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Published in:
IFAC-PapersOnLine

DOI:
10.1016/j.ifacol.2020.12.421

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 53-2 (2020) 16061–16068

Model-based Strategies of Drug Dosing for Pharmacokinetic Systems

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Abstract: The aim of this paper is to report analytical and individual-based methods for antibiotic dose selection, that are based on tools from system and control theory. A brief system analysis of standard population pharmacokinetic models proves that such models are nonnegative and stable. Then, an input-output analysis leads to an open-loop control law which yields a dosing for the "average" patient, based on the equilibrium trajectory of the system. This approach is then incorporated into a "worst-case" analysis based on the monotony of the state trajectories with respect to the clearance (model parameter). Finally, an heuristic method of an estimated state feedback is presented. Thanks to numerical simulations, these methods were successively illustrated on a model describing the pharmacokinetic of meropenem, an intravenous antibiotic for treatment of severe sepsis.

Keywords: Pharmacokinetic systems, monotone systems, variability, drug dosing, asymptotic analysis, worst-case design, state estimation, state feedback

1. INTRODUCTION

Pharmacokinetics (PK) is a particular field of clinical pharmacology that studies the link between the dose of a drug administered to patients and the drug exposure (concentrations) over time. Thanks to mathematical modeling, clinical pharmacology is an interesting and promising field of application of systems and control theory (see e.g. Bailey and Haddad (2005)). Examples reported in the literature include the automated anesthesia (Bailey and Haddad (2005)) and the artificial pancreas (Haidar (2016)). They involve closed-loop control strategies that are based on a control system which continuously adjusts the rate of infusion of the drug.

This paper focuses on antibiotic (AB) treatments given by constant intravenous (IV) infusion at regular dosing intervals. The aim of this work is to provide model-informed dosing guidance (decision-making aid) for patients, taking into account their characteristics (covariates), as well as clinical or practical constraints (e.g. target concentration for drug efficacy, dosing interval, infusion duration, costs). One important challenge is how to take into account the random components included in population PK models to describe the interindividual (or interoccasion) variability in parameters and drug concentrations (see e.g. Mould and Upton (2012)).

Dosing of antibiotics is frequently based on Monte Carlo simulations from a mathematical pharmacokinetic model to assess the probability of target attainment (PTA) at a population level (see Musuamba et al. (2017)). These probabilities are compared across alternative dosing regimens to select the "optimal" one (see e.g. Li et al. (2006), Jaruratanasirikul et al. (2015) and Mattioli et al. (2016)).

In the present work, alternative tools are presented, aiming at improving dosing recommendations at individual level. The pros and cons of these methods are discussed. An input-output analysis leads to a formula which determines the amount of drug to administer (dose), given the covariates (patient level) and the practical/clinical constraints. It can be seen as an open-loop control law. This input-output formula is then used in combination with a "worst-case" analysis to take into account the variability and the unknown realization of the random variables included in the model. The design of an (estimated) state feedback is also considered. The dosing strategies (control laws) reported in this paper are general methods applicable to any PK system described by a linear time-invariant state-space representation. The numerical results are reported for a case study drug , viz. meropenem, a β-lactam antibiotic used for treating severe infections (see e.g. Veiga and Paiva (2018) and references therein).

2. POPULATION PHARMACOKINETIC MODEL

This section describes the state-space representation of a general mammillary compartmental model and its interpretation in terms of pharmacokinetic model. A numerical example is given for meropenem.

2.1 State-space representation

A population pharmacokinetic (popPK) model describes the PK of a drug of interest at population level, accounting

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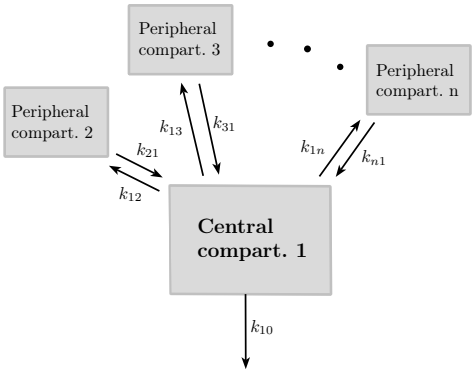


Fig. 1. A general n-compartment mammillary model

for different sources of variability in drug concentrations. A n-compartment popPK model (mammillary compartmental model, see Fig. 1) is described by

$$\dot{x}(t) = Ax(t) + bu(t), \quad y(t) = Cx(t) \tag{1}$$

where

$$A = \begin{pmatrix} -k_{10} - \sum_{j=2}^{n} k_{1j} & k_{21} & k_{31} & \cdots & \cdots & k_{n1} \\ k_{12} & -k_{21} & 0 & 0 & \cdots & 0 \\ k_{13} & 0 & -k_{31} & 0 & \cdots & \vdots \\ \vdots & \vdots & 0 & \ddots & & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & 0 \\ k_{1n} & 0 & 0 & \cdots & 0 & -k_{n1} \end{pmatrix} \tag{2}$$

and

$$b = (1\ 0\ \cdots\ 0)^T, \quad C = \begin{pmatrix} 1/S_1 & 0 & 0 \cdots 0 \\ 0 & 1/S_2 & 0 \cdots 0 \end{pmatrix}. \tag{3}$$

where the parameters can include random components. In the following deterministic analysis, unless otherwise stated, the PK parameters are assumed to be fixed to their nominal values.

This results in a transfer function of the form $\hat{G}(s) = \left(\hat{G}_1(s)\ \hat{G}_2(s)\right)^T$. The parameters k_{ij} [h^{-1}] represent rate constants and are positive. The state vector $x(t) = (x_1(t)\ x_2(t)\ x_3(t)\ \cdots\ x_n(t))^T$ corresponds to the drug amounts [g] in each compartment. Without lost of generality, x_1 and x_2 correspond to the plasma and the site of infection, respectively. The input function $u(t)$ is a piecewise constant function that corresponds to the drug infusion rate [g/h] into the central compartment (plasma). The output vector $y(t) = (y_1(t)\ y_2(t))^T$ corresponds to the drug concentrations [mg/L] in the plasma and at the infection site. For all $j \in \{1, 2\}$, S_j is a scaling factor used to convert an amount of drug [g] in concentration in units that are consistent with the observed values (e.g. [mg/L]). It is a scale volume of distribution $S_j = V_j/usv_j$, where *usv* stands for "unitless scalar value". The *volume of distibution* [L] is a virtual physiological concept defined by the volume in which the drug would be distributed if the compartment drug concentration was equal to the plasma concentration (i.e., for all $i \in \{1, \ldots, n\}$, $c_p[g/L] = x_i/V_i$). Note that the concentrations at the actual effect site are not always described/predicted by the model: This depends on the data available to adequately estimate the values of the relevant parameters. In that case, the matrix C becomes $C = (1/S_1\ 0\ \cdots\ 0)$.

The input function $u(t)$ (see Fig. 2) considered here depends on three parameters: the dose [g] denoted by D, the duration of the infusion [h] denoted by Δ, and the time between two doses (dosing interval) [h] denoted by T. For all $t \geq 0$,

$$u(t)\,[\text{g/h}] = \begin{cases} D/\Delta & \text{if } (t \bmod T) < \Delta \\ 0 & \text{if } (t \bmod T) \geq \Delta \end{cases} \tag{4}$$

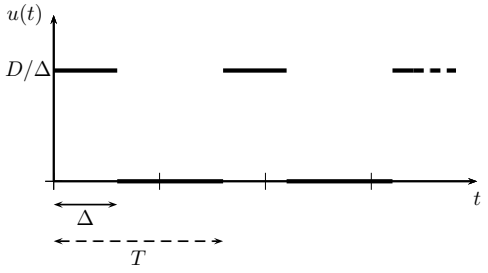


Fig. 2. System input function: drug infusion rate vs. time

Observe that Δ is necessarily smaller than T. This input structure is consistent with the current mode of administration of meropenem (case study). Administration by intravenous infusion of a fixed dose (called maintenance dose) at regular intervals is recommended for meropenem (see MHRA (2019)). Besides, continuous administration for treating severe infection has been studied recently (see e.g. Veiga and Paiva (2018) and Sjövall et al. (2018)). The latter can be seen as a limit case of the mode of administration considered here ($\Delta = T$).

2.2 System analysis

Clearly, the matrix $A \in \mathbb{R}^{n\times n}$ is compartmental, i.e. A is Metzler (all its off-diagonal elements are nonnegative) and $\sum_{i=1}^{n} a_{ij} \leq 0$ for all $j \in \{1, \ldots, n\}$ (Haddad et al., 2010, Definition 2.10).

In what follows, for any vector $v \in \mathbb{R}^l$, $v \gg 0$ ($v \ll 0$, respectively) means that all components of v are positive (negative, respectively).

As the state variables of (1) represent amounts of drug, it is expected that the state trajectories stay in the nonnegative orthant of $\mathbb{R}^n$ for all nonnegative initial conditions and nonnegative admissible input functions. Since A is a Metzler matrix and b is a nonnegative matrix, it is indeed the case by (Haddad et al., 2010, Proposition 4.1).

Proposition 1. The popPK system given by (1)-(3) is nonnegative.

Moreover, since the drug is eliminated by the organism, the following result should also be expected.

Proposition 2. The popPK system given by (1)-(2) is internally (exponentially) stable.

Proof. Any vector $\mu = (\mu_1\ \mu_2\ \mu_3\ \cdots\ \mu_n)^T$ such that $\mu_2 = \mu_3 = \cdots = \mu_n > 0$ and $k\mu_2 < \mu_1 < \mu_2$, where

$$k := \frac{k_{12} + k_{13} + \cdots k_{1n}}{k_{10} + k_{12} + k_{13} + \cdots k_{1n}} \in (0, 1),$$

is such that $A^T\mu \ll 0$. The conclusion follows by (Chellaboina et al., 2009, Proposition 7). □

2.3 Model of meropenem

A data set of measured concentrations in the plasma and at the site of infection (epithelial lining fluid (ELF)), from patients with severe nosocomial pneumonia, was available for model development (PROMESSE study, Frippiat et al. (2015)). A two-compartment model provided an adequate fit to the observed plasma concentrations. An additional compartment was added to describe the (sparse) concentrations measured in the ELF.

$$\begin{cases} \dot{x}_1(t) = -k_{10}x_1(t) - k_{12}x_1(t) - k_{13}x_1(t) + \\ \qquad\qquad k_{21}x_2(t) + k_{31}x_3(t) + u(t) \\ \dot{x}_2(t) = k_{12}x_1(t) - k_{21}x_2(t) \\ \dot{x}_3(t) = k_{13}x_1(t) - k_{31}x_3(t) \end{cases}$$

This system is schematized in Fig. 3. In this representation, the physiological parametrization (based on the concepts of volume of distribution and clearances) is prefered. The *(systemic) clearance* (CL [L/h]) is defined by the virtual volume of plasma cleared of drug per time unit, so that $CL = k_{10}V_1$. Likewise, the *intercompartmental clearance* (Q_{1i} and Q_{i1}, $i \in \{2, 3, \ldots, n\}$, [L/h]) is defined by the virtual volume of distribution cleared of drug, to go into the linked compartment, per time unit, so that $Q_{1i} = k_{1i}V_1$ and $Q_{i1} = k_{i1}V_i$. At distribution equilibrium, the same amount of drug goes from the central to the peripheral compartment and from the peripheral to the central compartment, i.e. $k_{1i}x_1 = k_{i1}x_i$, or equivalently $Q_{1i} = Q_{i1} =: Q_i$. To make notations more explicit, V_1, V_2, V_3, Q_2 and Q_3 are written V_c, V_E, V_p, Q_E and Q_p, respectively (c for central, E for ELF and p for peripheral), such that

$$CL = k_{10}V_c, Q_E = k_{12}V_c, Q_E = k_{21}V_E,$$
$$Q_p = k_{13}V_c \text{ and } Q_p = k_{31}V_p.$$

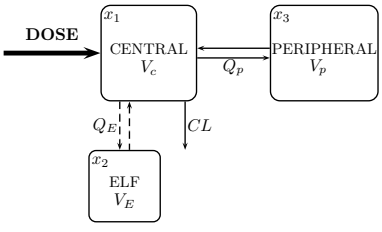


Fig. 3. PopPK model of meropenem describing plasma and ELF concentrations

Known physiological relationships were incorporated into the model. For example, the renal function influences the total clearance, as shown below with an allometric model:

$$CL_i = TVCL\left(\frac{GFR_i}{GFR_{\text{med}}}\right)^{\theta_{GFR}} \quad (5)$$

where CL_i, which denotes the clearance value of the i^{th} individual (without interindividual variability (IIV)), is a function of the typical parameter value in the population ($TVCL$) and of the glomerular filtration rate (GFR) of the individual i (GFR_i), normalized by the median value (GFR_{med}). These patient characteristics, which affect the PK of a drug, are called *covariates*. IIV is described by exponential models, meaning that parameters are assumed to be log-normally distributed, as exemplified below for the clearance:

$$CL_{\text{IIV}_i} = CL_i \cdot \exp(\eta_i) \quad (6)$$

where $CL_{i_{\text{IIV}}}$ is the clearance value of the i^{th} individual (with IIV), CL_i is the fixed effect (parameter nominal value of the i^{th} individual) and η_i is the individual realization of the random variable $\eta \sim \mathcal{N}(0, \omega^2)$ (random effect). The median of this log-normal distribution is given by CL_i, which corresponds to the realization of the random variable equal to zero.

Estimated model parameters are reported in Table 1. Two covariates were included in the model: the weight (WT) and the glomerular filtration rate (GFR), on the volumes of distribution and the clearance, respectively.

Table 1. PopPK model parameter estimates

Param.	Estimate	%RSE
$\boldsymbol{CL}$ (L/h)	7.94	4.95
IVV (ω^2(%CV))	0.126 (35.5)	9.41
θ_{GFR}	0.722	8.81
$\boldsymbol{V_c}$ (L)	13.6	6.27
IVV (ω^2(%CV))	0.14 (37.4)	16.8
θ_{WT}	0.949	30.2
$\boldsymbol{Q_E}$ (L/h)	6.73	18.3
$\boldsymbol{V_E}$ (L)	4.08	33.4
IVV (ω^2(%CV))	1.76 (133)	20.5
θ_{WT}	1.04	114
$\boldsymbol{Q_p}$ (L/h)	8.22	18.2
IVV (ω^2(%CV))	0.187 (43.2)	28.1
$\boldsymbol{V_p}$ (L)	10.1	15.4
$\boldsymbol{V_E/S_2}$ (usv_2)	249	9.69

RSE: relative standard error
CV: coefficient of variation

3. INDIVIDUALISED DRUG DOSING

In the scientific literature, model-based antibiotic dosing is mostly based on systemic concentrations, Monte Carlo simulations at population level and empirical comparison of successive dosing regimens through PTA analyses (see e.g. Usman et al. (2017)). However, infection-site concentrations are reported to be better predictors of antibiotic effect (see e.g. Lodise et al. (2011) and Veiga and Paiva (2018)) and there has been an increasing interest in the individualization of antibiotic dosing (see e.g. Sime et al. (2015) and Cotta et al. (2015)). The advantages of the analytical approaches presented below include the ability to select a dose based on patient's characteristics (covariates) and on systemic or infection-site concentrations. These methods were successfully applied to meropenem dosing thanks to the numerical popPK model described above, and compared to corresponding results of PTA analysis.

3.1 Input-output analysis

In the following, the state matrix $A \in \mathbb{R}^{n\times n}$ in (1) is assumed to have n distinct eigenvalues. Moreover, observe that the entries of the matrix A correspond to the individual patient, as the PK parameters are computed on the basis of patient characteristics, consistenly with the covariate-parameter models, e.g. as in (5).

Proposition 3. Consider the popPK system (1)-(3) with an input function of the form (4). The zero-state system

response $y(t)$ is given as follows, where N_t denotes the number of administrations already received at time t (including the ongoing administration, if appropriate): for all $j \in \{1,2\}$ and for all $t \geq 0$,

• if $(t \bmod T) < \Delta$ (during infusion),

$$y_j(t) = \frac{D}{\Delta}\left[\underbrace{\sum_{l=0}^{N_t-2}\sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}e^{\lambda_i(t-lT)}(1-e^{-\lambda_i\Delta})}_{\text{previous administrations}} + \underbrace{\sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}(e^{\lambda_i(t-(N_t-1)\,T)}-1)}_{\text{ongoing infusion}}\right]$$

• if $(t \bmod T) \geq \Delta$ (after infusion),

$$y_j(t) = \frac{D}{\Delta}\sum_{l=0}^{N_t-1}\sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}e^{\lambda_i(t-lT)}(1-e^{-\lambda_i\Delta}).$$

Coefficients F_{ji} and λ_i ($i \in \{1,2,3,\dots n\}$, $j \in \{1,2\}$) are directly related to the model parameters: λ_i denote the eigenvalues of the matrix A and F_{ji} are the residuals of the transfer function $\hat{G}_j(s)$ in the eigenvalues λ_i, i.e. $F_{ji} = \lim_{s\to\lambda_i}\left(\hat{G}_j(s)\,(s-\lambda_i)\right)$.

Hint. Compute the inverse Laplace transform of $\hat{y}(s) = \hat{G}(s)\hat{u}(s)$. The j^{th} component of the transfer function can be written in partial fraction expansion as:

$$\hat{G}_j(s) = \sum_{i=1}^{n}\frac{F_{ji}}{s-\lambda_i}.$$

To compute the Laplace transform $\hat{u}(s)$, the input function should be considered as a superposition of functions of the form

$$U_i(t) = K\mathbf{1}_{[iT,iT+\Delta[}(t), \quad t \geq 0$$

where $i \in \mathbb{N}$ and $\mathbf{1}_I$ is the characteristic function of the subset I. □

Let us denote by $y^N(\tilde{t})$ ($\tilde{t} \in [0,T[$) the system response on the N^{th} dosing interval, i.e. $y(t) = y^N(\tilde{t})$ where $t \in [(N-1)T, NT[$ and $\tilde{t} = t \bmod T$. The new variable $\tilde{t}$ indicates the position in the dosing interval after N administrations. Due to system stability, the concentration trajectory converges to an equilibrium trajectory, which will be called steady output (known in the pharmacology literature as the "steady-state" or "plateau"), i.e.

$$\lim_{N\to\infty} y^N(\tilde{t}) = y^\infty(\tilde{t})$$

Proposition 4. Consider the popPK system (1)-(3) with an input function of the form (4). The output trajectory converges to an equilibrium trajectory, i.e., for all $\tilde{t} \in [0,T[$,

$$y^N(\tilde{t}) - y^\infty(\tilde{t}) \xrightarrow{N\to\infty} 0$$

where the plateau y^∞ is given, for all $j \in \{1,2\}$, by

• if $\tilde{t} \in [0,\Delta]$,

$$y_j^\infty(\tilde{t}) = \frac{D}{\Delta}\left[\sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}\frac{e^{\lambda_i\tilde{t}}(1-e^{-\lambda_i\Delta})}{e^{-\lambda_i T}-1} + \sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}(e^{\lambda_i\tilde{t}}-1)\right]$$

• if $\tilde{t} \in [\Delta,T[$,

$$y_j^\infty(\tilde{t}) = \frac{D}{\Delta}\sum_{i=1}^{n}\frac{F_{ji}}{\lambda_i}\frac{e^{\lambda_i(\tilde{t}-T)}(1-e^{-\lambda_i\Delta})}{e^{-\lambda_i T}-1}.$$

It follows from Proposition 4 that the concentrations at the end and at the beginning of the dosing interval are equal: $\lim_{\substack{\tilde{t}\longrightarrow T\\ >}} y^\infty(\tilde{t}) = y^\infty(0)$, such that we can define

$$y^\infty(T) := y^\infty(0).$$

The concentration $y_1^\infty(T)$ corresponds to the minimal *plasma* concentration on the dosing interval (the lowest concentration observed just before a new administration). However, if there is a time disconnect between systemic and infection-site concentrations (due to e.g. delayed tissue penetration), $y_2^\infty(T)$ does not correspond to the minimal concentration at the site of infection. In the following, y and y^∞ are denoted by $y(D,\Delta,T;t)$ and $y^\infty(D,\Delta,T;\tilde{t})$, respectively, in order to highlight the dependence with respect to the input parameters. From now on, the infusion duration Δ [h] and the length of the dosing interval T [h] are assumed to be fixed.

3.2 Input-output formula for drug dosing

A natural approach consists in solving the following equation with respect to D:

$$y_j^\infty(D,\Delta,T;\tilde{t}=t^*) = \alpha \tag{7}$$

in order to compute the dose D [g] (*maintenance dose*) required to reach, at steady-state, a target (systemic or infection-site) concentration α [mg/L] at a given time $t^* \in [0,T]$. This relevant time t^* depends on the clinical objective. If it is required to reach this target concentration at the very first infusion, we should solve the following equation with respect to D:

$$y_j(D,\Delta,T;t=t^*) = \alpha.$$

This dose is called *loading dose* and is denoted by D_L. The loading dose is thus given at the first administration, i.e., for all $t \in [0,\Delta[$, $u(t) = D_L/\Delta$. The maintenance dose is then given at the following administrations, i.e., for all $t \in [iT, iT+\Delta[$ ($i \in \mathbb{N}_0$), $u(t) = D/\Delta$.

Meropenem is a time-dependent AB, meaning that treatment efficacy is measured in terms of percentage of time between two doses during which the drug concentration exceeds the minimal inhibitory concentration (MIC) (%T>MIC). In critically ill patients, it can be required to achieve 100 %T>MIC to ensure optimal clinical outcome (see e.g. Goncalves-Pereira et al. (2014) and Sime et al. (2015)). Clinical breakpoints for MIC are computed from in vitro experiments and provided by EUCAST (European Committee on Antimicrobial Susceptibility testing). They are also reported in different summaries of product characteristics of medicinal products containing meropenem (e.g. MHRA (2019)). Meropenem has a slight time disconnect

between systemic and infection-site concentrations, such that the time t^* related to 100 %T>MIC at the site of infection (ELF) is T. In this case, the analytical solution to (7) is given in the proposition below.

Proposition 5. Consider the popPK system (1)-(3) with an input function of the form (4). For any target concentration $\alpha > 0$ [mg/L], the *maintenance dose* [g] required to maintain the steady output trajectory y_j^∞ above the lower bound α is given by

$$D = \frac{\alpha\Delta}{\sum_{i=1}^{n} \frac{F_{ji}}{\lambda_i} \frac{1-e^{-\lambda_i\Delta}}{e^{-\lambda_i T}-1}}, \tag{8}$$

where j denotes the desired output ($j = 1$ for plasma concentration and $j = 2$ for infection-site concentration). For all $i \in \{1, 2, 3, \dots n\}$, λ_i denote the eigenvalues of the matrix A and F_{ji} are the residuals of the transfer function $\hat{G}_j(s)$ in λ_i.

This formula is called input-output (I/O) formula in what follows.

The parameters F_{ij} and λ_i are directly related to the PK parameters and, consequently, to the covariate values and the realization of the random variables. However, these realizations are, *a priori*, unknown. A way to overcome this difficulty is to incorporate the I/O formula into a worst-case analysis.

3.3 "Worst-case" analysis

A sensitivity analysis was performed on the popPK model described in Subsection 2.3 and revealed that, among all the PK parameters, the clearance has the most important influence on the model predictions. Therefore, we call "worst-case" the case of a patient for which the clearance value corresponds to the worst clearance regarding the objective to be achieved. All the other PK parameters are assumed to be fixed at their nominal/median value (realizations of the related random variables are set to zero).

Proposition 6. Consider the popPK system (1)-(2), where $b \in \mathbb{R}^{n\times 1}$ is any nonnegative matrix. The state trajectory $x(t; CL)$ is decreasing with respect to the clearance parameter, i.e. if $0 < CL_1 \leq CL_2$ and if $x(0, CL_1) \geq x(0, CL_2)$, then, for all $t \geq 0$, $x(t; CL_1) \geq x(t; CL_2)$.

Proof. Using the physiological parametrization, the state matrix A reads as:

$$A = \begin{pmatrix} -\frac{CL}{V_1} - \sum_{j=2}^{n} \frac{Q_j}{V_1} & \frac{Q_2}{V_2} & \frac{Q_3}{V_3} & \cdots \\ \frac{Q_2}{V_1} & -\frac{Q_2}{V_2} & 0 & \cdots \\ \frac{Q_3}{V_1} & 0 & -\frac{Q_3}{V_3} & 0 \\ \vdots & \vdots & 0 & \ddots \end{pmatrix}.$$

In the following, A is denoted A_{CL} to highlight the dependence with respect to the clearance parameter. The state trajectories $x(t; CL_1)$ and $x(t; CL_2)$ (where $CL_1 \leq CL_2$) are the solutions of the following Cauchy problems, respectively:

$$\begin{cases} \dot{x} = A_{CL_1}x + bu, & x(0) = x_0 \\ \dot{\tilde{x}} = A_{CL_2}\tilde{x} + bu, & \tilde{x}(0) = \tilde{x}_0 \end{cases}$$

where $0 \leq \tilde{x}_0 \leq x_0$. The state matrix A_{CL_2} can be written as

$$A_{CL_2} = A_{CL_1} + \begin{pmatrix} -\epsilon & 0 & \cdots \\ 0 & 0 & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix},$$

where $\epsilon = \frac{CL_2 - CL_1}{V_1}$. The dynamics of $x - \tilde{x}$ is described by the following differential equation:

$$\frac{d}{dt}(x-\tilde{x}) = A_{CL_1}(x-\tilde{x}) + (A_{CL_1} - A_{CL_2})\tilde{x},$$

which obviously describes a nonnegative system. Consequently, $x(t; CL_1) \geq x(t; CL_2)$ for all $t \geq 0$. □

Therefore, this result holds also for the equilibrium trajectory, i.e. whenever $0 < CL_1 \leq CL_2$, for all $\tilde{t} \in [0, T]$, $y^\infty(\tilde{t}; CL_1) \geq y^\infty(\tilde{t}; CL_2)$. Thanks to this result and given that the objective to be achieved is to maintain the steady output above a fixed level (MIC) for 100 % of the time of the dosing interval, the worst clearance corresponds to its highest value. However, according to identity (6), i.e.

$$CL_{\text{IIV}_i} = CL_i \cdot \exp(\eta_i),$$

we define the **"worst-case" realization** at $p \cdot 100\,\%$, where $0 < p < 1$ and $p = k/q$, as the k^{th} q-quantile. For example, the "worst-case" realization at 90 % ($p = 0.9$) is the 9^{th} deciles: $\eta^* = 1.28 \cdot \omega$.

Proposition 7. Consider the popPK system (1)-(3) with an input function of the form (4). Assume that the clearance parameter is set to its "worst-case" value at $p \cdot 100\,\%$. Then, for any target concentration level $\alpha > 0$ [mg/L], the *maintenance dose* [g] computed according to the I/O formula (8) enables to maintain the steady output trajectory y_j^∞ above the threshold α for $p \cdot 100\,\%$ of the simulated individuals, provided that all their PK parameters, except the clearance, are fixed to their nominal value.

3.4 PTA analysis

The methods, described in Subsections 3.2 and 3.3, to compute an individualized dose were applied to the developed model of meropenem (see Section 2.3). Figure 4 represents a simulated pharmacokinetic profile y_j^∞ (here, $j = 2$) using this model and an arbitrary dose. If we consider a high number of simulations denoted by n_{sim}, the probability of reaching 100 %T>MIC is estimated by:

$$\frac{\#\{y_j^\infty \mid y_j^\infty(T) > MIC\}}{n_{\text{sim}}}.$$

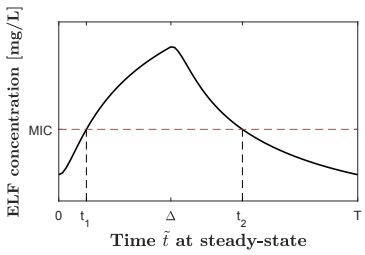


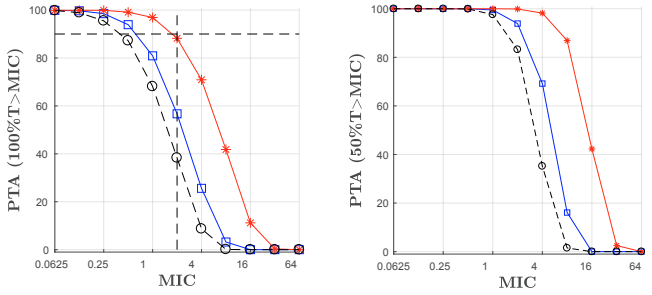
Fig. 4. Simulated PK profile

For each simulated PK profile, t_1 and t_2 denote the time points such that $t_1 < t_2$, $y_j^\infty(t_1) = \text{MIC}$ and

$y_j^\infty(t_2) = \text{MIC}$. The probability of reaching 50 %T>MIC is estimated by:

$$\frac{\#\{y_j^\infty \mid t_2 - t_1 \geq T/2\}}{n_{\text{sim}}}.$$

An analysis of the probabilities of target attainment (PTA) can be used to compare different dosing regimens. Two doses were computed by the I/O formula ($\alpha = 2$ mg/L, $j = 2$, $T = 8$ h and $\Delta = 0.5$ h), in the nominal case and in the "worst-case" at 90 % (see Propositions 5 and 7, respectively). The respective dosing regimens (1.52g/8h - 30'-infusion and 4.34g/8h - 30'-infusion) were simulated using 1000 virtual patients with a body weight of 75 kg and a level of glomerular filtration rate of 65 mL/min (Monte Carlo simulations). Figure 5 represents, for each dosing regimen, the percentage of simulated subjects which reached the PK/PD targets (100 %T>MIC or 50 %T>MIC) for different MIC in ELF (site of infection). They are compared with the dose recommended by the provider for adult patients with pneumonia: 1g by IV infusion over 30-minutes every 8 hours (MHRA (2019)). The MIC 2 mg/L is the EUCAST MIC breakpoint for susceptible strains.



(a) (b)

Fig. 5. PTA in ELF based on model predictions ($n_{\text{sim}} = 1000$), blue line with squares, red line with stars and black line with circles correspond to the dosing regimens associated to the nominal case, the "worst-case" and the provider recommendation, respectively

The dose associated to the "worst-case" provides a probability of success of about 90 % for a minimal inhibitory concentration of 2 mg/L, which was the target concentration used in the I/O formula. This conservative dose (4.34g) is obviously higher than the first one (1.52g). However, this dosing strategy enables to ensure that a larger proportion of the patients will reach the PK/PD target (Figure 5). That leaves open the question of a trade-off between the dose (in terms of risk of toxicity (Beumier et al. (2015)), cost, etc.) and the high probability to achieve the target.

3.5 Drawbacks and advantages of the I/O approach

The main drawbacks are related to its open-loop nature and the determistic approach of a problem including variability. However, this method leads to a feedback control law that is developed in the following section. An additional weakness is the determination of the relevant time t^* (see equation (7)) in the case of AB with important time disconnect between systemic and local concentrations. Besides, this I/O formula for dose selection has several clinical advantages:

(1) It is an analytical method, in contrast to the empirical (simulation-based) PTA approach. In case of meropenem, the PK/PD target is 40 % to 100 %T>MIC (see e.g. Frippiat et al. (2015) or Usman et al. (2017)).
(2) Provided that the model describes the local concentrations, the I/O formula can be used with a target concentration at the site of effect/infection ($j = 2$).
(3) The covariates are properly taken into consideration to compute an individualized drug dosing (modulo the realization of the random variables), unlike the standard PTA method which is most commonly performed at a population level.

4. STATE ESTIMATION AND FEEDBACK CONTROL LAW

In this section, the output matrix is given by

$$C = (1/S_1 \ 0 \ 0 \cdots \ 0)$$

in order to correspond to the output measured at regular interval for the state estimation, namely the plasma concentration. Recall that

$$C = \begin{pmatrix} 1/S_1 & 0 & 0 \cdots 0 \\ 0 & 1/S_2 & 0 \cdots 0 \end{pmatrix}.$$

is the one included in the transfer function, considered in the I/O formula (8) in Proposition 5, to convert amounts of drug in concentrations in both plasma and infection site.

In order to develop a state estimator, we consider the dynamical system (1)-(3) in a discrete-time setting. Let us denote by N_1 and N_2 the numbers of sampling intervals on any interval of the form $[iT, iT + \Delta[$ and $[iT + \Delta, (i+1)T[$, respectively ($i \in \mathbb{N}$). The parameters N_1 and N_2 are chosen to be the smallest integer such that $\frac{T}{\Delta} = 1 + \frac{N_2}{N_1}$ (i.e. same discretization steps). In the following, we will use the notations $h := \Delta/N_1$ and $N := N_1 + N_2$ to denote the discretization step and the total number of sampling intervals on any interval of the form $[iT, (i+1)T[$, respectively ($Nh = T$). The recurrence equation describing the state dynamics in discrete-time is given, for all $k \in \mathbb{N}$, by

$$x[k+1] = \tilde{A}x[k] + \tilde{b}u[k], \quad y[k] = Cx[k] \tag{9}$$

where $\tilde{A} = e^{Ah}$, $\tilde{b} = \int_0^h e^{A(h-t)}b\,dt$ and

$$u[k] = \begin{cases} D_i/\Delta & \text{if } (k \bmod N) < N_1 \quad (i = \lfloor k/N \rfloor) \\ 0 & \text{if } (k \bmod N) \geq N_1, \end{cases}$$

where D_i denotes the dose administered on the $(i+1)^{\text{th}}$ dosing interval and the symbol $\lfloor \cdot \rfloor$ denotes the integer part of a real number.

The discrete-time dynamical system above is obtained by discretizing the integral form of the state trajectory of (1):

$$x(t) = e^{At}x_0 + \int_0^t e^{A(t-\tau)}bu(\tau)d\tau$$

where the control input $u(t)$ is assumed constant on the sampling intervals. Moreover, since $u(t)$ is assumed to be piecewise constant on the dosing intervals, for the same initial condition ($x[0] = x(0)$), the solution of (9) is

equal to the solution of the continuous-time model at the sampling times, i.e. for all $k \in \mathbb{N}$, $x[k] = x(kh)$.

The nonnegativity and the internal stability of the discrete-time model (Haddad et al., 2010, Chapter 2) are directly derived from the nonnegativity and the internal stability of the continuous-time system.

The time scale of the state estimator is larger than the one of the dynamics (9) because we assume that the plasma concentration is measured only before each new administration, i.e. at time iT for all $i \in \mathbb{N}_0$. The state estimator is described, for all $i \in \mathbb{N}$, by

$$\begin{cases} \tilde{x}[i+1] = \mathcal{A}\tilde{x}[i] + \mathcal{B}u[i] + \mathcal{L}(\tilde{y}[i] - y[iN]), \quad \tilde{x}[0] = 0 \\ \tilde{y}[i] = C\tilde{x}[i] \end{cases}$$

where, $\mathcal{A} = \tilde{A}^N$, $\mathcal{B} = \sum_{l=N_2}^{N-1} \tilde{A}^l \tilde{b}$. For all $i \in \mathbb{N}$, $\tilde{x}[i]$ is the estimated state of $x[iN]$ and, therefore, of $x(iT)$. The output injection matrix $\mathcal{L}$ has to be designed such that $\mathcal{A} + \mathcal{L}C$ is stable, i.e., for all $\lambda \in \sigma(\mathcal{A} + \mathcal{L}C)$, $|\lambda| < 1$. Standard methods, such as pole placement or Kalman filter, can be used to determine $\mathcal{L}$.

The estimated state feedback described below is an heuristic method which is reported as an algorithm. It is based on the superposition principle: for any doses $D_1, D_2 > 0$, $y^\infty(D_1 + D_2, \Delta, T; \tilde{t}) = y^\infty(D_1, \Delta, T; \tilde{t}) + y^\infty(D_2, \Delta, T; \tilde{t})$. In this approach, we assume that empirical Bayes estimations (EBEs) are performed at a certain moment to recalculate the individual's PK parameter after appropriate measures of concentrations, as implemented in different software and website (see e.g. Wicha (2018)). The updated model describes then how the drug is behaving in that particular patient (Vinks (2002)). The Bayesian estimations of the random parameters are the most likely values given the observations and the population model, i.e. $\eta_i^* = \text{argmax}\, P(\eta_i | y_i, A, b, C)$ (see e.g. Mould and Upton (2013) and Nguyen et al. (2017)).

Algorithm 1. (Estimated state feedback).

Data: The typical parameter values of the model and the covariates of a virtual patient are known. The realizations of the random variables are unknown. The desired concentration level required in the j^{th} compartment is still denoted by α.

Initial step: The system $[A, b, C]$ is the nominal model. The first dose D_0 is computed thanks to the I/O formula (8). The output injection matrix $\mathcal{L}$ and the discrete-time state estimator are determined. For all $i \in \{0, \dots, i_0 - 1\}$, $D_i = D_0$. At time $i_0 T$, we define $GAP := \alpha - \tilde{x}_j[i_0]/S_j$. Replacing α by GAP in Formula (8) yields the following estimated state feedback law for dose adjustment:

$$\widetilde{D} = \frac{GAP \cdot \Delta}{\sum_{i=1}^{n} \frac{F_{ji}}{\lambda_i} \frac{1 - e^{-\lambda_i \Delta}}{e^{-\lambda_i T} - 1}}, \tag{10}$$

The dose is updated following $D_{i_0} = D_0 + \widetilde{D}$.

Intermediate step: The model is updated after EBEs. From now, $[A, b, C]$ corresponds to the PK parameters of the virtual patient. The output injection matrix $\mathcal{L}$ and the discrete-time state estimator are also updated, as well as the time between two adjustments of the dose (discussed in the remark below).

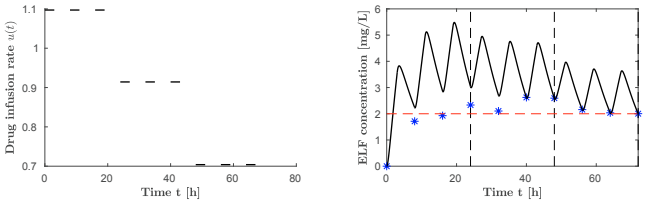
Recurrence step: For all $n \in \mathbb{N}_0$ and for all $i \in \{i_{n-1}, \dots, i_n - 1\}$, $D_i = D_{i_{n-1}}$. At time $i_n T$, we define $GAP := \alpha - \tilde{x}_j[i_n]/S_j$. The dose is updated following $D_{i_n} = D_{i_{n-1}} + \widetilde{D}$, where $\widetilde{D}$ is given by (10).

Remark. The dose adjustement (state feedback) should be performed at steady-state. The steady-state is assumed to be reached after 5 time constants τ related to the dominant mode ($\tau := |1/\lambda_F|$, where λ_F is the Frobenius eigenvalue (Horn and Johnson (1985))). The dominant mode has then reached a value less than 1 % of its initial value. The concept of time constant is close to the PK concept of half-life (see e.g. Toutain and Bousquet-Mélou (2004)). Eventually, the relevant dosing intervals to update the dose are given by:

$$\begin{cases} i_0 = \lfloor 5\tau_0/T \rfloor + 1 \\ i_n = i_{n-1} + \lfloor 5\tau/T \rfloor, \quad \forall n \in \mathbb{N}_0 \end{cases}$$

where τ_0 is the time constant of the nominal model (i.e. before the EBEs) and τ the time constant of the updated model (i.e. after the EBEs).

Let us consider a virtual patient with a body weight of 75 kg and a level of glomerular filtration rate of 65 mL/min. Figures 6(a) and 6(b) show the input function and the PK profile attributable to this feedback control law. The initial AB treatment was ∼1.1 g over 3 hours every 8 hours. The Bayesian estimations to recalculate the model parameters were performed at the end of the third dosing interval ($i_0 = 3$). The time constant was then re-evaluated for the updated model. The successive doses were 1.09 g, 0.914 g and 0.704 g. In this simulation, the control law was based on the estimated state at the infection site $\tilde{x}_2[i_n]$ ($j = 2$), while the measures were plasma samples.



(a) Input function (b) PK profile

Fig. 6. Illustration of the estimated state feedback algorithm, blue points correspond to the estimated state corrected by the scaling factor

5. CONCLUSION

Systems and control theory provides tools to address issues in clinical pharmacology, including dosing for clinical care of (critically ill) patients. In this paper, related to time-dependent antibiotics, we have described approaches to compute and update the dose/infusion rate of each administration, assuming that the infusion duration and the length of the dosing interval are fixed (previous clinician's decision).

Currently, the published model-based methods for AB dosing are mostly based on Monte Carlo simulations and related (systemic) PTA, such that they provide dosing recommendations at a population level. In the input-output approach presented here, it is no longer required

to compare different dose levels by numerical simulations. We have derived a formula in order to express the dose with respect to the infusion duration Δ and the dosing interval T, allowing to reach a predifined concentration (in the plasma or at the infection site) for each patient of interest, given their relevant characteristics (covariates). This input-output formula can then be incorporated into a worst-case analysis (which computes a conservative value, but takes into account the variability in drug concentrations), or can be used to design an estimated state feedback that is based on measurements of plasma concentration equally spaced in time. The drug dosing strategies derived here should be interpreted as decision-making aids providing guidelines to physicians. Meropenem was presented as a case study. Through numerical simulations, the methods were successfully applied with acceptable robustness and reliable results.

Except for the system analysis (Section 2.2) which is specific to compartmental popPK models, all the results can be applied e.g. to PBPK models. Such models are good candidates as they are more robust to predict concentrations in different populations and settings: the model structure and parameters are less dependent on the available data because they are based on pathophysiology considerations and drug's pharmacological properties (see Thémans et al. (2019) and references therein).

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