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Quantification of the variability in response to propofol administration in children

Klaske van Heusden, J. Mark Ansermino, Kristian Soltesz, Sara Khosravi, *Student Member, IEEE,* Nicholas West, Guy A. Dumont, *Fellow, IEEE*

Abstract—**Closed-loop control of anesthesia is expected to decrease drug dosage and wake up time while increasing patient safety and decreasing the work load of the anesthesiologist. The potential of closed-loop control in anesthesia has been demonstrated in several clinical studies. One of the challenges in the development of a closed-loop system that can be widely accepted by clinicians and regulatory authorities is the effect of inter-patient variability in drug sensitivity. This system uncertainty may lead to unacceptable performance, or even instability of the closed-loop system for some individuals. The development of reliable models of the effect of anesthetic drugs and characterization of the uncertainty is therefore an important step in the development of a closed-loop system. Model identification from clinical data is challenging due to limited excitation and the lack of validation data. In this paper, approximate models are therefore validated for controller design by evaluating the predictive accuracy of the closed-loop behavior. A set of 47 validated models that describe the inter-patient variability in the response to propofol in children is presented. This model set can be used for robust linear controller design provided that the experimental conditions are similar to the conditions during data collection.**

Index Terms—**Anesthesia, System identification, Robust control.**

I. INTRODUCTION

Propofol is an intravenously administered anesthetic drug characterized by its fast redistribution and metabolism. It is commonly used for induction and maintenance of anesthesia. Inter-patient differences in pharmacokinetics (PK)[1] and pharmacodynamics (PD)[2] affect individual responses to propofol infusion. Administration of propofol therefore requires continuous monitoring of the hypnotic state by the anesthesiologist, and adjusting of drug dosing to the individual need.

Traditionally the propofol infusion rate is controlled manually by the anesthesiologist. Computer aided open-loop de-

livery systems known as Target Controlled Infusion (TCI) systems are commercially available for adult patients. In this open-loop control setting, the target concentration needs to be adjusted by the anesthesiologist to maintain adequate anesthesia, due to widely varying individual patient responses to propofol. The use of TCI systems in children is limited due to the large inter-patient variability of PKPD behavior in children and the debated validity of pediatric PKPD models [2]. Closed-loop control of propofol infusion using feedback from a measure of the depth of hypnosis (DOH) can reduce the effect of inter-patient variability and improve control of DOH [3]. At the same time, this variability introduces a challenge for closed-loop control in anesthesia [4]. Uncertainty limits the achievable control bandwidth and characterization of the uncertainty is required to ensure stability and performance of the closed-loop system [4].

The goal of this study is to identify models of the effect of propofol on the DOH in children that describe the inter-patient variability in children age 6 to 16y, for the purpose of robust linear controller design. The WAV_{CNS} index[3] (NeuroSENSE monitor, NeuroWave Systems, Cleveland Heights, USA) is used as measure of the clinical effect. The NeuroSENSE monitor was developed specifically for use in closed-loop control. It does not introduce a delay and its dynamic behavior is consistent and well characterized [5], [6].

Model identification from clinical data from propofol anesthesia introduces fundamental challenges [7]. Propofol infusion profiles in clinical practice provide limited excitation, propofol is often used in combination with fast acting opioids like remifentanil that have a synergistic effect, and the response to propofol infusion is nonlinear. Nonlinear dynamic model structures are generally not identifiable from clinical data. If the data is not sufficiently rich, a good fit of the model with the data is insufficient for model validation. In this paper, simple models based on a linear approximation [8] are identified from clinical data from open- and closed-loop induction of anesthesia. In addition to evaluating the model fit, the models are validated for the design of linear controllers by comparing the predicted closed-loop behavior to measured responses under the same controller.

PKPD models that are traditionally used to describe the effect of propofol contain a third order linear PK model, and a PD model consisting of a first-order linear transfer

[1]Pharmacokinetics describe the transport and metabolism of a drug.

[2]Pharmacodynamics relate plasma drug concentration to clinical effect.

[3]The WAV_{CNS} index is a number between 0 and 100, where the measured effect in the absence of drugs is approximately 90 and $WAV_{CNS} = 0$ corresponds to the maximum DOH. The range $[40-60]$ corresponds to general anesthesia.

function and an output nonlinearity (a Wiener model) [2]. Simplifications in the model structure have been proposed to improve identifiability from clinical data: PKPD model structures with some parameters fixed [2], [8], [9], first-order plus time-delay (FOPTD) models with an output nonlinearity [7], [10], piecewise linear models [11] and a simplified model for the effect of both propofol and remifentanil including an output nonlinearity [12]. Identifiability of these proposed structures has not been evaluated. Normally only one set of clinical data is available per subject and identified models are often validated based on the model fit with the identification data set [10], [12], [7], [11]. Due to the limited excitation in the clinical data, the predictive capacity of these models validated based on the identification data is difficult to evaluate. Ten and fifteen minute ahead predictions were considered by [9] to evaluate the model quality for its intended use, i.e. real-time prediction of individual responses.

The models identified in this study are developed for the design of robust linear controllers. It is well known that simple linear models are often sufficient to achieve good control performance, even for systems with nonlinear behavior [13]. Such a linear approximate model depends on the experimental conditions [14], and can be considered a good model for a system controlled by a specific controller if the distance between the predicted and achieved closed-loop system is small for that specific controller [15], [16]. Validation of the model set identified in this study therefore includes evaluation of the predicted closed-loop response and a comparison of this response to clinical closed-loop data. Two model structures (PKPD and FOPTD) are considered. It is shown that the predicted closed-loop performance is comparable for these structures. The parameters for both model sets are given for 47 subjects. Both validated model sets can be used for controller design, provided the experimental conditions are similar to the conditions during data collection [16].

The PKPD and FOPTD model structures are described in Section II. Section III discusses the clinical data that was available for identification and highlights the characteristics of this data and their effect on model identification. Section IV describes the identification procedure and Section V summarizes the results. Model validation is discussed in Section VI. Concluding remarks are given in Section VII.

II. MODELING THE EFFECT OF PROPOFOL

A. PKPD model structure

The effect of propofol on the DOH is traditionally modeled using compartmental PKPD models [4], whose model structure is shown in Fig. 1A. The PK model relates the drug infusion rate $u(t)$ to the plasma concentration $C_p(t)$, $C_p(s) = PK(s)u(s)$, where $PK(s)$ can be written as

$$PK(s) = \frac{1}{V_1} \frac{(s+k_{21})(s+k_{31})}{(s+\pi)(s+\alpha)(s+\beta)}, \quad (1)$$

using the central compartment volume V_1 and the pharmacokinetic distribution time constants $\pi, \alpha, \beta, k_{21}$ and k_{31}. The PD model consists of a FOPTD transfer function, describing the dynamics between $C_p(t)$ and the concentration of propofol at
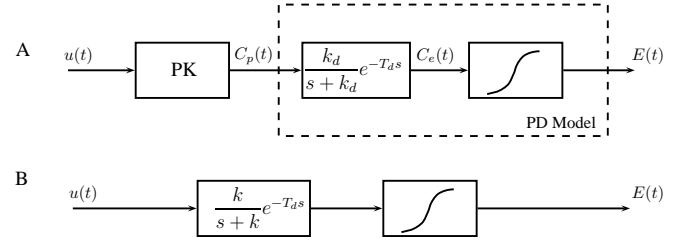

Fig. 1. Block diagrams of the proposed model structures. A: PKPD model structure. The PK model is followed by the PD model consisting of a linear first-order transfer function and the nonlinear Hill function. B: FOPTD structure. The dynamics of the effect of propofol on the DOH are grouped into a FOPTD transfer function. The nonlinearity is described by the Hill function.

the effect site $C_e(t)$, and the nonlinear Hill function defined as

$$E(t) = E_0 - E_0 \frac{C_e^\gamma(t)}{EC_{50}^\gamma + C_e^\gamma(t)}, \quad (2)$$

describing the relation between $C_e(t)$ and the clinical effect $E(t)$. EC_{50} is the effect-site concentration at which half of the maximum effect is achieved and γ determines the nonlinearity.

In this study, the PK model is fixed to reduce the number of variables to identify. Only the PD parameters are identified, following the approach in [8]. The Paedfusor PK model [17] is used to predict $C_p(t)$. The parameters of the PD model, E_0, k_d, T_d, EC_{50} and γ, are identified from data.

B. FOPTD model structure

FOPTD models are commonly used for controller design and their use to describe the effect of propofol on the DOH has been proposed [7], [10]. The FOPTD model directly relates the infusion rate to the clinical effect, as shown in Fig. 1B. In this model structure, the nonlinear Hill function is defined as

$$E(t) = E_0 - E_0 \frac{E_{LTI}^\gamma(t)}{E_{50}^\gamma + E_{LTI}^\gamma(t)}, \quad (3)$$

where $E_{LTI}(t)$ is the effect as predicted by the LTI block, see Fig. 1B. The system gain is modeled using E_{50} and the nonlinearity is parameterized by γ. The unknown parameters E_0, k, T_d, E_{50} and γ are identified. Note that the number of unknown parameters in this FOPTD structure is the same as the number of unknown parameters in the PKPD structure where the PK model is fixed.

III. CLINICAL DATA

Data from both open-loop and closed-loop controlled anesthesia was available for this identification study.

A. Open-loop data

Following approval from the institutional research ethics board (REB), data was analyzed for thirty (30) children undergoing elective general surgery using total intravenous anesthesia. Fig. 2A shows the data collection setup. Propofol and remifentanil were administered as an initial bolus followed by a continuous infusion, manually controlled by the anesthesiologist. Propofol infusion is represented by $u(t)$.

The clinical effect $E(t)$ is affected by the opioid infusion due to the synergistic effect of remifentanil. The clinical effect $E(t)$ is measured as the WAV_{CNS} index [6]. The measured DOH is affected by stimulation from the procedure, $d(t)$, and measurement noise $n(t)$. The monitor dynamics, relating the clinical effect $E(t)$ to the measured WAV_{CNS} index, are determined by the trending filter [6], and correspond to $G_M(s) = 1/(8s + 1)^2$ for a 30 second filter [8]. Propofol infusion rates were recorded manually. The WAV_{CNS} index was recorded every second throughout the case.

B. Closed-loop data

Propofol infusion rates and recordings of the WAV_{CNS} index were available from a clinical pilot study of closed-loop control of propofol anesthesia in children [1]. Following REB approval, and informed consent/assent, 69 children age 6-16y (11y$\pm$3, 34 male, 43kg$\pm$15, 150cm$\pm$17) ASA I-II[4], requiring anesthesia for elective upper and/or lower gastrointestinal endoscopic investigations were enrolled for this study.

Fig. 2B shows the setup for closed-loop control of DOH. The setpoint is defined by the anesthesiologist and the propofol infusion rate is calculated by the controller. The closed-loop system uses feedback from the NeuroSENSE DOH monitor. Propofol is delivered by an Alaris TIVA infusion pump (Care-Fusion, San Diego, USA) connected to an intravenous line. In addition to the robust PID controller, the control system contains necessary safety layers and alarms. During the cases, both information from the control system and the physiological monitors is recorded every second. Remifentanil was administered as a bolus ($0.5\mu g/kg$) prior to propofol administration followed by continuous infusion ($0.03\mu g/kg/min$).

Closed-loop data was recorded for 23 cases using an initial robust PID controller design [1]. The observed responses in these 23 cases indicated sufficient robustness and the controller was retuned to improve the speed of induction of anesthesia and the response to stimulation (PKPD models identified from data of these 23 cases were used for the controller redesign). This retuned system was evaluated in 46 additional cases. Consequently, data from a total of 69 cases of closed-loop control of propofol anesthesia were available for system identification.

C. Characteristics of clinical data from propofol anesthesia

Clinical data collected during typical cases of both open-loop and closed-loop controlled anesthesia are shown in Fig. 3. The effect of propofol depends on the remifentanil infusion due to the synergistic effect of these drugs. This synergy is not taken into account and the identified models will be affected by the remifentanil infusion. Consequently, the models can only be validated for similar experimental settings and comparable remifentanil administration.

As indicated in Fig. 2, the clinical data contains measurement noise, $n(t)$, as well as disturbances due to stimulation from the procedure, $d(t)$. The measurement noise is assumed

[4]American Society of Anesthesiologists physical status classification system. ASA I: normal healthy patient, ASA II: patient with mild systemic disease.
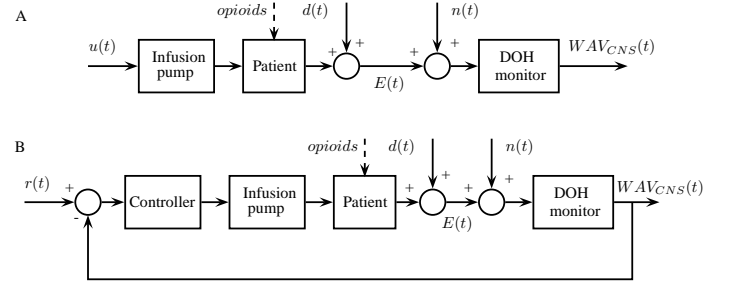

Fig. 2. Schematic view of the setup used for data collection. Fig. A: Open-loop setup, where $u(t)$ is the infusion rate, set directly by the anesthesiologist. The infusion pump delivers propofol to the patient. The synergistic effect of opioids is indicated with the dashed line. The DOH monitor provides a measure of the clinical effect ($WAV_{CNS}(t)$). Both stimulation from the procedure ($d(t)$) and measurement noise ($n(t)$) affect the measured WAV_{CNS}. Fig. B: Closed-loop setup for control of DOH, where $r(t)$ is the reference DOH set by the anesthesiologist.
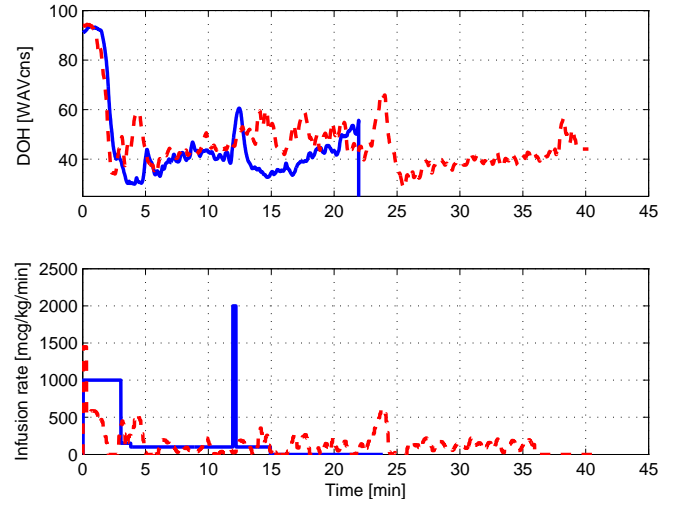

Fig. 3. Measured DOH (top figure) and corresponding propofol infusion rates (bottom figure) collected during two typical cases. Solid line: in this case the propofol infusion was controlled manually by the anesthesiologist. An initial bolus was followed by a continuous infusion. A bolus was given in response to stimulation after approx. 12 minutes. Drug infusion was stopped after approx. 15 minutes. Dashed line: in this case the propofol infusion rate was closed-loop controlled. Drug infusion was stopped after approx. 35 minutes.

to be zero mean. Nociceptive stimulation caused by the procedure decreases the clinical effect and cannot be assumed to be zero mean. The data from the open-loop controlled case shows an example of the effect of stimulation on the measured DOH after 12 minutes. The anesthesiologist gave a bolus of propofol after noticing the response to stimulation. The closed-loop controlled case shows several responses to stimulation, at the start of the case (after about 4 minutes) and during maintenance of anesthesia (around 15 and 23 minutes). Surgical stimulation cannot be measured, and because the associated disturbances are not zero mean, the effect of stimulation will introduce a bias in model identification.

During induction of anesthesia, nociceptive stimulation is generally limited, and data from induction of anesthesia can be used for identification to limit the effect of disturbances on the identified model [8], [10]. However, initial scope insertion during endoscopic procedures and the insertion of airway devices during general surgery can cause nociceptive
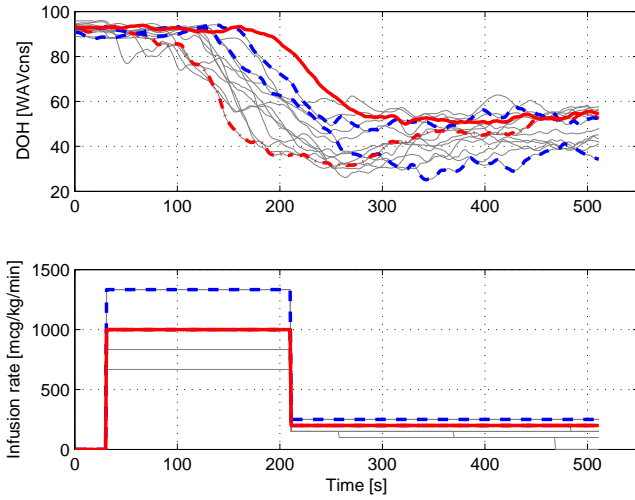
Fig. 4. Recorded WAV_{CNS} and propofol infusion rate for 14 subjects (grey thin lines) in open-loop protocol. One fast (dash-dot) and one slow response (solid line) are highlighted. The dashed lines highlight two average responses.

Fig. 5. Recorded closed-loop controlled WAV_{CNS} and propofol infusion rate for 36 subjects used for identification (grey thin lines). Different dynamic responses to propofol infusion are highlighted: two responses that show a gradual WAV_{CNS} decrease (dashed lines) and two cases that show a more abrupt decrease (dash-dot and solid line).

stimulation. Cases that show a significant reaction during induction of anesthesia need to be discarded to limit the bias in the identified model.

Nonlinear model structures including the structures shown in Fig. 1 are generally not identifiable from clinical data [12], [10]. During induction of anesthesia, the WAV_{CNS} changes from ≈ 90 (awake) to 50 (adequate anesthesia), corresponding to a step response. The effect of the nonlinearity γ cannot be distinguished from the dynamic parameters T_d and k_d (or k) due to the limited excitation in the step response. However, a linear approximation of the system identified from the step response can provide an adequate approximate model for controller design [13].

IV. MODEL IDENTIFICATION FROM CLINICAL DATA

A. Data selection

The quality of models identified from data depends strongly on the quality of that data. The clinical data was therefore inspected visually and manually selected before identification. To achieve this, we took clear signs of response to stimulation in the measured WAV_{CNS} into account as well as additional observations and information collected in the operation room.

1) Open-loop data: The first eight (8) minutes after the start of propofol infusion were used for model identification. Data was incomplete for six (6) cases. Induction of anesthesia required volatile anesthetics in two (2) cases. Five (5) cases were discarded due to corrupted data or insufficient data quality. Three (3) cases were discarded because they showed a strong reaction to stimulation during induction of anesthesia. The recorded data for the remaining 14 cases is shown in Fig. 4. Data interpolation at a stable WAV_{CNS} index was performed in four cases where 5 seconds (1 case), 10 seconds (2 cases) and 40 seconds (1 case) of data were missing. The recordings in Fig. 4 clearly show the inter-patient variability observed in the response to propofol anesthesia in children.
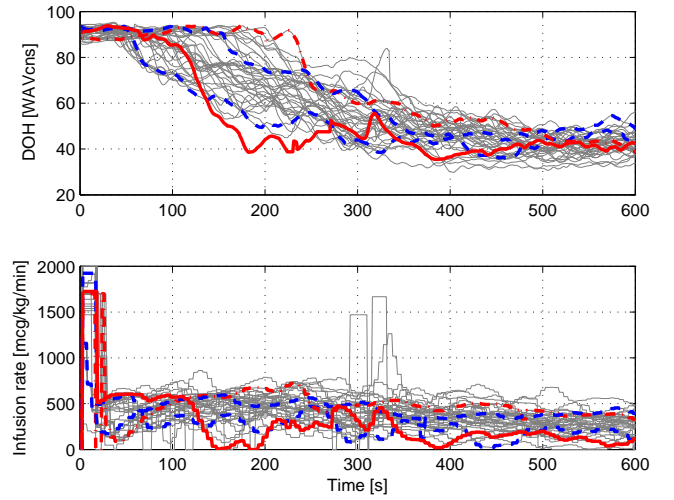
2) Closed-loop data: The speed of induction of anesthesia was slower in the closed-loop study than in the open-loop study, therefore the first 10 minutes after the start of propofol infusion were used for identification. Recordings of 33 out of the original 69 cases show a strong reaction to stimulation during the first 10 minutes after the start of propofol infusion and were discarded after visual inspection. Data from the remaining 36 subjects, shown in Fig. 5, were used for model identification.

Note that some reaction to stimulation due to insertion of airway devices or scope insertion during endoscopic investigations is common. The large number of cases discarded to avoid bias in the identified model as a result of stimulation is related to the low dose of remifentanil administered during these procedures. It is not a result of the use of closed-loop control.

B. Identification of the model parameters

In a two-step identification approach, a linear approximation is initially identified. This linear approximation of the step response is expected to provide an adequate approximation for controller design [13]. In a second step, the model fit is improved through optimization of the nonlinearity γ. In the first step, identifying the linearized model, the monitor dynamics and the PD model are commutative and the infusion profile or the plasma concentration can be filtered by G_M to account for these dynamics [8]. The nonlinearity is expected to be underestimated because the nonlinear behavior is approximated by a linear model in the first step. The trade-off between the dynamic parameters T_d and k_d (or k) and the nonlinearity γ is therefore expected to tend towards larger time delays, slower dynamics and smaller values for γ.

For each set of open- and closed-loop data, E_0 is estimated as the average effect measured during the first 50 seconds after the start of propofol infusion (no response is expected during this period). In some data sets the WAV_{CNS} index increased

at the start of the case, possibly related to pain on injection of propofol. This increase can lead to overestimation of T_d. The time delay is therefore limited to $T_d < 120s$. The models are discretized using the Euler method.

The FOPTD models are identified as follows: The infusion profile is filtered by the dynamics of the monitor G_M. A linearization of the model is identified using the output-error method [18]. In a second optimization step γ is identified.

Identification of the PKPD models requires calculation of the plasma concentrations $C_p(t)$ corresponding to the infusion profile $u(t)$. The Paedfusor population PK model [17] is used to predict $C_p(t)$. The $C_p(t)$ profiles are filtered by G_M. In the first optimization step, a linearization of the PD model is identified using the output-error method. In a second step the model fit is improved by identifying γ in eq. (2).

Remark: Direct identification from closed-loop data using the output-error approach is known to result in biased models. When the data is collected in closed-loop, the input to the system is correlated to the noise. In that case, direct identification using the system input (controller output) and output (measured WAV_{CNS}) is unbiased with respect to noise, only if both the system model and the noise model are in the model set [19]. Identification of the noise model or the use of indirect identification could be considered to provide a consistent estimate. For the identification of models with a fixed structure, i.e. the PKPD models or FOPTD models considered in this study, "tailor-made" parameterizations could be used. However, when undermodeling of the plant is present, these methods will also introduce bias.

Direct identification and indirect identification differ by the choice of noise model [19]. If there is no undermodeling of the plant, an unbiased plant model can be obtained when the structure of the noise model is chosen correctly. In case of undermodeling of the plant, there will be a bias for all methods. The frequency weighting of this bias depends on the identification method and corresponding noise model. If the signal-to-noise ratio is large or if the feedback noise contribution to the input of the identified model is small, the bias due to noise in the direct approach will be small [19].

When identifying a linear approximation of the response to propofol infusion during induction of anesthesia, a nonlinear plant is approximated by a linear model and undermodeling will be present. All closed-loop identification methods will therefore introduce bias [19]. Direct identification using the output-error approach was chosen because the optimization problem is relatively simple and the bias due to noise is expected to be small. The high-frequency noise is low-pass filtered by G_M. In the PKPD model structure additional low-pass filtering by the PK model removes most of the noise contribution to the input of the identified PD model. Advantages of alternative closed-loop identification methods (different bias weighting) are not expected to outweigh the cost of increased complexity of the optimization problem, the increased number of parameters to be identified and the increased risk of finding local minima. Validation of the predicted closed-loop response supports this choice.
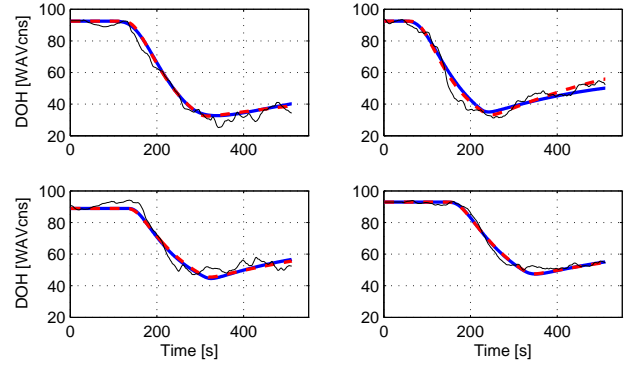

Fig. 6. Response of the identified models compared to the data for the four cases highlighted in Fig. 4. The figures show the predicted output of the FOPTD models (dashed lines), the predicted output of the PKPD models (thick solid lines) and the measured response (thin lines).

V. RESULTS

A. Open-loop data

For each of the 14 open-loop cases, a PKPD model and a FOPTD model were identified. For 8 out of the 14 cases, the FOPTD models achieve a better fit with the data than the PKPD models. The average of the root mean square residual errors between the data and the predicted model output was $3.61(\pm0.85)$ (mean rms($\pm$ std)) for the FOPTD models and $3.79(\pm0.85)$ for the PKPD models.

B. Closed-loop data

For each of the 36 closed-loop cases, a FOPTD model and a PKPD model were identified. The FOPTD models achieve a better fit than the PKPD models for 25 out of the 36 cases. The average of the root mean square (rms) residual errors (mean rms($\pm$ std)) between the data and the predicted model output was $3.55(\pm0.82)$ for the FOPTD models and $3.68(\pm0.79)$ for the PKPD models.

For both the open- and closed-loop data, the FOPTD models achieve a better fit on average than the PKPD models. This confirms the results of [10]. Note that the differences are not clinically relevant.

VI. MODEL VALIDATION

A. Comparing the model prediction to the identification data

The predicted output for each model is compared to the identification data and the fit is inspected visually. The fit was deemed sufficient for both the PKPD and the FOPTD models for 49 out of the 50 subjects and these 49 models are validated based on the fit with the identification. Examples of a sufficient fit are shown in Fig. 6 and 7. Fig. 8 shows the fit obtained for the $50th$ subject. The rms residual error for this subject is 5.25 for the FOPTD model and 5.08 for the PKPD model. After visual inspection, it is concluded neither the FOPTD nor the PKPD model captures the dynamics of the response. The data shows response to stimulation after ≈ 5 minutes. The models are biased because of this disturbance. This case accentuates the variability in response to stimulation and the need for visual inspection of both the data and the model predictions.
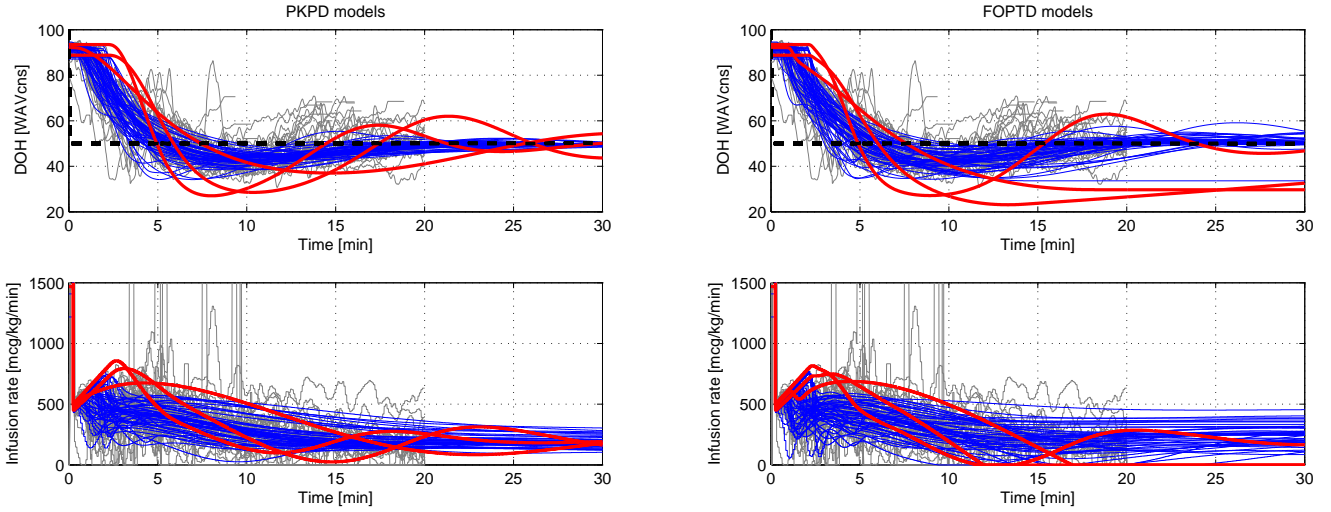
Fig. 9. Comparison of the simulated closed-loop responses of the 47 PKPD and FOPTD models (thin lines) and the recorded closed-loop data from 36 cases under the same controller (grey thin lines). The dashed line indicates the control setpoint. Data where the exact controller configuration differed from the simulated configuration or where occlusion of the infusion lines occurred were discarded. Note that 22 of the 47 models were identified from data in this data set. The closed-loop response of the PKPD models is shown left, the response of the FOPTD models is shown right. The three (3) outliers as discussed in Section VI-B are highlighted (thick lines).
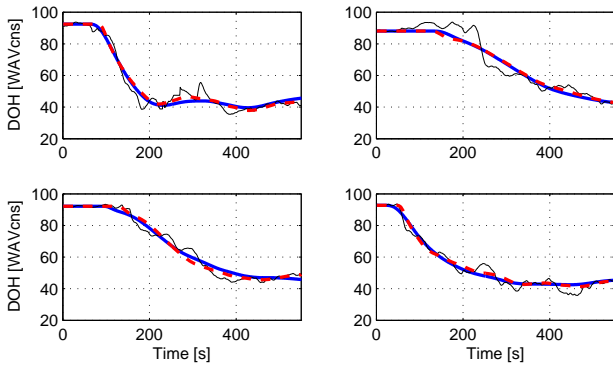

Fig. 7. Predicted response of the identified models compared to the data for the four cases highlighted in Fig. 5. The figures show the predicted output of the FOPTD models (dashed lines), the predicted output of the PKPD models (thick solid lines) and the measured response (thin lines).
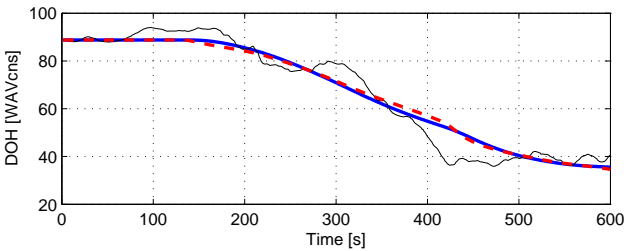

Fig. 8. Predicted response of the identified models compared to the data for the subject for which the fit was deemed insufficient based on visual inspection. The figure shows the predicted output of the FOPTD model (dashed line), the predicted output of the PKPD model (thick solid line) and the measured response (thin line).

B. Closed-loop response

Due to the limited excitation in clinical data and the resulting identifiability issues, different models with the same structure can provide an adequate fit with the data. Model validation based on rms errors and visual inspection of the fit is therefore insufficient. To overcome this limitation, the models identified in this study are validated for robust linear controller design. A good model for a system controlled by a specific controller achieves a small distance between the predicted and achieved closed-loop system for that controller [15], [16]. A minimal requirement for a validated model is therefore that the model achieves a small distance between the predicted and measured responses for the controller that was clinically evaluated. In the following, the models are therefore validated based on the predicted closed-loop performance of the models controlled by the redesigned PID controller as described in Section III-B.

Fig. 9 shows the simulated closed-loop response of the complete set of 50 identified models controlled by the clinically evaluated PID controller. The measured closed-loop responses under the same controller are shown for comparison. The induction time[5] for the PKPD and FOPTD models are similar (mean ($\pm$ std) 3.6 min ($\pm 42s$) and 3.7 min ($\pm 44s$) respectively). The overshoot upon induction is 8($\pm$3) for the PKPD models and 9($\pm$4) for the FOPTD models. The PKPD models shows less variability in the predicted settling time[6]; 13 min ($\pm$3.4 min) for the PKPD models, 13.4 min ($\pm$5.3 min) for the FOPTD models. The response of the FOPTD models that contain an integrator is not realistic (constant $WAV_{CNS} \approx 30$ and zero infusion).

The responses of the PKPD models show three (3) distinct outliers, highlighted in Fig. 9. One of these outliers corresponds to the models for the subject shown in Fig. 8, for which the model fit was insufficient. The simulated response of the two other outliers was compared to the observed response. The simulated response for the case shown in Fig. 10 corresponds

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[5]Defined as the time from the start of propofol infusion until the WAV_{CNS} reaches 60 and stays below 60 for at least 30 seconds.

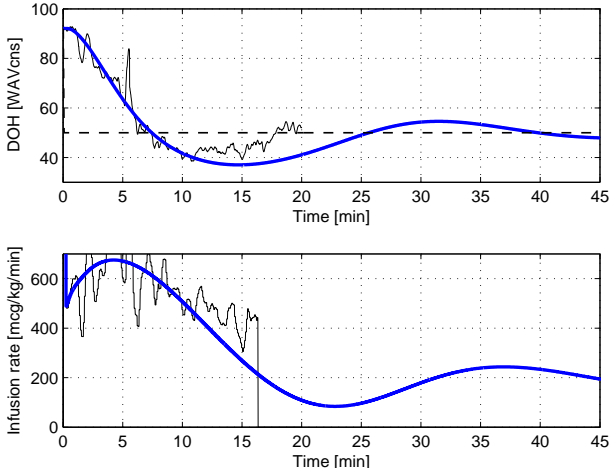[6]Defined as the time to stabilize in the range $45 - 55 WAV_{CNS}$.

Fig. 10. Comparison of the simulated (thick line) and the measured (thin line) closed-loop responses for one of the cases highlighted in Fig. 9. The PKPD model was used for simulation. The dashed line indicates the setpoint.
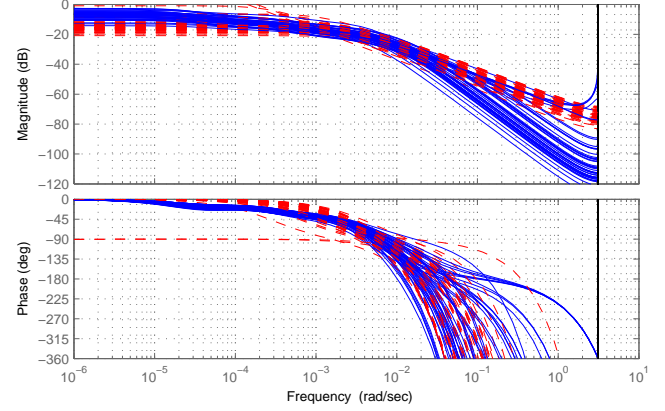

Fig. 11. Bode diagrams of models linearized for induction of anesthesia. Bode diagrams of the 47 PKPD models are shown in solid lines, Bode diagrams of the 47 FOPTD models are shown dashed. The input and output units are $\mu g/kg/min$ and $100 - WAV_{CNS}$ respectively.

to the measured response for up to 10 minutes, but deviates after these 10 minutes. The oscillation in the simulated system indicates smaller robustness margins than observed in practice. Similar dynamics were observed for the third outlier. The use of these three models in controller design would lead to overly conservative controllers, the three outliers highlighted in Fig. 9 are therefore considered invalid for controller design.

Comparison of the simulated closed-loop response of the remaining 47 models to the measured responses under the same controller shows that the model set captures the observed inter-patient variability and provides a good description of the system's response to induction of anesthesia. Note that the measured data is affected by nociceptive stimulation and that the setpoint for the controller was changed to 60 in some cases after 10 or more minutes (the anesthesiologist considered this lighter anesthetic state sufficient in these cases).

The identified models are based on a linear approximation. The inter-patient variability is therefore largely described by the linear dynamics of the models. This variability in the linear dynamics can be used for the design of robust linear controllers. The model sets of 47 models are validated for the design of robust linear controllers for induction and maintenance of anesthesia, provided that the experimental conditions are similar to the experimental conditions during data collection.

C. Model sets for robust linear controller design

Fig. 11 shows the Bode diagrams for both the PKPD and the FOPTD models. The models are normalized with respect to the subject's weight and the model gains are linearized for induction of anesthesia[7]. At high frequencies, the roll-off of the PKPD models is higher than the roll-off of the FOPTD models, as expected due to the different model orders. The differences in dynamics at low frequencies reflect inaccurate steady state gain estimates, due to the limited length of the data

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[7]The gain is calculated as $(E_0 - 50)/u_{50}$, where u_{50} is the steady state infusion rate corresponding to the setpoint $WAV_{CNS} = 50$.

segments used for identification. For intermediate frequencies, the dynamics of the FOPTD and PKPD models are similar and the gain and the phase shift of the identified models are comparable around the intended closed-loop bandwidth (between 10^{-3} and 3×10^{-2} rad/s). The variability is also comparable in this bandwidth. The closed-loop behavior of the FOPTD and PKPD models is therefore similar under the same controller.

A complete list of the identified parameters for both the PKPD and the FOPTD structure is given in Table I. The FOPTD model set shows more variability although the difference is marginal. The time response of the PKPD models is more realistic than the time response of the FOPTD models. Both model sets are appropriate for the design of linear robust controllers. Depending on the controller design method and the requirements imposed by that method, either the FOPTD or the PKPD model set can be favored. For these models based on a linear approximation:

- the model validity is limited to experimental conditions where the linearization is expected to provide a good approximation of the system behavior. If the experimental settings change significantly, for example significant changes in speed of induction or significant changes in opioid infusion, the models may not be adequate for controller design.
- the identified PD parameters in the PKPD structure have limited physiological meaning.
- the identified parameters in the FOPTD models have limited physiological meaning.
- the time delay in the FOPTD models represents the phase shift between the propofol infusion and the observed clinical effect and does not provide a realistic estimate of the time delay observed clinically for example during maintenance of anesthesia.

VII. CONCLUSION

This paper presents a set of models that describes the effect of propofol infusion in children age 6–16y, identified

TABLE I

MODEL PARAMETERS AND PATIENT DEMOGRAPHICS. MODELS FOR SUBJECT 1–14 ARE IDENTIFIED FROM OPEN-LOOP DATA. MODELS FOR SUBJECT 15–47 ARE IDENTIFIED FROM CLOSED-LOOP DATA. THE k_d VALUES THAT ARE ADJUSTED BECAUSE OF NEGATIVE DISCRETE POLES ARE HIGHLIGHTED. SINCE THE SAME DATA SET IS USED TO IDENTIFY THE PKPD MODELS AND THE FOPTD MODELS, E_0 HAS THE SAME VALUE FOR BOTH MODEL STRUCTURES. THE PRESENTED PD PARAMETERS FOR THE PKPD MODELS ARE IDENTIFIED BASED ON PLASMA CONCENTRATION PREDICTIONS USING THE PAEDFUSOR MODEL [17] AND SHOULD BE USED IN COMBINATION WITH THIS PK MODEL.

Patient	Age [y]	Weight [kg]	Height [cm]	Gender	PKPD models T_d [s]	k_d [min^{-1}]	EC_{50} [mg/l]	E_0	γ	FOPTD models T_d [s]	k [min^{-1}]	E_{50} [$\mu g/kg/min$]	γ
1	15	71	180.5	M	3	1.15	3.95	93.11	1.74	35	0.152	217	1.77
2	7	25.1	132	M	52	1.34	4.24	92.46	1.90	82	0.135	316	1.91
3	10	41.1	139	F	11	60	3.83	92.46	2.17	21	0.254	385	1.94
4	8	22	128	F	44	10.71	5.77	91.47	1.56	48	0.188	515	1.57
5	7	26.9	131.5	F	10	1.12	4.84	91.60	1.55	41	0.108	315	1.58
6	10	33.6	138	M	36	60	3.88	88.45	1.89	40	0.214	365	1.80
7	14	82.1	177	M	56	3.84	3.97	92.91	1.62	68	0.194	282	1.63
8	16	52.5	154.9	F	98	60	8.80	88.89	1.49	94	0.212	473	1.53
9	8	23.4	118.7		0	1.89	3.57	94.58	1.57	16	0.132	263	1.71
10	6	23	121	M	105	4.55	4.81	92.89	1.55	115	0.177	415	1.56
11	11	58.5			0	1.46	3.71	91.68	1.75	29	0.133	267	1.83
12	8	25.3	130	M	0	1.16	5.44	90.30	1.52	4	0.058	228	1.64
13	13	56.1	168	M	44	7.41	3.60	91.38	1.82	41	0.131	229	2.01
14	13	47.3	171.8	F	51	45.91	4.34	92.76	1.99	58	0.251	400	1.81
15	15	48	169	M	107	53.97	3.85	91.78	1.88	117	0.288	282	1.81
16	8	31	135	F	90	13.62	3.60	91.06	1.49	119	0.344	404	1.48
17	11	30	145	F	86	43.09	3.72	92.13	1.54	119	0.385	429	1.55
18	15	54	166	F	104	2.81	4.62	87.11	1.50	119	0.207	295	1.52
19	15	61	168	F	75	1.88	3.23	91.98	1.82	100	0.202	204	1.79
20	14	47	163	F	119	2.17	3.70	88.59	1.64	119	0.121	204	1.74
21	6	30	128	F	79	60	3.71	88.92	1.38	90	0.289	391	1.50
22	15	59	160	F	3	0.46	3.27	92.33	1.59	33	0.052	99	1.72
23	15	59	163	F	111	5.32	4.42	90.81	1.53	119	0.215	285	1.56
24	15	54	166	M	119	1.74	5.58	87.69	1.50	119	0.133	291	1.62
25	10	49	157	F	28	1.15	3.71	91.40	1.58	59	0.133	273	1.62
26	13	65	151	M	79	3.13	3.45	91.20	1.58	119	0.341	346	1.64
27	9	30	131	F	119	1.33	4.00	88.09	1.50	119	0.074	206	1.62
28	10	36	149	M	61	1.25	3.73	88.61	1.58	93	0.157	305	1.65
29	11	31	145	F	0	0.49	2.77	91.40	1.43	35	0.042	100	1.60
30	13	61	175	M	31	16.20	4.41	89.22	1.59	25	0.147	309	1.53
31	16	55	167	F	42	1.73	7.14	92.01	1.59	56	0.155	339	1.54
32	16	66	176	M	9	0.37	2.75	94.02	1.71	66	0.078	99	1.78
33	10	38	156	F	10	1.30	2.75	93.44	1.64	32	0.124	197	1.82
34	15	52	167	F	8	0.88	3.23	92.77	1.56	39	0.133	171	1.81
35	7	24	132	M	80	60	5.41	91.23	1.85	73	0.075	265	1.53
36	10	43	145	F	65	6.93	3.45	91.67	1.65	70	0.155	270	1.60
37	12	33	144	M	8	0.70	2.61	92.69	1.56	41	0.082	150	1.82
38	7	24	121	M	0	0.59	3.64	93.34	1.59	32	0.069	193	1.76
39	7	21	129	M	0	0.33	3.57	89.30	1.58	30	0.000	0	1.70
40	14	63	167	M	63	2.54	3.80	90.18	1.57	87	0.218	284	1.53
41	15	50	159	F	25	0.62	4.88	90.88	1.68	66	0.099	219	1.76
42	8	33	137	F	16	0.46	3.66	92.79	1.61	49	0.039	126	1.70
43	10	26	129	M	81	1.87	5.43	88.61	1.71	91	0.084	295	1.57
44	13	58	169	F	11	0.73	3.58	90.18	1.54	45	0.096	206	1.62
45	16	58	156	F	46	1.48	3.71	92.54	1.77	71	0.168	183	1.88
46	16	55	162	F	27	0.87	7.57	90.83	1.57	58	0.142	355	1.61
47	16	55	171	F	15	0.47	5.44	90.79	1.56	50	0.075	182	1.71

from clinical data of induction of anesthesia. Identification of nonlinear models from clinical data is challenging due to limited excitation in the signals. Furthermore, when the data is not sufficiently exciting, a good fit of the model with the identification data is not sufficient for model validation. To overcome these identifiability issues, control relevant approximate models are identified and validated for controller design by evaluating the predictive accuracy of the closed-loop response under a known controller. A PKPD structure with a time delay and output nonlinearity and a FOPTD structure with an output nonlinearity are considered. The presented models are validated for the design of robust linear controllers.

PKPD and FOPTD models are presented for 47 individuals. The FOPTD models obtain a better fit with the data. The predicted closed-loop behaviors are similar for both model sets under the same controller. As a consequence of the identifiability issues, the identified parameters have limited physiological meaning. Care should be taken in the interpretation of simulation results in experimental settings that are significantly different from the conditions during data collection. Both model sets provide a realistic indication of the inter-patient variability in the response to propofol infusion.

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