Pole placement based on model identification for automatic delivery of Rocuronium

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***Abstract*— This paper presents a dynamic pole placement procedure, based on a static state feedback to improve the performance of target control infusion (TCI) in the control of the neuromuscular blockade (NMB) level by administration of the muscular relaxant *rocuronium*, with particular emphasis on the reduction of both the average administered dose and the settling time. To apply this procedure, a suitable identification method for the patient model parameters, based on the model structure, is used. The resulting individualized control method of drug dosage for continuous infusion was validated by simulations based on real data collected during surgeries.**

I. INTRODUCTION

The design of suitable controllers for automated drug delivery during general anaesthesia has been deserving great attention over the past years [1] [2] [3] [4].

One of the different signals that are relevant for monitoring a patient subject to general anaesthesia is the neuromuscular blockade level. This is a measure of the degree of the patientâs muscle paralysis, which is induced by means of the administration of muscle relaxants in order to facilitate intubation and other surgical procedures.

In this paper we propose a simple control scheme for the automatic administration of the muscle relaxant *rocuronium* with the aim of tracking a desired neuromuscular (NMB) level during general anaesthesia.

As is well-known, the models relating the infusion dose of this drug with the NMB level usually have a Wiener structure, i.e., they consist of the series connection of a linear dynamic model with a static non-linearity (the Hill equation) [5].

The most straightforward way to determine the dose corresponding to a desired NMB level is by model inversion. However, this method may be inefficient in what concerns the tracking performance and/or the total amount of used drug [6] [7].

Here, a pole-placement procedure is applied, based on state-space design, prior to the system inversion. It turns out that a suitable choice of poles can decrease the total amount of administered drug while improving the tracking performance.

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Since we are aiming at personalized procedures, before applying our controller we first need to obtain a model for the patient under consideration.

For this purpose we consider the parameter parsimonious model (PPM) for the action of *rocuronium* on the NMB level introduced in [8] and apply the method for the identification of the patient parameters proposed in [9]. This method takes advantage of the structure of parameter parsimonious model as well as from the usual clinical procedure that consists in the administration of a drug bolus prior to continuous infusion. More concretely, the model parameters are identified from the patient's response to the initial bolus; the control scheme is initiated after the parameter identification is completed.

This paper is organized as follows. In section 2 the PPM is presented and the method for identifying its parameters proposed in [9] and applied to 10 patients selected from an extended database of 60 real cases [10]. In section 3 we present our control scheme, Section 4 presents several simulations using the parameters identified for real patients along with the discussion of the obtained results. Conclusions are presented in section 5.

II. *ROCURONIUM* MODEL: STRUCTURE AND PARAMETER IDENTIFICATION

The model for the effect of *rocuronium* on the neuromuscular blockade proposed in [4] consists of a series connection of two parts: one part with linear dynamics which relates the drug dosage, *u*, to the drug effect concentration, C_e and another part consisting of a static non linearity relating the effect concentration, C_e with the level of NMB, *R*, as shown in Figure 1.

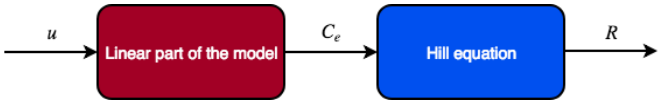

Fig. 1. Model for the effect of *rocuronium* on the NMB

The linear dynamics of the model corresponds to the transfer function:

$$G(s) = \frac{40\alpha^3}{(s+\alpha)(s+4\alpha)(s+10\alpha)} \quad (1)$$

This transfer function has a single parameter α which is patient dependent [4].

The static non linearity that relates the effect concentration, C_e and the level of neuromuscular blockade, R, is

represented by the Hill equation, [11]:

$$R = \frac{r_0}{1 + (\frac{C_e}{EC_{50}})^{\gamma}} \tag{2}$$

where r_0 is the effect (NMB level) at zero drug concentration, that is, the value of the NMB level when there is no concentration of muscle relaxant in the patient's body, and, according to the literature, assumes the value 100% (corresponding to total muscle activity); γ is a patient dependent parameter; and EC_{50} is the drug effect concentration corresponding to half of its effect (in this case, the *rocuronium* effect concentration that corresponds to an NMB level of 50%). Although this latter parameter is patient (and drug) dependent for *rocuronium*, in the model proposed in [11] it is given a fixed value, namely, $EC_{50} = 1$.

In order to identify the parameters α and γ we take advantage of the usual clinical procedure that consists in administrating an initial bolus of 600 $\mu g/kg$ of *rocuronium*, and only later start the automatically controlled drug administration by continuous infusion. Combined with the special structure of our model, this allows to estimate the patient parameters in the initial phase, from the bolus response. Such parameters will then later be used in the design of our control scheme.

More concretely, notice that from the Hill equation (2) one can conclude that, at the instant $t = T_{50}$ for which the NMB level $R(t)$ equals 50%, the value of the effect concentration $C_e(t)$ is:

$$C_e((T_{50})) = 1 \tag{3}$$

Since, as can be seen from (1), the transfer function from the *rocuronium* dose to the effect concentration C_e depends from α in a simple way, it is easy to compute the analytic expression of the corresponding response to the initial bolus as a time function depending from the parameter α. Denoting this response by $C_e^{\alpha}(t)$ and replacing $t = T_{50}$ (which has a known value), one obtains an equation

$$C_e^{\alpha}(T_{50})) = 1 \tag{4}$$

that can be numerically solved for α, yielding an estimate $\hat{\alpha}$ for this patient parameter, and hence for the linear part of the model, [9].

Moreover, it also gives an estimate $\hat{C}_e(t)$ of the bolus response of the effect concentration by putting $\alpha = \hat{\alpha}$ in (6).

The following table shows the real and the estimated values of α for 10 random patients of the database mentioned in the Introduction. As one can see, the estimation absolute error is less than 10^{-4}.

Now, in order to estimate the value of γ, for each patient, we register the instant T^* where the NMB bolus response attains the target value for the first time. According to clinical practice, this target value is equal to 10%. Thus, by Hill's equation:

$$10 = \frac{100}{1 + (\hat{C}_e(T^*))^{\gamma}} \tag{5}$$

and an estimate $\hat{\gamma}$ for γ can be obtained by solving this equation w. r. to γ.

TABLE I

REAL AND ESTIMATED VALUES OF α

Patient$_i$	α	$\hat{\alpha}$
1	0.0365	0.0365
2	0.0528	0.0528
3	0.0293	0.0293
4	0.0324	0.0324
5	0.0341	0.0341
6	0.0290	0.0288
7	0.0290	0.0290
8	0.0308	0.0311
9	0.0282	0.0281
10	0.0357	0.0356

The following table shows the real and the estimated values of α for the 10 patients of the database mentioned in the Introduction.

TABLE II

REAL AND ESTIMATED VALUES OF γ

Patient$_i$	γ	$\hat{\gamma}$
1	2.0733	2.0632
2	2.5362	2.5259
3	1.4728	1.4718
4	2.0473	2.0404
5	2.1193	2.1137
6	1.3419	1.3411
7	1.6105	1.3411
8	1.9499	1.9471
9	1.2615	1.2606
10	1.9576	1.9527

In this way, at time $t = T^*$, we have estimates ($\hat{\alpha}$, $\hat{\gamma}$) for the patient parameters. The corresponding model consists of the series connection of the transfer function

$$\hat{G}(s) = \frac{40\hat{\alpha}^3}{(s + \hat{\alpha})(s + 4\hat{\alpha})(s + 10\hat{\alpha})} \tag{6}$$

relating the drug dose *u* with the effect concentration C_e, with the Hill equation

$$R(t) = \frac{100}{1 + (C_e(t))^{\hat{\gamma}}} \tag{7}$$

A state space realization of $\hat{G}(s)$ in the canonical controllable form is given by:

$$\underbrace{\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix}}_{\dot{x}(t)} = \underbrace{\begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ -40\hat{\alpha}^3 & -54\hat{\alpha}^2 & -15\hat{\alpha} \end{bmatrix}}_{A} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_{x(t)} + \underbrace{\begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}}_{B} u \tag{8}$$

$$\underbrace{C_e}_{y(t)} = \underbrace{\begin{bmatrix} 40\hat{\alpha}^3 & 0 & 0 \end{bmatrix}}_{C} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_{x(t)}. \tag{9}$$

This model may be inverted in order to compute a constant infusion dose u_{ref} that leads the neuromuscular blockade to the desired reference level of 10% [4] [12].

Indeed, for a patient with parameters $(\hat{\alpha}, \hat{\gamma})$, inverting Hill's equation yields:

$$C_{ref} = 9^{\frac{1}{\hat{\gamma}}} \tag{10}$$

Moreover, since the steady-state gain of $\hat{G}(s)$ is equal to 1, one obtains for the reference infusion drug infusion dose:

$$u_{ref} = 9^{\frac{1}{\hat{\gamma}}} \tag{11}$$

This dose is administered from instant T^* on, and the corresponding evolution of the effect concentration $C_e(t)$ is computed using the state space model (8)-(9).

III. CONTROL SCHEME

In order to apply our control scheme, we consider the patient model identified as in the previous section. The linear part of the model has three poles, namely: $p_1 = -10\hat{\alpha}$, $p_2 = -4\hat{\alpha}$ and $p_3 = -\hat{\alpha}$. Our strategy will consist in placing the poles of the initial system in such a way that an excessive use of drug is avoided and simultaneously, the tracking performance is improved. In order to place the poles in $\bar{p}_1 = p_1$, $\bar{p}_2 = p_2$ and $\bar{p}_3 = \lambda p_3$, we consider the state space model (8)-(9) and compute the feedback gain K of the control law $u = -Kx + v$ such that the characteristic polynomial of the closed-loop system matrix $A - BK$ is equal to $\pi(s) = (s + \lambda\hat{\alpha})(s + 4\hat{\alpha})(s + 10\hat{\alpha})$. Simple computations show that the desired feedback gain is given by: $K = [40(\lambda - 1)\hat{\alpha}^3 \quad 14(\lambda - 1)\hat{\alpha}^2 \quad (\lambda - 1)\hat{\alpha}]$.

The application of the closed-loop $u = -Kx+v$ originates a closed-loop system

$$\begin{cases} \dot{x} = A^{cl}x + Bv \\ C_e = C_x \end{cases} \tag{12}$$

with

$$A^{cl} = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ -40\lambda\hat{\alpha}^3 & -(40 + 14\lambda)\hat{\alpha}^2 & -(14 + \lambda)\hat{\alpha} \end{bmatrix} \tag{13}$$

whose transfer function from v to C_e given by:

$$\hat{G}^{cl}(s) = \frac{40\hat{\alpha}^3}{(s + \lambda\hat{\alpha})(s + 4\hat{\alpha})(s + 10\hat{\alpha})} \tag{14}$$

The overall resulting system is shown in Figure 2.

As already mentioned, the reference value for the effect concentration C_e corresponding to the desired target value of 10% for the NMB is:

$$C_{ref} = 9^{1/\hat{\gamma}} \tag{15}$$

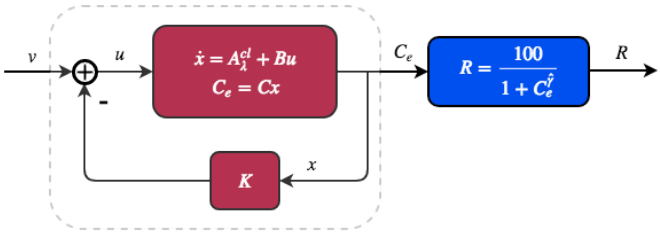

Fig. 2. Pole placement by state feedback scheme

Thus, the constant value v_{ref} for the new input v that guarantees a steady-state value of $9^{(1/\hat{\gamma})}$ for C_{ref}, is given by:

$$v_{ref} = \lambda \times 9^{(1/\hat{\gamma})} \tag{16}$$

This in turn allows to compute the infusion dose u to be administrated to the patient as:

$$u(t) = -Kx(t) + 3 \times 9^{1/\hat{\gamma}} \tag{17}$$

This dose will obviously only be given after the patient parameter identification phase, i.e., from instant T^* (mentioned in the previous section) on.

IV. SIMULATIONS AND RESULTS

The results obtained by this strategy for patients 2, 9, and 10 for $\lambda = 0.4, 0.6, 0.8, 1.0, 1.2$ and 2 are shown in the Figures 3, 4, 5, 6 and 7 together with the response corresponding to a bolus followed by constant drug infusion (i.e., corresponding to a "pure" TCI strategy without pole placement. The other patients have similar behavior. The average doses administered till the settling time T_s, and the settling time itself, for the model inversion without pole placement (TCI) and for our pole placement strategy are displayed in Tables 3, 4 and 5. Here T_s corresponds to a relative error of 20% witj respect to the NMB reference value (10), i.e., to NMB values between 8 and 12%. This range of values in accordance with clinical practice.

Note that, in these tables, the value $\lambda = 1$ corresponds to the TCI strategy.

TABLE III

PATIENT 2 AVERAGE DOSES (IN $\mu g/Kg/min$) AND SETTLING TIME (IN MINUTES) FOR THE POLE PLACEMENT STRATEGY CONTROL

λ	average doses	% of increase/ reduction	settling time	% of increase/ reduction
0.4	1.93	-18.5	77.30	-21.8
0.6	2.16	-8.5	89.33	-9.7
0.8	2.29	-3.2	96.11	-2.8
1	2.36	0	98.90	0
1.2	2.42	2.2	99.96	1.1

The doses and the effect concentration responses are similar for the 10 patients.

The simulations show that the best choice of λ for reducing both the amount of used drug and the settling time is $\lambda = 0.4$ (the lowest value among the considered ones). This

TABLE IV

PATIENT 9 AVERAGE DOSES (IN $\mu g/Kg/min$) AND SETTLING TIME (IN MINUTES) FOR THE POLE PLACEMENT STRATEGY CONTROL

λ	average doses	% of increase/ reduction	settling time	% of increase/ reduction
0.4	3.79	-30.2	56.56	-35.7
0.6	4.59	-15.3	65.92	-25.1
0.8	5.09	-6.1	77.24	-12.2
1	5.43	0	88.00	0
1.2	5.65	4.2	95.10	8.9

TABLE V

PATIENT 10 AVERAGE DOSES (IN $\mu g/Kg/min$) AND SETTLING TIME (IN MINUTES) FOR THE POLE PLACEMENT STRATEGY CONTROL

λ	average doses	% of increase/ reduction	settling time	% of increase/ reduction
0.4	2.24	-25.8	85.07	-27.6
0.6	2.64	-12.6	99.76	-15.1
0.8	2.87	-4.9	111.18	-5.4
1	3.02	0	117.53	0
1.2	3.12	3.35	120.65	2.7

corresponds to keeping the faster poles p_1 and p_2 and to slowering the dominant pole p_3. Although, at fist sight, this might seem counter-intuitive, one has to take into account the fact that the controller starts after the administration of an initial bolus, when the NMB level is much lower than the desired reference value. Under these circumstances slowering the dominant pole, reduces the amount of drug to be administrated and therefore allows a better recovery till the target value of 10%.

V. CONCLUSIONS

In this paper we considered the problem of tracking a desired level of neuromuscular blockade (NMB) by automatic administration of the muscle relaxant *rocuronium*, in the context of general anaesthesia.

As an alternative to the administration of a constant drug dose, a state feedback scheme was introduced in order to improve the performance of the delivery system.

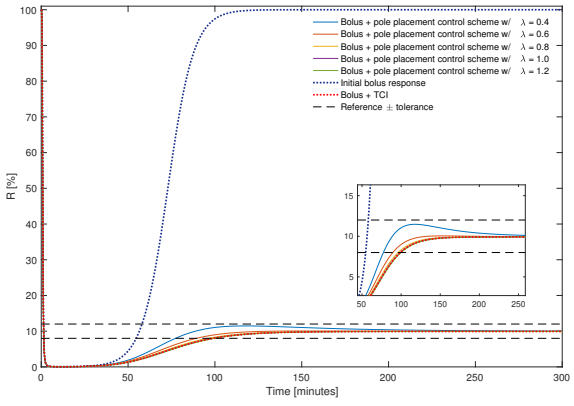

Fig. 3. NMB responses of Patient 2 for the following control strategies: bolus followed by TCI based on identified parameters without pole placement; bolus followed by TCI based on identified parameters with pole placement

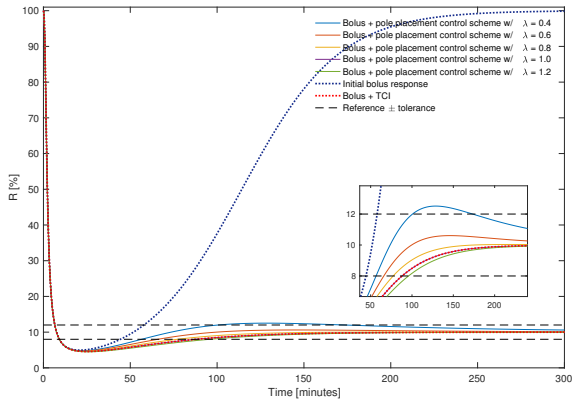

Fig. 4. NMB responses of Patient 9 for the following control strategies: bolus followed by TCI based on identified parameters without pole placement; bolus followed by TCI based on identified parameters with pole placement

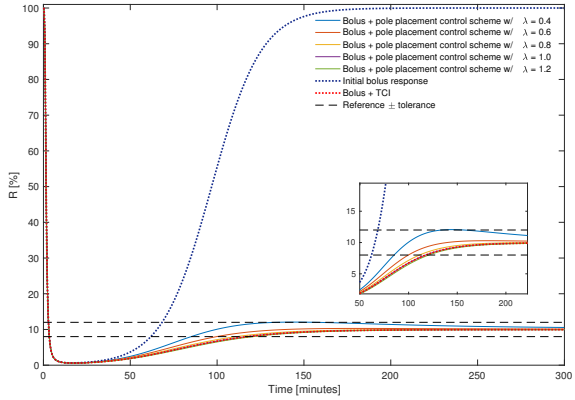

Fig. 5. NMB responses of Patient 10 for the following control strategies: bolus followed by TCI based on identified parameters without pole placement; bolus followed by TCI based on identified parameters with pole placement

This scheme is based on the parameter parsimonious model for the action of *rocuronium* proposed in [11], which only contains two patient dependent parameters.

In order to estimate this parameters a new simple estimation method, that takes advantage of the particular properties of the model as well as of the procedures used in clinical practice, namely the administration of a drug bolus in an initial phase.

More concretely, we simulated the administration of a bolus of 600 $\mu g/kg$ of *rocuronium* and, using the known model structure, estimated the patient parameters from the response to this bolus. The obtained estimates were then used in our previously designed controller, which was put into action after the initial phase.

The performed simulations show that a suitable choice of poles achieves a similar tracking performance as TCI with the advantage of reducing the dose administered in the

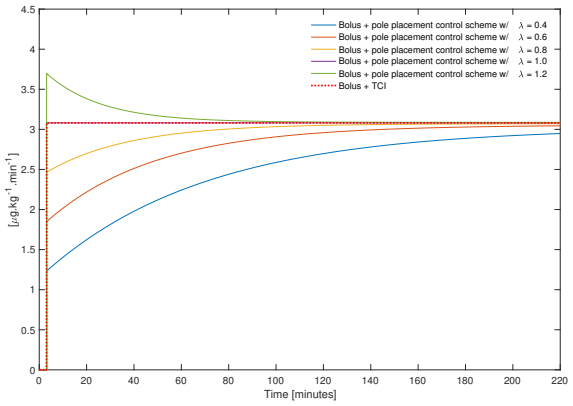

Fig. 6. Continuous infused doses delivered to Patient 10 after the initial bolus for the following control strategies: TCI based on identified patient parameters without pole placement; TCI based on identified patient parameters with pole placement.

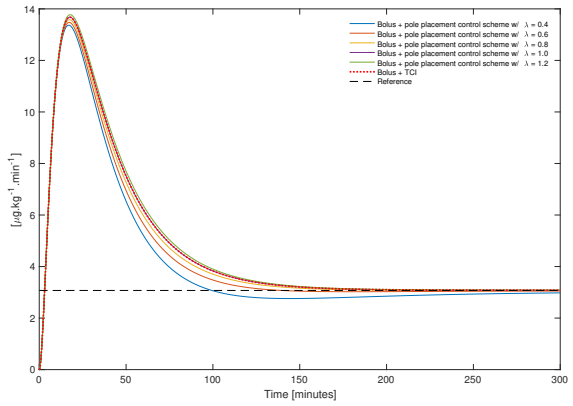

Fig. 7. Effect concentration on Patient 10 after the initial bolus for the following control strategies: TCI based on identified patient parameters without pole placement; TCI based on identified patient parameters with pole placement.

transient phase (and hence the overall average dose), and simultaneously improving the tracking performance..

Although the presented results still need further testing under other conditions as for instance in the presence of noise or for other target values, we consider them very promising and worthwhile exploited in future work.

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