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# Simulated Mid-ranging Control of Propofol and Remifentanil using EEG-measured Hypnotic Depth of Anesthesia

Kristian Soltesz, Guy A. Dumont *Fellow IEEE*, Klaske van Heusden, Tore Hägglund, J. Mark Ansermino

**Abstract**—This paper suggests an extension of an existing, clinically evaluated, closed-loop drug delivery system for hypnotic depth control using propofol. The extension introduces closed-loop administration of the analgesic drug remifentanil, thus forming a multiple input–single output (MISO) control system. Remifentanil acts and is metabolized at a significantly faster time scale than propofol. Direct control of analgesia is hindered by the current absence of a reliable real-time nociception monitor. However, several hypnotic depth monitors respond to nociception. Sudden changes in the measured hypnotic depth are frequently caused by changes in noxious stimulation. The novelty of this work lies in increasing the disturbance rejection bandwidth of the control system for hypnotic depth by directing the high frequency content of its control error to a remifentanil controller. Such a mid-ranging control system was implemented and tuned based on 23 patient models obtained from a previous clinical study and its performance is demonstrated through a simulation study.

**Index Terms**—Medical control systems, Drug delivery, Control system synthesis, Medical simulation.

## I. INTRODUCTION

The goal of clinical anesthesia is to avoid patient awareness (hypnosis) and minimize the response to noxious stimulation (analgesia) through the administration of anesthetic drugs. In addition, muscle relaxation may be required to facilitate surgical interventions. The administration of muscle relaxing drugs can, however, be considered independent of hypnosis and analgesia and will not be treated further in this work. An introduction to the challenges faced during clinical anesthesia for the engineer and a review of existing clinically and simulation evaluated closed-loop strategies for controlling the hypnotic component of anesthesia is provided in [1].

Most existing closed-loop strategies are based on the relation between spectral properties of the cortical EEG and the patient's depth of hypnosis (DOH). They are enabled by the existence of several commercially available DOH monitors, including the BIS and NeuroSense [2]. The main challenges in controlling DOH stem from the large inter-patient variability in drug sensitivity [3] together with the unpredictable nature of noxious stimulation from surgery

acting as an output disturbance [4] and measurement noise [5]. Furthermore, overdosing of hypnotic agent will prolong recovery and increase the frequency of post operative side effects.

Closed-loop control of analgesia is limited by the current absence of reliable nociception monitors [6], although several measurement indices are being developed [7], [8]. However, nociception is reflected in the DOH measurement, as presented in Section III-C.2. It is therefore possible to influence the DOH by altering the infusion rate of either the hypnotic or analgesic agent. Since remifentanil acts and is metabolized an order of magnitude faster than propofol, the disturbance rejection bandwidth of a propofol based DOH controller can be increased by allowing changes in the remifentanil infusion rate. This idea is clinically motivated by the fact that sudden variations in the DOH are normally associated with corresponding changes in noxious stimulation [4].

Simultaneous BIS-guided administration of propofol and remifentanil in closed-loop has been evaluated in a clinical study [9], in which a rule-based control strategy was employed. Previous publications addressing simulated BIS-guided administration of propofol and remifentanil in closed-loop include [10] and [11]. In [10] a linearized interaction model is used in an MPC scheme, while [11] introduces a fuzzy control strategy for closed-loop co-administration of the drugs.

The novelty of this paper lies in the use of mid-ranging control, which is a simple control paradigm well suited for the particular setting. The basic idea of mid-ranging control is the combined use of a slow actuator with a large range and a fast actuator with small range. The fast actuator deviates from the middle of its range to counteract disturbances which are too fast for the slow actuator, while the slow actuator is used to track the reference. This can be practically achieved by splitting the control error into a high frequency part, used to control the fast actuator, and a low frequency part, used to control the slow actuator. Within the process industry, mid-ranging controllers are commonly employed to control flows. This is done by connecting a slow, large range, and a fast, small range, valve in parallel. In fact, this setup is so common that mid-ranging control is often referred to as valve position control [12].

In the current context propofol is the slow actuator, while remifentanil is the fast actuator. The resulting MISO controller yields a simple structure, enabling straight-forward implementation and robustness analysis.

The paper is organized as follows: Section II presents the currently evaluated propofol–DOH control system.

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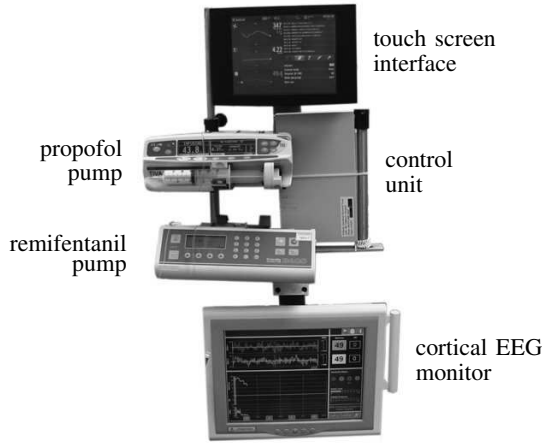


Fig. 1. The iControl closed-loop anesthesia system.

Patient modeling and controller synthesis are the subjects of Sections III and IV, respectively. Simulations and results are presented in Section V and discussed in Section VI.

## II. EXISTING CONTROL SYSTEM

The proposed mid-ranging control strategy is intended as an extension of an existing propofol-DOH controller. The controller utilizes the NeuroSense EEG monitor to control propofol infusion rate using a robustly tuned PID controller. A touch screen human-machine interface as well as communications between the controller, monitor and infusion pump are governed by the iControl<sup>1</sup> software. It was initially evaluated in a case study<sup>2</sup> [5] at the BC Children's Hospital, Vancouver, Canada, where it was successfully used during 23 upper and lower gastrointestinal endoscopies in ASA<sup>3</sup> I-II children, 6–15 years of age. Patient weights (mean $\pm$ SD) were 45 $\pm$ 3 kg and all patients were within the 5–95 % weight quantiles for age. The study was subsequently extended and to date<sup>4</sup> includes a total of 101 evaluated cases. A photograph of the iControl unit is shown in Fig. 1.

The clinical protocol used in the 23 study cases involved closed-loop administration of 10 mg/ml propofol for induction and maintenance of anesthesia. Remifentanyl, with a dose concentration of 10  $\mu$ g/ml, was simultaneously administered as a bolus of 0.5  $\mu$ g/kg at 200 ml/h, followed by constant infusion of 0.03  $\mu$ g/kg/min throughout each case. The remifentanyl bolus was manually timed to begin approximately one minute prior to initiation of the propofol infusion, in order to alleviate pain experienced on initiation of propofol infusion [13]. For the same reason, the filtered derivative of the PID controller was initialized to a non-zero value, producing a transient propofol spike at the beginning of infusion. No other hypnotic or analgesic drugs were co-administered.

<sup>1</sup>Health Canada Investigational Testing Authorization V Class III. Application #:168968

<sup>2</sup>Approved by the UBC Children's and Women's Research Ethics Board (H10-01174), Vancouver, Canada.

<sup>3</sup>American Society of Anesthesiologists physical status classification system.

<sup>4</sup>August 23, 2012.

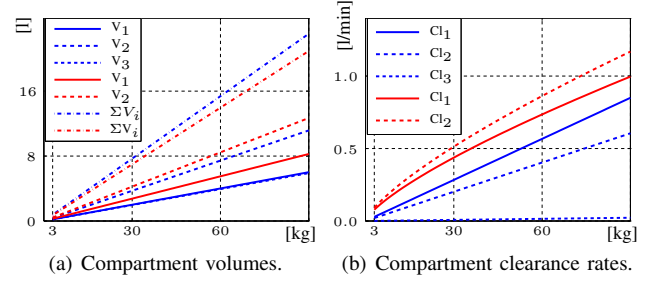


Fig. 2. Volumes  $V_i$  and clearances  $Cl_i$  of the Minto adult three compartment (blue) and Rigby-Jones pediatric two-compartment (red) pharmacokinetics as functions of body mass.

## III. MODELING

This section presents the models on which the control synthesis and simulations are subsequently based. Since the mid-ranging controller is proposed as an extension to the existing control system, it was assumed that the patients are children undergoing gastrointestinal endoscopy. However, the method can easily be adapted to a different category of patients or procedures.

### A. Pharmacokinetic Models

1) *Propofol*: The most common structure for pharmacokinetic models, relating infusion rate to blood plasma propofol concentration, is the compartmental model. Compartmental models are appealing from a control engineering perspective since they are equivalent to delay-free linear and time invariant (LTI) systems. Several pharmacokinetic models for propofol, relating demographic covariates such as patient age and body mass to volumes of distribution and clearance rates of the compartments, have been described in adults. Similar models have been determined from clinically collected blood samples in children. One such model is the Paedfusor model [14], used in this work.

2) *Remifentanyl*: Remifentanyl pharmacokinetics can also be described by compartmental models, including one for children by Rigby-Jones<sup>5</sup> [15], used in this work. By comparing this model to an adult model by Minto [16], it can be observed that remifentanyl pharmacokinetics in children and adults are similar, see Fig. 2.

3) *Pharmacokinetic Interaction*: The pharmacokinetic interaction between propofol and remifentanyl has been investigated in healthy adults [17]. It was concluded that 1) the pharmacokinetics of propofol are not changed by remifentanyl, 2) the central compartment clearance and elimination rate of remifentanyl are decreased in the presence of propofol and 3) the effect of propofol on the concentration-time course of remifentanyl is only clinically relevant when bolus doses of remifentanyl are administered. No similar study has been done in children. In this paper it is assumed that pharmacokinetic interaction between the two drugs does not exist in children to an extent that requires explicit consideration during model building.

<sup>5</sup>Several models are presented in [15]. The one used in this work is the Rigby-Jones model with patient weight as its only demographic covariate.

## B. Pharmacodynamic Models

1) *Propofol*: A pharmacodynamic model relates the blood plasma concentration of the drug to its clinical effect. The propofol pharmacodynamic model used in this work consist of a linear part:

$$V(s) = \frac{1}{C_{e,50}} \cdot \frac{k_d}{s + k_d} e^{-Ls} C_p(s), \quad (1)$$

as proposed in [1], in series with a nonlinearity:

$$E(t) = E_0 + (E_{\max} - E_0) \frac{v(t)^\gamma}{1 + v(t)^\gamma}. \quad (2)$$

The linear part (1) relates the plasma concentration  $C_p$  to  $v$ , being the effect site (brain) concentration, normalized by the concentration corresponding to 50 % of the achievable clinical effect,  $C_{e,50}$ . (I.e.,  $v = 1$  corresponds to 50 % of the achievable effect.) The linear dynamics are characterized by a lag,  $1/k_d$ , and time delay,  $L$ . The sigmoidal nonlinearity, or Hill function, (2), models the clinically observed dose-response relation. As  $C_p$  is increased, there is initially a region of little clinical effect, followed by a linear region around  $C_p = C_{e,50}$ . A saturation effect is observed for large  $C_p$ . The clinical effect in the absence of drug is  $E_0$ , while  $E_{\max}$  corresponds to the maximal achievable clinical effect.

Parameters  $\{E_0, \gamma, k_d, L\}$  were identified for each of the 23 cases in the previous clinical study<sup>6</sup> [5]. Only data from the induction phase of anesthesia (no interventions were performed during this period) was used, since noxious stimulation would otherwise constitute an unmeasurable disturbance. The Paedfusor pharmacodynamic model was used to obtain  $C_p(t)$  and the DOH monitor was modeled as described in Section III-C.

Fig. 3 shows the wakefulness measurement,  $WF^7$ , from one of the cases together with the simulated  $WF$  measurement provided by the corresponding identified patient model. The simulation of  $WF$  was obtained by driving the identified patient model with the recorded propofol infusion rate from the actual case and subsequently applying the monitor model disclosed in Section III-C to the resulting signal<sup>8</sup>. The model from this case will be used throughout the paper as an illustrative example.

2) *Interaction*: Propofol and remifentanil exhibit a pharmacodynamic synergy on the DOH. The most rigorous study, involving 24 adult volunteers, used to develop a response surface model was performed by Kern et al. [18]. Their response surface model is:

$$E(v_p, v_r) = \frac{(v_p + v_r + \alpha v_p v_r)^\gamma}{(v_p + v_r + \alpha v_p v_r)^\gamma + 1}, \quad (3)$$

where  $v_p$  is the propofol concentration normalized by  $C_{e,50}^p$ , corresponding to  $v$  in (2). Similarly,  $v_r$  is the remifentanil

<sup>6</sup>The identified parameter sets are disclosed in a not yet submitted manuscript.

<sup>7</sup>Assuming DOH ranges (0, 1),  $WF$  is defined as  $WF = 100(1 - \text{DOH})$  and measured by the  $WAV_{\text{CNS}}$  index, provided by the NeuroSense monitor.

<sup>8</sup>The observed offset between the red and blue signal is anticipated in presence of unmodeled noxious stimulation.

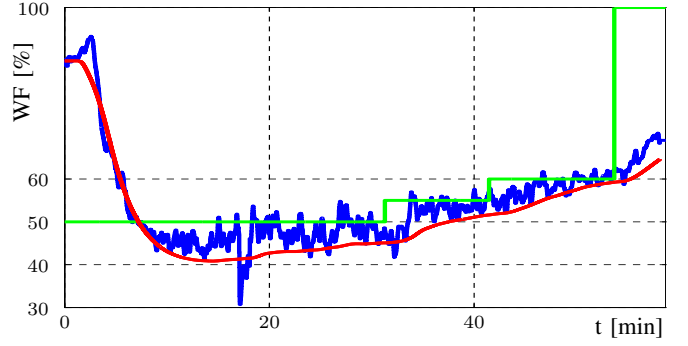


Fig. 3. Measured  $WF$  (blue) and corresponding model response (red) for one of the 23 clinical cases. The reference  $WF$  is shown in green.

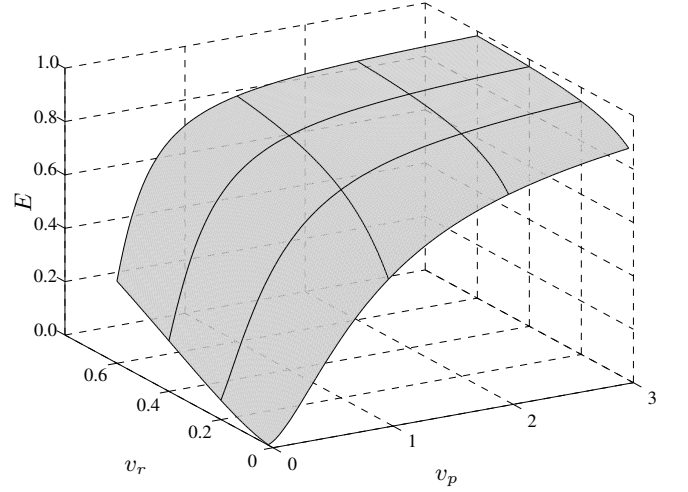


Fig. 4. Pharmacodynamic response surface relating effect site concentrations  $v_p$  and  $v_r$  (units of  $C_{e,50}$ ) to DOH  $E$  (ranging 0 to 1).

plasma concentration, normalized by the plasma concentration corresponding to 50 % clinical effect. Note that the  $C_{e,50}$  values published for remifentanil normally relate to analgesia, whereas in this context  $C_{e,50}^r$  relates to the hypnotic effect of the drug. The parameter  $\alpha$  determines the degree of interaction and synergy is characterized by  $\alpha > 0$ . By comparing (2) and (3) it is clear that the interaction is equivalent to the introduction of a new virtual drug with  $v = v_p + v_r + \alpha v_p v_r$ .

No similar study has been conducted in children, but the interaction has been reported [19]. This work therefore adopts the values  $\alpha = 5.1$  and  $C_{e,50}^r = 12.5$  ng/ml from [18], while using the  $\gamma$  values of the 23 identified models. Consequently, simulation results are consistent with the original models when  $v_r = 0$ . The response surface for  $\gamma = 1.6$ , being the  $\gamma$  value of the model in Fig. 3, and a clinically significant range of  $v_p$  and  $v_r$  is shown in Fig. 4.

## C. Monitor, Disturbance and Noise Models

1) *Monitor*: A suitable monitor for this work is the NeuroSense NS-701 [2] (NeuroWave Systems, Cleveland Heights, USA). It provides the  $WAV_{\text{CNS}}$  index of  $WF$ , ranging from 100 (fully awake) to 0 (iso-electric EEG). It is obtained by applying a wavelet transform to the EEG.

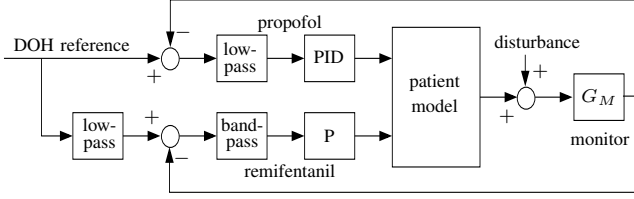


Fig. 5. Block diagram of the mid-ranging control system with reference low-pass and error band-pass filters in the remifentanil loop. PID and P are the propofol and remifentanil controllers, respectively.

The NS-701 has delay-free LTI dynamics, making it suitable for closed-loop applications. It is adequately modeled by

$$G_M(s) = \frac{1}{(T_M s + 1)^2}, \quad T_M = 8 \text{ s}, \quad (4)$$

The measurement noise of the NS-701 with the above trending dynamics corresponds to adding a sample from  $\mathcal{N}(0, 9.0)$  to each input sample of (4). See [5] for further details.

2) *Noxious Stimulation*: The level of noxious stimulation can be modeled as an output disturbance on the WF. Increased stimulation results in increased WF. Upper and lower gastrointestinal endoscopies are characterized by a sudden increase in stimulation as the endoscope is inserted. Once in place, stimulation drops rapidly and remains at a low level throughout the procedure. This sudden increase was modeled as an output disturbance step of 20 WAV<sub>CNS</sub> units added to the simulated clinical effect, being representative of observations in manually dosed cases [4].

#### IV. CONTROLLER SYNTHESIS

This section describes and motivates the tuning of the remifentanil controller and filters.

##### A. System Structure

The system structure is shown as a block diagram in Fig. 5. The propofol controller and DOH monitor are those used in [5]. The novel component is the remifentanil controller, consisting of a mid-ranging high-pass split filter applied to the control error, a proportional controller and low-pass filters on the control error and WF reference, respectively. The use of a P controller is justified by the fact that integral action is provided by the propofol loop. Furthermore, addition of prediction (e.g. derivative action) to the remifentanil loop would be of limited use since the remifentanil dynamics do not exhibit significant capacitive behavior, while the amount of measurement noise is relatively high.

##### B. Fundamental Limitations

The nominal infusion rate of remifentanil was chosen as  $u_r^0 = 0.03 \mu\text{g/kg/min}$ , in accordance with the previous study [5]. In this work, it was deemed clinically feasible to allow short term variations of the remifentanil infusion, ranging between  $u_r^{\min} = 0.01 \mu\text{g/kg/min}$  and  $u_r^{\max} = 0.30 \mu\text{g/kg/min}$ . Fig. 6 shows upper achievable bounds on WF variation by changing the remifentanil infusion rate from  $u_r^0$  (blue) to  $u_r^{\min}$  (red) and  $u_r^{\max}$  (green), respectively, for the

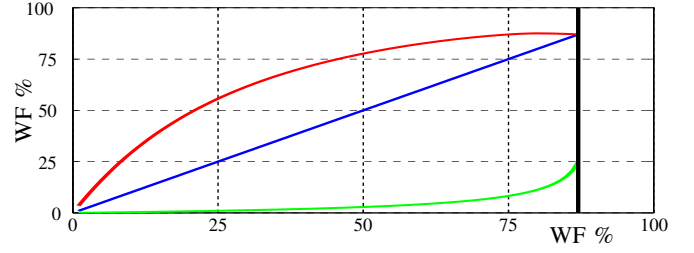


Fig. 6. Upper achievability bound on WF variation by changing the remifentanil infusion rate from  $u_r^0$  to  $u_r^{\min}$  (red) and  $u_r^{\max}$  (green) respectively, as a function of nominal WF (blue) corresponding to  $u_r^0$ .

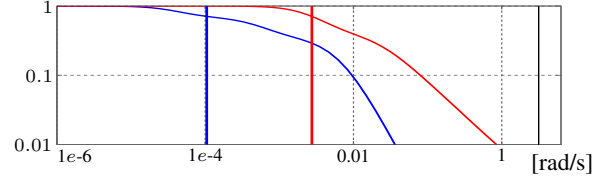


Fig. 7. Normalized Bode magnitude and  $-3$  dB bandwidths of propofol (blue) and remifentanil (red) patient models.

patient model corresponding to Fig. 3. The different nominal WF values (blue) were obtained by altering the propofol infusion rate, while keeping  $u_r = u_r^0$ . The vertical distance from the blue to the red and green lines are determined by (3).

The Bode magnitudes of the dynamic parts of the corresponding propofol and remifentanil patient models, normalized by their steady state gains, are shown in Fig. 7, together with their  $-3$  dB bandwidths.

##### C. Mid-ranging Split Filter

Fig. 8(a) shows the Bode magnitudes of the 23 propofol control loop sensitivity functions, linearized around 50 % WF. The vertical line at  $\omega_{HP} \approx 3.1 \cdot 10^{-3} \text{ rad/s}$  marks the average  $-3$  dB bandwidth among the models. Disturbance frequencies below  $\omega_{HP}$  are adequately attenuated by the propofol loop, motivating the application of the following high-pass mid-ranging split filter to the WF error signal:

$$H(s) = \frac{sT_{HP}}{sT_{HP} + 1}, \quad T_{HP} = \frac{1}{\omega_{HP}} = 325 \text{ s}. \quad (5)$$

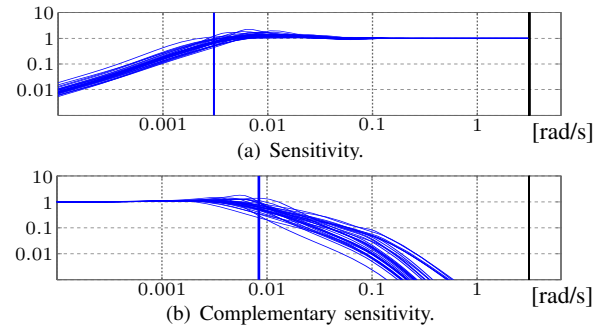


Fig. 8. Sensitivity magnitudes and average  $-3$  dB bandwidths of the propofol loops.



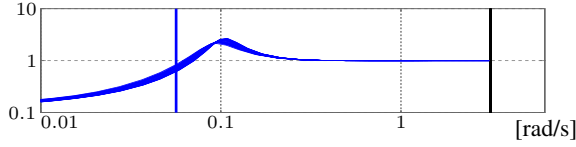


Fig. 9. Sensitivity magnitudes and average  $-3$  dB bandwidth of the remifentanyl loops.

#### D. Controller Tuning

Once the split filter was determined, the remifentanyl loop was linearized around its nominal operating point, corresponding to  $u_r^0 = 0.03 \mu\text{g/kg/min}$  and 50 % WF. The remifentanyl controller gain was subsequently maximized while maintaining a minimal gain margin of 2.0 among the 23 models. The corresponding minimal phase margin was  $56^\circ$ .

#### E. Low-pass Filters

Fig. 9 shows the sensitivity Bode magnitudes of the remifentanyl control loops. The average  $-3$  dB bandwidth among the 23 models,  $\omega_{LPe} \approx 5.6 \cdot 10^{-2} \text{ rad/s}$  is marked with a vertical line. The following low-pass filter was applied in series with (5) in order to improve high frequency noise attenuation:

$$L(s) = \frac{1}{sT_{LPe} + 1}, \quad T_{LPe} = \frac{1}{\omega_{LPe}} = 18 \text{ s}. \quad (6)$$

The current implementation of iControl supports WF reference changes in steps. The high frequency content of a step could saturate the remifentanyl control signal, reducing disturbance rejection ability at reference changes. In order to avoid this, the reference was low-pass filtered before entering the remifentanyl controller. Fig. 8(b) shows the complementary sensitivity functions corresponding to Fig. 8(a) and the average  $-3$  dB bandwidth  $\omega_{LPPr} \approx 8.4 \cdot 10^{-3} \text{ rad/s}$ . The following reference filter was chosen:

$$R(s) = \frac{1}{sT_{LPPr} + 1}, \quad T_{LPPr} = \frac{1}{\omega_{LPPr}} = 120 \text{ s}, \quad (7)$$

blocking reference frequencies above those which the propofol loop is expected to handle.

### V. SIMULATION RESULTS

#### A. Simulation Example

Closed-loop control simulations were conducted for each of the 23 patient models. In order to alleviate propofol infusion pain, a bolus of  $10 \mu\text{g/ml}$  remifentanyl was given at the pre-set upper infusion rate limit, 200 ml/h, of the pump. Its duration, typically around 10 s, was computed so that the corresponding patient model would reach a plasma concentration equal to the steady state value corresponding to  $u_r^0 = 0.03 \mu\text{g/kg/min}$ . A  $10 \text{ mg/ml}$  propofol bolus at 600 ml/h was added to the propofol control signal during the initial 15 s of infusion to alleviate propofol infusion pain.

Fig. 10 shows the outcome of a disturbance rejection simulation with the existing iControl system (blue) and the suggested mid-ranging controller (red) for the patient model of Fig. 3. Noxious stimulation, modeled as the solid green

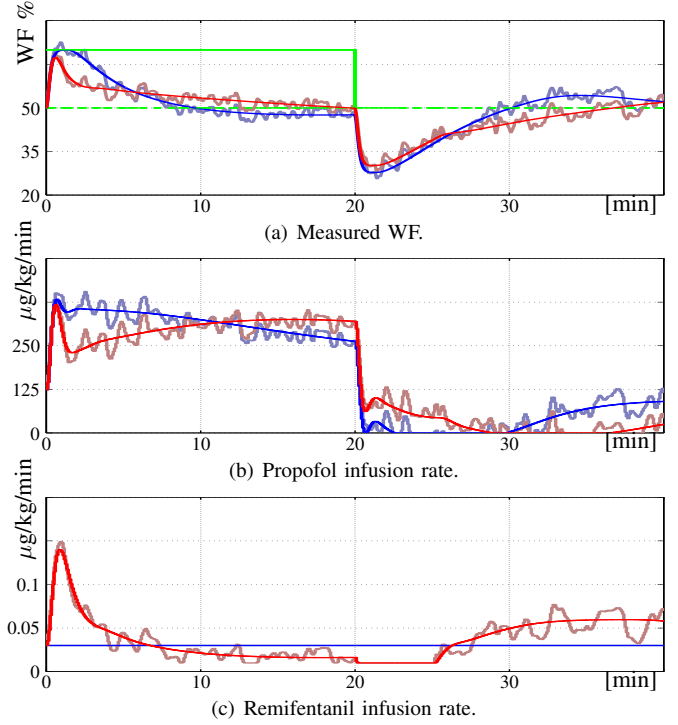


Fig. 10. Simulated response to output disturbance of the patient model in Fig. 3 (solid green), using current iControl setup (blue) and the proposed mid-ranging strategy (red). The dashed green line marks the WF reference.

output disturbance in Fig. 10(a), was applied once the system had reached steady state upon induction of anesthesia. The dark color plots are from noise-free simulations. The outcome of equivalent simulations with realistic measurement noise [5] yielded the light colored plots in Fig. 10.

Note that the controller is more efficient in attenuating the initial positive output disturbance step than the consequent negative one. This is because the nominal remifentanyl infusion rate  $u_r^0$  lies closer to  $u_r^{\min}$  than  $u_r^{\max}$ .

#### B. Performance Comparison

Population averages of common control performance measures were computed using the iControl system and the proposed mid-ranging controller, respectively.

The integral absolute error (IAE) is the time integral of  $|\text{reference} - \text{measurement}|$ . The Varvel measures [20] were originally developed for target controlled infusion (TCI) systems. These metrics have been broadly adopted for reporting performance of closed-loop control systems in anesthesia. Induction time is defined in accordance with [21].

Percentage improvements, going from iControl to the mid-ranging controller, are presented below for  $H(s) = 1$  in (5). The IAE caused by the output disturbance profile in Fig. 10(a) decreased by 42 %. The corresponding performance improvement in terms of the Varvel measures were: 13 % MDPE decrease, 59 % MDAPE decrease and a 67 % wobble decrease. Induction time of anesthesia was, however, increased by 2 %, but the corresponding overshoot decreased by 36 %. IAE following a negative WF reference step from 50 to 40 decreased by 35 % and stepping back up to 50,

the IAE decrease was also 35 %. The corresponding WF overshoots decreased by 79 % and 81 %, respectively. These numbers provide an upper performance bound. Decreasing  $T_{hp}$  in (5) will improve settling of the remifentanyl infusion to its nominal rate upon disturbances, simultaneously making disturbance rejection slower. Consequently, the choice of  $T_{hp}$  can be viewed as a trade-off between disturbance rejection and settling of the remifentanyl infusion rate to its nominal value. The herein suggested value of  $T_{hp} = 325$  s provides no significant change in the performance metrics. However, rapid changes in the WF signal are an indicator of changes in noxious stimulation, motivating the rejection of such disturbances by means of altering the remifentanyl infusion rate in favor of the propofol one.

## VI. DISCUSSION

This paper has presented a novel approach for extending a SISO DOH controller, using propofol and EEG-based monitoring, into a MISO DOH controller through the addition of closed-loop remifentanyl infusion. The purpose of the extension was primarily to increase the output disturbance rejection bandwidth. I.e., to improve compensation for noxious stimulation. This was achieved by means of a mid-ranging control strategy, for which a model based tuning method is presented in this paper.

The achievable performance of the mid-ranging control system was compared to that of a clinically evaluated SISO system, using simulated procedures on 23 clinically obtained patient models. In addition to improved response to noxious stimulation, reference tracking can be improved and the WF overshoot upon induction of anesthesia can be decreased. Measurement noise attenuation is comparable to the nominal system, as shown in Fig 10.

The remifentanyl control loop was designed with the existing iControl system in mind. However, the synthesis method can be applied to extend any EEG-monitored propofol DOH control system. The decision to leave the propofol control loop un-altered simplifies the synthesis procedure and makes operation with the remifentanyl loop in manual mode correspond to the nominal control system. It also implies that the system can be clinically evaluated in a conservative way, by limiting the actuator limits and gain of the remifentanyl loop.

Planning of clinical trials of this scheme is under way.

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