Closed-Loop Anesthesia in Children using a PID controller: A Pilot Study

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Abstract: The first study with a PID controller based automatic drug delivery system for propofol anesthesia in children is presented. It is shown that a robustly tuned PID controller is capable of delivering safe and adequate anesthesia. The design process of the control system is reviewed. Results are discussed and compared to those of two previous studies in adults.

Keywords: Medical applications, Biomedical control systems, PID control.

1. INTRODUCTION

This paper presents the first closed-loop controlled anesthesia study in children. A PID controller using a measurement derived from brain waves (EEG) to regulate the depth of hypnosis (DOH) by varying the infusion rate of propofol [1] was synthesized and clinically evaluated. The purpose of the study was to show that adequate and safe anesthesia can be delivered using a PID controller. The study also served as a basis for collecting data used for further improvements of the system.

Children exhibit large inter-patient variability in propofol pharmacokinetics [2] (PK) and pharmacodynamics [3] (PD), see Coppens et al. (2011). Safe control therefore dictates sufficient robustness with regard to process variation. In order to arrive at a robust controller design, a set of representative models of the effect of propofol on the DOH in children was identified using data collected prior to the study. The effect dynamics can be approximated by a well-damped linear time invariant (LTI) transfer function and a static monotonic output nonlinearity. The variability within the set of identified models is an indication of the expected inter-patient variability in the pediatric population and the PID controller was designed to be robust for each model in the set.

Section 2 provides a background to the automation of DOH control and introduces previous related work. Modeling and identification are topics of Section 3. The tuning problem is formulated and approached in Section 4. The protocol of the study is reviewed in Section 5. Results are presented in Section 6. A summarizing discussion and a comparison with previous studies are given in Section 7.

2. CLOSED-LOOP CONTROL OF ANESTHESIA

Manual administration Hypnotic drugs are traditionally administered by an anesthetist. Doses are determined primarily based on patient demographics, quantitatively measured signals (heart rate, blood pressure, oxygen saturation, breathing pattern) and qualitatively measured signs (movement, presence of certain reflexes). This corresponds to a rather advanced adaptive closed-loop controller. In addition, the anesthetist changes dosing depending on foreseeable events, e.g. doses are typically increased prior to an anticipated increase in surgical stimulation. There is hence also a feed forward control path. Continuous dose adjustments put a workload on the anesthesist, who is in a multi-tasking situation. Consequently, drug dosing errors are amongst the most common errors in the operating room.

Target Controlled Infusion There exist several PK models for propofol. Some of these models, Marsh et al. (1991), Kataria et al. (1994) and Absalom et al. (2003), were derived from pediatric data. They are parametrized using easily assessable demographic covariates such as age and body weight. Using a PK model it is possible to predict the time evolution of plasma concentration, C_p, given the past and present infusion rate u. It is hence possible to devise an open loop control strategy, which uses the prediction

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[1] Propofol is an intravenously administered drug. An electronically controlled infusion pump is used to ensure accuracy and enable automation.
[2] Pharmacokinetics describe the transport and metabolism of a drug.
[3] Pharmacodynamics relate plasma drug concentration to clinical effect.

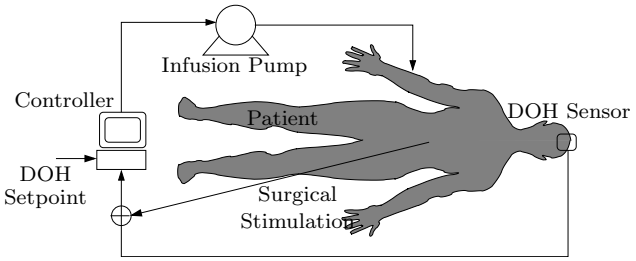


Fig. 1. Closed-loop DOH control system.

to track a target concentration. This paradigm is known as target controlled infusion (TCI) and is supported by several commercially available infusion pumps. Instead of adjusting the infusion rate, the anesthesist manipulates the target concentration, both reactively and proactively. A motivation for using TCI systems is that it on average enables a more optimal drug dose, decreasing postoperative care time and side effects including nausea and vomiting, see Liu et al. (2006). As with any open loop strategy, TCI is sensitive to model error and disturbances.

Closed-Loop Control The sensitivity of TCI systems could be decreased by closing a control loop from a DOH measurement signal. Recently developed EEG based monitors such as the Bispectral Index (BIS) (Liu et al. (1997)) and NeuroSense (Zikov et al. (2006)) provide a measure of DOH, needed for the development of a closed-loop control system. The NeuroSense was explicitly developed for control and has published LTI trending dynamics, whereas the BIS dynamics are proprietary and time varying. A schematic layout of a control system incorporating such a monitor is shown in Fig. 1. The predominant disturbance is caused by surgical stimulation that typically decreases DOH. Since the disturbance acts directly on the DOH, it is modeled as an output disturbance. Other disturbances are measurement noise and synergetic effects with co-administered drugs.

Closed-loop DOH control by propofol infusion, using the BIS monitor and PID control has previously been evaluated in adults by e.g. Absalom et al. (2002), Liu et al. (2006) and Liu et al. (2007). In the two first studies, the controller output constituted the setpoint of a TCI system, rather than controlling infusion rate directly. A prospective, randomized, multicenter study was conducted by Liu et al. (2006), with the conclusion that automatic control of consciousness is clinically feasible and outperforms manual control.

3. PATIENT MODELING AND IDENTIFICATION

Model Structure The PK models used in TCI systems are typically derived as mammillary three-compartment models. They are directly equivalent to a third order LTI transfer function $G_{C_p,u}$, relating infusion rate to plasma drug concentration. In order to account for the dynamics between plasma and effect site concentrations, an FOTD [4] system G_{C_e,C_p} is connected in series, yielding a fourth order LTI system $G_{C_e,u}$, see Bibian (2006).

A PD model relates C_e to the clinical effect E, which in this case is the DOH. $E = E_0 \approx 0$ corresponds to the fully awake state and $E = 1$ to total absence of cortical activity. $E = 0.5$ is a common setpoint for propofol hypnosis in general surgery. The relationship between C_e and E is well-described by the Hill sigmoid:

$$E(C_e) = E_0 + (1 - E_0)\frac{C_e^\gamma}{C_{e,50}^\gamma + C_e^\gamma}, \quad (1)$$

where $C_{e,50}$ is the C_e value corresponding to 50 % clinical effect and $\gamma > 1$ is a parameter determining the shape of the sigmoid. A NeuroSense NS-701 DOH monitor (NeuroWave, Cleveland, USA) was used. Its trending dynamics between E and measurement E_m are given by the 1 s zero order hold sampling of

$$G_{E_m,E}(s) = \frac{1}{(8s+1)^2}. \quad (2)$$

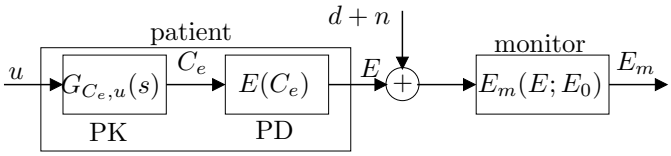


Fig. 2. Combined patient and monitor model with input u, measurement noise n, modeled surgical stimulation d, clinical effect E and measurement E_m.

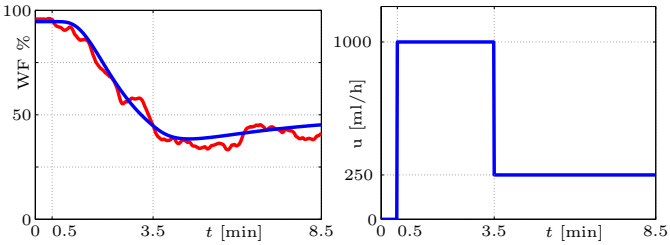
A block diagram of the combined patient model is shown in Fig. 2. The Alaris PK infusion pump (Cardinal Health, Dublin, USA) was used and assumed to have unit dynamics.

Patient Model Identification Propofol infusion and corresponding NeuroSense measurement profiles were collected during 30 pediatric elective general surgery cases. The patients were given an initial bolus of propofol and remifentanil, followed by constant rate infusion of both drugs, manually controlled by the anesthetist. Dose adjustments were guided by the NeuroSense monitor. Since identification was performed on data collected during induction [5] of anesthesia, it was essential to conduct parameter identification on DOH data corresponding to $d \approx 0$. Fourteen of the collected induction profiles were of quality adequate for identification and kept. Removal of profiles was due mainly to missing segments of data or a strong reaction to intubation, which was distinctly reflected early in the DOH signal, rendering it inadequate for identification. Within the kept cases patient weights were 42 ± 20 kg and corresponding ages were 10 ± 3 years. A representative profile, used for identification is shown in Fig. 3. To comply with existing literature, the term wakefulness (WF) [%] is used rather than DOH throughout the remainder of this paper. They relate through $WF = 100(1 - DOH)$.

The Paedfusor PK model, Absalom et al. (2003), was driven with the collected u-profiles, yielding simulated C_p-profiles. Parameters of a FOTD model, relating these to the clinical effect E, were identified using the output error method implemented in Matlab. Subsequently, γ in (1) was chosen to minimize the remaining residual. The initial effect E_0 in (1) was identified by averaging over E_m prior

[4] First order time delayed.

[5] Induction of anesthesia refers to the transient phase when the patient is taken from the fully awake state to a DOH suitable for the surgical procedure.



(a) Measured wakefulness. (b) Infusion rate of 10 mg/ml propofol solution.

Fig. 3. Representative induction phase of anesthesia, showing measured DOH (red) and simulated DOH using the identified model (blue).

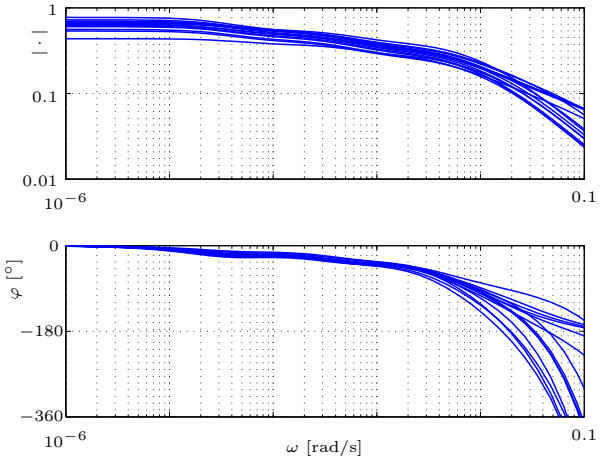


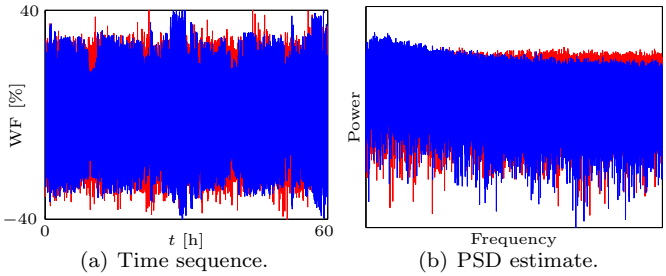
Fig. 4. Bode diagram of identified patient models relating u to C_e.

to the start of propofol infusion. The input was filtered using (2) to take monitor dynamics into account.

The main identification challenge lies in that the identification data is not informative enough to robustly distinguish between the LTI delay and the nonlinear effect of (1). The described method tends to overestimate the delay and underestimate γ.

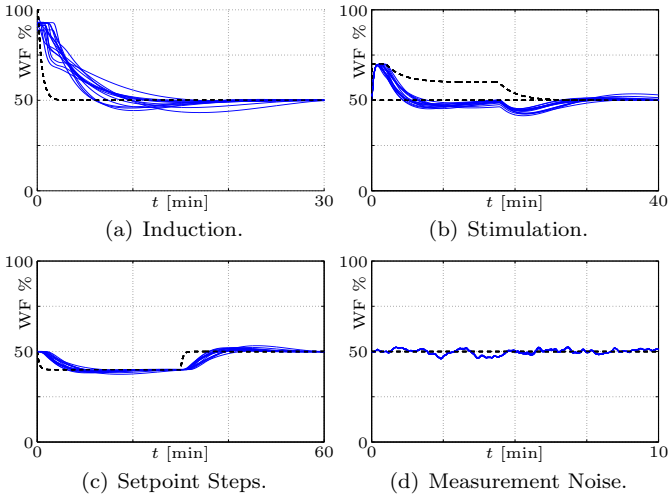
Fig. 4 shows the Bode diagrams of the identified models relating u to C_e [mg/l]. The plotted gains have been normalized with respect to patient mass.

Monitor Noise Model The recorded NeuroSense data sets were also used to obtain a measurement noise model. A low pass filter, with cut-off somewhat faster than the model bandwidth, was applied to the raw NeuroSense signals. The difference between the original and filtered signals is essentially the measurement noise. The sequence is shown in blue in Fig. 5(a). Fig. 5(b) shows an estimate of its power spectral density. The noise is adequately modeled by drawing from $\mathcal{N}(0, 9.0)$, which was done to generate the red time sequence and power spectral density estimate in Fig. 5. The modeled noise is intended to be added to the input of (2), since it was derived from the unfiltered NeuroSense signals.



(a) Time sequence. (b) PSD estimate.

Fig. 5. Measurement noise (blue) and model (red) time sequence and power spectral estimate.



(a) Induction. (b) Stimulation. (c) Setpoint Steps. (d) Measurement Noise.

Fig. 6. Simulated closed-loop anesthesia.

4. ROBUST PID TUNING

Design Objectives In the pilot study, the controller was evaluated during upper and lower gastrointestinal endoscopic investigations (see Section 5). The surgical stimulation during these procedures is limited, but patients are required to breathe spontaneously throughout the case. Since large DOH is associated with apnea, it is important to limit the DOH overshoot upon induction of anesthesia, while maintaining an acceptably short induction duration.

The limited number of identified models, previously reported large inter-patient variability and the fact that this was the first clinical trial in which DOH was to be automatically controlled in children prioritized safety through robustness to tight setpoint tracking. In particular, adequate gain margins were needed to account for the large inter-patient variability in sensitivity to propofol.

Tuning Methodology and Trade-Offs Controller performance was evaluated in the time domain using a Simulink simulator of the closed-loop system, containing the identified nonlinear models and a PID controller. The following simulation steps were conducted for each patient model:

(1) A DOH setpoint step from $r = 0$ to $r = 0.5$, to simulate the induction phase of anesthesia.
(2) A DOH disturbance d, modeling surgical stimulation.
(3) A DOH setpoint change to $r = 0.6$ and back.
(4) An episode with realistic NeuroSense measurement noise.

Their outcome for the final choice of controller parameters are shown in Fig. 6. The output disturbance profile d was

adopted from Dumont et al. (2009). In order to explicitly assess robustness, the sigmoids (1) were linearized around the nominal DOH setpoint $E = 0.5$ and connected in series with $G_{C_e,u}$ and $G_{E_m,E}$ to yield a set of LTI plant models. These were used in connection with the controller transfer function $G_{u,e}$ to compute gain and phase margins of the control system for each model.

PID tuning was based on both the time domain performance and the robustness margins obtained with the linearized models. The patient models provide little initial response, due to the sigmoid (1). This results in integrator build-up and increases the overshoot on induction of anesthesia. Rather than just decreasing integral action, which would result in slower reference tracking, the problem was diminished by providing a smooth setpoint profile. Such a profile is more feasible to track than a step and hence results in less integrator build-up. However, e.g. Scott et al. (1988), showed that slow intravenous infusion of propofol in awake patients is associated with pain – especially in children.

Controller Structure and Parameters A sample time of $h = 5$ s, which can be regarded as continuous in the current context, was chosen. The measurement E_m and its time derivative were low pass filtered with a time constant $T_{filt} = 15$ s to attenuate high frequency measurement noise. In order to provide a more feasible setpoint profile during induction of anesthesia, the setpoint was low pass filtered with a time constant $T_{sp} = 25$ s. Furthermore, the setpoint was excluded from the derivative action path, which is customary in order to avoid control signal spikes at setpoint changes. Integrator anti-windup was achieved by conditional integration; halting integrator updates whenever the actuator was saturated. In order to reduce the duration of propofol infusion pain, the state of the derivative filter was initialized to a non-zero value, resulting in a bolus, or derivative kick, facilitating a more rapid onset at the beginning of each case.

The final PID parameters are $\{K = 5.4 \cdot m, T_i = 255$ s, $T_d = 33$ s$\}$. The unit of the proportional gain is ml/h/kg, assuming the controller inputs to be $E_m \in (0, 1)$ and a corresponding DOH setpoint. The controller output is u [ml/h] of a 10 mg/ml propofol solution. Proportional gain is scaled by patient weight m [kg], which is standard in manual practice and also the basis for PK/PD models in pediatrics. This was the only demographic adjustment of an otherwise fixed controller tuning. The given parameters resulted in a worst case gain $G_m = 2.5$ and phase $\varphi_m = 34\ ^\circ$ margins among the linearized models.

5. CLINICAL PILOT STUDY

Following REB [6] approval, informed consent from a parent and assent from all children seven years or older, 23 children, ASA [7] I-II, requiring anesthesia for elective upper or lower gastrointestinal endoscopic investigations were enrolled. There was no overlap between this group and the model identification one. The target population for the study were children aged 6–15 years, within the 5–95 % weight quantiles for their age. Patient weights were 45 ± 13 kg and the corresponding ages were 12 ± 3 years. Upon arriving in the operating room, each patient was equipped with the NeuroSense electrodes and an intravenous catheter connected to the infusion pump. The procedure was initiated by the anesthetist, whereupon the closed-loop control system was responsible for the propofol administration throughout the endoscopy. Analgesia was maintained by a bolus of 0.5μg/kg remifentanil given over 60 s, starting about 1 min before infusion of propofol, followed by a constant infusion of 0.03 μg/kg/min.

Fig. 7. Human-machine interface, here shown in simulation mode.

All communication between the anesthetist and control system was through a software named iControl. The software was approved for clinical evaluation by Health Canada [8]. It was subject to an extensive usability study prior to the clinical study. iControl facilitates a touch screen interface, shown in Fig. 7. Apart from the PID controller and interface, the software is equipped with a safety layer, which for instance switches the system into TCI mode if the measurement signal is lost. It also provides the anesthetist with audible and visual feedback.

6. RESULTS

The system was evaluated in 23 clinical cases spanning 17–70 min. A compilation of WF measurements is shown in Fig. 8 and a representative case is shown in Fig. 9. The WF setpoint was manually changed a total of 14 times. All but one of these changes was to increase WF towards the end of the corresponding procedure, explaining the positive DOH trend found in Fig. 8. A compilation of the measured WF deviations from setpoint during maintenance of anesthesia is shown in Fig. 10.

The control system provided adequate anesthesia for all children in the study. Controller induced oscillations, reported for three cases in Absalom et al. (2002), did not occur, indicating sufficient robustness of the controller. Spontaneous breathing was maintained throughout all cases. Disturbance rejection was sufficient for these procedures, but needs to be improved for use in more stimulating ones. Induction of anesthesia took somewhat a longer time than desired.

Performance measures, shown in Table. 1, were computed. They are explained, discussed and compared with previous

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

[7] American Society of Anesthesiologists physical status classification system.

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

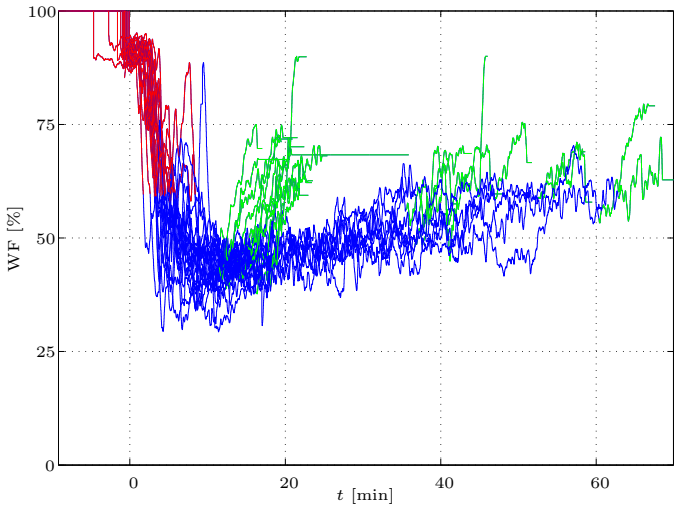
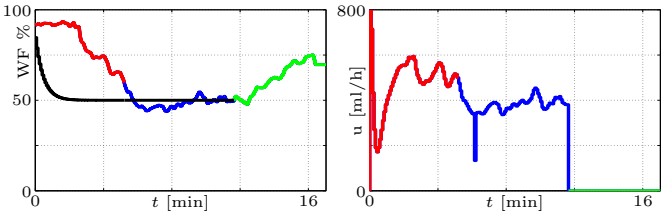


Fig. 8. Compilation of WF measurements during induction (red), maintenance (blue) and emergence (green) of anesthesia. Time $t = 0$ s corresponds to the start of propofol infusion.



(a) Wakefulness. (b) Infusion rate.

Fig. 9. A representative case. The WF setpoint is shown in black.

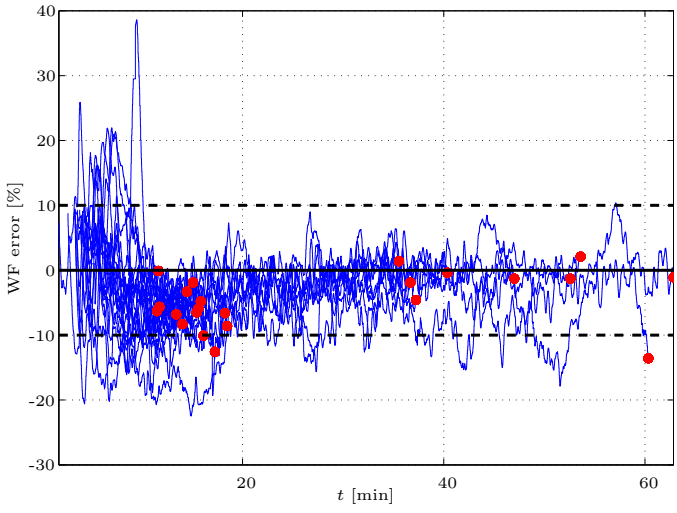
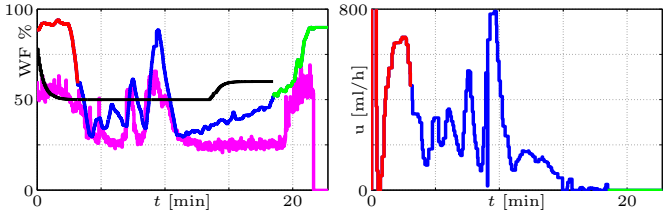


Fig. 10. Compilation of WF deviations from setpoint during maintenance of anesthesia. The end of each maintenance phase is marked by a red dot.

results of Absalom et al. (2002) and Liu et al. (2006) in Section 7.



(a) Wakefulness. (b) Infusion rate.

Fig. 11. The worst case. The variations in WF are likely to be caused by stimulation. The EMG reading (magenta) indicating movement shows increases in EMG prior to increases in WF.

7. DISCUSSION

Large variations in WF were observed in one case. The results of this case are shown in Fig. 11, which clearly shows that EMG [9] activity, indicating movement, preceded the increases in WF measurement. This confirms the anesthetist's view that the decrease in DOH was caused by repositioning of the patient, rather than insufficient robustness margins of the controller. This is also confirmed by the fact that the oscillations are not sustained as they were in Absalom et al. (2002). Although WF increased to over 80 %, this value was not associated with awareness according to the anesthetist, who based his opinion on vital signs and measured variables other than provided by the NeuroSense. Disturbance rejection was inadequate in this case.

Differences in protocol, shown in Table. 1, need to be addressed prior to making comparisons with previous studies by Absalom et al. (2002) and Liu et al. (2006). Apart from the architectural difference mentioned in Section 2, the current study had a different target group (children). Induction of anesthesia was administered by means of TCI in Liu et al. (2006) and Absalom et al. (2002), whereas it was handled by the closed-loop controller in the presented study. There were also differences in the type of surgical procedure and average case duration, see Table. 1. Since no artificial airway can be used in these procedures, a conservative tuning was essential in order not to cause apnea in the patients. With these differences in mind, performance measures were computed and compared to those of the two mentioned studies. Table. 1 presents these as mean and standard deviations over all cases.

Overshoot and undershoot durations were adopted from Liu et al. (2006), where they are defined as the time during the first 3 mins of the maintenance phase, during which the WF error was < -10 and > 20, respectively. The maintenance error is defined as WF setpoint subtracted from measurement during the maintenance phase of anesthesia. It is hence negative when the patient is too deeply anesthetized and vice versa. Offset is the mean maintenance error. Median performance error (MDPE), median absolute performance error (MDAPE) and a measure called wobble are computed from maintenance phase data. Wobble is defined as the median of the pointwise-in-time absolute difference between maintenance error and

[9] Electromyography, a technique for measuring electrical activity produced by skeletal muscles.

Table 1. Comparison of protocols and performance measures. Non-available data is marked ×.

Performance Measure	**Current Pilot Study**	**Absalom et al. 2002**	**Liu et al. 2006**
Target group	6–15 years, 28–79 kg, ASA I–II	18–80 years, ASA I–II	18–100 years, ASA I–III
Type of elective procedure	gastrointestinal endoscopy	orthopedic (hip, knee)	thoracic, vascular, urologic, gynecological, abdominal otolaryngic
Number of cases in study	23	10	83
Propofol administration during induction of anesthesia	closed-loop	TCI	TCI
Airway	no artificial airway	laryngeal mask	tracheal intubation
Case duration [min]	34.9 ± 17.3	70 ± ×	134 ± 86
Induction of anesthesia [min]	4.5 ± 1.6	n/a	5.3 ± 2.1
Overshoot duration [s]	25 ± 44	×	12 ± 26
Undershoot duration [s]	1 ± 4	×	10 ± 24
Maintenance phase error > 10 % [% of time]	3.0 ± 7.3	×	8 ± 8
Maintenance phase error < -10 % [% of time]	13.0 ± 18.8	×	3 ± 3
Absolute maintenance phase error > 10 %	16.1 ± 20.2	43 ± ×	11 ± 9
Offset [%]	-3.5 ± 3.2	0.9 ± 1.4	-1.9 ± 4.7
MDPE [%]	-8.2 ± 8.1	1.9 ± 2.3	-3.3 ± 5.4
MDAPE [%]	10.8 ± 6.5	8.0 ± 3.1	9.9 ± 3.4
Wobble [%]	5.5 ± 3.1	7.6 ± 3.5	8.1 ± 2.5

MDPE. See Varvel et al. (1992) for a thorough description of MD(A)PE and wobble.

In accordance with the design objectives, the closed-loop system was more robust (lower wobble) than those of the two compared studies but exhibited slower tracking. A subsequent duration of negative control error is a direct consequence of integrator build-up during induction of anesthesia. This is reflected in the offset and MD(A)PE values in Table. 1. It is likely that cases of longer duration would have resulted in improvements in these measures.

8. CONCLUSIONS

A PID controller based DOH control system was clinically evaluated. Adequate anesthesia was achieved and safety of the system was demonstrated. The robustness observed in this study suggests that induction time of anesthesia can be decreased and disturbance rejection increased, without compromising safety. The data collected in this study was used to adjust the control system. An improved version is currently evaluated clinically.

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