A simple positive control law for the *rocuronium*-induced neuromuscular blockade level

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Abstract: In this paper a new simplified control scheme for the neuromuscular blockade level that only requires the knowledge of one model parameter is proposed. The control law is designed to track a desired target neuromuscular blockade level. Furthermore, the performance of this approach is compared with the results of a PI controller. The results were validated by simulations based on real data collected during surgeries.

Keywords: Anesthesia, compartmental models, positive control law, parameter identification.

1. INTRODUCTION

The growing interest of automatic control of the administration of anesthetics during surgery is an example of the impact of automatic control and system identification techniques on devices and applications in the field of biomedicine.

Among the different signals that are relevant to monitor a patient during general anesthesia is the neuromuscular blockade (NMB) level. This signal provides information about the patient's state regarding muscle paralysis, induced to allow the intubation and other clinical procedures. The degree of the neuromuscular blockade can be assessed by applying a train-of-four of supramaximal twitch stimulus to the hand peripheral nerve. The NMB level corresponds to the first response measured and varies between 100% (normal muscle activity) and 0% (full paralysis).

To achieve an adequate NMB level several muscle relaxants can be administered: in this paper we consider the case of *rocuronium*, since nowadays it is widely used in clinical pratice. The relation between a drug dose and its effect is usually modelled by pharmacokinetic/pharmacodynamic (PK/PD) model. The pharmacokinetics describes the time course of the drug concentration in the plasma whereas the pharmacodynamics studies the relation between the drug concentration and its actual effect, Haddad (2010). Although based on physiological principles, PK/PD models have the drawback of needing a large number of parameters to characterize a patient, which is a burden for real time control purposes.

In order to overcome this drawback a simplified class of models was proposed in Silva et al. (2012), which involves a minimal number of patient dependent parameters. More concretely, similar to what happens for PK/PD models, it possesses a Wiener structure, *i.e.*, it consists of the series connection of a linear dynamical part with a static nonlinearity; moreover it has one patient dependent parameter in the linear part of the model and another one in the nonlinear part. Thus, intuitively, one would think that controllers based on such models would have to depend on two parameters to be identified from the patient data.

Here, a simplified control law that only requires knowledge of the parameter associated to the nonlinear model is presented. This control law is based on the positive control law proposed in Bastin and Provost (2010) for compartmental systems, which has already been applied to control the NMB level, using the two model parameters Almeida et al. (2011b), Almeida et al. (2011a). In order to implement our law, an estimation procedure for the only parameter on which it depends is also implemented.

2. TWO-PARAMETER WIENER MODEL

As mentioned in the Introduction, the NMB model proposed in Silva et al. (2012) for the description of the effect of the muscle relaxant *rocuronium* in the human body consists of one linear model followed by a nonlinear static equation.

The linear dynamics is modeled by

$$C_e(s) = \frac{k_1 k_2 k_3 \alpha^2}{(s+k_1\alpha)(s+k_2\alpha)(s+k_3\alpha)} U(s)\,, \qquad (1)$$

where $C_e(s)$ is the Laplace transform of the effect concentration, $c_e(t)$; $U(s)$ is the Laplace transform of the input drug dose $u(t)$; k_1, k_2 and k_3 are constants that have been suitably determined in Silva et al. (2012) as $k_1 = 1$, $k_2 = 4$ and $k_3 = 10$, and $\alpha > 0$ is a patient dependent parameter.

The transfer function model (1) can be realized in state-space form as:

$$\begin{cases} \dot{x}(t) = \alpha A x(t) + \alpha B u(t) \\ c_e(t) = [0\ 0\ 1]\, x(t) \end{cases} \qquad (2)$$

where

$$A = \begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix} = \begin{bmatrix} -10 & 0 & 0 \\ 4 & -4 & 0 \\ 0 & 1 & -1 \end{bmatrix}, \qquad (3)$$

$$B = \begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} 10 \\ 0 \\ 0 \end{bmatrix}.$$

The relation between the effect concentration $c_e(t)$ and the actual drug effect is given by the following nonlinear static equation know as Hill's equation:

$$y(t) = \frac{100}{1 + (c_e(t))^{\gamma}} \qquad (4)$$

where γ is the second patient dependent parameter.

3. ONE-PARAMETER CONTROL LAW

The control law used in this section is based on the one introduced in Bastin and Provost (2010), which was already applied in Almeida et al. (2011b) and Almeida et al. (2011a) to control the NMB level by means of the administration of a different muscle relaxant, namely, *atracurium*. The difference is that, here, the controller is independent from the parameter α, which constitutes a simplification with respect to the previous approaches.

The control law proposed in Bastin and Provost (2010) was designed for single input compartmental systems, Haddad (2010),:

$$\begin{aligned} \dot{x} &= F\,x + G\,u \\ z &= C\,x \end{aligned} \qquad (5)$$

in order to stabilize the total system mass $M(x)$, corresponding to the sum of the components of the state x, to a set-point M^*, by means of a positive control input. Due to the presence of the positive constraint, it this law is nonlinear. More concretely, it assumes the form:

$$\begin{aligned} u(t) &= max\,(0, \tilde{u}(t)) \\ \tilde{u}(t) &= \frac{-\mathbf{1}\,F\,x(t) + \tilde{\lambda}\,(M\,(x(t)) - M^*)}{\mathbf{1}\,G} \end{aligned} \qquad (6)$$

where $\mathbf{1}$ is a row with the same length as the state vector, and $\tilde{\lambda} > 0$ is a design parameter.

It has been shown in Almeida et al. (2011b) that the linear part of the simplified model, given by equations (2) and (4), has a compartmental structure. Moreover, when (5) is applied to (2), not only $M(x)$ converges to M^*, but, more importantly, the state x itself converges to the equilibrium point,

$$x^* = \begin{bmatrix} M^*/3 \\ M^*/3 \\ M^*/3 \end{bmatrix}.$$

Taking into account that the effect concentration c_e coincides with the third state component, this means that c_e also converges to the set-point $c_e^* = M^*/3$.

Consequently, for the purpose of stabilizing the NMB level at a desired set-point y^*, it is enough to fix M^* in such a way that

$$\begin{aligned} y^* &= \frac{100}{1 + (c_e^*)^{\gamma}} = \frac{100}{1 + \left(\frac{M^*}{3}\right)^{\gamma}} \\ \Leftrightarrow M^* &= 3\left(\frac{100}{y^*} - 1\right)^{1/\gamma} \end{aligned} \qquad (7)$$

Now, due to the particular structure of the linear part (2) of the two-parameter Wiener model, the matrices $F = \alpha\,A$ and $G = \alpha\,B$. Replacing, this in the expression of $\tilde{u}$ given in (6) yields:

$$\tilde{u}(t) = \frac{-\mathbf{1}\alpha\,A\,x(t) + \tilde{\lambda}\,(M\,(x(t)) - M^*)}{\mathbf{1}\alpha\,B} \qquad (8)$$

or, equivalently,

$$\tilde{u}(t) = \frac{-\mathbf{1}\,A\,x(t) + \lambda\,(M\,(x(t)) - M^*)}{\mathbf{1}\,B} \qquad (9)$$

where $\lambda = \tilde{\lambda}/\alpha > 0$ may be regarded as a new design parameter. Based on (9), the following simplified control law is here considered:

$$\begin{aligned} u(t) &= max\,(0, \tilde{u}(t)) \\ \tilde{u}(t) &= \frac{-\mathbf{1}\,A\,x(t) + \lambda\,(M\,(x(t)) - M^*)}{\mathbf{1}\,B} \end{aligned} \qquad (10)$$

Although the dependence from α has been eliminated, the implementation of this controller still requires the knowledge of the parameter γ, in order to compute the value of M^* corresponding to the reference NMB level y^* by means of equation (7).

According to clinical practice, the controller action is not to be started immediately at the beginning of the anesthesia procedure, but only when the patient starts to recover from an initial *bolus* of the anaesthetic.

A simple method to identify the parameter γ based on the recovery instant is explained next.

Note that, γ appears in the Hill equation, as:

$$y(t) = \frac{100}{1 + (c_e(t))^{\gamma}} \qquad (11)$$

This parameter is identified when the controller action begins, which (as mentioned before) corresponds to the time instant of the recovery after the initial *bolus*. This time, t^*, can be computed on-line by the algorithm OLARD introduced in Silva et al. (2009). At this time instant, an estimate $\hat{\gamma}$ of γ is obtained solving the Hill equation for γ, yielding:

$$\hat{\gamma} = \frac{log\left(\frac{100}{y(t^*)} - 1\right)}{log\left(c_e(t^*)\right)} \tag{12}$$

Note that, while the value of $y(t^*)$ is available for measurement, the same does not apply to $c_e(t^*)$, which corresponds to the third component of the state in the linear part of *rocuronium* model. However, this can be overcome by the introduction of a state observer.

4. SIMULATION RESULTS

This section presents the results obtained by the application of the control scheme proposed here to control the NMB level via the administration of the muscle relaxant *rocuronium*. In order to simulate a patient, the two-parameter Wiener model was considered, with parameters taken from a model data base constructed by identifying $\theta = (\alpha, \gamma)$ for 50 real patients, using the Galeno platform [1] .

Here, to illustrate our procedure, in a first stage, the values for the parameters corresponding to the patient number 7 $\theta_7 = (0.0293, 1.4728)$ were used for patient simulation.

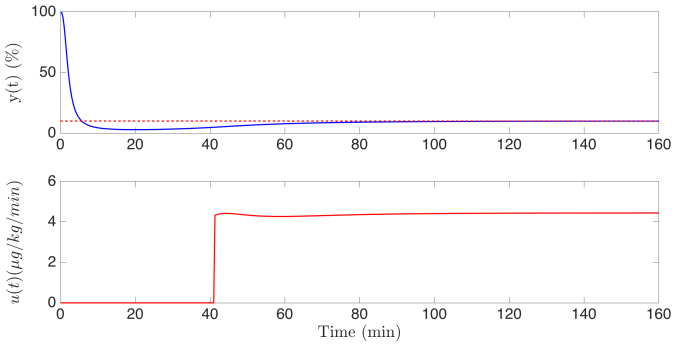

Fig. 1. NMB level evolution obtained with the application of the proposed control scheme applied at $t^* = 41.3\,min$.

The reference value for y^* was set to 10%, as usual in clinical practice. The value for the design parameter λ was taken as 6.5.

Moreover the identification of the parameter γ of the nonlinear model at the time instant $t^* = 41.3\,min$ is performed as mentioned in equation (8). The value of the estimated parameter is $\hat{\gamma} = 1.4755$. The proposed control scheme is applied from the time instant t^* on, considering the obtained estimates for the parameter γ.

[1] The Galeno platform was developed in the framework of the Portuguese funding agency (FCT) project Galeno, and incorporates several identification and control procedures for automation in the administration of anesthetics.

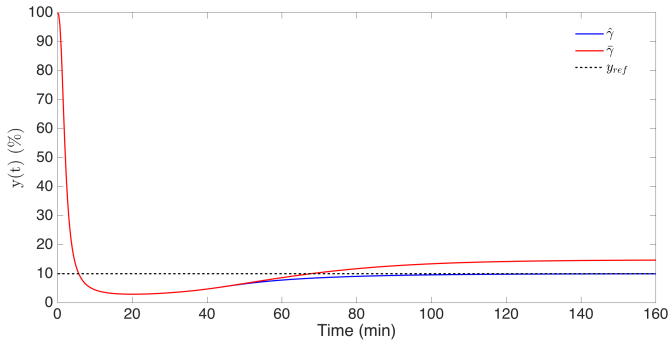

Fig. 2. NMB level evolution for scenarios (1) and (2) when the control law is applied at $t^* = 41.3\,min$.

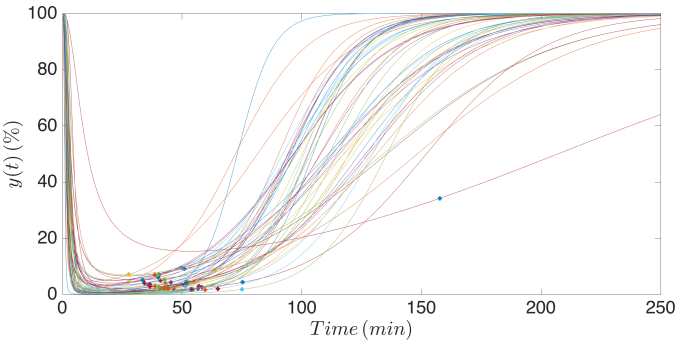

Fig. 3. NMB level evolution obtained after the administration of an initial *rocuronium bolus* to all patients of the Galeno database, and the corresponding t^*.

Fig. 1 shows the patient response and the input signal obtained by applying the described strategy.

To analyze the performance of the identification procedure, the controlled NMB response was obtained considering the following scenarios:

(1) The mean value for γ in the database, $\bar{\gamma} = 1.8499$, is taken;

(2) γ is taken to be given by the estimate $\hat{\gamma}$ obtained by our the identification procedure.

The corresponding results can be observed in Fig. 2. As it is possible to see, with our identification procedure the patient NMB tracks the desired level of 10%.

Fig. 3 illustrates the response of 50 real patients of the same initial *bolus* and the obtained t^*, showing the behaviour variability of the collected patient model data base for *rocuronium*.

In order to analyze the performance of the control scheme under a more realistic scenario, patient 7 was again considered and a noise signal was added to the real response. The noise signal was obtained from a typical NMB real case. For this scenario the value of $\hat{\gamma}$ is 1.3660. Fig. 4 shows the NMB level evolution and the input signal when noise is considered.

To further analyze the performance of the proposed simplified control scheme, we design a PI controller and compare the corresponding results.

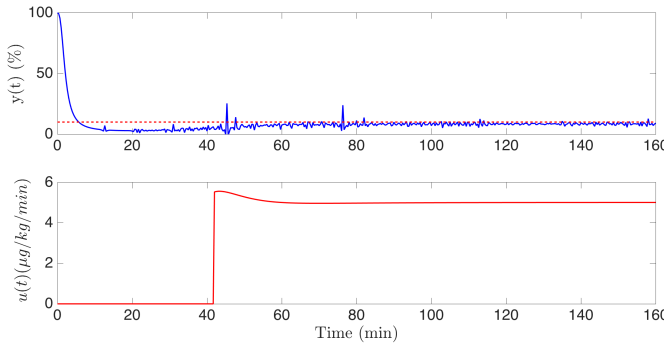

Fig. 4. NMB level evolution for patient 7 obtained with the application of the proposed control scheme at $t^* = 41.3\,min.$, when a typical NMB noise is added to the response signal

To design a PI we compute the characteristic polynomial of the closed loop transfer function of linear part of the system when

$$\tilde{u}(t) = -K_P c_e(t) - K_I \int_{t_0}^{t} c_e(\tau) d\tau.$$

For patient 7, this yields

$$H(s) = s^3 + 0.533s^2 + (0.0681 - 0.0018K_P)s + 0.0018(1 - K_I)$$

From a simple Routh-Hurwitz approach the following conditions for stability are derived:

$$K_I < 1$$
$$K_P < 38$$
$$K_I - 15K_P + 19.25 > 0$$

We chose $K_P = 1.2$, $K_I = 0.01$ and obtained a NMB response as shown in Fig. 5 for simulated patient number 7. Here the control input respects the positivity constraint (although no positivity requirement has been imposed).

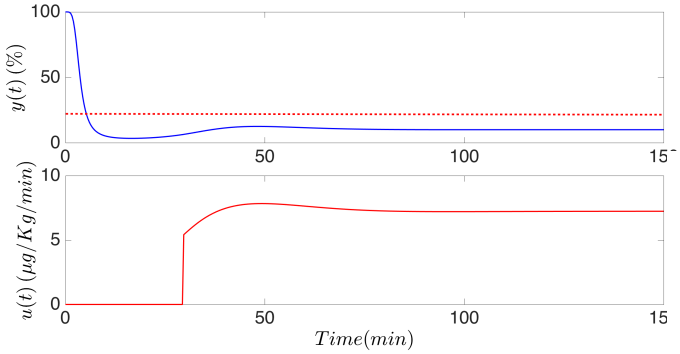

Fig. 5. Simulation of the NMB level response (upper plot) using the PI control input (bottom plot).

A global comparison of the simplified control scheme and the PI controller is presented in Fig. 7 for patients simulated using the available 50 models from the Galeno database.

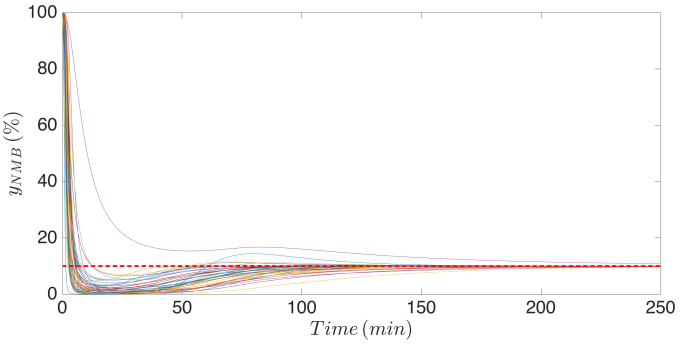

Fig. 6. Patient's NMB level response when the control input is determined by the simplified control scheme for all cases of the patient database.

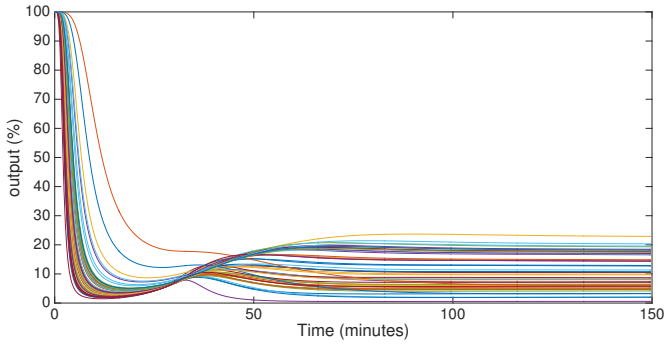

Fig. 7. Patient's NMB level response when the control input is determined by the PI controller for all cases of the patient database.

The trade-off between the amount of the drug and the NMB level offset for each controller strategy was evaluated considering the following cost functional:

$$J = \frac{1}{T} \int_{t=0}^{t=T} \left(\left(y_{NMB}^{ref} - y_{NMB}(t) \right)^2 + \kappa u^2(t) \right) dt\,, \tag{13}$$

where the gain κ was chosen to be equal to 1. The cost functional is presented in Fig. 8, which allows to reinforce the superior performance of our method.

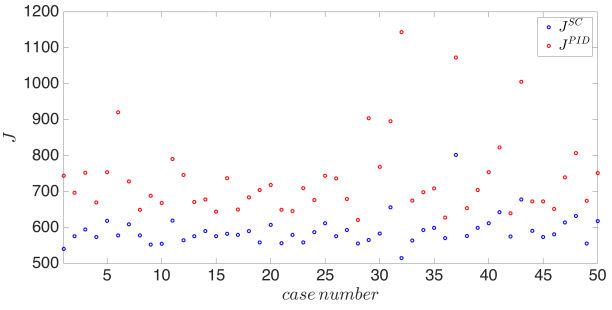

Fig. 8. Value of the cost functional evaluated for all the patient from the data base, blue: simple positive control law; red: PI control.

In order to further compare the performance of the simplified controller and the PI controller simulations were carried out for different values of the respective tunning parameters and the value of the cost function was computed for each case. For the simplified control the values of λ were taken as $\lambda = 0.2$, $\lambda = 2$, $\lambda = 6.5$, $\lambda = 10$ and $\lambda = 20$. And for the PI controller the integral gains were set at $K_I = 0.001$, $K_I = 0.005$,$K_I = 0.01$, $K_I = 0.05$ and $K_I = 0.1$.

Figure 9 and Figure 10 show the average response signal of the database models when the input is determined by the simplified controller and by the PI controller for differente values of λ and K_I, respectively.

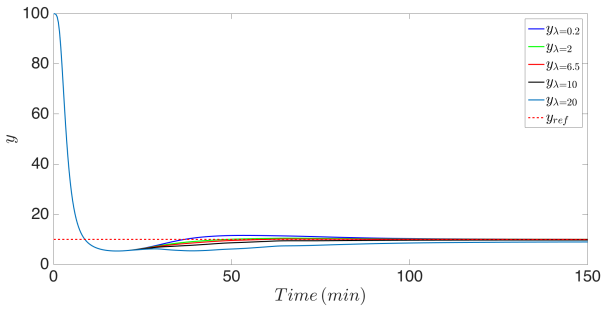

Fig. 9. Average NMB level response when the control input is determined by the simplified controller with different values for the parameter λ.

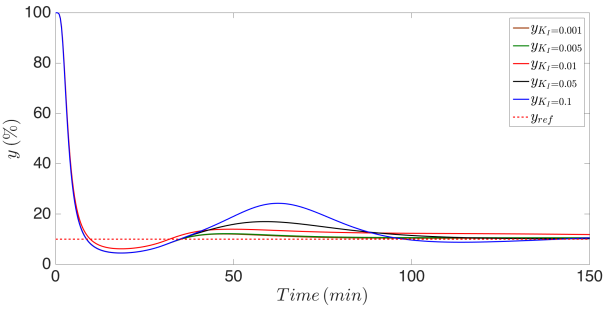

Fig. 10. Average NMB level response when the control input is determined by the PI controller with different values for the gain K_I.

The values of the cost functional were computed for each signal presented in Figures 9 and 10 and are presented in the following tables.

Table 1. Values of the cost functional for the simplified controller with different values of λ.

λ	0.2	2	6.5	10	20
J	147.0721	147.6503	149.2512	156.2092	184.2512

Table 2. Values of the cost functional for the PI controller with different values of K_I.

K_I	0.001	0.005	0.01	0.05	0.1
J	217.2177	215.9266	234.0704	226. 0829	248.0578

As it is possible to see in Table 1, the values of the cost functional are always smaller than the values of the cost functional computed for the PI controller case.

5. CONCLUSIONS

In this paper a simplified control scheme for the neuromuscular blockade that only requires the knowledge of the parameter of the nonlinear part of the model is considered. The control law is designed to control the amount of the muscle relaxant *rocuronium* that should be administered during a general anesthesia to track a desired NMB level of 10%. The results were validated by simulations based on real collected data and then compared with a more commonly used controller, a PI controller. The obtained results show that both control approach present the desired behaviour and the NMB level achieves the desired value. The PI controller seems to have a worse performance with respect to a cost function that takes into account both the tracking error and the amount of used drug. However, the simplified control scheme requires prior use of an online parameter identification procedure. Therefore further investigation is required in order to compare this identification effort with the one of tuning the PI.

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