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Identification for Control of Biomedical Systems using a very Short Experiment

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***Abstract*—This paper presents a combined experiment and identification procedure, well suited to obtain low-order dynamic models of a patients' response to continuous drug administration. The experiment requires no a priori information and is of very short duration. The identification method provides both a parametric low-order model, and an estimate of the parameter error covariance. It has been demonstrated to work well with very noisy measurements, as typically encountered in drug dosing applications.**

***Keywords*—Medical control systems, System Identification, Uncertain systems**

I. Introduction

Closed-loop controlled drug delivery is becoming a reality both in anesthesia (control of hypnotic depth and analgesia) and diabetes (control of blood sugar level). There exist several prototype systems, see [5, 7] for surveys, and it is realistic to believe that these technologies will meet broad clinical acceptance within a near future. In essence these systems function according to the block diagram shown in Figure 1.

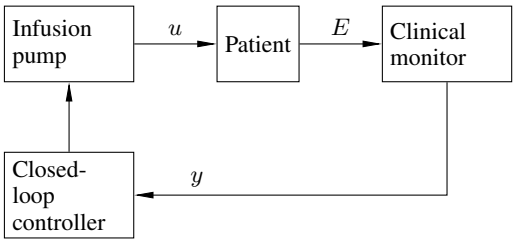


Fig. 1: Closed-loop drug delivery scenario, with control signal (infusion rate) u, clinical effect E, and corresponding measurement y.

For the anesthesia case, the control signal is the administration rate of an intravenously infused drug, such as propofol, and the measurement is typically an index reflecting consciousness, derived from EEG measurements. For the diabetes case, the control signal is the insulin infusion rate, while the blood glucose level is being measured.

The technical aspect that foremost limits the development of closed-loop drug delivery systems, is the availability of reliable patient models, dynamically relating drug infusion to clinical effect. For identification of such models to be successful, the patient(s) to be modeled need to be exposed to changes in the input (drug infusion rate), while the output (clinical effect) is measured. Clinical practice and ethics limit the amount of admissible excitation in such experiments, both with respect to input signal activity and duration.

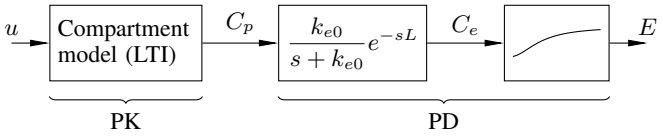


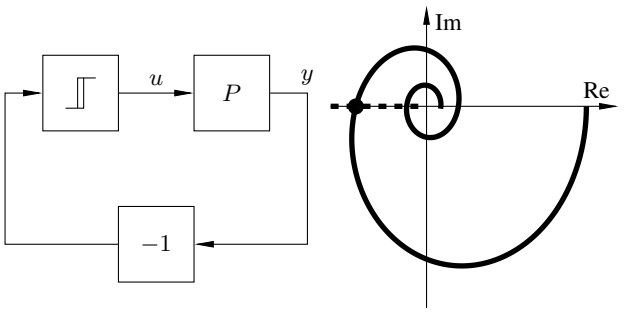
Fig. 2: Block diagram of PKPD model structure.

A quick review of typical model structures, and a motivation for the use of low-order approximations, is given in Section II. In Section III a short duration experiment, with limited activity in the control signal, is proposed. The use of the experiment outcome to identify low-order models, including uncertainty descriptions, is the topic of Section IV. The combination of experiment and parameter estimation method is demonstrated through a realistic example in Section V. Results are briefly discussed in Section VI.

II. Patient Models

It is customary to model the pharmacokinetics (PK), describing drug injection rate, distribution and elimination within the patient, using mammillary compartment models. These models are equivalent to linear time invariant (LTI) systems, where one of the states/compartments typically reflects the blood plasma concentration, C_p. A pharmacodynamic (PD) model then relates C_p to the clinical effect E, via the effect site (cortex for propofol) concentration C_e. The PD is typically a first order (time delay) FO(TD) system, with a sigmoid output nonlinearity, modeling saturation effects to very low drug concentrations and the fact that there is an upper bound on the clinical effect. The combination of the PK and PD model is termed the PKPD model. Figure 2 shows a block diagram of the PKPD model structure.

For control purposes, the static output nonlinearity of the PD model is typically handled either by linearization close to the intended operating point [12], or an inverting gain schedule [8]. The fact that the LTI part of the PKPD model lacks oscillatory modes (due to the compartment structure) allows



(a) Setup.

(b) Nyquist curve (solid) and negative inverse of relay describing function (dashed).

Fig. 3: Block diagram of relay experiment system, and frequency domain interpretation.

for good low-order approximations, as demonstrated in e.g. [13].

III. Experiment

A. Relay Methods

A method based on closing a negative feedback loop over the plant to be modeled, in series with a relay nonlinearity, $u = -\text{sgn}(y)u_{on}$, as shown in Figure 3a, was first presented in [2]. The inverse describing function of the relay intersects the plant dynamics Nyquist curve along the negative real axis, as shown in Figure 3b. For a large class of LTI systems, this results in limit cycle oscillations at the -180° phase angle of the plant. In its original version [2], the experiment is terminated once a stable limit cycle has been reached. Subsequently, the fundamental oscillation frequency and an estimate of the gain at the same frequency are identified from control and measurement signal peaks and corresponding times. This yields a model consisting of the system response at a single frequency, marked with a dot in Figure 3b. The relay method has seen several modifications: In [6] an integrator was connected in series with a second relay, to change the phase shift of the plant at which the limit cycle occurs. In [9, 3] an asymmetric relay was proposed. Unlike the symmetric relay, the output levels are $-u_{\text{off}} \neq u_{\text{on}}$ for the asymmetric relay. Once a stable limit cycle has been reached, this yields the possibility to identify parameters of a first order time delay (FOTD) model by only looking at switch durations and amplitudes. Formulas, based on describing function analysis, are presented in [9] and their practical application is demonstrated in [3].

The main strength common to all mentioned methods is that they produce experiments with excitation at frequencies relevant for controller synthesis – without the need of a priori plant information. This is indeed a desirable property for our application in mind, and a reason to that relay methods are widely used to tune industrial control systems. Their weaknesses are that they require the limit cycle to converge (long experiment time), and that only peak values are used for modeling (noise sensitive). In Section III-B, we propose a very short relay experiment, which, combined with the identification scheme of Section IV, preserves the strength of the relay methods, while removing their weaknesses.

B. Proposed Experiment

The experiment we are proposing is that presented in [3], with an asymmetric relay for which $u_{\text{on}} = -\gamma u_{\text{off}}$, and $\gamma = 1.5$. However, instead of the $6 - 8$ half periods typically needed for convergence, the experiment is terminated after only 3 half periods, as shown in Figure 4. Noise is assumed to be white, with zero mean and variance σ_n^2, and added to the process output y. An estimate $\hat{\sigma}_n^2$ of the noise variance is computed from open-loop data prior to the experiment, and the relay hysteresis level is set to $\mu = 2\hat{\sigma}_n$. These heuristic values for relay hysteresis μ and asymmetry γ have worked well in simulation, and the method is not particularly sensitive to changes away from them. (In order to limit the activity in u, it is desirable to keep μ small, while avoiding chattering triggered by n. Another measure to limit activity in u is to keep $\gamma \approx 1$, while a large value of γ corresponds to better excitation at low frequencies such as the DC.)

IV. Identification

A. Parameter Identification Scheme

The plant input u and output y, sampled at period h, are used to obtain parameter estimates $\bar{\theta} = [\bar{b}\ \bar{a}\ \bar{L}]^\top$ corresponding to the assumed FOTD model structure

$$\hat{P}(s) = \frac{b}{s+a}e^{-sL}. \tag{1}$$

This is done by a version of the output error method used in [11], presented below for the more general model structure

$$\hat{P}(s) = \frac{1}{s^k}\frac{b_1 s^{m-1} + b_2 s^{m-2} + \cdots + b_m}{s^n + a_1 s^{n-1} + \cdots + a_n}e^{-sL}, \tag{2}$$

parameterized in $\theta = [b^\top\ a^\top\ L]^\top$, where $b = [b_1\ \ldots\ b_m]^\top$ and $a = [a_1\ \ldots\ a_n]^\top$.

Continuous time models are used to limit the number of elements of θ, in presence of the delay L. The objective is to minimize (half the squared) $\mathcal{L}_2$-norm of the output error $e = y - \hat{y}$:

$$J(\theta) = \frac{1}{2}\int_0^\infty e^2(t)dt, \tag{3}$$

where $\hat{y}$ is the resulting output when $\hat{P}$ (parameterized in θ) is driven by u. The optimization problem is approached with a trust-region method [4]. To improve convergence, the method is provided with the parameter sensitivity gradient ∇J and Hessian ΔJ. The gradient w.r.t. θ is given by

$$\nabla J = \int_0^\infty e(t)\nabla\hat{y}(t)dt, \tag{4}$$

and the Hessian is

$$\Delta J = \int_0^\infty \nabla\hat{y}\nabla\hat{y}^\top + e(t)\Delta\hat{y}dt. \tag{5}$$

The first term of the integrand in (5) is quadratic (≥ 0), while the integral of the second term is small (≈ 0), under the realistic assumption that the output error is uncorrelated with its second derivative ($\mathbb{E}e\Delta\hat{y} = 0$). It is therefore fair

to approximate the Hessian by only the first term (although it is straightforward to extend the method outlined below, to include also the second term). In order to account for the k explicit integrators in (2), k zeros are appended to a, forming $\tilde{a} = [a^\top \ 0_{1\times k}]^\top$, while b is padded by leading zeros to make the same length: $\tilde{b} = [0_{1\times n-m+k} \ b^\top]^\top$. Using the results from [1] it is then possible to construct a continuous time LTI state space system, with output $[\hat{y} \ \nabla\hat{y}]^\top$, when driven by u. From y, $\hat{y}$, and $\nabla\hat{y}$, it is thereafter straightforward to compute J, ∇J and (the mentioned approximation of) ΔJ. The results of these computations are supplied in each iteration of a trust-region optimization algorithm (invoked from the Matlab `fmincon` command) to find the optimum $\bar{J}$ and corresponding (expected) parameter vector $\bar{\theta}$.

B. Parametric uncertainty

In addition to the expectation $\bar{\theta}$, the optimization provides the asymptotic covariance matrix

$$R_\theta = \mathbb{E}(\theta - \bar{\theta})(\theta - \bar{\theta})^\top = \frac{2}{N} J(\Delta J)^{-1}, \tag{6}$$

where N is the number of samples. The standard deviations of parameter estimates decreases proportional to $\sqrt{N}$, meaning that one cannot expect significantly improved estimation precision, merely by small increases in experiment duration.

C. Notes on convergence

In previous work [3, 11], relay experiments were used to obtain reasonable initial parameters for identification schemes similar to the one presented above in Section IV. As mentioned, this requires long experiment duration for the limit cycle oscillation to converge, while the use of extremum values in the data makes the procedure sensitive to noise. By evaluation on a set of 10^4 fourth order compartment models with random parameters, it turned out that initialization of the trust-region algorithm with the parameter vector $\theta = 0_{3\times 1}$ was sufficient to produce models with both good output fit and small parameter covariance, in the presence of an additive output white noise intensity corresponding to that of Figure 4a.

V. Results

A. Example Patient Model

In this section we demonstrate the proposed method, using a realistic example from anesthesia control. We will use a PK model with parameters computed from demographic parameters, according to a formula by Schnider [10]. For our example we will assume that the patient is male, 30 years old, weighs 70 kg, and is 174 cm tall, resulting in the PK model:

$$\dot{x} = \frac{1}{60}\begin{bmatrix} \frac{-Cl_1+Cl_2+Cl_3}{V_1} & \frac{Cl_2}{V_1} & \frac{Cl_3}{V_1} \\ \frac{Cl_2}{V_2} & \frac{Cl_2}{V_2} & 0 \\ \frac{Cl_3}{V_2} & 0 & -\frac{Cl_3}{V_3} \end{bmatrix} x + \frac{1}{60^2}\begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{bmatrix} u$$

$$C_p = [1 \quad 0 \quad 0]\, x, \tag{7}$$

with clearances $Cl = [1.68 \ 1.82 \ 0.84]^\top$ l·min^{-1}, and (virtual) compartment volumes $V = [4.27 \ 27.50 \ 238]^\top$ l. The input u (propofol infusion rate) is of unit mg·h^{-1} and the output C_p (plasma concentration) is of unit μg·ml^{-1}. The states are the per compartment drug concentrations. The PK model (7) is combined with a PD consisting of the first order system

$$G_{C_p,C_e} = \frac{k_{e_0}}{s + k_{e_0}}, \tag{8}$$

relating the plasma concentration C_p to the effect site concentration C_e, with $k_{e_0} = 0.46/60$ s^{-1}, and the static output nonlinearity

$$E = \frac{v^\gamma}{v^\gamma + 1}, \tag{9}$$

where $v = C_e/C_{e,50}$, $C_{e,50} = 1.8$ μg·ml^{-1} and $\gamma = 5.8$ (all being clinically relevant values[1]). Apart from the patient model, the NeuroSense monitor [14], used to measure the clinical effect, has low-pass LTI dynamics:

$$G_{NS}(s) = \frac{1}{(8s+1)^2}, \tag{10}$$

relating the measurement y to the clinical effect E. The typical operating point lies close to 50 % of clinical effect, i.e., $C_e = C_{e,50}$ and $E = 0.5$ (corresponding to stationary input $u_0 = 181$ mg·h^{-1} and output $y = 0.5$). Linearizing the combined PKPD model and monitor dynamics (7)–(10) around this point, we obtain the transfer function

$$P_{lin} = G_{u,C_p} \cdot G_{C_p,C_e} \cdot \frac{\gamma}{4C_{e,50}} \cdot G_{NS}, \tag{11}$$

where G_{u,C_p} is the transfer function corresponding to (7).

B. Experiment and Identification

The outcome of the proposed experiment is shown in Figure 4. The obtained FOTD model parameter vector is $\bar{\theta} = [\bar{b} \ \bar{a} \ \bar{L}]^\top = [\bar{K}/\bar{T} \ 1/\bar{T} \ \bar{L}] = [1.42\cdot 10^{-5} \ 2.82\cdot 10^{3} \ 55]^\top$, corresponding to

$$\bar{P}(s) = \frac{K}{sT+1} e^{-sL} = \frac{5.04\cdot 10^{-3}}{354s+1} e^{-55s}, \tag{12}$$

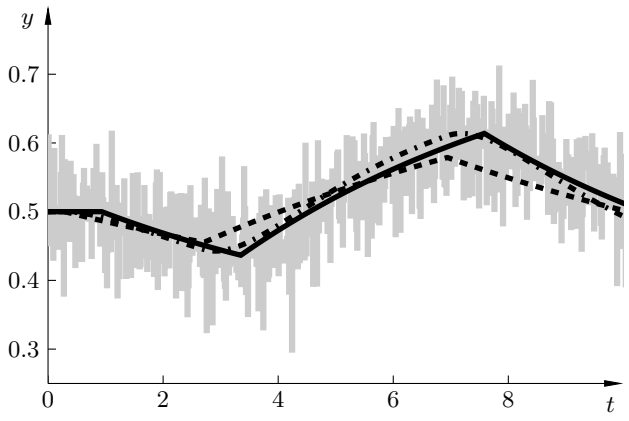
Over-estimation of the delay results from approximating the high order dynamics (11) by an FOTD system. The *natural logarithm* of the parameter covariance estimate is

$$\log(R_\theta) = \begin{bmatrix} -28.2 & -21.9 & -13.0 \\ -21.9 & -14.8 & -6.0 \\ -13.0 & -6.0 & 3.3 \end{bmatrix}, \tag{13}$$

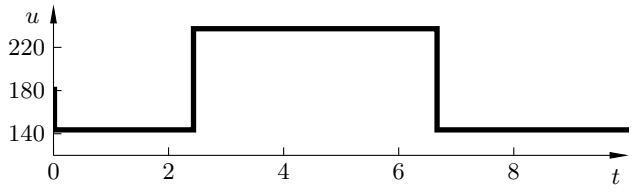
resulting in *relative* parameter standard deviations $\tilde{\sigma}_\theta = \sqrt{\mathrm{diag}(R_\theta)}/\bar{\theta} = [5.2 \ 21 \ 9.5]^\top 10^{-2}$, where division is element-wise. To get an additional sense of model quality, (12) can be compared with the FOTD model obtained by balanced reduction of the delay-free part of (11), while keeping the delay unchanged:

$$P_{bal}(s) = \frac{5.14\cdot 10^{-3}}{549s+1} e^{-16.5s}. \tag{14}$$

[1] In some literature, (9) has two additional calibration parameters E_0 and $E_{\max}$. The version presented here corresponds to (the calibrated) case of $E_0 = 0$ and $E_{\max} = 1$.



(a) Measurement y (grey), output of identified model (12) (black, solid), output of model from balanced reduction (black, dashed), and (unavailable) noise free measurement (black, dotted). Output is scaled such that $(0, 1)$ corresponds to (absence of drug, full clinical effect).



(b) Experiment input signal u [mg/h].

Fig. 4: Outcome of relay experiment. Time in minutes.

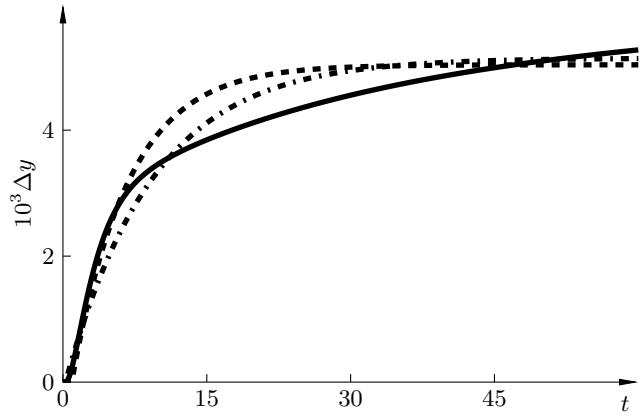


Fig. 5: Step responses of full model (11) (solid), identified model (12) (dashed), and FOTD model from balanced reduction (14) (dotted). $\Delta y = y - y_0$ denotes deviation from $y_0 = 0.5$, units as in Figure 4a.

From Figure 4a it is clear that the model, (14), obtained by balanced reduction, has a much larger output error than the corresponding identified model (12). Figure 5 shows the step response of the full model (11) together with those of the identified model (12) and the one obtained through balanced reduction (14). Note that, apart from poorer excitation, a much longer duration (1 h instead of 10 min) would be needed if using step response data, rather than relay feedback.

VI. Discussion

This paper has presented a novel combination of a relay based experiment and an output error identification scheme. The main strengths lie in the short experiment duration and excitation at a phase shift relevant to control (inherent to relay methods). The method works reliably in the presence of noise and provides an estimate of the parameter covariance, in addition to nominal values.

In this work the method was demonstrated for identification of FOTD models. However, given sufficient excitation and initialization, it works equally well for higher order models.

It can also be noted that the described method allows for identification of the patient dynamics, with the monitor dynamics (10) excluded. This is enabled by applying (10) to u, prior to the identification.

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