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Optimal time for constant drug infusion initialization in neuromuscular blockade control

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***Abstract*—This paper presents a control strategy for neuromuscular blockade (NMB) level, in order to determine the optimal time to initialize the administration of the muscle relaxant rocuronium by means of the continuous infusion of a constant dose. The constant value of muscle relaxant for a particular patient undergoing general anesthesia is computed in order to guarantee that the steady-state value of neuromuscular blockade level is the desired reference value. In order to apply this open-loop control strategy, the patient's NMB response to rocuronium is assumed to be modeled by a recently proposed parameter parsimonious model.**

I. Introduction

As is well-known, general anesthesia is obtained by means of the administration of three different kinds of drug, an opioid, an analgesic ans a muscle relaxant, in order to achieve analgesia, unconsciousness, and paralysis in the patient during surgery [1], [2], [3].

The automatic control of drug delivery in anesthesia and in particular the control of muscle relaxant administration, has deserved great attention in last years [2], [4], [5].

The administration of a muscle relaxant for surgery purposes essentially consists of two phases: in a first stage, a considerable quantity of drug (*bolus*) is injected in order to quickly decrease muscle activity; then when muscle relaxant is administered in order to maintain the desired level of neuromuscular blockade (NMB) during the surgery, which is usually set to 10% (where 100% corresponds to full activity and 0% corresponds to full paralysis).

Several methods have been proposed in the literature for the automatic control of the infusion of muscle relaxants [6], [7], [8], [9], [10]. A particularly simple, but non the less efficient, approach is TCI (Target Control Infusion) [1], [11], [12], which consists in administering a piecewise constant drug dose, suitably computed from the desired reference (target) level of neuromuscular blockade.

Following this approach, in this paper an analytical study is made of the optimal time to initiate the constant drug infusion in order to minimize the reference tracking error for the neuromuscular blockade level. The obtained results are illustrated by means of simulations, based a bank of identified real patient models.

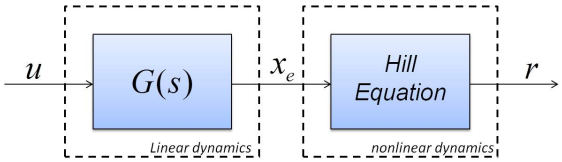


Figure 1: Structure of the mode for NMB level

II. Neuromuscular blockade model

The study presented in this paper focuses on the muscle relaxant rocuronium, but similar results can easily obtained for the drugs, such as, for instance, atracurium. The model adapted here to describe the relationship between the administered dose of rocuronium and the corresponding NMB level is the one proposed in [13].

This model consists of a linear part, than describes the drug effect concentration, followed by a nonlinear part, the Hill equation, that relates the effect concentration with the actual NMB level, as is depicted in 1.

In This figure, u [$\mu g.Kg^{-1}.min^{-1}$] denotes the drug dose, x_e [$\mu g.ml^{-1}$] is the effect concentration, and r [%] denotes the NMB level. The transfer function $G(s)$ is given by:

$$G(s) = \frac{k_1 k_2 k_3 \alpha^3}{(s + k_1\alpha)(s + k_2\alpha)(s + k_3\alpha)} \tag{1}$$

where k_1, k_2 e k_3 and α are positive patient dependent parameters. However, based an the previous knowledge of the patient population, good modeling results are obtained for fixed values of k_1, k_2 and k_3, namely $k_1 = 1$, $k_2 = 4$ and $k_3 = 10$, [10], [13]. This leaves α as only parameter to be identified in the linear part of the process dynamics, which can, for instance, be done during the initial phase of *bolus* administration, before initializing the controlled drug infusion. As for the nonlinear dynamics, the Hill equation is given by

$$r(t) = \frac{r_0}{1 + \left(\frac{x_e(t)}{EC_{50}}\right)^{\gamma}} \tag{2}$$

where $r_0 = 100$ is the NMB level by a zero value of the drug concentration, γ is a patient dependent parameter (than

can be identified as α), finally, EC_{50} [$\mu g.ml^{-1}$] is the drug effect concentration corresponding to a NMB of 50%. For rocuronium the value of EC_{50} can be taken equal to 1, independently of the patient under consideration.

III. Control strategy

The first step to design the control strategy proposed here is to invert the Hill equation, i. e., given a desired target value r^* for the NMB level, one computes the corresponding effect concentration of rocuronium

$$x_e^* = \left(\frac{100}{r^*} - 1\right)^{1/\gamma}. \tag{3}$$

In a second stage, a constant value u^* for the drug infusion is computed in order to guarantee that the steady-state value of $x_e(t)$ is x_e^*. This procedure is possible since the poles of the transfer function $G(s)$, $-k_1\alpha$, $-k_2\alpha$, $-k_3\alpha$, are all negative, which ensures the the stability of the process. Noting that a constant drug dose u^* corresponds to a step of amplitude u^*, it follows from the final value theorem [14] that

$$\lim_{t\to\infty} x_e(t) = G(0)u^*, \tag{4}$$

where $G(0)$ is the steady-state gain of G.

In this way, in order to achieve the desired target value x_e^*, the value of u^* must be given by

$$u^* = \frac{x_e^*}{G(0)}. \tag{5}$$

As mentioned earlier, due to clinical constraints infusion, the continuous drug infusion only starts a certain time after the initial *bolus* is administered, say at a certain time instant T. Since the transient phase after the beginning of the constant drug dose administration highly depends initialization time T, several attempts to optimize this value were carried out. The OLARD (OnLine tuned Algorithm for Recovery Detection) algorithm [15] was developed in order to identify the recovery time instant from the real noisy of NMB signal. Since then this value has been considered as a reference time for beginning the control action. Here the optimal vale of T is computed in order to minimize the global quadratic reference tracking error for the effect concentration:

$$E = \int_0^\infty |x_e(t) - x_e^*|^2 dt. \tag{6}$$

Note that this guarantees the minimization of the reference tracking error for the NMB level. More concretely, the administration of the typical rocuronium *bolus* of 500 $\mu g.Kg^{-1}$ is followed by the constant infusion of $u^* = x_e^*/G(0)$ $\mu g.Kg^{-1}$, starting at time T corresponds to setting the system input to:

$$u_T(t) = 500\delta(t) + u^* 1(t-T) \tag{7}$$

where $\delta(t)$ is the Dirac delta function and $1(t-T)$ denotes the unit step starting at time T. This produces sn output

$$x_e^T = 500 x_e^{imp}(t) + u^* x_e^{step}(t-T) \tag{8}$$

where $x_e^{imp}(t)$ and $x_e^{step}(t-T)$ are the impulse and delayed step responses of G, respectively given by:

$$x_e^{imp}(t) = \left(\frac{40\alpha}{27}e^{-\alpha t} - \frac{40\alpha}{18}e^{-4\alpha t} + \frac{40\alpha}{54}e^{-10\alpha t}\right) \tag{9}$$

$$x_e^{step}(t-T) = \begin{cases} 0 & , \quad t < T \\ \dfrac{40}{27}e^{-\alpha(t-T)} + \dfrac{40}{72}e^{-4\alpha(t-T)} & \\ \quad - \dfrac{40}{540}e^{-10\alpha(t-T)} + 1 & , \quad t \geq T \end{cases} \tag{10}$$

The corresponding error E is then given by:

$$\begin{aligned} E_\alpha(T) = &\int_0^T |x_e^{imp}(t) - u^*|^2 dt \\ &+ \int_T^\infty |(x_e^{imp}(t) + x_e^{step}(t-T)) - u^*|^2 d \end{aligned} \tag{11}$$

In order determine the minimum of $E(T)$, first the critical points are computed by means of the equation

$$\frac{d}{dT}E(T) = 0. \tag{12}$$

It can be shown by means that of simple but cumbersome computations that

$$\begin{aligned} \frac{d}{dT}E(T) = &\frac{56366280000\alpha}{280600848} u * e^{-10\alpha T} + \frac{10000\alpha}{63} u * e^{-4\alpha T} \\ &- \frac{86400000\alpha}{72171} u * e^{-\alpha T} + (u*)^2. \end{aligned} \tag{13}$$

Thus (12) is equivalent to

$$\begin{aligned} &\left(\frac{30496000\alpha}{41580}u*\right)x^{10} + \left(\frac{150000\alpha}{126}u*\right)x^4 \\ &- \left(\frac{160000\alpha}{297}u*\right)x + (u*)^2 = 0 \end{aligned} \tag{14}$$

where $x = e^{-\alpha T}$.

Thus the critical points $T_{critical}$ are given by

$$T_{critical} = \frac{-ln(\xi)}{\alpha} \tag{15}$$

where ξ are roots of (14). After these critical points are identified, are chooses among them the are that corresponds to a global minimum for $E(T)$.

For models where the optimal time cannot be determined, due to the fact that the roots of (14) are not real and positive, the time to initiate the continuous infusion is computed as follows. The "problematic" model is approximated by a "nonproblematic" one and the optimal time determined for the approximate model is used. The model approximation is based

on the Vinnicombe distance between two transfer functions, $G_1(s)$ and $G_2(s)$, $\delta_v(G_1, G_2)$, which is given by, [16]:

$$\delta_v(G_1, G_2) = ||(I + G_2G_2^*)^{-1/2}(G_2 - G_1)(I + G_1G_1^*)||_\infty \quad (16)$$

where $G_i^*(s) = G_i(-s)$, $i = 1, 2$ and takes values between $0 \leq \delta_v(G_1, G_2) \leq 1$ (where $\delta_v(G_1, G_2) = 0$ corresponds the same models and $\delta_v(G_1, G_2) = 1$ corresponds to very different models).

IV. Simulation Study

With the purpose of testing control strategy previously described, simulation studies have been carried out using database $\mathcal{R}$ containing 50 models identified from real patients subject to general anesthesia where the administered muscle relaxant was rocuronium.

The control strategy proposed in this paper is schematically represented in Figure 2, and can be described as follows:

- **Patient simulation:** a model from the bank $\mathcal{R}$ is chosen to the simulate the real patient's dynamics. At time $t = 0$ a typical *bolus* is administered to the patient ($u_\delta = 500\ \mu g.Kg^{-1}$);
- **Determination of the constant drug dose:** the constant dose of rocuronium, u^*, to be administered to the chosen patient is calculated from the desired reference level of neuromuscular blockade r^*;
- **Determination of the optimal initialization time T**.

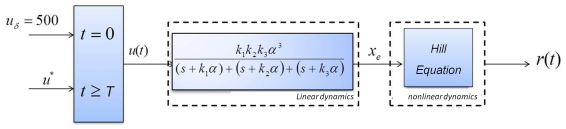
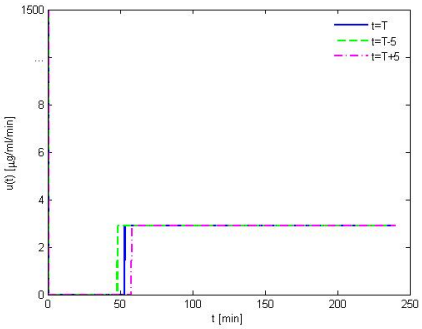


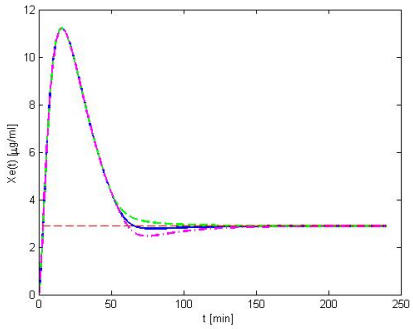
Figure 2: Structure of the control system

The first simulations to be carried out are simulations of the NMB signal for 3 patients in the database $\mathcal{R}$, patient 1 (P_1) and the patient 26 (P_{26}), for which it was possible to determine the optimal times (T_1 and T_{26}) and the patient 11 (P_{11}) where the initialization time T_{11}^* was obtained by the previously described approximation procedure. The results obtained for the times T_1, T_{26} and T_{11}^* are compared to the ones obtained for the same patients when an uncertainty, $\triangle t$, is associated to the respective times, yielding initialization times $t_1 = T_1 \pm \triangle t$, $t_{26} = T_{26} \pm \triangle t$ and $t_{11} = T_{11}^* \pm \triangle t$, respectively. In a second stage, the results obtained for the times T_1, T_{26} and T_{11}^* are compared with the ones obtained for the same patients when the initialization time is obtained by the OLARD algorithm .

The figures below show the dose drug profile administered $u(t)$, the effect concentration response $x_e(t)$ and the NMB response $r(t)$ of each patient. As mentioned before, the desired NMB level is taken to be 10%, $r^* = 10$.

Figures 3 and 4 shows the behavior of the control system for P_1 and P_{26}, respectively, during 240 minutes, where, after the administration of an initial *bolus* of rocuronium of 500 $\mu g.Kg^{-1}$, is initialized the continuous infusion of rocuronium from different time instants t: $t = T\ [min]$ (optimal time) and $t = T \pm \triangle t\ [min]$, $\triangle t = 5$. The optimal time, given by (14) and (15), for (P_1) and (P_{26}) was, respectively, $T_1 = 52,4071\ [min]$ and ${}_{26}T = 30,1375\ [min]$. From the analysis of Figures 3a and 4a is able to see that for the same initial *bolus* the constant drug dose given by TCI method is different for each patient. The TCI dose value , u^*, computed for P_1 is $2,8856\ \mu K.Kg^{-1}$ and for P_{26} is $5,6430\ \mu K.Kg^{-1}$. Observing the graphs of the effect concentration response shown in Figures 3b and 4b and the





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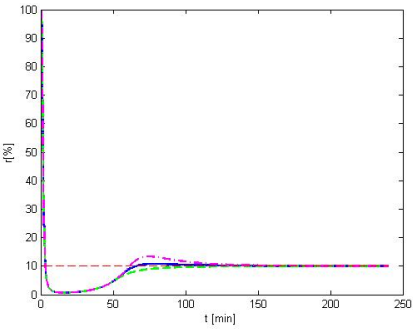
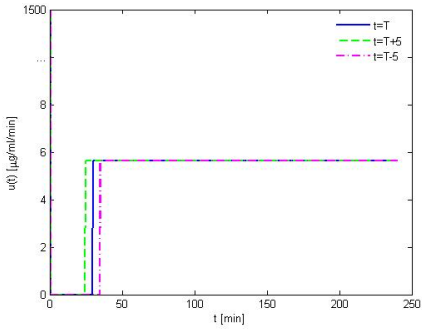
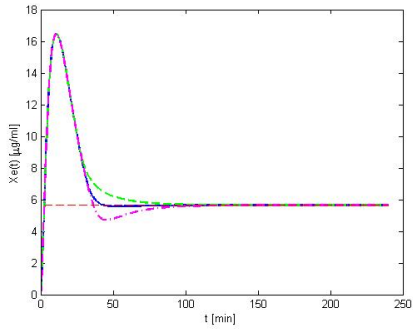


(c)

Figure 3: Simulations for the patient P_1 where the constant dose u^* is administered for $t = T\ [min]$ (optimal time) and $t = T \pm \triangle t\ [min]$ (where $\triangle t = 5$). (a) Administered drug doses profile. (b) Response of the effect concentration. (c) Response of the neuromuscular blockade level.





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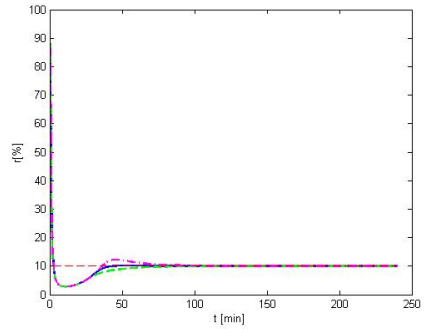
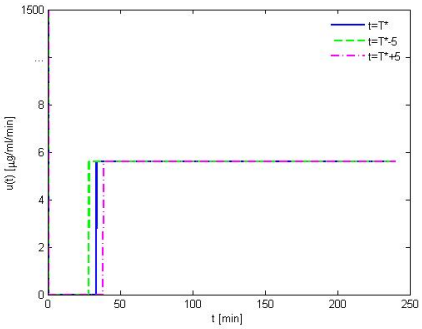
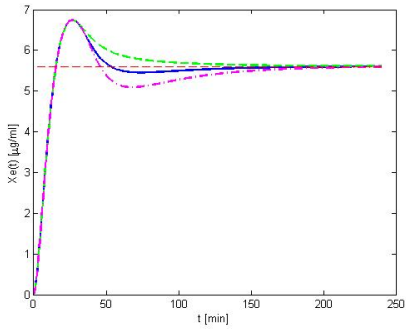


(c)

Figure 4: Simulations for the patient P_{26} where the constant dose u^* is administered from $t = T_{26}\ [min]$ (optimal time) and from $t = T \pm \triangle t\ [min]$ (where $\triangle t = 5$). (a) Administered drug doses profile. (b) Response of the effect concentration. (c) Response of the neuromuscular blockade level.





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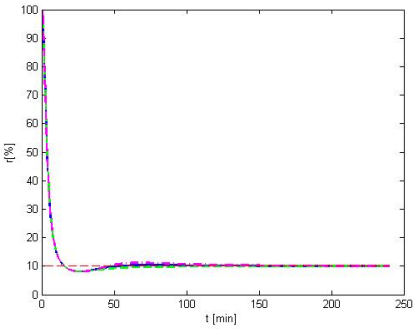
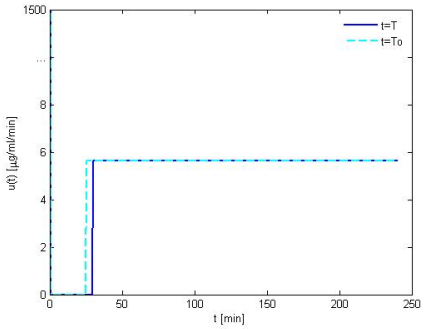


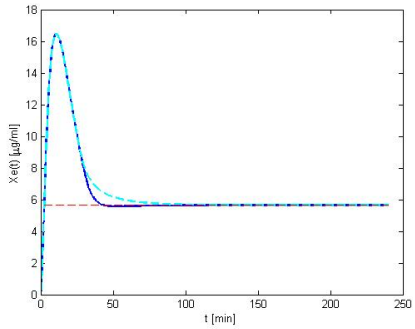
(c)

Figure 5: Simulations for the patient P_{11} where the constant dose u^* is administered from $t = T_{11} * \ [min]$ (approximate optimal time) and from $t = T_{11} \pm \triangle t\ [min]$ (where $\triangle t = 5$). (a) Administered drug doses profile. (b) Response of the effect concentration. (c) Response of the neuromuscular blockade level.

graphs of the NMB response shown in Figures 3c and 4c it is to see that the errors between the actual effect concentration and the reference effect concentration, and between the actual NMB and the reference NMB when the continuous infusion rocuronium is initialized in the respective optimal time instant (blue graphics) is indeed minimal.

Figure 5 shows the behavior of the control system for P_{11} during 240 minutes, where, after the administration of an initial *bolus* of rocuronium of 500 $\mu g.Kg^{-1}$ the continuous infusion of rocuronium is initialized from different time instants t: $t = T_{11}^*\ [min]$ (blue graphic) and $t = T_{11}^* \pm \triangle t\ [min]$, $\triangle t = 5$. The time T_i^*, computed as the optimal time for the closest model to P_{11} (according to the Vinnicombe metric) for which such time is possible to determine, and the constant drug dose u^*, obtained by the TCI method for P_{11}, are, respectively, $T_{11}^* = 34,09\ min$ and $u^* = 5,6064\ \mu g.Kg^{-1}$. From the analysis of the plots in Figure 5c are able to see that the time T_{11}^* is a good approximation of the optimal time T, once when associated an uncertainty of only 5 minutes is considered, the error between the real NMB level and the desired reference of the NMB level is greater.





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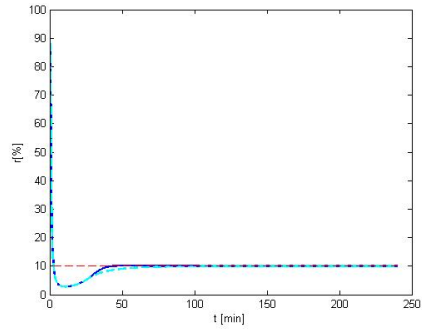
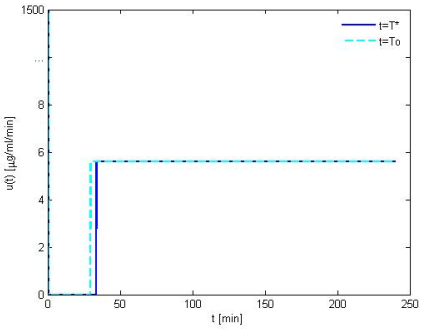
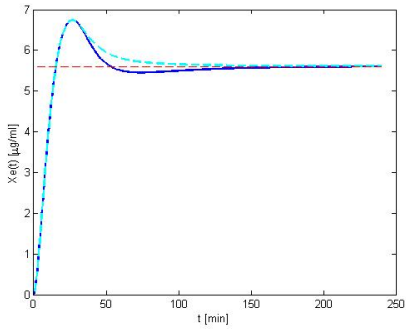


(c)

Figure 6: Simulations for the patient P_{26} where the constant dose u^* is administered from instant $t = T_{26}\ [min]$ (optimal time) and from instant $t = T_0\ [min]$ (given by the OLARD algorithm). (a) Administered drug doses profile. (b) Response of the effect concentration. (c) Response of the neuromuscular blockade level.





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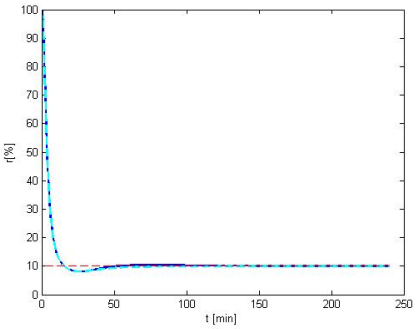

(c)

Figure 7: Simulations for the patient P_{11} where the constant dose u^* is administered from instant $t = T_{11}*\ [min]$ (approximate optimal time) and $t = T_0\ [min]$ (time obtained by the OLARD algorithm). (a) Administered drug doses profile. (b) Response of the effect concentration. (c) Response of the neuromuscular blockade level.

Figure 6 shows the behavior of the control system for the P_{26} during 240 minutes when the constant drug dose is administered from our optimal time $T_{26} = 30,1375min$ and from the OLARD time $T_0 = 25,7min$. Comparing the plots of the neuromuscular blockade response shown in Figure 6c it is possible to see that, when the constant dose of the rocuronium is administered from the optimal time T_{26}, the error is smaller.

Figure 7 allows to compare the behavior of the control system for the P_{11} during 240 minutes when the constant drug dose is administered from the time $T_{11}* = 34,09min$ and from the OLARD time $T_O = 30min$. Analyzing the plots of the neuromuscular blockade response shown in Figure 7c it is possible to see that the error between the real level of the NMB and the desired reference level is practically the same, although the error is slightly larger when the continuous infusion of rocuronium is initialized at time $T_{11}*$.

V. Conclusion

This paper presents a new strategy for the control of the administration of the muscle relaxant rocuronium to a

patient during surgical practice to reach and maintain a desired reference of the neuromuscular blockade level. Although the performed study focuses on the muscle relaxant rocuronium, similar results can easily obtained for other drugs, such as, for instance, atracurium.

The proposed control strategy is based on a TCI approach (with constant target) combined with the determination of the optimal time to initiate the constant drug infusion after the administration os a *bolus*, having as criterion the minimization of the error effect concentration response and the desired target effect concentration level. This in turn has a consequence the minimization of the reference tracking error for the NMB level.

The simulations performed for the optimal time confirmed that the error between real level of the neuromuscular blockade and the desired reference level of the neuromuscular blockade is, indeed, the minimum error, when the initialization time is taken to be the optimal one.

The optimal time T and T^* obtained by the control strategy described in this article yields better results than the time T_0 obtained by the OLARD algorithm.

VI. ACKNOWLEDGMENT

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