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PID control of data-driven patient response with fixed ratio co-administration of drugs for depth of hypnosis

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Abstract: In this work we make use of knowledge from clinical practice to deliver a trusted environment for feedback control of co-administration of two drugs to induce depth of hypnosis during general anesthesia. The clinical data we have provides valuable insight into the ratio used to determine the Propofol and Remifentanil infusion rates by means of specifying their corresponding effect site concentrations. A feedback closed loop with a fixed parameter PID controller tuned on population dynamics is used. To account the strong variations in gain of the system (patient) we propose an online identification of the dose-effect response from clinical data available during clinical protocol. Theoretical analysis is provided to justify the approach and simulations with real data from patient are given to support the theoretical insight. Limitations of this approach are discussed as to justify why ratio based co-administration is used in practice solely during the induction phase of general anesthesia.

Keywords: Closed-Loop Control of Anesthesia, PID Control, Depth of Hypnosis, Ratio Control, Model Estimation, Data Driven Control.

1. INTRODUCTION

Ratio control is widely used in chemical process industry as part of a closed loop control strategy and has the role of reducing the degrees-of-freedom in a input-output formulation of the process variables within the control objectives. Recently, ratio control has been revisited for interdisciplinary application in medicine, i.e. in controlling the depth of hypnosis during general anesthesia (Merigo et al., 2019; Schiavo et al., 2020, 2022a,b; Huff et al., 2024). Notably, it has proven useful in combination to optimized controller parameters to mitigate the strong variability of patient sensitivity to drug infusion values. In particular, the depth of hypnosis during induction phase is challenging for both control and patient model estimation. Several works have previously discussed these challenges and proposed solutions (De Keyser et al., 2015; De Keyser and Ionescu, 2012; Ionescu, 2018).

One of the most widely adopted and clinically accepted indicators for monitoring the Depth of Hypnosis (DoH) is the Bispectral Index (BIS) scale. The computerized system designed to assist the anesthesiologist in drug dosing is the so-called Target-Controlled Infusion. TCI provides a desired effect site concentration of the drug by calculating an infusion profile from inverted pharmacokinetic models specific to the patient (based on age, weight, height, gender). By definition, this is an open loop system, whereas the anesthesiologist closes it by adjusting the desired effect site concentration (Neckebroek et al., 2019).

DoH monitoring relies on the monitored Bispectral Index (BIS) as a controlled process variable while using the infusion of Propofol as a manipulated variable. Experi-

mental results have shown the effectiveness of this method across different control architectures, such as Proportional–Integral–Derivative (PID) control (Schiavo et al., 2022b), model-based control (Spataru et al., 2023), Model based Predictive Control (MPC) (Neckebroek et al., 2019; Pawlowski et al., 2022; Moussa et al., 2023), fuzzy control (Mendez et al., 2018; Padmanabhan et al., 2019). However, to achieve analgo-sedation state prior to surgery phase, it is necessary to use an opioid, i.e. Remifentanil, necessary to ensure lack of pain (analgesia). Given the synergy interaction of these drugs, their dose-effect to BIS variable is controlled around a value of BIS=50% depth of hypnosis.

In this paper we revisit these solutions for mimicking the actual clinical practice and clinical data available during induction phase of general anesthesia. In this way, a solution is given which feels more comfortable throughout a sense of trust in computer based anesthesia and facilitate the future interdisciplinary approach in decision support systems for anesthesia.

We propose here a theoretical framework of using a fixed ratio between the two inputs of the system. This is mirrored by clinical practice as revealed by our clinical data recorded from patients during induction phase of general anesthesia. This allows us to have a reduction from the multiple-input single-output (MISO) system, to the single-input single-output (SISO) system definition. The challenge is the strong variability in process gain, i.e. in patient response to dose-effect, reflecting the patient's sensitivity to the drug effect. We propose an online estimation mechanism of the dose-effect model for each patient based on actual data from clinical practice. The standardization of protocol for induction phase allows us to define regions where such model estimation is possible in absence of disturbances. This model adaptation greatly reduces the loop uncertainty, such that a PID control with nominal robustness (Ro=0.5) can be used. The limitations of the ratio control used in such control scheme are discussed and illustrate why this is applicable only during the induction phase.

The paper is organized as follows. Next, we provide the theoretical framework of co-administration of drugs with single output variable for depth of hypnosis. The third section provides clinical data to illustrate clinical practice based on decisions to administrate the two drugs for achieving depth of hypnosis and analgo-sedation states. The fourth section proposes the control structure with data driven dose-effect model estimation. Simulations of mimicked clinical protocol indicate the performance of the proposed methodology. Finally, limitations are discussed and a conclusion section summarizes the main outcome of this work.

2. THEORETICAL FRAMEWORK

During induction of hypnosis, the change from the awake to hypnotic state is performed by administrating Propofol, a hypnotic drug with dose-effect relationship given by a sigmoid function, known as the Hill curve:

$$E(t) = \frac{C_{ep}^{\gamma}(t)}{C_{ep}^{\gamma}(t) + C_{50p}^{\gamma}} \tag{1}$$

where C_{50p} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the C_{50p} determines the patient sensitivity to the drug. Properties of this nonlinear gain function and its adaptation mechanism have been addressed in (Ionescu, 2018). The effect-site concentration $C_{ep}(t)$ is calculated from pharmacokinetic model parameters based on patient characteristic such as age, weight, height and gender for Propofol (Schnider et al., 1998) and for Remifentanil (Minto et al., 1997), respectively. The parameters γ and C_{50} are strongly varying for each patient individually (De Keyser et al., 2015) and can be estimated from observed data during the induction of hypnosis state in absence of disturbance (Wahlquist et al., 2021).

Monitoring the effect of hypnotic agent is done through observing values of the Bispectral Index, an electroencephalogram signal based index, which is scaled between 0%-100%, with 100% denoting fully awake patient:

$$BIS(t) = E_0 - E_{max} \cdot E(t) \tag{2}$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol. The BIS index is calculated based on time intervals and often corrupted by artefacts from other sources of electric impedance (e.g. electric cutter or suture devices). When the signal quality falls below a given threshold, the corrupted time interval from which BIS is calculated is discarded and a time interval further in past time is used. This introduces variable time delays and solutions have been proposed in (Ionescu et al., 2011a; De Keyser and Ionescu, 2012).

When co-administrating Propofol and Remifentanil, the Hill curve becomes a nonlinear surface, expressed as dose-effect relationship by:

$$E = \frac{\left(\frac{C_{er}(t)}{C_{50r}} + \frac{C_{ep}(t)}{C_{50p}} + \sigma\frac{C_{er}(t)C_{ep}(t)}{C_{50r}C_{50p}}\right)^{\gamma}}{1 + \left(\frac{C_{er}(t)}{C_{50r}} + \frac{C_{ep}(t)}{C_{50p}} + \sigma\frac{C_{er}(t)C_{ep}(t)}{C_{50r}C_{50p}}\right)^{\gamma}} \tag{3}$$

where the initial and maximal effect scaling factors have been omitted and σ represents the degree of synergy between the drugs. The effect-site concentrations of Propofol and Remifentanil are denoted as C_{ep} and C_{er}, respectively, expressed in ml/h and they act in synergy (Ionescu et al., 2011b); this is visible in Figure 1, where it can be seen that the half-effect is obtained with less values than independently marked dose-effect C_{50} for each drug.

During induction phase, when BIS is further observed during the analgesia state region, then we can estimate the values of C_{50p}, C_{50r}, γ and σ directly from data in absence of disturbance. Notice that at all times during closed loop control, the surface is evaluated as a single point navigating in the space denoted by the range of values of our variables. Let us denote

$$A = \frac{C_{er}(t)}{C_{50r}} + \frac{C_{ep}(t)}{C_{50p}} + \sigma\frac{C_{er}(t)C_{ep}(t)}{C_{50r}C_{50p}} \tag{4}$$

Let us consider a generic ratio between the two drugs: $C_{er}(t) = R \cdot C_{ep}(t)$, then A becomes:

$$A(R) = \frac{R \cdot C_{ep}(t)}{C_{50r}} + \frac{C_{ep}(t)}{C_{50p}} + \sigma\frac{R \cdot C_{ep}(t)C_{ep}(t)}{C_{50r}C_{50p}} \tag{5}$$

In steady state, for half effect E=0.5 or equivalently BIS=50%, we have the equilibrium $C_{ep}(t) = C_{50p}$ and

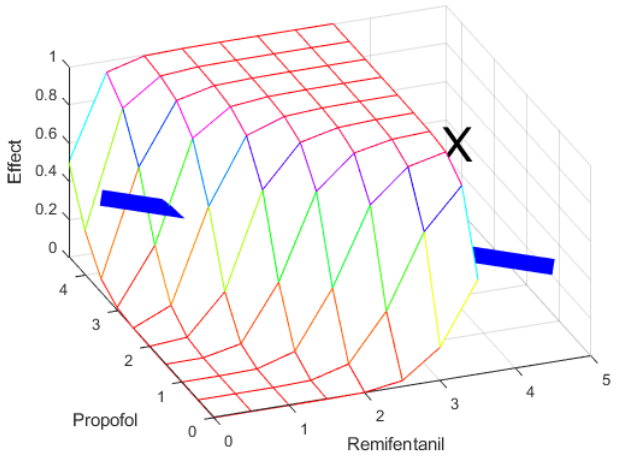

Fig. 1. Surface model of Propofol and Remifentanil for values: $\sigma = 1.2$ and $\gamma = 3$. The "X" marks the spot of half-effect E=0.5 corresponding to independent $C_50p = 3.5$ and $C_50r = 4.5$ values. The blue thick line is intersection of the E=0.5 value with the surface, indicating the half-effect solution of the surface from (3).

$C_{er}(t) = C_{50r}$. In this situation, (5) becomes:

$$A(C50ss) = \frac{R \cdot C_{50p}}{C_{50r}} + \frac{C_{50p}}{C_{50p}} + \sigma \frac{R \cdot C_{50p} C_{50p}}{C_{50r} C_{50p}} \tag{6}$$

and simplified rearranged to:

$$A(C50ss) = R \cdot \frac{C_{50p}}{C_{50r}}(1+\sigma) + 1 \tag{7}$$

The surface from (3) for dose-effect becomes

$$E_{ss} = \frac{\left(R \cdot \frac{C_{50p}}{C_{50r}}(1+\sigma) + 1\right)^{\gamma}}{1 + \left(R \cdot \frac{C_{50p}}{C_{50r}}(1+\sigma) + 1\right)^{\gamma}} \tag{8}$$

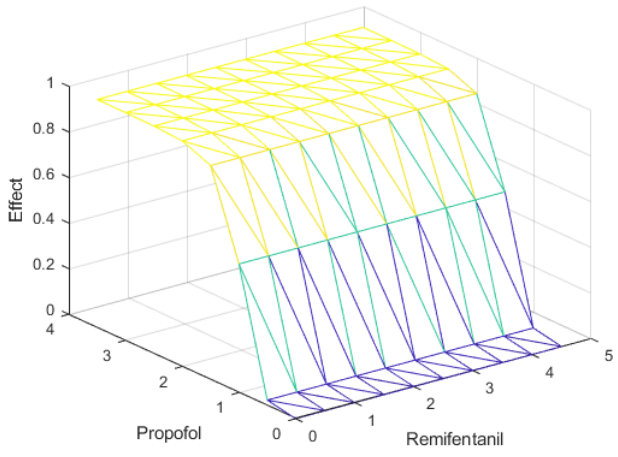

Fig. 2. Surface when ratio is used between the two drugs, for $\gamma = 5$.

Let us now consider the transient time for $C_e \rightarrow C_{50}$. Figure 2 depicts the surface when a ratio is used between the two drugs. Around the half-effect there is a linear dependence of the effect site concentrations and the effect,

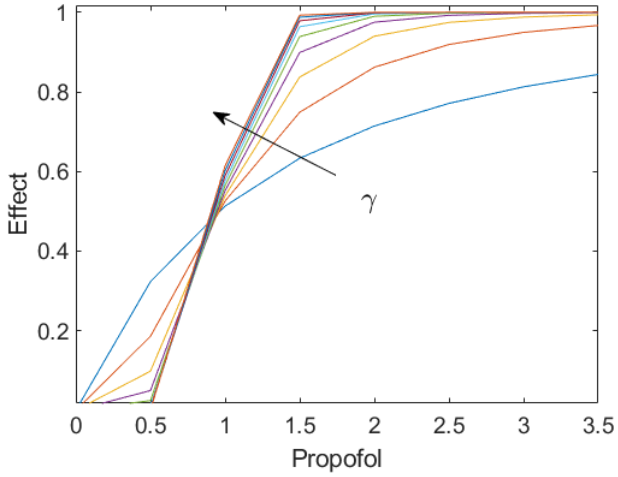

Fig. 3. Surface is independent on Remifentanil when a fixed ratio is used between the two drugs, for $1 \leq \gamma \leq 10$.

which holds for the ratio between two drug concentrations as well. In this case, we can assume that around $0.4 < E < 0.6$, or $40 < BIS < 60$ we also have $C_{50r} = R \cdot C_{50p}$. This is illustrated in Fig. 3. Relation (5) becomes:

$$A(R50t) = \frac{R \cdot C_{ep}}{R \cdot C_{50p}} + \frac{C_{ep}}{C_{50p}} + \sigma \frac{R \cdot C_{ep} C_{ep}}{R \cdot C_{50p} C_{50p}} \tag{9}$$

which eliminates the ratio R from the relation. In this case, during transient times, this term will remain unaffected whether the term $x(t) = \frac{C_{ep(t)}}{C_{50p}}$ is supra- or sub-unitary:

$$E_t = \frac{\left(2x(t) + \sigma \cdot x(t)^2\right)^{\gamma}}{1 + \left(2x(t) + \sigma \cdot x(t)^2\right)^{\gamma}} \tag{10}$$

which implies that the dose-effect relationship remains constant around the half-effect and with a fixed ratio between drugs. This conclusion is important for the control loop objective, as it allows to use linear feedback control with controller parameters tuned only once.

3. CLINICAL PROTOCOL AND DATA FROM INDUCTION PHASE OF GENERAL ANESTHESIA

Recently published protocol and data from 70 patients, illustrates in Fig. 4 the clinical practice of events to safely induce general anesthesia prior to surgery (Ionescu et al., 2024). In this figure we observe region Hypnotics, where only Propofol is administered, followed by a Train of Four stimulus test to verify the depth of hypnosis, followed by the Analgesics region where co-administration of Remifentanil is initiated. The end of this last region is the end of induction phase of general anesthesia.

Let us examine data for Patient 24 from the list of patients, i.e. a female of 36 years of age, with height 168 cm and weight 63 kg. As stated earlier, during the hypnotics region, one can identify the Hill curve for the real patient. The estimation uses a nonlinear least squares search function for steepest gradient in Matlab with function `lsqnonlin`, which gave the solution for the equation (1): $E0 = 96$, $E_{max} = 100$, $\gamma = 5.57$ and $C_{50p} = 12.03$. The result is given in Fig. 5.

Next, we also stated that during the analgesic region we can identify the surface model from the real data

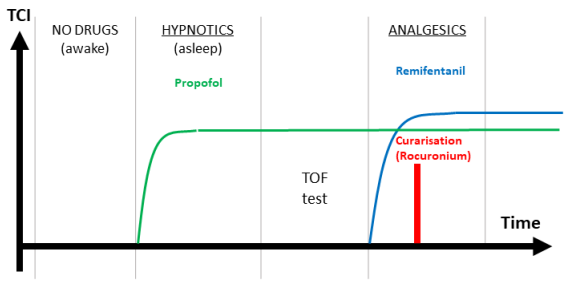

Fig. 4. Example of clinical protocol from our study reported in (Ionescu et al., 2024) during induction phase of general anesthesia. Propofol is used to induce hypnotic state, Remifentanil is used to induce the analgesic state and Rocuronium is given to ensure neuromuscular blockade.

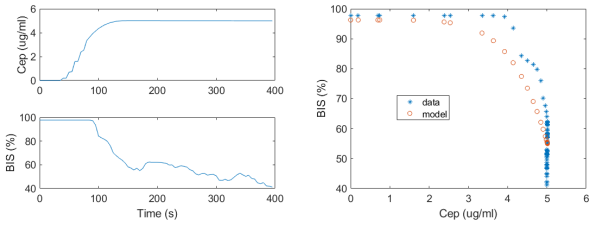

Fig. 5. Example of input-output for hypnotic region (left) and corresponding Hill curve identification (right) for Patient 24 from (Ionescu et al., 2024).

from the patient. In that region, the Remifentanil has an effect site in ratio to Propofol as depicted in Fig. 6. The anesthesiologist uses a ratio of 2 between the desired effect site concentration for Remifentanil with respect to that of Propofol. While reaching this target effect site concentration, one can observe that during transient time, the actual ratio varies as in Fig. 6.

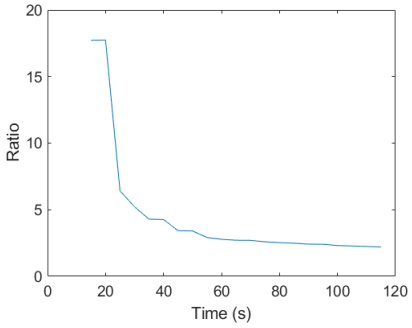

Fig. 6. Example of ratio between Remifentanil to Propofol (other volumetric units not included) from start of analgesic region until steady state, data for Patient 24 from (Ionescu et al., 2024).

Identification of the surface model reduced to a 2D relationship as from theory depicted in Fig. 3 was performed also using a nonlinear least squares search function for steepest gradient in Matlab with function `lsqnonlin`, which gave the solution for the equation (3): $E0 = 33$, $E_{max} = 100$, $\gamma = 18.57$, $\sigma = 2$ and $C_{50p} = 5.68$. Observe that due to synergy, the C_{50p} is now smaller than the value identified for the Hill curve single-drug effect, which again corresponds to theory. The result of identification is given in Fig. 7.

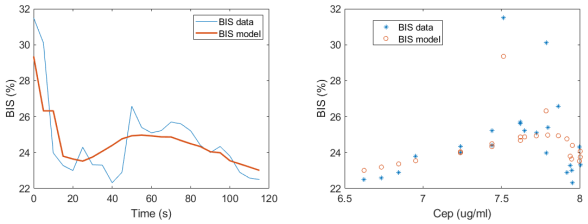

Fig. 7. Example of BIS data and BIS estimated during analgesic region (left) and corresponding reduced surface model identification (right) for Patient 24 from (Ionescu et al., 2024).

4. CONTROL SCHEME AND METHODOLOGY

The control scheme is depicted in Fig. 8. It uses the desired effect site concentration with model adaptation to achieve the level of hypnosis, and the analgo-sedation, respectively. The architecture employed is a standard ideal PID controller defined by its transfer function in (11).

$$C(s) = K_p \left(1 + \frac{1}{T_i s} + T_d s\right) \tag{11}$$

where, K_p represents the proportional gain, T_i denotes the integral time constant, T_d signifies the derivative time constant, implemented in its digital form to avoid derivative kick (on output instead of error). The filter on the reference is also used for trade-off of adaptation in presence of noise. The tuning of this controller is based on the method from (De Keyser and Ionescu, 2012), with a nominal robustness of 0.5 (we use the terminology "nominal" because the ultimate cycle autotuner also gives a robustness of 0.5), with parameters tuned on population based averaged PK model. The controller parameters for Patient 24 are $K_p = 11.51$, $T_i = 21.84$ and $T_d = 5.46$.

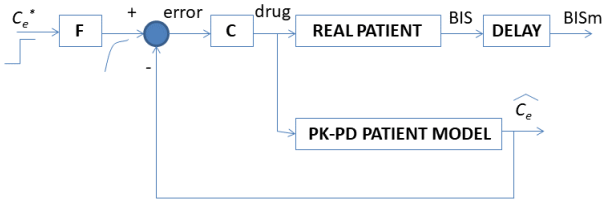

Fig. 8. Control scheme with patient model estimation.

The available measured BIS values (denoted by $BISm$ in Fig. 8) and the C_{ep} are related around BIS=50 by a linear approximation and possibly a time delay τ as aforementioned from the monitoring principles of BIS value. This can be written as:

$$BIS(t) = K * C_{ep}(t - \tau) + d \tag{12}$$

where the time delay is preselected from a predefined range of values and K and d are estimated at every sample time for every preselected time delay value. The solution is then the one that gives the minimal error according to $\frac{1}{N}\sum_{i=1}^{N} e^2$. Notice that in steady-state, the time delay is not necessary since $C_{ep} = C_{ep}^*$ which allows to extract and adapt the desired C_{ep}^* (i.e. the setpoint for the control

scheme in Fig. 8) for a desired BIS value at every sample time. In fact, for a desired BIS=50, this is nothing else than the estimation of the C_{50p} of the patient.

It is worth mentioning that in case PK-PD models are used from population based models reported in (Schnider et al., 1998) and (Minto et al., 1997), there will always be a difference between the calculated $C_e(t)$ and the actual $C_e(t)$ in the patient. By using adaptation of the dose-effect gain and the closed loop adaptation proposed here this difference will be corrected intrinsically by correcting the error in the dose-effect relationship and reducing the loop uncertainty (Gonzalez-Cava et al., 2021).

5. RESULTS AND LIMITATIONS

Simulation of patient 24 in closed loop with the values identified in section 3, allows us to test the control scheme proposed herein. The simulation sequence is mimicking the protocol depicted in Fig. 4, i.e. an initial region of Propofol only administration to bring the output to its setpoint BIS=50, based on effect-site concentration of Propofol desired value and adaptive gain of patient data with feedback PID control parameters from section 4. Without changing the controller parameters, co-administration is initiated at time $t = 300$ seconds, with a fixed ratio $R = 2$. Adaptation of model parameters gives us a new setpoint for effect site to realign the output to desired $BIS = 50$ value, by converging to the new value. The results obtained and illustrated in Fig. 9 show the agreement with identified Hill, respectively reduced surface model parameters for half effect site concentration of Propofol: its steady state values correspond to identified C_{50p} values.

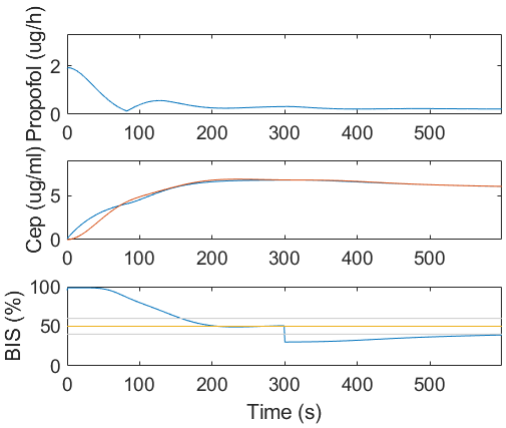

Fig. 9. Closed loop control of induction phase for Patient 24, mimicking clinical protocol. Middle plot illustrates the estimated C_{ep} and the adapted setpoint for C^*_{ep}. Bottom plot gives the values for BIS and its 40-60 interval, around setpoint BIS=50%.

The online estimations for the gain, offset and adapted setpoint C^*_{ep} for the control loop are depicted in Fig. 10.

Limitations in closed loop performance may be observed in the analgesic region, where a slow convergence to desired BIS values is present. This may be improved at the cost of a more aggressive adaptation of model parameters. In presence of noise, this is undesired and it requires a trade-off between speed of adaptation and sensitivity to noisy signals. The time delay here is assumed to be

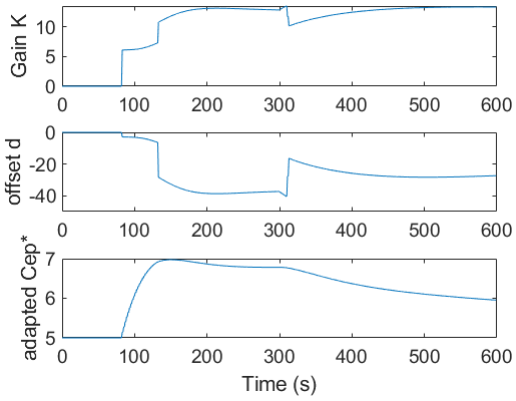

Fig. 10. Online estimations for dose-effect model parameters from (12) for Patient 24.

fixed throughout the simulation, at 10 seconds. As from our previous investigations in clinical data, we observed variations of delay from 10-120 seconds, which if unknown by the controller, significantly challenges the stability of the closed loop (Ionescu et al., 2011a). Using the proposed scheme, the delay is also estimated and can be included as part of the adapted model for each patient.

Ratio control with drug co-administration is only meaningful during induction phase of general anesthesia, as to mimic the actions followed by the anesthesiologist within clinical practice. The real challenge for control point of view starts at the maintenance phase, i.e. at the end of the time interval depicted in Fig. 4 starts the intubation, followed by the surgery regions. During maintenance phase it is difficult (if not impossible) to obtain a model of the patient due to presence of disturbances coming from intubation and surgical stimuli, also known as nociceptor stimulation. In order to exploit the full degrees-of-freedom available within a multiple-input multiple-output (MIMO) control loop, it is necessary to treat the administration of drug inputs Propofol and Remifentanil as independent variables. This requires also two outputs of independent variables, one being the BIS index and another one being the analgesia index. The latter has been evaluated recently in (Ionescu et al., 2024) and enables the MIMO closed loop control of anesthesia during maintenance phase.

6. CONCLUSION

In this paper we use real data to examine the evolution of dose-effect relationship in clinical protocol for induction phase of general anesthesia. A fixed ratio is used to co-administer two drugs for single output process control. Estimation of the dose-effect nonlinear relationship is performed from real data for a patient. This is used to simulate the patient in a realistic sequence of inducing hypnosis and analgo-sedation. An adaptive methodology for effect site concentrations of Propofol with feedback PID control is proposed to online adapt patient model parameters. The results indicate good performance of the closed loop. Limitations are discussed and justify the need for multivariable models for optimal drug management during the maintenance phase of anesthesia, which has to tackle disturbance effects of surgical stimulation. Next steps in our research pursue this multivariable approach.

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