An optimal control approach to reference level tracking in general anesthesia

J. Almeida[1]
almeidajfc@gmail.com

L.T. Paiva[1]
ltpaiva@fe.up.pt

T. Mendonça[2]
tmendo@fc.up.pt

P. Rocha[1]
mprocha@fe.up.pt

Abstract— In this paper the neuromuscular blockade level and the bispectral index level tracking problems by means of automatic control are considered in the context of general anesthesia. These tracking problems are formulated as optimal control problems that are numerically solved using direct methods. The obtained results are encouraging when compared with another strategy recently proposed in the literature.

I. INTRODUCTION

Anesthesia enables a patient to tolerate very painful surgical procedures. For this purpose the anesthesiologists administer several drugs while simultaneously maintaining all the vital functions of the patient. General anesthesia consists of three main components, namely: hypnosis, analgesia and muscle relaxation. Hypnosis is defined as the absence of consciousness and the inability of the patient to recall intra operative events. This is achieved by the administration of hypnotics and is measured by the electroencephalographic activity. The usual electroencephalogram (EEG)-derived indices for this purpose are: the Spectral Entropy (SE) [HOVS$^+$04], the Index of Consciousness (IoC) [CdKB$^+$08] and the Bispectral Index (BIS) [Gan97]. Among there, the BIS is the most widely used index to infer the hypnosis of a patient. It is related to the responsiveness level and the probability of recalling intra operative events, and ranges from 97.7 (fully awake and alert state) to 0 (total absence of brain activity). During a standard general anesthesia, the BIS level should vary between 40 and 60. Analgesia is obtained by the administration of analgesics and it allows the loss of the pain. The level of analgesia cannot be measured directly and must be estimated based on autonomic reactions, such as changes in blood pressure and heart rate, sweating, pupil reactivity and the presence of tears [Gui06]. It turns out that hypnotics and analgesics interact in such way that their effect is enhanced when administered together. In this way, both types of drugs contribute to the depth of anesthesia (DoA). It is commonly accepted that the DoA is also well described by the BIS level [Gan97]. On the other hand, muscle relaxants cause neuromuscular blockade and hence the loss of the capacity to move, which is essential for patient intubation, to facilitate the access to internal organs and to avoid movement responses as a result of surgical stimuli. The NeuroMuscular Blockade (NMB) level is measured from a muscle response at the hand of the patient subject evoked by stimulation of the adductor pollicis muscle through supra maximal train–of–four (TOF) stimulation of the ulnar nerve. It can be registered by electromyography (EMG), mecanomyography (MMG) or acceleromyography (AMG). More concretely, the NMB level corresponds to the first single response (T1) calibrated by a reference twitch, ranging between 100% (full muscular activity) and 0% (total paralysis). In the anesthesia practice, anesthetics are administered following standard dosing guidelines often based on an average patient [BH05]. The common procedure is to administer an initial dose of anesthetics, observe the response and adjust the dose according the desired output (e.g. NMB and BIS reference levels). However, there is a high inter and intra patient variability in what concerns the relation between the administered dose and the patient response. To achieve an individualized dose the anesthesiologists need to understand the pharmacokinetics (PK) and pharmacodynamics (PD) of the drugs in use, as well as the possible drug interaction. Mathematically, the effects can be modeled by a pharmacokinetic/pharmacodynamic (PK/PD) model. However due to the large number of patient dependent parameters present in the PK/PD models, in this paper simplified SISO/MISO Wiener models will be used to describe the relationship between the muscle relaxant dose and the NMB level, and the relation between the hypnotic and analgesic doses with the BIS level, respectively. These models were proposed by [MTT12] and [MTT14] and use a minimal number of parameters to characterize the patient while keeping a good modeling accuracy, [MJA$^+$14]. Some automatic control schemes have already been implemented based on such models [JcP11], [MLc14], [THM$^+$12]. Here alternative control schemes are proposed adopting optimal control techniques.

Indeed, in the last years, optimal control has been successfully applied in biomedical problems [DDV$^+$13], [NJ08], [BPdP14] which motivates its application also in the context of anesthesia. The relevant control objectives in this context consist in reference tracking for the desired NMB and/or BIS levels. In this work, the problem of reference tracking is formulated as an optimal control problem (OCP), and is solved using direct methods [J.T01]. These methods have become increasingly useful when computing the numerical solution of an OCP. Moreover, they are known to provide a very robust and general approach [PF15]. Two OCPs are

[1] Universidade do Porto, Faculdade de Engenharia, Rua Dr. Roberto Frias s/n, 4200–465 Porto PORTUGAL
[2] Universidade do Porto, Faculdade de Ciências, Rua do Campo Alegre s/n 4169–007 Porto PORTUGAL

formulated: one for the NMB case and another for the control of the depth of anesthesia. The optimal control of drug effects is clinically important not only since overdosing or underdosing imply risk for the patients but also due to economic reasons (related to the use of smaller drug amounts).

This paper is organized as follows. In Section II, both neuromuscular blockade model and the depth of anesthesia model are presented. In Section III, the optimal control problem formulations applied to the NMB and to the BIS reference tracking. The main results are shown in Section IV, and the conclusions are drawn in Section V.

II. DRUG ADMINISTRATION MODELS IN ANESTHESIA

In this section, two new models proposed in [MTT14], [MTT12] for the relationship between the drug input and the effect response are presented. The first one is a SISO Wiener model for the NMB level and the second one is a MISO Wiener model for the BIS level. As mentioned before, these two models have a parsimonious structure, *i.e.*, they use a minimal number of parameters to characterize the patient response.

A. NEUROMUSCULAR BLOCKADE

The relationship between the administered dose of muscle relaxant ($u(t)$) and the drug concentration in the relevant part of the patient body ($c_e(t)$) can be described by the following third–order linear dynamical model

$$C_e(s) = \frac{k_1 k_2 k_3 \alpha^3}{(s+k_1\alpha)(s+k_2\alpha)(s+k_3\alpha)} U(s), \qquad (1)$$

where $C_e(s)$ and $U(s)$ denote the Laplace transform of the output $c_e(t)$ and of the input signal $u(t)$, respectively. The values of $k = \begin{bmatrix} k_1 & k_2 & k_3 \end{bmatrix}$ are positive constants, fixed for all patients according to [MTT12]; α is a patient–dependent positive parameter.

The previous model can be written through the following state–space model

$$\begin{cases} \dot{\mathbf{x}}(t) = A_k(\alpha)\mathbf{x}(t) + B_k(\alpha)u(t) \\ c_e(t) = C\mathbf{x}(t) \end{cases} \qquad (2)$$

with

$$A_k(\alpha) = \begin{bmatrix} -k_3\alpha & 0 & 0 \\ k_2\alpha & -k_2\alpha & 0 \\ 0 & k_1\alpha & -k_1\alpha \end{bmatrix},$$

$$B_k(\alpha) = \begin{bmatrix} k_3\alpha \\ 0 \\ 0 \end{bmatrix}, \text{ and}$$

$$C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix},$$

where $\mathbf{x}(t)$ is the state vector. Note that the state $x_3(t)$ corresponds to the effect concentration $c_e(t)$.

The effect concentration is related to the actual effect of the drug by means of a static nonlinearity known as Hill equation,

$$y(t) = \frac{100 C_{50}^{\gamma}}{C_{50}^{\gamma} + c_e^{\gamma}(t)}, \qquad (3)$$

where γ is a patient–dependent parameter and C_{50} has a fixed value. Thus, this simplified model has only two parameters – α and γ – to be identified for each patient.

B. DEPTH OF ANESTHESIA

The MISO parsimonious Wiener model proposed in [MTT14] for the description of the joint effect of hypnotics and analgesics in the human body consists of two linear parts: one for the relationship between the hypnotic dose and its effect concentration and another for the effect concentration of the analgesic. These linear sub–models are connected in parallel and then followed by a nonlinear static equation that describes the drug interaction and corresponding effect.

Each individual linear model is similar to what was presented in section II.

The hypnotic linear dynamics is hence modelled by

$$C_e^H(s) = \frac{w_1 w_2 w_3 \beta^3}{(s+w_1\beta)(s+w_2\beta)(s+w_3\beta)} U^H(s), \qquad (4)$$

and the linear model for the effect concentration of the analgesic is similarly given by

$$C_e^A(s) = \frac{l_1 l_2 l_3 \eta^3}{(s+l_1\eta)(s+l_2\eta)(s+l_3\eta)} U^A(s), \qquad (5)$$

where $C_e^H(s)$ and $C_e^A(s)$ are the Laplace transforms of the effect concentration of the hypnotic and the analgesic, $c_e^H(t)$ and $c_e^A(t)$, respectively; $U^H(s)$ and $U^A(s)$ are the Laplace transforms of the input doses of the hypnotic and the analgesic $u^H(t)$ and $u^A(t)$, respectively.

Again, $w = \begin{bmatrix} w_1 & w_2 & w_3 \end{bmatrix}$ and $l = \begin{bmatrix} l_1 & l_2 & l_3 \end{bmatrix}$ are parameters that have been suitably determined in [MTT14], and α and η are patient–dependent parameters.

The state–space representation of the joint linear part is

$$\begin{cases} \dot{x}(t) = A(\beta, \eta)\mathbf{x}(t) + B(\beta, \eta)\mathbf{u}(t) \\ c_e(t) = C\mathbf{x}(t) \end{cases} \qquad (6)$$

where $\mathbf{x}(t)$ is the state vector and $\mathbf{u}(t)$ is the drug infusion rate, $\mathbf{u}(t) = \begin{bmatrix} u^H(t) & u^A(t) \end{bmatrix}^{\mathrm{T}}$. The output is defined as $\mathbf{c_e}(t) = \begin{bmatrix} c_e^H(t) & c_e^A(t) \end{bmatrix}^{\mathrm{T}}$.

The matrices of the state–space model are

$$A(\beta, \eta) = \begin{bmatrix} A_w(\beta) & 0_{3\times 3} \\ 0_{3\times 3} & A_l(\eta) \end{bmatrix},$$

$$B(\beta, \eta) = \begin{bmatrix} B_w(\beta) & 0_{3\times 1} \\ 0_{3\times 1} & B_l(\eta) \end{bmatrix}, \text{ and}$$

$$C = \begin{bmatrix} 0 & 0 & \dfrac{m}{C_{50}^H} & 0 & 0 & \dfrac{1}{C_{50}^A} \end{bmatrix}$$

where the matrices $A_w(\beta)$ and $A_l(\eta)$ and the vectors $B_w(\beta)$ and $B_l(\eta)$ are defined as

$$A_w(\beta) = \begin{bmatrix} -w_3\beta & 0 & 0 \\ w_2\beta & -w_2\beta & 0 \\ 0 & w_1\beta & -w_1\beta \end{bmatrix},$$

$$A_l(\eta) = \begin{bmatrix} -l_3\eta & 0 & 0 \\ l_2\eta & -l_2\eta & 0 \\ 0 & l_1\eta & -l_1\eta \end{bmatrix},$$

$$B_w(\beta) = \begin{bmatrix} -w_3\beta \\ 0 \\ 0 \end{bmatrix}, \text{ and}$$

$$B_l(\eta) = \begin{bmatrix} -l_3\eta \\ 0 \\ 0 \end{bmatrix}.$$

The nonlinear static equation proposed in [MTT14] to describe the drug interaction and the relation between the effect concentration and the actual drug effect is given by

$$y(t) = \frac{y_0}{1 + \left(mU^H(t) + U^A(t)\right)^\gamma}, \tag{7}$$

where $U^H(t) = \dfrac{c_e^H(t)}{C_{50}^H}$ and $U^A(t) = \dfrac{c_e^A(t)}{C_{50}^A}$; m and γ are patient–dependent parameters and C_{50}^H and C_{50}^A have fixed values for all patient, this can be viewed as a simplified Hill equation. $\theta = \begin{bmatrix} \beta & \eta & m & \gamma \end{bmatrix}^T$ is the parameter array, which means a considerable reduction of the number of parameters as compared to the PK/PD model [SLC+14].

III. OPTIMAL CONTROL PROBLEM

In this section, the formulations of the optimal control problems (OCP) for the drug administration in order to track a desired NMB level and a desired BIS level are presented.

A. PROBLEM FORMULATION

Let one consider the following optimal control problem with input and state constraints [R.B00]:

$$\min\ J(\mathbf{x}, \mathbf{u}) = \int_{t_0}^{t_f} L\left(t, \mathbf{x}(t), \mathbf{u}(t)\right) dt$$

subject to
- the dynamic constraints

$$\dot{\mathbf{x}}(t) = \mathbf{f}(t, \mathbf{x}(t), \mathbf{u}(t)) \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

- the input constraints

$$\mathbf{u}(t) \in \mathbb{U}(t) \subset \mathbb{R}^m \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

  and
- the end–point constraints

$$\mathbf{x}(t_0) \in \mathbb{X}_0 \subset \mathbb{R}^n \quad \text{and} \quad \mathbf{x}(t_f) \in \mathbb{X}_1 \subset \mathbb{R}^n,$$

where $\mathbf{x} : \left[t_0, t_f\right] \to \mathbb{R}^n$ is the state vector, $\mathbf{u} : \left[t_0, t_f\right] \to \mathbb{R}^m$ is the input control signal and $t \in \left[t_0, t_f\right]$ is the time interval. The functions involved comprise the running cost $L : \left[t_0, t_f\right] \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$ and the dynamic function $\mathbf{f} : \left[t_0, t_f\right] \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$.

1) Application to the NMB model: In this section, the optimal control problem formulation of the reference tracking for the NMB level is taken as follows:

$$\min \int_{t_0}^{t_f} \left(\mathbf{x}^T(t) - \mathbf{x}^e\right) Q \left(\mathbf{x}^T(t) - \mathbf{x}^e\right) + \mathbf{u}^T(t)R\mathbf{u}(t) dt$$

subject to
- the dynamic constraints

$$\dot{\mathbf{x}}(t) = A_k(\alpha)\mathbf{x}(t) + B_k(\alpha)\mathbf{u}(t) \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

- the input constraints

$$0 \leq \mathbf{u}(t) \leq \mathbf{u}_{\max} \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

  and
- the end–point constraints

$$\mathbf{x}(t_0) = \mathbf{x}(t^*) \quad \text{and} \quad \mathbf{x}(t_f) = \mathbf{x}^e,$$

where $Q = Q^T \geq 0$ and $R > 0$. Due to clinical restrictions the controller action begins when the patient recovers after an initial drug *bolus*. The time instant of the recovery is obtained by the algorithm developed in [MCa+] and $\mathbf{x}(t^*)$ corresponds to the value of the state vector in this time instant. The target value $\mathbf{x}^e$ is obtained by the inversion of Hill's equation (3) for a desired NMB level of 10%. Note that, the inversion of equation (3) only gives the target value fot $c_e(t) = x_3(t)$. However in equilibrium all states are equal, as can be seen easily from the matrices in the state–space form (2). Thus determining the desired equilibrium value of x_3 gives whole the desired equilibrium state vector $\mathbf{x}^e$.

2) Application to the DoA model: Similar to what was done for the NMB case, the BIS reference level tracking can be formulated as an optimal control problem in the following way:

$$\min \int_{t_0}^{t_f} \left(\mathbf{x}^T(t) - \mathbf{x}^e\right) Q \left(\mathbf{x}^T(t) - \mathbf{x}^e\right) + \mathbf{u}^T(t)R\mathbf{u}(t) dt$$

subject to
- the dynamic constraints

$$\dot{\mathbf{x}}(t) = A(\beta, \eta)\mathbf{x}(t) + B(\beta, \eta)\mathbf{u}(t) \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

- the input constraints

$$\underline{0}_{2\times 1} \leq \mathbf{u}(t) \leq \mathbf{u}_{\max} \quad \text{a.e. } t \in \left[t_0, t_f\right],$$

  and
- the end–point constraints

$$\mathbf{x}(t_0) = \underline{0}_{6\times 1} \quad \text{and} \quad \mathbf{x}(t_f) = \mathbf{x}^e,$$

where $Q = Q^T \geq 0$ and $R > 0$. The target value $\mathbf{x}^e$ is obtained by the inversion of Hill's equation (7) for a desired BIS level of 50. Notice that the inversion of (7) is not possible unless a degree of freedom is removed since $y(t)$ depends both on $U^H(t)$ and $U^A(t)$. A way to overcome this drawback was proposed in [FTP14] by fixing the ratio between $x_3(t) = c_e^H(t)$ and $x_6(t) = c_e^A(t)$ which amounts to fixing the ratio between $u^H(t)$ and $u^A(t)$. Hence, following this approach it is required that in equilibrium, $x_3(t) = \rho x_6(t)$ for at a certain value ρ that will be specified later.

B. PROBLEM SOLUTION

The previously formulated OCP's are solved using direct methods. These methods have become increasingly useful when computing the numerical solution of nonlinear optimal control problems (OCP) because they directly optimize the discretised OCP without using the maximum principle. Moreover, they are known to provide a very robust and general approach.

In a direct collocation method, the control and the state are discretized in an appropriately chosen mesh of the time interval. Then, the continuous–time OCP is transcribed into a finite–dimensional nonlinear programming problem (NLP) which can be solved using widely available software packages [Pai14].

The OCP's formulated in section III-A.1 and III-A.2 were solved using MATLAB R2014b combined with the ICLOCS, Imperial College London Optimal Control Software, version 0.1b [FKvW10]. This is an optimal control interface that uses the IPOPT solver, which is an open-source software package for large-scale nonlinear optimisation [WB06]. The proposed problems were solved in a computer with a Intel™ Core© i5 1.40 GHz.

IV. SIMULATION RESULTS

The results obtained solving the OCP for the problem of reference tracking of NMB level and for the BIS level are presented in the next two sections, respectively.

1) Neuromuscular blockade problem: In order to analyse the performance of the formulated OCP in section III-A.1 a bank of sixty patient responses wa*s* used. The model parameters

$$\theta_i = \begin{bmatrix} \alpha_i & \gamma_i \end{bmatrix}, \quad i = 1, \ldots, 60$$

were identified by an offline identification method [MTT12] using the responses of the muscle relaxant atracurium obtained during general anesthesia procedures. The values of k_1, k_2 and k_3 are fixed and equal to 1, 4 and 10, respectively.

Here, the eighth patient of the bank with parameter vector

$$\theta_8 = \begin{bmatrix} 0.0355 & 2.7160 \end{bmatrix}.$$

was considered. The parameter C_{50} was taken to be 3.2435. The matrix Q and the value R were empirically chosen as $Q = \mathbb{I}_3$ and $R = 1$.

The performance of the control input obtained by solving the optimal control problem (OCP) was compared with a controller based on a positive control law (PCL) proposed in [JcP11].

Figure 1 presents a comparison between the input signal, *i.e.*, the atracurium dose, obtained by the OCP solution (red line) and the input signal obtained by the PCL (blue line).

As it is possible to see, the OCP input signal is higher than the input signal obtained via PCL. This is confirmed by comparing the average infusion rates: $\bar{u} = 28.79 \mu g/kg/min$ when using the OCP and $\bar{u} = 27.51 \mu g/kg/min$ when using the PCL.

The corresponding NMB levels are depicted in Figure 2. Note that, as mentioned before the NMB controllers only
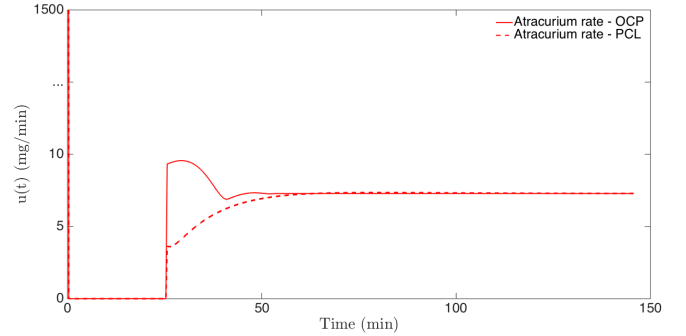

Fig. 1. Comparison between the input signal obtained by the optimal control problem (solid line) and the one obtained by the positive control law (dashed line).
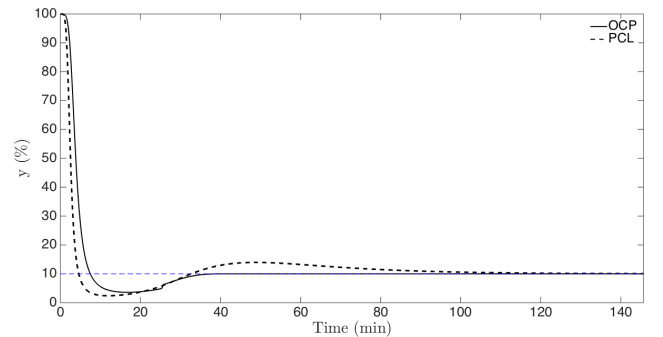

Fig. 2. Comparison between the NMB signal obtained by the optimal control problem (solid line) and the one obtained by the positive control law (dashed line).

start after the patient recoveries from an initial *bolus*, which happens here around $t = 25 \, min$. As can be seen, this level achieves the desired level of 10% in both cases.

Clearly, the controller based on the OCP solution presents a superior performance with a shorter transient and a good reference tracking.

A. Depth of anesthesia

The OCP formulated in section III-A.2 was solved for a bank of eighteen cases. Similar to the NMB case, the model parameters

$$\theta_i = \begin{bmatrix} \beta_i & \eta_i & m_i & \gamma_i \end{bmatrix}, \quad i = 1, \ldots, 18$$

were identified applying an offline identification method [MTT14] to the signals $u(t)$ and $y(t)$ obtained during general anesthesia where the used hypnotic was propofol and the analgesic was remifentanil. The values of w_1, w_2, w_3, l_1, l_2 and l_3 are fixed and equal to 1, 9, 10, 1, 2 and 3, respectively.

In this paper, the second patient from the bank was chosen to illustrate the BIS signal behavior when the optimal control input is applied. The parameter vector for this patient is

$$\theta_2 = \begin{bmatrix} 0.0874 & 0.0670 & 4.7014 & 0.9365 \end{bmatrix}.$$

The parameters C_{50}^H and C_{50}^A are fixed to 10 and 0.1, respectively, for all patients in the bank. The matrices Q and R were empirically chosen as $Q = \mathbb{I}_6$ and $R = \mathbb{I}_2$, respectively,

and the ratio between the third and the sixth state is $\rho = 2$. The BIS reference level to be tracking was set to 50%.

In order to analyse the performance of the control inputs obtained by the optimal control solver, a comparison against a positive control law (PCL) proposed in [FTP14] is made. This positive control law was designed so as to ensure that the tracking of the desired BIS level is achieved. Figure 3 shows the propofol rate (red line) and the remifentanil rate (blue line) obtained with both control approaches. The optimal control input is lower than the input signal via the PCL. This is confirmed by the results obtained for the average infusion rates: $\bar{u}^H = 1.78 \, mg/kg$ $\bar{u}^A = 0.99 \, mg/kg$ when using the OCP and $\bar{u}^H = 2.39 \, mg/kg$, $\bar{u}^A = 1.20 \, mg/kg$ when using the PCL.
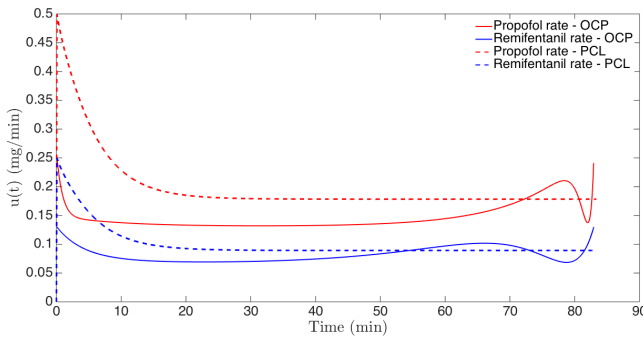

Fig. 3. Comparison between the input signals obtained by the optimal control problem (solid lines) and the ones obtained by the positive control law (dashed lines).

The corresponding BIS are depicted in Figure 4. As can be seen, with the optimal control input, the BIS achieves the desired level of 50% with a lower input when compared against the one given by PCL. The fact that the PCL leads the BIS level to a lower than the desired one since to be explained by the use of a higher drug amount in the infusion.

Although both approaches present a similar behavior, the optimal control approach, seems to be more conservative which may be an advantage to explore.

V. CONCLUSIONS

In this work, preliminary results were obtained using two optimal control problems to control the neuromuscular blockade and the depth of anesthesia. The proposed problems were solved using the IPOPT solver which is based on direct methods. For that purpose, simplified SISO/MISO Wiener models were used to describe the relationship between the muscle relaxant dose and the NMB level, and the relation between the hypnotic and analgesic doses with the BIS level, respectively.
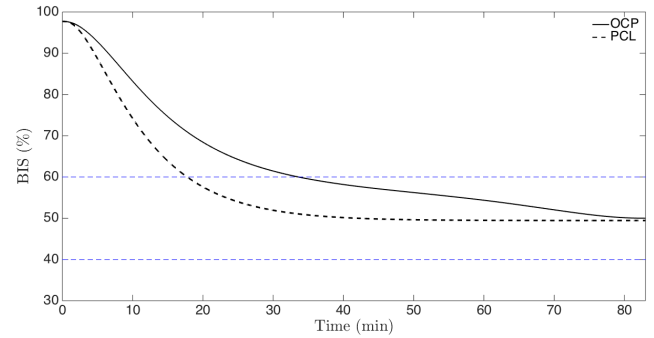
ACKNOWLEDGMENT

Fig. 4. Comparison between the BIS signal obtained by the optimal control problem (solid line) and the one obtained by the positive control law (dashed line).

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