Closed-loop control of anesthesia and hemodynamic system: a Model Predictive Control approach

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Abstract: This paper proposes a Model Predictive Control (MPC) approach of both anesthesia and hemodynamic systems. The designed control strategy has been validated on a novel and unique patient simulator. The aim of this paper is to evaluate the feasibility MIMO closed-loop control of anesthesia and hemodynamic variables taking into account the interaction (synergic and antagonistic) between subsystems. The proposed methodology takes into account patient variability, is robust to subsystems interaction and meets the clinical objectives. The algorithm is tested in simulation on a hypnosis-hemodynamic combined model for use during general anesthesia. The preliminary results are promising and show the effectiveness of the control procedure.

Keywords: anesthesia, hemodynamic regulation, closed-loop control of anesthesia, Model Predictive Control, optimal drug dosing.

1. INTRODUCTION

General anesthesia is a multi-facet drug infusion control problem as it requires solving a puzzle of several dynamic states adequately induced and maintained, while mitigating comorbidity induced risks and surgical stimulation (Dumont and Ansermino, 2013; Ghita et al., 2020). Hypnosis is the lack of consciousness, analgesia is the lack of pain and neuromuscular blockade is the lack of movement. To achieve a patient state that allows the surgeon to perform a procedure, hypnotic (e.g. remifentanil), opioids (e.g. propofol) and neuromucular blocking agents (e.g atracurrium) drugs have to be administered. Individual responses to hypnotic and opioid infusion vary significantly in adults and even more in children (van Heusden et al., 2014). When administered together propofol and remifentanil have a synergistic effect. The anesthesiologist needs to continuously monitor the patient state and adjust drug dosing in order to avoid under- and over-dosing. Underdosing can result in anxiety, tracheal tube intolerance, infection while over-dosing may cause hypotension, prolonged recovery time, delayed weaning from mechanical ventilation.

Along with the anesthetic variables, the anesthesiologist or critical care physician have to regulate and monitor hemodynamic parameters. Mean arterial pressure (MAP) and cardiac output (CO), carbon dioxide, oxygen levels, fluid levels and more are part of the hemodynamic system stabilization. To maintain the MAP and CO within acceptable operating intervals the practitioner administers sodium nitroprussdie (SNP) and dopamine (DPM).

Optimizing the administration of analgesics and hypnotics, as well as drugs for hemodynamic stabilization, are among the various mundane but time- and attention-intensive activities the anesthesiologist has to perform. These actions are repetitive and require constant vigilance, hence, they are prone to human error and are also associated to a significant inter- and intra-practitioner variability (Joosten et al., 2016). Due to the complexity, performance pressure and inter-patient variability, the performance of the anesthesiologist is sub-optimal. This may also have an impact on the long term outcomes (Dumont and Ansermino, 2013). The main challenge in general anesthesia is to achieve acceptable clinical outcomes while minimizing undesired effects. Drug infusion rates are traditionally manually controlled by the anesthesiologist. Computer aided open-loop delivery systems known as target controlled infusion (TCI) systems are available. These are based on population based pharmacokinetic (PK) and pharmacodynamic (PD) models to calculate the required infusion rates to reach the drug concentration set by the anesthesiologist. To account for patient inter-variability

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target concentrations have to be adjusted by the anesthesiologist (van Heusden et al., 2014).

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. Clinical trials reveal that closed-loop control of anesthesia can outperform manual control (Ghita et al., 2020). The considered control approaches in anesthesia vary from classical control strategies to advanced control algorithms (Padmanabhan et al., 2015; Schiavo et al., 2021; Hosseinzadeh et al., 2020; van Heusden et al., 2020; Ionescu et al., 2008; Neckebroek et al., 2013; Ghita et al., 2020).

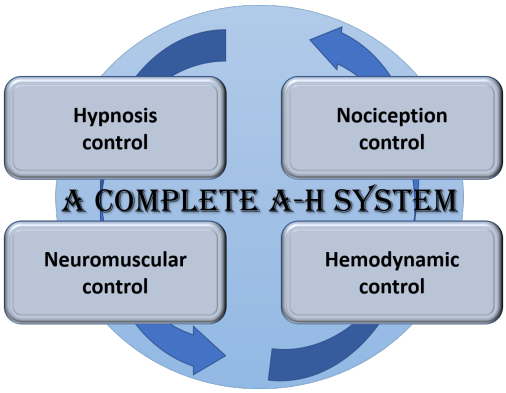

Fig. 1. A complete system for closed-loop control of anesthesia and hemodynamic variables.

This paper presents the first full MIMO control implementation for anesthetic and hemodynamic management schematically represented in Figure 1. In Section II the PK-PD models used for control design are presented. Simulations are performed using the Matlab/Simulink open-source benchmark patient simulator also described in this section. The feasibility of the tested control algorithm and its performance is discussed in Section III followed by a detailed discussion on the preliminary results. Conclusions and future perspectives are provided in Section IV.

2. MATERIALS AND METHODS

2.1 Models

The model usually used to predict/suggest the optimal dosage of drugs consists of two parts: 1) pharmacokinetic (PK) model and 2) pharmacodynamic (PD) model. The PK model relates the drug plasma concentration with the administered dose. A generic three-compartment PK model is given in figure 2. In this paper transfer rates between compartments are considered equal and the equivalent 4th-order linear transfer function model represented by equation (1) has been used for simulations.

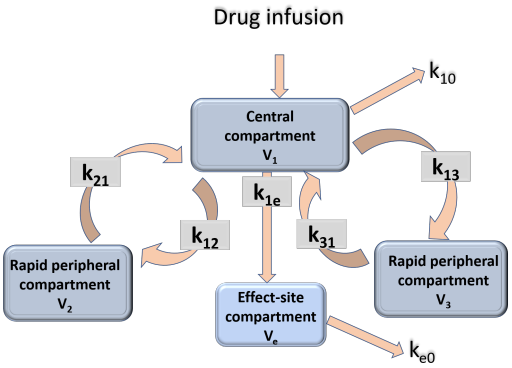

Fig. 2. Dose–response relationship for one drug. Pharmacokinetics are depicted as a multicompartmental model. Pharmacodynamics are shown as a sigmoidal model. Kinetics and dynamics are linked by an effect-site compartment (Ionescu, 2018).

$$
\begin{aligned}
A &= \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{1e} & 0 & 0 & -k_{e0} \end{bmatrix} \\
B &= \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} \\
C &= [0\ 0\ 0\ 1] \\
D &= 0
\end{aligned} \tag{1}
$$

The PD model relates the plasma concentration with the pharmacological end effect. The dose-effect response in the PD model is represented by a nonlinear Hill equation, which relates values of the drug concentration profiles with values of its effect. Propofol PK model parameters are calculated using the Schnider model (Minto et al., 1997a) and Remifentanil model parameters are calculated using Minto model (Minto et al., 1997b). There is a synergic effect when using Remifentanil in combination with Propofol, reducing the Propofol concentration for loss of consciousness by 25% and hence minimising the risk of over-dosages (Milne et al., 2003). The combined effect of two drugs is then a 3D nonlinear surface. A detailed description of the PK-PD models for the opioid and hypnotic drug, but also the models for the hemodynamic parameters along with the interaction between sub-systems are detailed in (Copot and Ionescu, 2018; Ionescu et al., 2021).

The nonlinearity of the Hill curve represents a great challenge from control standpoint. (Ionescu, 2018) introduced a computationally efficient Hill curve adaptation strategy for BIS in order to overcome this challenge. Time delays introduced by the sensor affects the closed-loop performance. Online time-delay estimation was suggested in (Ionescu et al., 2011) to compensate for the variable BIS delay for closed-loop control. Hitherto, there is no generally accepted device for monitoring of analgesia. Development of novel sensors to provide a reliable and objective value of the nociception/ antinocicetion balance has been impacted closed-loop delivery of proper dosing. A comprehensive review on the commercial solutions that have appeared in recent years is done by (Ghita et al., 2020). It tack-

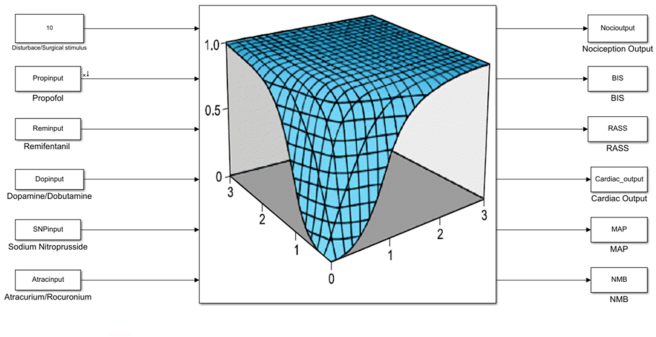

Fig. 3. The integral structure of anesthesia-hemodynamic simulator developed in Matlab–Simulink. The simulator consists of two main subsytems: Anesthesia and Hemodynamics (Ionescu et al., 2021).

les the monitoring limitations (e.g. non-specific markers, unknown robustness against the influence of other medications, influence of cofounding effects) of each device, deciding that the evidence to use one nociception monitor versus another is overall inconclusive. Nowadays in clinical practice the anesthesiologist asses the level of analgesia based on BIS signal and other parameters. Muscle relaxant drugs are frequently given during surgical operations. The non-depolarising types of drugs act by blocking the neuromuscular transmission, therefore producing muscle paralysis. The neuromuscular blockade level is measured from an evoked EMG obtained at the hand by electrical stimulation.

2.2 Patient Simulator

Closed loop simulations and closed loop clinical data for regulating depth of anesthesia using computer control algorithms have been published recently (Padula et al., 2016; Padmanabhan et al., 2015; Schiavo et al., 2021; Hosseinzadeh et al., 2020). We are at the very beginning of what we call - a new era of personalized medicine - enabled by advances in computer technology and powerful information processing tools, in which artificial intelligence tools are employed. In an effort to provide the cross-disciplinary community with suitable and accessible tools for systematic analysis of pros- and cons- of various control algorithms, a patient simulator has been programmed in Matlab/Simulink from MathWorks(R) software platform. This is an open source patient simulator, where the community can set, add and modify its components as know-how and insight become available. The Matlab-Simulink scheme of the simulator is given in figure 3.

There are 5 possible manipulated variables (drug dosing rates) and 5 direct controlled variables (outputs), along with numerous interaction effects.

The direct cause-effect models include:

- Propofol drug rate to hypnotic state evaluated with BIS variable;
- Remifentanil drug rate to analgesic state evaluated with RASS variable;
- Rocuronium/Atracurium drug rate to neuromuscular blockade state evaluated with NMB variable;
- Dopamine(DP)/Dobutamine(DB) drug rate to cardiac output state evaluated with CO variable;
- Sodium Nitroprusside drug rate to mean arterial pressure state evaluated with MAP variable.

The interaction models include:

- Propofol and Remifentanil synergic effects on BIS variable (surface model);
- Remifentanil effect lowering MAP and increasing CO;
- Increasing CO will increase clearance rates of Propofol, thereby increasing BIS values;
- Antagonistic effects between DP/SNP and CO/MAP;

2.3 Control Design

In this paper, a centralized MPC architecture with a input-output formulation is implemented. The developed strategy has the roots in the EPSAC (Extended Prediction Self-Adaptive Control) algorithm (De Keyser, 2003), with details for a distributed formulation provided in (Maxim et al., 2018). Hereafter, a brief summary of the method is provided.

Consider that the hypnosis-hemodynamic system can be described by the continuous time model:

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} \hat{G}_{11} & 0 & 0 & 0 \\ 0 & \hat{G}_{22} & 0 & 0 \\ \hat{G}_{31} & \hat{G}_{32} & \hat{G}_{33} & \hat{G}_{34} \\ \hat{G}_{41} & \hat{G}_{42} & \hat{G}_{43} & \hat{G}_{44} \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{bmatrix} \tag{2}$$

where the outputs y_i, $\forall i \in \{1,2,3,4\}$ are CeP (effect site concentration), RASS, CO and MAP, respectively, whereas the input variables u_i, $\forall i \in \{1,2,3,4\}$ are propofol, remifentanil, DPM and SNP.

Let us assume that the compact model (2) can be decomposed into N sub-systems, dynamically coupled through inputs and subject input constraints. Each sub-system $i, \forall i \in \mathcal{N}$, where $\mathcal{N}$ denotes the set $\{1,\ldots,N\} \subseteq \mathbb{N}$ has the following model:

$$\begin{aligned} y_i(k) &= G_{ii}(q^{-1})u_i(k) + \sum_{j \in \mathcal{N}_i} G_{ij}(q^{-1})u_j(k) + w_i(k) \\ w_i(k) &= \frac{1}{1-q^{-1}} e_i(k) \end{aligned} \tag{3}$$

where $u_i(k)$ and $y_i(k)$ are the input and output variables; the disturbance $w_i(k)$ is modelled as a white noise signal $e_i(k)$ filtered by an integrator to ensure zero offset tracking performance; q^{-1} is the backward shift operator; k denotes the discrete-time index; $G_{ii}(q^{-1})$, $G_{ij}(q^{-1})$, $\forall i \in \mathcal{N}$, $\forall j \in \mathcal{N}_i$ are discrete-time transfer functions with monic denominators. The set $\mathcal{N}_i = \{j \in \mathcal{N} : G_{ij}(q^{-1}) \neq 0\}$ denotes all the neighbours for sub-system i, excluding i itself. For our process with $\mathcal{N} = 4$, the neighbourhoods are $\mathcal{N}_1 = \{0\}$, $\mathcal{N}_2 = \{0\}$, $\mathcal{N}_3 = \{1,2,4\}$ and $\mathcal{N}_4 = \{1,2,3\}$).

It is noteworthy to mention that, since we separately manipulate the C_eP and $RASS$ variables through the Propofol and Remifentanil dosages, the first two neighbourhoods are empty, meaning that there are no interactions in the mathematical model. However, as previously mentioned, these hypnosis components are highly interacting, and this will be visible in the BIS index.

The input constraints are formulated as

$$u_i^{\min} \leq u_i \leq u_i^{\max}, \tag{4}$$

where $u_i^{\min}$, $u_i^{\max}$, $\forall i \in \mathcal{N}$ are the minimum and maximum input limits.

For each sub-system i, $\forall i \in \mathcal{N}$ a local agent minimizes a local cost function defined as (Maxim et al., 2018):

$$\begin{aligned} J_i(Y_i(k), U_i(k), \{U_j(k)\}_{j\in\mathcal{N}_i}) = \min_{U_i(k)} \Delta U_i^T Q_i \Delta U_i \\ + (R_{si} - Y_i)^T (R_{si} - Y_i) \\ \text{subject to (3) and (4)} \end{aligned} \tag{5}$$

based on the future output trajectory

$$Y_i(k) = [y_i(k+1|k) \ \ldots y_i(k+N_p|k)]^T, \quad \forall i \in \mathcal{N}$$

where the reference trajectory $R_{si}(k) \in \mathbb{R}^{N_p}$, $\forall i \in \mathcal{N}$ is assumed constant over the prediction horizon N_p and equal with the set-point at the current time instant k. Note that in (5), the first term minimizes the magnitude of the control increment $\Delta U_i(k) = [\Delta u_i(k|k) \ \ldots \Delta u_i(k+N_c-1|k)]^T$, $\forall i \in \mathcal{N}$, with N_c being the control horizon, while the second term penalizes the prediction error.

Furthermore, the control increment variable is defined as $\Delta u_i(k+l|k) = u_i(k+l|k) - u_i(k+l-1|k)$, obtaining $\Delta u_i(k+l|k) = 0$, $l \geq N_c$. The diagonal weight matrix $Q_i = \lambda_i I_{N_c}$ uses λ_i as a tuning parameter for adjusting the closed-loop speed.

The core idea is to make use of the superposition principle for linear systems, to define the future (predicted) response $Y_i(k)$ as the cumulative result of two effects:

$$Y_i(k) = \bar{Y}_i(k) + Y_i^{opt}(k), \tag{6}$$

where $Y_i^{\text{opt}}(k)$ is the effect of the optimizing future control actions $U_i(k)$, $\forall i \in \mathcal{N}$; $\bar{Y}_i(k)$ is the basic future scenario, computed using the sub-system's model prediction and the disturbance prediction given by filtering techniques.

Note that the optimal solutions $U_i(k)^*$, $\forall i \in \mathcal{N}$ are computed using the input trajectories received from the corresponding neighbours.

3. RESULTS AND DISCUSSION

In this paper centralized Model Predictive Control for hypnosis in presence of hemodynamic parameters is investigated. Here, the first attempts towards a completed picture of anesthesia paradigm have been undertaken. For the first hand results presented in this paper, the following simulation scenario has been employed. Four manipulated inputs propofol for hypnosis, remifenatnil for RASS, dopamine for cardiac output (CO) and sodium nitroprusside (SNP) for MAP and are taken into account. The aim of the analysis is to stabilize hypnosis via CeP variable, RASS using remifentanil, and the hemodynamic variables CO and MAP despite their interaction among each-other and with the anesthesia variables. In this initial study, only one type of patient is used, as afore-described in the subsection on the prediction models. The numerical values for each model are taken from (Ionescu et al., 2021). The recommended intervals for the input/output variable are given below.

BIS interval: 40-60%	Propofol infusion: 0 – 5 mg/kg*min
RASS score: (-5) – 4	Remifentanil infusion: 0 – 2.5 mcg/kg*min
CO: 65 - 110 ml/kg*min	Dopamine infusion: 0 – 10 mcg/kg*min
MAP: 65 – 110 mmHg	SNP infusion: 0 – 10 mcg/kg*min

Fig. 4. Input/Output ranges for the manipulated and controlled variables.

Reference tracking in presence of disturbance is tested and the results presented in figures 5-8.

The tuning parameters of the controller are: sampling interval of 1 second, a control horizon of $N_c = 1$ sample, and a prediction horizon of $N_p = 60$ samples. The optimization variables are $\lambda_i = 1$, $\forall i \in 1, 2$ and $\lambda_j = 0.1$, $\forall j \in 3, 4$. The inputs are limited to $u_1^{\min} = 0$ and $u_1^{\max} = 3.5$ for the propofol values, $u_2^{\min} = 0$ and $u_2^{\max} = 2.5$ for the remifentanil values, $u_3^{\min} = 0$ and $u_3^{\max} = 10$ for DMP dosage whereas $u_4^{\min} = 0$ and $u_4^{\max} = 10$ are the limits used for SNP input.

The performance of the proposed control algorithm was successfully validated against a disturbance rejection experiment, where a series of impulses with the height of 1 and various lengths were added to the first output. Thus, at sample times 100, 200, 270, 420, 500, 750, 1050, 1300 seconds, an impulse with the length of 50, 50, 50, 30, 50, 100, 100, 50 samples, respectively, was added to y_1, and the direct effect is best visible in figure 5, while the interaction reaction with the hemodynamic variables is depicted in figures 7-8.

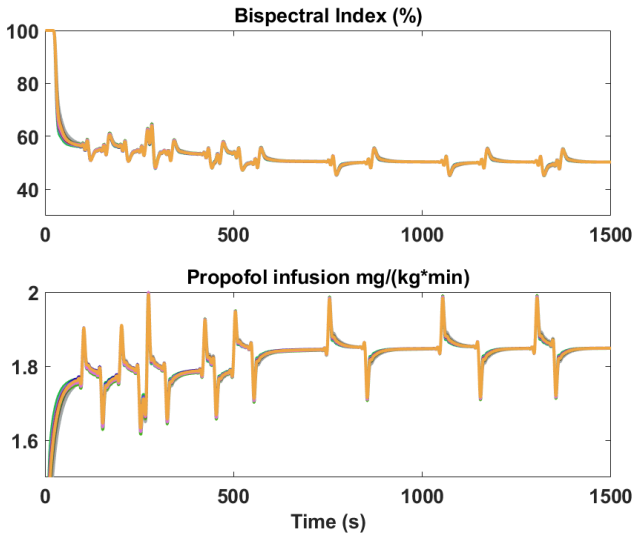

Fig. 5. Hypnotic output (BIS) in % as a function of simulated sampled time.

The management of anesthesia moves from single drug to multi-drug co-administration, making small but essential steps forward towards a fully computerized regulatory paradigm of personalised patient services. Co-administration of Propofol and Remifentanil for anesthesia regulation has been very recently re-assessed in simulation studies and in clinical trials (Neckebroek et al., 2019).

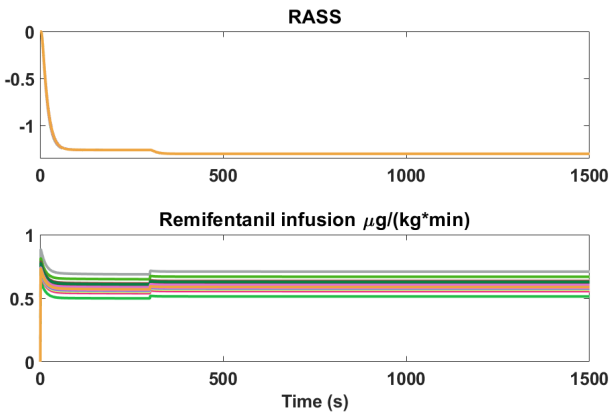

Fig. 6. Ramsay Agitation Score Scale (RASS) as a function of simulated sampled time.

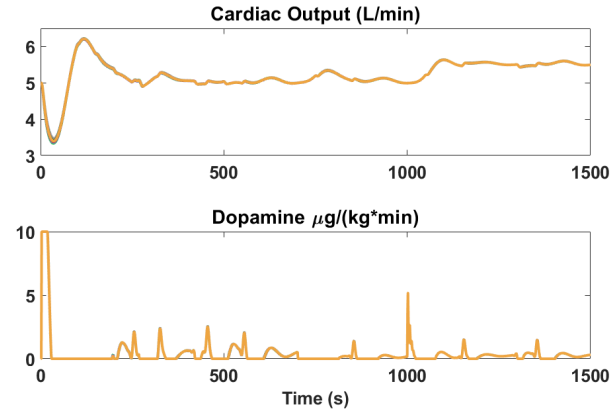

Fig. 7. Cardiac Output (CO) as a function of simulated sampled time.

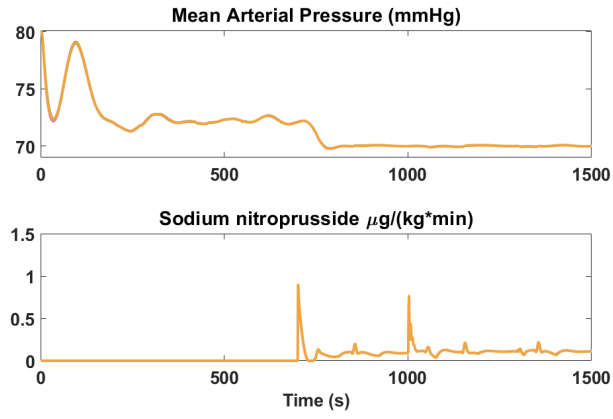

Fig. 8. Mean arterial pressure (MAP) as a function of simulated sampled time.

Closed loop control plays a crucial role in both the natural and engineering world. In anesthesia, closed-loop control promises to limit the impact of individual patient variability on performance, optimize anesthesiologist workload, increase time spent in a more desirable clinical state, and ultimately improve the safety and quality of anesthesia care. Physicians need to ensure a specific state variables in the operating range by administering a cocktail of drugs. It is well-known that the natural control algorithm to mimic medical decision-making is model predictive control. The challenge is the strong and dynamic coupling between the various sub-systems (anesthesia, hemodynamic, underlying risks) and the complexity of optimization variable matrix. For example, decoupling control techniques can be applied.

Using the A-H patient simulator from (Ionescu et al., 2021) with disturbance models, various drug infusion profiles can be evaluated against predicted outputs. The receding horizon principle implies that at the next control sample all optimization is reiterated based on the updated data feedback information. The maintenance phase of anesthesia needs an additional control loop. This is a supervisory control loop and it provides the set-point to the predictive control loop. Each surgical stimulus profile can be seen as an event, and event based control would be a good candidate. It could be manually triggered (e.g. anesthesiologist) or digitally based on signal profile (e.g. filtered derivative) to activate the next in line surgical activity sequence for which a disturbance model profile exists. This provides extra information to the supervisory controller which updates setpoints to lower level controls (predictive, PID, ratio). For example, a ramp-step form disturbance (e.g. intubation, internal organ handling) will require a lower interval limit setpoint value than a light step form disturbance (e.g. suture, skin closure).

The control objective in this A-H regulatory problem is not precision control, but rather maintaining the output variables (with synergic and antagonistic interactions) within safe intervals, hence, interval constraints need to be considered. Multiple objectives for output variables can be globally minimized through Pareto front optimization, but may be costly in terms of computational burden for fast online execution. Alternatively, would be possible to simplify the search problem by introducing priority levels, as investigated in (Ionescu et al., 2020).

4. CONCLUSION

Currently, the literature both clinical and biomedical engineering, both with roots in systems and control theory, have proposed numerous schemes to induce and maintain hypnosis and neuromuscular blockade and these two aspects of anesthesia are now mature for integration in a single environment. Hence, the missing piece in the anesthesia paradigm is analgesia, in this study the effect of Remifentanil is evaluated using the RASS variable.

The potential advantages of using closed-loop control of anesthesia are: optimal drug dosage specific for each patient profile; avoidance of under and over dosage; reduction in anesthetist intervention. However, when applied to drug administration closed-loop control, the administration of drugs in response to clinical effect (surgical manipulations) is based on knowledge of the fate of the drug and its effect in the human body. Several different parametric and non-parametric pharmacokinetic-dynamic models have been described in the literature as basic predetermined models for anesthesia applications. During control, the models need to be updated to meet the patient's individual pharmacological behavior; otherwise, the model does not reflect the actual control condition and is useless. The outcome

of this paper indicates that the proposed methodology is robust for inter-patient variability, nociception stimulation and anesthesiologist intervention (disturbance rejection) which is the main challenge in clinical practice.

4.1 Software

The open source simulator is available for download at the following link `https://nl.mathworks.com/matlabcentral/fileexchange/85208-open-source-patient-simulator`.

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