Rapid Nonovershooting Control for Simultaneous Infusion of Anesthetics and Analgesics

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Abstract: We propose a rapid nonovershooting tracking controller for the continuous infusion of anesthetics and analgesics to prevent overdosing and other harmful side effects on patients. The controller utilizes a state feedback control design methodology for multi-input multi-output systems to achieve a closed-loop eigenstructure that yields a nonovershooting transient response. The method is combined with a global optimization method to achieve a rapid nonovershooting response. The controller uses an extended Kalman filter to estimate system states from measurable outputs, and integral control is added to achieve robust tracking. The performance of the method is simulated on 20 patient models in two groups, and the results are compared against another recent study from the biomedical control literature.

Keywords: Biomedical control, Drug infusion, Nonovershooting control, genetic optimization

1 Introduction

Critically ill patients in the intensive care units (ICUs) usually require fine-tuning and long-term infusion of anesthetics and analgesics to reduce anxiety, delusions, relieve pain caused by intubation and extubation, increase patient tolerance after tracheal intubation and reduce patient ventilator asynchrony (Padmanabhan et al., 2019). However, when anesthetics and analgesics are injected simultaneously, the mechanism of action is complex, interlaced, and interacted (Ionescu et al., 2014). Excessive use of anesthetics and analgesics has many side effects, such as nausea, emesis, hypotension, and may even threaten the life of the patient (Padmanabhan et al., 2017; van den Berg et al., 2017). Under-dosing of anesthetics and analgesics may inadequately suppress pain sensations, causing patient distress. A reliable controller should be designed for ICU patients, which should also be robust in the condition of patient's parameter variability.

A patient simulator platform designed by (Ionescu et al., 2021) combines interdisciplinary expertise in medicine, clinical practice, and systems engineering collected over the past few decades. It provides accessible tools for the researchers, allowing system design, evaluation, and comparison of various control algorithms to achieve multi-drug delivery goals in anesthesia. The combination of control engineering knowledge and clinical methods have been intensively studied to improve the drug delivery process as it has many benefits for patient safety (Ghita et al., 2020). The control of anesthesia delivery can be defined as a tracking control problem, and the controller should make the closed-loop response achieve relatively small overshoot, quickly reach the tracking target, maintain the target for a long time, and be robust during the process of injecting anesthetics.

(Ionescu et al., 2014) and (Padula et al., 2015) introduced proportional-integral-derivative (PID) controller for propofol infusion, achieved successfully rapid tracking by the tuning the PID parameters. However, the PID control may become aggressive or even unstable when there are strong interactions from various input variables (Ionescu et al., 2014). Moreover, their responses all showed overshoot in the transient response. Also, Model Predictive Control in (Ionescu et al., 2011; Sawaguchi et al., 2008; Ionescu et al., 2008), and reinforcement learning-based control in (Padmanabhan et al., 2017; Moore et al., 2014) have been mentioned in the past several years,

In this paper we consider multiple-input multiple-output (MIMO) control strategy using state feedback to achieve the optimal drug delivery. The non-overshooting method was discussed for this biomedical problem by (Padmanabhan et al., 2019), who used a unified method for the design of nonovershooting tracking controllers which is proposed by (Schmid and Ntogramatzidis, 2010). However, the tracking convergence speed is relatively slow through this method. Decreasing the response time might help to reduce the risk of awareness, and also leaving anesthesiologists to be more attentive to the surgical procedure and the assessment of blood loss, etc (Ionescu et al., 2021). So, in this paper, we will introduce a way to design a fast nonovershooting controller by combining the nonovershooting control design methods of (Schmid and Ntogramatzidis, 2010) with the particle swarm optimization (PSO) algorithm (Kennedy and Eberhart, 1995).

2 Drug disposition model

Since the patient's pharmacokinetics will change according to their physiological condition, we use Schneider's

drug treatment model, which depends on patient's physical characteristics (Ionescu et al., 2011). It is one of the key recommended models in the field of clinical medicine, which is currently used to promote target-controlled infusions. The mass balance equation used to simulate drug delivery between compartments are given by (Padmanabhan et al., 2019), and the parameters are given in (Padmanabhan et al. 2019, *Table* 1). Note that we use $lbm = 1.07*weight - 148*(weight^2/height^2)$, with weight (kilogram) and height (centimeter).

The measured value of the bispectral index (BIS) index is in the range of 0 to 100, which represents the EEG signal. The net sedative effect when an anesthetic is used with an analgesic and a synergistic interaction is given by (Padmanabhan et al., 2019):

$$BIS(t) = BIS_0 \times \left(1 - \frac{(\frac{U^S(t)+U^A(t)}{U_{50}(\phi(t))})^{\gamma(\phi(t))}}{1 + (\frac{U^S(t)+U^A(t)}{U_{50}(\phi(t))})^{\gamma(\phi(t))}}\right) \quad (1)$$

where $\phi(t)$ is defined as $\frac{U^S(t)}{U^S(t)+U^A(t)}$. $\gamma(\phi(t))$, $t \geq 0$ denote the steepness of the concentration-response relation at ratio $\phi(t)$. The number of units associated with half of maximum effect at ratio $\phi(t)$ is demonstrated by $U_{50}(\phi(t))$. BIS_0 represents the BIS value of fully conscious patient. $U^S(t)$ and $U^A(t)$, $t \geq 0$, denote the normalized drug concentrations of the sedative and analgesic drugs, respectively. They can be represented as:

$$U^S(t) = \frac{c^S_{eff}(t)}{C^S_{50}}, \quad U^A(t) = \frac{c^A_{eff}(t)}{C^A_{50}} \quad (2)$$

where C^S_{50} and C^A_{50} denote the drug concentrations of the sedative and analgesic that cause 50% drug effects, respectively. $c^S_{eff}(t)$ and $c^A_{eff}(t)$ denote the effect-site concentrations of the sedative and analgesic drug respectively.

Remifentanil can relieve pain and relax muscles and the percentage of muscle relaxation indicates the amount of remifentanil in the blood. The relationship between the electromyogram index (EMG) and remifentanil concentration is given by (Ionescu et al., 2014):

$$EMG(t) = \frac{100 \times C^A_{eff}(t)}{3.4 \times C^A_{eff}(t) + 0.0063} \quad (3)$$

The value of the $EMG(t)$, $t \geq 0$, represents the percentage of muscle relaxation and varies from 0% to 100%. Combine equation (1)-(3) to get the state-space model:

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0 \quad (4)$$

$$y(t) = [BIS(t)\ EMG(t)]^T \quad (5)$$

where $A \in R^{8\times 8}$ is a compartmental matrix, $B \in R^{8\times 2}$ is an input matrix, $x(t) \in R^{8\times 1}$, $t \geq 0$, is the state vector, $u(t) = [u^S(t), u^A(t)]^T$ is the control input, and $y(t)$ is the system measurement. The initial values of the state vector x_0 is zero, as no prior drug infusion is assumed.

Using linear regression method to linearize the equation (1) and (3) yields the linear output model (Padmanabhan et al., 2019):

$$y(t) = \begin{bmatrix} BIS(t) \\ EMG(t) \end{bmatrix} = \begin{bmatrix} m_1 & m_2 \\ 0 & m_3 \end{bmatrix} \begin{bmatrix} C^S_{eff}(t) \\ C^A_{eff}(t) \end{bmatrix} + d \quad (6)$$

where $m_1 = -1.3263 \times 10^4$, $m_2 = -1.1910 \times 10^6$, $m_3 = 1.5561 \times 10^4$. $d = [c_1, c_2]^T$, $c_1 = 84.98$, and $c_2 = 0.0068$.

To achieve a robust response, the system is augmented with integral action:

$$A_a = \begin{bmatrix} A & 0 \\ -C & 0 \end{bmatrix},\ B_a = \begin{bmatrix} B \\ 0 \end{bmatrix},\ C_a = [\,C\ 0\,] \quad (7)$$

We note the augmented system has stable invariant zeroes of $z = [-0.1986, -0.3513, -0.0687, -0.0107]$.

In this paper, we simulated two sets of models with 10 patients each. For case 1, pharmacodynamic parameters (Padmanabhan et al. 2019, *Table* 2) are the same for all of the 10 patients, while those parameters (Padmanabhan et al. 2019, *Table* 4) are different in case 2 due to the pharmacokinetic and pharmacodynamic variability from the nominal model in the real world. So, case 2 is used to analyze the robustness of the controller and performance analysis of the system.

3 Controller design and optimization methods

In this section we briefly describe the main results from (Schmid and Ntogramatzidis, 2010) to obtain a state feedback law for a nonovershooting response. We also describe the optimisation method that will be used to obtain a rapidly converging nonovershooting response.

3.1 Nonovershooting tracking control

(Schmid and Ntogramatzidis, 2010) considered LTI systems is state space form

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t),\ x(0) = x_0 \\ y(t) &= Cx(t) + Du(t) \end{aligned} \quad (8)$$

where $x(t) \in R^n$, $u(t) \in R^m$, $y(t) \in R^p$, $rank(B) = m$, $rank(C) = p$, with $m \geq p$. They designed linear state feedback control laws such that, from a given initial condition $x(0)$, the output y would track a constant step reference $r \in \mathbf{R}^p$ with zero steady-state error, and without overshoot in all output components. Two vectors $x_{\rm ss} \in \mathbf{R}^n$ and $u_{\rm ss} \in \mathbf{R}^m$ exist that satisfy

$$0 = A\,x_{\rm ss} + B\,u_{\rm ss} \quad (9)$$

$$r = C\,x_{\rm ss} + D\,u_{\rm ss} \quad (10)$$

for any $r \in \mathbf{R}^p$. Application of the control input

$$u(t) = F(x(t) - x_{\rm ss}) + u_{\rm ss},\ t \geq 0 \quad (11)$$

and employing the change of variable $\xi := x - x_{\rm ss}$, yields the closed loop homogeneous system

$$\dot{\xi}(t) = (A + B\,F)\,\xi(t),\ \xi(0) = x_0 - x_{\rm ss}, \quad (12)$$

$$y(t) = (C + D\,F)\,\xi(t) + r. \quad (13)$$

The main idea of their design method was to employ the classic result on eigenstructure assignment given in (Moore, 1976) to obtain a feedback matrix F such that the output $y(t)$ was related to only a small number of the closed-loop systems's modes (poles). A key result is the following eigenstructure lemma, which is an adaptation of Moore's algorithm.

Lemma 3.1. (Schmid and Ntogramatzidis, 2010) Let $\mathcal{L} = \{\lambda_1, \ldots, \lambda_n\}$ be a self-conjugate set of n distinct complex

numbers. Let $\mathcal{S} = \{s_1, \ldots, s_n\}$ be a set of n (not necessarily distinct) vectors in $\mathbf{R}^p$. Assume that, for each $i \in \{1, \ldots, n\}$, the matrix equation

$$\begin{bmatrix} A - \lambda_i I & B \\ C & D \end{bmatrix} \begin{bmatrix} v_i \\ w_i \end{bmatrix} = \begin{bmatrix} 0 \\ s_i \end{bmatrix} \tag{14}$$

has solutions sets $\mathcal{V} = \{v_1, \ldots, v_n\} \subset \mathbf{C}^n$ and $\mathcal{W} = \{w_1, \ldots, w_n\} \subset \mathbf{C}^m$. Then, provided $\mathcal{V}$ is linearly independent, a unique real feedback matrix F exists such that, for all $i \in \{1, \ldots, n\}$,

$$(A + B\,F)\,v_i = \lambda_i\,v_i, \tag{15}$$

$$(C + D\,F)\,v_i = s_i. \tag{16}$$

(Schmid and Ntogramatzidis, 2010) gave several methods to design a nonovershooting state feedback algorithms, depending up on the number of control inputs m, controlled outputs p and the number of stable (left-hand complex plane) invariant zeros. Below we particularise these results to the case $D = 0$, $n = 10$, $m = p = 2$, and the system has 4 stable invariant zeroes, since these are the system parameters that are applicable to the augmented drug infusion model, with state matrices given in (7), that we consider in this paper.

Let $\{z_1, z_2, \ldots, z_4\}$ be the stable invariant zeros of the drug infusion system, and let $\mathcal{L} = \{\lambda_1,\ \ldots,\ \lambda_{10}\}$ denote the set of distinct stable closed loop eigenvalues of $A_a + B_a\,F$ to be chosen. Then, we choose $\lambda_i = z_i$ for $i \in \{1, \ldots, 4\}$, and for $i \in \{5 \ldots, 10\}$, the λ_i may be freely chosen to be any real distinct stable modes not coincident with the invariant zeros. Let $\{e_1, e_2\}$ be the canonical basis of $\mathbf{R}^2$, and let $\mathcal{S} = \{s_1, \ldots\ s_{10}\} \subset \mathbf{R}^2$ be such that

$$s_i = \begin{cases} 0 & \text{for } i \in \{1, \ldots, 4\}; \\ e_1 & \text{for } i = \{5,\ 6,\ 7\}; \\ e_2 & \text{for } i = \{8,\ 9,\ 10\}. \end{cases} \tag{17}$$

Applying Lemma 3.1 to these $\mathcal{L}$ and $\mathcal{S}$, we obtain sets $\mathcal{V}$ and $\mathcal{W}$. Provided $\mathcal{V}$ is linearly independent, applying Moore's algorithm to $\mathcal{V}$ and $\mathcal{W}$ yields F such that the vectors in $\mathcal{V}$ satisfy

$$(A_a + B_a\,F)\,v_i = \lambda_i\,v_i, \quad i \in \{1, \ldots, n\}, \tag{18}$$

$$C_a\,v_i = \begin{cases} 0 & i \in \{1, \ldots, 4\}, \\ e_1 & i \in \{5,\ 6,\ 7\} \\ e_2 & i \in \{8,\ 9,\ 10\}. \end{cases} \tag{19}$$

The closed-loop system in ξ-coordinates is

$$\begin{aligned} \dot{\xi}(t) &= (A_a + B_a F)\xi(t) \\ y(t) &= C_a\xi(t) + r \end{aligned} \tag{20}$$

We let $\xi_0 = x_0 - x_{ss}$ and define the coordinate vector $\alpha = V^{-1}\xi(0) = (\alpha_1, \alpha_2, ..., \alpha_{10})$. Then the tracking error $\epsilon(t) = r - y(t)$ is given by

$$\epsilon(t) = \begin{bmatrix} \alpha_5\,e^{\lambda_5 t} + \alpha_6\,e^{\lambda_6 t} + \alpha_7\,e^{\lambda_7 t} \\ \alpha_8\,e^{\lambda_8 t} + \alpha_9\,e^{\lambda_9 t} + \alpha_{10}\,e^{\lambda_{10} t} \end{bmatrix}. \tag{21}$$

Thus the eigenstructure assignment methods have ensured that both output components of ϵ contain only three of the system's ten closed-loop modes. (Schmid and Ntogramatzidis, 2010) gave necessary and sufficient conditions for the sum of three real exponential functions to converge to zero without changing sign, and this corresponds to the system output $y(t)$ tracking its target reference r without overshoot in both components. The tests are computationally straightforward and do not require simulating the system response.

Thus the nonovershooting design method of (Schmid and Ntogramatzidis, 2010) is an iterative procedure, involving the selection of candidate sets of closed-loop poles $\mathcal{L}$, constructing $\mathcal{V}$, $\mathcal{W}$ and F, computing the coordinate vector α and then testing the resulting error term (21) for overshoot. The authors claimed that, provided the components of errors terms contained at most three real exponentials, the search for nonovershooting poles was likely to be successful.

3.2 Particle swarm optimization algorithm

The particle swarm optimization method (Kennedy and Eberhart, 1995) seeks to optimise an objective function within a specified search space by randomly commencing with a population of candidate solutions, described as the initial particle positions. These particles are then iteratively moved within the search space according to the particle's position, velocity and corresponding cost. Each particle is influenced by its local best-known position and the global best-known position. Based on this scheme, particles move towards the global optimum position. The advantages of the PSO method are its ease of application, and its applicability to non-smooth objective functions for which gradient search methods may not be applicable.

We now briefly describe the algorithm. Suppose that there are N particles at position:

$$P_i(t) = position\ defined\ in\ the\ problem \tag{22}$$

where $i = 1, 2, ..., N$, the initial particles are uniformly randomly distributed in the search space. And the cost function for each particle is:

$$f(P_i) = objective\ defined\ in\ the\ problem \tag{23}$$

At each iteration the position is updated by:

$$P_i(t+1) = P_i(t) + v_i(t+1),\ i = 1, 2, ..., N \tag{24}$$

Where t is the iteration number, $v_i(t+1)$ is the velocity of each particles and is updated by (Mahdizadeh and Schmid, 2015):

$$\begin{aligned} v_i(t+1) = {} & w_i(t)v_i(t) + c_i(t)r_{1i}(t)[P_{i,Best}(t) \\ & -P_i(t)] + s_i(t)r_{2i}(t)[P_{Best}(t) - P_i(t)] \end{aligned} \tag{25}$$

where:

- Each particle keeps a record of it's cost $f(P_i)$ for each iteration, the best value for each particle is defined as:
$$f_{i,best}(t) := min[f(P_i(\tau)), 0 \le \tau \le t] \tag{26}$$
The corresponding position is:
$$P_{i,best}(t) := arg\ min[f(P_i(\tau)), 0 \le \tau \le t] \tag{27}$$
- So the global best value and the corresponding position is:
$$f_{best}(t) := min[f_{i,best}(t), i = 1, 2, ..., N] \tag{28}$$
$$P_{best}(t) := arg\ min[f_{i,best}(t), i = 1, 2, ..., N] \tag{29}$$
- $0 \le w_i(t) \le 1$ is the inertial bias, it determines the particle's tendency to maintain their direction of motion. Here define:
$$w_i = \begin{cases} w_0 > 0, & \text{if } f(P_i(t)) < f_{i,best}(t-1) \\ 0, & \text{otherwise} \end{cases} \tag{30}$$
to make each particle reaches a better position.

- $0 < c_i(t) < 2$ is the cognitive bias while $0 < s_i(t) < 2$ is the social bias, $r_{1i}(t)$ and $r_{2i}(t)$ are random numbers generated from uniform distribution for each particle's velocity update.

The algorithm continues until a stopping condition is reached, which may be a maximum number of iterations or computation time, or else when the improvements in the f_{best} value have been less than a certain threshold value for a specified number of iterations.

Applying PSO this to the nonovershooting problem, a set of candidate closed loop poles $\mathcal{L}$ represents a particle position P_i. To achieve a rapid nonovershooting response, we use the Integrated Absolute Error (IAE) as the cost function for PSO:

$$f(P_i) = IAE = \int (|BIS(t) - BIS_{REF}| + k\,|EMG(t) - EMG_{REF}|)\,dt \tag{31}$$

Where k is weighting parameter for the two outputs, with the tracking target $BIS_{REF} = 60$, and $EMG_{REF} = 29$. To let the two outputs have the same weight, we choose $k = 40/29$. The other coefficients mentioned earlier about PSO are not unique, and here we choose $N = 300, w_0 = 0.1, c_i = 1.9, s_i = 1.5$.

To realize a nonovershooting response, we use the nonovershooting design methods of (Schmid and Ntogramatzidis, 2010) in the initialization phase and the updating phase. Thus the particle position is only updated at each iteration if the new particle position corresponds to a nonovershooting set of closed-loop poles. Additionally, the range of effect-site concentrations is constrained by (Padmanabhan et al., 2019):

$$c^S_{eff} \in [0, 30]ug/ml, c^A_{eff} \in [0, 25]ng/ml \tag{32}$$

Where c^S_{eff} and c^A_{eff} are also system states. If any of these two values exceed this limit, we also do not update the particle's position.

Under the simulation sampling time $T_s = 0.001$ minutes, take the output value of the system simulation running for 30 minutes, the cost function is transformed into:

$$f(P_i) = \sum_{n=0}^{30/T_s} (|BIS(nT_s) - BIS_{REF}| + k\,|EMG(nT_s) - EMG_{REF}|) \tag{33}$$

Set the optimization time to 5 seconds of computation time, and using the state matrices corresponding to patient 1, the optimal pole locations were found to be:

$$\begin{aligned} L_1 &= \{\lambda_1, \ \ldots, \lambda_{10}\} \\ &= \{-0.1986, -0.3513, -0.0687, -0.0107, \ -1.1718, \\ &\quad -1.2542, \ -1.4121, \ -2.0555, \ -1.9008, \ -1.4564\} \end{aligned}$$

with the corresponding feedback gain:

$$F = \begin{bmatrix} -2.293 & -0.2852 & -0.1958 & -7.353 & 149.8 & \cdots \\ -0.0000 & -0.0000 & 0.0000 & -0.0000 & -4.047 & \cdots \end{bmatrix}$$
$$\begin{bmatrix} \cdots & -0.000 & -0.000 & 790.3 & -0.000343 & -0.072 \\ \cdots & -0.3585 & -0.0132 & -15.09 & -0.000 & 0.00076 \end{bmatrix}$$

Lastly, the feedback control law (11) is combined with the Kalman filter proposed by (Padmanabhan et al., 2019) to estimate the non-measured system states.

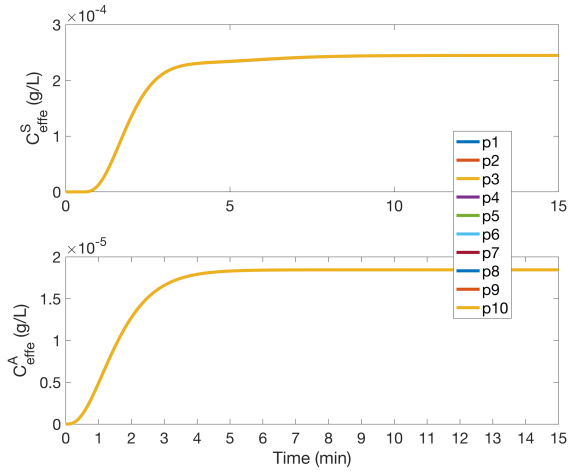

Fig. 1. Drug concentrations in the effect-site for the 10 patients (Case 1)

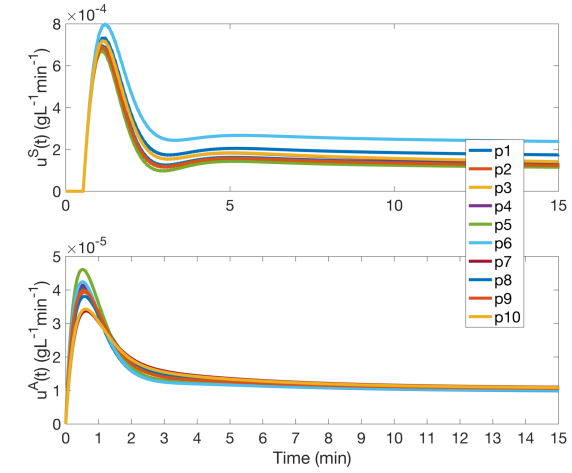

Fig. 2. Control inputs for the 10 patients (Case 1)

4 Simulation Results

Although the controller design is based on the approximated linear model given by equation (6), for simulation purposes we use the original nonlinear model given by equation (1) and (3). We will compare the transient performance against that given in (Padmanabhan et al., 2019).

Case 1 (Figure 1-3) shows that the responses and effect-site concentrations are strictly monotonic, and they are the same for all 10 patients since the pharmacodynamic parameters are assumed to be the same for the 10 patients. Besides, the closed loop poles are chosen to be the same, and the feedback gain is calculated separately based on each model. However, the control input are different because of the difference in the patient physiological features. And the output response can reach stability in about 5 minutes. Note that Case 1 is unrealistic as

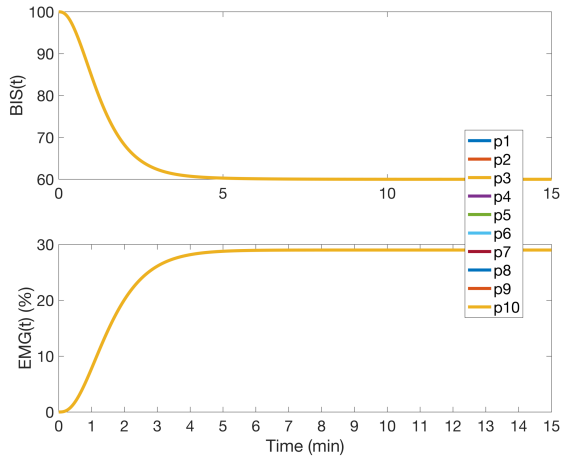

Fig. 3. Drug responses for the 10 patients (Case 1)

pharmacodynamic parameters cannot be the same for all patients in real life, and we simulate this situation to test whether the response can achieve strict nonovershooting in the case of an exact match of the model.

Case 2 (Figure 4-6) is to analyze the robustness of controller. Here we use the controller and the estimator derived from the model of Patient 1 to control the patients with different pharmacokinetic and pharmacodynamic parameters from Case 2. Note that set the control input $u(t) = max\{0, u(t)\}$ to ensure that the infusion rates are non-negative. Finally, the system responses remain similar even with significantly different pharmacokinetic and pharmacodynamic parameters. This demonstrates the robustness of the proposed rapid nonovershooting controller

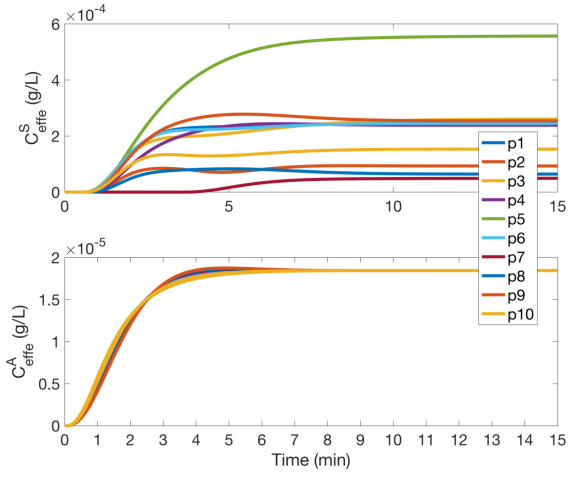

Fig. 4. Drug concentrations in the effect-site for the 10 patients (Case 2)

We 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), and percentage overshoot (OS) to quantify the performance of the proposed control

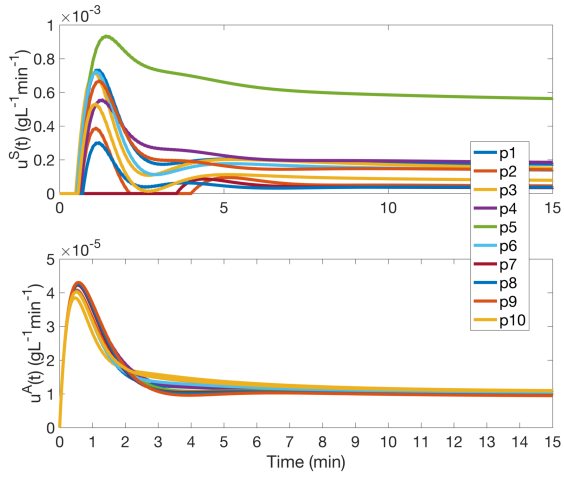

Fig. 5. Control inputs for the 10 patients (Case 2)

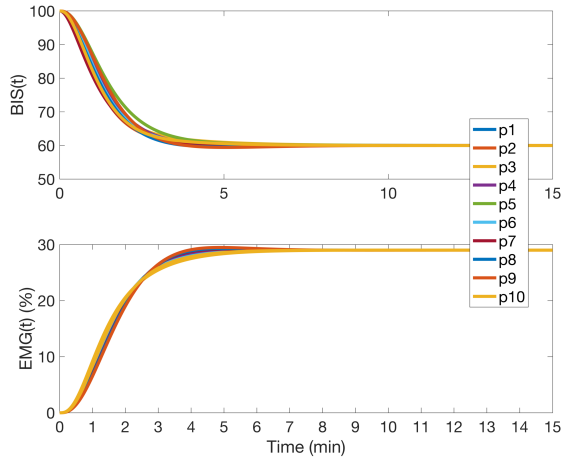

Fig. 6. Drug responses for the 10 patients (Case 2)

strategy (Padmanabhan et al., 2019; Moore et al., 2014). The instantaneous performance error (PE) is defined as:

$$PE_i(j) = \frac{Measured\ Value_i(j) - Target\ Value}{Target\ Value} * 100$$

where $i \in \{11, 12, .., 20\}$ denotes the ith patient. $j = 1, ..., N$, N is the data set for each patient. The MDPE, MDAPE, and RMSE can be calculated as:

$$MDPE_i = median(PE_i(j)), \quad j = 1, 2, ..., N \tag{34}$$

$$MDAPE_i = median(|PE_i(j)|), j = 1, 2, ..., N \tag{35}$$

$$RMSE_i = \sqrt{\frac{\sum_{j=1}^{N}(MeasuredValue_i(j) - Target)^2}{N}}$$

Induction phase duration (ID) is defined as the time from the start of administration until the drug's effect decreases and stays within the target value for 30 seconds. And the percentage overshoot (OS) is defined as:

$$OS_{BIS,i} = max_j \left(\frac{BIS_{target} - BIS_i(j)}{BIS_0 - BIS_{target}} \right) \times 100, j = 1, 2, ..., N \tag{36}$$

Table 1. Performance metrics for controlled variables BIS and EMG

Performance metrics	BIS [(Padmanabhan et al., 2019)]	EMG [(Padmanabhan et al., 2019)]
MDPE[%]	$7.9 \times 10^{-4} \pm 1.9 \times 10^{-3}$ [-0.0090 ± 0.0085]	$-2.5 \times 10^{-4} \pm 7.5 \times 10^{-4}$ [0.0027 ± 0.0329]
MDAPE[%]	$1.5 \times 10^{-3} \pm 1.2 \times 10^{-3}$ [2.817 ± 0.48]	$9.4 \times 10^{-4} \pm 8.2 \times 10^{-3}$ [7.87 ± 0.48]
Min-Max	59.43235 − 60.00018 [58.95 − 63.12]	29.00000 − 29.4737 [25.99 − 29.22]
IR	0.00297 [0.029]	0.00000881 [0.0001]
RMSE	4.95 ± 0.393 [4.91 ± 0.48]	0.04028 ± 0.001327 [0.050 ± 0.0006]
ID[min]	1.90 ± 0.22 [4 ± 0.6]	3.04 ± 0.14 [9.3 ± 1.2]
OS[%]	0 − 1.419 [0 − 2.625]	0.000009407 − 1.633 [0 − 0.75]

$$OS_{EMG,i} = max_j \left(\frac{EMG_i(j) - EMG_{target}}{EMG_{target}} \right) \times 100, j = 1, 2, ..., N \quad (37)$$

Table 1 shows the performance metrics compared with nonovershooting design by (Padmanabhan et al., 2019), and all of the 10 patients are within the acceptable performance range (Ionescu et al., 2014; Padmanabhan et al., 2019; Moore et al., 2014).

5 Conclusion

In this paper, we have proposed a state feedback controller design method to obtain a rapid nonovershooting tracking response for the drug disposition model, with the aim of minimizing the risk of overdose and underdose to improve patient safety. This design method can be applied to the simultaneous injection of multiple drugs, while targeting different types of patients. Additionally, the design method can be adjusted to modify the balance between the convergence of the BIS response and the EMG response, by adjusting the parameter k in the IAE index (31). Our simulation study showed that by augmenting the nonovershooting drug infusion method introduced in (Padmanabhan et al., 2019) with PSO optimization, we were able to replicate the nonovershooting performance and also achieve significantly more rapid convergence to the desired drug infusion levels.

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