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Design and clinical evaluation of robust PID control of propofol anesthesia in children

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***Abstract*—This paper describes the design of a robust PID controller for propofol infusion in children and presents the results of clinical evaluation of this closed-loop system during endoscopic investigations in children age 6y-17y. The controller design is based on a set of models that describes the inter-patient variability in the response to propofol infusion in the study population. The PID controller is tuned to achieve sufficient robustness margins for the identified uncertainty. 108 children were enrolled in the study, anesthesia was closed-loop controlled in 102 of these cases. Clinical evaluation of the system shows that closed-loop control of both induction and maintenance of anesthesia in children based on the WAV_{CNS} index as a measure of clinical effect is feasible. A robustly tuned PID controller can accommodate the inter-patient variability in children and spontaneous breathing can be maintained in most subjects.**

***Index Terms*—Anesthesia, robust control, clinical trials, PID control**

I. Introduction

Propofol is an intravenously administered anesthetic drug that is commonly used for induction and maintenance of anesthesia. In general anesthesia in the operating room, propofol is often used in combination with fast acting opioids like remifentanil [2]. Individual responses to propofol and remifentanil infusion vary largely in adults and even more in children [3]. When administered together, propofol and remifentanil have a synergistic effect. Underdosing of anesthetic drugs may lead to awareness or insufficient analgesia. Overdosing may cause the patient to stop breathing and could provoke cardiovascular collapse. The anesthesiologist therefore continuously monitors the patient state and adjusts drug dosing accordingly to balance the anesthetic state, autonomic function and response to noxious stimuli (see [4] for an introduction to clinical anesthesia).

Drug infusion rates in intravenous anesthesia are traditionally manually controlled by the anesthesiologist. Computer aided open-loop delivery systems known as target controlled infusion (TCI) systems are commercially available. TCI systems use population-based pharmacokinetic[1] (PK) and pharmacodynamic[2] (PD) models to calculate an adequate infusion profile to achieve the drug concentration defined by the anesthesiologist [2]. To accommodate the inter-patient variability, this target concentration needs to be adjusted by the anesthesiologist. Closed-loop control of drug infusion has the potential to reduce the effect of inter-patient variability and improve control of the general anesthetic state [4]. Feasibility of closed-loop control of propofol infusion based on continuous measurement of the depth of hypnosis (DOH) has been shown in several clinical studies in adults (e.g. [5], [6], [7], [8], [9], [10], [11], [12], [13], [14]). Such studies have had little impact on clinical practice due to concerns about the safety of these systems and the reliability of the sensors. Furthermore, demonstration of improved patient outcome is required to convince clinicians of the benefits of closed-loop controlled systems.

The large inter-patient variability in individual responses to propofol infusion is an important cause for concern in the safety of closed-loop systems. Oscillatory behaviour was observed in some clinical trials, for example in the evaluation of a PID controller [15] and a neuro-adaptive controller [16]. For wide acceptance of a closed-loop system by clinicians and regulatory authorities, guarantees of robust stability and performance are required. It has been shown in simulation that it is possible to design a closed-loop drug delivery system for control of DOH that is robust in the presence of significant inter-patient variability [17]. Using a combination of robust control techniques and models that describe the inter-patient variability [18], stability and performance of the closed-loop can be achieved despite large variability.

This study aims to 1) verify the feasibility of robust PID control of propofol infusion in children, using the WAV_{CNS} index (NeuroSENSE monitor, NeuroWave Systems Inc., Cleveland Heights, USA) as a measure of the clinical effect, 2) demonstrate that a robustly tuned PID controller can accommodate the large inter-patient variability observed in this patient group and 3) assess the performance that can be achieved with robust PID control. This paper describes the controller design process and provides technical details of this study. The presentation of the results from the clinical study focusses on evaluation of the achieved control performance, identification of limitations of the proposed design and directions for future research and improvements from a control

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Part of the data reported in this paper has been published in [1] and presented at STA2012, CAS2012 SPA2012 and WCA2012.

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

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

engineering perspective. A clinical perspective on this study is presented in [19].

This paper is organized as follows: Section II gives an overview of closed-loop control in anesthesia and describes the system requirements as well as the hardware used in this study. The controller design, including quantification of the uncertainty, is detailed in Section III. The clinical study and clinical results are described in Section IV. The achieved performance and limitations are discussed in Section V. Conclusions are given in Section VI.

II. Closed-loop control in anesthesia

A. Review of control in anesthesia

The state of general clinical anesthesia is a combination of hypnosis (also referred to as anesthesia), analgesia (suppression of nociception[3]) and muscle relaxation. From these three components of clinical anesthesia, control of depth of hypnosis has attracted the most attention in automation research [7], [8], [9], [10], [11], [13], [16]. Recently developed DOH monitors like the Bispectral Index (BIS) monitor and the NeuroSENSE monitor provide measures of DOH suitable for control[4]. Equivalent monitors for nociception have not been studied for closed-loop control. Most clinical studies have therefore been limited to control of DOH, and use manual control or TCI schemes for opioid infusion. Feasibility of control of both DOH and analgesia through propofol and remifentanil infusion based on feedback of the measured DOH has been shown recently [5], [6]. Control of muscle relaxation can be separated from control of DOH and nociception because neuromuscular blockade has no explicit interaction with anesthetic drugs and opioids and is not addressed in this study.

Closed-loop control systems that have been evaluated clinically vary widely in control strategy and experimental setup. In several studies, maintenance of anesthesia was closed-loop controlled, while induction of anesthesia was open-loop controlled using a TCI [10], [13] or manually controlled [20], [11]. Induction of anesthesia was closed-loop controlled in [8]. Several systems use TCI as a basis for the closed-loop system, where the closed-loop controller adjusts the setpoint of the target concentration based on feedback from the measure of the clinical effect [10], [8], [9], [13].

Randomized clinical trials, comparing closed-loop controlled anesthesia to open-loop strategies show the potential of closed-loop controlled anesthesia [6], [9], [13]. Stability issues observed in clinical trials using heuristically tuned controllers and controllers lacking robustness with respect to the inter-patient variability have also raised awareness for the need of robustness [20], [16], [15]. This study aims to show that a simple PID controller can provide robust control of DOH in children, if the controller tuning is based on robust control principles that take the inter-patient variability explicitly into account. Quantification of inter-patient variability is essential for this robust approach.

[3]Stress response caused by noxious stimuli such as surgery or the insertion of a large bore endoscope that can be perceived as pain.

[4]Measures of the DOH range from 0-100, where the awake state corresponds to 90-100, an isoelectric EEG corresponds to 0. The typical range for general anesthesia is 40-60.

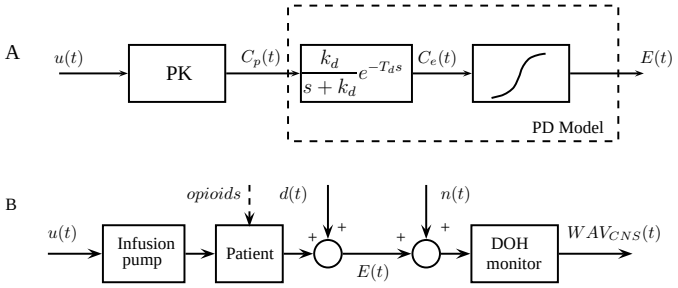

Fig. 1. A: PKPD model structure. The PK model is followed by the PD model consisting of a linear first-order transfer function and the nonlinear Hill function. Fig. B: Block diagram representing propofol anesthesia in open-loop. $u(t)$ is the infusion rate set by the anesthesiologist. The infusion pump delivers propofol to the patient. In this study, the opioid remifentanil was administered in addition to propofol, indicated by 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}.

B. Characteristics of propofol anesthesia

The effect of propofol on the DOH is traditionally modeled using compartmental pharmacokinetic-pharmacodynamic (PKPD) models. The PK model relates the propofol infusion rates to the plasma concentrations $C_p(t)$. The PD model relates $C_p(t)$ to the clinical effect. An LTI model describes the relation between $C_p(t)$ and the effect site concentrations $C_e(t)$, the relation between $C_e(t)$ and the clinical effect $E(t)$ is described by a nonlinear Hill function, as shown in Fig. 1A.

A block diagram representing propofol anesthesia in open-loop is shown in Fig. 1B. The dynamics of the infusion pump are assumed to be negligible. The patient response is nonlinear (see Fig. 1A). In this study, the opioid remifentanil is administered in addition to propofol. When administered together, propofol and remifentanil have a synergistic effect. The clinical effect of anesthetic and analgesic agents is affected by nociceptive stimulation caused by the procedure, $d(t)$. Nociception decreases the clinical effect and can therefore not be assumed zero mean. The response to such disturbances depends on the level of analgesia. The characteristics of the measurement noise are affected by the NeuroSENSE filter settings and are therefore represented by $n(t)$ entering the system before the DOH monitor.

C. Design criteria

The controller designed for this study was required to provide safe and adequate anesthesia for children aged 6-17y, ASA I–II[5]. The design was required to accommodate the inter-patient variability observed in this patient group.

The controller was evaluated during upper and lower gastrointestinal endoscopic investigations, during which the surgical stimulation is limited. Anesthesiologists attempt to maintain the patient breathing spontaneously throughout such cases. Since deep anesthesia is associated with apnea, it was particularly important in this study to limit the DOH overshoot

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

upon induction of anesthesia, while maintaining an acceptably short induction duration.

Slow intravenous infusion of propofol in awake patients is associated with pain, especially in children [21]. The design was therefore required to provide sufficient propofol infusion rates at the start of the propofol infusion to limit discomfort for the patient.

D. Monitoring depth of hypnosis

Several clinical studies evaluating closed-loop systems for propofol infusion use the BIS monitor for feedback. The dynamics of this monitor to step changes in the anesthetic state were examined in [22], where variable time delays (14-66 s) were found. In some cases the BIS monitor showed an overshoot before settling at the correct value after an anesthetic state transition. Nonlinearities and time delays introduced by the sensor reduce the achievable control performance in a closed-loop system. Online time-delay estimation was suggested in [23] to compensate for the variable BIS delay for closed-loop control.

In this study, the WAV_{CNS} index provided by the NeuroSENSE monitor is used for feedback. This monitor was developed specifically for closed-loop control. The WAV_{CNS} algorithm is deterministic [24], the monitor dynamics are linear, time invariant (LTI) [25] and are determined by a known trending filter.

E. The iControl software platform

A software platform (iControl) was developed for the clinical evaluation of the controller design. This software was approved for clinical evaluation by Health Canada[6]. The iControl platform uses feedback from the NeuroSENSE DOH monitor and propofol is delivered by an Alaris TIVA infusion pump (CareFusion, San Diego, USA) connected to an intravenous line. The system is operated through a touchscreen interface and was subject to an extensive usability study prior to the clinical study.

In addition to the robust PID controller, iControl contains necessary safety layers and collects real-time data from physiological monitors in the operating room. It provides the anesthesiologist with audible and visual feedback. During each case, both data from the control system and the physiological monitors are recorded every second. If no reliable measurement is available, the system automatically switches to the fallback mode. The complete system is shown in Fig. 2. In this study, a second infusion device, not connected to the iControl system, was used for remifentanil infusion.

III. Controller design

A. Quantification of the inter-patient variability

An accurate description of the inter-patient variability in drug sensitivity is essential for the design of robust controllers of DOH. Population-based PKPD models provide average models and possibly standard deviations for the model parameters, but do not provide an accurate description of the complete uncertainty set. Furthermore, the validity of available PK and PD models for children is debated [3]. The initial PID controller design used in this study was therefore based on a set of models identified from open-loop data collected during induction of anesthesia [1], [26].

[6]Investigational Testing Authorization – Class III. Application # 168968.

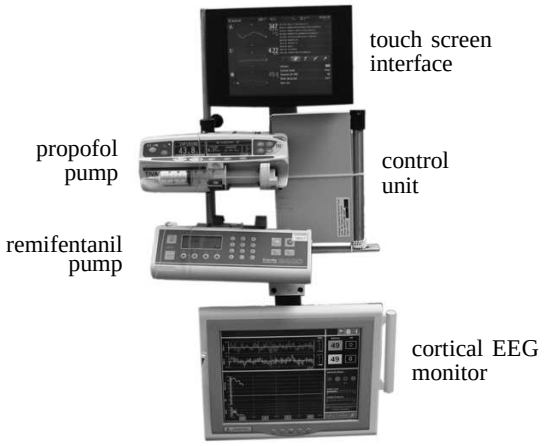

Fig. 2. The iControl closed-loop anesthesia system.

Following approval from the institutional ethics board, data was analyzed retrospectively for thirty (30) children undergoing elective general surgery using total intravenous anesthesia. Propofol and remifentanil were administered as an initial bolus followed by a continuous infusion, manually controlled by the anesthesiologist. Propofol infusion rates were recorded manually. The WAV_{CNS} index was recorded every second throughout each case. Disturbances due to stimulation caused by the procedure decrease the clinical effect and are not zero mean. To limit model bias due to such disturbances, only data from the first eight (8) minutes after the start of propofol infusion were used for model identification. Recordings that show a strong reaction to stimulation during these first 8 minutes were discarded. Data sets of fourteen (14) subjects were of sufficient quality for identification.

A model based on a PKPD model structure was identified for each of these 14 data sets. Plasma concentrations corresponding to the propofol infusion profiles were calculated using the Paedfusor PK model [27]. PD model parameters for the 14 individuals were identified, using a two-step identification procedure. In this approach, a linear approximation of the response at induction of anesthesia is identified in the first identification step. In a second identification step, the nonlinearity in the PKPD model structure is identified. The models identified using this approach are expected to underestimate the nonlinearity and overestimate the time delay. The variability in the response to propofol infusion is therefore largely described by the linear dynamics and the models can be used for the design of linear robust controllers. Details of this modeling study and model validation can be found in [26].

B. Robust PID controller design

A set of 14 subject models provides a limited representation of the uncertainty in the full study population. The initial controller design was therefore conservative, aiming at

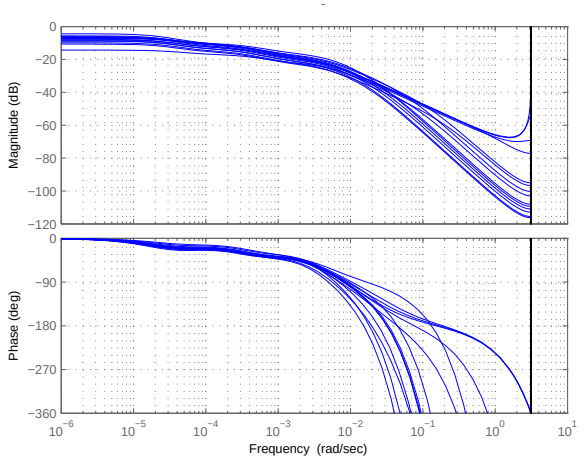

Fig. 3. Bode diagrams of models identified from open-loop data, linearized for induction of anesthesia. The assumed input and output units are $\mu g/kg/min$ and $100 - WAV_{CNS}$ respectively.

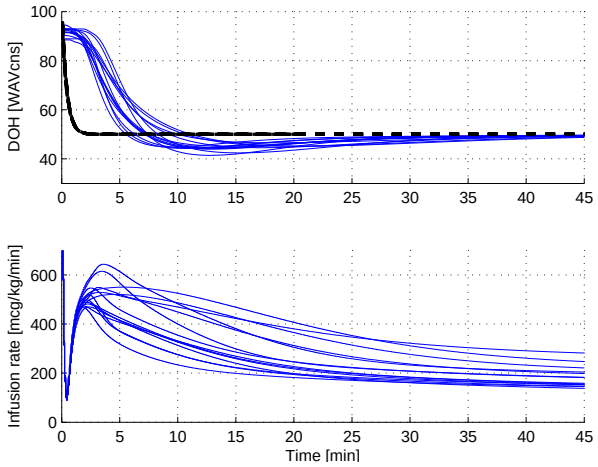

Fig. 4. Predicted closed-loop responses of induction of anesthesia for the 14 identified models from open-loop data, controlled by the initial robust PID controller design described in Section III-B.

large robustness margins, prioritizing safety over tight setpoint tracking. The PID controller was tuned to find an adequate balance between performance and robustness [1]. Manual loopshaping using linearized models was combined with time domain performance evaluation using the nonlinear models.

The 14 models were linearized for induction of anesthesia[7] to yield a set of LTI plant models [26]. The Bode diagrams of these linearized models are shown in Fig. 3. Robustness was evaluated in the frequency domain based on the loop functions for the 14 linearized models and the achieved phase and gain margins. Performance was evaluated based on time domain responses from simulation of induction of anesthesia and the response to disturbance rejection for the 14 nonlinear models.

The sampling time of the controller was chosen as $h = 5s$. The measured WAV_{CNS} index is filtered by a second-order filter with time constant of $T_{filt} = 15s$ to attenuate high frequency measurement noise. The setpoint was low-pass filtered with a time constant $T_{sp} = 25s$. Furthermore, the setpoint was excluded from the derivative action path, which is customary to avoid control signal spikes at setpoint changes. Integrator anti-windup was achieved by conditional integration; halting integrator updates whenever the actuator was saturated. The state of the derivative filter was initialized to a non-zero value resulting in a small bolus, to reduce the duration of propofol infusion pain. The controller input is the WAV_{CNS} index. The controller output is the infusion rate in ml/h of a $10mg/ml$ propofol solution. The controller gain is scaled by patient weight, which is standard in manual practice and also the basis for PKPD models in children. This was the only demographic adjustment of an otherwise fixed controller tuning.

The PID parameters of the initial controller design (parallel form) are $\{K = \frac{-5.4}{100}m,\ T_i = 225s,\ T_d = 33s\}$, where m is the subject's weight in kg. This controller results in a median gain margin of 8.3 and median phase margin of 65 degrees. The inter-patient variability is reflected in the range of the margins: gain margin, median (min, max), $8.3(4.0, 25.2)$, phase margin $65(52, 72)$ degrees, maximum modulus of the sensitivity function (M_s) $1.2(1.1, 1.5)$ and delay margin $286(209, 412)$ seconds. The worst case gain and phase margins are 4.0 and 52 degrees respectively. Predicted closed-loop responses of induction of anesthesia of the 14 nonlinear models controlled by this PID controller are shown in Fig. 4.

[7]The gain is calculated by linearizing the Hill function between E_0 (the measured effect in the absence of propofol) and $WAV_{CNS} = 50$.

C. Controller retuning

Controller performance was evaluated after clinical evaluation in 23 cases (see Section IV-A for the results). The DOH was stable during maintenance of anesthesia and the robustness margins were deemed largely sufficient for this group of patients. The average overshoot upon induction of anesthesia was 10 and the worst case overshoot was 20 WAV_{CNS} units. The controller was retuned to reduce induction time and increase the drug dose at the start of induction as desired by the anesthesiologist and to improve performance.

Note that the overshoot was larger than predicted in the simulations as shown in Fig 4. This could be explained by the different experimental conditions during open- and closed-loop induction of anesthesia. Due to the nonlinearity in the system and identifiability issues related to this nonlinear structure, the predictive accuracy of the model depends on the experimental conditions [26]. Additional models were identified from the collected closed-loop data and the controller was redesigned based on both the open-loop and closed-loop model sets.

1) Quantification of the inter-patient variability: Data from the first 10 minutes after the start of propofol infusion were used for identification. Nine (9) data sets that show a strong reaction to stimulation during the first 10 minutes after the start of propofol infusion were discarded to minimize model bias due to disturbances. 14 models were identified (see [26] for details). Consequently, the model set for controller redesign consisted of 28 models, including the 14 models identified from open-loop data.

2) Controller redesign: The controller was redesigned to improve speed of induction, improve the response to stimu-

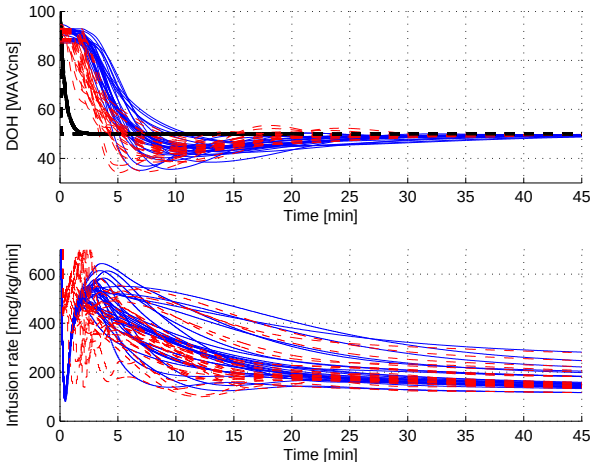

Fig. 5. Predicted closed-loop responses of induction of anesthesia for the 14 models identified from open-loop data and the 14 models identified from closed-loop data. Solid lines: responses for the initial controller design (Section III-B). Dashed lines: responses of the models controlled by the redesigned controller described in Section III-C. The thick lines indicate the setpoint.

lation and increase propofol infusion rates at the start of the case to alleviate pain related to slow propofol infusion. The PID parameters of the retuned controller are $\{K = \frac{-6.6}{100}m$, $T_i = 180s$, $T_d = 60s\}$. The non-zero initialization of the derivative filter to generate a small bolus at the start of induction of anesthesia was replaced by a bolus of $600ml/h$ for $15s$. The setpoint filter was removed, resulting in higher infusion rates at the start of induction of anesthesia.

Based on the extended model set of 28 models, median gain and phase margins for this redesigned controller were 3.6 and 49 degrees respectively. The range of margins reflecting the inter-patient variability is given by median (min, max), $3.6(1.9, 16.5)$ for the gain margin, $49(29, 70)$ degrees for the phase margin, $1.5(1.1, 2.4)$ for M_s and $174(87, 292)$ seconds for the delay margin. The worst case gain and phase margins are 1.9 and 29 degrees respectively. For comparison, the margins for the initial controller design based on this set of 28 models are given: gain margin, median (min, max), $4.6(2.1, 25.2)$, phase margin $56(38, 72)$ degrees, M_s $1.4(1.1, 2.2)$) and delay margin $237(113, 412)$ seconds.

The simulated response of induction of anesthesia of the retuned controller is compared to the initial design in Fig. 5. The predicted overshoot for both controller designs on the extended model set is similar, speed of induction is increased and the infusion rate at the start of induction is increased, as required. The controller redesign was fine-tuned during 8 cases (the setpoint filter was changed after 3 cases, the controller gain was calculated using the lean body mass in 5 cases). The final controller was evaluated in 71 cases (see Section IV).

IV. Clinical evaluation

Following REB approval[8], and informed consent/assent, 108 children aged 6-17 y, ASA I–II, requiring anesthesia for elective upper or lower gastrointestinal endoscopic investigations, were enrolled in the clinical study. Administration of propofol during induction and maintenance of anesthesia was closed-loop controlled in 102 cases (53 F, 49 M, age (median (range)) 12.5y (6-17), weight 48kg (19-75), height 156cm (112-185)). Three cases were excluded prior to induction of anesthesia: in one case, intravenous access could not be obtained; in two cases, the signal quality from the NeuroSENSE sensors was inadequate. Three further cases were excluded during the maintenance of anesthesia: the anesthesiologist switched the control system to TCI mode in two cases due to limited signal quality; in one case, a pump error prompted a switch to manual infusion.

[8]The UBC Children's and Women's Research Ethics Board (H10-01174), Vancouver, Canada.

TABLE I

Summary of clinical evaluation for the different controller settings. The number of cases is indicated where: one or more propofol boluses were given during induction or maintenance of anesthesia, the WAV_{CNS} setpoint was increased to > 50 or decreased to < 50, one or more episodes of airway obstruction/ apnea required intervention.

	Group 1 Initial controller and fine-tuning	Group 2 Redesigned controller
Number of cases	31	71
Propofol bolus during induction	3	3
Propofol bolus during maintenance	0	10
Setpoint > 50	13	21
Setpoint < 50	3	7
Airway obstruction or apneic episodes requiring intervention	1	10

Prior to induction of anesthesia, NeuroSENSE electrodes were applied and intravenous access was obtained. Following lidocaine ($0.5mg/kg$), remifentanil was administered as a bolus ($0.5\mu g/kg$) over 1 minute, followed by continuous infusion ($0.03\mu g/kg/min$). Oxygen at $2l/min$ was delivered via nasal cannulae. Both induction of anesthesia and maintenance of anesthesia were closed-loop controlled. The NeuroSENSE 30s trending filter was used. Boluses of propofol could be administered and setpoint changes could be made at the anesthesiologists discretion.

The controller design described in Section III-B was evaluated in 23 cases. For evaluation purposes, the results from these 23 cases are combined with the 8 cases where the controller was fine-tuned. These 31 cases are referred to as Group 1. The final controller design described in Section III-C was evaluated in 71 cases, referred to as Group 2.

A. Summary of the results

The results for the different controller configurations are summarized in Table I. Spontaneous breathing was successfully maintained in most cases, through limiting speed of induction and the overshoot, avoiding large DOH and consequently apnea. In 11 of the 102 cases, one or more episodes of airway obstruction or apnea required intervention (see [19] for details). The average minimum WAV_{CNS} index reported in the first three minutes after induction of anesthesia was 42 and the minimum of the reported values was 30 for the redesigned controller, see Table II. Due to the inter-patient variability in the response to anesthetic drugs, breathing can be affected in individuals also at lighter hypnotic states.

The recommended range of the WAV_{CNS} index during general anesthesia is $40-60$ [28]. The appropriate DOH depends on the patient, the requirements of the procedure and the intensity of nociceptive stimulation. During colonoscopy, a light anesthetic state is often sufficient. This is reflected in the number of cases where the anesthesiologist increased the WAV_{CNS} setpoint > 50, as indicated in Table I.

The achieved performance is summarized in Table II. Induction time (T_{ind}) is defined as the time from the start of propofol infusion until the measured WAV_{CNS} index first drops below 60 and remains below 60 for at least 30 (consecutive) seconds [9]. Predicted propofol plasma concentrations were calculated using the Paedfusor model [27] for subjects up to 16y old and the Schnider model [29] for 17y. Maintenance of anesthesia is defined as the period from T_{ind} until propofol infusion is stopped by the anesthesiologist (T_{end}). The overshoot upon induction of anesthesia is quantified as the lowest WAV_{CNS} reached in the first three minutes after T_{ind} [9]. Table II also indicates the lowest WAV_{CNS} reached during maintenance of anesthesia and the percentage of time that the WAV_{CNS} index is within 10 units of the setpoint during maintenance of anesthesia.

Performance measures derived from the Varvel performance measures for TCI [30] are defined according to [9]. These measures are commonly used to evaluate the performance of closed-loop systems in anesthesia. Median performance error (MDPE) represents the bias, median absolute performance error (MDAPE) is a measure of the inaccuracy, Wobble quantifies the intra-patient variability and global score (GS) combines these measures with the time in range:

$$PE(t) = 100\frac{WAV_{CNS}(t) - WAV_{set}(t)}{WAV_{set}(t)}$$
$$MDPE = median\{PE(t), t = T_{ind} \dots T_{end}\}$$
$$MDAPE = median\{|PE(t)|, t = T_{ind} \dots T_{end}\}$$
$$Wobble = median\{|PE(t) - MDPE|, t = T_{ind} \dots T_{end}\}$$
$$GS = \frac{MDAPE + Wobble}{\%\text{ of time within 10units of } WAV_{set}(t)},$$

where $WAV_{set}(t)$ is the WAV_{CNS} setpoint at time t.

The measured WAV_{CNS} index during induction and maintenance of anesthesia is shown in Fig. 6. An overshoot after induction of anesthesia is observed, similar to the overshoot predicted in simulation (see Fig. 5). Note that the setpoint was changed during maintenance of anesthesia in several cases (see Table I), resulting in a spread of the measured WAV_{CNS} index.

B. Observed inter-patient variability

Fig. 7 shows the measured WAV_{CNS} index during induction of anesthesia for the 71 cases in Group 2 evaluating the redesigned controller (Section III-C). Induction time T_{ind} varied from 1 min 17 s to 6 min 7 s.

The measured responses show a variability in sensitivity to propofol as well as a variability in the dynamic response; one of the highlighted cases (thick solid line) in Fig. 7 shows a gradual decrease in WAV_{CNS} in response to propofol

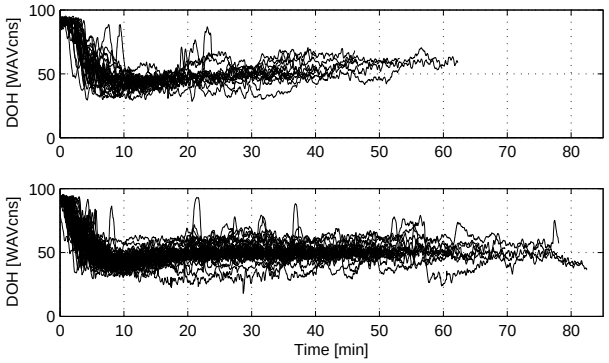

Fig. 6. Measured WAV_{CNS} index during induction and maintenance of anesthesia. Top figure: Results from 31 cases in Group 1. Bottom figure: Controller redesign evaluated in 71 cases in Group 2. Note that setpoint changes occurred during maintenance of anesthesia in some of the cases.

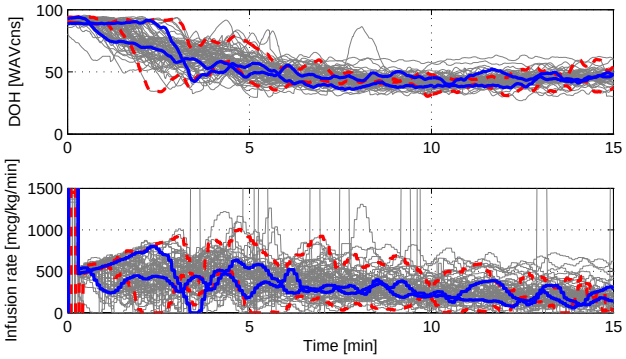

Fig. 7. Inter-patient variability during induction of anesthesia: Thin lines: measured WAV_{CNS} during the first 15 minutes of the 71 cases in Group 2 shown in Fig. 6. The thick dashed lines highlight one slow and one fast induction, the thick solid lines highlight two cases with average T_{ind}.

infusion, a second case (thick solid line) shows no significant change in WAV_{CNS} up to 2 min 30 s, followed by an abrupt decrease in WAV_{CNS} to below the setpoint. The responses highlighted by the thick dashed lines in Fig. 7 show one case where induction of anesthesia was fast (1 min 53 s) and one case where induction was slow (5 min 35 s). The overshoot for the subject with a high sensitivity to propofol is limited. The trade-off for this robustness is the longer induction time for subjects that are less sensitive to propofol.

Fig. 8 and Fig. 9 show the propofol dose and predicted plasma concentration (C_p) at T_{ind} as a function of age and weight for the complete study population (Group 1 and Group 2). These two demographic variables determine the dynamics of the Paedfusor pediatric PK model for propofol [27]. Fig. 8 shows that on average propofol consumption decreases with age, which confirms results of PKPD studies. However, the outliers in the different groups overlap. Similar overlap is observed with respect to weight. Note that the controller gain is weight dependent, corresponding to normal practice, but the controller tuning is fixed.

C. Typical cases

Fig. 10 shows the WAV_{CNS} index and propofol infusion rate during 8 cases from Group 2. The behaviour observed

TABLE II

SUMMARY OF RESULTS OF CLINICAL EVALUATION OF CLOSED-LOOP CONTROLLED PROPOFOL INFUSION FOR THE 31 CASES EVALUATING THE INITIAL CONTROLLER DESIGN AND FINE-TUNING IN GROUP 1 AND THE 71 CASES EVALUATING THE REDESIGNED CONTROLLER IN GROUP 2.

	Group 1 (31 cases)	Group 2 (71 cases)
	mean ± std, median (min, max)	mean ± std, median (min, max)
Case Duration $[min]$	28 ± 16, 20 (11, 62)	36 ± 22, 36 (5, 82)
T_{ind} $[min]$	4.5 ± 1.5, 4.2 (1.7, 8.3)	3.7 ± 1.2, 3.6 (1.3, 6.1)
Propofol infusion		
Propofol dose at T_{ind} $[mg/kg]$	2.36 ± 0.91, 2.18 (1.05, 5.15)	2.47 ± 0.92, 2.19 (0.97, 5.33)
Average dose during maintenance of anesthesia $[mcg/kg/min]$	236 ± 81, 213 (87, 379)	238 ± 99, 208 (90, 579)
Propofol plasma concentration		
C_p at T_{ind} $[mg/l]$	4.2 ± 1.5, 4.1 (1.7, 7.7)	4.2 ± 1.4, 3.9 (2.3, 8.0)
Mean C_p during maintenance of anesthesia $[mg/l]$	3.9 ± 1.0, 3.8 (2.4, 6.1)	3.9 ± 1.0, 3.8 (2.4, 7.2)
Max C_p during maintenance of anesthesia $[mg/l]$	4.9 ± 1.3, 4.5 (3.1, 7.8)	5.1 ± 1.4, 4.8 (2.8, 8.1)
Min C_p during maintenance of anesthesia $[mg/l]$	2.9 ± 0.9, 3.1 (1.4, 4.6)	3.1 ± 1.0, 2.9 (1.4, 6.9)
Measured WAV_{CNS}		
Overshoot: min WAV_{CNS} 3 minutes after T_{ind}	40 ± 5, 40 (29, 48)	42 ± 5, 41 (30, 53)
Min WAV_{CNS} during case	36 ± 4, 37 (28, 44)	36 ± 5, 36 (18, 48)
Time within 10 units of the setpoint [%]	80 ± 20, 85 (23, 100)	87 ± 11, 89 (52, 100)
Performance measures (as defined in [9])		
MDPE	-8.7 ± 7.8, -9.0 (-28.0, 14.3)	-6.2 ± 5.3, -4.6 (-19.8, 6.0)
MDAPE	11.5 ± 6.3, 10.6 (4.0, 30.4)	8.8 ± 4.2, 8.4 (3.2, 19.8)
Wobble	6.2 ± 3.5, 5.6 (2.6, 21.5)	6.0 ± 2.4, 5.2 (3.2, 14.2)
GS	28.8 ± 31.6, 20.4 (6.6, 167.3)	18.1 ± 9.7, 17.0 (6.8, 50.3)

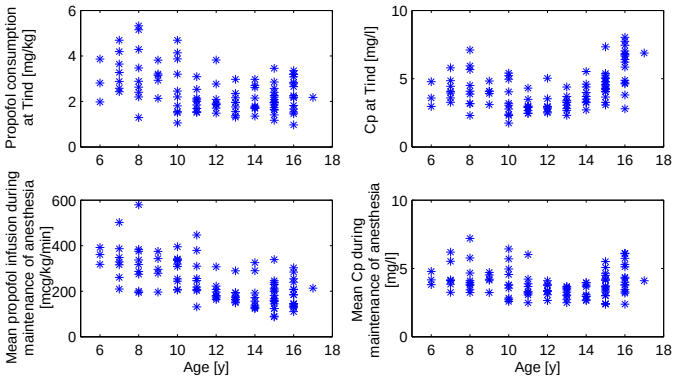

Fig. 8. Variability of the observed responses with respect to age within the complete study group of 102 subjects. Top left; propofol consumption at T_{ind}, top right; predicted plasma concentration C_p, bottom left; average propofol infusion during maintenance of anesthesia, bottom right; average predicted C_p during maintenance of anesthesia.

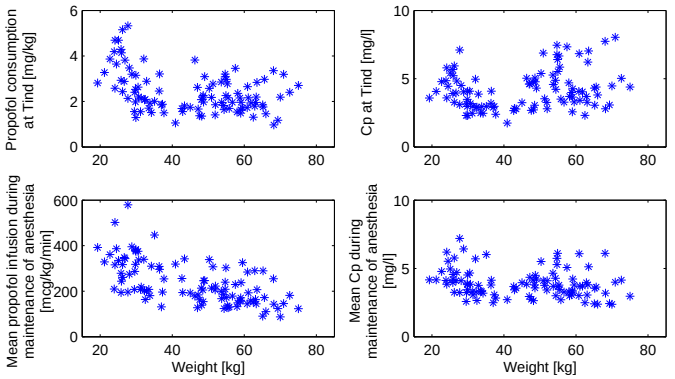

Fig. 9. Variability of the observed responses with respect to weight within the complete study group of 102 subjects. Top left; propofol consumption at T_{ind}, top right; predicted plasma concentration, C_p, bottom left; average propofol infusion during maintenance of anesthesia, bottom right; average predicted C_p during maintenance of anesthesia.

in these 8 cases is representative for the variety of situations encountered during clinical evaluation.

Fig. 10A and Fig. 10B show examples of longer cases where the GS was amongst the lowest achieved in this study (14 cases in Group 2 achieved a GS < 10). During these cases the WAV_{CNS} reflected a stable anesthetic state. During the case shown in Fig. 10A a response to stimulation resulted in an increase in the WAV_{CNS} upon scope insertion shortly after induction of anesthesia. The increased WAV_{CNS} index at the end of the case also indicates some response to stimulation.

Fig. 10C and Fig. 10D show the two cases corresponding to the two highest GS in Group 2. During the case shown in Fig. 10D, initial scope insertion was attempted three times. After successful scope insertion, the decrease in stimulation resulted in a decrease in WAV_{CNS}.

Fig. 10E and Fig. 10F show cases that achieved an average GS. In the case shown in Fig. 10E, the WAV_{CNS} is stabilized after some response to stimulation, shortly after induction of anesthesia. The anesthesiologist evaluated the anesthetic state to be insufficient and decreased the setpoint to 40. The WAV_{CNS} shows a response to stimulation and patient movement was reported before stabilization.

Fig. 10G and Fig. 10H are examples of cases that showed significant response to stimulation. During the case shown in Fig. 10G, patient movement was reported after ≈ 28 minutes. The controller responded to the increased WAV_{CNS} index and the anesthetic state was stabilized. After ≈ 35 minutes patient movement was reported again. The anesthesiologist gave a bolus of propofol resulting in an overshoot before the controller stabilized the anesthetic state. Patient movement was reported a third time after ≈ 50 minutes, and the controller responded to the increased WAV_{CNS} index. The response in Fig. 10H shows a similar fast and large increase in WAV_{CNS} and patient movement was recorded after ≈ 35 minutes. The anesthesiologist gave several boluses, resulting in an overshoot before the controller stabilized the anesthetic state. Stimulation

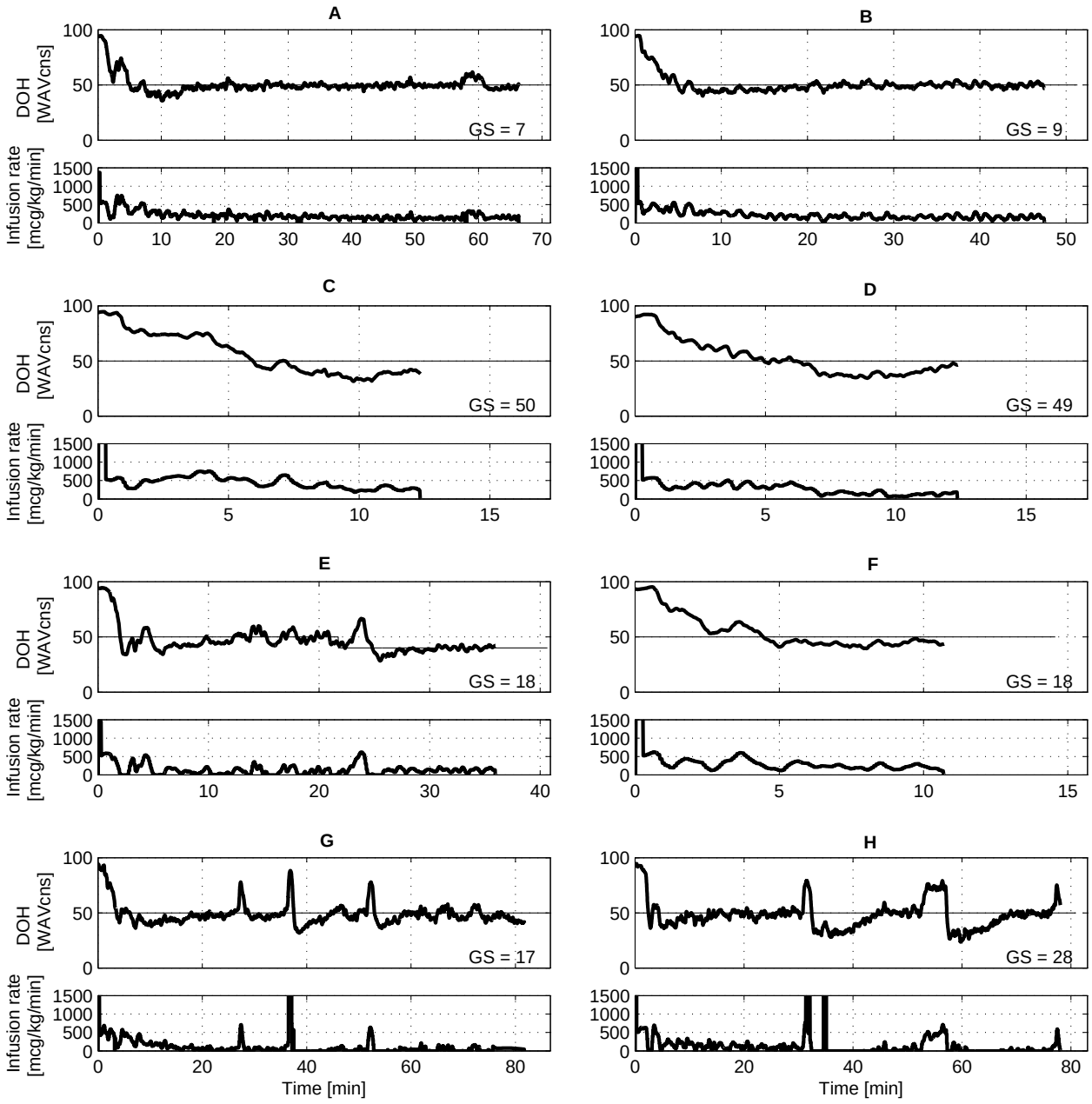

Fig. 10. Examples of the cases from Group 2, where the WAV_{CNS} index is controlled by the redesigned robust PID controller. The recorded WAV_{CNS} and corresponding infusion rate are shown. The global score (GS) is indicated for each of these eight examples.

resulted in overshoot again after ≈ 50 minutes. Note that these two cases are representative of the worst case disturbance rejection observed in six of the 108 cases in this clinical evaluation.

V. Discussion

A. Feasibility of robust PID control of propofol anesthesia in children

Robust controller design requires quantification of the system uncertainty and takes this uncertainty into account in the controller design. The robust PID controller design evaluated in this clinical study was based on a set of 28 models (see Section III-C). Fig. 11 shows the measured responses from clinical evaluation and compares these responses to the predicted responses. The variability and overshoot of the measured responses are comparable to the predicted variability and overshoot, confirming the validity of the robust controller design method and the relevance of the model set used for controller design.

The results of this clinical evaluation show that robust PID control of propofol infusion in children age 6-17y, using the WAV_{CNS} index as a measure of the clinical effect, is feasible and can accommodate the inter-patient variability in this patient group. The limited overshoot upon induction of anesthesia observed in the clinical evaluation and the absence of oscillatory behaviour confirm the predicted robustness margins.

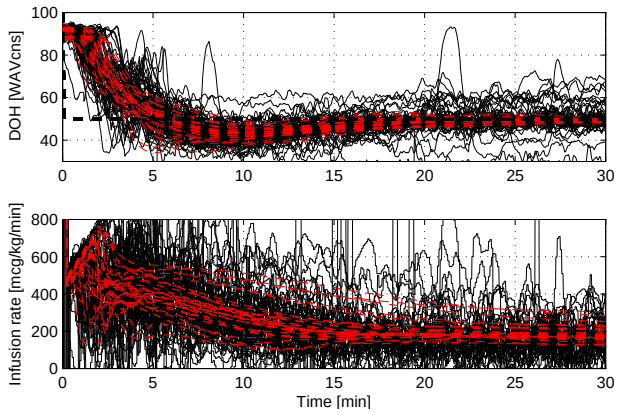

Fig. 11. Comparison of the predicted responses of the 28 models described in Section III-C controlled by the redesigned controller (dashed) and the measured responses of the 71 cases under the same controller in Group 2 (solid lines).

B. Performance and limitations

Robustness margins are essential in closed-loop control of propofol anesthesia, to avoid overdosing, large overshoot upon induction of anesthesia and oscillations in the anesthetic state. For clinical practice, the controller also needs to achieve the performance requirements: induction of anesthesia needs to be fast enough not to slow down the procedure, the anesthetic state needs to be stable during maintenance of anesthesia and fast disturbance rejection is required to limit the response to nociceptive stimulation and to avoid underdosing.

The summary of the results in Table II for Group 2 indicates the performance achieved with a simple, fixed, PID controller for children age 6-17y, a study population that exhibits significant inter-patient variability. The average speed of induction was acceptable for clinical practice, $\approx$ 4 minutes. For some individuals, the anesthesiologist decided to give a manual bolus of propofol to speed up induction of anesthesia (3 out of 71 cases in Group 2).

During maintenance of anesthesia, the DOH was stabilized at various setpoints, including 60 corresponding to a light anesthetic state, and controlled within 10 units of the setpoint for (median) 89% of the time. Disturbance rejection was sufficient for the endoscopic investigations considered in this study. Remifentanil infusion rates were relatively low, constant, and the same for all patients. Nociceptive stimulation is generally limited during endoscopic investigations, but when the procedure causes stimulation, a response can be expected given the limited use of opioids and the light anesthetic state. The worst case responses to stimulation observed in this study (see Fig. 10) indicate that the disturbance rejection and anti-nociception need to be improved for use in more stimulating procedures.

C. Outlook

Nociceptive stimulation during surgical procedures is variable, partly unpredictable and depends strongly on the type of procedure. Individual responses to remifentanil infusion are subject to inter-patient variability. Traditionally, the anesthesiologist adjusts opioid administration manually, according to the patients need, the procedure and the expected stimulation. Control of remifentanil will be essential in the development of a closed-loop system for anesthesia that can be used in a variety of surgical procedures.

In this study, both induction and maintenance of anesthesia were controlled using a simple PID controller. The response to propofol infusion at low drug concentrations is known to be nonlinear and relying on PID feedback control during induction of anesthesia leads to integrator build-up and overshoot. In this study, the observed response was clinically acceptable. If required, a nonlinear control strategy or the use of feed-forward control could improve the response upon induction of anesthesia. Any feed-forward or nonlinear control strategy will have to be robust to inter-patient variability.

The use of personalized (or adaptive) control to accommodate the inter-patient variability and to optimize control performance for individuals has been proposed [16], [8]. The results from this study are inconclusive on the need for personalized control; additional clinical evaluation of fixed control strategies and multivariable control of both propofol and remifentanil, possibly using nonlinear or feed-forward control, may show sufficient performance for this study population also during more stimulating procedures. Given the observed variability in both the drug sensitivity and the dynamics in the response to propofol infusion (see Fig. 7), the development of a robust adaptive control strategy will be technically challenging. Personalization of the controller design based on demographic variables is expected to provide limited improvement of control performance, due to the overlap observed in responses with respect to demographic variables (see Fig. 8 and 9).

VI. Conclusions

This study shows that robust closed-loop control of both induction and maintenance of anesthesia in children using a robust PID controller and the WAV_{CNS} index as a measure of clinical effect is feasible and that spontaneous breathing can be maintained. A robustly tuned PID controller can accommodate the inter-patient variability observed in children age 6-17y. The clinical evaluation shows that the designed robustness margins are sufficient and the observed responses are similar to the predicted responses. No oscillatory behaviour was observed, despite the large inter-patient variability.

The trade-off for robustness and safe control for the population is a limited speed of induction for patients that are less sensitive to propofol. In this study, the maximum induction time was approximately 6 minutes. The results are an indication of the performance that can be achieved with a simple fixed controller.

The controller provides adequate anesthesia for the endoscopic investigations considered in this study. Control of propofol infusion and limited use of opioids cannot prevent response to stimulation and some reaction can be expected. The addition of control of fast acting opioids (e.g. remifentanil) will be essential for the development of a fully automated system for anesthesia for more stimulating procedures.

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