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ORIGINAL PAPER

A computationally efficient Hill curve adaptation strategy during continuous monitoring of dose–effect relation in anaesthesia

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Abstract This paper discusses a possibility to simplify the number of parameters in the Hill curve by exploiting special mathematical functions. This simplification is relevant when adaptation is required for personalized model-based medicine during continuous monitoring of dose–response values. A mathematical framework of the involved physiology and modelling by means of distributed parameter progressions has been employed. Convergence to a unique dynamic response is achieved, allowing simplifying assumptions with guaranteed solution. Discussion on its use and comparison with other adaptation mechanism is provided.

Keywords Hill curve · Continuous fraction expansion · Mathematical model · Nonlinear dynamics · Variability · Dose–effect relation · Patient specificity

1 Introduction

In general, drug regulatory loops are becoming popular in clinical practice. Moreover, there is evidence to indicate that closed-loop control of drug dosing systems for anaesthesia performs better than manual control [1]. These systems rely on the availability of a model which often is defined as a compartmental model with additional nonlinear functions to account for pharmacokinetics and pharmacodynamics, respectively [2,3].

A great variability in patient parameters exists, but this does not pose any problem in the pharmacokinetic (PK) part of the patient model—its coefficients are usually well characterized by biometric indicators which can be directly specified for each patient (e.g. age, BMI, height, gender). By contrast, pharmacodynamic (PD) models are generic models based on population dynamics and cannot be specified for each patient [3]. This implies that robust control strategies are applied to cope with great variations in patient's dynamics and modelling errors [2]. The approach leads to suboptimal performance since robustness requires a trade-off between sensitivity to changes in patient dynamics and overall closed-loop dynamic performance. Alternatively, a pharmacodynamic model adaptation may be employed [4]. This approach is more appealing, but the relatively high number of model parameters and high degree of nonlinearity make this task tedious and linearized models are used instead [3].

Over the past century a significant amount of work has been dedicated to analysing, revisiting and applying the Hill curve as model for dose–response. Its relation to power-law and exponential functions has become almost dogmatic in the modelling community [5]. Notable works describe the existence of adaptation mechanism in the neurotransmitter system which

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follows a mixture between power-law and exponential dynamic functions [6,7].

Hitherto, the Hill curve has been considered as a static nonlinear characteristic, coupling the pharmacokinetic model to the pharmacodynamic model. The nomenclature is actually confusing in engineering terms, since pharmacodynamic implies the existence of a dynamic system, whereas the Hill curve is essentially treated as a static nonlinearity. Nevertheless, through its parameters, the Hill curve characterizes a broad variability in the patient response to the drug effect and thus its parameters vary from one individual to another. Moreover, resistance, or its complementary feature, sensitivity, to the drug dosing profile may change over time, denoting intra-patient variability.

From a ligand binding perspective, the Hill equation is not a realistic representation of the actual process and its limitations should be well recognized and consequently used with care [8]. For the examples in anaesthesia, this observation is important, since ion transporters such as Na–K pump form the basis element in nociceptor sensitization. The Hill model has been extensively used when the relationship between drug concentration and drug effect is nonlinear and saturable.

From a modelling perspective of time-variant dynamic systems, the Hill curve is not a suitable model for continuous monitoring of dose–effect relationship. The reason is its high number of parameters and high nonlinearity in the parameters, requiring complex, nonlinear identification tools. The objective of this work is to propose a mathematical framework which allows to greatly simplify the structure of the Hill curve, while preserving its features. Careful examination of the literature revealed that mathematical models for ligand binding for analysis are limited to static observations. Empirical developments of the Hill curve are here supported by suitable equivalent models. The proposed methodology uses convergence of continuous fraction expansions to simplify the number of Hill parameters.

2 Theoretical biology background

When drug kinetics are modelled, a series of reactions are characterized as part of the dynamical process involved. Physiologically based models for such reactions are preferred above mathematical models which offer merely tools at hand. The remainder of this section is then limited to the discussion of those physically plausible processes.

The ligand–receptor interaction involves a manifold of states in which the binding of molecules occurs sequentially:

$$R + 2L \rightleftharpoons RL + L \rightleftharpoons RL_2 \tag{1}$$

or independent, i.e. for two binding sites a and b, we have that:

$$R_{00} + 2L \rightleftharpoons \begin{matrix} R_{a0}L + L \\ R_{0b}L + L \end{matrix} \rightleftharpoons R_{ab}L_2 \tag{2}$$

The binding process is subjected to a rate which is dependent on the threshold of kinetics, which may also vary in time, as stimulating or inhibiting the binding process. This is a result of the dose–response when drug intake takes place, showed to lead to slightly different results in case of sequential or independent binding [8].

The physical explanation differs for the two schemes. Consider the binding process modelled by a distributed parameter system. In the sequential binding, it is necessary that the first compartment is to be filled before the second one starts to fill, etc. The molecules are assumed to be stacked progressively at the binding site. Such a process is encountered in cases of ion transporters, e.g. Na–K pump or Na–Ca exchanger where the Na ions stack on top of each other. In case of independent binding process, more sites are available simultaneously to the ligand. This scheme may be representative for multimeric proteins, e.g. ligand-gated ion channels or ligand-gated enzymes.

Employing Hill equation to observe the amount of binding points for the two schemes, a positive cooperativity was necessary to obtain accurate estimates. An important property thereof is that each successive ligand-bound state must decrease or increase, as in a recurrent manner. Also the 50% engagement of the receptors varied with the degree of cooperativity. So for the N compartments of the distributed parameter system one may have no cooperativity (recurrence $= 1$), positive (recurrence > 1) or negative (recurrence < 1). This property becomes significant in the sequential binding case, with positive recurrence, affecting the steepness of the Hill curve to approach saturation.

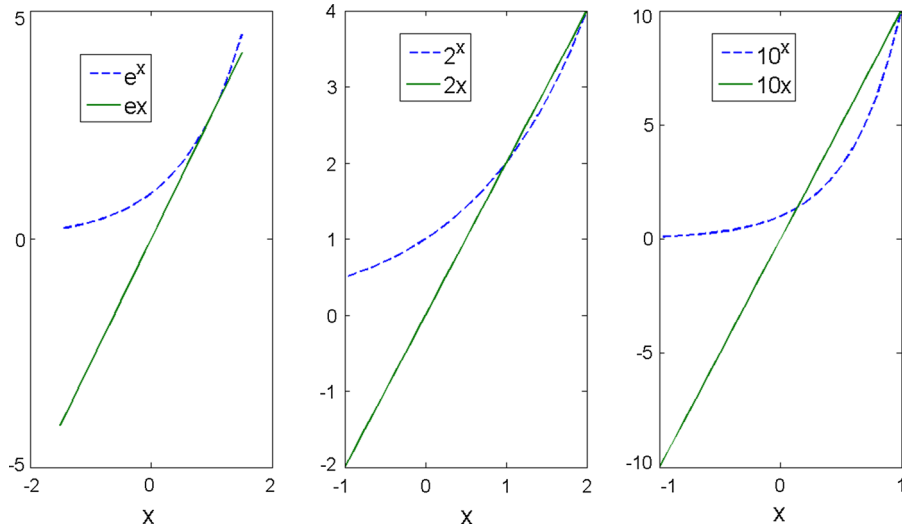

Fig. 1 Illustration of three cases of relevant functions

When modelled as a network, it has been shown to exhibit a cyclic component, in which reversibility may play an important role [8]. From a mathematical modelling point of view, this implies a biphasic dynamical system, requiring more than one Hill curves to model the complex time-varying dose–response curve. The steepness of the curve is then related to the interaction and positive cooperativity among multiple ligand binding sites.

For a sequential reaction scheme seen as a distributed parameter model, we have:

$$R+nL \rightleftharpoons RL+(n-1)L \rightleftharpoons \cdots \rightleftharpoons RL_{n-1}+L \rightleftharpoons RL_n \tag{3}$$

which is a recurrent progression of binding molecules. This can be modelled by continuous fraction expansion equations.

3 Mathematical formulation

3.1 Background

The rationale used in this work is based on approximating a exponential function to a linear function and finding the common point of tangent or intersection. Some textbook exampled can be used to illustrate the existence of minimum one point and maximum two point of convergence between the curves.

Equivalence of

$$e^x = e \cdot x, \quad \text{for } [-1.5; 1.5] \tag{4}$$

$$2^x = 2 \cdot x, \quad \text{for } [-1; 2] \tag{5}$$

$$10^x = 10 \cdot x, \quad \text{for } [-1; 1] \tag{6}$$

is illustrated in Fig. 1.

Intersection appears when the following equivalence holds: $a \cdot x = a^x$. One observes that for $x > 1$, $a \cdot x$ increases at a higher rate than a^x until another intersection occurs. For $x \gg 1$ this is reversed; i.e. a^x increases faster than $a \cdot x$. Hence, there are two solutions for every $a \neq e$, with $a > 0$.

Recall that $e = 2.71828$ and expresses the limits:

$$= \lim_{n \longrightarrow \infty} \left(1 + \frac{1}{n}\right)^n \tag{7}$$

$$= \lim_{x \longrightarrow 0} (1 + x)^{1/x} \tag{8}$$

For $a \in \Re^+ \backslash \{1\}$ let $k = \log(a)$ $\forall a \neq 0$ and $y = kx$ and $\beta = \frac{\exp(k)}{k} \neq 0$. Then $a^x = a \cdot x \longleftrightarrow \exp(y) - \beta y = 0$.

Let $f : \Re \rightarrow \Re : x \rightarrow \exp(x) - \beta x$. Find x such that $f(x) = 0$.

Case $\beta > 0$. Observe that $f(x) > 0, \forall x \in (-\infty, 0)$. Since $f(0) = 1 > 0$ and $f(\infty) = \infty$ there must exist a local minima with function value ≤ 0, which implies the existence of a solution.

Theorem *There is a solution in* $(0, \infty)$ *iff there is a critical point* $x_c \in (0, \infty)$ *with* $f(x_c) = 0$.

If $f'(x) = 0$, then $\exp(x) - \beta = 0 \longrightarrow x = \log(\beta)$. This implies the existence of a critical (unique) point.

The point is positive iff $\beta > 1$. The function value is then $f(\log(\beta)) = \beta - \beta\log(\beta) \leq 0$ iff $\beta \geq e$.

Theorem *There is a solution in* $(0, \infty)$ *iff* $\beta \geq e$.

Case $\beta < 0$. In this case we have $f(-\infty) = -\infty$ and $f(0) = 1 > 0$. This implies that a solution exists for $f(x) = 0$ in the interval $(-\infty, 0)$. This exists when $\beta > 0$, which is not fulfilled in this case.

Notice that positive defined systems, such as PK–PD models, require all solutions to be strictly positive.

To conclude, a solution exists when either $a < 1$ or $\frac{a}{\log(a)} \geq e$. Further calculations indicate there is exactly one solution for $a < 1$ or $\frac{a}{\log(a)} = e$; there are exactly two solutions for $\frac{a}{\log(a)} > e$.

Alternatively, if one fixes a and solves for x, an explicit solution can be obtained using the Lambert W function (i.e. `lambertw` in MATLAB). This gives

$$ra \cdot x = e^{(\ln a)x} \longleftrightarrow x \cdot e^{-(\ln a)x} = a^{-1} \tag{9}$$

$$\longleftrightarrow (\ln a)x \cdot e^{(\ln a)x} = \frac{-\ln a}{a} \longleftrightarrow \tag{10}$$

$$-(\ln a)x = W\left(-\frac{\ln a}{a}\right) \longleftrightarrow \tag{11}$$

$$x = -\frac{1}{\ln a} W\left(-\frac{\ln a}{a}\right) \tag{12}$$

which will always have one solution for the positive defined system by the PD model.

3.2 Hill curve specifics

When expressing the dose–response relationship, the Hill curve is a sum of related curves with different steepness coefficients. To better understand the implications of this relation, consider the elementary relation:

$$\frac{\mathrm{d}}{\mathrm{d}x} x^n = n \cdot x^{n-1} \tag{13}$$

A typical Hill equation representing pharmacological modelling of dose–response is given by:

$$\frac{C^\gamma}{C^\gamma + C_{50}^\gamma} \tag{14}$$

with C the concentration of molecules, C_{50} the concentration for achieving 50% effect and γ the degree of interaction between the ligand–receptor binding sites. Notice the values of this relation are always smaller than one. This relation can be decomposed as a continuous fraction expansion in backward form:

$$\frac{C^\gamma}{C^\gamma + C_{50}^\gamma} \rightleftharpoons \frac{\gamma C^{\gamma-1}}{\gamma C^{\gamma-1} + \gamma C_{50}^{\gamma-1}} \rightleftharpoons \cdots \frac{C}{C + C_{50}} \tag{15}$$

which, in the limit, the last element can be reduced to:

$$\frac{1}{1 + \frac{C_{50}}{C}} \tag{16}$$

with the ratio C_{50}/C representing the relative degree of changes in the actual concentration with respect to a predefined population value of C_{50} expected for achieving half effect. Introducing

$$f = \frac{C_{50}}{C} \tag{17}$$

and re-iterating the convergence, one obtains:

$$\frac{1}{1 + f^\gamma} \tag{18}$$

as the new form of the Hill curve. This is essentially the anomalous diffusion equation for distributed, homogeneous structured, well-mixed process dynamics.

A typical Hill curve is depicted in Fig. 2. In this figure, the slope of the curve is the steepness reaching saturation of the Hill curve. As the concentration C is changing, for the same values of 50% response, the slope will change and saturation times vary accordingly. If a sum of Hill curves is considered to be represented by the constitutive relation from (18), then the dose–response is free to change in its time derivative. The slope is related to the degree of cooperation in the ligand receptor binding process. Cyclic occurrences may delay or change the degree and thus affect the convergence of the scheme and, consequently, the slope of the dose–response curve.

4 Proposed approach

Figure 3 depicts relation (14) for several patients selected from [2], i.e. for significant variations in the values of γ and C_{50}. One may observe the difference in

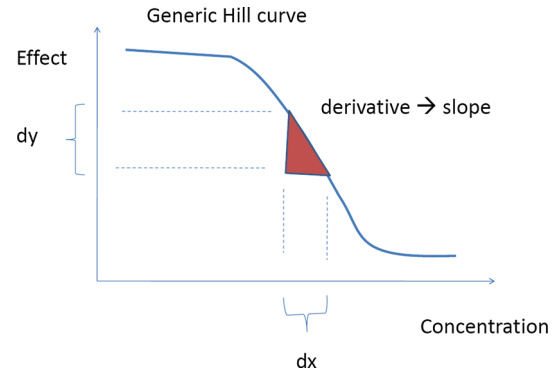

Fig. 2 Generic Hill curve and the concept of derivative in relation to the slope, or equivalently the steepness of the dose–effect relation

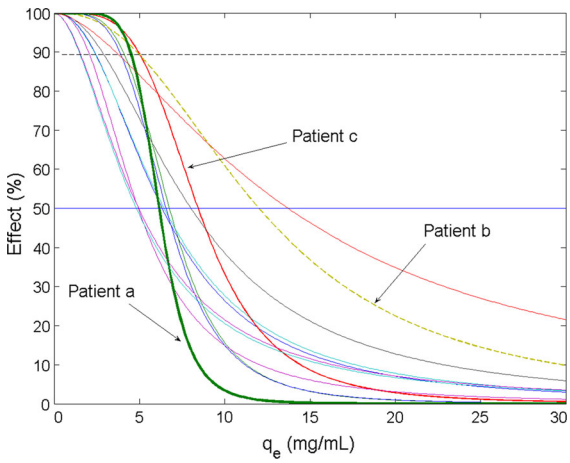

Fig. 3 Hill curve for several patients illustrating the concept of inter-patient variability

response for the same input of drug bolus. Hence, this figure gives an insight on the amount of inter-patient variability one may expect in practice. Patients *a* and *c* need a high effect site concentration before they start to react, i.e. effect starts to decrease. Patient *a* has a strong sensitivity to the drug after this minimum concentration of q_e [equivalent of C in relation (14)], and it decreases very fast to 0. Patient *c* has a less sensitivity to the drug, so it decreases slower. Finally, patient *b* requires less amount of drug infusion before it reacts, but the effect changes are extremely slow. It is clear that each patient's sensitivity to the drug is strongly influenced by the γ and C_{50} parameters.

If the Hill curve is normalized with values between 0% (full drug effect) and 100% (no drug effect), one obtains for a given γ value and for a given C concentration a line for the PD model of the patient. However, the sensitivity of the patient to the drug is also changing during treatment, i.e. the intra-patient variability concept.

To show the validity of the proposed simplified model, a simulation of the original form in (14) and the simplified form in (18) are performed. A generic population model indicates a value of the $C_{50} = 3.5$ [2,3]. Variations in the γ parameter values have been reported from 0.25 to 9.25, following real data reports [2]. The result of the original form is given in Fig. 4—top, while the result of the proposed form is given in Fig. 4—bottom. As observed, the results are identical, suggesting that the proposed model has a valid structure and function.

The identical result obtained supports the idea that not all parameters are independent and in this context a significant reduction in estimation effort can be achieved. Several parameters from (14) are known during the patient monitoring process. This information is either preoperatively available from the patient or via feedback loops from the monitoring devices. More specifically, the $E0$ parameter is immediately available as soon as the patient is connected to the sensor reading (BIS) and while still conscious (i.e. just before administration of hypnotic drugs). The C parameter can be initiated via the PK model determined from patient-specific parameters and from the measured hypnotic level (BIS) and by taking the inverse of (14) using nominal parameters for C_{50} and γ. Once the parameters C_{50} and γ are adapted, the C can be calculated using the same (14) with these updated values and continuous inflow of data from the BIS monitor.

It can be observed in Fig. 3 that the slope remains constant once below the threshold of BIS = 90 [9]. This implies twofold items:

1. that enough output data are available for identification (recall that input is stepwise or impulsewise and this is not a persistent excitation of the input to ensure good converge of covariance matrix for identification) and
2. that the linear approximation can be extracted, from which the slope immediately gives γ.

The linear approximation performed within each sample period according to the method described in [3] is then evaluated against relation (18) using the mathematical framework described in Sect. 3. A number of

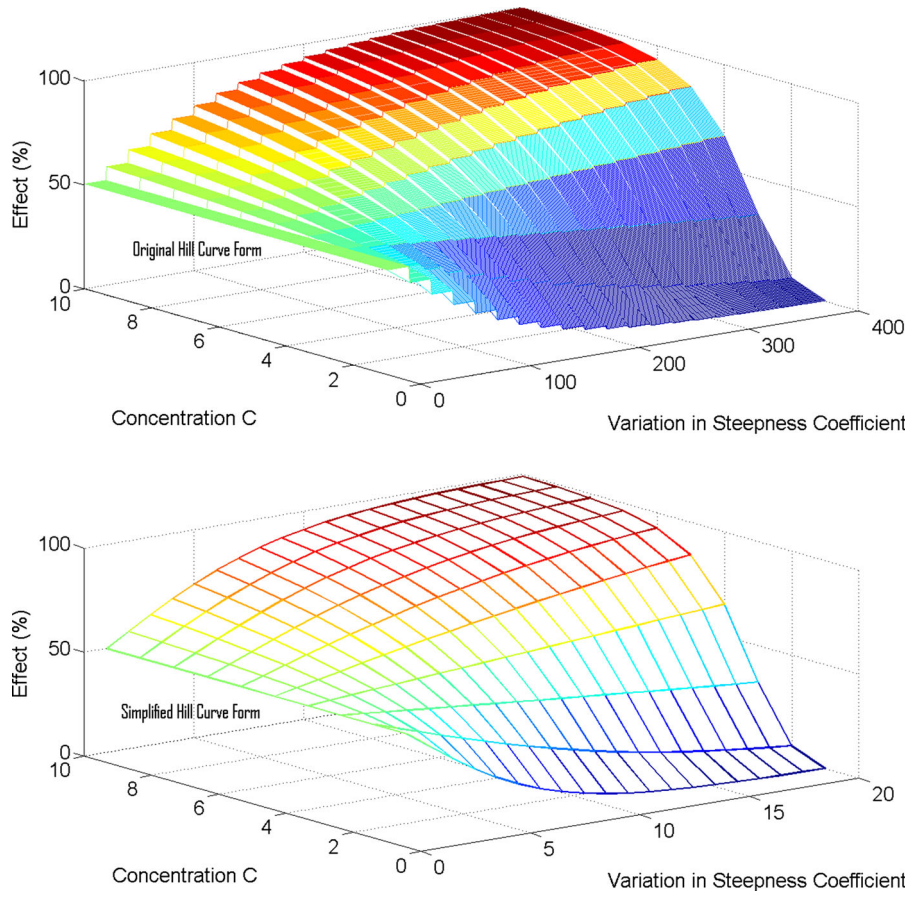

Fig. 4 Comparison between the original (top) and the proposed (bottom) model formulation

50 samples moving window are used—corresponding to 50 s (i.e. sampling period of $T_s = 1$ s).

5 Comparison

There are only few reported closed-loop algorithms adapting the Hill curve to patient-specific profiles when dose–response relations are used in drug regulatory problems. In the anaesthesia context, these are for neuromuscular blockade control [10] and for depth of hypnosis control [11–13]. To compare with the proposed form of the Hill curve, we employ the method described in [14]. The authors use the full nonlinear Hill curve to estimate during induction the patient-specific parameters. This is a nonlinear procedure based on Bayesian variances. The model estimator will continuously calculate a sigmoid model based on the patient's drug response as in (14). The Bayesian optimization yields minimization of the following cost function as the sum of all least squares:

$$\sum (\mathrm{BIS}_{\mathrm{sample}} - \hat{\mathrm{BIS}})^2 + (E_{0,p} - \hat{E}_{0,m})^2 \tag{19}$$

$$+ (E_{\max,p} - \hat{E}_{\max,m})^2 \tag{20}$$

$$+ (C_{50,p} - \hat{C}_{50,m})^2 + (\gamma_p - \hat{\gamma}_m)^2$$

where E_0 is the initial BIS value (usually between 90 and 100%), $E_{\max}$ is the maximum expected effect (i.e. a maximum of 100% effect), $\hat{x}$ denotes estimated values, p denotes population values, and m denotes model values. In practice, both the observations and the model parameters may vary in magnitude over several orders of magnitude. When this is the case, the model primarily works to minimize the error in the large observations and minimizes the deviation in the large parameters from the initial population estimate, as the larger numbers typically have much larger squared errors. This behaviour is undesirable and is handled by weighting the squared error by the expected variance. In the case of the model parameters, the expected variance represents the Bayesian uncertainty about the parameter estimate. As a consequence, the variance used to weight

Table 1 Results of simulation for comparison purposes

Patient	C_{50}	E_0	$E_{\max}$	γ
1	6.33	98.80	94.10	2.24
1-Bayes	5.89 ± 1.64	–	–	2.17 ± 0.13
1-Linear	7.19 ± 0.89	–	–	1.89 ± 0.08
2	13.70	83.10	151.00	1.65
2-Bayes	12.47 ± 1.89	–	–	1.52 ± 0.12
2-Linear	14.00 ± 1.08	–	–	1.67 ± 0.18
3	4.82	91.80	77.90	1.85
3-Bayes	4.56 ± 0.58	–	–	1.78 ± 0.34
3-Linear	4.99 ± 0.78	–	–	1.56 ± 0.44

Values reported as mean with standard deviations

the squared difference between parameter estimate and population estimate is defined as the Bayesian variances. The cost function from (19) is then completed with the variances for each covariate and a forgetting factor over the sampled interval of measured values. The actual minimization fully described in [14] uses the Levenberg–Marquardt method for fitting nonlinear models.

The dataset from [2] has been employed to compare the effectiveness of the two estimation algorithms. A desktop computer DELL Latitude E5530 running MATLAB R2014/Simulink with Optimization and System Identification Toolboxes has been used. The real values for simulation are given in Table 1, selected as being a nominal patient case and two extreme patient cases. The estimated values along with mean and standard deviations are also given. The estimation procedure was ran in the BIS interval 90–30%.

The Bayesian algorithm has estimates closer to the real simulated values; however, the time for estimating the parameter values takes significantly longer than the sampling period of a controller which may be used in closed loop (e.g. $T_s = 1$). The execution times of the proposed method for estimating relation (18) with the equivalence to a linear approximation are in the order of tens of milliseconds. We conclude the Bayesian algorithm is suitable for target-controlled infusion (open-loop control) and not for feedback-based closed-loop continuous control. If the parameters of the Hill curve are to be adapted only once, i.e. at the beginning of the closed-loop control, then both methods are equally suitable.

6 Discussion

6.1 On modelling

Drug release and effect dynamics have been extensively described by power-law functions for both continuous (i.e. intravenous) and intermittent administration (i.e. oral). Although specific dynamics have been observed in drug release profiles, these have been considered nonsignificant when power-law or exponential models were employed [5]. One may easily provide models combining both these dynamics with tools emerged from mathematics and physics by means of fractional calculus, with specific application of the Mittag-Leffler function. Several works have considered anomalous diffusion and fractal kinetics to improve model performance and provide a natural solution to observed profiles [15–17].

6.2 On adaptation

When analysing the inter-patient and intra-patient variability, the need for adaptation during continuous monitoring of dose–response relation becomes justified. In [9] it has been shown that the variability can increase up to 500% in terms of static gain, i.e. the sensitivity of one patient to the same amount of drug as that of another patient. It is clear that a generally valid model is obsolete. However, the drug effect curve follows a specific form as a function of the effect site concentration. In (14), the meaning of C_{50} is the value of the effect site concentration when the effect has reached 50%. In this context, this is not an independent unknown variable.

Moreover, one does not need to identify the absolute values of the unknown C, C_{50} and γ variables, but only their difference to the generic population model values used as a baseline reference, which are available for specific drugs in specialized literature.

Adapting the Hill curve during induction phase is necessary to overcome the inter-patient variability with respect to the population dynamics model parameters available as reference/start-up values. The particular advantage of this phase is that disturbances (e.g. surgical stimuli) are not present so the output of the system (drug effect on patient) can be correlated directly to the changes in the input drug rate profiles. Once the characteristic Hill curve is obtained in this patient-specific context, it can be used either in feedback-based control loops [11,12,18], or fuzzy-based loops [19], or predictive control loops [2,20].

During the maintenance phase, initiated after the induction phase is completed, the patient response to similar drug rates may change. This is a characteristic of a LPV system, since drug release from slow-acting tissue diffusion rates (e.g. in fat) may account for delayed dynamics. If this is not taking into account properly, over-dosing occurs, such as in other drug delivery problems [21,22]. On short term, this is not problematic, but adverse effects appear after the recovery time of the patient (e.g. nausea, vomiting, cardiac complications). A significant effect is that of anesthesiologist in the loop, which takes action to complement the actions of the regulatory loop algorithm [23]. These additional actions may be beneficial to the patient on short term but may destabilize the overall closed loop. The latter is due to the fact that the actions of the anesthesiologist are unknown to the regulatory algorithm, and they are seen as pure disturbances, creating additional changes in the drug infusion rates.

Other problems occur in the maintenance phase when adaptation of the Hill curve is employed, since there is a closed loop (i.e. feedback effects) and there is a disturbance profile, along with anesthesiologist actions, also seen as disturbances [23]. In fact, the actions of the anesthesiologist could be used to detect new dose–effect relationship Hill curve values, in the assumption of absence of surgical stimuli and stable patient dynamic signals.

6.3 On drug trapping

Naturally, tissue porosity, molecular binding and permeability vary within the organ, within the system and within the assumed compartment [24]. Taking tissue specificity into account when modelling PD dynamic profiles may lead to an increased model complexity. A trade-off between the usefulness and computational efficiency of such models must be made when evaluating the model objectives. If prediction for treatment optimization is envisaged, then one may include as many details as possible, to account for a personalized healthcare plan. If mere evaluation of dosing profiles and observational studies is involved, tissue specificity may be limited to the strictly necessary number of details. If data are available, data-driven modelling/identification may be performed and model parameters tuned to fit the specificity of the case.

Existence of hysteresis in the dose–effect curve is of great importance when trying to explain under- and over-dosing mechanisms [25]. Tissue heterogeneity accounts for a great deal of anomalous diffusion of molecules, and binding schemes may not preserve the recurrence once assumed. This will affect the C_{50} and the corresponding C values for the same patient. The tissue may be viewed as a sponge with several degrees of heterogeneous porosity, while also exhibiting nonlocal geometry and time-varying properties. This induces modulation effects and changes in the tolerance, the thresholds and the obtained effects equivalent for the same amount of drug concentration profiles. Hence, a challenging problem since in this context no unique solution exists to obtain the desired C_{50}, facilitating improper drug dosing profiles.

As such, time dependency has been considered hitherto. However, tissue heterogeneity is also structural, geometric and not only present in dynamic fluctuations. It may be worth considering introducing a time–spatial mathematical formulation to account for drug intake, whereas time and location may be specified. It is of great importance in pathology cases, where changes in tissue structure and morphology affect directly the dynamic profiles of drug diffusion, permeability and molecular binding. Specific structural changes with disease may also reveal various paths of deep tis-

sue trapping of drug and latency nodes which could explain effects observed in long-tailed observations. Some thoughts on this have been recently published in [26].

6.4 Other applications

The formulation given in this paper is in fact valid for other problem of dose–effect evaluations where the Hill curve is used. The alternative function is just minimal in the (nonlinear) parameters, which may be of benefit when employed in online (real-time) adaptation to the patient-specific dynamics.

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