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BIOCHEMICAL NETWORK OF DRUG-INDUCED ENZYME PRODUCTION: PARAMETER ESTIMATION BASED ON THE PERIODIC DOSING RESPONSE MEASUREMENT

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The well-known bottleneck of systems pharmacology, i. e., systems biology applied to pharmacology, refers to the model parameters determination from experimentally measured datasets. This paper represents the development of our earlier studies devoted to inverse (ill-posed) problems of model parameters identification. The key feature of this research is the introduction of control (or periodic forcing by an input signal being a drug intake) of the nonlinear model of drug-induced enzyme production in the form of a system of ordinary differential equations. First, we tested the model features under periodic dosing, and subsequently, we provided an innovative method for a parameter estimation based on the periodic dosing response measurement. A numerical example approved the satisfactory behavior of the proposed algorithm.

Keywords: dynamical system, systems pharmacology, biochemical network, input-output regulation, parameter estimation, fast Fourier transform

Classification: 92C45, 34A34, 65F60, 65K10

1. INTRODUCTION

Similar to other scientific domains, the expenses related to *in silico* modeling in pharmacology need not to be extensively apologized. *Vis à vis* both *in vitro* and *in vivo* experiments, physiologically-based pharmacokinetic (PBPK) and pharmacodynamic models represent an appealing tool for the assessment of drug safety before its approval, as well as a viable option in designing dosing regimens [26]. The PBPK models aim to provide quantitative descriptions of the absorption, distribution, metabolism, and excretion of chemicals in organisms, based on key physiological, biochemical and physicochemical factors of these processes [13]. Shortly, PBPK models represent the scientific extrapolations of dose-response analysis for humans, which is the major advantage of these models as such analysis *in vivo* is only possible for other species (e. g., rodents), and results remain far from validation for humans.

The application of PBPK models for the determination of internal (tissue) doses of chemicals, concerning differences in species, routes, and kinetics, has been undertaken since the 80s of last century [4, 6]. The PBPK models extrapolation has been explored

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in application to variability among individuals in a population [1, 2] as well as to the different life stages [5] and drug-drug interactions [8, 22]. In order to simulate dose metrics of relevance to risk assessment, the PBPK models should reflect a balance between the parsimony and plausibility principles [13]. The model structure should contain the minimal but essential elements characterizing a system (i. e., parsimony principle) and reflect the physiological reality, be consistent with the current state of knowledge (i. e., plausibility principle). The knowledge on the mechanisms of absorption, distribution, metabolism [9] and excretion for the particular chemical should be reflected in the PBPK model equations [10].

There are three major components of the PBPK model, concerning the system-specific properties, the drug properties, and the structural specificity [23]. The organ mass or volume, the blood flow, and the tissue composition represent system-specific properties. The drug properties are enzymatic stability, plasma-protein binding affinity, transporter activities, membrane permeability, and tissue affinity. The structural model is represented by the body's organs and tissues (compartments) anatomically arranged and linked by blood.

A hydrophilic chemical distributes homogeneously over the entire compartment, and a one-compartment model might be sufficient in this case [13]. A multicompartmental approach is needed for the chemicals with different pharmaco-kinetics in the different tissues. The tissues similarity in chemical concentration versus time course behavior is based on the blood perfusion rate: the richly perfused tissues and the poorly perfused ones. This approach should be considered for the model simplification and its consistency with the intended purpose and the underlying data because the model complexity and the number of compartments do not correlate with the accuracy of the model approximation.

The relevant processes in the compartment are described based on the chemical law of mass action and other biophysical laws, which finally take the form of non-linear ordinary differential equations (ODEs), whose size is equal to the total number of substances (further denoted as state variables). Finally, we point out that the estimation of unknown kinetic parameters (in our case, these include permeability coefficients, association and disassociation rates, elimination and production rates, etc.) is a major bottleneck in the ODE model building process in systems pharmacology and metabolic engineering [12].

To be specific, the goal of this paper is to highlight the new aspects related to the *in silico* computer modeling and simulations involved in PBPK models. On a (nonlinear) model introduced by Luke et al. [14] and further developed by Duintjer Tebbens et al. [7], we shall demonstrate the feasibility of the developed innovative method for parameter estimation. A periodic signal feeds the model; the response is approaching a periodic signal (for $t \to \infty$) as well. Preliminary results in this direction were presented in [17]. This paper contains an extended and more detailed presentation of this topic.

Contribution of the paper

- The precise nonlinear description in the form of nonlinear ODEs with periodic input is used as a base for the parameter identification algorithm, hence improving precision in comparison with (usually employed) linear models.

- A parameter identification algorithm based on the system's time-varying (almost periodic) response. This is in contrast with methods that make use of responses on one-time doses of the drug (such methods have been used so far).

These features constitute the novelty contained in this paper.

Outline of the paper: In the next section 2, the model is described in detail. Section 3 presents related numerical experiments discusses the relevance of our results and possible consequences of the analysis for more general cases. The last section concludes our work and points out some future goals.

Symbols: The symbol $\mathbb{R}$ denotes the set of real numbers, $\mathbb{C}$ stands for the set of complex numbers, **i** is the imaginary unit.

2. MODEL FORMULATION

In this study, the problem of output regulation *via* a periodic input, being a drug intake, is presented. This feature makes the model more realistic. For more details, the reader is referred to other papers devoted to mathematical modeling of drug-induced enzyme production networks, see [14, 7] and references within there. All necessary information for the setting of model equations describing the action of pregnane X receptor (PXR) causing the xenobiotic (drug) metabolizing enzyme induction are schematically given in Figure 1. Moreover, in Tables 1 and 2, the particular processes are displayed. The substances there are the state variables involved. The model parameters are the rate constants which can be taken from previously published papers; their values are reported in Table 3. To be specific, the sources of the values are taken from [14] (denoted by "Luke" in Table 3), [7] (denoted by "JDT") and [25] (denoted by "Svecova").

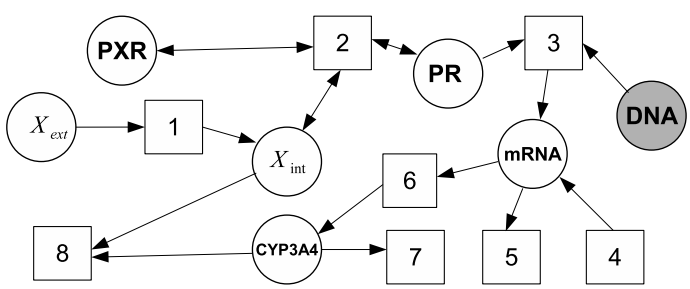

Fig. 1. Graph representation of the biochemical network associated with drug metabolism and the PXR-mediated drug-induced enzyme production process. Species nodes (identified by letters) are drawn as circles, and reaction nodes identified by numbers represent reactions and transport between species nodes. The grey species node DNA is not involved in the ODE system here presented.

No.	Description of the respective process within the network	Parameters
1	Xenobiotic (e. g. drug rifampicin) enters the cell (by permeation)	k_1
2	PXR binds to drug, formation of PR dimer (reversible)	$k_2,\ k_4$
3	PR dimer binds to DNA (increasing transcription)	k_5
4	mRNA background production	k_7
5	mRNA degradation	k_6
6	translation of mRNA (CYP3A4 production)	k_8
7	degradation of CYP3A4 protein	k_9
8	drug degradation (metabolizing by CYP3A4)	k_3

Tab. 1. The transport and reaction processes description with respective model parameters.

No.	Description of the respective state variable	Old name
1	Xenobiotic (drug) concentration – exterior	$\mathsf{X_{ext}}$
2	Xenobiotic concentration – interior	$\mathsf{X_{int}}$
3	PXR concentration	PXR
4	PR dimer concentration	PR
5	mRNA concentration	mRNA
6	CYP3A4 protein concentration	CYP3A4

Tab. 2. The description of model state variables.

Introducing the new notation for state variables, i. e. for a size six vector x according to

$$x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ x_5(t) \\ x_6(t) \end{pmatrix} \equiv \begin{pmatrix} \mathsf{X_{ext}}(t) \\ \mathsf{X_{int}}(t) \\ \mathsf{PXR}(t) \\ \mathsf{PR}(t) \\ \mathsf{mRNA}(t) \\ \mathsf{CYP3A4}(t) \end{pmatrix},$$

then the system of differential equations describing the process under study can be written as follows

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \begin{pmatrix} x_1'(t) \\ x_2'(t) \\ x_3'(t) \\ x_4'(t) \\ x_5'(t) \\ x_6'(t) \end{pmatrix} = Ax(t) + B(t) + \begin{pmatrix} a_d(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{1}$$

JDT-Param.	Value	Unit	Source	New name
k_{up}	$6.55 \cdot 10^{-3}$	min^{-1}	Luke	k_1
k_{dis}	$1.03{\cdot}10^{-4}$	min^{-1}	Luke	k_4
k_{mRNA}	39.3	min^{-1}	Luke	k_5
$k_{mRNA,deg}$	0.04	min^{-1}	Luke	k_6
k_{cyp}	2.5	min^{-1}	Luke	k_8
$k_{cyp,deg}$	$2.7 \cdot 10^{-4}$	min^{-1}	Luke	k_9
k_{assoc}	k_{dis}/k_{sv}	$\mu\text{M}^{-1}\text{min}^{-1}$	Svecova	k_2
k_{met}	$2.47{\cdot}10^{-5}$	$\mu\text{M}^{-1}\text{min}^{-1}$	Luke	k_3
$k_{mRNA,back}$	$1.36{\cdot}10^{-7}$	μM min^{-1}	JDT	k_7
s_{PXR}	$9.47 \cdot 10^{-7}$	μM	Luke	k_0
k_{sv}	5.6	μM	Svecova	k_{sv}
$d(t)$	0– 20	μMmin^{-1}	Luke&JDT	$a_d(t)$
a_{per}	0– 20	μM	dose per period	a_{per}

Tab. 3. The values of model parameters.

with the constant matrix (the linear part of the system)

$$A = \begin{pmatrix} -k_1 & k_1 & 0 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & k_4 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 & 0 \\ 0 & 0 & 0 & -k_4 & 0 & 0 \\ 0 & 0 & 0 & k_5 & -k_6 & 0 \\ 0 & 0 & 0 & 0 & k_8 & -k_9 \end{pmatrix}, \tag{2}$$

and the vector representing nonlinear (quadratic) and constant (zero order) parts

$$B(t) = \begin{pmatrix} 0 \\ -k_2 \cdot x_2(t)x_3(t) - k_3 \cdot x_2(t)x_6(t) \\ -k_2 \cdot x_2(t)x_3(t) \\ k_2 \cdot x_2(t)x_3(t) \\ k_7 \\ 0 \end{pmatrix}, \tag{3}$$

the initial conditions are

$$x(0) = \begin{pmatrix} x_1(0) \\ x_2(0) \\ x_3(0) \\ x_4(0) \\ x_5(0) \\ x_6(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ k_0 \\ 0 \\ \frac{k_7}{k_6} \\ \frac{k_7 k_8}{k_6 k_9} \end{pmatrix}. \tag{4}$$

Elsewhere, e. g. in [7], the initial condition $x_1(0)$ represented the amount of drug just after initially applied dose ($x_1(0) = 10$ μM). Here, the input (drug dosing) is modeled via a periodic function, and the initial state of drug concentration is the steady state

without dosing, i. e. $x_1(0) = 0$; the other components of initial state remain the same, i. e. $x_3(0) = k_0 = 9.47 \cdot 10^{-7}\mu$M, $x_5(0) = \frac{k_7}{k_6} = 7.075 \cdot 10^{-6}\mu$M and $x_6(0) = \frac{k_7 k_8}{k_6 k_9} = 6.55 \cdot 10^{-2}\mu$M, which are the initial concentration for PXR and steady state concentrations for mRNA and CYP3A4, respectively.

Remark 2.1. The function $a_d(t)$ (see the last but one row of Table 3) represents the dosing rate (units $[\mu M/min]$) of drug added into the system, and $k_{up}[1/min]$ is the first order diffusion coefficient encompassing the permeability coefficient and area of the membrane, $k_{assoc}\,[1/min]$, and $k_{dis}\,[1/min]$ are corresponding association, and dissociation constants, respectively. An important parameter (shown in [7]) is the total concentration (binded and free) of PXR, i. e. s_{PXR}, here denoted as $k_0\,[\mu M]$.

Remark 2.2. Our setting of the input variable, i. e., using a dosing function, is more general than it is made otherwise, e. g., in [14], where the dosing function $a_d(t)$ is not used. Instead, the administered dose is incorporated by putting the initial value of $\mathsf{X}_{\mathsf{ext}}$ to equal this dose (thus, it is only the Cauchy initial value problem that can be analyzed).

Experimental data & what can be measured

In principle, there are two possible datasets

1. Time series of fold induction of mRNA $\big($state variable $x_5(t)\big)$ while the drug rifampicin is being applied (either in one bolus or periodically).
2. A table of data relating $x_5(t^*)$ vs. a_{per}, i. e. dose dependent induction of mRNA (state variable $x_5(t)$) in the absence or presence of a total amount of one bolus (1, 2, 5, 10, 15, 20 μM) of drug rifampicin, for a specific time instant, e. g. for $t^* < T = 24$ (in hours after dosing).

Further, in this paper, we deal with time series, case 1, only.

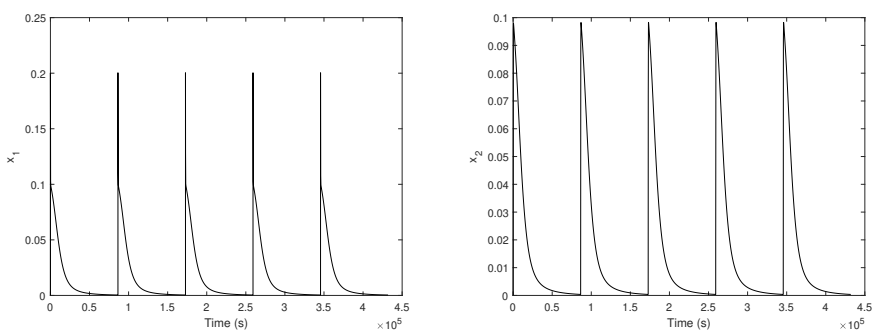

Fig. 2. Periodic dosing: Time series data for daily dosing of 20 μM of rifampicin (applied during 1 minute). Left: States $x_1(t)$ Right: Data for $x_2(t)$ over 5 days time span.

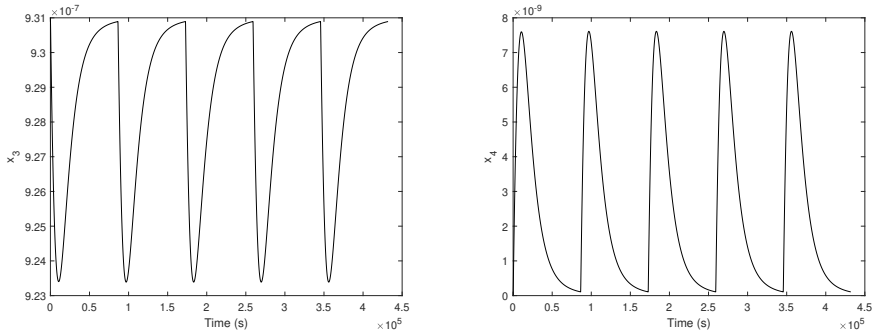

Fig. 3. Periodic dosing: Time series data for daily dosing of 20 μM of rifampicin. Left: States $x_3(t)$ Right: Data for $x_4(t)$ over 5 days time span.

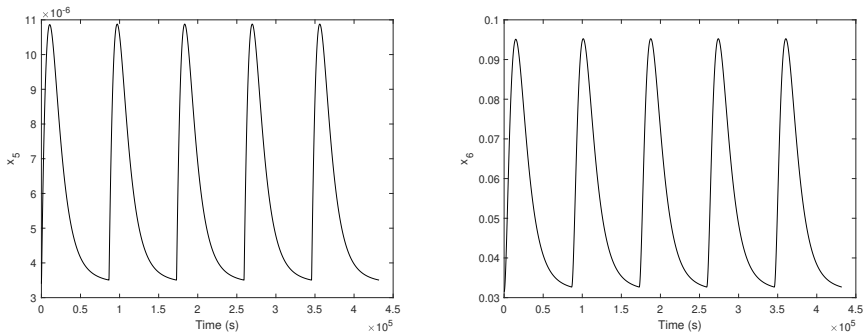

Fig. 4. Periodic dosing: Time series data for daily dosing of 20 μM of rifampicin. Left: States $x_5(t)$ Right: Data for $x_6(t)$ over 5 days time span.

3. IDENTIFICATION OF MODEL PARAMETERS

The main objective of developing an identification method was its reliability. To achieve this goal, it is necessary to excite all identified system modes sufficiently. A response to an aperiodic input or initial conditions does not satisfy this requirement. This happens because the system exhibits fast and slow dynamics. The effects of the fast dynamics would be hard to catch by the aperiodic signal as they attenuate rapidly. Thus, a method based on a periodic excitation was proposed. This achieves a permanent excitation of the whole dynamics of the system. Moreover, periodic excitation also corresponds well to the practical operating conditions of the system as in practice; the dosing is usually periodic. In the proposal of the identification algorithm, we assume that the periodic excitation has been conducted for a sufficiently long time so that the transient part of the response is attenuated enough. Hence the identification is based on the investigation of the periodic signals.

The model parameters in the resulting dynamical system (1), comprised in matrices (2) – (3), are the rate constants that can be taken from previously published papers; their values are reported in the Table 3.

In general, the values of some model parameters k_i, $i = 1, \ldots, 9$ cannot be easily obtained. This is applied above all for the parameters k_3 and k_0; let see Figure 9 in [14], where the sensitivity of the state variable mRNA (our state variable $x_5(t)$) concerning the model parameters is drawn[1]. While the parameter k_0 estimation was extensively studied in [7], here, we focus on the drug metabolization constant – parameter k_3, see the last row of Table 1, and for the literature (nominal) value, let see Table 3.

An algorithm for estimation of the parameter k_3 is described. A similar procedure can be developed for the identification of other model parameters.

Estimation of the drug metabolization constant (parameter k_3) – algorithm description

Let us briefly describe the proposed procedure: The response of the system to the periodic input (the periodic dosing) converges to a periodic function, let see Figures 2, 3 and 4. Hence, one can apply the fast Fourier transform (FFT) to the system's response with a small error. However, the results of the FFT are dependent on the parameter k_3. Nevertheless, the function that describes the relationship between parameter k_3 and these coefficients can be approximated. Another fact that needs to be considered is the limited availability of certain quantities: only the values of the function x_5 (representing the temporal dependency of the mRNA concentration) are measurable in practice. Hence the identification algorithm is dependent solely on values of the function x_5.

Now the procedure is described in a more detailed way. First, we make the following assumption:

Assumption 3.1. Assume the value of parameter k_3 lies in the interval $[k_{3,\min}, k_{3,\max}] \subset [0, \infty)$.

Remark 3.2. Assumption 3.1 is quite natural in practice. Usually, the bounds on the value of the constant to be estimated are known; the purpose of the identification algorithm is to deliver a precise mode value of this parameter.

As we are going to deal with solutions of (1) (especially with x_5) with different values of k_3 in the subsequent text, the following notation will be helpful.

Notation: Let Assumption 3.1 hold. Denote by $x_{5,k}$ the solution x_5 of (1) with parameter k_3 satisfying $k_3 = k$.

Choose an integer $N > 1$ and define a sequence $\{k_3^i \mid i = 1, \ldots, N\}$ so that $k_3^{(1)} = k_{3,\min} < \cdots < k_3^{(i)} < k_3^{(i+1)} < \cdots < k_3^{(N)} = k_{3,\max}$.

Assume also the response of the periodic function $a_d(t)$ and (4) converges to a periodic signal with the period denoted by T. This period is determined only by the input period (the dosing) and is independent of the value of the constant k_3. This follows from the

[1] This issue of parameter identifiability is closely related to the condition number (regularity) of the sensitivity matrix [3]; however, it is out of the scope of our present study.

fact that the periodic dosing can be regarded as an output of a periodic system. Such a system is naturally neutrally stable ([11, 19, 21]). As equations (1) describe a stable system, the center-manifold theory yields that the response of (1) converges to a periodic function with a period equal to the period of the dosing, see, e. g., [24] or [18]. This fact has been used by the authors for the identification of model parameters of a biological system (algae bioreactor) in [20] and [16].

From the above considerations follows that, for $\varepsilon > 0$, there exists $t > 0$ so that $|x_{5,k_3^{(i)}}(\tau) - x_{5,k_3^{(i)}}(\tau + mT)| \leq \varepsilon$ for every $m \in \mathbb{N}$, $\tau \geq t$ and every $i = 1, \ldots, N$.

Let $t > 0$ be as above. For every $i = 1, \ldots, N$ define $\bar{x}_i = x_{5,k_3^{(i)}}|_{[t,t+T]}$. Then, an integer $M > 0$ is chosen and for every i, the FFT is applied to the sequence $\bar{x}_i(t_j)$ where

$$t_j = t + \frac{T}{M-1}(j-1),\ j = 1, \ldots, M. \tag{5}$$

For every i, the result is a sequence of Fourier coefficients $\xi_{i,j} \in \mathbb{C}$, $i = 1, \ldots, N$, $j = 1, \ldots M$.

The next step is to apply the polynomial approximation of coefficients $\xi_{i,j}$. This means, for every $j = 1, \ldots, M$, real-valued polynomials of one real variable $\rho_j(\kappa)$, $\iota_j(\kappa)$ are sought so that the cost functional

$$J(j) = \sum_{i'=1}^{N} \|\rho_j(k_3^{(i')}) + \mathbf{i}\iota_j(k_3^{(i')}) - \xi_{i',j})\|^2 \tag{6}$$

is minimized.

The order of the approximating polynomials ρ and ι must be determined a priori and carefully chosen. If the degree of these polynomials is too low, the approximation is not precise enough. On the other hand, raising the degree too much overly increases the demand for storing their coefficients. The specific choice thus depends on the available soft- and hardware, and universal advice cannot be given.

The procedure described so far is conducted using simulations; hence it does not require any experimental data. However, suppose experimental data (denoted as $\mathbf{x}_5$) with the same period of dosing are available. In that case, one can estimate the parameter k_3 governing the experimental system as follows: taking the equal value of t as it was used in simulations, let us denote $\bar{\mathbf{x}} = \mathbf{x}_5|_{[t,t+T]}$. Then, apply the FFT on the sequence $\bar{\mathbf{x}}(t_j)$ where the points t_j satisfy (5). Denote the result of this application of the FFT by ξ_j.

Then, one searches for a parameter $\mathbf{k} \in [k_{3,\min}, k_{3,\max}]$ so that

$$\sum_{j=1}^{M} \|\rho_j(\mathbf{k}) + \mathbf{i}\iota_j(\mathbf{k}) - \xi_j\|^2 \tag{7}$$

is minimized. The choice of the optimization algorithm is then a technical problem.

Numerical example

Let us demonstrate the algorithm described in the previous section on the following example having some similarities with [20]. First, for the purpose of this paragraph,

denote by $k_{3,nom}$ the value $2.47 \cdot 10^{-5}$ which is the value of the parameter k_3 presented in Table 3. For the purpose of this paper, it will be called the "nominal value".

Then, the simulations were computed for 10 different values of the parameter k_3, thus $i = 10$. To be specific, the simulations were conducted for $0.25k_{3,nom}$, $0.5k_{3,nom}$, $0.75k_{3,nom}$, $0.8k_{3,nom}$, $k_{3,nom}$, $1.05k_{3,nom}$, $1.25k_{3,nom}$, $1.5k_{3,nom}$, $1.75k_{3,nom}$, and finally $2k_{3,nom}$. In all these computations the input was periodic with period $T = 1$ day. The software package Simulink was used to obtain the simulations [15].

By inspecting the simulations, one can see that after $t = 4$ day, the system's response does only insignificantly differ from a periodic signal. Hence the restrictions of the solutions of (1) on the interval corresponding to the fifth day were used to obtain the Fourier coefficients.

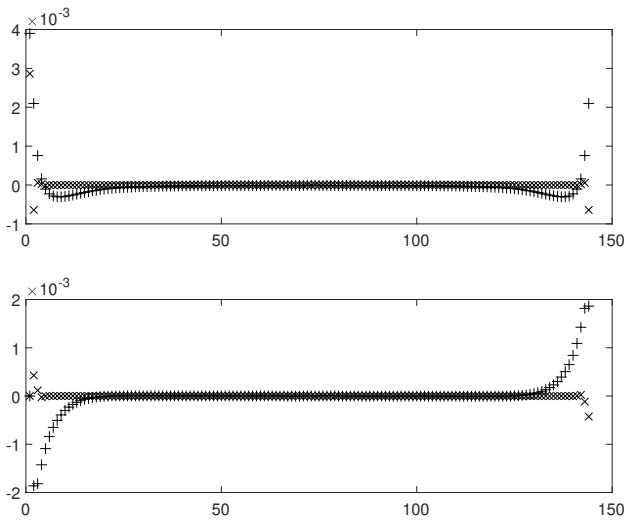

Fig. 5. The real part (top) and imaginary parts (bottom) of Fourier coefficients $\xi_{4,j}$ corresponding to $k_3 = 0.8k_{3,nom}$ (marked by $\times$) and $\xi_{7,j}$ which correspond to $k_3 = 1.25k_{3,nom}$ (marked by $+$). The second index j (in $\xi_{i,j}$) refers to the Fourier coefficient number (in x-axis).

The total number of Fourier coefficients for one value of i was $M = 144$. This choice requires finding 288 polynomials approximating both real and imaginary parts of all 144 Fourier coefficients. Choosing a suitable number of Fourier coefficients used to estimate the parameter k_3 will be investigated soon. A too high value of the number of Fourier coefficients is burdensome and time-consuming; on the other hand, if there are not enough Fourier coefficients to approximate, the results can be unsatisfactory. A similar situation occurs in choosing the degree of the approximating polynomial. In our example, it turned out that a suitable choice was to use polynomials of the third order. For the sake of illustration, Figure 5 shows the real part (top) and imaginary

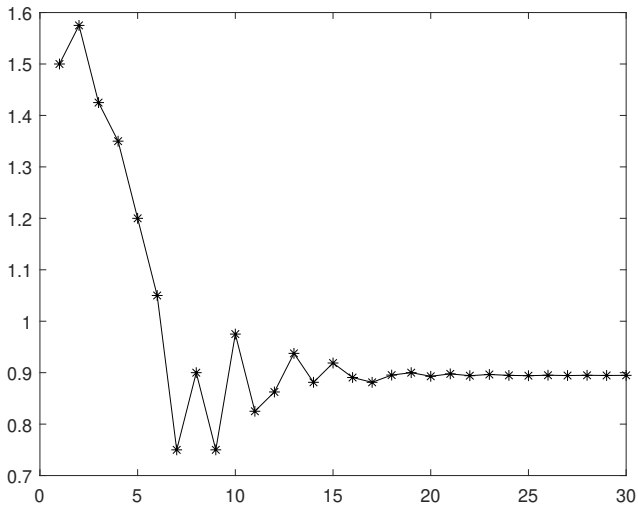

Fig. 6. Numerical process of the functional (7) minimization. The data were generated using the value of parameter k_3 (in y-axis as multiples of $k_{3,nom}$) as $0.9k_{3,nom}$.

parts (bottom) of coefficients $\xi_{4,j}$ (corresponding to $k_3 = 0.8k_{3,nom}$) and $\xi_{7,j}$ (which corresponds to $k_3 = 1.25k_{3,nom}$).

As no real-world data were available, the value $k_3 = 0.9 \cdot k_{3,nom}$ which is 90% of the value from Table 3 was used to emulate the measured values, i. e., the simulation using this value of parameter k_3 was conducted. Again, the restriction of the function x_5 on the interval corresponding to the fifth day was used to obtain the Fourier coefficients.

Then the minimization algorithm with the cost functional defined by (7) was started. Here, the minimization was computed with the help of the function *fminsearch* which is a part of the Matlab package. The algorithm yields as a resulting value $k_3 = 0.894 \cdot k_{3,nom}$. How the iterations converge to this value illustrates Figure 6. Here, the number of iterations is on the x-axis while the resulting value of k_3 (expressed as the multiple of $k_{3,nom}$) is on the y-axis. It can be seen that the minimization procedure yields the result after approximately 20 iterations.

When dealing with periodic signals, we mainly focused on finding the behavior imposed by the first several harmonics as these usually characterize the periodic signal well. Hence the method based on the Fourier coefficients was developed. This is the main reason why the FFT-based algorithm was used. The fact that the FFT is an efficient algorithm encouraged us to develop this kind of algorithm. Note that the algorithm is based on the least-squares optimization method. This method itself is dependent on several parameters that have a significant influence on its efficiency and speed. Hence a more detailed comparison in terms of speed, computational complexity, etc., is omitted. Moreover, in the context of this paper, this is a rather technical matter.

4. CONCLUSION AND OUTLOOK

Resuming, on the paradigmatic example of rifampicin metabolism and the PXR-mediated Xenobiotic Metabolizing Enzyme (XME) induction process, see Figure 1, we exposed an appealing tool of control engineering applied to systems biology, i. e., regulation based on the periodic input signal, being the xenobiotic (drug rifampicin) dosing. After testing the model features under periodic and nonrecurring dosing, we finally proposed an innovative method for a parameter estimation based on the periodic dosing response measurement. The method dwells on the application of the fast Fourier transform on the response of the system together with the polynomial approximation of Fourier coefficients. The problem of choosing a suitable number of Fourier coefficients used for estimation of the respective model parameters is left to the near future. A numerical example documented the satisfactory behavior of the proposed algorithm.

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REFERENCES

[1] H. A. Barton, W. A. Chiu, R. W. Setzer, M. E. Andersen, A. J. Bailer, F. Y. Bois, R. S. DeWoskin, S. Hays, G. Johanson, N. Jones, G. Loizou, R. C. MacPhail, C. J. Portier, M. Spendiff, and Y.-M. Tan: Characterizing uncertainty and variability in physiologically based pharmacokinetic models: State of the science and needs for research and implementation. Toxicolog. Sci. *99* (2007), 2, 395–402.

[2] F. Y. Bois: Applications of population approaches in toxicology. Toxicology Letters *120* (2001), 1–3, 385–394. DOI:10.1016/S0378-4274(01)00270-3

[3] A. Cintrón-Arias, H. T. Banks, A. Capaldi, and A. L. Lloyd: A sensitivity matrix based methodology for inverse problem formulation. J. Inverse and Ill-posed Problems *17* (2009), 6.

[4] H. Clewell and M. Andersen: Risk assessment extrapolations and physiological modeling. Toxicology and Industr. Health *1* (1985), 111-131.

[5] H. J. Clewell, P. R. Gentry, T. R. Covington, R. Sarangapani, and J. G. Teeguarden: Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. Toxicolog. Sci. *79* (2004), 2, :381–393. DOI:10.1590/S1678-31662004000300006

[6] R. Clewell, M. Andersen, and H. Barton: A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. Environmental Health Perspectives *110* (2002), 85-93. DOI:10.1289/ehp.0211085

[7] J. Duintjer Tebbens, C. Matonoha, A. Matthios, and Š. Papáček: On parameter estimation in an in vitro compartmental model for drug-induced enzyme production in pharmacotherapy. Appl. Math. *64* (2019), 2, 253–277.

[8] A. Galetin, H. Burt, L. Gibbons, and J. B. Houston: Prediction of time-dependent CYP3A4 drug-drug interactions: impact of enzyme degradation, parallel elimination pathways, and intestinal inhibition. Drug Metabolism and Disposition *34* (2005), 1, 166–175. DOI:10.1124/dmd.105.006874

[9] D. S. Gerhard Michal: Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology. Second edition. Wiley, 2012.

[10] L. E. Gerlowski and R. K. Jain: Physiologically based pharmacokinetic modeling: Principles and applications. J. Pharmaceut. Sci. *72* (1983), 10, 1103–1127. DOI:10.1002/jps.2600721003

[11] J. Huang: Nonlinear output regulation: theory and applications. Advances in design and control. Society for Industrial and Applied Mathematics, Philadelphia, 2004.

[12] G. Jia, G. Stephanopoulos, and R. Gunawan: Incremental parameter estimation of kinetic metabolic network models. BMC Systems Biology *6* (2012), 142, 1799-1819. DOI:10.1007/s11538-010-9508-5

[13] K. Krishnan: Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. Technical Report, World Health Organization, 2010.

[14] N. S. Luke, M. J. DeVito, I. Shah, and H. A. El-Masri: Development of a quantitative model of pregnane X receptor (PXR) mediated xenobiotic metabolizing enzyme induction. Bull. Math. Biol. *72* (2010), 7, 1799-1819.

[15] MATLAB: Simulink Toolbox. Simulation and Model-Based Design. The MathWorks Inc., Natick 2020.

[16] Š. Papáček, S. Čelikovský, B. Rehák, and D. Štys: Experimental design for parameter estimation of two time-scale model of photosynthesis and photoinhibition in microalgae. Math. Computers Simul. *80* (2010), 6, 1302–1309. DOI:10.1016/j.matcom.2009.06.033

[17] Š. Papáček, V. Lynnyk, and B. Rehák: Regulatory network of drug-induced enzyme production: parameter estimation based on the periodic dosing response measurement. In: Programs and Algorithms of Numerical Mathematics *20*, Institute of Mathematics, Czech Academy of Sciences, 2021.

[18] B. Rehák: Alternative method of solution of the regulator equation: L2-space approach. Asian J. Control *14* (2011), 4, 1150–1154. DOI:10.1002/asjc.416

[19] B. Rehák and S. Čelikovský: Numerical method for the solution of the regulator equation with application to nonlinear tracking. Automatica *44* (2008), 5, 1358–1365. DOI:10.1016/j.automatica.2007.10.015

[20] B. Rehák, S. Čelikovský, and Š. Papáček: Model for photosynthesis and photoinhibition: Parameter identification based on the harmonic irradiation O_2 response measurement. IEEE Trans. Automat. Control *53* (Special Issue) (2008), 101–108. DOI:10.1080/04597220801912762

[21] B. Rehák, S. Čelikovský, J. Ruiz-León, and J. Orozco-Mora: A comparison of two FEM-based methods for the solution of the nonlinear output regulation problem. Kybernetika *45* (2009), 427–444.

[22] A. Rostami-Hodjegan and G. Tucker: 'In silico' simulations to assess the 'in vivo' consequences of 'in vitro' metabolic drug–drug interactions. Drug Discovery Today: Technologies *1* (2004), 4, 441–448. DOI:10.1016/j.ddtec.2004.10.002

[23] M. Rowland, C. Peck, and G. Tucker: Physiologically-based pharmacokinetics in drug development and regulatory science. Ann. Rev. Pharmacology and Toxicology *51* (2011), 1, 45–73. DOI:10.1146/annurev-pharmtox-010510-100540

[24] N. Sakamoto and B. Rehák: Iterative methods to compute center and center-stable manifolds with application to the optimal output regulation problem. In: IEEE Conference on Decision and Control and European Control Conference, 2011.

[25] L. Svecova, R. Vrzal, L. Burysek, E. Anzenbacherova, L. Cerveny, J. Grim, F. Trejtnar, J. Kunes, M. Pour, F. Staud, P. Anzenbacher, Z. Dvorak, and P. Pavek: Azole antimycotics differentially affect rifampicin-induced pregnane X receptor-mediated CYP3A4 gene expression. Drug Metabolism and Disposition *36* (2007), 2, 339–348. DOI:10.1124/dmd.107.018341

[26] P. Zhao, M. Rowland, and S.-M. Huang: Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Clinical Pharmacology and Therapeutics *92* (2012), 17-20. DOI:10.1038/clpt.2012.68

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