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

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Abstract: The common goal of systems pharmacology, i.e. systems biology applied to the field of pharmacology, is to rely less on trial and error in designing an input-output systems, e.g. therapeutic schedules. In this paper we present, on the paradigmatic example of a regulatory network of drug-induced enzyme production, the further development of the study published by Duintjer Tebbens *et al.* (2019) in the Applications of Mathematics. Here, the key feature is that the nonlinear model in form of an ODE system is controlled (or periodically forced) by an input signal being a drug intake. Our aim is to test the model features under both periodic and nonrecurring dosing, and eventually to provide an innovative method for a parameter estimation based on the periodic dosing response measurement.

Keywords: dynamical system, regulatory network, input-output regulation, parameter estimation, FFT

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

1. Introduction

The physiologically-based pharmacokinetic (PBPK) and pharmacodynamic models aim to provide time-profiles of the concentrations of the involved substances, e.g. drugs, receptors, mRNA, metabolizing enzymes, in several parts of the body. Usually, this is done using compartmental models where it is assumed that substance concentrations are distributed homogeneously over the entire compartment [7]. The relevant processes are described based on chemical law of mass action and others bio-physical laws, taking finally the form of non-linear ordinary differential equations (ODEs), whose size is at least equal to the total number of substances (further denoted as state variables).

A well known bottleneck hindering the use of such mathematical models is that not all the model parameters are available (in our case these include permeability

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coefficients, elimination and production rates, etc.). Consequently, parameter estimation is an integral part of the systems pharmacology modeling process.

The goal of this paper is to highlight some new aspects related to the *in silico* computer modeling and simulations involved in PBPK models. On a model introduced by Luke et al. [3] and further developed by Duintjer Tebbens et al. [7], we shall demonstrate the feasibility of an innovative method for a parameter estimation. In the next section, this model is described in detail. Section 3 presents related numerical experiments, discusses 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.

2. The network of drug-induced enzyme production

We continue in direction of papers devoted to mathematical models describing the drug-induced enzyme production networks, see [3, 7] and references within there. In this study, we present the problem of output regulation *via* a periodic drug intake.

The model for the action of pregnane X receptor (PXR) causing the xenobiotic (drug) metabolizing enzyme induction is schematically given in Fig. 1. In Table 1 and Table 2, we briefly describe the individual processes it displays and individual substances – state variables involved, respectively. For more detailed description, the readers are referred to [7]. Let us comment, that some features of this process are similar to the well known enzyme kinetics (when an enzyme E acts on another chemical, so-called substrate S, producing a product P), see e.g. [6]. However, here, for a regulatory network containing transcription–translation reactions, the conservation property can not be applied as it is the case for (bio)chemical networks, let us see the series of articles of E. Bohl and I. Marek [1, 2, 4].

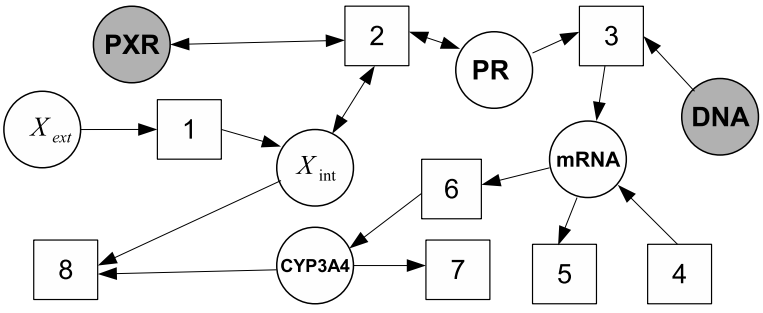

Figure 1: Graph representation of the network associated to a drug metabolism and the PXR-mediated drug-induced enzyme production process. Species nodes (identified by letters) are drawn as circles and reaction nodes identified by numbers represent reactions and transport between species nodes. Grey species nodes are 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

Table 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	PR dimer concentration	PR
4	mRNA concentration	mRNA
5	CYP3A4 protein concentration	CYP3A4

Table 2: The description of model state variables.

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

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

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

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

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

$$A = \begin{pmatrix} -k_1 & k_1 & 0 & 0 & 0 \\ k_1 & -(k_1 + k_2 k_{SP}) & k_4 & 0 & 0 \\ 0 & k_2 k_{SP} & -k_4 & 0 & 0 \\ 0 & 0 & k_5 & -k_6 & 0 \\ 0 & 0 & 0 & k_8 & -k_9 \end{pmatrix}, \tag{2}$$

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

$$B(t) = \begin{pmatrix} 0 \\ k_2 \cdot x_2(t) \cdot x_3(t) - k_3 \cdot x_2(t) \cdot x_5(t) \\ -k_2 \cdot x_2(t) \cdot x_3(t) \\ k_7 \\ 0 \end{pmatrix}; \tag{3}$$

the initial conditions are

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

Elsewhere, e.g. in [7], the initial condition $x_1(0)$ represented the amount of drug just after initially applied dose ($x_1(0) = 10\ \mu M$). 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. $x_4(0) = \frac{k_7}{k_6} = 7.075 \cdot 10^{-6} \mu M$ and $x_5(0) = \frac{k_7 k_8}{k_6 k_9} = 6.55 \cdot 10^{-2} \mu M$, which are the steady (initial) state concentrations for mRNA and CYP3A4, respectively.

Remark 1: Our setting of the input variable, i.e. using a dosing function is more general than it is made otherwise, e.g. in [3], where the dosing function $d(t)$ 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 which can be analysed).

Remark 2: Assume the input is nonzero in a finite interval. Then the state of (1) converges to a finite value. This value depends on the input. Since (1) is not linear, this dependence is nonlinear as well. For inputs with a constant value the limit value of the state x_4 is depicted in Fig. 2. The magnitude of the input is on the x-axis. One can see that, for larger input values, the growth of the limit value of the state x_4 gets slower. From this, one can infer that using a linear model, where this dependence is inevitably linear, may not be precise enough to obtain satisfactory results.

3. Model parameters estimation

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

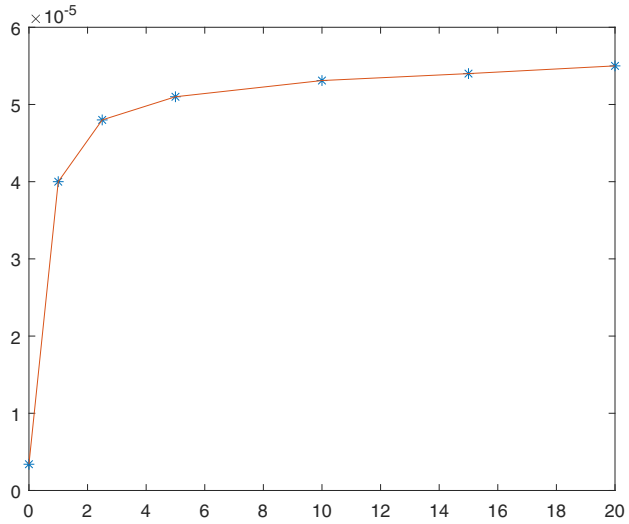

Figure 2: Dose dependent induction of mRNA (state variable x_4) in the absence or presence (1, 2, 5, 10, 15, 20 μM) of drug rifampicin (on the x-axis).

JDT-Param.	Value	Unit	Source	New name
k_{up}	$6.55 \cdot 10^{-3}$	min^{-1}	Luke	k_1
k_{assoc}	$k_{dis}/5.6$	$\mu\text{M}^{-1}\text{min}^{-1}$	Svecova	k_2
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_{met}	$2.47 \cdot 10^{-5}$	$\mu\text{M}^{-1}\text{min}^{-1}$	Luke	k_3
k_{dis}	$1.03 \cdot 10^{-4}$	min^{-1}	Luke	k_4
$k_{mRNA,back}$	$1.36 \cdot 10^{-7}$	$\mu\text{M min}^{-1}$	JDT2019	k_7
s_{PXR}	$9.31 \cdot 10^{-7}$	μM	JDT2019	k_{SP}
$d(t)$	0– 20	μMmin^{-1}	Luke&JDT	$a_d(t)$
a_{per}	0– 20	μM	dose per period	a_{per}

Table 3: The values of model parameters.

Here the function $a_d(t)$ represents the dosing rate (units $[\mu\text{M}/\text{min}]$) of drug added into the system, and $k_{up}[1/\text{min}]$ is the first order diffusion coefficient encompassing the permeability coefficient and area of the membrane, $k_{assoc}\,[1/\text{min}]$, and $k_{dis}\,[1/\text{min}]$ 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 $k_{SP}\,[\mu M]$.

Values of some parameters k_i, $i = 1, \ldots, 9$ cannot be easily obtained. In this section, an algorithm for estimation of the parameter k_3 is described. A similar

procedure can be developed for the estimation of the parameters k_4 and k_5. Let us briefly introduce the procedure: The response of the system to the periodic input (the periodic dosing) converges to a periodic function. Hence, with a small error, one can apply the fast Fourier analysis on the response of the system. However, the results of the FFT are dependent on the parameter k_3. Nevertheless, the function that describes the relation between the value of the parameter k_3 and these coefficients can be approximated. Another fact that needs to be taken into account is a limited availability of certain quantities: only the values of the function x_4 are measurable.

Estimation of the parameter k_3 – algorithm description

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

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

As we are going to deal with solutions of (1) (especially with x_4) with different values of k_3 in the subsequent text, the following notation will be useful.

Notation: Let $k \in [k_{3,\min}, k_{3,\max}]$. Denote by $x_{4,k}$ the solution x_4 of (1) with the parameter k_3 satisfying $k_3 = k$.

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

Assume also that 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 period of the input (the dosing) and is independent of the value of the constant k_3. Hence, for a pre-selected $\varepsilon > 0$ there exists $t > 0$ so that $|x_{4,k_3^{(i)}}(\tau) - x_{4,k_3^{(i)}}(\tau + mT)| \leq \varepsilon$ for every $m \in \mathbb{N}$, $\tau \geq t$ and every $i = 1, \dots N$.

Let $t > 0$ be as above. For every $i = 1, \dots, N$ define $\bar{x}_i = x_{4,k_3^{(i)}}|_{[t,t+T]}$. Then, an integer $M > 0$ is chosen and for every i, the FFT is applied to the sequence $\bar{x}_i(t_j)$ where

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

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

The next step is to apply the polynomial interpolation of coefficients $\xi_{i,j}$. This means, for every $j = 1, \dots, M$, real-valued polynomials of one real variable $p_{r,j}(\kappa)$, $p_{i,j}(\kappa)$ are sought so that

$$\sum_{i'=1}^{N} \|p_{r,j}(k_3^{(i')}) + i p_{i,j}(k_3^{(i')}) - \xi_{i',j})\|^2 \tag{6}$$

is minimal. The order of the interpolating polynomials must be determined a-priori.

The above procedure is carried out using simulations, hence it does not require any experimental data. However, if experimental data (denoted as $\mathbf{x}_4$) with the same period of dosing are available, one can estimate the parameter k_3 governing the

experimental system as follows: taking equal value of t as it was used in simulations, let us denote $\bar{\mathbf{x}} = \mathbf{x}_4|_{[t,t+T]}$. 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

$$\sum_{j=1}^{M} \|p_{r,j}(\mathbf{k}) + ip_{i,j}(\mathbf{k}) - \xi_j\|^2 \tag{7}$$

is minimized.

Numerical example

Let us demonstrate the algorithm on the following example having some similarities with our work [5]. First, for the purpose of this paragraph, denote by $k_{3,nom}$ the value 2.47×10^{-5} which is the value of the parameter k_3 in Table 3. It will be called the "nominal value". Then, the simulations were computed for 10 different values of the parameter k_3 (thus $i = 10$), namely 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 the period $T = 1$ day. The dosing was approximated by a sine curve with the amplitude of $\frac{1}{21600}$ with the added constant $\frac{1}{21600}$ (hence the dosage attains values between 0 and $\frac{1}{10800}$). The simulations were conducted in the software package Simulink.

After inspecting the simulations, it was chosen $t = 4$ days, hence the restrictions of the solutions of (1) on the interval corresponding to the fifth day were used to obtain the Fourier coefficients.

For the sake of illustration, Fig. 3 shows the real part (top) and imaginary parts (bottom) of coefficients $\xi_{4,j}$ (corresponding to $k_3 = 0.8k_{3,nom}$) and $\xi_{7,j}$ (corresponding to $k_3 = 1.25k_{3,nom}$). The total number of Fourier coefficients for one value of i was $M = 144$.

This choice requires to find 288 polynomials approximating both real and imaginary parts of all 144 Fourier coefficients. The way how to choose the number of Fourier coefficients used for estimation of the parameter k_3 will be investigated in the near future. It turned out that a suitable choice was to use polynomials of third order. As no real-world data were available, the value $k_3 = 0.9 \times k_{3,nom}$ which is 90% of the value from Table 3 was used to emulate the measured values. A simulation with this value was conducted. Again, the restriction of the function x_4 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 help of the function **fminsearch** which is a part of the Matlab package. The algorithm yields as a resulting value $k_3 = 0.894 \times k_{3,nom}$. How the iterations converge to this value illustrates Fig. 4. The number of iteration 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 convergence is quite fast, the minimization procedure yields the resulting value after 20 iterations.

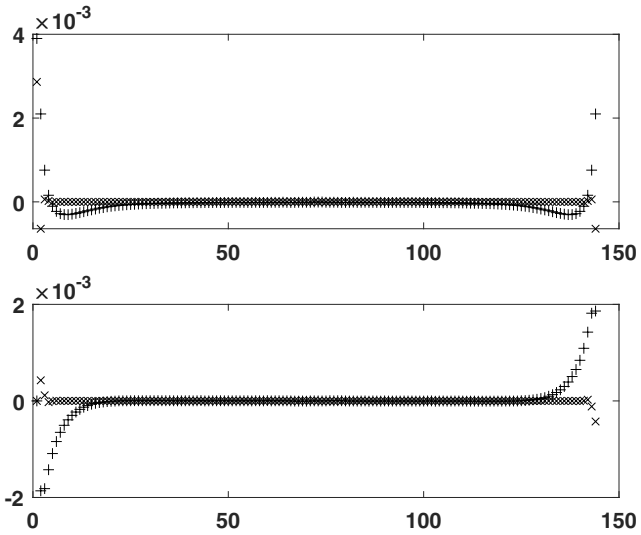

Figure 3: The real part (top) and imaginary parts (bottom) of Fourier coefficients $\xi_{4,j}$ corresponding to $k_3 = 0.8k_{3,nom}$ (marked by $\times$) and $\xi_{7,j}$ which correspond to $k_3 = 1.25k_{3,nom}$ (marked by $+$). The second index j (in $\xi_{i,j}$) refers to the Fourier coefficient number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

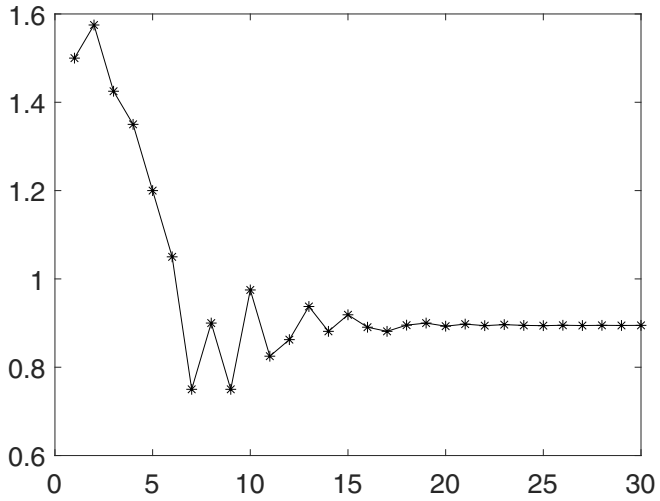

Figure 4: Minimization of the functional (7).

4. Conclusion

Resuming, on the paradigmatic example of rifampicin metabolism and the PXR-mediated Xenobiotic Metabolizing Enzyme (XME) induction process, we exposed an appealing tool of control engineering applied to systems biology, i.e. regulation

based on periodic input signal, being the xenobiotic (drug rifampicin) dosing. After testing the model features under both periodic and nonrecurring dosing, we finally proposed an innovative method for a parameter estimation based on the periodic dosing response measurement.

Though the final goal for future work, to provide an input-output regulation using an exosystem, which can be further used for an optimization of drug delivery, is out of reach for the moment, we made a first step that might contribute to its realization.

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References

[1] Bohl, E. and Marek, I.: Existence and uniqueness results for nonlinear cooperative systems. In: *Linear Operators and Matrices*, pp. 153–170. Birkhäuser Basel, 2002.

[2] Bohl, E. and Marek, I.: Input-output systems in biology and chemistry and a class of mathematical models describing them. Applications of Mathematics **50** (2005), 219–245.

[3] Luke, N. S., DeVito, M. J., Shah, I., and El-Masri, H. A.: Development of a quantitative model of pregnane x receptor (PXR) mediated xenobiotic metabolizing enzyme induction. Bulletin of Mathematical Biology **72** (2010), 1799–1819.

[4] Marek, I.: On a class of stochastic models of cell biology: Periodicity and controllability. In: *Positive Systems*, pp. 359–367. Springer Berlin Heidelberg, 2009.

[5] Rehák, B., Čelikovský, S., and Papáček, Š.: Model for photosynthesis and photoinhibition: Parameter identification based on the harmonic irradiation O_2 response measurement. IEEE Transactions on Automatic Control **53** (2008), 101–108.

[6] Segel, L. A. and Slemrod, M.: The quasi-steady-state assumption: A case study in perturbation. SIAM Review **31** (1989), 446–477.

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