Reference Tracking of Depth of Anesthesia Using Optimal Control

J. Almeida*   L.T. Paiva*   T. Mendonça†   P. Rocha*

Abstract

Optimal control theory has gained increasing importance in biomedical applications, *e.g.*, in the automatic administration of anesthetics during general anesthesia. One example of a monitored state is the depth of anesthesia, which is usually achieved by the joint administration of hypnotics and analgesics. This state is quantified by the bispectral index that varies between 97.7% and 0%. On the other hand, the amount of drug to be administered should be optimized both for patient health and for economical reasons. This motivates the use of optimal control in this field of application. In this contribution, a static state–feedback control law is considered. In order to determine a suitable feedback gain, a nonlinear optimal control problem is formulated and solved using direct methods. These methods have become increasingly useful when computing the numerical solution of an optimal control problem. Moreover, they are known to provide a very robust and general approach.

1 Introduction

Nowadays the optimal control theory has received increasing importance in biomedical applications [ISN+13, CL08, BPd14]. In particular, in the control of the joint administration of analgesics and hypnotics in the patients under general anesthesia these techniques are emerging. Standard physiological–based models are, in general, used to describe the relationship between the administered drug dose and the measurement of the corresponding effect – the depth of anesthesia (DoA). The bispectral index (BIS) [SC94] has a high sensitivity and specificity to measure the depth of anesthesia and will be used in this work. This index ranges between 97.7% (awake) and 0% (isoelectric electroencephalography), while an appropriate level for general anesthesia is between 40% and 60%. The most commonly used models to describe the effect of the propofol and remifentanil in the body human present a Wiener structure: a linear dynamics followed by a static nonlinearity. A three–compartment linear model combined with an effect compartment is used to explain the linear distribu-

tion of each drug, both propofol and remifentanil, in the different theoretical compartments of the human body [EFJ87]. This compartmental model is illustrated in Figure 1. The nonlinear concentration–response relationship for any ratio of the two drugs can be described by the generalized Hill's equation [RGL+08]. Since the high level of variability of the patient response and the high number of the model parameters, a reduced multiple input, single output (MISO) model has been introduced by [SWM14]. This new model has the advantage of involving a minimal number of parameters to describe the relationship between the drug profile and the effect concentration while keeping a good modelling accuracy [SLC+14]. This new model does not have a PK/PD structure but it maintains a Wiener structure with the Hill's equation as nonlinear part. Due to its advantages, this MISO Wiener model has already been used for the application of some controllers [dSWM12].

In this work, the problem of tracking the desired BIS target level of 50% is formulated as an optimal control problem (OCP) and will be solved by the use of direct methods [Bet01]. These methods have become increasingly useful when computing the numerical solution of the OCP. Moreover, they are known to provide a very robust and general approach [PF15]. The control of the drug effect is clinically important since overdosing or underdosing incur risks for the patients as well as due to economical reasons.

This paper is organized as follows. In Section 2, the DoA model is presented. This model is used to describe the relationship between the drug dose and the measured effect, the BIS. In Section 3, the optimal control problem formulation applied to the DoA model is described. The main results are shown in Section 4. The conclusions are drawn in Section 5.

2 Depth of anesthesia

During general anesthesia, it is necessary an adequate level of unconsciousness which is obtained by administration of hypnotics and analgesics. This level can be evaluated in terms of the bispectral index (BIS) [SC94]. The BIS values range from 97% (completely awake state) and 0% (isoleletric EEG) and it should be kept between 40% and 60% during a general anesthesia. In this work, the input signals are the dosage of propofol

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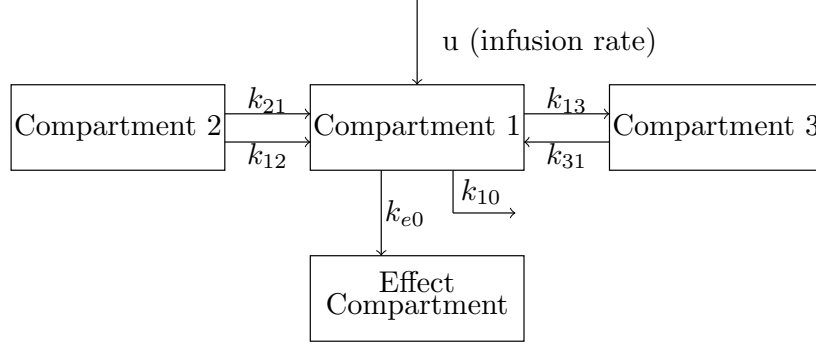†Universidade do Porto, Faculdade de Ciências, Rua do Campo Alegre s/n 4169–007 Porto PORTUGAL

Figure 1: Mammilary model for the pharmacokinetic for each drug.

and remifentanil, and the dynamic models for each drug are presented in subsection as well as the relationship between the effect concentration and the output signal – the BIS level.

2.1 DoA Model The effect of profofol and remifentanil in the human body is frequently modelled by a higher order pharmacokinetic/pharmacodynamic model. However, the model used in this work is the one proposed by [SWM14] since it has a minimal number of patient–dependent parameters.

2.1.1 Linear part A third–order continuous–time model is used for the linear dynamics of both propofol and remifentanil. The propofol linear dynamics is modelled by the following state–space representation:

$$\dot{\mathbf{x}}^p(t) = A^p(\alpha)\,\mathbf{x}^p(t) + B^p(\alpha)\,u^p(t)$$

$$(2.1) \quad = \begin{bmatrix} -10\alpha & 0 & 0 \\ 9\alpha & -9\alpha & 0 \\ 0 & \alpha & -\alpha \end{bmatrix} \mathbf{x}^p(t) + \begin{bmatrix} 10\alpha \\ 0 \\ 0 \end{bmatrix} u^p(t)$$

$$c_e^p(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \mathbf{x}^p(t)$$

where $c_e^p(s)$ is the effect concentration of propofol and $u^p(s)$ is the propofol infusion rate. Similarly, the remifentanil linear dynamics is modelled by

$$\dot{\mathbf{x}}^r(t) = A^r(\eta)\,\mathbf{x}^r(t) + B^r(\eta)\,u^r(t)$$

$$(2.2) \quad = \begin{bmatrix} -3\eta & 0 & 0 \\ 2\eta & -2\eta & 0 \\ 0 & \eta & -\eta \end{bmatrix} \mathbf{x}^r(t) + \begin{bmatrix} 3\eta \\ 0 \\ 0 \end{bmatrix} u^r(t)$$

$$c_e^r(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \mathbf{x}^r(t)$$

where $c_e^r(s)$ is the effect concentration of remifentanil and $u^p(s)$ is the remifentanil infusion rate. The parameters α and η are patient–dependent.

The joint representation of (2.1) and (2.2) becomes

$$\dot{\mathbf{x}}(t) = A(\alpha,\eta)\,\mathbf{x}(t) + B(\alpha,\eta)\,\mathbf{u}(t)$$

$$= \begin{bmatrix} A^p(\alpha) & \underline{0}_{3\times3} \\ \underline{0}_{3\times3} & A^r(\eta) \end{bmatrix} \mathbf{x}(t) + \begin{bmatrix} B_p & \underline{0}_{3\times1} \\ \underline{0}_{3\times1} & B_r \end{bmatrix} \mathbf{u}(t)$$

$$z(\mathbf{x}(t)) = \begin{bmatrix} 0 & 0 & \dfrac{m}{C_{50}^p} & 0 & 0 & \dfrac{1}{C_{50}^r} \end{bmatrix} \mathbf{x}(t)$$

where $\mathbf{x}(t) = [\mathbf{x}^p(t)\ \mathbf{x}^r(t)]^{\mathrm{T}}$ is the state and $\mathbf{u}(t) = [u^p(t)\ u^r(t)]^{\mathrm{T}}$ is the input.

2.1.2 Nonlinear part The nonlinear concentration–response relationship is described by the static Hill's equation [RGL+08]:

$$(2.3) \qquad h(\mathbf{x}(t)) = \frac{y_0}{1 + (z(\mathbf{x}(t)))^\gamma}$$

where γ is a patient–dependent parameter, y_0 is the baseline value, C_{50}^p and C_{50}^r are propofol and remifentanil normalizing constants, respectively, which were determined by offline identification over a real database [dSMW10]. The patient–dependent parameters to be identified are m and γ. This model has a total of four patient–dependent parameters

$$\theta = \begin{bmatrix} \alpha & \eta & m & \gamma \end{bmatrix}^{\mathrm{T}}.$$

3 Optimal control problem

In this section, the formulation of an optimal control problem (OCP) for the administration of both propofol and remifentanil is proposed for tracking a desired BIS level.

3.1 Problem formulation Let one consider the following optimal control problem with input and state constraints [Vin00]:

$$\min\ \mathrm{J}(\mathbf{x},\mathbf{u}) = \int_{t_0}^{t_f} \mathrm{L}\,(t,\mathbf{x}(t),\mathbf{u}(t))\,\mathrm{d}t$$
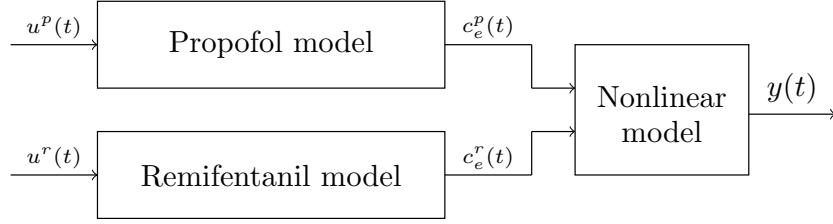
Figure 2: The MISO Wiener model for the DoA.

subject to

- the dynamic constraints

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

- the input constraints

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

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

3.1.1 Application to the DoA model In this section, the optimal control problem formulation is applied to the DoA model for tracking a reference level for the BIS.

The following OCP can be written for the DoA model:

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

subject to

- the dynamic constraints

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

- the input constraints

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

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 $Q = Q^{\mathrm{T}} \ge 0$ and $R > 0$, $\mathbf{x}(t) \in \mathbb{R}^6$ is the state, $\mathbf{u}(t) = [u^p(t) \; u^r(t)] \in \mathbb{R}^2$ is the input where $u^p(t)$ and $u^r(t)$ correspond to the drug profile of propofol and remifentanil, respectively. The outputs of the linear blocks in Figure 2 are given by $c_e^p(t) = x_3(t)$ and $c_e^r(t) = x_6(t)$. The target value $\mathbf{x}^e$ is obtained by the inversion of Hill's equation (2.3) for a desired BIS level of 50% and taking into account that the ratio between $x_3(t)$ and $x_6(t)$ is constant and equal to ρ, similar to what was done by [NMR14].

3.1.2 Solving the optimal control problem This OCP was 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 formulated in section 3.1.1 was 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 problem was solved in a computer with a Intel$^{\mathrm{TM}}$ Core$^{\copyright}$ i5 1.40 GHz.

4 Simulation results

To analyse the performance of the presented formulation, a bank $\mathcal{R}$ with real cases was used. The data was collected during eighteen breast surgeries where all patients were female (6 ASA I, 8 ASA II, 4 ASA III) with age: 54 ± 13 years, height: 160 ± 5 cm, and weight: 69 ± 18 kg.

The parameters of each patient

$$\theta_i = (\alpha_i, \ \eta_i, \ m_i, \ , \gamma_i) \,, \quad i = 1, \dots, 18$$

were identified by an offline method via the prediction error method [MAdS$^+$12]. In this paper, the second patient was chosen to illustrate the BIS signal when the optimal control input is computed and the parameter vector is

$$\theta_2 = (0.0874 \ \ 0.0670 \ \ 4.7014 \ \ 0.9365) \,.$$

The parameters C_{50}^p and C_{50}^r are 10 and 0.1, respectively. The matrices Q and R were empirically chosen as $\mathbb{I}_6$ and $R = \mathbb{I}_2$, respectively, and the ratio between the third and the sixth state is $\rho = 2$.

In order to analyse the performance of the input controllers obtained by the optimal control solver, a comparison against a positive control law (PCL) proposed in [NMR14] is made. This positive control law was designed in such a way that ensures 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. As expected, the optimal input corresponding to the proposed formulation is lower than the input signal obtained via PCL. This remark was confirmed by the results obtained for the total rate infusion: $\bar{u}^p = 1.7764$ $\bar{u}^r = 0.9944$ when using the OCP and $\bar{u}^p = 2.7054$, $\bar{u}^r = 1.3527$ when using the PCL.
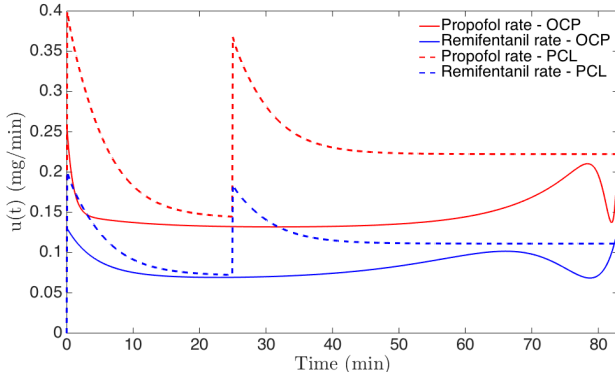
Figure 3: Comparison between the input signals obtained by the optimal control problem (solid lines) and the ones obtained by the positive control law (dashed lines).

Applying these inputs in the DoA model presented in section 2, the BIS was determined and depicted in Figure 4. As it can be seen, the BIS achieves the desired level of 50% and yet with a lower input when compared against the one given by PCL.
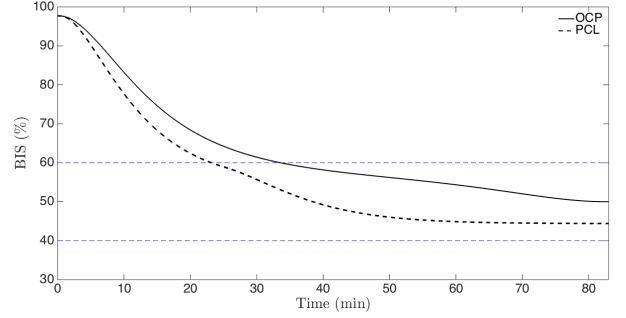
Figure 4: Comparison between the BIS signal obtained by the optimal control problem (solid line) and the one obtained by the positive control law (dashed line).

5   Conclusions

In this work, preliminary results were obtained using an optimal control problem to control the depth of anesthesia. The proposed problem was solved using the IPOPT solver which is based on direct methods. For that purpose, a reduced MISO Wiener to describe the patient's effect of a joint administration of hypnotics and analgesics was used. The results motivate the use of the closed–loop control methods that will be presented in a future work.

References

[Bet01]   John T. Betts. *Practical methods for optimal control using nonlinear programming*. SIAM, 2001.

[BPd14]   Biswas, M.H.A., Paiva, Luís Tiago, and de Pinho, MdR. A SEIR model for control of infectious diseases with constraints. *Mathematical Biosciences and Engineering*, 11:761–784, August 2014.

[CL08]   N. Cardoso and J.M. Lemos. Model predictive control of depth of anaesthesia: guidelines for controller configuration. 2008.

[dSMW10]   M.M. da Silva, T. Mendonça, and T. Wigren. Online nonlinear identification of the effect of drugs in anaesthesia using a minimal parameterization and BIS measurements. Technical Report 2010-008, Department of Information Technology, Uppsala University, March 2010.

[dSWM12]   M.M. da Silva, T. Wigren, and T. Mendonca. Exactly linearizing adaptive control of propofol and remifentanil using a reduced wiener model for the depth of anesthesia. In *Decision and Control (CDC), 2012 IEEE 51st Annual Conference on*, pages 368–373, Dec 2012.

[EFJ87]   Gepts E., Camu F., and Cockshott I. D.and Douglas E. J. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia & Analgesia*, 66(12):1256–1263, 1987.

[FKvW10] Paola Falugi, Eric Kerrigan, and Eugene van Wyk. *Imperial College London Optimal Control Software: User Guide*. Imperial College London London England, June 2010.

[ISN+13] Deepak D Ingole, DN Sonawane, Vihangkumar V Naik, Divyesh L Ginoya, and Vedika Patki. Implementation of model predictive control for closed loop control of anesthesia. In *Mobile Communication and Power Engineering*, volume 296, pages 242–248. Springer Berlin Heidelberg, 2013.

[MAdS+12] T. Mendonça, H. Alonso, M.M. da Silva, S. Esteves, and M. Seabra. Comparing different identification approaches for the depth of anesthesia using bis measurements system identification. In *16th IFAC Symposium on System identification*, pages 781–785, 2012.

[NMR14] F.N. Nogueira, T. Mendonça, and P. Rocha. Controlling the depth of anesthesia by a novel positive control strategy. *Computer Methods and Programs in Biomedicine*, 114(3):e87 – e97, 2014.

[Pai14] Luís Tiago Paiva. *Numerical Methods for Optimal Control and Model Predictive Control*. PhD thesis, University of Porto, 2014.

[PF15] Luís Tiago Paiva and Fernando A.C.C. Fontes. Adaptive time-mesh refinement in optimal control problems with constraints. *Discrete and Continuous Dynamical Systems*, 2015. (to appear).

[RGL+08] Agnes Rigouzzo, Laure Girault, Nicolas Louvet, Frederique Servin, Tom De-Smet, Veronique Piat, Robert Seeman, Isabelle Murat, and Isabelle Constant. The relationship between bispectral index and propofol during target-controlled infusion anesthesia: A comparative study between children and young adults. *Anesthesia & Analgesia*, 106(4), 2008.

[SC94] Jeffrey C. Sigl and Nassib G. Chamoun. An introduction to bispectral analysis for the electroencephalogram. *Journal of Clinical Monitoring*, 10(6):392–404, November 1994.

[SLC+14] M.M. Silva, J.M. Lemos, A. Coito, B.A. Costa, T. Wigren, and T. Mendonça. Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models. *Computer Methods and Programs in Biomedicine*, 113(1):23 – 36, 2014.

[SWM14] Margarida M. Silva, Torbjörn Wigren, and Teresa Mendonça. A reduced mimo wiener model for recursive identification of the depth of anesthesia. *International Journal of Adaptive Control and Signal Processing*, 28(12):1357–1371, 2014.

[Vin00] Richard B. Vinter. *Optimal Control*. Springer, 2000.

[WB06] Andreas Wächter and Lorenz T. Biegler. On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. *Mathematical Programming*, 106(1):25–57, March 2006.