A Nonovershooting Controller with Integral Action for Multi-input Multi-output Drug Dosing Control ⋆

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Abstract: In this paper, a nonovershooting tracking controller is proposed for the continuous infusion of multiple drugs that have interactive effects. The proposed controller design method exploits the freedom of eigenstructure assignment pertinent to the design of feedback controllers for multi-input, multi-output (MIMO) systems. For drug dosing, a nonovershooting tracking controller restricts the undesirable side effects of drug overdosing. The proposed tracking controller is based on an estimate of the full state using a hybrid extended Kalman filter (EKF) that is used to reconstruct the system states from the measurable system outputs. An integral control action is included in the controller design to achieve robust tracking in the presence of patient parameter uncertainty. Simulation results and performance analysis of the proposed control strategy are also presented using 20 simulated patients.

Keywords: Nonovershooting control, active drug dosing, biomedical control.

1. INTRODUCTION

Even though the critical task of anesthesia administration has been widely discussed in the literature and studied using clinical trials over the last few decades, several recent reviews on the existing methods highlight various aspects of the problem that needs further research attention [Van Den Berg et al. (2017), Ionescu et al. (2014)]. In the case of patients in ICU's, anesthetic and analgesic drugs are often required for several hours or days to facilitate cooperative treatment. Overdosing of such drugs have several side effects such as nausea, hypotension, delayed weaning from mechanical ventilation, immunosuppression, and in certain cases is even fatal to patients [Mehta et al. (2006)]. For continuous infusion of anesthetic and analgesic drugs for long periods, it is apparent that an appropriate closed-loop control strategy can be used to enhance patient safety.

We use a common sedation assessment measure such as the bispectral index (BIS) to quantify the sedation level of the patient. The primary hurdle in the design of a closed-loop controller for analgesic administration is the lack of a reliable pain assessment model. The most reliable and valid indicator of pain is the patient's self-report [Mehta et al. (2006)]. However, critically ill patients are often unable to verbally communicate the level of pain. In an attempt to identify novel and reliable tools to assess pain, several indices using the electroencephalogram (EEG), electromyogram (EMG), heart rate, respiratory rate, skin conductivity, and facial expression have been proposed [Mehta et al. (2006), Jin et al. (2016)].

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A semi-adaptive controller which relies on the remifentanil induced respiratory depression of the patient for the closed-loop drug titration is proposed in Jin et al. (2016). However, as pointed out in Ionescu et al. (2014), in the case of ICU patients who are supported by mechanical ventilators, respiratory depression may not be a reliable measure to assess analgesic concentration. Furthermore, it is risky to use heart rate and mean arterial pressure as feedback parameters for analgesic titration; this is primarily due to the variation caused by the concomitant infusion of cardiac depressive sedatives or underlying illness of the patient. Several studies point out the association of remifentanil concentration in the blood with muscle activity of a patient [Mehta et al. (2006), Van Den Berg et al. (2017)]. The EMG-based analgesic index proposed in Ionescu et al. (2014) relates analgesic concentration to EMG. Given that this variable is suitable for conducting in silico trials and also measurable, in this paper we use the EMG-based analgesic index to regulate the analgesic drug infusion rate.

In this paper, we develop a nonovershooting tracking controller for the combined administration of multiple drugs with interactive effects. The proposed controller can track desired outputs such as BIS levels and pain levels without incurring an overshoot in the system response by accounting for synergistic drug interaction, and hence, avoiding drug overdosing. Compared to the design strategies proposed for the combined administration of propofol and remifentanil in Ionescu et al. (2014) and Mahfouf et al. (2005), the advantage of the proposed method is its nonovershooting and robustness properties. The remainder of this paper is organized as follows. Section 2 presents an introduction to the drug kinetics and dynamics for the disposition of propofol and remifentanil followed by the design of

the nonovershooting controller for the simultaneous infusion of these interactive drugs. Simulation results and statistical analysis using the proposed controller for 20 simulated patients are given in Section 3. Conclusions are presented in Section 4.

2. METHODS

2.1 Drug disposition model

We use a three-compartment model to represent the drug disposition in the human body, where Compartment 1 models the intravascular blood, Compartment 2 models muscle tissue, and Compartment 3 models fat. An effect-site compartment is also used to account for the drug dynamics at the locus of the drug effect [Haddad et al. (2010)]. The mass balance equations used to model the drug transfer between the various compartments are given by [Ionescu et al. (2014)]

$$\dot{x}_1(t) = -(k_{10}^{\mathrm{S}} + k_{12}^{\mathrm{S}} + k_{13}^{\mathrm{S}})x_1(t) + k_{21}^{\mathrm{S}}\frac{v_2^{\mathrm{S}}}{v_1^{\mathrm{S}}}x_2(t) + k_{31}^{\mathrm{S}}\frac{v_3^{\mathrm{S}}}{v_1^{\mathrm{S}}}x_3(t) + u^{\mathrm{S}}(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{1}$$

$$\dot{x}_2(t) = k_{12}^{\mathrm{S}}\frac{v_1^{\mathrm{S}}}{v_2^{\mathrm{S}}}x_1(t) - k_{21}^{\mathrm{S}}x_2(t), \quad x_2(0) = x_{20}, \tag{2}$$

$$\dot{x}_3(t) = k_{13}^{\mathrm{S}}\frac{v_1^{\mathrm{S}}}{v_3^{\mathrm{S}}}x_1(t) - k_{31}^{\mathrm{S}}x_3(t), \quad x_3(0) = x_{30}, \tag{3}$$

$$\dot{c}_{\mathrm{eff}}^{\mathrm{S}}(t) = k_{\mathrm{e0}}^{\mathrm{S}}x_1(t) - k_{\mathrm{e0}}^{\mathrm{S}}(t)c_{\mathrm{eff}}^{\mathrm{S}}(t), \quad c_{\mathrm{eff}}^{\mathrm{S}}(0) = c_{\mathrm{eff0}}^{\mathrm{S}}, \tag{4}$$

and

$$\dot{x}_4(t) = -(k_{10}^{\mathrm{A}} + k_{12}^{\mathrm{A}} + k_{13}^{\mathrm{A}})x_4(t) + k_{21}^{\mathrm{A}}\frac{v_2^{\mathrm{A}}}{v_1^{\mathrm{A}}}x_5(t) + k_{31}^{\mathrm{A}}\frac{v_3^{\mathrm{A}}}{v_1^{\mathrm{A}}}x_6(t) + u^{\mathrm{A}}(t), \quad x_4(0) = x_{40}, \quad t \geq 0, \tag{5}$$

$$\dot{x}_5(t) = k_{12}^{\mathrm{A}}\frac{v_1^{\mathrm{A}}}{v_2^{\mathrm{A}}}x_4(t) - k_{21}^{\mathrm{A}}x_5(t), \quad x_5(0) = x_{50}, \tag{6}$$

$$\dot{x}_6(t) = k_{13}^{\mathrm{A}}\frac{v_1^{\mathrm{A}}}{v_3^{\mathrm{A}}}x_4(t) - k_{31}^{\mathrm{A}}x_6(t), \quad x_6(0) = x_{60}, \tag{7}$$

$$\dot{c}_{\mathrm{eff}}^{\mathrm{A}}(t) = k_{\mathrm{e0}}^{\mathrm{A}}x_4(t) - k_{\mathrm{e0}}^{\mathrm{A}}(t)c_{\mathrm{eff}}^{\mathrm{A}}(t), \quad c_{\mathrm{eff}}^{\mathrm{A}}(0) = c_{\mathrm{eff0}}^{\mathrm{A}}, \tag{8}$$

where $x_i(t)$, $t \geq 0$, $i = 1,2$, and 3, correspond to the masses of the sedative drug and $x_i(t)$, $t \geq 0$, $i = 4,5$, and 6, correspond to the masses of the analgesic drug in the first, second, and third compartment, respectively, $c_{\mathrm{eff}}^{\mathrm{S}}(t)$, $t \geq 0$, and $c_{\mathrm{eff}}^{\mathrm{A}}(t)$, $t \geq 0$, denote the effect-site concentrations of the sedative and analgesic drug, respectively, k_{ji}^{S} and k_{ji}^{A}, $i \neq j$, denote the rate of mass transfer between the jth and ith compartments, v_i^{S} and v_i^{A}, $i = 1,2$, and 3, are the volume of three compartments, and $u^{\mathrm{S}}(t)$, $t \geq 0$, and $u^{\mathrm{A}}(t)$, $t \geq 0$, are the infusion rates of the sedative and analgesic drug, respectively. Thus, the state vector is given by $x(t) = [x_1(t),\, x_2(t),\, x_3(t),\, c_{\mathrm{eff}}^{\mathrm{S}}(t),\, x_4(t),\, x_5(t),\, x_6(t),\, c_{\mathrm{eff}}^{\mathrm{A}}(t)]^{\mathrm{T}}$.

In Table 1, $lbm = 1.07weight - 148(weight^2/height^2)$, where lbm is the lean body mass of the patient, k_{e0} is the effect-site elimination rate constant, C_1 is the rate at which the drug is cleared from the body by the elimination process, and C_2 and C_3 are the rates of drug clearances between the central compartment and Compartments 2 and 3, respectively. When two drugs with synergistic interactive effects are administrated simultaneously, the effect of each drug varies according to the ratio of the two drugs and their normalized drug concentration. The measured value of the BIS index, denoted as BIS, ranges from 0 to 100. The net sedative effect of an anesthetic drug when administrated along with an analgesic drug having a synergistic interactive effect is given by [Ionescu et al. (2014)]

$$\mathrm{BIS}(t) = \mathrm{BIS}_0\left(1 - \frac{\left(\frac{U^{\mathrm{S}}(t)+U^{\mathrm{A}}(t)}{U_{50}(\phi(t))}\right)^{\gamma(\phi(t))}}{1+\left(\frac{U^{\mathrm{S}}(t)+U^{\mathrm{A}}(t)}{U_{50}(\phi(t))}\right)^{\gamma(\phi(t))}}\right), \tag{9}$$

where $\phi(t) \triangleq \frac{U^{\mathrm{S}}(t)}{U^{\mathrm{S}}(t)+U^{\mathrm{A}}(t)}$, $\gamma(\phi(t))$, $t \geq 0$, is the steepness of the concentration-response relation at ratio $\phi(t)$, and $U_{50}(\phi(t))$ is the number of units associated with 50% of maximum effect at ratio $\phi(t)$. Furthermore, $U^{\mathrm{S}}(t)$, $t \geq 0$, and $U^{\mathrm{A}}(t)$, $t \geq 0$, are the normalized drug concentrations of the sedative and analgesic drugs and are given by $U^{\mathrm{S}}(t) = \frac{c_{\mathrm{eff}}^{\mathrm{S}}(t)}{c_{50}^{\mathrm{S}}}$ and $U^{\mathrm{A}}(t) = \frac{c_{\mathrm{eff}}^{\mathrm{A}}(t)}{c_{50}^{\mathrm{A}}}$, where c_{50}^{S} and c_{50}^{A} are the drug concentrations of the sedative and analgesic that cause 50% drug effects, respectively.

Remifentanil causes pain reduction as well as muscle relaxation and the percentage of muscle relaxation indicates the amount of remifentanil in the blood. We use the EMG index proposed in Ionescu et al. (2014), which relates the effect-site remifentanil concentration to electromyographic measurements. The relationship between the EMG index and remifentanil concentration is given by

$$\mathrm{EMG}(t) = \frac{100 \times c_{\mathrm{eff}}^{A}(t)}{3.4 \times c_{\mathrm{eff}}^{A}(t) + 0.0063}\,. \tag{10}$$

The value of the EMG(t), $t \geq 0$, indicates the percentage of muscle relaxation and varies from 0% to 100%, and hence, (1)–(10) can be written as

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0, \tag{11}$$

$$y(t) = h(x(t)), \tag{12}$$

where $A \in \mathbb{R}^{8\times 8}$ is a state transition matrix, $B \in \mathbb{R}^{8\times 2}$ is an input matrix, $x(t) \in \mathbb{R}^8$, $t \geq 0$, is the state vector, $u(t) = [u^{\mathrm{S}}(t), u^{\mathrm{A}}(t)]^{\mathrm{T}}$ is the control input, and $y(t) = [\mathrm{BIS}(t),\ \mathrm{EMG}(t))]^{\mathrm{T}}$ is the system measurement.

As shown in the next section, in order to design a nonovershooting controller, a linear approximation of the measurements (9)

Table 1. Patient model parameters and equations for the sedative drug propofol and analgesic drug remifentanil .

Parameter	Sedative	Analgesic	Unit
v_1	4.27	$5.1 - 0.0201(age - 40) + 0.072(lbm - 55)$	l
v_2	$18.9 - 0.391(age - 53)$	$9.82 - 0.0811(age - 40) + 0.108(lbm - 55)$	l
v_3	2.38	5.42	l
C_1	$1.89 + 0.0456(weight - 77) - 0.681(lbm - 59) + 0.0264(height - 177)$	$2.6 - 0.0162(age - 40) + 0.0191(lbm - 55)$	$\mathrm{l\,min^{-1}}$
C_2	$1.29 - 0.024(age - 53)$	$2.05 - 0.0301(age - 40)$	$\mathrm{l\,min^{-1}}$
C_3	0.836	$0.076 - 0.00113(age - 40)$	$\mathrm{l\,min^{-1}}$
k_{e0}	0.456	$0.595 - 0.007(age - 40)$	$\mathrm{min^{-1}}$
k_{10}	C_1/v_1	C_1/v_1	$\mathrm{min^{-1}}$
k_{12}	C_2/v_1	C_2/v_1	$\mathrm{min^{-1}}$
k_{13}	C_3/v_1	C_3/v_1	$\mathrm{min^{-1}}$
k_{21}	C_2/v_2	C_2/v_2	$\mathrm{min^{-1}}$
k_{31}	C_3/v_3	C_3/v_3	$\mathrm{min^{-1}}$

and (10) is required. Using a linear regression model in the region of the required maintenance value for $\mathrm{BIS}(t)$, $t \geq 0$, and $\mathrm{EMG}(t)$, $t \geq 0$, (9) and (10) can be represented as

$$\begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix} = \begin{bmatrix} m_1 & m_2 \\ 0 & m_3 \end{bmatrix} \begin{bmatrix} c_{\mathrm{eff}}^{\mathrm{S}}(t) \\ c_{\mathrm{eff}}^{\mathrm{A}}(t) \end{bmatrix} + \begin{bmatrix} c_1 \\ c_2 \end{bmatrix}. \tag{13}$$

The parameter values m_i, $i = 1, 2$, and 3, and the constants c_i, $i = 1$ and 2, in (13) can be determined by multiple linear regression using a least squares method on randomly selected patient data relating the patient's pharmacokinetic and pharmacodynamic parameters and measured responses [Ionescu et al. (2014)]. Consequently, the linearized patient dynamical model can be written as

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0, \tag{14}$$

$$y(t) = Cx(t) + d, \tag{15}$$

where $C = \begin{bmatrix} 0 & 0 & 0 & m_1 & 0 & 0 & 0 & m_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_3 \end{bmatrix}$ and $d = [c_1,\ c_2]^{\mathrm{T}}$.

2.2 Nonovershooting controller design

The aim is to design a tracking controller in which the patient responses $\mathrm{BIS}(t)$, $t \geq 0$, and $\mathrm{EMG}(t)$, $t \geq 0$, asymptotically approach the desired target values $\mathrm{BIS}_{\mathrm{target}}$ and $\mathrm{EMG}_{\mathrm{target}}$ without any overshoot. The key idea behind the nonovershooting controller design is to obtain a state feedback gain that achieves a specific closed-loop eigenstructure such that the selected modes of the closed-loop system appear in each component of the output [Schmid and Ntogramatzidis (2010)]. In order to achieve robust tracking in the presence of system parameter uncertainty, an integral control action is included in the controller. We define the integral of tracking error as

$$e(t) = \int_0^t [y_{\mathrm{d}} - y(\tau)]\mathrm{d}\tau, \tag{16}$$

where $y_{\mathrm{d}} = [y_{\mathrm{d}1},\ y_{\mathrm{d}2}]^{\mathrm{T}}$ and $y(t) = [y_1(t),\ y_2(t)]^{\mathrm{T}}$ are the desired response and the measured response, respectively. Note that $\dot{e}(t)$, $t \geq 0$, is given by

$$\dot{e}(t) = y_{\mathrm{d}} - y(t), \quad e(0) = 0, \quad t \geq 0. \tag{17}$$

Next, using (14), (15), and (17) the augmented system Σ_{a} is given by

$$\begin{aligned} \dot{x}_{\mathrm{a}}(t) &= A_{\mathrm{a}}x_{\mathrm{a}}(t) + B_{\mathrm{a}}u(t) + Hy_{\mathrm{d}} - Hd, \ \ x_{\mathrm{a}}(0) = x_{\mathrm{a}0}, \\ y(t) &= C_{\mathrm{a}}x_{\mathrm{a}}(t) + d, \end{aligned} \tag{18}$$

where $x_{\mathrm{a}}(t) = [x(t),\ e(t)]^{\mathrm{T}} \in \mathbb{R}^{\hat{n}}$, $t \geq 0$, $\hat{n} = n + p$, $H = [\,0\ \ I\,]^{\mathrm{T}}$,

$$A_{\mathrm{a}} = \begin{bmatrix} A & 0 \\ -C & 0 \end{bmatrix}, \quad B_{\mathrm{a}} = \begin{bmatrix} B \\ 0 \end{bmatrix}, \quad C_{\mathrm{a}} = [C, 0_{p\times p}]. \tag{19}$$

The aim here is to design a control input $u(t) = K_{\mathrm{a}}x_{\mathrm{a}}(t)$ such that $A_{\mathrm{a}} + B_{\mathrm{a}}K_{\mathrm{a}}$ is asymptotically stable and the output $y(t)$, $t \geq 0$, tracks the reference input y_{d} without any overshoot. Since Σ_{a} is a MIMO system, we can associate multiple sets of $\hat{n}$ eigenvectors for a given set of $\hat{n}$ eigenvalues. We use this flexibility in eigenvector assignment to achieve the desired nonovershooting property. Specifically, we choose eigenvectors such that a specific set of closed-loop modes appear in the output. Note that for a specific set of $\hat{n}$ eigenvalues $\mathscr{L} = \{\lambda_1, \ldots, \lambda_{\hat{n}}\}$ and linearly independent eigenvectors $\mathscr{V} = \{v_1, \ldots, v_{\hat{n}}\}$, the associated feedback gain matrix K_{a} is unique.

The number of closed-loop modes that can be annihilated from the output signal depends upon the number of invariant zeros of (18) in the left-half plane (LHP). For an open-loop system with $\hat{n} - lp$ invariant zeroes in the LHP, denoted as z_i, $i = 1, \ldots, \hat{n} - lp$, the closed-loop eigenvalues are chosen such that $\lambda_i = z_i$, $i = 1, \ldots, \hat{n} - lp$ [Schmid and Ntogramatzidis (2010)]. The remaining closed-loop poles λ_i, $i \in \{\hat{n} - lp + 1, \ldots, \hat{n}\}$, can be chosen to be real and asymptotically stable. Finally, define the Rosenbrock system matrix $P_{\Sigma_{\mathrm{a}}} \triangleq \begin{bmatrix} A_{\mathrm{a}} - \lambda_i I & B_{\mathrm{a}} \\ C_{\mathrm{a}} & 0 \end{bmatrix}$.

Next, let $\mathscr{S} = \{s_1, \ldots, s_{\hat{n}}\} \subset \mathbb{R}^p$, where

$$s_i = \begin{cases} 0, & i \in \{1, \ldots, \hat{n} - lp\}, \\ e_1, & i \in \{\hat{n} - lp + 1, \hat{n} - lp + 2, \ldots, \hat{n} - lp + l\}, \\ \vdots & \vdots \\ e_p, & i \in \{\hat{n} - l + 1, \ldots, \hat{n}\}, \end{cases} \tag{20}$$

and $e_1, \ldots, e_p$ are basis vectors in $\mathbb{R}^p$. Furthermore, assume that, for $1 \leq i \leq \hat{n}$, the matrix equation

$$\begin{bmatrix} A_{\mathrm{a}} - \lambda_i I & B_{\mathrm{a}} \\ C_{\mathrm{a}} & 0 \end{bmatrix} \begin{bmatrix} v_i \\ w_i \end{bmatrix} = \begin{bmatrix} 0 \\ s_i \end{bmatrix} \tag{21}$$

has a solution characterized by $\mathscr{V} = \{v_1, \ldots, v_{\hat{n}}\} \subset \mathbb{C}^{\hat{n}}$ and $\mathscr{W} = \{w_1, \ldots, w_{\hat{n}}\} \subset \mathbb{C}^p$. Now, if the vectors in $\mathscr{V}$ are linearly independent, then there exists a unique feedback gain matrix K_{a} such that, for all $i \in \{1, \ldots, \hat{n}\}$,

$$\begin{aligned} (A_{\mathrm{a}} + B_{\mathrm{a}}K_{\mathrm{a}})v_i &= \lambda_i v_i, \\ C_{\mathrm{a}}v_i &= s_i. \end{aligned} \tag{22}$$

Now, solving (22) for the vectors in $\mathscr{S}$, we obtain $\mathscr{V} = \{v_1, \ldots, v_{\hat{n}}\}$ and $\mathscr{W} = \{w_1, \ldots, w_{\hat{n}}\}$, where

$$\begin{bmatrix} v_i \\ w_i \end{bmatrix} = \begin{cases} \mathscr{N}\left(P_{\Sigma_{\mathrm{a}}}(\lambda_i)\right), & i \in \{1, \ldots, \hat{n} - lp\}, \\ P_{\Sigma_{\mathrm{a}}}^{-1} \begin{bmatrix} 0 \\ s_i \end{bmatrix}, & i \in \{\hat{n} - lp + 1, \ldots, \hat{n}\}, \end{cases} \tag{23}$$

and $\mathscr{N}(\cdot)$ denotes the null space. Thus, vectors in $\mathscr{V}$ satisfy $s_i = C_{\mathrm{a}}v_i$ for all $i = 1, \ldots, \hat{n}$.

If the vectors in $\mathscr{V}$ are linearly independent, then applying Moore's algorithm we obtain K_{a} as

$$K_{\mathrm{a}} = \mathscr{W}\mathscr{V}^{-1}, \tag{24}$$

where $A_{\mathrm{a}} + B_{\mathrm{a}}K_{\mathrm{a}}$ has distinct eigenvalues corresponding to linearly independent eigenvectors given by $\mathscr{L}$ and $\mathscr{V}$, respectively. The solution $v_i \subset \mathbb{C}^{\hat{n}}$ and $w_i \subset \mathbb{C}^p$ is in the null space of $P_{\Sigma_{\mathrm{a}}}$ for $s = \lambda_i$, $i = 1, \ldots, \hat{n} - lp$. Now, let $v_{k,1}, v_{k,2}, \ldots, v_{k,l}$ and $\lambda_{k,1}, \lambda_{k,2}, \ldots, \lambda_{k,l}$ be the vectors in $\mathscr{V}$ with their respective eigenvalues associated with the standard basis vector e_k, $k \in 1, \ldots, p$.

Since the eigenvalues of the closed-loop system are asymptotically stable, it follows that the tracking error $(y_{\mathrm{d}} - y(t)) \to 0$ as $t \to \infty$. Next, define

$$\hat{A}_{\mathrm{a}} \triangleq A_{\mathrm{a}} + B_{\mathrm{a}}K_{\mathrm{a}}, \qquad \hat{H}_{\mathrm{a}} \triangleq Hy_{\mathrm{d}} - Hd, \tag{25}$$

so that (18) can be rewritten as

$$\dot{x}_{\mathrm{a}}(t) = \hat{A}_{\mathrm{a}}x_{\mathrm{a}}(t) + \hat{H}_{\mathrm{a}}, \quad x_{\mathrm{a}}(0) = x_{\mathrm{a}0}, \quad t \geq 0, \tag{26}$$

$$y(t) = C_{\mathrm{a}}x_{\mathrm{a}}(t) + d, \tag{27}$$

where, $x_{\mathrm{a}}(t) = e^{\hat{A}_{\mathrm{a}}t}x_{\mathrm{a}0} + e^{\hat{A}_{\mathrm{a}}t}\hat{A}_{\mathrm{a}}^{-1}\hat{H}_{\mathrm{a}} - \hat{A}_{\mathrm{a}}^{-1}\hat{H}_{\mathrm{a}}$.

Note that the state transition matrix can be written as $e^{\hat{A}_{\mathrm{a}}t} = Ve^{\Lambda t}V^{-1}$, where Λ is a diagonal matrix with the eigenvalues λ_i, $i = 1, \ldots, \hat{n}$, on the diagonal and V is a matrix composed of the associated eigenvectors. Thus,

$$x_{\mathrm{a}}(t) = Ve^{\Lambda t}V^{-1}x_{\mathrm{a}0} + Ve^{\Lambda t}V^{-1}\hat{A}_{\mathrm{a}}^{-1}\hat{H}_{\mathrm{a}} - \hat{A}_{\mathrm{a}}^{-1}\hat{H}_{\mathrm{a}}. \tag{28}$$

Now, defining

$$\alpha \triangleq [\,\alpha_1\ \ldots\ \alpha_{n-lp}\ \alpha_{1,1}\ \ldots\ \alpha_{1,l}\ \ldots\ \alpha_{p,1}\ \ldots\ \alpha_{p,l}\,]^{\mathrm{T}} = V^{-1}x_{\mathrm{a}0} \tag{29}$$

and

$$\beta \triangleq V^{-1}\hat{A}_{\rm a}^{-1}\hat{H}_{\rm a}, \tag{30}$$

the system output $y(t)$, $t \geq 0$, is given by

$$\begin{aligned} y(t) &= \sum_{i=\hat{n}-lp+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\alpha_i e^{\lambda_i t} + \sum_{i=\hat{n}-lp+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\beta_i e^{\lambda_i t} \\ &\quad - \sum_{i=\hat{n}-lp+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\beta_i + d, \\ &= \sum_{i=\hat{n}-3p+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\beta_i e^{\lambda_i t} - \sum_{i=\hat{n}-3p+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\beta_i + d, \end{aligned} \tag{31}$$

with $x_{\rm a0} = 0$, $\alpha = 0$, which implies that $\hat{n} - lp$ terms are annihilated at the system output $y(t)$, $t \geq 0$, and the remaining lp number of terms are distributed evenly into the p components of $y(t)$, $t \geq 0$ [Schmid and Ntogramatzidis (2010)].

Now, using Lemma A.2 of Schmid and Ntogramatzidis (2010), we can identify conditions to check the monotonicity of (31). Let $\lambda_1 < \lambda_2 < \lambda_3 < 0$ and define

$$f(t) \triangleq \beta_1 e^{\lambda_1 t} + \beta_2 e^{\lambda_2 t} + \beta_3 e^{\lambda_3 t}. \tag{32}$$

Note that $f(t)$ has a sign change for some $t > 0$ if and only if one of the following conditions hold:

i) $\beta_1\beta_2 > 0$, $\beta_1\beta_3 < 0$, and $|\beta_1 + \beta_2| > |\beta_3|$.
ii) $\beta_2\beta_3 > 0$, $\beta_1\beta_2 < 0$, and $|\beta_1| > |\beta_2 + \beta_3|$.
iii) (a) $\beta_1\beta_3 > 0$, $\beta_1\beta_2 < 0$, and $|\beta_2| \geq |\beta_1 + \beta_3|$;
(b) $\beta_1\beta_3 > 0, \beta_1\beta_2 < 0, |\beta_2| < |\beta_1 + \beta_3|$ and $t^* > 0$, and $|g_{\rm c}(t^*)| \geq |\beta_1 + \beta_2 + \beta_3|$, where $t^* = \frac{1}{\lambda_3 - \lambda_1}\ln\left(\frac{\beta_1(\lambda_2-\lambda_1)}{\beta_3(\lambda_3-\lambda_2)}\right)$ and $g_{\rm c}(t) = \beta_1(1 - e^{(\lambda_1-\lambda_2)t}) + \beta_3(1 - e^{(\lambda_3-\lambda_2)t})$.

Conditions i)–iii) give necessary and sufficient conditions under which an output of the form (32) changes sign [Schmid and Ntogramatzidis (2010)].

Even though the aforementioned design is based on the linearized model, the closed-loop is implemented using the measured variables $\mathrm{BIS}(t)$, $t \geq 0$, and $\mathrm{EMG}(t)$, $t \geq 0$, which are nonlinear functions of the system states. Hence, we use a hybrid extended Kalman filter (EKF) to estimate the system states that are required for state feedback. The discrete-time samples of the measured outputs $\mathrm{BIS}(t)$, $t \geq 0$, and $\mathrm{EMG}(t)$, $t \geq 0$, at the kth time step is given by

$$y_k = [\mathrm{BIS}(x(kT)),\ \mathrm{EMG}(x(kT))]^{\rm T}, \quad k = 1, 2, \ldots, \tag{33}$$

where T is the sampling time.

2.3 The hybrid extended Kalman filter [Simon (2006)]

Based on the continuous-time dynamics (11), discrete-time measurement (33), and including the process and measurement noise, we have

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t) + w(t), \quad x(0) = x_0, \quad t \geq 0, \\ y_k &= h(x_k) + v_k, \quad k = 1, 2, \ldots, \end{aligned}$$

where $x_k = x(kT)$, $w(t) \sim \mathcal{N}(0, Q)$ is a continuous-time white noise with covariance Q, and $v_k \sim \mathcal{N}(0, R)$ is a discrete-time white noise with covariance R. The hybrid extended Kalman filter for the above system is given as follows:

(1) Initialize the filter as follows: $\hat{x}_0^+ = \mathbb{E}[x_0]$ and $P_0^+ = \mathbb{E}[(x_0 - \hat{x}_0^+)(x_0 - \hat{x}_0^+)^{\rm T}]$, where $\mathbb{E}[\cdot]$ denotes expectation.
(2) For $k = 1, 2, \ldots$, perform the following:
(a) Integrate the continuous-time model of the state estimate and its covariance as follows:

$$\begin{aligned} \dot{\hat{x}}(t) &= A\hat{x}(t) + Bu(t), \quad \hat{x}((k-1)T) = \hat{x}_{k-1}^+, \\ \dot{P}(t) &= AP(t) + P(t)A^{\rm T} + Q, \quad P((k-1)T) = P_{k-1}^+, \end{aligned}$$

where $(k-1)T \leq t \leq kT$, $\hat{x}_{(k-1)}^+$ and $P_{(k-1)}^+$ are the initial conditions at the beginning of this integration process and at the end of this integration we have $\hat{x}_k^- = \hat{x}(kT)$ and $P_k^- = P(kT)$.
(b) At time k, incorporate the measurement y_k into the state estimate and estimation covariance as follows:

$$\hat{x}_k^+ = \hat{x}_k^- + K_k\left(y_k - h(\hat{x}_k^-)\right), \tag{34}$$

$$P_k^+ = (I - K_k J_k)P_k^-, \tag{35}$$

where $K_k = P_k^- J_k^{\rm T}(J_k P_k^- J_k^{\rm T} + R)^{-1}$, J_k is the partial derivative of $h(x_k)$ with respect to x_k evaluated at $\hat{x}_k^-$.

3. RESULTS AND DISCUSSION

For our simulations, we consider two cases. Namely, (1) a design for the controller and observer for each patient using the respective patient model, and (2) a design for the controller and observer using a nominal patient model.

Case 1: First, we consider the pharmacokinetic models of 10 patients obtained using the model (1)–(8) with parameters and patient features given in Table 1 and 2, respectively. The pharmacokinetic model of each patient is used to derive the controller gain $K_{\rm a}$ and estimator gain K_k, $k = 1, 2, \cdots$. Patients in the ICUs often require moderate sedation and analgesia for several hours. Hence, for our simulations, we set the desired target values to $\mathrm{BIS}_{\rm target} = 60$ and $\mathrm{EMG}_{\rm target} = 29$.

The value of the parameters m_i, $i = 1, 2$, and 3, and constants c_i, $i = 1$, and 2, in (13) can be estimated using the multiple linear regression method. The patient response for different combinations of effect-site concentrations $c_{\rm eff}^{\rm S}(t)$, $t \geq 0$, and $c_{\rm eff}^{\rm A}(t)$, $t \geq 0$, are obtained using the pharmacodynamic model (9) and (10). For regression, we set the values of the pharmacodynamic parameters to $C_{50}^{\rm S} = 3.1$ μg/ml, $C_{50}^{\rm A} = 34$ ng/ml, and $\gamma(\phi(t)) = 0.9$, and the range of effect-site concentrations to $c_{\rm eff}^{\rm S}(t) = [0,\ 30]$ μg/ml and $c_{\rm eff}^{\rm A}(t) = [0,\ 25]$ ng/ml. The value of $U_{50}(\phi(t))$, $t \geq 0$, in (9) is calculated using the approximation $U_{50}(\phi(t)) \approx 1 - \theta\phi(t) + \theta\phi^2(t)$, where $\theta = 0.22$. Using a linear regression, we obtain $m_1 = -1.3263 \times 10^4$, $m_2 = -1.1910 \times 10^6$, $m_3 = 1.5561 \times 10^4$, $c_1 = 84.98$, and $c_2 = 0.0068$.

Table 2. Patient features used to generate 10 simulated patients. Pharmacodynamic parameters of all the 10 patients are set to $C_{50}^S = 3.1$ μg/ml, $C_{50}^A = 34$ ng/ml, $\gamma(\phi(t)) = 0.9$, and $\theta = 0.22$ [Ionescu et al. (2014)].

Patient No.	Age [years]	Height [cm]	Weight [kg]	lbm
1	56	160	88	49.39
2	48	158	52	39.60
3	51	165	55	42.40
4	56	160	65	45.12
5	64	146	60	39.20
6	59	159	110	46.86
7	29	163	59	43.73
8	45	155	58	41.33
9	51	163	55	41.99
10	32	172	56	44.23

As mentioned earlier, for Case 1, we use the pharmacological features of the simulated patients 1 to 10 given in the Table 2 however, for brevity, we present the calculations involved in the design of nonovershooting controller for Patient 1. Using the system dynamics (1)–(8) and (13) we calculate the values of the system matrices $A_{\rm a}, B_{\rm a}$, and $C_{\rm a}$. The controllability matrix with respect to the pair $(A_{\rm a}, B_{\rm a})$ has full rank, and hence, the system is controllable. The stable invariant zeroes z_i, $i = 1,\ldots,\hat{n}-lp$, in the LHP are calculated using (19), which, for Patient 1, are $z_1 = -0.1986$, $z_2 = -0.0107$, $z_3 - 0.3513$, and $z_4 = -0.0687$. With 4 zeroes in the LHP, we have $\hat{n}-lp = 4$, where $\hat{n} = 10$, $p = 2$, and $l = 3$. As explained in Section 2, we use the stable LHP zeroes of the open loop system given by z_i, $i = 1,\ldots,4$, as the desired closed-loop poles of the system i.e. $z_i = \lambda_i$, $i = 1,\ldots,4$. Since the system is completely controllable, we can arbitrarily choose the remaining 6 poles such that the closed-loop system is asymptotically stable. We choose the remaining closed-loop poles λ_i, $i = 5,\ldots,10$, to be $\lambda = [-0.7125,\ -0.5445,\ -0.7139,\ -0.5510,\ -0.4,\ -0.9]$. Now, using (20), we get $s_i = 0$, for $i \in \{1,\ldots,4\}$, $s_i = e_1$, for $i \in \{5,6,7\}$, and $s_i = e_2$, for $i \in \{8,9,10\}$. Notice that, since $s_i = 0$, for $i \in \{1,\ldots,4\}$, the corresponding closed-loop mode associated with λ_i, $i \in \{1,\ldots,4\}$, does not appear at the system output.

Now, using (30) we get

$$\begin{aligned}\beta &= [\,\beta_1\ \beta_2\ \beta_3\ \beta_4\ \beta_{1,1}\ \beta_{1,2}\ \beta_{1,3}\ \beta_{2,1}\ \beta_{2,2}\ \beta_{2,3}\,]\\ &= [\,0\ 0\ 0\ 0\ -4.128\times10^4\ \ 446.46\ \ 4.086\times10^4\ \ 1.961\ \ -1.886\ \ -0.362\,].\end{aligned}$$

Next, to check the system output for sign changes, we consider the exponential term in (31) given by $\sum_{i=\hat{n}-3p+1}^{\hat{n}} e_{i-(\hat{n}-lp)}\beta_i e^{\lambda_i t}$ and use value of β to define

$$\begin{bmatrix} \beta_{1,1}e^{\lambda_{1,1}} + \beta_{1,2}e^{\lambda_{1,2}} + \beta_{1,3}e^{\lambda_{1,3}} \\ \beta_{2,1}e^{\lambda_{2,1}} + \beta_{2,2}e^{\lambda_{2,2}} + \beta_{2,3}e^{\lambda_{2,3}} \end{bmatrix} \triangleq \begin{bmatrix} f_1(t) \\ f_2(t) \end{bmatrix}. \qquad (36)$$

Note that $f_i(t)$, $i = 1$ and 2, is in the form of (32). Now, it can be easily verified that none of the Conditions i)–iii) are met for $f_1(t), t \geq 0$, and $f_2(t), t \geq 0$, with β given, and hence, (36) does not possess any sign changes implying that system output (31) is monotonic.

It is clear from Figures 1 and 2, that the responses of all 10 patients are monotonic without any overshoot. All 10 patients have similar responses due to the fact that the closed-loop poles λ_i, $i = 5,\ldots,10$, are chosen to be the same for all the 10 patients. Moreover, since the pharmacodynamic parameters for all the 10 patients are assumed to be the same, the values of the effect-site concentrations that are required to track given target values are the same for all the patients; see Figure 1.

Case 2: To analyze the robustness of the nonovershooting controller to pharmacokinetic and pharmacodynamic variability from the nominal model (Patient 1), we consider 10 patients with parameters given in Table 3. We use the controller gain $K_{\rm a}$ and estimator gain K_k, $k = 1,2,\cdots$, derived using the model of Patient 1 to control the continuous infusion of propofol and remifentanil in Patients 11 to 20. To ensure that the infusion rates are positive, we use the control input $u(t) = \max\{0, u(t)\}$, $t \geq 0$. Figures 3 and 4 show the responses of the 10 patients with different pharmacokinetic and pharmacodynamic parameters. Moreover, note that the controller is designed based on the approximated linear pharmacodynamic model given by (13). Hence, Figures 3 and 4 show an achieved robustness of the proposed nonovershooting controller with respect to interpatient variability. Next, to quantify the performance of the proposed nonovershooting controller for closed-loop control

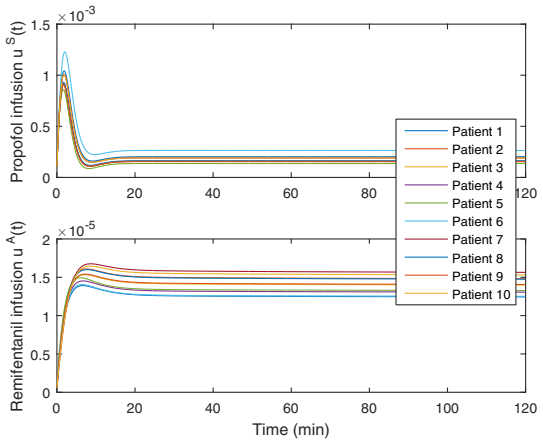

Fig. 1. Control inputs versus time for the 10 simulated patients (Case 1).

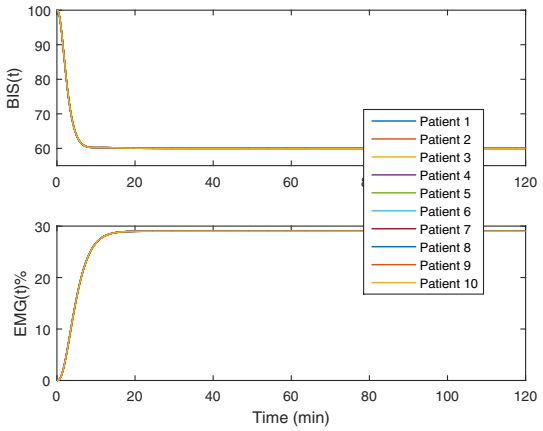

Fig. 2. BIS(t) and EMG(t) versus time for the 10 simulated patients, $\text{BIS}_{\text{target}} = 60$, $\text{EMG}_{\text{target}} = 29$ (Case 1).

Table 3. Patient features and pharmacodynamic parameters of the 10 simulated patients.

No.	Age [years]	Height [cm]	Weight [kg]	C_{50}^S [μg/ml]	C_{50}^A [ng/ml]	γ	θ
11	56	160	88	3.1	34	0.9	0.22
12	48	158	52	2	34	0.8	0.3
13	29	163	59	4	33	0.9	0.22
14	64	146	90	2	39.4	0.8	0.15
15	68	158	113	4	39	0.9	0.22
16	50	161	68	3.1	34	0.9	0.22
17	68	160	88	3.1	34	0.7	0.1
18	70	161	78	3	32	0.8	0.20
19	73	162	75	3.2	34	0.9	0.21
20	45	155	58	3	33	0.85	0.22

of multiple drugs, we can use the median performance error (MDPE), median absolute performance error (MDAPE), root mean square error (RMSE), interquartile range (IQ), minimum and maximum values of the controlled variable (min-max), induction duration (ID), percentage undershoot (US), percentage overshoot (OS), and percentage of time in adequate range (PTAR) [Soltesz et al. (2013)]. The instantaneous performance error is defined as $\text{PE}_i(j) \triangleq \frac{\text{Measured Value}(j) - \text{Target Value}}{\text{Target Value}} \times 100$, where $i \in \{1,\ldots,10\}$ represents the ith patient, $j = 1,\ldots,N$, represents the set of PE measurements for an indi-

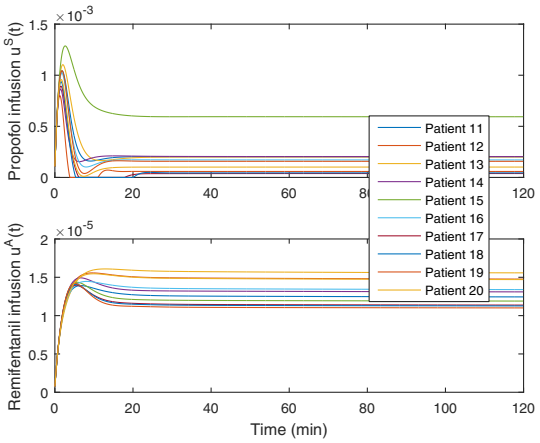

Fig. 3. Control inputs versus time for the 10 simulated patients (Case 2).

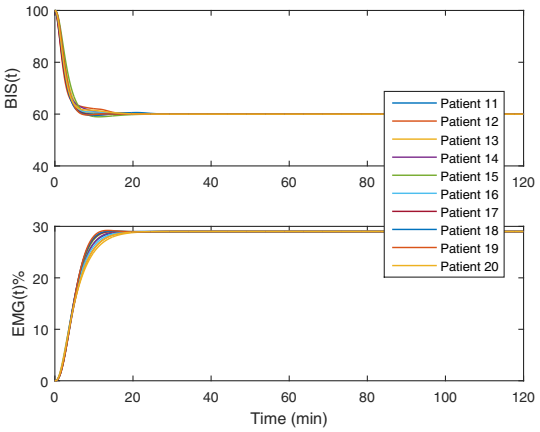

Fig. 4. BIS(t) and EMG(t) versus time for the 10 simulated patients, $\text{BIS}_{\text{target}} = 60$, $\text{EMG}_{\text{target}} = 29$ (Case 2).

vidual, N is the number of measurements for each patient, and Measured Value and Target Value refer to the measured and target values of the BIS and EMG. The MDPE gives the control bias observed and is computed by $\text{MDPE}_i = \text{median}(\text{PE}_i(j))$, whereas $\text{MDAPE}_i = \text{median}(|\text{PE}_i(j)|)$, and $\text{RMSE}_i = \sqrt{\frac{\sum_{j=1}^{N}(\text{Measured Value}(j) - \text{Target Value})^2}{N}}$. Induction phase duration (ID) is the time elapsed from the start of drug administration to the time when the drug effect falls to and remains within the range of target values $\text{BIS}_{\text{target}} \pm 10$ and $\text{EMG}_{\text{target}} \pm 3$ for 30 seconds. Percentage undershoot (US) is defined for the controlled variable BIS as $\text{US}_i = \max_j \left(\frac{\text{BIS}_{\text{target}} - \text{BIS}(j)}{\text{BIS}_0 - \text{BIS}_{\text{target}}} \right) \times 100$, and percentage overshoot (OS) is defined for the controlled variable EMG as $\text{OS}_i = \max_j \left(\frac{\text{EMG}(j) - \text{EMG}_{\text{target}}}{\text{EMG}_{\text{target}}} \right) \times 100$.

Table 4 shows the performance metrics of the proposed nonovershooting controller for the controlled variables BIS and EMG. In this table, the range of values of the defined performance metrics are given for Patients 11 to 20 (Case 2). Note that the amount of inaccuracy that is reflected in the values of the performance metrics for the 10 patients are within the acceptable performance range [Ionescu et al. (2014), Soltesz et al. (2013)].

Table 4. Performance metrics for controlled variables BIS and EMG (Case 2).

Performance Metrics	Controlled Variables	
	BIS	EMG
MDPE [%]	-0.0090 ± 0.0085	0.0027 ± 0.0329
MDAPE [%]	2.817 ± 0.48	7.87 ± 0.48
Min $-$ Max	$58.95 - 63.12$	$25.99 - 29.22$
Interquartile Range	0.029	0.0001
RMSE	4.91 ± 0.48	0.050 ± 0.0006
ID [min]	4 ± 0.6	9.3 ± 1.2
US/OS [%]	$0 - 2.625$	$0 - 0.75$
PTAR [%]	96.8 ± 0.55	92.25 ± 1

4. CONCLUSIONS

In this paper, a nonovershooting controller for the simultaneous infusion of sedatives and analgesics is proposed. Simulation results using 20 patients with varying pharmacokinetic and pharmacodynamic parameters show that the proposed nonovershooting controller design method is promising. Our simulation results show that the nonovershooting controller is robust to system parameter uncertainties. Including additional vital physiological parameters such as heart rate and respiratory rate in the controller design will be considered as a future research direction for this work.

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