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ORIGINAL RESEARCH

Lessons learned from closed loops in engineering: towards a multivariable approach regulating depth of anaesthesia

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Abstract In this paper is presented a brief state of art regarding the multivariable formulation for controlling the depth of anaesthesia by means of two intravenously administrated drugs, i.e. propofol and remifentanil. In a feasibility study of determining a suitable variable to quantify analgesia levels in patients undergoing cardiac surgery, the bispectral index and an electromyogram-based surrogate variable are proposed as the controlled variables. The study is carried on in the context of implementing a multivariable predictive control algorithm. The simulation results show that such a paradigm is feasible, although it does not guarantee perfect knowledge of the analgesia level—in other words, the variable is not validated against typical evaluations of the pain levels (e.g. clinical scores).

Keywords Anaesthesia · Analgesia · Predictive control · Multivariable control

1 Introduction

General anaesthesia plays an important role in surgery and intensive care unit (ICU) and requires critical assessment of induced quantities of drugs into the patient [1]. It is characterized by unconsciousness through the action of anaesthetics, but also by loss of the ability to perceive pain through the action of analgesics. Analgesics block the sensation of pain; the hypnotics produce unconsciousness, while the muscle relaxants prevent unwanted movement of muscle tone. The relationship between the hypnotic drug, Propofol, administered during general anaesthesia, and BIS (a signal derived from the electroencephalogram used to assess the level of consciousness during anaesthesia) is widely documented and several studies regarding the interaction model of Propofol and Remifentanil can be found in the literature [2–4].

When inducing and maintaining anaesthesia, anaesthesiologists select initial doses based on a variety of considerations, they observe the results, and then make adjustments based on several factors, at irregularly varying intervals. In control engineering terminology, this constitutes a closed loop control system, due to the feedback present in the observations and interventions of the anaesthesiologist. The closed-loop control system is characterized by special feature:

1. it has a *human controller* in the loop, and
2. the control actions are intermittent and irregular in time due to the human controller.

The purpose of computer-controlled closed-loop systems is to formalize the process of observation and intervention as to provide better and more accurate control. Such systems use a near continuous signal of drug effect, calculate the error between the observed value and the specified value (selected by the medical staff), and use this error in an algorithm to make frequent and regular adjustments to drug administration rates. Moreover, some computer-control systems try to predict the future drug effect to produce the optimal convergence to the desired result [4, 5].

In order to have an accurate feedback control, one or more real-time representative measures of the system's

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state should be available. Ideally, the control actuators or process inputs should, with minimal or known delay, cause predictable, linear changes in the process. In practice, drug administration is an asymmetrical process: we can actively infuse but cannot actively remove the drug from the patient. Because the relationship between dose and plasma concentration is so complex, target-controlled infusion (TCI) systems are a logical choice of control actuator, so that the control input is a target concentration rather than an infusion rate [3, 4, 6]. Many assumptions underpin the pharmacokinetic models used in TCI systems, the predictive accuracy of current models is imperfect, and the choice of model for Propofol is often controversial [7].

This paper presents results based on the use of Propofol and Remifentanil as anaesthetic, respectively analgesic drugs to regulate the depth of anaesthesia (DOA). A first attempt is made to provide a variable for the effect of Remifentanil drug infusion on the analgesic state of the patient. This is then tested in a closed loop control simulation by means of applying model based predictive control algorithm. Although the simulation results are not validated against external clinical scores, the paper can serve as an indicator of the challenges one needs to tackle when building a fully multivariable model for automated regulation of anaesthesia and analgesia.

The paper is organized as follows: the next section provides some insights on closed loop control challenges for DOA. The Sect. 3 introduces briefly the state of art for modelling anaesthesia and analgesia in a multivariable context. Section 4 describes the derivation of the output variable to measure the effect of Remifentanil infusions. Section 5 presents the simulation setup, followed by the simulation results and discussion. Finally, a Sect. 5 summarizes the main outcome of this paper and points to some further directions of research.

2 What we know

There has been a lot of recent development of closed loop control algorithms for regulating the single drug to single effect in monitoring and control workstations of DOA. Of these, we can summarize the following classes of control algorithms in order of their complexity: PID control [8], adaptive PID control [9], adaptive polynomial control [10, 11], Bayesian filtering [12, 13]; predictive control [5, 14, 15]. Optimal control strategies and nonlinear robust control such as H∞ have not been applied due to their high complexity and loss of pragmatism. Figure 1 shows these classes of control in function of mathematical complexity, loss of pragmatism and success rate.

Another problem is that of choosing optimally the manipulated variables (i.e. drugs to be applied to the patient) and the controlled variables (i.e. drug effects). This will have impact on whether the system has (non)linear dynamics, variable time delays, stability and robustness limitations. Induction and maintenance phase in DOA are clearly examples of states of the patient where different control strategies should be employed to obtain best performance for patient welfare. Figure 2 shows a typical, simplified, closed loop control block scheme. During induction, is important to follow reference trajectories (i.e. changes in the desired level of controlled variable, here BIS). During maintenance phase, is important to reject disturbances coming from patient, clinical intervention and effects from other that the manipulated variables (i.e. other drugs). From a control engineering insight, it is not possible to obtain simultaneously an optimal setpoint trajectory follow performance and optimal disturbance rejection. This is due to the fact that the closed loop dynamics are significantly different when analysed from setpoint to output, than when analysed from disturbance to output. In practice, a trade-off is usually done to accomplish good closed loop performance.

Finally, the presence of time varying delay is perhaps the most dangerous of all challenges for control. Such dynamics have been identified in the control of the BIS variable for DOA [16]. In order to illustrate the importance of the variations in the delay value, let us consider three cases:

$$P(s) = \frac{1}{10s+1} e^{-\tau_d s} \quad (1)$$

where the time delay $\tau_d$has three values: 0 (i.e. no time delay), 5 (i.e. time delay smaller than the time constant of the system) and 15 (i.e. time delay significantly higher than the time constant of the system). Figure 3 below shows the loss of robustness with increasing values of time delay. In practice, this time delay may vary; hence robustness varies during closed loop control of DOA. It is clear that adaptation of controller parameters is of crucial importance to maintain a desired robustness margin.

From control point of view, the error in estimating a good (slow) time constant is not crucial. However, the error in estimating a good delay value is of crucial importance. Mixing effects should thus not be modelled as time-delays, but rather as time constants. Tackling a higher order system is simpler for control than tackling a low order with time delays. Generally, as a rule-of-thumb, a robust controller (i.e. relatively slow/conservative acting) will accept estimation errors of about 10–25 %. It can remain stable for errors of 30–60 %, but its performance deteriorates and usually adaptation is preferable. Higher errors will lead to instability.

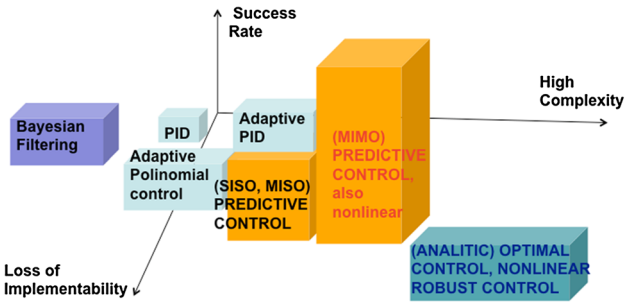

Fig. 1 Representation of control algorithms in a 3D space

3 The multivariable paradigm of automated DOA

For measuring the hypnotic component of anaesthesia, various indexes are present, mostly computerized from the spontaneous or evoked electroencephalogram (EEG) [4]. The Bispectral index (BIS) is a single composite measure derived from the spontaneous EEG and has been proven to have a high sensitivity and specificity to measure anaesthetic drug effect [2, 3]. BIS is now recognized as one of the reference measures of DOA for closed loop control purposes [4, 5, 8]. The singular control of the Bispectral index by means of Propofol drug infusion using computer-assisted DOA has been already established in the literature as advantageous to target-controlled infusion (open loop) [1, 3, 5, 17]. Hence, this paper will focus on the multivariable paradigm, which includes the effect of opioids (i.e. analgesic drugs).

In contrast to cerebral drug effect produced by hypnotics, an accurate measure for analgesia is still lacking. Opioids such as fentanyl, alfentanyl and Remifentanil are known to have synergistic effect on Propofol [6, 18, 19]. Since general anaesthesia is clinically defined as the balance between hypnosis, analgesia and paralysis, it is interesting to study the effect of drug interaction [18]. It has already been shown that neuromuscular blockade (i.e. the paralysis component of general anaesthesia) is not inter-related to the hypnotic and analgesic components (i.e. no drug interaction) [11, 19]. On the other hand, it has been shown that the use of Remifentanil in regulated DOA has a sparing effect on Propofol infusion rates, hence with much less over-dosage occurrences [18]. The challenge, however, is that these combinatorial effects are varying from one patient to another—interpatient variability—as well as varying within the same patient—intrapatient variability. Often the anaesthetists use a certain drug rate for a long period of time (tens of minutes) during similar surgical procedures, especially in countries where computer assisted DOA is not available. This leads to either under- or over-dosage in the patient, both having undesired effects. It was also found that the concentrations for Propofol for which the patient became awake were increasing with the duration of drug administration, showing

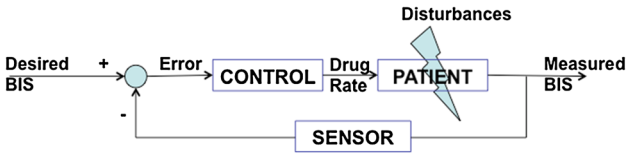

Fig. 2 Typical closed loop control block scheme

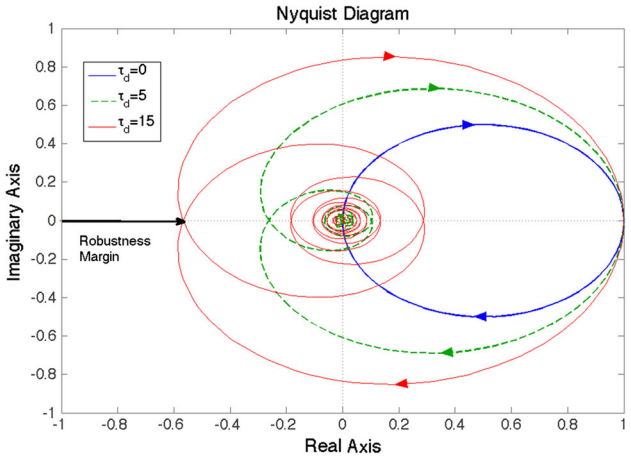

Fig. 3 Examples of loss of robustness with increasing values of time delay

the potential for hysteresis [6], thus more challenging from control point-of-view.

While feedback monitoring devices and methods are already available on the market for the depth of hypnosis (e.g. Bispectral Index BIS, Auditory Evoked Potential, WAV), there exists no "pain sensor" which measures analgesia directly [4, 20]. However, there are several systems for analgesia control reported in the literature. Most of them use a surrogate of variables to derive a fuzzy-expert system, which may assist the clinical nurse in determining the optimal analgesic drug rate. A fuzzy analgesia control system for induction, maintenance and recovery has been reported in [21] using three variables: heart rate, mean arterial pressure and an index derived from a (modified) standard deviation of the RR-intervals in the electrocardiogram format. Furthermore, a control system, which minimizes the risks associated with delivery of respiratory depressants to spontaneously breathing patients during medical procedures, has been proposed in [22]. This has been based on modelling the respiratory depressant effects of Remifentanil by means of pharmacokinetic (PK)-pharmacodynamic (PD) models in [22] provided the transcutaneous monitoring of partial pressure of carbon dioxide in tidal breathing. However, this strategy may fail in the event of mechanical ventilation, which alters the nominal depressant effect.

A combination of rule-based controller for Remifentanil infusion, based on measurements of mean arterial pressure, heart rate and systolic arterial pressure, and a fuzzy-PI

controller for Propofol infusion, based on pre-determined DOA levels, is proposed in [23]. A predictive controller with isoflurane and alfentanil is given in [24] controlling well four variables: bispectral index, mean arterial pressure, end tidal concentration and alfetanil concentration. However, from a control point of view, the control problem is ill-posed, since there are two manipulated variables to control four variables.

Finally, another approach to use cardio-respiratory surrogate variables to measure the level of analgesia led to the development of the *analgoscore*, which proved to be successful in a manifold of surgical interventions [25]. Unfortunately, no tests are performed on patients undergoing cardiac surgery, where these surrogate measures coming from the cardio-respiratory variables are obviously biased.

4 Proposed multivariable context

4.1 Patient models for propofol and remifentanil

In order to investigate the multivariable formulation from Fig. 4, the pharmacokinetic (PK) models for Propofol and Remifentanil are required. Additionally, the interaction model represented in Fig. 4 by the Hill block takes into account the synergistic effect of these two drugs on the output variable, the Bispectral index (BIS). In Fig. 4 the pharmacokinetic (PK)—pharmacodynamic (PD) blocks denote compartmental models. The PK-PD models most commonly used for Propofol and Remifentanil are the 4th order compartmental models described by Schnider [26] and Minto [27, 28] respectively.The PK-PD models are represented by the following equations:

$$\begin{aligned}
\dot{x}_1(t) &= -[k_{10}+k_{12}+k_{13}]x_1(t)+k_{21}x_2(t)+k_{31}x_3(t)+\frac{u(t)}{V_1}\\
\dot{x}_2(t) &= k_{12}\cdot x_1(t)-k_{21}\cdot x_2(t)\\
\dot{x}_3(t) &= k_{13}\cdot x_1(t)-k_{31}\cdot x_3(t)\\
\dot{x}_e(t) &= -k_{e0}\cdot x_e(t)+k_{1e}\cdot x_1(t)
\end{aligned} \tag{2}$$

where x_1 [mg/ml] denotes the drug concentration in the central compartment. The peripheral compartments 2 and 3 model the drug exchange of the blood with well and poorly diffused body tissues. The masses of drug in fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3, respectively. The parameters k_{ji}, for $i \neq j$, denote the drug transfer frequency from the jth to the ith compartment and $u(t)$ [mg/s] is the infusion rate of the anaesthetic drug into the central compartment.

The parameters $k_{ij}$of the PK models depend on age, weight, height and gender and can be calculated for Propofol:

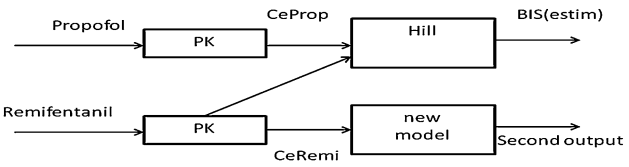

Fig. 4 Diagram of the proposed multivariable formulation. New Model and Second Output are not determined yet

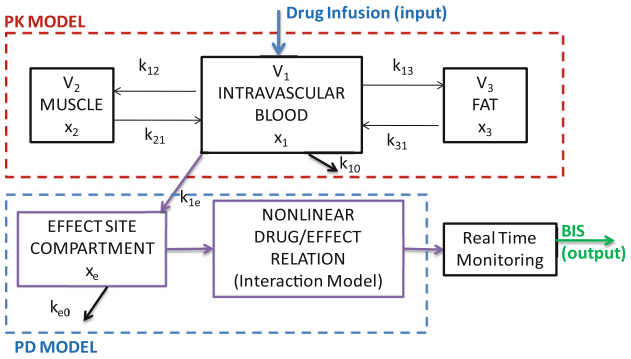

Fig. 5 Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model

$$\begin{aligned}
V_1 &= 4.27\,[l];\; V_3 = 2.38\,[l]\\
V_2 &= 18.9-0.391(age-53)\,[l]\\
C_{l1} &= 1.89+0.0456(weight-77)-0.0681(lbm-59)\\
&\quad +0.0264(height-177)[l\,\mathrm{min}^{-1}]\\
C_{l2} &= 1.29-0.024(age-53)[l\,\mathrm{min}^{-1}],\; C_{l3} = 0.836[l\,\mathrm{min}^{-1}],\\
k_{10} &= \frac{C_{l1}}{V_1}[\mathrm{min}^{-1}],\; k_{12} = \frac{C_{l2}}{V_1}[\mathrm{min}^{-1}],\; k_{13} = \frac{C_{l3}}{V_1}[\mathrm{min}^{-1}],\\
k_{21} &= \frac{C_{l2}}{V_2}[\mathrm{min}^{-1}],\; k_{31} = \frac{C_{l3}}{V_3}[\mathrm{min}^{-1}]
\end{aligned}$$

whereC_{l1} is the rate at which the drug is cleared from the body, and C_{l2} and $C_{l3}$are the rates at which the drug is removed from the central compartment to the other two compartments by distribution (Fig. 5). Similarly, for Remifentanil:

$$\begin{aligned}
V_1 &= 5.1-0.0201(age-40)+0.072(\mathrm{lbm}-55)[l]\\
V_2 &= 9.82-0.0811(age-40)+0.108(\mathrm{lbm}-55)[l]\\
V_3 &= 5.42[l]\\
C_{l1} &= 2.6-0.0162(age-40)+0.0191(\mathrm{lbm}-55)\,[l\mathrm{min}^{-1}]\\
C_{l2} &= 2.05-0.0301(age-40)\,[l\mathrm{min}^{-1}]\\
C_{l3} &= 0.076-0.00113(age-40)\,[l\mathrm{min}^{-1}]\\
k_{e0} &= 0.595-0.007(age-40)\,[\mathrm{min}^{-1}]
\end{aligned}$$

$$k_{10} = \frac{C_{l1}}{V_1}\left[\mathrm{min}^{-1}\right],\; k_{12} = \frac{C_{l2}}{V_1}\left[\mathrm{min}^{-1}\right],\; k_{13} = \frac{C_{l3}}{V_1}\left[\mathrm{min}^{-1}\right]$$

$k_{21} = \frac{C_{l2}}{V_2}\left[\text{min}^{-1}\right]$, $k_{31} = \frac{C_{l3}}{V_3}\left[\text{min}^{-1}\right]$.

The lean body mass (lbm) for men and women has the following expressions: $1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2}$ and $1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2}$, respectively, with weight (kg) and height (cm).

An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The concentration of drug in this compartment is represented by x_e. The drug transfer frequency from the central compartment to the effect site-compartment is equal to the frequency of drug removal from the effect-site compartment: $k_{e0} = k_{1e} = 0.456[\text{min}^{-1}]]$. The equation is often referred as the *effect-site compartment concentration*. When considering the effect of two drugs, the Hill curve becomes a surface, whose parameters represent the synergistic effect of both Propofol and Remifentanil effect site compartment concentrations. The concentration–response relations of the two drugs can be described by a normalized relation:

$$BIS(t) = E_0 - E_{\max}(\theta) \cdot \frac{\left(\frac{U_{prop}(t)+U_{Rem}(t)}{U_{50}(\theta)}\right)^{\gamma(\theta)}}{1 + \left(\frac{U_{prop}(t)+U_{Rem}(t)}{U_{50}(\theta)}\right)^{\gamma(\theta)}} \quad (3)$$

where $U_{prop}(t) + U_{Rem}(t)$ is the combined drug concentration; $\gamma(\theta)$ is the steepness of the concentration–response relation at ratio θ; $U_{50}(\theta)$ is the number of units (U) associated with 50 % of maximum effect at ratio θ; $E_{max}(\theta)$ is the maximum possible drug effect at ratio θ [29, 30], with the effect-site concentrations $C_{eprop}(t)$ and $C_{eRem}(t)$ normalized to their respective potencies $C_{50,\text{Pr}op}$ and $C_{50,Rem}$described by:

$$U_{prop}(t) = \frac{C_{eprop}(t)}{C_{50,prop}};\ U_{Rem}(t) = \frac{C_{eRem}(t)}{C_{50,Rem}} \quad (4)$$

and the ratio of the interacting drugs expressed by:

$$\theta(t) = \frac{U_{prop}(t)}{U_{Rem}(t) + U_{prop}(t)} \quad (5)$$

In this formulation, θ represents the concentration ratio of the new combined drug and ranges from 0 (Remifentanil only) to 1 (Propofol only). According to [27] $E_{max}(\theta)$ and E_0 are set to 100 and $U_{50}(\theta)$ can be expressed by a quadratic polynomial:

$$U_{50}(\theta) = 1 - \beta \cdot \theta + \beta \cdot \theta^2 \quad (6)$$

The unknown coefficient β can be estimated from the patient data. Since the interaction between the two drugs is supra-additive (the effect of the two drugs combined is higher than the sum of each separate effect), β should be a positive number. This means that $U_{50}(\theta)$ is lower than 1 for any value of θ between 0 and 1. To simulate the combined effect of Propofol and Remifentanil using the nonlinear expression from (3), the following values have been assigned [14]:

$$\beta = 0.22;\ \gamma(\theta) = 0.9;\ C_{50,Prop} = 3.1;\ C_{50,Rem} = 34 \quad (7)$$

4.2 Proposed model for the remifentanil effect

There have been several attempts to quantify the effect of Remifentanil on the analgesia level during surgery and intensive care. Some of these are summarized below.

Derived electroencephalogram measures: if we increase the level of Remifentanil the Cortical Input—a measure of the magnitude of cortical input—will significantly decrease. For quantifying the Propofol effect, one can use the Cortical State—a measure of the responsiveness of cortex—which is statistically independent of variations in the effect site Reminfentanil levels [31].

Respiratory effect: Remifentanil is a potent ventilatory depressant. Simulations demonstrated that Remifentanil concentrations well tolerated in the steady state will cause a clinically significant hypoventilation following bolus administration, confirming the acute risk of bolus administration of fast-acting opioids in spontaneously breathing patients [22, 32].

Haemodynamic Effects: Remifentanil induces a dose-dependent decrease in heart rate, arterial blood pressure and cardiac output consistent with μ-opioid agonism [22, 23].

Central Nervous System: Remifentanil induces dose-dependent changes in relative cerebral blood flow in areas involved in pain processing. Under Remifentanil/N_2O anaesthesia, the global cerebral blood flow is reduced [25]. As a consequence, intracranial pressure is reduced and autoregulation is preserved.

Bispectral index (BIS) derivative: our studies indicated that this signal is more sensitive to artefacts and it responds faster than the BIS signal. This suggests further that if this signal is used for feedback information, the control might have over-dosing effects.

Electromyography is a technique for evaluating and recording the activation signal of muscles. An electromyograph detects the electrical potential generated by muscle cells when these cells contract, and also when the cells are at rest. In this study, the relationship between Remifentanil effect-site concentration (C_{eRemi}) and the EMG is determined. For this, we make use of an illustrative signal measurement from one virtual patient undergoing general anaesthesia during intensive care. A scaled variable is proposed:

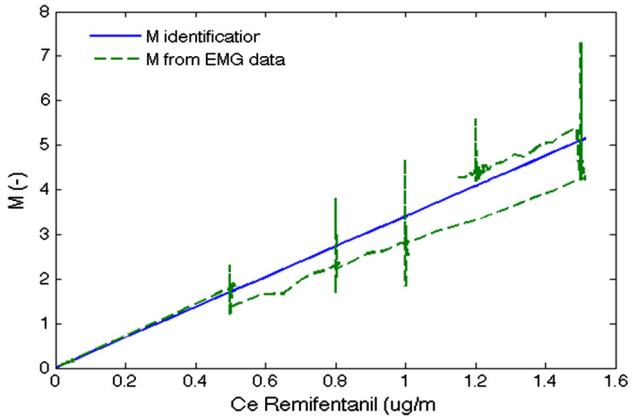

Fig. 6 Representation of C_{eRemi} versus M and the linear approximation for the virtual patient

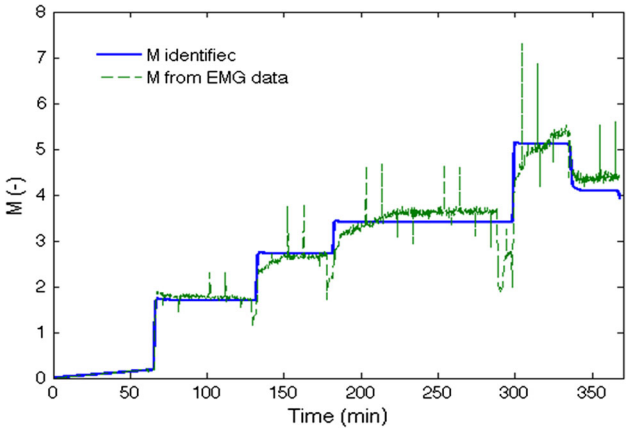

Fig. 7 Representation of the identified M and the *so-called* measured M

$$M = \frac{100 \cdot C_{e\text{Remi}}}{EMG} \tag{8}$$

thus M is determined as a function of the concentration of Remifentanil and the EMG signals. The concentration of Remifentanil versus the new value M is represented in the following figure for one patient in Fig. 6. With a green dashed line we have represented the relation between the concentration of Remifentanil and M using data measured during ICU and with a blue solid line we have the linear approximation of this relation. This linear approximation has the following formula:

$$M = 3.4 \times C_{e\text{Remi}} + 0.0063 \tag{9}$$

Using this equation and Eq. (8) we can determine a relationship for EMG as a function of concentration of Remifentanil:

$$EMG = \frac{100 \cdot C_{e\text{Remi}}}{3.4 \times C_{e\text{Remi}} + 0.0063} \tag{10}$$

Figure 7 is used to validate the model for M. With a green line we have M calculated using the measured data of EMG and C_{eRemi} and with a blue line we have M calculated using the linear approximation.

4.3 Extended prediction self-adaptive control

In this paper, we apply the Extended prediction self-adaptive control (EPSAC) strategy described in detail in [33]. The EPSAC–model predictive control (EPSAC–MPC) is based on a generic process model:

$$y(t) = x(t) + n(t) \tag{11}$$

The disturbance $n(t)$ includes the effects in the measured output $y(t)$ which do not come from the model input $u(t)$ via the available model. These non-measurable disturbances have a stochastic character with non-zero average value, which can be modelled by a coloured noise process:

$$n(t) = \left[C(q^{-1})/D(q^{-1})\right] \cdot e(t) \tag{12}$$

with: $e(t)$—uncorrelated (white) noise with zero mean value; $C(q^{-1})$ and $D(q^{-1})$—monic polynomials in the backward shift operator q^{-1} of orders n_c and n_d. The disturbance filter $C(q^{-1})/D(q^{-1})$ is defined as a pure integrator, to ensure zero steady state error.

The relationship between $u(t)$ and $x(t)$ is given by the generic dynamic system model:

$$x(t) = f[x(t-1), \quad x(t-2), \ldots, \quad u(t-1), u(t-2), \ldots]. \tag{13}$$

In our case the input applied to the patient, $u(t)$ is a vector containing the Propofol and Remifentanil delivery rates. The prediction model output is not represented by a nonlinear Hill curve, but by a linear approximation around the maintenance values (i.e. BIS values between 40 and 60 %) [14]:

$$x(t) = m_1 \cdot C_{eprop}(t - T_d) + m_2 \cdot C_{eRem}(t - T_d) \tag{14}$$

The process output is predicted at time instant t over the prediction horizon after the time delay T_d, based on the measurements available at that moment and the future outputs of the control signal. The predicted values of the output are:

$$y(t + k/t) = x(t + k/t) + n(t + k/t) \tag{15}$$

Prediction of $x(t + k/t)$ and of $n(t + k/t)$ can be done respectively by recursion of the process model and by using filtering techniques on the noise model (12) [33].

In EPSAC for linear models, the future response is considered as being the cumulative result of two effects:

$$y(t + k/t) = y_{base}(t + k/t) + y_{opt}(t + k/t) \tag{16}$$

where $y_{base}(t + k/t)$represents:

- effect of past control $\{u(t-1),\ u(t-2),\ldots\}$ (initial conditions at time t);
- effect of a *base* future control scenario, called $u_{\text{base}}(t+k|t), k \geq 0$, which is defined a priori; for linear systems the choice is irrelevant, a simple choice being $\{u_{\text{base}}(t+k|t) \equiv 0, k \geq 0\}$;
- effect of future (predicted) disturbances $n(t+k|t)$. and $y_{opt}(t+k|t)$ represents:
- effect of the *optimizing* future control actions $\{\delta u(t|t),\ \delta u(t+1|t),\ \ldots \delta u(t+N_u-1|t)\}$ with $\delta u(t+k|t) = u(t+k|t) - u_{\text{base}}(t+k|t)$. The *design* parameter N_u, called the *control horizon* (a well-known concept in MPC-literature), is considered in this paper equal to 1.

The controller output is obtained by minimizing:

$$J(\mathbf{U}) = \sum_{k=N_1}^{N_2} [r(t+k/t)) - y(t+k/t)]^2 \qquad (17)$$

where $r(t+k/t)$ is the desired *reference trajectory*. The detailed formulation is given in [33] together with a multivariable formulation. The single input single output formulation of EPSAC has been published in [5] on control of general anesthesia.

4.4 Simulation results

Since the performance of the predictive controller has already been shown superior to that of PID control strategies [4, 5, 14, 15, 24], this comparison has not been included in this paper. The simulation of the closed loop control performance is performed in the context of using the nonlinear patient simulator described in Sect. 4.1. In the predictive control algorithm, the prediction model for the patient is a linear approximation of the full nonlinear model. This linear approximation has been previously described in [14] and consists of the PKPD model from (2) to (7) with a linear approximation of the plane given by (14) with $m_1 = 12.83$ and $m_2 = 7.73$. The control algorithm has a sampling period of 5 s, a prediction horizon of 20 samples. The choice of these design parameters are relative to the dynamics of the fastest dynamics in the patient model (i.e. blood compartment).

Figure 8 depicts the simulation results during the induction phase. Bispectral index and EMG are controlled variables, at 50 %, respectively 29 % reference values. The manipulated variables are Propofol and Remifentanil. Although fast, the controller brings the patient to the desired values without overshoot. Recall that in this case, there are significantly large differences between the nonlinear model of the patient simulator and the linear approximation of the prediction model.

For the maintenance phase, a signal with clinically realistic disturbances has been applied. This signal has been developed and introduced in [17]. Figure 9 depicts the results of the disturbance rejection test during maintenance phase, where one can also observe the disturbance signal applied into the control scheme. The performance of the controller is quite good and stable. However, some high-peaks are observed in the BIS signal output as a result of the high disturbance effect. These peaks can be minimized if an adaptive control strategy is introduced, resulting in a patient-individualized DOA regulation framework. However, the topic of such adaptive control scheme is the subject of another paper. Moreover, one should keep in mind that the disturbance profile tested in this paper is rather aggressive, and not usually tested in practice. Since our controller seems to be having a good performance, we expect much better results for milder, more usual disturbance profiles.

4.5 Limitations

From a pragmatic point of view, it is indeed not obvious for non-control researchers why one should implement a more complex, multivariable control paradigm. Clinical studies where a modified PID controller had successful results are readily available [8]. However, this is indeed successful if the clinical variables are within the desired intervals. Often, the desired intervals and the fluctuations allowed in clinical practice may not be as optimal as those allowed from a control engineering point of view. Hence, the gap between clinical practice and control optimality is judged based on pragmatic approaches, which deliver nonetheless satisfactorily results. Theoretical support to show the advantage advanced PID control can indeed be found in [34–36], while those who discuss the advantages for multivariable control can be found in [37]. The study of these books boils down to the idea that in presence of strong interactions from various input variables, the single-input single-output PID closed loop control may become aggressive, oscillatory, or even unstable. Of course there are many ways, as discussed in [34–36] to 'modify' the PID control and have a suitable control for the desired loop. But this is nevertheless not the optimal approach. For instance, decouplers could be used, to ensure that no interactions are coming from other variables during control single loop Propofol infusion. Alternatively, a multivariable control methodology could be used to take into account these interactions and 'help' the control by making use of this available information (especially if synergic drugs are used, as in case of anaesthesia) [37]. In this way, in the presence of a patient model, theoretical analysis can be done to show that the global optimal solution is reached.

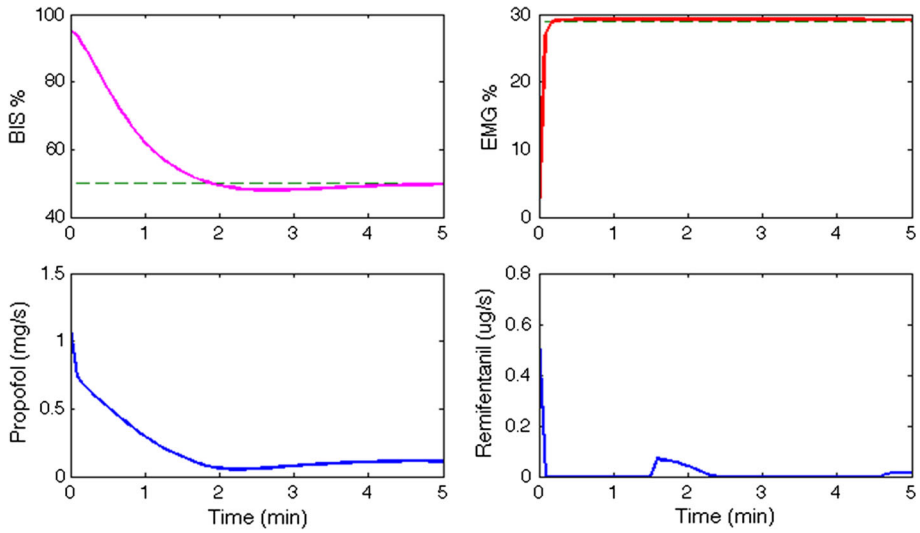

Fig. 8 Simulation test during the induction phase

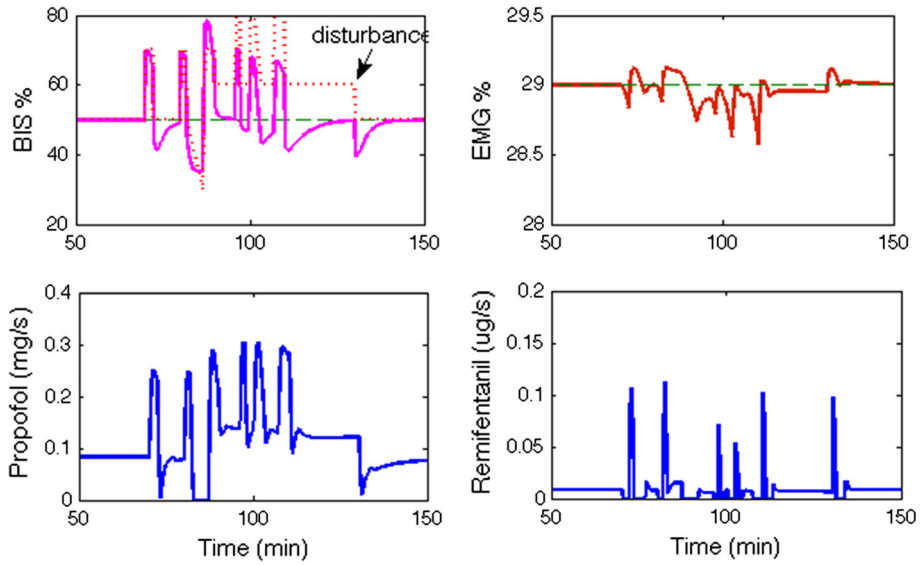

Fig. 9 Simulation test during the maintenance phase

Another limitation obvious in this study is the lack of clinical trials. This is indeed a significant drawback in order to convince the clinicians to use multivariable control instead of PID control. From our point of view, the current work is a mere 'proof of concept' that multivariable EPSAC can be used to control depth of anaesthesia. It is not certain that EMG is the optimal choice of variable for second output, but efforts are continuously being made to model pain transmission during unconsciousness [38, 39].

Finally, it is a limitation that a benchmark for a typical patient is not clearly stated in the research literature. The main challenge is to address the high inter-patient variability to find the most typical characteristics for testing closed loop controllers.

5 Conclusions

In this paper is presented a brief state of art regarding the multivariable formulation for controlling the depth of anaesthesia by means of two intravenously administrated drugs, i.e. Propofol and Remifentanil. In a feasibility study of determining a suitable variable to quantify analgesia levels in patients undergoing cardiac surgery, the Bispectral index and an electromyogram-based surrogate variable are proposed as the controlled variables. The study is carried on in the context of implementing a multivariable predictive control algorithm. The simulation results show that such a paradigm is feasible, although it does not guarantee perfect knowledge of the clinical analgesia level— in other words, the variable is not validated against typical evaluations of

the pain levels (e.g. Clinical scores). This means that the strategy is not yet ready for clinical practice. These results can be further improved if an adaptive control strategy is introduced, resulting in a patient-individualized DOA regulation framework. However, the topic of such adaptive control scheme is the subject of another paper.

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