/R, R/A, or NR/R/A. To account for the trade-off between efficacy and toxicity, we define two concentration-based TIs. The first, named responders TI, is:

$$TI_R(\text{Regimen}) = Prob_{Regimen}(R) \quad (8)$$

The second, named combined TI, is

$$TI_{Comb} = Prob_{Regimen}(A) + Prob_{Regimen}(R/A) + Prob_{Regimen}(NR/R/A) \quad (9)$$

where Comb is the combination of categories A, R/A and NR/R/A.

2.2.3 Selection of the best regimen

Based on the quantitative evaluation of a dosing regimen described above, we can exhaustively go through a set, which is a Cartesian product of all combinations of time step (using an interval of time) and a dose step (using a minimum dose unit), of potential drug regimens in order to find those that maximize or minimize the above TIs. Each TI can be considered as a kind of probability of an expected event given a regimen. In fact, our idea is inspired from the principle of maximum likelihood, where regimens play the role of model parameters in the traditional objective function optimization.

The best regimen will be selected as follows. A mono-objective approach would be to target a particular TI with the goal of determining the regimen that maximizes (or minimizes) this TI, by testing all possible fractionated doses and dosing times. However, a multi-objective approach considering a combination of TIs with associated weights would be preferable to allow a trade-off between efficacy and toxicity. For this, using a set of potential dosing regimens, we will calculate the corresponding TIs values, as well as their maximum and minimum. Then the performance of each dosing regimen can be evaluated by:

$$\text{Performance}(\text{Regimen}) = \sum_{i \in I} w_i \begin{cases} \dfrac{\max(TI_i(\cdot)) - TI(\text{Regimen})}{\max(TI_i(\cdot)) - \min(TI_i(\cdot))} & \text{for minimization} \\ \dfrac{TI(\text{Regimen}) - \min(TI_i(\cdot))}{\max(TI_i(\cdot)) - \min(TI_i(\cdot))} & \text{for maximization} \end{cases} \quad (10)$$

where $\max(TI_i(\cdot))$ ($\min(TI_i(\cdot))$) is the maximum (minimum) of TI_i for all dosing regimens within the considered set. Moreover, i = {Eff, Tox, R, Comb} and w_i are weights to ensure favoring or penalizing one of the TIs, with

$$\sum_{i \in I} w_i = 1$$

The normalization with the ranges of TIs is necessary here for the units uniformity such that the comparison can be reasonable.

2.2.4 Software and implementation

Data analysis and graphical outputs are performed using MATLAB (R2008, MathWorks, Inc.). The Pop-PK model of the studied drug is implemented and simulated using NONMEM (version VII, Icon Development Solutions, Ellicott City, MD). We have also developed a wrapper function based script in MATLAB to call NONMEM. This process is depicted in Fig.2.

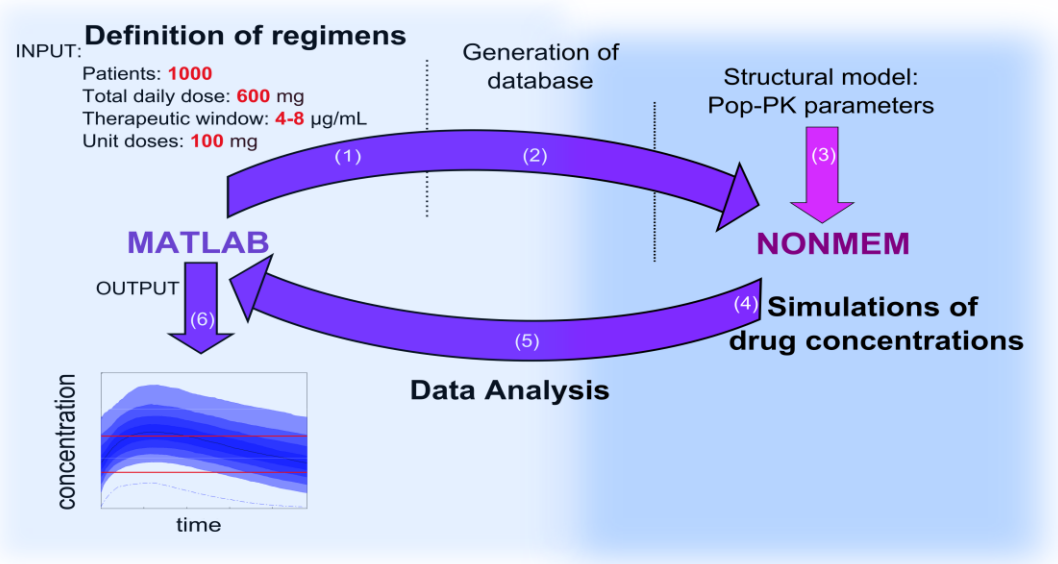

Fig. 2: Overview of the algorithm. In the initial step, the number of patients, TDD, TW and unit doses are defined. Then a set of potential dosing regimens is set up and transferred to NONMEM to simulate the associated steady-state drug concentrations. The results are sent back to MATLAB for the estimation of TIs and evaluation of dosing regimen performance

2.3 The case study of carbamazepine

To exemplify our developed methodology, the case study of carbamazepine (CBZ) was chosen.

2.3.1 Pop-PK model of carbamazepine

One reported Pop-PK model of CBZ, an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia, was used. This is a mono compartmental model with first-order absorption and elimination [12], developed for the sub-population of patients of 60 years and older. The log-normal and proportional error models are reported for the inter-individual and residual variability, respectively. The model parameters are reported in Table 1. This sub-population will serve here to exemplify our developed strategy at the group level.

Table 1: Pop-PK parameters of carbamazepine. F: bioavailability, CV: coefficient of variation. CL: clearance, V: apparent volume of distribution, Ka: absorption rate constant

PK parameters	Typical value	Variability (CV%)
CL/F (L/h)	3.59	18.1
V/F (L)	102	74
Ka (h^{-1})	0.197	-
Residual error	-	25.1

2.3.2 Therapeutic Window of carbamazepine

In order to evaluate the dosing regimens, we will refer to the TW of CBZ, which typically ranges between 4 to 12 µg/mL in a monotherapy context [15, 16]. Nevertheless this was reported as inappropriate for patients of 60 years and older who may present toxicity within the middle to upper therapeutic range [17]. Hence we use here a more restricted range between 4 and 8 µg/mL [18].

2.3.3 Set of tested dosing regimens for the selection procedure

Considering the most widely used dosing regimens, namely QD, BID, TID, and QID, we choose a TDD of 600 mg of CBZ as reported in [19]. For the last three regimens, all possibilities of fragmented doses that are multiples of a predetermined unit dose (100 mg here), with hourly-based dosing times, were tested.

III. Results

In the following, numerical results as well as graphical representations are used to illustrate the performance of the best regimens in terms of the introduced TIs.

3.1 Numerical evaluation of regimen performance

It would be interesting to compare our results with the findings in a previous work [19] where the authors highlighted the adjustment of doses following adverse effects. For this, we here choose the following set of weights w_{Tox} = 40%, w_{Comb} = 40%, w_{Eff} = 10%, and w_R = 10%, to be associated to TI_{Tox}, TI_{Comb}, TI_{Eff}, and TI_R, respectively, to put more emphasis on toxicity.

Table 2 reports numerical results for the best performing regimens based on Eq.10. The QD has a lower performance for each TI compared to BID, TID and QID. For example, TI_R of QD is 18.4% compared to 41.1%, 46.9% and 46.4% for BID, TID, and QID, respectively.

For time-based TIs, TI_{Eff} and TI_{Tox}, the BID regimen has a better performance compared to both TID and QID. Indeed, (TI_{Eff}, TI_{Tox}) of BID is (12.9%, 8.7%), compared to (12.5%, 9.1%) and (12.7%, 9%) for TID, and QID, respectively.

For concentration-based TI, TI_R and TI_{Comb}, the TID regimen has a better performance compared to both BID and QID. Indeed (TI_R, TI_{Comb}) of TID is (46.9%, 40.2%) compared to (41.1%, 41.4%) and (46.4%, 40.4%) for BID, and QID, respectively. The overall performance of regimens, calculated for all TIs using Eq. 10, enables to select the best one for BID, TID and QID. For example, when assessing the performance within the subset of all BID regimens, the one with 300q12 has an overall performance of 99.682% and is then ranked the first. A similar assessment can be done within the subsets of TID and QID regimens, resulting in an overall performance of 98.790% and 94.095%, respectively for the best ones. However, this (global) overall performance cannot be simply used to compare these three regimens together because their choice using Eq.10 is in fact based on their own subsets of BID, TID, or QID taken separately. A subtler comparison will be given below in Section 3.3.

Table 2: Best regimens for BID, TID and QID with their corresponding TIs values

		QD	BID	TID	QID
Regimen	dose (mg) time (hour)	600 0	300, 300 0, 12	200, 200, 200 0, 8, 16	100, 200, 100, 200 0, 5, 12, 17
Time-based TI (hours)	effective time toxic time	11 9.5	**12.9** **8.7**	12.5 9.1	12.7 9
Concentration-based TI (%)	responders (R) combined (Comb)	18.4 56.7	41.1 41.4	**46.9** **40.2**	46.4 40.4
Performance (Eq. 10)	(%)	-	**99.682**	98.790	94.095

3.2 Graphical representation of regimen performance

Two sets of graphical representations are presented here.

The first includes Figs.3-6, in which the left panels depict the steady state concentration-time curve associated to QD, BID, TID and QID, while the right panels depict the probabilities of these regimens with respect to six categories, respectively.

For example, in the left panel of Fig.3, we show the distributions of all steady-state concentration-time curves. Based on their density, we were able to calculate and draw their 10 to 90 percentiles lines, using a step of 10 as indicated in the figure. Moreover, we observe that around 50% of these PK profiles are located in TW, as a result of the large PK variability. However, the median curve traverses the TW_{max} line and enters the toxic zone. This raises concern about the toxic risk of QD regimen. For multiple dosing (BID, TID or QID), the median lines of the best regimen can always remain within TW, which indicates that a frequent administration may be preferred if toxicity is the predominant concern as illustrated in the left panels of Figs.4, 5 and 6, for BID, TID and QID, respectively.

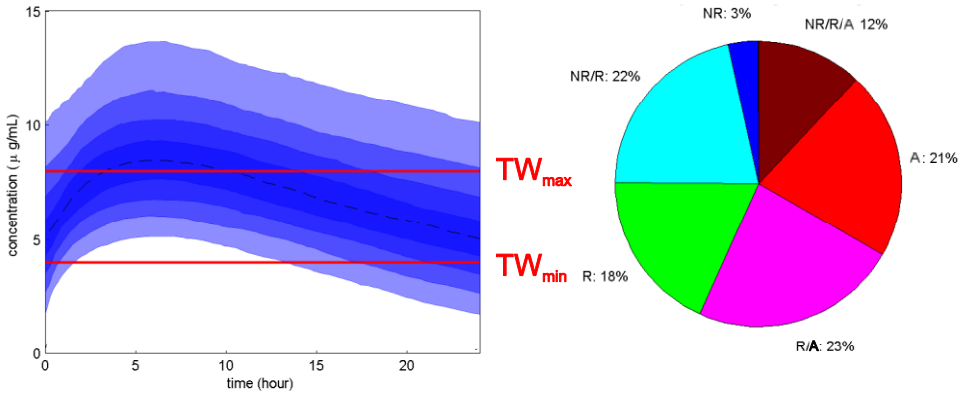

Fig. 3: Left: Concentration-time curves at steady state during a 24 hours for the best QD with dose of 600 mg. The middle dotted line represents the median. TW_{min} = 4µg/mL and TW_{max} = 8µg/mL; Right: Probabilities of QD with respect to six categories

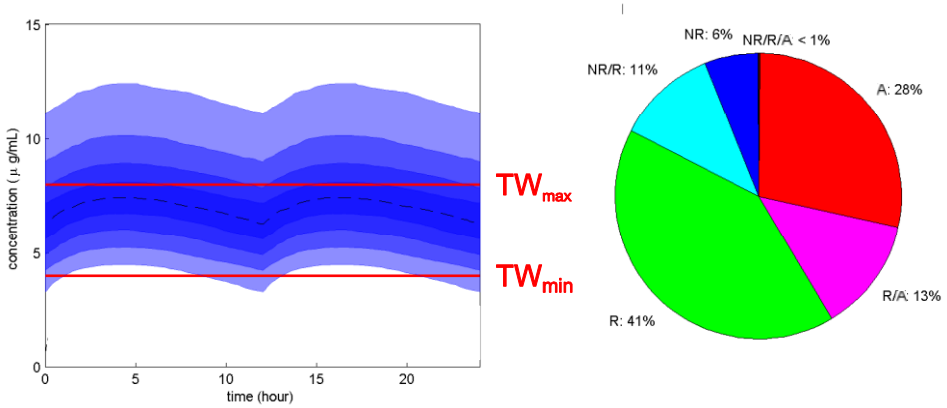

Fig. 4: Left: Concentration-time curves at steady state during a 24 hours for the best BID with dose of 600 mg. The middle dotted line represents the median. TW_{min} = 4µg/mL and TW_{max} = 8µg/mL; Right: Probabilities of BID with respect to six categories

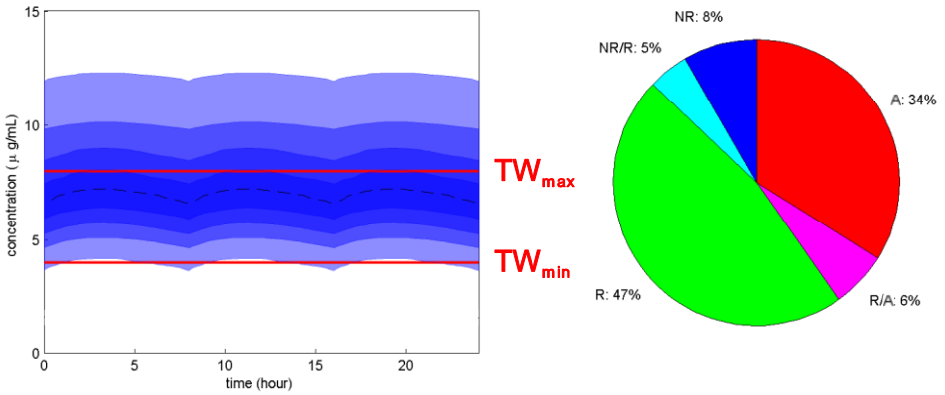

Fig. 5: Left: Concentration-time curves at steady state during a 24 hours for the best TID with dose of 600 mg. The middle dotted line represents the median. TW_{min} = 4µg/mL and TW_{max} = 8µg/mL; Right: Probabilities of TID with respect to six categories

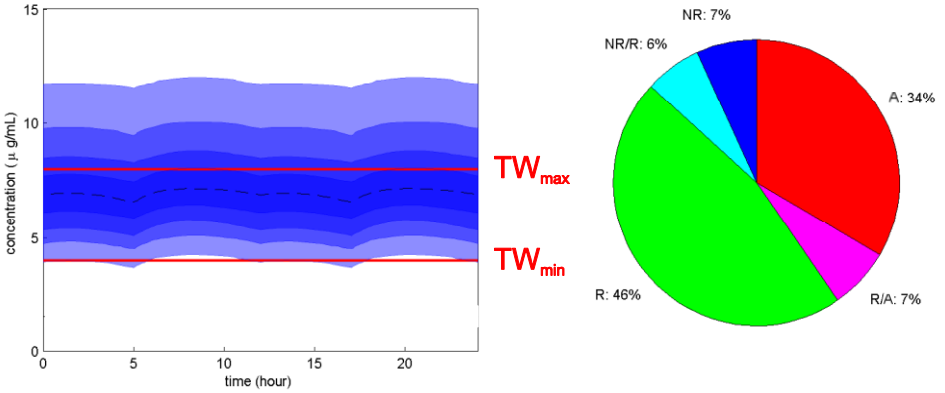

Fig. 6: Left: Concentration-time curves at steady state during a 24 hours for the best QID with dose of 600 mg. The middle dotted line represents the median. TW_{min} = 4µg/mL and TW_{max} = 8µg/mL; Right: Probabilities of QID with respect to six categories

In the right panels of Fig.3 and Fig.4, we have TI_R= 18% and TI_{Comb}= TI_A+ $TI_{R/A}$ +$TI_{NR/R/A}$ = 21%+ 23%+ 12% = 56% for QD, compared to TI_R = 41% and TI_{Comb}= 41% for BID. This indicates an improvement in the probability of both benefit and toxicity when the frequency of administration is increased. Similar results can be observed for TID and QID (Figs.5 and 6).

To further characterize the regimen performance, a second set of graphical representations is proposed here based on concentration-based TIs. Figs.7-10 depict the performance of QD, BID, TID and QID, respectively. The upper panels show the evolution over 24 hours of percentages of concentrations below (cyan), within (green), and beyond (red) TW, after the first daily dose, for all PK profiles in each category, namely NR, NR/R, R, R/A, A, and NR/R/A. In the lower panels, the distribution of effective times, *i.e.*, time where drug concentrations are within TW, of all PK profiles in each of the upper panel category are reported. We also note that presentations in the first, third, and fifth figures of the upper and lower panels, included in Fig.7, are, in fact, trivial since they represent the PK profiles entirely below, within and beyond the TW, respectively. They are included for the sake of illustration only for QD regimen, and dropped from Figs.8-10.

To illustrate the utility of these graphical representations, we will take Fig.7 as an example. In fact, each part of the upper panels can help identifying critical time zones for PK profiles in each category. If 80% is the threshold over which the regimen leads to toxicity, then, referring to the upper panel of Fig.7, we can see that 0 to 24 hours, 3 to 13 hours, and 4 to 8.5 hours can present toxicity for the categories A, R/A and NR/R/A, respectively. Combining these results with the information of their associated probabilities gives rise to a probability of 56% to be in the toxic zone during the time interval 4 to 8.5 hours, and of 44% to be toxic during the periods of 3 to 4 hours and 8.5 to 13 hours, and of 21% for the remaining daily time, approximately.

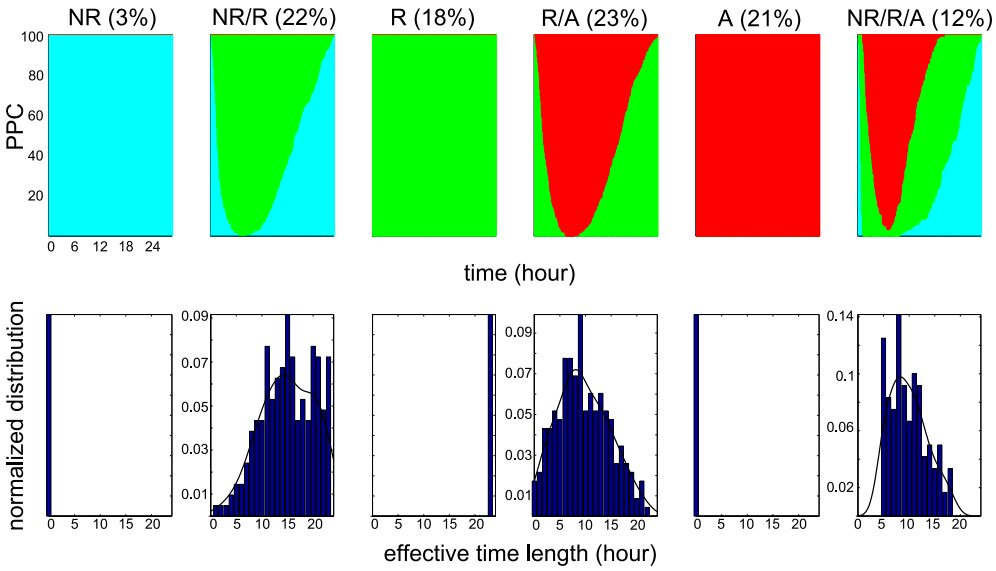

Fig. 7: Upper panel: Partition of percentages of concentrations (PPC) of QD vs time, below (cyan), within (green) and beyond (red) TW; Lower panel: histograms and their associated smooth fitting probability distributions of effective times of the upper therapeutic categories: NR, NR/R, R, R/A, A and NR/R/A, from left to right. In the NR and A categories, all effective times are zero, while in R category, all effective time are 24 h. Each of these three is thus represented by a vertical line

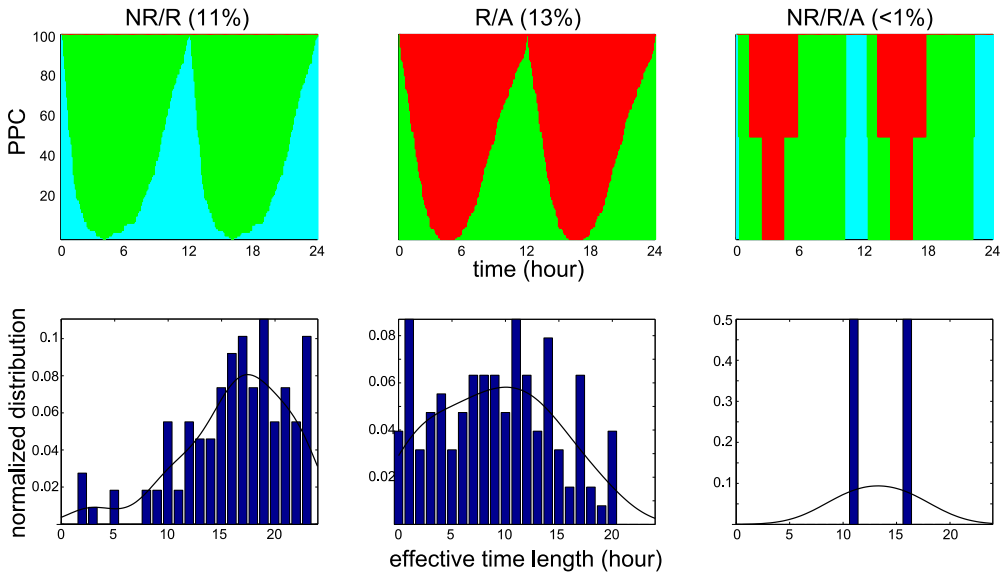

Fig. 8: Partition of percentages of concentrations (PPC) of BID vs time, below (cyan), within (green) and beyond (red) TW; Lower panel: histograms and their associated smooth fitting probability distributions of effective times of the upper therapeutic categories: NR/R, R, R/A, and NR/R/A, from left to right

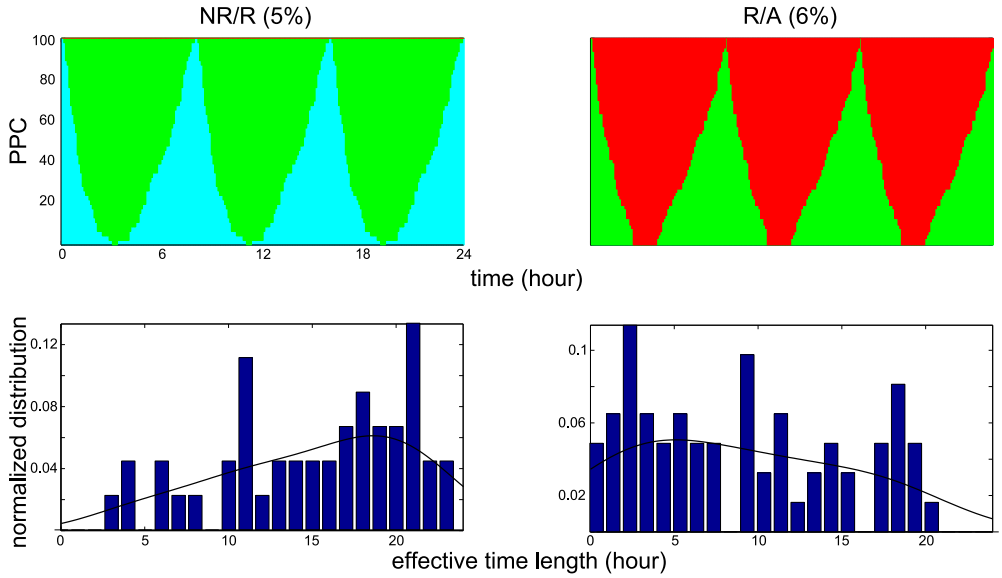

Fig. 9: Partition of percentages of concentrations (PPC) of TID in time, below (cyan), within (green) and beyond (red) TW; Lower panel: histograms and their associated smooth fitting probability distributions of effective times of the upper therapeutic categories: NR/R and R/A, from left to right

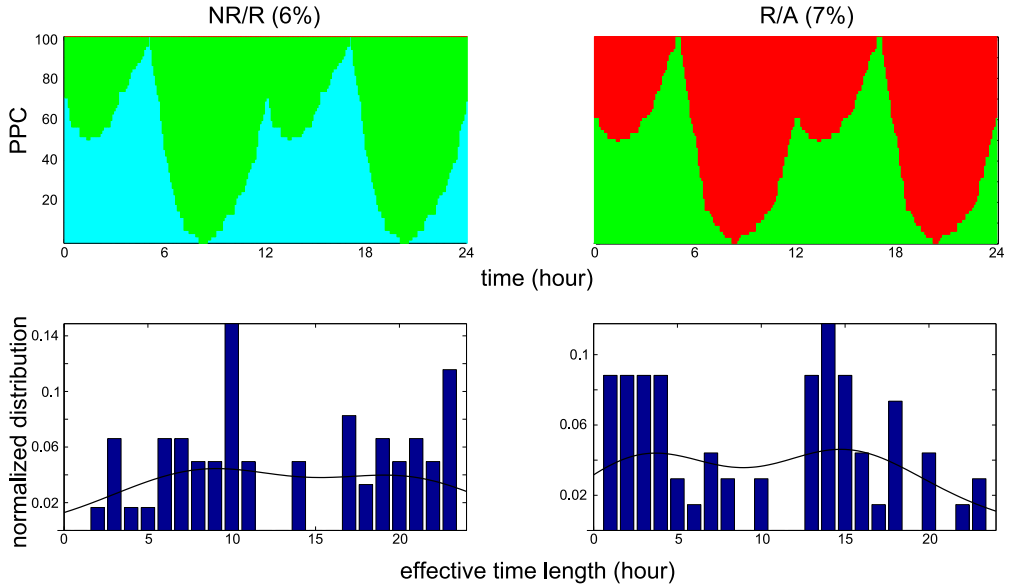

Fig. 10: Partition in time of percentages of concentrations (PPC) of QID vs time, below (cyan), within (green) and beyond (red) TW; Lower panel: histograms and their associated smooth fitting probability distributions of effective times of the upper therapeutic categories: NR/R and R/A, from left to right

This toxicity information could be a significant factor to be taken into account in drug monitoring practice.

3.3 Optimal choice of regimens

In the following, we discuss how to choose an optimal regimen among the four best regimens that we have determined above for QD, BID, TID and QID. This should be based on each TI value additional with common sense and pharmacological considerations.

For this end, we summarize in Fig.11 the four TI values of the best QD, BID, TID and QID regimens that were reported in Table 2. First, it is clear that, compared to the other regimens, QD has to be excluded since it presents the highest TI_{Comb} and the lowest TI_R, while TI_{Eff} and TI_{Tox} are almost similar for all regimens. Then, BID has similar TI values to TID and QID but clearly has a smaller TI_R, thus can also be refuted. Finally, TID and QID have almost the same TI values and hence TID should be preferred for its convenience.

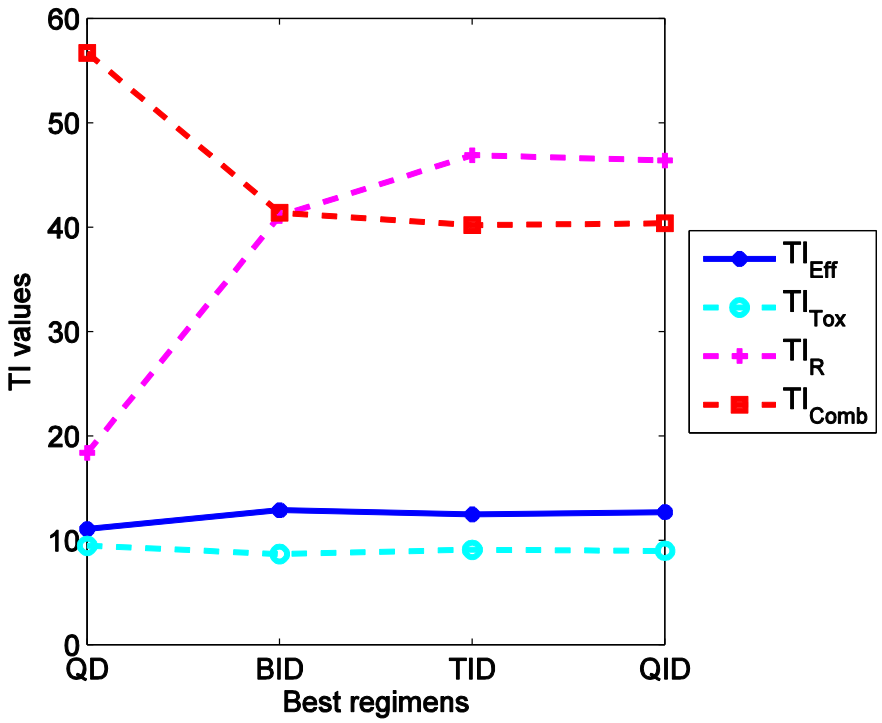

Fig. 11: TI values vs. best regimens. Time-based TIs (TI_{Eff}, TI_{Tox}) values are in hours whereas concentration-based TIs (TI_R, TI_{Comb}) values are in percentage

Remark: So far, different TIs have been discussed for a given dosing regimen. Our methodology can also help to find a set of suitable dosing regimens for a target therapeutic indicator value. For example, a group of QID regimens has been identified for a target of TI_{Comb} less than 40%, as illustrated in Table 3.

Table 3: Regimens satisfying $TI_{Comb} \leq 40\%$

Regimen	Dose (mg)	Time (h)	TI_{Comb} (%)
QID	100 200 100 200	0 6 12 18	39.8
QID	200 100 100 200	0 6 9 16	39.8
QID	200 100 100 200	0 7 9 16	39.8
QID	200 100 100 200	0 6 10 16	39.8
QID	200 100 100 200	0 5 12 17	39.8
QID	200 100 200 100	0 6 12 18	39.8
QID	100 200 100 200	0 5 11 17	40.0

IV. Discussion

Individualization of therapy is crucial for the optimization of therapeutic outcomes. However, its practical implementation continues to present challenges for the clinical community. Modeling and simulation approaches have proved to be an effective means that greatly contribute to this aspect [20]. However, these modeling based methods should be dictated by the contextual clinical needs. Indeed, while individual-based strategies can still be gold-standard in many therapeutic contexts [21, 22, 7], a high level of individualization, which generally involves *in situ* individual blood sampling, is always considered a burden to the health system.

In the current paper, we discuss how the dose adaptation process can capitalize on the potential of Pop-PK approaches, with additional therapeutic considerations. This was realized through the introduction of TIs that account for the probabilistic aspects of Pop-PK models but are in line with the classical metrics of therapy. To illustrate our approach in determining optimal drug regimens, carbamazepine was used as a drug model, with its Pop-PK model previously published in [12]. In fact, this Pop-PK model which was designed with a sub population of patients of 60 years and older, places our results within the group dosing category. While the TIs discussed here are defined in reference to TW, other therapeutic target concentrations can be used, as proposed by Holford [23, 24]. This is however beyond the context of the current work. In our analysis, when compared to the reported results for a TW range between 8 and 12 µg/mL, 20% more of elderly patients are exposed to toxicity all the time ($Prob_{300q12}(A)$ = 33.9% vs 9.5% for the reference TW) and 30% more during certain times for the TW ranging from 4 to 8 µg/mL (TI_{Comb} = 40.2% vs 10.9% for the reference TW). This is supported by

the suggestion of Rowan *et al* [19] who defined a dose reduction in 31.3% of patients because of side effects, which justifies our choice of a relative narrow TW for which the estimated toxicity increases by 30%.

Our predictions indicate significant changes for concentration-based TIs with increasing dosing frequency, though the results over all regimens, with the exception of QD, remain relatively close (Table 2 or Fig.11). For BID, 41.1% for TI_R and 41.4% for TI_{Comb}. Similar results are obtained for TID and QID, which are around 47% for TI_R and around 40% for TI_{Comb}. Moreover, both QD and BID regimens exhibit a high probability to belong to the hybrid categories NR/R, and R/A than TID and QID. TID has been found to be the best choice for the studied sub-population especially in terms of efficacy, with 200 mg × 3, at 0h, 8h and 16h (Table 2). This is in agreement with the findings by Rowan *et al* [19].

It is not surprising that the effective time of CBZ is not frequently mentioned in the literature, since it does not really inform the drug regimens performance, as illustrated in Fig.11. However, this concept is especially important for time dependent antimicrobials, where the time duration of concentrations exceeding the minimum inhibitory concentration or the minimum bactericidal concentration is the major determinant of bacteriologic efficacy of beta-lactam antibiotics. For example, 50% and 90% of the maximal bacterial kill rate were observed when ceftriaxone levels exceeded the minimum bactericidal concentration for only 50% and 60% of dosing intervals, respectively [25]. A future natural application of our approach would be to study constraints using a specific threshold that is to consider responders as patients who remain within the TW 80% of the time.

Additional to the problem of dose adaptation, our methodology can also be used to address question whether the same amount of dose, when partitioned differently, can always give rise to the same therapeutic effect. Our results showed that this commonly held assumption should be revised because equally dividing a fixed amount of daily dose and administering them at different times does not guarantee the same effect. Indeed, for a TDD of 600 mg, QD has an average TI_{Eff} of 11.1 hours compared to that for BID of 12.9 hours (Table 2). This difference is even more pronounced for their TI_R, with 18.4% and 41.1% for QD and BID, respectively (Table 2). This issue has previously been addressed in [26] for both time-dependent and concentration-dependent classes of antibiotics. However, this is the first time that this equivalent dose concept is introduced within a Pop-PK framework.

V. Conclusion

In this paper, a dose adaptation methodology, with the underlying possibility of a uniform dosing for a general population or certain sub-groups, has been proposed and developed. Based on the concept of TW, several therapeutic indices have been revisited and updated in the context of the Pop-PK approach to evaluate the performance of dosing regimens. This allowed us to determine the optimal regimen in terms of doses and dosing times. Moreover, we have shown the great potential of our method to identify flexible dosing regimens that can reach a given therapeutic target.

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List of abbreviations

A: adverse responders
BID: twice a day, *bis in die*
CAT: category
CBZ: carbamazepine
D: dose
NR: non-responders
NR/R: non-responders and responders, partially
NR/R/A: non-responders, responders and adverse responders, partially
PD: pharmacodynamics
PK: pharmacokinetics
Pop-PK/PD: population pharmacokinetic/pharmacodynamics
QD: once daily, *quaque die*
QID: four times a day, *quater in die*
R: responders
R/A responders and adverse responders, partially
τ: dosing time
TDD: total daily dose
TDM: therapeutic drug monitoring
TI: therapeutic indicator

TI_{Eff} : effective time
TI_{Tox}: toxic time
TI_{R}: responders
TI_{Comb}: comb
TID: three times a day, *ter in die*
TW: therapeutic window
TW_{max}: maximum of the therapeutic window range or minimum toxic concentration
TW_{min}: minimum of the therapeutic window range or minimum effective concentration

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